ORGANIC CHEMISTRY

A Modern Approach

Volume-II

About the Author



Nimai Tewari is a retired Associate Professor in Department of Chemistry Katwa College (affiliated to University of Burdwan), West Bengal. A Ph.D in Organic Chemistry from Calcutta University, he has taught the subject for a period of more than three decades. He has published various research papers in national and international journals. Apart from Organic Chemistry—A Modern Approach, Volume-II (including Volume-I of this title), Dr Tewari has authored four more books on Organic Chemistry for undergraduate and postgraduate students. His research interest includes Organic Synthesis and Heterocyclic Chemistry.

ORGANIC CHEMISTRY

A Modern Approach

Volume-II

Nimai Tewari

Associate Professor (Retired)
Department of Chemistry
Katwa College
West Bengal



McGraw Hill Education (India) Private Limited
CHENNAI

McGraw Hill Education Offices

Chennai New York St Louis San Francisco Auckland Bogotá Caracas
Kuala Lumpur Lisbon London Madrid Mexico City Milan Montreal
San Juan Santiago Singapore Sydney Tokyo Toronto

McGraw Hill Education (India) Private Limited

Published by McGraw Hill Education (India) Private Limited
444/1, Sri Ekambara Naicker Industrial Estate, Alapakkam, Porur, Chennai 600 116

Organic Chemistry—A Modern Approach (Volume-II)

Copyright © 2018, by McGraw Hill Education (India) Private Limited.

No part of this publication may be reproduced or distributed in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise or stored in a database or retrieval system without the prior written permission of the publishers. The program listings (if any) may be entered, stored and executed in a computer system, but they may not be reproduced for publication.

This edition can be exported from India only by the publishers,
McGraw Hill Education (India) Private Limited.

1 2 3 4 5 6 7 8 9 D102739 22 21 20 19 18

Printed and bound in India.

ISBN (13): 978-93-87886-19-3
ISBN (10): 93-87886-19-0

Director—Science & Engineering Portfolio: *Vibha Mahajan*
Senior Portfolio Manager: *Suman Sen*
Associate Portfolio Manager: *Laxmi Singh*

Senior Manager—Content Development: *Shalini Jha*
Content Developer: *Ranjana Chaube*

Production Head: *Satinder S Baveja*
Sr. Manager—Production: *Piyaray Pandita*

General Manager—Production: *Rajender P Ghansela*
Manager—Production: *Reji Kumar*

Information contained in this work has been obtained by McGraw Hill Education (India), from sources believed to be reliable. However, neither McGraw Hill Education (India) nor its authors guarantee the accuracy or completeness of any information published herein, and neither McGraw Hill Education (India) nor its authors shall be responsible for any errors, omissions, or damages arising out of use of this information. This work is published with the understanding that McGraw Hill Education (India) and its authors are supplying information but are not attempting to render engineering or other professional services. If such services are required, the assistance of an appropriate professional should be sought.

Typeset at Text-o-Graphics, B-1/56, Aravali Apartment, Sector-34, Noida 201 301, and printed at

Cover Printer:

Visit us at: www.mheducation.co.in
Write to us at: info.india@mheducation.com
CIN: U22200TN1970PTC111531
Toll Free Number: 1800 103 5875

Dedicated to

Sri Ramakrishna Paramhansa

CONTENTS

Preface *xiii*

1. Addition to Carbon–Carbon Multiple Bond **1.1–1.212**

Introduction 1.1

1.1 Electrophilic Addition *1.2*
1.1.1 Addition of Hydrogen Halides *1.6*
Solved Problems 1.14
Study Problems 1.22
1.1.2 Addition of Water and Alcohol *1.26*
Solved Problems 1.32
Study Problems 1.37
1.1.3 Oxymercuration-Demercuration *1.39*
Solved Problems 1.42
Study Problems 1.44
1.1.4 Addition of Halogens *1.45*
Solved Problems 1.56
Study Problems 1.62
1.1.5 Hydroboration-Oxidation *1.65*
Solved Problems 1.75
Study Problems 1.81
1.1.6 Ozonolysis of Alkenes and Alkynes *1.82*
Solved Problems 1.93
Study Problems 1.100
1.1.7 Addition of Carbenes and Simons-Smith Reaction *1.102*
Solved Problems 1.110
Study Problems 1.115
1.1.8 Hydroxylation of Alkenes *1.117*
Solved Problems 1.127
Study Problems 1.131
1.1.9 Hydrogenation *1.134*
Solved Problems 1.142
Study Problems 1.147

1.1.10 Diels–Alder Reaction *1.149*
Solved Problems *1.163*
Study Problems *1.175*

1.2 Nucleophilic Addition *1.178*
1.2.1 Cyanoethylation *1.178*
1.2.2 Direct and Conjugate Addition to α,β-Unsaturated Aldehydes and Ketones *1.180*
1.2.3 Michael Addition or Michael Reaction *1.182*
Solved Problems *1.186*
Study Problems *1.195*

1.3 Addition of Radicals and Radical Substitution of Benzylic and Allylic Hydrogens *1.199*
1.3.1 Radical Addition of Halogens and Hydrogen Halides and Radical Polymerization *1.200*
Solved Problems *1.205*
Study Problems *1.206*
1.3.2 Allylic Chlorination and Allylic Bromination *1.207*
Solved Problems *1.209*
Study Problems *1.211*

References *1.212*

2. Reactions of the Carbonyl Group and Reactions at the α-Carbon to the Carbonyl Group **2.1–2.346**

2.1 *Introduction* *2.2*

2.2 Nucleophilic Addition to Carbon-Oxygen Double Bond *2.5*
2.2.1 Structure of the Carbonyl Group *2.5*
2.2.2 Effect of Structure on Reactivity *2.5*
2.2.3 Stereochemistry of Nucleophilic Addition *2.8*
Solved Problems *2.10*

2.3 Addition of Oxygen Nucleophiles: Water and Alcohols (ROH) *2.11*
2.3.1 Addition of Water (Hydration) and Formation of *gem*-diols *2.11*
2.3.2 Mechanism for Hydrate Formation *2.11*
2.3.3 Kinetics of Hydrate Formation *2.11*
2.3.4 Thermodynamics of Hydrate Formation *2.13*
2.3.5 Formation of Stable and Isolable Hydrates *2.14*
2.3.6 Addition of Alcohols and Formation of Hemiacetals and Acetals *2.16*
2.3.7 Mechanism for Acid-catalyzed Hemiacetal and Acetal Formation *2.18*
2.3.8 Mechanism for Base-catalyzed Hemiacetal Formation (Base-catalyzed Acetal Formation does not take place) *2.20*
2.3.9 Hydrolysis of Acetals *2.20*
2.3.10 Acetals as Protecting Groups *2.22*
2.3.11 Tetrahydropyranyl Group as a Protecting Group *2.23*
Solved Problems *2.24*
Study Problems *2.33*

2.4 Addition of Sulphur Nucleophiles: Thiols (RSH) and Sodium Bisulphite ($NaHSO_3$) *2.38*
2.4.1 Addition of Thiols *2.38*
2.4.2 Mechanism for Thioacetal Formation *2.38*
2.4.3 Thermodynamics for Thioacetal Formation *2.39*
2.4.4 Importance of Thioacetals in Organic Synthesis *2.39*
2.4.5 Addition of Sodium Bisulphite ($NaHSO_3$) *2.40*
2.4.6 Mechanism for Bisulphite Additions *2.40*
2.4.7 Applications of Bisulphite Addition Reaction *2.41*
Solved Problems *2.42*
Study Problems *2.45*

2.5 Addition of Hydride Ion ($:H^{\ominus}$) and addition of electrons *2.46*
2.5.1 Reduction of carbonyl compounds by lithium aluminium hydride ($LiAlH_4$) *2.47*
2.5.2 Mechanism for the reduction of carbonyl compounds by lithium aluminium hydride ($LiAlH_4$) *2.47*
2.5.3 Reduction of aldehydes and ketones by sodium borohydride ($NaBH_4$) to form primary and secondary alcohols, respectively *2.50*
2.5.4 Mechanism for the reduction of an aldehyde or a ketone by sodium borohydride ($NaBH_4$) *2.51*
2.5.5 Reduction of carboxylic acids, amides and nitriles by borane (BH_3) *2.51*
2.5.6 Reduction of Acid Chlorides to the Corresponding Aldehydes by Lithium tri-*tert*-butoxyaluminium Hydride [$LiAlH(O\text{-}t\text{-}Bu)_3$] and Reduction of Esters and Nitriles to the Corresponding Aldehydes by Diisobutylaluminum Hydride (i–Bu_2AlH or DIBAL–H): *2.53*
2.5.7 Meerwein–Ponndorf–Verley (MPV) reduction *2.55*
2.5.8 Cannizzaro Reaction *2.57*
2.5.9 Tishchenko Reaction *2.64*
2.5.10 Bouveault-Blanc Reduction *2.65*
2.5.11 Pinacolization of Ketones *2.67*
2.5.12 Clemmensen Reduction *2.68*
Solved Problems *2.69*
Study Problems *2.81*

2.6 Addition of Nitrogen Nucleophiles *2.84*
2.6.1 Addition of Primary Amines and Formation of Imines *2.84*
2.6.2 Addition of Compounds like Hydroxylamine, Hydrazine and Substituted Hydrazines (Similar to Primary Amines and Formation of Imine Derivatives) *2.86*
2.6.3 Reductive Amination *2.88*
2.6.4 Wolff-Kishner Reduction *2.89*
2.6.5 Important uses of the Imine-Forming Reaction *2.91*
2.6.6 Addition of Secondary Amines and Formation of Enamines *2.91*
Solved Problems *2.96*
Study Problems *2.104*

2.7 Addition of Carbon Nucleophiles *2.106*
2.7.1 Addition of Hydrogen Cyanide (HCN) *2.106*
2.7.2 Addition of Grignard and Other Organometallic Compounds *2.109*
2.7.3 Addition of Acetylides *2.116*
2.7.4 Addition of Diazomethane (CH_2N_2) *2.116*
2.7.5 Addition of Ylides *2.118*
Solved Problems 2.127
Study Problems 2.142

2.8 Addition of Enolate Ions *2.145*
2.8.1 Aldol Reactions *2.145*
2.8.2 Stobbe Condensation *2.157*
2.8.3 Darzenes Condensation *2.160*
2.8.4 Benzoin Condensation *2.164*
2.8.5 Reformatsky Reaction *2.169*
2.8.6 Perkin Reaction *2.172*
2.8.7 Knoevenagel Condensation *2.175*
2.8.8 Mannich Reaction *2.180*
Solved Problems 2.182
Study Problems 2.203

2.9 Reactions at the α-carbon of Carbonyl Compounds of Aldehydes and Ketones *2.208*
2.9.1 Halogenation at the α-carbon of Aldehydes and Ketones *2.208*
2.9.2 Alkylation at the α-carbon of Aldehydes and Ketones *2.214*
2.9.3 The Claisen Condensation (Addition of Acid Derivatives to the α-carbon of Carbonyl Compounds) *2.227*
Solved Problems 2.236
Study Problems 2.273
2.9.4 Green Chemistry *2.279*
Solved Problems 2.283
Study Problems 2.285

2.10 Acyl Substitution *2.286*
2.10.1 Mechanism of Nucleophilic Addition–Elimination at the Acyl Carbon or Nucleophilic Acyl Substitution *2.286*
2.10.2 Reactions of Carboxylic Acids *2.290*
2.10.3 Reactions of Acid Chlorides *2.311*
2.10.4 Reactions of Esters *2.313*
2.10.5 Reactions of Amides *2.317*
2.10.6 Reactions of Carboxylic Acid Anhydrides *2.319*
2.10.7 Reactions of Nitriles *2.320*
Solved Problems 2.321
Study Problems 2.341

References 1.346

3. Electrophilic and Nucleophilic Substitutions in Aromatic Systems 3.1–3.181

Introduction 3.1

3.1 Electrophilic Aromatic Substitution *3.3*
3.1.1 Characteristics of Electrophilic Aromatic Substitution *3.3*
Solved Problems 3.24
Study Problems 3.39
3.1.2 Formation of Carbon–Nitrogen σ-Bond (Nitration, Nitrosation and Diazo coupling) *3.43*
Solved Problems 3.52
Study Problems 3.61
3.1.3 Formation of Carbon-Halogen σ-Bond (Halogenation): Bromination and Chlorination, Iodination, Fluorination *3.63*
Solved Problems 3.67
Study Problems 3.70
3.1.4 Formation of Carbon–Sulphur σ-Bond: Sulphonation and Chlorosulphonation *3.72*
Solved Problems 3.78
Study Problems 3.81
3.1.5 Formation of Carbon–Carbon σ-Bond: Friedel–crafts Reaction, Houben–Hoesch Reaction, Gattermann Formylation, Gattermann–Koch Fromylation, Reimer-Tiemann Reaction, and Kolbe-Schmitt Reaction *3.83*
Solved Problems 3.107
Study Problems 3.121
3.1.6 Use of electrophilic Aromatic Substitution Reactions in Organic Synthesis *3.124*
Solved Problems 3.141
Study Problems 3.146

3.2 Nucleophilic Aromatic Substitution *3.147*
3.2.1 The Addition-Elimination or S_NAr Mechanism *3.148*
3.2.2 The Elimination-Addition or Benzyne Mechanism *3.155*
3.2.3 S_N1 Mechanism *3.164*
3.2.4 Aromatic Nucleophilic Substitutions with Rearrangement *3.166*
Solved Problems 3.167
Study Problems 3.179

References 3.181

4. Rearrangement Reactions 4.1–4.161

Introduction 4.1

4.1 1,2-Rearrangements *4.3*
4.1.1 Nucleophilic Rearrangements to Electron Deficient Carbon *4.3*
Solved Problems 4.38
Study Problems 4.55

4.1.2 Nucleophilic Rearrangements to Electron-Deficient Nitrogen *4.60*
Solved Problems 4.80
Study Problems 4.99
4.1.3 Nucleophilic Rearrangements to Electron-Deficient Oxygen *4.102*
Solved Problems 4.109
Study Problems 4.113
4.1.4 Electrophilic Rearrangements *4.114*
Solved Problems 4.117
Study Problems 4.119
4.2 Non-1,2-rearrangements *4.120*
4.2.1 Favorskii Rearrangement *4.120*
4.2.2 Hofmann–Martius Rearrangement *4.127*
4.2.3 Orton Rearrangement *4.128*
4.2.4 Fries Rearrangement *4.128*
4.2.5 Benzidine Rearrangement *4.133*
4.2.6 Claisen Rearrangement *4.136*
4.2.7 Cope Rearrangement *4.140*
Solved Problems 4.143
Study Problems 4.157
References 4.161

Index ***I.1–I.5***

Preface

While teaching Organic Chemistry at the undergraduate level, I observed that students have to plough through several specific books within a short span of time and as a consequence, they often fail to assimilate the subject matter. It is this difficulty of the students that motivated me to undertake this concise and systematic work on Organic Chemistry in the light of the modern structural theories. The book has been designed primarily for students who have taken an honours course in Organic Chemistry at the undergraduate level.

The book is organised into four chapters: (i) Addition to Carbon-Carbon Multiple Bond, (ii) Reactions of the Carbonyl Group and Reaction at the α-carbon to the Carbonyl Group, (iii) Electrophilic and Nucleophilic Substitutions in Aromatic Systems, and (iv) Rearrangement Reactions.

I believe that Organic Chemistry can be best understood and learnt by solving problems. Each article of every chapter concludes with a number of solved as well as study problems to develop the proficiency of students that can be acquired only by practice. The book presents a large number of reactions supported with mechanistic explanation and diagrams.

I am pleased to note that Volume-I of this title has been received well by both teachers and students. This volume will also be highly useful for students in advanced courses who have had a basic course in Organic Chemistry in B.Sc. (Chemistry) Hons. It also aims to help the students preparing for competitive examinations like NET, GATE and SLET.

Acknowledgements

I would like to express my deep sense of gratitude to Mrs. Vibha Mahajan, Director, Science and Engineering Portfolio, for successful publication of this book. I also wish to thank Mr. Suman Sen and Mr. P. L. Pandita for taking keen interest in publishing this book. I am grateful to all of them.

I also owe a debt of gratitude to my friends and former colleagues for their constructive suggestions and to my students who encouraged me constantly. I extend my heartfelt

gratitude to my wife, Mrs. Dali Tewari, and my daughter, Aindrila Tewari (Mukherjee), for their support and encouragement during the long period of writing this book.

Valuable suggestions from the readers for further improvement of the book are most welcome. These can be shared at: n.tewari54@gmail.com

Nimai Tewari

1 CHAPTER

ADDITION TO CARBON–CARBON MULTIPLE BOND

Chapter Outline

Introduction

1.1 Electrophilic Addition
- 1.1.1 Addition of hydrogen halides
- 1.1.2 Addition of Water and Alcohol
- 1.1.3 Oxymercuration-Demercuration
- 1.1.4 Addition of Halogens
- 1.1.5 Hydroboration-Oxidation
- 1.1.6 Ozonolysis of Alkenes and Alkynes
- 1.1.7 Addition of Carbenes and Simons-Smith Reaction
- 1.1.8 Hydroxylation of Alkenes
- 1.1.9 Hydrogenation
- 1.1.10 Diels–Alder Reaction

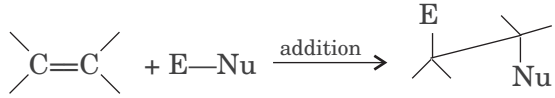
1.2 Nucleophilic Addition
- 1.2.1 Cyanoethylation
- 1.2.2 Direct and Conjugate Addition of α, β-Unsaturated Aldehydes and Ketones
- 1.2.3 Michael Addition

1.3 Addition of radicals and radical substitution of benzylic and allylic hydrogens
- 1.3.1 Radical addition of halogens and hydrogen halides and radical polymerization
- 1.3.2 Allylic chlorination and allylic bromination

INTRODUCTION

The characteristic feature of the structure of an alkene is the carbon–carbon double bond. It is thus the functional group of alkenes and it determines the characteristic reactions that alkenes undergo. These reactions are of two types:

(a) There are reactions that take place at the double bond itself and as a result, the double bond is destroyed. These reactions are called addition reactions and these are called so because in these reactions two molecules combine to yield a single molecule of the product. The reagent is simply added to the substrate, in contrast to a substitution reaction in which part of the reagent is substituted into a part of the substrate. This type of reaction can be depicted by using E for an electrophilic portion of a reagent and Nu for a nucleophilic portion, as follows:



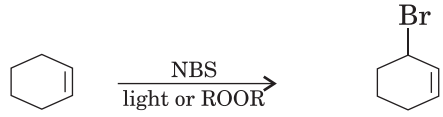
When an electrophile (or a positive pole of a dipole) initiates the process, the reaction is termed as *electrophilic addition reaction* and when a nucleophile (or a negative pole of a dipole) initiates the process, the reaction is said to be a *nucleophilic addition reaction.*

Since free radicals also seek electrons, therefore, alkenes also undergo *free-radical addition*. Besides these additions involving charged species and free radicals, alkenes undergo some *molecular additions* in which two unsaturated molecules or two such parts of a single molecule add to form a cyclic product. Therefore, depending upon the electronic nature of the addendum used, addition reactions may be classified as:

1. **Electrophilic additions**
2. **Nucleophilic additions**
3. **Free-radical additions**
4. **Molecular additions**

(b) There are some reactions that take place not at the carbon–carbon double bond, but at certain positions having special relationships to the double bond. The double bond, though not involved, plays an important role in the reaction. These are free radical substitution reactions known as *allylic substitutions*. For example:

$$\underset{\text{Propene}}{CH_3CH=CH_2} \xrightarrow[600^\circ C]{Cl_2} \underset{\text{Allyl chloride}}{ClCH_2CH=CH_2}$$



Cyclohexene 3-Bromocyclohexene

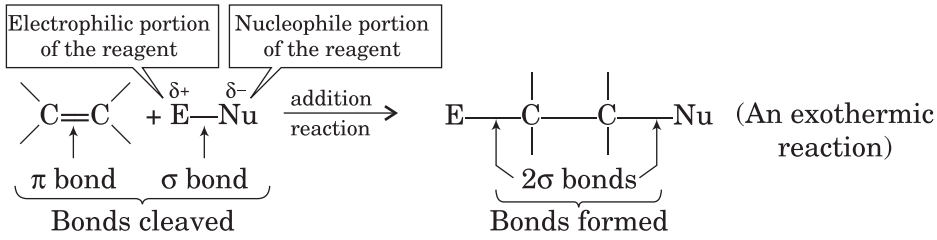
1.1 ELECTROPHILIC ADDITION

Because of the following two characteristics of the double bond, the electrophilic addition reactions take place:

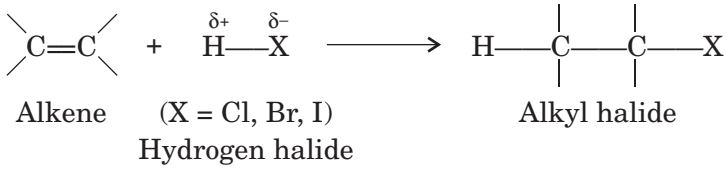
1. In a carbon–carbon double bond, there is a cloud of π electrons above and below the plane of the atoms. These π electrons are less involved than the σ electrons in holding together the two carbon atoms. As a result, they are themselves not tightly held. These loosely held and more exposed π electrons are particularly available to a reagent that is seeking electrons. It thus follows that in many reactions, the carbon–carbon double bond acts as a source of electrons, i.e., it acts as a nucleophile. The molecules or ions with which it reacts are those that are deficient in electrons

and can accept an electron pair, that is, are electrophiles. Each reaction starts with the addition of an electrophile to one of the sp^2 hybridized carbons of the alkene and ends with the addition of a nucleophile to the other sp^2 hybridized carbon. The result is that the π bond breaks and the two sp^2 carbons form two new σ bonds with the reagent.

2. In an addition reaction, one π bond and one σ bond are converted into two σ bonds. The energy released in making two σ bonds exceeds that required to break one σ bond and one π bond and, therefore, addition reactions are usually exothermic and energetically favourable.



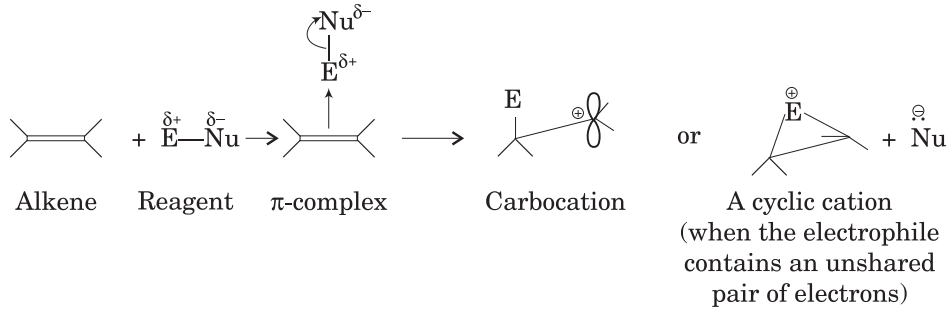
Hydrohalogenation, for example, is the electrophilic addition of hydrogen halides HX(X=Cl, Br and I) to alkenes to form alkyl halides.



Some other reactions of this type that we shall study in this chapter include addition of sulphuric acid, water (in the presence of an acid catalyst), halogen, etc.

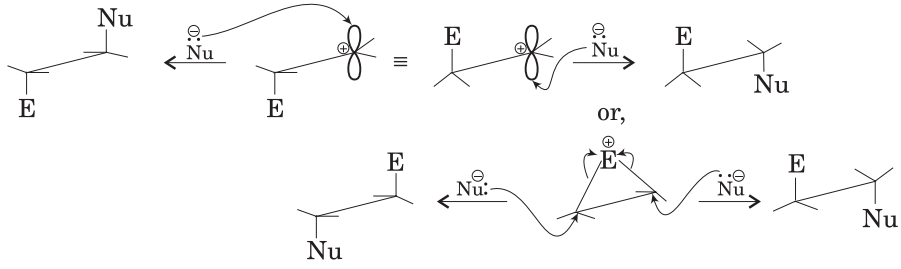
Mechanism The elelctrophilic addition to C═C usually occurs in two steps:

Step 1: The incoming reagent with its electrophilic portion in the front or the electrophile with its vacant orbital approaches the π cloud of the alkene in a perpendicular direction from above or below the plane of the six atoms to form a π-complex which may or may not be an actual intermediate. The π-complex then collapses to carbocation through the formation of a σ bond between the electrophilic portion of the reagent or the electrophile and any one of the doubly bonded carbon atoms. The overall result in the formation of a carbocation and nucleophile, $\ddot{N}u^{\ominus}$, from the alkene and the reagent, E—Nu. Electrophiles containing an unshared pair of electrons form a three-membered ring in which the electrophile bears a positive charge. This may be an intermediate when addition of halogens occurs or a true cyclic product when addition of neutral electrophiles such as carbenes, nitrenes, etc. occurs.

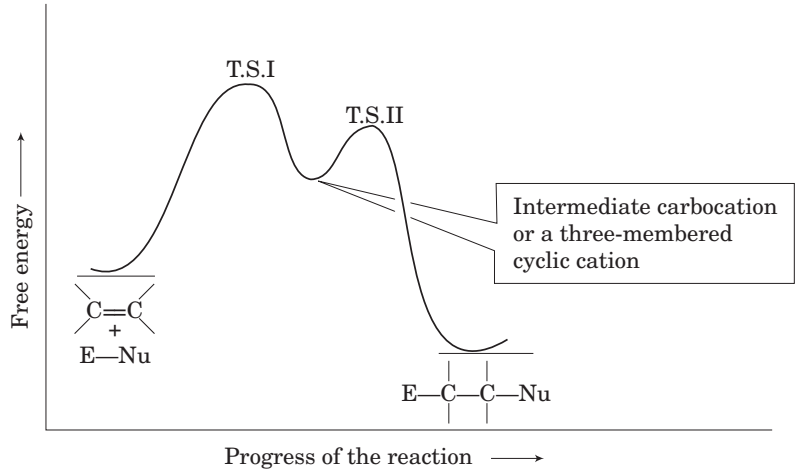


It is the rate-determining (slow) step of the reaction.

Step 2: The nucleophile combines with the intermediate carbocation or the three-membered cyclic cation to yield the addition product. It is a fast step.



The energy diagram for the reaction may be represented as follows:



In contrast to electrophilic additions, nucleophilic addition to carbon–carbon multiple bond is less common and this is because the negative charge cloud of the π orbital shields the molecule from attack of nucleophilic reagents. Since the C═C moiety can readily offer its loosely held π electrons to an electron-deficient species (electrophile), the additions are mostly electrophilic in nature.

Since the addition of the electrophile is the rate-determining step of the reaction, therefore, the rate of electrophilic addition to a carbon–carbon multiple bond depends on the relative electron density of a π bond. The more the multiple bond is electron rich, the more it is reactive towards an electrophilic addition. Electron-donating groups would, therefore, be expected to enhance the reactivity, and electron-withdrawing group would, therefore, be expected to decrease the reaction rate. The following relative rates of addition of Br_2 to different alkenes in CH_2Cl_2 solution at –78°C are actually observed in practice:

$$\underset{0.4}{CH_2{=}CH} \rightarrow Br \langle \underset{1}{CH_2{=}CH_2} \langle \underset{2.03}{CH_3{-}CH{=}CH_2} \langle \underset{5.53}{(CH_3)_2C{=}CH_2}$$

$$\langle \underset{10.4}{(CH_3)_2C{=}CHCH_3} \langle \underset{14.0}{(CH_3)_2C{=}C(CH_3)_2}$$

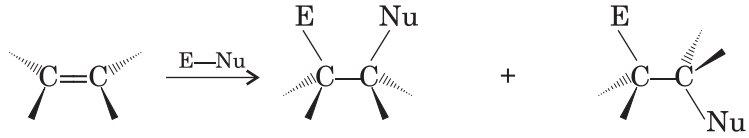
The rate increases with increasing the number of electron-releasing methyl groups on the doubly bonded carbon atoms. Bromine being electron-withdrawing (–I > + R) makes allyl bromide ($CH_2{=}CH{-}Br$) less reactive than ethylene. These observations, therefore, suggest that the addition of the electrophile is the rate-determining step of the reaction.

Although the reactivity increases, the rate of reactivity decreases because the crowding in the bromonium ion or in the T.S. leading to it progressively increases.

Kinetics: Since the step 1, i.e., the electrophilic addition to carbon–carbon double bond, is the slow step and the T.S. of this step involves both the substrate and the reagent (the electrophile), therefore, the reaction is expected to follow second-order kinetics.

$$\text{rate} = k\,[\text{substrate}]\,[\text{reagent}]$$

Stereochemistry: The steroechemistry of addition is often important in delineating the mechanism of a reaction. Because the carbon atoms of a double bond are both trigonal planar (sp^2), the elements E and Nu can be added to them from the same side or from opposite sides.



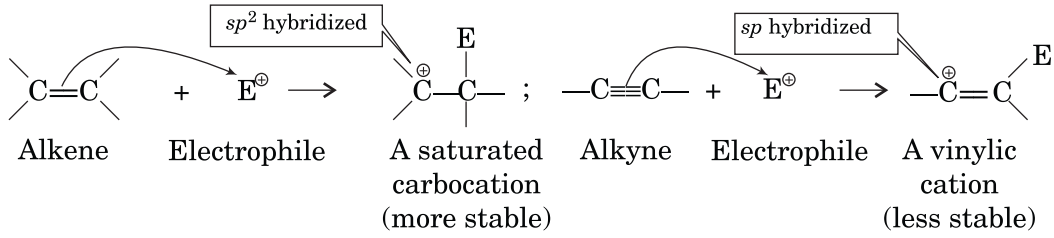
Alkene | *Syn*-addition (E and Nu are added from the same side) | *Anti*-addition (E and Nu are added from opposite sides)

Triple bonds are less susceptible to electrophilic attack than double bonds In general, the triple bonds are less susceptible to electrophilic attack than double bonds, even though the concentration of electrons in a triple bond is higher than that in a double bond. The reasons are as follows:

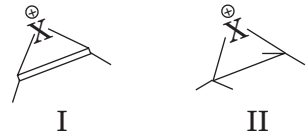
1. Because of smaller distance between the two triple bonded carbon atoms and better *p* orbital overlap, the electrons in the triple bond are held more tightly and hence, they are poorly available to an electrophile, i.e., it is harder for an attacking

electrophile to pull out a pair. There is evidence from far-UV spectra to support this conclusion.

2. An electrophile adds to a double bond to give a saturated carbocation. A similar addition to a triple bond gives a vinylic cation. A vinylic cation is less stable than the corresponding saturated carbocation because it possesses the linear (*sp*) arrangement instead of planar (sp^2) arrangement which, as suggested by quantum machanics, is the stabler configuration of carbocation.



3. If the reaction takes places via a bridged-ion intermediate, then those obtained from triple bond (I) will be highly strained and hence, less stable than those obtained from double bonds (II).



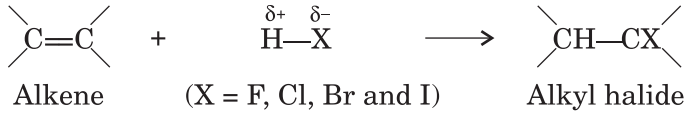
Furthermore, the cyclic ions from alkynes are antiaromatic and hence, less stable but those from alkenes are not.

However, it is to be noted that catalytic hydrogenation is an exception to the generalization that alkenes are more reactive than alkynes towards addition reactions.

1.1.1 Addition of Hydrogen Halides

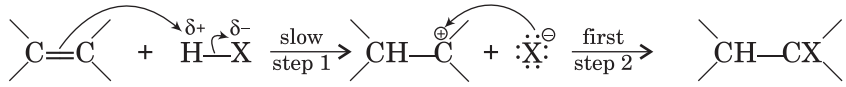
1.1.1.1 Reaction

The addition of hydrogen halides HX(X=F, Cl, Br and I) to alkenes to form alkyl halides is known as *hydrohalogenation.* These additions are usually carried out by dissolving the hydrogen halide in a solvent, such as acetic acid or methylene chloride, or by bubbling the gaseous HX directly into the alkene.



1.1.1.2 Mechanism

The mechanism for the addition of a hydrogen halide to an alkene involves the following two steps:



An alkene A carbocation An alkyl halide

In Step 1, the π electrons of the alkene form a bond by accepting a proton from HX and as a result, a carbocation (a more stable carbocation in the case of unsymmetrical alkene) and a halide ion ($X^{\ominus}$) are formed. This step is highly endothermic and its energy of activation is very high. As a consequence, it takes place slowly, and it is the rate-determining step of the reaction. In Step 2, the halide ion reacts with the highly reactive carbocation by donating an electron pair to form an alkyl halide. This exothermic step has a very low energy of activation. So, it takes place rapidly.

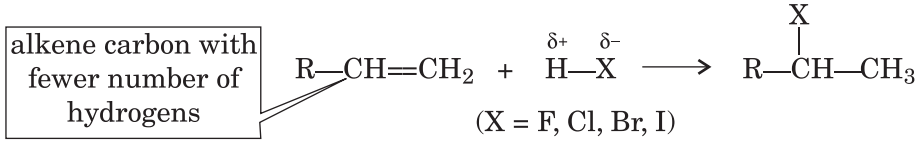
1.1.1.3 The Order of Reactivity of Hydrogen Halides

The order of reactivity of hydrogen halides is HI > HBr > HCl > HF. The reactivity of hydrogen halides depends on their acid strength. The acid strength decreases in the order: HI > HBr > HCl > HF (this follows from the fact that the H—F bond is by far the strongest and the H—I bond is the weakest) and because of this, the order of reactivity of HX is HI > HBr > HCl > HF.

1.1.1.4 Markownikoff's Rule

The problem of constitutional orientation (ascertaining which one of the two doubly bonded carbons ultimately forms bond with the electrophile and which one combines with the nucleophile) does not arise in the cases of addition of symmetrical reagents like Br_2, Cl_2, etc. (addendum) to both symmetrical (e.g., $CH_2{=}CH_2$,$CH_3CH{=}CHCH_3$, etc.) and unsymmetrical substrates e.g., $CH_3CH{=}CH_2$, $CH_3CH{=}C(CH_3)_2$, etc. However, this is very important for the addition of an unsymmetrical reagent (e.g., H_2O, H_2SO_4, HBr, HCl, etc.) to an unsymmetrical alkene. In most cases, the problem can be solved by applying a rule known as *Markowniff's rule.*

Definition: If an unsymmetrical alkene combines with a hydrogen halide (H—X), the halide ion adds to the carbon atom bearing the lesser number of hydrogen atoms.



The rule is further extended to the cases of other polar addition to unsymmetrical alkenes. It is stated as: '*the negative part of an addendum adds to that carbon atom of the double bond of an unsymmetrical alkene which contains the lesser number of hydrogen atoms*'.

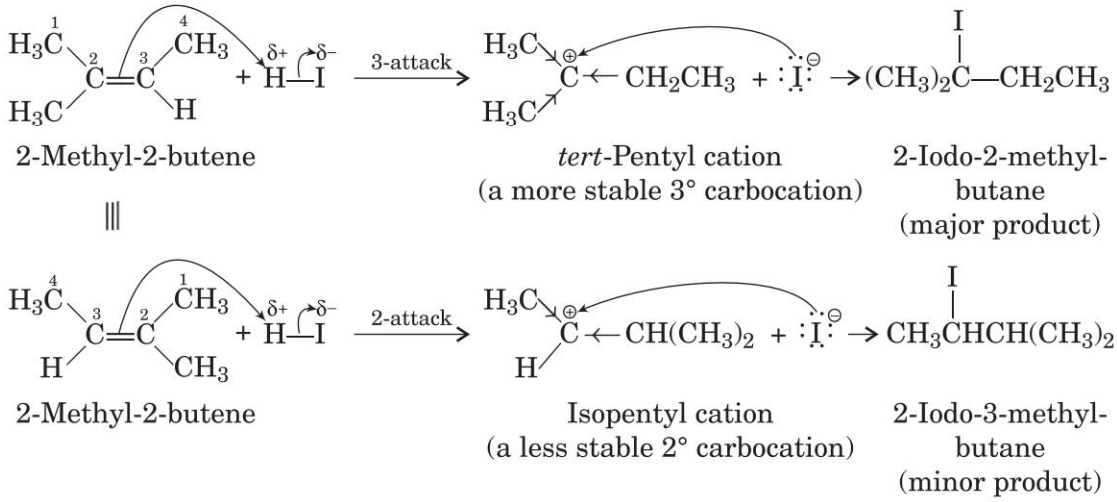
$$RCH{=}CH_2 + \overset{\delta+\ \ \delta-}{Y{-}Z} \longrightarrow RCHZ{-}CH_2Y \ (YZ = H_2O, H_2SO_2, ICl, \textit{etc.})$$

Modern statement: The modern statement of the Markownikoff's rule is as follows: In the ionic addition of an unsymmetrical addendum to a double bond of an unsymmetrical alkene, the positive portion of the addendum attaches itself to a doubly bonded carbon so as to yield the more stable carbocation as an intermediate.

The addition of HI to 2-methyl-2-butene takes place according to the Markownikoff's rule:

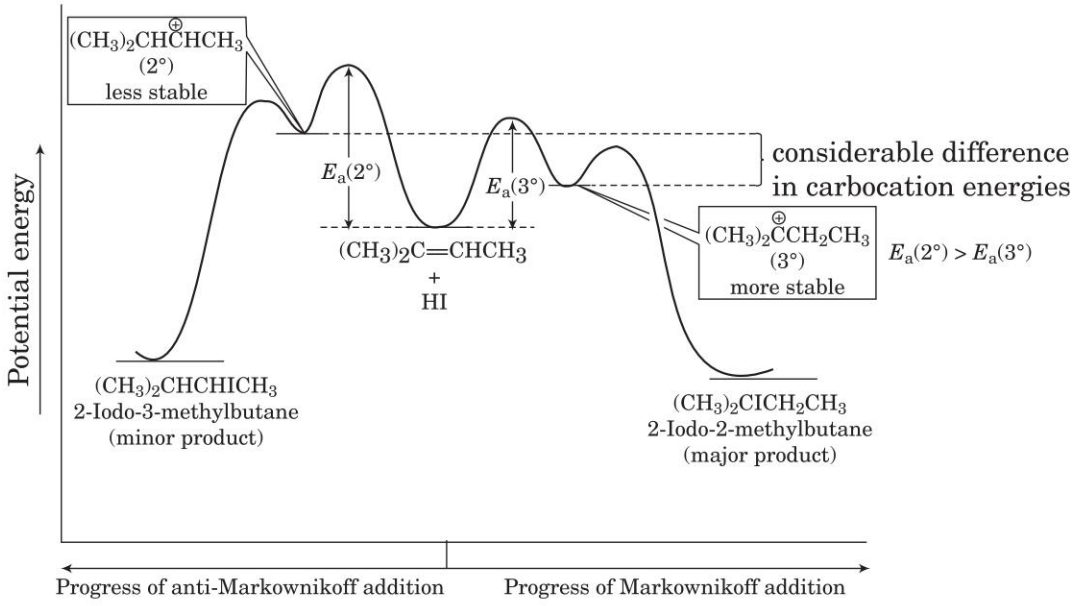
$$\underset{\text{2-Methyl-2-butene}}{(CH_3)_2C{=}CHCH_3} + HI \longrightarrow \underset{\substack{\text{2-Iodo-2-methylbutane}\\\text{(major product)}}}{(CH_3)_2ClCH_2CH_3} + \underset{\substack{\text{2-Iodo-3-methylbutane}\\\text{(minor product)}}}{(CH_3)_2CHCHICH_3}$$

Explanation: The Markownikoff addition of HI to 2-methyl-2-butene may be explained in terms of stabilities of carbocation intermediates that could be formed by attachment of a proton to one or the other doubly bonded carbon atom. Addition of the electrophile, $H^{\oplus}$, to 2-methyl-2-butene may yield two different carbocations: *tert*-pentyl cation (a 3° carbocation) and isopentyl cation (a 2° carbocation). In *tert*-pentyl cation, the positive carbon is stabilized by the inductive effect involving two methyl and one ethyl groups and hyperconjugative effect involving eight α–H atoms. On the other hand, in isopentyl cation, the positive carbon is stabilized by +I effect of two alkyl groups (isopropyl and methyl groups) and hyperconjugative effect involving four α–H atoms. So, the *tert*-pentyl cation is relatively more stable than the isopentyl cation and the reaction leading to *tert*-pentyl cation has a lower energy of activation than the reaction leading to isopentyl cation. The *tert*-pentyl cation is, therefore, formed at a faster rate than isopentyl cation and consequently, 2-iodo-2-methylbutane is obtained as the major product in this kinetically controlled reaction. Hence, the composition of the products obtained is controlled by the stability of the carbocations involved.



Regioselective reaction: A reaction in which two or more constitutional isomers (they differ in how their atoms linked) could be obtained as products but one of them predominates or obtained as the only product, is called a *regioselective reaction*. Since 2-methyl-2-butene reacts with HI to produce 2-iodo-2-methylbutane predominantly and propene reacts with HBr to form 2-bromopropane exclusively, therefore, these reactions are regioselective reactions.

Energy diagram: The energy diagram for the addition of HI to $(CH_3)_2C{=}CHCH_3$ is as follows:

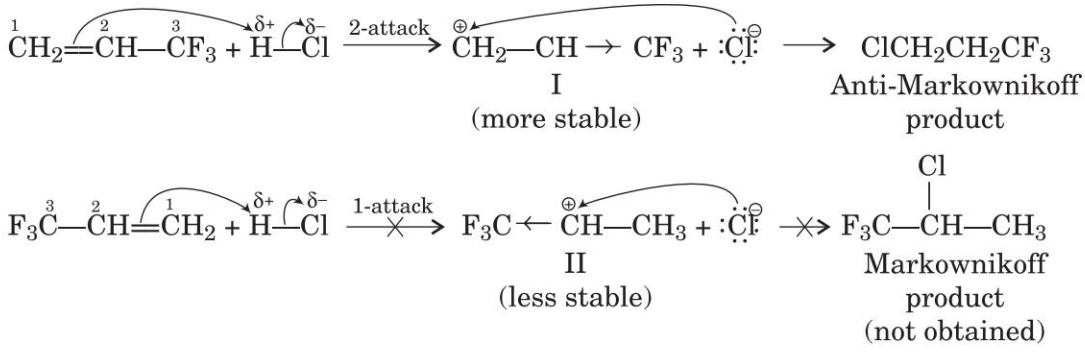


Exceptions of Markownikoff's rule: Due to special structural features of alkenes addition often takes place not according to the Markownikoff's rule. For example:

(i) $CH_2{=}CH{-}CF_3 + HCl \longrightarrow Cl\,CH_2CH_2\,CF_3$ (anti-Markownikoff product)

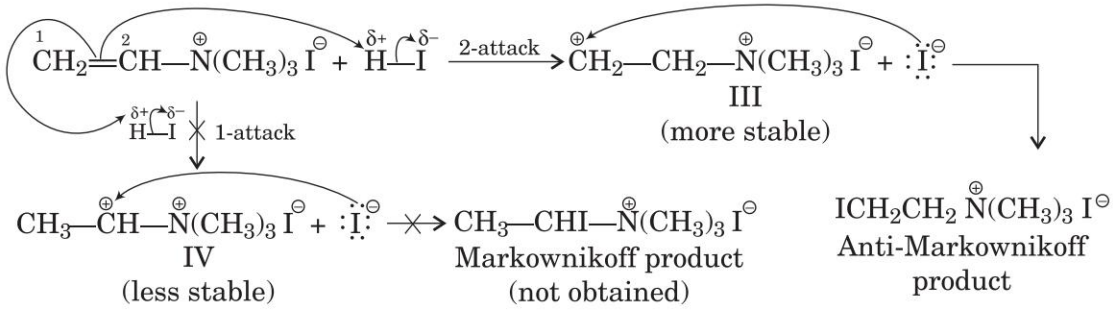
(ii) $CH_2{=}CH{-}\overset{\oplus}{N}(CH_3)_3I^{\ominus} + HI \longrightarrow ICH_2CH_2\,\overset{\oplus}{N}(CH_3)_3I^{\ominus}$ (anti-Markownikoff product)

When $H^{\oplus}$ adds to $CH_2{=}CH{-}CF_3$, one of the carbocations that could be formed is primary (I) and the other is secondary (II). In the carbocation II, the powerful electron-attracting $-CF_3$ group is directly attached to the positive carbon and so, it destabilizes the carbocation by intensifying the positive charge more than I in which the $-CF_3$ group is not directly attached to the positive carbon. As a result, the reaction proceeds through the relatively more stable carbocation I, although a primary one, to give the anti-Markownikoff product $ClCH_2CH_2CF_3$.



Since a primary carbocation is too unstable to be formed, the anti-Markownikoff product is probably obtained through a concerted addition process.

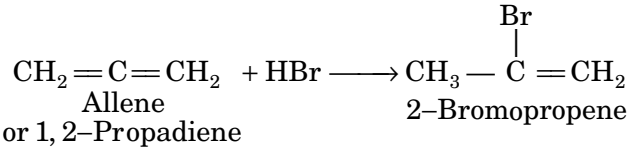
Addition of $H^{\oplus}$ to the doubly bonded carbons of the ammonium salt may produce a primary carbocation (III) and a secondary carbocation (IV). Because of repulsive destabilization, the carbocation IV (although a secondary one) with adjacent positive charges is relatively less stable than the carbocation III (a primary carbocation) in which the charges are separated by a saturated carbon atom. Thus, the proton becomes attached to the carbon adjacent to nitrogen to give the relatively stable carbocation III. Subsequent reaction of III with $I^{\ominus}$ gives the anti-Markownikoff product, $ICH_2CH_2\overset{\oplus}{N}(CH_3)_3I^{\ominus}$.



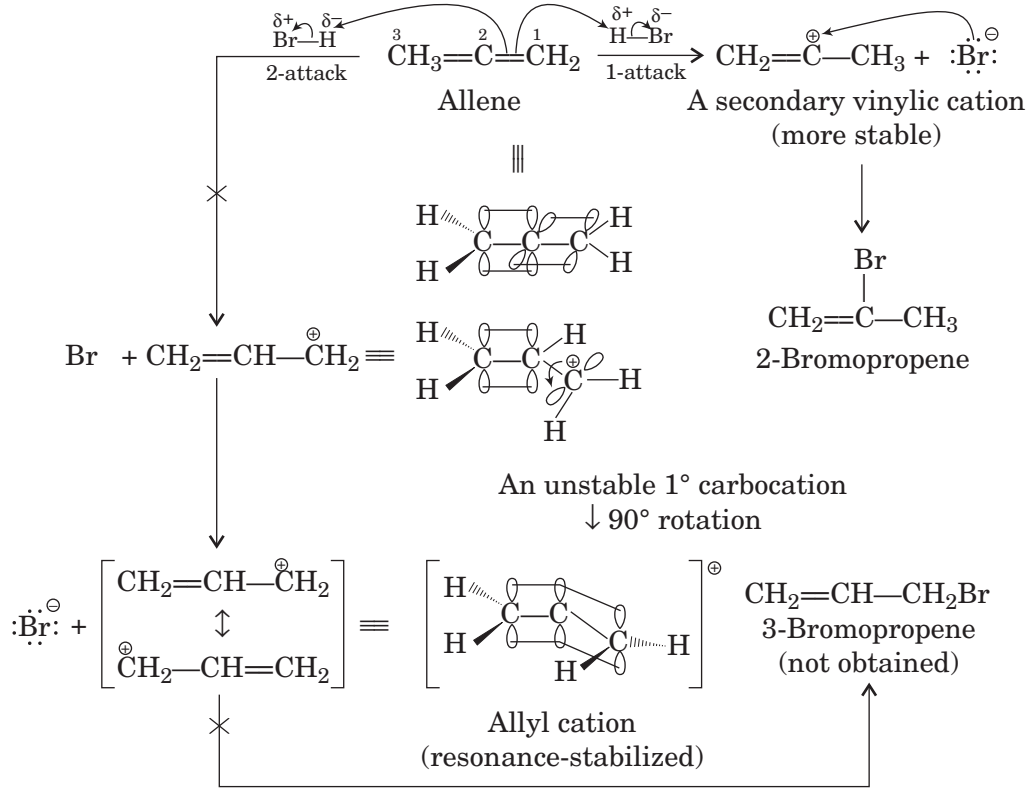
Another exception to Markownikoff's rule concerns the addition of HBr to alkenes when the addition is carried out in the presence of peroxides (i.e., compounds with the general formula ROOR). This (peroxide effect or Kharasch effect) will be discussed in **article 1.3.4.3**.

1.1.1.5 Addition of HX to Cumulated Dienes

Cumulated dienes undergo electrophilic addition of HX in accordance with the Markownikoff's rule, even though attack by the electrophile ($H^{\oplus}$) at the *sp* hybridized carbon would give a stable allylic cation. For example:



Explanation: Addition of $H^{\oplus}$ to the central *sp* hybridized carbon of allene or 1,2-propadiene does not give immediately a resonance-stabilized allylic cation because the three *p* orbitals are not parallel and it requires a rotation about the C—C bond for delocalization of electrons to take place. Therefore, attack by $H^{\oplus}$ at the central carbon produces initially a relatively unstable 1° carbocation. However, when $H^{\oplus}$ adds to a terminal sp^2 carbon, a relatively stable secondary vinylic cation is produced. So, the activation energy for the Markownikoff addition is lower than that for the anti-Markownikoff addition and consequently, the addition occurs in accordance with the Markownikoff's rule.

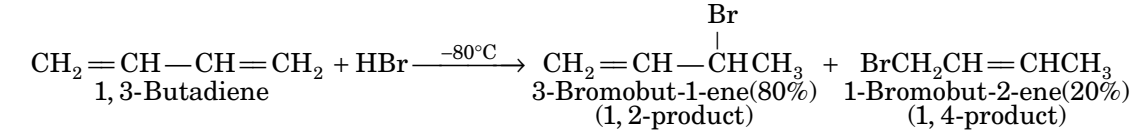


1.1.1.6 *Reaction of hydrogen bromide with 1, 3-butadiene (kinetic control versus thermodynamic control of a chemical reaction)*

When 1,3-butadiene is treated with HBr in the absence of air, a reaction occurs by an ionic mechanism to form both the 1,2- and 1,4-addition products. However, the proportions in

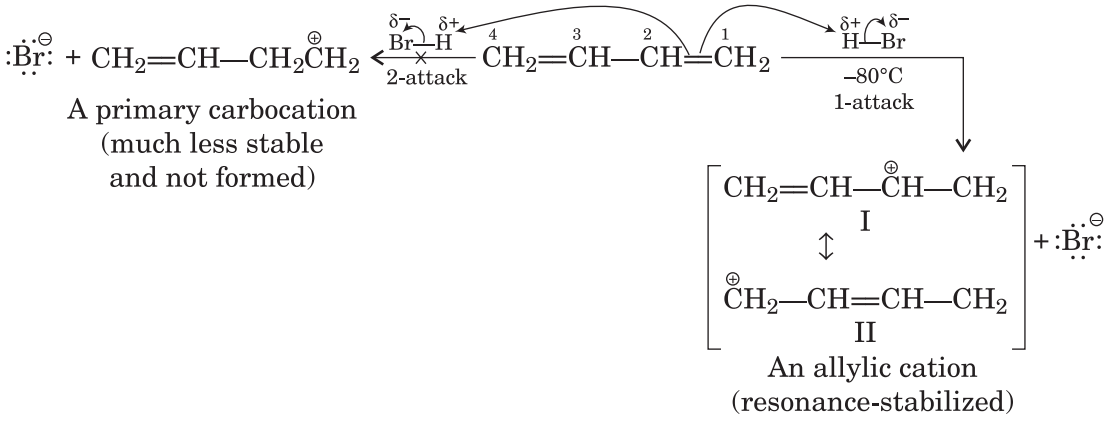
which these two products are obtained are markedly affected by the temperature at which the reaction is carried out.

When the reaction is carried out at low temperature (–80°C), a mixture containing 80 percent of the 1,2-product and 20 percent of the 1,4-product is obtained, i.e., the major product is formed by 1,2-addition.

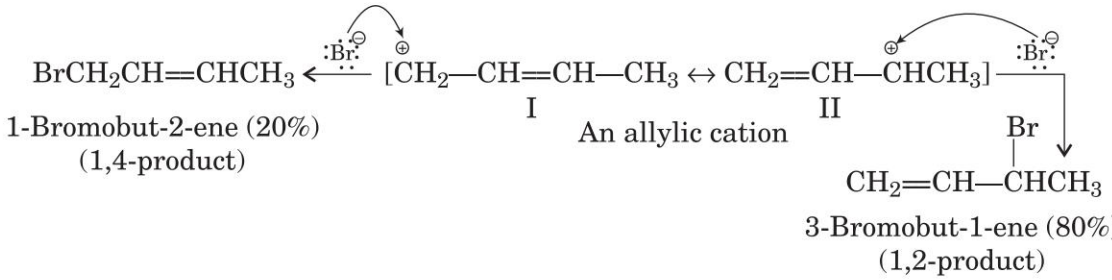


Mechanism: The reaction proceeds through the following two steps:

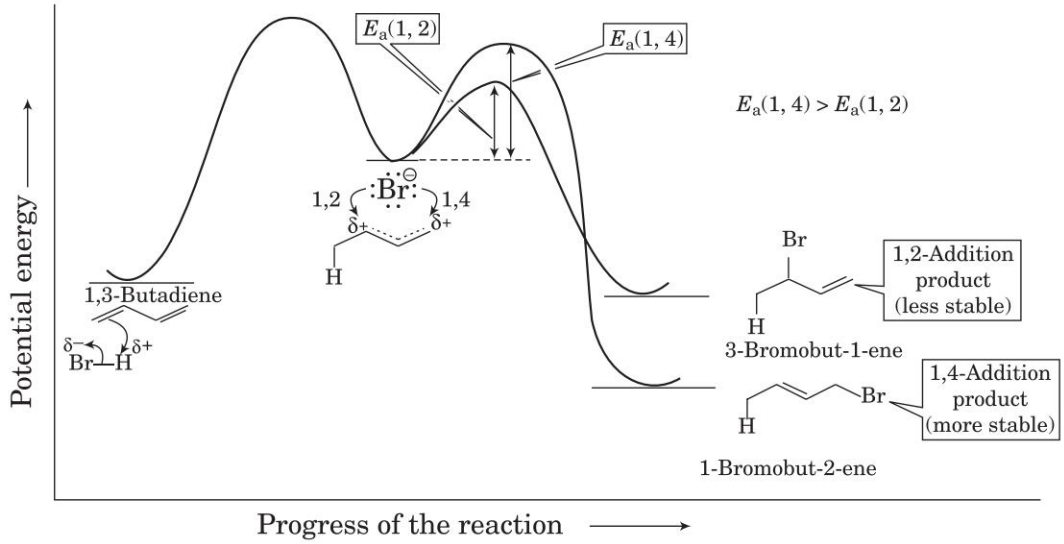
Step 1: In this step (which is the same whether the 1,2-product or the 1,4-product is being formed), the addition of $H^{\oplus}$ takes place at C-1 (but not at C-2 which give a much less stable 1° carbocation) of 1,3-butadien because the resulting carbocation is a relatively more stable (resonance-stabilized) allylic cation. It is the rate-determining step of the reaction.



Step 2: This is the product-determining step. The allylic cation is, in fact, a resonance hybrid of a secondary allylic cation (I) and a primary allylic cation (II). Because a secondary allylic cation is more stable than a primary allylic cation, the contribution of I to the hybrid is greater than that of II. Because of this, in the allylic cation, the interior carbon becomes relatively more positive than the terminal carbon and, therefore, the activation energy for the formation of 1,2-product is less than that for the formation of 1,4-product. As a consequence, the bromide ion attacks C-2 (the more positive carbon) more readily than C-4 (the less positive carbon) to give the 1,2-addtion product, 3-bromobut-1-ene, predominantly. Under these conditions, the reaction is said to be under **kinetic (or rate) control** because the product formed more rapidly predominates in the product mixture. The predominant product is called the **kinetic product**. The 1,4-addition product 1-bromobut-2-ene, however, is relatively more stable than the 1,2-addition product 3-bromobut-1-ene and it is called the thermodynamic product.



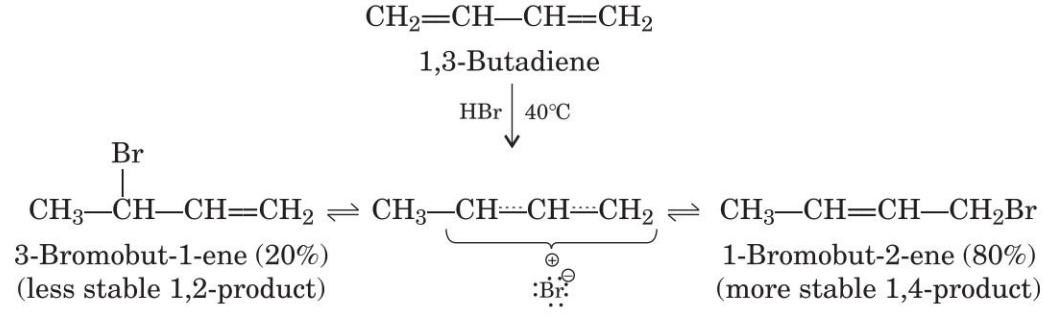
Energy profile diagram: This behaviour of 1,3-butadiene and hydrogen bromide can be more fully understood if we examine the energy profile diagram for the reaction shown in the following figure.



The energy of activation leading to the 1,2-product is less than that leading to the 1,4-product. As a result, the 1,2-product is formed at a rate faster than the 1,4-product and predominates at lower temperature. Since an internal double bond is more stable than a terminal double bond because of hyperconjugative effect, therefore, the 1,4-product is thermodynamically more stable than the 1,2-product and so, its valley is placed at a lower level than that of the 1,2-product. The product formation is irreversible because lower temperature does not provide sufficient energy to lift either product out of its deep potential energy valley.

At higher temperature (40°C), the intermediate ions have sufficient energy to cross both the barriers with relative case. Sufficient energy is also available for ionization of the products. Therefore, both the reactions are now reversible. Since the 1,4-product is thermodynamically more stable, its activation energy for ionization is much greater than that of the 1,2-product and consequently, the 1,4-product ionizes more slowly than the 1,2-

product. Under these conditions, the 1,2-product, which is still formed rapidly, rearranges to the more stable 1,4-product through the allyl cation because the overall change is energetically favourable. So, when an equilibrium is established between the products, the more stable 1,4-product predominates in the product mixture.



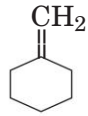
Under these conditions, the reaction is said to be under **thermodynamic (or equilibrium) control** because by equilibration the more stable product predominates. The predominant product is called **thermodynamic (or equilibrium) product.**

SOLVED PROBLEMS

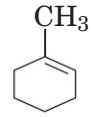
1. **Which out of 2-hexene and 3-hexene is expected to be more suitable for using as the substrate for synthesizing 3-bromohexane($CH_3CH_2CHBrCH_2CH_2CH_3$)? Give your reasoning.**

Solution Being an unsymmetrical alkene 2-hexene ($CH_3CH{=}CHCH_2CH_2CH_3$) reacts with HBr to form a mixture of 2-bromohexane (50%) and 3-bromohexane (~50%) and 3-bromohexane (~50%) and this is because the reaction proceeds through the formation of two carbocations. However, the symmetrical alkene 3-hexene ($CH_3CH_2CH{=}CHCH_2CH_3$) reacts with HBr to form 3-bromohexane exclusively because the reaction proceeds through the formation of a single carbocation. Therefore, 3-hexene is more suitable as the substrate for synthesizing 3-bromohexane.

2. **The addition of HBr to which of the following alkenes is more regioselective and why?**

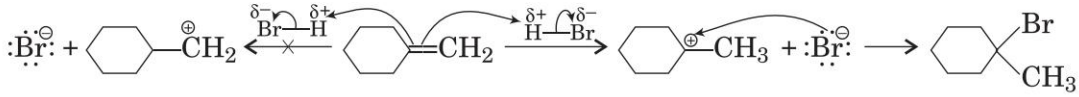


Methylenecyclohexane



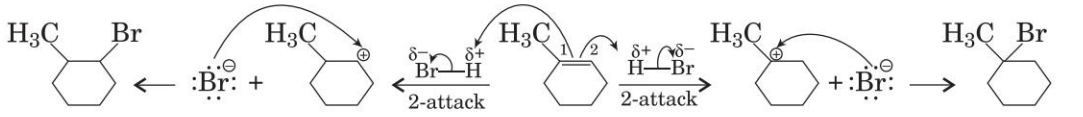
1-Methylcyclohexene

Solution When $H^{\oplus}$ adds to methylenecyclohexane, one of the carbocations that could be formed is tertiary and the other is primary. A tertiary carbocation is very much stable than a primary carbocation, which, in fact, is too unstable to be formed. Thus, 1-bromo-1-methylcyclohexane will be only product of this reaction.



A 1° carbocation (much less stable) | Methylenecyclohexane | A 3° carbocation (much more stable) | 1-Bromo-1-methyl-cyclohexane (100%)

On the other hand, when $H^{\oplus}$ adds to 1-methylcyclohexene, one carbocation that could be formed is tertiary and the other is secondary. Since a tertiary carbocation and a secondary carbocation are closer in stability, therefore, both 1-bromo-1-methylcyclohexane and 1-bromo-2-methylcyclohexane will be formed as the major product and the minor product, respectively.



1-Bromo-2-methylcyclohexane (minor) | A 2° carbocation (less stable) | 1-Methylcyclohexene | A 3° carbocation (more stable) | 1-Bromo-1-methyl-cyclohexane (major)

Hence, the addition of HBr to methylenecyclohexane is relatively more regioselective.

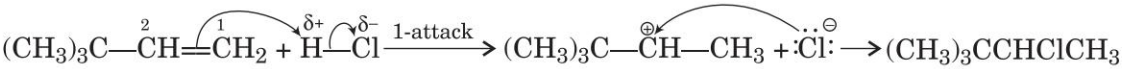
3. **The addition of HCl to 3,3-dimethylbut-1-ene leads to the formation of an unexpected product, 2-chloro-2,3-dimethybutane, in somewhat greater yield than 3-chloro-2,2-dimethylbutane, the expected Markownikoff product.**

$(CH_3)_3C-CH=CH_2 \xrightarrow{HCl}$ $(CH_3)_3CCHCl=CH_3$ + $(CH_3)_2CClCH(CH_3)_2$

3,3-Dimethylbut-1-ene | 3-Chloro-2,2-dimethylbutane (minor product) | 2-Chloro-2,3-dimethylbutane (major product)

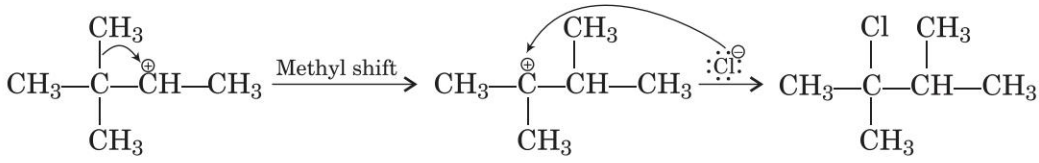
Explain this observation.

Solution The reaction starts like a normal addition of HCl, that is, by protonation of the double bond to yield the more stable carbocation with the greater number of alkyl groups at the electron-deficient carbon. Reaction of this carbocation with $Cl^{\ominus}$ occurs as expected to yield the expected Markownikoff product as the minor product.



3,3-Dimethylbut-1-ene | A 2° carbocation (less stable) | 3-Chloro-2,2-dimethylbutane (minor product)

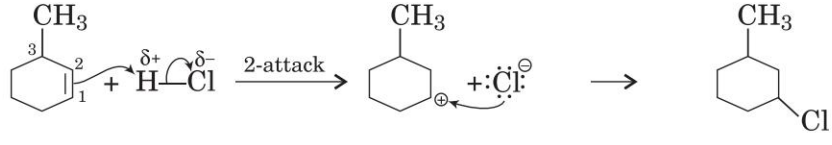
This intermediate secondary (2°) carbocation undergoes rearrangement (the methyl group moves with its pair of bonding electrons from the carbon adjacent to the positive carbon) to give a relatively more stable tertiary carbocation. The major product is formed by the attack of $Cl^{\ominus}$ on the new carbocation.



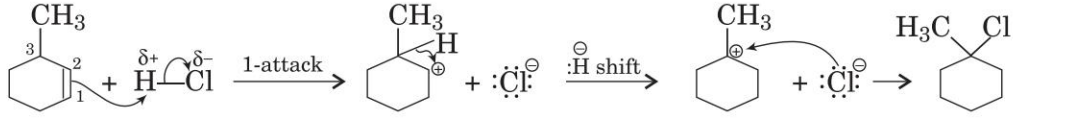
A 2° carbocation (less stable) | A 3° carbocation (more stable) | 2-Chloro-2,3-dimethylbutane (major product)

4. When HCl is allowed to react with 3-methylcyclohexene, 1-chloro-3-methylcyclohexane and 1-chloro-1-methylcyclohexane are obtained. Draw a mechanism to explain this result.

Solution The addition of $H^{\oplus}$ to 3-methylcyclohexene forms two different secondary carbocations. However, one of them undergoes rearrangement by a hydride shift to yield a more stable tertiary carbocation. Nucleophilic attack of $Cl^{\ominus}$ on the secondary and the tertiary carbocations produces 1-chloro-3-methylcyclohexane and 1-chloro-1-methylcyclohexane, respectively.

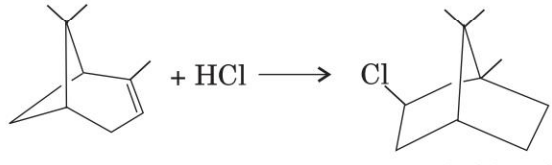


3-Methylcyclohexene | A 2° carbocation | 1-Chloro-3-methylcyclohexane



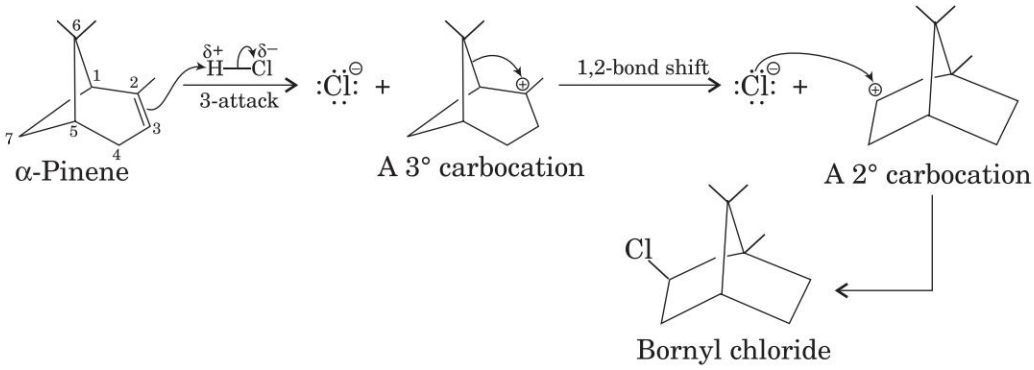
3-Methylcyclohexene | A 2° carbocation (less stable) | A 3° carbocation (more stable) | 1-Chloro-1-methylcyclohexane

5. Explain the mechanism of the following reaction:



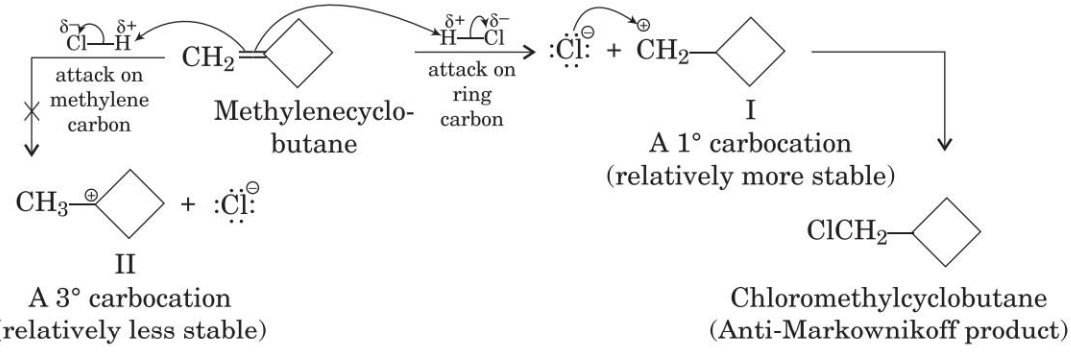
α-Pinene | Bornyl chloride

Solution When $H^{\oplus}$ adds to α-pinene, a stable 3° carbocation is formed predominantly. But this 3° carbocation readily rearranges to a less stable 2° carbocation which is normally not favourable. In fact, the rearrangement expands a strained four-membered ring to a much less-strained five-membered ring, and this relief of strain provides a driving force for the rearrangement. Nucleophilic attack of $Cl^{\ominus}$ on the 2° carbocation forms bornyl chloride.



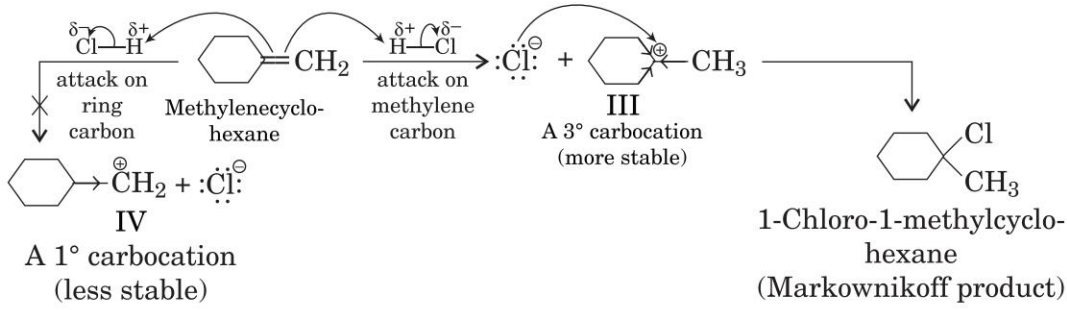
6. Methylenecyclobutane react with hydrogen chloride to give chloromethylcyclobutane (the anti-Markownikoff product), while methylenecyclohexane reacts with hydrogen chloride to yield 1-chloro-1-methylcyclohexane (the Markownikoff product). Account for these observations.

Solution When $H^{\oplus}$ adds to methylenecyclobutane, one of the carbocations that could be formed is primary (I) and the other is tertiary (II). The 3° carbocation II suffers from considerable angle strain (120° – 90° = 30°), whereas the 1° carbocation has small angle strain (109.5° – 90° = 19.5°). Because of greater angle strain, the carbocation II, although a 3° one, is less stable than the 1° carbocation I and the addition of HCl proceeds through the carbocation I to give anti-Markownikoff product chloromethylcyclobutane.



Since a primary carbocation is too unstable to be formed, the anti-Markownikoff product is probably obtained through a concerted addition process.

When $H^{\oplus}$ adds to methylenecyclohexane, one of the carbocations that could be formed is tertiary (III) and the other is primary (IV). The carbocation III suffers from a very little angle strain. Then, from electronic point of view the 3° cabocation III is relatively more stable than the 1° carbocation IV and therefore, the reaction proceeds through the carbocation III to give the Markownikoff product 1-chloro-1-methylcyclohexane.



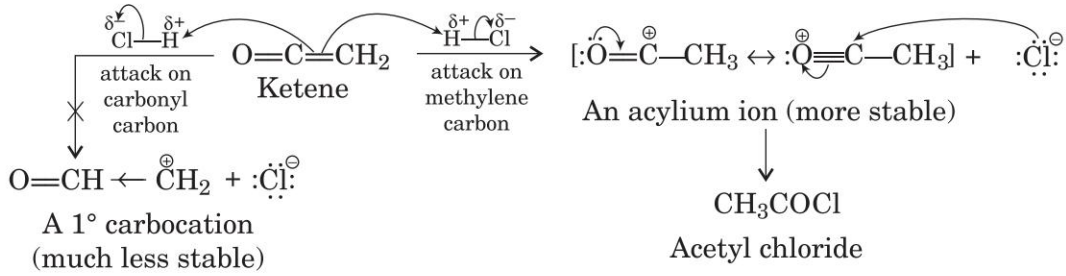
7. Predict the major product in each of the following reactions and give your reasoning.

(a) $CH_2=C=O + HCl \longrightarrow$ (b) $CH_3C\equiv CH + 2HBr \longrightarrow$

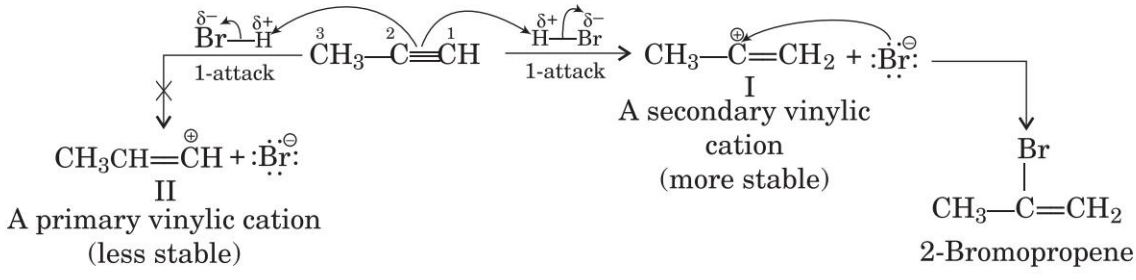
(c) $Ph-CH=CH_2 + HBr \longrightarrow$ (d) $CH_2=CH(CH_2)_2C(CH_3)=CH_2 \xrightarrow[(1\ mole)]{HCl}$

Solution

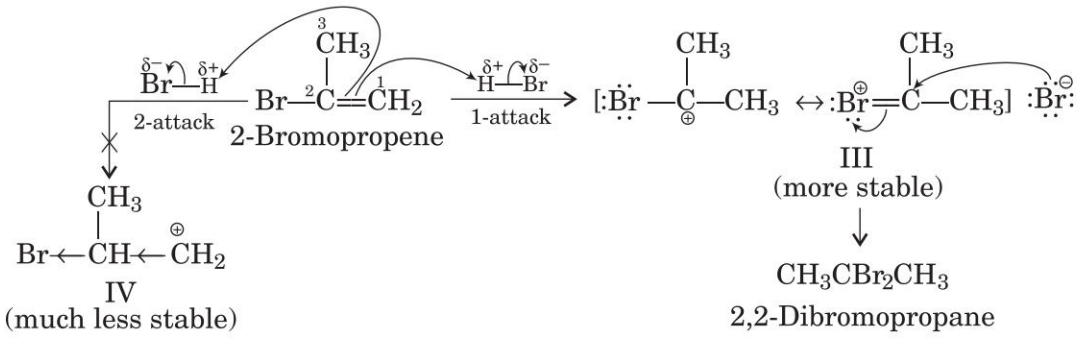
(a) Addition of $H^{\oplus}$ to ketene yields a resonance-stabilized acylium ion instead of a primary carbocation which is further destabilized by electron-with drawing inductive effect (–I) of the –CHO group.



(b) The addition of $H^{\oplus}$ to the two *sp* carbons of propyne may produce one secondary vinylic cation (I) and one primary vinylic cation (II). Since the secondary vinylic cation is relatively more stable (stabilized by the +I and hyperconjugative effect of the methyl group) than the primary vinylic cation, therefore, the reaction actually proceeds through the secondary vinylic cation which subsequently reacts with $Br^{\ominus}$ to yield 3-bromopropene.

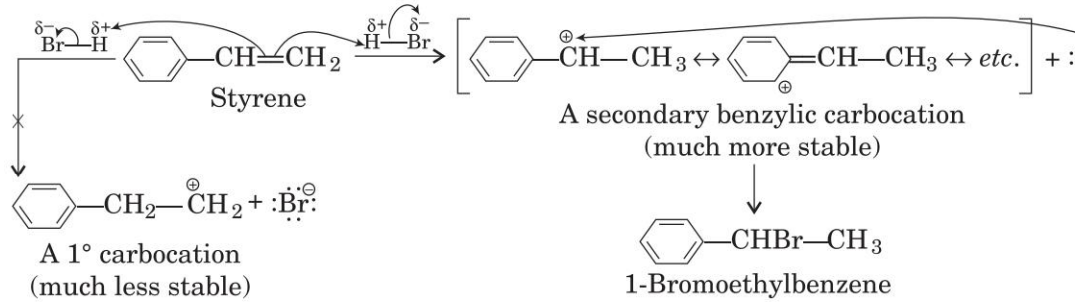


2-Bromopropene adds another molecule of HBr to form 2,2-dibromopropane as follows:



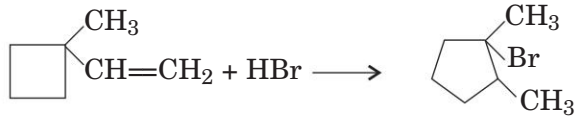
Addition of $H^{\oplus}$ to the C-1 carbon of 2-bromopropene leads to the formation of the carbocation III in which bromine withdraws electrons by its –I effect and donates electron by its +R effect. Since –I $\rangle$ + R, bromine is net electron-withdrawing and it destabilizes the carbocation. But the +I and hyperconjugative stabilizing effect of the two methyl groups is large enough to compensate this destabilization and in fact, it is more stable than the 1° carbocation IV (that could be formed by the addition of $H^{\oplus}$ to C-2) which is further destabilized by the –I effect of bromine. The reaction thus proceeds through the carbocation III to give 2,2-dibromopropane.

(c) When $H^{\oplus}$ adds to styrene ($PhCH{=}CH_2$), one of the carbocation that could be formed is secondary benzylic and the other is primary. The secondary benzylic carbocation is much more stable (stabilized by resonance) than the primary carbocation and for this reason, the reaction proceeds through the secondary benzylic carbocation to give $PhCHBrCH_3$ nearly exclusively.

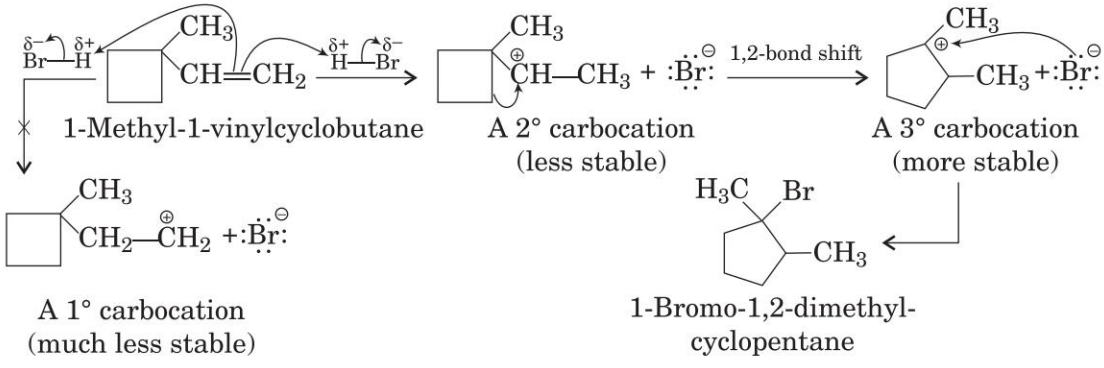


(d) Since one mole of HCl is allowed to react with this unsymmetrical diene, it adds preferentially to the more reactive or more electron-rich C-1—C-2 double bond to give 5-methylhex-1-ene ($CH_2{=}CHCH_2CH_2CClMe_2$) as the major product through the formation of a stable 3° carbocation. HCl also adds to the C-5—C-6 double bond to give 5-chloro-2-methylhex-1-ene as the minor product through the formation of a less stable 2° carbocation.

8. Explain the following observation:



Solution When $H^{\oplus}$ adds to 1-methyl-1-vinylcyclobutane, one of the carbocations that could be formed is secondary and the other is primary. The secondary carbocation readily rearranges by ring expansion (a 1,2-bond shift) to give a tertiary carbocation, which is more stable and, because of the five-membered ring, has less angle strain. Thus, the reaction proceeds not through the 1° carbocation but through the rearranged 3° carbocation to give 1-bromo-1,2-dimethylcyclopentane exclusively.



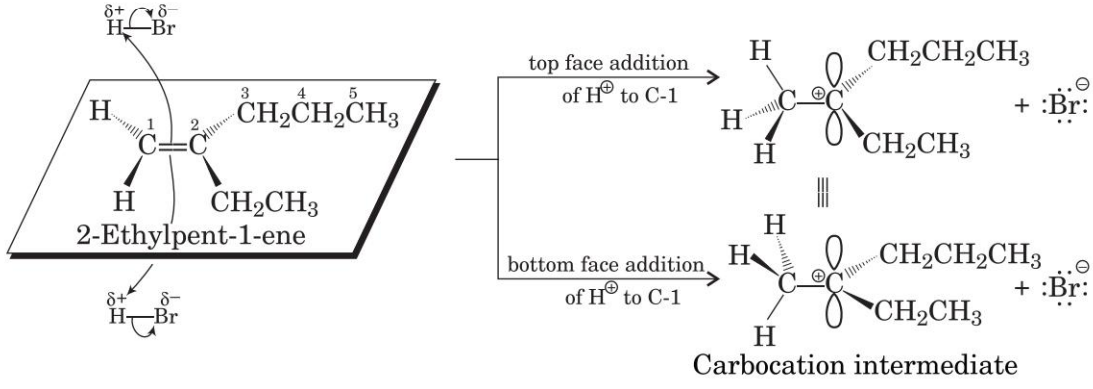
9. Explain the stereochemical outcome of the following reaction:

$$CH_3CH_2CH_2C(C_2H_5)=CH_2 + HBr \longrightarrow CH_3CH_2CH_2\overset{*}{C}BrCH_3C_2H_5$$

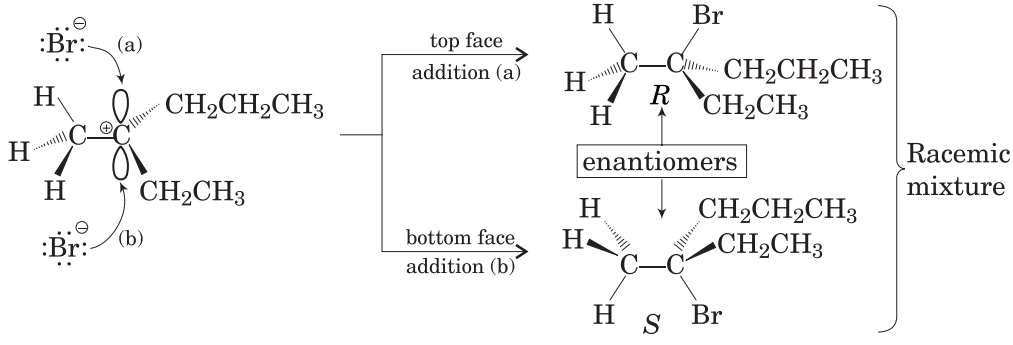
2–Ethylpent–1–ene → (±)–3–Bromo–3–methylhexane

Is the reaction stereoselective?

Solution Initial addition of the electrophile $H^{\oplus}$ (from HBr) occurs from either side of the planar double bond to form a carbocation. Both modes of addition (from above or below the plane) generate the same achiral carbocation.



The positively charged carbon is sp^2 hybridized, so the three atoms to which it is bonded lie in a plane. When the bromide ion attacks the carbocation from above the plane, one enantiomer of 3-bromo-3-methylhexane is formed, but when it attacks the carbocation from below the plane, the other enantiomer is formed. Because attack from either direction occurs with equal facility or equal probability, equal amounts of the two enantiomers are obtained, i.e., a racemic mixture (optically inactive) is obtained.

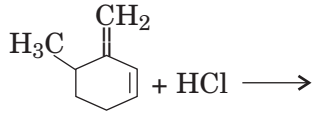


An addition reaction that forms a compound with one chirality centre from a reactant without any chirality centre is not stereoselective because it does not select for a particular stereoisomer. Thus, the reaction is not a stereoselective one.

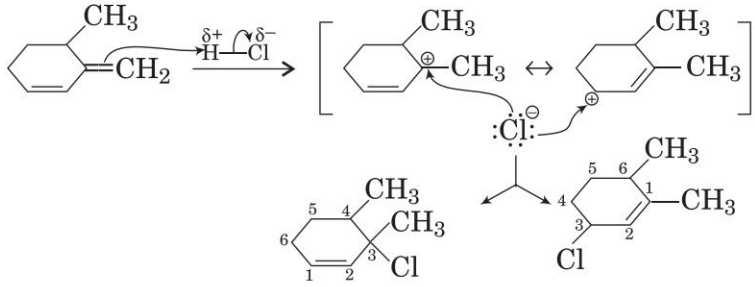
10. Is the temperature at which a reaction changes from being kinetically controlled to being thermodynamically controlled same for all the reaction? Explain.

Solution The temperature at which a reaction changes from being kinetically controlled to being thermodynamically controlled actually depends on the particular reaction. Each reaction that is irreversible under mild conditions, a reversible under vigorous conditions has a particular temperature at which the changeover occurs. In fact, the temperature required to shift the reaction of a conjugated diene with an electrophilic reagent from kinetic control to thermodynamic control depends on both the diene and the electrophilic reagent. The reaction of 1,3-butadiene with HCl, for example, remains under kinetic control at 45°C, even though the addition of HBr to the same diene is under thermodynamic control at that temperature. Since a C—Cl bond is stronger than a C—Br bond, therefore, a higher temperature is required for the products to undergo the reverse reaction. Thermodynamic control is achieved only when sufficient energy is applied to allow the reaction to be reversible.

11. Give the major 1,2- and 1,4-addition products of the following reaction and indicate which is the kinetic product and which is the thermodynamic product.



Solution The addition of $H^{\oplus}$ takes place at the methylene carbon because this leads to the formation of a carbocation in which the positive charge is shared by a tertiary allylic and a secondary allylic carbon. If the proton were to add to the other end of the conjugated system, the carbocation would be less stable because in that case the positive charge would be shared by a primary allylic and a secondary allylic carbon. Therefore, 3-chloro-3,4-dimethylcyclohexene is the 1,2-product and 3-chloro-1,6-dimethylcyclohexene is the 1,4-product.



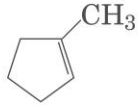
3-Chloro-3,4-dimethylcyclohexene *kinetic product*

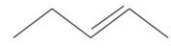
3-Chloro-1,6-dimethylcyclohexene *thermodynamic product*

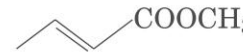
3-Chloro-3,4-dimethylcyclohexene is the kinetic product because, in the transition state (relatively more stable) for its formation, the positive charge is concentrated on a tertiary carbon. 3-chloro-1,6-dimethylcyclohexene is the thermodynamic product because it is relatively more stable due to its more highly substituted double bond (more stabilized by hyperconjugation).

Study Problems

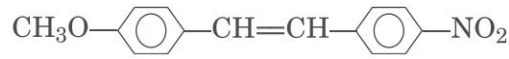
1. What alkene should be used to synthesize 2-bromopentene and why?
2. $C_6H_5CH{=}CHC_6H_5$ reacts with HBr faster than $CH_3CH{=}CHCH_3$, even though both compounds are 1,2-disubstituted alkenes. Explain.
3. What would be the major product obtained from the addition of HBr to each of the following compounds?

(a) 

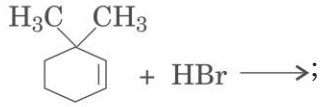
(b) 

(c) 

(d) $CH_3CH_2CH{=}CHI$

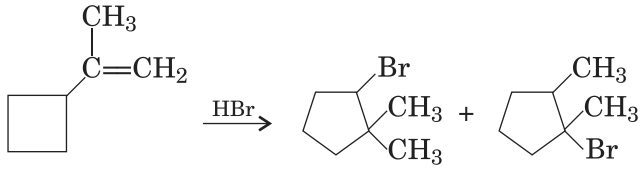
(e) 

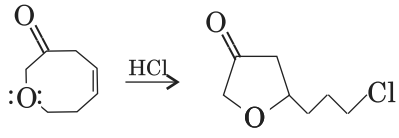
4. Predict the major product expected to be formed in each of the following reactions and give your reasoning:

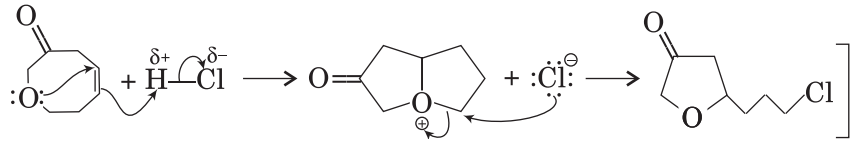
(a) 

(b) $(CH_3)_2CH{-}CH{=}CH_2 + HCl \rightarrow$

5. Propose a mechanism for each of the following reactions:

(a) 

(b) 

Hint: 

6. Explain why the following reactions give anti-Markownikoff product:

(a) $O_2NCH{=}CH_2 \xrightarrow{HCl} O_2NCH_2CH_2Cl$

(b) $CH_2{=}CHCOOH \xrightarrow{HCl} ClCH_2CH_2COOH$

7. Treatment of $Me_3CCH{=}CH_2$ and $Me_3CCHOHCH_3$ with concentrated hydrochloric acid gives the same two isomeric alkyl chlorides. What are these two products? Explain.

[**Hint:** $Me_2CClCHMe_2$ (major) and $Me_2CCHClMe$ (minor)]

8. Compare the regioselectivity of the reactions of HBr with

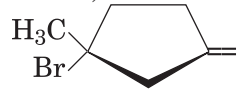
(a) $CF_3CH{=}CH_2$, (b) $BrCH{=}CH_2$ and (c) $CH_3OCH{=}CHCH_3$.

9. Use the Hammond postulate to explain why $(CH_3)_2C{=}CH_2$ reacts faster than $CH_3CH{=}CH_2$ in electrophilic addition of HBr.

10. Give the mechanism and the stereochemical course involved in the reaction that take place when 1,2-dimethylcyclohexene is allowed to react with HB to yield 1-chloro-1,2-dimethylcyclohexane.

11. Two stereoisomeric alkenes X and Y (molecular formula C_6H_{12}) react with HI to give the same single product and undergo catalytic hydrogenation to produce hexane. Identify X and Y.

[**Hint:** X and Y are *cis*-and *trans*-3-hexene.]

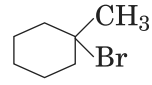
12. Predict the products (stereoisomers) of the following reaction and give the stereochemical course involved. 

Is the reaction stereoselective?

13. Rank the following alkenes in order of their increasing rate of reaction with HBr and explain the order:

(a)  (b)  (c)

14. Write down the structures of two different alkenes that would react with HBr to yield each of the following compounds as the major (or only) addition product.

(a) $(CH_3)_2\overset{\overset{Br}{|}}{C}CH(CH_3)_2$ (b) 

15. Predict the products of the following reaction and account for the formation of both products:

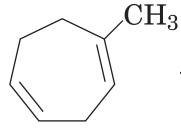
$$(CH_3)_2CH-CH=CH_2 + HBr \longrightarrow A\ (major) + B\ (minor)$$

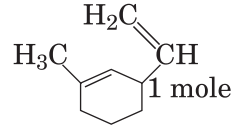
[**Hint:** The major product is obtained through the rearrangement of the initial carbocation involving a hydride shift.]

16. Only one of the following three alkyl bromides can be prepared as the major product of the addition of HBr to an alkene. Identify the alkene and explain why the other two cannot be prepared as the major product.

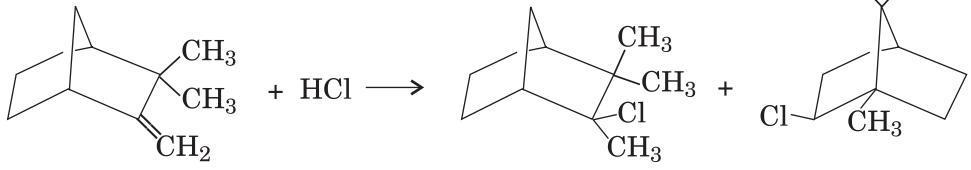
$\underset{A}{CH_3CH_2CH_2CH_2CH_2Br}$ $\underset{B}{CH_3CHBrCH_2CH_2CH_3}$ $\underset{C}{CH_3CHBrC(CH_3)_2C_2H_5}$

17. Predict the major product of each of the following reactions and show the stereoisomers that could be obtained:

(a)  + HCl (1 mole) $\longrightarrow$ (1 mole)

(b)  + HBr (1 mole) $\longrightarrow$ (1 mole)

18. Suggest a mechanism for the following reaction:



19. Arrange the following compounds in order of increasing reactivity towards addition of HBr:

$\underset{I}{CH_2=C(CH_3)OCH_3}$, $\underset{II}{CH_2=C(CH_3)CH_2OCH_3}$, $\underset{III}{CH_2=C(CH_3)_2}$

[**Hint:** II $\langle$ III $\langle$ I]

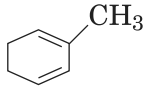
20. Explain why the reaction (a) takes place according to the Markownikoff's rule, while the reaction (b) does not:

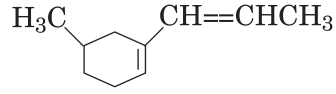
(a) $CH_2=CHF + HF \longrightarrow CH_3CHF_2$

(b) $CH_2=CHCF_3 + HF \longrightarrow FCH_2CH_2CF_3$

21. Predict the products expected to be formed when one mole of 1,3-pentadiene is allowed to react with 1 mole of HBr. What is the major product?

22. Identify the major 1,2- and 1,4-addition products expected to be obtained when each of the following compounds is treated with HCl. Indicate which is the kinetic product and which is the thermodynamic product.

(a) 

(b) 

(c) $CH_2=\underset{\displaystyle CH_3}{\overset{|}{C}}-CH=CHCH_3$

23. When acetylene is allowed to react with HCl, vinyl chloride is obtained through the formation of vinyl cation. However, when vinyl bromide is refluxed with alcoholic $AgNO_3$, the same vinyl cation is not obtained.

$$\underset{\text{Acetylene}}{HC\equiv CH} + HCl \longrightarrow \underset{\text{vinyl cation}}{CH_2=\overset{\oplus}{C}H} + :\ddot{Cl}:^{\ominus} \longrightarrow \underset{\text{Vinyl chloride}}{CH_2=CH-Cl}$$

$$\underset{\text{Vinyl bromide}}{CH_2=CH-Br} \xrightarrow[\text{reflux}]{AgNO_3/\text{alcohol}} \underset{\text{vinyl cation}}{CH_2=\overset{\oplus}{C}H} + AgBr\downarrow$$

Explain these observations.

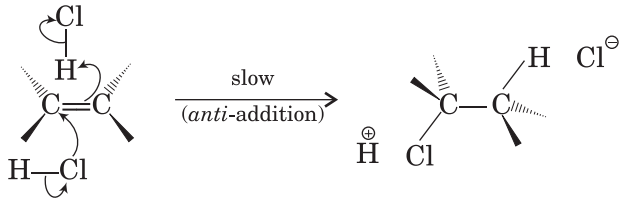
[**Hint:** Vinyl bromide is thermodynamically more stable than acetylene because of resonance:

$$CH_2=CH-\ddot{Br}: \leftrightarrow \overset{\ominus}{C}H_2-CH=\ddot{Br}:^{\oplus}$$

For this reason, the activation energy for the formation of vinyl cation from vinyl bromide is greater than that required for its formation from acetylene. This explains why the same vinyl cation is generated from acetylene by addition of $H^{\oplus}$ but not from vinyl bromide by C—Br bond cleavage.]

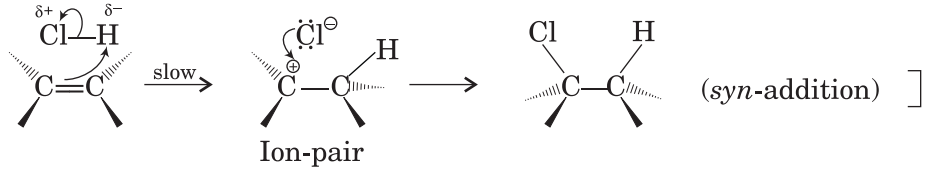
24. In HCl addition of some akenes (e.g., 2-methyl-1-butene, 2-methyl-2-butene, 1-methylcyclopentene, etc.), it is found that the *anti*-addition occurs following the rate law: rate = k [alkene] $[HCl]^2$, while some alkenes (e.g., styrene, 1-phenyl propene, indene, etc.) that undergo *syn*-addition follow the rate law: rate = k [alkene] [HCl]. Explain.

[**Hint:** A third-order rate expression is observed in *anti*-addition of HBr because the T.S. involves proton transfer to the alkene from one HCl molecule and capture of $Cl^{\ominus}$ ion from the second. The reaction occurs as follows:



The *anti*-stereochemistry is consistent with the expectation that the attack of $Cl^{\ominus}$ occurs from the opposite side of the π bond to which the proton is delivered.

A second-order rate expression is observed in *syn*-addition of HCl because in addition of a proton and attack by $Cl^{\ominus}$, only one HCl molecule is involved. The *syn*-stereochemistry is consistent with the expectation that the attack of $Cl^{\ominus}$ occurs from the same side of the π bond to which the proton is delivered. In fact, an ion pair is formed by alkyne protonation and it collapses to the product faster than rotation takes places. *Syn*-addition thus occurs because the proton and the halide ion are initially on the same face of the molecule.



25. Predict the regiochemistry of the following addition reactions. Explain your predictions.

(a) $(F_3C)_2C{=}C(CH_3)_2 + HBr \longrightarrow$; (b) $(CH_3O)_2C{=}C(CH_3)_3 + HBr \longrightarrow$

1.1.2 Addition of Water and Alcohol

1.1.2.1 Hydration of Alkenes

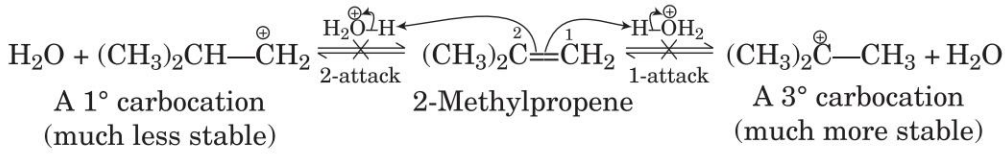
The acid-catalyzed addition of water to the double bond of an alkene is an important method for the preparation of low-molecular-mass alcohols. The reaction is called *hydration of alkenes*. The reaction is carried out at low temperature with dilute sulphuric acid which provides high concentration of water required to shift the equilibrium of this reversible reaction to the right. Other acids like phosphoric acid, perchloric acid, etc. can also be used as an acid catalyst. These reactions, too, are also regioselective, and the addition of water to the double bond occurs in accordance with the Markownikoff's rule. For example:

$$\underset{\substack{\text{2-Methylpropene}\\\text{(Isobutylene)}}}{(CH_3)_2C{=}CH_2} + H_2O \xrightarrow{H_2SO_4} \underset{\substack{\text{2-Methyl-2-propanol}\\\text{(}\textit{tert}\text{-Butyl alcohol)}}}{(CH_3)_3{-}COH}$$

Mechanism: 2-Methylpropene undergoes acid-catalyzed hydration in accordance with the Markownikoff's rule (both water and alkene are unsymmetrical) as follows:

$$H_2SO_4 + H_2O \rightleftharpoons H_3\overset{\oplus}{O}: + HSO_4^{\ominus}$$

Step 1: The elctrophile $H^{\oplus}$ adds to that sp^2 carbon of the double bond which is bonded to the most hydrogens to form the more stable tertiary (3°) carbocation rather than the much less stable primary (1°) carbocation.



It is the rate-determining (slow) step of the reaction.

Step 2: The carbocation undergoes nucleophilic attack by water to form the conjugate acid of *tert*-butyl alcohol.

$$(CH_3)_3\overset{\oplus}{C} + H_2\ddot{O}: \overset{\text{fast}}{\rightleftharpoons} (CH_3)_3C—\overset{\oplus}{\ddot{O}}H_2$$

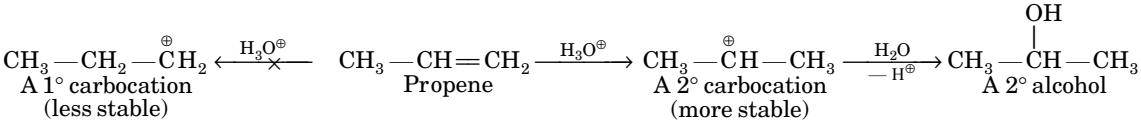
Step 3: *tert*-Butyl alcohol is obtained when its conjugate acid transfers a proton to water.

$$(CH_3)_3C—\overset{\oplus}{O}H + H_2\ddot{O}: \rightleftharpoons (CH_3)_3C—OH + H_3\overset{\oplus}{O}:$$

tert-Butyl alcohol

The oxygen–hydrogen bonds of water are too strong (water is too weakly acidic) to allow the hydrogen to act as an electrophile for hydration reaction. For this reason, water is unable to add to alkene in the absence of acid catalyst. Sulphuric acid (H_2SO_4) is the preferred acid catalyst for hydration because its conjugate base, $HSO_4^{\ominus}$, is too poor a nucleophile to compete with water in attacking the carbocation.

It is to be noted that acid-catalyzed hydrations of alknenes do not yield 1° alcohol except in the special case of the hydration of ethene ($CH_2=CH_2$). This is because the hydration reactions follow Markownikoff's rule. For example:

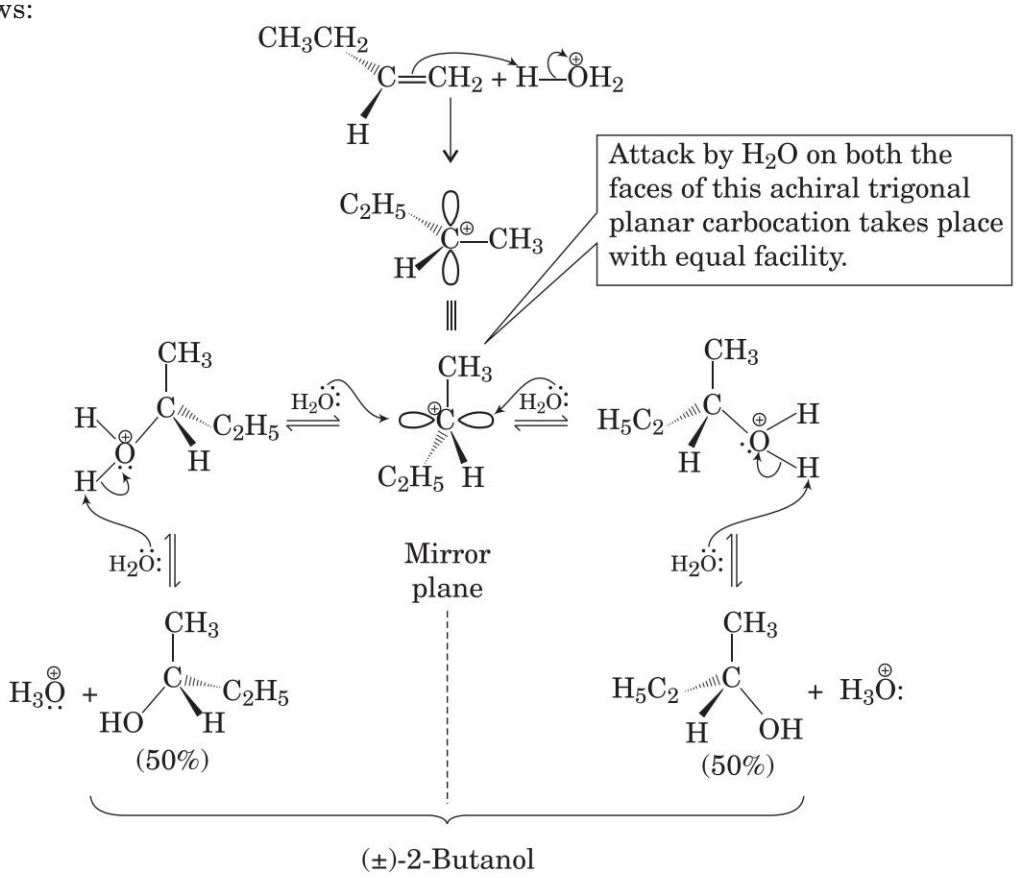


1.1.2.2 Stereochemistry of Hydration

If at least one of the two doubly bonded carbons of an alkene contains two different groups, hydration then leads to the formation of racemic alcohol. For example, 1-butene undergoes hydration to yield racemic 2-butanol ($CH_3CH_2\overset{*}{C}HOHCH_3$).

$$\underset{\text{1–Butene}}{CH_3CH_2CH=CH_2} + H_2O \xrightarrow{H_2SO_4} \underset{\text{(±)–2–Butanol}}{CH_3CH_2\overset{*}{C}HOHCH_3}$$

The stereochemical course of the acid-catalyzed hydration of 1-butene may be shown as follows:



Similarly, *cis*- or *trans*-3hexene on hydration produces (±)-3-hexanol.

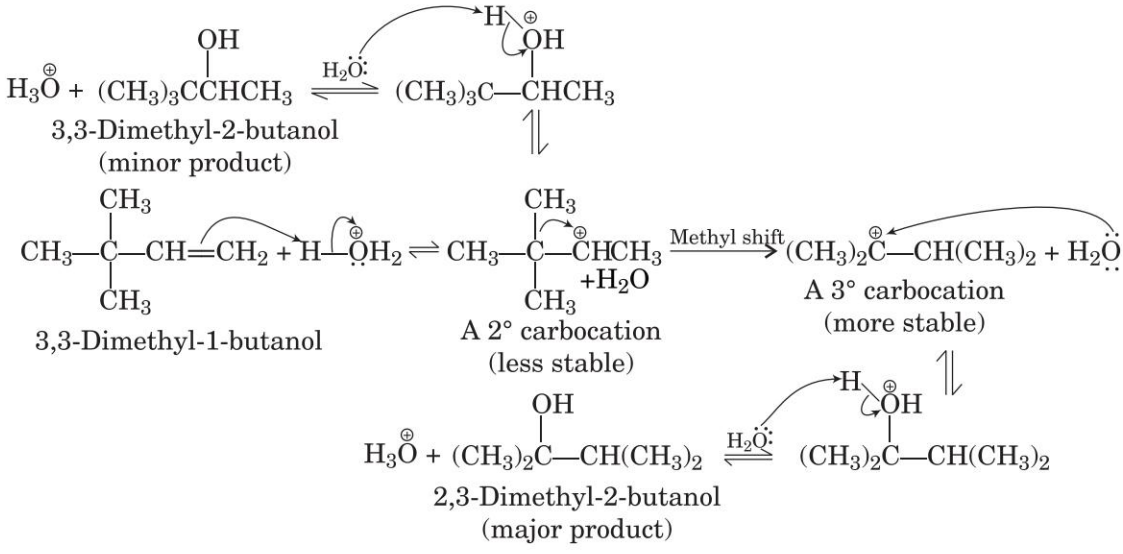
1.1.2.3 Rearrangement During Hydration

The initially formed carbocation sometimes rearranges to give a relatively more stable carbocation which leads to the formation of the major product. For example:

$$\underset{\text{3,3-Dimethyl-1-butene}}{(CH_3)_3C-CH=CH_2} \xrightarrow[H_2O]{H_2SO_4} \underset{\substack{\text{2,3-Dimethyl-2-butanol}\\\text{(major product)}}}{CH_3CH(OH)CH(CH_3)_2}$$

When $H^{\oplus}$ adds to 3,3-dimethyl-1-butene, a relatively more stable secondary (2°) carbocation rather than a much less stable primary (1°) carbocation is formed. This secondary carbocation then undergoes ready rearrangement (a 1,2-methyl shift) to give a much more stable tertiary (3°) carbocation. The major product is obtained by the attack of water on

this new carbocation followed by loss of $H^{\oplus}$. The secondary carbocation reacts with water to yield the minor product.

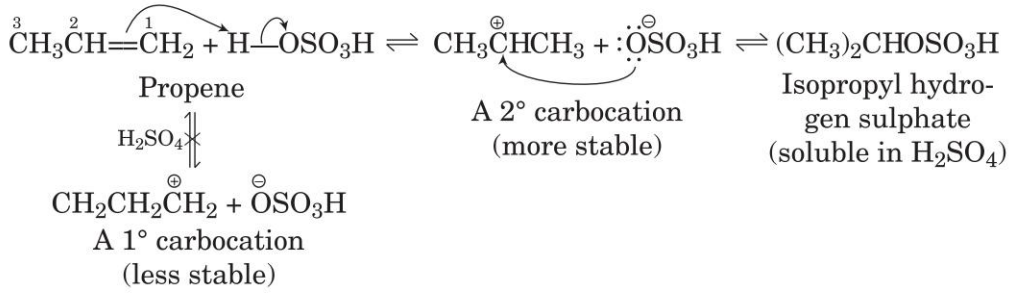


1.1.2.4 Hydration of Alkenes Through the Formation of Alkyl Hydrogen Sulphate Followed by its Hydrolysis

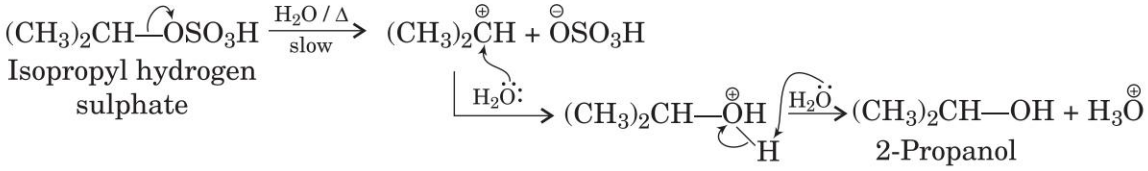
When alkenes are treated with cold concentrated sulphuric acid, they dissolve because they react (an electrophilic addition) to form alkyl hydrogen sulphates. When these alkyl hydrogen sulphates are heated with water, they undergo hydrolysis to yield alcohols. For example, 2-propanol can be prepared from propene as follows:

$$\underset{\text{Propene}}{CH_3CH{=}CH_2} + H_2SO_4 \xrightarrow{\text{cold}} \underset{\substack{\text{Isopropylhydrogen}\\ \text{sulphate}}}{(CH_3)_2CHOSO_3H} \xrightarrow[\text{heat}]{H_2O} \underset{\text{2–Propanol}}{CH_3CH(OH)CH_3}$$

Mechanism of H_2SO_4 addition: The reaction involves two steps. In the first step, propene donates a pair of electrons to a proton from sulphuric acid to form a relatively stable secondary (2°) carbocation rather than a much less stable primary (1°) carbocation. In the second step, the carbocation reacts with a hydrogen sulphate ion to form isopropyl hydrogen sulphate.



Mechanism of hydrolysis: Isopropyl hydrogen sulphate undergoes hydrolysis by the S_N1 mechanism when heated with water.



1.1.2.5 Acid-Catalyzed Addition of an Alcohol to an Alkene

When an alcohol is allowed to react with an alkene in the presence of sulphuric acid, an ether is obtained. Primary alcohols, for example, can be converted into *tert*-butyl ethers by dissolving them in H_2SO_4 and then adding 2-methylpropene to the mixture

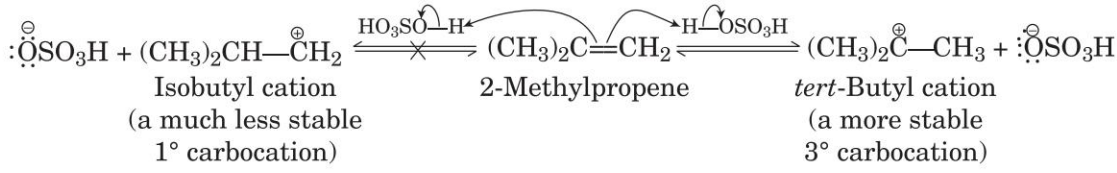
$$\underset{\text{A 1° alcohol}}{RCH_2OH} + \underset{\text{2-Methylpropene}}{CH_2{=}C(CH_3)_2} \xrightarrow{H_2SO_4} \underset{\text{A } \textit{tert}\text{-butyl ether}}{RCH_2OC(CH_3)_3}$$

This procedure is often used to 'protect' the –OH group of a 1° alcohol when another reaction is carried out on some other part of the molecule. The protecting *tert*-butyl group ($-CMe_3$) can be removed easily by hydrolyzing the ether with dilute acid.

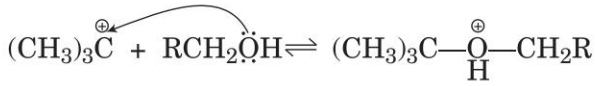
$$RCH_2O(CH_3)_3 \xrightarrow{H_3O^{\oplus}} \underset{\text{A 1° alcohol}}{RCH_2OH} + \underset{\textit{tert}\text{–Butyl alcohol}}{(CH_3)_3COH}$$

Mechanism of addition: The reaction involves the following three steps:

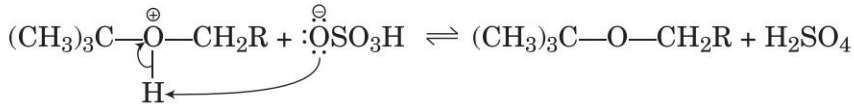
Step 1: Formation of *tert*-butyl cation (the rate-determining step).



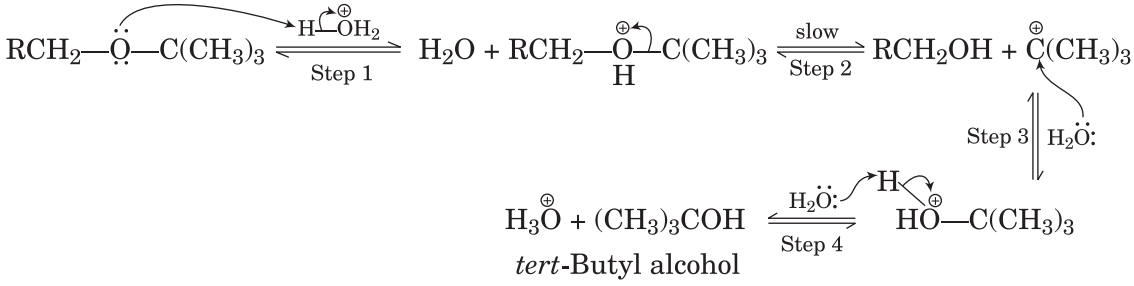
Step 2: Nucleophilic attack by the alcohol on the carbocation.



Step 3: Loss of proton from the conjugate acid of the ether.



Mechanism of hydrolysis: When treated with dilute acid, the resulting *tert*-butyl ether undergoes hydrolysis through the following steps (S_N1 mechanism):

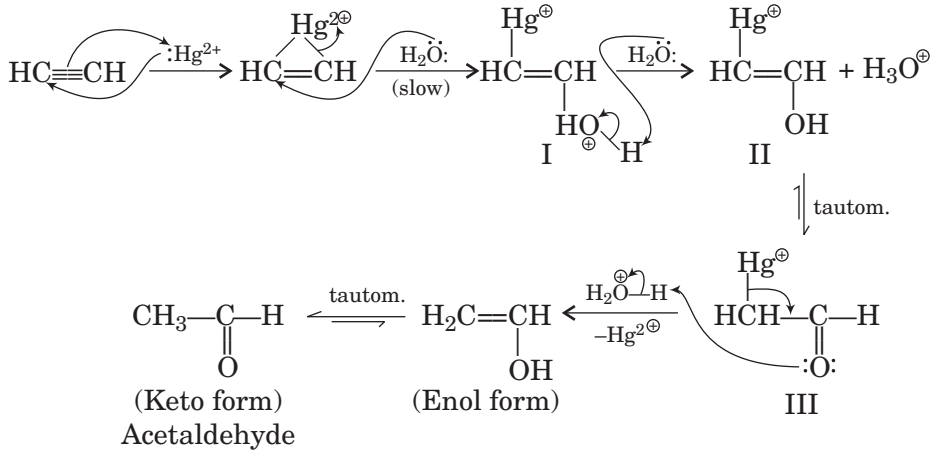


1.1.2.6 Hydration of Alkynes

Hydration of an alkyne occurs when the alkyne is treated with dilute H_2SO_4 at 60–80°C in the presence of mercuric ion (Hg^{2+}) as a catalyst and a carbonyl compound is obtained via the formation of an enol. For example, acetylene produces acetaldehyde on hydration.

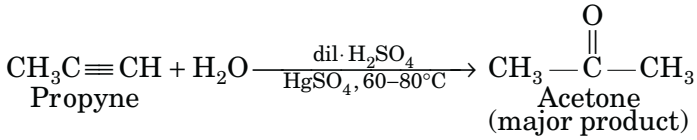
$$\underset{\text{Acetylene}}{HC{\equiv}CH} + H_2O \xrightarrow[HgSO_4,60\text{–}80^\circ C]{\text{dil}\cdot H_2SO_4} \underset{\text{Acetaldehyde}}{CH_3CHO}$$

Mechanism: The mechanism of this hydration reaction involves the steps as follows:

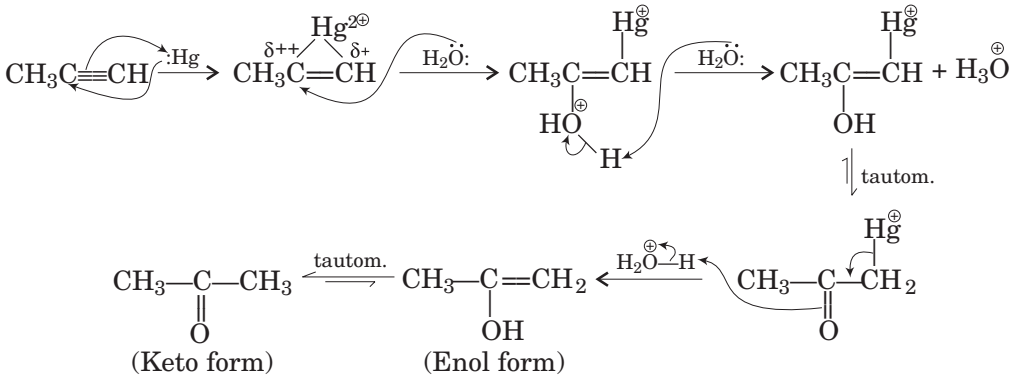


The first step in this mercuric-ion-catalyzed hydration of alkyne involves the formation of a cyclic mercurinium ion (the two of the electrons in mercury's filled 5d orbital are shown). In the second step, the cyclic intermediate undergoes nucleophilic attack by water to give the intermediate I. The intermediate I then loses a proton to form the mercuric enol II which immediately collapses to the mercuric aldehyde III. Loss of the mercuric ion forms acetaldehyde, an enol, which rearranges to give CH_3CHO.

Hydration of an unsymmetrical alkyne takes place in accordance with the Markownikoff's rule. Propyne ($CH_3C{\equiv}CH$), for example, undergoes mercuric-ion-catalyzed hydration to yield acetone (CH_3COCH_3) as the major product.



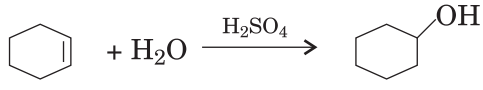
Mechanism: The mechanism of the reaction involves the steps as follows:



The more substituted middle carbon of the bridged ion bears the greater positive charge because the developing partial positive charge is better accommodated by this carbon. As a consequence, water attacks this carbon preferentially to yield acetone (CH_3COCH_3) as the major product. Attack of water on the less substituted terminal carbon of the bridged ion occurs to yield propanal (CH_3CH_2CHO) as the minor product.

SOLVED PROBLEMS

1.



(a) **What general conditions would be used to ensure a good yield of cyclohexanol?**

(b) **What general conditions would be used to carry out the reverse reaction, i.e., the dehydration of cyclohexanol to yield cyclohexene?**

Solution

(a) A high concentration of water is to be used because we want the carbocation produced to react with water. Also, a strong acid is to be used because its conjugate base is too weak as a nucleophile to complete with water. Therefore, an excellent method for hydration of alkenes is to use dilute H_2SO_4. A lower temperature also favours the process.

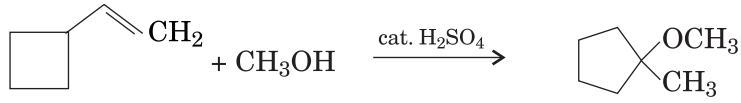
(b) A low concentration of water is used because water is eliminated from the substrate and therefore cyclohexanol is to be treated with concentrated H_2SO_4. Cyclohexene is distilled from the reaction mixture to draw the equilibrium towards product and the reaction mixture is heated to facilitate the elimination process.

2. Explain the following order of reactivity when these alkenes are subjected to acid-catalyzed hydration:

$$(CH_3)_2C{=}CH_2 \rangle CH_3CH{=}CH_2 \rangle CH_2{=}CH_2$$

Solution The reactivity of an alkene towards acid-catalyzed hydration depends on the stability of the carbocation formed by addition of $H^{\oplus}$ to the double bond in the rate determining step. The more the carbocation is stable, the more the alkene is reactive. $(CH_3)_2C{=}CH_2$ undergoes protonation to give the much more stable tertiary (3°) carbocation $(CH_3)_3\overset{\oplus}{C}$, $CH_3CH{=}CH_2$ takes up a proton to give the moderately stable secondary (2°) carbocation $(CH_3)_2\overset{\oplus}{C}H$ and the much less stable primary (1°) carbocation $CH_3\overset{\oplus}{C}H_2$ is expected to be obtained when ethylene adds to $H^{\oplus}$.

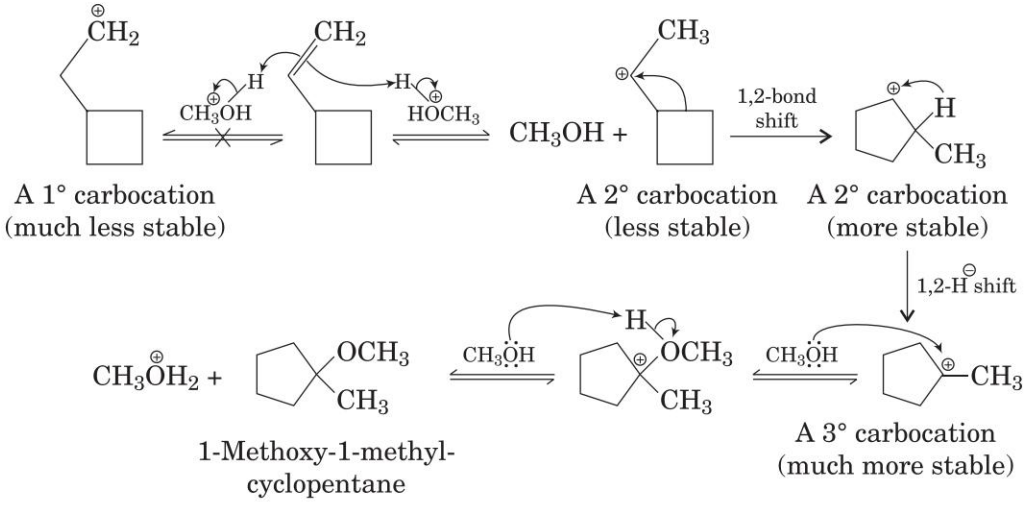
3. Propose a mechanism for the following reaction:



Vinylcyclobutane

1-Methoxy-1-methylcyclopentane
(major product)

Solution When $H^{\oplus}$ adds to vinylcyclobutane, a more stable secondary (2°) carbocation rather than a much less stable primary (1°) carbocation is generated. The secondary carbocation readily rearranges by ring expansion (a 1,2-bond shift) to give another secondary carbocation which is relatively more stable because the five-membered ring has less angle strain. The new secondary carbocation undergoes further rearrangement to give a much more stable tertiary (3°) carbocation by a 1,2-hydride shift. The tertiary carbocation reacts with methanol to form the ether 1-methoxy-1-methylcyclopentane as the major product.



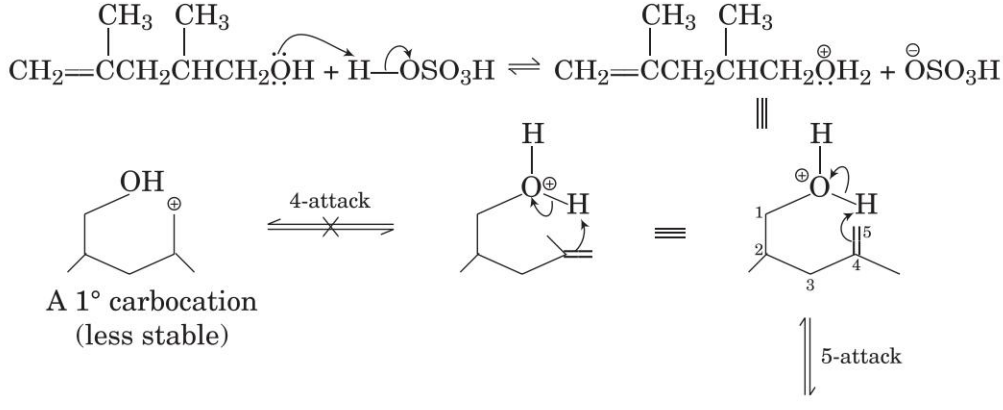
4. Predict the product and write a plausible mechanism for each of the following reactions:

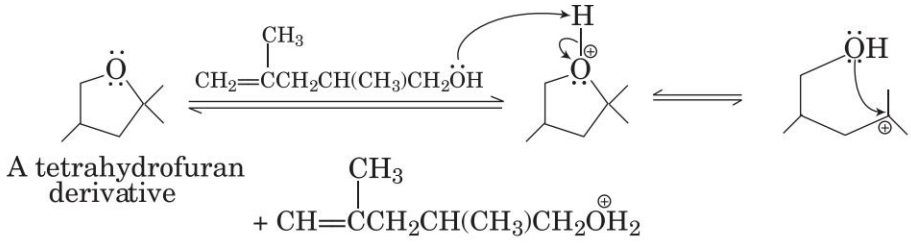
(a) $CH_2=C(CH_3)-CH_2-CH(CH_3)CH_2OH \xrightarrow[H_2SO_4]{H^\oplus}$

(b) $CH_2=CHCH_2CH_2CH_2COOH \xrightarrow[H_2SO_4]{H^\oplus}$

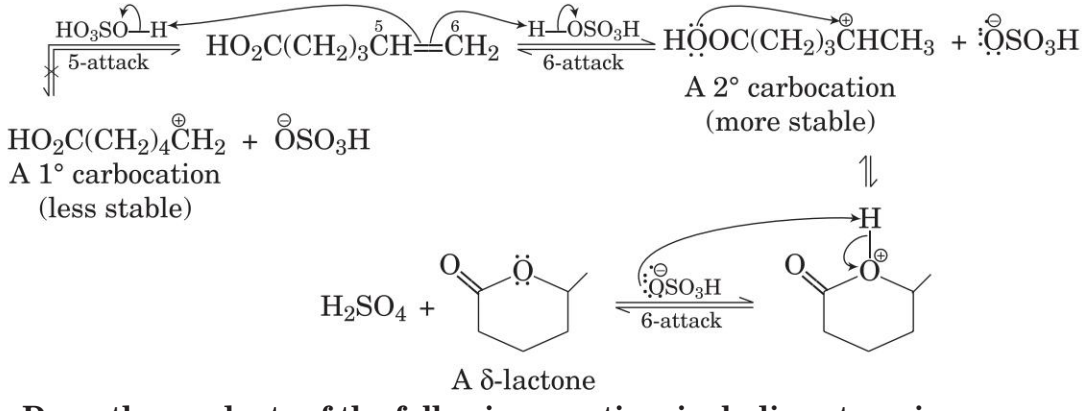
Solution

(a) In the presence of acid, the substrate undergoes intramolecular elelctrophilic addition to the double bond through the formation of a stable 3° carbocation to give a tetrahydrofuran derivative. The reaction takes place in accordance with the Markownikoff's rule.

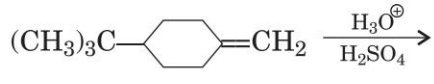




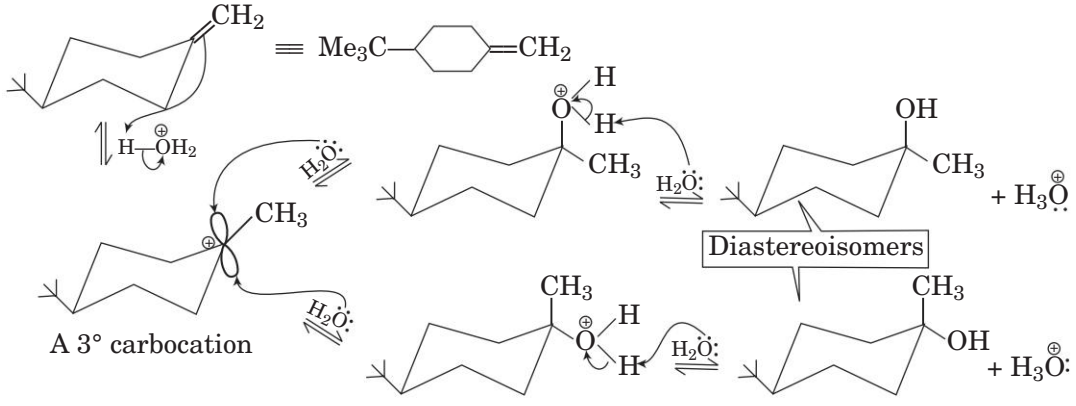
(b) In the presence of acid, the substrate undergoes lactonization through the formation of a relatively stable 2° carbocation. This intramolecular addition also follows the Markownikoff's rule.



5. Draw the products of the following reaction, including stereoisomers:



Solution The *tert*-butyl group ($-CMe_3$) is praticularly bulky and due to severe 1,3-diaxial interactions it cannot take up the axial position. A *tert*-butyl group-substituted cyclohexane, therefore, remains fixed in that particular chair conformation where the $-CMe_3$ group occupies an equatorial position. Therefore, the given compound undergoes acid-catalyzed hydration through the conformation in which $-CMe_3$ group is equatorial.

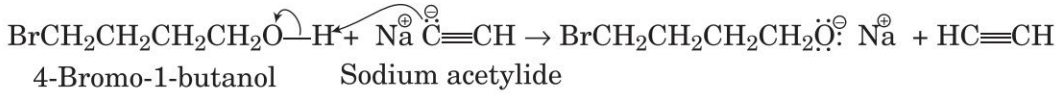


The addition of $H^{\oplus}$ to the methylene carbon of 4-*tert*-butylmethylenecyclohexane leads to the formation of a stable 3° carbocation. The carbocation then undergoes nucleophilic attack by water from either of its two faces to give two diastereoisomeric alcohols.

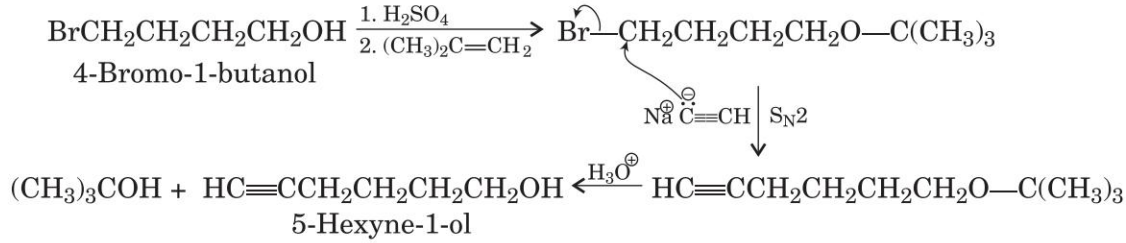
6. How would you carry out the following conversion?

$$\underset{\text{4-Bromo-1-butanol}}{BrCH_2CH_2CH_2CH_2OH} \longrightarrow \underset{\text{5-Hexyne-1-ol}}{HC{\equiv}CCH_2CH_2CH_2CH_2OH}$$

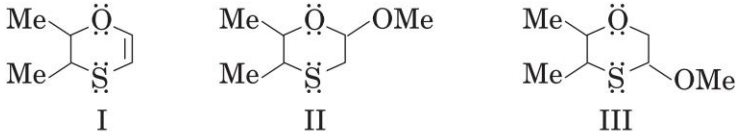
Solution 5-Hexyne-1-ol cannot be prepared simply by treating 4-bromo-1-butanol with sodium acetylide because the strongly basic acetylide ion takes up first the hydrogen of the hydroxyl group and itself becomes converted to acetylene, i.e., instead of a displacement reaction an acid-base reaction occurs.



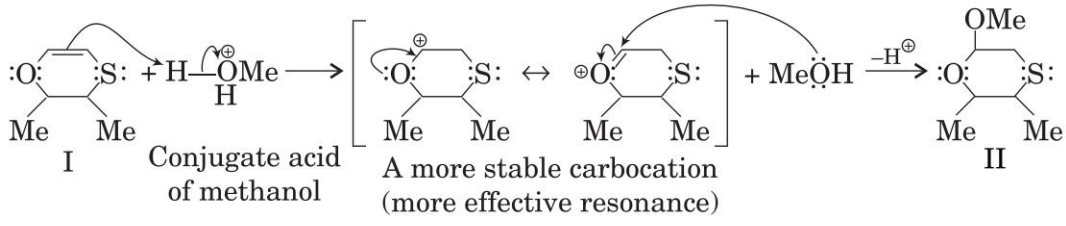
However, the desired compound can be easily prepared by protecting the –OH group by converting it into a *tert*-butyl ether and then treating the protected alcohol with sodium acetylide followed by hydrolysis for deprotection.

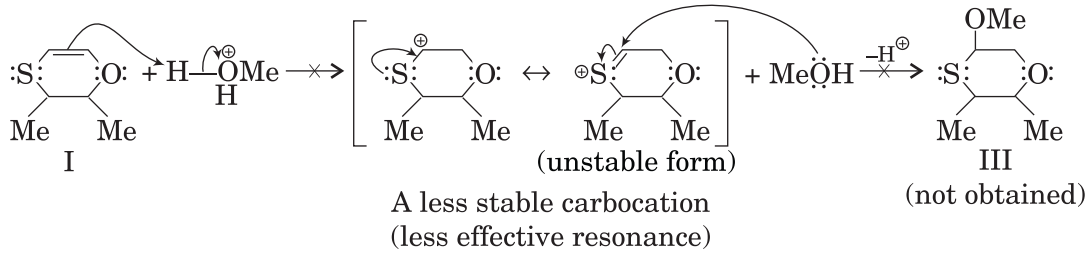


9. The compound I undergoes acid-catalyzed addition of methanol to produce the compound II and not the compound III. Explain this observation.



Solution The acid-catalyzed addition of methanol (CH_3OH) to the compound I occurs as follows:

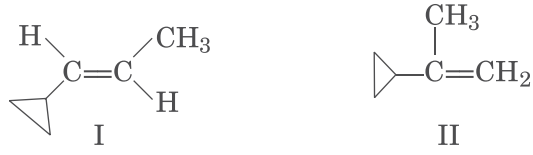




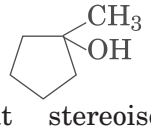
Due to larger size of sulphur and longer length of the bond involving sulphur (a second-row atom), the nuclei of carbon and sulphur are farther apart and for this reason, the requisite sideways overlap of parallel p orbitals necessary to form a stable π bond is much less effective. Hence, the normal π orbital double bonds involving sulphur are very weak and unstable. As a consequence, the carbocation obtained by protonation at the doubly bonded carbon β to sulphur is less stable than that obtained by protonation at the carbon β to oxygen. The reaction, therefore, takes place through the more stable carbocation to form the compound II.

Study Problems

1. The rates of acid-catalyzed hydration of the following two alkenes differ by a factor of over 7000 at 25°C. Which isomer is more reactive and why?



2. What two alkenes on acid-catalyzed hydration give rise to each alcohol as the major product?

(a) 

(b) $(CH_3)_2C(OH)CH_2CH_2CH_2CH_3$

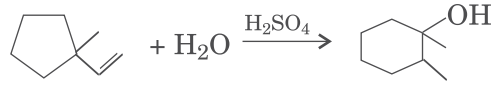
(c) $CH_3CH_2CH(OH)CH_3$

3. What stereoisomers are expected to be obtained when 1-pentene ($CH_3CH_2CH_2CH{=}CH_2$) is treated with dilute sulphuric acid?

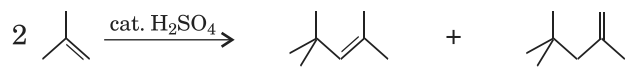
4. Write a reasonable mechanism for the following reaction:

$$(CH_3)_2C{=}CH_2 + MeOH \xrightarrow{cat\cdot H_2SO_4} (CH_3)_3C{-}OMe$$

5. Write a mechanism that explains the formation of the product:

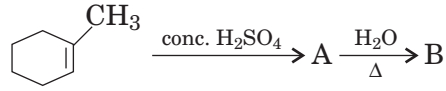


6. Suggest a mechanism for the following reaction and account for the distribution of products as major or minor:



Major product Minor product

7. Predict the product and suggest a mechanism for each step of the following reaction sequence:



8. Acid-catalyzed hydration of allene ($CH_2{=}C{=}CH_2$) gives acetone as the major product. Explain this observation.
[Hint: Protonation at the middle carbon (*sp* hybridized) does not take place because allylic stabilization of the resulting carbocation is not immediately possible as *p* orbitals are not parallel. See also **article 4.2.1.5**]

9.

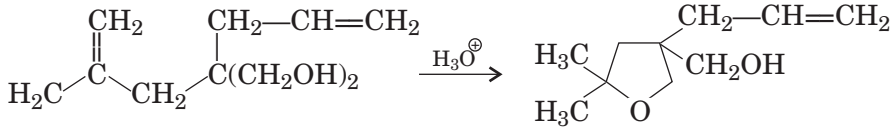
(a) Complete the following reactions with brief comments:

$$(CH_3)_2C{=}CH_2 \xrightarrow[\text{Pressure}]{H_2SO_4-H_2O} ? \xrightarrow{(CH_3)_3COH} ?$$

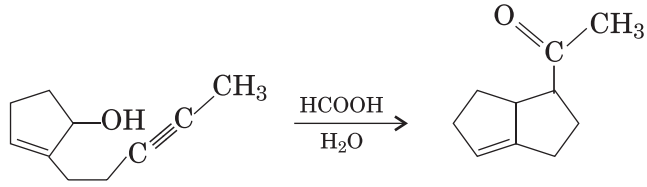
[Hint: $Me_3\overset{\oplus}{C}\overset{\ominus}{O}SO_3H$ (pressure is applied to get a large concentration of the carbocation in solution); $Me_3C{-}O{-}CMe_3$]

(b) Formulate a reasonable mechanism for each step of the following reactions:

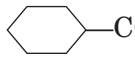
(i)



(ii)

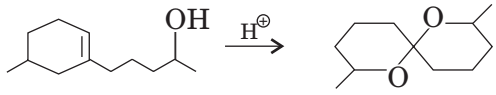


10. Predict the structure of the appropriate alkyne that can be used for the synthesis of each of the following ketones:

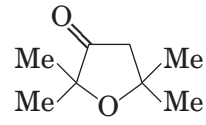
(a)  (b) $CH_3CH_2COCH_2CH_2CH_3$ (c) CD_3COCH_3

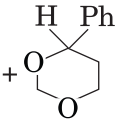
11. Suggest a mechanism for each of the following reactions:

(a)

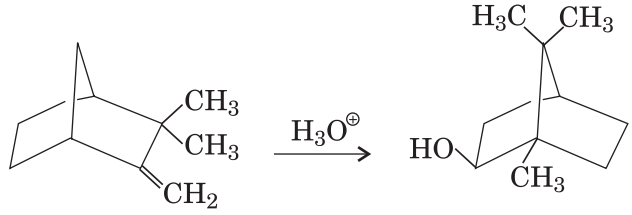


(b) $HOMe_2C{-}C{\equiv}C{-}CMe_2OH \xrightarrow[H_2SO_4/H_2O]{HgSO_4}$

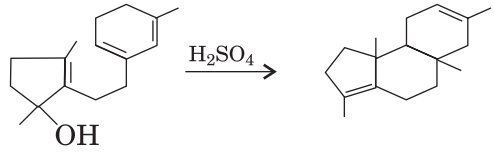


(c) $PhCH{=}{=}CH_2 + HCHO \xrightarrow[\text{(Prins reaction)}]{H_3O^{\oplus}} PhCHOHCH_2CH_2OH +$ 

12. Suggest a mechanism for the following reaction:



13. Explain the following transformation mechanistically:



14. Predict the product that would be obtained from the ionic addition of ICl to propene. **[Hint:** Because of the greater electronegativity of chlorine, the positive portion of ICl molecule is iodine $(\overset{\delta+}{I}—\overset{\delta-}{Cl})$]

1.1.3 Oxymercuration-Demercuration

An important laboratory procedure for synthesizing alcohols from alkenes is a two-step process called *oxymercuration–demercuration*. The sequence is highly regioselctive and addition of water occurs in accordance with the Markownikoff's rule. For example, 1-hexene undergoes hydration by this procedure to yield 2-hexanol.

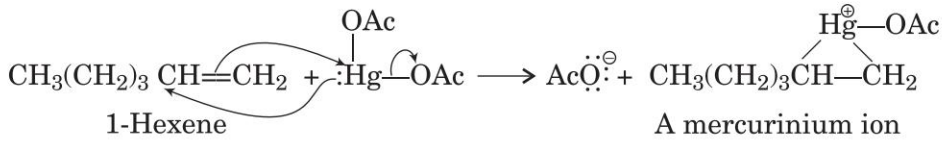
1.1.3.1 Oxymercuration

Alkenes react with mercuric acetate in a mixture of tetrahydrofuran and water to produce the corresponding β-hydroxyalkylmercury (II) acetates. The reaction is called *oxymercuration*. For example:

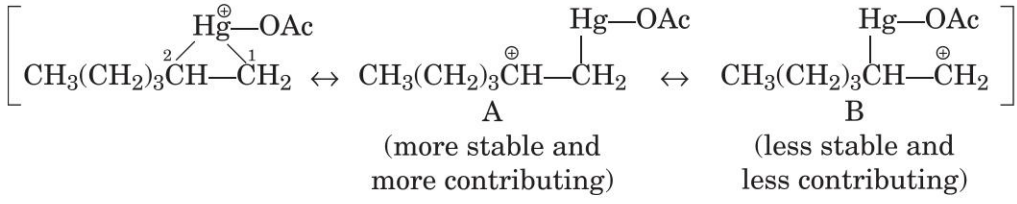
$$\underset{\text{1-Hexene}}{CH_3(CH_2)_3CH{=}CH_2} + \underset{\text{Mercuric acetate}}{Hg(OAc)_2} + H_2O \xrightarrow{THF} \underset{(95\%)}{CH_3(CH_2)_3CH(OH)CH_2HgOAc} + AcOH$$

Mechanism: The mechanism of oxymercuration involves the steps as follows:

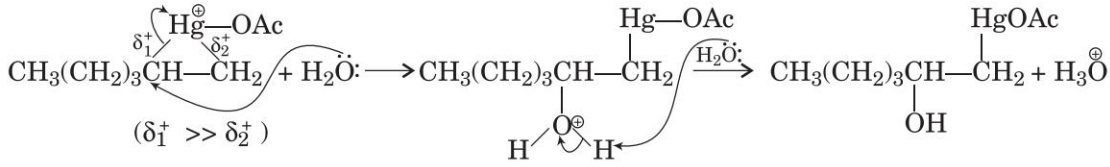
Step 1: The electrophilic mercury of mercuric acetate [$Hg(OAc)_2$] adds to the double bond to form a cyclic mercurinium ion (two of mercury's 5*d* electrons are shown). Since carbocation rearrangement does not occur, therefore, it can be concluded that the product of addition reaction is a cyclic mercurinium ion rather than a carbocation. This step usually goes to completion within a period of 20s to 10 min.



The cyclic ion can be described as a hybrid of three contributing structures. The structure B is less important than the structure A because A involves a more stable 2° carbocation while B involves a much less stable 1° carbocation. The greater contribution of A results in a hybrid which has more positive charge on C-2 (the more substituted carbon) than on C-1.



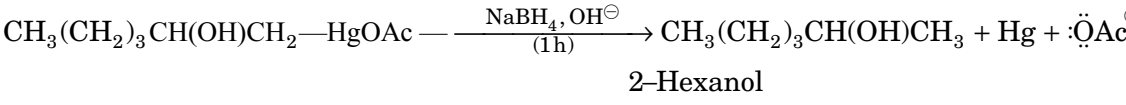
Step 2: The mercurinium ion undergoes nucleophilic attack by water (S_N2) to form a (hydroxyalkyl) mercury compound after proton loss.



The transition state of this step has much S_N1 character and the orientation is controlled not by steric factor but by polar factors. Because of this, attack by water in this S_N2 type reaction occurs at the more highly substituted carbon rather than at the less substituted carbon as required by the S_N2 mechanism. This process is highly regioselective (attack of water occurs almost exclusively at the more branched carbon). Since it is a case of backside attack, the net result is *anti*-addition of –OH and –HgOAc across the double bond of the alkene. The oxymercuration is, therefore, stereospecific also.

1.1.3.2 Demercuration

The *β*-hydroxyalkylmercury (II) acetate is not normally isolated but is treated directly with alkaline sodium borohydride ($NaBH_4/OH^{\ominus}$) which reduces it to an alcohol by replacing the acetoxymercuri group with hydrogen. This step is called *demercuration*. For example:



If $NaBD_4$ is used instead of NaBHu, $CH_3(CH_2)_3CH(OH)CH_2D$ is obtained.

The mechanism of demercuration is not well understood. This step is not necessarily stereospecific. Therefore, the overall process of oxymercuration–demercuration is not necessarily stereospecific (a mixture of *syn*- and *anti*-addition product of hydration is obtained).

1.1.3.3 Regioselectivity of Oxymercuration–Demercuration

Oxmercuration–demercuration is highly regioselective. In this sequence, the net orientation of the addition of the elements of water, H– and –OH, is in accordance with the Markownikoff's rule. The H– becomes attached to that doubly bonded carbon which contains a greater number of hydrogen atoms and the –OH group becomes attached to the more substituted carbon.

$$\underset{\underset{+}{\underset{HO—H}{}}}{R—CH=CH_2} \xrightarrow[2.\ NaBH_4,\ OH^{\ominus}]{1.\ Hg(OAc)_2\ /\ THF–H_2O} RCH(OH)CH_3$$

For example:

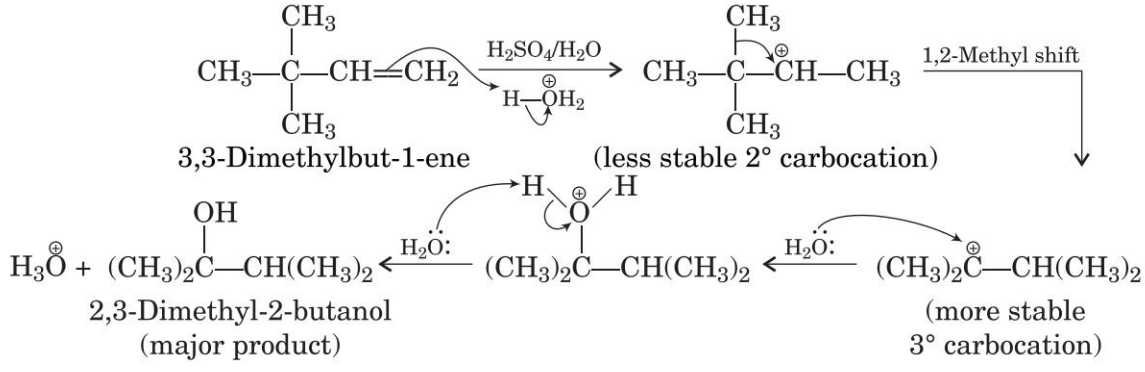
$$\underset{\text{1-Pentene}}{CH_3CH_2CH_2CH=CH_2} \xrightarrow[\substack{THF—H_2O\\(15\,s)}]{Hg(OAc)_2} CH_3CH_2CH_2\overset{\overset{OH}{|}}{C}HCH_2—HgOAc \xrightarrow[\substack{OH^{\ominus}\\(1h)}]{NaBH_4} \underset{\substack{\text{2-Pentanol}\\(93\%)}}{CH_3CH_2CH_2\overset{\overset{OH}{|}}{C}HCH_3}$$

1.1.3.4 Advantages of Oxymercuration–demercuration procedure for hydration of alkenes over the acid-catalyzed hydration

Addition of water by oxymercuration–demercuration has two advantages over the acid-catalyzed addition of water. These are as follows:

(i) It does not require acidic conditions that are harmful to many organic molecules.

(ii) Since the process involves a cyclic mercurinium ion (in which much of the positive charge is accommodated by the mercury moiety while only fractional positive charge is present on the highly substituted carbon atom) and not a free carbocation (which is responsible for rearrangement), therefore, rearrangement reactions do not take place. For example, 3,3-dimethylbut-1-ene undergoes acid-catalyzed hydration through carbocation rearrangement to give 2,3-dimethyl-2-butanol as the major product. The same alkene, when subjected to oxymercuration–demercuration, undergoes hydration with no rearrangement and produces 3,3-dimethyl-2-butanol predominantly.



Hydration by oxymercuration–demercuration:

$$(CH_3)_3C{-}CH{=}CH_2 \xrightarrow[2.\ NaBH_4/OH^{\ominus}]{1.\ Hg(OAc)_2,\ THF-H_2O} (CH_3)_3CCH(OH)CH_3$$

3,3-Diemthybut-1-ene → 3,3-Dimethyl-2-butanol (94%)

1.1.3.5 Solvomercuration–demercuration

When a solvent molecule acts as the nucleophile in the oxymercuration step the overall process is called *solvomercuration–demercuration.* For example:

$$(CH_3)_2C{=}CH_2 \xrightarrow[\text{solvomercuration}]{Hg(OCOCF_3)_2,\ THF-CH_3OH} (CH_3)_2C(OCH_3)CH_2HgCF_3COO \xrightarrow[\text{demercuration}]{NaBH_4,\ OH^{\ominus}} (CH_3)_3COCH_3$$

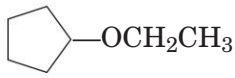
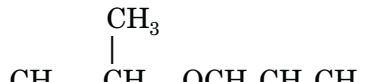
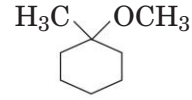
2-Methylpropene → *tert*-Butyl methyl ether

The electron-withdrawing fluorine atoms in mercuric trifluoroacetate enhance the electrophilicity of mercury. It has been found that addition of an alcohol works better in the presence of mercuric trifluoroacetate, $Hg(O_2CCF_3)_2$.

The mechanism of oxymercuration and solvomercuration or alkoxymercuration is essentially identical. The only difference is that water is the nucleophile in oxymercuration and an alcohol is the nucleophile in alkoxymercuration. Therefore, the product of oxymercuration–demercuration is an alcohol, whereas the product of alkoxymercuration–demercuration is an ether.

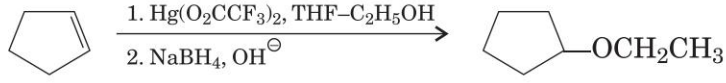
SOLVED PROBLEMS

1. How could each of the following ethers be synthesized from an alkene and an alcohol by solvomercuration-demercuration or alkoxymercuration-demercuration?

(a)  (b)  (c) 

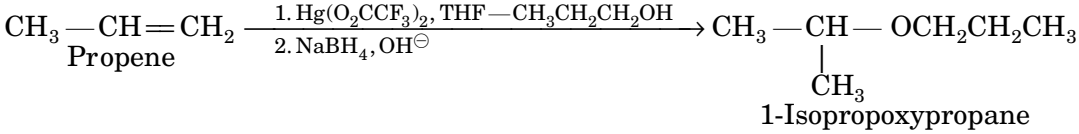
Solution

(a) Since one of the groups bonded to the ether oxygen is ethyl, therefore, it must be derived from the alcohol and the other group is derived from the alkene. Therefore, the alkene is cyclopentene and the alcohol is ethanol.

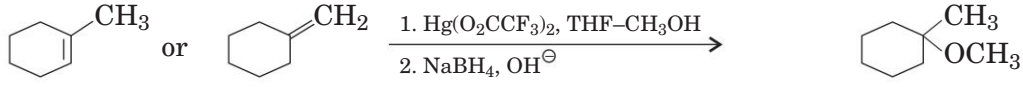


Ethoxycyclopentane

(b) Since the overall reaction follows Markownikoff's rule, the propyl group must originate from the alcohol and the other group is derived form the alkene. Therefore, the alkene is propene and the alcohol is 1-propanol.



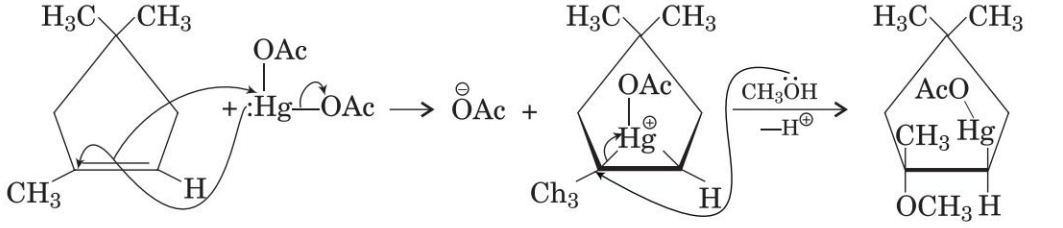
(c) Since one of the groups bonded to ether oxygen is methyl, therefore, it must be derived from the alcohol and the other group is derived from the alkene. Hence, the alkene is 1-methylcyclohexene or methylenecyclohexane and the alcohol is methanol.



1-Methylcyclohexene | Methylenecyclohexane | 1-Methoxy-1-methylcyclohexane

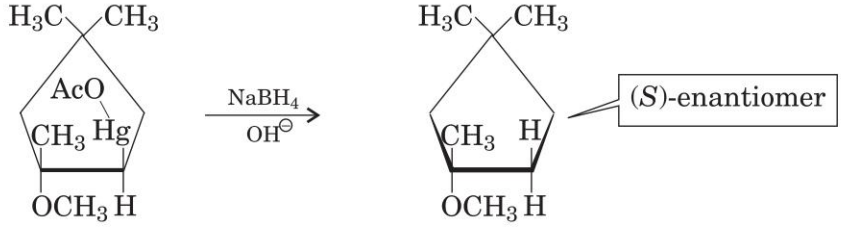
2. Show the intermediates and products that would be formed by olkoxymercuration-demercuration of 1,4,4-trimethylcyclopentene, using methanol as solvent. Give the stereochemical outcome of the reaction.

Solution Mercuric acetate adds to 1,4,4-trimethylcyclopentene to give the cyclic mercurinium ion. This ion has a considerable amount of positive charge on the more substituted tertiary carbon atom. Methanol attacks this carbon to give *trans*-intermediate (product of *anti*-addition).



1,4,4-Trimethylcyclopentene | mercurinium ion | *trans*-intermediate

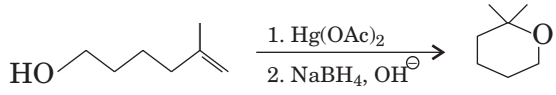
Reduction of the intermediate gives the Markownioff product, 1-methoxy-1,4,4-trimethylcyclopentane.



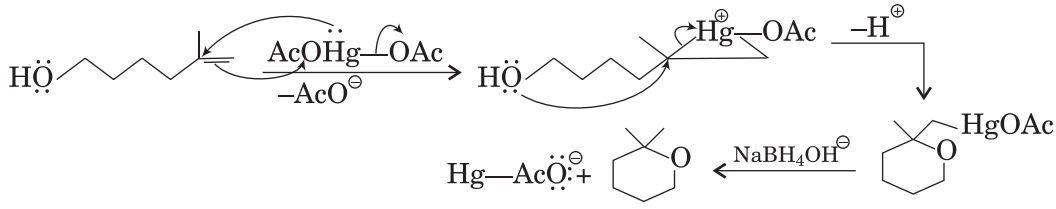
1-Methoxy-1,4,4-trimethylcyclopentane

Attack of $Hg(OAc)_2$ on the other face of the alkene produces the (*R*)-enantiomer of the resultant ether, therefore, an optically inactive racemic mixture is obtained.

3. The following reaction has been observed in oxymercuration-demercuration of this unsaturated alcohol. Propose a mechanism for this reaction.

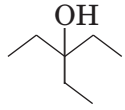


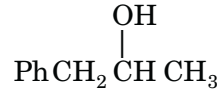
Solution The mechanism of the reaction is as follows:

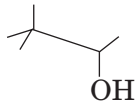


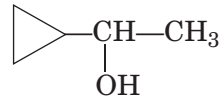
Study Problems

1. Write the structure of the appropriate alkene and specify the reagents required for the synthesis of the following alcohols by oxymercuration-demercuration

(a) 

(b) 

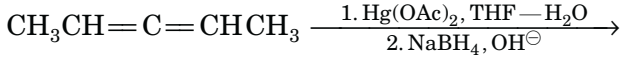
(c) 

(d) 

2. Predict the products and suggest a mechanism for the first step of the following reaction sequence:



3. Predict the product of the following reaction and give a suitable mechanism to account for its formation:



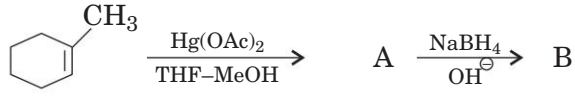
4. Give the alkene and the alcohol needed to prepare each of the following ethers by alkoxymercuration-demercuration:

(a) Dicyclohexyl ether (b) Di-*tert*-butyl ether

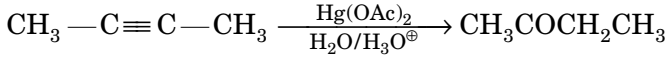
(c) 1-Phenyl-1-ethoxypropane

6. Give an example to prove that no rearrangement takes place in oxymercuration-demercuration.

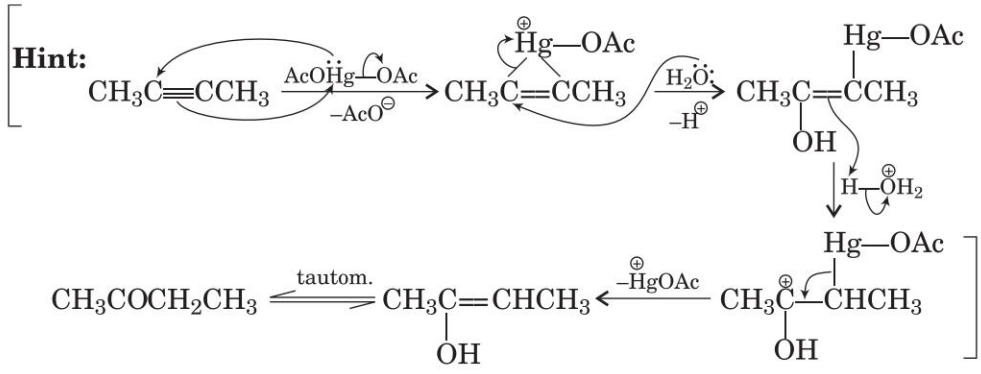
6. Draw the structure, including stereochemistry, of the major product A from the reaction between 1-methylcylohexene and mercury(II) acetate in methanol. Draw the structure, including stereochemistry, of the product B obtained from demercuration of A with sodium borohydride.



7. Suggest a mechanism for the following reaction:



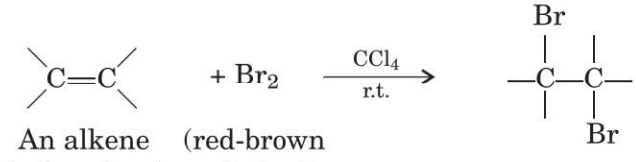
Hint:



1.1.4 Addition of Halogens

1.1.4.1 Addition of Bromine and Chlorine

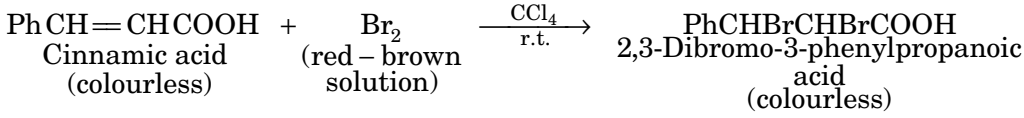
The presence of unsaturation in an organic compound can be easily detected by rapid decolourization of bromine in carbon tetrachloride solution.



An alkene (colour less) (red-brown solution)

A vicinal dibromide (colourless)

Example:



Similarly, Cl_2 adds to the double bond to produce a vicinal dichloride.

Example:

$$(CH_3)_2C{=}CH_2 + Cl_2 \xrightarrow{CH_2Cl_2} (CH_3)_2CClCH_2Cl$$

2-Methylpropene → 1,2-Dichloro-2-methylpropane (a vicinal dichloride)

1.1.4.2 Addition of Fluorine and Iodine

F_2 and I_2 are not used as reagents in electrophilic addition reactions. Fluorine reacts violently with alknes, so electrophilic addition of F_2 is not a synthetically useful reaction. Addition of I_2 to an alkene, on the other hand, is a thermodynamically unfavourable reaction. Vicinal diiodides are unstable at room temperature and because of this, they decompose back to the alkene and I_2.

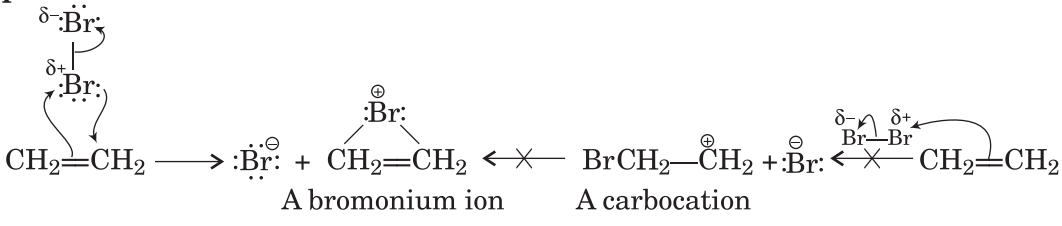
$$CH_3CH_2CH{=}CHCH_2CH_3 + I_2 \rightleftharpoons CH_3CH_2CHICHICH_2CH_3$$

3-Hexene ⇌ 3,4-Diiodohexane

1.1.4.3 Mechanism of Addition

Addition of Br_2 or Cl_2 to alkenes may be surprising at first glance because it is not immediately apparent that an electrophile, necessary to start an electrophilic addition reaction, is present. However, the bond between two halogen atoms is relatively weak and therefore, easily broken, when that π electrons of alkene approach a molecule of Br_2 or Cl_2, one of the halogen atoms accepts them and releases the shared electrons to the other halogen atom. Hence, in an electorphilic addition reaction, Br_2 behaves as if it were $\overset{\oplus}{Br}$ and $\overset{\ominus}{Br}$, and Cl_2 behaves as if it were $\overset{\oplus}{Cl}$ and $\overset{\ominus}{Cl}$. Ethylene, for example, reacts with bromine through the following two steps:

Step 1:

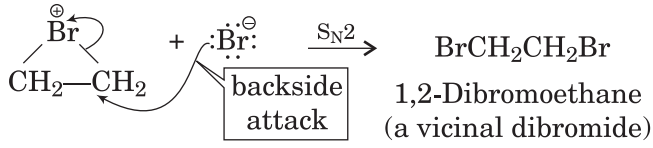


A bromonium ion — A carbocation

As the alkene displaces the distant bromine atom, the newly bonded bromine atom, due to its size and polarizability, donates an electron pair to the carbon that would otherwise be a carbocation. A cyclic bromonium ion is formed instead of a carbocation because the bromonium ion is more stable than the carbocation and that is due to the fact that all the atoms in the bromonium ion have complete octets (except hydrogen), whereas the positively charged carbon of the carbocation does not have complete octet. It is the rate-determining (slow) step of the reaction.

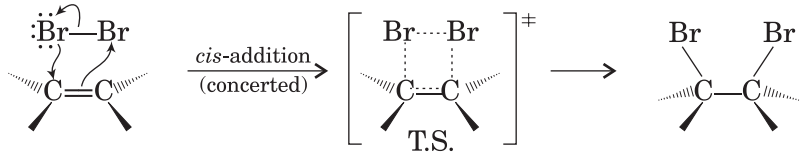
It is to be noted that an open carbocation would have been obtained if it is considerably stable (adjacent to a phenyl ring).

Step 2: In this step, $Br^{\ominus}$ attacks a carbon atom of the bromonium ion (an S_N2 process). As a result, the strain of the three-membered ring is released and vicinal dibromide is formed.

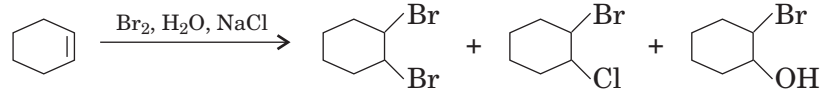


1.1.4.4 Evidence in favour of a two-step pathway

The following observations account for the fact that the addition proceeds through a two-step pathway and not through a four-centred one-step (concerted) pathway such as follows:



Observation (i): When an alkene is allowed to react with bromine in the presence of other nucleophiles, products, in addition to the expected vicinal dibromide, are obtained which contain bromine atom and one nucleophilic atom or group. For example, when cyclohexene is treated with an aqueous solution of bromine and sodium chloride, 1-bromo-2-chlorocyclohexane (II) and 2-bromocyclohexanol (III) are obtained in addition to 1,2-dibromocyclohexane (I).

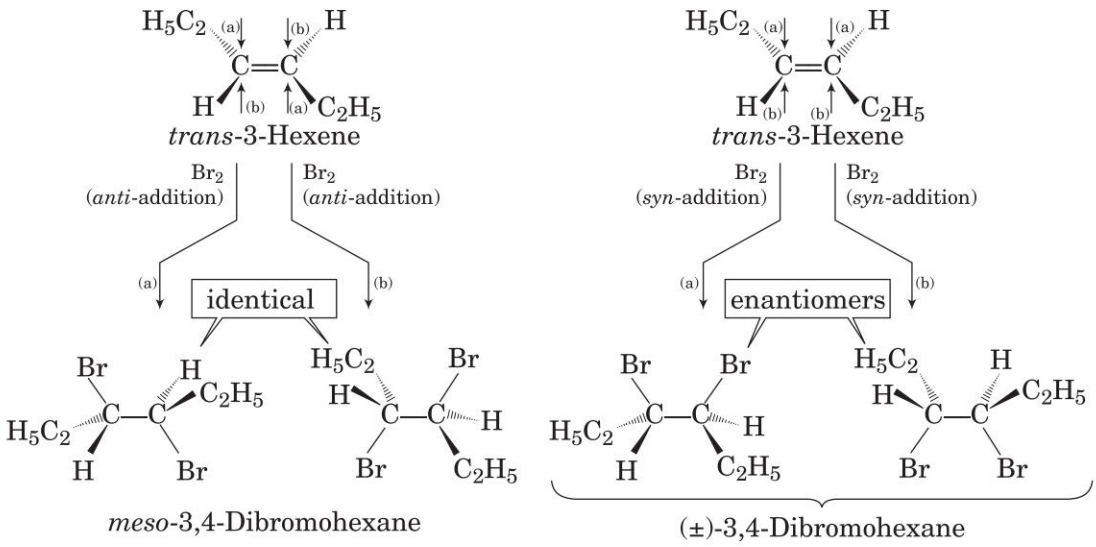


Cyclohexene I II III

That the dihalide II and the alcohol III are not obtained by mere displacement of a bromine atom in I by $:\ddot{Cl}:^{\ominus}$ or $H_2\ddot{O}:$ becomes clear from the fact that their formations are much rapid than expected by nucleophilic substitution under such conditions. In a concerted one-step pathway, there is no scope for nucleophilic attack by $:\ddot{Cl}:^{\ominus}$ or $H_2\ddot{O}:$.

Therefore, the formation of products like II and III suggests that the addition of bromine follows a two-step pathway and not a concerted one-step pathway involving a four-centred transition state.

Observation (ii): That the reaction proceeds through a two-step pathway can also be established by the bromination of alkenes which may yield different products through *syn*- and *anti*-additions. For instance, *trans*-3-hexene may give *meso*-dibromide on *anti*-addition and racemic dibromide on *syn*-addition.

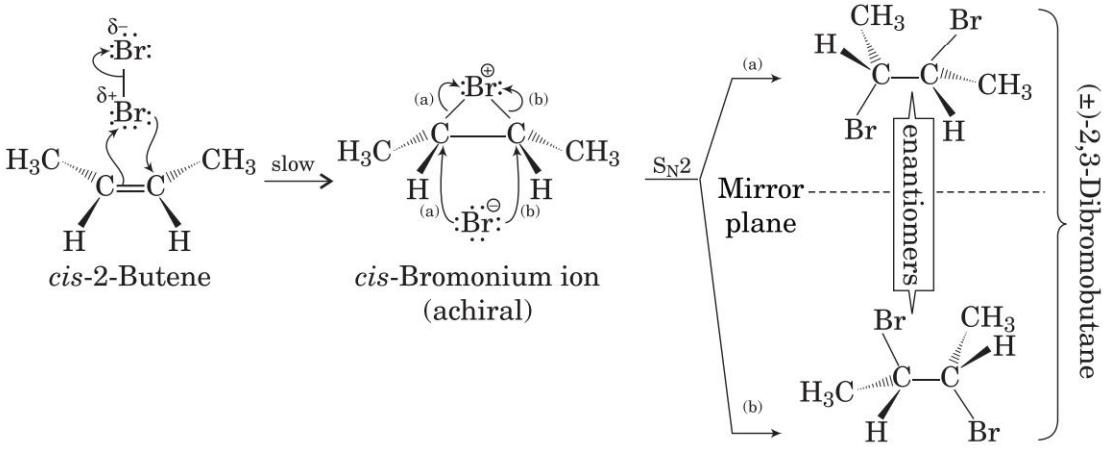


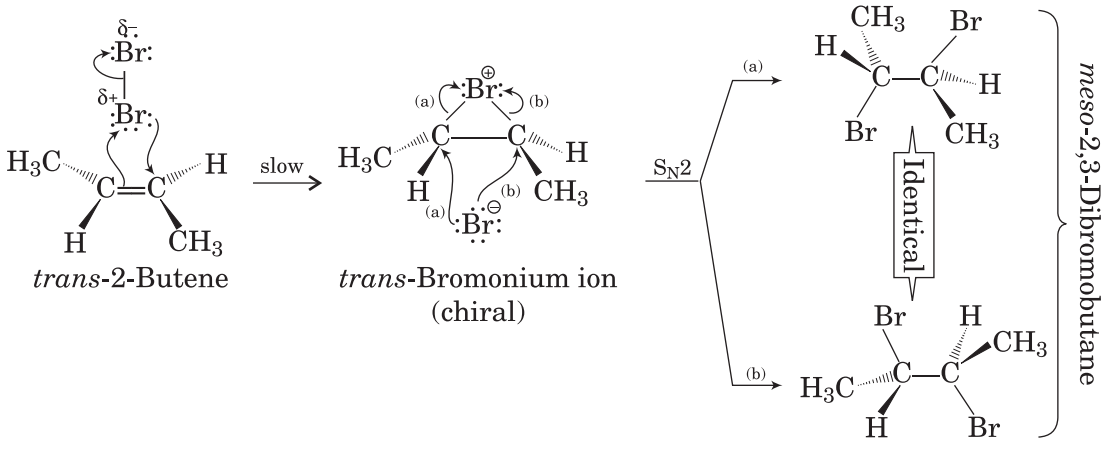
But in practice, the *meso*-3,4-dibromohexane has been found to be the only product. Absence of *syn*-addition product, i.e., absence of racemic 3,4-dibromohexane, cancels the possibility of four-centred one-step mechanism. Again, the atoms in a bromine molecule (Br–Br) are too close to each other to be able to add simultaneously on the two doublybonded carbon atoms in *anti* fashion. Therefore, the *anti*-addition product is obtained by the formation of two C—Br bonds in two separate steps, i.e., the addition takes place by a two-step process.

1.1.4.5 Reaction of Bromine with cis-and trans-2-butene

Halogen addition is stereospecifically *anti*; the groups add to opposite sides of the alkene. Thus, when *cis*-2-butene reacts with bromine, only racemic or (±)-2,3-dibromobutane is obtained and when *trans*-2-butene reacts with bromine, only *meso*-2-3-dibromobutane is obtained.

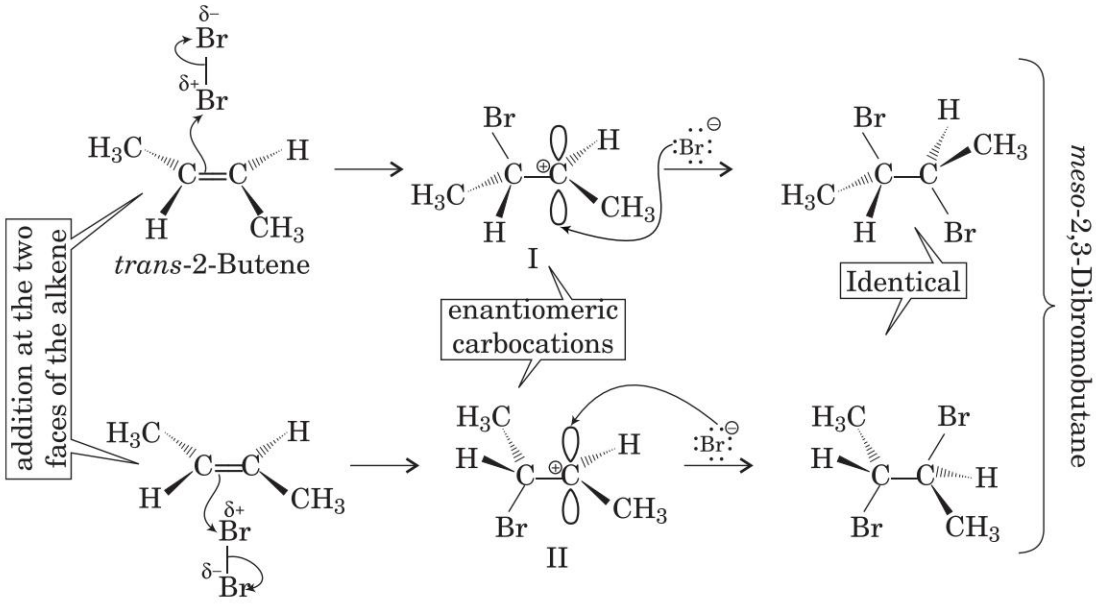
The mechanisms and the stereochemical courses of addition of Br_2 to *cis*- and *trans*-2-butene may be given as follows:



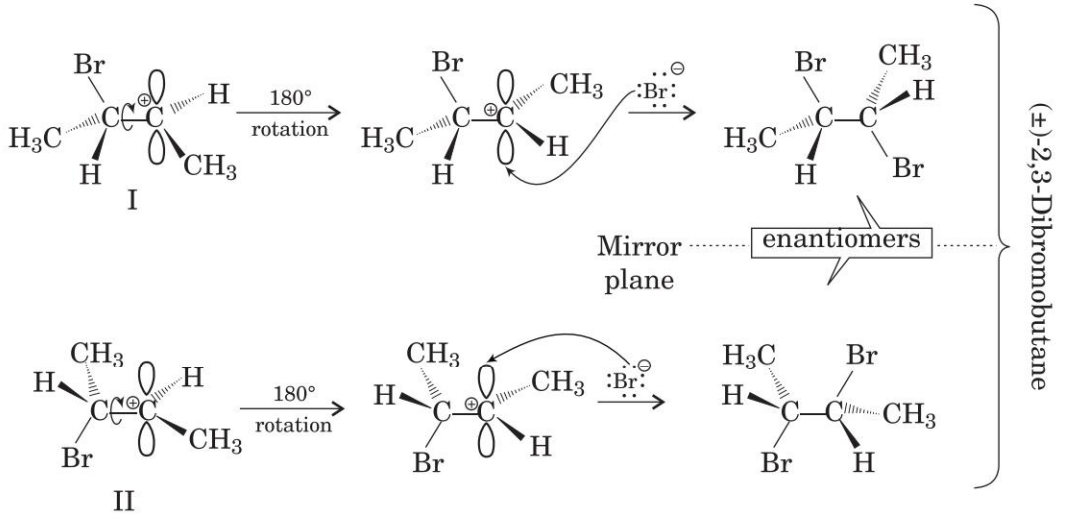


The first step (the rate-determining step) of each of the two reactions involves electrophilic attack by bromine on the double bond of the alkene and formation of a three-membered cyclic cationic intermediate called a bromonium ion via a π-complex. Due to larger size, the bromine atoms are relatively polarizable. When the Br_2 molecule approaches the π electron cloud of the alkene, its near end becomes positively polarized as a result of electron repulsion by the π electrons. A π-complex is initially formed when the alkene extends it π cloud to the positive part of the polarized Br_2 molecule. Subsequently, the alkene donates a pair of electrons to the closer positively polarized bromine atom, causing displacement of the distant bromine atom. As this takes place, the newly bonded bromine atom due to its size and polarizability, donates an electron pair to the carbon that would otherwise be a carbocation. As a result, a bridged bromium ion intermediate and a bromide ion ($Br^{\ominus}$) are formed. The Br atom in this intermediate is bonded to both the original doubly bonded carbon atoms and carries the positive charge. In the second step of the reaction, the bromonium ion undergoes nucleophilic attack (an S_N2 process) by the $:\ddot{\underset{\cdot\cdot}{Br}}:^{\ominus}$ ion. Since one side of the bridged bromonium ion is blocked, therefore, attack by $Br^{\ominus}$ on either of the C atoms takes place with equal facility from the opposite side of the bridge to produce the *anti*-addition product exclusively. Hence, on bromination the *cis*-isomer of 2-butene yields only racemic or (±)– 2,3-dibromobutane and the *trans*-isomer of 2-butene yields only *meso*-2,3-dibromobutane. The reaction is therefore stereospecific.

Proof against formation of an open carbocation: If *anti*-addition of Br_2 occurs through an open carbocation, the stereochemical outcome, for example, for *trans*-2-butene will be as follows:

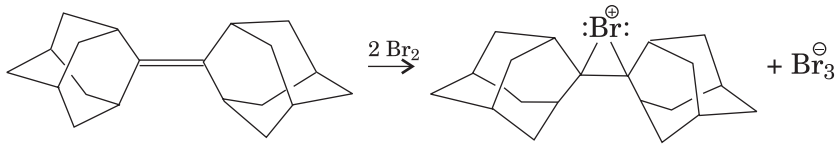


The intermediate carbocations may also lead to the formation of racemic or (±)-2,3-dibromobutane which is, in fact, the *syn*-addition product.



Therefore, both *meso* and racemic products are expected to be obtained from *trans*-2-butene. However, in practice only the *meso* dibromide is obtained. The *meso*-product would only be obtained if $Br^{\ominus}$ attacks the intermediate carbocations before rotation and exclusively from the face opposite to the existing C—Br bond. Since these assumptions are not acceptable, therefore, the addition of bromine must involve a bromonium ion intermediate and not an open carbocation.

The most important evidence in support of the formation of bromonium ion is that it has been possible to isolate the bromonium ion obtained when adamantylideneadamantane, a hindered alkene, is allowed to react with bromine.



Adamantylideneadamantane — A a stable bromonium ion

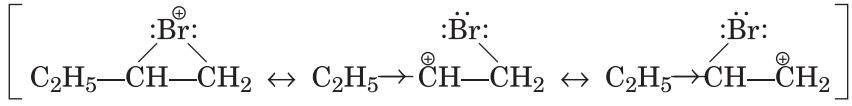
The brominium ion is stable to further addition of nucleophiles (S_N2 attack from the back side) due to its cage-like structure and for this reason, it is stable and isolable.

1.1.4.6 Addition Through Unsymmetrical Bromonium Ion

An unsymmetrical alkene adds to Br_2 to form an unsymmetrical bromonium ion which does not undergo nucleophilic attack equally well at both the carbon atoms and this is because one of them is relatively more positive than the other. For example, the addition of bromine to 1-butene in the presence of chloride ion proceeds through an unsymmetrical bromonium ion which undergoes nucleophilic attack at C-2 (the more positively prolarized carbon) to yield 1,2-dibromobutane along with 1-bromo-2-chlorobutane.

$$\underset{\text{1-Butene}}{CH_3CH_2-CH=CH_2} \xrightarrow[:\ddot{Cl}:^{\ominus}]{Br_2} \underset{\text{1,2-Dibromobutane}}{CH_2CH_2CHBrCH_2Br} + \underset{\text{1-Bromo-2-chlorobutane}}{CH_3CH_2CHClCH_2Br}$$

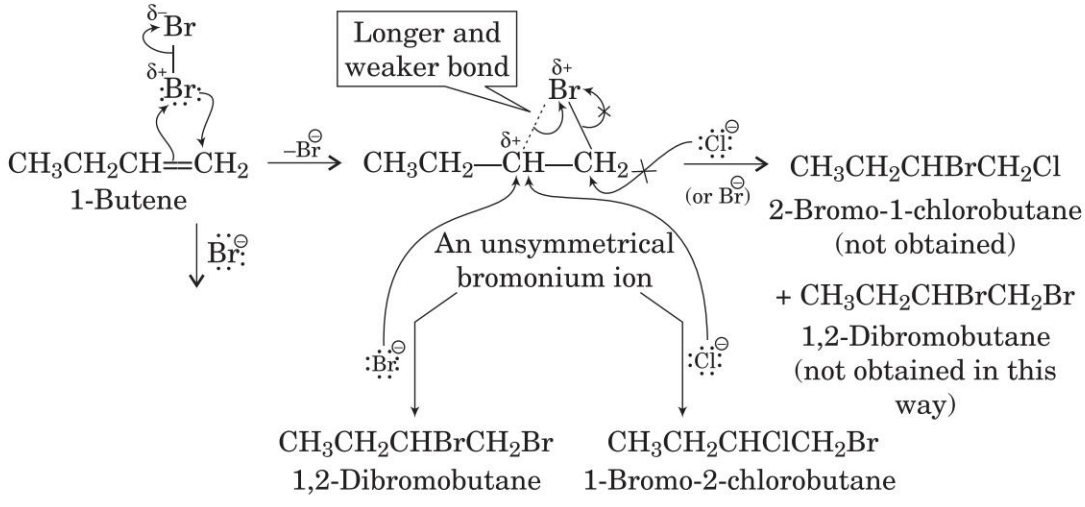
The initial electrophilic attack of Br_2 on the carbon–carbon double bond of 1-butene results in formation of a cyclic bromonium ion intermediate and a $Br^{\ominus}$ ion. In the bromonium ion, the positive charge is borne not only by the bromine atom but also by the two ring carbons. The sharing of positive charge can be represented by drawing the following three resonance structures:



I (most stable and most important) — II (A 2° carbocation (more stable and more important)) — III (A 1° carbocation (less stable and less important))

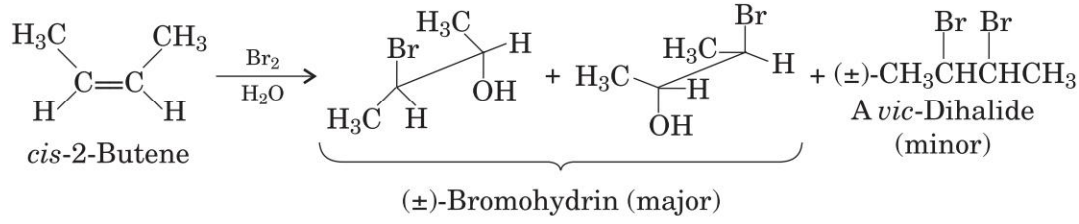
The structure I is the conventional structure for the bromonium ion while the structures II and III show that the bromonium ion carbons share part of the positive charge. The structure II (a more stable 2° carbocation) is more important, i.e., more contributing than the structure III (a much less stable 1° carbocation). Therefore, the secondary carbon bears

a larger part of the positive charge, and it is more strongly electrophilic. The bromonium ion is, therefore, an unsymmetrical one. Due to greater share of the positive charge, the transition state for attack at the more substituted carbon (even though the attack at this carbon is more hindered) is more stable and, so attack by $Br^{\ominus}$ or $Cl^{\ominus}$ ions takes place preferentially at the more electrophilic secondary carbon to give 1,2-dibromobutane and 1-bromo-2-chlorobutane, respectively.



1.1.4.7 Formation of Halohydrin

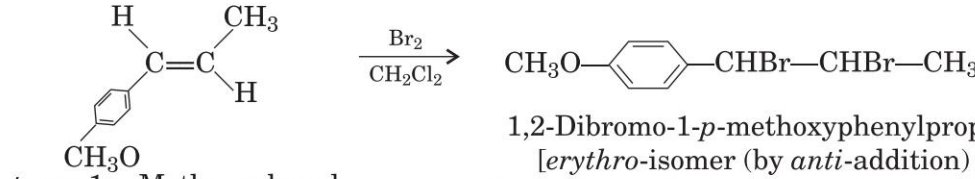
A halohydrin is an organic compound that contains both an –OH group and a halogen. When the halogenation of an alkene is carried out in aqueous solution, rather than in non-nucleophilic solvent like CH_2Cl_2, the major product is a halohydrin instead of a *vic*-dihalide. For example:



Mechanism: The mechanism of the reaction involves formation of a bromonium ion which subsequently undergoes nucleophilic attack by $Br^{\ominus}$ or H_2O (see **article no. 1.1.4.5**).

1.1.4.8 Nonstereospecific Addition of Br_2 to an Alkene

The addition of bromine to an alkene may not involve a cyclic bromonium ion intermediate if the structure of the alkene favours the formation of a carbocation which is considerably stable and because of this, the reaction becomes nonstereospecific. For example:



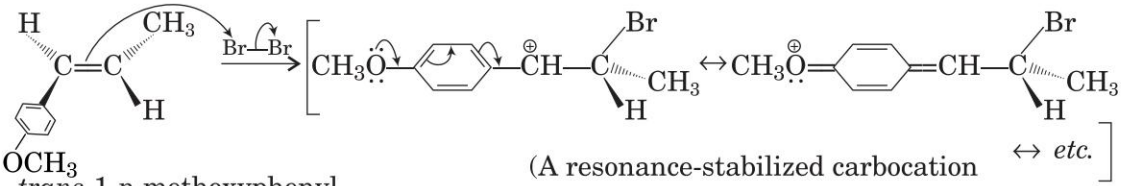
trans-1-*p*-Methoxyphenylpropene

1,2-Dibromo-1-*p*-methoxyphenylpropane [*erythro*-isomer (by *anti*-addition) is the major product and *threo*-isomer (by *syn*-addition) in the minor product.)

Addition of Br_2 to *trans*-1-*p*-methoxyphenylpropene leads to the formation of a resonance-stabilized carbocation. The freely rotating carbocation subsequently undergoes nucleophilic attack by the bromide ion to yield both *threo*- and *erythro*-1,2-dibromo-1-*p*-methoxyphenylpropane by *syn*- and *anti*-addition, respectively.

The steps are as follows:

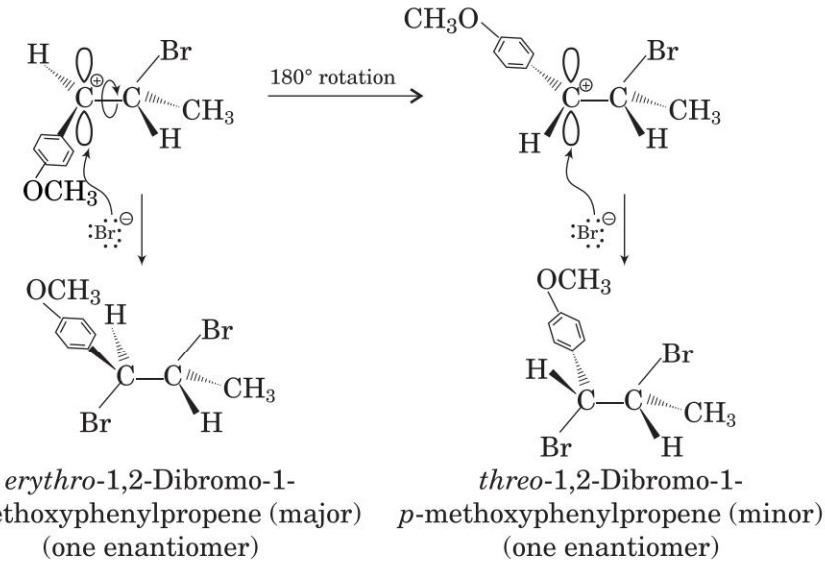
Step 1:



trans-1-*p*-methoxyphenylpropene

(A resonance-stabilized carbocation

Step 2:



erythro-1,2-Dibromo-1-*p*-methoxyphenylpropene (major) (one enantiomer)

threo-1,2-Dibromo-1-*p*-methoxyphenylpropene (minor) (one enantiomer)

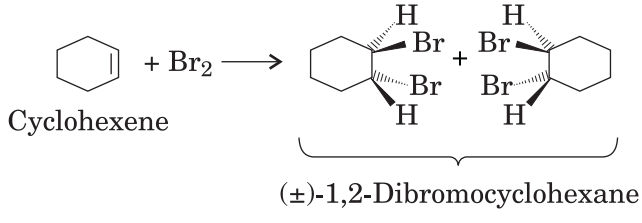
The other enantiomers of the *erythro*- and *threo*-forms are obtained when Br_2 adds to the other face of the alkene. The transition state leading to the formation of the *threo*-isomer is relatively less stable due to steric reason (*p*-$MeOC_6H_4$- and CH_3- groups are *gauche* to each other) and for this reason, it is obtained as the minor product.

1.1.4.9 Effect of solvent on the stereoselectivity of a reaction

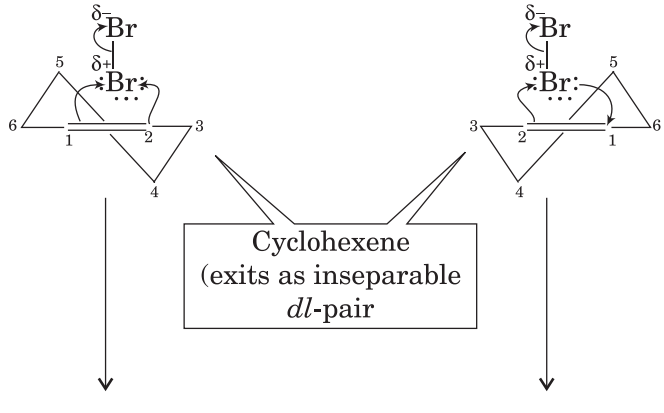
The ionizing power and ion-solvating ability of solvents increase with increase in their dielectric constants (ε). Therefore, a carbocation is more stabilized by a solvent having high dielectric constant than by a solvent having low dielectric constant. A stable carbocation gets sufficient time for undergoing free rotation about the single bond. Because of this, with an increase in dielectric constant of the solvent used, the population of the carbocation undergoing nucleophilic attack after bond rotation to yield the *syn*-addition product increases and the reaction becomes progressively less stereoselective. For example, *cis*-stilbene undergoes 100 percent *anti*-addition of Br_2 in cyclohexane having a very low dielectric constant (ε = 2.0), 77 percent in *tert*-butyl alcohol having somewhat higher dielectric constant (ε = 11) and 52 percent in nitromethane having considerably higher dielectric constant (ε = 35).

1.1.4.10 Mechanism and the Stereochemical Course of Addition of Bromine to Cyclohexene

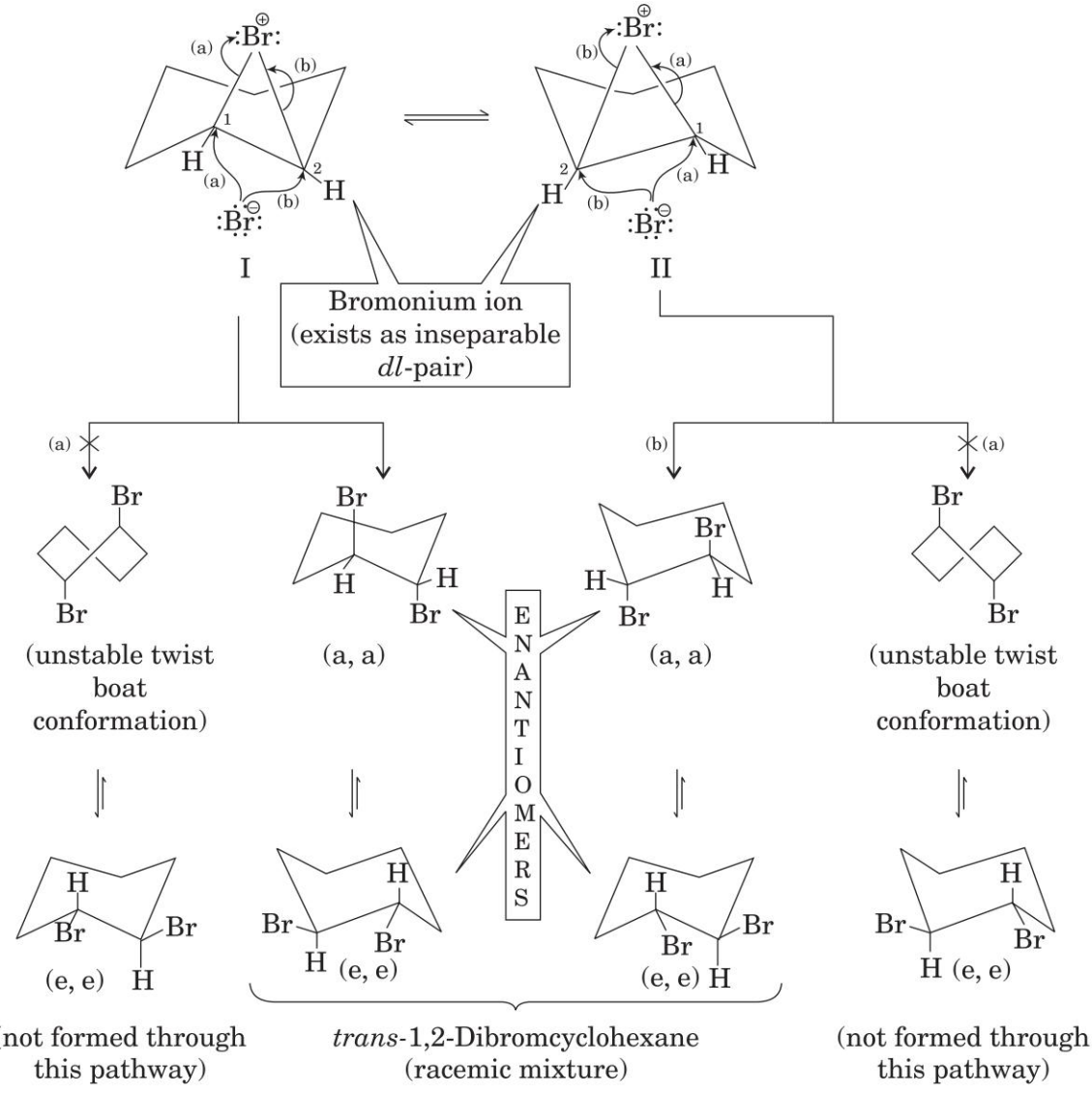
Cyclohexene adds to bromine to yield 1,2-dibromocyclohexane. *Anti*-addition occurs to give actually the racemic mixture of *trans*-1,2-dibromocyclohexane.



Bromine adds to cyclohexene through the steps as follows:



(Contd.)

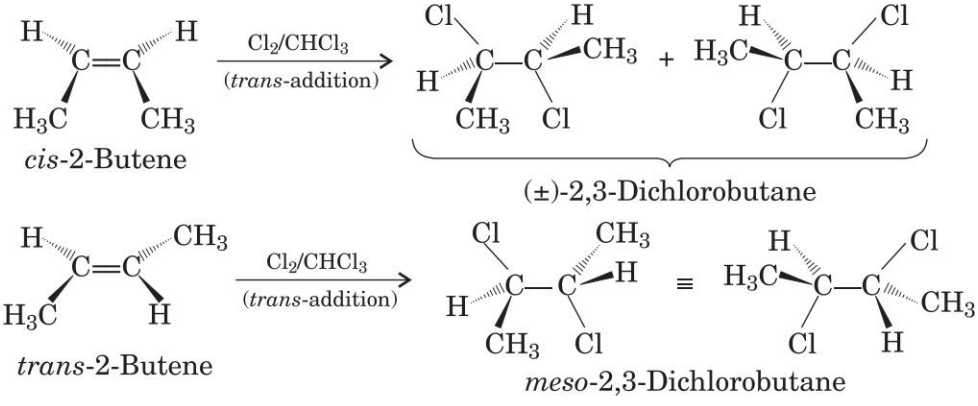


In the first step, a bromine molecule transfers a bromine atom to cyclohexene to form a bromonium ion. In the second step, a bromide ion attacks the back side of C-2 (an S_N2 process) in form I or II of the bromonium ion to produce the diaxial conformer of *trans*-1,2-dibromocyclohexane. This is rapidly converted into the more stable diequatorial form and when equilibrium is reached, the diequatorial form predominates. Nucleophilic attack at C-1 in I or II may also result in the formation of the diequatorial form, but the reaction does not proceed through this energetically unfavourable pathway involving a high energy twist boat conformation. The stereochemical outcome of the reaction is racemization because the two enantiomers of *trans*-1,2-dibromocyclohexane are formed in equimolar amounts.

SOLVED PROBLEMS

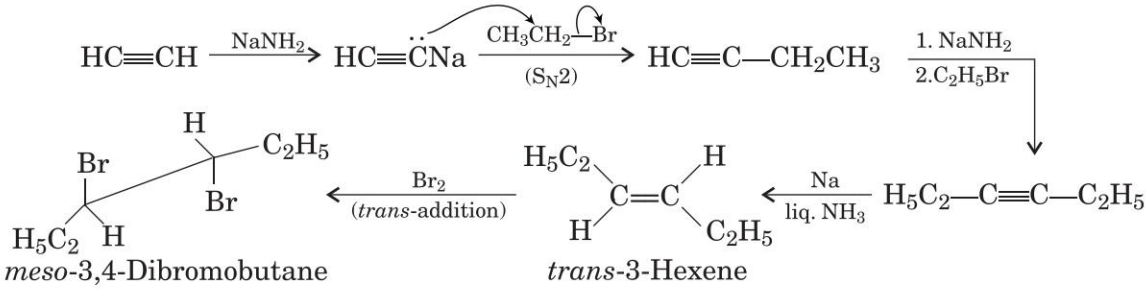
1. What is called a stereospecific reaction? Give an example.

Solution A stereospecific reaction is one in which the stereochemically different starting materials lead to stereochemically different products. For example, *cis*-2-butene undergoes chlorination to give only (±)-2,3-dichlorobutane while *trans*-2-butene undergoes chlorination to give only *meso*-2,3-dichlorobutane. Since the two diastereoisomeric 2-butenes produce two different stereoisomeric products, the reaction is a stereospecific one.



2. Starting from acetylene outline a stereospecific synthesis of *meso*-3,4-dibromohexane.

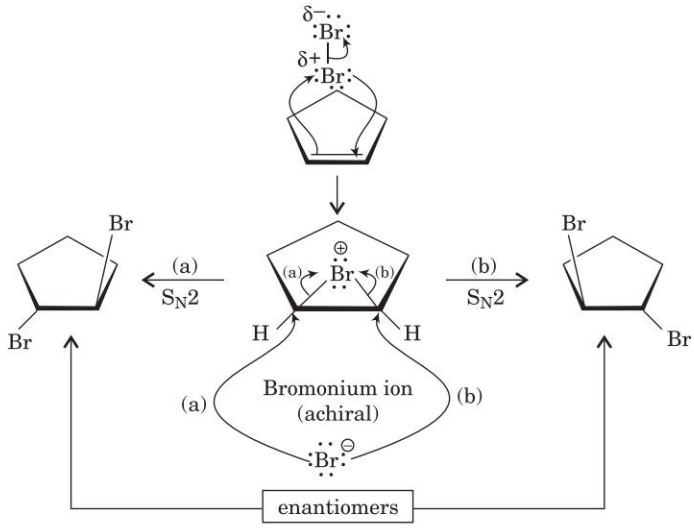
Solution



3. Predict the product and the stereochemical outcome of the following reaction:

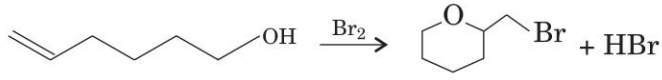
$$\text{Cyclopentene} + Br_2 \longrightarrow$$

Solution Cyclopentene reacts with Br_2 to give *trans*-1,2-dibromocyclopentane (a racemic mixture) as follows:

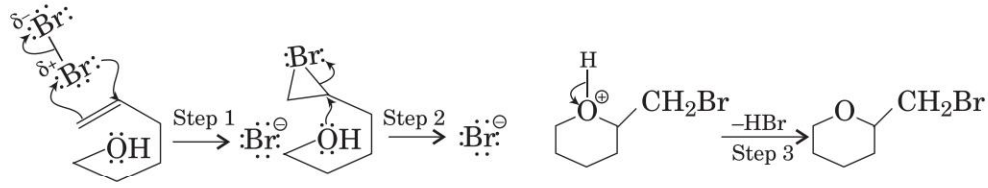


trans-1,2-Dibromopentane
(a racemic mixture)

4. The addition of the elements Br and OR to a double bond is a common method for constructing ring containing oxygen atoms. The reaction is called bromoetherification. Draw a stepwise mechanism for the following intramolecular bromoetherification reaction:

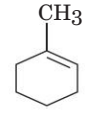


Solution The reaction proceeds through the steps as follows:



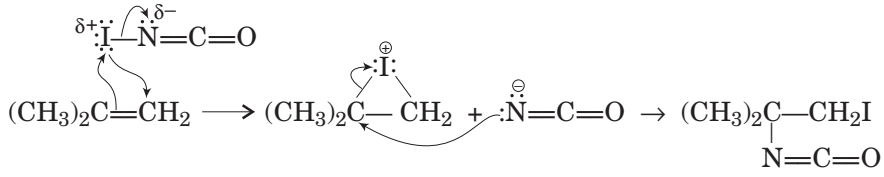
In step 1, a bromonium ion is formed. In step 2, the bromonium ion undergoes intramolecular nucleophilic attack by –OH at the more substituted carbon (because it is more positive and hence, more electrophilic) to yield the conjugate acid of a cyclic ether. In step 3, loss of proton occurs to form the ether.

5. Predict the product and suggest a mechanism for each of the following reactions:

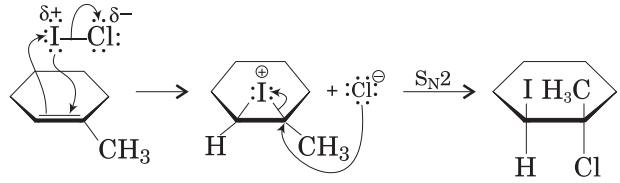
(a) $(CH_3)_2C{=}CH_2 + I{-}N{=}C{=}O \longrightarrow$ (b)  + ICl $\longrightarrow$

Solution

(a) In this case, iodoisocyanate is formed. The reaction occurs as follows:

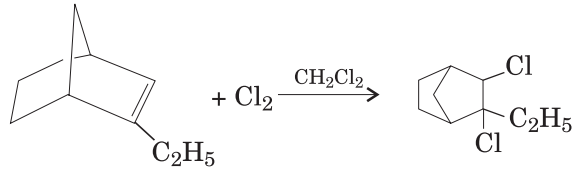


(b) *Anti*-addition of I Cl occurs to give the corresponding product as follows:

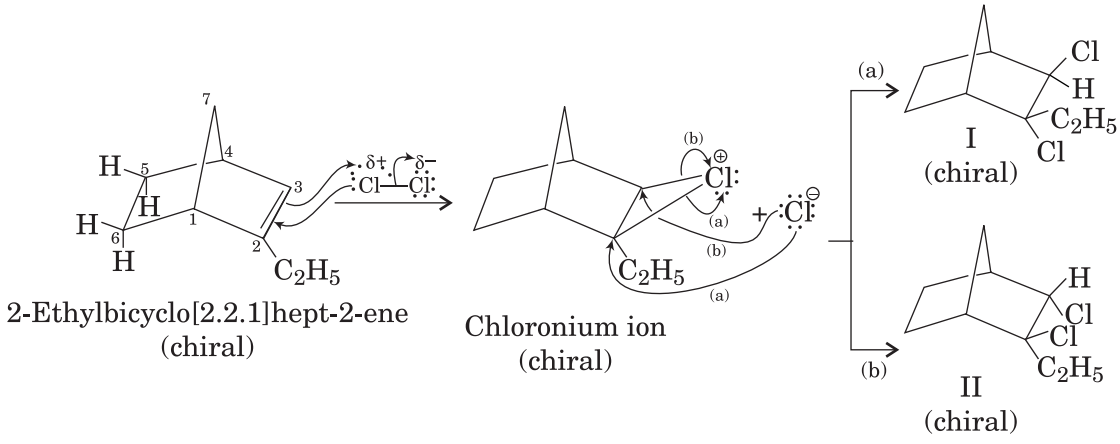


Since chlorine is more electronegative than iodine, therefore, iodine is the electrophilic end of the $\overset{\delta+}{I}—\overset{\delta-}{Cl}$ molecule. As a consequence, an iodonium ion is formed in the first step of the reaction. In the second step, $Cl^{\ominus}$ ion attacks the more substituted and more positive (electrophilic) ring carbon to give the product.

6. Give the mechanism and the stereochemical outcome of the following reaction:



Solution The starting bridgehead alkene is chiral and so, *trans*-addition of Cl_2 involving a chloronium ion intermediate leads to the formation of two optically active, i.e., chiral diastereoisomer I and II. Attack by Cl_2 from the opposite face of the double bond does not take place because of steric crowding caused by the boat-axial or *endo* hydrogens at C-5 and C-6.



2-Ethylbicyclo[2.2.1]hept-2-ene (chiral)

Chloronium ion (chiral)

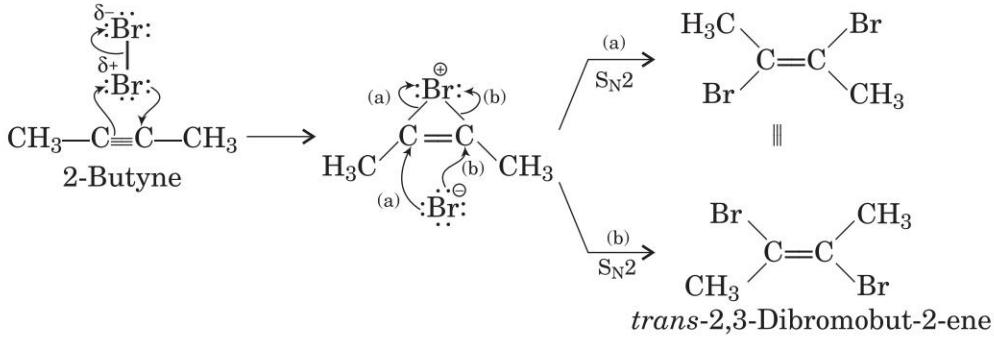
I (chiral)

II (chiral)

7. Give the mechanism of the following reaction and explain why it is slower than as compared to alkenes:

$$CH_3—C\equiv C—CH_3 \xrightarrow{Br_2} \textit{trans}\text{-}CH_3CBr{=}CBrCH_3$$

Solution The mechanism of the reaction is as follows:

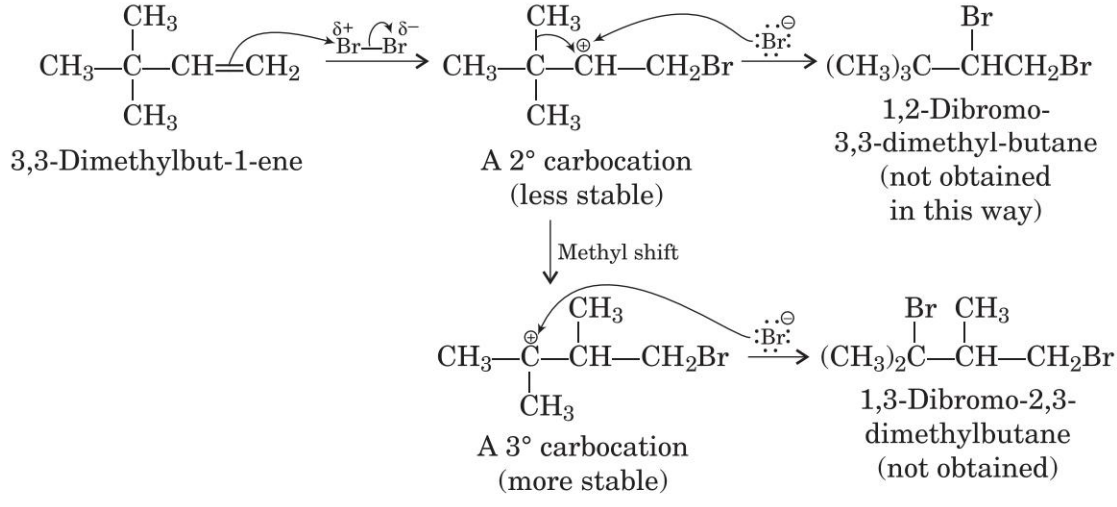


The reason for the low reactivity of an alkyne is that the intermediate bromonium ion has a double bond and the ring is highly strained as compared to the bromonium ion obtained form an alkene.

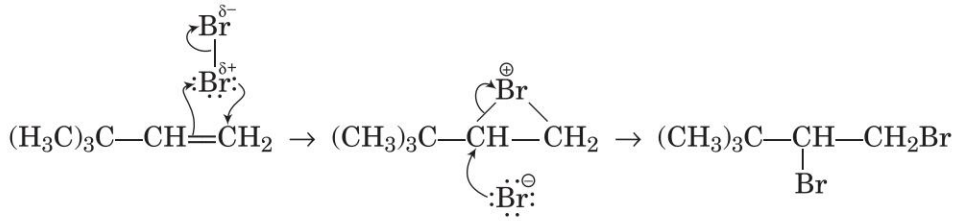
8. How can it be proved that the following reaction involves a bromonium ion intermediate instead of an open carbocation?

$$(CH_3)_3C—CH{=}CH_2 \xrightarrow{Br_2} (CH_3)_3C—CHBrCH_2Br$$

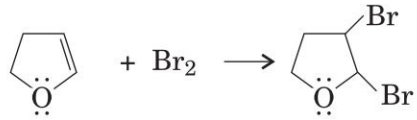
Solution If an open carbocation is involved, the reaction is expected to give 1,3-dibromo-2,3-dimethylbutane along with 1,2-dibromo-3,3-dimethylbutane. However, the former compound is not at all obtained. This observation suggests that the reaction proceeds through a bromonium ion intermediate instead of an open carbocation.



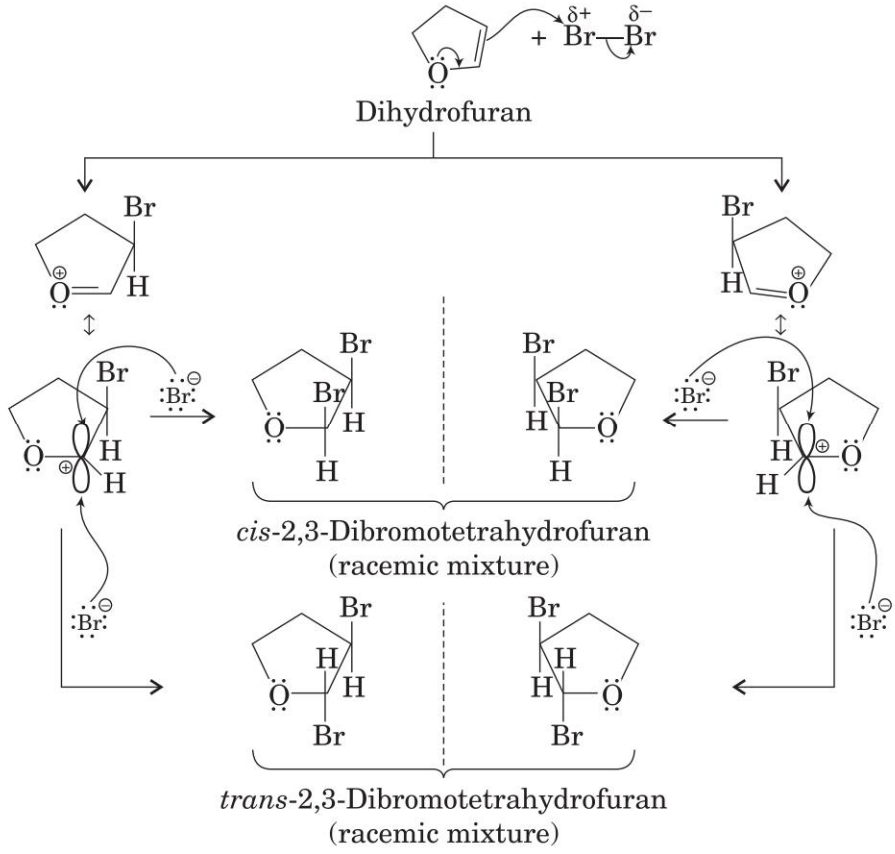
The reaction actually occurs as follows to give only 1,2-dibromo-3,3-dimethylbutane.



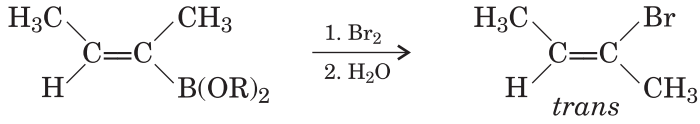
9. Give the mechanism and the stereochemical course involved in the following reaction:



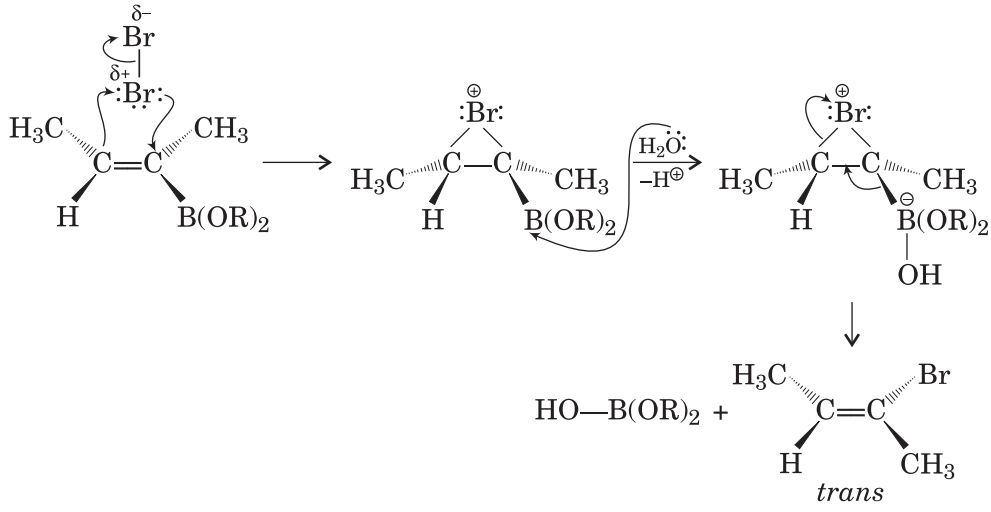
Solution Dihydrofuran undergoes electrophilic attack by Br_2 to give initially a resonance-stabilized carbocation instead of a bromonium ion as intermediate. The bromide ion ($Br^{\ominus}$) then attacks the carbocation from its two faces to give *cis*- and *trans*-2,3-dibromotetra hydrofuran which are two diastereoisomers. Each diastereoisomer is obtained as a racemic mixture. The reaction proceeds as follows:



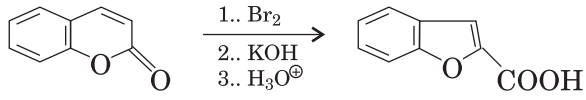
10. Suggest a mechanism for the following reaction:



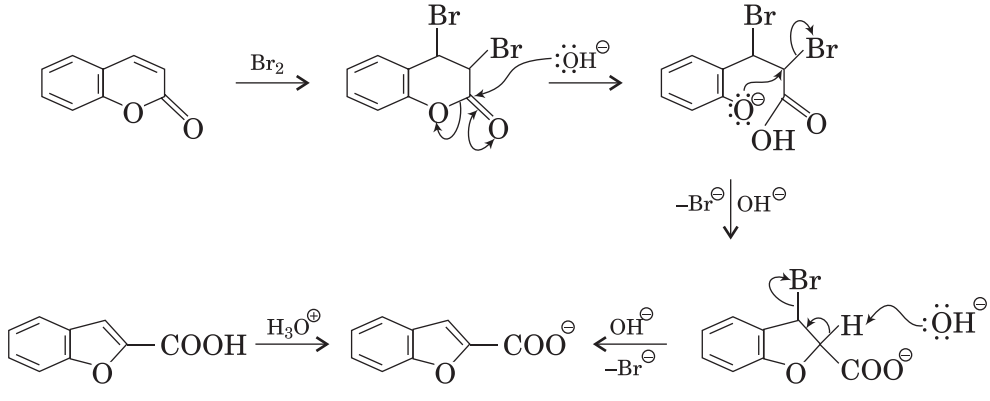
Solution The mechanism of the reaction involves the steps as follows:



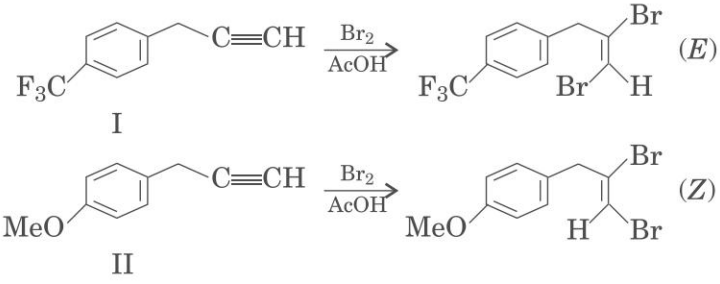
11. Explain the formation of the product:



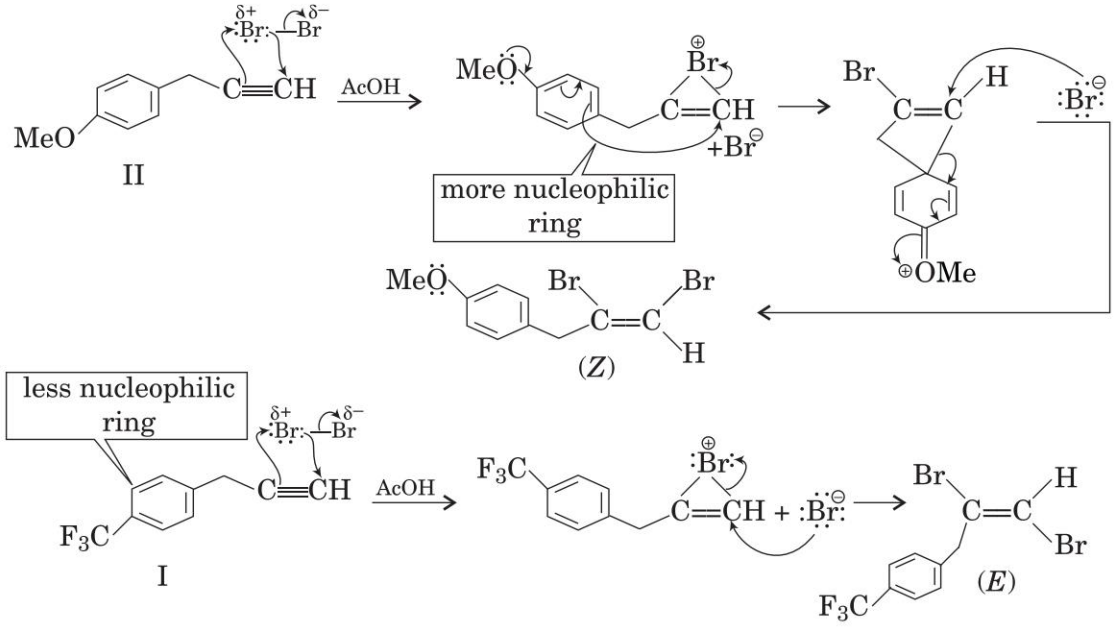
Solution



12. Provide mechanisms that explain the formation of the following products:



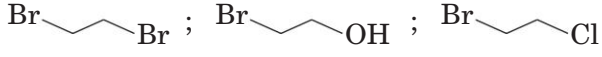
Solution The mechanistic courses of these two reactions may be given as follows:



Unlike the first case, the ring does not participate due to the presence of the electron-withdrawing $-CF_3$ group.

Study Problems

1. When ethylene is passed through an aqueous solution of bromine containing NaCl, the products of the reaction are as follows:

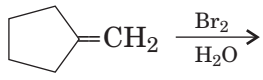


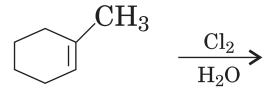
Write mechanisms to show the formations of these products.

2. Arrange the following compounds in order of increasing rate of addition to ethylene and give your reasoning:

I—I, I—Br, I—Cl

3. Draw the structural isomers expected to be formed in each of the following reactions:

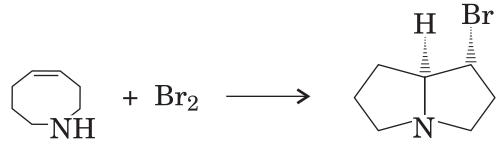
(a) 

(b) 

4. *Cis*- and *trans*-2-pentene reacts with Br_2 to yield two pairs of enantiomers. Explain.

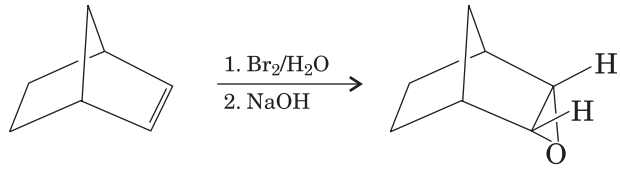
[Hint: The *cis*-isomer yields (*R,R*) and (*S,S*) enantiomers, while the *trans*-isomer yields (*R, S*) and (*S, R*) enantiomers. See also **article no. 4.2.4.5**.]

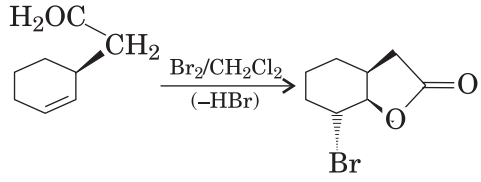
5. Account for the following observation:



[Hint: Formation of a bromonium ion followed by intramolecular S_N2.]

6. Give mechanism of each of the following reactions:

(a) 

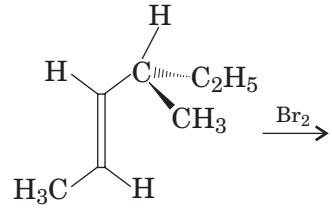
(b) 

[Hint:

(a) Formation of a *trans*-bromohydrin followed by an intramolecular S_N2 involving alkoxy oxygen.

(b) Formation of a bromonium ion followed by an intramolecular S_N2.**]**

7. Give the mechanism and the stereochemical outcome of the following reaction:

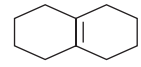


8. Account for the following observations:

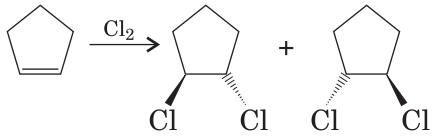
(a) Addition of bromine to vinyl chloride ($CH_2{=}CHCl$) occurs at a faster rate in acetic acid medium than in CCl_4 medium.

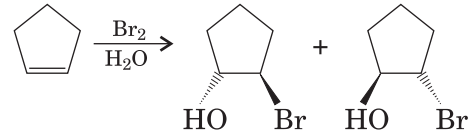
(b) When treated with Br_2/H_2O, allyl bromide gives chiefly the primary alcohol, $BrCH_2CHBrCH_2OH$, in contrast, propene under the same reaction conditions gives the secondary alcohol, $CH_3CHOHCH_2Br$.

9. Predict the major product and suggest a mechanism for each of the following reactions:

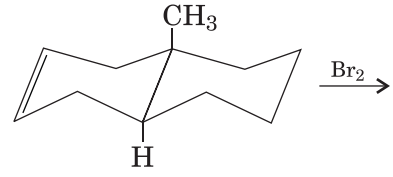
(a) $CH_3CH{=}CHCH_3 + CH_3SCl \longrightarrow$ (b)  + NOCl $\longrightarrow$

10. Draw a stepwise mechanism for each of the following reactions:

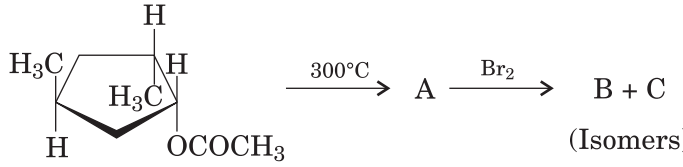
(a) 

(b) 

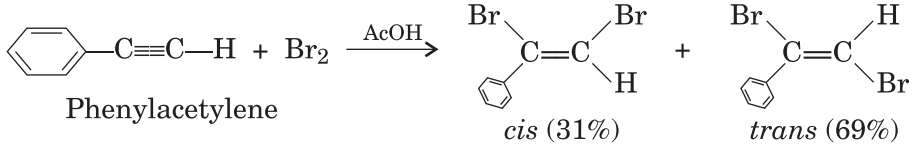
11. Draw the product(s) of each of the following reactions, including stereochemistry:

(a) $HO_2C{-}C{\equiv}C{-}CO_2H \xrightarrow[(1\ mole)]{Br}$ (b) 

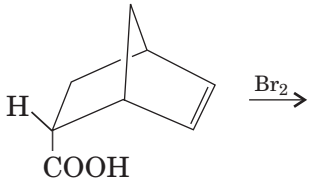
12. Identify the compounds A, B and C. Give mechanisms for these conversions.

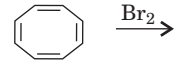


13. Addition of bromine to acetylenes give only *trans*-dibromides. However, phenylacetylene gives both *cis*- and *trans*-dibromides. Explain this observation.



14. Predict the product(s) and suggest a mechanism for each of the following reactions:

(a) 

(b) 

15. Bromine adds to 2-butene at a faster rate in the presence of the Lewis acid $AlBr_3$, but at a slower rate in the presence of KBr. Account for these observations.

[Hint: $AlBr_3$ polarizes Br_2 molecule to a greater extent and as a result electrophilic addition takes place more easily. In the presence of KBr, Br_2 combines with $Br^{\ominus}$ to form the complex polyhalide ion $Br_3^{\ominus}$. As a result, the tendency of Br_2 molecule to act as an electrophile decreases.]

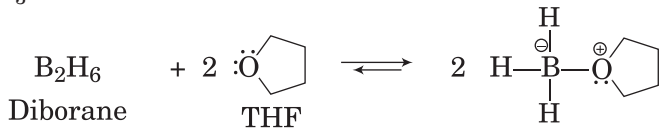
1.1.5 Hydroboration-Oxidation

1.1.5.1 Hydroboration

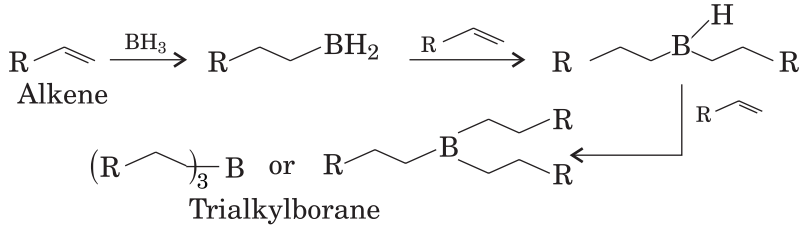
Borane (BH_3), a neutral molecule, is electrophilic in nature because boron has an empty 2*p* orbital and therefore, readily accepts a pair of electrons in order to have complete octet.

The addition of borane to an alkene is called hydroboration.

Hydroboration of an alkene can be accomplished with diborane (B_2H_6), a gaseous dimer of borane (BH_3) or more conveniently with a reagent prepared by dissolving diborane in tetrahydrofuran (THF). When diborane is added to THF, it reacts to form a Lewis acid-base complex of borane (the Lewis acid) and THF (the Lewis base). The complex is represented as BH_3 : THF.



Although borane, BH_3, is unknown, its dimer B_2H_6 undergoes additions as if it were the monomer. Borane (BH_3) can add to a carbon–carbon double bond since it is strong electrophile. Furthermore, as BH_3 has three B – H bonds, it can add to as many as three carbon-carbon double bonds to give a trialkylborane. Being electron deficient the boron atom preferentially attacks the most electron rich doubly bonded carbon atom.



1.1.5.2 Anti-Markownikoff's Hydration of alkenes (hydroboration-Oxidation)

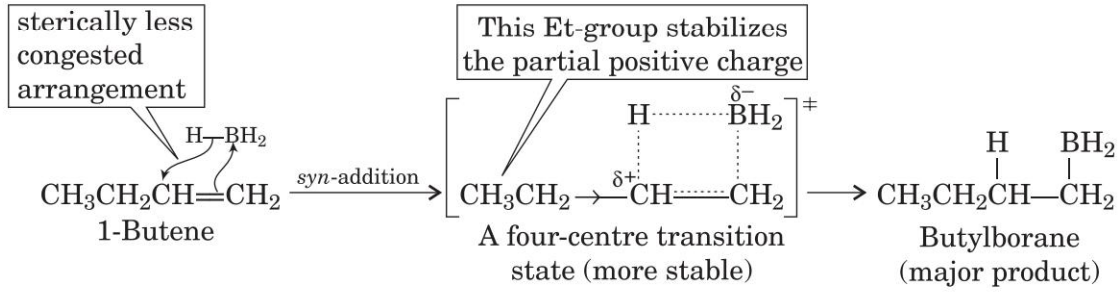
Hydration of an unsymmetrical alkene in *anti*-Markownikoff fashion can be effected by an indirect, convenient and high yielding process known as hydroboration-oxidation. The process involves addition of borane (BH_3) to the double bond followed by oxidation and hydrolysis of the resulting alkyl borane with alkaline solution of hydrogen peroxide. For example:

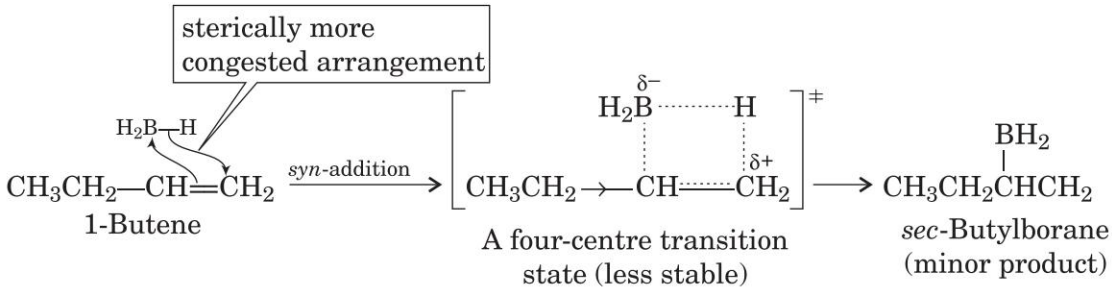
$$3\underset{\text{1-Butene}}{CH_3CH_2CH=CH_2} \xrightarrow[THF/0°C]{BH_3} (CH_3CH_2CH_2CH_2)_3B$$

$$\xrightarrow[NaOH/H_2O]{H_2O_2} 3\underset{\text{1-Butanol}}{CH_3CH_2CH_2CH_2OH} + Na_3BO_3$$

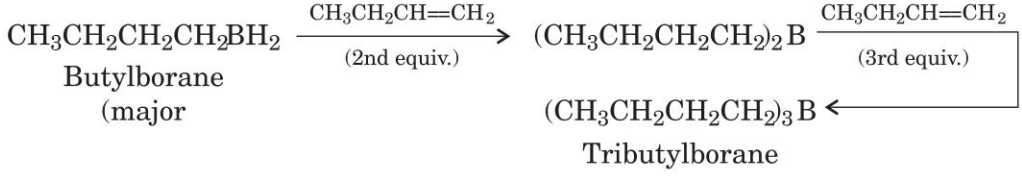
Mechanism of hydroboration: Because of the tendency of boron to accept an electron pair for completing its octet and also, because H is more electronegative than B, the B—H bond is polarized to give boron a partial positive charge ($\overset{\delta-}{H}—\overset{\delta+}{B}$), making BH_2 the electrophile and H the nucleophile in hydroboration reaction. As boron accepts the π electrons from the alkene, it eliminates a hydride ion that also adds to alkene. However, unlike the addition of Br_2, HBr, H_2O, etc. the addition of borane to an alkene takes place in one step, i.e., it is a concerted reaction in which all the bond-breaking and bond-making processes occur in a single step. The electrophilic boron atom adds to the sp^2 carbon that is bonded to most hydrogens. The addition, in fact, occurs through a four-centre transition state. A π-complex is formed initially by a donation of π electrons of the double bond to the vacant p orbital on boron. The π-complex then forms the transition state in which the boron atom is partially bonded to the less substituted doubly bonded carbon atom and the H atom is partially bonded to the more substituted doubly bonded carbon atom. As the transition state is approached, shifting of electrons in the direction of B atom and away from the more substituted C atom of the double bond occurs. As a consequence, the more substituted carbon atom, which is better able to accommodate positive charge, acquires a partial positive charge. This results in a relatively stable transition state that leads to the formation of Markownikoff addition product (because the negative part of the addendum adds to the carbon containing least number of hydrogens) predominantly.

Also, steric hindrance associated with alkylborane and particularly with dialkylborane causes the addition of boron to occur at the sp^2 carbon that is bonded to the most hydrogens because that is the less sterically hindered of the two sp^2 carbons. Therefore, the orientation of BH_3 addition is favoured not only by electronic factor but also by steric factor.

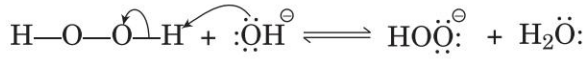




The resulting alkylborane in which boron contains two more hydrogens reacts in a similar way with 2nd and 3rd equivalent of 1-butene to form di- and tributylborane respectively.



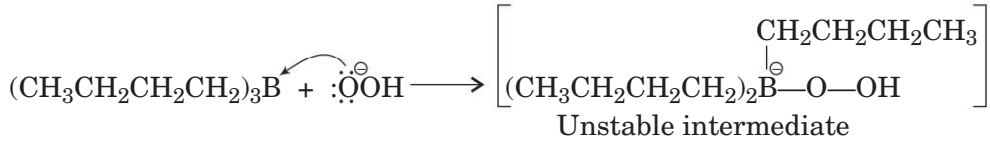
Mechanism of oxidation: When the hydroboration reaction is over, aqueous sodium hydroxide and hydrogen peroxide (H_2O_2) are added to the reaction mixture. Hydrogen peroxide reacts with alkali to form hydroperoxide ion $HO\ddot{O}:^{\ominus}$.



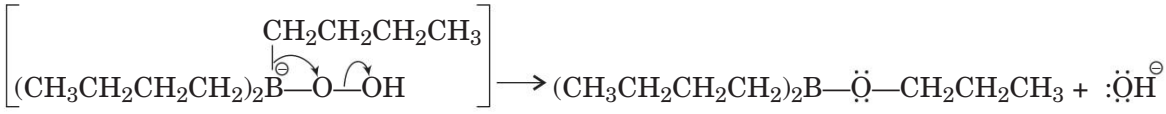
The end result is the replacement of boron in alkyl borane by an OH group. Because the replacement of boron by an OH group is an oxidation reaction (oxygen is being added to the compound), the overall reaction is called hydroboration-oxidation.

The mechanism of oxidation of the trialkylborane involves the steps as follows:

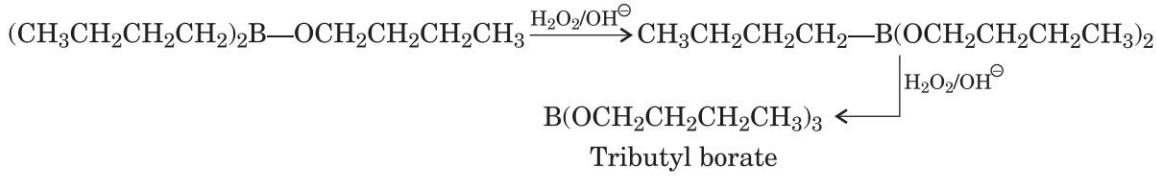
Step 1: This involves nucleophilic attack by the hydroperoxide ion on the electron-deficient boron atom of the trialkylborane molecule to give an unstable tetracovalent boron intermediate.



Step 2: The resulting compound undergoes rearrangement. An alkyl group migrates with its bonding electrons from boron to oxygen (a 1,2-anionic shift) and thereby displaces a hydroxide ion to form a borinic ester. The driving force for the rearrangement is the formation of the strong boron–oxygen bond.

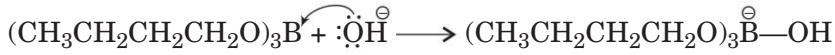


The sequence is repeated twice to yield a trialkyl borate ester.

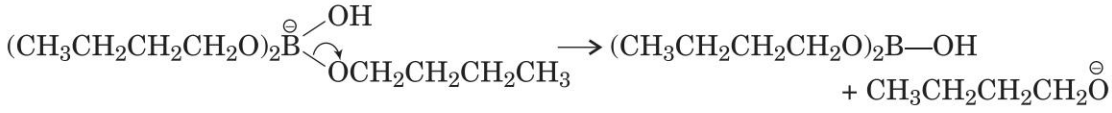


The borate ester is finally hydrolyzed by alkali. The reaction involves the steps as follows:

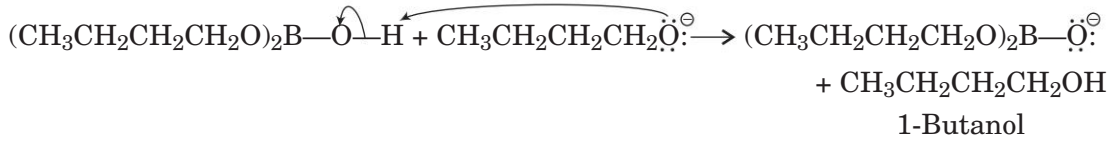
Step 1: The borate ester undergoes nucleophilic attack by the $OH^{\ominus}$ ion.



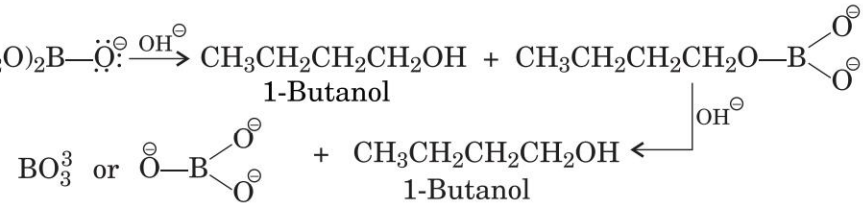
Step 2: An alkoxide ion departs from the borate anion, reducing the formal charge on boron to zero.



Step 3: A molecule of 1-butanol is obtained as a result of proton transfer.

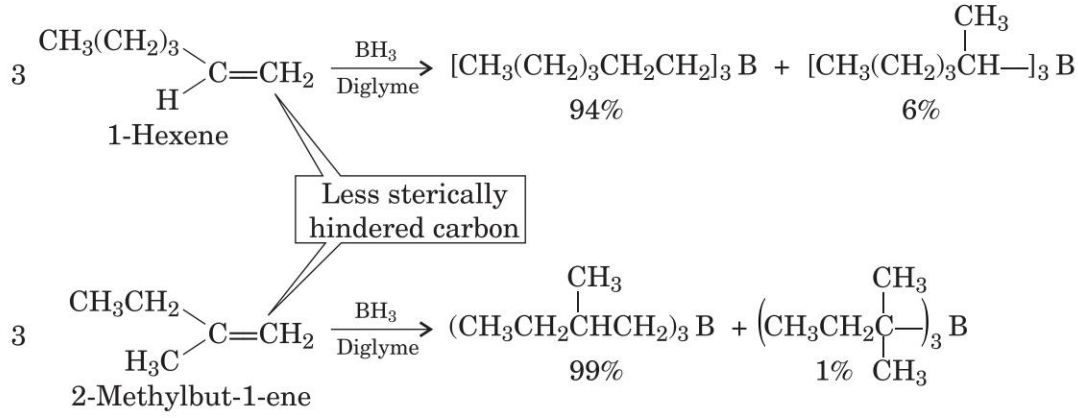


The three preceding steps are repeated two times to give two more equivalent of 1-butanol.



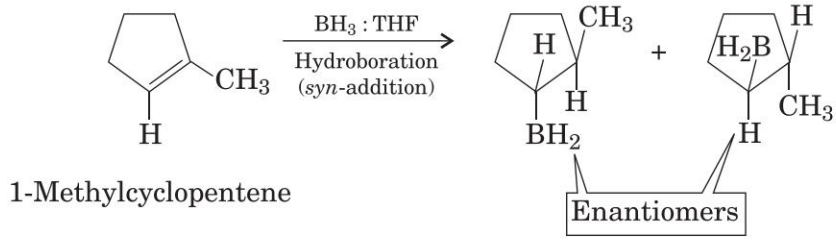
1.1.5.3 Regiochemistry of Hydroboration-Oxidation

Hydroboration is regioselective and therefore, hydroboration-oxidation reactions are regioselective. The boron atom usually bonds to the less substituted carbon atom and the hydrogen atom to the more substituted carbon atom. The regioselectivity is caused mostly by steric factors, although electronic factors also play a part. For example:

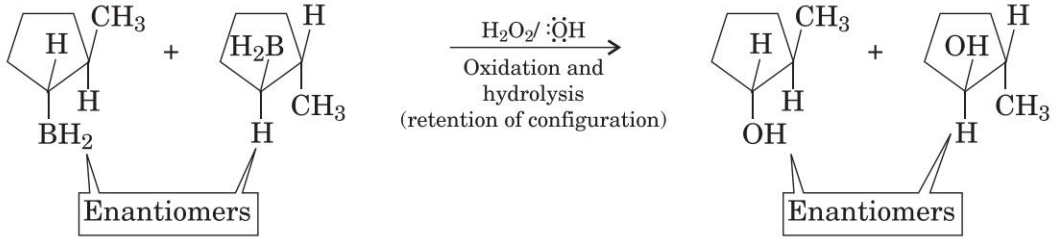


1.1.5.4 Stereochemistry of Hydroboration-Oxidation

Since the addition of borane (BH_3) to the double bond of an alkene is a one-step (concerted) process involving a four-atom transition state, therefore, the boron atom and the hydrogen atom add to the same face of the double bond. Thus, hydroboration results in *syn*-addition of –H and the $–BH_2$ group. When 1-methylcyclopentene, for example, is allowed to react with BH_3 in THF, a mixture of two enantiomers is obtained as a result of top face and bottom face addition of BH_3.



In oxidation of alkylborane followed by hydrolysis, the boron atom is replaced by a hydroxyl group with retention of configuration, i.e., the hydroxyl group replaces the boron atom where it stands in the alkylborane.



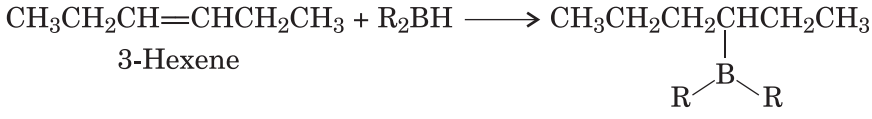
The net result of the two steps (hydroboration and oxidation) is the *syn*-addition of –H and –OH. Therefore, hydroboroation-oxidation reactions are stereospecific.

1.1.5.5 Isomerizations of Alkylboranes

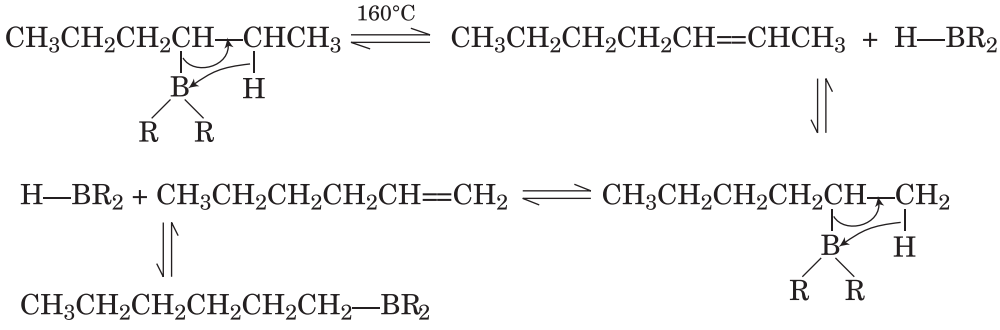
Alkylboranes undergo isomerization at higher temperatures because the hydroboration reactions are reversible at higher temperatures and there is a tendency of boron to become attached to the carbon at the end of the chain where steric crowding is minimum.

These isomerizations are synthetically useful because they enable us to convert a thermodynamically more stable internal alkene to a thermodynamically less stable terminal alkene. For example, 3-hexene ($CH_3CH_2CH{=}CHCH_2CH_3$) can be converted into 1-hexene ($CH_3CH_2CH_2CH_2CH{=}CH_2$) through the steps as follows:

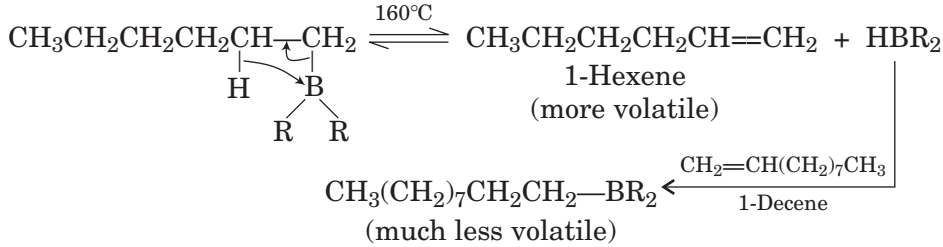
Step 1: Hydroboration of 3-hexene is carried out by treating with a suitable dialkylborane (e.g., disiamylborane; R_2BH, where $R{=}Me_2CHCHMe–$).



Step 2: The resulting alkylborane is then isomerized by heating. The isomerization, which takes place through a sequence of elimination-addition reactions, leads to formation of another alkylborane in which boron is attached to the terminal carbon of the chain.



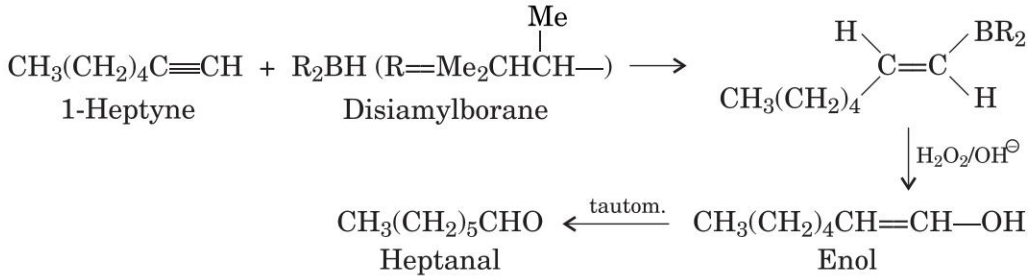
Step 3: The isomerized alkylborane is then heated with the high-boiling alkene 1-decene, $CH_2{=}CH(CH_2)_7CH_3$,(bp 170°C) when it dissociates to give 1-hexene and the starting dialkylborane (R_2BH). 1-Decene adds to R_2BH as it generates and converts it to a much less volatile alkylborane. The more volatile 1-hexene (bp <170°C) is removed by simple distillation.



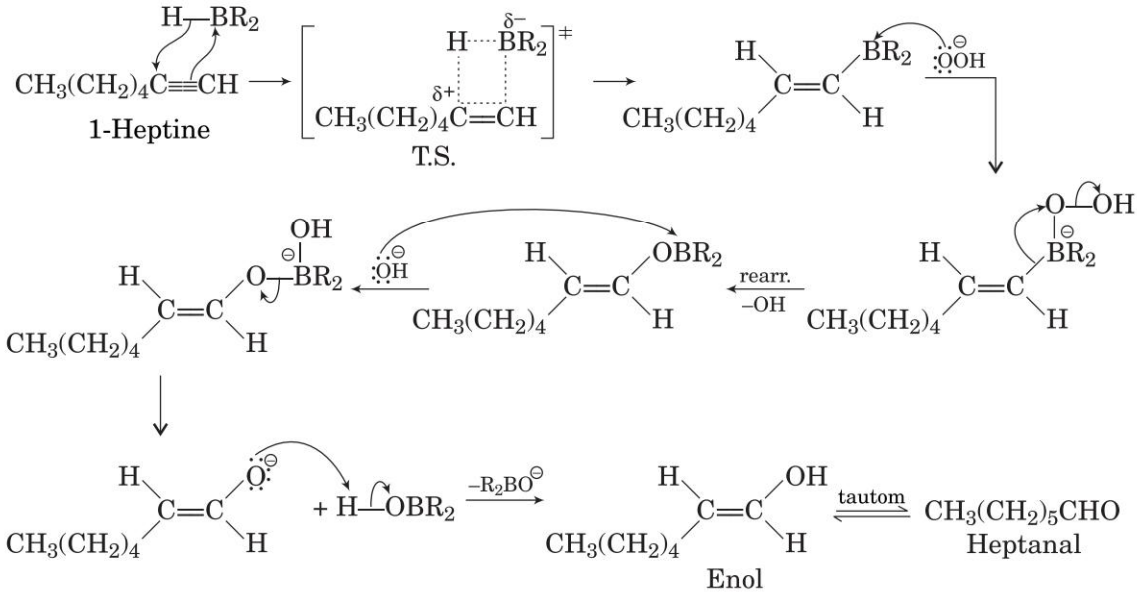
1.1.5.6 Synthetic Uses of Hydroboration Reaction

A number of conversions can be carried out by using the hydroboration reaction. These are as follows:

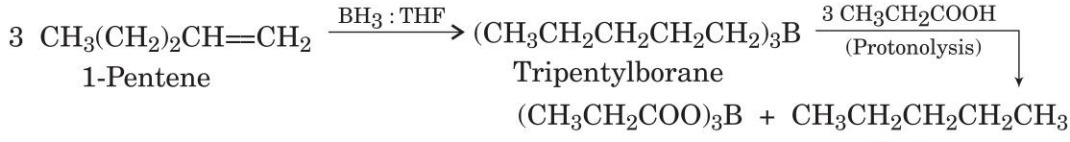
(a) **Conversion of a terminal alkyne to an aldehyde:** A terminal alkyne can be converted to the corresponding aldehyde by carrying out its hydroboration with di(3-methyl-2-butyl) borane or disiamylborane (Sia_2BH) followed by oxidation and hydrolysis of the resulting vinylborane with alkaline hydrogen peroxide (the name 'disiamyl' comes from 'di-secondary-iso-amyl'). This crowded borane is a very selective hydroborating agent. When it reacts with the terminal alkyne, boron becomes attached to the less crowded terminal carbon predominantly. Also, hydroboration, which cannot be stopped at the alkenylborane stage by using BH_3:THF, can be stopped by using Sia_2BH. 1-Heptyne, for example, can be converted into heptanol as follows:



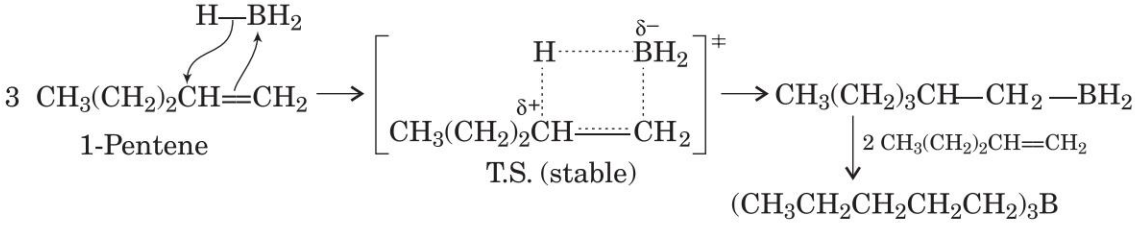
Mechanism:



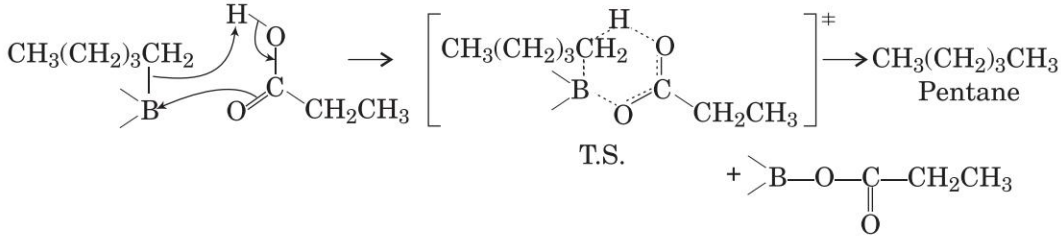
(b) **Conversion of an alkene to the corresponding alkane:** When an alkene is subjected to hydroboration by treating with BH_3: THF followed by treatment of the resulting alkylborane with anhydrous propanoic acid (CH_3CH_2COOH), an alkane is obtained. For example, 1-pentene can be converted into pentane as follows:



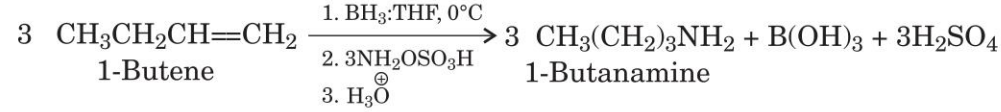
Mechanism:



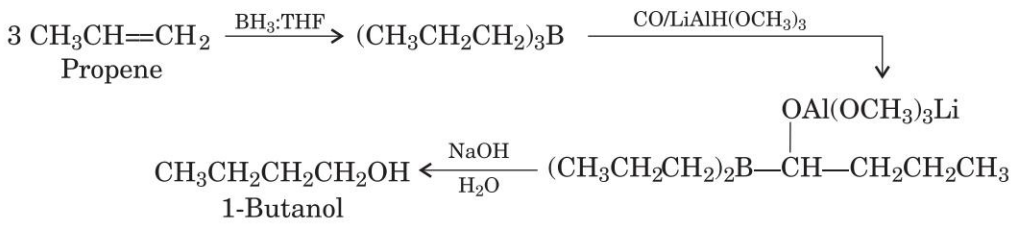
The trialkylborane undergoes protonolysis concertedly through a six-membered cyclic transition state to give pentane, when treated with propaonic acid.



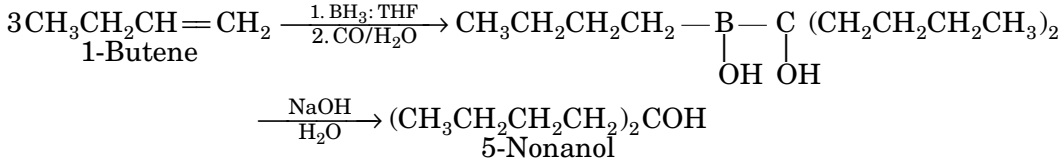
(c) **Conversion of an alkene to a primary amine:** When an alkene is subjected to hydroboration and the resulting alkylborane is treated with hydroxylamine-O-sulphonic acid, H_2NOSO_3H, an intermediate ammonium boride is obtained. This undergoes rearrangement to give a compound which on acidic hydrolysis produces the primary amine. For example, 1-butene can be converted into 1-butanamine as follows:



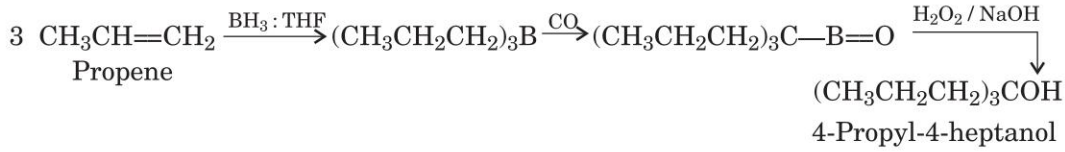
(d) **Conversion of an alkene into a primary alcohol with one more carbon atom:** An alkene can be converted into a primary alcohol with one more carbon atom by carbonylation of the corresponding alkylborane in the presence of lithium trimethoxyaluminium hydride [$LiAlH(OCH_3)_3$] followed by alkaline hydrolysis of the resulting compound. For example, propene can be converted into 1-butanol ($CH_3CH_2CH_2CH_2OH$) as follows:



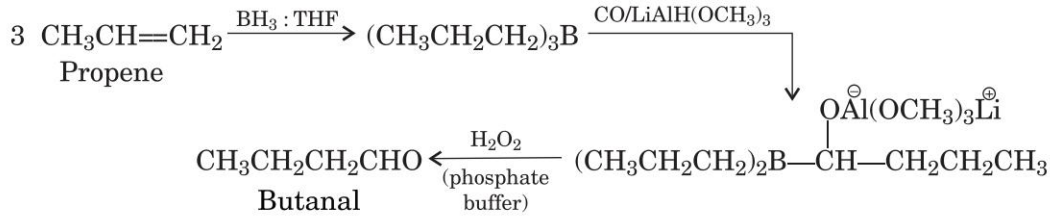
(e) **Conversion of an alkene into a secondary alcohol:** An alkene can be converted into a secondary alcohol containing (2 × no. of carbon atoms in the alkene +1) carbon atoms by carbonylation of the corresponding alkylborane in the presence of water followed by hydrolysis of the resulting compound. For example, 1-butene can be converted into 5-nonanol [$(CH_2CH_2CH_2CH_2)_2CHOH$] as follows:



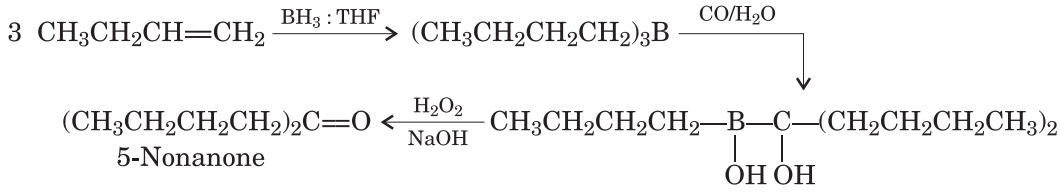
(f) **Conversion of an alkene into a tertiary alcohol:** An alkene can be converted into a tertiary alcohol containing (3 × no. of carbon atoms of the alkene +1) carbon atoms by carbonylation of the corresponding alkylborane followed by oxidation and hydrolysis of the resulting compound. For example, propene can be converted into 4-propyl-4-heptanol [$(CH_3CH_2CH_2)_3COH$] as follows:



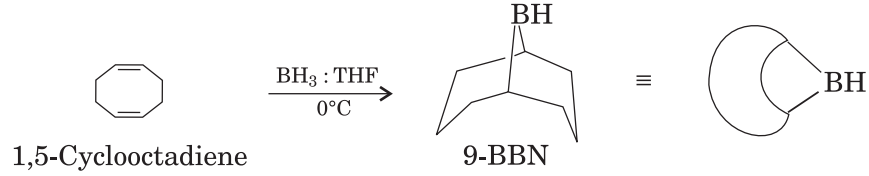
(g) **Conversion of an alkene into an aldehyde:** An alkene can be converted into an aldehyde with one more carbon atom by carbonylation of the corresponding alkylborane in the presence of lithium trimethoxyaluminium hydride followed by oxidation and hydrolysis of the resulting compound with H_2O_2 (pH 7). For example, propene can be converted into butanal ($CH_3CH_2CH_2CHO$) as follows:



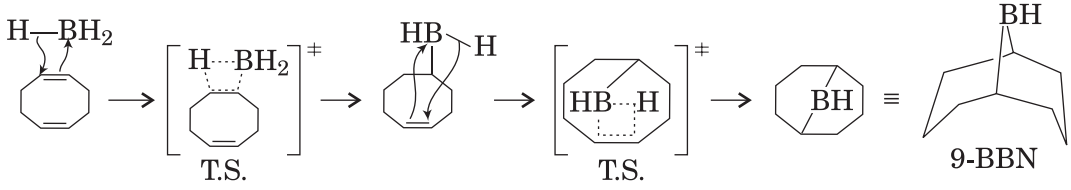
(h) **Conversion of an alkene into a ketone:** An alkene can be converted into a ketone containing (2 × no. of carbon atoms of the alkene +1) carbon atoms by carbonylcation of the corresponding alkyl borane in the presence of water followed by oxidation and hydrolysis of the resulting compound with $H_2O_2/OH^{\ominus}$. For example, 1-butene can be converted into 5-nonanone [$(CH_3CH_2CH_2CH_2)_2C{=}O$] as follows:



(i) **9-BBN and its uses:** 9-Borabicyclo[3.3.1]nonane (commonly known as 9-BBN) can be prepared by carrying out hydroboration of 1,5-cyclooctadiene.



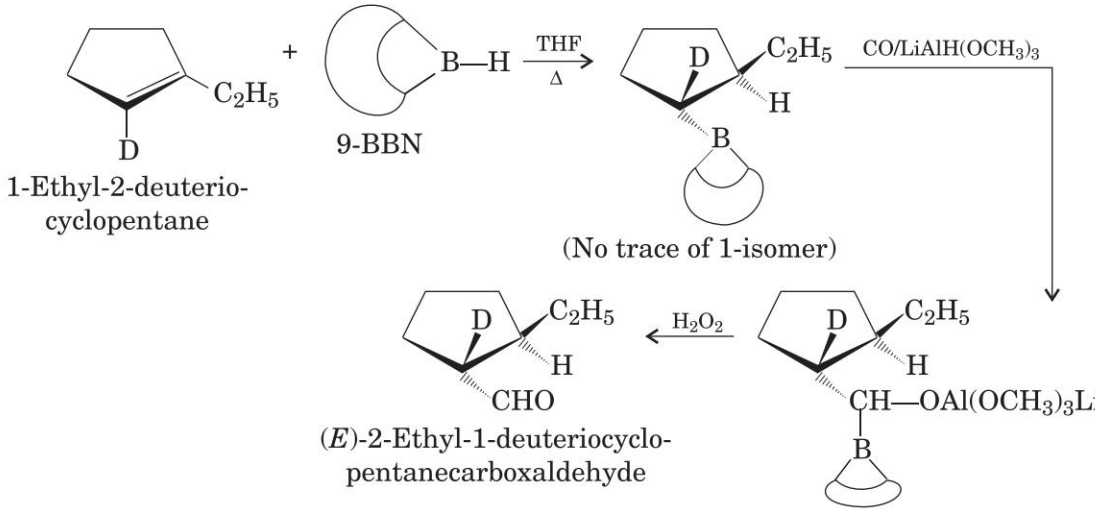
Mechanism: The mechanism of hydroboration of 1,5-cyclooctadiene to yield 9-BBN is as follows:



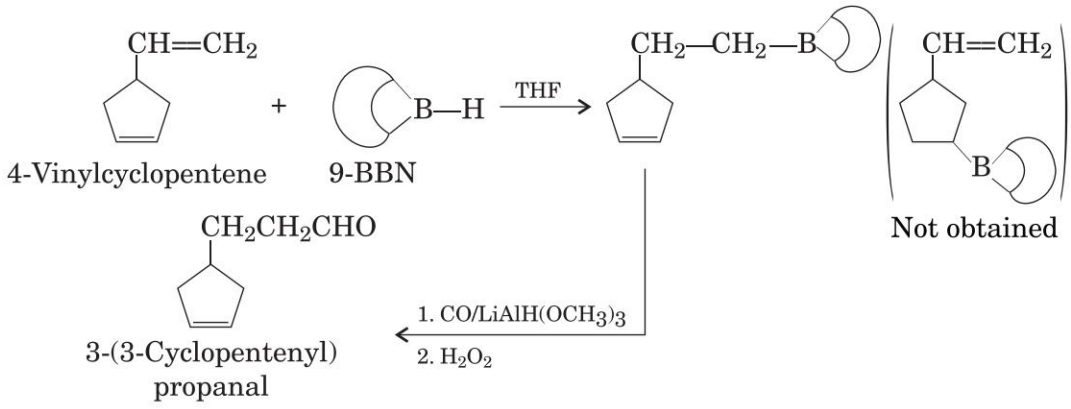
It is to be noted that hydroboration of the two double bonds of 1,5-cyclooctadiene takes place in two possible ways to give a mixture of 1,4- and 1,5-isomer. The 1,5-isomer, i.e., 9-BBN is thermodynamically more stable because it contains two stable and strain-free six-membered rings and so, it is formed predominantly.

The two important uses of 9-BBN are as follows:

(i) Only one of the three alkyl groups of a trialkylborane is converted into an aldehyde by carbonylation-reduction-oxidation sequence and the wastage of the alkene used cannot be avoided. This can, however, be avoided by carrying out hydroboration with 9-BBN. Also, a –CHO group can be much selectively introduced at the less hindered doubly-bonded carbon by using the sterically hindered reagent 9-BBN. For example:



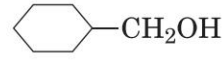
(ii) When 9-BBN is allowed to react with a compound containing two double bonds, hydroboration at the less crowded double bond takes place exclusively. For example:

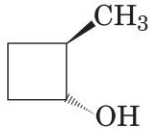


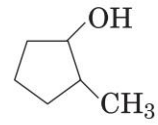
SOLVED PROBLEMS

1. Provide the structure of an alkene that would give each of the following alcohols as the major (or only) product on hydroboration-oxidation:

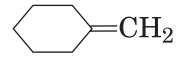
(a) $CH_3CH_2CH(CH_3)CH(CH_3)OH$

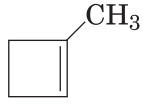
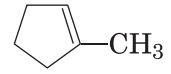
(b) 

(c) 

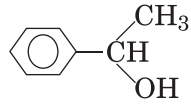
(d) 

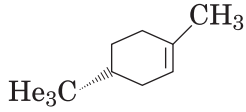
Solution

(a) $CH_3CH_2\underset{\displaystyle CH_2}{\overset{|}{C}}=CHCH_3$ (b) 

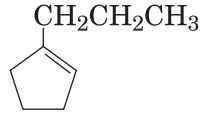
(c)  (d) 

2 Predict the product (s) in each step of the following reaction sequences. Give sterochemistry when it is appropriate.

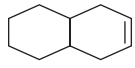
(a)  $\xrightarrow[\Delta]{H_2SO_4}$ A $\xrightarrow{BH_3 : THF}$ B $\xrightarrow{H_2O_2/OH^{\ominus}}$ C

(b)  $\xrightarrow{BH_3 : THF}$ D $\xrightarrow{H_2O_2/OH^{\ominus}}$ E

(c) $CH_3—C\equiv C—C_2H_5 \xrightarrow{BH_3 : THF}$ F + G $\xrightarrow{H_2O_2/OH^{\ominus}}$ H + I; F + G $\xrightarrow{CH_3CH_2COOD}$ J + K

(d)  $\xrightarrow{Sia_2BH}$ L $\xrightarrow[Diglym]{160°C}$ M $\xrightarrow{H_2O_2/OH}$ N

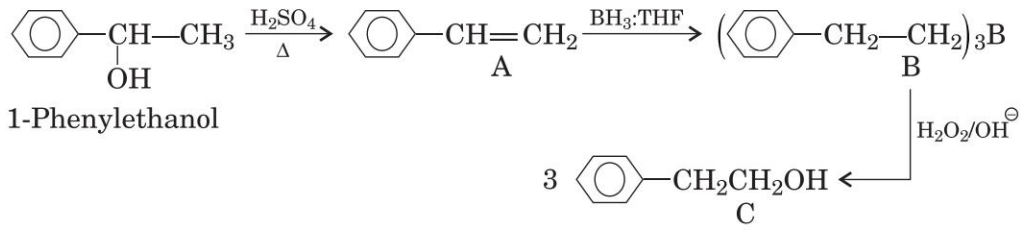
(e)  $\xrightarrow{BH_3: THF}$ O $\xrightarrow[H_2SO_4]{Na_2Cr_2O_7}$ P

(f)  $\xrightarrow{BD_3: THF}$ Q $\xrightarrow{CH_3COOT}$ R

(g) $CH_3CH_2CH_2—\underset{\displaystyle CH_3}{\overset{|}{C}}=CH_2 \xrightarrow{BD_3: THF}$ S $\xrightarrow{Ag\ NO_3/KOH}$ T

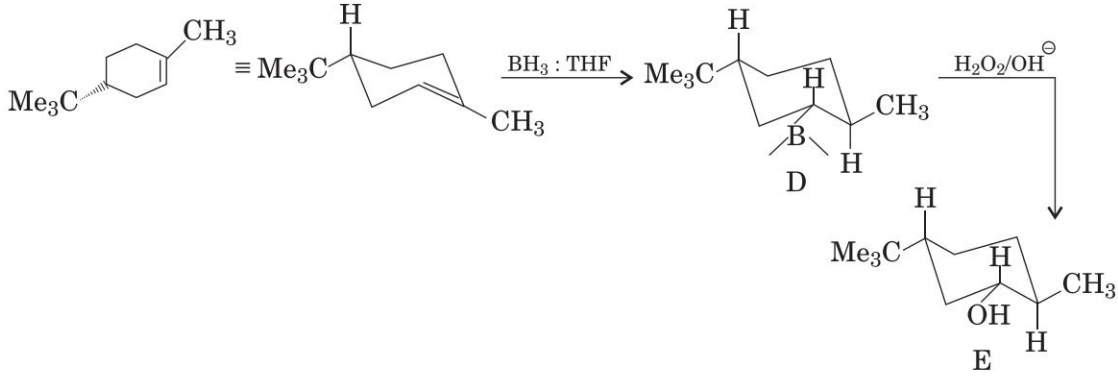
Solution

(a) 1-Phenylethanol produces styrene (A) when heated with concentrated H_2SO_4. Hydroboration-oxidation of styrene produces 2-phenylethanol (C).

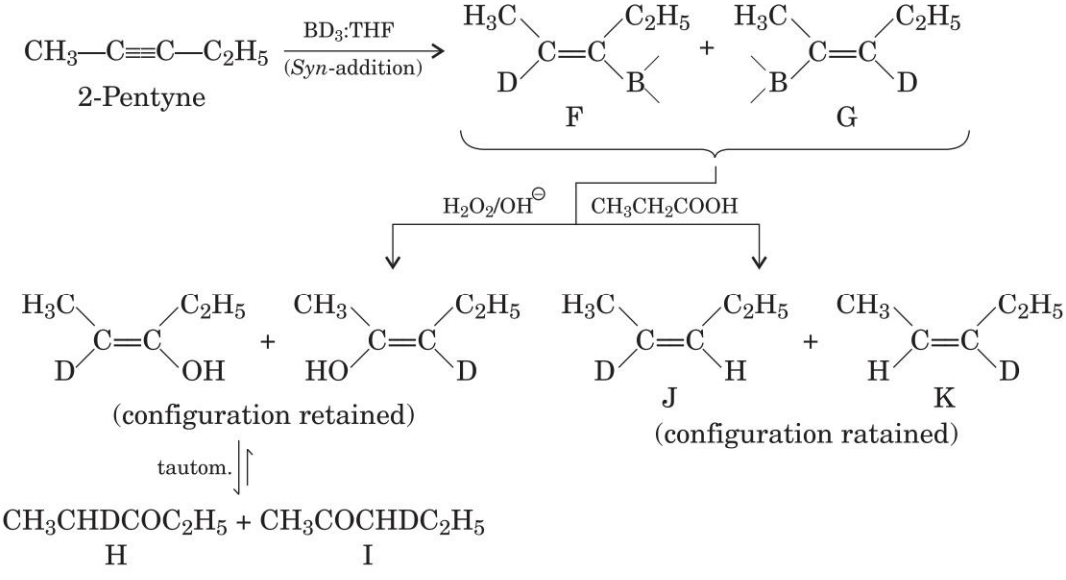


1-Phenylethanol

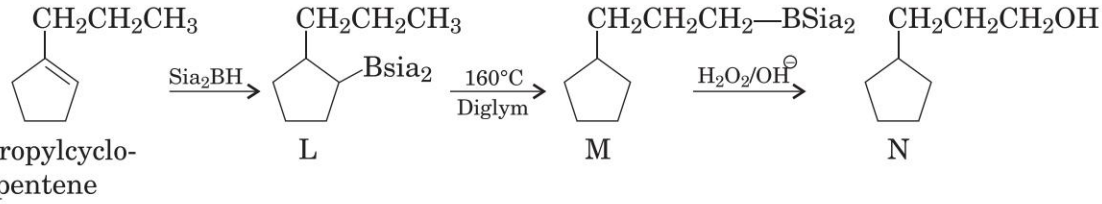
(b) The addition of BH_3 to the double bond is stereospecifically *syn* and the conversion of C—B to the C—O bond by oxidation and hydrolysis proceeds with retention of configuration. Therefore, the products of this reaction sequence are as follows:



(c)

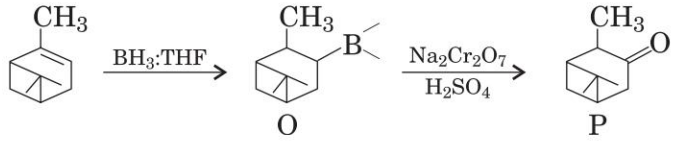


(d)



1-Propylcyclo-pentene L M N

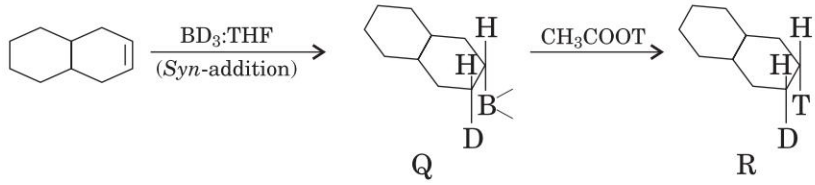
(e)



O P

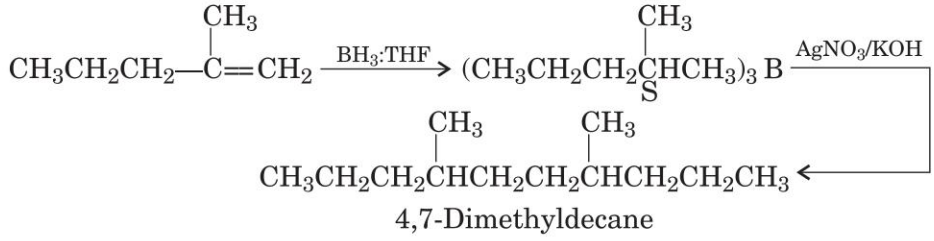
It is possible to convert alkylboranes to ketones if acidic dichromate is used as the oxidant.

(f)



Q R

(g)

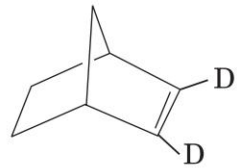


4,7-Dimethyldecane

Alkylboranes on treatment with basic silver nitrate ($AgNO_3$) lead to coupling of the alkyl groups.

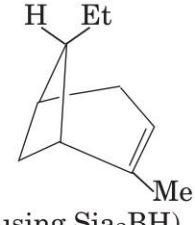
3. Write the structure, for the alcohol obtained by hydroboration-oxidation of each of the following alkenes:

(a)



(using Sia_2BH)

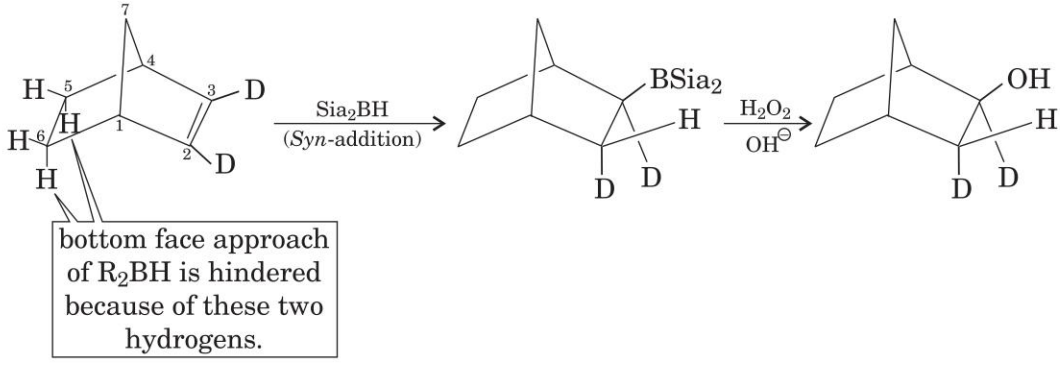
(b)



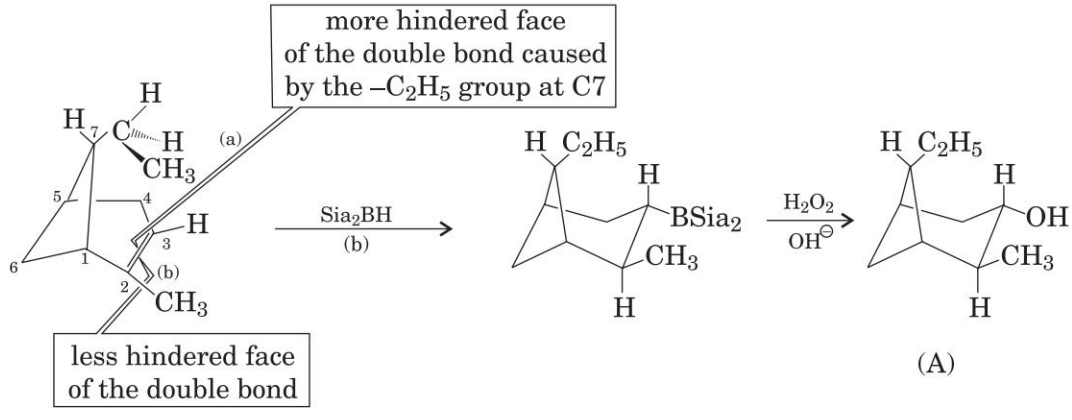
(using Sia_2BH)

Solution

(a) If the two faces of the double bond are not equivalent in terms of steric hindrance, hydroboration takes place preferentially from the less crowded or less hindered face of the double bond. In this bicyclic alkene, the bottom face of the double bond is more hindered than the top face because of the two boat-axial or endohydrogens at C-5 and C-6.



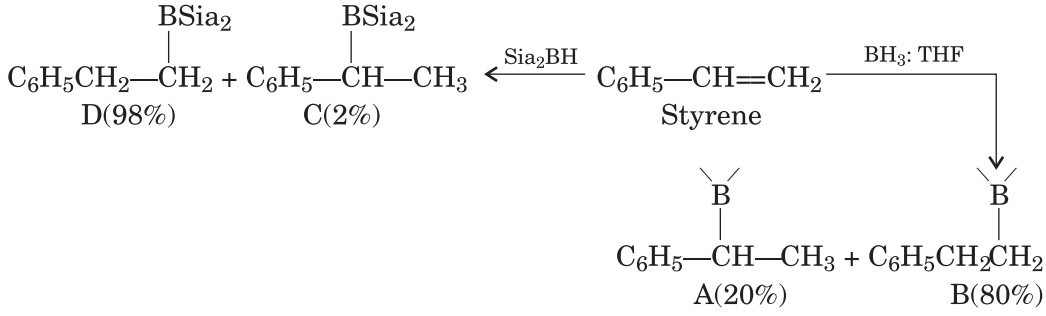
(b)



The addition of Sia_2BH occurs preferably from the less-hindered bottom face (b) of the double bond to yield mainly the alcohol (A).

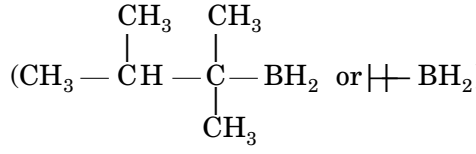
4. $C + D \xleftarrow{Sia_2BH} \underset{\text{Styrene}}{C_6H_5CH=CH_2} \xrightarrow{BH_3:THF} A + B$ **Identify A, B, C and D and compare the distribution of products is one reaction with that of the other reaction.**

Solution



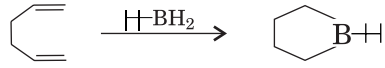
The regioselectivity in hydroboration-oxidation is caused mostly by steric factors. When BH_3 adds to styrene, 80% event of addition of boron occurs at the less substituted and less sterically hindered carbon. However, when the sterically hindered borane Sia_2BH is used for hydroboration, the reaction becomes more regioselective. Because of greater steric hindrance at the more substituted carbon, 98% event of addition of boron occurs at the less substituted carbon.

5. What is called thexylborane? Give its two important uses.

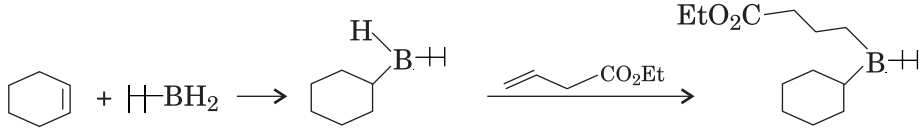
Solution 2,3-Dimethyl-2-butylborane  is called thexylborane.

Thexylborane is a valuable hydroborating agent and it is the most readily available of the monalkylboranes. Its two important uses are as follows:

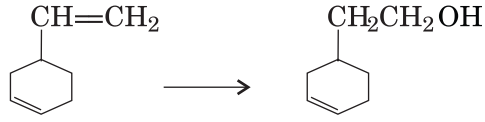
(i) It is useful for the cyclic hydroboration of dienes. For example:



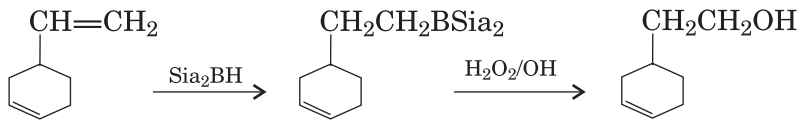
(ii) It is also used to make trialkylboranes containing three different alkyl groups by stepwise addition to two different alkenes. For example:



6. How would you accomplish the following transformation?



Solution This transformation can be carried out by using the sterically hindered disiamylborane which reacts more rapidly with terminal double bond than internal double bond.



Study Problems

1. How would you accomplish the following transformations:

(a) $(CH_3)_2C{=}CH_2 \longrightarrow (CH_3)_2\overset{\overset{OH}{|}}{C}{-}CH_3$

(b) $(CH_3)_2C{=}CH_2 \longrightarrow (CH_3)_2CHCH_2OH$

2. How would you carry out the following transformations:

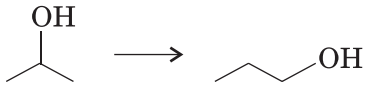
(a) $CH_3(CH_2)_2C{\equiv}CH \longrightarrow CH_3(CH_2)_3CHO$

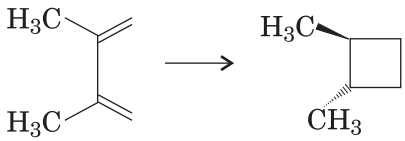
(b) $CH_3(CH_2)_2C{\equiv}CH \longrightarrow CH_3(CH_2)_2COCH_3$

3. How can $CH_3(CH_2)_3CHDCHO$ can be prepared from $CH_3(CH_2)_3C{\equiv}CH$?
[Hint: Sia_2BD is to be used instead of Sia_2BH**]**

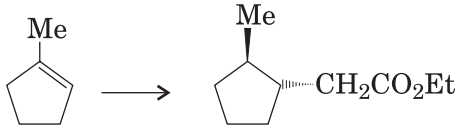
4. Explain why a B—O bond is much stronger than a B—C bond.

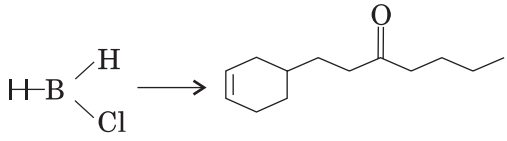
5. Show how one may accomplish each of the following transformations in a practical manner:

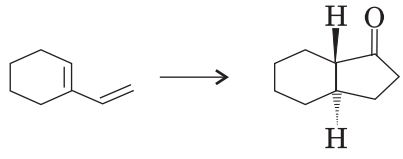
(a) 

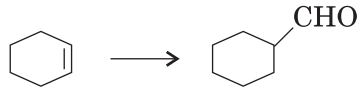
(b) 

(c) $CH_3CH{=}CH_2 \longrightarrow CH_3(CH_2)_3COCH_3$

(d) 

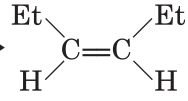
(e) 

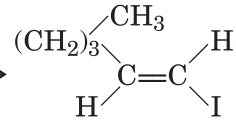
(f) 

(g) 

6. Show how hydroboration of an appropriate alkene can be used to prepare (*S*,*S*)- and (*R*,*R*)-PhCH(CH_3)CH(OH)Ph.

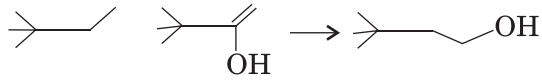
7. How would you carry out the following transformations:

(a) $EtC{\equiv}CEt \longrightarrow$ 

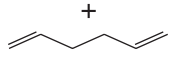
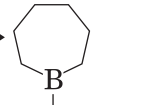
(b) $CH_3(CH_2)_3C{\equiv}CH \longrightarrow$ 

8. When BH_3 is allowed to react with a large excess of 2-methylbut-2-ene and 2,3-dimethylbut-2-ene, "disiamylborane". ($Me_2CHCHMe$-)$_2BH$ and "thexylborane", $Me_2CHCMe_2BH_2$ are obtained instead of trialkylboranes—explain.

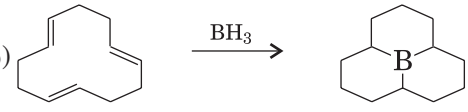
9. Indicate suitable reagents to carry out the following conversions (show the intermediate compounds):



10. Suggest a mechanism for each of the following reactions:

(a) $(CH_3)_2CHC(CH_3)_2BH_2 +$  $\longrightarrow$ 

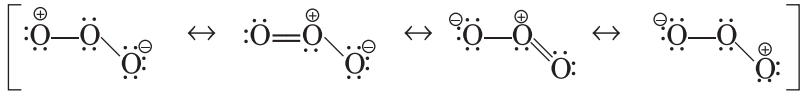
$(CH_3)_2CHC(CH_3)_2$

(b) 

1.1.6 Ozonolysis of Alkenes and Alkynes

1.1.6.1 Structure of Ozone

Ozone (O_3) is a resonance hybrid of the following four resonance structures:

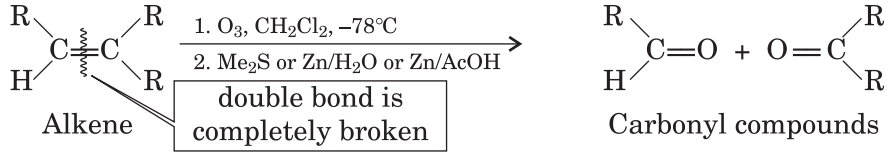


I II III IV

The positive oxygen atoms in structure II and III are not electrophilic because they possess octet of electrons. However, the positive oxygens in structures I and IV possess sextet of electrons. The other terminal oxygen atoms are anionic centres with a pair of electrons. Therefore, the terminal atoms of ozone may function as either an electrophile or a nucleophile. For this reason, ozone undergoes ready 1,3-dipolar addition to carbon–carbon double or triple bond initiated by its electrophilic end.

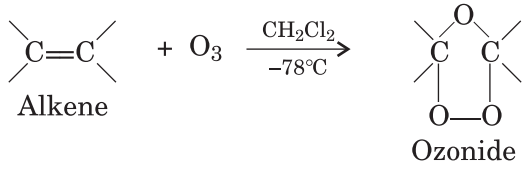
1.1.6.2 Ozonolysis

When ozone (O_3) is bubbled into a very cold (–78°C) solution of an alkene in CH_2Cl_2, the double bond breaks to form an ozonide. On treatment of the resulting solution with dimethyl sulfide, Me_2S (or Zn/water or Zn/AcOH), the ozonide dissociates to give two molecules of carbonyl compound (same or different). Thus, the overall process results in cleavage of the alkene at the double bond, with each doubly bonded carbon becoming doubly bonded to an oxygen atom. This oxidative cleavage of double bond with ozone is called *ozonolysis*.



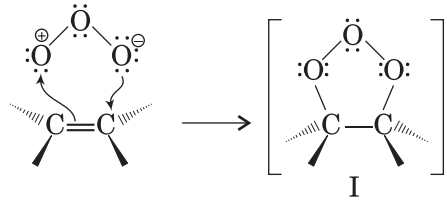
1.1.6.3 Mechanism of Ozonide Formation

An alkene in CH_2Cl_2 reacts with ozone at –78°C to form an ozonide:

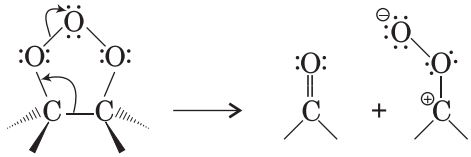


The mechanism of the reaction involves the steps as follows:

Step 1: The alkene undergoes 1,3-dipolar concerted addition of ozone to form an unstable primary ozonide or molozonide (I) stereospecifically (the stereochemical relationship of the alkyl groups in the original alkene will be preserved in the ozonide).

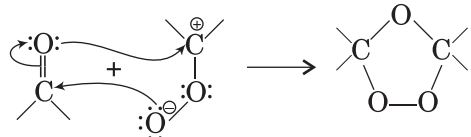


Step 2: The molozonide undergoes a reverse 1,3-dipolar addition to give a carbonyl compound (II) and a zwitterion known as carbonyl oxide (III).



I II III

Step 3: The carbonyl oxide (III) turns over and recombines with the carbonyl compound (II) in the opposite sense to give an ozonide (IV).



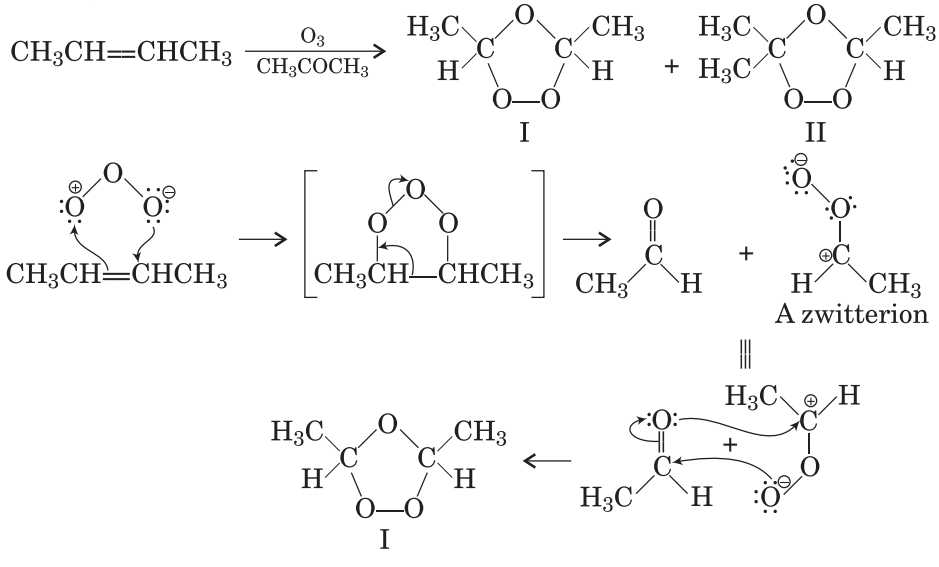
II III IV
Ozonide

It is to be noted that the ozonide is thermodynamically more stable than the molozonide because ozonide contains fewer weak oxygen–oxygen bonds than the molozonide. For this reason, the molozonide readily rearranges to a more stable ozonide.

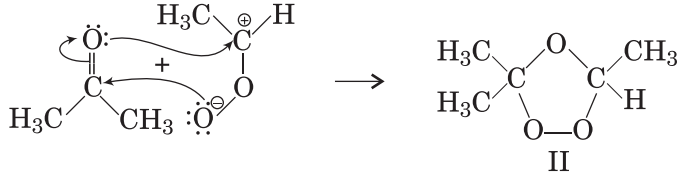
1.1.6.4 Evidence in Favour of the Mechanism

The mechanism of the reaction is supported by the following observations:

(i) When the ozonolysis of but-2-ene, for example, is carried out in the presence of acetone, the ozonide II, in addition to the expected ozonide I, is isolated (a 'crossover' experiment).

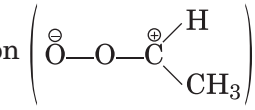


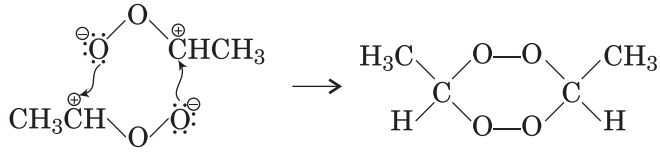
The cabonyl oxide or the zwitterion reacts with acetone (CH_3COCH_3) to form the other ozonide II.



II

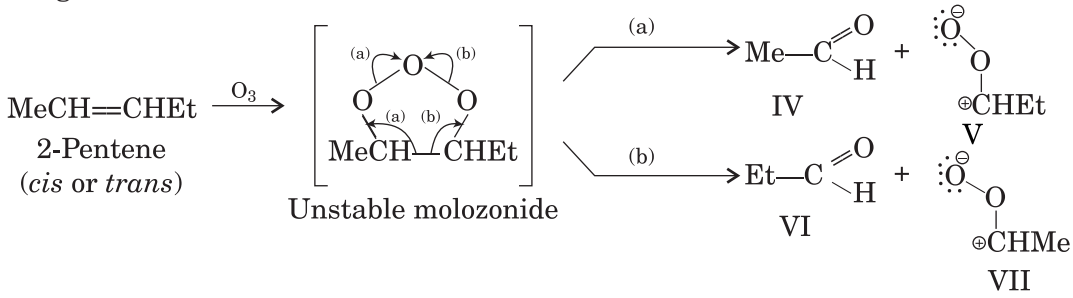
The formation of the ozonide II, therefore, suggests that a zwitterion must have been formed, i.e., the reaction must involve fission of the molozonide followed by recombination of the fragments to form the ozonide.

(ii) The diperoxide III has been isolated along with the ozonides I and II. This also proves the formation of the carbonyl oxide or zwitterion 



III

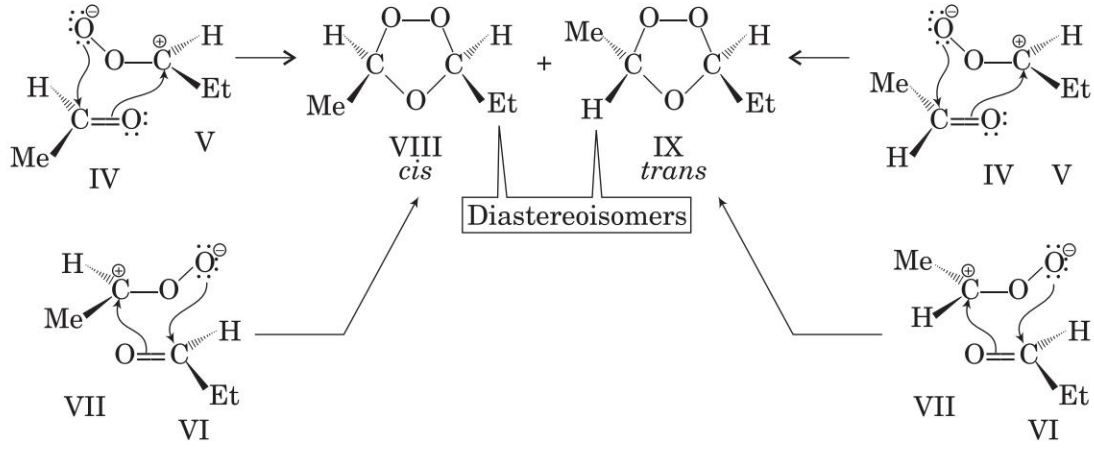
(iii) When an unsymmetrical alkene (RCH═CHR′) is allowed to react with ozone, then two carbonyl compounds and two carbonyl oxides or zwitterions are expected to be formed and their combination can lead to three different ozonides (structural isomers). Also, because the ozonides have cyclic structure, each can exist in both *cis*- and *trans*-forms. That is, six ozonides (three pairs of diastereiosomers) are possible from an unsymmetrical alkene. When 2-pentene, for example, is subjected to react with O_3, all six ozonides have been isolated. This is, in fact, a strong evidence in favour of the mechanism of fission of molozonide followed by recombination of the fragments.



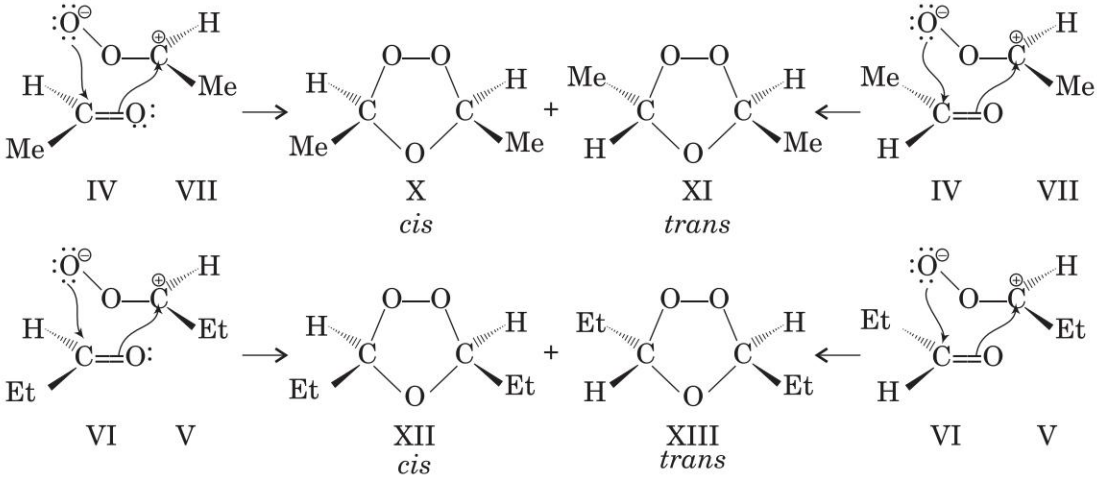
Unstable molozonide

IV V VI VII

Now, IV and V or VI and VII may combine to give the two diastereoisomers VIII and IX.



Again, IV and VII may combine to produce two diastereoisomers X and XI, and V and VI may combine to yield the two diastereoisomers XII and XIII.

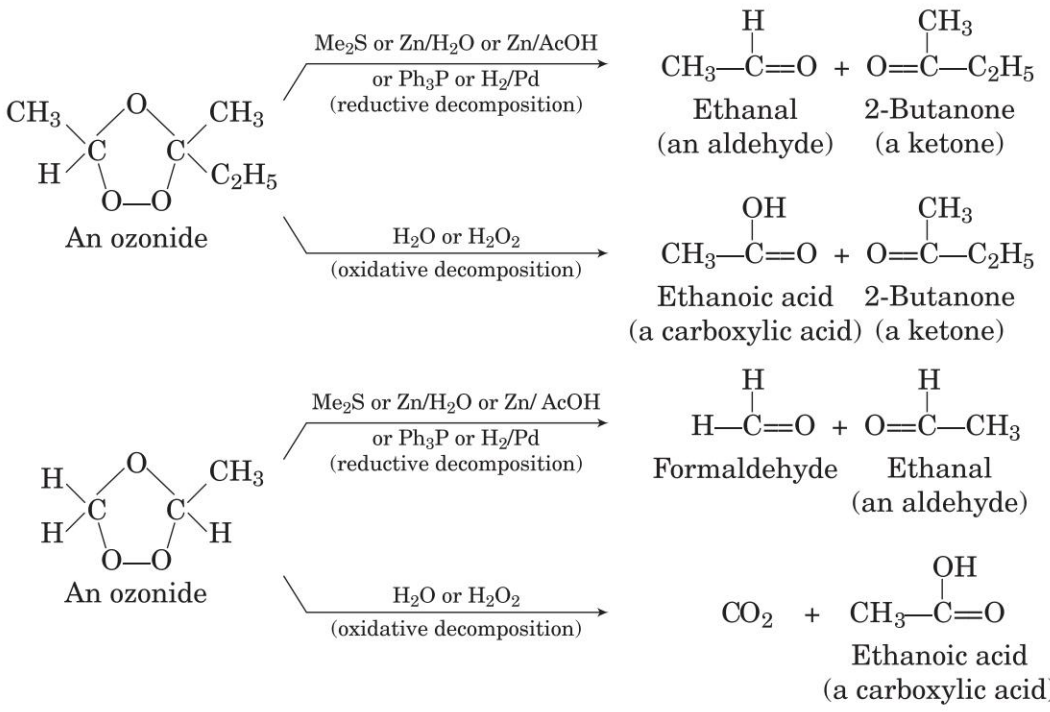


1.1.6.5 Reagents used for the Decomposition of Ozonides and the Nature of Products to be Formed

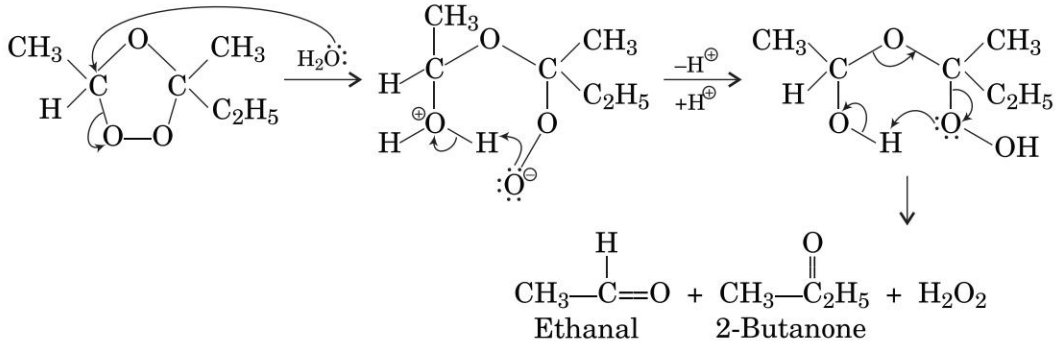
An ozonide can be decomposed either by reductive or by oxidative work-up. The reagents used for reductive decomposition are H_2/Pd, Zn/H_2O, $(CH_3)_2S$, Zn/AcOH or triphenylphosphine (Ph_3P). On the other hand, oxidative decomposition usually takes place on simple hydrolysis but is assured by adding hydrogen peroxide.

The nature of the products obtained on cleaving the ozonide actually depends on the nature of the two doubly bonded carbons. If a doubly bonded carbon bears two carbon substituents, that carbon becomes a ketone on reductive or oxidative decomposition. If a doubly bonded carbon bears a hydrogen and a carbon substituent, that carbon becomes an aldehyde on reductive decomposition and a carboxylic acid on oxidative decomposition and if a doubly bonded carbon bears two hydrogens, that carbon becomes formaldehyde

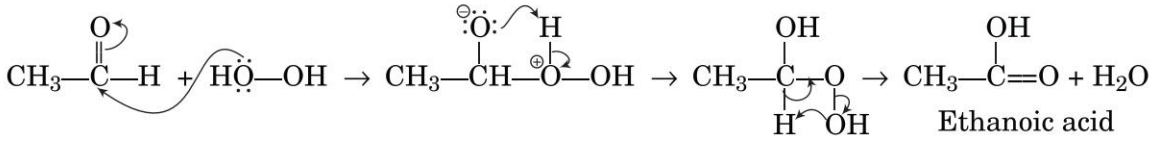
(HCHO) on reductive decomposition and carbon dioxide on oxidative decomposition. For example:



Mechanism of oxidative cleavage:



The aldehyde ethanal is then oxidized by H_2O_2 to give the carboxylic acid ethanoic acid as follows:



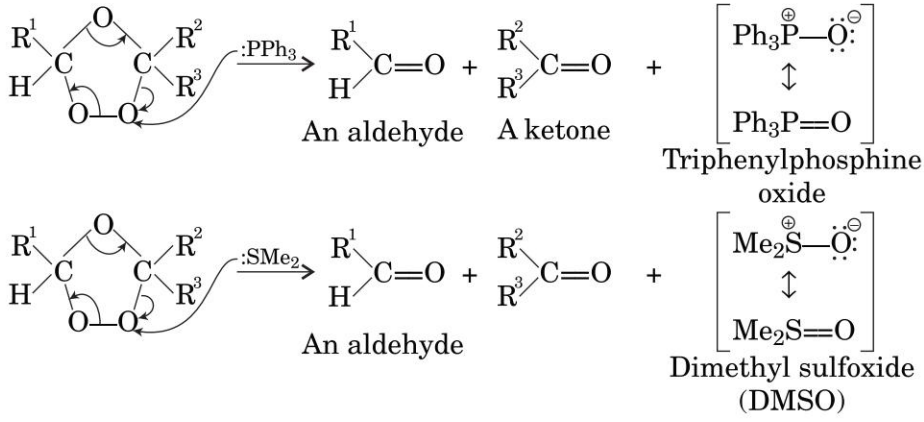
Formaldehyde obtain from a terminal alkene may undergo oxidation by H_2O_2 to give CO_2.

If Zn dust in used along with water for decomposing the ozonide, it destroys H_2O_2 by reduction and thereby prevents the oxidation of aldehyde.

$$H_2O_2 + Zn \xrightarrow{\text{reduction}} Zn(OH)_2$$

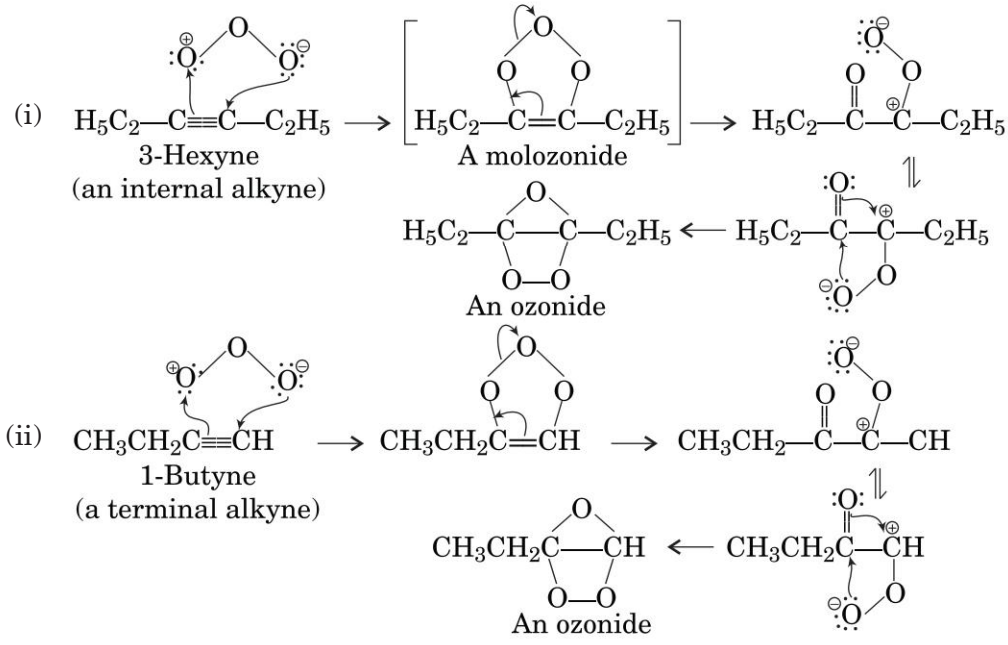
Therefore, treatment of an ozonide with Zn/H_2O is actually a case of reductive decomposition.

Mechanism of reductive cleavage involving Ph_3P and SMe_2:



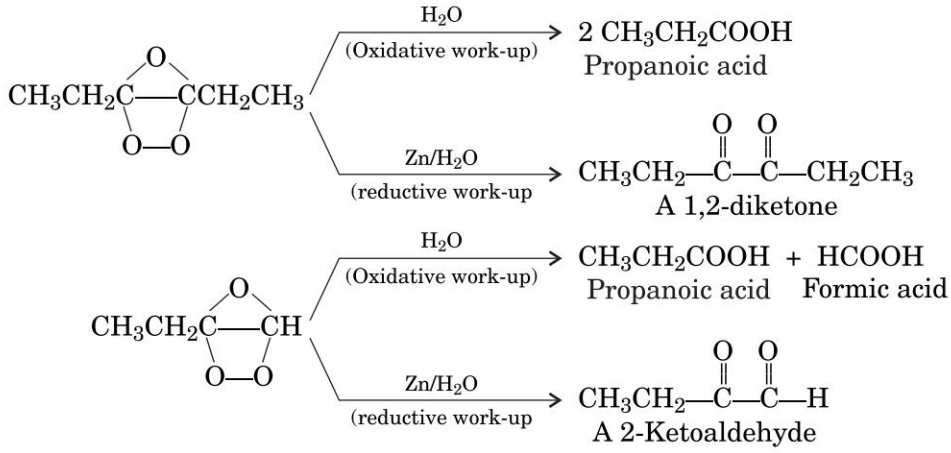
1.1.6.6 Ozonolysis of Alkynes

Alkynes react with ozone to form ozonides by a mechanism similar to alkene. For example:

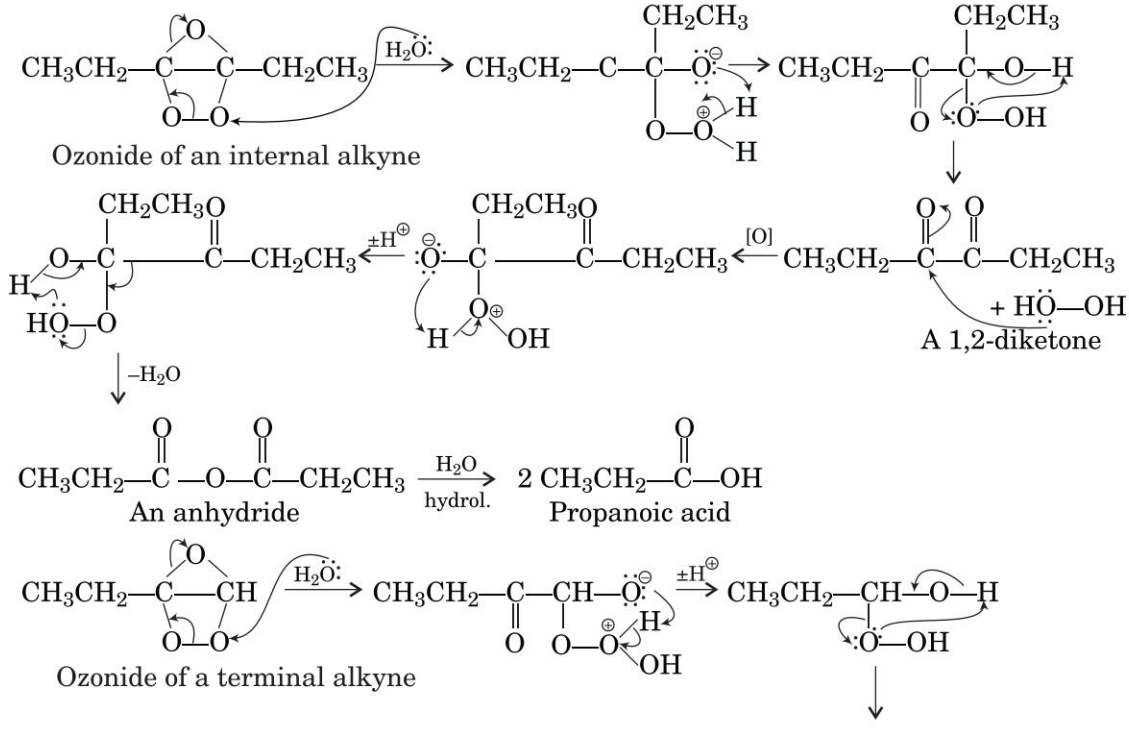


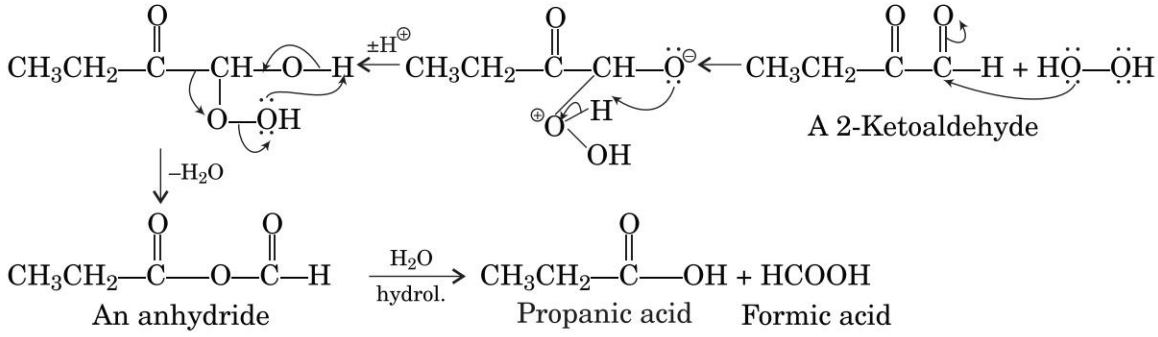
Cleavage of ozonides:

Oxidative cleavage of the ozonide obtained from an internal alkyne produces a carboxylic acid, but its reductive cleavage produces a 1,2-diketone. On the other hand, oxidative cleavage of the ozonide obtained from a terminal alkyne produces a carboxylic acid along with formic acid but its reductive cleavage produces a 2-ketoaldehyde. For example:



Mechanism of oxidative cleavage: The plausible mechanism of oxidative cleavage is as follows:



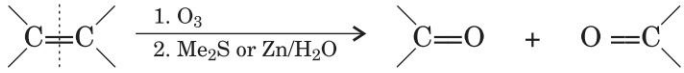


Formic acid may undergo oxidation by H_2O_2 to yield CO_2.

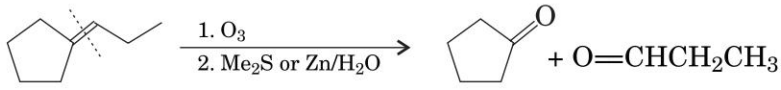
If zinc dust is used with water (reductive work-up), H_2O_2 will be destroyed and in the first case a diketone and in the second case a ketoaldehyde will be obtained.

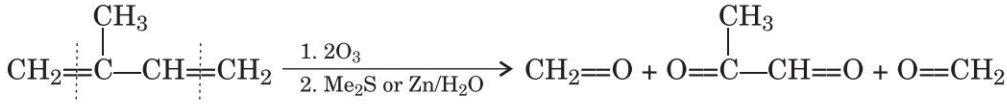
1.1.6.7 Prediction of Product(s) Obtained on Treatment of Alkenes and Alkynes with O_3 Followed by Reductive Work-Up

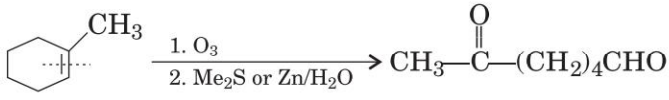
Ozonolysis with reductive work-up by using Me_2S or Zn/H_2O cleaves a carbon–carbon double bond into two carbonyl fragments. Therefore, to determine the product of ozonolysis, the C═C bond is to be replaced with C═O + O═C.



Thus, depending on their structures the following alkenes give products as follows:

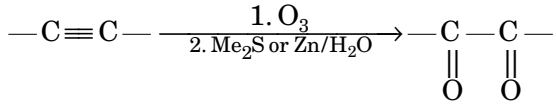
(i) 

(ii) 

(iii) 

(iv) 

In the case of alkynes, a —C≡C— bond is to be replaced with $O{=}\overset{|}{C}{-}\overset{|}{C}{=}O$.



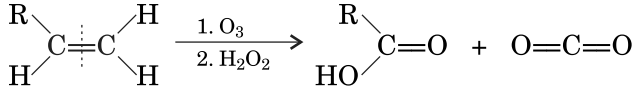
For example:

(i) $CH_3-C\equiv C-CH_3 \xrightarrow[2.\ Me_2S \text{ or } Zn/H_2O]{1.\ O_3} CH_3-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}-CH_3$

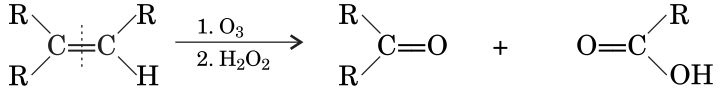
(ii) $CH_3-C\equiv C-H \xrightarrow[2.\ Me_2S \text{ or } Zn/H_2O]{1.\ O_3} CH_3-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}-H$

1.1.6.8 Prediction of Product(s) Obtained on Treatment of Alkenes and Alkynes with O_3 Followed by Oxidative Work-Up with H_2O_2

If any of the two doubly bonded carbon of an alkene contains a hydrogen atom, oxidative work-up converts that carbon to a carboxyl group (–COOH). In fact, the initially formed aldehyde is immediately oxidized to a carboxylic acid by H_2O_2. Again, working up under oxidizing conditions it would convert a terminal $=CH_2$ group into carbon dioxide (CO_2). If any doubly bonded carbon is bonded to two carbon-containing substituents that carbon will be converted into a ketone.



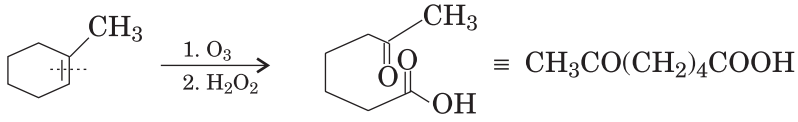
A carboxylic acid



A ketone A carboxylic acid

For example:

(i) $CH_3CH_2\underset{\underset{CH_3}{|}}{C}=CH_2 \xrightarrow[2.\ H_2O_2]{1.\ O_3} CH_3CH_2\underset{\underset{CH_3}{|}}{C}=O + CO_2$

(ii) 

$\equiv CH_3CO(CH_2)_4COOH$

(iii) $(CH_3)_2C=CHCH_3 \xrightarrow[2.\ H_2O_2]{1.\ O_3} (CH_3)_2C=O + O=\underset{\underset{OH}{|}}{\overset{\overset{CH_3}{|}}{C}}$

When alkynes are treated with O_3 followed by oxidative work-up with H_2O_2, internal alkynes are converted to carboxylic acids, whereas terminal alkynes afford carboxylic acids and CO_2.

$$-C\equiv C- \xrightarrow[2.\ H_2O_2]{1.\ O_3} -COOH + HOOC-$$

$$—C\equiv C—H \xrightarrow[2.\ H_2O_2]{1.\ O_3} —COOH + CO_2$$

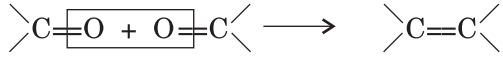
For example:

(i) $CH_3CH_2C\equiv CCH_3 \xrightarrow[2.\ H_2O_2]{1.\ O_3} CH_3CH_2\overset{OH}{\underset{|}{C}}=O + O=\overset{OH}{\underset{|}{C}}—CH_3$

(ii) $CH_3CH_2CH_2C\equiv CH \xrightarrow[2.\ H_2O_2]{1.\ O_3} CH_3CH_2CH_2\overset{OH}{\underset{|}{C}}=O + CO_2$

1.1.6.9 Prediction of the Structure of Starting Alkene or Alkyne from the Product(s) of Ozonolysis

Working up the ozonide under reducing conditions converts the two doubly bonded carbons into two carbonyl carbons. Therefore, the structure of the original alkene may be obtained by joining the two carbonyl carbons with a double bond.



For example:

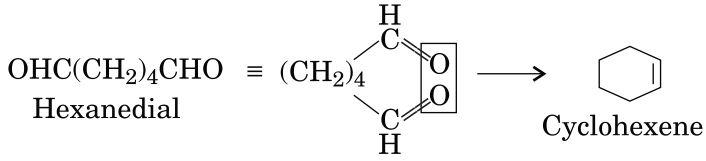
(i) If an alkene produces butanal and formaldehyde, the starting alkene must be 1-pentene.

$$\underset{\text{Butanal}}{CH_3CH_2CH_2CH=O} + \underset{\text{Formaldehyde}}{O=CH_2} \longrightarrow \underset{\text{1-Pentene}}{CH_3CH_2CH_2CH=CH_2}$$

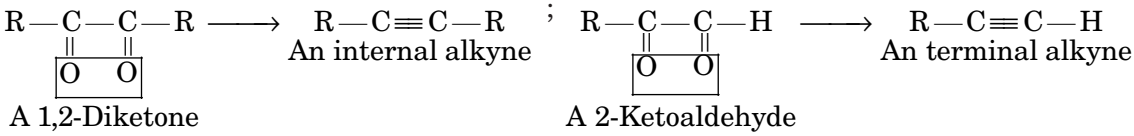
(ii) If an alkene produces acetone and acetaldehyde, the starting alkene must be 2-methylbut-2-ene.

$$\underset{\text{Acetone}}{(CH_3)_2C=O} + \underset{\text{Acetaldehyde}}{O=CHCH_3} \longrightarrow \underset{\text{2-Methylbut-2-ene}}{(CH_3)_2C=CH—CH_3}$$

(iii) If an alkene produces only hexanedial, the starting alekne must be cyclohexene.



The structure of a starting alkyne can be predicted as follows:



1.1.6.10 Uses of Ozonoysis

The two important uses of ozonolysis are as follows

(i) Ozonolysis can be used to determine the position of the double bond in an alkene by reasoning backward from the structures of the products. For example, if oxonolysis of an alkene (reductive work-up) forms acetone and butanal as products, we can conclude that the alkene is 2-methylhex-2-ene

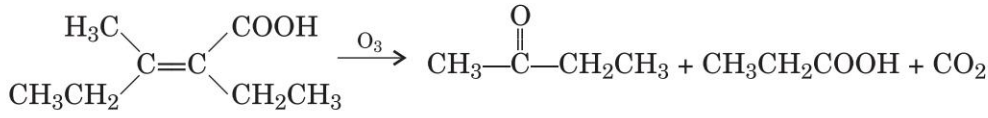
$$(CH_3)_2C{=}O + O{=}CHCH_2CH_2CH_3 \longrightarrow (CH_3)_2C{=}CHCH_2CH_2CH_3$$

Acetone Butanal 2-Methylbut-2-ene

(ii) Ozonolysis is used as a means for preparing carbonyl compounds (aldehydes and ketones) and carboxylic acids from unsaturated hydrocarbons.

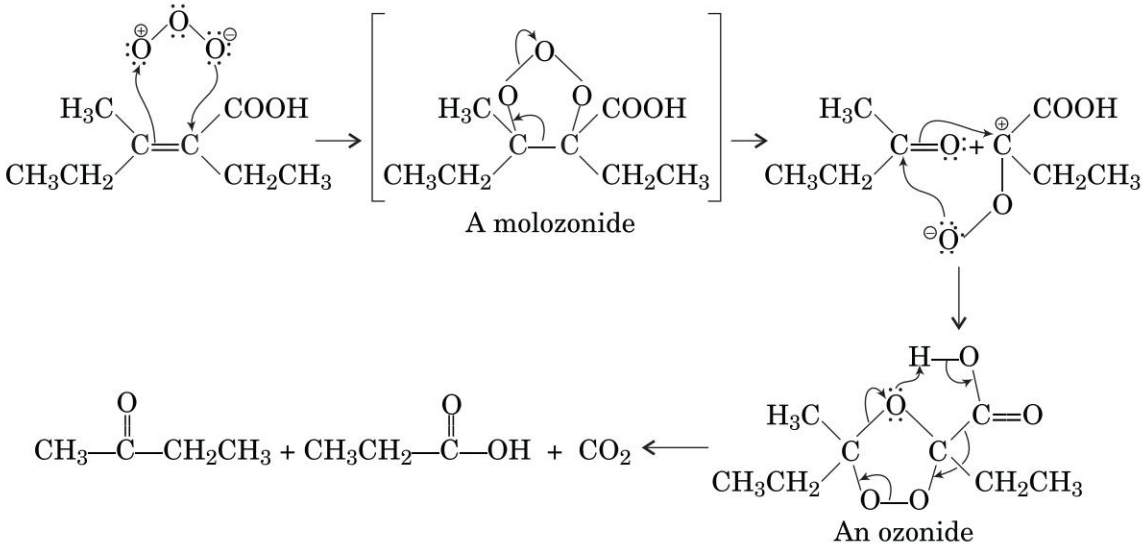
SOLVED PROBLEMS

1. Write down the mechanism of the following reaction:



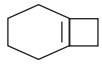
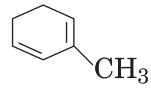
Explain why oxidative or reductive work-up is not required in this case.

Solution The mechanism of the reaction involves the steps as follows:



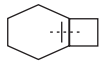
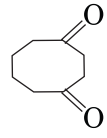
Since the ozonide undergoes ready decomposition through decarboxylation, oxidative or reductive work-up is not required in this case.

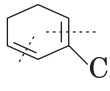
2. Preduct the product(s) obtained when each of the following compounds is treated with O_3 followed by reductive work-up with Me_2S or Zn/H_2O.

(a)  (b)  (c) $(CH_3)_2C{=}CH_2$

(d) $CH_3CH{=}\overset{\displaystyle CH_3}{\overset{|}{C}}{-}CH{=}CH_2$ (e) $(CH_3)_2C{=}C{=}CHCH_3$

Solution

(a)  $\xrightarrow[2.\ Me_2S \text{ or } Zn/H_2O]{1.\ 2O_3}$ 

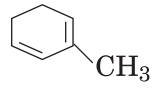
(b)  $\xrightarrow[2.\ Me_2S \text{ or } Zn/H_2O]{1.\ 2O_3}$ $OHCCH_2CH_2CHO + CH_3{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}CHO$

(c) $(CH_3)_2{\doteqdot}CH_2 \xrightarrow[2.\ Me_2S \text{ or } Zn/H_2O]{1.\ O_3} CH_3COCH_3 + HCHO$

(d) $CH_3CH{\doteqdot}\overset{\displaystyle CH_3}{\overset{|}{C}}{-}CH{\doteqdot}CH_2 \xrightarrow[2.\ Me_2S \text{ or } Zn/H_2O]{1.\ 2O_3} CH_3CHO + CH_3{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}CHO + HCHO$

(e) $(CH_3)_2C{\doteqdot}C{\doteqdot}CHCH_3 \xrightarrow[2.\ Me_2S \text{ or } Zn/H_2O]{1.\ 2O_3} CH_3COCH_3 + O{=}C{=}O + CH_3CHO$

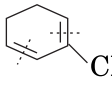
3. Give the products expected to be formed when each of the following alkenes is treated with ozone followed by oxidative work-up with H_2O_2:

(a) $CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CHCH_3$ (b) $(CH_3)_2C{=}CH_2$ (c) 

Solution

(a) $CH_3CH_2C{\doteqdot}CHCH_3 \xrightarrow[2.\ H_2O_2]{1.\ O_3} CH_3COCH_2CH_3 + CH_2COOH$

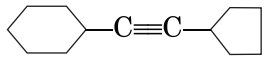
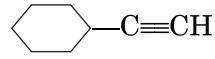
(b) $(CH_3)_2C{\doteqdot}CH_2 \xrightarrow[2.\ H_2O_2]{1.\ O_3} CH_3COCH_3 + CO_2$

(c)  $\xrightarrow[2.\ H_2O_2]{1.\ 2O_3}$ $HO_2CCH_2CH_2COOH + [CH_3{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}CHO]$

$\downarrow H_2O_2$

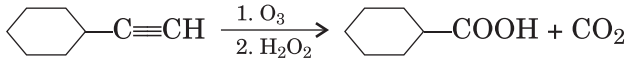
$CH_3COOH + CO_2$

4. Draw the products obtained when each of the following alkynes is treated with O_3 followed by H_2O_2:

(a)  (b)  (c) $CH_3C{\equiv}CCH_2CH_2C{\equiv}CH$

Solution

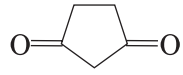
(a) 

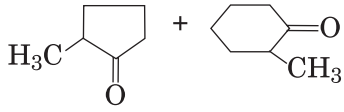
(b) 

(c) $CH_3C{\equiv}CCH_2CH_2C{\equiv}CH \xrightarrow[2.\ H_2O_2]{1.\ 2\,O_3} CH_3COOH + H_2OCCH_2CH_2CO_2H + CO_2$

5. Write structures of the alkenes that would yield the following carbonyl compounds when treated with O_3 followed by Me_2S or Zn/H_2O (give stereochemistry when appropriate):

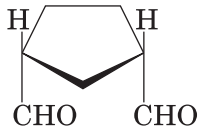
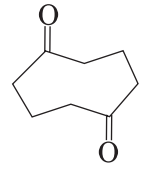
(a) $CH_3CH_2CHO + (CH_3)_2CHCHO$ (b) $CH_3CO(CH_2)_4CHO$

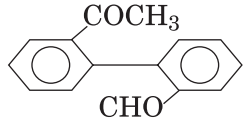
(c) only 2-butanone (d) $2CH_3COCH_2CH_3$ + 

(e)  (f) $CH_3CH_2CHO + CH_3COCHO + HCHO$

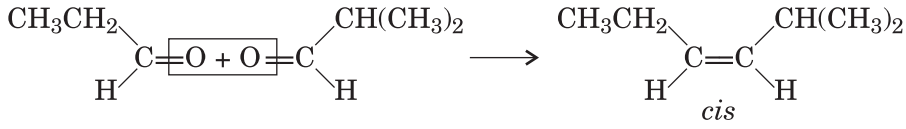
(g) (*R*)-2-Ethylcylopentanone (h) (*S*)-2-Ethylcyclopentanone

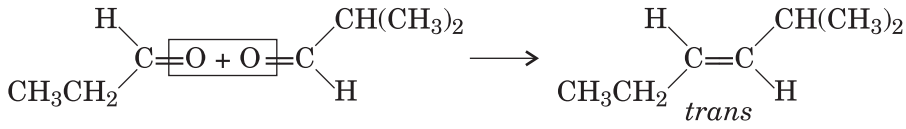
(i) $2CH_3CH_2CHO + CO_2$ (j) $2CH_3COCH_2CH_3 + 2CO_2$

(k)  (l) 

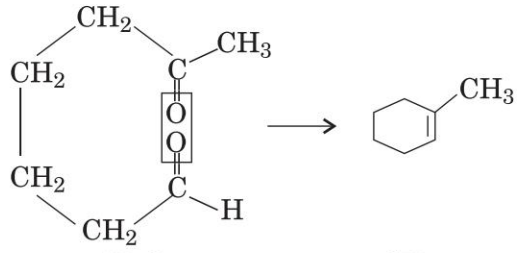
(m) 

Solution

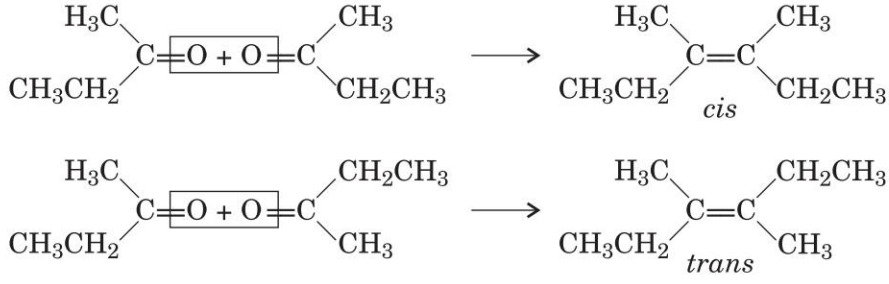
(a) 

or 

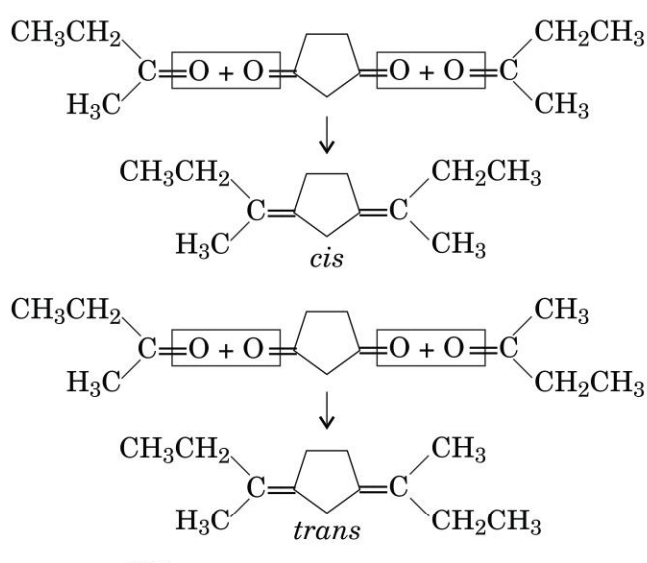
(b)



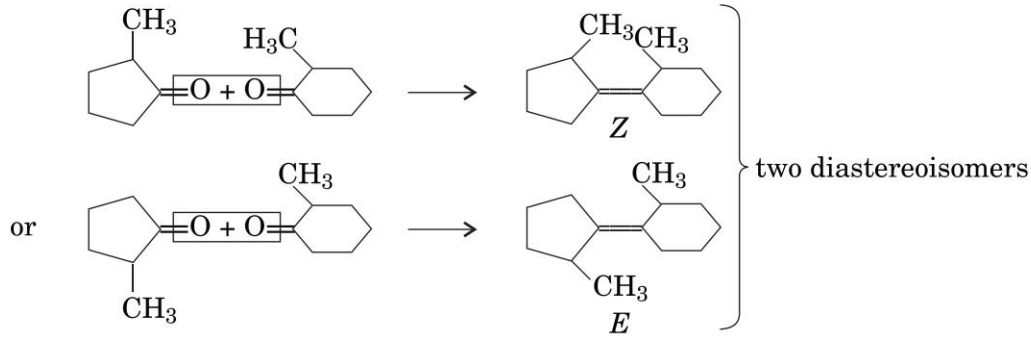
(c)



(d)



(e)



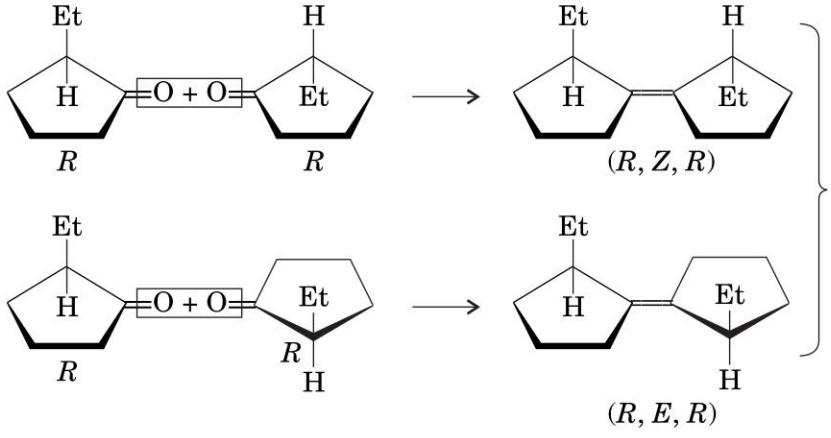
(f) $CH_3CH_2—CH=\boxed{O+O}=\overset{CH_3}{\overset{|}{C}}—CH=\boxed{O+O}=CH_2 \longrightarrow CH_3CH_2CH=\overset{CH_3}{\overset{|}{C}}—CH=CH_2$

3-Methyl-1,3-hexadiene

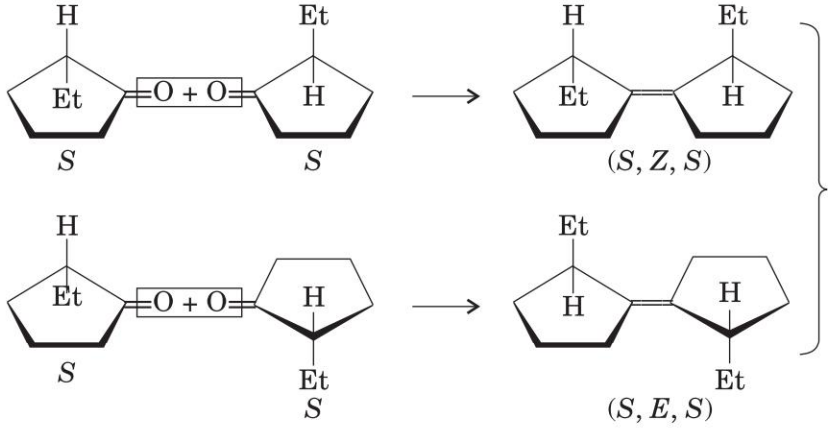
or $CH_3CH_2CH=\boxed{O+O}=CH—\overset{CH_3}{\overset{|}{C}}=\boxed{O+O}=CH_2 \longrightarrow CH_3CH_2CH=CH—\overset{CH_3}{\overset{|}{C}}=CH_2$

2-Methyl-1,3-hexadiene

(g)



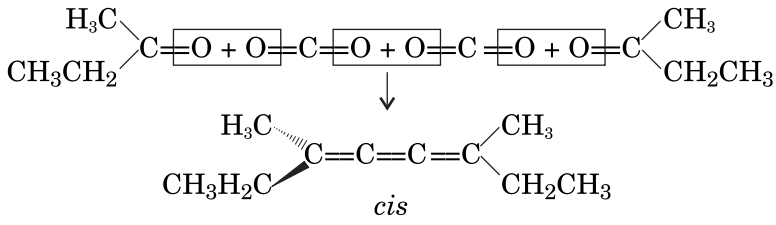
(h)



(i) CH_3CH_2, H, C=O + O=C=O + O=C, CH_2CH_3, H $\longrightarrow$ CH_3CH_2, H, C=C=C, CH_2CH_3, H, *S*

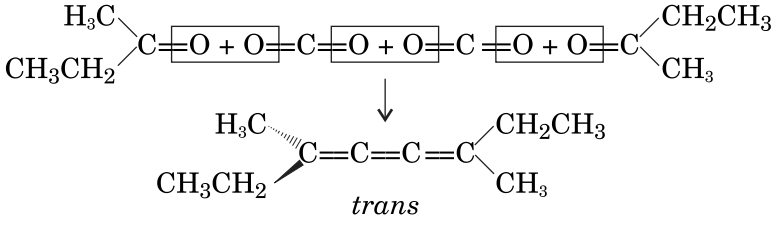
or CH_3CH_2, H, C=O + O=C=O + O=C, H, CH_2CH_3 $\longrightarrow$ CH_3CH_2, H, C=C=C, H, CH_2CH_3, *R*

(j)



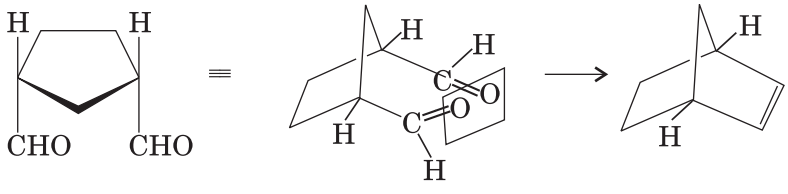
cis

or,

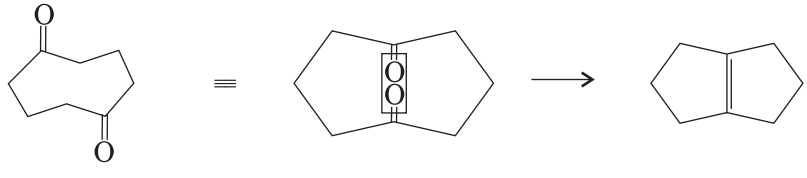


trans

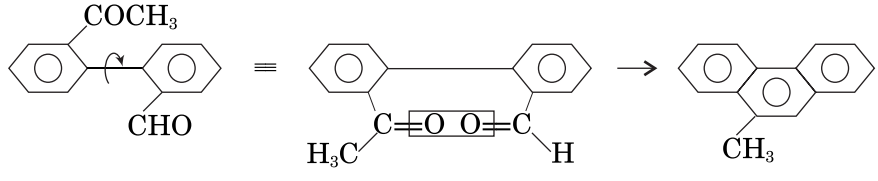
(k)

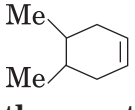


(l)



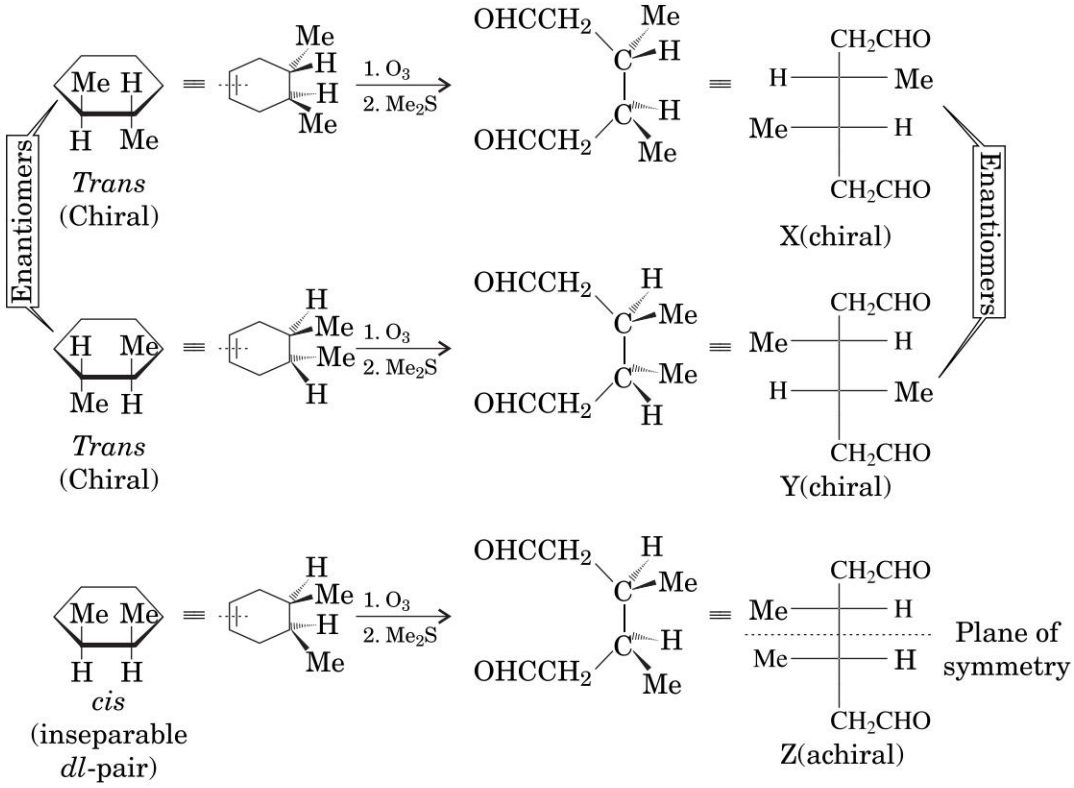
(m)



6. 

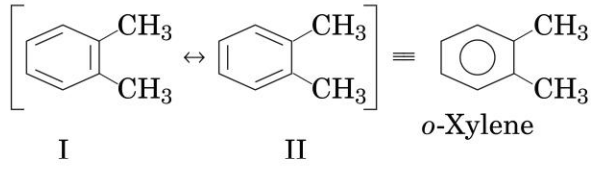
X or Y or Z **X, Y and Z are stereoisomeric forms of the reaction product. What are X, Y and Z? Designate them as chiral or achiral. What product would be formed if the methyl groups were *cis* or *trans* to each other in the starting alkene.**

Solution The *trans*-diastereoisomer of the starting alkene exists as two enantiomeric forms. On ozonolysis, one enantiomer leads to the formation of the chiral dialdehyde X and the other enantiomer leads to the formation of the enantiomeric dialdehyde Y. On the other hand, when the *cis*-diastereoisomer (which exists as inseparable *dl*-pair) of the starting alkene is subjected to ozonolysis, it produces the achiral *meso*-compound Z.

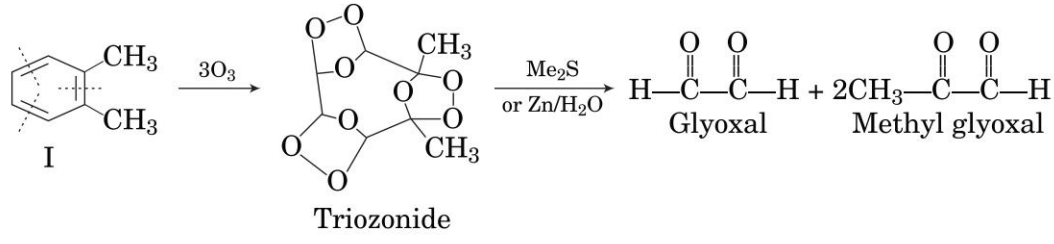


7. Explain why ozonolysis of *o*-xylene produces a mixture of dimethyl glyoxal, methyl glyoxal and glyoxal in 1:2:3 ratio.

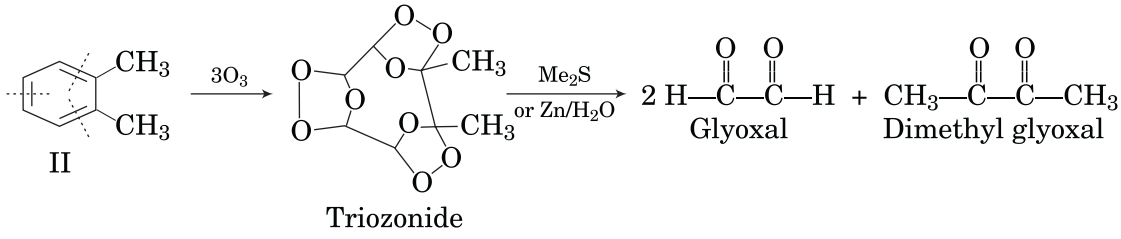
Solution *o*-Xylene is a resonance hybrid of structures I and I.



Therefore, ozonolysis of this compound may take place through both the structures. From structure I, glyoxal and methyl glyoxal are obtained in 1:2 ratio.



On the other hand, from structure II, glyoxal and dimethyl glyoxal are obtained it 2:1 ratio.

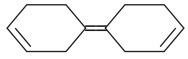


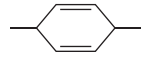
Therefore, ozonolysis of *o*-xylene produces a mixture of dimethyl glyoxal, methyl glyoxal and glyoxal in a 1:2:3 ratio.

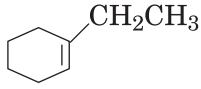
Study Problems

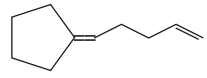
1. Give an example of an alkene that will form the same products on ozonolysis regardless of whether the ozonide is worked-up under oxidizing conditions (H_2O_2) or reducing conditions (Zn/H_2O or Me_2S).
[Hint: The alkene which gives two ketone molecules on ozonolysis.]

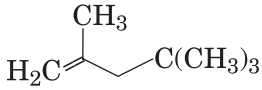
2. Draw the products formed when each of the following alknes is treated with O_3 followed by Me_2S:

(a) 

(b) 

(c) 

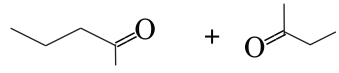
(d) 

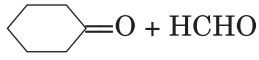
(e) 

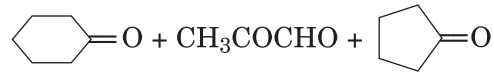
(f) $CH_2{=}C{=}C{=}C(CH_3)_2$

3. What alkene forms the following set of products after reaction with O_3 followed by Me_2S?

(a) $OHC\,(CH_2)_4COCH_3$

(b) 

(c) 

(d) 

(e) $2\,Me_2CO + 2\,CO_2$

(f) $CH_3COCH_2CH_2\,C(COCH_3)HCH_2\,CHO + HCHO$

(g) CH_3CH_2CHO only

(h) $CH_3COCH_2CH_3$ only

4. What aspect of alkene structure cannot be determined by ozonolysis?

5. Draw the products obtained when each of the following alkynes is treated with O_3 followed by H_2O_2:

(a) $Ph—C\equiv C—Ph$ (b) $CH_3CH_2C\equiv C\ CH_3$

(c) $CH_3CH_2CH_2CH_2C\equiv CH$ (d) $CH_3CH_2C\equiv CCH_2CH_2C\equiv CH$

6. What alkyne (or diyne) yields each set of products when treated with O_3 followed by H_2O_2?

(a) $(CH_3)_2CHCH_2COOH + CO_2$ (b) $HO_2C(CH_2)_{14}CO_2H$

(c) $(CH_3)_2CHCH_2COOH$ only

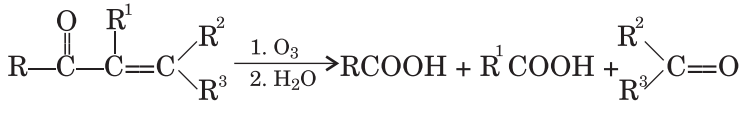
(d) $CH_3CH_2CH_2COOH + HO_2C\ CH_2CH_2CO_2H + CH_3CO_2H$

7. Oximene and myrcene are two isomeric hydrocarbons ($C_{10}H_{16}$). On catalytic hydrogenation, both yield 2,6-dimethyloctane. On ozonolysis, oximene yields CH_3COCH_3, HCHO, $CH_2(CHO)_2$ and CH_3COCHO and myrcene yields $(CH_3)_2CO$, HCHO (two equiv.) and $OHCCH_2CH_2COCHO$. Identify the structures of oximene and myrcene.

8. Compound A ($C_{10}H_{16}$) consumes two moles of H_2 on catalytic hydrogenation. When A is treated with O_3 followed by reductive work-up, two diketones, B($C_6H_{10}O_2$) and C($C_4H_6O_2$) are obtained. Suggest a reasonable structure (or structures) for A.

9. Compound A (C_8H_{12}) reacts with two moles of H_2. A produces butanedial ($OHCCH_2CH_2CHO$) as the only product when treated with O_3 followed by reductive work-up with Zn/H_2O. Identify A.

10. Suggest a mechanism for the following reaction:



11. Write down the structure and configuration of the alkene that give a mixture of (*R*)- and (*S*)-2-methycylclobutanone on treatment with O_3 followed by Me_2S.

12. Determine the structure of the compound A($C_{10}H_{14}$) that on catalytic hydrogenation consumes three moles of H_2 to yield 1-isopropyl-4-methylcyclohexane. A on reductive ozonolysis gives the following compounds:

$$HCHO;\ OHC\ CH_2COCOCH_3;\ CH_3COCH_2CHO$$

13. Write down all possible structures for the compound X($C_{10}H_{16}$) that undergoes oxidative and reductive ozonolysis to yield two moles of the same compound Y (C_5H_8O). X consumes three moles of H_2 in the presence of catalyst. None of these two compounds is resolvable.

14. A tertiary alcohol is dehydrated to yield an alkene. When the alkene is treated with O_3 followed by Zn/H_2O, equal amounts of 3-pentanone and ethanal are obtained. Find out the structure of the alcohol.

15. Predict the structure of an aromatic hydrocarbon which on treatment with O_3 followed by Zn/H_2O produces CH_3COCHO and $CHC—CHO$ in 2:1 molar ratio.

16. Which of the following two olefins is more prone towards ozonolysis reaction and why?

$$\underset{\text{I}}{Me_2C{=}CMe_2} \text{ and } \underset{\text{II}}{Me_2C{=}C(CO_2Et)_2}$$

[Hint: The double bond in I is more electron rich and so, it is more prone towards ozonolysis.**]**

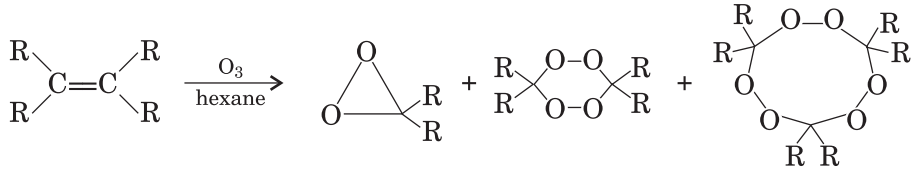
17. Identify the diastereoisomic compounds A, B, C and D in the following reaction:

$$\text{A or B or C or D} \xrightarrow[2.\ Me_2S]{1.\ 2O_3} CH_3CH_2CHO + OHC{-}CHO + C_2H_5CHO$$

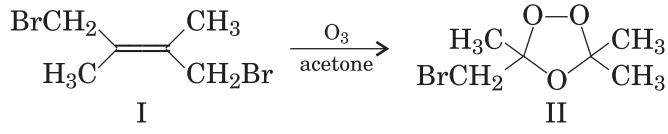
[Hint: *cis-cis*, *trans-trans*, *cis-trans* and *trans-cis* isomers of 2,4-heptadiene.]

18. Write down the two possible enol forms of hexane-2,4-dione and give the products expected to be formed on their ozonolysis.

19. Suggest a mechanism for the following reaction:



20. Treatment of I with O_3 in solvent acetone leads to II as the major product. Explain.



1.1.7 Addition of Carbenes and Simons-Smith Reaction

1.1.7.1 Carbenes and Their Classification on the Basis of the Spin States of Electrons

Carbenes are electrically neutral reaction intermediates containing a bivalent carbon atom in which the C atom is covalently bonded to two other atoms or groups and has two other valence electrons distributed between the two nonbonding orbitals, i.e., carbenes are neutral species containing a carbon with only six valence electrons. The general formula of carbenes is $:CR_2$. The simplest member $:CH_2$, often called methylene or simply carbene, is the parent. Carbenes are named by mentioning the substitutes attached to the divalent carbon, e.g., $:CBr_2$, dibromocarbene; :CHPh, phenylcarbene, etc. However, when the divalent carbon of a carbene is a part of a ring or an unsaturation, suffix -ylidine is used. For example:

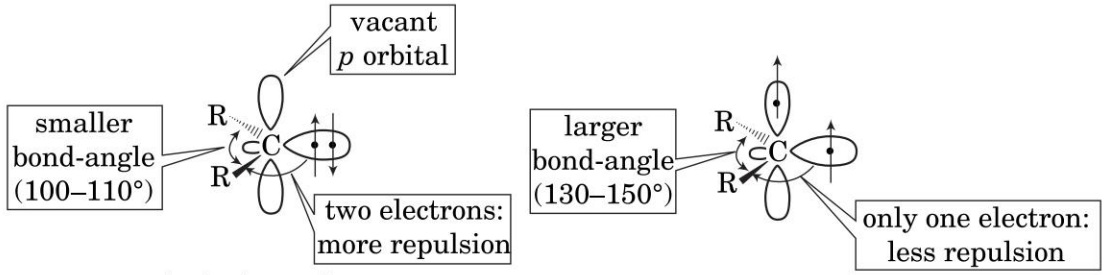


Cyclopentylidine $\qquad CH_2{=}C:$ Vinylidine

Depending upon the spin states of the nonbonding electrons, carbenes are divided into two classes. If the two nonbonding electrons remain spin paired, it is called a singlet carbene, while the carbene having unpaired spins of electrons is referred to as a triplet carbene.

1.1.7.2 Structure and Stability of Carbenes

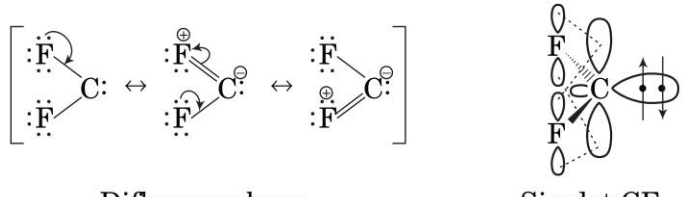
The C atom in a singlet carbene is sp^2-hybridized (trigonal hybridization). Two of these three sp^2 hybrid orbitals are utlized in forming covalent bonds, while the third hybrid orbital contains the unshared pair of electrons. There remains a vacant p orbital. A singlet carbene, therefore, resembles a carbocation and it appears to have a bent shape (bond angle 100–110°). Although a few triplet carbenes are linear (sp-hybridized), most of them are bent species (bond angle 130–150°) where the carbon is sp^2-hybridized, and the two nonbonding electrons occupy an sp^2 orbital and an unhybridized p orbital with parallel spin.



A singlet carbene A triplet carbene

Carbenes are generally more stable (about 40 kJ mol^{-1}) as triplets because the energy to be gained by bringing the electron in the p orbital down into the sp^2 orbital is insufficient to overcome the repulsion that exists between two electrons in a single orbital. The triplet state of carbene is, therefore, expected to be the ground state.

It is to be noted that the dihalocarbenes are singlet in the ground state, i.e., they are more stable than the corresponding triplets because they are considerably stabilized by resonance involving unshared p electrons of the halogen atom with the vacant p orbital on carbon. Because of similar size of the overlapping orbital of fluorine and carbon (very effective $2p$–$2p$ overlap), the resonance interaction is much more effective in $:CF_2$ and so, singlet variety of $:CF_2$ is much more stable than its triplet variety.



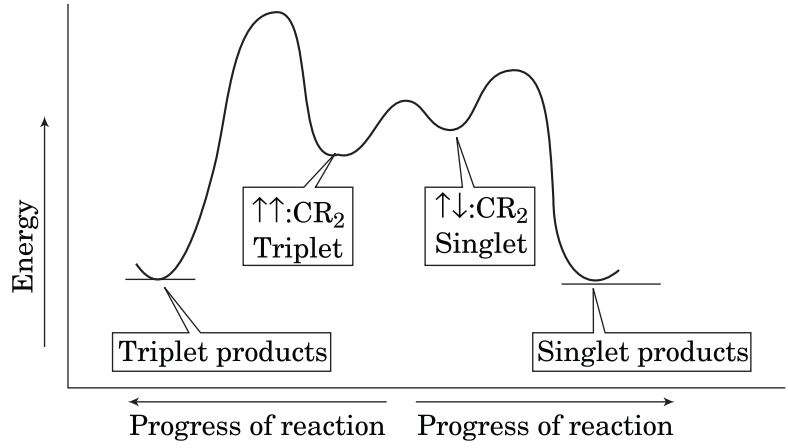
Difluorocarbene
(resonance-stabilized)

Singlet:CF_2

1.1.7.3 Equilibrium Between the Two Spin States and Reactivity

All carbenes have the potential to exist in either the singlet state or the triplet sate (the two species remain in equilibrium), so what we mean when we say that $:CH_2$ is a triplet carbene, the triplet state for this carbene is more stable (lower in energy) than the singlet state.

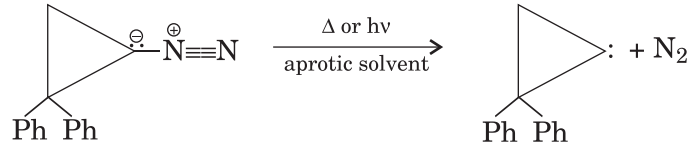
Even though there is more triplet carbene present at equilibrium, its reactions cannot compete with those of the small amount of the much more reactive singlet carbene and this is because the activation barriers surrounding the less stable singlet carbene is substantially lower than those surrounding the more stable triplet carbene. It is for this reason, most of the chemistry of carbene comes from the singlet, i.e., reactions of the singlet are the ones that are normally observed.



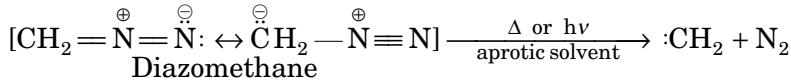
1.1.7.4 Generation of Carbenes

Carbenes can be generated from diazoalkanes, ketenes, ylides, epoxides and cyclopropane derivatives by thermal or photochemical decomposition and by α-elimination involving formation of carbanions.

(a) **From diazoalkanes:** The photolysis or thermolysis of diazoalkanes in aprotic solvents provides the most common root to carbenes. For example:



Methylene ($:CH_2$) is formed when diazomethane is subjected to photolysis or thermolysis.



(b) **From ketenes:** Ketenes on pyrolysis or photolysis loose carbon monoxide to form carbenes. For example:

$$\underset{\text{Ketene}}{CH_2{=}C{=}O} \text{ or } \underset{\text{Diphenylketene}}{Ph_2C{=}C{=}O} \xrightarrow{\Delta \text{ or } h\nu\,(\lambda = \langle 280\text{nm})} \underset{\text{Methylene}}{:CH_2} \text{ or } \underset{\text{Diphenylcarbene}}{Ph_2C: + CO}$$

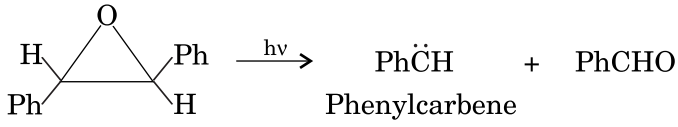
(c) **From ylides:** Carbenes can be generated by photolysis or thermolysis of sulphur, phosphrus and nitrogen ylides. For example:

$$\underset{\text{A sulphur ylide}}{Me_2\overset{\oplus}{S}-\overset{\ominus}{\ddot{C}}HCOPh} \xrightarrow{h\nu} \underset{\text{Benzoylcarbene}}{:CHCOPh} + Me_2S$$

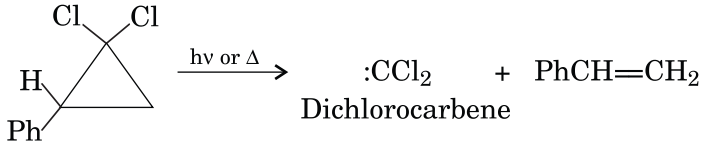
$$\underset{\text{A phosphorus ylide}}{Ph_3\overset{\oplus}{P}-\overset{\ominus}{\ddot{C}}HPh} \xrightarrow{\Delta} \underset{\text{Phenylcarbene}}{:CHPh} + Ph_3P$$

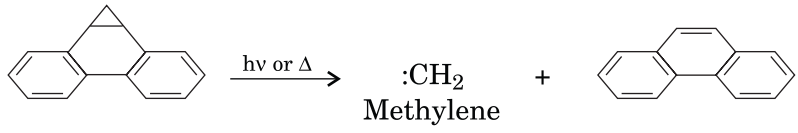
$$\underset{\text{A nitrogen ylide}}{Me_3\overset{\oplus}{N}-\overset{\ominus}{\ddot{C}}H_2} \xrightarrow{\Delta} \underset{\text{Methylene}}{:CH_2} + Me_3N$$

(d) **From epoxides:** Phenyl substituted carbenes are formed from phenyl substituted oxiranes or epoxides by photolysis. For example:

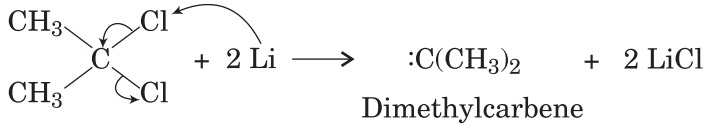


(e) **From cyclopropane derivatives:** Photolysis or thermolysis of cyclopropane derivatives leads to the formation of carbenes. For example:

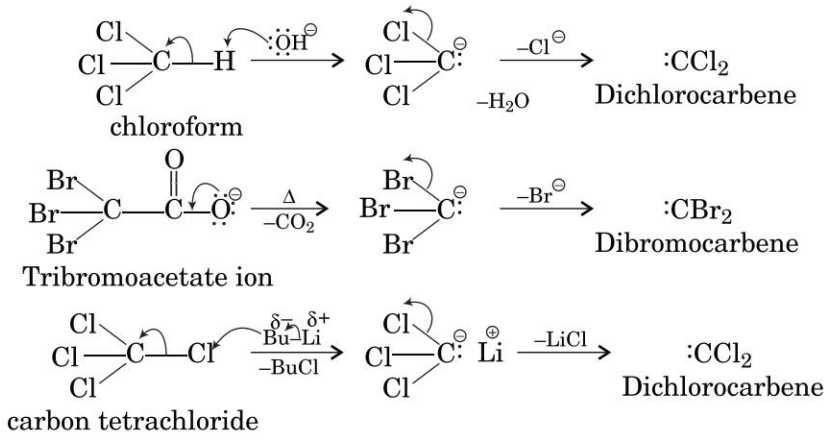




(f) **From *gem*-dichloro alkanes:** When *gem*-dichloroalkanes are treated with metallic lithium, carbenes are generated. For example:

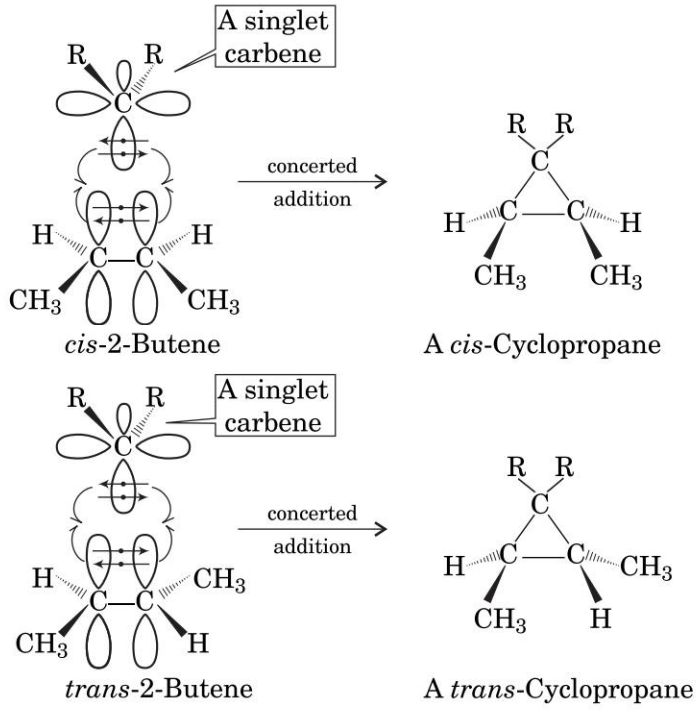


(g) **By α-elimination reactions:** Carbenes can be generated by α-elimination reactions in which both the atoms/groups are lost from the same carbon. For example:

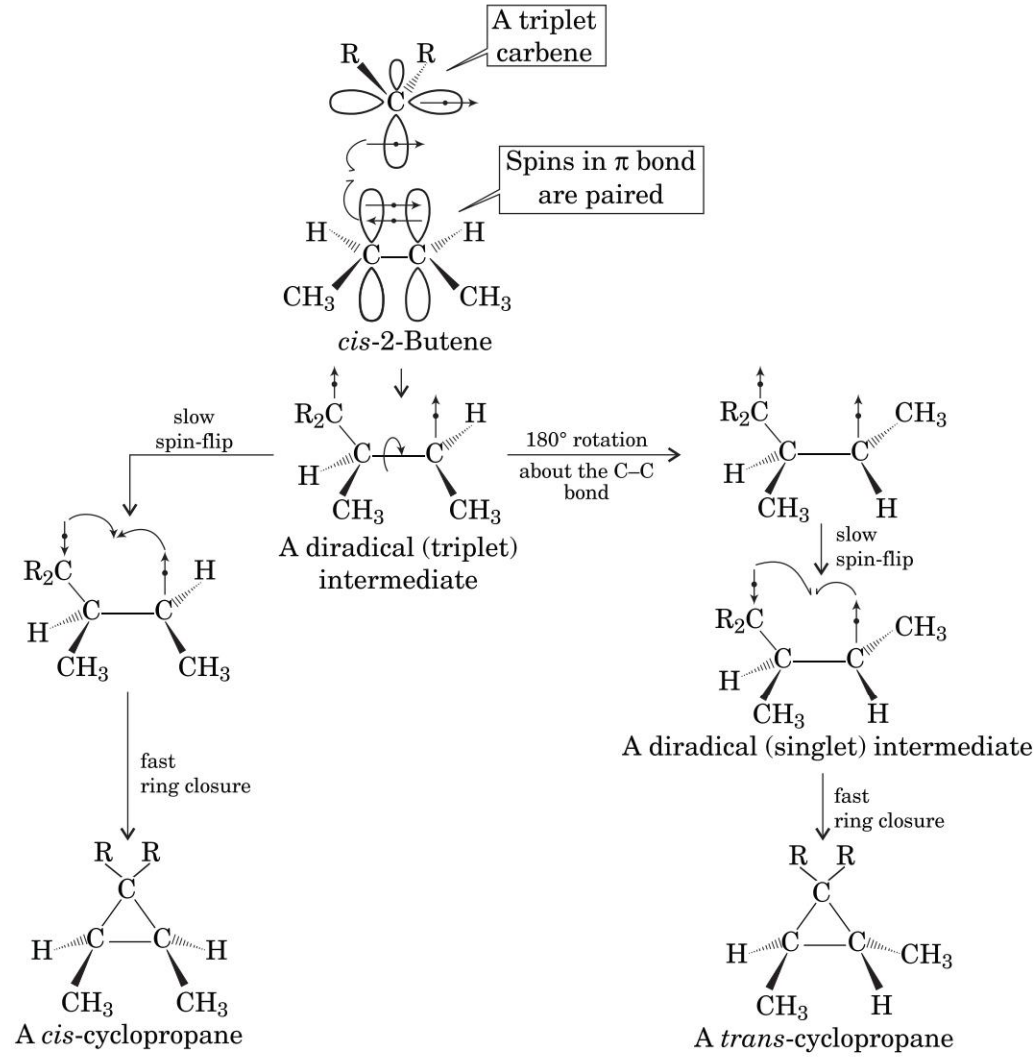


1.1.7.5 Stereospecific addition of a singlet carbene and nonstereospcific addition of triplet carbene to C=C bond to give cyclopropanes

The addition of a singlet carbene to an alkene (an electrophilic addition) is a concerted process (the two σ bonds are formed simultaneously) as the unshared electrons of the carbene are in favourable spin for ready bond formation. In this process, the original stereochemical relationship of the groups on the alkene is preserved, i.e., the addition is stereospecific and *syn*. It thus follows that singlet carbene reacts with *cis*-2-butene to yield a *cis*- cyclopropane and reacts with *trans*-2-butane to yield a *trans*- cyclopropane.



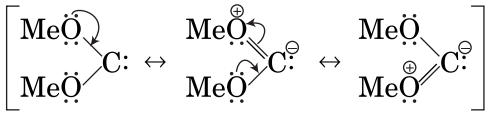
A triplet carbene, which is diradical in nature, adds to the carbon–carbon double bond of *cis*-2-butene, for example, by a free radical two-step pathway involving addition followed by recombination. As the two unpaired electrons in a triplet carbene have parallel spins, there is spin restriction on the simultaneous formation of two σ bonds. In the first step of this reaction, one of the unpaired electrons forms a σ bond with that π-electron which has the opposite spin and as a result, a diradical is formed. The diradical with two unpaired electrons having parallel spin (a triplet intermediate) undergoes spin-flipping by some appropriate collisions and then form the other σ bond to give a *cis*-cyclopropane. Since spin-flipping is relatively slow on the time scale of molecular rotation, a free rotation about the C—C bond takes place during this time. Spin-flipping followed by ring closure then produces a *trans*-cyclopropane. The reaction is, therefore, nonstereospecific (stereoselective).

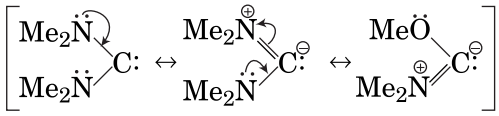


Trans-2-butene, by a similar process, produces a mixture of a *cis*- and a *trans*-cyclopropane

1.1.7.6 Nucleophilic Carbenes

Because of electron deficiency (incomplete octet of carbon), carbenes are normally electrophilic. However, there are some carbenes in which the singlet structures are stabilized by incorporating the vacant *p* orbital into some delocalized electronic system and as a consequence of resonance interaction, their electrophilic character is suppressed and nucleophilic character is developed. Such carbenes are called nucleophilic carbenes. For example:

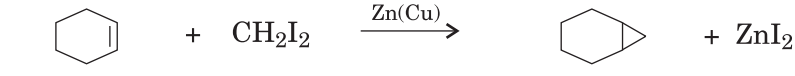
(i) 

(ii) 

1.1.7.7 Carbenoids and the Simmons–Smith Reaction

Although dihalocarbenes react with alkenes to give cyclopropanes in good yield, this is not usually the case of methylene, $:CH_2$, the simplest carbene. The reaction of $:CH_2$ with alkene often produces a complex mixture of products and therefore, the reaction cannot be reliably used for cyclopropane synthesis. A useful cyclopropane synthesis was developed by H.E. Simmons and R. D. Smith in 1959.

When alkenes are treated with methylene iodide (CH_2I_2) in the presence of zinc-copper couple (zinc dust that has been activated with an impurity of copper), cyclopropanes are obtained, this reaction is called the *Simmons–Smith reaction*. For example:



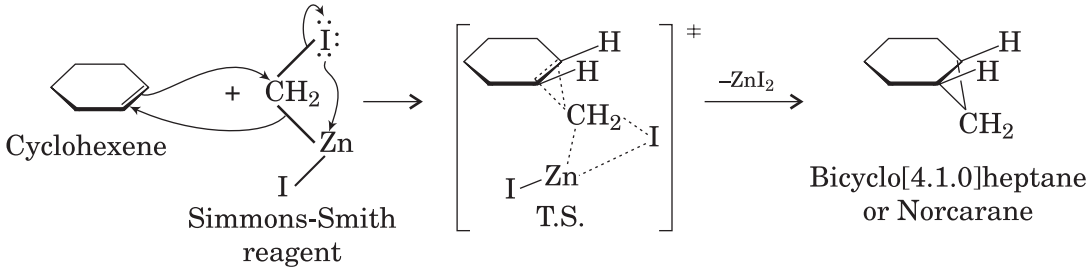
Cyclohexene — Methylene iodide — Bicyclo[4.1.0]heptane or Norcarane (61%)

The active reagent in this reaction is the α-haloorganometallic compound (a compound with halogen and a metal on the same carbon) ICH_2ZnI obtained by the following reaction similar to the formation of a Grignard reagent.

$$CH_2I_2 + Zn(Cu) \longrightarrow \underset{\substack{\text{Simmons–Smith reagent}\\ \text{(a carbenoid)}}}{I—CH_2—ZnI}$$

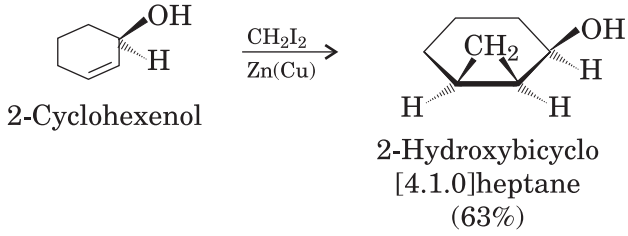
This kind of reagent is termed a *carbenoid* because it it not a free carbene but has carbenelike reactivity.

Mechanism: A concerted stereospcific transfer of methylene (:CH_2) from the carbenoid to the double bond of the alkene takes place to create a cyclopropane ring. This addition, like the addition of dichloromethylene, is a *syn*-addition. The reaction occurs as follows:

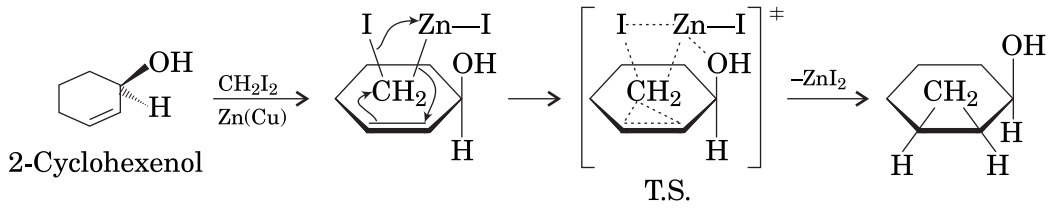


Cyclopropanation by the Simmon–Smith reaction is preferred over that involving diazomethane because diazomethane is toxic and at the same time it is explosive in nature. Furthermore, free :CH_2 inserts in $\rangle C—H$ bond to yield $\rangle C—CH_3$. No such problem arises in reactions involving carbenenoids.

When an allylic alcohol, for example, 2-cyclohexenol, is subjected to the Simmons–Smith reaction for cyclopropanation, the methylene group adds stereoselectively to the same face of the double bond as the —OH group. Furthermore, the reaction occurs at a much faster (100 times) rate than their unfunctionlized alkene equivalents. The stereoselectivity and the rate enhancement can be explained by the coordination between Zn atom and the hydroxyl group.



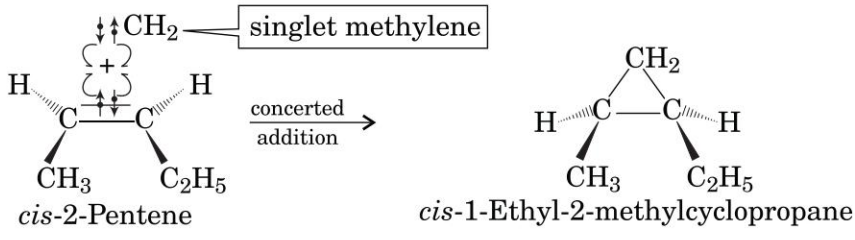
The mechanism of the reaction is as follows:



SOLVED PROBLEMS

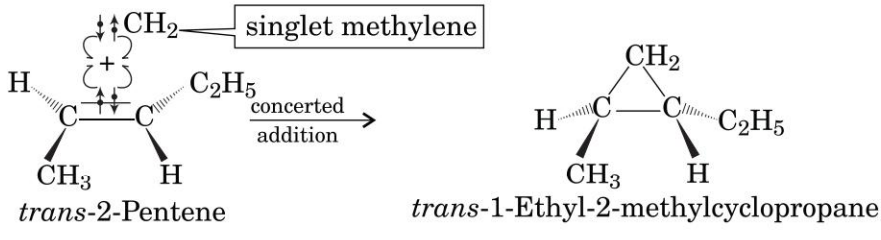
1. Photolysis of diazomethane (CH_2N_2) in liquid *cis*-2-pentene gives only *cis*-1-ethyl-2-methylcyclopropane and in liquid *trans*-2-penetene gives only *trans*-1-ethyl-2-methylcyclopropane. However, a mixture of *cis*- and *trans*-1-ethyl-2-methylcyclopropane is obtained when a gaseous mixture of either *cis*- or *trans*-2-pentene and diazomethane is photolyzed. Account for these observations.

Solution Diazomethane undergoes photolytic decomposition in the liquid phase to produce singlet methylene ($:CH_2$). In liquid phase the singlet methylene is very close to the alkene molecule and so, it reacts with the alkene molecule before being converted into the stable triplet state. For singlet methylene, the two nonbonding electrons have paired (opposite) spins and so, it produces the two new cyclopropane C — C bonds simultaneously by combining with the two paired electrons in the π bond of the alkene. The reaction thus takes place in a concerted fashion, preserving the original stereochemical relationship of the groups on the alkene. The addition is, therefore, stereospecific and *syn*. For this reason, photolysis of diazomethane in liquid *cis*-2-pentene gives only *cis*-1-ethyl-2-methylcyclopropane and in liquid *trans*-2-pentene gives only trans-1-ethyl-2-methylcyclopropane.



cis-2-Pentene

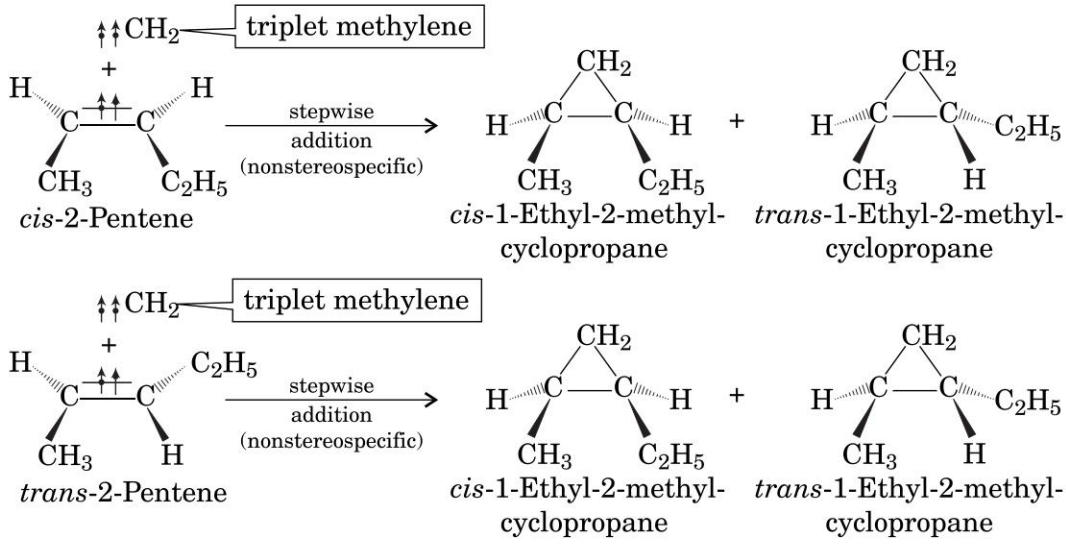
cis-1-Ethyl-2-methylcyclopropane



trans-2-Pentene

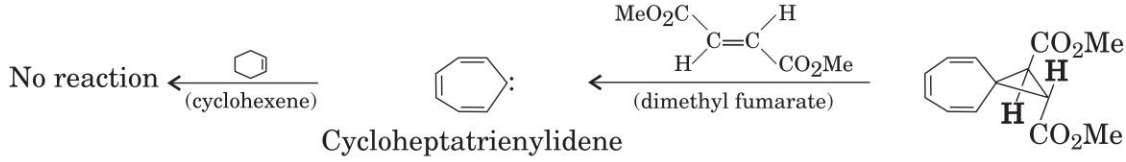
trans-1-Ethyl-2-methylcyclopropane

When diazomethane is subjected to photolysis in the gas phase where the alkene is present in low concentration, the initially formed singlet methylene gets enough time to react with the alkene molecule and in the mean time it becomes converted into the stable triplet state by transferring energy to its surroundings. Triplet methylene, which is diradical in nature, adds to the carbon–carbon double bond by a free radical two-step pathway involving addition followed by recombination. As a result the reaction becomes nonstereospecific (stereoselective) and for this reason, when a gaseous mixture of both *cis*- or *trans*-2-pentene and diazomethane is photolyzed, a mixture of both *cis*- and *trans*-1-ethyl-2-methylcyclpropane is obtained.



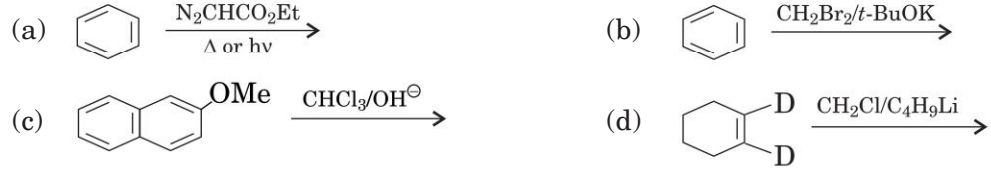
For mechanism of the reaction see article 1.1.7.5.

2. Explain the following observations:



Solution Because of resonance interaction, cycloheptatrienylidene is a nucleophilic carbene. For this reason, it reacts with the electrophilic alkene dimethyl fumarate to form a cyclopropane derivative stereospecifically, but not with the nucleophilic alkene cyclohexene.

3. Predict the product and suggest a mechanism for each of the following reactions:



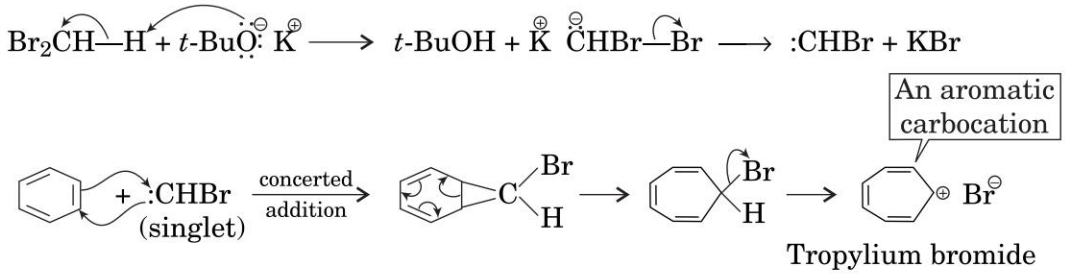
Solution

(a) $:N\equiv\overset{\oplus}{N}-\overset{\ominus}{\ddot{C}}HCO_2Et \xrightarrow{h\nu \text{ or } \Delta} :CHCO_2Et + N_2$

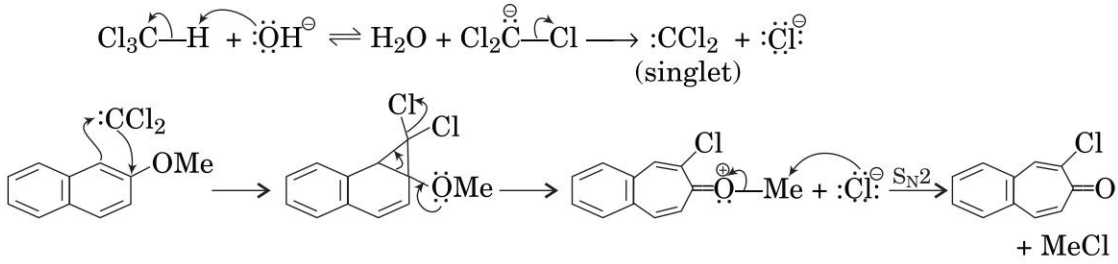


Diazoacetic ester dissociates to give the carbene :$CHCO_2Et$ which reacts with benzene concertedly to give a cycloheptatriene ester by ring expansion.

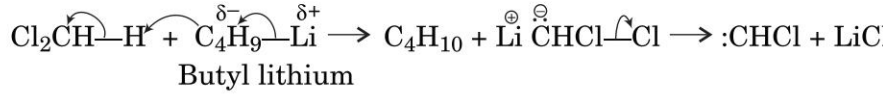
(b) Dibromomethane reacts with the base *t*-BuOk to form the carbene :CHBr which reacts with benzene to yield tropylium bromide.



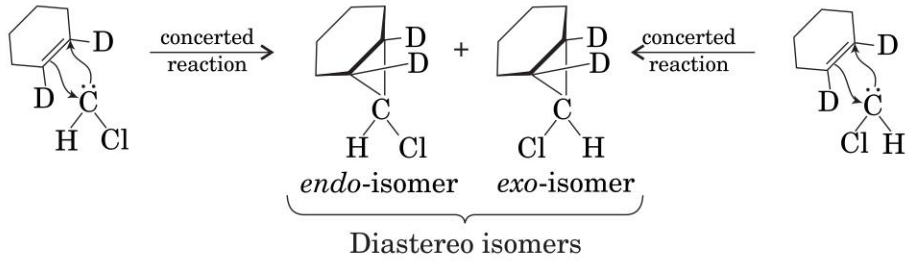
(c) Chloroform reacts with alkali to produce dichlorocarbene (:CCl_2). It adds to 2-methoxynaphthalene at the 1,2-position (because this double bond is activated by the –OMe group at C-2) to give an unstable cyclopropane derivative which readily dissociates to yield a ketone.



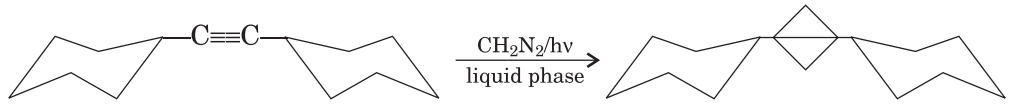
(d) Methylene chloride (CH_2Cl_2) reacts with the base butyllithium to form chlorocarbene (:CHCl) by an α-elimination process:

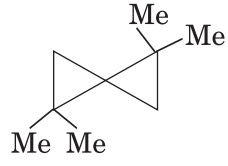


Chlorocarbene (singlet) adds to 1,2-dideuteriocyclohexene by a concerted *syn* process to yield a mixture of two stereoisomeric chlorocyclopropane derivatives (*endo*- and *exo*-isomers).



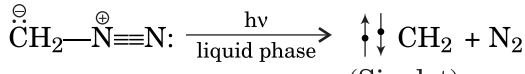
4. Explain the formation of product in each of the following reactions:

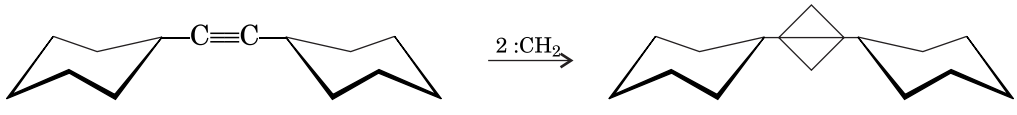
(a) 

(b) $Me_2C{=}C{=}CMe_2$ $\xrightarrow[\text{liquid phase}]{CH_2N_2/h\nu}$ 

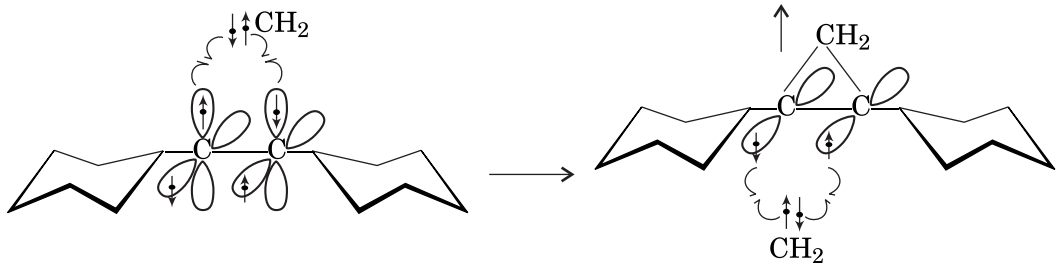
Solution

(a) Since alkyne contains two π bonds, therefore, it reacts with two moles of singlet methylene to give finally a bicylobutane derivative.



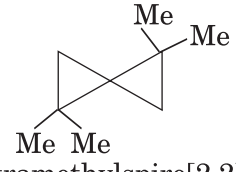


Dicyclohexyl acetylene → 1,3-Dicyclohexylbicyclo[1.1.0]butane

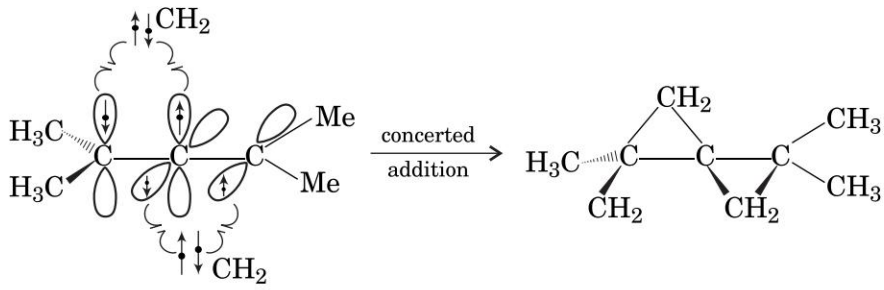


(b) 2,4-Dimethyl-2,3-pentadiene (an allene) contains two mutually perpendicular π orbitals. Singlet methylene obtained on photolysis of diazomethane in liquid phase adds to the π orbitals in a concerted fashion to produce the tetramethyl derivative of spiro[2,2]pentane in which the two orthogonal cyclopropane rings are joined by a common tetrahedral carbon atom.

$\overset{\ominus}{\cdot\cdot}CH_2—\overset{\oplus}{N}{\equiv}N:$ $\xrightarrow[\text{liquid phase}]{h\nu}$ $CH_2 + N_2$

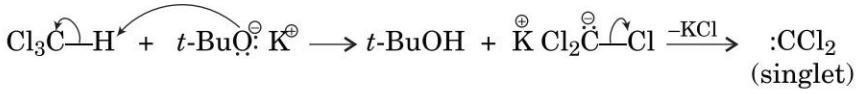
$Me_2C{=}C{=}CMe_2 + 2\ :CH_2 \longrightarrow$ 

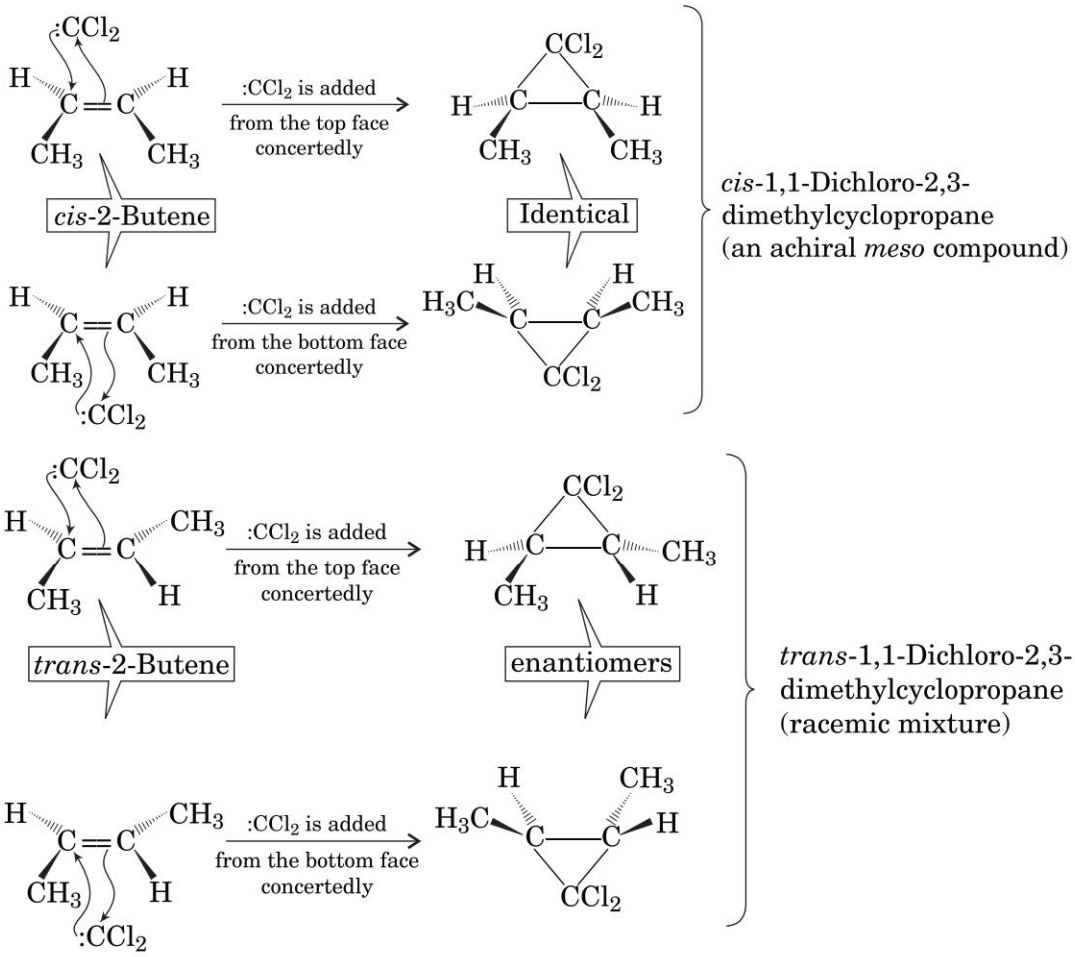
2,4-Dimethyl-2,3-pentadiene → 1,1,4,4-Tetramethylspiro[2.2]pentane



5. Draw the products obtained when *cis*- and *trans*-2-butene are treated with $CHCl_3$ and *t*-BuOK and comment on the stereochemical outcome of these two reactions.

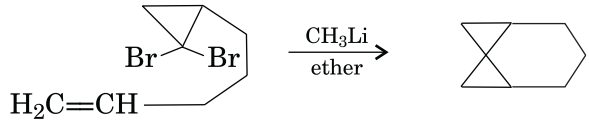
Solution



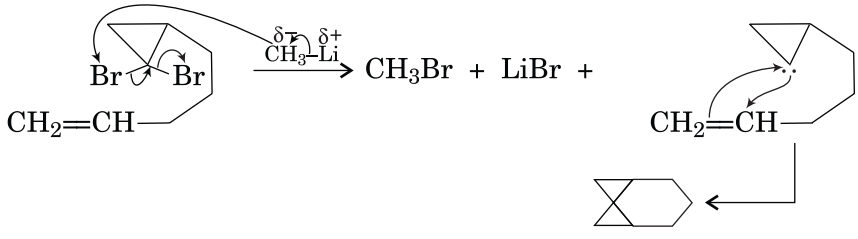


Addition of :CCl_2 from either side of *cis*-2-butene yields an achiral *meso* compound, while addition from either side of *trans*-2-butene yields a racemic mixture (an equal amount of two enantiomers).

6. Suggest a mechanism for the following reaction:

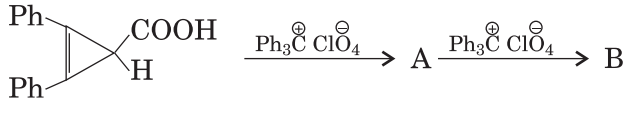


Solution This is a case of intramolecular addition of carbene to a double bond.

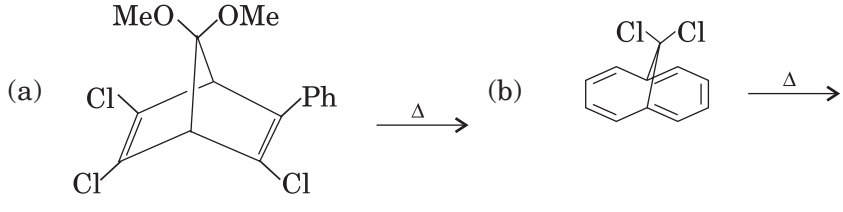


Study Problems

1. Predict the product obtained in each step of the following reaction sequence:



2. Predict the product and suggest a mechanism for each of the following reactions:

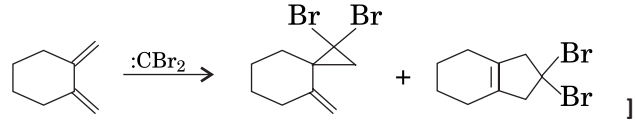


3. If in the gas phase photolysis of diazomethane, there is present a little oxygen in the system, *cis*-2-butene gives only *cis*-1,2-dimethylcyclopropane and *trans*-2-butene gives only *trans*-1-2-dimethylcyclopropane, i.e., the reaction becomes stereospecific. Explain these observations.

4. Identify A and B in the following reaction:

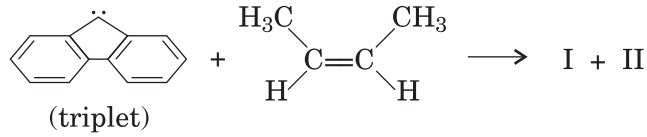
$$CH_3CH{=}C{=}CH_2 + \underset{(1\text{ equiv.})}{:CH_2(\text{singlet})} \longrightarrow A + B$$

5. Give the products expected to be formed when a triplet carbene is allowed to react with a conjugated diene like $CH_2{=}CH{-}CH{=}CH_2$ and explain their formation. **[Hint:** A cyclopropane and cyclopentene derivative will be formed. For example:



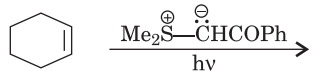
]

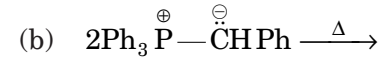
6. Identify the products I and II in the following reaction and explain their formation:



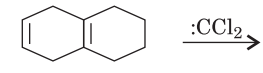
7. Explain why olefins like dimethyl fumarate do not form cyclopropanes with normal carbenes.

8. Give the products expected to be obtained in each of the following reactions:

(a) 

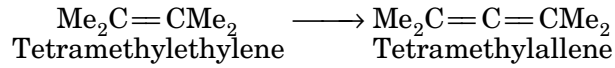
(b) 

(c) 

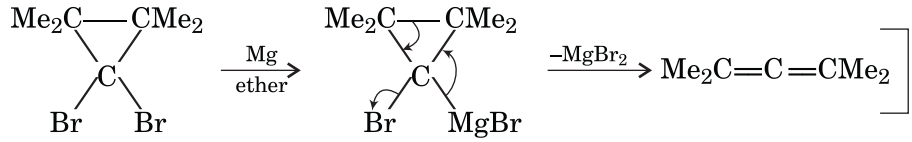
(d) 

9. Explain why dimethoxy carbene does not react with propene.

10. Outline the steps of the following conversion and give the mechanism involved in each step:



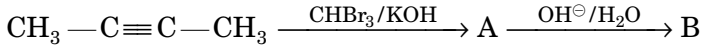
Hint:



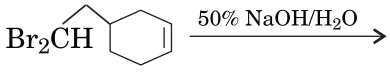
11. Draw the structures of carbene addition products of a resolvable allene. Would the product(s) be resolvable? Justify.

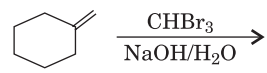
12. Which one is more stable between $:CF_2$ and $:CCl_2$ and why?

13. Predict the products A and B in the following reaction sequence and explain their formation:

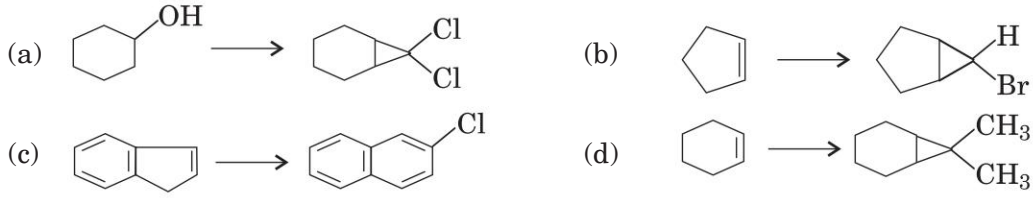


14. Identify the products of the following reactions:

(a) 

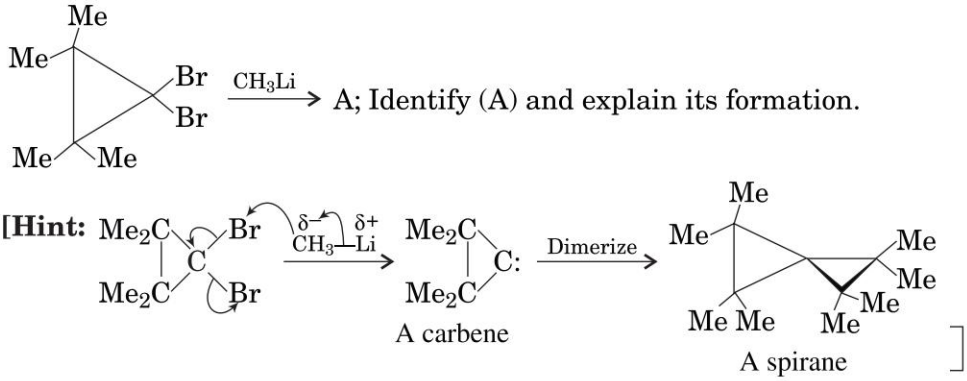
(b) 

15. Show how you would accomplish each of the following synthetic conversions:



16. What stereoisomers are expected to be obtained when *trans*-3-hexene is treated with CH_2I and Zn(Cu)?

17.



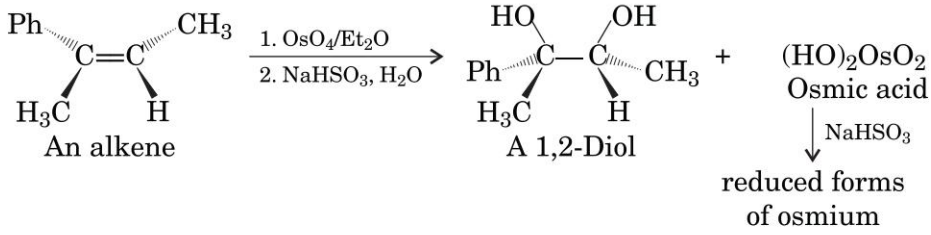
1.1.8 Hydroxylation of Alkenes

1.1.8.1 Syn- and Anti-Hydroxylation of Alkenes

The conversion of alkenes to 1,2-diols by oxidation and subsequent hydrolysis is known as hydroxylation of alkenes. Depending on the reagent, when the two new –OH groups are added to the same side of the double bond, it is called *syn*-hydroxylation and when they are added to the opposite sides of the double bond, it is called *anti*-hydroxylation.

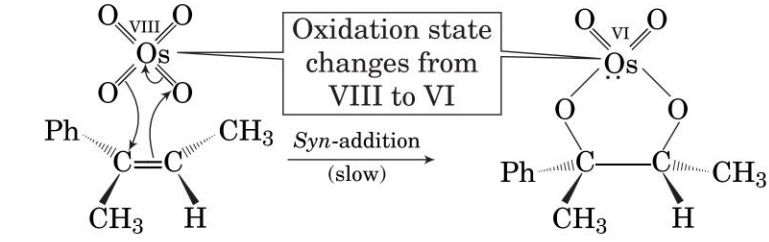
1.1.8.2 Syn-Hydroxylation of Alkenes by Osmium Tetroxide

Syn-hydroxylation of alkenes may be carried out conveniently by osmium tetroxide (OsO_4), a highly toxic, volatile and very expensive reagent. The process involves treatment of an alkene with OsO_4 in an inert solvent like ether or dioxane followed by simple hydrolysis of the resulting osmate ester in the presence of sodium bisulphite ($NaHSO_3$). $NaHSO_3$ converts the osmium-containing by-product into reduced forms of osmium that are easy to remove by filtration. For example:

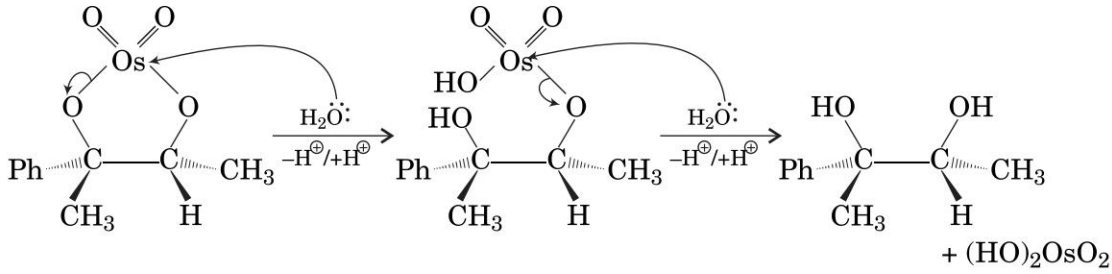


Mechanism: *Syn*-hydroxylation of the alkene by osmium tetroxide proceeds through the following two steps:

Step 1: Osmium tetroxide (OsO_4) adds its two oxygen atoms to the same side or face of the double bond concertedly to yield a cyclic osmate ester. Osmium in OsO_4 is in +8 oxidation state. Metals in high oxidation states are oxidizing agents because they attract electrons. This electron-attracting ability of Os (VIII) results in a concerted (one-step) cycloaddition reaction between OsO_4 and the alkene. OsO_4, in fact, behaves almost as a dipolar ion, even though it is not a formal 1,3-dipolar species.

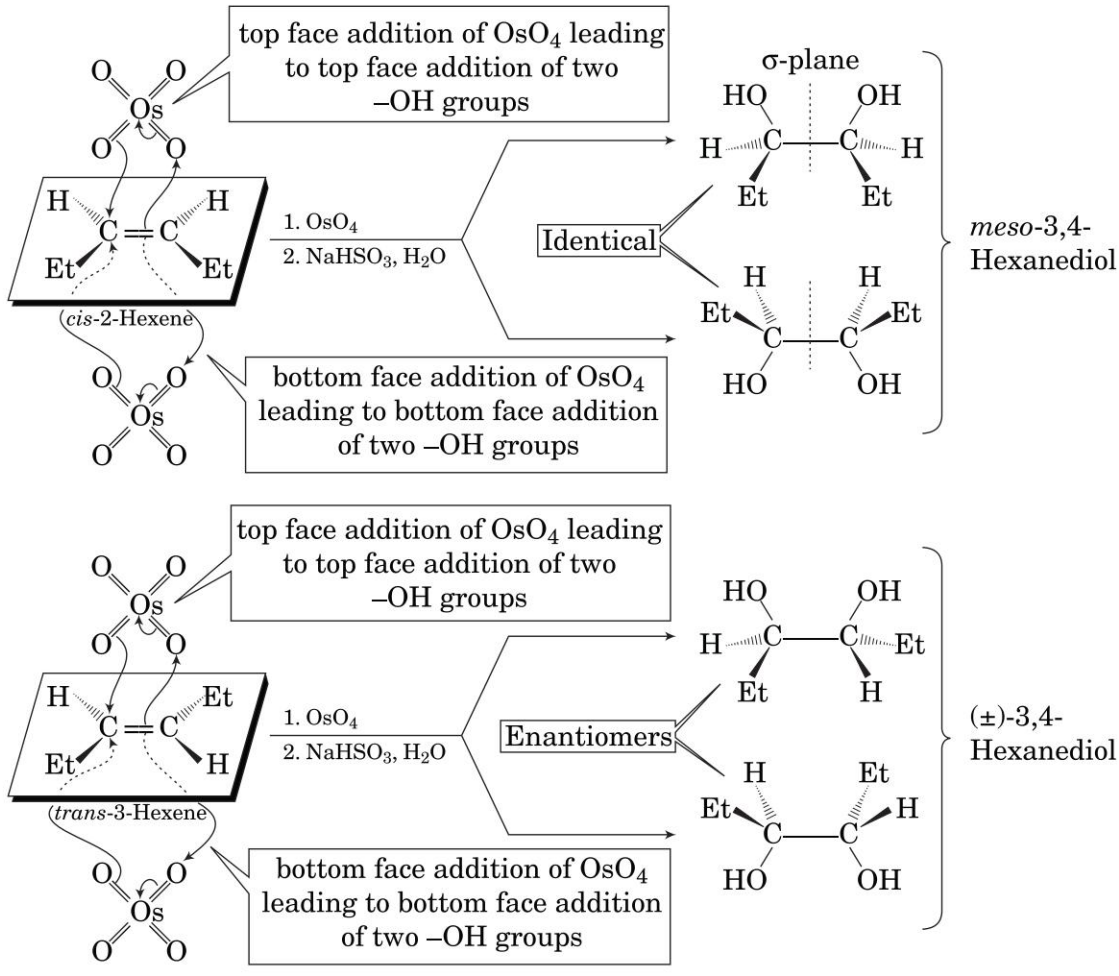


Step 2: Hydrolysis of the osmate enter gives the 1,2-diol.

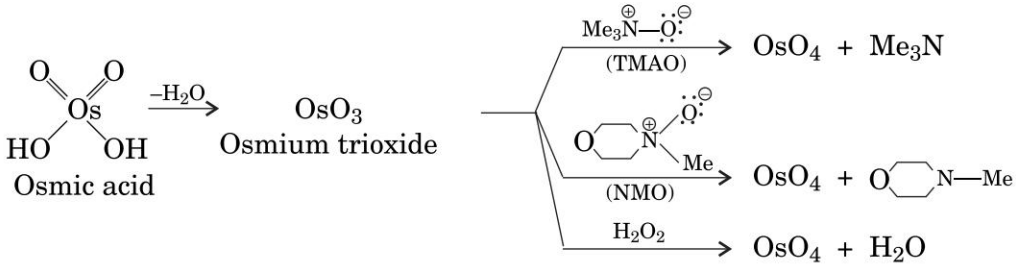


Since, in the first step, both the C—O bonds are formed simultaneously to form a cyclic osmate ester and in the second step, its hydrolysis involves cleavage of O—Os bonds, therefore, the overall reaction results in a stereospecific *syn*-hydroxylation. A cycloalkene, for example, forms a *cis*-1,2-diol.

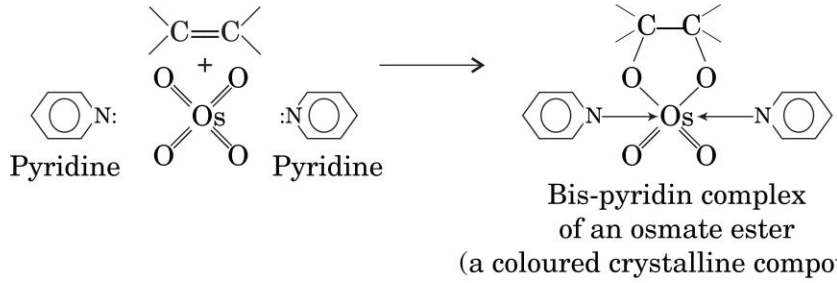
Proof of *syn*-stereospecificity: The *syn*-stereospecificity of the reaction can be proved by the fact that *cis*-3-hexene gives optically inactive *meso*-3,4-hexanediol and *trans*-3-hexene gives optically inactive racemic or (±)-3,4-hexanediol (resolvable).



Overcoming limitation of OsO_4: Unlike $KMnO_4$ (which also causes *syn*-hydroxylation), OsO_4 is more selective oxidant and is soluble in organic solvents. However, it is much more expensive than $KMnO_4$ and is also toxic. To overcome these limitations, hydroxylation is to be carried out by using a catalytic amount of OsO_4 in the presence of an oxidant [an amine oxide, e.g., trimethylamine-*N*-oxide (TMAO) or *N*-methylmorpholine-*N*-oxide (NMO) that recycles the Os (VI) byproduct (osmic acid) back to OsO_4. That is, once a small amount of OsO_4 is used up, osmic acid is oxidized within the reaction mixture by the amine oxide to re-form OsO_4. Hydrogen peroxide (H_2O_2) may also be used for recovering OsO_4 from osmic acid.

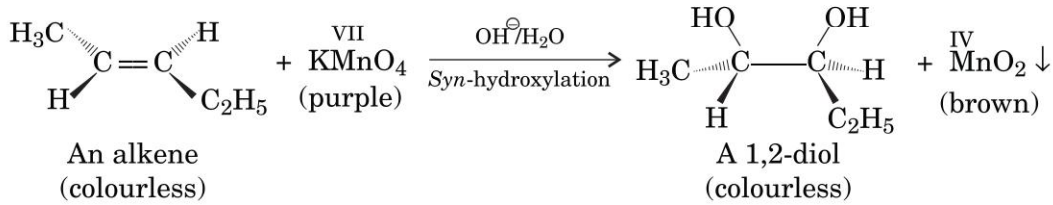


Proof of the formation of intermediate osmate ester: The formation of the osmate ester can be proved by its isolation. When the addition of OsO_4 to an alkene is carried out in the presence of pyridine, usually a theoretical amount of a coloured crystalline compound in obtained.



1.1.8.3 Syn-Hydroxylation of Alkenes by Basic Solutions of Potassium Permanganate ($KMnO_4$)

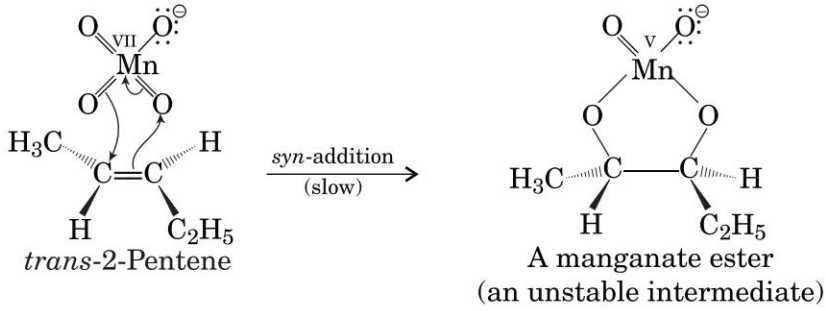
An alkene can also be oxidized to 1,2-diol (*syn*-hydroxylation) by a basic solution of potassium permanganate ($KMnO_4$) at room temperature or below. In this reaction, the purple colour of permanganate disappears and a brown-black precipitate of manganese dioxide (MnO_2) appears. Because of this, the reaction is frequently used as a chemical test (Bayer test) for the presence of unsaturation (i.e., carbon–carbon multiple bond) in an unknown compound containing no easily oxidizable functional group. For example:



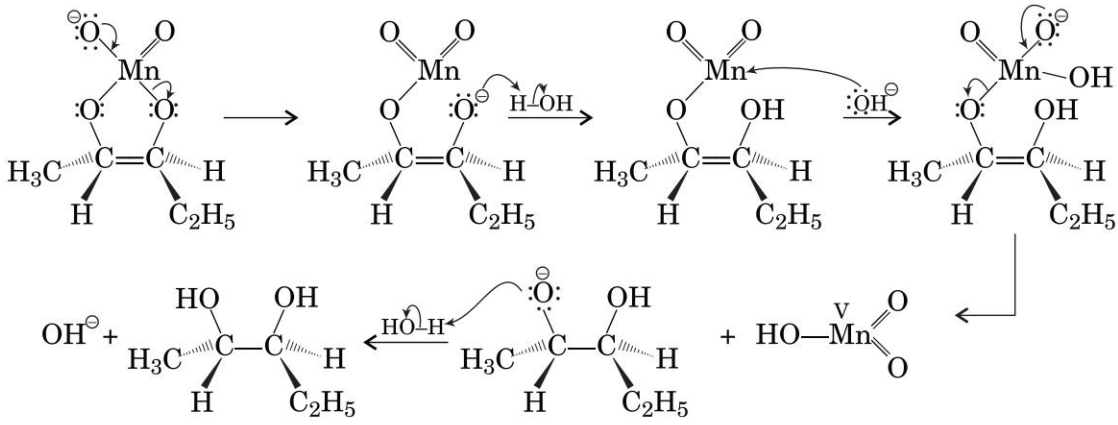
Mechanism: *Syn*-hydroxylation of the alkene by potassium permanganate ($KMnO_4$) proceeds through the following two steps:

Step 1: The permanganate ion ($MnO_4^{\ominus}$) adds its two oxygen atoms to the same side or face of the double bond concertedly to yield a cyclic manganate ester. Manganese in $MnO_4^{\ominus}$ is in +7

oxidation state. Metals in high oxidation states are oxidizing agents because they attract electrons. The electron-attracting ability of Mn (VII) results in a concerted (one-step) cycloaddition reaction between $MnO_4^{\ominus}$ and alkene. By accepting extra electrons Mn goes to the lower oxidation state. $MnO_4^{\ominus}$ behaves almost as a dipolar ion, even though it is not a formal 1,3-dipolar species.



Step 2 : Ready hydrolysis (cleavage of Mn—O bonds) of the manganate ester gives the diol.



Since, in the first step, both the C—O bonds are formed simultaneously to form the cyclic manganate ester and in the second step, its hydrolysis involves cleavage of O—Mn bonds (as evidenced from the labelling experiment using $Mn\overset{18}{O}_4^{\ominus}$), therefore, the overall reaction results in stereospecific *syn*-hydroxylation. A cycloalkene, for example, forms a *cis*-1,2-diol.

Proof of *syn*-stereospecificity: The *syn*-steroeospecificity of the reaction can be proved by the fact that *cis*-2-butene gives optically inactive *meso*-2,3-butanediol and *trans*-2-butene gives optically inactive racemic or (±)-2,3-butanediol (resolvable). The stereochemical course is similar to that shown in **article No. 1.1.8.2**.

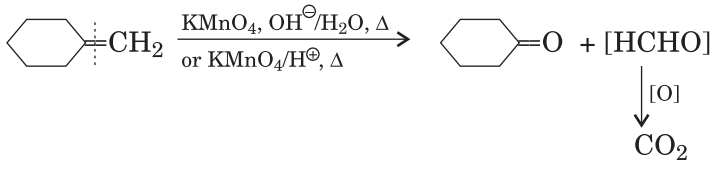
1.1.8.4 Cleavage of C═C by Acidic or Alkaline Solution of $KMnO_4$

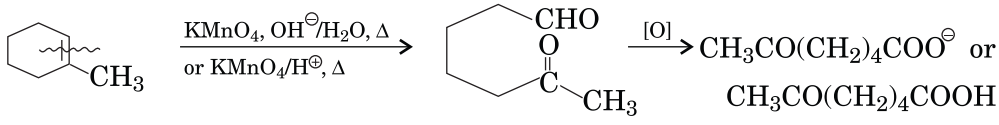
When heated with an acidic or alkaline solution of $KMnO_4$, alkenes undergo over oxidation involving cleavage of the double bond (through the formation of glycols) to yield ketones, carboxylic acids/salts and carbon dioxide. A terminal $=CR_2$ becomes converted into

a ketone, a terminal $=CHR$ becomes converted into a carboxylic acid or its salt and a terminal $=CH_2$ becomes converted into carbon dioxide. For example:

(i) $CH_3CH_2\overset{\overset{CH_3}{|}}{C}=CHCH_3 \xrightarrow[\text{or } KMnO_4/H^{\oplus},\Delta]{KMnO_4, OH^{\ominus}/H_2O, \Delta} CH_3CH_2\overset{\overset{CH_3}{|}}{C}=O + [CH_3CHO] \xrightarrow{[O]} CH_3COO^{\ominus} \text{ or } CH_3COOH$

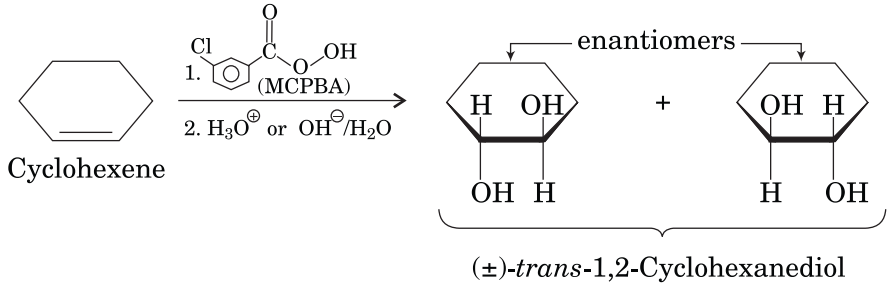
(ii) $(CH_3)_2=C(CH_3)_2 \xrightarrow[\text{or } KMnO_4/H^{\oplus},\Delta]{KMnO_4, OH^{\ominus}/H_2O, \Delta} 2\,CH_3-\overset{\overset{O}{\|}}{C}-CH_3$

(iii) 

(iv) 

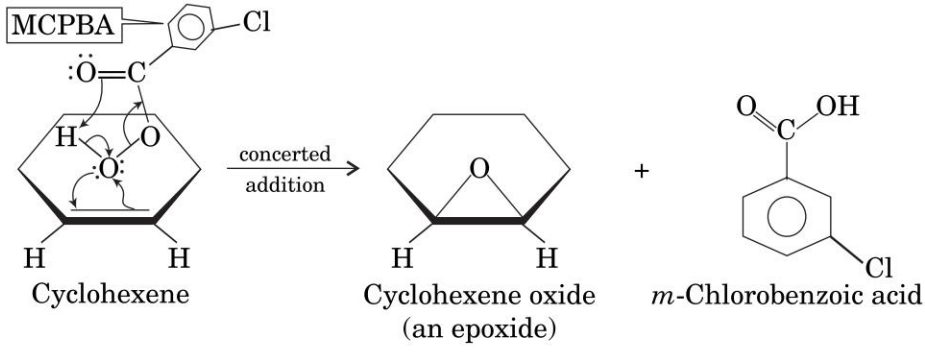
1.1.8.5 Anti-Hydroxylation of Alkenes by Treating with a Peroxy Acid Followed by Acid- or Base-Catalyzed Hydrolysis

Anti-hydroxylation of an alkene may be carried out by epoxidation of that alkene with a peroxy acid (RCOOOH – sometimes called simply a peracid) like peroxyacetic acid (CH_3COOOH), peroxybenzoic acid (C_6H_5 COOOH), *m*-chloroperoxybenzoic acid or MCPBA (*m*-ClC_6H_4COOOH), or trifluoroperoxyacetic acid (CF_3COOOH) followed by acid- or base-catalyzed hydrolysis of the epoxide formed. For example:



Mechanism: In the first step of this reaction sequence, the peroxyacid epoxidizes the alkene by a concerted electrophilic reaction where several bonds are broken and several bonds are formed at the same time. The oxygen atom of the –OH group of the peroxyacid accepts a pair of electrons from the π bond of the alkene, causing the weak O—O bond to break. The electrons of the O—O bond are delocalized onto the carbonyl group. The

electrons left behind as the O—H bond breaks add to that doubly bonded carbon which becomes electron deficient when the π bond breaks.

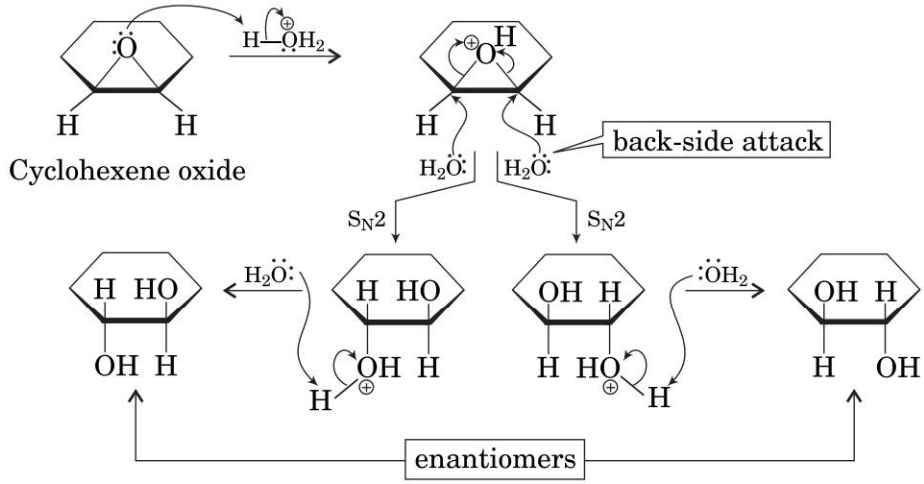


The streochemistry of the alkene is retained in the epoxide because both the carbon–oxygen bonds of the epoxide are formed simultaneously. Therefore, the epoxidation reaction is stereospecific.

The peroxyacid adds an O atom from either above or below the plane of the double bond to form a single achiral epoxide, so in this case only one representation is shown.

In the second step, acid- or base-catalyzed hydrolysis of the epoxide takes place to form (±)-*trans*-1,2-cyclohexanediol.

Acid-catalyzed ring opening:

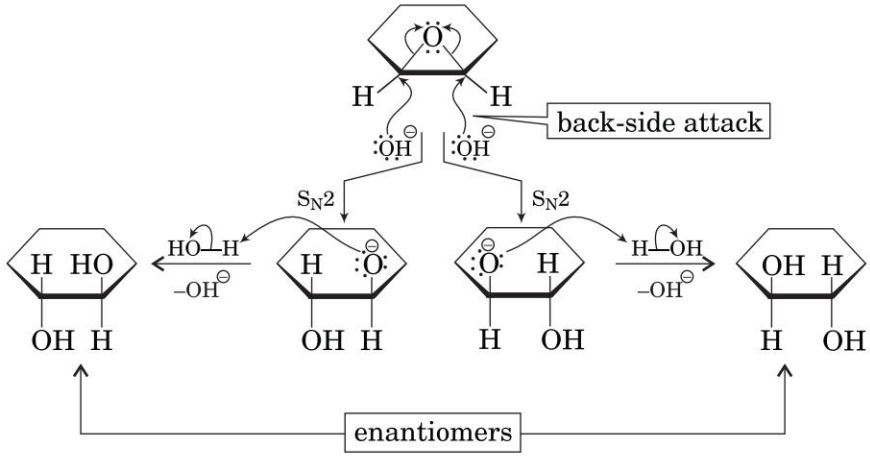


(±)-*trans*-Cyclohexanediol

The epoxide undergoes protonation and as a result, the ring oxygen becomes a better leaving group. Nucleophilic attack (S_N2) by the weak nucleophile water on the protonated epoxide takes place from the opposite side to the epoxy bridge. This results in formation of the 1,2-diol. Because one –OH group of the 1,2-diol comes from the epoxide and one –OH

group comes from the nucleophile H_2O, the overall result is stereospecific *anti*-addition of two –OH groups to the alkene.

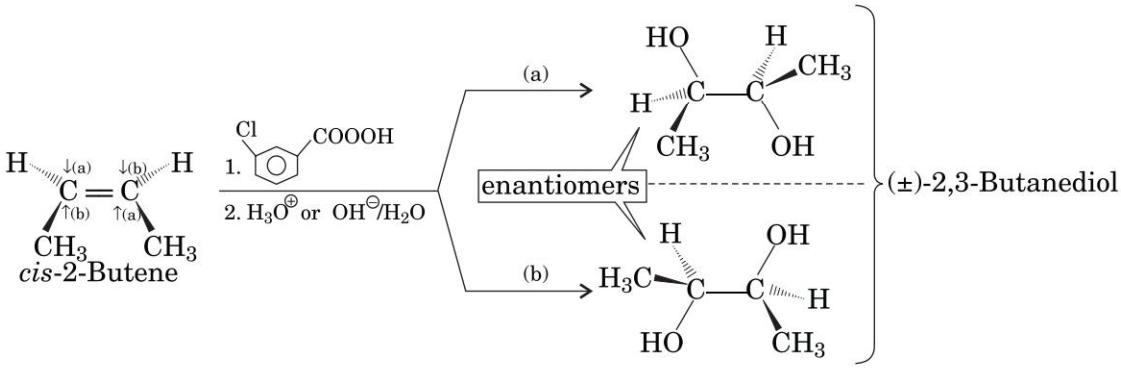
Base-catalyzed ring opening



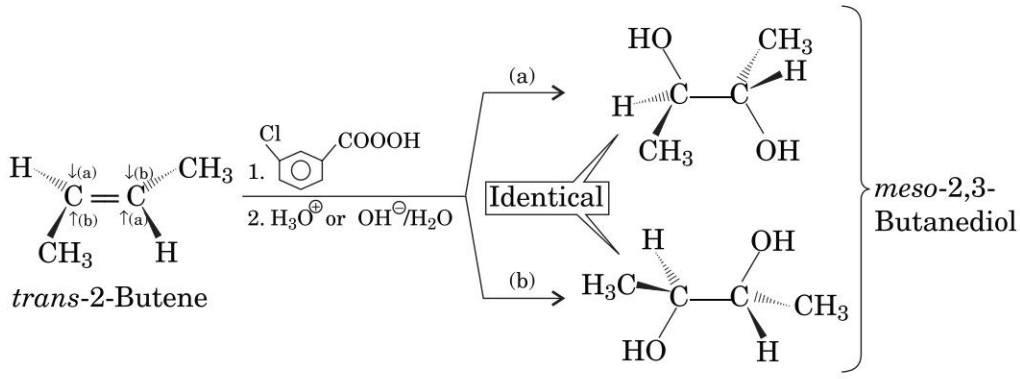
(±)-*trans*-1,2-Cyclohexanediol

The epoxide undergoes nucleophilic attack (S_N2) by $OH^{\ominus}$ from the opposite side to the oxygen bridge to form an alkoxide which takes up a proton from water to yield the 1,2-diol. Because one –OH group of the diol comes from the nucleophile $OH^{\ominus}$ and one comes from the epoxide, the overall result is stereospecific *anti*-addition of two –OH groups to the alkene.

Proof of *anti*-stereospecificity: The *anti*-stereospecificity of the overall reaction can be proved by the fact that *cis*-2-butene produces optically inactive racemic or (±)-2,3-butanediol (resolvable) and *trans*-2-butene produces optically inactive *meso*-2,3-butanediol (nonresolvable).

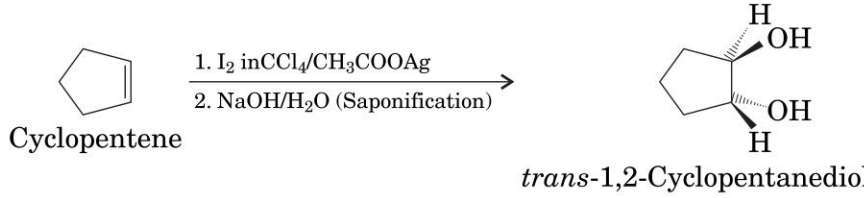


cis-2-Butene

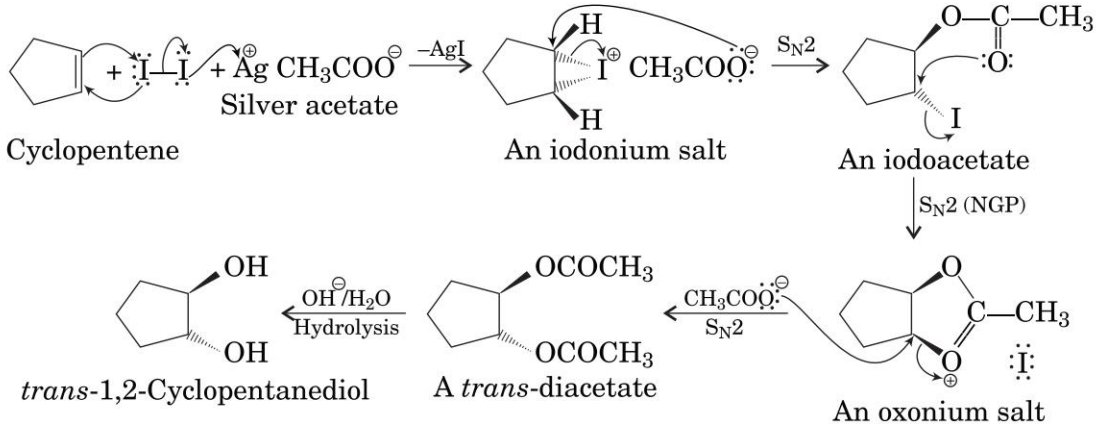


1.1.8.6 Prevost Oxidation (a Method of Preparing Trans-1,2-diols From Alkenes)

When a solution of iodine in CCl_4 and an equimolar amount of silver acetate (CH_3COOAg) or silver benzoate (PhCOOAg) is treated with alkene under dry conditions, the alkene is converted into diacetyl derivative of the corresponding *trans*-diol. The diacetate on alkaline hydrolysis (saponification) produces the *trans*-diol. The reaction is called the *Prevost oxidation.* For example:



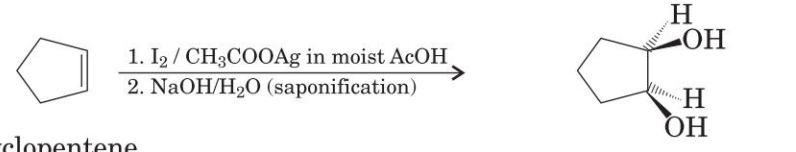
Mechanism: The mechanism of the Prevost reaction involves the steps as follows:



Cyclopentene reacts with iodine in the presence of silver acetate to give an iodonium salt. The iodonium ion undergoes ring-opening by an S_N2 attack involving $CH_3COO^{\ominus}$ as the nucleophile to yield a *trans*-iodoacetate. The iodoacetate undergoes an intramolecular S_N2

reaction (neighbouring group participation) to yield an oxonium salt which is subsequently opened up by an S_N2 attack by acetate ion to yield a *trans*-diacetate. On saponification the diacetate produces *trans*-1,2-cyclopentanediol.

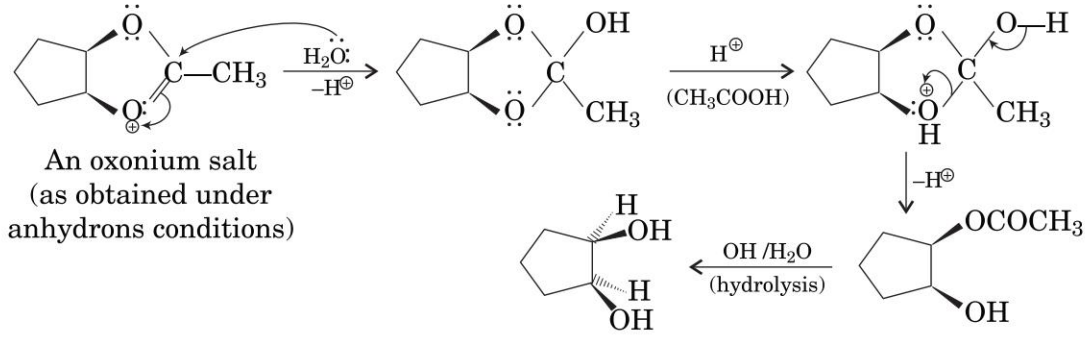
Woodward modification of Prevost oxidation: When the Prevost oxidation is not carried out under anhydrous conditions but in the presence of water, a *cis*-diacetate is obtained, which on saponification yields *cis*-diol. This is what is called the Woodward modification of the Prevost oxidation. For example, when cyclopentene is treated with I_2 and CH_3COOAg in moist acetic acid, the monoacetate of *cis*-1,2-cyclopentanediol is obtained, which on saponification produces the *cis*-diol.



Cyclopentene

cis-1,2-Cyclopentanediol

Mechanism: The mechanism of the reaction involves the steps as follows:

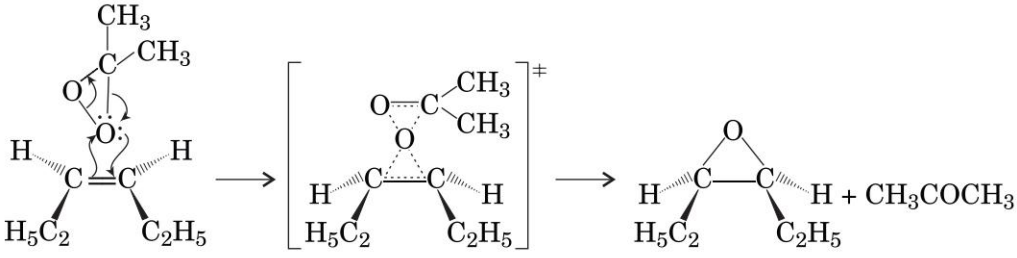


An oxonium salt (as obtained under anhydrons conditions)

cis-1,2-Cyclopentanediol

1.1.8.7 Epoxidation of Alkenes by Dimethyldioxirane

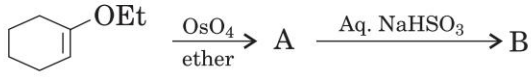
Dimethyl dioxirane is a powerful epoxidation reagent. It transfers one oxygen atom to a carbon–carbon double bond causing stereospecific epoxidation. *Cis*-3-Hexene, for example, reacts with dimethyldioxirane produces *cis*-1,2-diethyloxirane. The reaction occurs by a one-step (concerted) pathway involving a butterfly transition state.

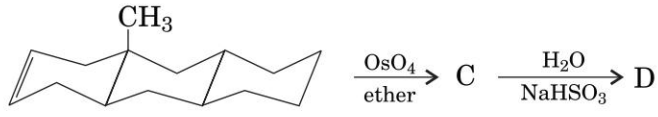


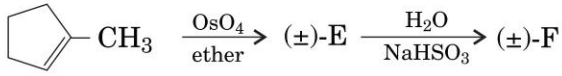
cis-3-Hexene butterfly T.S. *cis*-1-2-Diethyloxirane

SOLVED PROBLEMS

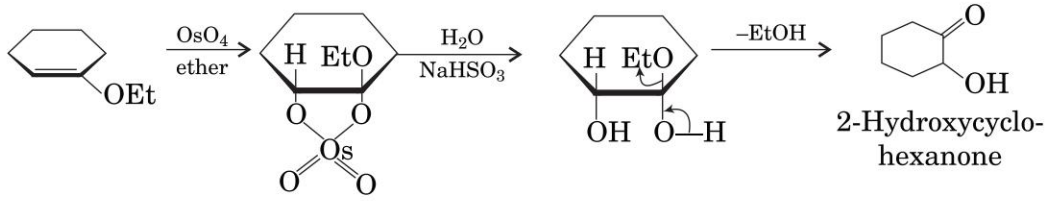
1. Identify the product (with stereochemistry if appropriate) obtained in each step of the following reaction sequences:

(a) 

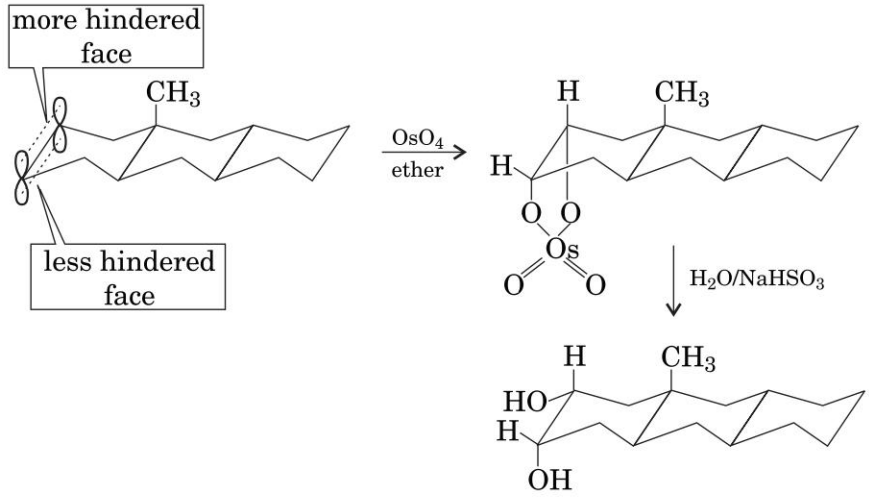
(b) 

(c) 

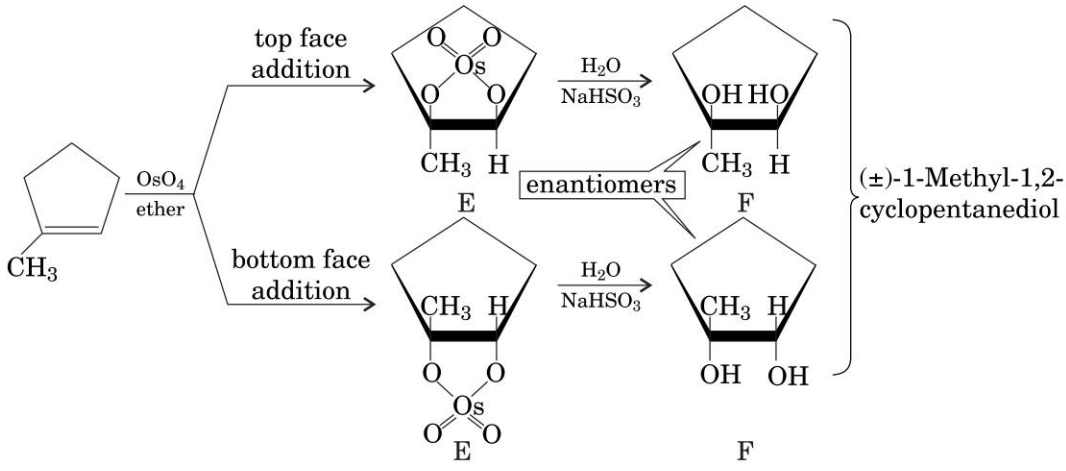
Solution

(a) 

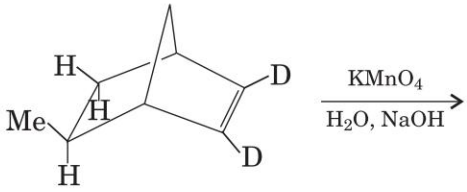
(b) Because of large steric requirement of OsO_4, it attack the regid perhydroanthracene system from the less hindered side (opposite to the $–CH_3$ group) to give finally a *cis*- 1,2-diol.



(c)

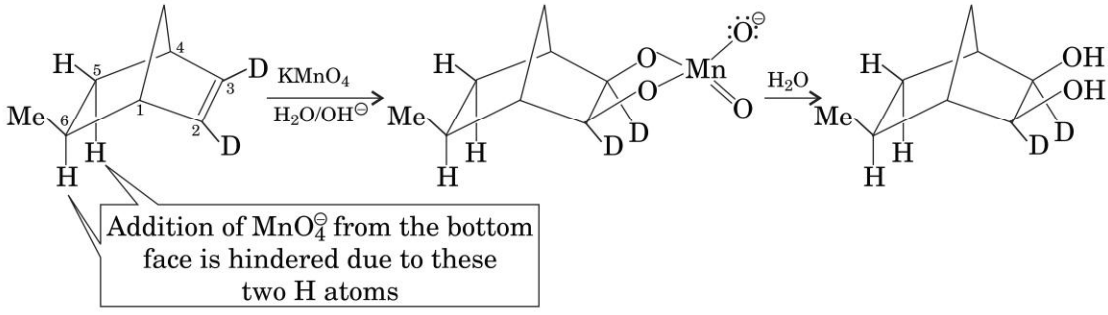


2. Identify the product (with stereochemistry if appropriate) obtained in the following reaction:

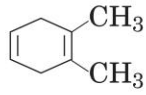
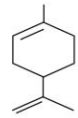
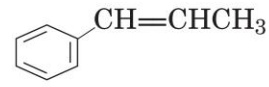


Solution

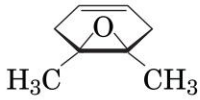
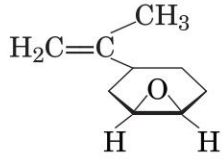
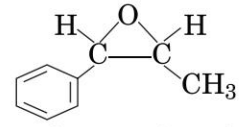
When the two faces of the double bond is not equivalent, *syn*-hydroxylation occurs preferentially from the less sterically hindered face of the double bond. In this bicyclic compound, the bottom face of the double bond is sterically more hindered compared to the top face because of the two hydrogens at C-5 and C-6, respectively. *Syn*-hydroxylation, therefore, takes place from the upper side to form the corresponding diol.



3. Give the major product of the reaction of each of the following compounds with one equivalent of *m*-chloroperoxybenzoic acid (MCPBA). Indicate the configuration of the product.

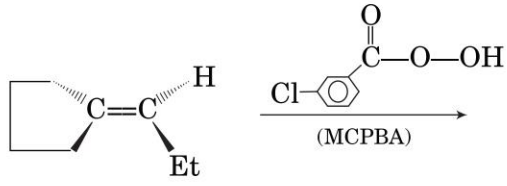
(a)  (b)  (c) 

Solution Because epoxidation results from the reaction of an electrophilic oxygen atom (in peroxyacid) with a nucleophilic alkene, the rate of epoxidation increases with increase in the electron density of the double bond of the alkene. Therefore, if a diene is treated with one equivalent of peroxyacid, the more substituted double bond undergoes epoxidation preferentially. Thus, the major products expected to be formed from the given compounds are as follows:

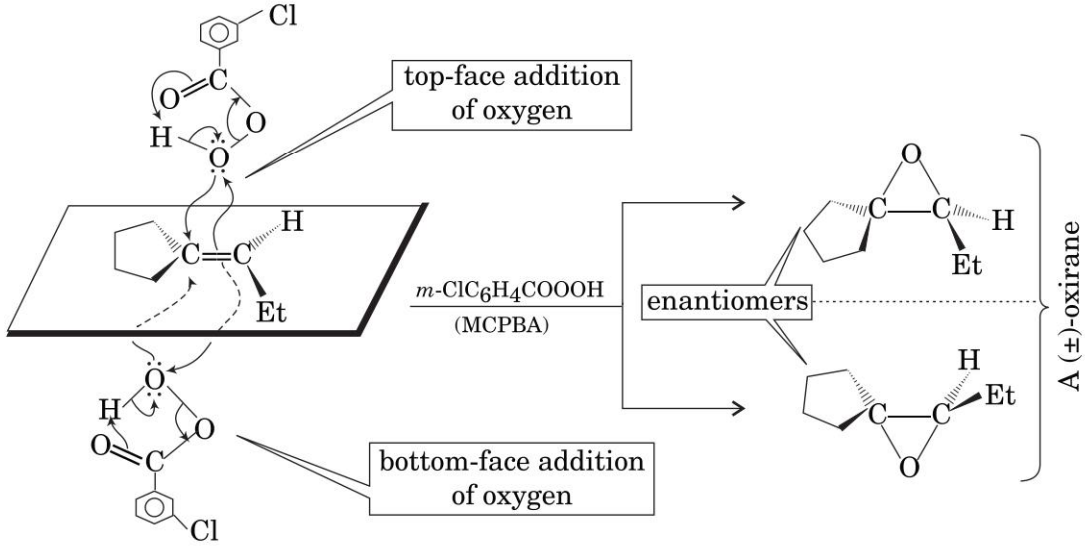
(a)  (b)  (c) 

(Because of aromatic stability, the ring does not undergo epoxidation.)

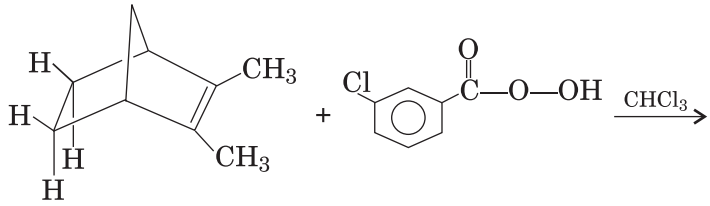
4. Give the mechanism and predict the stereochemical outcome of the following reaction:

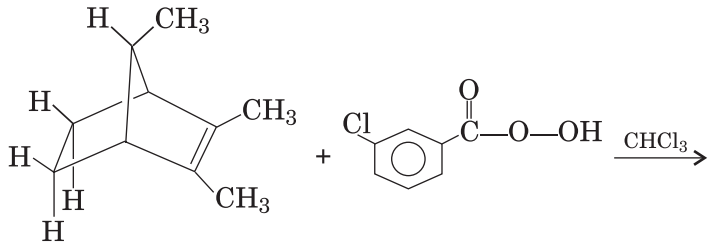


Solution Epoxidation of the alkene by MCPBA occurs from either above or below the plane of the double bond (two enantiotopic faces) at an equal rate through enantiomeric transition states having equal energy and results in formation of equal amounts of two enantiomeric oxiranes (racemic mixture).



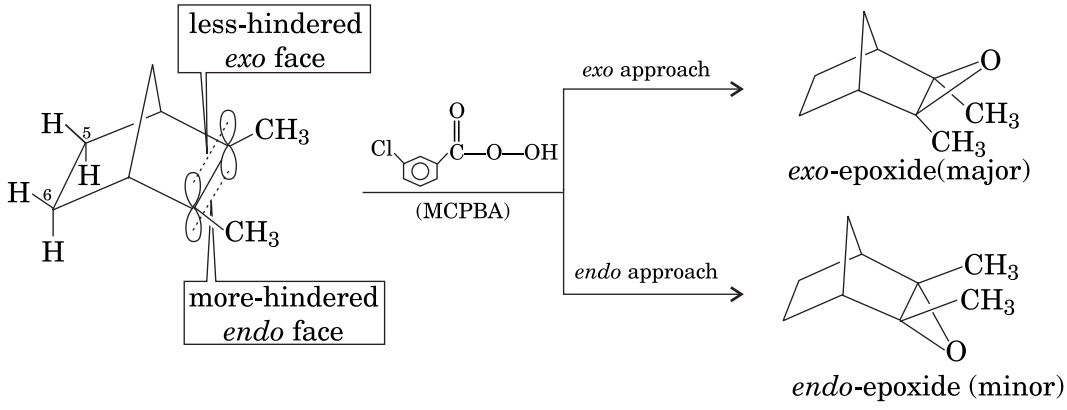
5. Predict the major and minor products in each of the following reactions and give your reasoning:

(a) 

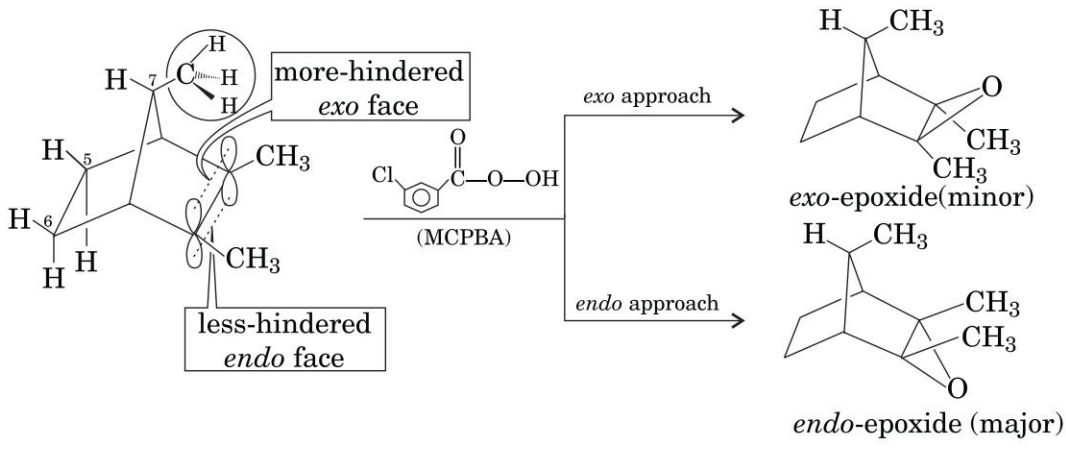
(b) 

Solution

(a) Epoxidation of this bicyclic compound occurs preferably from the less-hindered *exo* face to give the *exo*-epoxide as the major product. The boat-axial or endo hydrogens at C-5 and C-6 hinder the endo approach of MCPBA.



(b) Epoxidation of this bicyclic alkene occurs preferably from less-hindered *endo* face to give the *endo*-epoxide as the major product because the methyl group at C-7 hinders the *exo* approach of MCPBA.

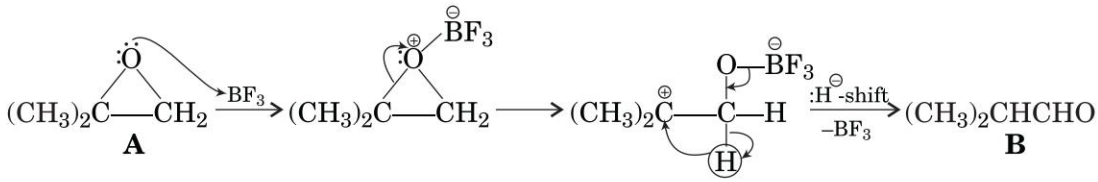


6. Isobutene $\xrightarrow[CH_2Cl_2]{RCOOOH}$ A $\xrightarrow[ethere]{BF_3}$ B. Identify A and B and suggest a mechanism for the formation of B.

Solution

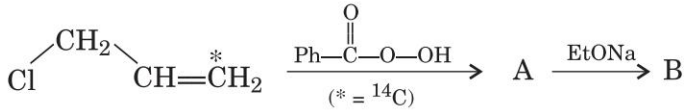
$$A \Rightarrow (CH_3)_2C(O)CH_2 \quad ; \quad B \Rightarrow (CH_3)_2CHCHO$$

The mechanism of the second reaction is as follows:



Study Problems

1. Identify A and B in the following reaction sequence and give the mechanism of formation of B from A.



2. A (An alkene) $\xrightarrow[2.\ H_3O^{\oplus}\text{ or }OH^{\ominus}/H_2O]{1.\ MCPBA}$ (2*R*, 3*R*)-2,3-Butanediol + (2*S*, 3*S*)-2,3-Butanediol

B (An alkene) $\xrightarrow[2.\ H_3O^{\oplus}\text{ or }OH^{\ominus}/H_2O]{1.\ MCPBA}$ (2*R*, 3*S*)-2,3-Butanediol

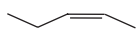
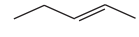
Identify the alkenes A and B. How are they related to each other stereochemically?

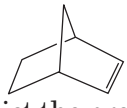
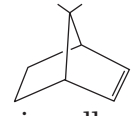
3. Magnesium monoperoxyphthalate (MMPP) epoxidizes alkenes much like MCPBA. However, MMPP is relatively more stable and it may be safer to use for industrial preparations. Propose a mechanism for the reaction of *cis*-2-methylhept-3-ene with MMPP and predict the structure of the product.

4. How would you accomplish the following conversions?

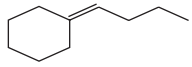
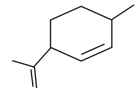
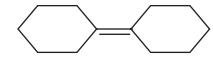
(a) *cis*-3-Hexene → (±)-3,4-Hexanediol
(b) *trans*-3-Hexene → *meso*-3,4-Hexanediol
(c) *cis*-3-Hexene → *meso*-3,4-Hexanediol
(d) *trans*-3-Hexene → (±)-3,4-Hexanediol

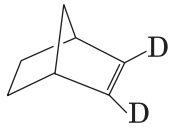
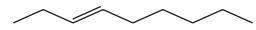
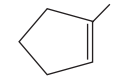
5. Predict the major products of the following reactions:

(a)  $\xrightarrow{OsO_4/H_2O_2}$; (b)  $\xrightarrow[H_2O_2]{OsO_4}$

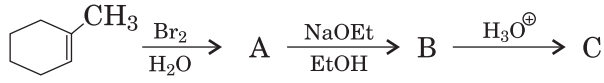
(c)  $\xrightarrow{OsO_4/H_2O_2}$; (d)  $\xrightarrow{OsO_4/H_2O_2}$

6. Predict the products obtained when the following alkenes are heated with an acidic or alkaline solution of $KMnO_4$.

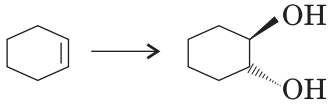
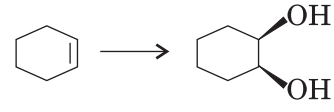
(a)  (b)  (c) 

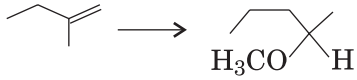
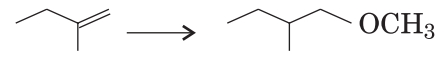
(d)  (e)  (f) 

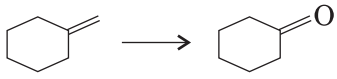
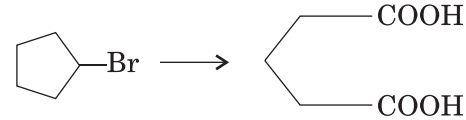
7. Identify A, B and C in the following reaction sequence:

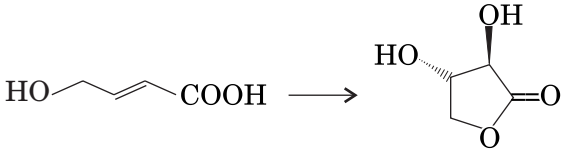


8. Show how one may accomplish each of the following conversions in a practical manner:

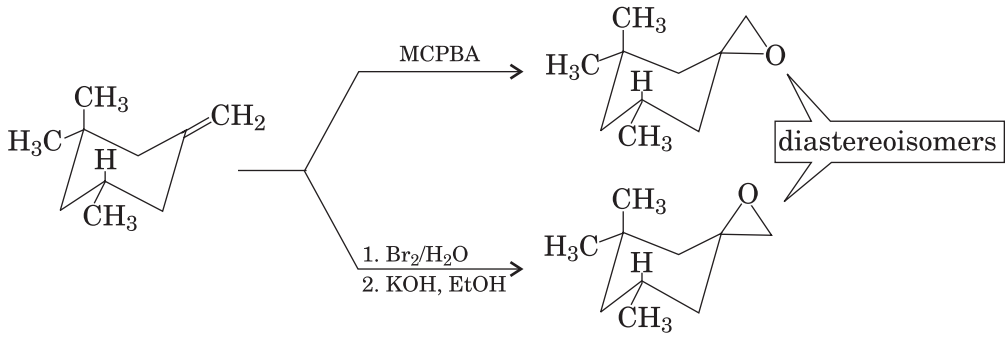
(a)  (b) 

(c)  (d) 

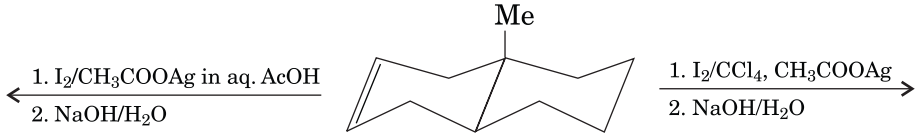
(e)  (f) 

(g) 

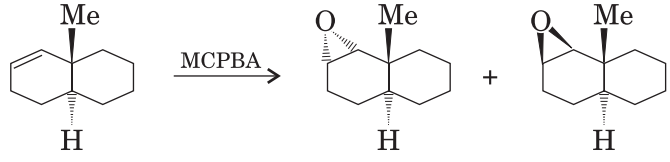
9. Explain the following observations:



10. Predict the major product and suggest a mechanism for each of the following reactions:

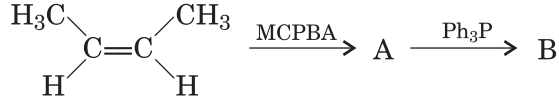


11. Explain the following observation:



I II (major) III (minor)

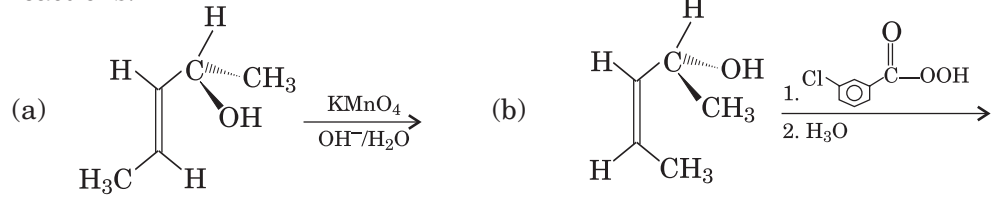
12. Identify A and B in the following reaction sequence:



cis-2-Butene

Suggest a mechanism for the second step of this reaction sequence:
[**Hint:** The compound B is trans-2-butene.]

13. Give the mechanism and the stereochemical outcome of each of the following reactions:



1.1.9 Hydrogenation

1.1.9.1 Catalytic Hydrogenation

Alkenes react with hydrogen in the presence of a variety of metal catalysts to add one hydrogen atom to each doubly bonded carbon atom to form an alkane. This is what is called catalytic hydrogenation. For example:

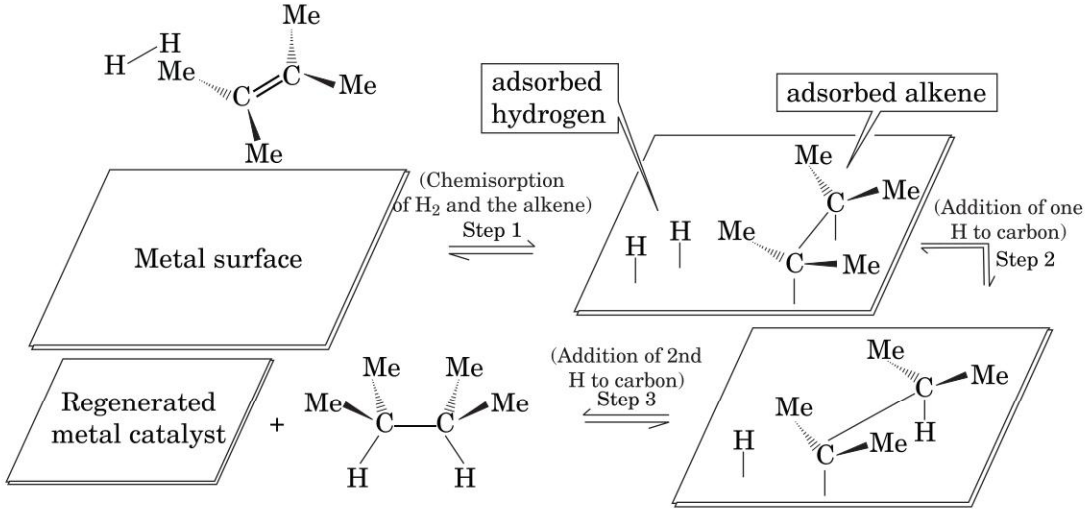
$$\underset{\text{2–Methylpropene}}{(CH_3)_2C{=}CH_2} + H_2 \xrightarrow{Pd/C} \underset{\text{2–Methylpropane}}{(CH_3)_2CHCH_3}$$

Catalysts usually used in this process are finely divided platinum, palladium, nickel or rhodium deposited on the surface of powdered carbon (charcoal).

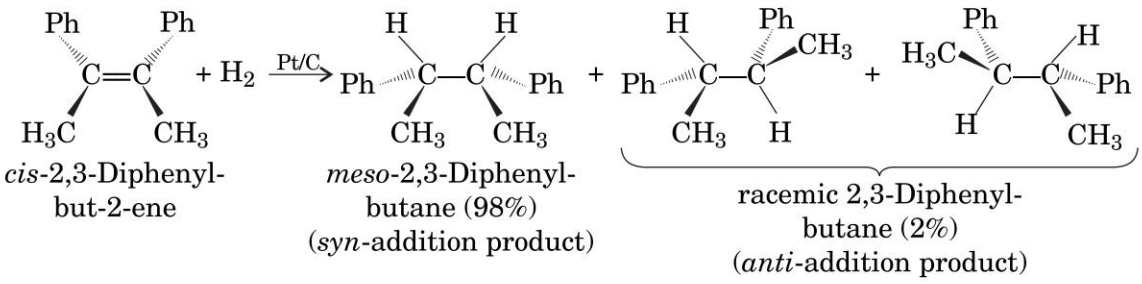
Without a catalyst, the energy barrier to the reaction would be enormous because the H—H bond is very strong. The catalyst decreases the energy of activation for breaking the H—H bond. For this reason, hydrogenation of alkenes at room temperature takes place in the presence of a catalyst but not in the absence of a catalyst, even though the reaction is an exothermic one (see **article no. 1.13.4** of Volume-I)

1.1.9.2 Mechanism and Stereochemistry of Catalytic Hydrogenation

The mechanism for the hydrogenation of an alkene for example, 2,3-dimethylbut-2-ene, involves the steps as follows:



Stereochemistry: A stepwise transfer of hydrogen atoms takes place, and this produces an alkane before the organic molecule leaves the catalyst surface. As a consequence, both hydrogen atoms usually add from the same side of the molecule, i.e., the reaction results in stereoselective *syn*-addition of H_2. As the two H atoms do not add to the double bond simultaneously, some *anti*-addition product is also obtained. After step 2 the carbon attached to the catalyst surface may rotate about the C—C σ bond to give, after addition of the second hydrogen, an *anti*-addition product. For example:



cis-2,3-Diphenyl-but-2-ene

meso-2,3-Diphenyl-butane (98%) (*syn*-addition product)

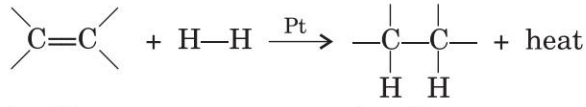
racemic 2,3-Diphenyl-butane (2%) (*anti*-addition product)

1.1.9.3 Heat of hydrogenation

The quantity of heat released when one mole of an unsaturated compound is hydrogenated is called the heat of hydrogenation.

A catalyst does not change the energy difference between the reactants and products and it only reduces the energy of activation resulting in a faster reaction. For this reason, the heat of hydrogenation of an alkene in the presence of a catalyst is the same as it would be had hydrogenation occurred in the absence of a catalyst.

The hydrogenation reaction may be represented as



An alkene An alkene

Hydrogenation involves breaking of one C═C bond and one H—H bond and making of one C—C bond and two C—H bonds. Bond breaking requires energy, while bond making releases energy. Therefore, the increase in heat content, i.e., ΔH° = Energy supplied to the system (for bond breaking) – Energy released by the system (for bond making). Now, C═C, H—H, C—C and C—H bond energies are 145.8, 104.2, 82.6 and 98.7 kcal/mol, respectively.

$$\therefore \quad \Delta H^\circ = (145.8 + 104.2) - (82.6 + 2 \times 98.7)$$
$$= 250 - 280 = -30 \text{ kcal/mol}$$

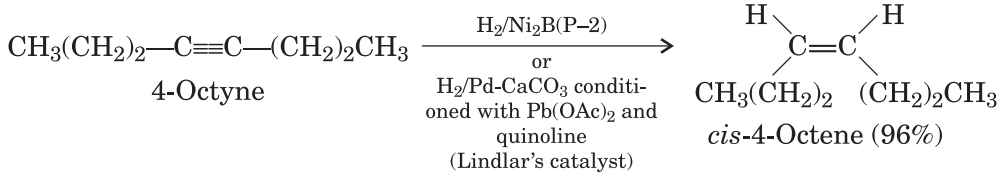
The negative value of ΔH° suggests that the reaction is exothermic in nature.

1.1.9.4 Reactivity of Alkynes as Compared to Alkenes

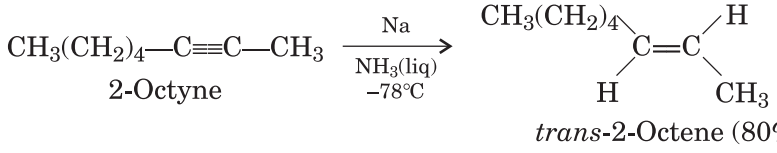
Adsorption of alkenes on the surface of the metal catalyst occurs only when the plane of the π bond approaches perpendicularly, i.e., when head on approach occurs. However, because of cylindrical shape of the π cloud of alkynes, any approach along the axis of the cylinder can be successful. Because of this, the transition states for addition of hydrogen to alkynes will be lower in energy than that for addition to alkenes. As a consequence, alkynes undergo catalytic hydrogenation at a rate faster than alkenes, i.e., alkynes are relatively more reactive than alkenes.

1.1.9.5 Syn- and Anti-Addition of Hydrogen to an Alkyne Leading to the Formation of Cis- and Trans-Alkenes

Like alkenes, alkynes can be hydrogenated in the presence of many catalysts. Alkenes are the first products, but they are not stable under the reaction conditions and usually undergo hydrogenation to give alkanes. However, it is possible to stop the alkyne hydrogenation at the alkene stage if hydrogenation of alkynes is carried out in the presence of special catalysts such as P-2 (Ni_2B) or Lindlar's catalyst which is, in fact, a quinoline poisoned palladium catalyst ($Pd—CaCO_3$ conditioned with lead acetate and quinoline). The alkenes formed by hydrogenation with Ni_2B or Lindlar's catalyst have *cis* stereochemistry because the usual *syn*-addition of hydrogen has occurred. For example:



Anti-addition of hydrogen to the triple bond of alkynes takes place when they are treated with lithium or sodium metal in ammonia or ethylamine at low temperatures. For example:

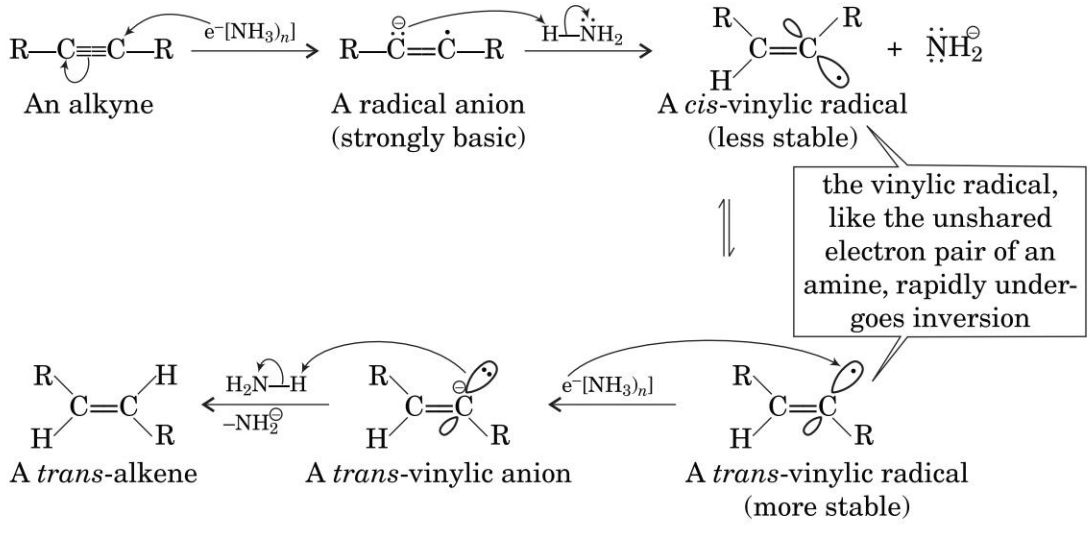


Mechanism: The mechanism of the reaction involves successive electron transfer from sodium (solvated electron) and proton transfer from ammonia.

When sodium is dissolved in ammonia, the sodium atom loses its odd electron (the *s* orbital electron) to give a sodium ion and a solvated electron, which is an electron surrounded by solvent molecules.

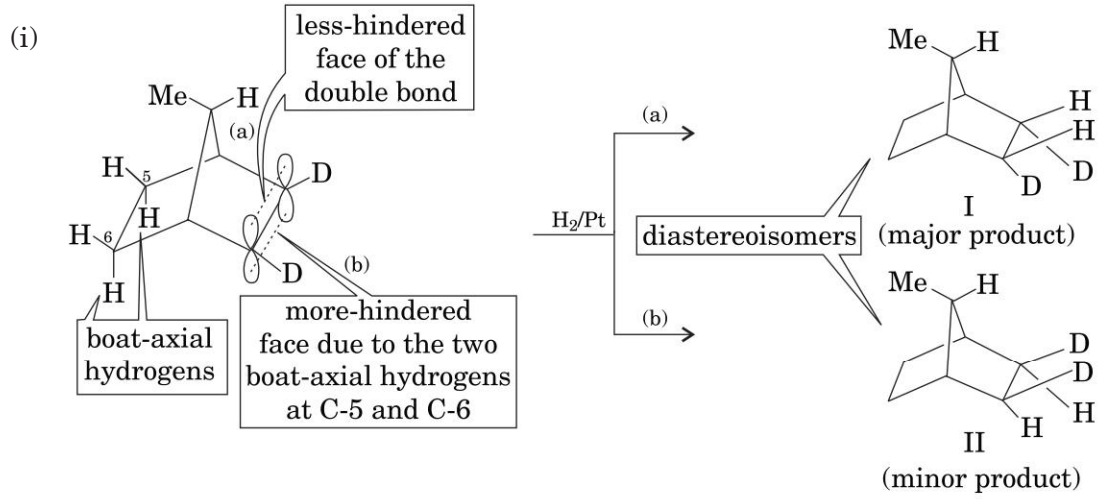
$$Na^{\cdot} + NH_3 \longrightarrow \overset{\oplus}{Na} \quad + \quad \underset{\text{solvated electron}}{e^-[NH_3]_n}$$

In the first step of this process, this complexed electron is added to the alkyne to form a radical anion. In the second step, the radical anion abstracts a proton from ammonia to form a vinylic radical (the unpaired electron on a vinylic carbon). The vinylic radical can have the *cis* or *trans* configurations and they remain in equilibrium. However, the equilibrium favours the more stable *trans*-vinylic radical in which the larger alkyl groups are as far from each other as possible and there is no steric strain. In the third step, a second solvated electron is added to the vinylic radical to form a *trans*-vinylic anion. This step actually determines the stereochemistry of the product. In the final step, the *trans*-vinylic anion removes a proton from a second molecule of NH_3 to produce the *trans*-alkene.



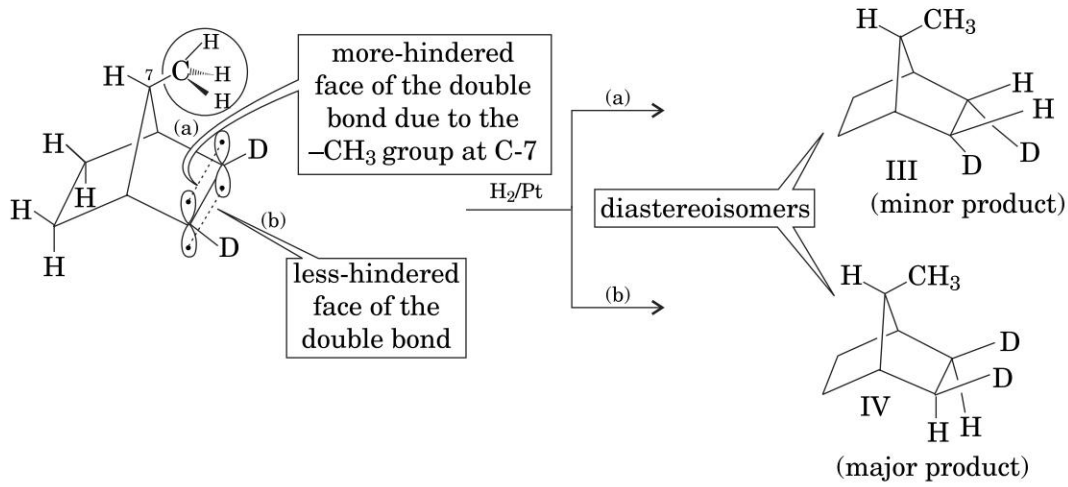
1.1.9.6 Diastereoselective Hydrogenation of Alkenes

In diastereoselective reactions, reactions lead to the formation of diastereoisomers in unequal amounts and this is because one face of the double bond is sterically more hindered than the other. For example:



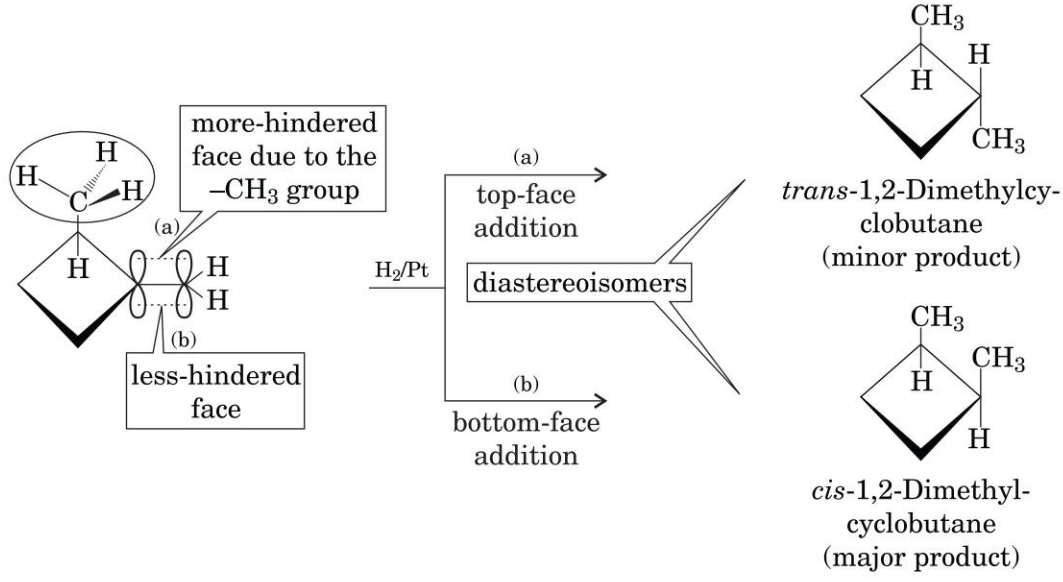
The less hindered face of the carbon–carbon double bond is adsorbed on the surface of the metal catalyst (Pt). This results in the introduction of adsorbed H_2 at that face to yield the diastereoisomer I predominantly.

(ii)



Syn-addition of hydrogen takes place to the less-hindered face of the C═C (preferentially chemisorbed to minimize steric interactions) to yield the diastereoisomer IV predominantly.

(iii)



The preferentially chemisorbed less crowded face of the C═C undergoes *syn*-addition of H_2 to yield *cis*-1,2-dimethyl cyclobutane as the major product.

1.1.9.7 Birch Reduction

Benzene and its derivatives can be reduced to nonconjugated 1,4-cyclohexadienes by treatment with sodium or lithium in a mixture of liquid ammonia and an alcohol. The dissolving metal reduction of this type is called the *Birch reduction*. For example:

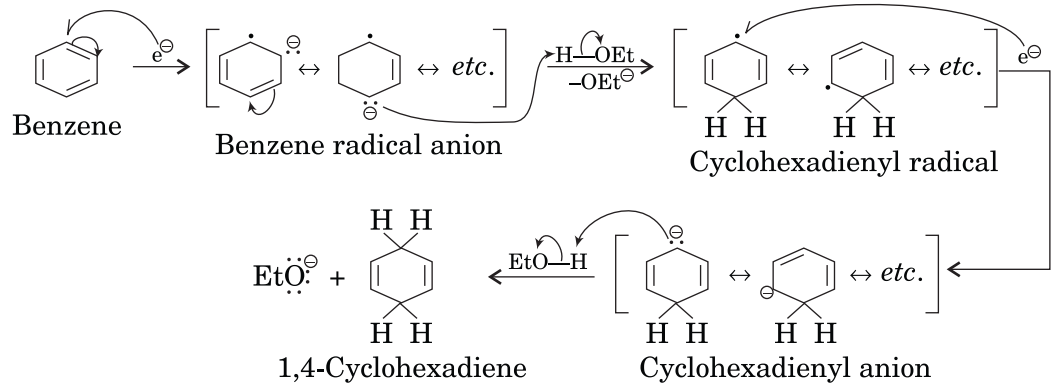


Benzene 1,4-Cyclohexadiene (90%)

Mechanism: The mechanism of the reaction involves successive electron transfer from sodium (solvated electron) and proton transfer from alcohol. A solution of Na in liquid ammonia contains solvated electrons.

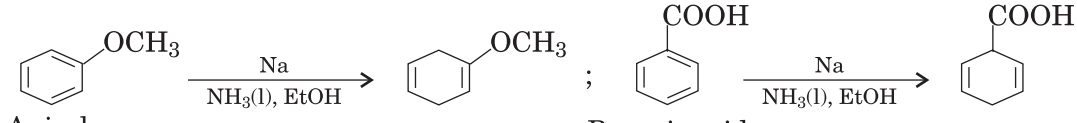
$$Na^{\cdot} + NH_3 \longrightarrow \overset{\oplus}{Na} + \underset{\text{Solvated electron}}{e^-[NH_3]_n}$$

A solvated electron in first added to benzene to produces a delocalized benzene radical anion. The strongly basic radical anion then removes a proton from alcohol to give a delocalized cyclohexadienyl radical. Transfer of a second solvated electron leads to the formation of a delocalized cyclohexadienyl anion which subsequently takes up a proton to give 1,4-cyclohexadiene.



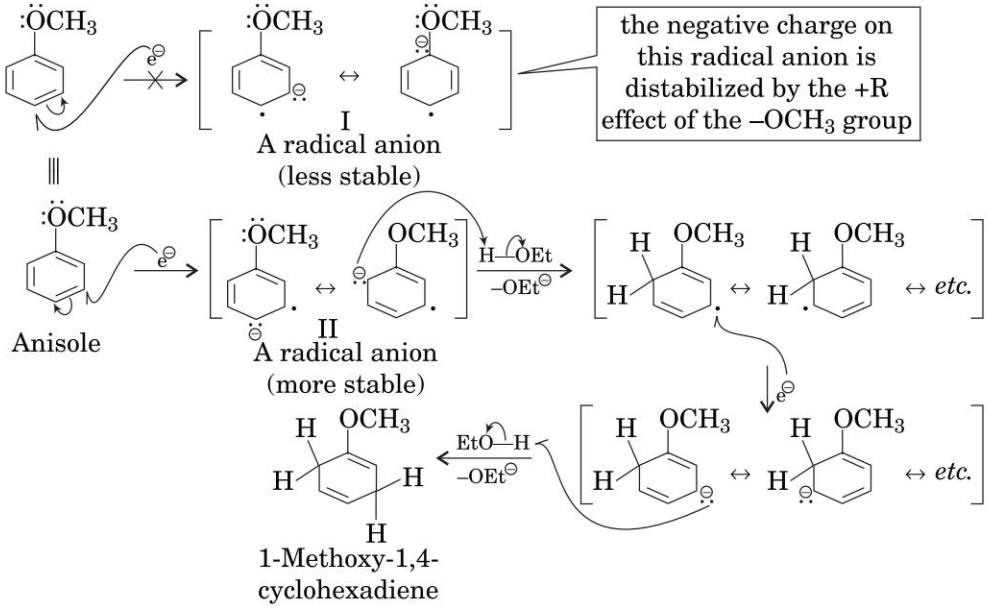
It is to be noted that reason for the formation of 1,4-cyclohexadiene (the rate-controlled product) in preference to the more stable conjugate 1,3-cyclohexadiene is not clearly understood.

The nature of the Birch reduction product depends on the electron-releasing and electron-withdrawing character of the group already present in the ring. When anisole is subjected to the Birch reduction, the electron donating $-OCH_3$ group is found to be attached with a doubly bonded carbon in the product. However, when benzoic acid is subjected to this reduction, the electron-withdrawing –COOH group is found to be attached with a saturated carbon in the product.

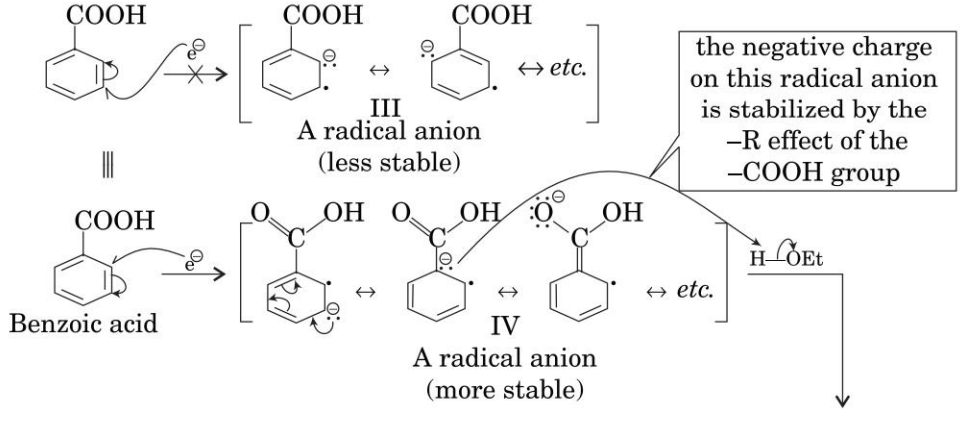


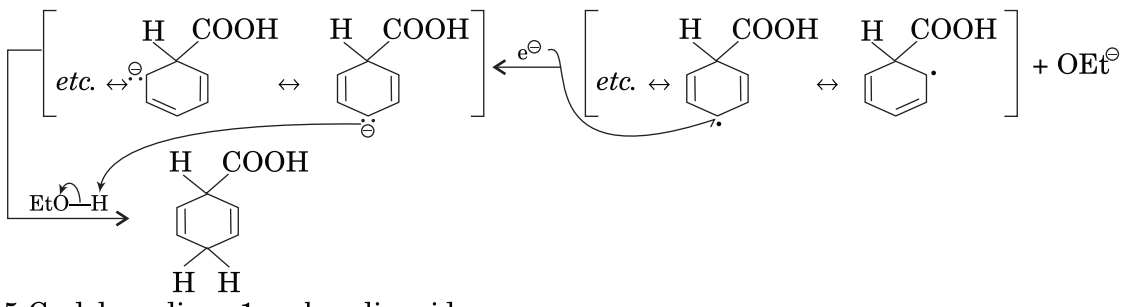
Anisole ; Benzoic acid

Explanation: The two ring carbons undergoing reduction go through anionic intermediates. An electron-attracting group stabilizes a carbanion by charge delocalization, while an electron-releasing group destabilizes it. In the case of anisole, the electron-releasing $-OCH_3$ group destabilizes the negative charge on the ring carbon bonded to it. As a consequence, the reaction proceeds not through the less stable radical anion I but through the more stable radical anion II to yield finally 1-methoxy-1,4-cyclohexadiene.



On the other hand, in benzoic acid, the electron-attracting –COOH group stabilizes a negative charge on the ring carbon bonded to it. As a consequence, the reaction not proceeds through the less stable radical anion III but through the more stable radical anion IV to yield finally 2,5-cyclohexadiene-1-carboxylic acid.

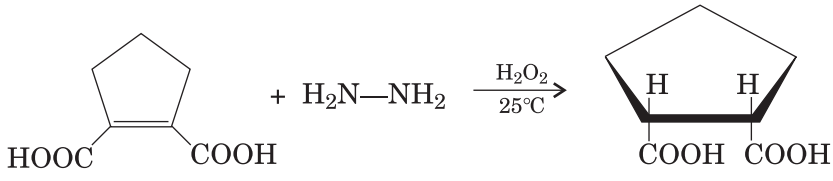




2,5-Cyclohexadiene-1-carboxylic acid

1.1.9.8 Reduction of Carbon–Carbon Multiple Bond with Hydrazine (NH_2NH_2) in the Presence of Hydrogen Peroxide (an Oxidizing Agent)

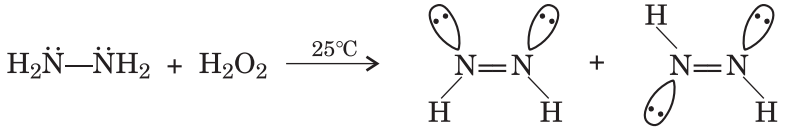
An alkene or alkyne can be reduced with hydrazine in the presence of H_2O_2 through the intermediate formation of diimide (also called diimine), HN═NH, the actual reducing agent involved. Diimide is formed *in situ* by the oxidation of hydrazine. It is a highly selective reducing agent and offers a useful alternative to catalytic hydrogenation of carbon–carbon multiple bonds. Unlike catalytic hydrogenation, it reduces only symmetrical multiple bonds like C═C, C≡C, N═N, etc. and multiple bonds between C and heteroatoms like C≡N, C═O, N═O, etc. When cyclopentene-1,2-dicarboxylic acid, for example, is treated with NH_2—NH_2/H_2O_2, *meso*-cyclopentane-1,2-dicarboxylic acid is obtained.



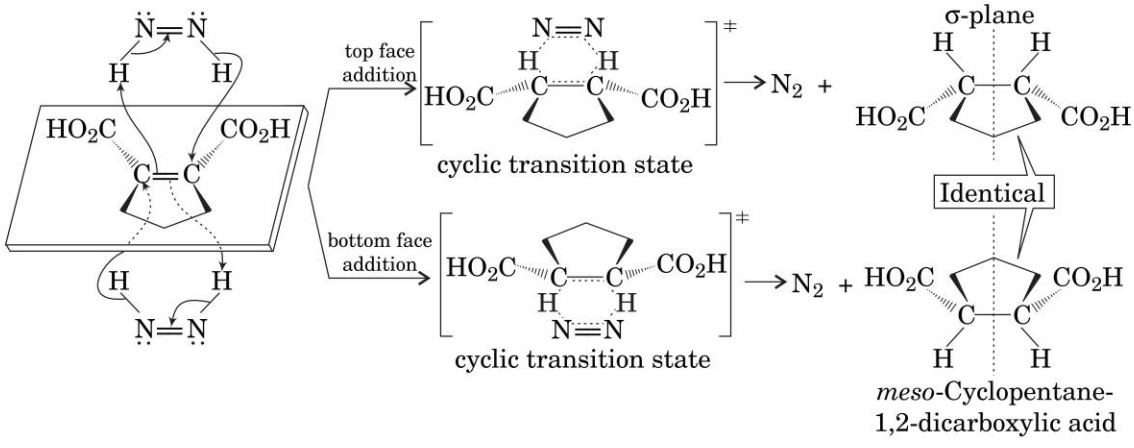
Cyclopentene-1,2-dicarboxylic acid

meso-Cyclopentane-1,2-dicarboxylic acid

Mechanism: Hydrogen peroxide oxidizes hydrazine to give both the *anti* and *syn* forms of diimide. However, it is the *syn* form which reduces the double bond. The reaction involves transfer of two hydrogen atoms to the two doubly bonded carbon atoms concertedly through a six-membered cyclic transition state.



cis-Diimide *trans*-Diimide

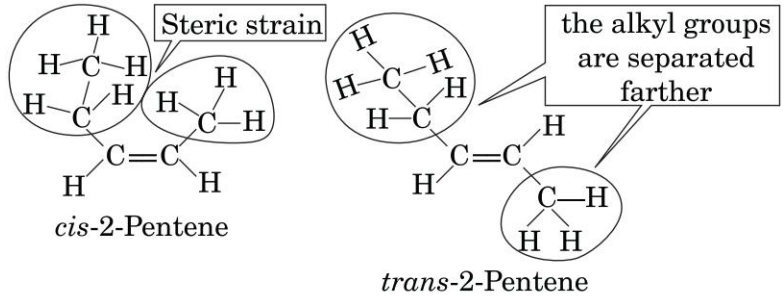


Stereochemistry: The reaction is stereospecific and takes place by the *syn*-addition of hydrogen to the double bond. Because of this, reduction of cyclopentene-1,2-dicarboxylic acid produces optically inactive *meso*-cyclopentane-1,2-dicarboxylic acid. Like catalytic hydrogenation, the addition takes place preferably to the less-crowded side of the double bond.

SOLVED PROBLEMS

1. Explain why the heat of hydrogenation of *cis*-2-pentene is –28.6 kcal/mol, whereas it is –27.6 kcal/mol for the *trans*-isomer.

Solution The relative stabilities of alkenes are reflected by their heat of hydrogenation values. The more the heat evolved on hydrogenation, the more the alkene is unstable. The ΔH° values of the two isomeric 2-pentenes suggest that the *cis*-isomer is thermodynamically less stable than the *trans*-isomer and that is due to the steric strain (i.e., the nonbonded repulsive interaction between the electron clouds) that arises when the two alkyl groups remain on the same side of the double bond.

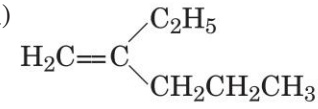


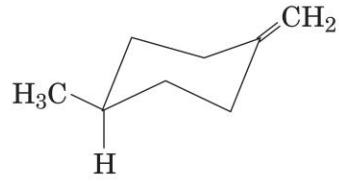
2. Arrange the following alkenes in order of increasing rate of hydrogenation and give your reasoning:

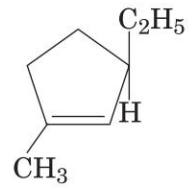
$CH_3CH{=}C(CH_3)_2$ (I) *trans*-$CH_3CH{=}CHCH_3$ (II) $(CH_3)_2C{=}C(CH_3)_2$ (III) $CH_3CH{=}CH_2$ (IV)

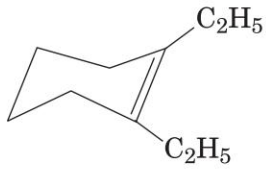
Solution The order of increasing rate of hydrogenation is: III < I < II < IV. This is because crowding decreases in the order: III < I < II < IV and less crowded double bonds complex more readily to the catalyst surface, resulting in a faster reaction.

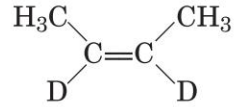
3. Draw all the stereoisomer formed when each of the following alkenes is treated with H_2 in the presence of Pt (catalyst):

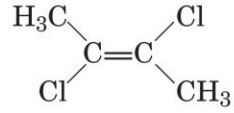
(a) 

(b) 

(c) 

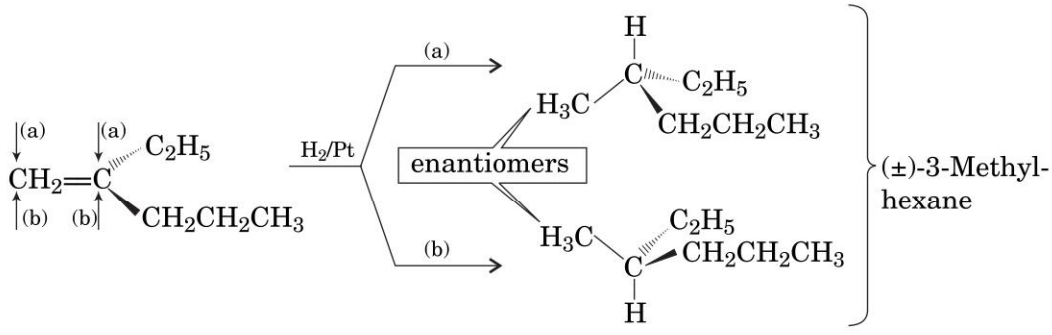
(d) 

(e) 

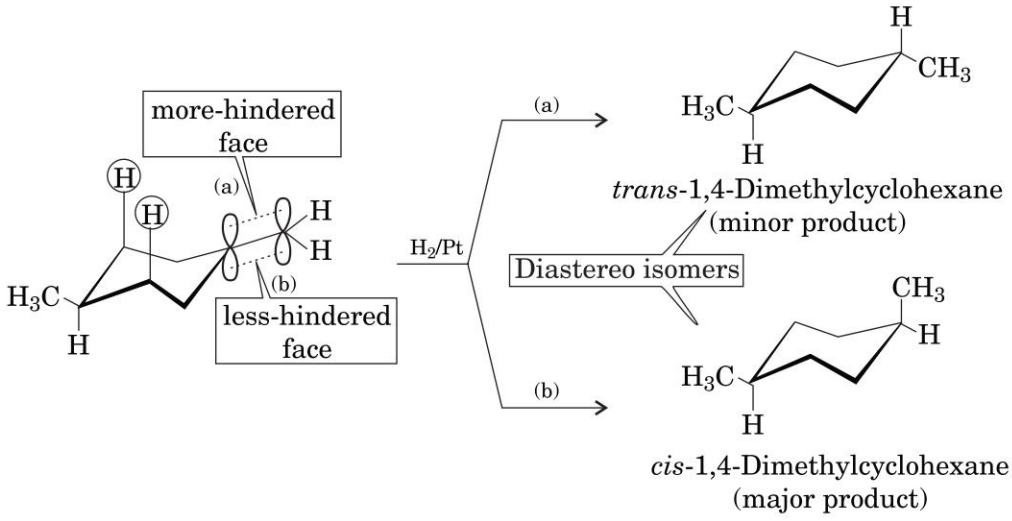
(f) 

Solution

(a) *Syn*-addition of H_2 occurs to both sides of the trigonal planar double bond equally well to yield two enantiomeric hydrocarbons in equal amounts (racemic mixture).

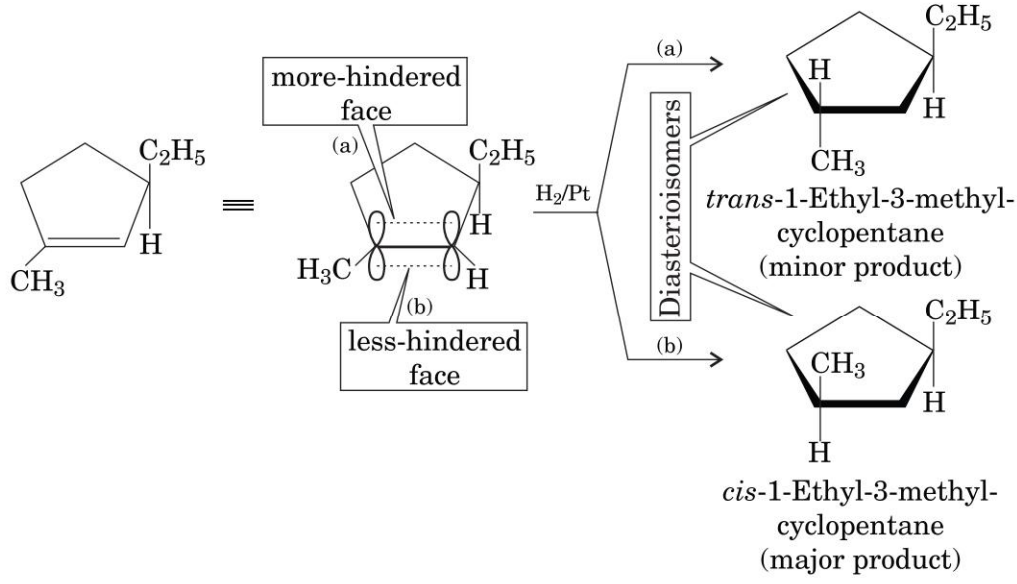


(b)

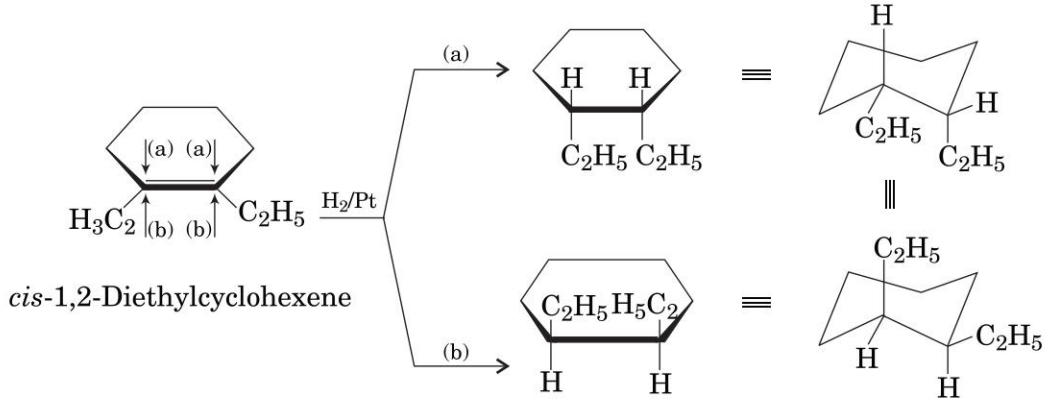


The less-hindered equatorial face of the double bond is adsorbed preferably on the surface of the metal catalyst. As a result, the adsorbed H_2 is added preferably at that face to yield *cis*-1,4-dimethylcyclohexane predominantly.

(c) The less hindered face of the double bond is adsorbed on the surface of the metal catalyst, resulting in the introduction of adsorbed H_2 preferably at that face to give *cis*-1-ethyl-3-methylcyclopentane as the major product.



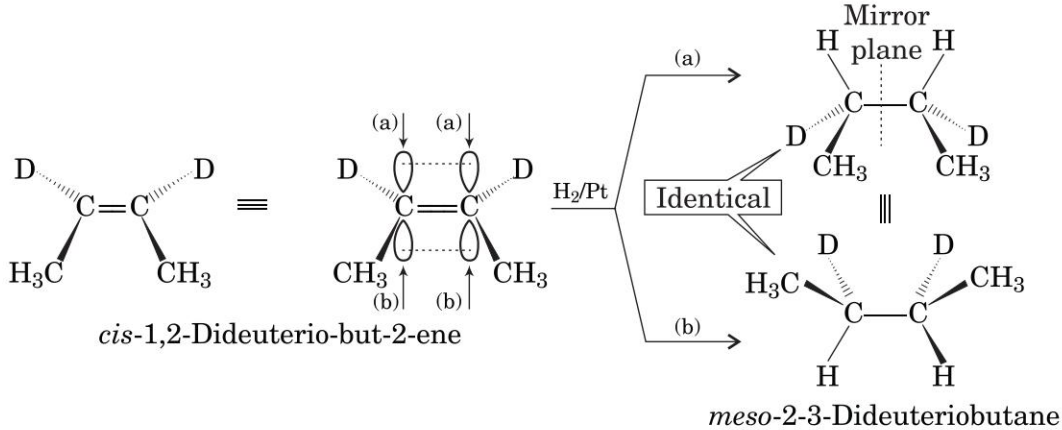
(d) Addition of hydrogen from both the faces of C═C in 1,2-diethylcyclohexene occurs with equal facility to yield *cis*-1,2-diethylcyclohexane which exists as inseparable *dl* pair.



cis-1,2-Diethylcyclohexane

cis-1,2-Diethylcyclohexane
(exists as inseparable *dl* pair)

(e)

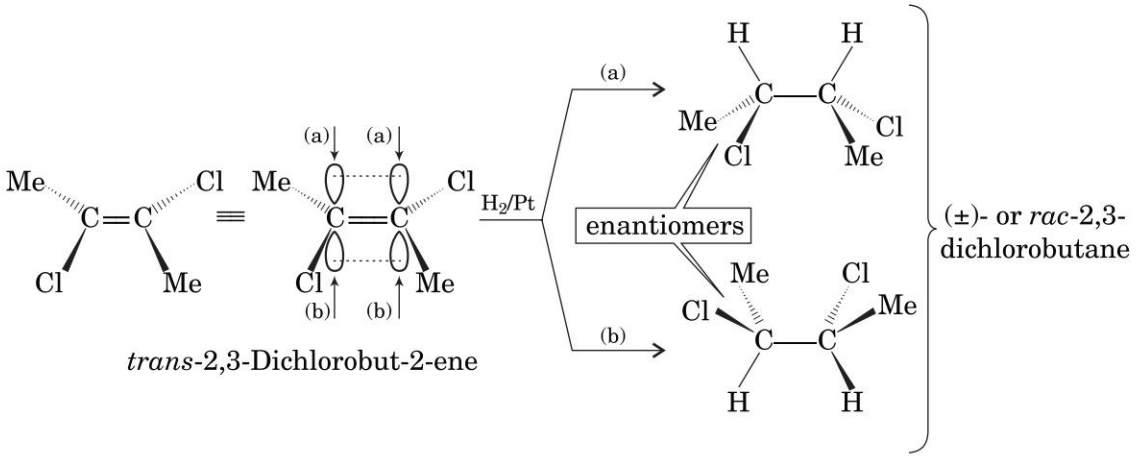


cis-1,2-Dideuterio-but-2-ene

meso-2-3-Dideuteriobutane
(optically inactive)

Syn-addition of hydrogen takes place to both the faces of the double bond equally well to yield *meso*-2-3-dideuteriobutane.

(f) *Syn*-addition of hydrogen occurs to both the faces of C═C in *trans*-2,3-dichlorobut-2-ene equally well to yield (±)- or *rac*-2,3-dichlorobutane.



trans-2,3-Dichlorobut-2-ene

4. Identify the reagents (A–D) required to carry out the following transformations?

(a) $CH_2{=}CHCH_2CH_2C{\equiv}CCH_3 \xrightarrow{A} CH_2{=}CHCH_2CH_2$ (with CH_3 and H on the C=C)

(b) H_3C–C$_6$H$_4$–$CH_2CH{=}CHCH_3 \xrightarrow{B} H_3C$–C$_6H_4$–$CH_2CH_2CH_2CH_3$

(c) H_3C–C$_6$H$_4$–$CH{=}{=}CHCOCH_3 \xrightarrow{C} Me$–C$_6H_4$–$CH_2CH_2COCH_3$

(d) $H_2C(CH_2)_5C{\equiv}C{-}CH_2 \xrightarrow{D}$ $H_2C(CH_2)_5$ bridging to a C=C bearing H and CH_2

Solution

(a) A═H_2/Lindlar's catalyst; (b) H_2/Ni, 40 atm, 200°C (aromatic rings endergo hydrogenation only at higher temperature and pressure); (c) H_2/Ni, 25°C (Ac═O bond undergoes hydrogenation very slowly compared to a C═C bond); (d) Na/NH_3(l), EtOH (a nine-membered ring can accommodate a trans-double bond).

5. (a) What do you mean by heterogenous and homogeneous catalysts? Give examples.

(b) What is called Wilkinson's catalyst? Give the mechanism for reduction of a double/triple bond by this catalyst.

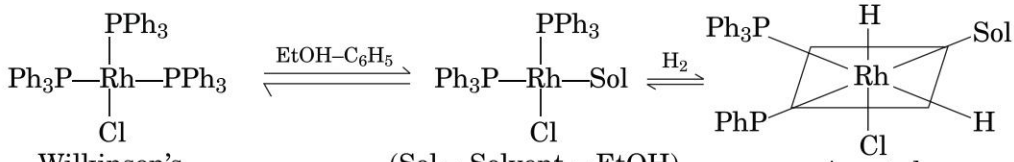
Solution

(a) Catalysts that are insoluble in the reaction mixture, i.e., catalysts that are in a different phase from the reactant solution are called heterogeneous catalysts. On

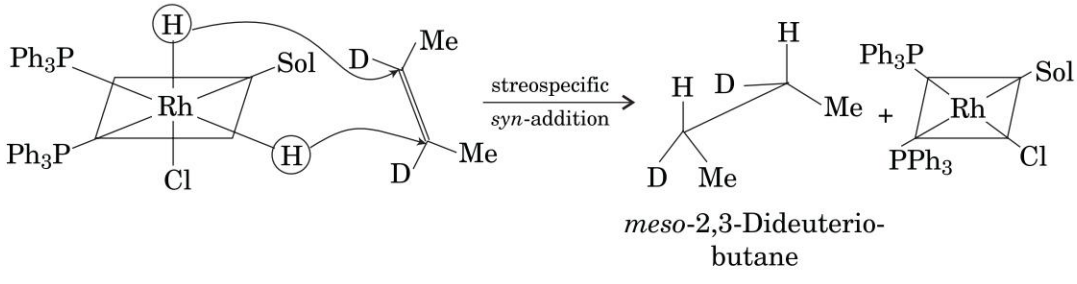
the other hand, catalysts that are soluble in the reaction mixture, i.e., catalysts that are in the same phase as the reactant solution are called homogeneous catalysts. Metal catalysts used in catalytic hydrogenation are heterogeneous catalysts, whereas the acid catalyst used in the hydration of alkenes is a homogeneous catalyst.

(b) A most effective homogeneous catalyst is *tris*(triphenylphosphine)rhodium chloride [$(Ph_3P)_3RhCl$]. This is commonly known as Wilkinson's catalyst.

The mechanism for reduction of a double bond by this catalyst is as follows:



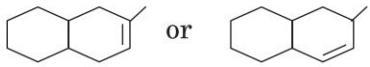
Now, the metal hydride rapidly transfers two H atoms to a conconjugated C═C or a C≡C bond of a substrate. A stereospecific *syn*-addition of hydrogen takes place. When 2,3-dideuterobut-2-ene is reduced with Wilkinson's catalyst, *meso*-2,3-dideuteriobutane is obtained.



Study Problems

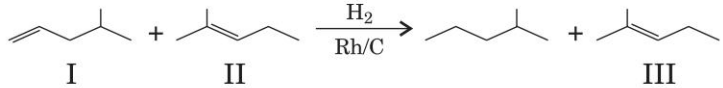
1. Which alkene in each pair has the larger heat of hydrogenation?

(a) $Me_3CCH{=}CHCMe_3$ (*cis*) or $Me_3CCH{=}CHCMe_3$ (*trans*)

(b)  or .

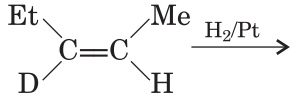
2. Cyclobutene has a heat of hydrogenation of –30.7 kcal/mol, compared with –26.6 kcal/mol for cyclopentene. Expain.

3. Explain why it is possible to hydrogenate the alkene I in the presence of the alkene II.

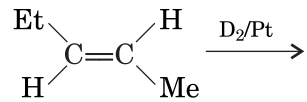


4. Explain why heats of hydrogenation cannot be used to compare the relative stability of 2-methylpent-2-ene and 3-methylpent-1-ene.

5. Predict the stereochemical outcome of each of the following reactions:

(a) 

cis-2,3-Dideuteriopent-2-ene

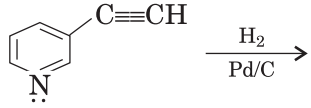
(b) 

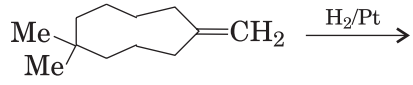
trans-2-Pentene

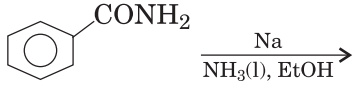
6. Hydrogenation of optically active 3,7-dimethyl-1-octene using Pt a as catalyst gives optically active 2,6-dimethyloctane. However, if Pd/C is used as a catalyst, the product 2,6-dimethyloctane is found to be racemic. Explain these observations.
[Hint: In the presence of Pd, 3,7-dimethyl-1-octene undergoes isomerization to give 3,7-dimethyl-2-octene. Hydrogen adds to this alkene from both the faces of the double bond equally well to yield racemic 2,6-dimethyloctane.]

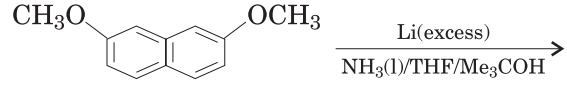
7. Two isomeric compounds A and B (molecular formula C_7H_{14}) are both dextrorotatory. On catalytic hydrogenation, both yield the same compound C(C_7H_{16}) which is optically active. Identify A, B and C.
[Hint: A and B are not enantiomers and C is $(CH_3)_2CH\overset{*}{C}H(CH_3)CH_2CH_3$]

8. Given the product formed in each of the following reactions:

(a) 

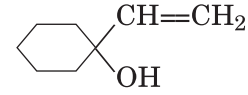
(b) 

(c) 

(d) 

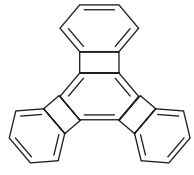
9. How would you carry out the following transformations?

(a) $HC{\equiv}CH \longrightarrow CH_3(CH_2)_6CH_3$

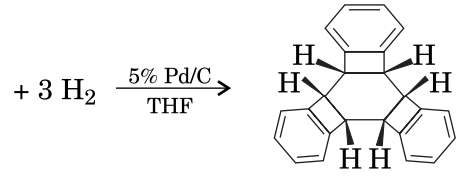
(b) $HC{\equiv}CH \longrightarrow$ 

10. Write structures of the products obtained when 3-hexyne is treated with sodium in liquid ammonia and then with D_2 over Pd/C.

11. Explain why the central benzene ring of [4]phenylene undergoes catalytic hydrogenation readily under conditions usually used for ordinary alkenes, but the other benzene rings do not.



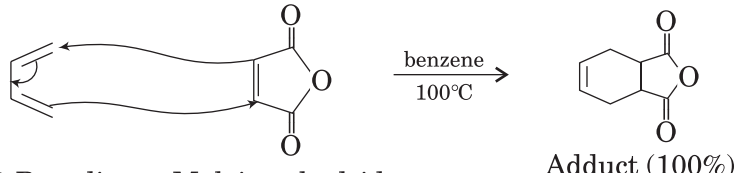
[4]Phenylene



1.1.10 Diels–Alder Reaction

1.1.10.1 Diels–Alder Reaction

The thermal 1,4-cycloaddition reaction between a conjugated diene (a 4π-electron system) and a compound containing an active multiple bond, called a dienophile (a 2π-electron system which 'loves a diene'), to form a six-membered cyclic product (often called an adduct) with one double bond is called the Diels–Alder reaction. A typical example of the Diels-Alder reaction is the reaction that occurs when 1,3-butadine and maleic anhydride are heated together at 100°C to form the corresponding adduct in quantitative yield. We can account for all the bond changes by using curved arrows.

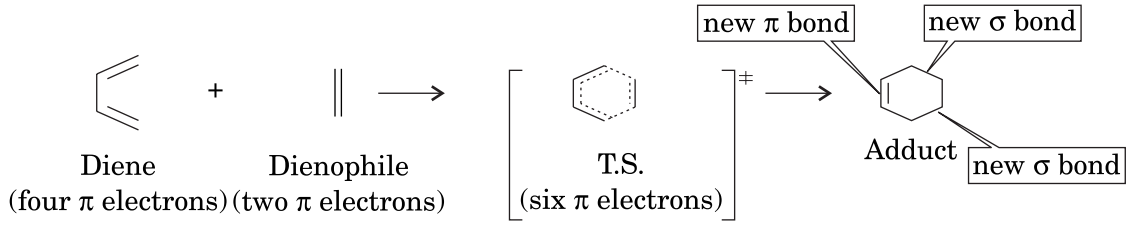


1,3-Butadiene (diene) Maleic anhydride (dienophile) Adduct (100%)

In the Diels–Alder reaction, two new σ bonds are formed at the expense of two π bonds of the diene and dienophile. Since σ bonds are usually stronger than π bonds, *formation of the adduct is usually favoured energetically.* However, most Diels–Alder reactions are reversible.

A significant difference between a Diels–Alder reaction (which is simply a 1,4-addition to a conjugated diene) and the 1,4-addition reactions that we have considered previously, however, is that the Diels–Alder reaction is a concerted reaction, i.e., the addition takes place in a single step. The other 1,4-addition reactions we have already studied take place in two steps. In the first step, the electrophile adds to the diene and in the second step, the nucleophile adds to carbocations.

The Diels–Alder reaction is, in fact, an example of a *pericyclic reaction*, a reaction that takes place in one step by a cyclic shift of electrons. More precisely, the Diels–Alder reaction is a [4+2] cycloaddition reaction and this is because, out of the six π elctrons involved in the cyclic transition state, four come from the diene and two come from the dienophile.



Diene (four π electrons) Dienophile (two π electrons) T.S. (six π electrons)

All Diels–Alder reactions have the following common features:

1. The Diels–Alder reaction is a thermal cycloaddition reaction because they are initiated by heat.
2. These reactions form new six-membered rings.
3. These reactions involve breaking of three π bonds and formation of two new C—C σ bond and one new C—C π bond.
4. These reactions are concerted, i.e., all old bonds are broken and all new bonds are formed simultaneouly in a single step.

1.1.10.2 The Widely Accepted Mechanism of the Diels–Alder Reaction and Evidence in its Support

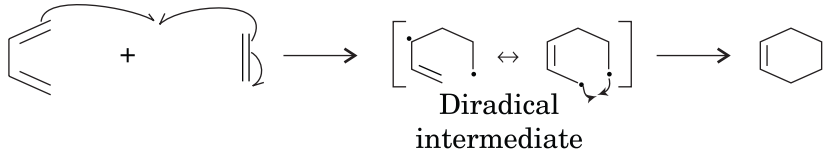
The bulk of evidence suggest that most Diels–Alder reactions take place by the one-step (concerted) cyclic mechanism, although it is possible that a diradical or even a diion mechanism, i.e., a stepwise mechanism may be taking place in some cases. These two pathways differ in the timing of bond-making and bond-breaking steps. In the concerted mechanism, the two σ bonds are formed simultaneously and the reaction proceeds through a six-membered cyclic transition state. In the stepwise mechanism, the diene and the dienophile fasten at one end to form initially an intermediate diradical or diion. The other ends then combine to form the ring.

(a) **Concerted mechanism:**

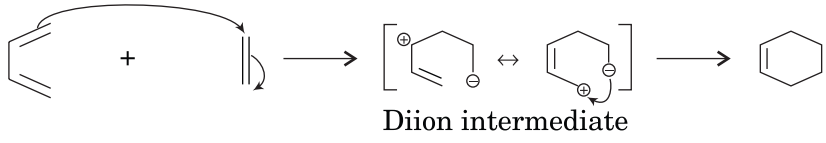


(b) **Stepwise mechanisms:**

(i) ***Radical mechanism***



(ii) ***Ionic mechanism***

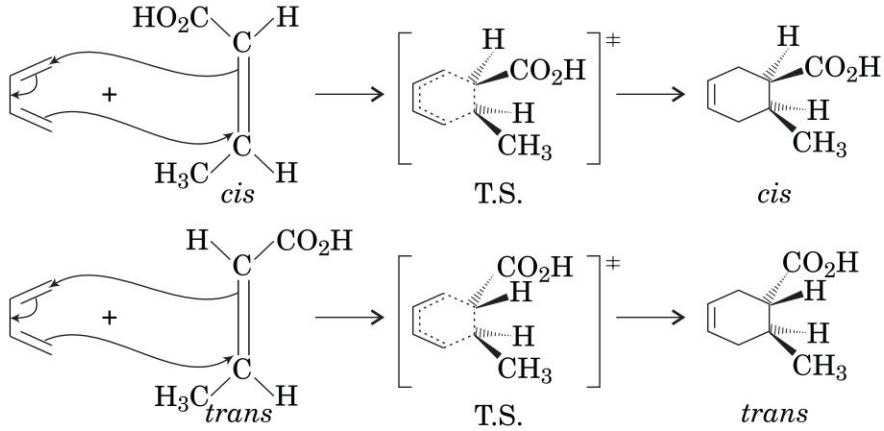


The main evidence in favour of the mechanism (a) is as follows:

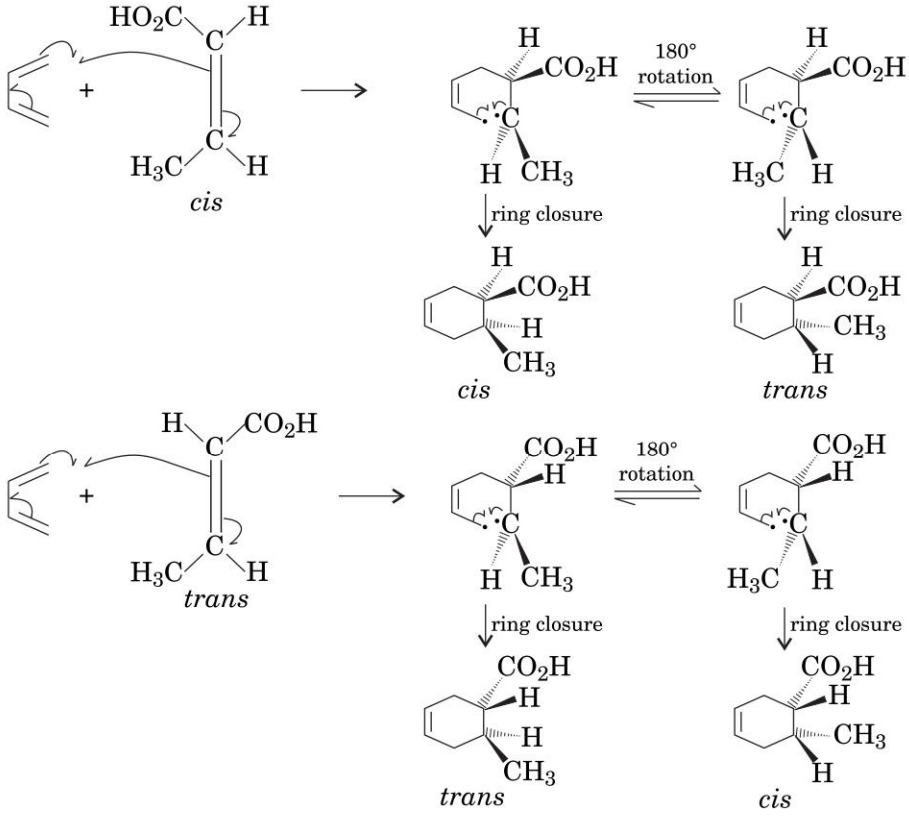
1. The reaction is stereospecific in both the diene and the dienophile. A completely free diradical or diion will be unable to retain its configuration in the adduct. Butadiene, for example, reacts with *cis*-2-butenoic acid to yield *cis*-6-methylcyclohex-3-enoic acid, whereas with the *trans*-acid it gives *trans*-6-methylcyclohex-3-enoic acid. It

is possible only if the reaction involves a concerted pathway and not a stepwise pathway. A stepwise pathway leads to the formation of a mixture of *cis*- and *trans*-isomes from both the isomeric 2-butenoic acids.

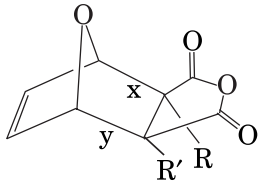
Concerted pathway:



Stepwise pathway:



2. In general, the rates of Diels–Alder reactions depend very little on the nature of the solvent used. This observation would rule out a diion intermediate because polar solvents are expected to increase the rates of reactions that develop charges in the transition state.
3. In the decomposition of following compound, the isotope effect k_I/k_{II} is equal to 1.00 within experimental error. If the bond x breaks before the bond y, there must be a secondary isotope effect. This result strongly suggests that the bonds x and y undergo cleavage simultaneously. This is a retro (reverse) Diels–Alder reaction and then, in accordance with the principle of microscopic reversibility, it is evident that in the forward reaction the two σ bonds are formed simultaneously.



I: R = H, R′ = D
II: R = D, R′ = H

4. The reaction possesses a large negative entropy of activation ($\Delta S^{\#}$).

1.1.10.3 Factors Favouring Diels–Alder Reactions

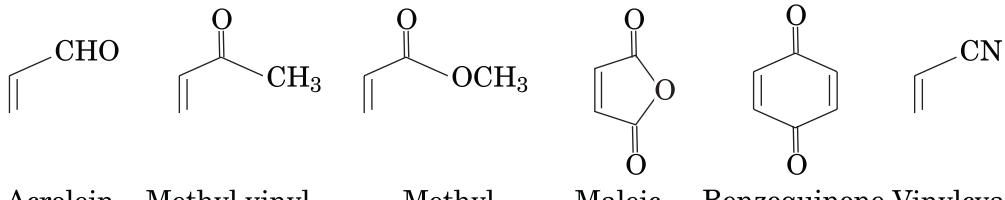
The factors favouring Diels–Alder reactions are as follows:

1. Electron-withdrawing groups in the dienophile facilitate the reaction, i.e., increase the reaction rate. In a Diels–Alder reaction, the 1,3-diene acts as a nucleophile and the dienophile acts as an electrophile. Because of this, an electron-withdrawing group makes the dienophile more electrophilic and thereby more reactive by withdrawing electrons from the carbon–carbon double bond. If there is one or more than one electron-withdrawing group, then the reactivity of the dienophile increases as follows:

$CH_2{=}{=}CH_2$, $CH_2{=}{=}CH–EWG$, EWG—CH═CH—EWG

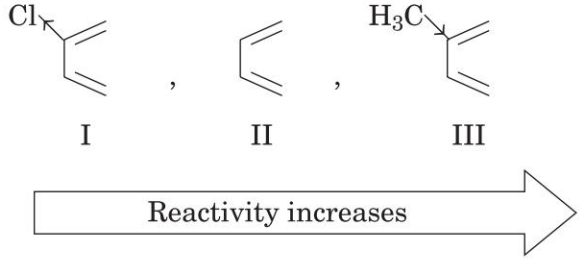
Reactivity increases

1,3-Butadiene, for example, reacts with maleic, *cis*-$HO_2CCH{=}CHCO_2H$, acid at a rate faster than *cis*-2-butenoic acid, *cis*-$CH_3CH{=}CHCOOH$.
Some common dienophiles used in the Diels–Alder reactions are as follows:



Acrolein | Methyl vinyl ketone | Methyl acrylate | Maleic anhydride | Benzoquinone | Vinylcyanide

2. Electron-donating groups in the diene facilitate the reaction, i.e., increase the rate of the reaction. 2,3-Dimethyl-1,3-butadieine, for example, is nearly five times as reactive in Diels–Alder reactions as is 1,3-butadieine. The methyl group increases the electron density of the diene by their +I effects.
   The electron-withdrawing groups in the diene, on the other hand, decreases its reactivity towards a dienophile. Chlorine withdraws electron from the diene system by its -I effect. For this reason, 1,3-butadiene (II) is more reactive than 2-chloro-1,3-butadiene (I) but less reactive than 2-methyl-1,3-butadiene (III).

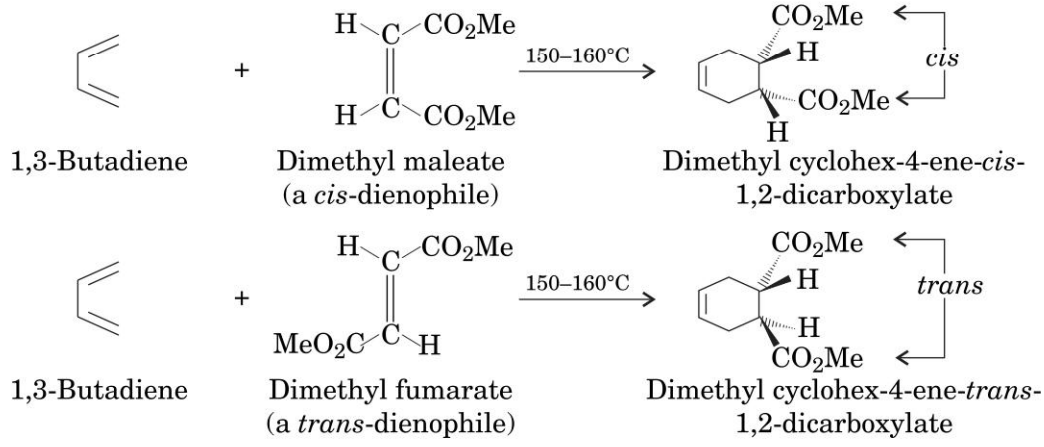


3. Some reactions are favoured at high temperature and high pressure.
4. Lewis acids like $AlCl_3$, $SnCl_4$, etc. may catalyze some Diels–Alder reactions through coordination with the dienophile having groups like –COOR, –CHO, $\rangle C{=}O$, etc., so that it acts as a better electron acceptor.

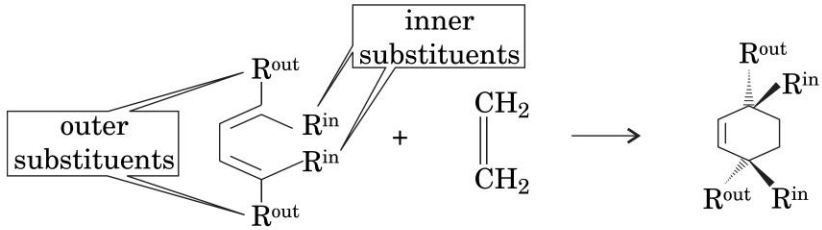
1.1.10.4 Stereochemical Aspects of the Diels–Alder reaction

Some stereochemical aspects of the Diels–Alder reaction are as follows:

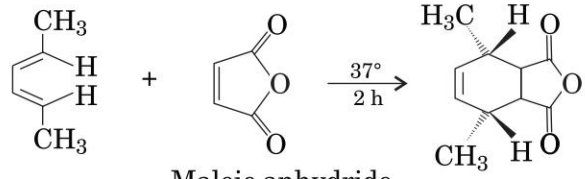
1. The Diels–Alder reaction is stereospecific. The reaction is a *syn*-addition with respect to both the diene and the dienophile. Each component adds to the other at one face of the π system. There is no opportunity for any of the substituents to change their stereochemical positions during the course of this concerted reaction. Because of this, the configuration of the dienophile is retained. Two examples that illustrate this aspect of the reaction are given below:



The *syn*-addition of the diene is revealed if the terminal carbons of the diene unit are prochiral centres. Let us classify the groups at the terminal carbons of the diene as inner substituents (R^{in}) or outer substituents (R^{out}). A *syn*-addition requires that in the adduct, the two inner substituents always have a *cis* relationship; the two outer substituents also have *cis* relationship and an inner substituent on one carbon is always *trans* to an outer substituent on the other.

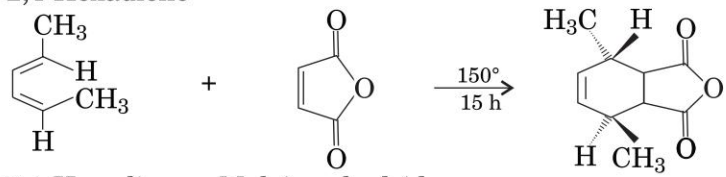


These points can be well demonstrated by the following reaction of stereoisomeric 2,4-hexadienes with maleic anhydride.



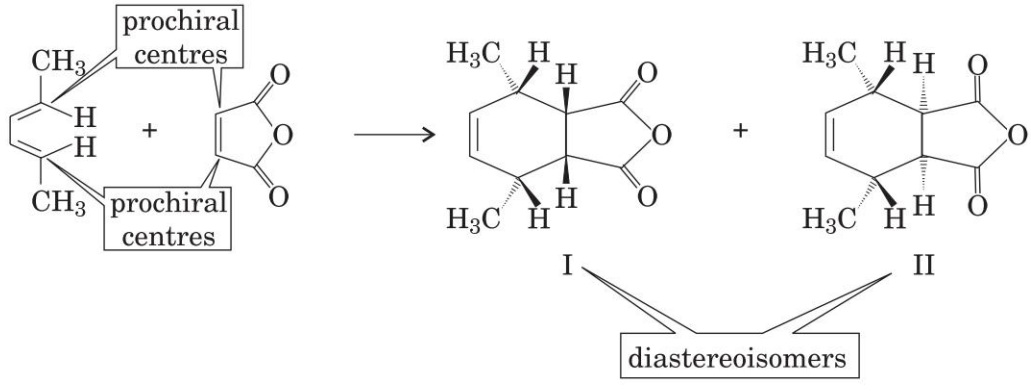
Maleic anhydride

(2*E*, 4*E*)-2,4-Hexadiene

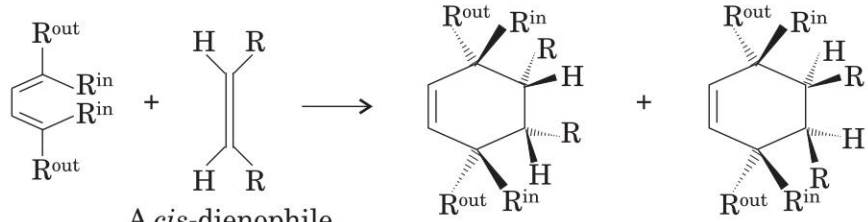


(2*E*, 4*Z*)-2,4-Hexadiene Maleic anhydride

2. If the carbons of the dienophile and the terminal carbons of the diene are all prochiral centres, two diastereoisomeric *syn*-addition products (I and II) are possible. For example:

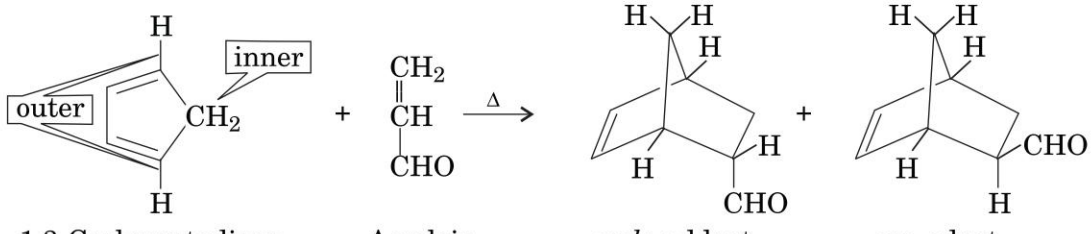


These two possiblities may be classified with a more general equation in which a *cis*-alkene reacts with a diene:

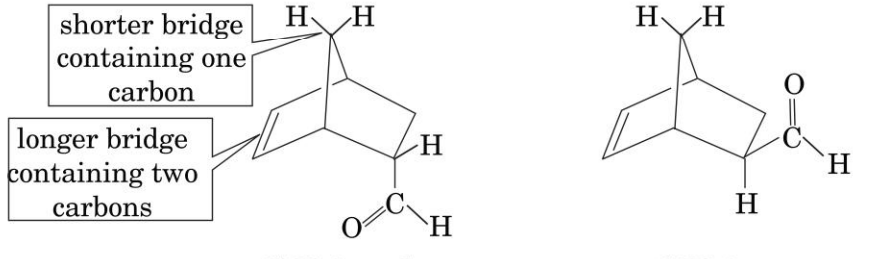


The adduct in which the alkene substituents R are *cis* to the outer diene substituents (R^{out}) is said to have *endo* stereochemistry and the adduct in which the alkene substituent R are *trans* to the outer diene substituents (R^{out}) is said to have *exo* stereochemistry (both endo and exo adducts are racemates).

The *endo* and *exo* adducts may also be designated easily when cyclic dienes are used and bicyclic products are formed. For example:

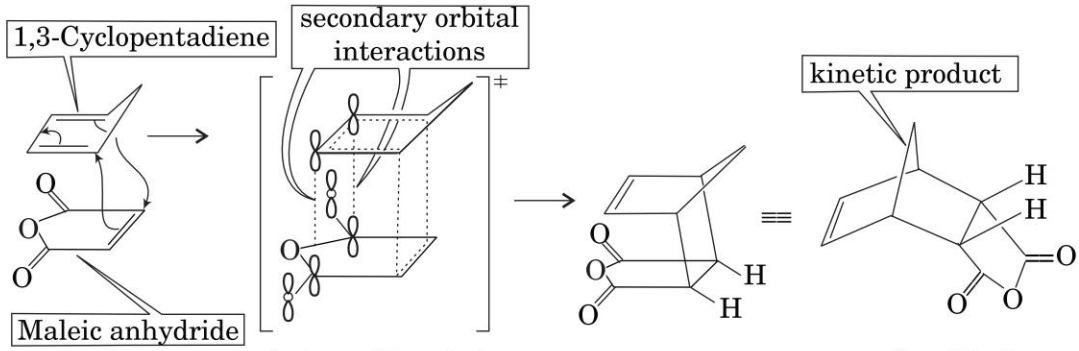


In fact, a substituent on one bridge is endo if it is closer to the longer bridge that joins the two carbon atoms common to both the rings and a substituent is *exo* if it is closer to the shorter bridge that joins the two carbons common to both rings.

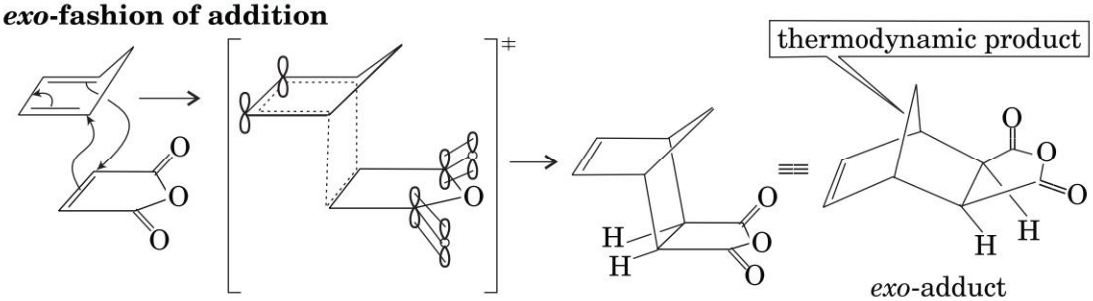


The rule of *endo* addition: When *endo* and *exo* products are possible in Diels–Alder reactions involving cyclic 1,3-diene, the *endo* product is preferred, i.e., the *endo* product becomes, the major or only product in the reaction. The concerted Diels–Alder reaction occurs with the diene and the dienophile arranged one above the other. The substituent, for example, –CHO can be oriented either directly under the diene (*endo*-fashion) to form the *endo*-adduct or away from the diene (*exo*-fashion) to form the *exo*-adduct. The *endo*-adduct is the major product because the transition state leading to this adduct is stabilized by the interaction of the *p* orbitals of the –CHO group in the dienophile $CH_2{=}CHCHO$ with the *p* orbitals of the new double bond going to be formed in the diene. This stabilising interaction, called secondary orbital interaction, can only occur if the substituent with the *p* orbitals lies underneath (*endo*) rather than away from (*exo*) the diene. The endo fashion of addition is, therefore, an energetically favourable arrangement when the reaction is kinetically controlled.

***endo*-fashion of addition:**



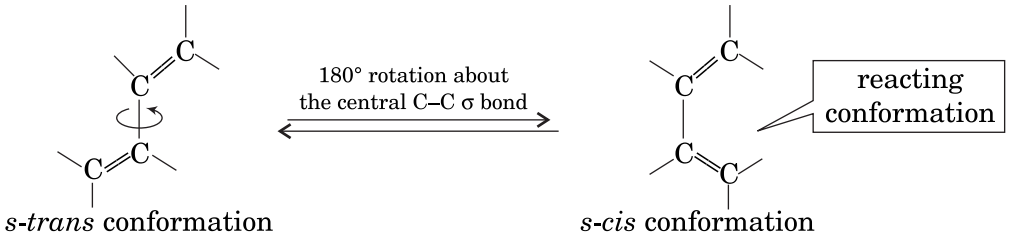
***exo*-fashion of addition**



It is to be noted that the *exo*-adduct is thermodynamically more stable than the *endo*-adduct and at a higher temperature, when the equilibrium is reached, the *endo*-adduct equilibrates to give the *exo*-adduct (the thermodynamic product) predominantly.

In the adduct, there are two bridges across the ends of the new σ bonds: a one-C-atom bridge and a two-C-atom bridge. There is less steric strain in the *exo*-adduct because in it the smaller one-atom bridge eclipses the anhydride ring but more steric strain in the *endo*-adduct because the two-atom bridge now eclipses the anhydride ring. Therefore, the *exo*-adduct is thermodynamically more stable than the *endo*-adduct.

3. Acyclic dienes may exist in *s-cis* or *cisoid* conformation and *s-trans* or *transoid* conformation. By *s-cis* and *s-trans* we mean that the double bonds are, respectively, *cis* and *trans* about the single bond (*s* = single).



s-trans conformation
more stable)

s-cis conformation
(less stable)

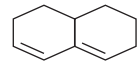
It is the *s-cis* conformation which takes part in the Diels–Alder reaction, even though the *s-trans* conformation is thermodynamically more stable and predominates at equilibrium. This is because in this concerted reaction, both ends of the conjugated diene must close to the π-bond of the dienophile to form two σ bonds simultaneously.

Reaction in the *s-trans* conformations would, if it takes place, produce a six-membered ring with a highly strained double bond. This unfavourable course of the Diels–Alder reaction has never been observed.

The equilibrium between the *s-trans* and *s-cis* conformation is, however, prevented in cyclic dienes when the two double bonds are constrained (locked) in the *s-cis* conformation and when the two double bonds are constrained (locked) in the *s-trans* conformation. The former dienes are unusually reactive, while the latter dienes are unreactive.



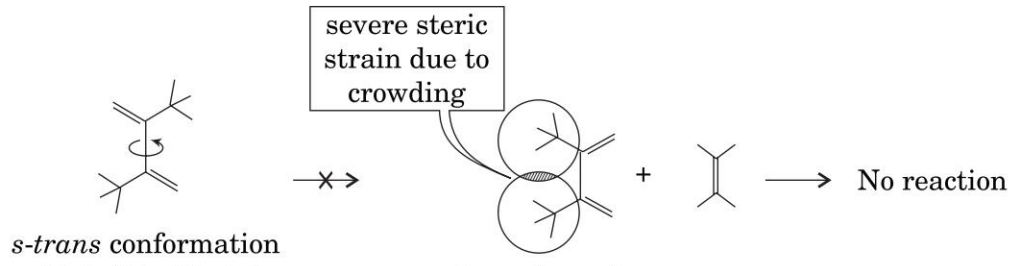
A very reactive
s-cis-1,3-diene



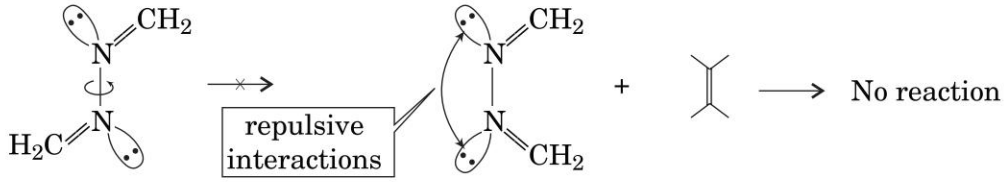
An unreactive
s-trans-1,3-diene

The rotation is also prevented when the *s-cis* conformation suffers from severe steric strain and when the *s-cis* conformation suffers from severe repulsive interactions caused by nonbonding electrons. For example:

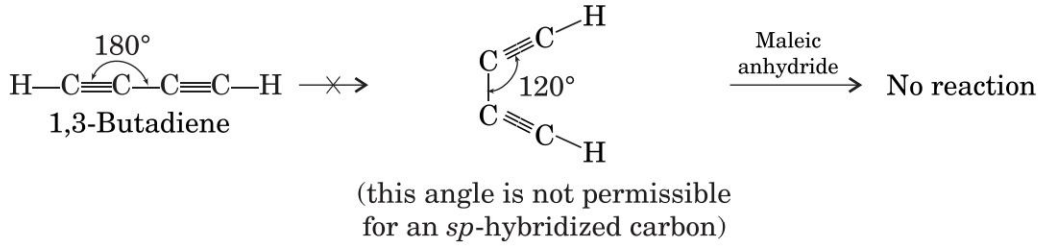
(i) 2,3-Di-*tert*-butyl-1,3-butadiene does not take part in the Diels–Alder reaction because the required *s-cis* conformation is destabilized by the steric strain caused by the two very bulky *tert*-butyl ($-CMe_3$) groups.



(ii) 2,3-Diazadiene ($CH_2{=}\ddot{N}{-}\ddot{N}{=}CH_2$) does not undergo the Diels–Alder reaction because, due to repulsive interactions between the unshared electron pairs on two N atoms, it is unable to exist in the *s-cis* conformation.

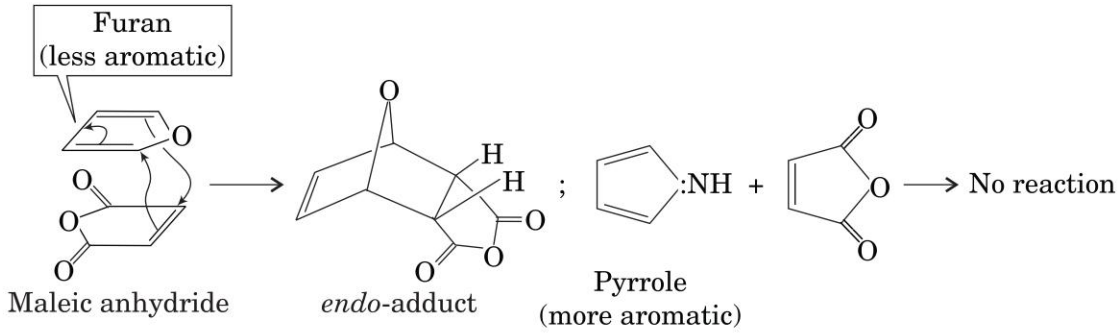


1,3-Butadiynes being linear in shape (carbon atoms are *sp*-hybridized) cannot take up the angular shape required for fastening the dienophile with its both ends at the same time (a concerted process) and for this reason, they do not undergo the Diels–Alder reaction. For example:

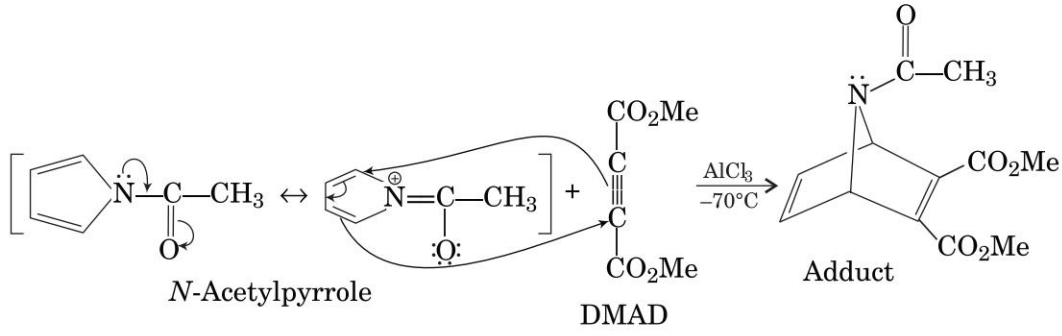


1.1.10.5 Aromaticity of Five-Membered Heterocycles and Behaviour as a Diene

Furan can act as a diene in the Diels–Alder reaction while pyrrole cannot. This can be explained in terms of aromaticity of the heterocycle involved. Since oxygen is more electronegative than nitrogen, it is much more reluctant to involve its unshared pair of electrons in maintaining aromaticity requiring $(4n + 2)\pi$ electrons, where $n = 1$ and therefore furan is less aromatic than pyrrole in which the unshared pair of electrons on relatively less electronegative nitrogen is well involved in maintaining aromaticity. Because of this, furan can act as a diene in the Diels–Alder reaction by destroying its aromatic system but pyrrole does not. Furan, for example, reacts with maleic anhydride to form the *endo*-adduct, while pyrrole remains inert in the presence of maleic anhydride.

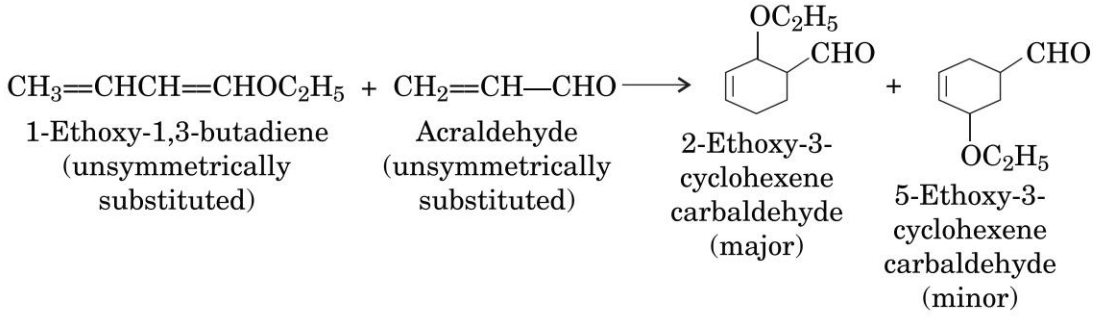


However, the presence of the electron-withdrawing $-COCH_3$ group on the nitrogen atom reduces the aromatic character of pyrrole and because of this, *N*-acetylpyrrole undergoes the Diels-Alder reaction by acting as a diene. It reacts with dimethylacetylenedicarboxylate (DMAD), an effective dienophile in the presence of the Lewis acid $AlCl_3$ to give the corresponding adduct.

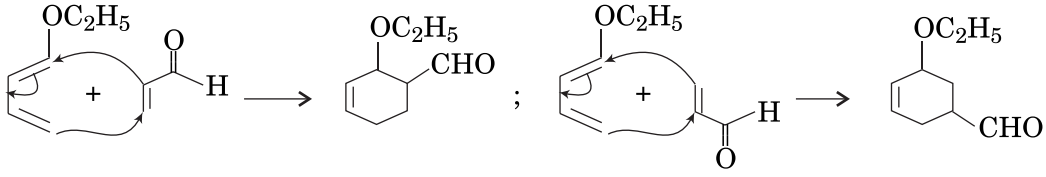


1.1.10.6 Predicting the Product When Both the Reactants (the Diene as Well as the Dienophile) are Unsymmetrically Substituted

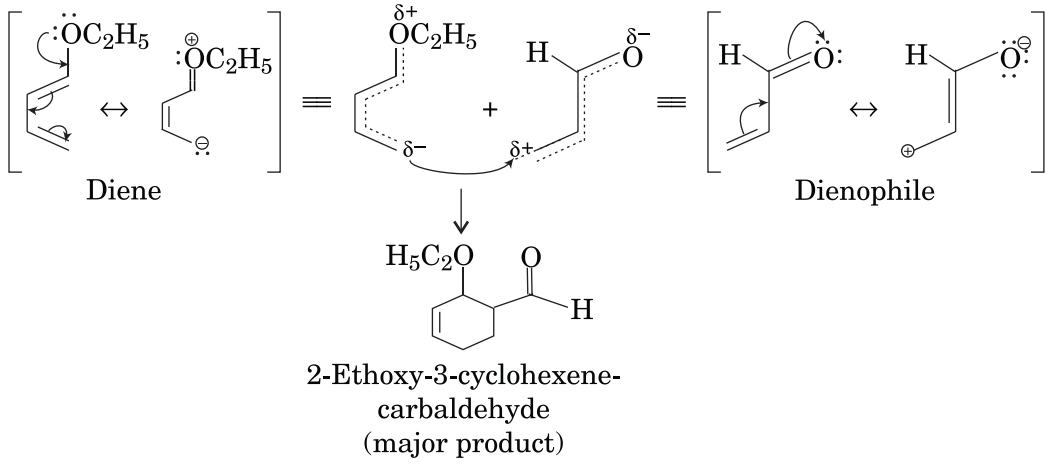
In each of the previously discussed Diels–Alder reactions, only one product is formed (ignoring stereochemistry) because in each of these reactions at least one of the reactants (diene or dienophile) is symmetrically substituted. However, if both the diene and the dienophile are unsymmetrically substituted, two products (structural isomers) are expected to be formed. For example:



The diene and the dienophile may combine with each other in two different fashions to yield the two products.



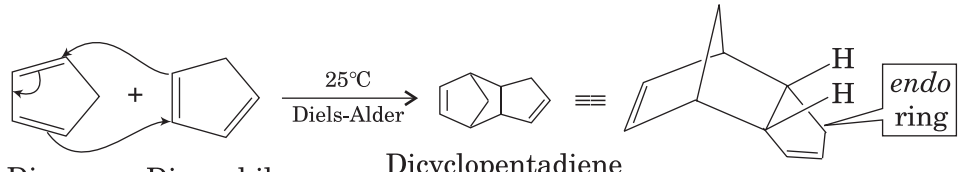
Which of the two products will be produced as the major product can be predicated by analysing the charge distribution in each of the reactants. Since the ethoxy group ($-OC_2H_5$) of the diene donates electrons by +R effect, a partial negative charge is developed at the terminal carbon atom (C-4). On the other hand, the formyl group (–CHO) of the dienophile withdraws electrons by its –R effect and as a result, a partial positive charge is developed on the terminal carbon (C-3). The partially positively charged carbon atom of the dienophile undergoes attack preferentially by the partially negatively charged carbon atom of the diene to yield 2-ethoxy-3-cyclohexenecarbaldehyde as the major product.



2-Ethoxy-3-cyclohexene-carbaldehyde (major product)

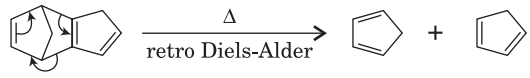
1.1.10.7 Retro Diels–Alder Reaction

1,3-Cyclopentadiene is so reactive that on standing at room temperature it slowly undergoes a Diels–Alder reaction with itself (one molecule acts as a diene and another acts as a dienophile).



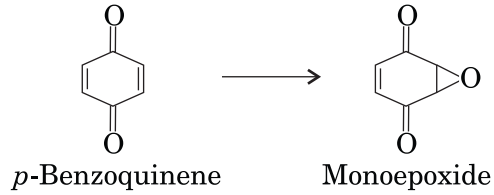
Diene Dienophile Dicyclopentadiene (dimer)

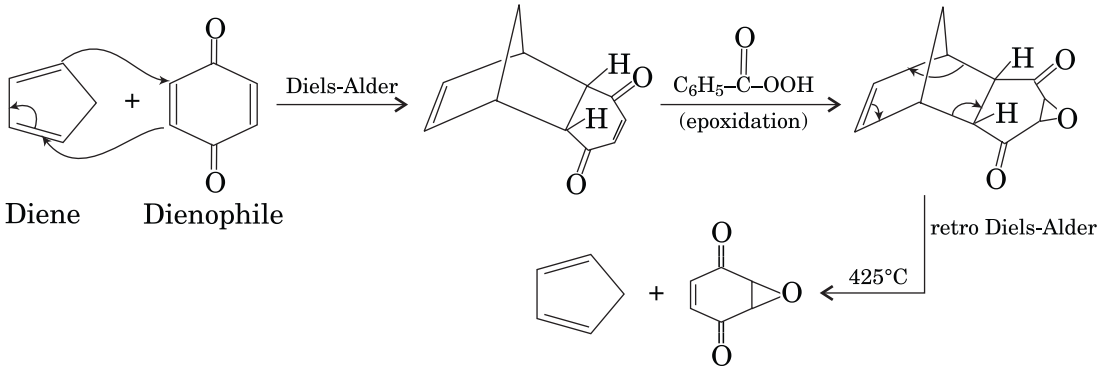
However, the reaction is reversible and because of this, when dicyclopentadiene is distilled, it dissociates to give two molar equivalents of cyclopentadiene.



Such thermal dissociation of cycloadduct into its fragments is called the *retro Diels–Alder reaction.* According to the principle of microscopic reversibility, the forward and the reverse reactions should follow a similar mechanism. Since the formation of the adduct is concerted process, the reverse reaction should also be concerted, i.e., the two components are eliminated in a single step. The *endo*-isomer decomposes faster than the *exo*-isomer.

The retro Diels–Alder reaction is used in the synthesis of organic compounds that are inaccessible by other routes. For example, the retro Diels–Alder reaction can be used to convert *p*-benzoquinone to the corresponding monoepoxide.

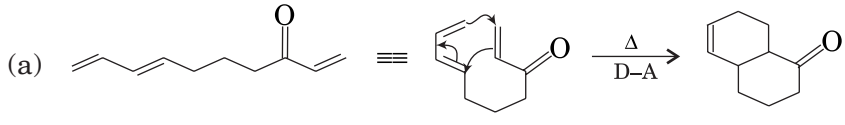


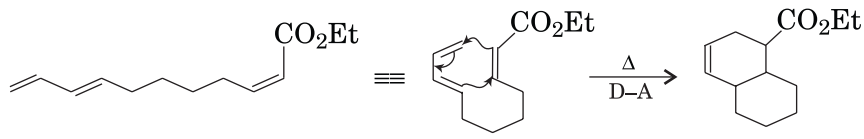


In fact, by the Diles–Alder reaction one of the double bonds of benzoquinone is eliminated and by the retro Diels–Alder reaction it is regenerated.

1.1.10.8 Intramolecular Diels–Alder Reaction

Intramolecular Diels-Alder reactions are possible when a substrate contains both an 1,9-diene system and a dienophile system. For example:

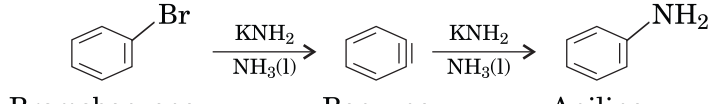


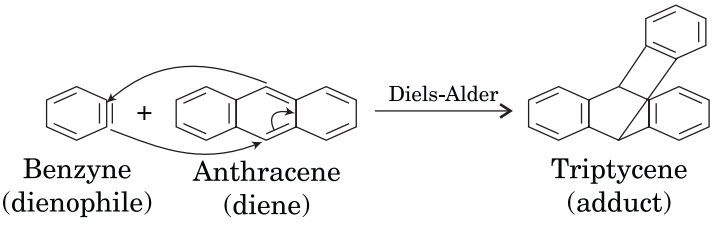
(b) 

1.1.10.9 Synthetic Applications of the Diels–Alder Reaction

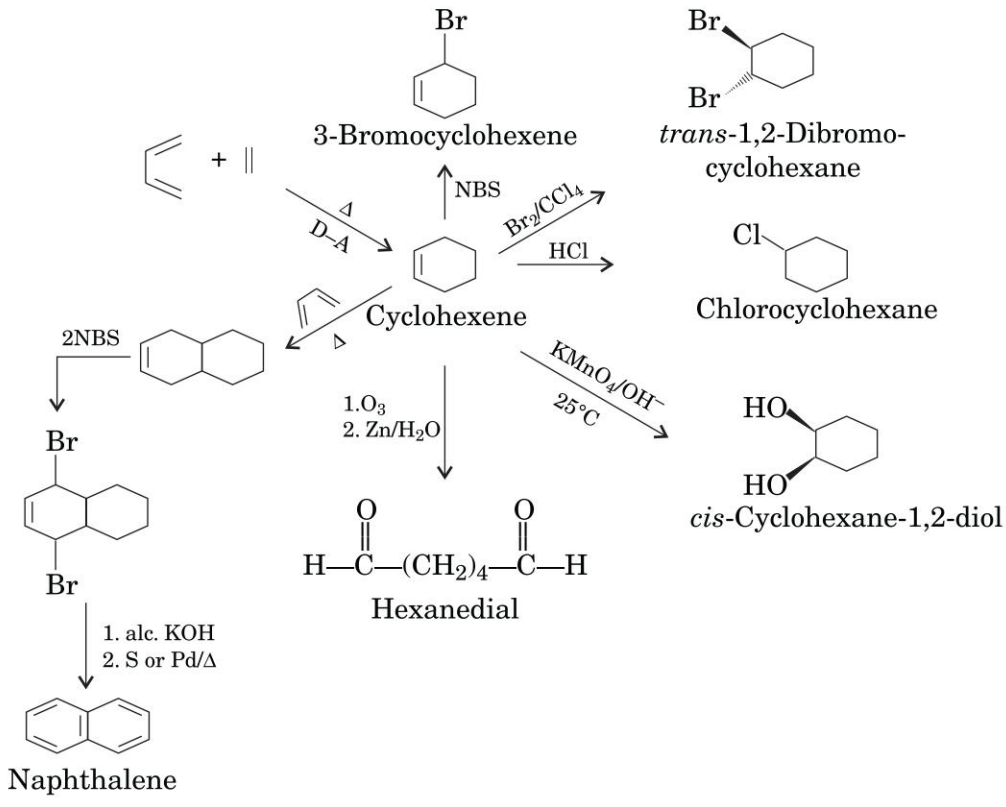
The Diels–Alder reaction has a great synthetic value because the reaction procedure is very simple and a wide variety of compounds take part in the reaction leading to the formation of a six-membered ring.

1. Due to its stereospecific nature, the reaction has been used to synthesize many natural products which otherwise would be difficult to prepare.
2. Captan (an agricultural fungicide) is synthesized industrially by using the Diels–Alder reaction between 1,3-butadiene and maleic anhydride in one of the steps involved.
3. The intramolecular Diels–Alder reaction, in which the diene and the dienophile are suitably placed within a molecule, has been extensively used in the synthesis of natural products like alkaloids, terpenoids and steroids.
4. Since the reaction is stereospecific, it has been used to determine the configurations of the reactants by determining the configuration of the adduct. For example, maleic and fumaric acids can be identified from the products.
5. The reaction is used to trap and ascertain the formation of the highly reactive benzyne intermediate in a reaction and thereby helps to determine the mechanism of a reaction. When the following reaction, for example, is carried out in the presence of anthracene, the adduct triptycene is isolated. It provides a direct evidence for the intermediacy of benzyne.



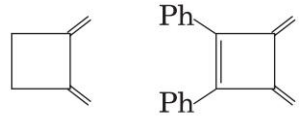


6. The Diels–Alder reaction produces a six-membered ring with a double bond that can be used to introduce other functionalities. We see, therefore, that the Diels–Alder reaction is a key route to the preparation of many important compounds.



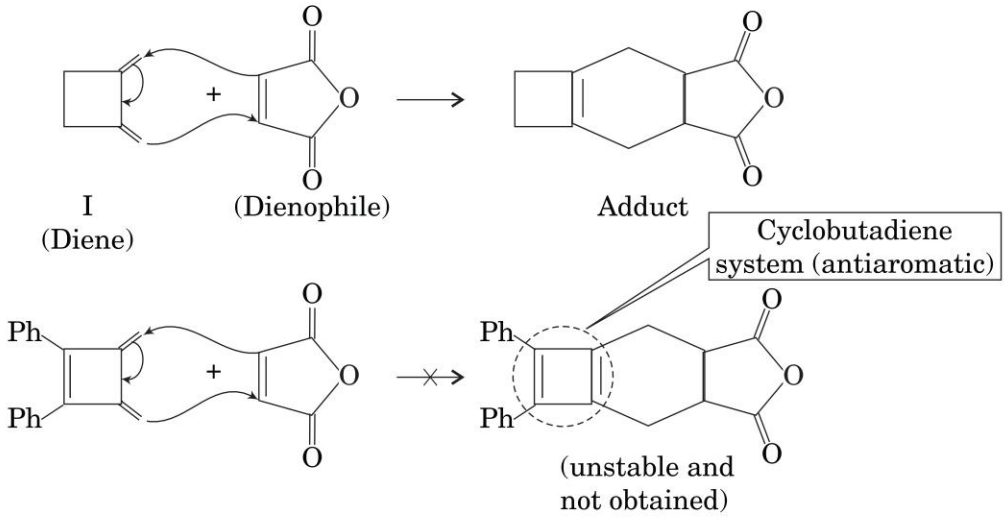
SOLVED PROBLEMS

1. The diene I reacts with maleic anhydride (the dienophile) to give an adduct, while the diene II does not. Explain this observations.



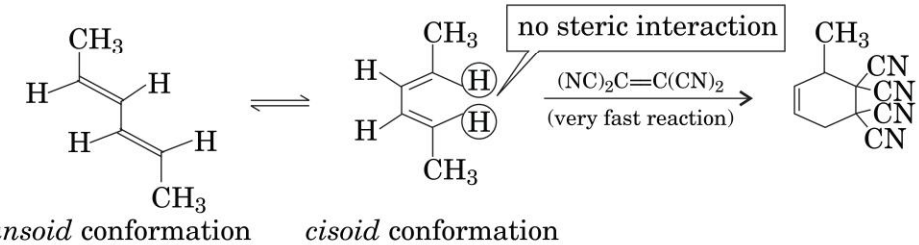
I II

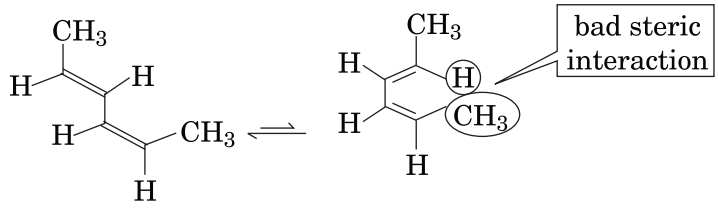
Solution The diene I reacts with malecic anhydride to give the corresponding adduct because the adduct is stable. However, the adduct expected to be formed from II is very unstable because the new double bond constitutes an antiaromatic cyclobutadiene (a $4n\pi$ electron system, where $n = 1$) system. And, for this reason, the triene II does not undergo the Diels–Alder reaction.



2. A mixture of 0.2 mole (2*E*, 4*E*)-2,4-hexadiene and 0.2 mole of (2*E*, 4*Z*) -2,4-hexadiene is allowed to react with 0.2 mole of TCNE [$(NC)_2C{=}C(CN)_2$]. After the reaction is completed, one isomer of the starting 2,4-hexadiene is found to remain unreacted. Which isomer does not react and why?

Solution The *cisoid* conformation of (2*E*, 4*Z*)-2,4-hexadiene is destabilized by a significant van der Waals repulsion (steric strain) between the methyl group and a diene hydrogen. The transition states for the Diels-Alder reactions of this dinene, which require a *cisoid* conformation, are destabilized by the same effect. As a consquence, the Diels-Alder reaction of (2*E*, 4*E*)-2,4-hexadiene is much slower than the corresponding reaction of (2*E*, 4*E*)-2,4-hexadiene, which does not have the destabilizing repulsion in its *cisoid* conformation. For this reason, when a mixture of 0.2 mole of (2*E*, 4*E*)-2,4-hexadiene and 0.2 mole of (2*E*, 4*Z*)-2,4-hexadiene is allowed to react with 0.2 mole to TCNE, the latter isomer is found to remain unreacted.

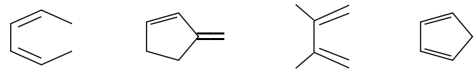




transoid conformation *cisoid* conformation

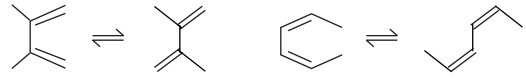
(2*E*, 4*Z*)-2,4-Hexadiene
(much less reactive with TCNE)

3. Arrange the following dienes in order of decreasing reactivity towards tetracyanoethylene as dienophile in the Diels-Alder reaction:



I II III IV

Solution 1,3-Cyclopentadiene (IV) is the most reactive diene because it has the double bonds locked in the required *s-cis* conformation. The diene II is the least reactive (actually it does not react) because it has the double bonds locked in the *s-trans* conformation. 2,3-Dimethyl-1,3-butadiene (III) and 2,4-hexadiene (I) are of intermediate reactivity because they can exist both in the *cisoid* and *transoid* conformations. 2,4-Hexadiene (I) is less able to adopt the required *s-cis* conformation because of steric interaction between the two terminal methyl groups. As a consequence, it is less reactive than 2,3-dimethyl-1,3-butadiene (III)



Therefore, the order of decreasing reactivity of these dienes towards TCNE in the Diels–Alder reaction is:



IV III I II

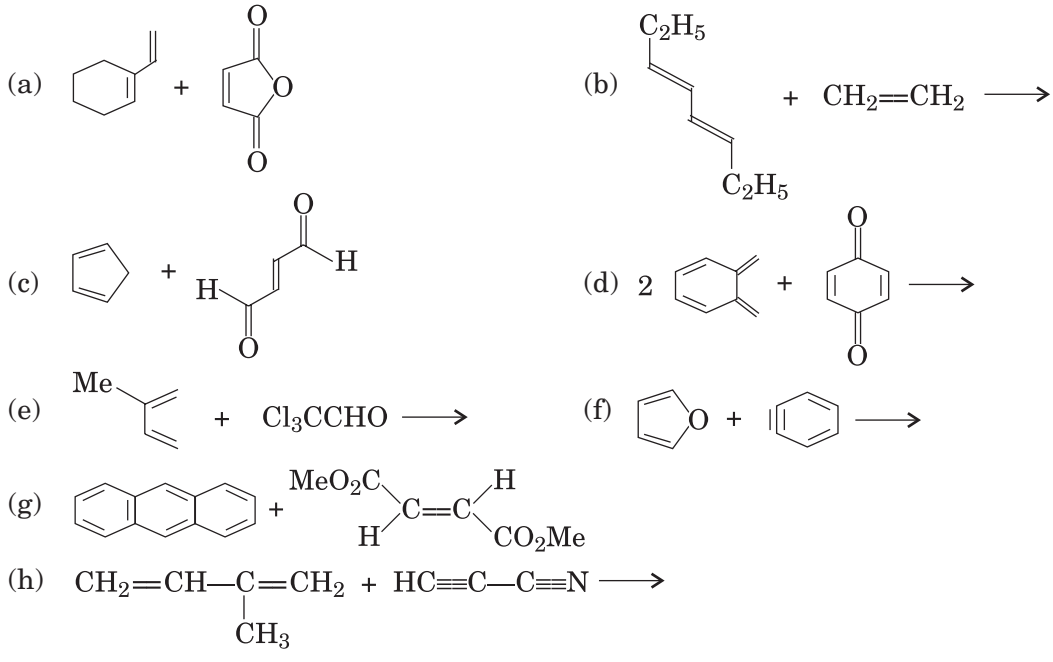
4. List the following dienophiles in order of decreasing reactivity and give your reasoning:

$$\underset{\text{I}}{CH_2{=}CHCOOH} \qquad \underset{\text{II}}{CH_2{=}CH_2} \qquad \underset{\text{III}}{HO_2CCH{=}CHCO_2H}$$

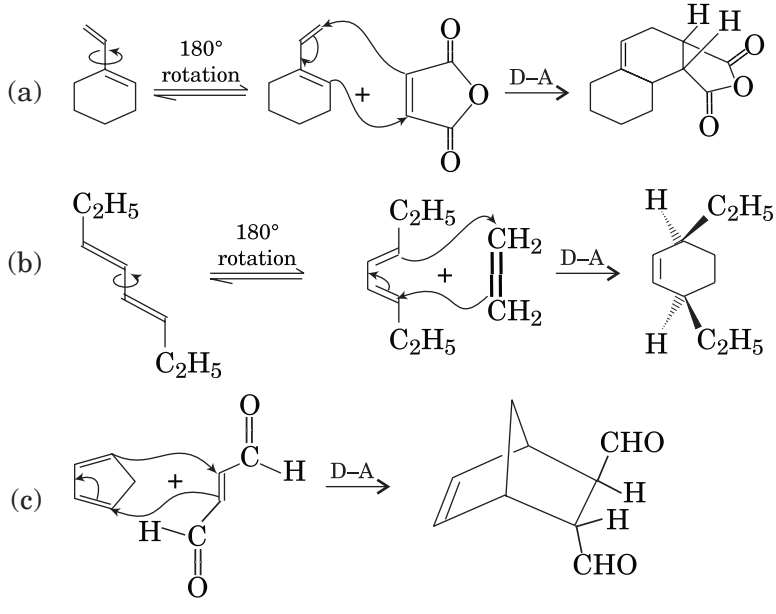
Solution Electron withdrawing substituents in the dienophile increase the rate of the Diels–Alder reaction and the rate increases progressively with an increase in the number of such substituents. It thus follows that propenoic acid (I) containing one electron-

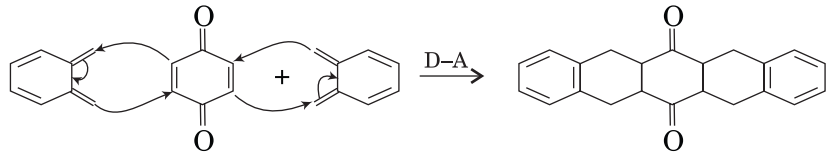
withdrawing –COOH group is more reactive than ethylene (II) but less reactive than butenedioic acid (III) containing two –COOH groups. Therefore, the order of decreasing reactivity of these three dienophile is: III ⟩ I ⟩ II.

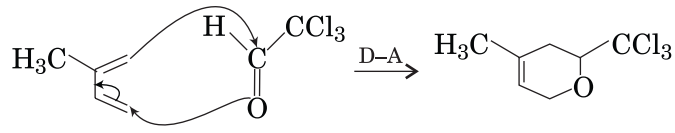
5. What products would you expect from the following reactions? Give stereochemistry in appropriate cases.

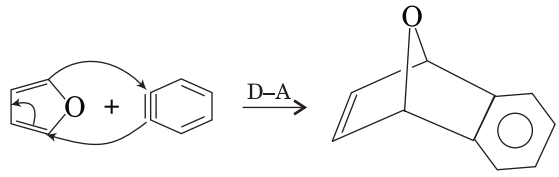


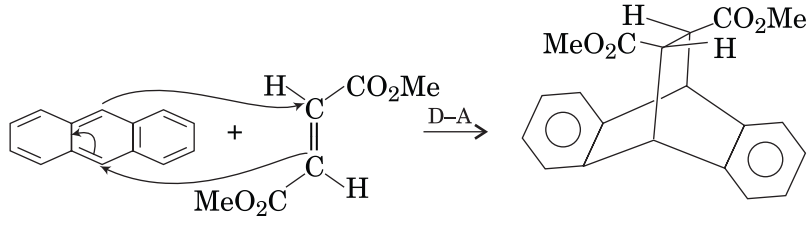
Solution

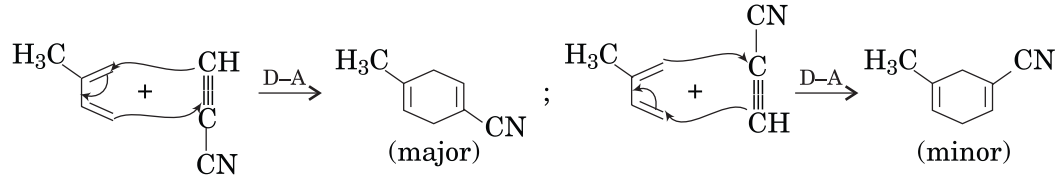


(d) 

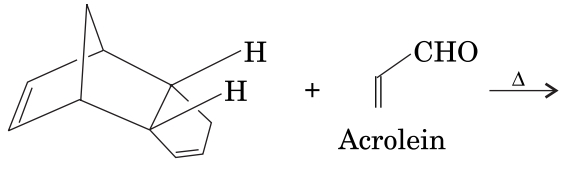
(e) 

(f) 

(g) 

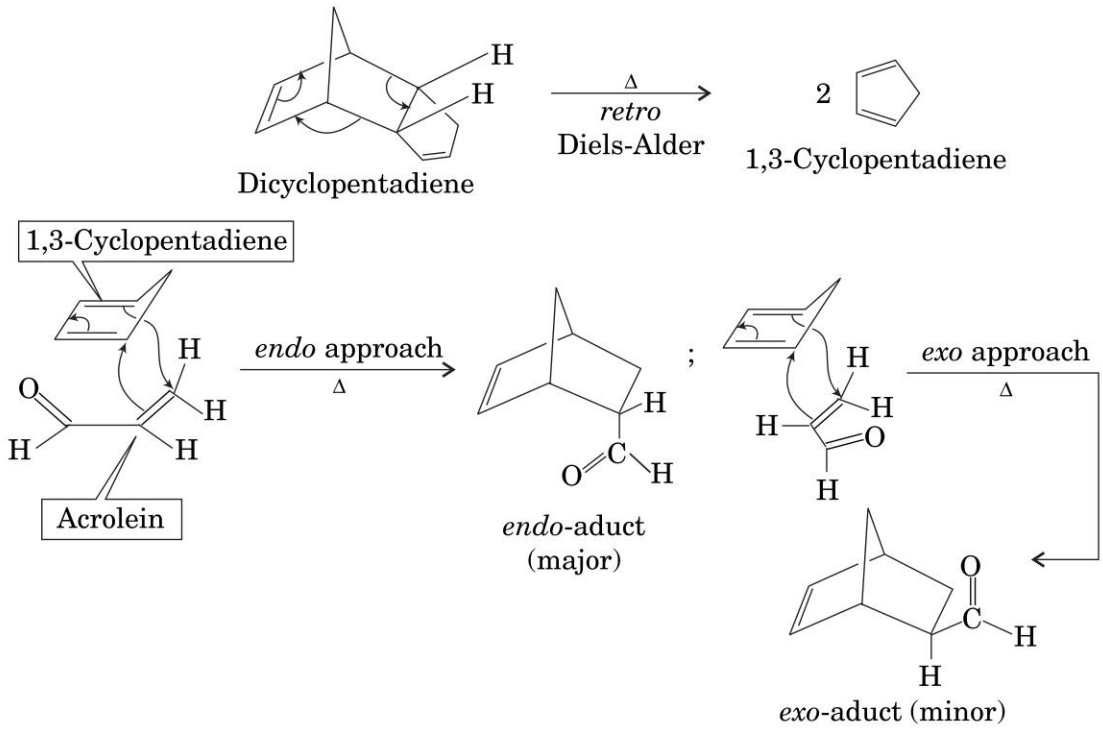
(h) 

6. What happens when dicyclopentadiene is heated with acrolein?

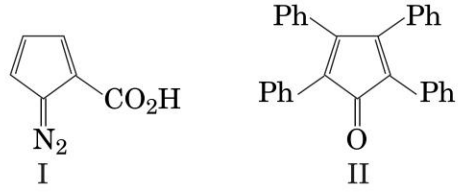


Dicyclopentadiene Acrolein

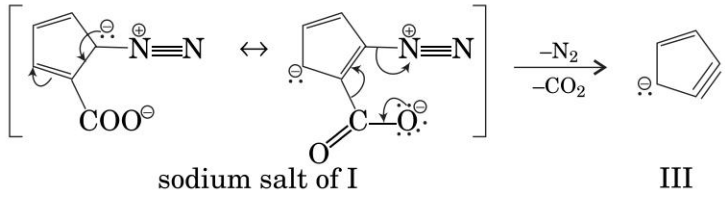
Solution The Dieles-Alder reaction is reversible in nature and so, when dicyclopentadiene is heated, it undergoes retro Diels-Alder reaction to yields two molar equivalents of cyclopentadiene. It then reacts with acrolein to give the corresponding adduct. The endo-adduct is obtained predominantly because its formation involves more stable transition state (stabilized by secondary orbital interaction).

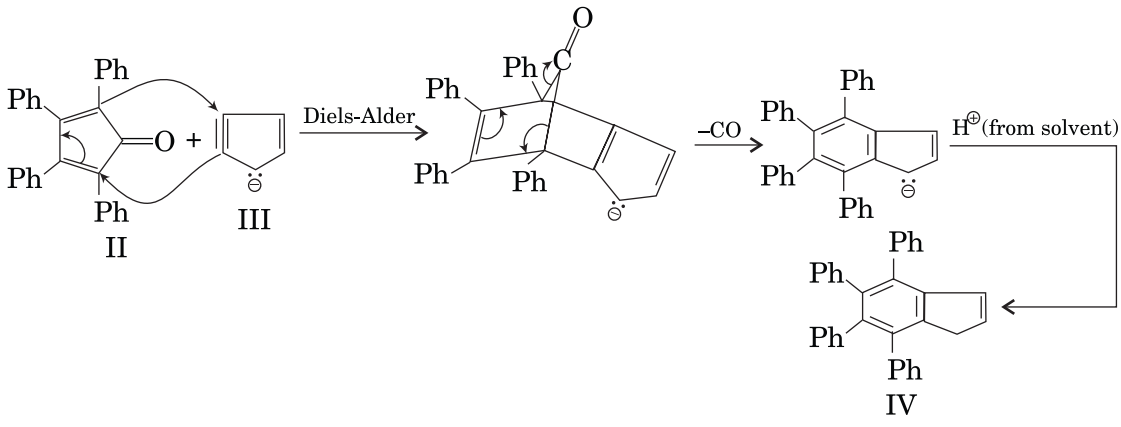


7. Predict the product obtained when the sodium salt of diazocyclopentadiene-2-carboxylic acid (I) is heated in solution with tetracyclone (II) and give a likely mechanism for its formation.



Solution When the sodium salt of the compound I is heated, N_2 and CO_2 are evolved to yield the anion III which, like benzyne, can act a dienophile in the Diels-Alder reaction. The anion III then reacts with the compound II (a diene) to give an adduct. Finally, the adduct dissociates by expulsion of CO to yield, after proton take up from the solvent, 4,5,6,7-tetraphenylindene (IV).





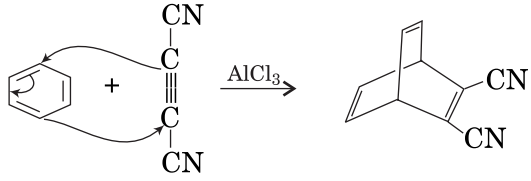
8. Unlike anthracene benzene does not undergo the Diles-Alder reaction under normal conditions. However benzene reacts with dicyanoacetylene in the presence of the Lewis acid $AlCl_3$ to give the corresponding adduct. Explain these observations.

Solution The resonance energy of benzene is 150.6 kJ mol^{-1} and that of anthracene is 351.5 kJ mol^{-1}. That is, the resonance energy per ring of anthracene is 117.16 kJ mol^{-1}. Since the resonance energy per ring is less in the case of anthracene, unlike benzene it undergoes the Diels-Alder reaction by destroying the aromaticity of one ring.

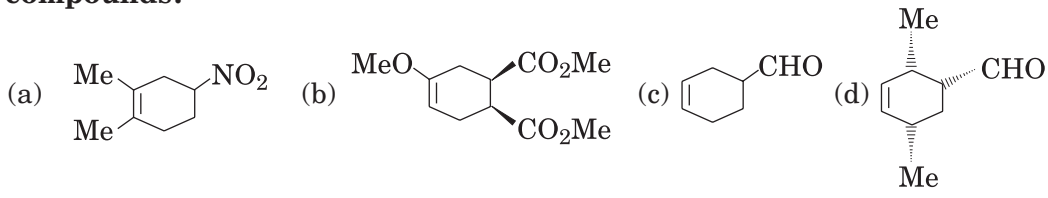


Benzene (resonance energy: 150.6 kJ mol^{-1}) Anthracene (resonance energy: 351.6 kJ mol^{-1})

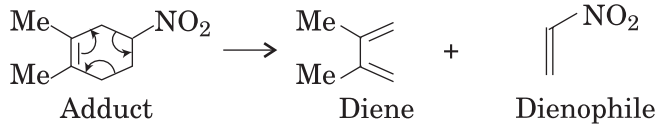
Benzene undergoes the Diels-Alder reaction with dicyanoacetylene in the presence of the Lewis acid $AlCl_3$ because the Lewis acid lowers the energy of the transition state, i.e., reduces the activation energy by coordinating with —C≡N: group.



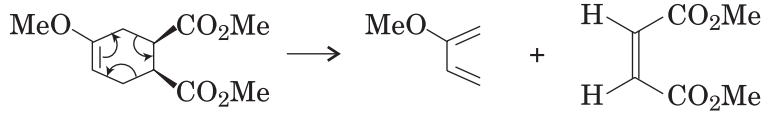
9. Which diene and dienophile could be used to prepare each of the following compounds?



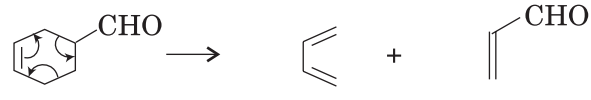
Solution

(a) 

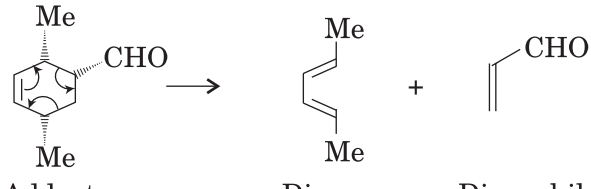
Adduct Diene Dienophile

(b) 

Adduct Diene Dienophile

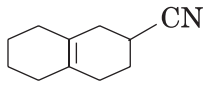
(c) 

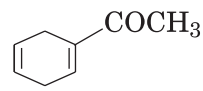
Adduct Diene Dienophile

(d) 

Adduct Diene Dienophile

10. What diene and dienophile are needed to prepare each of the following compounds? Indicate the preferred reactants.

(a) 

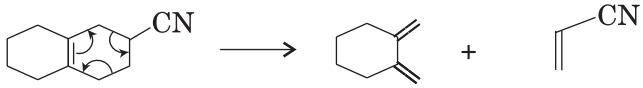
(b) 

Solution

(a) **The two possibilities are:**

(i) 

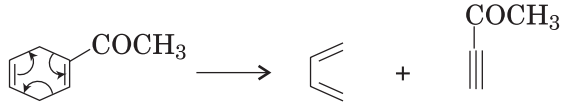
Adduct Dienophile Diene

(ii) 

Adduct Diene Dienophile

The reactants in (ii) would be more preferred because the dienophile with the electron-withdrawing –CN group reacts faster than that without such a group.

(b) **The two possibilities are:**

(i) 

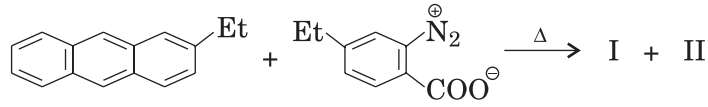
Adduct Diene Dienophile

(ii) 

Adduct Dienophile Diene

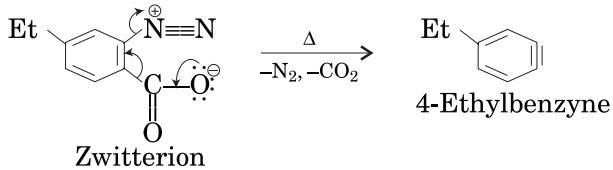
The reactants in (i) would be more preferred because the dienophile containing the electron-withdrawing $-COCH_3$ group reacts faster than that without such a groups. Also, in (ii), the diene contains the electron-withdrawing $-COCH_3$ group and so, the reaction is disfavoured.

11. Identify the products of the following reaction and comment on their optical activity:

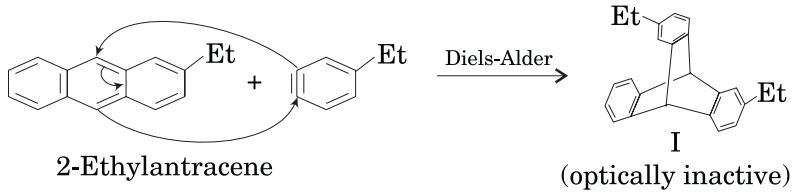


2-Ethylanthracene

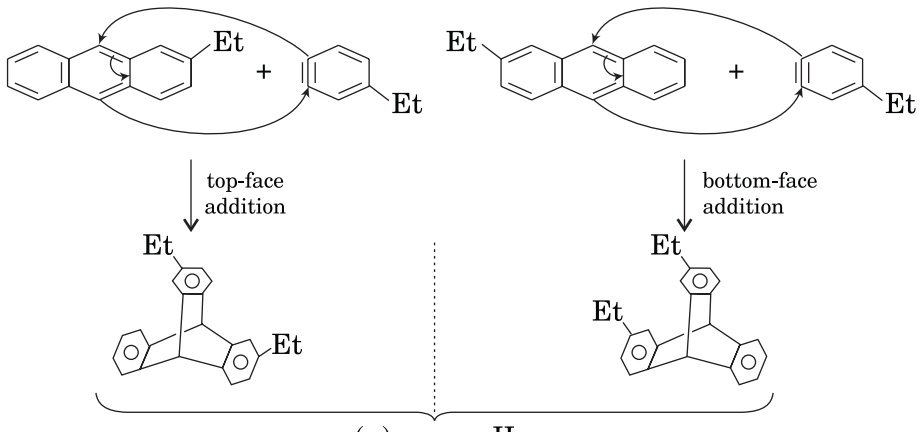
Solution When the zwitterion is heated, it eliminates a molecule of CO_2 and a molecule of N_2 to give 4-ethylbenzyne. The unstable benzyne intermediate then readily adds to 2-ethylanthracene (at 9,10-position) in two fashions to give two isomeric products I and II (triptycene derivatives). The compound I having a plane of symmetry is optically inactive, while the compound II with no element of symmetry is optically active. In fact, the addition of the benzyne to 2-ethylanthracene takes place from both the faces with equal facility and as a result, two enantiomers are obtained in equal amounts. That is, II is obtained as a recemic mixture which is optically inactive.



Zwitterion 4-Ethylbenzyne

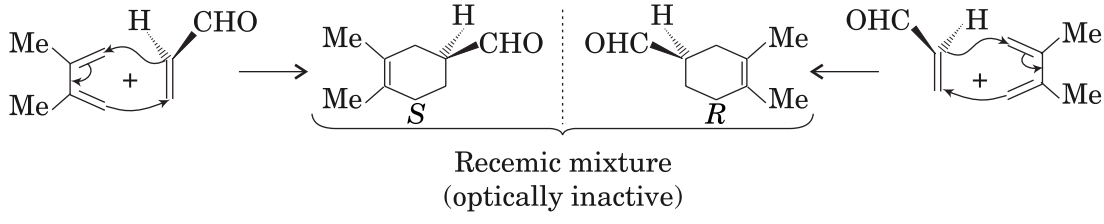


2-Ethylantracene I (optically inactive)



12. Explain why the product obtained from the reaction of 2,3-dimethyl-1,3-butadiene and acrolein (CH_2═CH—CHO) is found to be optically inactive.

Solution A chirality centre is created in the adduct of this Diels-Alder reaction because the dienophile contains a prochiral centre. Since the dienophile adds to the diene through both of its faces equally well, identical amounts of the *R* and *S* enantiomers are formed. That is, the product is a racemic mixture and so, it is found to optically inactive.

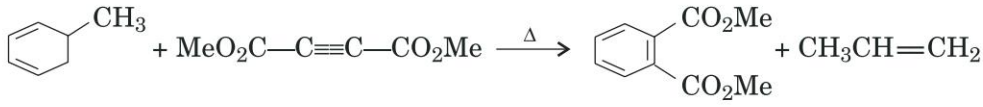


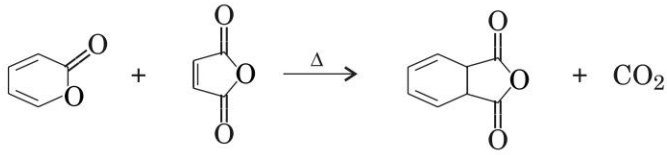
13. Which diene is relatively more reactive in a Diels-Alder rection and why?

CH_2═CH—CH═$CHOCH_3$ or CH_2═CH—CH═CH—CH_2OCH_3

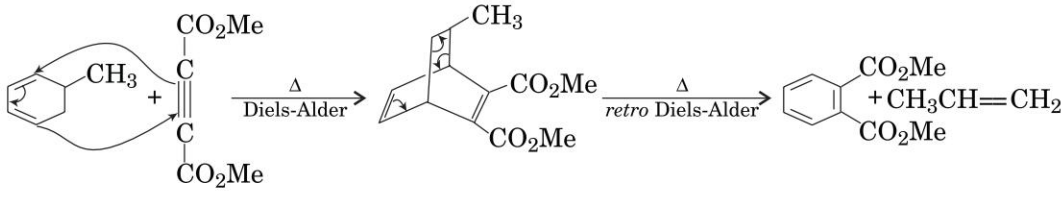
Solution Being conjugated with the diene system, the –OCH_3 group in CH_2═CH—CH═CH—OCH_3 donates electrons by its +R effect and makes the diene electron rich. On the other hand, the –OCH_3 group is not conjugated with the diene system in CH_2═CH—CH═CH—CH_2—OCH_3 and so, instead of donating electrons, it withdraws electron from the diene system by its –I effect. The electron-rich diene CH_2═CH—CH═CH—OCH_3 is, therefore, more reactive than the electron-deficient diene CH_2═CH—CH═CH—CH_2OCH_3.

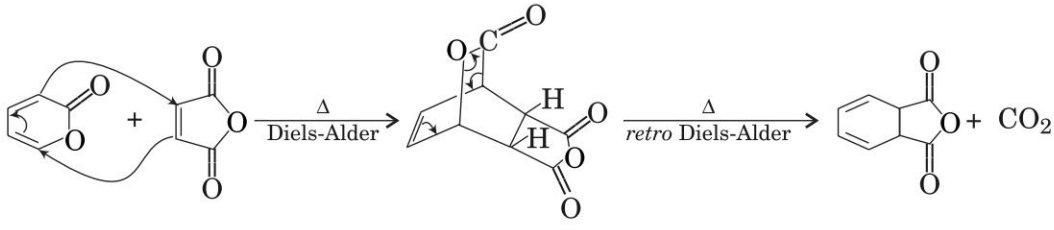
14. Suggest a mechanism for each of the following transformations involving a Diels-Alder and a retro Diels-Alder reaction:

(a) 

(b) 

Solution

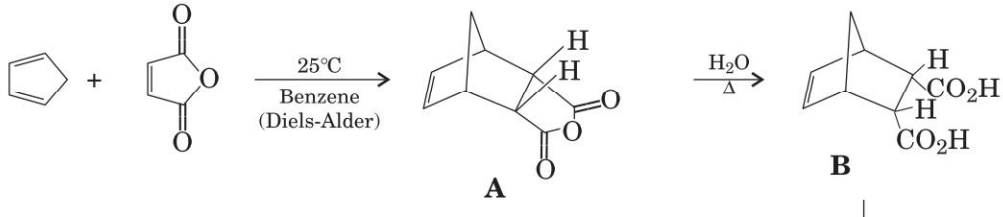
(a) 

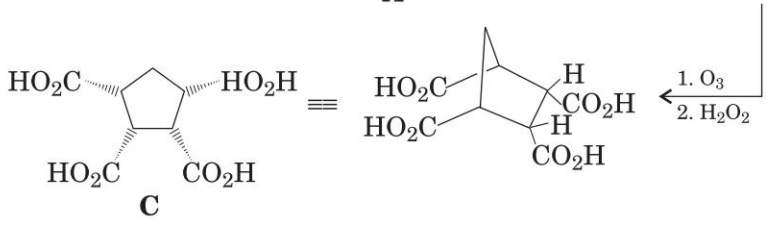
(b) 

15. Give structures for the compounds A, B and C in the following reaction sequence:

1,3-Cyclopentadiene + Maleic anhydride $\xrightarrow[\text{Benzene}]{25^\circ C}$ A $\xrightarrow{H_2O/\Delta}$ B $\xrightarrow[2.\ H_2O_2]{1.\ O_3}$ C

Solution

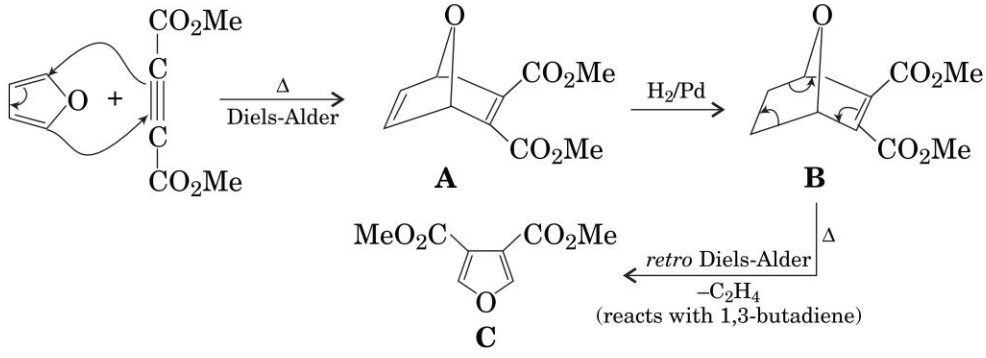




16. Provide structures for the compounds A, B and C in the following reaction sequence:

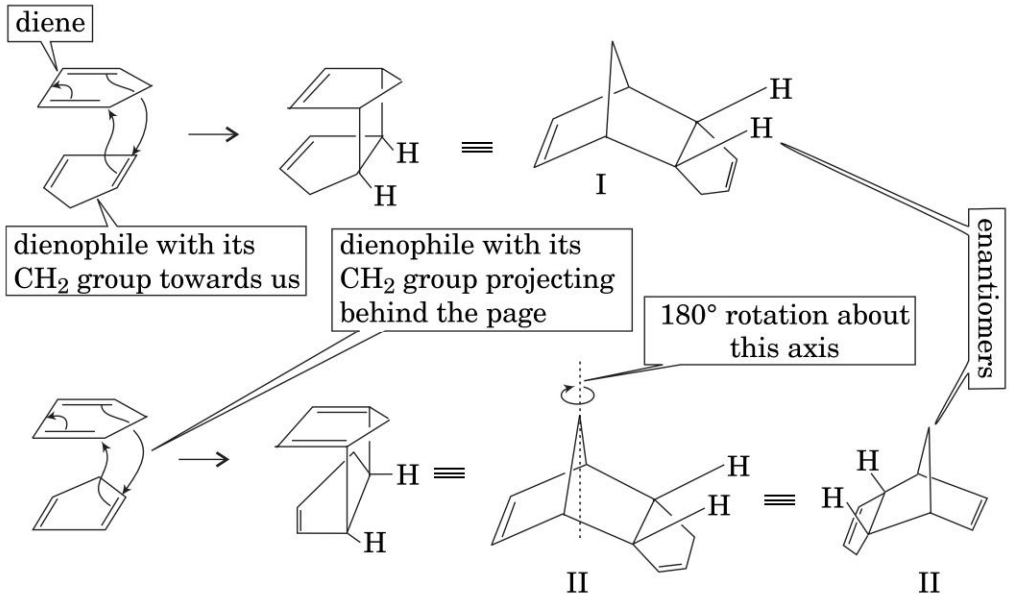


Solution



17. The dimerization of cyclopentadiene, which occurs primarily through an endo transition state, produces a racemic mixture. Show how the two molecules align in three dimensions to form each enantiomer.

Solution The formation of two enantiomeric dicyclopentadiene can be shown as follows:

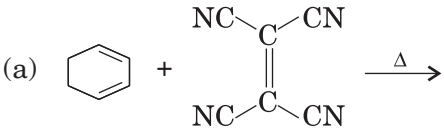


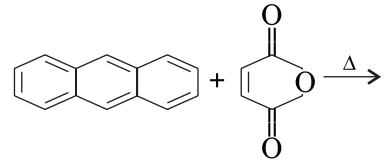
The enantiomer I is formed if the dienophile approaches from below the diene and with its CH_2 group towards us and the enantiomer II is formed if the dienophile aligns below the diene but with its CH_2 group projecting behind the page.

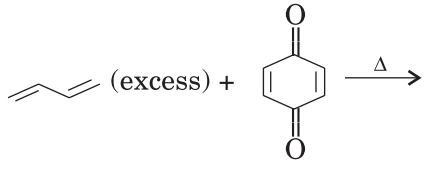
[Alternatively, the enantiomer I can be obtained if the dienophile aligns above the diene but the CH_2 group projecting behind the page and the enantiomer II can be obtained if the dienophile aligns above the diene with its CH_2 grops towards us.]

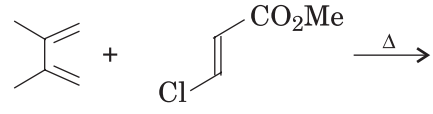
Study Problems

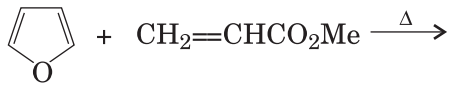
1. Predict the products of the following reactions:

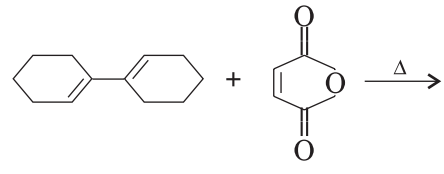
(a) 

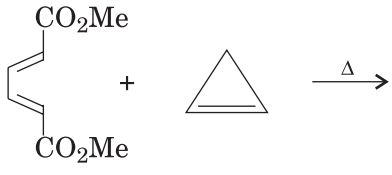
(b) 

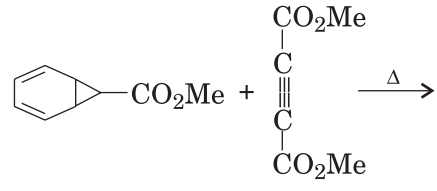
(c) 

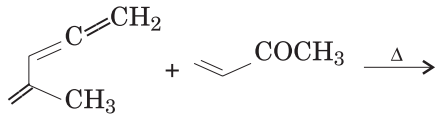
(d) 

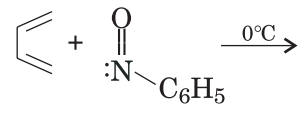
(e) 

(f) 

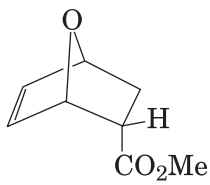
(g) 

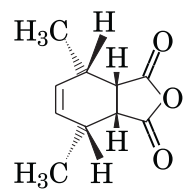
(h) 

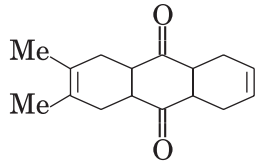
(i) 

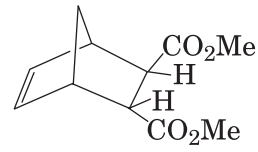
(j) 

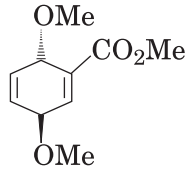
2. What diene and dienophile are required to prepare each of the following Diels-Alder products?

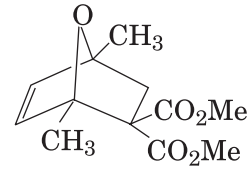
(a) 

(b) 

(c) 

(d) 

(e) 

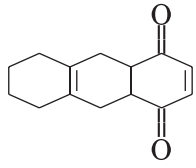
(f) 

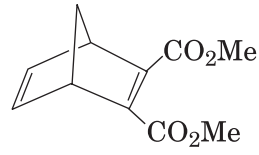
3. Explain why the maleic anhydride requires more drastic conditions to react with (2*E*, 4*Z*)-2,4-hexadiene compared to (2*E*, 4*E*)-2,4-hexadiene.

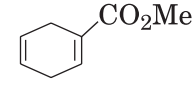
4. *N*-*p*-nitrophenylpyrrole reacts with $MeO_2C—C\equiv C—CO_2Me$ to give the corresponding adduct, while pyrrole does not. Account for this observation.

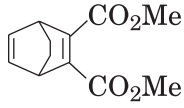
5. The predominant *endo*-product of the reaction between cyclopentadiene and maleic anhydride is formed as a racemic mixture. Explain this observation.
[Hint: Either face of the diene can interact with the dienophile. When the dienophile adds to one face of the diene, the product is formed as one enantiomer, and when the dienophile adds to the other face of the diene, the product is formed as the other enantiomer. Both faces of the diene are equally likely to be attacked by the dienophile.]

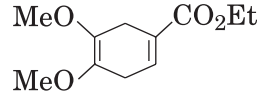
6. Give two different ways to prepare the following compounds by the Diels-Alder reaction. Explain which method is more suitable.

(a) 

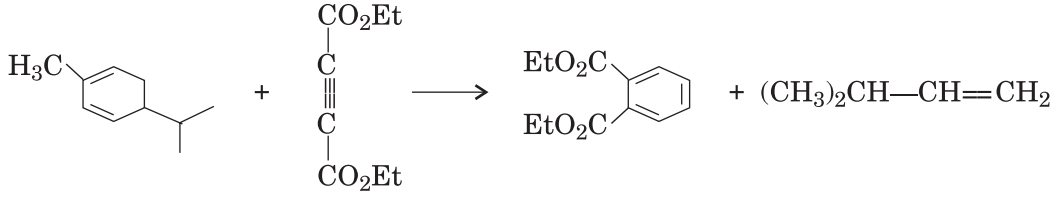
(b) 

(c) 

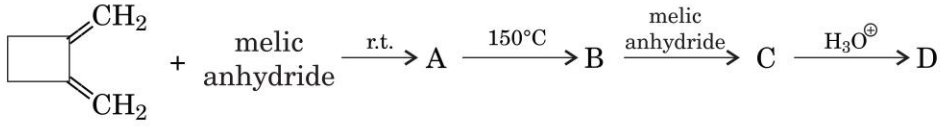
(d) 

(e) 

7. Write the mechanism of the following transformation. What is the driving force for the 2nd step of this transformation?

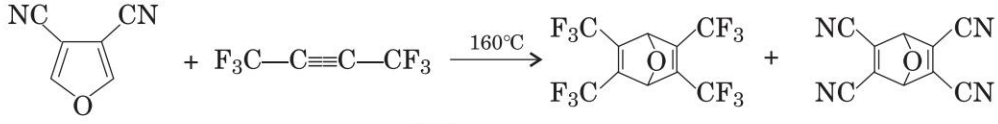


8. Predict the products A, B, C and D in the following sequence of reactions:

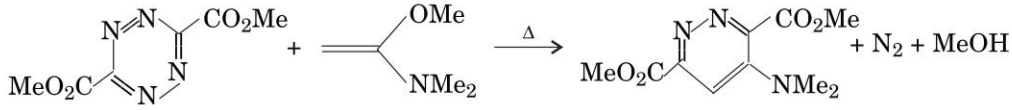


9. Account for the following observations:

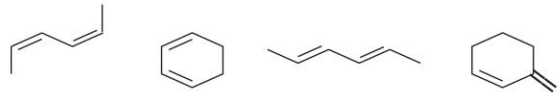
(a)



(b)



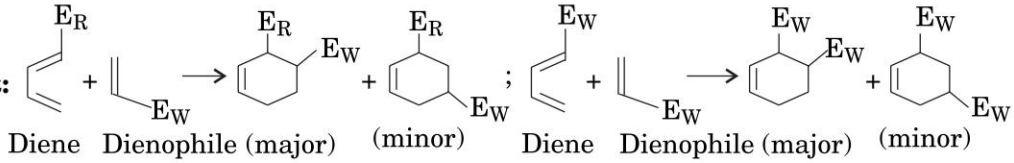
10. Arrange the following dienes in order of decreasing reactivity in Diels-Alder reaction. Give your reasoning.



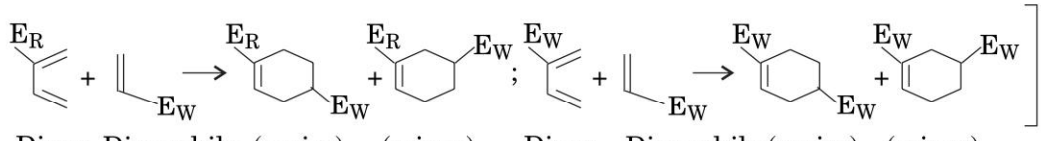
I II III IV

11. Write down a schematic chart of major and minor products in the Diels-Alder reaction where there is an electron-releasing (E_R) group or an electron-withdrawing (E_W) group in the diene and an electron-withdrawing group (E_W) in the dienophile.

Hint:



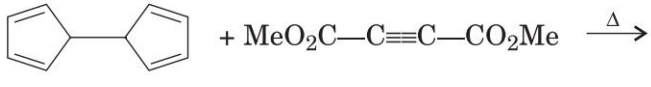
Diene Dienophile (major) (minor) Diene Dienophile (major) (minor)



Diene Dienophile (major) (minor) Diene Dienophile (major) (minor)

12. Explain why the products obtained whtn 1,3-butadiene is allowed to react with *cis*- and *trans*-1,2-dichloroethylene are optically inactive.

13. Predict the products of the following reaction:



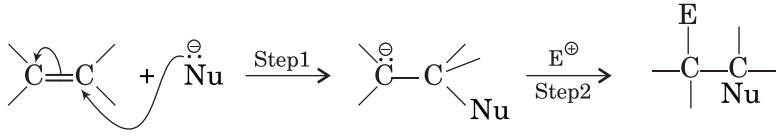
I + II
(two isomers having
molecular formula $C_{16}H_{16}O_4$)

14. How can the useful reductant diimide (HN═NH) be prepared from diethyl azodicarboxylate ($EtO_2C—N═N—CO_2Et$) using the Diels-Alder and the retro Diels-Alder reaction?

1.2 NUCLEOPHILIC ADDITION

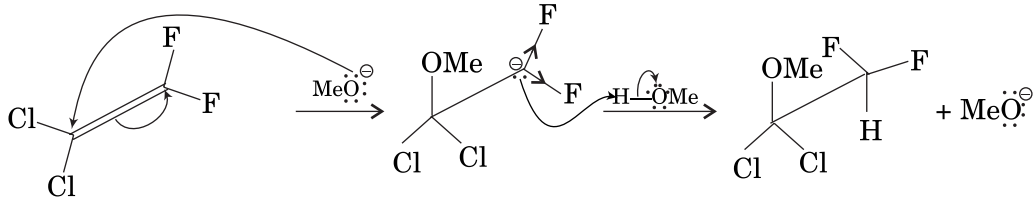
The two doubly bonded carbon atoms in an alkene are sandwiched between negative charge clouds and so, a nucleophile cannot attack them easily. However, if electron-withdrawing substituents like –CHO, –COR, –COOR, –CN, $–NO_2$, –SOR, $–SO_2R$ or F are present on the multiply bonded carbon atoms, the π electron density decreases and then nucleophilic attack on the electron-deficient carbon of the π bond takes place easily.

Mechanism: A nucleophilic addition to a double bond proceeds through the following two steps:



Intermediate carbanion

In step1, the incoming nucleophile attacks the more electron-deficient doubly bonded carbon atom and forms an intermediate carbanion which is stabilized by the attached electron-withdrawing group(s). In Step 2 the intermediate carbanion then couples with a positively charges species ($E^{\oplus}$, e.g., $H^{\oplus}$) to yield the addition product. For example



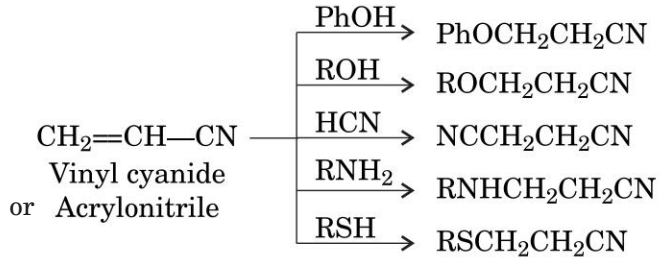
Due to the involvement of an open carbanion, the addition is no longer stereospecific.

Cyanoethylation and Michael addition are two typical examples of nucleophilic addition to electron-deficient π bonds having considerable synthetic importance.

1.2.1 Cyanoethylation

The addition of cyanoethyl group, $–CH_2CH_2CN$, to a nucleophile by treating vinyl cyanide with effective nucleophilic source, YH (most commonly ROH, PhOH, RNH_2, RSH, etc.) usually in the presence of a base (that generates a stronger nucleophile by abstracting an active hydrogen as proton) is called cyanoethylation.

Examples:



Mechanism: The mechanism of the cyanoethylation reaction involves three steps. This can be well illustrated by the reaction of diethyl malonate with vinyl cyanide in the presence of sodium ethoxide to yield diethyl (2-cyanoethyl) malonate.:

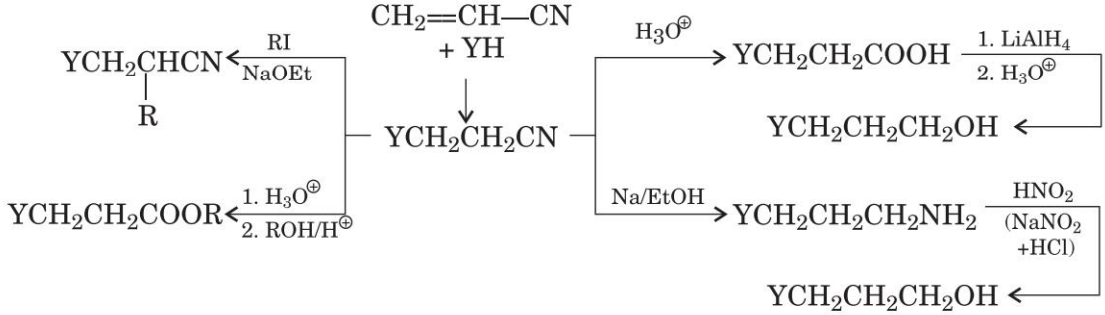
Step 1: $:\ddot{O}\overset{\ominus}{E}t + H\text{—}CH(CO_2Et)_2 \rightleftharpoons EtOH + \overset{\ominus}{C}H(CO_2Et)_2$

Step 2: $(EO_2C)_2\overset{\ominus}{C}H + CH_2{=}CH\text{—}C{\equiv}N: \rightleftharpoons \left[(EtO_2C)_2CH\text{—}CH_2\text{—}CH{=}{=}C{=}{=}\ddot{N}:^{\ominus} \leftrightarrow (EtO_2C)_2CH\text{—}CH_2\text{—}\overset{\ominus}{C}H\text{—}C{\equiv}N: \right]$

Step 3: $(EtO_2C)_2CH\text{—}CH_2\text{—}\overset{\ominus}{C}H\text{—}C{\equiv}N: \overset{H\text{—}OEt}{\rightleftharpoons} (EtO_2C)_2CH\text{—}CH_2\text{—}CH_2\text{—}C{\equiv}N:$

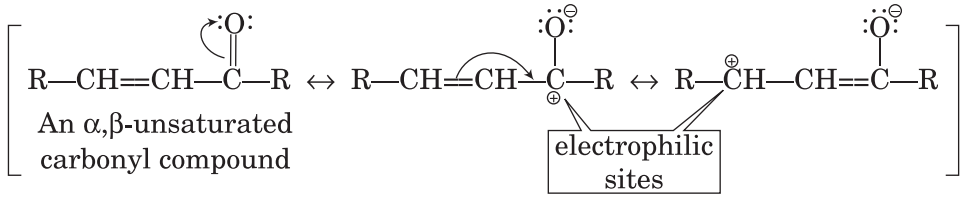
1.2.1.1 Synthetic uses of Cyanoethylation

Cyanoethylation is synthetically useful because it is a typical procedure by which three carbons can be introduced in a compound at a time. Its synthetic utility also lies with the cyano group (–CN), which can easily be converted to other functional groups by reduction, hydrolysis, etc. Various compounds can, therefore, be prepared by using the cyanoethylation process.

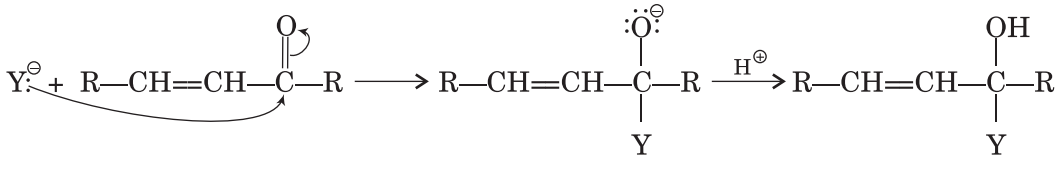


1.2.2 Direct and Conjugate Addition to α, β-Unsaturated Aldehydes and Ketones

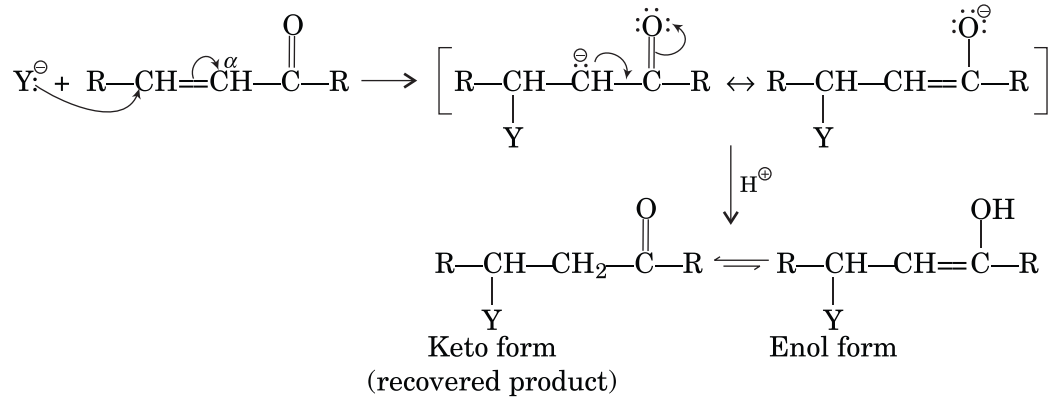
From the contributing resonance structures for an α,β-unsaturated carbonyl compound it becomes clear that the molecule has two electrophilic sites—the carbonyl carbon and the β-carbon.



Therefore, a nucleophile can add either to the carbonyl carbon or to the β-carbon of the α,β-unsaturated carbonyl compound. Nucleophilic addition to the cabonyl carbon is called direct addition or 1,2-addition. This may be shown as follows:

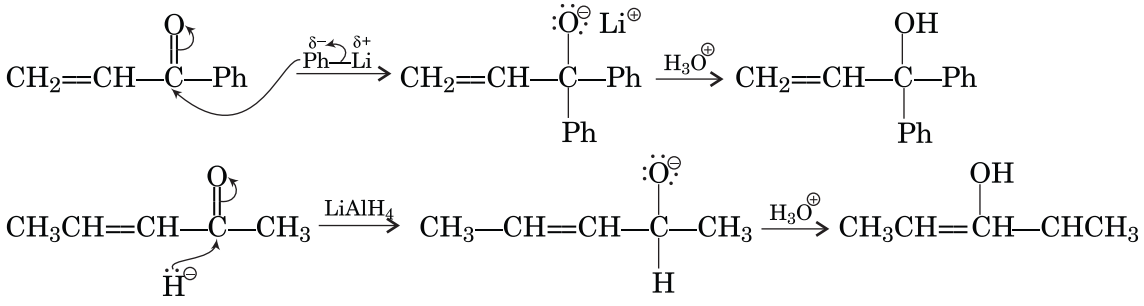


Nucleophilic addition to the β-carbon of an α,β-unsaturated carbonyl compound is called conjugate addition and this is because addition occurs across the conjugated system. Conjugate addition is also called 1,4-addition. The enolate ion can be protonated on either oxygen or carbon. The enol readily tautomerizes to a carbonyl compound. So, the overall reaction amounts to addition to the carbon–carbon double bond, with nucleophile adding to the β-carbon and a proton from the reaction medium adding to the α-carbon. This may be shown as follows:

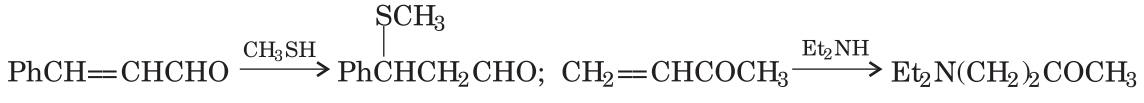


Nature of the nucleophile and mode of addition: It is the nature of the nucleophile which determines whether the product obtained from nucleophilic addition to an α,β-unsaturated carbonyl compound is the direct addition product or the conjugate addition

product. Nucleophiles that are strong bases, such as organolithium compounds and hydride ion, tend to form a direct or 1,2-addition product. For example:



Nucleophiles that are relatively weak bases, such as cyanide ion, amines, thiols, halide ions and enolate ions derived from β-dicarbonyl compound, tend to give a conjugate or 1,4-addition product. For example:

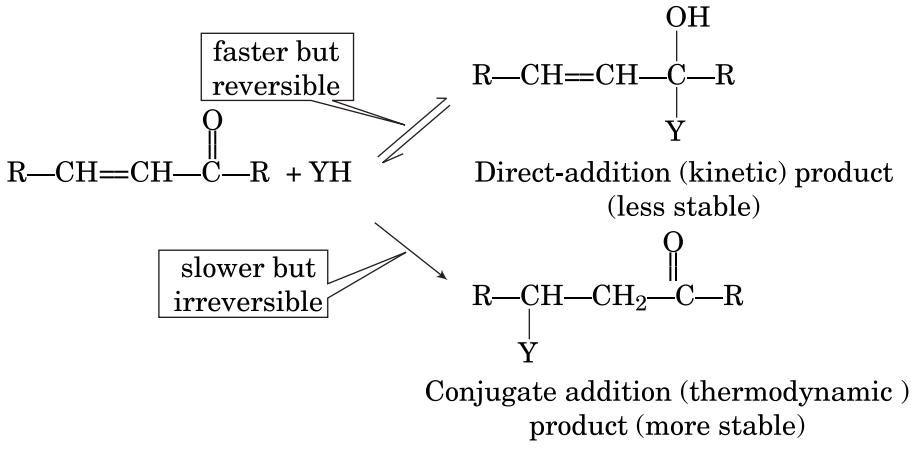


In fact, hard nucleophiles tend to react at the carbonyl carbon (hard) of an enone and lead to direct addition, whereas soft nucleophiles tend to react at the β-carbon (soft) of an enone and lead to conjugate addition.

Conjugate addition retains a carbonyl group at the expense of a carbon–carbon double bond, while direct addition retains a carbon–carbon double bond at the expense of a carbonyl group. Since a C═O bond is considerably stronger than a C═C bond, therefore, *conjugate addition gives a more stable product***.** Although other bonds are cleaved and formed as well, but the major effect is the relative strength of the two kinds of double bonds.

The nature of the addition product can be more clearly explained by considering whether the addition reaction is irreversible or reversible. Direct addition takes place more rapidly than conjugate addition. The final product of the reaction, therefore, depends on whether the direct addition is irreversible or reversible. If the direct addition is irreversible, the direct-addition product will be the final product of the reaction. However, if the direct addition is reversible, the initially formed direct-addition product eliminates the nucleophilic reagent YH to yield the starting carbonyl compound which then undergoes conjugate addition. Since the conjugate addition is irreversible, the conjugate-addition product accumulates and ultimately becomes the major product of the reaction. The direct addition is irreversible if the nucleophile is a strong base and this is because strong bases are poor leaving groups and cannot be eliminated from the direct-addition product. Therefore, strong bases form a direct addition product. The direct addition is reversible if the nucleophile is a weak base and, therefore, can be easily eliminated from the direct-

addition product. Therefore, weak bases form a conjugate-addition product even though it is formed more slowly.



1.2.3 Michael Addition or Michael Reaction

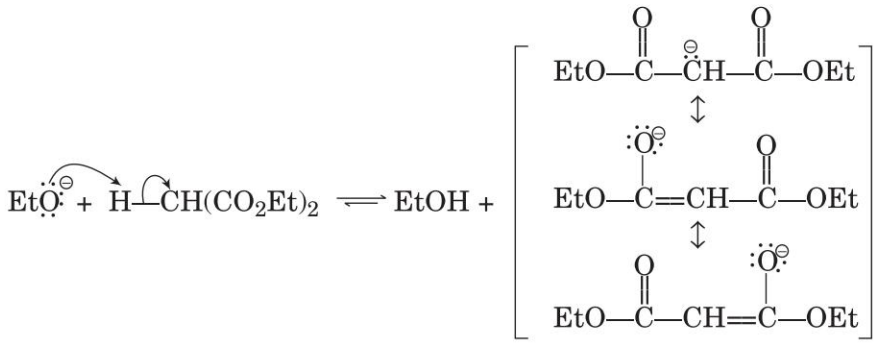
The conjugate addition of a stabilized enolate ion to the activated double bond of α,β-unsaturated carbonyl compounds, esters, amides, nitriles, sulphonyls, quinones, nitro compounds, etc. leading to the formation of a new carbon–carbon bond is called a *Michael addition* or *Michael reaction*. The usual sources of stabilized enolate ions are compounds containing active methylene groups like acetoacetic ester, diethyl malonate, cyanoacetic ester, cyclopentadienes, benzylcyanide, nitroalkanes, terminal alkynes, etc. However, the enolates that work best in Michael additions are those that are flanked by two electron-withdrawing groups, i.e., enolates of β-diketones, β-ketoesters, β-diesters and β-keto nitriles. Because these enolates are relatively weak bases and they are quite bulky, addition occurs preferably at the β-carbon. The enolates are generated from the above-mentioned compounds by using strong bases like alkoxides, amides, secondary or tertiary amines, hydrides, etc. The following reaction is an example of Michael addition:

$$\underset{\text{Methyl vinyl ketone}}{CH_3-\overset{O}{\overset{\|}{C}}-CH=CH_2} + \underset{\text{Diethyl malonate}}{CH_2(CO_2Et)_2} \xrightarrow[EtOH]{NaOEt(cat.)} \underset{(65-71\text{ percent})}{CH_3-\overset{O}{\overset{\|}{C}}-CH_2CH_2CH(CO_2Et)_2}$$

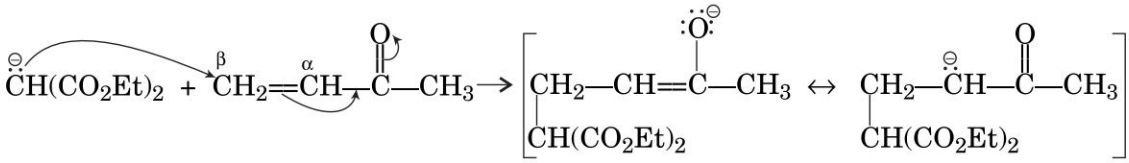
The compound containing activated double bond (the electrophile), which accepts a pair of electrons, is called a *Michael acceptor* and the stabilized enolate ions (the nucleophile), which donates a pair of electrons, is called a *Michael donor*.

Mechanism of Michael addition: The mechanism of Michael addition (taking diethyl malonate as a Michael donor and methyl vinyl ketone as a Michael acceptor) consists of the following steps:

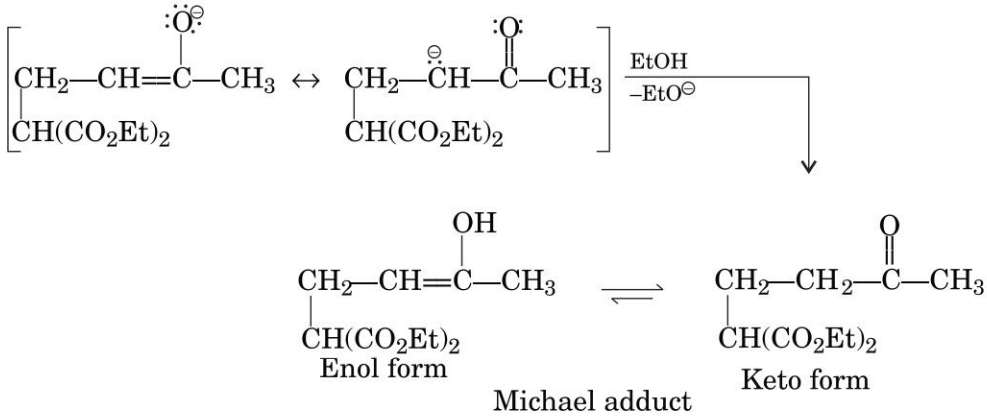
Step 1: The base, $Et\ddot{O}:^{\ominus}$, abstracts a proton from diethyl malonate to form a resonance-stabilized enolate ion.



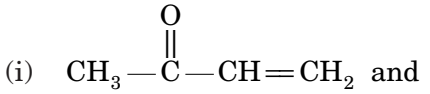
Step 2: The enolate ion adds to the β-carbon of the α,β-unsaturated carbonyl compound to form another resonance-stabilized enolate ion.



Step 3: The enolate ion takes up a proton from the solvent EtOH to produce a mixture of ketone and its enol. However, the enol form readily tautomerizes to the more stable keto form.



Synthesis of Michael adduct from two possible pairs of Michael donor and Michael acceptor: When two pairs of Michael donor and Michael acceptor lead to the same Michael adduct, then it is possible to find out the more suitable pair by considering the nature of the Michael donor (the base) and the way by which it can be generated. For example, the compound $CH_3COCH_2CH_2CH(CO_2Et)_2$ can be obtained from either of the following two pairs of addends:

(i)  and $CH_2(CO_2Et)_2$ and

(ii) $CH_2=C(CO_2Et)_2$ and $CH_3-\overset{\overset{O}{\|}}{C}-CH_3$

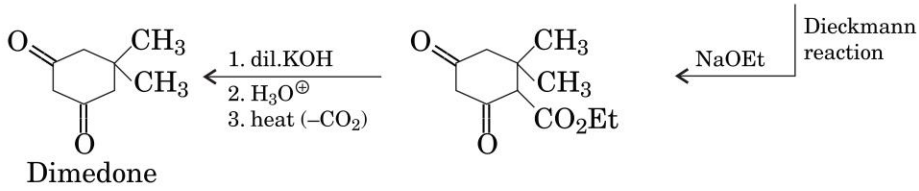
Weaker bases tend to give conjugate addition, while stronger bases tend to give direct addition. Out of the two possible carbon acids, $CH_2(CO_2Et)_2$ gives the weaker conjugate base $\overset{\ominus}{\ddot{C}}H(CO_2Et)_2$ (more stable) but CH_3COCH_3 gives the stronger conjugate base $CH_3CO\overset{\ominus}{\ddot{C}}H_2$ (less stable). Again, the formation of $\overset{\ominus}{\ddot{C}}H(CO_2Et)_2$ requires a mild reaction condition and a weaker base, whereas the formation of $CH_3CO\overset{\ominus}{\ddot{C}}H_2$ requires more drastic reaction conditions and a stronger base. Therefore, it is preferable to use the first pair of reactants to obtain better yield of $CH_3COCH_2CH_2CH(CO_2Et)_2$ by Michael addition.

1.2.3.1 Synthetic Applications of the Michael Reaction

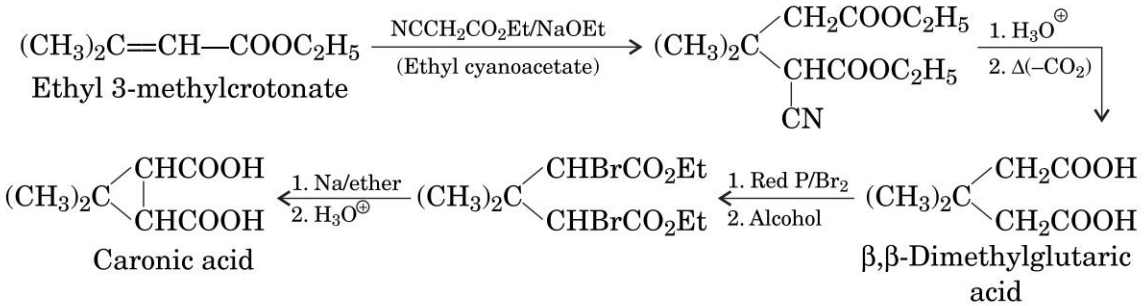
The Michael reaction is of great importance in organic synthesis because it serves to form carbon-carbon bond and a variety of organic compounds can be synthesized with the help of this reaction.

1. **Synthesis of alicyclic compounds:** Alicyclic compounds can easily be prepared by using this reaction. A very useful reagent dimedone (5,5-dimethylcyclohexane-1,3-dione) can be prepared from mesityl oxide and diethyl malonate as follows:

$$\underset{\text{Mesityl oxide}}{CH_3COCH=C(CH_3)_2} + \underset{\text{Diethyl malonate}}{CH_2(CO_2Et)_2} \xrightarrow[\text{Michael addition}]{\text{NaOEt/EtOH}} CH_3COCH_2C(CH_3)_2CH(CO_2Et)_2$$

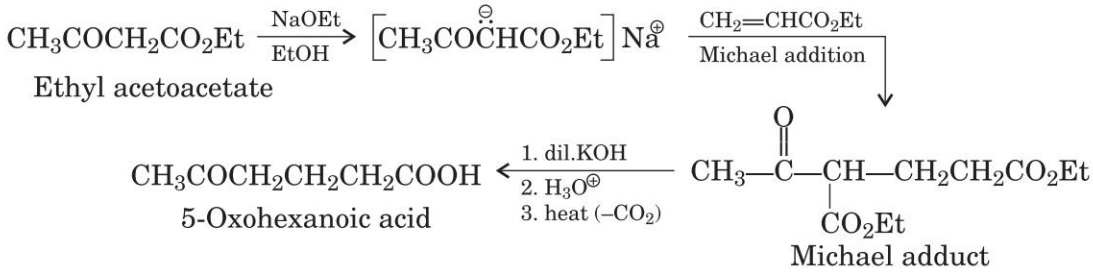


Caronic acid (a cyclopropane derivative) can be prepared by using this reaction as follows:

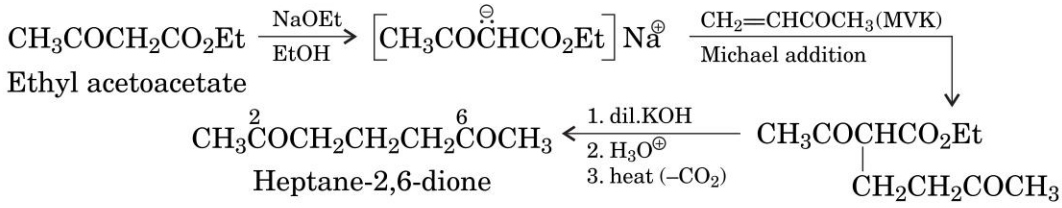


2. **Synthesis of keto acids and diketones:** The Michael reaction also constitutes a useful method for the synthesis of keto acids and diketones.

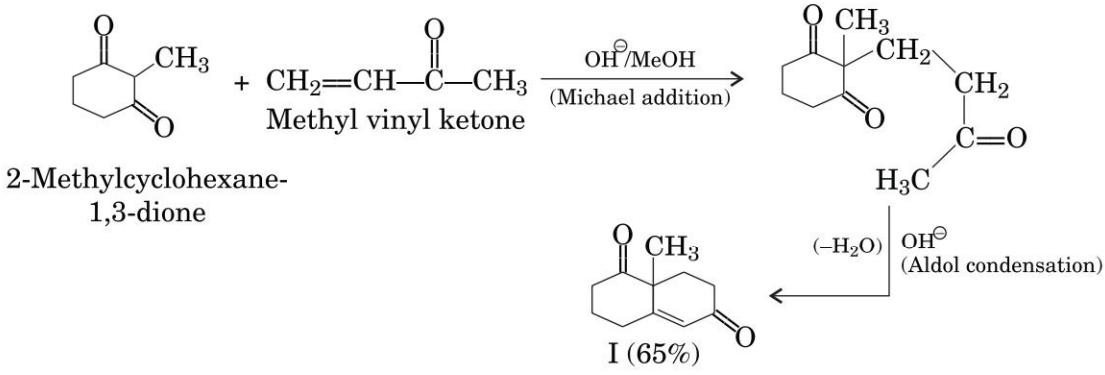
(i) **Synthesis of 5-oxohexanoic acid (a keto acid)**



(ii) **Synthesis of heptane-2,6-dione (a diketone)**

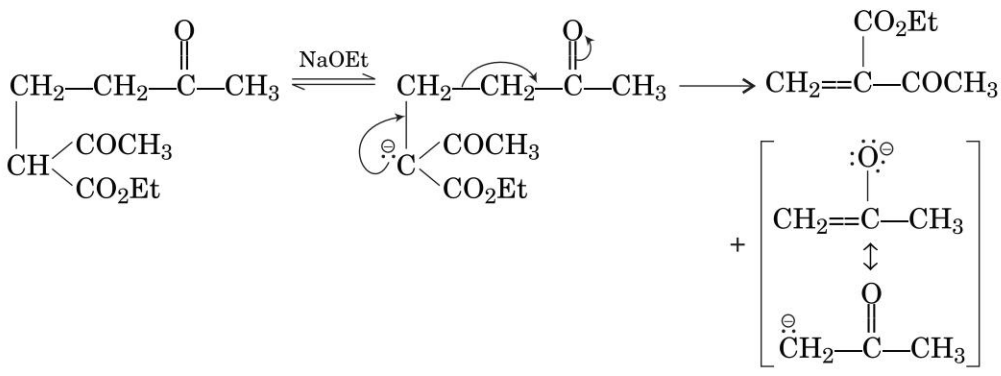


3. **Robinson annulation reaction:** A Michael addition followed by a simple aldol condensation may be used to build one ring onto another. This procedure is called the *Robinson annulation* (ring-forming) *reaction*. The bicyclic compound I, for example, can be synthesized by Robinson annulation as follows:



1.2.3.2 Michael Retrogression

The Michael addition is reversible in nature and the base used as a catalyst is regenerated in the process. For this reaction, only a small amount of catalyst is usually used. If a large amount of basic catalyst is used, the initially formed Michael addition product undergoes cleavage to produce another pair of α,β-unsaturated compound and an enolate ion. This reverse reaction is called *'Michael retrogression'*. For example:



To minimise the process of Michael retrogression an excess of the compound producing the stabilized enolate ion (donor) should be used.

SOLVED PROBLEMS

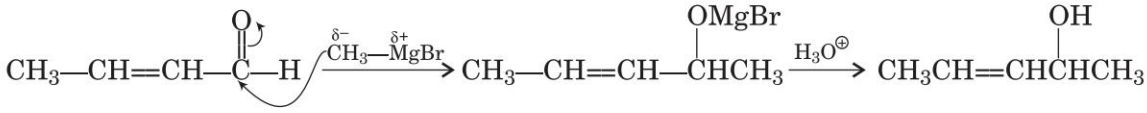
1. Predict the products of the following reactions:

(a) $CH_3CH{=}CHCHO \xrightarrow[2.\ H_3O^{\oplus}]{1.\ CH_3MgBr}$

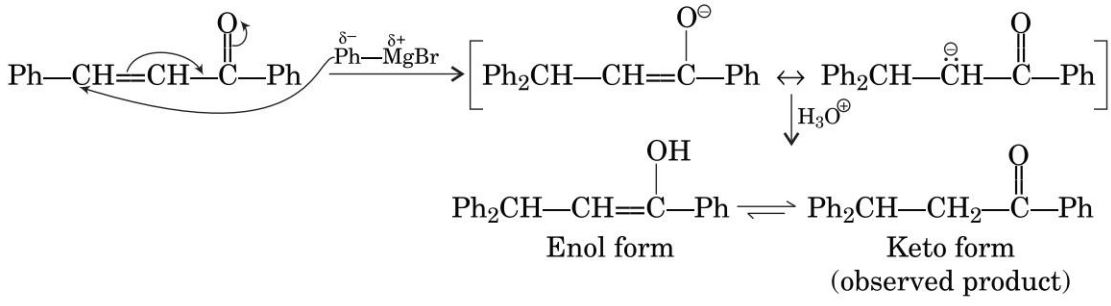
(b) $PhCH{=}CHCOPh \xrightarrow[2.\ H_3O^{\oplus}]{1.\ PhMgBr}$

Solution

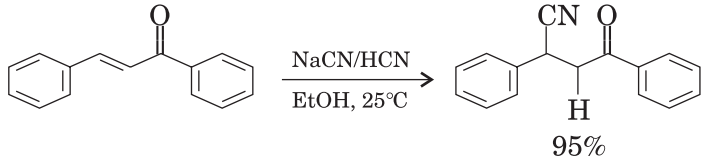
(a) Because Grignard reagents are strong bases, they react with α,β-unsaturated aldehydes (and most α,β-unsaturated ketones) to form direct addition products. Therefore, the reaction takes place as follows:



(b) If the carbonyl carbon is bonded to a bulky group, the conjugate addition product is formed predominantly. If fact, the bulky group sufficiently slows down the rate of direct addition to allow competition from conjugate addition. Therefore, the given reaction takes place as follows:

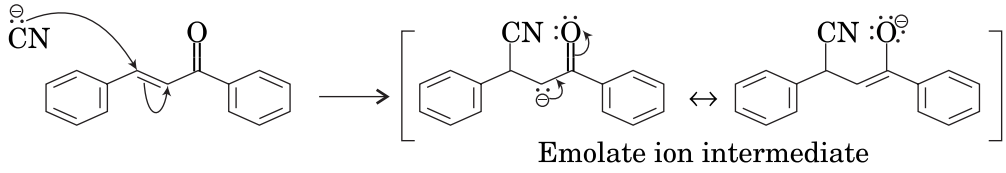


2. Suggest a mechanism for the following reaction:

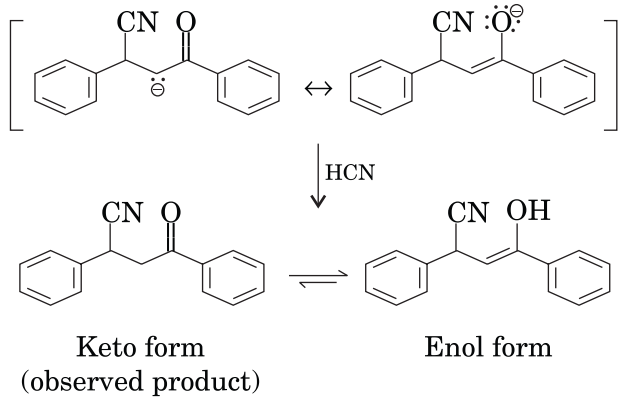


Solution The mechanism of the reaction involves the steps as follows:

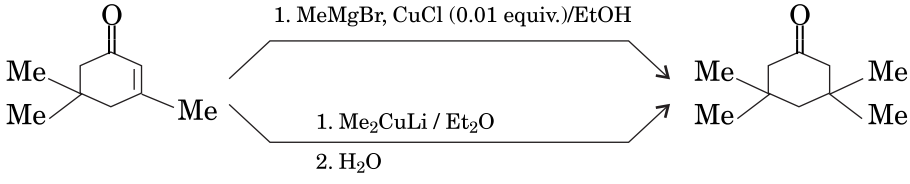
Step 1: The cyanide ion ($CN^{\ominus}$) being a relatively weak base and soft nucleophile attacks the β-carbon of the α,β-unsaturated ketone to form a resonance-stabilized enolate ion intermediate.



Step 2: The enolate ion undergoess protonation on either oxygen or carbon. However, the enol tautomer spontaneously converted into the more stable keto form. The overall result of the reaction is, therefore, net addition of HCN to the carbon–carbon double bond.

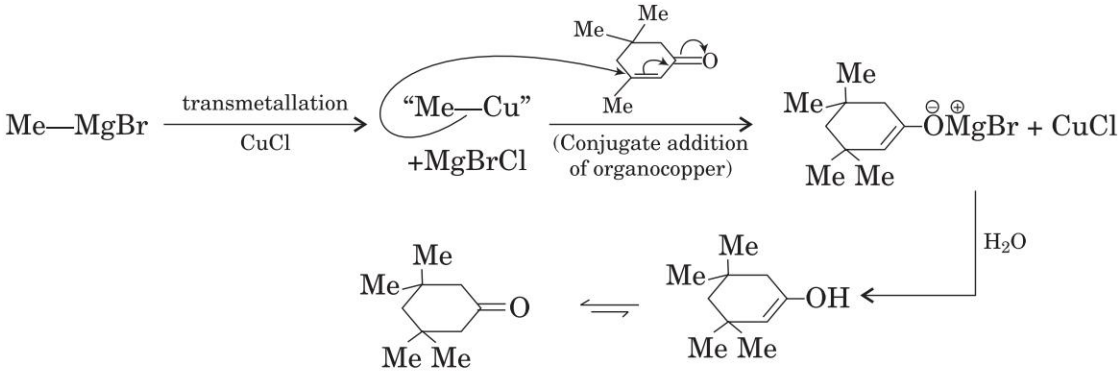


3. Write mechanism that account for the common product of the following two reactions:



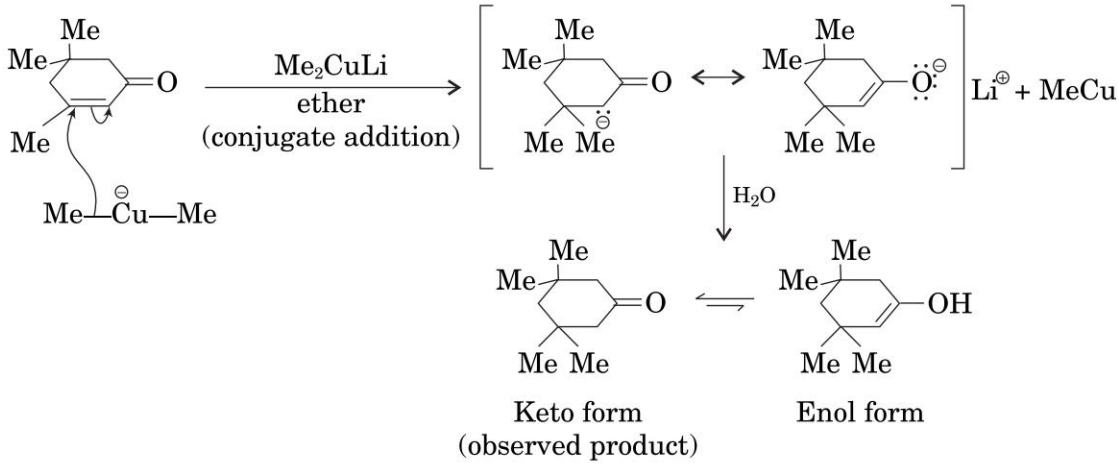
Solution In the first reaction, copper works by transmetallating the Grignard reagent to give an organo-copper reagent. Organocoppers are softer than Grignard reagents and therefore, they add in a conjugate fashion to the softer C═C bond. Only a catalytic amount

of copper salt is required because once the organocopper has been added, the copper salt is available to transmetallate some more Grignard. The reaction takes place as follows:

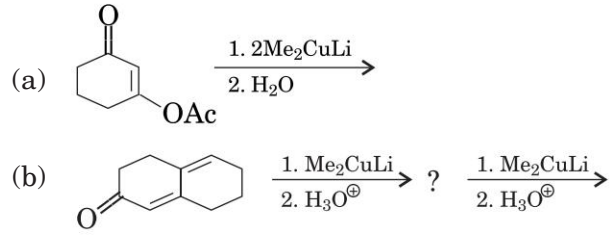


The organocopper is shown as 'Me–Cu' because its precise structure is not known

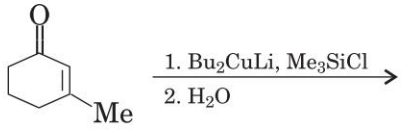
The mechanism of the second reaction involving lithium dialkylcuprate (Me_2CuLi) is similar to the first reaction. Attack of an alkyl anion ($Me^{\ominus}$) from the dialkylcuprate reagent on the double bond gives a resonance-stabilized enolate ion. Protonation of the enolate ion by water gives the conjugate-addition product.



4. Prdict the product and suggest a mechanism for each of the following reactions:

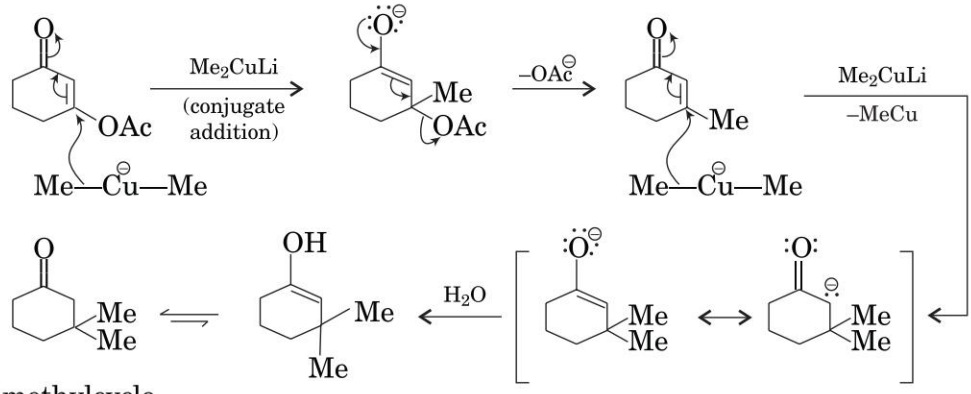


(c) $Me—C\equiv C—CO_2Me \xrightarrow[2.\ H_3O^{\oplus}]{1.\ Me_2CuLi\ (1\ equiv.)}$

(d) 

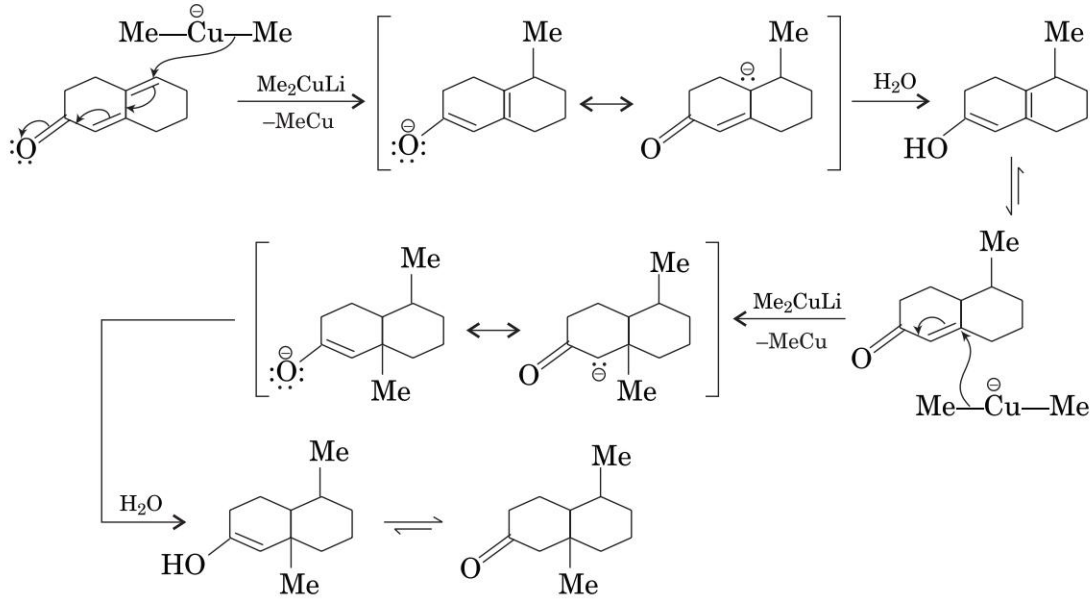
Solution:

(a) Two successive conjugate additions to the α,β-unsaturated ketone involving lithium dialkylcuprate result in the formation of 3,3-dimethylcyclohexanone.

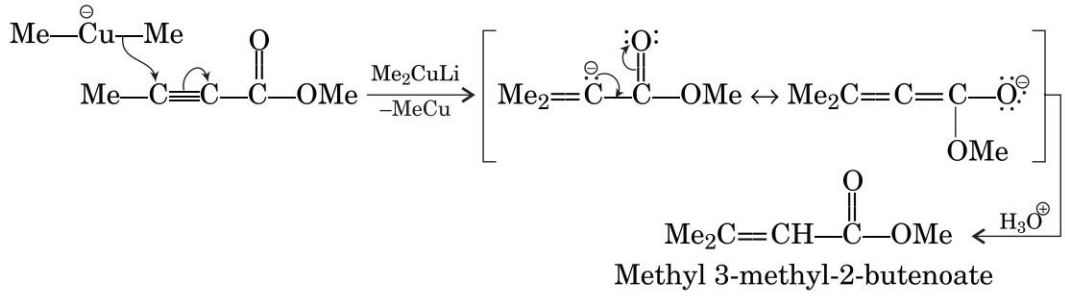


3,3-Dimethylcyclohexanone

(b) The first conjugate addition takes place to the γ,δ-double bond and the second conjugate addition takes place to the α,β-double bond.

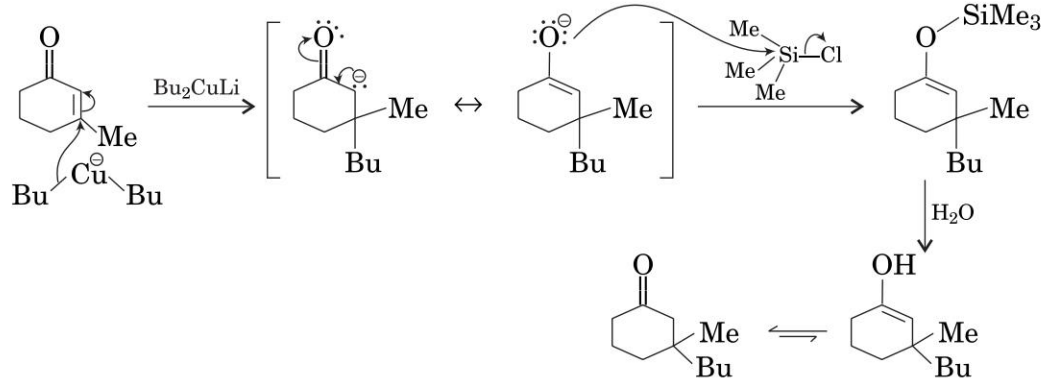


(c) Methyl 3-butynoate is converted to methyl 3-methyl-2-butenoate when it undergoes conjugate addition of $Me^{\ominus}$ from lithium dimethylcuprate (1 equiv.).



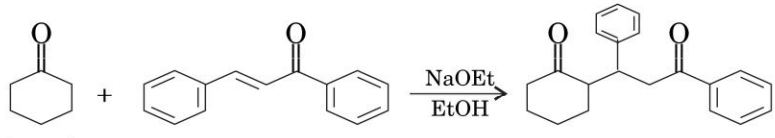
Methyl 3-methyl-2-butenoate

(d) The conjugate addition of Bu_2CuLi in the presence of chlorotrimethylsilane leads to the formation of a silyl enol ether that decomposes to the carbonyl compound when water is added.

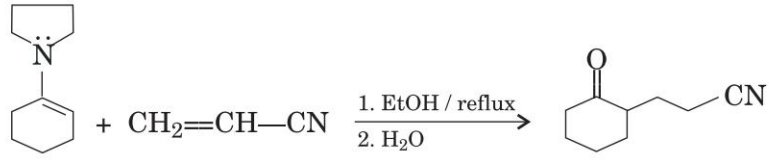


5. Suggest a mechanism for each of the following reactions:

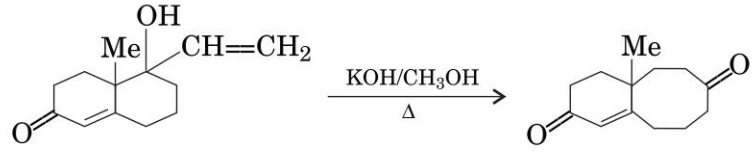
(a)

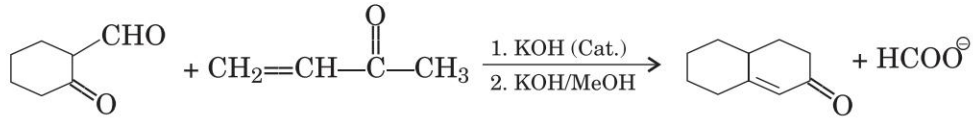


(b)

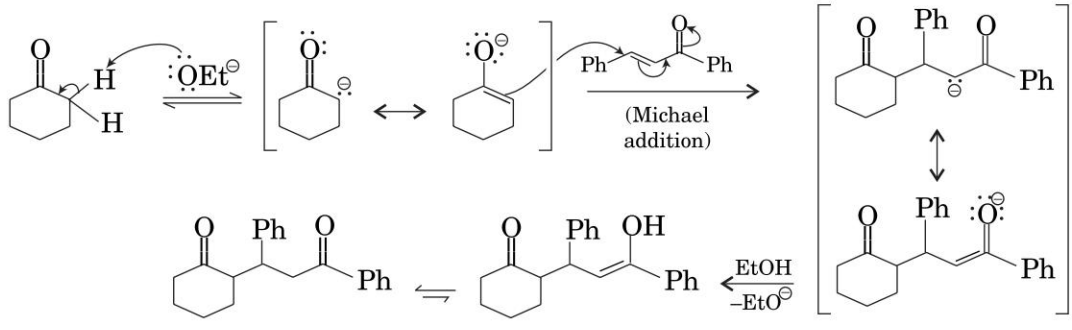


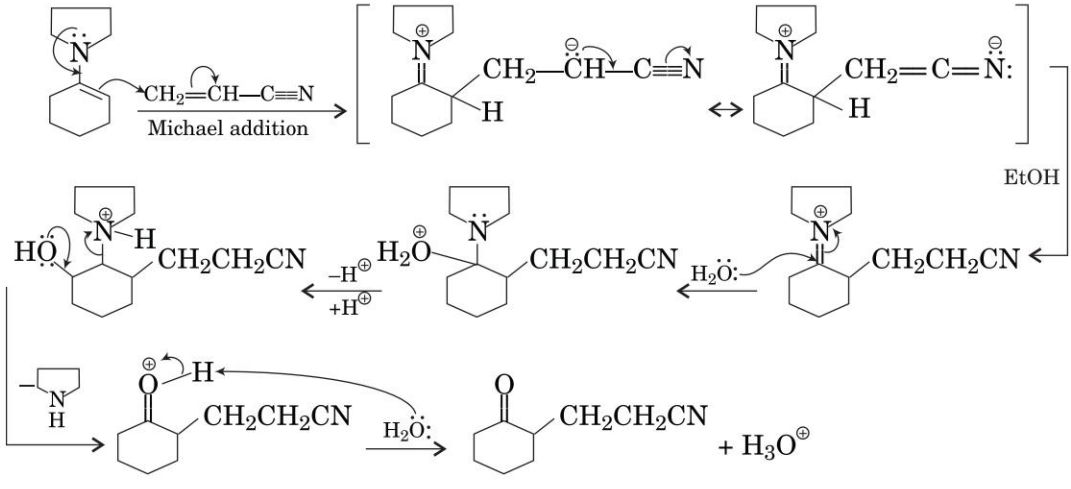
(c)

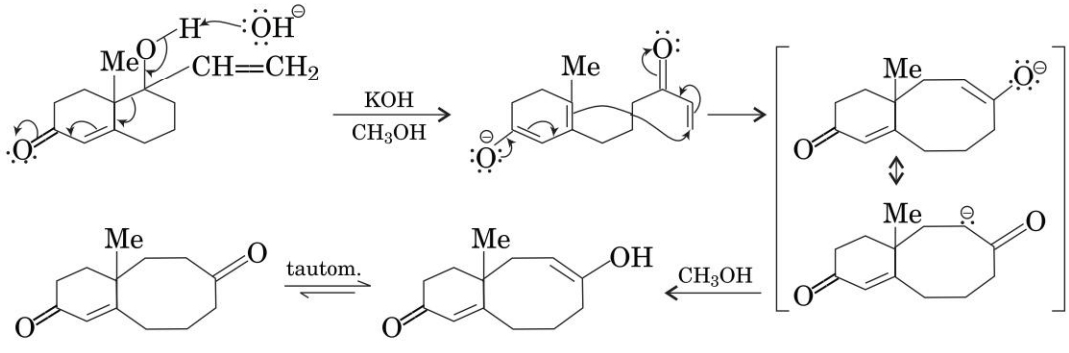


(d) 

Solution

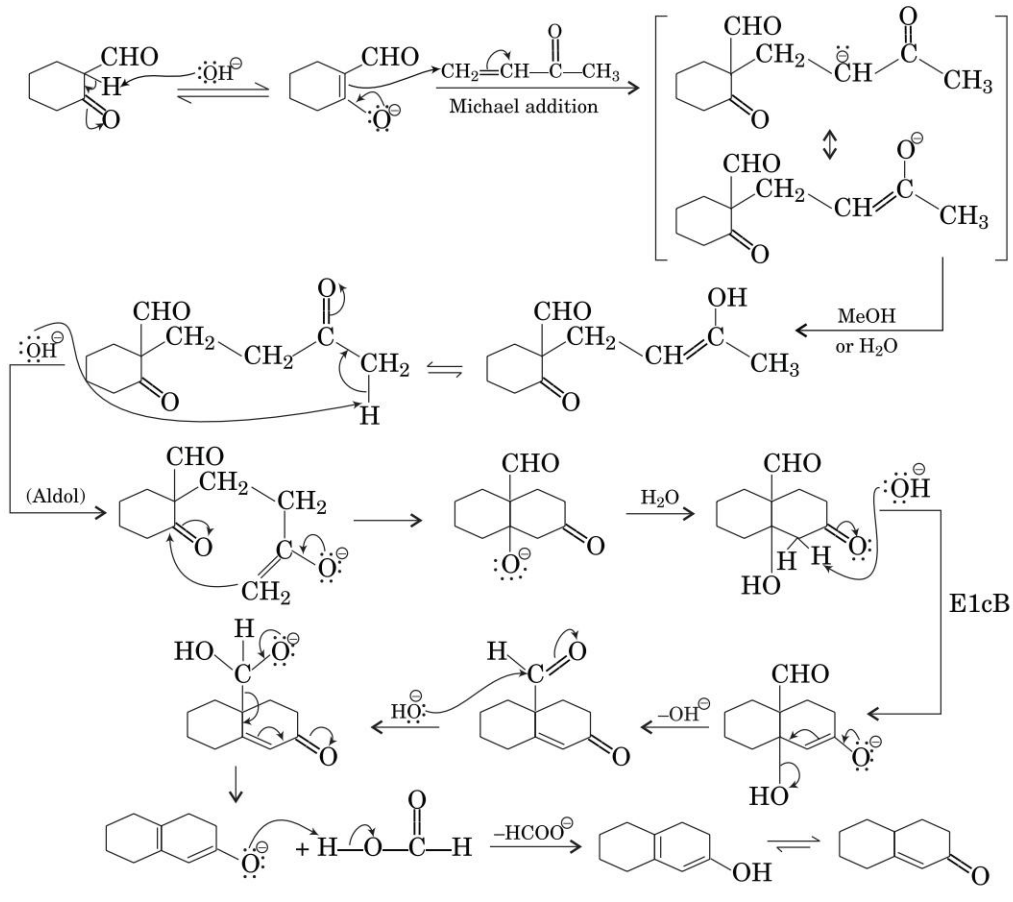
(a) 

(b) 

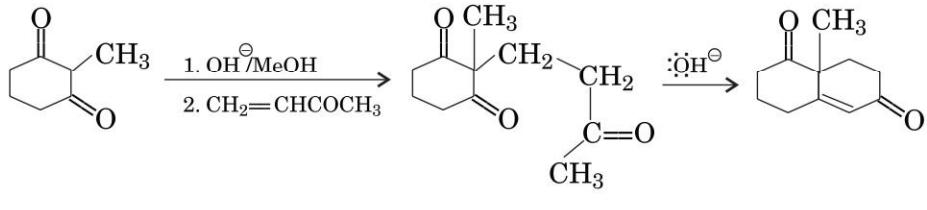
(c) 

This is an example of intramolecular Michael addition

(d)

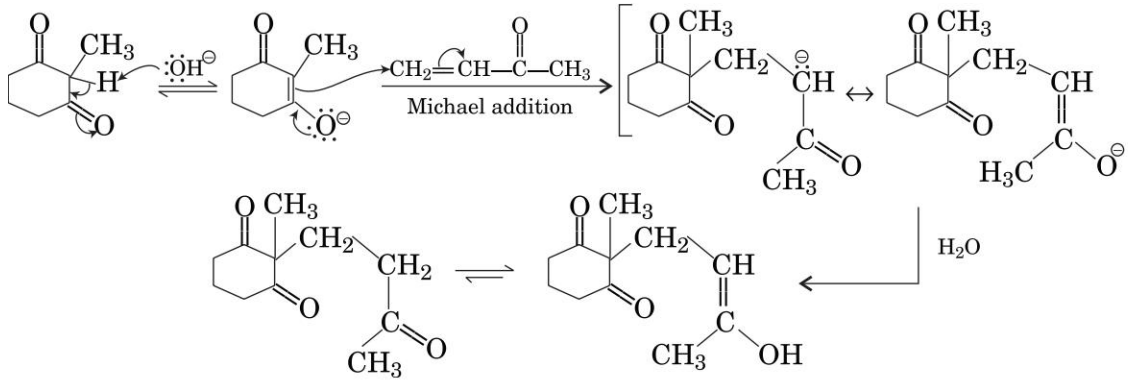


6. Suggest a mechanism for each step of the following reaction sequence (*Robinson annulation*):

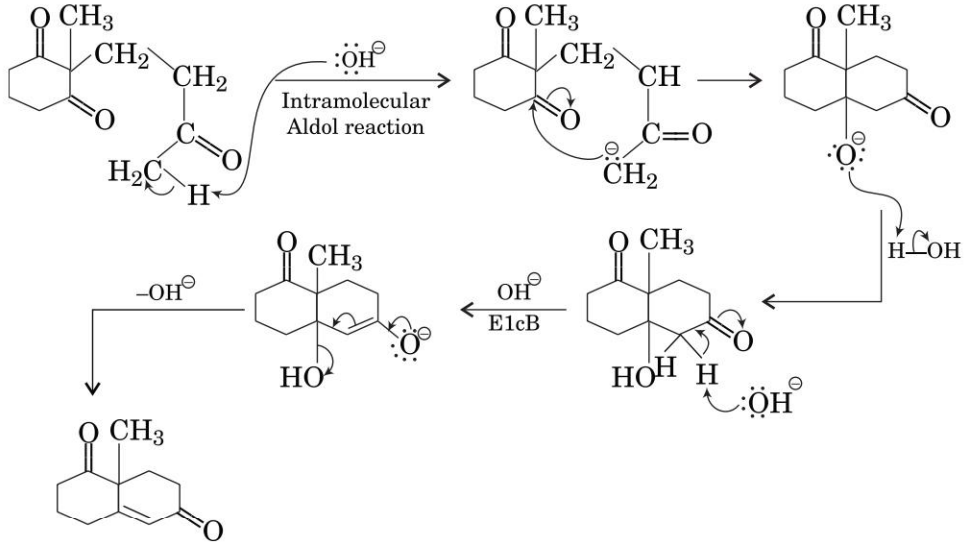


Solution

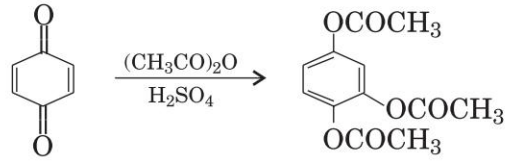
Mechanism of first step:



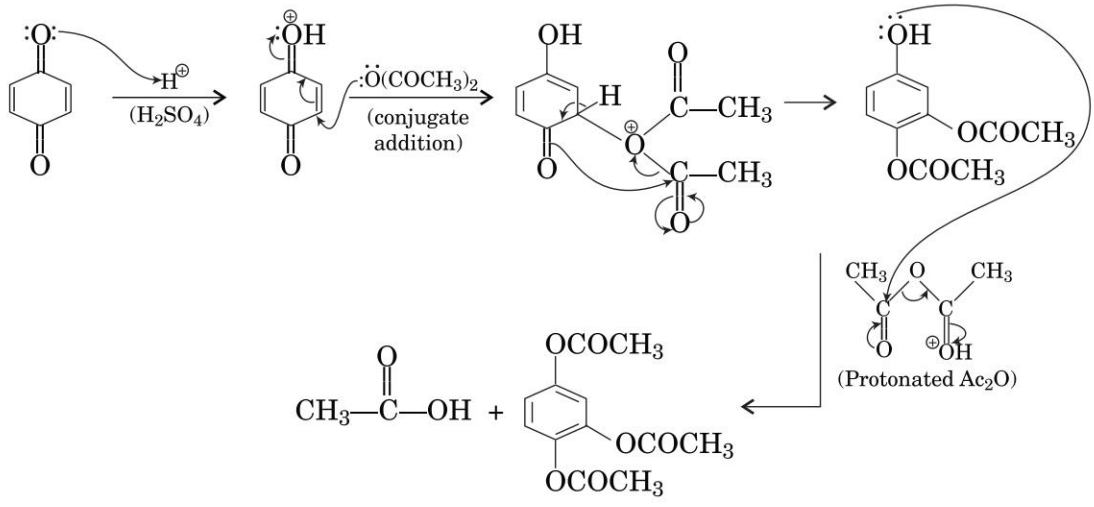
Mechanism of second step:



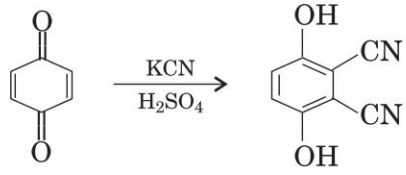
7. Provide a mechanism for the following reaction known as *Thiele acetylation:*



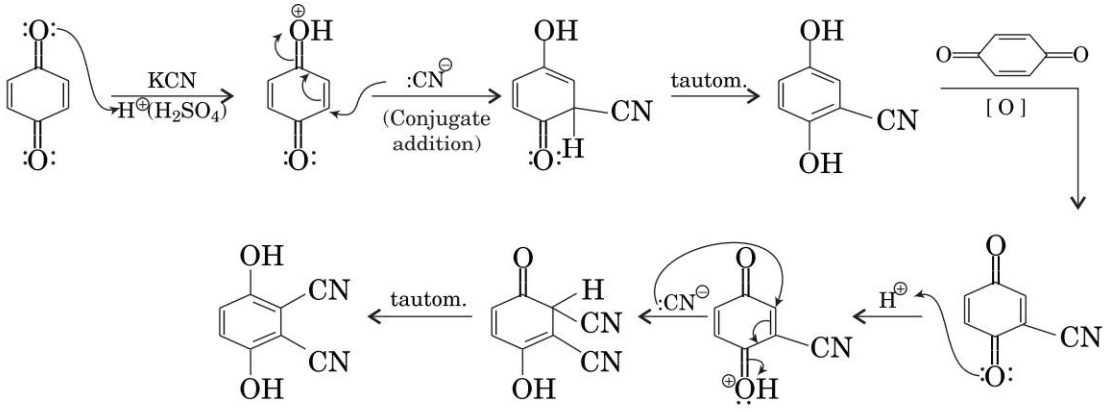
Solution The mechanism of the reaction involves the steps as follows:



8. Provide a mechanism that explains the formation of the following product:

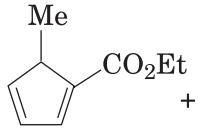


Solution The mechanism of the reaction involves the steps as follows:

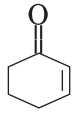


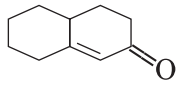
Study Problems

1. Predict the product and suggest a mechanism for each of the following reactions:

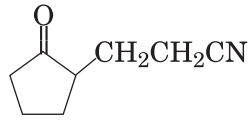
(a)  + $CH_3CH(CO_2Et)_2 \xrightarrow[EtOH]{NaOEt}$

(b) $(CH_3)_2C{=}CHCOCH_3 + CH_3MgBr \xrightarrow[2.\ H_3O^{\oplus}]{1.\ ether}$

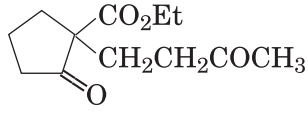
(c)  + $(CH_3)_2CuLi \xrightarrow[2.\ H_3O^{\oplus}]{1.\ ether}$

(d)  $\xrightarrow[2.\ H_3O^{\oplus}]{1.LiAlH_4}$

2. Show how the following compounds might be synthesized from suitable Michael donors and acceptors:

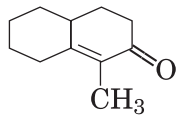
(a) 

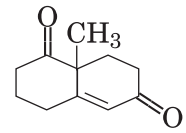
(b) $Ph-CHCH_2COOH$ with CH_2COOH

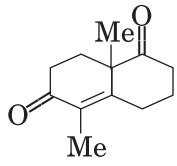
(c) 

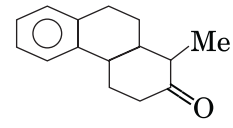
(d) $CH_3COCH_2CH_2CH(CO_2Et)_2$

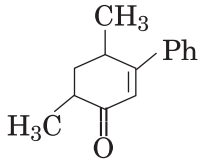
3. Show how you would use Robinson annulation to synthesize the following compounds:

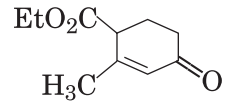
(a) 

(b) 

(c) 

(d) 

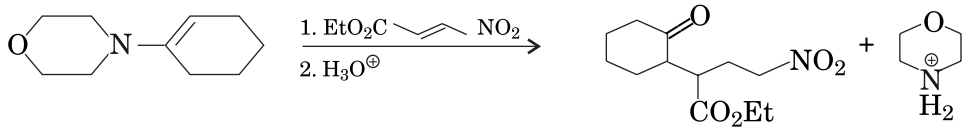
(e) 

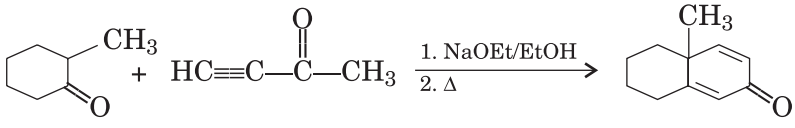
(f) 

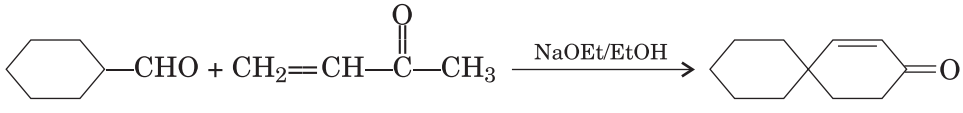
4. Outline a preparation of 2-octanone ($CH_3CH_2CH_2CH_2CH_2CH_2COCH_3$) by using a conjugate-addition reaction.

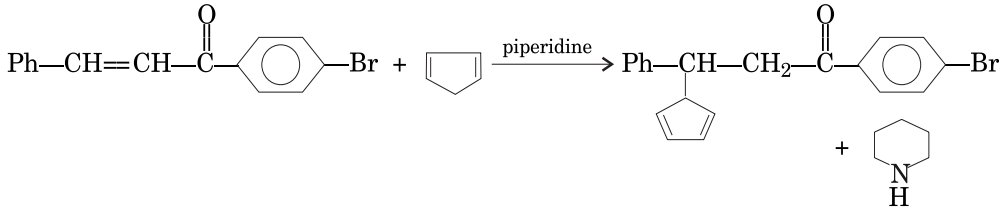
[Hint: Lithium dibutylcuprate and methyl vinyl ketone are to be used as reactants.]

5. Suggest mechanisms for the following reactions:

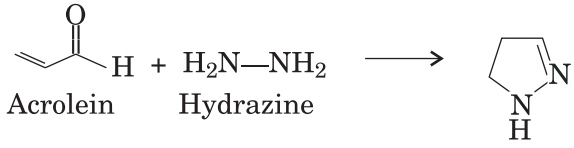
(a) 

(b) 

(c) 

(d) 

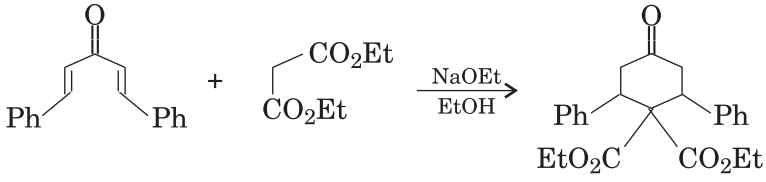
6. When acrolein is allowed to react with hydrazine, dihydropyrazole is obtained:

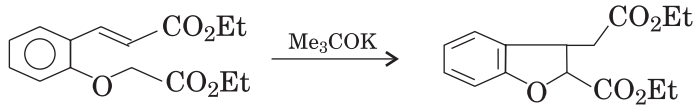


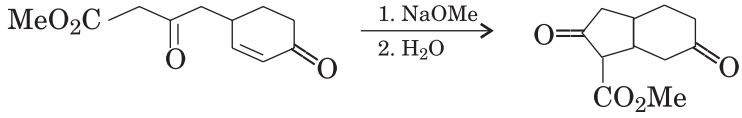
Acrolein Hydrazine Dihydropyrazole

Provide a mechanism that explains this reaction.

7. Suggest mechanisms for the following transformations:

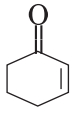
(a) 

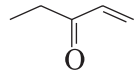
(b) 

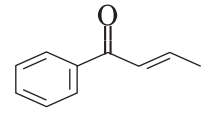
(c) 

[Hint: Intramolecular Michael addition is involved in all the three transformations.]

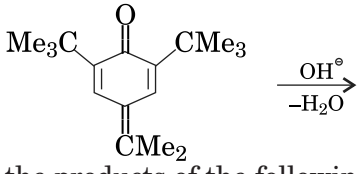
8. Draw the product obtained when each of the following compounds is treated with either $(CH_2{=}CH)_2CuLi$ followed by H_2O, or $HC{\equiv}CLi$, followed by H_2O.

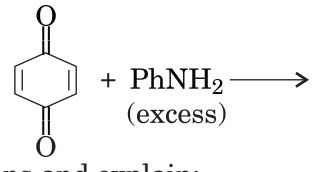
(a) 

(b) 

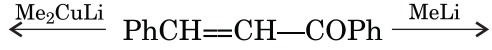
(c) 

9. Identify the product of the following reaction and explain:

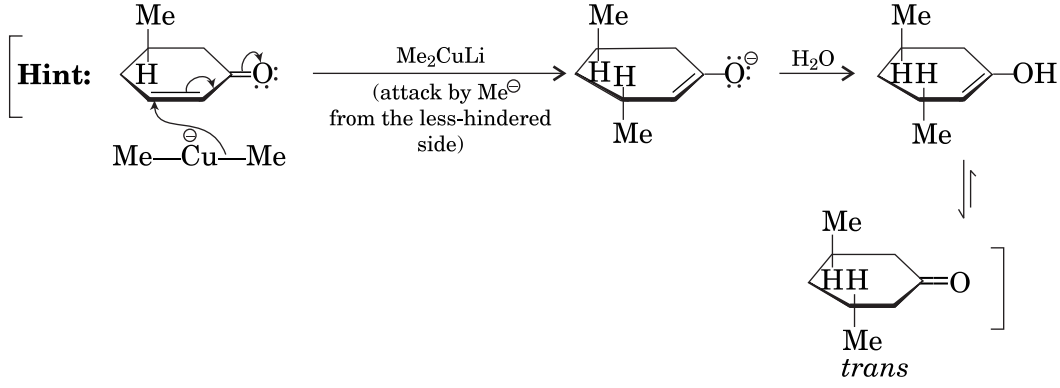
(a) 

(b) 

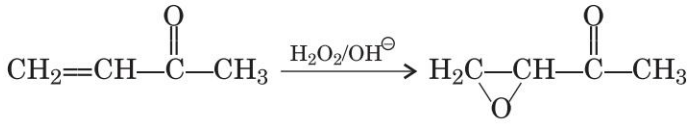
10. Give the products of the following reactions and explain:

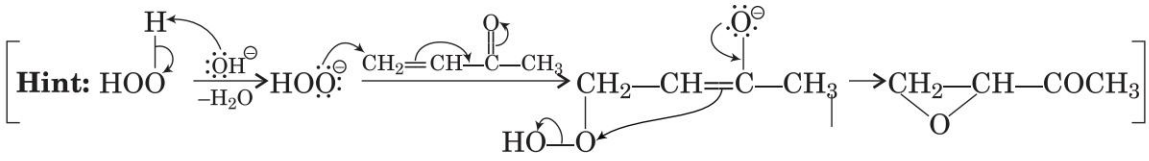


11. 5(β)-Methyl-2-cyclohexenone is treated with Me_2CuLi and the resulting compound is then hydrolysed. Explain the above reaction and comment on the stereochemistry of the final product.

Hint: 

12. Write a mechanism that accounts for the formation of the product:



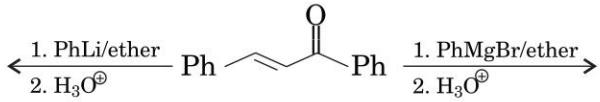


13. Explain the following observations:

$$CH_3COCH_2CH_2CN \xleftarrow[80°C]{NaCN,\ HCl} CH_3COCH{=}CH_2 \xrightarrow[5\text{–}10°C]{NaCN,\ HCl} CH_3CN(OH)CH{=}{}_2CH_2$$

[Hint: At lower temperature, the reaction of the enone with relatively weak base (softer nucleophile) $CN^{\ominus}$ is irreversible and so, the thermodynamically less stable 1,2-addition product (the kinetic product) is obtained predominantly. On the other hand, at higher temperature, the reaction is reversible and the thermodynamically more stable 1,4-addition or conjugate-addition product (the thermodynamic product) is obtained predominantly. The C═C adduct obtained from 1,4-addition is thermodynamically more stable than the C═O adduct because the former contains a residual C═O bond, and this is stronger than the residual C═C bond in the latter.]

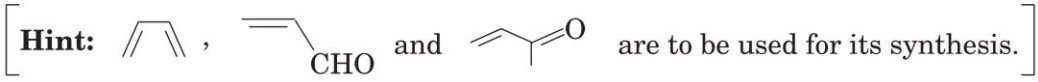
14. Predict the products of the following reactions. Give explanations.



[Hint: Since the carbonyl carbon is bonded to a bulky phenyl group, therefore, conjugate-addition product, Ph_2CHCH_2COPh, is formed preferentially in the first reaction, even though Grignard reagents are strong bases. The organolithium reagent PhLi is also a strong base but unlike PhMgBr it gives the usual 1,2- or direct-addition product, $PhCH{=}CHC(OH)Ph_2$, because of less-steric hindrance.]

15. Suggest the steps for the synthesis of the following spiro compound using the Diels-Alder reaction followed by Robinson annulation:

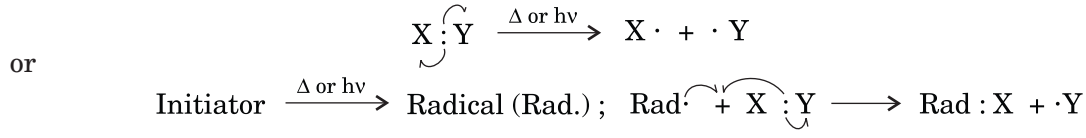




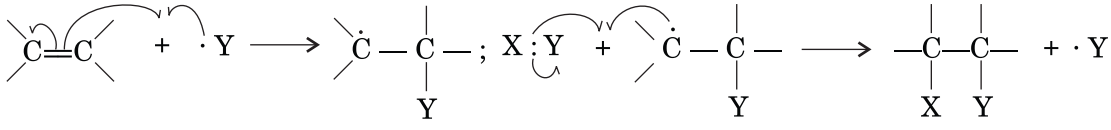
1.3 ADDITION OF RADICALS AND RADICAL SUBSTITUTION OF BENZYLIC AND ALLYLIC HYDROGENS

Radical addition to carbon–carbon double bond: the most important type of radical reactions are the radical additions to carbon–carbon double bonds. These reactions take place either in the gas phase or in inert non-polar solvents in the presence of heat or light (hν) or catalytic amount of radical initiators such as organic peroxides, labile azo compounds, etc. The addition reactions involve the general steps of radical reactions, i.e., the initiation, chain propagation and termination. Let us discuss the addition of XY to a C═C bond, where X and Y may or may not be identical.

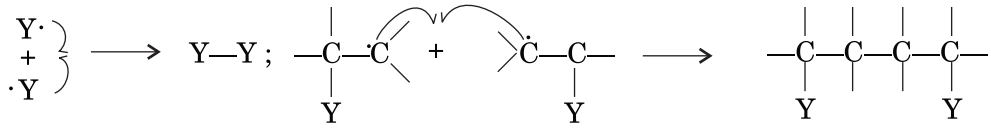
Chain initiation step:



Chain propagation step:



Chain termination step:



The initial radical adds to the C═C bond in such a way that generates a more stable carbon radical. The carbon radicals are stabilized by resonance and hyperconjugative effects and the order of stability is:

$$\text{PhĊH}_2\text{ (benzyl)} \approx \text{CH}_2\text{═CH—ĊH}_2\text{ (allyl)} \rangle 3^\circ\text{ alkyl} \rangle 2^\circ\text{ alkyl} \rangle 1^\circ\text{ alkyl}$$

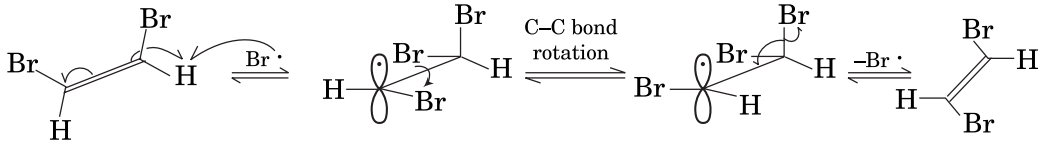
When both the chain propagation steps of a reaction are exothermic, the reaction is energetically favourable and occurs most readily. Most of the radical addition reaction are non-stereospecific. There are, however, most examples of stereoselective reactions even at higher temperatures.

1.3.1 Radical Addition of Halogens and Hydrogen Halides and Radical Polymerization

1.3.1.1 Reactivity of Halogens Towards Radical Addition to Alkenes

The order of reactivity of halogens towards homolytic addition to alkenes is $F_2 > Cl_2 > Br_2 > I_2$. This runs parallel with the reactivity of the radicals. Fluorine is so reactive that its addition is practically impossible and this is because the reaction is much vigorous and often leads to unwanted side reactions. Chlorination is quite fast and occurs readily. Bromination is not so fast and is usually reversible, while iodination takes place with difficulty if at all, and is readily reversible.

Reversible addition of bromine and iodine to the a C═C bond may be used to convert a less stable geometric isomer to a more stable one. Thus, when *cis*-1,2-dibromoethene, for example, is irradiated with UV light in the presence of a catalytic amount of Br_2, it is converted into its *trans*-isomer.

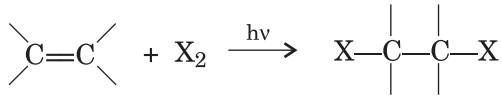


cis-1,2-Dibromoethene

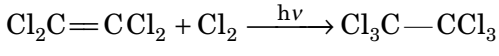
trans-1,2-Dibromo-ethene

1.3.1.2 Radical Addition of Cl_2 and Br_2

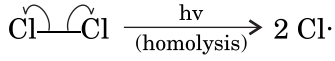
Both Cl_2 and Br_2 add across the π bond by a free radical chain process. The reactions require a free-radical initiator or the reaction may be initiated by light.

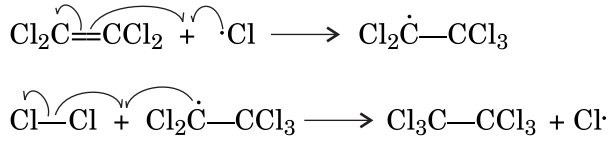
General Reaction: 

Chlorine, for example, reacts with tetrachloroethene in the presence of light to yield hexachloroethane.

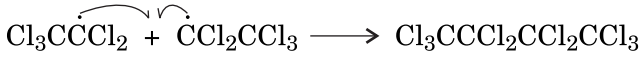


The reaction takes place as follows:

1. **Chain-initiating step:** 

2. **Chain-propagation steps:** 

3. **Chain-terminating step:**



Each molecule of Cl_2, on photochemical fission, gives rise to two Cl atoms, i.e., two chlorine radicals, each of which is capable of initiating a continuing reaction chain. Chlorine atoms are electrophilic in nature because the element is electronegative and Cl· will readily take up an electron to complete its octet. Thus, Cl· adds readily to the double bond of $Cl_2C{=}CCl_2$ to form the radical $Cl_2\dot{C}{-}CCl_3$. This, in turn, abstracts a chlorine atom from a second molecule of Cl_2 to yield the end-product of addition, i.e., $Cl_3C{-}CCl_3$ plus a further atom of chlorine. The Cl· so left in the reaction reacts with another molecule of the alkene and the reaction is continued as a chain process. When nearly all of $Cl_2C{=}CCl_2$ and Cl_2 have been used up, the concentration of $Cl_2\dot{C}CCl_3$ is very small and then chain termination takes place by its dimerization.

The reaction is found to be inhibited by the presence of oxygen because the molecule of oxygen having two unpaired electrons and behaving as a diradical (·O—O·) combines with the highly reactive radical intermediate $Cl_2\dot{C}CCl_3$ and thereby converts it to the very much less reactive peroxy radical $Cl_3CCCl_2{-}O{-}O\cdot$, which is unable to carry on the chain.

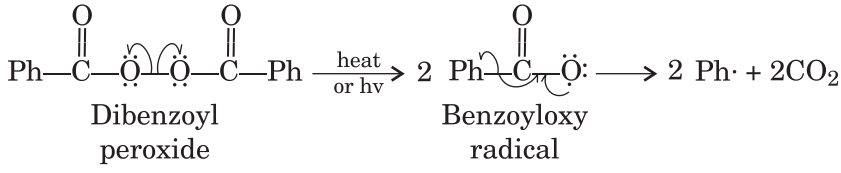
1.3.4.3 Radical Addition of HBr to Unsymmetrical Alkenes

The radical addition of HBr to an unsymmetrical alkene leads to the formation of *anti*-Markownikoff product. When 1-butene ($CH_3CH_2CH{=}CH_2$), for example, reacts with HBr in the presence of heat or light and a small amount of radical initiator like dibenzoyl peroxide, di-*tert*-butyl peroxide, etc. 1-bromobutane, the *anti*-Markownikoff product is obtained. The reversal of orientation in HBr addition in the presence of peroxides is called the *peroxide effect* or *Kharasch effect* (named after M.S. Kharasch of the University of Chicago).

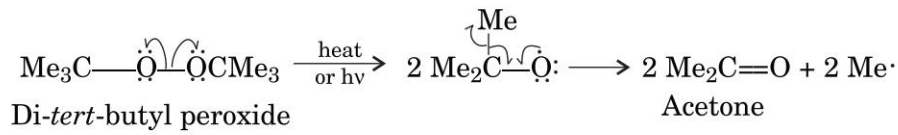
$$\underset{\text{1-Butene}}{CH_3CH_2CH{=}CH_2} + HBr \xrightarrow[(R = PhCO \text{ or } Me_3C)]{ROOR/\Delta \text{ or } h\nu} \underset{\text{1-Bromobutane}}{CH_3CH_2CH_2CH_2Br}$$

Mechanism of the reaction: The mechanism for the anti-Markownikoff addition of hydrogen bromide to 1-butene (an unsymmetrical alkene) is a free-radical chain reaction which involves the steps as follows:

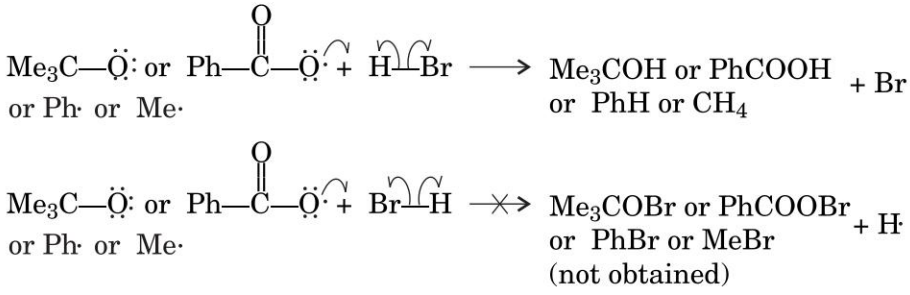
Step 1: Homolysis of dibenzoyl peroxide (the oxygen–oxygen bond of peroxide is very weak) in the presence of heat or light produces two benzoyloxy radicals which then rapidly decarboxylates to give two phenyl radicals.



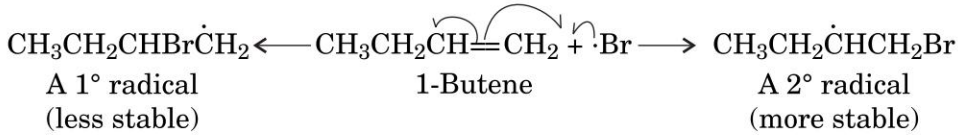
Similarly, di-*tert*-butyl peroxide yields two *tert*-butoxy radicals which in turn produce acetone and two methyl radicals.



Step 2: The radicals formed in the first step abstract hydrogen atom from HBr to form bromine radical. The process is exothermic and has low energy of activation. Abstraction of bromine atom by the radical is not energetically favourable and so it does not take place.



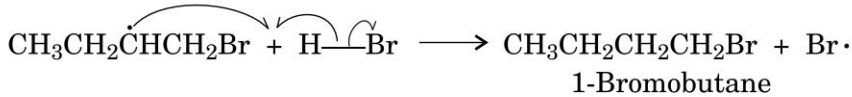
Step 3: A bromine radical adds to the double bond of 1-butene to produce the more stable 2° alkyl radical.



If bromine adds to 1-butene at the secondary carbon atom, a less stable, primary radical would have been the result and also, addition at the secondary carbon atom would have also been more hindered sterically.

[It is to be noted that, like carbocations, radicals are stabilized by electron-donating alkyl groups, so a tertiary alkyl radical is more stable than a secondary alkyl radical and a secondary alkyl radical is more stable than a primary alkyl radical.]

Step 4: The resulting 2° radical abstracts a hydrogen atom from HBr to yield 1-bromobutane, the anti-Markownikoff product and a bromine radical or atom which uses itself in step 3 to continue the chain reaction.



The first two steps are chain initiation steps and the last two steps are chain propagation steps.

Reason for the difference in the orientation of HBr addition in the presence or absence of peroxides: In the absence of peroxides, HBr adds to an unsymmetrical alkene by an ionic mechanism in which proton adds first with a doubly bonded carbon

atom to form a more stable carbocation. In the presence of peroxides, on the other hand, a radical mechanism operates in which the bromine atom adds first to a doubly bonded carbon to form a more stable free radical. For this reason, the orientation of HBr addition in the absence of peroxide differs from that of the addition in the presence of peroxide.

The peroxide effect is observed for the addition of HBr but not for the addition of HF, HCl or HI: This observation can be explained by considering the $\Delta H°$ values for the two propagation steps in the radical chain reaction. For ethylene the $\Delta H°$ values for the two propagation steps are as follows:

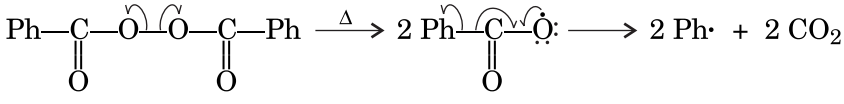
H—X	$\Delta H°$(kcal/mol) $X\cdot + CH_2=CH_2 \rightarrow XCH_2-\dot{C}H_2$	$\Delta H°$(kcal/mol) $XCH_2-\dot{C}H_2 + H-X \rightarrow XCH_2-CH_3 + X\cdot$
H—F	–45 (exothermic)	+37 (endothermic)
H—Cl	–26 (exothermic)	+5 (endothermic)
H—Br	–5 (exothermic)	–11 (exothermic)
H—I	+7 (endothermic)	–27 (exothermic)

The more the $\Delta H°$ is negative, the more the reaction is favourable thermodynamically. For HF the second step is highly endothermic and thermodynamically unfavourable. Also for HCl it is again the second step that is little endothermic. For HI it is the first step that is slightly endothermic. However, both the steps are thermodynamically favourable only for the addition of HBr because both of them are exothermic. It is for this reason the peroxide effect is observed for the addition of HBr only.

[In a radical chain reaction, the propagation steps compete with termination steps. Termination steps are always exothermic because only bond making (and no bond breaking) takes place. Therefore, propagation can compete with termination when both propagation steps are exothermic. When HF, HCl or HI adds to an alkene in the presence of an organic peroxide, any chain reaction that is initiated is terminated rather than propagated because propagation cannot compete with termination. As a consequence, the radical chain reaction does not take place and only ionic addition takes place to give Markownikoff product.]

1.3.4.4 Radical Addition of CX_4 (X = Br, Cl) to Alknes

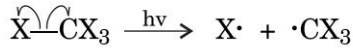
Carbon-carbon bonds may be formed by the addition of halomethyl radicals ($\cdot CX_3$) radicals to alkenes. The $\cdot CX_3$ (X = Cl, Br) may be generated by the action of peroxides on, or by photolysis of CX_4.



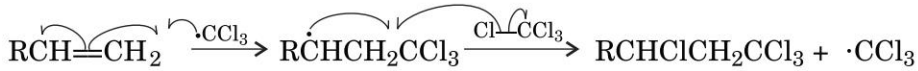
Dibenzoyl peroxide



or,

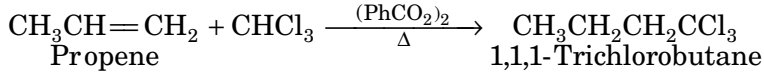


The two propagation steps of CCl_4 addition are as follows:

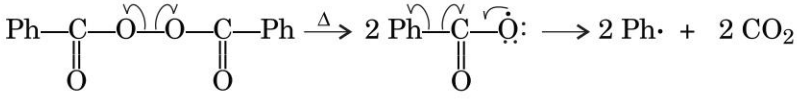


That the relatively inert CCl_4 adds in this way may seem a little surprising, but the $\Delta H°$ values for both steps of the reaction chain are exothermic: –75 kJ mol^{-1} and –17 kJ mol^{-1}.

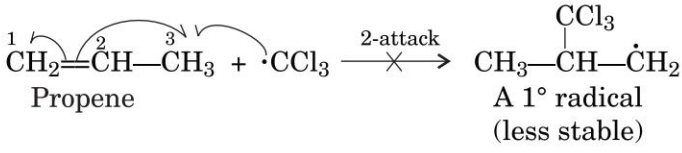
Addition of chloroform to an unsymmetrical alkene takes place in *anti*-Markownikoff fashion when carried out in the presence of peroxide. For example:

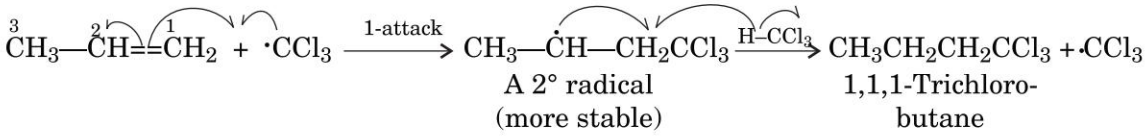


Dibenzoyl peroxide (a radical initiator) initiates a free radical chain reaction by generating phenyl radicals:







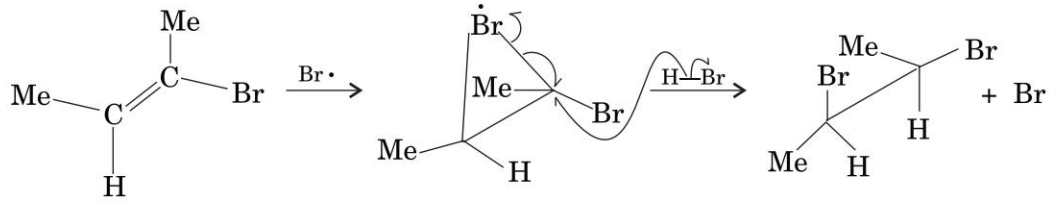


The reaction proceeds through the more stable 2° radical to yield 1,1,1-trichlorobutane.

SOLVED PROBLEMS

1. Explain why the addition of liquid HBr at –80°C to *cis*-2-bromobut-2-ene was found to proceed with high *trans*-stereospecificity, and to yield *meso*-2,3-dibromobutane almost exclusively.

Solution Under such conditions, the alkene undergoes free radical addition of HBr. The addition proceeds *via* a cyclic bromonium radical (analogous to the cyclic bromonium cations involved in the polar addition of bromine to alkenes) and the overall addition is then completed through attack by HBr from the less hindered side (away from the bridging Br) to yield the product of overall *trans* addition. Since the starting alkene is *trans*-2-butene, therefore, the reaction results in formation of *meso*-2,3-dibromobutane almost exclusively.



cis-2-Bromobut-2-ene — A cyclic bromonium radical — *meso*-2,3-Dibromobutane

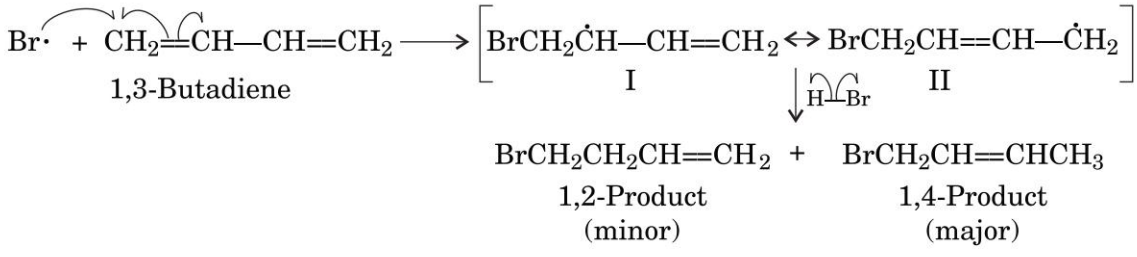
2. Predict the products obtained when 1,3-butadiene is allowed to react with HBr in the presence of air.

Solution When exposed to air and sunlight, organic compounds undergo autooxidation to generate hydroperoxides and peroxides. These compounds containing very weak O—O bond dissociates to form alkoxyl (RO·) and hydroxyl (HO·) radicals. These radicals abstract hydrogen atom from HBr to form bromine atom. Also, HBr reacts with oxygen, which behaves as a diradical (·O–O·) to form bromine atom.

$$RO\overset{\frown}{-}OR \longrightarrow 2\,RO\cdot \quad ; \quad RO\overset{\frown}{-}OH \longrightarrow RO\cdot + HO\cdot$$

$$RO\cdot + H\overset{\frown}{-}Br \longrightarrow ROH + Br\cdot \quad ; \quad \cdot O{-}O\cdot\,(O_2) + H\overset{\frown}{-}Br \longrightarrow \cdot OOH + Br\cdot$$

The bromine atom then adds to 1,3-butadiene to form a resonance-stabilized allylic radical.



The resonance structure I is less stable than II because the double bond is at the terminal position and the electron-attracting Br atom is α to the electron deficient radical carbon. So, the contribution of II in the resonance hybrid is greater than I and as a consequence, the allylic radical abstracts a hydrogen atom from HBr to from 1-bromo-2-butene (the 1,4-addition product) as the major product.

Study Problems

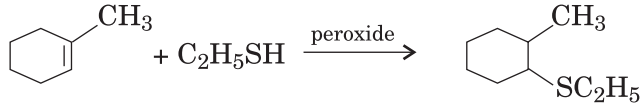
1. Write down the propagation steps that take place when HBr adds to 1-methylcyclohexene in the presence of an organic peroxide.

2. Identify the two alkenes that react with HBr to yield 1-bromo-1-methylcyclohexane. Will both alkenes give the same product when they are allowed to react with (i) HBr/peroxide, (ii) HCl or (iii) HCl/peroxide.

3. Write down the structure of three six-carbon alkenes that form the same product when treated with HBr/peroxide or only HBr.

4. Suggest a mechanism for the free-radical addition of HBr to cyclohexene initiated by AIBN(azoisobutyronitrile).

5. Propose a reasonable mechanism for each of the following reactions:

(a) 

(b) $CH_2{=}CH(CH_2)_5CH_3 + CBr_4 \xrightarrow[h\nu]{\text{peroxide}} Br_3CCH_2\,\underset{\displaystyle Br}{\overset{\displaystyle |}{C}}(CH_2)_5CH_3$

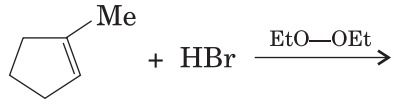
6. Show how you would accomplish the following conversions:

(a) 1-Methylcyclohexane → 1-Bromo-1-methylcyclohexene

(b) 1-Methylcyclohexanol → 1-Bromo-2-methylcyclohexane

(c) 2-Methyl-2-butanol → 2-Bromo-3-methylbutane

7. Predict the major products of the following reactions and provide mechanisms that account for their formation:

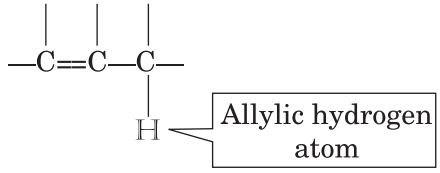
(a) 

(b) $CH_3{-}CH{=}CH{-}Ph + HBr \xrightarrow[\Delta]{Me_3CO-OCMe_3}$

1.3.2 Allylic Chlorination and Allylic Bromination

1.3.2.1 Allylic Substitution

The hydrogen atoms of any saturated carbon atom adjacent to a double bond are called allylic hydrogen atoms and any reaction in which an allylic hydrogen atom is replaced is called an allylic substitution.



1.3.2.2 Allylic Chlorination

Any reaction in which an allylic hydrogen atom is replaced by a Cl atom is called allylic chlorination. When propene ($CH_3CH{=}CH_2$), for example, is allowed to react with chlorine in the gas phase at 400°C, if undergoes allylic chlorination.

$$\underset{\text{Propene}}{CH_2{=}CH{-}CH_3} + Cl_2 \xrightarrow[\text{gas phase}]{400^\circ C} \underset{\substack{\text{3-Chloropropene}\\\text{(allyl chloride)}}}{CH_2{=}CH{-}CH_2Cl} + HCl$$

Mechanism: The mechanism for this allylic chlorination involves the steps as follows:

Chain-initiating step: In this step, the chlorine molecule dissociates into chlorine atoms.

$$Cl{-}Cl \xrightarrow{\Delta} 2\,Cl\cdot$$

First chain-propagating step: In this step, the chlorine atom abstracts one of the allylic hydrogen atoms.

$$CH_2{=}CH{-}CH_2{-}H + \cdot Cl \longrightarrow \underset{\text{Allyl radical}}{\left[CH_2{=}CH{-}\dot{C}H_2 \leftrightarrow \dot{C}H_2{-}CH{=}CH_2\right]} + HCl$$

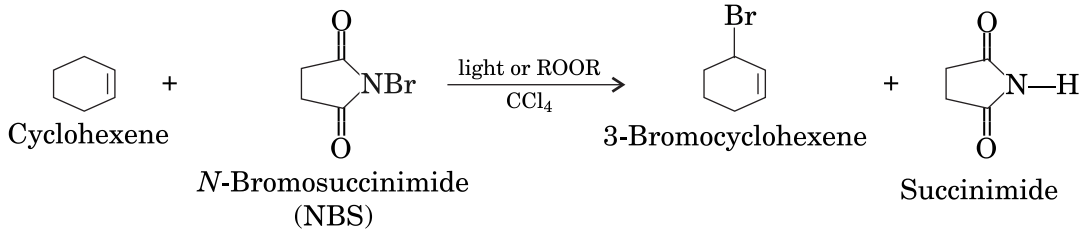
Second chain-propagating step: In this step, the allyl radical reacts with a molecule of chlorine to yield a molecule of allyl chloride and a chlorine atom.

$$CH_2{=}CH{-}\dot{C}H_2 + Cl{-}Cl \longrightarrow \underset{\text{Allyl chloride}}{CH_2{=}CH{-}CH_2Cl} + Cl\cdot$$

The chlorine atom then brings about a repetition of the first chain-propagating step.

1.3.2.3 Allylic Bromination with N-bromosuccinimide

Allylic bromination of an alkene involving low concentration of Br_2 can be effectively carried out with *N*-bromosuccinimide. Cyclohexne, for example, undergoes allylic bromination when it is treated with *N*-bromosuccinimide (NBS) in CCl_4 in the presence of peroxides or light. The reaction is also known as *Wohl-Zigler bromination*.

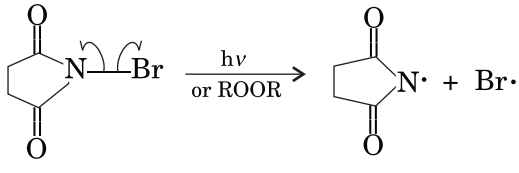


N-Bromosuccinimide (NBS)

Mechanism: The mechanism of allylic bromination with NBS involves the steps as follows:

Initiation:

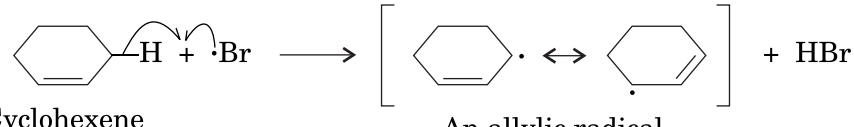
Step 1: The reaction is initiated by the formation of a small amount of Br· by homolysis of the weak N—Br bond in NBS itself in the presence of light.



Propagation:

The three propagation steps for this reaction are as follows:

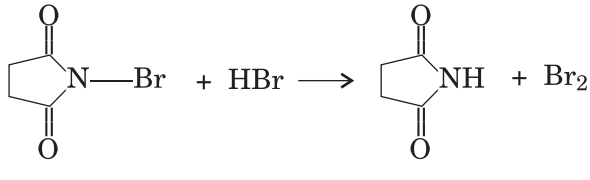
Step 2: The bromine atom abstracts an allylic H atom from the alkene molecule to give hydrogen bromide and a resonance-stabilized allylic radical.



Cyclohexene

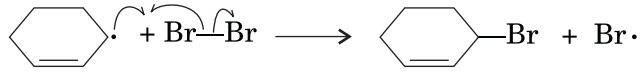
An allylic radical

Step 3: The HBr thus formed reacts with NBS (by an ionic mechanism) to form a bromine molecule.



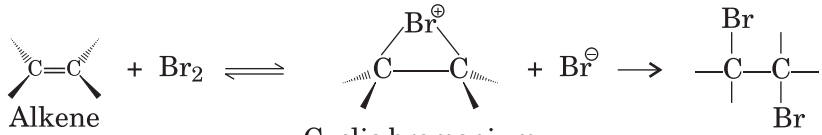
N-Bromosuccinimide is nearly insoluble in carbon tetrachloride and so, it provides a constant but low concentration of Br_2 in the reaction mixture.

Step 4: The allylic radical formed in step 2 (the first propagation step) abstracts a bromine atom from a bromine molecule to yield 3-bromocyclohexene and a bromine atom, which brings about repetition of step 2.



3-Bromocyclohexene

Addition of Br_2 to the C═C bond to form vicinal dibromide does not take place under this reaction conditions: This observation can be explained as follows. In the first step of the electrophilic addition of Br_2 to an alkene, one atom of the bromine molecule adds to the doubly bonded carbons in a reversible process. The other bromine atom then adds as an anion in the second step to complete the reaction.



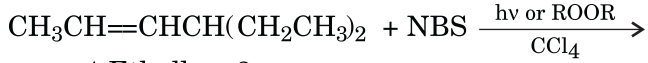
Alkene — Cyclic bromonium ion — Vicinal dibromide (addition product)

When the concentration of bromine is low, the equilibrium for the first step will lie far to the left and the concentration of the intermediate bromonium ion and $Br^{\ominus}$ will be very low. As a consequence, the probability of a bromonium ion finding a bromide ion in its vicinity for the second step to take place is also very low. As a result of this, the overall rate of ionic addition is slow and allylic substitution competes successfully with it.

The use of nonpolar solvent like carbon tetrachloride (CCl_4) also slows down the addition, Since there is no polar molecule to stabilize the $Br^{\ominus}$ ion by solvation, it is stabilized by coordination with another bromine molecule, giving the more stable tribromide ion ($Br_3^{\ominus}$). In a nonpolar solvent, the rate expression for addition is, therefore, second order in Br_2, i.e., rate = k [alkene] $[Br_2]^2$, when the concentration of Br_2 is very low, the $[Br_2]^2$ term becomes negligible and the rate of addition becomes extremely slow and so, the substitution reaction predominates.

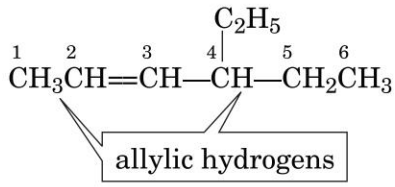
SOLVED PROBLEMS

1. Predict the products of the following reaction and rank them in order of decreasing yield:



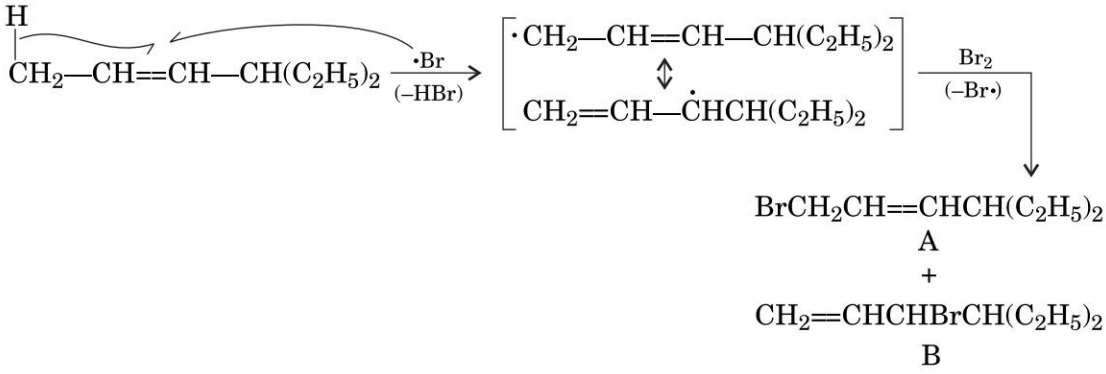
4-Ethylhex-2-ene

Solution

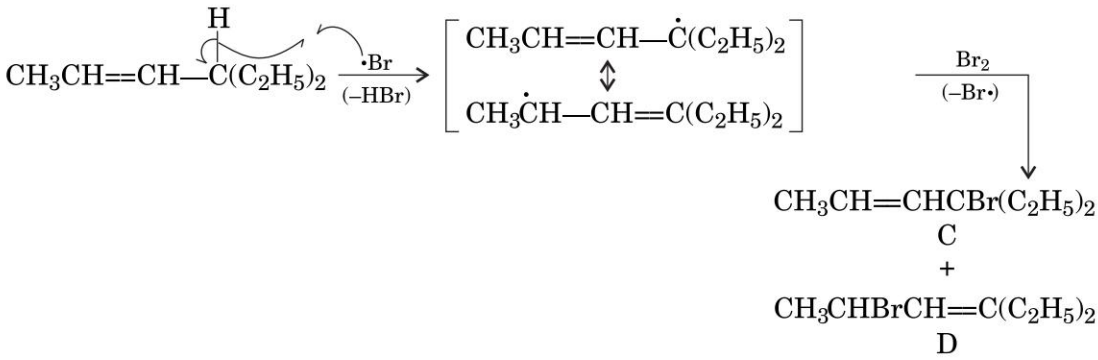


The three C-1 hydrogens and the C-4 hydrogen of 4-ethylhex-2-ene are allylic in nature. Substitution of a C-1 hydrogen produces two allylic bromides (A and B) and substitution of the C-4 hydrogen produces other two allylic bromides (C and D).

Path I:

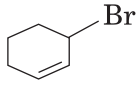
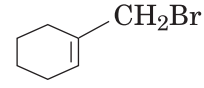


Path II:



The 3° allylic C-4 hydrogen is relatively more reactive than the 1° allylic C-1 hydrogens and consequently, the path II and the products (C and D) obtained through it dominate over path I and the products (A and B) obtained through it. Again a more substituted allylic bromide is thermodynamically more stable and so, predominates over a less substituted allylic bromide. Therefore, the decreasing order of their yields is: D (path II, more substituted) 〉 C (path II, less substituted) 〉 A (path I, more substituted) 〉 B (path I, less substituted).

2. Which one of the following compounds can be prepared in good yield by allylic bromination of an alkene and why?

 or $CH_3CH_2CH_2CH{=}CHCH_2Br$ or 

Solution

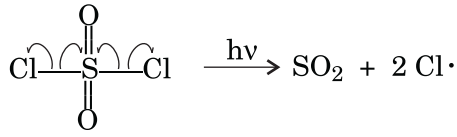
When all the allylic hydrogen are equivalent allylic bromination gives only one product and so, the allylic bromide is expected to be obtained in good yield. Out of the three starting alkenes, all the allylic hydrogens in cyclohexene are equivalent and therefore, 3-bromocyclohexene can be prepared in good yield by allylic bromination. 2-Hexene (the starting alkene for the 2nd compound) and 1-methylcyclohexene (the starting alkene for the 3rd compound) produce four and five bromoalkenes respectively on allylic bromination.

3. Provide the mechanism for the allylic chlorination of propene ($CH_3CH{=}CH_2$) with (a) sulfuryl chloride (Cl_2SO_2) in the presence of light.

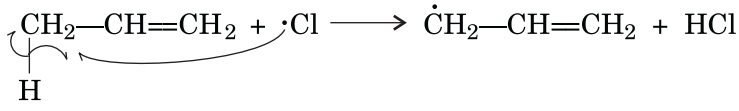
Solution

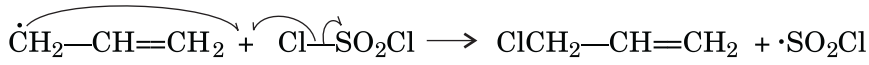
$$\underset{\text{Propene}}{CH_3CH{=}CH_2} \xrightarrow[h\nu]{Cl_2SO_2} \underset{\text{3–Chloropropene}}{ClCH_2CH{=}CH_2}$$

The mechanism of the reaction is as follows:

Initial step: 

Propagation steps:

Step 1: 

Step 2: 

$$\cdot SO_2Cl \longrightarrow SO_2 + Cl\cdot \text{ (used in step 1)}$$

Study Problems

1. Explain why the substitution becomes the favoured reaction at high temperatures.

[**Hint:** ΔS° of the addition in which two molecules combine to form a single molecule is negative. At high temperatures, the unfavourable $T\Delta S^\circ$ term in the relation

$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$ overshadows the favourable ΔH° making ΔG° positive and so, addition does not take place.]

2. When 1-octene is allowed to react with NBS in CCl_4 in the presence of light, 1-bromooct-2-ene is obtained in 80 percent yield. Explain this observation.

3. Designate the type of each set of hydrogens in $(CH_3)_2C{=}CHCH_2CH(CH_3)_2$ and rank them in order of decreasing reactivity towards radical substitution. Give your reasoning.

[Hint: The hydrogens of this alkene may be labelled as follows:

$$(\overset{a}{C}H_3)_2C{=}\overset{b}{C}H\overset{c}{C}H_2\overset{d}{C}H_2\overset{e}{C}H(\overset{f}{C}H_3)_2$$

The decreasing order of reactivity towards radical substitution is c (2° allylic) > a(1° allylic) > e(3°) > d(2°) 〉 > f(1°) b(vinylic) and this is because the C—H bond dissociation energy decreases in the order: vinylic 1° 〉 2° 〉 3° 〉 1° allylic 〉 2° allylic.**]**

4. Predict the product expected to be obtained when toluene is irradiated in the presence of bromotrichloromethane ($BrCCl_3$). Give your reasoning.

REFERENCES

1. March, J, *Adv. Org. Chem.,* Chapter – 15.
2. Brown H C, *Boranes in Organic Chemistry*; Cornell University: Ithaca, 1972.
3. P B D *de la* Mare and R Bolton, *Electrophic Additions to Unsaturated Systems,* Elsevier Publishing Co., London, (1966), F. Freeman. *Chem. Rev.,* **75**, 439 (1975).
4. G H Schmid and D Garrah, The *Chemistry of Double Bonded Functional Groups,* S Patai, Ed., Wiley, New York (1977), Chap (IX).
5. F A Carey and R M Sundberg, *Advances in Organic Chemistry,* 5th ed, Springer, Berlin, (2007).
6. K C Pande and S Weinstein, *Tetrahedron lett*., 3393 (1964).
7. W Markowni Koff, *Ann*., **153**, 256 (1970).
8. Samuel P. McManus, *Organic reactive intermediates*, Academic Press.
9. Clayden, Greeves, Warren, Wothers, *Organic Chemistry*, Oxford University Press.
10. Herbert O House, *Modern Synthetic Reaction*, Second Edition, Benjamin.
11. Thomas H Lowry, Kathleen Schuller Richardson, *Mechanism and Theory in Organic Chemistry*, Addison – Wesley
12. Robert Thornton Morrison & Robert Neilson Boyd, *Organic Chemistry*, Sixth Edition, Prentice Hall of India.
13. Michael J Robinson, *Organic Stereo Chemistry*, Oxford University Press.
14. Peter Sykes, *A Guide book to Mechanism in Organic Chemistry,* Sixth Edition, Orient Longman.
15. Thomas N Sorrell, *Organic Chemistry*, Viva.

2 CHAPTER

REACTIONS OF THE CARBONYL GROUP AND REACTIONS AT THE α-CARBON TO THE CARBONYL GROUP

Chapter Outline

2.1 Introduction

2.2 Nucleophilic addition to carbon-oxygen double bond

- 2.2.1 Structure of the carbonyl group
- 2.2.2 Effect of structure on reactivity
- 2.2.3 Stereochemistry of nucleophilic addition

2.3 Addition of Oxygen Nucleophiles: Water and Alcohols(ROH)

- 2.3.1 Addition of water (hydration) and formation of *gem*-diols
- 2.3.2 Mechanism for hydrate formation
- 2.3.3 Kinetics of hydrate formation
- 2.3.4 Thermodynamics of hydrate formation
- 2.3.5 Formation of stable and isolable hydrates
- 2.3.6 Addition of alcohols and formation of hemiacetals and acetals
- 2.3.7 Mechanism for acid-catalyzed hemiacetal and acetal formation
- 2.3.8 Mechanism for Base-catalyzed hemiacetal formation (base-catalyzed acetal formation does not take place)
- 2.3.9 Hydrolysis of acetals
- 2.3.10 Acetals as protecting groups
- 2.3.11 Tetrahydropyranyl group as a protecting group

2.4 Addition of Sulphur Nucleophiles: Thiols (RSH) and sodium bisulphite ($NaHSO_3$)

- 2.4.1 Addition of thiols
- 2.4.2 Mechanism for thioacetal formation
- 2.4.3 Thermodynamics for thioacetal formation
- 2.4.4 Importance of thioacetals in organic synthesis
- 2.4.5 Addition of sodium bisulphite ($NaHSO_3$)
- 2.4.6 Mechanism for bisulphite additions
- 2.4.7 Applications of bisulphite addition reaction

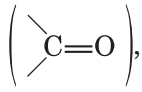
2.5 Addition of Hydride Ion ($:H^{\ominus}$) and addition of electrons

- 2.5.1 Reduction of carbonyl compounds by lithium aluminium hydride ($LiAlH_4$)
- 2.5.2 Mechanism for the reduction of carbonyl compounds by lithium aluminium hydride ($LiAlH_4$)
- 2.5.3 Reduction of aldehydes and ketones by sodium borohydride ($NaBH_4$) to form primary and secondary alcohols, respectively
- 2.5.4 Mechanism for the reduction of an aldehyde or a ketone by sodium borohydride ($NaBH_4$)

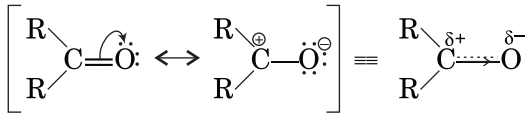
2.5.5 Reduction of carboxylic acids, amides and nitriles by borane (BH_3)
2.5.6 Reduction of acid chlorides to aldehydes by lithium tri-*tert*-butoxylaluminium hydride [$LiAlH(O\text{-}t\text{-}Bu)_3$] and reduction of ester and nitriles to aldehydes by diisobutylaluminium hydride (i-Bu_2AlH or DlBAL-H)
2.5.7 Meerwein–Ponndorf–Verley (MPV) reduction
2.5.8 Cannizzaro reaction
2.5.9 Tishchenko reaction
2.5.10 Bouveault-Blanc reduction
2.5.11 Pinacolization of Ketones
2.5.12 Clemmensen reduction
2.6 Addition of Nitrogen Nucleophiles
2.6.1 Addition of primary amines and formation of imines
2.6.2 Addition of compounds like hydroxylamine, hydrazine and substituted hydrazines (similar to primary amines) and formation of imine derivatives
2.6.3 Reductive amination
2.6.4 Wolff-Kishner reduction
2.6.5 Important uses of the imine-forming reaction
2.6.6 Addition of secondary amines and formation of enamines
2.7 Addition of Carbon Nucleophiles
2.7.1 Addition of hydrogen cyanide (HCN)
2.7.2 Addition of Grignard and other organometallic compounds
2.7.3 Addition of acetylides
2.7.4 Addition of diazomethane (CH_2N_2)
2.7.5 Addition of ylides
2.8 Addition of Enolate ions:
2.8.1 Aldol Reaction
2.8.2 Stobbe Condensation
2.8.3 Darzenes Condensation
2.8.4 Benzoin condensation
2.8.5 Reformatsky reaction
2.8.6 Perkin reaction
2.8.7 Knoevenagel condensation
2.8.8 Mannich reaction
2.9 Reactions At The α-carbon of carbonyl compounds of Aldehydes and Ketones
2.9.1 Halogenation at the α-carbon of aldehydes and ketones
2.9.2 Alkylation at the α-carbon of Aldehydes and Ketones
2.9.3 The Claisen condensation (addition of acid derivatives to the α-carbon of carbonyl compounds
2.9.4 Green chemistry
2.10 Acyl Substitution
2.10.1 Mechanism of Nucleophilic Addition–Elimination at the Acyl Carbon or Nucleophilic Acyl Substitution
2.10.2 Reaction of Carboxylic Acids
2.10.3 Reactions of Acid Chlorides
2.10.4 Reactions of Esters
2.10.5 Reactions of Amides
2.10.6 Reactions of Carboxylic Acid Anhydrides
2.10.7 Reactions of Nitriles

2.1 INTRODUCTION

The carbonyl group is one of the most important functional groups because it comprises a large number of synthetically useful reactions. In fact, the carbonyl group may be regarded as the backbone of organic chemistry. Most of the reactions of aldehydes, ketones, carboxylic acids, esters, anhydrides, and amides involve carbonyl group.

In the carbonyl group  , carbon and oxygen are joined by a double bond, which is polarized by the strongly electronegative oxygen atom. This electron imbalance in the π bond renders the carbonyl carbon electron-deficient and causes the carbonyl group

as a whole to exercise an electron-attracting effect. The carbonyl $\diagup C{=}O$ group may be represented as resonance hybrid of the following two resonance structures:

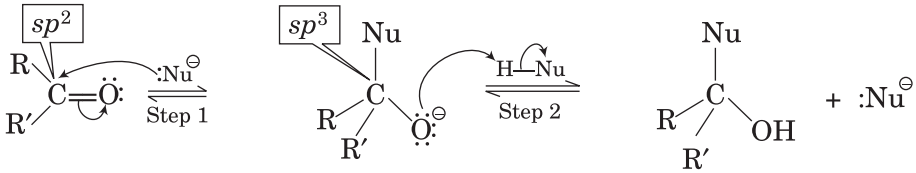


It thus follows that the carbonyl carbon remains partially positively charged, while the oxygen atom remains partially negatively charged.

The C═O linkage, by analogy with C═C, undergoes addition reactions owing to the presence of the π bond and due to its bipolar nature, polar attack on it could be initiated either by electrophilic attack of $X^{\oplus}$ or X on oxygen or by nucleophilic attack of $Y^{\ominus}$ or Y: on carbon.

Nucleophilic addition to the carbon–oxygen double bond occurs, therefore, in either of the two general ways such as follows:

1. When a strong nucleophile ($:Nu^{\ominus}$) is the reagent, addition usually occurs as shown below, converting the trigonal planar carbonyl compound (aldehyde or ketone) in a tetrahedral product.

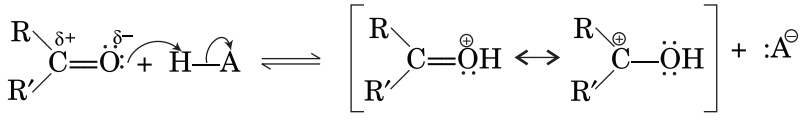


Carbonyl compound (trigonal planar) | Tetrahedral intermediate | Tetrahedral product

In step 1, the nucleophile uses its electron pair to form a bond to the carbonyl carbon atom. As a consequence, the electron pair of the carbon–oxygen π bond shifts to the electronegative oxygen atom and the hybridization state of both C and O changes from sp^2 to sp^3. Therefore, the important aspect of this step is the ability to the carbonyl oxygen atom to accommodate the electron pair of the carbon–oxygen double bond. In step 2, the alkoxide oxygen, because of its strongly basic nature, abstracts a proton from H–Nu or some other acid.

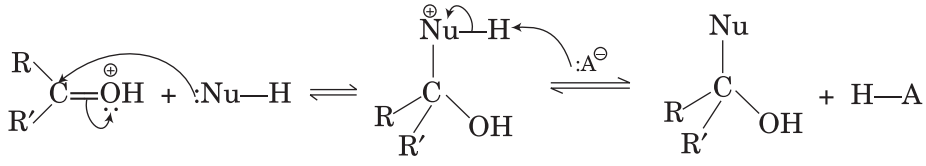
2. When an acid catalyst is present, reaction of the carbonyl oxygen with the acid enhances the electrophilicity of the carbonyl group and in that case nucleophilic addition can take place by a weak nucleopohile. The mechanism for the reaction is as follows:

Step 1:



In this step, an unshared pair of electrons accepts a proton from the acid (or coordinates with a Lewis acid) to produce an oxonium ion. The oxonium ion is highly reactive towards nucleophilic attack at the carbonyl carbon because the carbonyl carbon carries more positive charge than it does in the unprotonated carbonyl compound.

Step 2:



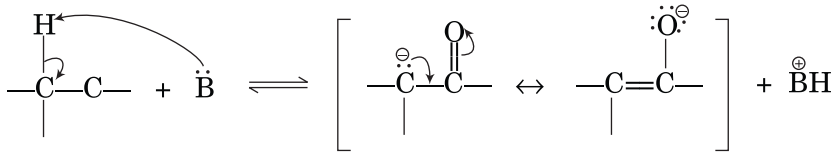
In the first step of this two-step process, the oxonium ion accepts a pair of electrons of the nucleophile ($\ddot{\text{N}}\text{u}\,\text{H}$) and in the second step, the base $:\text{A}^{\ominus}$ takes up a proton from the positively charged atom to regenerate the acid.

Similar activation, though to a smaller extent, can also arise through hydrogen bonding of an acid (HA) or even a hydroxylic solvent like alcohol (ROH) to the carbonyl oxygen atom:



In the absence of such activation, weak nucleophiles like $\text{H}_2\ddot{\text{O}}:$, $\text{MeO}\ddot{\text{H}}:$, etc. may only react very slowly, but strong nucleophiles like $:\overset{\ominus}{\text{C}}\text{N}$, $\text{S}\overset{2}{\text{O}}_3^{\ominus}$, etc. do not require such aid. The additions may be base-catalysed where the base converts the weak nucleophile HY: into the stronger one $:\ddot{\text{Y}}^{\ominus}$, for example, HCN + base $\rightarrow :\text{CN}^{\ominus}$. Although acids activates the carbonyl carbon atom to nucleophilic attack, they simultaneously reduce the effective concentration of the nucleophile, for example, $:\overset{\ominus}{\text{C}}\text{N} + \text{H} - \text{A} \rightarrow \text{HCN} + \ddot{\text{A}}^{\ominus}$, $\text{R}\ddot{\text{N}}\text{H}_2 + \text{H} - \text{A} \rightarrow \text{R}\overset{\oplus}{\text{N}}\text{H}_3 + \ddot{\text{A}}^{\ominus}$. Therefore, many simple addition reactions of carbonyl compounds are found to have an optimum pH. This factor can be of great importance for preparative purposes.

Since the C═O group has –I effect and the carbanion obtained by the loss of α–H is resonance-stabilized. Therefore, the α-hydrogen atom possesses considerable acidic character.

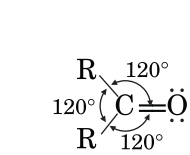


The resonance-stabilized carbanion acts as a nucleophile and takes part in varied types of condensation reactions.

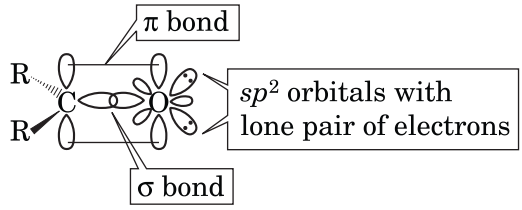
2.2 NUCLEOPHILIC ADDITION TO CARBON-OXYGEN DOUBLE BOND

2.2.1 Structure of the carbonyl group

The carbonyl carbon atom is sp^2 hybridized. The three sp^2 orbitals form σ bonds to the carbonyl oxygen and two substituents. The carbonyl oxygen is also sp^2 hybridized. One of its sp^2 orbital is used to for σ bond with the carbonyl carbon. Each of the other two sp^2 orbitals contains a lone pair. The π bond between the carbon and oxygen is formed by the overlap of the remaining p orbital of carbonyl oxygen with the remaining p orbital of the carbonyl carbon. The sp^2 hybridization implies that the carbonyl group is planar, and the bond angles are 120° approximately.

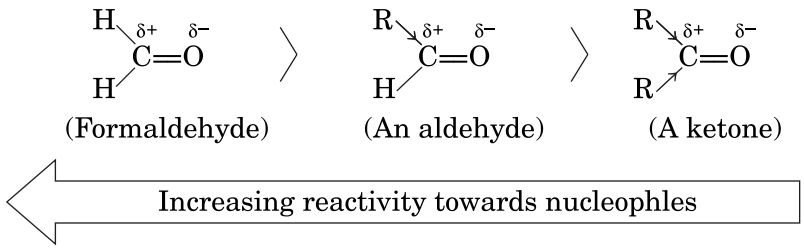


Carbonyl compound

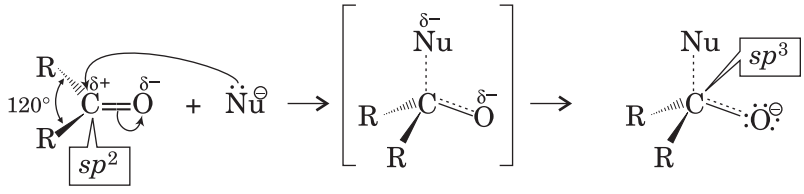


2.2.2 Effect of structure on reactivity

Both electronic and steric effects caused by the groups attached to the carbonyl carbon influence the reactivity of the carbonyl compounds towards nucleophilic additions. Since in the simple nucleophilic addition reactions the rate-determining step involves attack by the nucleophile, $\ddot{N}u^{\ominus}$ on the positively polarized carbonyl carbon atom, therefore, any effect that increases the positive character of the carbonyl carbon will increase the rate of addition, while any effect that decreases the positive character of the carbonyl carbon will decrease the rate of addition. That is, any effect that stabilizes the transition state (decreases E_{act}) for attack by a nucleophile will increase the rate of addition, while any effect that destabilizes the transition state (increases E_{act}) will result in a slower rate of addition. An alkyl group, being electron-releasing (+I effect), decreases the positive character of the carbonyl carbon and thereby reduces the rate of nucleophilic attack. On the other hand, an electron-attracting group (e.g., $-CH_2NO_2$,$-CCl_3$ etc.) causes a faster rate of nucleophilic attack by increasing the positive character of the carbonyl carbon. In fact, an electron-releasing group destabilizes the transition state by intensifying the negative charge and thus causes a slower rate of addition. But an electron-attracting group stabilizes the transition state by spreading out the negative charge and thus causes a faster rate of addition. It thus follows that the reactivity of the carbonyl compound also decreases with increasing alkyl substitution. A ketone with two alkyl groups is less reactive than an aldehyde with only one. Formaldehyde having no alkyl group is naturally more reactive than an aldehyde. Therefore, the increasing order of reactivity from the electronic point of view is:



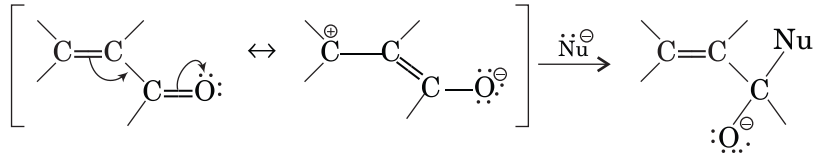
Steric effect also plays an important role in determining the reactivity of carbonyl compounds. The sp^2 hybridized (trigonal) carbonyl carbon atom in reactant is converted to an sp^3 hybridized (tetrahedral) carbon atom in the adduct. The groups attached with the central carbon atom thus moves closer together as the reaction proceeds. Because of this, the adduct as well as the transition state that resembles the adduct becomes more crowded. Since crowding increases the energy of the transition state, i.e., makes the transition state less stable (increases E_{act}), therefore, the rate of reaction drops as the number and size of the groups attached to the carbonyl carbon increases.

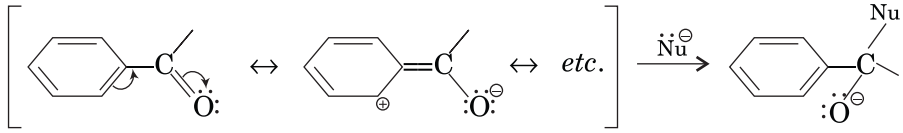


The transition state for addition to formaldehyde ($H_2C{=}O$) containing two small H atom is, therefore, less crowded than the transition state for addition to an aldehyde (R CHO) containing only one alkyl group, which in turn is less crowded than the transition state for addition to a ketone ($R_2C{=}O$) containing two alkyl groups. Therefore, the increasing order of reactivity from steric point of view is similar to that from electronic point of view (shown above).

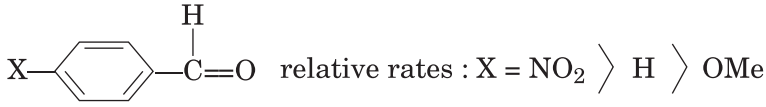
In general, aldehydes are more reactive than ketones towards nucleophilic attack for both steric and electronic reasons.

The compounds in which C═O groups is conjugated with a carbon–carbon double bond or a benzene ring reacts at a slower rate compared to their saturated analogues. This is because the resonance stabilization in the starting compounds is lost on going to the adduct and the transition state that precedes them.





However, if there is an electron-withdrawing group on the C═C moiety or at the *ortho*- or *para*-position of the benzene nucleus, the positive character of the carbonyl carbon increases and as a result, the rate of addition increases. A decrease in reaction rate is observed if there is an electron-donating group instead of an electron-withdrawing group. The influence of electronic effect alone may be seen in the following series of compounds:



Increase in the size of the nucleophile, with a given carbonyl compound, may also lead to a drop in reaction rate due to steric crowding.

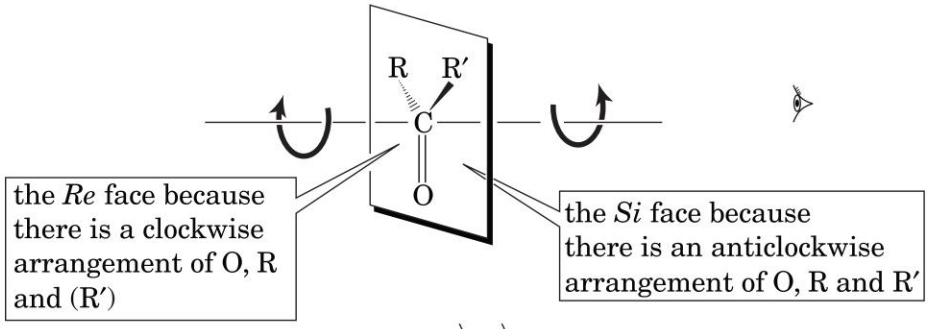
Except some reactions with very strong nucleophiles like $AlH_4^{\ominus}$, RMgBr, etc. many additions to C═O group are reversible. In general, the factors that affect the rate of reaction (k) influence the position of equilibrium (K) much in the same way. This is due to the fact that the transition state for simple addition reactions probably resembles the adduct more closely than it does the starting carbonyl compound. Thus, the K values for cyanohydrin formation are found to reflect this operation of both steric and electronic factors:

Carbonyl compound	*K*
CH_3CHO	Very large
O_2N—C$_6$H$_4$—CHO	1420
C$_6$H$_5$—CHO	210
MeO—C$_6$H$_4$—CHO	32
$CH_3COCH_2CH_3$	38
Ph CO CH_3	0.8
Ph CO Ph	very small

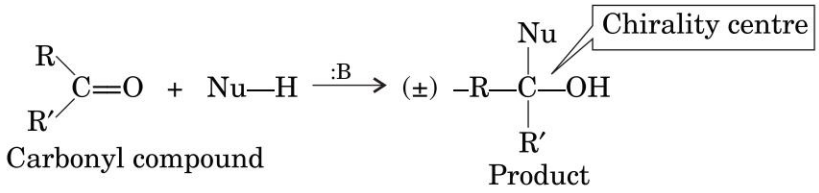
For a given carbonyl compound, the equilibrium constant K is also influenced by the size of the nucleophile. The K value for bisulphite addition (SO_3^{2-}) to $(CH_3CH_2)_2C{=}0$ is only 4×10^{-4}. K is also influenced by the nature of the bond that is formed by the nucleophile to the carbonyl carbon atom.

2.2.3 Stereochemistry of nucleophilic addition

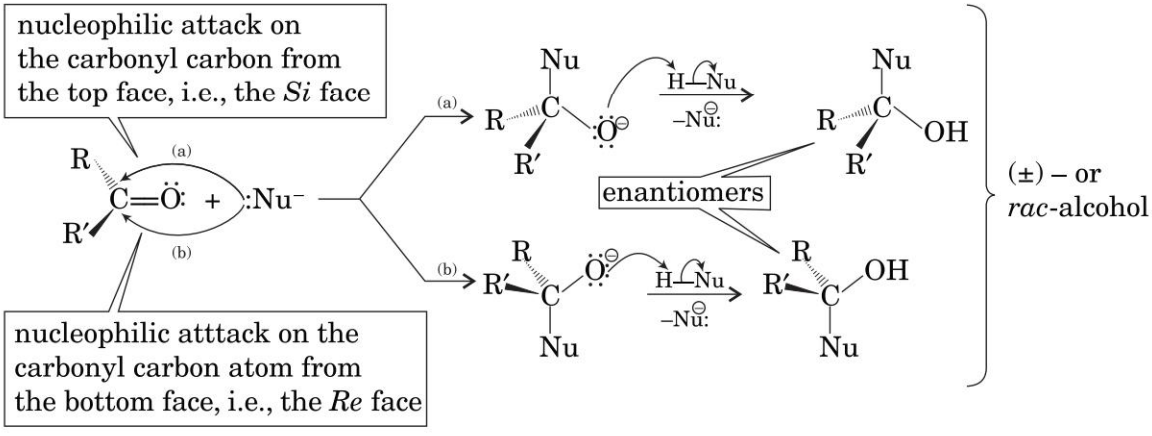
A carbonyl compound of the type R COR′ (where R and R′ are alkyl groups or R is alkyl and R′═H) has two equivalent faces and these are named as *Re* face and *Si* face.



Addition of Nu—H to RR′C═0 creates a chirality centre in the product and produces a racemic mixture (a mixture of equimolar amounts of two enantiomers) and this is because the two faces (the *Re* face and the *Se* face) of the carbonyl compound are equivalent and attack by the nucleophile on the carbon of the planar trigonal $\diagdown C{=}O \diagup$ system from above or below the place occurs with equal facility, i.e., statistically equally likes as the environments are the same.

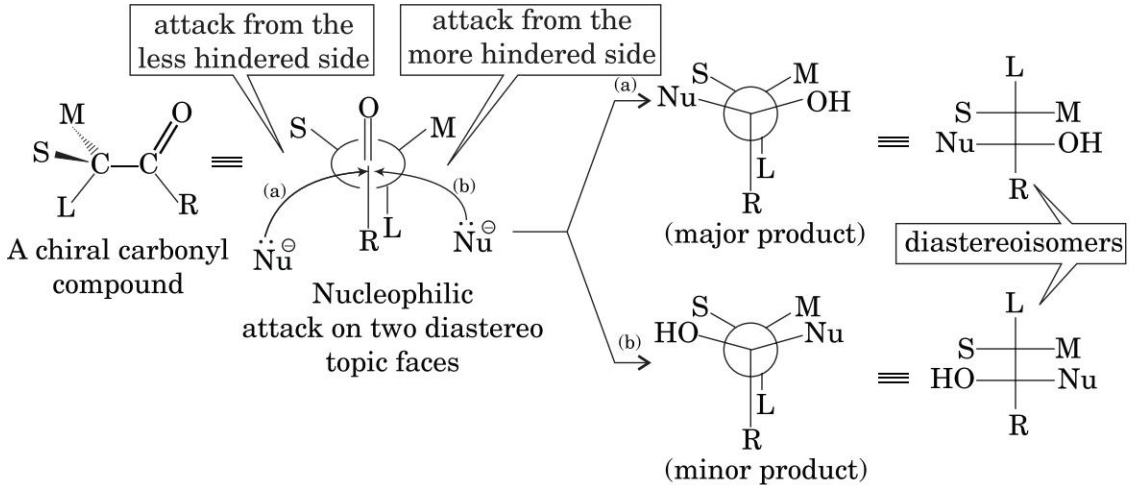


The stereochemical course of the reaction may be shown as follows:

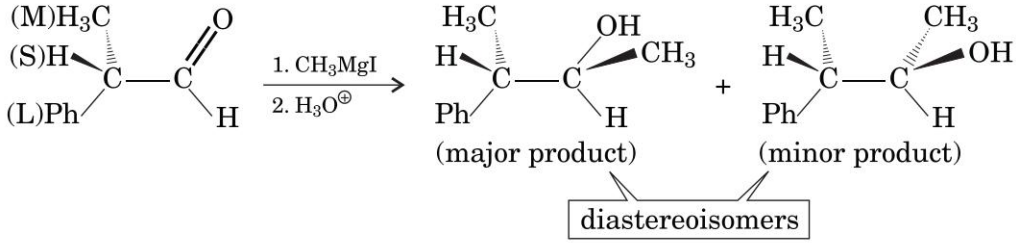


Addition of NuH to $R_2C{=}O$, however, introduces no chirality centre into the product and the product alcohol is achiral.

When any one of the two alkyl groups R and R′ is chiral, the environments of nucleophilic attack on the carbonyl carbon from the two faces of the carbonyl compound are no longer equivalent, and therefore, attacks from above and below the planar $\diagdown C{=}O\diagup$ system are not statically equally likely. As a result, the products will not be formed in equal amounts. In that case, the Cram's rule predicts the major addition product. According to Cram's rule, which considers only the steric effect, nucleophilic addition to a carbonyl carbon atom of a chiral carbonyl compound like $RCO\overset{*}{C}LMS$, where L, M and S stand for large, medium and small groups respectively, will take place from the less hindered side (involving low energy transition state), i.e., from the side of the small group (S) in a conformation where the $\diagdown C{=}O\diagup$ group is flanked by two smaller groups (M and S) with the large group (L) remaining nearly eclipsed with R and results in the formation of one diastereoisomer predominantly. The stereochemical course is as follows:



Example:

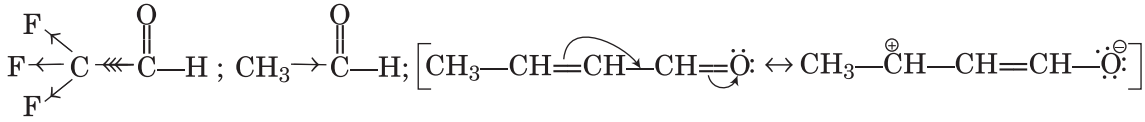


SOLVED PROBLEMS

1. Arrange the following compounds in order of increasing reactivity towards nucleophilic addition reaction and give your reasoning.

CH_3CHO, CF_3CHO, $CH_3CH{=}CHCHO$

Solution: The reactivity of these three aliphatic aldehydes increases in the order $CH_3CH{=}CHCHO \langle CH_3CHO \langle CF_3CHO$. The strong –I effect of the $–CF_3$ group in CF_3CHO makes the carbonyl carbon highly reactive towards nucleophilic attack, while +I effect of the $–CH_3$ group in CH_3CHO makes the carbonyl carbon relatively less reactive towards nucleophilic attack. Because of resonance, the positive character of the carbonyl carbon of the *a*, *β*-unsaturated aldehyde $CH_3CH{=}CHCHO$ reduces considerably and therefore, it is much less reactive than CH_3CHO.

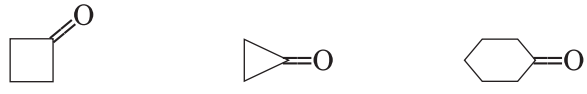


2. Rank the following ketones in order of decreasing reactivity towards nucleophilic addition and give your reasoning.

$MeCOCMe_3$, $MeCOMe$, $Me_3CCOCMe_3$

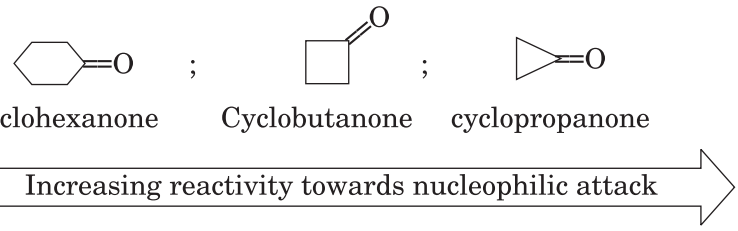
Solution A *tert*-butyl group ($–CMe_3$) is very much bulky (space-filling) and relatively more electron-releasing than a methyl group ($–CH_3$). Therefore, from steric (mainly) and electronic point of view the reactivity of the carbonyl compounds decreases with increase in the number of *tert*-butyl group in the molecule. Hence, the decreasing order of reactivity of these three ketones is $MeCOMe \rangle MeCOCMe_3 \rangle Me_3CCOCMe_3$. In fact, the highly hindered ketone Me_3COCMe_3 does not react at all except possibly with very small and highly reactive nucleophiles.

3. Rank the following cyclic ketones in order of increasing reactivity towards nucleophilic attack and give reasons.



Cyclobutanone Cyclopropanone Cyclohexanone

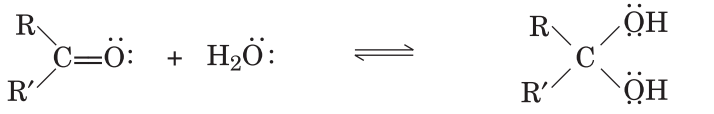
Solution The order of reactivity of these cyclic ketones can be explained in terms of angle strain relief during nucleophilic addition. Attack of a nucleophile on the carbonyl carbon of these ketones creates a tetrahedral centre with a relief of angle strain. The normal bond angles around a carbonyl group are about 120°, whereas the C—CO—C bond angle in cyclopropane is 60°. So, it suffers from an angle strain of (120°–60°), i.e., 60°. Similarly, cyclobutanone suffers from an angle strain of (120°–90°) or 30° and cyclohexanone suffers from an angle strain of (120°–116°) or 4°. Since reactivity increases with increase in angle strain, therefore, cyclopropanone is more reactive than cyclobutanone, which in turn is more reactive than cyclohexanone, i.e., the order of increasing reactivity is



2.3 ADDITION OF OXYGEN NUCLEOPHILES: WATER AND ALCOHOLS (ROH)

2.3.1 Addition of water (hydration) and formation of *gem*-diols

Water is addeds to an aldehyde or ketone to form a hydrate. When an aldehyde or a ketone is dissolved in water, an equilibrium is established between the aldehyde or ketone and its hydrate. A hydrate is a molecule with two –OH groups on the same carbon. Hydrates, which are in actuality 1,1-diols, are also called geminal diols or simply *gem*-diols (*gem* comes from *geminus*, Latin for "twin").

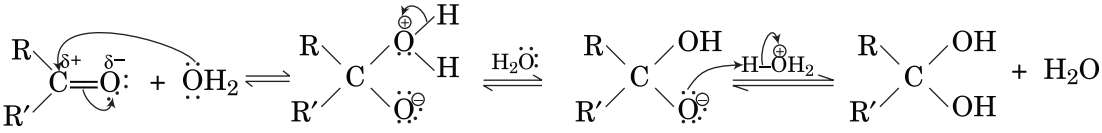


An aldehyde or a ketone (R and R′ = alkyl; R = alkyl and R′ = H or R and R′ = H)

A *gem*-diol or a hydrate

2.3.2 Mechanism for hydrate formation

The mechanism for hydrate formation involves the step as follows:

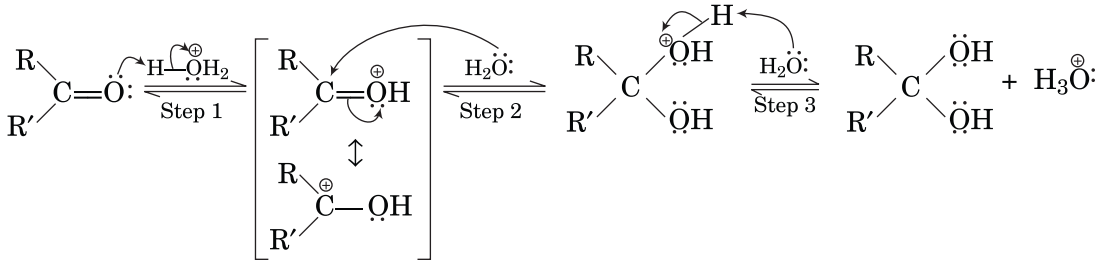


In the first step, the carbonyl compound undergoes nucleophilic attack by water to form a zwitterion. In the second step, a proton is lost from the positive oxygen atom and in the third step, a proton is gained at the negative oxygen atom.

2.3.3 Kinetics of hydrate formation

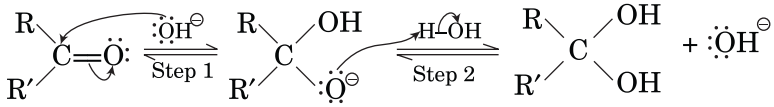
Water, being a poor nucleophile, is added relatively slowly to a carbonyl group. The rate of the reaction can be increased when an acid or a base is used as a catalyst. It is to be noted that a catalyst has no effect on the position of equilibrium. A catalyst only affects rate at which the equilibrium is reached. That is, a catalyst affects the rate at which an aldehyde or a ketone is converted to a hydrate and it has no effect on the amount of aldehyde or ketone converted to hydrate. The mechanisms for acid- and base-catalyzed hydrations are discussed as follows.

(i) Mechanism for acid-catalyzed hydrate formation The mechanism for acid-catalyzed addition of water to a carbonyl group involves the steps as follows:



In step 1, the carbonyl group undergoes protonation to form a resonance-stabilized cation. In step 2, the nucleophile (H_2O) attacks the protonated carbonyl compound to form the conjugate acid of the hydrate and in step 3, deprotonation occurs to form the neutral addition product, i.e., the hydrate.

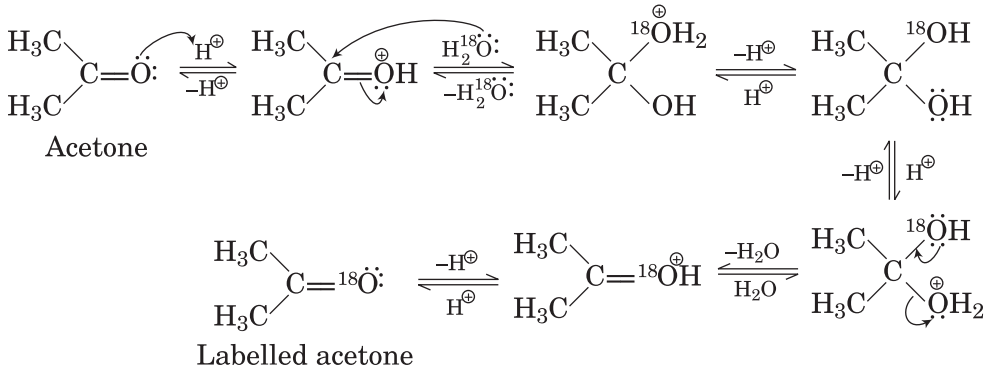
(ii) Mechanism for base-catalyzed hydrate formation



In step 1, the nucleophile $OH^{\ominus}$ attacks the carbonyl group, cleaving the π bond and moving a pair of electrons onto the oxygen atom. In step 2, the alkoxide anion abstracts a proton from water to produce the *gem*-diol or the hydrate.

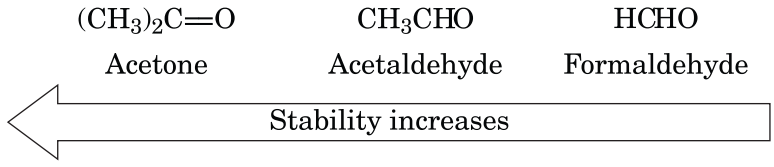
Because these reactions are reversible, the conversion of *gem*-diols to aldehydes and ketones is also catalyzed by acid or base, and according to the *principle of microscopic reversibility* the steps of the mechanism are reversed.

The amount of hydrate from the reaction of water with a ketone is generally too small to detect. That a hydrate that has been formed can be proved by carrying out the reaction of a ketone with ^{18}O-lablled water and isolating the ketone after equilibrium has been established. Finding that the isotopic oxygen has been incorporated into the ketone proves that a *gem*-diol or hydrate must have been formed. For example, labelled acetone ($Me_2C{=}{}^{18}\ddot{O}:$) has been isolated (analyzed by mass spectroscopy).

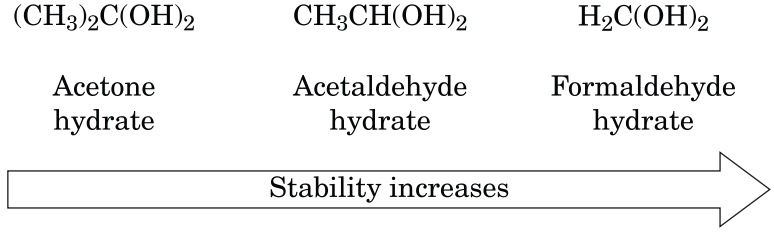


2.3.4 Thermodynamics of hydrate formation

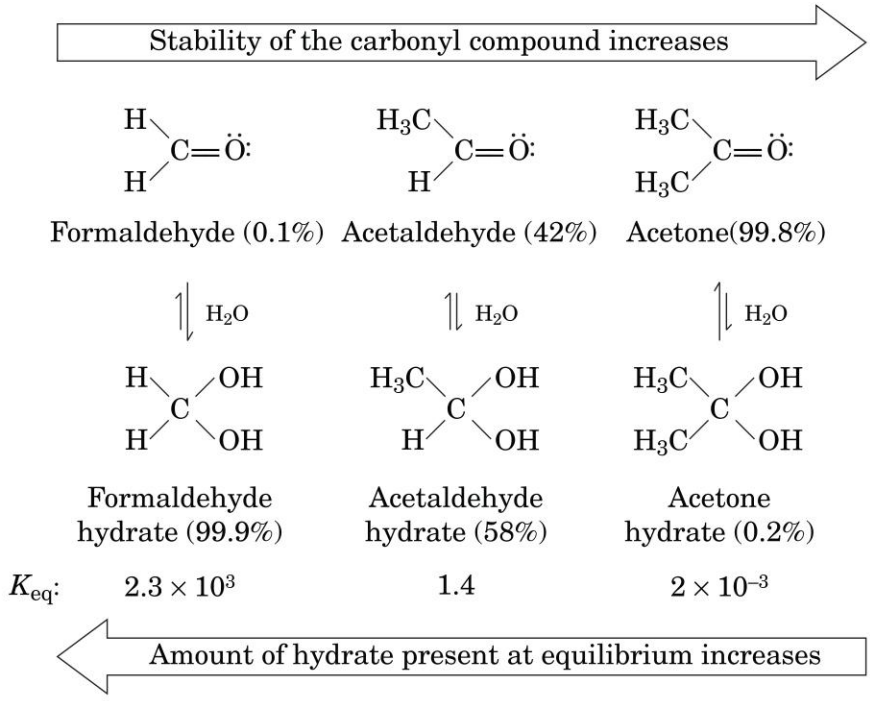
The extent to which an aldehyde or a ketone is hydrated in an aqueous solution depends on the relative stabilities of the starting material and the product. With less stable carbonyl compound equilibrium favours the hydrate, whereas with more stable carbonyl compound, equilibrium favours the starting carbonyl compound. Electron-donating alkyl groups make the carbonyl compound more stable (less reactive) by reducing the positive character of the carbonyl carbon. Therefore, acetone is more stable than acetaldehyde which in turn is more stable than formaldehyde.



Alkyl groups make the hydrate less stable. Steric interactions between the alkyl groups are responsible for the decreased stability of the hydrate. The electron clouds of the alkyl groups do not interfere with each other in the starting carbonyl compound because the bond angles of the sp^2 hybridized carbon are 120°. However, the bond angles in the tetrahedral hydrates (the central carbon is sp^3 hybridized) are 109.5° and because of this, alkyl groups are relatively closer to one another. The electron clouds of the alkyl groups now interfere with each other and causes steric strain. Therefore, formaldehyde hydrate is more stable than acetaldehyde hydrate which in turn is more stable than acetone hydrate.

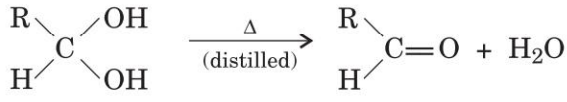


That the increasing the number of alkyl groups on the carbonyl carbon decreases the amount of hydrate at equilibrium can be illustrated by comparing the amount of hydrate obtained from formaldehyde, acetaldehyde and acetone.



In conclusion, the percentage of hydrate of *gem*-diol present at equilibrium depends on both electronic and steric effects. Electron donation and bulky substituent decrease the percentage of hydrate present at equilibrium. On the other hand, electron withdrawal and small substituent increase the percentage of hydrate present at equilibrium.

The equilibrium for hydration of most ketones is unfavourable, whereas aldehydes exists primarily as the hydrate in aqueous solution. It is not possible to isolate most hydrates from the aqueous solution in which they are formed. This is because evaporation of water simply displaces the overall equilibrium to the right and the hydrate reverts to the carbonyl compound.



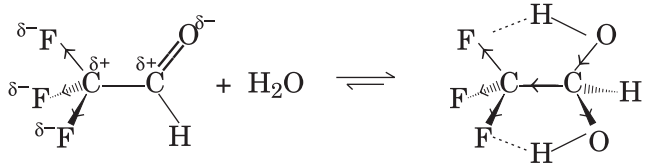
(R = alkyl or H)

2.3.5 Formation of stable and isolable hydrates

Electron-attracting groups bonded to the carbonyl carbon destabilizes the carbonyl compound relative to the hydrate. As a result, the amount of hydrate at equilibrium increases and it can be easily isolated. Sometimes release in angle strain causes the hydrate to predominate at equilibrium. Some typical examples are discussed as follows:

(i) Trifluoroacetaldehyde (CF_3CHO)

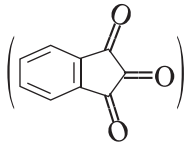
Trifluoroacetaldehyde forms a large amount of hydrate at equilibrium and the hydrate is isolable. The two positive ends of the dipoles exist in the trifluoromethyl and the carbonyl groups repel each other electrostatically. In the resulting hydrate, the carbonyl dipole is replaced by the much weaker dipole of the diol. Therefore, a much greater destabilizing effect caused by the $-CF_3$ group operates in the molecule, but not in the hydrate and so, the hydrate is relatively more stable than the starting aldehyde. Also, the hydrate is stabilized by strong intramolecular hydrogen bonding involving F atoms as well as by the strong electron-attacking –I effect of the $-CF_3$ group that resists the expulsion of $OH^{\ominus}$ or H_2O to regenerate the aldehyde.



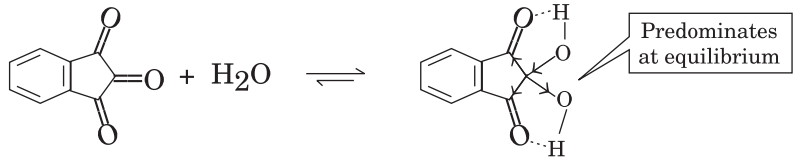
Trifluoroacetaldehyde
(less stable)

Trifluoroacetaldehyde
hydrate
(more stable)

Because of much higher stability of the hydrate relative to the aldehyde, the hydrate predominates at equilibrium can be isolated.

(ii) Indane-1,2,3–trione 

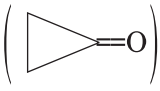
The positive ends of the two adjacent $\overset{\delta_+}{C}=\overset{\delta_-}{O}$ dipoles in indane-1,2,3-trione repel each other electrostatically and this has a destabilizing effect on the molecule. Addition of water to the middle carbonyl group reduces this destabilization considerably because the carbonyl dipole is replaced by the much weaker dipole of the diol. Moreover, the hydrate is stabilized by intramolecular hydrogen bonding as well as the electron-attracting inductive effect (–I) of the existing carbonyl groups that resist the loss of $OH^{\ominus}$ or H_2O to regenerate the original trione.



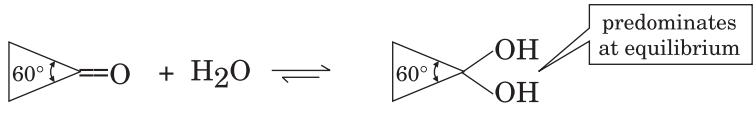
Indane-1,2,3-trione
(less stable)

Indane-1,2,3-trione
hydrate or Ninhydrin
(more stable)

Because of much higher stability of the hydrate relative to the starting trione, the hydrate predominates at equilibrium and can be isolated.

(iii) Cyclopropanone 

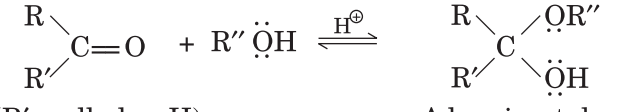
The bond angles around a trigonal planar carbonyl carbon is about 120°, while in cyclopropanone the C—CO—C bond angle is 60°. So, the compound suffers from a great deal of angle strain which is about 120°–60°= 60°. When water is added to the C═O group, a tetrahedral centre is created in which the preferred C—C—C bond angle is about 109.5°. Since the real C—C—C bond angle is still about 60°, the hydrate possesses angle strain that amounts to about 109.5°– 60° = 49.5°. Therefore, the angle strain (I strain) for the hydrate is less than that for cyclopropanone and for this reason, the hydrate is relatively more stable than cyclopropanone. Thus, the driving forces for hydration are considered as the relief in bond angle strain. Because of much higher stability of the hydrate relative to the cyclic ketone, the hydrate predominates at equilibrium and can be isolated.



Cyclopropanone (less stable) — Cyclopropanone hydrate (more stable)

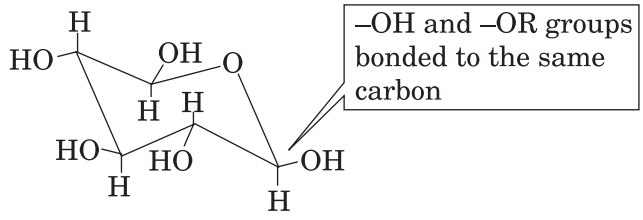
2.3.6 Addition of alcohols and formation of hemiacetals and acetals

Aldehydes and ketones react with one equivalent of alcohols to form hemiacetals (*Hemi* is the Greek prefix "half") and two equivalents of alcohols to from acetals by an equilibrium reaction. In a hemiacetal, there is an –OH and an –OR group attached to the same carbon atom (the carbonyl carbon of the original carbonyl compound). The hemiacetal results by the nucleophilic addition of an alcohol to the carbonyl group of an aldehyde or ketone. An alcohol, like water, is a poor nucleophile, so the rate of the reaction is increased by an acid catalyst (e.g., *p*-toluenesulphonic acid, TsOH; gaseous HCl or concentrated H_2SO_4).



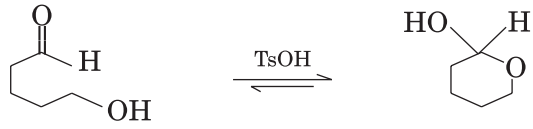
(R′ = alkyl or H) An aldehyde or a ketone — A hemiacetal (usually too unstable to isolate)

Most open chain hemiacetals are not much stable and cannot be isolated. However, cyclic hemiacetals with five- or six-membered rings are usually much stable. Glucose (and most simple sugars), for example, exists primarily in a cyclic hemiacetal form.



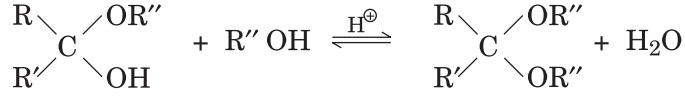
(+)-Glucose
(a cyclic hemiacetal)

Similarly, 5-hydroxypentanal forms a very stable hemiacetal in the presence of acid catalyst. Such intramolecular reactions leading to the formation of six-membered (or five-membered) rings are faster than the corresponding intermolecular reactions. The two reacting functional groups, in this case –OH and $\rangle C=O$, are held in close proximity, and therefore the probability of the reaction increases.



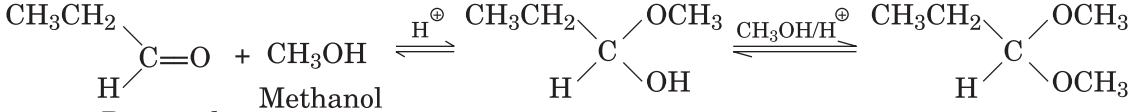
5-Hydroxypentanal (6.1%) ⇌ A cyclic hemiacetal (93.9%)

An acetal has two –OR groups attached to the same carbon atom (the carbonyl carbon of the original carbonyl compound). When a second equivalent of alcohol is added to the reaction mixture, the hemiacetal reacts with it to form an acetal.



A hemiacetal ⇌ An acetal

Propanal, for example, reacts with two equivalents of methanol in the presence of acid catalyst (e.g., gaseous HCl of *p*-toluenesulphonic acid, TsOH) to give an acetal through the formation of a hemiacetal.



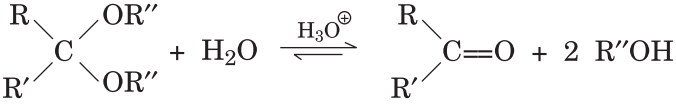
Propanal + Methanol ⇌ A hemiacetal ⇌ An acetal

Acetals are obtained in high yield if water eliminated from the hemiacetal is removed from the reaction mixture as it is formed.

In the laboratory, this can be done in a variety of ways. A drying agent can be added that eliminates water by reacting with it. Alternatively, the water can be distilled out from the

reaction mixture as it is formed by using a Dean-Stark apparatus. Driving the equilibrium to the right-hand side by removing one of the products is an application of Le Chatelier's principle.

Because acetal formation is reversible, an acetal can be transformed back to the aldehyde or ketone if it is treated with dilute acid.



An acetal A carbonyl compound

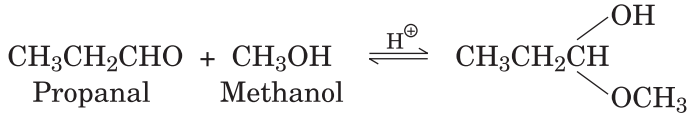
Base can also catalyse the formation of a hemiacetal from a carbonyl compound but not the formation of an acetal from a hemiacetal.

[**N.B.** whether the carbonyl compound is an aldehyde or a ketone, the product with an –OH and an –OR group and the product with two –OR groups bonded to the same carbon are called hemiacetal and acetal, respectively. Although the product with one –OH and one –OR group and the product with two –OR groups obtained from a ketone are often called hemiketal and ketal, respectively, these terms have now been dropped from IUPAC nomenclature.]

2.3.7 Mechanism for acid-catalyzed hemiacetal and acetal formation

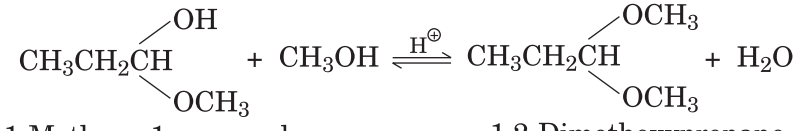
The mechanism for acid-catalyzed acetal formation takes place in two parts: the addition of one equivalent of alcohol to the C = O group of a carbonyl compound to form a hemiacetal, followed by the conversion of the hemiacetal to the acetal. The two parts for the acid-catalyzed conversion of propanal to 1,2-dimethoxypropane (an acetal) may be written as follows:

Part 1:



Propanal Methanol 1-Methoxy-1-propanol (a hemiacetal)

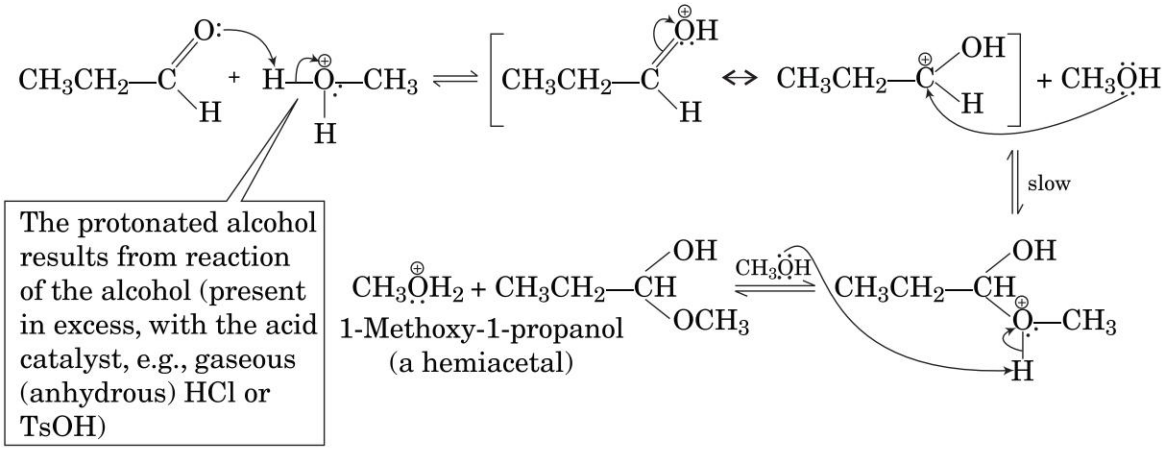
Part 2:



1-Methoxy-1-propanol 1,2-Dimethoxypropane (an acetal)

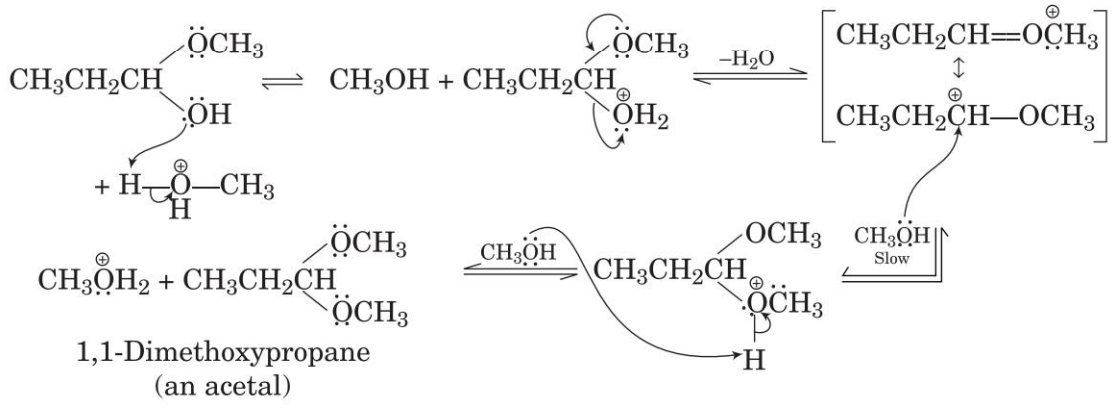
Mechanism for acid-catalyzed hemiacetal formation (Part 1)

The reaction proceeds through the following three steps. In the first step, the carbonyl compound undergoes protonation to form an oxonium cation and becomes more susceptible to nucleophilic attack. In the second step, the nucleophile (CH_3OH) attacks the carbonyl carbon to form a protonated tetrahedral intermediate. It is the rate-determining step of the reaction. In the third step, loss of a proton occurs from the intermediate to yield a hemiacetal.



Mechanism for acid-catalyzed acetal formation (Part 2)

The reaction proceeds through the following four steps (4th–7th). In the fourth step, the –OH group in hemiacetal undergoes protonation and becomes a good leaving group (H_2O). In the fifth step, loss of water takes place to form a resonance-stabilized cation. It is the rate-determining step of the reaction. In the sixth step, the resonance-stabilized cation undergoes nucleophilic attack by CH_3OH to form a protonated acetal and in the seventh and final step, loss of a proton takes places to form the acetal 1,1-dimethoxypropane.



2.3.8 Mechanism for Base-catalyzed hemiacetal formation (base-catalyzed acetal formation does not take place)

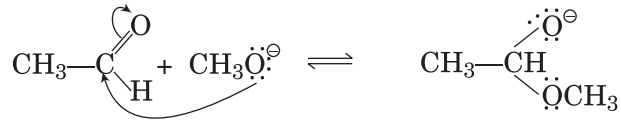
The following reaction proves that hemiacetal formation may also be catalyzed by base:

$$CH_3CHO + CH_3OH \xrightarrow{CH_3O^{\ominus}} CH_3CH(OH)CH_3$$

Acetaldehyde — A hemiacetal

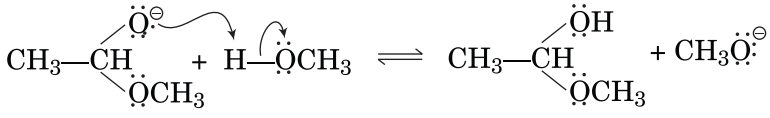
The reaction proceeds through the following two steps:

Step 1: The aldehyde undergoes nucleophilic attack by $CH_3\ddot{O}:^{\ominus}$ on the carbonyl carbon to form an alkoxide intermediate.



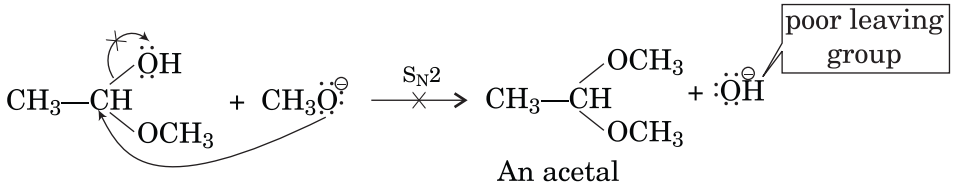
Acetaldehyde — An alkoxide

Step 2: A proton is abstracted by the alkoxide intermediate from methanol to form the hemiacetal.



A hemiacetal

The base-catalyzed acetal formation would require the displacement of $OH^{\ominus}$ by $CH_3O^{\ominus}$. But this reaction is most unfavourable and does not take place because the hydroxide ion (a strong base) is a very poor leaving group. For this reason, formation of acetal from hemiacetal cannot be catalyzed by a base. That is, in base, the reaction cannot go beyond hemiacetal formation.

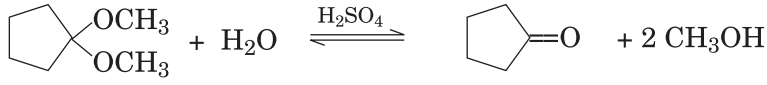


An acetal (not obtained)

2.3.9 Hydrolysis of acetals

Conversion of an aldehyde or ketone to an acetal is a reversible reaction. Therefore, an acetal can be easily hydrolyzed to an aldehyde or ketone by treatment with aqueous acid.

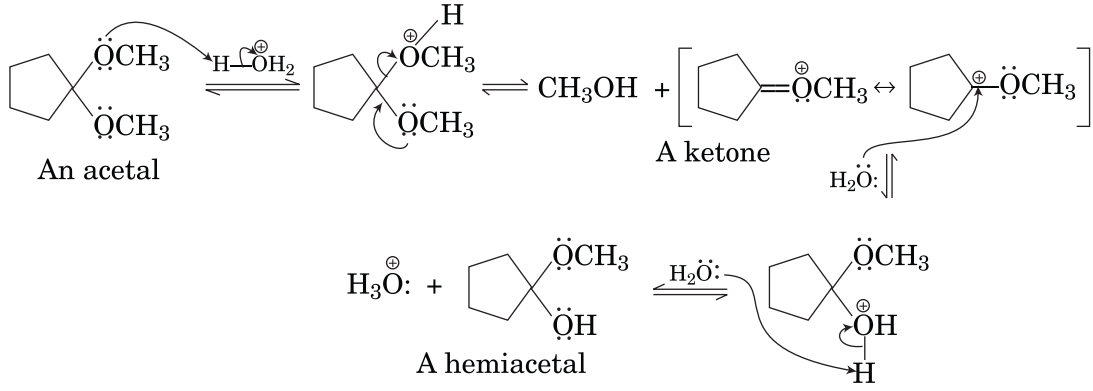
In the presence of a large excess of water, the equilibrium is driven to the left following the Le Chatelier's principle. For example:



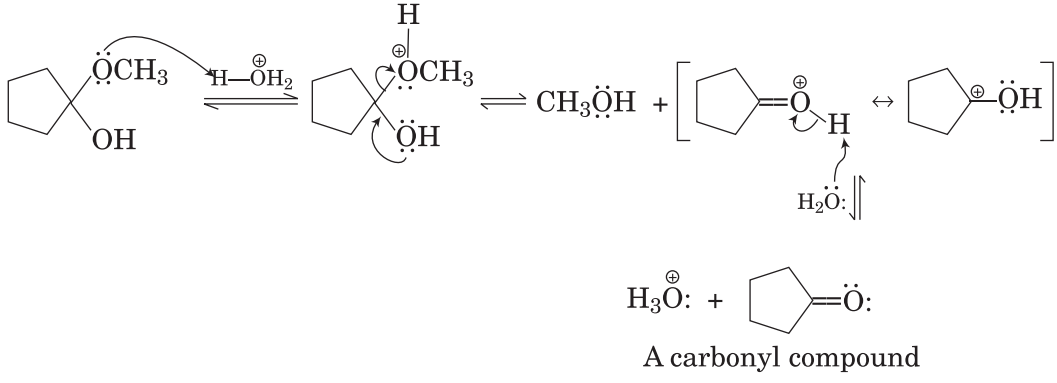
An acetal A ketone

Mechanism The mechanism for the hydrolysis of an acetal is the reverse of the formation of acetal and involves two parts: conversion of the acetal to the hemiacetal, followed by conversion of the resulting hemiacetal to the carbonyl compound.

Mechanism for the conversion of acetal to the corresponding hemiacetal The reaction, which involves elimination of a molecule of CH_3OH and addition of a molecule of water, proceeds through the steps as follows:

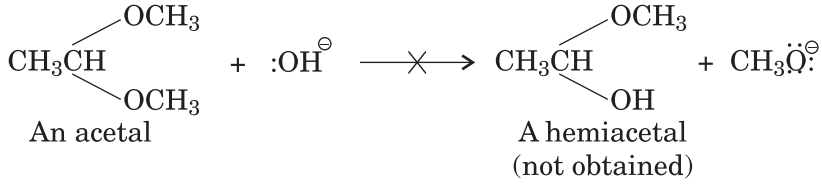


Mechanism for the conversion of hemiacetal to the corresponding carbonyl compound The reaction, which involves elimination of a molecule of CH_3OH and formation of a carbon-oxygen π bond, proceeds through the steps as follows:



It is to be noted that acetals are quite stable to hydrolysis by base. $RO^{\ominus}$ being a strong base is a poor leaving group and so, it cannot be displaced by the nucleophile $OH^{\ominus}$, i.e., an S_N2 reaction is unsuccessful in this case. Moreover, the backside attack is inhibited

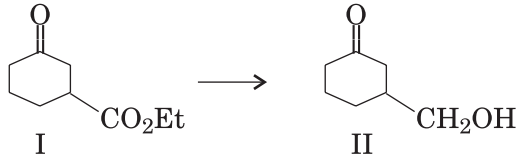
due to molecular overcrowding at the attacking site. For these reasons, acetals are quite stable to base-catalyzed hydrolysis. For example, 1,1-dimethoxyethane (an acetal) cannot be converted to the corresponding hemiacetal by treating with alkali.



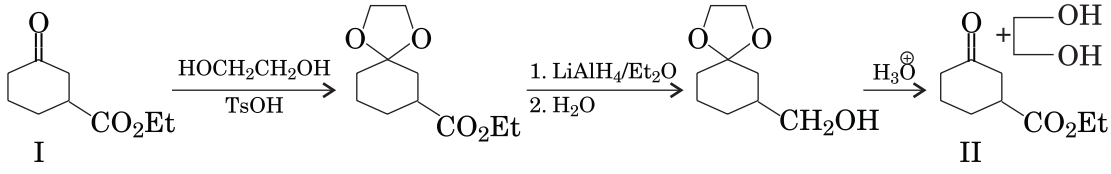
2.3.10 Acetals as protecting groups

If a compound contains more than one functional group that will react with a given reagent and we want only one of them to react, it is necessary to protect the second functional group from the reagent. A group that protects a functional group from a synthetic operation that it would not otherwise survive is known as a *protecting group*.

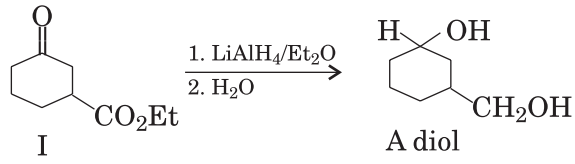
Although acetals are hydrolyzed to aldehydes or ketones in aqueous acid, they are quite stable to bases. Again, since they are ethers, they do not react with reducing or oxidizing agents. Because of these properties, acetals are used to protect aldehydes or ketones from undesired reactions in basic solution. When basic conditions are employed for some reaction on some other part of the molecule of a carbonyl compound, it is first converted into an acetal, the reaction is then carried out and finally, the original carbonyl group is regenerated by hydrolyzing the acetal with aqueous acid. As an example, let us consider the problem of converting compound I to compound II.



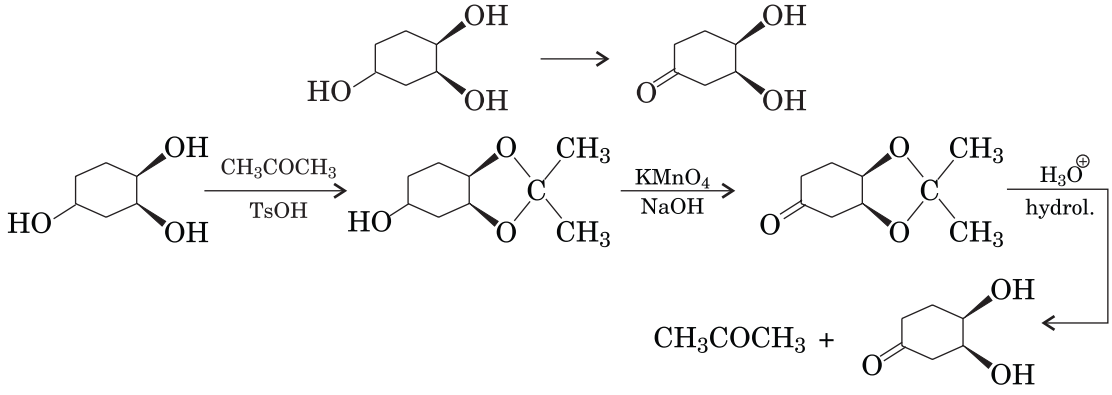
A keto group is more easily reduced than an ester group because it is relatively more reactive. Therefore, any reducing agent (e.g., $LiAlH_4$ or N_2/Ni) that can reduce the ester group of I reduces the keto group as well. But if the keto group is protected by converting it to a cyclic acetal (the ester group does not react), the ester group can be reduced in basic solution without affecting the cyclic acetal. After completion of the ester reductions, the desired product II can be obtained by hydrolyzing the cyclic acetal with aqueous acid.



If the C═O group is not protected before reduction, both of the functional groups will be reduced to form a diol.

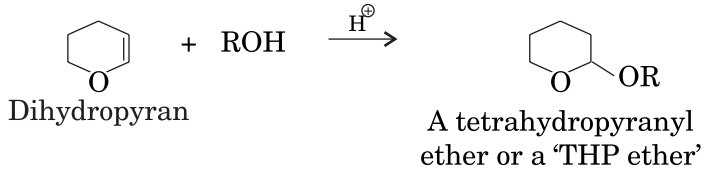


Acetals also offer a convenient method for protecting hydroxyl groups particularly in 1,2- or 1,3-position. The following conversation, for example, can be carried out by protecting the –OH groups, at C-1 and C-2. Also, they are *cis*-to each other.

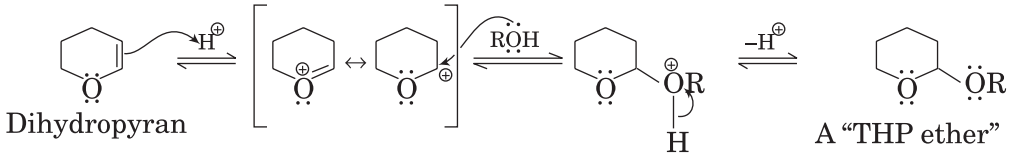


2.3.11 Tetrahydropyranyl group as a protecting group

Under acid catalysis (anhydrous HCl or H_2SO_4), an alcohol reacts with dihydropyran to give a tetrahydropyranyl ether (called a 'THP ether').



Mechanism The mechanism of the reaction involves the steps as follows:

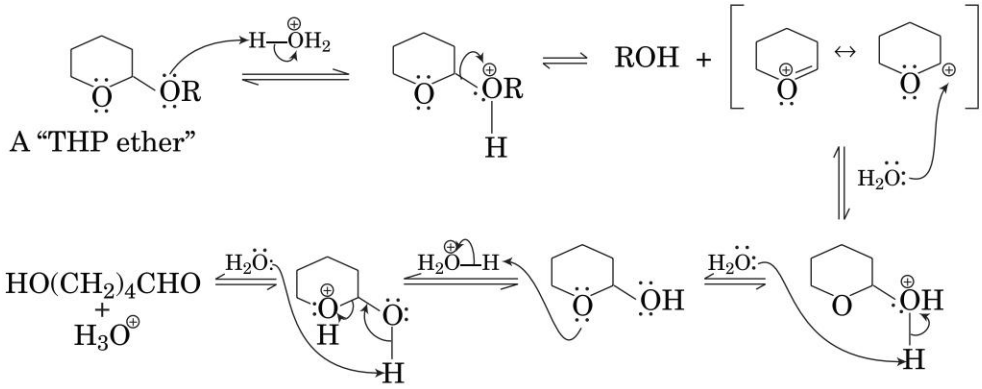


Dihydropyran undergoes protonation to form a resonance-stabilized carbocation. Nucleophilic attack by ROH on this carbocation followed by proton loss produces a tetrahydropyranyl ether.

The 'THP ether', being an acetal, is stable to base, but hydrolyzed by dilute acid. The tetrahydropyranyl group can be used as a protecting group for alcohols and phenols because it can be removed easily by treating the 'THP ether' with aqueous acid.



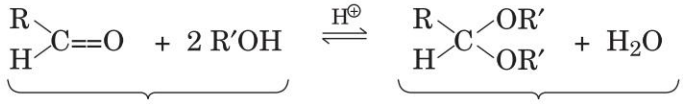
Mechanism The mechanism of the reaction may be given as follows:



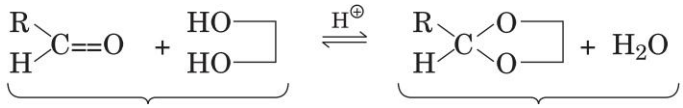
SOLVED PROBLEMS

1. **Formation of acetal is not a favoured reaction when ketones are allowed to react with simple alcohols in the presence of trace of anhydrous acid. However, formation of cyclic acetal is a favoured reaction when a ketone is treated with an excess of 1,2-diol in the presence of a trace of acid. Account for these observations.**

Solution These observations can be explained in terms of the $\Delta S°$ values of these two reactions involving a simple alcohol and 1,2-diol. When a ketone reacts with a simple alcohol to form an acetal, a decrease in the number of molecules occurs (three molecules to two molecules).

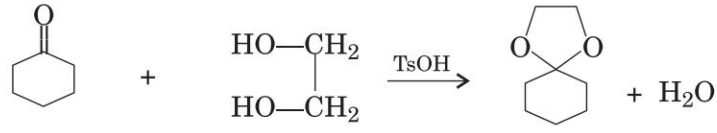


Therefore, there is considerable decrease in entropy ($\Delta S°$ is negative). Because of this unfavourable entropy contribution to the free energy, the reaction is less favourable (this becomes clear from the relation $\Delta G° = \Delta H° - T\Delta S°$). However, when a ketone reacts with a 1,2-diol to form a cyclic acetal, the number of product molecules remains equal to the number of reactant molecules.



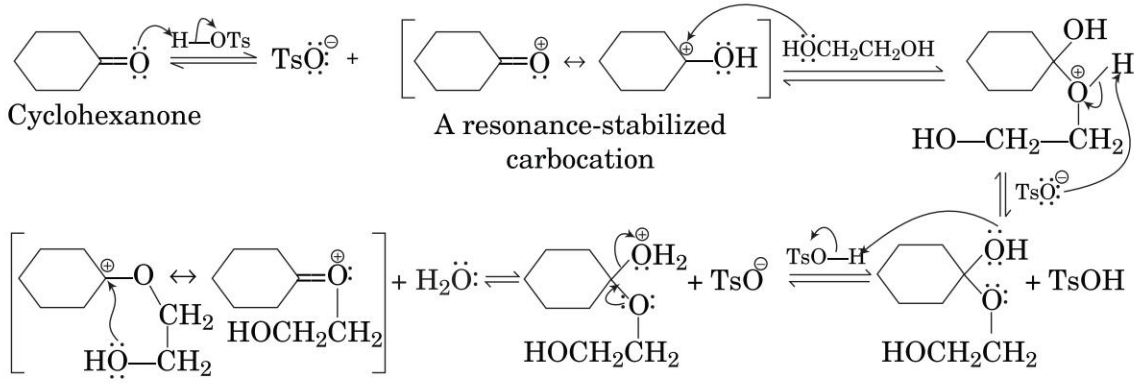
Therefore, the entropy effect is usually very small in this case. Because of this, the contribution of entropy to the free energy of the reaction is relatively more favourable. Formation of a cyclic acetal is, therefore, a favoured process as compared to the formation of a simple acetal.

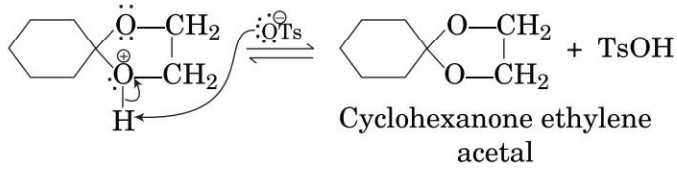
2. Draw a stepwise mechanism for the following reaction:



Cyclohexanone Ethylene glycol Cyclohexanone ethylene acetal

Solution The mechanism of the reaction leading to the formation of a cyclic acetals involves the steps as follows:

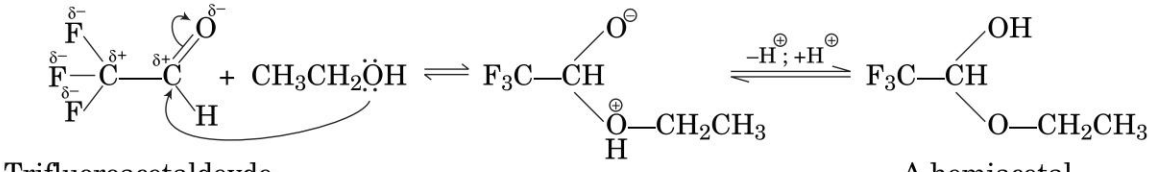




3. Trifluoroacetaldehyde (CF_3CHO) reacts rapidly with ethanol to form the corresponding hemiacetal. However, it gives acetal very slowly in the presence of anhydrous acid. Offer an explanation for this observation.

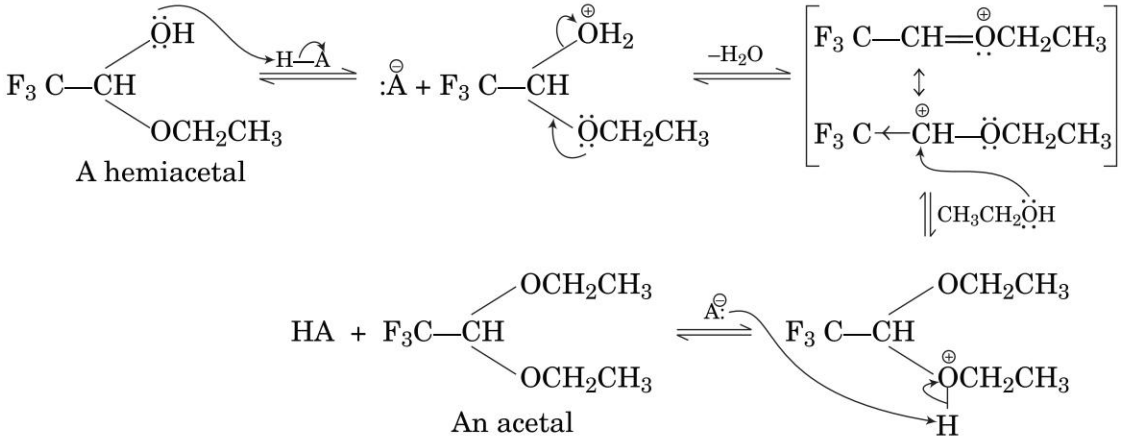
Solution Trifluoroacetaldehyde reacts rapidly with ethanol to form the corresponding hemiacetal because on nucleophilic attack on the carbonyl carbon by the alcohol molecule

the destabilization caused by the electron-attracting $-CF_3$ group (electrostatic repulsion between the two positively polarized carbon) is reduced considerably.



Trifluoroacetaldeyde A hemiacetal

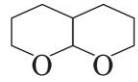
The hemiacetal is converted to the corresponding acetal very slowly in the presence of an acid catalyst because the electron-attracting (–I) $-CF_3$ group inhibits the loss of water from the protonated hemiacetal (the rate-determining step) to generate a destabilized carbocation in which the charge is considerably intensified.

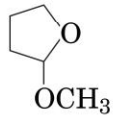


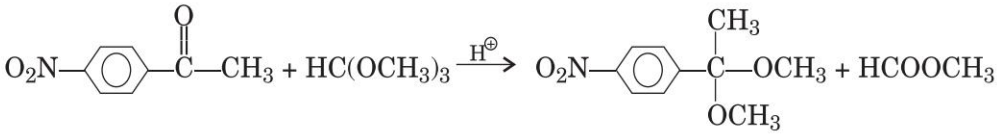
A hemiacetal

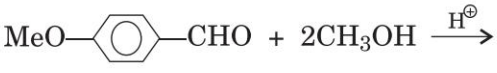
An acetal

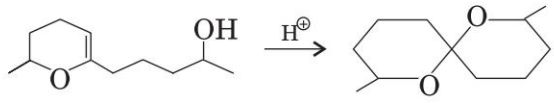
4. Suggest a mechanism for each of the following reaction:

(a) $(HOCH_2CH_2CH_2)_2CHCHO \xrightarrow{TsOH}$ 

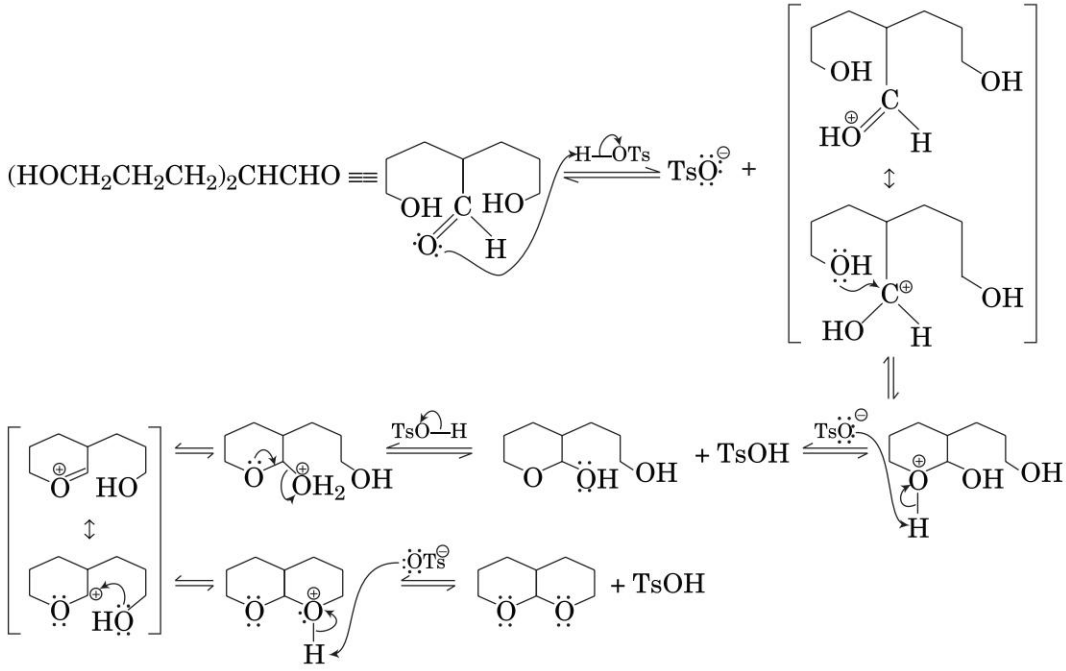
(b) $HOCH_2CH_2CH_2CHO \xrightarrow[TsOH]{CH_3OH}$ 

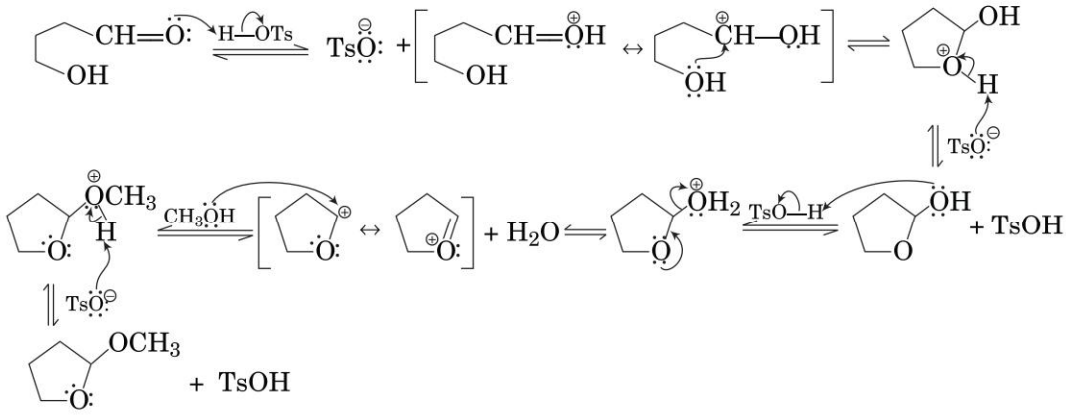
(c) 

(d) 

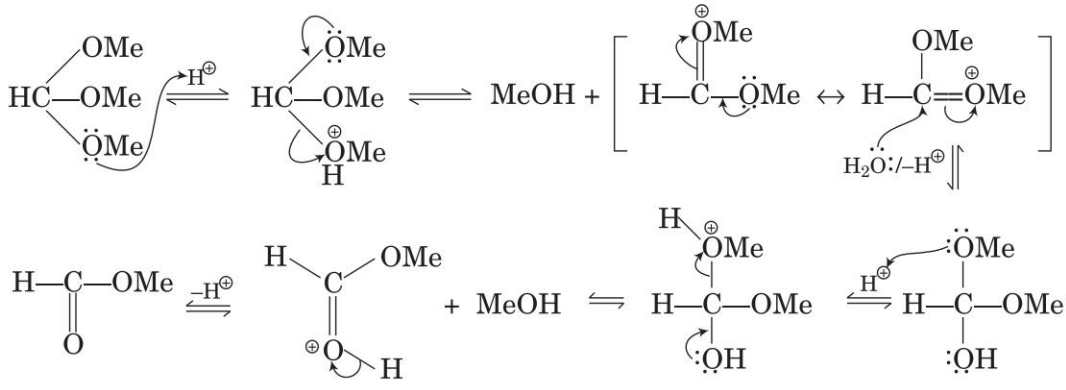
(e) 

Solution

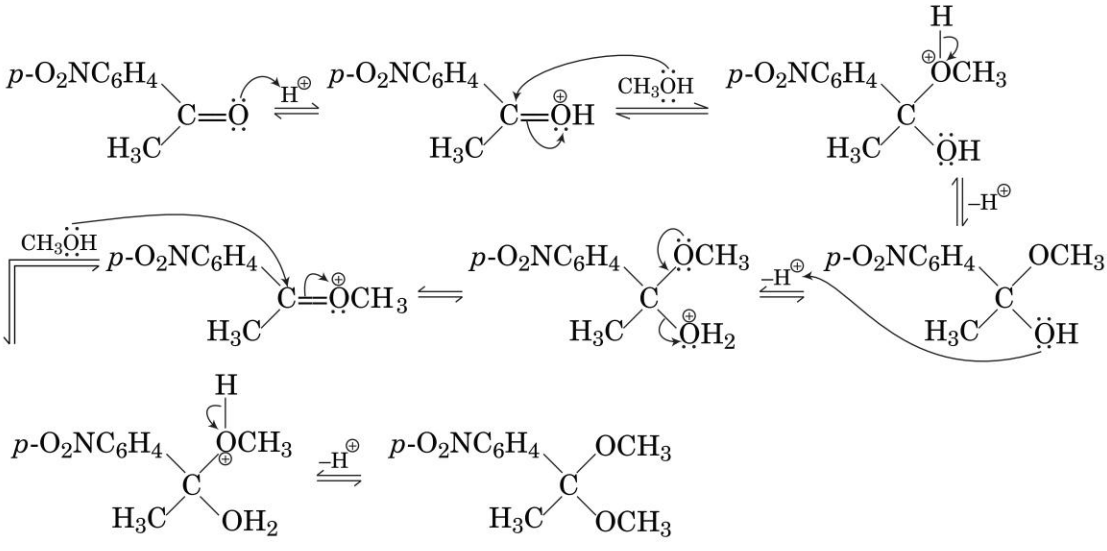
(a) 

(b) 

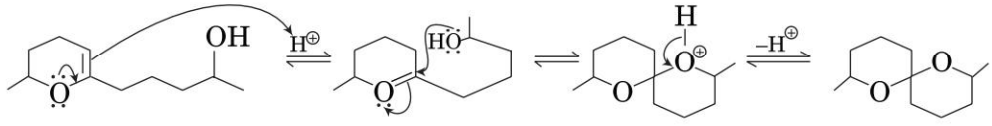
(c) The ortho-ester $HC(OMe)_3$ undergoes hydrolysis to yield to equivalents of MeOH and one equivalent of methyl formate (HCOOMe).



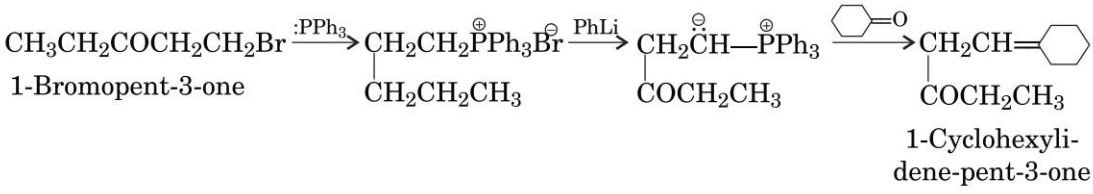
Methanol thus obtained reacts with $p-O_2NC_6H_4COCH_3$ in the presence of acid to yield an acetal.



(d)



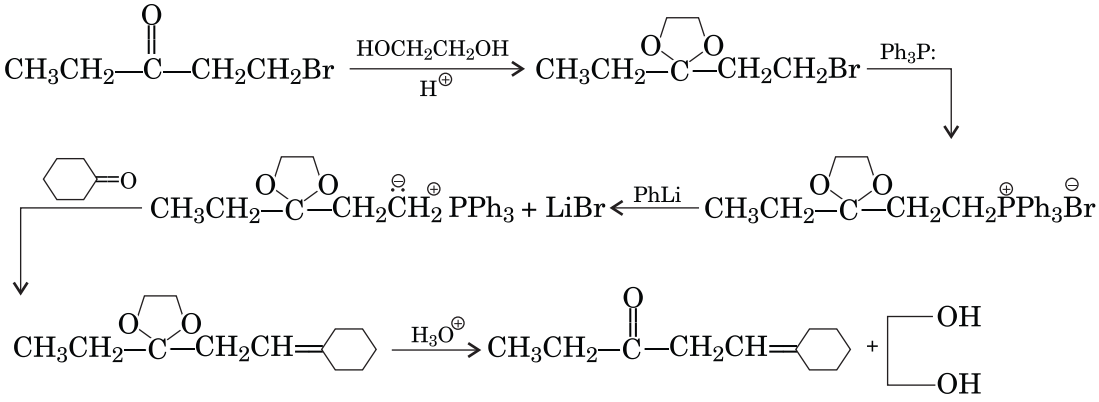
5. Explain why the following synthesis of 1-cyclohexylidene-pent-3-one involving the Wittig reaction fails.



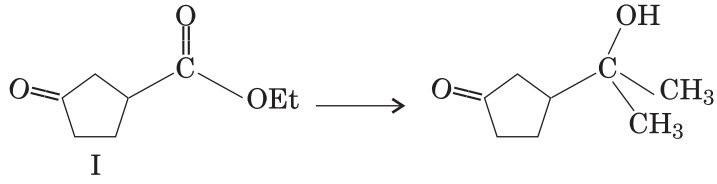
How can the desired compound be synthesized?

Solution The given synthesis of 1-cyclohexylidenepent-3-one involving the Wittig reaction fails because in the second step phenyl-lithium (PhLi) would attack irreversibly on the carbonyl carbon.

This ketone can, however, be synthesized by protecting the carbonyl group by forming a cyclic acetal.



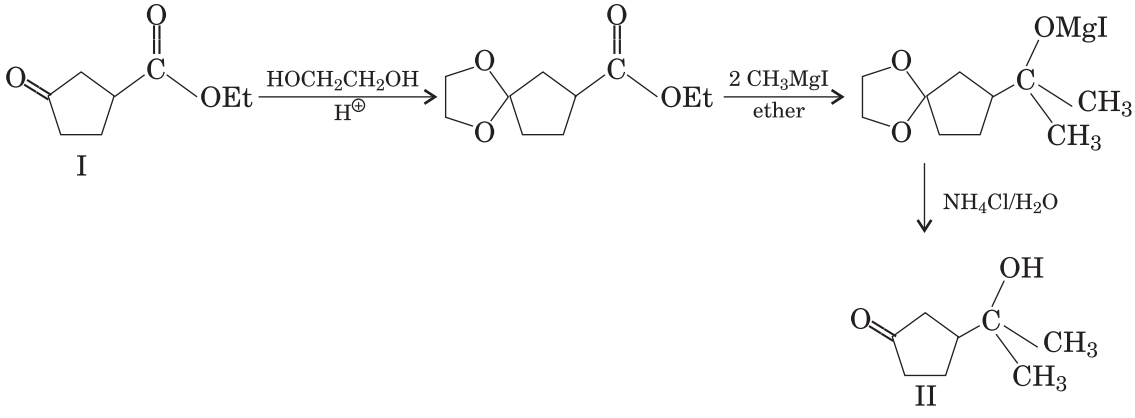
6. Show how might a cyclic acetal be used in carrying out the following transformation:



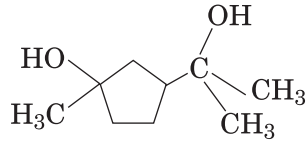
I

Explain why would a direct addition of CH_3MgI to I fail to yield II.

Solution This transformation can be carried out as follows:

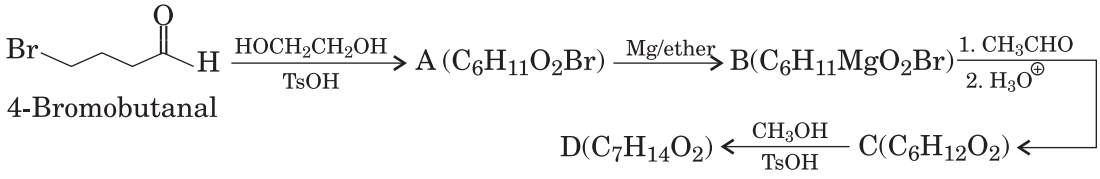


If the compound I is allowed to react directly with methylmagnesium iodide (MeMgI), addition takes place at the ketonic group as well as the ester group to give the following product (after hydrolysis):

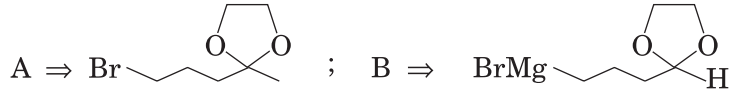


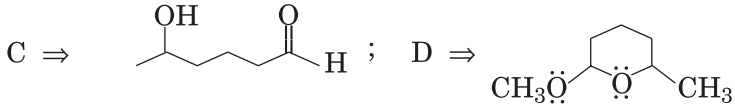
It is for this reason direct addition of CH_3MgI to I fails to yield II.

7. Identify the compounds A to D in the following reaction sequence (the compound C gives positive Tollens' test, but A and D do not):



Solution

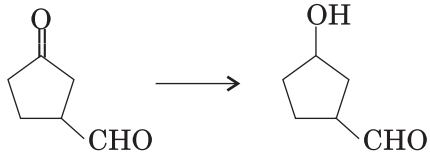




Since the compound C contains a free –CHO group, therefore, it gives positive Tollens' test.

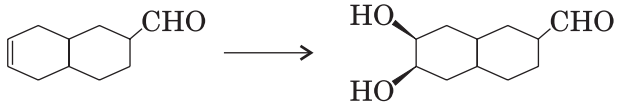
8. Show how you would accomplish the following transformations by way of acetals. Explain why such protection of the $\rangle C{=}O$ or the –OH function is required.

(a)

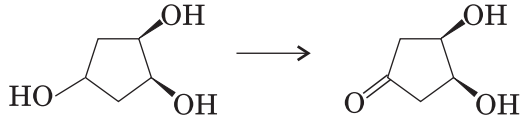


(b) $OHC-C_6H_4-CH_2CH_2CHO \longrightarrow HOCH_2-C_6H_4-CH_2CH_2CHO$

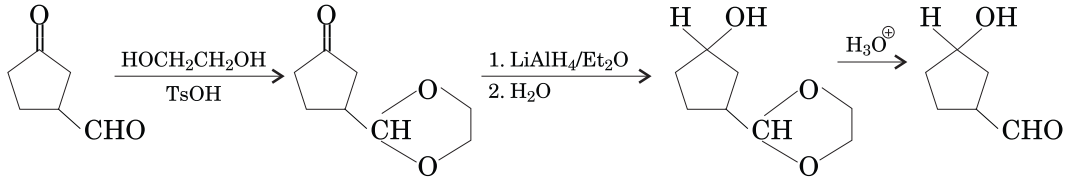
(c) $ClCH_2CH_2CH_2CHO \longrightarrow CH_3OCH_2CH_2CH_2CHO$

(d) 

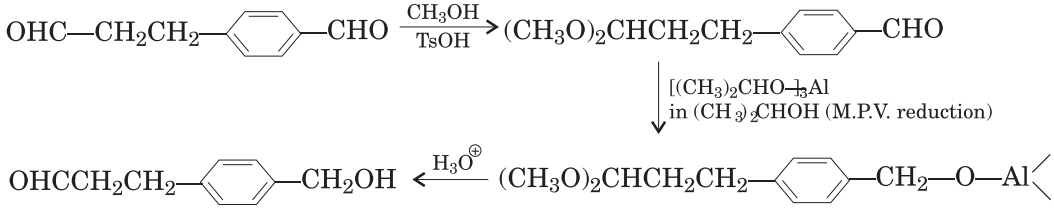
(e) $CH_3CH{=}CH{-}CHO \longrightarrow CH_3C{\equiv}C{-}CHO$

(f) 

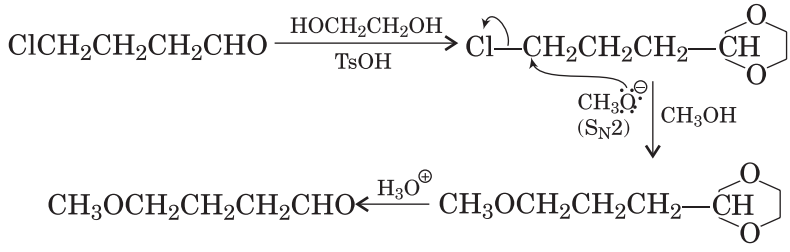
Solution

(a) 

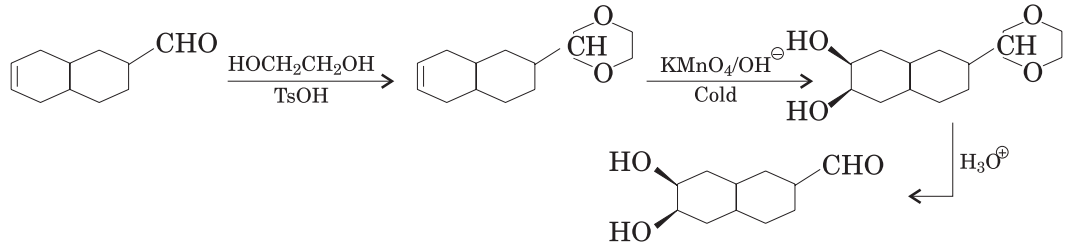
The –CHO group being relatively more reactive than the $\rangle C{=}O$ group is protected preferentially by forming acetal to avoid reduction with $LiAlH_4$.

(b) 

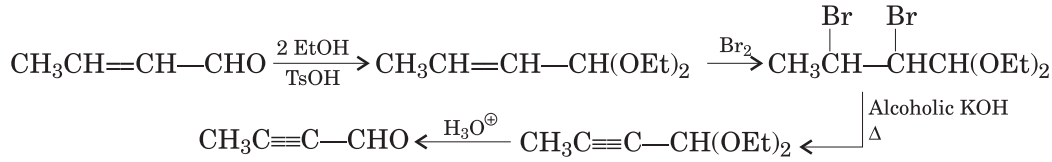
The –CHO group, which is not conjugated with the benzene ring, is more reactive and therefore, it is protected preferentially (when treated with MeOH/TsOH) to avoid reduction.

(c) 

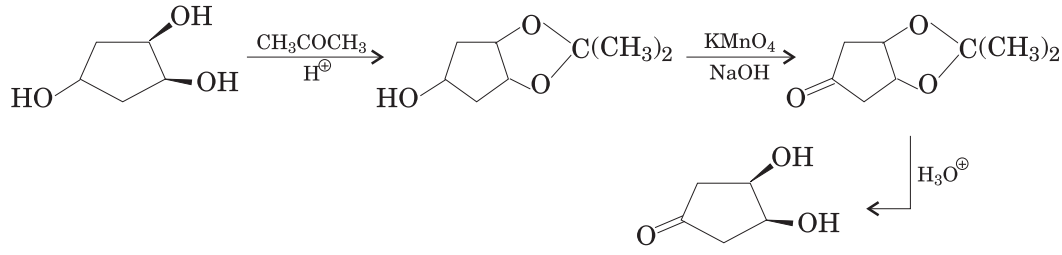
The –CHO group is protected to avoid base-catalyzed polymerization of the substrate.

(d) 

The –CHO group is protected to avoid oxidation by permanganate.

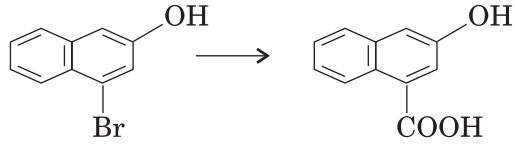
(e) 

The –CHO group is protected to avoid base-catalyzed polymerization of the compound obtained on addition of Br_2.

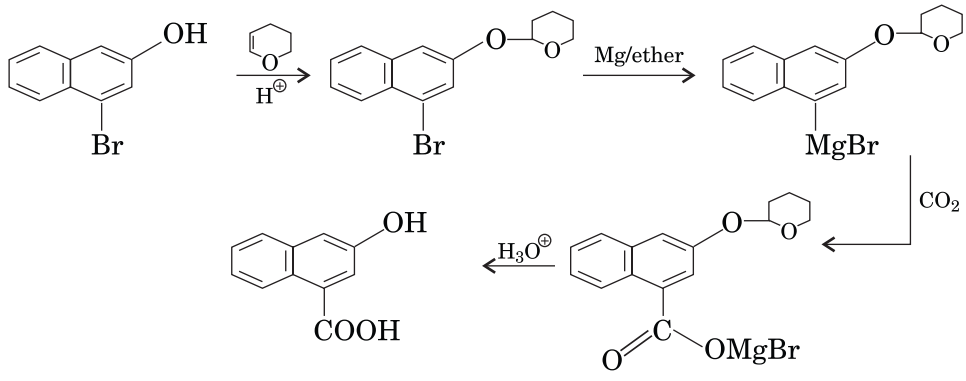
(f) 

The vicinal *cis* –OH groups are protected by forming an acetal to avoid oxidation by alkaline permanganate.

9. Show how you would accomplish the following transformation through the formation of a 'THP ether':



Solution

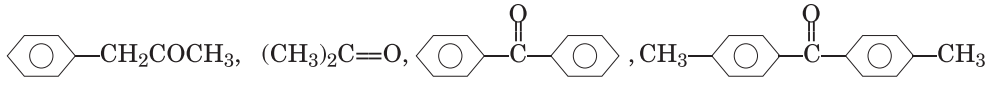


Study Problems

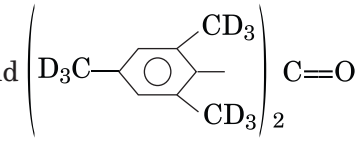
1. Arrange the following compounds in order of increasing reactivity towards nucleophilic addition and give your reasoning:

(a) $ClCH_2CHO$, $BrCH_2CHO$, CH_3CF_2CHO

(b) CH_3COCH_3, CF_3CHO, $CH_3CH{=}CHCHO$, CH_3CHO

(c) 

2. Rank the following carbonyl compounds in order of increasing reactivity nucleophilic attack and give your reasoning:

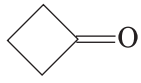
CD_3CHO, $PhCOCD_3$, PhCOPh, PhCDO and 

3. The hydrates of carbonyl compounds or *gem*-diols are generally too unstable to be isolated. Explain why the hydrates of the following carbonyl compounds can easily be isolated:

(a) CF_3COCF_3

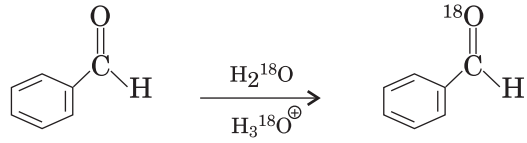
(b) PhCOCOCOPh

(c) Cl_3CCHO

(d) 

4. The formation of an acetal requires anhydrous acid, whereas in aqueous acid it undergoes ready hydrolysis. Explain.

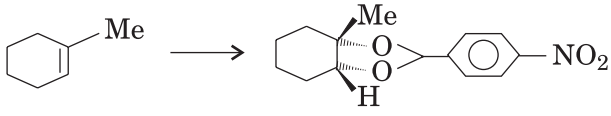
5. Propose a mechanism for the following reaction:



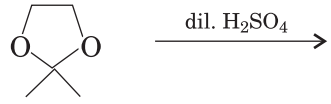
6. Provide reagents needed to accomplish each of the following transformations:

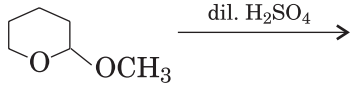
(a) 

(b) 

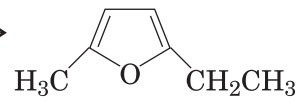
(c) 

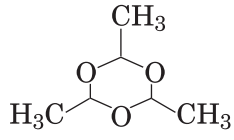
7. Predict the products expected to be formed in the following reactions:

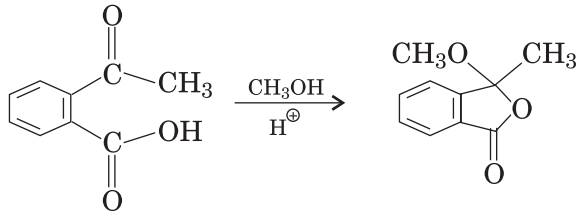
(a) 

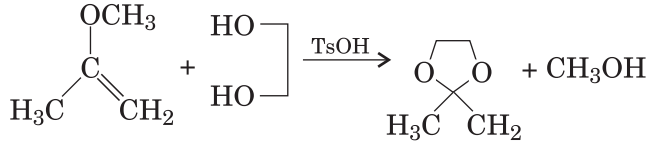
(b) 

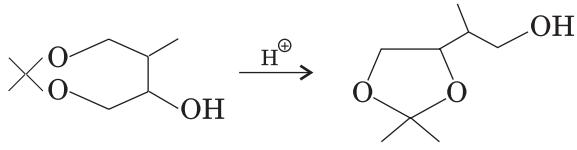
8. Suggest a mechanism for each of the following reactions:

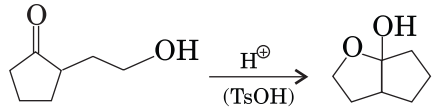
(a) $CH_3COCH_2CH_2COCH_2CH_3 \xrightarrow{H^\oplus}$ 

(b) $3\ CH_3CHO \xrightarrow{H^\oplus}$ 

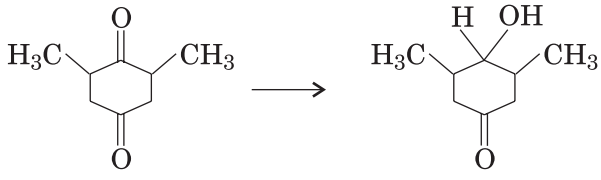
(c) 

(d) 

(e) 

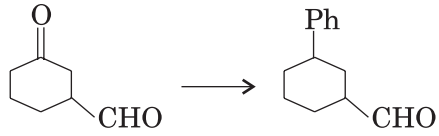
(f) 

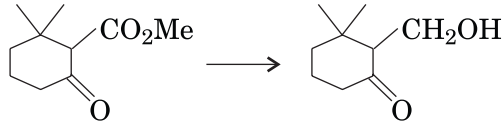
9. Show how you would accomplish the following transformations:

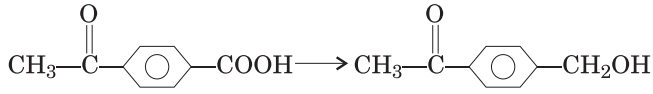
(a) 

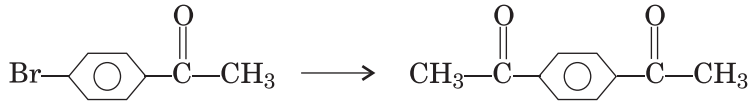
(b) $BrCH_2CH_2COCH_3 \rightarrow HC{\equiv}CCH_2CH_2COCH_3$

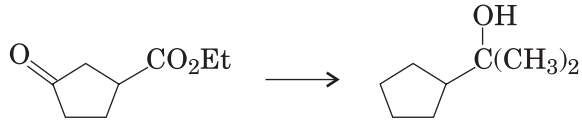
(c) $CH_3COCH_2CH_2C{\equiv}CH \rightarrow CH_3COCH_2CH_2C{\equiv}CCH_3$

(d) 

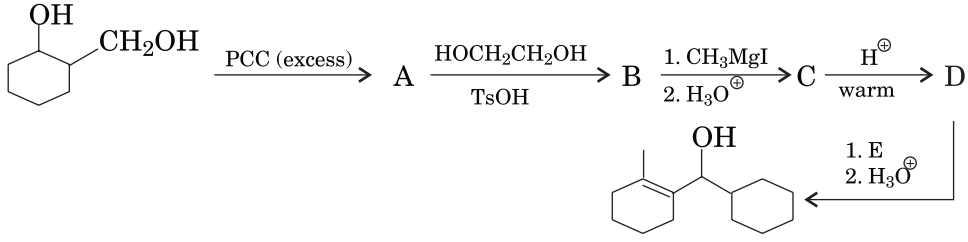
(e) 

(f) 

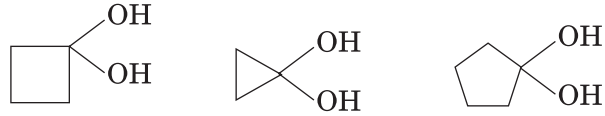
(g) 

(H) 

10. Write down the structures for compounds A through E:



11. Rank the following *gem*-diols in order of increasing stability towards dehydration and give your reasoning:

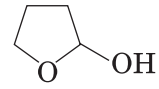


I II III

12. Explain the following results (position of equilibrium):

(a) $(CH_3)_2CHCOCH_3 + CH_3OH \overset{H^{\oplus}}{\rightleftharpoons} (CH_3)_2CH-\underset{\displaystyle CH_3}{\overset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}-OCH_3$ ($K_{eq} < 1$)

(a hemiacetal)

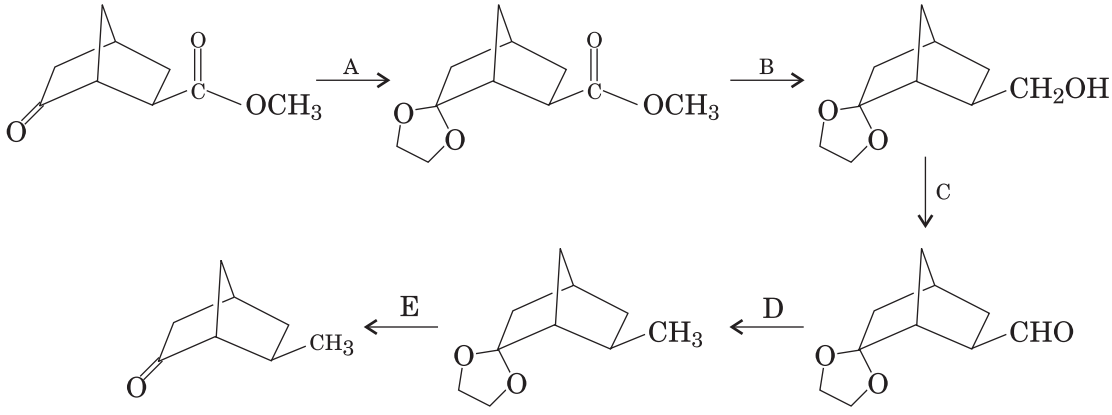
(b) $HOCH_2CH_2CH_2CHO \overset{H^{\oplus}}{\rightleftharpoons}$  $(K_{eq} > 1)$

(a hemiacetal)

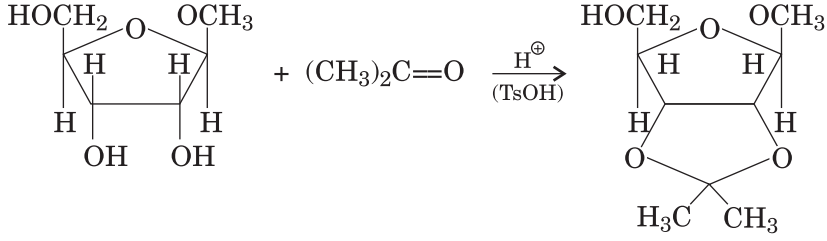
[**Hint:** The formation of a cyclic hemiacetal is the consequence of a more favourable entropy contribution to the free energy of the reaction.]

13. Explain why an ortho ester, $RC(OR')_3$, undergoes hydrolysis at a faster rate than an acetal $RCH(OR')_2$, which in turn undergoes hydrolysis at a faster rate than an ether, RCH_2OR'.

14. Suggest reagents (A—E) appropriate for each step of the following reaction sequence:



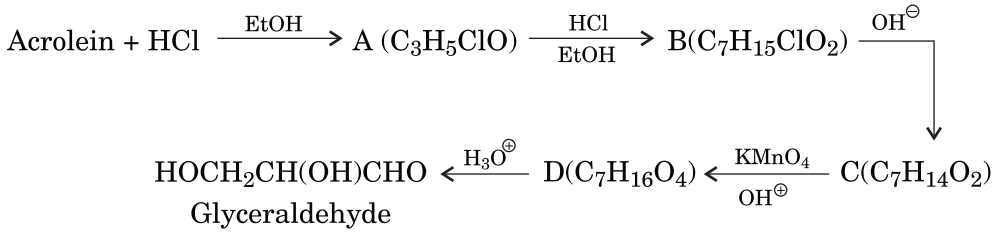
15. Methyl β-ribofuranoside reacts with acetone to give a compound which is acid-labile but base-stable.



(a) Propose a mechanism for this reaction.

(b) Explain why these two hydroxyl groups the are ones that reacted.

16. Provide structures for compounds A through D and give mechanisms for their formations:



17. Draw the structures of the hemiacetals expected to be formed from the hydroxy aldehydes I and II. Explain why this cyclization process givens an optically active product from II, but an optically inactive product from I.



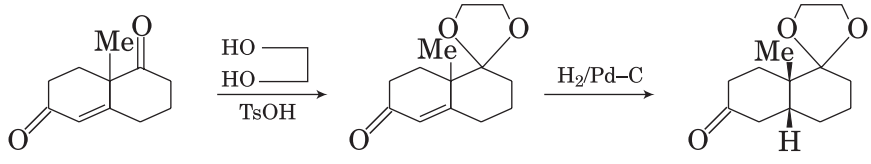
I II

18. Devise a synthesis to convert cyclohexanone and 4-bromobutanal to the hydroxyaldehyde A:

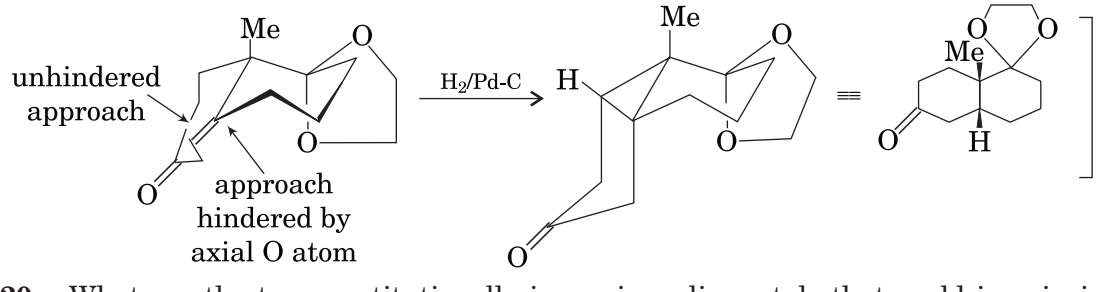


Cyclohexanone α-bromobutanal A

19. Account for the chemoselectivity of the first step reaction and the steroeoselectivity of the second step reaction.



[**Hint:** One C═O group is conjugated but the other is not. Since acetal formation is thermodynamically controlled, the nonconjugated C═O group reacts to form acetal. A conformational diagram of the intermediate shows that there is an axial oxygen atom belonging to the acetal preventing the bottom face of the alkene from getting close to the catalyst. The axial–Me group is further away and more in the plane of the plane of the double bond.



20. What are the two constitutionally isomeric cyclic acetals that could in principle be found in the acid-catalyzed reaction of acetone (propanone) and glycerol (1,2,3-propanetriol)? In fact only one of the two isomeric compounds is formed which can be resolved into enantiomers. Which isomer is the one that is produced?

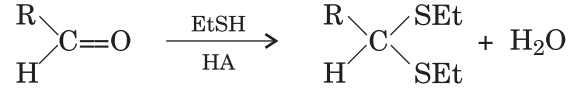
21. Account for the fact that anhydrous acids bring about formation of acetals, whereas aqueous acids bring about hydrolysis of acetals.

22. The equilibrium constants for hydration of compounds containing –COCOCO– grouping are very large. Account for this observation.

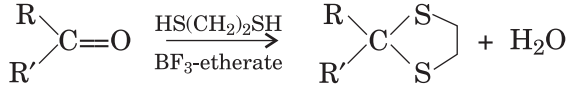
2.4 ADDITION OF SULPHUR NUCLEOPHILES: THIOLS (RSH) AND SODIUM BISULPHITE ($NaHSO_3$)

2.4.1 Addition of thiols

Thiols (RSH), the sulphur analogs of alcohols (ROH), readily react with aldehydes and ketones under acid catalyzed conditions (protic or Lewis acid) to form thioacetals.

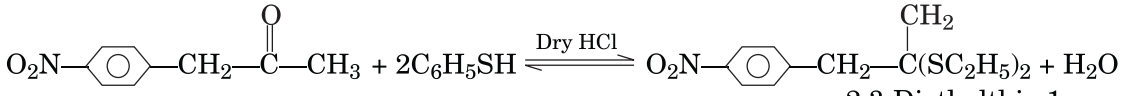


An aldehyde A thioacetal



A ketone A cyclic thioacetal

These reactions are, however, faster than the formation of acetals because the sulphur atom is more nucleophilic than the oxygen atom. An example of thioacetal formation is given below.

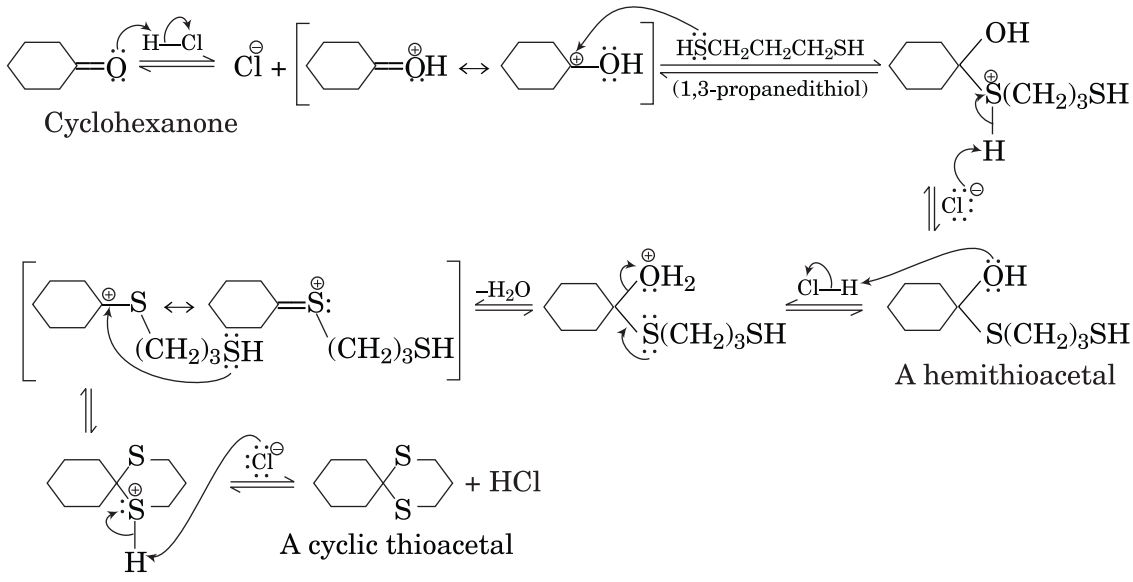


1-*p*-Nitrophenyl-2-propanone Ethanethiol 2,3-Diethylthio-1-*p*-nitrophenyl-propane (A thioacetal)

Hemithioacetals, the sulphur analogues of hemiacetals, are usually stable enough and can be isolated.

2.4.2 Mechanism for thioacetal formation

The mechanism for addition of a thiol to a carbonyl compound to form a thioacetal through the formation of a hemithioacetal is exactly the same as the mechanism for the addition of an alcohol to formation of a hemiacetal. The mechanism for the reaction between cyclohexanone with 1,3-propane dithiol in the presence of HCl to give the corresponding thioacetal may be shown as follows:

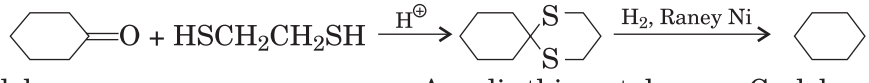


2.4.3 Thermodynamics for thioacetal formation

The formation of thioacetal in an exothermic process. In thioacetal formation, one C═O bond (bond energy: 176 kcal/mol) and two S—H bond (bonds energy: 83 kcal/mol) are broken, while two C—S bonds (bond energy: 65 kcal/mol and two O—H bonds (bond energy: 111 kcal/mol) are formed. Therefore, $\Delta H°$ = (–65 × 2) + (–111 × 2) – [(–176) – (–83 × 2)] = –10 kcal/mol. Since $\Delta H°$ is negative the reaction is exothermic.

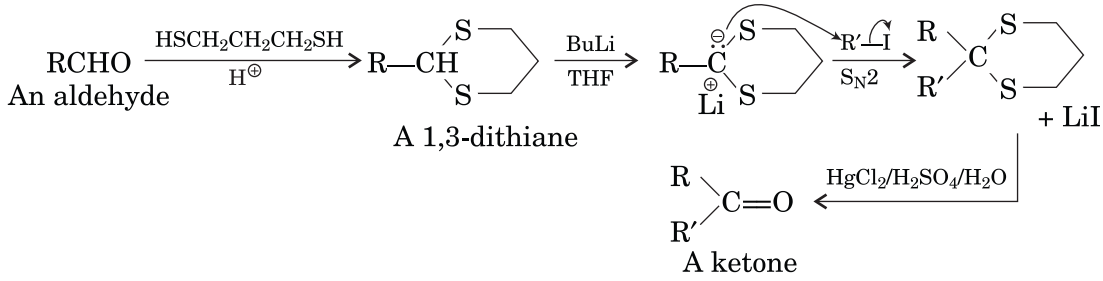
2.4.4 Importance of thioacetals in organic synthesis

If the carbonyl-containing compound is sensitive to both acids and bases, then it cannot be reduced using either the Clemmensen reduction (acidic conditions) or the Wolff-Kishner reduction (basic conditions). However, a carbonyl group $\rangle C{=}O$ can be converted to a methylene group (—CH_2—) without using extremes of pH. This is done by converting the carbonyl group to a thioacetal group and then reducing this product with Raney nickel catalyst that contains adsorbed hydrogen. This last step is called 'desulfurization' which replaces the C—S bonds with C—H bonds. For example:



Thioacetals are stable in aqueous acid. However, they can be readily decomposed by $HgCl_2$/$CdCO_3$, aq. acetone or $HgCl_2/H_2SO_4/H_2O$. Therefore, thioacetals are useful protective function of the C═O group requiring protection for carrying out a reaction in acidic medium.

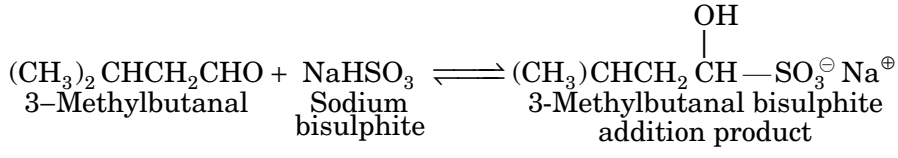
Thioacetals are also useful in organic synthesis by creating a reverse polarization at the carbonyl carbon of an aldehyde (*umpolung)* which may be a site for an electrophile. The hydrogen on the carbon flanked by the two S atoms is considerably acidic because the carbanion obtained on loss of that hydrogen is stabilized by delocalization to each S atom by *p-d* π bonding. An aldehyde can be easily converted to a ketone by taking this advantage.



Thioacetals are, therefore, important in organic synthesis. [It is to be noted that H atom on the carbonyl carbon of an acetal cannot be abstracted by a base because a carbanion, if formed, would not be stabilized by resonance since an oxygen atom does not have a *d* orbital for back bonding.]

2.4.5 Addition of sodium bisulphite ($NaHSO_3$)

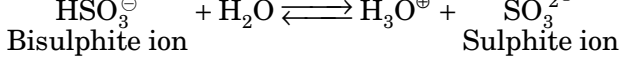
When aldehydes, methyl ketones and some cyclic ketones (generally seven-membered and smaller) are shaken with a concentrated aqueous solution of sodium bisulphite, $NaHSO_3$, they react to form nicely crystalline addition products commonly referred to as bisulphite addition products. For example, when 3-methylbutanal is treated with a saturated solution of sodium bisulphite, it produces the bisulphite adduct in good yield.



Addition of the large nucleophile $SO_3^{2\ominus}$ to the carbonyl carbon in very sensitive to steric hindrance because the groups attached to the carbonyl carbon become closer in the nearly tetrahedral transition state. And, for this reason, most higher ketones do not give bisulphite adduct in appreciable amounts.

2.4.6 Mechanism for bisulphite additions

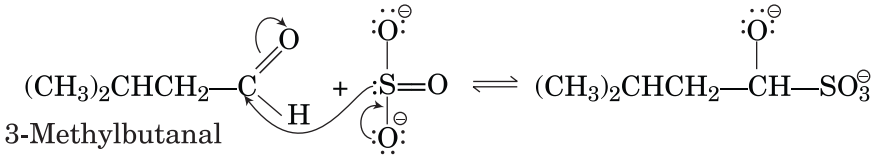
It is the sulphite ion (and not the bisulphite ion) which is involved in this addition reaction.



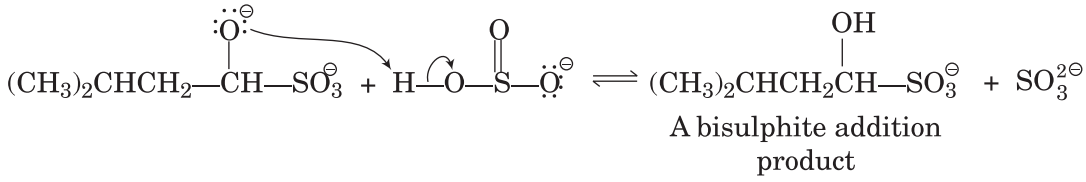
No catalyst is required in this reaction because sulphite is an effective nucleophilic agent in which sulphur is the attacking atom.

The mechanism of the reaction involves the steps as follows:

Step 1 The carbonyl carbon of 3-methylbutanal undergoes nucleophilic attack by the sulphite ion (an ambident nucleophile) through the sulphur atom and this is because sulphur is more nucleophilic (less electronegative, larger in size and more polarizable) than oxygen.

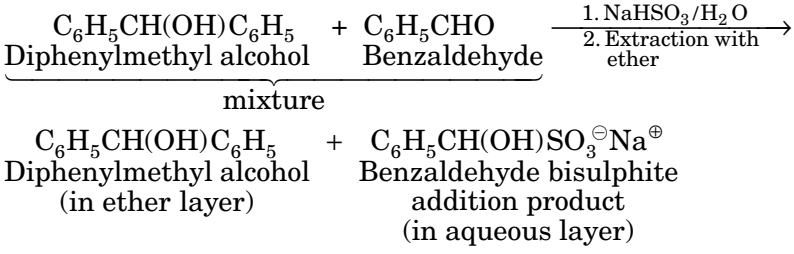


Step 2 $HSO_3^{\ominus}$ protonates the resulting compound to yield the bisulphite adduct.



2.4.7 Applications of bisulphite addition reaction

The bisulphite addition reaction is reversible and so, the addition product can be easily converted to the starting carbonyl compound when treated with dilute aqueous acid (dilute, HCl) or base (dilute, Na_2CO_3 solution) or with formaldehyde (HCHO). Thus, the formation of bisulphite addition products affords a convenient method for separating carbonyl compounds from non-carbonyl compounds. Benzaldehyde, for example, can be separated from diphenylmethyl alcohol by this procedure. When the mixture of these two compounds is shaken with a concentrated aqueous solution of sodium bisulphite ($NaHSO_3$), benzaldehyde is converted to its bisulphite adduct. The mixture is then extracted with ether. The alcohol dissolves in ether, while the adduct remains dissolved in an aqueous phase. The aqueous layer is then separated and treated with dil. HCl or dil. Na_2CO_3 solution or with formaldehyde when benzaldehyde regenerates.



$$C_6H_5CH(OH)SO_3^{\ominus}Na^{\oplus} \xrightarrow[\Delta]{HCl/H_2O} C_6H_5CHO + SO_2\uparrow + H_2O + NaCl$$

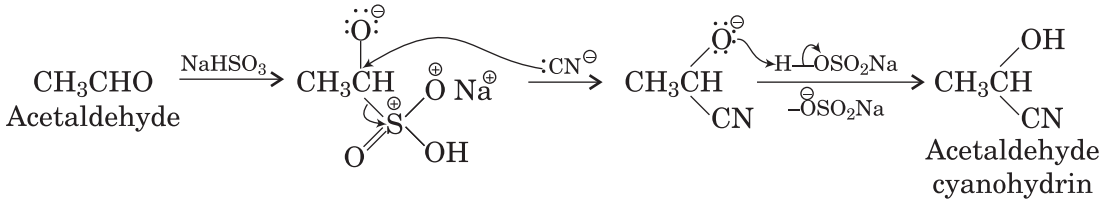
$$C_6H_5CH(OH)SO_3^{\ominus}Na^{\oplus} \xrightarrow[\Delta]{Na_2CO_3/H_2O} C_6H_5CHO + Na_2SO_3 + NaHSO_3$$

$$\underset{\text{(soluble in water)}}{C_6H_5CH(OH)SO_3^{\ominus}Na^{\oplus}} \xrightarrow[H_2O]{HCHO} C_6H_5CHO + \underset{\text{Formaldehyde bisulphite addition product}}{H_2C(OH)SO_3^{\ominus}Na^{\oplus}}$$

The bisulphite addition product of benzaldehyde (PhCHO) undergoes an exchange reaction with formaldehyde because formaldehyde is relatively more reactive than benzaldehyde in which the positive character of the carbonyl carbon is reduced by resonance interaction with the benzene ring.

The bisulphite compound of formaldehyde has a special significance. It is very difficult to work with formaldehyde (HCHO) because it is quite reactive to undergo polymerization. However, its bisulphite adduct is stable and can be used to regenerate monomeric formaldehyde when required.

Bisulphite addition products can be used in the preparation of cyanohydrin by avoiding the release of poisonous hydrogen cyanide (HCN) gas during the usual process (NaCN + H_2SO_4 or HCl). For example:



SOLVED PROBLEMS

1. Show how would you carry out the following transformations using thioacetal formation reaction:

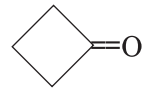
(a) $MeCHO \rightarrow MeCOCHMe_2$

(b) $p\text{-}H_3CC_6H_4CHO \rightarrow p\text{-}CH_3C_6H_4CH_3$

(c) $CH_3CH_2CHO \rightarrow CH_3CH_2CH_2CH_2CH_3$

(d) $C_6H_5CHO \rightarrow C_6H_5CDO$

(e) $CH_3CHO \rightarrow CH_3COCOCH_3$

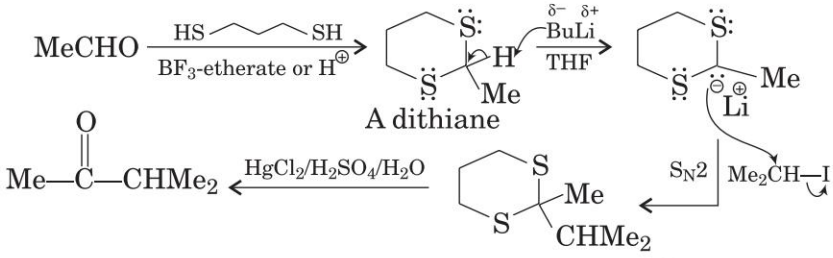
(f) HCHO → 

(g) PhCHO → $(S)-PNCO\overset{*}{C}HEt$ (Me)

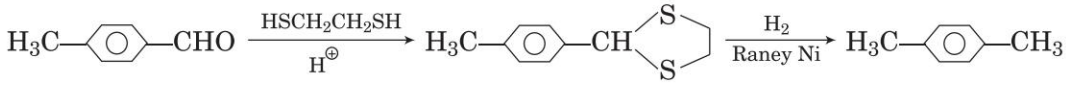
(h) $CH_3CHO \rightarrow CH_3COCH_2CH(OH)CH_3$

Solution

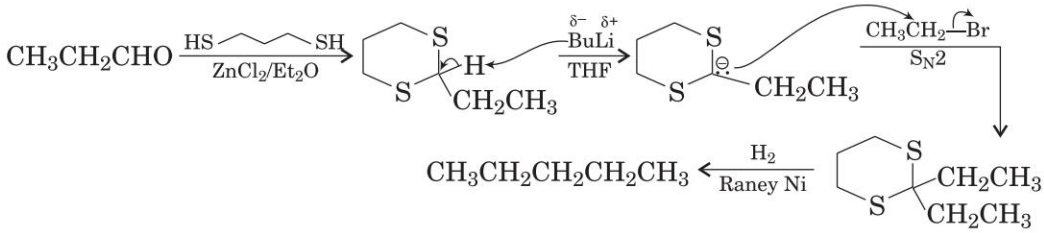
(a)



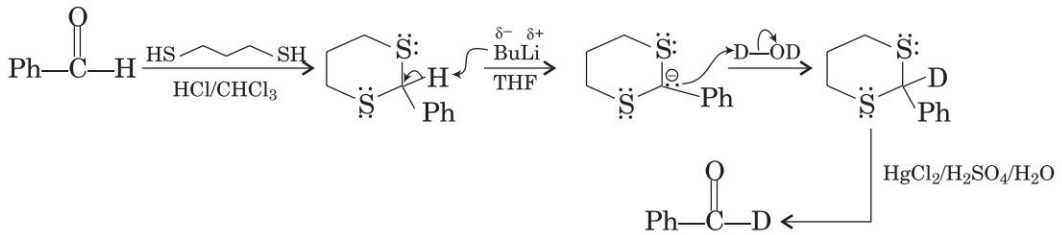
(b)



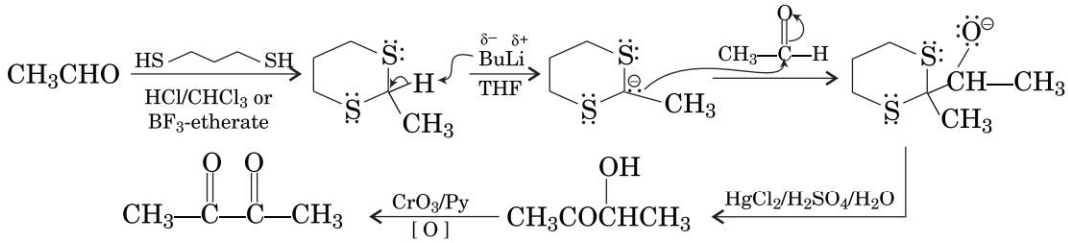
(c)



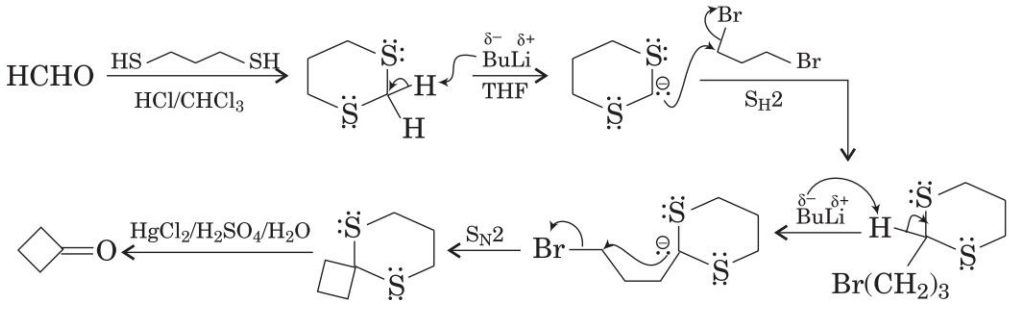
(d)

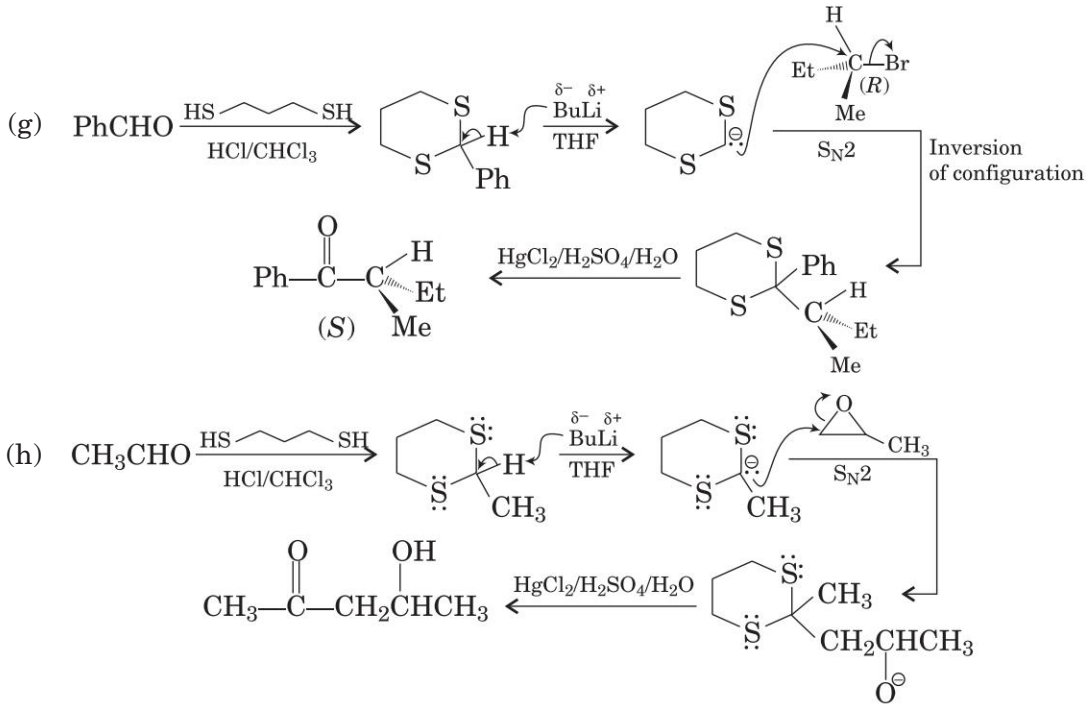


(e)



(f)



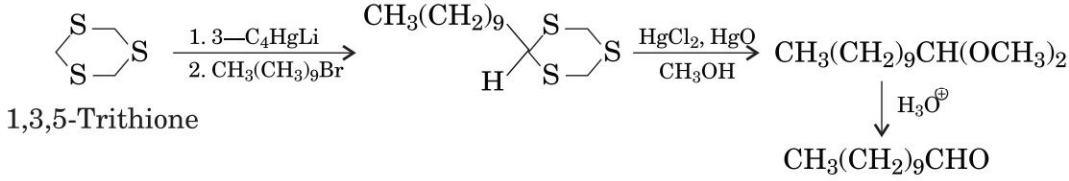


2. For the synthesis of aldehydes, 1,3,5-trithiane provides a convenient alternative to 1,3-dithiane. How would you carry out the following transformation using 1,3,5-trithiane?

$$CH_3(CH_2)_9\,Br \longrightarrow CH_3(CH_2)_9\,CHO$$

The trithiane method cannot be used to prepare ketones–why?

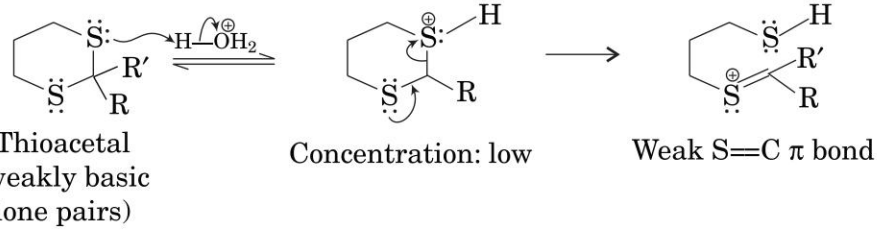
Solution

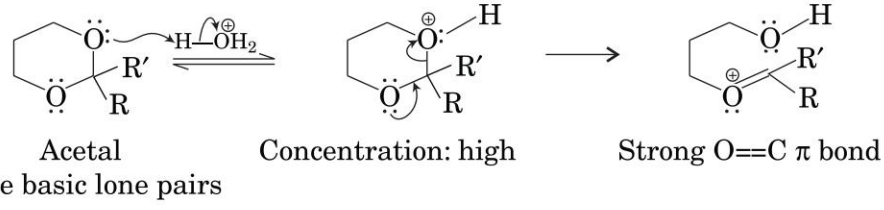


The trithiane method cannot be used to prepare ketones because further alkylation of 2-alkyl-1,3,5-trithianes occurs at the 4-position.

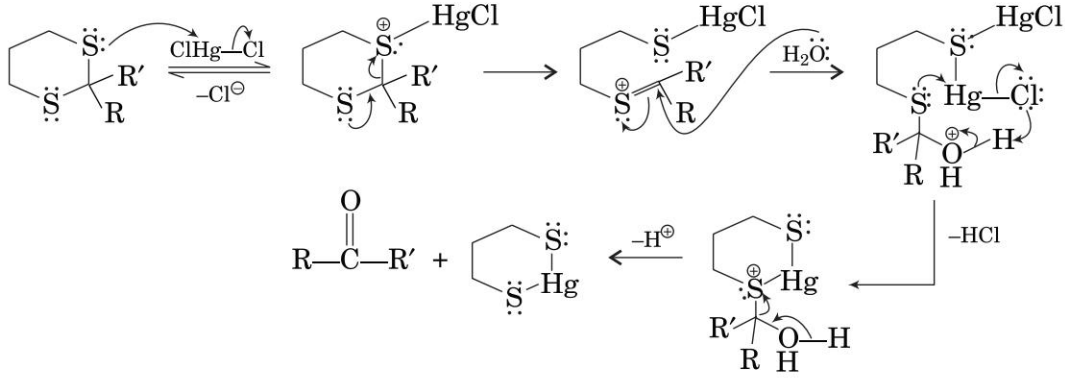
3. Although acetals regenerate the corresponding carbonyl compounds when treated with aqueous acid, 1,3-dithianes are stable in dilute acid. However, 1,3-dithianes can be decomposed by $HgCl_2$/dilute H_2SO_4 to yield the corresponding carbonyl compounds. Explain this observation.

Solution Due to the following two reasons, unlike acetals, thioacetals (1,3-dithianes) fail to undergo the normal acid-catalyzed hydrolysis: (i) since sulphur is less basic than oxygen, therefore, the concentration of the protonated species is much lower at a given pH, and (ii) the sulphur 3*p* lone pairs are less able to form a stable π bond to carbon (*p* orbitals are of dissimilar size) than are the oxygen 2*p* lone pairs (2*p*–2*p* overlap).



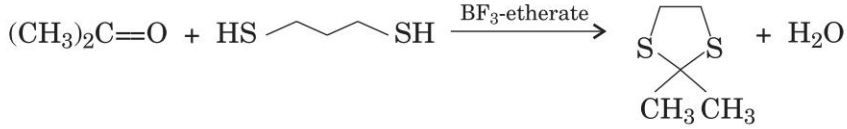


The hydrolysis of 1,3-dithianes can be carried out smoothly by using a Hg(II) reagent (e.g., $HgCl_2$) which is a better electrophile than $H^{\oplus}$. Strong coordination complexes are formed between Hg(II) and sulphides and the reaction is catalyzed by mercury which acts as a sulphur-selective Lewis acid. The reaction proceeds through the steps as follows:



Study Problems

1. Suggest a mechanism for the following reaction:



2. Predict the product obtained when phenylglyoxal (PhCOCHO) is allowed to react with two equivalents of $CH_2CH_2CH_2SH$. Give your reasoning.

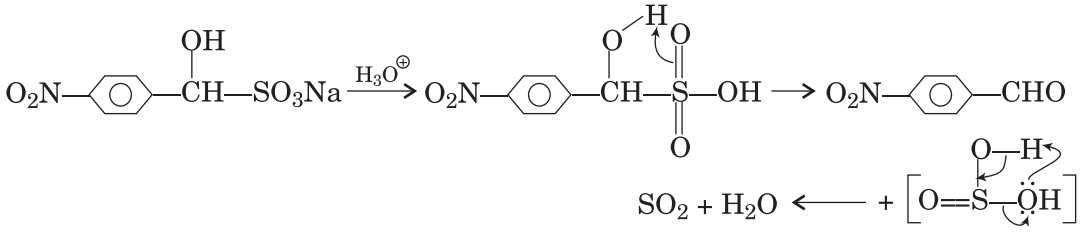
3. Explain why many ketones, including diisopropyl ketone, are unable to form stable bisulphite adducts.

4. Suggest a mechanism for each of the following reactions:

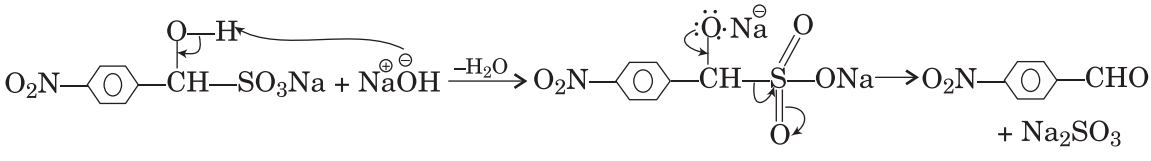
(a) $O_2N-C_6H_4-CH(OH)SO_3^{\ominus}\,Na^{\oplus} \xrightarrow[\Delta]{HCl/H_2O} O_2N-C_6H_4-CHO + NaCl + H_2O + SO_2\uparrow$

(b) $O_2N-C_6H_4-CH(OH)SO_3^{\ominus}\,Na^{\oplus} \xrightarrow[\Delta]{Na_2CO_3/H_2O} O_2N-C_6H_4-CHO + Na_2SO_3 + NaHSO_3$

[**Hint:** In acidic medium:



In alkaline medium $Na_2CO_3 + H_2O \rightleftharpoons NaHCO_3 + NaOH$



5. How would you carry out the following transformations by way of a thioacetal (dithiane)?

(a) $PhCHO \longrightarrow PhCH^{18}O$

(b) $Me-C_6H_4-CHO \longrightarrow Me-C_6H_4-COCO_2Me$

2.5 ADDITION OF HYDRIDE ION ($:H^{\ominus}$) AND ADDITION OF ELECTRONS

- **Reduction by lithium aluminium hydride ($LiAlH_4$), sodium borohydride ($NaBH_4$), borane (BH_3), diisobutylaluminium hydride, DIBAL-H ($Me_2CHCH_2AlHCH_2CHMe_2$)**
- **MPV reduction**
- **Cannizzaro reaction**
- **Tisehenko reaction**
- **Bouveault-Blane reduction**
- **Pinacolization of ketones**
- **Clemmensen reduction**

2.5.1 Reduction of carbonyl compounds by lithium aluminium hydride ($LiAlH_4$)

Lithium aluminium hydride, usually written as LAH, is a good hydride ion donor. It is one of the most used and versatile reducing agents in organic chemistry. It is capable of reducing efficiently the carbonyl groups of aldehydes, ketones, carboxylic acids and acid derivatives. It can also reduce a nitro group. However, it does not reduce a C═C or C≡C bond.

$LiAlH_4$ reduces an aldehyde, a carboxylic acid or an acid chloride to primary alcohol, an ester to a primary alcohol along with a primary, secondary or tertiary alcohol, a ketone to a secondary alcohol, an amide to an amine, and a nitrile to a primary amine.

$$\underset{\text{An aldehyde}}{R{-}CHO} \text{ or } \underset{\text{A carboxylic acid}}{RCOOH} \text{ or } \underset{\text{An acid chloride}}{RCOCl} \xrightarrow[2.\ H_3O^{\oplus}]{1.\ LiAlH_4/El_2O} \underset{\text{A 1° alcohol}}{RCH_2OH}$$

$$\underset{\text{An ester}}{RCOOR'} \xrightarrow[2.\ H_3O^{\oplus}]{1.\ LiAlH_4/El_2O} \underset{\text{A 1° alcohol}}{RCH_2OH} + \underset{\text{A 1° or 2° or 3° alcohol}}{R'OH}$$

$$\underset{\text{A ketone}}{RCOR} \xrightarrow[2.\ H_3O^{\oplus}]{1.\ LiAlH_4/El_2O} \underset{\text{A 2° alcohol}}{RCHOHR}$$

$$\underset{\text{An amide}}{RCONHR'} \xrightarrow[2.\ H_3O^{\oplus}]{1.\ LiAlH_4/El_2O} \underset{\text{An amine}}{RCH_2NHR'}$$

$$\underset{\text{A nitrile}}{RCN} \xrightarrow[2.\ H_3O^{\oplus}]{1.\ LiAlH_4/El_2O} \underset{\text{An amine}}{RCH_2NH_2}$$

The reduction of lithium aluminium hydride ($LiAlH_4$) requires anhydrous conditions because it reacts violently with water and the heat evolved is sufficient to ignite the liberated hydrogen gas which is highly inflammable.

$$LiAlH_4 + 4H_2O \rightarrow 4H_2\uparrow + LiOH + Al(OH)_3$$

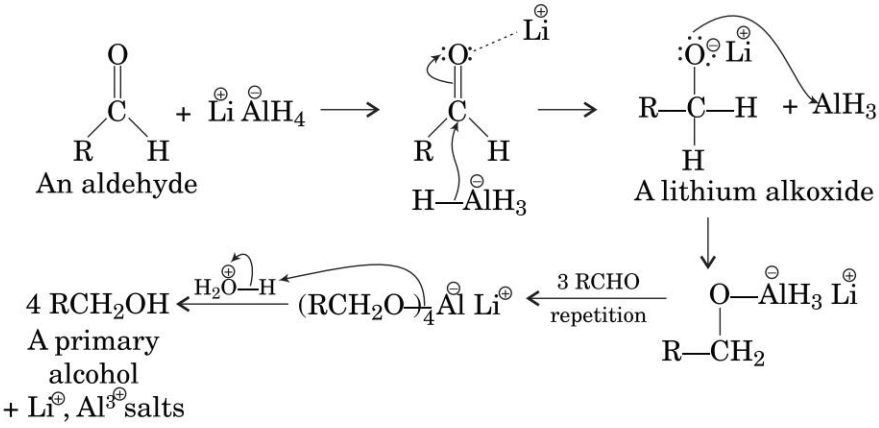
[$LiAlH_4$ can be prepared conveniently by treating $AlCl_3$ with an excess of LiH.

$$AlCl_3 + 4LiH \rightarrow LiAlH_4 + 3LiCl]$$

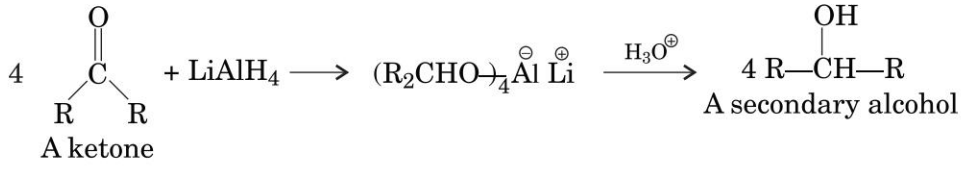
2.5.2 Mechanism for the reduction of carbonyl compounds by lithium aluminium hydride ($LiAlH_4$)

(i) **Reduction of aldehydes to primary alcohols and ketones to secondary alcohols:** The reaction involves nucleophilic attack of the hydride ion ($H^{\ominus}$) delivered from $AlH_4^{\ominus}$ to the electrophilic carbonyl carbon atom. The lithium ion

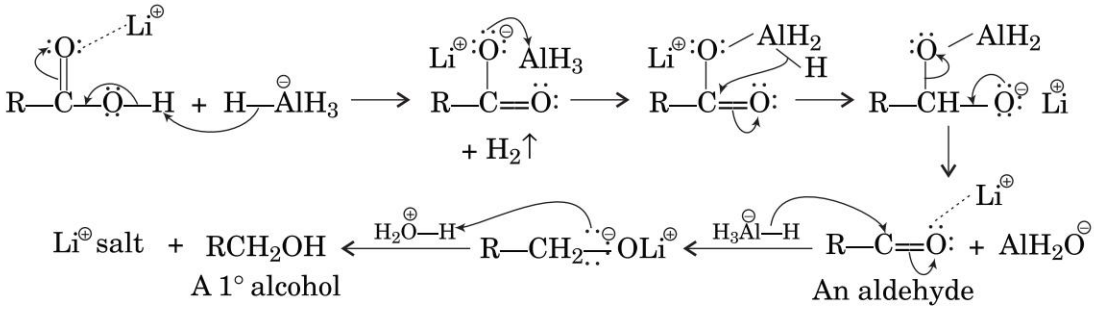
acts as a Lewis-acid catalyst by coordinating to the carbonyl oxygen. The addition product, an alkoxide salt, reacts with the better Lewis acid AlH_3 to form a lithium aluminium alkoxide which provides hydride ion for a subsequent step until all four hydrogen atoms are used. After the reduction is completed, the alcohol product exists as an aluminium complex. This complex is finally decomposed by an aqueous HCl solution (or even an aqueous solution of a weak acid such as NH_4Cl) to yield the alcohol. One mole of $LiAlH_4$ converts four moles of an aldehyde to four moles of 1° alcohol or four moles of a ketone to four moles of a 2° alcohol.



Similarly,

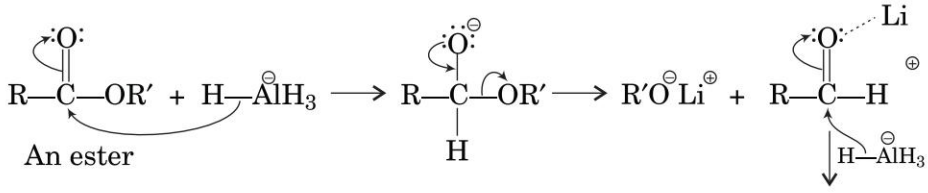


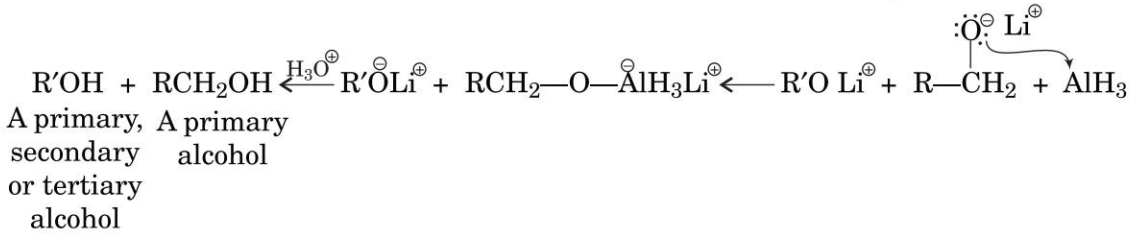
(ii) **Reduction of carboxylic acids to form primary (1°) alcohols:** In the first step of the reaction, the hydride ion (a strong base) reacts with the acid hydrogen of the carboxylic acid to form H_2. Then, two successive additions of hydride ion takes place with an aldehyde being formed as an intermediate.



(iii) **Reduction of esters to form a primary alcohol along with a primary, secondary or tertiary alcohol:** When an ester is allowed to react with hydride ion

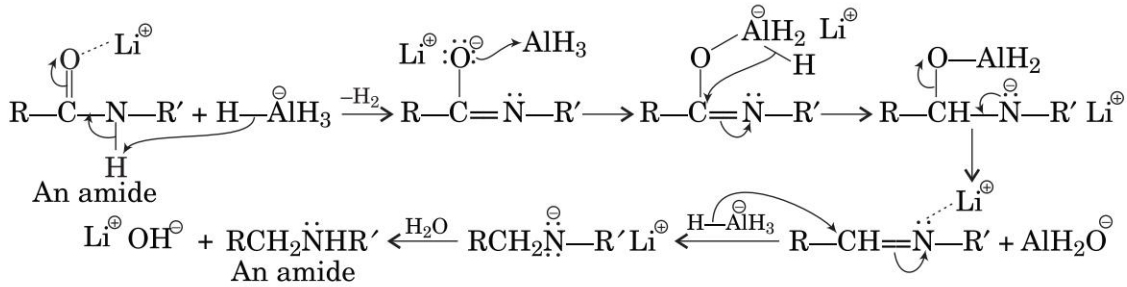
from $LiAlH_4$, the first reaction is a nucleophilic acyl substitution because an ester has a group (–OR′) that can be substituted by hydride ion. This reaction produces an aldehyde. The aldehyde then undergoes nucleophilic addition reaction with a second equivalent of hydride ion to form an alkoxide ion, which on protonation yields a primary alcohol. The reaction cannot be stopped at the aldehyde stage because an aldehyde is relatively more reactive than an ester towards nucleophilic attack.



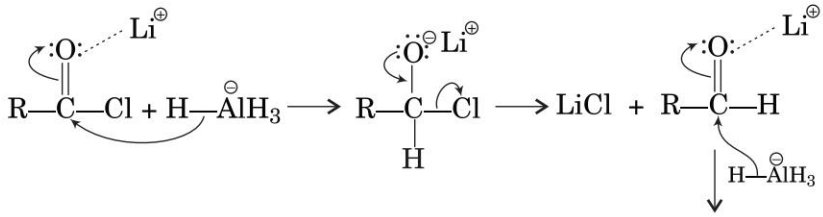


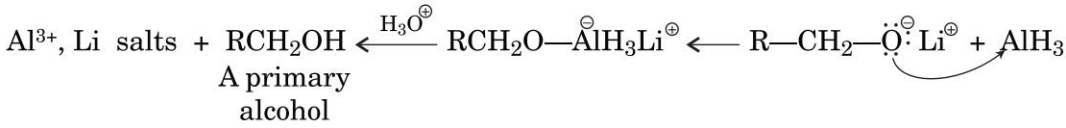
It is to be noted that the acyl group $\left(R-\overset{|}{C}=O\right)$ of an ester always converted into a primary alcohol (RCH_2OH) and the nature of the other alcohol depends on R′–, i.e., on the alcohol (1° or 2° or 3°) used to prepare the original ester.

(iv) **Reduction of amides to form amines:** When amides are allowed to react with $LiAlH_4$, they also undergo two successive additions of hydride ion. Depending on the number of substituents bonded to amide nitrogen, the product may be a primary, secondary or tertiary amine. Overall, a carbonyl group is converted into a methylene (–CH_2–) group in this reaction. Since H_2O rather than $H_3O^{\oplus}$ is used in the final step of the reaction, therefore, the product is an amine rather than ammonium ion.

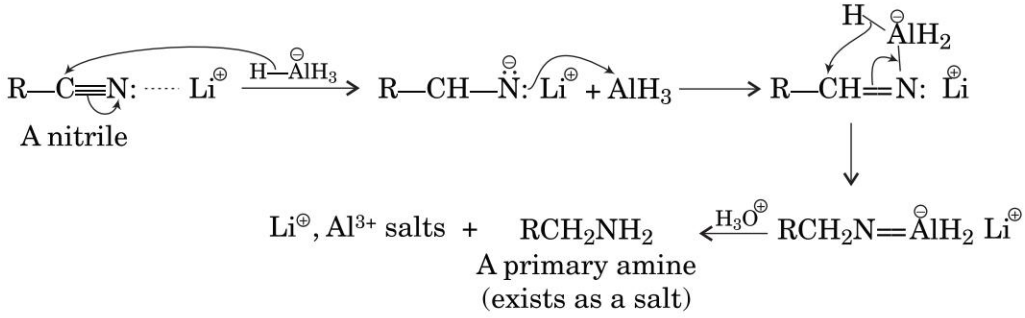


(v) **Reduction of acid chlorides to primary alcohols:** Acid chlorides also undergo two successive additions of hydride ion when they react with $LiAlH_4$.



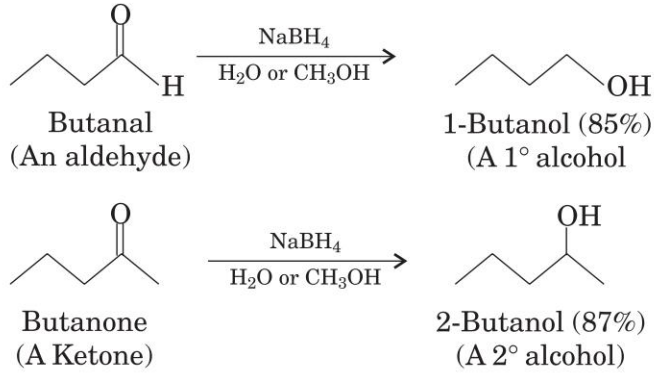


(vi) **Reduction of nitriles to form a primary amine:** Nitriles also undergo two successive additions of hydride ion when they react with $LiAlH_4$.



2.5.3 Reduction of aldehydes and ketones by sodium borohydride ($NaBH_4$) to form primary and secondary alcohols, respectively

Sodium borohydride is a very common reducing agent in organic chemistry. Unlike $LiAlH_4$, it is a less vigorous and more selective reagent which reduces aldehydes and ketones, but not carboxylic acids, esters, amides, nitriles, nitro compounds and carbon—carbon multiple bond. Acid chlorides can, however, be reduced in diglyme solution. Unlike LAH, $NaBH_4$ reacts only very slowly with alcohols and water and so, the reaction can be carried out in alcohol or in water. Also, it is less soluble in ether but readily soluble in water or alcohol. For example:

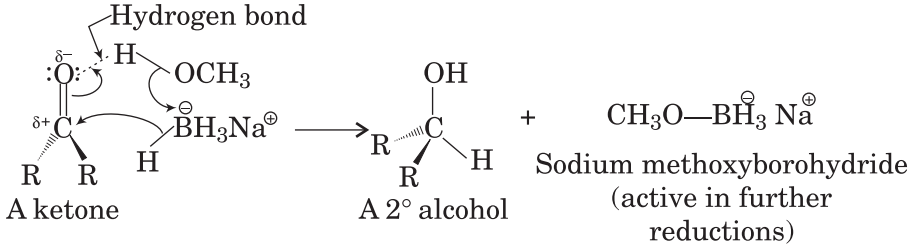


[Sodium borohydride can be prepared by heating a mixture of sodium hydride with trimethoxyborane at an elevated temperature of 300°C.

$$4\ NaH + B(OMe)_3 \rightarrow NaBH_4 + 3\ MeONa]$$

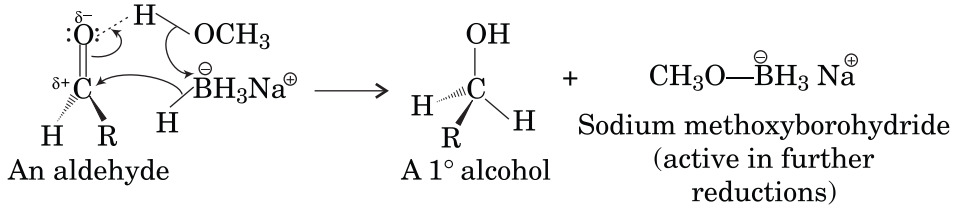
2.5.4 Mechanism for the reduction of an aldehyde or a ketone by sodium borohydride ($NaBH_4$)

The reaction involves a concerted process in which the hydride ion ($:H^{\ominus}$) from boron attacks the carbonyl carbon atom as the carbonyl oxygen atom takes up the proton from alcohol (CH_3OH) or water (H_2O) and the alkoxide ion ($CH_3O^{\ominus}$) or hydroxide ion ($OH^{\ominus}$) complexes with boron. Hydrogen bonding between the alcohol or water and the carbonyl group serves as a weak acid catalysis that activates the carbonyl group. All the four hydrogens of the reagent are gradually transferred to the four molecules of the carbonyl compound. A ketone gives a secondary alcohol.



The reaction is repeated until all hydrogen atoms attached to boron in sodium methoxybrohydride ($CH_3O\overset{\ominus}{B}H_3Na^{\oplus}$) have been transferred to the carbonyl carbon.

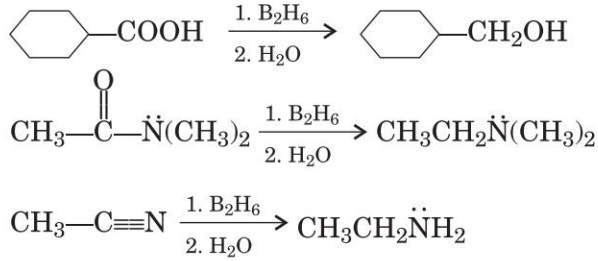
Similarly, an aldehyde gives a primary alcohol.



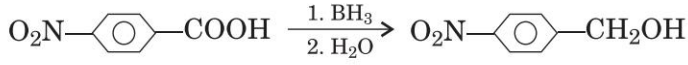
THF can be used as a solvent when the reaction is carried out in the presence of electrophilic metal cations like $Li^{\oplus}$ or $Mg^{2\oplus}$. Therefore, $LiBH_4$ can be used as the reducing agent when THF is used as the solvent.

2.5.5 Reduction of carboxylic acids, amides and nitriles by borane (BH_3)

Borane is represented as BH_3 but it exists as diborane (B_2H_6). Diborane reacts as if it were the monomer borane. BH_3 is a very effective reagent to reduce carboxylic acid to the corresponding alcohol. Amides can be effectively reduced to the corresponding amines and nitriles can be reduced to the corresponding primary amines by BH_3. For example:

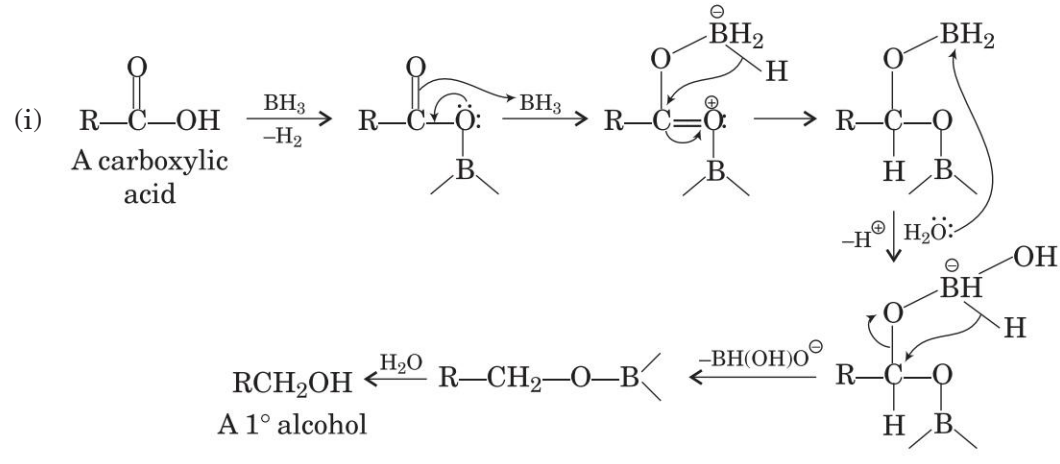


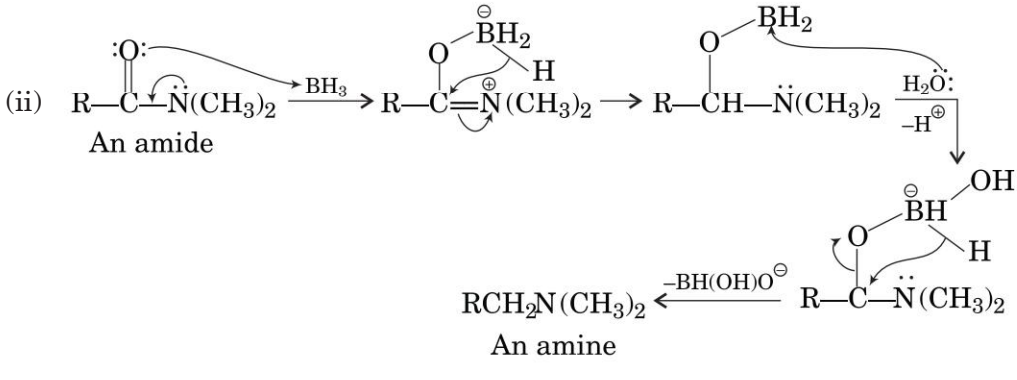
The method has the advantage, compared with LAH, that esters and nitro groups are not reduced. For example:

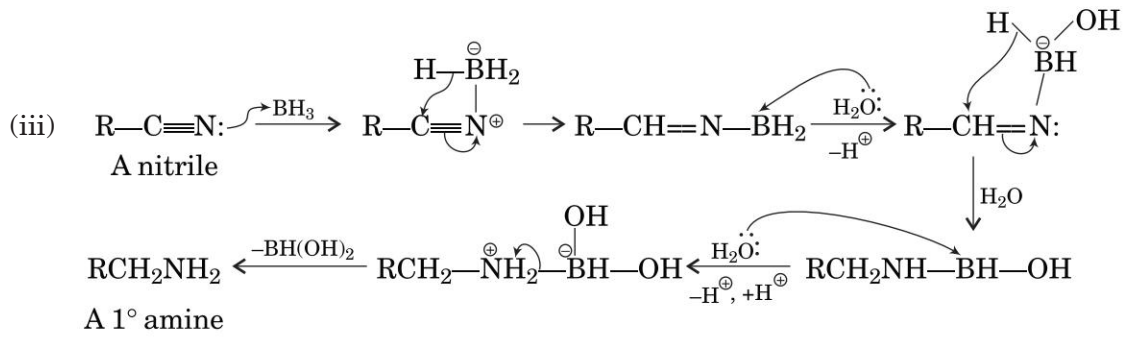


p-nitrobenzoic acid *p*-Nitrobenzyle alcohol (80%)

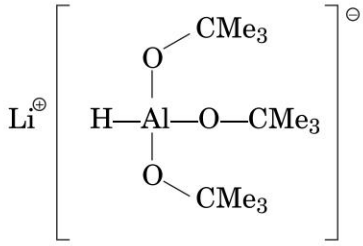
Mechanism for the reduction



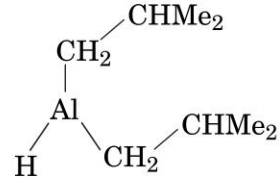




2.5.6 Reduction of acid chlorides to the corresponding aldehydes by lithium tri-*tert*-butoxyaluminium hydride [$LiAlH(O\text{-}t\text{-}Bu)_3$] and reduction of esters and nitriles to the corresponding aldehydes by diisobutylaluminum hydride ($i\text{–}Bu_2AlH$ or DIBAL–H):



Lithium tri-*tert*-butoxyaluminium hydride



Diisobutylaluminium hydride (i-Bu_2AlH or DIBAL-H)

(i) $RCOCl \xrightarrow[2.\ H_2O]{1.\ LiAlH(O\text{-}t\text{-}Bu)_3,\ Et_2O,\ -78^\circ C} RCHO$

An acid chloride — An aldehyde

(ii) $RCOOR' \xrightarrow[2.\ H_2O]{1.\ DIBAL\text{-}H,\ hexane,\ -78^\circ C} RCHO$

An ester — An aldehyde

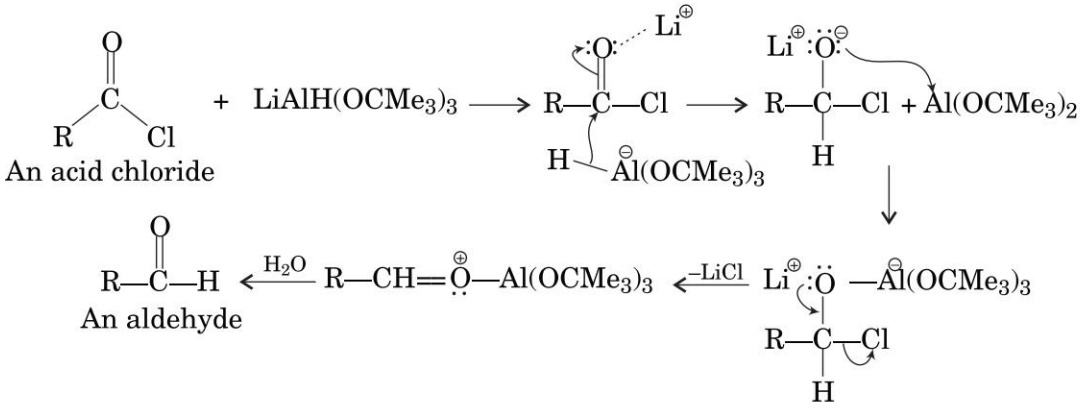
(iii) $R—C\equiv N \xrightarrow[2.\ H_2O]{1.\ DIBAL\text{-}H,\ hexane,\ -78^\circ C} RCHO$

A nitrile — An aldehyde

These two reagents are relatively less reactive than LAH because they are much more sterically hindered.

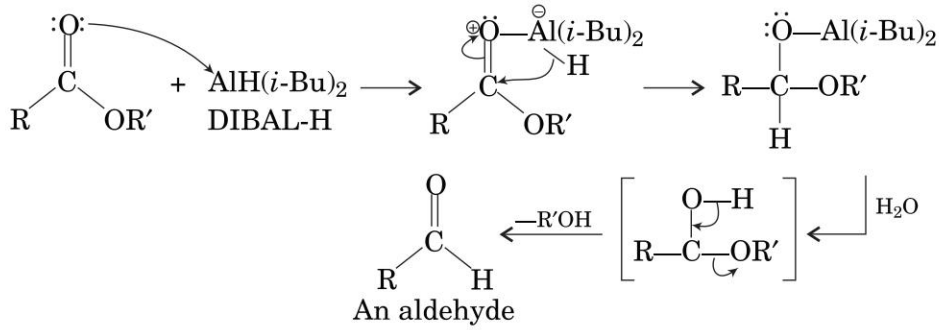
Mechanisms for the reductions

(i) The mechanisms for the reduction of acid chloride by $LiAlH(OCMe_3)_3$ involves the steps as follows:



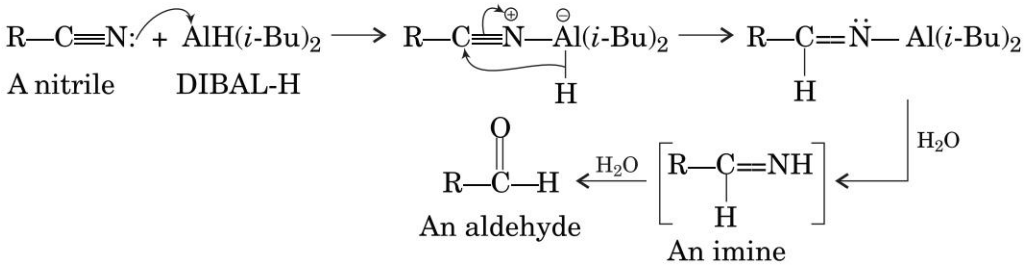
The reaction involves nucleophilic attack of the hydride ion delivered from $\overset{\ominus}{\text{Al}}\text{H(OCMe}_3)_3$ to the electrophilic carbonyl carbon. The $Li^{\oplus}$ ion acts as a Lewis-acid catalyst by coordinating to the carbonyl oxygen. Then, acting as a Lewis acid, the aluminium atom accepts an electron pair from oxygen. The resulting intermediate loses a chloride ion as an electron pair from oxygen assists. The aluminium complex is finally hydrolysed to yield an aldehyde.

(ii) The reduction of an ester to an aldehyde by DIBAL–H takes place as follows:



In the first step, the aluminium atom accepts an electron pair from the carbonyl oxygen in a Lewis acid-base reaction. In the second step, transfer of a hydride ion to the carbonyl carbon occurs to bring about its reduction. In the final step, the aluminium complex is hydrolyzed to produce an aldehyde.

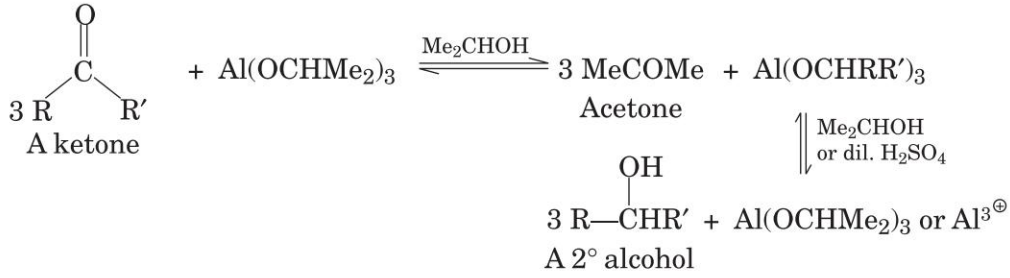
(ii) The reduction of a nitrile to an aldehyde by DIBAL–H occurs as follows:



In the first step, the aluminium atom accepts an electron pair from the nitrile in a Lewis acid-base reaction. In the next step, transfer of a $:H^{\ominus}$ ion to the carbonyl carbon occurs to bring about its reduction. In the final step, the aluminium complex is hydrolyzed to yield an aldehyde through the intermediate formation of an imine.

2.5.7 Meerwein–Ponndorf–Verley (MPV) reduction

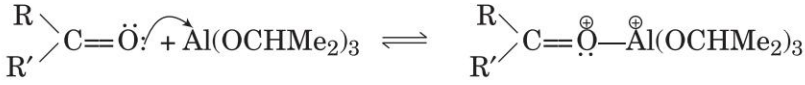
The reduction of a ketone to the corresponding secondary alcohol or an aldehyde to the corresponding primary alcohol by the action of aluminium isopropoxide in isopropyl alcohol medium is called the *Meerwein–Ponndorf–Verley* (MPV) *reduction.*



Since the reaction is completely reversible, therefore, it can be driven essentially to completion by distilling out acetone (the lowest boiling component in the mixture having b.p. 56°C) as it is formed or by adding excess of isopropyl alcohol. Both of these processes help to shift the equilibrium to the right.

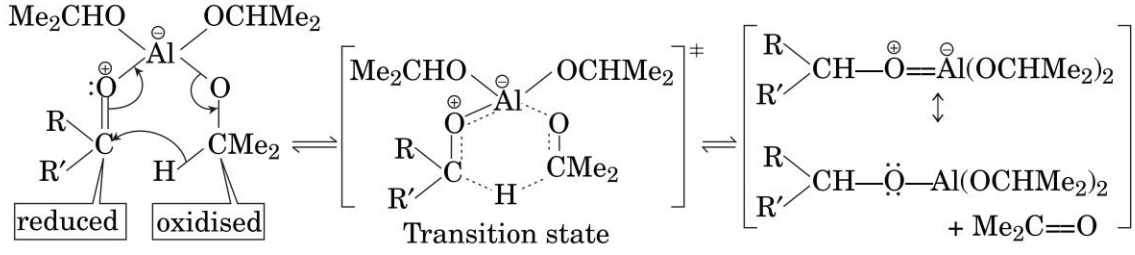
Mechanism of the reaction: The mechanism of the reaction involves the steps as follows:

Step 1: A bond is formed between the carbonyl oxygen and aluminium which is a very strong Lewis acid.

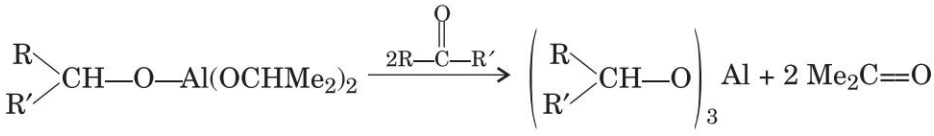


Lewis acid–Lewis base complex

Step 2: Since in the resulting complex the two reacting groups are clamped together by the aluminium atom and is nicely set up for an intramolecular transfer of hydride ion ($:H^{\ominus}$), therefore, a hydride ion transfer occurs smoothly through a six-membered cyclic transition state. This simultaneously reduces a molecule of the carbonyl compound and oxidises an isopropoxide group to acetone.

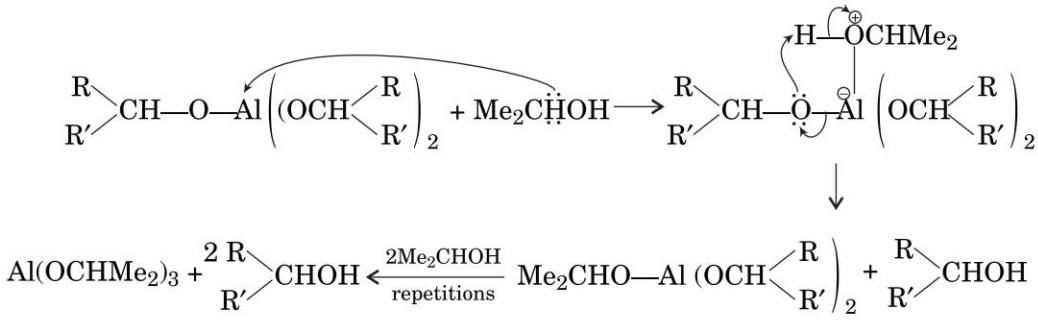


Repetition of this process leads to a new aluminium alkoxide.

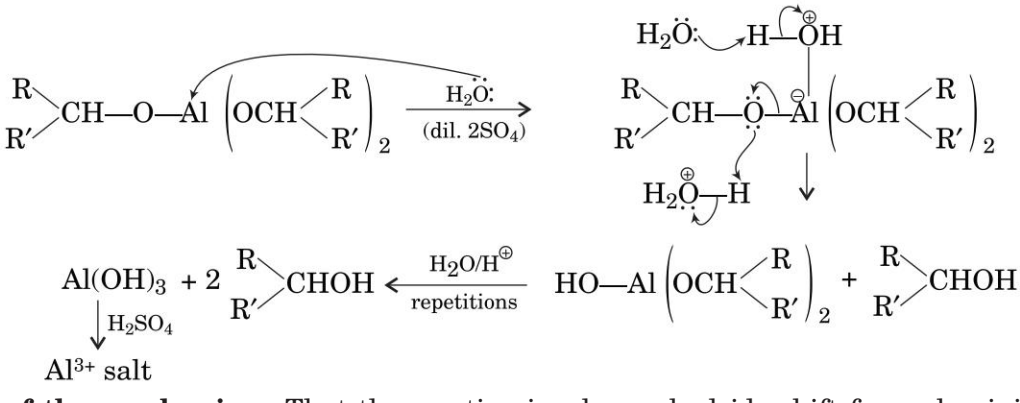


Step 3: The new aluminium alkoxide is decomposed by (i) the solvent isopropyl alcohol or (ii) dil.H_2SO_4.

(i)



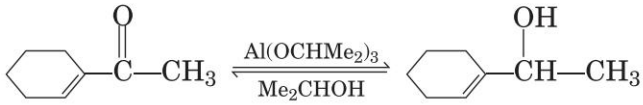
(ii)

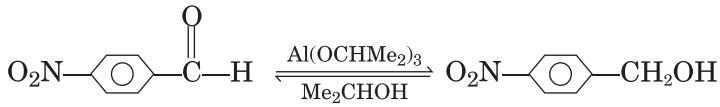


Proof of the mechanism: That the reaction involves a hydride shift from aluminium isopropoxide can be established by the fact that when an alkoxide like $Al(OCDMe_2)$ is used, then deuterium is found to be incorporated to the carbon atom of the reduced alcohol.

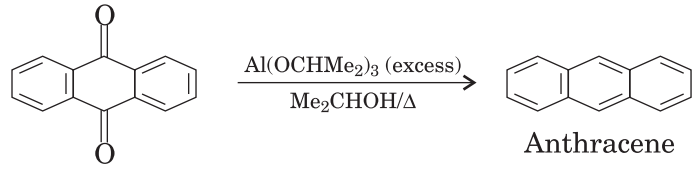
Synthetic applications: The reaction is synthetically useful because this chemoselective reaction taking place under very mild conditions can be used to reduce —CHO and $\diagdown C{=}O$ groups in the presence of other reducible groups like C=C, $-NO_2$, *etc*. Therefore, the reaction can be used to prepare unsaturated alcohols, nitro-alcohols, *etc*. For example:

(i)



(ii) 

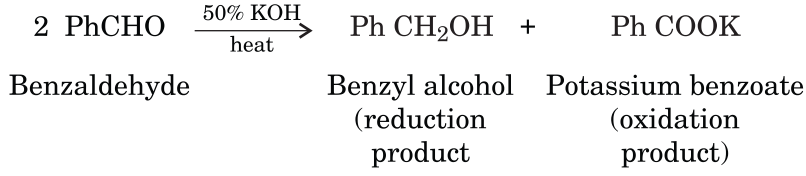
Complete reduction of keto groups may take place with excess of the reagent at higher temperature. For example anthraquinone undergoes reduction to yield anthracene, when excess of aluminium isopropoxide is used.



Anthraquinone Anthracene

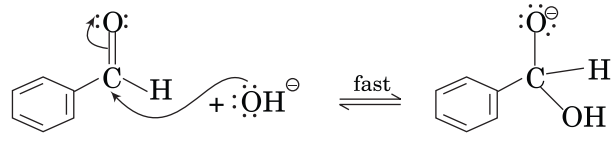
2.5.8 Cannizzaro reaction

When non-enolizable aldehydes, i.e., the aldehydes which do not have α-H atom (e.g., HCHO, PhCHO, Me_3CCHO etc.) are heated with strong bases (usually 50% aqueous sodium or potassium hydroxide solution), they undergo a redox disproportionation reaction (self-oxidation-reduction) in which one molecule of the aldehyde acts as oxidising agent and gets reduced to the corresponding alcohol, while another molecule gets oxidised to the corresponding carboxylate ion. This reaction is known as the *Cannizzaro reaction*. For example:



Mechanism of the reaction: The mechanism of the reaction involves the steps as follows:

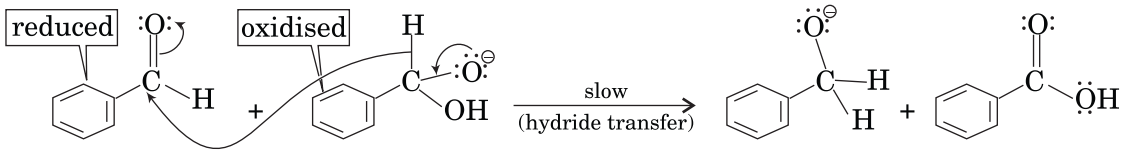
Step 1: Rapid reversible addition of $:\ddot{O}H^{\ominus}$ ion to the carbonyl carbon of benzaldehyde to yield the intermediate A (the monoanion of a *gem*-diol), a potential hydride donor.



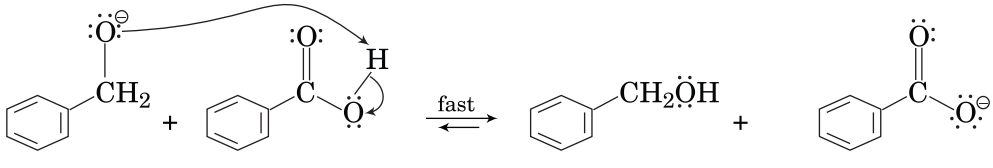
Benzaldehyde A

Step 2: Slow transfer of a hydride ion from A to the electrophilic carbonyl carbon of another benzaldehyde molecule. The presence of the negative charge on a assists the loss of $:H^{\ominus}$. This is a direct transfer of a hydride ion from one molecule to another molecule and not a

stepwise process.



Step 3: Rapid proton exchange between the carboxylic acid and the alkoxide ion to form the salt of the acid and a primary alcohol (a stable pair). A strong acid and a strong base reacts to produce a weak acid and a weak base.



Benzyl alcohol Benzoate ion

The resulting alcohol can be separated by distillation leaving behind a sodium salt of the acid in solution. The acid is then recovered by acidifying the solution.

By a similar mechanism formaldehyde (HCHO) leads to the formation of methanol (CH_3OH) and sodium formate (HCOONa) and 2,2-dimethylpropanal (Me_3CCHO) leads to the formation of 2,2-dimethyl-1-propanol (Me_3CCH_2OH) and sodium 2,2-dimethylpropanoate ($Me_3CCOONa$).

[The hydride transfer step (step 2) is not to be confused with the expulsion of hydride as a leaving group. Hydride is not a good leaving group and cannot be lost in this way. However, if there is an electrophile positioned in exactly the proper place to accept the hydride, it can be transferred in a step that simultaneously reduces the receptor aldehyde and oxidizes the donor aldehyde. In fact, if there were a way to hold the hydride acceptor in the right position, the reaction would be much easier, because the requirement for ordering the reactants in just the correct way (entropy) would be satisfied automatically.]

Proof of the mechanism

That the hydrogen atom that becomes attached to one aldehyde molecule comes not from the solvent (H_2O) but directly from a second molecule of aldehyde can be proved by carrying out the reaction in D_2O/NaOD and identifying the products. It has been observed that no carbon-deuterium bond appears in the alcohol.

$$\underset{\text{Benzaldehyde}}{PhCHO} \xrightarrow[D_2O]{NaOD} PhCH_2OD + PhCOONa \quad NO\left(PhCHDOD\right)$$

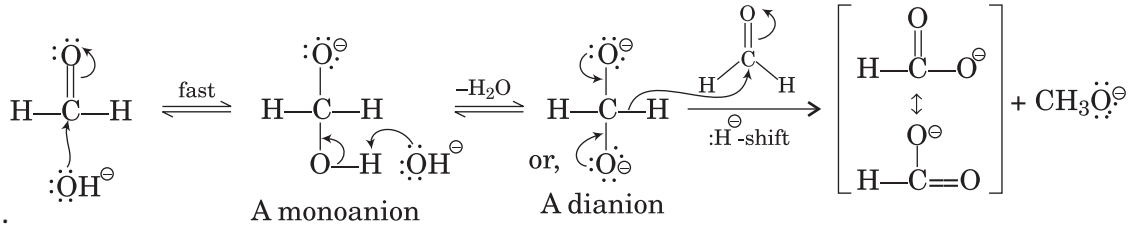
If $:H^{\ominus}$ becomes free, it may equilibrate with D_2O($:H^{\ominus} + D_2O \rightleftharpoons HOD + D:^{\ominus}$ and the resultant $:D^{\ominus}$ may then add to the carbonyl carbon of the other aldehyde molecule. Since no C_6H_5CHDOD is obtained, it is clear that the second hydrogen atom of the methylene group of benzyl alcohol must have come directly from a second molecule of benzaldehyde and not from the solvent. Further support for the suggested reaction pathway is provided by carrying out the complementary reaction on benzaldehyde in which the aldehyde hydrogen is deuterium-labelled, but this time is water:

$$Ph{-}\overset{\overset{O}{\|}}{C}{-}D \xrightarrow[H_2O]{NaOH} PhCD_2OH + PhCOO^{\ominus}$$

As the suggested pathway would require, all the deuterium labels are found in the methylen3e group of the product alcohol.

Alternative mechanism in very concentrated alkali

Kinetic studies have shown that when the reaction is carried out in very concentrated alkali, the rate equation corresponds to: rate = $k[HCHO]^2[OH^{\ominus}]^2$ when the aldehyde is formaldehyde. The mechanism of the reaction which corresponds to this rate equation involves a dianion. The steps are as follows:



Due to the presence of two strong electron-releasing $-\ddot{O}:^{\ominus}$ groups, the dianion becomes a more powerful hydride donor than the monoanion. Also, the loss of $:H^{\ominus}$ from the dianion yields the resonance-stabilized $HCOO^{\ominus}$ ion directly. This also increases its ability as a $:H^{\ominus}$ ion donor.

Crossed Cannizzaro reaction

When two different aldehydes and none of them containing α-hydrogen atom take part in a Cannizzaro reaction, then it is called a *crossed Cannizzaro reaction.* For example:

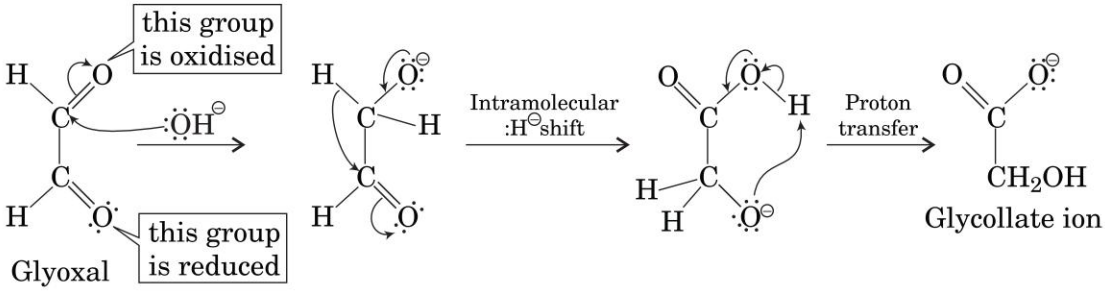
$$\underset{\text{Benzaldehyde}}{PhCHO} + \underset{\text{Formaldehyde}}{HCHO} \xrightarrow[\Delta]{50\%\,NaOH} \underbrace{PhCOO^{\ominus} + CH_3OH}_{\text{(minor)}} + \underbrace{HCOO^{\ominus} + PhCH_2OH}_{\text{(major)}}$$

When one of the two aldehydes in a crossed Cannizzaro reaction is formaldehyde (HCHO), it undergoes oxidation preferentially, i.e., the formate salt ($HCOO^{\ominus}Na^{\oplus}$) and the alcohol corresponding to the other aldehyde are formed nearly exclusively. Because of much higher reactivity of formaldehyde (the carbonyl carbon possesses considerable positive

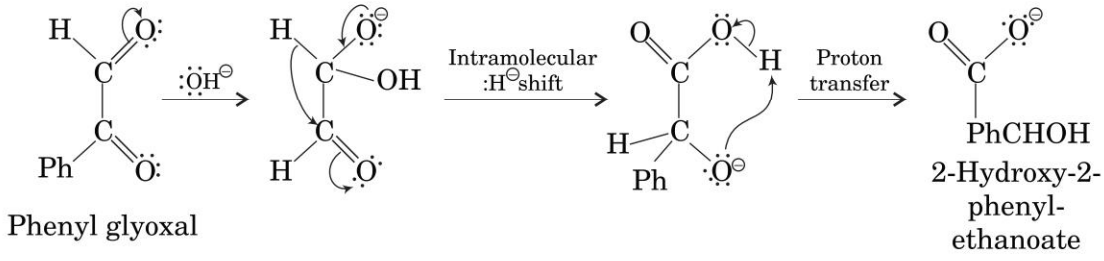
character), it undergoes preferential attack by the hydroxide ion to form an adduct that transfers a hydride ion to the relatively less reactive benzaldehyde (due to resonance the positive character of the carbonyl carbon is reduced). Thus, the formate ion and benzyl alcohol become the major product in this reaction. Therefore, a crossed Cannizzaro reaction in which one of the two aldehydes is formaldehyde is synthetically useful because in such a reaction the other aldehyde can be quantitatively reduced to the corresponding alcohol.

Intramolecular Cannizzaro reaction

The Cannizzaro reaction may also be intramolecular. Glyoxal, for example, when treated with highly concentrated solution of sodium hydroxide, is converted into sodium glycolate through an intramolecular hydride transfer mechanism. The rate of the reaction is first order with respect to both glyoxal and the hydroxide ion. The mechanism of the reaction is as follows:



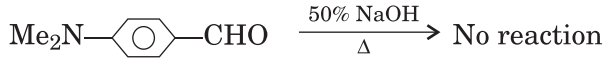
Intramolecular reaction is also observed in α-keto aldehydes like phenyl glyoxal (PhCOCHO). In this case, the more reactive (elelctrophilic) –CHO group undergoes nucleophilic attack by $OH^{\ominus}$ and the aldehyde hydrogen shifts as $:H^{\ominus}$ to the adjacent keto group.



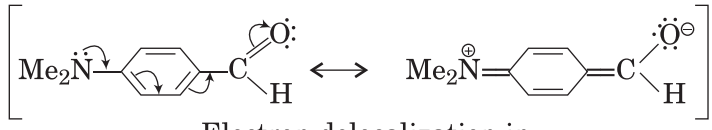
Some exceptions to the Cannizzaro reaction

Some non-enolizable aldehydes (i.e., the aldehydes having no α-H) do not undergo the Cannizzaro reaction for some special reasons. Some examples are discussed below:

(a) *N*, *N*-Dimethyl-*p*-aminobenzaldehyde does not undergo the Cannizzaro reaction.

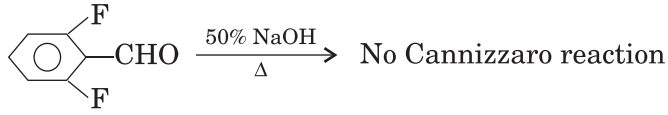


Due to the +R effect of the $-\ddot{N}Me_2$ group at the *para*-position, the electrophilicity of the carbonyl carbon is reduced considerably and because of this, attack by $:\ddot{O}H^{\ominus}$ on it does not take place, i.e, this aldehyde does not undergo the Cannizzaro reaction.

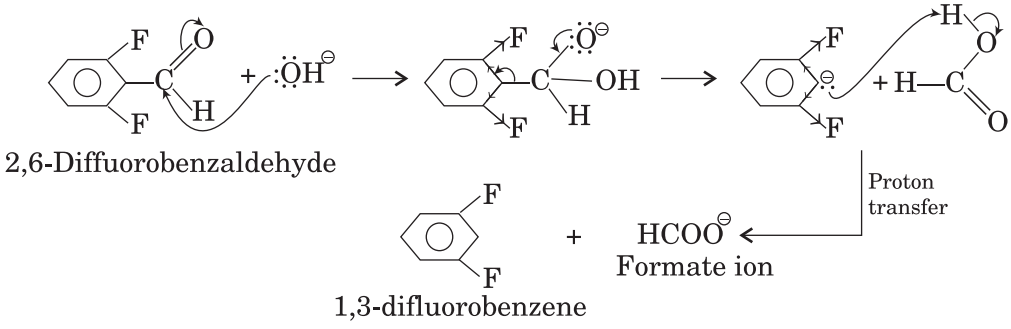


Electron delocalization in
N, *N*-Dimethyl-*p*-aminobenzaldehyde

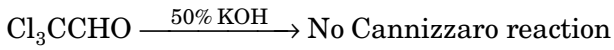
(b) 2,6-Difluorobenzaldehyde does not undergo the Cannizzaro reaction.



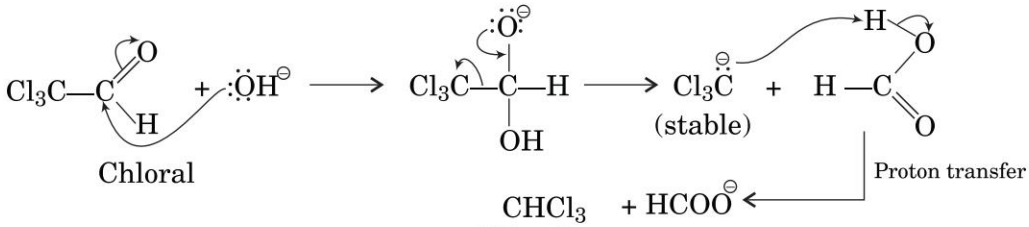
Since the *ortho* substituents in this aromatic aldehyde are highly electronegative fluorine atoms, therefore, a negative charge on C-1 will be highly stabilized by their strong –I effects. For this reason, the anion obtained by the addition of $OH^{\ominus}$ to the carbonyl carbon undergoes cleavage of the C—C bond instead of $H^{\ominus}$ transfer to yield finally 1,3-difluorobenzene and formate ion ($HCOO^{\ominus}$). The reaction takes place as follows:

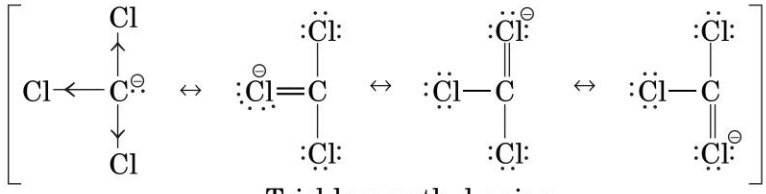


(c) Charcoal (Cl_3CCHO) does not undergo the Cannizzaro reaction.



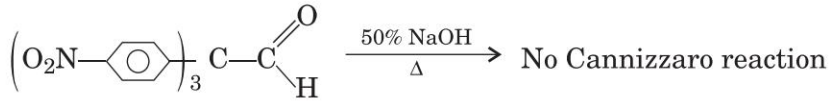
Because of very much stability of the trichloromethyl anion, $\ddot{C}Cl_3^{\ominus}$ (due to –I and electron-withdrawing *d* orbital resonance effect), the intermediate anion undergoes cleavage of C—C bond instead of $H^{\ominus}$ transfer to yield finally chloroform ($CHCl_3$) and formate ion ($HCOO^{\ominus}$). It is for this reason, chloral does not undergo the Cannizzaro reaction.



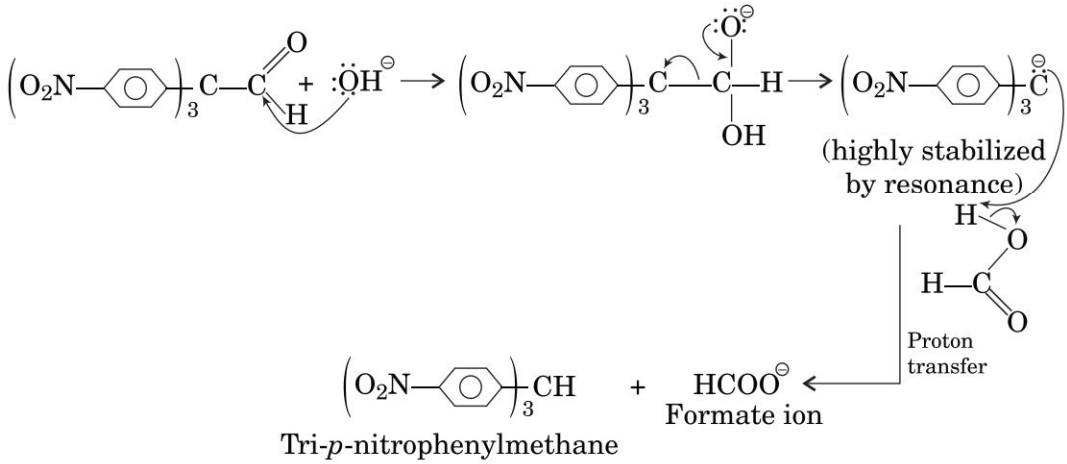


Trichloromethyl anion
(stabilized by –I and *d* orbital resonance effects)

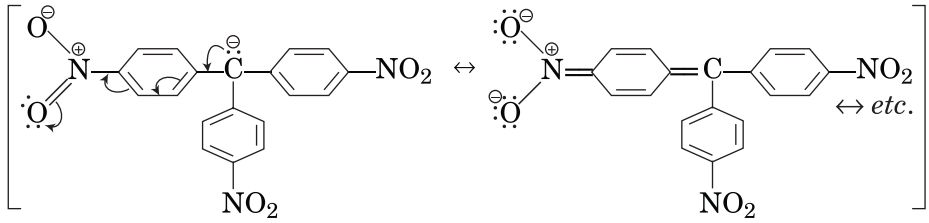
(d) Tri-*p*-nitrophenylacetaldehyde does not undergo the Cannizzaro reaction.



In this case also the intermediate anion undergoes heterolysis of the C—C bond instead of $:H^{\ominus}$ transfer and this is because the negative charge in the resultant anion (the conjugate base of tri-*p*-nitrophenylmethane) is highly stabilized by the –R effect of the three $-NO_2$ groups. For this reason, this aldehyde does undergo the Cannizzaro reaction.

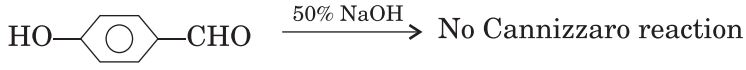


Tri-*p*-nitrophenylmethane

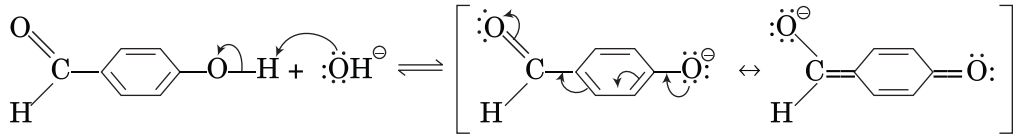


Resonance-stabilized tri-*p*-nitrophenylmethyl anion

(e) *p*-Hydroxybenzaldehyde does not undergo the Cannizzaro reaction.



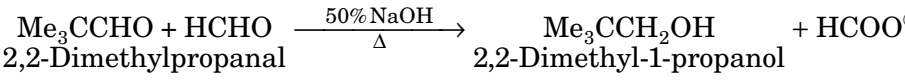
When *p*-hydroxybenzaldehyde (the phenolic-OH hydrogen is considerably acidic) is treated with concentrated alkali, it is converted to the corresponding phenoxide ion which is stabilized by the –R effect of the —CHO group at the *para*-position. As a result, the positive character, i.e., the electrophilicity of the carbonyl carbon is reduced and because of this, attack by $OH^{\ominus}$ on it does not take place, i.e., this aldehyde does not undergo the Cannizzaro reaction.



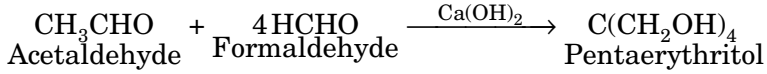
p-Hydroxybenzaldehyde A resonance-stabilized phenoxide ion

Synthetic Applications

1 The crossed Cannizzaro reaction involving formaldehyde is a good synthetic tool because the other aldehyde is converted predominantly to the corresponding alcohol. For example, Me_3CCHO is converted to Me_3CCH_2OH when treated with alkali in the presence of HCHO.



The crossed Cannizzaro reaction finds application in the industrial manufacture of pentaerythritol, $C(CH_2OH)_4$, (2,2-*bis*-hydroxymethyl-1,3-propanediol) which is widely used in the preparation of surface coatings and in the synthesis of the important explosive pentaerythritol tetranitrate (PETN, $C(CH_2ONO_2)_4$]. This commercially important compound can be synthesized by treating acetaldehyde with an excess of formaldehyde in the presence of calcium hydroxide.



The reaction involves aldol condensation of acetaldehyde with three molecules of formaldehyde followed by a crossed Cannizzaro reaction in the last step.

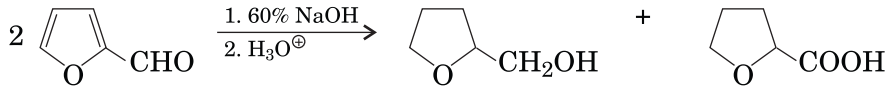
2 Some valuable compound like glycolic acid and mandelic acid can be prepared by the intramolecular Cannizzaro reaction.

$$\underset{\text{Glyoxal}}{OHC-CHO} \xrightarrow[2.\ H_3O^{\oplus}]{1.\ 50\%\ NaOH} \underset{\text{Glycolic acid}}{HOCH_2COOH};$$

$$\underset{\text{Phenylylyoxal}}{PHCOCHO} \xrightarrow[2.\ H_3O^{\oplus}]{1.\ 50\%\ NaOH} \underset{\text{Mandelic acid}}{PhCHOHCOOH}$$

3. Various types of alcohols and acids can be easily synthesized using the classical Cannizzaro reaction

$$\underset{\text{Glyoxalic acid}}{2\,OHC-CO_2H} \xrightarrow[2.\ H_3O^{\oplus}]{1.\ 50\%\ NaOH} \underset{\text{Glycolic acid}}{HOCH_2COOH} + \underset{\text{Oxalic acid}}{HO_2C-CO_2H}$$



Furfural Furfural alcohol 2-Furoic acid

2.5.9 Tishchenko reaction

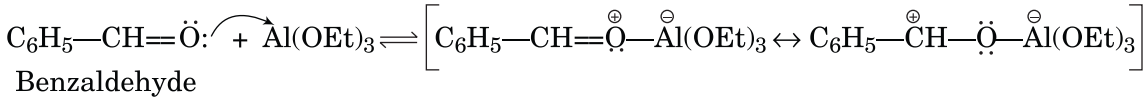
All aldehydes, whether they are enolizable or not, i.e., whether they contain α-H atom or not, undergo the Cannizzaro reaction on treatment with aluminium ethoxide, $Al(OEt)_3$ (a Lewis acid) instead of a base not to give the self oxidation-reduction (redox disproportionation) products, i.e., the carboxylic acid (salt) and the alcohol but to give an ester formed from these two aldehyde molecules. This modified form of the Cannizzaro reaction is known as the *Tishchenko reaction*. Benzaldehyde, for example, yields benzyl benzoate when treated with aluminium ethoxide.

$$\underset{\substack{\text{Benzaldehyde}\\ \text{(two molecules)}}}{C_6H_5CHO + C_6H_5CHO} \xrightarrow{Al(OEt)_3} \underset{\text{Benzyl benzoate}}{C_6H_5COOCH_2C_6H_5}$$

Mechanism of the reaction

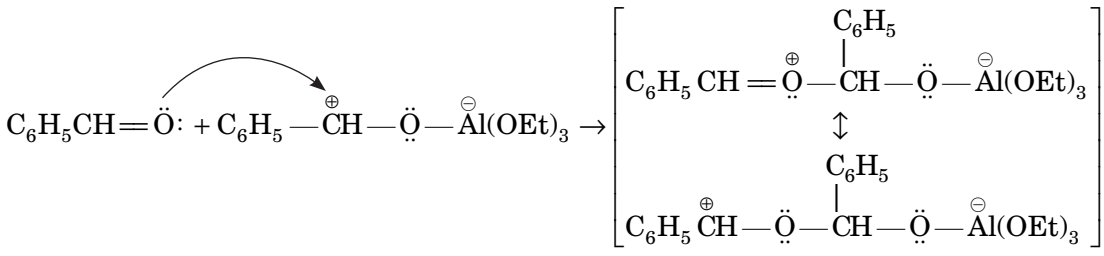
The mechanism of the reaction involves the steps as follows:

Step 1: Benzaldehyde co-ordinates with aluminium ethoxide (the Lewis acid) to form a complex.

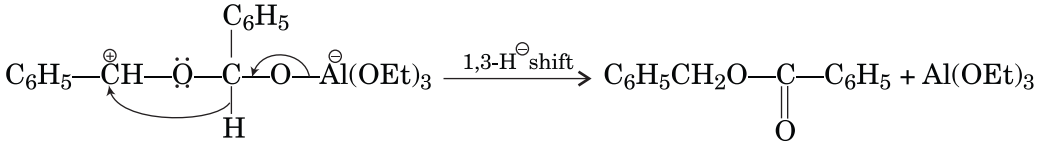


Benzaldehyde

Step 2: The cationic carbon of the complex undergoes nucleophilic attack by the O atom of another aldehyde molecule.



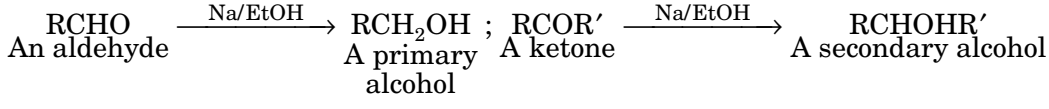
Step 3: A 1,3-hydride shift with simultaneous expulsion of $Al(OEt)_3$ occur to yield benzyl benzoate.

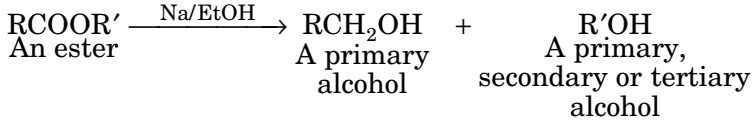


Benzyl benzoate

2.5.10 Bouveault-Blanc reduction

Reduction of aldehydes, ketones or esters by means of excess of metallic sodium and ethanol on *n*-butanol as the reducing agent is known as the *Bouveault-Blanc reduction.*



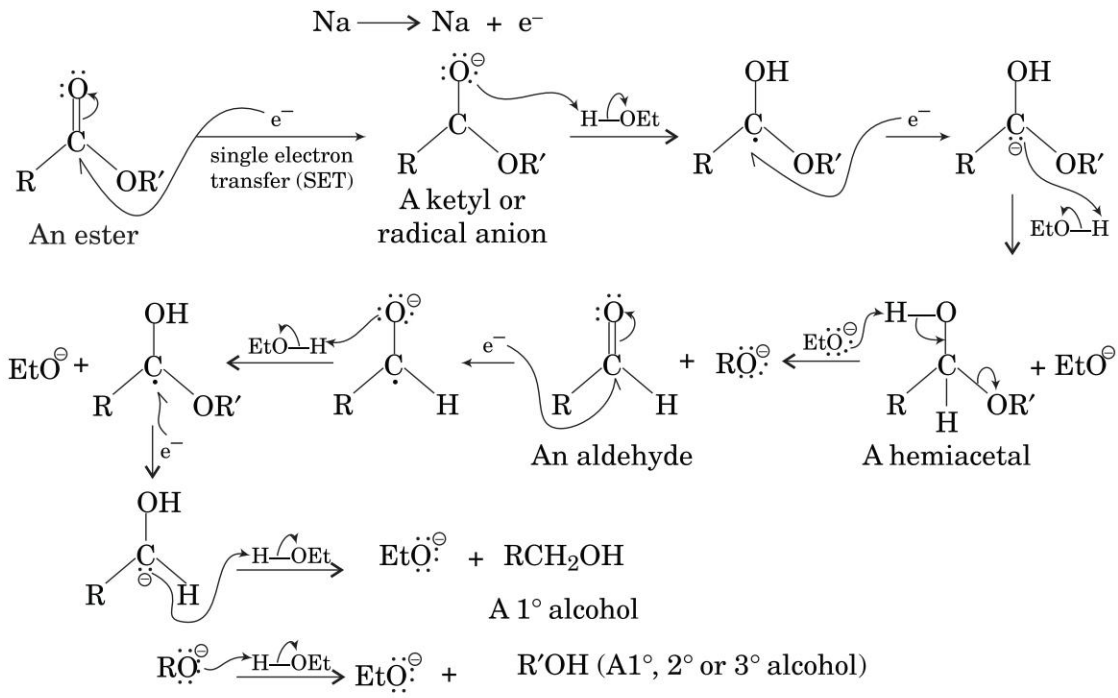


This dissolving metal reduction (dissolution of the metal occurs as the reduction proceeds) is an inexpensive substitute for LAH reductions of esters in the industrial production of alcohols and was the only alternative prior to the development of the metal hydride reducing agents.

Mechanism of the reaction

In the Bouveault-Blanc reduction of esters, the ester is first converted into an aldehyde. The aldehyde is then further reduced to a primary alcohol. The solvated electrons are the necessary nucleophile in this reaction.

The mechanism of the reaction involves the steps as follows:



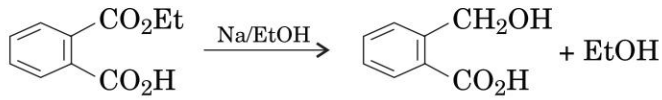
In step 1, nucleophilic attack by an e^- on the electron-deficient carbonyl carbon occurs to form a radical anion or ketyl. In step 2, a proton is abstracted by the alkoxy oxygen from the solvent alcohol. In step 3, another electron is added to the carbonyl carbon to form a carbanion. In step 4, a proton is abstracted from EtOH by the carbanion to form a hemiacetal. In step 5, elimination of R′OH from the hemiacetal by the base $EtO^{\ominus}$ occurs to form an aldehyde. In step 6, an electron is again added to the carbonyl carbon to form a radical anion. In step 7, a proton is abstracted from EtOH to form a radical. In step 8, another electron is added to the carbonyl carbon to form a carbanion and in step 9, a proton is abstracted from EtOH by the carbanion to form a primary alcohol.

The acyl group $\left(R-\overset{|}{C}=O\right)$ of an ester always converted into a primary alcohol (RCH_2OH) and the nature of the other alcohol depends on –R′, i.e., on the alcohol (1°, 2° or 3°) used to prepare the original ester.

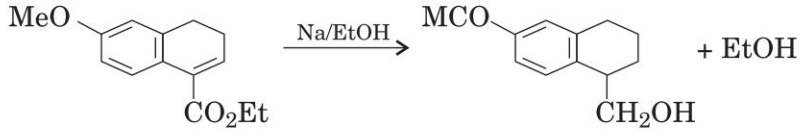
Synthetic applications

The reaction is synthetically useful because of its ability to reduce selectively a $-CO_2R$ group in the presence of a non-conjugated carbon–carbon double bond or a $-COOH$ group. For example:

$$\underset{\text{Butyl oleate}}{CH_3(CH_2)_7\,CH=CH(CH_2)_7\,CO_2\,C_4H_9} \xrightarrow[-C_4H_9OH]{Na/EtOH} \underset{\text{Oleyl alcohol}}{CH_3(CH_2)_7\,CH=CH(CH_2)_7\,CH_2OH}$$



However, a carbon–carbon double bond conjugated with an ester group is reduced along with the ester functionality under Bouveault–Blanc procedure. For example:



A diester can be converted to a diol by this process.

$$EtO_2C(CH_2)_8CO_2Et \xrightarrow{Na/EtOH} HOCH_2(CH_2)_8CH_2OH$$

Diethyl sebacate — 1,10-Decanediol

2.5.11 Pinacolization of Ketones

Less reactive metals than sodium, for example, magnesium or aluminium or their amalgams (the metal-mercury alloy) in aprotic solvent like benzene, reduce ketones to metal pinacolates, which on acidification yield pinacols.

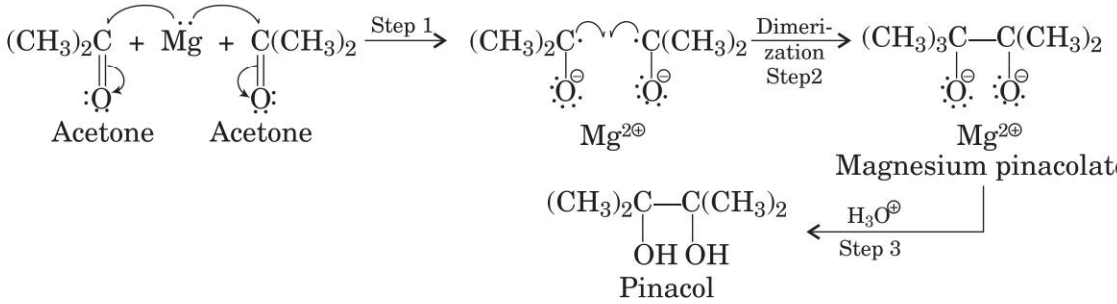
This reduction of ketones with metal dissolved in aprotic solvent is known as *pinacolization of ketones.* For example:

$$2\ CH_3COCH_3 \xrightarrow[2.\ H_3O]{1.\ Mg(Hg)/benzene/\Delta} (CH_3)_2C(OH)C(OH)(CH_3)_2$$

Acetone — 2,3-Dimethylbutane-2,3-diol (Pinacol)

Mechanism of the reaction

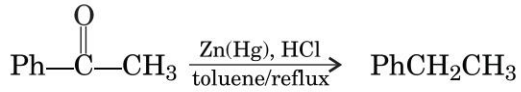
The mechanism of the reaction involves the steps as follows:



In Step 1, single electron transfer from the metal to the carbonyl carbon occurs to form a radial anion or a ketyl. In step 2, the ketyl undergoes dimerization to form magnesium pinacolate and in step 3, protonation of the metal pinacolate occurs to yield pinacol.

2.5.12 Clemmensen reduction

The conversion of an aldehyde or a ketone to the corresponding alkane by refluxing for several hours with concentrated hydrochloric acid and amalgamated zinc (Zn/Hg) in a hydrophobic solvent like toluene is called *Clemmensen reduction*. For example:

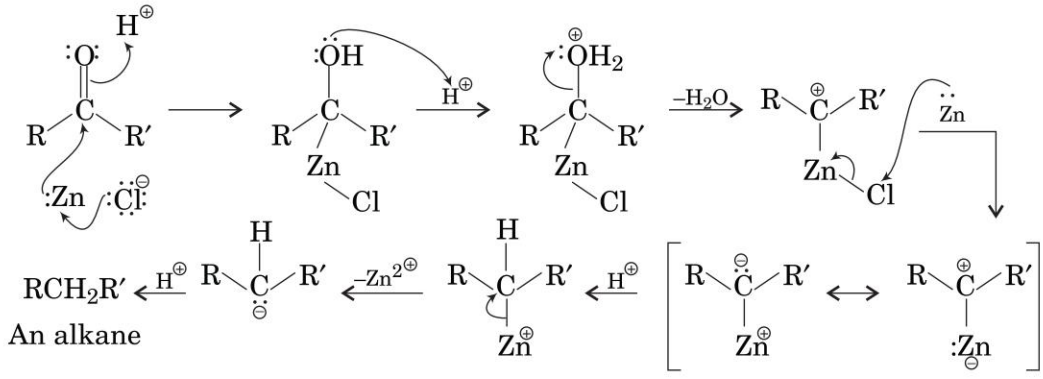


Acetophenone (A carbonyl compound) — Ethylbenzene (An alkane)

Amalgamation of zinc is needed to raise its hydrogen overvoltage to such a level where the metal survives as a reducing agent in acid solution and is not consumed by reacting with the acid to form H_2. The choice of HCl is made because its anion $Cl^{\ominus}$ is not reduced by metallic zinc.

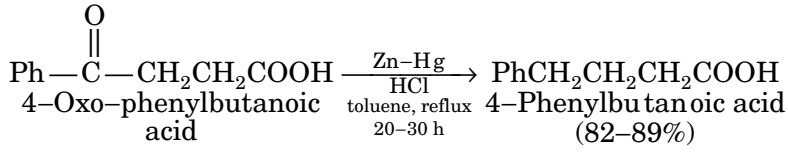
Mechanism of the reaction

The reduction taking place by the formation of the zinc organyls as intermediates may be shown as follows:

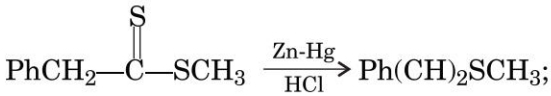


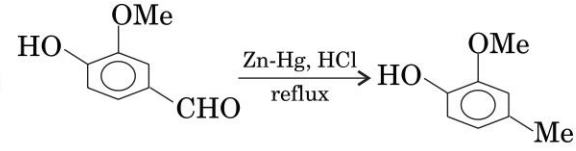
Synthetic applications

Clemmensen reduction is very popular among the chemists for carrying out reductions of a variety of organic substrates possessing other groups. For example:



4–Oxo–phenylbutanoic acid — 4–Phenylbutanoic acid (82–89%)





The Clemmensen reduction is complementary to the Wolff-Kishner reduction, which is run under strongly basic conditions.

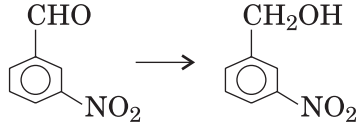
SOLVED PROBLEMS

1. Explain why LAH usually fails to reduce a carbon–carbon multiple bond. Why does a double bond in conjugation with an aromatic ring on one side and a carbonyl group on the other side get reduced by LAH easily?

Solution A carbon–carbon multiple bond is an electron-rich moiety and is susceptible to electrophilic attack. A hydride ion is an electron-dense species and thus acts as a strong nucleophile. So, a hydride ion cannot come close to carbon–carbon multiple bond due to repulsive interaction and thus, it fails to reduce a multiple bond. On the other hand, the electron-attracting effect of an aromatic ring on one side and that of the carbonyl group (C═O) on the other side make the carbon–carbon multiple bond electron-deficient and as a consequence, the hydride ion becomes able to attack the multiple bond. For this reason, such a carbon–carbon multiple bond is reduced by LAH. For example:

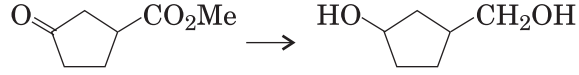
$$\underset{\text{3-Phenyl-2-propanal}}{PhCH{=}CHCHO} \xrightarrow[2.\ H_3O^{\oplus}]{1.\ LiAlH_4} \underset{\text{3-Phenyl-1-propanol}}{PhCH_2CH_2OH}$$

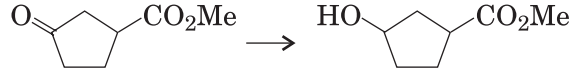
2. Predict the reducing agent ($LiAlH_4$, $NaBH_4$, $NaBH(OMe)_3$ or B_2H_6) to be used to accomplish each of the following transformations:

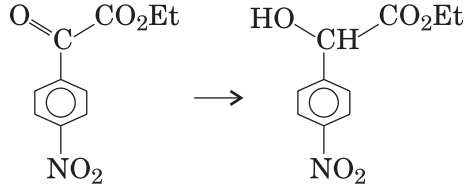
(a) 

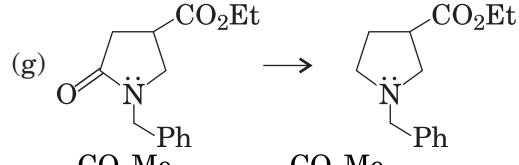
(b) $CH_3CH{=}CH{-}CHO \rightarrow CH_3CH{=}CHCH_2OH$

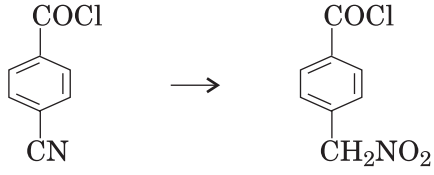
(c) $PhCH{=}CHCHO \rightarrow PhCH_2CH_2CH_2OH$

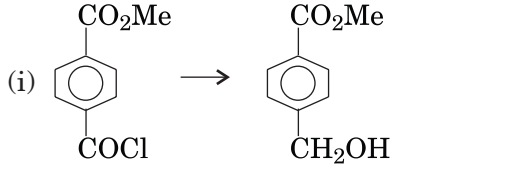
(d) 

(e) 

(f) 

(g) 

(h) 

(i) 

Solution

(a) $NaBH_4/CH_3OH$; (b) $NaBH_4/CH_3OH$;

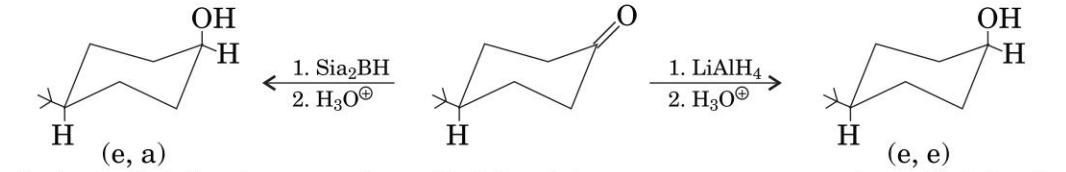
(c) $LiAlH_4$/ether ; (d) $LiAlH_4$/ether ;

(e) $NaBH_4/CH_3OH$; (f) $NaBH_4/CH_3OH$;

(g) B_2H_6/THF ; (h) B_2H_6/THF ;

(i) $NaBH_4/CH_3OH$ or $NaBH(OMe)_3$

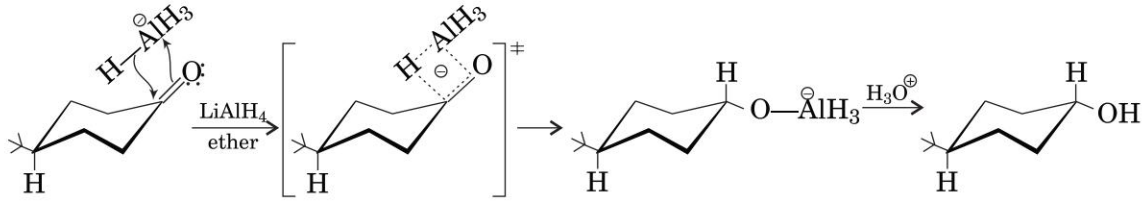
3. When 4-*tert*-butylcyclohexanone is reduced by $LiAlH_4$, the corresponding *trans*-alcohol is obtained predominantly, while *cis*-alcohol is obtained predominantly when the ketone is reduced by disiamylborane (Sia_2BH).



(e, a) *cis*-4-*tert*-Butylcyclohexanol (major) — 4-*tert*-Butylcyclohexanone — (e, e) *trans*-4-*tert*-Butylcyclohexanol (major)

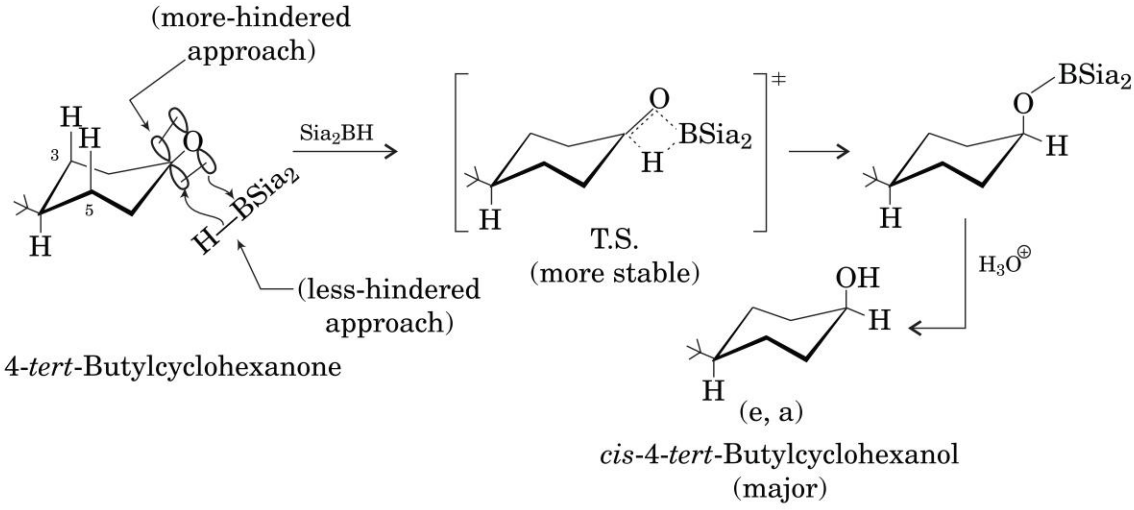
Account for these observations.

Solution 4-*tert*-Butylcyclohexanone is an unhindered ketone because it has no axial substituent at C-3 and C-5 atoms. For this reaso n, LAH ($LiAlH_4$) reacts with this ketone to yield mainly the thermodynamically more stable equatorial alcohol, i.e., the *trans*-alcohol (*product development control).*

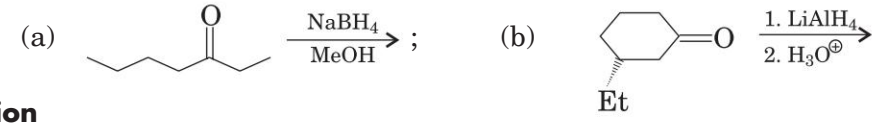


4-*tert*-Butylcyclohexanone (stable conformation) — T.S. (more stable) — (this may react with three more ketone molecules) — *trans*-4-*tert*-Butyl-cyclohexanol (major)

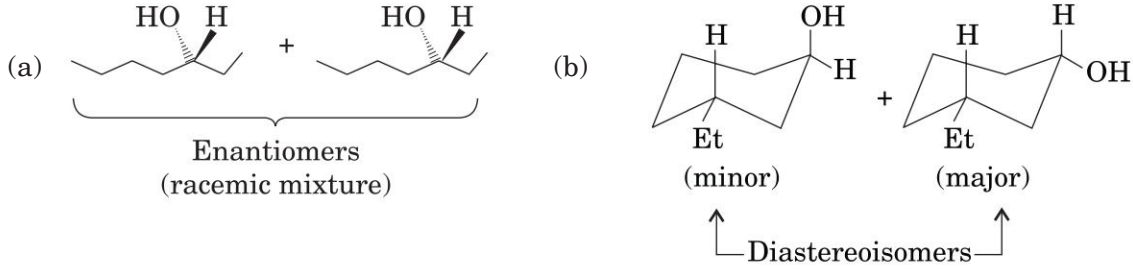
Disiamylborane (Sia_2BH or R_2BH, where R = $Me_2CHCH(Me)$–) containing two bulky —$CH(Me)CHMe_2$ groups is a hindered reducing agent. For this reason, it becomes involved in steric interaction with the axial hydrogens at C-3 and C-5 in an axial approach. To avoids the 1,3-diaxial interaction in axial approach, the reagent attacks the C=O group form the less-hindered equatorial side to yield the thermodynamically less stable axial alcohol, i.e., the *cis*-alcohol predominantly (*steric approach control*).



4. Identify the products of each reaction and include all of the stereoisomers formed:

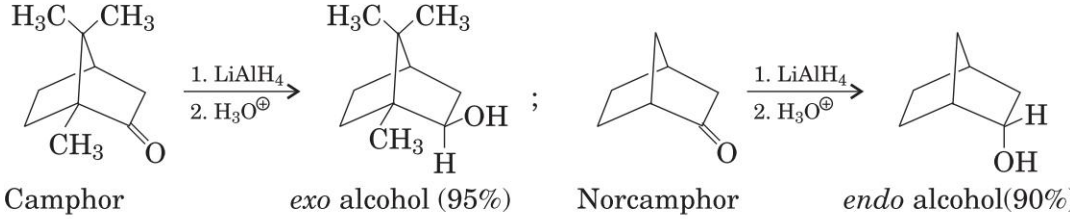


Solution



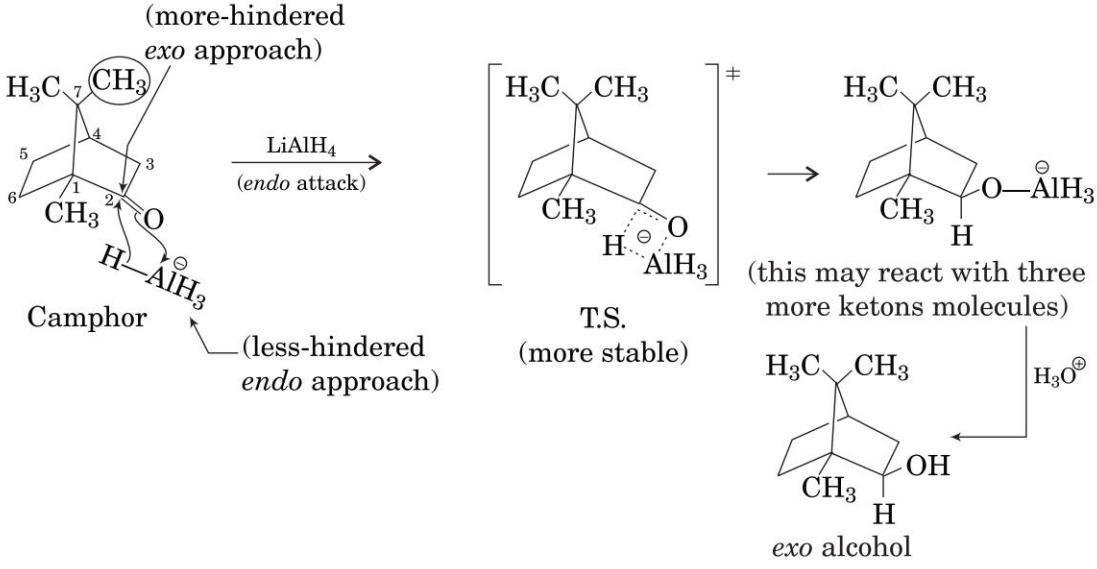
Attack by $H^{\ominus}$ on the achiral acyclic ketone occurs on the two faces with equal facility to give a racemic mixture. But attack on the chiral cyclic ketone occurs on the two faces not with equal facility and as a result, unequal amount of two diastereoisomers are obtained.

5. LAH reduction of comphor leads to preferential formation of *exo* alcohol, while that of norcamphor leads to preferential formation of endo alcohol.

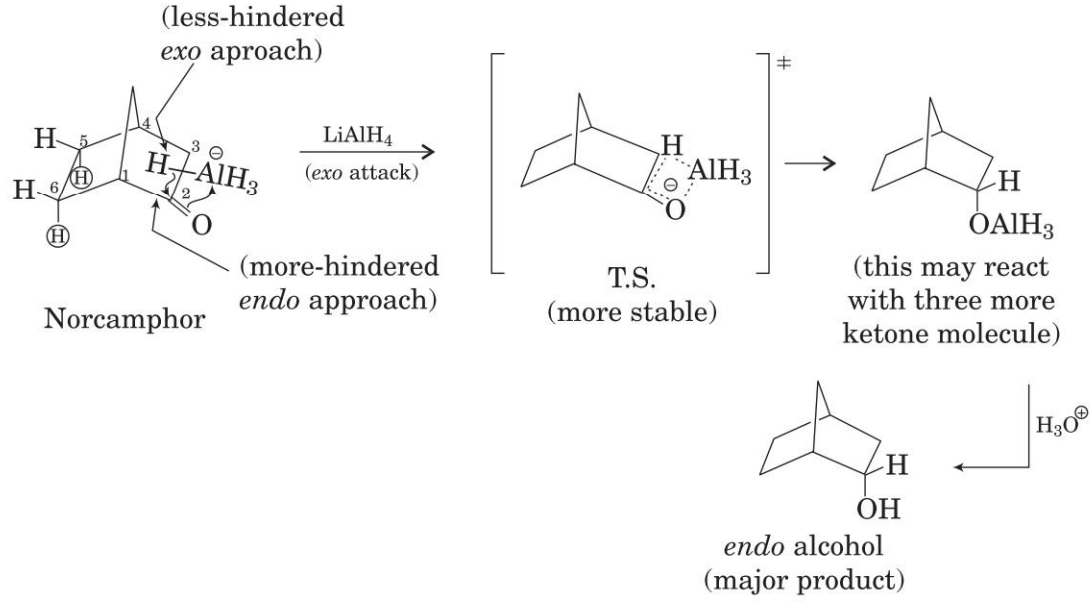


Account for these absorvations

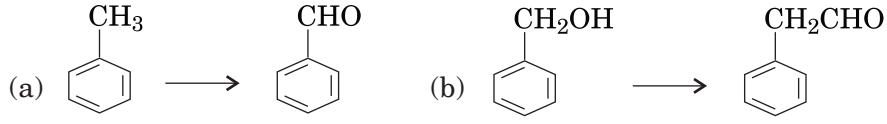
Solution The approach of $\overset{\ominus}{\text{AlH}_4}$ to deliver the hydride ion ($:H^{\ominus}$) to the carbonyl carbon of camphor occurs from the less hindered *endo* side to yield mainly the *exo* alcohol and this is because the *exo* approach is sterically more hindered due to the encircled $—CH_3$ group at C-7 (the one which is placed just above the C-2—C-3 bond).



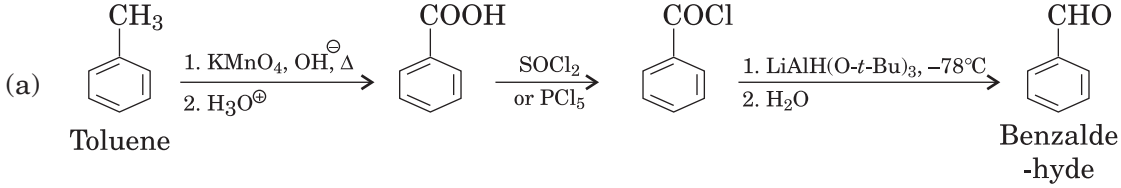
On the other hand, the approach of $\overset{\ominus}{\text{AlH}_4}$ to deliver the hydride ion ($:H^{\ominus}$) to the carbonyl carbon of norcamphor occurs from the less hindered *exo* side to give the *endo* alcohol predominantly and this is because the *endo* approach is sterically hindered due to the boat-axial or *endo* hydrogens (encircled) at C-5 and C-6.

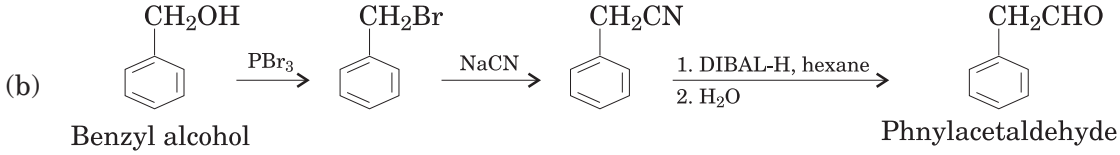


6. How would you carry out the following transformations using LiAlH (O-t-Bu)$_3$ or DIBAL-H in one of the steps?

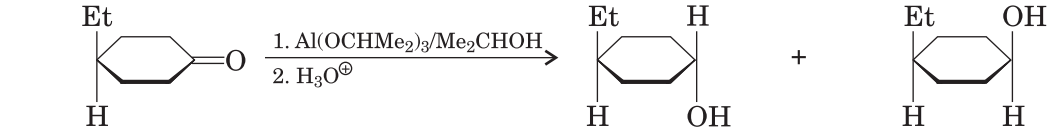


Solution

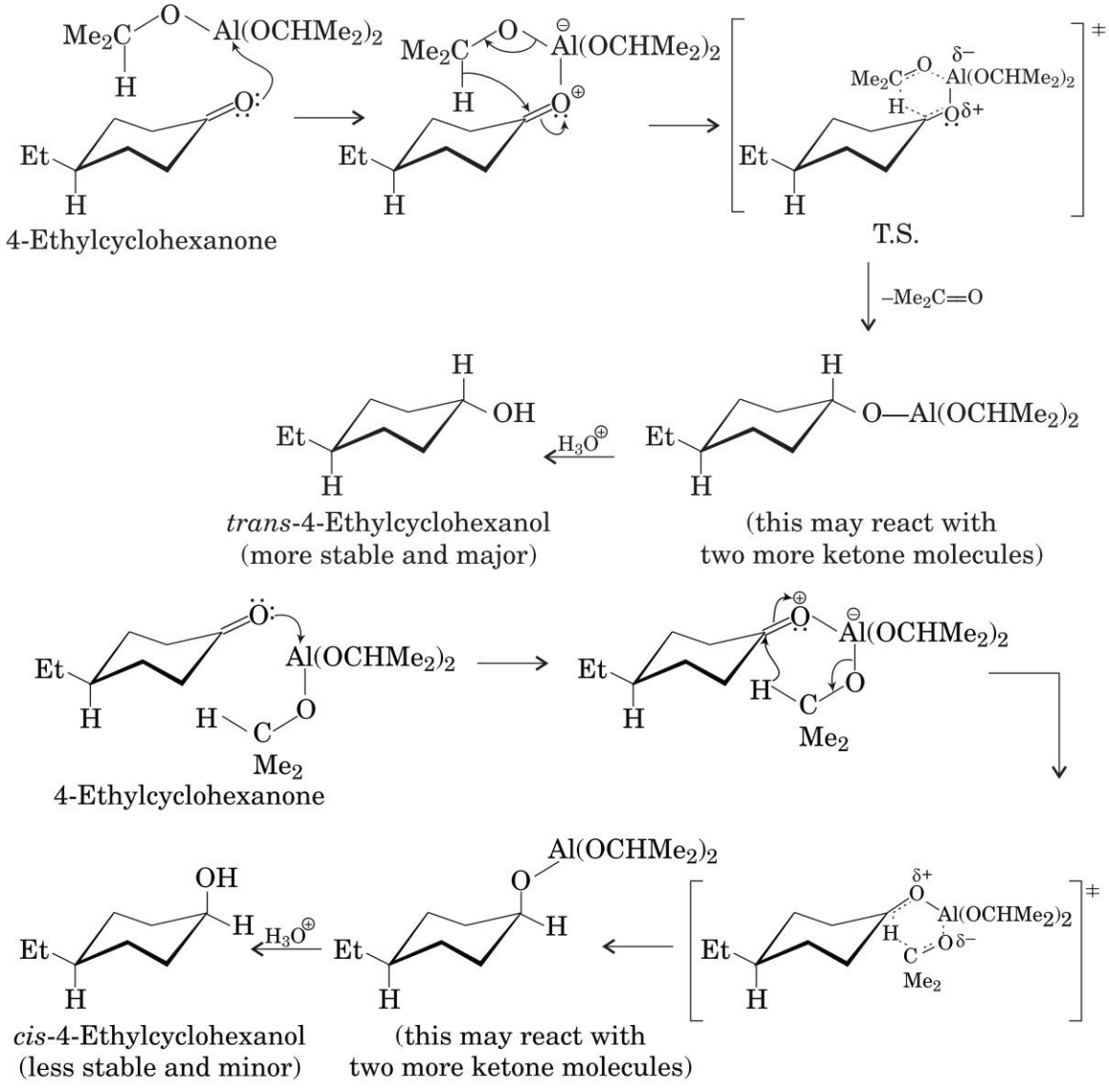




7. Explain the following observation:



Solution Cyclohexanones which is sterically hindered by axial substituents at C-3 and C-5 atoms gives preferentially the axial alcohol due to favourable approach of the attacking reagent from the less hindered equatorial side (*steric approach control*). However, in the absence of any steric hindrance such as mentioned the alternative axial mode of attack leading to the formation of the thermodynamically more stable equatorial alcohol usually takes place preferentially (*product development control*). There is no axial substituent at C-3 or C-5 in the give ketone and the attacking reagent for hydride reduction is not very bulky. Therefore, attack at the carbonyl carbon takes places from the axial side to yield the equatorial alcohol (the thermodynamically more stable *trans*-isomer) predominantly.

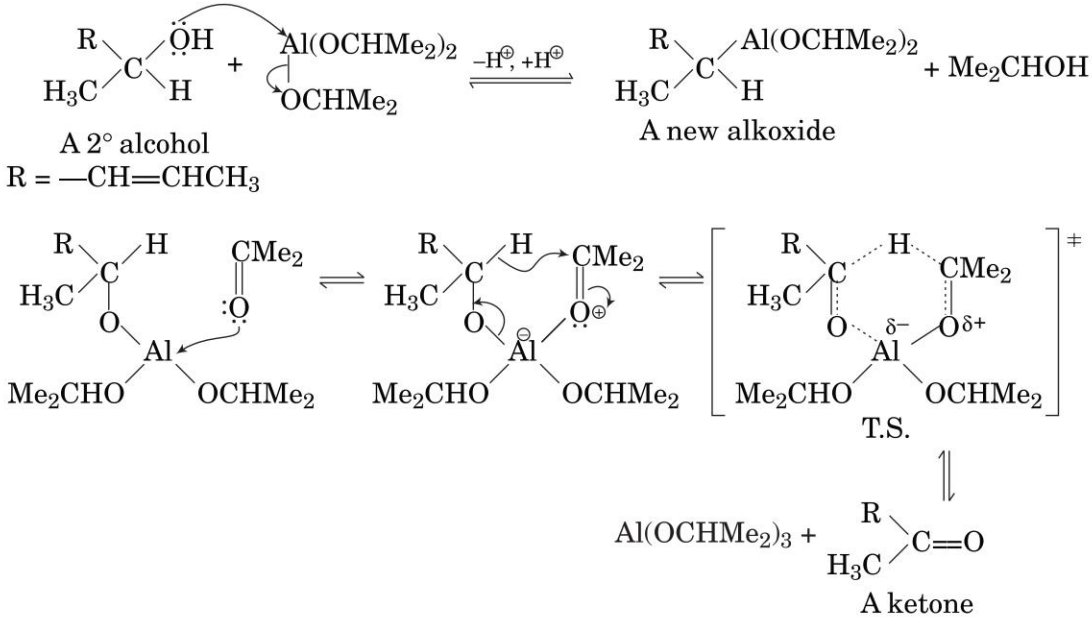


8. What is called Oppenauer oxidation? Discuss its mechanism with a suitable example.

Solution Oxidation of 1° and 2° alcohols to aldehydes and ketones, respectively, using aluminium alkoxides like aluminium isopropoxide, aluminium *tert*-butoxide, etc., in the presence of a hydride ion acceptor like acetone, butanone, cyclohexanone or *p*-benzoquinone is called *Oppenauer oxidation.* For example:

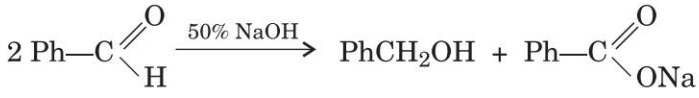
$$CH_3CH{=}CHCHOHCH_3 \underset{CH_3COCH_3}{\overset{Al(OCHMe_2)_3}{\rightleftharpoons}} CH_3CH{=}CHCOCH_3 + (CH_3)_2CHOH$$

Mechanism: This reaction is actually the reverse of Meerwein–Ponndorf–Verley reduction. The alcohol first reacts with the aluminium alkoxide to form a new alkoxide. This alkoxide then reacts with acetone molecule when a hydride ion ($:H^{\ominus}$) from the alkoxide is transferred to the carbonyl carbon of acetone through a cyclic transition state. Finally, aluminium isopropoxide is regenerated along with the oxidized product $CH_3CH{=}CH{-}COCH_3$.

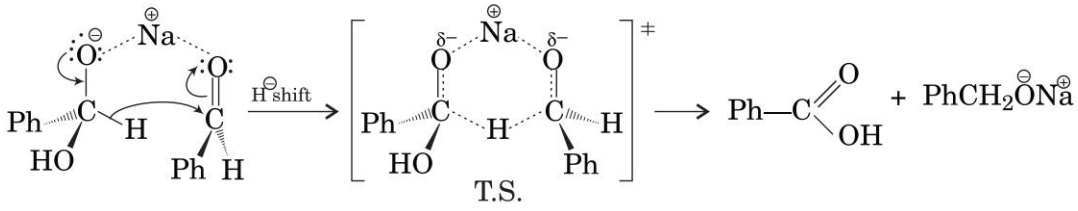


The use of excess acetone shifts the equilibrium to the right.

9. Give the mechanism for the hydride transfer step of the following reaction and draw the transition state:



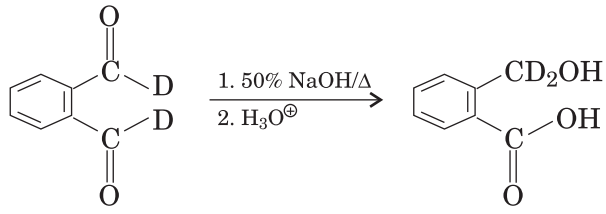
Solution The mechanism for the hydride transfer step of the given reaction is as follows:

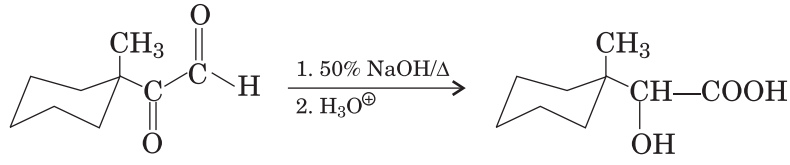


10. Suggest a mechanism for each of the following reactions:

(a) $2\ HCHO \xrightarrow{50\%\ NaOH} CH_3OH + HCOONa$

(b) $2\ Me_3CCHO \xrightarrow{50\%\ NaOH} Me_3CCH_2OH + Me_3CCOONa$

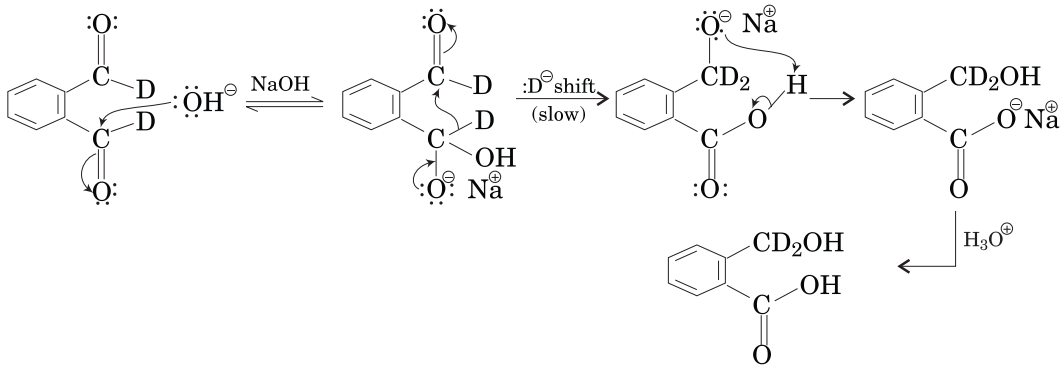
(c) 

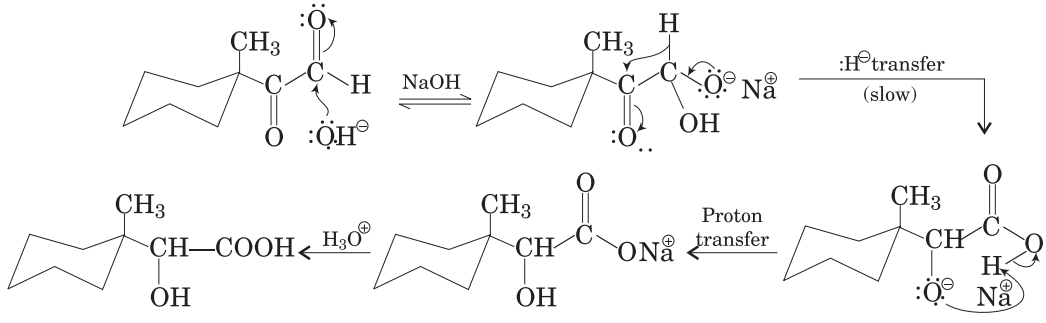
(d) 

Solution

(a) **See article no. 2.5.8.**

(b) **See article no. 2.5.8.**

(c) 

(d) 

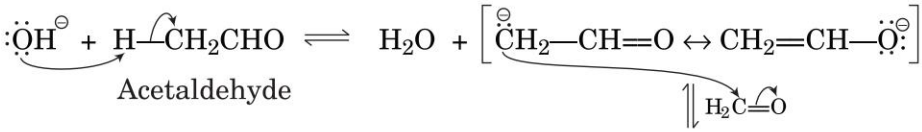
11. Provide a mechanism that explains the formation of pentaerythritol:

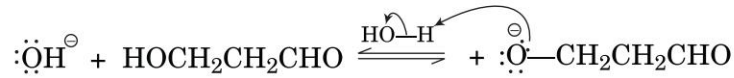
$$\underset{\text{Acetaldehyde}}{CH_3CHO} + \underset{\text{Formaldehyde}}{4\,HCHO} \xrightarrow{Ca(OH)_2} \underset{\text{Pentaerythritol}}{C(CH_2OH)_4}$$

Solution Three crossed aldol reactions followed by one crossed Cannizzaro reaction leads to the formation of pentaerythritol.

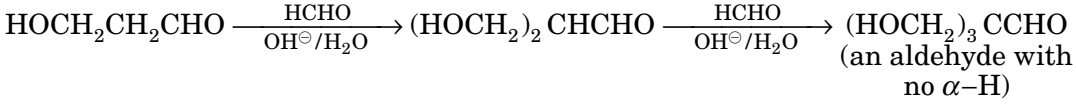
The mechanism of the reaction may be outlined as follows:

Aldol reactions:

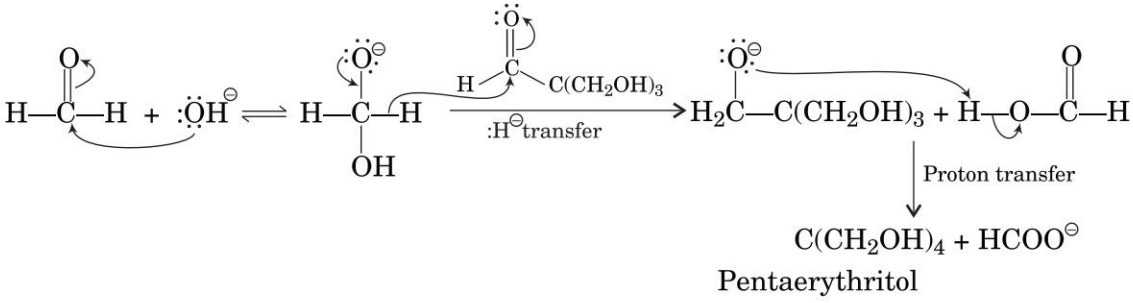




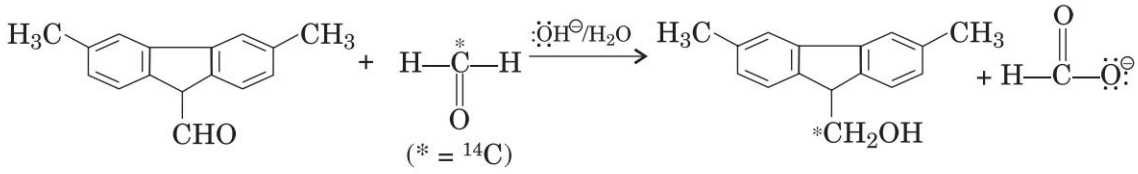
Similarly,



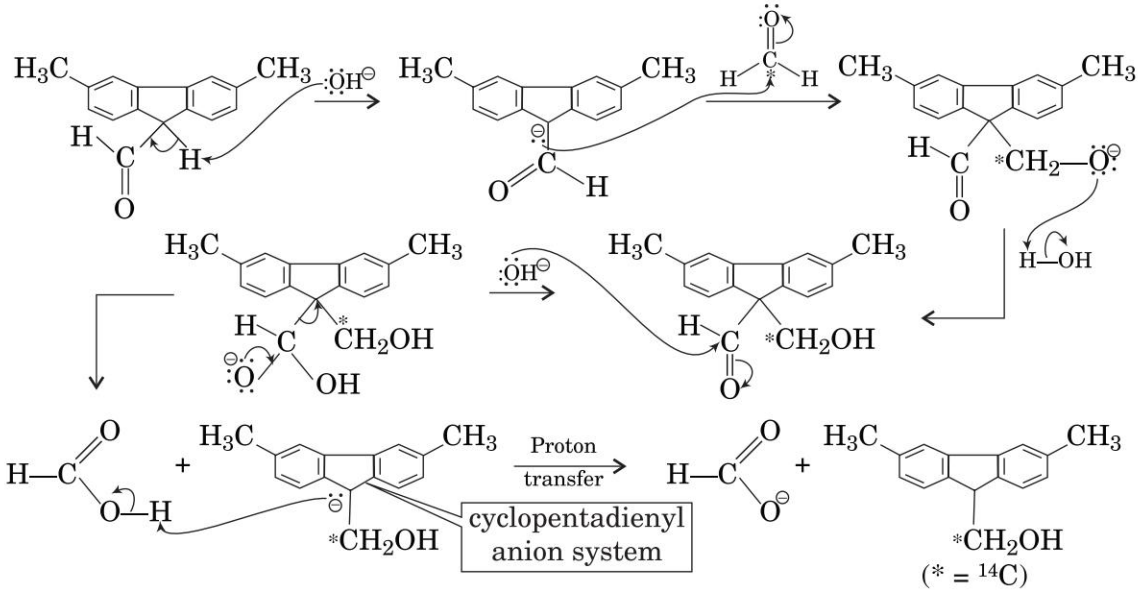
Cannizzaro reaction:



12. Provide a reasonable mechanism for the following reaction:

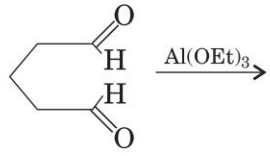


Solution The mechanism of the reaction involves the steps as follows:



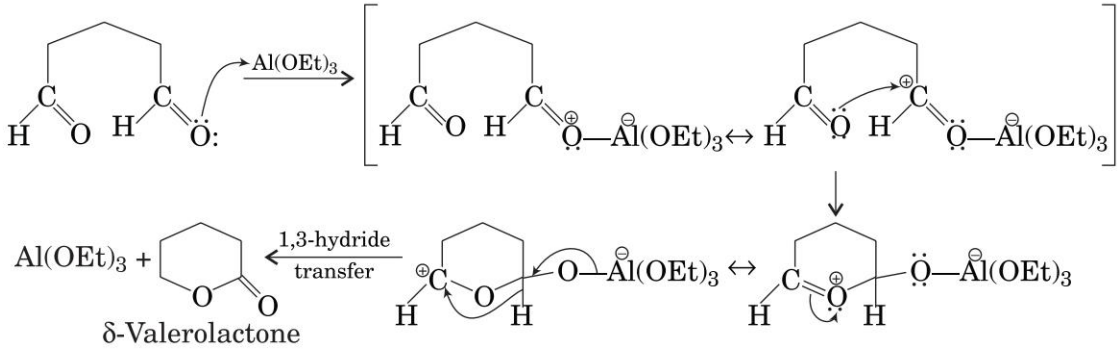
The enolizable aldehyde first undergoes a crossed aldol reaction with HCHO to give an aldol. The alkoxide ion obtained from the aldol by the addition of $OH^{\ominus}$ to the aldehyde function undergoes heterolysis of C—C bond because this leads to a stable carbanion which constitutes a stable aromatic system (cyclopentadienyl anion).

13. Predict the product of the following reaction and provide mechanism that account for its formation:

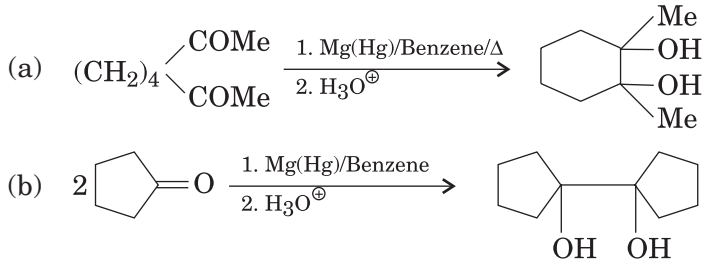


Solution The dialdehyde undergoes an intramolecular Tischenko reaction in the presence of $Al(OEt)_3$ to give δ-valerolactone (a six-membered cyclic ester of δ-lactone).

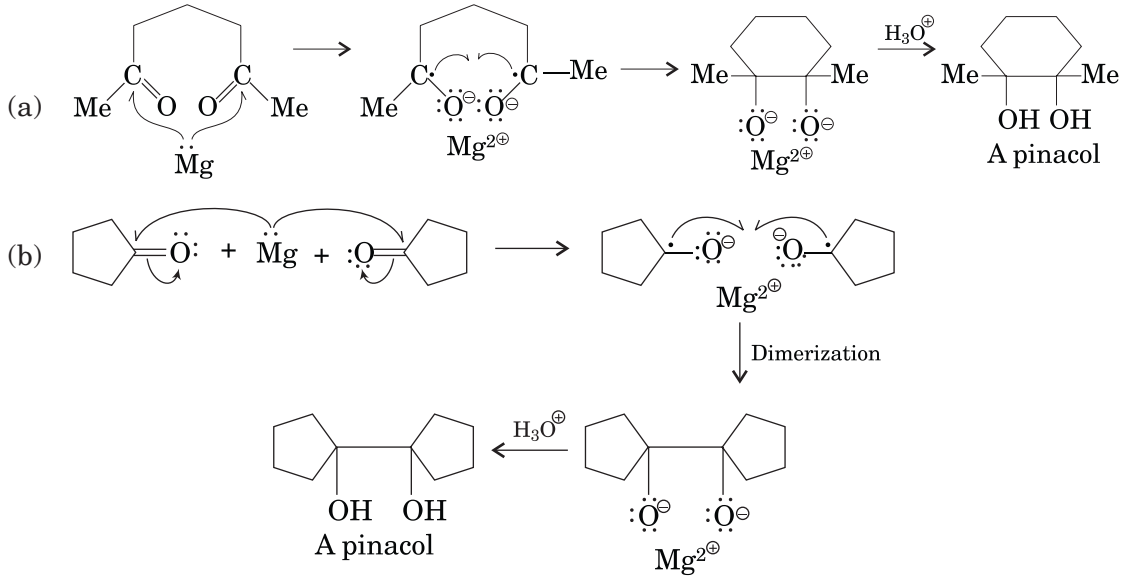
The reaction proceeds through the steps as follows:



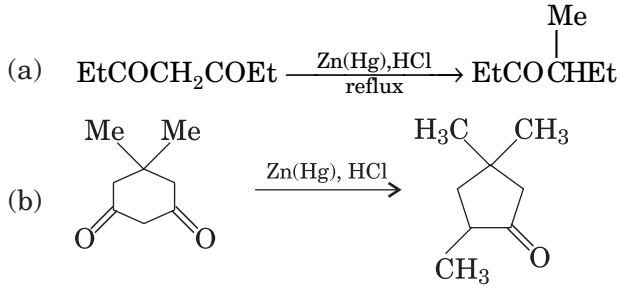
14. Provide a mechanism for each of the following reactions:



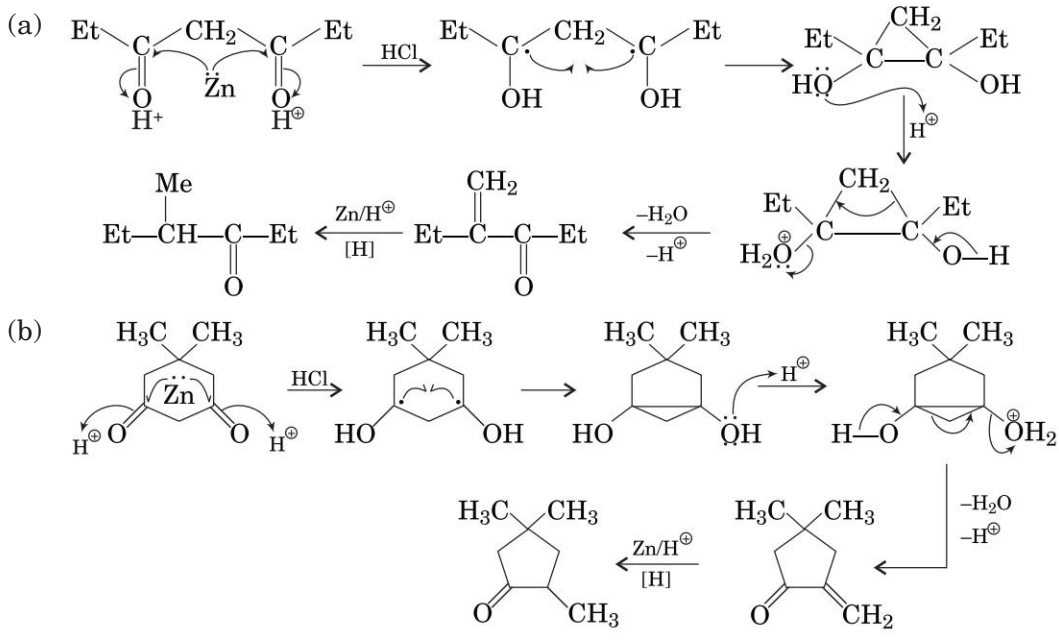
Solution



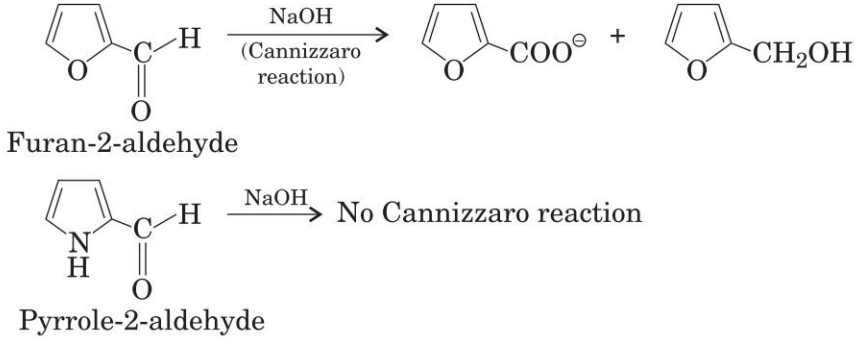
15. Suggest a mechanism for each of the following reactions:



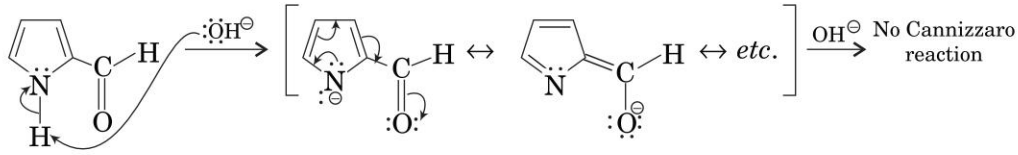
Solution



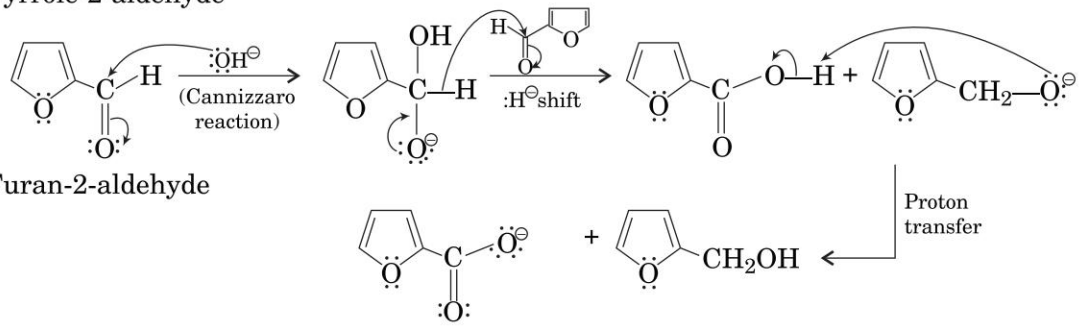
16. Account for the following observations:



Solution Pyrrole-2-aldehyde, being considerably acidic reacts with alkali to form its conjugate base. Because of extensive electron delocalization, the positive character of the carbonyl carbon in the conjugate base is considerably reduced. As a result, nucleophilic attack on the carbonyl carbon by $OH^{\ominus}$ does not take place, i.e., pyrrole-2-aldehyde does not undergo the Cannizzaro reaction. No such deactivation of the carbonyl group occurs in furan-2-aldehyde because in the presence of alkali there is no possibility of formation of a full-fledged negative charge on oxygen.



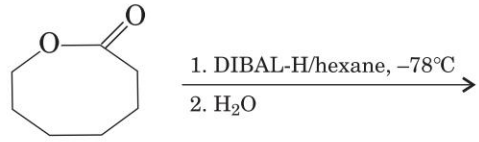
Pyrrole-2-aldehyde



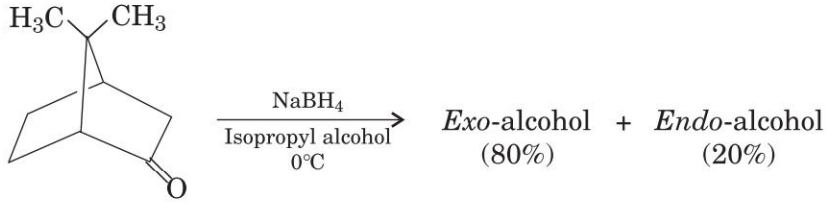
Furan-2-aldehyde

Study Problems

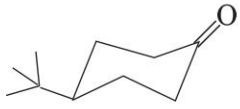
1. Predict the product of the following reaction and suggest a mechanism that accounts for its formation:

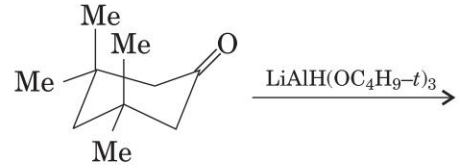


2. Explain the following observation:



3. Predict the major product in each of the following reactions and explain its formation:

(a) 

(b) 

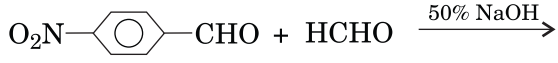
(c) $Me_2CCOCH(Me)CH_2CHO \xrightarrow{LiAlH(OC_4H_9-t)_3}$

[**Hint:** (c) The less sterically hindered carbonyl group gets reduced preferentially than the more sterically hindered one.]

4. Predict the product of the following reaction:

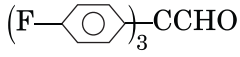
$$m\text{-}BrC_6H_4CHO \xrightarrow[D_2O]{NaOD} A + B$$

5. Predict the product of the following reaction and provide mechanism that explains their formations:

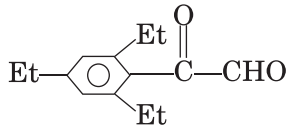


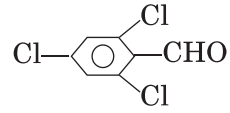
[**Hint:** *p*-Nitrobenzaldehyde undergoes oxidation because the carbonyl carbon is more electrophilic in nature.]

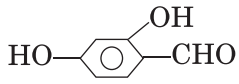
6. Explain why the following aldehydes with no α-H atom do not undergo Cannizzaro reaction when treated with concentrated alkali:

(a) 

(b) I_3CCHO

(c) 

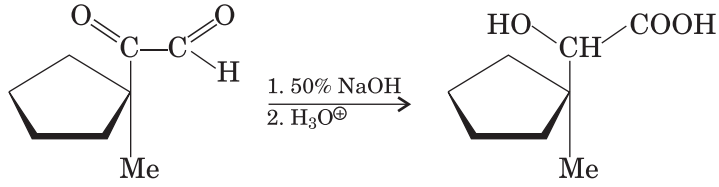
(d) 

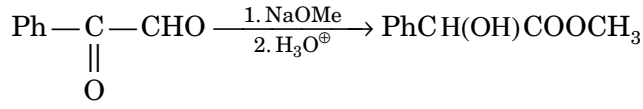
(e) 

[**Hint:** (c) On $:H^{\ominus}$ shift, the carbonyl carbon adjacent to the ring becomes tetrahedral and this tetrahedral becomes involved in severe steric interaction with the *ortho* ethyl group.]

7. *p*-Nitrobenzaldehyde undergoes the Cannizzaro reaction much faster than benzaldehyde, while *p*-methoxybenzaldehyde undergoes the Cannizzaro reaction very much slower than benzaldehyde, offer plausible explanation for these observations.

8. Provide a mechanism for each of the following reactions.

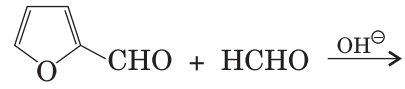
(a) 

(b) 

9. Identify the products of the following crossed Cannizzaro reactions:

(a) $Me_3CCHO + HCHO \xrightarrow{OH^{\ominus}}$

(b) $PhCHO + HCHO \xrightarrow{OH^{\ominus}}$

(c) $p\text{-}O_2NC_6H_4CHO + HCHO \xrightarrow{OH^{\ominus}}$ (d)  $\xrightarrow{OH^{\ominus}}$

10. An aldehyde undergoes the Cannizzaro reaction to form an acid (A) and an alcohol (B). The acid A reduces Tollen's reagent and the alcohol B on oxidation produces the acid A. Identify the aldehyde.

11. What is the fundamental difference between the Cannizzaro reaction and the Tishchenko reaction? Explain with suitable examples.

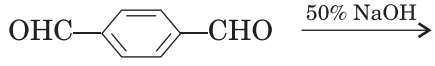
12. Predict the products expected to be formed when a mixture of CH_3CHO and HCHO is treated with $Al(OEt)_3$ (the Tishchenko reaction). Outline the mechanisms for their formations.

[**Hint:** Four esters are expected to be obtained and these are: HCO_2CH_3, $CH_3CO_2C_2H_5$, $HCO_2C_2H_5$ and $CH_3CO_2CH_3$.]

13. Aldehydes possessing α-H atoms usually do not undergo the Cannizzaro reaction under the alkaline reaction conditions. Offer an explanation.

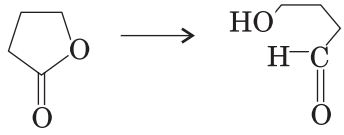
[**Hint:** The rate of enolate formation leading to an aldol is much faster than the rate of the addition of $OH^{\ominus}$ to —CH═O and for this reason, aldehydes with α-H atoms do not undergo the Cannizzaro reaction.]

14. Predict the products of the following reaction and provide mechanism that accounts for their formation:



[**Hint:** A Cannizzaro reaction in which both the —CHO group may be reduced, both of them may be oxidized or one may be oxidized and the other may be reduced.]

15 Select the most convenient hydride transfer reducing agent for each of the following transformations:

(a) 

(b) $CH_3CH_2CO_2Et \rightarrow CH_3CH_2CH_2OH$

(c) $CH_3CH_2COOCH_3CH_2 \rightarrow CH_3CH_2CH_2OH$

(d) 

(e) $CH_3COOCH_3 \rightarrow CH_3CHO$

16. Select a suitable reducing agent to convert an amide RCONHR into each of the following compounds:

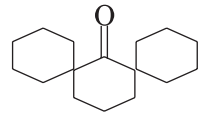
(a) RCH_2NHR (b) RCHO (c) RCH_2OH

17. Offer plausible explanations for the following:

(a) $NaBH_4$ cannot reduce a —COOH group, but borane reduces it to a 1° alcohol.

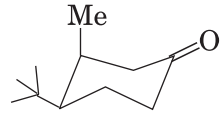
(b) $LiBH_4$ reduces the C═O group of amides, but $NaBH_4$ cannot.
(c) Both $AlH_4^{\ominus}$ and $AlHR_2$ can reduce RCOOH to RCH_2OH, but the mechanistic course of the reductions is different.

18. The following carbonyl compound does not undergo the Clemmensen reduction – Why?



19. Formaldehyde is almost always oxidized in the crossed Cannizzaro reaction – Why?

20. Give the mechanism of reduction of the following anancomeric ketone with aluminium isopropoxide in isopropanol.



[**Hint:** Equatorial approach of the reagent is sterically favoured and therefore, transfer of $:H^{\ominus}$ ion takes place from the equatorial side leading to the formation of structurally less stable alcohol with axial —OH group. Axial approach of $:H^{\ominus}$ ion from the isopropoxy group is subjected to steric hindrance (due to the axial $—CH_3$ group at C–3) and as a consequence, equatorial alcohol is formed in a very small amount.]

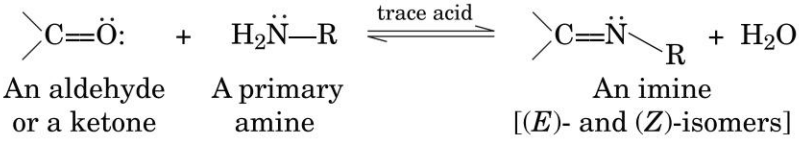
2.6 ADDITION OF NITROGEN NUCLEOPHILES

- **Addition of primary amines and formation of imines**
- **Addition of compounds (like primary amine) such as hydroxyl amine, hydrazine and substituted hydrazines and formation of imine derivatives**
- **Reductive amination**
- **Wolff-Kishner reduction**
- **Addition of secondary amines and formation of enamines**
- **Stork enamine reaction**

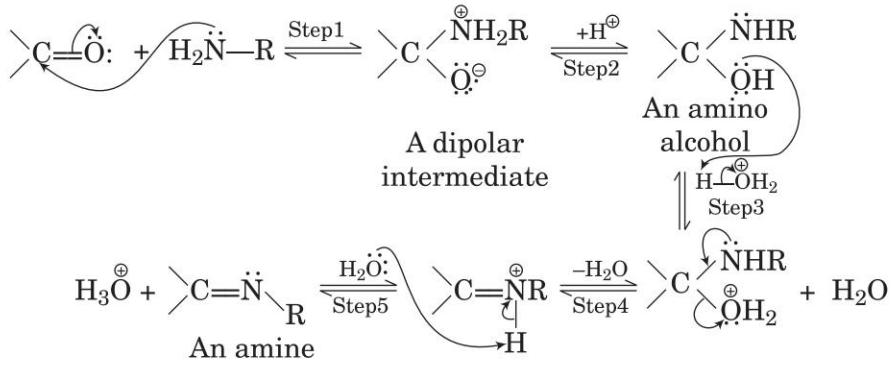
2.6.1 Addition of primary amines and formation of imines

Aldehydes and ketones react with primary amines ($R–NH_2$) to form imines. An imine is a compound with a carbon–nitrogen double bond. The overall reaction results in replacement of C═O by C═NR with the loss of a molecule of water. A C═N group is similar to a C═O group. The nitrogen atom of an imine is sp^2 hybridized. Two of its sp^2 orbitals forms two σ bonds with carbon and a substituent, and the third sp^2 orbital is occupied by a lone pair. The *p* orbital of N and the *p* orbital of C overlap with each other to form a π bond. Imine formation is acid-catalysed and the product can form a mixture of (*E*)- and

(*Z*)-isomers. Imines are also called *Schiffs bases*. The overall process is a condensation reaction and an imine is a condensation product.



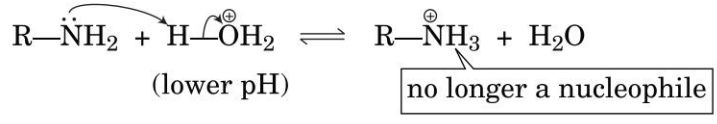
Mechanism of the reaction The mechanism of this reversible reaction involves the steps as follows:



In step 1, the carbonyl compound undergoes nucleophilic attack by the amine to form a dipolar intermediate. In step 2, protonation and deprotonation of the intermediate occur to produce an aminoalcohol (or carbinolamine). In step 3, the –OH group of the aminoalcohol undergoes protonation and becomes converted to a good leaving group. In step 4, the protonated aminoalcohol loses a molecule of water to form a resonance-stabilized iminium ion. It is the rate-determining step of the reaction. In step 5, the iminium ion undergoes deprotonation to form an imine.

The equilibrium can be forced towards the imine by removing water as it is formed (step 4) or by precipitation.

Adjustment of the pH of the medium during formation of imine The formation of imine generally takes place at a much faster rate between pH 4 and 5 and slowly at very low or very high pH. Dehydration of the amino alcohol is the rate-determining step of the reaction. As the acidity decreases (higher pH), the rate of the reaction decreases because less and less of the aminoalcohol is present in the reactive protonated form. As the acidity increases, the rate of the reaction decreases because more and more of the amine becomes protonated and as a result, less and less the amine present in the nucleophilic nonprotonated form.

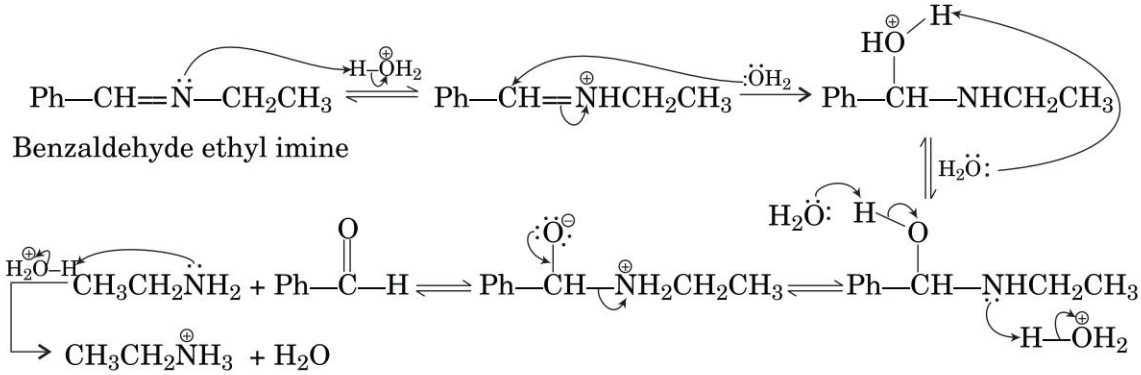


For this reason, it is necessary to adjust the reaction medium to just the right acidity. A pH between 4 and 5 is, in fact, an effective compromise.

Hydrolysis of imines Imine formation is reversible, and most imines can be hydrolysed back to the amine and the ketone or aldehyde in aqueous acidic solution. For example:

$$\underset{\text{Benzaldehyde ethyl imine}}{PhCH{=}N{-}CH_2CH_3} \xrightarrow{H_3O^{\oplus}} \underset{\text{Benzaldehyde}}{PhCHO} + \underset{\text{Ethylamine (salt)}}{CH_3CH_2\overset{\oplus}{N}H_3}$$

The mechanism for the hydrolysis of an imine is simply the reverse of the mechanism for its formation (the principle of microscopic reversibility). Therefore, the hydrolysis of benzaldehyde ethyl imine involves the steps as follows:

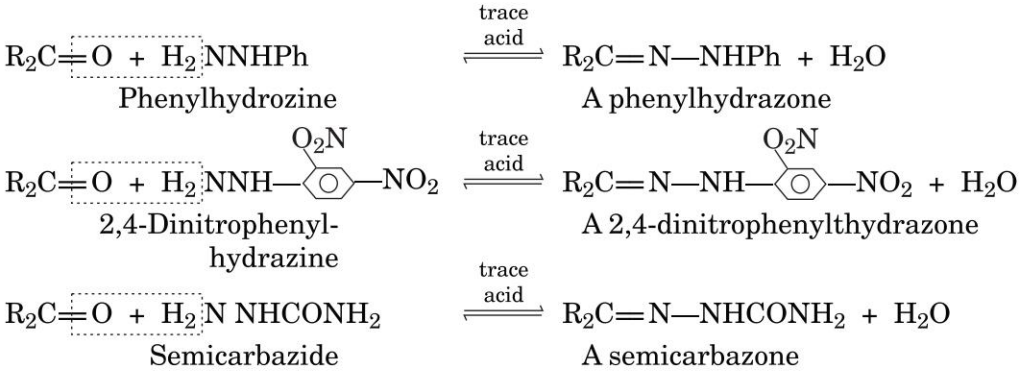


2.6.2 Addition of compounds like hydroxylamine, hydrazine and substituted hydrazines (similar to primary amines) and formation of imine derivatives

Compounds such as hydroxylamine (NH_2OH), hydrazine (NH_2NH_2) and substituted hydrazines such as phenylhydrazine (NH_2NHPh), 2,4-dinitrophenylhydrazine (NH_2NH—C$_6$H$_3$(NO$_2$)$_2$) and semicarbazide ($NH_2NHCONH_2$), are similar to primary amines in that they have a $—NH_2$ group. Thus, like primary amines (RNH_2), they react with aldehydes and ketones to form imines which are, in fact, called imine derivative because the substituent attached to the N atom of the imine is not as R group. The imine derivatives obtained when hydroxylamine reacts with an aldehyde or a ketone is called oxime and the imine derivatives obtained when hydrazine, phenylhydrazine, 2,4-dinitrophenylhydrazine and semicarbazide react with an aldehyde or a ketone are called hydrazone, phenylhydrazone, 2,4-dinitrophenylhydrazone and semicarbazone, respectively.

$$\underset{\text{Hydroxylamine}}{R_2C{=}O + H_2NOH} \xrightleftharpoons{\text{trace acid}} \underset{\text{An oxime}}{R_2C{=}NOH + H_2O}$$

$$\underset{}{R_2C{=}O + H_2NNH_2} \xrightleftharpoons{\text{trace acid}} \underset{\text{A hydrazone}}{R_2C{=}N{-}NH_2 + H_2O}$$



The mechanism by which these imine derivatives form is similar to the mechanism for imine formation from a primary amine ($R—NH_2$).

The nitrogen nucleophiles like hydroxylamine, hydrazine, phenylhydrazine, semicarbazide etc., are very susceptible to aerial oxidation. In order to protect these electron rich compounds from aerial oxidation, they are converted into their solid hydrochloride salts. These salts do not get oxidized easily in the presence of air.

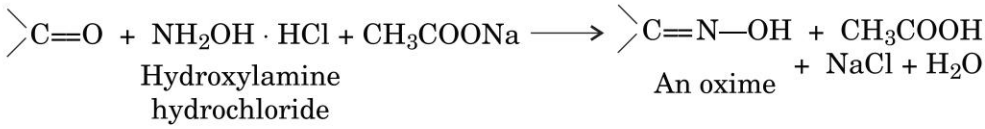
$NH_2OH \cdot HCl$ or $\overset{\oplus}{N}H_3OHCl^{\ominus}$ (Hydroxylamine hydrochloride)

$NH_2NH_2 \cdot HCl$ or $NH_2\overset{\oplus}{N}H_3Cl^{\ominus}$ (Hydrazine hydrochloride)

$C_6H_5NHNH_2 \cdot HCl$ or $C_6H_5NH\overset{\oplus}{N}H_3Cl^{\ominus}$ (Phenylhydrazine hydrochloride)

$NH_2CONHNH_2 \cdot HCl$ or $NH_2CONH\overset{\oplus}{N}H_3Cl^{\ominus}$ (Semicarbazide hydrochloride)

These salts do not normally react with carbonyl compounds because the unshared pair of electrons on the N atom of the $—NH_2$ group is no longer available (used up in forming a co-ordinate bond with $H^{\oplus}$). However, they react in the presence of sodium acetate. The role of sodium acetate (CH_3COONa) is that it reacts with these salts and releases the free nitrogen nucleophile. Furthermore, the liberated acetic acid acts as a catalyst by offering an optimum pH in the presence of sodium acetate. For example, when hydroxylamine hydrochloride is allowed to react with a carbonyl compound in the presence of sodium acetate, the corresponding oxime is formed according to the following reaction:



The reaction, in fact, occurs in two stages. Hydroxylamine hydrochloride first reacts with sodium acetate to form hydroxylamine, acetic acid and sodium chloride. The equilibrium is favoured by the formation of weaker acid and weaker base from stronger acid and stronger base.

$$\underset{\text{(stronger acid)}}{NH_2OH{\cdot}HCl} + \underset{\text{(stronger base)}}{CH_3COONa} \rightleftharpoons \underset{\text{(weaker base)}}{NH_2OH} + \underset{\text{(weaker acid)}}{CH_3COOH} + NaCl$$

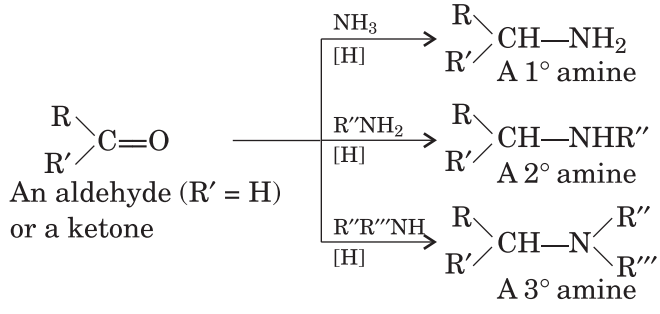
The liberated hydroxylamine then reacts with the carbonyl compound in the presence of acetic acid and sodium acetate to form the corresponding oxime.

$$\underset{}{>C{=}O} + \underset{\text{Hydroxylamine}}{H_2NOH} \longrightarrow \underset{\text{An oxime}}{>C{=}N{-}OH} + H_2O$$

The reactions leading to the formation of axime, hydrazone, and related derivatives from aldehydes and ketones are reversible. These imine derivatives undergo acid-catalyzed hydrolysis to give the starting carbonyl compound and the nitrogen nucleophile.

2.6.3 Reductive amination

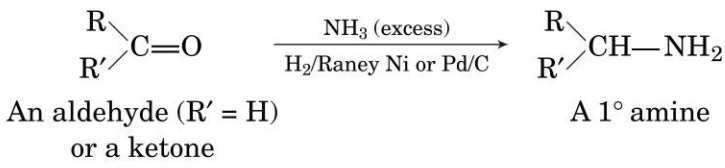
Aldehydes or ketones can be converted into amines through catalytic or chemical reduction in the presence of NH_3 or an amine. Ammonia and a primary amine are used to prepare a primary and a secondary amine respectively through the formation of an imine (Schiff's base). A secondary amine is used to prepare to tertiary amine through the formation of an enamine. This process of preparing primary, secondary and tertiary amines is called *reductive amination*.

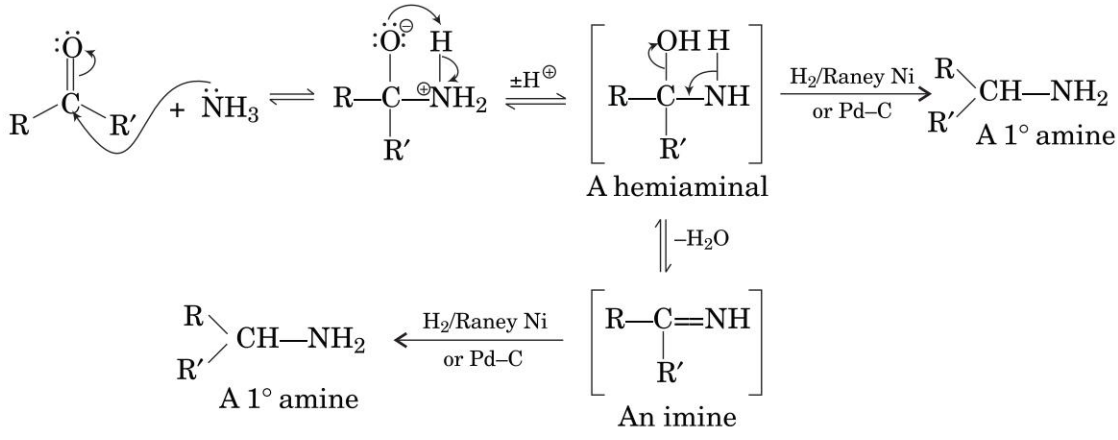


The reducing agents used include hydrogen and a catalyst (such as Ni) or $NaBH_3CN$ or $LiBH_3CN$ (sodium or lithium cyanoborohydride).

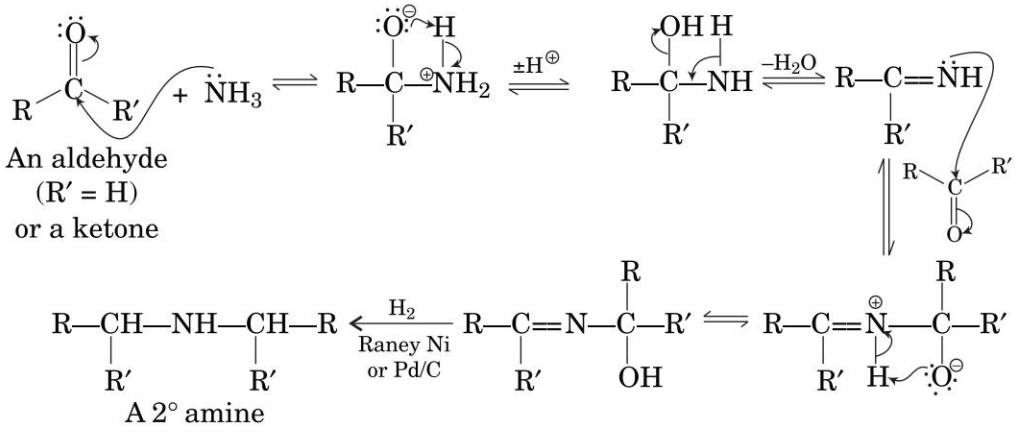
The reductive amination of an aldehyde or ketone may also be called reductive alkylation of the amine.

Mechanism of the reaction The mechanism of reductive amination leading, for example, to a primary amine may be given as follows:



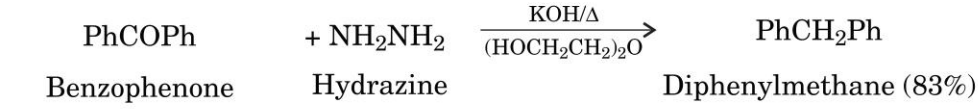


A secondary amine is formed when an excess of the carbonyl compound is used. This may be shown as follows:



2.6.4 Wolff-Kishner reduction

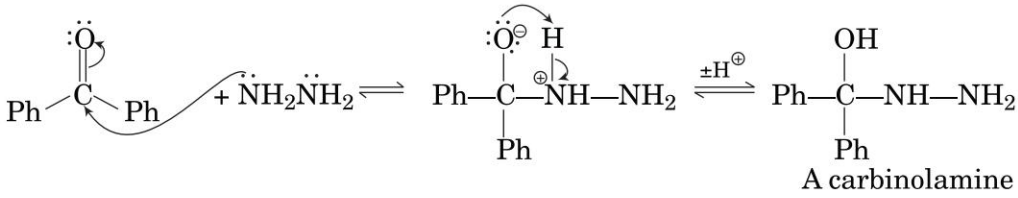
When an aldehyde or a ketone is heated with hydrazine ($\ddot{N}H_2\ddot{N}H_2$) in the presence of strong base (NaOH or KOH), the carbonyl group is reduced to methylene (—CH_2—) group. This reaction is called the *Wolff-Kishner reduction.* For example:



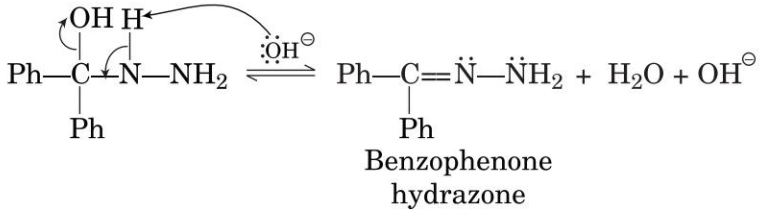
Mechanism of the reaction The reaction takes place in two stages.

First stage: Hydrazine reacts with benzophenone to yield the corresponding hydrazone. This occurs in two steps:

Step 1: Nucleophilic addition of hydrazine to the carbonyl group to form a carbinolamine.

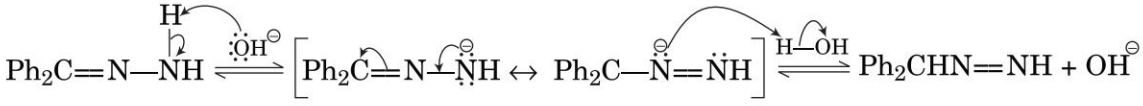


Step 2: Elimination of a molecule of water to form the hydrazone.

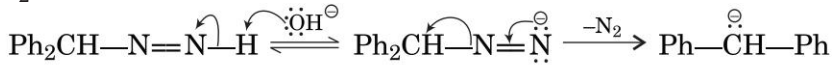


Second stage: The strong base converts the $\rangle C{=}N{-}NH_2$ group into a methylene ($-CH_2-$) group. This occurs in three steps:

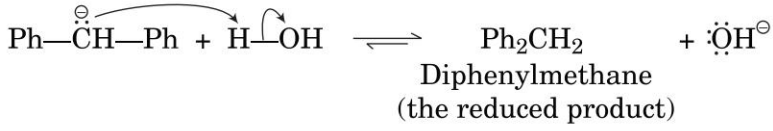
Step 1: The hydrazone undergoes base-catalysed isomerization.



Step 2: The isomer of hydrazone reacts with alkali to form a carbanion by eliminating a molecule of N_2.



Step 3: The carbanion undergoes protonation to yield diphenylmethane.



Synthetic applications

(i) Both the Clemmensen and the Wolff-Kishner reduction convert a $\rangle C{=}O$ group to a $—CH_2—$ group. However, the first one takes place under strongly acidic conditions and the second one takes place under strongly basic conditions. A keto-alcohol can be reduced to yield the corresponding alcohol not by the Clemmensen method but by the Wolff-Kishner method. This is because the keto-alcohol undergoes dehydration in the presence of acid.

$$\underset{\text{4-Hydroxy-2-hexamone}}{CH_3COCH_2CHOHCH_2CH_3} \xrightarrow[\text{(not Clemmensen reduction)}]{\text{Wolff-Kishner reduction}} \underset{\text{3-Hexanol}}{CH_3CH_2CH_2CHOHCH_2CH_3}$$

(ii) Wolff-Kishner reduction has been used in steroid chemistry for the reduction of carbonyl groups. Clemmensen reduction is found to be unsuitable because steroid molecules may undergo acid catalyzed rearrangement through initial protonation of the carbonyl oxygen. Moreover, steroid molecules with alcoholic —OH group may undergo acid catalyzed dehydration.

2.6.5 Important uses of the imine-forming reaction

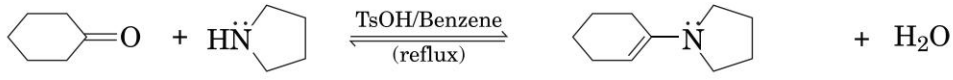
The three important uses of the imine-forming reaction are as follows: (i) While many carbonyl compounds are liquids, most of their oximes, 2,4-dinitrophenyl hydrazones and semi carbazones are relatively insoluble solids with sharp, characteristic melting points. The melting point of such derivatives of an unknown carbonyl compound can be compared with the melting point for the same derivative of a known carbonyl compound or with data found in a reference table and on this basis, an unknown carbonyl compound can be identified. (ii) The imine-forming reaction can be used to prepare amines from aldehyde or ketones (reductive amination). (iii) An imine can be hydrolyzed to yield the corresponding carbonyl compound and therefore, this reaction can also be used to isolate an aldehyde or ketone from a reaction mixture containing some other organic compounds.

2.6.6 Addition of secondary amines and formation of enamines

Aldehydes and ketones react with secondary amines (R_2NH) in the presence of a trace of an acid (e.g., TsOH, a useful catalyst in nonaqueous medium) to form enamines which are *α,β*-unsaturated tertiary amines, i.e., tertiary amines with a double bond in the α,β-position relative to the nitrogen atom. The general equation for enamine formation may be give as follows:

$$\rangle CH—\overset{|}{C}{=}O + R_2NH \underset{}{\overset{\text{cat. HA}}{\rightleftharpoons}} \rangle C{=}\overset{|}{C}—NR_2 + H_2O$$

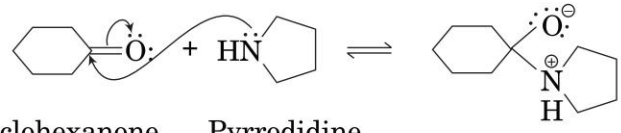
For example, phyrrolidine reacts with cyclohexanone in the presence of *p*-toluenesulphonic acid (TsOH) to form the enamine *N*-(1-cylohexyl)pyrrolidine.



Cyclohexanone Pyrrolidine (a 2° amine) *N*-(1-Cyclohexyl) pyrrolidine (An enamine)

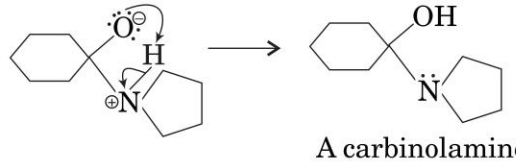
Mechanism of the reaction The mechanism for enamine formation is exactly the same as that for imine formation except for the last step. In enamine formation, which involves a secondary amine, there is no proton for removal from the nitrogen in the iminium cation intermediate. Thus, a neutral imine cannot be formed. A proton is lost from a carbon adjacent to the former carbonyl carbon instead, resulting in an enamine. The mechanism of this reversible reaction involves the steps as follows:

Step 1: Nucelophile attack of the secondary amine pyrrolidine on the carbonyl carbon of cyclohexanone leads to the formation of a dipolar tetrahedral intermediate.



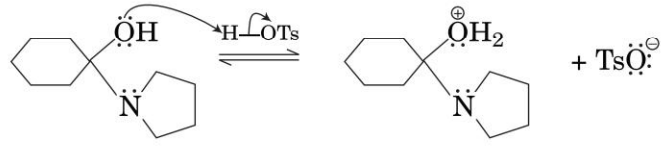
Cyclohexanone Pyrrodidine

Step 2: The intermediate undergoes intramolecular proton transfer to yield a carbinolamine or aminoalcohol.

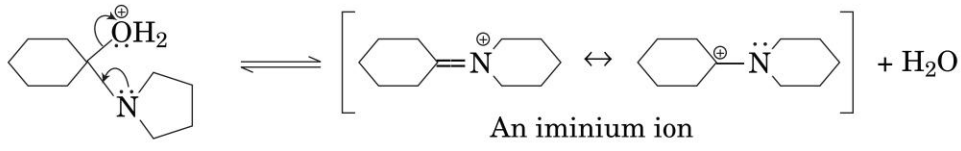


A carbinolamine or aminoalcohol

Step 3: The —OH group of the carbinolamine undergoes protonation by the catalytic acid and becomes a good leaving group (an $-\overset{\oplus}{O}H_2$ group).

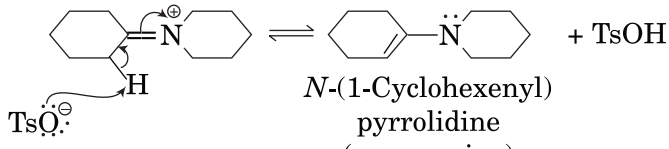


Step 4: The protonated carbinolamine loses a molecule of water to form a resonance-stabilized iminium ion.



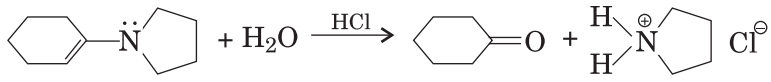
An iminium ion

Step 5: The iminium ion undergoes deprotonation to form an enamine. Proton removal occurs from the carbon adjacent to the iminium group because there is no proton to be removed from the nitrogen atom of the iminium cation.

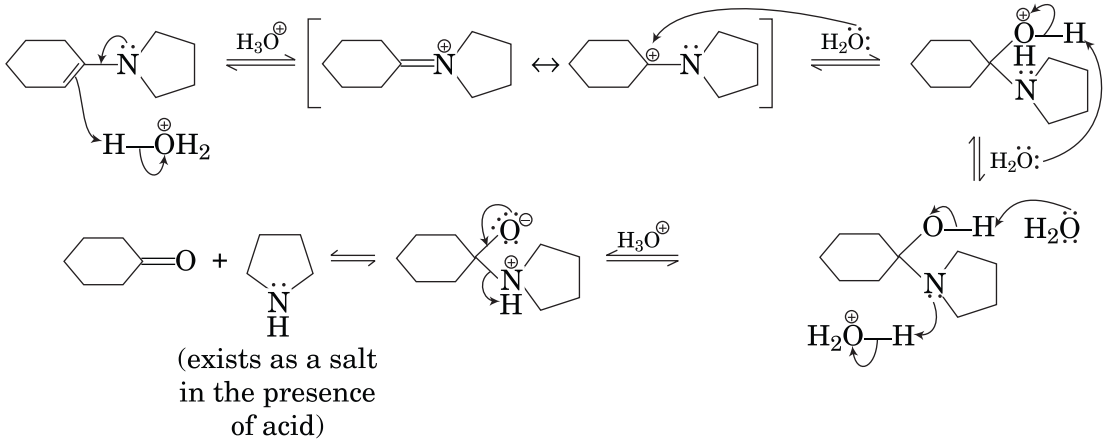


Some relevant points (i) The equilibrium can be forced towards the enamine by removing water as it is formed (in step 4). So it is necessary to remove water from the reaction mixture during enamine preparation. (ii) Water is usually removed from the reaction mixture by azeotropic distillation with benzene. (iii) In cyclic secondary amines (e.g. pyrrolidine, piperidine, and morpholine), the carbon atoms attached with the N atom are held back by the ring system. So, they possess less steric crowding around nitrogen than open chain amines and for this reason, cyclic 2° amines are generally used in enamine synthesis.

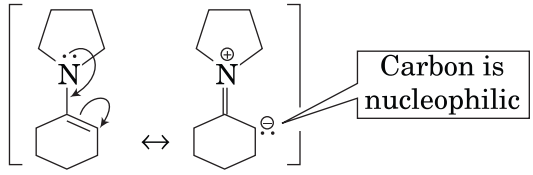
Hydrolysis of enamines Enamines undergo hydrolysis by dilute aqueous acid to yield the carbonyl compound and the secondary amine. For example:



The mechanism for hydrolysis of an enamine is simply the reverse of the mechanism for its formation (the principle of microscopic reversibility). Therefore, the hydrolysis of this enamine involves the steps as follows:



Use of enamines in organic synthesis An enamine can be represented as a resonance hybrid of the following two structures (I and II):

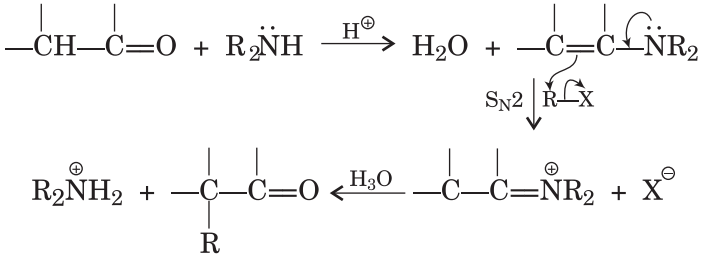


I II

An enamine

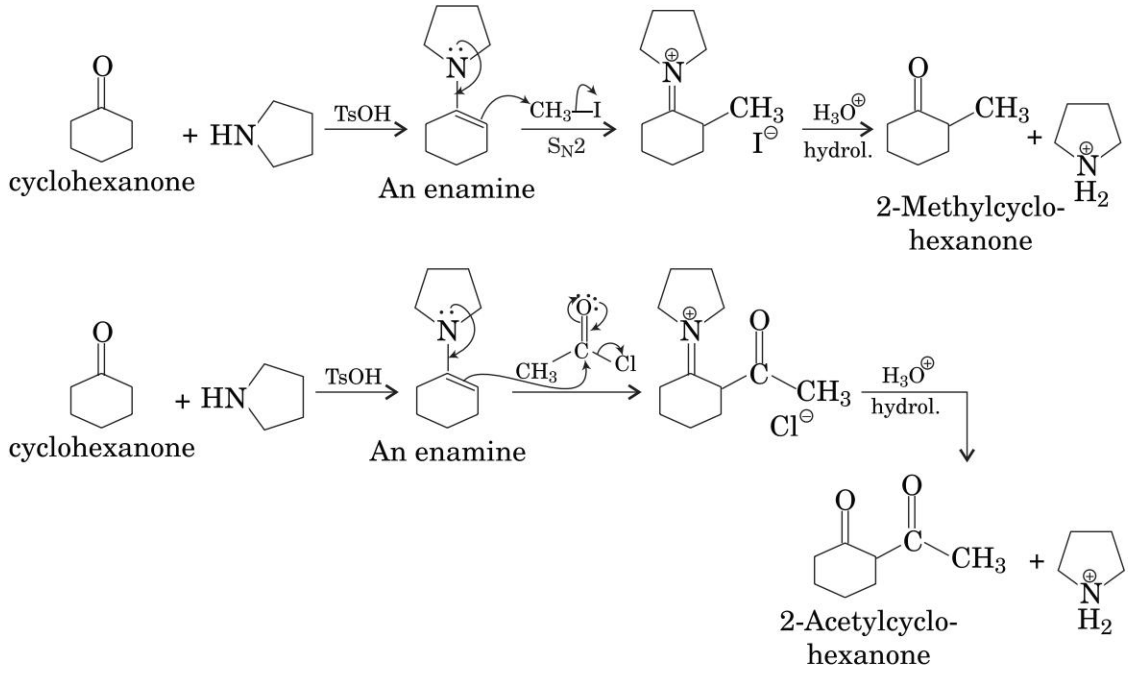
From the resonance structures it becomes evident that an enamine behaves as an ambident nucleophile due to nitrogen with its lone pair of electrons (in structure I) and the electron-rich carbon (in structure II). However, the electron rich carbon being more polarizable is a better nucleophile and is more potent than nitrogen to attack an electrophilic species (in reactions like alkylations, acylations and Michael additions). The product may then be hydrolyzed to regenerate the carbonyl group, therefore, enamines can be used as a synthetic equivalent of aldehyde or ketone enolates because the alkene carbon of an enamine reacts the same way as does the α carbon of an aldehyde or ketone enolate and after hydrolysis, the products obtained are the same. That is, when an enolate is treated with an alkyl halide (R–X) or acyl halide (RCOX) followed by hydrolysis, the net result is the alkylation or acylation of the carbonyl compound at the α position. Enamines are, therefore, useful synthetic intermediates for the formation of carbon–carbon bonds. The synthesis of α-alkyl or α-acyl compounds by way of an enamine is known as the *Stork enamine reaction*. This method is more advantageous over other alkylation methods in providing preferential monoalkylation of ketones and the alkylation usually takes place on the less substituted side of the starting ketone. Aldehydes can also be alkylated by this reaction.

The generalized sequence of the Stork enamine reaction (alkylation of an unactivated ketone through the formation of an enamine) is as follows:

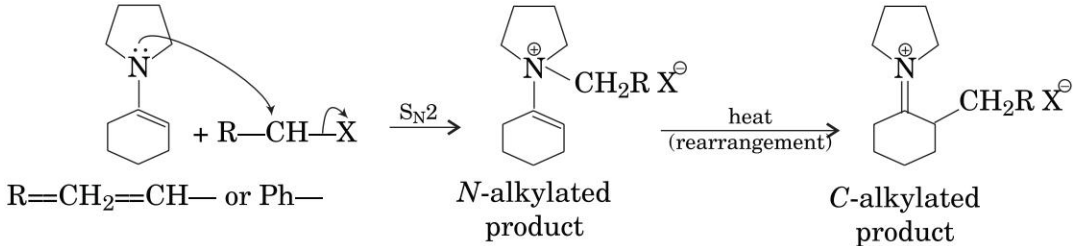


The ketone is first converted to the corresponding enamine. The enamine is then alkylated by allowing it to react with an alkyl halide. The resulting iminium ion is then hydrolyzed by dilute acid to yield the alkylated ketone.

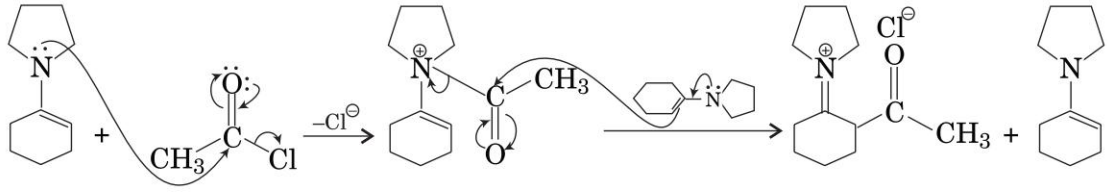
Stork enamine synthesis of 2-methylcyclohexanone and 2-acetylcyclohexanone (a β-diketone) may be shown as follows:



It is to be noted that alkylation may lead to the formation of a considerable amount of *N*-alkylated product. When this *N*-alkylated product is heated, it becomes converted in to a *C*-alkyl compound. This rearrangement is particularly favourable when the alkyl halide is an allylic halide, benzylic halide or α-haloacetic ester.

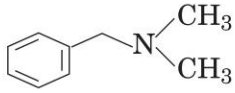


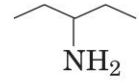
Similarly, *N*-acylation may take place in this synthesis. However, the *N*-acyl product is unstable and can act as an acylating agent itself.

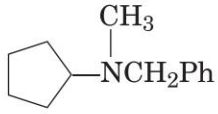


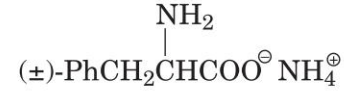
SOLVED PROBLEMS

1. How can the following amines be prepared through reductive amination?

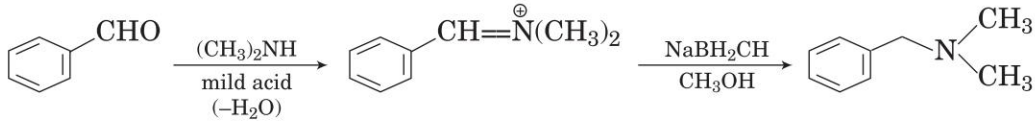
(a) 

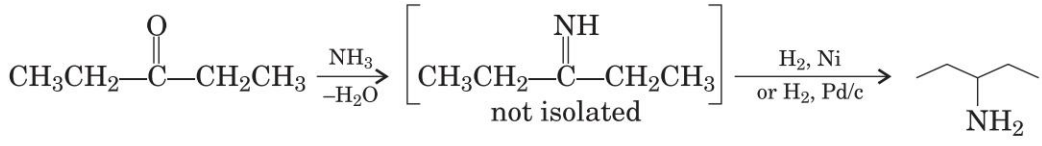
(b) 

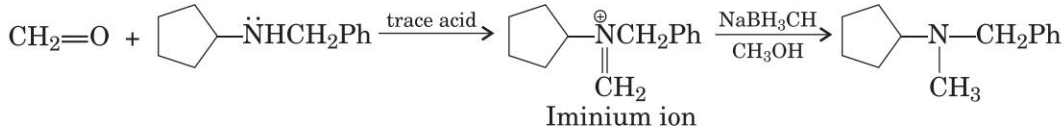
(c) 

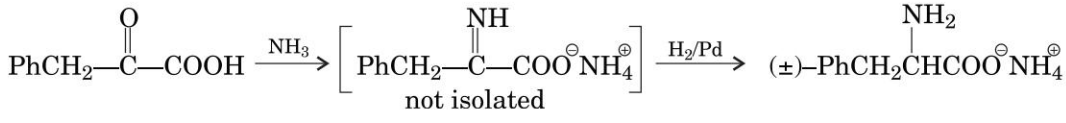
(d) 

Solution

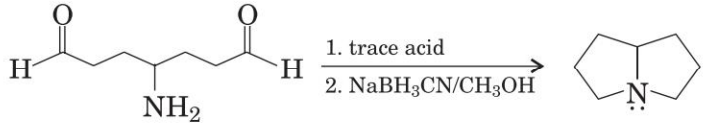
(a) 

(b) 

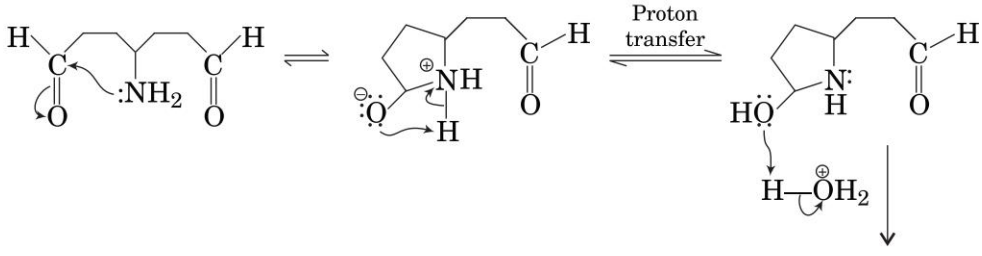
(c) 

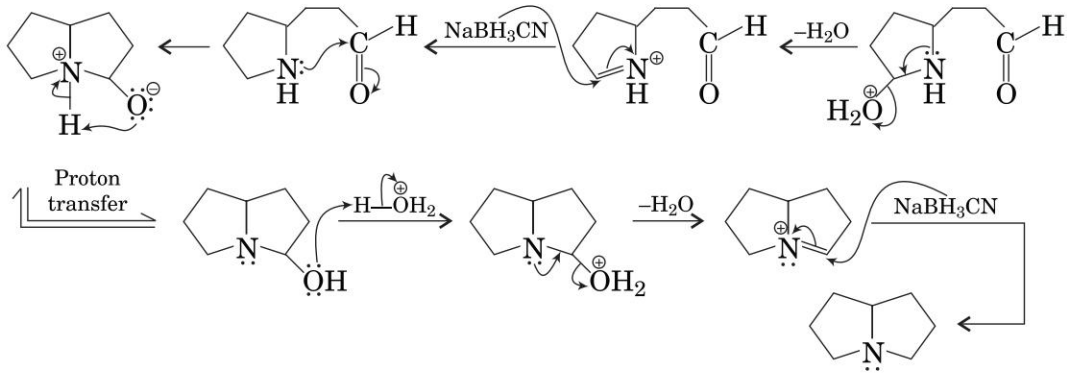
(d) 

2. Suggest a mechanism for the following reaction:

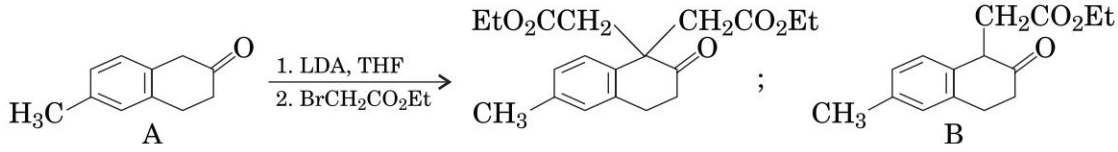


Solution

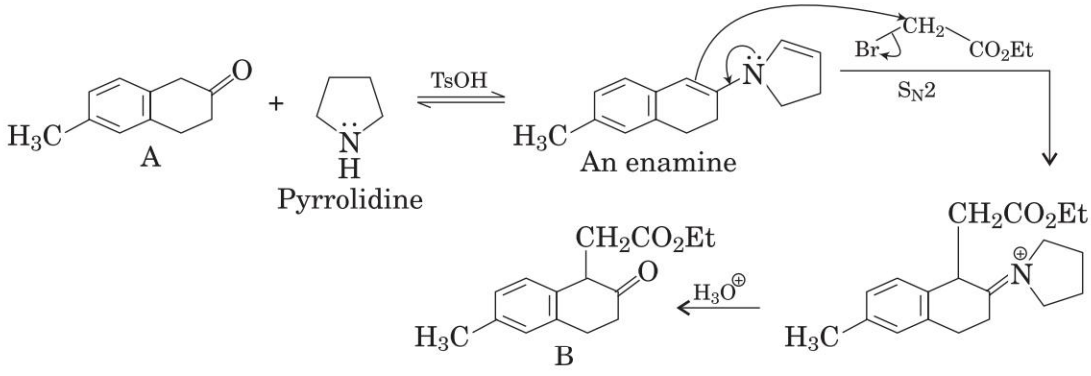




3. It is very difficult to stop the alkylation of the enolate of the ketone A before dialkylation occurs. Show how would you use an enamine to prepare the monoalkylated ketone B.



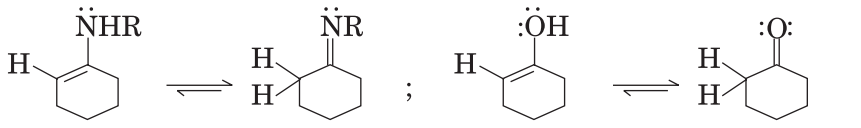
Solution The monoalkylated ketone B can be prepared by way of an enamine as follows:



The double bond of enamine is formed in that particular side because it is stabilized by conjugation with the ring.

4. Explain why primary or tertiary amines cannot be used to prepare enamines.

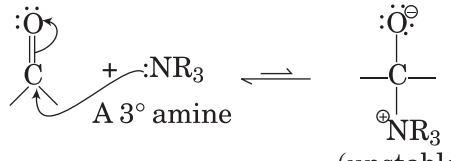
Solution Since a primary amine ($R—NH_2$) has two hydrogens attached to nitrogen, it can form an imine as well as an enamine. However, just as most aldehydes and ketones are more stable than their corresponding enols, most imines are more stable than their corresponding enamines.



An enamine (less stable) | An imine (more stable) | An enol (less stable) | A ketone (more stable)

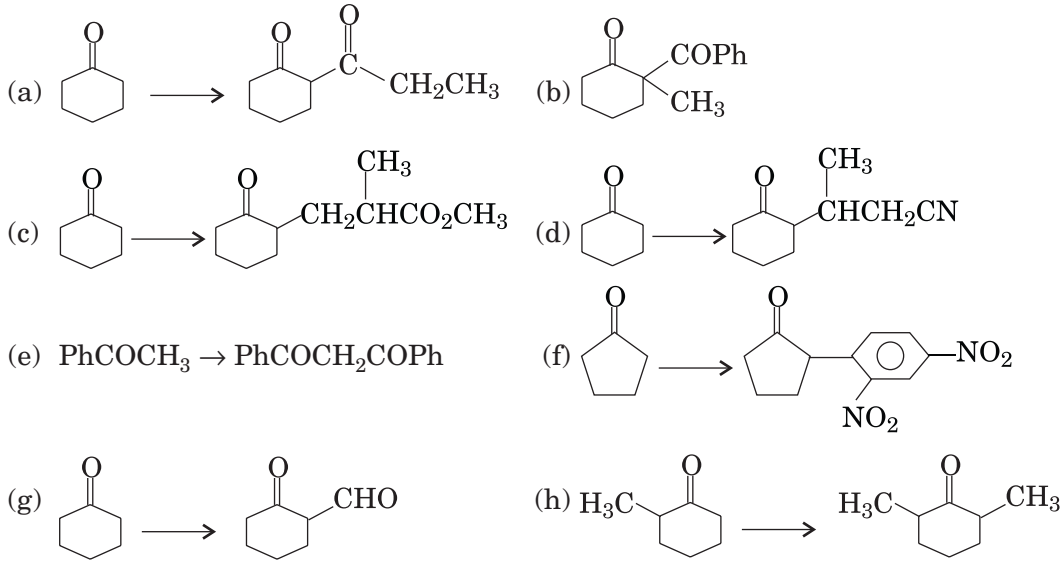
For this reason, primary amines react with aldehydes or ketone to form imines instead of enamines.

Tertiary amines ($R_3\ddot{N}$) do not react with aldehydes or ketones to form stable derivatives. Although most tertiary amines are good nucleophiles, they have no NH hydrogens and therefore, they cannot even form aminoalcohols. Their adduct with aldehydes or ketones are unstable and can only break down to yield the starting materials.

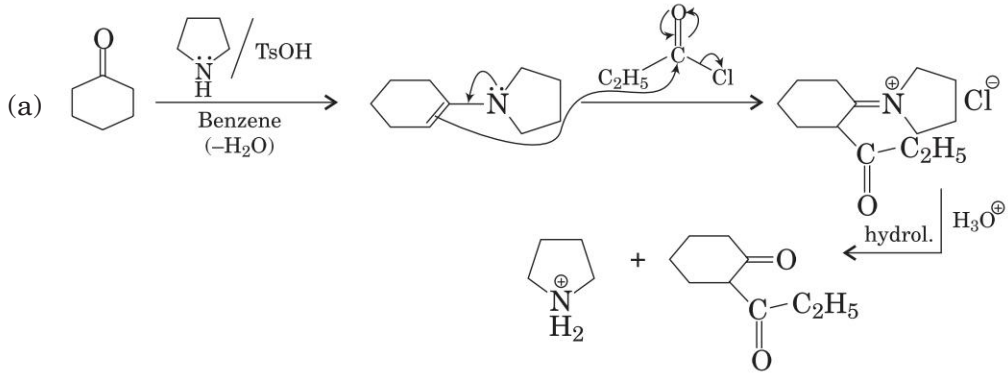


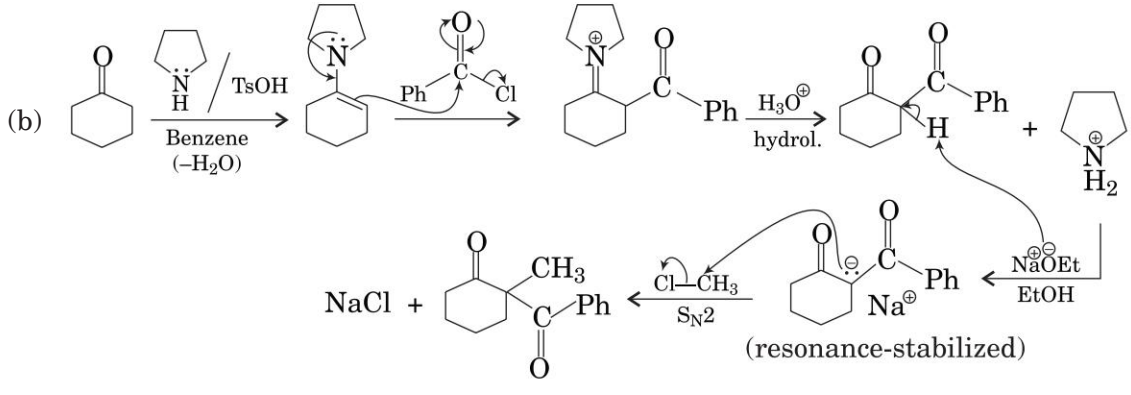
(unstable adduct)

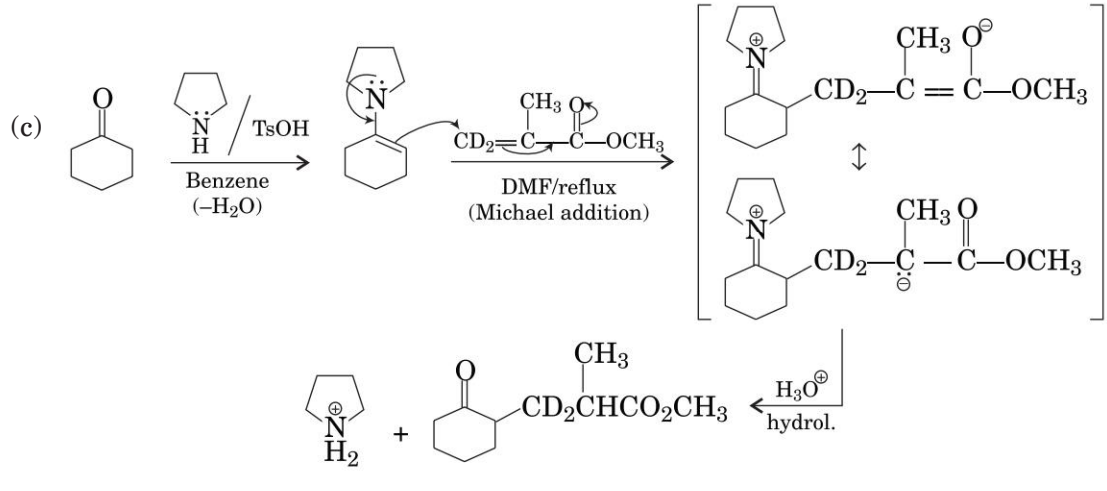
5. Show how you would accomplish each of the following conversions using the Stork enamine reaction:



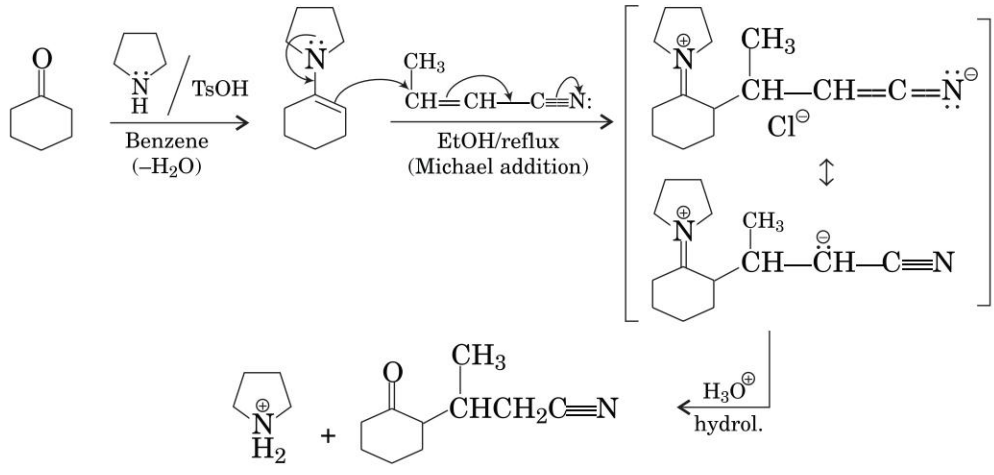
Solution


(a)
TsOH
Benzene
(–H2O)
C2H5
Cl
Cl⊖
hydrol.
H3O⊕

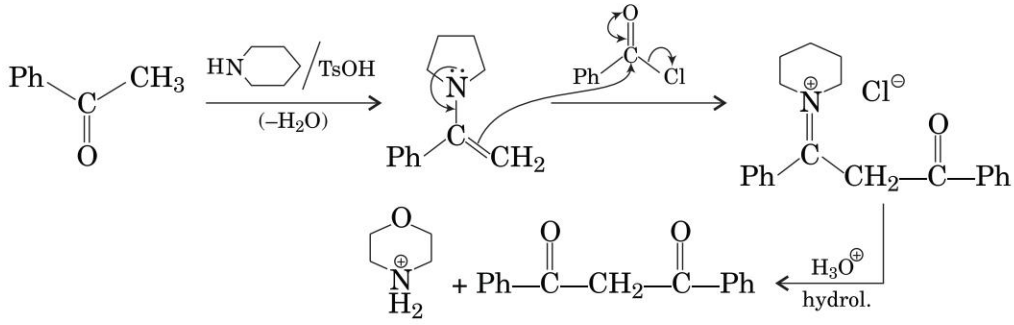

(b)
TsOH
Benzene
(–H2O)
Ph
Cl
H3O⊕
hydrol.
NaOEt
EtOH
NaCl +
Cl—CH3
SN2
(resonance-stabilized)


(c)
TsOH
Benzene
(–H2O)
DMF/reflux
(Michael addition)
H3O⊕
hydrol.

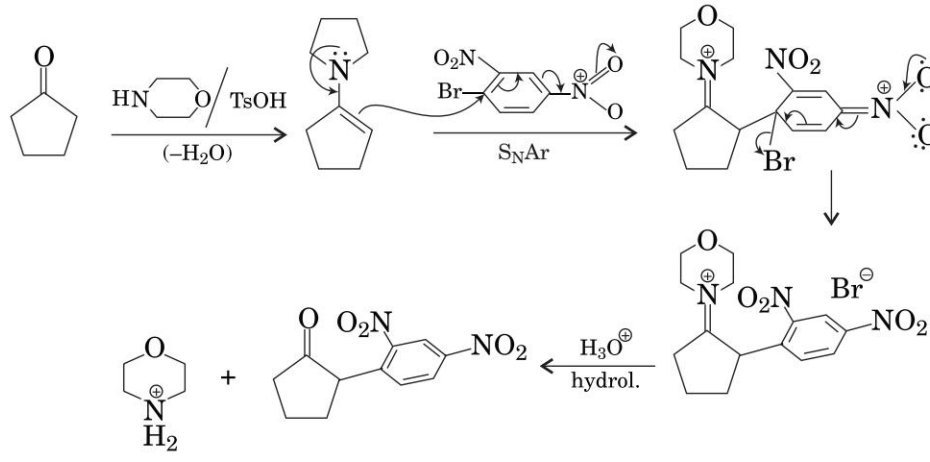
(d)

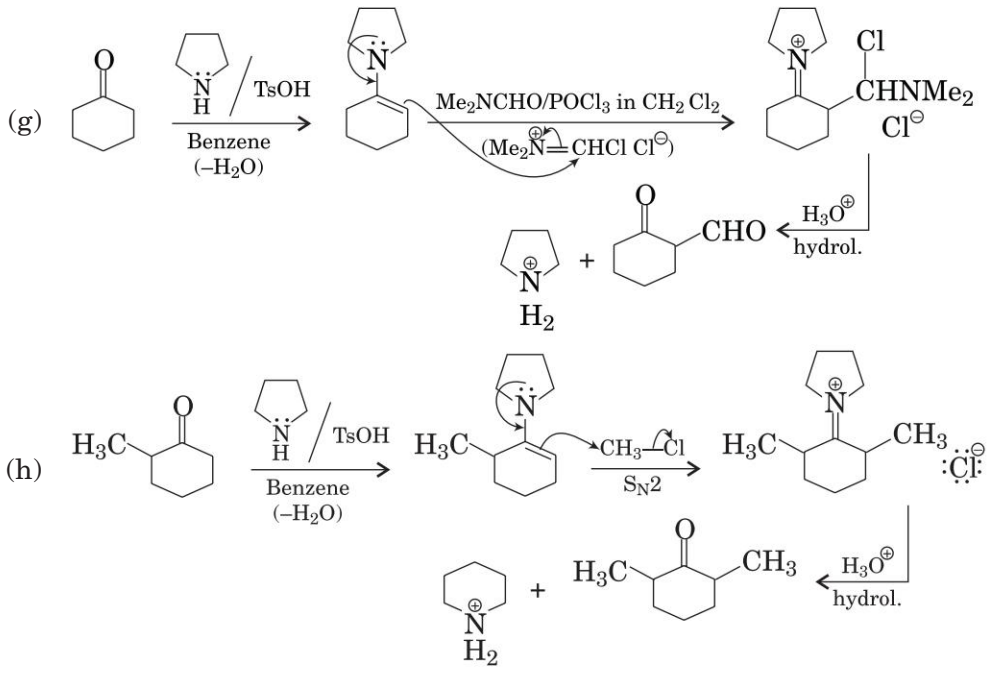

TsOH
Benzene
(–H2O)
CH3
CH═CH—C≡N:
EtOH/reflux
(Michael addition)
Cl⊖
CH3
CH—CH═C═N⊖
CH—CH—C≡N
H3O⊕
hydrol.
CHCH2C≡N

(e)

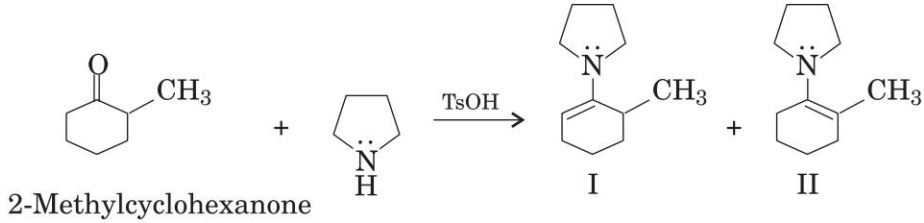

Ph
CH3
HN
TsOH
(–H2O)
Ph
Cl
Cl⊖
Ph—C—CH2—C—Ph
+ Ph—C—CH2—C—Ph
H3O⊕
hydrol.

(f)


HN
O
TsOH
(–H2O)
O2N
Br
SNAr
NO2
Br
Br⊖
O2N
NO2
H3O⊕
hydrol.

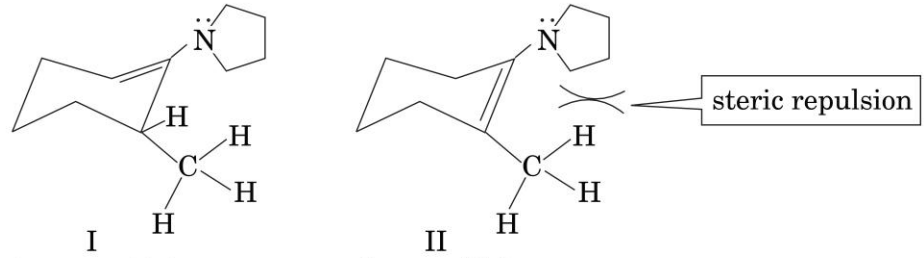


6. Which one is the major product in the following reaction and why?



2-Methylcyclohexanone

Solution Conjugation between the lone pair of electrons on the nitrogen atom and the π-electrons of the C=C bond demands coplanarity of bonds. Because of this, the enamine II is destabilized by a serious nonbonded repulsion arising out of $A^{1,3}$-strain (allylic strain). The enamine I is not destabilized due to steric reason because the methyl group assumes a quasiaxial position to avoid steric interaction.



I
(more stable)

II
(less stable)

7. (a) **What are called metalloenamines?**

(b) **How would you carry out the following transformation by way of a metalloenamine?**

$$(CH_3)_2CHCHO \longrightarrow (CH_3)_2C(CHO)(CH_2Ph)$$

Solution

(a) Many imines, obtained from enolizable aldehydes or ketones and aliphatic primary amine, can be easily deprotonated on treatment with lithium diisopropylamide or Grignard reagents. The metal salts so formed are called *metalloenamines*.

(b) $Me_2CHCHO + Me_3C\ddot{N}H_2 \xrightarrow[\text{reflux}]{\text{Benzene}} Me_2C(H)—CH=NCMe_3$ (An imine)

$Me_2C(H)—CH=NCMe_3 \xrightarrow[\text{THF/reflux}]{Li^{\oplus}\ddot{N}^{\ominus}(CHMe_2)_2}$

$Me_2C(CH_2Ph)—CH=NCMe_3 \xleftarrow[S_N2]{Ph,\ Cl,\ CH_2}$ $Me_2C(CH_2Ph)—CH=NCMe_3 \xleftarrow[\text{hydrol.}]{H_3O^{\oplus}} Me_3C\overset{\oplus}{N}H_3 + Me_2C(CH_2Ph)(CHO)$

$[Me_2\ddot{C}—CH=N—CMe_3 \leftrightarrow Me_2C=CH—\ddot{N}CMe_3]$

8. Reductive amination of a ketone is almost always a better procedure for the synthesis of an amine of the type $RR'CHNH_2$ than treatment of an alkyl halide ($RR'CHX$) with NH_3. Explain this observation.

Solution Because of steric reason, the S_N2 reaction between a secondary halide ($RR'CHX$) and ammonia does not proceed smoothly and the reaction would inevitably be accompanied by considerable elimination (E2), thereby decreasing the yield of the desired amine ($RR'CH—NH_2$). Multiple *N*-alkylation may also take place.

9. Give structures for the products of reductive amination with H_2/Ni of (a) $CH_3CH_2CH_2CHO$ with (i) NH_3, (ii) $C_2H_5NH_2$, and (iii) $C_2H_5NHCH_3$ and (b) $CH_3COCH_2CH_3$ with amines in (a).

Solution

(a) (i) $CH_3(CH_2)_3NH_2$, (ii) $CH_3(CH_2)_3NHCH_2CH_3$ (iii) $CH_3(CH_2)_3N(CH_3)C_2H_5$

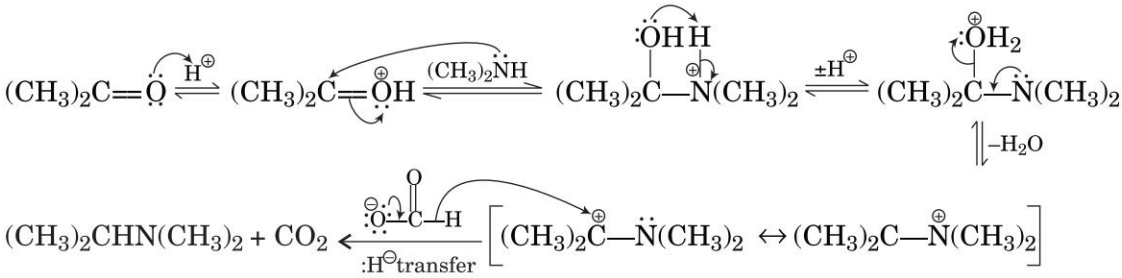
(b) (i) $CH_3CH_2CH(CH_3)NH_2$, (ii) $CH_3CH_2CH(CH_3)NHCH_2CH_3$, (iii) $CH_3CH_2CH(CH_3)N(CH_3)C_2H_5$

10. In Leuckart-Wallach reaction, reductive alkylation of an amine occurs when it is treated with a carbonyl compound in the presence of excess of formic acid (HCOOH), which acts as the reducing agent by transferring a hydride ion. For example:

$$(CH_3)_2{=}O + (CH_3)_2NH \xrightarrow[-CO_2,\ -H_2O]{HCOOH} (CH_3)_2CH—\ddot{N}(CH_3)_2$$

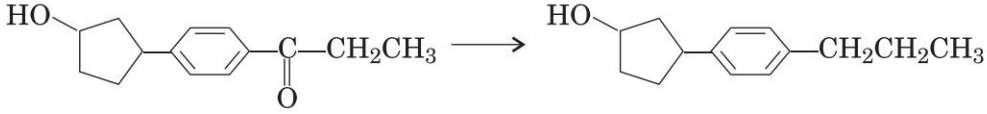
Suggest a mechanism for the reaction.

Solution The mechanism of the reaction may be outlined as follows:

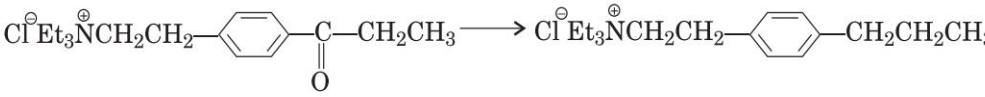


11. Which one of the Clemmensen and the Wolff-Kishner reduction (both of which converts a $>C=O$ group to a $>CH_2$ group) is appropriate for each of the following transformations? Give your reasoning.

(a)

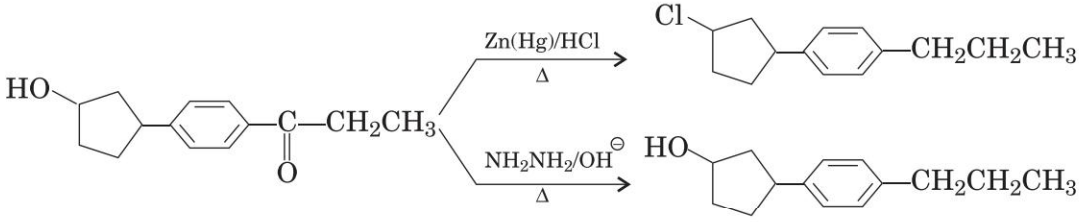


(b)

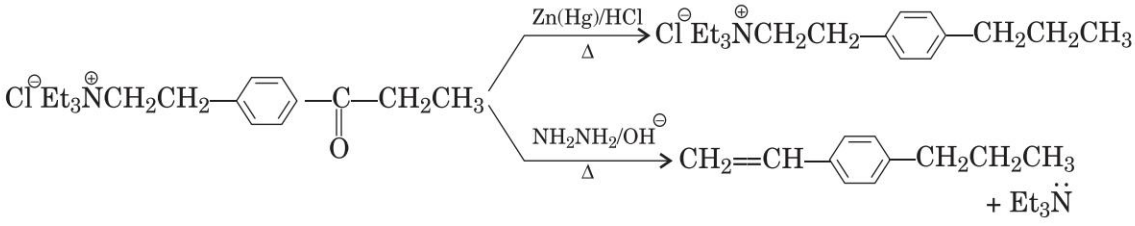


Solution

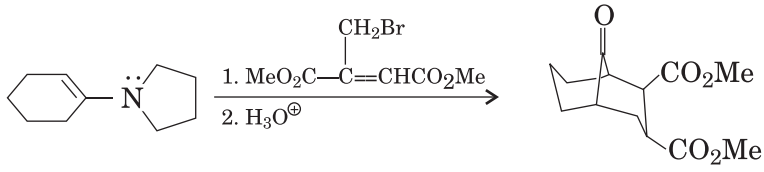
(a) Under acidic conditions of the Clemmensen reduction (Zn–Hg/HCl), the alcoholic —OH group undergoes substitution (protonation of —OH group followed by nucleophilic attack by $:\ddot{Cl}^{\ominus}$). However, under the basic conditions of the Wolff-Kishner reduction ($NH_2NH_2/OH^{\ominus}$), the —OH group would remain unchanged. Therefore, this conversion is to be carried out by the Wolff-Kishner method.



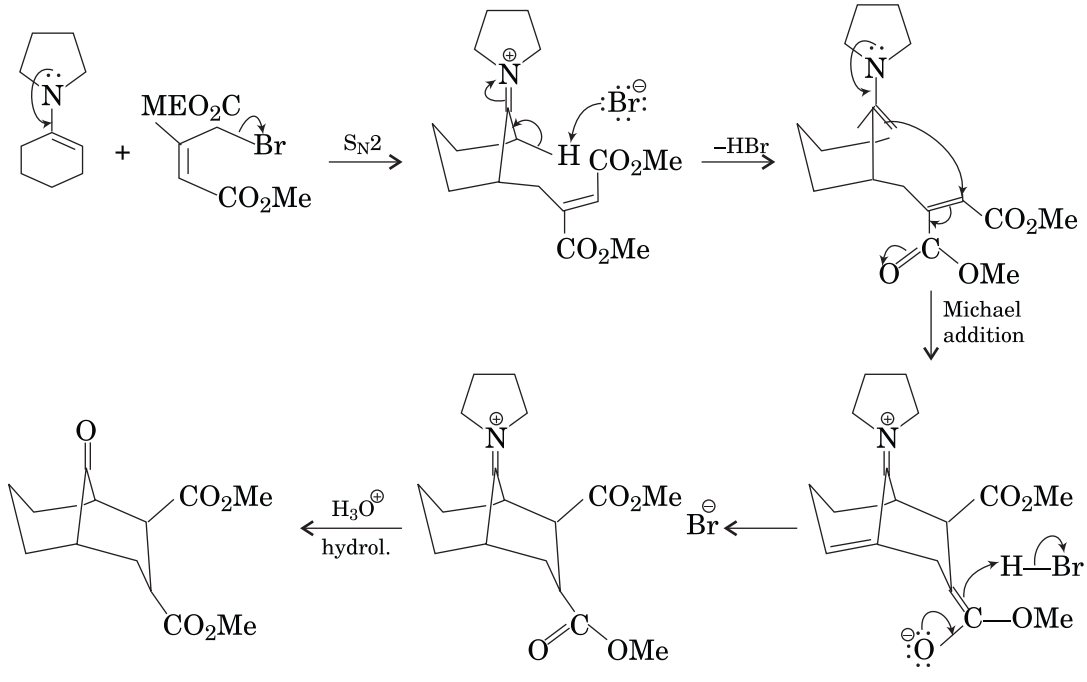
(b) Under the basic reaction conditions required for the Wolff-Kishner reduction, the quaternary ammonium ion would undergo Hofmann elimination reaction to form a double bond. However, it remains inert in the acidic conditions of the Clemmensen reduction. Therefore, this conversion is to be carried out by the Clemmensen method.



12. Propose a mechanism for the following reactions:



Solution The reaction involves alkylation of the enamine followed by a Michael addition.



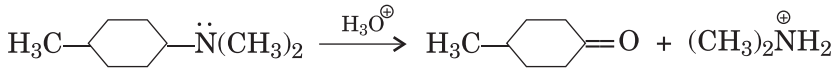
Study Problems

1. Depending on the reaction conditions, two isomeric imines (molecular formula C_8H_9N) are obtained by the reaction of PhCHO and CH_3NH_2. Explain and draw the structures of the two isomeric imides.
2. When semicarbazide ($NH_2CONHNH_2$) reacts with a carbonyl compound (an aldehyde or a ketone) to form a semicarbazone derivative, only one nitrogen atom of semicarbazide acts as a nucleophile and attack the carbonyl carbon atom. The product of the reaction is $\rangle C{=}NNHCONH_2$ rather than $\rangle C{=}NCONHNH_2$. How do you account for this observation?
3. The nucleophilicity of a double-bonded carbon of enamines makes them particularly useful reagents in organic synthesis. Which carbon is expected to be nucleophilic and why?

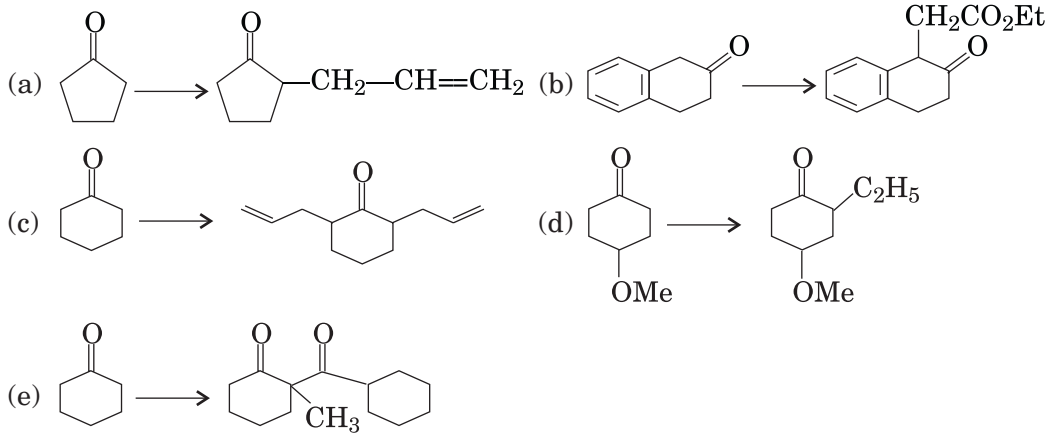
4. How do the mechanisms of the acid-catalyzed hydrolysis of an imine and an enamine differ?

5. Tertiary amines do not form stable addition products with aldehydes or ketones – why?

6. Suggest a mechanism for the hydrolysis of the following enamine:

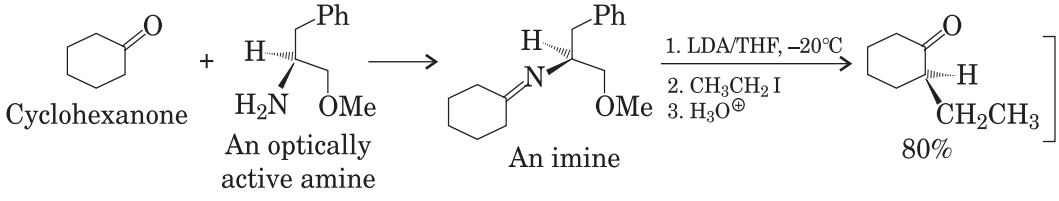


7. Show how you would accomplish each of the following conversions using the Stork enamine reaction:



8. The metalloenamine reaction is used for enantioselective alkylation of ketones, using optically active amine. Give an example.

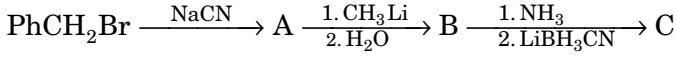
[**Hint:**



9. Show how you might synthesize each of the following amines from benzaldehyde by reductive amination:

(a) Dibenzylamine
(b) Benzylamine
(c) *N*-Ethylbenzylamine
(d) *N*-Benzylpiperidine
(e) *N*, *N*-Demethylbenzylamine
(f) $CH_3(CH_2)_4NH_2$
(g) $CH_3(CH_2)_5$ NHPh
(h) $PhCH_2NHPh$

10. Identify the products A, B and C in the following reaction sequence:



11. Sodium cyanoborohydride ($NaBH_3CN$) is a useful alternative reducing agent in small-scale reductive aminations —Why?

[**Hint:** The electron-attracting –CN group retards hydride donation and because of this, the reactant $\rangle C{=}O$ is reduced by $NaBH_3CN$ more slowly than it reacts with imines to form amines. The protonated imine formed at the pH of the reaction medium is an electrophile, and is rapidly reduced.]

12. Explain why phentermine, $PhCH_2(CH_3)_2NH_2$, cannot be prepared by reductive amination method.

13. Give the product obtained in each of the following reactions:

(a) O_2N—C$_6$H$_4$—CHO $\xrightarrow[2.\ NaBH_3CN]{1.\ CH_3NH_2}$ (c) C$_6$H$_{10}$=O $\xrightarrow[2.\ NaBH_3CN]{1.\ (CH_3CH_2CH_2)_2NH}$

14. Why are the derivatives of ammonia like hydroxylamine (NH_2OH), phenylhydrazine ($PhNHNH_2$), etc., best preserved in the laboratory in the form of their salts?

15. When semicarbazide (1 mole) is allowed to react with a mixture of cyclohexanone (1 mole) and benzaldehyde (1 mole), the immediately isolate product consists almost entirely the semicarbazone of cyclohexanone. However, the product is isolated after several hours, it consists almost exclusively the semicarbazone of benzaldehyde. Account for these observations.

[**Hint:** The reaction is reversible in nature. The more reactive cyclohexanone reacts at a rate faster than the less reactive benzaldehyde (resonance effect reduces the positive character of the aldehydic carbon) to form mainly the semicarbazone of cyclohexanone (the kinetic product). However, because of conjugation, the semicarbazone of benzaldehyde is thermodynamically more stable than that of cyclohexanone. Hence, the product isolated after several hours, i.e., after the equilibrium is established, is mainly the semicarbazone of benzaldehyde (the thermodynamic product).]

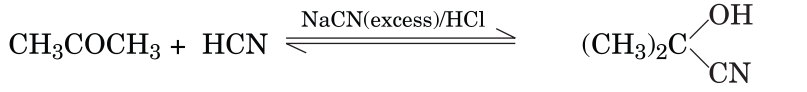
2.7 ADDITION OF CARBON NUCLEOPHILES

- Addition of hydrogen cyanide
- Addition of Grignard reagents and other oragnometallics
- Addition of acetylides
- Addition of diazomethane
- Addition of yields and the Wittig reaction

2.7.1 Addition of hydrogen cyanide (HCN)

Hydrogen cyanide (HCN) adds to the carbonyl groups of aldehydes and most ketones to form compounds called cyanohydrins. Cyanohydrins form at a faster rate under conditions where cyanide ions are present to act as the nucleophile. Therefore, use of any base that can

generate $CN^{\ominus}$ ions form HCN increases the reaction rate as compared to the use of HCN alone. Because hydrogen cyanide is a highly toxic and volatile liquid that is dangerous to handle, the best way to carry out this reaction is to generate hydrogen cyanide during the reaction by adding HCl to a mixture of aldehyde or ketone and excess sodium cyanide (NaCN). Excess NaCN is used in order to make sure that some $CN^{\ominus}$ ion is available to act as a nucleophile. For example:



Acetone — Acetone cyanohydrin

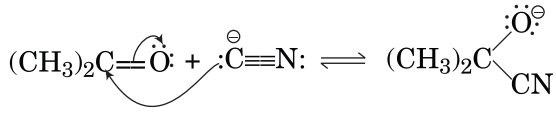
Mechanism of the reaction

The mechanism of the reaction involves the steps as follows:

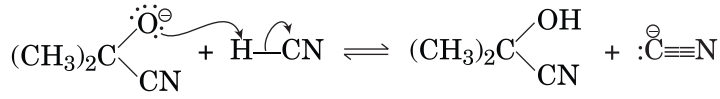
Initial step Sodium cyanide reacts with dilute hydrochloric acid to form hydrogen cyanide which, being mildly acidic, slightly dissociates to give cyanide ion. Some NaCN remains unreacted to provide sufficient $CN^{\ominus}$ ion.

$$NaCN + HCl \rightleftharpoons HCN + NaCl\,;\ HCN + H_2O \rightleftharpoons H_3O^{\oplus} + :\overset{\ominus}{C}N$$

Step 1: The nucleophilic attack by the cyanide ion on the carbonyl carbon leads to the formation of an intermediate alkoxide. This is the rate-determining step of the reaction.



Step 2: The intermediate alkoxide take up a proton from HCN to produce the cyanohydrin.

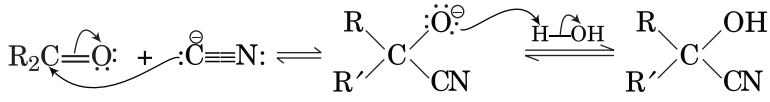


Some relevant topics

(i) **The addition of hydrogen cyanide itself to a carbonyl group is slow, but in the presence of a base or NaCN it is fast.** This may be explained as follows. The nucleophilic attack by the cyanide ion ($CN^{\ominus}$) to the carbonyl carbon is the rate-determining step of the reaction. Because of weak acidity, HCN provides only a small concentration of the nucleophilic cyanide ion and for this reason, the addition of HCN itself to a carbonyl group is slow. A small amount of a strong base can activate hydrogen cyanide by converting it to $CN^{\ominus}$ ($HCN + :B \rightleftharpoons \overset{\oplus}{B}H + CN^{\ominus}$), i.e., in the presence of a base the concentration of cyanide ion increases and so, the addition occurs rapidly. Also, in the presence of NaCN the concentration of $CN^{\ominus}$ ion becomes higher and so, in that case also the reaction takes place rapidly.

(ii) **A highly acidic medium reduces the reaction rate.** This may be explained as follows. The concentration of the unionized HCN is the highest in a highly acidic medium and consequently, the concentration of $:CN^{\ominus}$ ion is the lowest. The reaction rate depends on the concentration of the $CN^{\ominus}$ ion (because it is involved in the rate-determining step) and so, a highly acidic medium retards the rate of the reaction.

(iii) **A cyanohydrin cannot be prepared by treating a ketone with an aqueous solution of sodium cyanide.** This can be explained as follows. In aqueous medium as the addition of $CN^{\ominus}$ to the carbonyl group proceeds, a weak base $CN^{\ominus}$ is replaced by a strong base $OH^{\ominus}$.



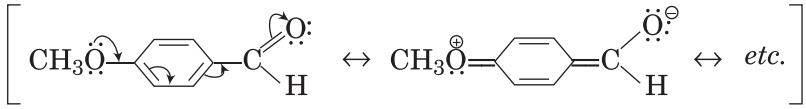
Since a stronger base (or acid) is not favoured at equilibrium, cyanohydrin formation is less favourable in this case. Despite the high concentration of the cyanide ion, aqueous NaCN is, therefore, a relatively ineffective reagent for cyanohydrin formation. Hence, a cyanohydrin cannot be prepared by treating a ketone with an aqueous solution of NaCN.

(iv) There is difference in relative values of equilibrium constants for the formation of cyanohydrin of various carbonyl compounds and this difference can be explained in terms of the difference in stability between the carbonyl compound and the cyanohydrine. K_{eq} for the formation of benzaldehyde cyanohydrin is 210, where as that for the formation of anisaldehyde cyanohydrin is only 32.

$$C_6H_5CHO + HCN \rightleftharpoons C_6H_5CH(OH)CN + HCN \quad K_{eq} = 210$$

$$p\text{-}CH_3OC_6H_4CHO + HCN \rightleftharpoons p\text{-}CH_3OC_6H_4CH(OH)CN \quad K_{eq} = 32$$

The electron-donating (+R) methoxy group (—OCH_3) provides electron density to the electron-withdrawing (–R) —CHO group by delocalization of electrons through the benzene ring. The resonance interaction between the two such complementary groups is very much favourable. Consequently, anisaldehyde (*p*-methoxybenzaldehyde) is stabilized by resonance more than benzaldehyde.

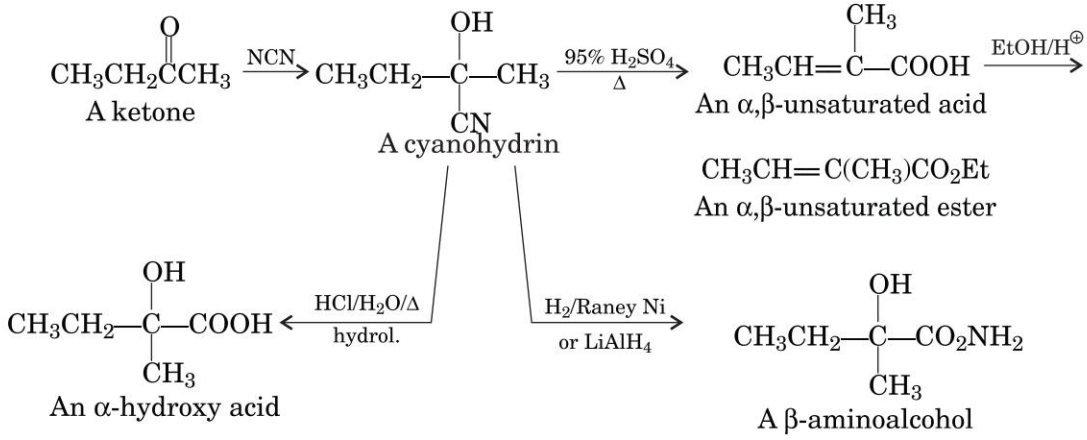


Resonance in anisaldehyde

The value of K_{eq} for a reaction depends on the standard free energy difference ($\Delta G°$) between the products and starting materials. Since the carbonyl group is absent in the product cyanohydrin, its interaction with the rest of the system is lost. Therefore, it may arbitrarily be assumed that both the cyanohydrin products are very close in energy. Again, cyanohydrine are thermodynamically more stable than the corresponding carbonyl

compounds. Therefore, the value of $\Delta G°$ for the formation of benzaldehyde cyanohydrin is more negative than that for the formation of anisaldehyde cyanohydrin and for this reason, anisaldehyde has a much lower value of K_{eq} for the formation of cyanohydrine as compared to benzaldehyde.

Synthetic applications The reaction is synthetically useful because the resulting cyanohydrins can be used to prepare α-hydroxy acids, α,β-unsaturated acids, unsaturated esters, and β-amionalcohols. For example, the acid-catalyzed hydrolysis of a cyanohydrin forms an α-hydroxycarboxylic acid. When a cyanohydrin is heated with 95% H_2SO_4, it undergoes dehydration and hydrolysis to form an α,β-unsaturated carboxylic acid which on esterification gives an α,β-unsaturated ester. Reduction of a cyanohydrin by $LiAlH_4$ or H_2/Raney nickel produces a primary amine with an —OH group on the β-carbon. For example:



The reaction is also useful in the *Kiliani-Fischer synthesis* for extending the carbon chain of a sugar.

2.7.2 Addition of Grignard and other organometallic compounds

Compounds having carbon–metal bonds are known as *organometallic compounds*. *Grignard reagents* are organomagnesium halides having the general formula R—MgX, where R is a hydrocarbon group such as alkyl (1°, 2° or 3°), allylic, aralkyl or aryl and X is Cl, Br or I.

A Grignard reagent can be prepared usually by allowing an organic halide to react with magnesium shavings in dry alcohol-free ether.

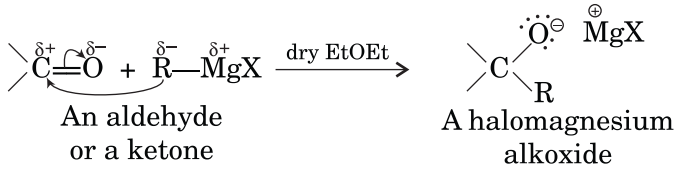
$$\underset{\text{An alkyl haldie}}{R—X + Mg} \xrightarrow{\text{dry ether}} \underset{\text{A Grignard reagent}}{\overset{\delta-}{R}—\overset{\delta+}{Mg}X} \qquad (X = Cl, Br \text{ or } I)$$

Example:

$$\underset{\text{Iodomethane}}{CH_3I} + Mg \xrightarrow{\text{dry ether}} \underset{\text{Methylmagnesium iodide}}{CH_3-MgI}$$

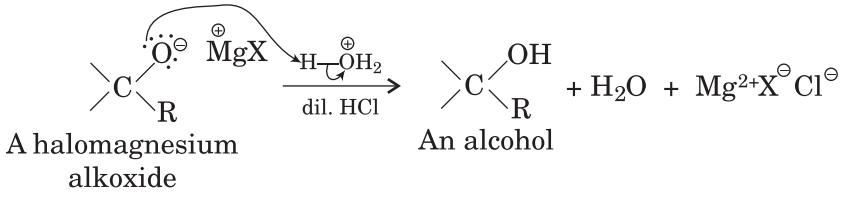
Since magnesium is highly electropositive, $\overset{\delta-}{C}-\overset{\delta+}{Mg}$ bond is strongly polar having negatively polarized carbon and, therefore, they are strongly basic and excellent nucleophiles. The basic and nucleophilic species is a carbanion ($:R^{\ominus}$). In fact, they react like $R^{\ominus}:Mg^{\oplus}X$.

When a Grignard reagent is allowed to react with a carbonyl compound the nucleophilic carbanion ($: R^{\ominus}$) attacks the carbonyl carbon to form a halomagnesium alkoxide.

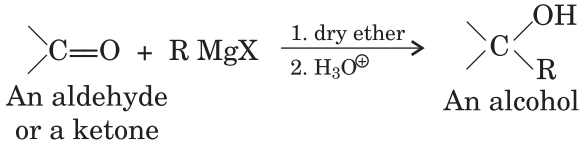


Synthetic applications

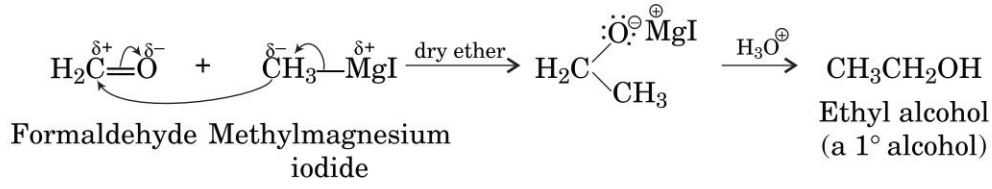
(i) When the halomagnesium alkoxide obtained on addition of a Grignard reagent to an aldehyde or a ketone is decomposed by the addition of water or dilute mineral acid, the corresponding alcohol is obtained.

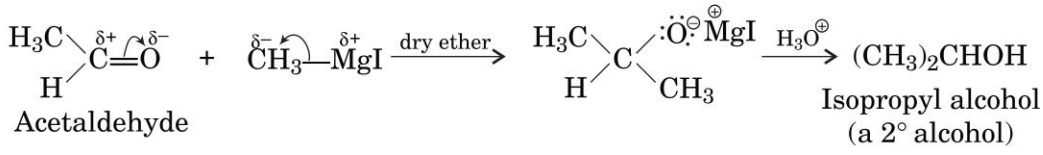


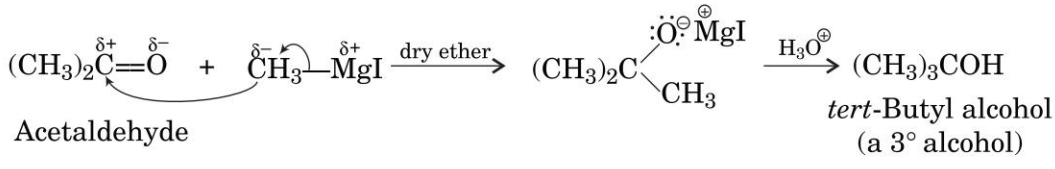
Therefore, the reaction of a Grignard reagent with an aldehyde or a ketone is good method for preparing an alcohol.



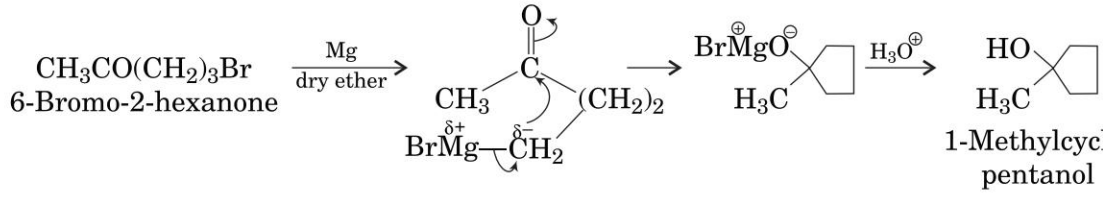
The type of alcohol expected to be obtained from a Grignard reagent and a carbonyl compound actually depends on the number of hydrogen atoms attached to the carbonyl carbon atom, i.e., on the type of the carbonyl compound used. The carbonyl carbon of formaldehyde (HCHO) bears two hydrogen and so, it reacts with a Grignard reagent to yield a primary alcohol (RCH_2OH). The carbonyl carbon of other aldehydes (RCHO) bears one hydrogen and so, they react with Grignard reagents to yield secondary alcohols (R_2CHOH). The carbonyl carbon of ketones (RCOR) bears no hydrogen and so, they react with Grignard reagents to yield tertiary alcohols (R_3COH). For example :





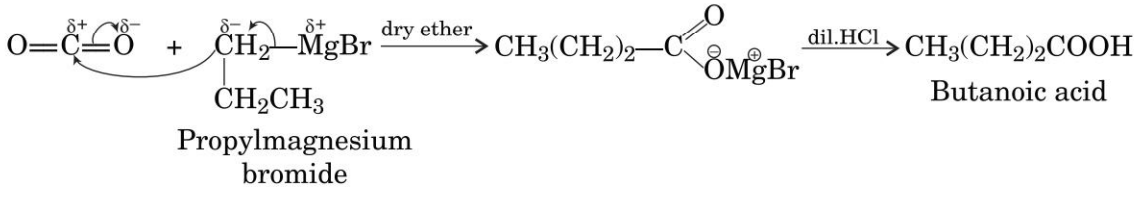


A cyclic secondary or tertiary alcohol can be prepared by an intramolecular Grignard reaction. For example:

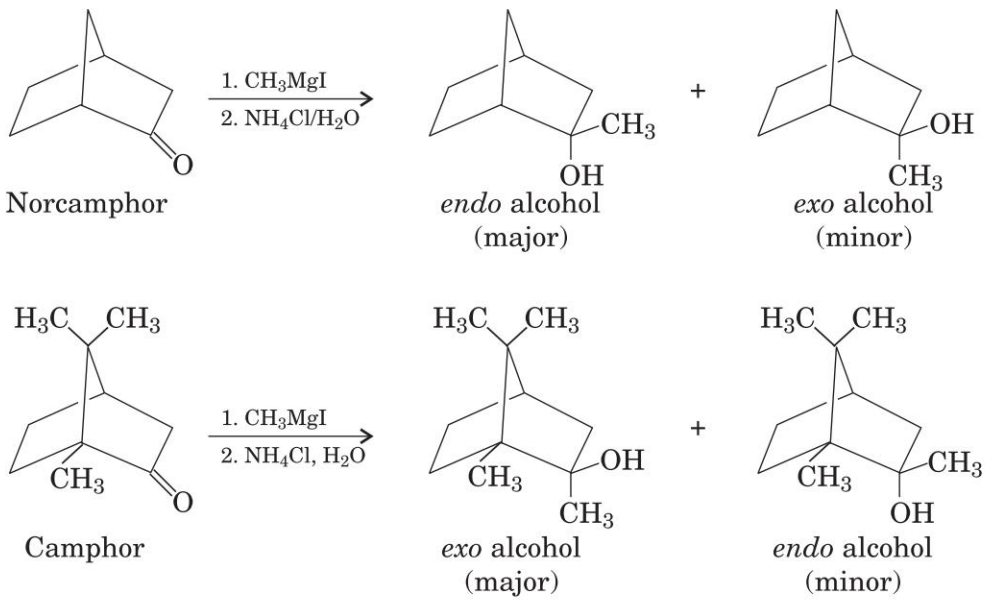


It is to be noted that a tertiary alcohol undergoes dehydration in the presence of acid and for this reason, the halomagnesium alkoxide is often decomposed by an aqueous solution of NH_4Cl.

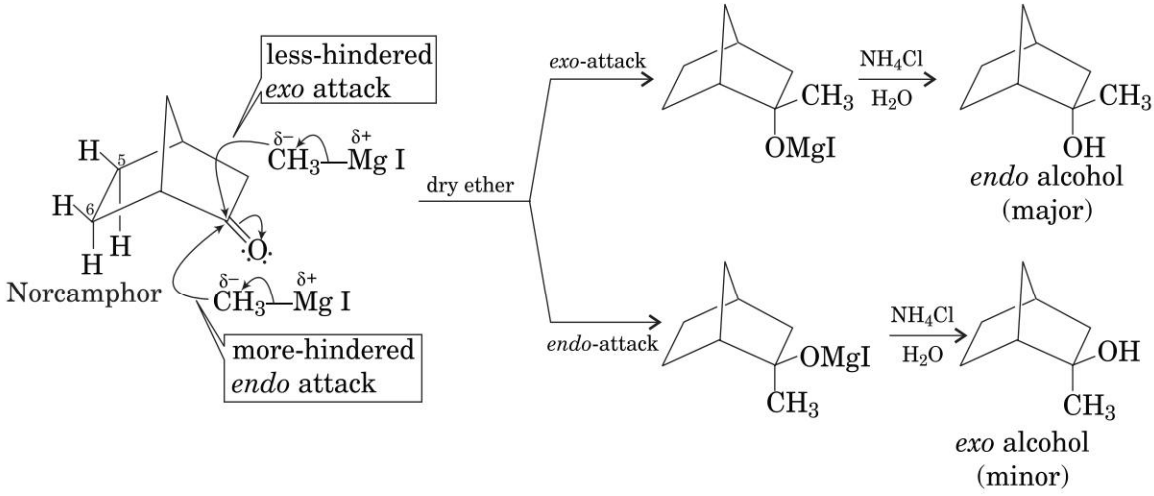
(ii) Carboxylic acids with one more carbon atom than the Grignard reagent can be prepared by allowing a Grignard reagent to react with carbon dioxide (CO_2). For example:



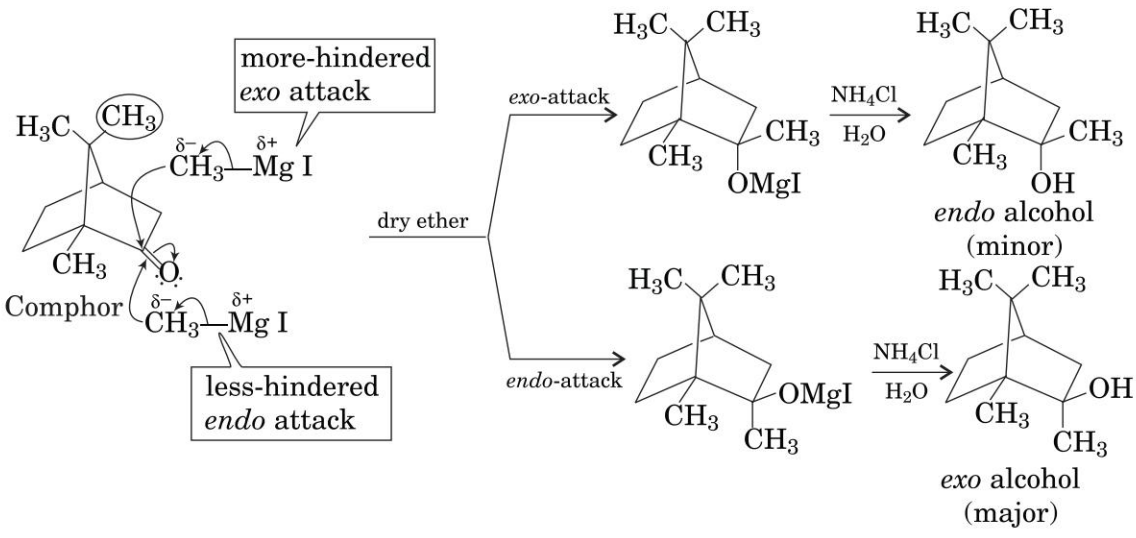
Stereoselectivity of Grignard addition to bicyclic ketones The bicyclic ketone norcamphor reacts with the Grignard reagent CH_3MgBr to give the *endo* alcohol as the major product, while the bicyclic ketone camphor reacts with CH_3MgBr to give the *exo* alcohol as the major product.



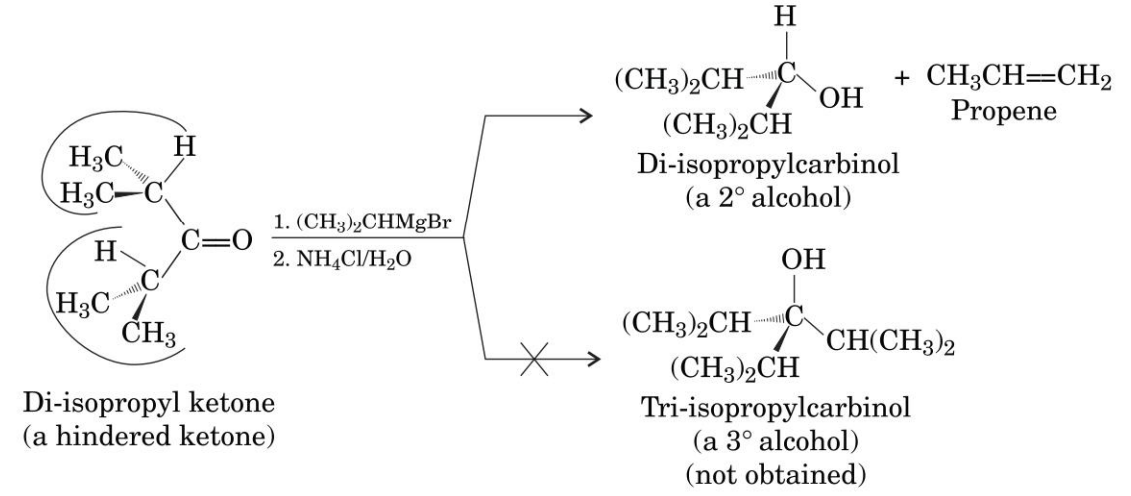
The Grignard reagent methylmagnesium iodide (MeMgI) approaches the C═O group of norcamphor from the less-hindered *exo* side to give mainly the *endo* alcohol and this is because the *endo* approach leading to the *exo* alcohol is sterically more hindered due to the two boat-axial H's at C-5 and C-6.



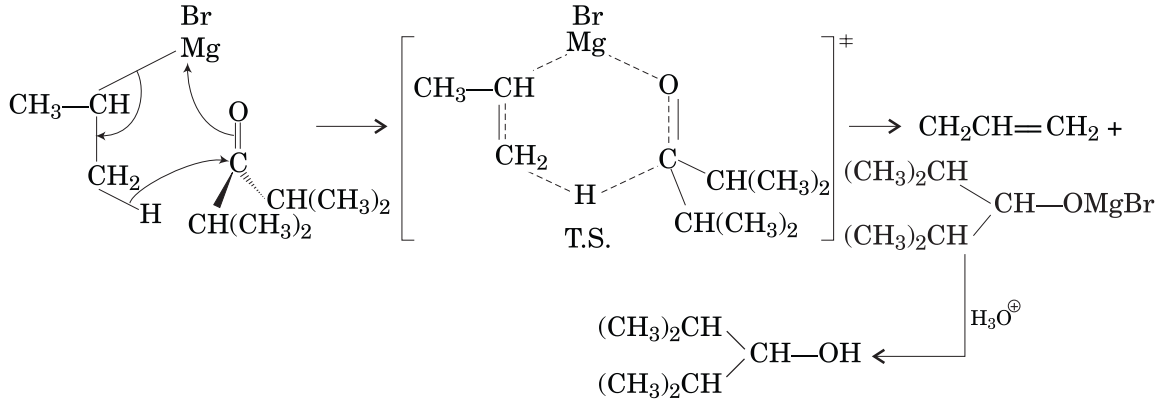
On the other hand, CH_3MgI approaches the carbonyl group of camphor from the less hindered *endo* side to give mainly the *exo* alcohol and this is because the *exo* approach is sterically more hindered due to one —CH_3 group (just above the carbonyl group) at C-7.



Reducing property of Grignard reagents When the hydrocarbon group of a Grignard reagent and the two groups of a ketone are highly branched, normal addition reaction does not take place due to steric strain in the transition state leading to the tetrahedral product. In such a case, reduction of the ketone by the Grignard reagent occurs if the Grignard reagent contains a hydrogen on the carbon adjacent to the point of attachment of —MgX (i.e., a β hydrogen). When isopropylmagnesium bromide, for example, is allowed to react with di-isoproypyl ketone, no tri-isopropylcarbinol (a 3° alcohol) is obtained as a result of normal addition reaction instead di-isopropylcarbinol (a 2° alcohol) is obtained through reduction.



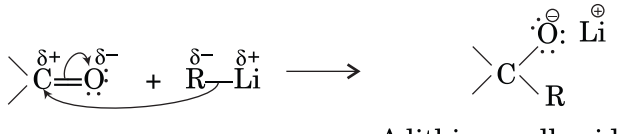
The mechanism of this abnormal reaction involves transfer of a hydride ion ($:H^{\ominus}$) from the Grignard to the carbonyl carbon via a six-membered cyclic transition state.



It is to be noted that Grignard reagents like MeMgX or PhMgX cannot act as reducing agents because they have no β-H.]

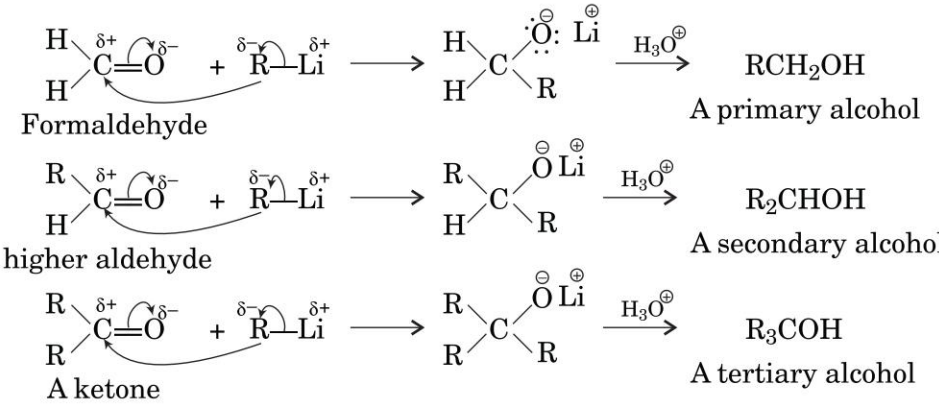
Limitations in Planning Grignard of synthesis of alcohols In planning the synthesis of an alcohol by using a Grignard reagent, it is to be noted that the Grignard reagent must be stable and the substrate (the alkyl halide from which the Grignard reagent is prepared and the compound which is allowed to react with the Grignard reagent) must not contain an acidic hydrogen (hydrogen attached to the electronegative oxygen, nitrogen, sulphur, or even the triply bonded carbon). This is because a Grignard reagent, being a very strong base, abstracts the acidic hydrogen rapidly and itself decomposes to yield a hydrocarbon. Thus, compounds containing groups like —OH, —NH_2, —SH, —COOH, —SO_3H or —C≡CH cannot be used for preparing Grignard reagents. Again, the Grignard reagent is a powerful nucleophile and so, it reacts rapidly with compounds containing carbon–oxygen or carbon-nitrogen multiple bonds. Thus, organic halides containing groups like $\diagdown$C=O**,** —COOR, —COX, —$CONH_2$ or —CN cannot be used for preparing Grignard reagents. A Grignard reagent reduces a —NO_2 group and an epoxy group is opened up by it. Therefore, these two groups also must not present in the starting organic halide. Since Grignard reagent reacts readily with water, therefore, the alkyl halide, the carbonyl compound and, the ether used as a solvent must be absolutely dry. Also, the reaction system must be protected from O_2 and CO_2 of air because they react with a Grignard reagent.

Addition of organolithium compounds An organolithium compound (RLi) reacts with an aldehyde or a ketone to yield the corresponding alkoxide. The carbonyl carbon undergoes nucleophilic attack by the carbanion ($:R^{\ominus}$) originated from $\overset{\delta-}{R}—\overset{\delta+}{Li}$.



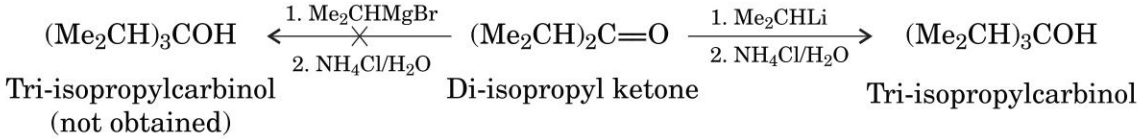
A lithinom alkoxide

As in the case of Grignard reagents, organolithium compounds react with formaldehyde to form primary alcohols, with higher aldehydes (RCHO) to form secondary alcohols, and with ketones (RCOR) to form tertiary alcohols.

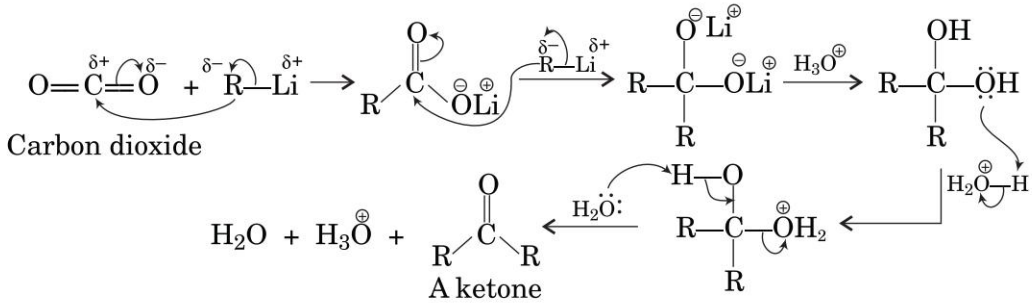


Synthetic applications

(i) Primary, secondary and tertiary alcohols can be prepared by allowing an organolithium compound to react with a suitable carbonyl compound (already discussed). Organolithium compounds or organolithium reagents are especially useful and often advantageous over the organomagnesium compounds or Grignard reagents. This is due to the fact that they are relatively more reactive (C—Li bond is more polar than C—Mg bond) and less susceptible to steric factors and so, they can give normal addition products with hindered ketones. Also, the complicating side reactions like enolization and reduction are less important with organolithium compounds. For example, isopropyllithium reacts with di-isopropyl ketone to produce tri-isopropylcarbinol in good yield, while isopropylmagnesium bromide fails completely to give that 3° alcohol.

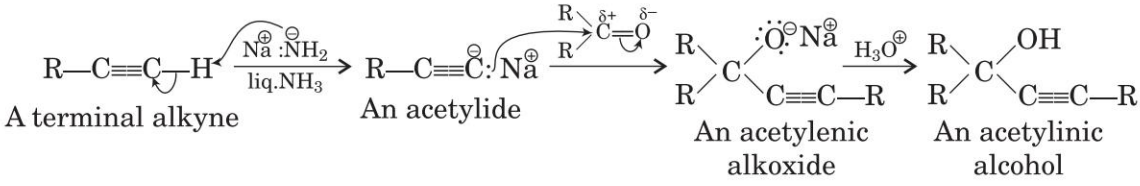


(ii) An organolithium compound (RLi) reacts with carbon dioxide to form a carboxylate anion which subsequently reacts with a second molecule of RLi to yield, after acidification, a ketone.

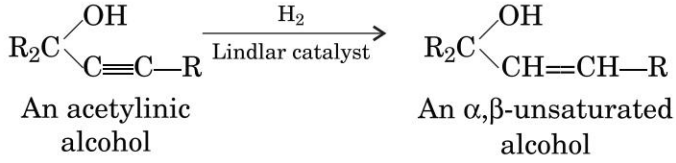


2.7.3 Addition of acetylides

Terminal alkynes (RC≡CH and HC≡CH) are marked acidic and may be converted to their anions by the influence of strong base like $:\ddot{N}H_2^{\ominus}$ in liquid ammonia. These carbanions are called acetylides or alkynides which are strong nucleophiles due to highly concentrated negative charge on the more polarizable carbon atom and add readily to the $\rangle C{=}O$ group. The resulting alkoxides on protonation yield acetylenic alcohols.

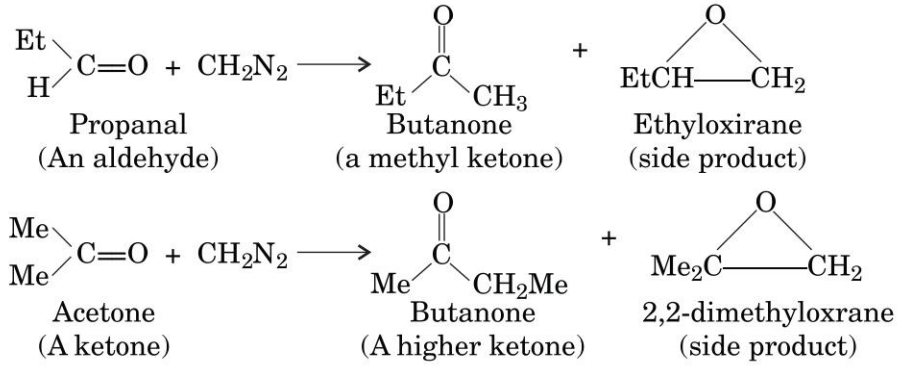


Uses of the reaction The reaction is especially useful synthetically in that the C≡C linkage now present may be converted to various other units under proper chemical treatment. For example, the acetylenic alcohol can be reduced to the corresponding alkene by H_2 in the presence of Lindlar catalyst.

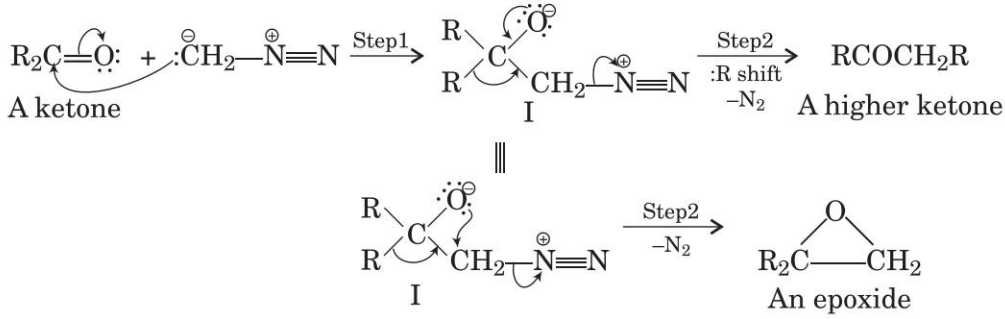


2.7.4 Addition of diazomethane (CH_2N_2)

Diazomethane is a dipolar species having structure $\ddot{C}H_2—\overset{\oplus}{N}{\equiv}N.$ The carbon atom of this reagent, therefore, possesses considerable nucleophilicity and reacts readily with aldehydes and ketones. Aldehydes and ketones can be converted to their homologs with diazomethane. Aldehydes are converted to methyl ketones and ketones are converted to the next higher ketones. The process actually involves methylene-insertion through a rearrangement. Epoxides are obtained as side products in both the cases. For example:

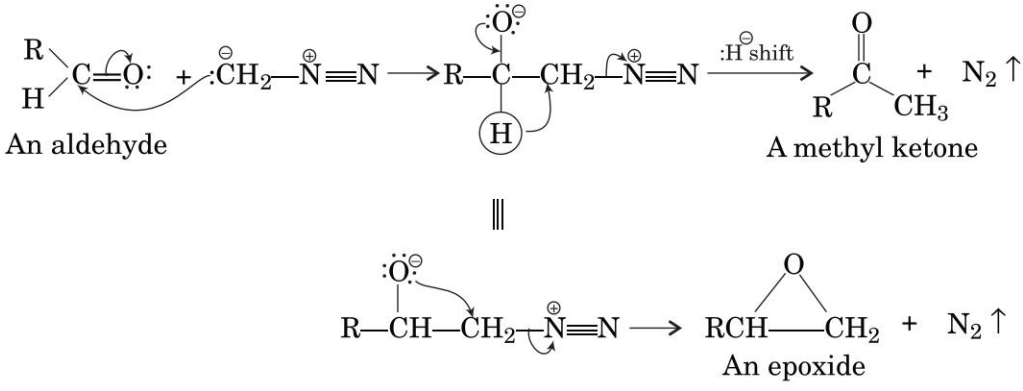


Mechanism of the reaction The mechanism of the reaction in which the substrate is a ketone involves the steps as follows:



In step 1, the ketone undergoes nucleophilic attack by diazomethane to form a betaine (I). In step 2, the betaine I loses a molecule of nitrogen with simultaneous migration of R to form a homologous ketone. Nucleophilic attack by the alkoxy oxygen on the methylene carbon forms an epoxide as a side product.

Aldehydes give fairly good yield of methyl ketones, that is, migration of hydrogen occurs in preference to alkyl.



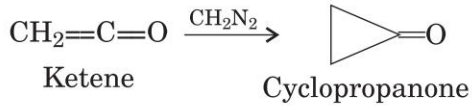
Synthetic applications

(i) Homologation of aldehydes and ketones can be effectively carried out by this reaction.

Ring expansion can be effected by this reaction. For example, cyclopentanone can be converted into cyclohexanone.

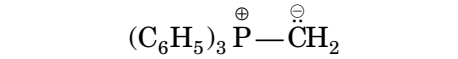


(ii) Cyclopropanone can be prepared by allowing ketene to react with diazomethane.

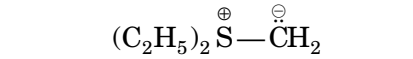


2.7.5 Addition of Ylides

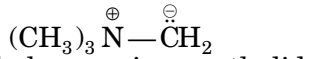
A ylide is a dipolar molecule with no net charge but which has a negative carbon atom adjacent to a positive heteroatom (both atoms have octets), the most usual being sulphur, phosphorus or nitrogen. Examples of phosphorus, sulphur and nitrogen ylides are as follows:



Triphenylphosphonium methylide
(Methylenetriphenylphsophorane)
A phosphorus ylide

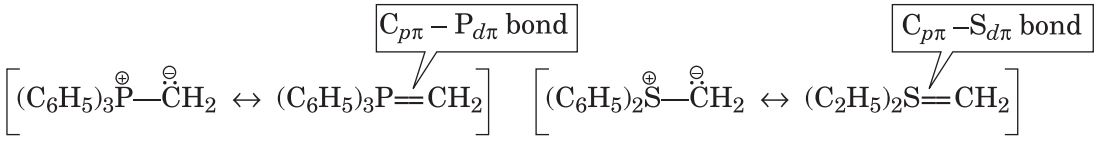


Diemthylsulphonium methylide
(Methylenediethylsulphurane)
A sulphur ylide



Trimethylammonium methylide
A nitrogen ylide

The unshared electron pair on the anionic carbon is involved in $d\pi$–$p\pi$ back bonding with the vacant *d* orbital of sulphur or phosphorus (two second-row elements). The sulphur and phosphorus ylides are, therefore, stabilized by resonance.



A phosphorous ylide
(resonance-stabilized)

A sulphur ylide
(resonance-stabilized)

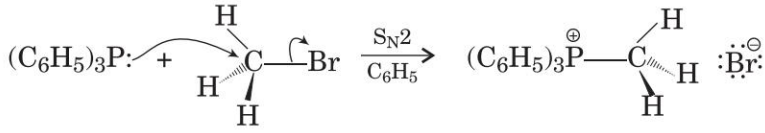
On the other hand, nitrogen (also a second-row element) cannot expand its octet and so, nitrogen ylides are not stabilized by *d*-orbital resonance. It is for this reason phosphorus and sulphur ylides are relatively more stable than nitrogen ylides. The π bond between carbon and phosphorus or carbon and sulphur is weak, and the charged structure is the major contributor. The carbon atom actually bears a partial negative charge, balanced by a corresponding positive charge on phosphorus or sulphur. Because of this carbanion character, the ylide carbon is strongly nucleophilic. So, it attacks a carbonyl carbon to give a charge-separated short-lived intermediate called a *betaine* (a dipolar species also called a *zwitterion).*

Wittig reagents and their preparation Phosphorous ylides, alkylidenetriphenylphosphoranes,  , are known as Wittig reagents. The simplest Witting reagent is methylenetriphenylphosphorane,  .

A Wittig reagent can be prepared by subjecting an alkyl halide (methyl, 1° or 2°) to react with triphenylphosphene, $(C_6H_5)_3P$:, followed by treatment of the resulting

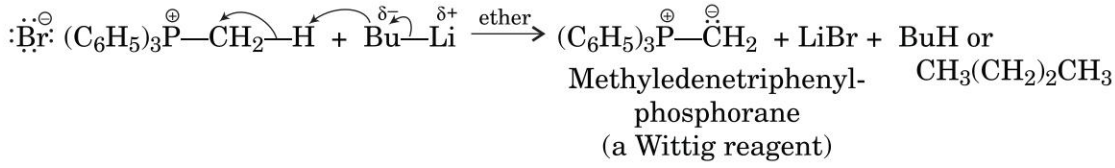
phosphonium salt with a strong base such as PhLi, BuLi, NaH, etc. For example, methylenetriphenylphosphorane, $(C_6H_5)_3\overset{\oplus}{P}—\overset{\ominus}{\ddot{C}}H_2$, can be prepared by the following two reactions:

Reaction 1: Triphenylphosphine, $(C_6H_5)_3\ddot{P}$, is an excellent nucleophile (the less electronegative and larger phosphorus atom is much polarizable) and a weak base. It displaces (S_N2) the bromide ion from methyl bromide (CH_3Br) to yield the salt methyltriphenylphosphonium bromide $(PH_3\overset{\oplus}{P}—CH_3B\overset{\ominus}{r})$.

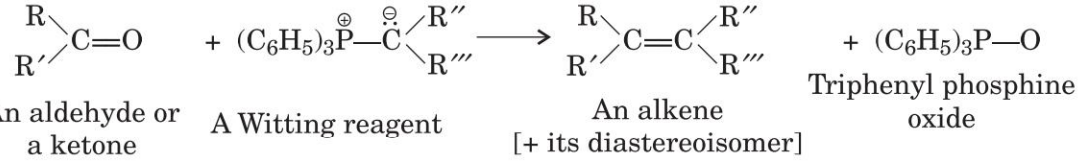


Depending on the nature of the alkyl halide the rate of the reaction increases in the order: 2° < 1° < Methyl.

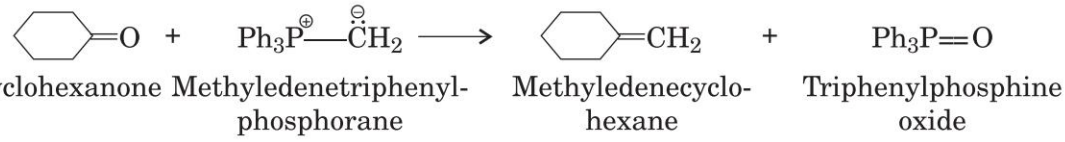
Reaction 2: Butyllithium (BuLi), a strong base, abstracts a proton from the carbon attached to phosphorus to give methyledenetriphenylphosphorane. This is an acid-base reaction.



The Wittig reaction and its mechanism The reaction of an aldehyde or a ketone with alkylidenetriphenylphosphorane to form alkenes (replacement of C═O by C═CRR′) is known as the *Wittig reaction.*

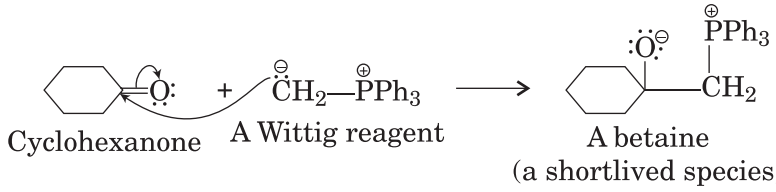


Specific example:

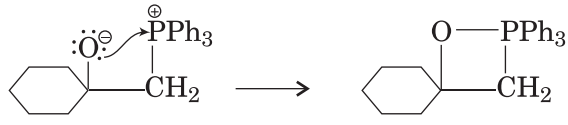


The mechanism of the Wittig reaction involves the following three steps:

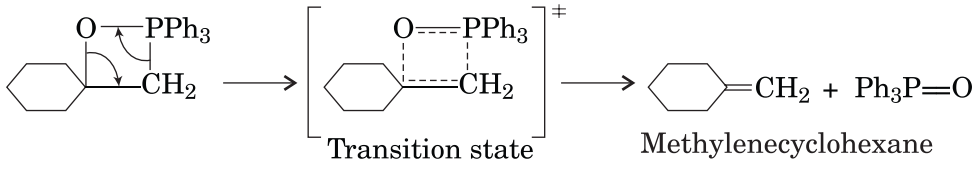
Step 1: The nucleophilic carbon of the Wittig reagent (a ylide) attacks the carbonyl carbon of cyclohexanone to form a dipolar intermediate known as betaine.



Step 2: The betaine closes to form a four-membered ring compound known as oxaphosphetane.



Step 3: The unstable oxaphosphetane readily decomposes through a four-membered cyclic transition state to form the corresponding alkene, i.e., methylcyclohexane and triphenylphosphine oxide ($Ph_3P=O$).



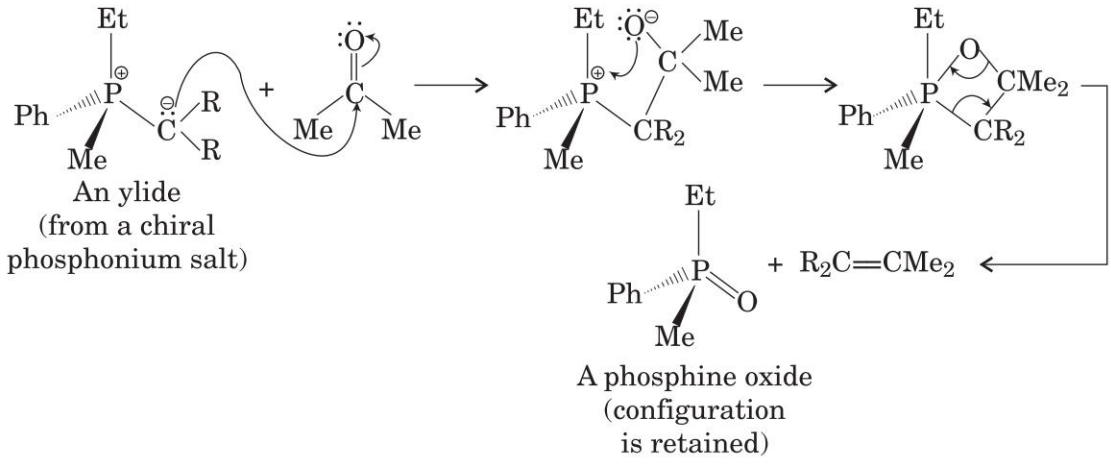
The driving force for the reaction is the formation of highly stable, i.e., very strong ($DH° = 540$ kJ mol^{-1}) phosphorus-oxygen bond in triphenylphosphine oxide ($Ph_3P=O \leftrightarrow Ph_3\overset{\oplus}{P}-\overset{\ominus}{O}$) at the expense of phosphorus–carbon bond.

The evidence in favour of the mechanism may be given as follows:

(i) The entropy of activation ($\Delta S^{\#}$) for the reaction is found to be negative. This observation agrees with the formation of a cyclic intermediate.

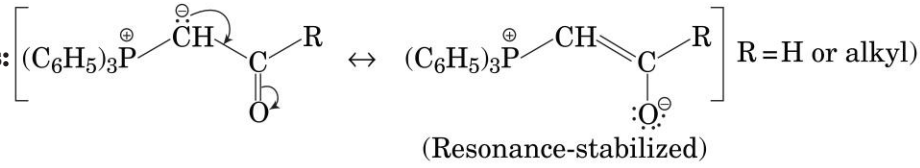
(ii) In some cases, the cyclic intermediate oxaphosphetane has been isolated and in some other cases, the dipolar betaine intermediate has been isolated.

(iii) If a chiral phosphonium salt is used to prepare the ylide, the phosphine oxide obtained finally is found to retain its configuration. Therefore, this observation suggests that the reaction takes place through a four-membered cyclic intermediate and the P—O bond is formed before the P—C bond is cleaved.

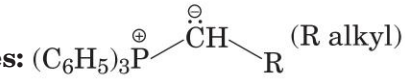


Stereoselectivity in the Wittig reaction: It has been observed that some Wittig reactions are *Z*-selective and some are *E*-selective. The stereoselectivity actually depends on the nature of the substituent attached to the negatively charged carbon of the ylide. Those ylides are called stabilized yields when the substituents are conjugating and anion-stabilizing and this is because the negative charge is then stabilized not only by the phosphorus atom but also by the adjacent functional group. Ylides with alkyl groups adjacent to the negative charge are called unstabilized ylides.

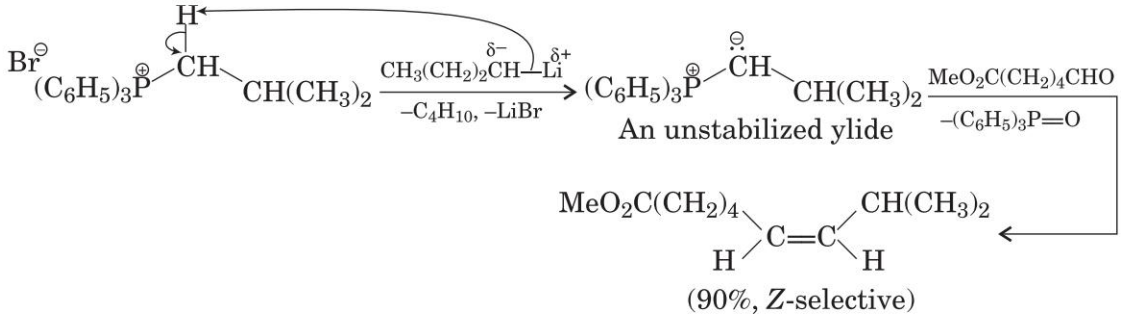
Stabilized ylides:



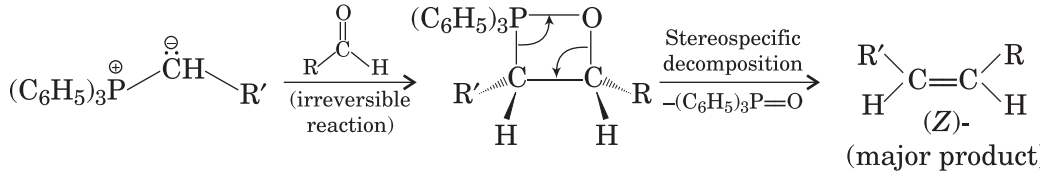
Unstabilized ylides:



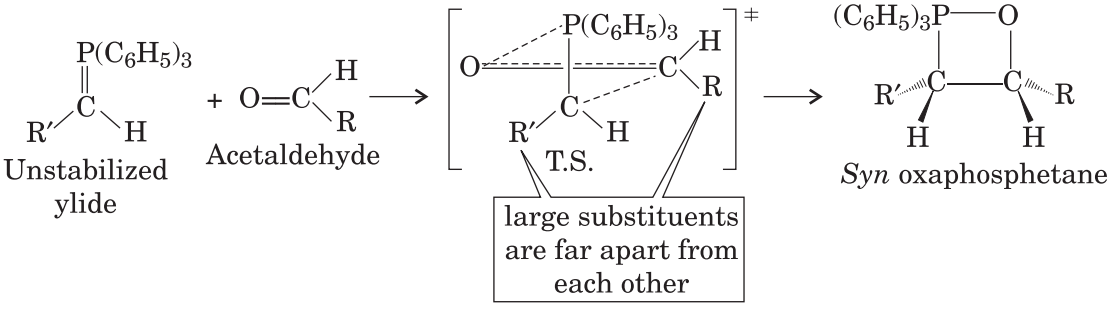
With unstabilized ylides the Wittig reaction is *Z*-selective, i.e., the (*Z*)-diastereoisomer is formed predominantly. For example:



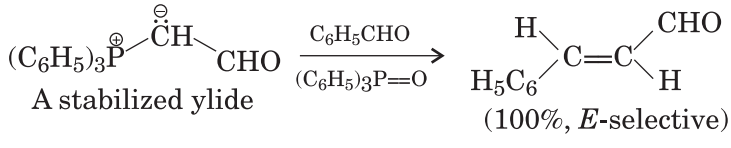
Explanation for *Z*-selectivity In the *Z*-selective Wittig reaction, the first step involves a kinetically controlled stereoselective addition of the Wittig reagent to the carbonyl group and the second step involves a stereospecific elimination of $Ph_3P=O$ from the intermediate oxaphosphetane to form the *Z*-alkene predominantly.



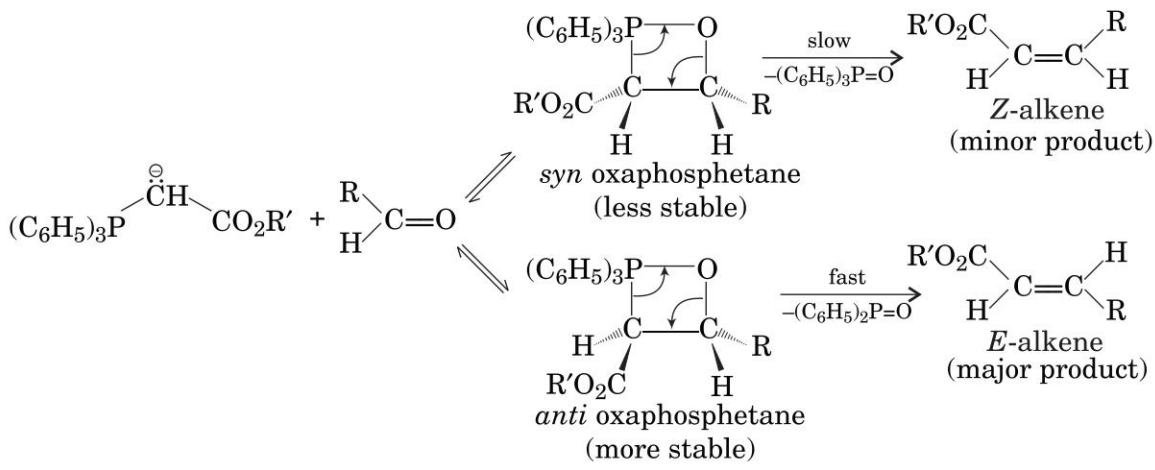
In the first step, the ylide and the aldehyde approach one another at right angles and keeping the large substituent far apart from each other and the reaction proceeds through the transition state as shown below. As a result, the *syn* oxaphosphetane is formed.



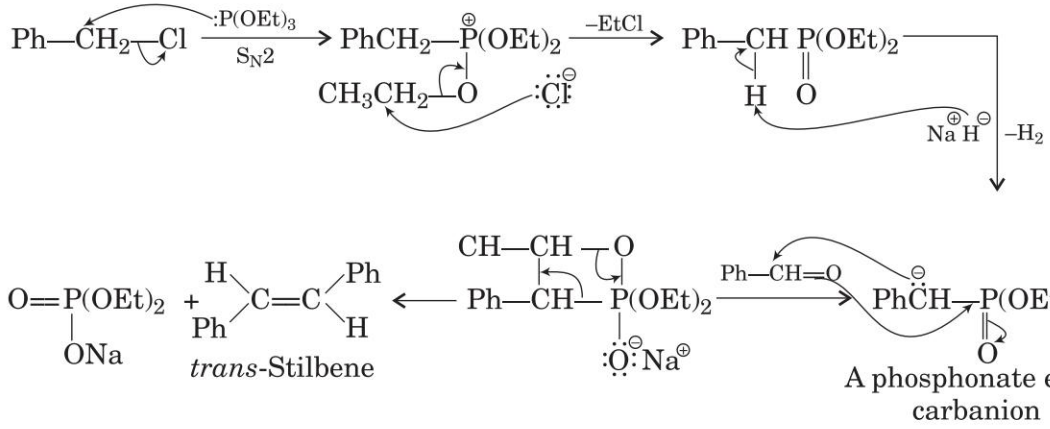
The Wittig reaction is *E*-selective with stabilized ylides. For example:



Explanation for *E*-selectivity Because of the extra stability of the ylide, the reaction leading to the oxaphosphetane is reversible. Stereoselectivity in the first step leading to an oxaphosphetane is, therefore, thermodynamically controlled and not kinetically controlled. An equilibrium is now established between the two diastereoisomeric oxaphosphetanes and the thermodynamically more stable *anti* diastereoisomer with two bulky substituents on opposite sides of the ring is 'siphoned off' to yield the *E*-alkene at a faster rate than the *syn* diastereoisomer yields *Z*-alkene.



The Horner–Wadsworth–Emmons reaction (a modification of the Wittig reaction) In this reaction, a phosphonate ester carbanion (prepared by a reaction of a trialkyl phosphite, $P(OR)_3$, with an appropriate halide followed by treatment with a base such as sodium hydride, potassium *tert*-butoxide, and butyllithium) is treated with an aldehyde or a ketone to form an alkene. The product is usually the (*E*)-alkene. The following reaction sequence is an example.

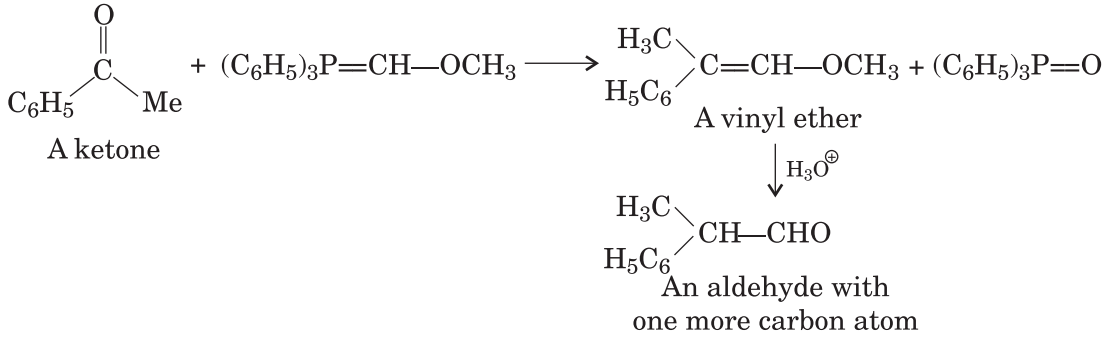


Triphenyl phosphite is first treated with benxyl chloride to form the corresponding phosphonate ester. The phosphonate ester is then treated with sodium hydride to yield a carbanion. The phosphonate ester carbanion is finally treated with benzaldehyde to yield *trans*-stilbene (84%).

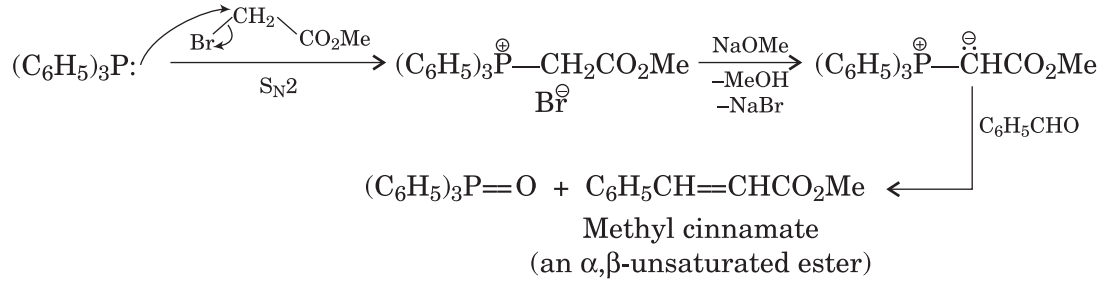
Synthetic Applications of the Wittig reaction: Some useful synthetic applications of the Wittig reaction are illustrated below.

(i) The reaction is a very useful method for the synthesis of alkenes since the location of the double bond is specific in the product. Thus, the Wittig synthesis of alkene is completely regioselective.

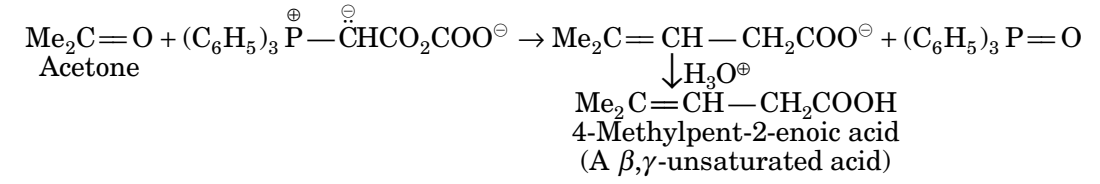
(ii) Vinyl ethers may be prepared and ketones may be stepped up to aldehydes containing one more carbon atoms ($R_2C{=}O \rightarrow R_2CHCHO$) by this reaction. For example



(iii) The Wittig reaction is an excellent procedure for converting an aldehyde to an α, β-unsaturated ester. The ester may be hydrolysed if the carboxylic acid is desired. For example

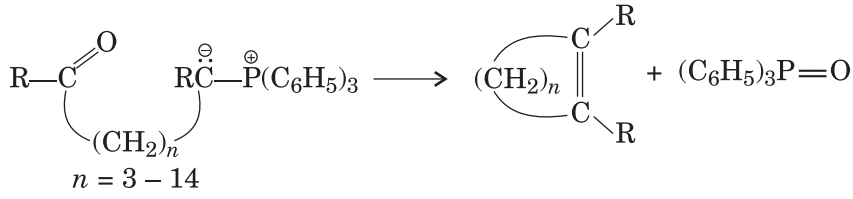


(iv) This reaction can be used to prepare β,γ-unsaturated acids. For example:

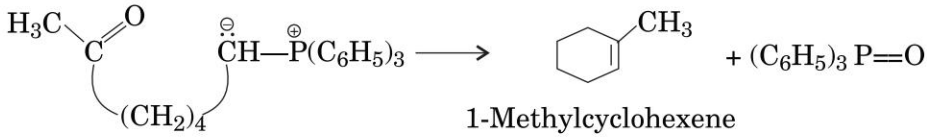


It is the only convenient method for preparing β,γ-unsaturated acid because in all other methods isomerization to the more stable (due to conjugation) α,β-unsaturated acid results.

(v) Intramolecular Wittig reaction is useful in preparing cycloalkene containing 5-16 carbons.



Example:



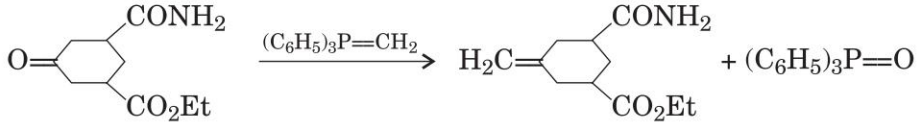
1-Methylcyclohexene

(vi) Allenes can be prepared by allowing a Wittig reagent to react with a ketene. For example:

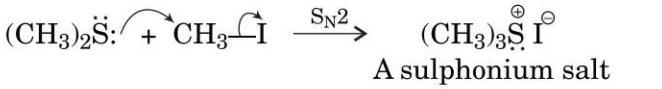
$$(C_6H_5)C{=}C{=}O + (C_6H_5)_3\overset{\oplus}{P}{-}\overset{\ominus}{C}Me_2 \rightarrow (C_6H_5)_2C{=}C{=}CMe_2 + (C_6H_5)_3P{=}O$$

A ketene — An allene

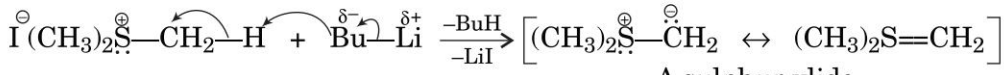
(vii) Chemoselective insertion of double bond is possible by this reaction because other carbonyl groups (like that of amide or ester) do not react. For example:



Preparation of sulphur ylides and their reaction with aldehydes and ketones: When a sulphnium salt is treated with a base (e.g., BuLi), an α-hydrogen is eliminated to form a sulphur ylide. For example:

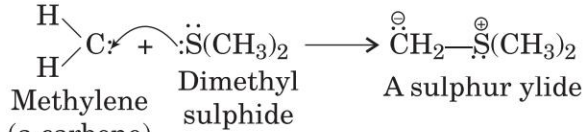


A sulphonium salt



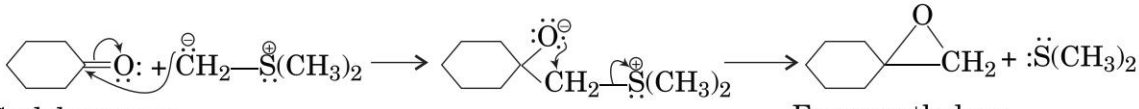
A sulphur ylide

Sulphur ylides can also be prepared by the reaction of a carbene with an alkyl sulphide. For example:



Methylene (a carbene) — Dimethyl sulphide — A sulphur ylide

Sulphur ylides react with aldehydes or ketones to form the corresponding epoxides. For example:

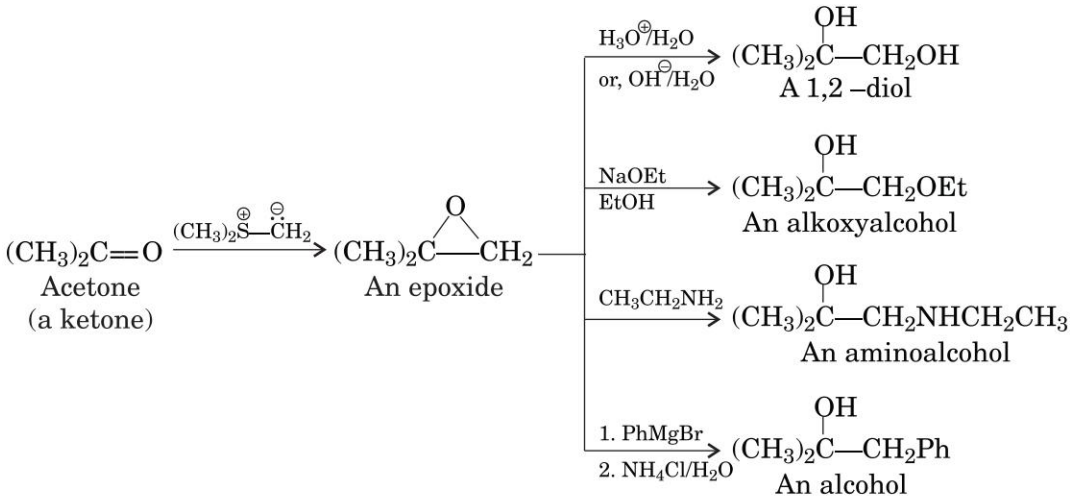


Cyclohexanone — Epoxymethylene-cyclohexane (an epoxide)

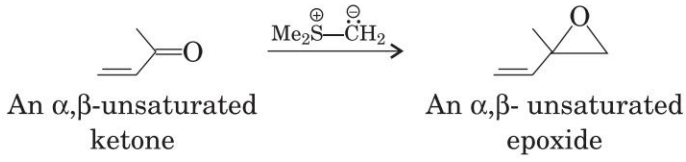
Because of relatively weaker affinity of sulphur for oxygen compared with that of phosphorus (bond energy: P—O = 130 kcal/mol and S—O = 112 kcal/mol), sulphur ylides react with carbonyl compounds not to yield alkenes but to yield epoxides.

Synthetic applications:

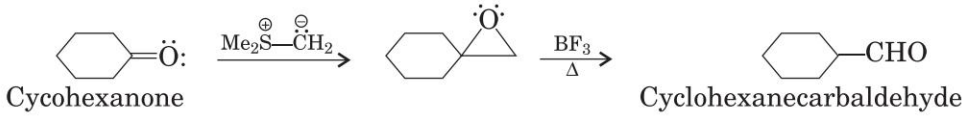
(i) The reaction of aldehydes or ketones with sulphur ylides is used to prepare epoxides which in turn be converted to some useful compounds like 1,2-diols, alkoxyalcohols, aminoalcohols and alcohols. For example



(ii) Sulphur ylides does not act as a Michael donor with α,β-unsaturated carbonyl compounds rather they attack the carbonyl group. The α,β-unsaturated epoxides can be easily prepared. For example:

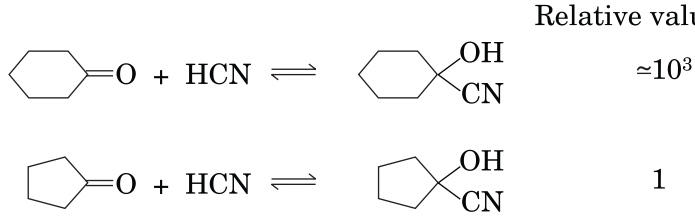


(iii) Since the epoxides undergo rearrangement (via hydride transfer) to carbonyl compounds when treated with Lewis acid (e.g., BF_3), the overall process can be used for stepping up ketones to aldehydes containing one more carbon atom ($R_2C{=}O \rightarrow R_2CH{-}CHO$). For example



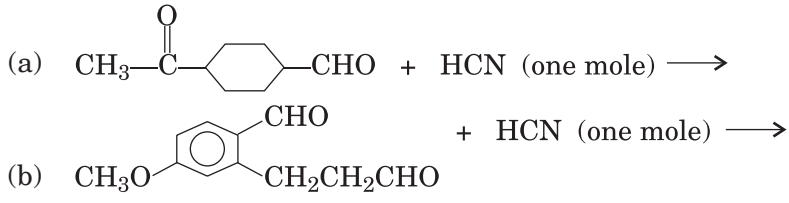
SOLVED PROBLEMS

1. Explain the following observations regarding the equilibrium constant for cyanohydrin formation:



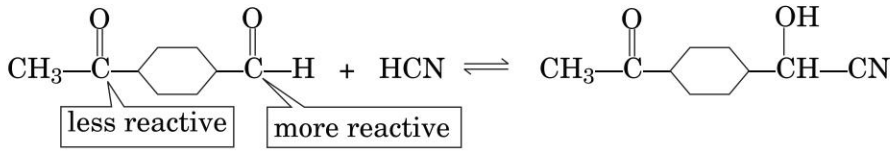
Solution When cyclopentanone is converted to its cyanohydrin (the hybridized state of the C of C═O switches from sp^2 to sp^3), the bond opposition or torsional strain (eclipsing interaction with an H on each flanking C) increases, but the angle strain somewhat decreases. However, the relief of angle strain is less than sufficient to compensate for the increased bond opposition or torsional strain and because of this, the process is energetically less favourable. In cyclohexanone, on the other hand, the equatorial H's at C-2 and C-6 are partially eclipsed with the carbonyl oxygen ($\theta = 4.3°$) due to flattening. The combined effect of torsional strain and angle strain (120° – 116° = 4°) destabilized cyclohexanone relative to its cyanohydrin which is free of any bond opposition and angle strain. The formation of cyclohexanone cyanohydrin is, therefore, energetically much favourable. It is for this reason the equilibrium constant for cyanohydrin formation is much greater for cyclohexanone than for cyclopentanone.

2. Predict the product of the following reactions and provide explanations for their formations:

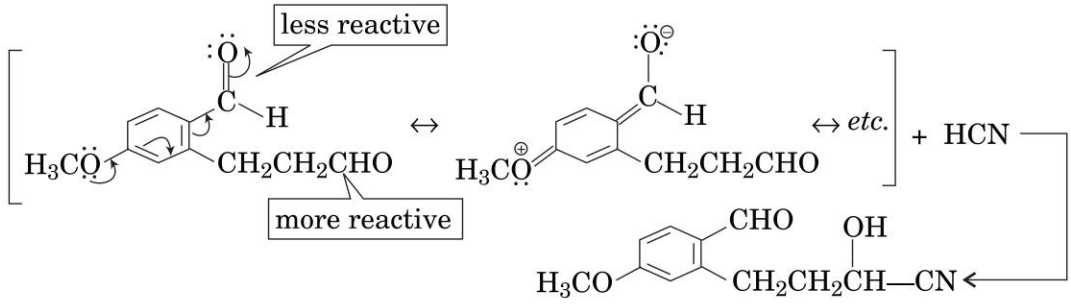


Solution

(a) Because of electronic as well as steric factors, the aldehyde carbonyl group is more reactive towards nucleophilic addition than the keto carbonyl group. The carbonyl carbon atom of a ketone carries two electron-releasing (+I) groups, whereas that of an aldehyde has only one. Therefore, the carbonyl carbon of a ketone is less positively polarized, i.e., less electrophilic and has less tendency to be attacked by a nucleophile compared to the aldehyde carbonyl carbon. Furthermore, nucleophilic addition to a keto carbonyl group results in greater crowding in the transition state leading to the tetrahedral product. Therefore, it is the aldehyde carbonyl which undergoes addition of HCN (1 mole) to yield the corresponding cyanohydrin.



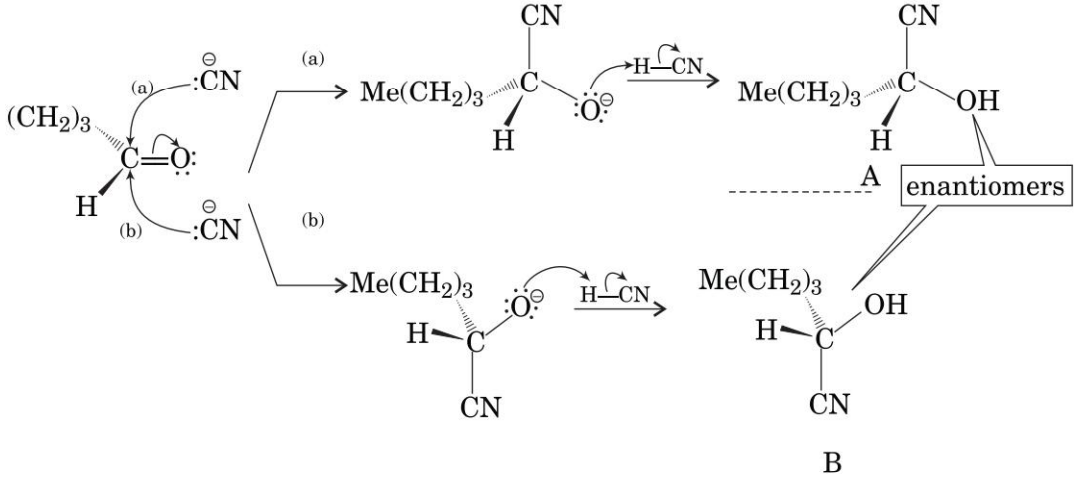
(b) Since the electron-releasing (+R) —OCH_3 group and the electron-withdrawing (–R) —CHO groups are placed *para* to each other in the ring, there occurs an effective resonance interaction between them through the ring π bonds. Because of this, this carbonyl carbon becomes less positively polarized, i.e., less electrophilic than the other carbonyl carbon which is not directly attached to the ring. Addition of HCN (1 mole), therefore, takes place preferably on the —CHO group attached to the aliphatic side chain.

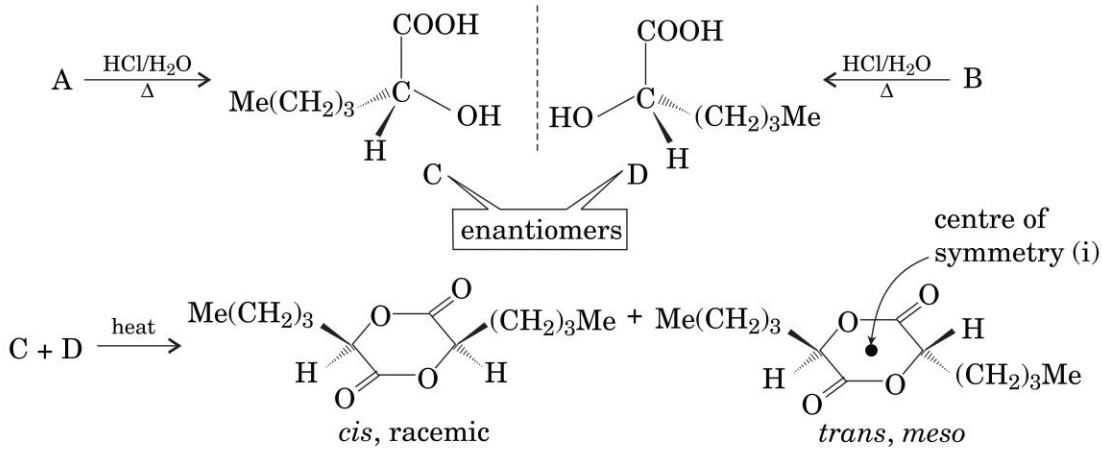


3. $Me(CH_2)_3CHO \xrightarrow[NaCN]{HCN} \underbrace{A + B}_{\text{two isomers}} \xrightarrow[\Delta]{HCl/H_2O} \underbrace{C + D}_{\text{two isomers}}$

Identify A, B, C and D. On heating, C plus D produces two isomeric cyclic compounds of which one is resolvable. Identify the products and explain the change.

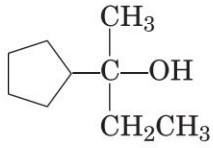
Solution



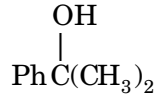


When the two enantiomeric α-hydroxycarboxylic acids (C and D) are heated together, an intermolecular lactonization occurs to yield two diastereoisomeric cyclic compounds of which the chiral *cis*-isomer is resolvable.

4. Give the Grignard reagent and carbonyl compound or ethylene oxide that can be used to prepare the following alcohols. If more than one combination of reactants is possible give each of the combinations.

(a) 

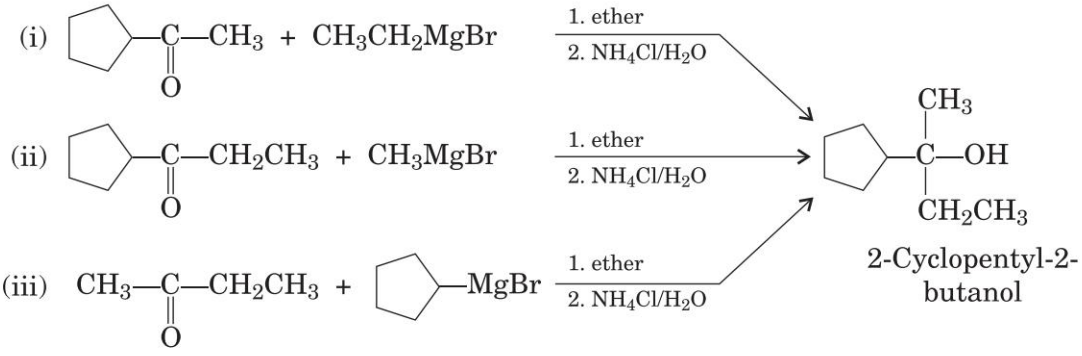
(b) $CH_3CH_2CH_2CH_2OH$

(c) 

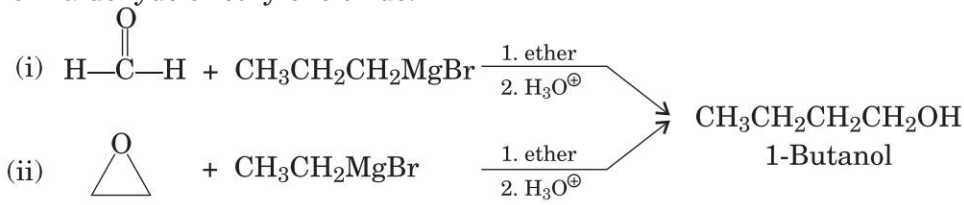
(d) 

Solution

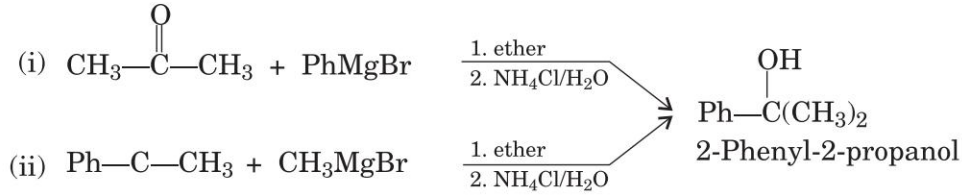
(a) Since it is a tertiary alcohol, it is to be prepared by allowing a Grignard reagent to react with a ketone. Three combinations of reactants are possible because all the three groups attached to the carbon bearing OH are different. Any one of the three alkyl groups might be added in the form of a Grignard reagent.



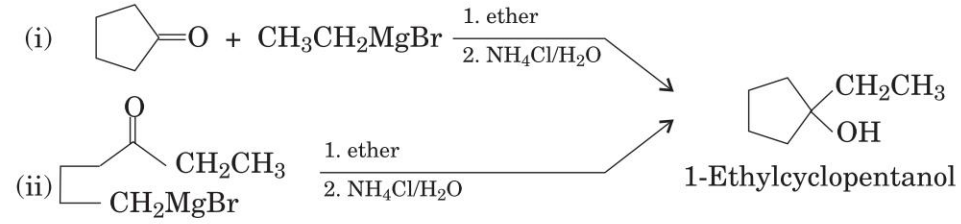
(b) This primary alcohol can be prepared by treating a suitable Grignard reagent with formaldehyde or ethylene oxide.



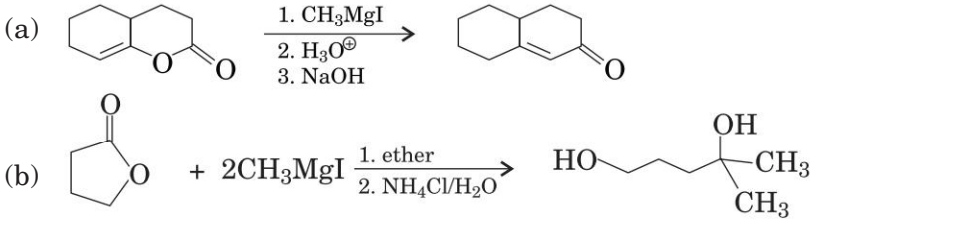
(c) This tertiary alcohol is to be prepared by the reaction between a Grignard reagent and a ketone. Two combinations of reactants are possible because the carbon bearing OH is attached to two types of groups. Any one type of group might be added in the form of a Grignard reagent.



(d) This 3° alcohol with two identical groups (ring bonds) attached to the carbon bearing OH may be prepared by two ways.

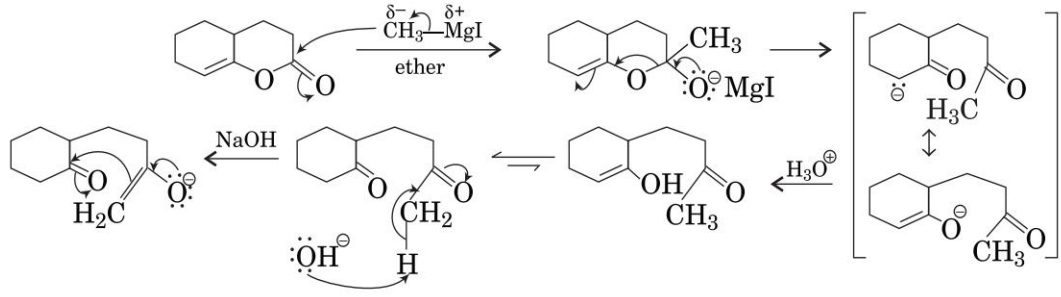


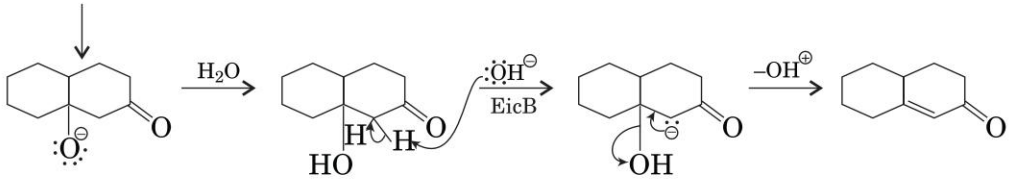
5. Propose a reasonable mechanism for each of the following reactions:



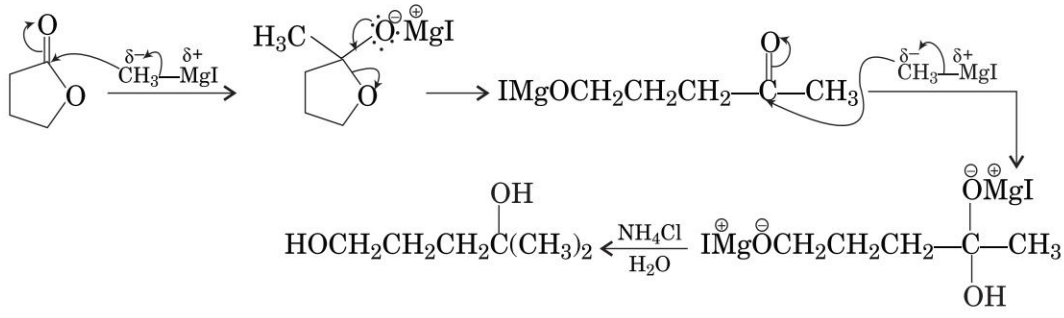
Solution

(a)

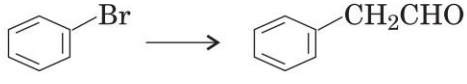


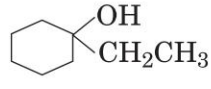


(b)

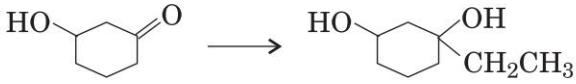


6. How would you carry out each of the following transformations?

(a) 

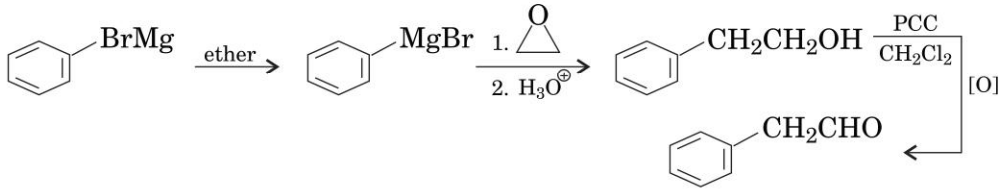
(b) $CH_3CH_2OH \longrightarrow$ 

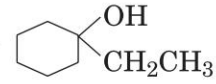
(c) $HC{\equiv}CH \rightarrow HO_2C{-}C{\equiv}C{-}CO_2H$

(d) 

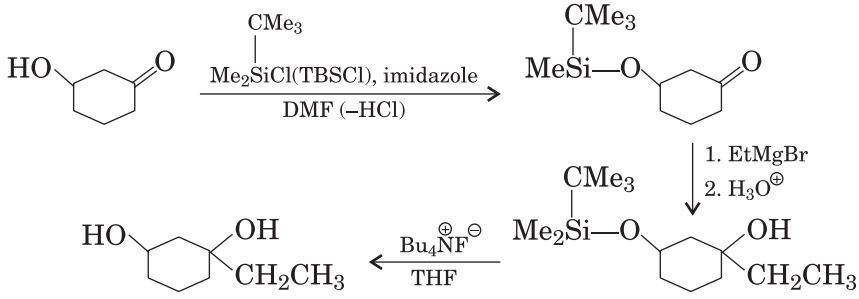
(e) 

Solution

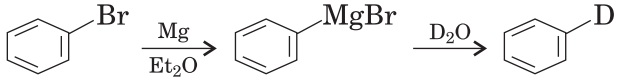
(a) 

(b) $CH_3CH_2OH \xrightarrow{PBr_3} CH_3CH_2Br \xrightarrow[ether]{Mg} CH_3CH_2MgBr \xrightarrow[2.\ NH_4Cl/H_2O]{1.} $ 

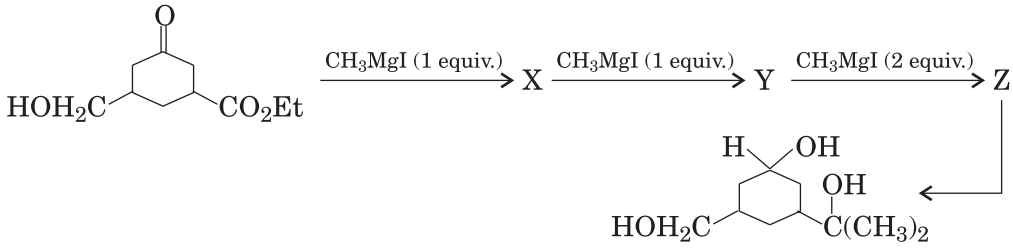
(c) $HC{\equiv}CH \xrightarrow[(-2CH_4\uparrow)]{2CH_3MgI} IMgC{\equiv}CMgI \xrightarrow[2.\ H_3O^{\oplus}]{1.\ 2CO_2} HO_2C{-}C{\equiv}C{-}CO_2H$

(d) 

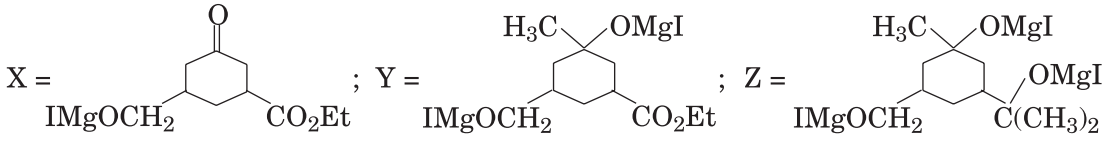
To avoid reaction with the Grignard the —OH group is first protected by converting it to a *tert*-butyldimethylsilyl (TBS) ether. The protecting group is finally removed by treating with $Bu_4\overset{\oplus}{N}\overset{\ominus}{F}$ in THF.

(e) 

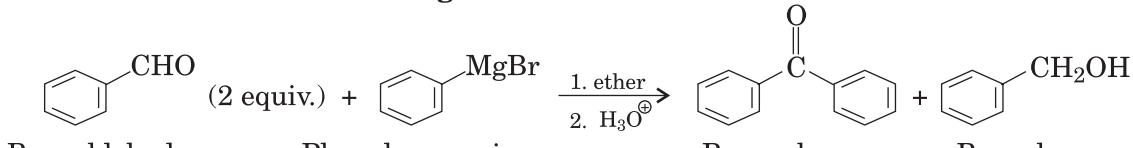
7. Identify the intermediates X, Y, and Z in the following reaction sequence and explain:



Solution The decreasing order of reactivity of various functional groups towards a Grignard reagent is as follows: active hydrogen (i.e., hydrogen attached to electronegative atom) ⋙ —CHO ⟩ ⟩C=O ⟩—CO_2R**.** Therefore, in the first step, CH_3MgI reacts with the alcoholic —OH group to form X, in the second step, it reacts with the keto carbonyl group to yield Y and in the third step, two equivalents of it react with the ester group to form Z.

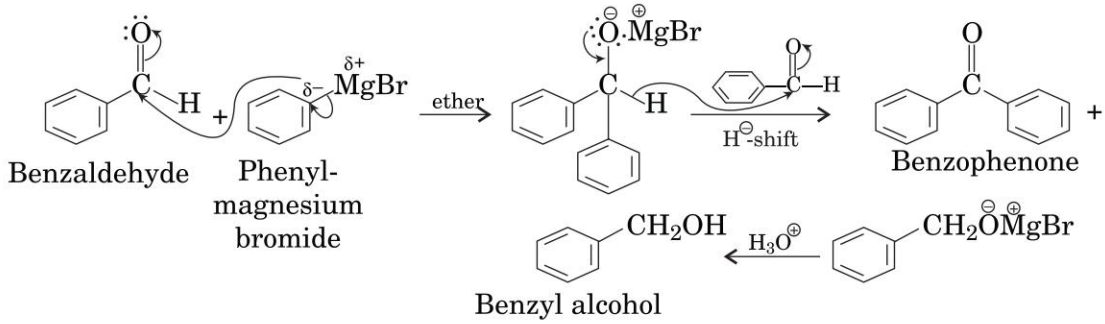


8. Account for the following observation:

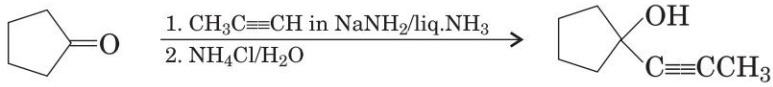


Benzaldehyde — Phenylmagnesium bromide — Benzophenone — Benzyl alcohol

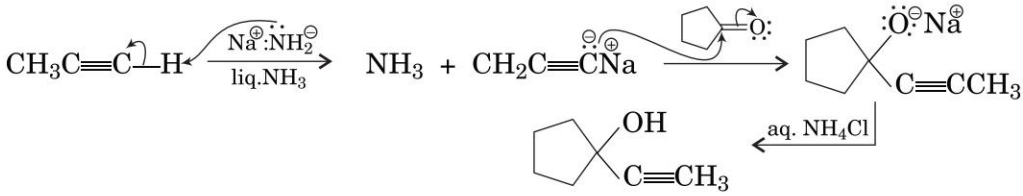
Solution Phenylamagnesium bromide (PhMgBr) reacts with two equivalents of benzaldehyde (PhCHO) to yield benzophenone (a ketone) and benzyl alcohol (a primary alcohol) by transfer of a hydride ion (as in *Cannizzaro reaction*). The mechanism of the reaction is as follows:



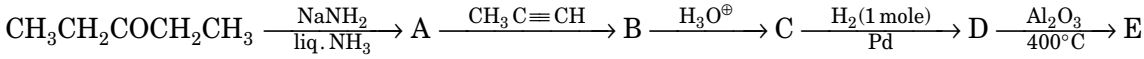
9. Metal alkynides, i.e., the organometallic derivatives of terminal alkynes readily add to aldehydes and ketones. Provide a mechanism that explains the formation of the following product:



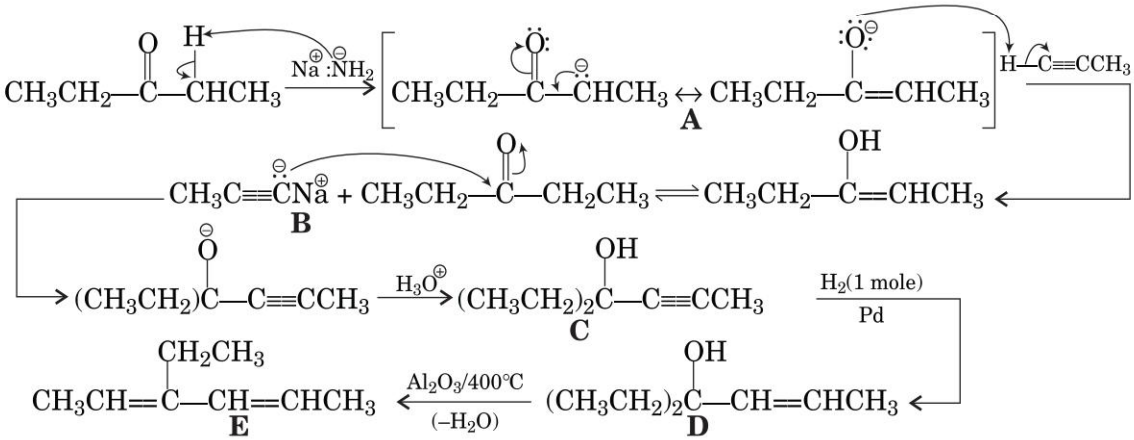
Solution



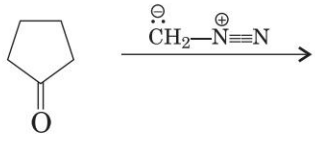
10. Identify the compounds A—E in the following reactions sequence:

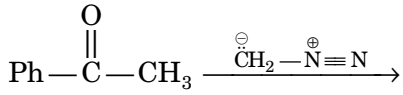


Solution



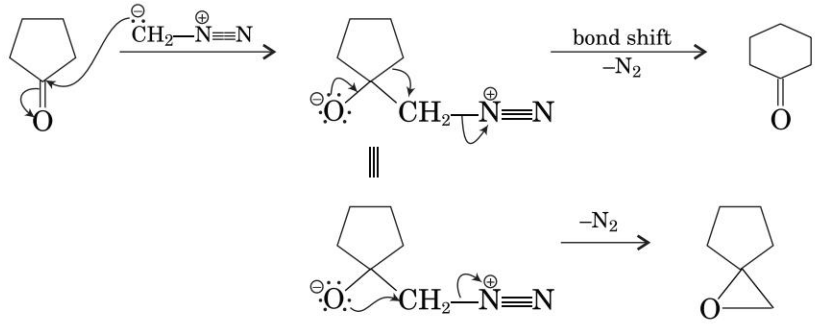
11. Predict the product of each of the following reactions and provide the mechanism involved in each case:

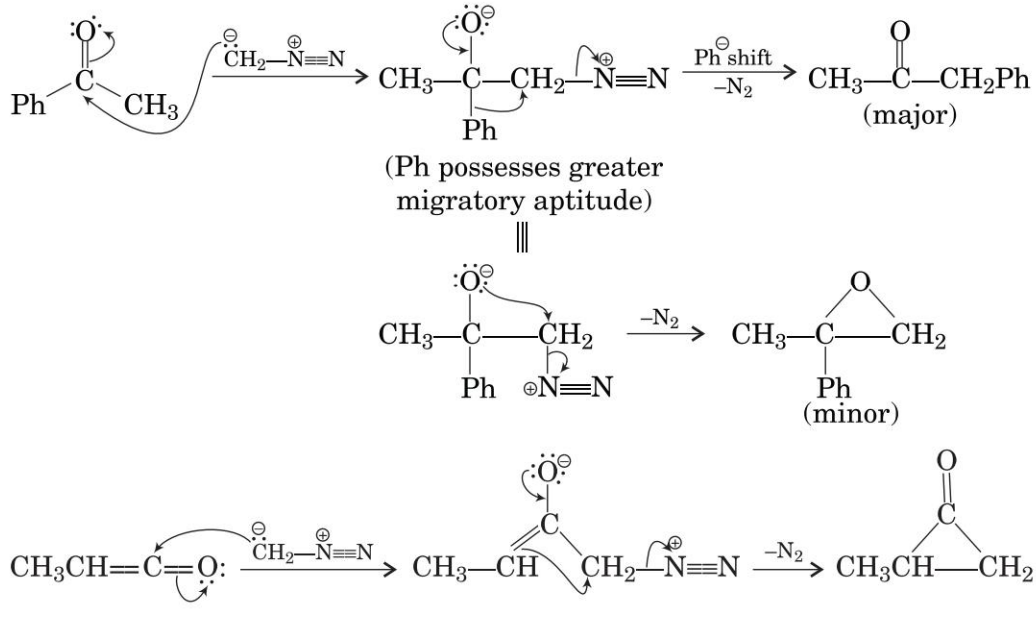
(a) 

(b) 

(c) $CH_3CH{=}C{=}O \xrightarrow{\ominus\!\!:CH_2-\overset{\oplus}{N}\equiv N}$

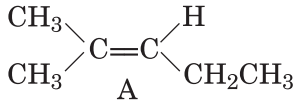
Solution

(a) 

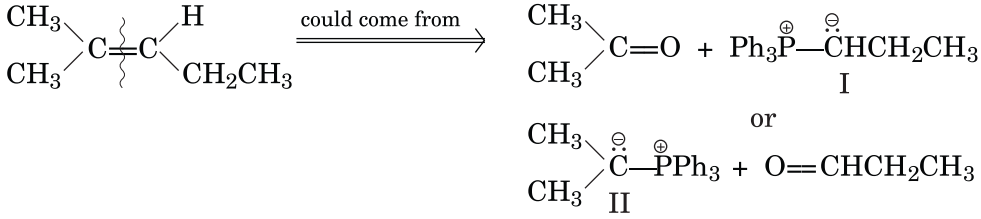
(b) 

(c)

12. Predict the suitable starting materials needed to synthesize the alkene A by a Wittig reaction. Give its synthesis.



Solution To determine the necessary starting materials, the molecule A is to be divided mentally at the double bond and then it is to be decided which of the two components should come from the carbonyl compound and which should come from the ylide.



In general, the ylide should come from an unhindered alkyl halide (R—X). Triphenylphosphine, $Ph_3\ddot{P}$, is a bulky reagent, which reacts by the S_N2 fashion best with unhindered primary and methyl halides. It occasionally reacts with secondary halides, but these reactions are sluggish and often give poor yields.

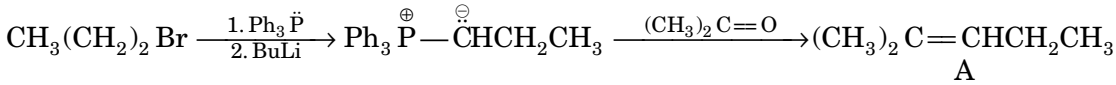
What alkyl halide is needed to prepare each Wittig reagent is determined as follows:

$$Ph_3\overset{\oplus}{P}—\underset{I}{\overset{\ominus}{\ddot{C}}HCH_2CH_3} \Rightarrow Ph_3\overset{\oplus}{P}—\underset{X^{\ominus}}{CH_2CH_2CH_2CH_3} \Rightarrow Ph_3\ddot{P} + \underset{\text{(suitable for } S_N2)}{\underset{A\ 1^\circ \text{ halide}}{CH_3CH_2CH_2X}}$$

$$Ph_3\overset{\oplus}{P}—\underset{II}{\overset{\ominus}{\ddot{C}}}(CH_3)_2 \Rightarrow Ph_3\overset{\oplus}{P}—\underset{X^{\ominus}}{CH(CH_3)_2} \Rightarrow Ph_3\ddot{P} + \underset{\text{(Not much suitable for } S_N2)}{\underset{A\ 2^\circ \text{ halide}}{(CH_3)_2CH—X}}$$

Therefore, to prepare the Wittig reagent I, a 1° alkyl halide, $CH_2CH_2CH_2X$ (e.g.,$CH_3CH_2CH_2Br$), is required and to prepare the Wittig reagent II, a 2° alkyl halide, $(CH_3)_2CH—X$ (e.g., Me_2CHBr), is required. Hence, from the steric point of view (the most important factor for an S_N2 reaction) the 1° alkyl halide $CH_3CH_2CH_2X$ and acetone (MeCOMe) are the better starting materials for the synthesis of the alkene A.

Synthesis of A:



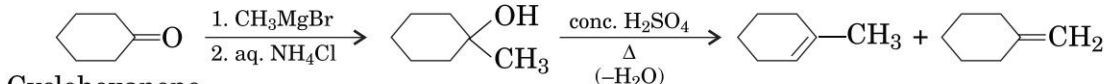
13. Illustrate the advantage in using the Wittig reaction over the elimination method to synthesize alkenes with a suitable example.

Solution An advantage in using the Wittig reaction over the elimination method to synthesize alkenes is that we always know the location of the double bond. Whereas other methods of alkene synthesis often result in formation of a mixture of constitutional isomers, the Wittig reaction always give a single constitutional isomers. For example, cyclohexanone can be converted into methylene cyclohexane by two methods and these are: (i) a two-step method consisting of Grignard addition followed by dehydration and (ii) a one-step Wittig reaction.



Cyclohexanone Methylenecyclohexane

In the two-step method, treatment of cyclohexanone with CH_3MgI produces a 3° alcohol after acidification. Dehydration of the alcohol with concentrated sulphuric acid forms a mixture of alkenes, in which the desired disubstituted alkene (thermodynamically less stable) is the minor product.



Cyclohexanone A 3° alcohol 1-Methylcyclohexene (major product) Methylenecyclohexane (minor product)

The reaction of cyclohexanone with $Ph_3\overset{\oplus}{P}-\overset{\ominus}{\ddot{C}}H_2$, on the other hand, produces the desired alkene as the only product. The newly formed double bond always joins the carbon atom with the negatively charged carbon atom of the Wittig reagent. In other words, the position of the double bond is always unambiguous in the Wittig reaction, i.e., the reaction is completely regioselective. The Wittig reaction is, therefore, an especially attractive method for preparing many alkenes.



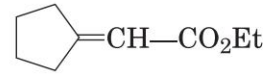
Cyclohexanone Wittig reagent Methylenecyclohexane (the only product)

14. Show how Wittig reactions might be used to synthesize the following compounds. Give better combination of reactants in each case.

(a) $Ph-CH=C(CH_3)_2$

(b) $Ph-\overset{CH_3}{\overset{|}{C}}=CH_2$

(c) $Ph_2C=CH-O-C_6H_4-NO_2$

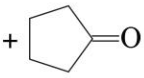
(d) 

Solution Since triphenylphosphine (Ph_3P) is a hindered nucleophile, it reacts best with unhindered primary and methyl halides in S_N2 reactions. Therefore, the ylide should come from an unhindered alkyl halide.

(a) $Ph—CH=\!=C(CH_3)_2 \Rightarrow$ Wittig from $PhCH_2Br + CH_3COCH_3$

(b) $Ph—\underset{\displaystyle CH_3}{\overset{|}{C}}=\!=CH_2 \Rightarrow$ Wittig from $CH_3I + PhCOCH_3$

(c) $Ph_2C=\!=CH—O—C_6H_4—NO_2 \Rightarrow$ Wittig from $O_2N—C_6H_4—OCH_2Br + Ph—\overset{\displaystyle O}{\overset{\|}{C}}—Ph$

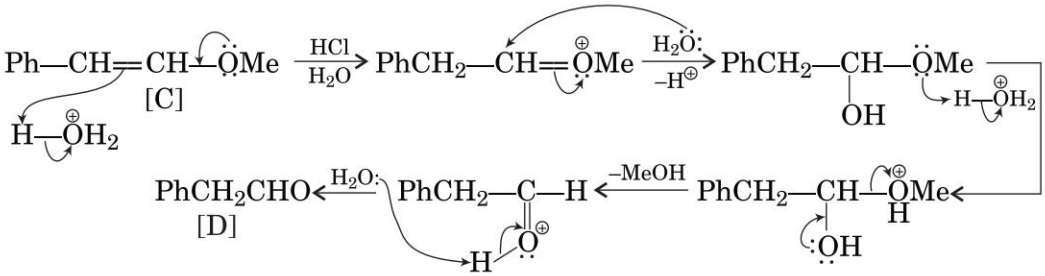
(d)  $\Rightarrow$ Wittig from $BrCH_2CO_2Et +$ 

15. Write the structures of [A] to [D] in the following reaction sequence. Explain the formation of [D] from [C].

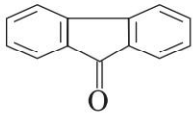
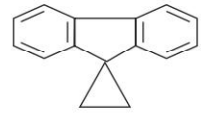
$$MeOCH_2Cl \xrightarrow{Ph_3P} [A] \xrightarrow{PhLi} [B] \xrightarrow[-Ph_3PO]{PhCHO} [C] \xrightarrow{HCl/H_2O} [D] + MeOH$$

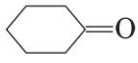
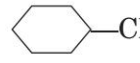
Solution [A] $\Rightarrow MeOCH_2—\overset{\oplus}{P}Ph_3Cl^{\ominus}$; B $\Rightarrow MeO—\overset{\ominus}{C}H—\overset{\oplus}{P}Ph_3$; H[C] $\Rightarrow PhCH=CHOMe$;
[D] $\Rightarrow PhCH_2CHO$

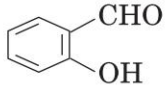
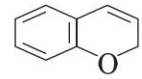
[C] undergoes hydrolysis by dilute acid to give [D] as follows:

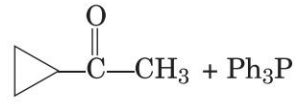


16. Suggest a mechanism for each of the following reactions:

(a)  $+ 2\ Ph_3P=CH_2 \longrightarrow$  $+ Ph_3P=O$

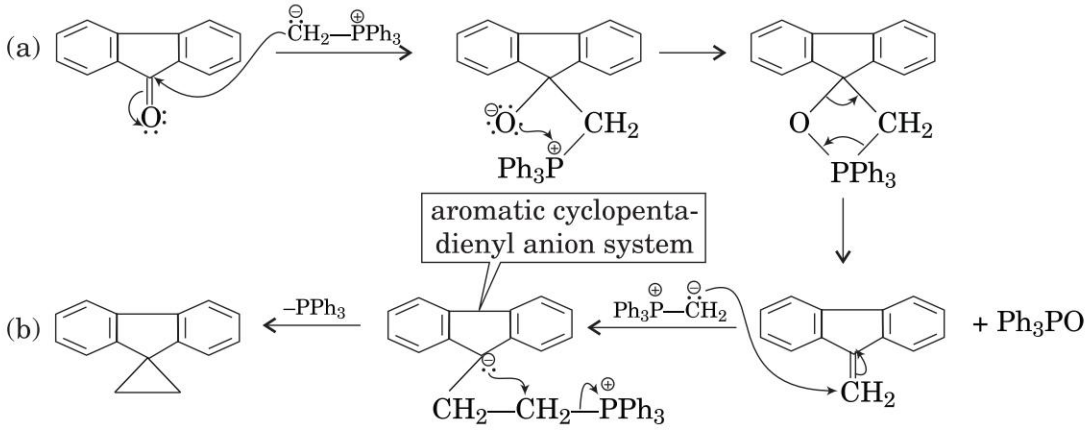
(b)  $\xrightarrow[1.\ H_3O^{\oplus}]{1.\ Ph_3P=CHOCH_3}$  $+ Ph_3P=O$

(c)  $+ CH_2=CH—\overset{\oplus}{P}Ph_3\overset{\ominus}{Br} \xrightarrow{Base}$  $+ Ph_3P=O$

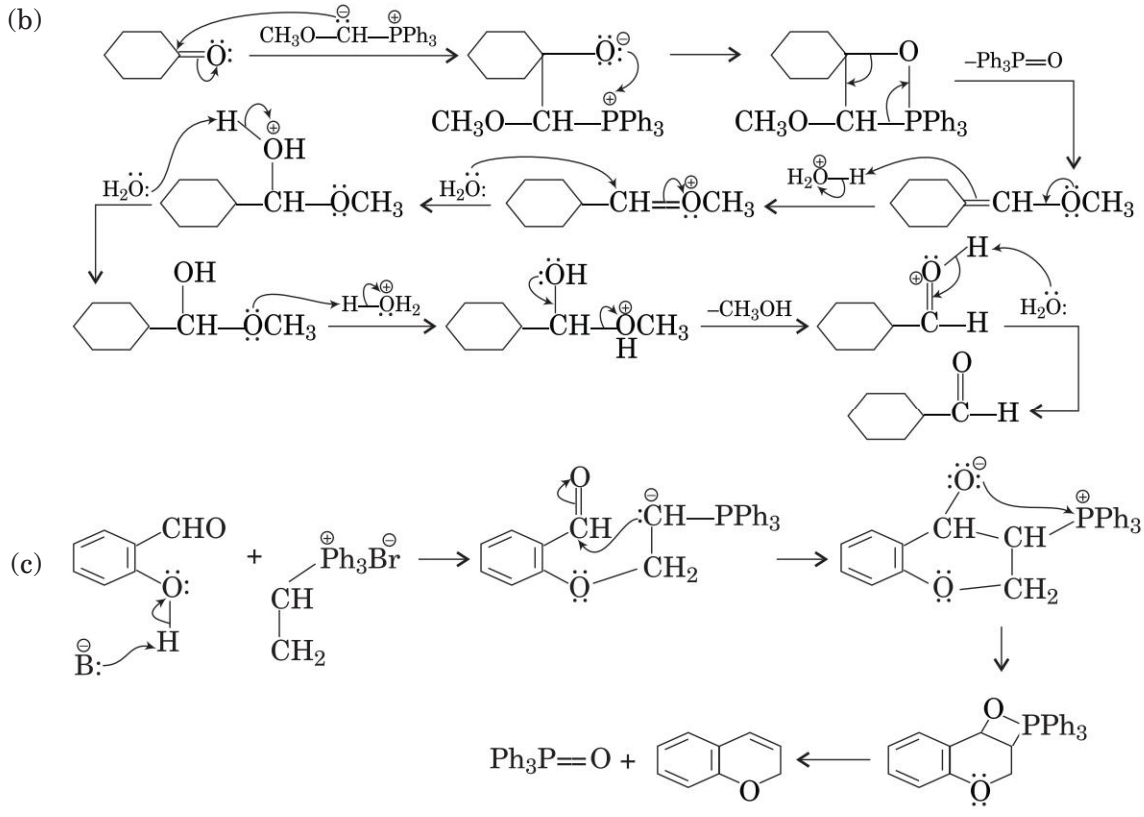
(d) $CH_3COCH=CH_2 \xrightarrow{Ph_3P=CH_2}$  $+ Ph_3P$

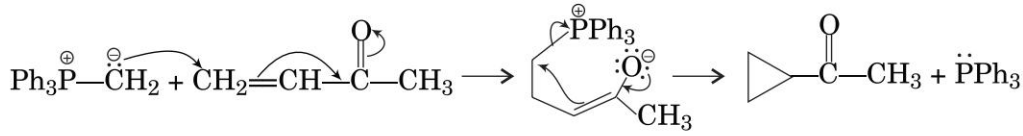
(e) $BrCH_2CO_2Et \xrightarrow[3.\ Me_2C{=}O]{1.\ \ddot{P}(OEt)_3,\ 2.\ NaOEt} Me_2C{=}CH{-}CO_2Et$

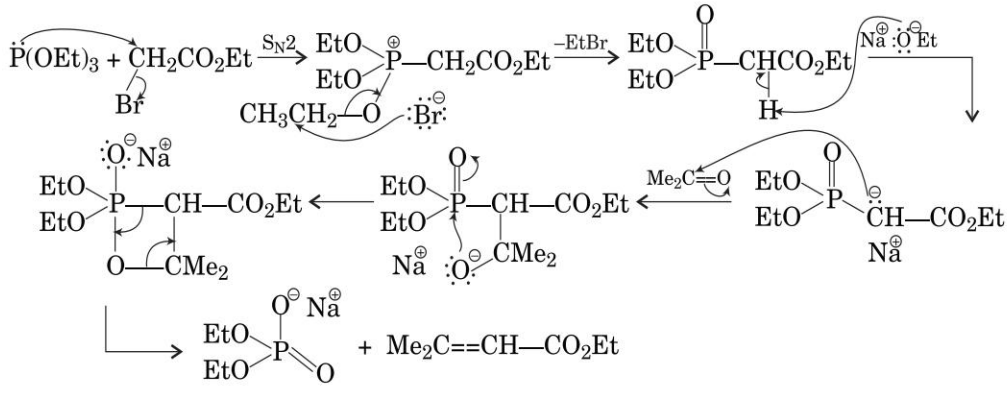
Solution



The second molecule of $Ph_3\overset{\oplus}{P}{-}\overset{\ominus}{C}H_2$ attacks the methylene carbon because the resulting anion constitutes an aromatic cyclopentadienyl anion system.



(d) 

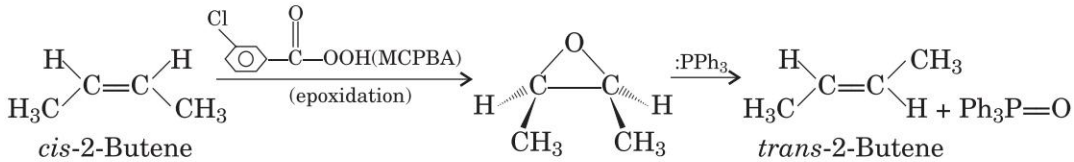
(e) 

17. How would you carry out the following transformation? Give mechanisms of the steps involved.



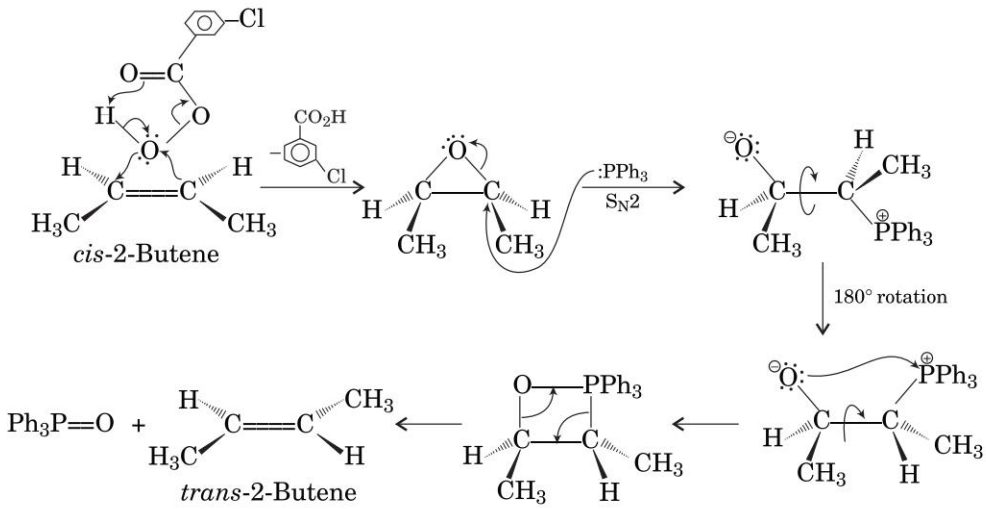
cis-2-Butene *trans*-2-Butene

Solution



cis-2-Butene *trans*-2-Butene

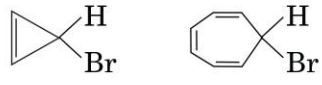
Mechanism:



cis-2-Butene *trans*-2-Butene

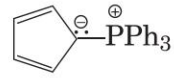
18. Explain the following observations:

(a) **The following bromides (I and II) cannot form ylide:**



I II

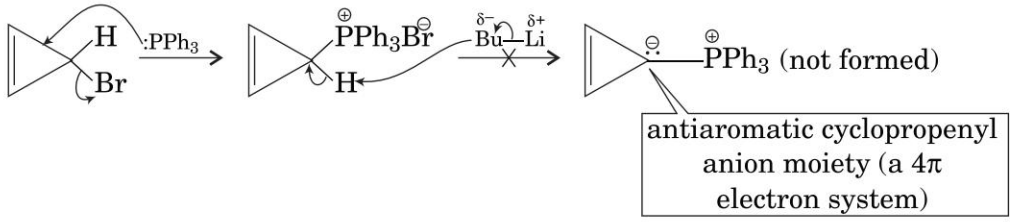
(b) **Although the Wittig reagents are highly reactive, the following ylide does not participate in the Wittig reaction:**

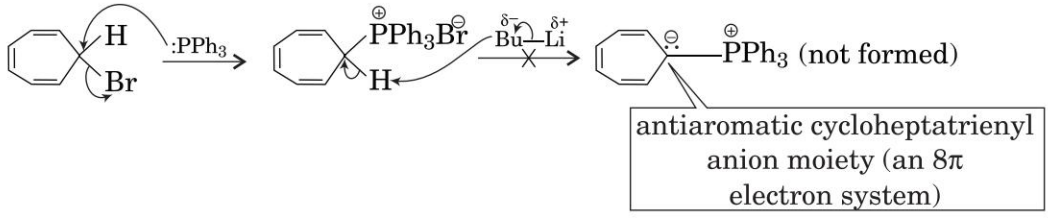


(c) **2,2,5,5-Tetramethylhex-3-ene cannot be prepared by the Wittig reaction.**

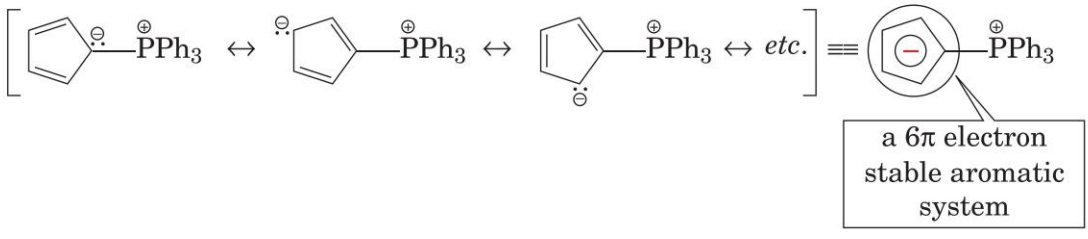
Solution

(a) When these two compounds are allowed to react with $Ph_3\ddot{P}$ followed by BuLi, antiaromatic rings with carbanionic centre are expected to be obtained. Since the antiaromatic systems are very unstable, the formation of ylide is inhibited.



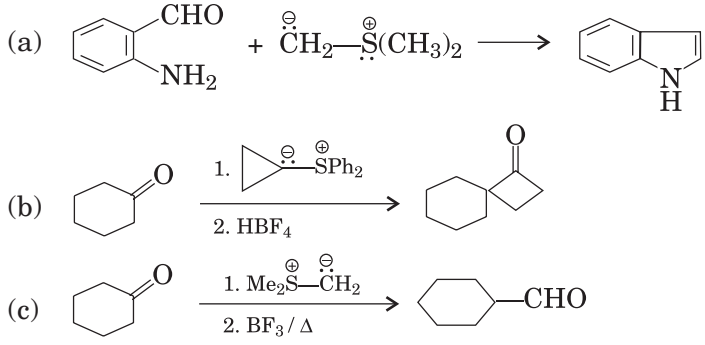


(b) This ylide contains a much stable aromatic cyclopentadienyl moiety (a closed-shell of 6π electron, i.e., a $(4n + 2)\pi$ electron system, where $n = 1$). The negative charge on the ring carbon is highly delocalized and completely involved in maintaining the aromatic sextet and hence, no longer available for nucleophilic attack on the carbonyl carbon of an aldehyde or a ketone.

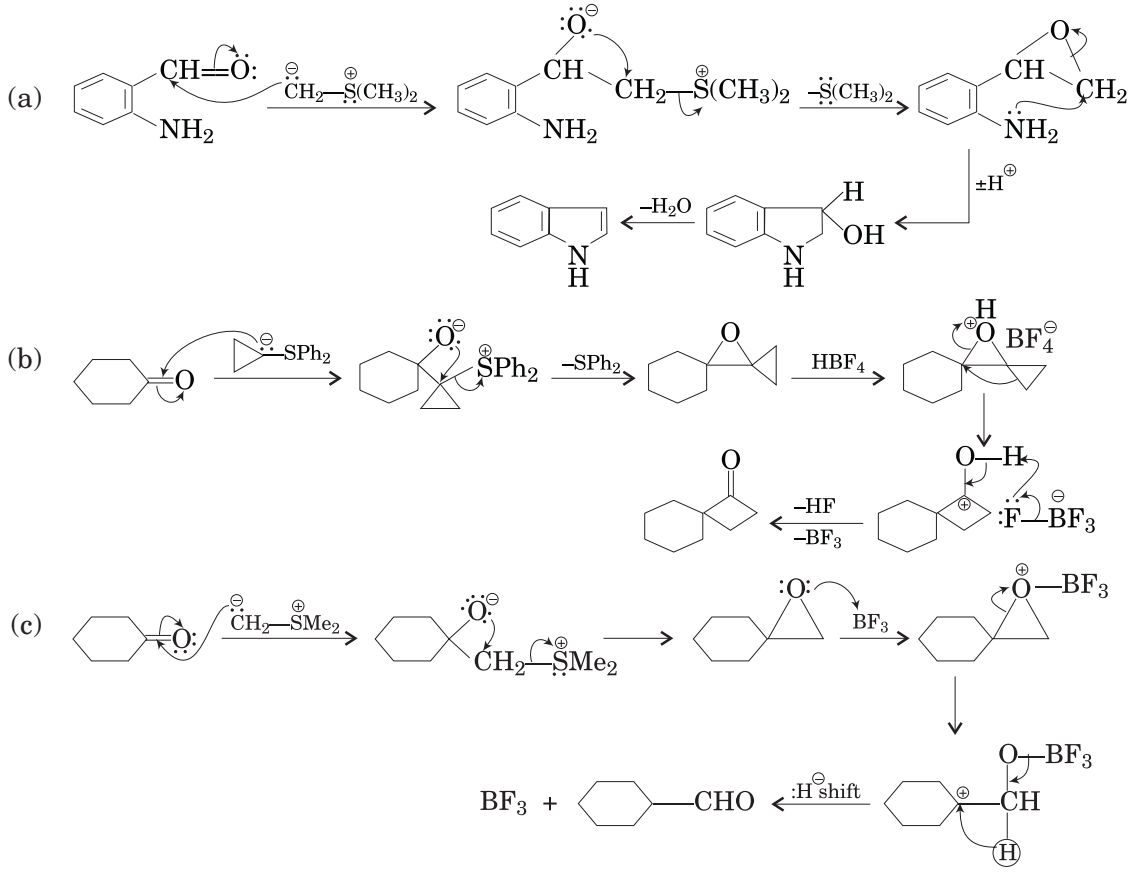


(c) To prepare 2,2,5,5-tetramethylhex-3-ene by the Wittig reaction we need to have a phosphorus ylide by a neopentyl halide with the hindered nucleophile $Ph_3\ddot{P}$ (an S_N2 reaction). However, neopentyl halides do not undergo S_N2 reaction due to steric hindrance even though the halogen–bearing carbon is primary. It is for this reason, 2,2,5,5-tetramethylhex-3-ene cannot be prepared by the Wittig reaction.

19. Provide an arrow pushing mechanism for each of the following reactions:



Solution



Study Problems

1. Explain why aldehydes and ketones react with a weak acid such as HCN in the presence of $:\overset{\ominus}{C}N$ ion, but they do not react with strong acids such as HCl or H_2SO_4 in the presence of $Cl^{\ominus}$ or $HSO_4^{\ominus}$ ion.

2. What happens when a cyanohydrin is treated with alkali? Give an example.
[**Hint:** The cyanohydrin loses a proton followed by a $CN^{\ominus}$ to yield back the carbonyl compound.]

3. Estimate $\Delta H°$ for the following two reactions and hence explain which one of the following reactions is thermodynamically more favourable.

(a) $Me_2C{=}O + HCN \rightleftharpoons Me_2C(OH)(CN)$

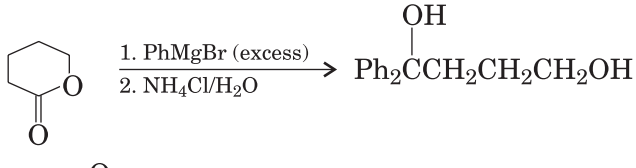
(b) $Me_2C{=}O + HCl \rightleftharpoons Me_2C(OH)(Cl)$

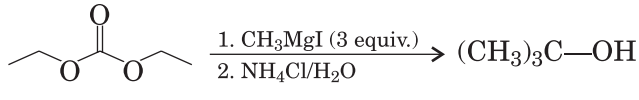
[Bond energy (kcal/mol): H—Cl 103 ; C—Cl 84 ; H—CN 130 ; C—CN 122]

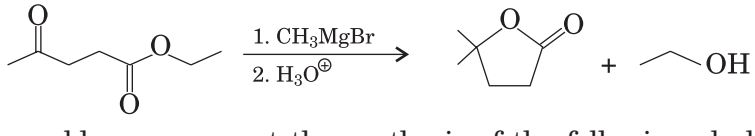
4. Which is the more favourable equilibrium situation for cyanohydrin formation : CH_3CHO + NaCN or CH_3CHO + HCl (both in water) and why?

5. What happens when the α,β-unsaturated carbonyl compound $CH_2{=}CHCOCH_3$ is treated with HCN?
[**Hint:** The nucleophile cyanide ion ($:CN^{\ominus}$) is a relatively weak base and so, it usually form conjugate or 1,4-addition product.]

6. Provide an arrow pushing mechanism for each of the following reactions:

(a) 

(b) 

(c) 

7. How would you carry out the synthesis of the following alcohols by a Grignard reaction?

(a) $CH_3CH_2C(CH_3)_2OH$ (three ways)

(b) $CH_3CH_2CH_2C(OH)CH_3Ph$ (three ways)

(c) $Ph(CH_2)_3OH$ (two ways)

(d) Ph_3COH (two ways)

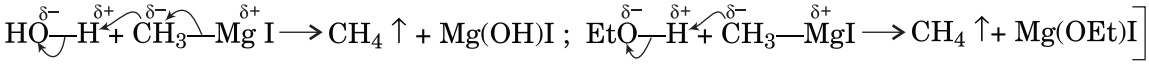
8. How may stereoisomers are obtained from the reaction of 2-pentanone with EtMgBr followed by acidification?
[**Hint:** Two enantiomers of 3-methyl-3-hexanol]

9. How would you carry out the following transformations?
(a) $PhCH_2CH_2Br \rightarrow PhCH_2CH_2D$
(b) $PhCH_2CH_3 \rightarrow PhCHDCH_3$
(c) $PhCH_2CH_3 \rightarrow p\text{-}DC_6H_4CH_2CH_3$
[**Hint:**
(a) 1. Mg/Et_2O, 2. D_2O; 3. D_2O;
(b) 1. NBS, 2. Mg/Et_2O, 3. D_2O;
(c) 1. Br_2/Fe, 2. Mg/Et_2O, 3. D_2O;

10. Methylmagnesium bromide (MeMgBr) does not react with hexamethylacetone – Why?

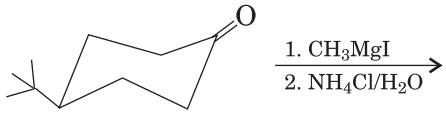
11. R is δ+ in R—I. Give a reaction of R—I in which it is converted to a compound in which the polarity of R is reversed.

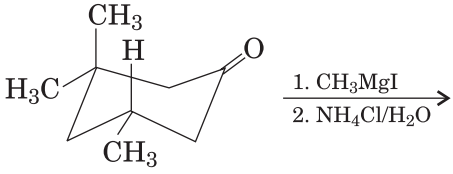
12. What happens when CH_3MGI is treated with acetone which is not completely dry or contains some alcohol as impurity?
[**Hint:** The Grignard reagent decomposes by reacting with water or alcohol because they contain active hydrogen.



13. Using $CH_3CH_2C{\equiv}CH$ and $BrCH_2CH_2CHO$ devise a synthesis of $CH_3CH_2C{\equiv}CCH_2CH_2CHO$ (use other reagents you need)

14. Identify the products in the following reactions and mark the major product in each case:

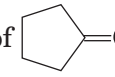
(a) 

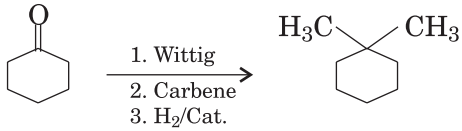
(b) 

[**Hint:** Addition of CH_3MgI to cyclohexanones occurs mainly from the less hindered equatorial side to form axial alcohol as the major product (steric approach control). The percentage of the axial alcohol increases further if the substrate has axial substituent at C-3 or at C-5.]

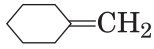
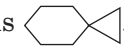
15. How would you carry out the following transformations:
(a) Ethyne → 4-Hexyne-3-ol
(b) Ethyne → 1-Phenyl-2-butyne-1-ol
(c) Ethyne → 2-Methyl-3-heptne-2-ol

(d) Ethyne → 3-Pentyne-1-ol

16. Carry out the synthesis of  using the Wittig reaction. Comment on the choice of the starting materials.

17. 

Provide specific reagents for this conversion and also draw the structure of the intermediates of this reaction sequence.

[**Hint:** 1. $Ph_3P{=}CH_2$ 2. $\ddot{C}H_2$ (CH_2N_2 / $h\nu$) 3. H_2/Pt-C or Pd-C; The first intermediate is  and the second intermediate is  .]

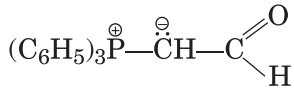
18. Write structures of A, B and C in the following reaction sequence:

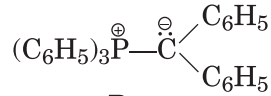
$$TsO(CH_2)_4\,OTs \xrightarrow[\Delta]{Ph_3P(excess)} A \xrightarrow[(2\,equiv.)]{PhLi} B \xrightarrow[(2\,equiv.)]{PhCHO} C$$

19. Suggest structures for A—D and give mechanisms by which these could be formed:

$$BrCH_2CO_2Et \xrightarrow{(EtO)_3P} A \xrightarrow{NaH} B \xrightarrow{\text{cyclohexanone}} C + D$$

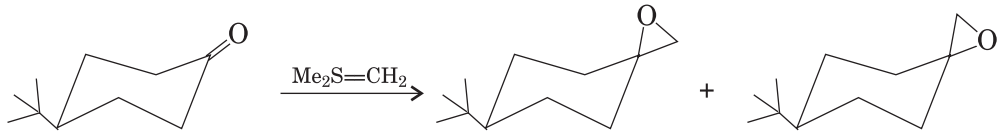
20. Explain why the following ylide A does not react with ketones and the ylide B is unreactive even towards aldehydes.


A

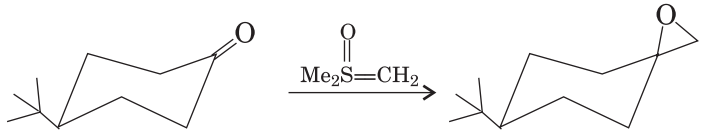

B

[**Hint:** If the negative charge of the ylide is delocalized by resonance to a very large degree or if the carbanionic centre is highly hindered, or both, the ylide may not attack a given carbonyl group.]

21. Explain the following observations:

(a) 

I (major) + II (minor)

(b) 

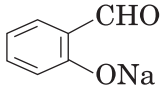
I (100%)

[**Hint:**

(a) $Me_2S{=}CH_2$ adds irreversibly to aldehydes and ketones. Equatorial approach of the sulphur ylide is sterically more favoured and so, it leads to formation of I as the major product.

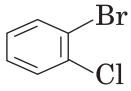
(b) $(CH_3)_2S(O){=}CH_2$ adds reversibly to a carbonyl compound. This gives almost exclusively the product I with equatorial C—C bond (thermodynamically more stable because of less diaxial interaction due to smaller size of oxygen). The reaction is thermodynamic controlled.]

22. Provide structures for compounds A—J in the following reaction sequences:

(a)  + $CH_2{=}CH{-}\overset{\oplus}{P}Ph_3\overset{\ominus}{Br} \xrightarrow{H^{\oplus}} A \xrightarrow{PhLi} B$

(b) $Br(CH_2)_3Br + 2Ph_3P \rightarrow C \xrightarrow{NaOEt} D \xrightarrow{o\text{-}OHCC_6H_4CHO} E$

(c)  $\xrightarrow{HBr} F \xrightarrow[2.\ PhLi]{1.\ Ph_3P} G \xrightarrow{Cyclopentanone} H$

(d)  $\xrightarrow[Et_2O]{Mg} I \xrightarrow[2.\ aq.NH_4Cl]{1.\ CH_3CH_2CHO} J$

2.8 ADDITION OF ENOLATE IONS

- Aldol reactions
- Stobbe condensation
- Darzens glycidic ester condensation
- Benzoin condensation
- Reformatsky reaction
- Perkin reaction
- Knoevenagel condensation (Doebner condensation)
- Mannich reaction

2.8.1 Aldol Reactions

Two molecules of an aldehydes or two molecules of a ketone dimerize in the presence of aqueous base to form a *β*-hydroxyaldehyde or a *β*-hydroxyketone. This reaction is called *aldol addition reaction*. For example, when treated with dilute NaOH at room temperature, acetaldehyde undergoes base-catalyzed dimerization to produce 3-hydroxybutanal.

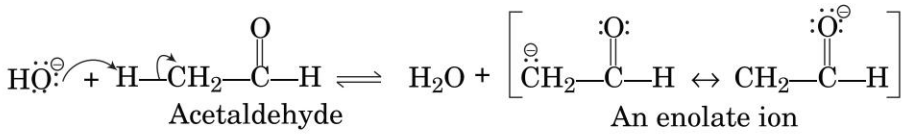
$$\underset{\text{Acetaldehyde}}{CH_3CHO} \xrightarrow[H_2O]{NaOH} \underset{\substack{\text{3-hydroxybutanol (50\%)}\\ \text{(Aldol)}}}{CH_3CH(OH)CH_2CH_3}$$

The mechanism for aldol addition illustrates two important characteristics of carbonyl compounds and these are: (i) the acidity of their *α*-hydrogens and (ii) the tendency of the

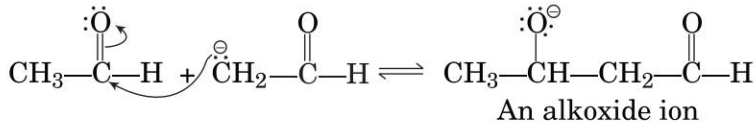
carbonyl carbon to undergo nucleophilic attack. In this reaction, one molecule of a carbonyl compound — after loss of a proton from an α-carbon — reacts as a nucleophile and attacks the electrophilic carbonyl carbon of a second molecule of the carbonyl compound.

Mechanism of the reaction The mechanism of the reaction involves the steps as follows:

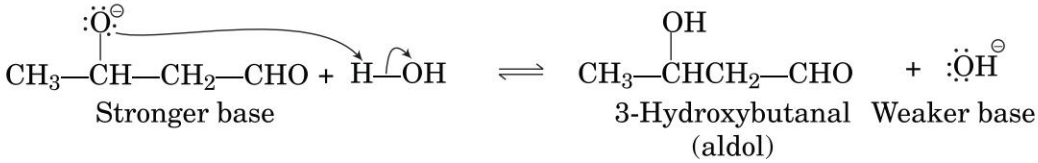
Step 1: The base (a hydroxide ion) removes a proton from the α-carbon of a molecule of acetaldehyde to give a resonance-stabilized enolate ion. It is the slow (rate-determining) step of the reaction.



Step 2: The enolate ion acts as a carbanion nucleophile and attacks the electrophilic carbonyl carbon of a second molecule of acetaldehyde, producing an alkoxide ion.

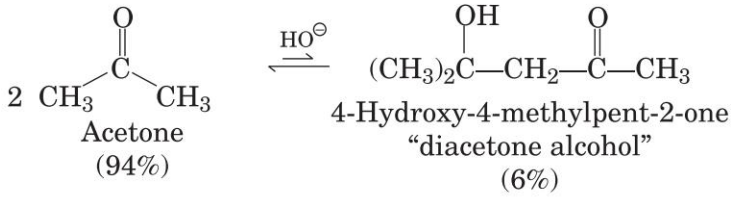


Step 3: The alkoxide ion abstracts a proton from a molecule of water to form 3-hydroxybutanal (aldol). This occurs because the alkoxide ion is a stronger base than the hydroxide ion.



Since the addition product obtained from an aldehyde is both an aldehyde and alcoh*ol*, it has been given the common name aldol and the reaction is named after it.

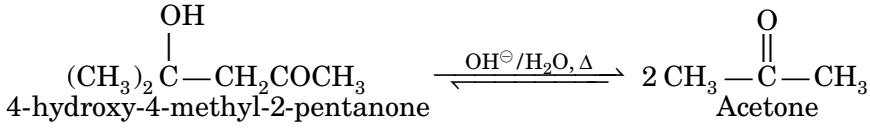
It is to be noted that with ketones, the addition step leading to the aldol is unfavourable due to steric hindrance. Also, the C═O bond in a ketone is stronger than in an aldehyde (about 3 kcal/mol) and the addition is endothermic. The equilibrium thus favours the aldol precursors rather than the aldol product. For example, treatment of propanone (acetone) with base does indeed lead to some 4-hydroxy-4-methylpent-2-one, but the conversion is poor because of an unfavourable equilibrium with the starting material.



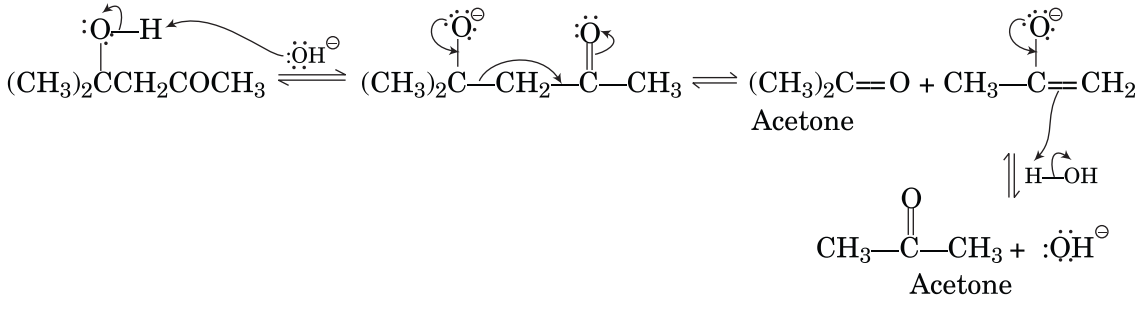
Aldol addition of ketone, for example, acetone, is sometimes accomplished by a clever experimental method. Acetone is boiled so it condenses into a chamber containing an insoluble basic catalyst [$Ba(OH)_2$]. The reaction can take place only in the catalyst chamber. When the solution returns to the boiling flask, it contains about 6% diacetone alcohol. Diacetone alcohol is less volatile (boiling point is higher) than acetone, remaining in the flask while acetone vaporizes easily and condenses in contact with the catalyst. After several hours, nearly all the acetone is converted to diacetone alcohol.

Dehydration of the aldol addition product (under more vigorous conditions) can draw the equilibrium towards completion, whether the reactant is an aldehyde or a ketone. The addition of enolates to both aldehydes and ketones are also feasible when a stronger base like lithium diisopropylamide (LDA) is used in an aprotic solvent.

Retro-aldol reaction Since the steps in an aldol addition reaction are readily reversible, therefore, the aldol addition product, i.e., the *β*-hydroxy aldehyde or ketone reverts back to the starting aldehyde or ketone under favourable reaction conditions. This type of reaction is called a *retro-aldol reaction.* For example, when 4-hydroxy-4-methyl-2-pentanone is heated with strong alkali, acetone is obtained by a retro-aldol process.



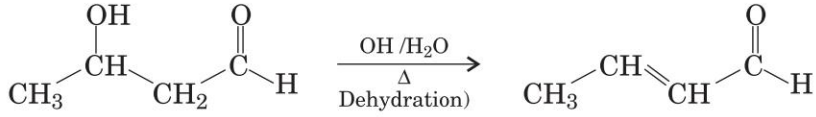
The mechanism of the reaction may be outlined as follows:



Base abstracts the proton from the *β*-hydroxyl group. As the alkoxide reverts to the carbonyl group, the C-3—C-4 bond breaks with expulsion of the resonance-stabilized enolate ion as a leaving group. This liberates one of the starting acetone molecules. The enolate takes up a proton from water to give the other acetone molecule.

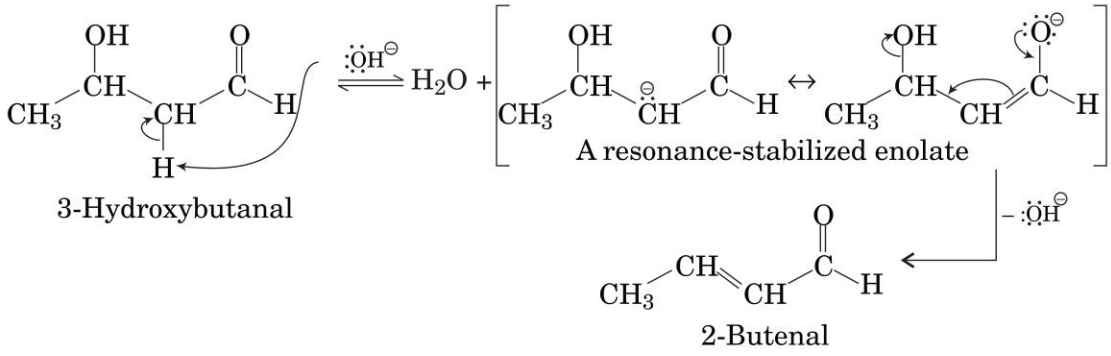
Aldol condensation reaction A condensation is a reaction in which two molecules combine to form a larger molecule with the elimination of a small molecule like alcohol or water. When the aldol addition product is dehydrated, a conjugated *α,β*-unsaturated carbonyl system is obtained. The overall process of aldol addition followed by dehydration is called an *aldol condensation reaction.* The product is called an enal or enone depending on the

carbonyl group in the product. The enal or enone is stabilized by having a conjugate set of double bonds. Because of such stability of the resulting enal or enone system, the dehydration reaction is exothermic and the dehydration equilibrium is almost irreversible, even though $OH^{\ominus}$ is a very poor leaving group. For example, 3-hydroxybutanal, the aldol addition product of acetaldehyde, dehydrates on heating in the presence of alkali to yield 2-butenal.



3-Hydroxybutanal — 2-Butenal (an enal)

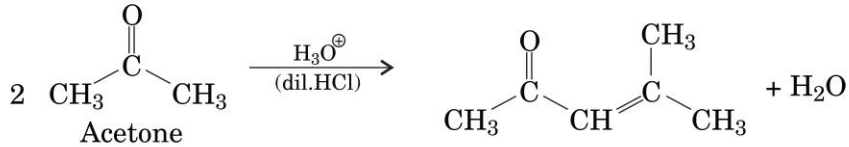
The mechanism of the reaction involves the steps as follows:



3-Hydroxybutanal

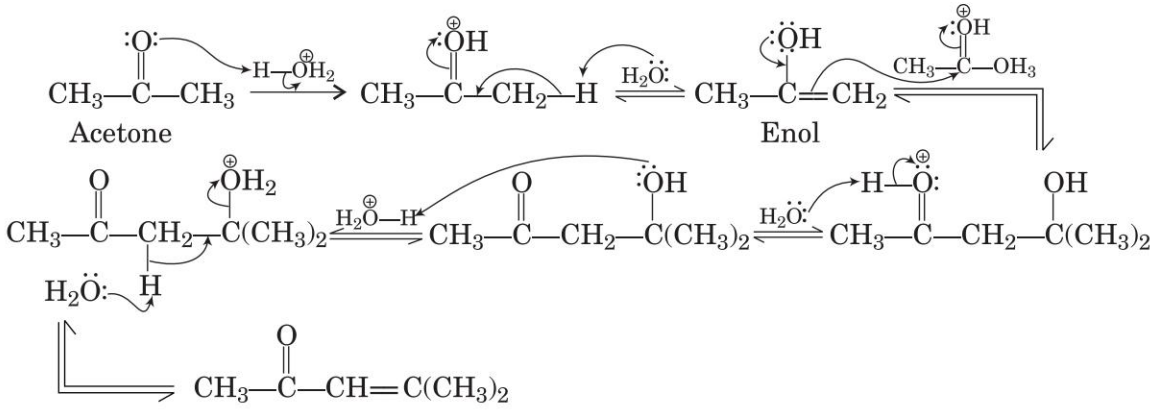
Base abstracts the acidic α-hydrogen to form a resonance-stabilized enolate. The enolate subsequently loses a hydroxide ion to yield the enal. The reaction may be designated as an E1cB (*E*limination *U*nimolecular *C*onjugate *B*ase) reaction.

Acid-catalyzed aldol condensation Aldol reactions can take place under acid catalysis in which case it is impossible to stop the reaction at the aldol stage. Elimination of a molecule of water from the aldol takes place readily to yield the α,β-unsaturated carbonyl compound. This is one procedure by which ketones can successfully be used in an aldol reaction. For example, acetone forms aldol condensation product 4-methylbut-3-en-2-one on treatment with dilute hydrochloric acid.



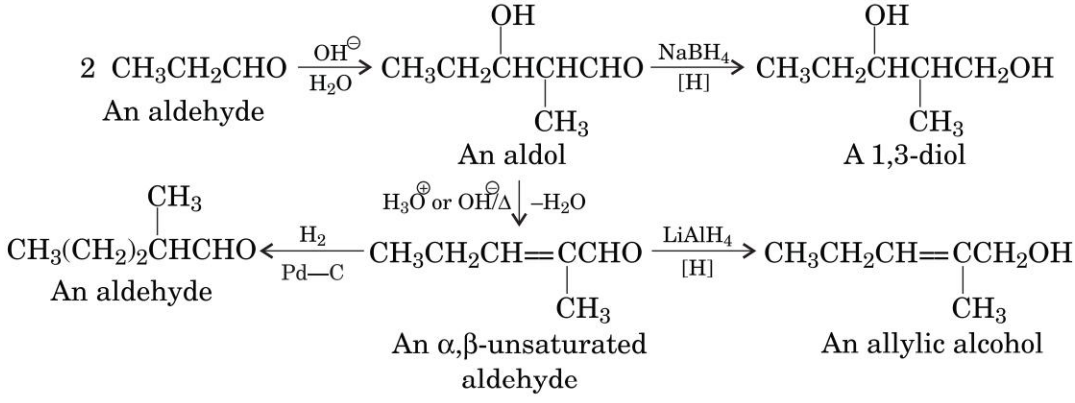
Acetone — 4-Methylbut-3-en-2-one

Mechanism of the reaction The mechanism of acid-catalyzed aldol condensation of acetone involves the steps as follows:

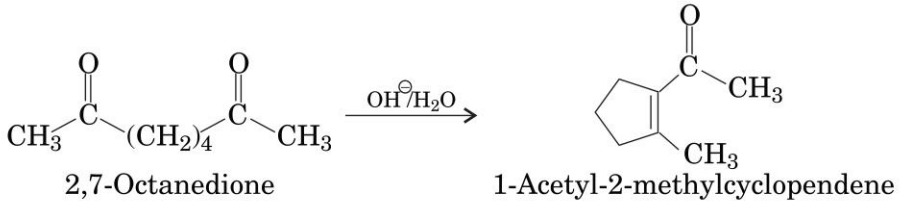


Acetone undergoes acid-catalyzed enolization. The enol then adds to a protonated acetone to yield, after proton loses a β-hydroxy ketone. This undergoes spontaneous acid-catalyzed dehydration to yield the corresponding α,β-unsaturated kentone.

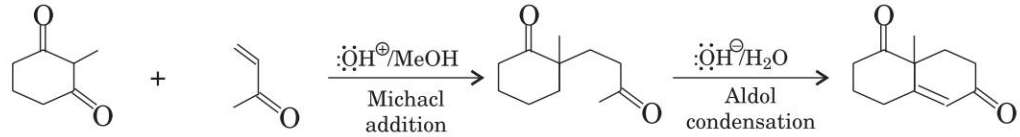
Synthetic applications of aldol reaction The aldol reaction offers an important synthetic procedure for carbon–carbon bond formation. Since the aldol addition products contain two functional groups (—OH and —CHO), these can be converted to a number of useful compounds like 1,3-diols, saturated alcohols, α,β-unsaturated aldehydes, allylic alcohols and aldehydes. For example:



Intramolecular aldol reaction of diketones are often useful for making five- and six-membered rings. For example, 1-acetyl-2-methylcyclopentene can be prepared from 2,7-octanedione by an internal aldol addition followed by dehydration.



One of the steps in the important *Robinson annulation* (ring forming) reaction, which is widely used in the synthesis of steroids and terpendoids, is an aldol cyclization reaction. For example:



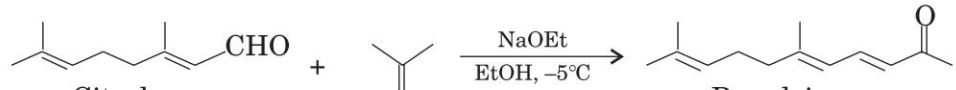
2-Methylcyclohexane-1,3-dione + Methyl vinyl ketone

Because of favourable entropy change, such ring closures occur easily, even when a ketone condenses with a ketone.

The aldol reaction also has many industrial applications. Propenal(acrolein), a starting material in numerous industrial processes, can be prepared by the mixed aldol reaction of formaldehyde and acetaldehyde.

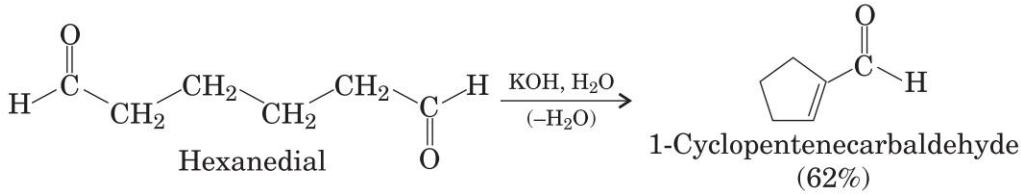
$$\underset{\text{Formaldehyde}}{HCHO} + \underset{\text{Acetaldehyde}}{CH_3CHO} \xrightarrow[300°C]{\text{Sodium silicate}} \underset{\substack{\text{Propenal}\\(\text{Acrolein})}}{CH_2{=}CH{-}CHO}$$

Pseudoionone, an intermediate in the synthesis of Vitamin A and some perfume fragrances, is prepared by a crossed aldol condensation between acetone and the natural oil citral.



Citral (lemongrass oil) + Acetone → Pseudoionone (49%)

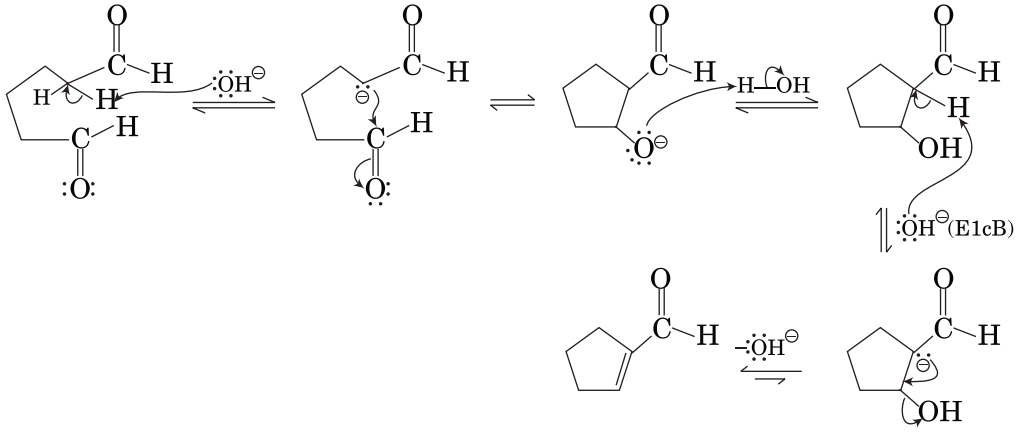
Intramolecular aldol condensation It is possible to carry out aldol condensation between an enolate ion and a carbonyl group in the same molecule. Such a reaction is called an *intramolecular aldol condensation.* This reaction in which a dialdehyde, a keto aldehyde, or a diketone is used as the substrate offers a convenient way to synthesize molecules with five-membered, six-membered and sometimes even larger rings. When a dilute solution of hexanedial, for example, is treated with aqueous base, 1-cyclopentene carbaldehyde is obtained. As soon as an enolate ion is generated at one of the termini of the molecule, it attacks the carbonyl carbon atom at the other.



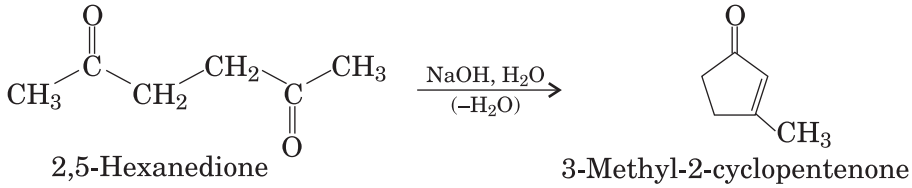
Hexanedial → 1-Cyclopentenecarbaldehyde (62%)

The possibility of attack by the enolate at carbonyl carbon of a different molecule, i.e., the possibility of an intermolecular aldol condensation is minimized by the low concentration of dicarbonyl compound and the favourable kinetics of the five-membered ring formation.

Mechanism of the reaction The reaction proceeds through the steps as follows:



Intramolecular aldol condensations of ketones are a ready source of cyclic and bicyclic α,β-unsaturated ketones. Thus, reaction of 2,5-hexanedione results in formation of 3-methyl-2-cyclopentenone containing a least strained five-membered ring.



2,5-Hexanedione

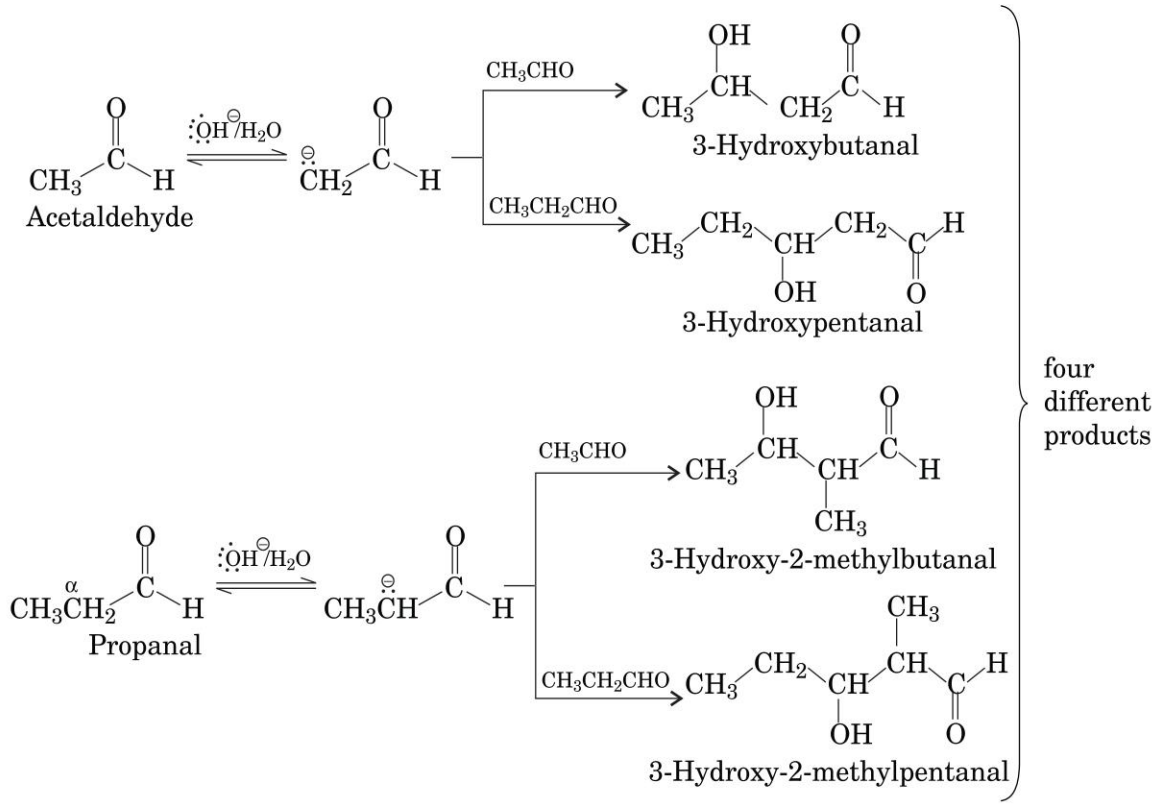
3-Methyl-2-cyclopentenone
(42%)

Intramolecular aldol condensation of ketones is readily achieved when the intermolecular analogue is relatively more difficult. In intermolecular reaction, the process must overcome the loss of entropy arising from the conversion of two molecules into one as the initial hydroxy ketone product forms. In contrast, in an intramolecular reaction, an acyclic substrate is merely converted into a cyclic product, a process 'costing' much less in entropic terms and therefore, it is thermodynamically more favourable.

It is to be noted that the term aldol condensation has been used historically to refer to the aldol addition reaction as well as to the addition and dehydration reaction together.

Crossed aldol addition An aldol reaction between two different carbonyl compounds in called a *crossed aldol addition reaction.*

Crossed aldol additions are not synthetically useful when both of the carbonyl compounds have α-hydrogens and this is because these reactions produce a complex mixture of all possible β-hydroxy carbonyl compounds and the product of interest, i.e., the desired product, is not obtained in very high yield. Also, isolation of that product from the mixture is in most cases extremely tedious. The crossed aldol addition reaction between acetaldehyde (ethanal) and propanal given four products.



A crossed aldol addition is synthetically useful only when it gives a good yield of a single product. Such a reaction can be carried out by using an aldehyde lacking an α-hydrogen (i.e., an aldehyde which cannot form an enolate in the presence of a base) and by slow addition of the carbonyl compound with an α-hydrogen to the mixture of that aldehyde and alkali. The aldehyde lacking an α-hydrogen does not undergo self-addition reaction and one of the crossed additions. Again, under such conditions, the concentration of the carbonyl compound with an α-hydrogen will always be very low and most of it will be present as an enolate ion in the presence of a large excess of the other component. Therefore, its self-addition reaction is also prevented. Hence, the reaction between the enolate ion and the aldehyde lacking α-hydrogen is the main reaction that will take place. For example, 2,2-dimethylpropanal reacts with acetaldehyde to yield 3-hydroxy-4,4-dimethylpentanal predominantly.

$$\underset{\text{2,2-Dimethylpropanal (placed in base)}}{(CH_3)_3CCHO} + \underset{\text{Acetaldehyde (added slowly)}}{CH_3CHO} \xrightarrow{NaOH/H_2O} \underset{\text{3-Hydroxy-4,4-dimethylpentanal}}{(CH_3)_3CCH(OH)CH_2CHO}$$

Crossed aldol addition involving formaldehyde has been found to be synthetically most useful.

$$\underset{\text{Formaldehyde}}{HCHO} + \underset{\text{3-Methylbutanal}}{(CH_3)_2CHCH_2CHO} \xrightarrow[\text{water–ether}]{K_2CO_3} \underset{\text{2-Hydroxymethyl-3-methylbutanal (52\%)}}{(CH_3)_2CH\underset{\displaystyle CH_2OH}{\underset{|}{C}}HCHO}$$

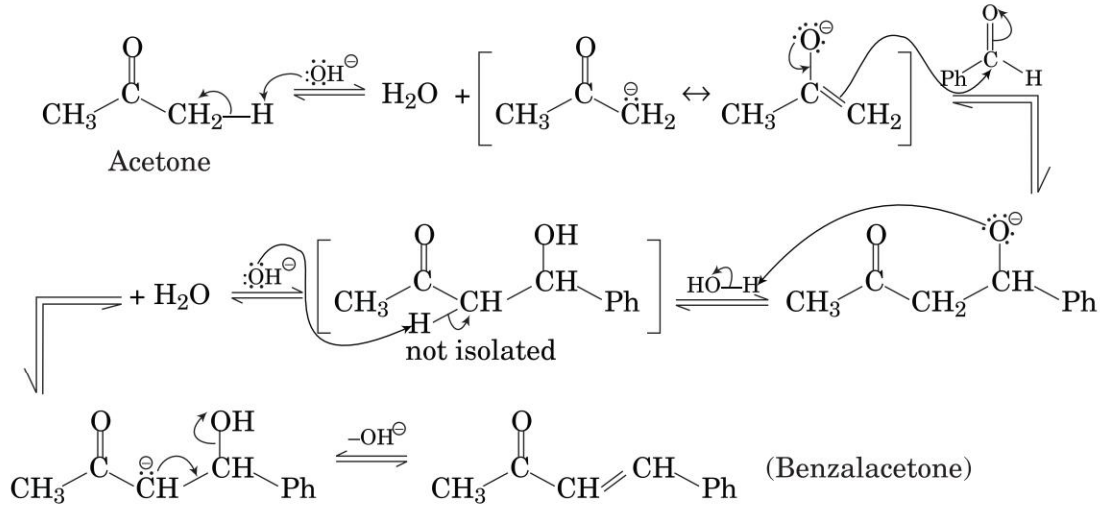
Formaldehyde is not only incapable of forming an enolate, but also it is so reactive towards nucleophilic addition that it suppresses self-condensation of the other component by reacting very rapidly with any enolate present.

Aromatic aldehydes cannot form enolates and so, they have been used successfully in a large number of crossed aldol reactions.

Claisen-Schmidt condensation Crossed aldol condensation in which a ketone reacts with an aromatic adlehyde is known as Claisen-Schmidt condensation. For example:

$$\underset{\text{Benzaldehyde}}{PhCHO} + \underset{\text{Acetone}}{CH_3COCH_3} \xrightarrow[100°C]{\text{aqueous NaOH}} \underset{\text{4-Phenylbut-3-en-2-one or Benzalacetone (78\%)}}{PhCH{=}CH{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}CH_3}$$

Mechanism of the reaction The reaction proceeds through the steps as follows:

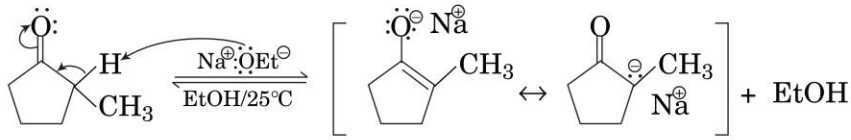


This reaction involving aromatic aldehydes always occurs with the dehydration of the mixed addition product because the resulting α,β-unsaturated product is particularly stable (the double bond formed by dehydration is conjugated to both the aromatic ring and the carbonyl group).

The reaction is synthetically useful because two of the four usual crossed-aldol products cannot form due to lack of α-hydrogen in the aromatic aldehyde and the ketone does not

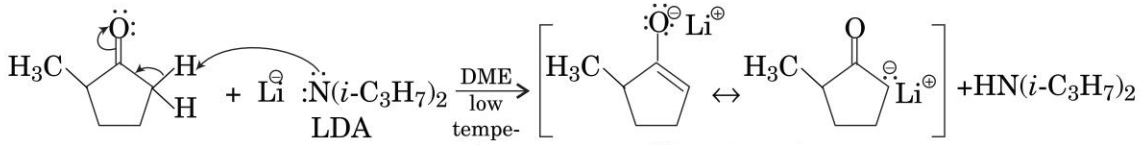
self-condense appreciably due to steric hindrance in the aldol addition stage. In fact, both the rate and equilibrium for the addition of enolate to the aldehyde are more favourable than they are for addition to a second molecule of the ketone.

Thermodynamic and kinetic enolates The enolate with the more highly substituted C═C bond is the thermodynamically more stable enolate (in the same way an alkene with more highly substituted double bond is the more stable alkene) and it will be formed predominantly under conditions that permit the establishment of an equilibrium. This enolate is called the *thermodynamic enolate*. Such an enolate can be formed when a relatively weak base is used in a protic solvent. For example:



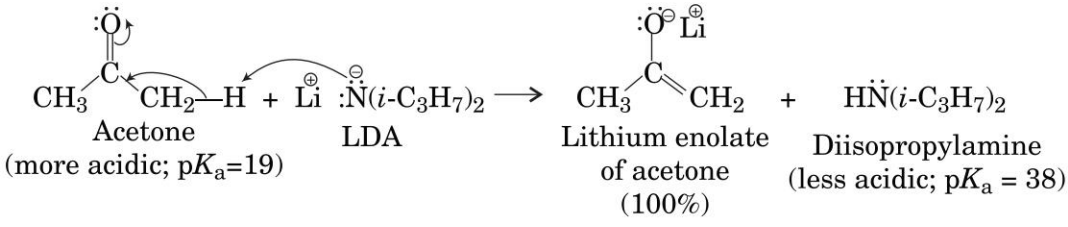
2-Methylcyclopentanone Thermodyanamic enolate

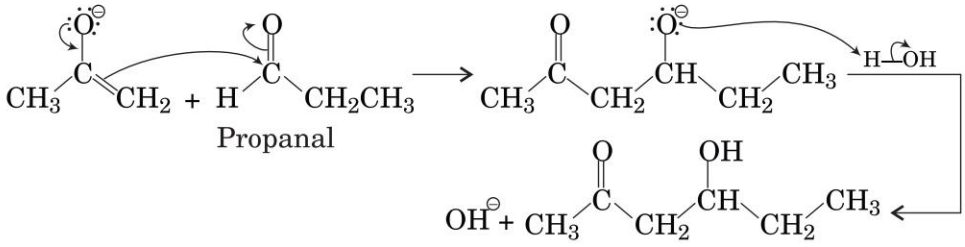
Since removal of a hydrogen from the less substituted α-carbon to produce an enolate is less sterically hindered, therefore, the enolate with the less substituted double bond is usually formed faster. This enolate is formed predominantly when the reaction is kinetically controlled. This is what is called the *kinetic enolate*. When the sterically hindered base lithium diisopropylamide (LDA) is used in an aprotic solvent, kinetic enolates are formed. This strong and bulky base rapidly removes the proton from the less substituted α-carbon of the ketone. 1,2-Dimethoxyethane (DME), $CH_3OCH_2CH_2OCH_3$ or THF is used as the solvent in this reaction. The temperature must be low (–78°C) to prevent the kinetic enolate from equilibrating to the thermodynamic enolate.



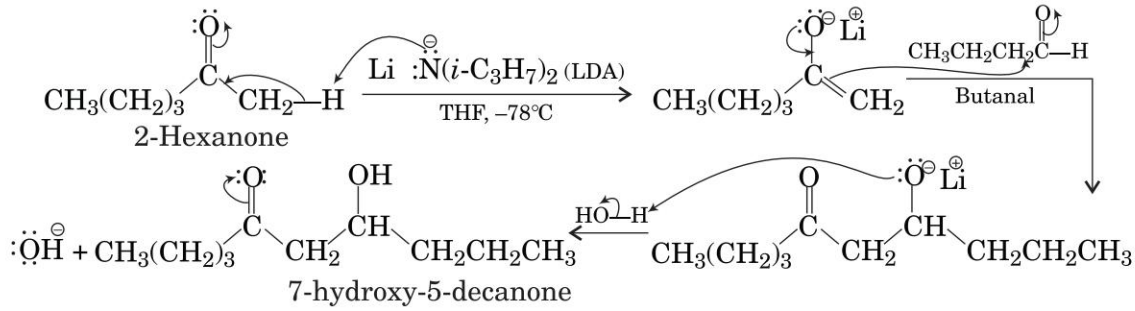
2-Methylcyclopentanone Kinetic enolate

Directed aldol reaction A directed aldol reaction (the method which directs the aldol reaction to a desired direction) is a variation of the crossed–aldol reaction that clearly defines the carbonyl compound which becomes the nucleophilic enolate and reacts at the electrophilic carbonyl carbon. In a directed aldol reaction, the enolate of one carbonyl component is prepared with LDA (lithium diisopropylamide), a very strong base. The reaction of LDA with a ketone is irreversible and almost all the ketone is rapidly converted into its enolate (often called *performed enolate*) without leaving any ketone for self-addition. The aldehyde (or ketone) is subsequently added to cold performed enolate solution of the ketone and a rapid crossed–aldol reaction occurs with high efficiency. Usual work-up with water produces the desired aldol. For example.

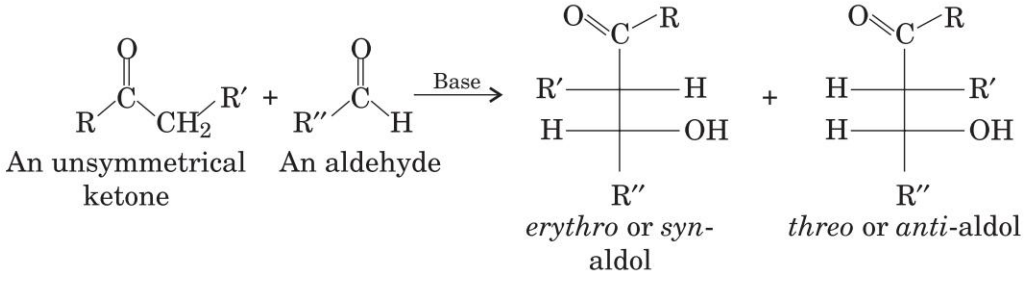




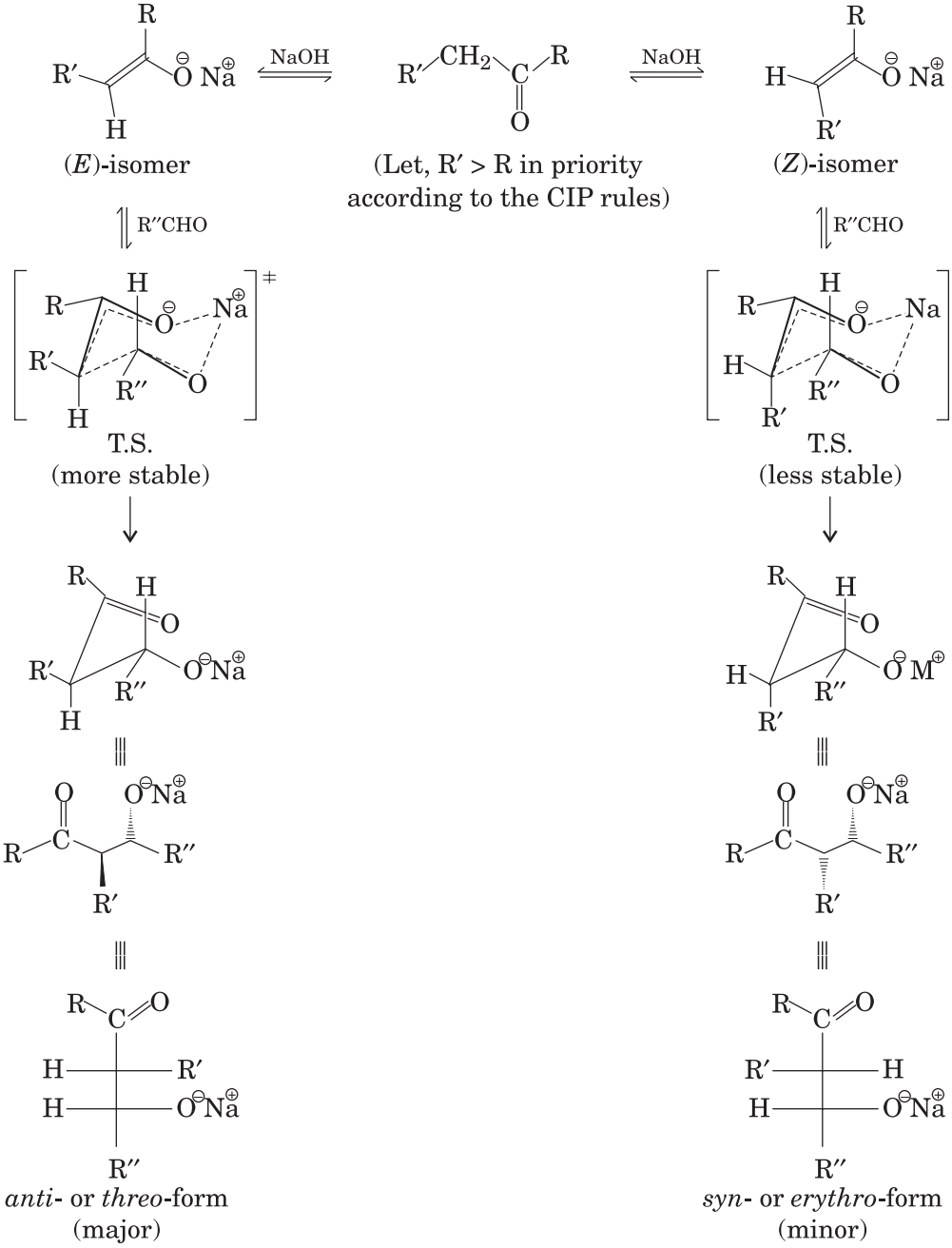
When an unsymmetrical ketone is used, LDA selectively deprotonates the less substituted side of the ketone to form the kinetic enolate (i.e., regioselectivity can be achieved when an unsymmetrical ketone is used) which on reaction with an aldehyde forms the corresponding crossed aldol without yielding any other product. For example, 7-hydroxy-5-decanone can be prepared in good yield by the following directed aldol reaction.



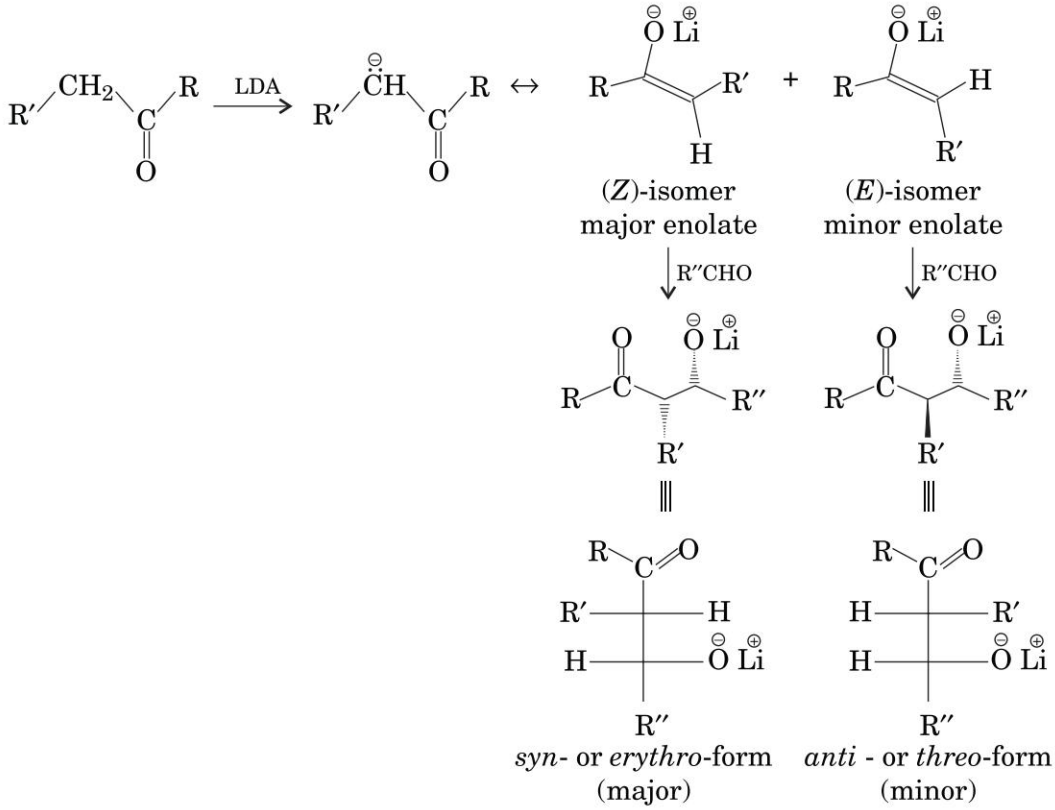
Stereochemical aspect of aldol addition When two molecules of the same achiral aldehydes are involved in aldol addition reaction, a single chirality centre is created and the reaction leads to the formation of enantiomeric aldols (racemic mixture). However, when an unsymmetrical achiral ketone reacts with an achiral aldehyde, two chirality centres are created in the product and as a result, two diastereoisomeric aldols (*threo* or *anti* and *erythro* or *syn*) are formed.



Under thermodynamic conditions, i.e., by using weaker base (such as $OH^{\ominus}$), high temperature and long reaction time, the (*Z*)- and (*E*)- forms of enolates remain in rapid equilibrium and in such a case diasteroselectivity is controlled by the relative stability of the cyclic transition states. Only one enantiomer of each product is shown in the following sequence of reactions.

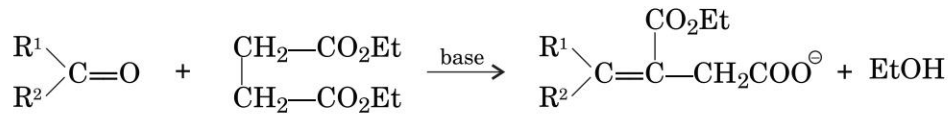


The chair-like transition state (including the metal ion as a member of the six-membered ring) leading to the formation of the *threo-* or *anti*-aldol has both R′ and R″ in approximately equatorial positions, whereas in that leading to the *erythro-* or *syn*-aldol *R′* assumes the less stable axial position. Since the transition state leading to the *anti*-aldol possesses lower energy, it will be formed at a faster rate and consequently it predominates in the product mixture. This type of diastereoselectivity is, therefore, due to thermodynamic control. The reaction can also be made to take place through kinetic control by the use of very strong base like LDH, low temperature, and short reaction time. Under such conditions, (Z)-enolate is formed rapidly (almost irreversibly) and predominantly to give the *syn*-aldol as the major product. The *syn*-product is the kinetic product. Therefore, in this case, the relative amount of the diastereoisomeric enolate determines the product composition.

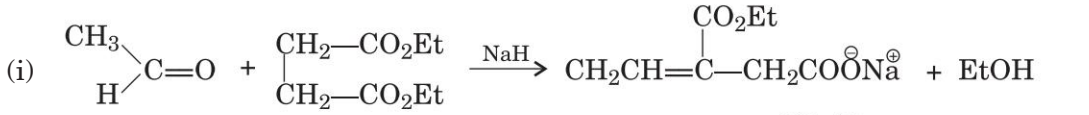


2.8.2 Stobbe Condensation

The condensation reaction of aldehydes and ketones with succinic esters, e.g., diethyl succinate, $(CH_2CO_2Et)_2$, in the presence of bases like sodium hydride (NaH), potassium *tert*-butoxide ($Me_3CO^{\ominus}K^{\oplus}$) or sodium ethoxide (NaOEt) to produce the monoesters of α-alkylidene- or arylidenesuccinate salt is called the *Stobbe Condensation*. The salt on acidification yields the corresponding acid.

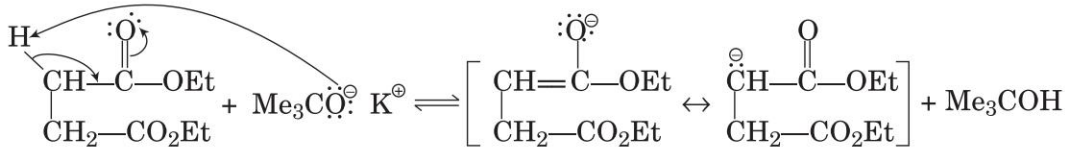


For example:

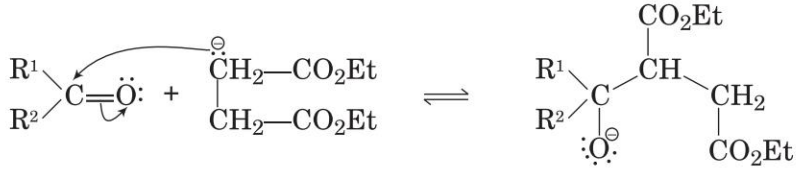


Mechanism of the reaction The mechanism of the reaction involves the steps as follows:

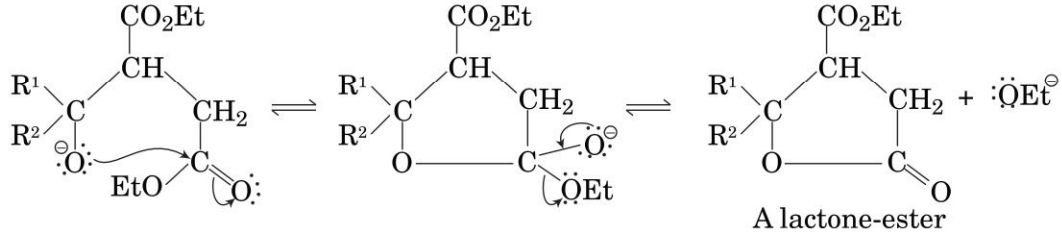
Step 1: The base abstracts an α-H from diethyl succinate to form an ester-enolate.



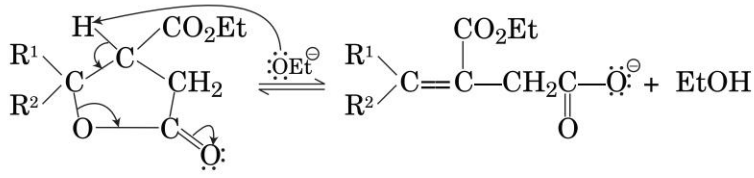
Step 2: The aldehyde or ketone undergoes nucleophilic attack by the enolate ion to form an intermediate alkoxide ion.



Step 3: An intramolecular acyl substitution occurs to form a lactone-ester.



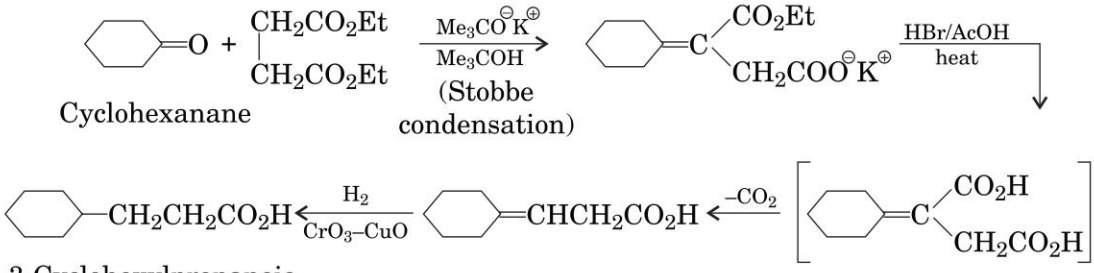
Step 4: The lactone-ester undergoes ring opening (by an E1 or E2 mechanism) to give the monoester of α-alkylidene- or arylidenesuccinate salt.



Isolation of the intermediate lactone-ester and formation or an olefin strongly supports the above mechanism.

Synthetic applications Some important applications of the Stobbe condensation are as follows:

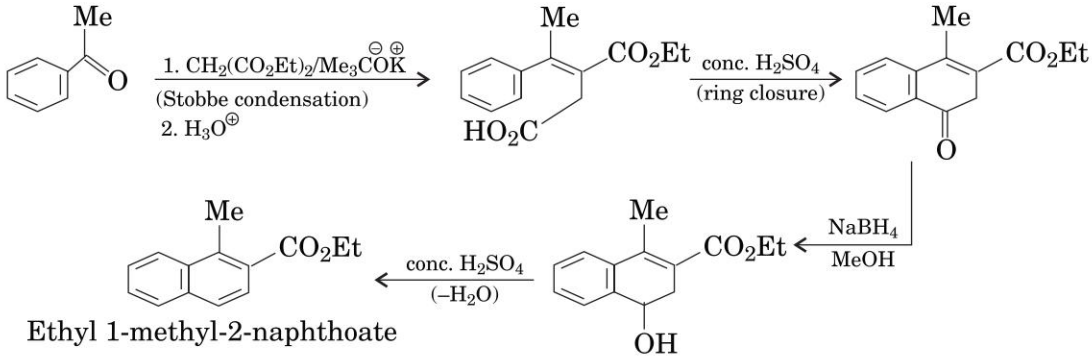
(i) A propionic acid residue can be introduced at the site of the carbonyl group by the Stobbe condensation. Thus, saturated carboxylic acids with four carbon chain and above can be prepared by using this reaction. For example:



Cyclohexanane

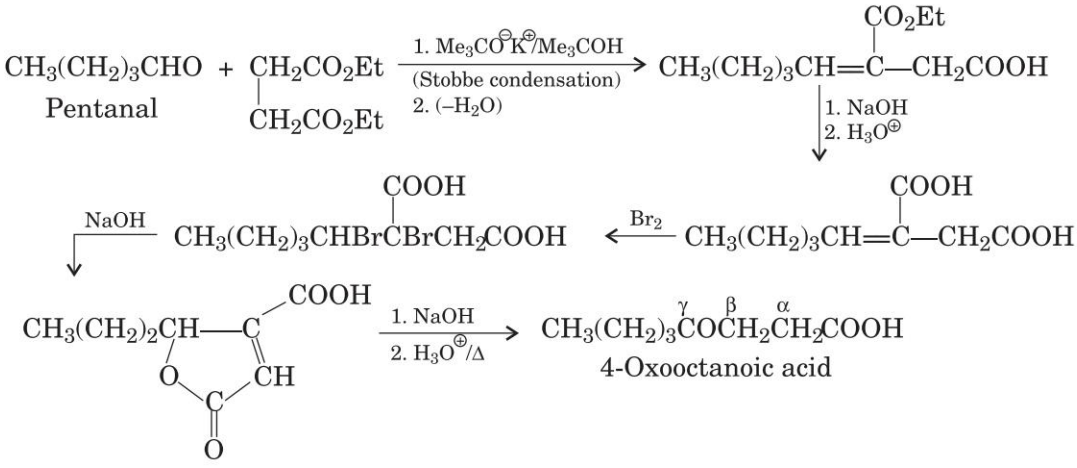
3-Cyclohexylpropanoic acid

(ii) The Stobbe condensation can be used for extension of aromatic rings to prepare polycyclic aromatics. For example:



Ethyl 1-methyl-2-naphthoate

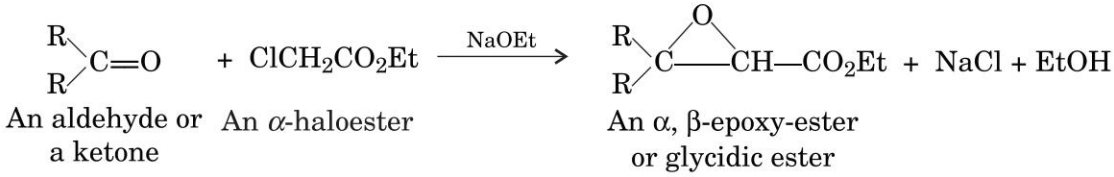
(iii) This reaction can be used to prepare γ-ketoacids conveniently. For example:



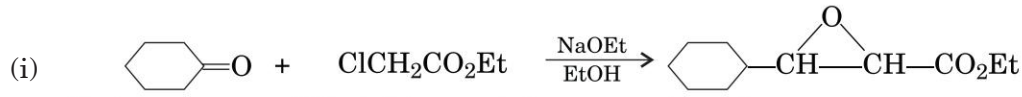
4-Oxooctanoic acid

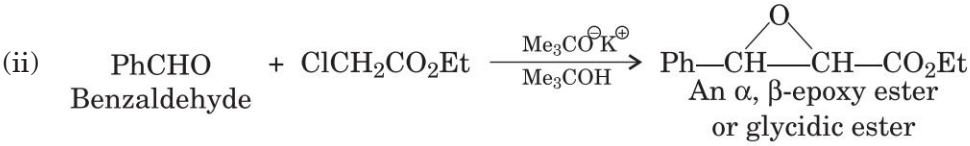
2.8.3 Darzens Condensation

When an aldehyde or a ketone is allowed to react with an α-haloester containing at least one α-H atom in the presence of a base like $NaNH_2$, NaOEt, or *t*-BuOK, an α,β-epoxy ester (also called glycidic ester) is obtained. This reaction is known as the *Darzens condensation* or *Darzens glycidic ester condensation.*



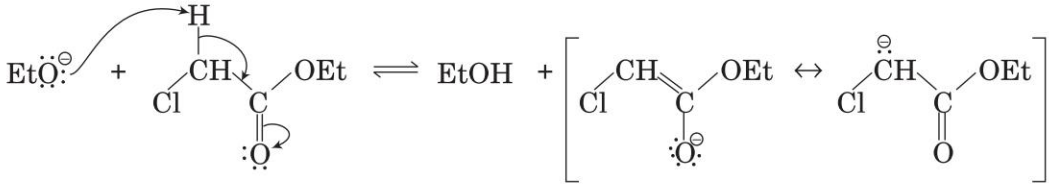
For example:



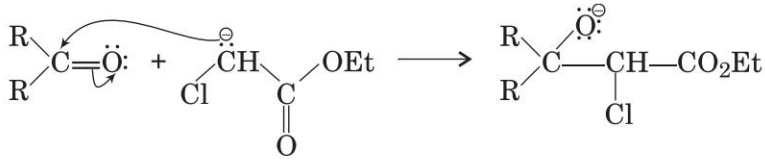


Mechanism of the reaction The mechanism of the reaction involves the steps as follows:

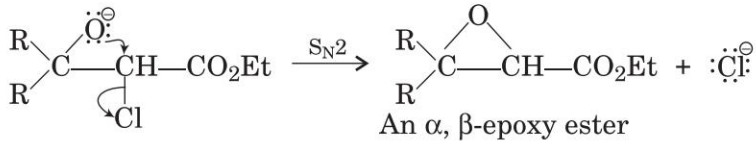
Step 1: The strong base abstracts an α-H atom from the α-chloroester to form a resonance-stabilized enolate ion.



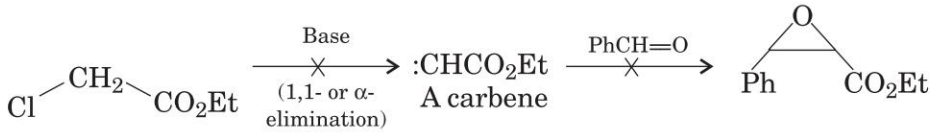
Step 2: Nucleophilic attack by the enolate ion occurs on the carbonyl carbon to form an intermediate chloroalkoxide.



Step 3: Intramolecular S_N2 displacement of the chloride ion by the alkoxy oxygen atom occurs to yield and α,β-epoxy ester or glycidic ester.

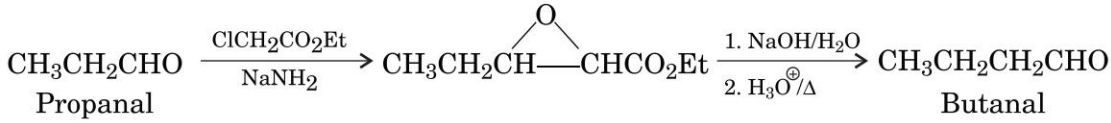


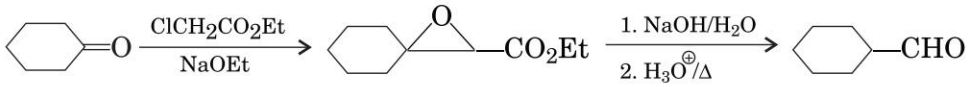
Proof of the mechanism That the reaction proceeds via an ester enolate anion and not through addition of carbene (formed by 1,1-elimination as shown below) is demonstrated by the fact that the intermediate haloalkoxide has been isolated, especially with α-fluoroesters since $F^{\ominus}$ is a very poor leaving group in S_N2 process.



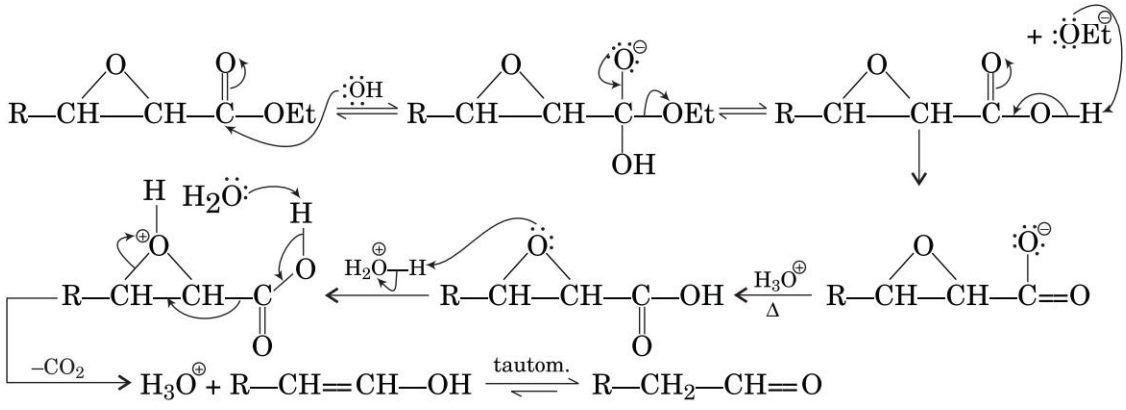
Synthetic applications Some important synthetic applications of this reactions are as follows:

(i) The glycidic esters on alkaline hydrolysis followed by acidification give glycidic acids which when heated in the presence of acid produce aldehydes or ketones containing one more carbon atom than the starting carbonyl compounds. In fact, an aldehyde (RCHO) is converted to the next higher aldehyde (RCH_2CHO) and a ketone ($R_2C{=}O$) is converted to a longer chain aldehyde (R_2CHCHO). Dorzens methodology is, therefore, used for the synthesis of aldehydes and ketones, as a homologation reaction. For example:



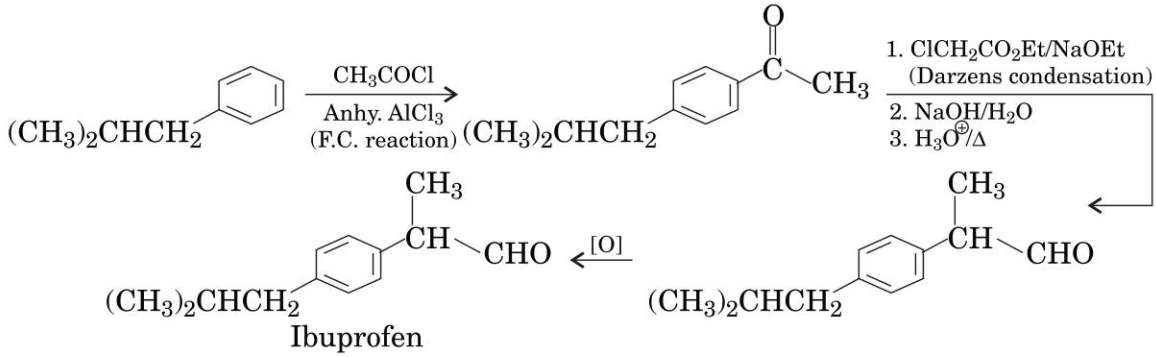


[The mechanism of the second step is as follows:

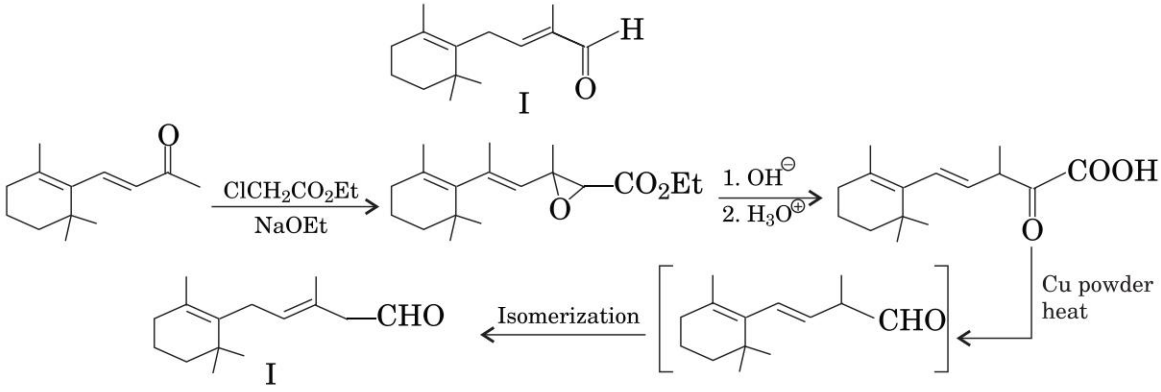


The process involves alkaline hydrolysis of ester ($B_{AC}2$ mechanism) followed by acid-catalyzed ring-opening with simultaneous decarboxylation.]

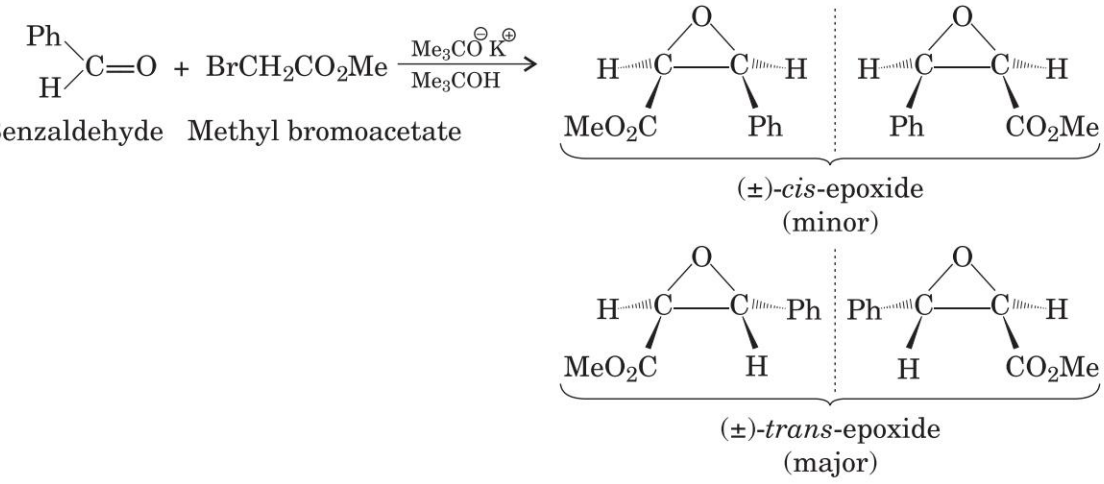
(ii) Ibuprofen, p-$Me_2CHCH_2C_6H_4CH(CH_3)COOH$, an important analgesic and anti-inflammatory drug has been synthesized by using this procedure in one of the steps.



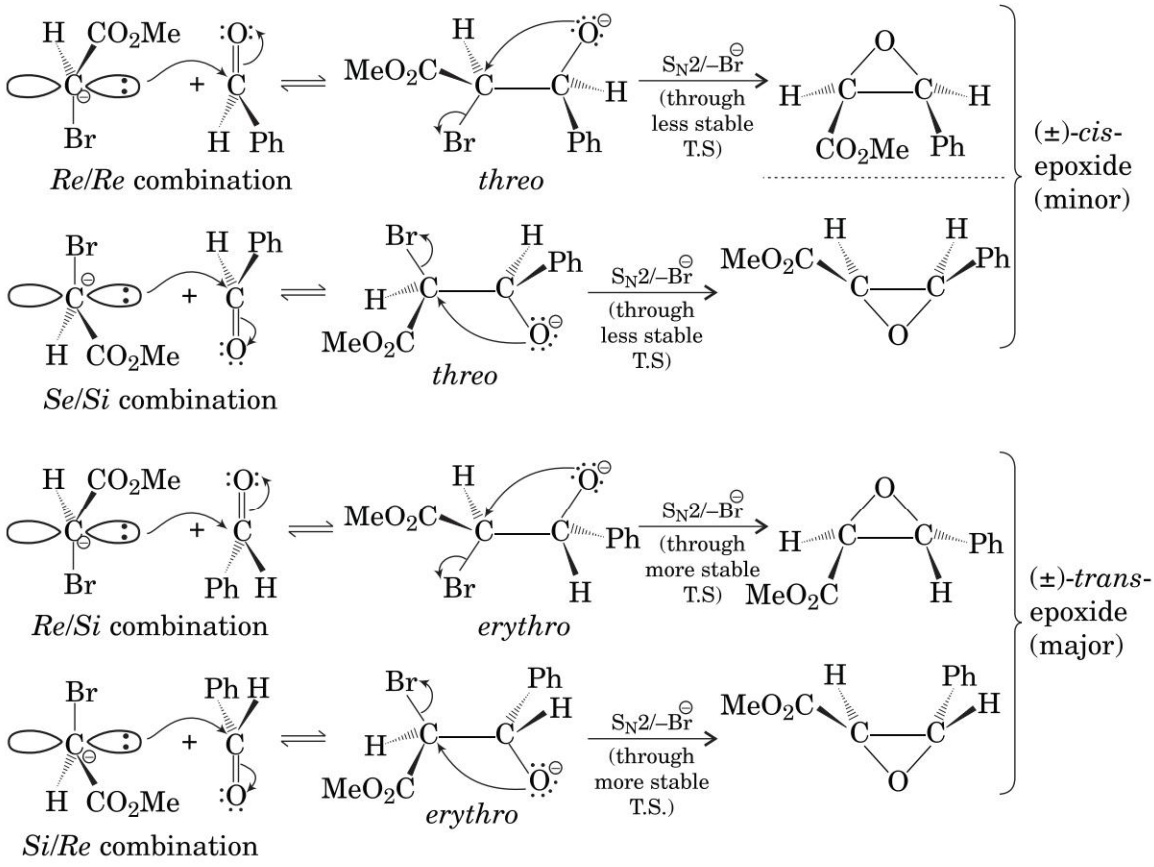
(iii) The following aldehyde (I), an intermediate in an industrial synthesis of vitamine A, can be synthesized from β-ionone using Darzens condensation.



Stereochemical aspect of Darzens condensation Darzens condensation may yield two diastereoisomeric glycidic esters if the carbonyl compound is an aldehyde (RCHO) or an unsymmetrical ketone (RCOR′). The isomer having the ester group and the bulky substituent at Cβ stereochemically *anti* actually predominates. The transition state for epoxide formation is reached more easily from the *erythro* than from the *threo*-chloro alkoxide leading to *trans*-epoxide as the major product. Furthermore, both the diastereoisomers are obtained as racemic mixture. For example:



The stereochemical course that accounts for the formation of (±)-*cis* and (±)–*trans* epoxide is as follows:



2.8.4 Benzoin condensation

When an aromatic aldehyde is refluxed with an aqueous alcoholic solution of KCN or NaCN, an α-hydroxy ketone (called a benzoin) is obtained. This selfcondensation of aromatic aldehydes especially catalyzed by cyanide ion ($CN^{\ominus}$) in called the *benzoin condensation.*

$$\underset{\text{Ar aromatic aldehyde}}{2\ \text{ArCHO}} \xrightleftharpoons[\Delta]{\text{KCN/EtOH/H}_2\text{O}} \underset{\text{An } \alpha\text{-hydroxyketone or benzoin}}{\text{ArCHOHCOAr}}$$

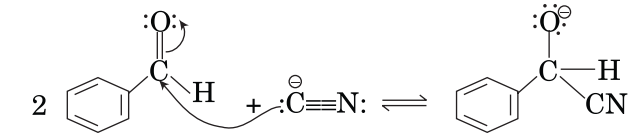
Example:

$$\underset{\text{Benzaldeyde}}{2\ \text{PhCHO}} \xrightleftharpoons[\Delta]{\text{KCN/EtOH/H}_2\text{O}} \underset{\text{Benzoin (92\%)}}{\text{PhCOCHOHPh}}$$

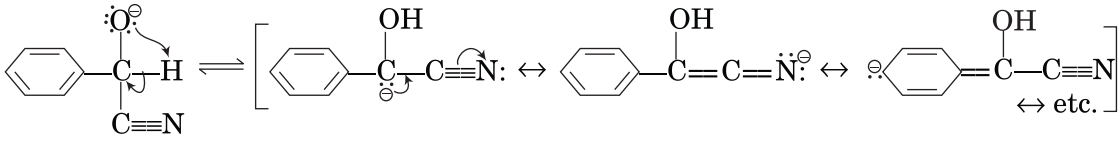
The two molecules of the aldehyde behave differently. One of them donates the aldehyde hydrogen to the oxygen (of the aldehyde function) of the other. Hence, the former molecule is known as the 'donor' and the latter as the 'acceptor'. The reaction is reversible in nature.

Mechanism of the reaction This completely reversibly reaction involves the steps as follows:

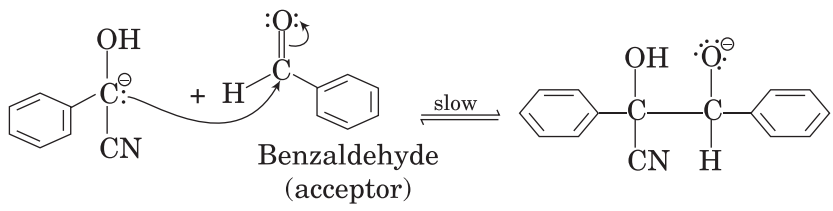
Step 1: The cyanide ion ($CN^{\ominus}$), being a good nucleophile, attacks the carbonyl carbon of a benzaldehyde molecule (the donor molecule) to form an alkoxide.



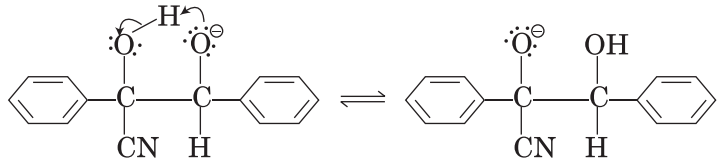
Step 2: The tetrahedral alkoxide undergoes internal transfer of a proton from carbon to oxygen to form a resonance-stabilized carbanion. It is the electron-attracting –CN group which makes the aldehydic hydrogen acidic and stabilizes the carbanion by delocalization of electrons. The negative charge of the carbanion is further delocalized on the benzene ring.



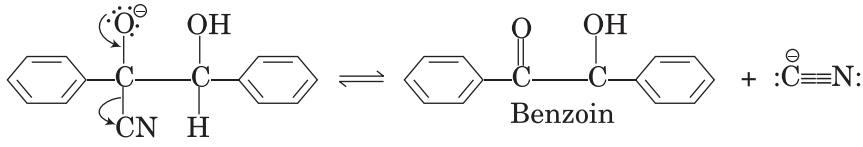
Step 3: A second molecule of benzaldehyde (the acceptor molecule) undergoes nucleophilic attack on the carbonyl carbon by the resulting carbanion to form another alkoxide. It is the rate-determining step of the reaction.



Step 4: The alkoxide of benzoin cyanohydrin is obtained by a rapid proton transfer.



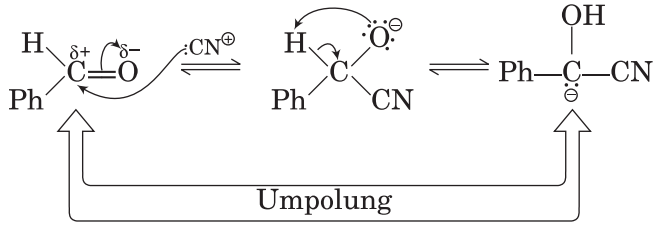
Step 5: Benzoin is formed by the rapid loss of $CN^{\ominus}$ (a good leaving group).



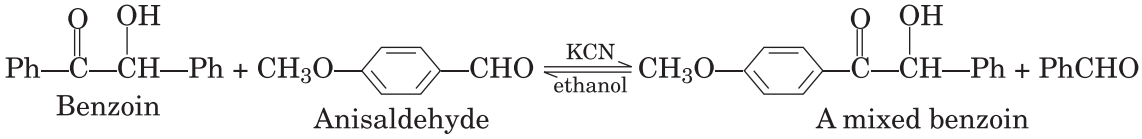
Some relevant topics:

(i) **Cyanide ion—a very specific and unique catalyst** The cyanide ion is a very specific anion that catalyzes the benzoin condensation. The reasons are as follows: (a) $CN^{\ominus}$ is a very good nucleophile and can attack readily the electron–deficient carbonyl carbon of the 'donor' aldehyde molecule; (b) the –CN group, due its electron–withdrawing ability, increases the acidity of the aldehydic hydrogen atom and thereby facilitates its transfer to oxygen to form a carbanion; (c) the intermediate carbanion is stabilized by the –CN group through electron delocalization and (d) since $CN^{\ominus}$ is a very good leaving group, it is lost rapidly in the last step of the reaction.

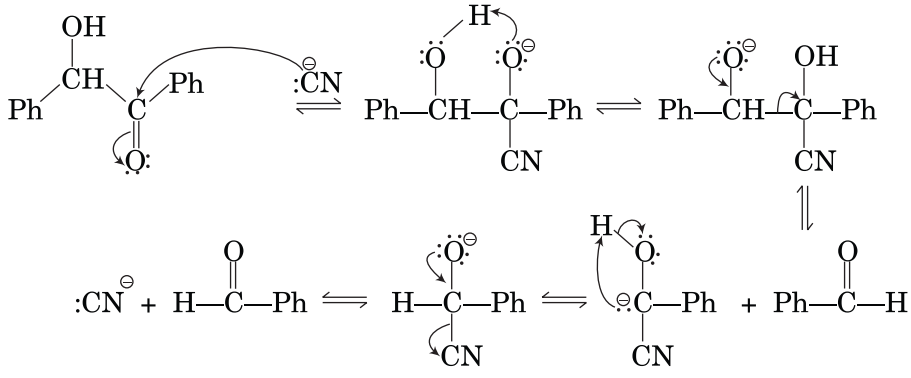
(ii) **Concept of 'umpolung' in benzoin condensation** The carbonyl carbon atom of an aldehyde is positively polarized. Therefore, it is electrophilic in nature and reacts with nucleophiles. When $CN^{\ominus}$ ion attacks the carbonyl carbon of the donor aldehyde molecule (step 1) and the aldehydic hydrogen migrates to the anionic oxygen (step 2), the same carbon becomes negatively charged and reacts with the electrophilic carbonyl carbon of the acceptor molecule (step 3). This reversal of polarity of the carbonyl carbon atom is called **umpolung** (German for polarity reversal).



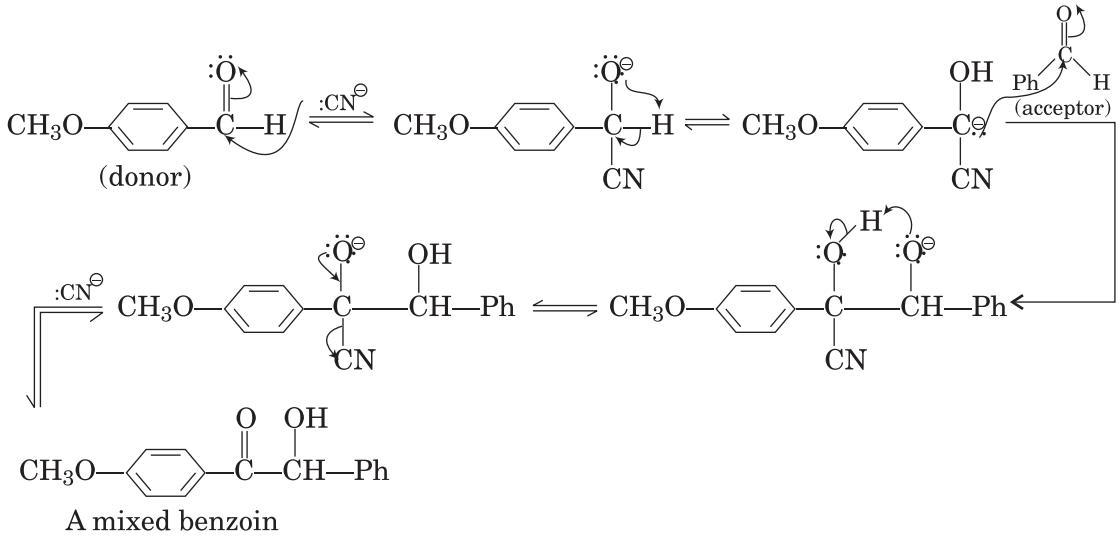
(iii) **Proof in favour of the reversibility of the benzoin condensation** That the benzoin condensation is a completely reversible process can be proved by the fact that when benzoin (PhCOCHOHPh) is treated with another aldehyde in the presence of ethanolic KCN, a mixed benzoin is obtained. For example:



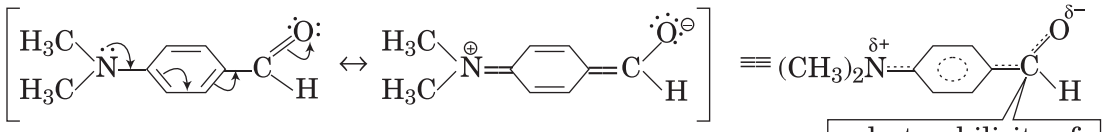
Under the reaction conditions benzoin becomes reversibly converted into benzaldehyde (PhCHO), benzaldehyde then reacts with anisaldehyde which acts as a donor molecule to yield the mixed benzoin *p*-$CH_3OC_6H_4COCHOHPh$. The reverse reaction is called *retro*-benzoin condensation.



Then,



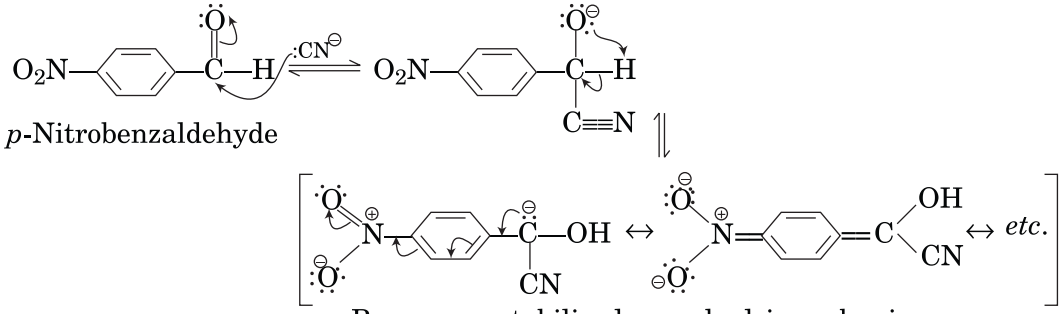
(iv) **Effect of substituents in the aromatic ring of aldehyde** When electron-donating groups like $-NH_2$, $-NR_2-$, $-OMe$, $-OH$, etc. and electron-withdrawing groups like $-NO_2$, $-SO_3H$, etc. are present at the *ortho* or *para* position and are conjugated with the $-CHO$ group, the benzoin condensation is inhibited. When an electron-releasing group remains conjugated with the aldehyde function, the electrophilic character of the carbonyl carbon decreases due to effective electron delocalization and as result, the nucleophilic attack by the cyanohydrin carbanion on the carbonyl carbon is largely prevented. For example, *p-N,N*-dimethylaminobenzaldehyde (which cannot act as an acceptor) does not undergo benzoin condensation because of extensive electron delocalization as shown below:



Resonance in *p-N,N*-dimethylaminobenzaldehyde

electrophilicity of the carbonyl carbon is reduced

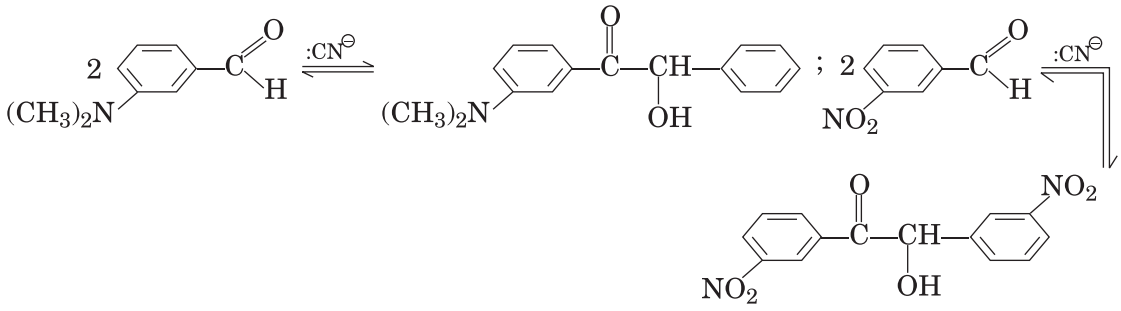
When an electron-attracting group like $-NO_2$ remains conjugate with the aldehyde function, then the initial nucleophilic attack by $CN^{\ominus}$ on the carbonyl carbon is facilitated due to its increased electrophilicity and the cyanohydrin caranion is easily formed. However, that carbanion fails to react with a second molecule of aldehyde (the acceptor molecule) due to extensive electron delocalization which markedly reduces its nucleophilicity. Thus, *p*-nitrobenzaldehyde does not undergo benzoin condensation as it is unable to act as a donor.



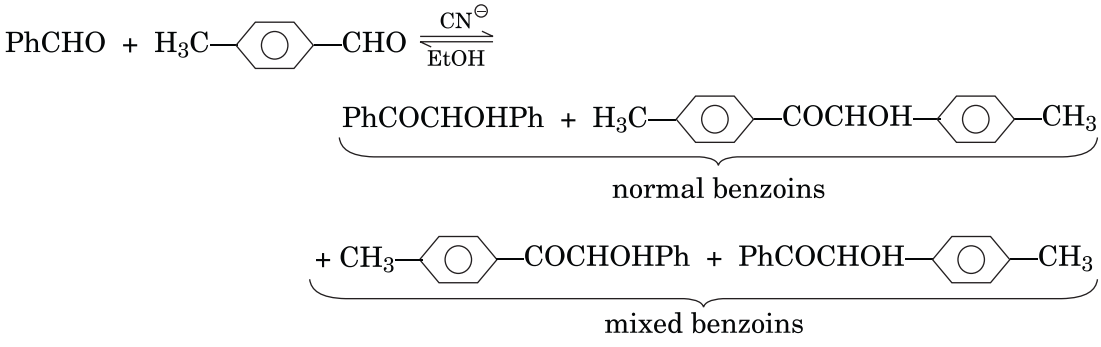
p-Nitrobenzaldehyde

Resonance-stabilized cyanohydrin carbanion

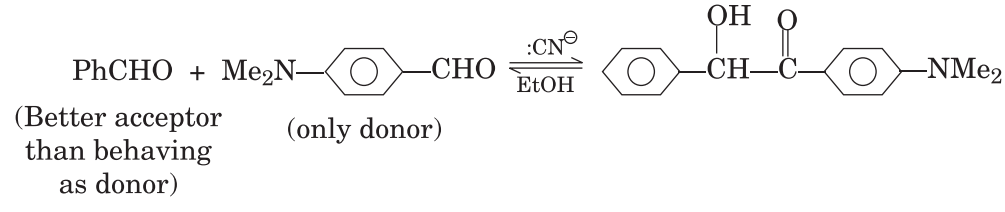
However, when groups like $-NMe_2$ or $-NO_2$ are present at the *meta*-position to the $-CHO$ group, they do not remain conjugated with the aldehydic group and no electron delocalization is possible to affect the nucleophilicity or electrophilicity of the aldehydic carbon. As a consequence, *m-N,N*-dimethylaminobenzaldehyde and *m*-nitrobenzaldehyde undergo normal benzoin condensation to give the corresponding benzoins.



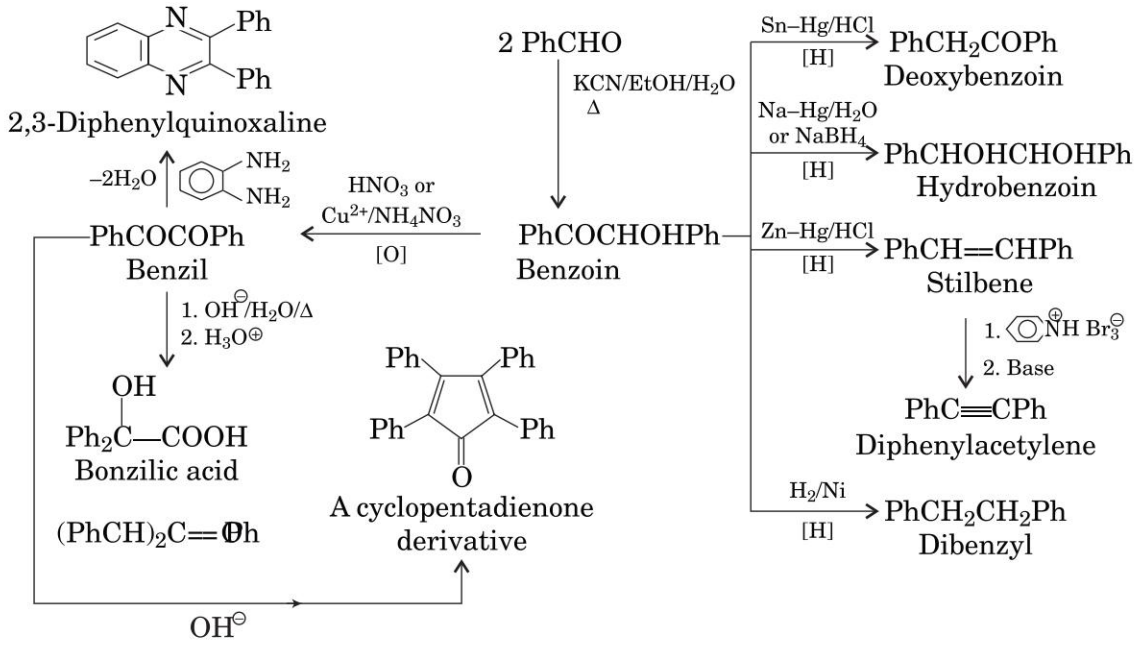
Mixed benzoin condensation When two different aromatic aldehydes are allowed to condense together in the presence of an aqueous ethanolic KCN, the reaction is called mixed benzoin condensation. If both the aldehydes have comparable reactivity, they play the same role and the reaction may produce four products, of which two are mixed benzoins and the other two are normal or single benzoins. For example:



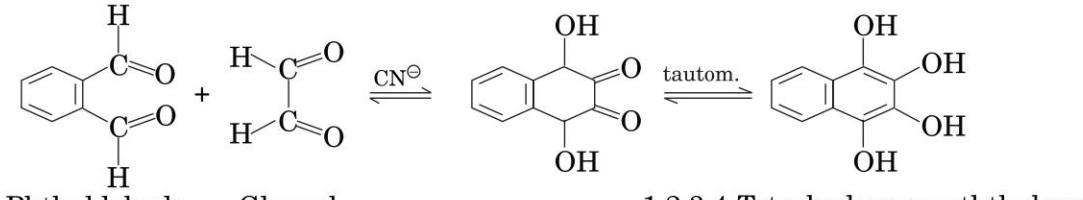
In general, in all the mixed benzoin condensation between benzaldehyde and an aldehyde containing an electron-releasing group at the *p*-position, the keto group always remains attached to the benzene ring containing the electron-releasing group, i.e., the latter aldehyde always acts as the donor molecule. For example:



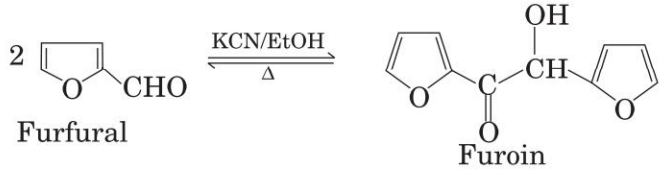
Synthetic applications Benzoin condensation is a synthetically useful reaction because, α-hydroxy ketones or benzoins, the products of this reaction are useful intermediates for the synthesis of a number of important compounds. Benzoins can be oxidized or reduced to various products, depending upon the reactions conditions. For example, starting with benzaldehyde (PhCHO) we can prepare deoxybenzoin, hydrobenzoin, stilbene, diphenylacetylene, dibenzyl, benzil, benzilic acid, etc.



Polynuclear compounds can be synthesized by using crossed-benzoin condensations. For example:



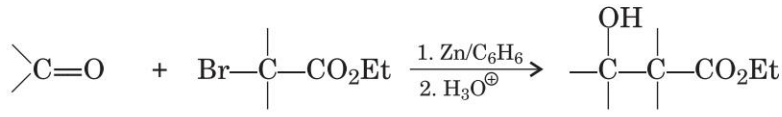
Furoin can be prepared from furfural by benzoin condensation.



Furoin can be oxidised to yield furil (1,2-diketone) and when heated with aqueous KOH, furil gives furilic acid.

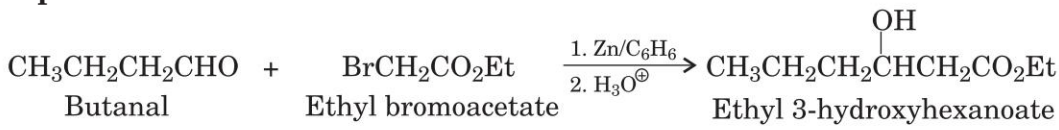
2.8.5 Reformatsky reaction

The reaction of an α-haloester, usually an α-bromo ester, with an aldehyde or ketone in the presence of zinc in an inert solvent (e.g., ether, benzene, toluene, THF, etc.) to produce, after hydrolysis, β-hydroxy esters is called the *Reformatsky reaction.*



An aldehyde or a ketone | An α-bromo ester | A β-hydroxy ester

Example:



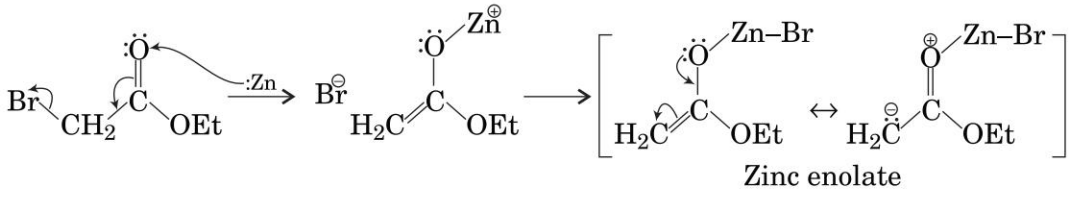
Butanal | Ethyl bromoacetate | Ethyl 3-hydroxyhexanoate

The carbonyl compound used may be aliphatic, aromatic, or heterocyclic, and may contain various functional groups.

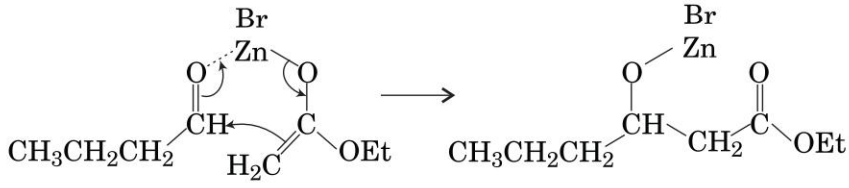
It is to be noted that organozinc compounds are much less reactive than either Grignard reagent (RMgX) or alkyl lithium (RLi) and so, they chemoselctively attack the carbonyl group of an aldehyde or a ketone and not the ester group. Therefore, self-condensation reaction does not take place. By taking this advantage of low reactivity of organozinc compounds over organomagnesium or oganolithium compounds *β*-hydroxy esters can be prepared by the Reformatsky reaction. Also, the organozinc compounds do not attack $-C\equiv N$, $-\overset{|}{C}=N-$, or CO_2.

Mechanism of the reaction The mechanism of the reaction involves the steps as follows:

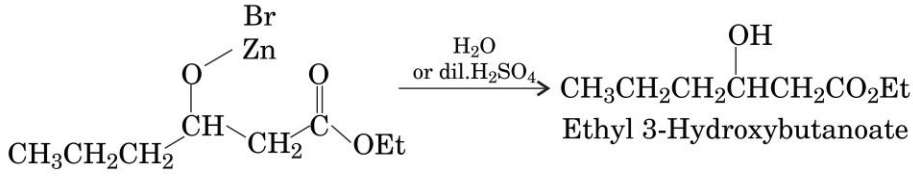
Step 1: The *α*-bromo ester reacts with zinc in benzene to produce a zinc enolate.



Step 2: The zinc enolate adds to the carbonyl group of the aldehyde to form a zinc alkoxide.

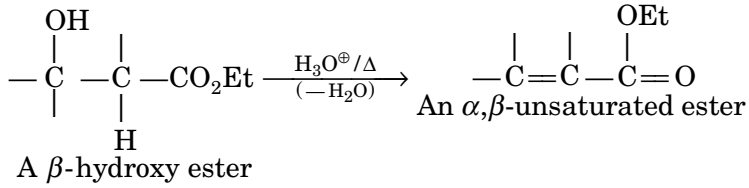


Step 3: The alkoxide on hydrolysis produces a *β*-hydroxy ester.



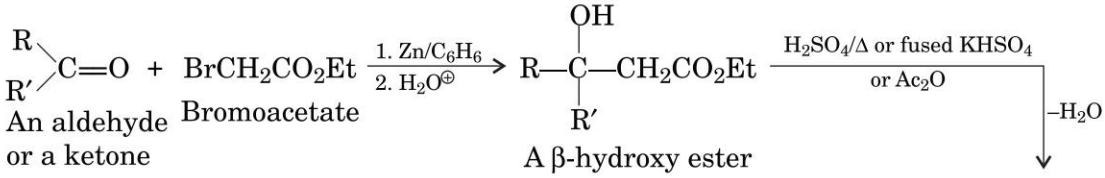
Ethyl 3-Hydroxybutanoate

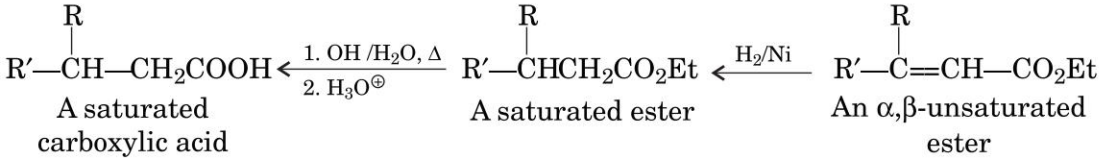
When the hydrolysis is carried out with dilute mineral acid under heated conditions, the resulting β-hydroxy ester may undergo ready dehydration to yield an α,β-unsaturated ester because dehydration produces a system in which the carbon–carbon double bond is conjugated with the carbon–oxygen double bond of the ester function.



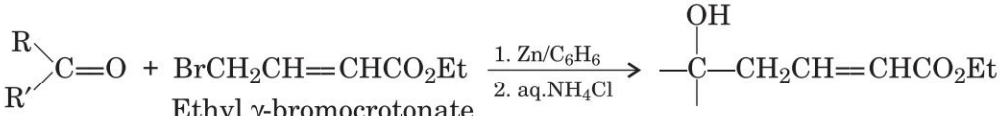
Synthetic application: Some important application of the Reformatsky reaction are as follows:

(i) The hydroxy ester obtained in the Reformatsky reaction can be dehydrated to yield α,β-unsaturated esters. Catalytic hydrogenation of the unsaturated esters followed by hydrolysis yields saturated carboxylic acids. The complete procedure thus constitutes a useful two-carbon chain extension process.

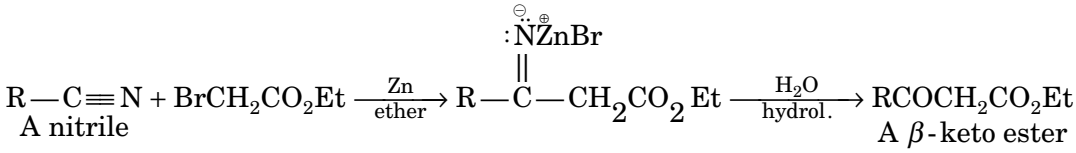




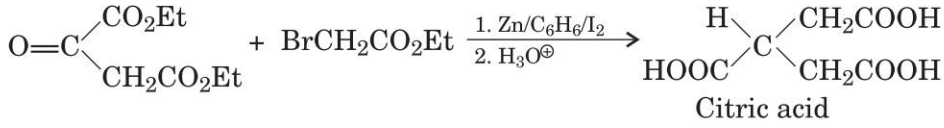
Ethyl γ-bromorcotonate may also be used in the Reformatsky reaction and its use permits an analogous four-carbon atom chain lengthening process.



(ii) A modification of the Reformatsky reaction is the *Blaise reaction* in which a nitrile is made to react with an α-halo ester to get a β-keto ester.

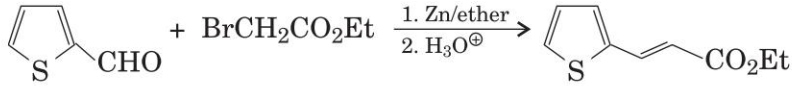


(iii) Citric acid can be prepared by this reaction.



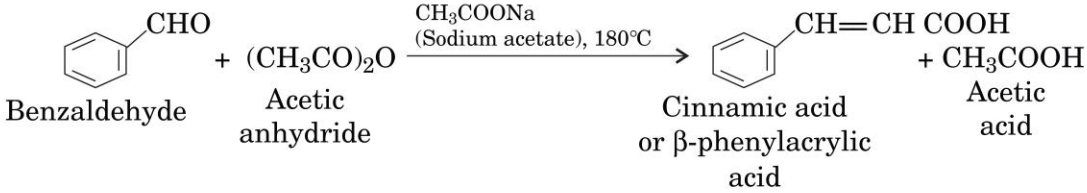
Citric acid

(iv) 2-Formylthiazole may be converted to the corresponding α,β-unsaturated ester by this reaction.



2.8.6 Perkin reaction

The aldol-type condensation of an aromatic aldehyde with an aliphatic acid anhydride containing at least two α-H atoms in the presence of sodium of potassium salt of the acid corresponding to the anhydride (which acts as a basic catalyst) to form a β-aryl α,β-unsaturated carboxylic acid or β-arylacrylic acid is known as the *Perkin reaction*. For example:



Benzaldehyde

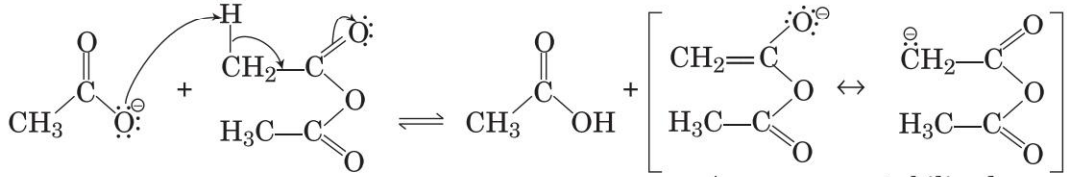
Acetic anhydride

Cinnamic acid or β-phenylacrylic acid

In some cases, β-hydroxy carboxylic acid is isolated when the anhydride bears only one α-hydrogen, because dehydration cannot take place in that case.

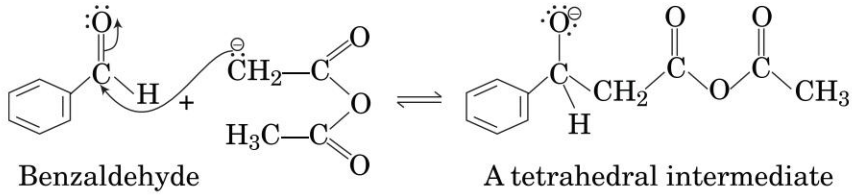
Mechanism of the reaction: The mechanism of the reaction involves the step as follows:

Step 1: Acetate ion (from anhydrous sodium acetate), acting as a basic catalyst, abstract an α-H atom from acetic anhydride to form a resonance-stabilized carbanion.

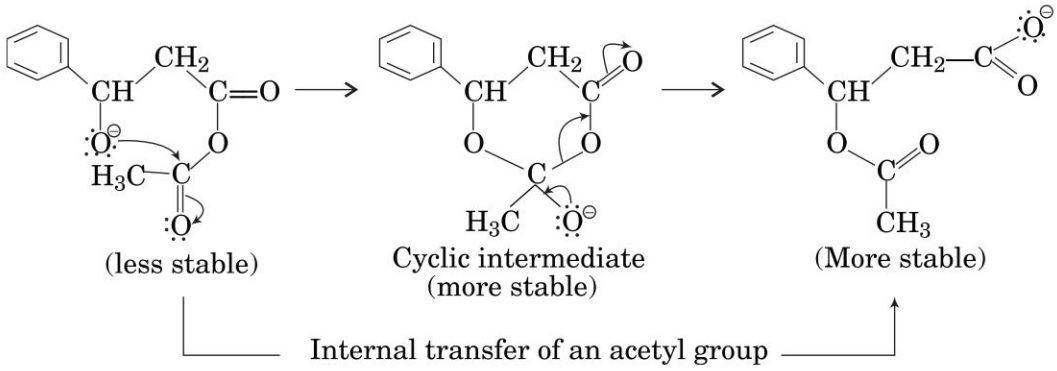


A resonance-stabilized carbanion

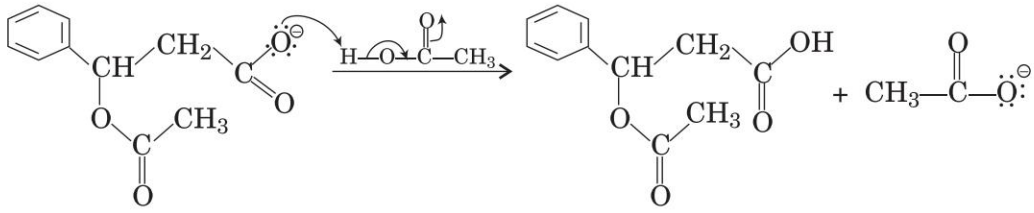
Step 2: The carbonyl carbon of benzaldehyde undergoes nucleophilic attack by the carbanion to form a tetrahedral alkoxide ion intermediate.



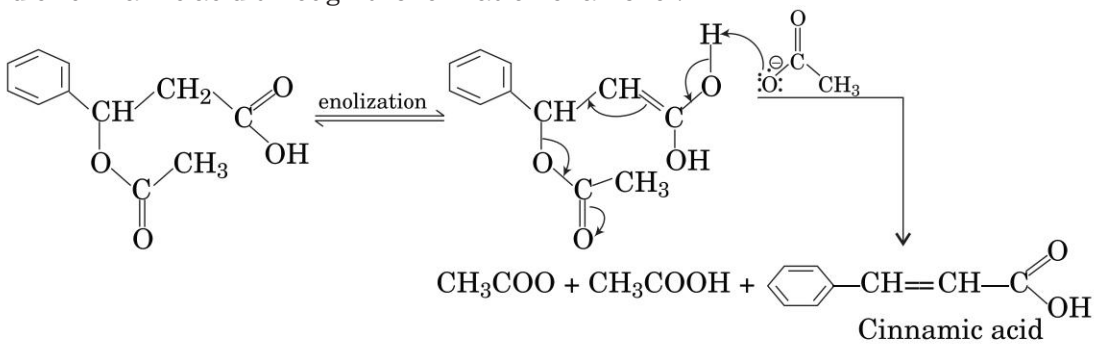
Step 3: Intramolecular attack upon the anhydride end of the molecule by the newly created alkoxide ion occurs to form a cyclic intermediate which subsequently opens up (carboxylate is the best leaving group from this tetrahedral intermediate). Thus, an intramolecular acetylation takes place.



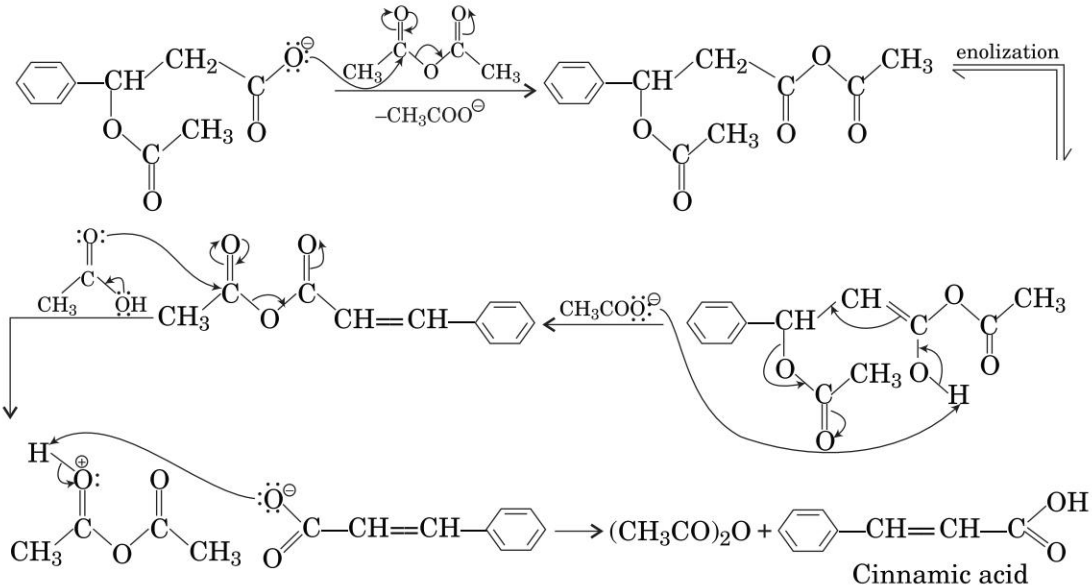
Step 4: The carboxylate ion undergoes protonation to form the corresponding carboxylic acid.



Step 5: One acetic acid molecule is eliminate by base (the acetate ion) to form β-phenylacrylic acid or cinnamic acid through the formation of an enol.



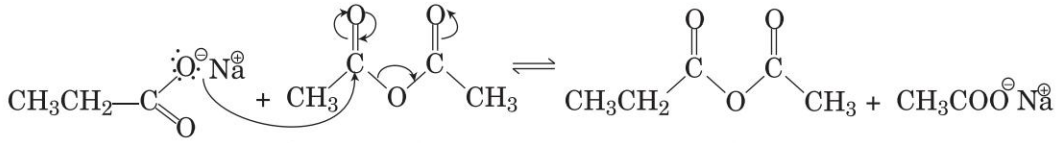
Cinnamic acid may also be formed from the carboxylate ion as follows:



A mixture of (*E*)- and (*Z*)-cinnamic acid is obtained. However, the formation of the (*E*)-isomer is preferred because the transition state leading to it is relatively more stable.

It is to be noted that in the Perkin reaction, the anhydride and the sodium salt should be from the same carboxylic acid.

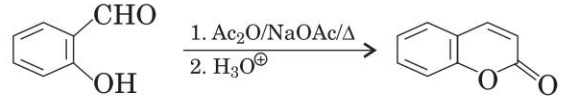
When the sodium salt of a carboxylic acid not corresponding to the anhydride is used, the following type of exchange reaction may take place at higher temperature. For example:



As a result, both the anhydrides react with the aromatic aldehyde to give a mixture of two α,β-unsaturated acids. It is for this reason, in the Perkin reaction, the anhydride and the sodium salt should be from the same carboxylic acid.

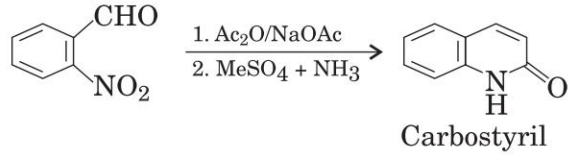
Synthetic application Some useful organic compounds can by synthesized by using the Perkin reaction.

(i) **Synthesis of Coumarin:**



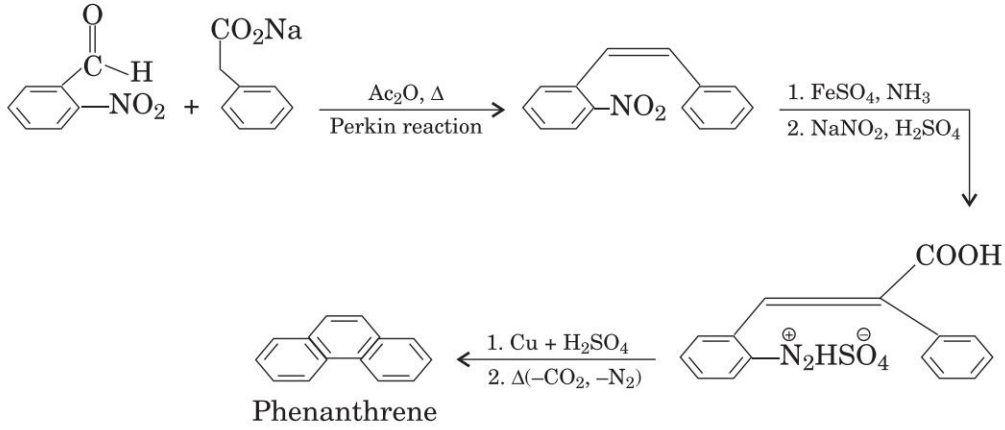
Coumarin is a natural perfume and is also used as an artificial flavour. When heated with NaOEt, it is converted into coumaric acid.

(ii) **Synthesis of carbostyril:**



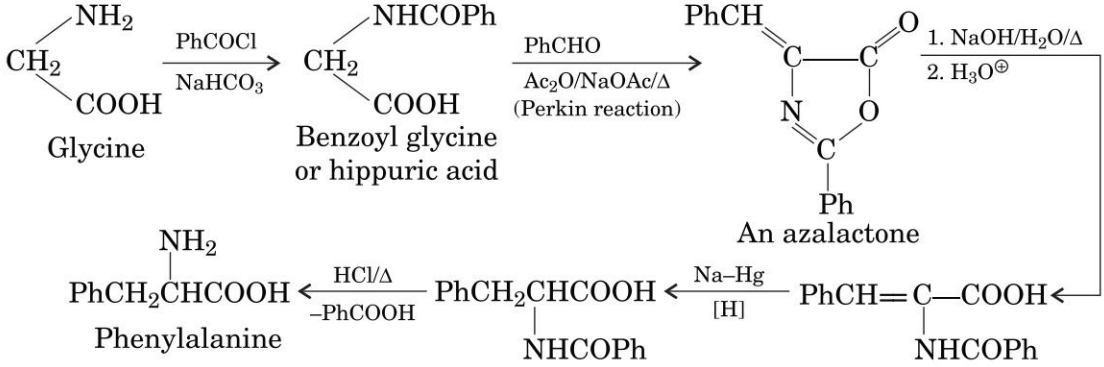
Carbostyril

(iii) **Synthesis of phenanthrene:**



Phenanthrene

(iv) **Synthesis of phenylalanine (an α-amino acid):**



Glycine

Benzoyl glycine or hippuric acid

An azalactone

Phenylalanine

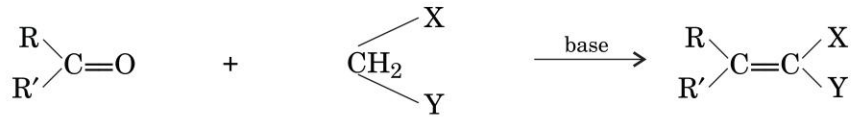
(v) **Synthesis of vinylog of cinnamic acid:**

$$\underset{\text{Cinnamaldehyde}}{Ph-CH=CH-CHO} \xrightarrow{Ac_2O/NaOAc/\Delta} \underset{\text{Cinnamylacrylic acid}}{Ph-CH=CH-CH=CH-COOH}$$

2.8.7 Knoevenagel condensation

The base-catalyzed aldol-type condensation reaction of aldehydes of ketones, usually without any α-hydrogen, with compounds having active methyl group (a $-CH_2-$ group flanked by two electron-withdrawing groups), for example, acetoacetic ester, malonic ester, cyanoacetic ester, etc. in the presence of mild basic catalyst like pyridine, piperidine,

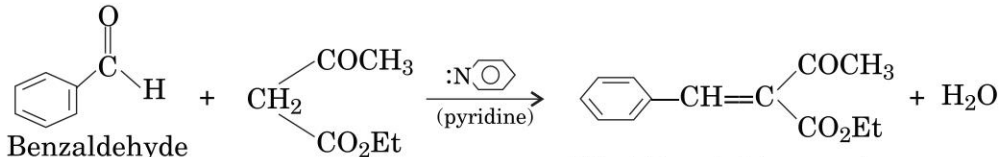
diethylamine (Et_2NH) or triethylamine (Et_3N) to afford α,β-unsaturated esters or related compounds is known as the *Knoevenagel condensation.*



(R′ = H, alkyl or aryl) X and Y = –CHO, –COR, –COOR, –CN, $–NO_2$, etc.

Examples:

(i)



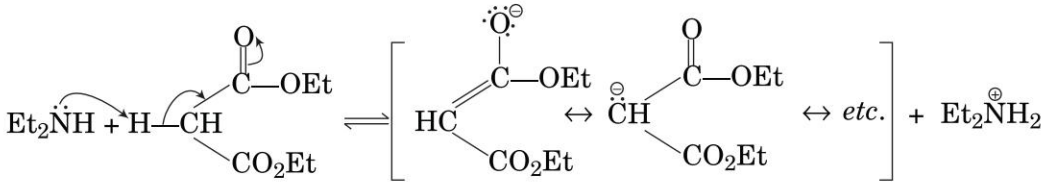
(ii) CH_3CHO + $CH_2(CO_2Et)_2$ $\xrightarrow{Et_3\ddot{N}}$ $CH_3CH{=}CH(CO_2Et)_2 + H_2O$

Acetaldehyde Diethylmalonate Ethyl 2-carboethoxybut-2-enoate (an α,β-unsaturated ester)

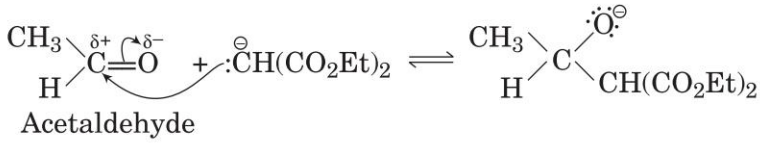
Aromatic aldehydes are more useful than aliphatic aldehydes in Knoevenagel reaction.

Mechanisms of the reaction The mechanisms of the reaction involve the steps as follows:

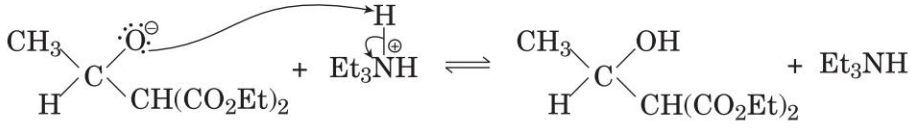
Step 1: Reversible abstraction of an acidic methylene proton by base to form a resonance-stabilized carbanion



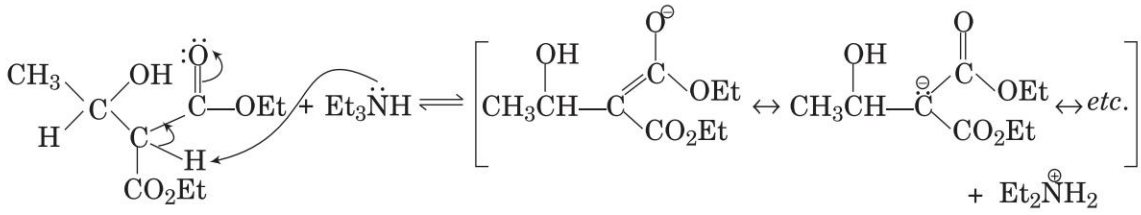
Step 2: Nucleophilic attack of the carbanion at the electron-deficient carbonyl carbon atom to form an alkoxide.



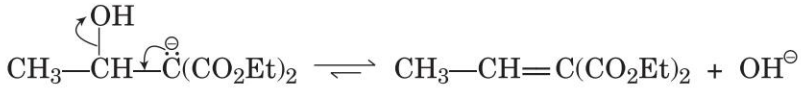
Step 3: Protonation of the alkoxide to form the corresponding alcohol.



Step 4: Abstraction of another reactive methylene hydrogen by base to form a resonance-stabilized carbanion.



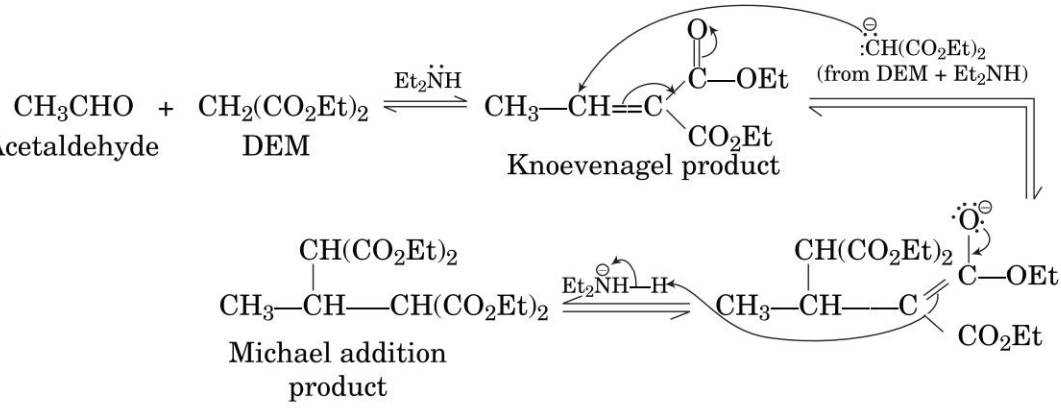
Step 5: Loss of $OH^{\ominus}$ to form an α,β-unsaturated ester.



The $OH^{\ominus}$ ion reacts with $Et_2\overset{\oplus}{N}H_2$ to form H_2O and Et_2NH. The dehydration process taking place in the last two steps is, in fact, an E1cB pathway.

Some relevant topics:

(i) Excess of active methylene compound should be avoided in the Knoevenagel condensation because excess use of active methylene compound leads to the formation of Michael addition compound. For example, if an excess of malonic ester is used in the following reaction, one will get the Michael addition product instead of the Knoevenagel condensation product.

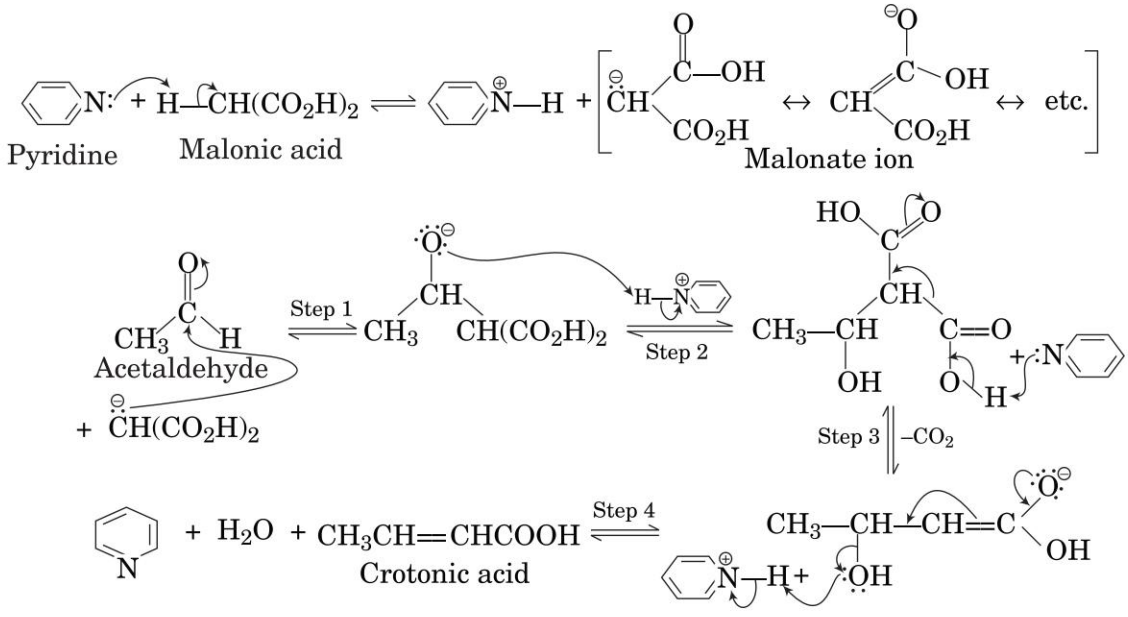


(ii) **Cope-Knoevenagel reaction:** The Knoevenagel reaction is reversible favouring the equilibrium to the left and hence the yield of the product is usually not satisfactory. Cope introduced a modified procedure by performing the reaction in benzene and removing the water as an azeotropic mixture. This causes the equilibrium to be shifted to the right, i.e., the product side. The reaction in which this modified technique is applied is called the *Cope-Knoevenagel reaction.*

(iii) **Doebner condensation:** An α,β-unsaturated carboxylic acid may directly be prepared by heating a carbonyl compound with malonic acid in hot pyridine. This modification of Knoevenagel condensation in which decarboxylation usually occurs during condensation is known as the *Doebner condensation.* For example, when a acetaldehyde is heated with malonic acid in the presence of pyridine, crotonic acid or but-2-enoic acid is obtained.

$$\underset{\text{Acetaldehyde}}{CH_3CHO} + \underset{\text{Malonic acid}}{CH_2(CO_2H)_2} \xrightarrow[100^\circ C]{\text{pyridine}} \underset{\substack{\text{Crotonic acid}\\ \text{or but-2-enoic acid}}}{CH_3CH{=}CHCOOH}$$

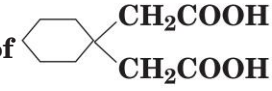
Mechanism: The mechanism of the reaction is as follows:

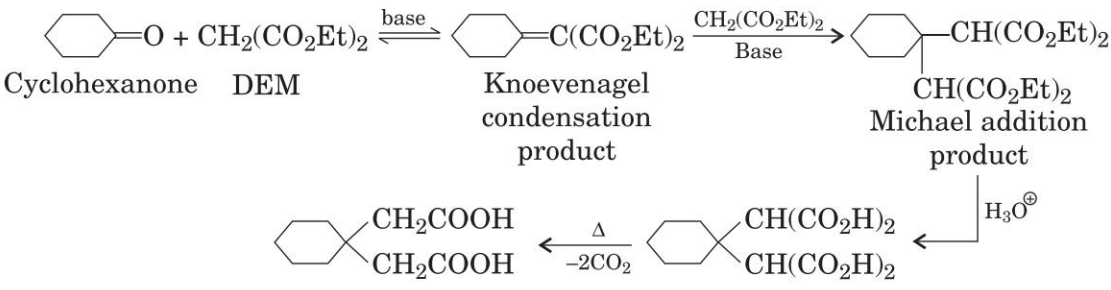


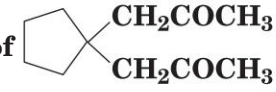
The resonance-stabilized malonate ion is initially formed. In step 1, acetaldehyde undergoes nucleophilic attack by the malonate ion. In step 2 , the resulting alkoxide undergoes protonation. In step 3, decarboxylation occurs to form a resonance-stabilized carbanion. In step 4, loss of $OH^{\ominus}$ occurs to form an α,β-unsaturated carboxylic acid.

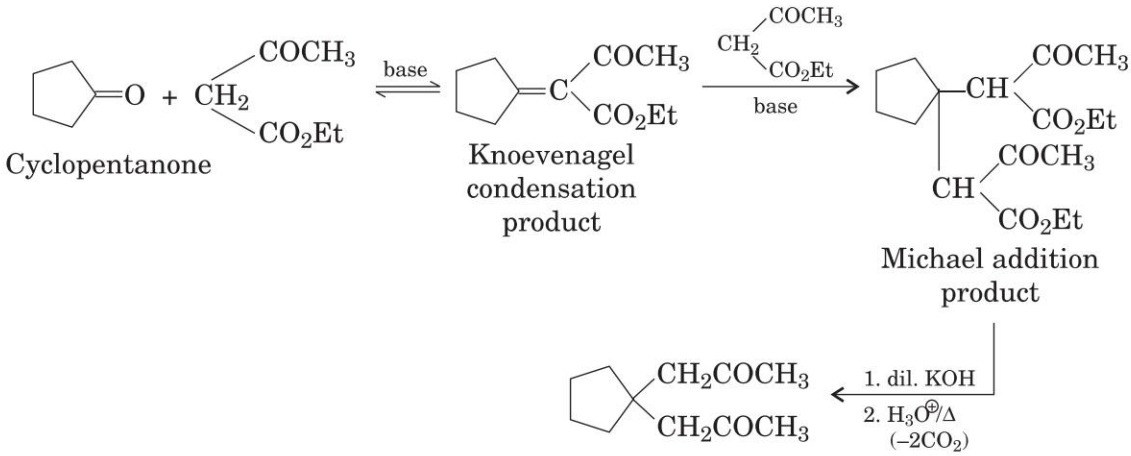
Synthetic applications

(i) Knoevenagel condensation followed by Michael addition is a unique combination of reactions to synthesize varieties of carboxylic acids and ketones. For example:

(a) **Synthesis of**  **(Cyclohexane-1,1-diacetic acid)**

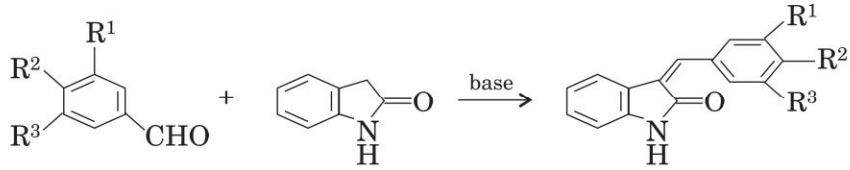


(b) **Synthesis of** 



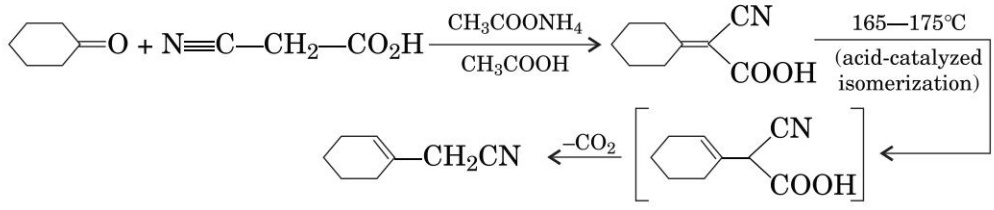
(ii) Some other important organic compounds can be prepared by using this reaction. For example:

(a) **Synthesis of 3-benzylidene-1,3-dihydroindol-2-ones**



These compounds have been known as pharmacological agents for several years.

(b) **Synthesis of β,γ-unsaturated nitrile**

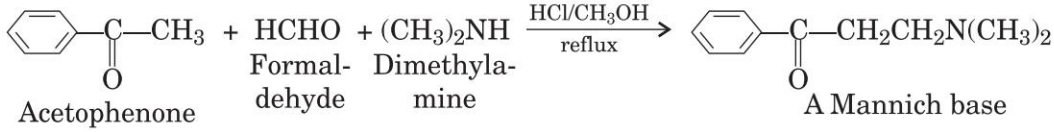


2.8.8 Mannich reaction

The condensation of an enolizable carbonyl compound (an aldehyde or a ketone) with formaldehyde and ammonia or a primary or secondary amine to form its aminomethyl or substituted aminomethyl derivative (called a Mannich base) is known as the *Mannich reaction.*

The reaction is usually carried out in acid solution (but may also be base-catalyzed). The commonly used solvents are water, methanol, and ethanol. Usually, secondary amines (e.g., dimethylamine, diethylamine, piperidine, etc.) are used to avoid side reactions.

Examples:

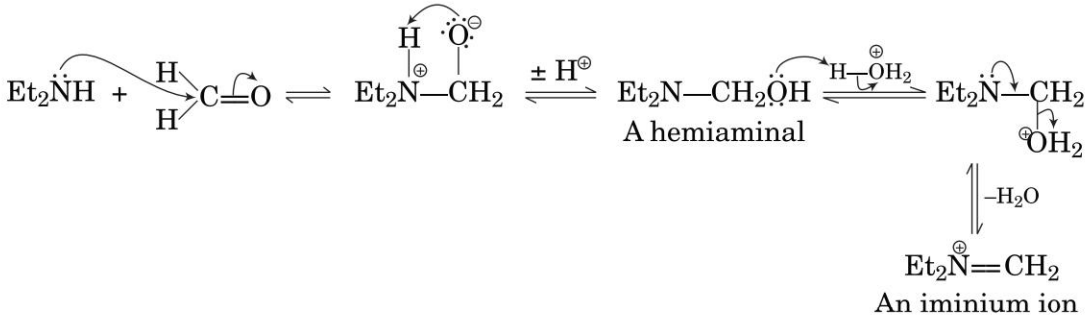
(i) 

(ii) $CH_3COCH_3 + HCHO + (C_2H_5)_2\ddot{N}H \xrightarrow[\text{reflex}]{HCl/CH_3OH} CH_3CO(CH_2)_2N(C_2H_5)_2$

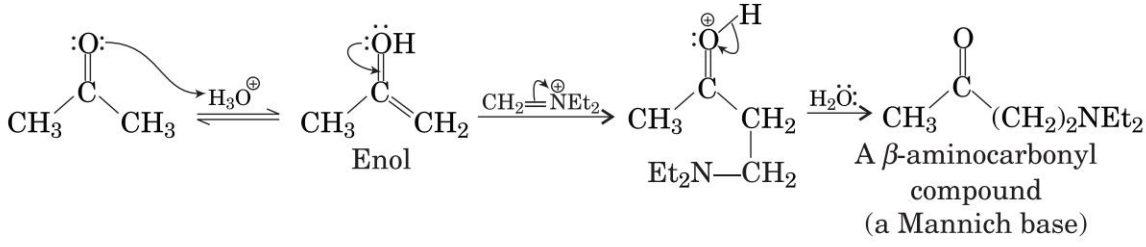
Acetone; Formaldehyde dimethylamine; A Mannich base

Mechanism of the reaction: The mechanism of the reaction involves the steps as follows:

Step 1: Formaldehyde reacts with dimethylamine $(Me_2\ddot{N}H)$ to form an iminium ion. A hemiaminal is formed initially which then loses a molecule of water.



Step 2: The enol form of the active hydrogen compound reacts with the iminium cation to form a β-aminocarbonyl compound (a Mannich base).



Some relevant topics:

(i) With an unsymmetrical ketone, the more substituted enol predominates in the acid-catalyzed condition of the reaction and therefore, aminomethylation occurs at the more substituted α-position. For example:

$$\underset{\text{3-Methyl-2-butanone}}{CH_3COCH(CH_3)_2} + HCHO + (CH_3)_2NH \xrightarrow[\text{reflux}]{HCl/CH_3OH} \underset{(76\%)}{CH_3COC(CH_3)_2CH_2N(CH_3)_2} + \underset{(22\%)}{(CH_3)_2NCH_2CH_2COCH(CH_3)_2}$$

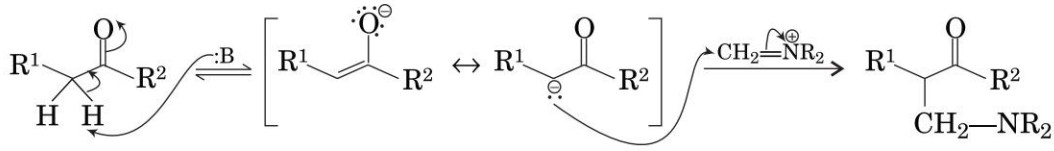
$$\underset{\text{Less substituted enol (less stable)}}{CH_2{=}C(OH)CH(CH_3)_2} \overset{H_3O^{\oplus}}{\rightleftharpoons} CH_3COCH(CH_3)_2 \overset{H_3O^{\oplus}}{\rightleftharpoons} \underset{\text{More substituted enol (more stable)}}{CH_3C(OH){=}C(CH_3)_2}$$

(ii) With ammonia and primary amines, the reaction may proceed further since the first formed Mannich base still contains replaceable hydrogen on nitrogen atom and hence, polyalkylation will take place. For example:

$$\underset{\text{Acetone}}{2\,CH_3COCH_3} + 2\,HCHO + \underset{\text{Methylamine}}{CH_3NH_2} \xrightarrow[\Delta]{HCl/MeOH} \underset{\text{Second Mannich base}}{CH_3N(CH_2CH_2COOH_3)_2}$$

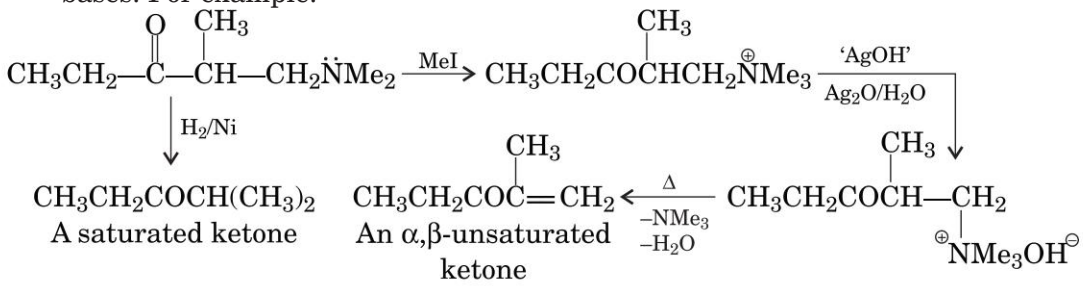
(iii) The Mannich reaction can be carried out without acid catalyst, if performed iminium salt like Eschenmoser's salt ($Me_2\overset{\oplus}{N}{=}CH_2I^{\ominus}$) is used.

(iv) The Mannich reaction can also be catalyzed by base; the reaction proceeds through the enolate of the carbonyl compound.



Synthetic applications: Some important applications of the Mannich reaction are as follows:

(i) α,β-Unsaturated ketones and saturated ketones can be prepared from Mannich bases. For example:



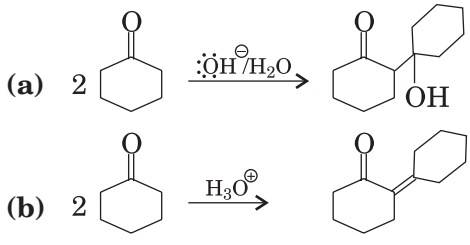
The α,β-unsaturated ketones (Michael acceptors) can be used for the synthesis of ring system in *Robinson annulation* process.

(ii) 3-Indole derivatives, 2-pyridine derivatives, 3-thiophen derivatives, etc., can be prepared by using Mannich bases.

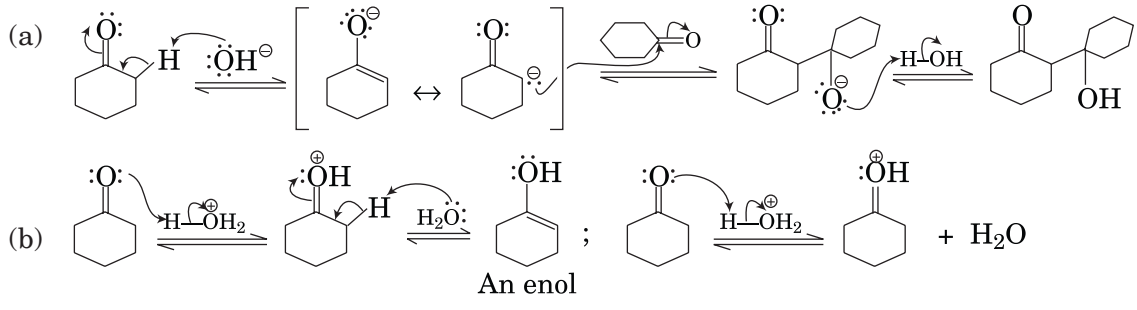
(iii) Various natural products like atropin (used in medicine as an anticholinergic), cocaine (an alkaloid which is a strong stimulant mostly used as a recreational drug), etc. have been synthesized by the Mannich reaction.

SOLVED PROBLEMS

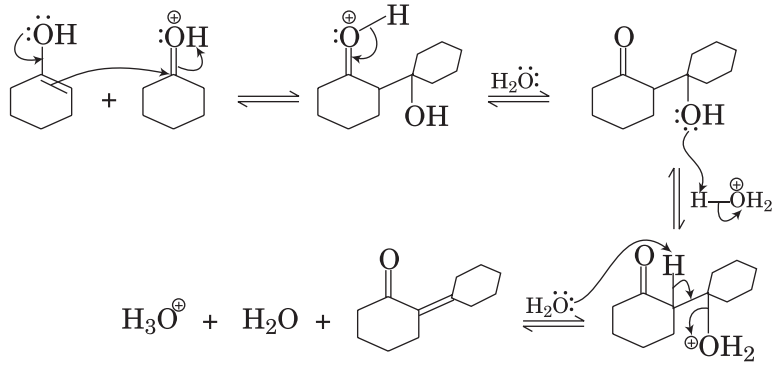
1. Suggest a mechanism for each of the following reactions:



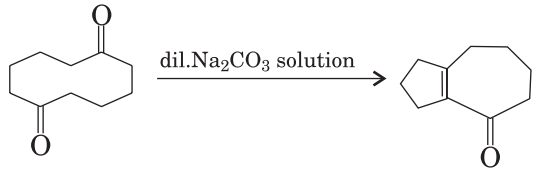
Solution

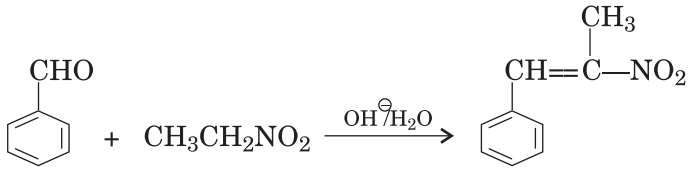


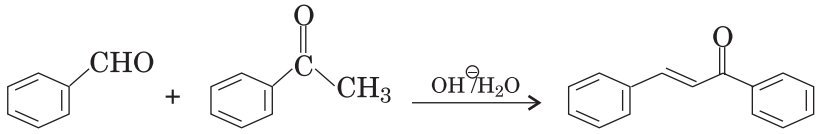
Now, the enol reacts with the protonate ketone to form finally the aldol condensation product.

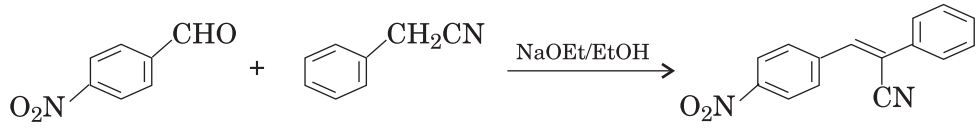


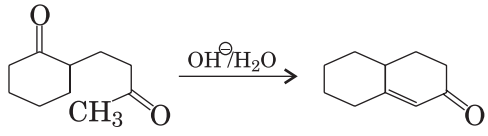
2. Provide an arrow formalism mechanism for each of the following reactions:

(a) 

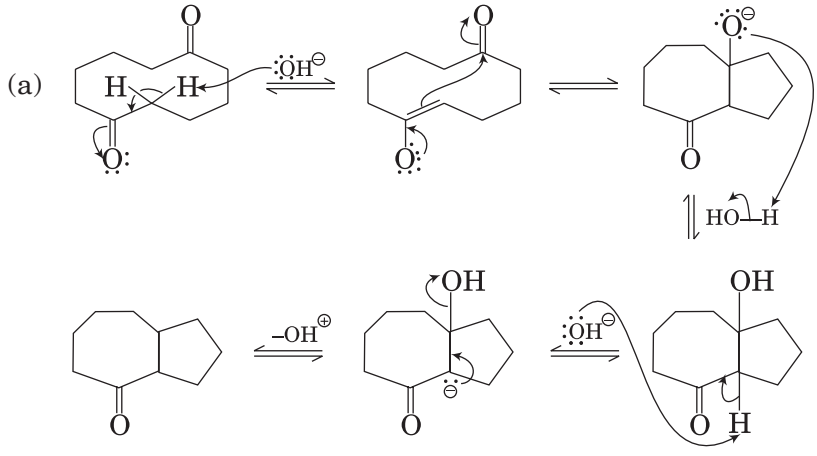
(b) 

(c) 

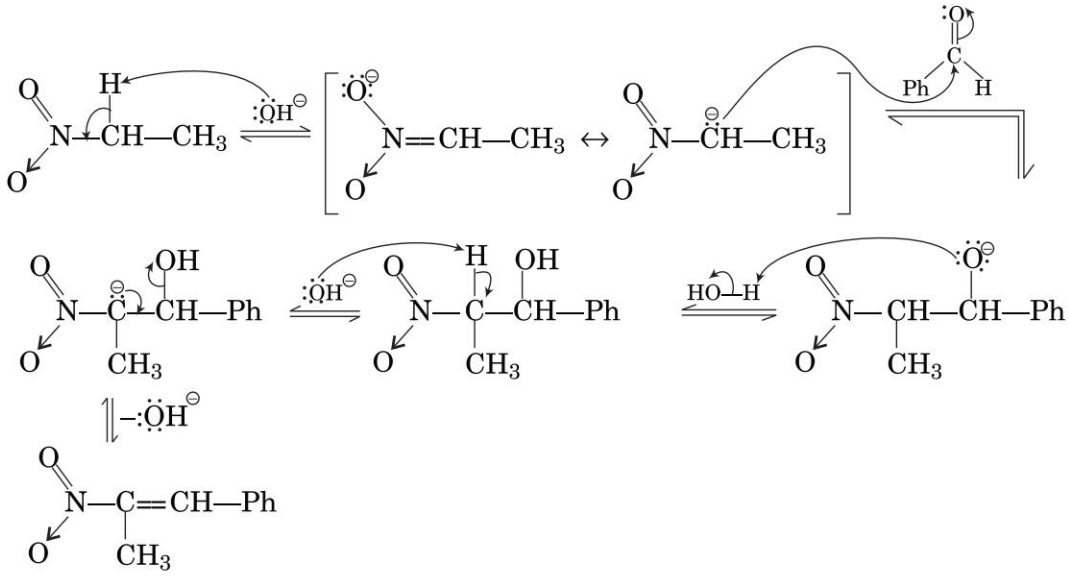
(d) 

(e) 

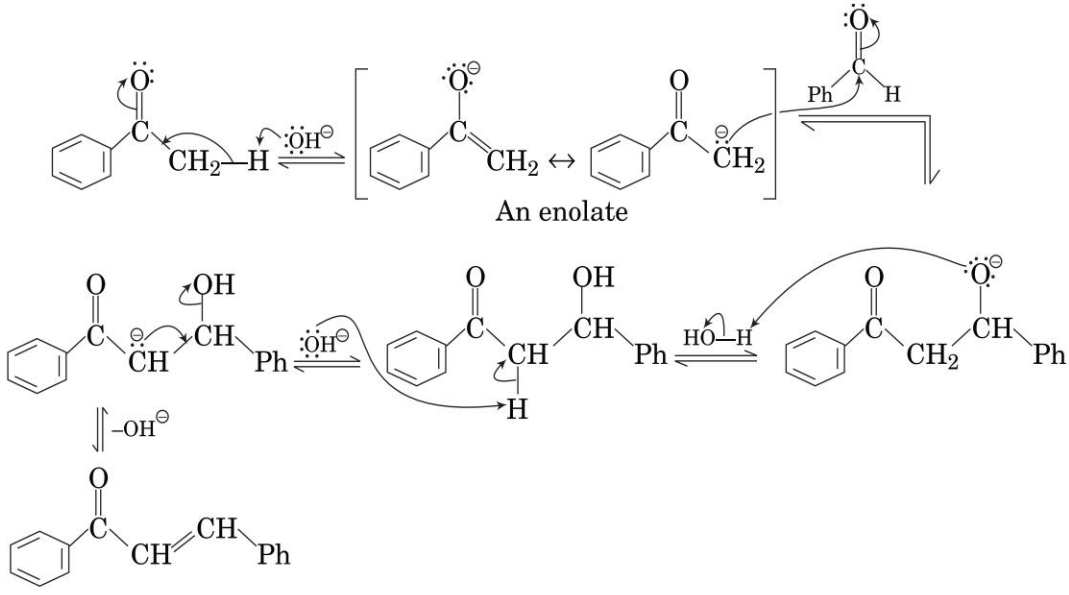
Solution

(a) 

(b)

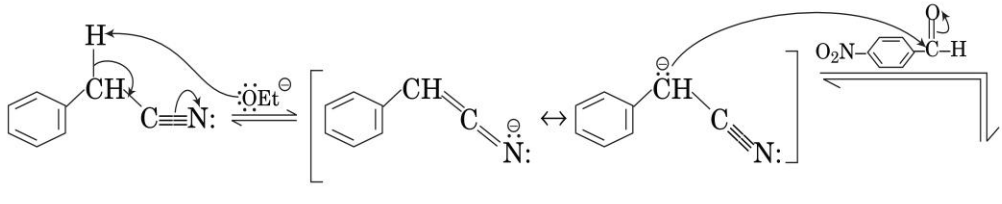


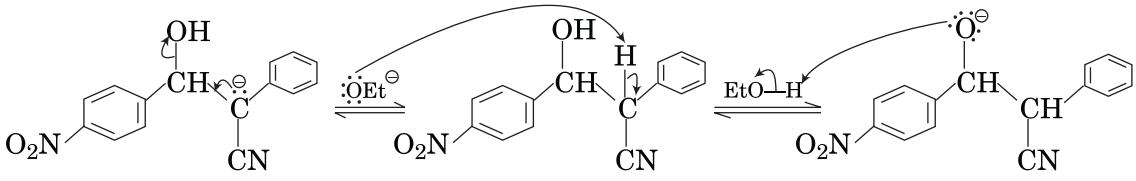
(c)

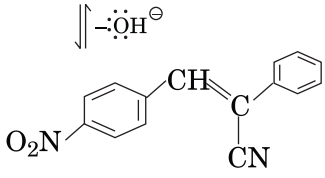


An enolate

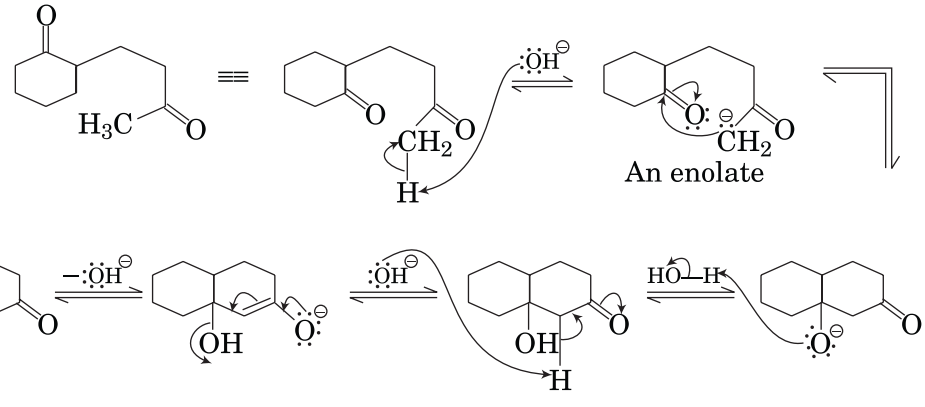
(d)





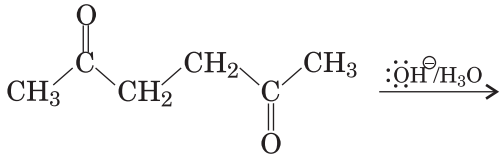


(e)

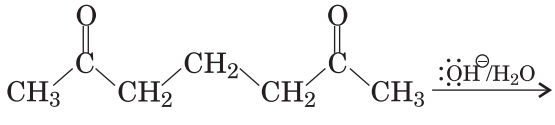


3. Predict the product of the following reactions and provide mechanism that accounts for their formations:

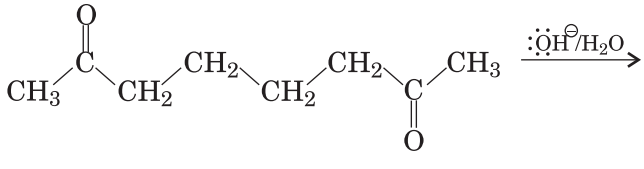
(a)



(b)

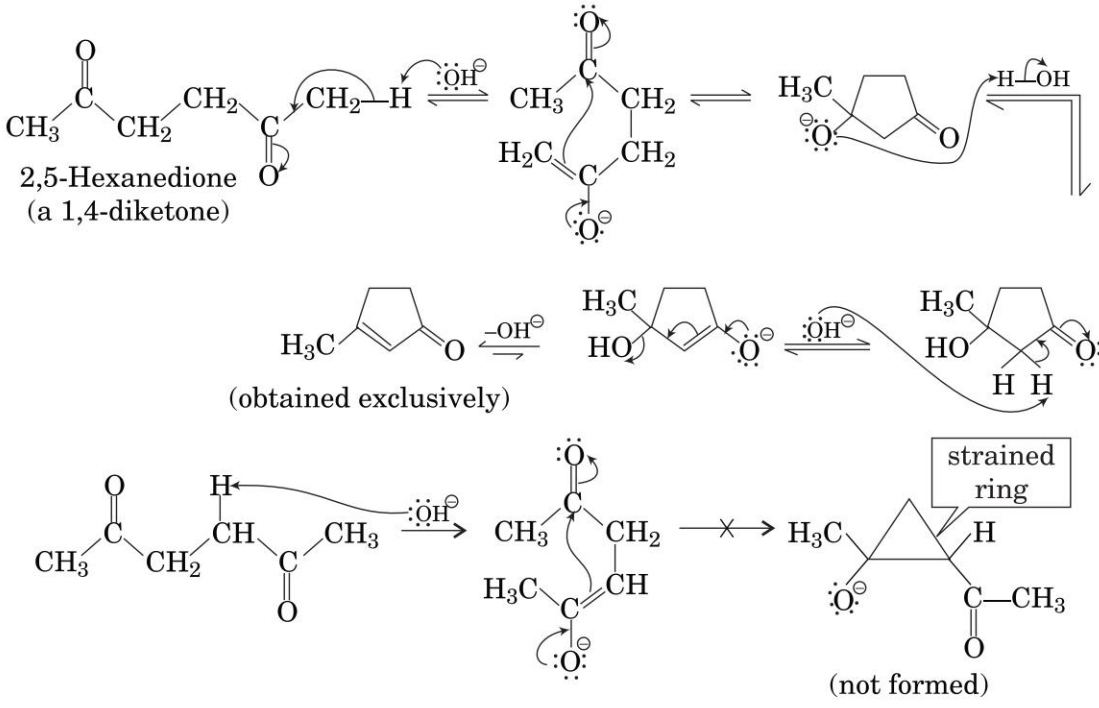


(c)

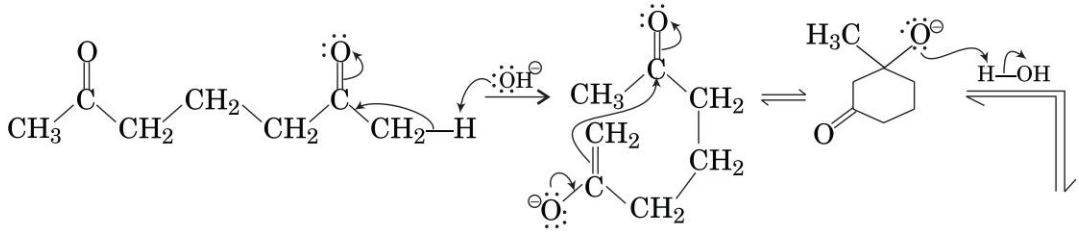


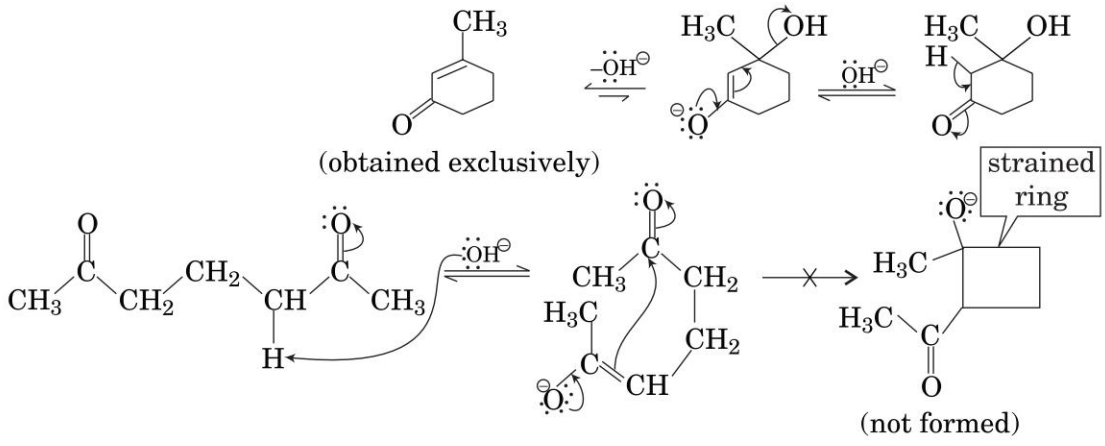
Solution

(a) Because this 1,4-diketone has two different sets of α-hydrogens, two different intramolecular addition products can potentially be formed. One product would contain a five-membered ring and the other would contain a three-membered ring. Since a five-membered ring thermodynamically more stable than a three-membered ring, therefore, the five-membered ring product is the only product formed from the intramolecular aldol reaction of this 1,4-diketone.

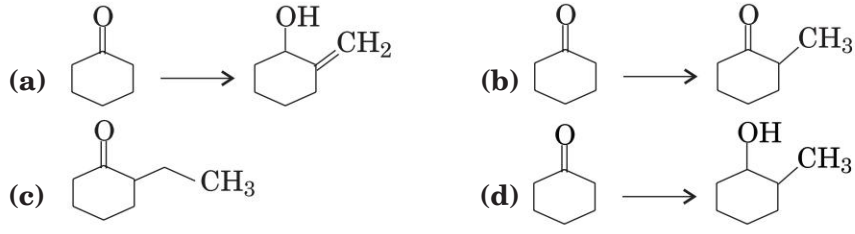


(b) An intramolecular aldol addition of this 1,5-diketone can lead to either a six- or a four-membered ring product. Due to angle strain, the four-membered ring product is thermodynamically less stable than the six-membered ring product and because of this, the six-membered ring product is obtained exclusively.

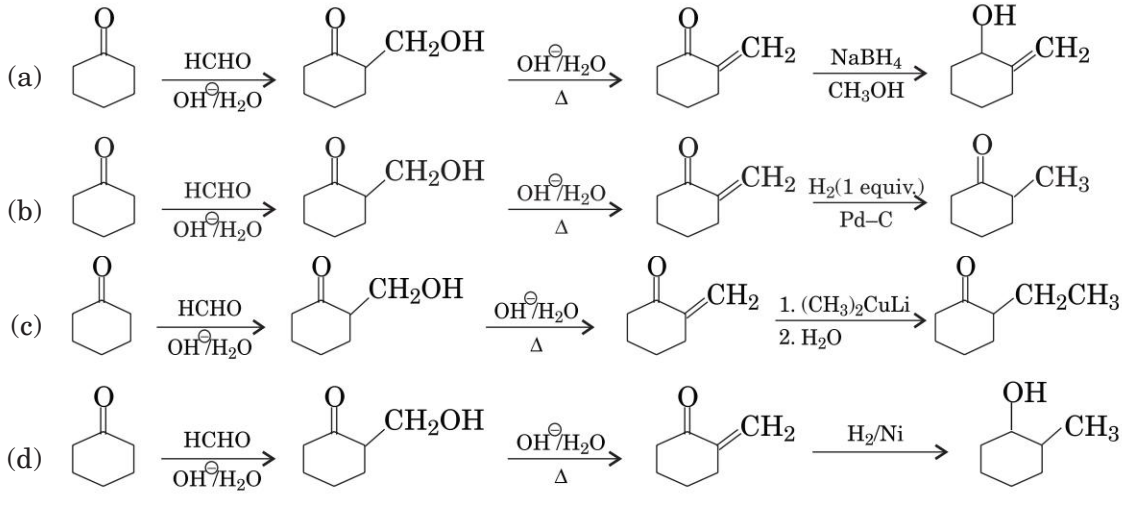




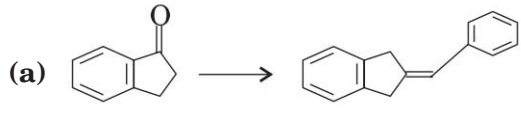
4. How would you carry out the following transformations?

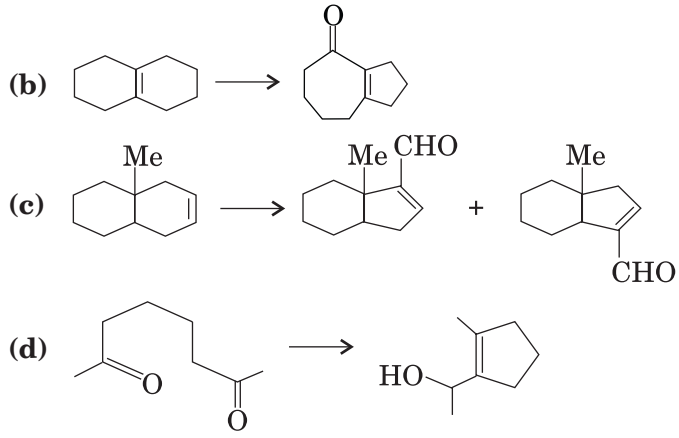


Solution

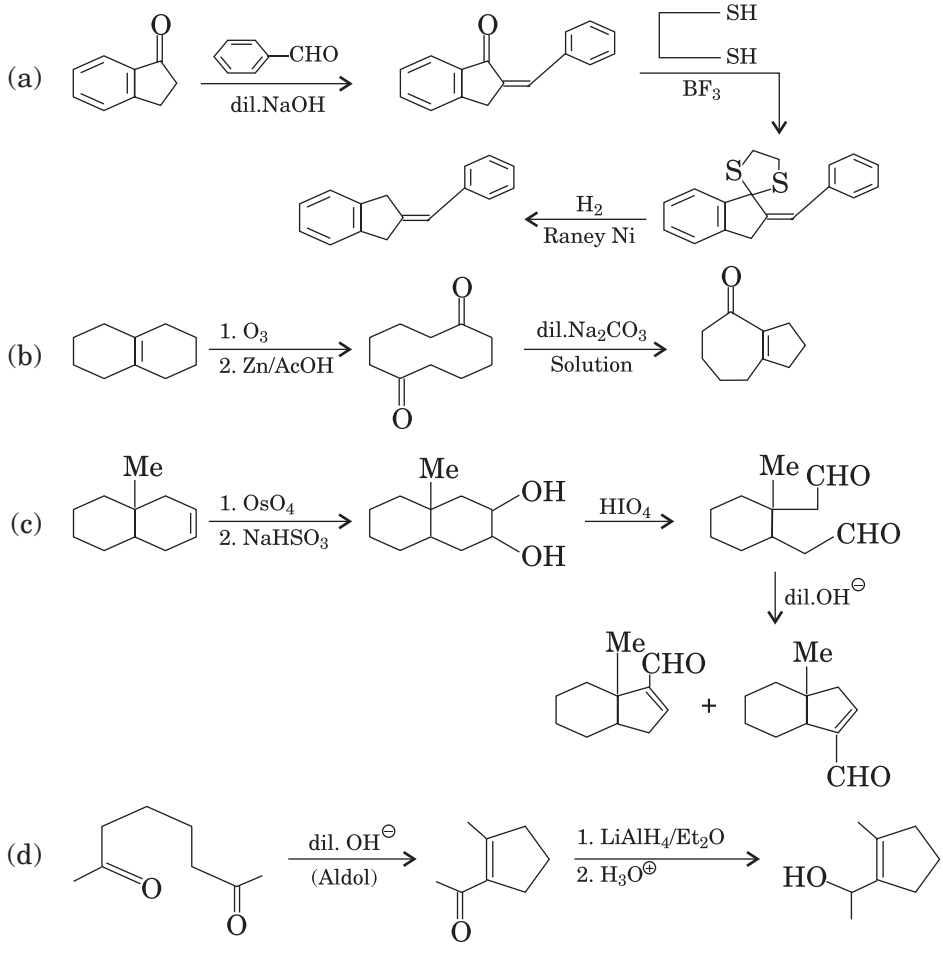


5. How would you carry out the following transformations?



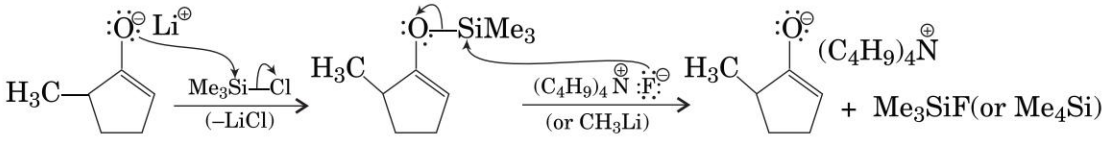

(b)
O
(c)
Me
Me
CHO
+
Me
CHO
(d)
O
O
HO

Solution


(a)
O
CHO
dil.NaOH
O
SH
SH
BF3
S
S
H2
Raney Ni
(b)
1. O3
2. Zn/AcOH
O
O
dil.Na2CO3
Solution
O
(c)
Me
1. OsO4
2. NaHSO3
Me
OH
OH
HIO4
Me
CHO
CHO
dil.OH⊖
Me
CHO
+
Me
CHO
(d)
O
O
dil. OH⊖
(Aldol)
O
1. LiAlH4/Et2O
2. H3O⊕
HO

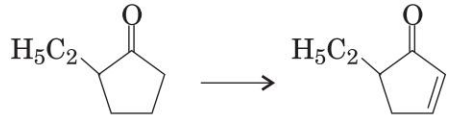
6. A kinetic enolate can be trapped by converting it to an enol trimethylsilyl ether and after purification it can be converted back to the enolate by treating the silyl ether with tetrabutylammonium fluoride $[(C_4H_9)_4\overset{\oplus}{N}F^{\ominus}]$ or with methyllithium (CH_3Li). Give an example and provide mechanism of the reactions involved.

Solution When the kinetic enolate obtained from 2-methylcyclopentanone is treated with chlorotrimethylsilane, it undergoes silylation exclusively at the oxygen atom. This is because the nucleophilic substitution at the Si atom by the O atom of the enolate to form the enol trimethylsilyl ether is a highly exothermic process (Si—O bond is much stronger than Si—C bond). The next reaction is also a nucleophilic substitution at the Si atom by $F^{\ominus}$. Although $F^{\ominus}$ is a poor nucleophile, the reaction occurs because $F^{\ominus}$ ion has extremely strong affinity for Si (Si—F bond energy is very high; 594 kJ mol).

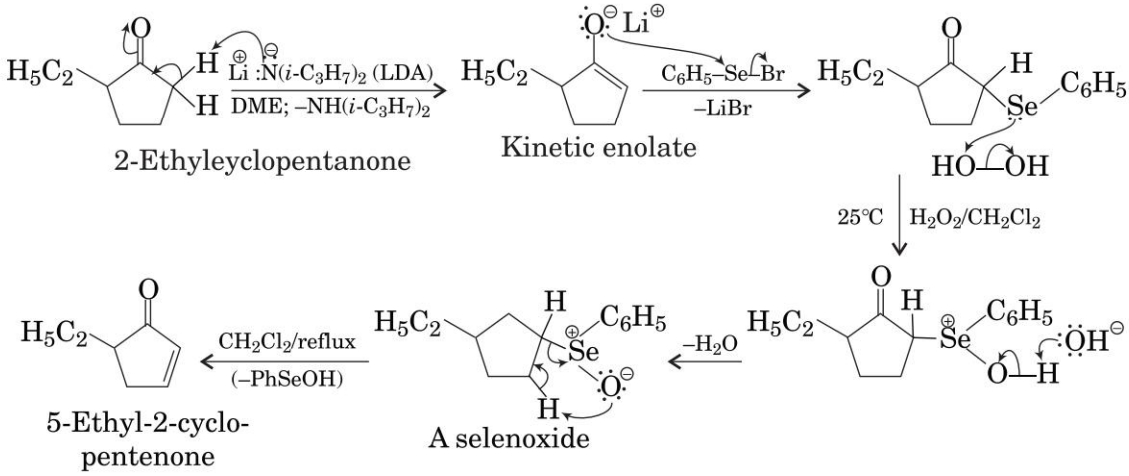


A kinetic enlate — An enol trimethylsilyl ether — A kinetic enolate

7. How would you carry out the following transformation using α-selenation? Give mechanisms of the steps involved.

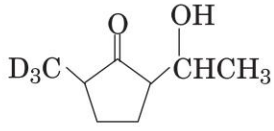


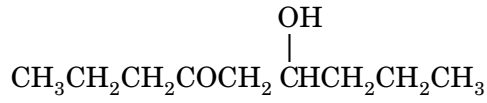
Solution Synthesis of 5-ethyl-2-cyclopentenone involving α-selation may be outlined as follows:



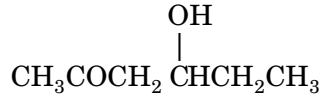
2-Ethyleyclopentanone — Kinetic enolate — A selenoxide — 5-Ethyl-2-cyclo-pentenone

8. Starting with ketone and aldehydes of your choice outline a directed aldol synthesis of each of the following:

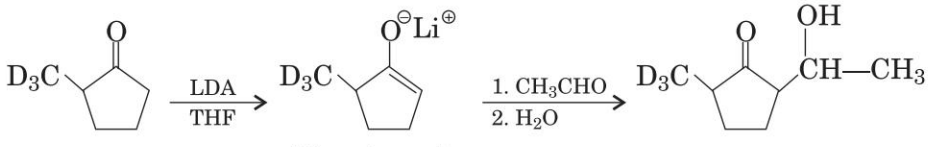
(a) 

(b) 

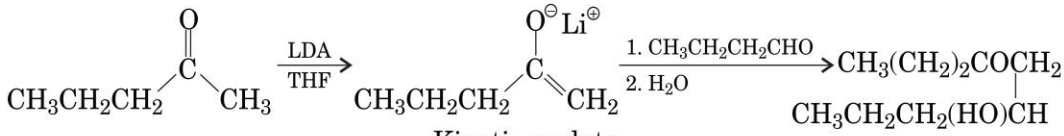
(c) 

(d) 

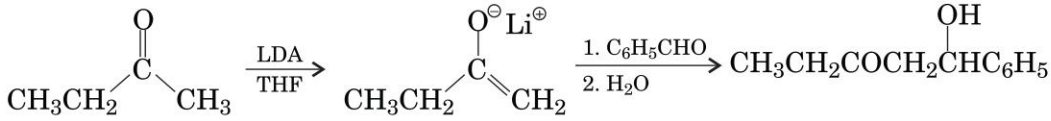
Solution

(a) 

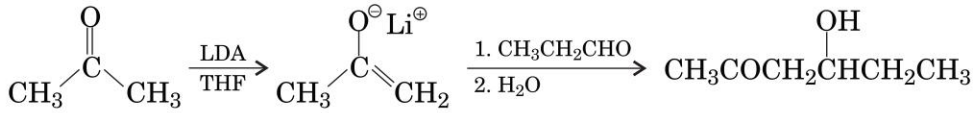
Kinetic enolate

(b) 

Kinetic enolate

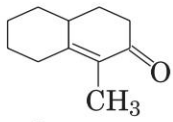
(c) 

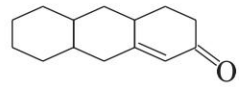
Kinetic enolate

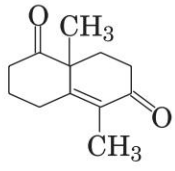
(d) 

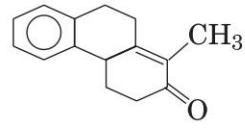
Kinetic enolate

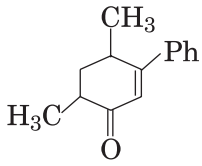
9. Predict the appropriate reactants required for the synthesis of each of the following compounds using Robinson annulation (a ring-forming reaction):

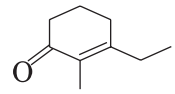
(a) 

(b) 

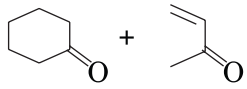
(c) 

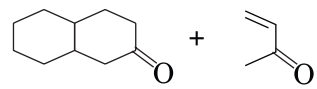
(d) 

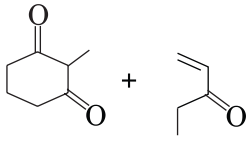
(e) 

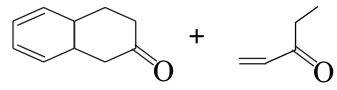
(f) 

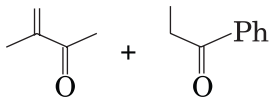
Solution It is possible to arrive at the appropriate reactants by breaking through the double bond and the bond between β- and γ-carbons on the other side of the carbonyl group.

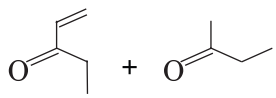
(a) 

(b) 

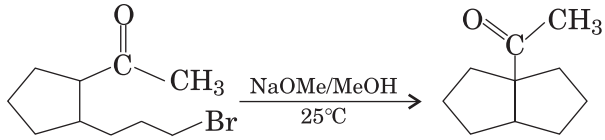
(c) 

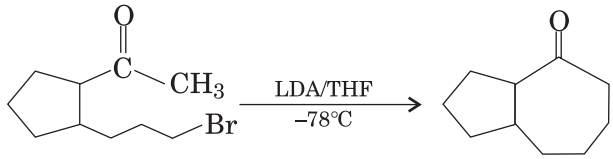
(d) 

(e) 

(f) 

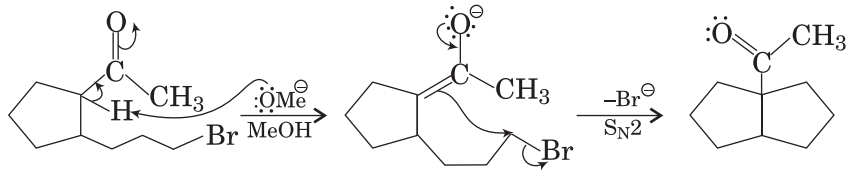
10. Give mechanism for these cycloalkylation reactions and explain why the different reaction conditions favour different products:

(a) 

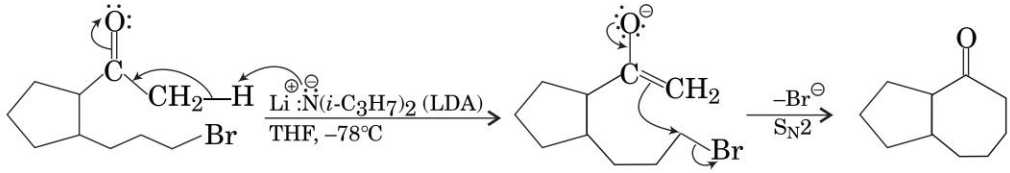
(b) 

Solution

(a) The bromoketone reacts with NaOMe in MeOH (a relatively weak base in a protic solvent) to form a thermodynamic enolate with the more highly substituted double bond. The enolate then undergoes cyclization by the displacement (S_N2) of $Br^{\ominus}$ to produce another cyclopentane ring.

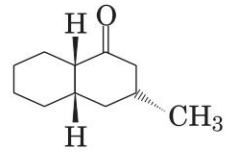


(b) The bromoketone reacts with the strong and sterically hindered base LDA (lithium diisopropylamide) to produce a kinetic enolate with less substituted double bond. The enolate then undergoes cyclization involving displacement (S_N2) of $Br^{\ominus}$ to form a seven-membered ring.



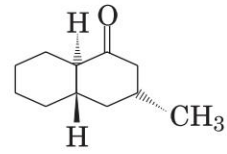
11. Account for the following isomerizations:

(a)



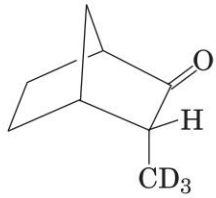
cis-3-Methyldecal-1-one

NaOEt/EtOH



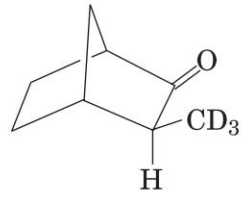
trans-3-Methyldecal-1-one

(b)



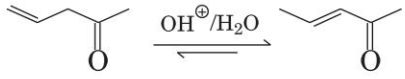
endo-isomer

$H_3O^{\oplus}/H_2O$



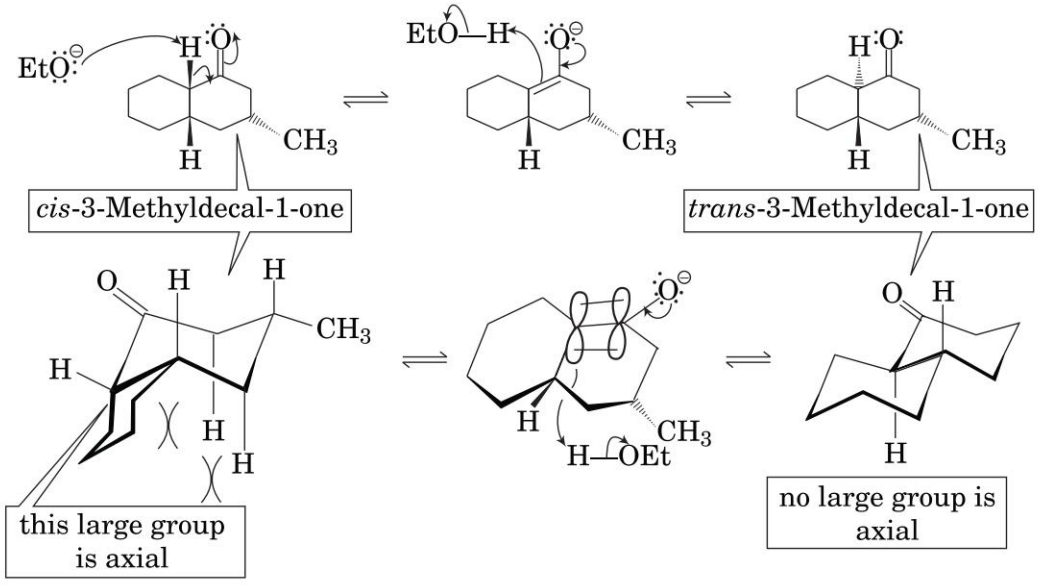
exo-isomer

(c)

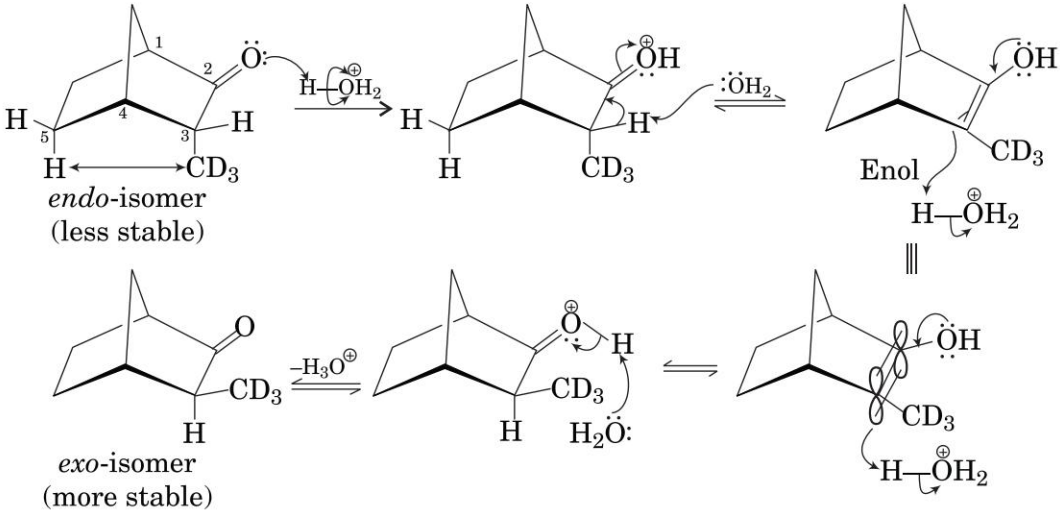


Solution

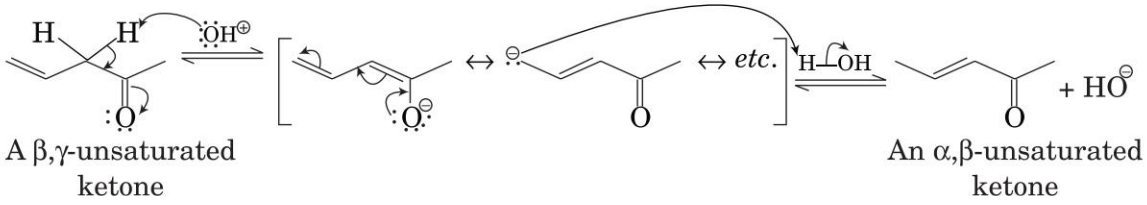
(a) In *cis*-3-methyldecal-1-one, a large group is axial. Therefore, because of 1,3-diaxial interactions, it is thermodynamically less stable than the *trans*-isomer in which no large group is axial. It is for this reason, the *cis*-decalone undergoes base-catalyzed isomerization to produce the *trans*-isomer through intermediate formation of an enolate.



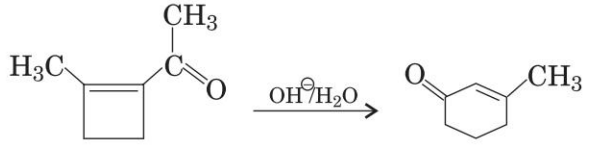
(b) In the *endo*-isomer of the bicyclic ketone, the *endo*-CD_3 group at C-3 becomes involved in steric interaction with the *endo* H-atom at C-5. No such steric interaction operates in the *exo*-isomer. Therefore, the *endo*-isomer is thermodynamically less stable than the *exo*-isomer and for this reason, the *endo*-isomer undergoes acid-catalyzed isomerization to yield the *exo*-isomer through the intermediate formation of an enol.



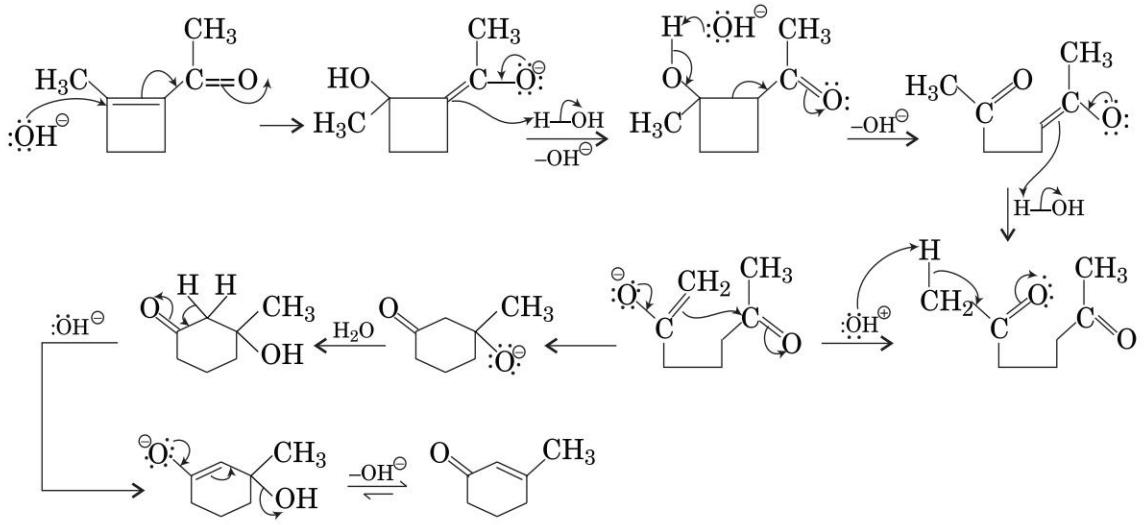
(c) An α,β-unsaturated carbonyl compound is thermodynamically more stable (due to conjugation) than a β,γ-unsaturated carbonyl compound. For this reason, this β,γ-unsaturated ketone undergoes base-catalyzed isomerization to yield the corresponding α,β-unsaturated ketone.



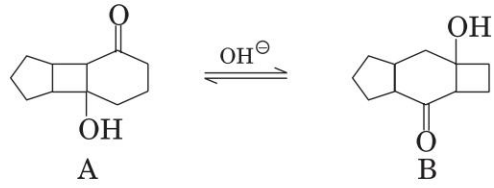
12. Provide an arrow pushing mechanism for the following reaction:



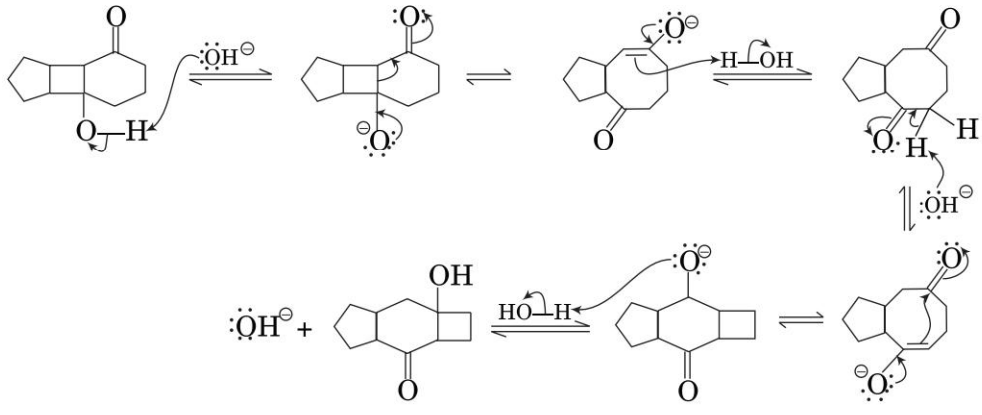
Solution The reaction proceeds through the steps (a retro-aldol followed by an aldol) as follows:



13. The following two ketones A and B can be readily interconverted upon treatment with base. Show how this interconversion takes place.

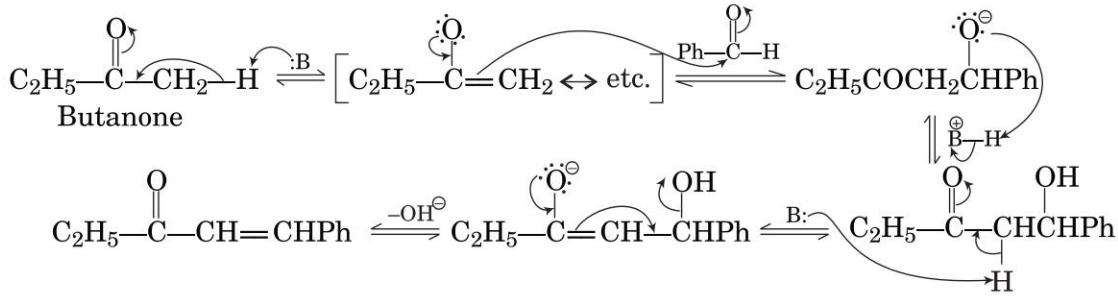


Solution This base-catalyzed isomerization takes place as follows:

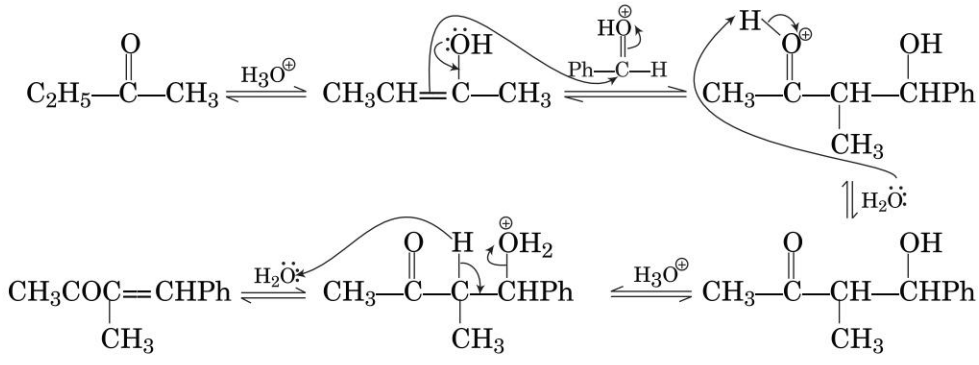


14. Benzaldehyde (PhCHO) reacts with butanone ($CH_3COCH_2CH_3$) in the presence of a base to yield $PhCH{=}CHCOCH_2CH_3$, but in the presence of acid to yield $PhCH{=}CH(CH_3)COCH_3$. Explain these observations.

Solution Base abstracts the more acidic primary hydrogen atom attached to C-1 ($\overset{1}{C}H_3\overset{2}{C}O\overset{3}{C}H_2\overset{4}{C}H_3$). The enolate ion, $:\overset{\ominus}{C}H_2COCH_2CH_3$, adds to PhCHO to give, after dehydration, $PhCH{=}CHCOCH_2CH_3$.



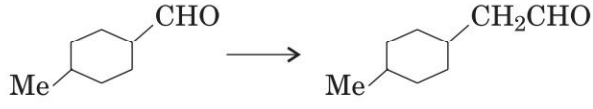
In the presence of acid, the thermodynamically more stable, i.e., the more substituted enol (with six hyperconjugable hydrogen) is formed predominantly. It adds to the protonated aldehyde ($PhCH{=}\overset{\oplus}{O}H$) to yield, after dehydration, $PhCH{=}C(CH_3)COCH_3$.



15. How would you carry out the following transformations?

(a) $PhCHO \rightarrow PhCH_2COPh$

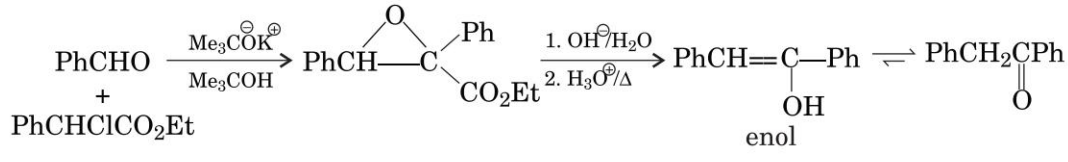
(b)



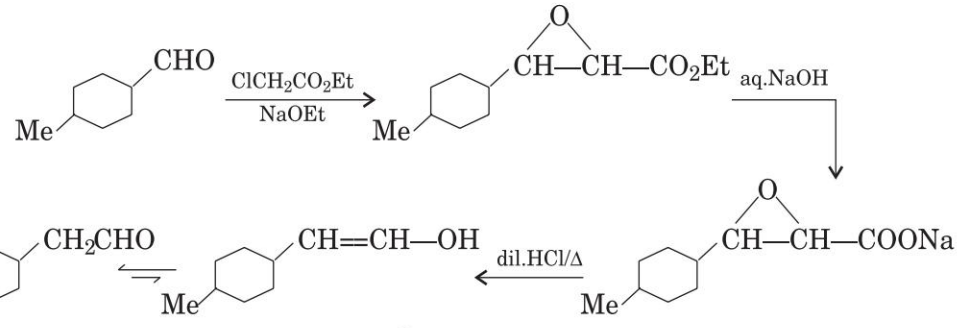
(c) $PhCHO \rightarrow PhCOCH_2COPh$

Solution

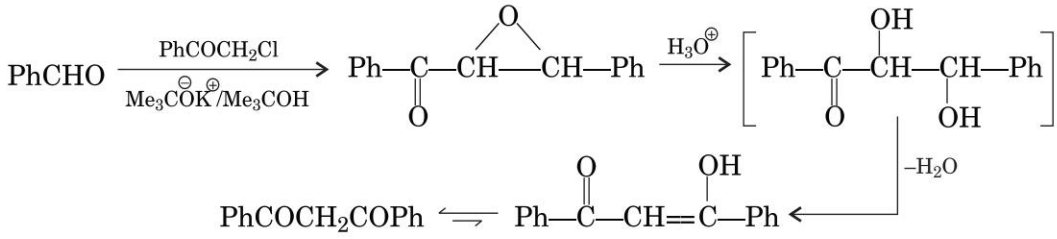
(a)



(b)

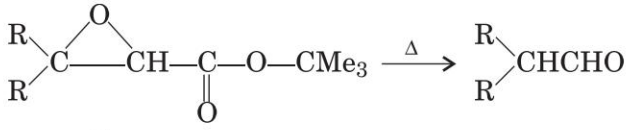


(c)

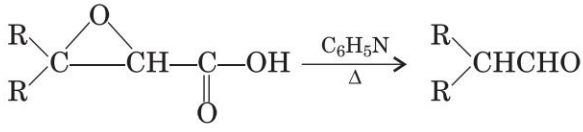


16. Suggest a mechanism for each of the following reactions:

(a)

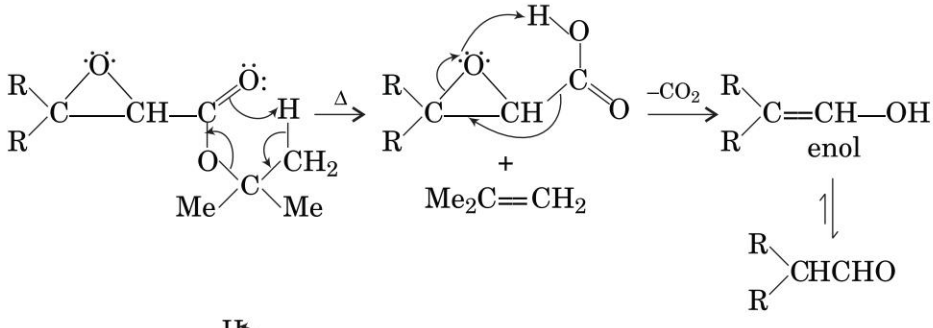


(b)

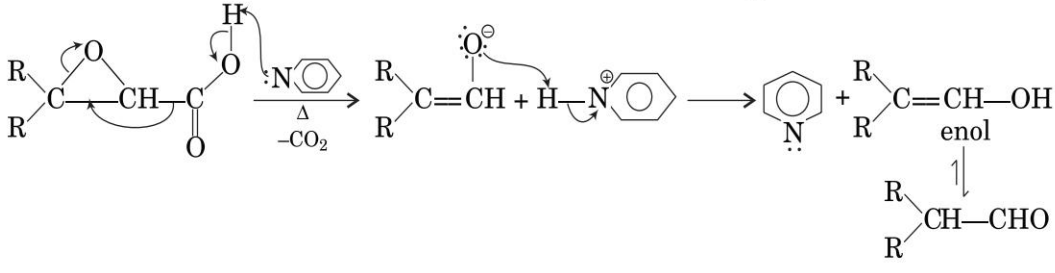


Solution

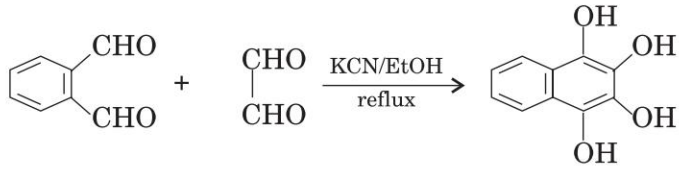
(a)

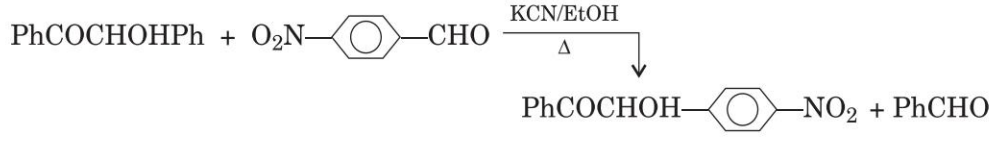


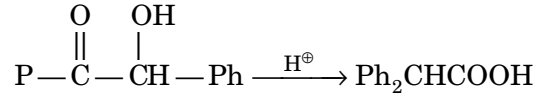
(b)



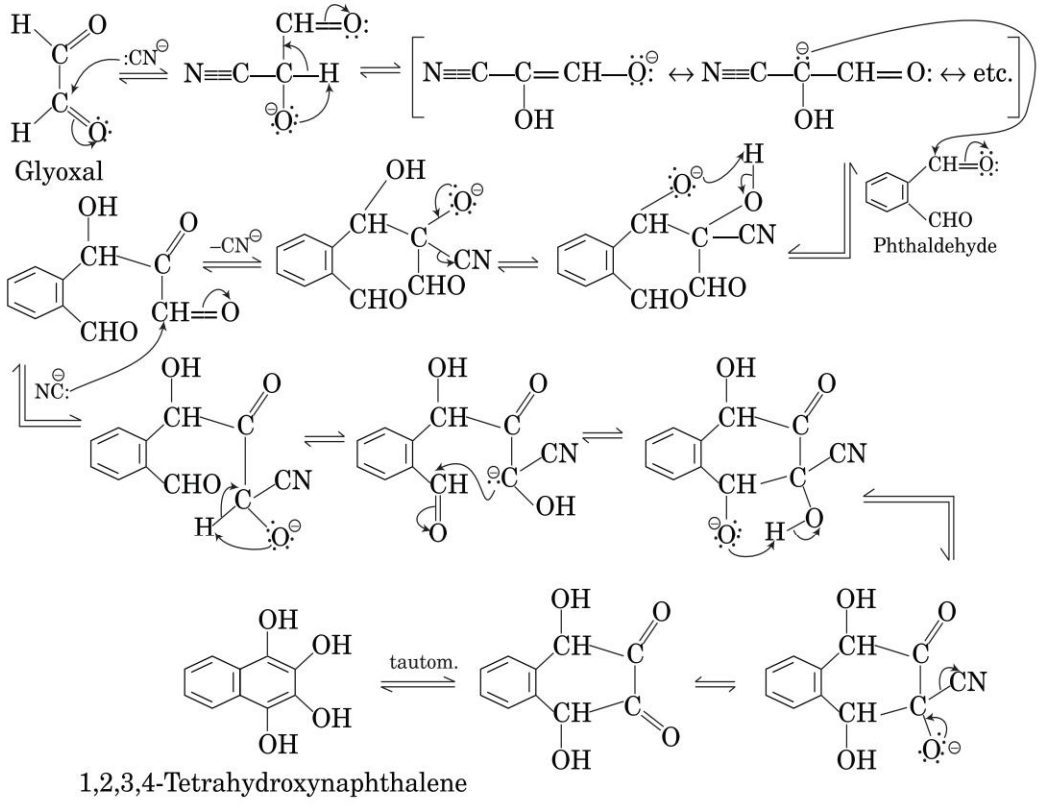
17. Suggest a mechanism for each of the following reactions:

(a) 

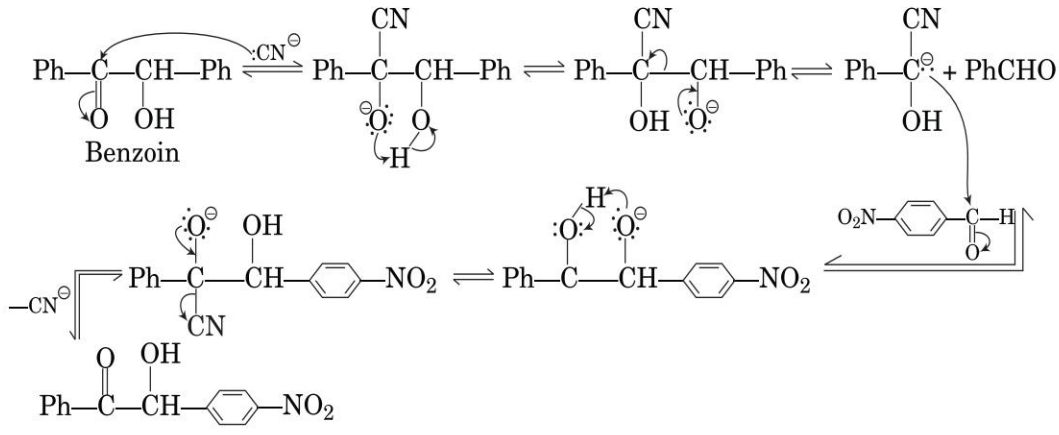
(b) 

(c) 

Solution

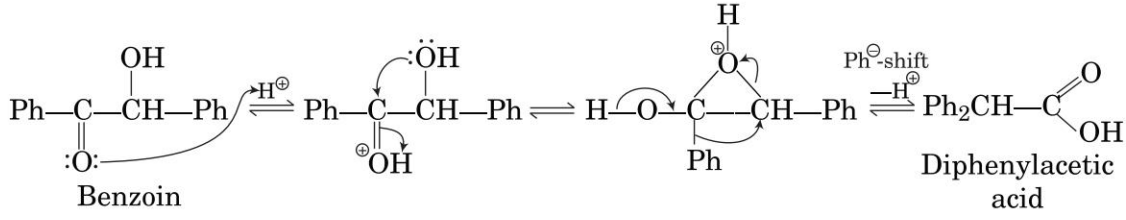
(a) 

(b)



Benzoin undergoes *retro* benzoin condensation in the presence of $CN^{\ominus}$ to yield benzaldehyde and a resonance-stabilized carbanion. The carbanion reacts with *p*-nitrobenzaldehyde to yield a new benzoin.

(c) Benzoin undergoes rearrangement in the presence of acid to yield diphenylacetic acid.



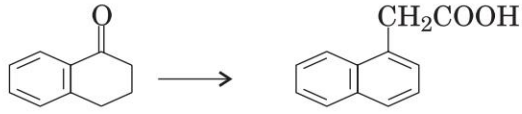
18. Benzaldehyde undergoes Cannizzaro reaction on treatment with $OH^{\ominus}$, but benzoin condensation when treated with $CN^{\ominus}$. Explain why this difference occurs. Clearly indicate the role of $CN^{\ominus}$ in benzoin condensation.

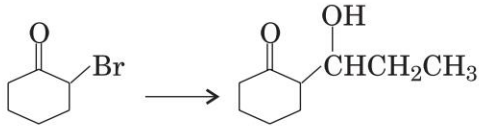
Solution The hydrogen atom attached to carbon in the intermediate $PhCH(OH)O^{\ominus}$ is not acidic and leaves the system as $H^{\ominus}$. On the other hand, the H-atom attached to carbon in the intermediate $PhCH(CN)O^{\ominus}$ is acidic and migration of this carbon to the anionic oxygen atom occurs to form a carbanion (i.e., it is a case of proton transfer) which is resonance-stabilized by both –Ph and –CN groups. Therefore, –CN plays a vital role in increasing the acidity of hydrogen in $PhCH(CN)O^{\ominus}$ ion.

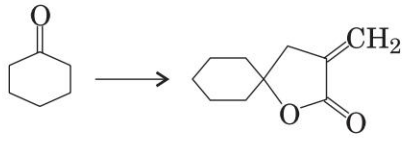
19. Explain why *β*-hydroxy esters can be prepared by the Reformatsky reaction but not by the Grignard reaction.

Solution Organozinc compounds are relatively less reactive than organomagnesium compounds or Grignard reagents. So, unlike Grignard reagents the organozinc compounds do not react with the ester group, i.e., the self-condensation reaction does not take place. It is for this reason, *β*-hydroxy esters can be prepared by the Reformatsky reaction but not by the Grignard reaction.

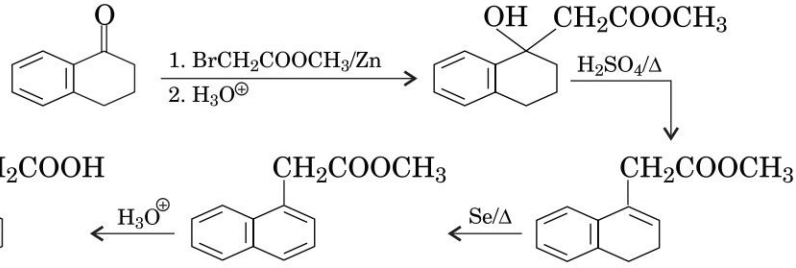
20. How would you carry out the following transformations?

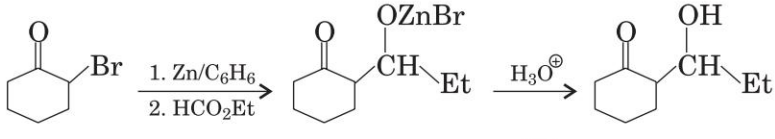
(a) 

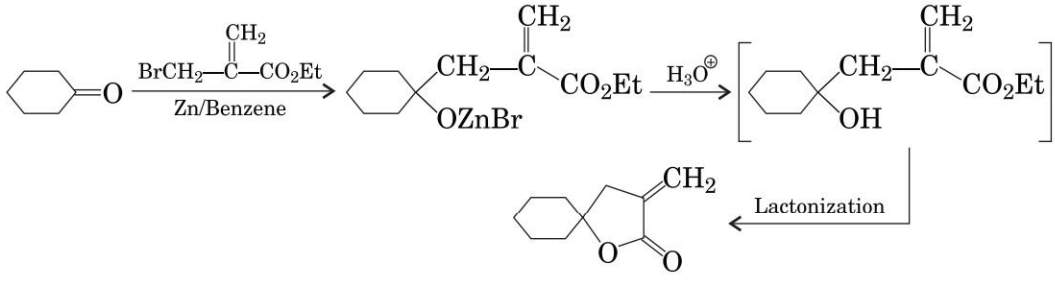
(b) 

(c) 

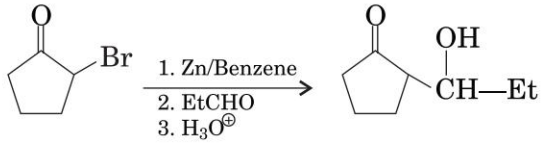
Solution

(a) 

(b) 

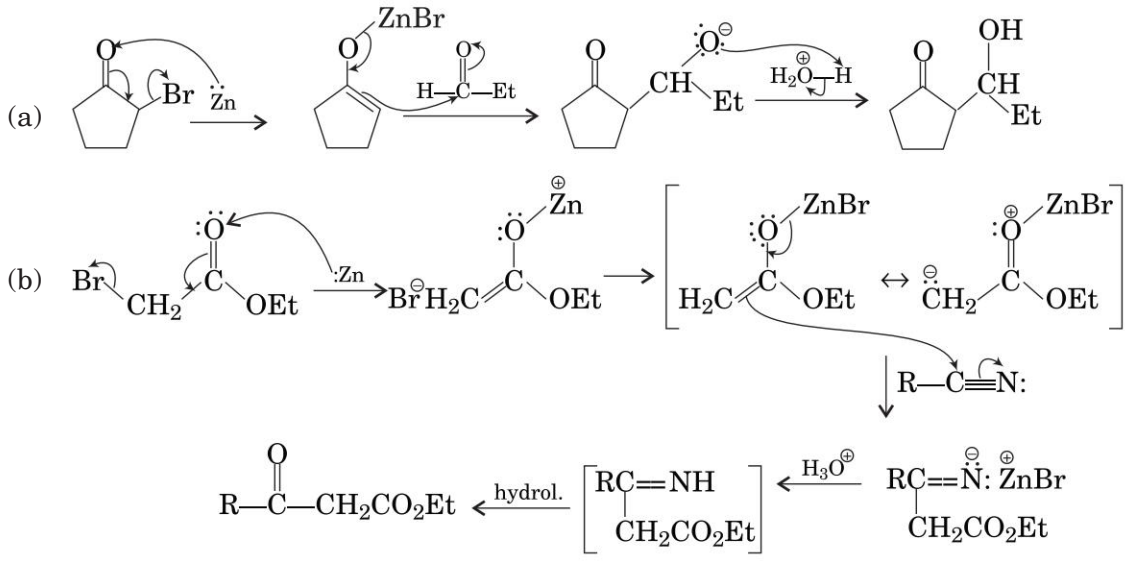
(c) 

21. Suggest a mechanism for each of the following reactions:

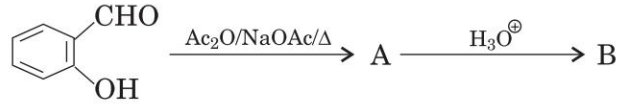
(a) 

(b) $RC{\equiv}N + BrCH_2CO_2Et \xrightarrow[2.\ H_3O^{\oplus}]{1.\ Zn/ether} R—C(=O)—CH_2CO_2Et$

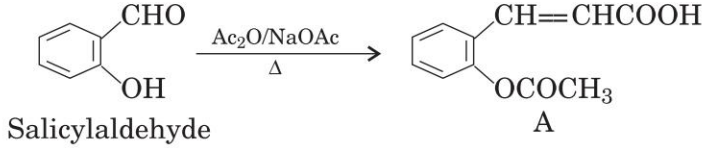
Solution



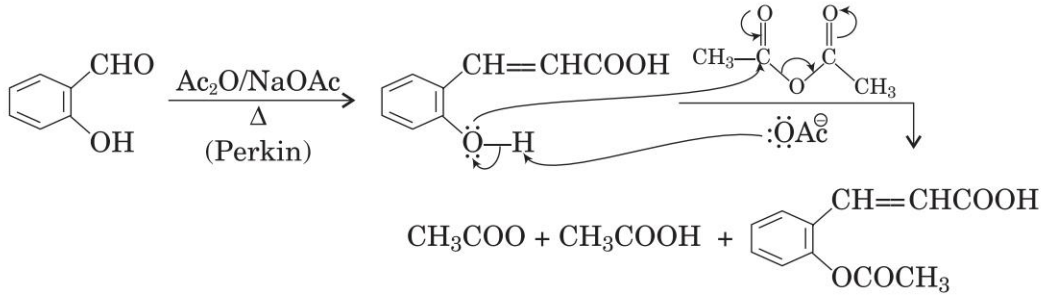
22. Identify the products A and B in the following reaction sequence and give mechanism for their formation:



Solution In the first step, salicylaldehyde undergoes Perkin reaction and simultaneous acetylation of the phenolic —OH group to yield the α,β-unsaturated acid A.

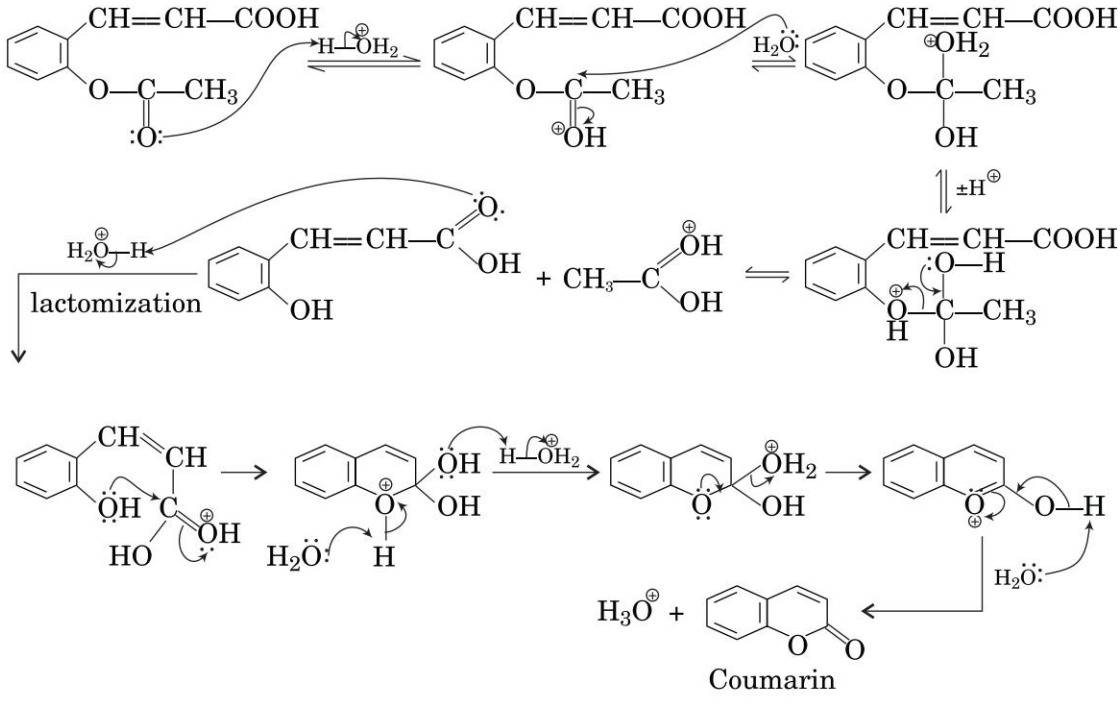


Mechanism:

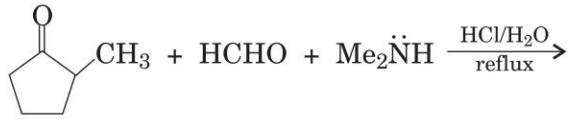


For the mechanism of Perkin reaction see **article no. 2.8.6.**

When A is treated with dilute acid, it undergoes hydrolysis ($A_{Ac}2$ mechanism) followed by ring closure (lactonization) to yield the lactone B known as coumarin.

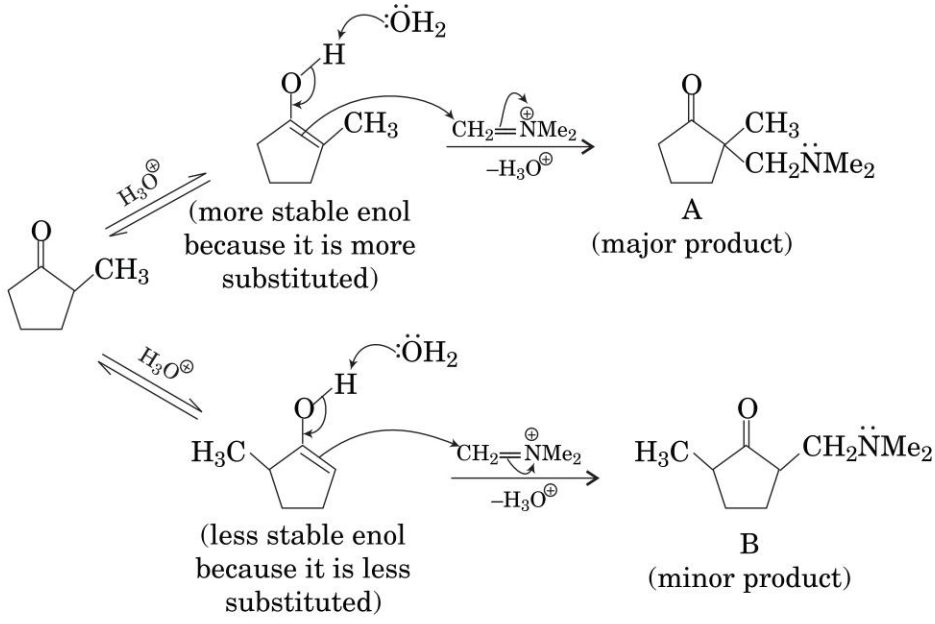


23. Predict the major product of the following reaction and provide a mechanism that accounts for its formation:



2-Methylcyclopentanone

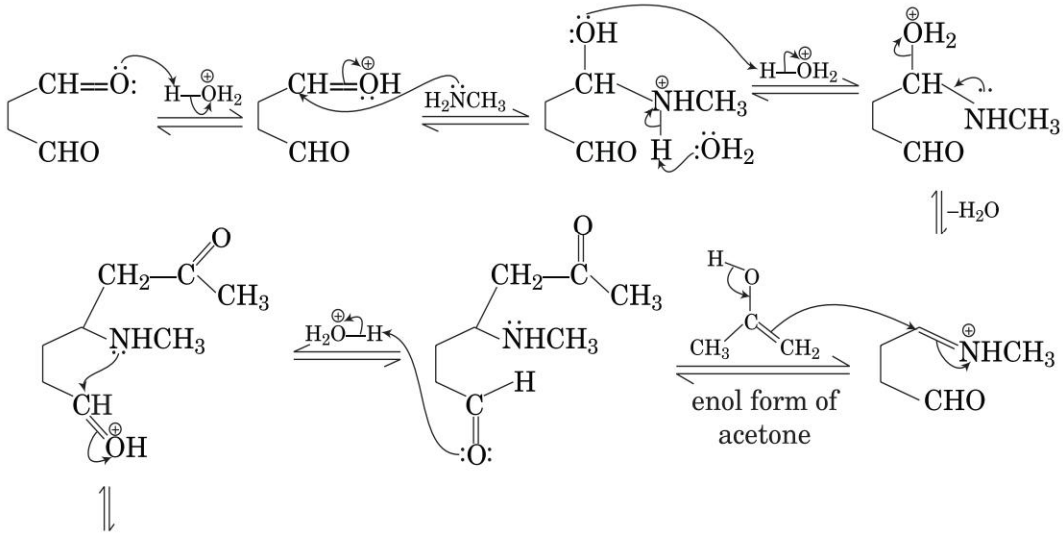
Solution The more substituted enol is thermodynamically more stable and therefore, predominates in the equilibrium mixture. This unsymmetrical ketone thus reacts with the iminium ion mainly through the more substituted enol to give the Mannich base A as the major product and the Mannich base B as the minor product.

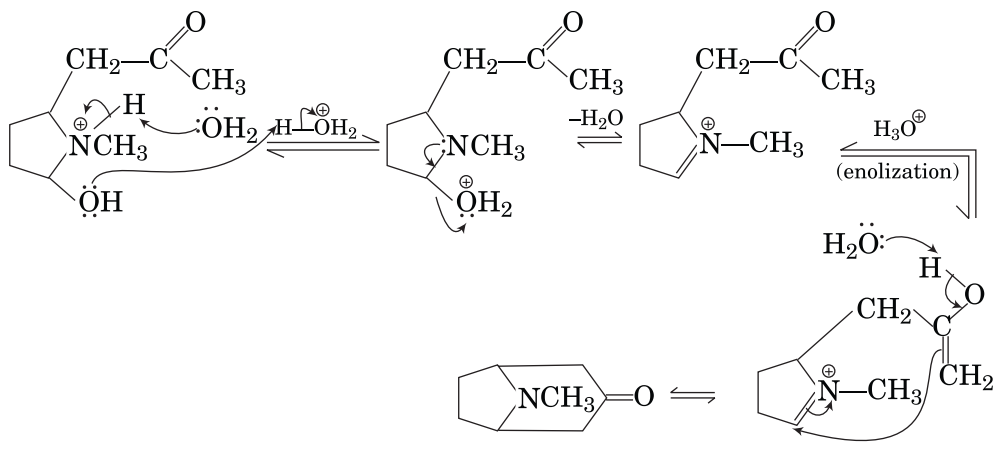


24. Write a curved-arrow mechanism for the following reaction:



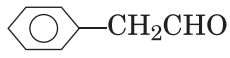
Solution

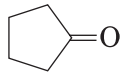




Study Problems

1. Predict the products of the following reactions and suggest mechanism that account for their formation:

(a) 2  $\xrightarrow{\text{dil.NaOH}}$

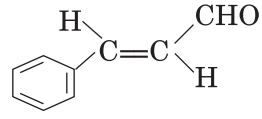
(b) 2  $\xrightarrow{\text{dil.NaOH}}$

(c) $(CH_3)_3CCHO + CH_3-C(=O)-C_6H_4-CH_3 \xrightarrow{\text{dil.NaOH}}$

2. The acid-catalyzed aldol condensation of acetone produces some 2,6-dimethylhepta-2,5-dien-4-one in addition of 4-methylpent 3-en-2-one. Give a mechanism that explains the formation of the dienone.

3. Show all the aldol addition products formed by the reaction of propanal with butanal in aqueous base.

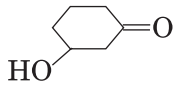
4. Cinnamaldehyde is used as a flavouring agent in cinnamon candies. Show how can cinnamaldehyde be synthesized by a crossed aldol reaction.

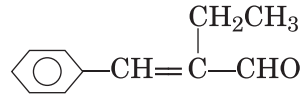


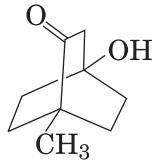
Cinnamaldehyde

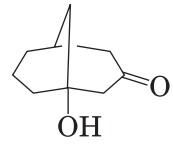
[**Hint:** CH_3CHO is added slowly to a 10% solution of PhCHO and then the mixture is heated.]

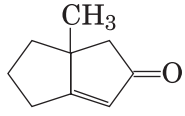
5. What starting material/materials is/are needed to prepare each compound by an aldol reaction?

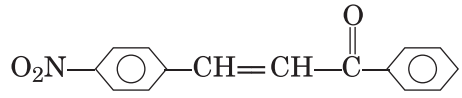
(a) 

(b) 

(c) 

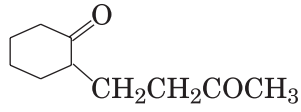
(d) 

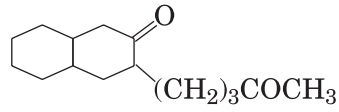
(e) 

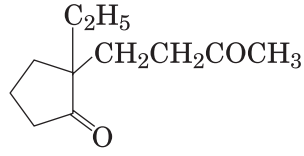
(f) 

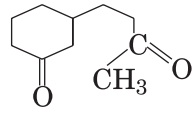
[**Hint:** The α and β carbons of the carbonyl group to be located and the molecule is to be broken into two components between the α and β carbons.]

6. Give the product expected to be obtained when each of the following compounds is treated with base:

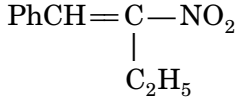
(a) 

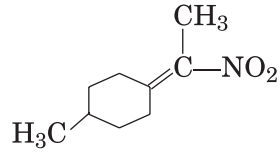
(b) 

(c) 

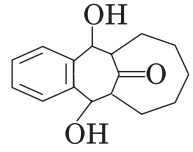
(d) 

7. Show how you would synthesize each of the following:

(a) 

(b) 

(c) $HOCH_2CH_2NO_2$

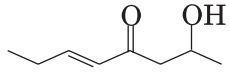
(d) 

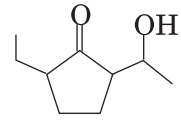
8. What experimental conditions would favour the cyclization process in an intramolecular aldol reaction over an intermolecular aldol reaction. Compare the ΔS for these two fashions of aldolization.

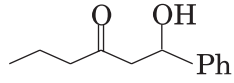
[**Hint:** A very dilute solution of the compound to be cyclized is to be used. When a 'high dilution technique' is followed, the probability is greater, one end of a

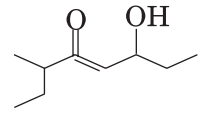
molecule will react with the other end of the same molecule rather than with a different molecule.]

9. Starting with ketones and aldehydes of your choice, outline a directed aldol synthesis of each of the following compounds using lithium enolates:

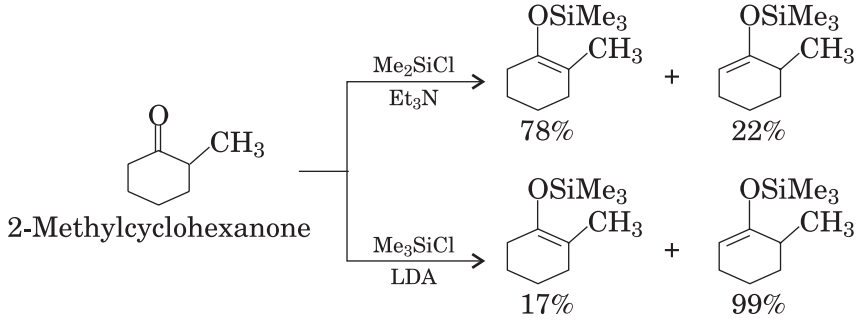
(a) 

(b) 

(c) 

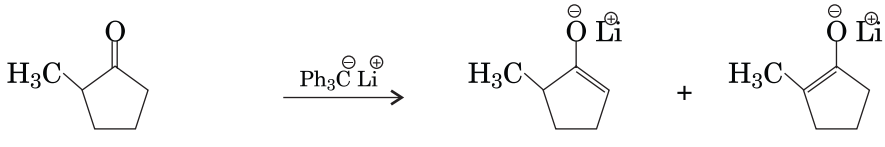
(d) 

10. Explain the following observations:



[**Hint:** A thermodynamic enolate is formed predominantly in the presence of the relatively weak base Et_3N. On the other hand, a kinetic enolate is formed predominantly in the presence of the strong and sterically hindered base LDA (lithium diisopropylamide).]

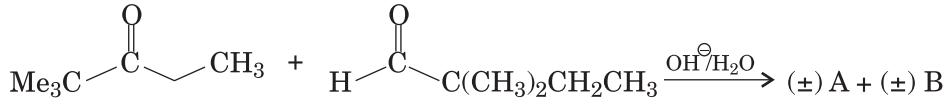
11. When 2-methylcyclopentanone is treated with the sterically hindered base $Ph_3\overset{\ominus}{C}L\overset{\oplus}{i}$ (triphenylmethyllithium) under the two sets of conditions, as shown below, the two possible enolates are formed in different ratios. Account for these observations.



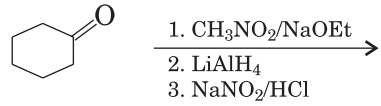
Condition I:	Ketone is added to excess base	72%	28%
Condition II:	Excess ketone is added to base	6%	94%

[**Hint:** To consider the principles of kinetic versus thermodynamic control.]

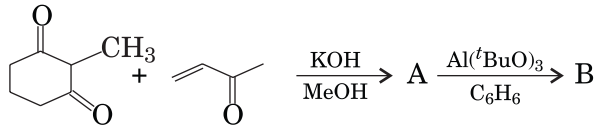
12. Account for the formation of two diastereoisomeric products (A and B) in the following crossed aldol reaction:



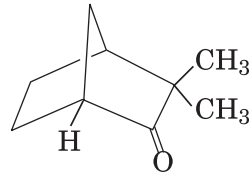
13. Analyze the following reaction:



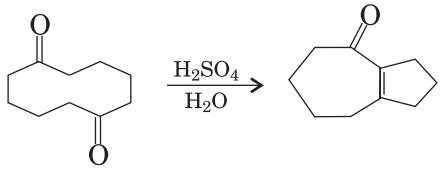
14. Complete the following with explanation:

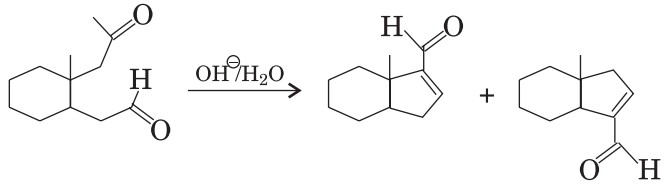


15. Explain why the following compound does not undergo base-catalyzed exchange in D_2O even though it has an α-H atom.

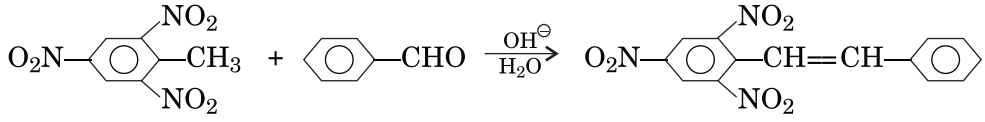


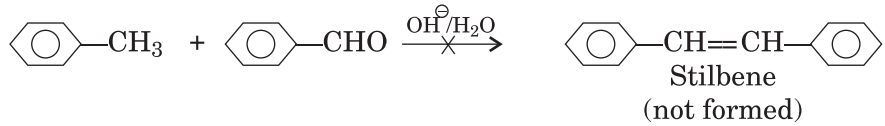
16. Provide a mechanism for each of the following transformations:

(a) 

(b) 

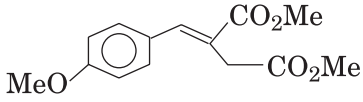
17. Explain the following observations:

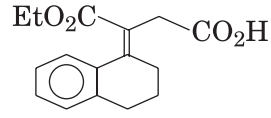
(a) 

(b) 

Stilbene
(not formed)

18. How can you synthesize the following compound using Stobbe condensation?

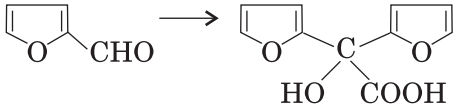
(a) 

(b) 

19. Explain why *m*-nitrobenzaldehyde undergoes benzoin condensation but *p*-nitrobenzaldehyde does not.

20. When the benzoin $Ar^1CHOHCOAr^1$ is heated with an aldehyde Ar^2CHO in the presence of alcoholic KCN, a mixed benzoin $Ar^2CHOHCOAr^1$ is obtained. Explain this observation.

21. How would you carry out the following transformations, using benzoin condensation in one of the steps?

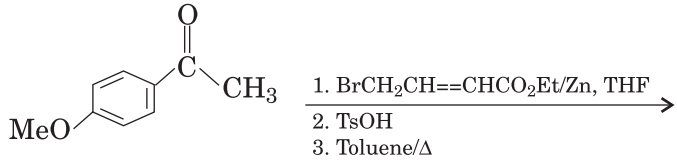
(a) 

(b) $PhCHO \rightarrow Ph-C\equiv C-Ph$

22. Unlike *p*-nitrobenzaldehyde, *o*-nitrobenzaldehyde undergoes benzoin condensation. Explain.

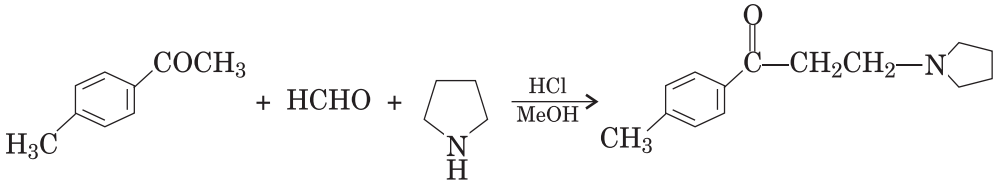
[**Hint:** In the case of *o*-isomer, steric inhibition of resonance occurs and this makes the anionic carbon of $o-O_2NC_6H_4\overset{\ominus}{\ddot{C}}(OH)CN$ a stronger nucleophile (i.e., makes it able to act as a donor) than that of the *p*-isomer.]

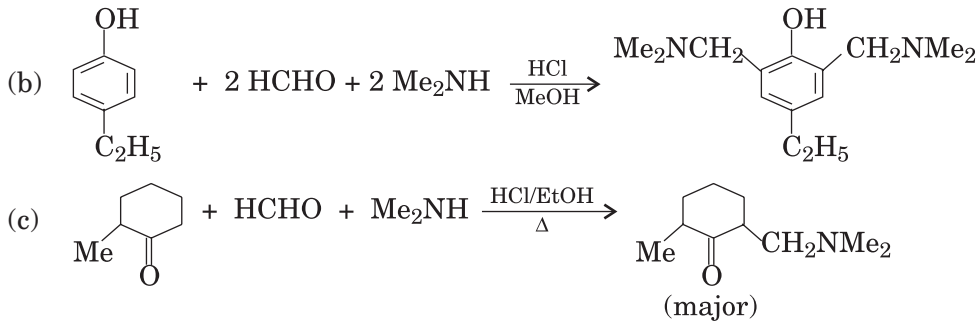
23. Predict the product and suggest a reasonable mechanism for the following reaction:



24. In Knoevenagel condensation, a catalytic amount of carboxylic acid is often used if a secondary amine is used as a base – Why?

25. Draw stepwise, detailed mechanisms that account for the formation of the following Mannich bases:

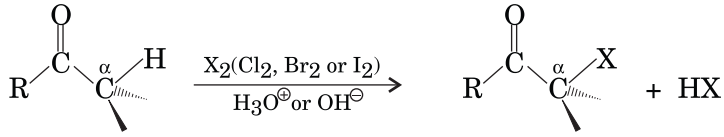
(a) 



2.9 REACTIONS AT THE α-CARBON OF CARBONYL COMPOUNDS OF ALDEHYDES AND KETONES

2.9.1 Halogenation at the α-carbon of aldehydes and ketones

When an aldehyde or a ketone is treated with halogen in the presence of acid or base, substitution of X for H on the α-carbon takes place and this results in formation of an α-halo aldehyde or ketone. Halogenation readily occurs with Cl_2, Br_2 and I_2.



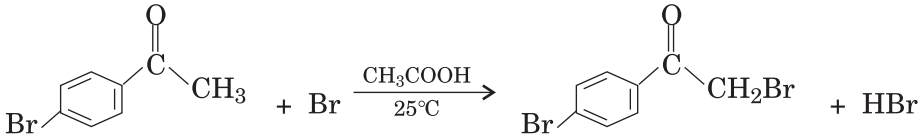
An aldehyde or a ketone R = H or alkyl)

An α-halo aldehyde or ketone

In this reaction, one electrophile ($X^{\oplus}$) is substituted for another (H^+) on the α-carbon.

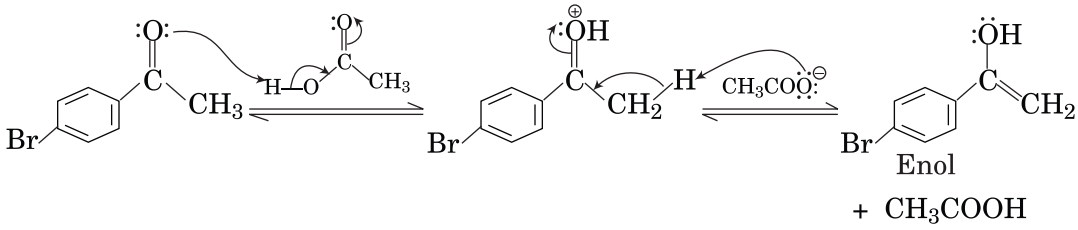
2.9.1.1 Acid-catalyzed halogenation at the α-carbon

Halogenation is often carried out by treating a carbonyl compound with a halogen in acetic acid. In this case, acetic acid acts as both the solvent and the acid catalyst for the reaction. For example:

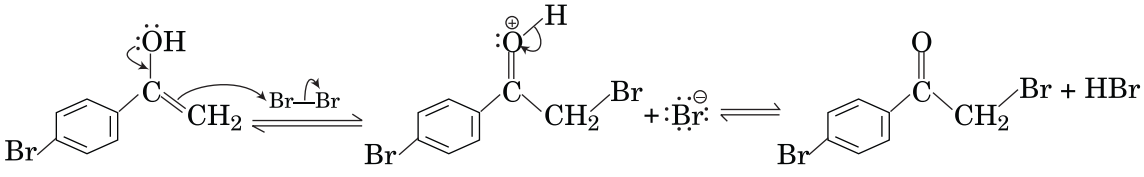


Mechanism of the reaction The mechanism of the reaction consists of two parts: slow tautomerization of the ketone to form the corresponding enol followed by rapid reaction of the enol with the halogen.

Part 1: The ketone is converted into its tautomer by the two-step process involving protonation of the carbonyl oxygen followed by deprotonation of the α-carbon atom (the rate-determining step).



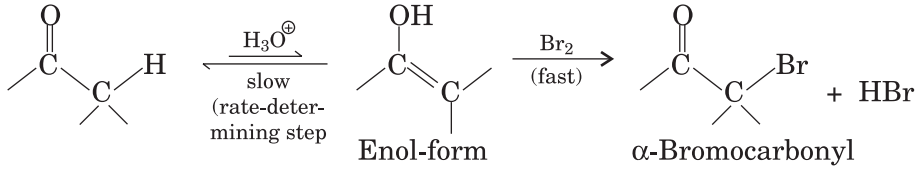
Part II: The enol is converted into α-haloketone by the two-step process involving the addition of the halogen to the enol followed by deprotonation.



Critical views Acid-catalyzed halogenation is, in fact, a particularly instructive case study that shows the importance of the rate law in determining the mechanism of the reaction. The rate law of acid catalyzed halogenation, under usual conditions, has been found to be

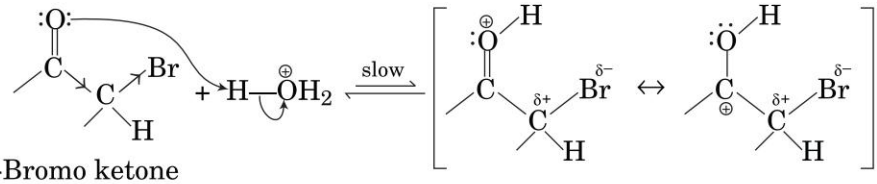
$$\text{rate} = k[\text{ketone}]\ [H_3O^{\oplus}]$$

This rate law suggests that even though it is a halogenation reaction, *the rate is independent of the halogen concentration*. That is, halogen cannot be involved in the transition state of the rate-determining step of the reaction. From this observations and others, it becomes clear that the formation of enol is the rate-determining step in acid-catalyzed halogenation of aldehydes and ketones. Since the halogen is not involved in the formation of enol, it does not appear in the rate law.



The formation of enol consists of two steps. It is the second step (loss of the α-proton) which is actually the rate-limiting step of acid-catalyzed enolization.

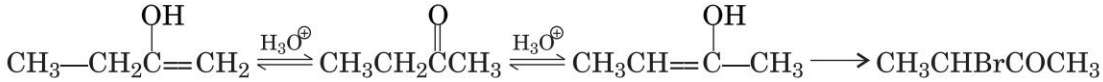
Only one halogen atom is introduced at a given α-carbon in acidic solution. It thus follows that the introduction of a second halogen atom is much slower than the introduction of the first. This is due to the fact that the enol formation itself is slowed by the introduction of the first halogen. The introduced halogen atom inductively withdraws electrons and disfavours the first step in enol formation, i.e., the protonation of the carbonyl oxygen.



α-Bromo ketone (protonation is disfavoured by the –I effect of Br)

The dipole in C–Br bond destabilizes the protonated carbonyl and makes it difficult to form

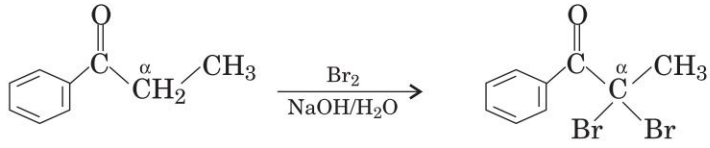
It is to be noted that bromination of an unsymmetrical ketone like butanone ($CH_3COCH_2CH_3$) occurs through the formation of the thermodynamic enolate and consequently, it is the nonterminal α-carbon which undergoes bromination.



Kinetic enlote (minor) | Butanone | Thermodynamic enolate (majore)

2.9.1.2 Base-promoted halogenation

Halogenation at the α-carbon in the presence of base takes place through slow formation of an enolate (or enol) followed by a rapid reaction of the enolate (or enol) with halogen (X_2). Halogenation in base is relatively less useful because it is difficult to stop the reaction after the introduction of one halogen atom at the α-carbon. For example, when propiophenone is treated with Br_2 and aqueous NaOH, a dibromo ketone in obtained by the replacement of both α-Hs.

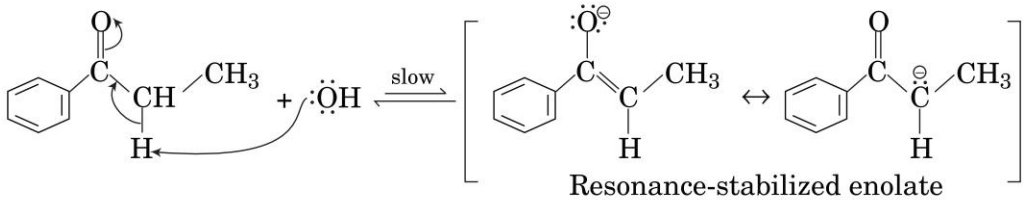


Propiophenone | α,α-Dibromopropiophenone

This reaction is called *base-promoted* instead of *base-catalyzed*, because a full equivalent of the base is consumed in the reaction.

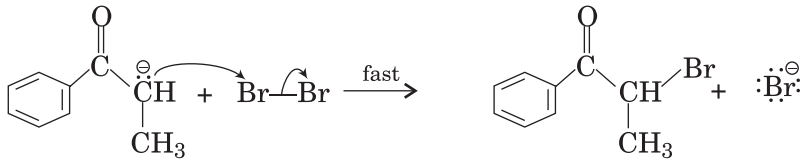
Mechanism of the reaction The mechanism of the reaction involves the steps as follows:

Step 1: Deprotonation of the carbonyl compound by the base to form an enolate.

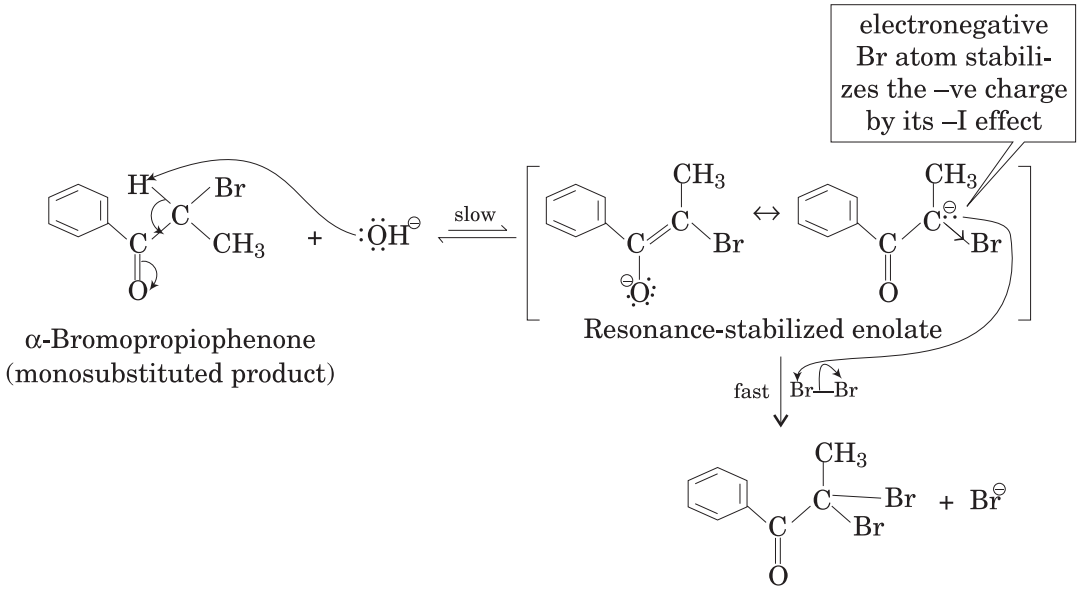


Resonance-stabilized enolate

Step 2: The nucleophilic enolate reacts with Br_2 (the electrophile) to form the monosubstitution product.



That it is difficult to stop the reaction after addition of one Br atom is due to the fact that the electron-attracting inductive effect or Br stabilizes the second enolate. As a result, the α-H atom of α-bromopropiophenone becomes more acidic than the α-H atoms of propiophenone, making it easier to be removed by the base. Therefore, the second bromine atom is readily introduced by the same two steps, i.e., deprotonation followed by nucleophilic attack.

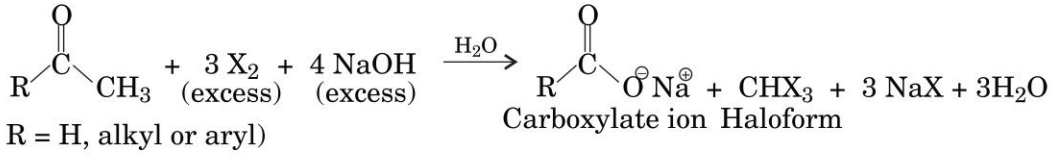


α-Bromopropiophenone
(monosubstituted product)

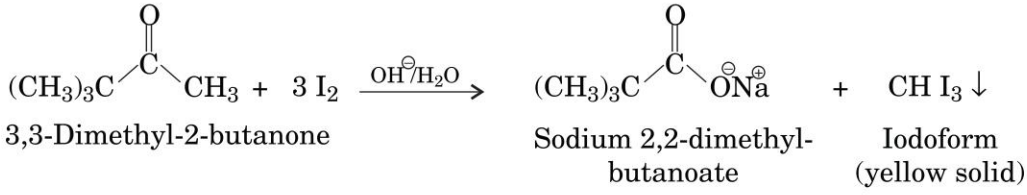
α,α-Dibromopropiophenone
(disubstituted product)

These two steps are repeated until all the α-hydrogens, for example, of a methyl ketone ($R—COCH_3$) are replaced by halogen. Each successive halogenation is more rapid than the previous one because the electron-attracting halogens atom increases the acidity of the remaining α-hydrogens. It is for this reason, all of the α-hydrogens are replaced by halogens.

Haloform reaction When acetaldehyde (CH_3CHO) or a methyl ketone ($R\ COCH_3$) is treated with excess halogen (X_2; X = Cl, Br or I) in the presence of excess base ($OH^{\ominus}$), a carboxylate ion ($HCOO^{\ominus}$ or $RCOO^{\ominus}$) and a haloform, i.e., either chloroform ($CHCl_3$), or bromoform ($CHBr_3$) or iodoform (CHI_3) are produced. This reaction producing haloform (CHX_3) is known as the haloform reaction.



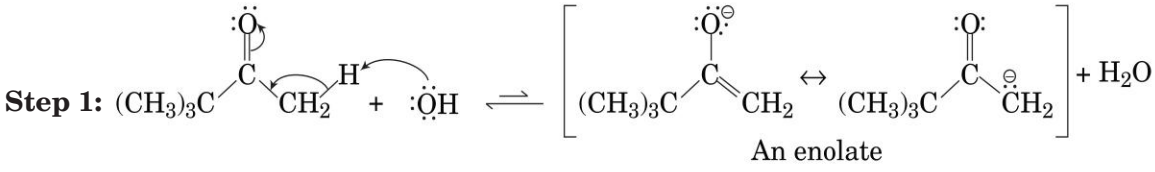
Example:



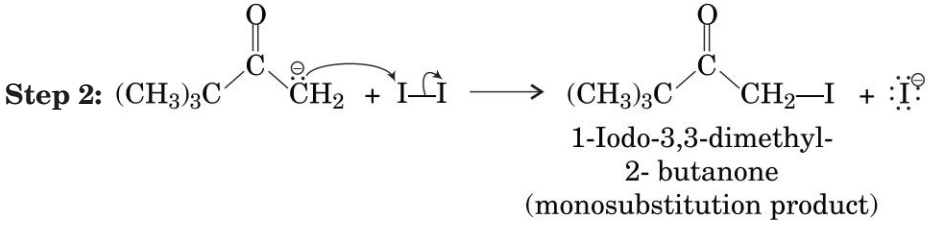
Mechanism of the reaction The mechanism of the reaction consists of two parts:

Part I: The three H atoms of the $—CH_3$ group are replaced by iodine via the two-step mechanism. In step 1, deprotonation of the methyl group by base occurs to form a nucleophilic enolate and in step 2, the enolate reacts with iodine to form the substitution product.

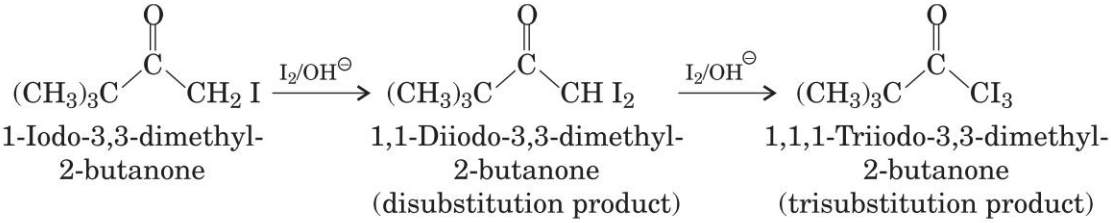
Step 1:



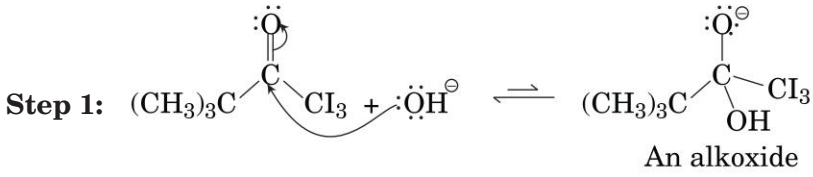
Step 2:

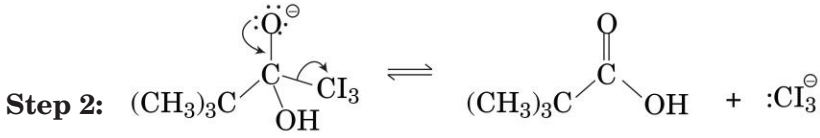


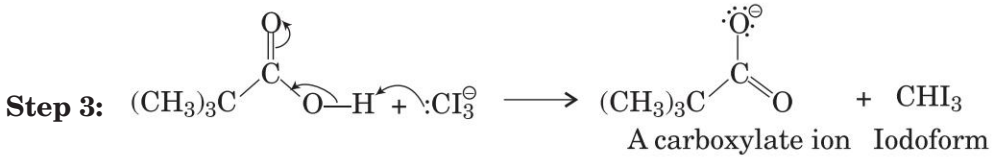
These two steps are then repeated twice more to form the triiodo substitution product.



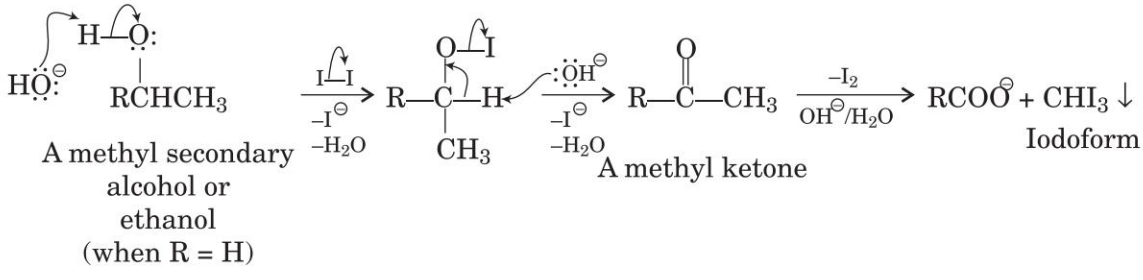
Part II: The resulting trihalo carbonyl compound (not isolated) undergoes a nucleophilic acyl substitution reaction. This involves three steps. In step 1, $OH^{\ominus}$ adds to the carbonyl group of the ketone (a typical nucleophilic addition). In step 2, the resulting alkoxide being unstable readily undergoes C—C bond cleavage by the loss of $:CI_3^{\ominus}$ (a good leaving group) and in step 3, the carbanion takes up a proton from the carboxylic acid to form iodoform and the carboxylate ion (the stabler pair).





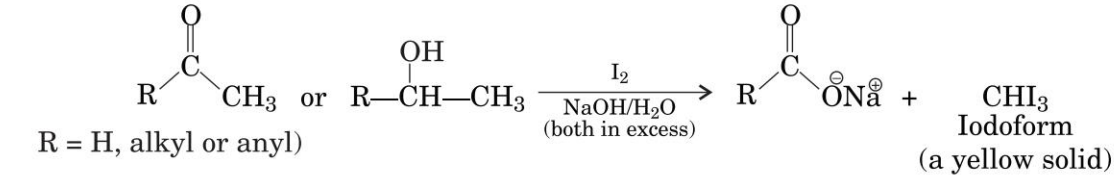


It is to be noted that the compounds containing the $-CHOHCH_3$ group gives a positive iodoform test. This is due to the fact that such compounds are first oxidized to methyl ketones by halogen in the presence of alkali. These methyl ketones then react with I_2/NaOH to yield iodoform.

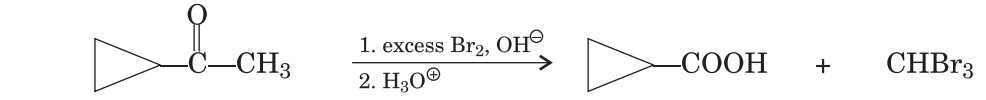


Applications of the reaction The two important applications of the Haloform reaction are as follows:

(i) Because iodoform (CHI_3) is a highly insoluble, bright yellow solid, the haloform reaction involving iodine and aqueous sodium hydroxide (the so-called iodoform test) is a useful method for identification of compounds containing $—COCH_3$ or $—CHOHCH_3$ group.

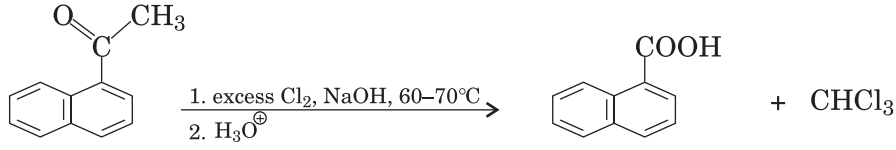


(ii) The haloform reaction is synthetically useful as a means of converting methyl ketones to carboxylic acids (particularly when the methyl ketone is relatively more available than the corresponding carboxylic acid). For example:



Cyclopropyl methyl ketone | Cyclopropane carboxylic acid (55%) | Bromoform (liquid)

The reaction is used to prepare aromatic acids where strong oxidising agents like CrO_3/AcOH destroy the aromaticity of the ring containing the $—COCH_3$ or $—CHOHCH_3$ group. For example:

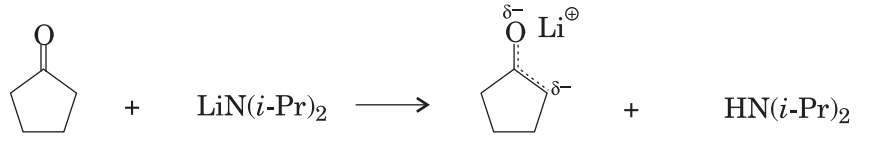


1-Naphthyl methyl ketone | α-Naphthoic acid | Chloroform (liquid)

When the haloform reaction is used in synthesis, chlorine and bromine are most commonly used as the halogen (X_2). This is because chloroform ($CHCl_3$) and bromoform ($CHBr_3$) are both liquids and can be easily separated from the aqueous solution containing the carboxylate ion.

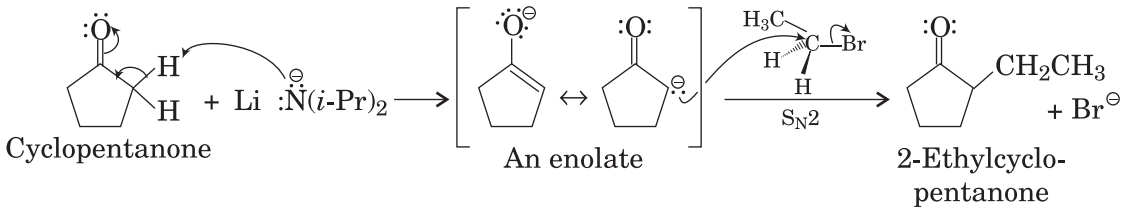
2.9.2 Alkylation at the α-carbon of Aldehydes and Ketones

Putting an alkyl group at the α-carbon of an aldehyde or a ketone is synthetically an important reaction because it provides another way to form a C—C bond. The alkylation is carried out by first removing a proton from the α-carbon with a very strong base to form an enolate and then allowing the enolate to react with an appropriate alkyl halide. When a very strong base like LDA (lithium diisopropylamide) is used, the equilibrium lies far to the right, i.e., the carbonyl compound is converted to the corresponding enolate nearly exclusively. For example:



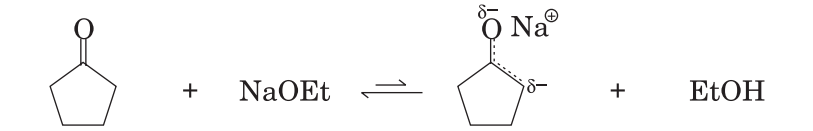
Ketone (stronger acid) $pK_a = 19$ | LDA (stronger base) | Enolate (weaker base) | Diisopropylamine (weaker acid) $pK_a = 36$

Since the reaction between the enolate and the alkyl halide is an S_N2 one, methyl and primary alkyl halides are to be used for alkylation because of steric reason. 2-Ethylcyclopentanone, for example, can be prepared as follows:



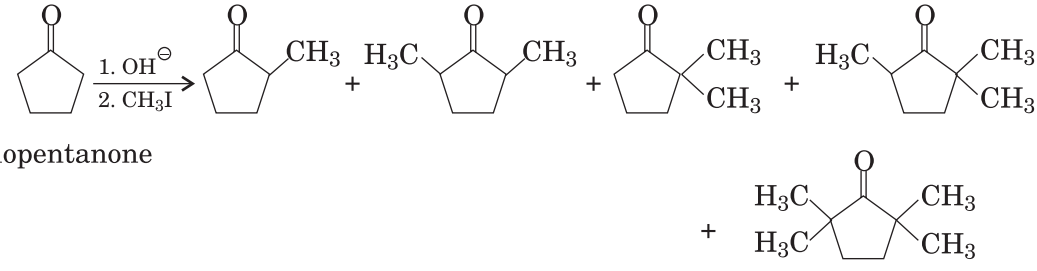
Because the enolate has two nucleophilic sites (the oxygen and the α-carbon), it can react at either of these two sites. However, it turns out that most enolates are better nucleophiles at carbon. So, alkylation takes place faster at carbon than at oxygen. One reason for this fact is that the highest occupied molecular orbital of the nucleophile enolate has more electron density at the carbon than at oxygen. The selectivity may also be a result of counter ion (e.g., Li) coordination between the enolate and the electrophile. Since the counter ion is complexed with oxygen, the site of higher electron density, alkylation at oxygen, becomes sterically hindered.

When a weaker base (weaker than enolate) such as hydroxide ion ($:\ddot{O}H^{\ominus}$) or an alkoxide ion ($R\ddot{O}:^{\ominus}$) is used, a very small amount of the desired monoalkylated compound is produced. Actually, these weaker bases form only a small amount of enolate ion at equilibrium. The equilibrium lies far to the left. For example:



Weaker acid ($pK_a = 19$)	Weaker base	Stronger base	Stronger acid ($pK_a = 16$)

Therefore, after the monoalkylation stage, there is still a large amount of base present in solution. The unreacted base can form enolate ion from the monoalkylated ketone as well as from the starting ketone. As a result of this, di-, tri- and even some *tetra*-alkylated ketone may be formed.

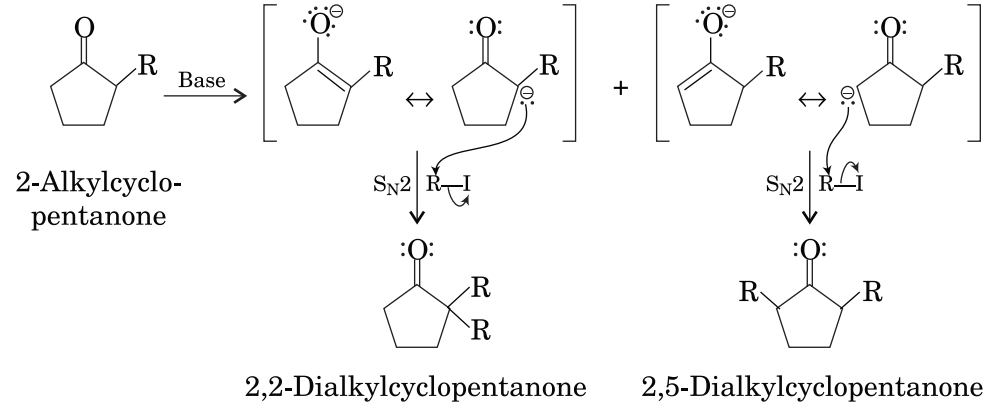


Furthermore, these strongly nucleophilic bases give side reactions with the alkyl halide. LDA avoids these side reactions. Because it is a much stronger base, LDA converts the ketone entirely to its enolate. All the LDA is consumed in enolate formation leaving the enolate to react without interference from the LDA. Also, LDA is a very bulky base and

thus a poor nucleophile, so it generally remains unreactive towards the alkyl halide. For this reason, typical bases such as sodium hydroxide or an alkoxide ion cannot be used to form enolates for alkylation.

2.9.2.1 Regioselective formation of enolates and alkylation of unsymmetrical ketones

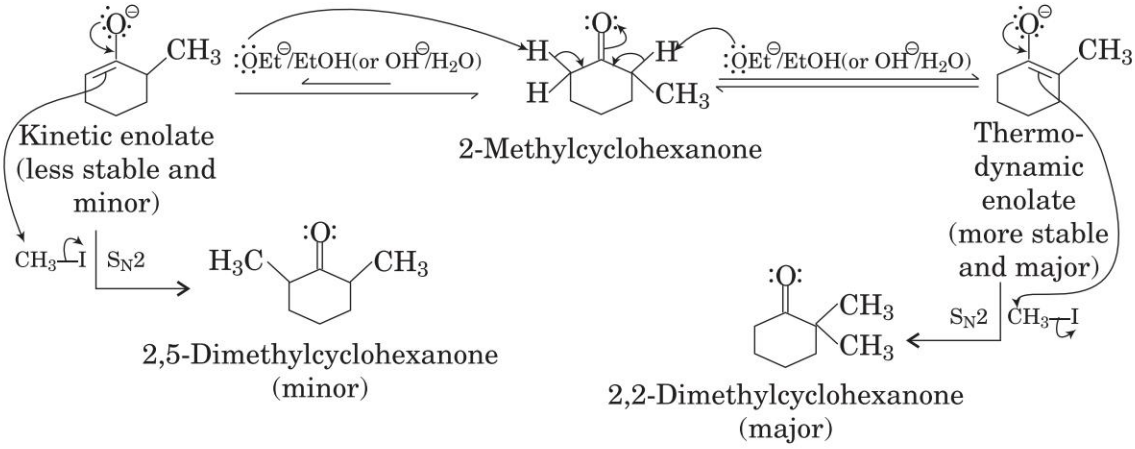
If the ketone used for alkylation via enolate formation is unsymmetrical and has hydrogen on both the α-carbons, two monoalkylated products are expected to be obtained because either α-carbon can undergo alkylation. For example, when alkylation of 2-alkylcyclopentanone is carried out with one equivalent of akyl iodide, both 2,5-dialkylcyclohexonone and 2,2-dialkylcyclopentanone are formed.



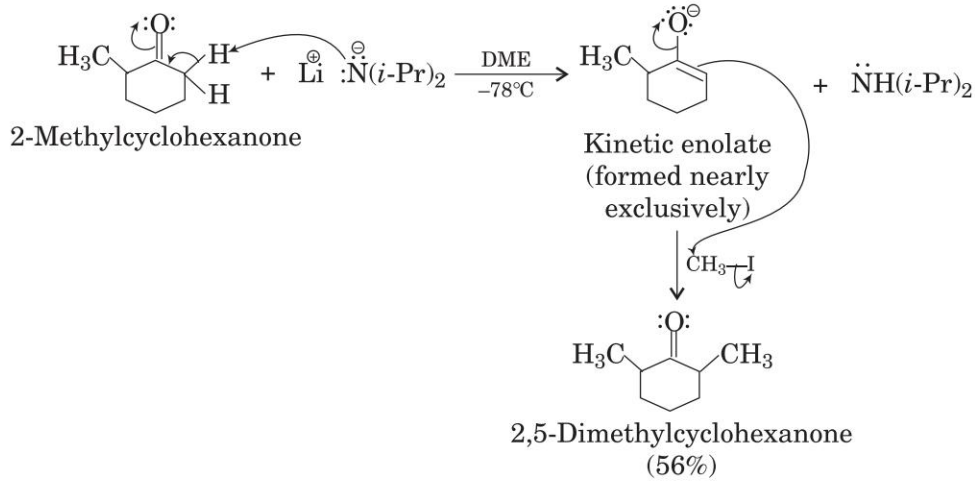
The relative amounts of the two products depend on which enolate actually predominates and that actually depends on whether the enolate is formed under conditions of thermodynamic control (an acid-base equilibrium is favoured) or under conditions of kinetic control (equilibrium is disfavoured).

The thermodynamic enolate is that which is the most stable (i.e., most highly substituted) among the possible enolates. The thermodynamic enolate predominates under conditions of thermodynamic control where interconversion among possible enolates occurs via a deprotonation-protonation equilibrium and that causes the more stable enolate to exist in higher concentration. The formation of the thermodynamic enolate is favoured by using hydroxide or an alkoxide in a protic solvent. The enolate ion leading to 2,2-dialkylcyclopentanone is the thermodynamic enolate because it is the more stable enolate ion having the more substituted double bond. Therefore, 2,2-dialkylcyclopentanone is the major product when the reaction is carried out under conditions that cause enolate ion formation to be reversible.

For example, the formation of a thermodynamic enolate (major) from 2-methylcyclohexanone and its reaction with methyl iodide to form 2,5-dimethycylclohexanone as the major product may be shown as follows:



The kinetic enolate is that which is formed at a much faster rate. It is usually formed by expulsion of the least sterically hindered α-hydrogen. The kinetic enolate predominates under condition of kinetic control that actually do not favour to establish equilibrium among the possible enolates. When a very strong and sterically hindered base in an aprotic solvent, such as LDA in tetrahydrofuran (THF) or dimethoxyethane (DME), is used, the formation of the kinetic enolate is much favoured. The enolate ion leading to 2,6-dialkylcyclopentanone is the kinetic enolate ion because it is formed faster, since the α-hydrogen that is removed to make this enolate is more accessible to the hindered base like LDA and it is slightly more acidic. For example, the formation of a kinetic enolate from 2-methylcyclohexanone and its reaction with methyl iodidie to form 2,5-dimethylcyclohexanone predominantly may be shown as follows:



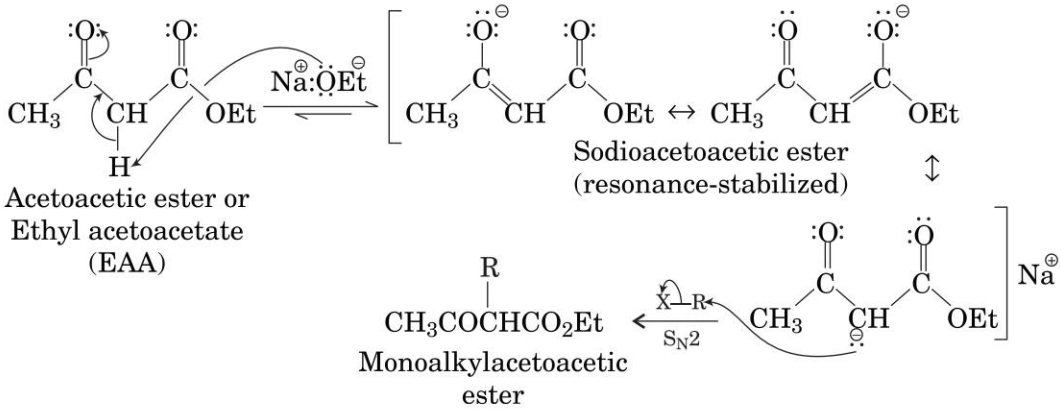
2.9.2.2 Factor complicating the process of alkylation

The alkylation reaction may be complicated by several factors. The enolate ion is a fairly strong base. Therefore, alkylation (an S_N2 rection) is normally feasible using only

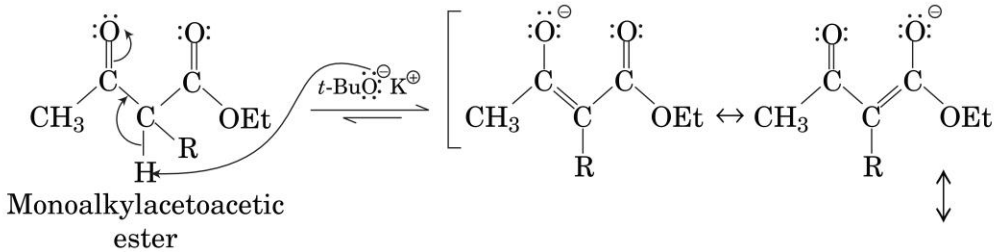
halomethanes or primary alkyl halides; otherwise E2 elimination converting the alkyl halide into an alkene becomes a major side reaction. Alkylation of aldehydes usually fails because their enolates undergo a highly favourable condensation reaction (aldol condensation). Even the alkylation of ketones may be problematic because the monoalkylation product may undergo alkylation a second time. Furthermore, if the ketone is unsymmetrical, alkylation may take place at either of the two α-carbons, leading to two regioisomeric substitution products.

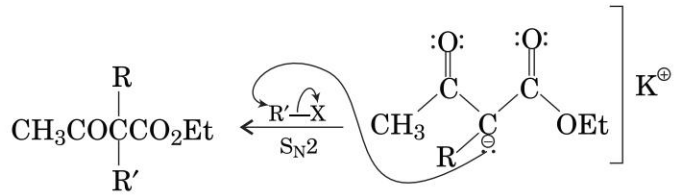
2.9.2.3 Alkylation of β-dicarbonyl compounds

β-Dicarbonyl compounds are quite strong acids. The pKa of diethyl malonate (DEM) is 13.3 and other β-dicarbonyl compounds are similarly acidic. The enolate ions formed from these compounds can be alkylated in S_N2 reactions. Since the β-dicarbonyl compounds are sufficiently acidic, their alkylation through the enolate using an alkoxide base is easy. For example:



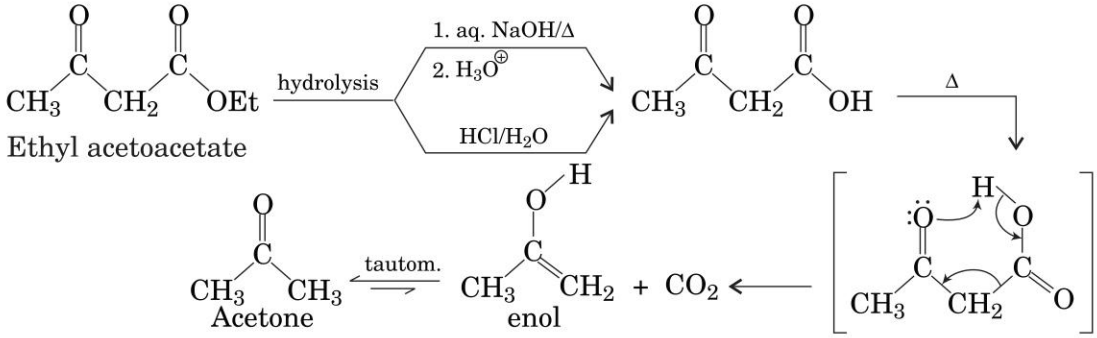
The once-alkylated compound still contains one active methylene hydrogen and therefore, remain acidic. Hence, a second alkylation, if required, is possible. Because a monoalkylacetoacetic ester is somewhat less acidic than acetoacetic ester itself due to the electron-releasing inductive effect (+I) of the added alkyl group, it is usually helpful to use a strong base than the ethoxide ion ($OEt^{\ominus}$) for the second alkylation. Use of potassium *tert*-butoxide is common because it is a stronger base than sodium ethoxide. Furthermore, because of its steric bulk, it does not cause *trans* esterification.





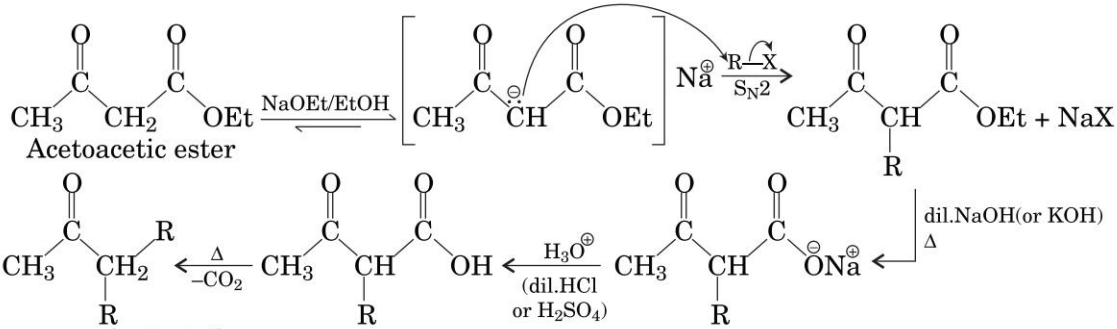
Dialkylacetoacetic ester

Hydrolysis and decarboxylation of β-dicarbonyl compounds When a β-keto ester such as ethyl acetoacetate is hydrolyzed by acid or base, the resulting β-keto acid is not very stable and decarboxylates (i.e., loses CO_2) when heated. The end result is one molecule of a ketone and one of carbon dioxide. For example:

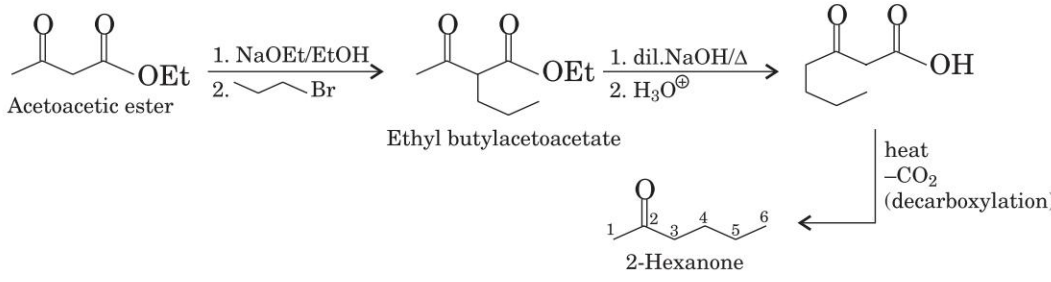


Synthesis of methyl ketones: The acetoacetic ester synthesis The combination of alkylation followed by ester hydrolysis and finally decarboxylation allows ethyl acetoacetate to be converted ultimately into 3-substituted or 3,3-disubstituted methyl ketones. This process or way to synthesize a methyl ketone is called the **acetoacetic ester synthesis.**

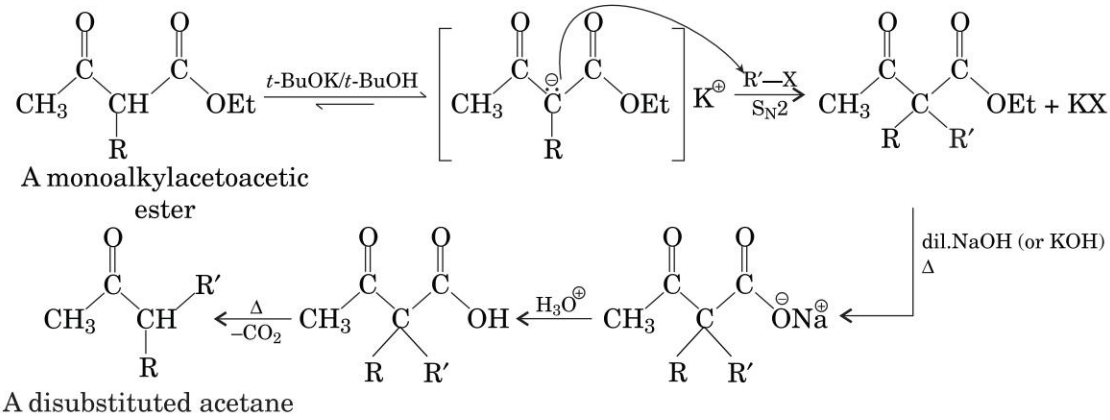
Synthesis of monosubstituted acetone To synthesize a monosubstituted acetone or a monosubstituted methyl ketone, alkylation of ethyl acetoacetate in first carried out. Then the monoalkylacetoacetic ester is hydrolyzed using aqueous sodium or potassium hydroxide. The mixture on acidification produces an alkyl-acetoacetic acid. When this β-keto acid is heated to 100°C, it undergoes decarboxylation to yield a monosubstituted acetone.



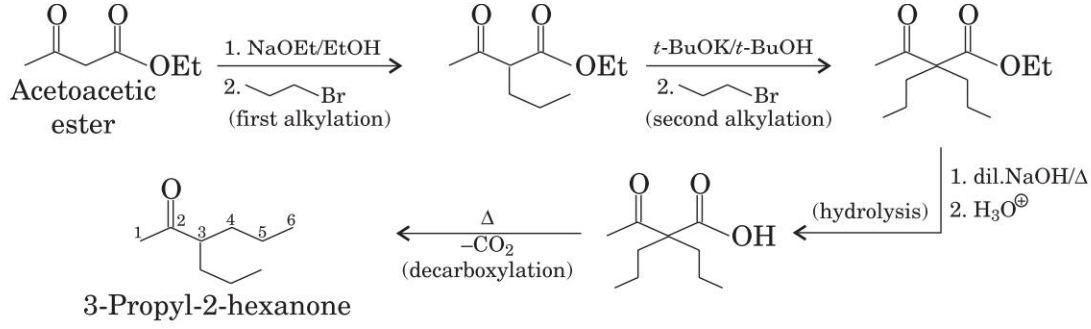
Example: The acetoacetic ester synthesis of 2-hexanone (a methyl ketone) may be outlined as follows:



Synthesis of disubstituted acetone To synthesize a disubstituted acetone or a disubstituted acetone or a disubstituted methyl ketone, alkylation of monoalkylacetoacetic ester is first carried out. The dialkylacetoacetic ester is then hydrolyzed using aqueous sodium or potassium hydroxide. The mixture is acidified and the resulting dialkyacetoacetic acid is heated to yield a disubstituted acetone by the loss of CO_2.

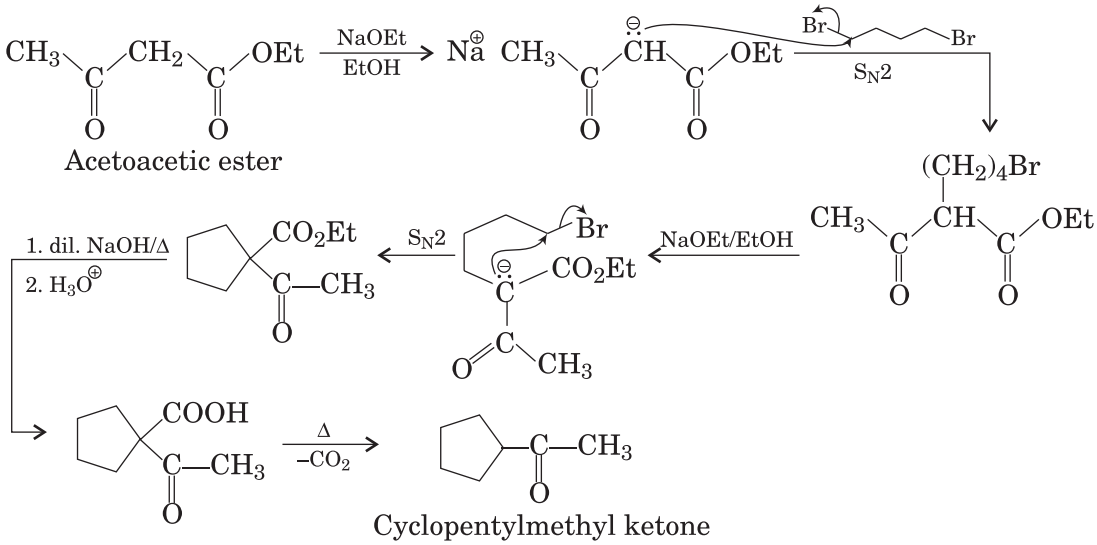


Example: The actoacetic ester synthesis of 3-propyl-2-hexanone (a methyl ketone) may be outlined as follows:



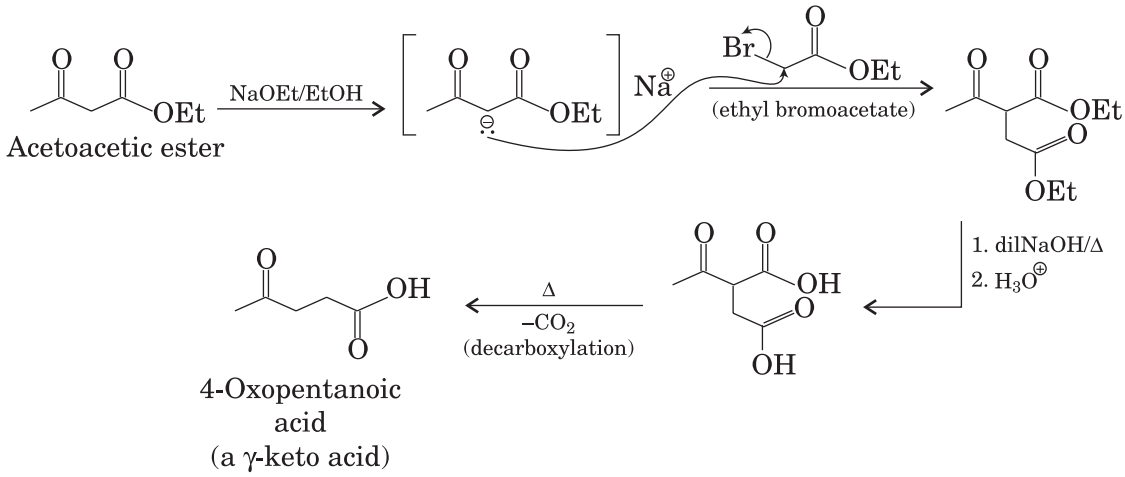
The acetoacetic ester synthesis can also be used to synthesize cycloalkyl methyl ketones, keto acids, diketones and carboxylic acids.

(i) **Synthesis of cycloalkyl methyl ketones:** When one molar equivalent of sodioacetoacetic ester is allowed to react with one molar equivalent of a dihaloalkane, a haloalkylacetoacetic ester is obtained. This, when treated with sodium ethoxide, undergoes an internal alkylation reaction to form, after hydrolysis and decarboxylation, a cycloalkyl methyl ketone. It is possible to prepare rings containing three, five, six and seven carbon atoms, but not four. An example is the synthesis of cyclopentyl methyl ketone.



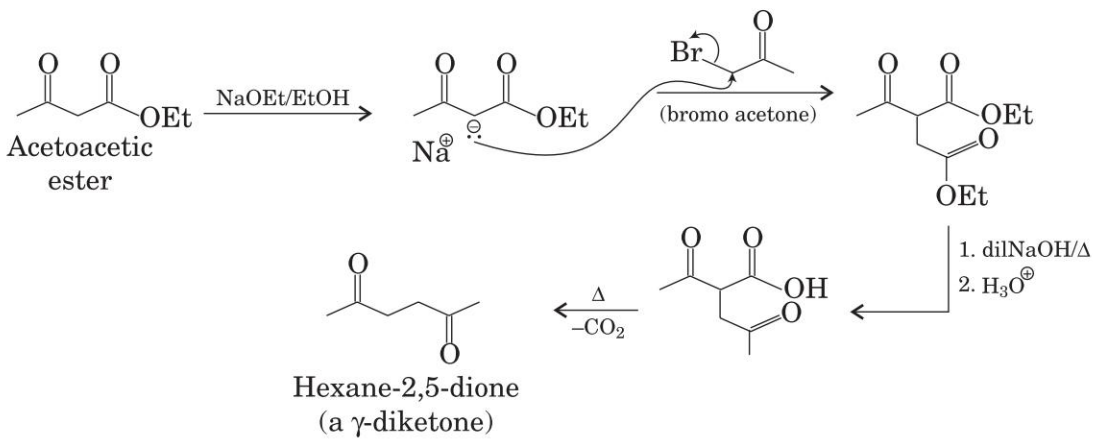
Cyclopentylmethyl ketone

(ii) **Synthesis of keto acids:** When the acetoacetic ester synthesis is carried out using an α-halo ester, a γ-keto acid is obtained. This offers a much convenient synthesis of γ-keto acids. For example:



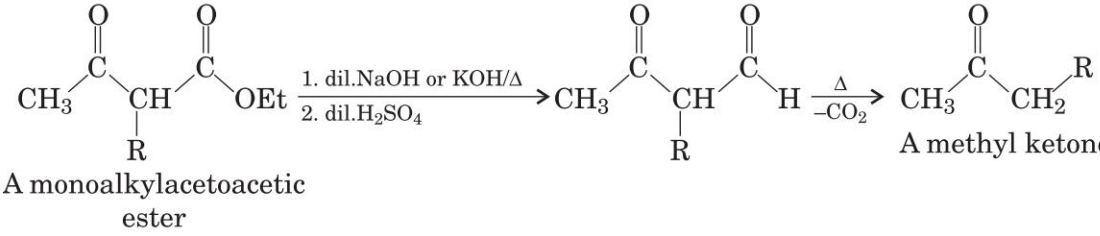
4-Oxopentanoic acid
(a γ-keto acid)

(iii) **Synthesis of diketones:** The use of an α-halo ketone in an acetoacetic ester synthesis provides a general method for the synthesis of γ-diketones. For example:

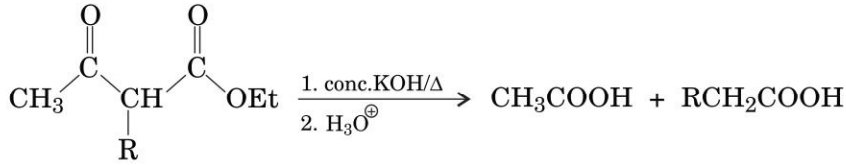


Before discussing the synthesis of carboxylic acids, we must discuss the two types of hydrolysis with alkali: (i) ketonic hydrolysis and (ii) acid hydrolysis.

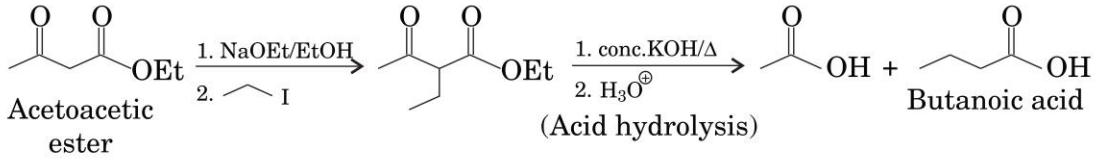
Ketonic hydrolysis: Ketonic hydrolysis, so called because a ketone is the chief product, is carried out by boiling with dilute aqueous sodium or potassium hydroxide solution, and is followed by acidification (by dil. H_2SO_4) and warming.



Acid-hydrolysis: Acid hydrolysis, so called because an acid is the chief product, is carried out by boiling with concentrated ethanolic potassium hydroxide solution followed by acidification.

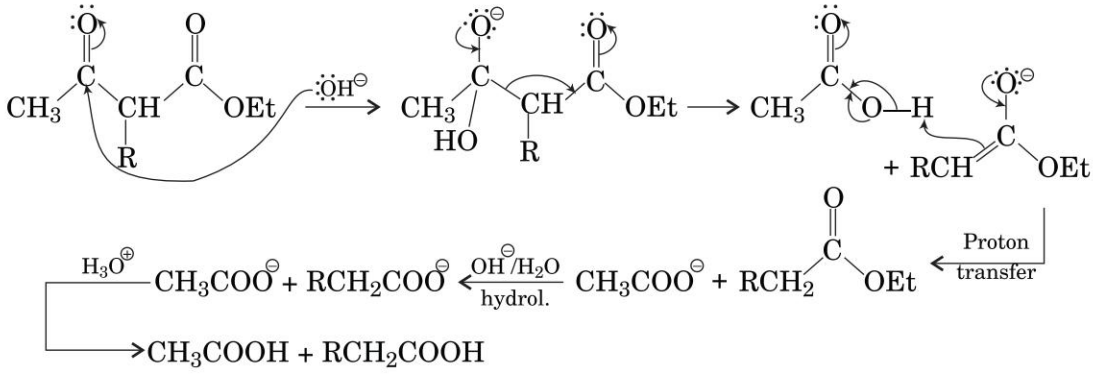


(iv) **Synthesis of carboxylic acids:** In this case, the mono- or dialkylacetoacetic ester is subjected to acid hydrolysis. For example:



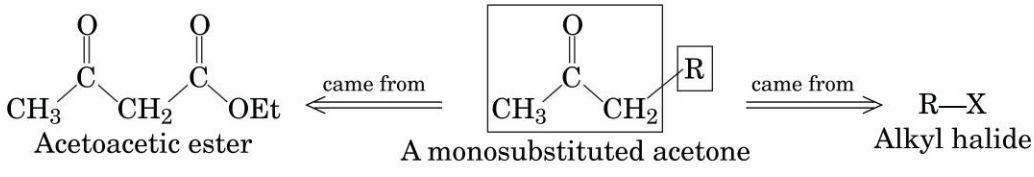
It is to be noted that 'ketonic hydrolysis' and 'acid hydrolysis' of acetoacetic ester derivatives always take place simultaneously, but one or the other can be made to predominate by adjusting the concentration of the alkali used. Thus, in the preparation of acids, there will always be some ketone formed as a by-product and vice versa. For this reason, it is better to use diethyl malonate [$CH_2(CO_2Et)_2$] to synthesize acids since the yields are greater.

Mechanism:

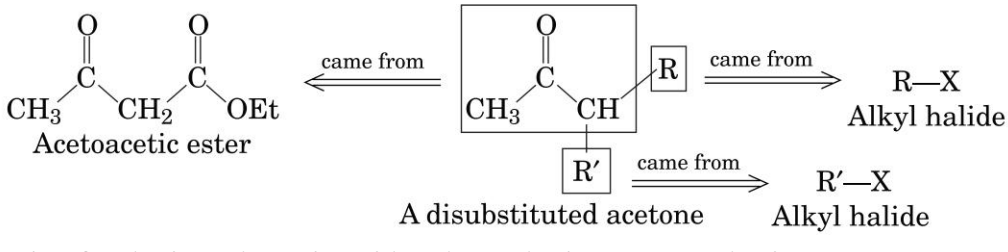


Retrosynthetic analysis: To use the acetoacetic ester synthesis, we have to determine what starting materials are required to prepare a given ketone and for this, we have to work backwards in the retrosynthetic direction. This involves a two-step process: (i) the alkyl groups bonded to the α-carbon to the carbonyl group are to be identified and (ii) the molecule is to be cleaved into two (or three) components by remembering the fact that each alkyl group bonded to the α-carbon comes from an alkyl halide and the remainder of the molecule, i.e., the CH_3COCH_2 moiety, comes from $CH_3COCH_2CO_2Et$.

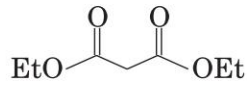
(i) **For a methyl ketone with one R group**



(ii) **For a methyl ketone with two R groups**

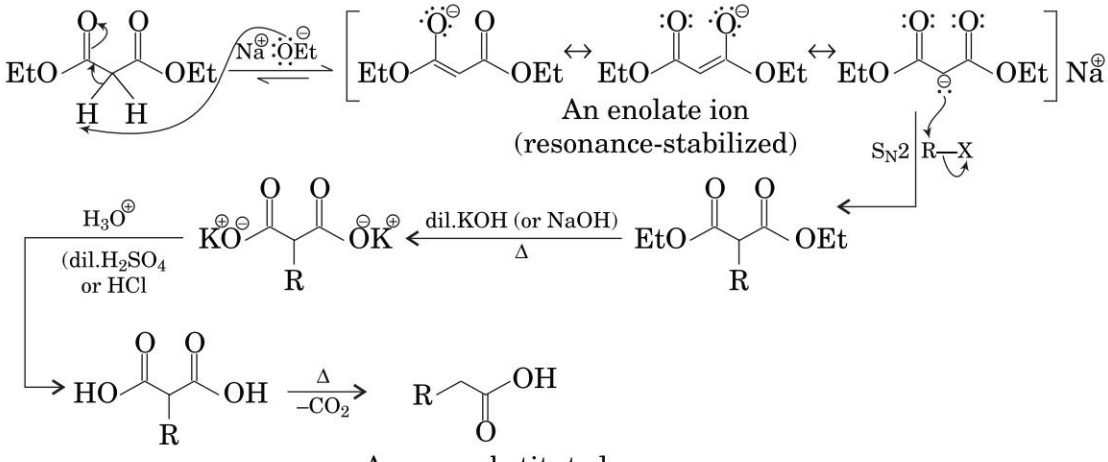


Synthesis of substituted acetic acids: The malonic ester synthesis: The combination of alkylation followed by ester hydrolysis and finally decarboxylation allows diethyl malonate (malonic ester) to be converted ultimately into 2-alkyl or 2,2-dialkylated acetic acids. This strategy for preparing substituted acetic acids is called the malonic ester synthesis.



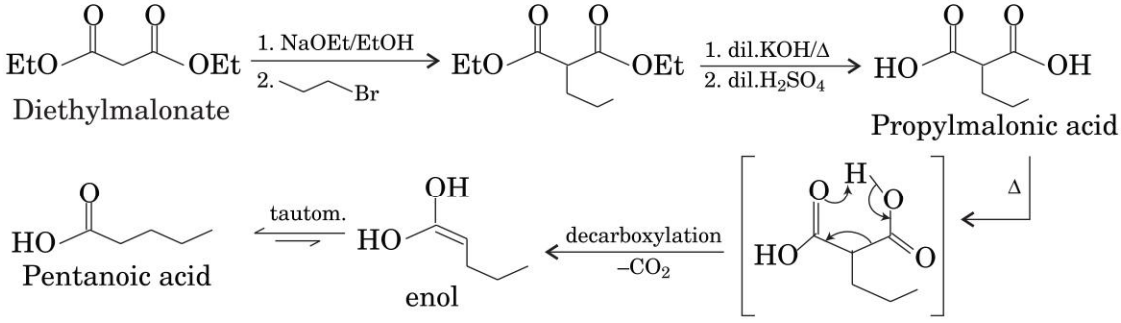
Diethyl malonate (DEM)
or malanic ester
(a β-dicarboxylic acid ester)

Synthesis of a monosubstituted acetic acid: The synthesis of a monosubstituted acetic acid (similar to the synthesis of a monosubstituted acetone from EAA) may be outlined as follows:

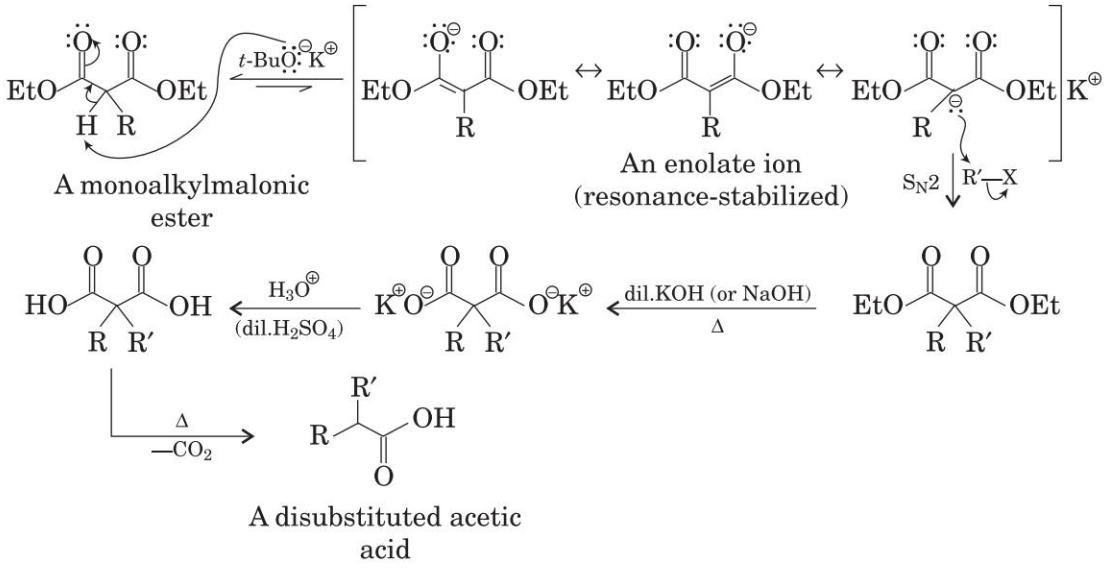


A monosubstituted
acetic acid

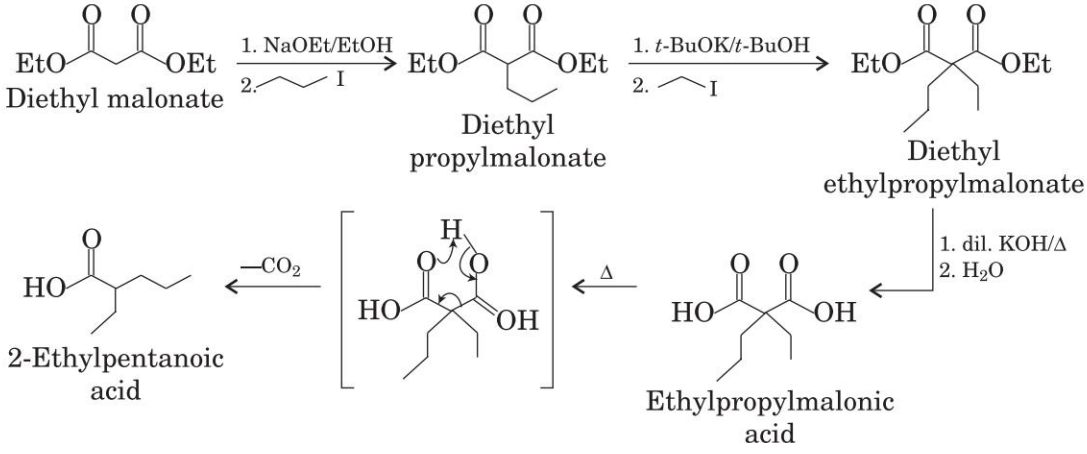
Example: A malonic ester synthesis of pentanoic acid may be outlined as follows:



Synthesis of a disubstituted acetic acid The synthesis of disubstituted acetic acid (similar to the synthesis of a disubstituted acetone from EAA) may be outlined as follows:



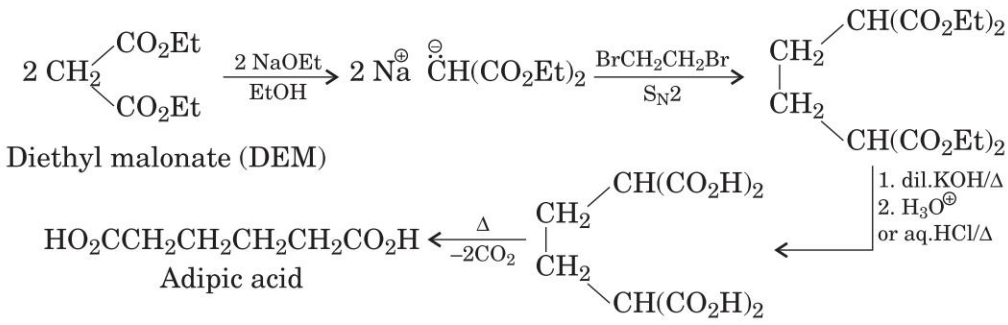
Example: The malonic ester synthesis of 2-ethylpentanoic acid may be outlined as follows:



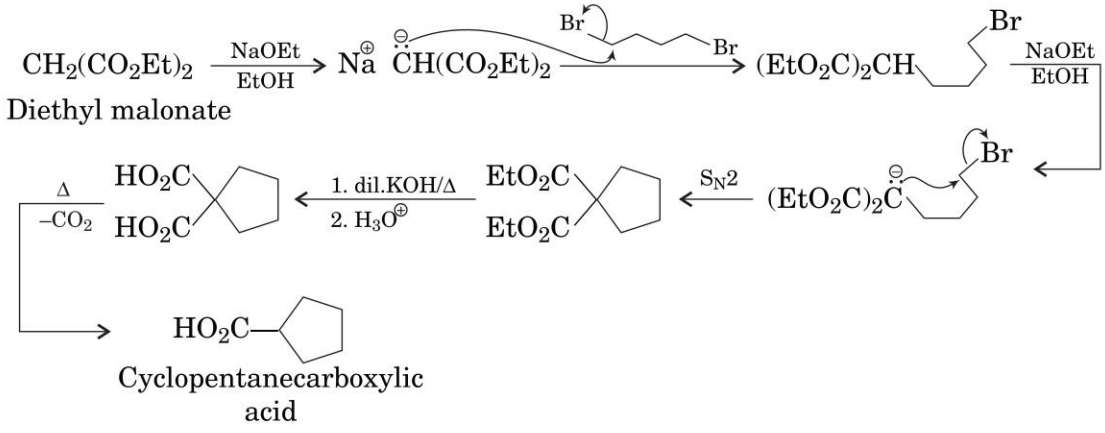
It is to be noted that it is usually better to introduce the larger group before the smaller (steric effect).

The malonic ester synthesis can also be used to synthesize dicarboxylic acids and alicyclic carboxylic acids.

(i) **Synthesis of dicarboxylic acids:** When two molar equivalents of sodiomalonic ester are allowed to react with a dihaloalkane, two consecutive alkylations take place to give a *tetra*ester. The *tetra*ester on hydrolysis followed decarboxylation yields a dicarboxylic acid. An example is the synthesis of adipic acid ($HO_2CCH_2CH_2CH_2CO_2H$).

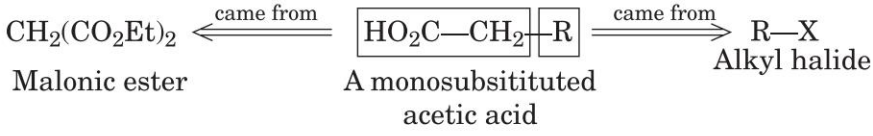


(ii) **Synthesis of alicyclic carboxylic acids:** When one molar equivalent of sodiomalonic ester is allowed to react with one molar equivalent of a dihaloalkane, a haloalkylmalonic ester is obtained. This, when treated with sodium ethoxide, undergoes an internal alkylation reaction to form an alicyclic carboxylic acid after hydrolysis and decarboxylation. This method has been used to prepare three-, four-, five-, and six-membered rings. An example is the synthesis of cyclopentanecarboxylic acid.

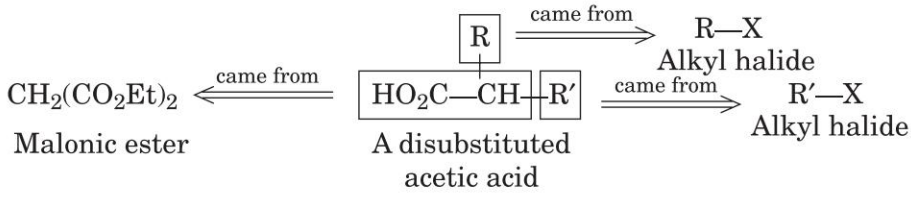


Retrosynthetic analysis To use the malonic ester synthesis we have to determine what starting materials are required to prepare a given carboxylic acid and for this, we have to work backwards in the retrosynthetic direction. This involves a two-step process: (i) the alkyl groups bonded to the α-carbon to the carbonyl group are to be identified and (ii) the molecule is to be cleaved into two (or three) components by remembering the fact that each alkyl group bonded to the α-carbon comes from the alkyl halide and the remainder of the molecule, i.e., the CH_2COOH or CHCOOH moiety, comes from $CH_2(CO_2Et)_2$.

(i) **For a monosubstituted acetic acid**

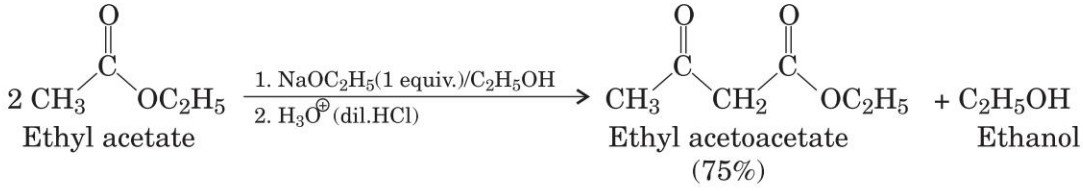


(ii) **For a disubstituted acetic acid**



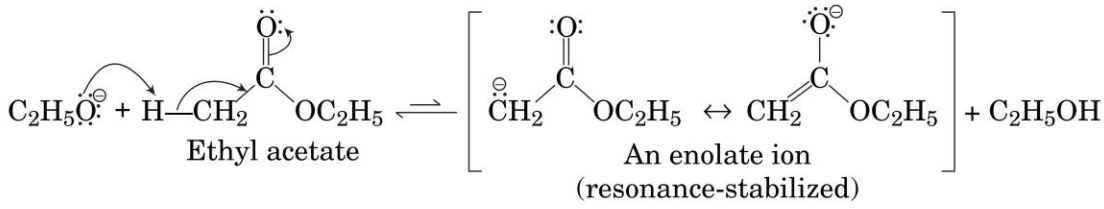
2.9.3 The Claisen condensation (addition of acid derivatives) to the α-carbon of carbonyl compounds

When an ester containing α-hydrogen atoms is treated with a strong base such as sodium ethoxide (usually the alkoxide of the ester alcohol group), a condensation reaction occurs to yield a β-keto ester. This synthetically useful carbon–carbon bond forming reaction is called the *Claisen condensation*. The reaction is, in fact, an acyl substitution reaction at the α-carbon. The best-known example of this reaction is that when ethyl acetate is treated with sodium ethoxide (one equivalent) in ethanol and the resulting mixture is acidified, ethyl acetoacetate or ethyl 3-oxobutanoate is obtained.



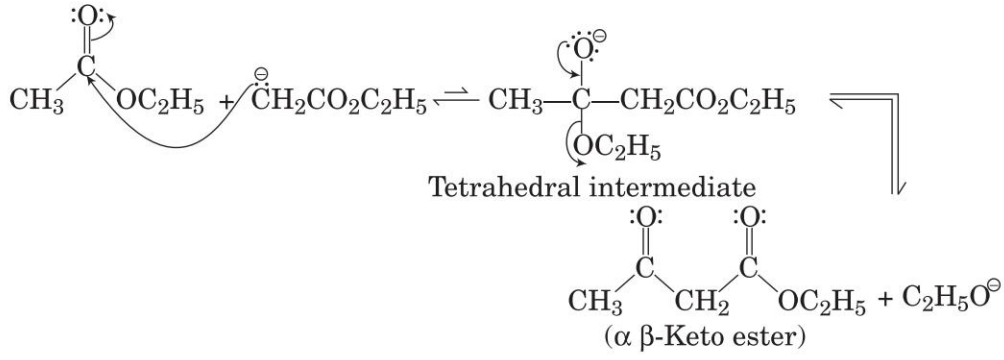
Mechanism of the reaction The mechanism of the reaction involves the steps as follows:

Step 1: Abstraction of a proton from the α-carbon of the ester by the ethoxide ion leads to the formation of a resonance-stabilized enolate ion.



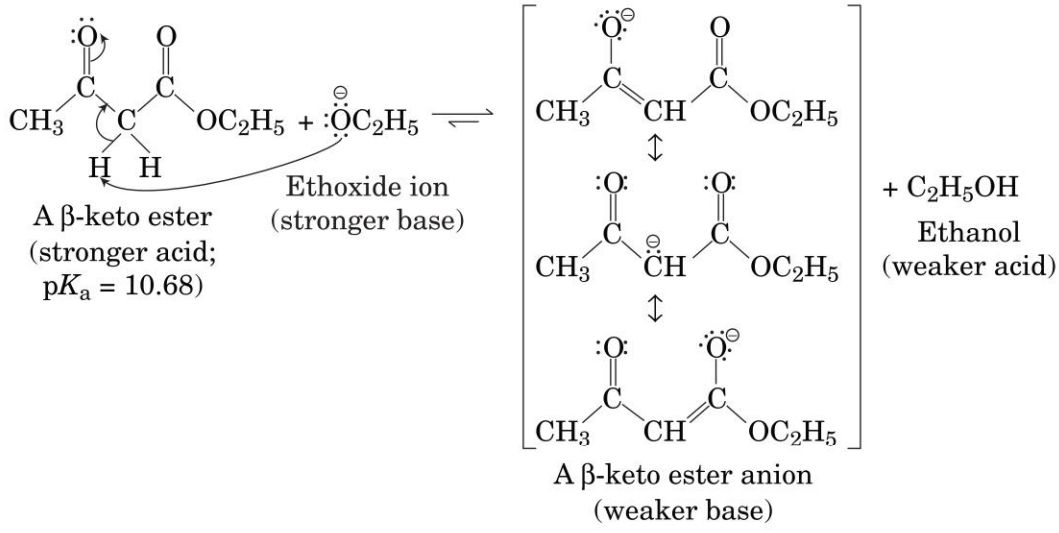
The formation of the ester enolate ion is an unfavourable equilibrium because ethyl acetate is a weaker acid (p*K*a = 25) than ethanol (p*K*a = 16).

Step 2: The enolate ion being a strong nucleophile attacks the carbonyl carbon of another ester molecule to form a tetrahedral intermediate. This unstable intermediate expels an alkoxide ion, resulting in substitution of the alkoxide by the group derived from the enolate. The net result is a nucleophilic addition-elimination or nucleophilic acyl substitution at the ester carbonyl group.



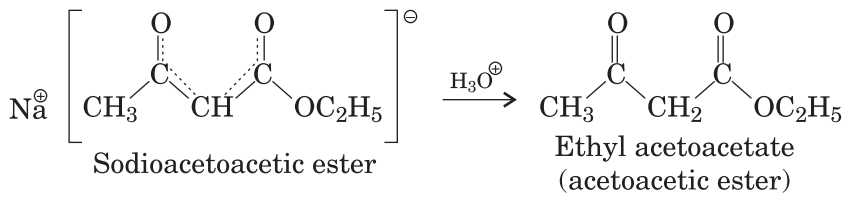
The acylation step is also not favourable (the equilibrium constant near 1). Although the β-keto ester EAA is obtained at the end of this step, the yield is very low because all the equilibrium up to this point lies far on the side of the reactants, i.e., all the equilibrium up to this point has been unfavourable.

Step 3: An ethoxide ion removes a proton from the newly formed substitution product, resulting in a resonance-stabilized β-keto ester anion. Since a strong acid readily reacts with a stronger base to give a weaker acid and a weaker base, this step is highly favourable (strongly exothermic) and draws the overall equilibrium towards product formation.



The formation of this resonance-stabilized enolate salt is, therefore, essential to the success of the reaction. The overall equilibrium can be made even more favourable by distilling ethanol from the reaction mixture as it forms.

The unionized β-keto ester product is formed when the mixture is acidified with dilute HCl.

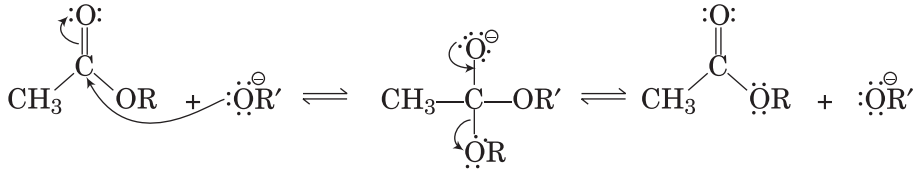


Sodioacetoacetic ester

Ethyl acetoacetate
(acetoacetic ester)

Some relevant topics:

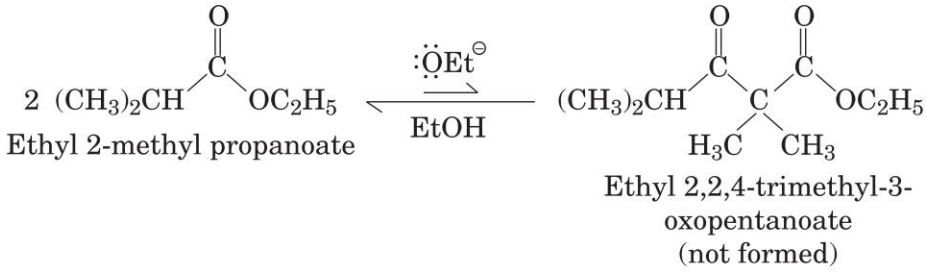
(i) **The alkoxide base used to form the enolate should have the same alkyl group as the ester:** The alkoxide base used in the Claisen condensation may attack the carbonyl carbon of the ester to give usual carbonyl substitution reaction (transesterification). Therefore, when the base and the ester alkoxy group are different, a different ester is generated in the reaction mixture and this results in formation of two different β-keto esters.



To avoid this problem of transestrification, the conjugate base of the alcohol portion of the ester is used as the alkoxide base since in that case substitution leads to the same ester.

(ii) **Fundamental difference between the Claisen condensation and the Michael addition reaction:** A fundamental difference between the Claisen condensation and the Michael addition reaction is that in the Claisen condensation, the product is a stronger acid than the reactant while in the Michael addition reaction, the reactant is a stronger acid than the product. It thus follows that while a full equivalent of base can drive the Claisen condensation to completion, only a low concentration of base is required to produce a high yield of the Michael addition product. The Michael addition is said to be base-catalyzed while the Claisen condensation is said to be base-promoted.

(iii) **Ester containing only one α-H fails to undergo the reaction in the presence of NaOEt, but gives the reaction in the presence strong bases like NaH, $NaNH_2$, etc.** It is the formation of the final enolate anion (highly stabilized by resonance) which is, in fact, the most essential step to the success of the Claisen condensation because it is the only step which has favourable equilibrium. For this final step reaction to take place, there must be one acidic hydrogen in the product and two α-hydrogens in the original ester. Ethyl 2-methylpropanoate (Me_2CHCO_2Et) has only one α-H atom and the β-keto ester expected to be formed ($Me_2CHCOCMe_2CO_2Et$) does not contain an active α-H atom. For this reason, the final enolate anion cannot be formed under the reaction conditions and the equilibrium of the overall reaction lies almost completely on the left, i.e., the β-keto ester is not formed in this reaction.



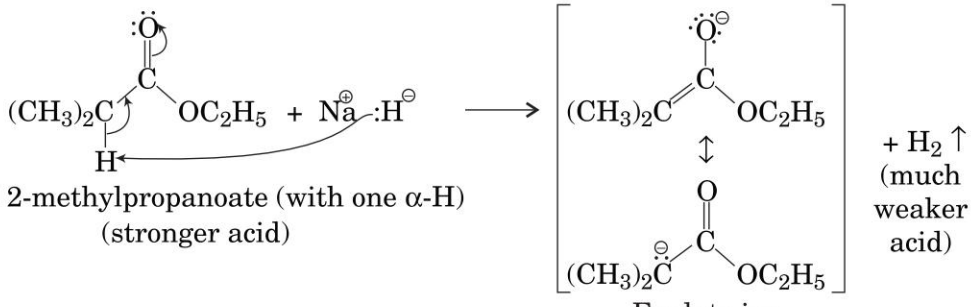
Ethyl 2-methyl propanoate

Ethyl 2,2,4-trimethyl-3-oxopentanoate (not formed)

In the presence of very strong base like sodium hydride (NaH), sodium amide ($NaNH_2$), triphenylmethyl sodium (Ph_3CNa) or lithium diisopropylamide (LDA), $[(Me_2CH)_2\overset{\ominus}{N}\overset{\oplus}{Li}]$, the first step of the reaction becomes essentially irreversible because the conjugate acids of these bases are very weak and in some cases they liberate as a gas (in which case the equilibrium is favoured due to the Law of mass action). The reaction is thus driven to yield the β-keto ester $Me_2CHCOCMe_2CO_2Et$ in good yield, since the position of the equilibrium of the final step will no longer matter.

In the presence of these strong bases, the reaction becomes a two-step process that may be outlined as follows:

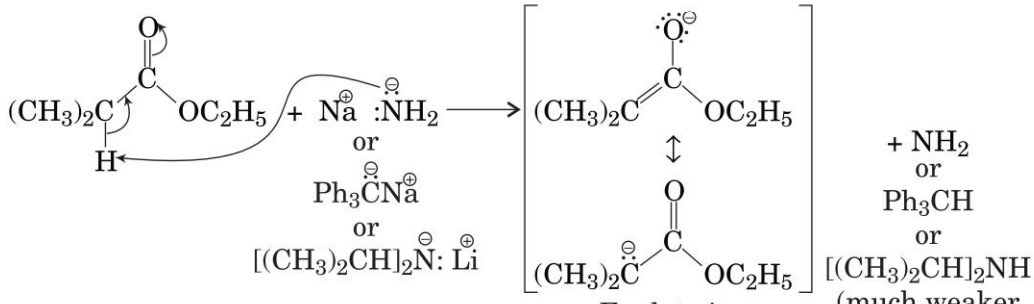
Step 1:



Ethyl 2-methylpropanoate (with one α-H) (stronger acid)

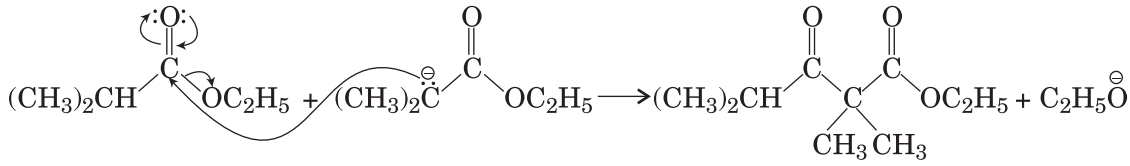
Enolate ion

Similarly,



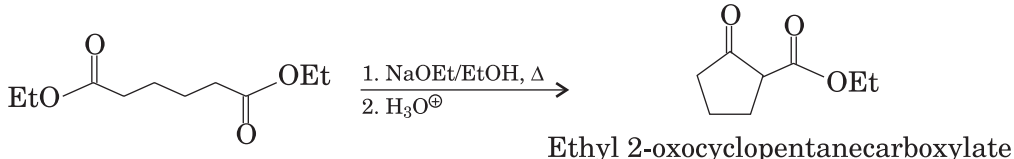
Enolate ion

Step 2:



A β-keto ester
(formed in good yield)

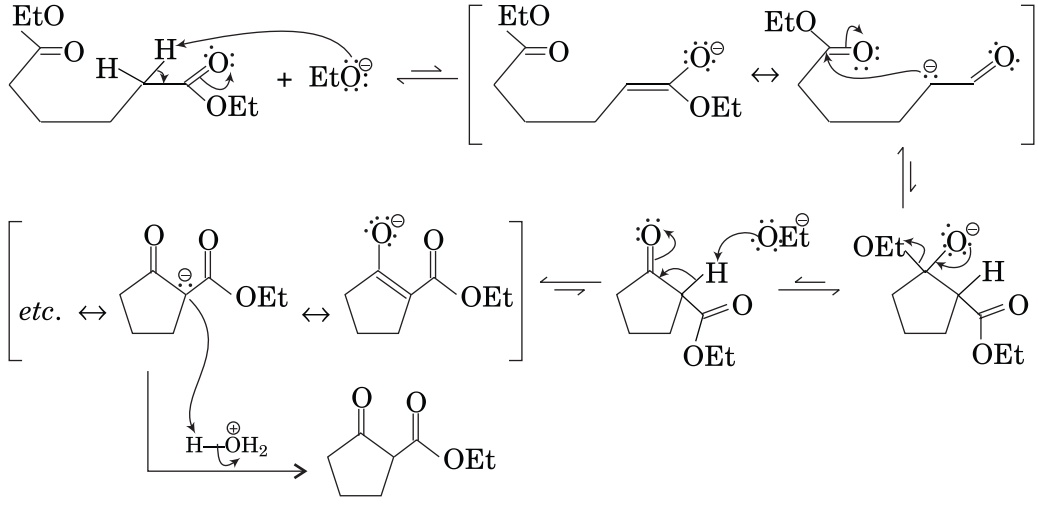
The Dieckmann condensation An intramolecular Claisen condensation is called *Dieckmann condensation.* For example, when diethyl hexanedioate is heated with sodium ethoxide in ethanol followed by acidification of the mixture, ethyl 2-oxocyclopentanecarboxylate is obtained.



Diethyl hexanedioate
(Diethyl adipate)

Ethyl 2-oxocyclopentanecarboxylate
(81%)

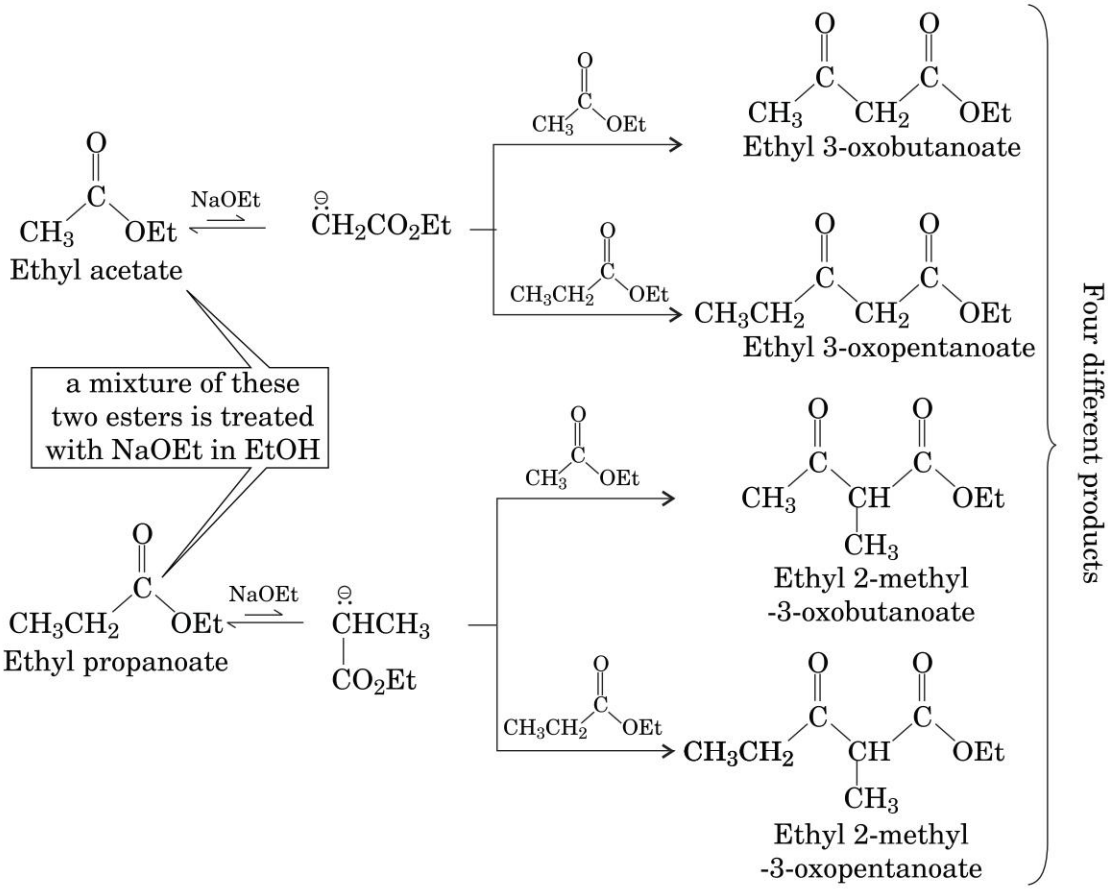
Mechanism: The mechanism of the reaction involves the step as follows:



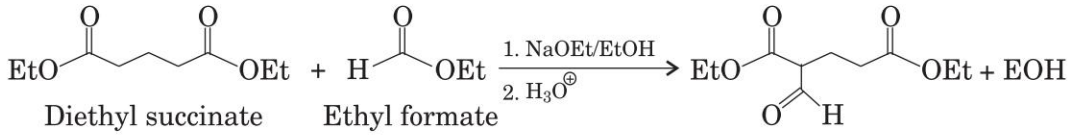
In the first step, the ethoxide ion removes an α-hydrogen. In the second step, the enolate ion attacks the carbonyl carbon at the other end of the chain. In the third step, an ethoxide ion is expelled. In the fourth step, the ethoxide ion removes the acidic hydrogen flanked by the two carbonyl groups. This favourable equilibrium drives the reaction. Finally, when the mixture is acidified, the enolate undergoes ready protonation to give the cyclic β-keto ester.

It is to be noted that rings smaller than five are disfavoured due to angle strain and rings larger than seven are less favourable entropically because a greater number of conformations are available to a longer chain starting compound, in which case intermolecular condensation becomes a competitive reaction.

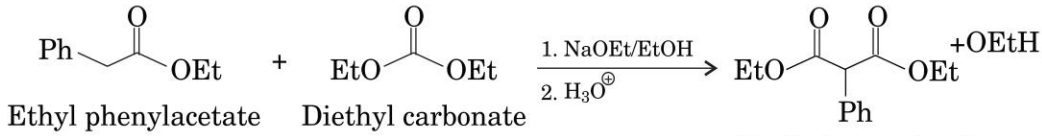
Crossed Claisen condensation The Claisen condensation between two different esters is called a *crossed Claisen condensation.* The crossed Claisen condensation between two esters that both have α-hydrogens gives a mixture of four *β*-keto esters that are typically difficult to separate. Therefore, such reactions in most cases are not synthetically useful. For example:



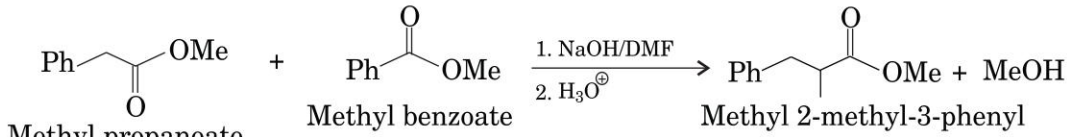
A crossed Claisen condensation is generally useful, i.e., a good yield of a single product is obtained when one of the esters is specially reactive or has no *α*-hydrogen such as formates (HCO_2R), oxalates (ROOC—COOR), carbonates (ROCOOR) or benzoates (PhCOOR) and therefore, is incapable of undergoing self-condensation. The self-condensation can also be avoided if the ester containing *α*-hydrogen is added slowly to the mixture of the ester lacking *α*-hydrogen and the base. For example:

(i) 

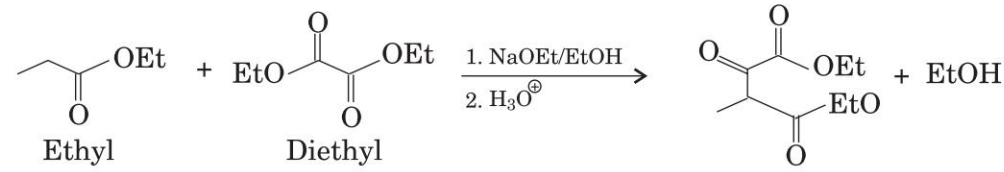
Diethyl succinate Ethyl formate Diethyl formylsuccinate (70%)

(ii) 

Ethyl phenylacetate Diethyl carbonate Diethyl phenylmalonate (86%)

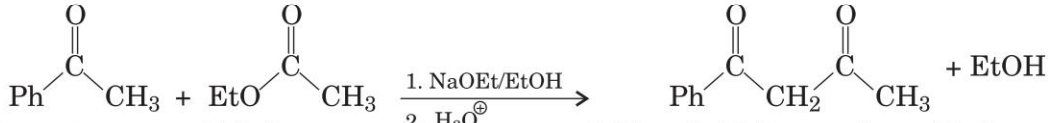
(iii) 

Methyl propanoate Methyl benzoate Methyl 2-methyl-3-phenyl 3-oxopropanoate (56%)

(iv) 

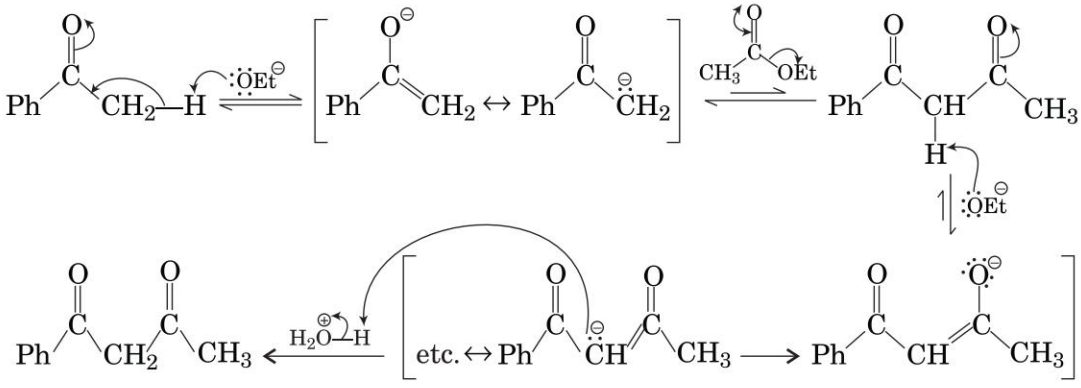
Ethyl propanoate Diethyl oxalate Diethyl 3-methyl-2-oxo-butanedioate (70%)

Another type of crossed Claisen condensation is the reaction of ketones with esters. Since ketones are far more acidic than esters, the enolate ion of the ketone is formed readily and that attacks the carbonyl carbon of the ester group. For example:

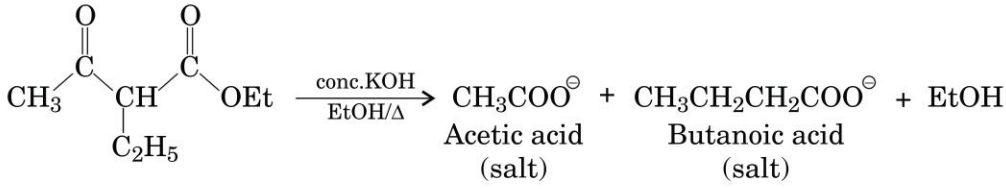


Acetophenone Ethyl acetate 1-Phenyl-1,3-butanedione (70%) (a β-diketone)

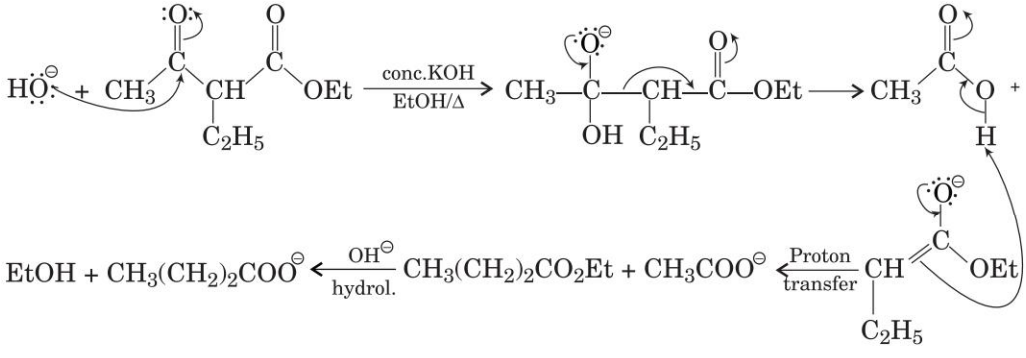
Mechanism:



Retro-Claisen condensation The Claisen condensation can be reversed in the presence of strong base. The process is called a *retro-Claisen condensation*. In this reaction, a β-keto ester is cleaved to form two molecules of acid (as salt). For example, when ethyl 2-ethyl-3-oxobutanoate is heated with conc. KOH solution in ethanol, acetate and butanoate salt are obtained.

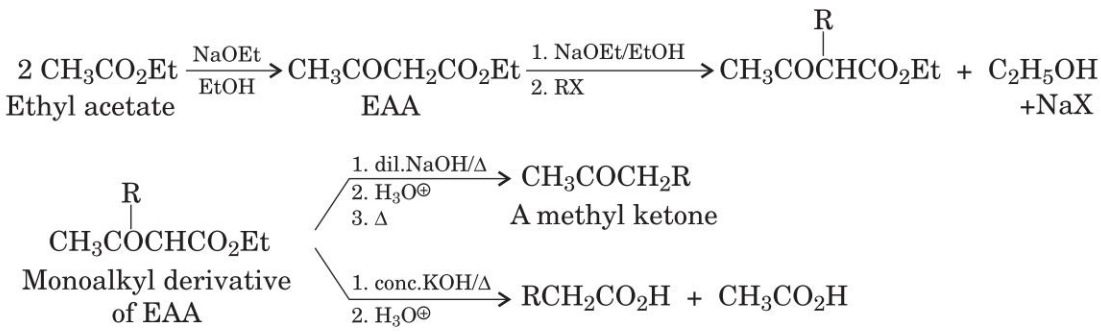


Mechanism: The reaction proceeds through the steps as follows:

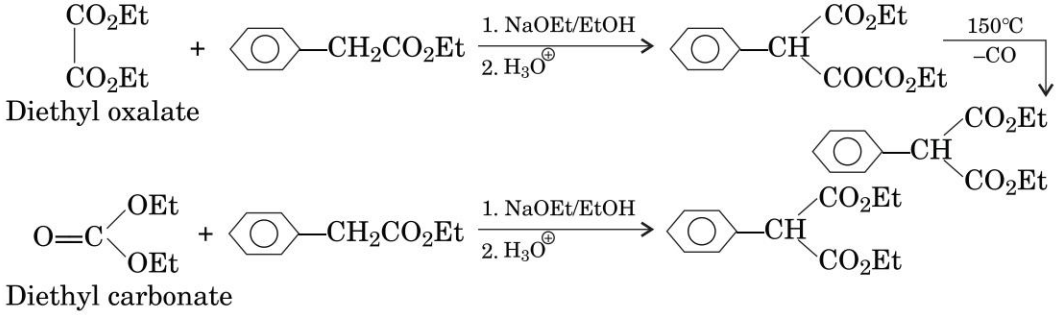


Synthetic applications The Claisen condensation is a very useful reaction and is the key synthetic step of many significant organic molecules. A few useful applications of the Claisen condensation are metioned below:

(i) A very important product of the Claisen condensation is the β-keto ester, ethyl acetoacetate (EAA). It can be easily alkylated, and the alkyl derivative under different conditions undergoes ketonic and acid hydrolysis to yield methyl ketones and carboxylic acids, respectively.

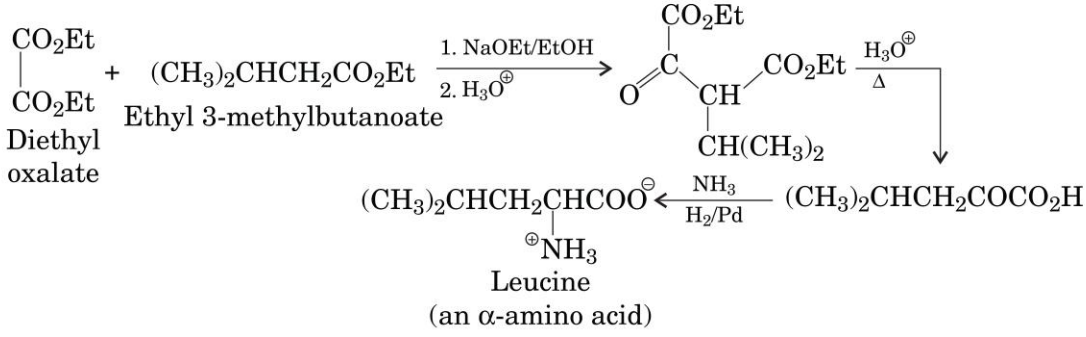


(ii) Various important organic compounds can be prepared by the mixed (crossed) Claisen condensations involving esters with no α-H atom. For example, condensations with ethyl formate (HCO_2Et) and ethyl benzoate ($PhCO_2Et$) are used for formylation and benzoylation, respectively, during the synthesis of various natural products, e.g., equineline, thiamine (vitamin B1), flavone (chrysin), nicotine, etc. Condensations with diethyl oxalate give oxalyl derivatives which lose CO on heating to yield malonic ester derivatives. Malonic ester derivatives can also be obtained when the condensation is carried out with diethyl carbonate.

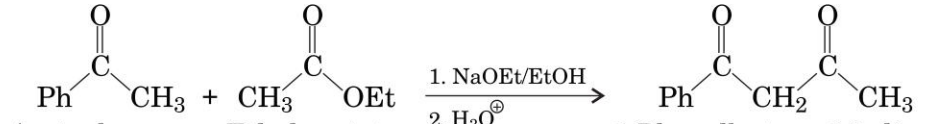


Phenyl substituted malonic esters are synthetically very useful, e.g., synthesis of phenobarbitone (5-phenyl-5-ethylbarbituric acid) which is used in medicine as hypnotics and sedative.

The crossed Claisen condensation involving diethyl oxalate is also the first step in a useful synthetic route to α-amino acids. Leucine, for example, can be synthesized as follows:



(iii) β-Diketones can be prepared by the crossed Claisen condensations involving ketones and esters. Since ketones are relatively more acidic than esters, it is the ketone which forms the enolate ion in these reactions. For example:



Acetophenone + Ethyl acetate → 1-Phenylbutane-1,3-dione (a β-diketone)

(iv) Intramolecular Claisen condensations (Dieckmann reactions) leading to the formation of cyclic β-keto esters are useful in the preparation of five and six-membered rings. For example:

(i) $EtO_2C(CH_2)_4CO_2Et \xrightarrow[2.\ H_3O^{\oplus}]{1.\ NaOEt/EtOH}$ 2-Carboethoxycyclopentanone $+ C_2H_5OH$

(ii) $EtO_2C(CH_2)_4CH(CH_3)CO_2Et \xrightarrow[2.\ H_3O^{\oplus}]{1.\ NaH/C_6H_6}$ 2-Carboethoxy-6-methylcyclohexanone (90%) $+ C_2H_5OH$

SOLVED PROBLEMS

1. How does the base-promoted halogenation of ketones differ from the acid-catalyzed halogenation?

Solution The base-promoted halogenation of ketones yields the polyhalogenated compounds. The halogens are electron-withdrawing (possess –I effect) and so the α-hydrogens of the first formed α-haloketone become more acidic and are easily replaced by halogens in the presence of alkali. The α,α-dihaloketone is much more acidic due to the –I effect of two halogen atoms and its α-hydrogen is much easily replaced by halogen in the presence of alkali. That is, if the ketone contains a $—COCH_3$ group, it gets converted into a $—COCX_3$ group. The intermediate monohalo- and dihaloketones cannot be isolated. Because of the same electron-attracting effect of halogen atom, monohaloketones show much less tendency to protonation and subsequent enolization under acid-catalyzed conditions. Therefore, it is possible to isolate them under acid-catalyzed conditions unlike under base-catalyzed conditions.

2. Which of the following compounds are expected to give a positive iodoform test? Give reasons.

(a) Acetone **(b)** 3-Hexanone **(c)** Ethanol
(d) 2-Pentanol **(e)** 3-Hexanol **(f)** Acetaldehyde
(g) Phenacyl iodide

Solution The compounds containing the $CH_3CO—$ or $CH_3CH(OH)—$ group give a positive iodoform test and from this knowledge the compounds that give positive iodoform test can be identified.

(a) Acetone (CH_3COCH_3) containing the $CH_3CO—$ group gives a positive iodoform test.

(b) 3-Hexanone ($CH_3CH_2COCH_2CH_2CH_3$) does not respond to this test as it contains no $CH_3CO—$ group.

(c) Ethanol ($H—CH(OH)CH_3$) gives a positive iodoform test as it contains $—CH(OH)CH_3$ group.

(d) 2-Pentanol [$CH_3CH(OH)CH_2CH_2CH_3$] containing the $CH_3CH(OH)–$ group gives a positive iodoform test.

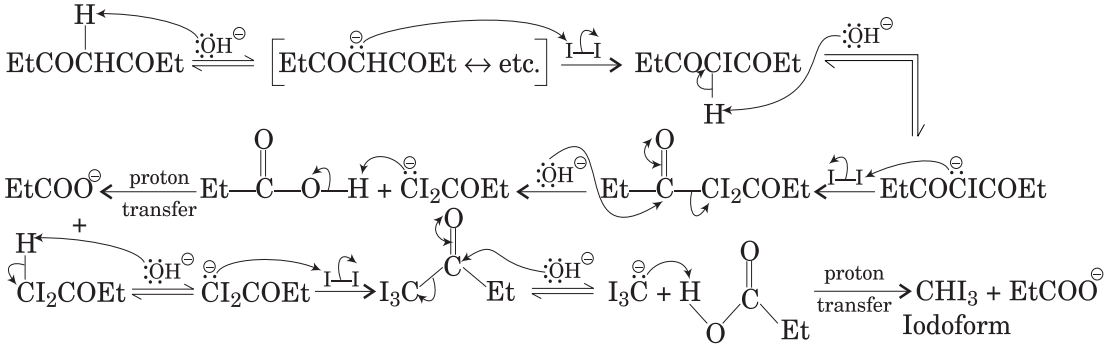
(e) 3-Hexanol [$CH_3CH_2CH(OH)CH_2CH_2CH_3$] does not respond to this test as it contains no $CH_3CH(OH)–$ group.

(f) Acetaldehyde (CH_3CHO) containing the $CH_3CO–$ group gives a positive iodoform test. In fact, it is the only aldehyde which responds to this test.

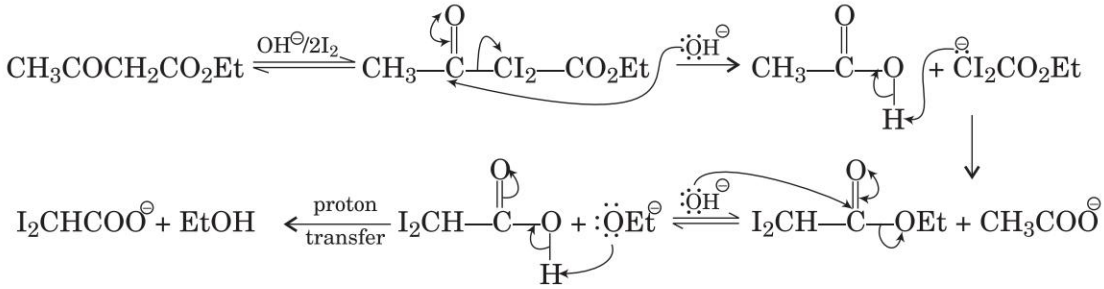
(g) Phenacyl iodide ($PhCOCH_2I$) gives a positive iodoform test because it contains a $–COCH_2I$ group which is generated by monoiodination of the $–CH_3CO$ group of acetophenone ($PhCOCH_3$).

3. The diketone $CH_3CH_2COCH_2COCH_2CH_3$ (heptane–3,5-dione) gives a positive iodoform test, even though it contains no $–COCH_3$ group. However, the ketoester $CH_3COCH_2CO_2Et$ (ethyl acetoacetate) does not respond to this test, even though it contains a $–COCH_3$ group. Explain these observations mechanistically.

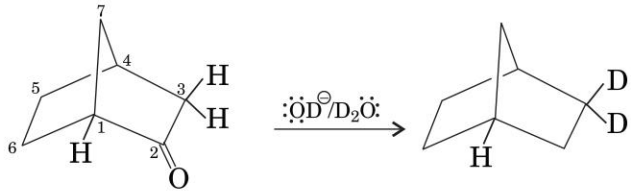
Solution There is an active methylene group ($—CO—CH_2—CO—$) in the diketone molecule. Since the methylene hydrogens are relatively more acidic than other hydrogens in the molecule, the compound undergoes iodination in the presence of base to yield $CH_3CH_2COCI_2COCH_2CH_3$ first. The compound then undergoes nucleophilic attack by $OH^{\ominus}$ followed by C—C bond cleavage to give $I_2CHCOCH_2CH_3$. This diiodo ketone undergoes haloform reaction to yield iodoform (CHI_3). The sequence may be outlined as follows:



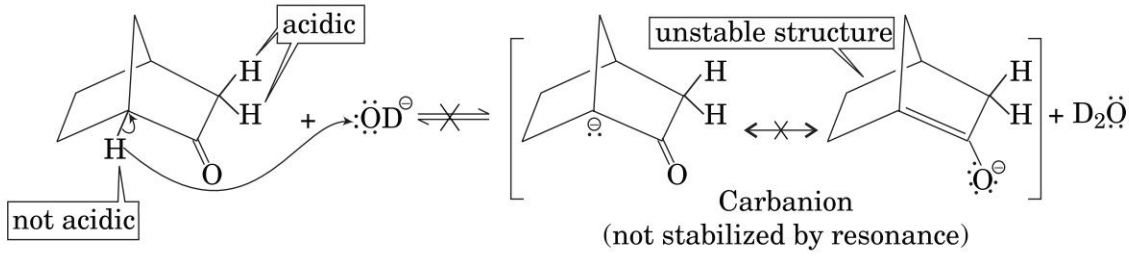
Ethyl acetoacetate ($CH_3COCH_2CO_2Et$) also contains an active methylene group. So, it also undergoes iodination to yield $CH_3COCI_2CO_2Et$ first. This diiodo compound undergoes nucleophilic attack by $OH^{\ominus}$ on the more positive ketonic carbonyl carbon (due to the +R effect of the –OEt group, the carbonyl carbon of the $-CO_2Et$ group is less positive) followed by C—C bond cleavage to yield a diiodoester. The diiodoester then undergoes alkaline hydrolysis to yield diiodoacetate ion ($OEt^{\ominus}$ is a better leaving group than $\ddot{C}HI_2$) instead of iodoform. The reaction sequence may be written as follows:

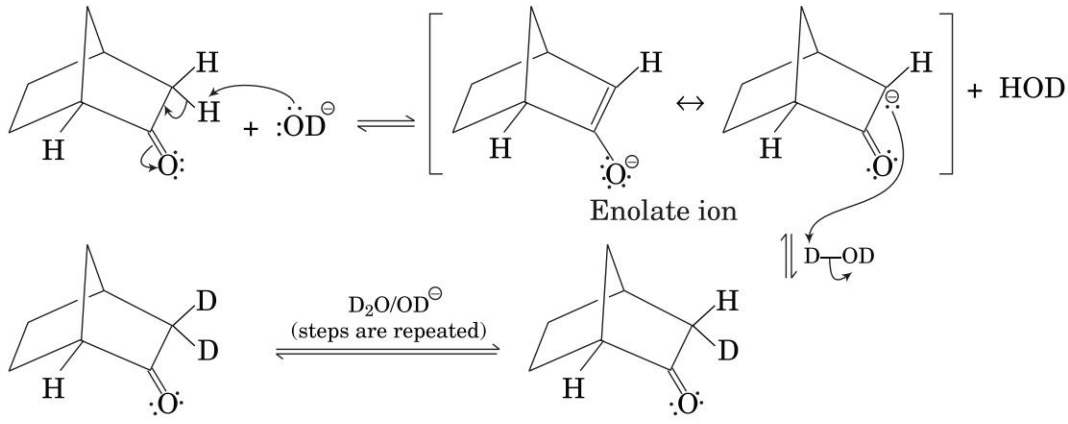


4. The bicyclic ketone in the following reaction exchanges only the two α-hydrogens attached to C-3 and not the bridgehead α-hydrogen (attached to C-1). Account for this observation.



Solution The carbanion that might be obtained as a result of abstraction of the bridgehead hydrogen (i.e., C-1 hydrogen) by base ($:\ddot{O}D^{\ominus}$) is not stabilized by resonance involving the C═O group and this is because according to the Bredt's rule a double bond cannot be formed at the bridgehead position due to steric reason. So, the base cannot abstract this bridgehead hydrogen and its substitution by D does not take place. On the other hand, the enolate obtained as a result of abstraction of a C-3 α-hydrogen is stabilized by resonance. Therefore, these two relatively acidic hydrogens are substituted by D, through the formation of enolate.

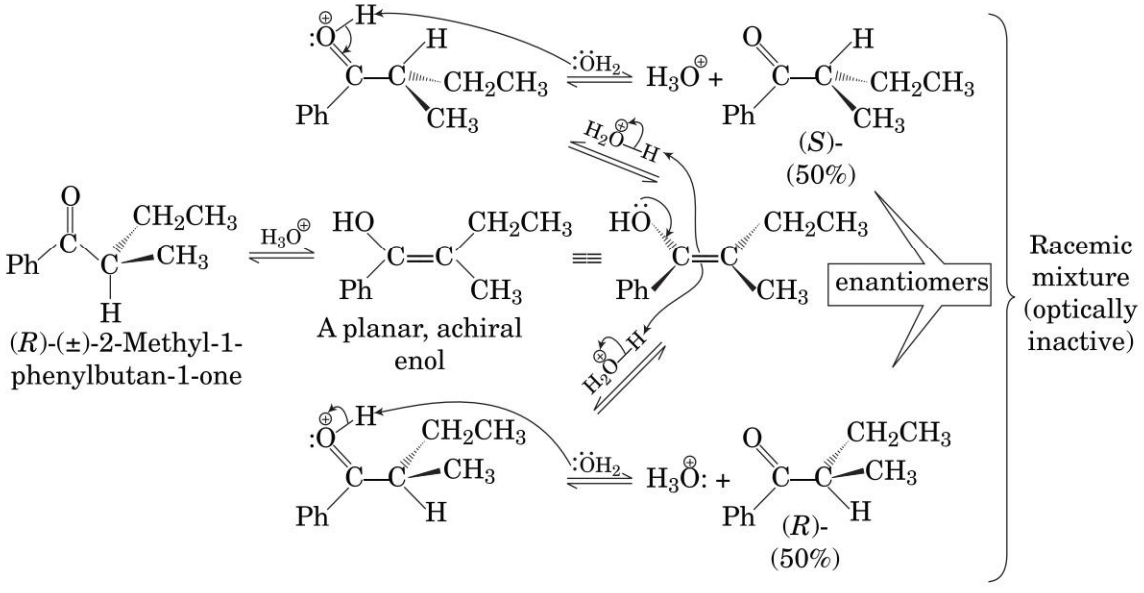




5. When (*R*)-(+)-2-methyl-1-phenylbutan-1-one or (*S*)-(–)-2-methyl-1-phenylbutan-1-one is treated with either acid or base, the solution gradually loses its optical activity. Provide a mechanistic explanation for this observation.

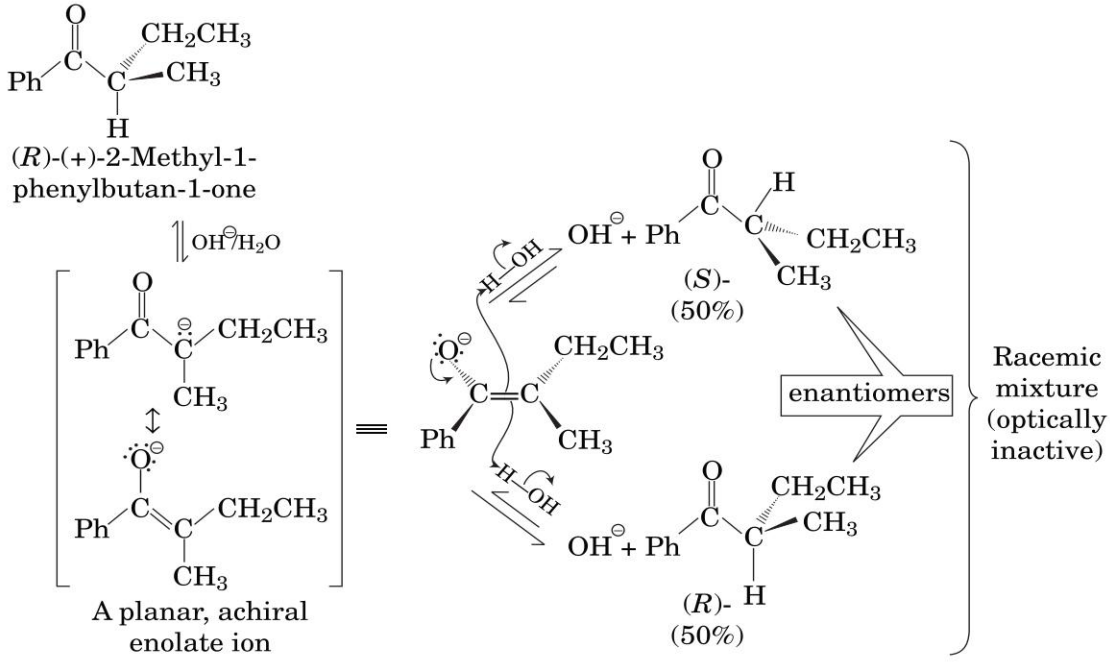
Solution When a solution of (*R*)-(+)- or (*S*)-(–)-2-methyl-1-phenylbutan-1-one is treated with an aqueous solution NaOH, it undergoes base-catalyzed racemization and when treated with aqueous solution HCl, it undergoes acid-catalyzed racemization. For this reason, the solution gradually loses its optical activity.

In the presence of acid, an achiral, planar enol is formed. Reformation of the keto-form occurs by protonation from either of the two enantiotropic faces of the enol with equal facility to form equal amounts of the two enantiomers.



Racemization of the (*S*)-enantiomer occurs similarly.

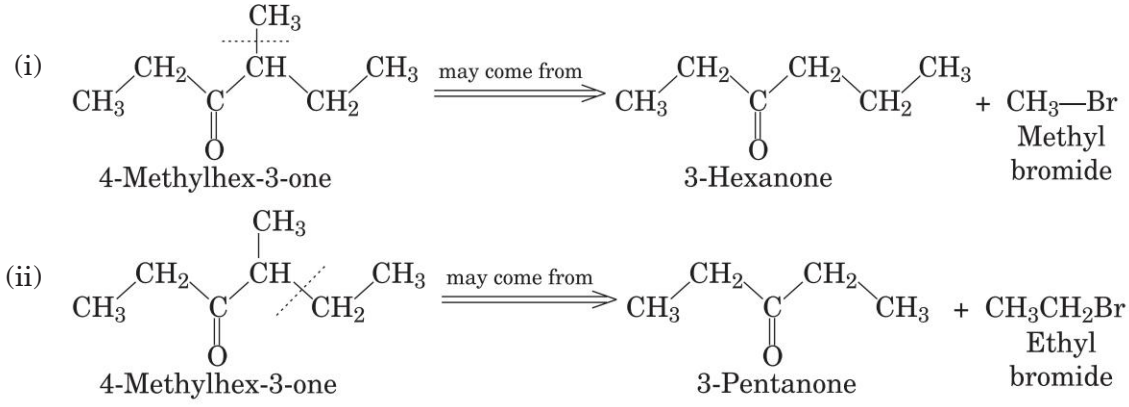
In the presence of base, an achiral, planar enolate is formed. Reformation of the keto-form occurs by protonation from either of the two enantiotropic faces of the enolate with equal facility to produce equal amounts of the two enantiomers.



Racemization of the (*S*)-enatiomer occurs similarly.

6. How can 4-methylhex-3-one $(CH_3CH_2CO\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CH_3)$ **can be prepared by alkylating a ketone containing no more than six carbon atoms. Which one of the possible sets of reactants is more appropriate and why?**

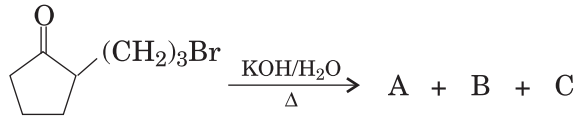
Solution Any one of the following two sets of ketone and alkyl halide could be used for the synthesis of 4-methylhex-3-one:



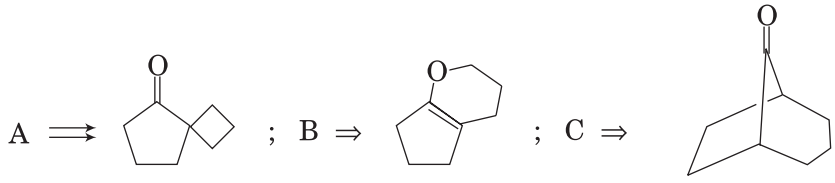
The set (ii) is the preferred stets of starting materials because 3-pentanone being a symmetrical ketone reacts with base to form a single enolate and therefore only one α-substituted ketone, i.e., the desired ketone, will be obtained.

On the other hand, the unsymmetrical ketone 3-hexanone can form two different enolates and hence, two α-substituted ketones can be formed. As a consequence, the yield of the target molecule will be decreased.

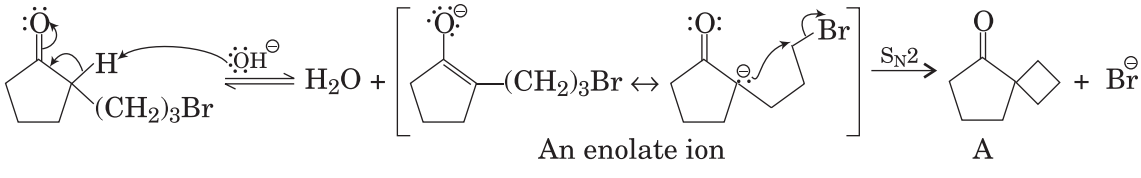
7. Predict the products (A, B and C) of the following reaction (intramolecular alkylation) and give mechanisms to explain their formation.



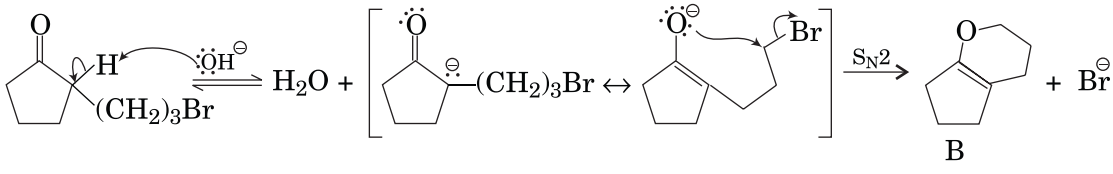
Solution



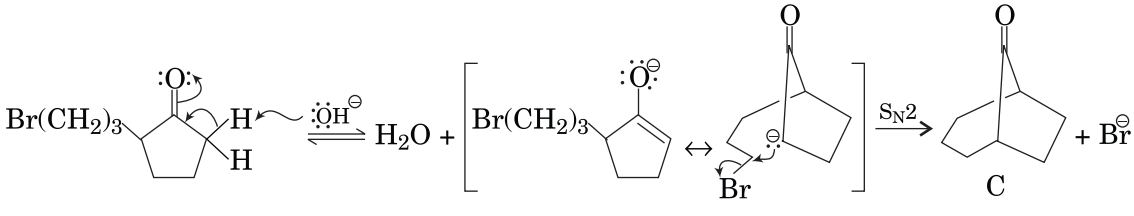
Formation of A:



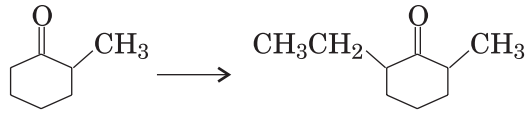
Formation of B:



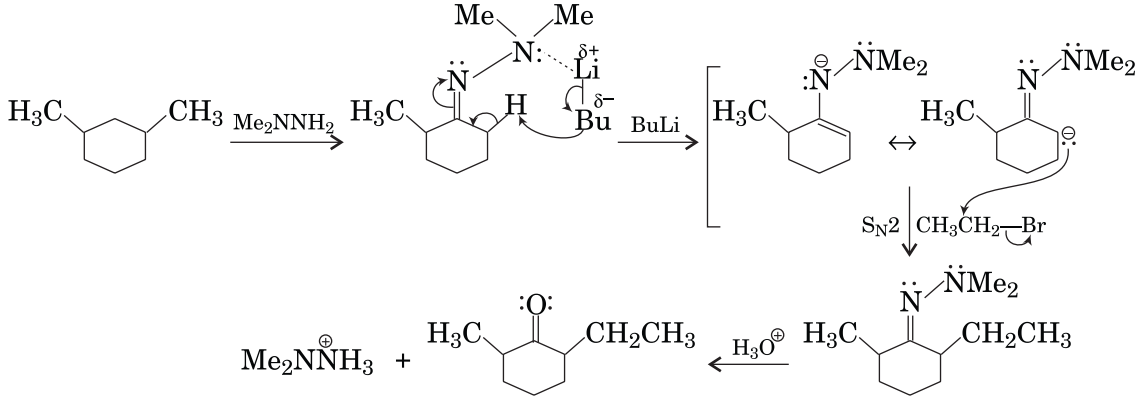
Formation of C:



8. How would you carry out the following transformation by using *N*, *N*-dimethylhydrazine. Give your reasoning.



Solution The less substituted α-carbon of the ketone can be alkylated (without having to control the conditions of the reaction to make certain that the reaction does not become reversible) by making the *N*,*N*-dimethyl-hydrazone of the ketone followed by treating the hydrazone with the base BuLi. The base abstracts a hydrogen from the less substituted α-carbon to form a carbanion (resonance-stabilized) which is treated with CH_3CH_2Br to yield the alkylated hydrazone. The hydrazone is hydrolyzed with dilute acid to get back the ketone.

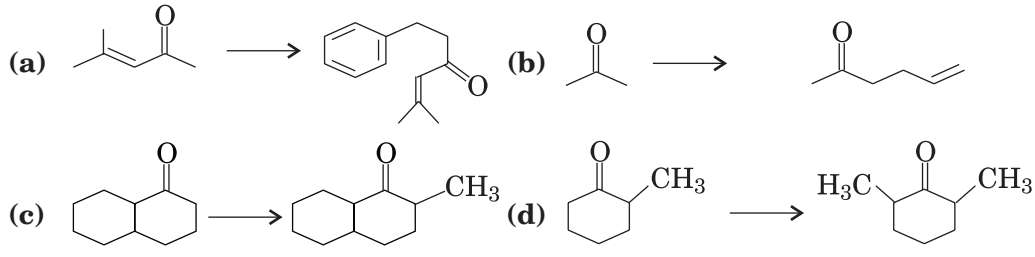


To avoid steric strain, the dimethylamino group in the resulting hydrazone (in the first step) is pointing away from the more substituted α-carbon. The nitrogen atom of the $-NMe_2$ group directs the base the less substituted carbon by coordinating with the lithium ion of butyllithium $(\overset{\delta-}{Bu}\overset{\delta+}{Li})$.

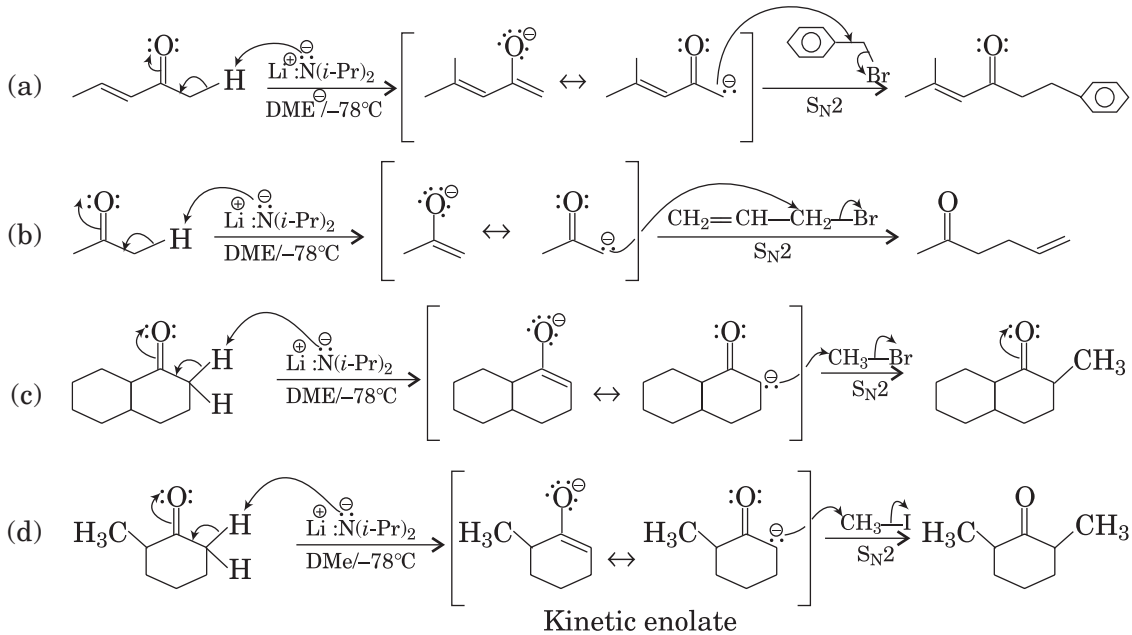
9. How does the alkylation of an enamine compare with the alkylation of an enolate?

Solution Alkylation by way of enamine is far superior, because it minimizes double or multiple alkylation. It has the additional advantage that it can be used to prepare alkylated aldehydes.

10. How would you carry out the following transformations via a lithium enolate?

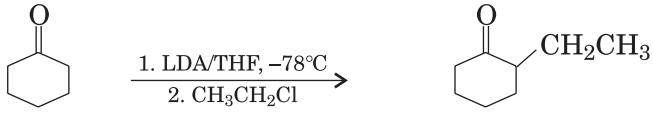


Solution



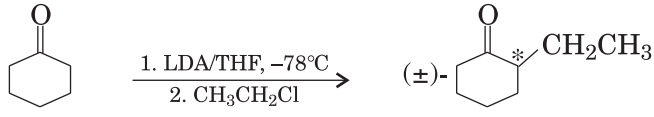
Kinetic enolate

11. Predict the stereochemical outcome of the following reaction:



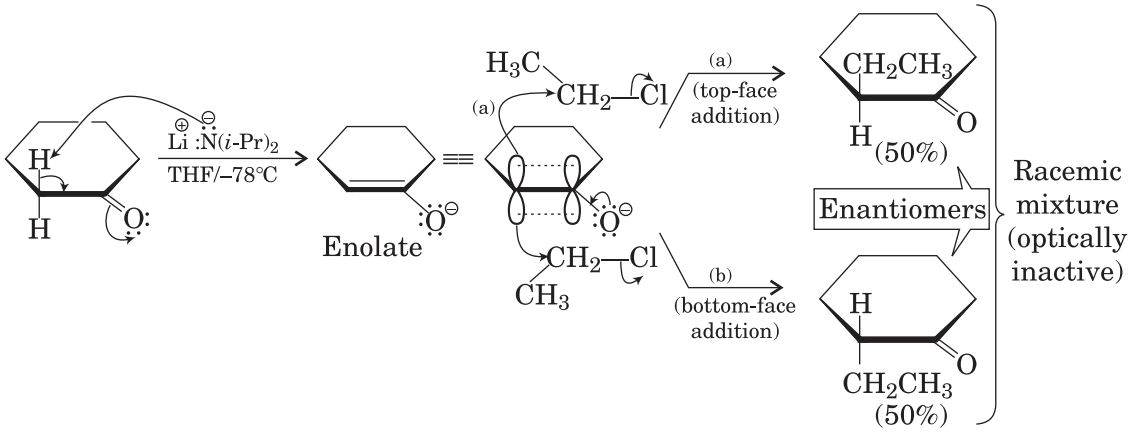
Cyclohexanone 2-Ethylcyclohexanone

Solution In enolate alkylation, an achiral starting material yields an optically inactive racemic product. When cyclohexanone (an achiral starting material) is converted to 2-ethylcylclohexanone by treatment with the strong base LDA in THF followed by CH_3CH_2Cl, a stereogenic centre is created. Since alkylation of the enolate occurs from the two enantiotropic faces of the enolate with equal facility, the two enantiomers of the alkylated ketone are obtained in equal amounts, i.e., an optically inacitve racemic mixture is formed.



Racemic mixture
(optically inactive)

The stereochemical course of the reaction may be shown as follows:



12. Show how would you use acetoacetic ester synthesis to prepare the following ketones:

(a) Butanone ($CH_3COCH_2CH_3$)

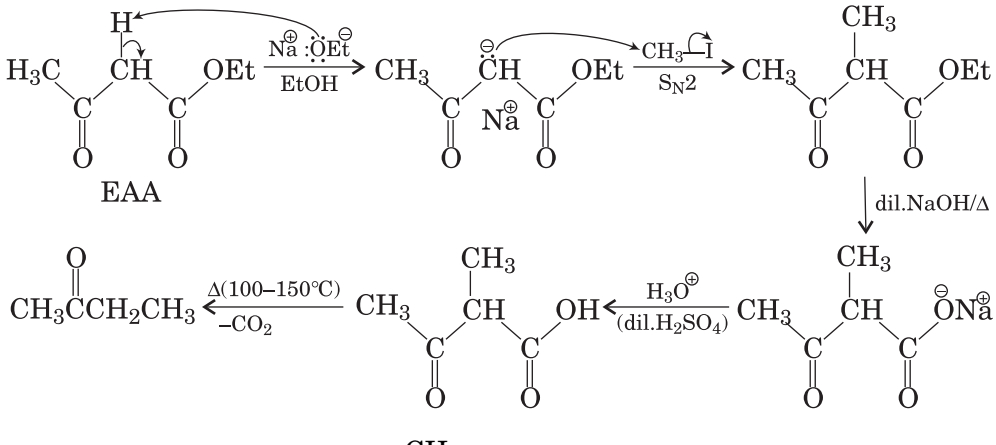
(b) 3-Methylbutanone [$CH_3COCH(CH_3)_2$]

(c) 3-Methylpentan-2-one ($CH_3COCCH_2CH_3$, CH_3)

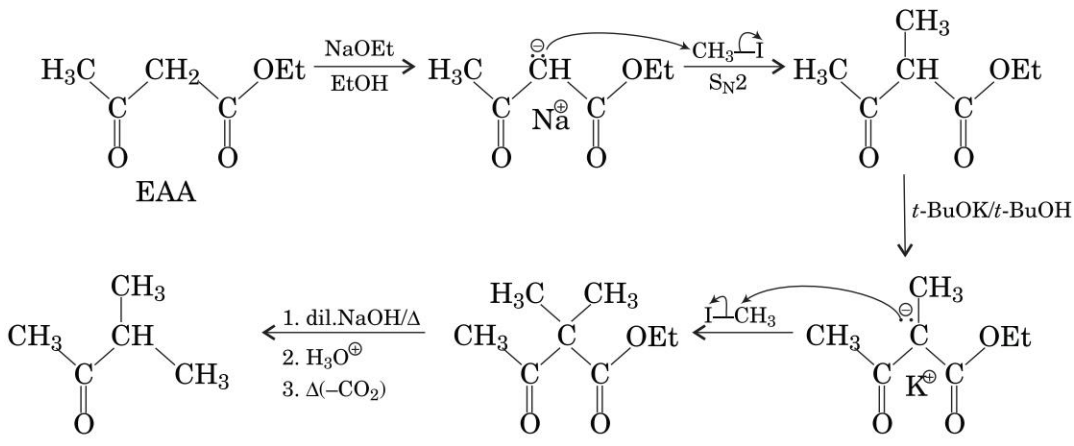
(d) Cyclopropyl methyl ketone

Solution

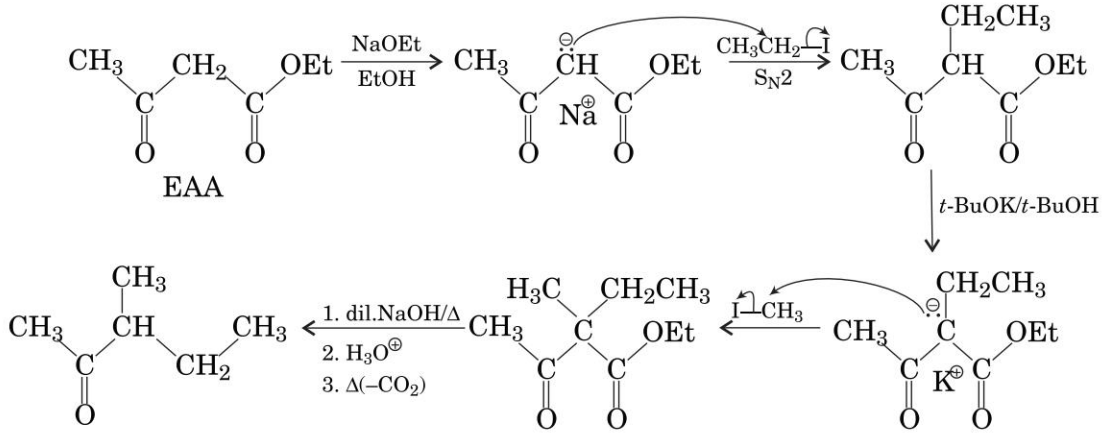
(a) **Butanone** ($CH_3COCH_2CH_3$)



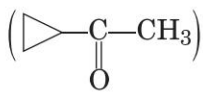
(b) **3-Methylbutanone** ($CH_3COCHCH_3$, CH_3)

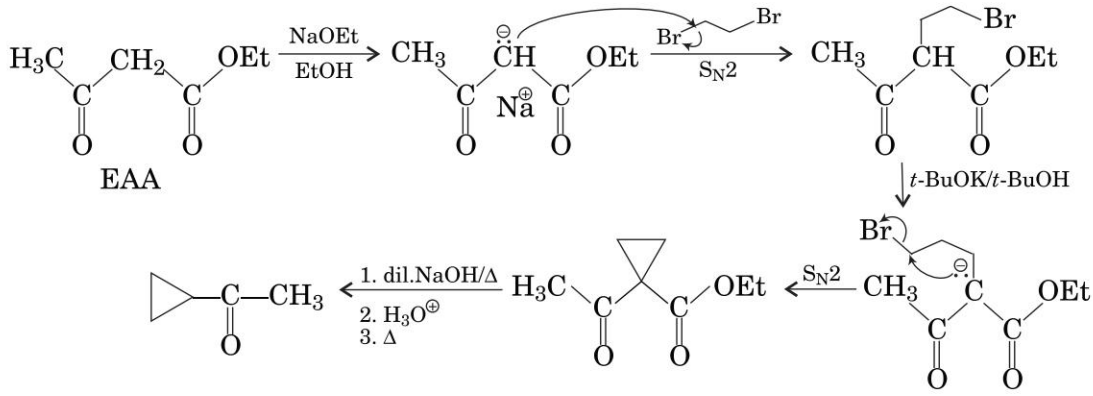


(c) **3-Methylpentan-2-one** ($CH_3COCHCH_2CH_3$, CH_3 on the CH)



Because of steric reason, the larger alkyl group, $-C_2H_5$, is to be introduced before the smaller alkyl group, $-CH_3$.

(d) **Cyclopropyl methyl ketone** ()



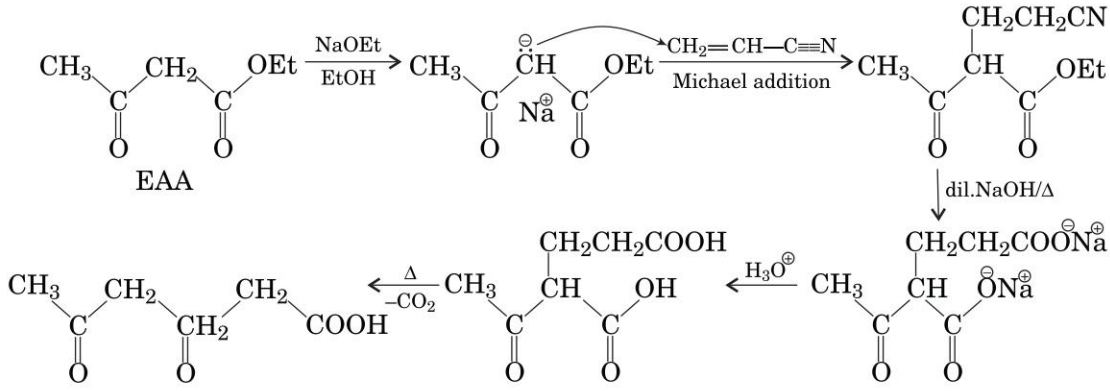
13. How would you carry out the synthesis of the following ketonic acids starting from ethyl acetoacetate?

(a) 5-Oxohexanoic acid ($CH_3COCH_2CH_2CH_2COOH$)

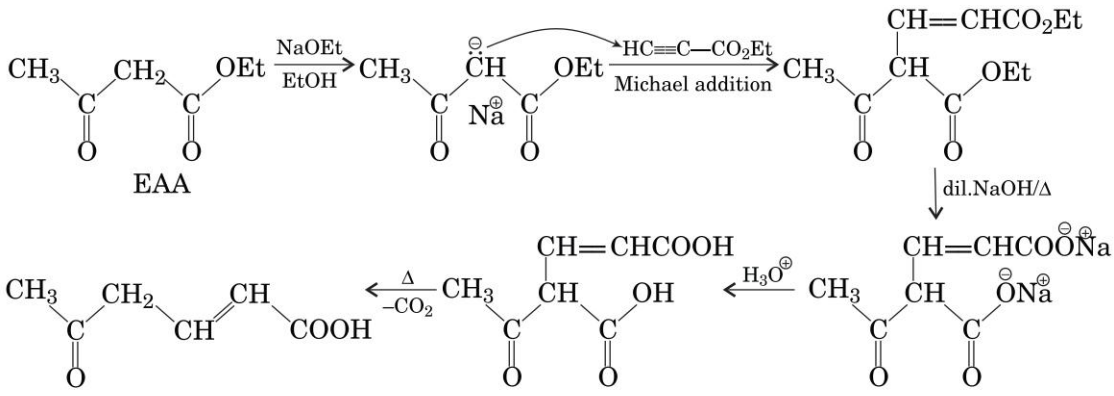
(b) 5-Oxo-2-hexenoic acid ($CH_3COCH_2CH{=}CHCO_2H$)

Solution

(a) **5-Oxohexanoic acid** ($CH_3COCH_2CH_2CH_2COOH$)



(b) **5-Oxo-2-hexenoic acid** ($CH_3COCH_2CH{=}CHCOOH$)



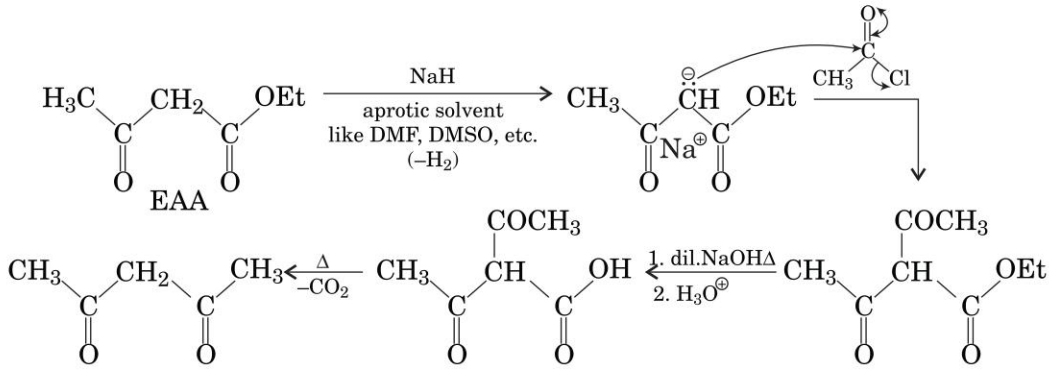
14. Outline all steps in a acetoacetic ester synthesis of each of the following diketones:

(a) Pentane-2,4-dione ($CH_3COCH_2COCH_3$)

(b) Heptane-2,6-dione ($CH_3COCH_2CH_2CH_2COCH_3$)

Solution

(a) **Pentane-2,4-dione** ($CH_3COCH_2COCH_3$)

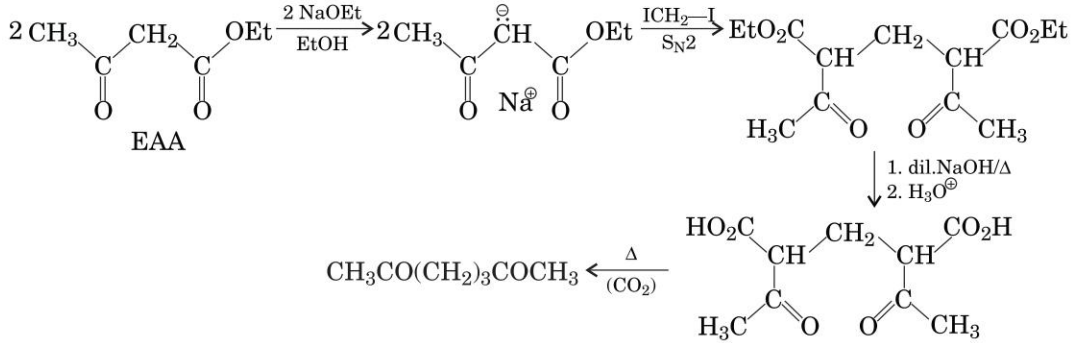


The use of NaOEt in EtOH is avoided in this synthesis because ethanol reacts with acid chloride to form an ethyl ester:

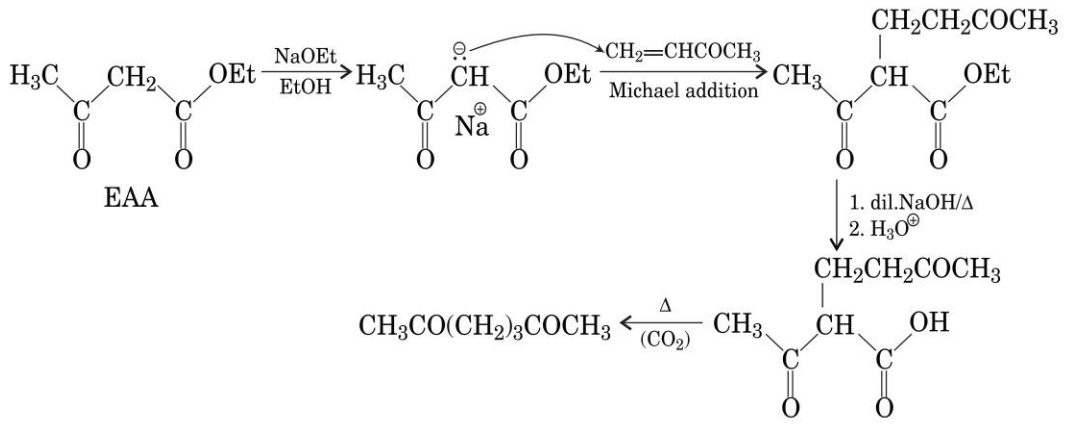
$$CH_3COCl + EtOH \rightarrow CH_3CO_2Et + HCl$$

(b) **Heptane-2,6-dione** ($CH_3COCH_2CH_2CH_2COCH_3$)

(i)



(ii)



15. How would you use the acetoacetic ester synthesis to prepare each of the following carboxylic acids?

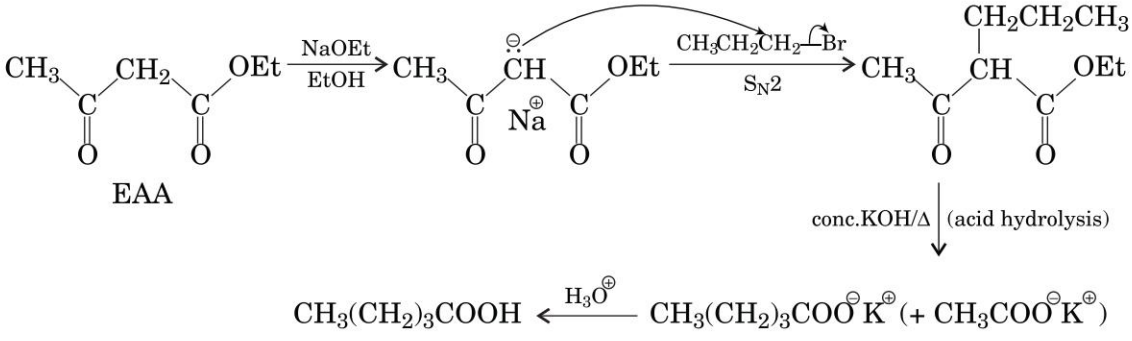
(a) Pentanoic acid ($CH_3CH_2CH_2CH_2COOH$)

(b) Succinic acid ($HO_2C\,CH_2CH_2CO_2H$)

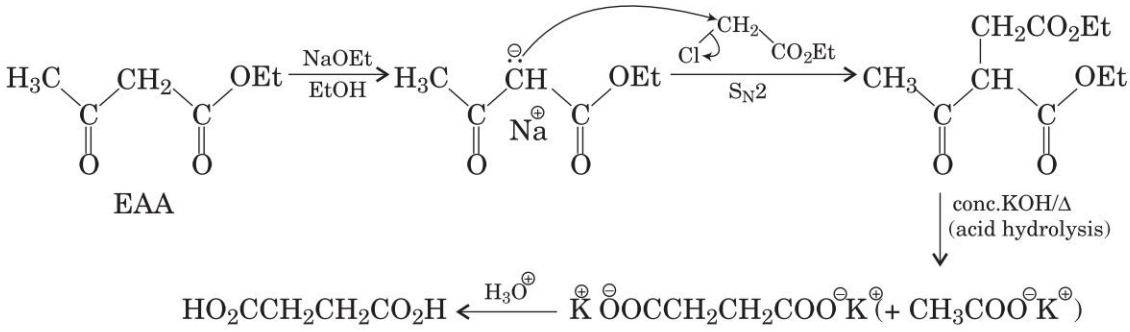
(c) Crotonic acid ($CH_3CH{=}CHCOOH$)

Solution

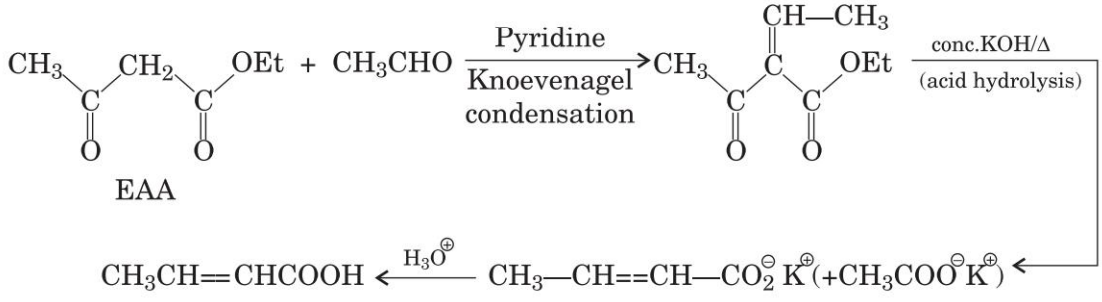
(a) **Pentanoic acid** ($CH_3CH_2CH_2CH_2COOH$)



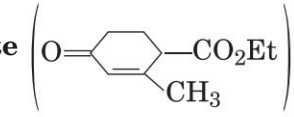
(b) **Succinic acid** ($HO_2C\,CH_2CH_2CO_2H$)

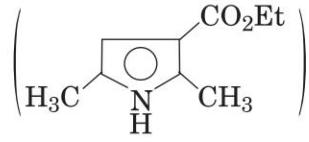


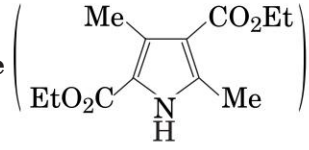
(c) **Crotonic acid** ($CH_3CH{=}CHCOOH$)

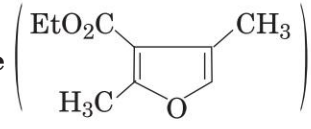


16. Show how you would use acetoacetic ester to prepare each of the following compounds:

(a) Ethyl 2-methyl-4-oxo-2-cyclohexene carboxylate 

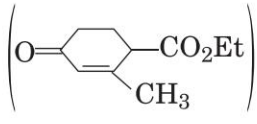
(b) Ethyl 2,5-dimethylpyrrole-3-carboxylate 

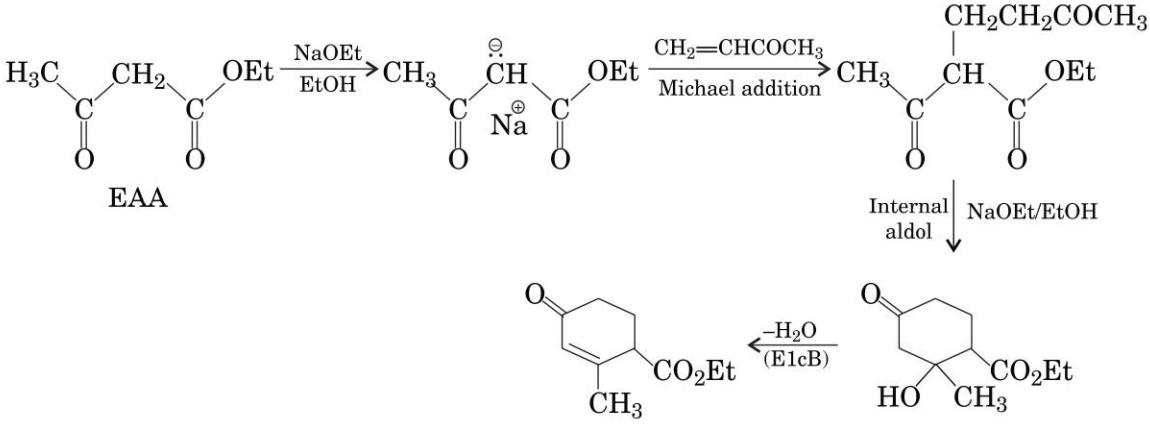
(c) Ethyl 3,5-dimethylpyrrole-2,4-dicarboxylate 

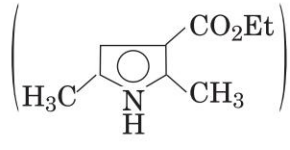
(d) Ethyl 2,4-dimethylfuran-3-carboxylate 

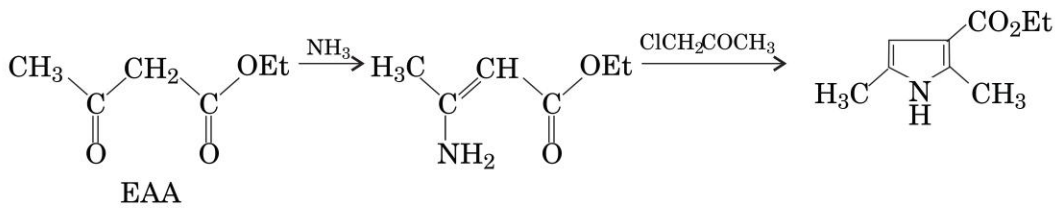
Solution

(a) **Ethyl 2-methyl-4-oxo-2-cyclohexene carboxylate**

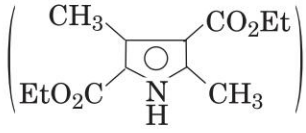


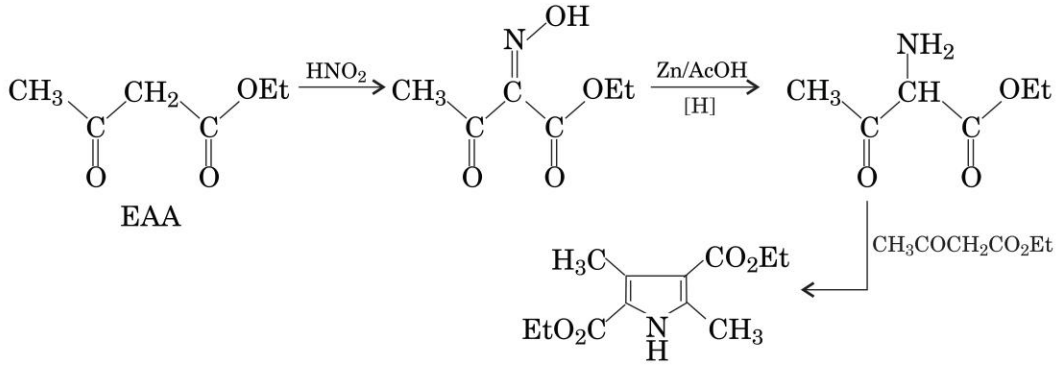


(b) **Ethyl 2,5-dimethylpyrrole-3-carboxylate** 

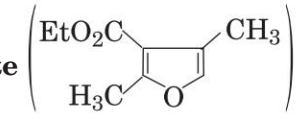


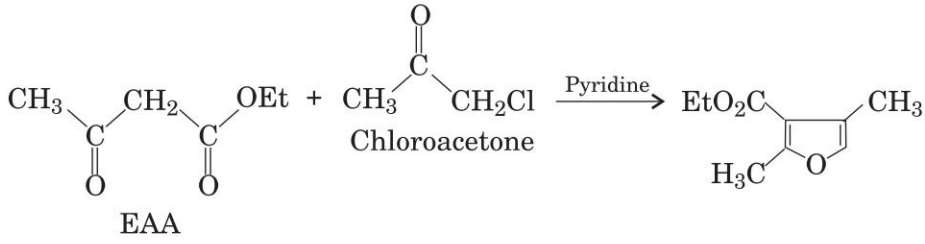
(c) **Ethyl 3,5-dimethylpyrrole-2,4-dicarboxylate**



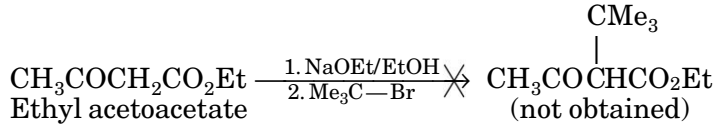


(d) **Ethyl 2,4-dimethylfuran-3-carboxylate**





17. (a) Explain why the following transformation cannot be accomplished:

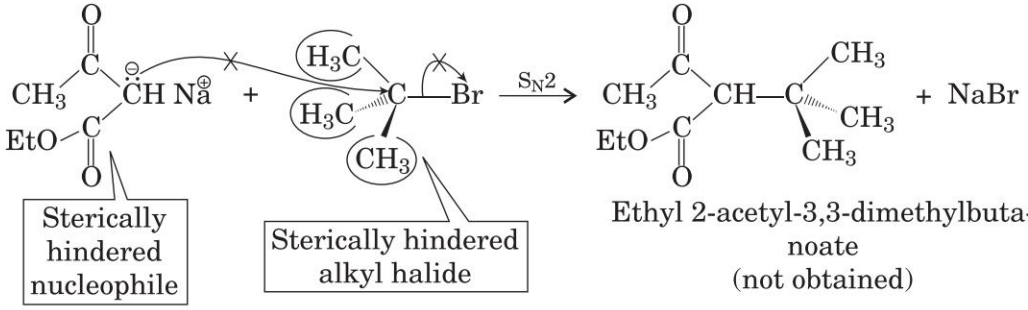


(b) What is the product actually obtained in this case?

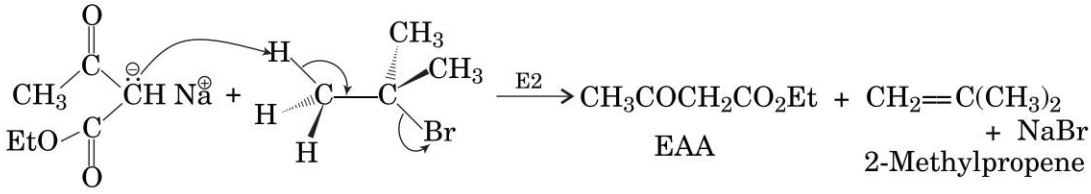
(c) How can a *tert*-butyl group be introduced into methylene carbon of EAA for carrying out the synthesis of 4,4-dimethyl-2-pentanone ($CH_3COCH_2CMe_3$)? Give the mechanism of *tert*-butylation of EAA.

Solution

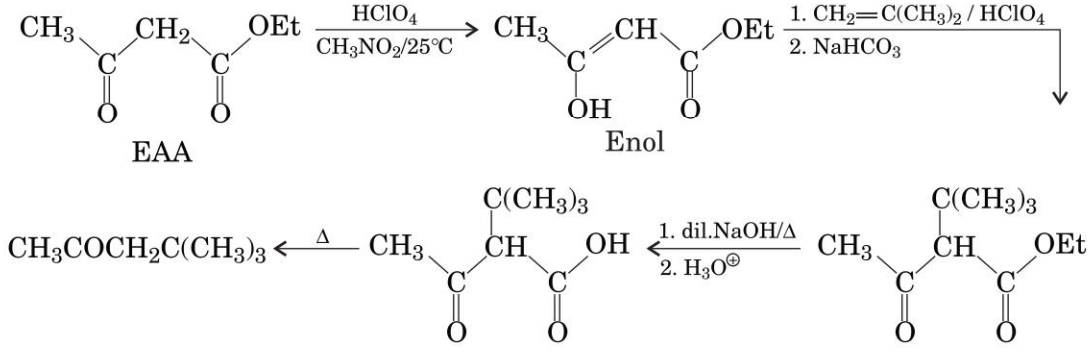
(a) Because the bulky alkyl groups present a strong hindrance to the approaching nucleophile from the backside of the leaving group, tertiary substrates do not react by an S_N2 mechanism. The alkylation of EAA is an S_N2 reaction and, therefore, the reaction of sodio EAA *tert*-butyl bromide does not take place.



(b) When ethyl acetoacetate is treated with NaOEt in EtOH and the resulting sodio salt is allowed to react with Me_3CBr, an elimination (E2) reaction leading to 2-methylpropene takes place.



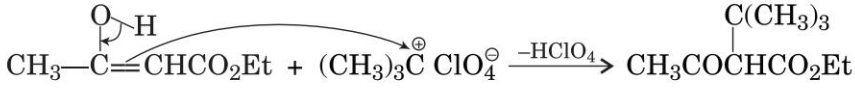
(c) A *tert*-butyl group can be introduced into the methylene carbon EAA by an indirect process in which EAA is treated with 2-methylpropene in the presence of perchloric acid ($HClO_4$). Therefore, 4,4-dimethyl-2-pentanone can be prepared as follows:



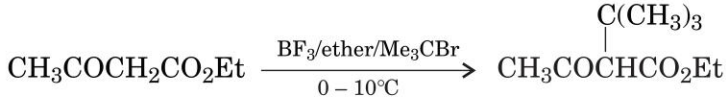
The mechanism of *tert*-butylation of EAA is as follows:



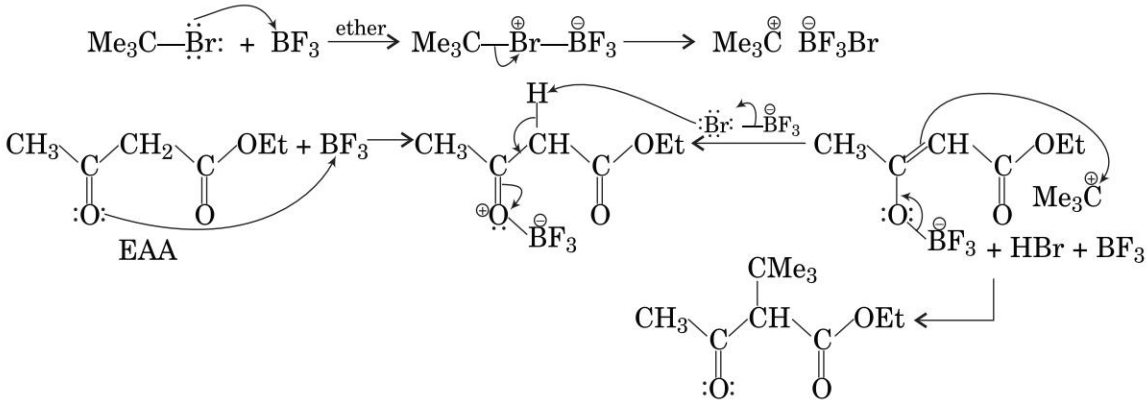
2-Methylpropene



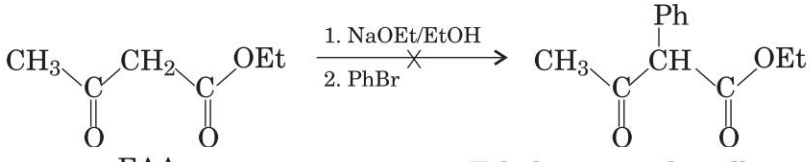
A *tert*-butyl group can also be introduced into the methylene carbon of EAA by allowing EAA to react with Me_3CBr in the presence of the Lewis acid BF_3.



The mechanism of the reaction is as follows:

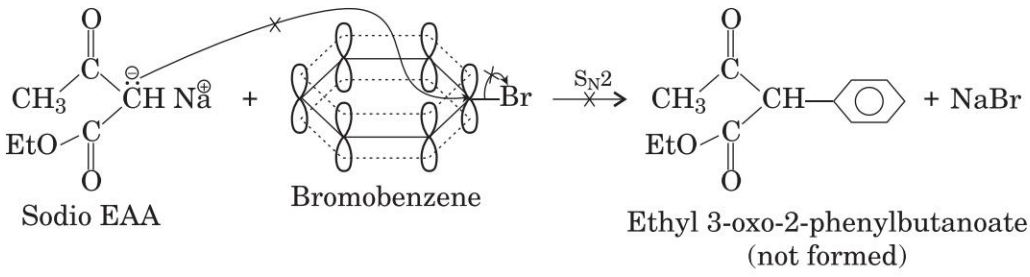


18. Explain why the following transformation cannot be accomplished (i.e., bromobenzene cannot be used as the acylating agent):

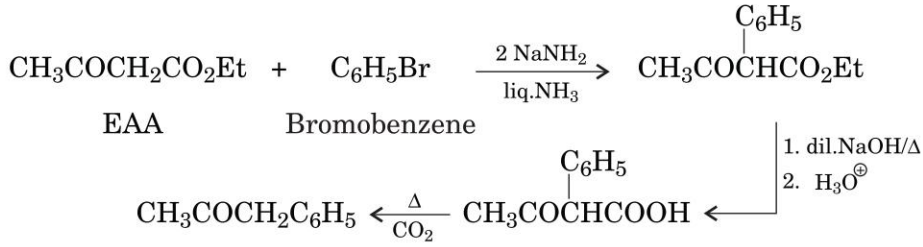


How can benzyl methyl ketone (CH_3COCH_2Ph) be prepared from ethyl acetoacetate by introducing a phenyl group into its methylene carbon? Discuss the mechanism of phenylation of EAA.

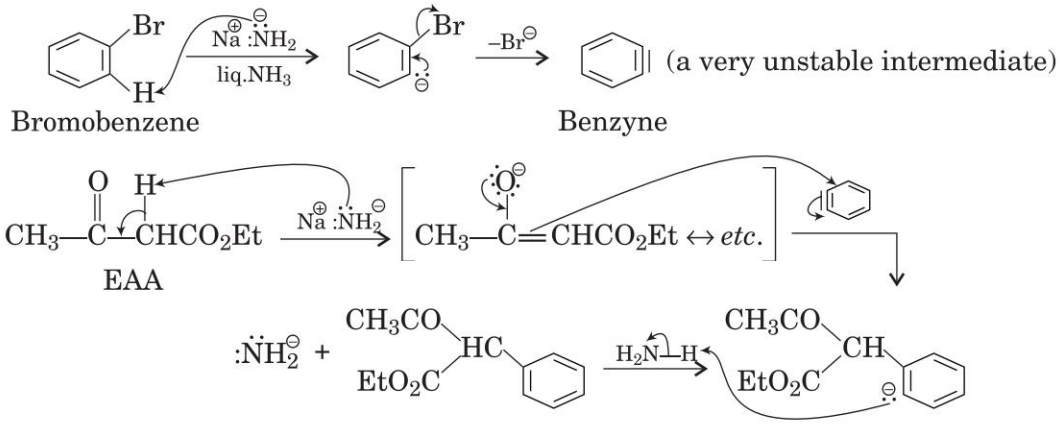
Solution Because of resonance interaction of the unshared pair of electrons on bromine with the ring π-electrons, the C—Br bond becomes somewhat shorter and stronger. Also, the ring π-electrons repel the approach of the negatively charged nucleophile from the backside. For this reason, bromobenzene does not undergo nucleophilic substitution (S_N2) reaction, i.e., it cannot be used as an arylating agent in an acetoacetic ester synthesis.



Phenylation of EAA leading to the formation of benzyl methyl ketone may be carried out by a process involving benzyne as an intermediate. Ethyl acetoacetate is treated with bromobenzene in the presence of two molar equivalents of the strong base sodamide ($NaNH_2$). One equivalent of base is used to convert bromobenzene to benzyne and the other equivalent is used to convert EAA to its sodio salt. The highly reactive intermediate benzyne then reacts with the sodio salt of EAA to yield phenyl substituted EAA which on ketonic hydrolysis gives benzyl methyl ketone (CH_3COCH_2Ph).



The mechanism of phenylation of EAA is as follows:



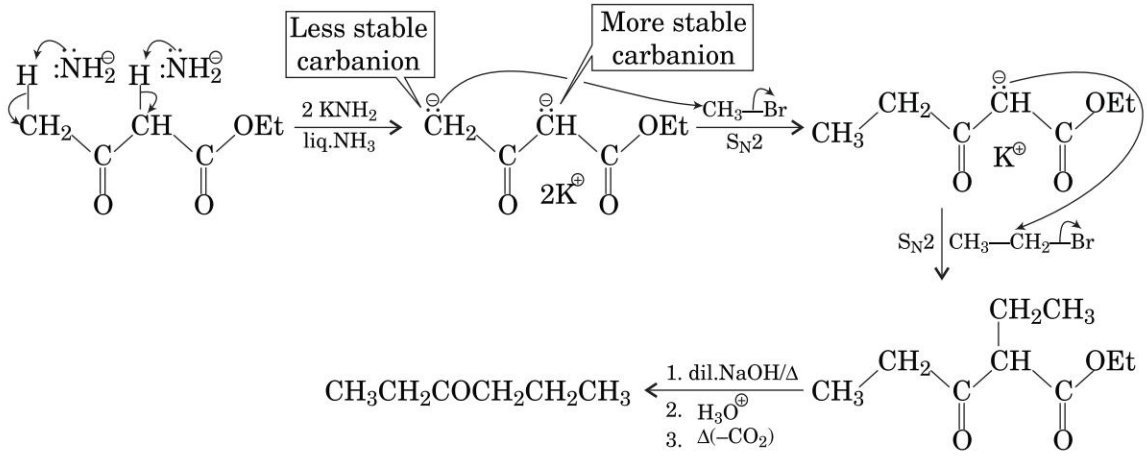
19. How would you carry out the following transformation?

$$CH_3COCH_2CO_2Et \longrightarrow CH_3CH_2COCH_2CH_2CH_3$$

EAA Hexan-3-one

Solution From the structure of the ketone, it becomes evident that ethyl acetoacetate is to be alkylated at the terminal carbon atom, i.e., at C-4 as well as at C-2. When EAA

is treated with two equivalents of a very strong base such as KNH_2 in liquid ammonia, a resonance-stabilized dianion is formed. In this dianion, the terminal carbanion is more nucleophilic than the other involving α-carbon atom. This is because the negative charge on C-4 is stabilized by only one carbonyl groups, while the negative charge on C-2 is stabilized by the two adjacent carbonyl groups. Therefore, when one mole of alkyl halide is used, the alkylation takes place at the terminal (C-4) carbon. In this case, the dianion is allowed to react first with methyl bromide and then with ethyl bromide to yield, after ketonic hydrolysis, hexan-3-one.

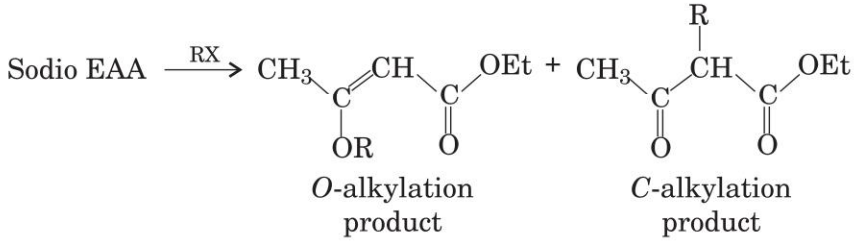


20. (a) Mention the side reaction that prevails with EAA but not with DEM (diethyl malonate).

(b) Discuss the effect of the following factors on the ratio of *C*-versus *O*-alkylation: (i) solvent used, (ii) countercation involved, (iii) leaving ability of X in RX and (iv) size of R in RX.

Solution

(a) *O*-alkylation competes with *C*-alkylation to give an enol ether:



(b) (i) Protic solvents usually favour *C*-alkylation because the $O^{\ominus}$ is deactivated by ion pairing by H-bonding. In aprotic solvents, there is an increase in *O*-alkylation because the metal ion H^+ coordinates with the aprotic solvent, and the $O^{\ominus}$ is set free to react.

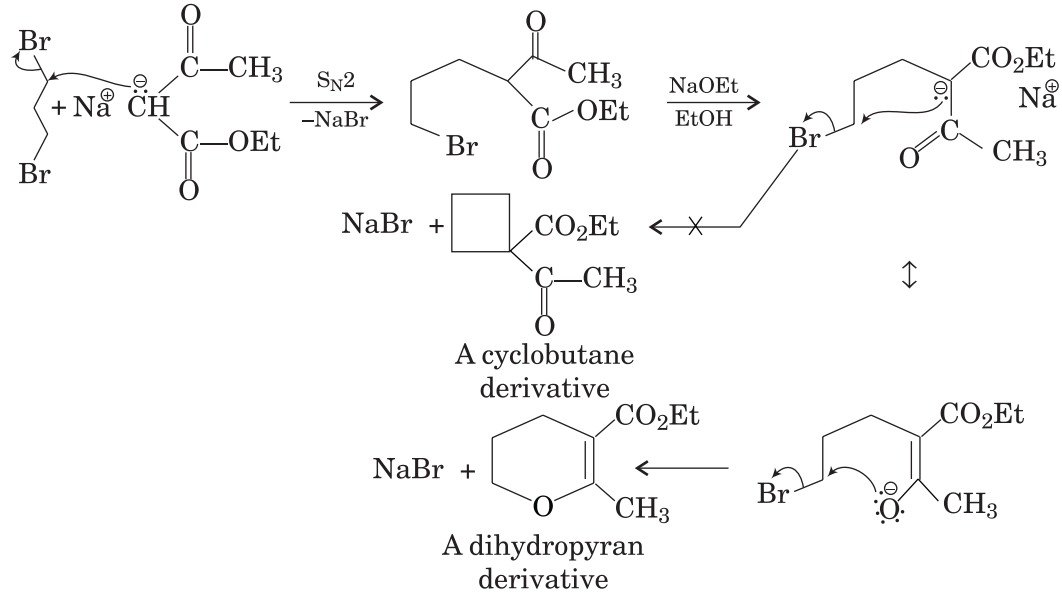
(ii) *C*-alkylation is favoured in the case of Li^+ because it preferably coordinates with $O^{\ominus}$. However, since $Na^{\oplus}$ and $K^{\oplus}$ poorly coordinate with O^-, there is an increase in *O*-alkylation

(iii) A more easily polarized nucleophile (soft base) reacts faster with RX when X is easily polarized, i.e., RX is a soft acid. On the other hand, a less easily polarized nucleophile (hard base) reacts faster with RX when X is not easily polarized, i.e., RX is a hard acid. A carbanion being a soft base reacts faster with the softest alkyl halide R-I. Therefore, the order of *C*-alkylation is R–I ⟩ R–Br ⟩ R–Cl ⟩ $ROSO_2OR$,. Since $O^{\ominus}$ is a hard base, the order of *O*-alkylation is exactly the reverse.

(iv) The *O*-alkylation is favoured with increase in size of R.

21. By using acetoacetic ester, it is possible to prepare rings containing three, five, six and seven carbon atoms, but not four; all attempts to synthesize a four-membered ring result in the formation of a dihydropyran derivative. Explain the observation.

Solution When sodio EAA is allowed to react with 1,3-dibromopropane, alkylation occurs. However, when the resulting compound is treated with NaOEt/EtOH, the enolate ion obtained does not undergo intramolecular C-alkylation. This is due to the fact that the distance between the two reacting carbon atoms is not favourable and the cyclobutane derivative, which is expected to be formed, suffers from angle strain. Therefore, it is an energetically unfavourable pathway. In an alternate pathway, the negative oxygen of the enolate comes very close to the carbon–bearing bromine and displaces (S_N2) bromine to form a relatively unstrained six-membered ring. The reaction, therefore, proceeds through this energetically favourable pathway to yield a dihydropyran derivative.



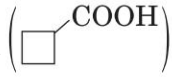
22. How would you use the malonic ester synthesis to prepare each of the following carboxylic acids?

(a) Propanoic acid (CH_3CH_2COOH)

(b) 2-Methylpropanoic acid [$CH_3CH(CH_3)COOH$]

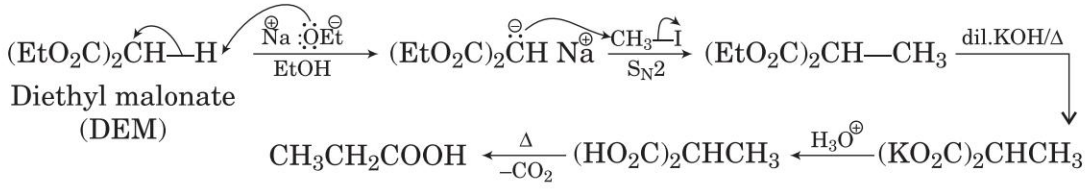
(c) Phenylacetic acid ($PhCH_2COOH$)

(d) Crotonic acid ($CH_3CH=CHCOOH$)

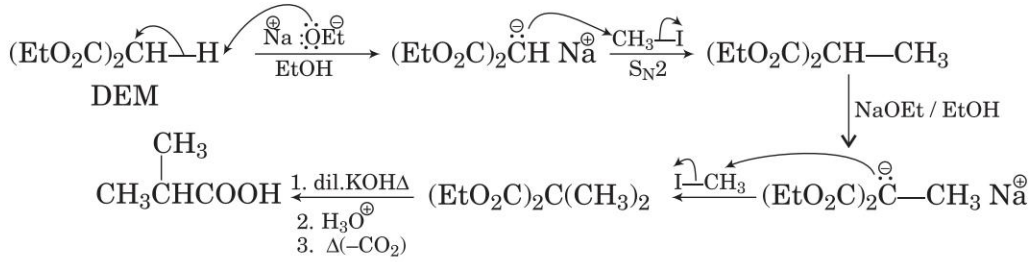
(e) Cyclobutanecarboxylic acid 

Solution

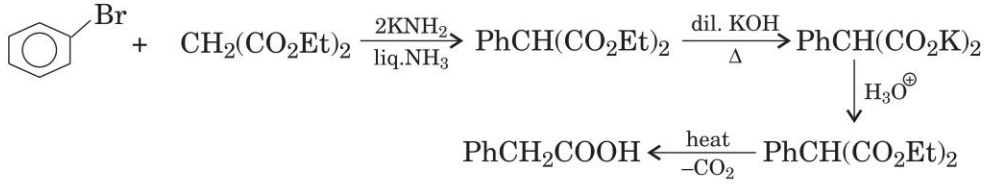
(a) **Propanoic acid** (CH_3CH_2COOH)



(b) **2-Methylpropanoic acid** [$CH_3CH(CH_3)COOH$]

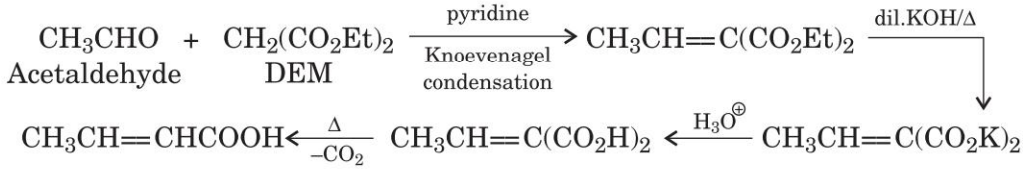


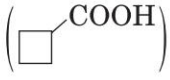
(c) **Phenylacetic acid** ($PhCH_2COOH$)

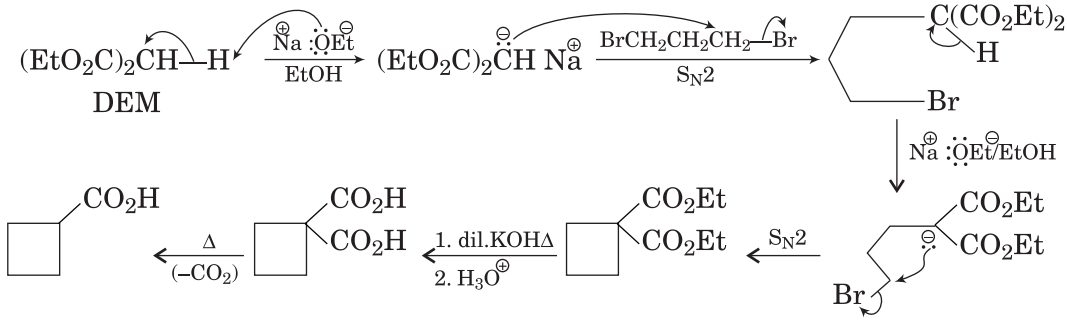


The phenyl group introduced in DEM through the formation by benzyne intermediate.

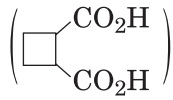
(d) **Crotonic acid** ($CH_3CH=CHCOOH$)

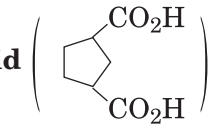


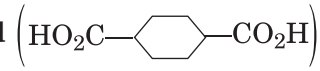
(e) Cyclobutanecarboxylic acid 

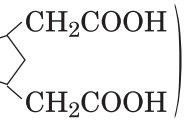


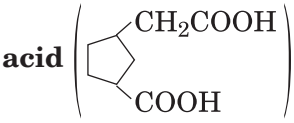
23. Outline all steps in a malonic ester synthesis of each of the following di-, tri- and tetracarboxylic acids:

(a) Cyclobutane-1,2-dicarboxylic acid 

(b) Cyclopentane-1,3-dicarboxylic acid 

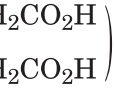
(c) Cyclohexane-1,4-dicarboxylic acid 

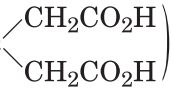
(d) Cyclopentane-1,1-diacetic acid 

(e) Cyclopentane-1-carboxyl-1-acetic acid 

(f) Adipic acid ($HO_2C\ CH_2CH_2CH_2CH_2CO_2H$)

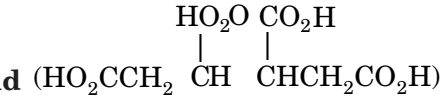
(g) Succinic acid ($HO_2C\ CH_2CH_2CO_2H$)

(h) β-Methylglutaric acid 

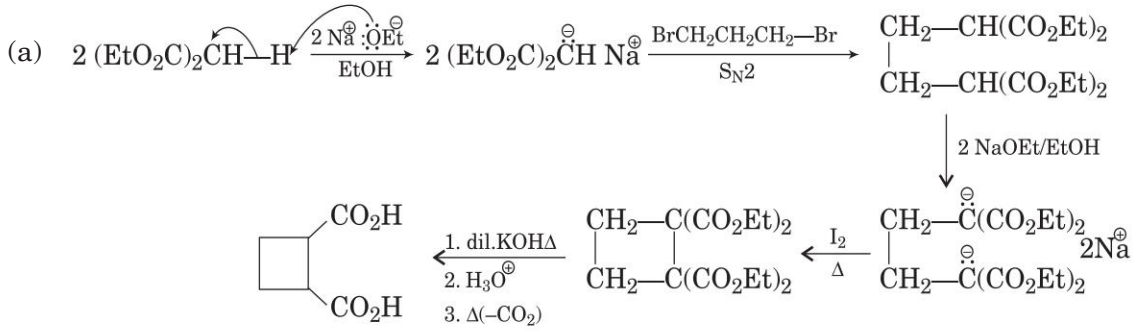
(i) β,β-Dimethylglutaric acid 

(j) α,β-Dimethylglutaric acid [$HO_2CCH(CH_3)CH(CH_3CH_2CO_2H$]

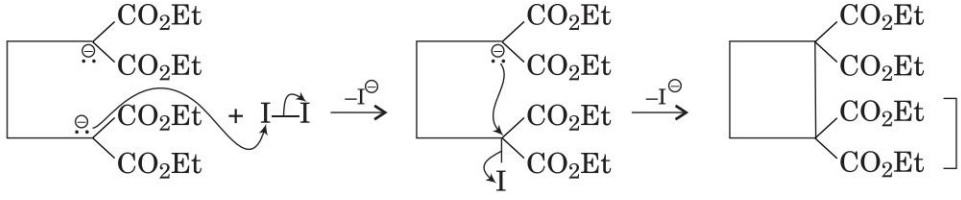
(k) Propane-1,2,3-tricarboxylic acid or tricarballylic acid [$HO_2CCH(CH_2COOH)_2$]

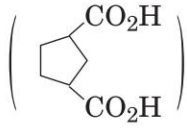
(l) Butane-1,2,3,4-tetracarboxylic acid 

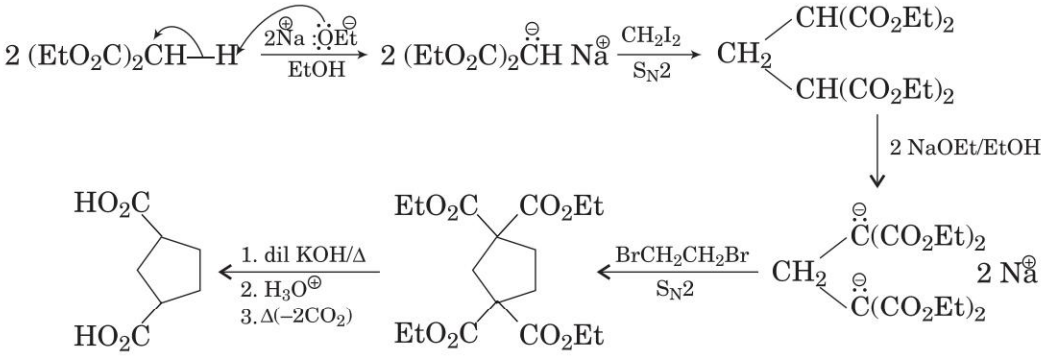
Solution

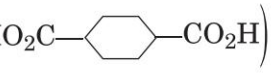
(a) 

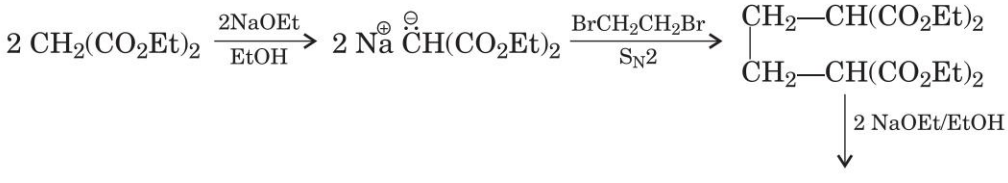
[Mechanism for oxidative ring closure by I_2:

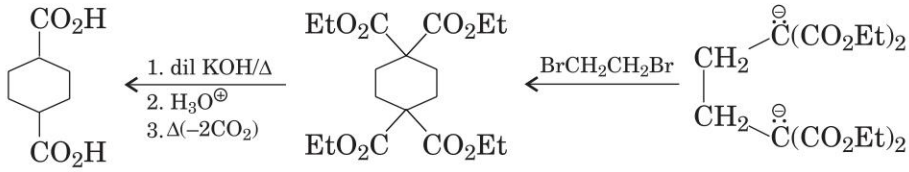


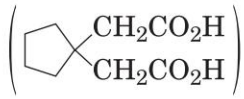
(b) **Cyclopentane-1,3-dicarboxylic acid** 

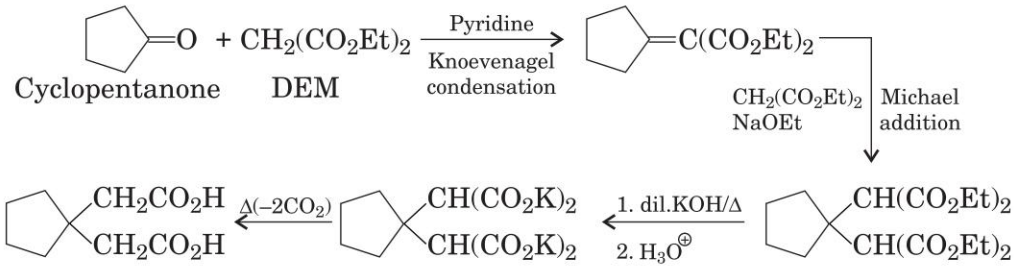


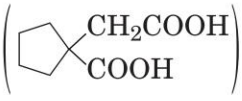
(c) **Cyclohexane-1,4-dicarboxylic acid** 

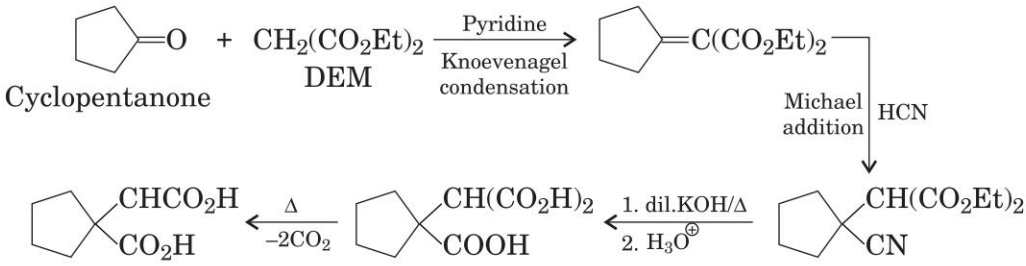




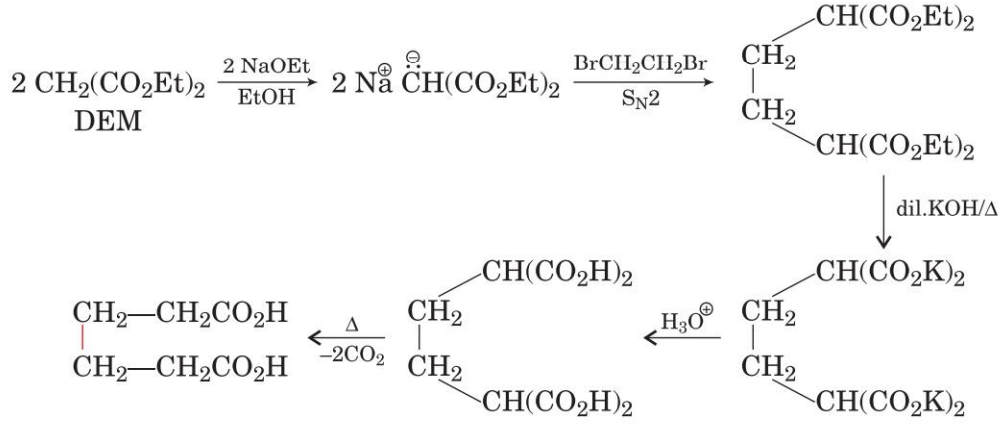
(d) **Cyclopentane-1,1-diacetic acid** 



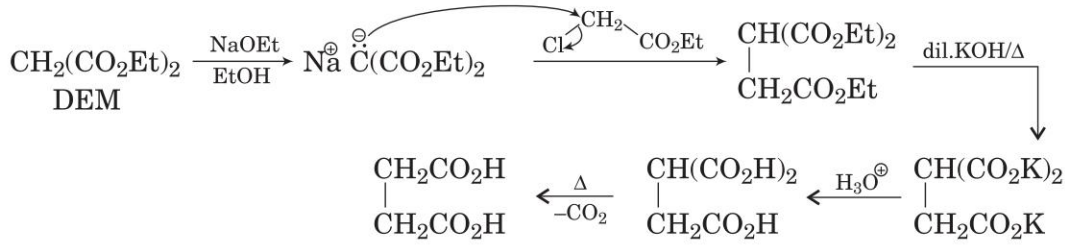
(e) **Cyclopentane-1-carboxyl-1-acetic acid** 



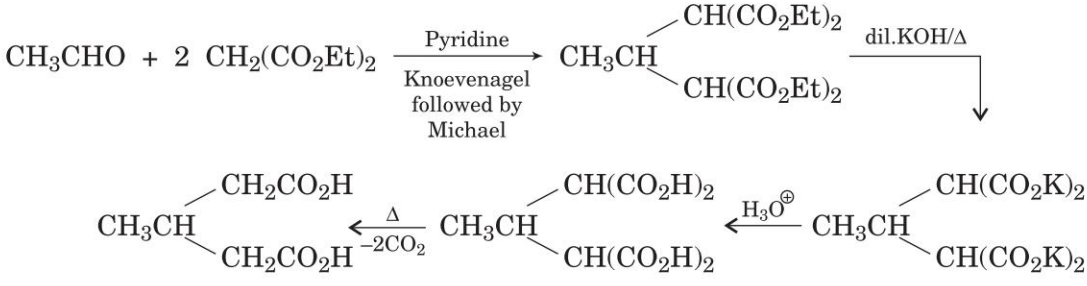
(f) **Adipic acid** ($HO_2C\ CH_2CH_2CH_2CH_2CO_2H$)



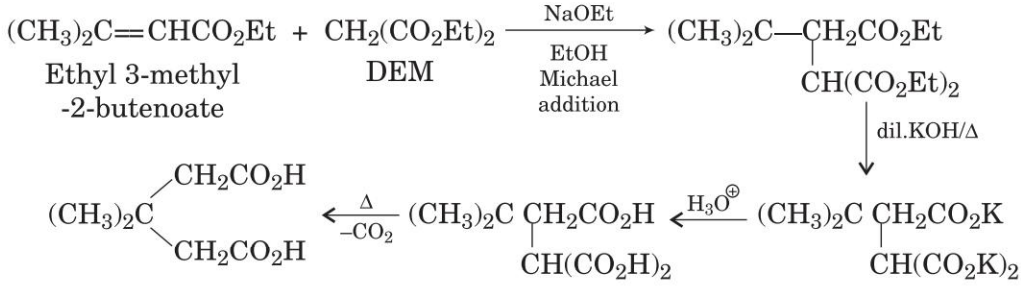
(g) **Succinic acid** ($HO_2C\,CH_2CH_2CO_2H$)



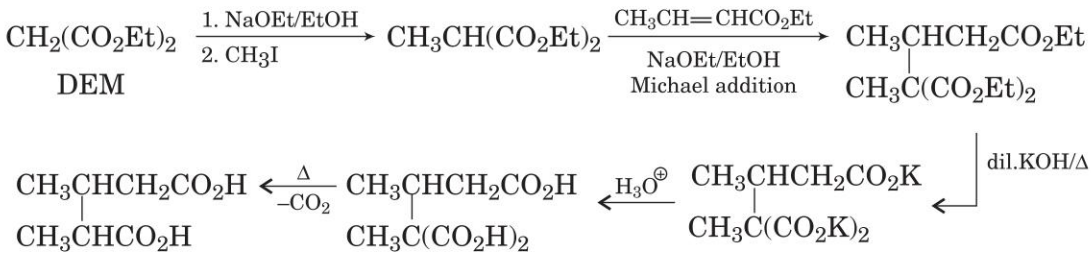
(h) **β-Methylglutaric acid** $\left(CH_3CH(CH_2CO_2H)_2\right)$



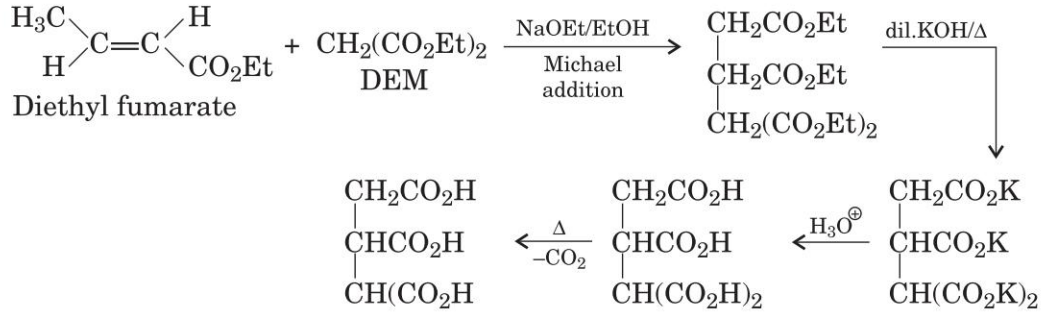
(i) **β,β-Dimethylglutaric acid** $\left((H_3C)_2C{=}C(CH_2CO_2H)_2\right)$



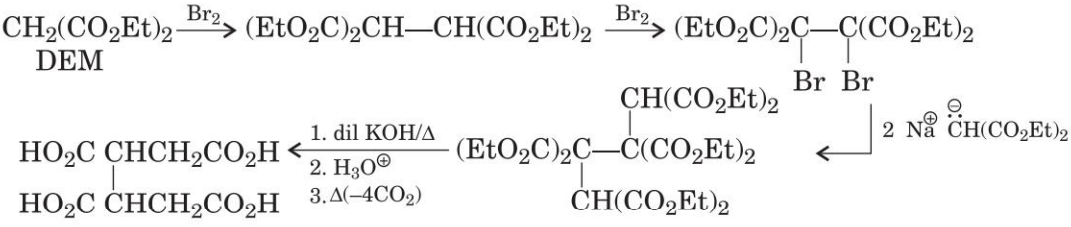
(j) **α,β-Dimethylglutaric acid** $(HO_2C\,CH(CH_3)\,CH(CH_3)\,CH_2CO_2H)$



(k) **Propane-1,2,3-tricarboxylic acid** ($HO_2CCH_2CH(CO_2H)CH_2CO_2H$)



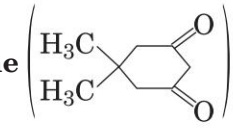
(l) **Butane-1,2,3,4-tetracarboxylic acid** ($HO_2CCH_2CH(CO_2H)CH(CO_2H)CH_2CO_2H$)



24. Show how you would use diethyl malonate to prepare each of the following ketones/ketonic acids:

(a) 2-Butanone ($CH_3COCH_2CH_3$)

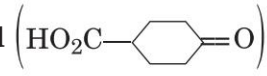
(b) 5,5-Dimethylcyclohexane-1,3-dione or dimedone



(c) Phenylpropanone ($PhCH_2COCH_3$)

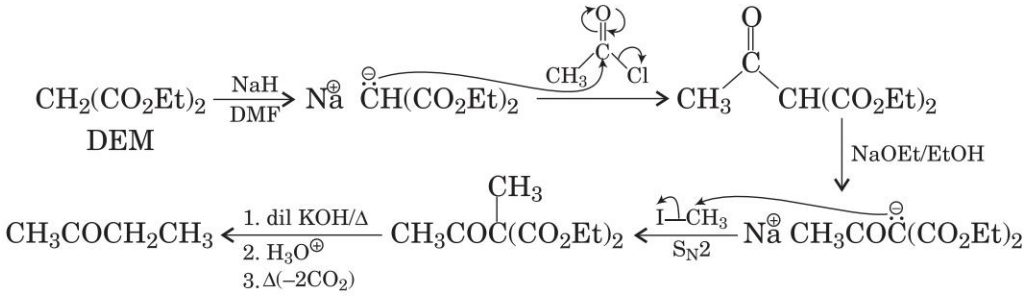
(d) 2-Oxobutanoic acid ($CH_3CH_2COCO_2H$)

(e) 4-Oxocyclohexanecarboxylic acid

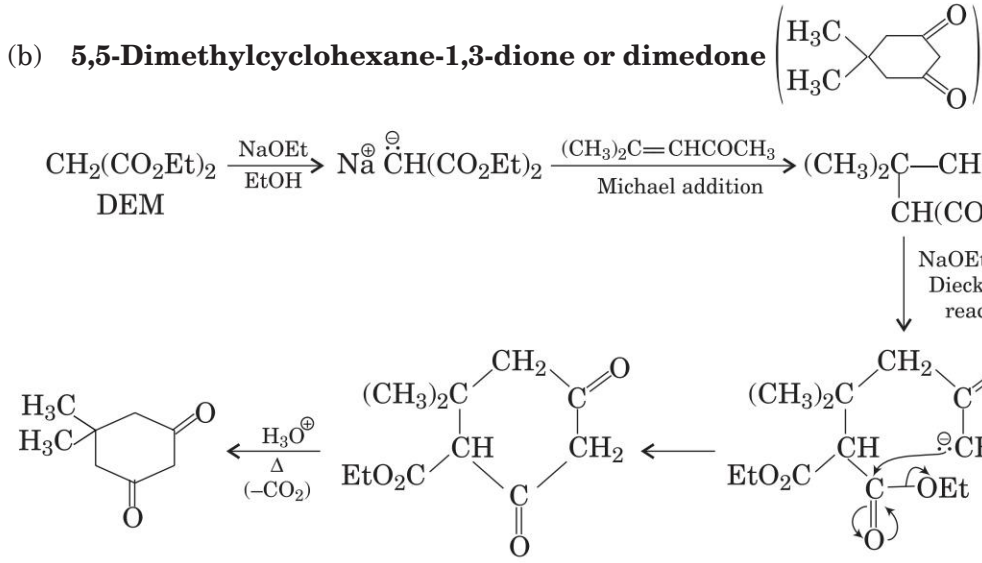


Solution

(a) **2-Butanone** ($CH_3COCH_2CH_3$)

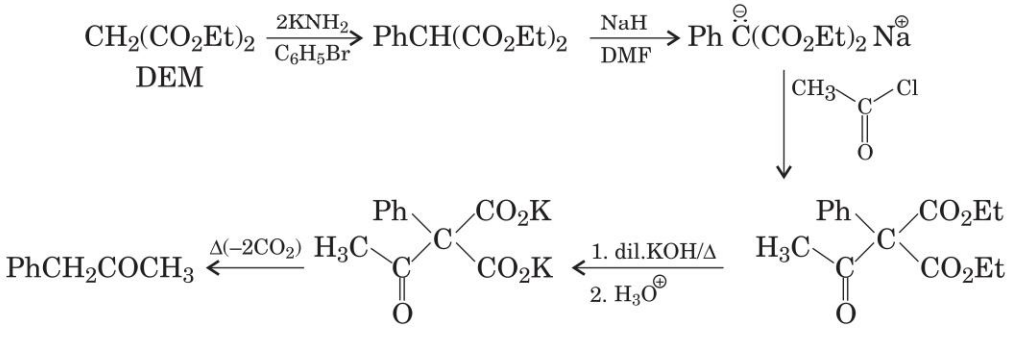


(b) **5,5-Dimethylcyclohexane-1,3-dione or dimedone**

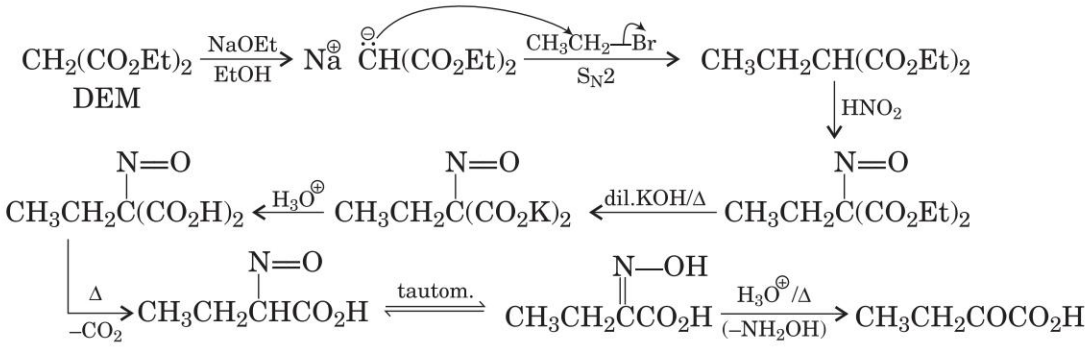


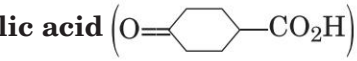
Acidic hydrolysis is carried out because ring cleavage is very common in the case of alkaline hydrolysis.

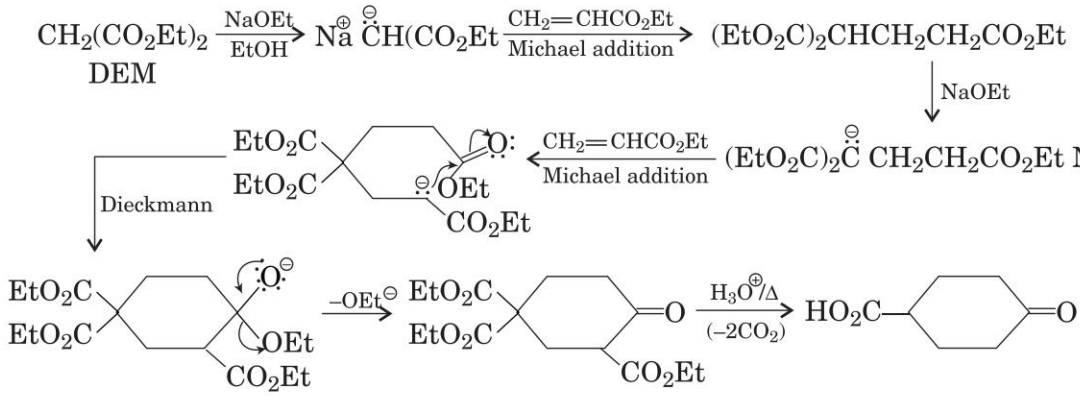
(c) **Phenylpropanone** ($PhCH_2COCH_3$)



(d) **2-Oxobutanoic acid** ($CH_3CH_2COCO_2H$)



(e) **4-Oxocyclohexanecarboxylic acid** 



25. Explain why each of the following compounds cannot be synthesized from diethyl malonate in the usual way:

(a) $Et_3CCH_2CO_2H$

(b) $CH_3CH_2CH{=}CHCH_2CO_2H$

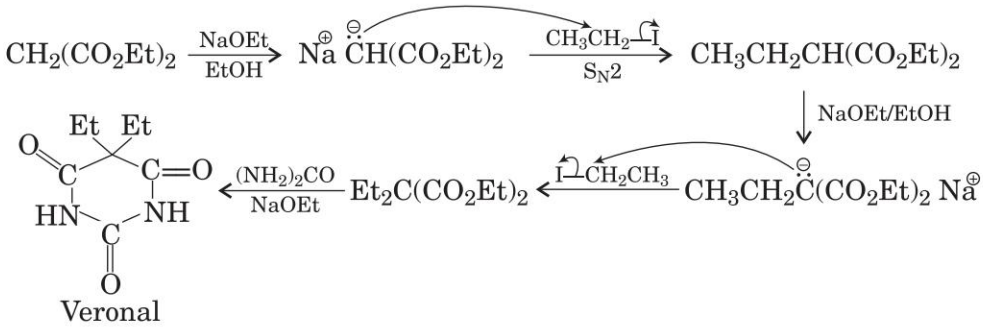
(c) $PhCH_2CO_2H$,

(d) $(CH_3)_3CCH_2CH_2CO_2H$

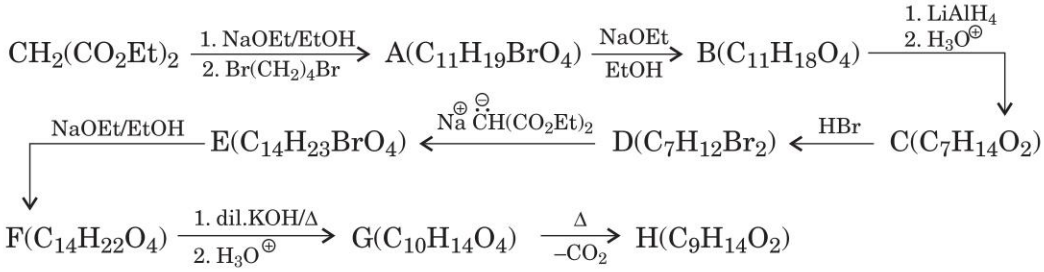
Solution The alkylation of diethyl malonate through the formation of its sodio salt is a typical S_N2 reaction which is very susceptible to steric effect. These compounds cannot be synthesized because: (a) a 3° alkyl halide (Et_3CX) does not undergo S_N2 reaction due to steric reason, (b) a vinyl halide ($CH_3CH_2CH{=}CHX$) and (c) an aryl halide (PhX) do not undergo S_N2 reaction because the electrons of the double bond or the benzene ring repeal the approach of the negatively charged nucleophile from the backside and (d) a neopentyl halide ($Me_3\ CCH_2X$) does not undergo S_N2 reaction due to the same steric reason.

26. How would you synthesize the sedative drug veronal (barbital) or 5,5-diethylbarbituric acid using DEM readily available alkyl halide and an inorganic reagent?

Solution

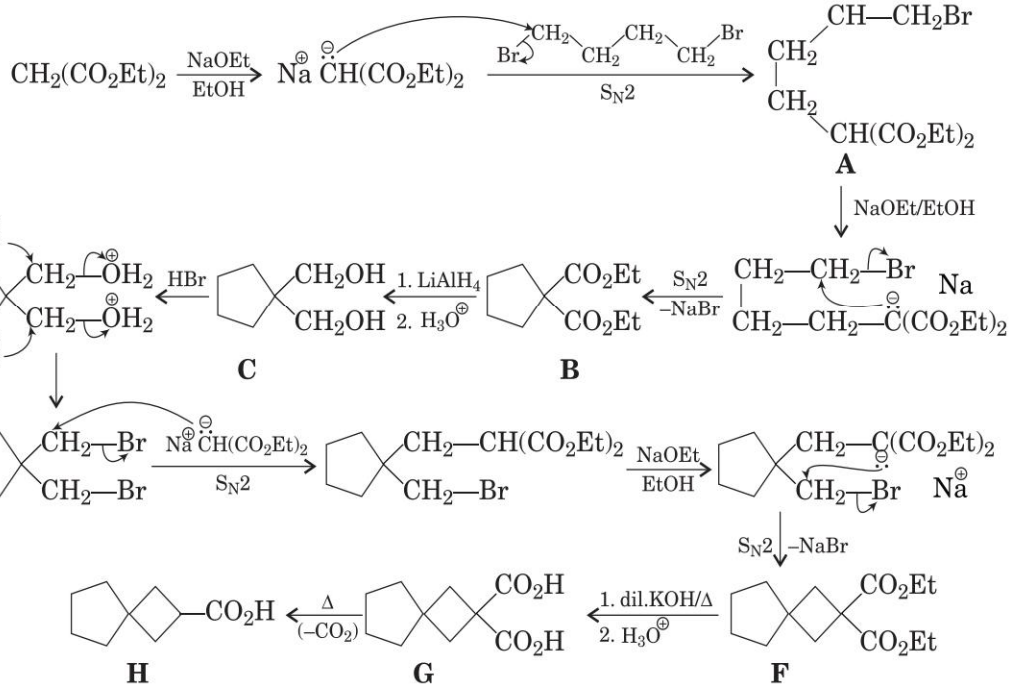


27. (a) Write down the structures of the product (A—H) in the following reaction sequence:

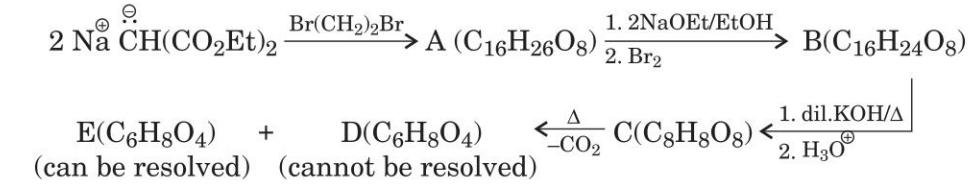


Solution

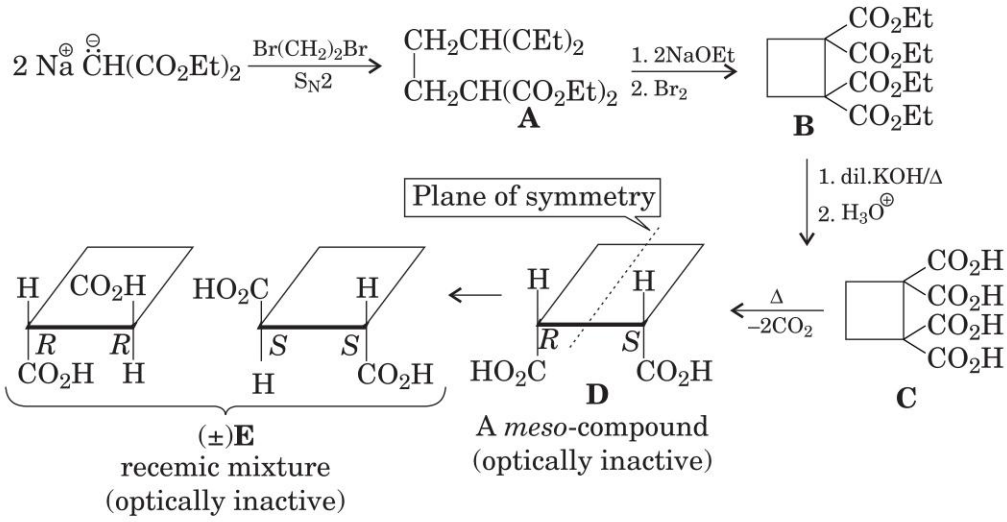
(a)



28. Give structures for the compounds A—E. Predict the stereochemical outcome of the last step of this reaction sequence. Give configurational designations of the products.



Solution

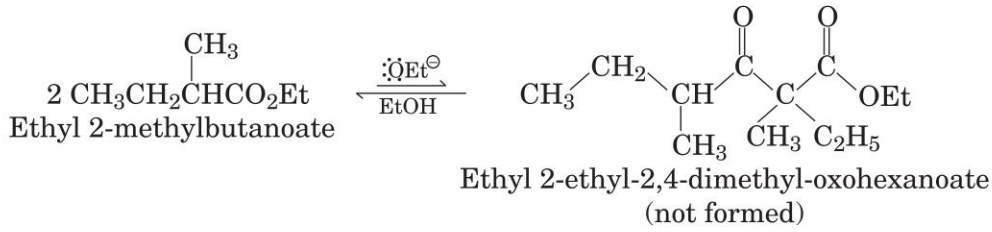


When the compound C is heated, it undergoes decarboxylation and after decarboxylation, each of the carbons bearing carboxyl groups becomes chiral. Since there are two similar asymmetric carbons, it exists as two optically active enantiomers (E) and one optically inactive *meso*-compound (D). Therefore, E can be resolved, but D cannot.

The chirality centres of the two enantiomeric forms have configurations *R*,*R* and *S*,*S*. The configurational designation of the *meso*-compound is *R*,*S*.

29. Ethyl 2-methylbutanoate fails to undergo the Claisen condensation in the presence of sodium ethoxide but not in the presence of very strong base sodium amide. Explain these observations.

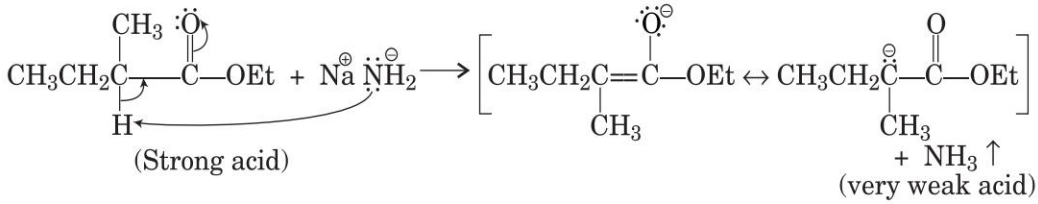
Solution The formation of the final enolate anion of the β-keto ester is the most essential step to the success of the Claisen condensation because it is the only step which has favourable equilibrium. For this final step reaction to take place, there must be an acidic hydrogen in the product and two α-hydrogen in the original ester. Ethyl 2-methylbutanoate [$CH_3CH_2CH(CH_3)CO_2Et$] has only one α-hydrogen atom, and the β-keto ester that would be formed does not contain an active α-H atom. For this reason, the final enolate anion cannot be formed under the reaction conditions and the equilibrium of the overall reaction lies almost completely on the left, i.e., the β-keto ester is not formed in this reaction.



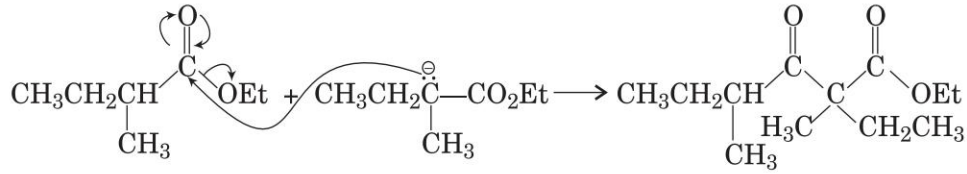
In the presence of very strong base $NaNH_2$, the first step of the reaction is essentially irreversible because the conjugate acid of this base is very weak and also it liberates as a gas. Thus, the equilibrium is also favoured due to law of mass action. The reaction thus proceeds to form the β-keto ester in good yield, since the position of the equilibrium of the last step will no longer matter.

The reaction sequence may be outlined as follows:

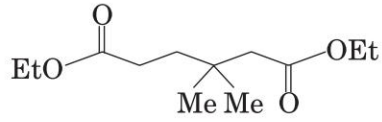
Step 1:



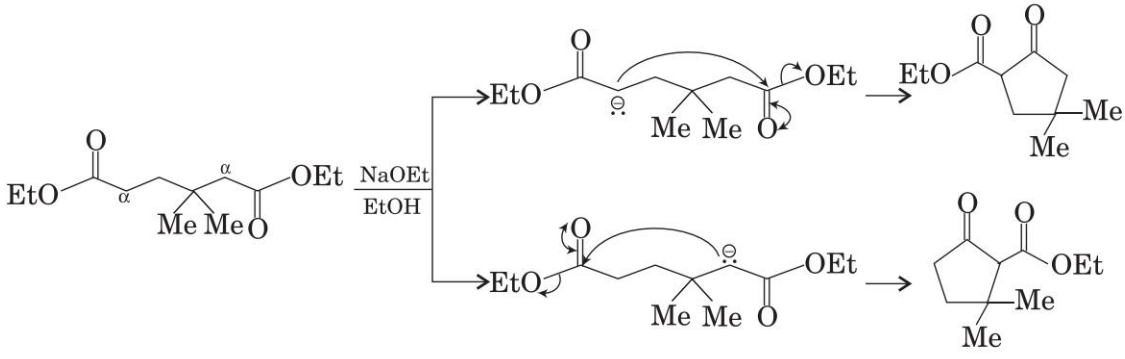
Step 2:



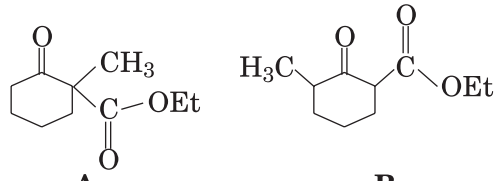
30. Predict the structures of the two β-keto esters expected to be formed in the Dieckmann condensation of the following diester:



Solution Since the two α-positions are non-equivalent, two Dieckmann condensation products are expected to be obtained.

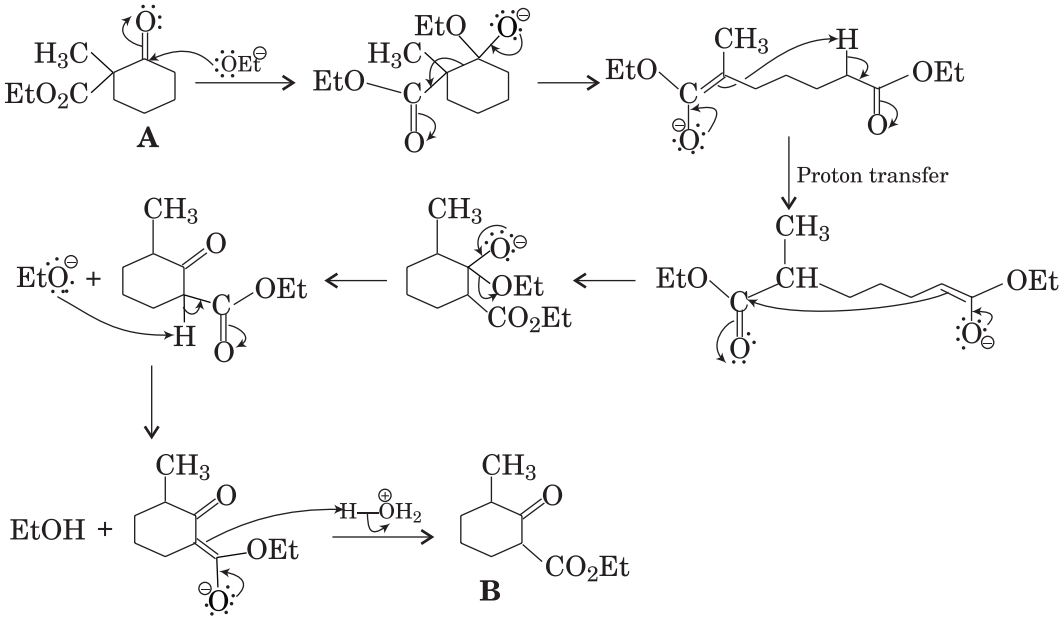


31. Explain why the compound A, when treated with one equivalent of NaOEt, followed by acidification, is completely converted into the compound B.



A **B**

Solution When the β-keto ester A is treated with one equivalent of NaOEt, it undergoes retro-Claisen condensation followed Dieckmann condensation to yield the β-keto ester B. This may be shown as follows:

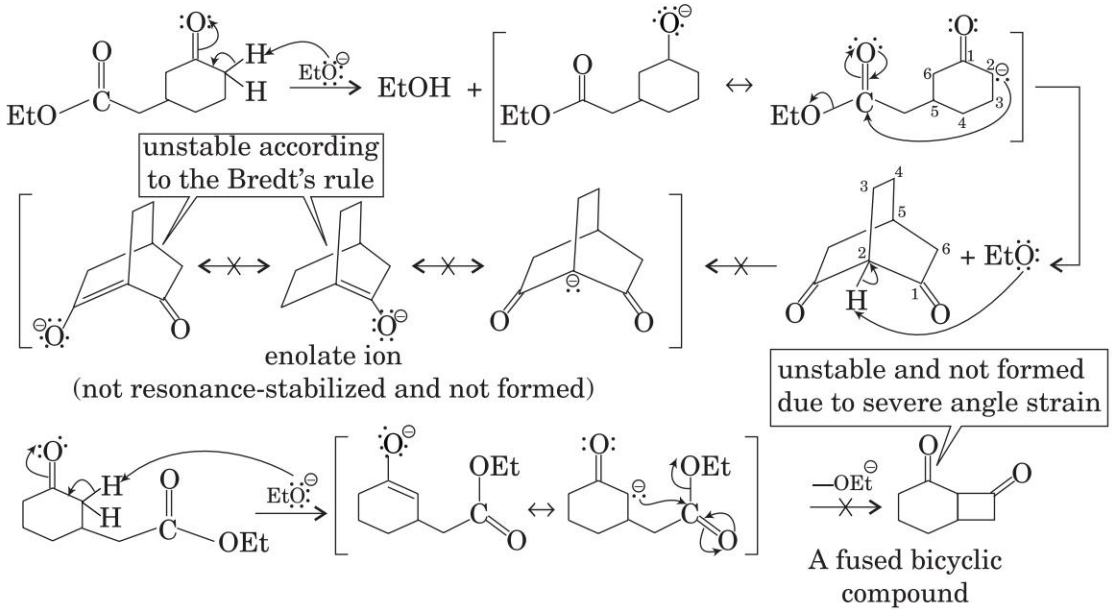


32. The following γ-keto ester does not undergo intramolecular crossed Claisen condensation:

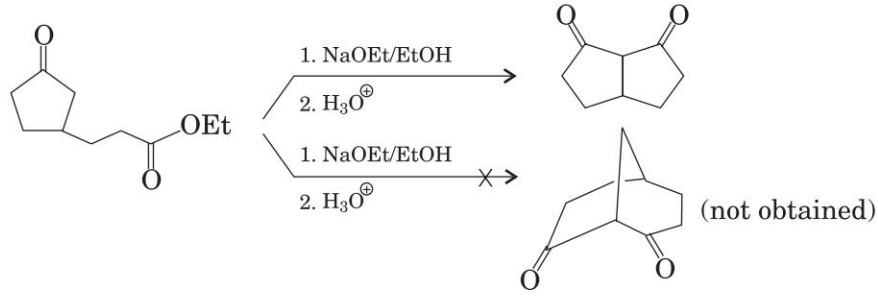


Account for this observation.

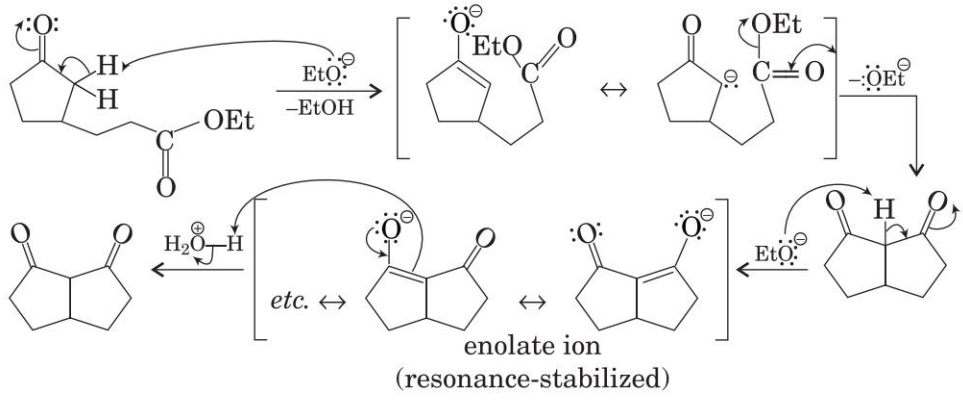
Solution This γ-keto ester does not undergo intramolecular crossed Claisen condensation because cyclization through the formation of one enolate anion would give a bridged bicyclic diketone which cannot form a stable enolate ion (essential for the success of the reaction) because it would have an impossible bridgehead double bond and the other enolate ion would give a strained (unstable) four-membered rings containing a C═O group.



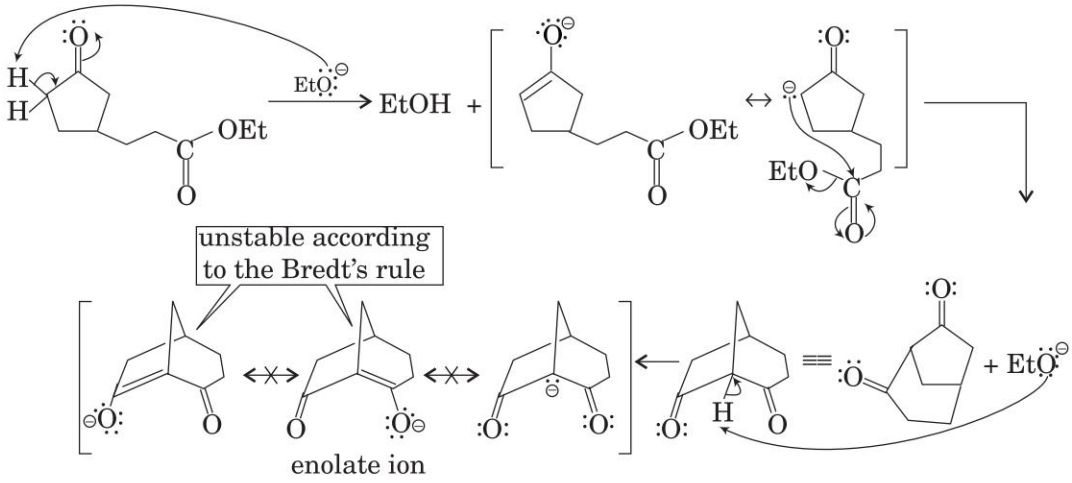
33. Explain the following observations:



Solution The ketonic ester undergoes intramolecular crossed Claisen condensation through the formation of an enolate ion to produce a fused bicyclic diketone that can easily form a stable enolate ion (the negative charge is flanked by two C═O group) which is essential for the success of the reaction

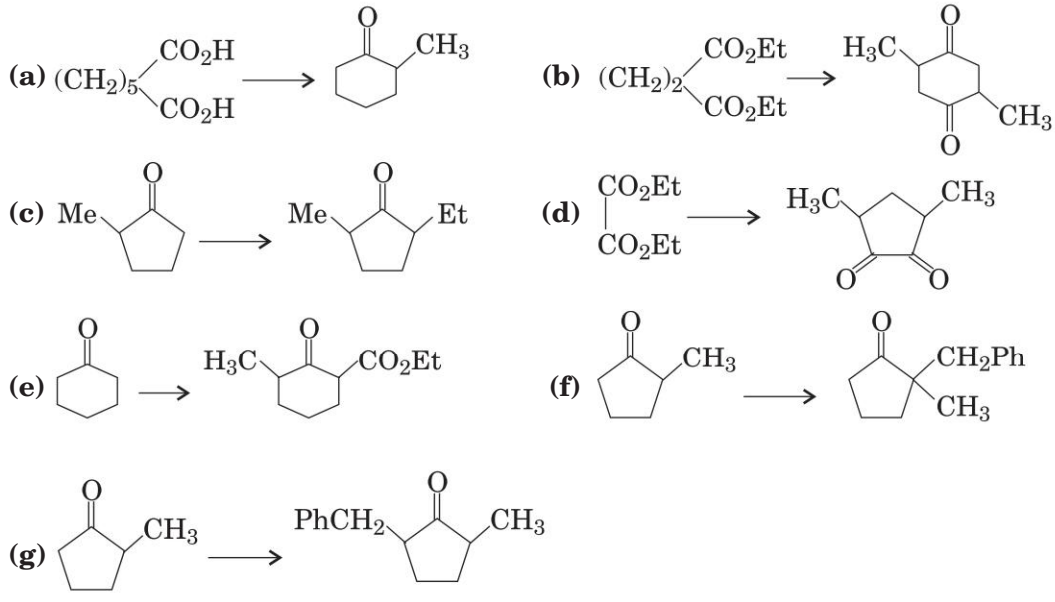


The ketonic ester, however does not undergo the reaction involving the other enolate ion and this is because that cyclization would give a bridged bicyclic diketone which cannot form a stable enolate ion. It is not stabilized by resonance because two out of three structures are unstable due to presence of bridgehead double bond.

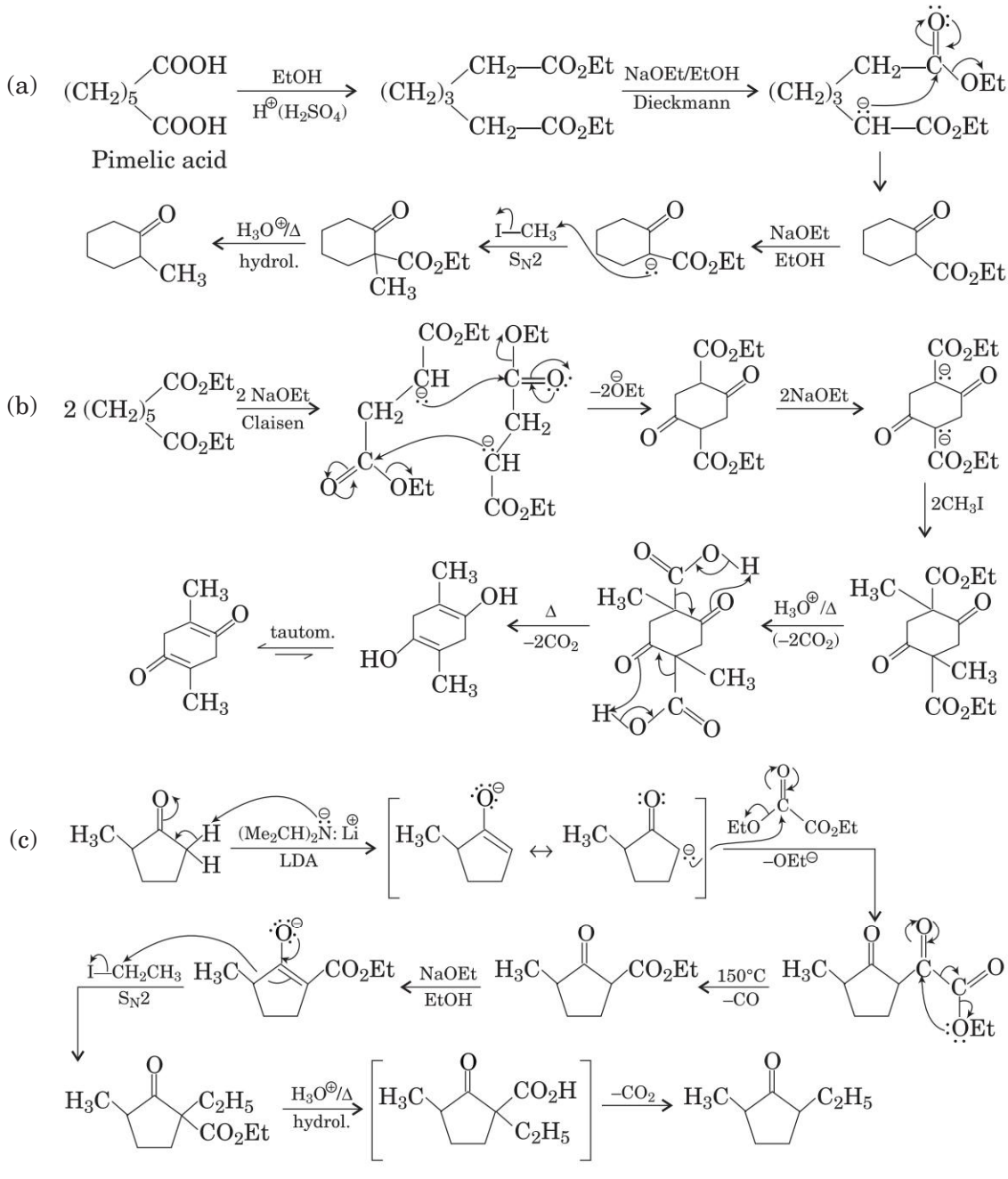


enolate ion
(not resonance-stabilized and not formed)

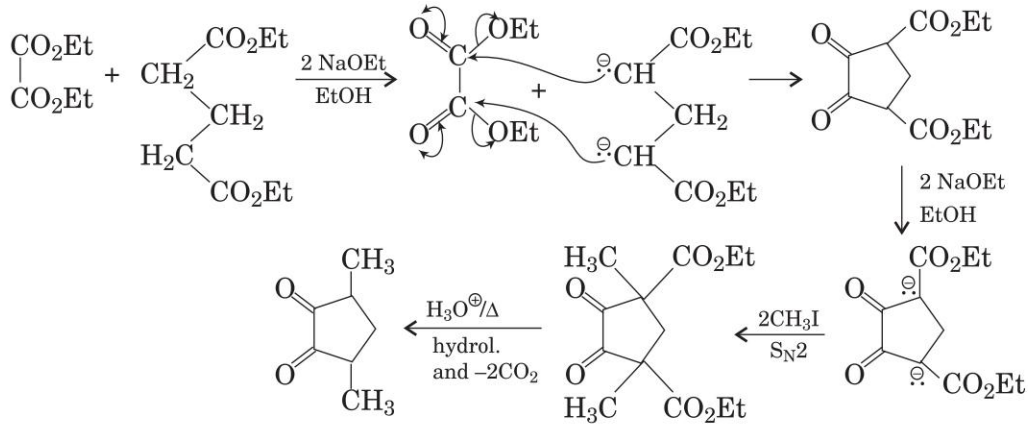
34. Show how each of the following transformations could be accomplished. Give the mechanism involved in each step of these transformations.



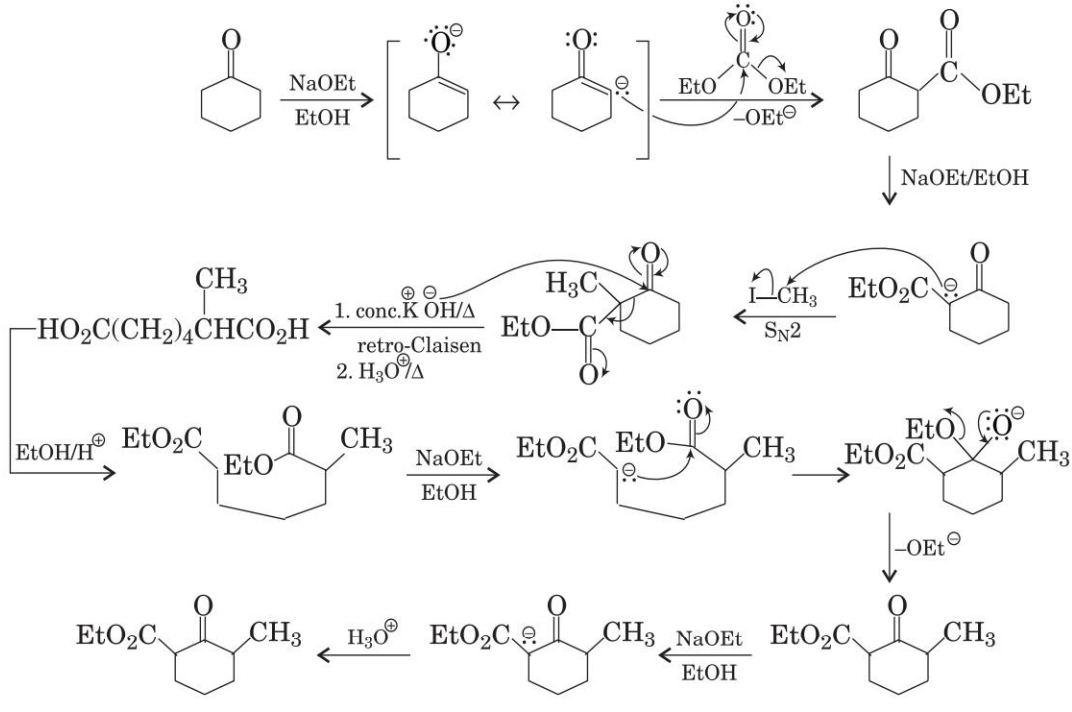
Solution


(a)
Pimelic acid
EtOH
H⊕(H2SO4)
NaOEt/EtOH
Dieckmann
NaOEt
EtOH
I—CH3
SN2
H3O⊕/Δ
hydrol.
(b)
2 NaOEt
Claisen
–2OEt
2NaOEt
2CH3I
H3O⊕/Δ
(–2CO2)
Δ
–2CO2
tautom.
(c)
(Me2CH)2N: Li⊕
LDA
EtO
CO2Et
–OEt⊖
150°C
–CO
NaOEt
EtOH
I—CH2CH3
SN2
H3O⊕/Δ
hydrol.
–CO2

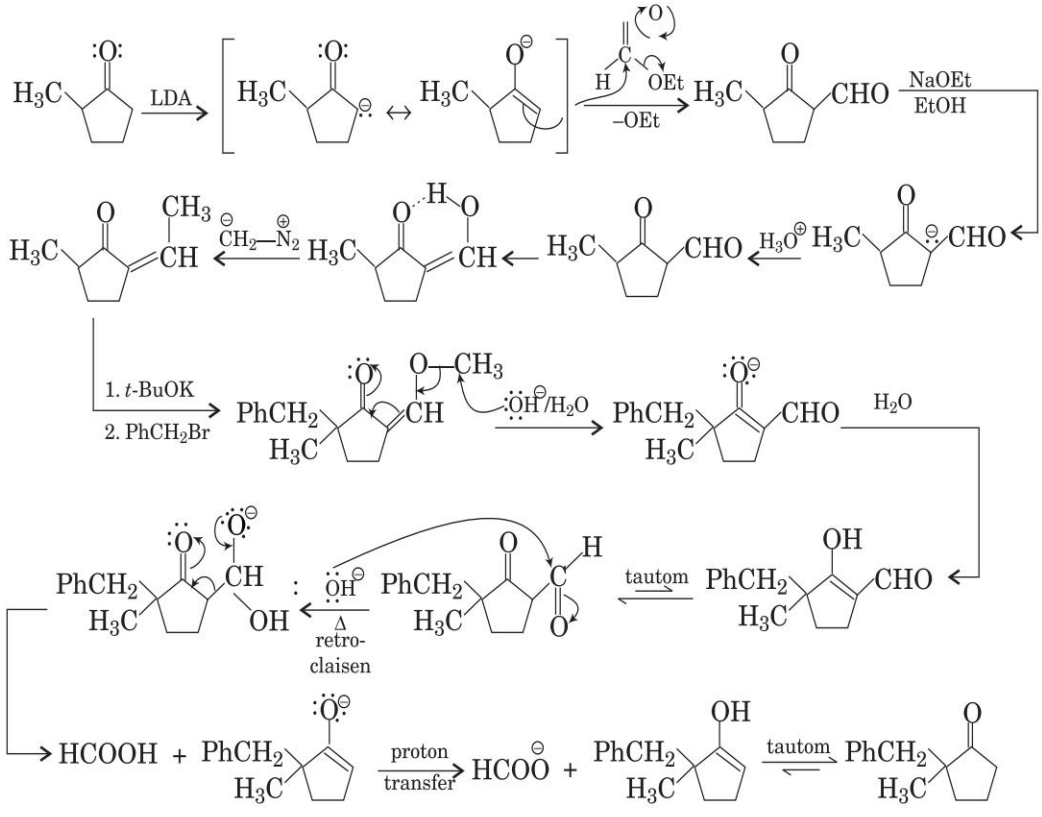
(d)


CO2Et
CO2Et
+
CH2
CO2Et
CH2
H2C
CO2Et
2 NaOEt
EtOH
OEt
CH
CO2Et
CH2
2 NaOEt
EtOH
H3O⊕/Δ
hydrol.
and –2CO2
2CH3I
SN2
CH3
H3C
CO2Et

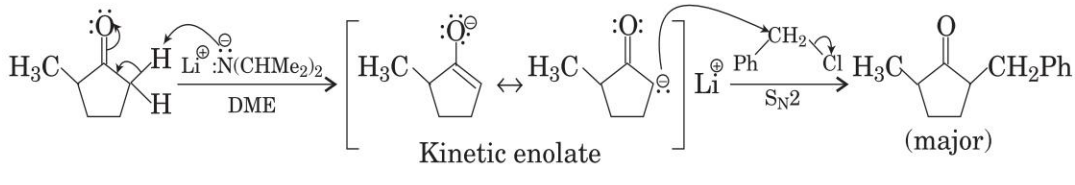
(e)


NaOEt
EtOH
EtO
OEt
–OEt⊖
OEt
NaOEt/EtOH
CH3
HO2C(CH2)4CHCO2H
1. conc.K OH/Δ
retro-Claisen
2. H3O⊕/Δ
H3C
EtO—C
I—CH3
SN2
EtO2C
EtOH/H⊕
EtO2C
EtO
CH3
NaOEt
EtOH
EtO2C
EtO
CH3
–OEt⊖
H3O⊕
NaOEt
EtOH

(f)



(g)



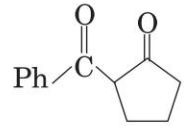
35. Give the starting material (s) for the synthesis of the following compounds via the Claisen condensation or crossed Claisen condensation:

(a) $PhCH_2CH_2CO\underset{\displaystyle CH_2Ph}{\underset{|}{C}}HCOOCH_3$

(b) $OHC-\underset{\displaystyle Ph}{\underset{|}{C}}H-CO_2CH_3$

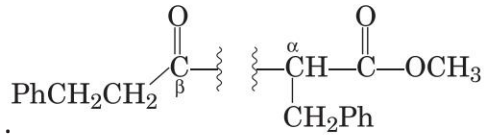
(c) $EtO_2C-\overset{\displaystyle O}{\overset{\|}{C}}-\underset{\displaystyle CHCO_2Et}{\underset{|}{C}}H-CH_3$

(d)

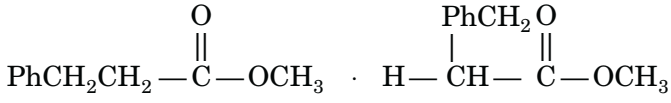


Solution

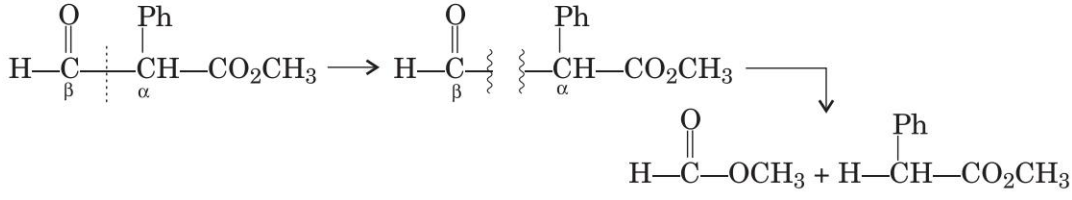
(a) The structure is to be cleaved at the α,β-bond (α,β to the ester carbonyl). This is the bond formed in the Claisen condensation.



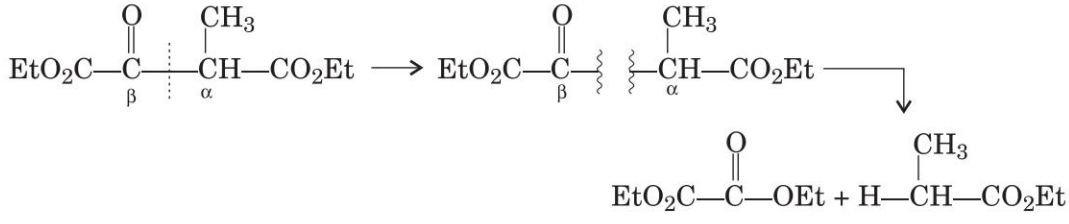
Now, the α-hydrogen that is lost is replaced and the alkoxy group that is lost from the carbonyl group is replaced. Two molecules of methyl 3-phenylpropanoate result.



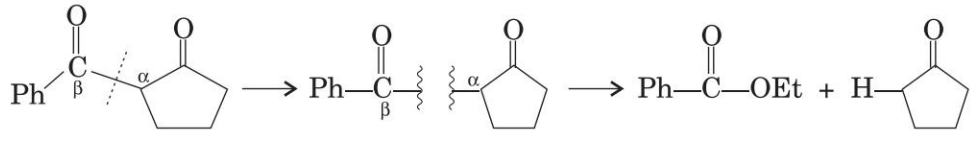
(b)



(c)

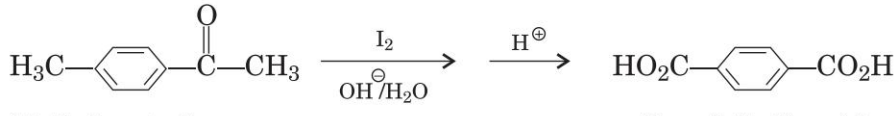


(d)



Study Problems

1. When *p*-methylacetophenone is oxidized with an excess of iodine in base, it forms terephthalic acid in moderate yield. Explain why the methyl group on the benzene ring is oxidized.



p-Methylacetophenone

Terephthalic acid (47%)

2. Why do we say that the halogenation of ketones in a base is "base promoted" rather than "base catalysed" reaction?

3. (a) Provide a reasonable mechanism for the following reaction:

$$CH_3CH_2CH(OH)CH_3 \xrightarrow{I_2/NaOH} CH_3CH_2COO^{\ominus}Na^{\oplus} + CHI_3$$

(b) What structural feature in an alcohol is necessary for the haloform reaction to take place and why?

4. Predict the structure of the starting compound which when treated with I_2/NaOH followed by acidification produce:

(a) $PhCH{=}CHCOOH + CHI_3$

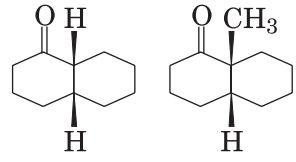
(b) $PhCH_2COOH + CHI_3$

(c) $HO_2C\ CH_2CH_2CO_2H + 2CHI_3$

(d) 

5. Explain why the following compound does not undergo acid-catalysed bromination, even though it has an α-hydrogen.

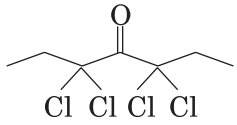
6. The bicyclic ketone A rapidly equilibrates with a stereoisomer upon treatment with base, but the ketone B does not. Explain.



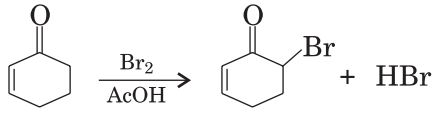
A B

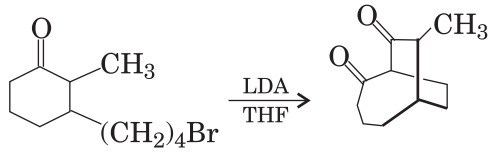
7. Mention the most suitable experimental conditions for the synthesis of each of the following compounds from the corresponding nonhalogenated ketone:

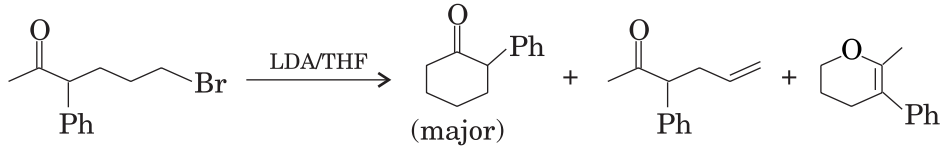
(a) $PhCHBrCOCH_3$

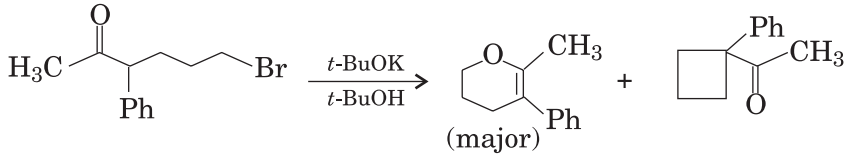
(b) 

8. Draw a stepwise mechanism for each of the following reactions:

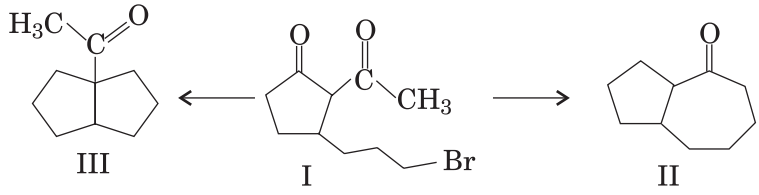
(a) 

(b) 

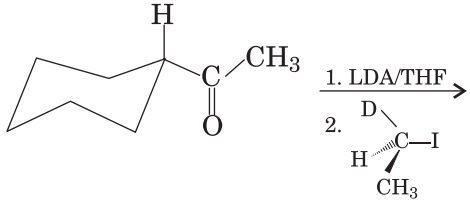
(c) 

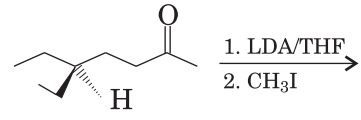
(d) 

9. Offer suitable reaction conditions (i.e., base, solvent and temperature) required to convert the haloketone I to either the ketone II or the ketone III by an intramolecular alkylation reaction.

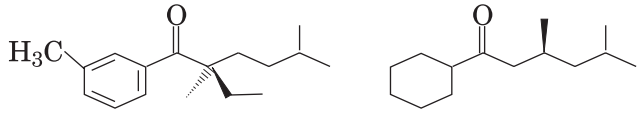


10. Give the products and mention stereochemical outcome of each of the following alkylation reactions:

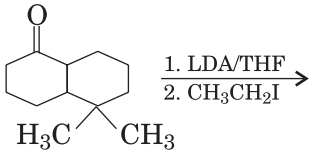
(a) 

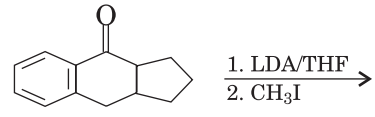
(b) 

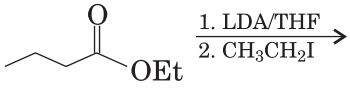
11. Would optically active ketones such as the following undergo acid- or base-catalysed racemization? Give your reasoning.

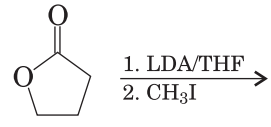


12. Predict the major product of the following reactions:

(a) 

(b) 

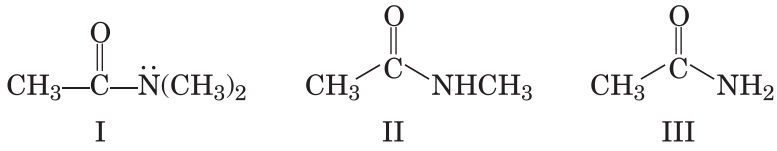
(c) 

(d) 

13. Explain the following observations:

(a) A base cannot remove a proton from the α-carbon of a carboxylic acid.

(b) A base can remove a proton from the α-carbon of I but not from the α-carbon of either II or III.

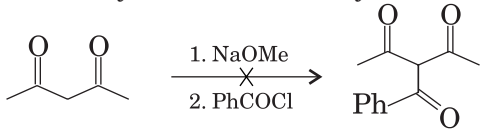


I II III

(c) LDA is used to remove the α-hydrogen of essentially all the carbonyl compounds.

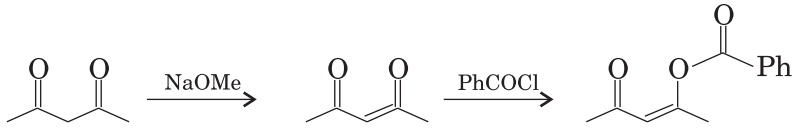
(d) Alkylation of an α-carbon cannot be carried out by using a tertiary alkyl halide.

(e) Alkylation of a carboxylic acid requires two equivalents of LDA.

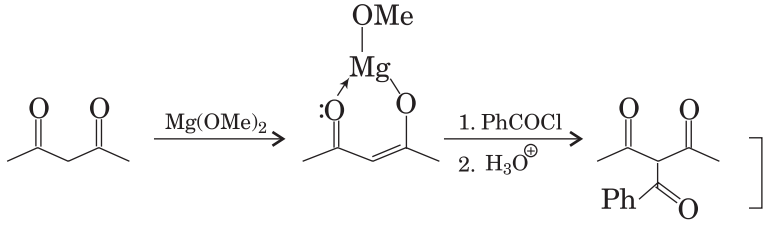
14. 

Explain this observation. How can the target molecule be synthesized?

[**Hint:** With a sodium enolate and a reactive acylating agent like PhCOCl, a charge-controlled reaction (hard-hard interaction) will take place at the oxygen atom to yield an enol ether.



The target molecule can be made by using a magnesium enolate in which Mg is chelated by the two suitably placed oxygen atoms which blocks the reaction at either. As a consequence, *C*-alkylation takes place.

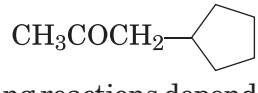


15. How would you prepare each of the following ketones using the acetoacetic ester synthesis?

(a) $CH_3COCH(CH_2CH_3)_2$

(b) Cyclohexyl methyl ketone

(c) $CH_3CO\overset{\displaystyle CH_2Ph}{\overset{|}{C}}HCH_2CH{=}CH_2$

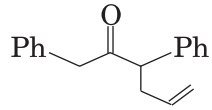
(d) 

16. Explain why the product obtained in the following reactions depends on the number of equivalents of base used in the reaction:

$$CH_3COCH_2CO_2Et \xrightarrow[2.\ CH_3Br]{1.\ NaOEt\ (1\ equiv.)} CH_3CO\underset{\displaystyle CH_3}{\underset{|}{C}}HCO_2Et$$

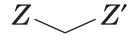
$$CH_3COCH_2CO_2Et \xrightarrow[2.\ CH_3Br\ \ 3.\ H_3O^{\oplus}]{1.\ NaOEt\ (2\ equiv.)} CH_3CH_2COCH_2CO_2Et$$

17. Explain why the following substituted acetone derivative cannot be made by the usual acetoacetic ester synthesis:



18. What are called active hydrogen compounds? Give examples.

[**Hint:** Because of the acidity of the methylene hydrogen, compounds having lwo electron-withdrawing groups attached to the same carbon atom called active hydrogen compounds or active methylene compounds.



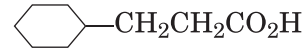
Active hydrogen compound

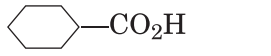
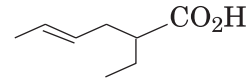
(Z and Z' are electron-withdrawing groups)

The electron-withdrawing groups include –COR, –CHO, $-CO_2R$, $CONR_2$, –CN, $-NO_2$, –SOR, $-SO_2R$, $-SO_3R$ or $-SO_2NR_2$.

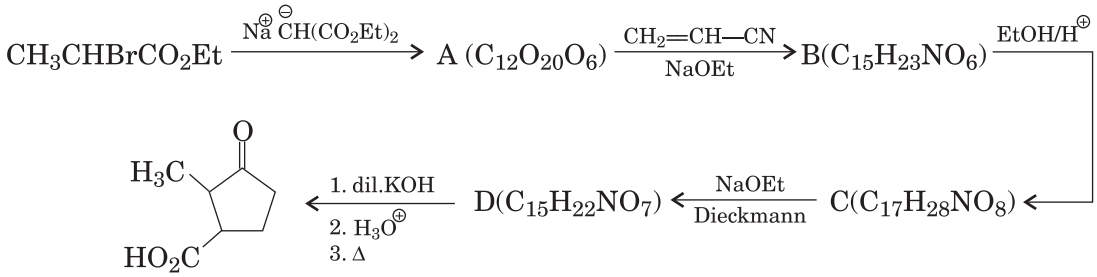
19. All ketones are prepared by using the acetoacetic ester synthesis produce iodoform (CHI_3) when treated with I_2/NaOH –Why?

20. Show how you would use the malonic ester synthesis to prepare the following compounds:

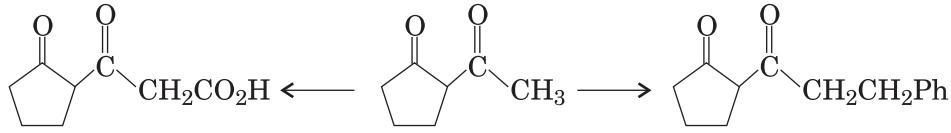
(a) $(CH_3CH_2CH_2)_2CHCO_2H$ (b) 

(c)  (d) 

21. Give structures for compounds A–D:



22. How would you carry out the following transformations?

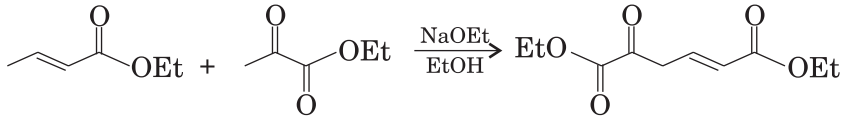


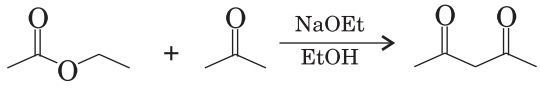
[**Hint:** A dianion is generated first by using two equivalents of KNH_2 in liq. NH_3 and then it is allowed to react with $PhCH_2Cl$ or CO_2 followed by acidification.]

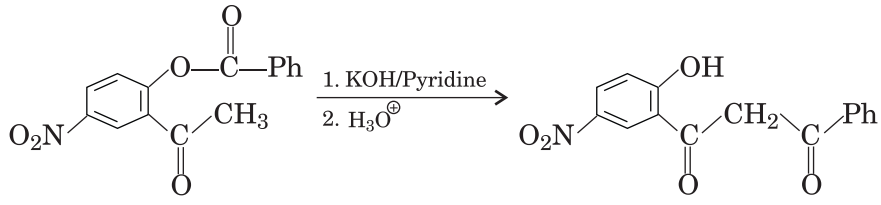
23. Explain why the aldol condensation requires only a catalytic amount of base but the Claisen condensation needs a full equivalent, i.e., the aldol condensation is a base-catalysed reaction, while the Claisen condensation is a base-promoted reaction.

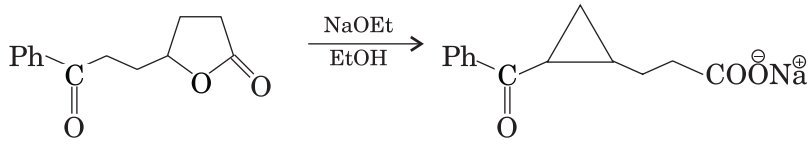
[**Hint:** In the aldol condensation, the final protonation step generates a hydroxide ion (OH^-) which can carry out another aldol reaction. The Claisen condensation, on the other hand, requires a full equivalent of base because in the last step of the reaction, the alkoxide ion is consumed by the removal of one of the two active hydrogen atoms.]

24. Write a reasonable mechanism for each of the following reactions:

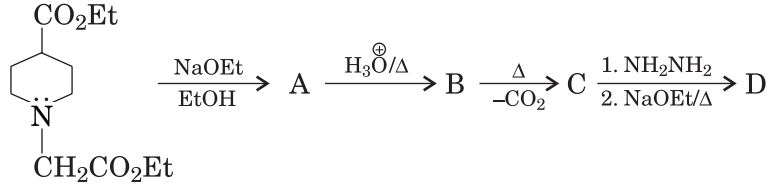
(a) 

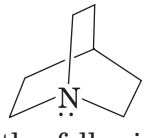
(b) 

(c) 

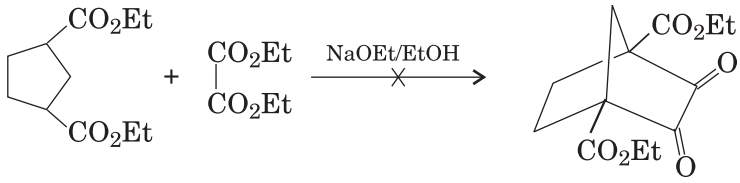
(d) 

25. Provide structures for compounds A–D and mechanisms leading to their formation:



[**Hint:** D = ]

26. Explain why the following Claisen condensation leading to the formation of a bicyclic compound does not take place.



27. The Claisen condensation of ethyl acetate does not take place when NaOH is used as a base. Explain.

2.9.4 Green Chemistry

Introduction

To meet the demands of modern civilization, various types of chemical products are required. Chemical innovations have improved the quality of virtuously every aspect of life such as food, shelter, medicine, transportation, and availability of new materials. Such innovations, however, often lead to the formation of hazardous substances and often requires hazardous starting materials. Though chemists are aware of the hazards like explodability, flammability, corrosiveness, etc. due to the chemicals or the methods of their preparations, they are not concerned about the hazards like toxicity, carcinogenicity, nonbiodegradibility, etc. associated with these chemicals. Apparently harmless chemicals such as carbon dioxide, nitrous oxide (N_2O), chlorofluorocarbons (CFC's), fertilizers, detergents, etc. may also cause serious and irreversible changes in the environment like global warming, ozone depletion in the statosphere leading to the formation of ozone hole, severe floods and draughts, eutrophication of waterlands, etc. To prevent or minimise the formation of hazardous substances, i.e., to prevent the environment from pollution, the chemists are required to design the chemical products and processes so that the generation of harmful and polluting substances is decreased or eliminated. They are now designing syntheses that use and generate substances that cause little or no toxicity to health or to the environment. Although such green chemical syntheses can be cost effective, they reduce the expense for such things as waste disposal, regulatory compliance and liability. A sustainable future can be achieved by applying the principles of green chemistry.

2.9.4.1 Definition of green chemistry

Green chemistry may be defined as the benign chemistry that causes no harm either to human or to the environment. It is, in fact, a tool to minimize the negative impact of the chemicals and the process involved in their syntheses.

2.9.4.2 Principles of green chemistry

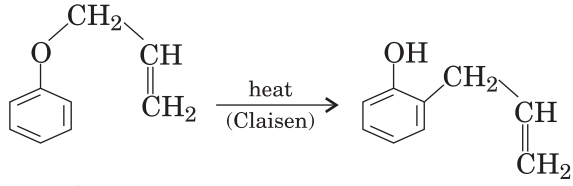
Anastas and Warner have formulated the twelve principles of green chemistry. These are, in fact, the guidelines for practicing green chemistry to protect the environment. These principles are as follows:

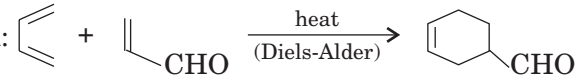
1. **Waste product formation is to be minimised:** It is much better to prevent the formation of waste product than to treat of clean up the waste after its formation.

In terms of zero waste technology (ZWT), the waste product should be zero or minimum in a chemical synthesis. ZWT also aims to use the waste product of one synthesis as the starting material for the other synthesis.

2. **Synthesis should be atom efficient:** In green synthesis, attempt is to be made to avoid formation of any by-product by incorporating all the atoms of the reactants into a single product. Therefore, the synthesis should be atom economical or atom efficient and for this, green chemists should be encouraged to adopt additions, rearrangements or pericyclic reactions to obtain a single product with high atom efficiency.

Addition reaction: $RCH{=}CHR + X_2 \longrightarrow RCH\,X\,CH\,X\,R$

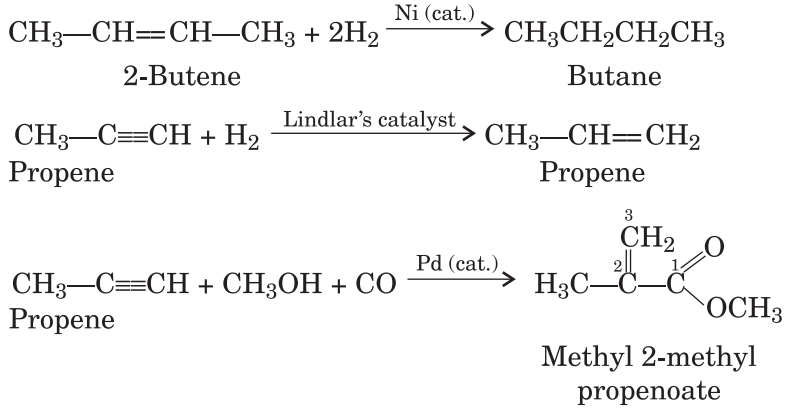
Rearrangement: 

Pericyclic reaction: 

3. **Formation of toxic material is to be avoided:** Green chemists should adopt such synthetic procedures that avoids the generation of toxic and environmentally hazardous substances.
4. **Nontoxic starting materials are to be used:** In a number of chemical industries, not only the waste product but also the starting materials are quite harmful. Therefore, the use of toxic and environmentally hazardous substances should be avoided. For example, adipic acid, $HO_2C(CH_2)_4CO_2H$, is widely used in polymer industries (e.g., manufacture of nylon) is synthesized from benzene, a carcinogenic substance and air pollutant. For this reason, adipic acid is now synthesized enzymatically from glucose, a nontoxic substance.
5. **Minimizing auxiliary substance:** If possible, the use of auxiliary substances like solvent, separating agents, protecting agents, deprotecting agents, etc. should be avoided. It they cannot be avoided, they should be eco-friendly. The use of green solvents like water, and super critical carbon dioxide is much more preferred than the use of halogenated organic solvents like chloroform, carbontetrachloride, dichloromethane, etc. If possible, solvent free synthesis is to be carried out. The Claisen rearrangement, for example, can be carried out in solid phase, i.e., in the absence of solvent.
6. **Minimum energy consumption:** The energy consumption in chemical industries should be minimized to make the process more and more economic. Energy requirements in the synthesis of chemical products in industries including metallurgies are known to have an adverse effect on the environment and this is because the energy consumed by these industries is mostly the energy which is fossil fuel derived. Green chemistry aims to minimize the energy of chemical

transformations and decreasing the activation energy of the reactions involved by using recyclable catalysts. To minimize energy consumption, green chemists should eliminate some energy consuming steps like distillation, crystallization, steam distillation, sublimation etc. Microwave energy can be used to achieve instant high temperature and ultrasound energy can also be used occasionally to perform some reactions. Energy from the waste product can also be used for heating the reactants and other things.

7. **Starting materials should be from renewable sources:** About 95% of the bulk chemicals used nowadays are petroleum based. By 2050 AD petroleum (a nonrenewable source of energy) will be a very rare commodity because its stock will be limited. CO_2, obtained from petrochemical oxidation is the main green house gas responsible for global warming. Therefore, an alternative and renewable source of starting materials is urgently required. If it is technically and economically possible, the renewable resource like biomass (very rich in carbohydrate) should be used as the raw material or feedstock. For example, D-(+)-glucose, obtained from biomass, can be enzymatically transformed into lactic acid which may act as the platform compound for aliphatic chemicals. Similarly, catechol, the platform compound for aromatic chemicals, can be obtained from D-(+)-glucose by the action of *E. coli* bacteria.
8. **Minimisation of steps:** Blocking of position, protection deportation of groups, temporary modification of physical and chemical processes, etc., should be avoided as far as possible during a synthesis and this is because in such cases atom economy becomes less. Green chemistry aims to minimize the number of steps to synthesize a target molecule. Biocatalytic reaction often need no protection of selective groups.
9. **Catalyzed reactions:** The main foundation pillar of green chemistry today is to use catalysts in synthetic processes. Catalyzed synthetic processes reduce energy requirements. Moreover, the catalysts can be recycled. Also, the yield is better, maximum amount of starting material is utilized and production of the waste material is minimum in such a reaction. Some catalytic reactions with 100% atom economy are as follows:



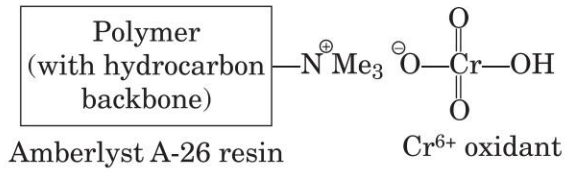
The catalyzed reaction involved in Heck, Suzuki, Sonogashira and Stille synthesis take place under ambient conditions in harmless solvents and the catalyst in each case can be recycled.

10. **Biodegradability of chemical product:** A chemical substance, after its function is over, should degrade easily to harmless products, i.e., they should not persist in the environment. DDT, for example, is an effective pesticide, but its stability in environment causes several environmental hazards. Thus, biodegradable pesticides and polymers (plastic is a polymer which is not degradable) are always preferred. However, ready biodegradability of a synthetic chemical does not qualify it to be free from any adverse effect. The manner in which it is degraded in the environment and the nature of the degraded products are also important. Although soaps and detergents, for example, are readily biodegradable, these are degraded by microorganisms present in water bodies at the cost of dissolved oxygen. Moreover, the polyphosphate binders used in detergents cause eutrophication. Therefore, soaps and detergents cause serious water pollution. Similarly, the important weedicides 2,4-D and 2,4,5-T are readily biodegradable. However, their degradation product, dioxin, is found to be a carcinogenic compound.
11. **Chemically safer substances are to be used:** The starting materials to be used in a chemical reaction should not be hazardous, i.e., there should not be any chance of chemical accident, explosion, fire and emission. The risk is minimum if the chemical process involves solid substances rather than gaseous and volatile liquid substances.
12. **Generation of hazardous substances is to be monitored efficiently:** Analytical methodologies should be very much developed for efficient in-process monitoring which is quite essential to avoid generation of hazardous substance and to avoid accident.

2.9.4.3 Planning of green synthesis

Green synthesis means the use of environmentally benign methods to synthesize compounds. Therefore, planning of green synthesis must involve use of safer reagents, less solvent, development of reactions that form fewer by-products and generation of less waste.

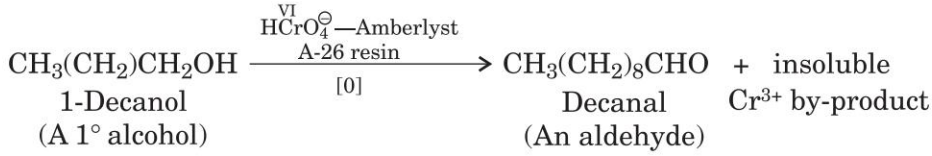
Green approach to oxidation: Since toxic oxidizing agents like osmium tetroxide (OSO_4) and ozone (O_3) and corrosine acids (such as H_2SO_4) are used in many oxidation methods and many of them generate carcinogenic bi-products like Cr^{3+}, alternative reactions have been developed. One important method involves the use of a polymer-supported Cr^{6+} reagent: **$HCrO_4^-$ –Amberlyst A-26 resin.** Although Cr^{3+} is obtained as a by-product, it can be easily removed from the product by filtration. The Amberlyst A-26 resin consists of a complex hydrocarbon network with $NH_4^{\oplus}$ ion appendages that serve as counter ions to the chromium oxidant, $HCrO_4^{\ominus}$.



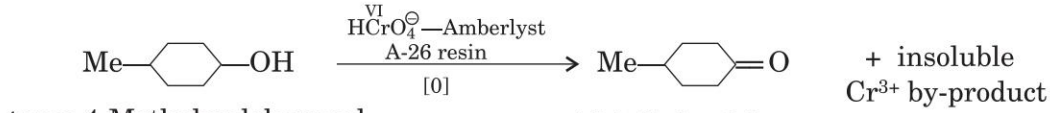
Amberlyst A-26 resin Cr^{6+} oxidant

(A "greener" form of Cr^{6+} reagent)

When an alcohol is heated with the insoluble polymeric reagent, it undergoes oxidation to yield a carbonyl compound, with formation of an insoluble Cr^{3+} by-product. The metal by-product can be removed by filtration with added solvent. Also, it can be regenerated and reused in another reaction. With this "greener" from of Cr^{6+} reagent, primary alcohols are oxidized to aldehydes and secondary alcohols are oxidized to ketones. For example:



1-Decanol (A 1° alcohol) Decanal (An aldehyde)

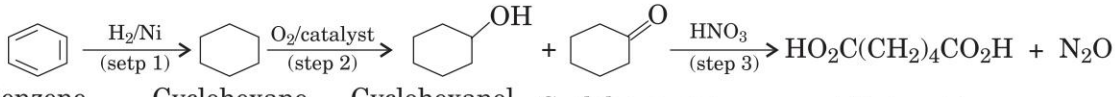


trans-4-Methylcyclohexanol (A 2° alcohol) 4-Methylcyclohexanone (A ketone)

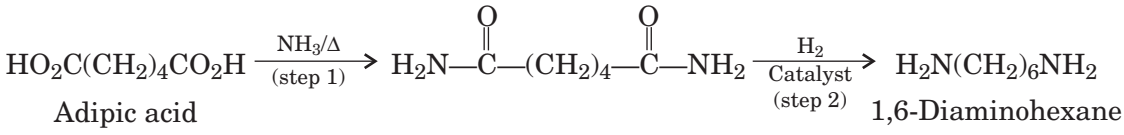
SOLVED PROBLEMS

1. One of the foundation pillars of Green Chemistry is to use the raw material or feedstock obtained from renewable resources (e.g., biomass). What are the disadvantages of the synthesis of nylon-6,6 from benzene? How can it be prepared from environmentally friendly raw materials?

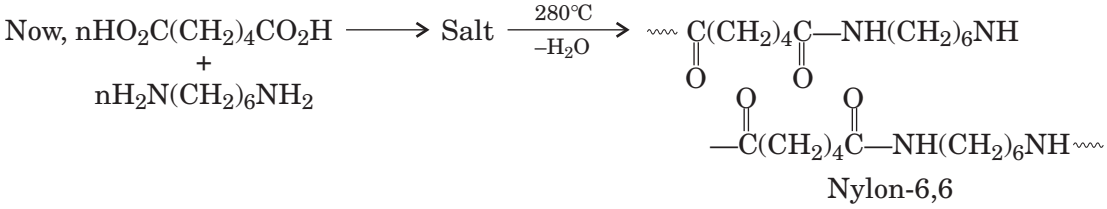
Solution Nylon-6,6 is prepared industrially from adipic acid, $HO_2C(CH_2)_4CO_2H$ and 1,6-diaminohexane, $H_2N(CH_2)_6NH_2$. Both of these starting materials originate from benzene, a product of petroleum refining.



Benzene (from petroleum) Cyclohexane Cyclohexanol Cyclohexanone Adipic acid



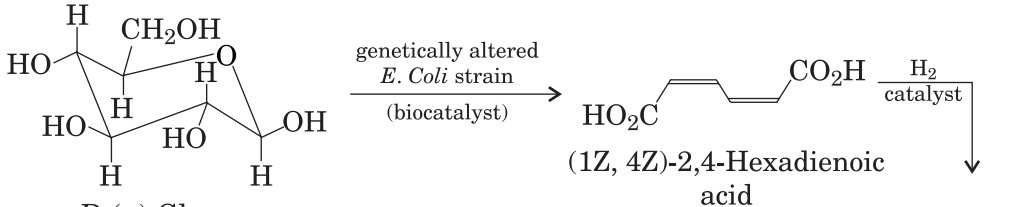
Adipic acid 1,6-Diaminohexane



Nylon-6,6

The disadvantages of this synthesis of nylon-6,6 are as follows: (i) petroleum is a nonrenewable feedstock; (ii) benzene is a carcinogen and liver toxin and so, its use is undesirable in large scale production; (iii) oxidation with HNO_3 in the third step produces N_2O which depletes ozone in the stratosphere in the same way as chlorofluorocarbons; (iv) N_2O absorbs thermal energy from the earth's surface like CO_2 and therefore, it may also cause global warming.

Adipic acid can be synthesized from D-(+)-glucose, a monosaccharide available from plant sources as follows:



D-(+)-Glucose (an environmentally friendly raw material)

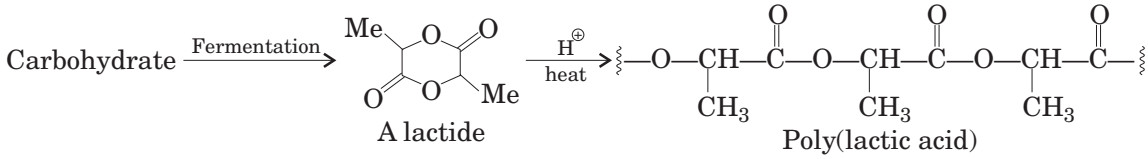
(1Z, 4Z)-2,4-Hexadienoic acid

$HO_2C(CH_2)_4CO_2H$

Adipic acid

2. Provide a green synthesis of poly(lactic acid) which is an especially attractive polymer choice, because it readily degrades.

Solution The green synthesis of PLA involves fermentation of carbohydrates (obtained from corn) to yield a cyclic lactone called lactide followed by heating the lactide with acid.



A lactide

Poly(lactic acid)

3. Show that a catalytic reaction is more atom efficient than the normal stoichiometric reaction using chemical reagents.

Solution This may be shown by comparing stoichiometric oxidation with catalytic oxidation of 1-phenylethanol to yield acetophenone.

Stoichiometric reaction:

$$3PhCH(OH)CH_3 + 2CrO_3 + 3H_2SO_4 \rightarrow 3PhCOCH_3 + Cr_2(SO_4)_3 + 6H_2O$$

$\therefore$ Atom efficiency = 360/860 = 42%

Catalytic reaction:

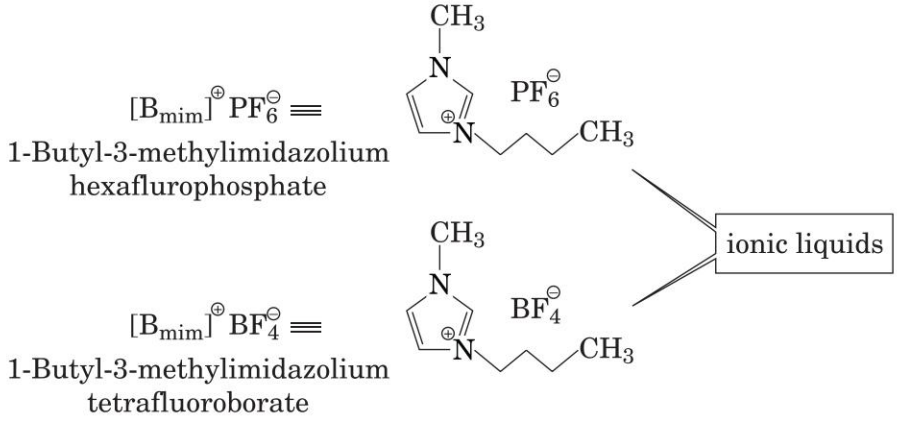
$$2PhCH(OH)CH_3 + O_2 \rightarrow 2PhCOCH_3 + H_2O$$

$\therefore$ Atom efficiency = 240/276 = 87% and the bi-product is H_2O

Therefore, it becomes clear that a catalytic reaction is more atom efficient than the normal stoichiometric reaction using chemical reagents.

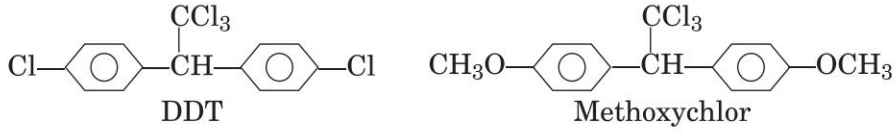
4. **For avoiding volatile organic compounds (VOC), organic reactions are often carried out in ionic liquids. Two such ionic liquids are $[B_{min}]^{\oplus}PF_6^{\ominus}$ and $[B_{min}]^{\oplus}BF_4^{\ominus}$ where, B_{min} = 1-butyl-3-methylimidazolium cation. Provide structures of the molecules of these two ionic liquids.**

Solution The structures of these two ionic liquids are as follows:



Study Problems

1. (a) What do you mean by the term Green Chemistry?
   (b) What are the foundation pillars of Green Chemistry (GC)?
2. The main foundation pillar of GC today is catalysis in synthetic processes. Explain this statement.
3. DDT is an environment pollutant because of its nonbiodegradability. Explain why methoxychlor, which is used instead of DDT, is readily biodegradable.



[**Hint:** Due to presence of electron-releasing $-OCH_3$ groups methoxychlor undergoes ready oxidation and biodegradation.]

4. Soaps and detergents are easily biodegradable yet these are considered as water pollutant–why?
5. The weedicide 2,4-D undergoes ready biodegradation, even though it acts as a soil pollutant. Account for these observations.
6. What do you mean by green solvents? Give examples.
7. Give examples of two atom efficient processes.
8. Ready biodegradability of a synthetic chemical does not qualify it to be free from any adverse effect—why?

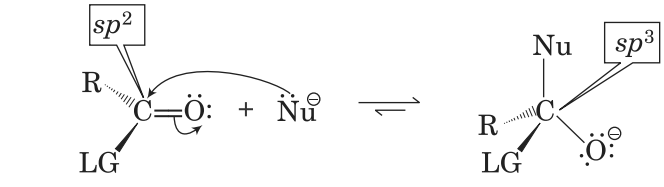
2.10 ACYL SUBSTITUTION

Nucleophilic Addition–Elimination at the Acyl Carbon

2.10.1 Mechanism of Nucleophilic Addition–Elimination at the Acyl Carbon or Nucleophilic Acyl Substitution

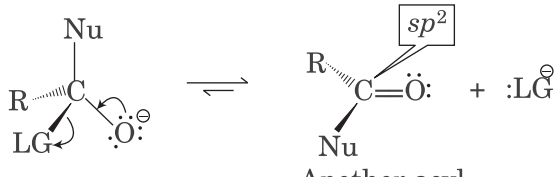
Acyl substitution by nucleophilic addition–elimination takes place in two steps. In step 1, the nucleophile adds to the carbonyl carbon atom to form a tetrahedral intermediate. This intermediate is not stable and cannot be isolated. In step 2, a leaving group is eliminated from the intermediate to yield a substitution product. The reaction is successful if the leaving group is a weaker base than the attacking nucleophile.

Step 1:



An acyl compound (LG acts as a leaving group) — Tetrahedral intermediate

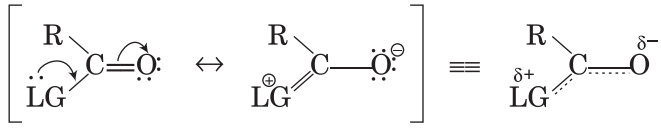
Step 2:



Another acyl compound

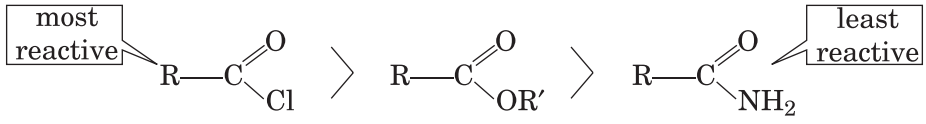
Reactivity of the acyl compounds: The reactivity of the acyl compounds depends on both the steps, but the second step is more important. The formation of a tetrahedral intermediate in step 1 is influenced by the same factors as in addition to aldehydes and ketones. It depends on the extent of partial positive charge developed on the carbonyl

carbon atom. The nonbonding electrons on the leaving group LG become involved in resonance with the carbonyl double bond. As a result, the partial positive charge on the carbonyl carbon atom reduces and the nucleophilic attack on it occurs less readily.



Resonance in the acyl compound

Therefore, with increase in the effectiveness of the resonance interaction, the reactivity of the acyl derivative progressively decreases. The weaker the basicity of LG, the smaller the contribution from the resonance contributor with a positive charge on LG. The less the acyl compound is stabilized by electron delocalization, the more reactive it will be. Also, weaker bases are better at withdrawing electrons inductively from the cabonyl carbon, which increases the carbonyl carbon's susceptibility to nucleophilic attack. The reactivity of acyl compounds also depends on the electronic and more particularly the steric effect caused by R. When a trigonal acyl compound is converted to a tetrahedral intermediate, the attached groups become close to each other, and so, a moderate steric strain occurs in the transition state that resembles the tetrahedral intermediate. The reaction is, therefore, susceptible to the steric effect caused by the group R. The reactivity of the acyl compounds depends mainly on the second step of the reaction, i.e., on the tendency of the leaving group LG to depart. Weak bases (the conjugate bases of strong acids) are better leaving groups because they are stable and possess enhance capacity to accommodate the bonding electrons, i.e., the negative charge. Therefore, the less basic and more stable the leaving group, the more reactive is the acyl compound. In general, the overall order of reactivity of acyl compounds is:



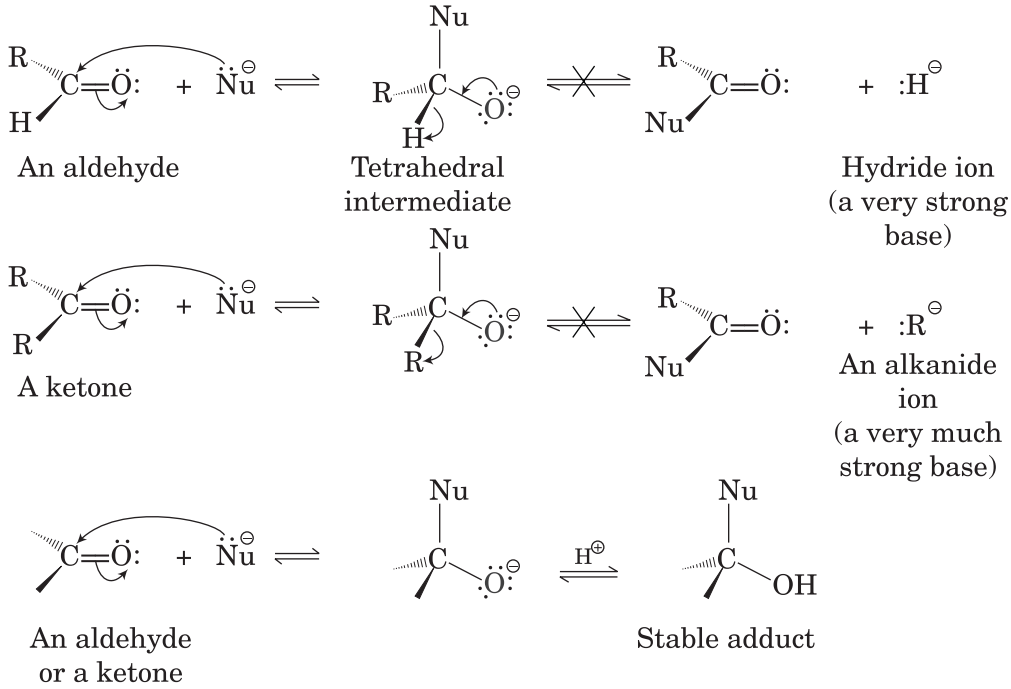
Acyl chloride Ester Amide

This order can be explained as follows. Although oxygen is more electronegative than chlorine, its resonance interaction with the carbonyl group in an ester is more effective than the resonance interaction of chlorine with the carbonyl group in an acyl chloride and this is because of the size similarities between carbon and oxygen (poor orbital overlap between the large 3*p* orbital on chlorine and the smaller 2*p* orbital on carbon). The resonance interaction in an amide is most effective because of the size similarity of nitrogen with carbon. Also, nitrogen is not better at withdrawing electrons inductively from the carbonyl carbon compared to oxygen. Because of this, the cabonyl carbon of an acyl chloride is more positive than the carbonyl carbon of an ester which in turn is more positive than the carbonyl carbon of an amide. Again, the chloride ion ($Cl^{\ominus}$) is a weaker base (pK_a of its conjugate acid HCl is –7), the alkoxide ion ($RO^{\ominus}$) is a stronger base

(pK_a of its conjugate acid ROH is ~15–16) and the amide ion ($NH_2^{\ominus}$) is a much stronger base (pK_a of its conjugate acid NH_3 is 36). So, their leaving ability follows the order: $Cl^{\ominus}$ > $RO^{\ominus}$ > $NH_2^{\ominus}$. Therefore, the electrophilicity of the carbonyl carbon and the leaving ability of the groups suggest that an acyl chloride is more reactive towards nucleophilic addition–elimination (acyl substitution) than an ester which in turn is more reactive than an amide.

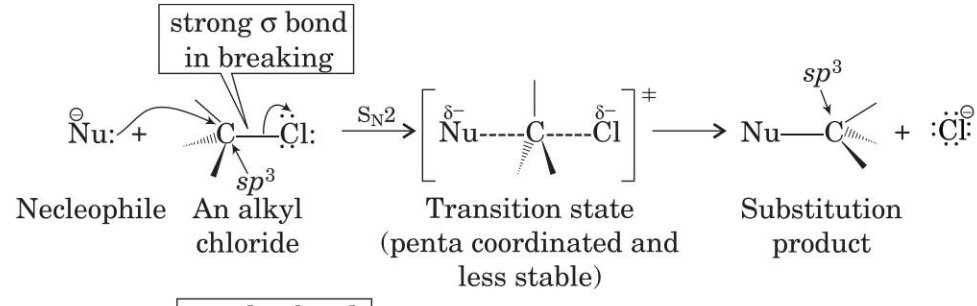
Some relevant topics:

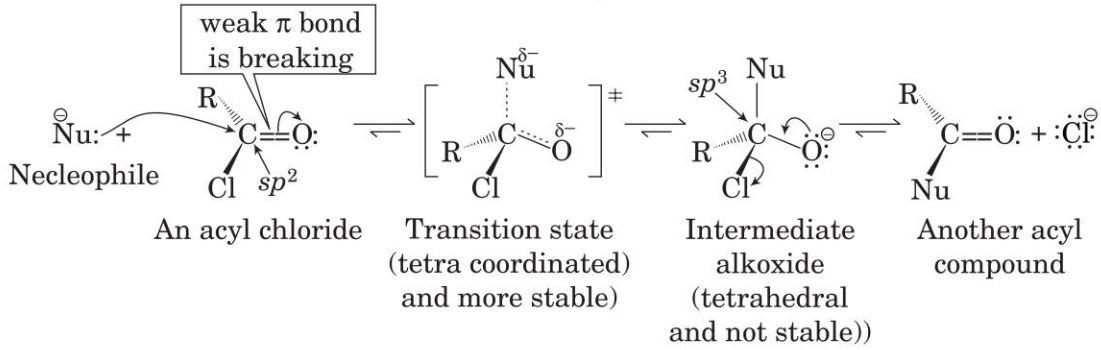
(i) Aldehydes and ketones undergo addition rater than substitution: For an aldehyde or ketone to undergo nucleophilic addition–elimination, i.e., to undergo nucleophilic acyl substitution, the tetrahedral intermediate would have to eliminate a hydride ion, $:H^{\ominus}$ (the conjugate base of very weak acid H_2, pK_a = 35) or an alkanide ion, $:R^{\ominus}$, (the conjugate base of very much weak acid RH, pK_a = >60). As both of them are very stronger base, both of them are very unstable and hence show little tendency to depart, i.e., they are very poor leaving groups. For this reason, aldehydes and ketones undergo nucleophilic addition rather than substitution.



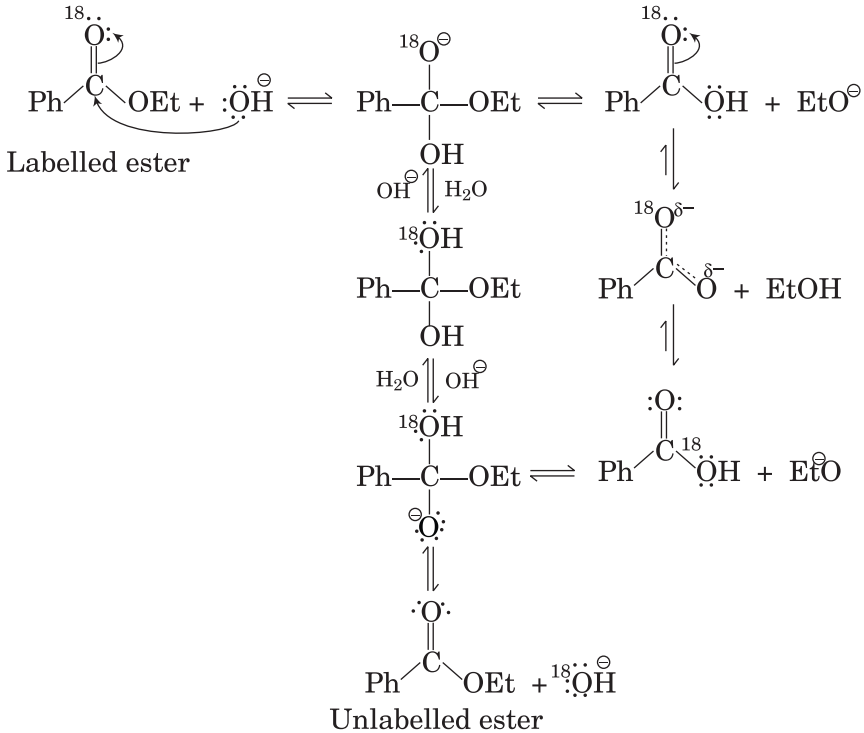
(ii) An acyl chloride is more reactive than an alkyl chloride: S_N2 attack on a tetrahedral carbon involves a much crowded transition state in which the central carbon atom is penta coordinated and in this displacement process, a strong σ bond must be partially broken to promote attachment of the nucleophile. On the other hand, the nucleophilic attack on the cabonyl carbon of a trigonal planar acyl

compound involves a relatively unhindered transition state leading to a tetrahedral intermediate and in this case, the attachment of the nucleophile requires breaking of a relatively weak π bond. Hence, the substitution reaction that takes place at an acyl carbon (sp^2 hybridized) is energetically more favourable than the reaction taking place at a saturated carbon (sp^3 hybridized) and therefore, acyl chlorides are more reactive than alkyl chlorides towards a given nucleophile.





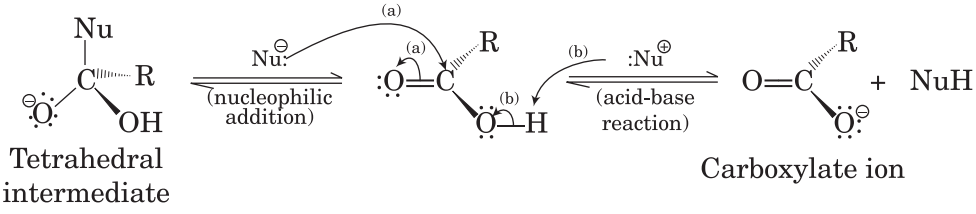
(iii) Proof of the mechanism for nucleophilic addition-elimination: The nuclephilic addition-elimination reactions take place by a mechanism in which a tetrahedral intermediate is formed and then collapsed to give the trigonal product. The intermediate is too unstable to be isolated. By a labelling experiment, it can be proved that such an intermediate has been formed during acyl substitution. When the base-promoted hydrolysis of ethyl benzoate $(\mathrm{Ph}\overset{18}{\mathrm{C}}\mathrm{OOC_2H_5})$ in which the carbonyl oxygen is labelled with ^{18}O is carried out and ethyl benzoate is isolated from the reaction mixture before completion of the reaction, it is found that some of the ester is no longer labled. If the reaction had taken place by a concerted (one-step) displacement mechanism, all the isolated ester would have remained labelled because the carbonyl group would not have participated in the reaction. However, if the mechanism involves a tetrahedral intermediate, only then some of the isolated ester would no longer be labelled because some of the ^{18}O would have been transferred to the hydroxide ion. This experiment, therefore, provides evidence for the reversible formation of a tetrahedral intermediate



(iv) Condition for acyl substitution: A carboxylic acid derivative will undergo a nucleophilic addition-elimination reaction or acyl substitution, provided the newly added group in the tetrahedral intermediate (i.e., the nucleophile) is not a much weaker base than the group attached to the acyl group in the reactant, i.e., the leaving group.

2.10.2 Reactions of Carboxylic Acids

We may apply the general addition-elimination sequence to the conversion of carboxylic acids into their derivatives. However, there are two problems: (i) the hydroxide ion is a poor leaving group and (ii) the carboxy proton is acidic, and most nucleophiles are bases. Therefore, the nucleophilic attack on carbonyl carbon (path *a* in the following equation) can encounter interference from an acid-base reaction (path *b*). When the nucleophile is very basic (e.g. $RO^{\ominus}$), the carboxylate ion is formed irreversibly and nucleophilic addition to the carbonyl carbon becomes very much difficult.



However, with less basic nucleophiles, especially under acidic conditions, the ready reversibility of the carboxylate ion formation permits nucleophilic addition to compete and ultimately leads to substitution by the addition-elimination process. Esterification of a carboxylic acid is a typical example in which an alcohol and a carboxylic acid react to produce an ester and water. The nucleophilic alcohol is a weak base and acid is present to protonate the carbonyl oxygen, activating it towards nucleophilic attack, and the hydroxyl oxygen, converting it to a better leaving group, water.

2.10.2.1 Formation of Acyl Chlorides

When a carboxylic acid is allowed to react with an acid chloride of inorganic acids like phosphorus pentachloride (PCl_5), phosphorus trichloride (PCl_3) or thionyl chloride ($SOCl_2$), an acyl chloride is obtained in good yield.

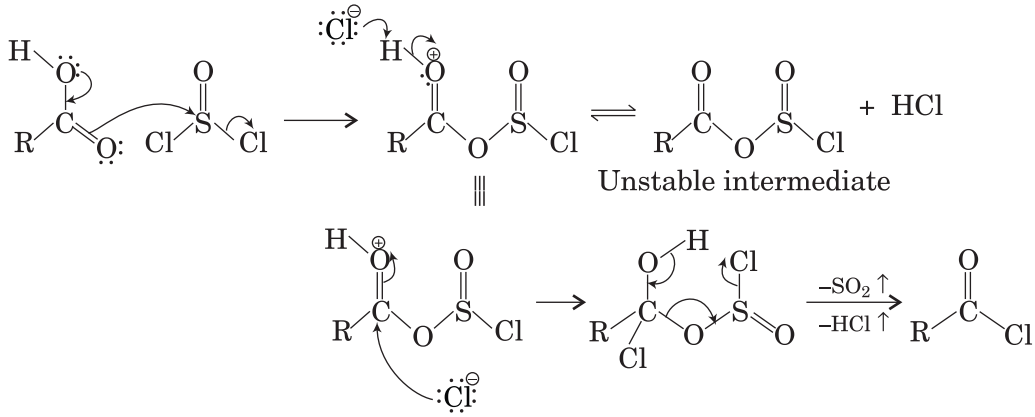
(i) $\mathrm{R{-}C(=O){-}OH + SOCl_2 \longrightarrow R{-}C(=O){-}Cl + SO_2 + HCl}$ (Thionyl chloride)

(ii) $\mathrm{3\ R{-}C(=O){-}OH + PCl_3 \longrightarrow 3\ R{-}C(=O){-}Cl + H_3PO_3}$ (Phosphorus trichloride)

(iii) $\mathrm{R{-}C(=O){-}OH + PCl_5 \longrightarrow R{-}C(=O){-}Cl + POCl_3 + HCl}$ (Phosphorus pentachloride)

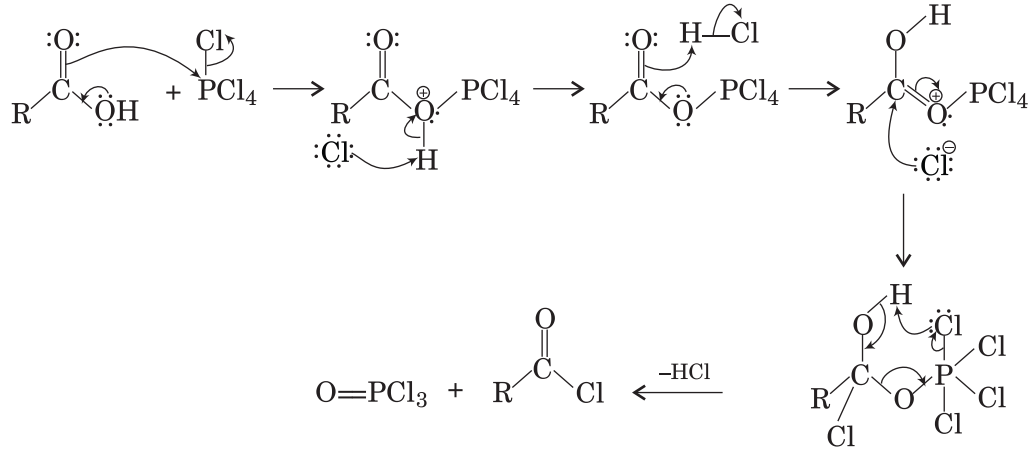
All these reactions involve nucleophilic addition-elimination by a chloride ion on a highly reactive intermediate such as a protonated acyl chlorosulphite, a protonated acyl chlorophosphite, or a protonated acyl chlorophosphate. The acyl leaving groups of these intermediates are even better than the acyl chloride product.

The mechanism for the reaction (i) is as follows:



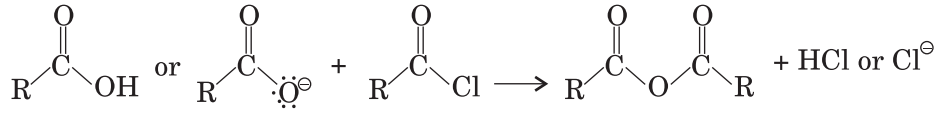
The carboxylic acid reacts with $SOCl_2$ to form a highly electrophilic protonated chlorosulphite (powerful enough to react even with the weak nucleophile $Cl^{\ominus}$) which reacts with $Cl^{\ominus}$ to give a tetrahedral intermediate. The intermediate then releases SO_2 and HCl to form the acyl chloride.

The mechanism for the reaction (iii) is as follows:

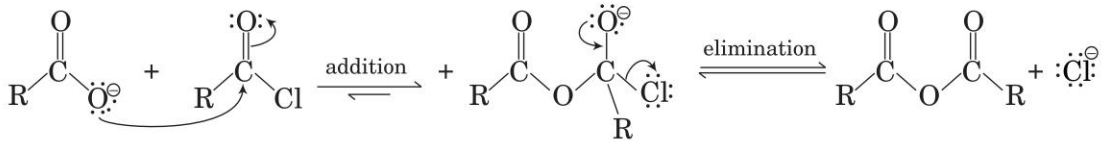


2.10.2.2 Formation of Acid Anhydrides

Carboxylic acids and their conjugate bases, the carboxylate anions ($RCOO^{\ominus}$), react with acid halides to give acid anhydrides.

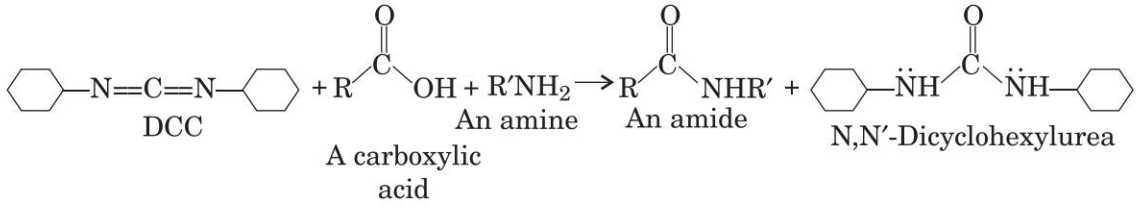


Mechanism: The mechanism of the reaction involves addition of the carboxylate anion to the carbonyl group of the acid chloride to give a tetrahedral intermediate that can lose a $Cl^{\ominus}$ ion (a good leaving group) to form an anhydride.

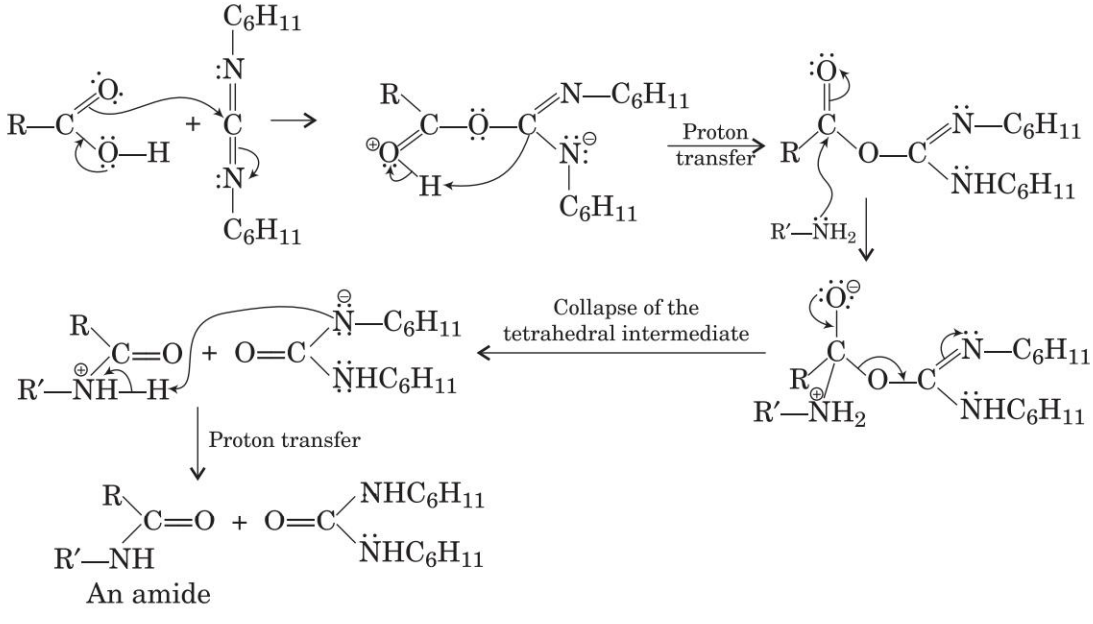


2.10.2.3 Formation of Amides

Amide formation from the carboxylic acid is much easier if the acid is first activated by an activating agent like dicyclohexylcarbodmide (DCC).



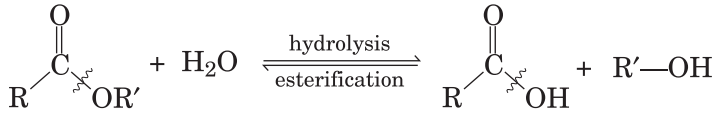
The mechanism of the reaction may be sketched as follows:



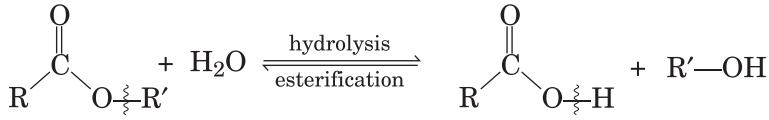
2.10.2.4 Esterification of Carboxylic Acids and Hydrolysis of Esters

The hydrolysis of esters and esterification of carboxylic acids may proceed through a number of distinct mechanisms. The plurality of mechanism of these two processes is due to the fact that: (i) the hydrolysis and esterification may take place either through an acyl-oxygen bond cleavage or an alkyl-oxygen bond cleavage:

Acyl-oxygen cleavage:



Alkyl-oxygen cleavage:



(ii) the hydrolysis is base-promoted or acid-catalysed, where the esterification is only acid-catalysed, (iii) both hydrolysis and esterification may take place either by a unimolecular or a bimolecular mechanism.

Out of eight possible mechanisms for ester hydrolysis only six have been observed. Since in principle, the acid-catalysed reactions (hydrolysis and esterification) are reversible but not base-promoted hydrolysis, only four mechanisms are possible for esterification. However, only three of them have been observed. *Esterification in basic medium is not possible because the carboxylic acid becomes converted into a resonance-stabilized carboxylate anion that does not undergo nucleophilic attack*.

These mechanistic courses are designated by some shorthand notations in which A and B refers to the acidic or basic (or neutral) medium; the subscripts AC and AL, respectively denote acyl- and alkyl-oxygen bond cleavage and the number 1 and 2 represents the molecularity of the rate-determining step of the reaction. Thus, $A_{AC}2$ hydrolysis indicates a bimolecular acid-catalysed hydrolysis of an ester which involves acyl-oxygen bond cleavage.

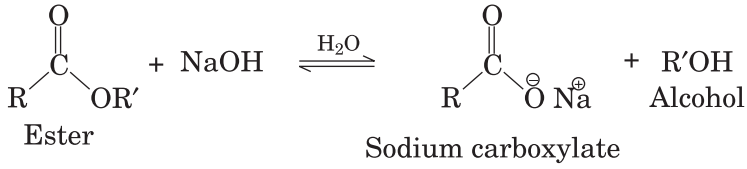
The feasibility of reactions involving various mechanisms may be shown in tabular form as follows:

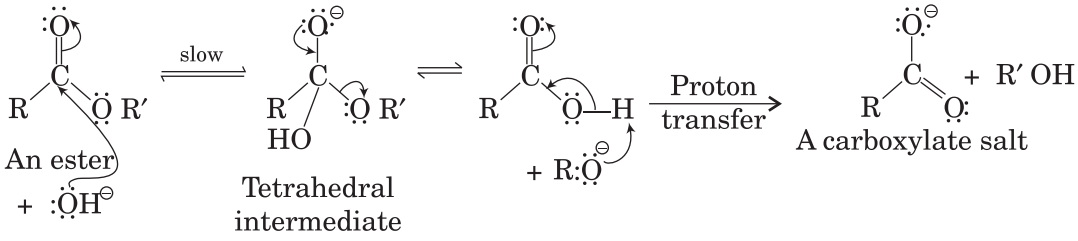
Type of mechanism	Hydrolysis of ester	Esterification of carboxylic acid
$B_{AC}1$	—	—
$B_{AC}2$	very common	—
$A_{AC}1$	special cases	special cases
$A_{AC}2$	very common	very common
$B_{AL}1$	special cases	—
$B_{AL}2$	rare	—
$A_{AL}1$	very common for 3 alcohols	very common for 3 alcohols
$A_{AL}2$	—	—

It is to be noted that the hydrolysis of an ester is base-promoted, not base-catalysed, because the base ($OH^{\ominus}$) is the nucleophile that adds to the ester and forms part of the product. It participates in the reaction and does not regenerate after completion of the reaction.

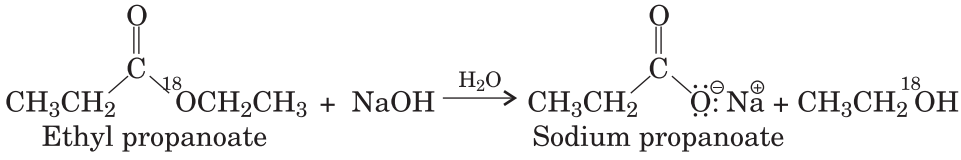
The various mechanistic courses are described below:

1. **$B_{AC}2$ mechanism** (Base-promoted, Acyl-oxygen cleavage, bimolecular): An ester undergoes alkaline hydrolysis (saponification) by this mechanistic pathway. That it is a second order reaction is suggested by kinetic studies. Therefore, it is a bimolecular process. The reaction proceeds by an acyl-oxygen bond cleavage and involves an addition-elimination sequence in which displacement of $RO^{\ominus}$ by the nucleophile $OH^{\ominus}$ takes place via the formation of a tetrahedral intermediate. The highly exothermic last step drives the hydrolysis to completion (because the carboxylic acid is a much stronger acid than alcohol) and hence, saponification is effectively irreversible.



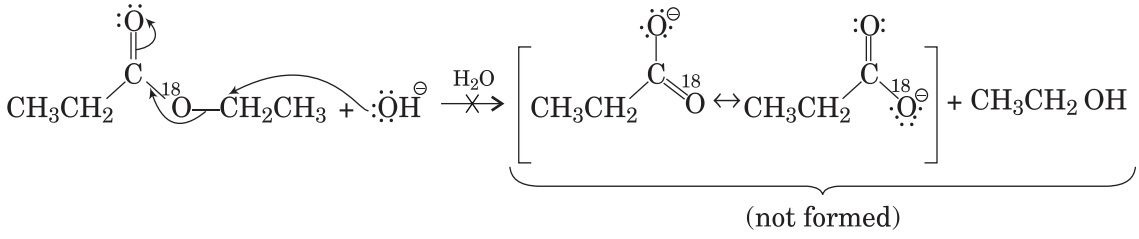


Evidence for the mechanism: That acyl-oxygen bond cleavage has taken place can be established by ^{18}O labelling experiments and stereochemical studies. When ethyl propanoate labelled with ^{18}O in the ether-type oxygen of the ester is subjected to hydrolysis with aqueous NaOH, all of the ^{18}O shows up in ethanol that is formed. None of the ^{18}O appears in the propanoate ion:

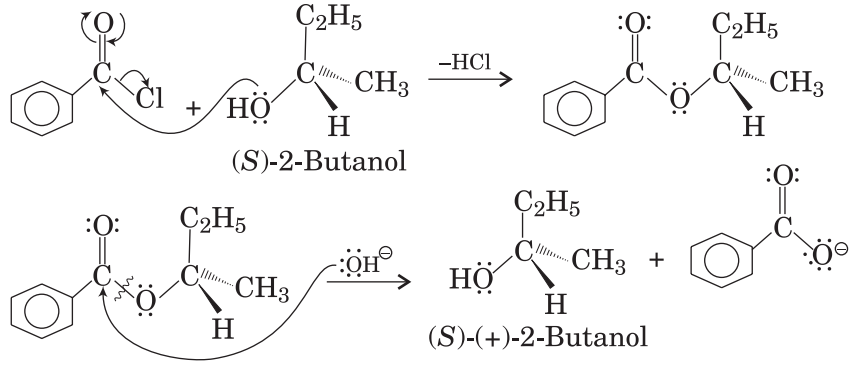


The result of this labelling experiment is consistent with the mechanism given above. If the $OH^{\ominus}$ ion had attacked the carbon instead of the acyl carbon, the alcohol obtained would not have been labelled. Attack at the alkyl carbon is almost

never observed (except some special cases).

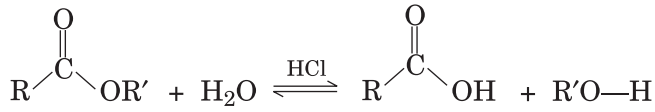


The stereochemical evidence for the acyl-oxygen bond cleavage is as follows. When (*S*)-(+)-2-butanol having specific rotation +13.8° is converted into the benzoate ester by allowing it to react with benzoyl chloride and that ester is hydrolysed by dilute alkali, (*S*)-2–butanol of rotation +13.8° is obtained. This complete retention of configuration strongly suggests that acyl-oxygen bond cleavage occurs.

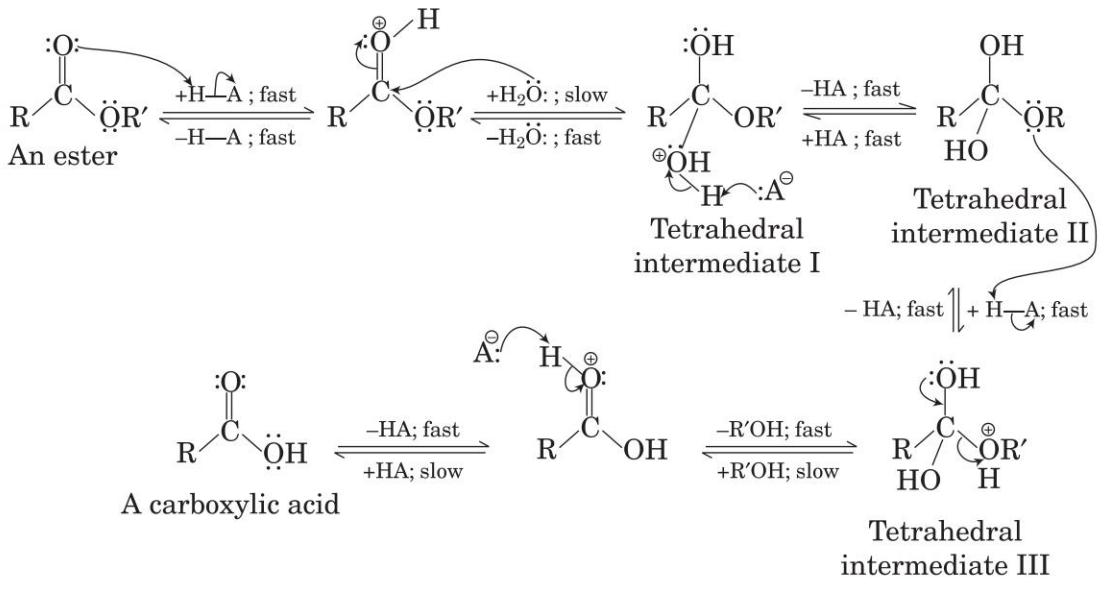


That a tetrahedral intermediate has been formed can also be proved by ^{18}O labelling experiment. It is already discussed in the **article 2.4.1**.

2. **$A_{AC}2$ mechanism** (Acid-catalysed, Acyl-oxygen cleavage, bimolecular): It is the most common mechanism of acid-catalysed hydrolysis of esters. The reaction is reversible and according to the *principle of microscopic reversibility* the mechanism for acid-catalysed esterification of a caboxylic acid is exactly the reverse of that of acid-catalysed hydrolysis of its ester.



The mechanism of acid-catalysed hydrolysis of an ester follows the most familiar nucleophilic addition-elimination at the acyl carbon or nucleophilic acyl substitution. This may be outlined as follows:

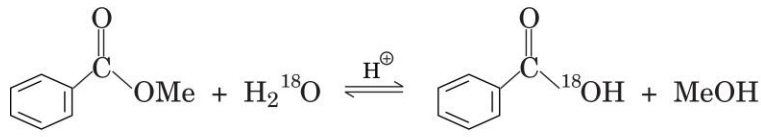


Protonation in the first step makes the carbonyl carbon more electrophilic. Nucleophilic addition of H_2O in the second step forms a protonated tetrahedral intermediate (I). Loss of proton occurs in the third step to form a neutral tetrahedral intermediate (II). The –OR′ group undergoes protonation in the fourth step and becomes converted into a good leaving group (R′OH). A new protonated tetrahedral intermediate (III) is thereby formed. In the fifth step, alcohol (R′OH) is eliminated, and in the sixth and final step, loss of proton occurs to form the carboxylic acid.

In the forward process (hydrolysis), water acts as a nucleophile and displaces alcohol to form an acid via the intermediate I, II and III. In the backward process (esterification), alcohol acts as a nucleophile and displaces water to form an ester via the same intermediates formed in the reverse order.

The result obtained in this reversible process depends on the conditions we choose. If we want to esterify an acid, we have to use an excess of alcohol and, if possible, water is to be removed as it is formed (to make the equilibrium favourable according to the Le Chatelier's principle). On the other hand, if we want to hydrolyse an ester, we have to use a large excess of water, i.e., the ester is to be refluxed with dilute aqueous HCl or dilute aqueous H_2SO_4.

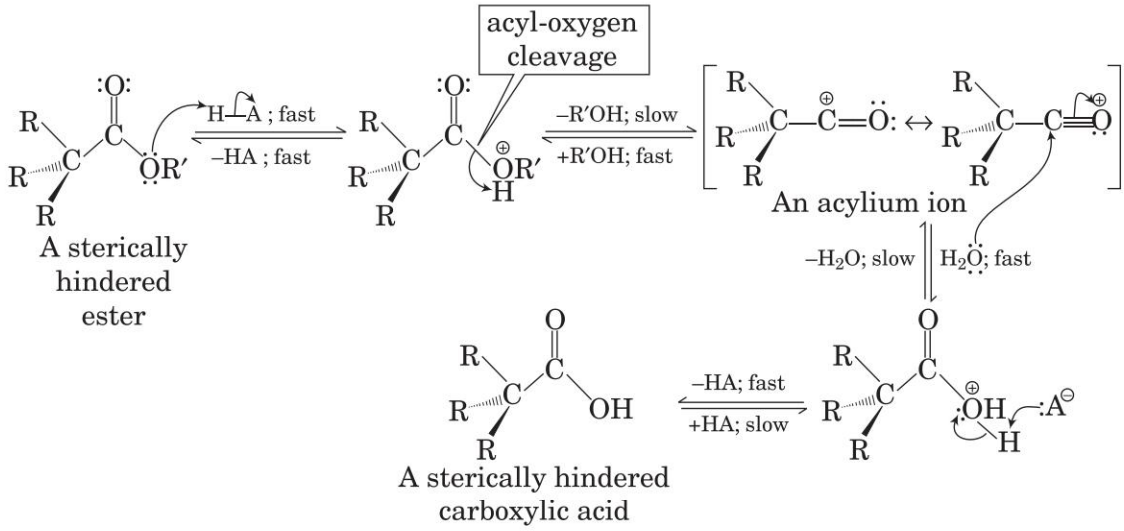
Evidence for the mechanism: That acyl-oxygen bond cleavage has taken place can be established by ^{18}O labelling experiment and stereochemical studies. For instance, the acid-catalysed hydrolysis of methyl benzoate in water enriched with ^{18}O gives methanol with no extra ^{18}O. Therefore, acyl-oxygen bond cleavage must have taken place.



Methyl benzoate — Benzoic acid (lebelled)

Esters with chiral R′ groups on hydrolysis produces alcohols with retention of configuration. This observation also supports acyl-oxygen bond cleavage. The formation of the tetrahedral intermediate can be established by isolation of unlabelled ester from a labelled ester (as in alkaline hydrolysis).

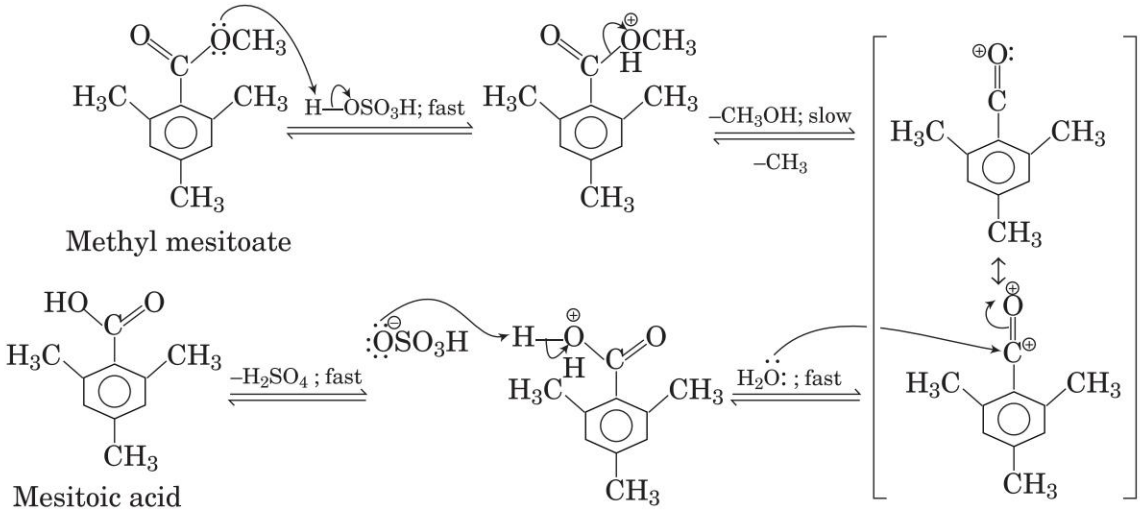
3. **$A_{AC}1$ mechanism** (Acid-catalysed, Acyl-oxygen cleavage, unimolecular): The hydrolysis and esterification of sterically hindered esters by the $A_{AC}2$ mechanism involving a tetrahedral intermediate are inhibited because of steric crowding involved in the transition state leading to that intermediate. For this reason, hydrolysis of such hindered esters occurs by $A_{AC}1$ mechanism that takes place only in powerful ionizing solvents (e.g., conc. H_2SO_4).



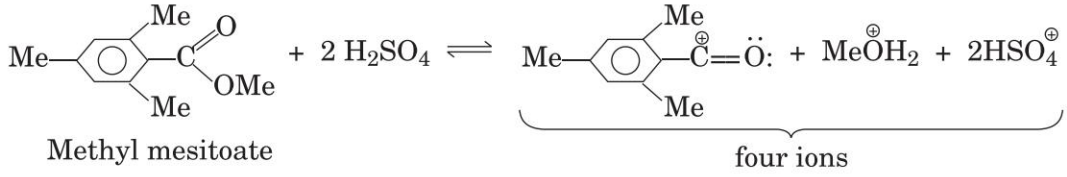
Since all the steps are reversible, therefore, the mechanism of the backward reaction is in principle (the principle of microscopic reversibility) applicable for esterification of sterically hindered carboxylic acids. The reaction proceeds through the formation of an intermediate acylium ion by acyl-oxygen bond cleavage and this requires protonation of the less favoured –OR or –OH oxygen atom rather than the carbonyl oxygen atom. The reaction is unimolecular because the rate depends on the concentration of the ester (in the case of hydrolysis) or the acid (in the case of esterification).

For example, the sterically hindered ester methyl mesitoate or methyl 2,4,6-trimethylbenzoate undergoes hydrolysis by this mechanism. The backward

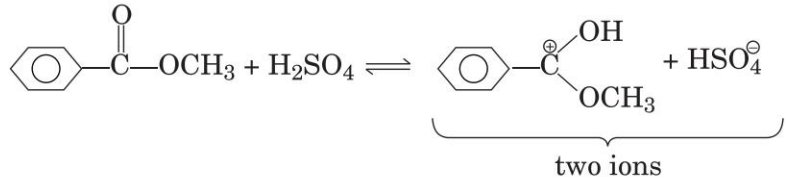
reaction applies for the esterification of the sterically–hindered mesitoic acid or 2,4,6-trimethylbenzoic acid.



Evidence for the mechanism: A number of experimental observations support this mechanistic course. Methyl mesitoate, for example, causes a four-fold depression in the freezing point of sulphuric acid (the van't Hoff factor i is 4) as much as would be predicted from its molecular weight. This can be explained in terms of the following equilibrium involving four ions:



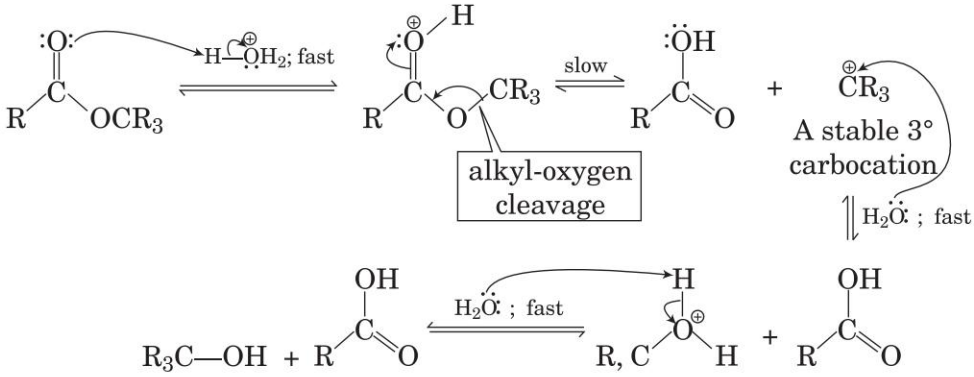
The depression of freezing point has been observed to be only two fold (the van't Hoff factor i is 2) in a comparable solution of methyl or isopropyl benzoate. This indicates a normal acid-base reaction leading to the formation of two ions:



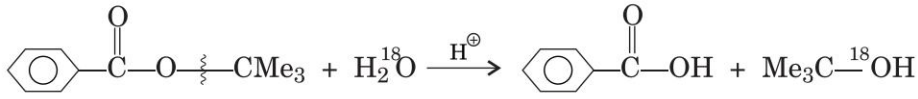
The reaction of methyl mesitoate, therefore, proceeds through an intermediate acylium ion (in this case mesitoylium ion) formed by acyl-oxygen heterolysis.

Also, the recovered unhydrolyzed ester is found not to take up ^{18}O from the medium, the electron-releasing groups are found to increase the rate and the entropy of activation ($\Delta S^{\ddagger}$) is positive. All these observations are consistent with the $A_{AC}1$ mechanism for the hydrolysis of methyl mesitoate.

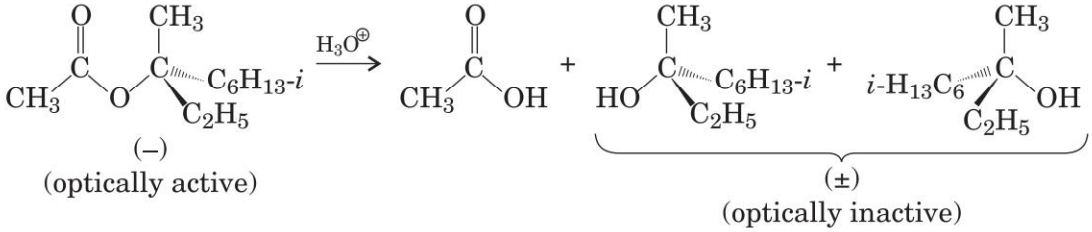
4. **$A_{AL}1$ mechanism** (Acid-catalysed, Alkyl-oxygen cleavage, unimolecular): Esters (RCOOR′) in which the alkyl group R′ can form a stable carbocation (e.g., a 3° carbocation, a benzyl cation, *etc*.) undergo acid-catalysed hydrolysis by this mechanism. Since all the steps are reversible, the mechanism of the backward reaction is in principle (the principle of microscopic reversibility) applicable for the esterification of carboxylic acids with alcohols which can form stable carbocations.



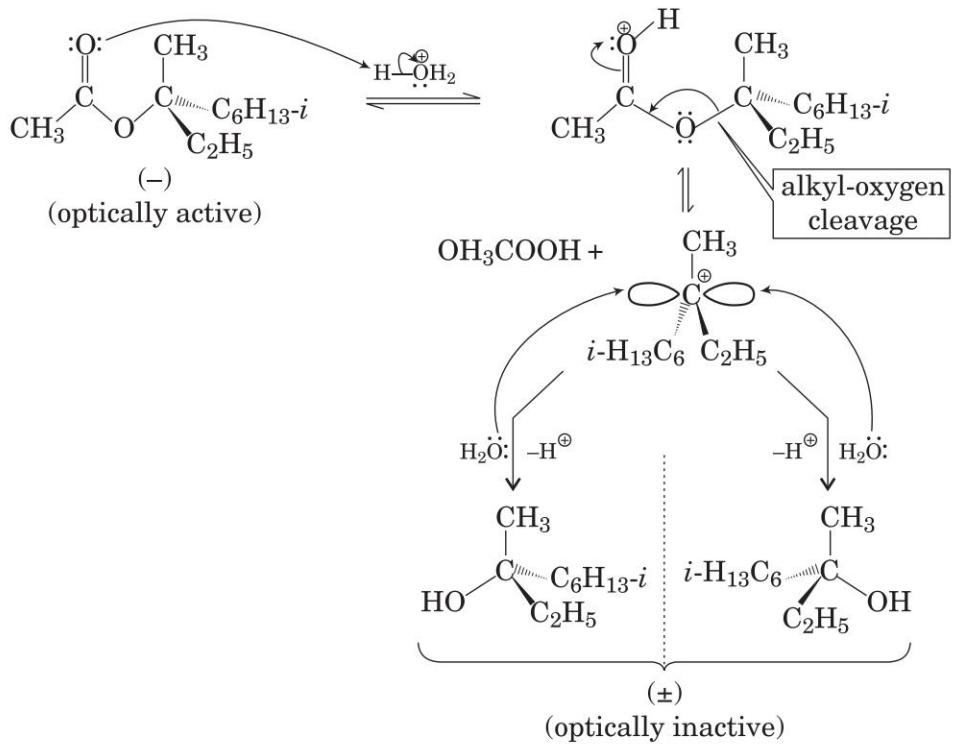
Evidence for the mechanism: That alkyl-oxygen bond cleavage has taken place can be established by isotopic labelling experiment. When acid-catalysed hydrolysis of *tert*-butyl benzoate, for example, is carried out in water enriched with ^{18}O, *tert*-butyl alcohol containing ^{18}O is obtained.



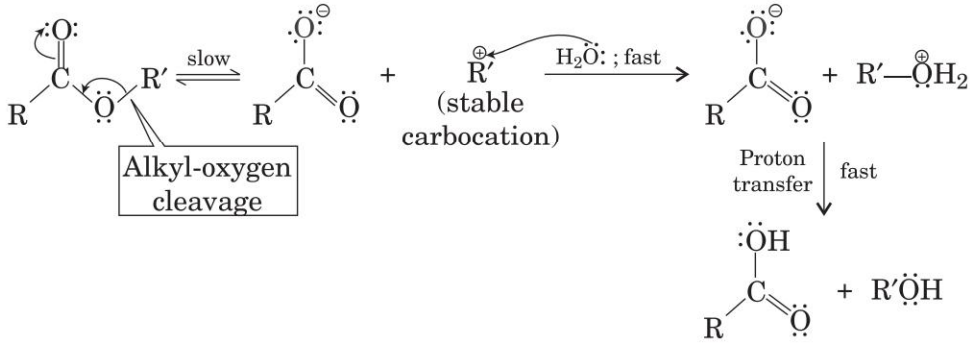
The alkyl-oxygen bond cleavage is also supported by stereochemical studies. When the following optically active ester, for example, is hydrolysed in the presence of acid, the solution becomes optically inactive due to formation of racemic alcohol.



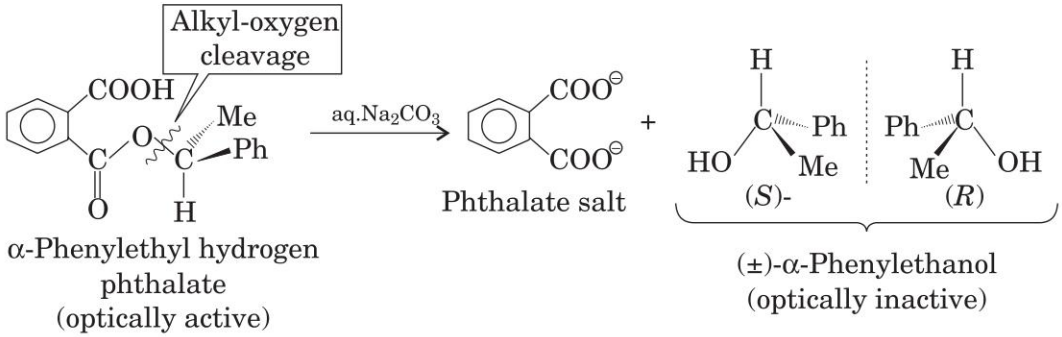
Since racemization occurs, therefore, an intermediate carbocation must have been formed by alkyl-oxygen bond cleavage. The planar carbocation undergoes nucleophilic attack by H_2O from the two enantiotopic faces with equal facility to yield two enantiomeric alcohols in equal amounts. The stereochemical course of the reaction may be sketched as follows:



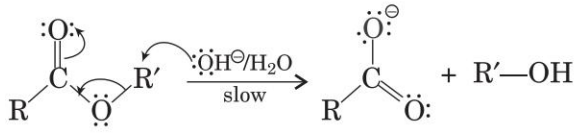
5. **$B_{AL}1$ mechanism** (Base-promoted, Alkyl-oxygen cleavage, unimolecular): Esters undergoes hydrolysis by this mechanism when the alkyl group R′ is capable of forming a relatively stable carbocation, the solvent possesses high ionizing power (thereby encouraging the alkyl-oxygen cleavage) and the medium is weakly alkaline or neutral (thereby inhibiting the S_N2 mechanism).



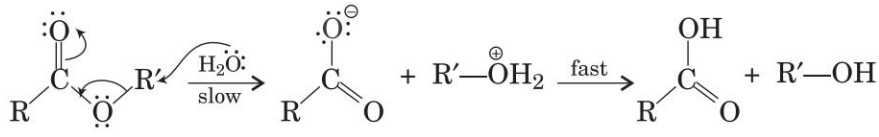
Evidence for the mechanism: An example of the $B_{AL}1$ mechanism is the hydrolysis of optically active α-phenylethyl hydrogen phthalate in faintly alkaline solution. That this mechanism operates can be proved by the fact that racemic α-phenylethanol is obtained; this is in keeping with the formation of an intermediate carbocation by alkyl-oxygen bond heterolysis.



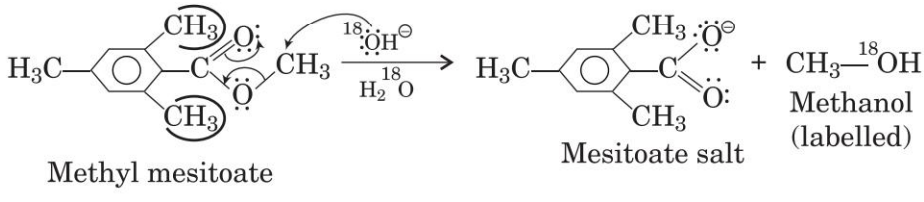
6. **$B_{AL}2$ mechanism** (Base-promoted, Alkyl-oxygen cleavage, bimolecular): This extremely uncommon mechanism is found to operate only in some special cases. This mechanism (similar to S_N2 reaction in aliphatic saturated compounds like alkyl halide, alkyl tosylates, etc.) actually operates in very weakly alkaline (e.g., 0.0011 M NaOH) or neutral solution and when the nucleophilic attack on the ester carbonyl group is inhibited due to steric crowding caused by the alkyl groups around it.



or,



Methyl mesitoate, for example, undergoes hydrolysis in very weakly alkaline solution by this mechanism and this is because the carbonyl group is highly hindered by the presence of two *ortho*-methyl groups. The mechanism can be proved by a labelling experiment.

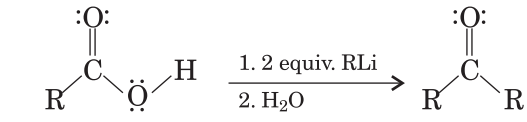


Methyl mesitoate

Mesitoate salt

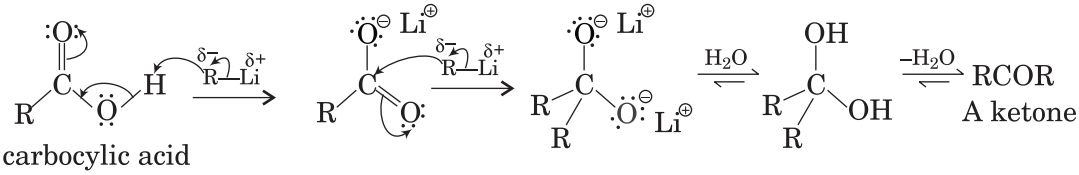
2.10.2.5 Formation of Ketones and Primary Alcohols

Carboxylic acids react with two equivalents of an organolithium reagent to give the corresponding ketone.



A carboxylic acid A ketone

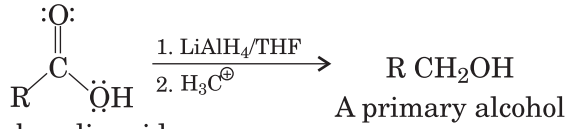
The mechanism of the reaction is as follows:



A carbocylic acid A ketone

The first step in the reaction is the formation of the lithium salt of carboxylic acid (an acid-base reaction). Although the resulting species already contains a negative charge, the organo-lithium reagent is a strong enough nucleophile to add to it to give a dianion. The dianion reacts with water to form a *gem*-dial. The unstable *gem*-dial loses a molecule of water to produce a ketone.

Lithium aluminium hydride ($LiAlH_4$) is capable of reducing carboxylic acids to the corresponding primary alcohols that are obtained upon aqueous acidic work-up.

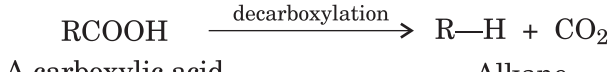


A carboxylic acid A primary alcohol

For mechanism see **article 2.5.2.**

2.10.2.6 Decarboxylation

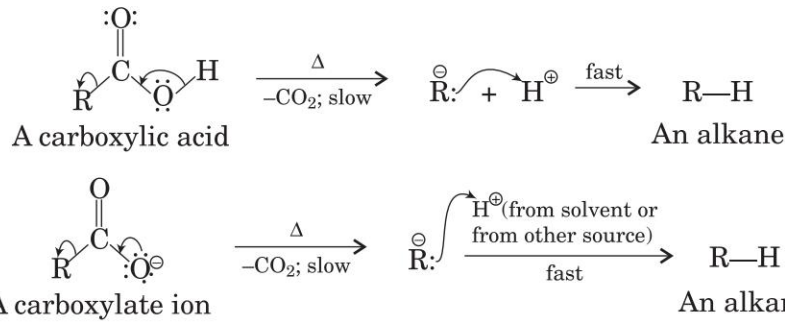
The reaction whereby a carboxylic acid (RCOOH) loses CO_2 is called a decarboxylation reaction.



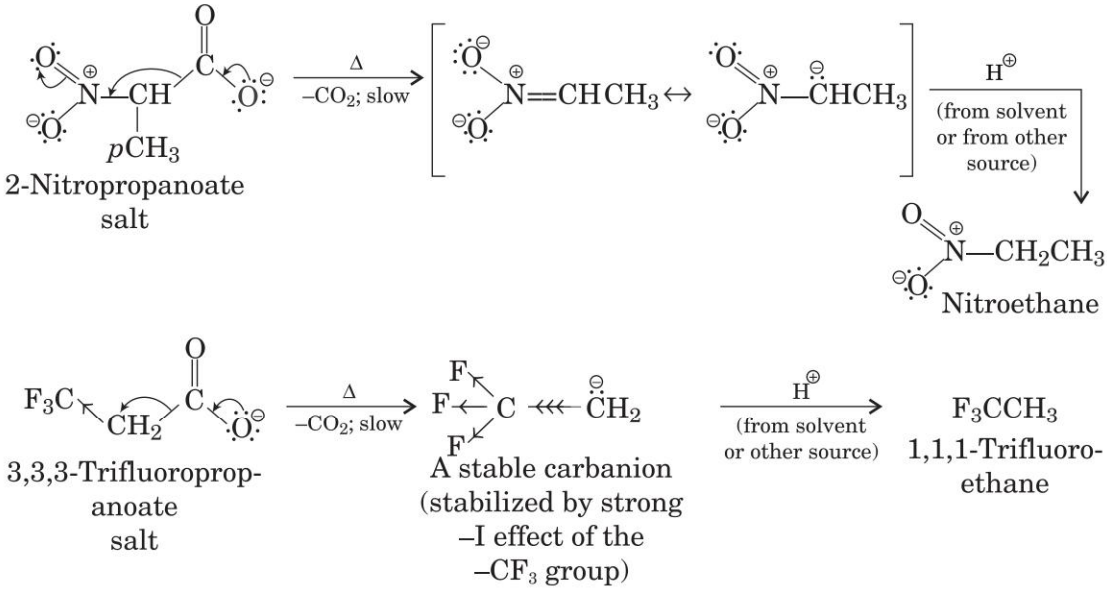
A carboxylic acid Alkane

Although, due to release of unusually stable carbon dioxide, decarboxylation of most acids is exothermic, in practice the reaction is not always very easy to carry out because the reaction is slow due to formation of an unstable carbanion.

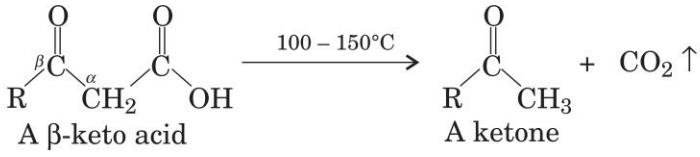
Decarboxylation of a carboxylic acid or its salt takes place via the formation of a carbanion intermediate that subsequently takes up a proton from the solvent or other source to form a C—H bond.



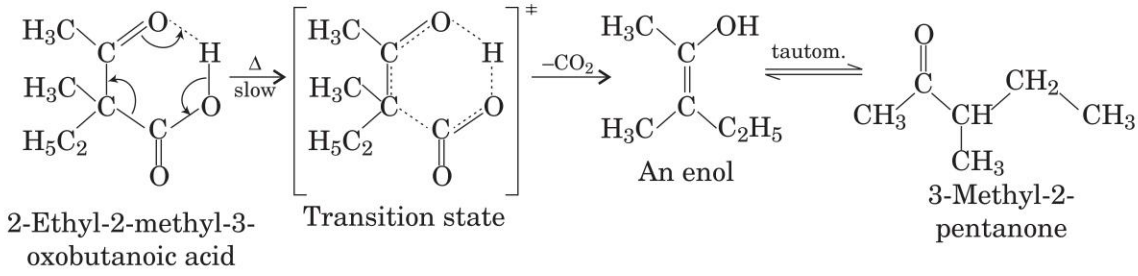
Decarboxylation is promoted by any factor that increases the stability of the resulting carbanion because the formation of a carbanion is the key step of decarboxylation. Therefore, electron-attracting groups in R that could stabilize the carbanion by delocalizing the negative charge are expected to promote decarboxylation. It thus follows that acids with electron-attracting groups, such as $-NO_2, -C \equiv N, >CO, -CX_3$, etc. attached to the α-carbon (proper position to accept the C—C bonding electrons) decarboxylate quite easily. The corresponding carboxylate anions (e.g., $CH_3COCH_2COO^{\ominus}$, $O_2NCH_2COO^{\ominus}$, $Cl_3CCH_2COO^{\ominus}$ *etc.*) thus undergo readily decarboxylation because the resulting carbanions are considerably stabilized. For example:



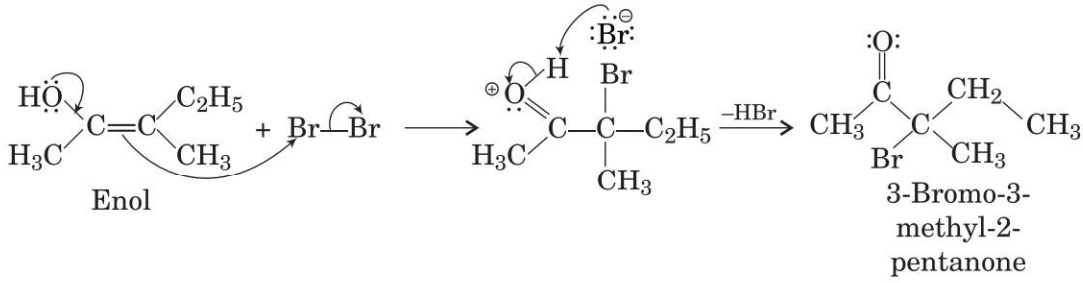
Decarboxylation of β-keto acids: Carboxylic acids that have a carbonyl group, i.e., one carbon removed from the carboxyl group, are called β-keto acids. For example, acetoacetic acid (CH_3COCH_2COOH) is a β-keto acid. They decarboxylate readily when heated to 100–150°C. Some of them even decarboxylate slowly at room temperature.



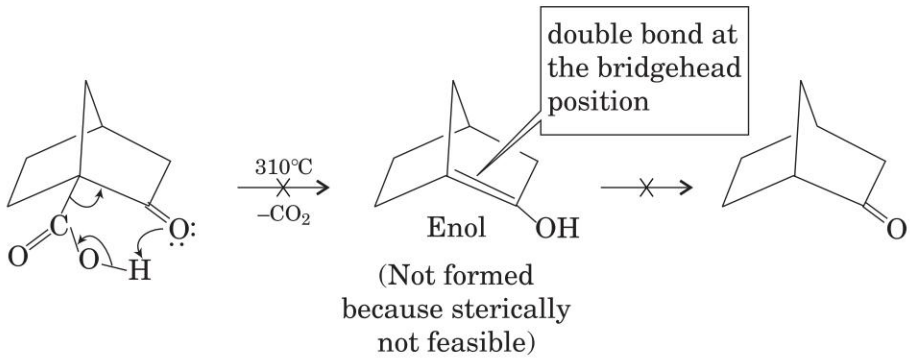
Mechanism of the reaction: The decarboxylation of a β-keto acid proceeds through a six-membered cyclic transition state and the process of decarboxylation is promoted by the incipient proton transfer to the keto group through hydrogen bonding. An intermediate enol is formed which rapidly tautomerizes to the more stable keto form. For example, the decarboxylation of 2-ethyl-2-methyl-3-oxobutanoic acid may be shown as follows:



Evidence for the mechanism: That an enol has been formed as an intermediate can be proved by a trapping experiment. When decarboxylation of the above keto acid is carried out in the presence of bromine (Br_2), 3-bromo-3-methyl-2-pentanone is obtained. Since 3-methyl-2-pentanone remains unchanged in the presence of bromine under the condition of decarboxylation as also is the starting β-keto acid, therefore, the isolation of $CH_3COCBr(CH_3)CH_2CH_3$ is a clear evidence for the intermediacy of an enol which forms in the rate-determining step.



Another piece of evidence supporting the enol mechanism is that bicyclic β-keto acids, which cannot form enols because strain prevents formation of a double bond at the bridgehead position (Bredt's rule), are stable towards decarboxylation. For example, the following β-keto acid can be distilled at 310°C without decomposition.

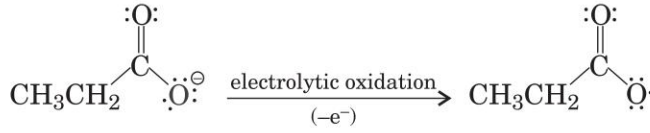


Electrochemical oxidative decarboxylation of carboxylic acid salts: The electrochemical oxidative decarboxylation of carboxylic acid salts is known as the Kolbe electrolysis reaction. For example:

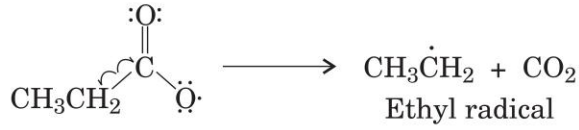
$$\underset{\text{Sodium propanoate}}{2\,CH_3CH_2COONa} \xrightarrow[\text{electrolysis}]{H_2O} \underset{\text{Butane}}{CH_3CH_2CH_2CH_3} + 2CO_2$$

Mechanism of the reaction: The reaction proceeds through the steps as follows:

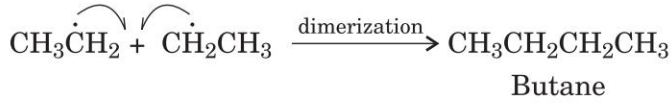
Step 1: At the anode the carboxylate ion loses an electron to become a carboxy radical.



Step 2: The carboxy radical decarboxylate to give an alkyl radical $(\dot{R})$:

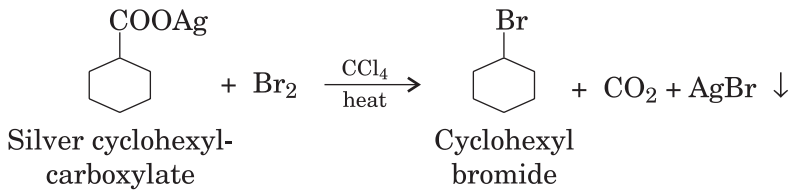


Step 3: Two free radicals then dimerizes to yield the hydrocarbon butane.



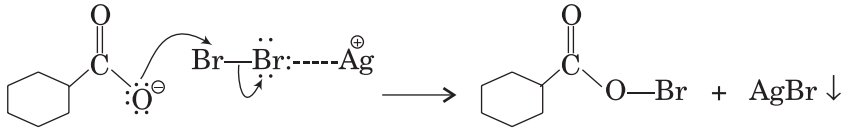
2.10.2.7 Formation of Alkyl Bromides (the Hunsdiecker Reaction)

The conversion of silver salts of carboxylic acids to one-carbon less alkyl halides by treating silver carboxylate with halogens (bromine is the most often used halogen: chlorine and iodine have also been used) in a refluxing inert solvent (e.g., CCl_4, $CHCl_3$ or ether) under anhydrous conditions is known as the *Hunsdiecker reaction*. For example:

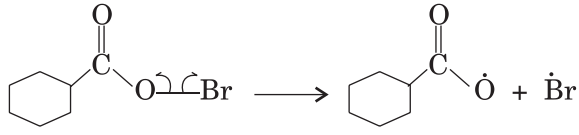


Mechanism of the reaction: The mechanism of this decarboxylative halogenation reaction involves the steps as follows:

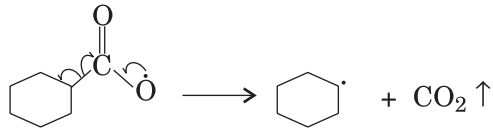
Step 1: Reaction of the silver carboxylate with bromine to form an acyl hypobromite.



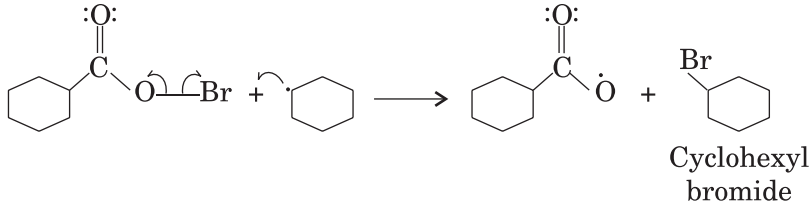
Step 2: The acyl hypobromite decomposes to give a carboxy or acyloxy radical and a bromine radical by means of homolytic bond fission,



Step 3: The carboxyl radical undergoes decarboxylation to yield an alkyl radical.



Step 4: The cyclohexyl radical abstracts a bromine atom from a second molecule of acyl hypobromite to produce cyclohexyl bromide and a carboxyl radical.

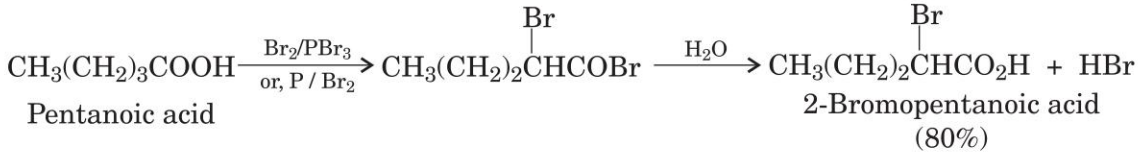


Then, the steps 3 and 4 are repeated and so on.

2.10.2.8 Halogenation of Carboxylic Acids [the Hell-Volhard-Zelinsky (HVZ) Reaction]

When carboxylic acids containing α-hydrogen are treated with bromine and phosphorus tribromide (PBr_3) or the equivalent, a mixture of phosphorus and excess bromine (Br_2)

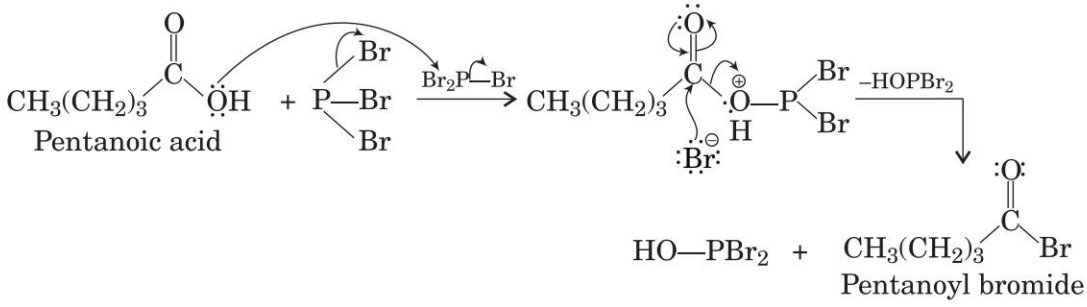
and the intermediates α-bromo acyl bromides are hydrolysed, α-bromocarboxylic acids are obtained. α-Chlorocarboxylic acids may be prepared similarly, but the reaction is less specific because of some free radical chlorinations. This reaction is called the *Hell-Volhard-Zelinsky reaction*, and is sometimes nicknamed as the *HVZ reaction*. For example



Mechanism of the reaction: The mechanism of the reaction is as follows:

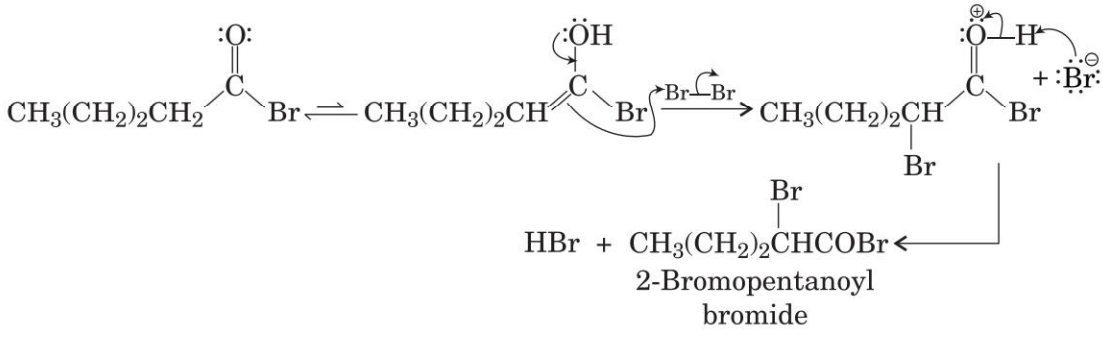
***First stage reaction*:** Formation of 2-bromopentanoyl bromide from pentanoic acid involves the following two steps:

Step 1: Pentanoic acid reacts with PBr_3 to yield pentanoyl bromide.



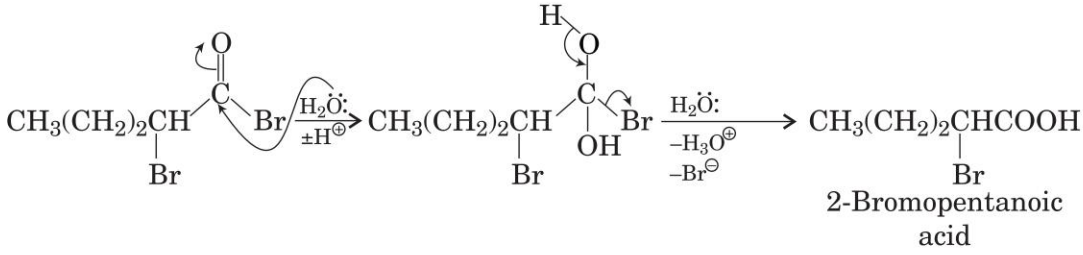
[$HOPBr_2$ can react readily with more of the starting acid. Therefore, one mole of phosphorus tribromide can convert three moles of acid to acyl bromide.]

Step 2: The resulting pentanoyl bromide undergoes enolization and the enol reacts with bromine to yield 2-bromopentanoyl bromide.



Bromination of the acyl bromide through enol formation takes place much readily due to greater acidity of the α-H atom caused by the electron-withdrawing inductive effect of both the carbonyl group and the bromine atom.

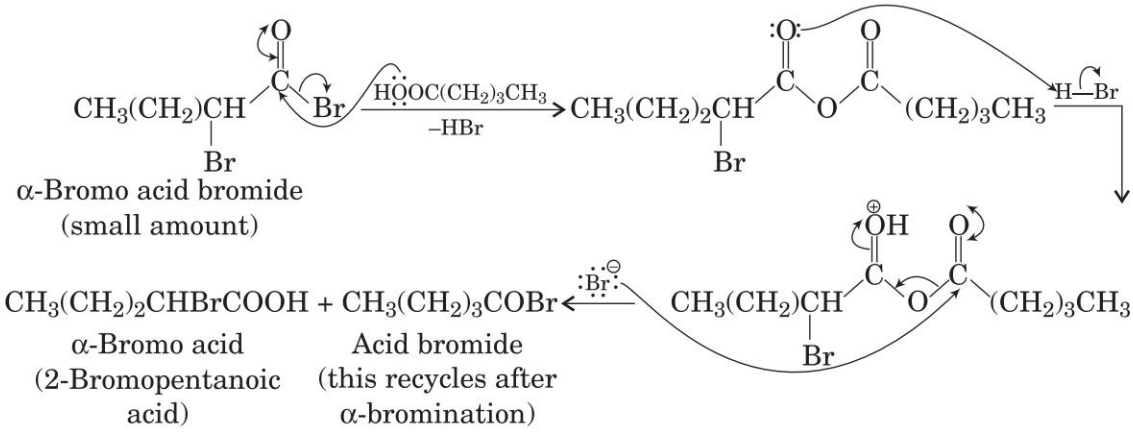
***Second stage reaction*:** Hydrolysis of the 2-bromopentanoyl bromide to yield 2-bromopentanoic acid takes place as follows:



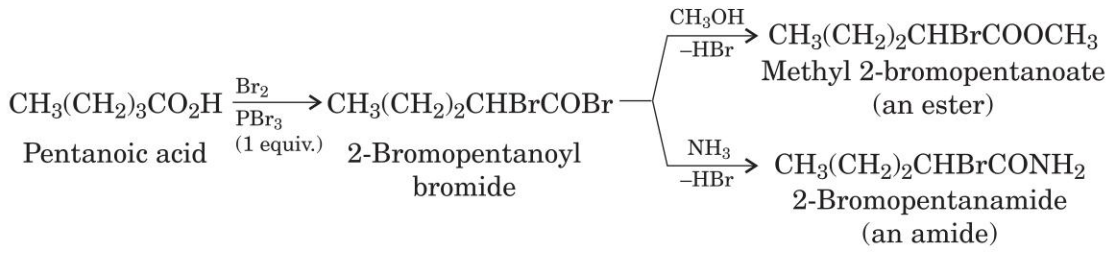
If two equivalents of reagents are used, both of the two α-H atoms of pentanoic acid ($CH_3CH_2CH_2CH_2COOH$) undergo replacement by bromine to yield 2,2-dibromopentanoic acid ($CH_3CH_2CH_2CBr_2COOH$).

Some relevant topics:

(i) **Reaction of a carboxylic acid with Br_2 in the presence of a catalytic amount of PBr_3 instead of a full equivalent:** When a catalytic amount of PBr_3 is used instead of a full equivalent, α-bromo acid is obtained instead of α-bromo acid bromide. Use of a catalytic amount of PBr_3 causes the formation of only a small amount of α-bromo acid bromide at any one time. This small amount of α-bromo acid bromide then reacts with the carboxylic acid to form an anhydride. The anhydride undergoes protonation and then cleaved by $Br^{\ominus}$ ion to yield the α-bromo acid and a new molecule of acid bromide. This acyl bromide undergoes bromination and then recycles.



(ii) **Nature of the product obtained when the carboxylic acid is treated first with Br_2/PBr_3(1 equiv.) followed by an alcohol or ammonia:** When pentanoic acid, for example, is treated with Br_2 and one equivalent of phosphorus tribromide (PBr_3), 2-bromopentanoyl bromide is obtained. This acyl bromide reacts with an alcohol, for example, methanol, to yield the ester methyl 2-bromopentanoate and with ammonia to yield the amide 2-bromopentanamide.

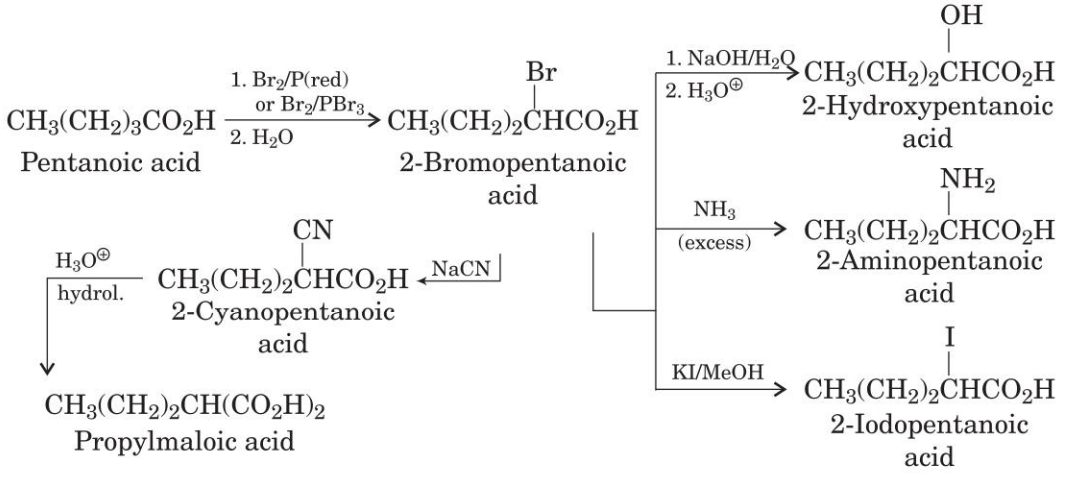


Synthetic applications of the HVZ reaction: Some important applications of the HVZ reaction may be given as follows:

(i) Carboxylic acids do not normally undergo substitution reactions at the α-carbon because the –OH group is much more acidic than the α-carbon. Since bromination or chlorination of carboxylic acids by the HVZ reaction takes place readily and exclusively at the α-position, the reaction offers a very efficient method for the synthesis of α-bromo- or α-chlorocarboxylic acids.

(ii) The presence of α-H in a carboxylic acid can be detected by this reaction because only α-H containing carboxylic acids undergo this reaction.

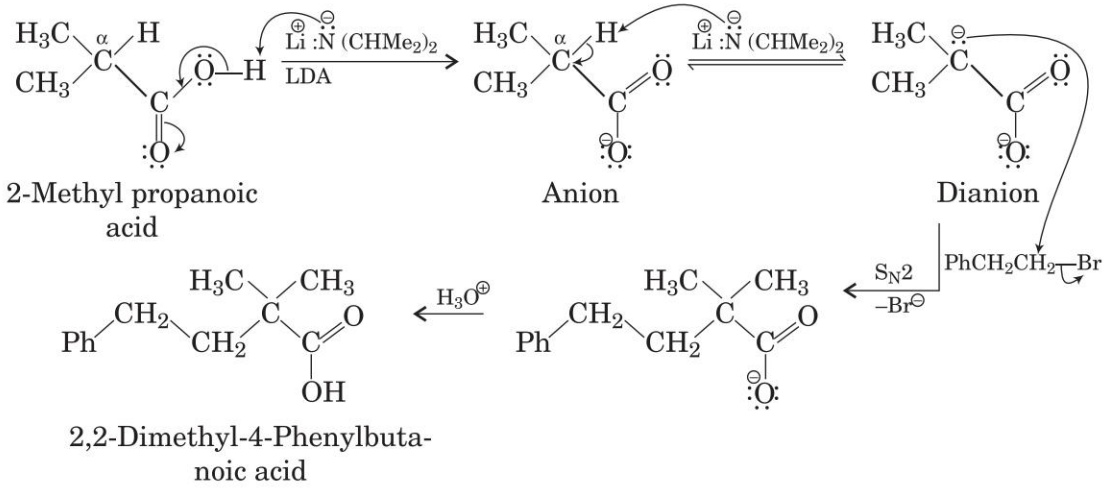
(iii) α-Halo acids are important synthetic intermediates because they are capable of reacting with a variety of nucleophiles. Thus, when α-halo acids are treated with NaOH, NH_3 KI and NaCN, α-hydroxy acids, α-amino acids, α-iodo acids and α-cyanoacids are respectively obtained. α-Cyano acids may further be converted to synthetically important compounds like malonic acid and its derivatives.



2.10.2.9 Alkylation of Carboxylic Acids

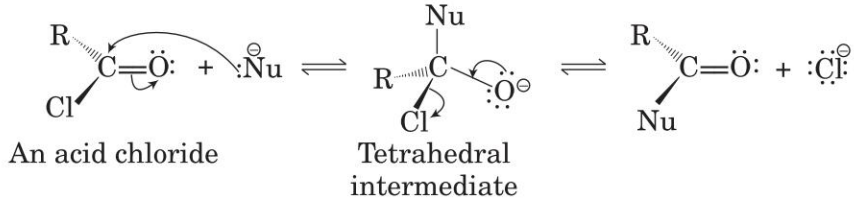
Carboxylic acids can be alkylated, but for alkylation two equivalents of strong base are necessary because this reaction proceeds through a dianion. The first equivalent of base takes up the carboxyl hydrogen to give the carboxylate salt. If the base used is a strong base but a weak nucleophile, a second hydrogen can be removed from the α position. The

typical base used is lithium diisopropylamide (LDA). The dianion can now be alkylated by treating with an alkyl halide. After alkylation, the resulting carboxylate ion can be reprotonated to obtain the neutral product. For example:

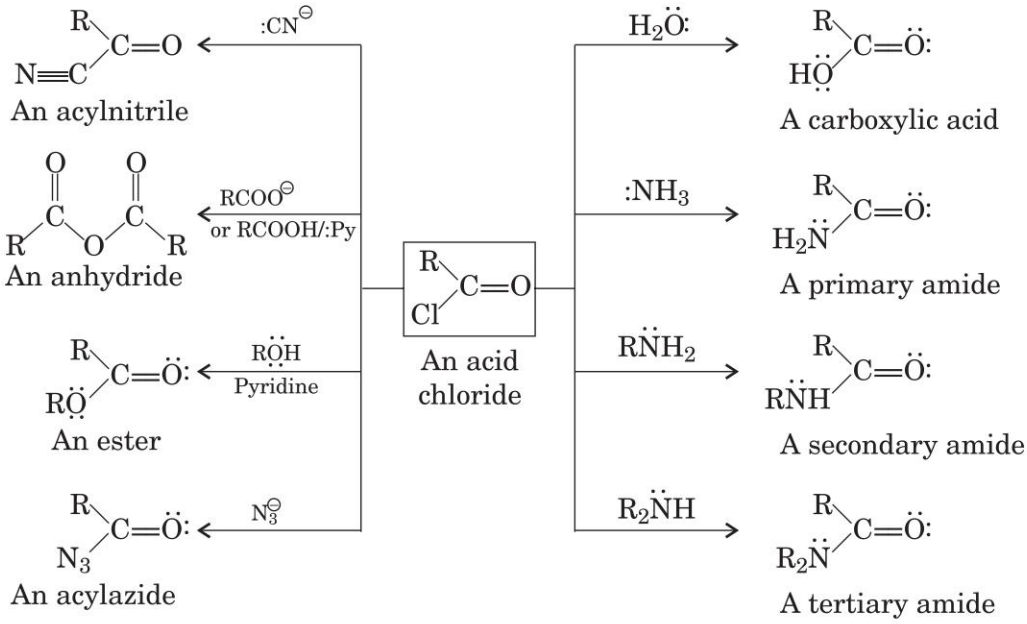


2.10.3 Reactions of Acid Chlorides

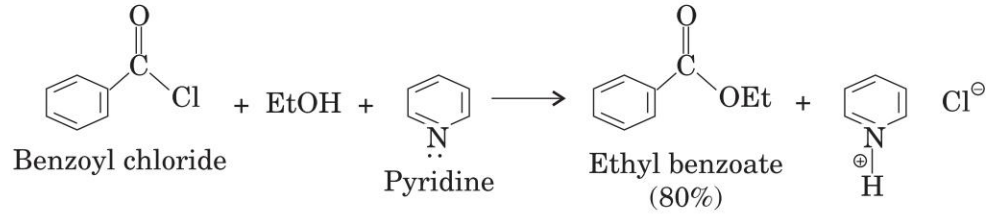
Acid chlorides are especially reactive towards nucleophiles. Their carbonyl groups, being the least stabilized by resonance, have the highest energy and are the most reactive. Therefore, an initial addition reaction with a nucleophile is relatively facile. Furthermore, the Cl atom of RCOCl is an excellent leaving group, and ready to depart once the tetrahedral intermediate has been formed. The result is a very much facile and common example of the addition-elimination mechanism.



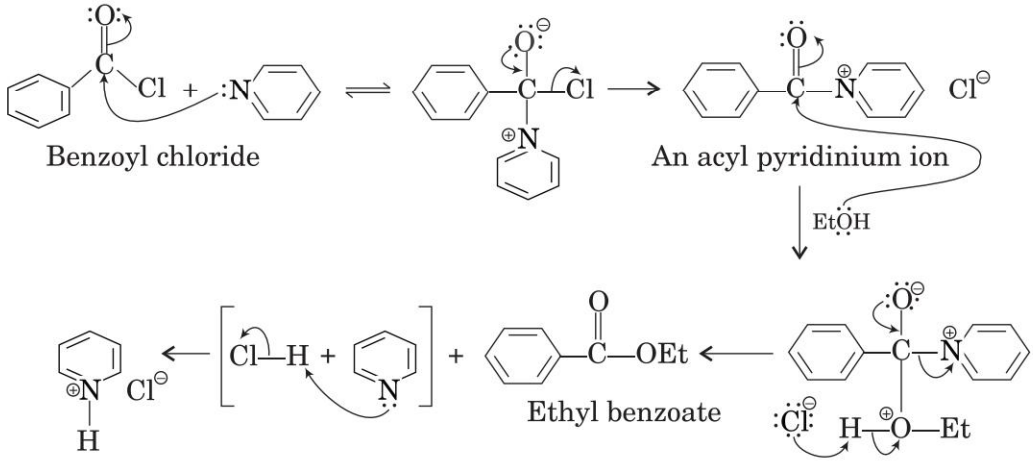
By using a number of nucleophiles a variety of compounds can be synthesized from acid chlorides. Therefore, acyl chlorides are synthetically very useful.



The reaction of acyl chlorides with alcohols is one of the best methods to synthesize an ester. For example:



The mechanism of the reaction may be sketched as follows:



2.10.4 Reactions of Esters

Esters are less reactive than acid chlorides and anhydrides in addition reactions, but more reactive than amides.

2.10.4.1 Hydrolysis of Esters

Esters can be converted into their parent carboxylic acid under either basic or acidic aqueous conditions. The process is called *ester hydrolysis*. This topic has already been discussed in **article 2.10.2.4.**

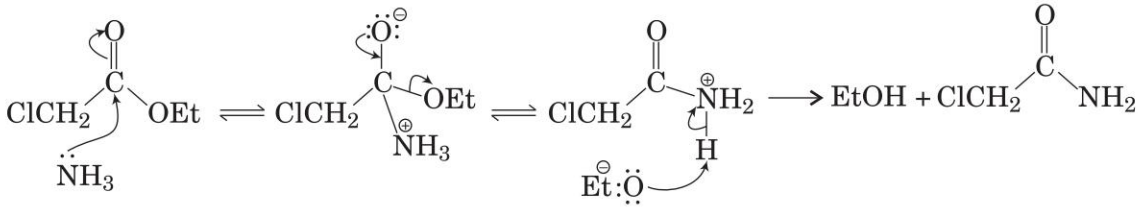
2.10.4.2 Reaction with Ammonia or Amines to Form Amides

Esters undergo nucleophilic addition-elimination at their acyl carbon atoms when they are allowed to react with ammonia (called *ammonolysis*) or with primary and secondary amines. For example:

$$ClCH_2CO_2Et + NH_3(aq) \xrightarrow{0–5°C} ClCH_2CONH_2 + EtOH$$

Ethyl chloroacetate — Chloroacetamide (87%)

Mechanism:



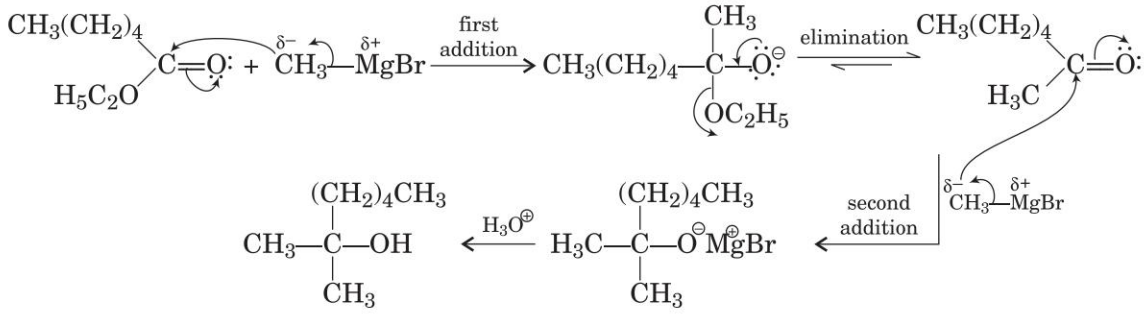
2.10.4.3 Reaction with Grignard Reagents

The reaction of a Grignard reagent with an ester is another example of the addition-elimination process. Since they are strong nucleophiles, they react further with the initial products ketones. The ketones are not as well stabilized by resonance as are the esters and so are more reactive in the addition reaction. The reaction is a general synthesis of tertiary alcohols. For example:

$$CH_3(CH_2)_4CO_2C_2H_5 \xrightarrow[2.\ H_3C^{\oplus}]{1.\ CH_3MgBr\ (2\ equiv.)} CH_3(CH_2)_4C(OH)(CH_3)_2$$

Ethyl hexanoate — 2-Methyl-2-heptanol

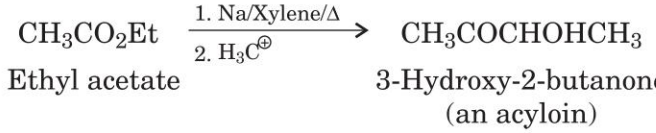
Mechanism of the reaction:



2.10.4.4 Acyloin Condensation

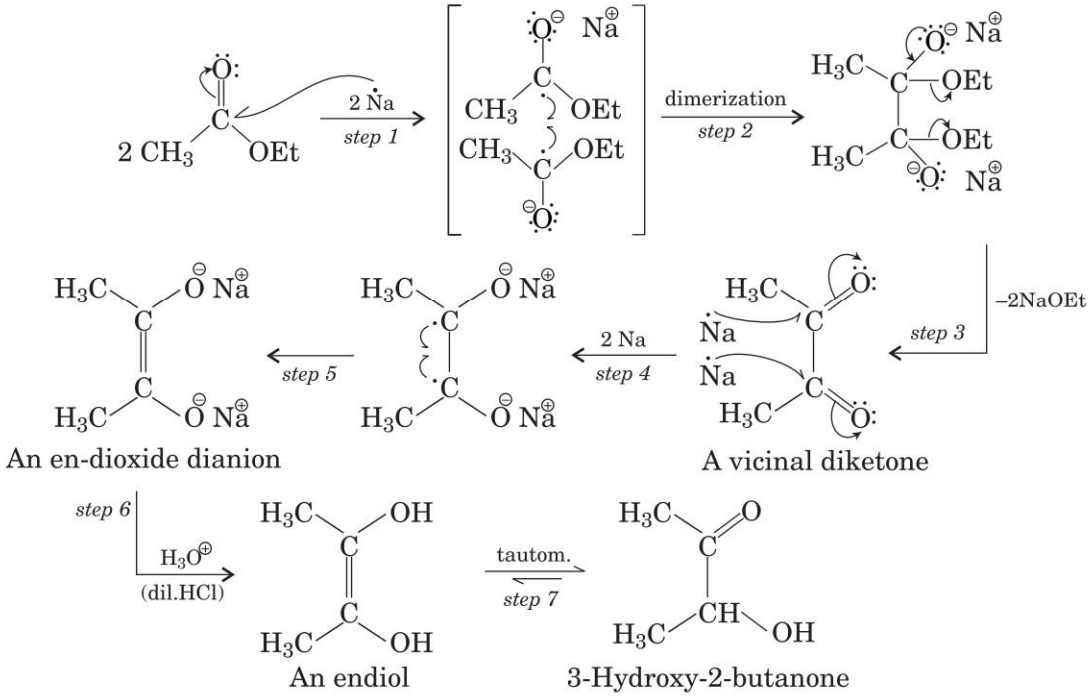
When aliphatic esters are refluxed with metallic sodium in aprotic solvents like ether, benzene, toluene, xylene, etc. and subsequently with acid or alcohol, a bimolecular reductive coupling occurs to form α-hydroxy ketones or acyloins.

The reaction is called the *acyloin condensation*. For example:



Ethyl acetate — 3-Hydroxy-2-butanone (an acyloin)

Mechanism of the reaction: The reaction involving a free-radical mechanistic pathway may be sketched as follows:



An en-dioxide dianion — A vicinal diketone — An endiol — 3-Hydroxy-2-butanone

Step 1: A radical anion is formed when the carbonyl carbon of ester undergoes nucleophilic attack by the electron of metallic sodium.

Step 2: The two radical anions couple (reductive coupling) to form a dianion.

Step 3: A 1,2-diketone is formed by the loss of both the alkoxy groups. The process is facile because of steric strain in the dianion and the good leaving ability of the alkoxy groups.

Step 4: A dianion diradical is formed by the addition of two electrons from two Na atoms to both the carbonyl carbons.

Step 5: The two odd electrons combine to form an en-dioxide dianion.

Step 6: On acidification the dianion forms an endiol.

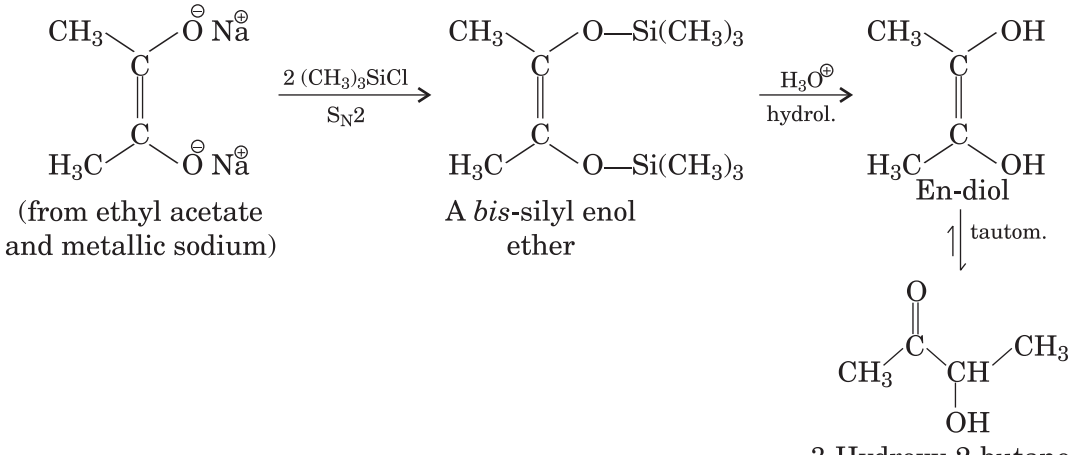
Step 7: The endiol undergoes ready tautomerization to yield the more stable keto-form, i.e., the α-hydroxy ketone or acyloin.

Some relevant topics:

(i) **A competiting side reaction during closing of five- six- and seven-membered rings:** Ethoxide ion is generated in the medium during acyloin condensation and so, the base-promoted ester condensation (the Dieckmann condensation) competes with the acyloin condensation during closing of five-, six- or seven-membered rings. This side reaction can be avoided by carrying out the reaction in the presence of chlorotrimethylsilane, Me_3SiCl. This reagent traps the ethoxide ion ($EtO^{\ominus}$) as it is formed.

$$Me_3SiCl + EtO^{\ominus} \longrightarrow Me_3Si-OEt + :\ddot{\underset{\cdot\cdot}{Cl}}\cdot^{\ominus}$$

Also, this reagent reacts with the dianion of the endiol and thereby protects the oxygen-sensitive en-dial as the *bis*-silyl enol ether. The silyl enol ether is then hydrolyzed by dilute acid to yield the acyloin. This technique is usually followed to improve the yield of acyloin. For example:



(from ethyl acetate and metallic sodium)

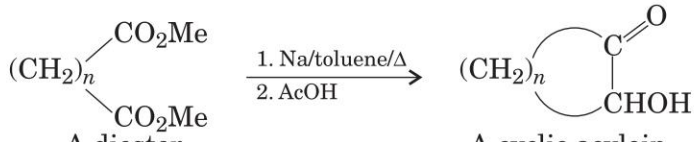
A *bis*-silyl enol ether

3-Hydroxy-2-butanone

(ii) **Application of high dilution technique for the synthesis of large rings:** According to the high dilution principle, when a very dilute solution of a substrate is used, the distance between different molecules becomes much greater than the distance between the two functional groups of the same molecule. As a consequence, a cyclic compound is formed by the reaction between two close functional groups of the same molecule instead of a linear condensation product by intermolecular reaction. The acyloin condensation used for the synthesis of large rings must be performed under conditions of high dilution to avoid intermolecular reactions.

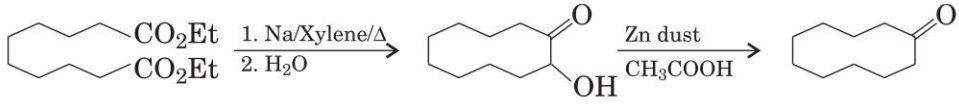
Synthetic applications: Some important applications of the acyloin condensation are as follows:

(i) The acyloin condensation is an important procedure for the synthesis of 6–20 membered cyclic acyloins from diesters.



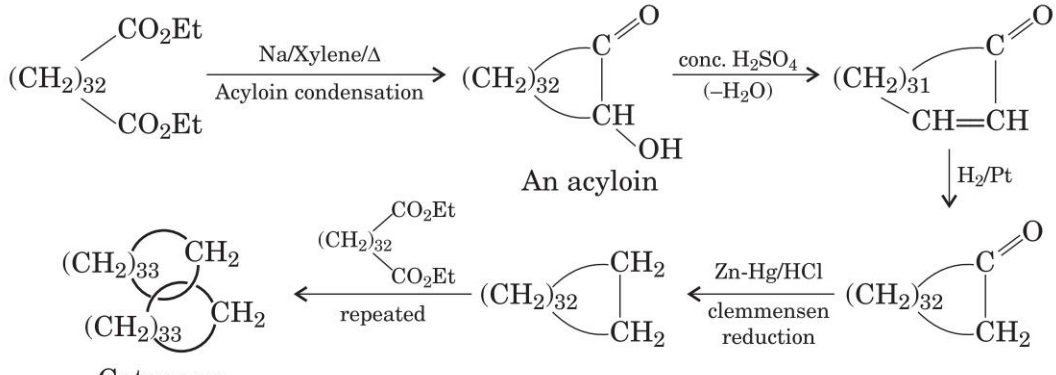
A diester where n = 4 to 18 — A cyclic acyloin

(ii) The acyloin condensation is used to prepare macrocyclic ketones. The following example illustrates a useful transformation of an acyloin to a ketone.



(iii) A good application of acyloin condensation is the synthesis of anopterine, a diterpene alkaloid from *Anopterus* species. The compound has high level of antitumor activities.

(iv) From long-chain α,ω-diesters, catena compounds (although the yield is low) can be prepared by subjecting the diester to acyloin condensation. Catena compounds are actually large ring compounds where two rings are not joined by any C–C bond formation but held together like links in a chain. For example:



An acyloin

Catenane
(a catena compound)

2.10.5 Reactions of Amides

Amides ($RCONH_2$, RCONHR or $RCONR_2$) are the least reactive of the acyl compounds. They do not react with halide ions, alcohols or water because, in each case, the incoming nucleophile is a weaker base than the leaving group of the amide. (i.e., $\overset{\ominus}{N}H_2$, $\overset{\ominus}{N}HR$ or $\overset{\ominus}{N}R_2$). However, amides react with water, i.e., undergo hydrolysis in the presence of acid or base and these nucleophilic addition-eliminations require relatively harsh conditions.

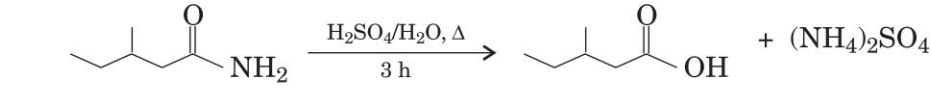
2.10.5.1 Acid-Catalyzed Hydrolysis of Amides

Acidic hydrolysis of amides takes place more slowly than the corresponding hydrolysis of an ester. Thus, acidic hydrolysis of amides requires for any conditions a prolonged heating in strong aqueous acid.

$$RCONH_2 + H_3O^{\oplus} \xrightarrow[\text{heat}]{H_2O} RCO_2H + \overset{\oplus}{N}H_4$$

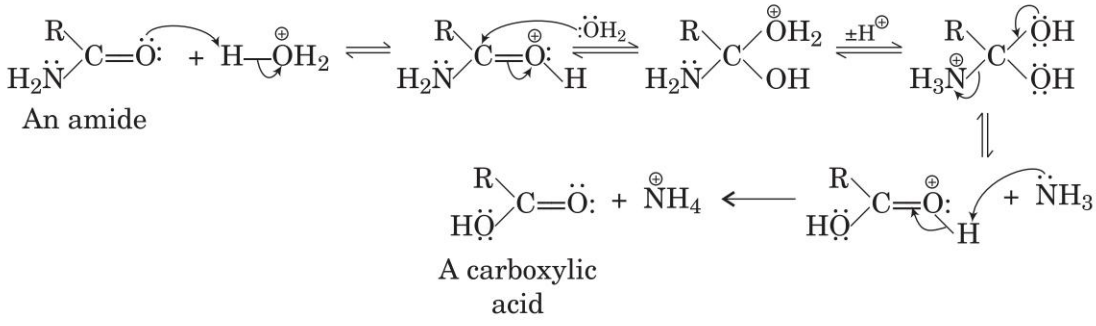
An amide — A carboxylic acid

Example:



3-Methylpentanamide — 3-Methylpentanoic acid

Mechanism of the reaction: The mechanism for the acid-catalyzed hydrolysis of an amide is similar to that given for the acidic hydrolysis of an ester (**article 2.4.2.4**). Water acts as a nucleophile and attacks the protonated amide to give a tetrahedral intermediate. Then a proton is lost at one oxygen and gained at the nitrogen to form another tetrahedral intermediate. Now, of the two possible leaving groups in this tetrahedral intermediate ($OH^{\ominus}$ and NH_3), NH_3 is the weaker base, so it is the one eliminated to give a protonated carboxylic acid. Transfer of a proton to ammonia leads to the corresponding carboxylic acid and ammonium ion. The last step is irreversible because a strong acid and a strong base reacts to produce a weak acid and a weak base.



2.10.5.2 Base-Promoted Hydrolysis of Amides

Amides undergo hydrolysis when heated strongly under basic conditions.

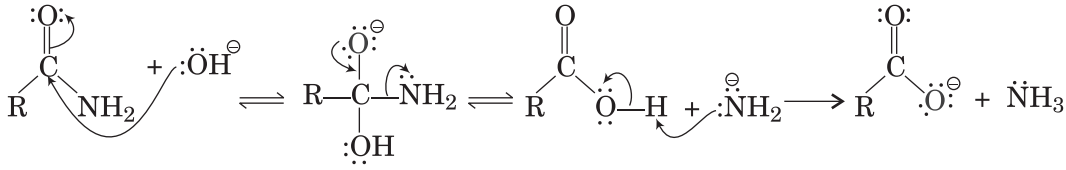
$$\underset{\text{An amide}}{RCONH_2} + OH^{\ominus} \xrightarrow[\text{heat}]{H_2O} \underset{\text{A carboxylate ion}}{RCOO^{\ominus}} + \ddot{N}H_3$$

Acidic aqueous work-up then produces the acid.

Example:

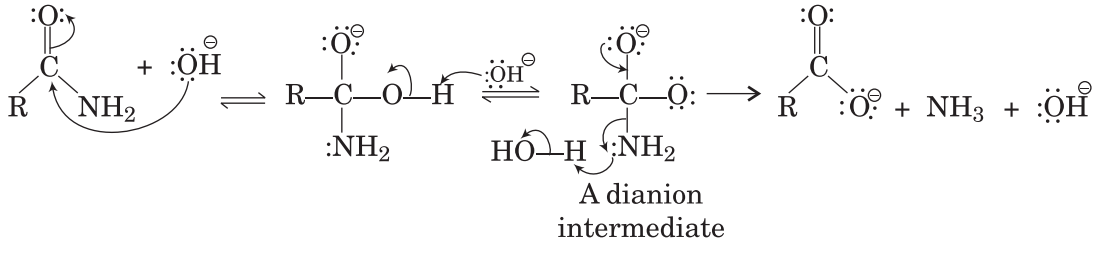
$$\underset{\text{Benzamide}}{C_6H_5CONH_2} \xrightarrow[\text{heat}]{NaOH/H_2O} \underset{\text{Sodium benzoate}}{C_6H_5COO^{\ominus}Na^{\oplus}} + \ddot{N}H_3 \uparrow$$

Mechanism of the reaction: The mechanism of the reaction involves the steps as follows:



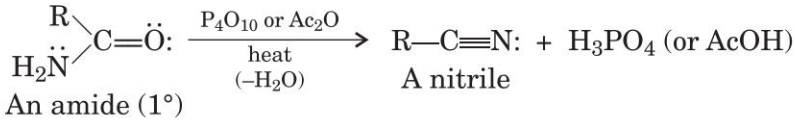
The hydroxide ion attacks the carbonyl carbon to form a tetrahedral intermediate rapidly. In the next step, $\overset{\ominus}{N}H_2$ is eliminated (occasionally) and when this happens, the carboxylic acid that is formed immediately loses a proton. Since this step is irreversible (the negatively charged carboxylate ion is unreactive and a strong acid and a strong base produce a weak acid and weak base), it disturbs the equilibrium and drives the reaction towards products.

The reaction may also take place through the formation of a dianion intermediate:

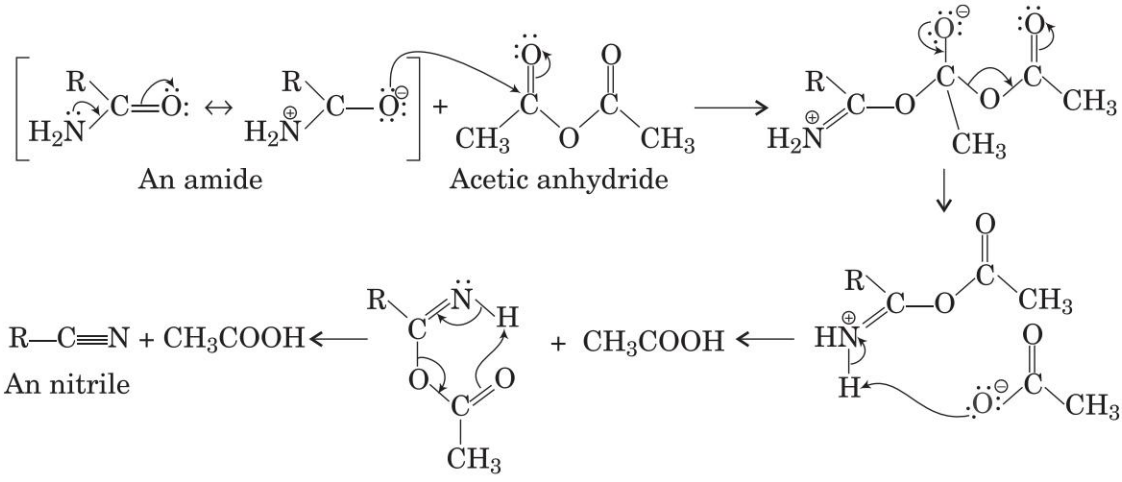


2.10.5.5 Dehydration of Amides

When primary amides ($RCONH_2$) are boiled with acetic anhydride ((Ac_2O) or heated with phosphorus pentoxide, nitriles are obtained.



Mechanism of the reaction: An amide reacts with acetic anhydride to yield a nitrile as follows:



In fact, a molecule of acetic anhydride abstracts a molecule of water from the amide and undergoes hydrolysis to give two molecules of acetic acid (CH_3COOH).

2.10.6 Reactions of Carboxylic Acid Anhydrides

The leaving group of an anhydride (RCO–O–COR) is a carboxylate ion (its conjugate acid has a pK_a of ~ 5). This indicates that an anhydride is less reactive than an acyl chloride but more reactive than an ester or a carboxylic acid. An acid anhydride reacts with an alcohol to form an ester and a carboxylic acid, with water to form two equivalents of a carboxylic acid, and with an amine to form an amide and a crboxylate ion. In the last reaction, two equivalent of amine should be used so that sufficient amine must be present to react both the carbonyl compound and the proton produced in the reaction. For example:

$$CH_3COOCOCH_3 + CH_3CH_2OH \longrightarrow CH_3COOCH_2CH_3 + CH_3CO_2H$$

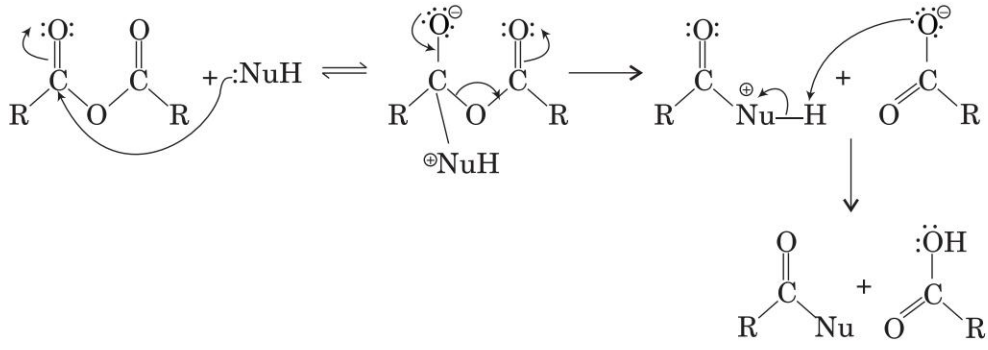
Acetic anhydride Ethanol Ethyl acetate Acetic acid

$$CH_3COOCOCH_3 + H_2O \longrightarrow CH_3CO_2H$$

$$CH_3COOCOCH_3 + 2\,CH_3NH_2 \longrightarrow CH_3CONHCH_3 + CH_3COO + \overset{\oplus}{N}H_3CH_3$$

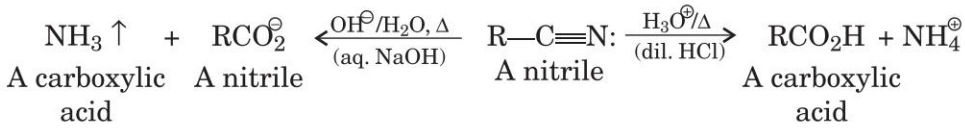
Acetic anhydride Methylamine *N*-Methyletha-namide Acetate salt

General mechanism: The nucleophilic addition-elimination of anhydrides may be sketched as follows:

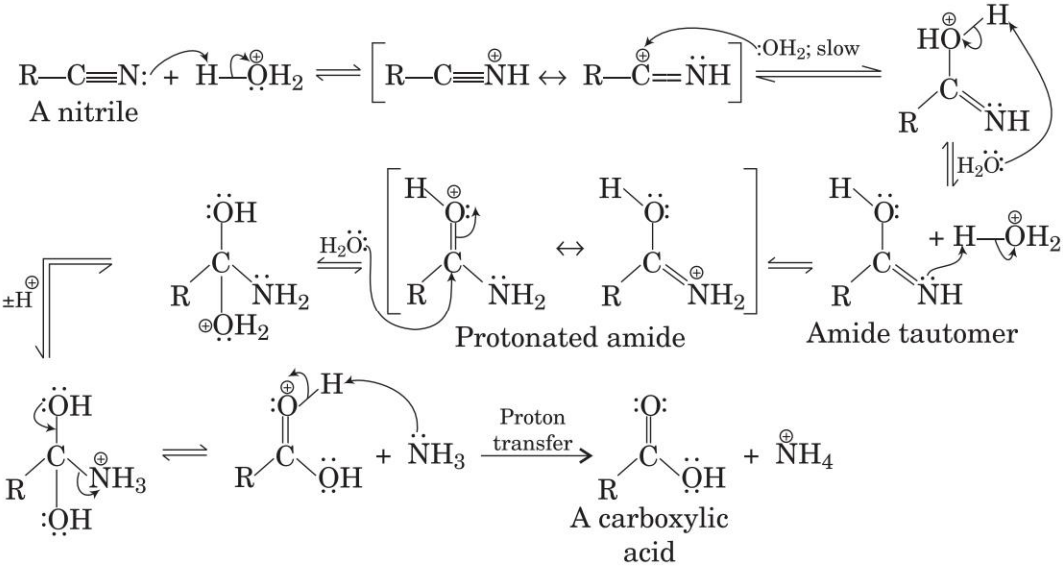


2.10.7 Reactions of Nitriles

Nitriles are considered to be carboxylic acid derivatives because like all the other carboxylic acid derivatives, they can be hydrolyzed to carboxylic acids.



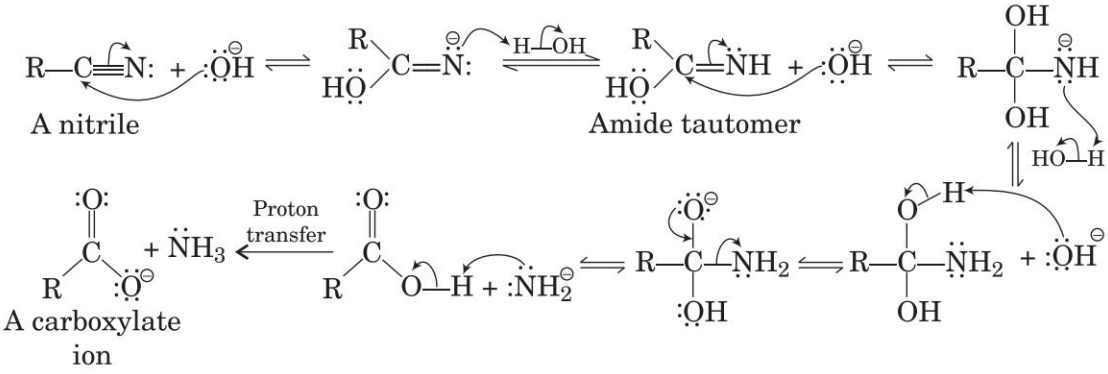
Mechanism of the acidic hydrolysis of a nitrle:



In the first step of the acidic hydrolysis of a nitrile, the nitrogen atom undergoes protonation. Protonation makes the carbon more electrophilic and more susceptible to nucleophilic attack by the weak nucleophilce H_2O. The loss of a proton from the oxygen atom then

forms a tautomer of amide. The gain of a proton at the nitrogen atom gives a protonated amide. From this point, all the steps are similar to those given for the acidic hydrolysis of an amide.

Mechanism of the basic hydrolysis of a nitrile:



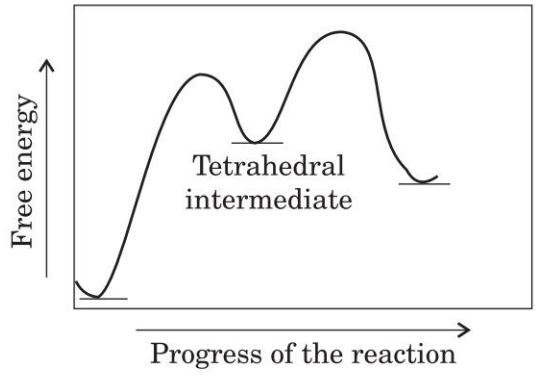
In the first step of basic hydrolysis, a hydroxide ion attacks the nitrile carbon atom. The resulting anion on protonation produces the amide tautomer. Further attack by $OH^{\ominus}$ ion leads to hydrolysis in a manner similar to that for the basic hydrolysis of an amide **(article 2.10.5.2)**.

SOLVED PROBLEMS

1. **Draw the reaction coordinate diagrams for nucleophilic acyl substitution in which: (a) the nucleophile is a weaker base than the leaving group, (b) the nucleophile is a stronger base than the leaving group, and (c) the nucleophile and the leaving group have similar basicities. Predict the fate of the reaction in each of these cases.**

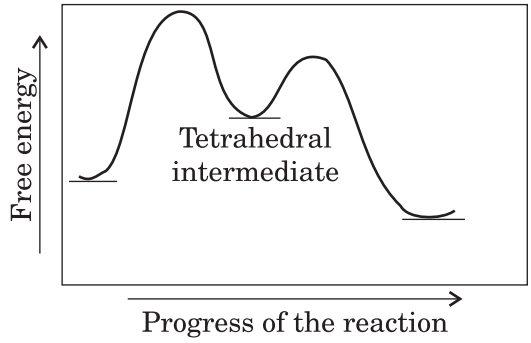
Solution

(a)



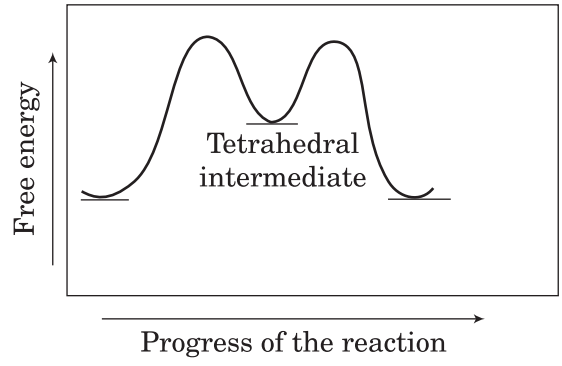
If the incoming nucleophile is a weaker base than the leaving group, the easier pathway is for the tetrahedral intermediate to expel the newly added group and regenerate the reactants.

(b)



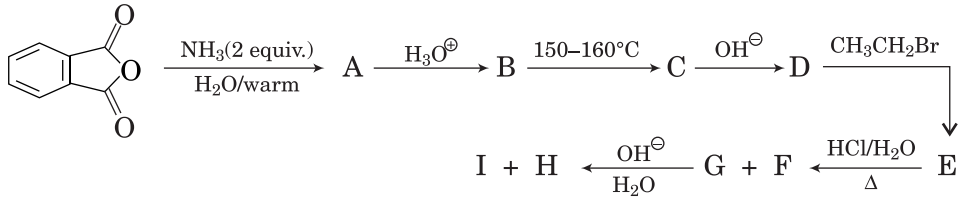
If the incoming nucleophile is a stronger base than the leaving group, the easier pathway is for the tetrahedral intermediate to expel the leaving group and form a substitution product.

(c)

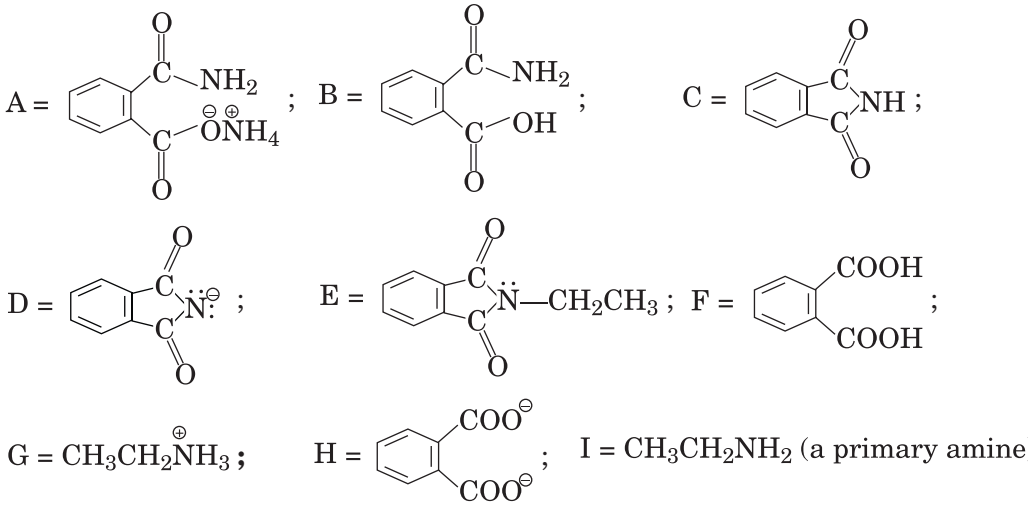


If the incoming nucleophile and the leaving group have similar basicities, the tetrahedral intermediate can expel either group with equal case. Consequently, a mixture of reactants and substitution product will result.

2. Provide the missing compounds, A–I, in the following synthesis of a primary amine:

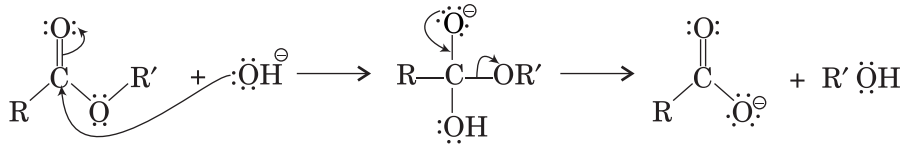


Solution

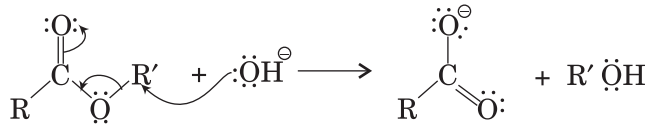


3. There are three possible mechanistic course for the hydroxide-ion-promoted hydrolysis of esters:

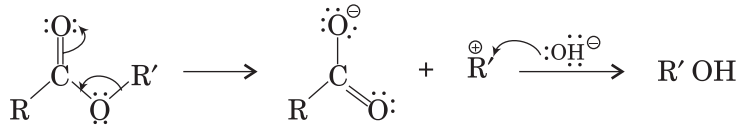
(a) A nucleophilic acyl substitution (addition-elimination) mechanism:



(b) An S_N2 mechanism:

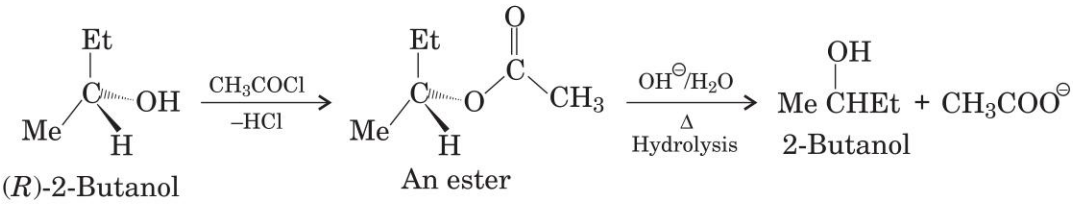


(c) An S_N1 mechanism:



Devise an experiment that would distinguish among these three mechanistic courses.

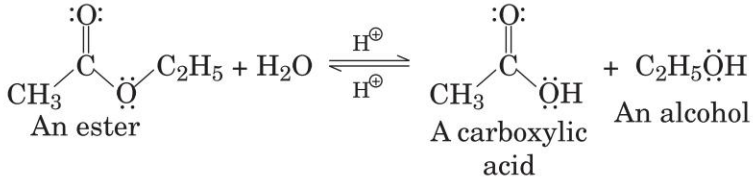
Solution A chiral alcohol of known specific rotation is first converted into an ester using a method that does not break any bond to the chirality centre. The ester is then hydrolyzed and the specific rotation of the alcohol isolated is determined. For example:



If the hydrolysis is a nucleophilic acyl substitution (addition-elimination) reaction, the product alcohol will have the same specific rotation as the reactant alcohol and this is because no bonds to the chirality are broken. If it is an S_N2 reaction, the product alcohol will be (*S*)-2-butanol having the exactly opposite specific rotation and this because the mechanism requires backside attack by the nucleophile $OH^{\ominus}$ at the chirality centre. If it is an S_N1 reaction, the product alcohol will have no specific rotation because the mechanism requires the formation of a planar trigonal carbocation which undergoes nucleophilic attack from the two enantiotopic faces equally likely to form the two enantiomers in equal amounts causing racemization.

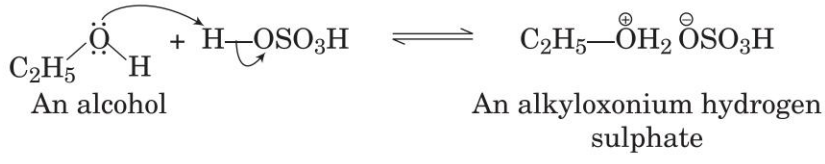
4. **The mechanisms of acid-catalyzed hydrolysis and esterfication ($A_{AC}2$ mechanism) are the reverse of each other. Which result will be obtained depends on the conditions we choose. Comment on the conditions required for hydrolysis of an ester and for the esterification of a carboxylic acid by $A_{AC}2$ mechanism.**

Solution



For the hydrolysis of an ester, a large excess of water is to be used, i.e., the ester is to be refluxed with dilute aqueous HCl or dilute aqueous H_2SO_4 so as to shift the equilibrium (according to the law of mass action) from left-hand side to right-hand side.

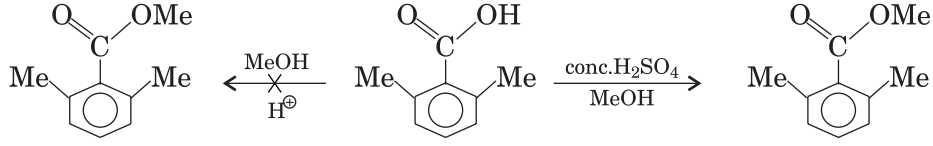
For the esterification of a carboxylic acid, and excess of alcohol with a small amount of a strong acid catalyst (conc. H_2SO_4) is to be used and if possible, the water eliminated from the acid and alcohol is to be removed as it is formed. It to be noted that the amount of the acid catalyst must not be large because in that case acid convers much of alcohol to the corresponding oxonium salt and makes the alcohol inactive as a nucleophile.



5. The presence of bulky substituents in either the alcohol group or the acid group slows down both esterification and hydrolysis by the $A_{AC}2$ mechanism. Account for these observations.

Solution Both hydrolysis and esterification in the presence of acid involve the rate-determining formation of a tetrahedral intermediate from a trigonal substrate with consequent increase in crowding in the transition state. The presence of bulky substituents near the site of reaction, whether in the alcohol or in the acid, makes the transition state leading to the tetrahedral intermediate highly crowded and thermodynamically less stable. As a consequence, the reactions (hydrolysis and esterification) become very slow.

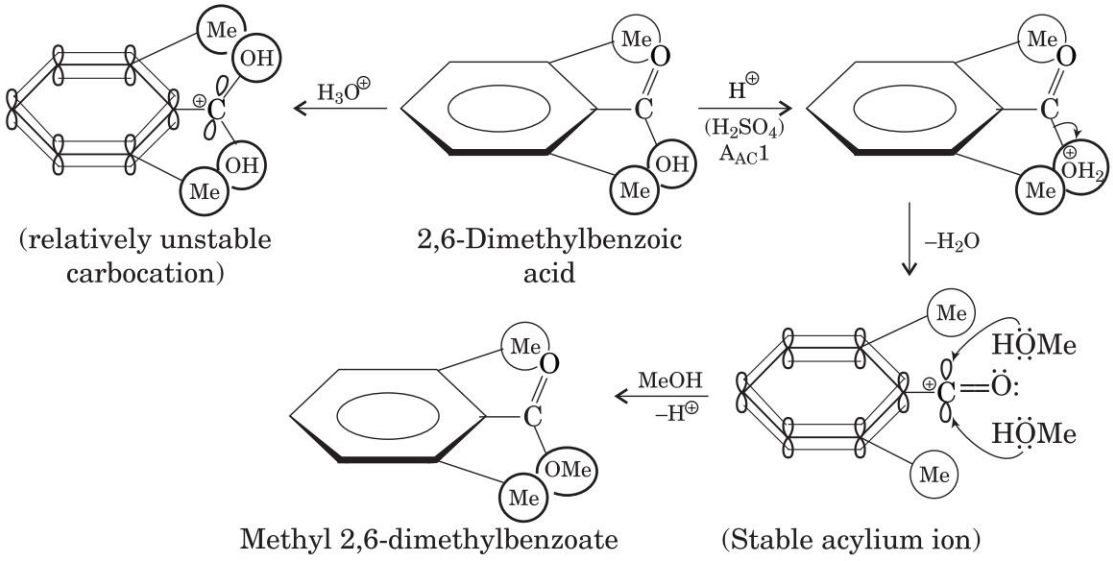
6. 2, 6-Dimethyl benzoic does not undergo esterification under ordinary acid-catalysis conditions ($A_{AC}2$ mechanism), whereas in concentrated sulphuric acid it undergoes esterifcation quantitatively. Explain these observations.



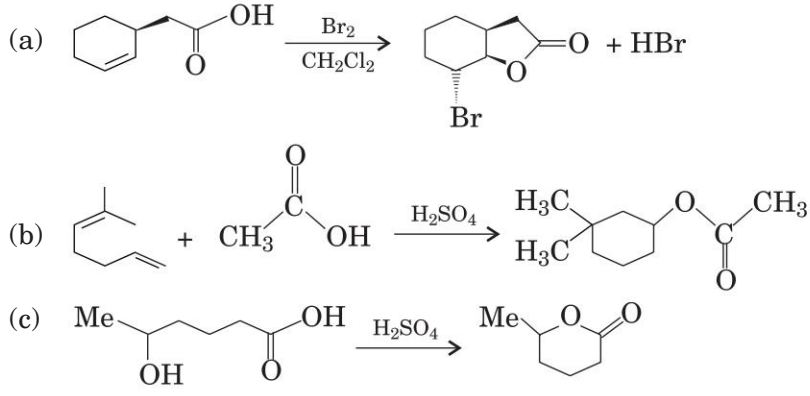
Methyl 2,6-dimethylbenzoate | 2,6-Dimethyl-benzoic acid | Methyl 2,6-dimethyl-benzoate

Solution Under normal acid-catalysis conditions the carbonyl oxygen of 2,6-dimethylbenzoic acid undergoes protonation as usual. The bulky *ortho*-Me groups force the planar protonated carbonyl group $\left(-C^{\oplus}(OH)(OH)\right)$ out of the plane of the benzene ring and as a consequence, the *p*-orbital on the carbonyl carbon is prevented from being parallel to the *p*-orbital on the adjacent ring carbon and thus overlapping is prevented. Because of this steric inhibition of delocalization of the positive charge, the protonated carbonyl group becomes unstable. Now, the nucleophilc $MeOH$ has to attack the positive carbonyl carbon from a direction at right angles to the plane in which the protonated carbonyl group is lying. However, the approach of the nucleophile from the desired directions is inhibited because these two directions are blocked by the two relatively bulky *ortho* methyl groups. It is for this reason, esterification does not take place under normal acid-catalysis conditions.

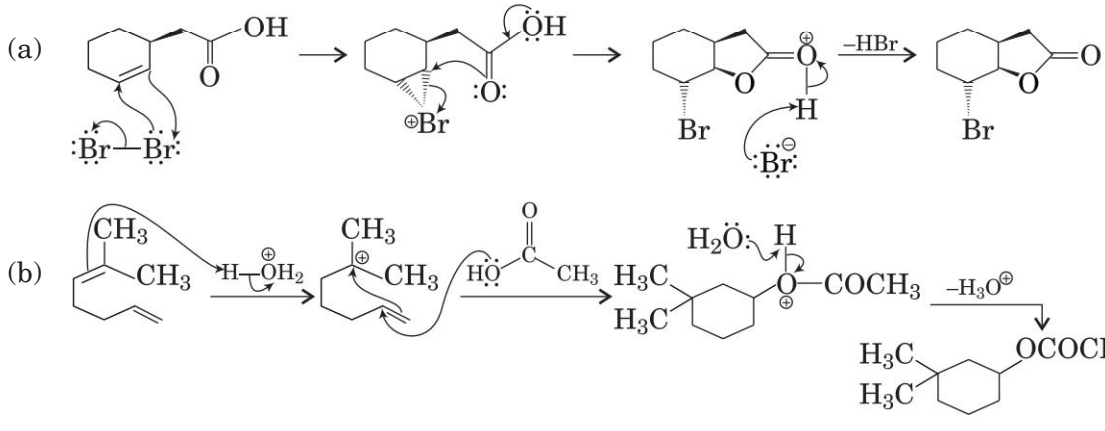
In the presence of concentrated H_2SO_4, the hydroxyl oxygen undergoes protonation (which is not normal) and then loses of water to form an acylium ion. The *p*-orbital on the positive carbon is no longer prevented from being parallel with the *p*–orbital of the ring carbon and so the ion is stabilized by delocalization of this positive charge over the π orbital system of the ring. Again, due to the linear shape of the acylium ion, the approach of the nucleophile $MeOH$ from the directions at right-angles to the plane of the molecule is no longer prevented and so, this ion undergoes nucleophilic attack by MeOH from that directions to yield a methyl ester after loss of proton.

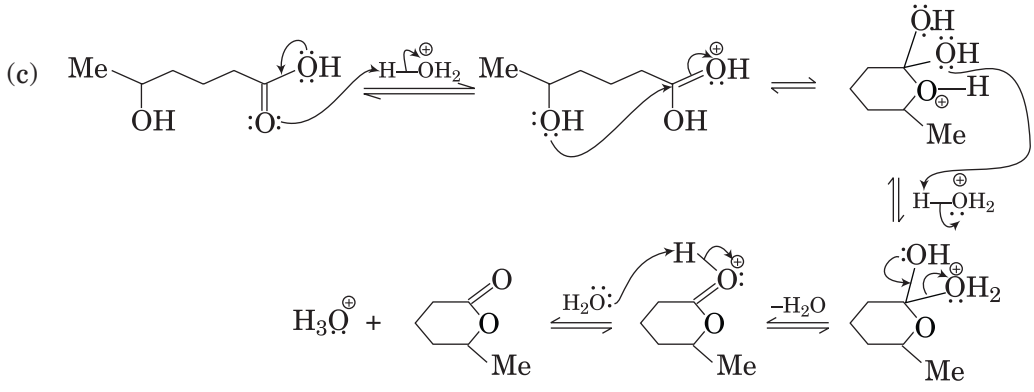


7. Propose a reasonable mechanism for each of the following reactions:



Solution





10. Explain the following observation

(a) When a solution of trianisylacetic acid [(p-$CH_3OC_6H_4)_3CCOOH$] in conc. H_2SO_4 is powered into methanol (MeOH) the ether (p-$CH_3OC_6H_4)_3$ COMe is obtained.

(b) The two 1,3-cyclobutanedicarboxylic acids (*cis*- and *trans*) have be assigned configuration on the basic of the fact that one can be converted into an anhydride and the other cannot. However, the method cannot be used to assign configurations to the 1,2-cyclohexandicarboxylic acids.

(c) Ethyl fluoroacetate (FCH_2CO_2Et) undergoes alkaline hydrolysis ($B_{AC}2$) at a much faster rate than ethyl acetate (CH_3CO_2Et).

(d) Methyl 2-methylpropanoate (Me_2CHCO_2Me) undergoes alkaline hydrolysis ($B_{AC}2$) at a much slower rate than methyl acetate ($MeCO_2Me$).

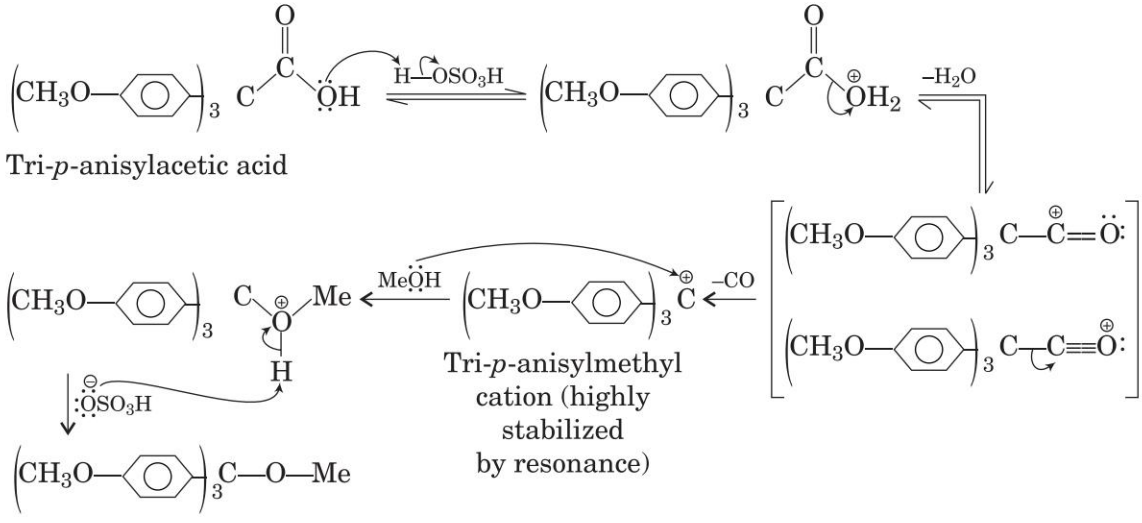
(e) Electron-withdrawing substituents in the *meta*– and *para*– positions enhance the rate of $B_{AC}2$ hydrolysis of substituted methyl benzoates, while the effect is negligible for $A_{AC}2$ reactions.

(f) The rate of hydrolysis of phenyl propanoate (CH_3CH_2OOPh) increases many–fold at neutral pH by the presence of a –COO group in the *ortho*-position.

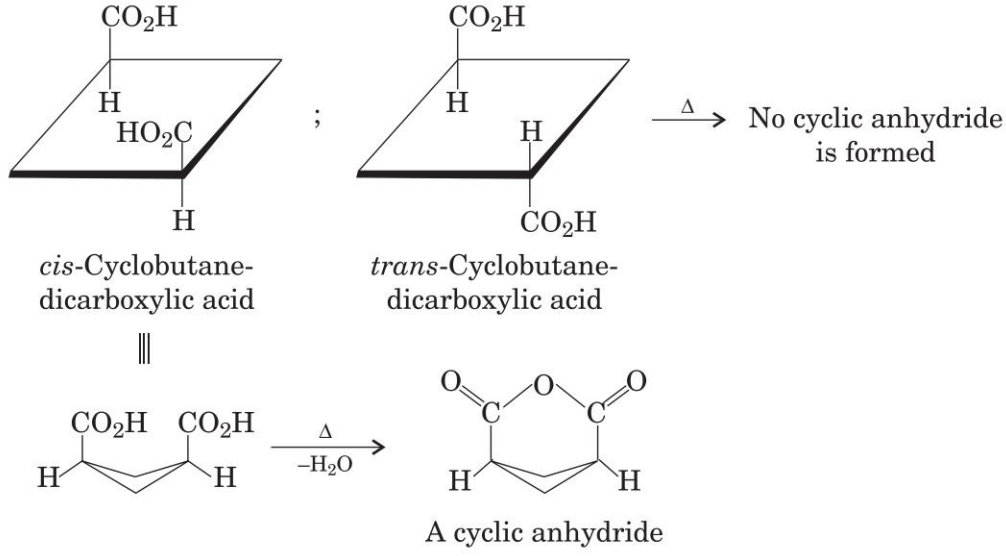
Solution

(a) The sterically hindered carboxylic acid (o-$H_3COC_6H_4)_3CCOH$ undergoes esterification by the $A_{AC}1$ mechanism in the presence of concentrated H_2SO_4. The reaction involves abnormal protonation on the –OH oxygen atom of the –COOH group and formation of an acylium ion by the loss of a molecule of water. Instead of reacting with a molecule of alcohol, this acylium ion eliminates a molecule of carbon monoxide to form trianisylmethyl cation that then reacts with methanol to form (p-$H_3COC_6H_4)_3C—O—CH_3$ after proton loses. The driving force for the elimination of CO from the acylium ion is the formation of very stable carbocation

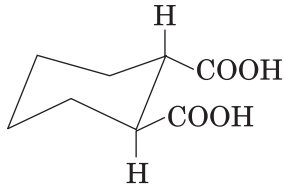
$(p-H_3COC_6H_4)_3\overset{\oplus}{C}$ (highly stabilized by resonance) with consequent relif of steric strain (sp^3 hybridized carbon in acylium ion to sp^2 hybridize carbon in $(p-H_3COC_6H_4)_3\overset{\oplus}{C}$).



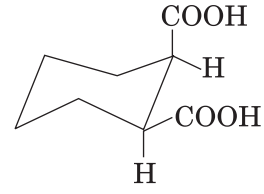
(b) Because of the proximity of the two –COOH groups, the *cis*- isomer of 1,3-cyclobtanedicarboxylic acid is capable of forming a cyclic anhydride, while the *trans* acid does not.



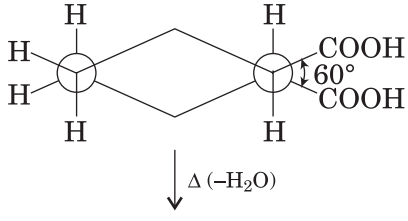
This method can not be used to assign configurations to the 1,2- cyclohexanedicarboxylic acid. This is because both *cis* and *trans* acids, in which the two –COOH groups are same distance apart, are capable of forming cyclic anhydride.

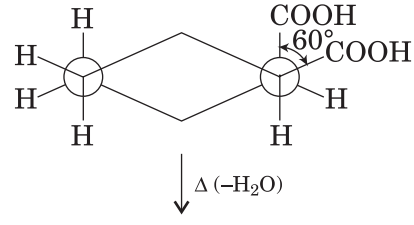


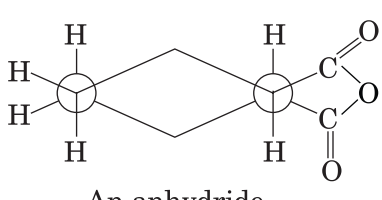
trans-1,2-Cyclohexanedicarboxylic acid



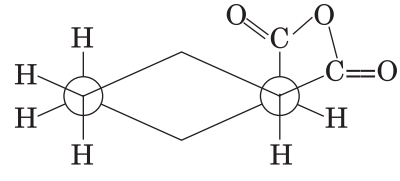
cis-1,2-Cyclohexanedicarboxylic acid







An anhydride



An anhydride

(c) Electron-attracting groups in either the acyl or alkyl part of the ester make the carbonyl carbon more positively polarized and thereby make the attack of the nucleophile $OH^{\ominus}$ on it easier. This causes an increase in reaction rate because it is the rate-determining step of the reaction. In ethyl fluoroacetate (FCH_2CO_2Et), the most electronegative F atom exerts its strong electron-withdrawing inductive effect (–I) and consequently, the carbonyl carbon becomes relatively more positive than that of ethyl acetate (CH_3CO_2Et). For this reason, ethyl fluoroacetate undergoes hydrolysis at a much faster rate than ethyl acetate.

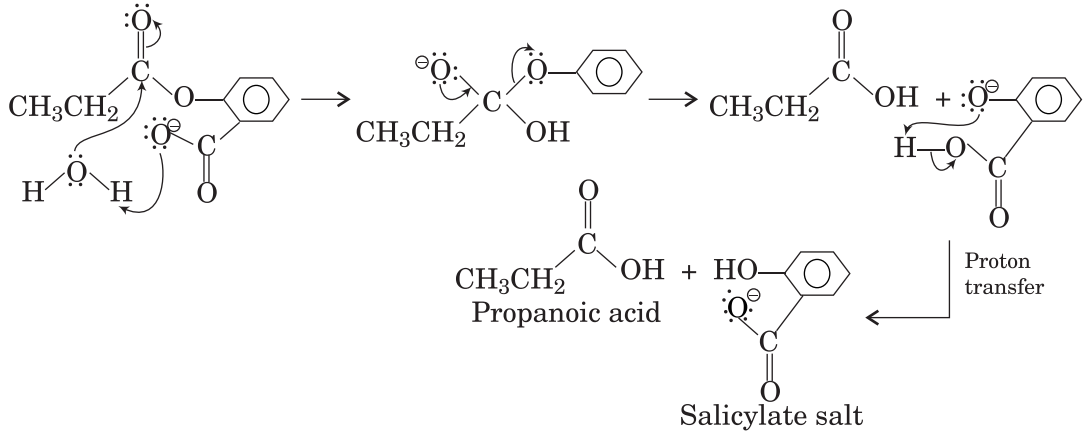
(d) The alkaline hydrolysis of this ester ($B_{AC}2$ mechanism) proceeds through the rate-determining formation of a tetrahedral intermediate. Since formation of this intermediate involves change in hybridization of the trigonal carbon atom from sp^2 to sp^3, steric crowding in the transition state leading to that intermediate increases and consequently, the reaction rate decreases as the size of *R* increases. Since the isopropyl group, (Me_2CH–) is much larger, i.e., more space-filling than the methyl group (—CH_3), methyl 2-methylpropanoate undergoes alkaline hydrolysis at a

much slower rate than methyl acetate. The stronger +I effect of the Me_2CH- group also plays a role in decreasing the reaction rate by reducing the positive character of the carbonyl carbon.

(e) In $B_{AC}2$ hydrolysis of substituted methyl benzoates, the electron-withdrawing substituents at *meta*- and *para*- positions increase the positive character of the carbonyl carbon and as a result, the rate of the reaction involving rate-determining attack by $OH^{\ominus}$ on the carbonyl carbon increases. However, in $A_{AC}2$ mechanism, the carbonyl oxygen becomes protonated initially and consequently, the carbonyl carbon becomes sufficiently positive. The electron-withdrawing groups at the *meta*- or *para*- position cannot increase the positive character of the carbonyl carbon much greater than it already posseses. For this reason, the electron-withdrawing effect of these substituents is negligible for the $A_{AC}2$ reaction.

(f) The *ortho*- caroxylate group (an interamolecular general base catalyst) increases the nucleophilicity of water molecule by taking up a proton and thereby increases the rate of formation of the tetrahedral intermediate through a low-energy transition state, Thus for this reason, the rate of hydrolysis of phenyl propanoate increases by the presence of a carboxylate group in the *ortho*–position.

The reaction proceeds as follows:



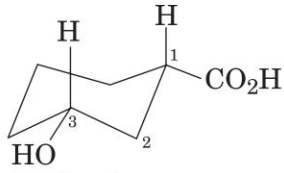
9. Explain the following observations:

(a) *Cis*-3-Hydroxycyclohexane carboxylic acid readily forms lactone on heating, whereas the trans-isomer does not.

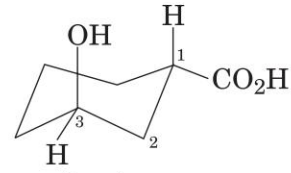
(b) *Cis*-4-Hydroxycyclohexane carboxylic acid lactonizes on heating but the *trans*-isomer does not.

Solution

(a) The more stable conformation of *cis*-3-hydroxycyclohexane carboxylic acid is that in which the two substituents occupy equatorial position and the more stable conformation of its *trans*-isomer is that in which the bulkier –COOH group is equatorial and the –OH group is axial

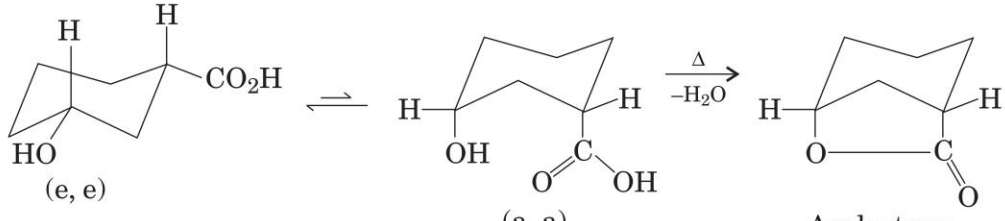


(e, e)
cis-3-Hydroxycyclohexane-carboxylic acid



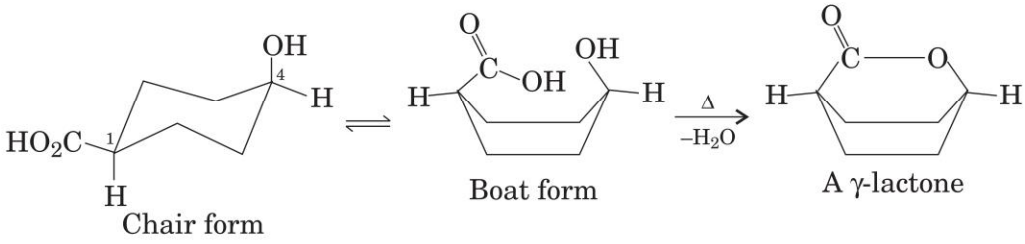
(e, a)
trans-3-Hydroxycyclohexane-carboxylic acid

When the *cis*-isomer is heated, it undergoes readily lactonization through the ring inversion process. In the flipped conformation, both the –COOH and –OH groups assume *syn*- diaxial positions and come closer to each other (within the reacting distance) to yield a lactone. The reaction is favourable from the standpoint of entropy, even though the inverted conformation is sterically unfavourable (due to 1,3– diaxial interactions). The *trans*-isomer does not undergo lactonization because the two groups do not come closer to each other in any conformation.



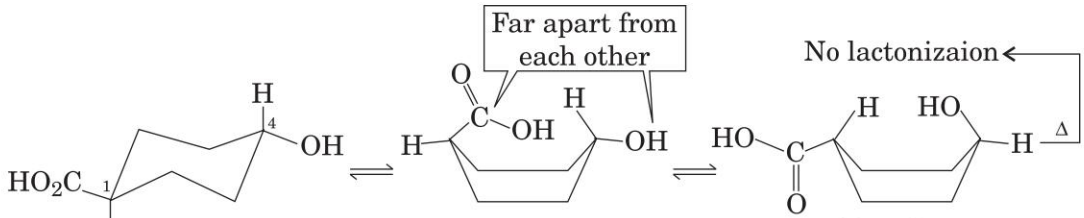
cis-3-Hydroxycyclohexane-carboxylic acid

(b) *Cis*-4-Hydroxycyclohexane carboxylic acid lactonizes readily on heating and this is because in its boat conformation, the –COOH and –OH groups assume flagpole positions and come within the reacting distance.



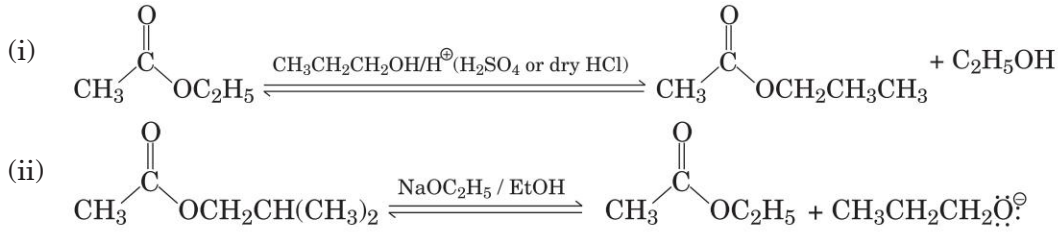
cis-4-Hydroxycyclohexanecarboxylic acid

In the boat conformation of the *trans*-isomer, on the other hand, only one of the two groups can assume the flagpole position and as a consequence, they do not come within the reacting distance. For this reason, the compound does not undergo lactonization on heating.



trans-4-Hydroxycyclohexanecarboxylic acid

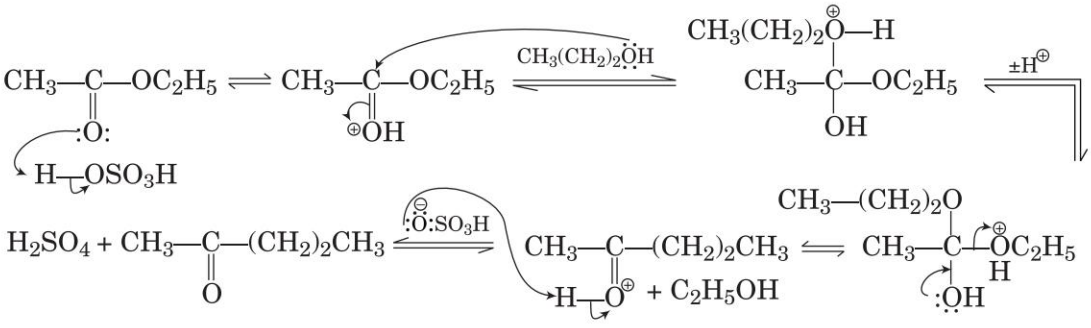
10. Explain why the following reactions are called *trans*-esterification:



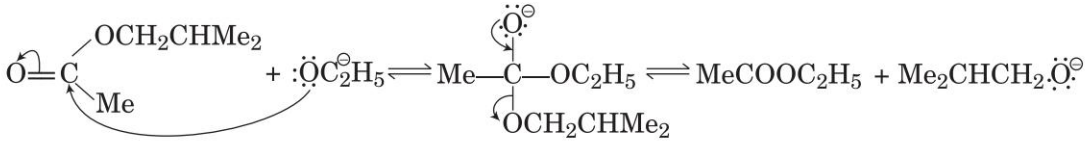
Give mechanisms of these reactions.

Solution In these reactions, an ester is inter converted into another ester in the presence of acid or base as catalyst. So, these reactions are called transesterfication or alcoholysis of esters.

Mechanism of acid-catalysed transesterification involving acyl-oxygen bond cleavage may be sketched as follows:



Mechanism of base-catalysed transesterification involving acyl-oxygen bond cleavage may be outlined as follows:



11. Propose a mechanism that accounts for each of the following reactions:

(a) $RCOO^{\ominus} + BrCN \xrightarrow{200-300^{\circ}C} RCN + CO_2$

(b) $R-NC \xrightarrow{H_3O^{\oplus}} HCOOH + R\overset{\oplus}{N}H_3$

(c) $RC\equiv N + R'COOH \xrightarrow{300^{\circ}C} RCOOH + R'C\equiv N$

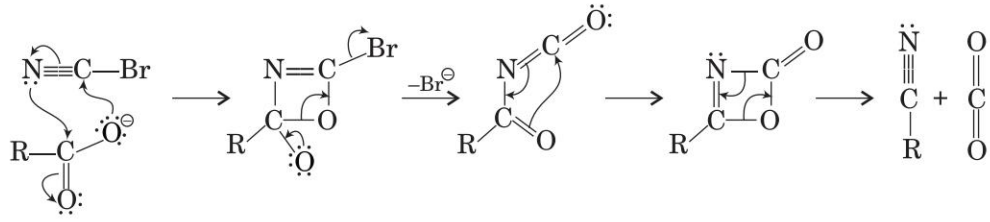
(d) $Et_2NH \xrightarrow[\Delta]{HCHO/HCOOH} Et_2NCH_3$

(e) $Et_2-C\equiv N + H_2O_2 \xrightarrow{aq.NaOH} EtCONH_2 + O_2$

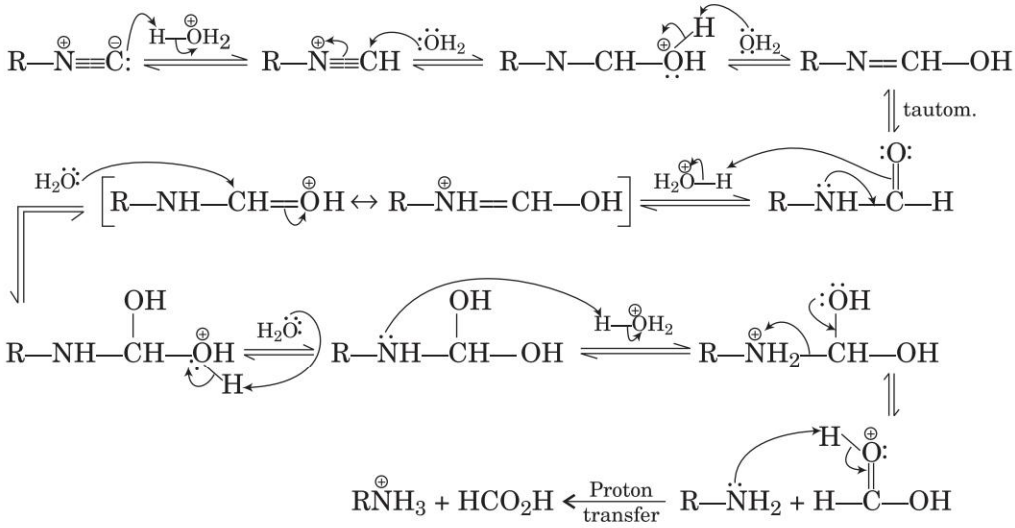
Explain why alkyl isocyanides (RNC) do not undergo alkaline hydrolysis.

Solution

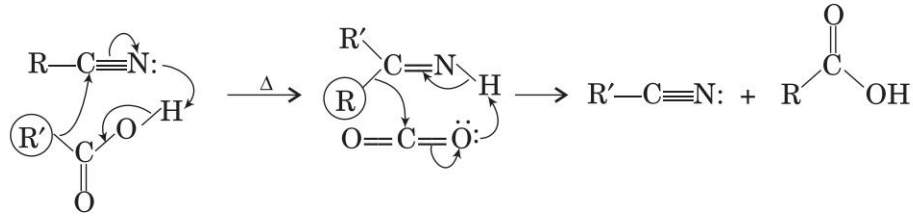
(a)



(b) Hydrolysis of an isocyanide in the presence of acid:



(c)



(d) $Et_2\ddot{N}H + H_2C{=}\ddot{O}: \xrightarrow{\pm H^{\oplus}} Et_2\ddot{N}{-}CH_2{-}\ddot{O}H \xrightarrow{H^{\oplus}} Et_2\overset{\oplus}{N}H{-}CH_2{-}\overset{\oplus}{O}H \xrightarrow{-H_2O} Et_2\overset{\oplus}{N}{=}CH_2$

$Et_2N{-}CH_3 \xleftarrow[-CO_2]{-H^{\oplus}}$ (H—O—C(=O)—H)

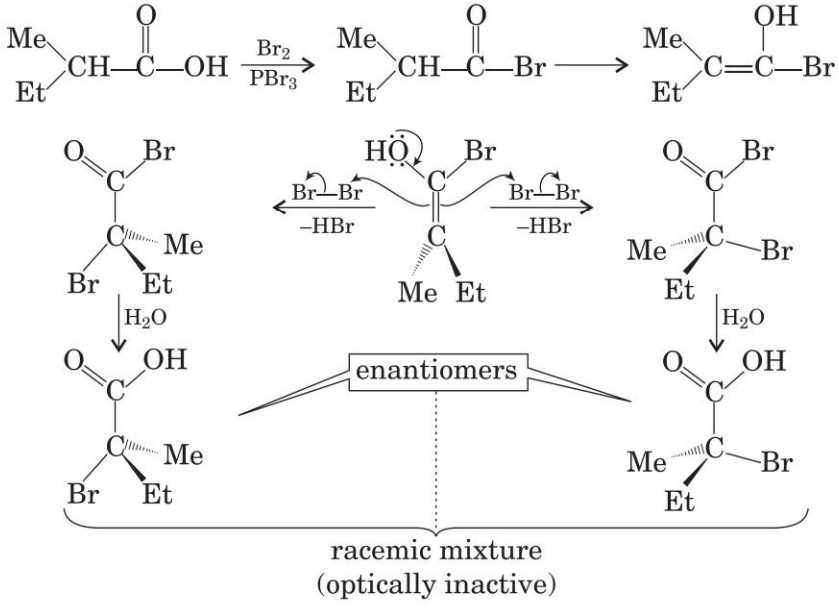
(e) $H{-}O{-}O{-}H \rightleftharpoons HO{-}\ddot{O}: \xrightarrow{Et{-}C{\equiv}N:} Et{-}C(=N:)(O{-}O{-}H) \xrightarrow{H{-}OH} Et{-}C(=NH)(O{-}OH)$

$Et{-}C(=O){-}NH_2 + O_2 + H_2O \leftarrow$ (HO: H—O—O—H)

Isocyanides ($R{-}\overset{\oplus}{N}{\equiv}\overset{\ominus}{C}:$) cannot be hydrolysed by alkalis. This is because the carbon atom bearing a negative charge cannot coordinate with the OH ion. Again, the outer shell of the positively charged tetracovalent nitrogen atom is saturated and consequently, it is unable to accommodate two more electrons in that shell. Therefore, it also cannot coordinate with the $OH^{\ominus}$ ion.

12. What is the stereochemical outcome of the HVZ reaction of a chiral acid containing an α-H atom?

Solution When a chiral acid containing α-H atom is subjected to the HVZ reaction, then finally a racemic mixture is obtained. Enolization causes the chiral centre to be transformed into an enantiotopic face. Bromination from the two enantiotopic faces gives the racemic mixture. For example:



13. Suggest the mechanism of decarboxylation for each of the following carboxylic acids:

(a) 4-Hydroxy-1-naphthalenecarboxylic acid $\xrightarrow{\Delta}$

(b) 2,2-Dimethyl-3-pentanoic acid $\xrightarrow{\Delta}$

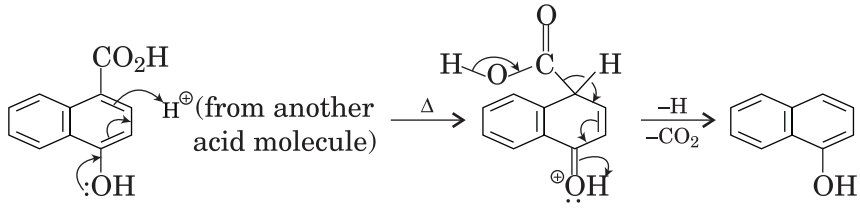
(c) 4,4-Dimethyl cyclohexane-1,1- dicarboxylic acid $\xrightarrow{\Delta}$

(d) Sodium (E)-3-bromo-2-ethyl-2-pentanoate $\xrightarrow{\Delta}$

(e) 2-Cyano-2-cyclopentylpropanoic acid $\xrightarrow{\Delta}$

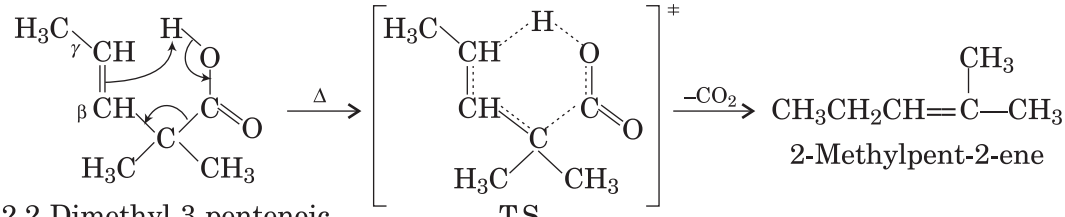
Solution

(a) Decarboxylation occurs by the arenium-ion mechanism involving $H^{\oplus}$ as the electrophile:



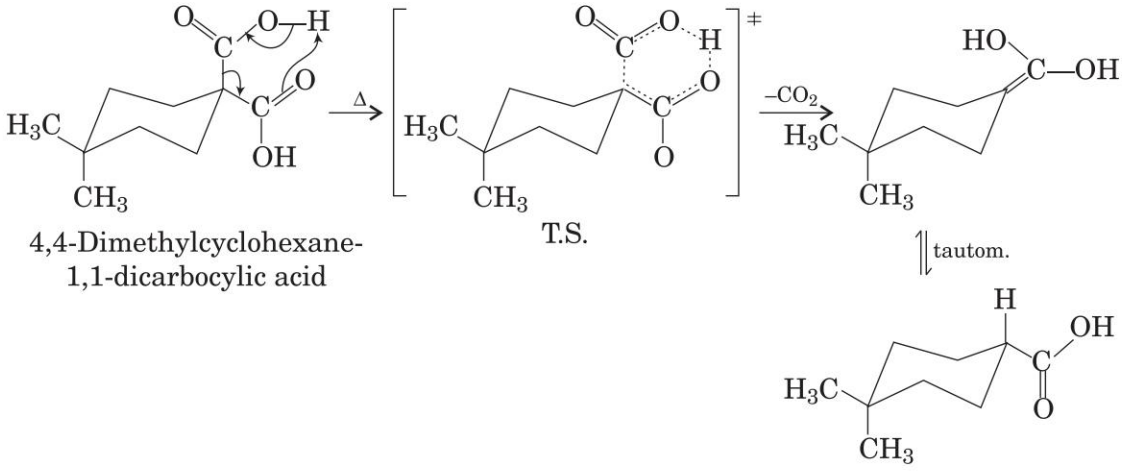
4-Hydroxy-1-naphthalene-carboxylic acid — 1-Naphthol

(b) Due to presence of unsaturation at the β,γ-position, this carboxylic acid decarboxylates via a six-membered cyclic transition state as follows:

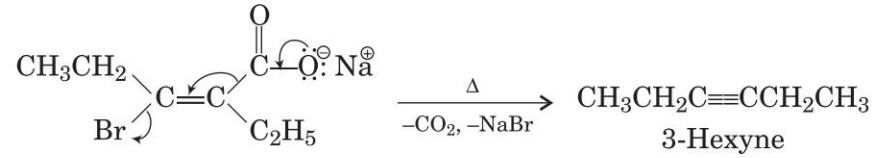


2,2-Dimethyl-3-pentenoic acid — T.S. — 2-Methylpent-2-ene

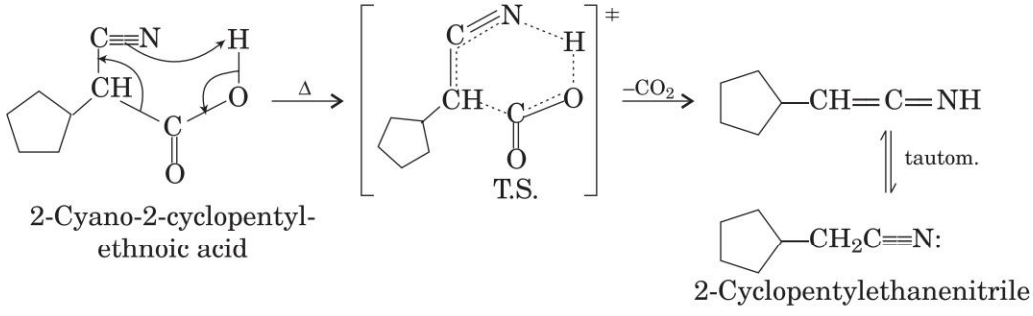
(c) This 1,1-dicarboxylic acid decarboxylates readily for reasons similar to a β-Keto acid. The decarboxylation, therefore, occurs through a six-membered cyclic transition state involving a concerted hydrogen transfer.



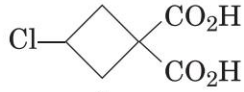
(d) The compound undergoes decarboxylative elimination to yield 3-hexyne.



(e) This α-cyano acid decarboxylates via a six-membered cyclic T.S. involving a concerted hydrogen transfer.

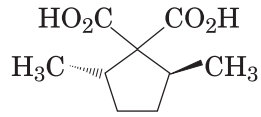


14. (a) Decarboxylation of the compound I gives two separable products. Draw their structures and explain the observation.



I

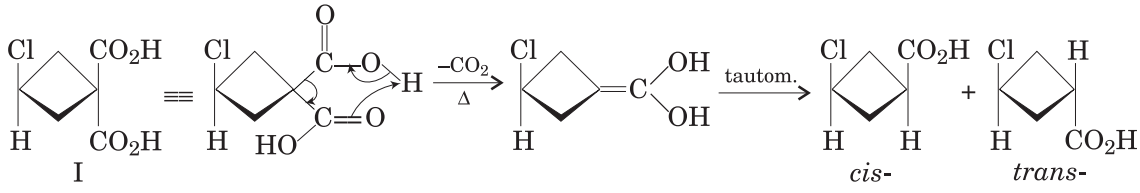
(b) How many products are expected to be formed when the compound II is decarboxylated?



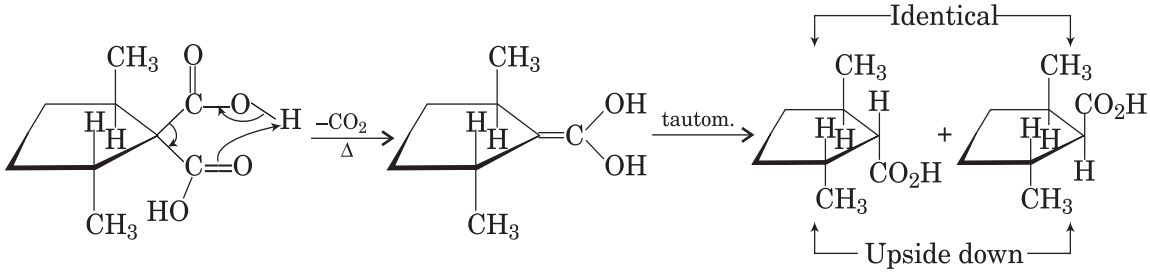
II

Solution

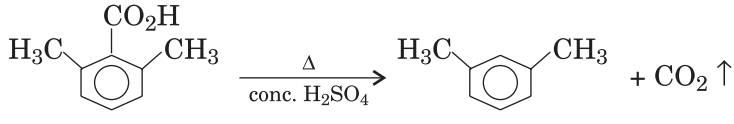
(a) The compound I is a 1,1-dicarboxylic acid. When it is heated, any one of the two –COOH groups may undergo decarboxylation. Therefore, decarboxylation of this dicarboxylic acid may produce two diastereoisomeric (geometric isomers) 3-Chlorocyclobutane carboxylic acid. These can be easily separated.



(b) The dicarboxylic acid II decarboxylates to yield only one product. This may be shown as follows:



15. Explain the following observations:

(a) 

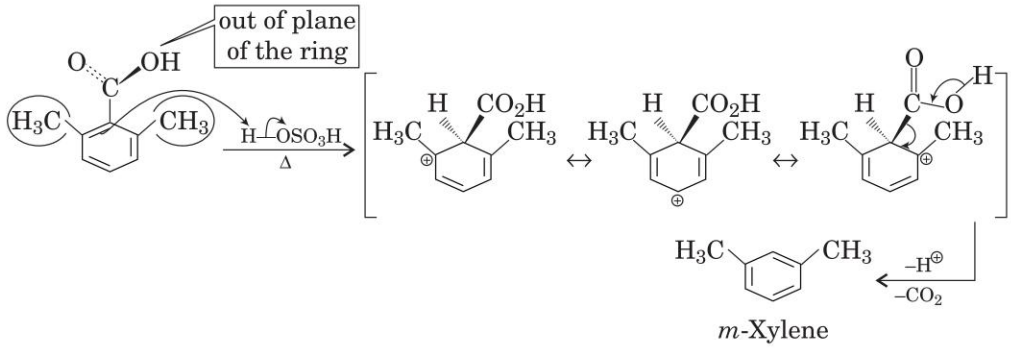
(b) The α,β- unsaturated acid $Me_2CHCH{=}CHCO_2H$ fails to decarboxylates on heating, while the acid $Me_3CCH{=}CHCO_2H$ fails to decarboxylate under similar conditions

(c) Oxopentanoic acid decarboxylates on heating, but 4-oxopentanoic acid does not.

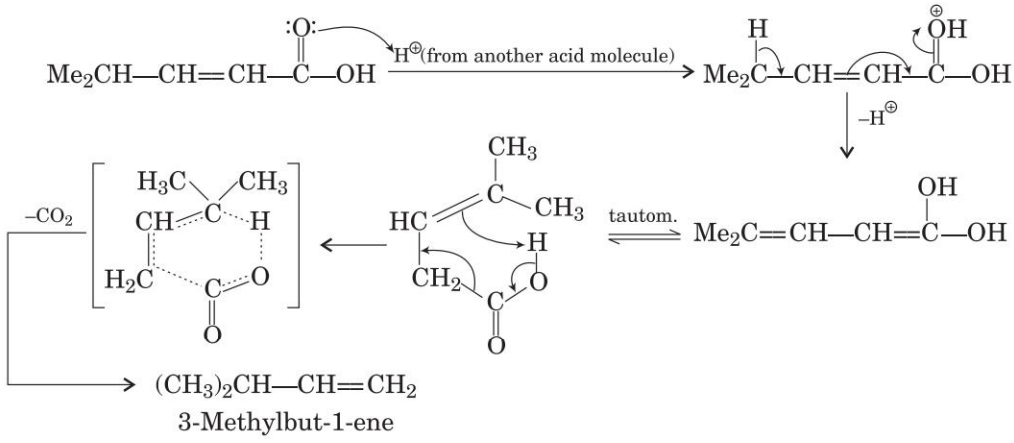
(d) *dl* $-CH_3(CH_2)_3CHOHCO_2H$, on heating, produces two isomeric cyclic compounds of which one is resolvable.

Solution

(a) In this benzoic acid derivative, the –COOH group is forced out of the plane of the aromatic ring because of steric interaction caused by the two *ortho* methyl groups. Decarboxylative expulsion of the –COOH group takes place easily by the arenium-ion mechanism, since the electrophilic attack by $H^{\oplus}$ does not involve much loss of resonance energy. The process may be shown as follows:

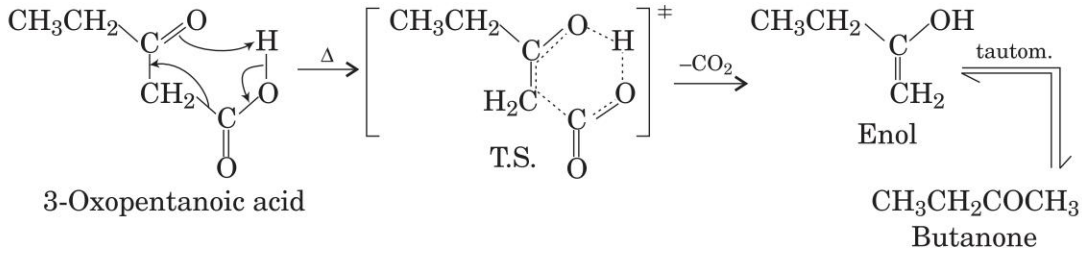


(b) The α,β- unsaturated acid $Me_2CHCH{=}CHCO_2H$ first undergoes acid-catalysed isomerization to yield the β,γ- unsaturated acid $Me_2C{=}CH{-}CH_2CO_2H$. It then decarboxylates via a six-membered cyclic transition state involving a concerted hydrogen transfer.



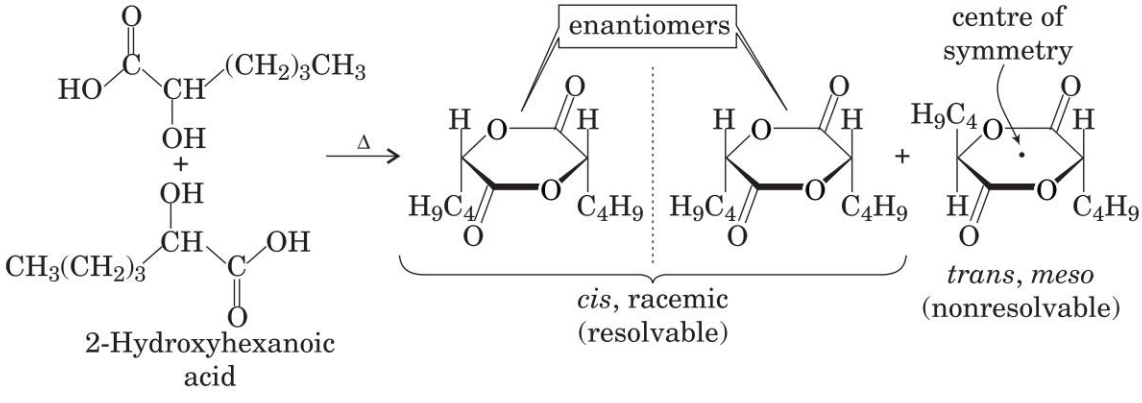
The α,β- unsaturated acid, $Me_3CCH{=}CHCO_2H$ fails to isomerize to the corresponding α,γ- unsaturated acid due to obsence of γ- hydrogen. For this reason, this acid fails to decarboxylate under the same reaction conditions.

(c) The carbonyl group in the β-keto acid $CH_3CH_2COCH_2CO_2H$ (3-oxopentanoic acid) accepts the electrons from the bond to the –COOH group which is breaking. Therefore, when heated, it undergoes readily decarboxylation through a six-membered cyclic transition state.

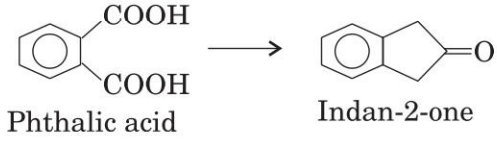


On the other hand, the carbonyl group in the β-keto acid $CH_3COCH_2CH_2COOH$ (4-oxopentanoic acid) is unable to accept the electrons from the bond to the –COOH group and so it does not undergo decarboxylation when heated under similar conditions.

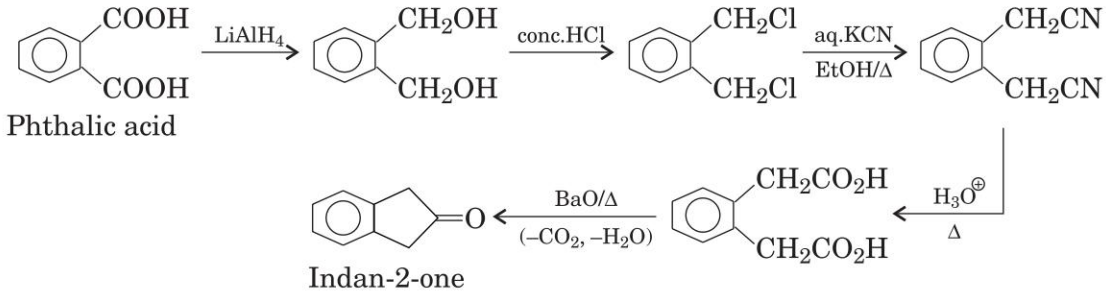
(d) When this α-hydroxycarboxylic acid is heated, it undergoes intermolecular lactonization to yield two diastereoisomeric cyclic compounds (*cis*- and *trans*-isomers). The *cis* isomer is chiral and resolvable, while the *trans*- isomer is achiral (*meso*) and not resolvable. Two molecules of the same enantiomer combine to produce the cis- compound and two molecules of the two-enantiomers combine to produce the trans-compound.



16. How would you carry out the following transformation?



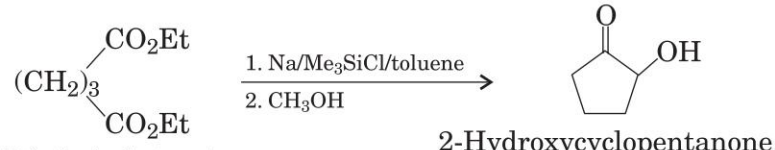
Solution



Phthalic acid

Indan-2-one

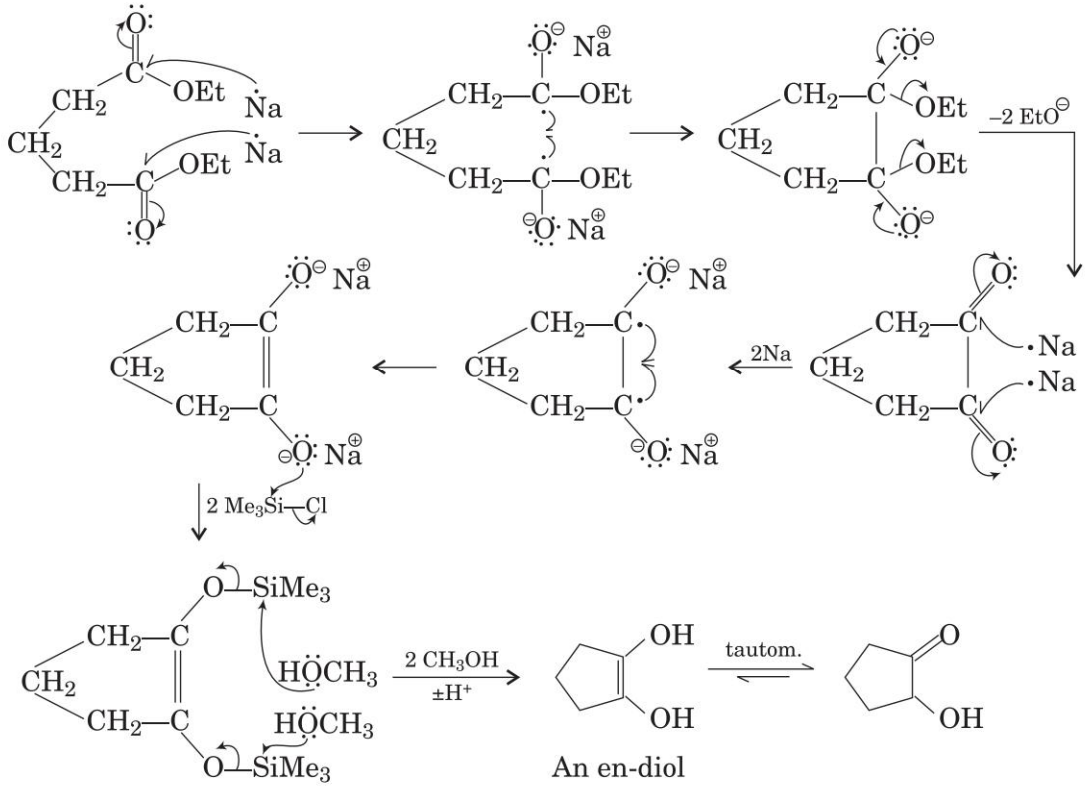
17. Propose a reasonable mechanism for the following reaction:



Diethyl glutarate

2-Hydroxycyclopentanone

Solution The mechanism of this reaction (an acyloin condensation) involves the steps as follows:



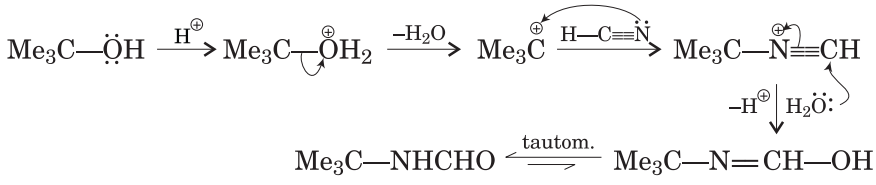
An en-diol

18. Give efficient methods for preparation of $Me_3C–NH_2$ and $Me_3C–CN$.

Solution A very good method for preparing primary amines containing a *tert*-alkyl group involves the Ritter reaction (a reaction between a 3° alcohol or an alkene with nitrile or HCN in the presence of H_2SO_4 to give an amide) followed by the alkaline hydrolysis of the resulting amide.

$$Me_3COH \xrightarrow[H_2SO_4]{NaCN}, \ HCONHCMe_3 \xrightarrow[\text{hydrol.}]{OH^{\ominus}/H_2O} Me_3CNH_2 + HCOO^{\ominus}$$

Mechanism:

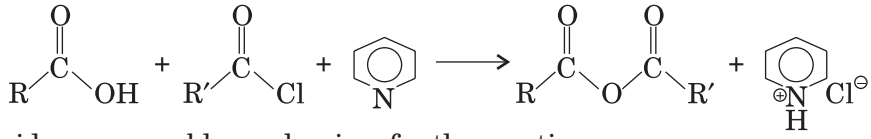


The best method of preparing tertiary alkyl cyanides ($Me_3C–CN$) is to treat a *tert*-alkylmagnesium chloride with cyanogen chloride.



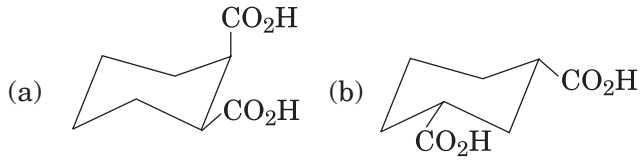
Study Problems

1. Less reactive acyl compounds can be synthesized from the more reactive ones, but the reverse is usually difficult. Account for these observations.
2. How can the two analgesics, acetyl salisylic acid (aspirin) and acetaminophen (the active ingredient in Tylenol be prepared using acetic anhydride (Ac_2O)?
3. Carboxylic acids react with acyl chlorides in the presence of pyridine to give carboxylic acid anhydride.



Provide a reasonable mechanism for the reaction.

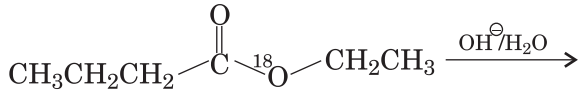
4. Direct dehydration by heating two molecules of carboxylic acid is not a successful method for the preparation of acyclic anhydrides. However, five-and six-membered cyclic anhydrides are often prepared smoothly by direct dehydration procedure. Explain these observations.
5. Draw the structure of the cyclic anhydride that forms when each of the following dicarboxylic acids is heated:



(c) *meso*- α,β-Dimethylsuccimic acid

6. The hydoxide-ion-promoted hydrolysis of an ester is not a reversible reaction– Why?

7. Predict the products expected to be obtained when the following labelled ester is treated with OH/H_2O if there occurs (i) alkyl C–O bond cleavage or (ii) acyl C–O bond cleavage:



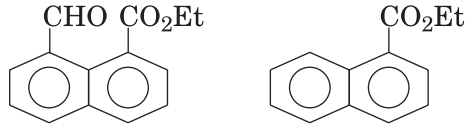
What actually happens in this case and why?

8. Explain the following observations:

(a) Propanoyl chloride readily decomposed by water, but benzoyl chloride reacts with water very slowly.

(b) Methyl mesitoate depresses the freezing point of H_2SO_4 four times as much as would be predicted from its molecular weight.

(c) The ester I undergoes alkaline hydrolysis at a rate very must faster than the ester II.



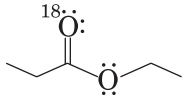
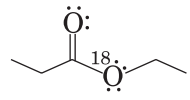
I II

[**Hint**: (c) Due to steric hindrance, the $-CO_2Et$ group in I goes out of the plane of the ring and as consequently, the elelctrophilicity of the carbonyl carbon atom increases due to lack of resonance interaction with the ring. On the other hand, in II, *peri*-steric hindrance is minimum due to presence of small H-atom at C-8.]

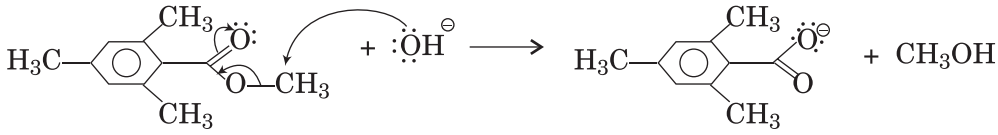
9. Explain the order of the rate of esterification of the following carboxylic acids with methanol:

$MeCH_2CO_2H > MeCHCO_2H > Me_3CCO_2H > Et_3CCO_2H >> (Me_2CH)_2CHCO_2H$

10. When each of the following istopically labelled esters is hydrolyzed with aqueous alkali, where does the label end up in the product?

(a)  (b) 

11. The base-promoted hydrolysis of methyl 2,4,6-trimethyl-benzoate or methyl mesitoate takes place through a nucleophilic attack on the alcohol carbon instead of the acyl carbon.

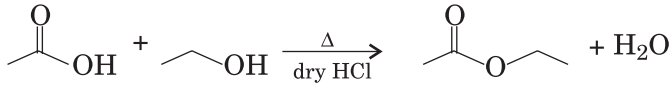


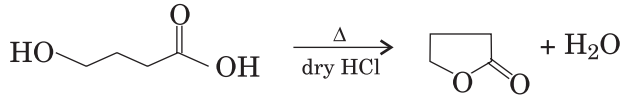
Methyl mesitoate
(Methyl 2,4,6-trimethylbenzoate)

(a) How would you account for this unusual behaviour?

(b) Offer a labelling experiment that would confirm this mode of attack.

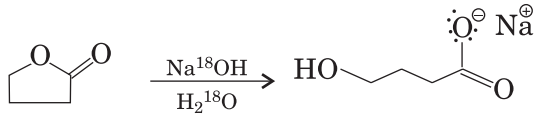
12. The amount of the product obtained in the second reaction is larger than that obtained in the first reaction even though the value of $\Delta H°$ for these two reactions is almost same. Account for this observation.

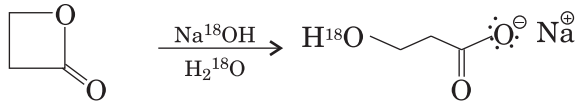
(a) 

(b) 

[**Hint:** The entropy contribution to the free energy ($\Delta G°$) is more favourable in the case of second reaction which is a process of lactonization (formation of cyclic ester).]

13. Explain the following observations:

(a) 

(b) 

[Hint: The γ-lactone in (a) undergoes normal nucleophilic acyl substitution, while the β-lactone in (b), which is under severe angle strain, undergoes S_N2 reaction because of immediate strain release.]

14. The relative rate of alkaline hydrolysis ($B_{AC}2$) of ethyl *p*-substituted benzoates, *p*-$GC_6H_4CO_2Et$, are:

G =	NO_2	Cl	H	CH_3	OCH_3
	110	4	1	0.5	0.2

How would you account for this order of reactivity?

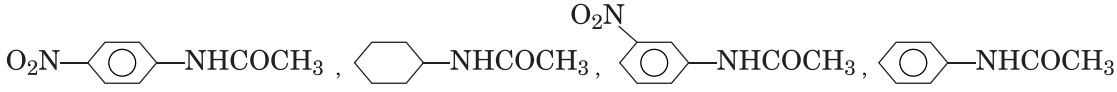
15. The relative rates of alkaline hydrolysis ($B_{AC}2$) of alkyl acetate, CH_3COOR, are:

R =	Me	Et	Me_2CH	Me_3C
	1	0.6	0.15	0.008

What are the two factors that may probably of use here?

16. Where would you expect to find the labelled oxygen if acid-catalysed hydrolysis of ethyl benzoate is carried out in ^{18}O-labelled water. Write a detailed mechanism to support your answer.

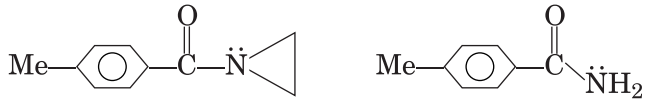
17. Arrange the following amides in order of decreasing reactivity towards hydroxide-ion-promoted hydrolysis:



I II III IV

[**Hint:** I > III > IV > II; the reactivity increases as the positive character of the carbonyl carbon increases.]

18. The amide I undergoes alkaline hydrolysis at a rate much faster (10^5 times) than the amide II. Explain.



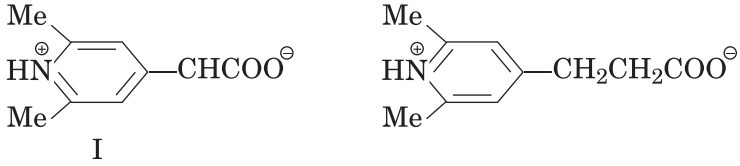
I II

[**Hint:** The unshared pair of electrons on nitrogen in I is practically not involved in the resonace interaction with the C═O group because in that case ring strains sufficiently increase. Consequently, the positive character of the carbonyl carbon in I becomes much higher than the positive character of the carbonyl carbon in II and so, the compound I undergoes readily nucleophilic attack by $OH^{\ominus}$ compared to II.]

19. Imidazole increases the rate of hydrolysis of phenyl ethanoate. Explain.
[Hint: It is a case of nucleophilic catalysis.]

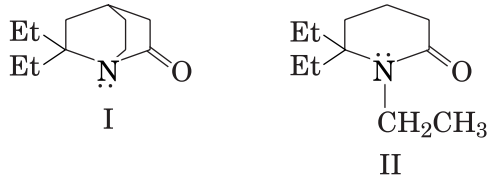
20. Account for the following observations:

(a) The compound I decarboxylatees more easily than the compound II.



I

(b) The bicyclic lactam I is much more readily hydrolysed than the moncyclic lactam II.



I II

(c) Strong bases as $\overset{\ominus}{O}R$ (from esters) and $NH_2^{\ominus}$ (fromamides) can be leaving groups in nucleophilic transacylations.

(d) Although the loss of CO_2 from a carboxylic acid is an exothermic process (ΔH = –7 kcal/mol), most simple acyclic carboxylic acids do not decarboxylate, even on heating. A β-keto acid, on the other hand, decarboxylates readily on mild heating.

(e) Alkaline hydrolysis of benzonitrile ($PHC \equiv N$) affords the salt of benzoic acid but that of 2,6-dimethylbenzonitrile gives the corresponding amide.

(f) Methyl benzoate and methyl 4-nitrobenzoate are hydrolysed at almost the same rate by dilute mineral acid.

(g) $PhC \equiv C - COOH$ undergoes readily decarboxylation when heated with alkali.

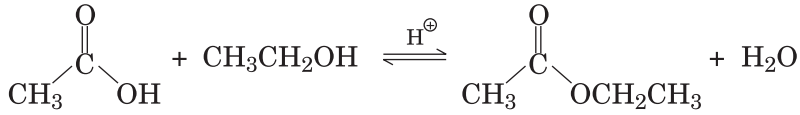
(h) Me_2NCOOH (a carbamic acid) decarboxylates readily, while its salt does not decarboxylate and is quite stable.

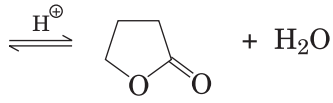
(i) Pyridine-2-carboxylic acid decarboxylates much more readily than its 3- or 4- isomers.

[**Hint:** (d) The activation energy of decarboxylation of most simple acyclic carboxylic acids is usually so great that the rate of the reaction is negligibly slow. A β-Keto acid decarboxylates readily on heating because the activation energy of this decarboxylation process, which involves a stable six-membered cyclic transition state, is relatively small.

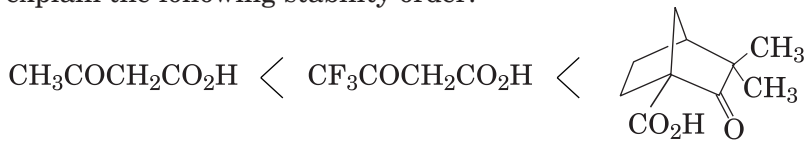
(e) The linear $-C\equiv N$ group in 2,6-dimethylbenzonitrile undergoes nucleophilic attack by $OH^{\ominus}$, but the planar $-CONH_2$ group which is now out of the plane of the ring due to two *ortho* $-CH_3$ groups, does not undergo nucleophilic attack by $OH^{\ominus}$. So, in this case, complete hydrolysis does not take place and instead of an acid, an amide is obtained finally.

21. Which of the following two reactions conducted at the same temperature is expected to have larger value of equilibrium constant and why?

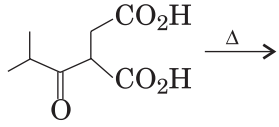
(a) 

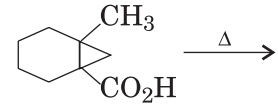
(b) 

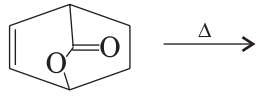
22. Write the mechanism of decarboxylation of the β-keto acid $CH_3COCH_2CO_2H$ and hence explain the following stability order:



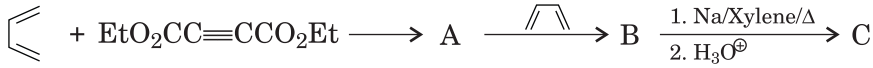
23. Predict the products of the following reactions and provide mechanisms that accounts for their formation:

(a) 

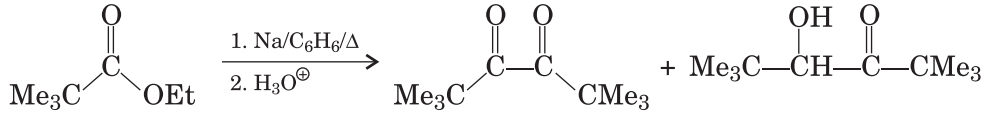
(b) 

(c) 

24. Give structures for compounds A, B and C:



25. Explain the following observation:



Ethyl 2,2-dimethyl-propanoate (major) (minor)

26. 1,4-Diazabicyclo [2.2.2] otane (DABCO) is a tertiary amine which can function as a catalyst in transesterification reactions. Propose a mechanism to show how it functions.

REFERENCES

1. H O House, *Modern Synthetic Reactions*, 2nd ed., W.A. Bejamin.
2. B P Mundy and M G Ellerd, *Named Reactions and Reagents in Organic Synthesis*, 2nd ed. John Wiley and Sons, New York, (2005).
3. R A Sheldon *et al*., *Chem Rev*., **104**, 4105 (2004).
4. H Smith, *Organic Reactions in Liquid Ammonia*, Vol.1, Part II, Inter Science Publishers, Inc., New York, (1963).
5. A A Frost and R G Pearson, *Kinetics and Mechanism*, 2nd ed., John Wiley and Sons, New York, (1971).
6. M S Kharasch and O Reinmuth, *Grignard Reactions of Non-metallic Substances*, Prentice Hall, Inc., New York, (1954).
7. Andrew Streitwieser, Clayton H. Heathcock, Edward M Kosower, *Introduction to Organic Chemistry,* Fourth Edition, Macmillan.
8. George S Zweifel, Mechael H Nantz, *Modern Organic Synthesis*, W H Freeman and Company.
9. Stanly H Pine, *Organic Chemistry*, Fifth Edition, McGraw-Hill.
10. James B Hendrickson, Donald J Cram, George S Hammond, *Organic Chemistry*, 3rd Edition, McGraw-Hill.
11. Robert S Ward, *Bifunctional Compounds*, Oxford University Press.
12. Gutsche C D, *The Chemistry of Carbonyl Compounds*; Prentice-Hall: Englewood Cliffs, NJ, 1967.
13. Thomas H Lowry, Kathleen Schuller Richardson, *Mechanism and Theory in Organic Chemistry*, Addison-Wesley.
14. R O C Norman, *Principles of Organic Synthesis*, Methuen and Co. Ltd., London, (1968).
15. Ralph J Fessenden, Joan S Fessenden, *Organic Chemistry*, Fifth edition, Brooks/ Cole Publishing Company.

3 CHAPTER

ELECTROPHILIC AND NUCLEOPHILIC SUBSTITUTIONS IN AROMATIC SYSTEMS

Chapter Outline

Introduction

3.1 Electrophilic Aromatic Substitution

- 3.1.1 Characteristics of Electrophilic Aromatic Substitution
- 3.1.2 Formation of Carbon–Nitrogen σ-Bond
- 3.1.3 Formation of Carbon-Halogen σ-Bond (Halogenation): Bromination and Chlorination, Iodination, Fluorination
- 3.1.4 Formation of Carbon–Sulphur σ-Bond
- 3.1.5 Formation of Carbon–Carbon σ-Bond:
- 3.1.6 Use of Electrophilic Aromatic Substitution Reactions in Organic Synthesis

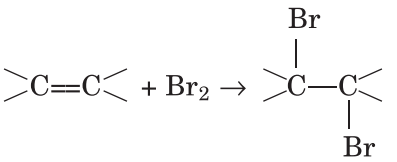
3.2 Nucleophilic Aromatic Substitution

- 3.2.1 The Addition-Elimination or S_NAr Mechanism
- 3.2.2 The Elimination-Addition or Benzyne Mechanism
- 3.2.3 S_N1 Mechanism
- 3.2.4 Aromatic Nucleophilic Substitutions with Rearrangement

INTRODUCTION

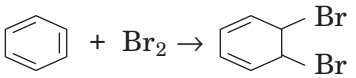
Aromatic hydrocarbons, similar to alkenes and alkynes, are electron rich and, therefore, reactive to electrophiles or electron-deficient species. However, in contrast to alkenes and alkynes, the reaction pattern of aromatic compounds with electrophiles differs in two

fundamental aspects: (i) the reaction is relatively very slow and (ii) the reaction leads to the formation of substitution product rather than the addition product. The reason for this difference is as follows. In alkenes and alkynes, the addition reaction is exothermic, quite fast and favourable and this is because stronger σ-bonds are formed at the expense of weaker π-bonds. For example:



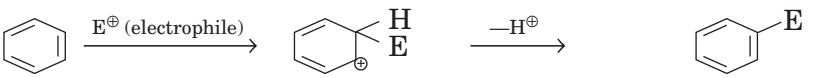
$\Delta H = -30$ kcal mol^{-1}

On the other hand, electrophilic addition to C═C bond of an aromatic system does not normally take place because of endothermicity of the reaction. This is due, in fact, to the complete loss of aromaticity in the product. For example:



$\Delta H = +2.5$ kcal mol^{-1}

The reaction of an electrophile with an aromatic compound, therefore, follows an alternative route. It leads to substitution product through the formation of an intermediate resonance-stabilized carbocation (σ-complex) intermediate that regains aromaticity. The reaction is overall exothermic.



Benzene (aromatic) — σ-complex (non aromatic) — Substituted benzene (aromatic)

Since the substitution is induced by an electrophile, the process is known as *Electrophilic Aromatic Substitution*, which is commonly abbreviated as ArS_E.

Attack by nucleophiles on an unsubstituted benzene nucleus will be much more difficult than attack by electrophiles. This is so (i) because the π electron cloud of the nucleus is likely to repel an approaching nucleus loving species or nucleophile, and (ii) because its π orbital system is much less capable of delocalising (and so stabilising) the extra electrons in the negatively charged intermediate than the positively charged intermediate (σ-complex). Both (i) and (ii) would be overcome to some extent if a sufficiently powerful electron-attracting substituent was present and nucleophilic attack might then be possible.

Electrophilic aromatic substitution is the most important reaction of aromatic compounds because it has broad application for a wide variety of aromatic compounds. In contrast, nucleophilic aromatic substitution has restricted applications.

3.1 ELECTROPHILIC AROMATIC SUBSTITUTION

3.1.1 Characteristics of Electrophilic Aromatic Substitution

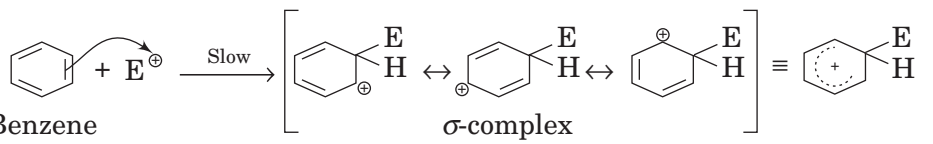
3.1.1.1 General mechanism of electrophilic aromatic substitution reaction

In an electrophilic aromatic substitution reaction, an electrophile substitute for a hydrogen of an aromatic compound.

There is a negatively charged cloud above and below the plane of an aromatic ring. Electrophiles, being positively charged or electron-deficient species, are very prone to attack the negatively charged cloud of the delocalised π electrons. Therefore, it is expected that electrophilic reactions will take place on the aromatic ring much readily. However, an aromatic compound wants to preserve its aromatic character and hence its stability, and therefore, it is somewhat reluctant to utilise its π electrons. For this reason, the reaction of aromatic compounds with electrophiles take place rather slowly. Nevertheless, the most important type of reactions that the aromatic compounds undergo is the bimolecular electrophilic substitutions.

An electrophilic aromatic substitution reaction proceeds through the following two steps:

Step 1: In this step, the electrophile, $E^{\oplus}$, accepts a pair of π electrons of benzene (the aromatic compound) to form a resonance-stabilized carbocation intermediate known as an *arenium ion* or a *benzenonium ion* or a *Wheland intermediate* or a σ-*complex*. It is called a sigma complex because the electrophile is joined to the benzene ring by a new sigma bond.

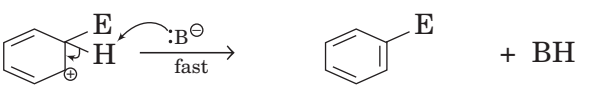


Benzene (aromatic)

σ-complex (nonaromatic)

This step is slow (rate-determining) and endergonic because in this step benzene loses its aromatic stability and becomes converted into a nonaromatic intermediate.

Step 2: In this step, the σ-complex loses a proton from the carbon that has formed a new bond with the electrophile to yield a benzene derivative. This step is fast and strongly exergonic because this step restores the stability-enhancing aromaticity. The removal of proton is helped off by a base in the reaction mixture (generally the counter ion of the electrophilic species although solvents can also serve this purpose).



σ complex

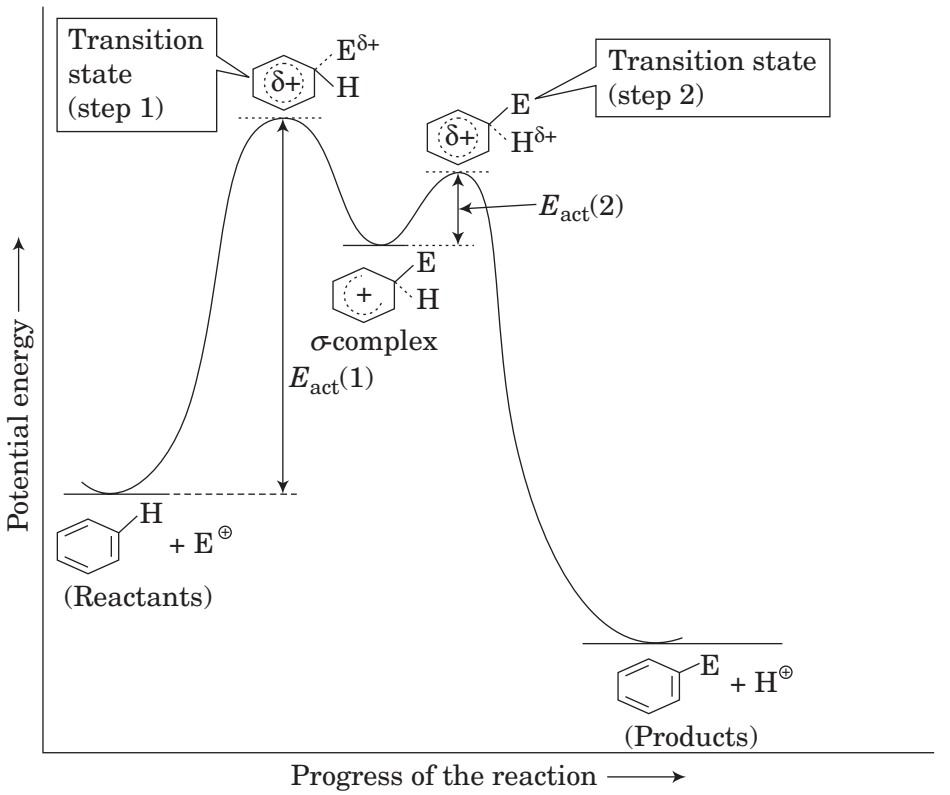
Substituted benzene (aromatic)

3.1.1.2 Kinetics

Since the step 1 is slow and the two species, i.e., the substrate and the electrophile participate in this step, the reaction is bimolecular and follows second-order kinetics, i.e., rate = k [Substrate][Electrophile]. So, the reaction is designated as ArS_E2, i.e., Aromatic Electrophilic Substitution Bimolecular. The IUPAC designation for this mechanism is $A_E + D_E$ which indicates that *Addition of Electrophile* and *Departure of Electrophile* follow stepwise process.

3.1.1.3 Energy diagram

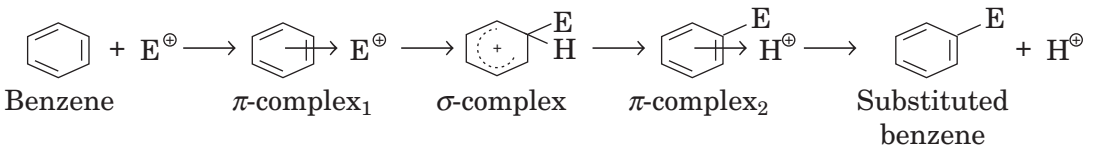
The energy diagram illustrating the energy changes associated with the two steps of electrophilic aromatic substitution ($PhH + E^{\oplus} \rightarrow PhE + H^{\oplus}$) is given below. Because the first step is rate-determining, its transition state is higher in energy.



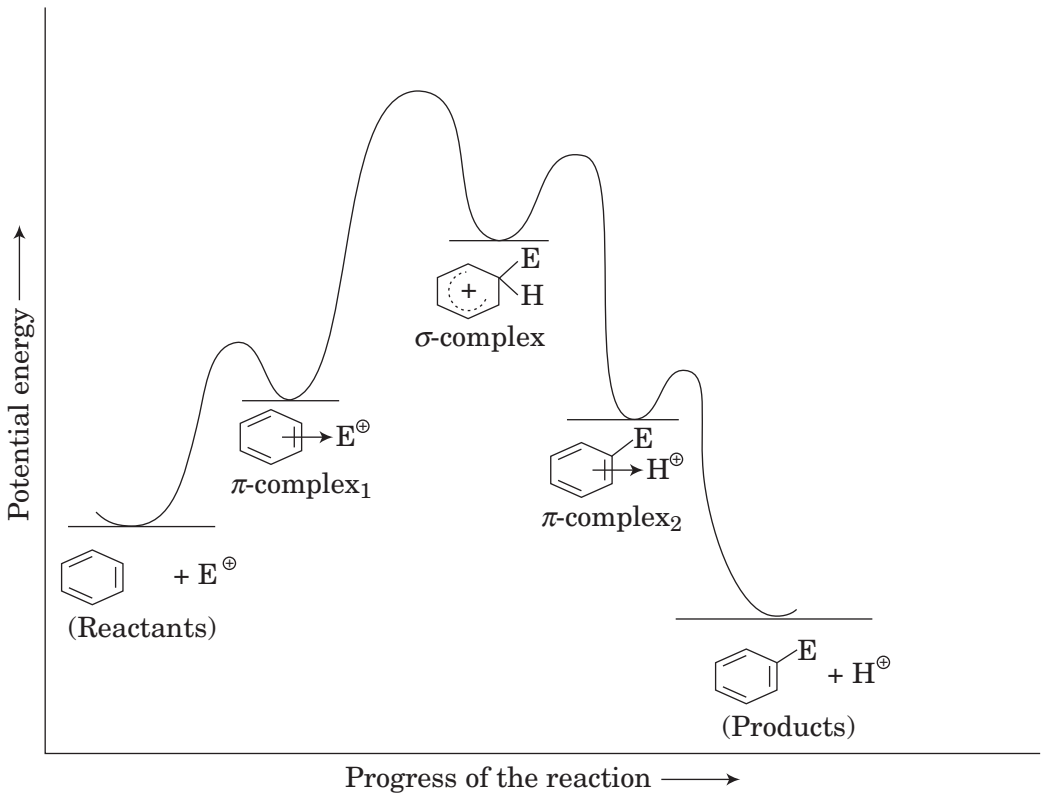
3.1.1.4 Concept of π-complex and energy diagram showing both π- and σ-complex

The above scheme for substitution is an over-simplification. The initial step of electrophilic aromatic substitution involves formation of a weak complex in which benzene π system

acts as electron donor and the electrophile acts as electron acceptor. This adduct is called a π-complex. The electrophile in the π-complex then removes a pair of electrons from the ring and enters into covalent bond formation with any of the ring carbon to yield the σ-complex. It is so called because the electrophile is joined to the ring carbon by a new sigma bond. This σ complex then loses a proton which before departing from the substrate again forms a π complex. Therefore, a complete picture of the mechanism of electrophilic aromatic substitution would be as follows:



The π-complex formation and dissociation are, however, extremely rapid, and π complexation is not significant in determining either the rate of the reaction or the nature of the product for the vast majority of aromatic electrophilic substitutions. The idealized energy diagram for aromatic substitution showing π complexation is as follows:

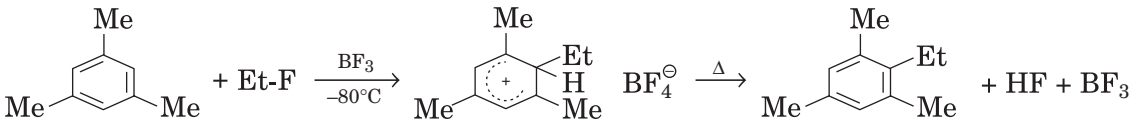


The general mechanism shown above is irreversible but certain electrophilic substitutions may also be reversible.

3.1.1.5 Evidence for the mechanism

The evidence for the arenium ion mechanism is mainly of two kinds:

1. *Isolation of σ-complex or arenium ion intermediates:* Very strong evidence for the arenium ion mechanism comes from the isolation of arenium ions in a number of cases. For example, the arenium ion I has been isolated as a solid with a melting point of –15°C from treatment of mesitylene with ethyl fluoride and the Lewis acid catalyst BF_3 at –80°C (Friedel-Crafts alkylation). When I is heated, the normal substitution product II is obtained.



Mesitylene σ-complex I II

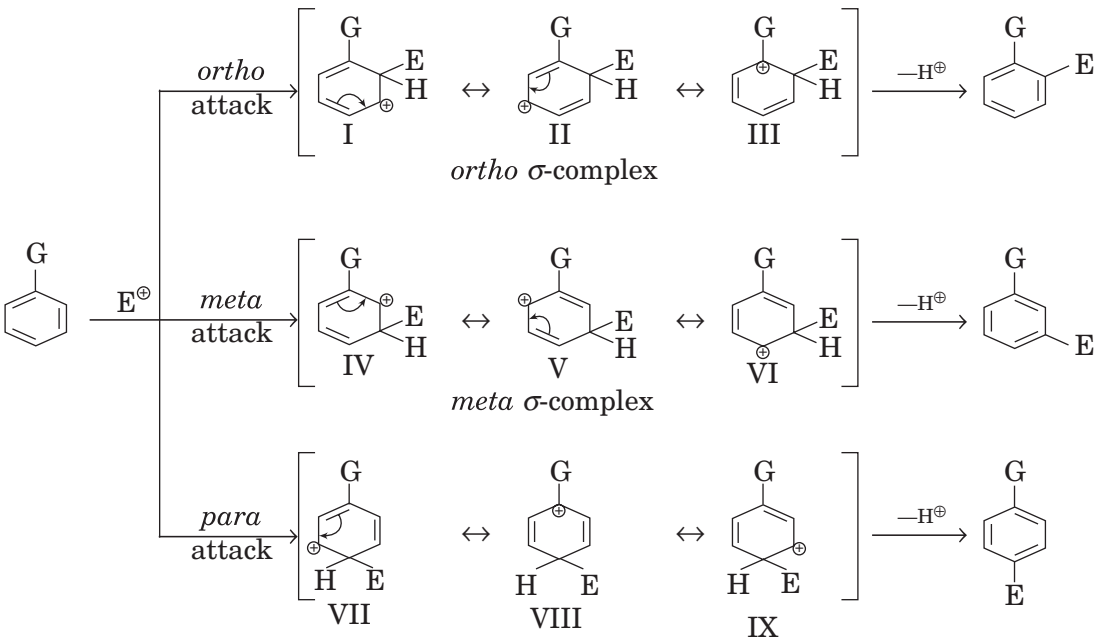
2. *Isotope effects:* If the hydrogen ion departs before the arrival of the electrophile (S_E1 mechanism) or if the arrival and departure are simultaneous, there should be substantial isotope effect, i.e., deuterated substrates should undergo substitution more slowly than the nondeuterated compounds and this is because in each case, the C—H bond is broken in the rate-determining step. However, in the arenium ion mechanism, the C—H bond breaking is not involved in the rate-determining step, so no isotope effect is expected to be found. This was actually observed in most cases. For example, when C_6D_6 is subjected to nitration under similar conditions, the reaction does not show any primary kinetic isotope effect, i.e. $k_H/k_D = 1$. This result is incompatible with either the S_E1 or the simultaneous mechanism.

3.1.1.6 Reactivity of ArS_E2 reactions and the orientation of the attacking electrophile in monosubstituted benzenes

When electrophilic aromatic substitution is carried out on a monosubstituted benzene, the rate of the reaction and the orientation of the incoming group depend on the electronic character of the substituent already present in the ring. Electron-donating (+I, +R or hyperconjugative effect) groups enhance the electron density of the ring and thereby increase the stability of the σ complex. As a result, the aromatic electrophilic substitution becomes easier and faster. Such groups are called *activating groups*. On the other hand electron-withdrawing (–I, –R or hyperconjugative effect) groups reduce the electron density of the ring and thereby destabilize the corresponding σ-complex. As a result, the reaction becomes slower and often nonproductive. Such groups are called *deactivating groups*.

Activating groups enhance the electron density at the *ortho* and *para* positions of the ring and direct the incoming electrophiles to those positions. Such groups are, therefore, called *ortho* and *para directors* or *ortho-para* directing groups. On the other hand, the

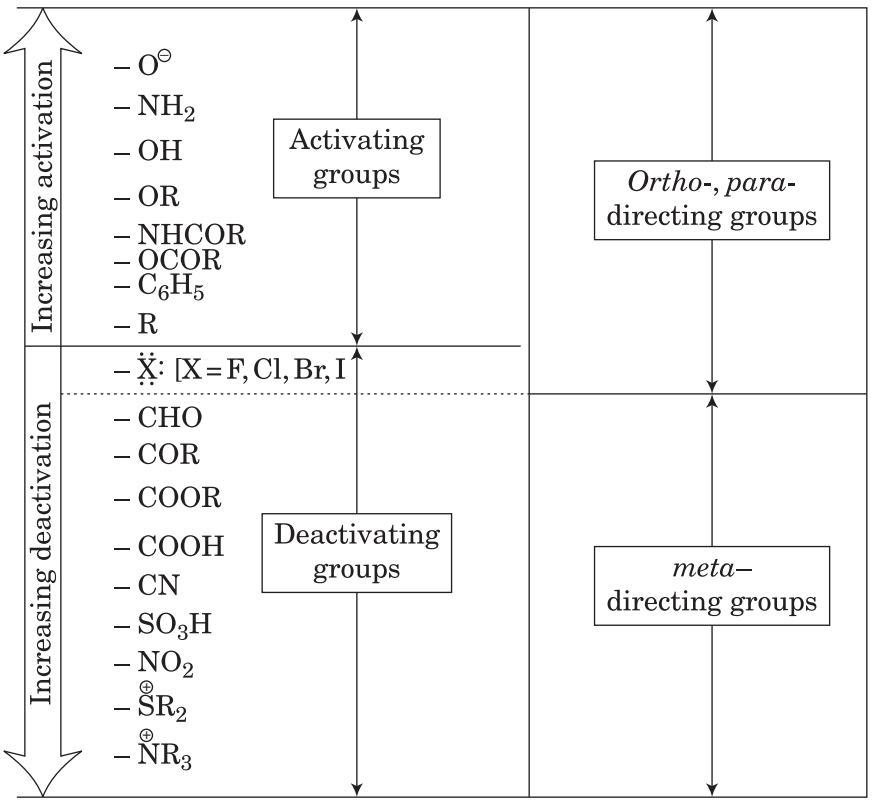
deactivating groups reduce the electron density at the *ortho* and *para* positions and normally direct the incoming electrophile to the *meta* position, because it is relatively more electron rich. These groups are called *meta directors* or *meta*-directing groups. The orienting effect of a substituent can also be explained in terms of the relative stabilities of the intermediate σ complexes leading to different substitution products. The orienting effect of a substituent is, in fact, a consequence of the relative rate of formation of the intermediate σ complexes leading to different products. Now, it is the stability of the transition state on which the rate of formation of a particular substitution intermediate depends. Since the transition state closely resembles the intermediate in energy and geometry, the more a particular intermediate will be stable the more the transition state will be stable, i.e., the more readily the corresponding product will be formed. Thus, the orienting effect of a substituent depends on the relative stabilities of various σ-complexes leading to different products. For determining the stabilities of various σ-complexes, it is necessary to examine the contributing structures of the three σ-complex resonance hybrids.



When we examine these structures, we see that both the *ortho* and *para* σ-complexes have one contributing structure (III and VIII) in which the substituent is attached to a positively charged ring carbon. If G is an electron-releasing (activating) substituent (e.g., $-CH_3$, –OH, $-NH_2$, etc.), it stabilizes the structures III and VIII by electronic effects and consequently, the *ortho* and *para* σ-complexes to which those structures belong are

also stabilized. Unlike *ortho* and *para*, the *meta* σ-complex contains no especially stable structure and thus, it is less stable than the *ortho* and *para*. The electrophilic substitution, as a result, takes place preferentially at the *ortho* and *para* positions. If G is an electron-attracting (deactivating) substituent (e.g., $-CCl_3$, $-NO_2$, –CN, etc.), it destabilizes the structures III and VIII and consequently destabilizes the *ortho* and *para* σ complexes. The *meta* σ complex is found to contain no such unstable structure and consequently, it becomes the more stable intermediate among the three. In fact the *meta* σ-complex is less destabilized than the *ortho* and *para* σ complexes. Therefore, in this case, the electrophilic substitution takes place preferably at the *meta* position.

Orientaion and Reactivity Effects of Ring Substituents



Three generalizations emerge from examining this table.

1. All *meta* directing groups are deactivating groups.
2. All *ortho*-, *para*-directing groups except for the halogens are activating groups.
3. The halogens are deactivating groups.

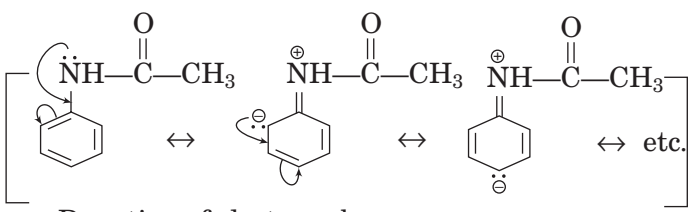
Polar effects and directing nature of some groups

Groups	Polar effects	Directing nature
1. $-O^{\ominus}$	+I, +R	*ortho*, *para*
$-NR_2$, $-NH_2$, –OH, –NHCOR,		
–OR, –SR, –OCOR	–I, +R	*ortho*, *para*
–F, –Cl, –Br, –I, –Ph, $-CH=CH_2$	–I, +R	*ortho*, *para*
2. –Me, $-CH_2Me$, $-CHMe_2$	+I, hyperconjugative	*ortho*, *para*
$-CMe_3$	+I	*ortho*, *para*
3. $-\overset{\oplus}{N}H_3$, $-\overset{\oplus}{N}R_3$, $-\overset{\oplus}{S}R_2$, $-\overset{\oplus}{P}R_3$ $-CF_3$, $-CCl_3$	–I	*meta*
4. $-NO_2$, $-SO_3H$, –CN, –COOH,		
–COOR, –COR, $-B(OH)_2$,	–I, –R	*meta*
–CHO		

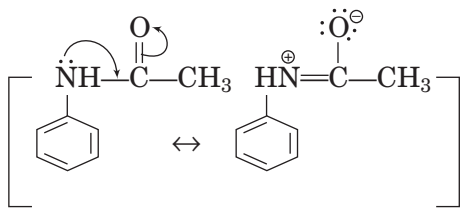
All substituents that donate electrons into the ring inductively or by resonance are *ortho*, *para* directors, and all substituents that cannot donate electrons into the ring inductively or by resonance are *meta* directors.

Mode of activation and deactivation of strongly, moderately and weakly activating and deactivating groups, respectively: All the strongly activating groups like $-NH_2$, –OH, –OR etc. donate electrons into the ring by resonance and withdraw electrons from the ring by the –I effect. Since they behave as strong activators, therefore, electron donation into ring by resonance (+R) is more significant than electron withdrawal from the ring by the inductive effect (–I).

The moderately activating groups, like –NHCOR and –OCOR, also donate electrons into the ring by +R effect and withdraw electrons from the ring by –I effect. However, the +R effect is less effective than that of the strongly activating groups because donation of electrons by resonance also takes place towards the C═O group. Nevertheless, these groups denote electrons by resonance more strongly than they withdraw electrons inductively.



Donation of electrons by resonance towards the ring



Donation of electrons by resonance towards the C═O group

The weakly activating alkyl groups like CH_3, C_2H_5, etc. donate electrons into the ring by +I and hyperconjugative effects. Aryl and –CH = CHR groups can donate electrons into the ring by resonance and can withdraw electrons from the ring by resonance. That they

are weak activators is due to the fact that they are slightly more electron-donating than electron-withdrawing.

Halogens donate electrons into the ring by resonance and withdraws electrons from the ring by –I effect. Since halogens have been found to be weakly deactivating, therefore, the –I effect exerted by them is stronger than the electron-donating +R effect.

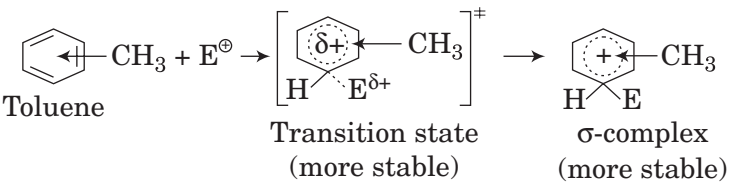
All the moderately deactivating groups, like –CHO, –COR, –COOR, etc., have carbonyl group (C═O) directly attached to the ring carbon. Carbonyl groups withdraw electrons both by inductive (–I) and resonance (–R) effects.

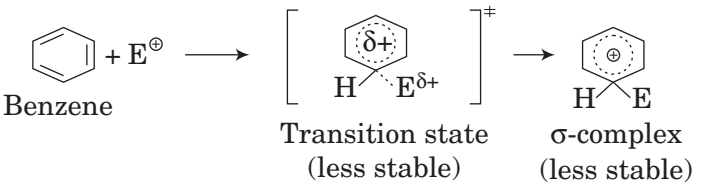
The strongly deactivating groups like $-\overset{\oplus}{N}R_3$, $-NO_2$, $-CF_3$, $-SO_3H$, etc. are much powerful electron withdrawers. The $-\overset{\oplus}{N}R_3$ and $-CF_3$ groups withdraw electron by much stronger –I effect. Whereas the other groups withdraw electrons both by –I and –R effects.

Classification of electron-donating and electron-withdrawing groups in terms of their structure and electronic effects: The electron-donating groups may be classified as follows: (i) the key atom, i.e., the atom of the group which is bonded to the ring has an unshared pair of electrons and that electrons can be delocalized into the ring. Groups like $-\ddot{O}:^{\ominus}$, $-\ddot{N}H_2$, $-\ddot{O}H$, etc. belong to this category. However, halogens ($-\ddot{X}:$) containing unshared pairs of electrons are net electron-withdrawing, (ii) the key atom is bonded to an electron rich π-system like $>C{=}C<$, $-C_6H_5$, $-C_6H_4CH_3$, etc. (iii) the key atom has no unshared pair of electrons, but donates electrons by inductive (+I) or hyperconjugative effect. Alkyl groups (e.g., $-CH_3$, $-C_2H_5$, $-CMe_3$, etc.) belong to this category. The electron-withdrawing groups may be classified on the basis of their structure as follows: (i) groups like $-\overset{\oplus}{N}R_3$, $-\overset{\oplus}{N}H_3$, $-\overset{\oplus}{S}R_2$, etc. in which the key atom (with no unshared pair of electrons) has a full-fledged positive charge, (ii) the key atom containing no unshared electron pair is bonded to a highly electronegative atom by a multiple bond. The electronegative terminal atom pulls the electron pair of the multiple bond both inductively or by resonance and thereby places a partial positive charge on the key atom. For example, $-\overset{\delta+}{C}\equiv\overset{\delta-}{N}$, $>\overset{\delta+}{C}=\overset{\delta-}{O}$, $-\overset{\oplus}{N}\begin{matrix}=O\\ -O^{\ominus}\end{matrix}$, etc. (the key atom of the nitrogroup, i.e., the N atom has a formal positive charge), (iii) the key atom containing no unshared pair of electrons is bonded to several electronegative atoms and due to their cumulative –I effects, a partial positive charge is placed on it. Groups like $-CF_3$, $-CCl_3$, etc. belong to this category.

Reactivity and orienting effects of some groups

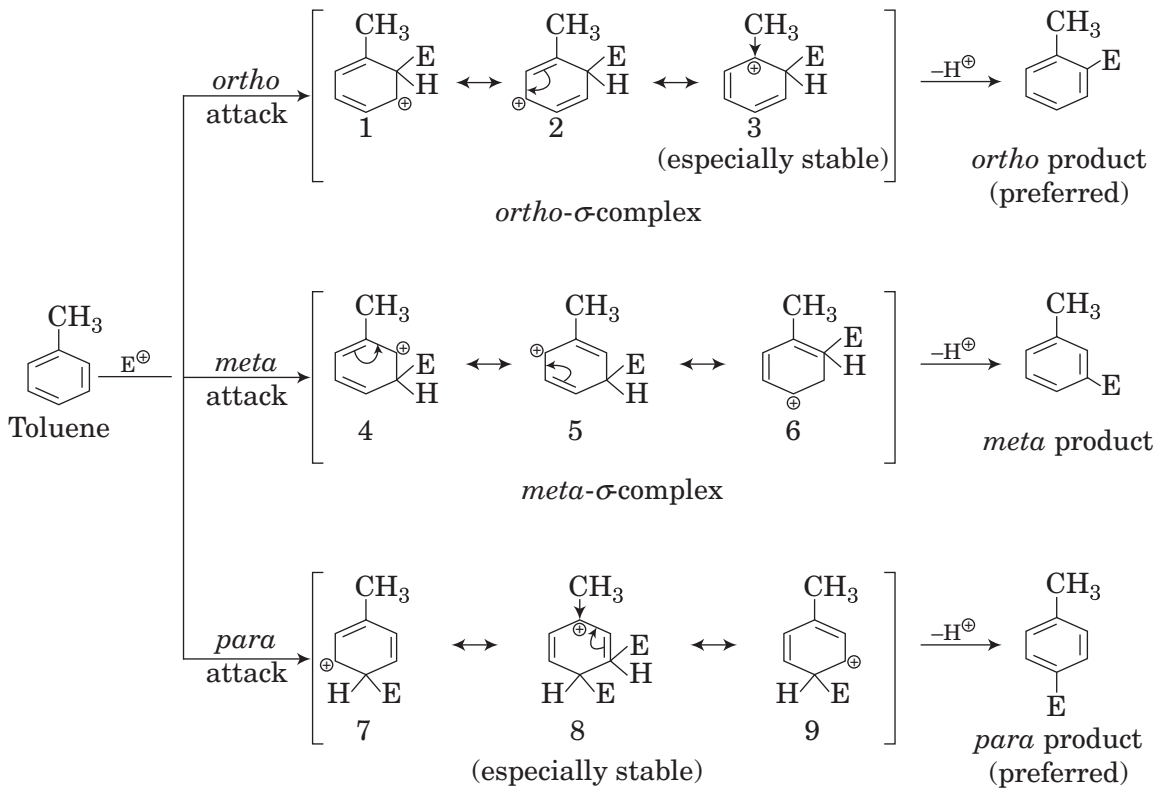
(i) **The $-CH_3$ group in toluene:** Toluene undergoes electrophilic substitution at a rate faster than benzene. This is because the $-CH_3$ group in toluene releases electrons to the ring through +I and hyperconjugative effect and stabilizes the intermediate σ-complex compared to that involved in the case of benzene. Therefore, the methyl group is an activating group.



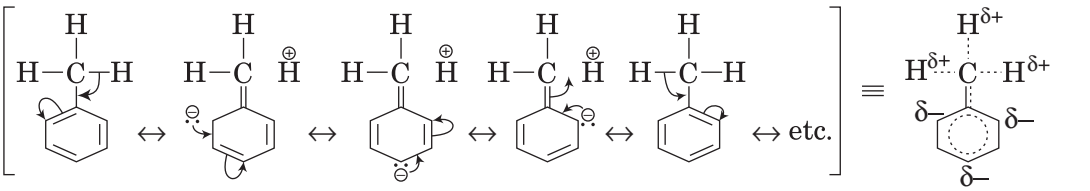


[It is to be noted that a *tert*-butyl ($-CMC_3$) group in less activated than a $-CH_3$ group as it cannot release electrons by hyperconjugation.]

The orienting effect of the methyl group may be explained in terms of relative stabilities of the σ-complexes leading to different substitution products.

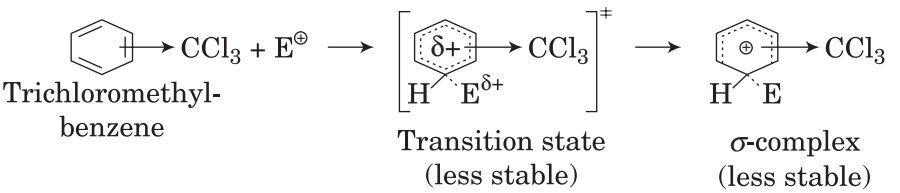


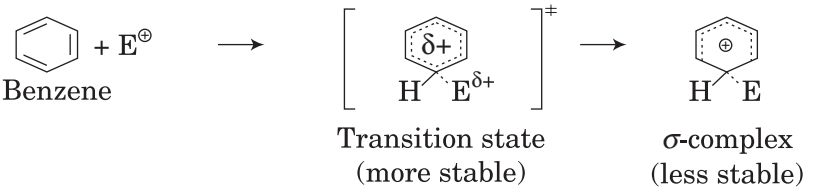
Each of the *ortho*- and *para*-σ-complexes contains one extra stable structure (3 and 8) which is a tertiary carbocation and in which the methyl group stabilizes the adjacent positive charge by its +I and hyperconjugative effects. The *meta* σ-complex contains no such stable structure. Because of this, the *ortho*- and *para*-σ-complexes and the transition states leading to them are more stable than the *meta*-σ-complex and the transition state leading to it. As a result, the *ortho*- and *para*-substituted products are formed readily and predominantly. Orientation of the incoming electrophile is normally a consequence of kinetic control of the product formation. The directive influence of the $-CH_3$ group may also be explained on the basis of the charge distribution in the substrate toluene. The $-CH_3$ group by its hyperconjugative effect makes the *ortho*- and *para*-positions more electron rich and because of this, the incoming electrophile undergoes nucleophilic attack by the carbons of these positions readily to yield the *ortho*- and *para*-substituted products predominantly.



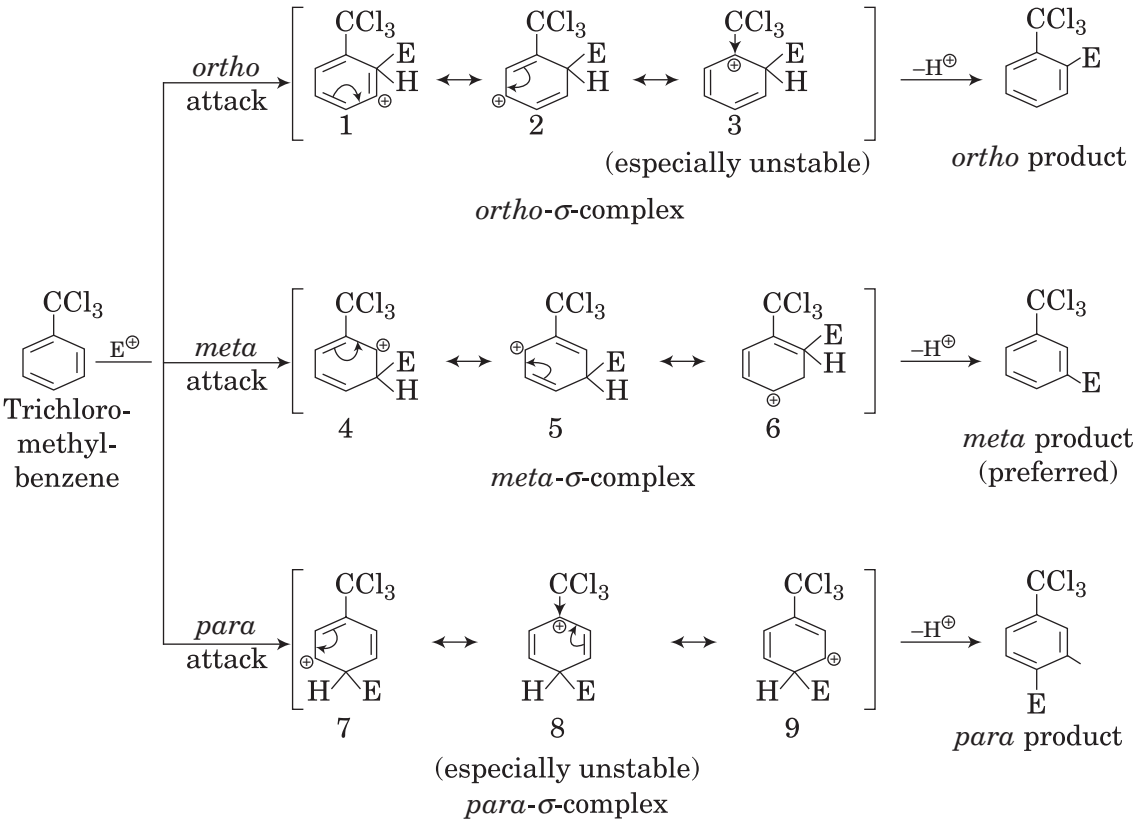
Hyperconjugation in toluene (3 hyperconjugable H′s) Hybrid structure

(ii) **The trichloromethyl group ($-CCl_3$) in trichloromethylbenzene:** The $-CCl_3$ group in $C_6H_5CCl_3$ withdraws electrons from the ring by the inductive (–I) and hyperconjugative effects and destabilizes the intermediate σ-complex and the transition state leading to it. Because of this, trichloromethylbenzene undergoes electrophilic substitution at a rate much slower than the corresponding reaction of benzene. Therefore, the $-CCl_3$ group is a strong deactivating group.



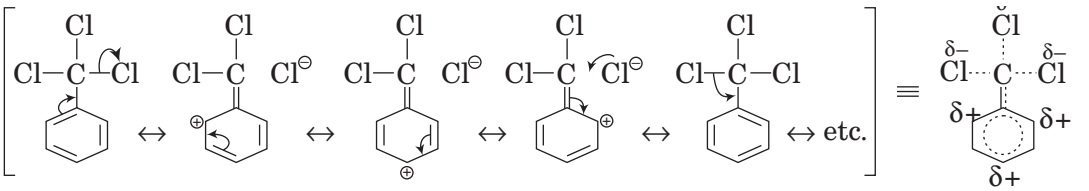


The orienting effect of the trichloromethyl group (–CCl_3) may be explaining in terms of relative stabilities of the σ-complexes leading to different substitution products.



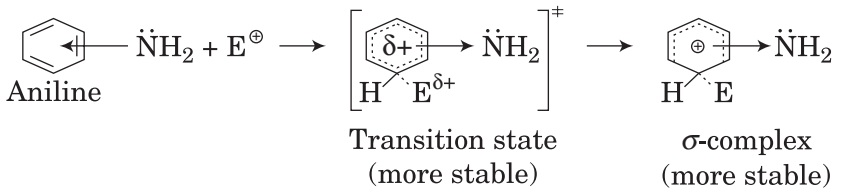
Each of the *ortho*- and *para*-σ-complexes contains a very unstable structure (3 and 8) in which the positive charge is located on the ring carbon that bears the electron-withdrawing –CCl_3 group. The *meta*-σ-complex contains no such unstable structure. Because of this, the *ortho*- and *para*-σ-complexes and the transition states leading to them are less stable than the *meta*-σ-complex and the transition state leading to it. As a consequence, the *meta*-substituted product is formed readily and predominantly. However, it is to be noted that *meta*-substitution is favoured only in the sense that it is the least unfavourable of the three unfavourable pathways.

The orienting effect may also be explained on the basis of the charge distribution on the substrate. The –CCl_3 group by its hyperconjugative effect makes the *ortho*- and *para*-positions electron deficient and as a result, the incoming electrophile attacks the *meta* carbon to yield the *meta*-substituted product predominantly.

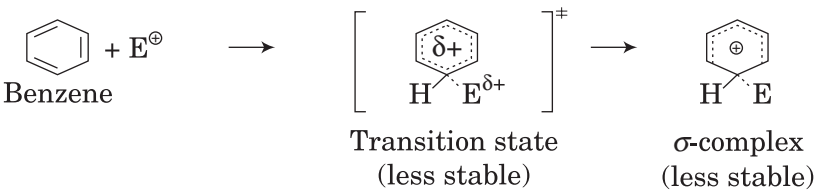


Hyperconjugation in trichloromethylbenzene Hybrid structure

(iii) **The amino ($-NH_2$) group in aniline:** Since nitrogen is more electronegative than carbon, the $-NH_2$ group withdraws electrons from the ring inductively. However, such electron withdrawal is not significant because the difference between the electronegativities of nitrogen and carbon in aniline is not large (the carbon of the benzene ring is sp^2 hybridized and so it is somewhat more electronegative than it would be if it were sp^3 hybridized). Again, the $-NH_2$ group donates electrons by +R effect (using nonbonding electron pair on nitrogen) and since the much stronger resonance effect greatly outweighs the inductive effect (i.e., +R > –I), the $-NH_2$ group by its net electron-release stabilizes the σ-complex and the transition state leading to it. Because of this aniline undergoes electrophilic aromatic substitution at a rate faster than the corresponding reaction of benzene. Therefore, the amino group ($-NH_2$) is a strong activating group.

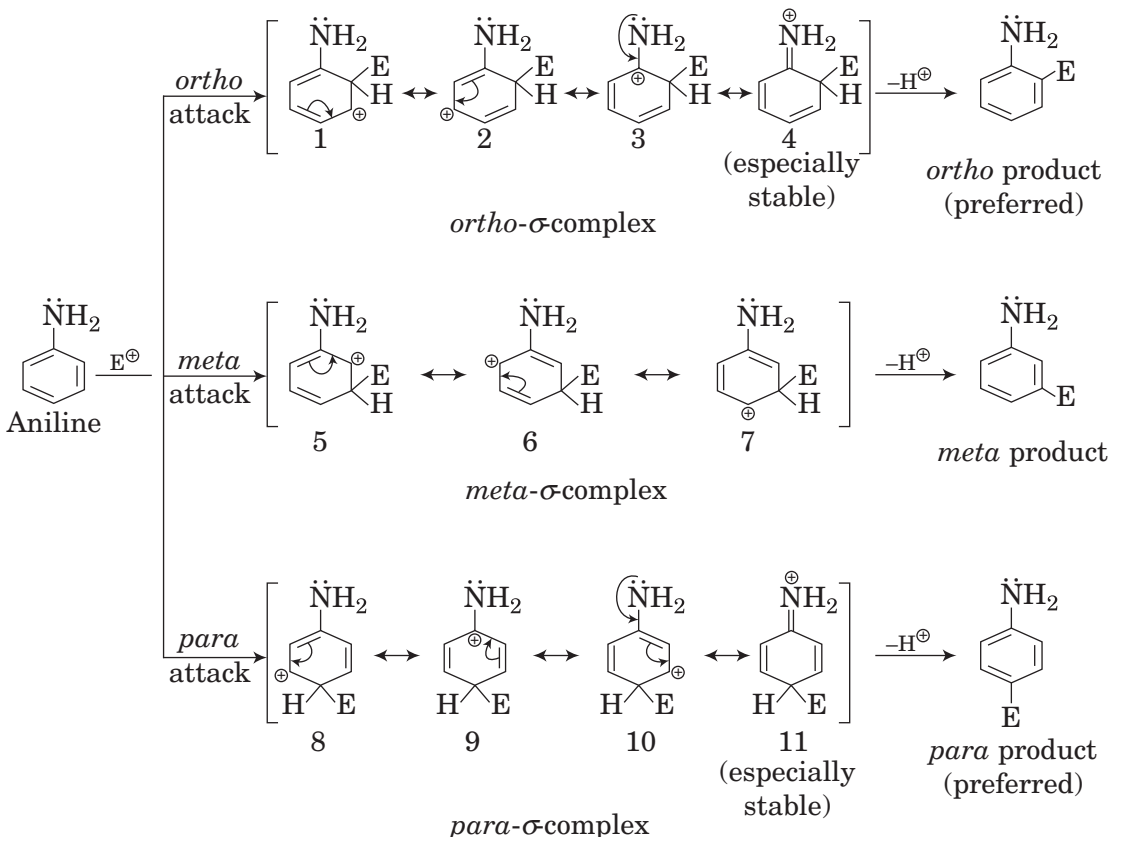


Aniline Transition state (more stable) σ-complex (more stable)



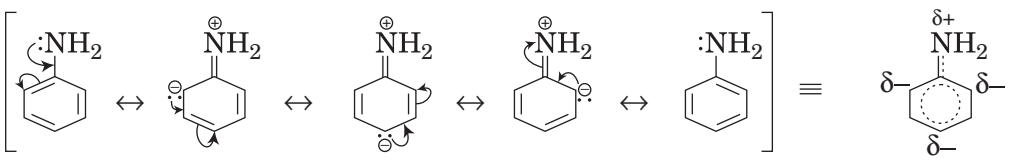
Benzene Transition state (less stable) σ-complex (less stable)

The orienting effect of the amino group may be explained in terms of relative stabilities of the σ-complexes leading to different substitution products.

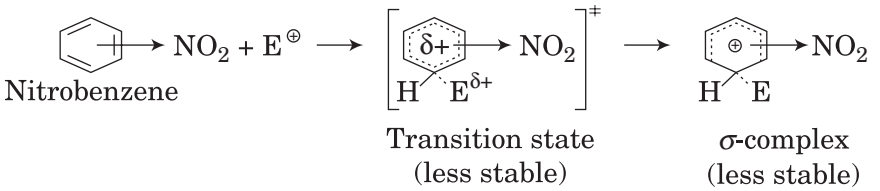


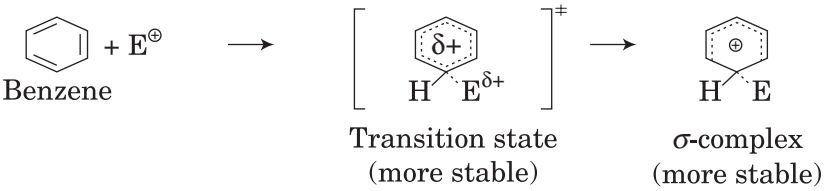
Each of the *ortho*- and *para*-σ-complexes contains one extra-stable resonance structure (4 and 11) in which all the atoms have their octet filled up and also, there is an additional covalent bond (between nitrogen and carbon). The *meta*-σ-complex contains no such stable structures. Because of this, the *ortho*- and *para*-σ-complexes and the transition states leading to them are much more stable than the *meta*-σ-complex and the transition state leading to it. As a consequence, the *ortho*- and *para*-substituted products are formed readily and predominantly.

The orienting effect may also be explained on the basis of the charge distribution in the substrate. The $-NH_2$ group by its +R effect makes the *ortho*- and *para*-positions more electron rich and so, the incoming electrophile attacks these carbons to give the *ortho* and *para*-substituted products predominantly.

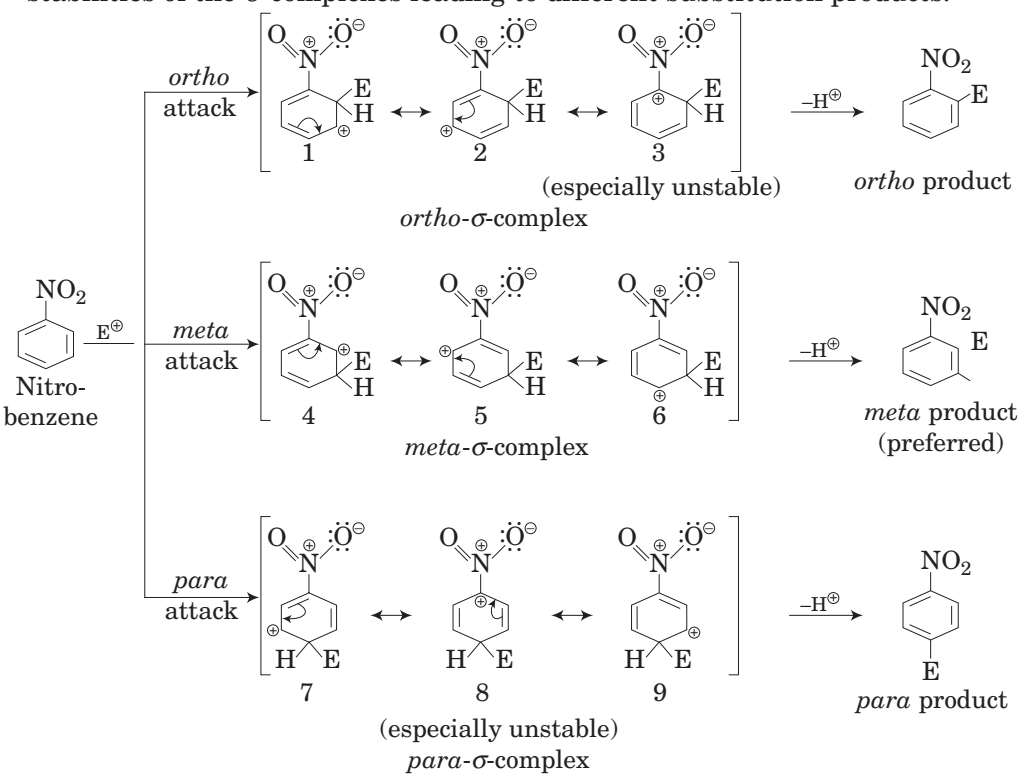


(iv) **The nitro ($-NO_2$) group in nitrobenzene:** The nitro group in nitrobenzene withdraws electrons from the ring through –I and –R effects and destabilizes the intermediate σ-complex and the transition state leading to it. Because of this, nitrobenzene undergoes electrophilic substitution reaction at a rate much slower than the corresponding reaction of benzene. Therefore, the $-NO_2$ group is a strong deactivating group.



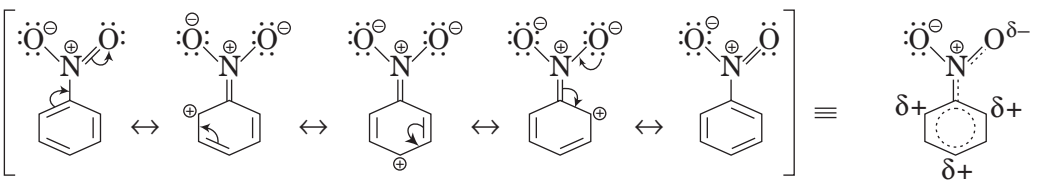


The orienting effect of the nitro group may be explained in terms of relative stabilities of the σ-complexes leading to different substitution products.



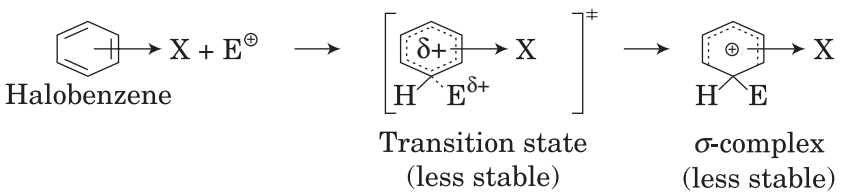
Each of the *ortho*- and *para*-σ-complexes contains one particularly unstable resonance structure (3 and 8) carrying positive charges on adjacent atoms. Since like charges repel, this close proximity of two positive charges is especially unstable. The *meta*-σ-complex contains no such unstable structure. Because of this, the *ortho*- and *para*-σ-complexes and the transition state leading to them are less stable than the *meta*-σ-complex and the transition state leading to it. As a consequence, the *meta*-substituted product is formed readily and predominantly. However, if it is to be noted that *meta* substitution is favoured only in the sense that it is least unfavourable of the three unfavourable pathways.

The nature of orientation may also be explained on the basis of the charge distribution in the substrate. The $-NO_2$ group by its –I effect withdraws electrons from all positions and by its –R effect it withdraws electrons from the *ortho* and *para* positions only. Thus, the *ortho*- and *para*-positions become relatively more electron deficient than the *meta*-position and as a result, the incoming electrophile undergoes attack by the *meta*-carbon readily to give the *meta*-substituted product predominantly.

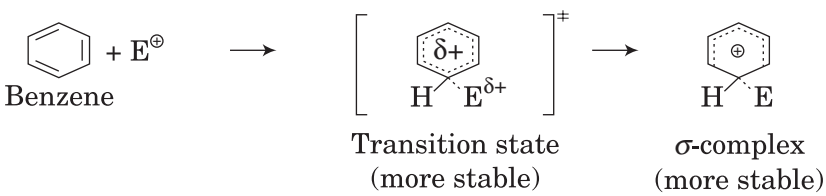


Resonance in nitrobenzene Hybrid structure

(v) **The halogen atom in halobenzene:** In halobenzenes, the halogen substituents (–X) withdraw electrons from the ring by their –I effect and releases electrons by their +R effect. Since –I effect is stronger than +R effect, therefore, halogens by their net electron-withdrawal destabilizes the positively charged σ-complex and the transition state leading to it. Because of this, halobenzenes undergo electrophilic substitution reaction at a rate slower than the corresponding reaction of benzene. Therefore, halogens are ring deactivators.

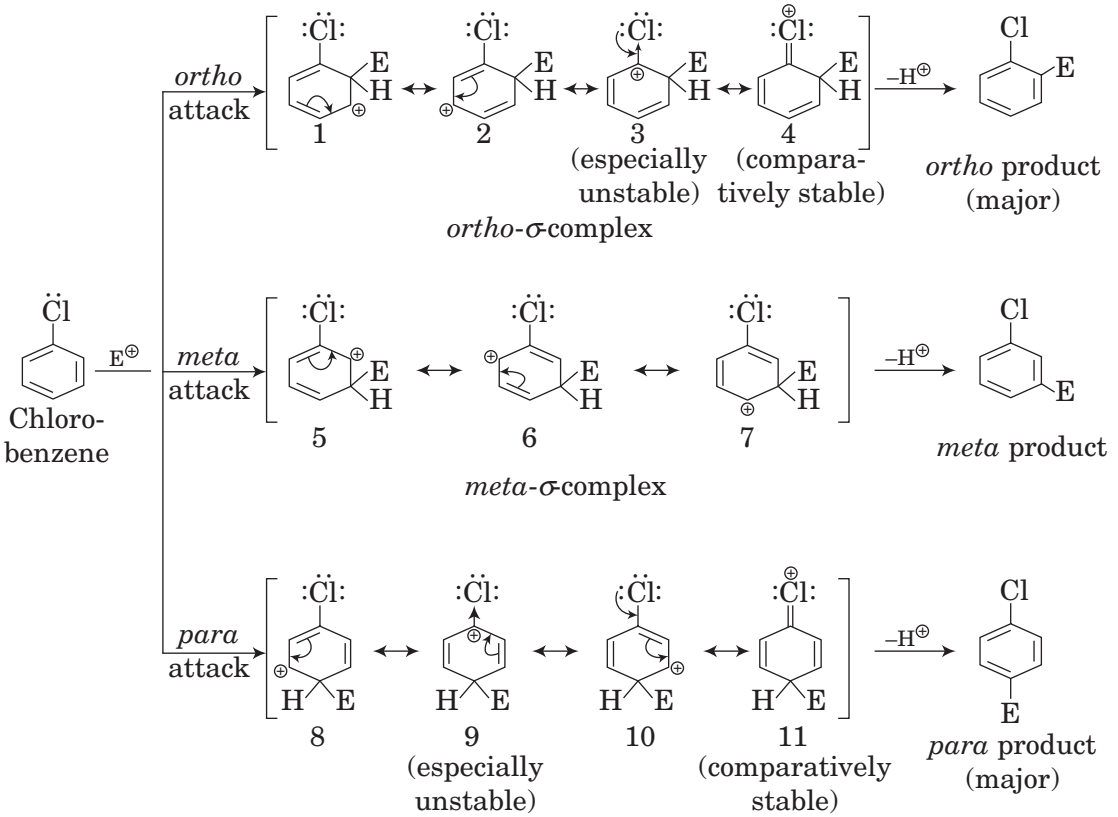


Halobenzene Transition state (less stable) σ-complex (less stable)



Benzene Transition state (more stable) σ-complex (more stable)

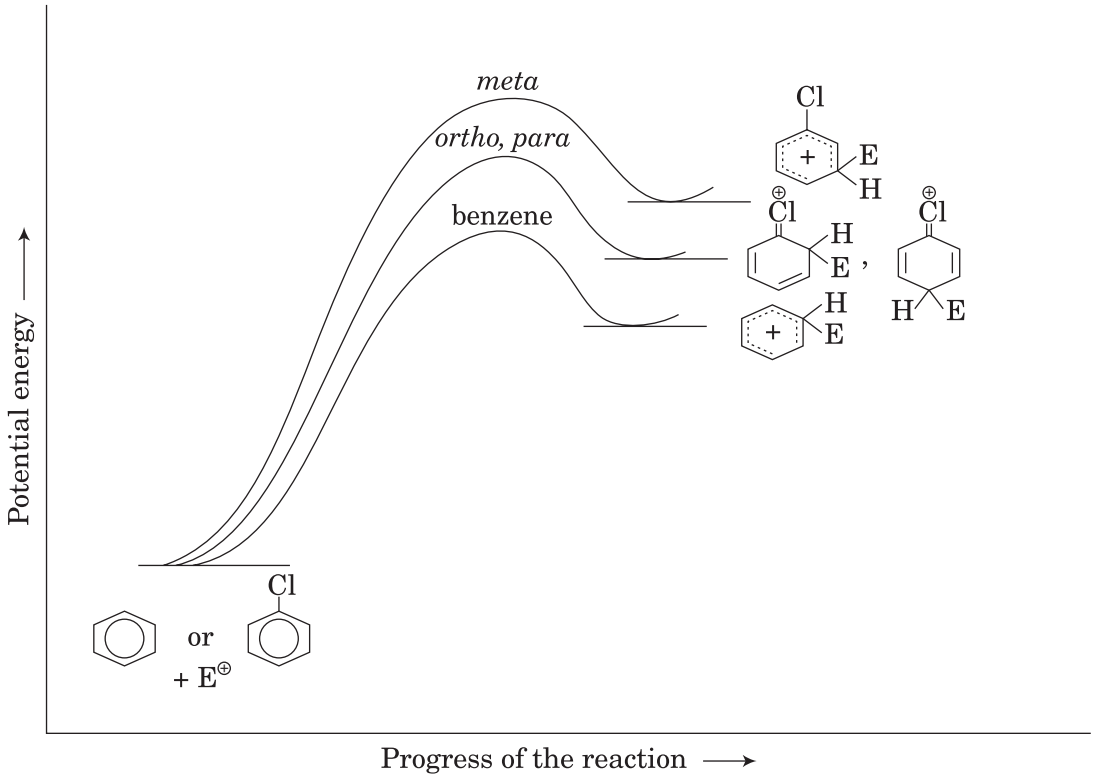
The orienting effect of $-\ddot{\underset{\cdot\cdot}{X}}:$, for example, $-\ddot{Cl}:$ may be explained in terms of relative stabilities of the σ-complexes leading to different substitution products.



Each of the *ortho*- and *para*-σ-complexes contains one unstable resonance structure in which charge is located on the ring carbon that bears the electron-withdrawing Cl atom (structure 3 and 9). Again, each of these σ-complexes contains one relatively stable structure where all the atoms have a complete octet of electrons (structures IV and XI). The destabilization caused by a former structure and stabilization caused by a latter structure result in a net stabilization of the *ortho*- and *para*-σ-complexes relative to the *meta*-σ-complex which contains no comparatively stable structure in which every atom has a complete outer octet of electrons. Therefore, the halo substituent causes the free energies of activation leading to *ortho*- and *para*-substitution to be lower than the free energy of activation leading to *meta*-substitution. Because of this, the *ortho*- and *para*-substitution products are formed rapidly and predominantly. Therefore, a halo substituent is an *ortho*, *para*-director. In fact, a halo substituent withdraws electrons from all the positions inductively, i.e., it deactivates all the positions. However, by resonance effect it donates electrons to *ortho*- and *para*-positions, i.e., it makes the deactivation less for the *ortho*- and *para*-positions than for the *meta*-position. The result is the predominant

formation of *ortho*- and *para*-substitution products. Reactivity is thus controlled by the stronger electron-withdrawing inductive effect, while orientation is controlled by weaker but more selective electron-donating resonance effect.

The energy diagram which compares energies of the transition states and intermediates for electrophilic attack on chlorobenzene and benzene is as follows:



3.1.1.7 Partial rate factor

Partial rate factor is a quantitative term which measures the magnitude of reactivity at any position in a benzene derivative in comparison with that at a single position in benzene. For a particular reaction, it can be calculated by the following formula:

$$\text{PRF} = \frac{(\text{Percent } o/m/p)}{100} \times \frac{(\text{Number of benzene positions})}{(\text{Number of } o/m/p \text{ positions})} \times \frac{(\text{Substrate reactivity})}{(\text{Benzene reactivity})}$$

Let us think $k_{C_6H_5R}$ as the rate constant for the overall rate of the molecule C_6H_5R. This is equal to the total rate constants at the *ortho*, *meta* and *para* positions:

$$k_{C_6H_5R} = 2k_{o\text{-R}} + 2k_{m\text{-R}} + k_{p\text{-R}}$$

The factor 2 is included because there are two *ortho* and two *meta* positions in a monosubstituted benzene. Similarly, the rate constant for benzene $(k_{C_6H_6})$ is six times the

rate constant for substitution at one position, i.e., k_H and this because all the six positions are equivalent.

$$k_{C_6H_6} = 6k_H$$

or
$$k_H = \frac{k_{C_6H_6}}{6} \quad (1)$$

The percentage in which the three isomers are formed can be calculated as follows:

$$\text{Percent } ortho = \frac{2k_{o-R}}{k_{C_6H_5R}} \times 100 \quad (2)$$

$$\text{Percent } meta = \frac{2k_{m-R}}{k_{C_6H_5R}} \times 100 \quad (3)$$

$$\text{Percent } para = \frac{k_{p-R}}{k_{C_6H_5R}} \times 100 \quad (4)$$

Now, according to the definition of partial rate factors, these can be expressed as follows:

$$o_f^R = \frac{k_{o-R}}{k_H},\ m_f^R = \frac{k_{m-R}}{k_H} \text{ and } p_f^R = \frac{k_{p-R}}{k_H}$$

Equation (2) can be rearranged to obtain:

$$k_{o-R} = \frac{k_{C_6H_5R}}{2} \times \frac{\text{Percent } ortho}{100}$$

This equation is divided by equation (1)

$$o_f^R = \frac{k_{o-R}}{k_H} = \frac{6}{2} \times \frac{k_{C_6H_5R}}{k_{C_6H_6}} \times \frac{\text{Percent } ortho}{100} \quad (5)$$

Similar equations can be written for the *meta* and *para* positions:

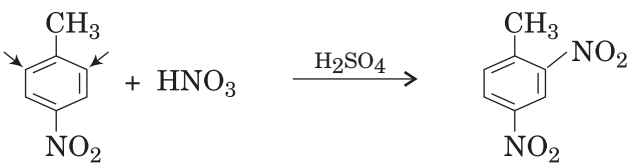
$$m_f^R = \frac{k_{m-R}}{k_H} = \frac{6}{2} \times \frac{k_{C_6H_5R}}{k_{C_6H_6}} \times \frac{\text{Percent } meta}{100} \quad (6)$$

$$p_f^R = \frac{k_{p-R}}{k_H} = 6 \times \frac{k_{C_6H_5R}}{k_{C_6H_6}} \times \frac{\text{Percent } para}{100} \quad (7)$$

3.1.1.8 Rules for predicting orientation in disubstituted benzenes

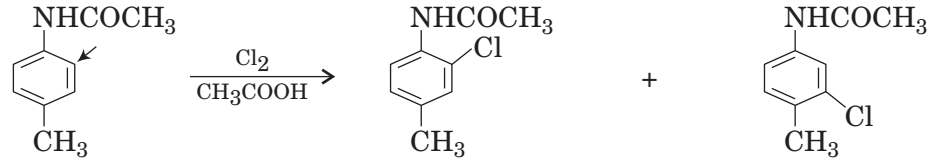
The rules for predicting orientation in disubstituted benzenes are as follows:

1. If both the groups direct to the same position on the ring, the orientation can be inferred from either group. For example:



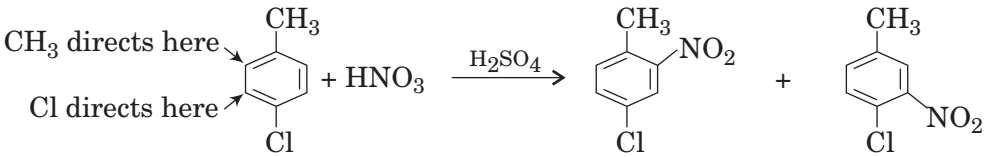
p-Nitrotoluene 2,4-Dinitrotoluene

2. If two groups direct to different positions, a strongly activating group will win out over a weakly activating group or a deactivating group. The amide group, for example, is a much stronger activating group than the methyl group. The following example shows that the amide group determines the outcome of the reaction.



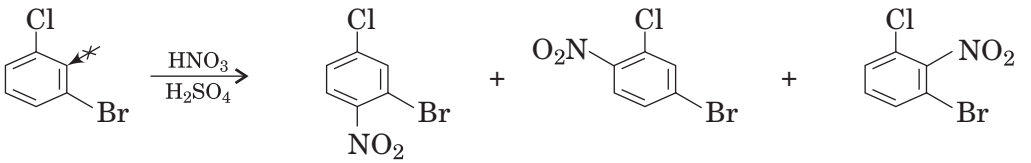
p-Methylacetanilide | 2-Chloro-4-methyl-acetanilide (major product) | 3-Chloro-4-methyl-acetanilide (minor product)

3. If two groups have similar activating properties, neither will dominate and a mixture of products will be obtained. For example:



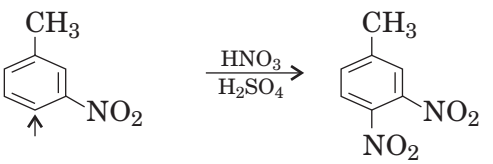
p-Chlorotoluene | 4-Chloro-2-nitrotoluene | 4-Chloro-3-nitrotoluene

4. Very little substitution occurs in the sterically hindered position between *meta* substituents. For example:



m-Bromochlorobenzene | 1-Bromo-5-chloro-2-nitrobenzene (62%) | 1-Bromo-3-chloro-4-nitrobenzene (37%) | 1-Bromo-3-chloro-2-ntirobenzene (1%)

5. If *ortho*, *para*-directing and *meta*-directing groups are not reinforcing, the *ortho*, *para*-directing controls the orientation. The incoming group goes mainly *ortho* to the *meta*-director.
For example:

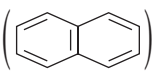


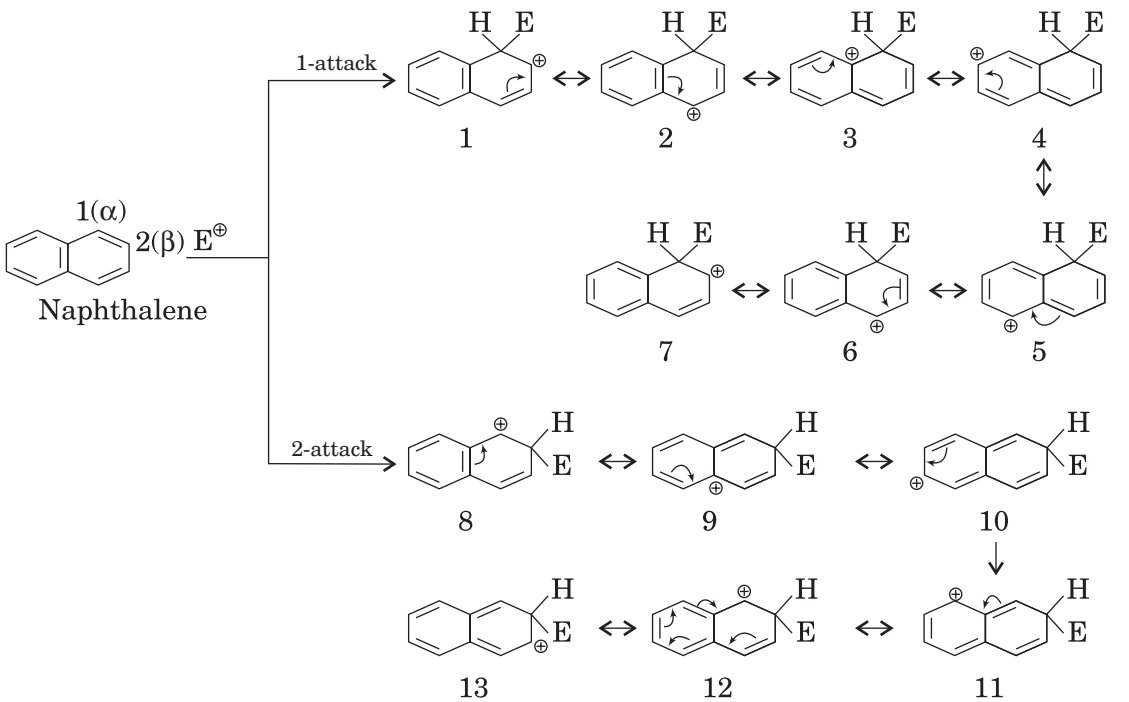
3,4-Dinitroluene (major product)

3.1.1.9 Representative electrophilic aromatic substitution reactions of benzene

The representative electrophilic aromatic substitution reactions of benzene are (i) **nitration** (one ring hydrogen is replaced by an $-NO_2$ group), (ii) **sulphonation** (one ring hydrogen is replaced by a $-SO_3H$ group), (iii) **halogenation** (one ring hydrogen is replaced by a halogen atom), (iv) **Friedel-Craft alkylation** (one ring hydrogen is replaced by an alkyl group) and (v) **Friedel-Craft acylation** (one ring hydrogen is replaced by an acyl group).

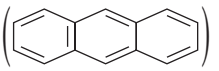
3.1.1.10 Electrophilic substitution reactions of polynuclear aromatic hydrocarbons

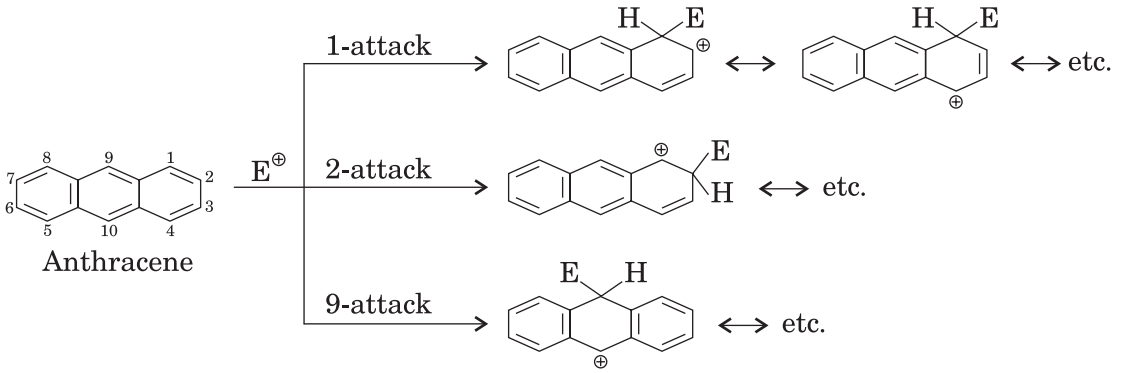
(a) Naphthalene  Naphthalene has two nonequivalent positions (1 and 2). The electrophilic substitution in naphthalene occurs preferentially at 1-position. This can be explained in terms of relative stabilities of the σ-complexes leading to different substitution products. The resonance structures of the σ-complexes for 1- and 2-attack may be written as follows:



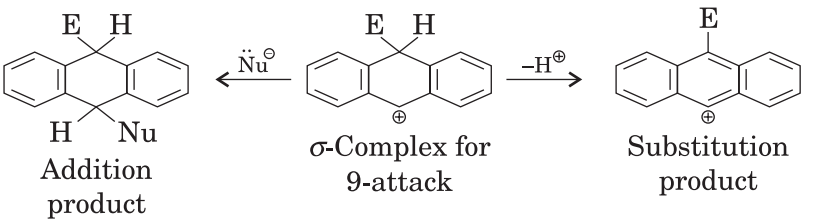
The σ-complex resonance hybrid for 1-attack contains seven contributing resonance structures of which four have unchanged benzene ring (1, 2, 6 and 7), whereas the σ-complex resonance hybrid for 2-attack contains six resonance structures of which only two have benzene rings (8 and 12). Since the canonical structures with benzene rings are relatively more stable than those without benzene ring, the σ-complex for 1-attack

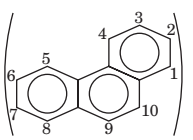
is more stable than for 2-attack. Furthermore, the σ-complex for 1-attack contains one more resonance structure which also increases its stability to some extent. Consequently, electrophilic substitution on naphthalene occurs predominantly at 1-position.

(b) Anthracene  Anthracene has three nonequivalent positions (1, 2, 9 or 10). When anthracene is allowed to undergo electrophilic attack, it gives preferably 9- or 9, 10-disubstituted product or 9, 10-addition product. The cause of preferential substitution or addition at 9, 10-positions can be easily understood from a survey of stabilities of the σ-complexes for attack at 1-, 2- and 9-positions (only these positions are non equivalent).



The intermediate σ-complex obtained by the attack at 1- or 2-positions contains a naphthalene moiety, whereas the intermediate obtained by the attack at 9-position contains two benzene rings. Since the resonance energy of two benzene rings (2 × 36 = 72 kcal/mol) exceeds that of one naphthalene moiety (61 kcal/mol), therefore, the σ-complex for the 9-attack is most stable among the three. The reaction, therefore, proceeds preferably through this most stable σ-complex which loses a proton to give the 9-substituted product or adds a nucleophile to give the 9, 10-addition product.



(c) Phenanthrene  The cause of preferential substitution at 9-position or addition at 9, 10-positions can be easily understood from a survey of stabilities of the σ-complexes for attack at 1-, 2-, 3-, 4-, and 9-positions (only these positions are non-equivalent). The attack at 1-, 2-, 3-, or 4-position leads to an intermediate σ-complex that contains a naphthalene moiety, whereas the attack at 9-position gives an intermediate in which two benzene rings are retained.

3.1.1.11 Reversibility of ArS_E2 reaction

Although most of the ArS_E2 reactions are irreversible and the products are controlled kinetically (formation of the product is guided by the substrate reactivity), sulphonation and iodinations are exceptions.

SOLVED PROBLEMS

1. Based on its structure and properties, what kind of reactions should benzene undergo?

Solution Benzene contains six π electrons delocalized in six *p* orbitals that overlap above and below the plane of the ring. Due to the presence of these loosely held π electrons, the benzene ring is electron rich, and so it reacts with electrophiles. Since benzene's six π electrons satisfy Huckel's rule, the molecule is aromatic and especially stable. Reactions that keep the aromatic ring intact are therefore favoured. Therefore, benzene should undergo electrophilic aromatic substitution — a hydrogen atom is replaced by an electrophile.

2. How does electrophilic aromatic substitution differ from S_N1 and S_N2 reactions or free radical substitution?

Solution In S_N1 and S_N2 reactions, the attacking group is a nucleophile or Lewis base and the group displaced is a weaker base. In a free radical substitution, the attacking species R• removes an H•. However, in electrophilic aromatic substitution, an $H^{\oplus}$ is replaced by an electrophile $E^{\oplus}$, preserving the aromatic system.

3. (a) Which one is the rate-determining step of the electrophilic aromatic substitution and why?
(b) Explain why the second step of the reaction is fast.
(c) Describe the orbital hybridization of the C's in the arenium ion intermediate.
(d) Comment on the thermochemical nature of the steps involved in the reaction.

Solution

(a) The formation of the intermediate arenium ion (Step 1) is the slow and rate-determining step of the reaction because the aromaticity of the benzene ring is lost in this step.

(b) The second step of the reaction is fast because the aromaticity of the benzene is restored.

(c) In the arenium ion, the carbon that bears the electrophile is sp^3 hybridized. The other five C's are sp^2 hybridized.

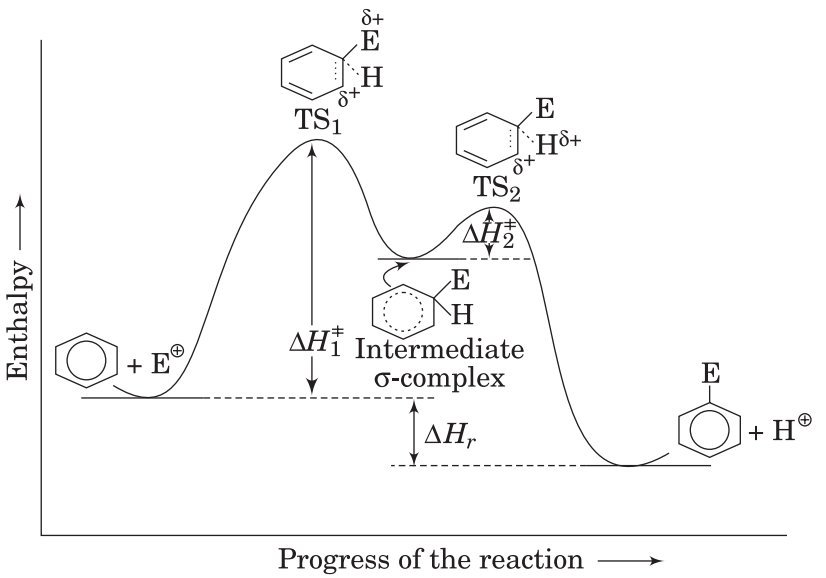
(d) The first step of the reaction, i.e., the reaction leading from benzene and an electrophile to the arenium ion is highly endothermic, because the aromatic stability of the benzene ring is lost. The second step of the reaction, i.e., the reaction leading from the arenium ion to the substituted benzene, by contrast, is highly exothermic because it restores aromaticity to the system.

4. (a) Draw an enthalpy diagram for the reaction: PhH + $E^{\oplus}$ → PhE + $H^{\oplus}$, indicating the intermediate, the transition states for the two steps, relative energies of activation for the two steps, and the heat of reaction ΔH_r.

(b) Why are most aromatic substitution reactions irreversible?

Solution

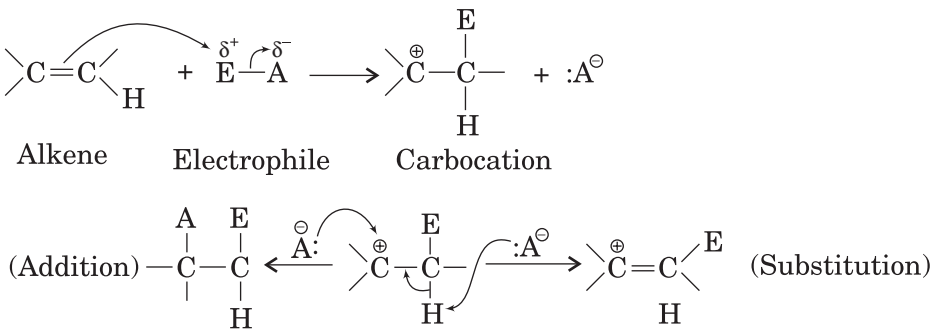
(a) The enthalpy diagram for the reaction:
PhH + $E^{\oplus}$ → PhE + $H^{\oplus}$ is as follows:



(b) The energy barrier $\Delta H_2^{\ddagger}$ for the reaction of the sigma complex to form products is less than $\Delta H^{\ddagger}$ for the reverse rejection of $E^{\oplus}$. It is for this reason most aromatic substitution reactions are irreversible.

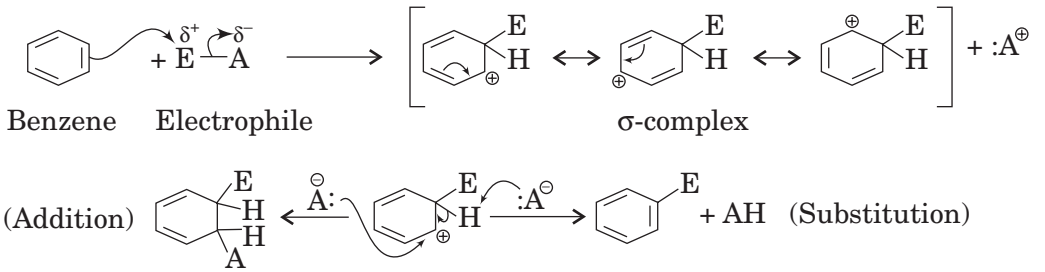
5. Explain why alkenes usually undergo electrophilic addition reactions while benzenes usually undergo electrophilic substitution reactions.

Solution When the pair of electrons of an alkene is transferred to an electrophile, a carbocation intermediate is obtained. The carbocation may react further in two ways. It may add a nucleophile to accomplish addition across the double bond or it may lose an atom or group to accomplish substitution. The sequence of addition is thermodynamically more favourable (exothermic) than the sequence of substitution and for this reason, the alkenes usually undergo electrophilic addition rather than substitution.



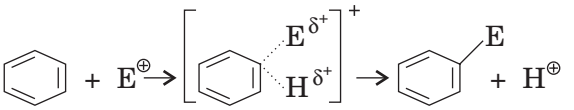
The addition of the electrophilic reactant $\overset{\delta+}{E}-\overset{\delta-}{A}$ to the double bond is exothermic because the energy consumed by breaking of the E–A and π bonds is almost always less than that liberated by formation of the C–E and C–A bonds.

An electrophile adds to the benzene ring to form a resonance-stabilized nonaromatic carbocation known as an arenium ion or σ-complex. The σ complex may react further in two ways. It may add a nucleophile to give the product of overall addition or it may lose a proton to give the product of substitution. The addition product is nonaromatic and is far less stable than the starting aromatic compound. The substitution product, on the other hand, is aromatic and usually somewhat more stable than starting benzene. The sequence of substitution is, therefore, thermodynamically more favourable than the sequence of addition and for this reason, benzenes usually undergo electrophilic substitution rather than addition.



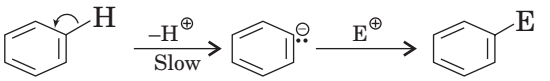
6. Provide evidence in favour of the fact that the electrophilic aromatic substitution reactions take place not by a concerted mechanism (arrival and departure of the electrophiles are simultaneous, i.e., the C–E bond formation and the C–H bond breaking are simultaneous) or by a stepwise S_E1 mechanism (the hydrogen ion departs before the arrival of the electrophile and the C–H bond is broken in the rate-determining step) but by the stepwise arenium ion mechanism (ArS_E2) in which the C–H bond is not broken in the rate-determining first step.

Concerted mechanism:



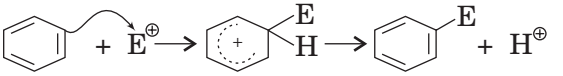
T.S.

Stepwise (S_E1) mechanism:



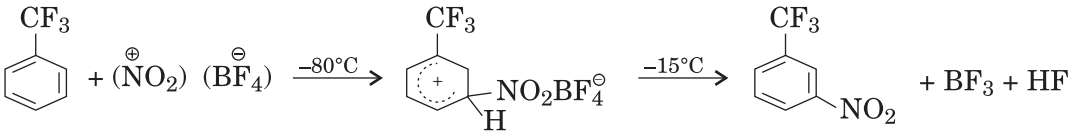
Carbanion intermediate

Stepwise (ArS_E2) mechanism:



σ-complex

Solution In a large number of cases, the arenium ion or σ complex intermediates have been detected and in some cases they have been isolated as salts. For example, when trifluoromethylbenzene is treated with nitronium tetrafluoroborate at –80°C, a σ complex is obtained which is isolated as a coloured solid. The σ-complex results in formation of the nitro compound when the temperature is allowed to rise to –15°C.



σ-complex salt
(isolated as coloured solid)

The isolation of arenium ion or σ complex intermediates, therefore, suggest that the electrophilic aromatic substitution reactions proceed not by a concerted or stepwise S_E1 mechanism but by a stepwise ArS_E2 mechanism.

Again, electrophilic aromatic substitution reactions, in general, do not exhibit primary kinetic isotope effect. For example, nitration (an electrophilic aromatic substitution of benzene (C_6H_6) and hexadeuterobenzene (C_6D_6)) were found to take place at almost equal rate.

$$C_6H_6 \xrightarrow[50\text{–}60^\circ C]{\text{conc. } HNO_3 + \text{conc. } H_2SO_4} C_6H_5NO_2; \quad C_6D_6 \xrightarrow[50\text{–}60^\circ C]{\text{conc. } HNO_3 + \text{conc. } H_2SO_4} C_6D_5NO_2$$

Benzene Hexadeuterobenzene

A C–D bond is stronger than a C–H bond. Therefore, a C–H bond breaks readily than a C–D bond. Then, if the rate-determining step of the reaction involves breaking of the C–H bond, hexadeuterobenzene is expected to undergo nitration at a slower rate than benzene. Since nitration occurs at nearly equal rate, the rate-determining step does not involve breaking of the C–H bond. Hence, the reaction does not operate by a concerted mechanism (a single-step process which is rate-determining) or by a stepwise S_E1 mechanism (C–H bond breaking is rate-determining). A stepwise ArS_E2 mechanism actually operates and

the breaking of the C–H bond, i.e., the second step, is not the rate-determining one. The first step, i.e., the C–E bond formation step is actually the rate-determining step of this two-step process.

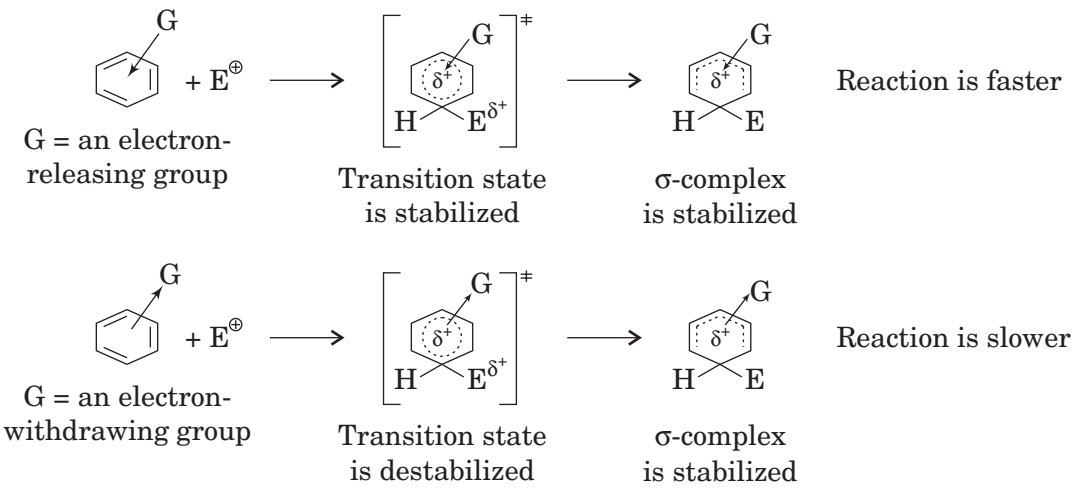
7. (a) How does a ring substituent regulate the rate of electrophilic aromatic substitution?

(b) Explain why there should be a strong resemblance between the arenium ion itself and the transition state leading to it.

(c) Draw a figure that shows the electron-withdrawing and electron-releasing abilities of substituents affect the relative energies of activation or transition state of electrophilic aromatic substitution reactions.

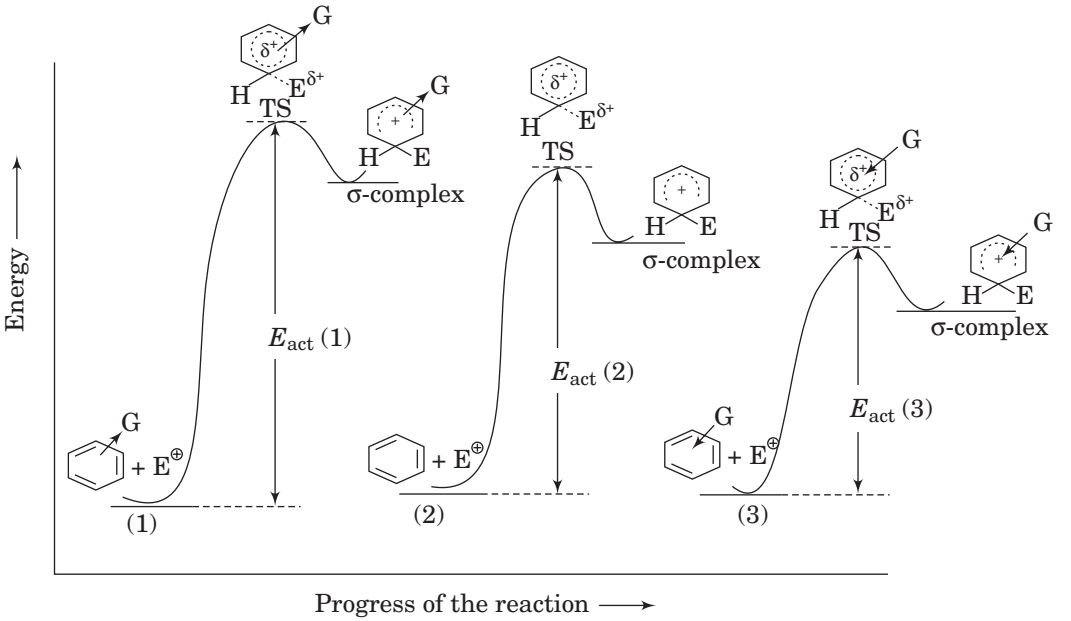
Solution

(a) The rate of an electrophilic aromatic substitution reaction depends on the energy of activation of the rate-determining step, i.e., it depends on the stability of the transition state involved in that step. Any factor that increases the energy of the transition state relative to that of the reactants decreases the relative rate of the reaction. It does this because it increases the energy of activation of the reaction. In the same way, any factor that decreases the energy of the transition state relative to that of the reactants lowers the energy of activation and increases the relative rate of the reaction. Since it is difficult to assess the energy of the transition state directly, the energy of the arenium ion or the σ complex may be considered instead of the transition state as the former closely resembles the latter in energy and geometry (the Hammond-Leffler postulate). Therefore, a substituent that stabilizes a σ complex (a delocalized carbocation) by donating electrons (by +I, +R and hyperconjugative effects) will increase the rate of substitution by stabilizing the transition state and a substituent that destabilizes a σ-complex by withdrawing electrons (by –I, –R and hyperconjugative effects) will decrease the rate of substitution by destabilizing the transition state.



(b) The arenium ion or the σ complex is a high-energy intermediate, and the step that leads to it is a highly endothermic step. Thus, according to the Hammond-Leffler postulate, there should be a strong resemblance between the product (intermediate) arenium ions or σ complex itself and the transition state leading to it.

(c)



In the reaction (1), the electron-withdrawing group G raises the transition state energy. Because of this, the energy of activation barrier is the highest, and the reaction is the slowest. The reaction (2), with no substituent, serves as a reference for comparison. In the reaction (3), the electron-donating group G stabilizes the transition state. For this reason, the energy of activation barrier is the lowest, and the reaction is the fastest.

8. (a) How does a group that is already present in an aromatic ring influence the course of further substitution in the ring?
(b) What do you mean by activating and deactivating groups?
(c) What do you mean by *ortho*-, *para*- or *meta*-directing groups?
(d) Classify the groups in terms of their structure and electronic effects.
(e) How do the activating and deactivating effects account for the orientation of the entering $E^{\oplus}$?

Solution

(a) See **article no. 3.1.1.6.**
(b) See **article no. 3.1.1.6.**
(c) See **article no. 3.1.1.6.**
(d) There are three classes of groups:
(i) All activating groups direct the incoming electrophile ($E^{\oplus}$ to the *ortho* and *para* positions.

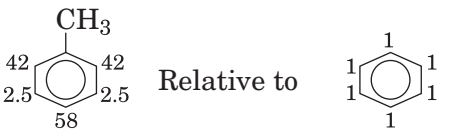
(ii) Most deactivating groups direct the incoming electrophile ($E^{\oplus}$) to the *meta* position.

(iii) A few deactivating groups (e.g., halogens, –CH=CHCO$_2$H, *etc.*) direct the incoming electrophile ($E^{\oplus}$) to the *ortho* and *para* positions.

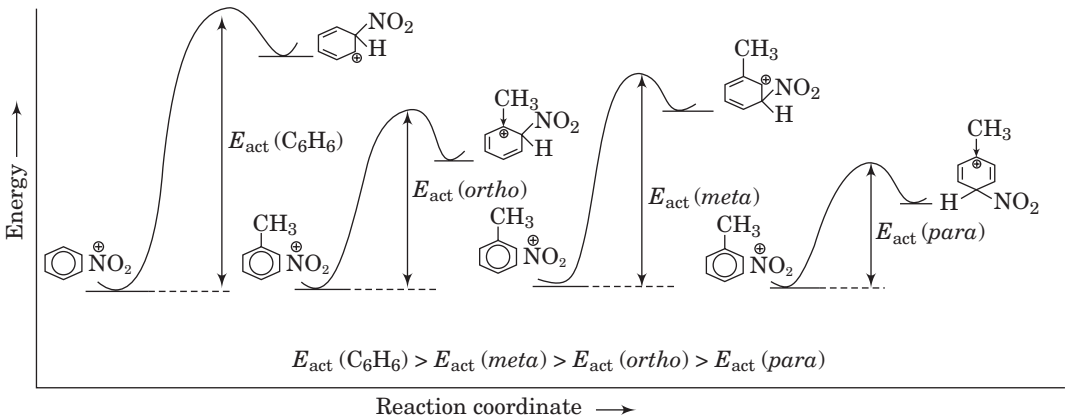
(e) Activating and deactivating effects are strongest at the *ortho* and *para* positions. Activating groups stabilize all σ-complexes, but *ortho* and *para* more than *meta*. Deactivating groups destabilize all σ complexes but *ortho* and *para* more than *meta*.

9. Give the relative rates of attack at the various positions in toluene compared with a single position in benzene and draw comparative energy diagrams for nitronium ion ($\overset{\oplus}{N}O_2$) attack (a) on benzene and at the (b) *ortho*, (c) *meta*, and (d) *para* positions of toluene.

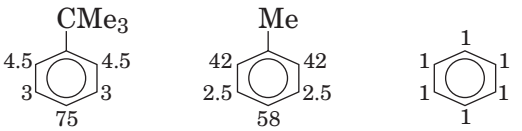
Solution The methyl group being an electron-releasing substituent activates all of the ring carbons of toluene towards electrophilic attack. However, the *ortho*- and *para* positions are activated more than the *meta* positions. The relative rates of attack at the various positions in toluene compared with a single position in benzene are as follows (for nitration at 25°C).



Comparative energy diagrams:



10. The rates of nitration (the substitution reaction in which the electrophile is $\overset{\oplus}{N}O_2$) relative to a single position of benzene at the various positions of *tert*-butylbenzene and toluene are as shown below:



(a) How reactive is *tert*-butylbenzene towards nitration compared with benzene?

(b) How reactive is toluene towards nitration compared with *tert*-butylbenzene.

(c) Predict the distribution among the various mononitration products of *tert*-butylbenzene.

Solution

(a) Benzene has six equivalent positions at which nitration can take place. Summing the individual relative rates of attack at each position in *tert*-butylbenzene and benzene, we get,

$$\frac{\textit{tert}\text{-Butylbenzene}}{\text{Benzene}} = \frac{2(4.5) + 2(3) + 75}{6(1)} = \frac{90}{6} = 15$$

Therefore, *tert*-butylbenzene undergoes nitration 15 times as fast as benzene, i.e., it is 15 times more reactive than benzene.

(b) Similarly, summing the individual relative rates of attack at each position in toluene and *tert*-butylbenzene, we get,

$$\frac{\text{Toluene}}{\textit{tert}\text{-Butylbenzene}} = \frac{2(42) + 2.5(2) + 58}{2(4.5) + 2(3) + 75} = \frac{147}{90} = 1.63$$

Therefore, toluene undergoes nitration 1.63 times as fast as *tert*-butylbenzene, i.e., it is 1.63 times more reactive than *tert*-butylbenzene.

(c) *Ortho* product = $\frac{100 \times 9}{90}$ = 10%; *Meta* product = $\frac{100 \times 6}{90}$ = 6.7%.

Para product = $\frac{100 \times 75}{90}$ = 83.3%

11. How can the *ortho*, *para* directive effect of the methyl group in toluene be proved experimentally?

Solution When toluene is nitrated with concentrated nitric and sulphuric acids, we get mononitrotoluenes in the following relative proportions:

$$\underset{\text{Toluene}}{C_6H_5CH_3} \xrightarrow[\overset{\oplus}{(NO_2)}]{HNO_3/H_2SO_4} \underset{\substack{o\text{-Nitrotoluene}\\(59\%)}}{o\text{-}CH_3C_6H_4NO_2} + \underset{\substack{m\text{-Nitrotoluene}\\(4\%)}}{m\text{-}CH_3C_6H_4NO_2} + \underset{\substack{p\text{-Nitrotoluene}\\(37\%)}}{p\text{-}CH_3C_6H_4NO_2}$$

If the methyl group had no inductive effect on the ring, we would expect to obtain the products in purely statistical amounts. Since there are two *ortho* H atoms, two *meta* H

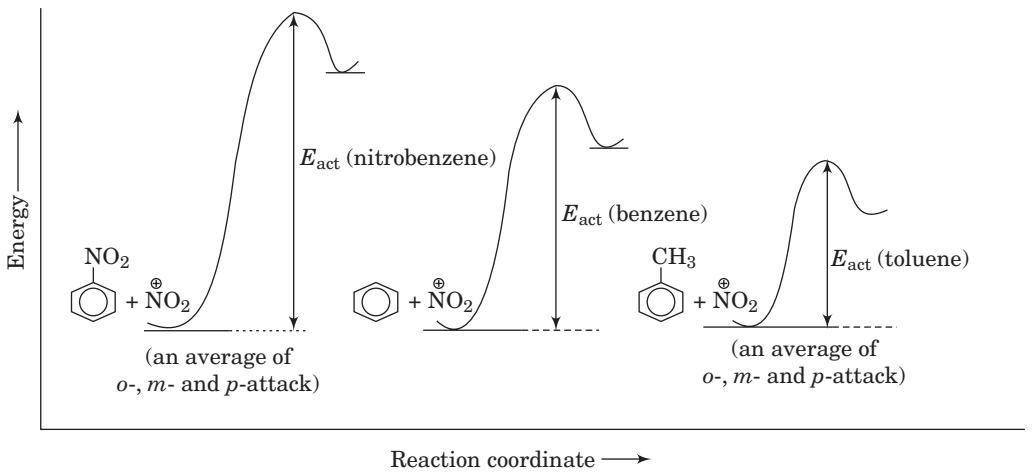
atoms and one *para* H atom, we would expect to get 40% *ortho*, 40% *meta*- and 20% *para*-products. Thus, we would expect that only 60% of the mixture of mononitrotoluenes would have the nitro group in the *ortho* or *para* position and 40% of the mixture would have the nitro group in the *meta* position. However, in actuality, we get 96% of combined *O*- and *p*-nitrotoluenes and only 4% *m*-nitrotoluene. This experimental observation, therefore, shows that the methyl group exerts an *ortho*, *para* directive effect.

12. Arrange benzene, nitrobenzene and toluene in order of decreasing rate of nitration and explain the order. Draw comparative energy diagrams for nitronium ion attack at benzene, nitrobenzene and toluene.

Solution The rates of nitration of benzene, nitrobenzene and toluene decrease in the order: toluene > benzene > nitrobenzene.

The methyl group in toluene increases the electron density of the ring by +I and hyperconjugative effects and thereby stabilizes the positively charged σ-complex and the transition state leading to it. As a result, the E_{act} of the reaction becomes lower than that of benzene. The nitro group in nitrobenzene withdraws electrons from the ring by –I and –R effects and thereby destabilizes the σ-complex and the transition state leading to it. As a result, the E_{act} of the reaction becomes higher than that of benzene. So, the order of E_{act} of the rate-determining step of nitration reaction is nitrobenzene > benzene > toluene. Therefore, the order of decreasing rate of nitration is toluene > benzene > nitrobenzene.

Comparative energy diagrams:



13. Explain the following observations:

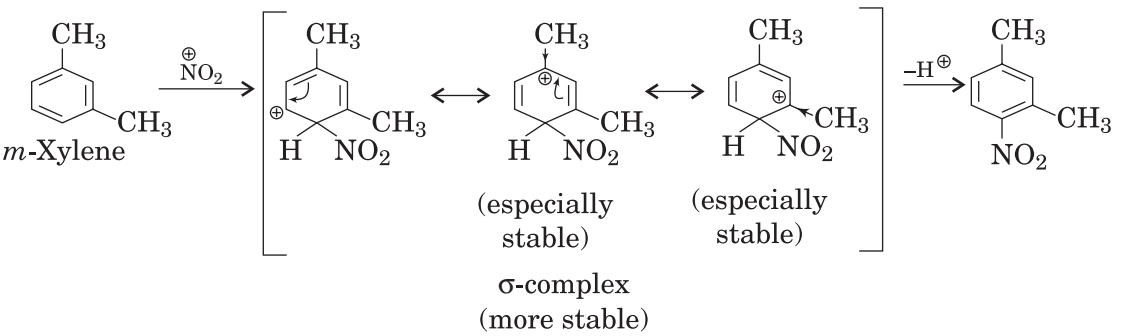
(a) *m*-Xylene undergoes nitration at a rate faster than *p*-Xylene.

(b) Although the $-NH_2$ group in aniline is *ortho*, *para*-directing, *m*-nitroaniline may be prepared by direct nitration of aniline in the presence of 98% H_2SO_4.

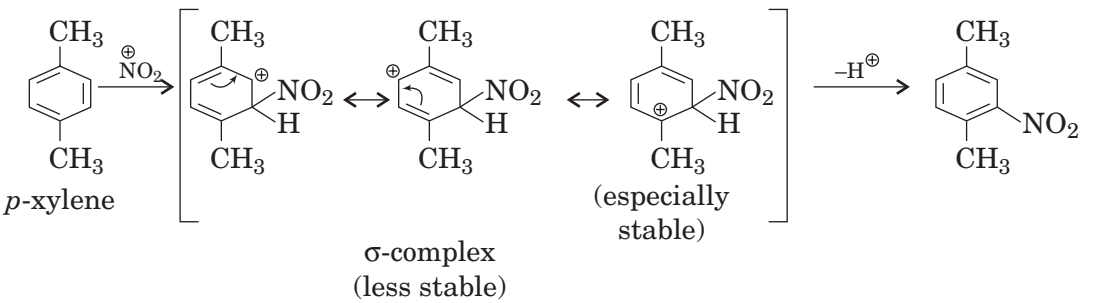
(c) Phenyl group is an *ortho*, *para*-directing.

Solution

(a) Since both the groups in *m*-xylene are *ortho*, *para*-directing methyl groups, therefore, electrophilic attack will take place at the position *ortho* to one methyl and *para* to the other. The σ-complex obtained as a result of such attack by $\overset{\oplus}{N}O_2$ (the electrophile involved in nitration) is highly stabilized due to the presence of two especially stable resonance structures which are tertiary carbocations and in which the methyl group stabilizes the adjacent positive charge by its +I and hyperconjugative effects.

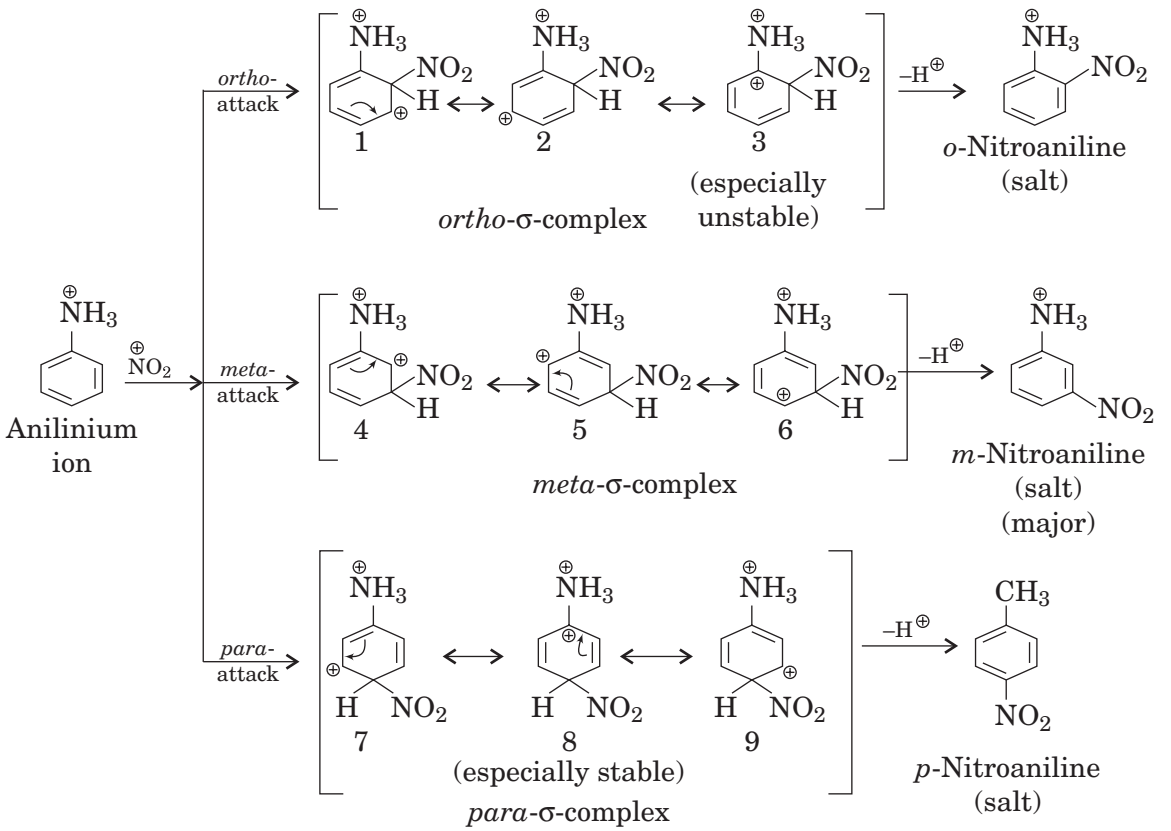


On the other hand, the σ-complex obtained on electrophilic attack on *p*-xylene (all the positions are equivalent) contains only one such especially stable structure and therefore, it is relatively less stable.



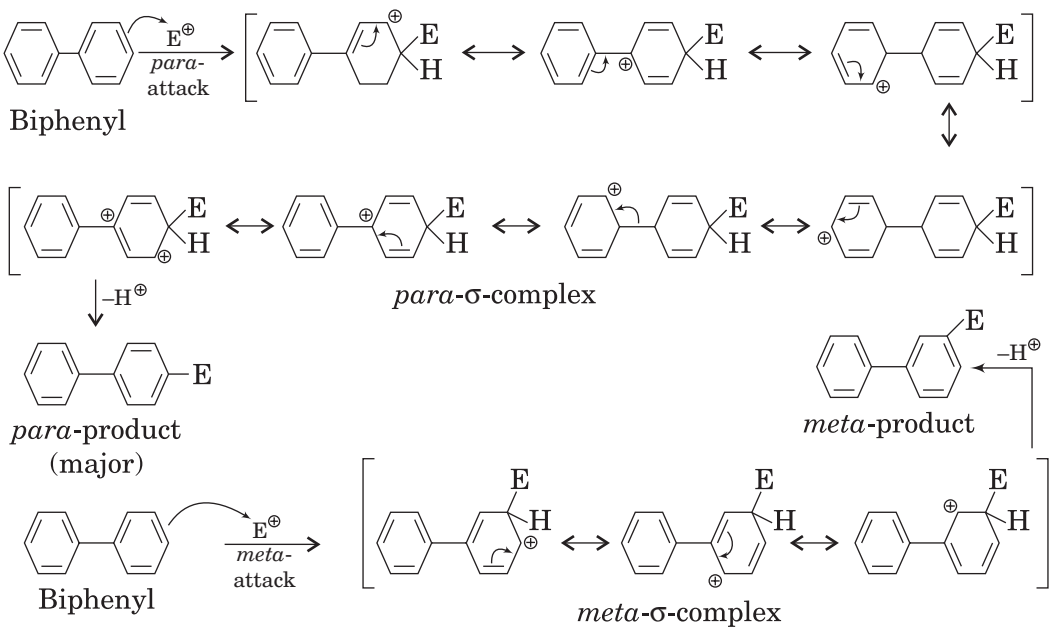
Due to greater stabilization of the σ-complex and the transition start leading to it, *m*-xylene undergoes nitration at a rate faster than *p*-xylene.

(b) In the presence of 98% H_2SO_4, the $-NH_2$ group of aniline undergoes protonation and converted into the $-\overset{\oplus}{N}H_3$ group which is deactivating and *meta*-directing. That the $-\overset{\oplus}{N}H_3$ group is *meta*-orienting may be explained in terms of relative stabilities of the σ-complexes.



Each of the *ortho*- and *para*-σ-complexes contains one particularly unstable resonance structure (3 and 8) carrying positive charges on adjacent atoms. The *meta*-σ-complex contains no such unstable structure. The *meta*-σ-complex and the transition state leading to it is, therefore, more stable than the other two σ-complexes and the transition state leading to them. As a consequence, nitration at the *meta*-position takes place readily and predominantly. Hence, *m*-nitroaniline may be prepared by direct nitration of aniline in the presence of strong (98%) H_2SO_4.

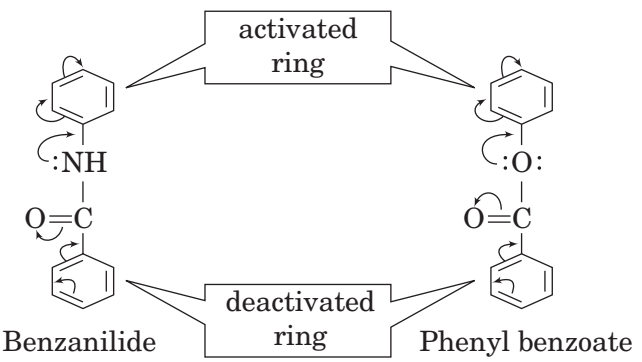
(c) When electrophilic attack occurs at *ortho*- and *para*-positions, the positive charge on the intermediate σ-complex is delocalized by the second phenyl group. However, when electrophilic attack occurs at the *meta*-position, the positive charge on the intermediate σ-complex cannot be delocalized by the second ring, i.e., delocalization of charge remains confined to one ring.



The σ-complexes resulting from attack at the *ortho*- and *para*-positions are, therefore, relatively more stable than the σ-complex resulting from attack at the *meta*-position. Thus, the reaction proceeds through the *ortho*- and *para*-σ-complexes to give the *ortho*- and *para*-products readily and predominantly. Hence, the phenyl group is an *ortho*, *para*-directing.

14. Which ring of benzanilide (PhCONHPh) and phenylbenzoate (PhCOOPh) would you expect to undergo electrophilic substitution reaction more readily and why?

Solution



The ring directly attached to the nitrogen atom in benzanilide or the ring directly attached to the oxygen atom in phenyl benzoate undergoes electrophilic substitution reaction more readily because the nitrogen or the oxygen atom can stabilize the intermediate σ-complex

by donating an unshared pair of electrons, i.e., by +R effect. On the other hand, the ring directly attached to the electron-withdrawing $>C{=}O$ group in both of the compounds undergoes electrophilic substitution much slowly because the group destabilizes the intermediate σ-complex by withdrawing electrons inductively and by resonance (–R).

15. Explain the following approximate rate order for nitration of halobenzenes:

$$C_6H_5F > C_6H_5I > C_6H_5Cl \approx C_6H_5Br$$

Solution The electronegativ values of halogens (F = 4.1, Cl = 2.8, Br = 2.7 and I = 2.2) suggests that the expected order of –I effect is F > Cl > Br > I and the +R effect (due to the non bonding electrons) order is F < Cl < Br < I. A combined effect must result a rate order different from the observed one. Hence, it is clear that the +R effect does not follow the order based on electronegativity. Although electronegativity has some role, the +R effect is controlled mainly by the *p*-orbital overlap effect. An effective overlap leads to a stronger resonance effect and such an overlap will take place if orbitals of comparable size are involved. As a 2*p* orbital of carbon interacts with 2*p*, 3*p*, 4*p* and 5*p* orbitals of F, Cl, Br and I, respectively, the electron-releasing resonance effect (+R) follows the order: F > Cl > Br > I. In the case of fluorine, the +R effect is very large and so, it nearly cancels the stronger –I effect. In the case of iodine, the –I effect outweighs the +R effect which is relatively very small. In the case of chlorine and bromine the –I effect largely outweighs the +R effect which is relatively small. Therefore, the halogens are net electron-withdrawing and the order of net electron-withdrawl is F < I < Cl ≈ Br. The rate of nitration thus follows the order: $C_6H_5F > C_6H_5I > C_6H_5Cl \approx C_6H_5Br$.

16. For each of the following groups of substituted benzenes indicates: (i) the substrate which is most reactive in an electrophilic substitution reaction, (ii) the substrate which is least reactive in an electrophilic substitution reaction and (iii) the substrate that would yield the highest percentage of *meta*-product. Explain

(a) $\underset{\text{I}}{C_6H_5CH_3}$ $\underset{\text{II}}{C_6H_5CHCl_2}$ $\underset{\text{III}}{C_6H_5CCl_3}$

(b) $\underset{\text{I}}{C_6H_5\overset{\oplus}{N}Et_3}$ $\underset{\text{II}}{C_6H_5CH\overset{\oplus}{N}Et_2}$ $\underset{\text{III}}{C_6H_5CH_2CH_2\overset{\oplus}{N}Et_3}$

(c) $\underset{\text{I}}{C_6H_5O(CH_2)_2CH_3}$ $\underset{\text{II}}{C_6H_5CH_2OCH_2CH_3}$ $\underset{\text{III}}{C_6H_5COOCH_2CH_3}$

Solution

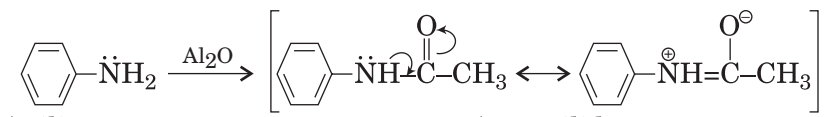
(i) In the series (a), the most reactive in an electrophilic substitution reaction is I because $–CH_3$ is more electron-releasing than $–CHCl_2$. In the series (b), III is most reactive because $–CH_2CH_2\overset{\oplus}{N}Et_3$ is more electron-releasing than $—CH_2\overset{\oplus}{N}Et_3$. In the series (c), I is most reactive because oxygen with unshared pair of electrons is directly attached with the ring and exerts its +R effect.

(ii) In the series (a), the least reactive is III, in the series (b), the least reactive is I and in the series (c), the least reactive is III. This is because all substituents are electron withdrawing (—CCl_3, —NEt_3 by –I and —$COOCH_2CH_3$ by –R).

(iii) In the series (a), (b) and (c), the substrates that would yield the highest percentage of *meta*-product are III, I and III, respectively, and this is because all these groups stabilize the *m*-σ-complex relative to the *o*- and *p*-σ-complexes.

17. Explain why *p*-nitroaniline is prepared in the laboratory not by nitrating aniline directly but by nitrating acetanilide followed by hydrolysis.

Solution Very powerful $-NH_2$ group causes the benzene ring to be so reactive that undesirable reaction may take place. Nitration of aniline, for example, results in considerable destruction of the benzene ring because it is oxidized by the nitric acid. Polynitration of aniline also takes place. Direct nitration of aniline is, therefore, not a satisfactory method for the preparation of *p*-nitroaniline. To prepare *p*-nitroaniline the $-NH_2$ group of aniline is to be protected by acetylation and that is because acetylation restricts the nitration at the mononitration stage by lowering the activating power of the $-NH_2$ group. An amide group ($-NHCOCH_3$) is not only moderately activating but also does not make the ring highly susceptible to oxidation during nitration. The carbonyl group of $-\ddot{N}HCOCH_3$ delocalizes the unshared electron pair on nitrogen and thereby reduces their availability for conjugation with the ring.



Aniline Acetanilide

Furthermore, since the $-NHCOCH_3$ group is more space-filling, to avoid steric crowding at the *o*-position nitration occurs preferentially at the *p*-position.

18. When alkylbenzenes are nitrated under the same set of conditions, the *ortho*/*para*-ratio is highest in the case of toluene and lowest in the case of *tert*-butyl-benzene. Explain.

Alkylbenzene:	C_6H_5Me	$C_6H_5CH_2Me$	$C_6H_5CHMe_2$	$C_6H_5CMe_3$
Ortho/*para*-ratio:	1.57	0.93	0.48	0.21

Solution Steric effect is one of the factors that determines the ratio of *ortho*- and *para*-products in the substitution reaction of a monosubstituted benzene. Since an *ortho*-position is adjacent to the substituent, therefore, the approach of the incoming electrophile is hindered because of steric repulsion. Such steric problem does not arise in the *para*-attack because the substituent is far from the attacking point. Again, the steric hindrance for *ortho*-attack increases as the size of the substituent increases. Consequently, the yield of the *ortho*-product decreases and that of the *para*-product increases, i.e., the *ortho*/*para* ratio drops. In the given series, the size of R increases on going from $-CH_3$ to $-C(CH_3)_3$ and so, the *ortho*/*para* ratio falls gradually.

19. When halobenzenes are nitrated under the same set of conditions, the *ortho*/*para* ratio is highest in the case of iodobenzene and lowest in the case of fluorobenzene, even though the size of halogen increases from F to I.

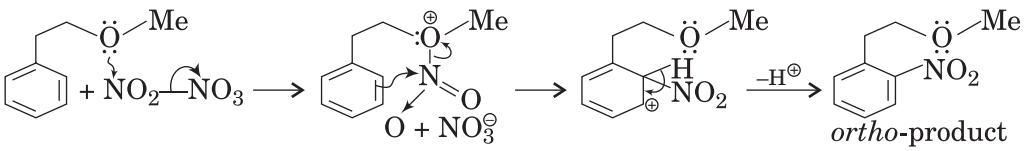
X (*o*/*p* ratio): –F (0.14), –Cl (0.44), –Br (0.60), –I (0.63)

Explain the observation.

Solution The –I effect decreases on going from –F to –I. Therefore, on going from –F to –I, the *ortho*-position becomes less deactivated and the amount of the *ortho*-product increases. The size of the halogen atom increases from F to I. So, steric effect is expected to the *o*/*p* ratio. However, electronic effect outweighs steric effect and, therefore, the *ortho*/*para* ratio increases on going from –F to –I.

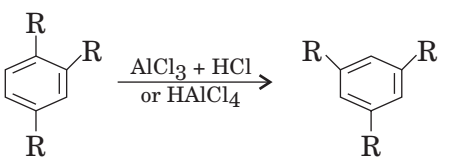
20. When methyl phenylethyl ether is nitrated with N_2O_5 in methyl cyanide, 69% *ortho*-product and 28% *para*-product are obtained. However, when nitration of the same compound is carried out by the common nitrating agent (conc. HNO_3 and conc. H_2SO_4), 32% of *ortho*-product and 59% *para*-product are obtained. Explain these observations.

Solution The interaction between the O atom of the ether linkage and N_2O_5 occurs in the first step of the reaction to form an oxonium ion. The developing $\overset{\oplus}{N}O_2$ ion then attacks the ring in a concerted step to form a σ-complex which subsequently loses a proton to form *o*-product. Since the distance between the developing $NO_2^{\oplus}$ ion and the *ortho*-position being small, the $\overset{\oplus}{N}O_2$ ion attacks the *ortho*-position preferentially to give the *o*-product as the major product.



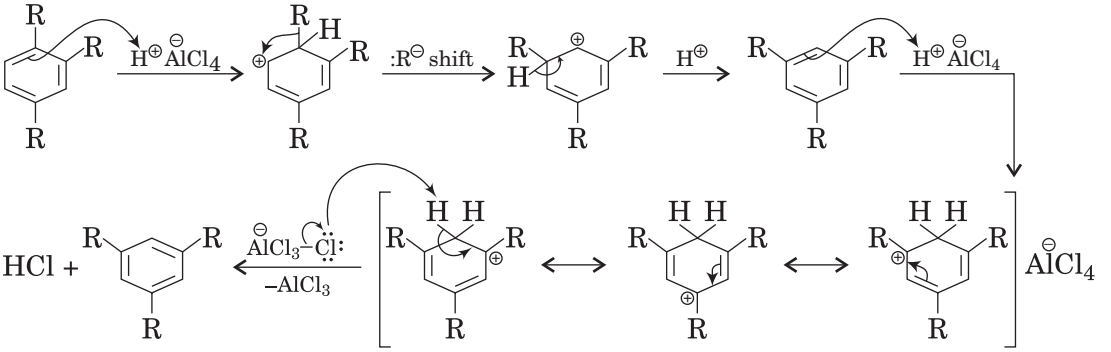
When the nitration reaction is carried out with the common nitrating agent, i.e., conc. HNO_3 and conc. H_2SO_4, the reaction does not proceed through the intermediate oxonium ion. Because of steric congestion at the *ortho*-position, the $\overset{\oplus}{N}O_2$ ion preferably attacks the *para*-position and as a result, the *para*-product is obtained predominantly.

21. Explain the following observation



Solution In the presence of ($AlCl_3$ + HCl) 1,2,4-trialkylbenzene rearranges slowly but irreversibly to the less sterically hindered, thermodynamically more stable

1,3,5-trialkylbenzene. The preference for 1,3,5-trialkyl isomer is a consequence of having the more stable σ-complex, whose positive charge resides only on 3° carbons, bonded to R, in contrast to any other tri-R-substituted σ-complex.

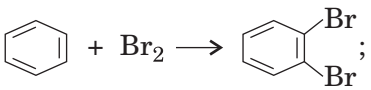


Stable σ-complex

Study Problems

1. The addition of bromine to an alkene is exothermic by about 30 kcal/mol, whereas addition to benzene is estimated to be endothermic by about 2.5 kcal/mol.

$$CH_2CH{=}CH_2 + Br_2 \longrightarrow CH_3CHBrCH_2Br; \qquad \Delta H = -30 \text{ kcal/mol}$$



; $\Delta H° = 2.5$ kcal/mol

Account for these observations

2. Why is benzene less reactive towards electrophiles than an alkene, even though it has more π electrons than an alkene?

3. Classify the following groups as activating groups (*ortho-para* directors), deactivating groups (*meta* directors) and deactivating groups (*ortho para* directors):

$-OCH_3$, $-NO_2$, $-CF_3$, $-Cl$, $-CN$, $-C_6H_5$, $-O^{\ominus}$,

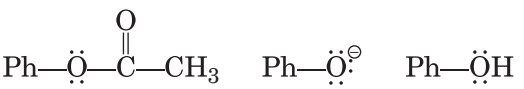
$-CHO$, $-CH = CHCOOH$, $-COOH$ and $-SO_3H$

4. What percentage of each nitrotoluene would you expect if substitution were to take place on a purely statistical basis?

5. Use resonance theory to explain why the hydroxyl group (–OH) of phenol is an activating group and *ortho–para* director.

6. Phenyl acetate ($PhOCOCH_3$), although undergoing reaction at the *ortho* and *para* positions, is less reactive towards electrophilic aromatic substitution than phenol. Explain this observation.

7. Arrange the following in order of decreasing reactivity in electrophilic aromatic substitution. Explain your reasoning.



8. The nitrogen-containing substituents (e.g., $-NH_2$, $-\ddot{N}HR$, $-\ddot{N}R_2$, –NHCOR) are more strong activating than the corresponding oxygen-containing substituents (e.g., –OH, –OR, –OCOR). Explain.

9. Account for the percentages of *m*-orientation in the following compounds: (a) $C_6H_5CH_3$ (4.4%), $C_6H_5CHCl_2$ (33.8%), $C_6H_5CCl_3$ (64.6%); (b) $C_6H_5\overset{\oplus}{N}(CH_3)_3$ (100%), $C_6H_5CH_2\overset{\oplus}{N}(CH_3)_3$ (88%), $C_6H_5CH_2CH_2\overset{\oplus}{N}(CH_3)_3$ (19%).

10. Although nitration of aniline is slow and gives mostly *meta* substitution, nitration of acetanilide ($PhNHCOCH_3$) is fast and gives mainly *para* substitution. Explain these observations.

11. When bromine is added to two beakers, one containing phenyl isopropyl ether ($PhOCHMe_2$) and the other containing cyclohexene, the colour of bromine in both beakers disappears. What observation could you make during performing this test that would allow you to distinguish the alkene from the aryl ether.

12. Predict the product expected to be formed when HCl adds to 1-bromocyclohexene. Suggest a mechanism for this reaction and explain how this mechanistic interpretation is in accord with the *ortho*, *para*-directing effect of bromine on an aromatic ring. Also, explain why 1-bromocyclohexene adds hydrogen chloride more slowly than cyclohexene.

13. From each of the following sets, select the most reactive and the least reactive substrates towards ring nitration:

(a) Bromobenzene, benzene, nitrobenzene, ethylbenzene

(b) *m*-Nitrotoluene, *m*-dinitrobenzene and toluene

(c) Mesitylene, *m*-xylene, benzene and toluene

(d) 4-Chloronitrobenzene, chlorobenzene, 1-chloro-2,4-dinitrobenzene

14. Account for the following observations:

(a) *m*-Dinitrobenzene undergoes bromination very slowly.

(b) 1, 3, 5-Trimethylbenzene in HF (solvent) is a better electrical conductor than solution of 1, 4-dimethylbenzene in HF.

(c) Benzene requires higher temperature than toluene for nitration.

(d) The nitroso group, –N = O, is an *ortho*-*para* director, although the $-NO_2$ group is *meta*- directing.

(e) The $-B(OH)_2$ group in phenylboronic acid, $PhB(OH)_2$, is *meta*-directing.

(f) The $-\overset{\oplus}{P}Me_3$ and $-\overset{\oplus}{A}sMe_3$ groups yield more *meta*-substitution product than the $-\overset{\oplus}{N}Me_3$ group.

(g) Electrophilic substitution in 4-phenylpyridine takes place in the benzene ring.

(h) Oxygen is more electronegative than chlorine or bromine and especially iodine). Yet the –OH group is an activating group, whereas halogens are deactivating in nature.

(i) When *p-tert*-butylphenol is treated with dilute acid, a mixture of phenol and *tert*-butylalcohol is obtained.

(j) $C_6H_5CMe_3$ undergoes nitration at a rate slower than C_6H_5Me, even through the $–CMe_3$ group contains three electron releasing –Me part.

(k) Phenyl triphenylmethyl ether, $PhOCPh_3$, on treatment with acid, yields *p*-triphenylmethylphenol.

(l) Nitration of cinnamic acid affords *p*-nitrocinnamic acid.

[**Hint:** (f) This is attributed to the acceptance of the aromatic π electrons by the vacant *d* orbitals of phosphorus and arsenic atoms to make p_π-d_π bonding.

(h) In the case of the hydroxyl (–OH) group, +R effect is stronger than –I effect because the overlap of a 2*p* orbital of oxygen with a 2*p* orbital of carbon (i.e., orbitals of similar size) is very much effective. In the case of –Cl, on the other hand, +R effect is weaker than –I effect because the overlap of a 2*p* orbital of carbon with a relatively larger 3*p* orbital of chlorine is less effective.

(k) Cleavage of ether to form $\overset{\oplus}{C}Ph_3$ followed by electrophilic substitution at the *para*-position of phenol.

(i) Alkyl groups that are *para* to strong electron-releasing group can be removed from the aromatic rings under acidic conditions if they can form stable carbocations.]

15. Rank the following compounds in order of increasing rate of nitration and give your reasoning:

$$C_6H_5CH_3,\ C_6H_6,\ C_6D_6,\ C_6H_5NO_2,\ C_6H_5Cl$$

16. Which one is more reactive in electrophilic substitution: benzene or naphthalene?

[**Hint:** Naphthalene is more reactive because it is less aromatic than benzene (the resonance energy of each ring in naphthalene is 127.6 kJ/mol, whereas the resonance energy of benzene is 150.6 kJ/mol).]

17. How can Hammond postulate be used to predict the orientation of E by C_6H_5G?

18. The *ortho*/*para* ratio decreases in the nitration of the series given below:

Substrate:	$C_6H_5CH_3$	$C_6H_5CH_2Cl$	$C_6H_5CHCl_2$	$C_6H_5CCl_3$
ortho/*para* ratio:	1.57	0.75	0.53	0.23

Explain this observation.

19. Explain the following observation:

$$p\text{-}MeC_6H_4Me \xrightarrow[(HAlCl_4)]{HCl + AlCl_3} m\text{-}MeC_6H_4Me$$

20. Give the principal monosubstitution products from the following reactions and indicate whether each reaction is faster or slower than benzene.

(a) Nitration of $C_6H_5 – C_6H_5$

(b) Nitration of $C_6H_5NO_2$

(c) Nitration of $C_6H_5CH = CHCOOH$

(d) Bromination of $C_6H_5CBr_3$

(e) Sulpholation of $C_6H_5CH(CH_3)_2$

(f) Bromination of C_6H_5I

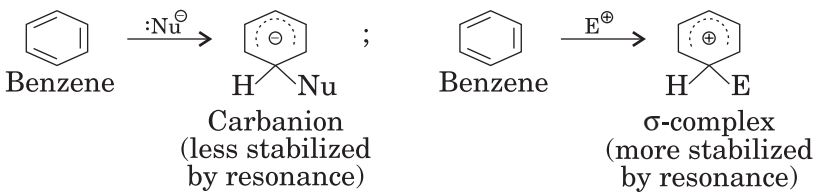
(g) Acylation of $C_6H_5CMe_3$

21. The $-NHCOCH_3$ group activates the ring in acetanilide, whereas deactivates the ring in 2, 6-dimethylacetanilide. Explain this observation.

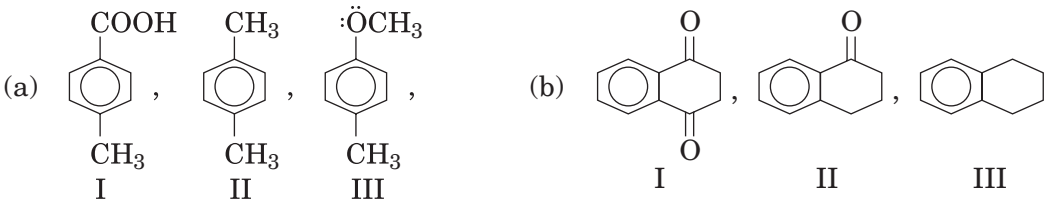
[**Hint:** Steric inhibition of resonance (SIR) causes the deactivation in 2, 6-dimethylacetanilide because in that case delocalization of the unshared pair on nitrogen with the C═O groups makes nitrogen considerably positively polarized.]

22. Explain why most substitutions at an aromatic ring carbon are electrophilic and not nucleophilic.

[**Hint:** Benzene (the representative of all the aromatic compounds) has loosely held six π electrons delocalized in six *p* orbitals. Therefore, benzene ring is an easily available source of electrons that can be offered to an electrophile. However, this negative π electron cloud repels an approaching nucleophile (electron rich species). Also, the π orbitals of the carbanion obtained by the interaction between the aromatic system and the nucleophile are less capable of stabilizing the negative charge, whereas the π orbitals of the σ-complex obtained by the interaction between the aromatic ring and the electrophile are more capable of stabilizing it by delocalizing the positive charge. This explains why most substitutions taking place at an aromatic ring carbon are electrophilic and not nucleophilic.



23. Arrange the compounds in each of the following groups in order of increasing reactivity towards electrophilic aromatic substitution. Give your reasoning.



24. Hexadeuterobenzene is prepared by treatment of benzene with excess of D_2SO_4. Give mechanism of the reaction.

25. Explain the following statements:

(a) A phenyl group (Ph–) is an *ortho*-, *para*-directing that activates a benzene ring towards electrophilic attack.

(b) A nitroso group (–N=O) is an *ortho*, *para*-directing that deactivates a benzene ring towards electrophilic substitution.

26. Explain why most aromatic substitution reactions are irreversible?

[**Hint:** The energy barrier $\Delta G_2^{\ddagger}$ for the reaction of the σ-complex to form products is less than $\Delta G_r^{\ddagger}$ for the reverse rejection of $E^{\oplus}$, the electrophile.]

27. What is the essential role of the catalysts used for aromatic electrophilic substitutions?

[**Hint:** The catalyst makes the reagent more electrophilic, thereby raising the ground state energy, lessening the $\Delta G^{\ddagger}$ of TS_1, and enabling the substitution to proceed at a faster rate. The catalyst plays this role by either actually forming the electrophile or by polarizing the reagent.]

28. Explain why pyridine is less reactive than benzene in electrophilic aromatic substitution and yields 3-substituted products.

3.1.2 Formation of Carbon–Nitrogen σ-Bond

3.1.2.1 Nitration

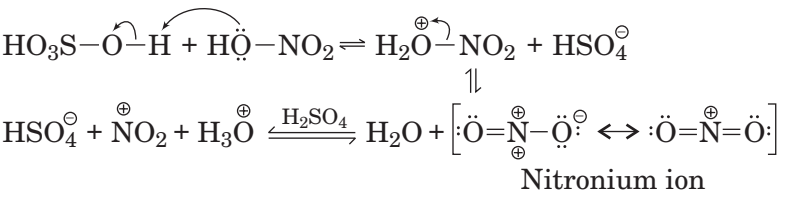
The reaction in which the nitro group, $-NO_2$, is introduced into an aromatic ring by electrophilic substitution is called nitration. The introduced $-NO_2$ group can easily be converted to the other suitable functional group. Benzene, for example, undergoes nitration when treated with a mixture of concentrated nitric and sulphuric acids (mixed acid). Sulphuric acid is a catalyst, allowing nitration to take place more readily at lower temperatures by increasing the concentration of the electrophile, the nitronium ion $(\overset{\oplus}{N}O_2)$.

$$\underset{\text{Benzene}}{C_6H_6} + HNO_3 + H_2SO_4 \xrightarrow{50\text{–}55^\circ C} \underset{\substack{\text{Nitrobenzene}\\(81\%)}}{C_6H_5NO_2}$$

Benzene reacts with hot concentrated nitric acid to give nitrobenzene. But the reaction is slow and less convenient.

Other nitrating agents Other nitrating agents which are used depending on the nature of the substrate are as follows: (i) concentrated HNO_3 in glacial CH_3COOH, (ii) dilute HNO_3, (iii) fuming HNO_3 in concentrated H_2SO_4, (iv) fuming HNO_3 in fuming H_2SO_4, (iv) acylnitrates, e.g. acetylnitrate, benzoylnitrate, etc. in organic solvents, (v) nitronium salts, e.g. $\overset{\oplus}{N}O_2BF_4^{\ominus}$, $\overset{\oplus}{N}O_2\overset{\ominus}{C}lO_4$ or $\overset{\oplus}{N}O_2CH_3COO^{\ominus}$, (vi) nitrogen pentoxide (N_2O_5) in carbon tetrachloride.

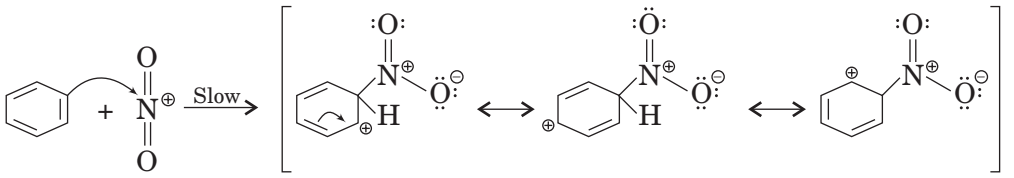
Mechanism of the reaction Nitric acid reacts with sulphuric acid to form nitronium ion $(\overset{\oplus}{N}O_2)$, the electrophile involved in nitration reaction. nitric acid acts as a base and accepts a proton from the stronger acid, sulphuric acid. The conjugate acid of nitric acid then dissociates to produce a nitronium ion.



Net reaction: $HNO_3 + 2H_2SO_4 \rightleftharpoons H_3O^{\oplus} + \overset{\oplus}{N}O_2 + 2HSO_4^{\oplus}$

The nitration reaction (a typical electrophilic aromation substitution) then takes place through the steps as follows:

Step 1: The nitronium ion attacks the π system of the benzene ring in this rate-determining (slow) step to form a resonance-stabilized arenium ion or σ-complex.

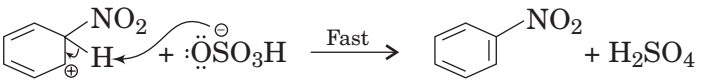


Benzene (aromatic)

An arenium ion or σ-complex (nonaromatic)

Aromaticity of benzene is lost in this step.

Step 2: The arenium ion or σ-complex loses a proton to some Lewis base in the reaction mixture, e.g. $HSO_4^{\ominus}$ or H_2O, to yield nitrobenzene. Aromaticity is regained in this step.



Nitrobenzene (aromatic)

Evidence in favour of involvement of the nitronium ion $(\overset{\oplus}{N}O_2)$ That the nitronium ion, $\overset{\oplus}{N}O_2$, is the electrophile involved in this reaction can be proved by the following observations:

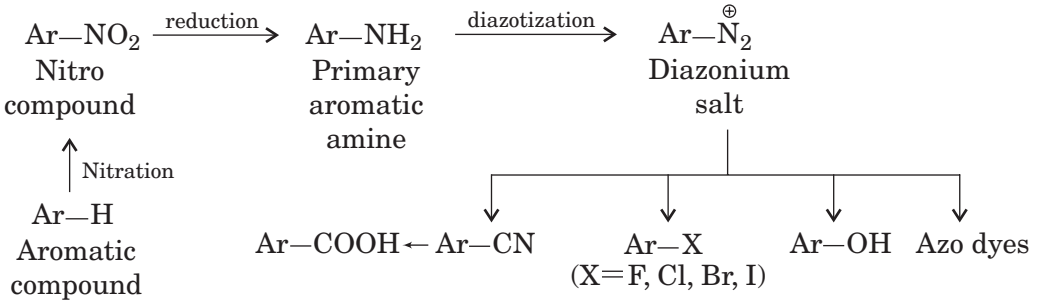
(i) The freezing point of concentrated sulphuric acid is lowered about four times when concentrated nitric acid is mixed with it. The four fold depression of freezing point indicates the formation of four ions in the mixed acid. The result is in agreement with the following acid-base reaction leading to the formation of nitronium ion $(\overset{\oplus}{N}O_2)$.

$$HNO_3 + 2H_2SO_4 \rightleftharpoons \overset{\oplus}{N}O_2 + H_3\overset{\oplus}{O} + 2HSO_4^{\ominus}$$

(ii) The characteristic peak in the Raman spectrum of nitric acid disappears when sulphuric acid is added to it. Two new peaks appear at 1400 cm^{-1} and 1050 cm^{-1} respectively. The former peak is due to the linear triatomic nitronium ion $(\overset{\oplus}{N}O_2)$ and the latter one is due to hydrogen sulphate ion $(HSO_4^{\ominus})$.

Applications Aromatic nitration is the best way to introduce nitrogen-containing substituents to the benzene ring. The nitro group functions as a directing group in further substitutions and as a masked amino function.

Reduction of nitro compounds to amines is an essential and important step in what is probably the most important synthetic route in organic chemistry. The primary aromatic amines obtained by the reduction of nitro compounds can be readily converted into diazonium salts. The diazonium group, in turn, can be replaced by a large number of other groups. In most cases this sequence is, in fact, the best method of introducing these other groups into the aromatic ring. Furthermore, the diazonium salts can be used to synthesize the azo dyes, an extremely important class of compounds.



Some relevant topics:

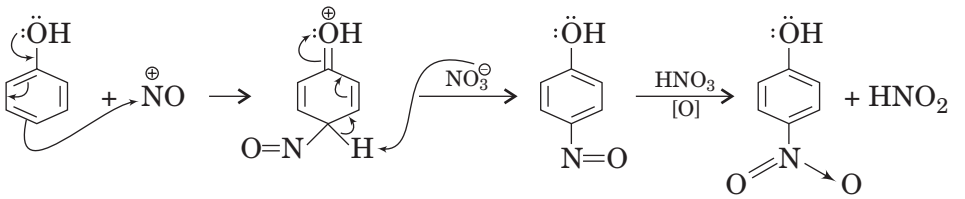
(i) Nitration through nitrosation: The activated compound phenol undergoes ready nitration even in dilute nitric acid. This conversion occurs through nitrosation of phenol followed by oxidation. A little nitric acid first oxidises phenol and becomes converted to nitrous acid which then reacts with nitric acid to produce nitrosonium ion $(\overset{\oplus}{N}O)$.

$$C_6H_5OH + HNO_3 \xrightarrow{[O]} \text{Oxidation products of phenol} + HNO_2$$

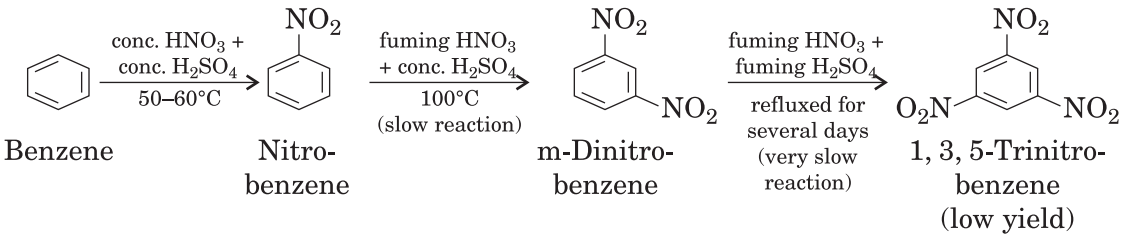
$$O{=}N{-}\ddot{O}H + H{-}O{-}NO_2 \rightleftharpoons O{=}N{-}\overset{\oplus}{O}H_2 + NO_3^{\ominus}$$

$$O{=}N{-}\overset{\oplus}{\ddot{O}}H_2 + HNO_3 \rightleftharpoons :\overset{\oplus}{N}{=}O + H_3O^{\oplus} + NO_3^{\ominus}$$

$$HNO_2 + 2HNO_3 \rightleftharpoons :\overset{\oplus}{N}O + N_3O^{\oplus} + 2NO_3^{\ominus}$$



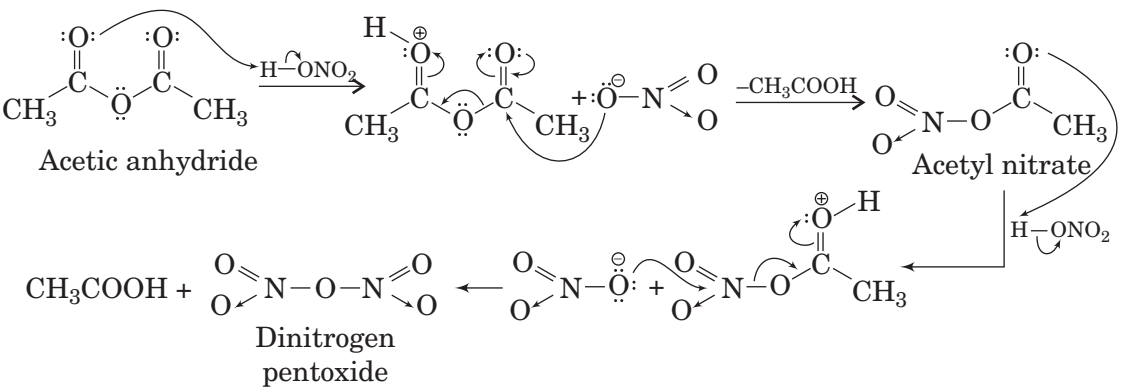
(ii) Polynitration and preparation of 1,3,5-trinitrobenzene Since the nitro group is a strong ring deactivator, it is easy to stop the reaction after mononitration stage. Polynitration is usually slow, low yielding and requires vigorous conditions.



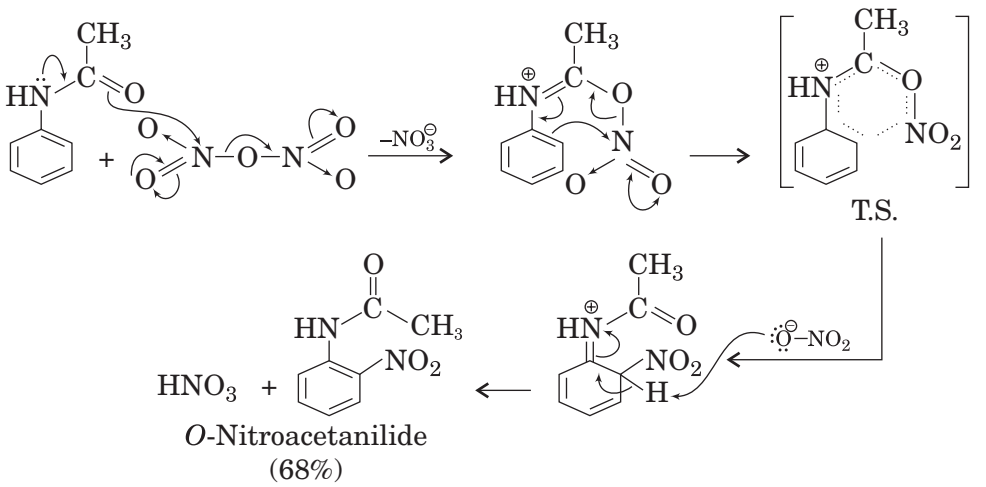
To obtain better yield, 1,3,5-trinitrobenzene is prepared not from benzene but from toluene in which the activating $-CH_3$ group helps to introduce the $-NO_2$ groups. Toluene is first nitrated with fuming HNO_3 and fuming H_2SO_4 at 85–100°C. The resulting 2,4,6-trinitrotoluene is oxidized with $Na_2Cr_2O_7/H_2SO_4$ to yield 2,4,6-trinitrobenzoic acid which, when heated, undergoes decarboxylation to yield 1,3,5-trinitrobenzene.

(iii) Synthesis of *o*-nitroacetanilide from acetanilide When nitration of acetanilide (Ph $NHCOCH_3$) is carried out with concentrated nitric and sulphuric acids (mixed acid), *p*-nitroacetanilide is obtained as the major product (98%) as the *ortho*-position is sterically more crowded due to the bulky group $-NHCOCH_3$. However, when nitration carried out with Ac_2O-HNO_3, it occurs predominantly at the sterically hindered *ortho*-position to yield *o*-nitroacetanilide as the major product.

The nitrating species involved in nitration with Ac_2O-HNO_3 is dinitrogen pentoxide (N_2O_5) which is generated as follows:



Accetanilide reacts with N_2O_5 through the acetamido group to give an intermediate. The intermediate undergoes intramolecular nitration preferentially at the *ortho*-position through a six-membered cyclic transition state. The resulting σ-complex loses a proton to give *o*-nitroacetanilide predominantly.

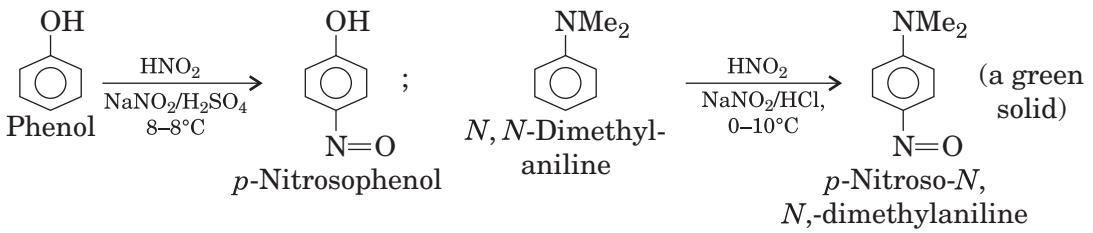


3.1.2.2 Nitrosation

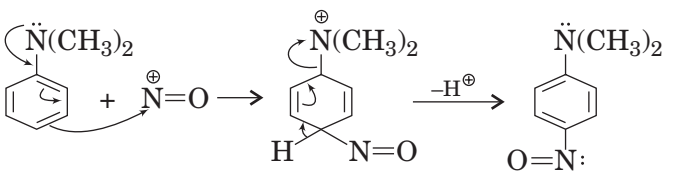
The reaction in which the nitroso group, –N=O, is introduced into an aromatic ring by electrophilic substitution is called nitrosation. The nitrosonium ion $(\overset{\oplus}{N}O)$ is about 1014 times less reactive than $\overset{\oplus}{N}O_2$ and hence nitrosation occurs only in strongly activated aromatic rings like that of phenols, tertiary amines, etc. The nitrosonium ion is generated by treating $NaNO_2$ with acid like HCl, H_2SO_4 or often with AcOH.

$$NaNO_2 + HCl \longrightarrow NaCl + HO-N=O \xrightarrow{HCl} H_2\overset{\oplus}{O}-N=O \quad Cl^{\ominus} \longrightarrow H_2O + Cl^{\ominus} + \overset{\oplus}{N}=O$$

Nitrons acid converts phenols into *p*-nitrosophenols and tertiary aromatic amines to chiefly *p*-nitroso-*N*, *N*-dialkylaniline. For example:



Mechanism:

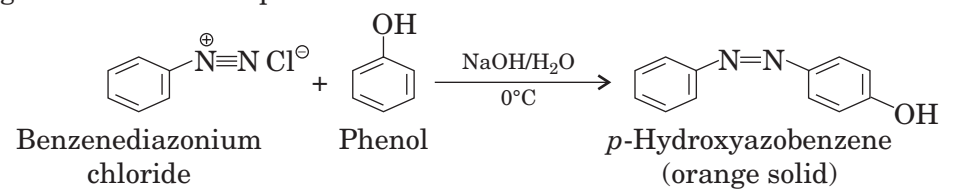


Primary aromatic amines (e.g., aniline) reacts with nitrous acid to yield diazonium salts; this is one of the most important reactions in organic chemistry. Secondary aromatic amines react with nitrous acid to yield *N*-nitrosamines (light yellow oily liquids insoluble in water).

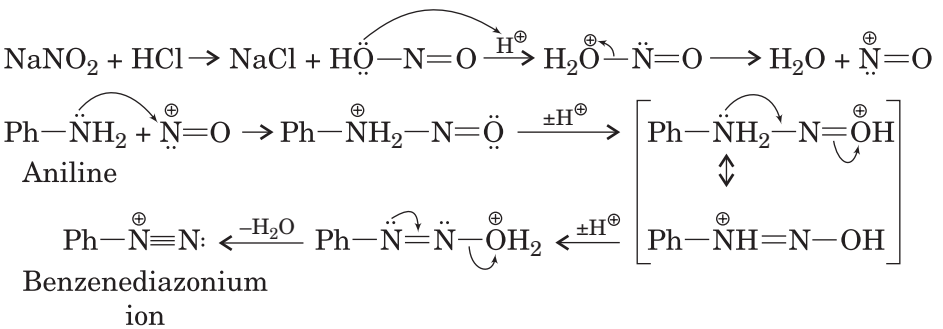


3.1.2.3 Diazo coupling

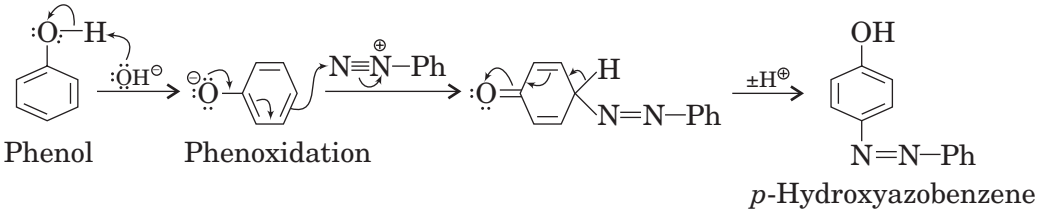
Aryl diazocation ($Ar\overset{\oplus}{N}_2$) is another less reactive nitrogen electrophile which is bulky in nature. It may attack the highly activated aromatic rings of phenoxide ion ($Ph–O^{\ominus}$), *N*,*N*-dialkyl aromatic amines ($Ph-\ddot{N}R_2$) or pyrrole (a heterocyclic compound) to give the corresponding substitution products. This reaction is referred to as *diazo-coupling*. Benzenediazonium ion, for example, couples with phenol in cold alkaline medium to yield an orange-coloured azo-compound:



The electrophile ($Ph\overset{\oplus}{N}_2$) is generated by the reaction of aniline with HNO_2 ($NaNO_2$/HCl) at 0–5°C.

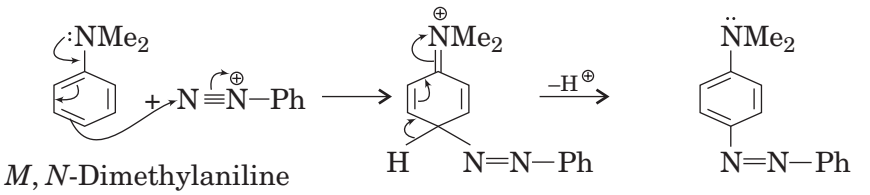


The electrophilic substitution reaction, i.e., the diazocoupling then occurs as follows:



The diazonium cation (the electrophile) attacks the activated *p*-position of the phenoxide ion to form an unstable azodienone which readily tautomerizes to yield *p*-hydroxyazobenzene. Because of steric crowding, the bulky electrophile couples predominantly at the *para*-position.

Tertiary aromatic amines like *N*,*N*-dimethylaniline couple almost exclusively at the *para*-position under mild acidic or neutral pH when the concentration of the diazocation is maximum.



M, *N*-Dimethylaniline

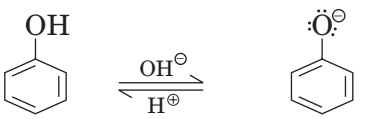
p-*N*, *N*-Dimethylaminoazobenzene

Role of pH in diazocoupling reaction It is most important that the coupling medium be adjusted to the right degree of acidity or alkalinity. In fact, the role of pH is very important in diazocoupling reaction. In the presence of hydroxide ion, the diazonium ion exists in equilibrium with an unionized compound, Ar – N = N – OH, and salts ($Ar - N = N - \overset{\oplus\oplus}{O}Na$) derived from it:

$$Ph-\overset{\oplus}{N}\equiv N\ OH^{\ominus} \underset{H^{\oplus}}{\overset{NaOH}{\rightleftharpoons}} Ph-\ddot{N}=\ddot{N}-OH \underset{H^{\oplus}}{\overset{OH^{\ominus}}{\rightleftharpoons}} Ph-\ddot{N}=\ddot{N}-O^{\ominus}$$

Diazoniunion (couples) — Diazohydroxide (does not couple) — Diazoate ion (does not couple)

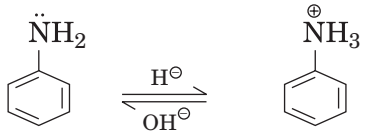
A phenol is appreciably acidic; in aqueous solution it exists in equilibrium with the phenoxide ion:



Phenol (couples slowly) — Phenoxide ion (couples readily)

The fully developed negative charge makes $-O^{\ominus}$ much more powerfully electron-releasing than –OH and so, the phenoxide ion is therefore much more reactive than the unionized phenol towards electrophilic aromatic substitution. In weakly alkaline solutions, the concentrations of the phenoxide ion as well as the diazonium ion are relatively high and for this reason, coupling occurs most readily in slightly alkaline solutions. The optimum pH for coupling with phenols is 9.

Acid converts an amine into its ion, which, because of the positive charge, is very much unreactive towards the weakly electrophilic diazonium ion.

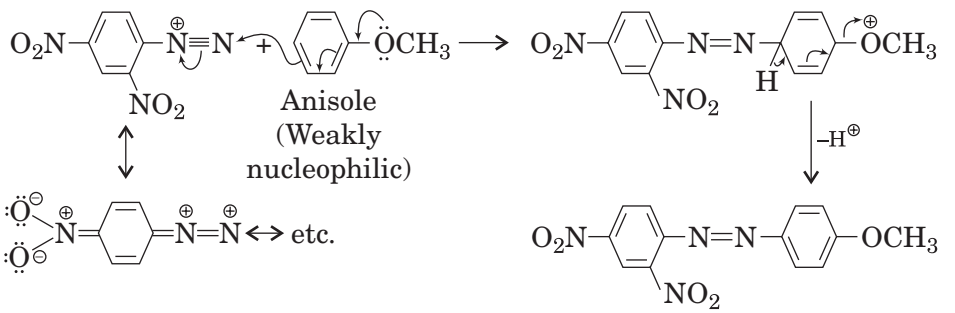


Aniline (couples) Anilinium ion (does not couple)

The higher the acidity of the medium, the higher the proportion of unreactive ammonium salt and the lower the rate of coupling. In weakly acidic solutions, the concentration of the free amine is relatively high and at the same time, the concentration of the diazonium ion is at a maximum and for this reason, coupling occurs most readily in slightly acidic solutions. The optimum pH for coupling with aromatic amines is 5–7. Therefore, the coupling reactions of diazonium salts with phenols and amines require an optimum pH.

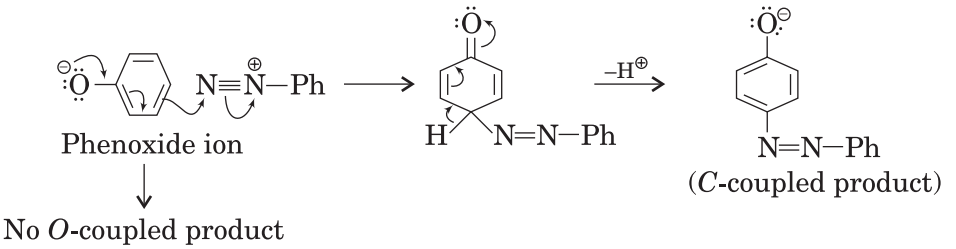
Some relevant topics

(i) **For a coupling reaction to take place either the substrate (the nucleophile) or the diazonium cation (the electrophile) must be strong.** The weakly electrophilic benzenediazonium cation, $PhN_2^{\oplus}$, does not couple with the weakly nucleophilic anisole, $PhOCH_3$ (a full-fledged negative charge cannot be developed on oxygen), but couples with phenoxide ion which is strongly nucleophilic. Anisole, however, reacts with the strongly electrophilic 2,4-dinitrobenzenediazonium cation in which the *ortho-* and *para*-nitro groups increase the electrophilic character of the cation by withdrawing electrons from the $-N_2^{\oplus}$ group through the benzene ring.

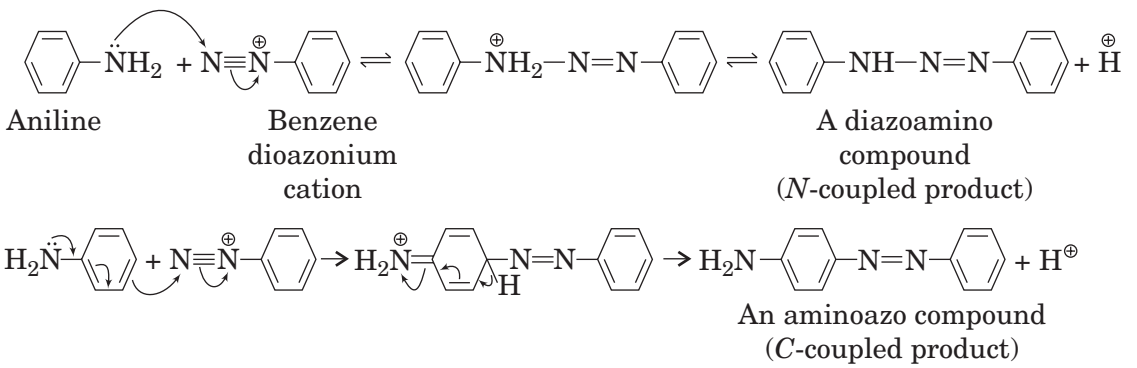


(ii) $PhN_2^{\oplus}Cl^{\ominus}$ **couples with phenol in alkali medium to give only *C*-coupled compound but couples with aniline in weakly acidic conditions to give *N*-coupled compound and in moderately acidic conditions to give**

***C*-coupled compound.** The phenoxide ion may couple with $PhN_2^{\oplus}$ either on oxygen or on carbon. On the basis of electron density *O*-coupling is expected to be favoured. But, in fact, *C*-coupling occurs and that is because the C–N bond (bond energy: 68 kcal/mol) is stronger than the O–N bond (bond energy: 48 kcal/mol). Therefore, the position of the attack is controlled not by the relative electron density of the various positions but by the relative strengths of the bonds formed in the two products.



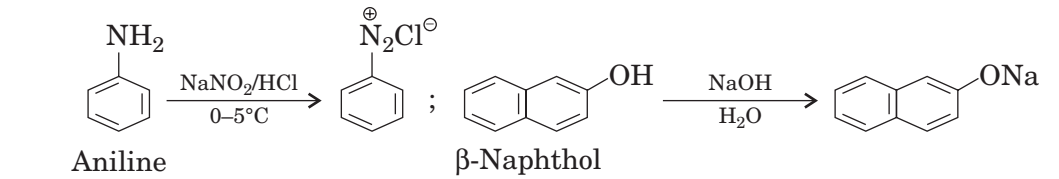
In aniline, the position of attack is controlled not by the relative strengths of the bond formed but by the relative electron-density of various positions. Since the electron–density on nitrogen is greater than on ring carbon, *N*-coupling occurs in weakly acidic medium. However, in moderately acidic conditions, the resulting diazoamino compound rearranges to yield the *C*-coupled aminoazo compound. The formation of the diazoamino compound is reversible and because of this, under this low pH conditions the reverse reaction occurs to form aniline and $PhN_2^{\oplus}$. These then react to form a σ-complex which on proton loss produces the corresponding aminoazo compound. Since the resulting C–N bond is thermodynamically more stable (higher bond energy) than the N–N bond, therefore, the compound, once formed, persists. Thus, formation of *C*- or *N*-coupled compound from aniline and $PhN_2^{\oplus}$ depends on the pH of the medium at which the reaction is carried out.

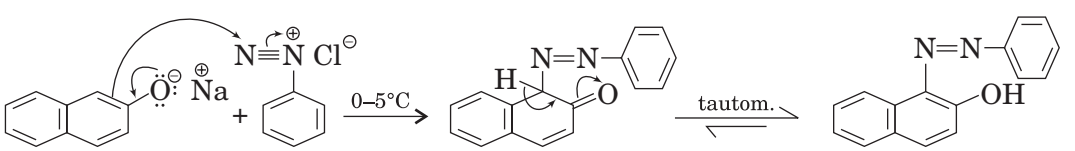


Applications of diazo coupling reaction Some important applications of diazo coupling reaction are as follows:

(a) Because of their colours, the azo compounds are of tremendous importance as dyes and in fact, about half of the dyes in industrial use today are azo dyes. This reaction is a good means for preparing azo dyes like methyl orange (an acid-base indicator), congo red (used as an indicator and for dying cotton directly), etc. For example:

(b) The reaction is used to detect the primary aromatic amino group and phenolic –OH group in qualitative organic analysis. Formation of an orange-red dye on addition of a cold diazotized solution of the sample into a cold alkaline solution of β-napthol indicates that the sample must contain an aromatic primary amino group. Similarly, formation of an orange-red dye on addition of a cold diazotized solution of aniline into a cold alkaline solution of the sample indicates the presence of phenolic OH group in the sample. For example, aniline may be detected by the following reaction when β-naphthol is known and β-naphthol may be detected when aniline is known.





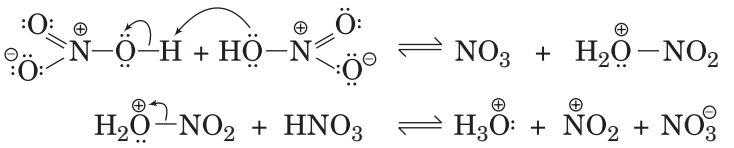
Benzeneazo-β-naphthol
(red azo-dye)

(b) A diazo coupling reaction may also be used to detect the presence of nitrite in the laboratory.

SOLVED PROBLEMS

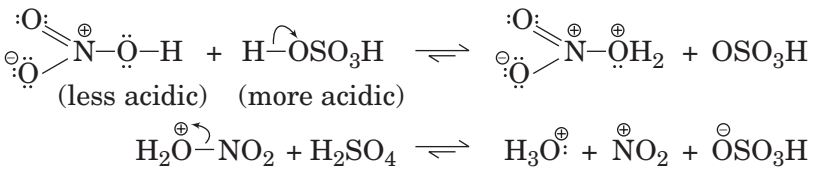
1. Explain why nitration of benzene occurs more rapidly in a mixture of concentrated nitric and sulphuric acids than concentrated nitric acid alone (given that the p*K*a of H_2SO_4 is –9 and that of HNO_3 is –1.4).

Solution In concentrated nitric acid, the electrophile, $\overset{\oplus}{N}O_2$ (nitrounium ion) involved in aromatic nitration is generated as follows:



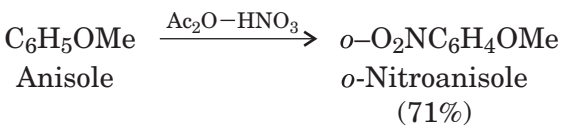
The rate of nitration depends on the concentration of the electrophile $\overset{\oplus}{N}O_2$. Since nitric acid is not strong enough (p*K*a = –1.4) it cannot protonate well another HNO_3 molecule in step 1 and the water molecule produced from $H_2\overset{\oplus}{O}–NO_2$. Thus, the equilibrium of both the reactions is less favourable. And, the position of equilibrium of the overall reaction lies far to the left. The result is that the nitric acid contains but little $\overset{\oplus}{N}O_2$ and consequently, the rate of nitration is very slow indeed.

In a mixture of concentrated HNO_3 and concentrated H_2SO_4, the nitronium ion $(\overset{\oplus}{N}O_2)$ is generated as follows:

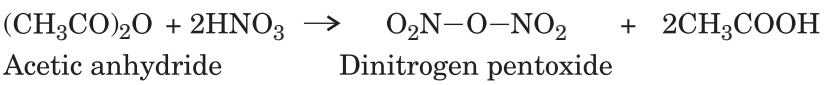


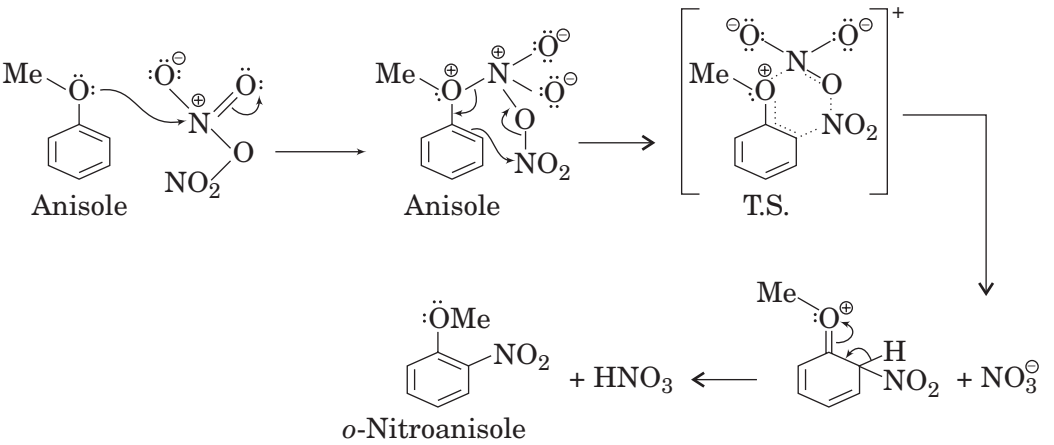
The relatively strong H_2SO_4 (p*K*a = –9) protonates HNO_3 (in step 1) and H_2O (obtained from $H_2\overset{\oplus}{O}–NO_2$ in step 2) well and thereby makes the equilibriums of both the reactions favourable. As a result, a large amount of nitronium ion $(\overset{\oplus}{N}O_2)$ is available and that causes a faster rate of nitration.

2. When anisole is nitrated with $Ac_2O–HNO_3$, *o*-nitro-anisole is obtained in good yield, even though the *ortho*-position is sterically more crowded. Explain this observation mechanistically.



Solution Anisole as usual on nitration with mixed acid yields *para*-nitroanisole as the major product. However, when the nitration is carried out with $(Ac_2O + HNO_3)$, i.e. with di-nitrogen pentoxide, the *ortho*-nitroanisole is obtained predominantly. This occurs because of some special role played by the –OMe group as obtained below:





3. Explain the following observations:

(a) *p*-Xylene undergoes nitration much faster than benzene.

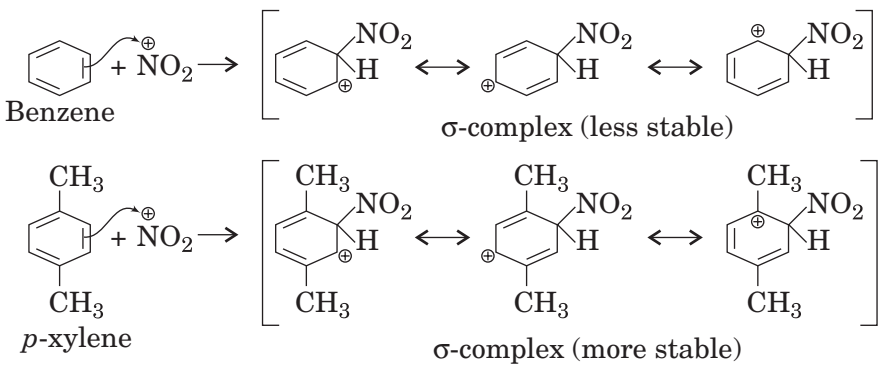
(b) Fluoroboric acid (HBF_4) accelerates the rate of nitration with acetyl nitrate ($AcONO_2$).

(c) The rate of nitration of benzene with conc. HNO_3 decreases sharply on addition of KNO_3.

(d) The nitration of anisole ($C_6H_5OCH_3$) is much faster than the nitration of thioanisole ($C_6H_5SCH_3$) under the same conditions.

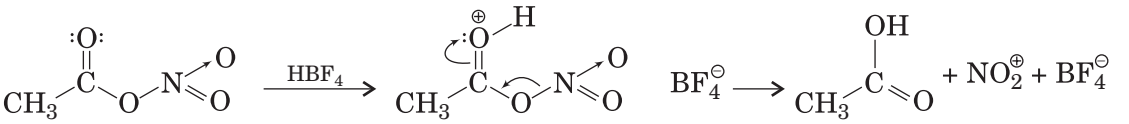
Solution

(a) The σ-complexes for nitration of benzene and *p*-xylene may be drawn as follows:



The σ-complex for benzene has the positive charge on three 2° carbons, whereas the σ-complex for *p*-xylene have the positive charge on two 2° carbons and one 3° carbon. Thus, the σ-complex for *p*-xylene contains one relatively stable resonance structure and for this reason, it is relatively more stable compared to that of benzene. Since formation of the σ-complex is the rate determining step of the reaction, *p*-xylene undergoes nitration at a rate faster than benzene.

(b) The nitronium ion ($\overset{\oplus}{N}O_2$), the active nitrating agent is readily formed when the acetyl nitrate is allowed to react with flouoroboric acid, HBF_4. The nonnucleophilic $BF_4^{\ominus}$ ion does not react with $\overset{\oplus}{N}O_2$.



Acetyl nitrate Acetyl nitrate Acetic acid

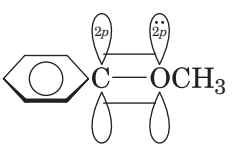
That's why fluoroboric acid accelerates the rate of nitration with acetyl nitrate.

(c) In concentrated nitric acid, the nitronium ion ($\overset{\oplus}{N}O_2$), the active nitrating agent is formed according to the following equation:

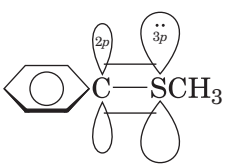
$$3HNO_3 \rightleftharpoons H_3O^{\oplus} + \overset{\oplus}{N}O_2 + 2NO_3^{\ominus}$$

Addition of KNO_3 causes the equilibrium to be shifted to the left due to increase in concentration of the common ion $NO_3^{\ominus}$. As a consequence, the concentration of $\overset{\oplus}{N}O_2$ ion decreases and so, the rate of nitration decreases.

(d) The resonance interaction of sulphur electron pair with the ring π electrons is much less effective than the interaction of oxygen electron pairs because the sulphur valence electrons reside in orbitals with higher quantum numbers. Because these 3*p* orbitals and the carbon 2*p* orbitals of benzene ring have different sizes and different number of nodes, they do not overlap so effectively. Since this overlap is the basis of the resonance effect, the resonance effect (+R) of sulphur is weak. Therefore, although sulphur is less electronegative than oxygen, the $–SCH_3$ group is less activate compared to the $–OCH_3$ group and for this reason, nitration of anisole is much faster than the nitration of thioanisole under the same reaction conditions.

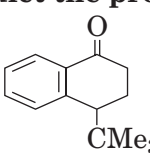


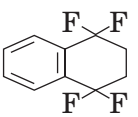
Anisole
(effective overlap of carbon and oxygen 2*p* orbitals)

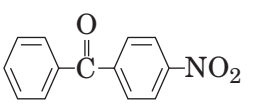


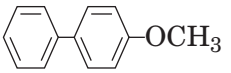
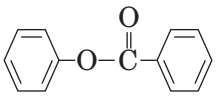
Thioanisole
(less effective overlap of carbon 2*p* and sulphur 3*p* orbitals)

4. Predict the products of mononitration of the following compounds:

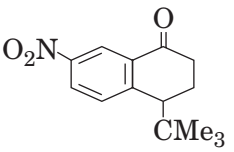
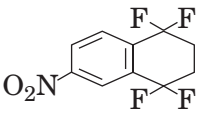
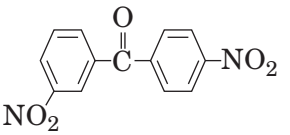
(a) 

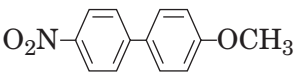
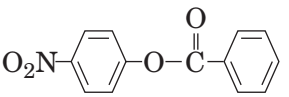
(b) 

(c) 

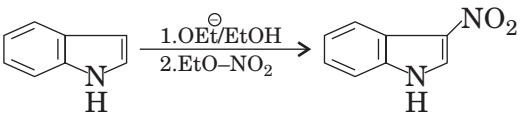
(d)  (e) 

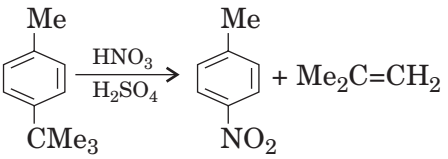
Solution

(a)  (b)  (c) 

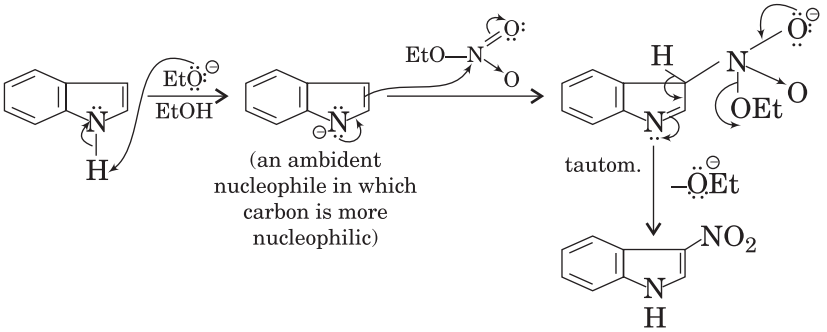
(d)  (e) 

5. Suggest a mechanism for each of the following reactions:

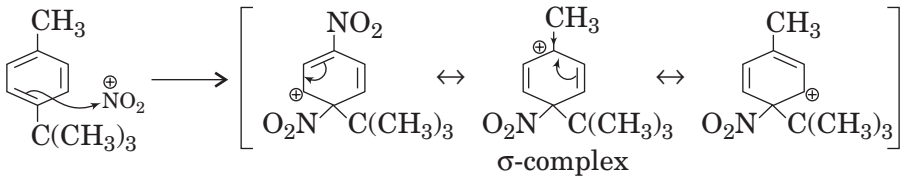
(a) 

(b) 

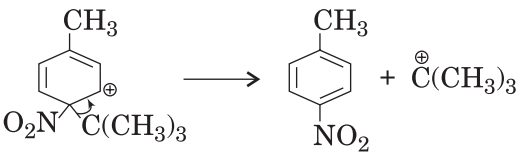
Solution

(a) 

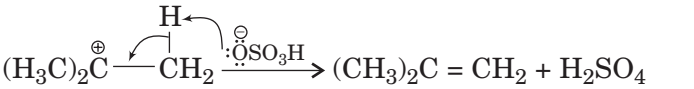
(b) $HNO_3 + 2H_2SO_4 \longrightarrow H_3\overset{\oplus}{O}: + \overset{\oplus}{N}O_2 + 2HSO_4^{\ominus}$

Step 1: 

Step 2: Since $\overset{\oplus}{C}(CH_3)_3$ is a very stable 3° carbocation, it is expelled, i.e. the $-C(CH_3)_3$ group is substituted by the $-NO_2$ group.



The resulting *tert*-butyl cation then loses a portion to yield 2-methylpropene;



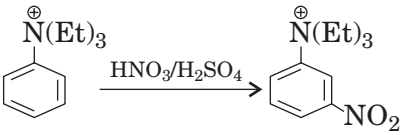
The substitution of $-C(CH_3)_3$ by $-NO_2$ is an example of *ipso*-substitution.

6. Indicate whether each of the following aromatic compounds will undergo nitration faster or slower than benzene, and write the structure of the principal mononitration product in each case. Give your reasoning.

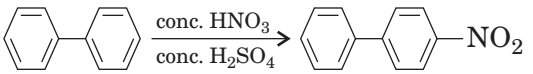
(a) $C_6H_5\overset{\oplus}{N}Et_3$ **(b)** $C_6H_5—C_6H_5$ **(c)** $C_6H_5B(OH)_2$ **(d)** *m*-$CH_3OC_6H_4C_6H_5$

Solution

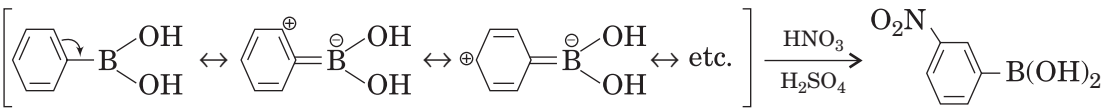
(a) Since $-\overset{\oplus}{N}(Et)_3$ is a deactivating group (withdraws electrons from the ring by –I effect), therefore, nitration will take place at a rate slower than benzene. Since the group is *meta*-directing, the *meta*-product will be obtained predominantly.



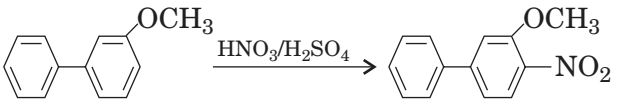
(b) Since $-C_6H_5$ is an activating and *ortho*, *para*-directing group, nitration occurs at a rate faster than benzene predominantly at the *para*-position of one of the rings (the *ortho*-positions sterically crowded).



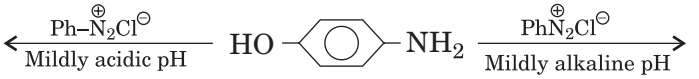
(c) The electronic configuration of boron is a sextet, but the shell can be expanded to an octet. This can be achieved by electron-withdrawal from the ring by –R effect. The $-B(OH)_2$ group is, therefore, a deactivating (the compound undergoes nitration at a rate slower than benzene) and *meta*-directing group. Thus, the *meta*-product will be obtained predominantly.



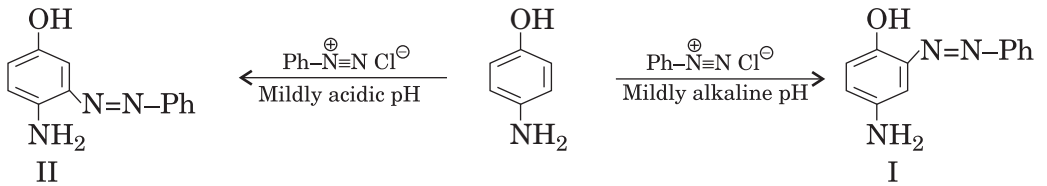
(d) The ring containing the $-OCH_3$ group (as well as a phenyl group) is more activated and so, it undergoes nitration. Since $-OCH_3$, group is more powerful, substitution occurs with respect to it. Because of steric crowding, the position *para* to $-OCH_3$ and one *ortho* position to $-OCH_3$ do not undergo nitration readily. Nitration occurs readily and predominantly at the position *para* to C_6H_5 and *ortho* to $-OCH_3$ to give the major product.



7. Predict the products of the following reactions with plausible mechanism in each case:

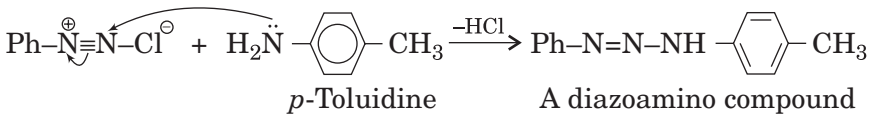


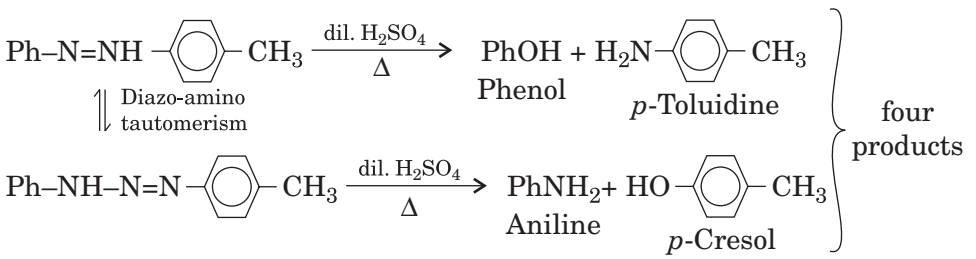
Solution When a substrate contains both the –OH and $-NH_2$ groups, the regioselectivity of diazocoupling reaction depends on the pH of the medium. The *para*-positions with respect to both the –OH and $-NH_2$ groups are blocked and so coupling occurs in the position *ortho* to either group. In weakly alkaline medium, the hydroxide ion does not convert $PhN_2^{\oplus}$ largely to Ph–N=N–OH (diazohydroxide) which does not couple. Also, in such medium, it is the phenoxide ion that is present, and since it activates the ring more than does the $-NH_2$ group, coupling occurs *ortho* to the negatively charged oxygen atom to give the product I. In feebly acidic medium, the concentration of the free amine is relatively high and at the same time the concentration of the diazonium salt is at a maximum and because of this; coupling occurs *ortho* to the $-NH_2$ group to give the product II.



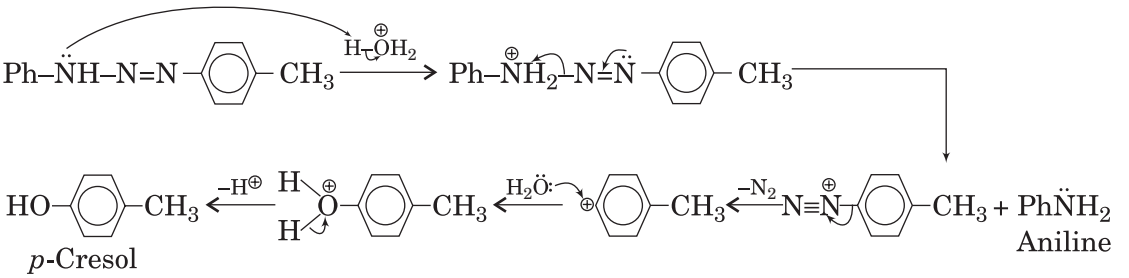
8. *p*-Toluidine reacts with benzenediazonium chloride to form a compound which, on boiling with dil. H_2SO_4, gives four products (excluding nitrogen). Write the products with appropriate mechanism.

Solution *p*-Toluidine reacts with benzenediazonium chloride to form a diazoamino compound. This compound gives four products when heated with dilute sulphuric acid.

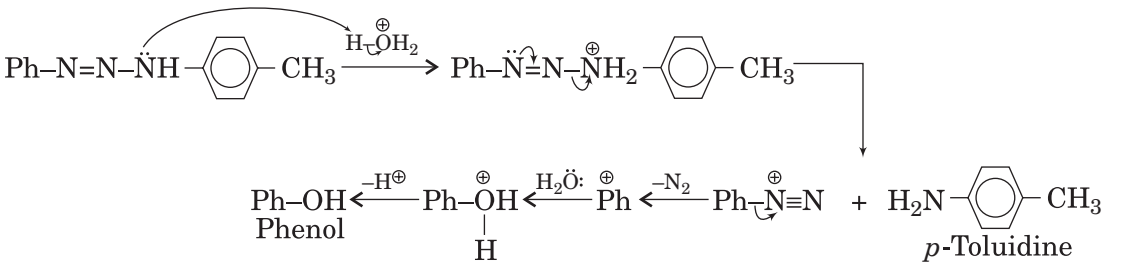




The mechanism of formation of these four products may be outlined as follows:



Similarly,



9. Explain the following observations:

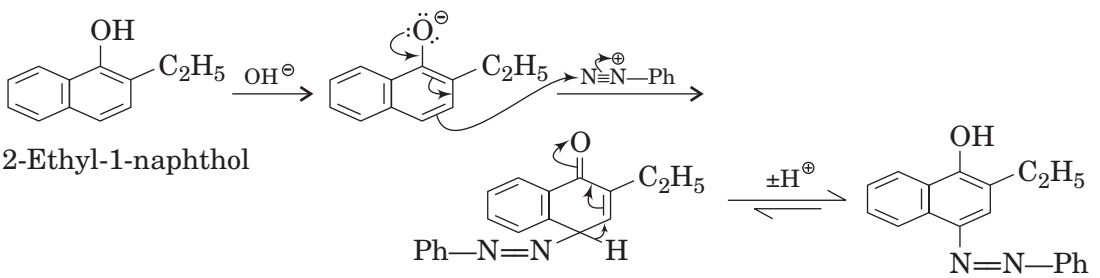
(a) 2-Ethyl-1-naphthol couples with $PhN_2^{\oplus}Cl^{\ominus}$, whereas 1-ethyl-2-naphthol does not.

(b) *N*, *N*-Dimethylaniline couples with $PhN_2^{\oplus}Cl^{\ominus}$, whereas *N*,*N*,2,6-tetramethylaniline does not.

(c) *o*-Phenylenediamine reacts with HNO_2($NaNO_2$/HCl) to yield the heterocyclic compound benzotriazole.

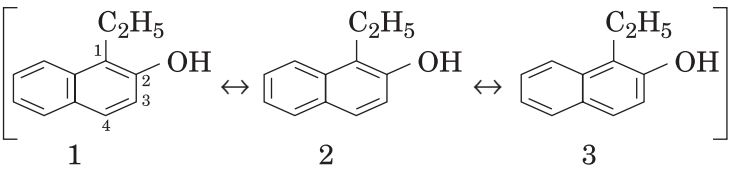
Solution

(a) To avoid steric strain at the *ortho*-position, benzenediazonium chloride couples with phenols almost exclusively at the *para*-position if it is not already substituted. If the *para*-position is not open, coupling occurs at the *ortho*-position. In 2-ethyl-1-naphthol, the position *para* to the –OH group is unoccupied and so, it undergoes ready coupling with $PhN_2^{\oplus}Cl^{\ominus}$ in faintly alkaline medium.



2-Ethyl-1-naphthol

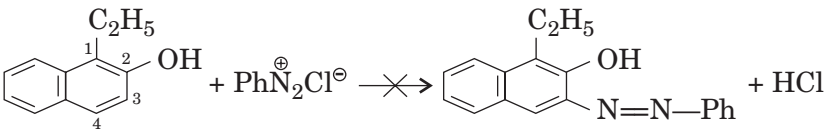
In 1-ethyl-2-naphthol, the position *para* to the –OH group is blocked by benzene ring bond and one *ortho*-position (C-1) is blocked by the ethyl group. Although the other *ortho*-position (C-3) is open, coupling does not take place. This observation can be explained in terms of '*Fries rule*' which states that the most stable resonance structure of a ploynuclear compound is that in which a maximum number of rings are in the benzenoid form. 1-Ethyl-2-naphthol may be represented as a hybrid of the following three resonance structures:



1 2 3

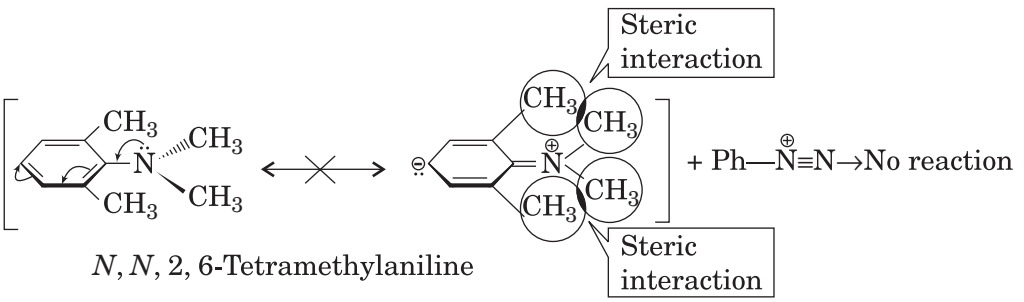
1-Ethyl-2-naphthol

According to the Fries rule, the contribution of the resonance structure 1 (with two benzenoid rings) is the highest and so, the compound behaves like the structure 1. Such bond fixation causes C-3 to be very weakly nucleophilic (to increase the electron-density at C-3 the aromaticity of both the rings is to be destroyed) and thus, unable to attack the weakly electrophilic diazonium cation.



1-Ethyl-2-naphthol

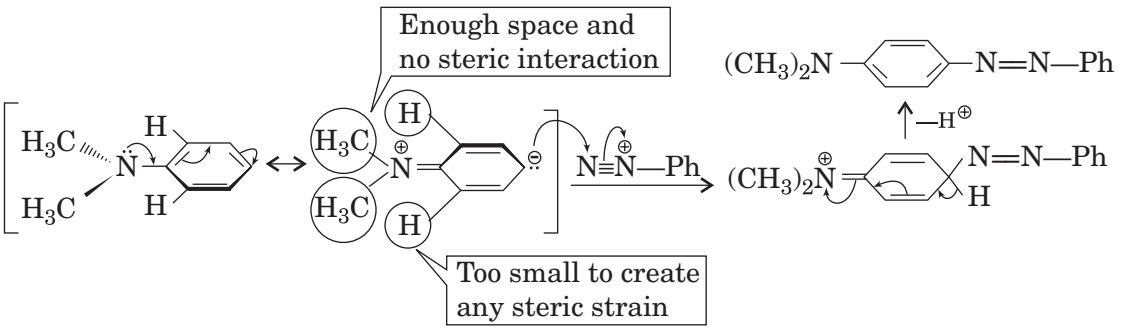
(b) To avoid steric strain in the planar conformation, the $-NMe_2$ group in *N*,*N*,2,6-tatramethylaniline goes out of the plane of the ring and as a consequence, the $-NMe_2$ group is unable to make the *para* position electron rich by exerting its +R effect (steric inhibition of resonance). Attack by this weakly nucleophilic *para*-position on $\overset{\oplus}{PhN}_2$, therefore, does not take place.



N, *N*, 2, 6-Tetramethylaniline

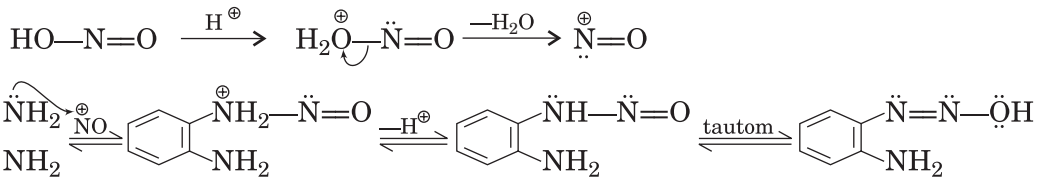
On the other hand, in *N*,*N*-dimethylaniline, the $-NMe_2$ group remains in the plain of the ring as there is no steric strain in the planar information due to the smaller size of hydrogen. This group thus donates electrons effectively by its +R effect. As

a consequence, the *para*-position becomes strongly nucleophilic and coupling with weakly electrophilic $PhN_2^{\oplus}$ takes place readily.

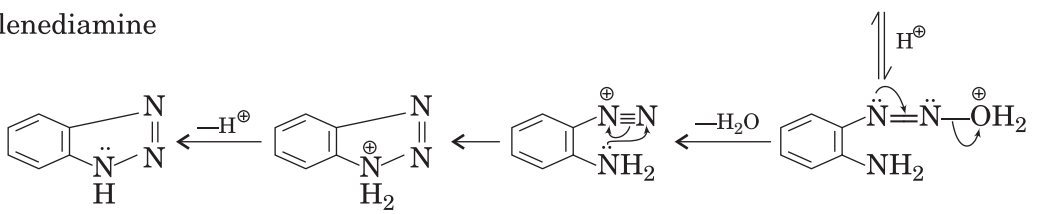


(c) One of the $-NH_2$ groups of *o*-phenylenediamine undergoes *diazotization* in the presence of $HNO_2(NaNO_2/HCl)$ and converted into the $-N^{\oplus}\equiv N$ group. An intramolecular *N*-coupling reaction then takes place to form benzotriazole.

$$NaNO_2 + HCl \rightarrow HNO_2 + NaCl$$



o-Phenylenediamine



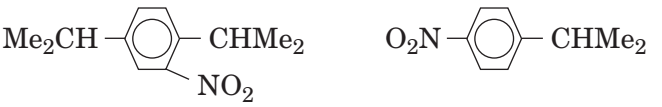
Benzotriazole

Study Problems

1. Show by an arrow the preferred product of mononitration of each of the three isomeric methoxytoluenes and explain your choices.
2. Show by an arrow the preferred product of mononitration obtained from each of the three isomeric nitrotoluenes and give reasoning for your choices.
3. Nitration of phenyl acetate (I) results in *para*-substitution of the nitro group, but nitration of dimethyl phenyl phosphate (II) results in *meta*-sbubstitution of the nitro group. Explain why the two compounds undergo nitration at different positions.

$C_6H_5—OCOCH_3$ (I) $\qquad$ $C_6H_5—OPO(OCH_3)_2$ (II)

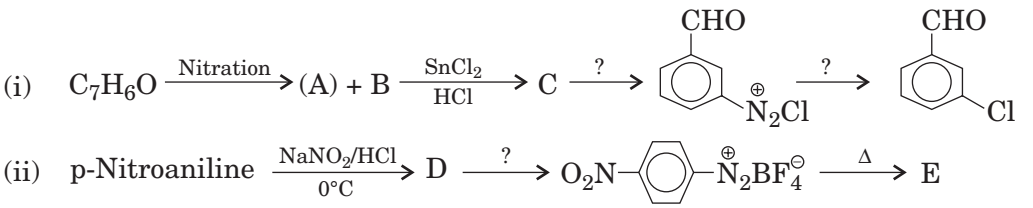
4. Nitration of *p*-diisopropylbenzene gives two products I and II, the latter being formed in major amount. Explain the observation.



I II

5. Explain mechanistically the difference in the pattern of coupling of benzenediazonium cation with (i) aniline and (ii) *N*, *N*-dimethylaniline.

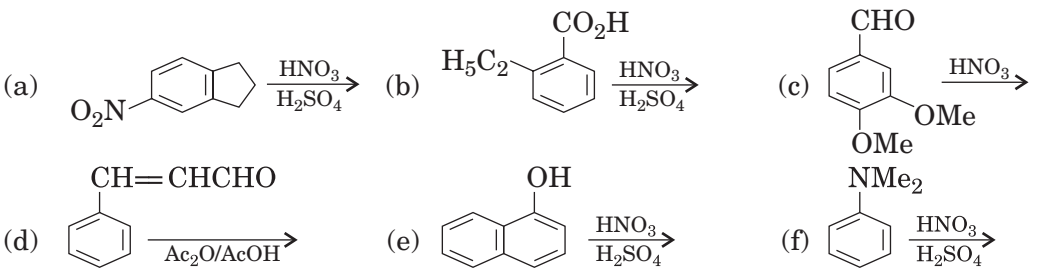
6. Complete the following reactions:



7. How can you distinguish chemically between C_6H_5NHMe and $C_6H_5NMe_2$?

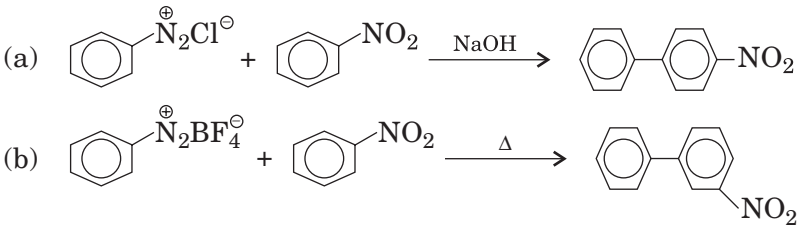
8. When *p*-chloroaniline is diazotised with $NaNO_2$/HBr, the resulting diazonium salt solution couples with *N*, *N*-dimethylaniline to give largely 4-bromo-4′-dimethylaminozobenzene. Explain this observation.

9. Predict the major products and suggest mechanisms for the following reactions:



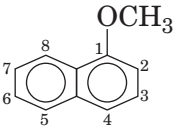
10. When the aromatic compound (molecular formula $C_6H_4Br_2$) is treated with HNO_3/H_2SO_4, three different isomers (molecular formula $C_6H_3Br_2NO_2$) are obtained. Identify the starting compound and its nitroderivatives.

11. Suggest a mechanism for each of the following reactions:



[**Hint:** (a) $Ph—\overset{\oplus}{N}\equiv NCl^{\ominus} \xrightarrow{OH^{\ominus}} Ph\overset{\curvearrowleft}{—}N=N\overset{\curvearrowleft}{—}OH \rightarrow \dot{P}h + N\equiv N + \dot{O}H$; nitrobenzene then reacts with $\dot{P}h$ to give the product (a radical substitution).]

12. Explain why nitration of cinnamic acid produces *p*-nitrocinnamic acid.
13. Although mesitylene is very weakly nucleophilic, it couples with 2,4,6-trinitrobenzenediazonium chloride. Explain.
14. Would 1-methoxynaphthalene nitrate more rapidly or more slowly than naphthalene at (i) C-4, (ii) C-5, and (iii) C-6? Explain your reasoning.



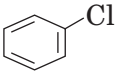
1-Methyoxynaphthalene

3.1.3 Formation of Carbon-Halogen σ-Bond (Halogenation): Bromination and Chlorination, Iodination, Fluorination

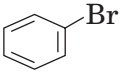
3.1.3.1 Bromination and chlorination of benzene

Benzene reacts with bromine and chlorine in the presence of Lewis acids as a catalyst to form the corresponding halobenzene in good yield. The Lewis acids typically used are aluminium chloride ($AlCl_3$) and iron chloride ($FeCl_3$) for chlorination and iron bromide ($FeBr_3$) for bromination. The ferric chloride and ferric bromide catalysts react readily with moisture in the air during heating, which inactivates them. The avoid this problem, they are generated in the reaction mixture from iron filings and chlorine (or bromine). As a result, the halogen component of the Lewis acid becomes the same as the halogen used for the substitution reaction (Cl_2 and $FeCl_3$ or Br_2 and $FeBr_3$).

$$2Fe + 3Cl_2 \longrightarrow 2FeCl_3 \quad ; \quad 2Fe + 3Br_2 \longrightarrow 2FeBr_3$$

Chlorination:  $+ Cl_2 \xrightarrow[\text{or Fe}]{FeCl_3}$  $+ HCl$

Benzene — Chlorobenzene (90%)

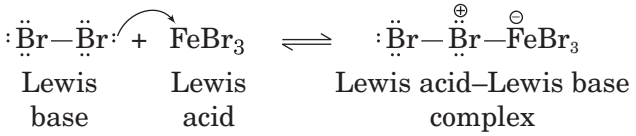
Bromination:  $+ Br_2 \xrightarrow[\text{or Fe}]{FeBr_3}$  $+ HBr$

Benzene — Bromobenzene (75%)

Mechanism for electrophilic aromatic bromination Bromine (Br_2), by itself, is not a strong enough electrophile (Lewis acid) to react with the weakly nucleophilic benzene. The function of the catalyst $FeBr_3$ is to convert bromine into a stronger electrophile that can smoothly react with the aromatic compound. Ferric bromide does this by forming a complex with bromine.

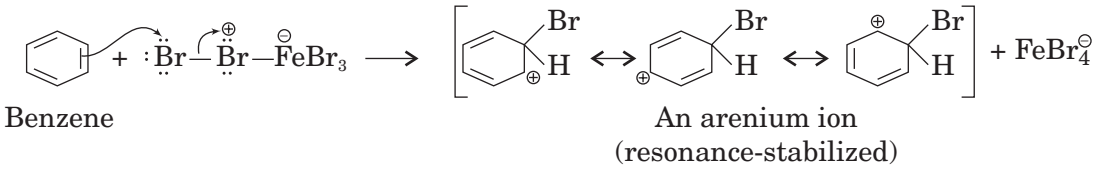
The reaction proceeds through the steps as follows:

Step 1: Bromine combines with $FeBr_3$ to form a complex which is a better electrophile than bromine. This is because $FeBr_4^{\ominus}$ is a better leaving group than $Br^{\ominus}$.

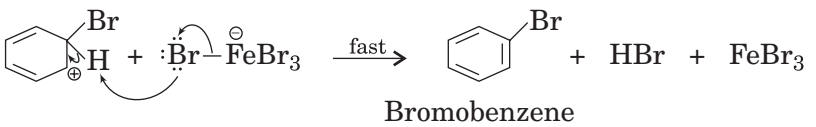


Benzene is nucleophilic enough to displace $FeBr_4^{\ominus}$ from Br_2–$FeBr_3$ complex.

Step 2: The complex is attacked by the π electrons of the benzene ring to form a resonance-stabilized arenium ion or cyclohexadienyl cation. This is the rate-determining step of the reaction because the aromaticity of the benzene ring is destroyed.

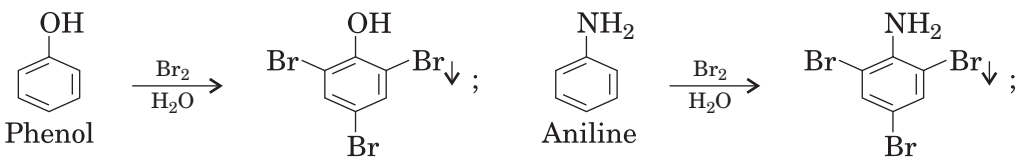


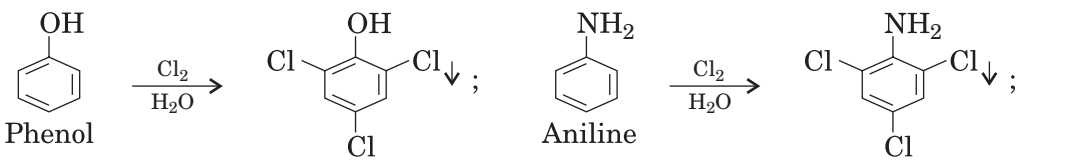
Step 3: A proton is removed from the arenium ion by a bromide ion (complexed to $FeBr_3$) to form bromobenzene and HBr. The catalyst $FeBr_3$ is regenerated. This step is fast because the aromaticity of the benzene ring is restored.



The mechanism for chlorination of benzene is the same as that for bromination.

Halogenation of activated aromatic compounds For activated aromatic compounds like phenols, anilines, etc., no catalyst is required to activate the halogen and the reaction is so fast that it is difficult to step the reaction at monohalogenation stage particularly when bromination is carried out with Br_2/H_2O.

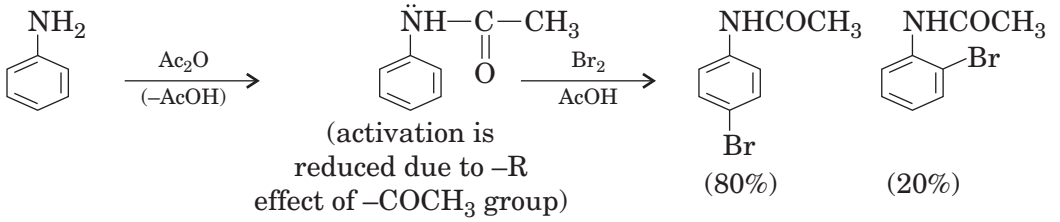




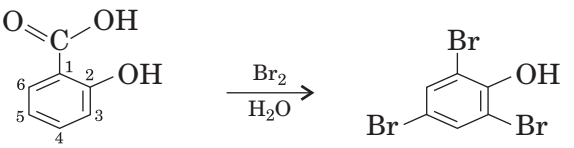
However, the substitution can be controlled by using nonpolar solvents like CS_2, CCl_4, etc. For example, when phenol is allowed to react with a carbon-disulphide solution of bromine at 0°C, a mixture of *ortho*- and *para*-bromophenol (major) is obtained.

$$\underset{\text{Phenol}}{C_6H_5OH} + Br_2 \xrightarrow[0°C]{CS_2} \underset{o\text{-Bromophenol}}{o\text{-}BrC_6H_4OH} + \underset{\substack{p\text{-Bromophenol}\\(\text{major})}}{p\text{-}BrC_6H_4OH}$$

When bromination of aniline is carried out after reducing the activating effect of the NH_2 group by acetylation, monohalo product is obtained. Because of steric crowding at the *ortho*-position, *para*-product is obtained predominantly.

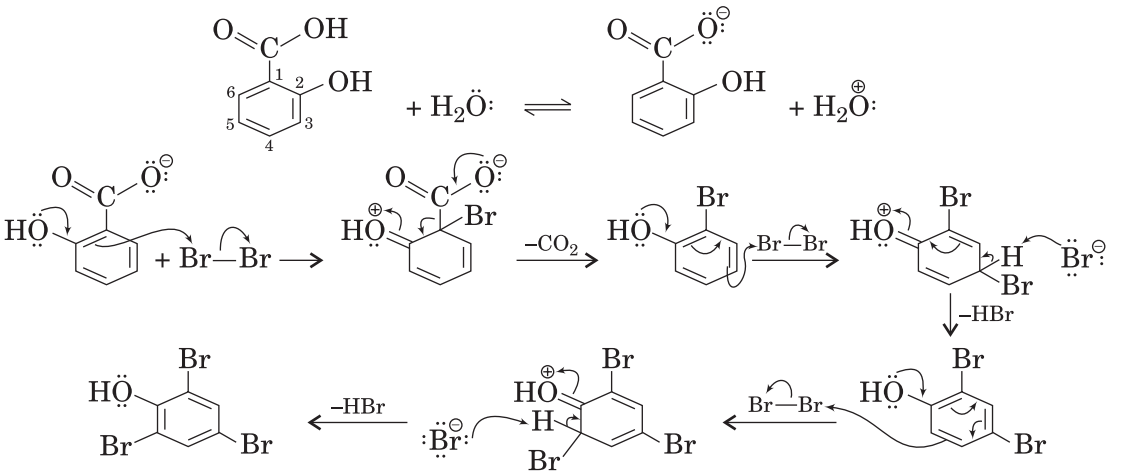


The reaction of phenol with Br_2/H_2O is so effective that even a –COOH or $–SO_3H$ group at *ortho*- or *para*-position is displaced by bromine. For example, when salicylic acid or *o*-hydroxybenzoic acid is treated with Br_2/H_2O, 2,4,6-tribromo-phenol is obtained.



Salicylic acid or *o*-Hydroxybenzoic acid — 2,4,6-Tribromophenol

Mechanism of the reaction Bromination occurs at C-3 (*ortho*- to –OH) and C-5 (*para*-to –OH) and decarboxylative bromination occurs at C-1. The reaction takes place as follows:



3.1.3.2 Iodination of benzene

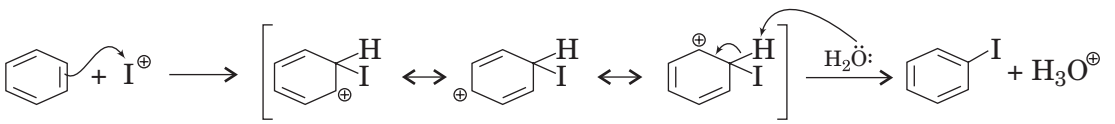
Substitution of iodine in aromatic compounds is difficult because iodine is the least reactive of the halogens and moreover, the reaction is essentially reversible. Iodination of benzene requires an oxidizing agent, such as nitric acid or H_2O_2 in the presence of H_2SO_4. Nitric acid is consumed in the reaction, so it is a reagent (an oxidant) rather than a catalyst. Iodination probably involves iodinium ion ($I^{\oplus}$) as the electrophile. The iodinium ion results from the oxidation of I_2 by HNO_3.

$$2H^{\oplus} + 2HNO_3 + I_2 \longrightarrow 2I^{\oplus} + 2NO_2 + 2H_2O$$

$$C_6H_6 + I_2 \xrightarrow{HNO_3} C_6H_5I$$

Iodobenzene
(85%)

Mechanism of the reaction In step 1, the electrophile $I^{\oplus}$ adds to the benzene ring to form an arenium ion. In step 2, a base (e.g., H_2O) in the reaction mixture removes the proton from the carbon that formed the bond with the electrophile.



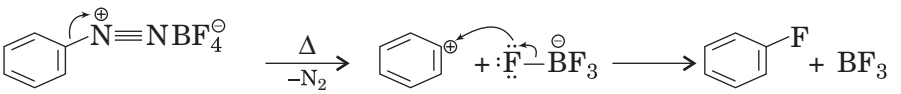
An arenium ion or σ-complex

3.1.3.3 Fluorination of benzene

Since fluorine reacts with aromatic compounds violently to produce a variety of products, direct fluorination of benzene with fluorine is not feasible at room temperature. Fluorination has been reported with acetyl hypofluorite (CH_3COOF), with XeF_2, and with an *N*-fluoroperfluoroalkylsulfonamide, for example, (CF_3SO_2) NF. However, none of these methods is not as good as the *Schiemann reaction* (heating diazonium tetrafluoroborates) which is the most common method for introducing fluorine into aromatic rings.

$$Ph\text{—}\overset{\oplus}{N}\equiv N\ BF_4^{\ominus} \xrightarrow{\Delta} PhF + N_2 + BF_3$$

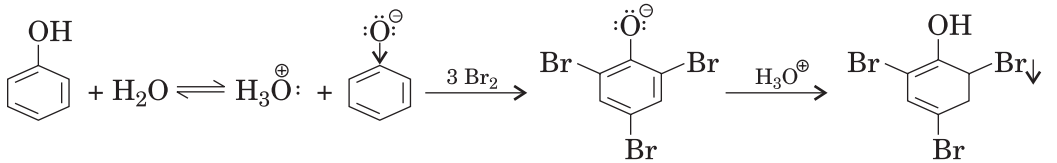
Mechanism of the reaction



SOLVED PROBLEMS

1. Account for the difference in behaviour of phenol with Br_2/H_2O and Br_2/CS_2.

Solution Phenol ionizes in water to give phenoxide ion ($PhO^{\ominus}$) which is the reacting species. Due to powerful electron release by the negatively charged oxygen through its stronger + R effect and +I effect, the phenoxide ring is highly activated and for this reason polybromination occurs to yield 2,4,6-tribromophenol (a white solid). On the other hand, in the nonpolar solvent CS_2 phenol remains undissociated. The ring is now less activated because of –I effect and relatively weak +R effect of the –OH group and for this reason, monobromination occurs to give a mixture of *o*- and *p*-bromophenol.



Phenol (ring is less activated) | Phenoxide ion (ring is more activated) | 2,4,6-Tribromophenol (White solid)

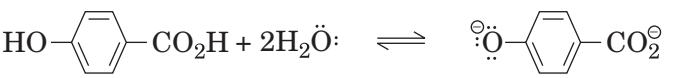
$$C_6H_5OH + Br_2 \xrightarrow{CS_2} \underset{o\text{-Bromophenol}}{o\text{-}BrC_6H_4OH} + \underset{p\text{-Bromophenol}}{p\text{-}BrC_6H_4OH}$$

Phenol

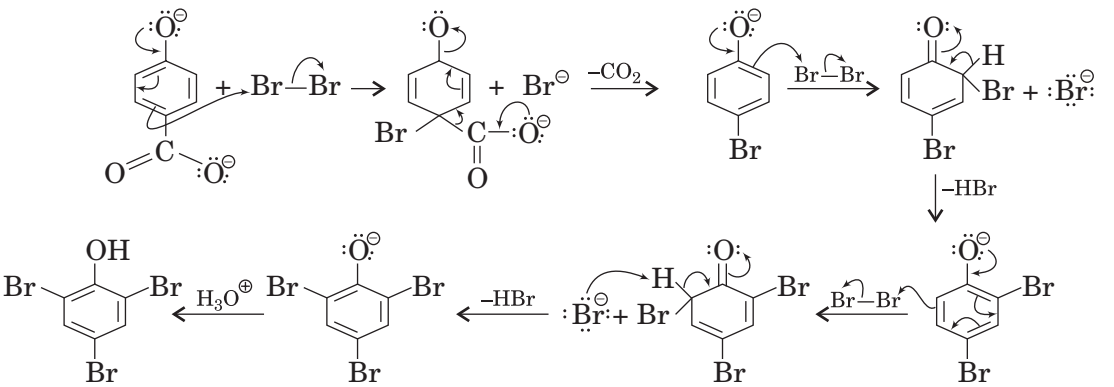
2. *p*-Hydroxybenzoic acid and *p*-hydroxybenzenesulphonic acid react with bromine water to give a common substitution product. Explain with mechanism.

Solution Both of these two acids undergo normal bromination at the two positions *ortho*- to the –OH group. In addition to that *p*-hydroxybenzoic acid undergoes decarboxylative bromination and *p*-hydroxysulphonic acid undergoes desulphonative bromination. Thus, both of these two acids react with bromine water to yield the common substitution product 2,4,6-tribromophenol.

Bromination of *p*-hydroxybenzoic acid:

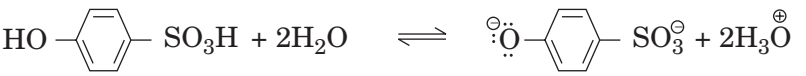


p-Hydrobenzoic acid | Dianion



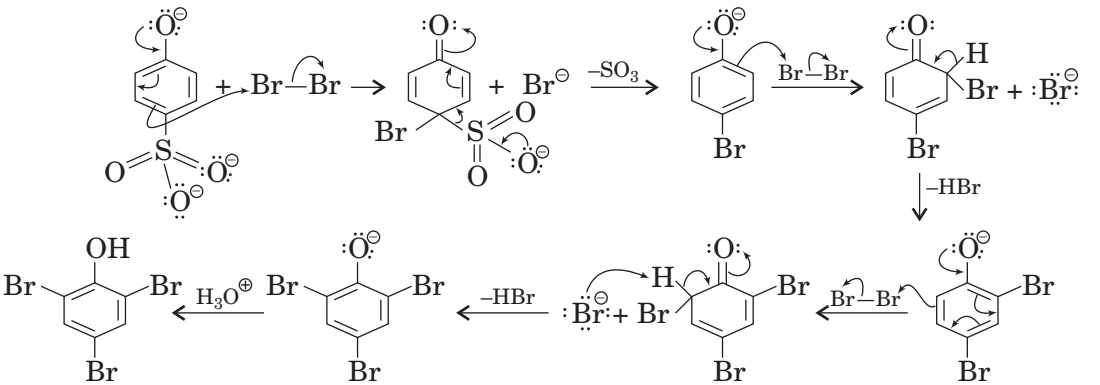
2,4,6-Tribromophenol

Bromination of *p*-hydroxybenzenesulphonic acid



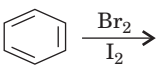
p-Hydroxybenzene sulphonic acid

Dianion

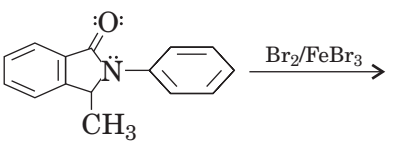


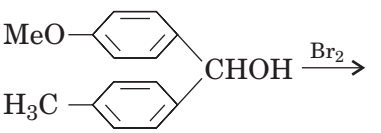
2,4,6-Tribromophenol

3. Predict the product and suggest a reasonable mechanism for each of the following reactions

(a) 

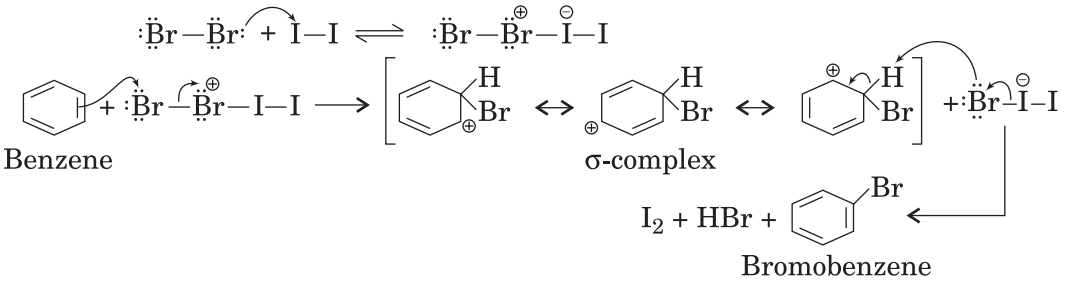
(b) 

(c) 

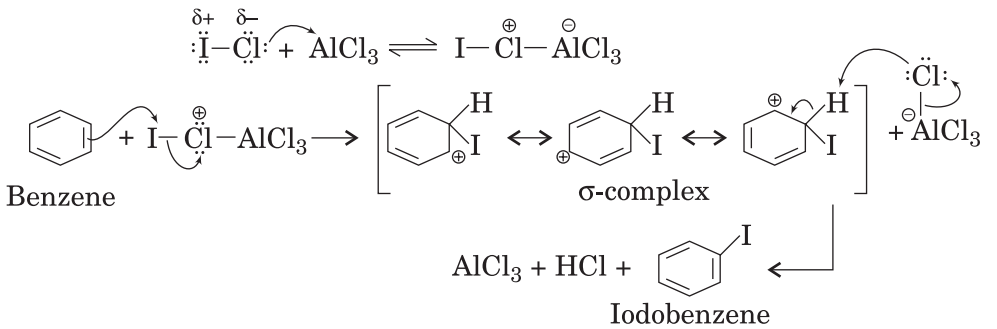
(d) 

Solution

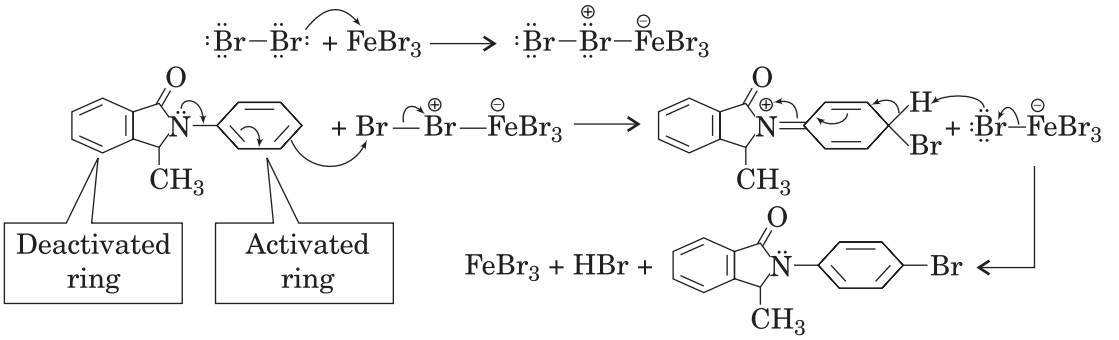
(a) Iodine accepts an unshared pair of electrons from bromine atom of Br_2 by expansion of its octet and thereby produce the complex $Br-\overset{\oplus}{B}r-\overset{\ominus}{I}-I$. This Lewis acid–Lewis base complex then acts as the electrophile in bromination of benzene.
The reaction takes place as follows:



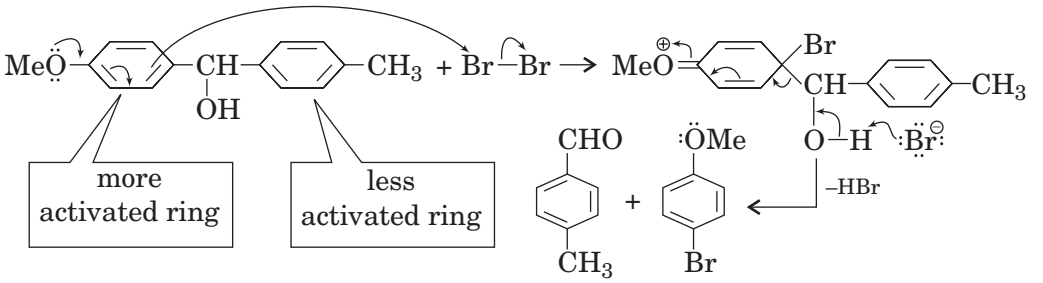
(b) Due to higher electronegativity of chlorine compared to iodine, iodine monochloride polarizes as $\overset{\delta+}{I}-\overset{\delta-}{Cl}$ and therefore, it combines with the Lewis acid $AlCl_3$ through its negative end to produce the Lewis acid-Lewis base complex $I-\overset{\oplus}{C}l-\overset{\ominus}{A}lCl_3$. This complex then acts as the electrophilic species in iodination of benzene.



(c) Due to the +R effect of nitrogen, the ring attached to it is activated. However, due to –R effect of C==O, the ring attached to it is deactivated. For this reason, the former ring undergoes bromination to give the product. Again, the two *ortho*-positions are sterically hindered and so, substitution occurs preferably at the *para*-position.

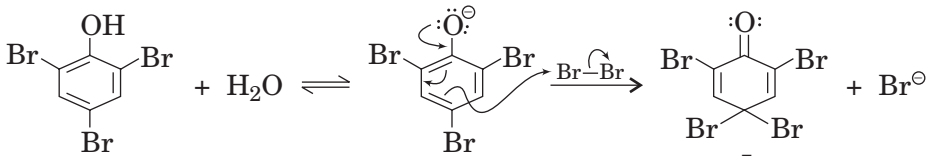


(d) The ring of the *p*-anisyl group is more activated than the ring of the *p*-tolyl group and so, electrophilic attack by Br_2 occurs on the former ring to form an arenium ion. It then undergoes aromatisation through O—H and O—C bond cleavage to yield *p*-bromoanisole and *p*-methylbenzaldehyde.
The reaction may be shown as follows:



4. When 2,4,6-tribromophenol is treated with an excess of bromine water, a yellow, nonacidic compound (I), molecular formula $C_6H_2OBr_4$, is produced. Write the structure of the compound and explain its formation.

Solution Because of increased acidity, 2,4,6-tribromophenol rapidly ionises in water to form the corresponding anion. The anion readily undergoes bromination to yield 2,4,4,6-tetrabromocyclohexa-2,5-dione ($C_6H_2OBr_4$).

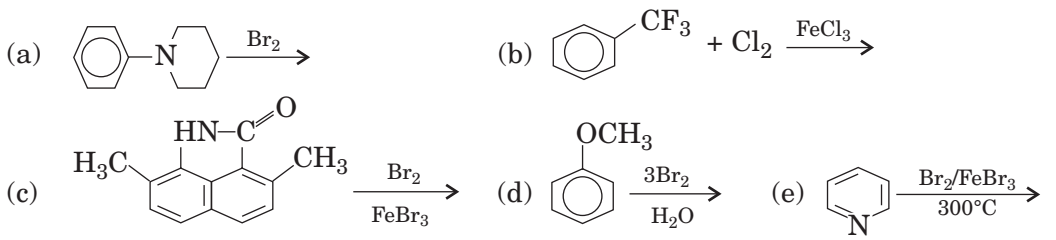


2,4,6-Tribromophenol ($C_6H_2OBr_4$)

Because of stable *p*-quinonoid structure in the product, attack occurs at the *p*-position.

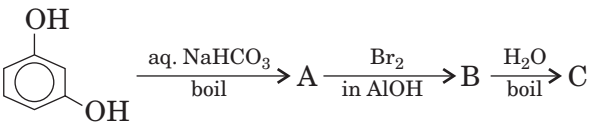
Study Problems

1. Explain why hydration inactivates $FeBr_3$.
2. Why does the reaction of benzene with Br_2 or Cl_2 require a catalyst when the reaction of an alkene with these reagents does not require a catalyst?
3. Which one between *m*- or *p*-xylene reacts more rapidly with $Cl_2/FeCl_3$ and why?
4. Predict the major products of the following reactions and explain your reasoning:



5. Explain what happens when anthracene is treated with bromine (1 mole) and then heated with alkali.
[**Hint:** 9,10-Addition of Br_2 followed by loss of HBr in the presence of alkali.]

6. Complete the following:



7. (a) How would you carry out the following transformation?

$$\text{Aniline} \longrightarrow \text{1,3,5-Tribromobenzene}$$

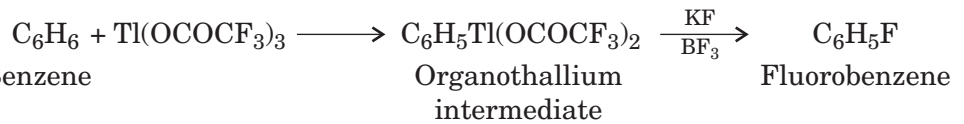
(b) Explain why bromination of mesitylene requires no Lewis acid catalyst.

8. Explain what will happen when $ArCMe_3$ is treated with $Br_2/AlBr_3$.

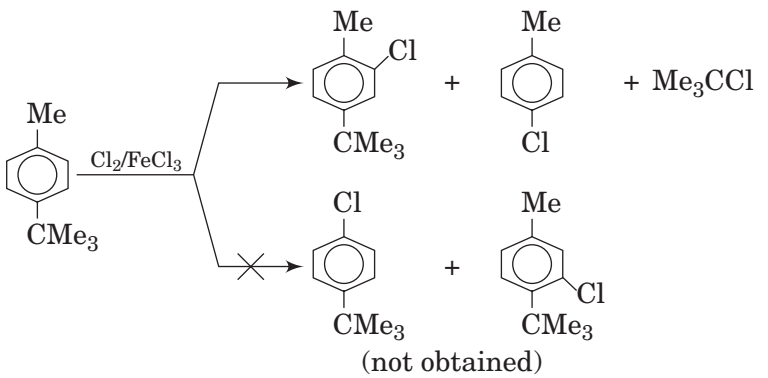
9. Toluene reacts with $Cl_2/h\nu$ to give benzylchloride. While it reacts with Cl_2/Fe to give a mixture of *o*- and *p*-chlorotoluene. Explain.

10. Naphthalene reacts with Br_2/Fe at a faster rate than benzene. Explain.
[**Hint:** Due to lower loss of resonance energy, formation of σ-complex (step 1) for naphthalene is faster than that of benzene.]

11. Controlled fluorination of benzene, although difficult, can be accomplished by a two-step thallation procedure. Benzene is allowed to react with thallium tris(trifluoroacetate), $Tl(OCOCF_3)_3$, to yield an organothallium intermediate which, when treated with KF and BF_3, produces fluorobenzene. Propose a reasonable mechanism for the first step (the thallation of benzene).



12. Explain the following observations



[**Hint:** Because of less steric crowding Cl enters *ortho* to Me and because of greater stability of $\overset{\oplus}{C}Me_3$, the *t*-butyl group is substituted by Cl.]

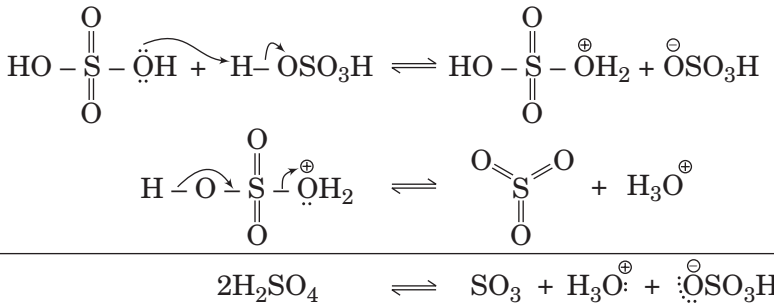
3.1.4 Formation of Carbon–Sulphur σ-Bond: • Sulphonation and Chlorosulphonation

3.1.4.1 Sulphonation

Another electrophilic substitution reaction of benzene is its conversion into benzenesulphonic acid ($PhSO_3H$). This reaction is called *sulphonation*. When benzene is treated with fuming sulphuric acid (sulphuric acid that contains added sulphur trioxide, SO_3) or heated with concentrated sulphuric acid at 80°C, benzenesulphonic acid is obtained. The latter reaction is, however, takes place more slowly. Under either condition, the electrophile appears to be sulphur trioxide (SO_3) or protonated sulphur trioxide $\overset{\oplus}{S}O_3H$. Sulphonation, unlike many electrophilic aromatic substitution reactions, is reversible.

$$\underset{\text{Benzene}}{C_6H_6} \xrightarrow[\text{or concentrated } H_2SO_4/80°C]{\text{fuming } H_2SO_4,\ 25°C} \underset{\text{Benzenesulphonic acid}}{C_6H_5SO_3H}$$

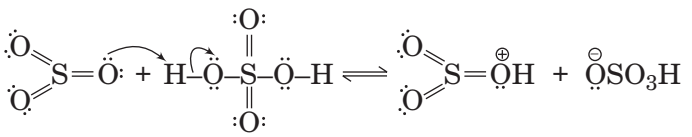
Mechanism of the reaction In concentrated sulphuric acid, SO_3 is generated by the following reaction in which H_2SO_4 acts as both an acid and a base



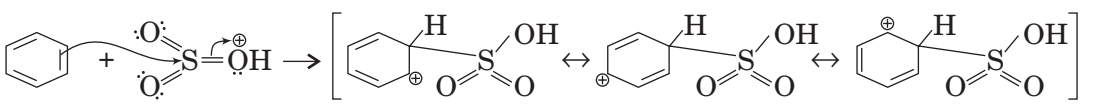
Sulphonation occurs by two mechanisms that operate simultaneously.

(i) The mechanism, when the electrophile is protonated SO_3, involves the steps as follows:

Step 1: SO_3 is protonated to form $SO_3H^{\oplus}$ (the electrophile)

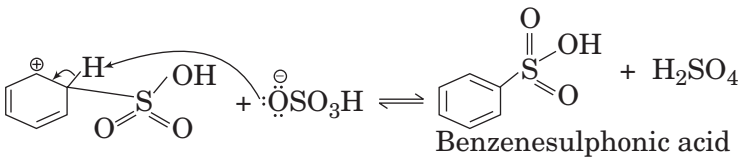


Step 2: The protonated sulphur trioxide is attacked by the π system of the benzene ring to form a resonance-stabilized arenium ion or σ-complex. It is the rate-determining step of the reaction.

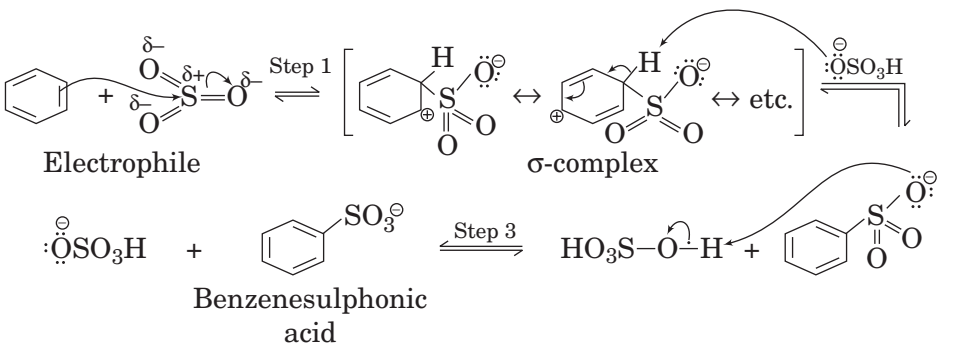


Benzene (protonated SO_3) An arenium ion or σ-complex

Step 3: The arenium ion loses to a proton to form benzenesulphonic acid. The aromaticity of the ring is restored and the acid catalyst is regenerated.

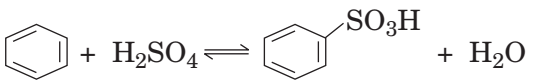


(ii) The mechanism, when the electrophile is sulphur trioxide (SO_3), involves the steps as follows:



Difference of sulphonation from other aromatic electrophilic substitutions Sulphonation differs from other electrophilic substitution reaction in two ways:

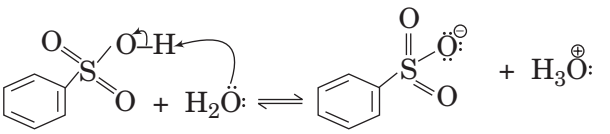
1. All the steps in sulphonation reaction are equilibria. The overall reaction is, therefore, reversible. The position of the equilibrium can be influenced by the conditions employed.



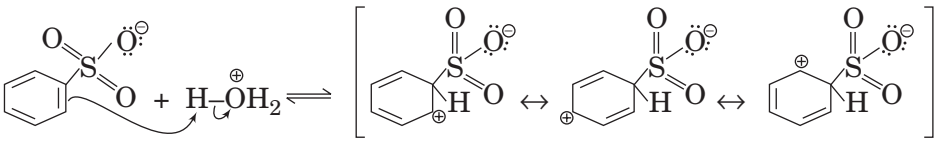
If the ring is to be sulphonated (introduction of a sulphonic acid group) concentrated or fuming H_2SO_4 is to be used. Under such conditions, the position of equilibrium lies appreciably to the right-hand side, and benzenesulphonic acid is obtained in good yield. On the other hand, if the ring is to be desulphonated (removal of a sulphonic acid group) benzenesulphonic acid is to be heated with dilute H_2SO_4 or HCl or is to be treated with superheated steam. Under such conditions (with a high concentration of water), the equilibrium lies appreciably to the left-hand side and desulphonation occurs.

Mechanism of desulphonation According to the principle of microscopic reversibility, the mechanism of desulphonation is just the reverse of sulphonation. Hence, desulphonation is also an electrophilic aromatic substitution where the electrophilic is the proton, $H^{\oplus}$. The mechanism of desulphonation may be outlined as follows:

Step 1: Being a strong acid benzenesulphonic acid it undergoes dissociation in the presence of water.

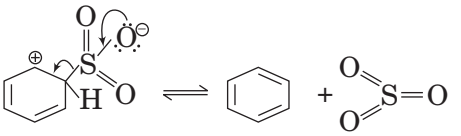


Step 2: The electrophile $H^{\oplus}$ is attacked by the benzenesulphonate ion to form the intermediate arenium ion or σ-complex. It is the rate-determining (slow) step of the reaction.



An arenium ion or σ-complex

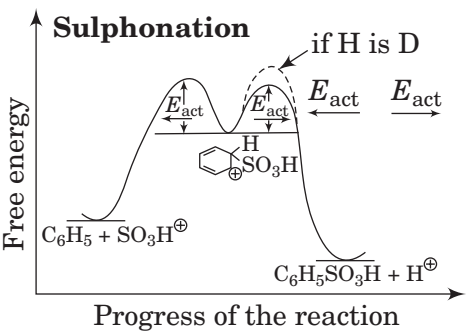
Step 3: The σ-complex undergoes aromatisation with expulsion of SO_3 to form benzene.

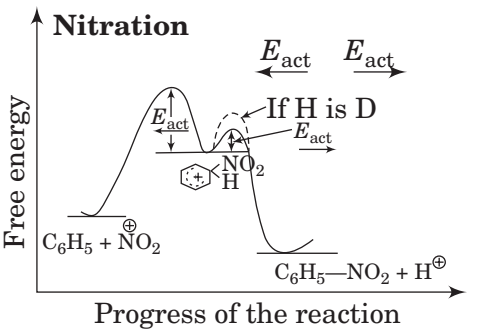


The resulting sulphur trioxide reacts with water to form H_2SO_4.

[In some cases of electrophilic aromatic substitution, displacement of one ring substituent by another occurs. This process is called *ipso*-substitution (*ipso*, Latin, on itself). It thus follows that desulphonation of benzenesulphonic acid (displacement of SO_3H by H) is an example of *ipso* substitution.]

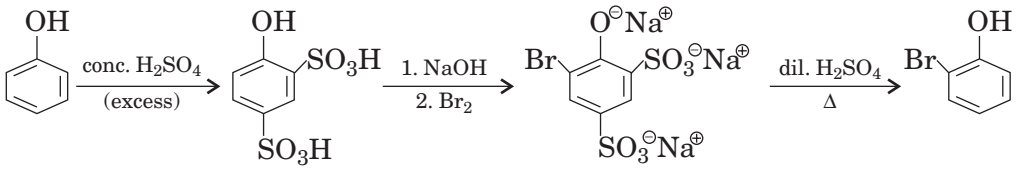
2. Sulphonation shows a kinetic isotope effect. When the rate of sulphonation of C_6H_6 and that of C_6D_6 is compared, it shows $k_H/k_D \simeq 2$. From the reversibility of the reaction, it becomes clear that the activation energies in returning the intermediate to the reactants and their passing down to the product are approximately equal. It is not true for other electrophilic aromatic substitutions like nitration, halogenation, etc. In common electrophilic aromatic substitutions, the intermediate requires much less energy to go to the products. The situations may be compared by the following energy diagrams:





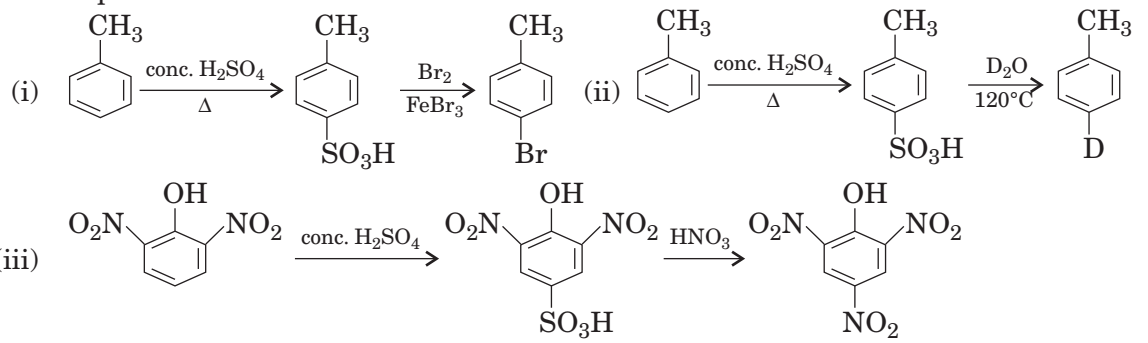
The energy of activation for the second step is higher for C_6D_6 both in sulphonation and nitration. But for nitration, the activation energy for the second step in the case C_6D_6 is still lower than activation energy of the reverse of the first step and so, the isotope effect is not significant. However, in sulphonation the activation energy of the second step in the case of C_6D_6 is slightly higher than the activation energy for the reverse of the first step. Because of this, more deuterated arenium ions than ordinary ions revert to the starting material, and so the overall sulphonation is slower for the deuterated benzene (C_6D_6). Thus, the particular shape of the free energy curve that makes sulphonation reversible also permits an isotope effect to be observed.

Use of sulphonation and desulphonation reactions A sulphonate group may be introduced into the aromatic system to temporarily block the position from electrophilic aromatic substitution, i.e., a sulphonate group can be used as a blocking group and when it is no longer needed, it can be removed from the system. A sulphonate group can also be used as a directing group to influence the position of another substitution relative to it. That sulphonation-desulphonation is a useful synthetic tool that can be well illustrated by the synthesis of *o*-bromophenol from phenol. It is difficult to get *o*-bromophenol from phenol by direct bromination as it readily forms 2,4,6-tribromophenol. However, this may be accomplished by sulphonation-desulphonation technique.



The sulphonation-desulphonation technique can also be used to introduce –Br, –D or $-NO_2$ group into the aromatic system.

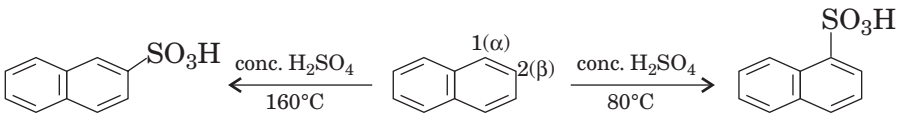
For example:



Today, one of the largest uses of the sulphonation reaction is the production of detergents. Alkylbenzenes prepared by the Friedel–Crafts reaction are sulphonated in high yield to form benzenesulphonic acids whose salts are *detergents*.

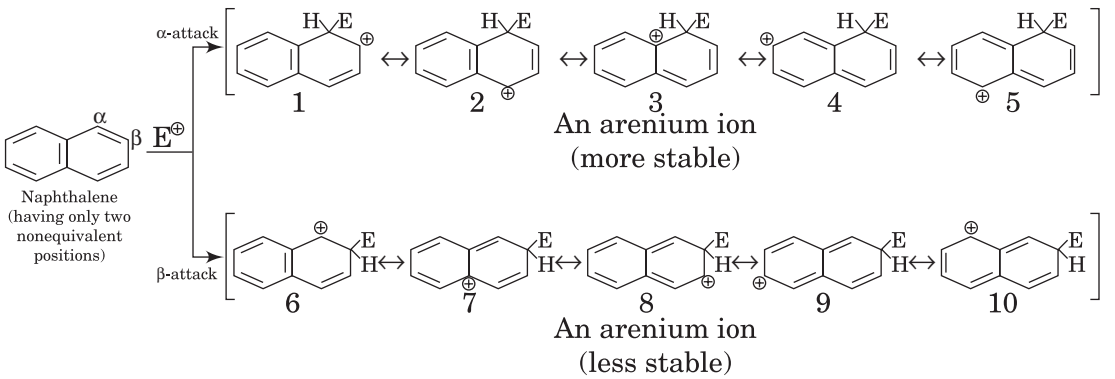
Sulphonation of naphthalene (Kinetic control versus thermodynamic control) When a reaction produces more than one product, the product that is formed most readily is called the *kinetically controlled product* or simply *kinetic product*. Reactions that produce the kinetic product as the major product are said to be *kinetically controlled reactions*. On the other hand, the most stable product is called the *thermodynamically controlled product* or *simply thermodynamic product*. Reactions that lead to the formation of the thermodynamic product as the major product are said to be *thermodynamically controlled reactions*.

Naphthalene undergoes sulphonation at 80°C to yield mainly α-naphthanelesulphonic acid, but at 160°C it yields mainly β-naphthalenesulphonic acid.

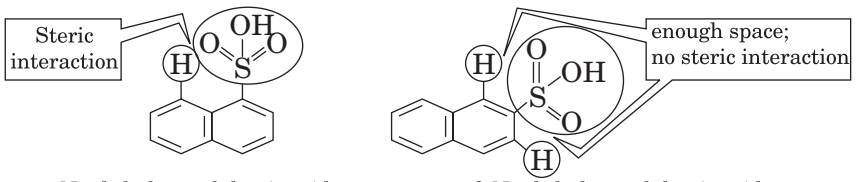


2- or β-Naphthalenesulphonic acid (85%) — Naphthalene — 1- or α-Naphthalenesulphonic acid (96%)

The sulphonation reaction is readily reversible at an elevated temperature. However, at low temperature, the reaction is practically irreversible. Since the reaction does not reach equilibrium at low temperatures, the product isolated is one that formed at a faster rate (kinetic product). Rapid formation of α-acid is due to greater stabilisation of the intermediate arenium ion or σ-complex or the transition state leading to it and this is because the arenium ion for α-substitution contains two structures (1 and 2), but the arenium ion for β-substitution contains only one structure (6) in which an aromatic ring is retained.



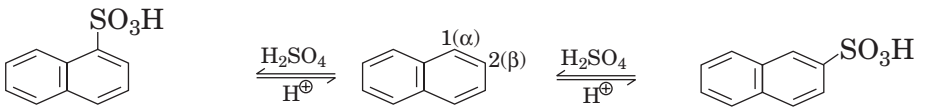
The α-acid is thermodynamically less stable than the β-acid, even though it is formed rapidly. Because of steric interaction between the bulky $-SO_3H$ group at C-1 and the hydrogen at C-8 (or *peri*-position), the α-acid is less stable than the β-acid.



1- or α-Naphthalenesulphonic acid (less stable)

2- or β-Naphthalenesulphonic acid (more stable)

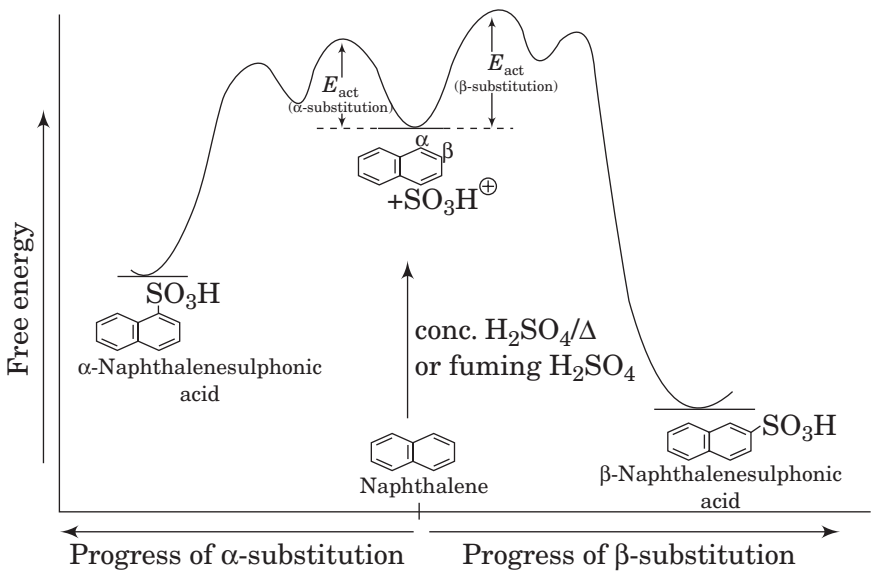
At higher temperature (160°C), the major product is β-naphthalenesulphonic acid. Under this equilibrium conditions, the less stable but readily formed α-acid undergoes ready desulphonation to yield naphthalene which undergoes new attack at C-2 to yield the more stable β-acid (the thermodynamic product). Once formed the β-acid resists desulphonation due to much higher energy of activation.



α-Naphthalenesulphonic acid (rapid formation as well as desulphonation)

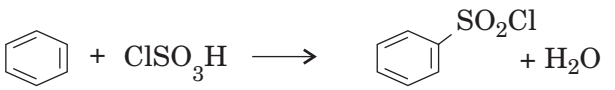
β-Naphthalenesulphonic acid (slow formation as well as desulphonation)

The energy diagram for the sulphonation of naphthalene is as follows:



3.1.4.2 Chlorosulphonation

Aromatic compounds, which are not strongly deactivated, reacts with chlorosulphonic acid ($ClSO_3H$) at room temperature to yield the corresponding sulphonyl chloride derivatives. For example, benzene forms benzene-sulphonyl chloride ($PhSO_2Cl$).



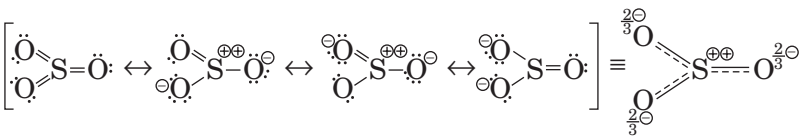
Benzene — Chlorosulphonic acid — Benzenechlorosulphonyl chloride

Applications *p*-Toluene sulphonyl chloride, prepared by chlorosulphonation of toluene, is extensively used for protection of –OH or $–NH_2$ group. Aromatic sulphonyl chlorides are used to prepare important 'Sulpha' drugs like sulphanilamide, sulphadiazine, sulphathiazole, etc.

SOLVED PROBLEMS

1. **Explain why the S-atom in SO_3 is highly electron deficient and can act as the electrophilic centre.**

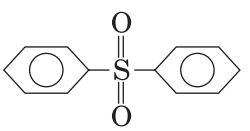
Solution Sulphur trioxide (SO_3) molecule may be represented as a resonance hybrid of the following four resonance structures or canonicals:



Resonance structures of SO_3 — Hybrid structure

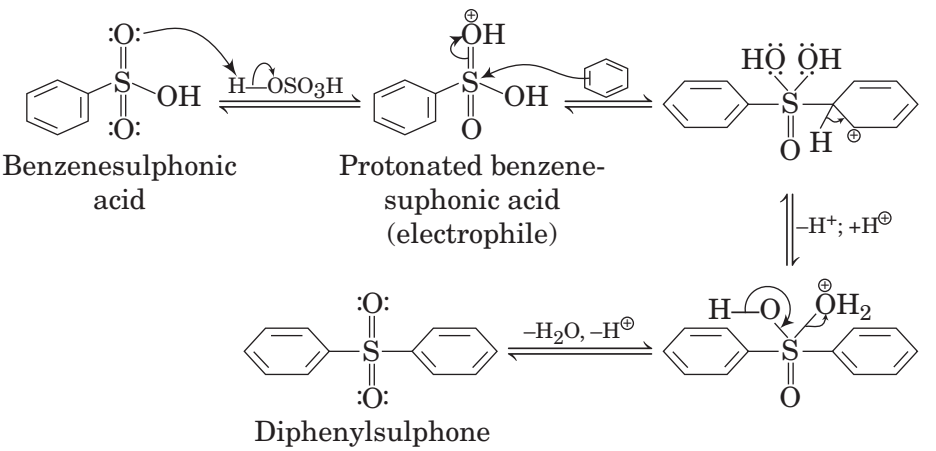
From the hybrid structure it becomes clear that the S-atom in SO_3 is highly electron deficient and can act as the electrophilic centre.

2. **Diphenylsulfone is a by-product that is formed in the sulphonation of benzene. Give a curved-arrow mechanism for its formation.**



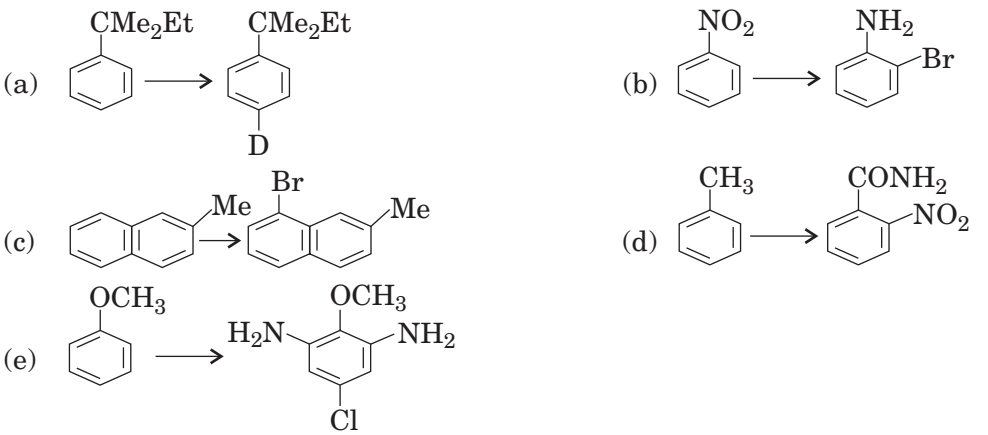
Diphenylsulphone

Solution The mechanism for the formation of diphenylsulfone during sulphonation of benzene may be outlined as follows:

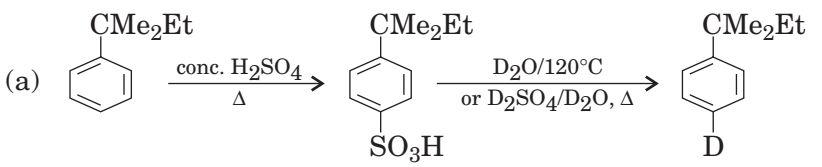


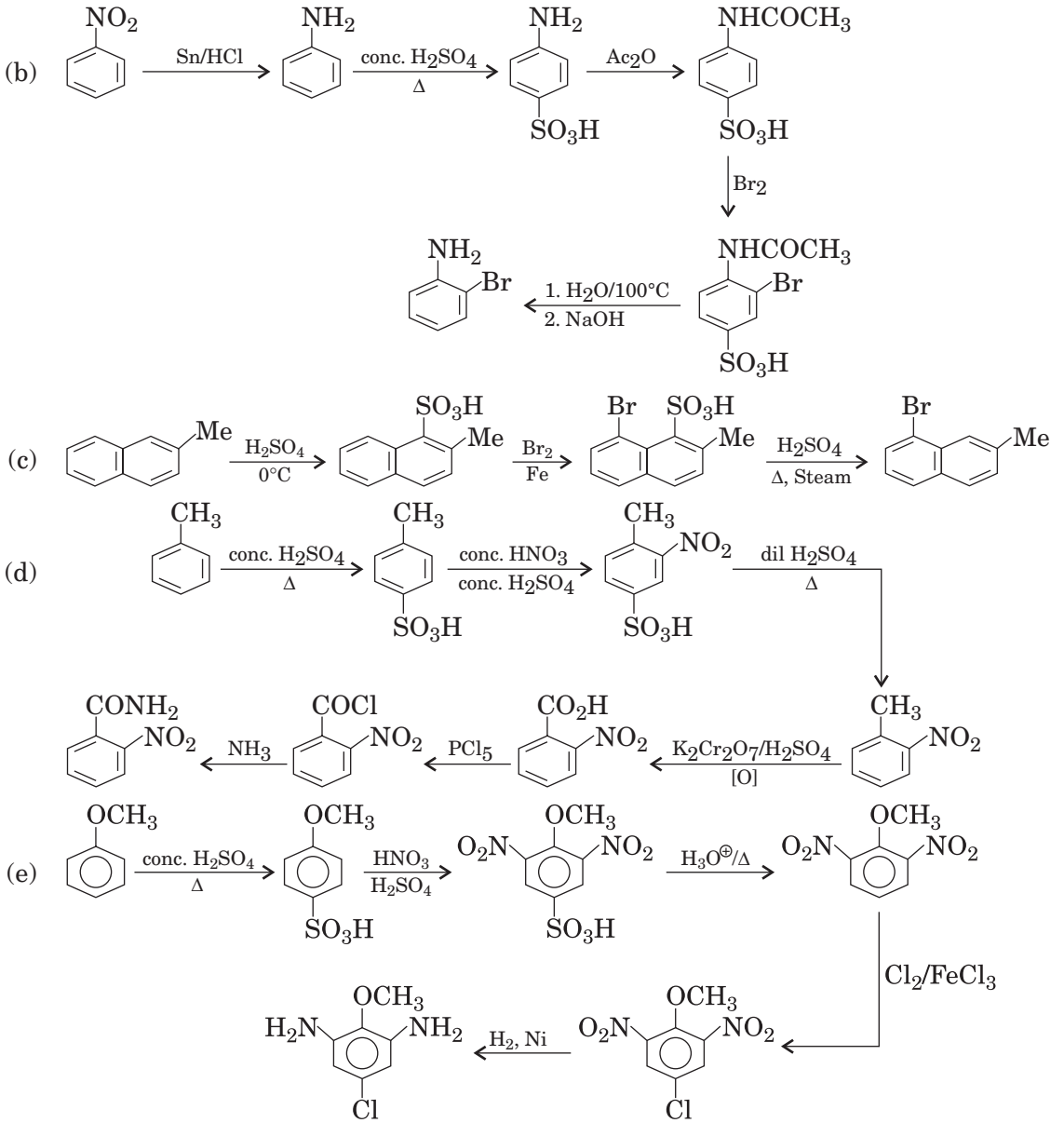
Benzenesulphonic acid first undergoes protonation. The protonated benzensulphonic acid (which acts as an electrophile) is then attacked by benzene to form an arenium ion. In the third step, the arenium ion loses a proton and one —OH group accepts a proton. Finally, loss of water along with a proton results in formation of diphenylsuphone. In fact, it is another electrophilic aromatic substitution taking place during sulphonation of benzene.

3. Show how would you accomplish the following transformations using sulphonation-desulphonation technique:



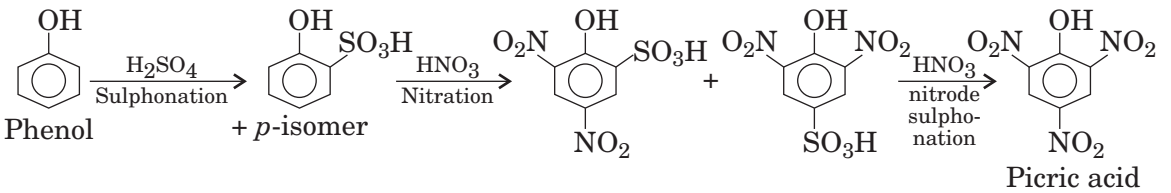
Solution



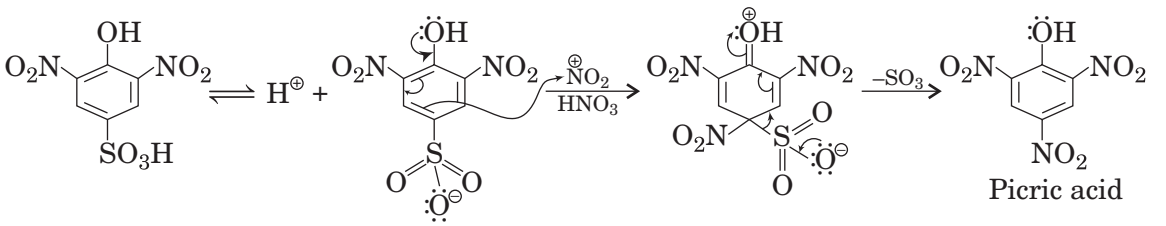


4. How can picric acid be prepared from phenol using sulphonation-nitrodesulphonation procedure? Give the mechanism of nitrodesulphonation (an *ipso* substitution).

Solution Phenol readily undergoes oxidation, but sulphonic acid derivatives are not easily oxidised. Sulphonation of phenol thus protects the compound from oxidation when nitrated with HNO_3. Picric acid is prepared from phenol as follows:

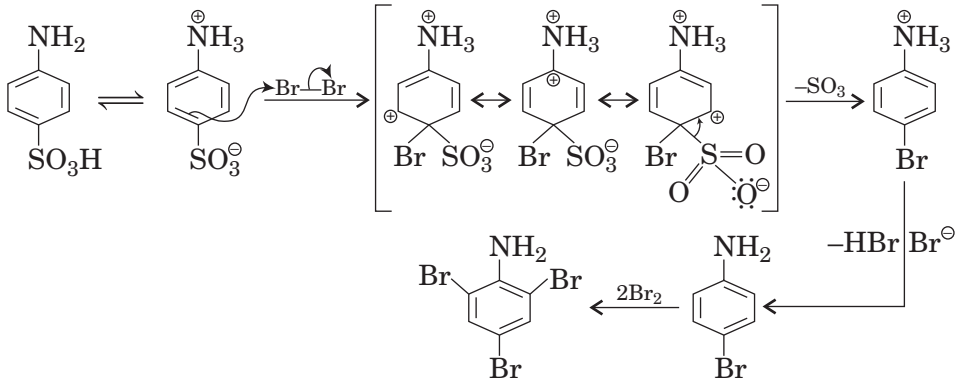


The mechanism of nitrodesulphonation is as follows:



5. Treatment of sulphanilic acid (p-$H_2NC_6H_4SO_3H$) with three moles of bromine yields 2,4,6-tribromoaniline. Outline the most probable mechanism for the replacement of –SO_3H by –Br. To what class of organic reactions does this reaction belong?

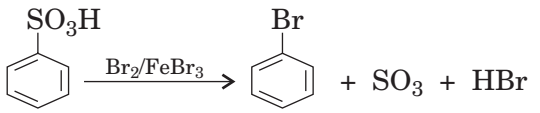
Solution The mechanism for the replacement of –SO_3H by –Br may be outlined as follows:

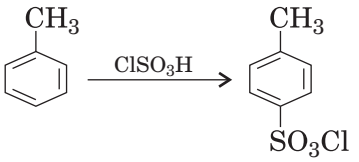


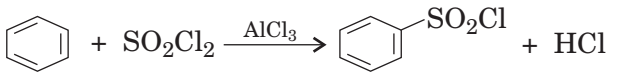
The reaction belongs to the class of *ipso*-substitution because in this reaction one ring substituent is displaced by another.

Study Problems

1. Suggest a mechanism for each of the following reactions:

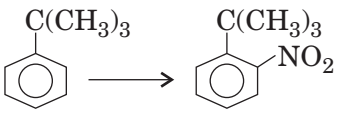
(a) 

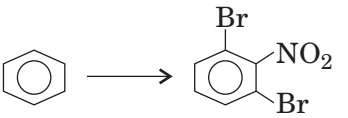
(b) 

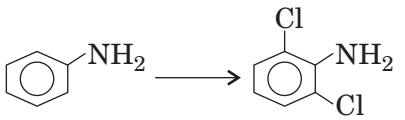
(c) 

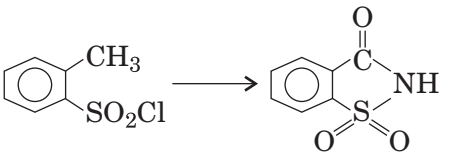
[**Hint:** (e) 

2. How would you carry out the following transformation?

(a) 

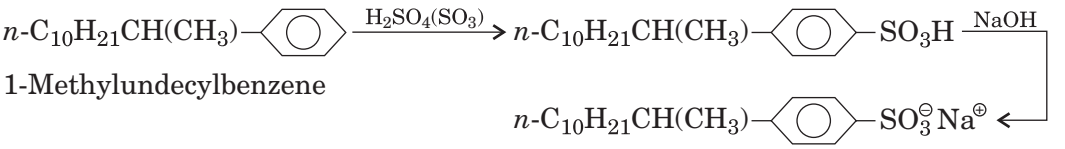
(b) 

(c) 

(d) 

(Saccharin)

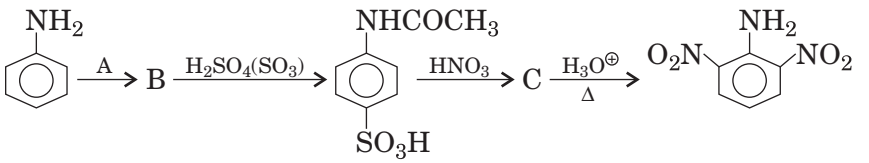
3. What are detergents? Outline the preparation of a detergent.
[**Hint:**

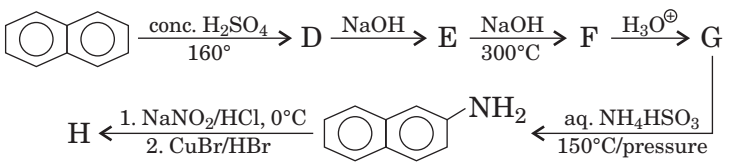


1-Methylundecylbenzene

Sodium *p*-(1-methylundecyl) benzenesulphonate
(A detergent)]

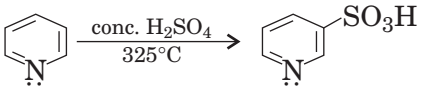
4. Identify the missing intermediates and reagents indicated by letter in the following reaction sequences:

(a) 

(b) 

5. When benzene is mixed with deuterated sulphuric acid, D_2SO_4, it is slowly converted to perdeuterobenzene, C_6D_6. This reaction is much faster than sulphonation. Suggest a mechanism for the reaction.

6. Pyridine undergoes sulphonation at a rate slower than benzene and sulponation occurs under vigorous conditions in the C-3 position predominantly. Explain these observations.



7. On being heated with SO_3 in H_2SO_4, 1, 2, 4, 5-tetramethyl-benzene was converted to a product of molecular formula $C_{10}H_{14}O_3S$ in good yield (94%). Suggest a reasonable mechanism for the formation of the product.

8. Discuss the principle of preparing thiophine-free benzene.
[**Hint:** Thiophine being more reactive (less aromatic) than benzene readily undergoes sulphonation at room temperature and thiophine-2-sulphonic acid is soluble in water.]

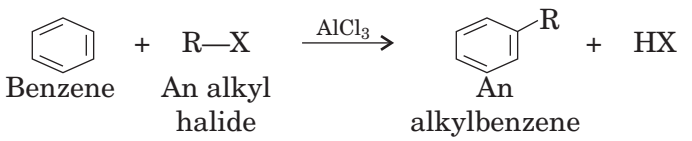
3.1.5 Formation of Carbon–Carbon σ-Bond: • Friedel–crafts Reaction • Houben–Hoesch Reaction • Gattermann Formylation • Gattermann–Kach Fromylation • Reimer-Tiemann Reaction • Kolbe-Schimitt Reaction

3.1.5.1 Friedel–Crafts reaction

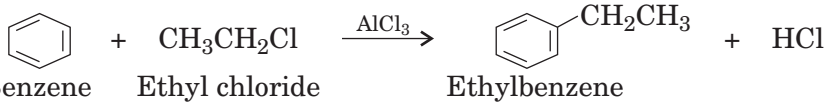
Charles Friedel and James M. Crafts discovered a new method for the preparation of alkylbenzenes (ArR) and acylbenzenes (ArCOR) in 1877. These reactions are called the Friedel–Crafts alkylation and acylation reactions. In principle, such reactions could be carried out with benzene in the presence of a sufficiently electrophilic carbon-based electrophile.

3.1.5.1(A) Friedel–Crafts alkylation

When a haloalkane is allowed to react with benzene in the presence of anhydrous aluminium chloride (a Lewis acid), an alkylbenzene is obtained. This reaction is called the *Friedel–Crafts alkylation*.



Example:



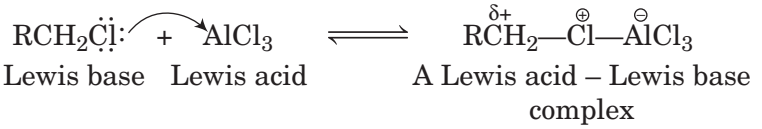
Other alkylating reagents are alcohols, alkenes, epoxides and sometimes strained cycloalkanes like cyclopropane. These produce the necessary carbocations by the influence

of an appropriate acid catalyst (protic or Lewis). For halides and alcohols, the reactivity order is allylic ≈ benzylic $\rangle$ tertiary $\rangle$ secondary $\rangle$ primary, which is identical to stability order of the corresponding carbocations expected to be generated. The reactivity of the haloalkanes increases with the polarity of the C–X bond in the order RI $\langle$ RBr $\langle$ RCl $\langle$ RF. The reactivity order of the Lewis acids generally used in this reaction is $AlBr_3 > AlCl_3 > FeCl_3 > SbCl_5 > SnCl_4 > BCl_3 < BF_3$. The Friedel–Crafts alkylation reactions are not restricted to the use of alkylhalide and $AlCl_3$. Any pair of reagents that form carbocations can alkylate benzene.

Mechanism of the reaction Depending on the alkyl halide used, the Friedel–Crafts alkylation reaction (an aromatic S_E2 reaction) follows two different mechanistic pathways:

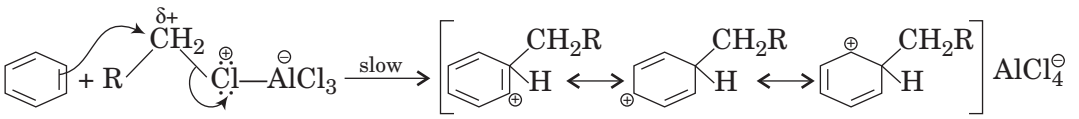
(a) If the alkyl halide used in methyl or primary, the reaction proceeds through the steps as follows:

Step 1: A Lewis acid-base reaction occurs between the alkyl halide (e.g. CH_3Cl, RCH_2Cl) and $AlCl_3$ to form a complex.



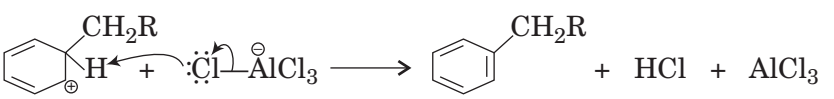
This coordination places a partial positive charge on the carbon bearing the halogen, rendering it more electrophilic. Even though this complex is not a simple carbocation, it acts as if it were and it transfers a positive alkyl group to the aromatic ring carbon. This complex does not dissociate before being attacked by the ring because the carbocations if produced as such will be very much unstable ($\overset{\oplus}{C}H_3$ or $R\overset{\oplus}{C}H_2$).

Step 2: The complex (the electrophile) is attacked by the benzene ring to produce an arenium ion or a σ-complex. It is the rate-determining (slow) step of the reaction.



An arenium ion or σ-complex

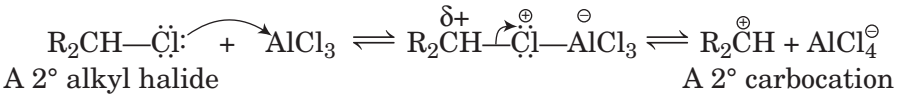
Step 3: A proton is removed from the arenium ion to form an alkylbenzene. HCl is also liberated and $AlCl_3$ is regenerated in this step.

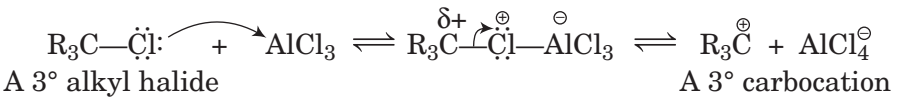


An alkylbenzene

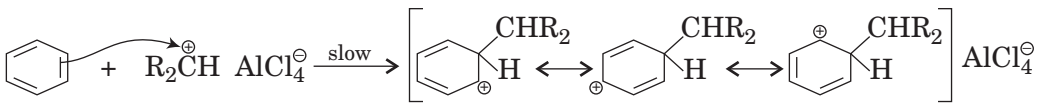
(b) If the alkyl halide used in secondary or tertiary, the reaction proceeds through the steps as follows:

Step 1: The alkyl halide coordinates with $AlCl_3$ to form a complex which dissociates to form a relatively stable 2° or 3° carbocation ($R_2\overset{\oplus}{C}H$ or $R_3\overset{\oplus}{C}$).





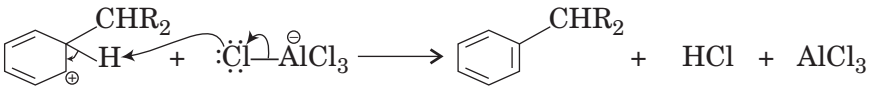
Step 2: The carbocation $R_2\overset{\oplus}{C}H$ (or $R_3\overset{\oplus}{C}$) acting as an electrophile, reacts with benzene to produce an arenium ion or σ-complex.



An arenium ion or σ-complex

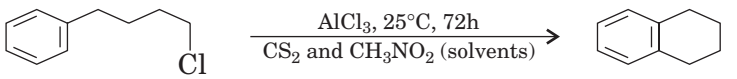
It is the rate-determining-(slow) step of the reaction.

Step 3: The $Cl^{\ominus}$ ion from $AlCl_4^{\ominus}$ takes up a proton from the arenium ion and as a result, it undergoes aromatization to form the corresponding alkylbenzene.



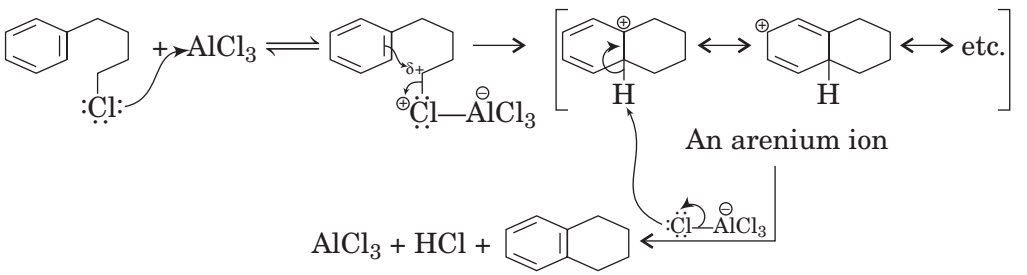
An alkylbenzene

Intramolecular Friedel–Crafts alkylation When benzene containing a side chain with a halogen atom is treated with $AlCl_3$, it undergoes ring closure (a new ring is formed onto the benzene nucleus). This is called intramolecular Friedel–Crafts alkylation. For example:



1–Chloro-4-phenylbutane Tetralin

Mechanism of the reaction The mechanism of the reaction involves the steps as follows:



Limitations of Friedel–Crafts alkylation The limitations of the Friedel–Crafts alkylation reaction are as follows:

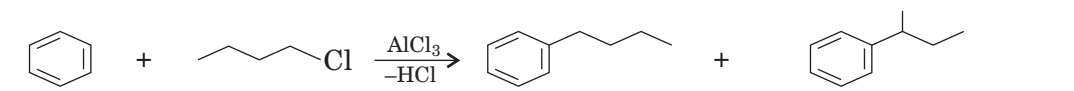
(i) Polyalkylation Bromination, nitration and sulphonation introduce an electron-withdrawing group into the benzene ring, which renders the product less susceptible than the starting material to electrophilic attack. In contrast, an alkylated benzene (C_6H_5R) is more electron rich than unsubstituted benzene and thus more susceptible to electrophilic attack. Because of this, polyalkylation occurs and the desired monoalkylated compound is obtained in low yield.

For example:

$$\underset{\text{Benzene}}{C_6H_6} + CH_3Cl \xrightarrow[-HCl]{AlCl_3} \underset{\text{Toluene}}{C_6H_5CH_3} + \text{di-, tri-, tetra- and pentamethylbenzenes}$$

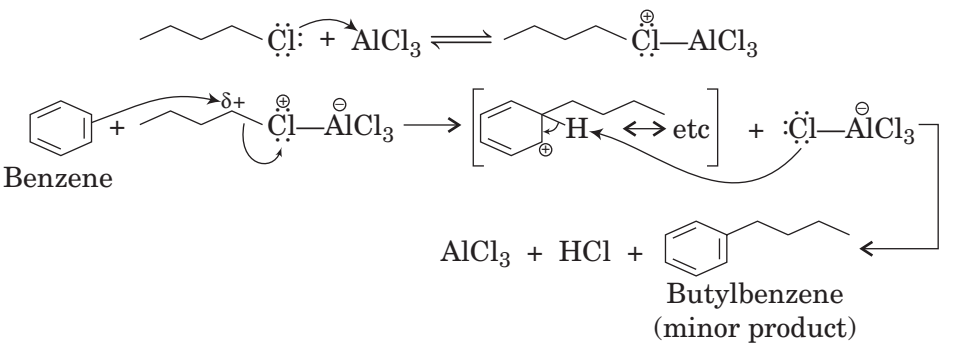
However, use of an excess of the aromatic compound favours monoalkylation.

(ii) Rearrangement of the developing less stable carbonation Skeletal rearrangement of a developing less stable carbocation to a more stable one often results in formation of an undesired rearranged product predominantly. For example, reaction of 1-chlorobutane with benzene in the presence of aluminium chloride produces (1-methylpropyl)-benzene as the major product.

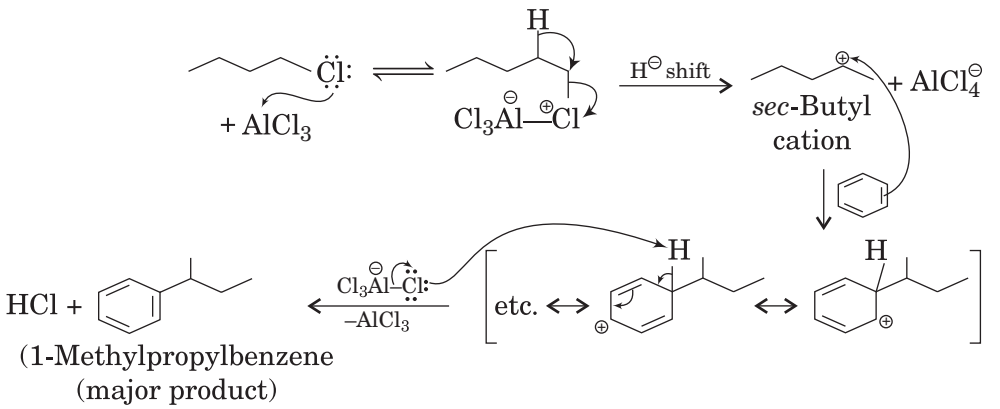


Benzene 1-Chlorobutane Butylbenzene (minor product) (1-Methylpropyl)-benzene (major product))

Mechanism of the reaction:

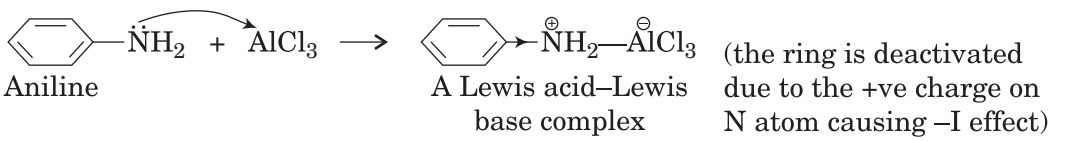


In this case, the Lewis acid–Lewis base complex (although obtained from an 1° alkyl halide) ionizes (because the developing less stable 1° carbocation rearranges to a more stable 2° carbocation) to form a secondary butyl cation which reacts with benzene to yield the major product.



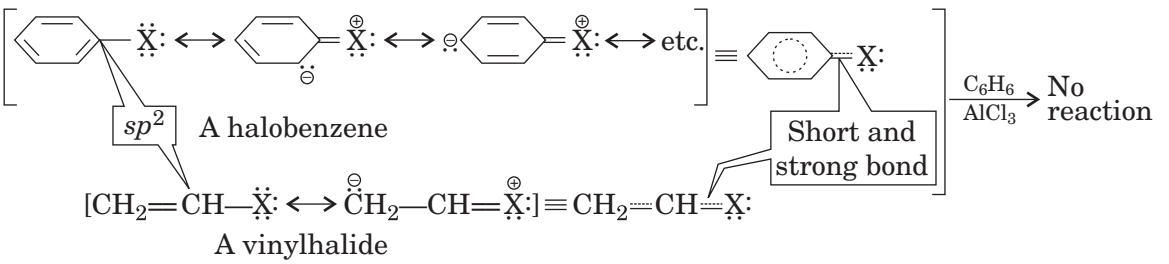
(iii) No reaction with substrates containing strong –I or –R group Strongly electron-attracting groups like $-CF_3$, $-NO_2$, $-SO_3H$, –CN, –CHO, –COR, –COOH, $-CO_2R$, COX, etc. deactivate the aromatic ring and do not allow the substrate to undergo the Friedel–Crafts reaction. In fact, an aromatic compound in which the ring is deactivated more than that of halobenzene does not usually undergo the Friedel–Crafts reaction. This is because the weakly electrophilic carbocation does not undergo nucleophilic attack by a weakly nucleophilic deactivated ring. Nitrobenzene is often used as a solvent in Friedel-Crafts alkylation reaction because it remains unreactive in the reaction conditions. Nitrotoluene can be prepared from benzene by carrying out methylation followed by nitration but not the reverse.

(iv) Substrates containing strong +R group does not undergo the Friedel-Crafts reaction Strongly activating groups like $-NH_2$, –NHR, $-NR_2$, –OH, –OR, *etc.* present in an aromatic ring form complexes with the Lewis acid $AlCl_3$. As a result, an $-NH_2$ group, for example, becomes converted into an electron-withdrawing (deactivating) $-\overset{\oplus}{N}H_2-\overset{\ominus}{A}lCl_3$ group and causes deactivation of the ring. For this reason, the reaction does not take place.

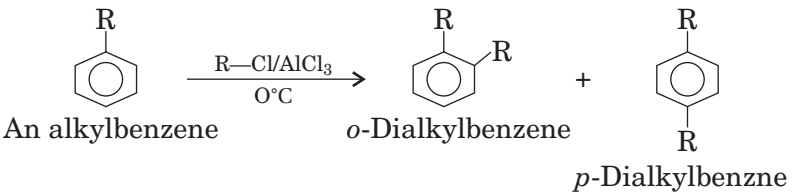


(v) In this reaction, aryl and vinyl halides cannot be used instead of alkyl halides The C–X bond in an aryl or vinyl halide is shorter and stronger because: (i) due to delocalization of the unshared pair of electrons on halogen with the ring π electrons the C–X bond gets some double bond character and (ii) a bond formed by overlap of an sp^2 orbital should be

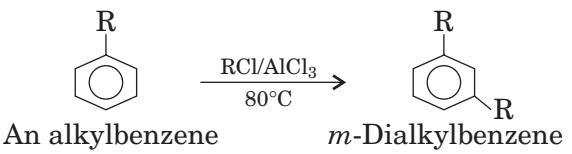
shorter than the corresponding bond involving an sp^3 orbital. It is not possible for the Lewis acid to ionize such a stronger C–X bond.



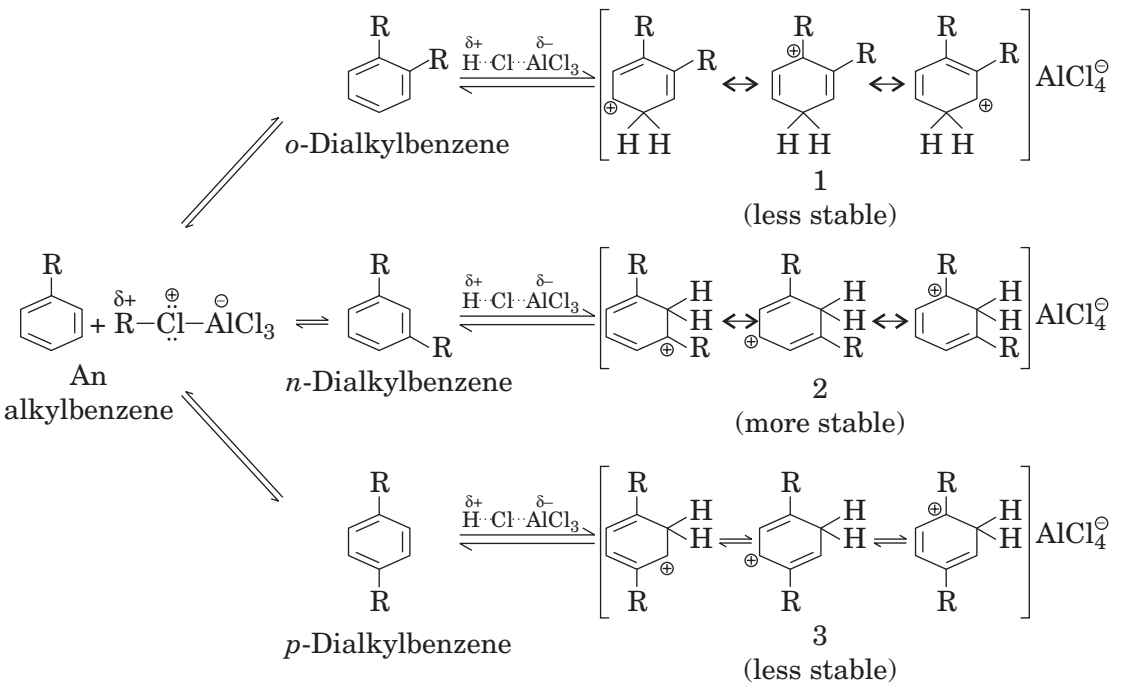
Friedel-Crafts alkylation of alkylbenzene (kinetic control versus thermodynamic control) At lower temperature, the Friedel-Crafts alkylation reaction is kinetically controlled and since an alkyl group is *ortho*-, *para*-directing, *o*- and *p*-dialkylbenzenes are obtained predominantly.



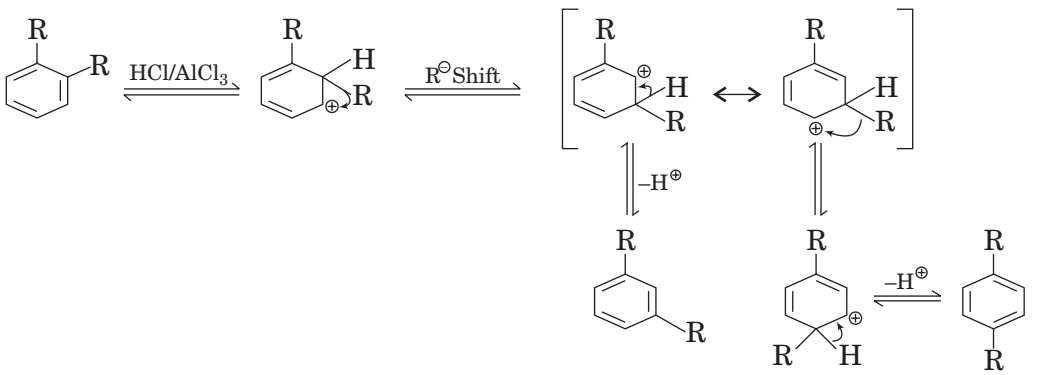
At higher temperature, the reaction is reversible and this thermodynamically controlled reaction results in the formation of *m*-dialkylbenzene predominantly.



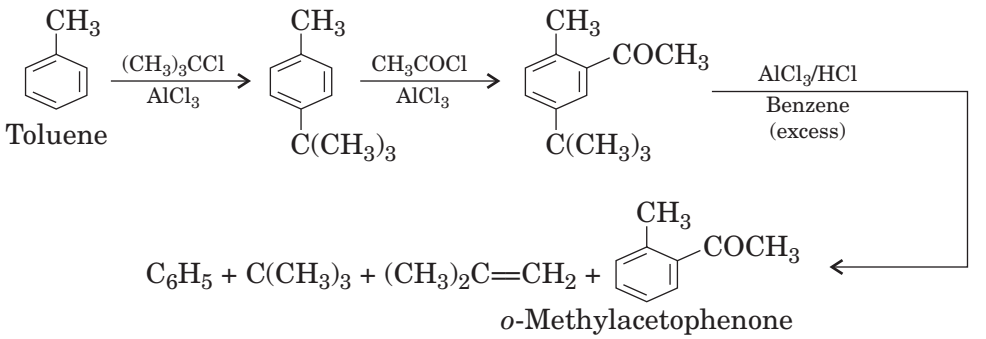
Under these equilibrium conditions each of the initially formed kinetic products, i.e., *o*-, *m*-, and *p*-dialkylbenzenes take up $H^{\oplus}$ from the complex $(\overset{\delta+}{H}\cdots Cl\cdots \overset{-\delta}{AlCl_3})$ to form three other arenium ions (1, 2 and 3). The arenium ion obtained from the *m*-dialkylbenzene is thermodynamically more stable because both the $-CH_3$ groups are involved in stabilizing the positive charge by +I and hyperconjugative effects. Therefore, under these equilibrium conditions all the arenium ions slowly converted into the arenium ion 2 and so, the *m*-dialkylbenzene is obtained predominantly when the mixture is worked-up by water.



One isomer may also be converted to another by intramolecular rearrangement (1, 2-shift).

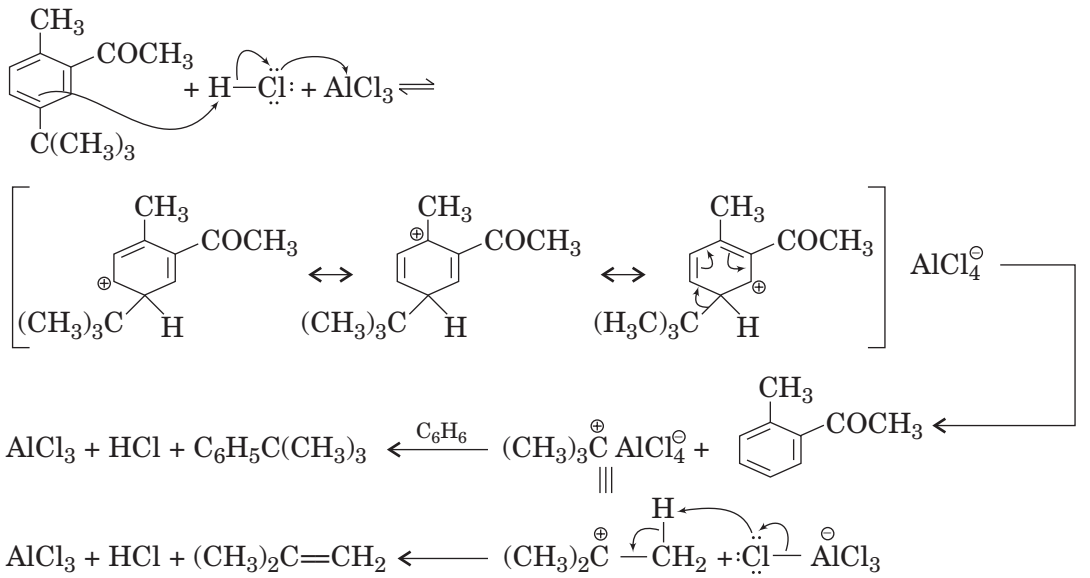


Reversibility of Friedel–Crafts alkylation becomes advantageous when the alkyl group is —CMe_3 and this is because it can be easily removed as a stable 3° carbocation ($\overset{\oplus}{C}Me_3$) by treating the substrate with $AlCl_3$/HCl in excess benzene. Thus, a *t*-butyl group can be used to block a particular position of the ring because after the purpose is solved the group can be easily removed. For example, *o*-methylacetophenone can be prepared from toluene as follows:



A *tert*-butyl group is better as a blocking group than a $-SO_3H$ group because the $-CMe_3$ group activates the ring to undergo further electrophilic substitution smoothly, whereas the $-SO_3H$ group deactivates the ring.

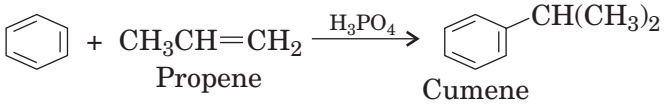
Mechanism for the removal of the $-CMe_3$ group:



Applications The Friedel–Crafts alkylation reaction has limitations in synthesis. It is effective only when product mixtures are easily separated on reactions conditions can be so controlled as to favour one desired product. Two important applications are as follows:

(i) Some synthetically important hydrocarbons can be prepared by this reaction. For example:

(a) The reaction can be used to prepare cumene, an important industrial intermediate, in the manufacture of phenol.



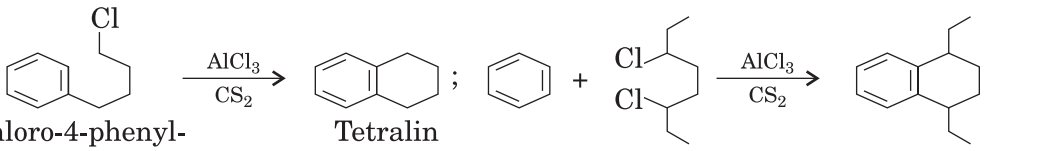
(b) Some other important hydrocarbons like diphenylmethane, dibenzyl and triphenylmethane can be prepared by this reaction.

$$C_6H_6 + \underset{\text{Benzyl chloride}}{C_6H_5CH_2Cl} \xrightarrow{AlCl_3} \underset{\text{Diphenylmethane}}{C_6H_5CH_2C_6H_5}$$

$$2\,C_6H_6 + \underset{\text{1,2–Dichloroethane}}{ClCH_2CH_2Cl} \xrightarrow{AlCl_3} \underset{\text{Dibenzyl}}{C_6H_5CH_2CH_2C_6H_5}$$

$$3\,C_6H_6 + \underset{\text{Chloroform}}{CHCl_3} \xrightarrow{AlCl_3} \underset{\text{Triphenylmethane}}{(C_6H_5)_3CH}$$

(ii) Intramolecular Friedel–Craft alkylations can be used to fuse a new ring onto the benzene nucleus. For example:

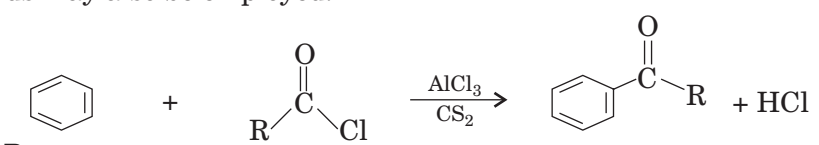


1-Chloro-4-phenyl-butane — Tetralin — 3,6-Dichloro-octane — 1,4-Diethyltetra-lin

(iii) Alkylation with Me_3CCl is used to protect a particular position in the ring because the group can be easily removed after the purpose is solved.

3.1.5.1(B) Friedel-Crafts Acylation

When an acyl halide (usually the chloride, RCOCl) is allowed to react with benzene in the presence of anhydrous aluminium chloride, an acyl group, RCO–, is introduced into the ring, i.e., an aromatic ketone is obtained. This reaction is known as Friedel–Crafts acylation. In this electrophilic aromatic substitution the electrophile is an acylium ion ($R—C\equiv\overset{\oplus}{O}:$). The acylating agent is usually an acyl halide although anhydrides and carboxylic acids may also be employed.



Benzene — An acyl chloride (R=alkyl or aryl) — An aromatic ketone

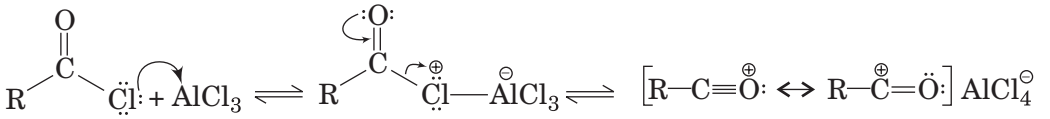
Examples:

$$\underset{\text{Benzene}}{C_6H_6} + \underset{\text{Acetyl chloride}}{CH_3COCl} \xrightarrow[CS_2]{AlCl_3} \underset{\text{Acetophenone}}{C_6H_5COCl} + HCl$$

$$\underset{\text{Toluene}}{C_6H_5CH_3} + \underset{\text{Benzoyl chloride}}{PhCOCl} \xrightarrow[PhNO_2]{AlCl_3} \underset{\substack{p\text{-Methylbenzophenone}\\(92\%)}}{p\text{-}CH_3C_6H_4COPh}$$

Mechanism of the reaction The mechanism of the reaction involves the steps as follows:

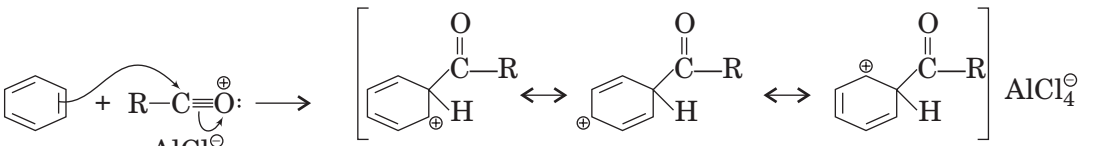
Step 1: The acyl chloride reacts with aluminium chloride to form initially a Lewis acid–Lewis complex which subsequently dissociates to form a resonance-stabilized acylium ion, $R - C \equiv \overset{\oplus}{O}:$ (the electrophile).



A Lewis acid–Lewis base complex

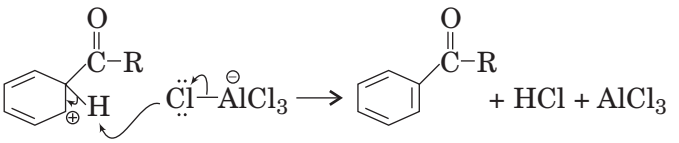
An acylium ion (resonance-stabilized)

Step 2: The acylium ion undergoes nucleophilic attack by the ring π electrons to form an arenium ion or σ-complex. It is the rate-determining (slow) step of the reaction.

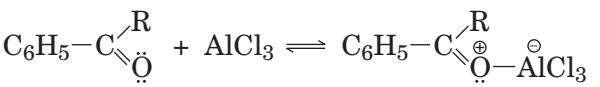


An arenium ion or σ-complex

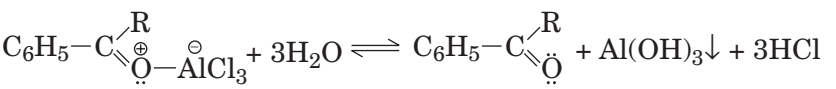
Step 3: The arenium ion gives up a proton and gets aromatized to yield an aromatic ketone.



Step 4: The resulting ketone, acting as a Lewis base, reacts with aluminium chloride (a Lewis acid) to form another complex.



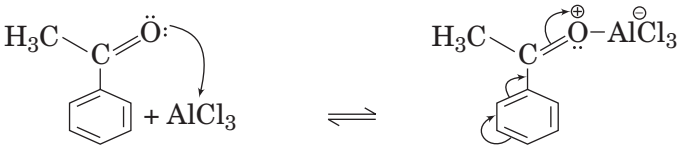
Step 5: When the complex is treated with water, it undergoes hydrolysis to regenerate the ketone.



Some relevant topics

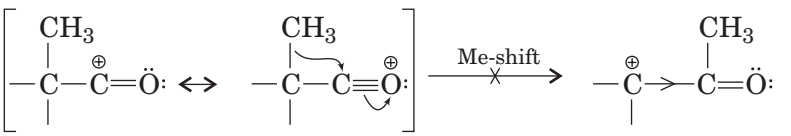
(i) Polyacylations, unlike polyalkylations, are not a problem in Friedel-Crafts acylations The acyl group (RCO–) by itself is an electron attracting group, and when it forms a complex

with the Lewis acid $AlCl_3$ in the last step of the reaction, it becomes even more electron-attracting. This strongly inhibits further substitution and makes monoacylation quite easy.



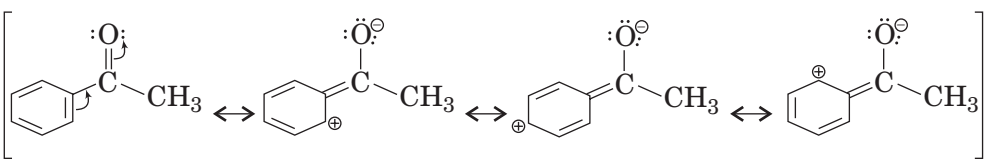
An aromatic ketone (ring is deactivated) ⇌ Complex (ring is much deactivated)

(ii) Rearrangement is not a problem in Friedel–Crafts acylations Although carbocation rearrangement is a problem in Friedel–Crafts alkylations, it is not a problem in the case of acylations. This is due to the fact that an acylium ion does not undergo rearrangement because the putative rearranged cation in which the positive carbon bears an electron-withdrawing carbonyl (C═O) group is much less stable, i.e., the process is energetically not at all favourable.

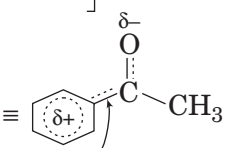


An acylium ion (more stable) — A carbocation (much less stable and not formed)

(iii) An acyl group cannot be easily removed from the benzene ring, i.e. acylation is practically irreversible Although alkylation has been found to be reversible at higher temperature, acylation is irreversible. Unlike an alkyl group, an acyl group becomes involved in resonance interaction with the ring. Because of this, the C—C bond becomes shorter and stronger (possesses some double bond character) and so, replacement of an acyl group by hydrogen does not take place.

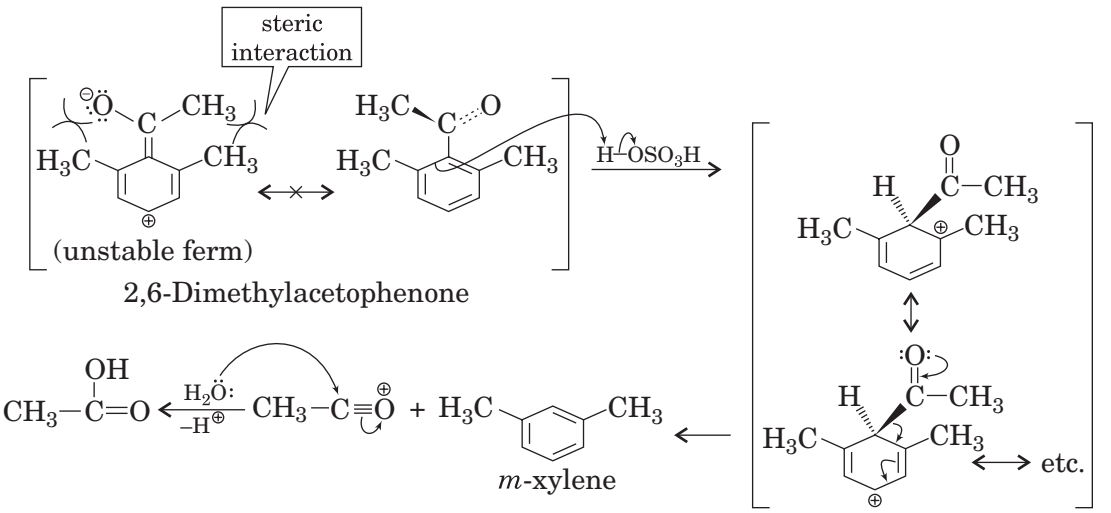


Resonance in acetophenone

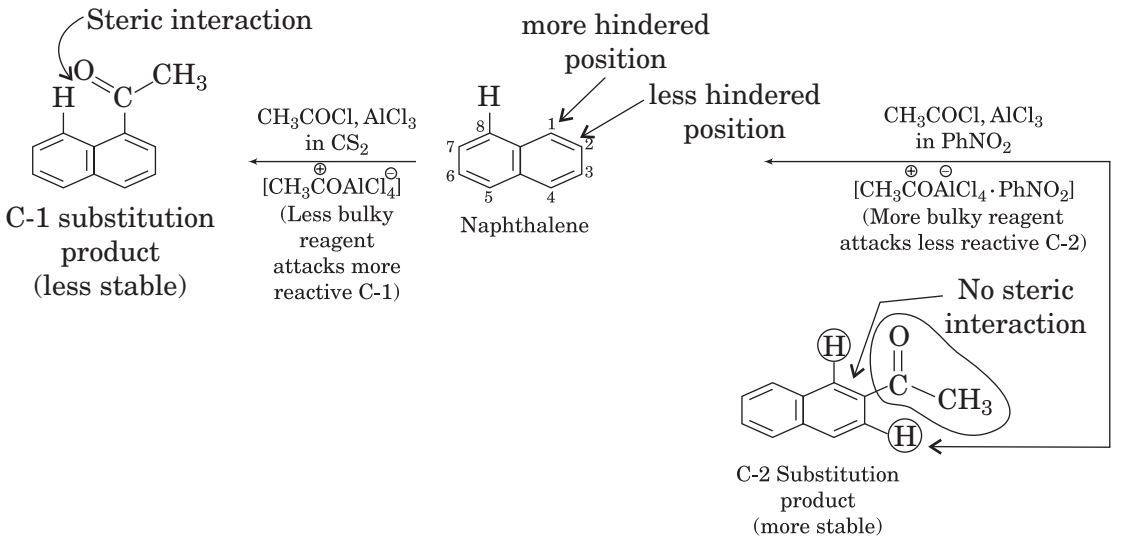


shorter and stronger bond

Deacylation may, however, take place if the $-COCH_3$ group goes out of the plane of the ring due to steric reason and as a result resonance interaction with the ring is inhibited. For example, 2,6-dimethylacetophenone undergoes deacylation when treated with conc. H_2SO_4. Because of steric interaction with the *ortho*- methyl groups, the $-COCH_3$ group goes out of the plane of the ring. Cleavage of the acetyl group, therefore, occurs easily because electrophilic attack by $H^{\oplus}$ does not involve as much loss of resonance energy as would be the case with acetophenone (in which there is no steric interaction with small *ortho*- hydrogens).



(iv) The relatively bulky acyl group (–COR) goes preferably to the less crowded position of the ring Since the acylating agent and the Lewis acid are quite bulky, the *para*- product is usually obtained during acylation of an *ortho*, *para*-directing monosubstituted arene. Toluene, for example, on nitration produces 60% *o*-nitrotoluene, whereas on Friedel–Crafts acylation it gives only 15% *ortho*-product. When CS_2 issued as a solvent, the effective size of the acylation agent is not large because CS_2 is not involved with $[\overset{\oplus}{R}COAlCl_4^{\ominus}]$. However, when $PhNO_2$ is used as a solvent it becomes involved with the complex $[\overset{\oplus}{R}COAlCl_4^{\ominus}]$ to form a relatively large complex $[\overset{\oplus}{R}COAlCl_4^{\ominus} \cdot PhNO_2]$. Thus, the effective size of the acylating agent becomes very large and the acylation occurs almost exclusively at the less hindered site. Naphthalene, for example, undergoes acetylation in CS_2 at the more reactive site C-1 (the σ-complex is more stable), while in nitrobenzene acetylation occurs at the less reactive position C-2 in order to avoid steric interaction with the *peri*-hydrogen at C-8 and the bulky reagent.



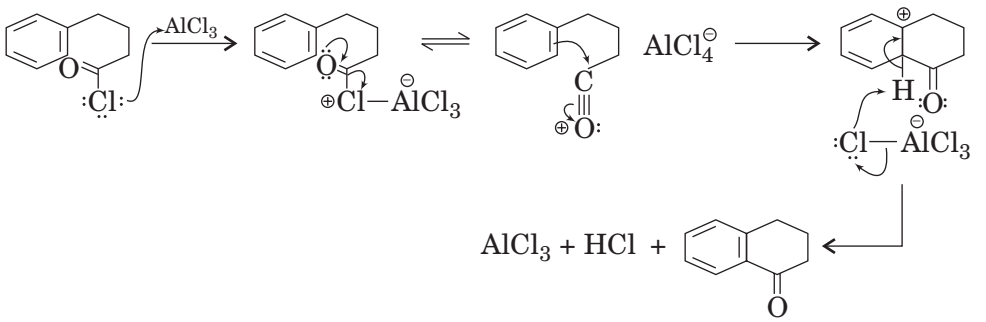
Intramolecular Friedel-Crafts Acylation When benzene containing a side chain with a halocarbonyl group is treated with $AlCl_3$, it undergoes ring closure (a new ring is formed onto the benzene nucleus). This is called intramolecular Friedel–Crafts acylation.

For example:



4-Phenylbutanoyl chloride — α-Tetralone

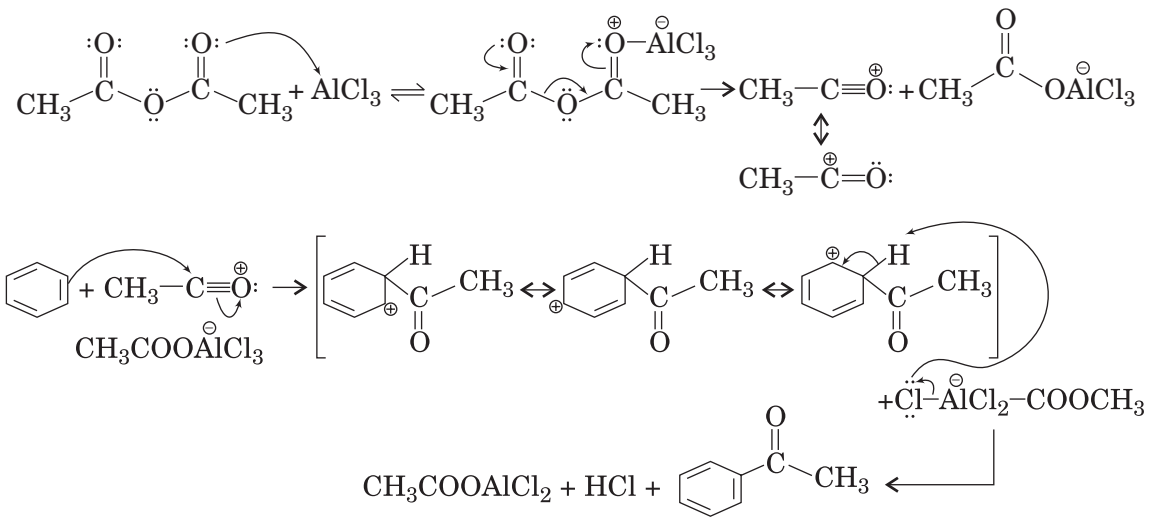
Mechanism of the reaction: The mechanism of the reaction involves the steps as follows:



Friedel-Crafts acylation using carboxylic acid anhydrides Acylation can also be carried out using carboxylic acid anhydrides, $(RCO)_2O$. For example, when benzene is allowed to react with acetic anhydride in the presence of aluminium chloride, acetophenone is obtained in good yield.

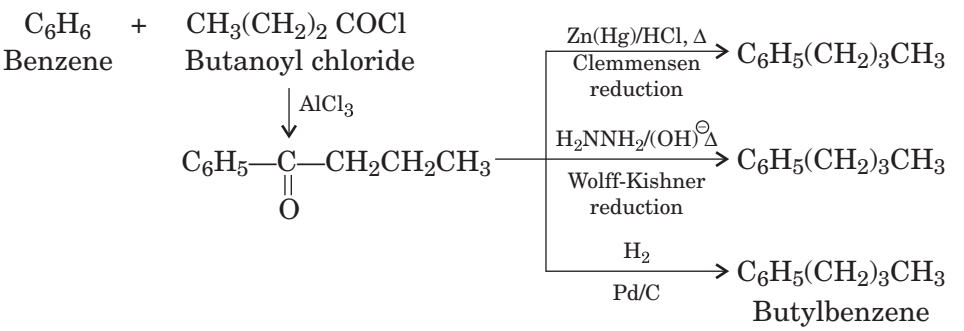
$$C_6H_6 + \underset{\text{Acetic anhydride}}{(CH_3CO)_2O} \xrightarrow[\substack{\text{(excess benzene)}\\ 80^\circ C}]{AlCl_3} \underset{\substack{\text{Acetophenone}\\ (85\%)}}{C_6H_5COCH_3} + CH_3COCH_3$$

Mechanism of the reaction: A Lewis acid–Lewis base complex is first formed which subsequently dissociates to form an acylium ion (the electrophile).



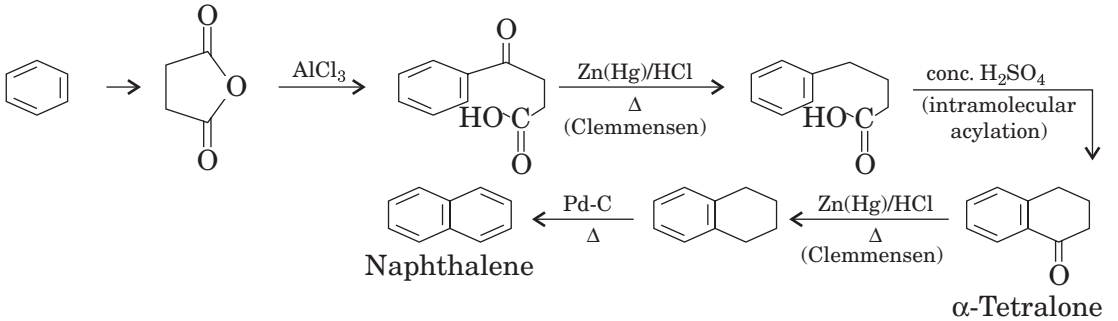
Applications Some important applications of Friedel–Crafts acylation reaction are as follows:

(i) A Friedel–Crafts alkylation reaction cannot produce an alkylbenzene containing a straight-chain alkyl group in good yield because the incipient primary carbocation will rearrange to a more stable carbocation. Acylium ions, however, do not undergo rearrangement. Therefore, a straight chain alkyl group can be conveniently placed on a benzene ring by means of a Friedel-Crafts acylation, followed by reduction of the C=O group to $\diagdown CH_2$ group. Two of the most effective methods for carbonyl reduction are the Clemmensen reduction which involves refluxing the ketone with zinc amalgam in hydrochloric acid and the Wolff–Kishner reduction which involves heating the hydrazone of the ketone with a strong base. Since the ketone carbonyl group is adjacent to the benzene ring, it can also be reduced to a methylene group by catalytic hydrogenation (H_2 + Pd/C). Thus, butylbenzene may conveniently be prepared from benzene by acylation–reduction technique.



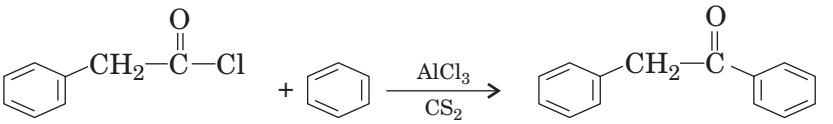
(ii) Intramolecular acylation is extremely useful in preparation of polycyclic compounds like naphthalene, anthracene and phenanthrene.

Howorth synthesis of naphthalene:



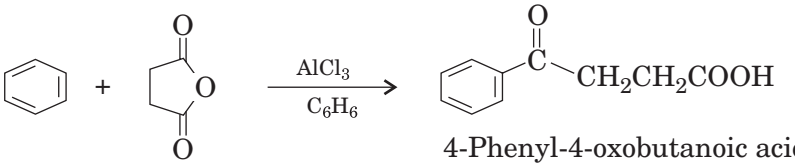
It is to be noted that the Cemmensen reduction is carried out twice in the process. The reason for reduction before ring closure is as follows. The carbonyl group in the keto acid (the product of the first step reaction) deactivates the ring and so, effective ring closure by treating it with conc. H_2SO_4 does not take place. For an effective ring closure the $\diagdown C{=}O$ group is reduced by Clemmensen method to a moderately activating alkyl group.

(iii) The reaction is a very good method for preparing aromatic ketones. For example:



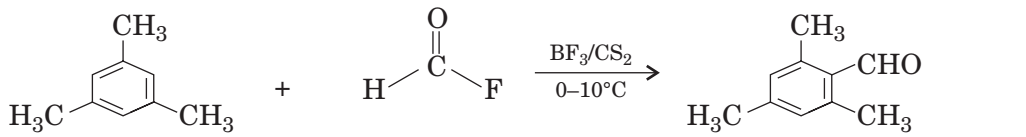
Phenylacetyl chloride — Benzyl phenyl ketone (85%)

Keto acids may also be prepared by using succinic anhydride as the acylating agent. For example:



Succinic anhydride — 4-Phenyl-4-oxobutanoic acid (84%)

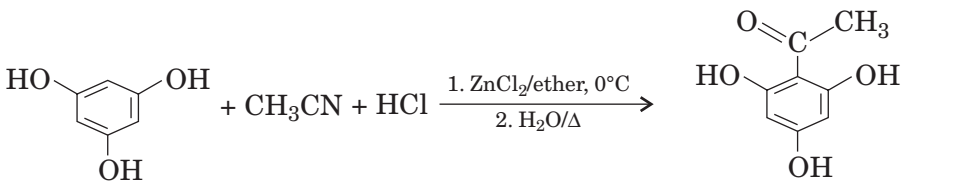
(iv) A useful method for formylation involves treatment of the aromatic compound with formyl fluoride in the presence of BF_3 in CS_2 solvent. For example:



1,3,5-Trimethylbenzene (Mesitylene) — Formyl fluoride — 2,4,6-Trimethylbenzaldehyde (70%)

3.1.5.2 Houben-Hoesch reaction

When a highly activated aromatic compound like polyhydroxy phenols, phenolic ethers and aromatic heterocycles is treated with alkyl cyanide and dry HCl in the presence of a Lewis acid catalyst (the most common being $ZnCl_2$) and the initially formed ketamine hydrochloride (an iminium salt) is hydrolysed, acylation occurs to form an aromatic ketone. This reaction, an alternative to Friedel–Crafts acylation, is known as the *Houben–Hoesch reaction*. For example, when phloroglucinol is treated with methylcyanide and HCl in the presence of $ZnCl_2$ and the ketamine hydrochloride so obtained is hydrolyzed, phloroacetophenone is obtained in good yield.

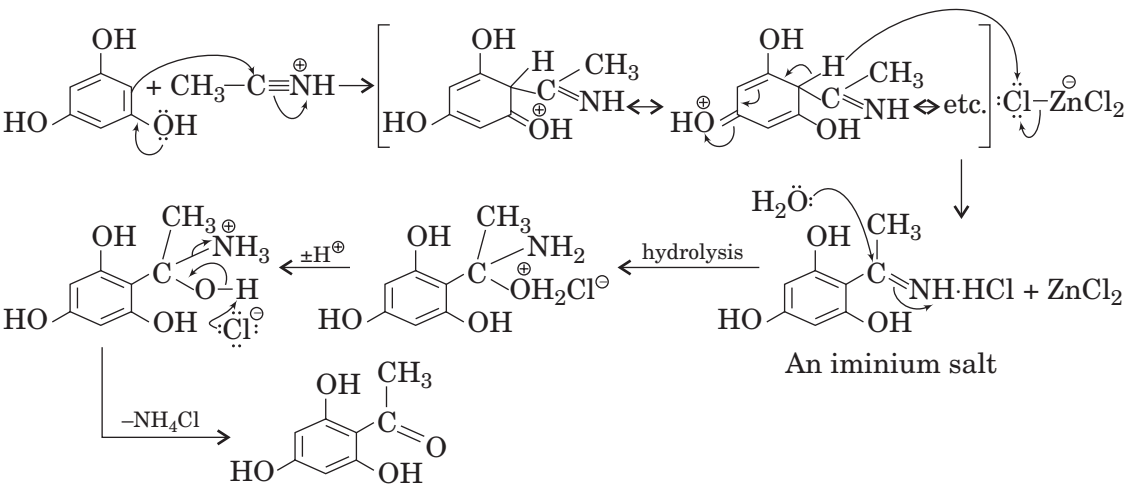


Phloroglucinol — Phloroacetophenone (87%)

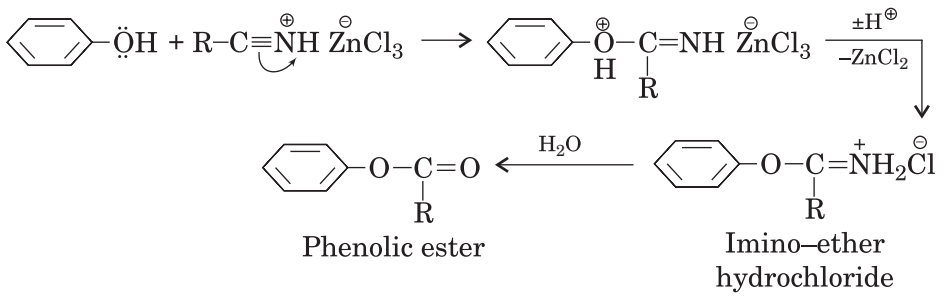
Mechanism of the reaction Methyl cyanide undergoes protonation by HCl in the presence of $ZnCl_2$ to form $CH_3\overset{\oplus}{C}=NH$, the electrophile involved in this substitution reaction.

$$[CH_3-C\equiv N: + H-\ddot{Cl}: + ZnCl_2] \longrightarrow [CH_3-C\equiv\overset{\oplus}{N}H \leftrightarrow CH_3-\overset{\oplus}{C}=NH]\ \overset{\ominus}{Z}nCl_3$$

The reaction then proceeds through the steps as follows:

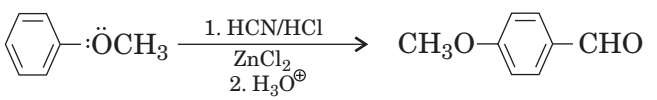


The reaction is not successful with phenol due to the formation of an imino–ether hydrochloride (resulting from the attack by the hydroxy oxygen on the electrophile), which on hydrolysis yields a phenolic ester.



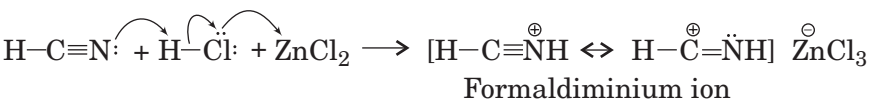
3.1.5.3 Gattermann formylation

When an activated aromatic compound (e.g., phenolic ethers, polyhydroxy phenols, polyalkyl aromatic hydrocarbons, polycyclic aromatic hydrocarbons, etc.) is treated with HCN and HCl in the presence of the Lewis acid, $ZnCl_2$ and the resulting iminium chloride is hydrolyzed with dilute mineral acid, an aromatic aldehyde is obtained. This process of introduction of a –CHO group into the aromatic ring is known as *Gattermann formylation*. For example, when anisole is treated with HCN and HCl in the presence of $ZnCl_2$ and the resulting iminium chloride is hydrolyzed, *p*-methoxybenzaldehyde is obtained.



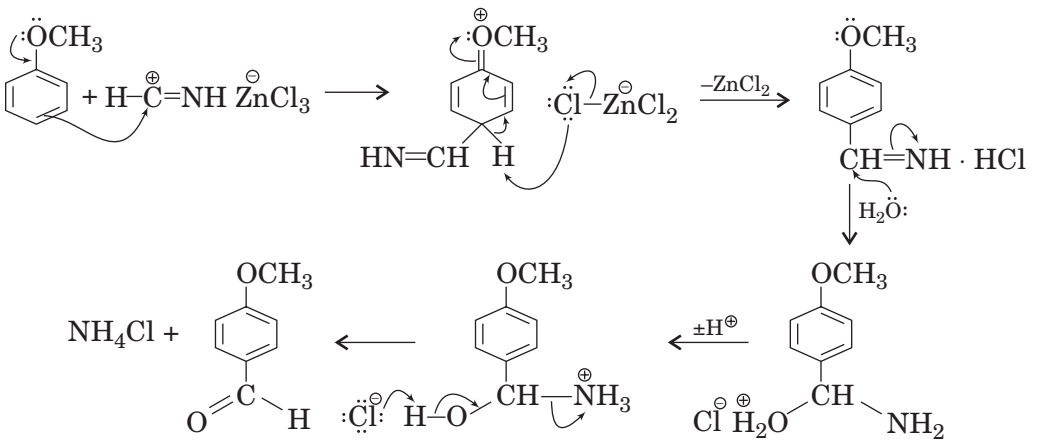
Anisole *p*-Methoxybenzaldehyde

Mechanism of the reaction The electrophile involved in this reaction is formaldiminium ion ($H-\overset{\oplus}{C}=NH$) which is formed as follows:



Formaldiminium ion

The reaction then proceeds through the steps as follows:



To avoid poisonous HCN, it is convenient to use $Zn(CN)_2$ which reacts with conc. HCl to produce the required HCN *in situ*.

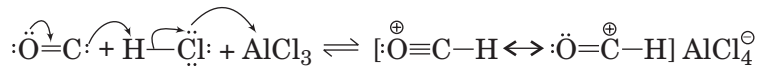
$$Zn(CN)_2 + 2HCl \rightarrow ZnCl_2 + 2HCN$$

3.1.5.4 Gattermann-Koch formylation or Gattermann-Koch aldehyde synthesis

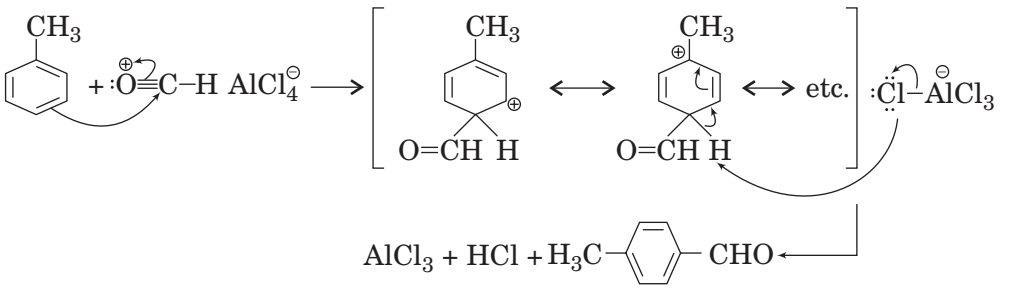
The formylation of benzene and alkylbenzenes using carbon monoxide and HCl in the presence of $AlCl_3$ and a small amount of cuprous chloride, CuCl (co-catalyst) is known as *Gattermann-Koch formylation* or *Gattermann-Koch aldehyde synthesis*. Aromatic compounds which are more reactive than halobenzene or nitrobenzene may be formylated by this method though phenols, and aromatic amines are not suitable substrates for this reaction. For alkylbenzenes the –CHO group enters mainly into the *para*-position. For example:

$$\underset{\text{Toluene}}{C_6H_5CH_3} + CO + HCl \xrightarrow[Cu_2Cl_2]{AlCl_3} \underset{\text{p-Methylbenzaldehyde}}{p\text{-}CH_3C_6H_4CHO}$$

Mechanism of the reaction The elctrophile involved in this substitution reaction is the formyl cation ($H-\overset{\oplus}{C}=O$) which is generated as follows:



The substitution reaction then takes place as follows:



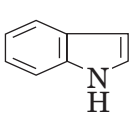
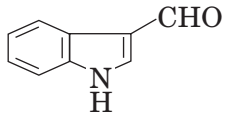
3.1.5.5 Vilsmeier–Haack reaction

Formylation of activated aromatic or heterocyclic compounds with *N*, *N*-disubstituted formamides and phosphorous oxychloride is known as the *Vilsmeier–Haack reaction*. *N*-Phenyl-*N*-methylformamide is a common reagent, although other arylalkyl amides and dialkyl amides are also in use.

For example:

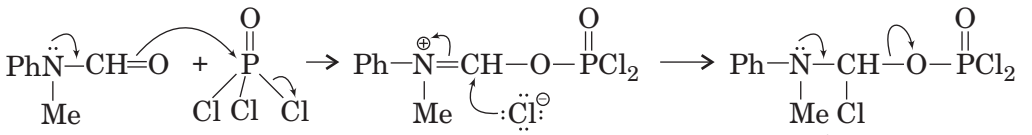
(i) $C_6H_5NMe_2$ + PhN(Me)CHO $\xrightarrow[2.\ H_2O]{1.\ POCl_3}$ p-$Me_2NC_6H_4CHO$

N,*N*-Dimethylaniline — *p*-Dimethylaminobenzaldehyde

(ii)  + $(CH_3)_2NCHO$ (Dimethylforamide) $\xrightarrow[2.\ H_2O]{1.POCl_3}$ 

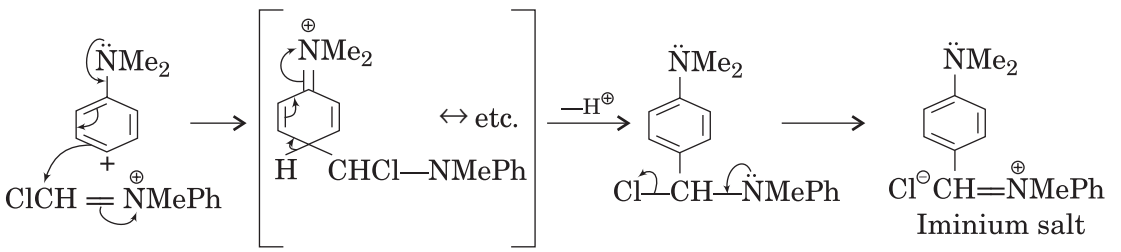
Indole — 3-Formylindole

Mechanism of the reaction The formamide reacts with phosphorous oxychloride ($POCl_3$) to form a chloroiminium ion (the active electrophile) which subsequently reacts with the active substrate to give, after hydrolysis, the aromatic aldehyde.



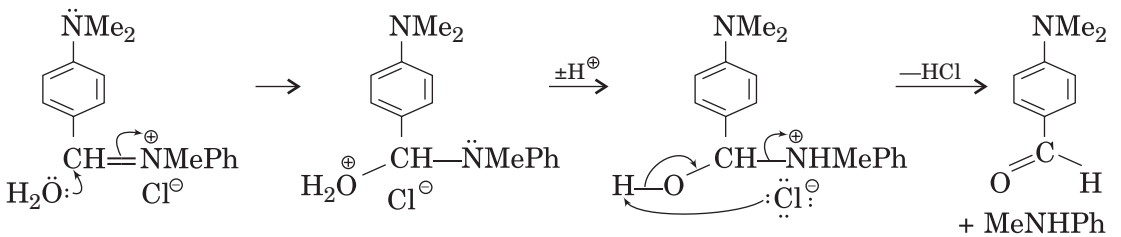
(Chloroiminium salt)
(Vilsmeier–Haack reagent)

The reaction of the electrophile with the active aromatic compound *N*, *N*-dimethylamine, for example, takes place as follows:



Iminium salt

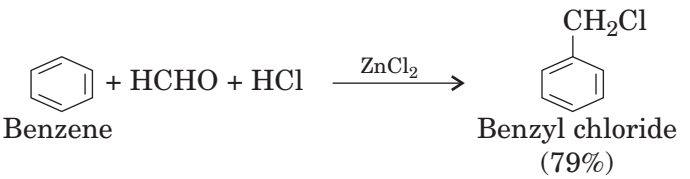
The iminium salt on hydrolysis gives the aldehyde:



+ MeNHPh

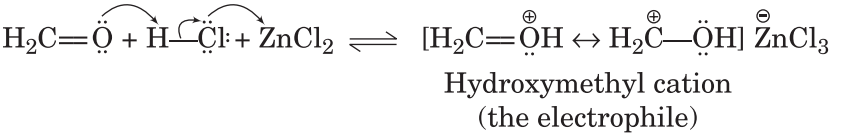
3.1.5.6 Chloromethylation

When compounds like alkyl benzenes, alkoxybenzenes and halobenzenes are treated with formaldehyde (as formaline or paraformaldehyde) and HCl in the pressence of a Friedel–Crafts catalyst like $ZnCl_2$, $SnCl_4$, $AlCl_3$, etc. an H atom of them compound gets replaced by the chloromethyl ($–CH_2Cl$) group. This reaction is known as *chloromethylation*. For example:

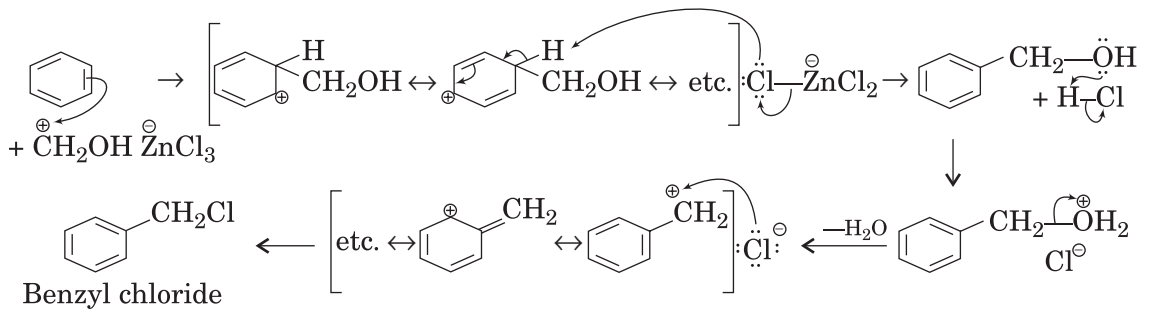


The alcohol produced initially is converted to the corresponding chloro derivative as rapidly as it is formed.

Mechanism of the reaction



The reaction then proceeds as follows:



Applications The reaction has a wide scope because the chloromethyl ($–CH_2Cl$) group can be conveniently converted into other groups like $–CH_2OH$ (by aq. NaOH), $–CH_3$ (by Zn-Cu couple reduction), –CHO [by $Pb(NO_3)_2/CO_2$], $–CH_2CN$ (by aq. KCN), $–CH_2COOH$ (by aq. KCN followed by hydrolysis), $–CH_2CO_2R$, etc.

3.1.5.7 Hydroxyalkylation

Reaction of formaldehyde with aromatic substrates in the presence of acid or base leading to introduction of $–CH_2OH$ group into the ring is called *hydroxyalkylation*. The most important example is the reaction of phenol with formaldehyde in the presence of dilute acid or dilute alkali to yield mainly *p*-hydroxybenzyl alcohol along with a small amount of the *o*-isomer.

$$C_6H_5OH + HCHO \xrightarrow{\text{dil.NaOH}} p\text{-}Na\overset{\oplus}{O}\overset{\ominus}{}C_6H_4CH_2OH + o\text{-}Na\overset{\oplus}{O}\overset{\ominus}{}C_6H_4CH_2OH$$

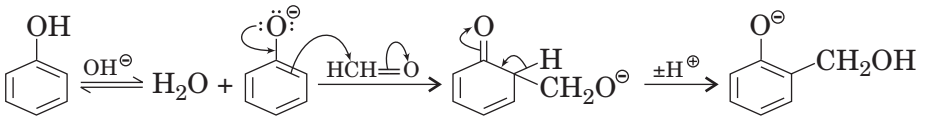
$$C_6H_5OH + HCHO \xrightarrow{\text{dil.}H_2SO_4} p\text{-}HOC_6H_4CH_2OH + o\text{-}HOC_6H_4CH_2OH$$

Phenol	*p*-Hydroxybenzyl alcohol (major)	*o*-Hydroxybenzyl alcohol (minor)

Base-catalyzed hydroxymethylation reaction of phenols is commonly known as the *Lederer-Manasse reaction*.

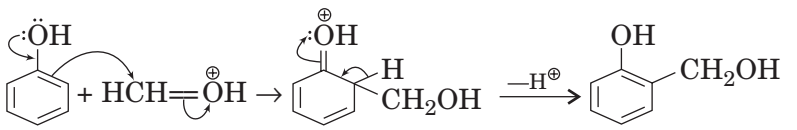
Mechanism of the reaction

(i) **Base-catalyzed condition:** In this condition, the phenoxide ion acts as an actual substrate.



Similarly, the *p*-isomer is formed.

(ii) **Acid-catalyzed condition:** In this condition, protonated formaldehyde behaves as the electrophile.



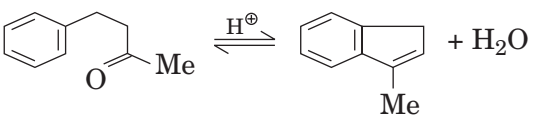
A similar reaction produces the *p*-isomer.

Applications

(i) When phenol is treated with excess of formaldehyde in presence of dilute sodium hydroxide, repetition of hydroxyalkylation occurs and finally a three dimensional polymer known as phenol-formaldehyde resin or *Bakelite* is obtained. Bakelite is a hard and rigid thermosetting plastic. It is used for manufacturing electrical insulators, radio and telephone equipments, fountain-pen barrels, etc.

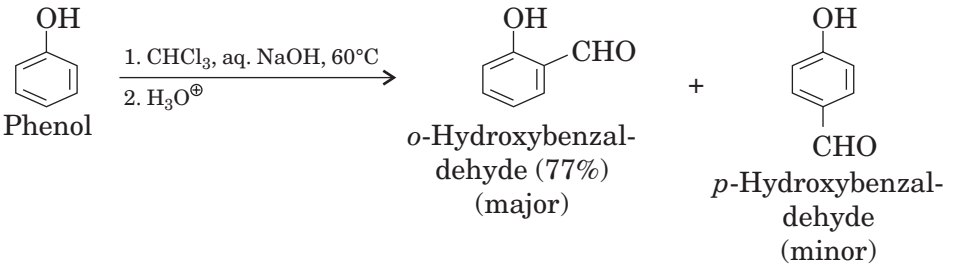
(ii) DDT, well known insecticide, has been prepared by hydroxyalkylation of chlorobenzene with chloral in the presence of conc. H_2SO_4.

(iii) Intramolecular hydroxyalkylation followed by dehydration is a very common procedure for the synthesis of polycyclic compounds.
For example:

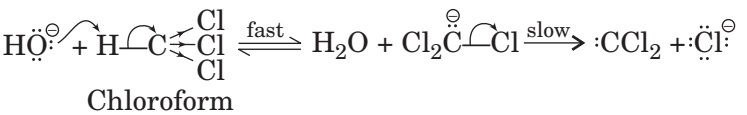


3.1.5.8 Reimer–Tiemann reaction

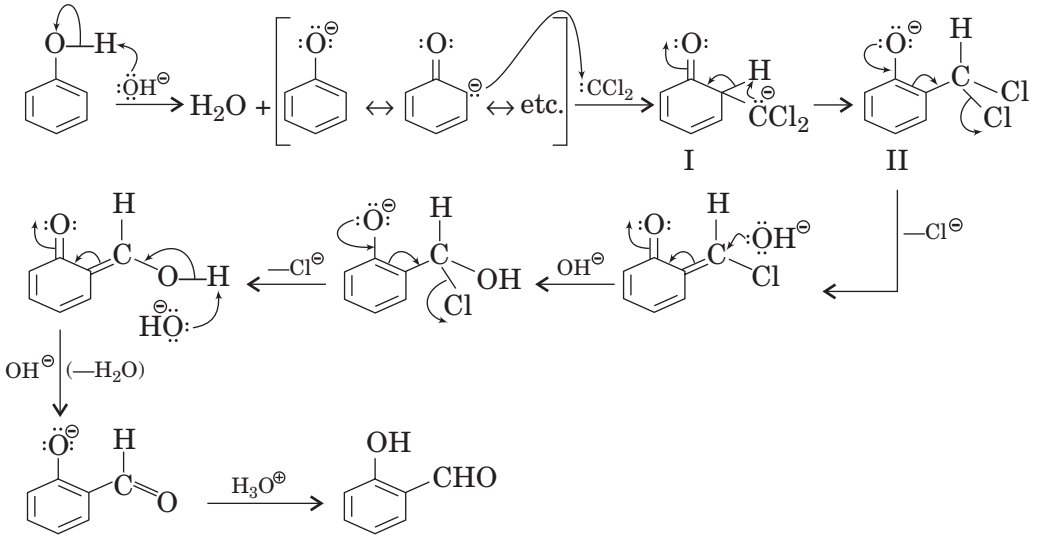
Formylation of phenols and some heterocyclic compounds like pyrroles, thiophenes and activated furans by treating with chloroform in strong aqueous alkali is known as the *Reimer–Tiemann reaction*. The reaction leads preferentially to the formation of *ortho*-formylated product. For example, phenol produces *o*-hydroxybenzaldehyde as the major product when treated with $CHCl_3$/aq. NaOH followed by acidification.



Mechanism of the reaction The electrophile involved in this electrophilic aromatic substitution is dichlorocarbene ($:CCl_2$) which is generated from chloroform by the action of alkali through an 1,1- or α-elimination reaction.



The reaction then proceeds through various steps as follows:

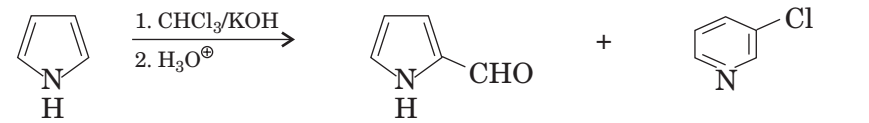


The activated *ortho*-position of the phenoxide ion attacks the electrophile dichlorocarbene (carbon is in sextet state) to form an unstable intermediate (I) which subsequently aromatized by loss of a proton to form a phenoxide ion containing a dichloromethyl group

(II). Alkaline hydrolysis of the resulting dichloro compound followed by acidification produces the corresponding aldehyde (*o*-hydroxybenzaldehyde or salicylaldehyde). The *p*-isomer is obtained similarly.

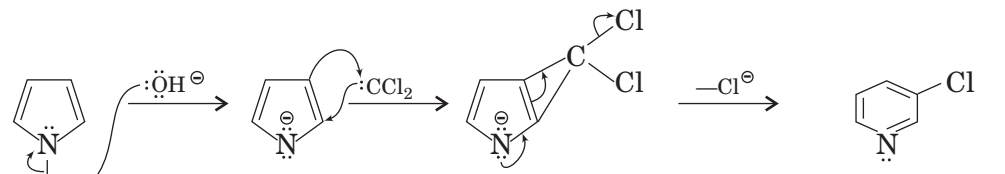
Proof of involvement of dichlorocarbene as the electrophilic species The involvement of dichlorocarbene ($:CCl_2$) as the electrophilic species receives support from the following observations:

(i) When pyrrole is subjected to the Reimer–Tiemann reaction, the abnormal product 3-chloropyridine is obtained due to ring-expansion along with the normal product. Formation of the ring-expanded side-product confirms the involvement of $:CCl_2$.



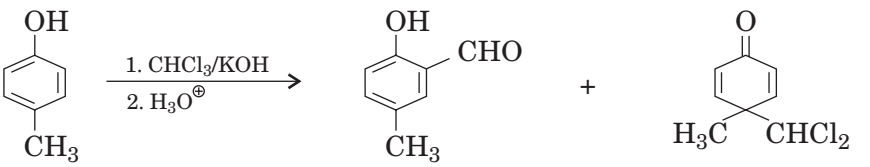
Pyrrole Pyrrole-2-aldehyde 3-Chloropyridine

The formation of 3-chloropyridine may be shown as follows:



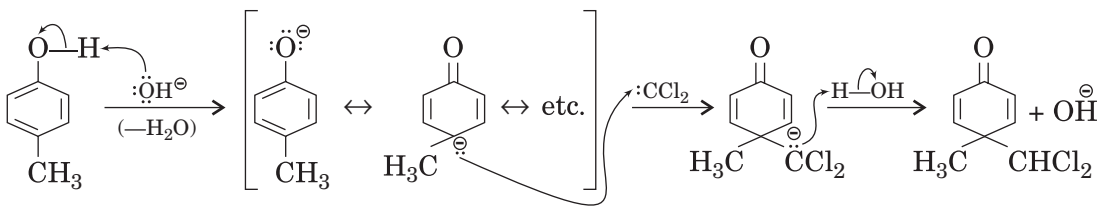
Pyrrole 3-chloropyridine

(ii) *p*-Cresol also gives an abnormal product (a cyclohexadienone containing dichloromethyl group) along with the normal *o*-aldehyde product.



p-Cresol (normal product) (abnormal product)

The formation of the abnormal product may be shown as follows:

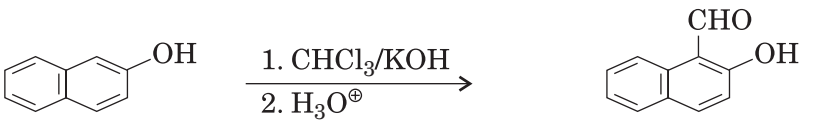


The formation of the abnormal product, therefore, confirms the involvement of dichlorocarbene as the electrophile in the Reimer-Tiemann reaction.

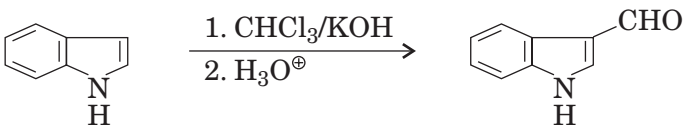
It is to be noted that the $-CHCl_2$ group does not undergo alkaline hydrolysis because of steric reason (the carbon bearing both $-CH_3$ and $-CHCl_2$ groups represents a neopentyl type system which fails to undergo either S_N2 or S_N1.

Applications The important applications of the Reimer–Tiemann reaction are as follows:

(i) The reaction offers a useful method for introducing a formyl group in phenolic compounds as well as certain heterocyclic compounds.
For example:

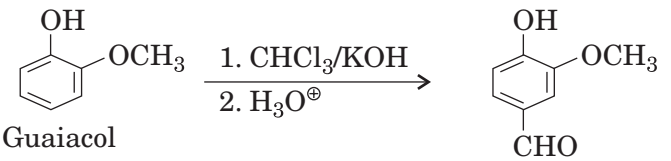


2-Naphthol 2-Hydroxy-1-naphthaldehyde



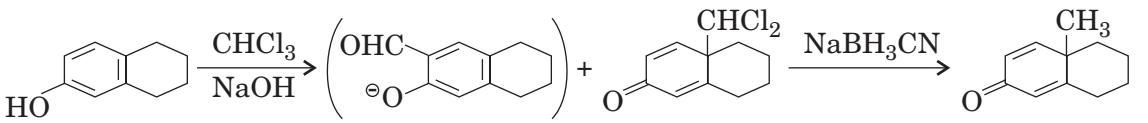
Indole Indole-3-aldehyde

(It is used to synthesize the essential amino acid tryptophan



Guaiacol Vanillin
(a flavouring agent)

(ii) This particular reaction may be used for introducing an angular methyl group in phenols having a ring system fused at the *p*-position.

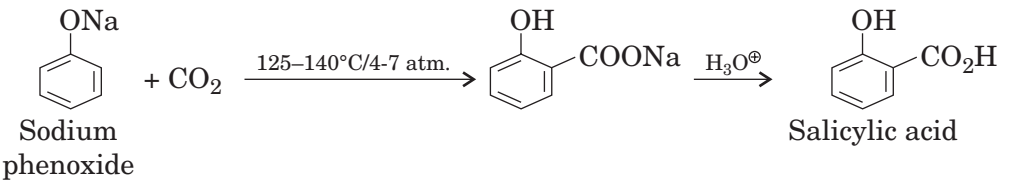


(normal product) (abnormal product)

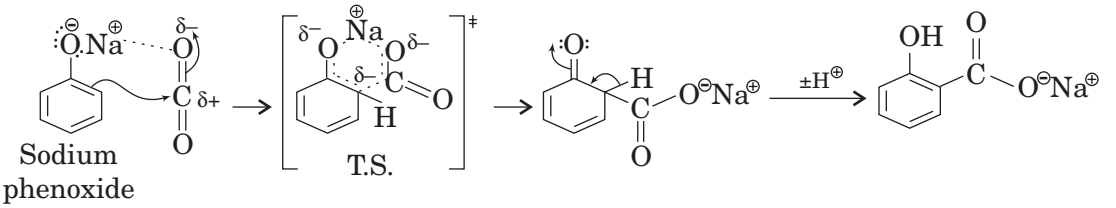
The process is usually used in steroid chemistry.

3.1.5.9 Kolbe–Schmitt reaction

The method of carboxylation of sodium phenoxide by heating with carbon dioxide under pressure, mostly at the *ortho*-position, is known as the *Kolbe–Schmitt reaction*. For example, salicylic acid can be prepared conveniently in good yield by this reaction:



Mechanism of the reaction The mechanism of this electrophilic aromatic substitution is supposed to proceed through the initial formation of a complex (I) between the two reactants so that the carbon atom of CO_2 becomes electron-deficient and takes up position to be attacked by the electron rich *ortho*-ring carbon. In fact, the transition state for *ortho* attack is favoured due to formation of a six-membered chelate.



Some relevant topics

(i) Phenols being weakly nucleophilic does not react with the weakly electrophilic CO_2. So, phenol cannot be used instead of phenoxide (strongly nucleophilic) in this reaction.

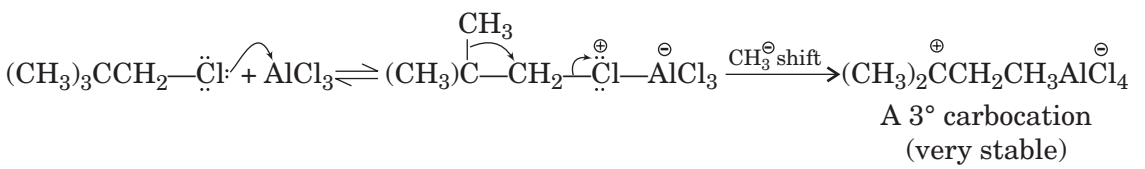
(ii) Because of larger size of $K^{\oplus}$, chelation in the case of potassium phenoxide is less likely to take place and as a consequence, the phenoxide undergoes substitution mainly at the *para*-position to yield *p*-hydroxybenzoic acid.

SOLVED PROBLEMS

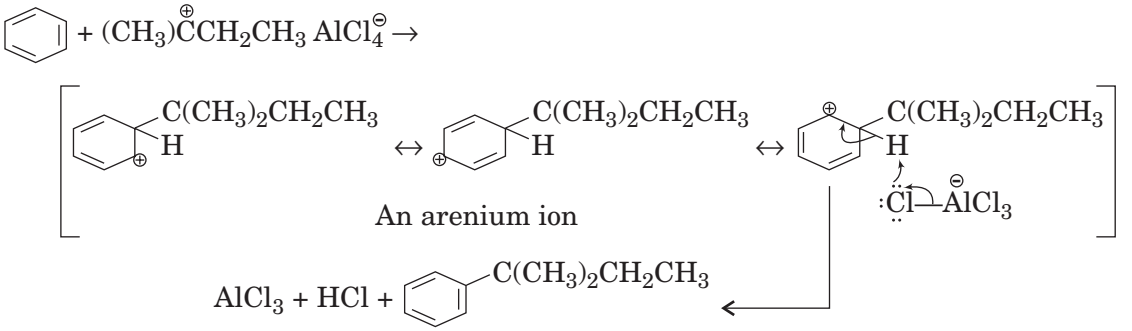
1. What would be the major product of the Friedel–Crafts alkylation of benzene using the following alkyl chlorides? Give your reasoning.
(a) $(CH_3)_3CCH_2Cl$ (b) $(CH_3)_2CHCH_2Cl$

Solution

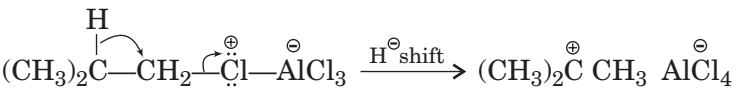
(a) The carbocation expected to be formed when $AlCl_3$ reacts with neopentyl chloride would be a less stable primary carbocation and for this reason, it rearranges to the more stable tertiary carbocation by a 1,2-$CH_3^{\ominus}$ shift before it can react with the benzene ring.



The 3° carbocation then reacts with benzene to yield 2-methyl-2-phenylbutane as the major product.

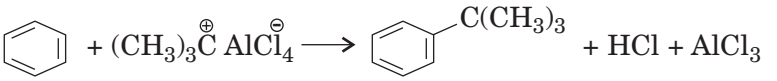


(b) The incipient primary carbocation rearranges to a more stable tertiary carbocation by $H^{\ominus}$ shift.

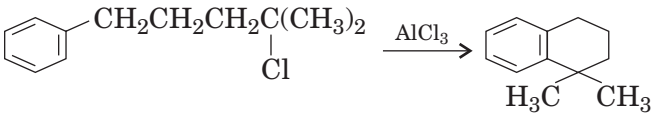


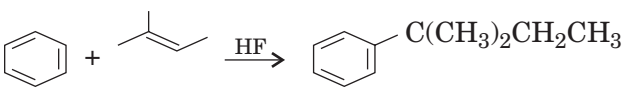
Complex *tert*-Butyl cation

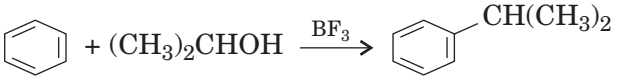
Therefore, the major product is *tert*-butylbenzene.

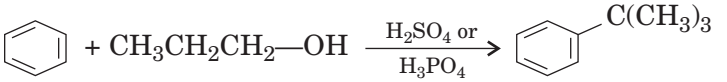


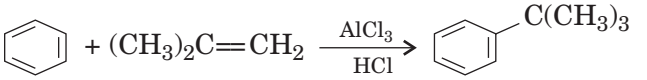
2. Suggest a mechanism for each of the following alkylation reactions

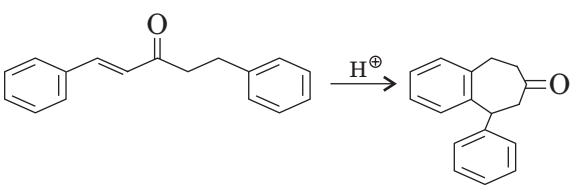
(a) 

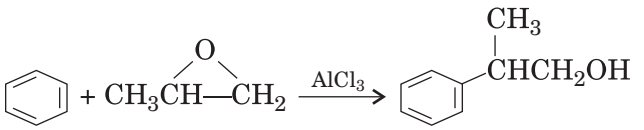
(b) 

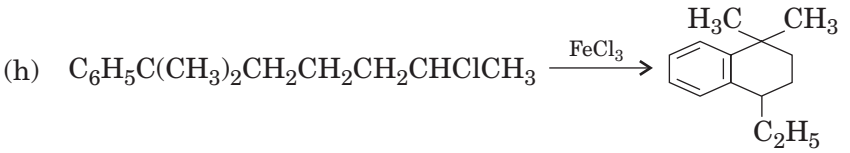
(c) 

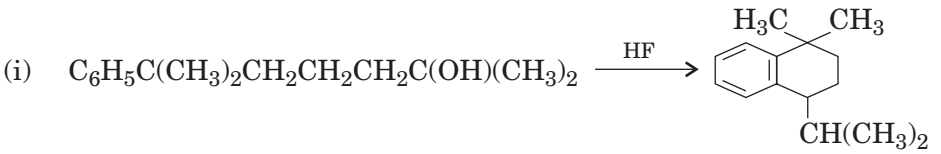
(d) 

(e) 

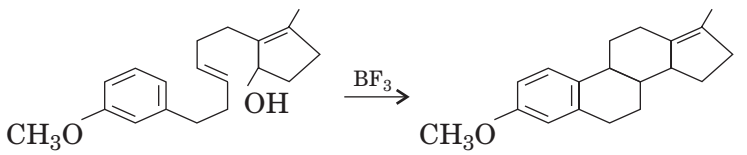
(f) 

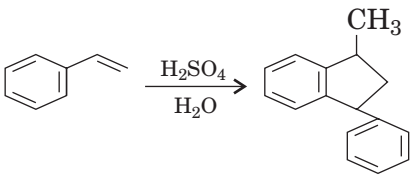
(g) 

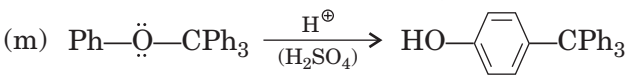
(h) 

(i) 

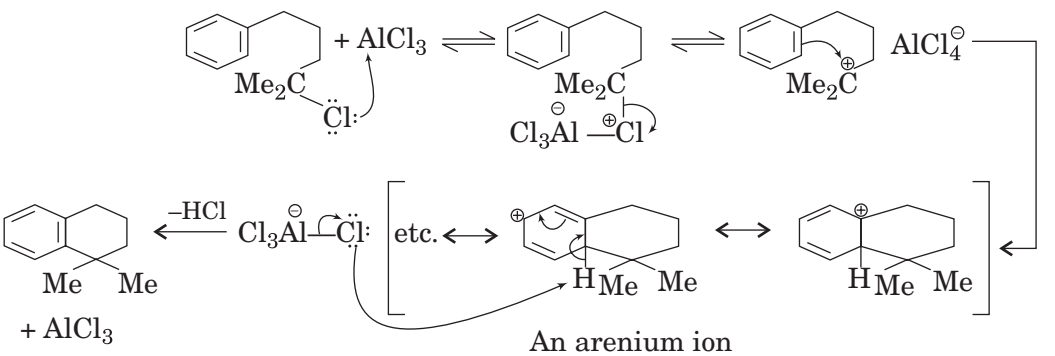
(j) 

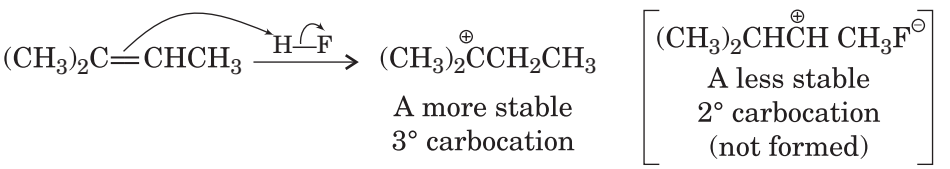
(k) 

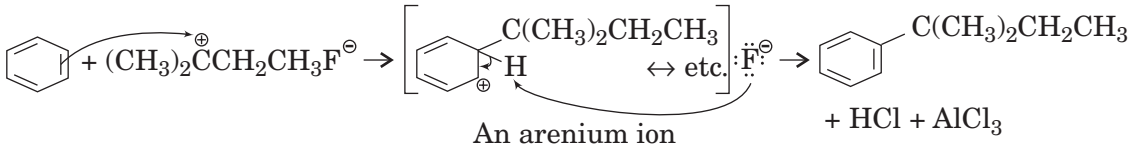
(l) 

(m) 

Solution The mechanisms of these reactions may be outlined as follows:

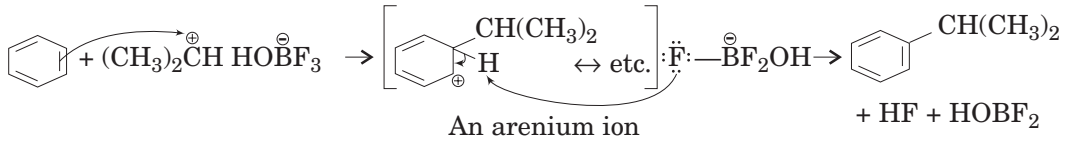
(a) 

(b) 



(c) $(CH_3)_2CH—\ddot{O}H + BF_3 \rightleftharpoons (CH_3)_2CH—\overset{\oplus}{O}(H)—\overset{\ominus}{B}F_3 \rightleftharpoons (CH_3)_2\overset{\oplus}{C}H\ HO—\overset{\ominus}{B}F_3$

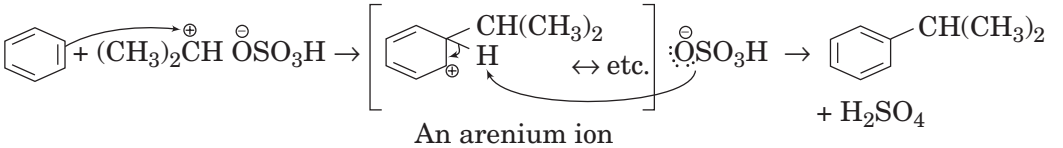
Lewis base Lewis acid



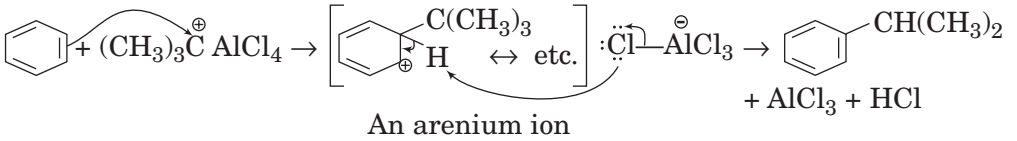
(d) $CH_3CH_2CH_2—\ddot{O}H \xrightarrow{H—OSO_3H} CH_3\overset{H}{\underset{|}{C}}H—CH_2—\overset{\oplus}{O}H_2 \xrightarrow[H^{\ominus}\text{-shift}]{-H_2O} CH_3\overset{\oplus}{C}H\ CH_3\ OSO_3H$

(The incipient 1° carbocation rearranges to a more stable 2° carbocation)

Isopropyl cation (a 2° carbocation)



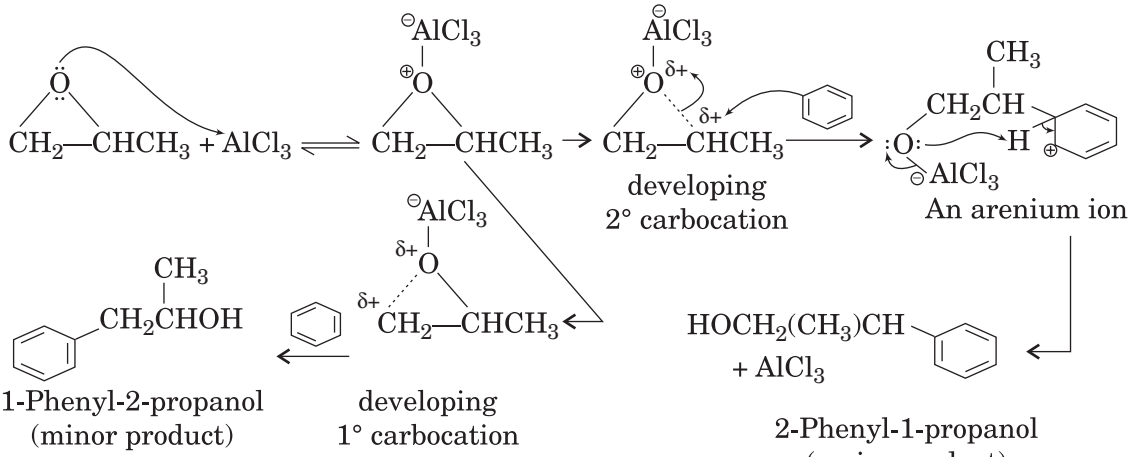
(e) $(CH_3)_2C{=}CH_2 + H—\ddot{C}l: + AlCl_3 \rightleftharpoons (CH_3)_2\overset{\oplus}{C}\ CH_3\ AlCl_4^{\ominus}$



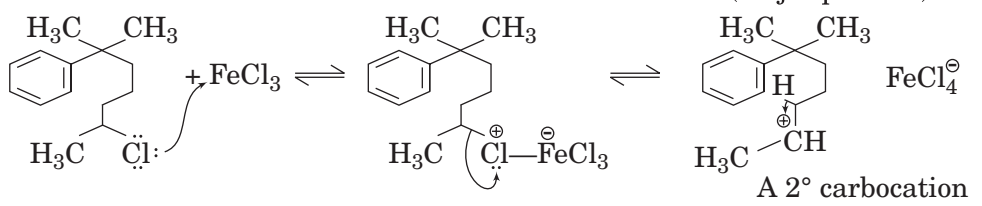
(f) $PhCH{=}CHC{=}O$ ($-(CH_2)_2$) $\xrightarrow{H^{\oplus}}$ $PhCHCH_2C{=}O$ ($-(CH_2)_2$) $\longrightarrow$ $O{=}$ (Ph, H) $\xrightarrow{-H^{\oplus}}$ $O{=}$ (Ph)

The carbon α to $C = 0$ undergoes protonation to form a relatively stable 2° benzylic cation. Intramolecular alkylation then leads to the formation of the product.

(g) The epoxy oxygen coordinates with $AlCl_3$ to form a complex. Now, in between the two epoxy carbons, the one which is more substituted is more positive because it is a developing secondary carbocation rather than a primary carbocation. Attack by benzene thus occurs at the more substituted carbon to form the corresponding primary alcohol.

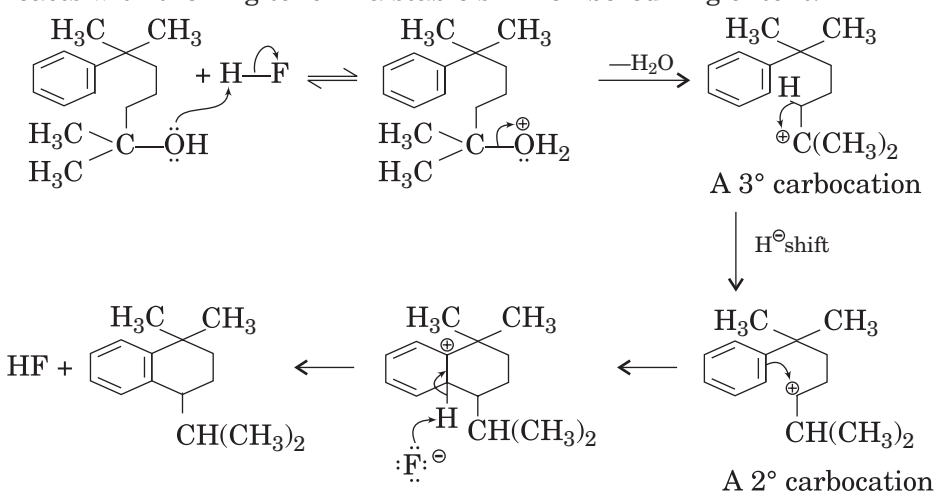


(h)



The first 2° carbocation rearranges to give the second 2° carbocation because this reacts with the ring to form a stable six-membered ring onto it.

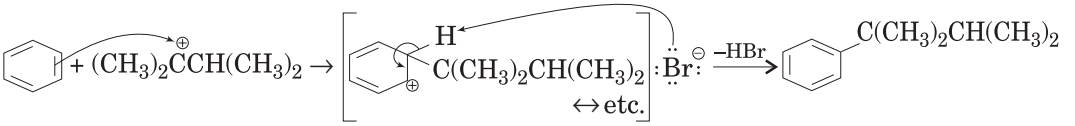
(i)



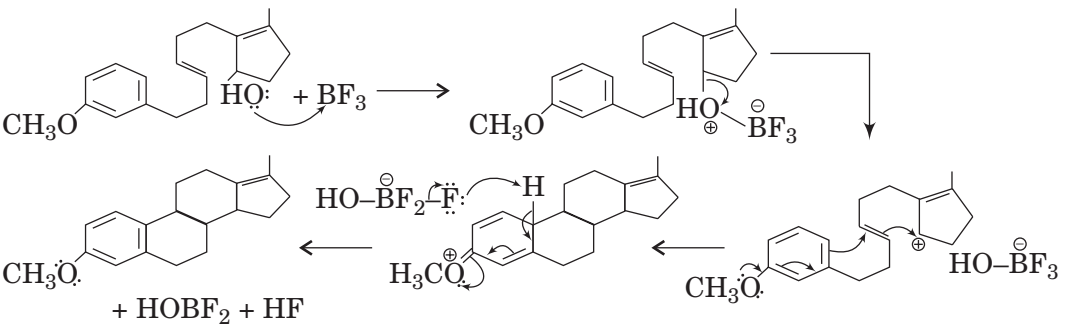
Due to the same basic reason [problem (h)], a 3° carbocation rearranges to a 2° carbocation (a process not normally favourable) before ring closure.

(j) $(CH_3)_3C{-}CH{=}CH_2 + H{-}Br \rightarrow (CH_3)_2\overset{CH_3}{\overset{|}{C}}{-}\overset{\oplus}{C}H{-}CH_3\ Br^{\ominus} \rightarrow (CH_3)_2\overset{\oplus}{C}\ CH(CH_3)_2\ Br^{\ominus}$

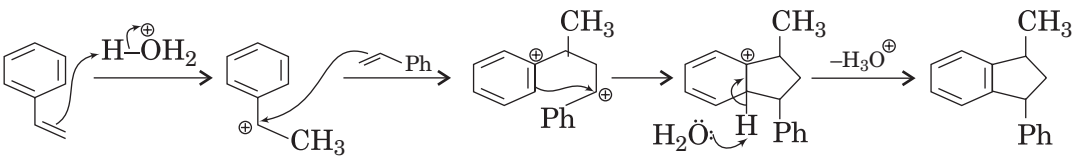
A 2° carbocation (less stable) — A 3° carbocation (more stable)



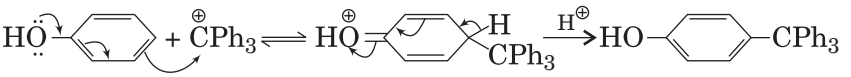
(k)



(l)



(m) $Ph - \ddot{O} - CPh_3 \overset{H^{\oplus}}{\rightleftharpoons} Ph - \overset{\oplus}{\underset{H}{O}} - CPh_3 \rightleftharpoons PhOH + Ph_3\overset{\oplus}{C}$ (a very stable carbocation)



3. Nitrobenzene ($C_6H_5NO_2$) is used as a solvent in the Friedel–Crafts reaction. Why?

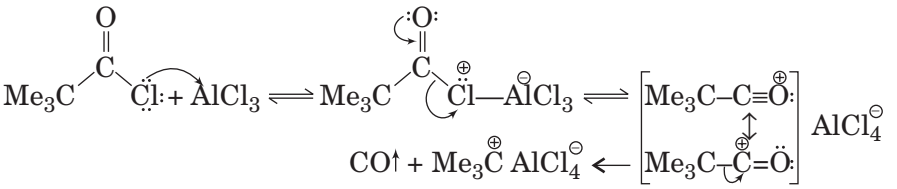
Solution Since the $-NO_2$ group deactivates the ring of nitrobenzene more than that of halobenzenes, nitrobenzene does not undergo the Friedel–Crafts reaction. Also, the substrate, the reagent and the catalyst get either dissolved or suspended in highly polar nitrobenzene. For these reasons, nitrobenzene is used as a solvent in the Friedel–Crafts reaction.

4. Explain the following observations:

$$HCl + CO\uparrow + C_6H_5CMe_3 \xleftarrow[AlCl_3]{C_6H_6} Me_3CCOCl \xrightarrow[AlCl_3]{C_6H_5OCH_3} p\text{-}CH_3OC_6H_4COCH_3 + HCl + AlCl_3$$

$+ AlCl_3$ — 2,2-Dimethylpropanoyl chloride

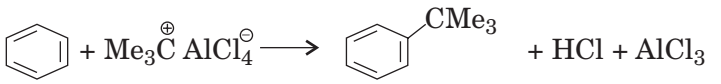
Solution 2,2-Dimethylpropanoyl chloride reacts with $AlCl_3$ to form a complex which dissociates to form an acylium ion ($Me_3C—\overset{\oplus}{C}=O$). This acylium ion can further dissociate to form a very stable 3° carbocation ($\overset{\oplus}{C}Me_3$).



Since the ring of anisole ($C_6H_5\ddot{O}CH_3$) is relatively more activated due to the +R effect of the $–OCH_3$ group, anisole reacts readily with the acylium ion to form *p*-$CH_3OC_6H_4$—$COCMe_3$.



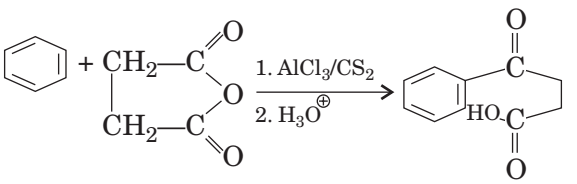
Since benzene is a relatively unreactive substrate, $Me_3C—\overset{\oplus}{C}=O$ gets enough time to form $\overset{\oplus}{C}Me_3$ by dissociation. Thus, benzene reacts with $\overset{\oplus}{C}Me_3$ to form *tert*-butylbenzene.



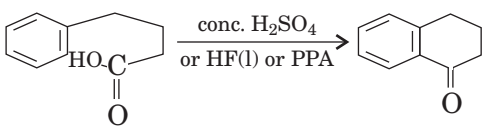
tert-Butylbenzene

5. Provide a reasonable mechanism for each of the following reactions:

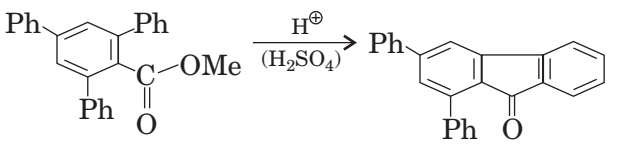
(a)



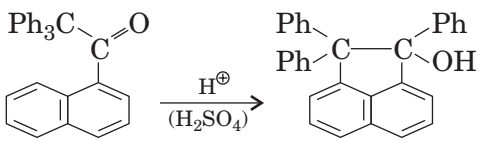
(b)



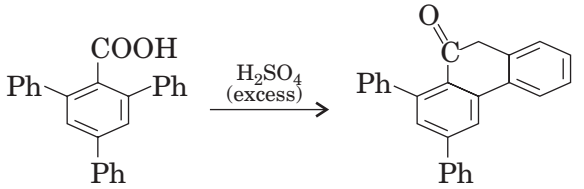
(c)



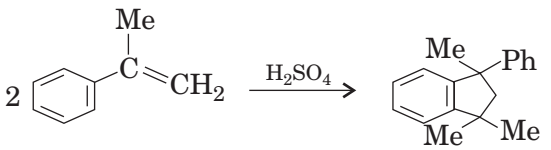
(d)



(e)

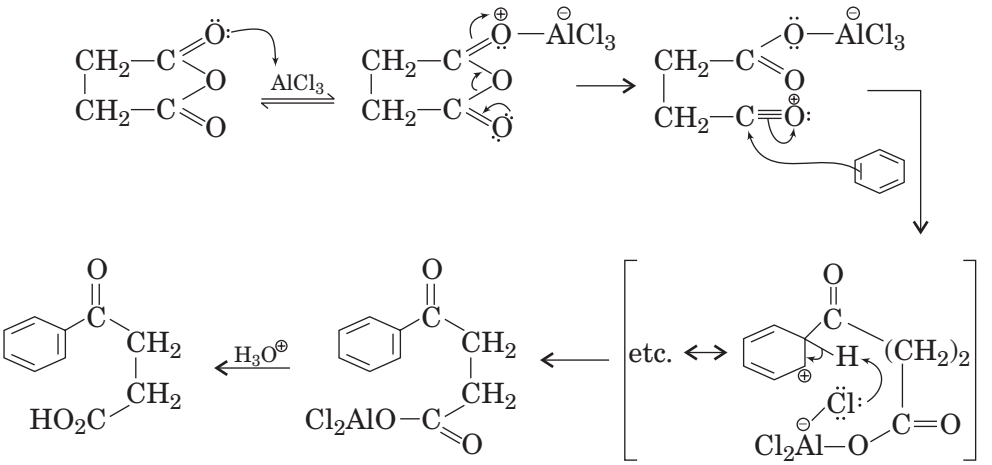


(f)

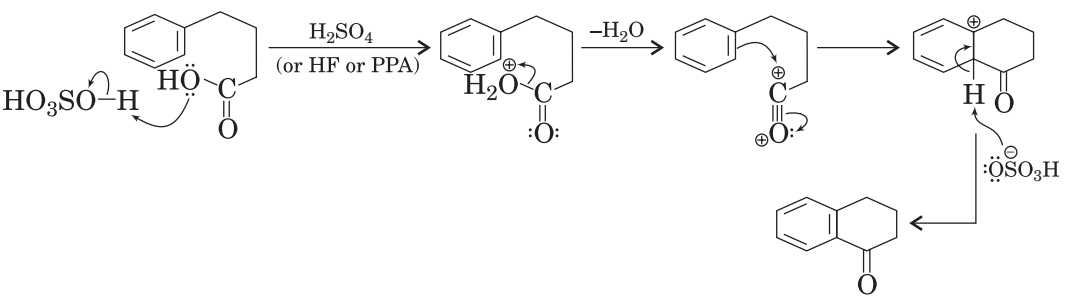


Solution

(a)

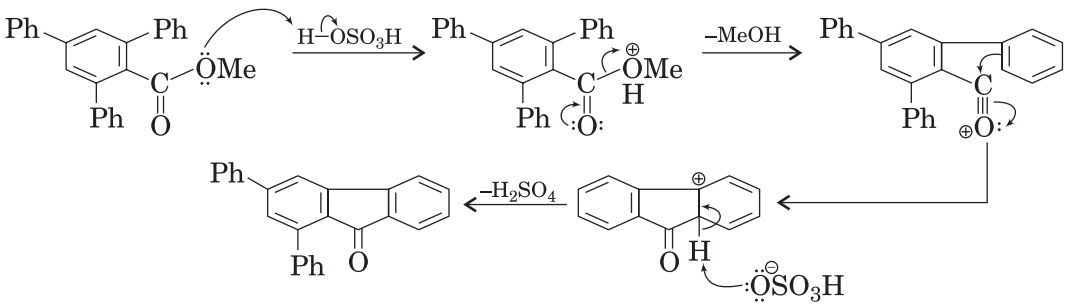


(b)

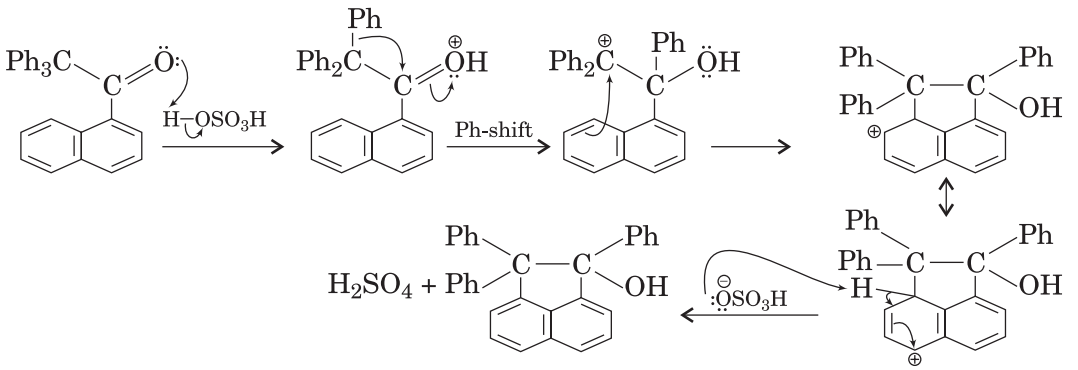


In the presence of strong acids like H_2SO_4 (powerful ionizing medium), protonation takes place on the less favoured hydroxyl oxygen instead of carbonyl oxygen to produce an acylium ion.

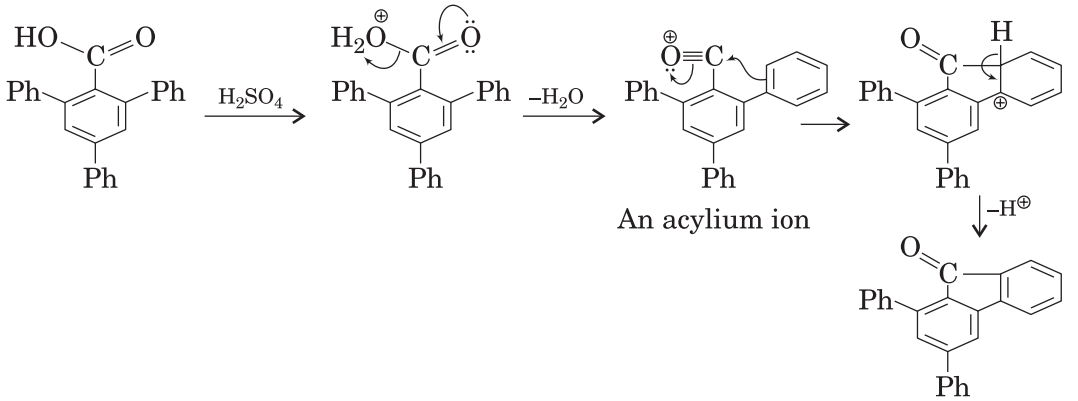
(c)


Ph
Ph
OMe
C
O
H–OSO3H
Ph
Ph
OMe
H
C
O
Ph
–MeOH
Ph
C
O
Ph
Ph
–H2SO4
O
H
:OSO3H

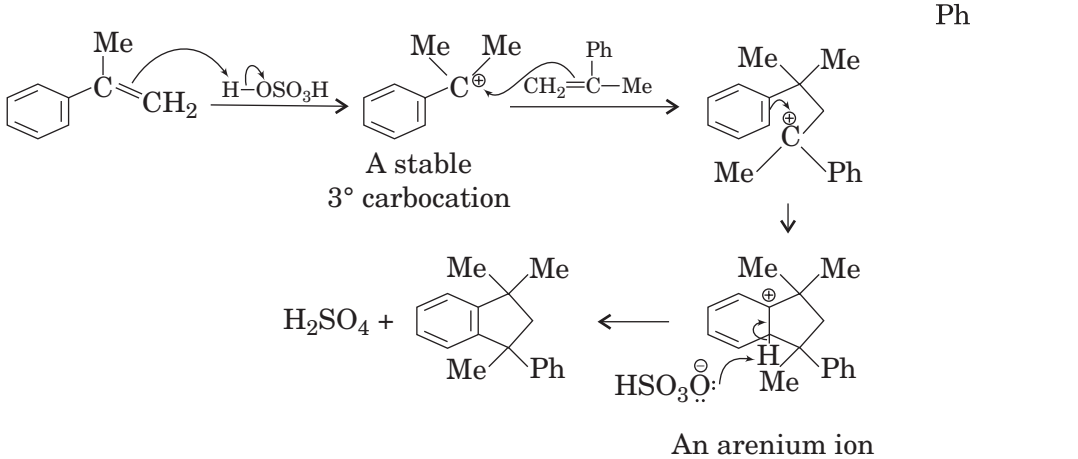
(d)


Ph3C
C
O
H–OSO3H
Ph
Ph2C
C
OH
Ph-shift
Ph2C
Ph
C
OH
Ph
Ph
C
C
OH
H2SO4 + Ph
Ph
C
C
Ph
OH
:OSO3H
Ph
Ph
C
C
Ph
H
OH

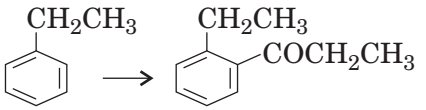
(e)

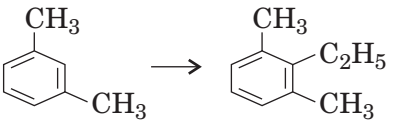

HO
C
O
Ph
Ph
Ph
H2SO4
H2O
C
O
Ph
Ph
Ph
–H2O
O
C
Ph
Ph
An acylium ion
O
H
C
Ph
Ph
–H⊕
O
C
Ph
Ph

(f)

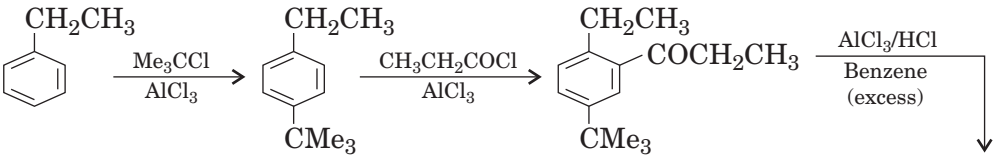

Me
C
CH2
H–OSO3H
Me
Me
C
A stable
3° carbocation
CH2=C–Me
Ph
Me
Me
C
Me
Ph
Me
Me
H2SO4 +
Me
Ph
Me
Me
H
Me
Ph
HSO3O:
An arenium ion

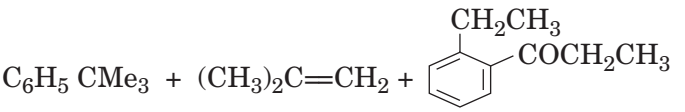
6. Provide methods for the following conversions (use *t*-Bu as a blocking group):

(a) 

(b) 

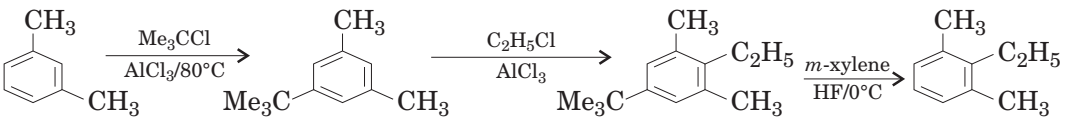
Solution

(a) 



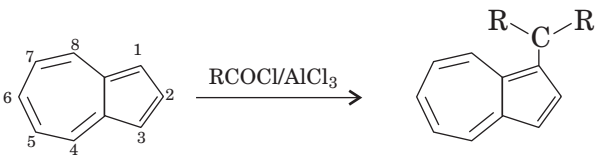
o-Ethylpropiophenone

In the first step, the bulky $-CMe_3$ groups goes exclusively to the position *para* to the $-C_2H_5$ group. In the second step, the $-COCH_2CH_3$ group is forced to occupy the position *ortho* to the $-C_2H_5$ group and in the third step, the $-CMe_3$ group is expelled from the ring by treating with $AlCl_3$/HCl in excess of benzene.

(b) 

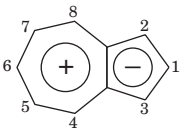
Under the equilibrium conditions, the $-CMe_3$ group occupy the position *meta*- to both the methyl groups. In the second step, the $-C_2H_5$ group occupies the relatively spacious position (between two $-CH_3$ groups rather than a $-CMe_3$ and a $-CH_3$ group) and in the third step, the $-CMe_3$ group is removed by treating with HF in *m*-xylene.

7. Explain why azulene undergoes acylation at position-1 of the five-membered ring. Give the mechanism of the reaction.



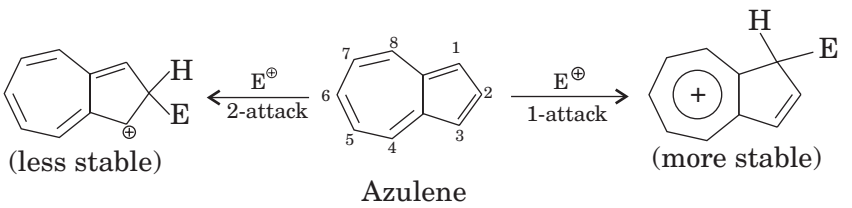
Azulene 1-Acylazulene

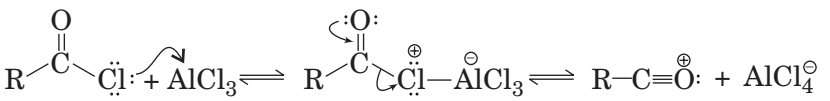
Solution Azulene (a ten-π-electron system) is aromatic. Its seven-membered ring is positively polarised and the five-membered ring is negatively polarised.

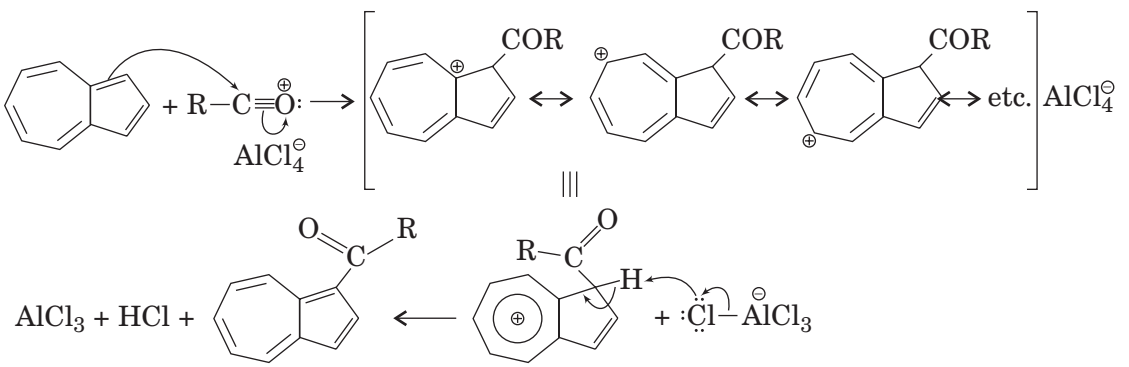


(Azulene
(aromatic)

Therefore, electrophilic aromatic substitution preferably occurs at the five-membered ring because it can well accommodate a positive charge. Now, there are two non-equivalent positions (C-1 and C-2) in the five-membered ring where substitution may take place. But substitution actually occurs at 1-position because 1-attack leads to a stable intermediate carbocation in which the seven-membered ring is an aromatic system [tropylium ion, $(4n + 2)\pi$ system, where $n = 1$].







The resulting ketone forms a complex with $AlCl_3$. The complex is finally decomposed by adding water into the reaction mixture.

8. Use practical methods for the following conversions:

(a) $(C_6H_5)_2C = O$ from C_6H_6 and $C_6H_5CH_3$

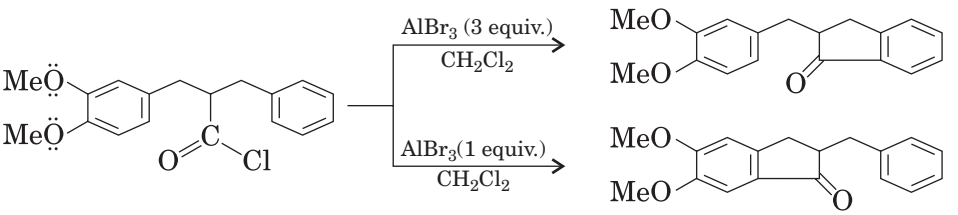
(b) $(C_6H_5)_2CH_2$ from C_6H_6 and $C_6H_5CH_3$

Solution

(a) $C_6H_5CH_3 \xrightarrow[2.\ H_3O^{\oplus}]{1.\ KMnO_4/OH^{\ominus}/\Delta} C_6H_5COOH \xrightarrow{SOCl_2} C_6H_5COCl \xrightarrow[AlCl_3]{C_6H_6} C_6H_5COC_6H_5$

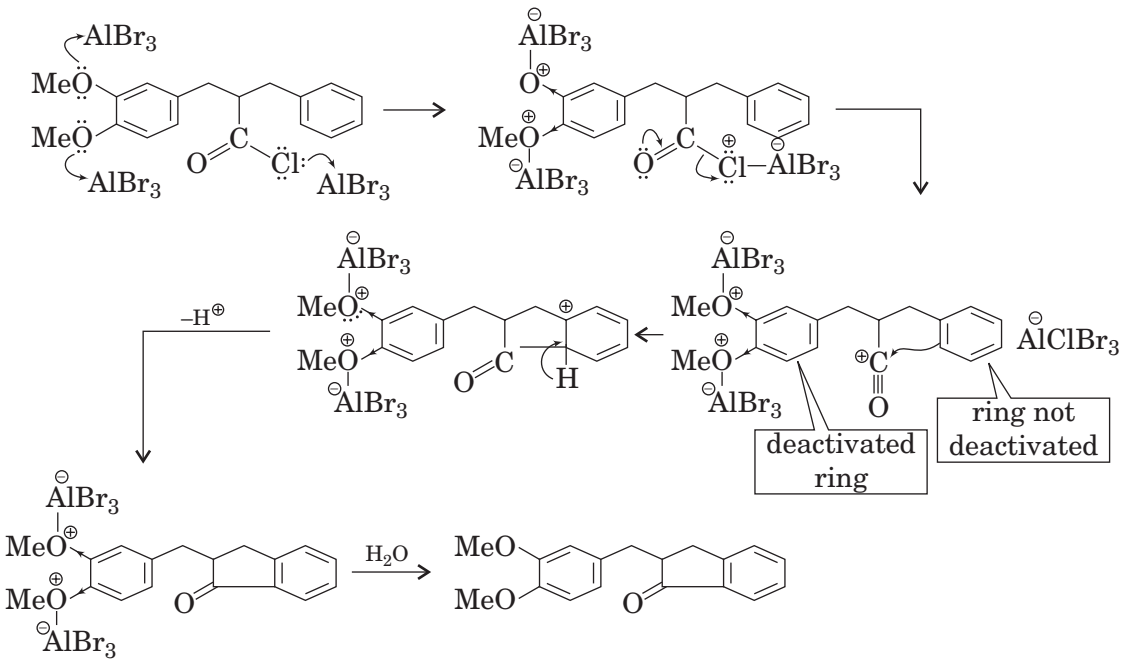
(b) $C_6H_5CH_3 \xrightarrow[\text{boiling conditions}]{Cl_2} C_6H_5CH_2Cl \xrightarrow[AlCl_3]{C_6H_6} C_6H_5CH_2C_6H_5$

9. Explain the following observations:

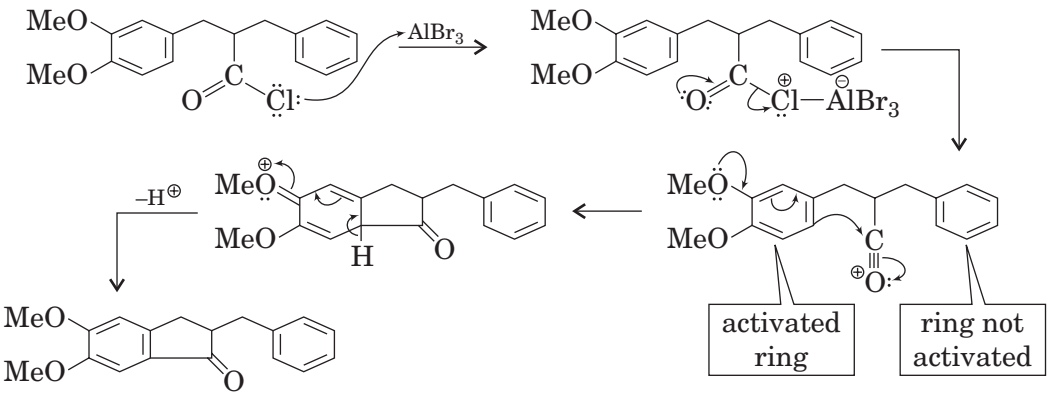


Solution In the presence of 3 equivalents of $AlBr_3$ (Lewis acid), the two electron-releasing $-\ddot{O}Me$ groups coordinate with $AlBr_3$ and converted into electron-attracting $-\overset{\oplus}{\underset{Me}{O}}-\overset{\ominus}{A}lBr_3$ groups which deactivate the ring. So, acylation takes place on the relatively activated other ring. In the presence of 1 equivalent of $AlBr_3$, the OMe groups remain free and make the ring more activated relative to the other ring. So, this ring undergoes acylation to give the corresponding ketone.

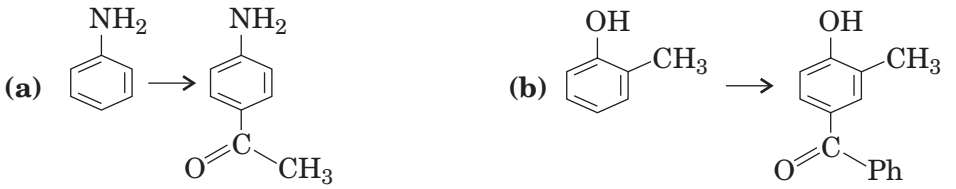
With 3 equivalents of $AlBr_3$:



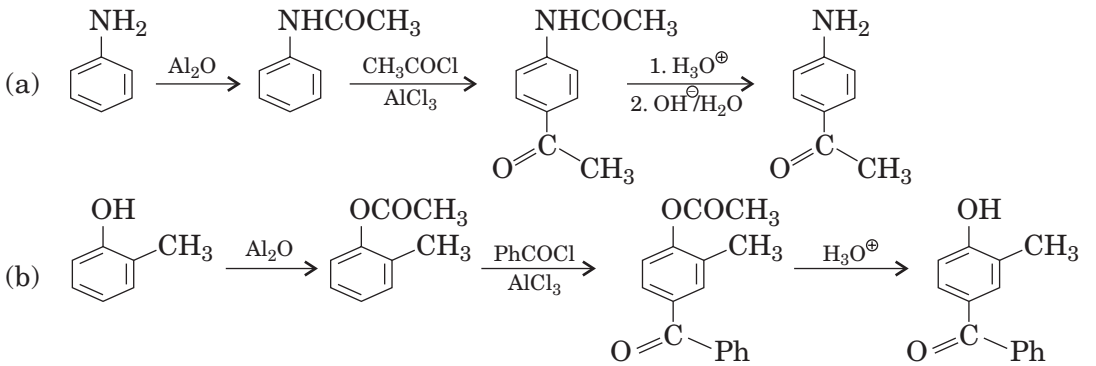
With 1 equivalent of $AlBr_3$:



10. How would you carry out the following transformations?

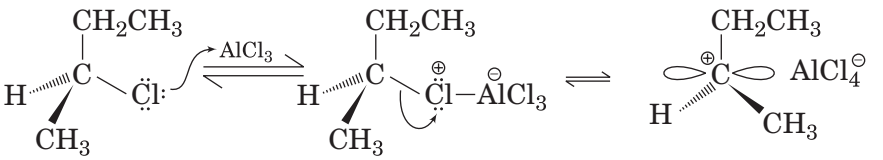


Solution

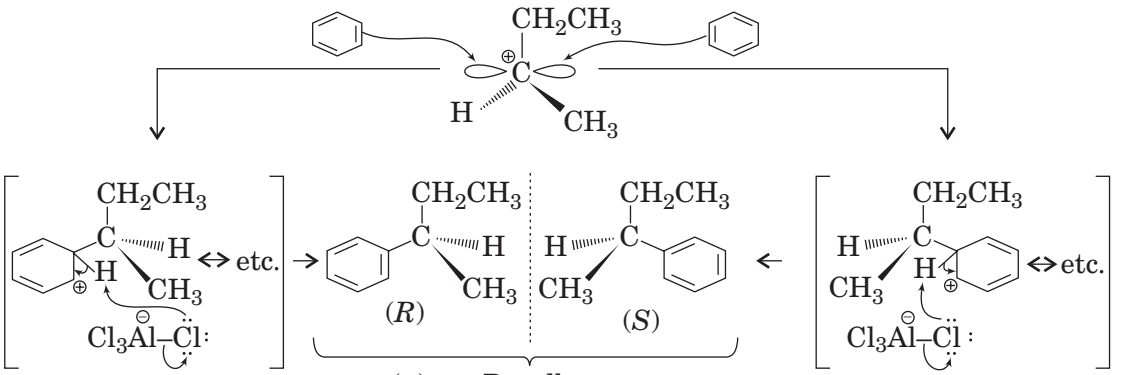


11. The Friedel–Crafts alkylation of benzene with (*S*)-2-chlorobutane and $AlCl_3$ affords *sec*-butylbenzene. Would you expect the product to exhibit optical activity? Explain your answer.

Solution The chiral alkyl chloride (*S*)-2-chlorobutane undergoes ionisation in the presence of $AlCl_3$ to form a planar 2° carbocation. The carbocation undergoes nucleophilic attack by benzene from both sides with equal facility to yield the two enantiomers of ***sec***-butybenzene in equal amounts, i.e. an optically inactive racemic mixture is obtained.

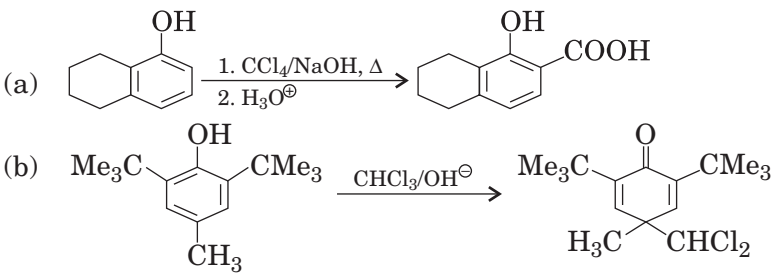


(*S*)-2-Chlorobutane

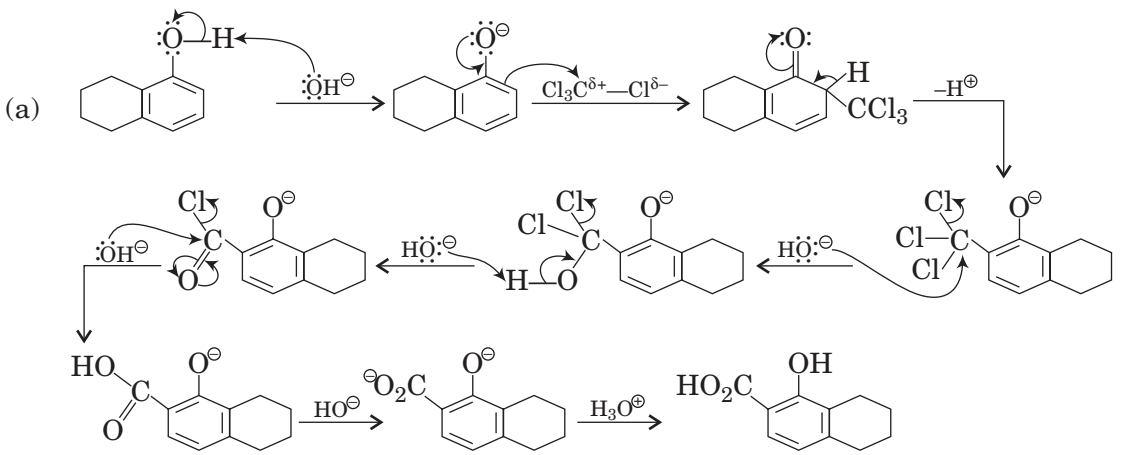


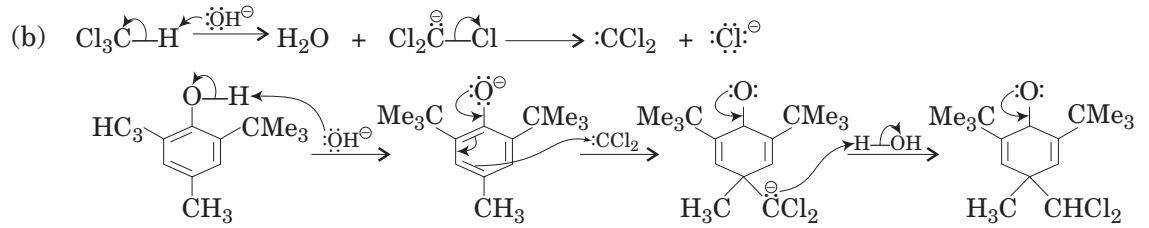
(±)-*sec*-Butylbenzene
(optically inactive)

12. Suggest plausible mechanism for each of the following reactions:



Solution



(b) 

Study Problems

1. Explain the following observations:

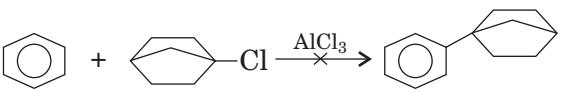
(a) When *p-tert*-butylphenol is treated with dilute acid, a mixture of phenol and *tert*-butyl alcohol is obtained.

(b) A large excess of aromatic starting material is to be used to obtain a good yield of monoalkylation product in the Friedel–Crafts alkylation.

(c) Although tropylium bromide is aromatic, it does not undergo the Friedel–Crafts reaction.

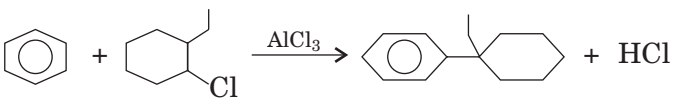
(d) Pyridine does not undergo the Friedel–Crafts reaction.

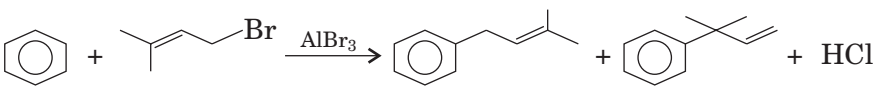
(e) 1-Chloronorbornane cannot be used to alkylate benzene in the presence of aluminium chloride.

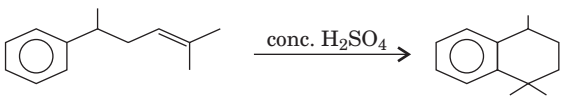


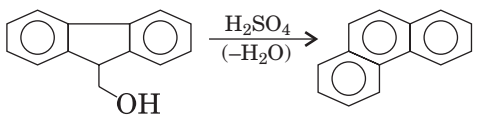
(f) Benzene cannot be used as a solvent in the Friedel–Crafts alkylation of bromobenzene.

2. Draw a stepwise mechanism for each of the following reactions:

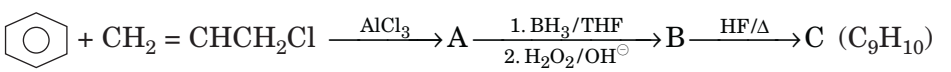
(a) 

(b) 

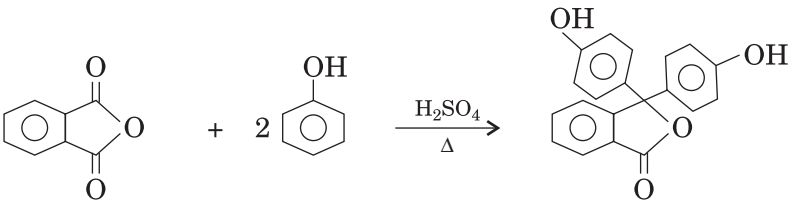
(c) 

(d) 

3. Provide structures for A, B and C in the following reaction sequence:

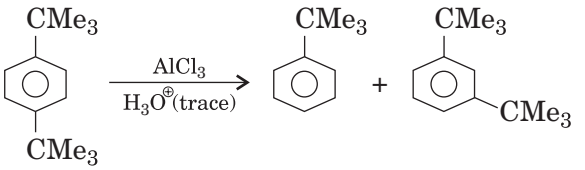


4. Propose a mechanism for the synthesis of phenolphthalein (an acid-base indicator):

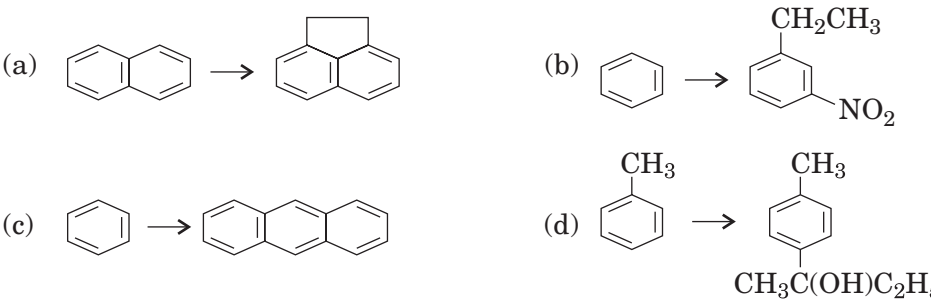


Phthalic analydride Phenol Phenolphthalein

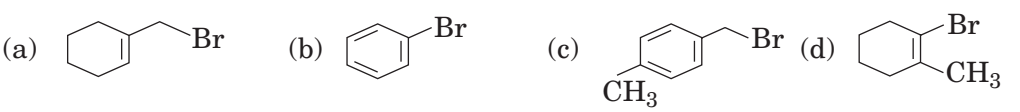
5. When *p*-di-*tert*-butylbenzene is treated with anhydrous aluminium chloride and a trace of water, a mixture of the starting material and the products (as given below) is recovered. Give a mechanistic interpretation for this observation and suggest why no *o*-isomer is formed.



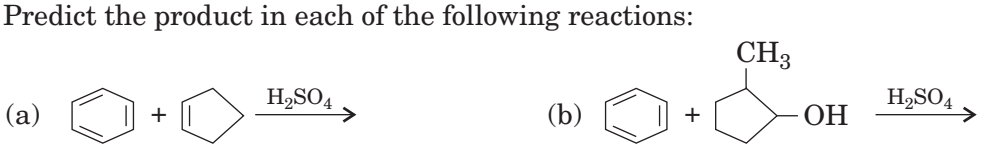
6. How would you carry out the following transformations?



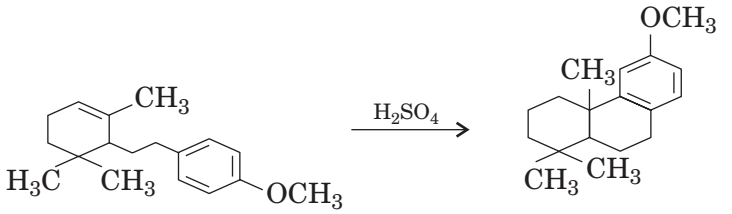
7. Which halides remain inert in a Friedel–Crafts alkylation reaction? Give your reasoning.

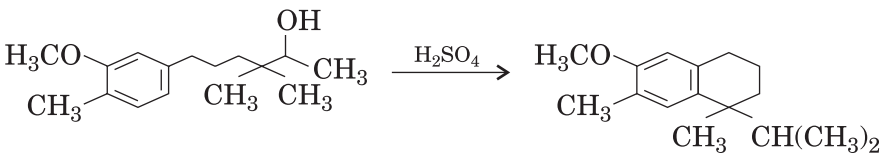


8. Predict the product in each of the following reactions:

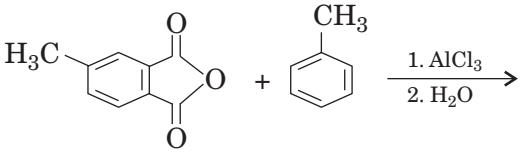


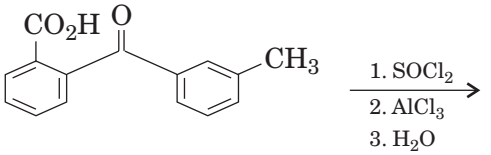
9. Provide a reasonable mechanism for each of the following cyclization reactions:

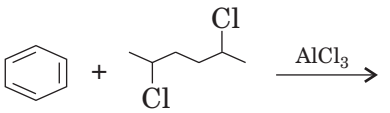
(a) 

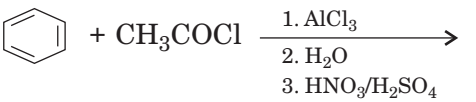
(b) 

10. Predict the product of the following reactions:

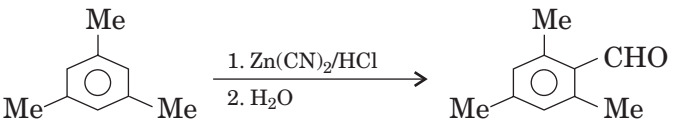
(a) 

(b) 

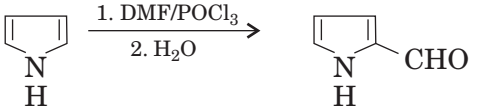
(c) 

(d) 

11. Provide a reasonable mechanism for the following reaction (Gattermann formylation):

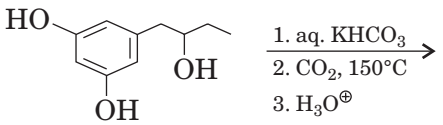


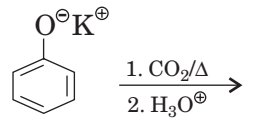
12. Give the mechanism of the following reaction (Vilsmeier–Haack reaction):



Pyrrole Pyrrole-2-aldehyde

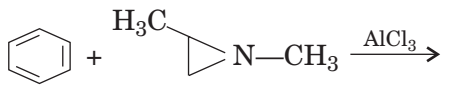
13. Predict the product and propose a mechanism for each of the following reactions:

(a) 

(b) 

14. Explain why benzene does not undergo the Reimer-Tiemann reaction when treated with $CHCl_3$/NaOH.
[**Hint:** Weakly nucleophilic benzene (the ring is not so activated is unable to attack the weakly electrophilic dichlorobenzene ($:CCl_2$).]

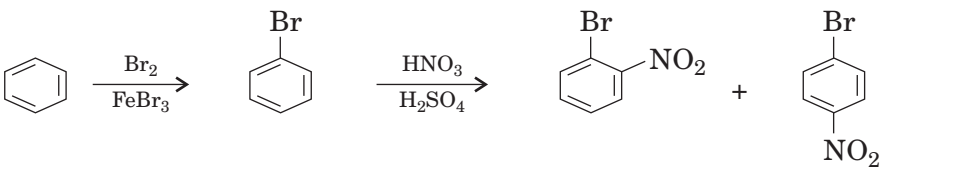
15. Benzene undergoes electrophilic aromatic substitution reaction with aziridines in the presence of $AlCl_3$. Predict the major and minor products of the following reaction:



3.1.6 Use of Electrophilic Aromatic Substitution Reactions in Organic Synthesis

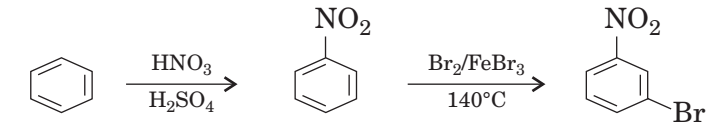
The substitution reactions of aromatic compounds and the reactions of the side chains of alkyl and alkenylbenzenes, when taken together, offer a very useful set of reactions for organic synthesis. It is possible to synthesize a large number of benzene derivatives by using these reactions skillfully. Both activating/deactivating and directing effects of substituents can come into play in planning an organic synthesis involving electrophilic substitution reactions. The importance of directing effects and choosing proper order of reactions is illustrated in syntheses given below:

(i) Synthesis of *p*-bromonitrobenzene The key to this synthetic problem is whether the bromine or the nitro group should be the substituent to be introduced first into the benzene ring. Since bromine is an *ortho-para* director, it is to be introduced first.



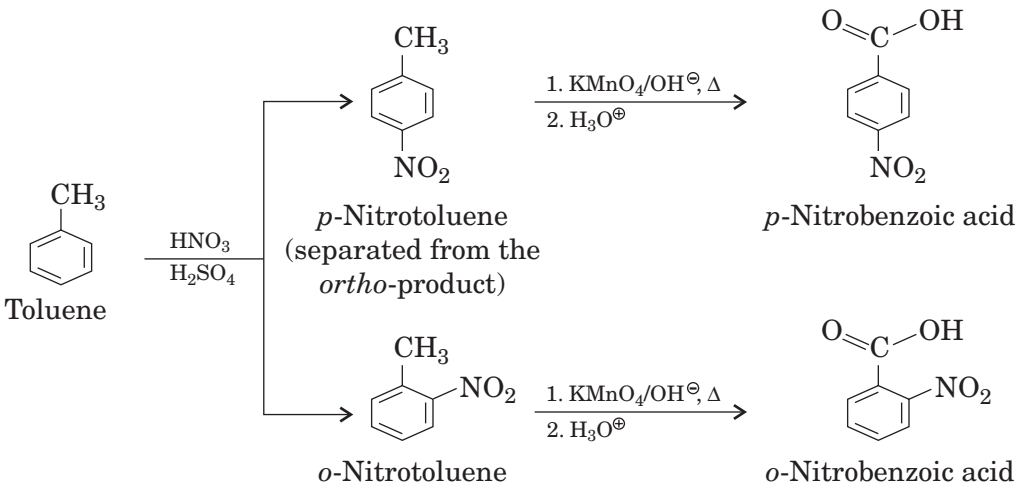
Benzene — Bromobenzene — *o*-Bromonotro-benzene — *p*-Bromonitro-benzene

The *ortho* and *para* isomers can be separated by various methods because they possess different physical properties. Introduction of the nitro group first followed by bromination would give *m*-bromonitrobenzene because the $–NO_2$ group is a *meta*-directing group.



Benzene Nitrobenzene *m*-Bromonitrobenzene

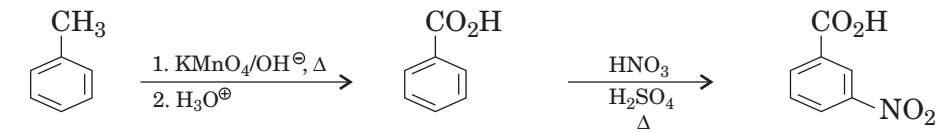
(ii) Syntheses of *o*-, *m*- and *p*-nitrobenzoic acids Since the methyl group of toluene is an *ortho-para* directing, therefore, it is possible to synthesize the *ortho*- and *para*-nitrobenzoic acids from toluene by nitrating it, separating the *ortho*- and *para*-nitrotoluenes, and then oxidizing the methyl groups to carboxyl groups by a suitable oxidizing agent.



Toluene *p*-Nitrotoluene (separated from the *ortho*-product) *p*-Nitrobenzoic acid

o-Nitrotoluene *o*-Nitrobenzoic acid

However, *m*-nitrobenzoic acid can be synthesized by reversing the order of the reactions. The methyl group is first oxidized to a carboxyl group (an electron-withdrawing group) which directs nitration to the *meta*-position.

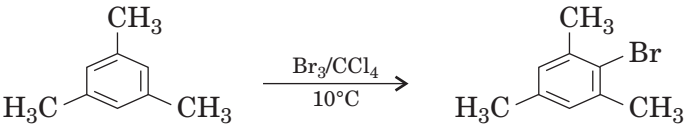


Toluene Benzoic acid *m*-Nitrobenzoic acid

The activating or deactivating effects of substituents in an aromatic compound also determine the conditions that is to be used in electrophilic substitution reaction. For example:

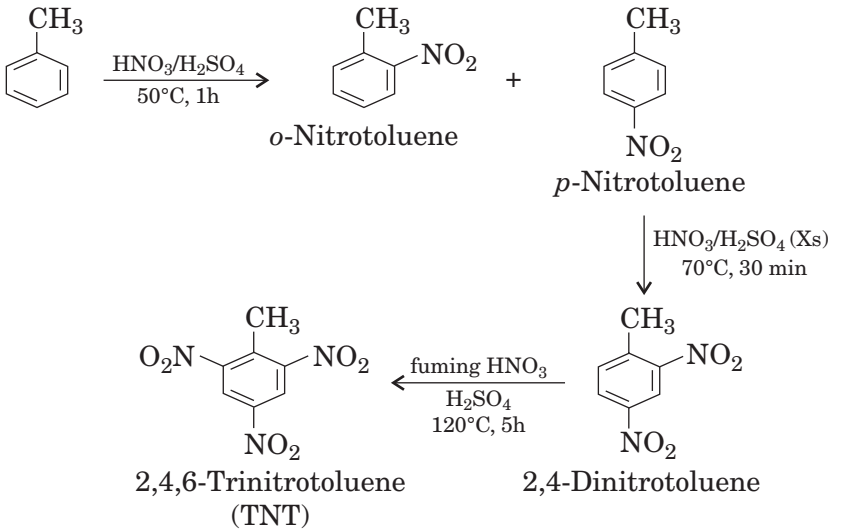
(i) The bromination of nitrobenzene require harsh conditions of heat and a Lewis acid catalyst because the nitro group deactivates the ring towards electrophilic substitution. In fact, the conditions are more severe than the conditions required for the bromination of benzene, because benzene is relatively more reactive. Mesitylene can be brominated under very mild conditions (a Lewis acid catalyst is

not even required) because the ring is activated by three electron-releasing methyl groups.



Mesitylene — 2,4,6-Trimethylbromobenzene

(ii) When a deactivating group like $-NO_2$ is being introduced by an electrophilic substitution reaction, it is easy to introduce one group at a time because introduction of more than one such group required progressively harsher conditions. The following three equations show the conditions required for successive nitrations. It is to be noted that each additional nitration requires more severe conditions.



o-Nitrotoluene — *p*-Nitrotoluene

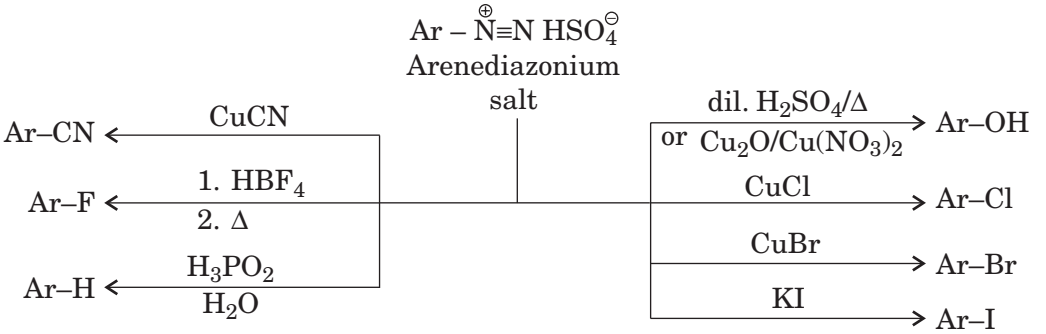
2,4,6-Trinitrotoluene (TNT) — 2,4-Dinitrotoluene

In contrast, when an activating group is introduced by electrophilic substitution, additional substitutions can take place easily under the conditions of the first substitution. In the Friedel–Crafts alkylation, for example, polyalkylation occurs easily and one way to avoid polyalkylation is to use a large excess of the starting compound.

3.1.6.1 Syntheses using Diazonium Salts

Arenediazonium salts are highly useful intermediates in the synthesis of aromatic compounds, because the diazonium group $(-\overset{\oplus}{N}_2)$ can be replaced by any one of a number of other atoms or groups like –F, –Cl, –Br, –I, –CN, –OH and even –H. Diazonium salts are conveniently prepared by diazotizing primary aromatic amines which can be synthesized through reduction of nitro compounds that are readily available through direct nitration

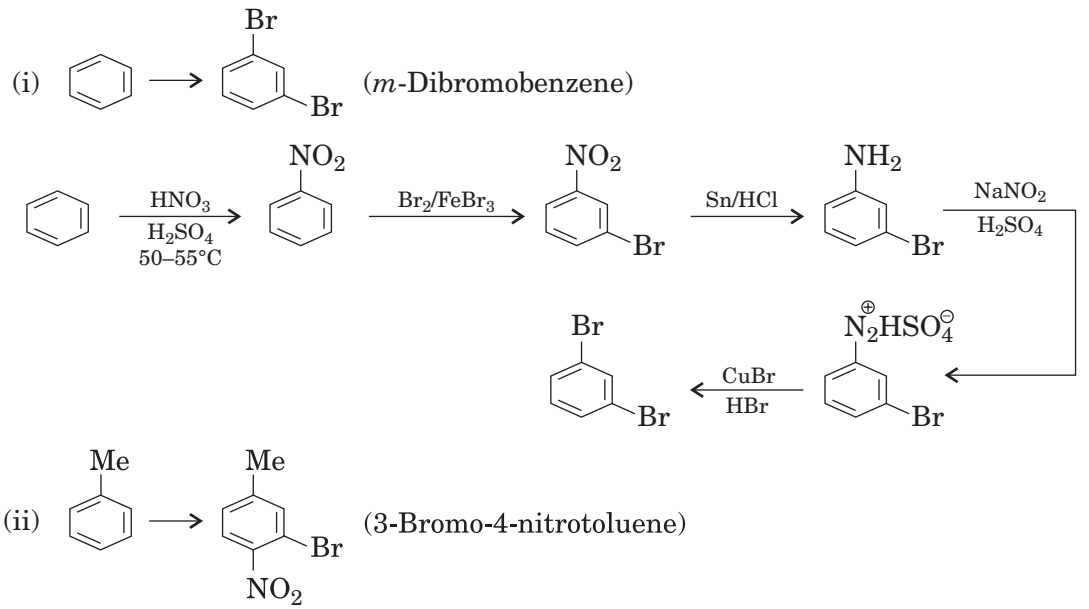
reactions. Most arenediazonium salts are unstable at temperatures > 5–10°C and may explode when dry. However, most of the replacement reactions of diazonium salts do not require their isolation. The replacement takes place if the reagent is simply added to the salt solution and the mixture is warmed. Replacement of the diazonium group by various groups can be outlined as follows:

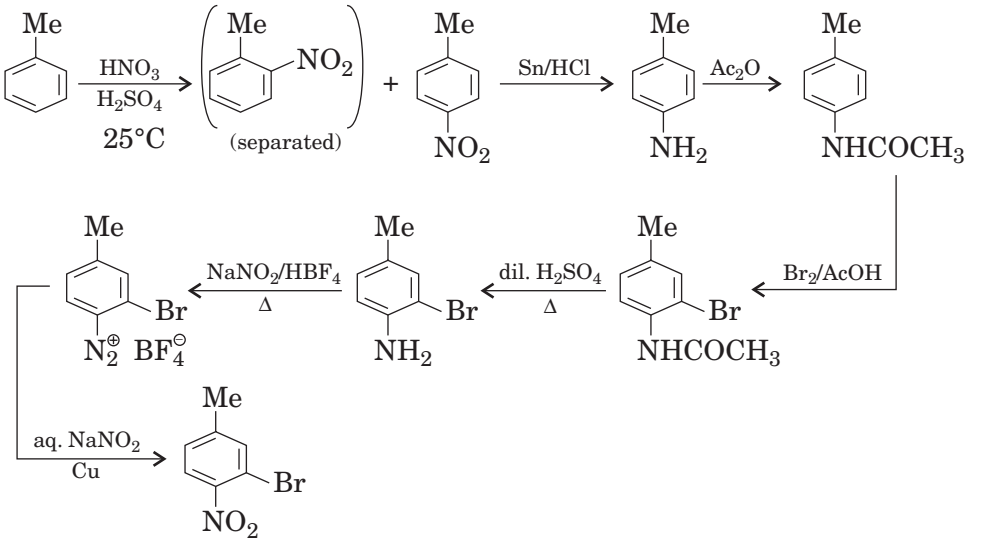


Only the replacement of the diazonium group by –F requires isolation of the relatively stable arenediazonium fluoroborate salt, $ArN_2^{\oplus}BF_4^{\ominus}$, followed by its heating.

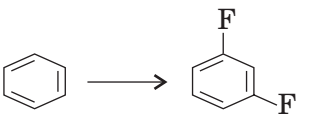
3.1.6.2 Synthesis of various compounds starting with benzene and other aromatic substrates

(a) Synthesis of aromatic halogen and nitro compounds:

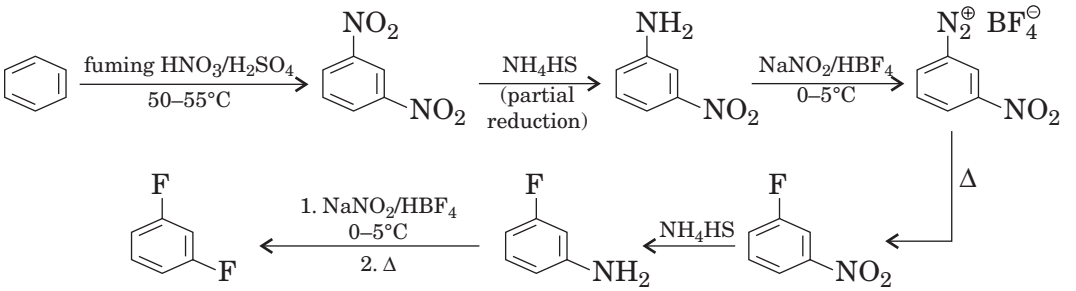




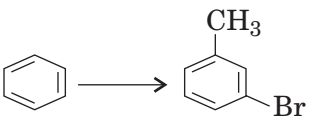
(iii)



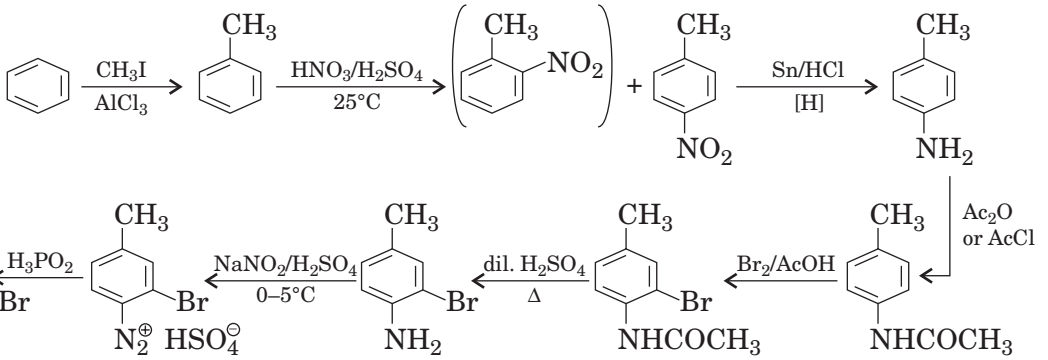
(*m*-Difluorobenzene)

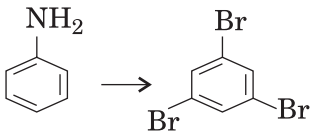


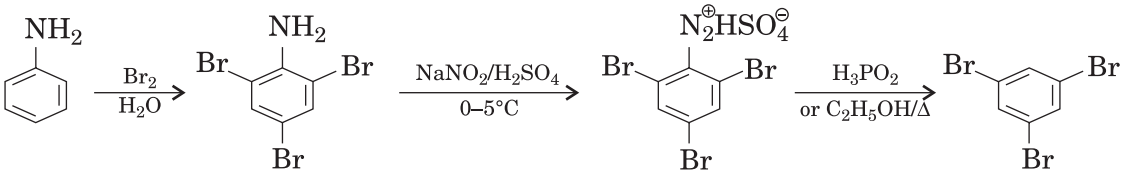
(iv)

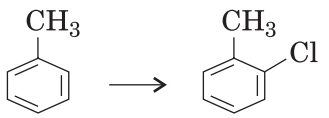


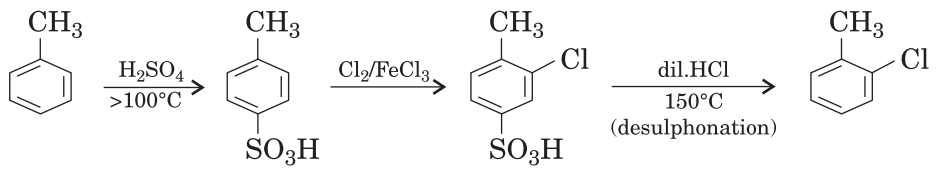
(*m*-Bromotoluene)

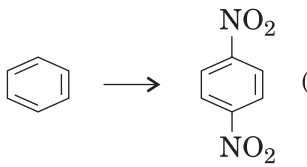


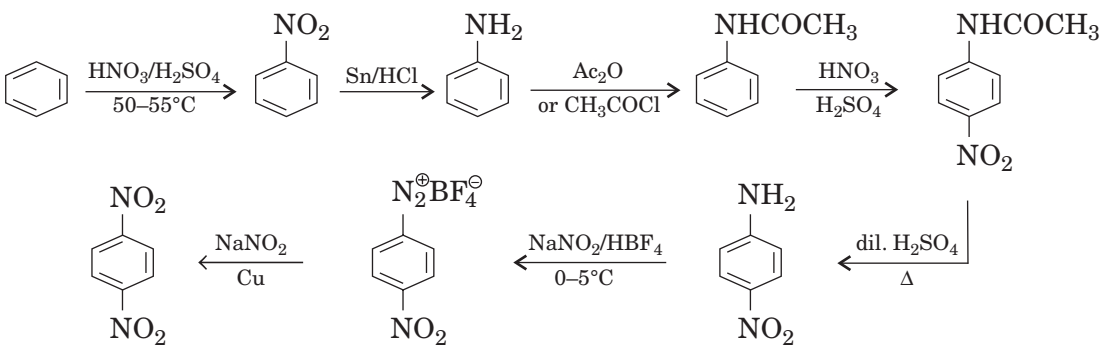
(v)  (1, 3, 5-Tribromobenzene)



(vi)  (*o*-Chlorotoluene)

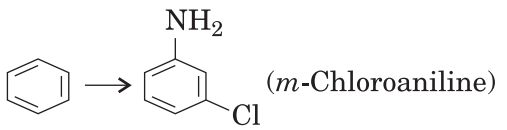


(vii)  (*p*-Dinitrobenzene)

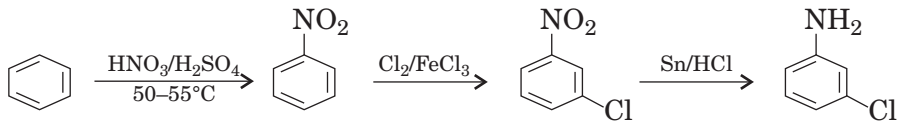


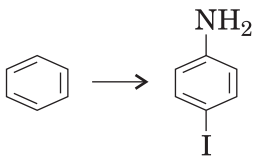
When aniline is treated with acetic anhydride (Ac_2O) or acetyl chloride (CH_3COCl), the amino group is converted to an acetamido group ($-NHCOCH_3$). The $-NHCOCH_3$ group is only moderately activating, and it does not make the ring highly susceptible to oxidation during nitration. Thus, with the amino group of aniline protected in acetanilide, direct nitration becomes possible.

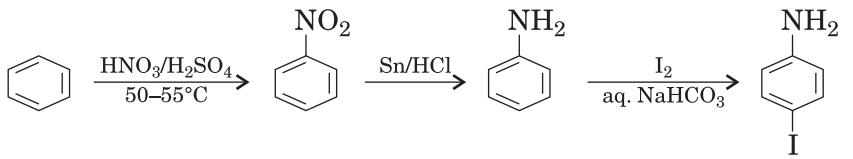
(b) Synthesis of aromatic amino compounds

(i) 

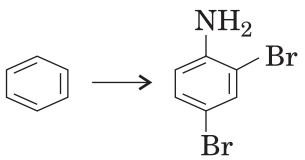
(*m*-Chloroaniline)



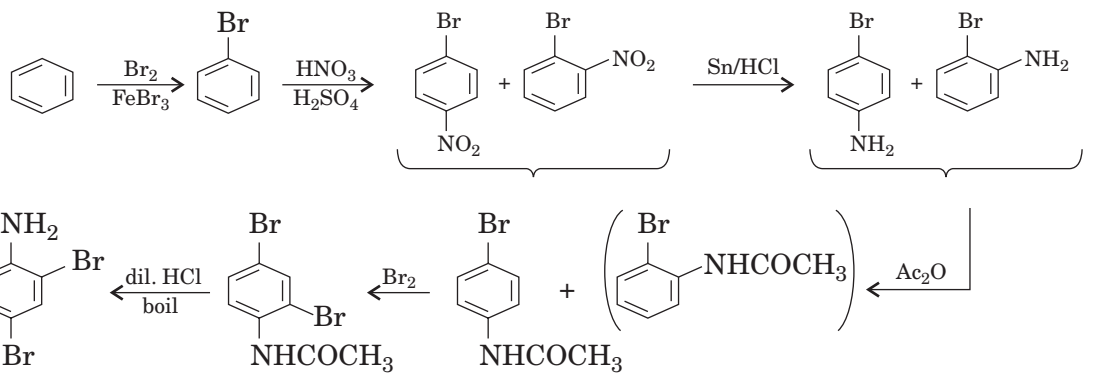
(ii) 

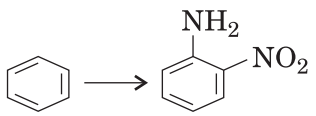


Because iodine is far less reactive than chlorine or bromine, it is possible to isolate the mono-iodo compound (*p*-).

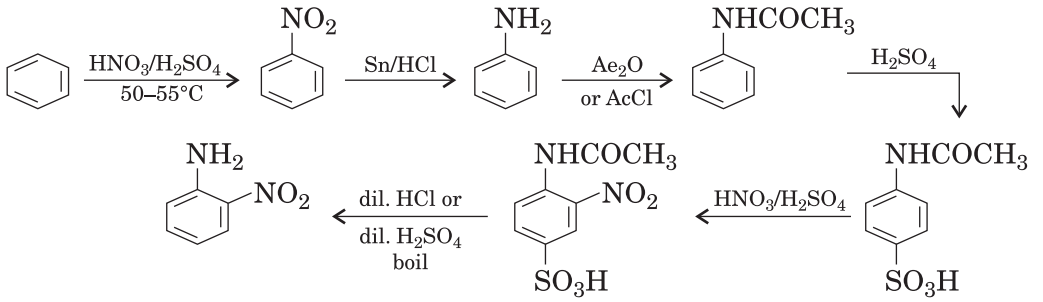
(iii) 

(2, 4-Dibromoaniline)



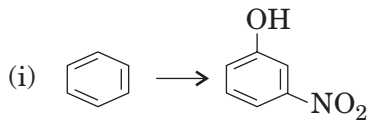
(iv) 

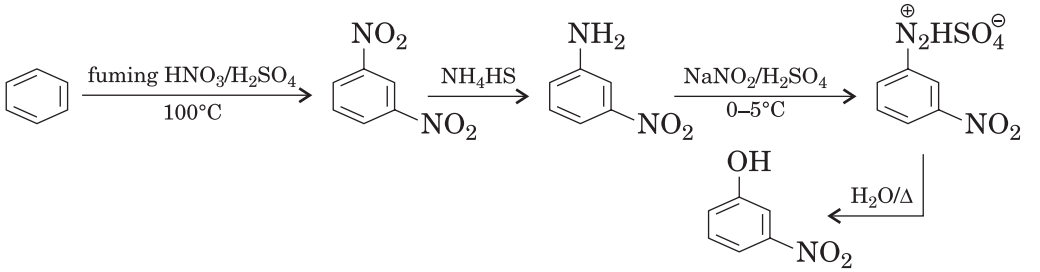
(*o*-Nitroaniline)

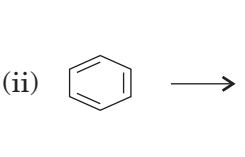


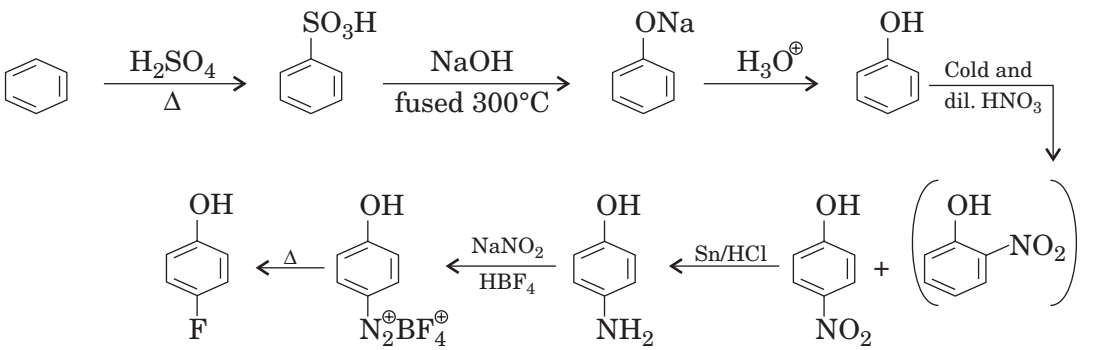
The $-SO_3H$ group is used as a 'blocking group' in this synthesis. In the last step, desulphonation and hydrolysis of the actamido group ($-NHCOCH_3$) take place simultaneously.

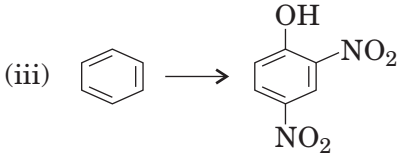
(c) Synthesis of phenols, phenolic ethers and aromatic alcohols

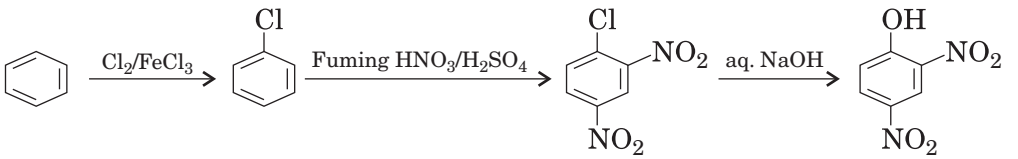
(i)  (*m*-Nitrophenol)



(ii)  (*p*-fluorophenol)

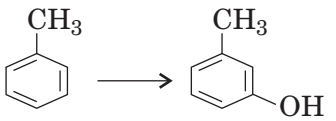


(iii)  (2,4-Dinitrophenol)

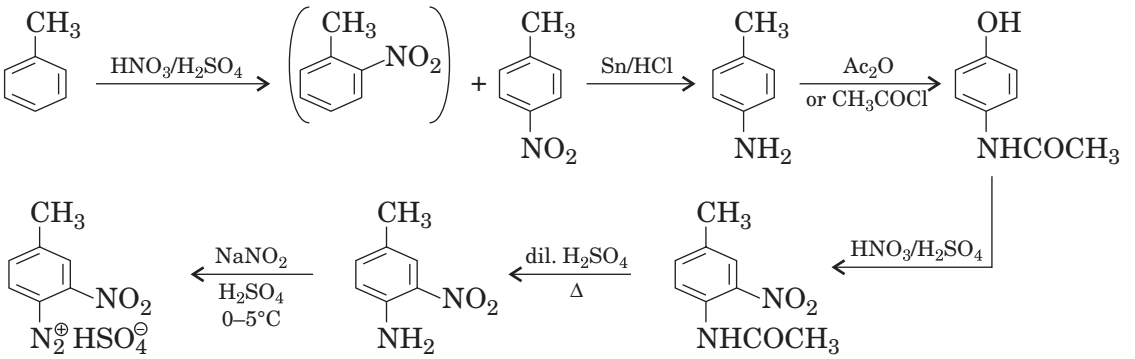


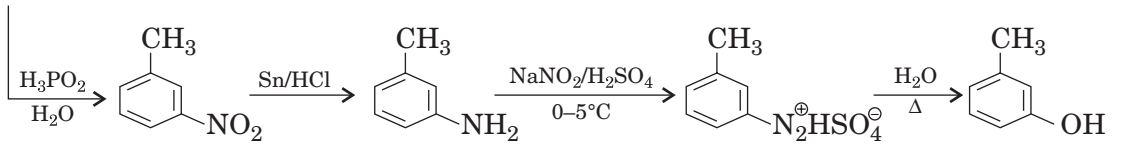
The *ortho*- and *para*-nitro groups activate the chlorine atom towards nucleophilic substitution reaction (S_N2Ar) and so, it is easily displaced by the hydroxyl group when treated with aqueous alkali.

(iv)

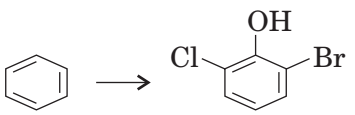


(*m*-cresol)

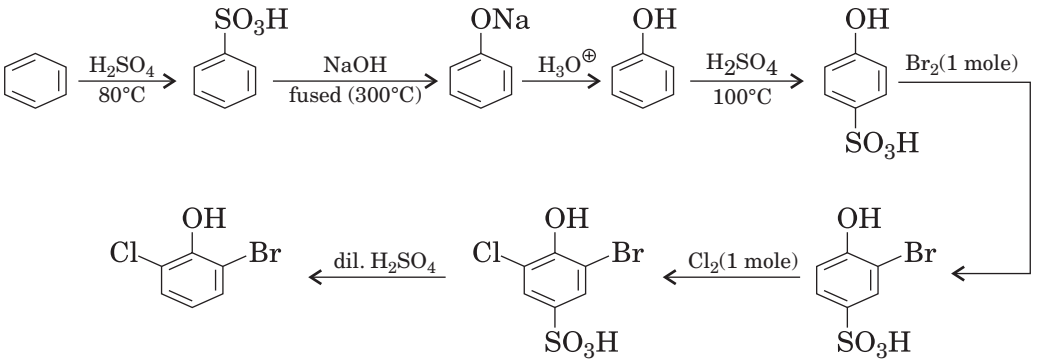


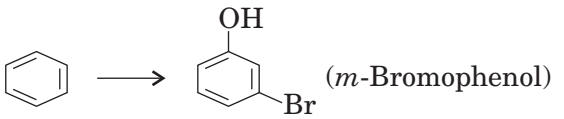


(v)

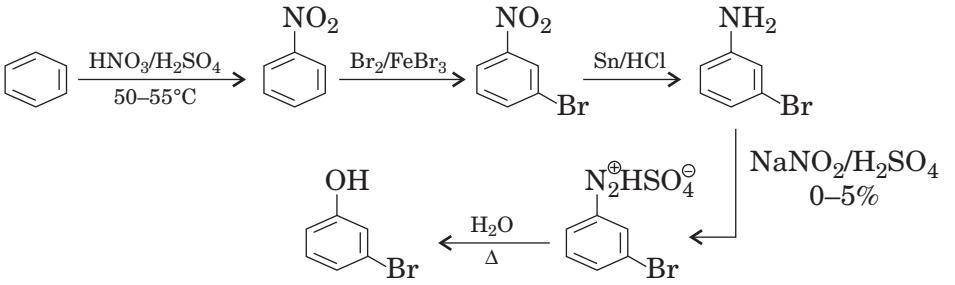


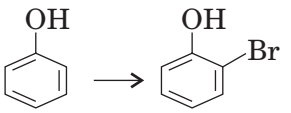
(2-Bromo-6-chlorophenol)



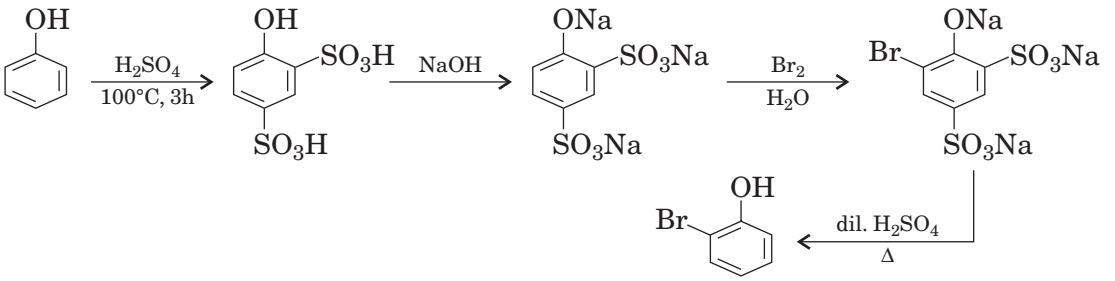
(vi) 

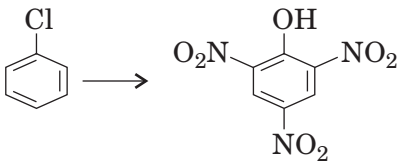
(*m*-Bromophenol)



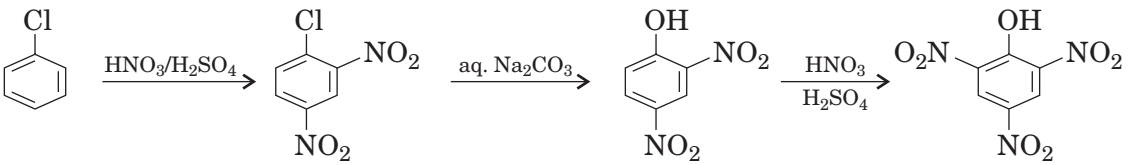
(vii) 

(*o*-Bromophenol)

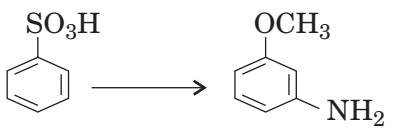


(viii) 

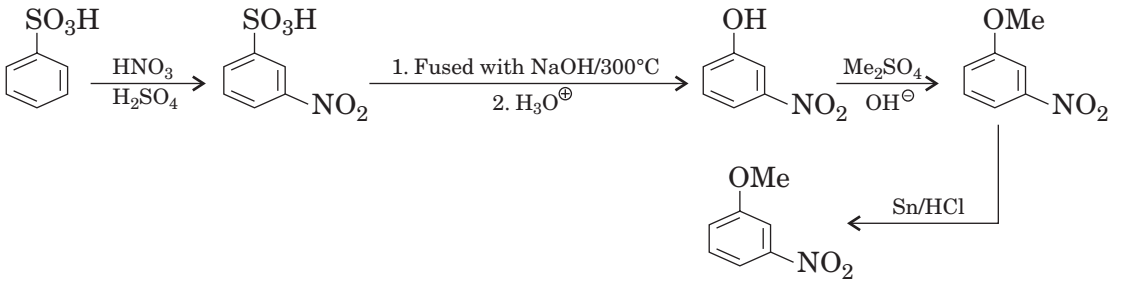
(Picric acid)

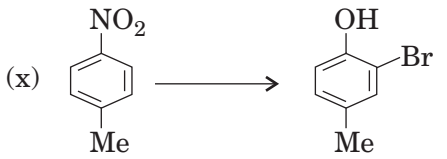


The interesting point to be noted is that the presence of the nitro-group protects, to a large extent, the hydroxyl group from oxidation. The second step is a nucleophilic aromatic substitution (S_N2Ar). For synthesis from phenol see solved problems of **article no. 3.1.4**.

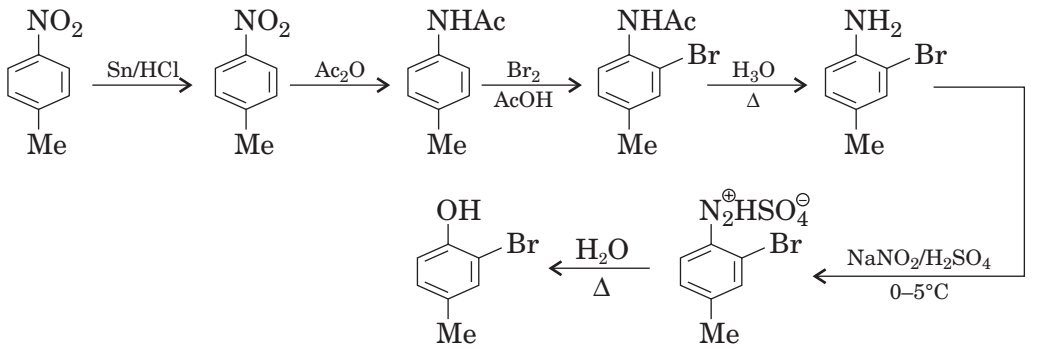
(ix) 

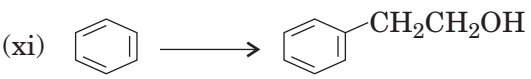
(*m*-Methoxyaniline)



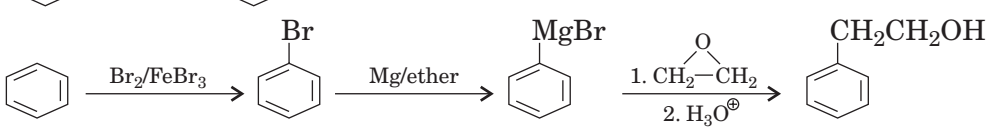


(2-Bromo-4-methylphenol)

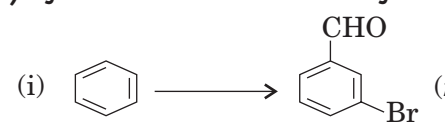




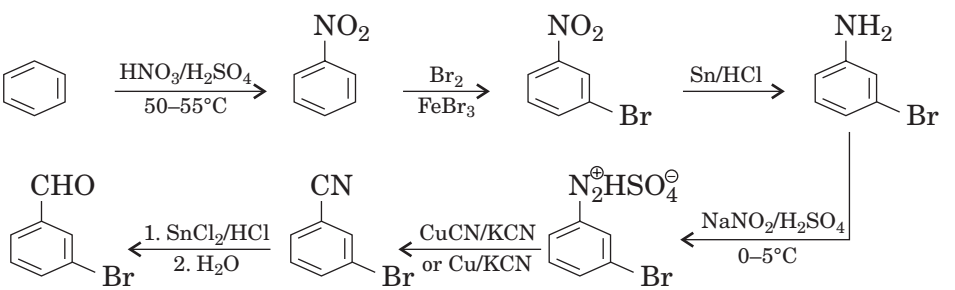
(2-Phenylethanol)

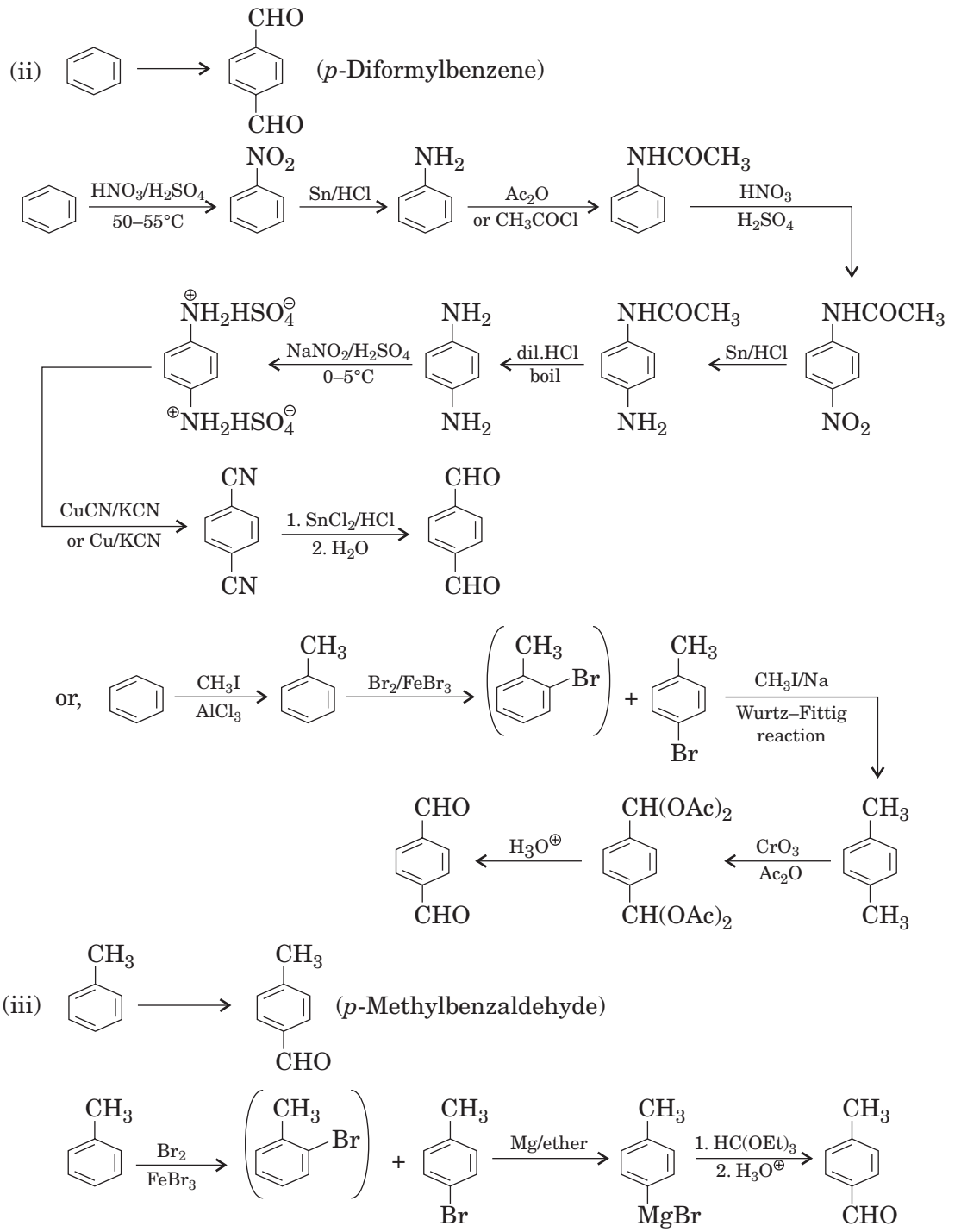


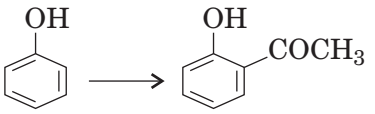
(d) Synthesis of aromatic aldehydes and ketones



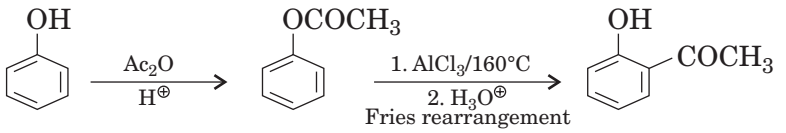
(*m*-Bromobenzaldehyde)

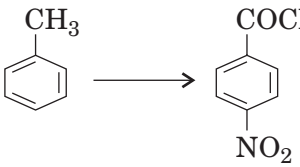



(ii)
CHO
CHO
(p-Diformylbenzene)
NO2
NH2
NHCOCH3
HNO3/H2SO4
50–55°C
Sn/HCl
Ac2O
or CH3COCl
HNO3
H2SO4
NHCOCH3
NO2
Sn/HCl
NHCOCH3
NH2
dil.HCl
boil
NH2
NH2
NaNO2/H2SO4
0–5°C
NH2HSO4
NH2HSO4
CuCN/KCN
or Cu/KCN
CN
CN
1. SnCl2/HCl
2. H2O
CHO
CHO
or,
CH3I
AlCl3
CH3
Br2/FeBr3
CH3
Br
CH3
Br
CH3I/Na
Wurtz–Fittig
reaction
CH3
CH3
CrO3
Ac2O
CH(OAc)2
CH(OAc)2
H3O⊕
CHO
CHO
(iii)
CH3
CH3
CHO
(p-Methylbenzaldehyde)
CH3
Br2
FeBr3
CH3
Br
CH3
Br
Mg/ether
CH3
MgBr
1. HC(OEt)3
2. H3O⊕
CH3
CHO

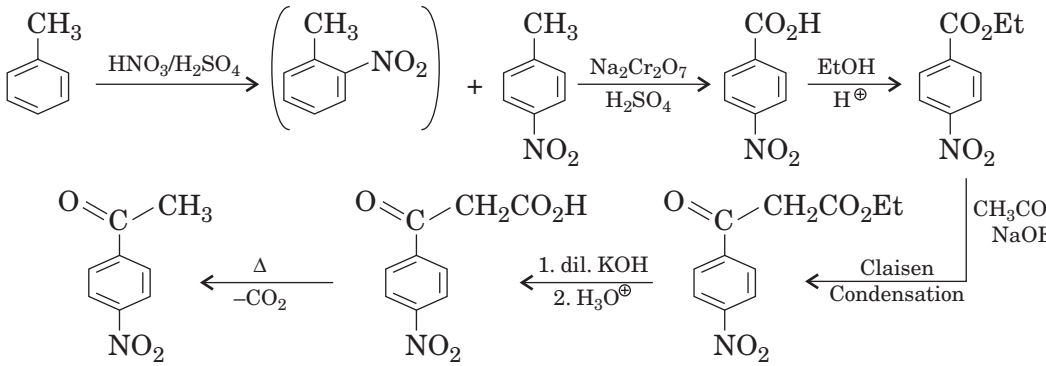
(iv) 

(*o*-Hydroxyacetophenone)

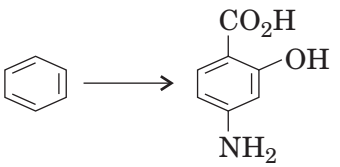


(v) 

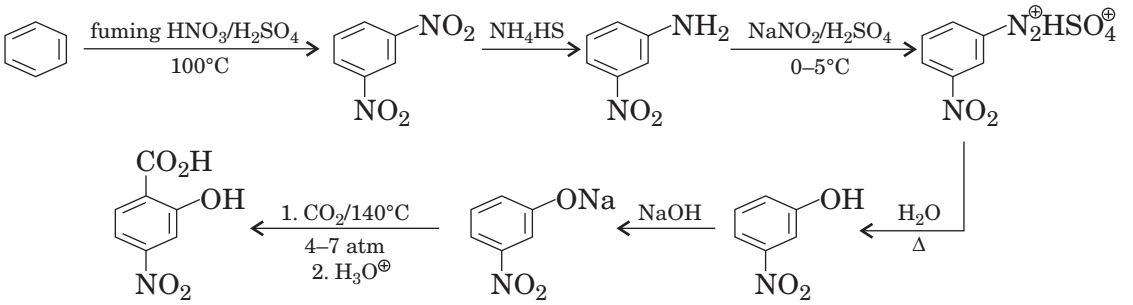
(*p*-Nitroacetophenone)

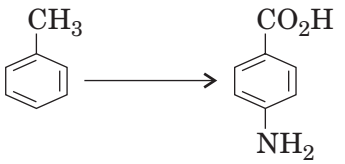


(e) Synthesis of aromatic carboxylic and sulphonic acids

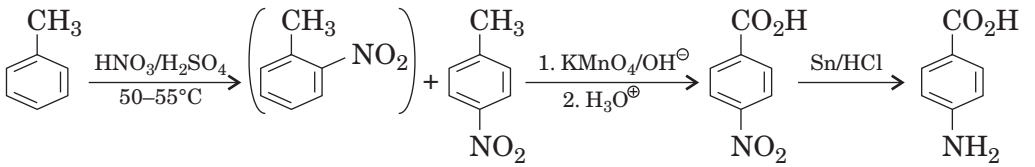
(i) 

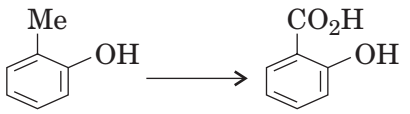
(4-Amino-2-hydroxybenzoic acid)



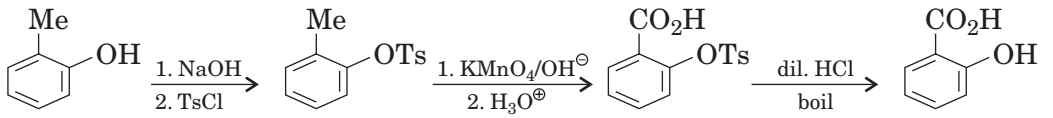
(ii) 

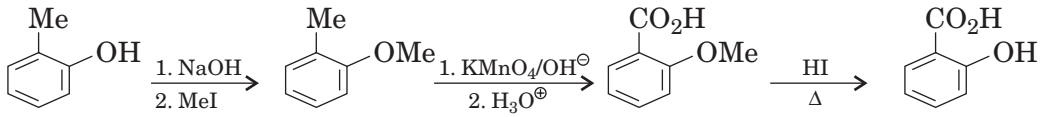
(*p*-Aminobenzoic acid)

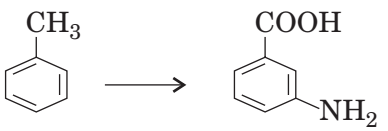


(iii) 

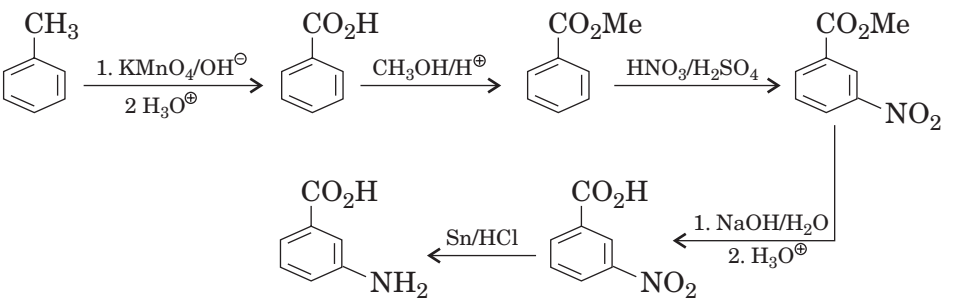
(*o*-Hydroxybenzoic acid)



or, 

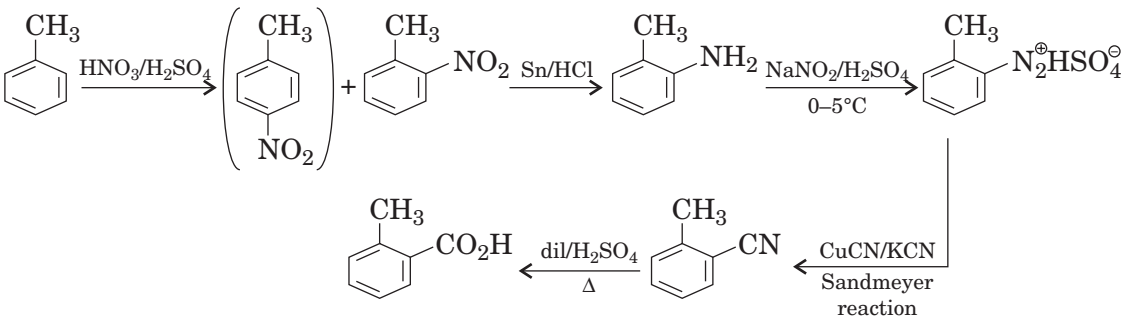
(iv) 

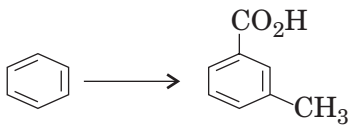
(*m*-Aminobenzoic acid)

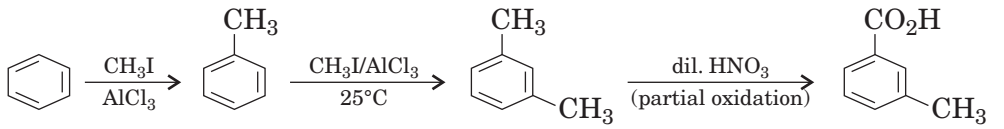


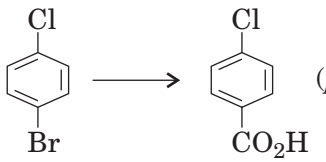
(v) 

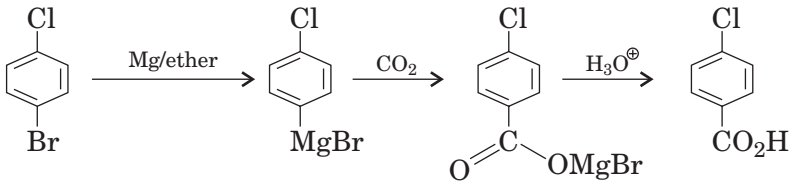
(*o*-Toluic acid or 2-Methylbenzoic acid)

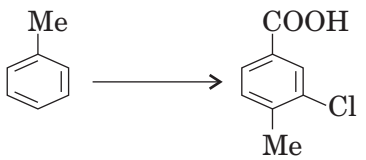


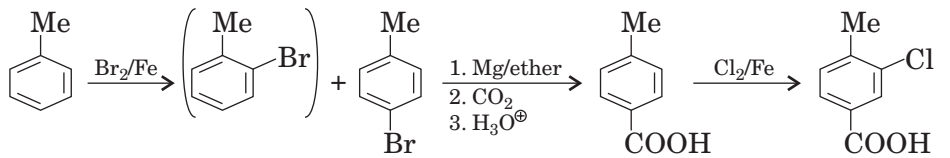
(vi)  (*m*-Toluic acid)

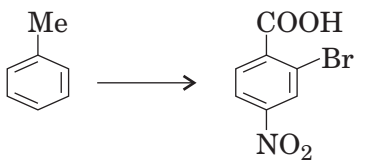


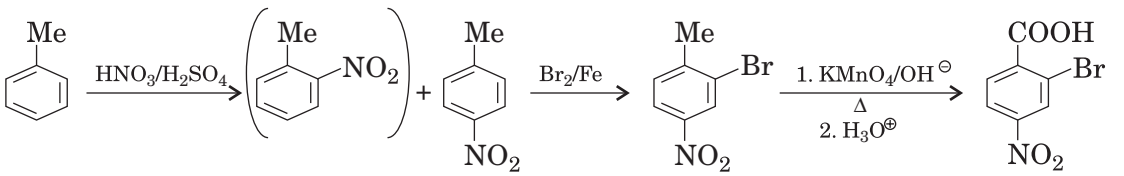
(vii)  (*p*-Chlorobenzoic acid)

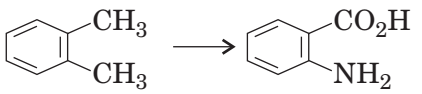


(viii)  (3-Chloro-4-methylbenzoic acid)



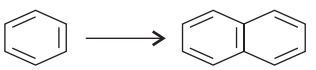
(ix)  (2-Bromo-4-nitrobenzoic acid)



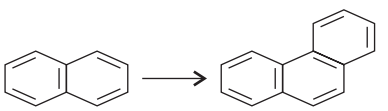
(x)  (Anthranilic acid or 2-aminobenzoic acid)

(f) Synthesis of polynuclear hydrocarbons

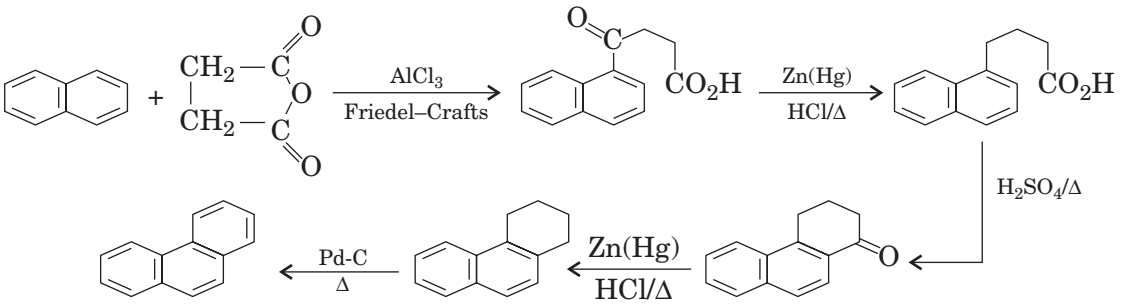
Hawarth Synthesis:

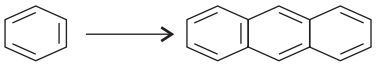
(i)  (Naphthalene)

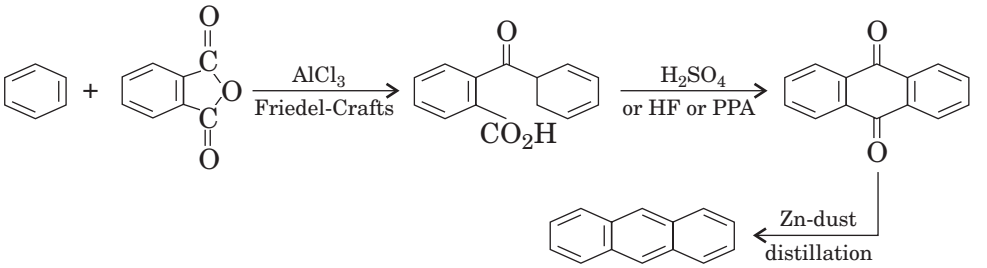
[see **article no. 3.1.5.1(B)**.]

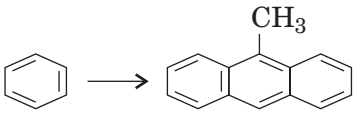
(ii)  (Phenanthrene)

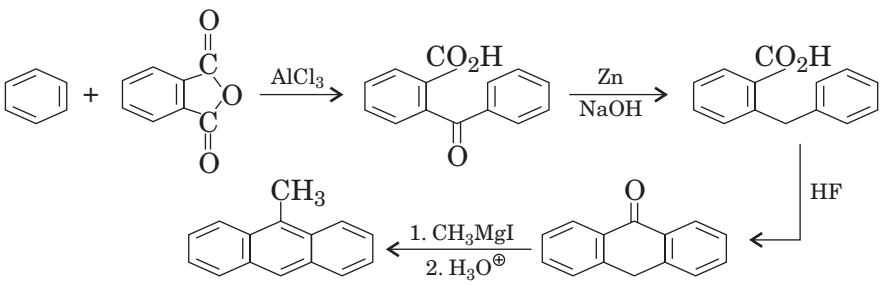
Hawarth Synthesis:

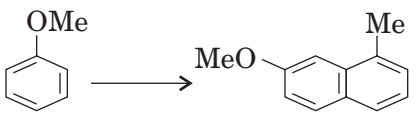


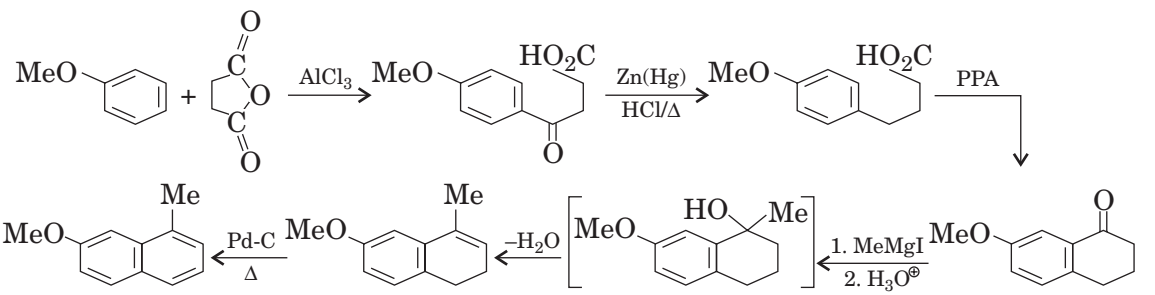
(iii)  (Anthracene))

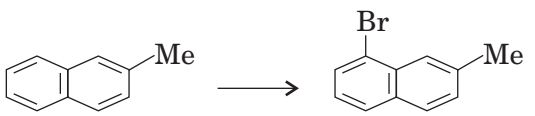


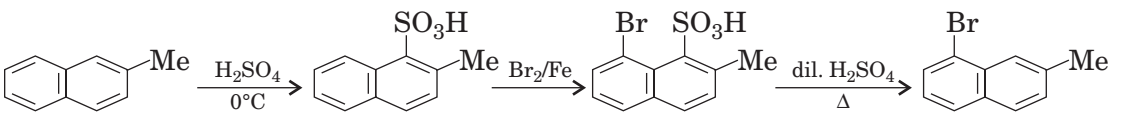
(iv)  (9-Methylanthracene)

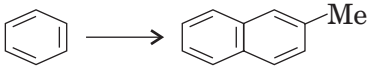


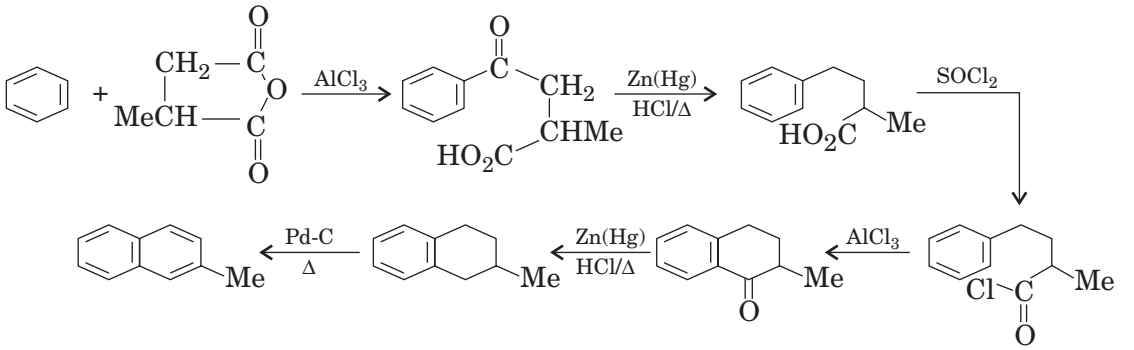
(v)  (7-Methoxy-1-methylnaphthalene)



(vi)  (1-Bromo-7-methylnaphthalene)



(vii)  (2-Methylnaphthalene)

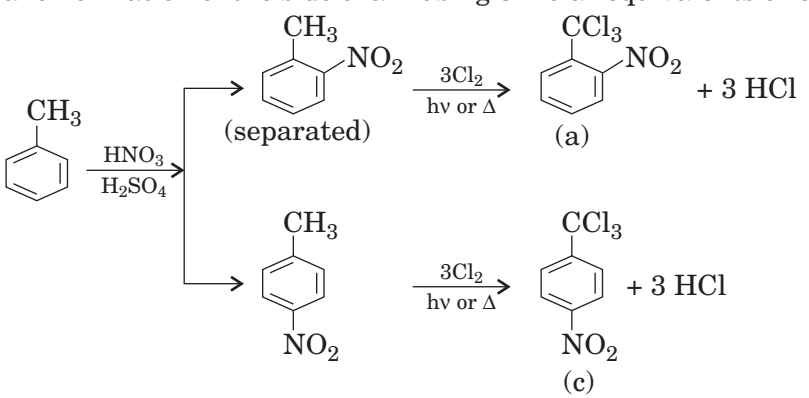


Benzene bonds to the less crowded acylium carbon after the anhydride is attacked by the Lewis acid $AlCl_3$.

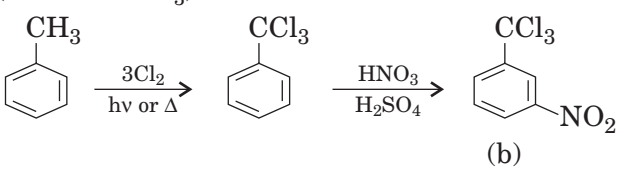
SOLVED PROBLEMS

1. Starting with toluene, outline a synthesis of (a) 1-trichloro-methyl-2-nitrobenzene, (b) 1-trichloromethyl-3-nitrobenzene and (c) 1-trichloromethyl-4-nitrobenzene.

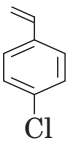
Solution Compounds (a) and (c) can be obtained by ring nitration of toluene followed by benzylic radical chlorination of the side chain using 3 molar equivalents of Cl_2.

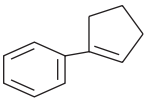


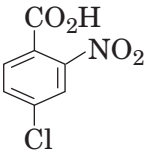
To prepare the compound (b), the order of reactions should be reverse. The $-CH_3$ group is first converted into the *meta*-directing $-CCl_3$ group, which causes the $-NO_2$ group to enter the desired position (*meta* to $-CCl_3$).

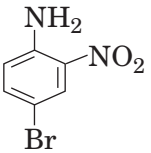


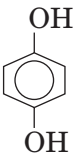
2. Synthesize each compound from benzene:

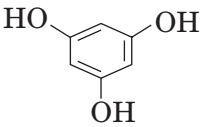
(a) 

(b) 

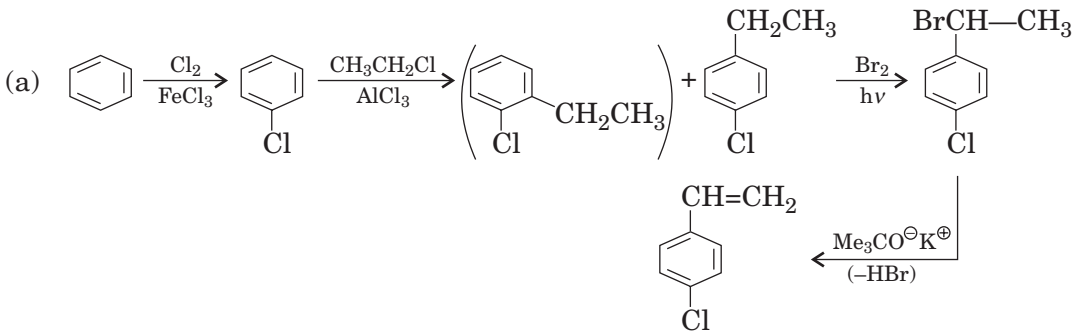
(c) 

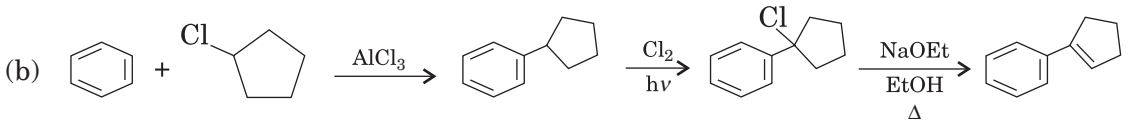
(d) 

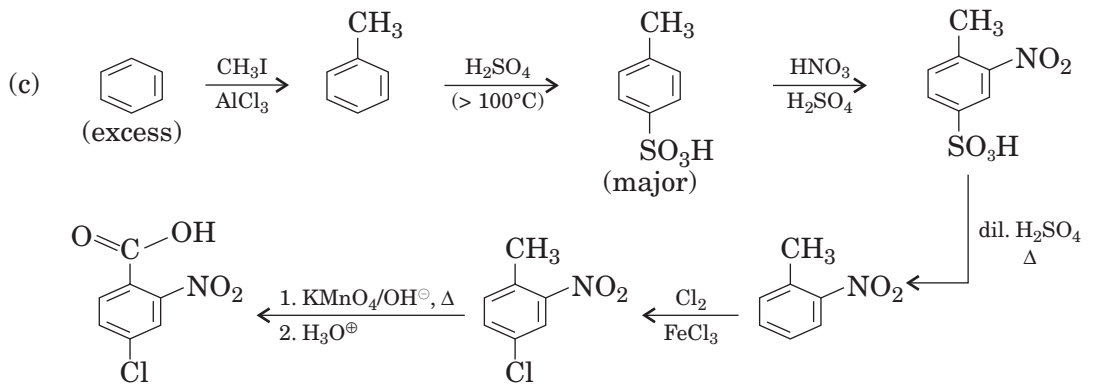
(e) 

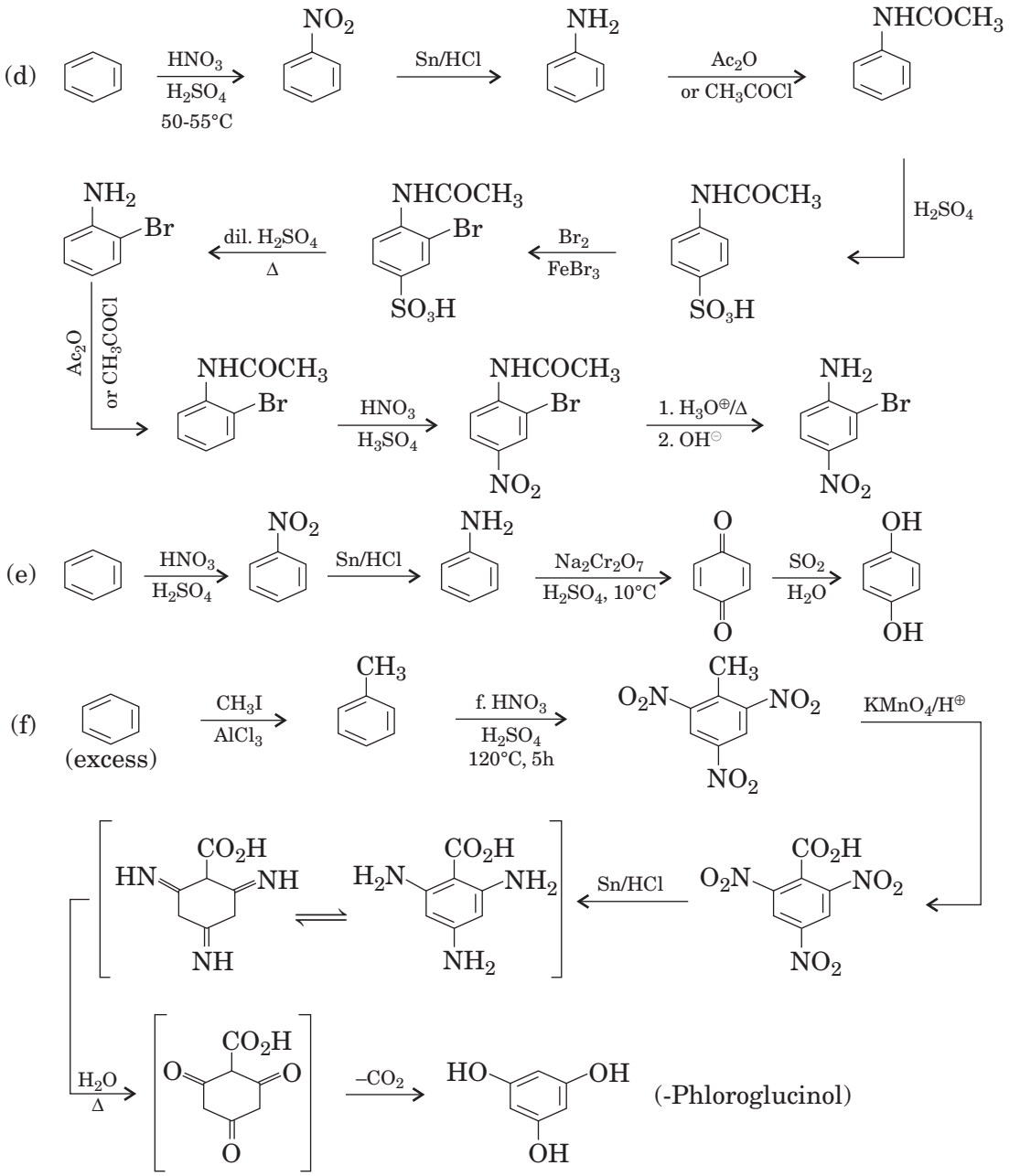
(f) 

Solution

(a) 

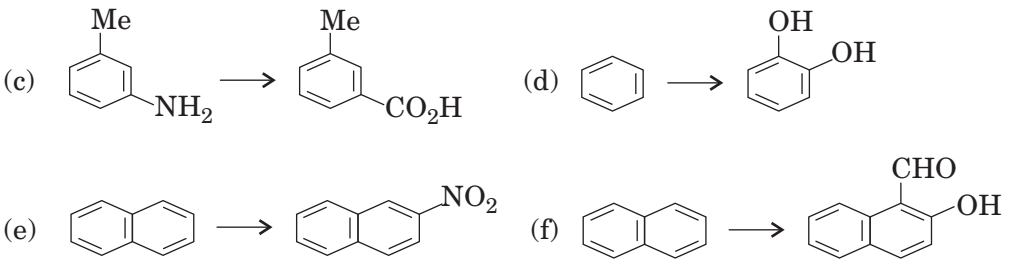
(b) 

(c) 

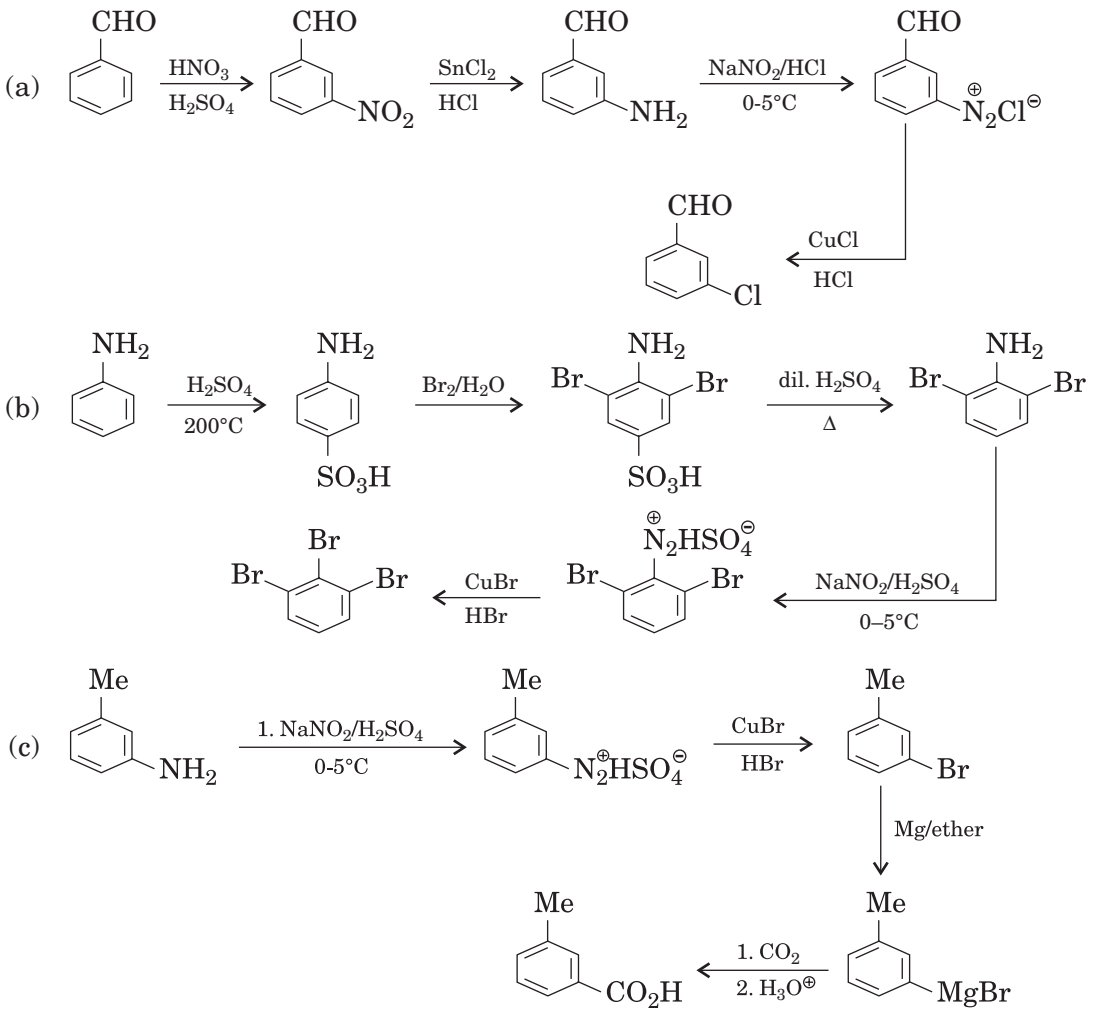

(d)
HNO3
H2SO4
50-55°C
Sn/HCl
Ac2O
or CH3COCl
H2SO4
Br2
FeBr3
dil. H2SO4
Δ
Ac2O
or CH3COCl
HNO3
H3SO4
1. H3O⊕/Δ
2. OH⊖
(e)
HNO3
H2SO4
Sn/HCl
Na2Cr2O7
H2SO4, 10°C
SO2
H2O
(f)
(excess)
CH3I
AlCl3
f. HNO3
H2SO4
120°C, 5h
KMnO4/H⊕
Sn/HCl
H2O
Δ
–CO2
(-Phloroglucinol)

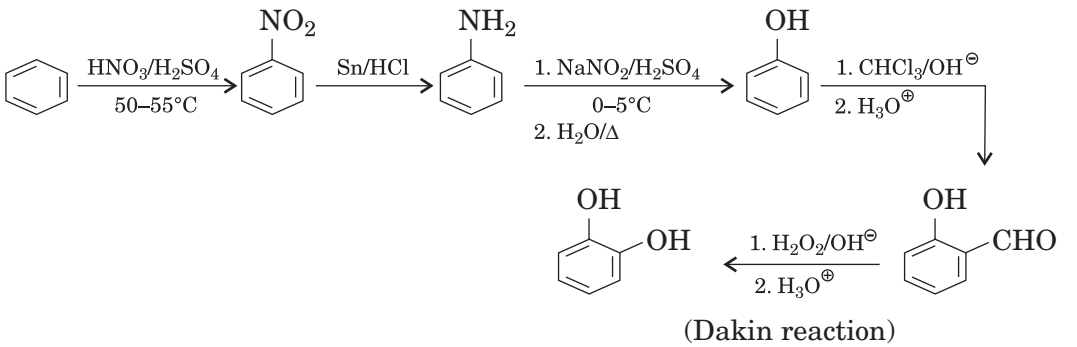
3. Convert:


(a)
(b)

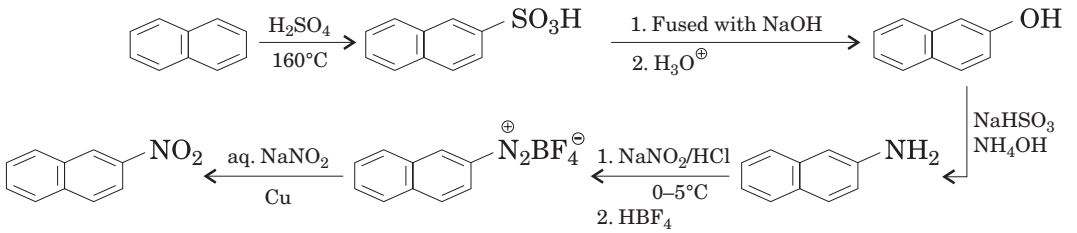

(c)
Me
NH2
Me
CO2H
(d)
OH
OH
(e)
NO2
(f)
CHO
OH

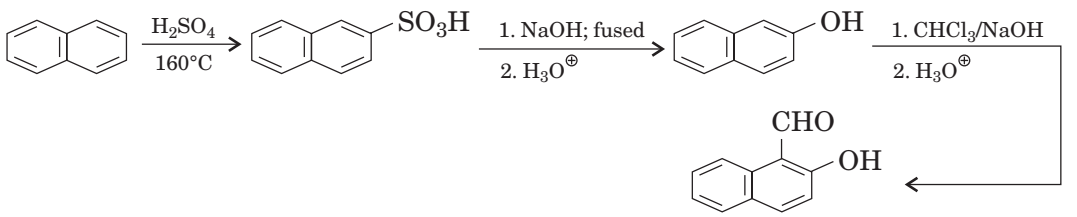
Solution


(a)
CHO
HNO3
H2SO4
NO2
SnCl2
HCl
NH2
NaNO2/HCl
0-5°C
N2Cl
CuCl
HCl
Cl
(b)
NH2
H2SO4
200°C
SO3H
Br2/H2O
Br
dil. H2SO4
Δ
NaNO2/H2SO4
0–5°C
N2HSO4
CuBr
HBr
(c)
Me
NH2
1. NaNO2/H2SO4
0-5°C
CuBr
HBr
Br
Mg/ether
MgBr
1. CO2
2. H3O⊕
CO2H

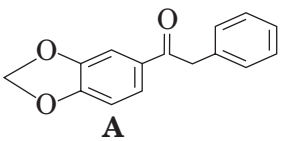
(d) 

(Dakin reaction)

(e) 

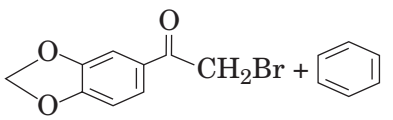
(f) 

4. Write out two different routes to the ketone A using a Friedel-Crafts reaction and indicate which one is better. Give your meaning.

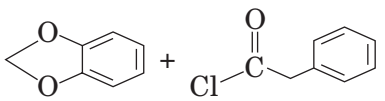


A

Solution The two different routes to the ketone A are as follows:

(i) 

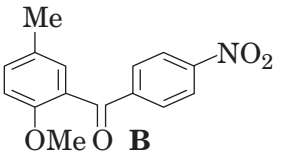
A (by a Friedel-Crafts alkylation)

(ii) 

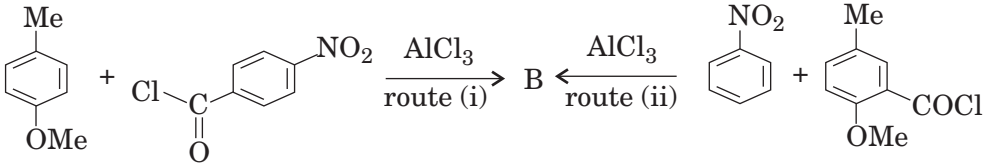
A (by a Friedel-Crafts acylation)

Between these two possible routes (ii) is better because it gives us an acyl rather than an alkyl halide and an activated benzene ring (+R effect of two RO-graphs).

5. Two students have written two different routes for the synthesis of the following ketone (B). Indicate which route is feasible and which one is not at all feasible. Give reasons.



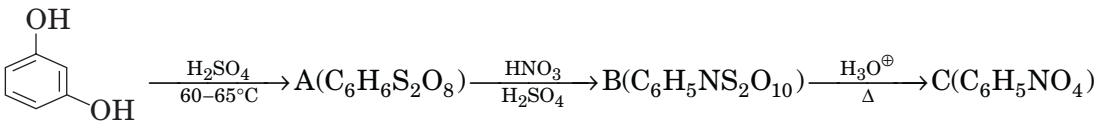
Solution The two possible routes the students have written for the synthesis of the ketone B are



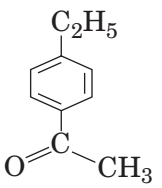
The route (ii) is not at all feasible because nitrobenzene does not undergo the Friedel-Crafts reaction and also it is a *meta*-directing group. The route (i) is not only feasible but also much better because the activated ring (+R effect of –OMe and +I and hyperconjugative effect of $-CH_3$) undergoes the Friedel-Crafts acylation smoothly and –OMe group is more powerfully *ortho*-directing than the –Me group.

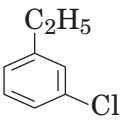
Study Problems

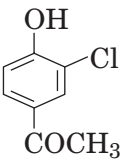
1. Propose structures for compounds A—C:

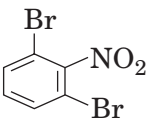


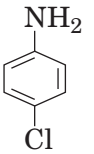
2. Propose a reasonable synthesis of each of the following multiply substituted arenes from benzene:

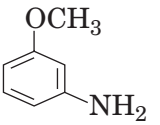
(a) 

(b) 

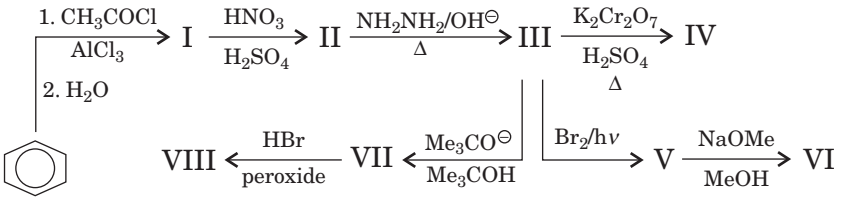
(c) 

(d) 

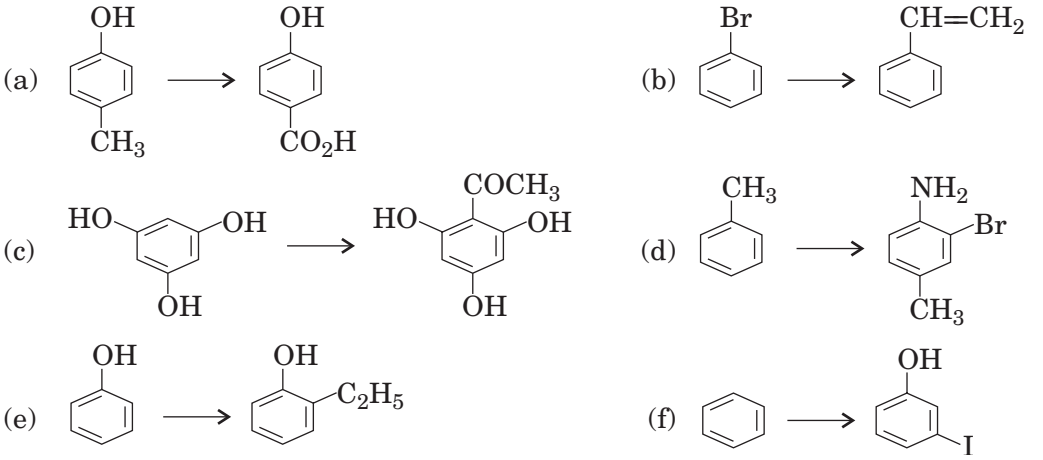
(e) 

(f) 

3. Identify the compounds I–VIII:

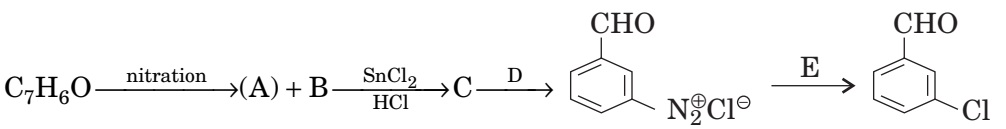


4. How would you carry out the following conversions?



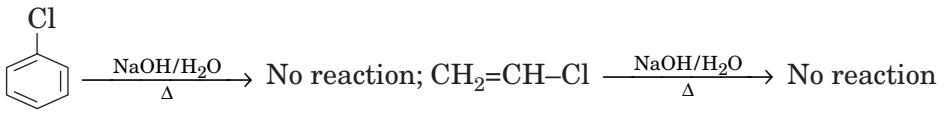
[**Hint:** (a) p-$CH_3C_6H_4OH \xrightarrow[NaOH]{PhSO_2Cl} p$-$CH_3C_6H_4OSO_2Ph \xrightarrow[2.\ H_3O^{\oplus}]{1.\ KMnO_4/OH^{\ominus},\ \Delta} p$-$HO_2CC_6H_4OSO_2Ph \xrightarrow{H_3O^{\oplus}} p$–$HO_2C$–$C_6H_4OH$ (e) $C_6H_5OH \xrightarrow{AC_2O/H^{\oplus}} C_6H_5OCOCH_3 \xrightarrow[2.\ H_3O^{\oplus}]{1.\ AlCl_3/160°C} o$–$HOC_6H_4COCH_3 \xrightarrow[HCl]{Zn(Hg)} o$–$HOC_6H_4C_2H_5$]

5. Complete the following reaction sequence:

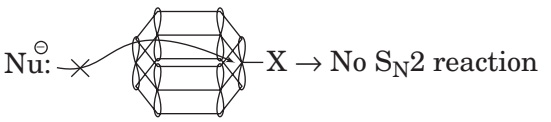


3.2 NUCLEOPHILIC AROMATIC SUBSTITUTION

In contrast to aromatic electrophilic substitutions, aromatic nucleophilic substitutions are less common. Simple aryl halides (like vinylic halides) are relatively unreactive towards nucleophilic substitution (S_N1 or S_N2) under conditions that favour rapid nucleophilic substitution with alkyl halides. Chlorobenzene, for example, can be boiled with aqueous NaOH for days without yielding a detectable amount of phenol (or sodium phenoxide). Similarly, vinyl chloride remains unreactive when heated with aqueous alkali.

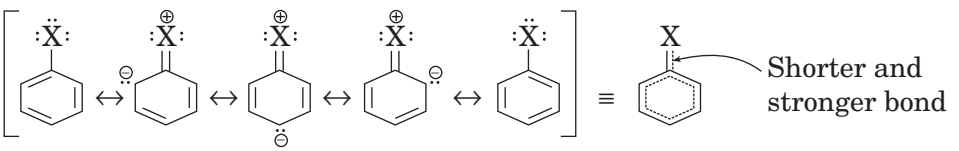


This lack of reactivity can be explained on the basis of several factors. The benzene ring of an aryl halide prevents back-side attack in an S_N2 reaction.



(attack is prevented due to repulsive interaction between the π-electron cloud and the electron-rich nucleophile)

Since phenyl cations are very unstable because the aryl cation is forced to assume a nonoptimal geometry and hybridization, therefore, S_N1 reactions do not occur. The C–X bond of aryl (and vinylic) halides are shorter and stronger than those of alkyl, allylic and benzylic halides and that is due to the fact that (i) the carbon of either type of halide is sp^2 hybridized, and therefore, the electrons of the carbon orbital are closer to the nucleus than those of an sp^3 hybridized carbon, i.e., an sp^2 orbital is relative smaller in size and (ii) resonance strengthens the C–X bond by giving it some double-bond character.



Resonance in halobenzene

There are, however, exceptions and aromatic nucleophilic substitutions are not uncommon. Aryl halides can be considerably reactive towards nucleophiles if they bear electron-attracting substituents *ortho* or *para* to the leaving group or when they are allowed to react under some special conditions (reactions catalyzed by very strong bases).

Aromatic nucleophilic substitution reactions may be effected by the following mechanistic routes depending upon the nature of the substrate and the reaction conditions:

(a) Addition-elimination mechanism or S_NAr mechanism
(b) Elimination-addition mechanism or benzyne mechanism
(c) S_N1 mechanism
(d) Substitution via rearrangement

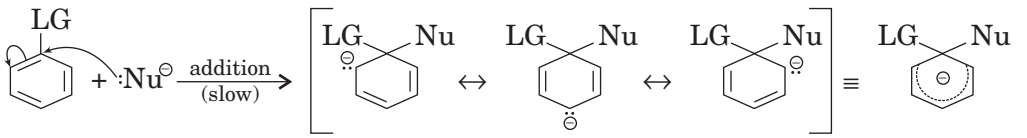
3.2.1 The Addition-Elimination or S_NAr Mechanism

This is the most important mechanism for aromatic nucleophilic substitution. The reactions following this mechanistic course involve displacement of groups like $X^{\ominus}$(X = F,

Cl, Br, I) $SO_3^-, NO_2^{\ominus}$, $H^{\ominus}$, etc. The attacking nucleophiles are usually $RO^{\ominus}$, $NH_2^{\ominus}$, $OH^{\ominus}$, piperidine, etc.

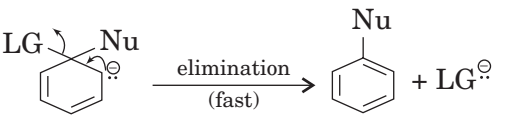
The mechanism involves the steps as follows:

Step 1: The nucleophile attacks the *ipso* carbon (the ring carbon bearing the leaving group, –LG) to form a resonance-stabilized carbanion intermediate (also called a Meisenheimer intermediate). As a result, the sp^2 carbon of the ring undergoing nucleophilic attack becomes sp^3 and the ring loses its aromaticity. This step is usually the rate-determining (slow) step of the reaction.

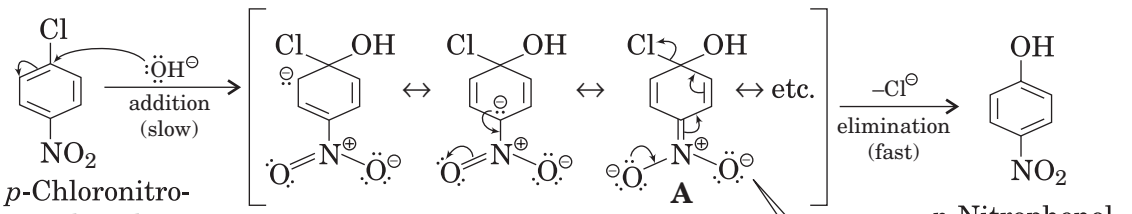


Resonance-stabilized carbanion
(a Meisenheimer intermediate or complex)

Step 2: The leaving group ($LG^{\ominus}$) is eliminated from the intermediate carbanion and a substitution product is obtained.



This mechanism is generally found where activating groups (i.e., electron-attracting groups) are present on the ring. In fact, the intermediate carbanion cannot be formed unless some electron-withdrawing group (e.g., $–NO_2$, –CN, etc.), capable of accommodating the negative charge, is present in the *ortho*- or *para*-position. Such group decrease the electron density in the benzene ring making it more susceptible to nucleophilic attack and stabilizes the carbanion by delocalizing the negative charge. *p*-Chloronitrobenzene, for example, reacts with alkali as follows:



p-Chloronitrophenol

p-Nitrophenol

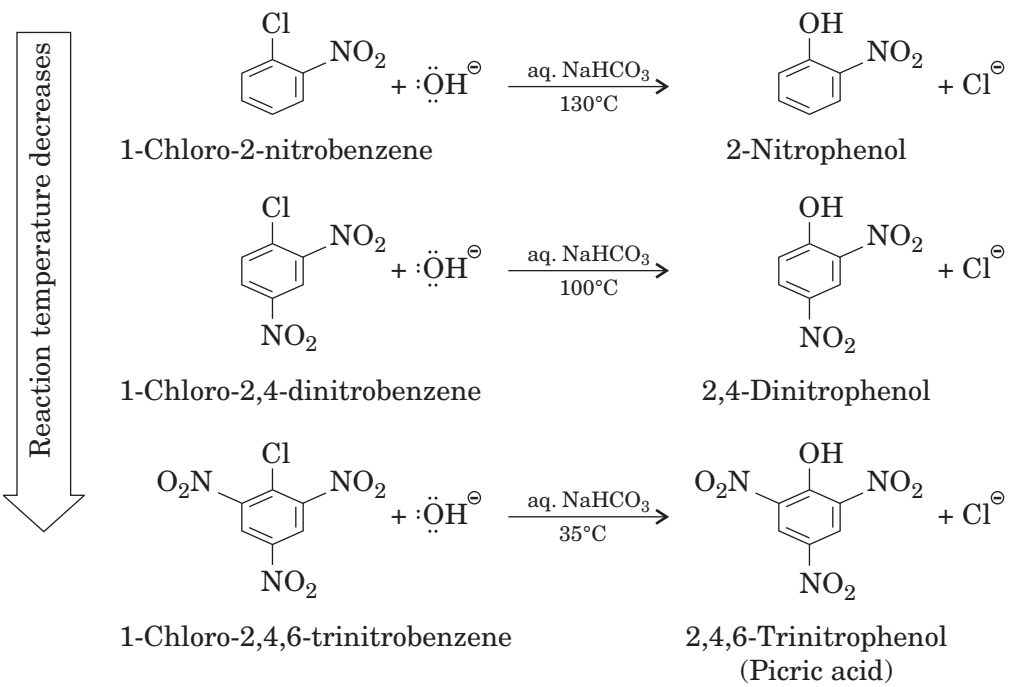
Carbanion intermediate
(a Meisenheimer intermediate or complex)

especially stable structure

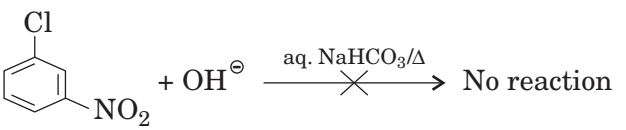
In the first step, addition of a hydroxide ion to *p*-chloronitrobenzene produces the carbanion and in the second step, elimination of a chloride ion yields the substitution product as the aromaticity of the ring is recovered.

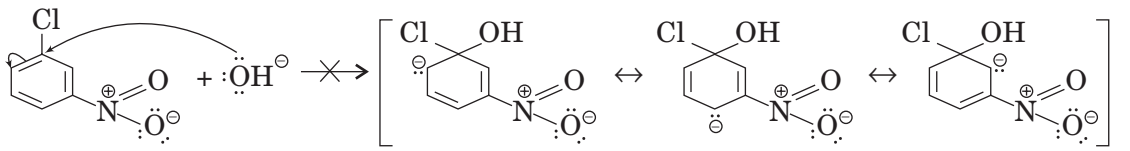
The resonance structure A is especially stable because in **A** the negative charge is accommodated by the highly electronegative oxygen atom of the $-NO_2$ group. Due to the presence of this especially stable structure, the carbanion resonance hybrid becomes very stable and the reaction occurs smoothly.

As the number of electron-withdrawing *ortho* or *para* nitro groups increases, the reaction becomes progressively easier. This is because the stability of the carbanion intermediate and the transition state leading to it progressively increases. It becomes clear from the following three reactions. The temperature required to bring about the reaction becomes progressively lower with increase in the number of $-NO_2$ groups.



A *meta*-nitro group does not exert a similar activating effect because it is not in proper conjugation with the negative charge of the carbanion intermediate. For this reason, *m*-chloronitrobenzene gives no corresponding reaction.

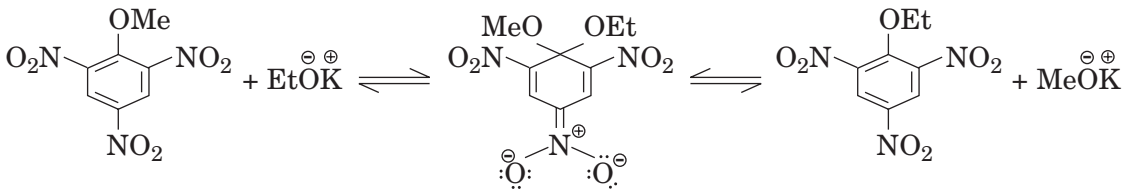




meta-NO_2 group does not provide resonance stabilization of the negative charge

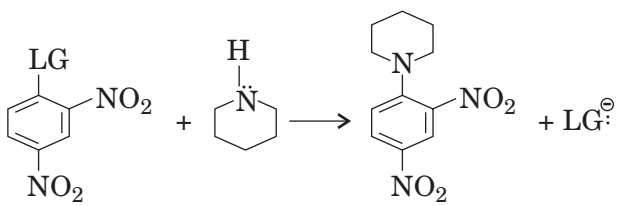
Evidence for the S_NAr or addition-elimination mechanism: There is a great deal of evidence for this mechanism. Only two of them are discussed below:

(i) The most convinving evidence is that a number of intermediate carbanions such as I (the adduct of methyl picrate and potassium ethoxide or ethyl picrate and potassium methoxide) has been isolated and their structures has been determined by NMR and X-ray crystallography. The isolated intermediates can form the substitution product when resubjected to the reaction conditions.



Methyl picrate — bolable Meisenheimer complex — Ethyl picrate

(ii) The rates of reaction of various 1-substituted 2,4-dinitrobenzenes with piperidine have been found to differ only by factor of ~5.



LG = Cl, Br, I, SOPh, SO_2Ph, $OC_6H_4NO_2$-*p*

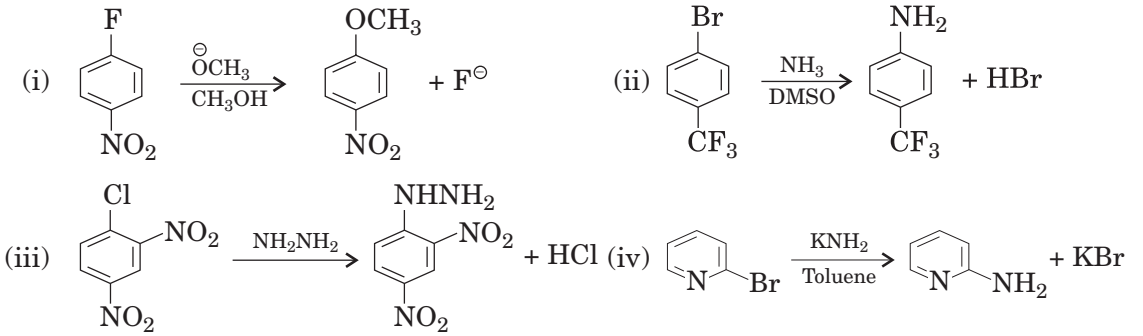
This behaviour would not be expected in a reaction in which the Ar–LG bond is broken in the rate-determining step. That is, this observation proves that the reaction is a two-step process.

When LG = F, the relative rate is 3300 (compared with I = 1). The very fact that fluoro is the best leaving group among the halogens in most aromatic nucleophilic substitutions is good evidence that the mechanism is different from S_N1 and S_N2 mechanisms, where fluoro is by far the poorest leaving group of the halogens. Since fluorine stabilizes the intermediate carbanion by its electron-withdrawing inductive (–I) effect (greater than

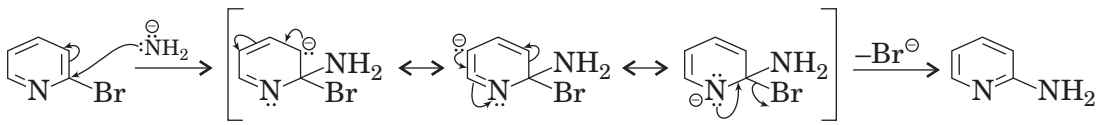
that of other halogens), the rate of the reaction increases. This observation, thus, suggests that the first step is the rate-determining step of the reaction. Because the loss of $F^{\ominus}$ is not rate-determining, the basicity of $F^{\ominus}$, or equivalently, the strength of the C–F bond, is not important in determining the reaction rate.

S_NAr reactions involving various leaving groups: Not only halide ions but also oxy anions, nitrogen anions, hydride ion and sulphite ion may be the leaving groups in S_NAr reactions.

1. ***Displacement of halide ions*:** Although it has already been discussed, some other examples are given below:



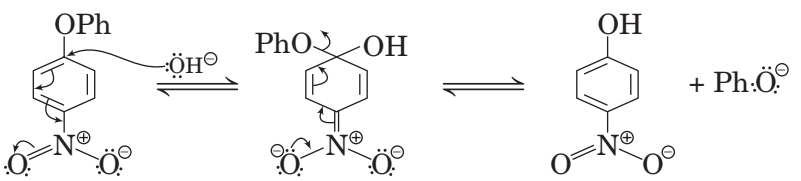
The mechanism of the reaction (iv) may be outlined as follows:



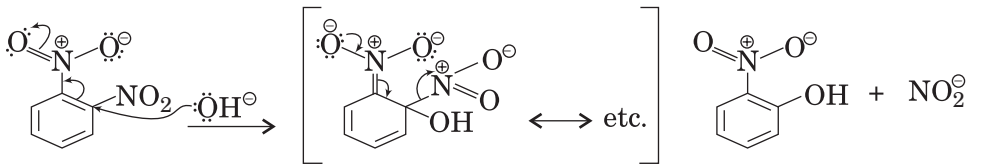
2-Bromopyridine A resonance-stabilized carbanion 2-Aminopyridine

Pyridine nucleus behaves like nitrobenzene because of electron-attacking character of the ring nitrogen and so, it undergoes smooth S_NAr reaction. Displacement actually occurs if the leaving group remains at C-2/C-6 or C-4 position because in that case the intermediate carbanion becomes more stable (it contains one stable resonance structure in which the negative charge is accommodated the electronegative N atom).

2. ***Displacement of oxy anions*:** Phenyl ethers (e.g., PhOMe) are stable under basic conditions. However, if there is an –R group at *ortho* or *para* positions, the substrate becomes quite reactive towards nucleophiles such as $OH^{\ominus}$, $RO^{\ominus}$, $S^{\ominus}H$ etc. For example:

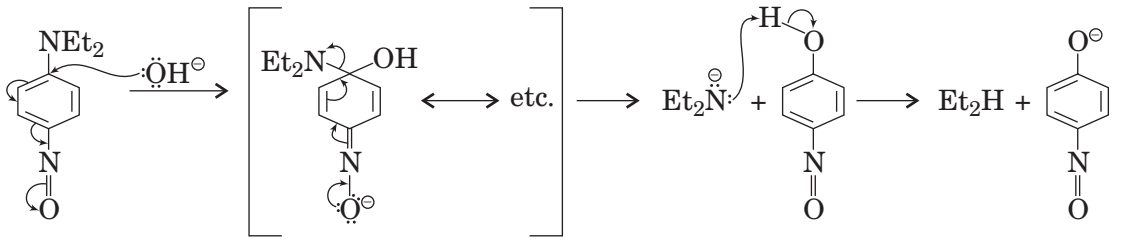


3. ***Displacement of nitrogen anions*:** A nitrite ion ($NO_2^{\ominus}$) can be readily displaced from an aromatic substrate if another nitro group present at *ortho* or *para* position activates the ring towards nucleophilic attack. For example:

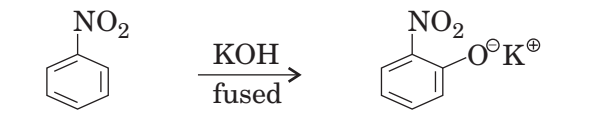
(i) 

o-Dinitrobenzene

(ii) Amino substituents may also undergo displacement as amide ions through S_NAr mechanism. When *p*-nitroso-*N*, *N*-diethylaniline, for example, is treated with alkali, *p*-nitrosophenoxide is obtained. In this case, the *p*-nitroso group activates the ring towards nucleophilic attack.

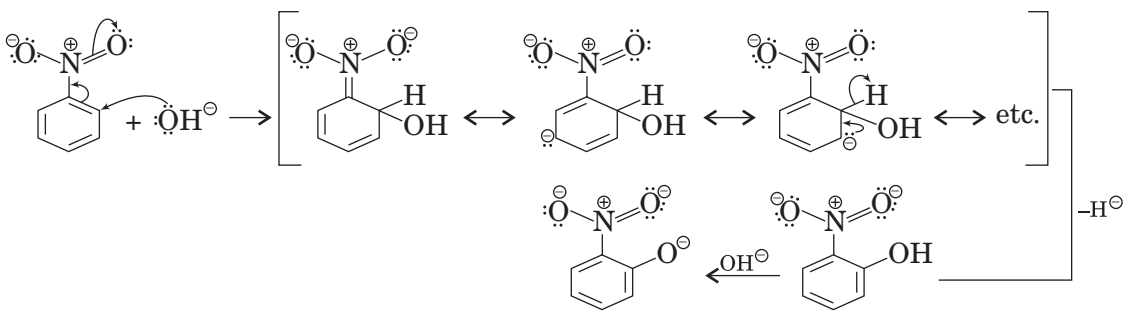


4. ***Displacement of hydride ion*:** Hydride ion ($H^{\ominus}$) cannot be displaced from benzene because the π electron cloud repels the incoming nucleophile and the carbanion intermediate is very poorly stabilized by electron delocalization. However, a hydride ion can be easily displaced from an aromatic ring containing a powerful electron-attracting group like $-NO_2$ is treated with a strong nucleophile. For example, when nitrobenzene is fused with KOH, *o*-nitrophenol (K salt) is obtained as the major product.



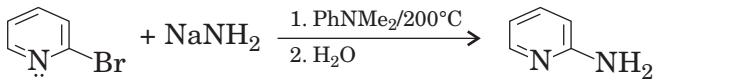
Nitrobenzene — *o*-Nitrophenol (salt) (major)

Mechanism:



In the first step, nucleophilic attack by $OH^{\ominus}$ occurs on the carbon *ortho* to the $-NO_2$ group (the activated position) to form a resonance-stabilized carbanion intermediate. In the second step, a hydride ion ($H^{\ominus}$) leaves from the intermediate to give the substituted compound. Although $OH^{\ominus}$ is a better leaving group than $H^{\ominus}$ (a relatively strong base), $H^{\ominus}$ leaves because aerial oxygen destroys $H^{\ominus}$, by oxidising it to H_2O, as it is formed.

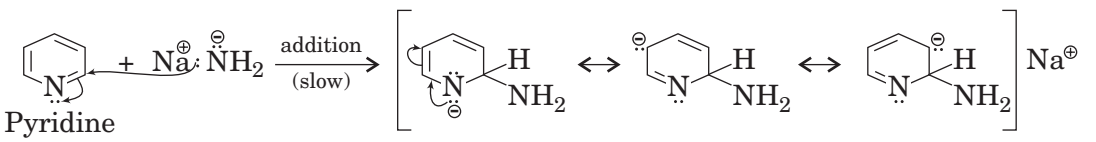
Hydride ion can also be displaced from C-2 of pyridine nucleus by powerful nucleophiles through S_NAr mechanism. When pyridine is refluxed with $NaNH_2$, 2-aminopyridine is obtained. The reaction is known as *Chichibabin (Tschitschibabin) reaction*.



Pyridine — 2-Aminopyridine (70–80%)

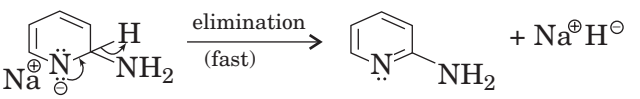
Mechanism: The mechanism of the reaction involves the steps as follows:

Step 1: Pyridine undergoes nucleophilic attack by $\overset{\ominus}{N}H_2$ at 2-position to form a resonance-stabilized carbanion intermediate.

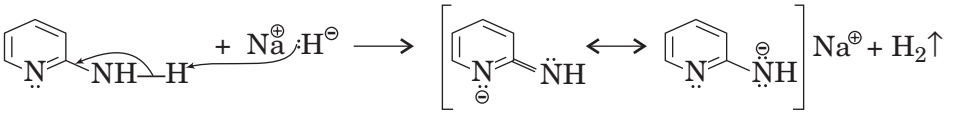


Pyridine

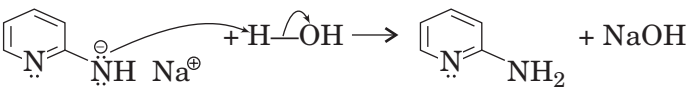
Step 2: The intermediate loses $H^{\ominus}$ to yield 2-aminopyridine. Re-aromatization of the intermediate is the driving force for $H^{\ominus}$ loss.



The hydride ion being a very strong base immediately abstract a proton (relatively acidic) from the $-NH_2$ group of 2-aminopyridine to form a sodio salt and H_2.



2-Aminopyridine is finally recovered by adding cold water to the reaction mixture.



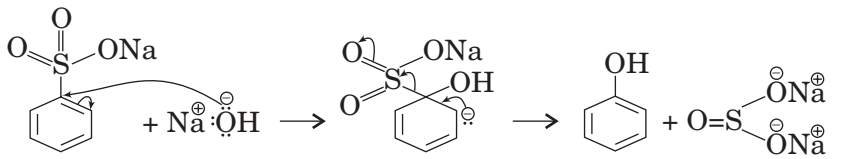
2-Aminopyridine

5. ***Displacement of sulphite ion***: An important preparation of phenols involves conversion of arenesulphonic acids to the corresponding phenoxides by fusing with sodium or potassium hydride followed by acidification of the resulting phenoxides.

For example:

$$\underset{\text{Sodium benzene sulphonate}}{C_6H_5SO_3Na} \xrightarrow[300°C]{NaOH,\ fusion} 2Na^{\oplus} + SO_3^{2\ominus} + C_6H_5OH \xrightarrow{OH^{\ominus}} C_6H_5O^{\ominus} \xrightarrow{H_3O^{\oplus}} \underset{\text{Phenol}}{C_6H_5OH}$$

Mechanism:



Difference between S_NAr and S_N2 mechanism in aliphatic systems: The differences between S_NAr reaction and S_N2 reaction of alkyl halides are as follows:

(i) There is an actual intermediate in S_NAr reaction (the Meisenheimer complex). However, there in no evidence for an intermediate in any S_N2 reaction.

(ii) The S_NAr reaction is a front side displacement. There occurs no inversion of configuration. The S_N2 reaction of an alkyl halide, in contrast, is a backside displacement taking place with inversion of configuration.

(iii) The effect of halogen on the reaction rate is different in the two reactions. Aryl fluorides react most rapidly in S_NAr reactions, whereas alkyl fluorides react most slowly in S_N2 reactions.

3.2.2 The Elimination-Addition or Benzyne Mechanism

Although aryl halides such as chlorobenzene and bromobenzene are relatively inert towards common nucleophiles under normal conditions, they show marked reactivity under highly forcing conditions. Chlorobenzene can be converted into phenol by heating with aqueous NaOH under pressure at 350°C.

$$\underset{\text{Chlorobenzene}}{C_6H_5Cl} \xrightarrow[350°C/150\ atm]{aq.\ NaOH} NaCl + C_6H_5OH \xrightarrow{OH^{\ominus}} C_6H_5O^{\ominus} \xrightarrow{H_3O^{\oplus}} \underset{\text{Phenol}}{C_6H_5OH}$$

Bromobenzene reacts with the very powerful base KNH_2 in liquid ammonia to yield aniline.

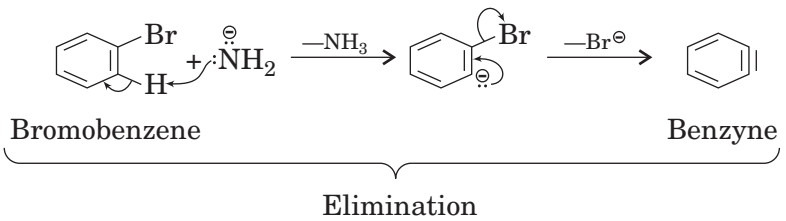
$$C_6H_5Br \xrightarrow[liq.\ NH_3;\ -33°C]{KNH_2} C_6H_5NH_2 + KBr$$

Investigations show that these reactions take place through an elimination-addition mechanism (different from that of S_NAr mechanism) that involves the formation of a highly unstable neutral intermediate called benzyne (or dehydrobenzene).

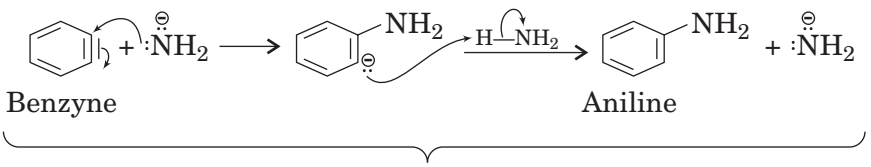
The mechanism can be illustrated with the reaction of bromobenzene and amide ion in liquid NH_3. It involves the following two steps:

Step 1: This step involves elimination of a molecule of HBr from bromobenzene (via an E1cB pathway). The amide ion abstracts one of the *ortho* protons because they are the

most acidic. The negative charge that develops on the *ortho* carbon is stabilized by the –I effect of bromine. The anion then loses a bromide ion to form the highly unstable, and thus highly reactive, benzyne.

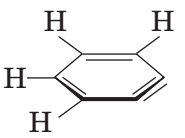


Step 2: The amide ion attacks the so-called triple bond of benzyne to form a carbanion. The carbanion finally takes up a proton from ammonia to yield aniline.

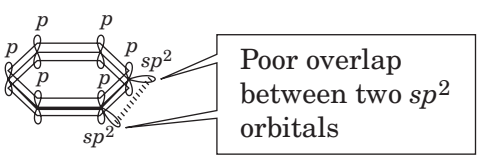


In the conversion of the substrate to benzyne, either the removal of proton or the loss of the halide ion can be rate-determining. When the leaving group is Br or I (i.e., when *ortho* H's are less acidic), proton removal is rate-determining and when Cl or F is the leaving group (i.e., when *ortho* H's are more acidic), cleavage of the C—X bond is rate-determining.

Structure and reactivity of benzyne: Benzyne is an unusual species. One of the two π bonds in the triple bond of benzyne is perpendicular to the π-electron system of the aromatic ring. Therefore, it retains the aromatic sextet. The extra π bond is formed from two sp^2 orbitals and since the two sp^2 orbitals are directed 60° away from each other, their overlap is very much less effective. Again, because alkynes require linear geometry (the optimal angle in triple bonds is 180°), it is difficult to incorporate them into six-membered rings. Therefore, benzyne is highly strained. For these reasons, although benzyne is neutral and aromatic, it is a very unstable and reactive intermediate, which has never been isolated (benzyne is 49 kcal/mol less stable than ordinary alkyne). However, it has been detected and trapped in various ways.



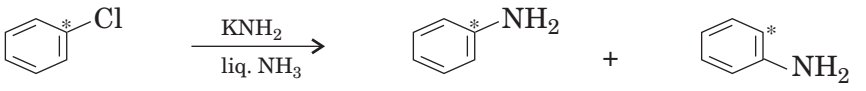
Benzyne



Orbital diagram of benzyne

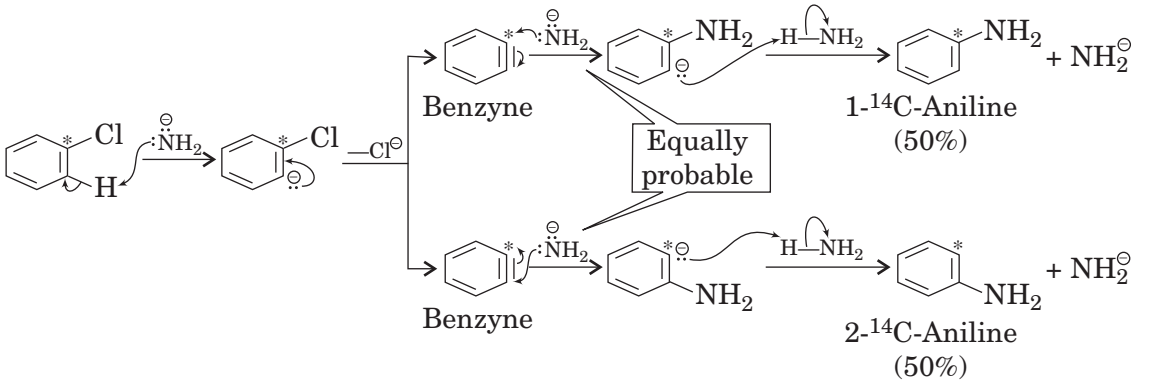
Evidence for an elimination-addition mechanism involving benzyne intermediate: The convincing evidence for the intermediacy of benzyne is the following:

(i) Evidence for a mechanism involving benzyne intermediate is obtained in a very clever isotopic labelling experiment. When chlorobenzene in which the carbon bearing chlorine is labelled with radioactive isotope ^{14}C is treated with KNH_2 in liquid ammonia, a mixture containing equal amounts of 1-^{14}C-aniline and 2-^{14}C-aniline is obtained.

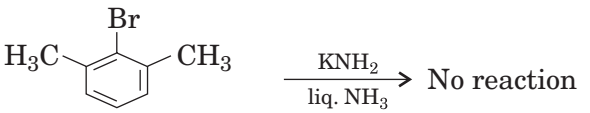


1-^{14}C-Chlorobenzene 1-^{14}C-Aniline (50%) 2-^{14}C-Anline (50%)

Now, the radioactivity cannot actually move from one carbon to the other. The only way to account for this result is that somehow C-1 and C-2 have become equivalent and indistinguishable at some point in the reaction. As a result, subsequent reactions will occur at both the labelled and unlabelled carbons with equal rates. It thus follows that the symmetrical intermediate benzyne must have been formed during the reaction and it then undergoes nucleophilic attack by $NH_2^{\ominus}$ at either of the equivalent triple bonded carbons to give two differently labelled anilines in equal amounts. The process may be shown as follows:

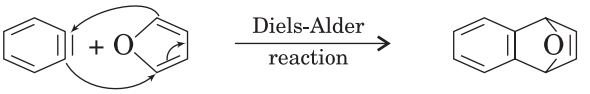


(ii) If the aryl halide contains two *ortho* substituents, the reaction should not be able to take place. This is indeed the case. When 1-bromo-2,6-dimethylbenzene, for example, is allowed to reach with KNH_2 in liquid ammonia, no reaction takes place. This observation, therefore, supports the intermediacy of benzyne in the reaction of halobenzene with KNH_2 in liq. NH_3.



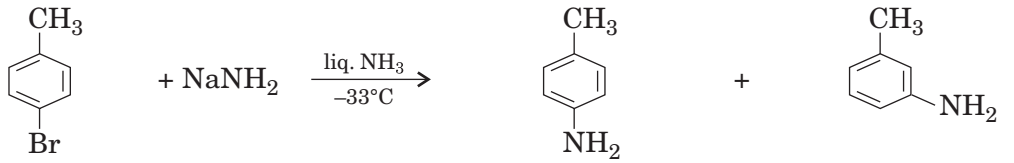
1-Bromo-2,6-dimethyl-benzene

(iii) The benzyne intermediate can be trapped by a Diels-Alder reaction. When the reaction between bromobenzene and KNH_2 in liquid NH_3 is carried out in the presence of furan, a Diels-Alder adduct is obtained in addition to the substitution product. this offers a direct evidence for the intermediacy of benzyne.



Benzyne (dienophile) Furan (diene) Diels-Alder adduct

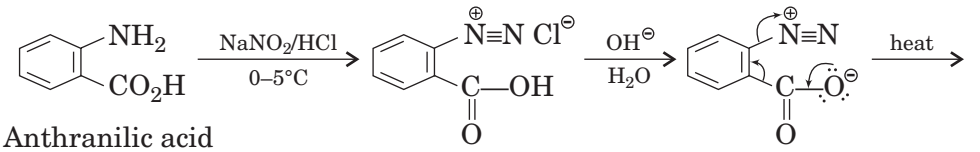
***Cine*-substitution:** Substitution at a site different from the one occupied by the leaving group is called *cine*-substitution. Thus, the formation of *m*-toluidine from *p*-bromotoluene involving the benzyne intermediate is an example of *cine*-substitution.



p-Bromotoluene *p*-Toluidine (direct substitution product) *m*-Toluidine (*cine*-substitution product)

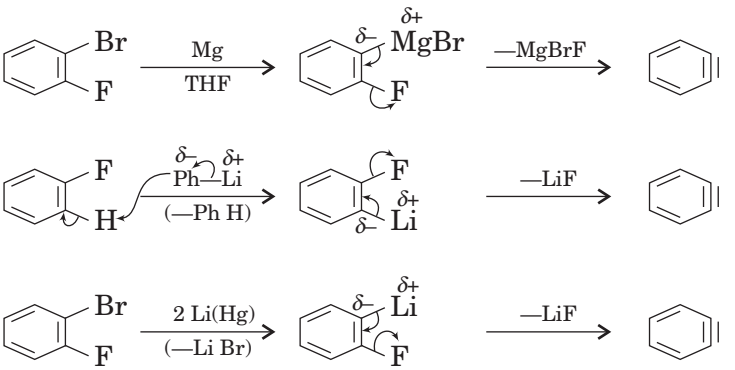
Several other methods for the production of benzyne are as follows:

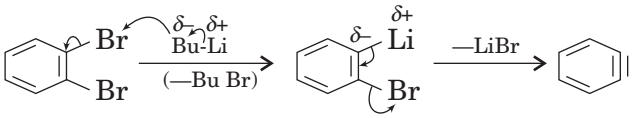
(i)



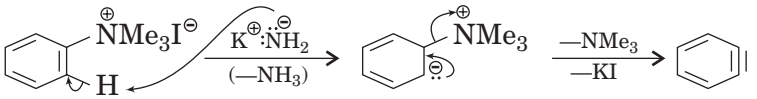
Anthranilic acid

(ii) Through formation of organometallic compound:

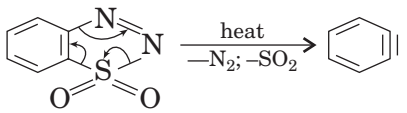




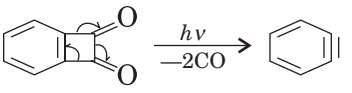
(iii)



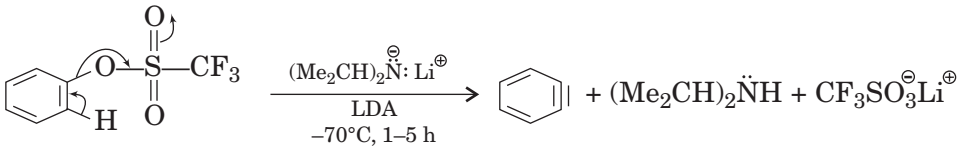
(iv)



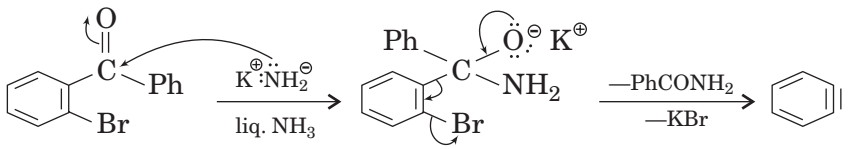
(v)



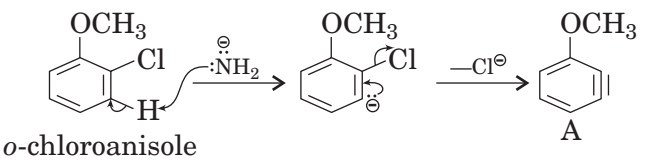
(vi)



(vii)

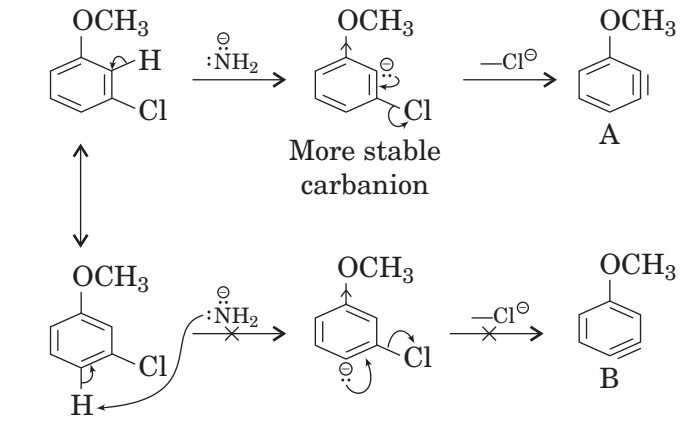


Regioselection in the formation of aryne and its amination in substituted halobenzene: The regioselection in aryne formation and its subsequent amination is often controlled by the elctronic nature of the group present in the substrate. For example, both *o*-chloroanisole and *m*-chloroanisol react with KNH_2 in liquid ammonia to produce *m*-anisidine as the only product. This can be explained by the polar effect of the $–OCH_3$ group. *o*-Chloroanisole reacts with KNH_2 to from only one aryne (A) and this is because the compound contains only one *ortho* proton with respect to chlorine.

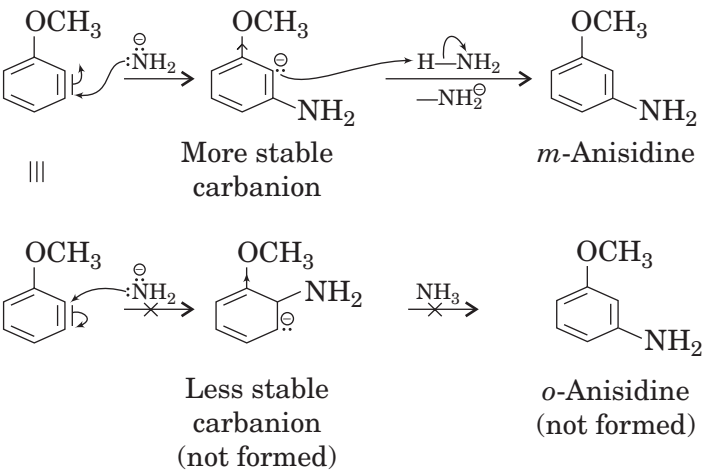


o-chloroanisole

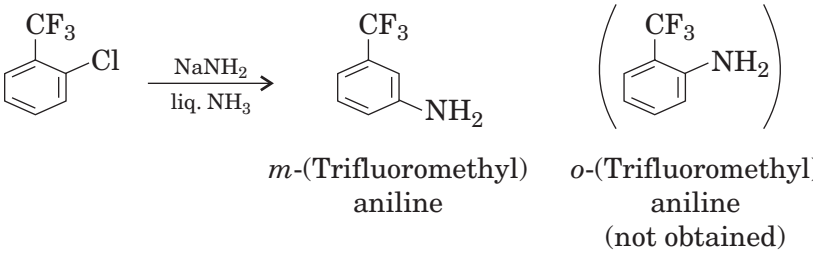
Since there are two *ortho* protons with respect to chlorine in *m*-chloroanisole, two isomeric arynes (A and B) are expected to be formed. However, only the aryne A is formed because the carbanion leading to A is relatively more stabilized by the –I effect of the $–OCH_3$ group (this group is closer to the negative charge) than the carbanion leading to B.



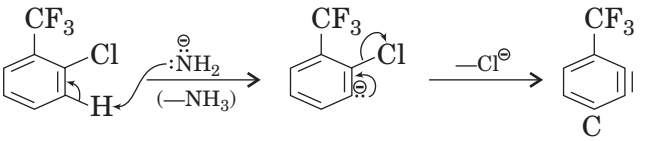
For the same basic reason, the aryne A undergoes nucleophilic attack by $:\overset{\ominus}{\underset{\cdot\cdot}{N}}H_2$ at C-3 instead of C-2 to produce a relatively stable carbanion which on protonation gives *m*-anisidine.



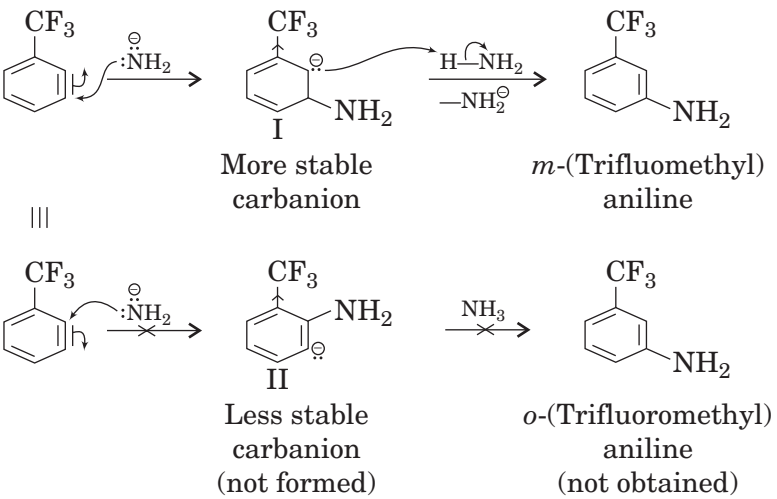
A similar situation arises when 1-chloro-2-trifluoromethyl-benzene is allowed to react with $NaNH_2$ in liquid NH_3. Although both *o*- and *m*-(trifluoromethyl)aniline are expected to be formed, only the latter aniline is obtained.



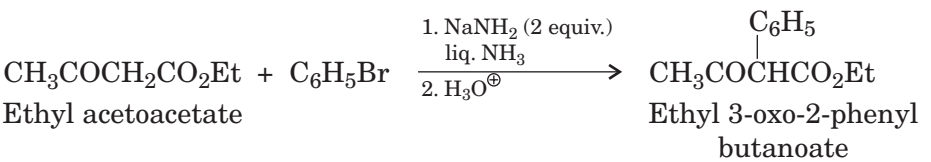
Since there is only one *ortho* proton with respect to chlorine, only one aryne(C) is formed.



The aryne C then adds an amide ion in the way that produces the more stable carbanion I (in which the negative charge is stabilized by the strong –I effect of the closer trifluoromethyl group) rather than the less stable carbanion II. The carbanion I then accepts a proton from ammonia to form *m*-(trifluoromethyl)aniline.

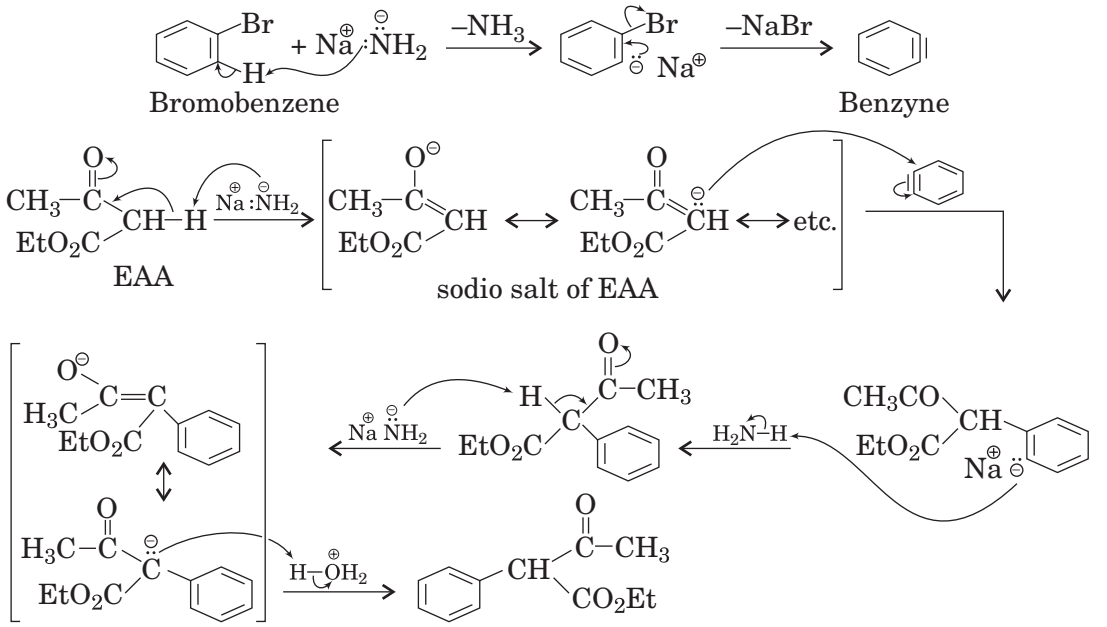


Phenylation: The process of forming a carbon–carbon bond to a phenyl group involving benzyne is called *phenylation*. For example, when ethyl acetoacetate is treated with bromobenzene in the presence of two molar equivalents of sodium amide ($NaNH_2$), phenylation of ethyl acetoacetate occurs.



In this case, one mole of $NaNH_2$ reacts with bromobenzene to produce benzyne and the other mole reacts with ethyl acetoacetate to give its sodio salt. The carbanion of the sodio salt (i.e., the conjugate base of ethyl acetoacetate) then adds to benzyne to form a phenyl anion which subsequently takes up a proton from NH_3 to form the phenylated ethyl acetoacetate. Since it contains one acidic proton, it reacts readily with the base $NaNH_2$ to yield the corresponding sodium salt. The phenylated compound is recovered by acidification with dilute acid.

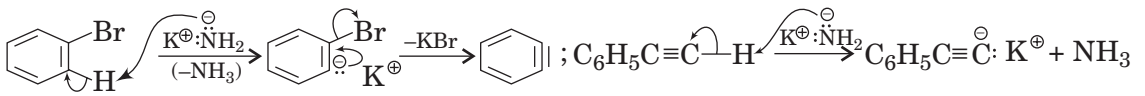
Mechanism:



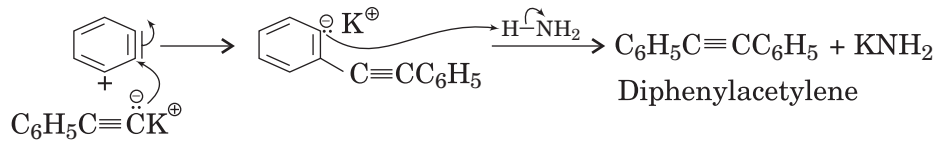
Similarly, when phenylacetylene (with an acidic terminal proton) is allowed to react with bromobenzene in the presence of two molar equivalents of KNH_2, diphenylacetylene is obtained.

$$\underset{\text{Bromobenzene}}{C_6H_5Br} + C_6H_5C{\equiv}CH \xrightarrow[\text{liq. } NH_3]{2\ KNH_2} \underset{\text{Diphenylacetylene}}{C_6H_5C{\equiv}CC_6H_5}$$

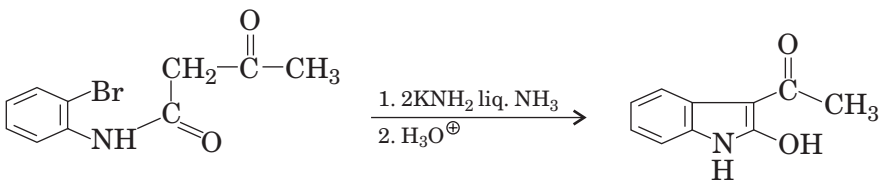
Mechanism:



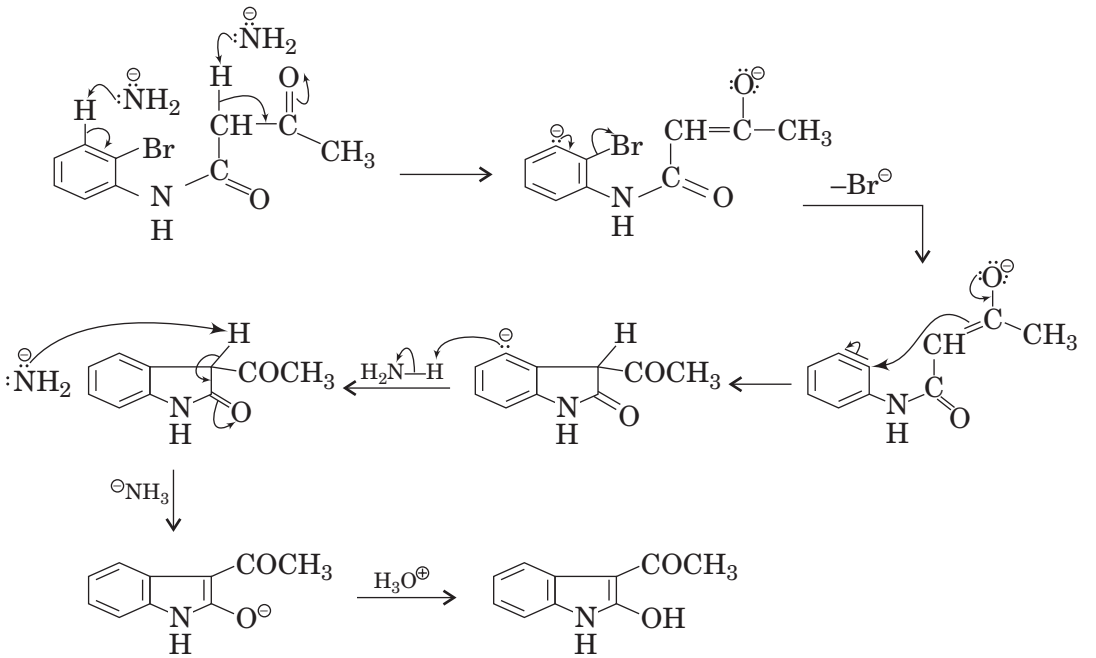
Then,



Intramolecular phenylation occurs when benzyne and the carbanion become the part of the same molecule. For example:

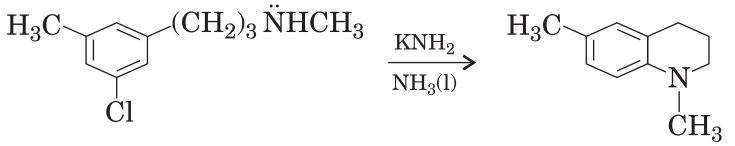


Mechanism:

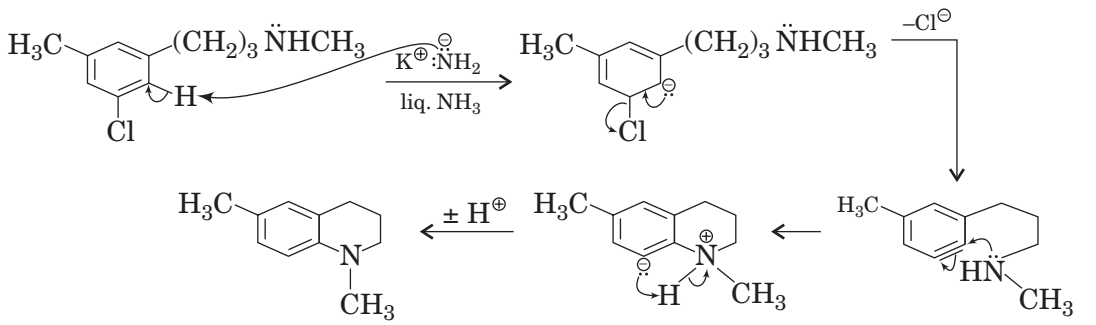


Syntheses of heterocyclic compounds by reactions involving aryne intermediates When an aryl halide containing a side chain with a hetero atom is allowed to react with KNH_2 in liquid NH_3, a heterocyclic compound is obtained. For example:

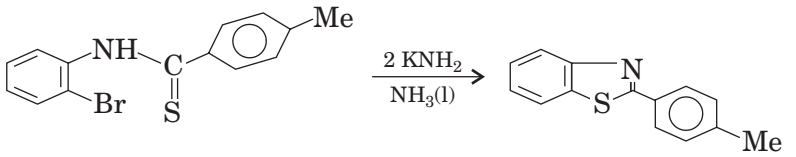
(i)



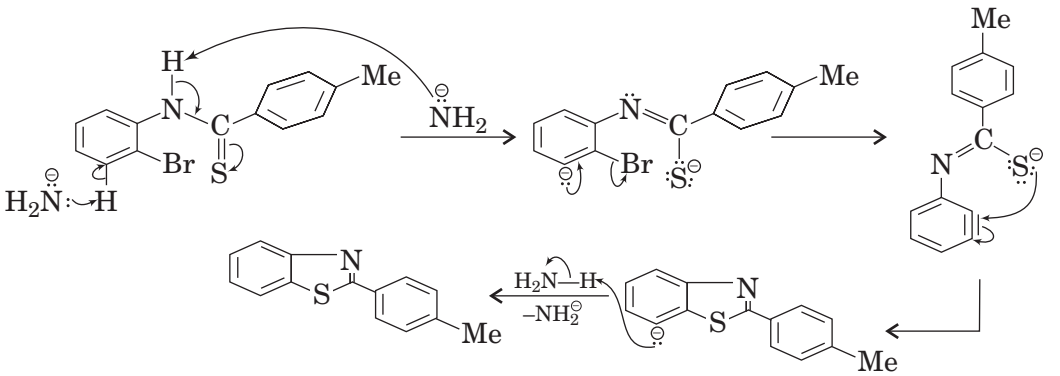
Mechanism:



Potassium amide eliminates a molecule of HCl from the aryl chloride to form an aryne which undergoes nucleophilic attack by the $-\ddot{N}HCH_3$ group to yield 2,3,4-trihydro-6, *N*-dimethylquinoline. The reaction involving the other possible aryne (formed by the expulsion of the other *ortho* proton with respect to Cl) does not take place because ring closure leading to a deformed seven-membered ring is not possible.

(ii) 

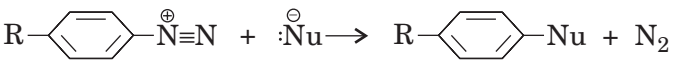
Mechanism:



One mole of KNH_2 is used to abstract the acidic proton attached to nitrogen and the other mole is used to form an aryne. Intramolecular nucleophilic attack by the negative sulphur atom on a triple-bonded carbon then leads to the formation of 2-*p*-tolylthiazole.

3.2.3 S_N1 Mechanism

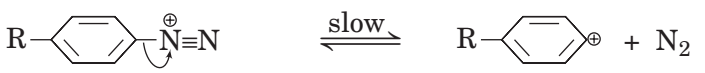
Since aryl cations are very much unstable, aromatic substitutions by the S_N1 mechanism are very rare excepting the decomposition of arenediazonium ion prepared by treating aromatic primary amines (anilines) with HNO_2($NaNO_2$/HCl or H_2SO_4).



Arenediazonium ion

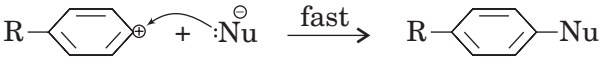
The mechanism of the reaction involves the steps as follows:

Step 1: This reversible step involves the formation of an aryl cation by dissociation of the C–N bond of the arenediazonium ion. Since an aryl cation is highly unstable (its positive charge cannot be delocalized by the π-orbital system of the ring because the vacant sp^2 orbital is located in the plane of the ring and perpendicular to the π-orbital system), its formation is very slow. Hence, it is the rate-determining (slow) step of the reaction. In spite of the instability, the aryl cation is formed as an intermediate because N_2 is an extremely effective leaving group (N≡N bond energy = 946 kJ/mol) and in fact, it is the driving force for this step.

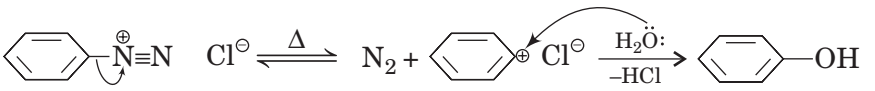


An Arenediazonium ion An aryl cation

Step 2: The nucleophile (an anion or the neutral solvent molecule) attacks the aryl cation to yield the substitution product.

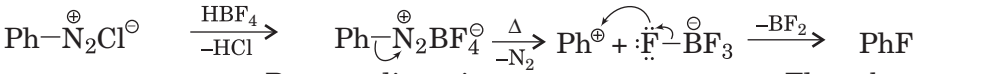


For example, when benzenediazonium chloride is strongly acidified (usually by adding H_2SO_4) and then boiled, the hydroxyl group of water replaces N_2, forming phenol.



Benzenediazonium chloride — Phenyl cation — Phenol

An aryl fluoride can be prepared by allowing an aryldiazonium chloride to react with fluoroboric acid (HBF_4) followed by gentle heating of the precipitated diazonium fluoroborate. For example:



Benzenediazonium chloride — Benzenediazonium fluoroborate — Fluorobenzene

Evidence in favour of the S_N1 mechanism The evidence for the S_N1 mechanism with aryl cations as intermediates is as follows:

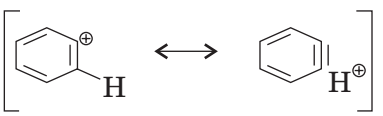
(i) The reaction rate is first order in diazonium salt and independent of the concentration of $N_u^{\ominus}$.

$$\text{rate} = k[ArN_2^{\oplus}]$$

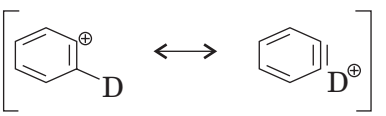
(ii) When high concentrations of halide salts are added, the product is found to be an aryl halide but the rate is independent of the concentration of the added salts.

(iii) The effects of ring substituents on the rate of the reaction are consistent with a unimolecular rate-determining cleavage.

(iv) When reactions were carried out with substrates deuterated in the *ortho* position, isotope effects of about 1.22 were obtained. The stabilization of phenyl cation by hyperconjugation is expected to be reduced if hydrogen is replaced by deuterium.



More effective hyperconjugation



Less effective hyperconjugation (because C—D bond is stronger than C—H bond)

(v) That the first step is reversible can be proved by the fact that when $Ar^{15}N{\equiv}N$ is used as the substrate, the recovered starting material is found to contain not only $Ar^{15}N{\equiv}N$, but also $Ar\,N{\equiv}^{15}N$. This could arise only if the molecule of nitrogen breaks away from the ring and then recombines.

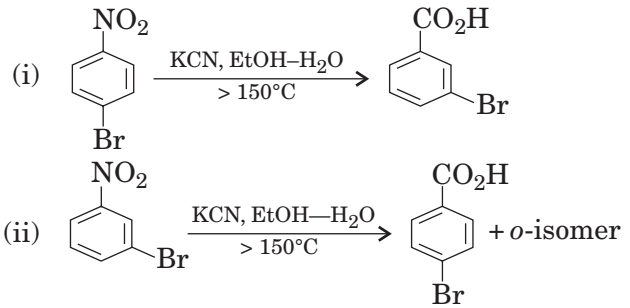


3.2.4 Aromatic Nucleophilic Substitutions with Rearrangement

Examples of aromatic nucleophilic substitutions with rearrangement are as follows:

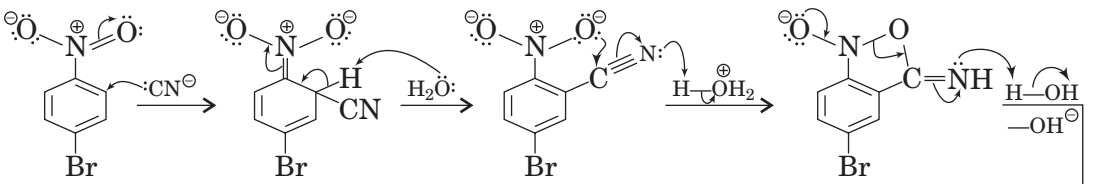
1. ***von Richter rearrangement*:** When *meta*- and *para*-nitrohalobenzenes are heated with aqueous-alcoholic potassium cyanide solution above 150°C, the $-NO_2$ group is lost and a –COOH group is introduced at the position *ortho* to the $-NO_2$ group (a *cine* substitution).

This reaction is called *von Richter reaction*. For example:

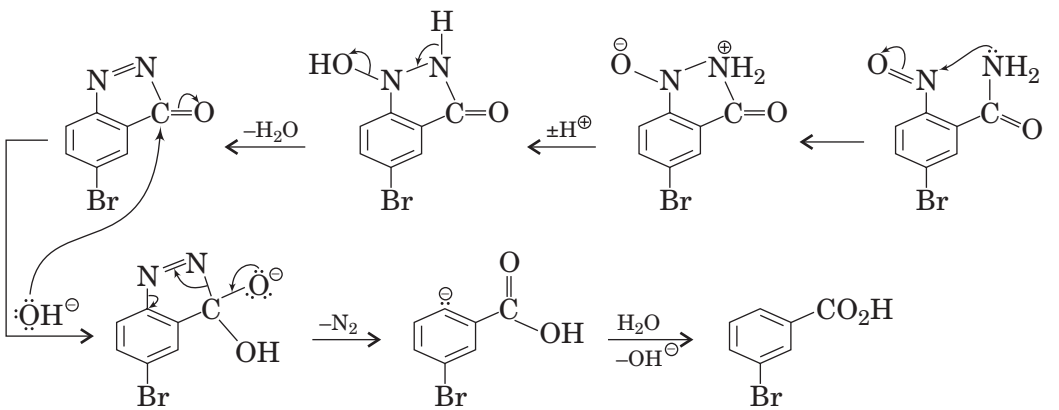


Mechanism:

The mechanism of the reaction involves the steps as follows:

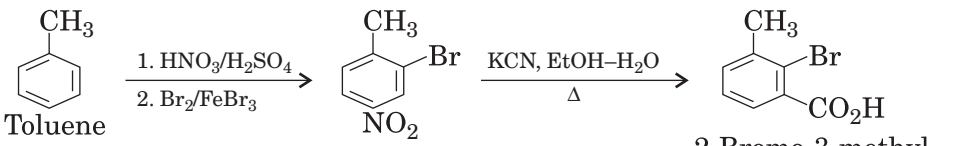


p-Bromonitrobenzene



m-Bromobenzoic acid

A very interesting application of the von Richter reaction is that 2-bromo-3-methylbenzoic acid, which cannot be prepared by any other means, can be prepared smoothly by this reaction.



Toluene

2-Bromo-3-methyl-benzoic acid

2. ***Sommelet–Hauser rearrangement*:** When benzylic quaternary ammonium salts are heated with strong base like an alkali-metal amide, benzyl dialkylamines are produced through a rearrangement called ***Sommelet-Hauser rearrangement***. For example:

$$\underset{\text{A benzylic quaternary ammonium salt}}{C_6H_5CH_2\overset{\oplus}{N}Me_3\ \ I^{\ominus}} \xrightarrow[-NH_3;\ -NaI]{NaNH_2} \underset{\text{A benzyl dialkylamine}}{o\text{-}CH_3C_6H_4CH_2NMe_2}$$

3. ***Rearrangement of aryl hydroxylamines*:** When aryl hydroxylamines are treated with acid, they rearrange to give aminophenols. This reaction is known as the ***Bamberger rearrangement***. For example:

$$\underset{\text{Phenyl hydroxylamine}}{C_6H_5NHOH} \xrightarrow{H^{\oplus}} \underset{p\text{-Aminophenol}}{p\text{-}H_2NC_6H_4OH}$$

[See Chapter 4 of Volume II for the mechanisms of the last two rearrangements.]

SOLVED PROBLEMS

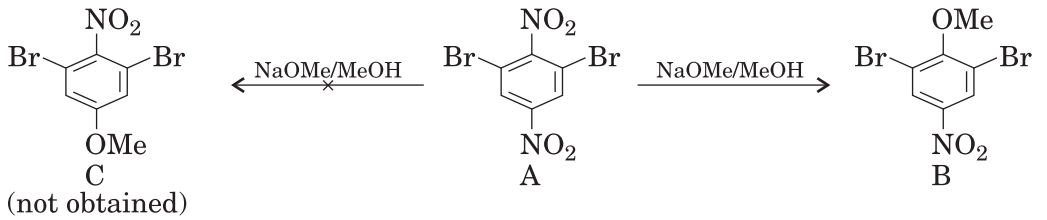
1. In S_N2 reactions of alkyl halides, alkyl fluorides are the least reactive alkyl halides, whereas in nucleophilic aromatic substitutions (S_NAr), aryl fluorides are the most reactive aryl halides. Explain.

Solution The best leaving groups in the S_N2 reaction are those that react to give the weakest bases. Fluoride ($F^{\ominus}$) is the strongest base of the halide ions. Consequently, alkyl fluorides are the least reactive of the alkyl halides in S_N2 reactions. Furthermore, because of the highest strength of the C—F bond among C—X bonds, $F^{\ominus}$ is the poorest leaving group. In fact, alkyl fluorides react so slowly that they are useless as leaving groups in most S_N2 reactions.

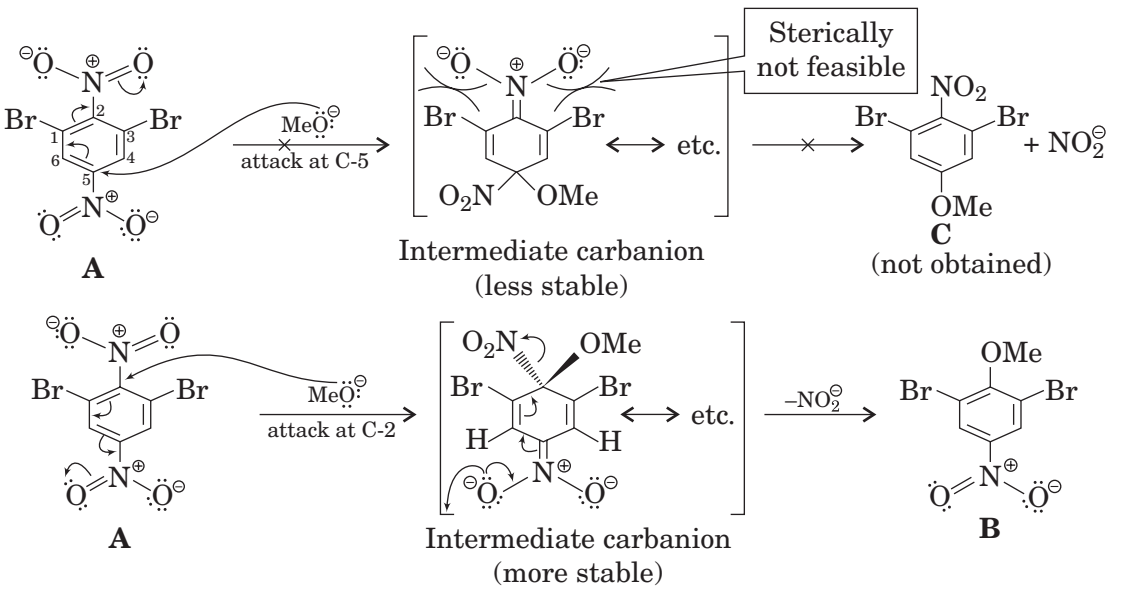
In an S_NAr reaction, fluorine, because of its much stronger-I effect, makes the ring carbon considerably positive and very much susceptible to nucleophilic attack. Furthermore, it stabilizes the intermediate carbanion (the *Meisenheimer complex*) and the transition state leading to it considerably stable. As a result, the first step (the rate determining step) of the

two step process occurs readily and the rate of the reaction increases significantly. Because the loss of halide ion is not rate-determining, the basicity of the halide, or equivalently, the strength of the C—X bond, is not important in determining the reaction rate.

2. Explain the following observations:

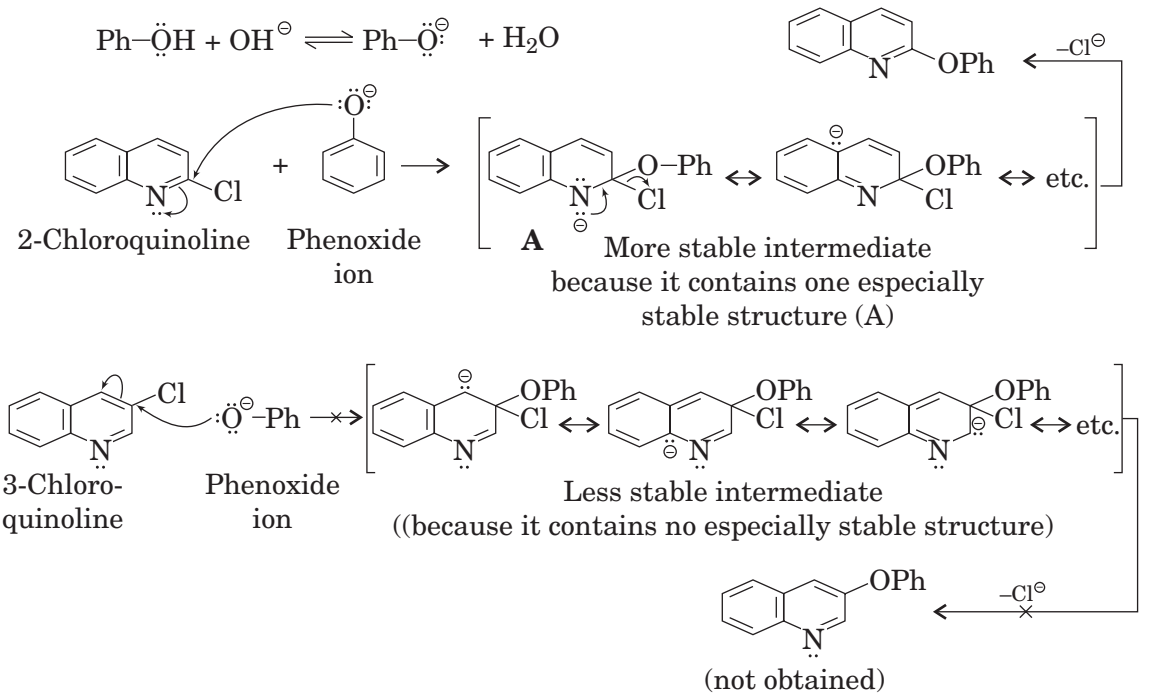


Solution When a $-NO_2$ group (planar) lies in the plane of the benzene ring, an effective resonance interaction with the ring π-electrons takes place. In the intermediate carbanion leading to C, the bromine atoms prevent sterically the $-NO_2$ group at C-2 to become coplanar with the ring and so, delocalization of the negative charge is prevented, i.e., the $-NO_2$ group cannot help to stabilize the intermediate carbanion. For this reason, the reaction does not proceed through this less stable intermediate to give the compound C. Such steric inhibition of resonance is absent in the intermediate leading to B. The negative charge is effectively delocalized by the $-NO_2$ group at C-5 which always remains coplanar with the ring (*ortho* hydrogens are too small to create any steric congestion with bromine atoms). The intermediate leading to B is, therefore, relatively more stable and so, the compound A reacts with sodium methoxide to yield B readily through a pathway having lower energy of activation of the rate-determining step.

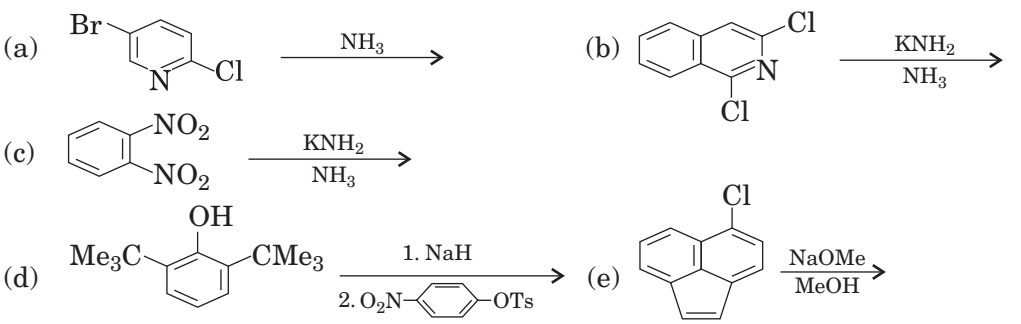


3. 2-Chloroquinoline reacts with phenol in the presence of alkali to yield an ether, whereas 3-chloroquinoline gives no corresponding reaction. Explain.

Solution The ring nitrogen (which behaves like the nitro group in nitrobenzene) stabilizes the anionic intermediate obtained on nucleophilic attack on 2-chloroquinoline by accommodating the negative charge. However, the ring nitrogen is unable to stabilize the anionic intermediate resulting from attack on 3-chloroquinoline due to lack of conjugation. It is for this reason, 2-chloroquinoline reacts with phenoxide ion (i.e., phenol in the presence of alkali) to give an ether, whereas 3-chloroquinoline does not.

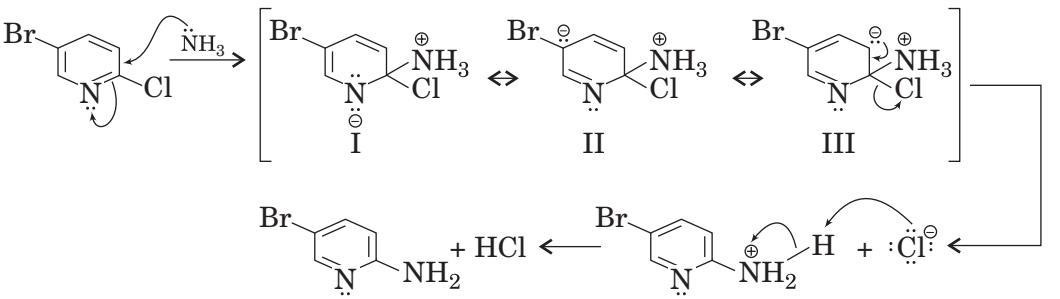


4. Complete each reaction giving the major product and explain your reasoning:

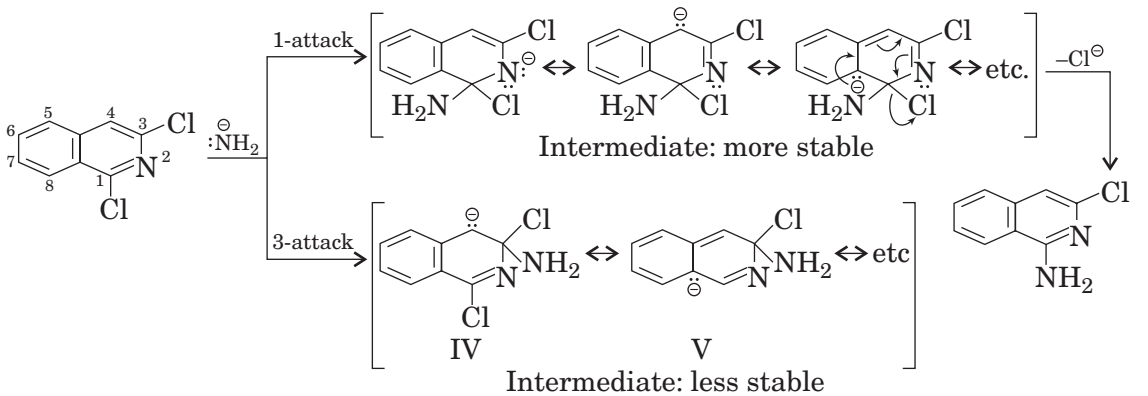


Solution

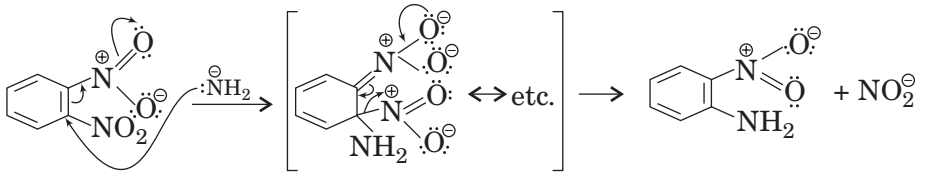
(a) The anionic intermediate obtained on nucleophilic attack on the carbon-bearing bromine is not much stable because the ring nitrogen cannot accommodate the negative charge. However, the anionic intermediate obtained on nucleophilic attack on the carbon-bearing chlorine is relatively stable because the negative charge can be accommodated by the electronegative N atom. Therefore, the latter reaction takes place to give the substitution product.



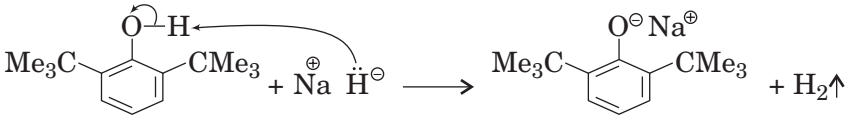
(b) The intermediate anions expected for nucleophilic attack at C-1 and C-3 of this isoquinoline derivative are as follows:



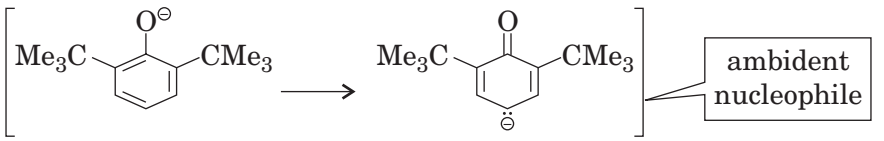
The intermediate anion for 1-attack contains two resonance structures (I and II) in which the aromaticity of the benzene ring is preserved. Furthermore, in one of them the negative charge is accommodated by the electronegative N atom. The intermediate for 3-attack contains only one resonance structure (IV) in which the aromaticity of the benzene ring is preserved and the negative charge in it is placed on less electronegative carbon atom rather than more electronegative nitrogen atom. Therefore, the intermediate for 1-attack is relatively more stable than that for 3-attack. Because of this, thin dichloroisoquinoline reacts with potassium amide to give mainly the 1-substitution product.

(c) 

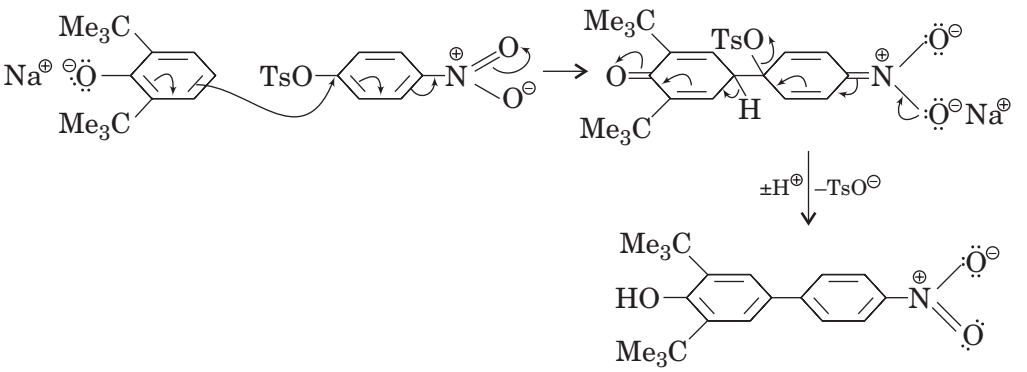
One $-O_2$ group is readily displaced by $\overset{\ominus}{N}H_2$ because the other $-NO_2$ group presents at its *ortho* position activates the ring by stabilizing the intermediate anion.

(d) 

A resonance structure for the 2,6-di-*tert*-butylphenoxide ion shows that the carbon *para* to the oxygen is a nucleophilic centre, i.e., the species can act as an ambident nucleophile.

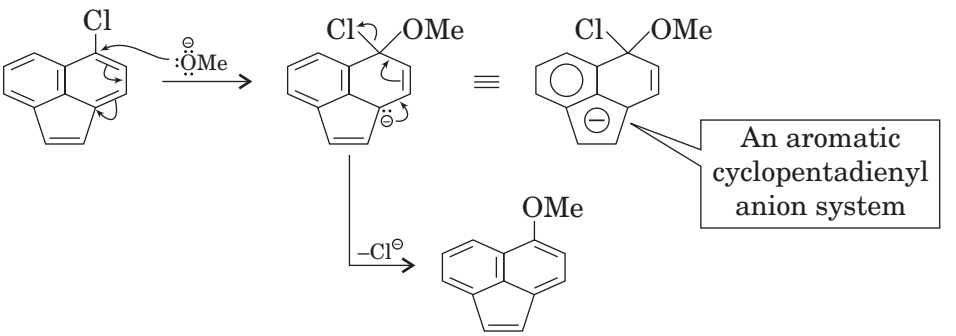


Because of steric crowding about oxygen due to the two bulky *o-tert*-butyl groups, attack through oxygen does not take place. The *para* carbon is the main nucleophilic centre and an S_NAr reaction takes place at that position to form a biphenyl derivative.

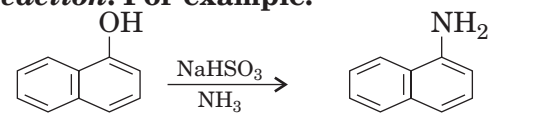


A biphenyl derivative

(e) The compound undergoes S_NAr reaction to give the corresponding methyl ether. The compound apparently contains no activating (electron-withdrawing) group. Even though the reaction occurs. And, this is because, the intermediate is stabilized by formation of an aromatic cyclopentadienyl anion system.



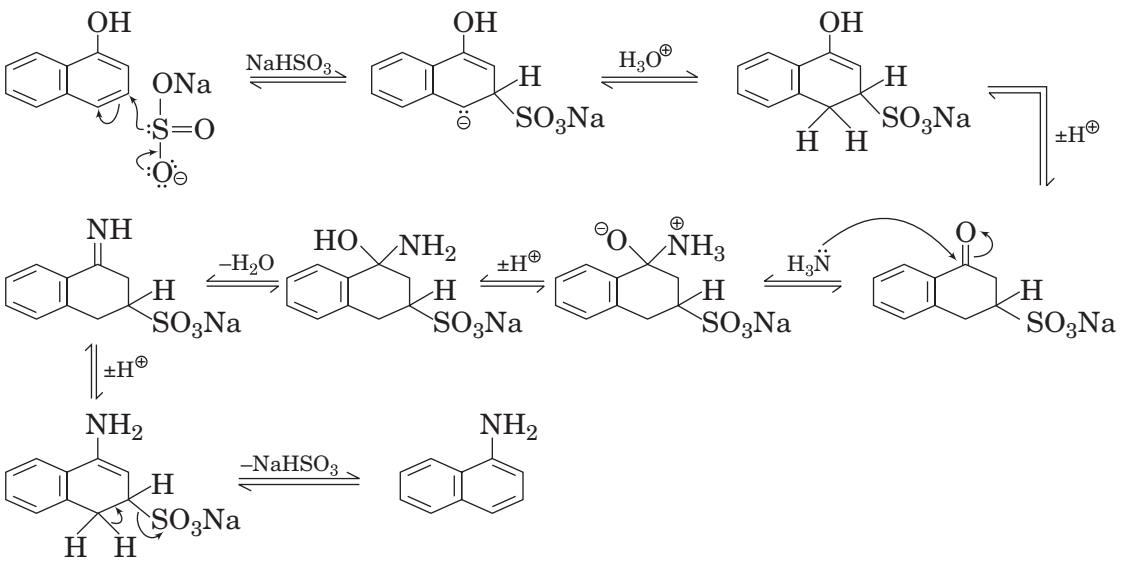
5. The reaction of naphthols with ammonia and sodium bisulphite is called the *Bucherer reaction*. For example:



Suggest a mechanism for the reaction.

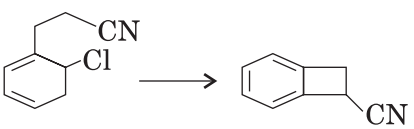
Solution The mechanism of the Bucherer reaction amounts to a kind of overall addition-elimination. The reaction proceeds through the steps as follows:

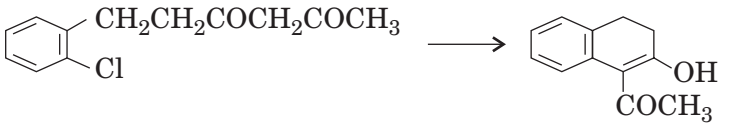
$$NaHSO_3 + H_2O \rightleftharpoons NaSO_3^{\ominus}\ H_3O^{\oplus}$$

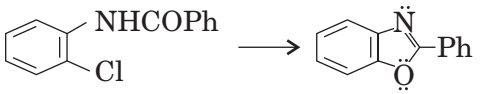


6. How would you carry out the following transformations? Give the mechanism involved in each case.

(a) $CH_2(CO_2Et)_2 \longrightarrow C_6H_3CH_2CO_2H$ (b)

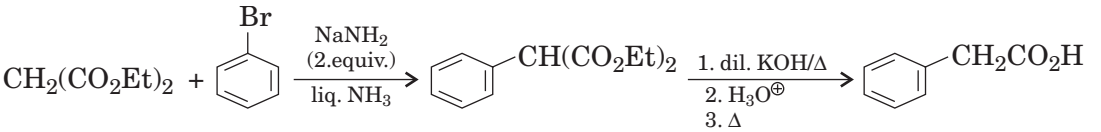


(c) 

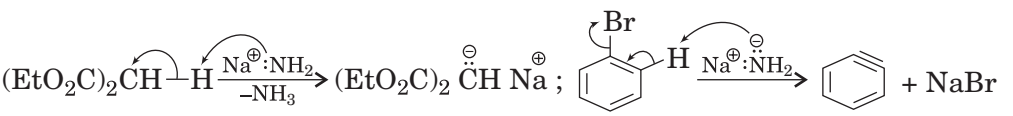
(d) 

Solution

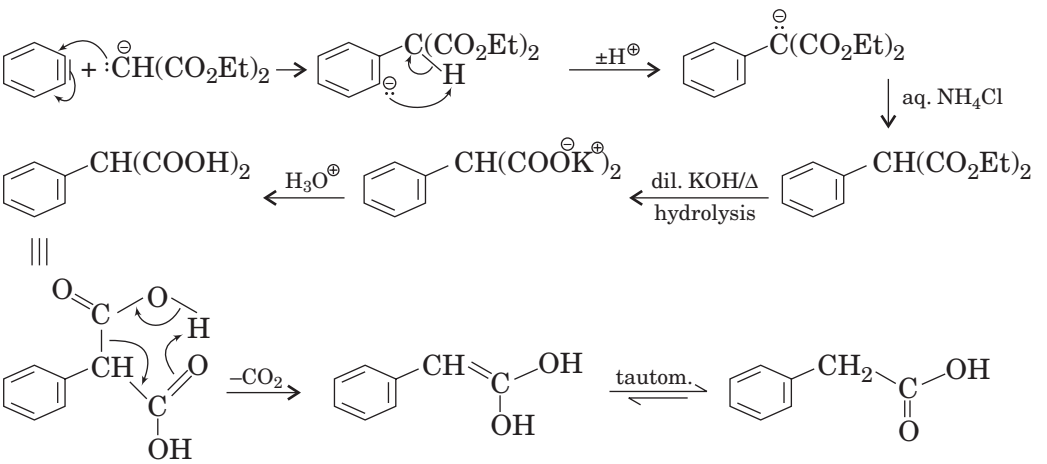
(a) This may be carried out as follows:



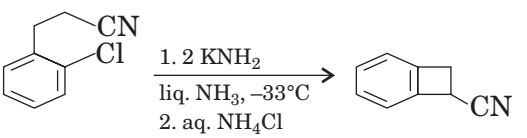
One molar equivalent of $NaNH_2$ converts diethyl malonate to its anion and the second molar equivalent of $NaNH_2$ converts bromobenzene to benzyne



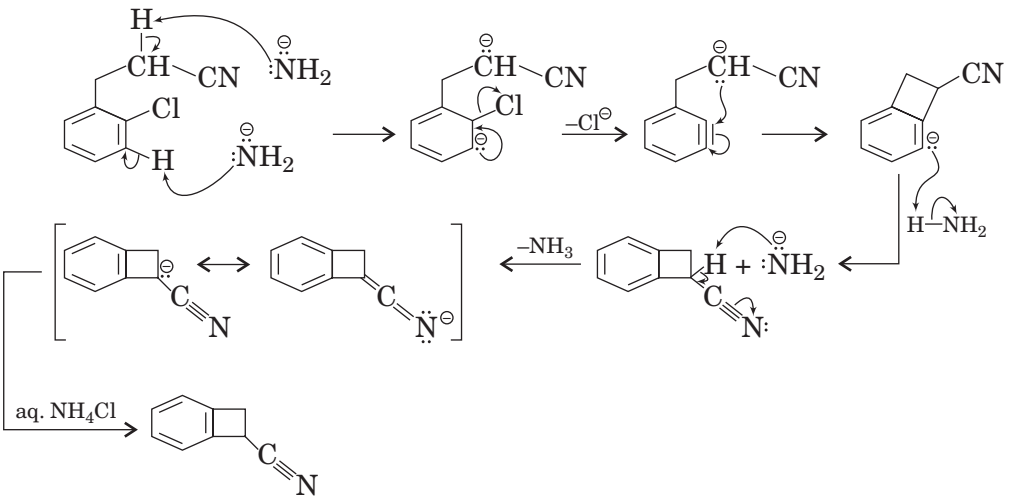
The anion then adds to the benzyne as it forms in the mixture.



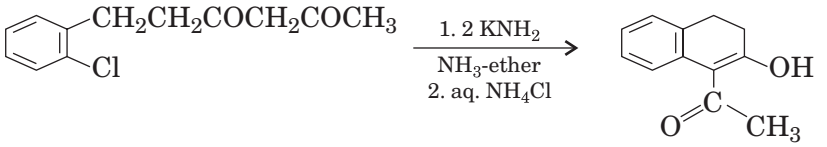
(b) This may be carried out as follows:



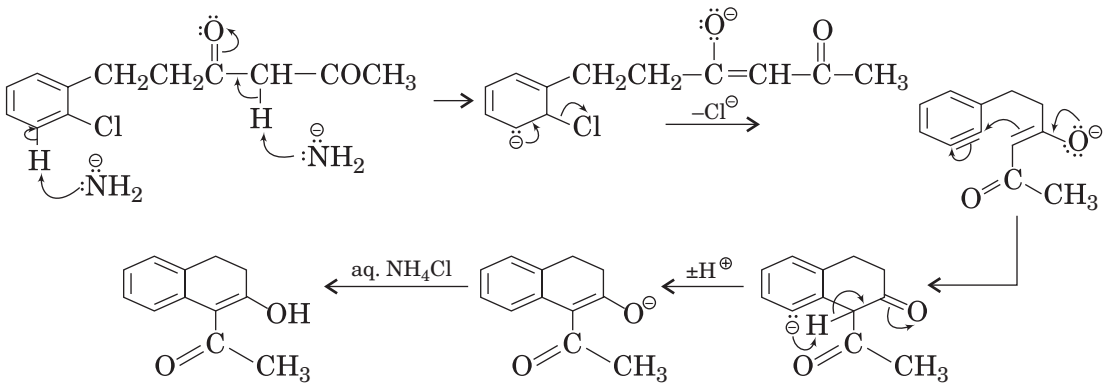
One molar equivalent of KNH_2 is used to form an aryne and the other molar equivalent of KNH_2 is used to take up the acidic (the conjugate base is stabilized by –CN) α-proton leading to a carbanion. An intramolecular addition then occurs to form the desired product.



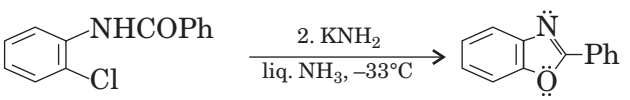
(c) This may be carried out as follows:



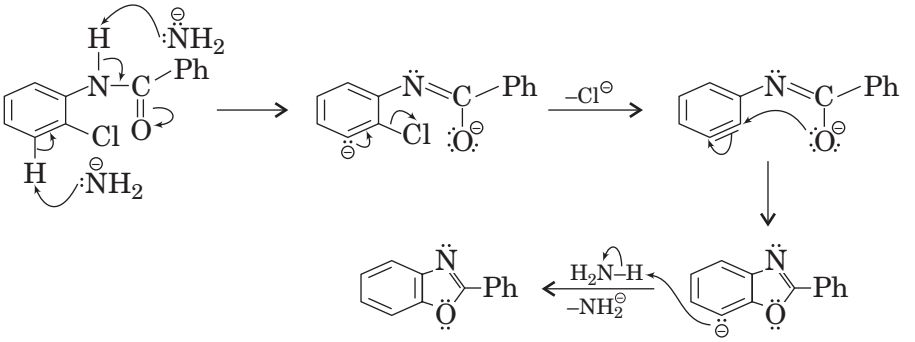
One molar equivalent of KNH_2 is used from an aryne and the other molar equivalent is used to take up a proton from the reactive methylene group leading to a resonance-stabilized carbanion. An intramolecular addition then occurs to form a new six-membered ring.



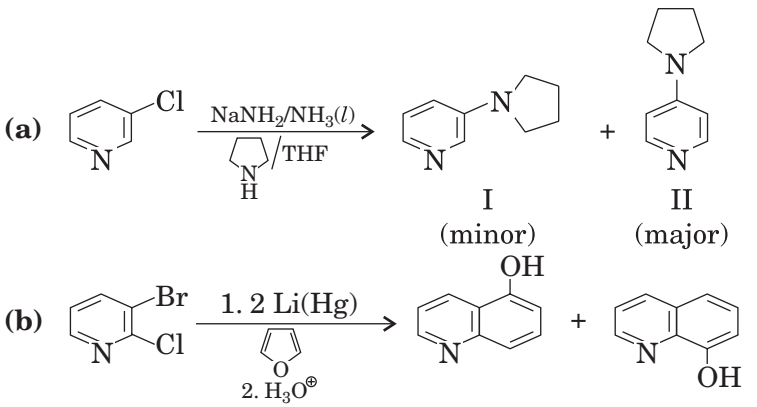
(d) This conversion can be effected as follows:



A similar reaction occurs through the formation of an aryne to yield 2-phenylbenzoxazole.

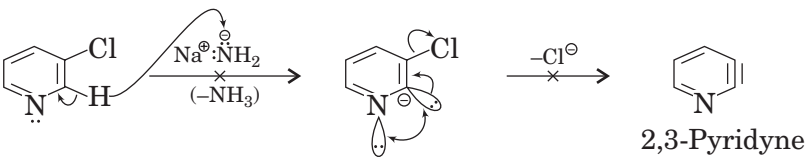


7. Account for the following observations:

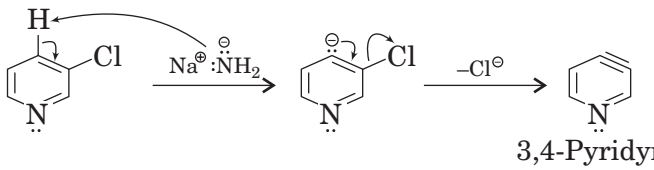


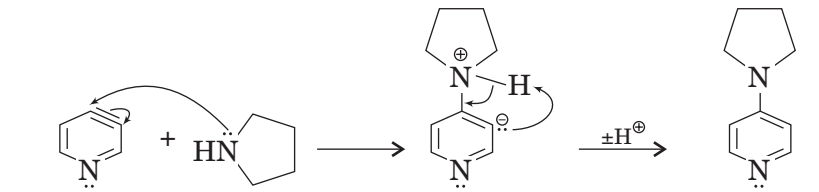
Solution

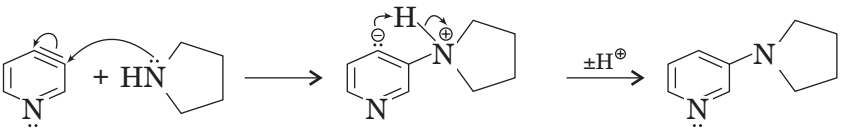
(a) 3-Chloropyridine reacts with $NaNH_2$ in liquid ammonia to form only 3,4-pyridyne. 2-3-Pyridyne is not formed because of repulsive destabilization of intermediate carbanion. 3-4-Pyridyne then undergoes attack at C-3 by pyrrolidine to give I as the minor product through a less stable carbanion (the negative charge is not close to electronegative nitrogen). II is obtained as the major product because the reaction proceeds through a more stable carbanion (the negative charge is close to nitrogen).



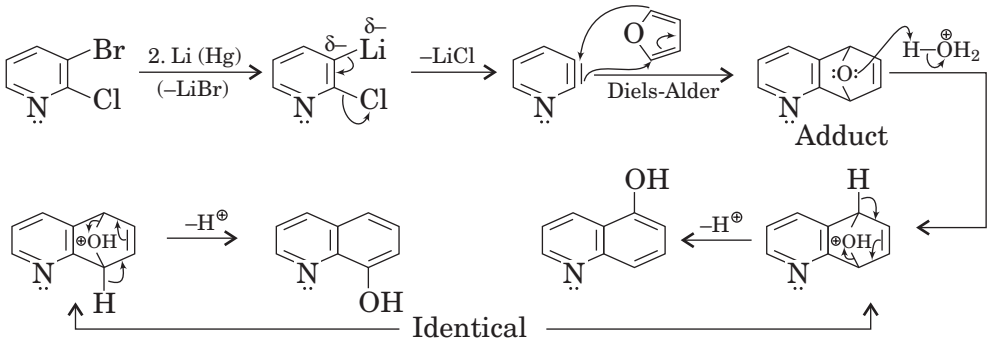
Less stable
(due to repulsive
interaction between two
adjacent unshared pairs)





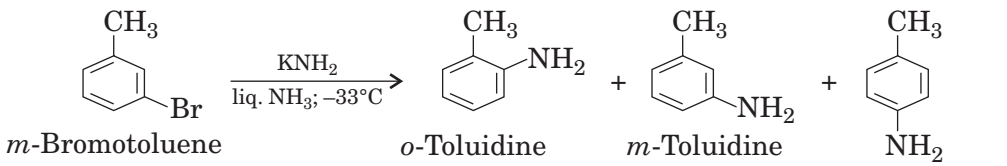


(b) 3-Bromo-2-chloropyridine reacts with lithium amalgam to form 2,3-pyridine which subsequently undergoes a Diels-Alder reaction with furan to give an adduct. The adduct undergoes hydrolysis in aqueous acid to give to isomeric hydroxyquinolines.



8. Explain the following observations:

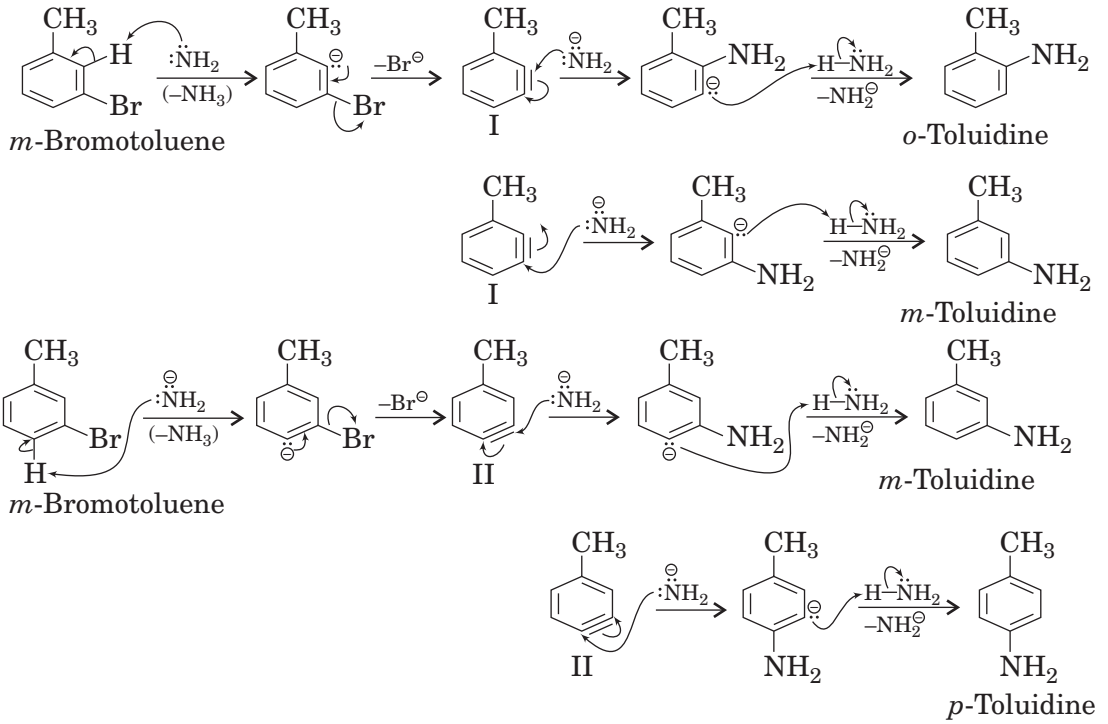
(a)



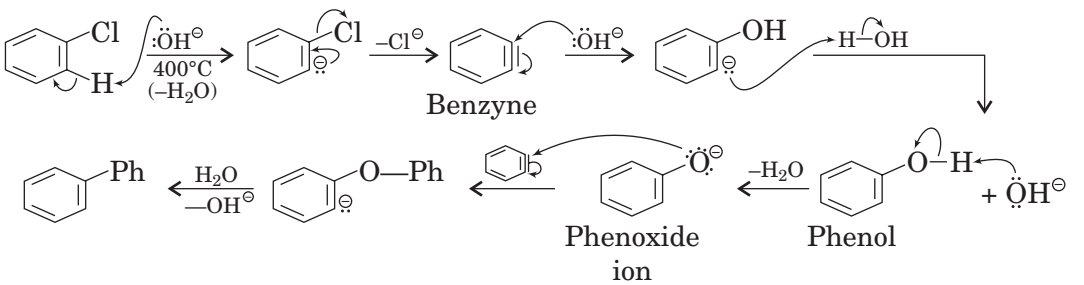
(b) When phenol is prepared commercially from chlorobenzene and NaOH at about 400°C, the major side product is diphenyl ether.

Solution

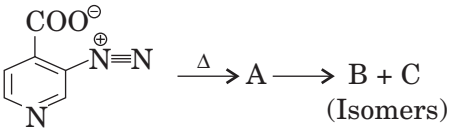
(a) In *m*-bromotoluene, the hydrogens *ortho* to bromine are not equivalent and so, it reacts with KNH_2 in liquid NH_3 to form two arynes (I and II). Now, the aryne I produces a mixture of *o*- and *m*-toluidine and the aryne II produces a mixture of *m*- and *p*-toluidine. Therefore, the reaction leads to the formation of a mixture of three toluidines. The process may be outlined as follows:



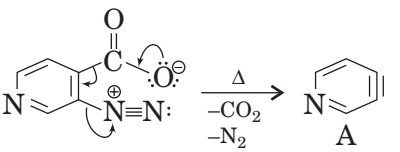
(b) Chlorobenzene reacts with NaOH at about 400°C to form benzyne which subsequently reacts with alkali to form phenol. In the presence of alkali phenol exists as phenoxide which reacts with benzyne to yield diphenyl ether as the major side product. The reaction takes place as follows:



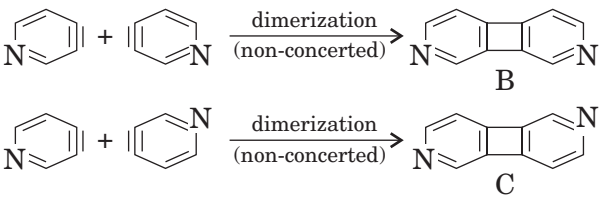
9. Provide structures of A, B and C:



Solution Thermal decomposition of the pyridine diazonium carboxylate produces 3,4-pyridine (A) which subsequently dimerizes to yield the isomeric compounds B and C. The reaction proceeds as follows:



Now, A undergoes dimerization in two ways to give B and C.



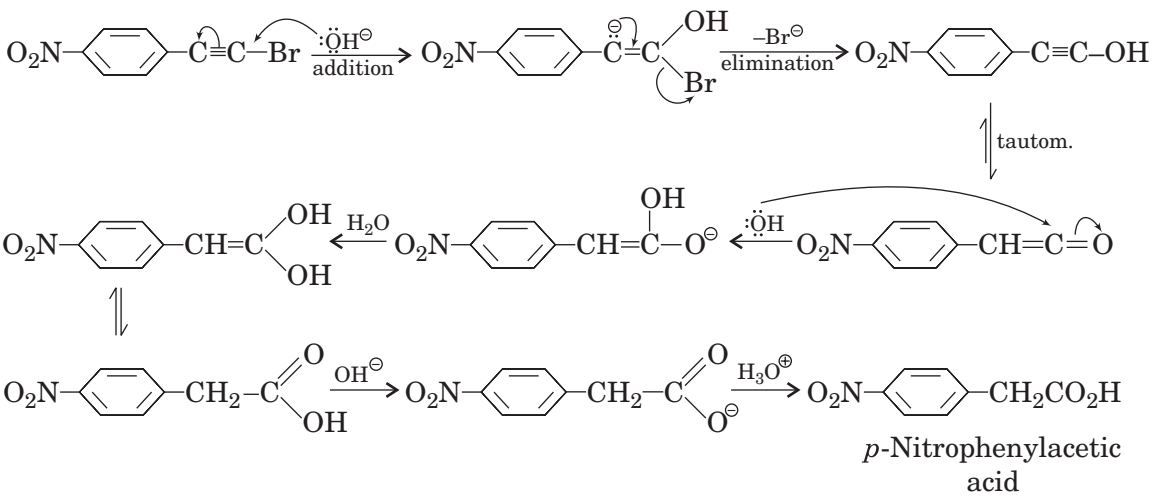
10. Give a curved-arrow mechanism for each of the following reactions:

(a) $O_2N-C_6H_4-C\equiv C-Br \xrightarrow[2.\ H_3O^{\oplus}]{1.\ KOH,\ H_2O–EtOH/\Delta} O_2N-C_6H_4-CH_2CO_2H$

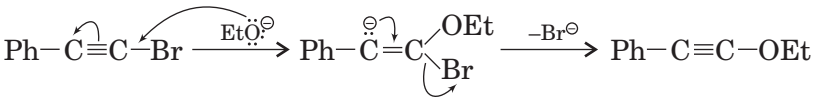
(b) $Ph-C\equiv C-Br \xrightarrow[EtOH]{NaOEt} Ph-C\equiv C-OEt$

Solution

(a) The reaction also proceeds by an *addition-elimination* mechanism:



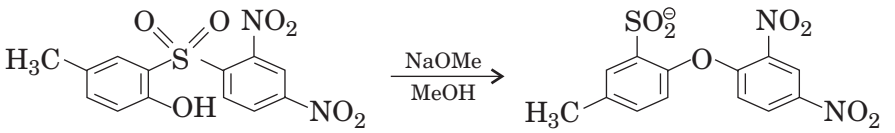
(b) The reaction also proceeds by an *addition-elimination* mechanism:



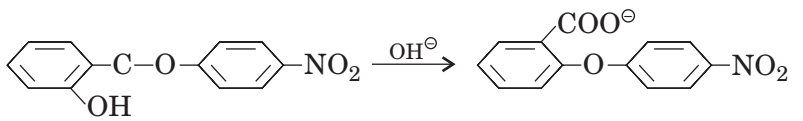
Study Problems

1. Hydroxide ion catalyzes the reaction of piperidine with 2,4-dinitroanisole but has no effect on the reaction of piperidine with 1-chloro-2,4-dinitrobenzene. Explain why $OH^{\ominus}$ ion plays different role in two reactions.
2. *p*-Fluoronitrobenzene is more reactive than *p*-chloronitrobenzene towards hydroxide ion. What does this observation tell about the rate-determining step for nucleophilic aromatic substitution (S_NAr).
3. When *o*-chlorotoluene is subjected to the conditions used in the Dow process (i.e. heating with aqueous NaOH at 350°C under high pressure), *o*- and *m*-cresols are obtained. What does this observation suggests about the mechanism of the Dow process.
4. Provide a reasonable mechanism for each of the following reactions:

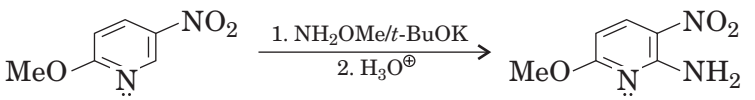
(a)



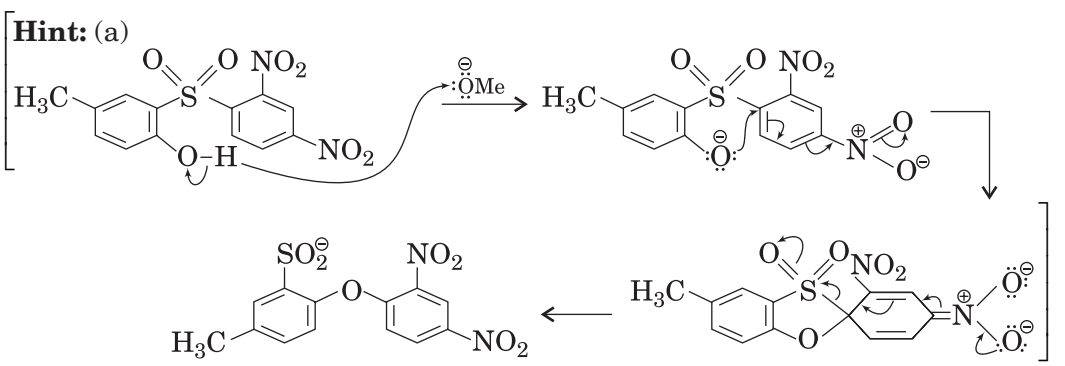
(b)



(c)



Hint: (a)



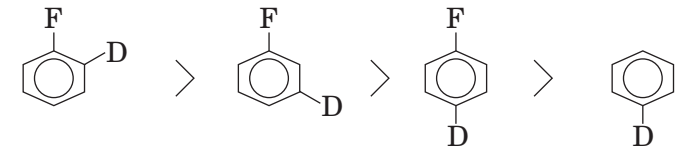
5. When a trace of potassium amide is added to a solution of chlorobenzene and potassium triphenylmethyl, $Ph_3C^{\ominus}K^{\oplus}$, in liquid ammonia, a rapid reaction occurs to give a product having molecular formula $C_{25}H_2O$. Predict the product. What is the role played by KNH_2 and why is it required?
[**Hint:** The product is Ph_4C ($C_{25}H_2O$).]

6. When diazotized 4-nitro-2-aminobenzoic acid is heated in *tert*-butyl alcohol, CO_2 and N_2 gases are released and *m*- and *p*-nitrophenyl *tert*-butyl-ethers are recovered. How do you account for this observation.

7. When either A or B is treated with $KNEt_2/NHEt_2$, there is obtained a good yield of a compound having molecular formula $C_9H_{11}N$. Identify the compound and show its formation.

o-$ClC_6H_4CH_2CH_2NHCH_3$ *m*-$ClC_6H_4CH_2CH_2NHCH_3$

8. In KNH_2/liq.NH_3, protium-deuterium exchange takes place at the following relative rates:

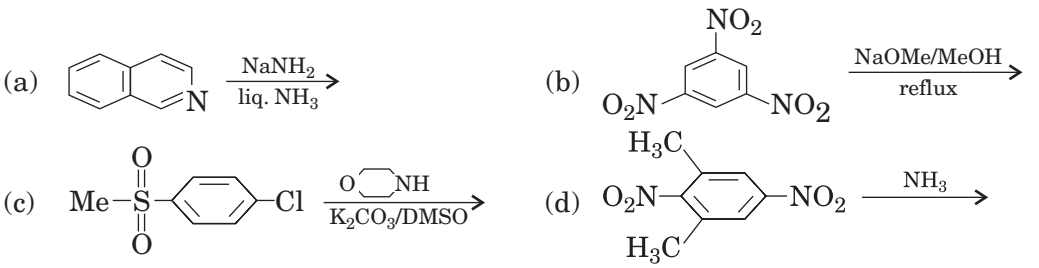


4000000 4000 200 1

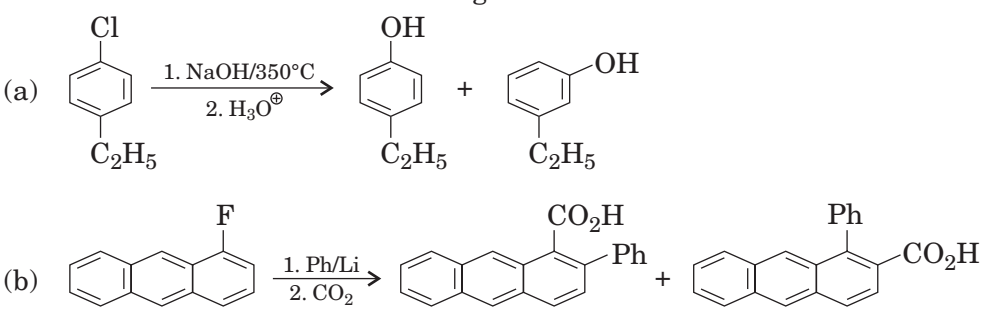
How do you account for this sequence of reactivity?

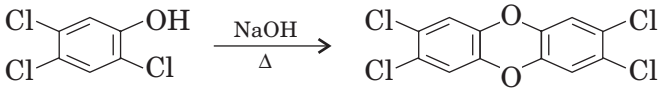
9. Reduction of 2,6-dibromobenzenediazonium chloride is expected to yield *m*-dibromobenzene. However, the reaction yields chiefly *m*-bromochlorobenzene. How do you account for this observation?

10. Predict the product and suggest a mechanism for each of the following reactions:

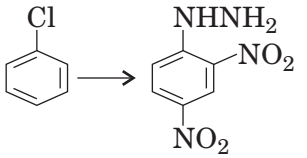


11. Provide mechanisms for the following reactions:

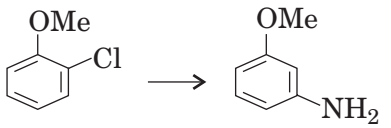


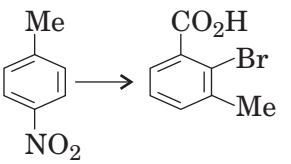
(c) 

12. How would you carry out the following transformation?

(a) 

(b) 

(c) 

(d) 

13. When 2,6-dideuteriofluorobenzene is treated with KNH_2 in liquid ammonia, aniline is not obtained. However, the deuterium atoms exchange with the hydrogen atoms of the solvent. Explain this result.

REFERENCES

1. R O C Norman and R Taylor, *Electrophilic Substitution in Benzenoid Compounds*; Elsevier : New York, 1965.
2. H J Ridd, "Mechanism of Nitration" ; Accts. Chem. Res. 1971, **4**, 248.
3. G A Olah, *Friedel- Crafts Chemistry*; Wiley : New York, 1973.
4. L M Stock, *Aromatic Substitution Reactions*, Prentice-Hall, Inc., Englewood Cliffs, NJ (1968).
5. J Miller, *Aromatic Nucelophilic Substitutions*, Elsevier Publishing Co., New York, (1968).
6. G H Williams, *Homolytic Aromatic Substitution*, Pergamon Press Inc., New York, (1960).
7. P B D *de la* Mare and J H Ridd., *Aromatic Substitution – Nitration and Halogenation*, Academic Press, New York, (1959).
8. L J Andrews and R M Keefer, Molecular Complexes in Organic Chemistry, Holden-Day, Sun Francisco, (1964).
9. D E Pearson and C A Bnchler, *Synthesis*, 455 (1971).
10. W R Hoffmann, *Dehydrobenzene and Cycloalkynes*; Academic: New York, 1967.
11. F Pietra, "Mechanism for Nucleophilic and Photonucleophilic Aromatic Substitution"; Quart. Revs. (London) 1969, **23**, 504.
12. P Y Bruce, *Organic Chemistry*, Third Edition, Pearson.
13. Francis A Carey, *Organic Chemistry*, Fifth Edition, McGraw Hill.
14. R K Parashar, *Reaction Mechanism in Organic Synthesis*, Wiley.
15. Peter Sykes, *The Search for Organic Reaction Pathways*, Longman.

4 CHAPTER

REARRANGEMENT REACTIONS

Chapter Outline

Introduction

4.1 1,2-Rearrangements

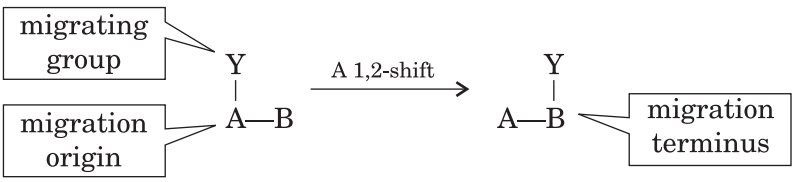
- 4.1.1 Nucleophilic Rearrangements to Electron Deficient Carbon
- 4.1.2 Nucleophilic Rearrangements to Electron Deficient Nitrogen
- 4.1.3 Nucleophilic Rearrangements to Electron Deficient Oxygen
- 4.1.4 Electrophilic Rearrangements

4.2 Non-1,2-Rearrangements

- 4.2.1 Favorskii Rearrangement
- 4.2.2 Hofmann–Martius Rearrangement
- 4.2.3 Orton Rearrangement
- 4.2.4 Fries Rearrangement
- 4.2.5 Benzidine Rearrangement
- 4.2.6 Claisen Rearrangement
- 4.2.7 Cope Rearrangement

INTRODUCTION

In majority of organic reactions, the basic skeletons of molecules remain unchanged though there occurs change in functional groups. However, there are some organic reactions which involve change in the basic skeleton of the molecules. These are called *rearrangement reactions*, and since they are accompanied with the migration of an atom or a group within the molecule, they are also called *molecular rearrangements.* Most are migrations from an atom to an adjacent one (called 1,2-shift), but some are over longer distances. The atom from which the group migrates is known as migration origin and the atom to which it migrates is termed as migration terminus. For example, in the conversion of Y–A–B to A–B–Y, Y is the migrating group. A and B are the migration origin and the migration terminus, respectively.

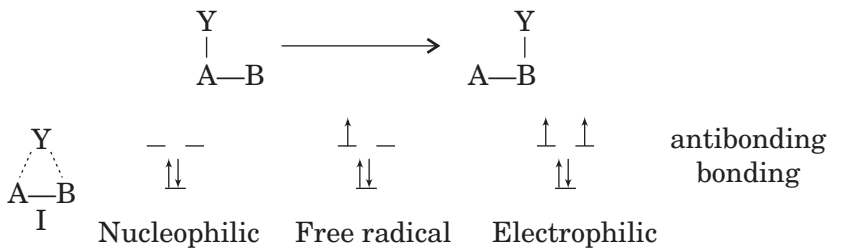


However, the migrating group may either be an anion or a cation or a free radical and accordingly the rearrangement reactions are broadly classified as:

1. *Nucleophilic* or *aninotropic rearrangements* (where the migrating group moves with its bonding electrons, i.e. moves as an anion to an electron deficient centre).
2. *Electrophilic* or *cationotropic rearrangements* (where the migrating group moves without its bonding electrons, i.e. moves as a cation to an electron rich centre); in the case of migrating hydrogen, *prototropic rearrangements.*
3. *Free radical rearrangements* (where the migrating group moves with just one electron). These are relatively less common.

Apart from these, there is another class of rearrangement reactions, where the cleavage and formation of σ bonds occur simultaneously through cyclic transition state. These are called *sigmatropic rearrangements.* These are actually pericyclic rearrangements which occur with conservation of orbital symmetry by the action of heat or light with or without inert solvent. Another type of pericyclic rearrangements is called *electrocyclic rearrangements.*

Nucleophilic 1,2-shifts are much more common than electrophilic or free radical 1,2-shifts. This can be explained as follows:



Let us consider the transition states (or in some cases, intermediates) involved. The transition state or intermediate for all the three cases can be represented by I, in which the two-electron A–Y bond overlaps with the orbital on atom B, which contains zero, one and two electrons, in the case of nucleophilic, free radical and electrophilic migration, respectively. The overlap of these orbitals gives rise to three new orbitals (one bonding and two degenerate antibonding orbitals). In a nucleophilic migration, where only two electrons are involved, both can go into the bonding orbital and I is a low-energy transition state; but in a free radical or electrophilic migration, there are, respectively, three or four electrons that must be accommodated and, therefore, antibonding orbitals must be occupied. This causes the transition states to be less stable. For this reason, nucleophilic

1,2-shifts are much more common than electrophilic or free radical 1,2-shifts. Therefore, it is not surprising that, when 1,2-electrophilic or free radical shifts are found, the migrating group Y is usually aryl or some other group that can accommodate the extra one or two electrons and thus effectively removes them from the three-membered T.S. or intermediate.

In any rearrangement, there are two possible modes of reaction. The rearrangements in which the group Y becomes completely detached from A and may end upon the B atom of a different molecule are called *intermolecular rearrangements* and the rearrangements in which Y goes from A to B in the same molecule without detaching itself completely from the molecule, i.e. the rearrangements in which there must be some continuing tie holding Y to the A–B system, preventing it from becoming completely free are called *intramolecular rearrangements.* Strictly speaking, only the intramolecular type fits our definition of a rearrangement, but the general practice is to include under the title "rearrangement" all net rearrangements irrespective of their intra- or intermolecular nature. The actual course of migration, i.e. whether the rearrangement is intramolecular or intermolecular can easily be determined by using crossover experiments. In this type of experiment, rearrangement is carried out on a mixture of Y–A–B and Z–A–C, where Z is closely related to Y (say, -Me vs –Et) and B to C. If only A–B–Y and A–C–Z are recovered, the reaction is intramolecular, but if A–B–Z and A–C–Y are recovered along with A–B–Y and A–C–Z, the reaction is intermolecular.

In nucleophilic or anionotropic rearrangement, the electron deficient migration terminates in common cases (i) electron-deficient carbon, (ii) electron-deficient nitrogen and (iii) electron-deficient oxygen.

4.1 1,2-REARRANGEMENTS

4.1.1 Nucleophilic Rearrangements to Electron Deficient Carbon

4.1.1.1 Wagner–Meerwein rearrangement

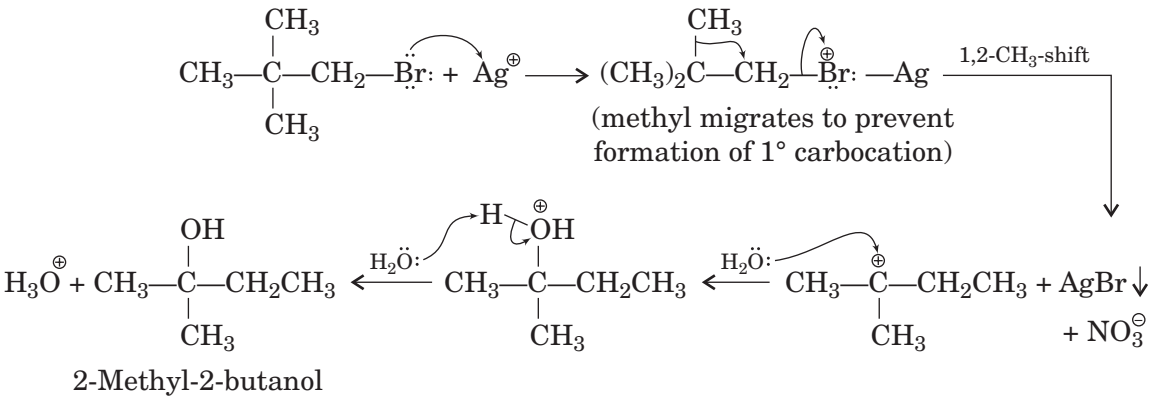
Wagner–Meerwein rearrangement was originally proposed to explain the skeletal rearrangements in bicyclic terpenes (e.g. conversion of isoborneol to camphene). G. Wagner and H. Meerwein revealed the ionic nature of this rearrangement and explain this rearrangement on the basis of carbocation generation during the course of the reactions and their stabilities. According to them, an initial carbocation, if it is less stable, would immediately rearranges to a more stable carbocation through a 1,2-shift of an adjacent carbon-carbon bond of a cyclic system, an alkyl group, or an aryl group. All such reactions involving the change in carbon skeleton through the rearrangement of carbocation intermediates are collectively known as *Wagner–Meerwein rearrangements*.

Example: Solvolysis of neopentyl bromide (1-bromo-2,2-dimethylpropane) in water containing $AgNO_3$ leads to the formation of 2-methyl-2-butanol instead of expected neopentyl alcohol (2,2-dimethyl-1-propanol). Thus, the solvolysis of neopentyl bromide does not take a normal course.

$$(CH_3)CCH_2OH \xleftarrow{H_2O,\ AgNO_3} (CH_3)_3CCH_2Br \xrightarrow{H_2O,\ AgNO_3} (CH_3)_2C(OH)CH_2CH_3$$

Neopentyl alcohol — Neopentyl bromide — 2-Methyl-2-butanol

Mechanism: The reaction proceeds through the steps as follows:



2-Methyl-2-butanol

The silver ion coordinates with Br atom and causes ionization of the alkyl bromide (electrophilic catalysis). Due to very unstable nature, the expected 1° carbocation is not formed. A simultaneous migration of a methyl from the β-carbon leads to the formation of a stable 3° carbocation which then reacts with water to give 2-methyl-2-butanol.

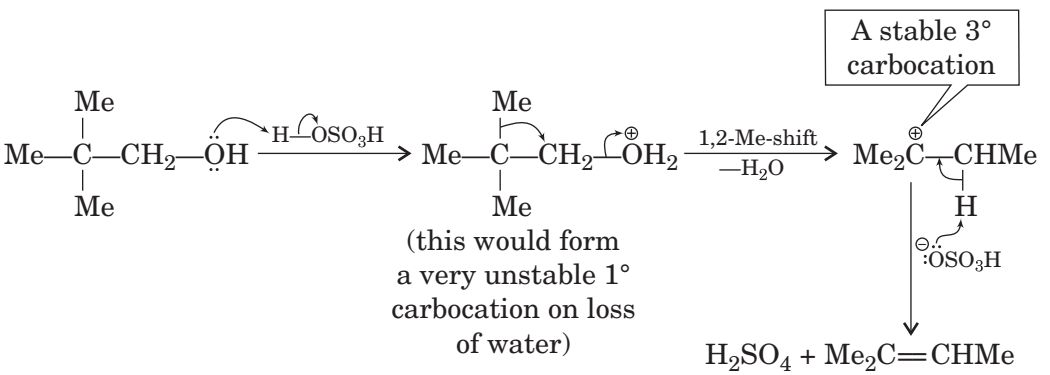
Some other cases of Wagner-Meerwein rearrangement (classified in terms of the migrating group):

1. Migration of alkyl group

(a) *Acid-catalyzed dehydration of alcohol*

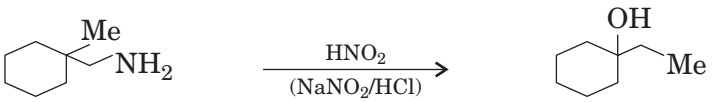
$$\underset{\text{Neopentyl alcohol}}{Me_3CCH_2OH} \xrightarrow[(H_2SO_4)]{H^{\oplus}} \underset{\text{2–Methylbut–2–ene}}{Me_2C{=}CHMe} + H_2O$$

Mechanism:



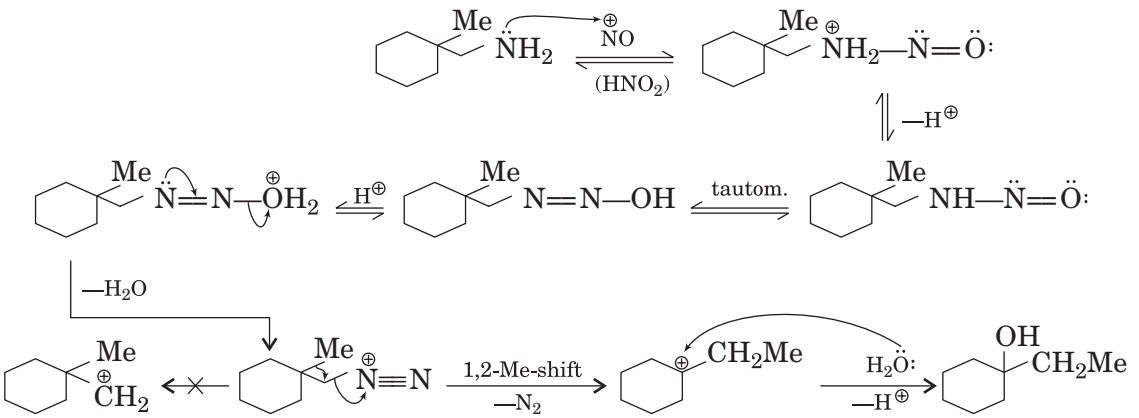
When neopentyl alcohol is treated with concentrated H_2SO_4, water is eliminated not to form an unstable 1° carbocation ($Me_3C\overset{\oplus}{C}H_2$) but to form a stable 3° carbocation by simultaneous Me-shift. Loss of a proton from the tertiary carbocation results in formation of 2-methylbut-2-ene.

(b) *Deamination of aliphatic amines by treating with nitrous acid*



1-Methylcyclohexylmethylamine 1-Ethyl-1-cyclohexanol

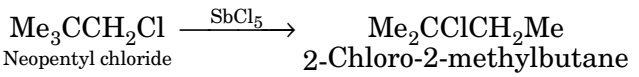
Mechanism:



A 3° carbocation (stable)

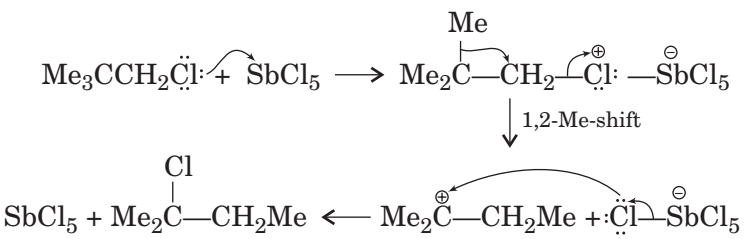
When this primary amine is treated with nitrous acid ($NaNO_2$/HCl), it undergoes diazotization. The resulting aliphatic diazonium cation is very unstable. So, it readily loses N_2 not to form the corresponding unstable 1° carbocation but to form a very stable 3° carbocation by simultaneous Me-shift. The carbocation then reacts with water to form the corresponding 3° alcohol.

(c) *Isomerization of neopentyl chloride in the presence of the Lewis acid $SbCl_5$*



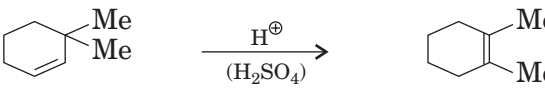
Neopentyl chloride 2-Chloro-2-methylbutane

Mechanism:



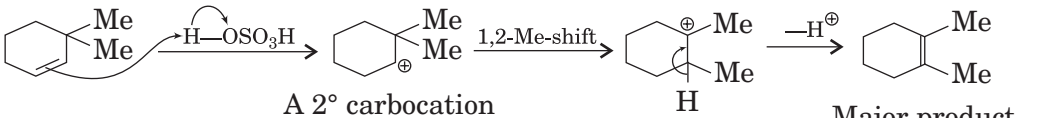
The Cl atom of neopentyl chloride coordinates with the Lewis acid $SbCl_5$ to form a complex. The complex dissociates not to form the unstable 1° carbocation $Me_3C\overset{\oplus}{C}H_2$ but to form a very stable 3° carbocation $Me_2\overset{\oplus}{C}CH_2Me$ by simultaneous migration of methyl. The resulting 3° carbocation then undergoes nucleophilic attack by $Cl^{\ominus}$ originated from $SbCl_6^{\ominus}$ to form an isomer of the starting chloride.

(d) *Acid-catalyzed isomerization of alkenes*



3,3-Dimethylcyclohexene 1,2-Dimethylcyclohexene

Mechanism:



A 2° carbocation (less stable)

A 3° carbocation (more stable)

Major product (more stable due to more substituted C═C)

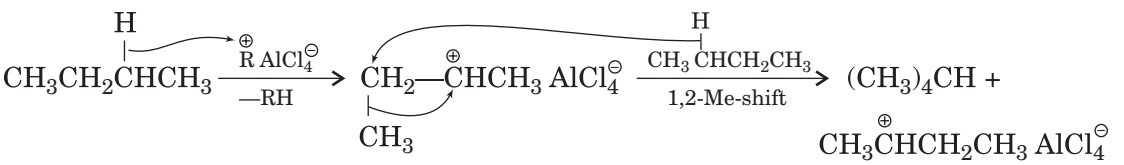
The alkene undergoes protonation to give a relatively less stable 2° carbocation which subsequently rearranges by 1,2-Me-shift to form a more stable 3° carbocation. Loss of a proton then takes place to yield 1,2-dimethylcyclohexene as the major product because it contains more substituted double bond and thermodynamically more stable.

(e) *Isomerization of alkanes in the presence of Lewis acid and a catalytic amount of alkyl halide*

$$\underset{\text{Butane}}{CH_3CH_2CH_2CH_3} \xrightarrow{RCl/AlCl_3} \underset{\text{2-Methylpropane}}{(CH_3)_3CH}$$

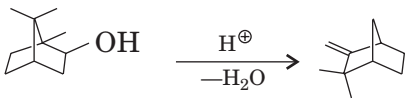
Mechanism: The transformation involves formation of a 2° carbocation $(CH_3CH_2\overset{\oplus}{C}HCH_3$ by expulsion of a hydride ion from the starting alkane under the influence of the carbocation ($R^{\oplus}$) formed by the reaction of RCl and $AlCl_3$. It then undergoes 1,2-migration of CH_3-group with simultaneous transfer of a hydride ion from new molecule of butane to avoid formation of a 1° carbocation.

$$R—\ddot{Cl}: + AlCl_3 \rightleftharpoons R—\overset{\oplus}{\ddot{Cl}}: —\overset{\ominus}{Al}Cl_3 \longrightarrow \overset{\oplus}{R}\,AlCl_4^{\ominus}$$



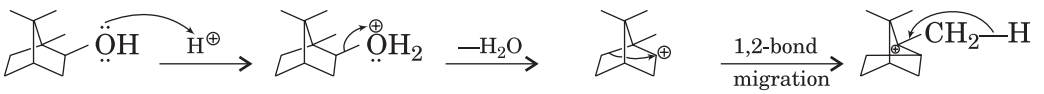
2. Migration of C–C σ-bond

(a) *Isoborneol undergoes acid-catalyzed dehydration to yield camphene*

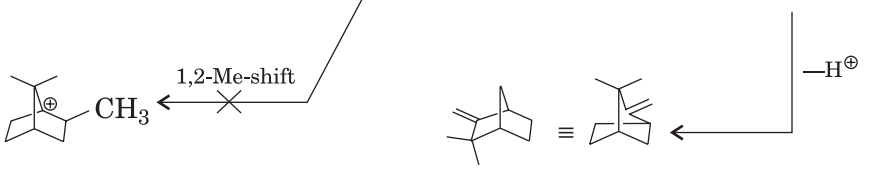


Isoborneol Camphene

Mechanism:



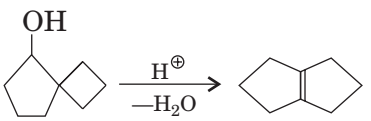
Isoborneol A 2° carbocation (less stable) A 3° carbocation (more stable)



An unstable bridgehead carbocation Camphene

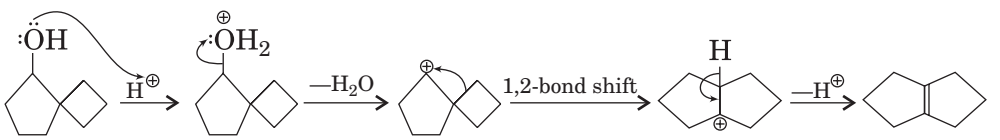
The initially formed less stable 2° carbocation undergoes rearrangement not by methyl shift to form a less stable bridgehead carbocation (which suffers from angle strain and cannot be stabilized by hyperconjugation violating Bredt's rule) but by bond migration to give a more stable 3° carbocation. This on proton loss produces camphene.

(b)



This spirocyclic alcohol undergoes acid-catalyzed dehydration to yield a bicyclic alkene.

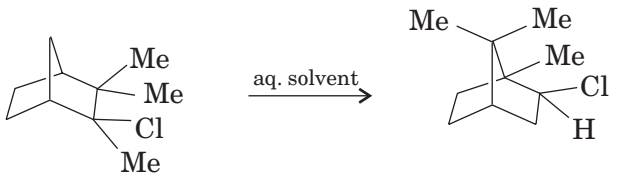
Mechanism:



A 2° carbocation (less stable) A 3° carbocation (more stable)

Protonation of the alcohol followed by loss of a molecule of water produces a less stable 2° carbocation. This 2° carbocation then rearranges to give a relatively more stable 3° carbocation. Relief of strain in expansion from a four-to-five membered ring facilitates this rearrangement process. Loss of proton leads to the formation of a more susbstituted alkene as it is thermodynamically more stable.

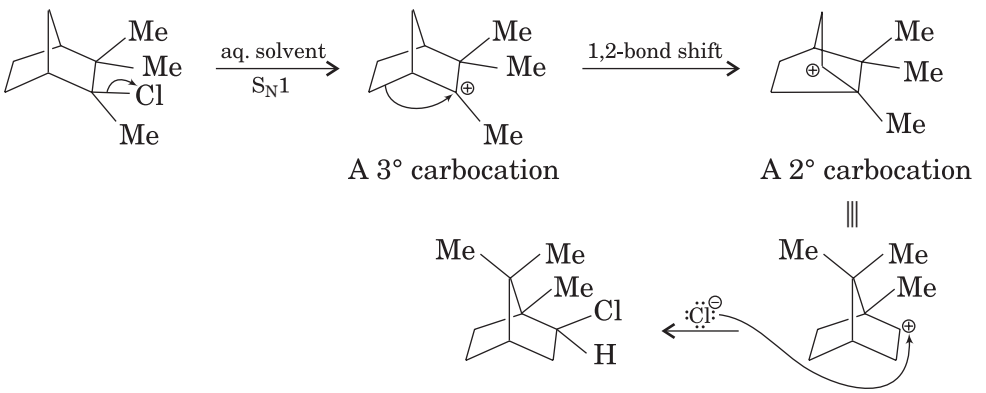
(c)



Camphene hydrochloride Isobornyl chloride

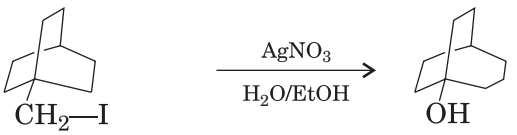
When camphene hydrochloride is treated in aqueous solvent, it isomerizes to yield isobornyl chloride.

Mechanism:



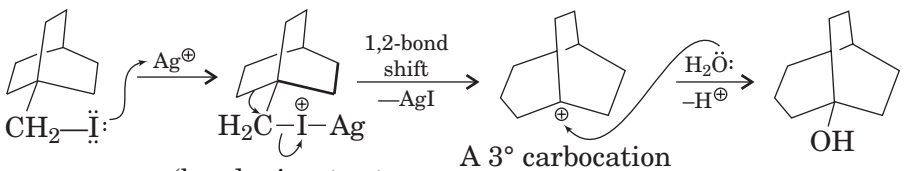
Relief of steric strain involving *endo* methyl at C-3 and the *endo* hydrogen at C-5 makes the bond migration favourable, even though a 3° carbocation is converted to a 2° carbocation in the rearrangement step. The resulting carbocation then combines with $Cl^{\ominus}$ ion to yield isobornyl chloride, in which chlorine is *exo*, due to the same steric reason.

(d)



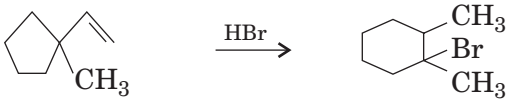
When the iodoalkane is treated with H_2O/EtOH in the presence of $AgNO_3$, it undergoes ring expansion to yield a bicyclic alcohol in which the –OH group is attached to the bridgehead carbon.

Mechanism:



(bond migrates to prevent formation of unstable 1° carbocation)

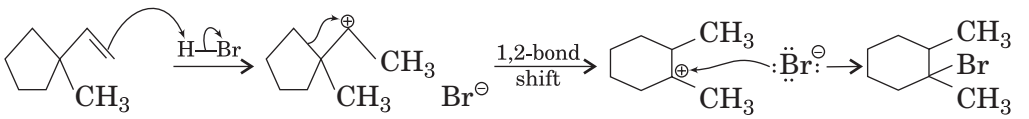
The silver ion coordinates with I atom and causes ionization of the alkyl iodide. Due to very unstable nature of the expected 1° carbocation, it is not formed. A simultaneous migration of a σ-bond leads to the formation of a relatively stable 3° carbocation which subsequently reacts with water to yield the alcohol.

(e) 

1-Methyl-1-vinylcyclo-pentane — 1-Bromo-1,2-dimethyl-cyclohexane

When this alkene is treated with HBr, it undergoes ring expansion to give a bromocyclohexane.

Mechanism:



A 2° carbocation (less stable) — A 3° carbocation (more stable)

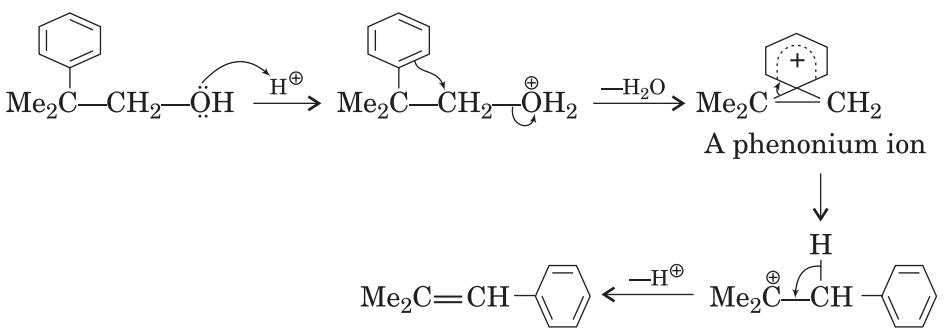
Addition of $H^{\oplus}$ to the double bond occurs to form a more stable 2° carbocation instead of a 1° carbocation. Bond migration instead of methyl migration then occurs because this leads to the formation of a relatively stable six-membered ring.

3. Migration of aryl group

$$\underset{\text{2-Methyl-2-phenyl-1-propanol}}{PhCMe_3CH_2OH} \xrightarrow[-H_2O]{H^{\oplus}} \underset{\text{2-Methyl-1-phenylpropene}}{Me_2C{=}CHPh}$$

This 1° alcohol undergoes acid-catalyzed dehydration involving migration of a phenyl group to yield an alkene.

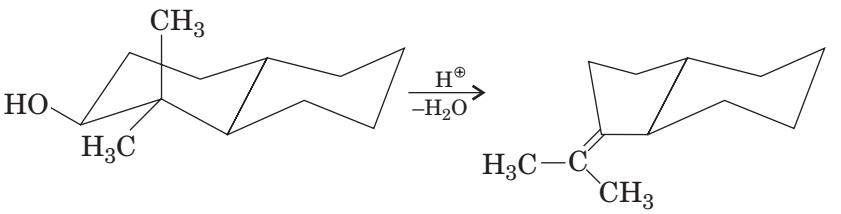
Mechanism:



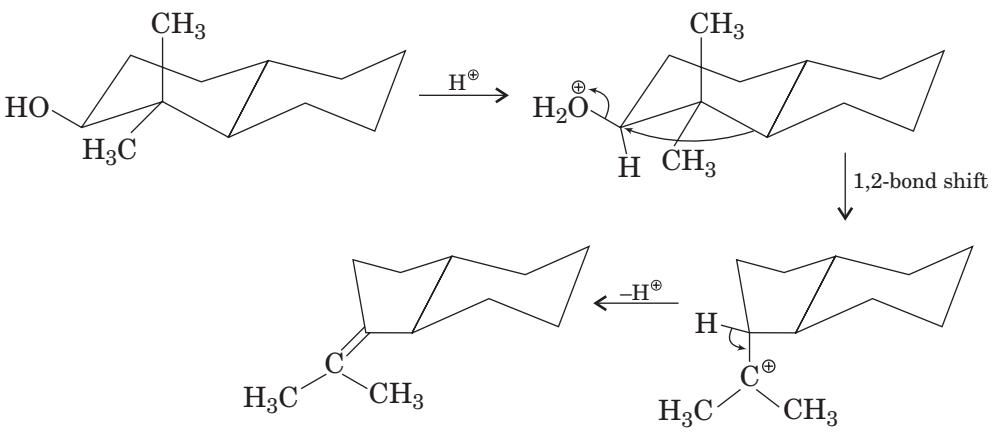
The conjugate acid of the starting 1° alcohol undergoes intramolecular nucleophilic attack on the carbon bearing the good leaving group $-\overset{\oplus}{O}H_2$ by the phenyl group (a case of neighbouring group participation) to form a low-energy (stable) intermediate. The phenyl group being an electron-rich system has a far greater migratory aptitude than the methyl group. During migration (1,2-shift) the phenyl group provides anchimeric assistance to make the reaction fast. In step 3, the phenonium ion undergoes C—C bond cleavage to form a stable 3° carbocation which produces the alkene on proton loss.

Characteristic features of 1,2-anionotropic or nucleophilic rearrangements:

1. Stereospecific migration occurs in such rearrangements, i.e. the leaving group and the migrating species should be stereochemically *anti* to each other. This has been observed in the following example.

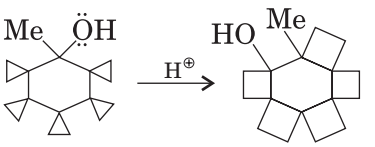


Mechanism:

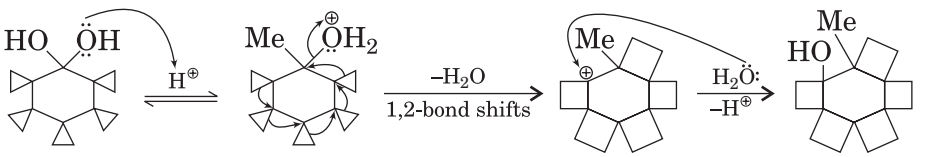


In a cyclohexane system, the migrating group approaches the carbon bearing the leaving group from the direction opposite to that of the leaving group. An equatorial group can only be *trans* and coplanar with a ring residue. Therefore, when the rigid (cannot flip) *trans* 2-decalol derivative is treated with acid, a particular ring residue (carbon atom of ring junction) migrates to give a 3° carbocation. The carbocation on proton less produces the thermodynamically stable more substituted alkene.

2. The rearrangement may often be simultaneous as observed in the following isomerization reaction:



Mechanism:



4.1.1.2 Hydride shift

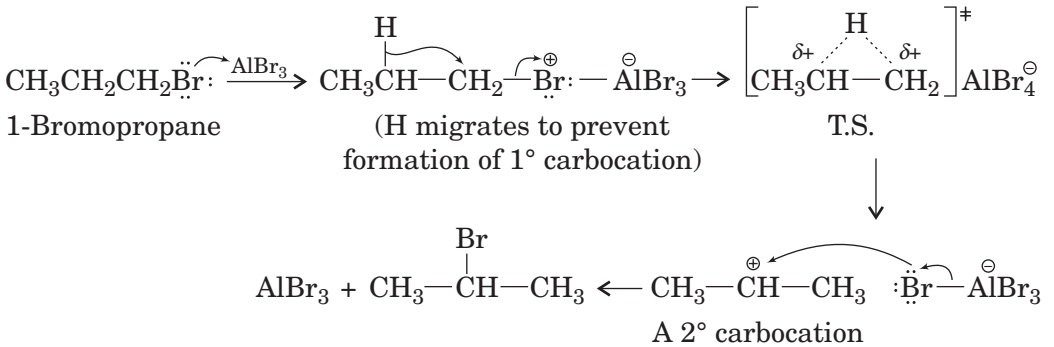
Migration of hydrogen as anion ($:H^{\ominus}$) is called hydride shift.

(a) *1, 2-Hydride shift*

Due to the same basic reason, 1, 2-hydride shift, similar to 1,2-migration of alkyl and aryl group, is also a very common event. For example:

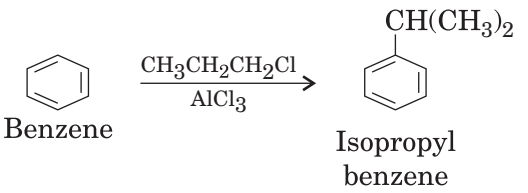
(i) When 1-bromopropane is treated with the Lewis acid $AlBr_3$, it undergoes isomerization to yield 2-bromopropane.

Mechanism:

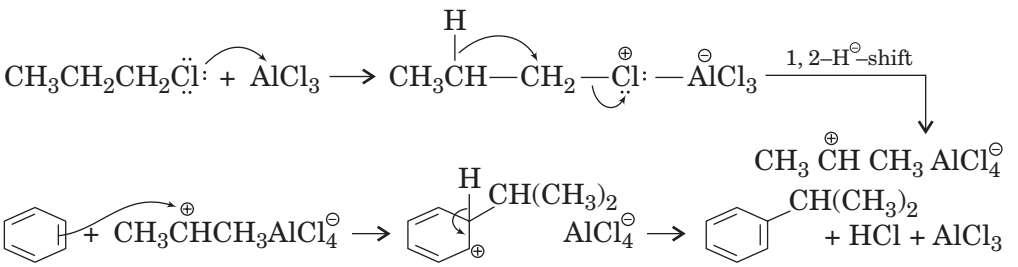


The complex formed by coordination of bromine with the Lewis acid $AlBr_3$ dissociates not to give a very unstable 1° carbocation but to give a relatively stable 2° carbocation by $H^{\ominus}$-shift. $Br^{\ominus}$ from $AlBr_3$ then attacks the carbocation to form 2-bromopropane.

(ii) The unexpected major product in some Friedel–Crafts alkylation reaction can be explained by the isomerization of the alkyl group involving 1,2-hydride shift. For example, in the following reactions, isopropyl benzene is obtained as the major product instead of *n*-propylbenzene.



Mechanism:

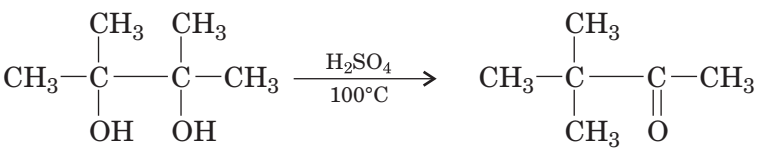


(b) *Long range hydride shift*

Although the hydride shift beyond 1,2, is rare along a chain but it may also take over a longer distance across a ring (transannular hydride shift).

4.1.1.3 Pinacol rearrangement

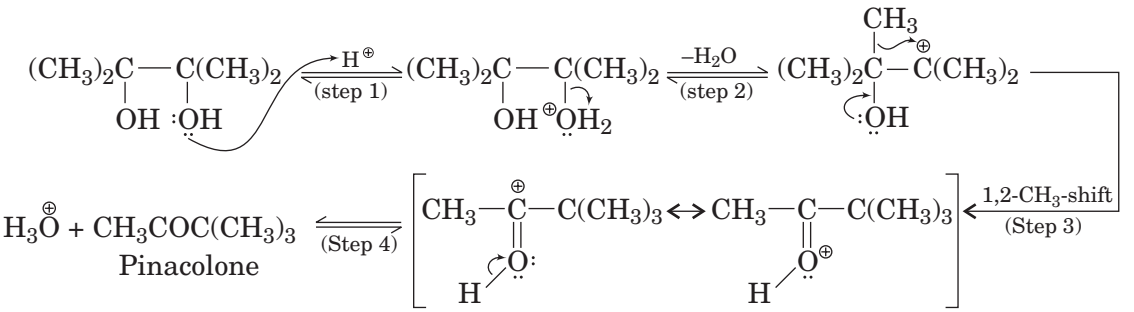
When acyclic and cyclic 1,2- or *vic*-diols (also known as glycols) are treated with acids (H_2SO_4 or H_3PO_4), they undergo a facile dehydrative rearrangement involving 1,2-alkyl, aryl or hydride shift to produce ketones or aldehydes. These rearrangements are called *pinacol* or *pinacol–pinacolone rearrangements*. The most well-known example of the reaction is the acid-catalyzed conversion of pinacol (2,3-dimethylbutane-2,3-diol) to pinacolone (3,3-dimethylbutane-2-one). Hence, the name of the reaction is given *pincol* or pinacol–pinacolone rearrangement.



2,3-Dimethylbutane-2,3-diol (Pinacol)

3,3-Dimethylbutan-2-one (Pinacolone)

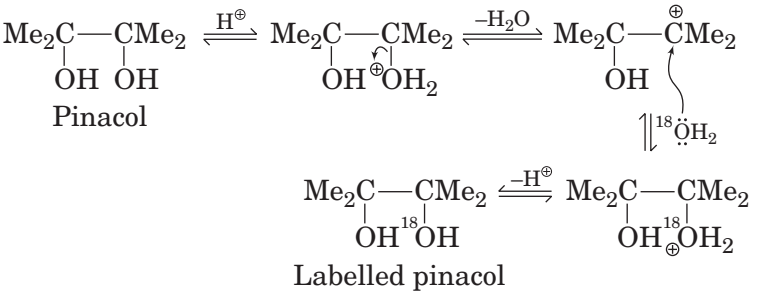
Mechanism of the reaction The mechanism of the reaction involves the steps as follows:



In step 1, pinacol undergoes reversible protonation of one hydroxyl group to give an oxonium ion. In step 2, the oxonium ion loses a molecule of water to form a stable 3° carbocation. This is the rate-determining (slow) step of the reaction. In step 3, a methyl group migrates (a 1,2-shift) to form a resonance-stabilized carbocation which is, in fact, the conjugate acid of pinacolone. The extra stability of the new 3° carbocation is the driving force for the rearrangement. The migrating methyl group begins to attach itself to the positive carbon before separating from its original position, i.e. it never becomes detached from the substrate skeleton and, therefore, the rearrangement is an intramolecular one. In step 4, the conjugate acid of pinacolone loses a proton to form pinacolone.

Some relevant topics

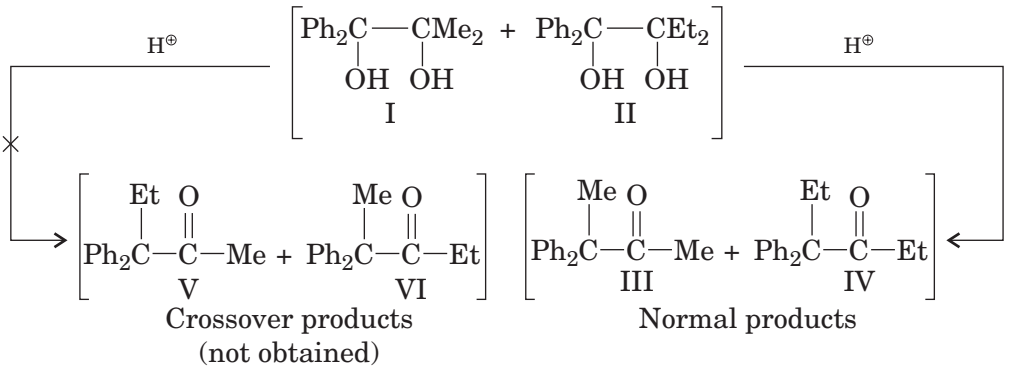
1. *Evidence for the intermediacy of carbocation:* That the rearrangement involves the formation of a carbocation can be proved by the following experiment. When pinacol is treated with acid in $H_2{}^{18}O$ solution, the recovered unrearranged pinacol is found to contain the ^{18}O isotope. This observation, therefore, suggests that this rearrangement involves reversible formation of a carbocation.



2. *Evidence for the intramolecular nature of the rearrangement:* The intramolecular nature of the rearrangement can be established by a crossover experiment and by a labelling experiment.

(a) *Crossover experiment:* When the following two pinacols I and II (that are similar in structure and that rearrange separately at comparable rates) are subjected to rearrange together in the same solution, only the normal rearrangement products

III and IV are obtained. The mixed (crossover) products V and VI are not obtained. This observation suggests that the migrating group never becomes free, i.e. it does not become detached from the rest of the molecule during rearrangement. Hence, the rearrangement is intramolecular in nature.



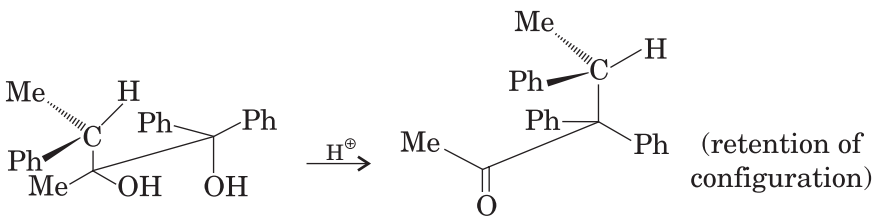
(b) *Labelling experiment:* When the following pinacol rearrangement involving a hydride transfer is carried out in D_2O, no deuterium is found to be incorporated in the final rearranged product. This observation also proves that the rearrangement is strictly intramolecular.

$$(p\text{-}CH_3OC_6H_4)_2CD-CHO \xleftarrow[D_2O]{H^{\oplus}} (p\text{-}CH_3OC_6H_4)_2C(OH)\,CH_2OH \xrightarrow[D_2O]{H^{\oplus}} (p\text{-}CH_3OC_6H_4)_2CH-CHO$$

(not obtained)

[If the $H^{\ominus}$ ion becomes free, it may equilibrate with D_2O and the resultant $D^{\ominus}$ ion may then add to the positive carbon to give $(p\text{-}CH_3OC_6H_4)_2CDCHO$.]

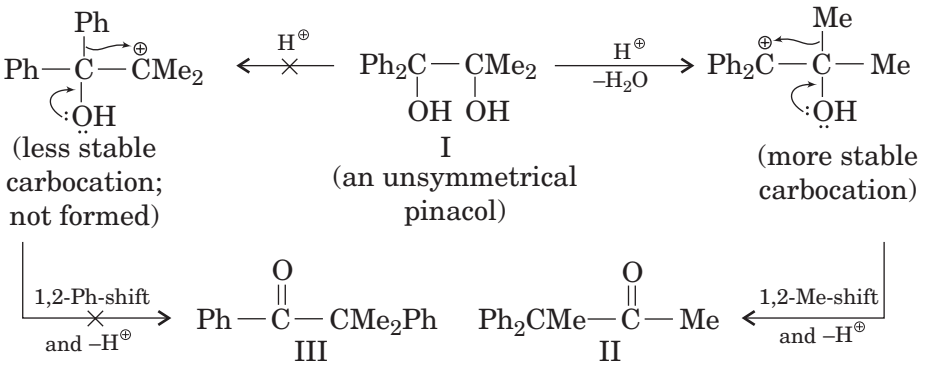
(c) When the migrating group is chiral, it migrates with retention of configuration. For example:



Retention of configuration at the migrating chiral centre indicates that the group never becomes detached from the rest of the molecule, i.e. the rearrangement is intramolecular.

3. *Loss of hydroxyl group as water:* Any of the two –OH groups may be lost as water from a symmetrical pinacol like RRC(OH)C(OH)RR or RR′C(OH)RR′ because the same carbocation is formed no matter which hydroxyl group leaves. However, in the case of an unsymmetrical pinacol [RRC(OH)C(OH)R′R′], that hydroxyl group leaves whose

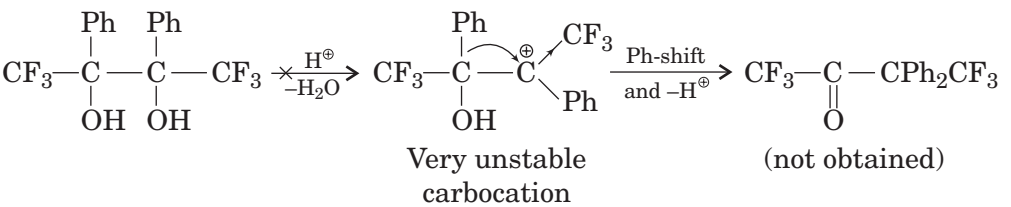
expulsion leads to the formation of a more stable carbocation. For example, 2-methyl-1, 1-diphenylpropane-1,2-diol(1) gives 3,3-diphenylbut-2-one (ii) instead of 2-methyl-1,2-diphenyl-1-propanone.



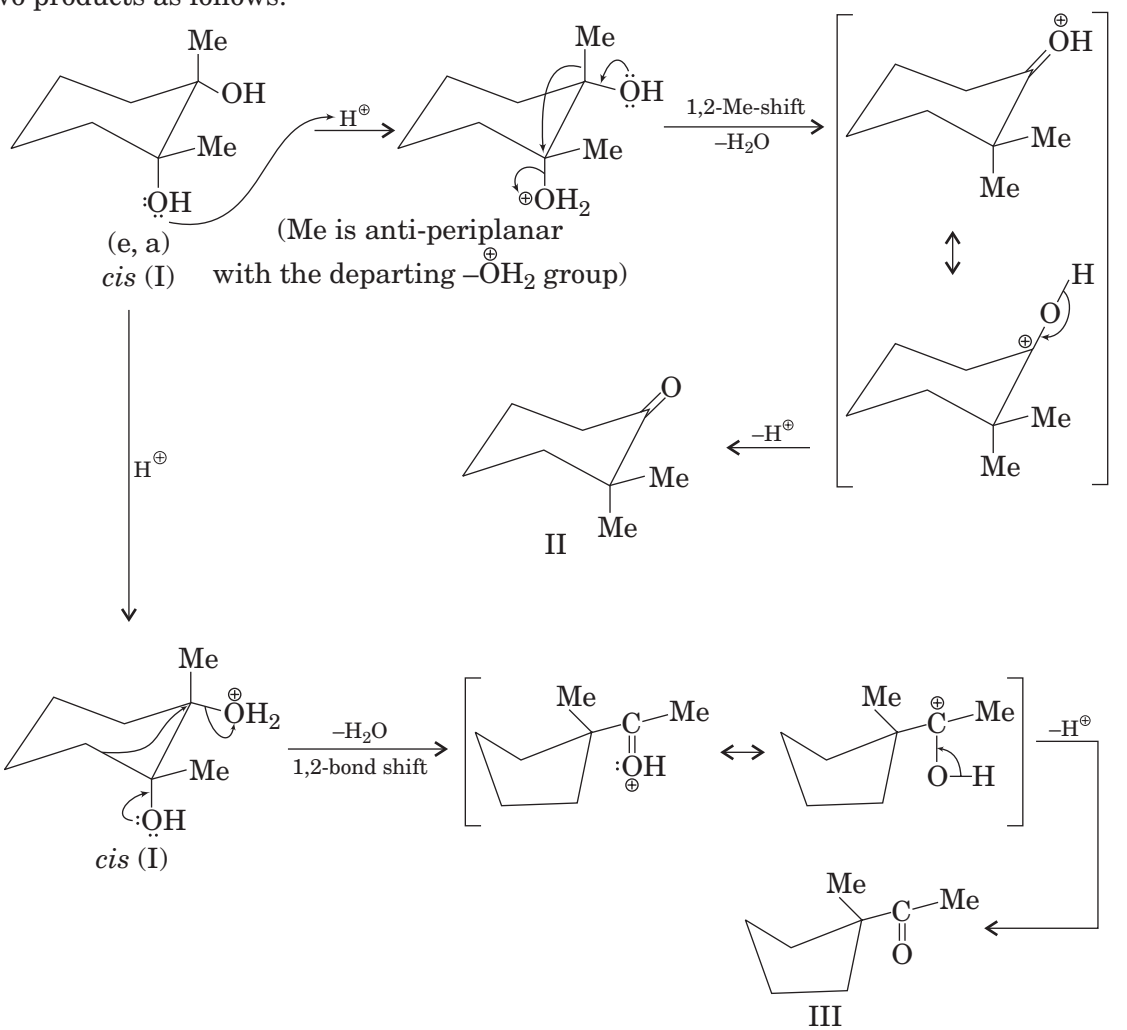
4. *Relative migratory aptitude of the migrating groups:* The ease with which a particular group will undergo nucleophilic 1,2-shift is known as its migratory aptitude. If the two groups at the migration origin are different, a competition arises between the groups for migration. Since it is a case of nucleophilic migration, the group which is more electron-rich preferentially migrates. The migrating tendency of a group sometimes depends on its position in the most stable conformation of the molecule and also on whether the group that does not migrate is better at stabilizing the carbocation generated on the migration origin. The migratory aptitude of aryl is greater than alkyl. However, the migratory aptitude of hydrogen is often unpredictable. In some cases, its migration is preferred to that of aryl and in other cases, migration of alkyl is preferred to that of hydrogen. Among the aryl migrating groups, electron-donating substituents in the *para* and *meta* positions increase the migratory aptitudes, while the same substituents in the *ortho* positions decrease them. Electron-withdrawing groups decrease migratory aptitude in all positions. In general, the relative ease of migration is found to be

$$p\text{-MeOC}_6\text{H}_4\text{–} \gg p\text{-MeC}_6\text{H}_4\text{–} \gg m\text{-MeOC}_6\text{H}_4\text{–} \gg \text{C}_6\text{H}_5\text{–} \ll p\text{-ClC}_6\text{H}_4\text{–} \gg$$
$$o\text{-MeOC}_6\text{H}_4\text{–} \gg \text{H} \ll \text{Me}_3\text{C–} \gg \text{Me}_2\text{CH–} \gg \text{MeCH}_2\text{–} \gg \text{Me–}$$

5. *Unreactive nature of 1,2-diols containing strong electron-withdrawing group:* The diol $F_3CPhC(OH)C(OH)PhCF_3$ containing strong electron-withdrawing $–CF_3$ group does not undergo pinacol rearrangement and this is because the $–CF_3$ group highly disfavours the formation of a carbocation. In fact, by intensifying the positive charge, it destabilizes the carbocation and thereby increases the energy of activation of the rate-determining step.

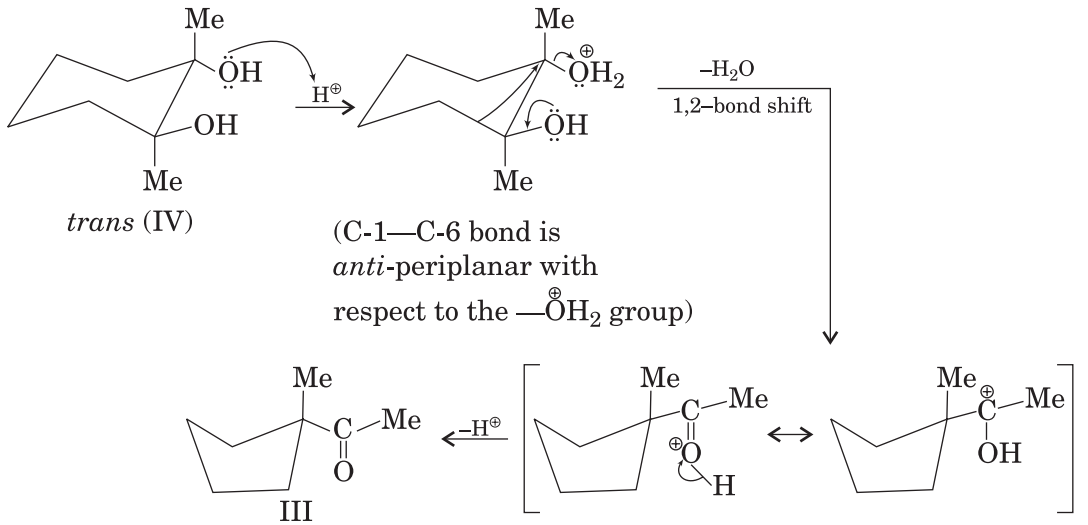


6. *The rearrangement is stereospecific and involves migration of the group which is stereochemically anti to the departing* $-\overset{\oplus}{O}H_2$ *group:* The rearrangement occurs in an *anti*-manner and a C—C σ-bond may also play the role of migrating group if there is no alkyl and aryl group with right geometry at the migration origin. For example, *cis*-1, 2-dimethylcyclohexane-1,2-diol(I) undergoes acid-catalyzed pincol rearrangement to give, two products as follows:

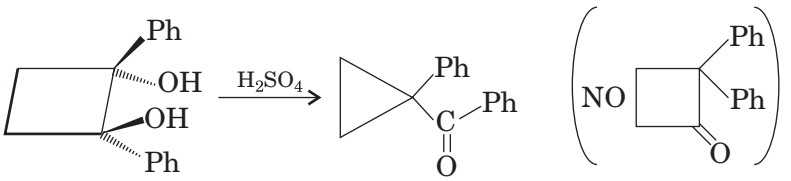


When the axial –OH-group leaves, the axial methyl group on the adjacent carbon migrates to give 2,2-dimethylcyclohexanone (II). However, when the equatorial –OH leaves, bond migration occurs to yield 1-acetyl-1-methylcyclopentane (III).

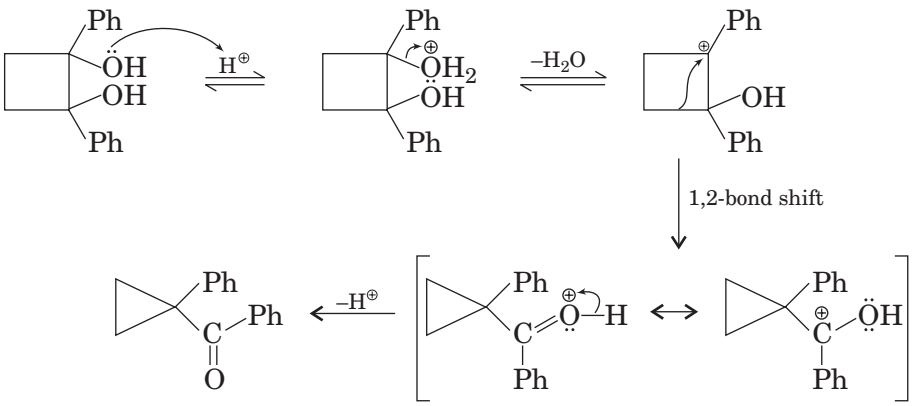
Because of intramolecular hydrogen bonding, the *trans*-isomer (IV) exists almost entirely in the form in which the two –OH groups are equatorial. So, it reacts through this conformational isomer to yield the ring-contracted product III.



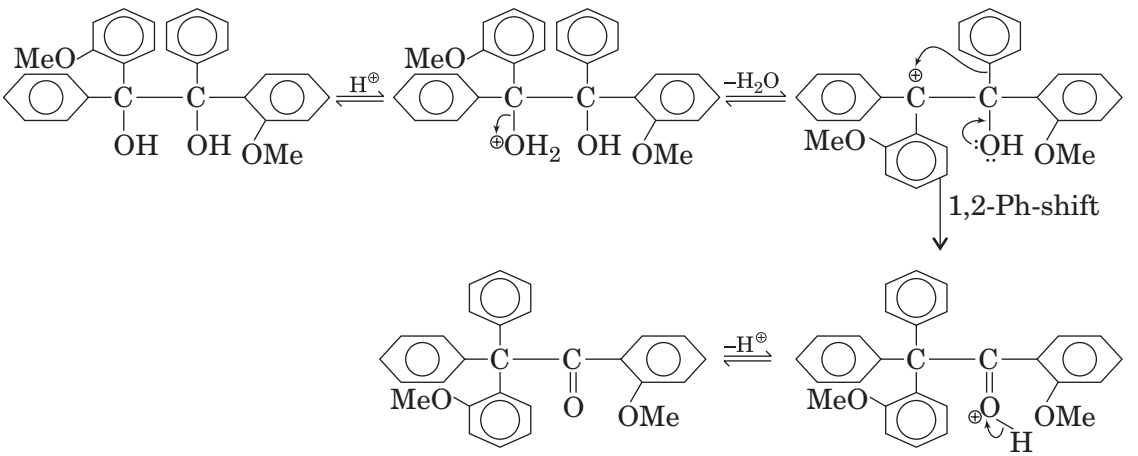
7. *An unusual pinacol rearrangement (a strained ring contracts to an even smaller ring):* The following pinacol rearrangement is an unusual case in which strained four-membered ring contracts to an even smaller three-membered ring.



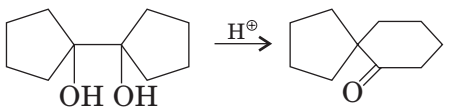
The phenyl group possesses a high migratory aptitude, so the failure to obtain 2,2-diphenylcyclobutanone as a product might seem surprising. However, the carbocation obtained as a result of a phenyl shift would be just as strained as its precursor, but shifting of a ring methylene group, i.e. C—C σ-bond shift, generates an unstrained cation which is resonance stabilized by the phenyl and oxygen substituents. The absence of sp^2-hybridized carbon atom in the small ring may also contribute to the stability of the observed product. The mechanism of the reaction may be given as follows:



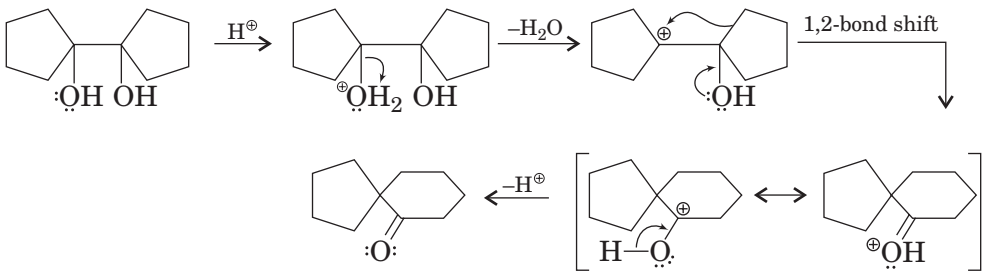
8. *Steric factor often plays the deciding role in product formation:* In the following example, the *o*-methoxyphenyl group is expected to have greater migratory aptitude from electronic point of view. But, because of steric reason, its migratory aptitude is less than phenyl. In fact, the migration of *o*-$MeOC_6H_4$-group causes large steric interaction in the would be product. Therefore, in this case phenyl migration takes place predominantly.

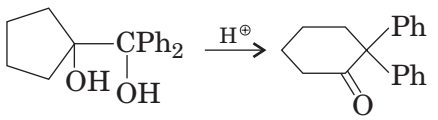


Some typical examples of pinacol rearrangement

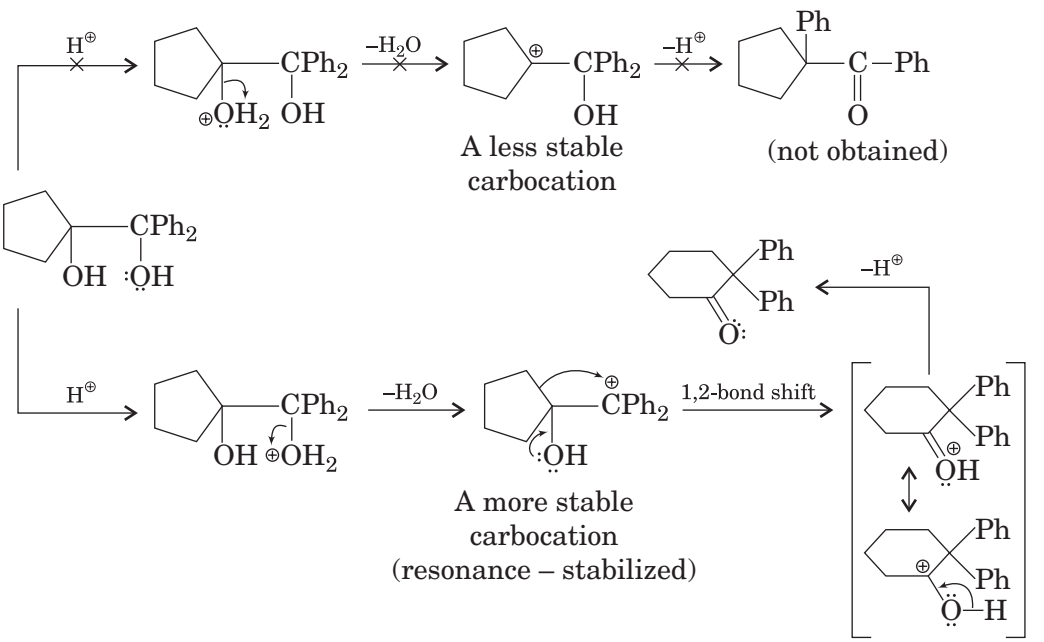
1. 

Mechanism:

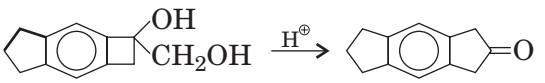


2. 

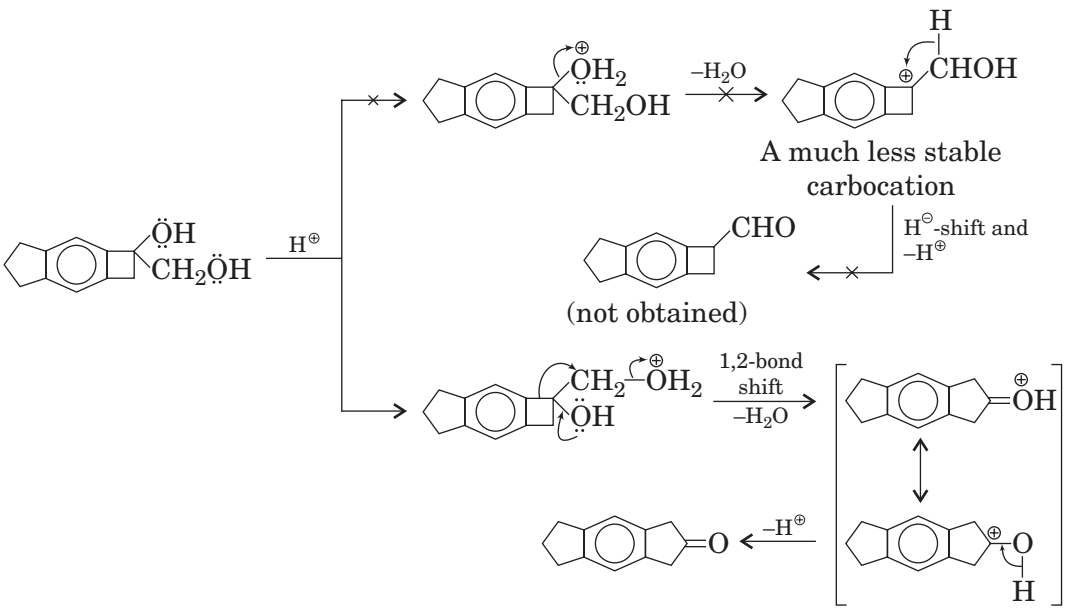
Mechanism:



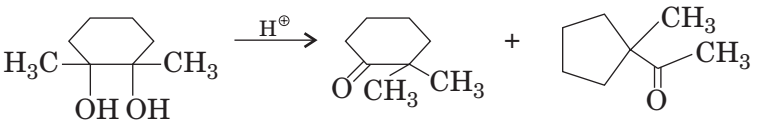
The –OH group on the carbon bearing the phenyl groups undergoes protonation and leaves as water because it leads to the formation of a very stable carbocation (a benzylic cation resonance – stabilized by two phenyl groups).

3. 

Mechanism:

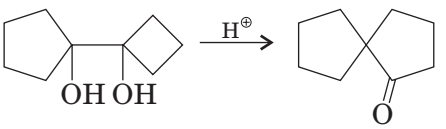


The tertiary –OH group does not leave because this leads to the formation of a very much less stable tertiary carbocation (angle strain: 120° – 90° = 30°). Consequently, the reaction proceeds by the loss of the primary –OH group to give a cyclopentanone derivative through ring expansion by simultaneous 1,2-bond migration.

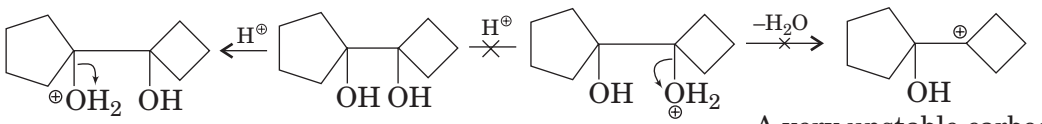
4. 

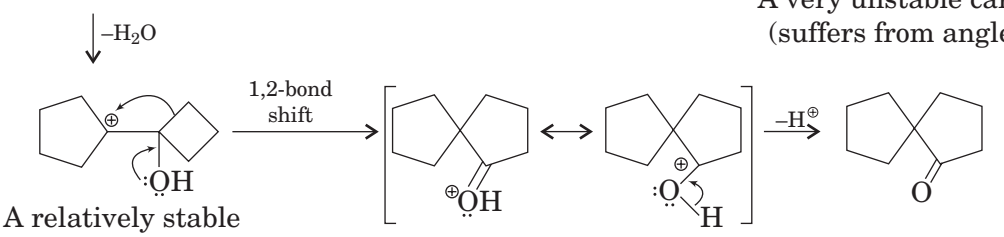
Mechanism:

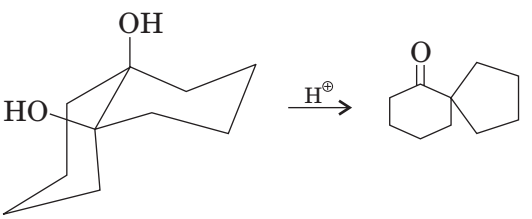
Since the pinacol is symmetrical, the nature of product depends on the migratory aptitude of the two groups. In this case, both bond-shift and Me-shift occurs to give the two products because their migratory aptitudes are more or less same.

5. 

Mechanism:

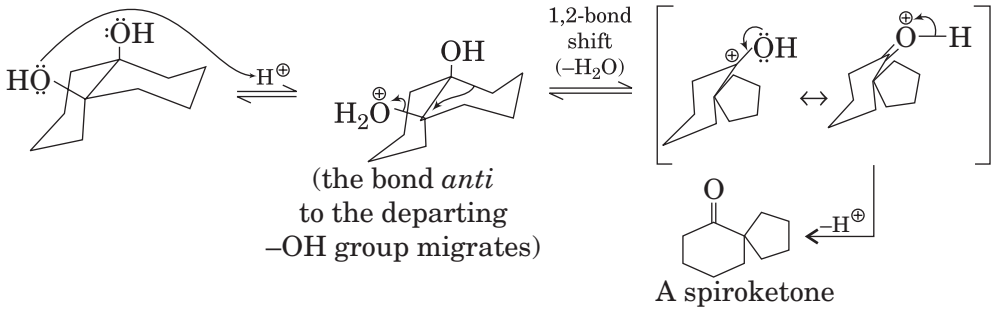




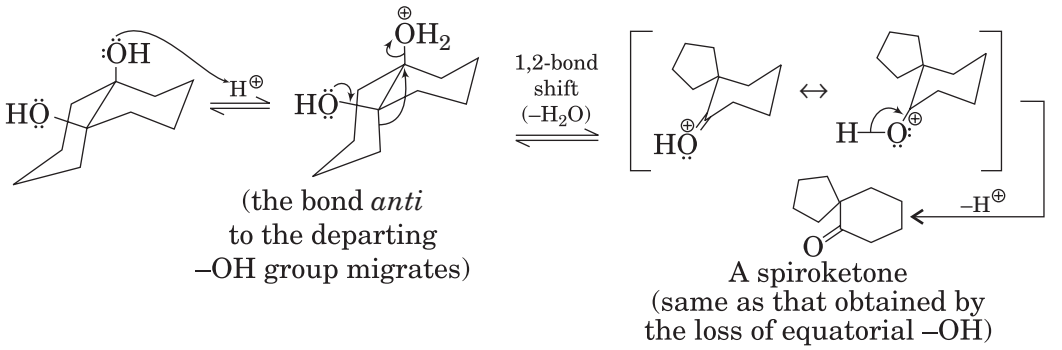
6. 

Mechanism:

(i) **Loss of equatorial –OH:**



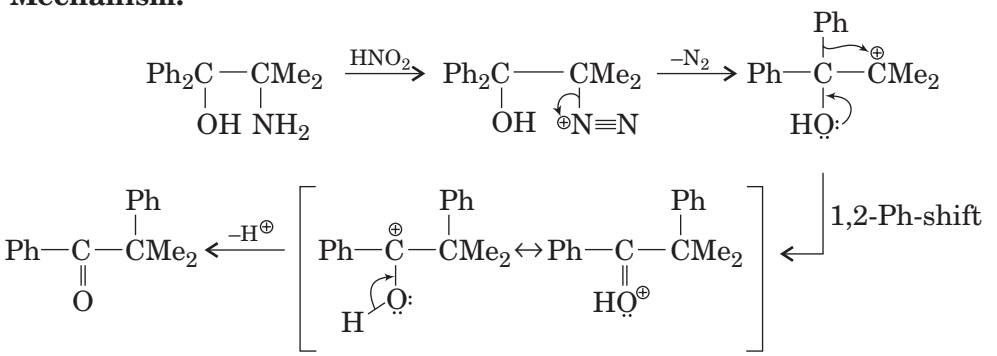
(ii) **Loss of axial –OH:**



Semipinacol rearrangements Semipinacol rearrangements are those rearrangements which are similar to pinacole rearrangements in mechanism and products but have no choice about which way to go. This type of rearrangement has been observed in the case of halohydrins and aminohydrins when specific reagents are used. A few examples of semipinacol rearrangement are given below.

1. $Ph_2C(OH)-CMe_2(NH_2) \xrightarrow[(NHO_2)]{NaNO_2/HCl} Ph-C(=O)-CPhMe_2$

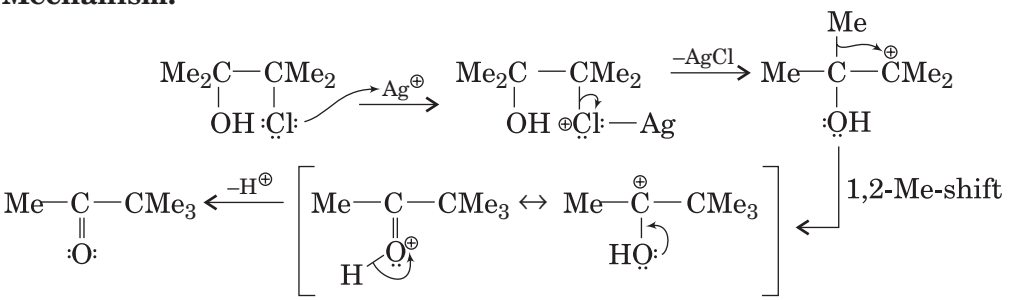
Mechanism:



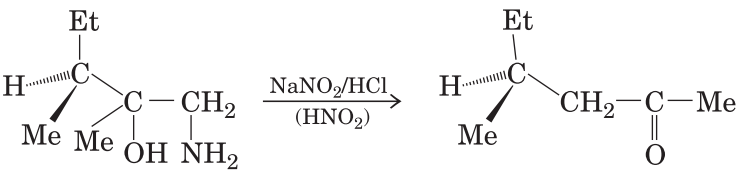
The aminohydrin reacts with HNO_2 to form an unstable diazonium cation which readily loses N_2 to form a 3° carbocation. The carbocation then undergoes phenyl migration to yield, after proton loss, a ketone (2-methyl-1,2-diphenyl-1-propanone).

2. $Me_2C(OH)-C(Cl)Me_2 \xrightarrow{\text{aq. } AgNO_3} Me-C(=O)-CMe_3$

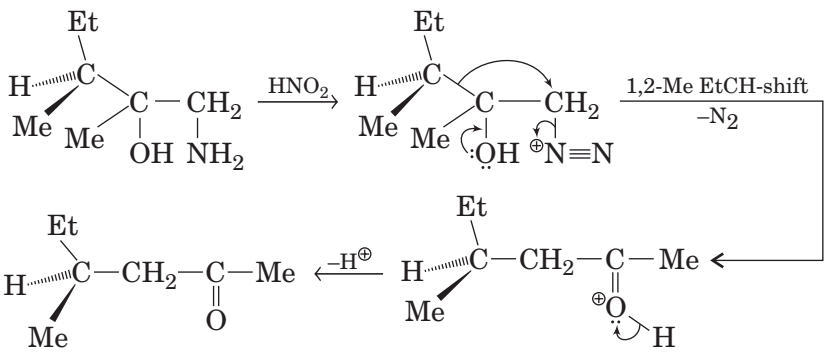
Mechanism:



The silver ion coordinates with chlorine to form a complex which dissociates to form AgCl and a 3° carbocation. The carbocation then undergoes methyl shift to form, after proton loss, pinacolone ($MeCOCMe_3$).

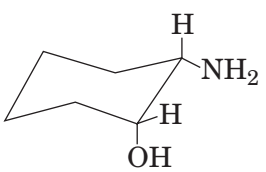
3. 

Mechanism:



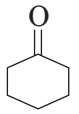
The unstable diazonium cation readily loses N_2 not to form an unstable 1° carbocation but to form a resonance-stabilized carbocation by simultaneous shift of the chiral alkyl group. The configuration of the group is retained because it does not free during rearrangement.

4. (i)



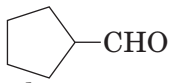
cis-2-Aminocyclohexanol

$\xrightarrow[(NaNO_2/HCl)]{HNO_2}$



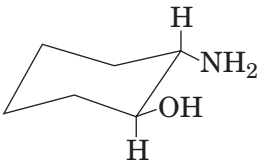
Cyclohexanone

+



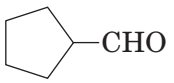
Cyclopentane-carboxaldehyde

(ii)



trans-2-Aminocyclohexanol

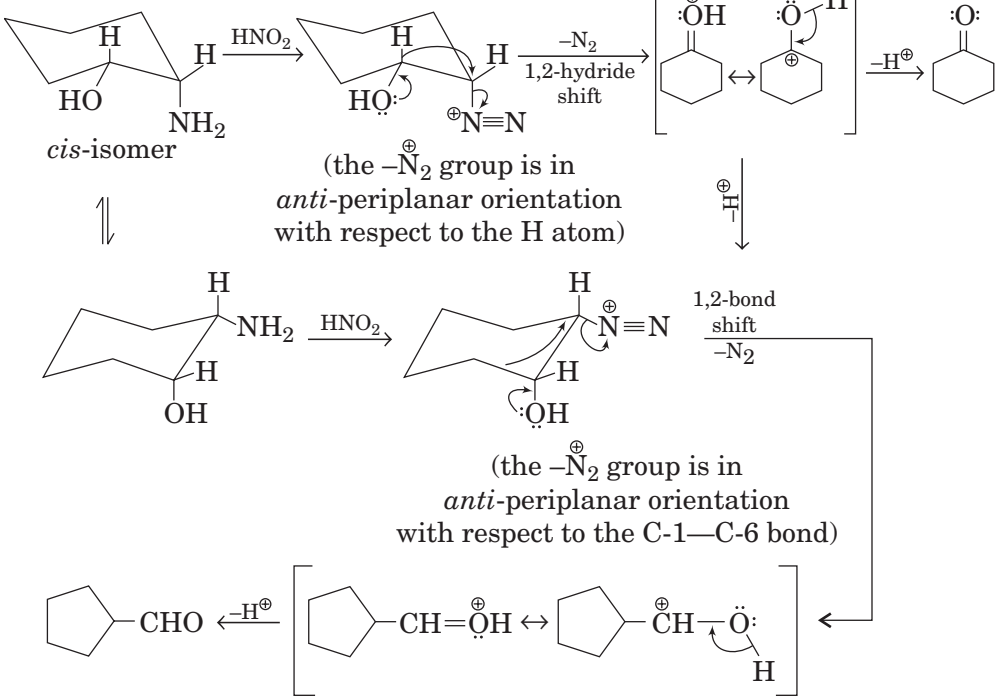
$\xrightarrow[(NaNO_2/HCl)]{HNO_2}$



Cyclopentane-carboxaldehyde

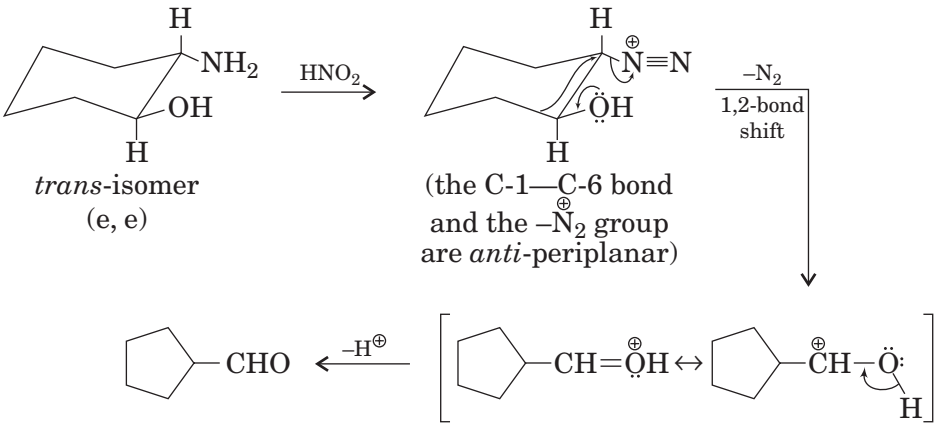
Mechanism:

(i)



The diazonium ion corresponding to the axial amino conformation of the *cis*-2-aminocyclohexanol undergoes loss of N_2 with simultaneous migration of the axial hydrogen (which is conformationally *anti* to the departing nitrogen) to yield cyclohexanone. On the other hand, the equatorial amino conformation undergoes migration of the ring bond (which is conformationally *anti* to the departing nitrogen) to yield cyclopentanecarboxaldehyde.

(ii)

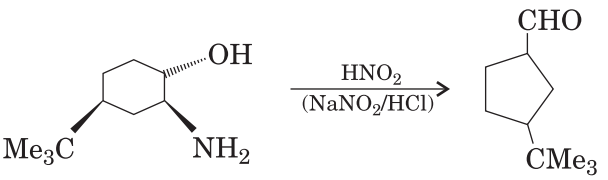


trans-isomer (e, e)

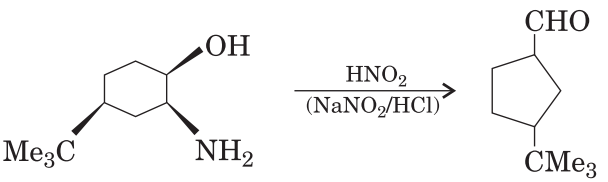
(the C-1—C-6 bond and the $-\overset{\oplus}{N}_2$ group are *anti*-periplanar)

The *trans*-isomer exists nearly exclusively in the thermodynamically more stable diequatorial conformation. Therefore, this isomer reacts through this conformation to yield cyclopentanecarboxaldehyde.

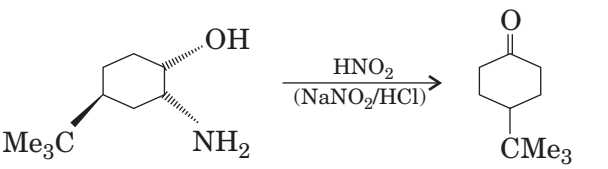
5. (i)



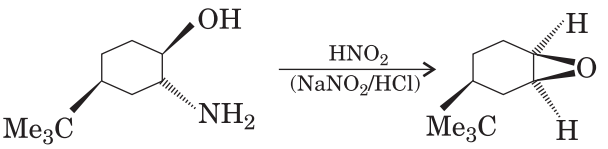
(ii)



(iii)

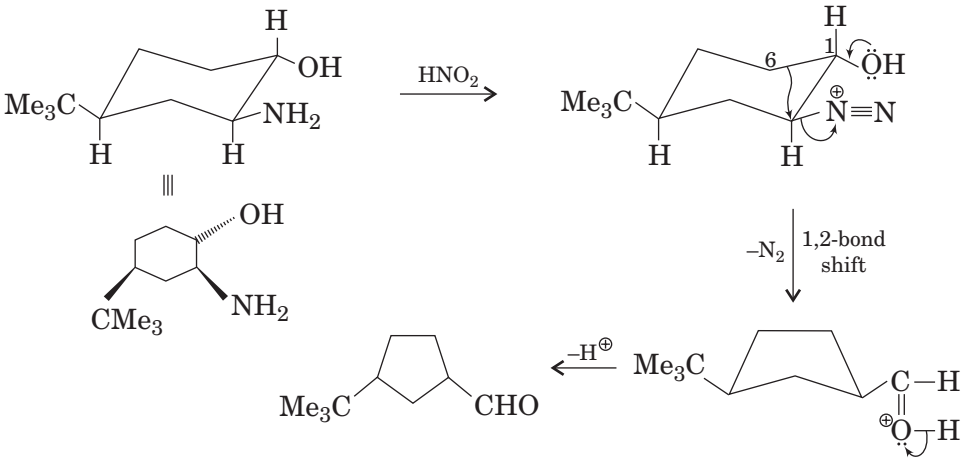


(iv)



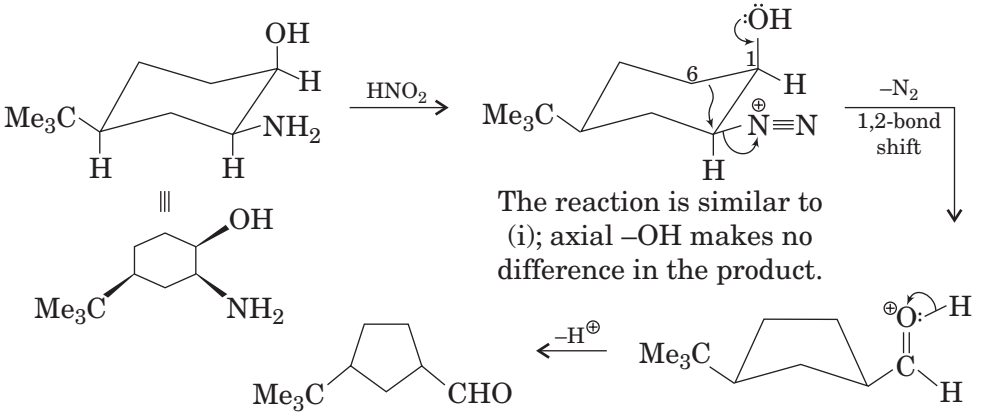
Mechanism: The tertiary butyl group is particularly very bulky and cannot take up axial position due to severe steric interaction, which is energetically very unfavourable. The *tert*-butyl group substituted cyclohexanes, therefore, remain fixed in the chair conformation where Me_3C-group remains in equatorial position. The above four diastereoisomers are, therefore, conformationally biased or anancomeric and react through this conformation.

(i)

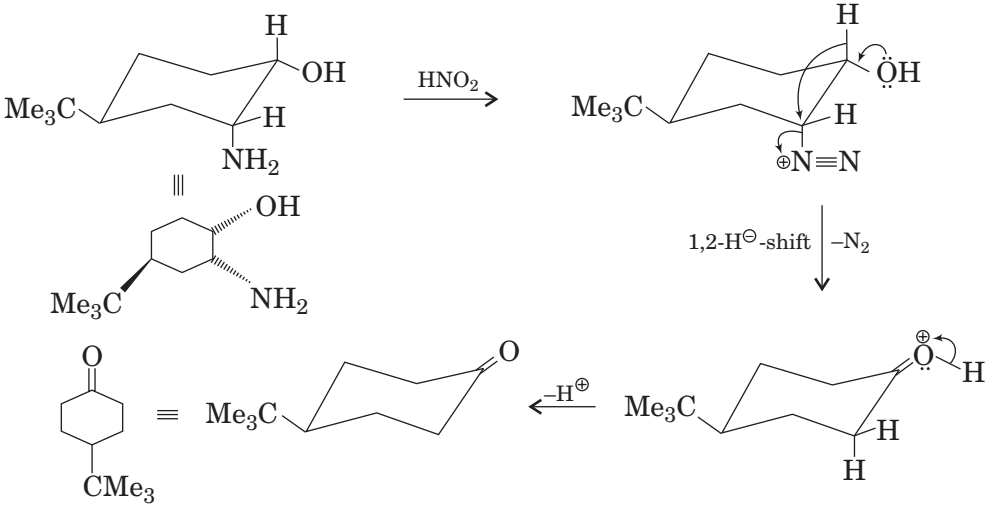


C-1—C-6 bond migration occurs because it is *anti*-periplanar with an equatorial leaving group $-\overset{\oplus}{N}_2$. This results in the formation of a ring-contracted product.

(ii)

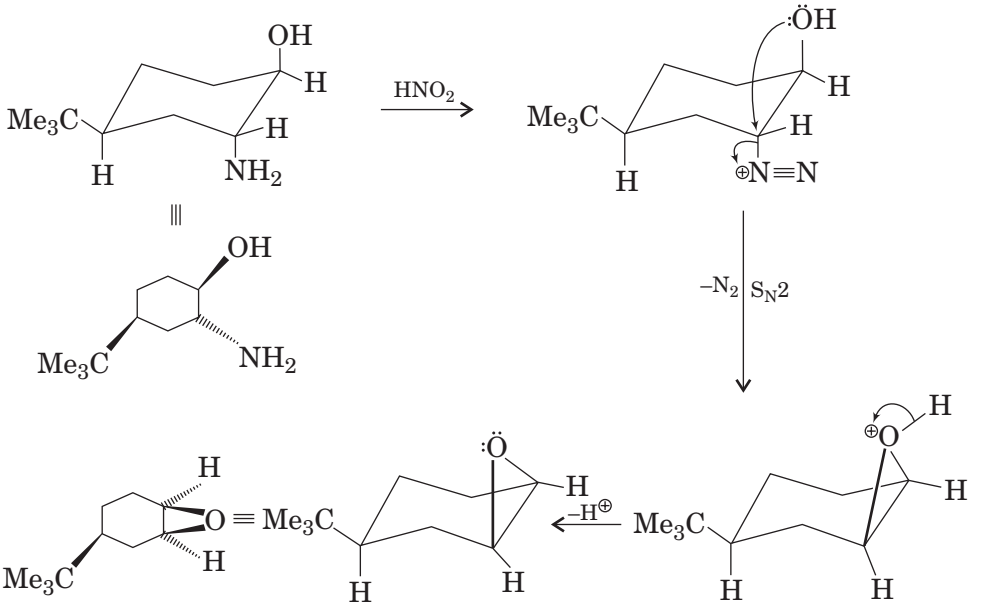


(iii)



Hydrogen is *anti*-periplanar with the leaving group $-\overset{\oplus}{N}_2$. So, it migrates to give a cyclohexanone derivative.

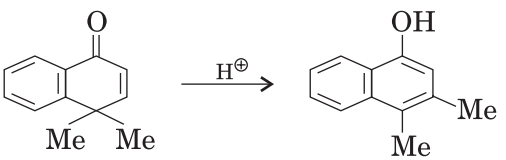
(iv)



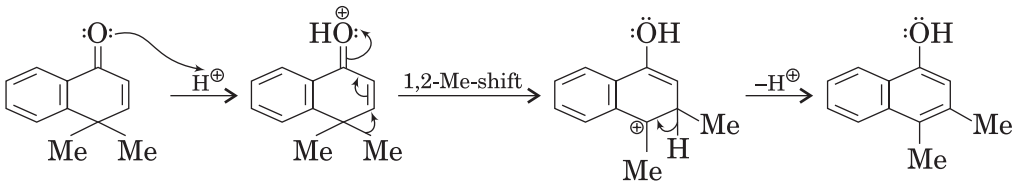
The diazonium cation undergoes intramolecular S_N2 reaction to give, after proton loss, an epoxide.

4.1.1.4 Dienone–Phenol rearrangement

The acid-catalyzed rearrangement of substituted cyclohexadienones to the corresponding phenolic compounds involving 1,2-shift of an alkyl group or a C—C σ-bond is known as *dienone–phenol rearrangement*. In fact, it is a case of reversal of pinacol rearrangement and may be regarded as retro pinacol rearrangement. For example:

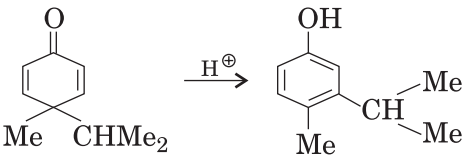


Mechanism of the reaction The driving force of the reaction is the creation of an aromatic system in the product. Mechanistically, the reaction involves initial protonation at the dienone oxygen followed by 1,2-alkyl shift and subsequent aromatization by loss of a proton. This may be shown as follows:

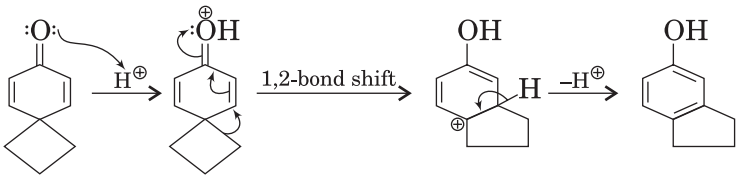


Characteristic features

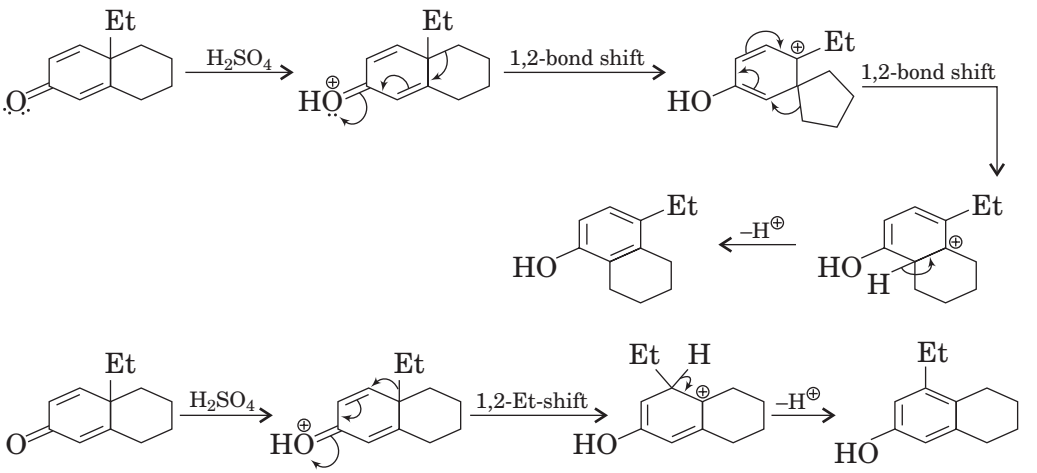
(i) If the migration origin has two different groups, the group having greater migratory aptitude shifts preferentially. For example:



(ii) When there is a ring instead of alkyl groups, enlargement of the ring through migration of the C–C σ-bond takes place. For example:

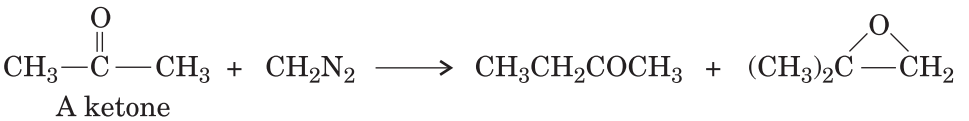


(iii) When there are an alkyl group and a ring bond at the migration origin, either the alkyl group or the ring bond may migrate, and the actual course of the reaction is guided by the structural feature of the molecule as well as by the reaction conditions. For example:

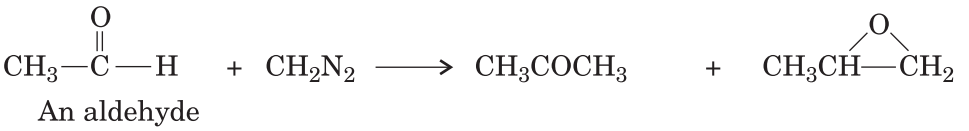


4.1.1.5 Homologation of ketones by diazomethane

Diazomethane (CH_2N_2) converts a ketone to its next higher homologue. It reacts with aldehydes to produce methyl ketones. An epoxide is formed as a byproduct in both the cases. For example:

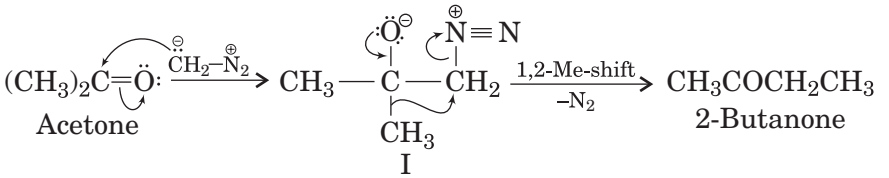


A ketone



An aldehyde

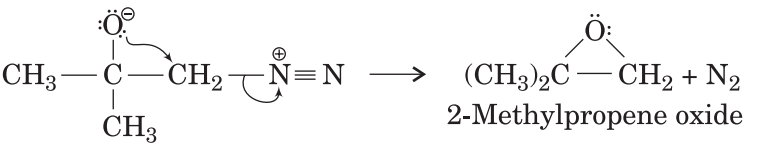
Mechanism of the reaction Diazomethane is a dipolar species ($\overset{\ominus}{C}H_2—\overset{\oplus}{N}\equiv N$). Since its carbon atom is nucleophilic, it can be reactive to aldehydes and ketones. The mechanism of its reaction with a ketone may be outlined as follows:



Acetone — 2-Butanone

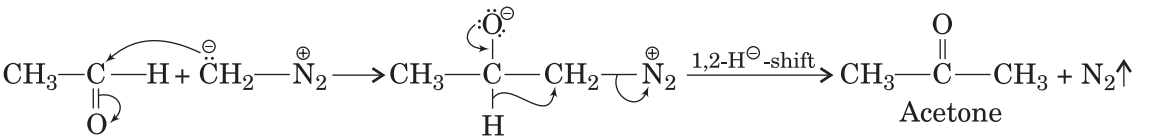
I

Diazomethane adds to the carbonyl carbon of the ketone to form a betaine (I). The intermediate betaine undergoes loss of N_2 with simultaneous migration of methyl (a 1,2-shift) to form the next higher ketone. Loss of nitrogen followed by migration of methyl does not take place because a 1° carbocation is very much unstable. The betaine I may also undergo intramolecular S_N2 to form an epoxide as follows:

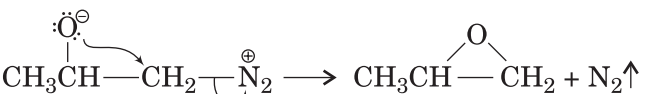


2-Methylpropene oxide

Diazomethane reacts with an aldehyde as follows:



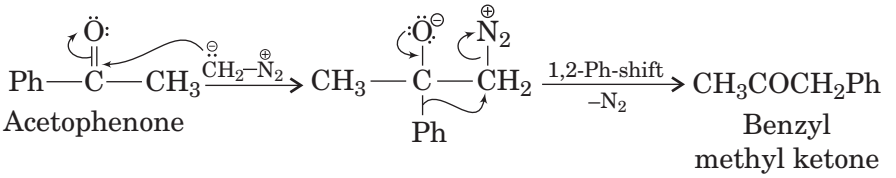
Acetaldehyde — Acetone



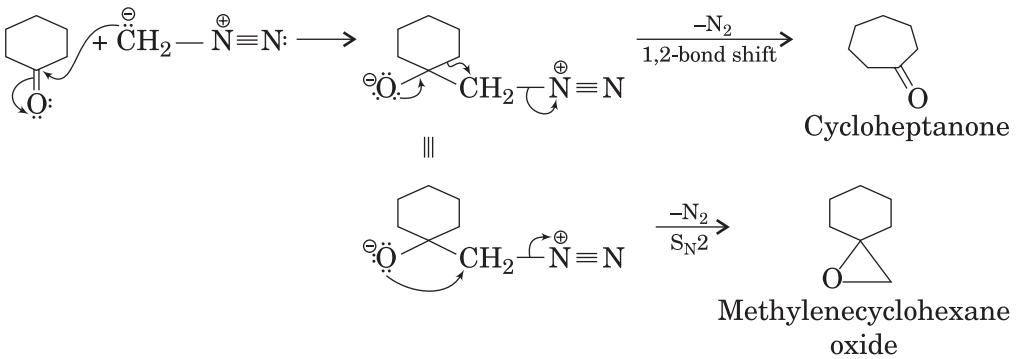
Propene oxide

Characteristic features

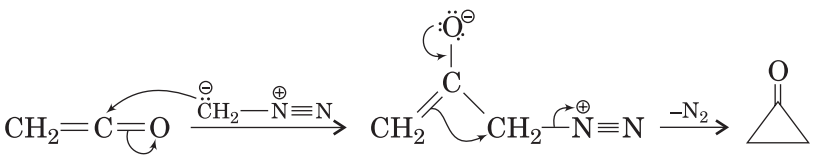
(i) When the two groups at the migration origin are different, that group will migrate which has greater migratory aptitude. For example, when acetophenone is allowed to react with diazomethane, the phenyl group migrates to yield benzyl methyl ketone.



(ii) Cyclic ketones react with diazomethane to undergo ring expansion. Cyclohexanone, for example, reacts with CH_2N_2 to produce cycloheptanone. A little epoxide is obtained.

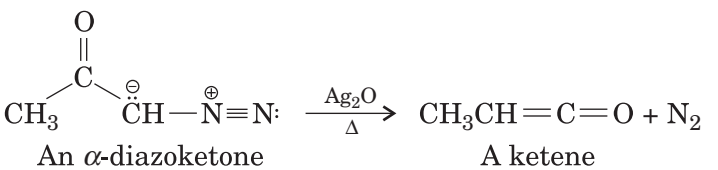


(iii) Cyclopropanone can be prepared by allowing ketene to react with diazomethane.

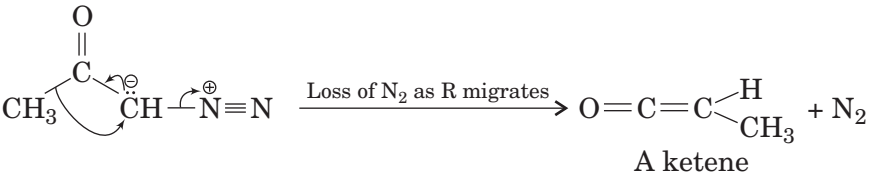


4.1.1.6 Wolff rearrangement and Arndt–Eistert synthesis

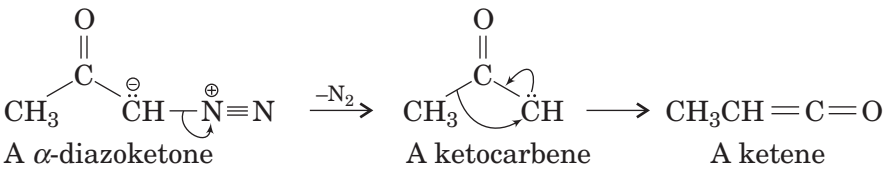
The conversion of α-diazoketones into ketenes by applying heat in the presence of silver oxide is called the *Wolff rearrangement*. For example:



Mechanism of the reaction The mechanism of the reaction involving migration of the R group with simultaneous removal of N_2 is as follows:

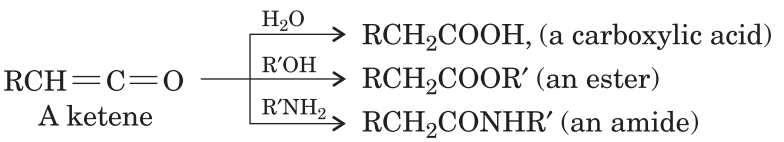


The diazoketone may produce a carbene first by releasing nitrogen. The R group may then migrate to the electron-deficient divalent carbon (a 1,2-shift) to yield a ketene, i.e. the process may be stepwise.

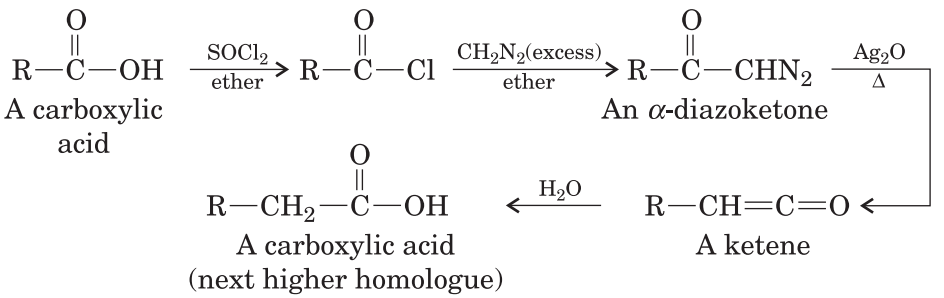


The mechanistic complication in a Wolff rearrangement comes from the notion that it may not be the carbene, but the diazoketone itself, that produces the ketene. The carbene is not necessarily involved. The question is not completely settled yet, but the best evidence currently favours at least some direct formation of the ketene from most diazoketones.

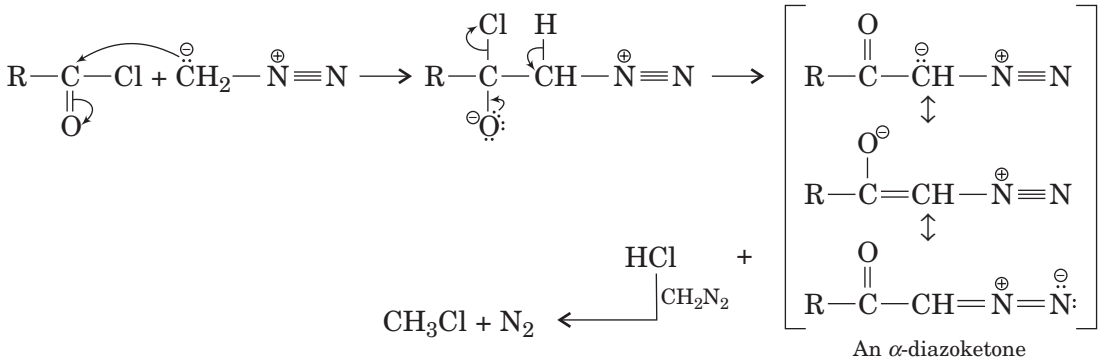
It is to be noted that the ketene readily adds a nucleophilic solvent molecules, which may be H_2O to give an acid, ROH to give an ester or RNH_2 to give an amide.



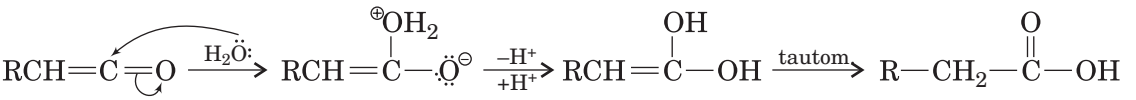
Arndt–Eistert Synthesis The Wolff rearrangement has practical utility in the Arndt–Eistert synthesis (a most useful chain-lengthening reaction), which involves conversion of an acyl halide (e.g. an acid chloride) to a carboxylic acid with one more carbon atom in the chain. Since the acyl halide can easily be prepared from a carboxylic acid, therefore, a carboxylic acid (RCOOH) can easily be converted into its next higher homologue (RCH_2COOH). The overall process starting with the original acid is as follows:



Mechanism of formation of α-diazoketone from an acid chloride and hydrolysis of ketone to form an acid: The acid chloride reacts with diazomethane to form a tetrahedral intermediate that readily loses a molecule of HCl to form an α-diazoketone.

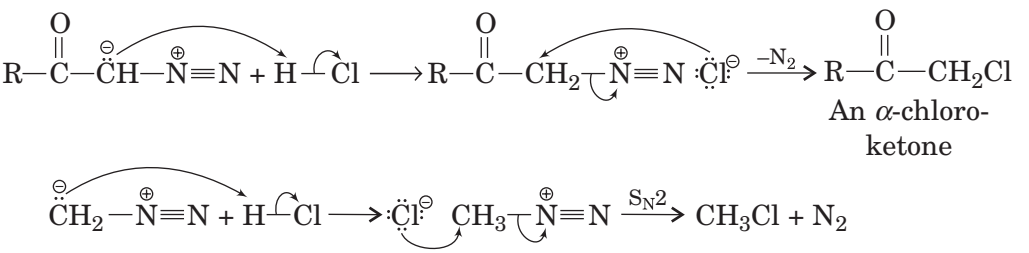


The ketene undergoes readily hydrolysis as follows:

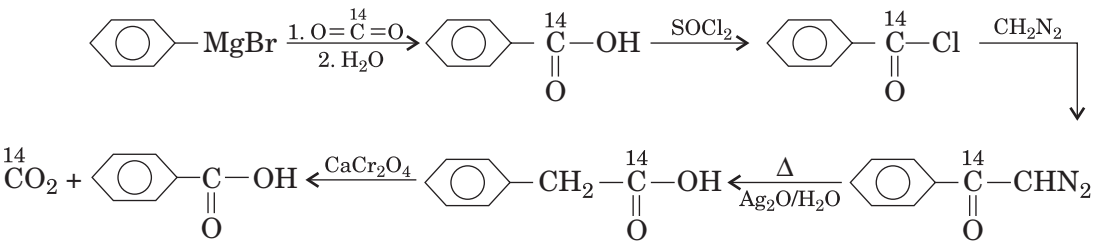


Some relevant topics

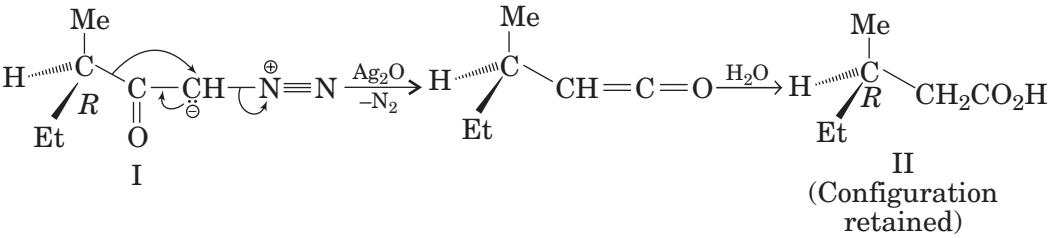
(i) **In Arndt–Eistert synthesis excess of diazomethane is to be used:** Diazomethane reacts with acid chloride to form HCl along with the diazoketone. This HCl may convert the diazoketone into an α-chloroketone. Excess diazomethane is used to avoid this undesirable side reaction. It destroys the resulting HCl as it is formed.



(ii) **A lebelling experiment to prove that the carbonyl carbon of the α-diazoketone becomes the carboxyl carbon of the resulting acid:** An α-diazoketone in which the carbonyl carbon is ^{14}C labelled is prepared and when subjected to the Wolff rearrangement, it produces phenylacetic acid. This on oxidative decomposition produces benzoic acid and C-labelled CO_2. This observation, therefore, suggests that the carbonyl carbon of the starting ketone becomes the carbonyl carbon of the resulting acid.



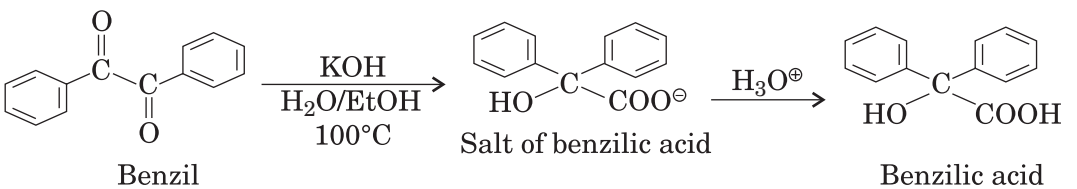
(iii) **The Wolff rearrangement is intramolecular in nature:** When an α-diazoketone containing a chiral R group is subjected to the Wolff rearrangement, the configuration of this group is found to be retained in the product acid. For example, the (*R*)-α-diazoketone I produces the (*R*)-carboxylic acid II.



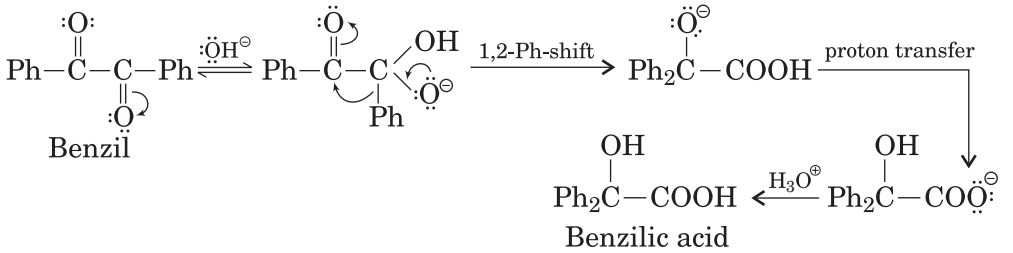
This observation, therefore, suggests that the R group does not migrate as a free carbanion, i.e. it never becomes detached from the substrate skeleton, and hence, it is an intramolecular rearrangement. Free carbanions, being configurationally unstable, are expected to give products with retention as well as inversion of configuration (a racemic product).

4.1.1.7 Benzilic acid rearrangement

When 1,2-diketones are treated with strong base, they undergo a rearrangement to yield salts of α-hydroxy carboxylic acids. Since the initial investigations of the reaction were carried out on benzil (1,2-diphenylethan-1,2-dione) and the product, after acid quench, is benzilic acid (2-hydroxy-2,2-diphenylacetic acid), the name of the rearrangement is *benzilic acid rearrangement*. The reaction occurs with both aliphatic and aromatic α-diketones. Usually, diaryl diketones give very good yield, but α-diketones having enolizable hydrogen give low yields due to completing aldol reactions.



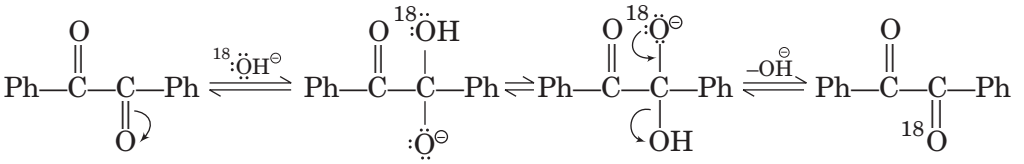
Mechanism of the reaction The mechanism of the reaction involves the following steps:



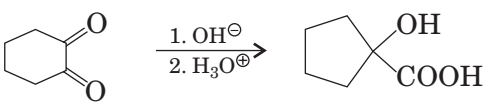
The benzilic acid rearrangement is initiated by $OH^{\ominus}$ ion, and it is mechanistically similar to the intramolecular Cannizzaro reaction. However, this reaction involves a 1,2-shift of an aryl or alkyl group to an electron-deficient carbonyl carbon. In the first step of the reaction, one of the carbonyl groups undergoes nucleophilic attack by $OH^{\ominus}$ ion to give a tetrahedral intermediate. In the second step, the phenyl group migrates to the adjacent carbonyl carbon to form another tetrahedral intermediate. In the next step, proton transfer occurs to form a α-hydroxycarboxylic acid salt (benzilate anion). This is the actual product of the rearrangement which on acidification gives benzilic acid.

Characteristic features

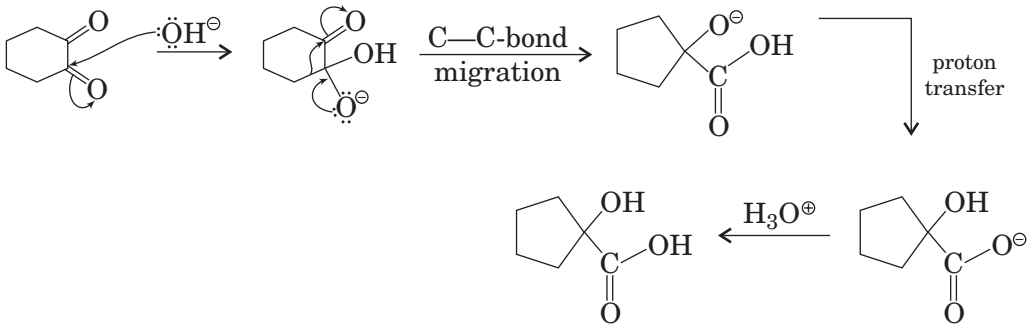
1. **The first step of this rearrangement is the rapid reversible attack by $OH^{\ominus}$ on a carbonyl carbon:** When the reaction is carried out in $H_2^{18}O$, the unreacted benzil has been found to contain ^{18}O. This observation suggests that the first step (nucleophilic attack by $OH^{\ominus}$ on $\rangle C{=}O$) is rapid and reversible.



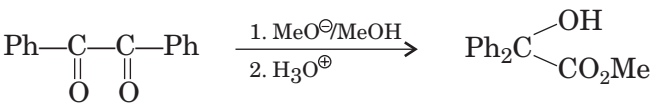
2. **In cyclic 1,2-diketones, C—C bond migration leading to ring contraction takes place:** Cyclohexane-1,2-dione, for example, when treated with alkali and then quenched by dilute acid, 1-hydroxycyclopentane carboxylic acid is obtained.



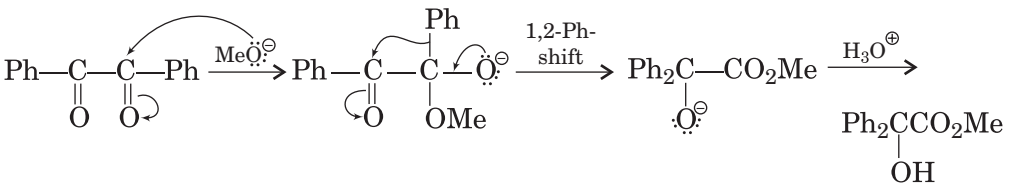
Mechanism:



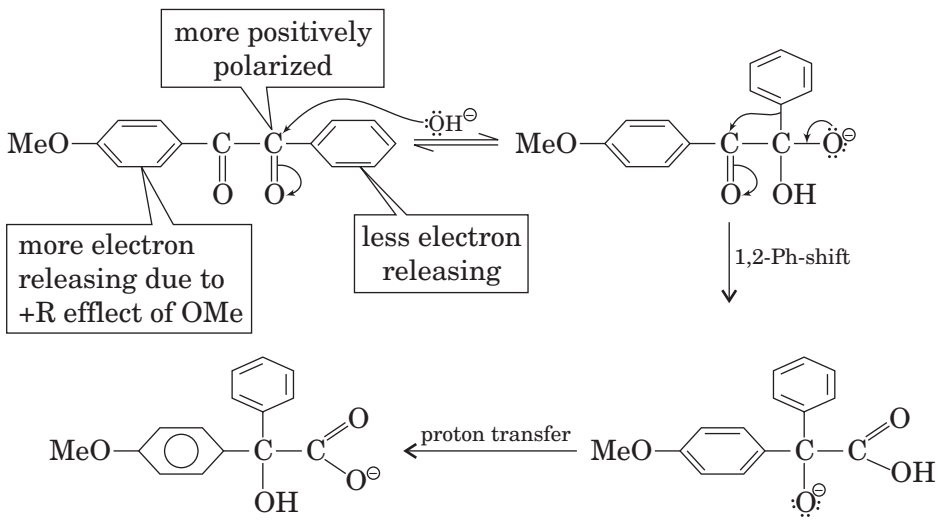
3. **Alkoxide bases like $MeO^{\ominus}$ can also be used instead of hydroxide base to get an ester:** Benzil, for example, when treated with $MeO^{\ominus}$/MeOH followed by acidification, produces methyl 2-hydroxy-2,2-diphenylethanoic acid.



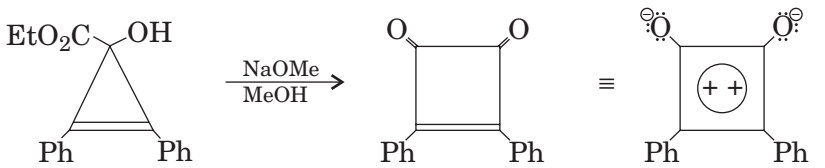
Mechanism:



4. **With unsymmetrical diketones, the more reactive carbonyl carbon undergoes nucleophilic attack by $OH^{\ominus}$:** The carbonyl group, which is attached to less electron-releasing or electron-withdrawing of the two aryl groups is relatively more electrophilic and hence, undergoes ready attack by $OH^{\ominus}$. For example:

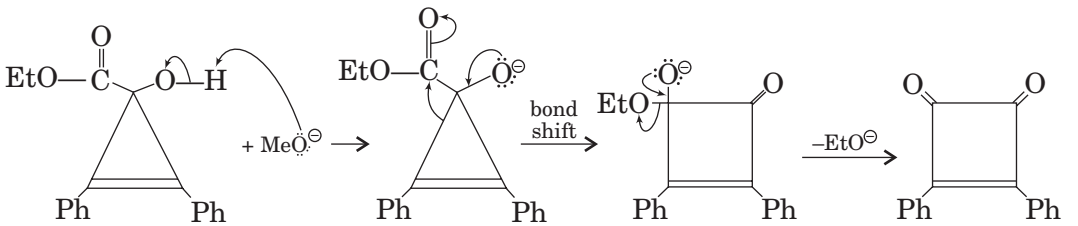


5. **Some α-hydroxyesters undergo retro-benzilic acid rearrangement when treated with $MeO^{\ominus}$/MeOH:** The following hydroxyester, for example, produces a 1,2-diketone when treated with NaOMe/MeOH.



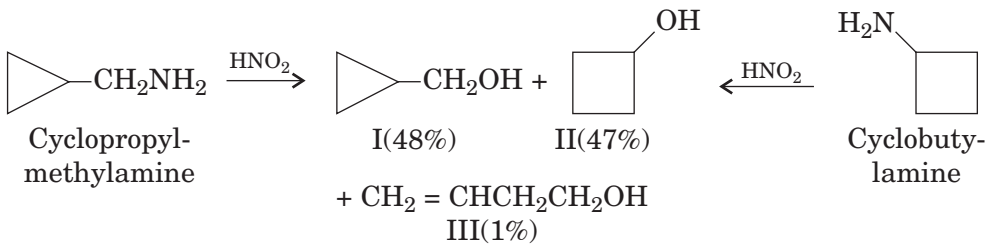
[an aromatic system containing 2π electrons; $(4n + 2)\pi$, where $n = 0$]

Mechanism:



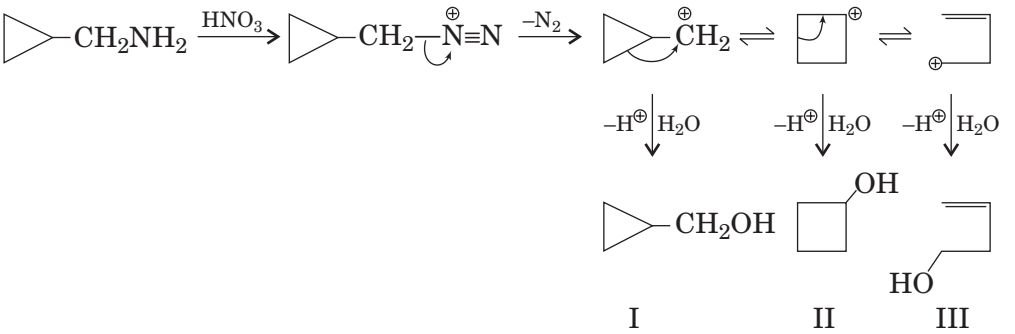
4.1.1.8 Demjanov rearrangement

Cycloalkylmethylamines and cycloalkylamines undergo diazotization when treated with nitrous acid to give products by ring expansion and ring contraction, respectively, through the formation of carbocation intermediates. Such a reaction is called *Demjanov* or *Demyanov rearrangement*. When cyclopropylmethylamine and cyclobutylamine, for example, are separately treated with nitrous acid, they produce a same mixture of cyclopropylcarbinol (I), cyclobutanol (II) and a small amount of but-3-en-1-ol (III).

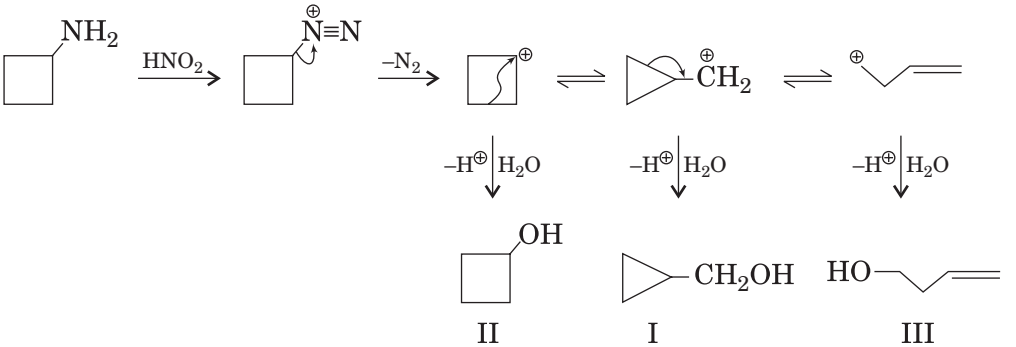


Mechanism of the reaction The Demjanov rearrangement proceeds through a carbocation formed by the loss of N_2 from the intermediate diazonium ion. The carbocation may undergo ring expansion as well as ring contraction depending on its structure.

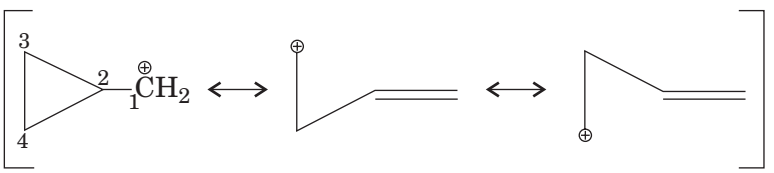
Cycloprophylmethylamine reacts as follows:



Cyclobutylamine reacts as follows:



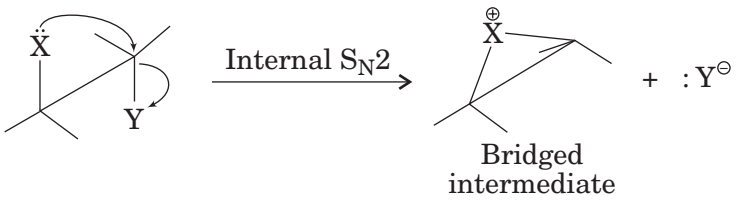
Cycloprophylmethyl cation is considerably stable because both the ring bonds (C-2—C-3 and C-2—C-4 σ bonds) having an appreciable p character help to stabilize the positive charge by delocalization. For this reason, ring contraction of cyclobutyl cation occurs to form the cyclopropylmethyl cation.



Cyclopropylmethyl cation
(resonance-stabilized)

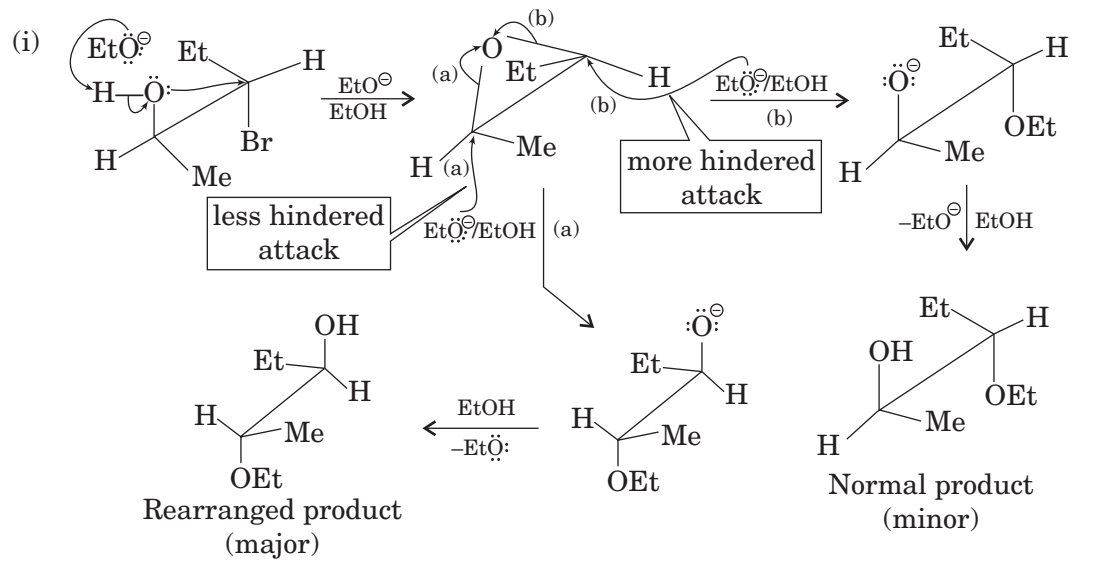
4.1.1.9 Migration of heteroatoms

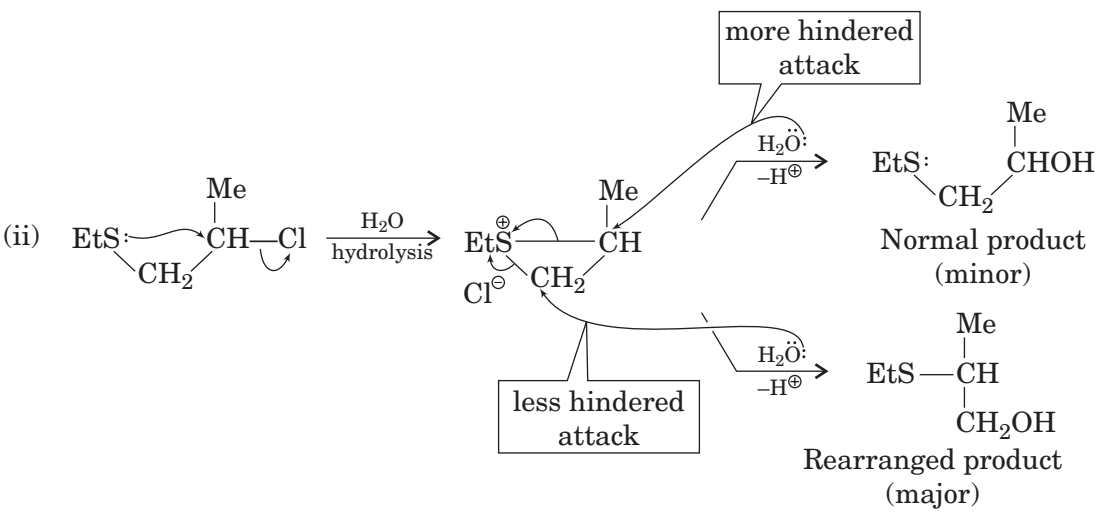
In addition to carbon and hydrogen, 1,2-migrations of oxygen, sulphur and nitrogen are also possible to electron-deficient carbon. The reaction, which proceeds through bridged intermediate, involves the neighbouring group participation mechanism (intramolecular S_N2). The bridge is subsequently opened up by the attack of the nucleophile present in the reaction medium.



When a symmetrical substrate like $MeCH_2SCH_2CH_2Cl$ is subjected to hydrolysis with dilute NaOH solution, no rearranged product is formed on ring opening. However, in the case of an unsymmetrical substrate, which form an unsymmetrical bridge, the nucleophile attacks both the ring carbons forming the normal as well as the rearranged product.

For example:

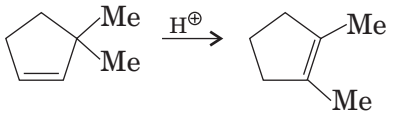




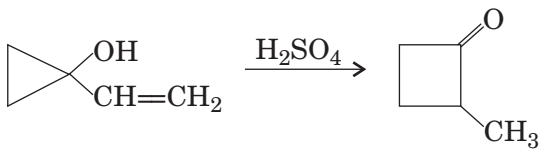
SOLVED PROBLEMS

1. Suggest a mechanism for each of the following reactions:

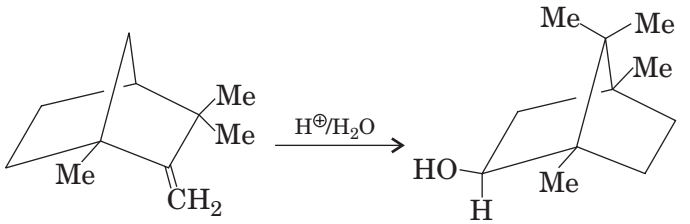
(a)



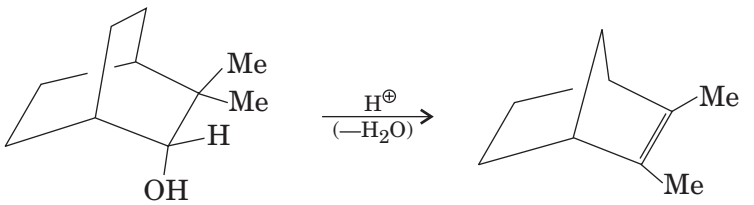
(b)



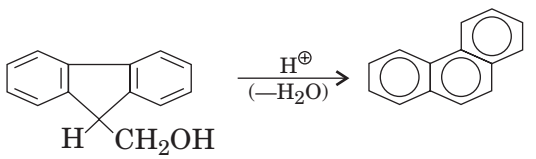
(c)



(d)

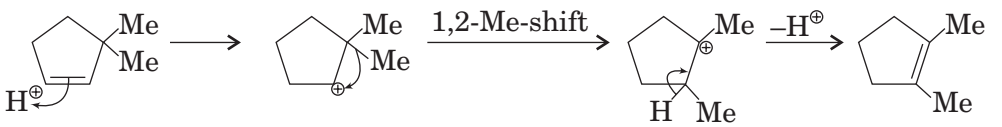


(e)



Solution

(a)

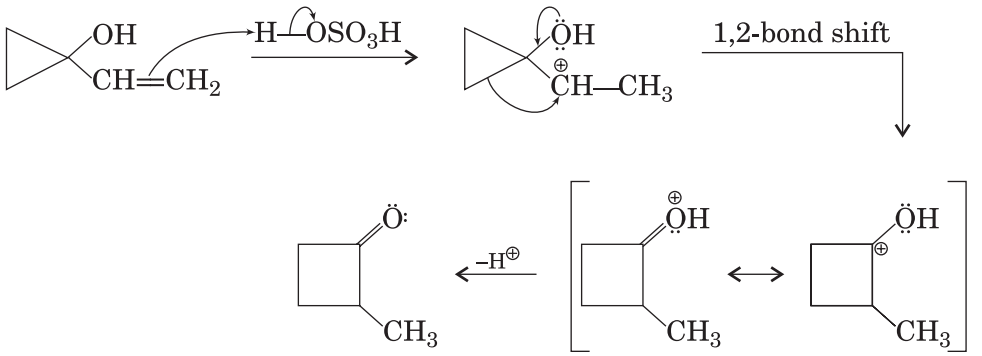


A 2° carbocation (less stable)

A 3° carbocation (more stable)

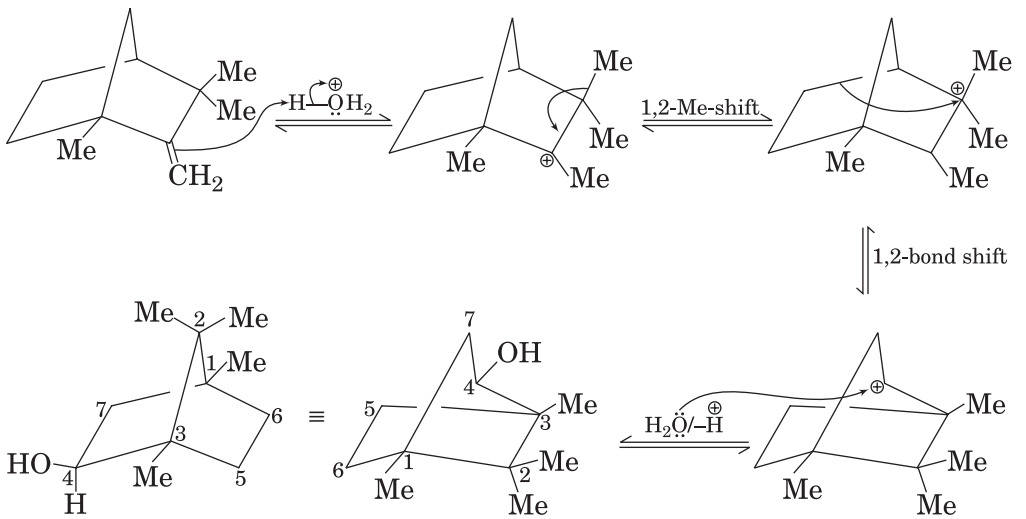
The initially formed less stable 2° carbocation rearranges by a 1,2-methyl shift to yield a more stable 3° carbocation. Loss of proton from it then produces the more stable (more substituted) alkene as the major product.

(b)

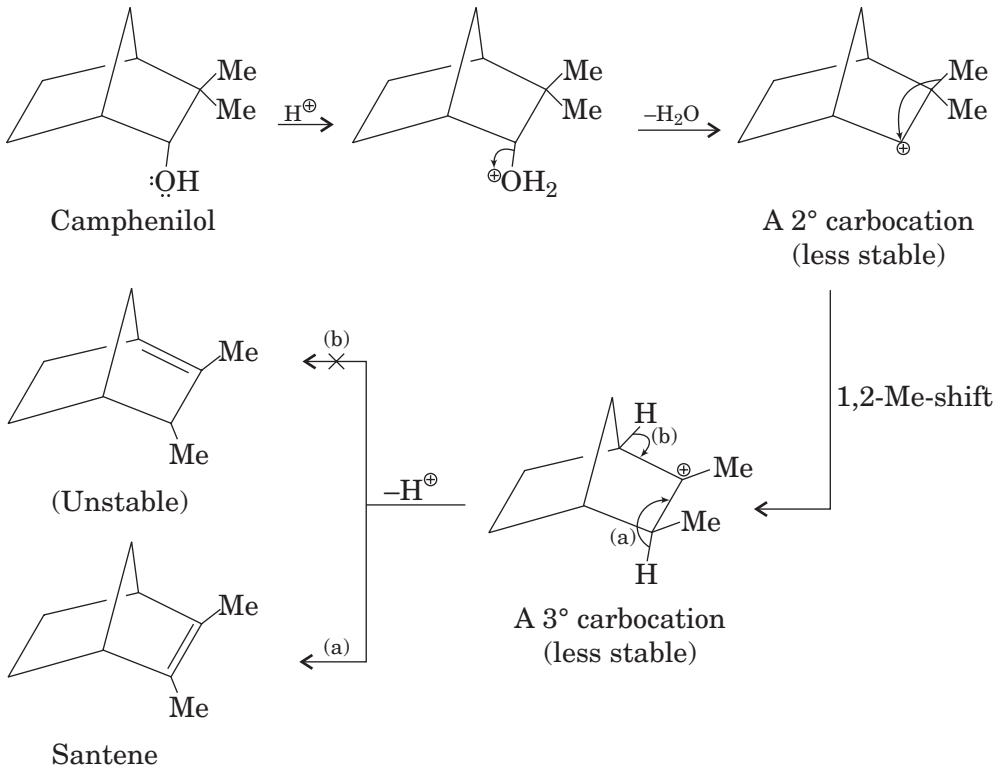


The initially formed less stable 2° carbocation rearranges by a 1,2-bond shift to yield a more stable (resonance-stabilized) carbocation. Its stability is also due to less angle strain as compared to cyclopropane ring.

(c)

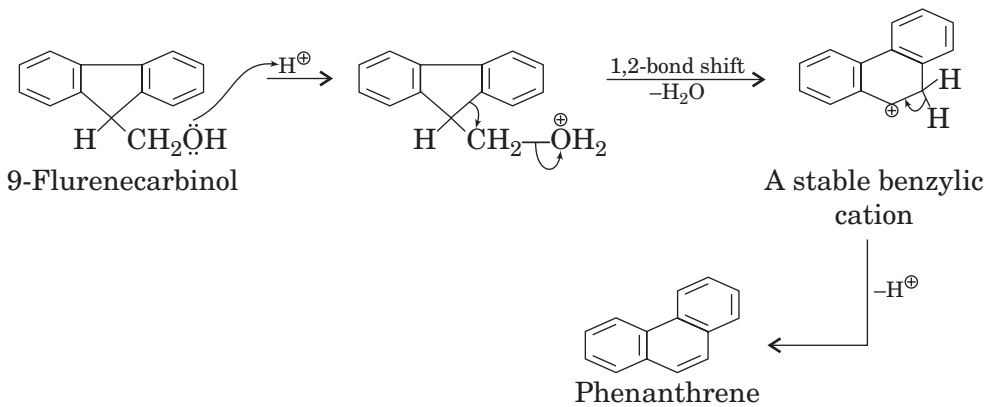


(d)



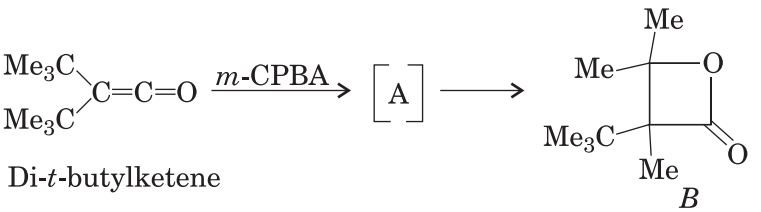
The initially formed 2° carbocation rearranges by a methyl shift to give a relatively more stable 3° carbocation. This loses a β-hydrogen to give the more substituted alkene santene but not the more substituted alkene with a bridgehead double bond that is too unstable to be formed (Bredt's rule).

(e)



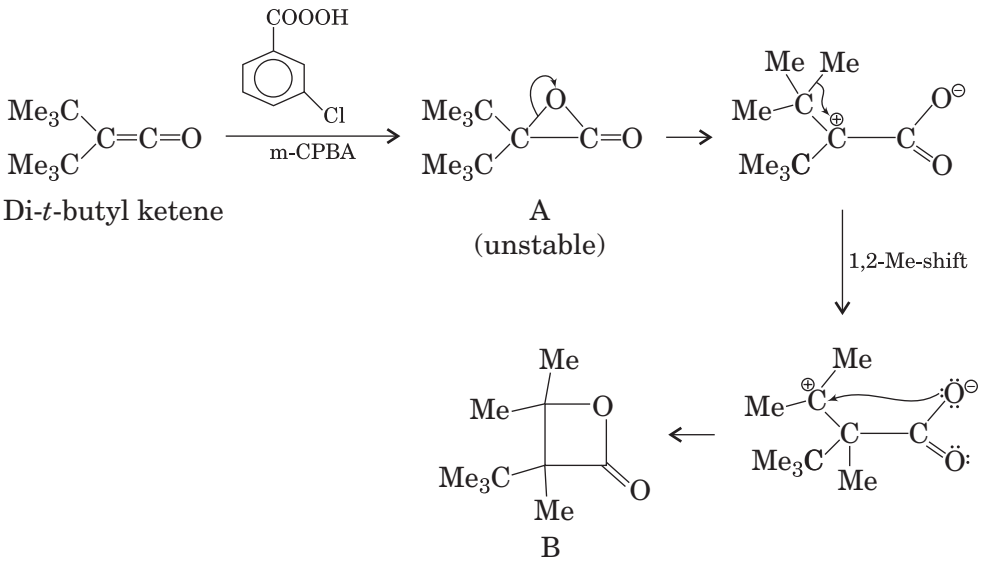
The alcohol undergoes dehydrative rearrangement in the presence of acid to form phenanthrene. In step 2, since loss of water may produce a very unstable 1° carbocation, a simultaneous bond migration occurs to form a stable benzylic cation (resonance-stabilized).

2. Di-*t*-butyl ketene reacts with *m*-CPBA to form an unstable compound A that readily decomposes to give the four-membered lactone B. Predict the structure of A and give the mechanism for the conversion of A to B.

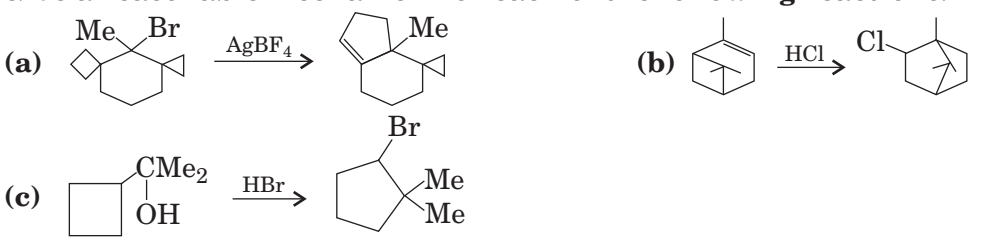


Di-*t*-butylketene

Solution When di-*t*-butyl ketene is treated with *meta*-chloroperbenzoic acid, it undergoes epoxidation to form an unstable three-membered lactone (A). Because of the ring strain, it readily opens up to form a 3° carbocation. This rearranges to give another 3° carbocation by Me-shift. The carbocation then undergoes intramolecular nucleophilic attack by the carboxyl oxygen to form the four-membered lactone B.

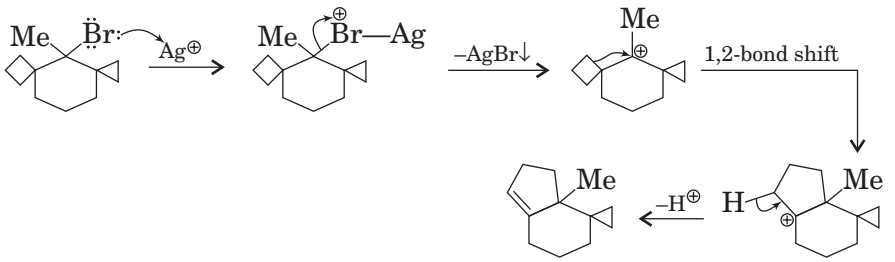


3. Give a reasonable mechanism for each of the following reactions:



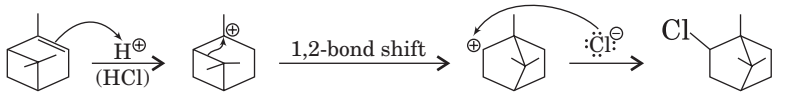
Solution

(a)



The silver ion coordinates with Br atom and causes ionization of the alkyl bromide to form a 3° carbocation. The carbocation rearranges to give another 3° carbocation. Relief of strain in expansion from a four- to five-membered ring facilitates this rearrangement process.

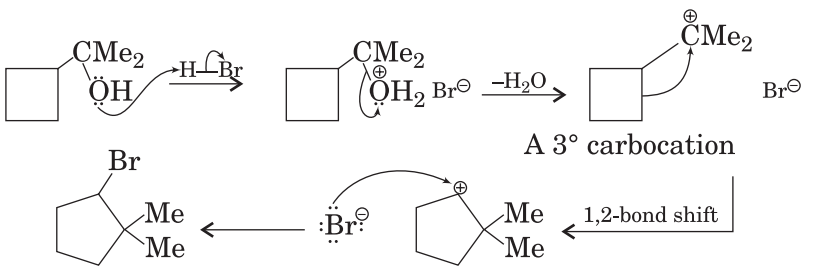
(b)



A 3° carbocation (with strain) — A 2° carbocation (without strain)

Cations can be made more stable if they become less strained, so, for example, four-membered rings adjacent to a positive carbon readily rearrange to five-membered rings in order to relieve ring strain. Though the rearrangement step transforms a stable 3° carbocation into a less stable 2° carbocation, relief of strain in expansion from a four- to a five-membered ring makes the bond migration favourable.

(c)



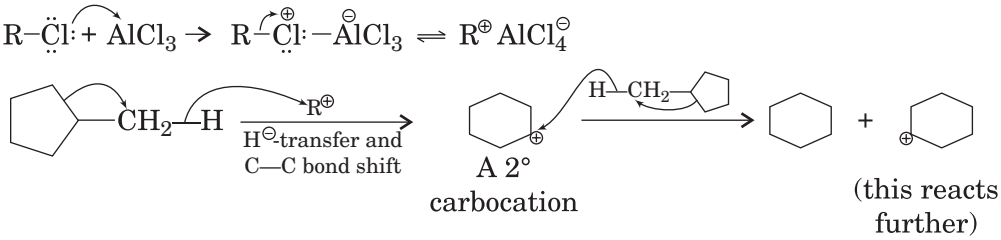
Although a 3° carbocation is initially formed, the angle and torsional strain of the four-membered ring is reduced by a methylene group shift or bond shift resulting in ring expansion to a 2° carbocation. This is the driving force of this rearrangement.

4. Methylcyclopentane rearranges to give cyclohexane when treated with the Lewis acid $AlCl_3$ in the presence of catalytic amount of an alkyl halide (RCl). Provide a reasonable mechanism for this transformation.



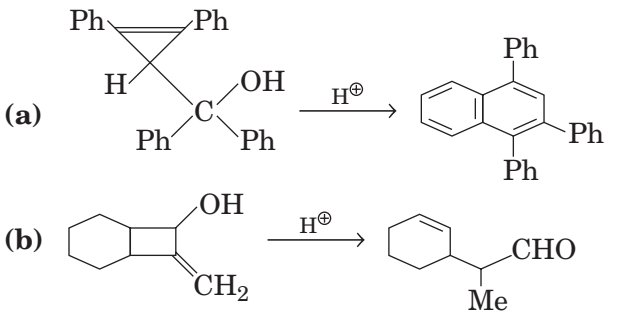
Methylcyclopentane — Cyclohexane

Solution The reaction proceeds through the steps as follows:



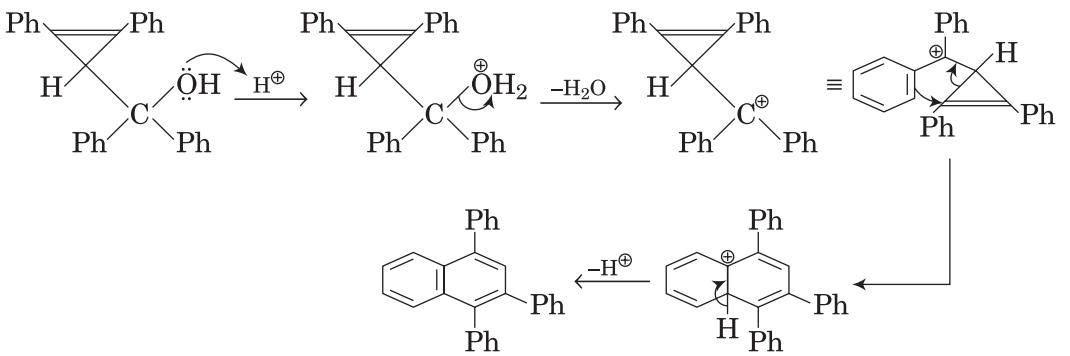
The reaction involves the formation of a 2° carbocation by removal of $H^{\ominus}$ from the substrate under the influence $R^{\oplus}$ with simultaneous bond migration (to avoid the formation of a very unstable 1° carbocation).

5. Suggest a mechanism for each of the following two rearrangements:

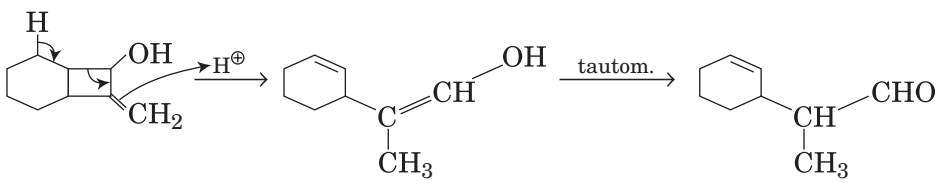


Solution

(a) The mechanism of this reaction involves the steps as follows:



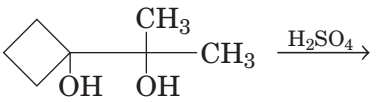
(b)



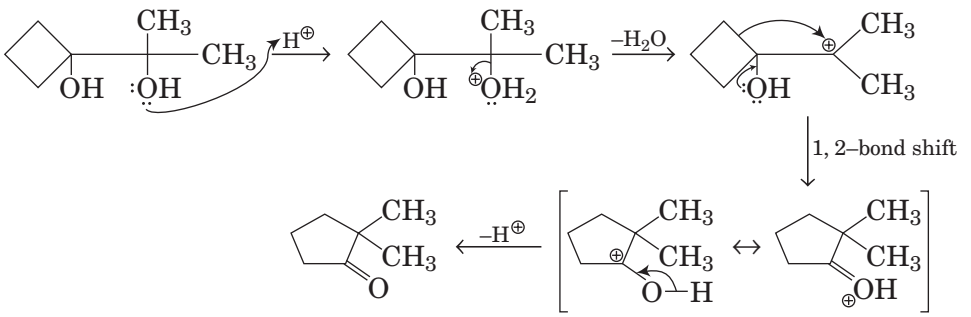
The hydroxyl group does not undergo protonation to be lost as water because a positive charge on a four-membered ring is not stable due to angle strain. An

alternate reaction involving protonation of the double bond with simultaneous ring opening and proton loss occurs to yield, after tautomerization, an aldehyde.

6. Predict the product of the following reaction and explain its formation:

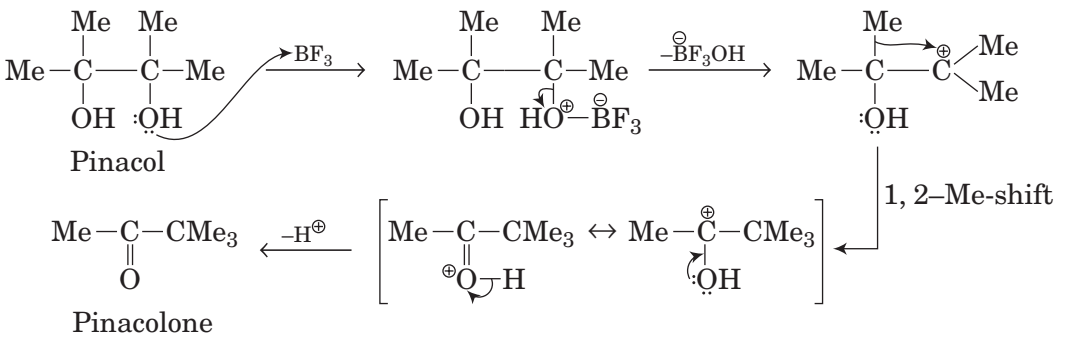


Solution This is a pinacol rearrangement in which a C—C σ-bond of the ring is the migrating group. Migration of methyl does not take place because the formation of the cyclobutyl $C^{\oplus}$ is unlikely as ring strain increases in going from 90° to 120°. Four-membered rings adjacent to cation readily rearrange to five-membered rings in order to relieve ring strain. The mechanism of the reaction may be written as follows:

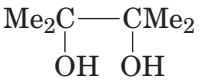


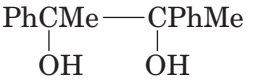
7. When pinacol ($Me_2COHCOHMe_2$) is treated with the Lewis acid BF_3, pinacolone is obtained. Give the mechanism of the reaction.

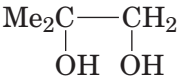
Solution



8. Predict the product expected to be formed when each of the following 1,2-diols is treated with conc. H_2SO_4 and explain your choice if more than one product is possible.

(a) 

(b) 

(c) 

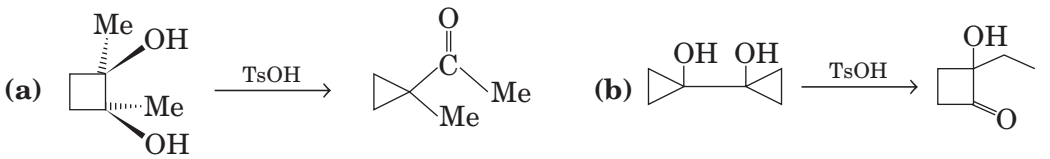
Solution

(a) Pinacolone (3,3-dimethylbutan-2-one), $MeCOCMe_3$.

(b) $Ph_2MeCC(=O)—Me$. This is because Ph migrates in preference to Me.

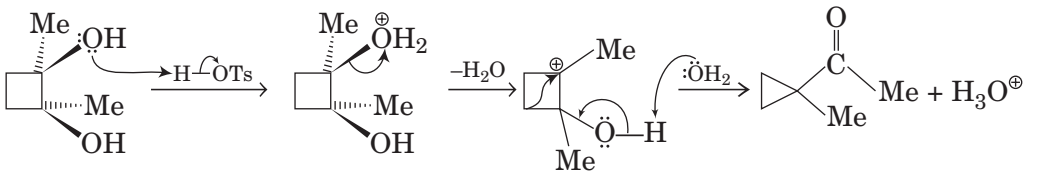
(c) Me_2CHCHO. The 3°-OH is lost as water to give a more stable 3° carbocation. Hydride migration occurs to yield an aldehyde.

9. Suggest mechanisms for the following two reactions:



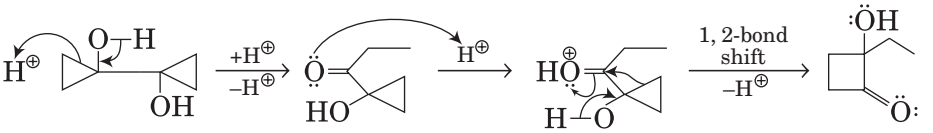
Solution

(a)

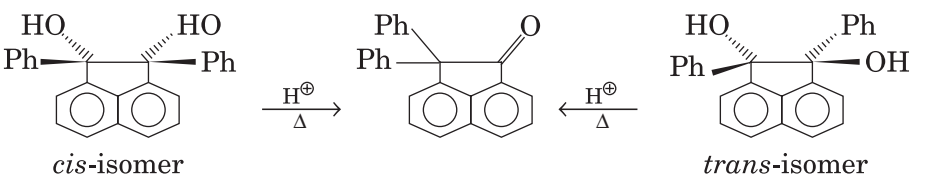


The diol involved in this pinacol rearrangement is symmetrical so it does not matter which —OH becomes protonated. Both three- and four-membered rings are strained and the σ-bonds are more reactive (higher HOMO energy) than normal. This makes ring contraction an easy process, even though the strain is not relieved.

(b) The cyclopropane ring opens up in the presence of acid (TsOH) to yield a hydroxy-ketone. The hydroxy ketone then rearranges in a pinacol fashion to yield another hydroxy ketone with ring expansion of the remaining cyclopropane.



10. Which diol will rearrange faster in pinacol rearrangement and why?



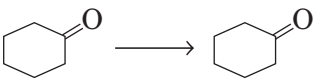
cis-isomer *trans*-isomer

Solution After expulsion of an –OH group as H_2O in the presence of acid, a phenyl group stabilizes the intermediate carbocation through the formation of a phenonium ion (a case of neighbouring group participation). In order for the phenyl group to participate in this

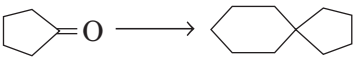
fashion, it should be *trans* to the leaving group $-\overset{\oplus}{O}H_2$ and this is because a back-sided participation (S_N2) is energetically more favourable. It thus follows that the *cis*-diol (in which the hydroxyl groups are *cis*, but each phenyl group is *trans* to a hydroxyl group) is more reactive than the *trans*-diol (in which each phenyl group is *cis* to a hydroxyl group). Hence, the *cis*-diol reacts at a faster rate than the *trans*-diol.

11. How would you carry out the following transformations?

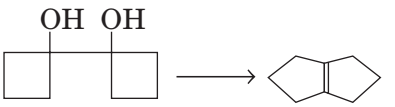
(a) $Me_2C = CH_2 \longrightarrow Me_2CCHO$ **(b)**



(c)



(d)



Solution

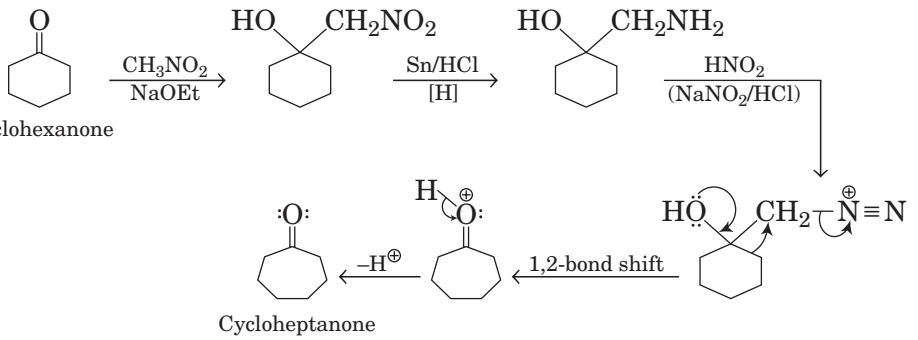
(a) $(CH_3)_2C{=}CH_2 \xrightarrow{Cl_2} (CH_3)_2\overset{Cl}{\overset{|}{C}}-CH_2Cl \xrightarrow[Ag_2O]{Moist} (CH_3)_2\overset{OH}{\overset{|}{C}}-CH_2OH$

2-Methylpropene

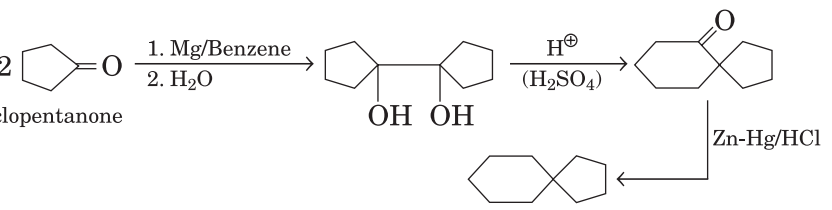
$\xrightarrow[(pinacol\ rearrangement)]{H_2SO_4} (CH_3)_2CH-CHO$

2-Methylpropanal

(b)

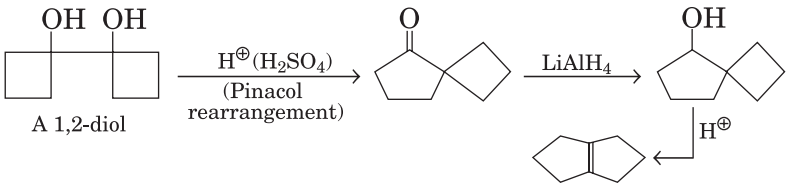


(c)



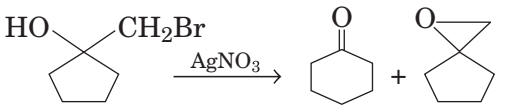
Spiro[4, 5]decane

(d)

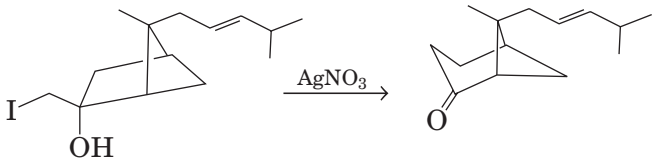


12. Suggest a mechanism for each of the following semipinacol rearrangements:

(a)

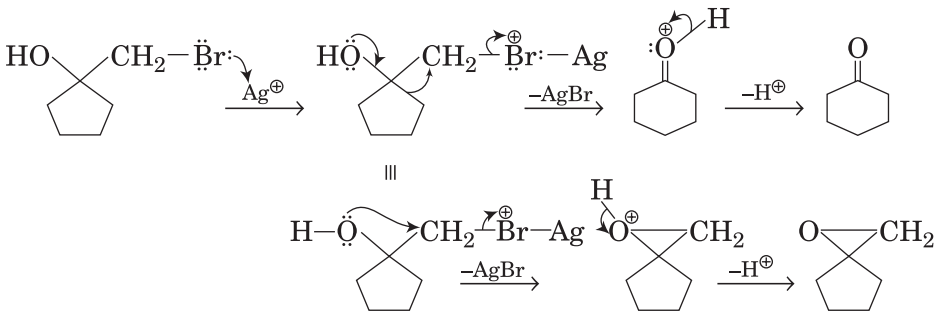


(b)

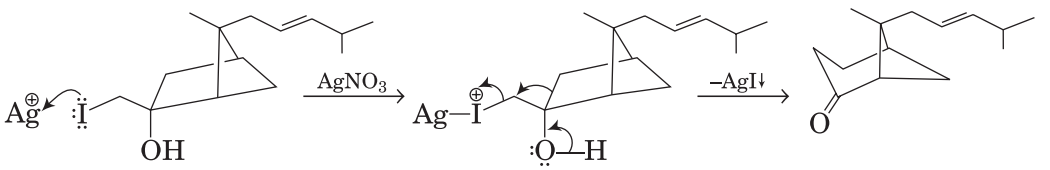


Solution

(a)

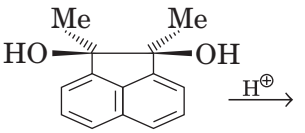


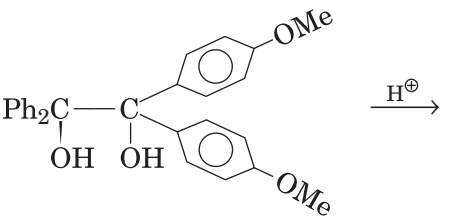
(b)



The silver ion coordinates with iodine to form a complex. The complex then dissociates involving bond migration (so as to prevent the formation of a very unstable 1° carbocation) to yield, after proton loss, a bicyclic ketone.

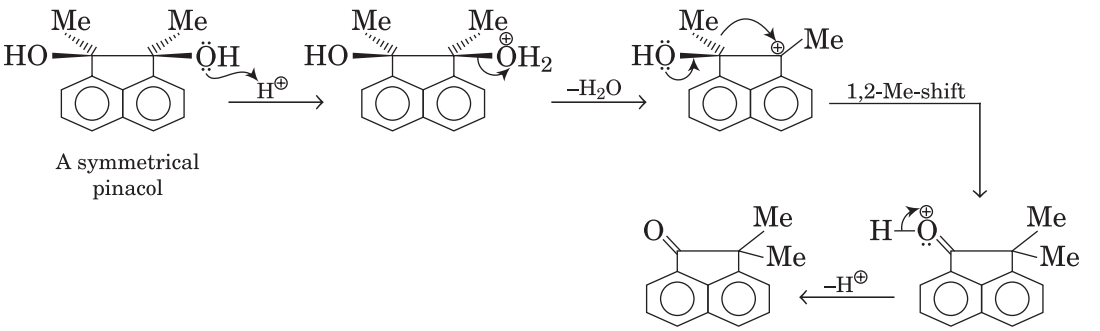
13. Predict the product and suggest a mechanism for each of the following pinacol rearrangements:

(a) 

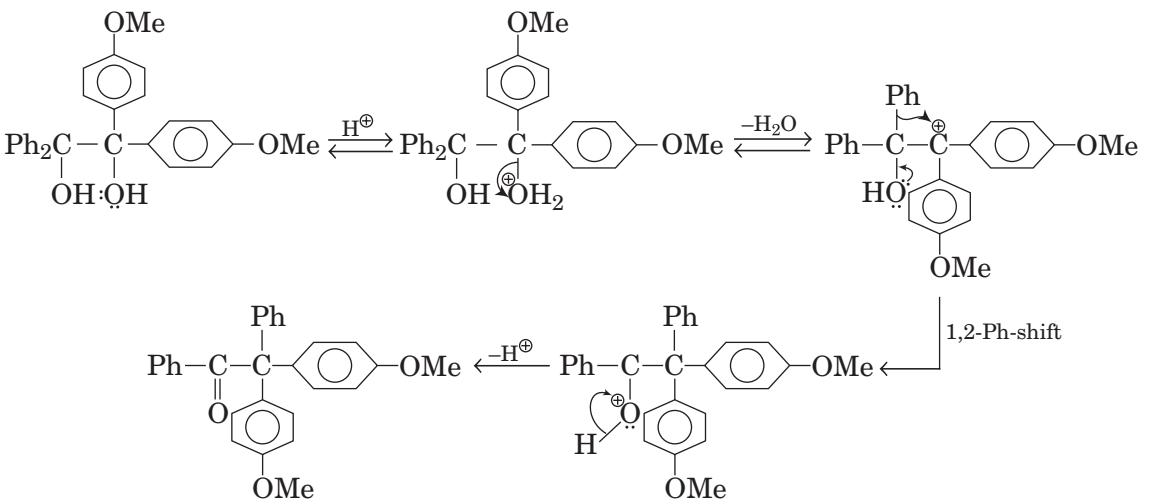
(b) 

Solution

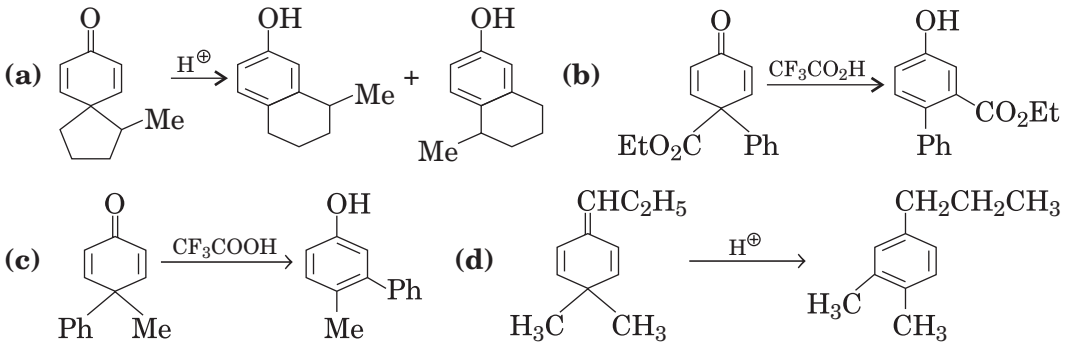
(a) This acenaphthene derivative undergoes pinacol rearrangement to give an acenaphthone derivative.



(b) This is an unsymmetrical pinacol. Therefore, the hydroxyl group attached to carbon containing two electron-releasing *p*-methoxyphenyl group will leave as water to form the relatively stable carbocation (more resonance-stabilized compared to the other possible carbocation).

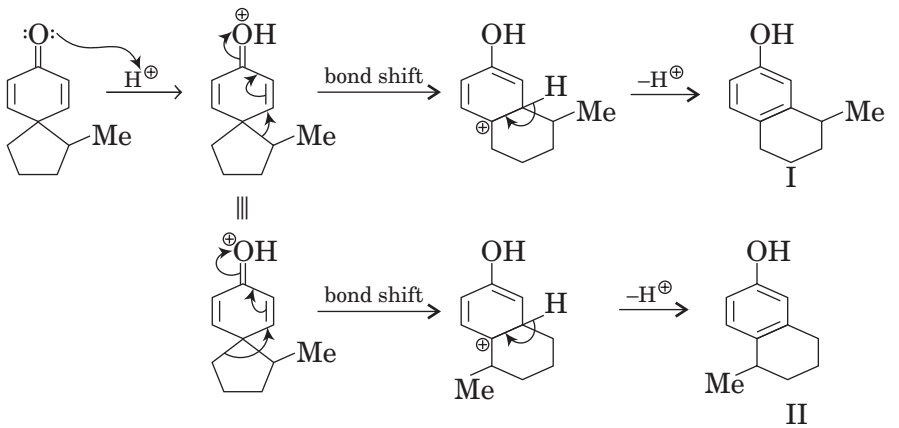


14. Sketch a suitable mechanism for each of the following reactions:



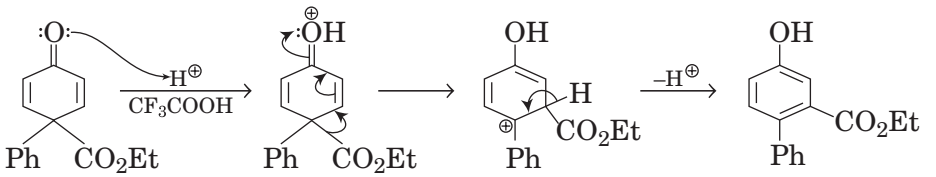
Solution

(a)



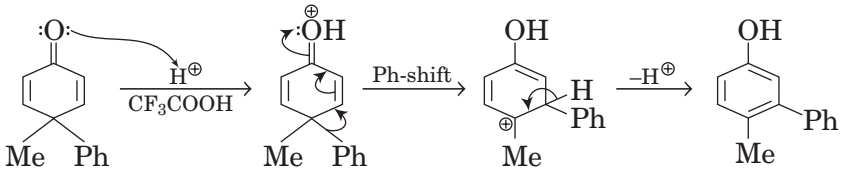
Migration of two different bonds gives rise to two isomeric tetrahydro-β-naphthols (I and II).

(b)

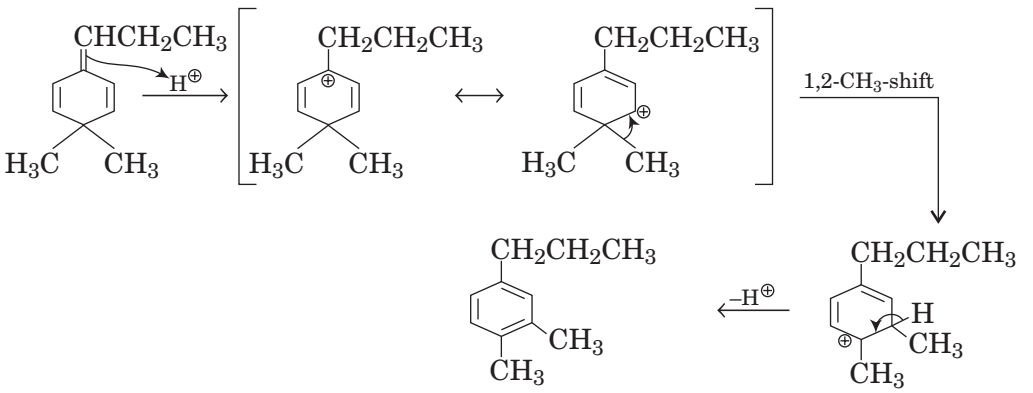


In this case, CO_2Et migrates, even though Ph has greater migratory aptitude. The reason is that the $-CO_2Et$ group is cation-destabilizing that it prefers to migrate rather than be left behind next door to a positive carbon.

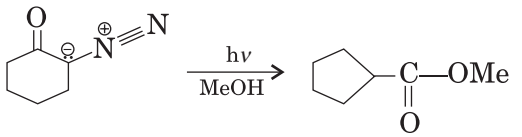
(c)



Ph migrates because its migratory aptitude is greater than Me.

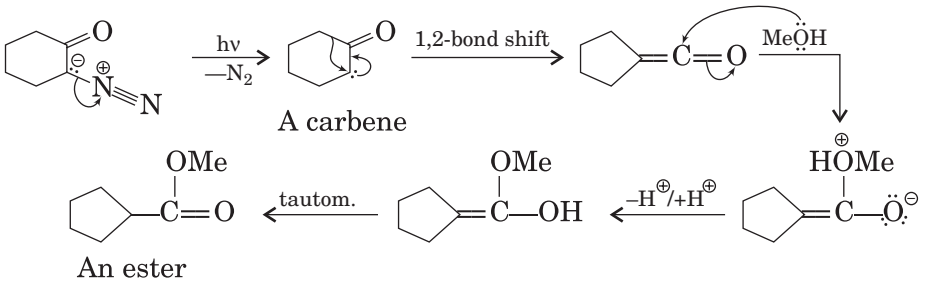
(d) 

15. Suggest a mechanism for the following reaction:



Solution

Cyclic diazoketones undergo ring contraction. The reaction proceeds as follows:



16. How would you carry out the following transformations?

(a) $Me_2CHCOOH$
(b) Me_2CHCH_2OH
(c) Me_2CHCH_2I
(d) $Me_2C{=}CH_2$

→ Me_2CHCH_2COOH
3-Methylbutanoic acid

Solution

(a) $Me_2CHCOOH \xrightarrow[\text{ether}]{SOCl_2} Me_2CHCOCl \xrightarrow[\text{ether}]{CH_2N_2} Me_2CHCOCHN_2 \xrightarrow[H_2O]{Ag_2O} Me_2CHCH_2COOH$

2-Methylpropanoic acid

3-Methylbutanoic acid

(b) $\underset{\text{2-Methyl-1-propanol}}{Me_2CHCH_2OH} \xrightarrow[H_2SO_4]{K_2Cr_2O_7} Me_2CHCOOH \xrightarrow[3.\ Ag_2O/H_2O]{1.\ SOCl_2/ether,\ 2.\ CH_2N_2/ether} \underset{\text{3-Methylbutanoic acid}}{Me_2CHCH_2COOH}$

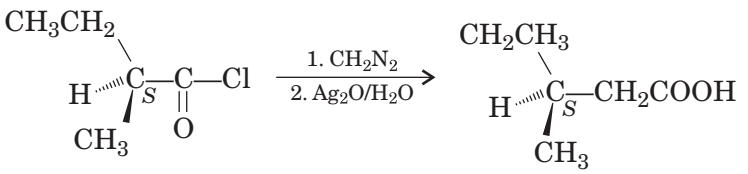
(c) $\underset{\text{1-Iodo-2-methylpropane}}{Me_2CHCH_2I} \xrightarrow{\text{aq. NaOH}} Me_2CHCH_2OH \xrightarrow[3.\ CH_2N_2/ether,\ 4.\ Ag_2O/H_2O]{1.\ K_2Cr_2O_7/H_2SO_4,\ 2.\ SOCl_2/ether} \underset{\text{3-Methylbutanoic acid}}{Me_2CHCH_2COOH}$

(d) $\underset{\text{2-Methylpropene}}{Me_2C{=}CH_2} \xrightarrow[2.\ H_2O_2/OH^{\ominus}]{1.\ B_2H_6/Et_2O} Me_2CHCH_2OH \xrightarrow[3.\ CH_2N_2/ether,\ 4.\ Ag_2O/H_2O]{1.\ K_2Cr_2O_7/H_2SO_4,\ 2.\ SOCl_2/ether} \underset{\text{3-Methylbutanoic acid}}{Me_2CHCH_2COOH}$

17. Predict the product and explain the stereochemical outcome of the following reaction (Arndt–Eistert synthesis):

$$(S)\text{–}CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HCOCl \xrightarrow[2.\ Ag_2O/H_2O]{1.\ CH_2N_2}$$

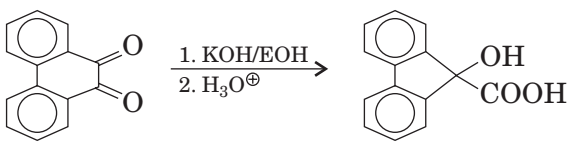
Solution (*S*)–$CH_3CH_2CH(CH_3)CH_2COOH$ will be obtained as the final product in the above reaction sequence. When the chiral alkyl group migrates, it begins to form a bond to the migration terminus as the bond from the migration origin is breaking. As a result, there is retention of configuration.



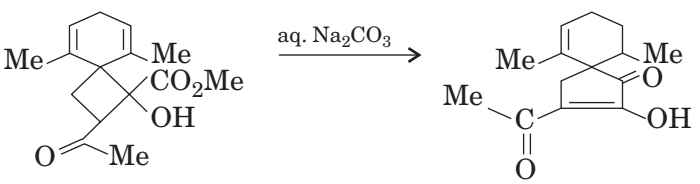
(configuration is retained)

18. Suggest an arrow formalism mechanism for each of the following reactions:

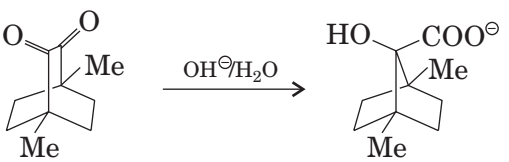
(a)



(b)

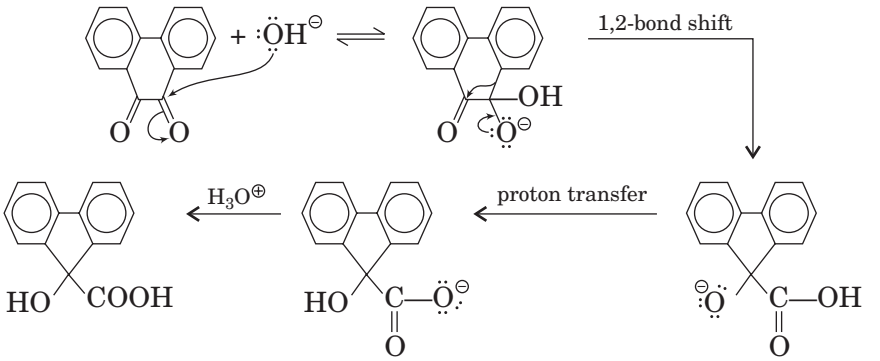


(c)

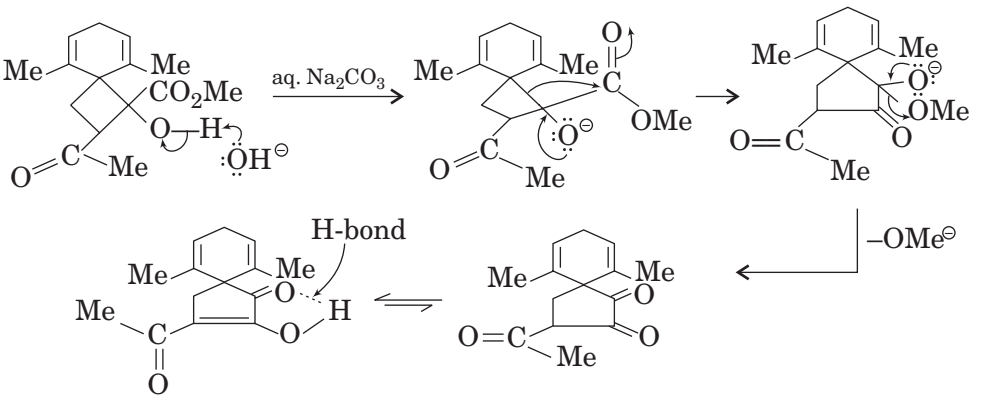


Solution

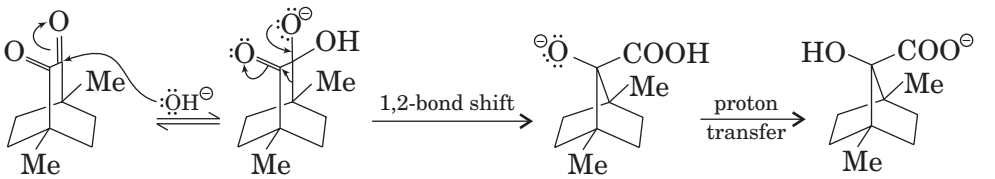
(a)



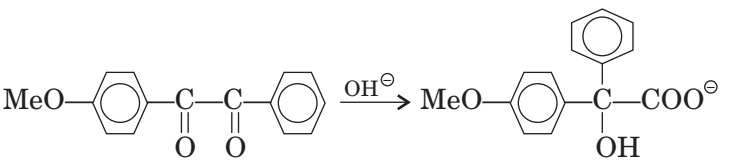
(b) A retro benzilic acid rearrangement:



(c)

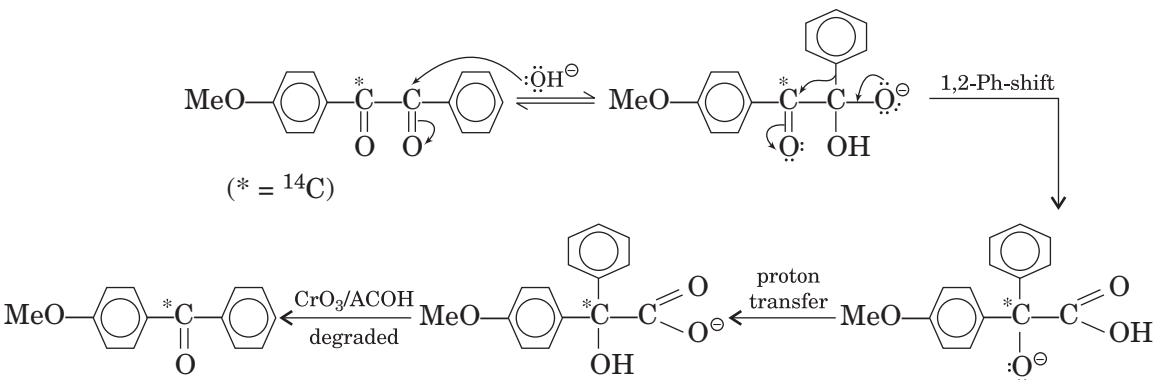


19. How can it be proved that in the following benzilic acid rearrangement, the phenyl group migrates?

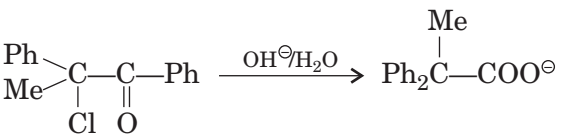


Solution The carbonyl group which is attached to the less electron-releasing of the two aryl group is relatively more electrophilic and hence, it undergoes nucleophilic attack by $OH^{\ominus}$ and consequently, the less electron-releasing group migrates preferentially to the other carbonyl group. Therefore, in this reaction, the less electron-releasing phenyl group

will migrate. This can be proved by a labelling experiment. When this diketone labelled by ^{14}C is subjected to benzilic rearrangement and the resulting benzilate anion is degraded by CrO_3/AcOH, a diaryl ketone is obtained. The resulting ketone is purified and analysed for ^{14}C with mass spectroscopy. An increase of molecular mass by two units than the normal (unlabelled) ketone has been observed. From this experiment, it becomes clear that the phenyl group must migrate during rearrangement.

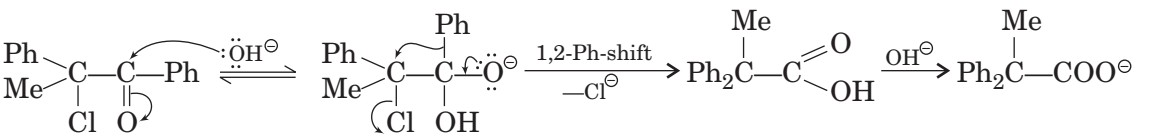


20. When α-haloketones having no α-H are treated with hydroxide, similar rearrangement is observed. This is known as semibenzilic acid rearrangement. For example:

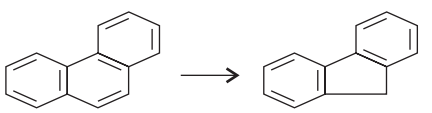


Give the mechanism of the reaction.

Solution The mechanism of the reaction involves the steps as follows:

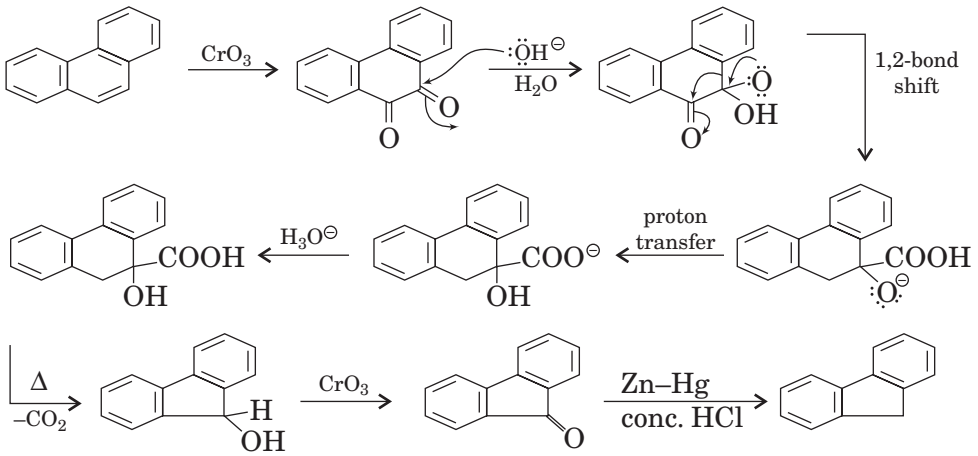


21. How would you carry out the following transformation?

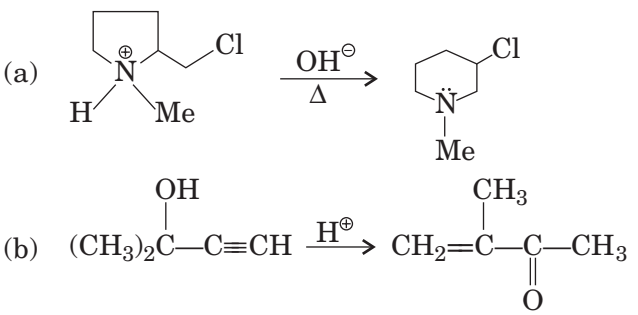


Phenanthrene Fluorene

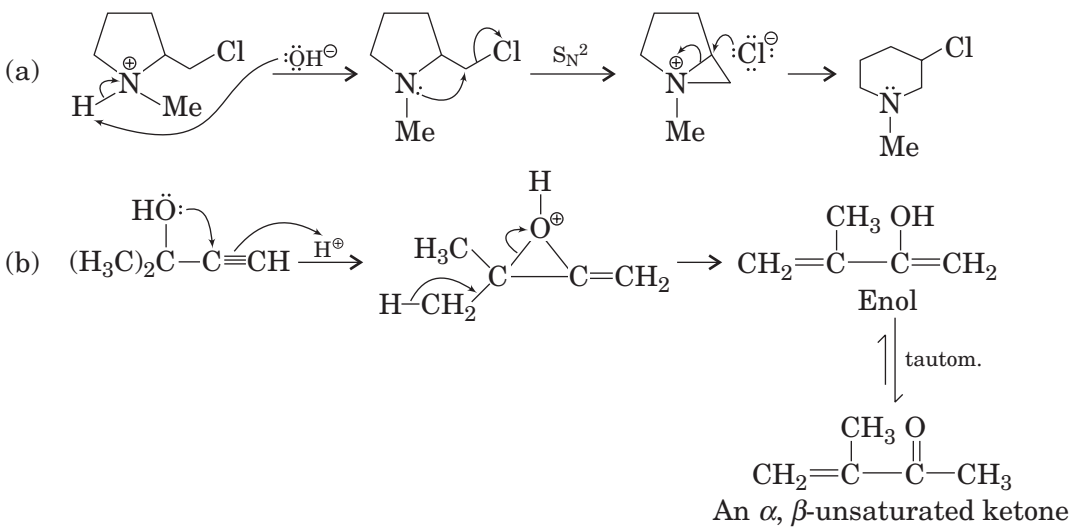
Solution



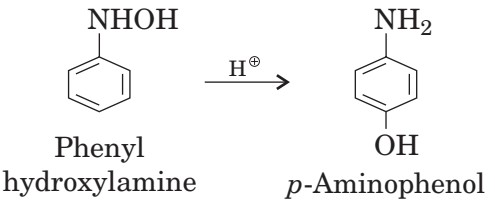
22. Provide a reasonable mechanism for each of the following reactions involving migration of heteroatoms:



Solution



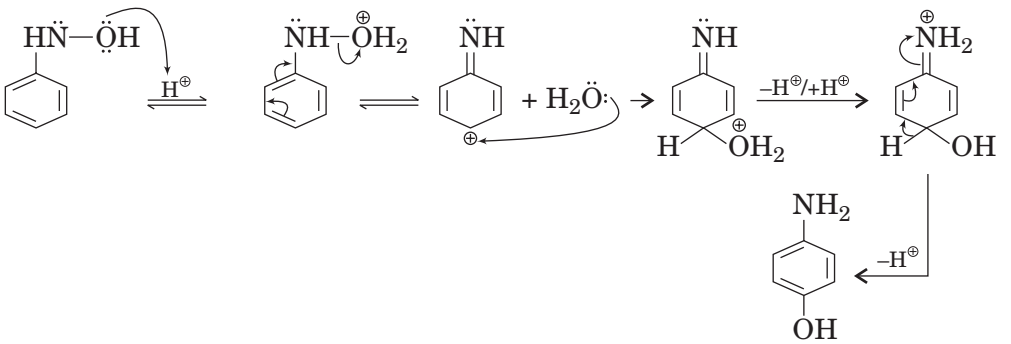
23. When aryl hydroxylamines are treated with acid, they are converted to *p*-aminophenols. This reaction is called *Bamberger rearrangement* which proceeds through intermolecular mechanism. For example:



Phenyl hydroxylamine — *p*-Aminophenol

Write down the mechanism of the reaction.

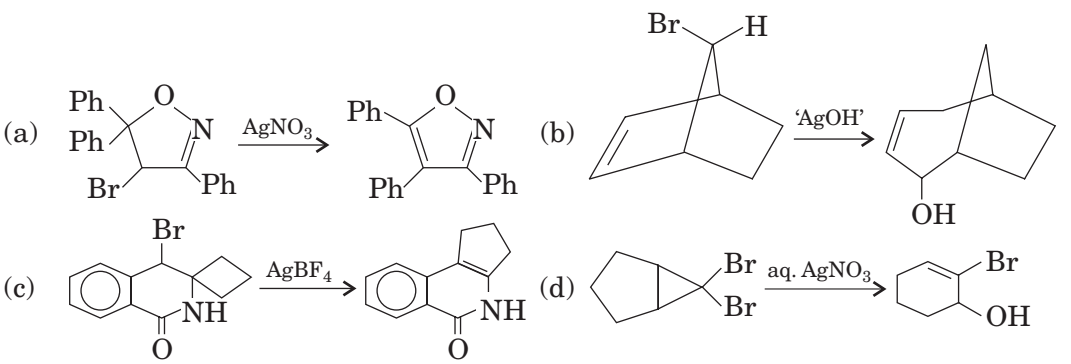
Solution The mechanism of the reaction involves the following steps:

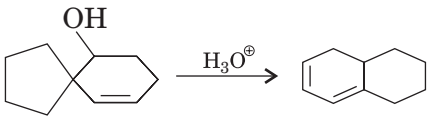


Protonation of phenylhydroxylamine followed by loss of water produces a cationic intermediate. Water attacks the intermediate at the *para*-position to produce, after proton loss, *p*-aminophenol.

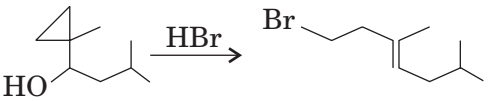
Study Problems

1. Suggest a mechanism for each of the following reactions:

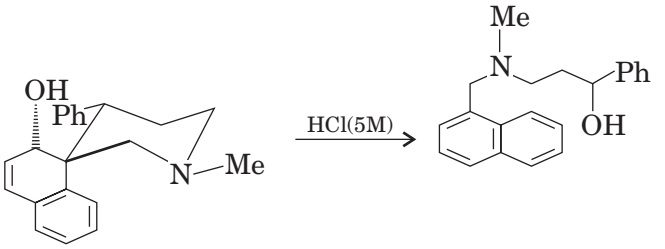


(e) 

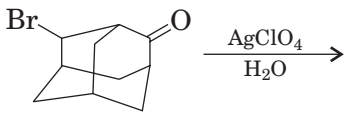
2. Suggest a mechanism for the following reaction and explain the alkene geometry:

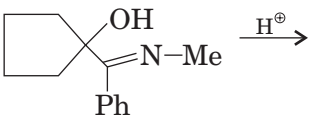


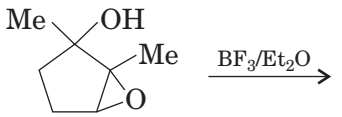
3. Suggest a reasonable mechanism for the following transformation:

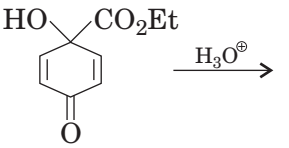


4. Predict the product and suggest a reasonable mechanism for each of the following reactions:

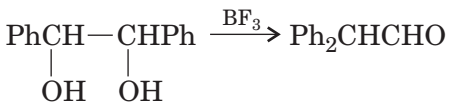
(a) 

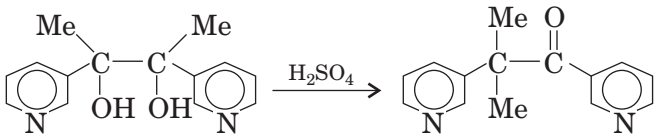
(b) 

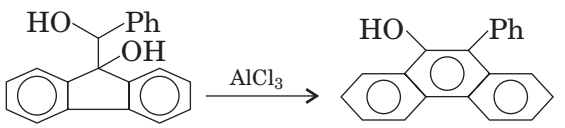
(c) 

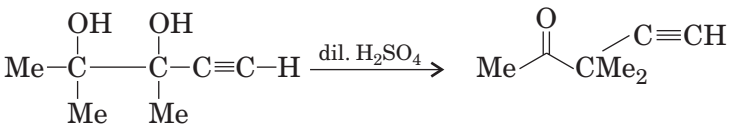
(d) 

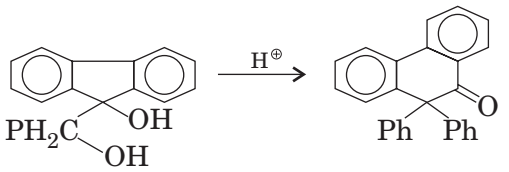
5. Write a suitable mechanism for each of the following rearrangements and give reasons:

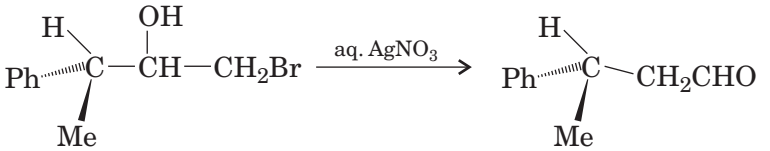
(a) 

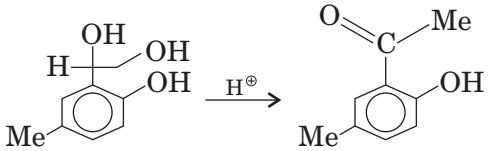
(b) 

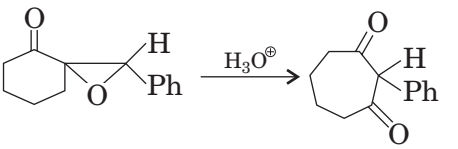
(c) 

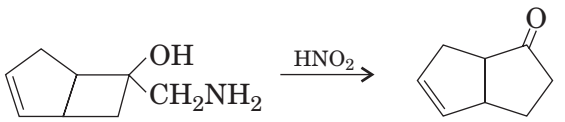
(d) 

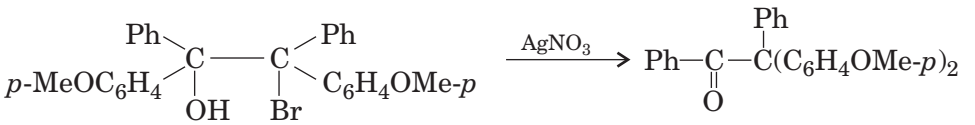
(e) 

(f) 

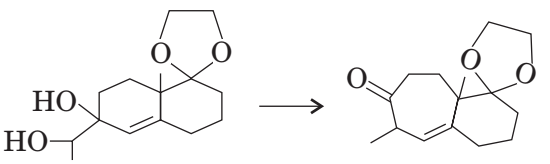
(g) 

(h) 

(i) 

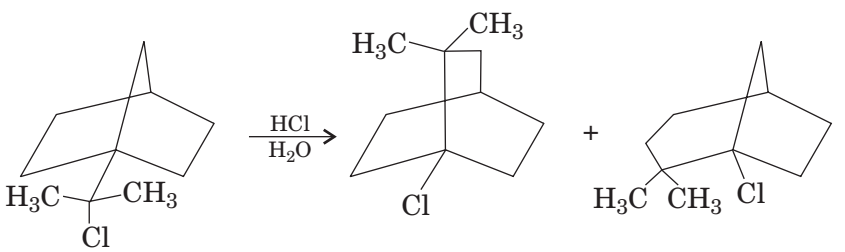
(j) 

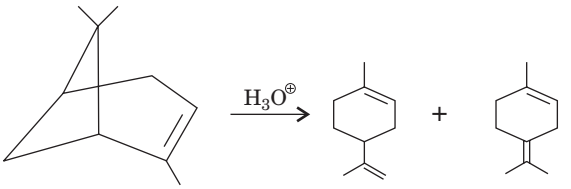
6. How would you carry out the following transformation?

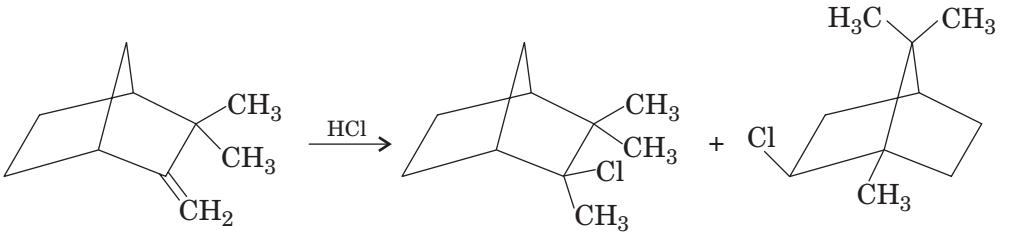


Explain why a normal acid-catalyzed pinacol rearrangement cannot be used for this transformation.

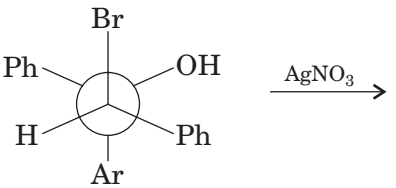
7. Write mechanisms that account for the products obtained in the following reactions:

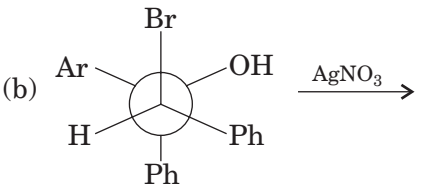
(a) 

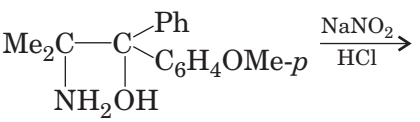
(b) 

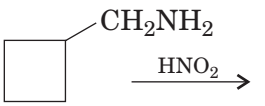
(c) 

8. Give the products of the following reactions with mechanistic explanations:

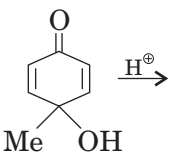
(a) 

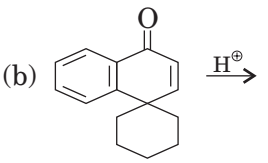
(b) 

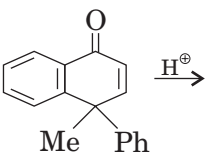
(c) 

(d) 

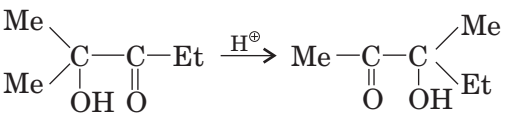
9. Predict the product and suggest a mechanism for each of the following dienone-phenol rearrangements:

(a) 

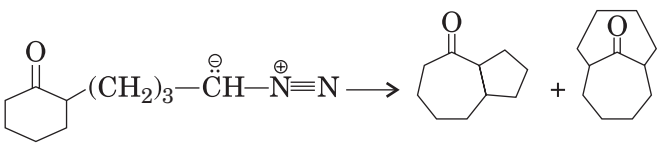
(b) 

(e) 

10. Rearrangement of α-hydroxyketone by the influence of acid is very similar to dienone-phenol rearrangement. Propose a reasonable mechanism for the following reaction:



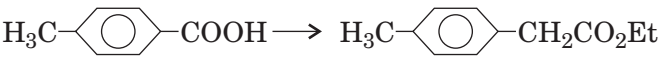
11. Sketch a reasonable mechanism for the following reaction:



[**Hint:** Migration of two different ring bonds leads to the formation of two isomeric ketones.]

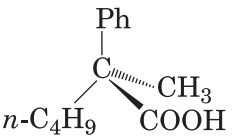
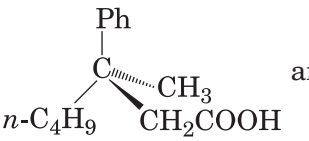
12. How would you carry out the following transformations?

(a) $Me_3CBr \rightarrow Me_3C\ CH_2COOH$

(b) 

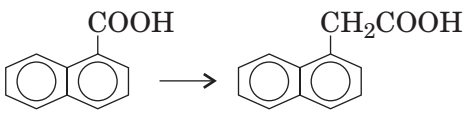
(c) $Me_2C{=}C{=} \rightarrow Me_3COO_2Me$

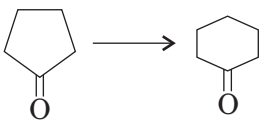
[**Hint:** (a) formation of Me_3CCOOH through Grignard synthesis followed by Arndt–Eistert synthesis. (b) Arndt–Eistert synthesis using EtOH as solvent. (c) Treatment with CH_2N_2/CH_2Cl_2 followed by $MeO^{\ominus}$/MeOH.]

13. Convert:  to  and vice versa.

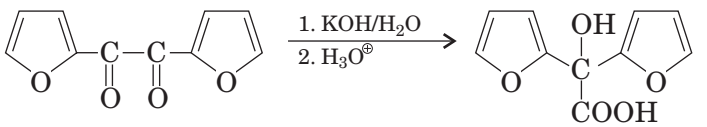
[**Hint:** The reagents required for reverse conversion are: (i) PCl_5, (ii) NH_3, (iii) Br_2/NaOH, (iv) $NaNO_2$/HCl (HNO_2) and (v) $K_2Cr_2O_7/H_2SO_4$.]

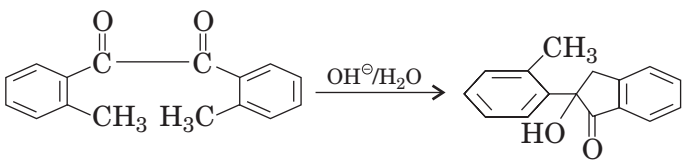
14. Illustrate the use of diazomethane for the following conversions:

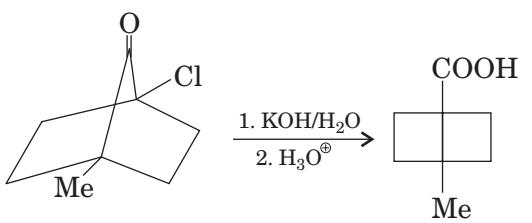
(a) 

(b) 

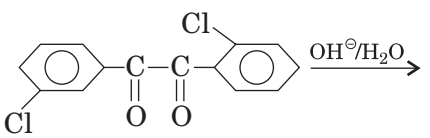
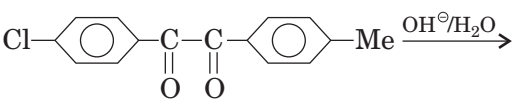
15. Write a reasonable mechanism for each of the following reactions:

(a) 

(b) 

(c) 

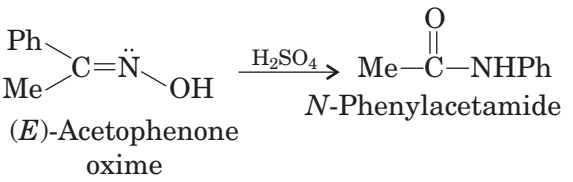
16. Predict the product and suggest a mechanism for each of the following reactions:

(a)  (b) 

4.1.2 Nucleophilic Rearrangements to Electron-Deficient Nitrogen

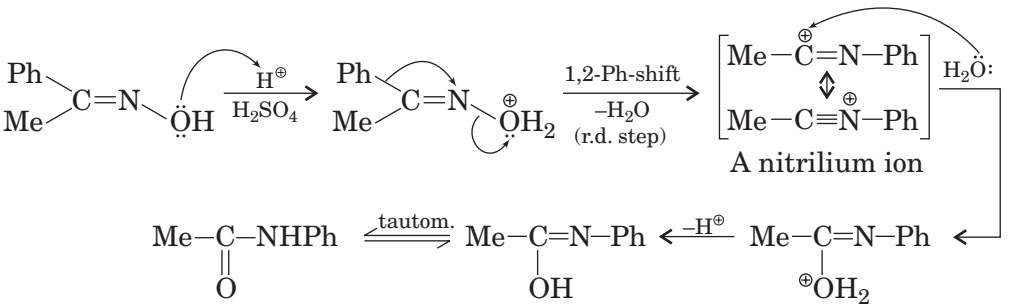
4.1.2.1 Beckmann rearrangement

When ketoximes are treated with acidic reagents like H_2SO_4, PCl_5, PPA, $PhSO_2Cl$, $SOCl_2$, P_2O_5, BF_3, Al_2O_3, SO_3, etc., they rearrange to give *N*-substituted amides. This reaction is called the *Beckmann rearrangement*. For example, the (*E*)-diastereoisomer of acetophenone oxime produces *N*-phenylacetamide.



(*E*)-Acetophenone oxime — *N*-Phenylacetamide

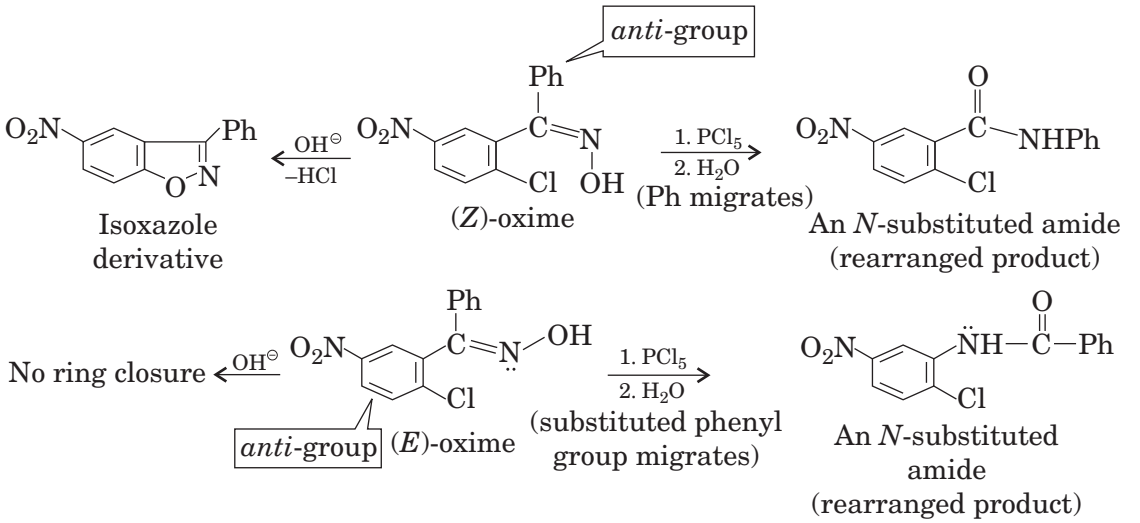
Mechanism of the reaction The mechanism of the reaction involves the steps as follows:



In the first step of the reaction, the hydroxyl group takes up a proton and converted into a better leaving group. In the second step, water is lost with simultaneous migration of the group *trans* to the leaving group to form a nitrilium ion. In the third step, the nitrilium ion intermediate undergoes nucleophilic attack by water to form, after proton loss, an imidol that readily tautomerizes to give the corresponding *N*-substituted amide.

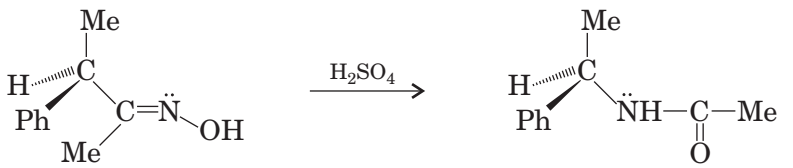
Characteristic features

(i) **The migrating group in this rearrangement approaches the nitrogen atom from the opposite side to the departing –OH group:** This has been confirmed experimentally by carrying out the rearrangement using ketoximes of known configuration. For example, two diastereoisomic oximes can be obtained from 2-chloro-5-nitrobenzophenone. The configurations of these oximes may be confirmed by a ring closure experiment. The oxime which on treatment with alkali produces an isoxazole derivative by eliminating a molecule of HCl must be (*Z*)-oxime (–OH and –Cl are close) and the oxime which does not give such a product must be the (*E*)-oxime (–Cl and –OH are not close). When these oximes of known configuration are subjected to Beckmann rearrangement, it has been observed that the group *anti* to the –OH group always migrates to give the product.



(ii) **The rearrangement is intramolecular:** That the rearrangement is intramolecular can be proved by the following two experiments:

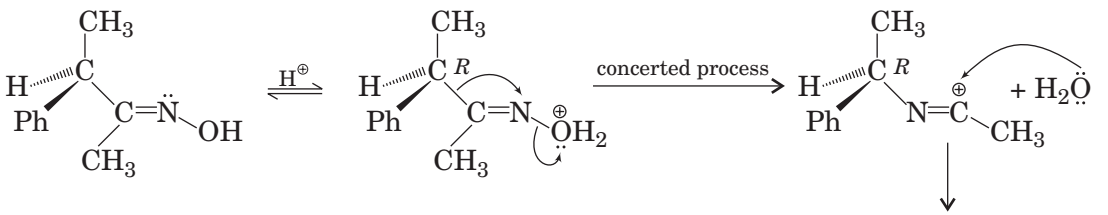
(a) **Stereochemical evidence:** When the migrating group bears a chiral centre, the configuration of the chiral centre is retained in the product. For example, when (*R*)-*α*-phenylethyl methyl ketoxime is treated with sulphuric acid, (*R*)-*N*-*α*-phenylethylacetamide is obtained with almost 100% optical purity.

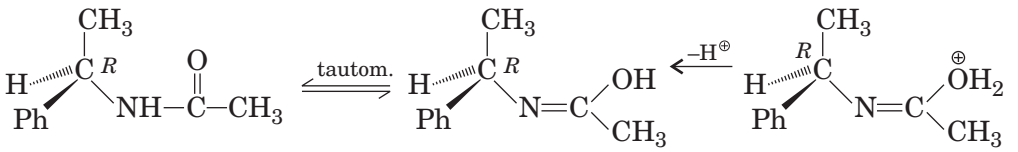


(*R*)-2-Phenylethylmethyl ketoxime

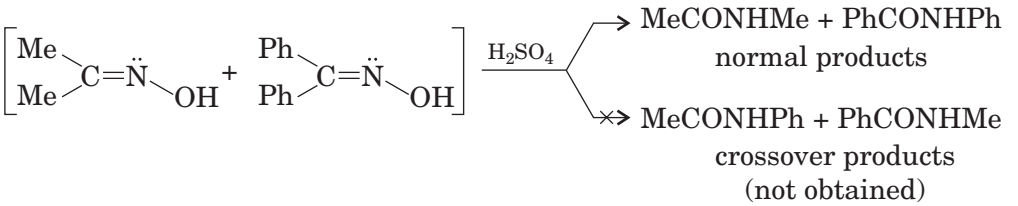
(*R*)-*N*-α-Phenylethylacetamide (configuration retained)

This shows that the migrating group does not become completely detached from the reminder of the molecule. Thus, the cleavage of C–C *σ*-bond and the formation of new C–N *σ*-bond take place on the same side of the chiral carbon in a synchronous manner. Discrete carbanion formation may lead to the formation of racemic product. The rearrangement is thus strictly intramolecular.



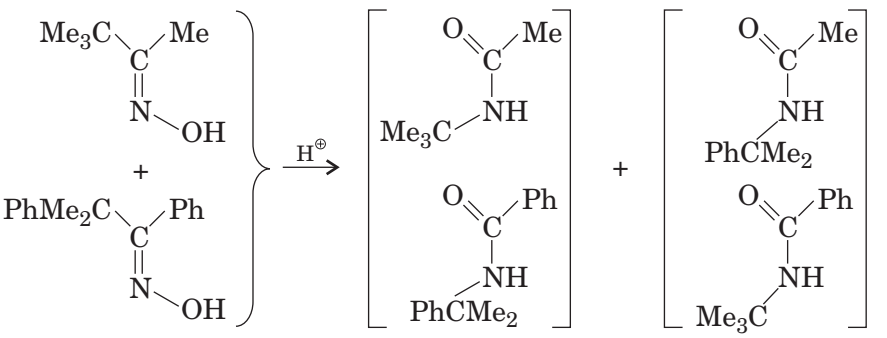


(b) **Crossover experiment:** When the following two different ketoximes are subjected to the Beckmann rearrangement simultaneously in the same solution, no crossover product is obtained.

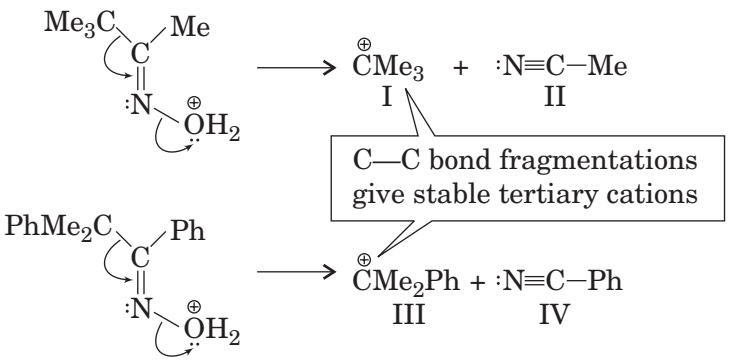


This crossover experiment also proves that the migrating group never becomes free from the rest of the molecule during rearrangement, otherwise crossover products would have been obtained. The rearrangement is, therefore, intramolecular in nature.

(c) **The Beckmann fragmentation and evidence in favour of intermolecular mechanism:** When an oxime containing a *tert*-butyl group *anti* to the –OH group and another oxime with a $PhMe_2C$– group *anti* to the –OH group are mixed together and treated with acid, two crossover products along with the expected products are obtained. This observation suggests that each migrating tertiary group must have lost contact with the amide fragment it started out with. Each molecule reacts by a fragmentation mechanism to give a *tert*-alkyl cation and a nitrile. These cations then react indiscriminately to give four different amides. The rearrangement, particularly in these cases, are, therefore, intermolecular in nature and this observed because the migrating groups provide some degree of cation stabilization.

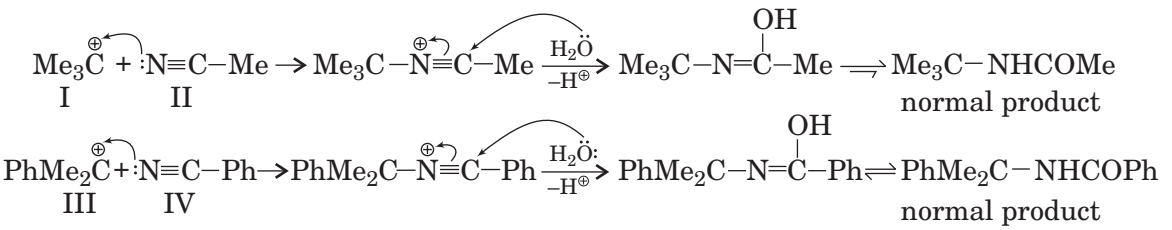


Mechanism:

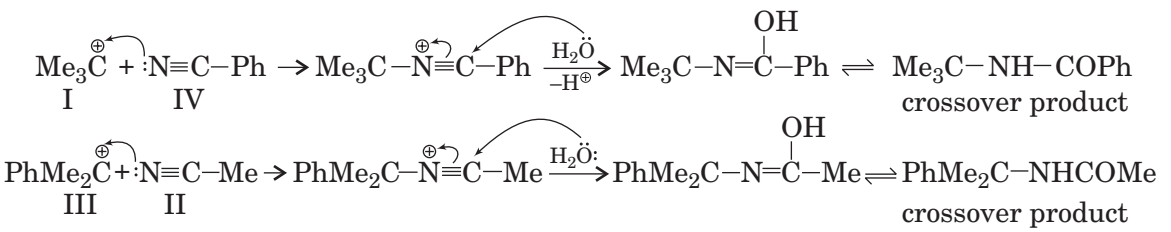


Now, I combines with II and IV to give a normal and a crossover product, respectively. Similarly, III combines with IV and II to give a normal and a crossover product, respectively.

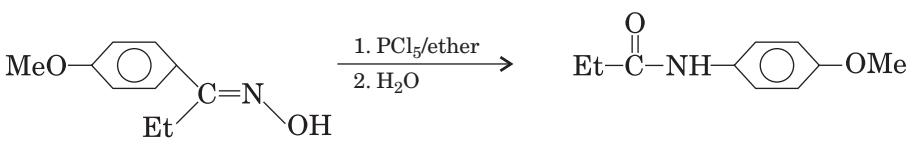
Formation of normal products:



Formation of crossover products:

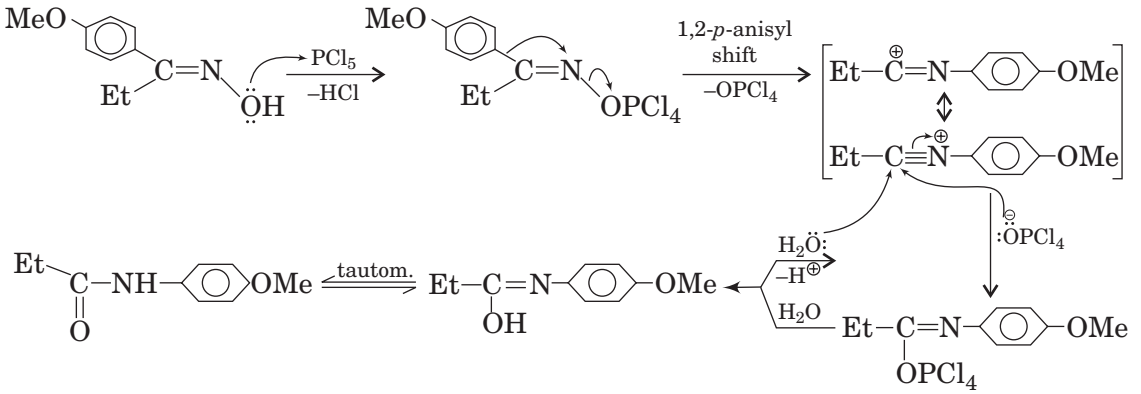


Examples of Beckmann rearrangements in which PCl_5, $PhSO_2Cl$ and $(CF_3CO)_2O$ are used as reagents:

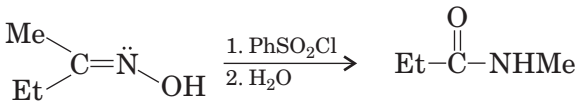
1. 

(*E*)-Ethyl *p*-Anisylketoxime *N*-*p*-Anisylpropionamide

Mechanism: The reaction proceeds through the steps as follows:

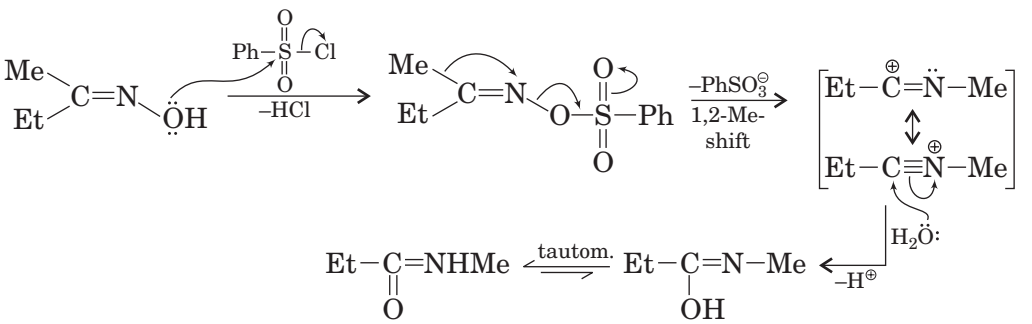


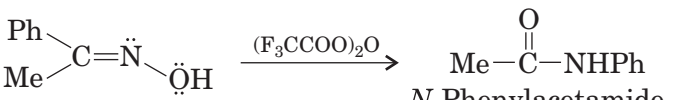
PCl_5 converts the oxime –OH groups into a good leaving group –$OPCl_4$. The *p*-anisyl group situated *trans* to the leaving group then migrates to form a nitrilium ion. The nitrilium ion reacts with water to produce finally the anilide. The nitrilium ion may also add to $\overset{\ominus}{O}PCl_4$ to give an intermediate which on hydrolysis produces the anilide.

2. 

(*Z*)-2-Butanone oxime *N*-Methylpropionamide

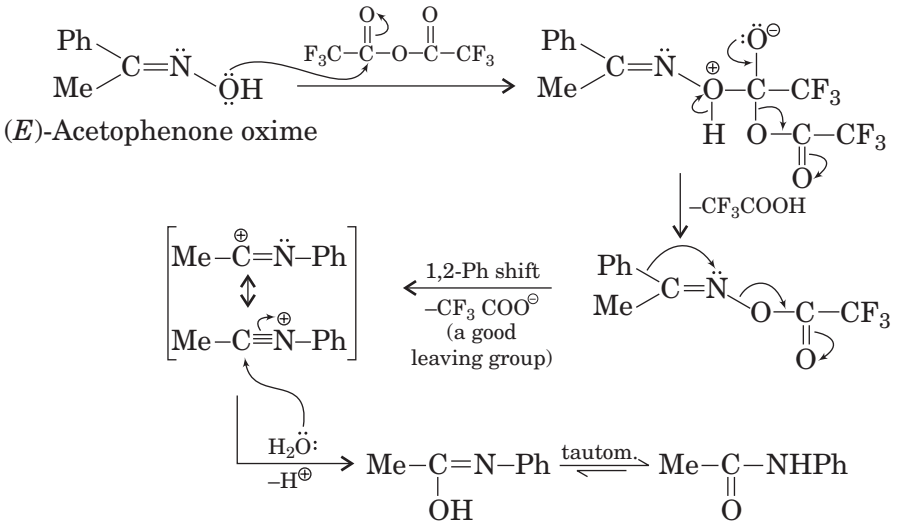
Mechanism: The reaction proceeds through the steps as follows:



3. 

(*E*)-Acetophenone oxime *N*-Phenylacetamide

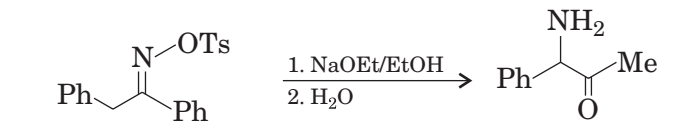
Mechanism: The mechanism of the reaction may be outlined as follows:



Trifluoroacetic anhydride converts the hydroxyl group of oxime to a good leaving group ($CF_3 \leftarrow COO^{\ominus}$ is the conjugate base of a strong acid).

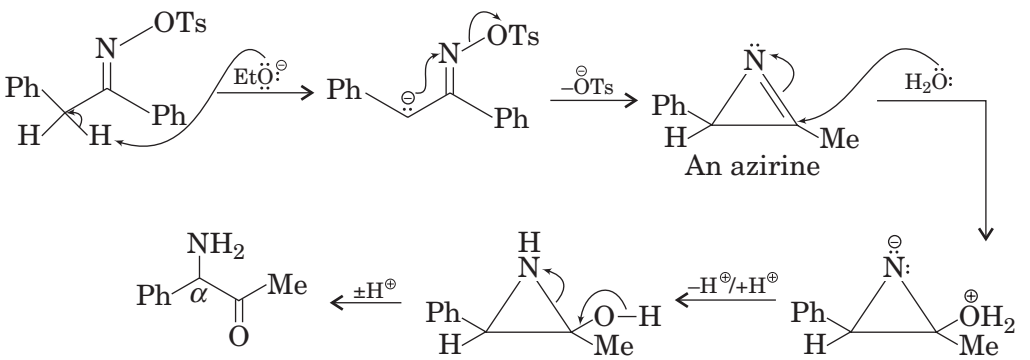
4.1.1.2 Neber rearrangement

The conversion of ketoxime tosylate into α-amino ketones by the action of a base such as ethoxide or pyridine is known as *Neber rearrangement*. For example:



A Ketoxime tosylate α-Amino ketone

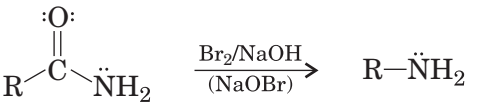
Mechanism of the reaction The mechanism of the reaction involves initial deprotonation and then internal displacement of tosyl group to form an azirine intermediate. The azirine on hydrolysis yields an α-amino ketone.



Unlike Beckmann rearrangement, Neber rearrangement is nonstereospecific in nature. This is because, when an oxime of an unsymmetrical ketone with different acidities of α-Hs is used, the carbon containing the more acidic hydrogen actually participates irrespective of the stereochemistry of the tosylate.

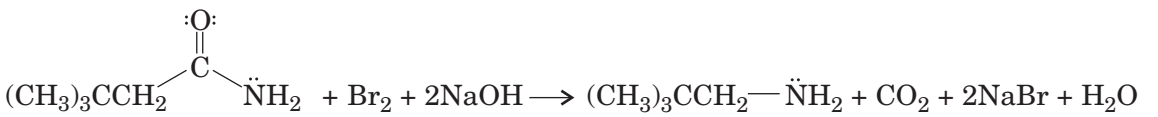
4.1.2.3 Hofmann rearrangement

When a primary amide is treated with an alkaline solution of bromine (sodium hypobromite) or chlorine (sodium hypochlorite), the corresponding primary amine with one carbon atom less is obtained. The reaction involving loss of the carbonyl carbon is known as the *Hofmann rearrangement*. This is also called the *Hofmann hypobromite reaction* or *Hofmann degradation*.



A primary amide A primary amine

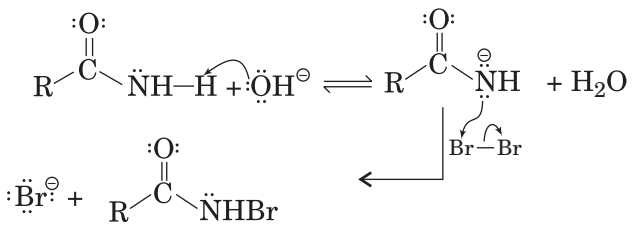
When 3,3-dimethylbutanamide, for example, is treated with bromine and alkali, 2,2-dimethyl-1-propanamine is obtained.



3,3-Dimethylbutanamide 2,2-Dimethyl-1-propanamime

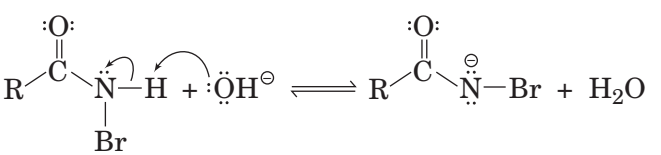
Mechanism of the reaction The mechanism of the reaction involves the steps as follows:

Step 1: The amide undergoes base-promoted bromination to produce an *N*-bromoamide. The process involves ionization of the amide N–H followed by reaction of the resulting anion with bromine.

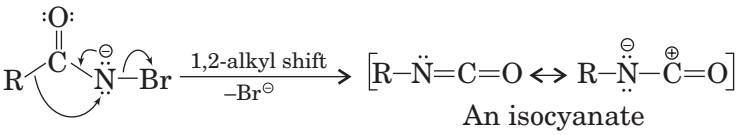


An *N*-bromoamide

Step 2: The *N*-bromoamide is even more acidic than the starting amide due to the presence of the electronegative bromine atom and so, it also ionizes to produce the corresponding anion.



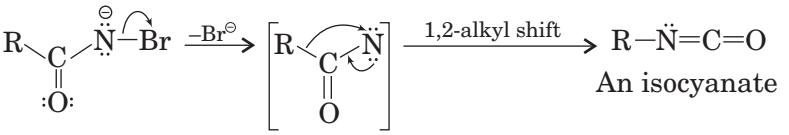
Step 3: The *N*-bromo anion then rearranges to an isocyanate. The rearrangement involves migration of R from carbon to nitrogen with simultaneous loss of bromine.



An isocyanate

The rearrangement is, therefore, concerted.

This step may involve loss of bromine to form an unstable nitrene intermediate followed by the actual migration of R.

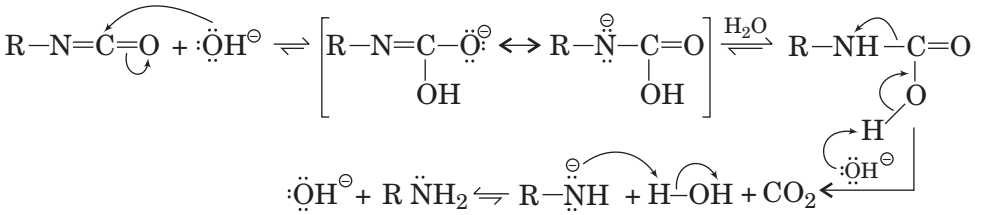


An isocyanate

An acylnitrene

However, the question of whether a nitrene is involved in this rearrangement is not completely settled and most of the available evidence favours the concerted reaction.

Step 4: The isocyanate cannot be isolated because it cannot survive in the presence of base. It undergoes hydrolysis readily to give the corresponding carbamic acid. The unstable carbamic acid decarboxylates to give the end-product amine.



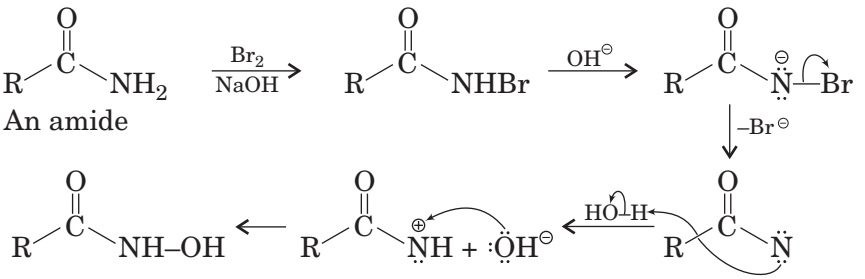
An examination of the first two steps of this mechanism shows that, initially, two hydrogen atoms must be present on the nitrogen atom of the amide for the reaction to take place. Therefore, the Hofmann rearrangement is limited to amides of the type $RCONH_2$. Kinetic studies show that the step 3 is the rate-determining step of the reaction.

Evidence in favour of the mechanism The evidence in favour of the mechanism of the Hofmann rearrangement are as follows:

(i) Under suitable conditions, it is possible in the case of some amides to trap or isolate RCONHBr, RCO$\overset{\ominus}{\text{N}}$BrNa$^{\oplus}$ and R—N=C=O. When subjected to normal reaction conditions, these intermediates result in the formation of usual reaction products at a rate not slower than the rate of the overall reaction. Hence, the mechanistic pathway suggested for this reaction is that which accounts for the formation of these intermediates.

(ii) That the rearrangement is a concerted (one-step) intramolecular process can be proved by the following observations:

(a) If the rearrangement is a two-step process involving an acylnitrene, a hydroxamic acid is expected to be formed by the reaction of this intermediate with water. But hydroxamic acids have never been isolated during Hofmann rearrangement. Hence, it is not a two-step process involving a nitrene intermediate.

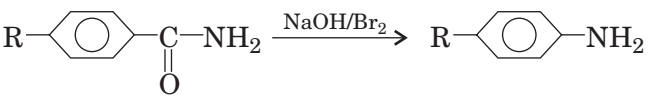


An amide

A hydroxamic acid

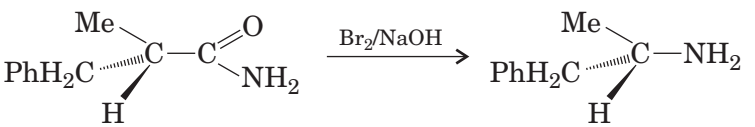
An acylnitrene

(b) When the migrating group is aryl, the rate of rearrangement increases by the presence of electron-releasing substituent in the *para*-position of the ring. The reactivity of R in the following reaction is of the order: *p*-NO_2 – < *p*-Cl– < –H < *p*-CH_3 – < *p*-OCH_3–.



The reaction rate thus depends on the nature of the substituent in the migrating aryl group. This observation suggests that the rearrangement is concerted and the rearrangement step is the rate-determining step of the reaction.

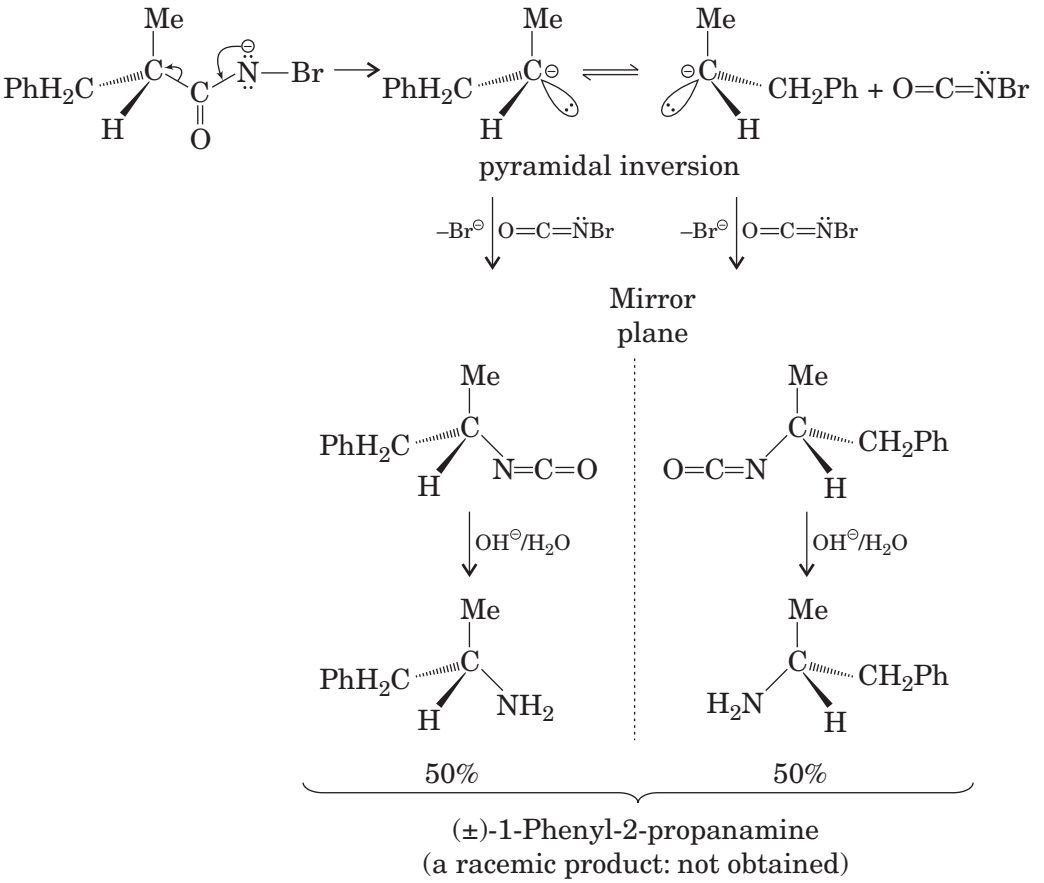
(c) When the migrating group is chiral, the rearrangement is found to take place with retention of configuration in the migrating group. For example, when (*S*)-2-methyl-3-phenylpropanamide is treated with Br_2/KOH, (*S*)-1-phenyl-2-propanamine of essentially same optical purity is obtained.



(configuration retained)

This observation suggests that the migrating group never becomes detached during the rearrangement, i.e. the rearrangement is a concerted (one-step) intramolecular process. Formation of a discrete carbanion before the loss

of bromide ion should have given racemized isocyanate and subsequently racemized amines because a carbanion may undergo pyramidal inversion very rapidly. This may be shown as follows:



(d) When the rearrangement is carried out with a mixture of two primary amides with one of them labelled with ^{15}N, then no crossover products are obtained. For example:

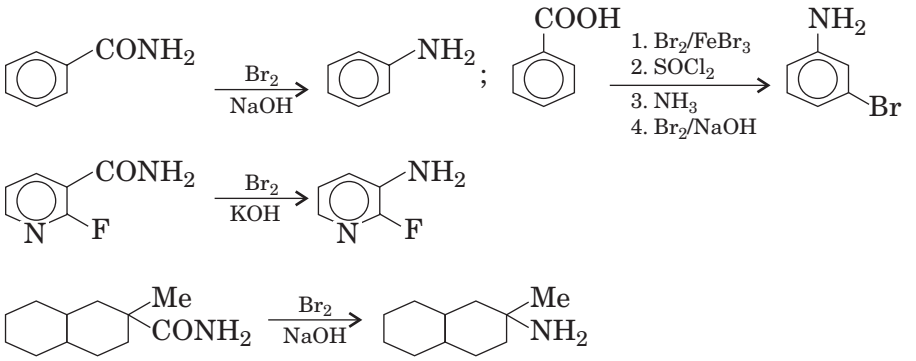
$$C_2H_5{}^{15}NH_2 + CH_3NH_2 \xleftarrow[\text{NaOH}]{Br_2} \left[\begin{matrix} CH_3CO{}^{15}NH_2 \\ + \\ C_2H_5CONH_2 \end{matrix}\right] \xrightarrow[\text{NaOH}]{Br_2} CH_3{}^{15}NH_2 + C_2H_5NH_2$$

crossover products (not obtained) — normal products

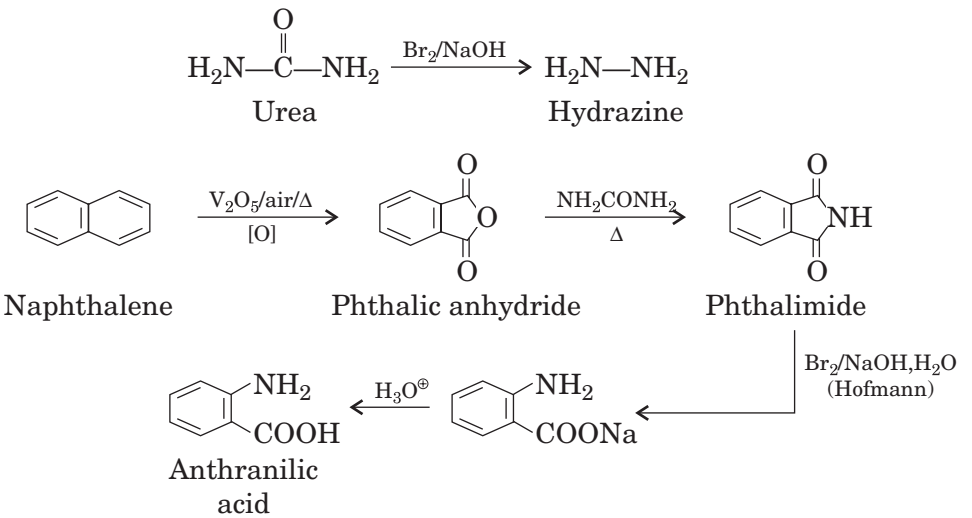
The observation of this crossover experiment suggests that the migrating group does not become detached from the rest of the molecule, i.e. the rearrangement is an intramolecular concerted (one-step) process.

Applications The Hofmann rearrangement finds immense applications in organic synthesis. A few instances are given below:

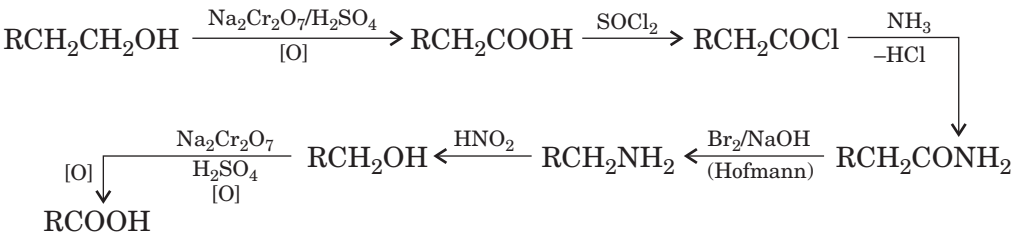
(i) **Synthesis of amines:**



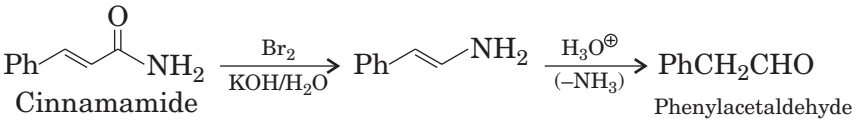
(ii) Hydrazine and anthranilic acid, the two important chemicals, can be prepared by using this reaction:



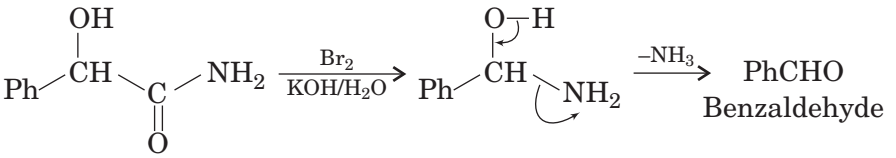
(iii) An alcohol or a carboxylic acid may be descended to its lower homologue by using this reaction:



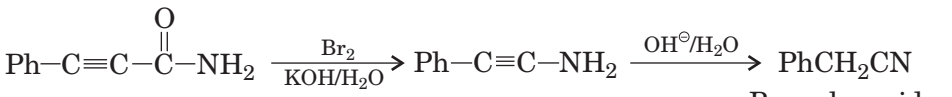
(iv) Aldehydes and nitriles can be synthesized by using this reaction. For example,



Cinnamamide — Phenylacetaldehyde



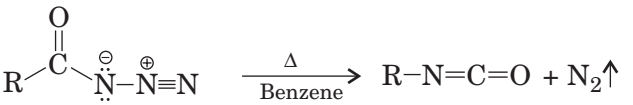
Mandelamide — Benzaldehyde



3-Phenylpropynamide — Benzylcyanide

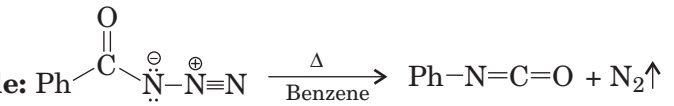
4.1.2.4 Curtius rearrangement

Thermal decomposition of acyl azides in benzene or chloroform solution to produce the corresponding isocyanates is known as the *Curtius rearrangement*.



An acylazide — An isocyanate

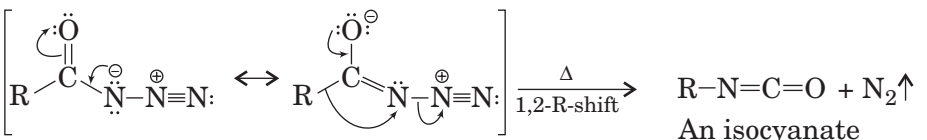
Example:



Benzoyl azide — Phenyl isocyanate

These isocyanates may be isolated if the pyrolysis is carried out in the absence of any nucleophilic solvent.

Mechanism of the reaction The mechanism of this rearrangement involves migration of R from carbon to nitrogen with simultaneous loss of N_2.

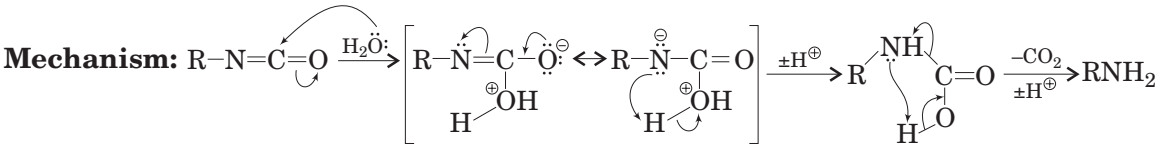


An acylazide — An isocyanate

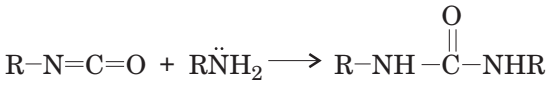
Reaction of isocyanate with solvent Reaction of isocyanates with water, amines (RNH_2) and alcohols gives amines, ureas and carbamates, respectively with loss of one carbon atom.

$$R - N = C = O + H_2O \longrightarrow \underset{\text{An amine}}{R - NH_2} + CO_2$$

Mechanism:

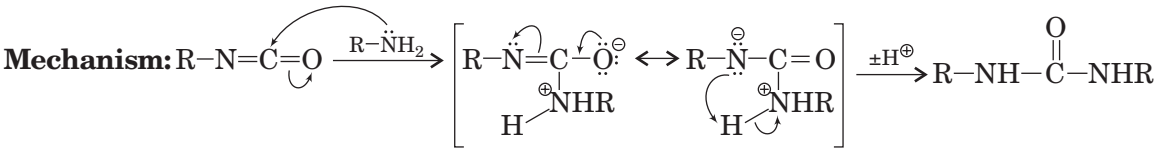


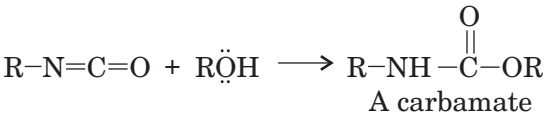
A carbamic acid
(unstable)



An urea

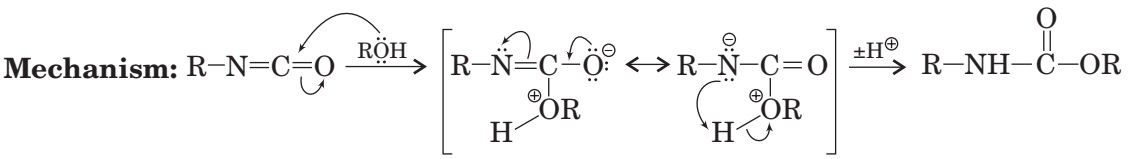
Mechanism:





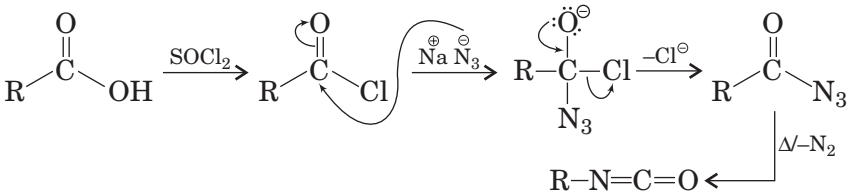
A carbamate

Mechanism:

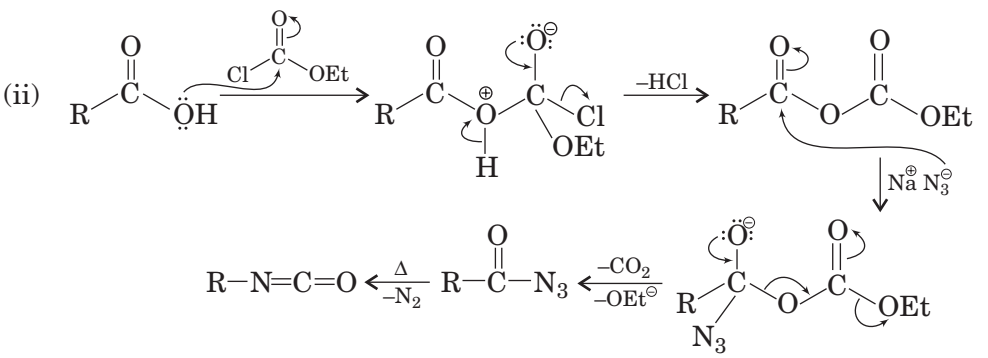


Formation of acyl azides The acyl azides can be prepared by allowing the corresponding acyl halides or mixed anhydrides to react with alkali azides or trimethylsilyl azides. They can also be prepared by treating acyl halides with N_2H_4 (hydrazine) followed by reaction with HNO_2.

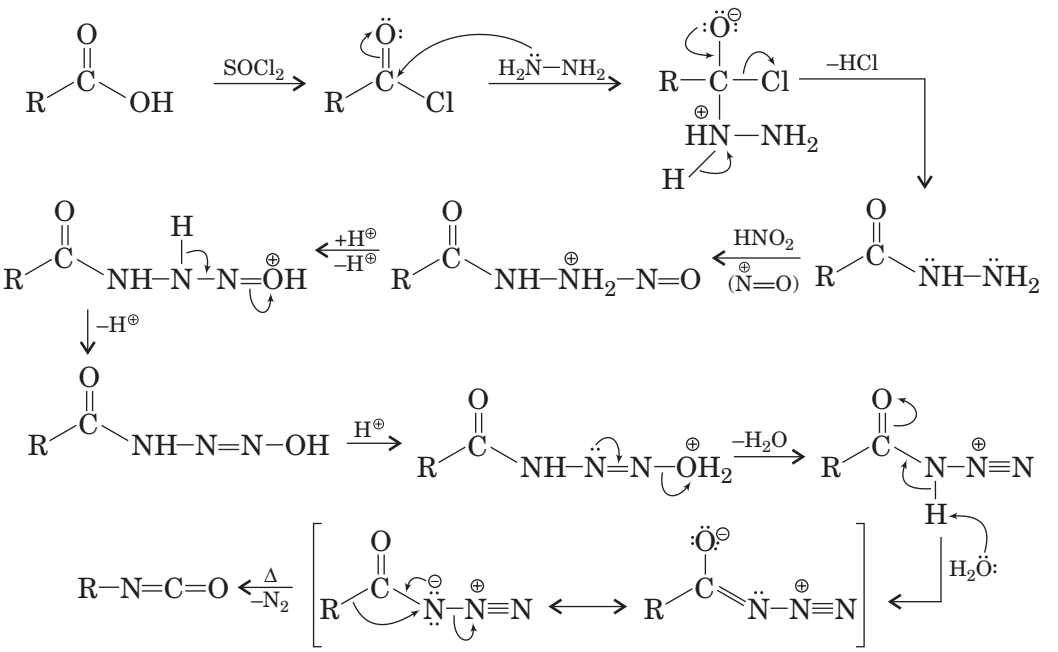
(i)



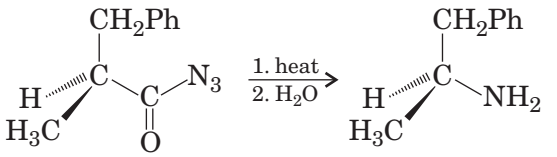
(ii)



(iii)



Evidence in favour of the mechanism Curtius rearrangement is an intramolecular concerted process and does not involve an intermediate acylnitrene. For example, neither insertion, addition nor amide products are isolated in the thermal Curtius rearrangement. The values of entropy of activation are also in good agreement in favour of concerted mechanism. The rearrangement takes place with complete retention of stereochemical configuration in the migrating chiral alkyl group. This also supports the concerted mechanism. For example:

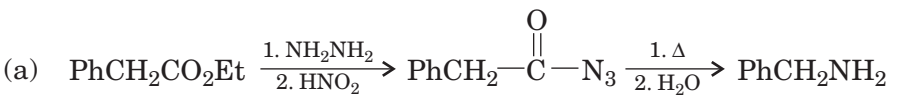


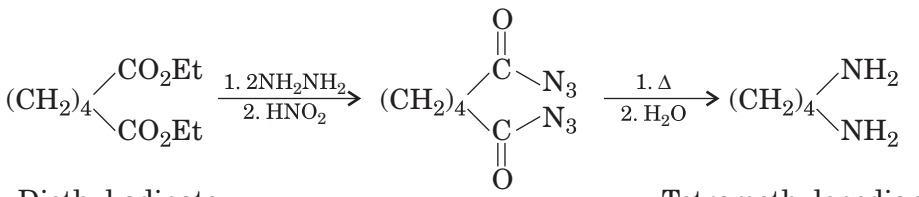
(*S*)-(+)-isomer (*S*)-(–)-isomer

Therefore, this method is used to prepare an optically active (chiral) primary amine from an optically active (chiral) carboxylic acid with 100% retention of configuration. Certain photochemical Curtius rearrangements are found to involve nitrene intermediates.

Applications The important synthetic applications of the Curtius rearrangement are as follows:

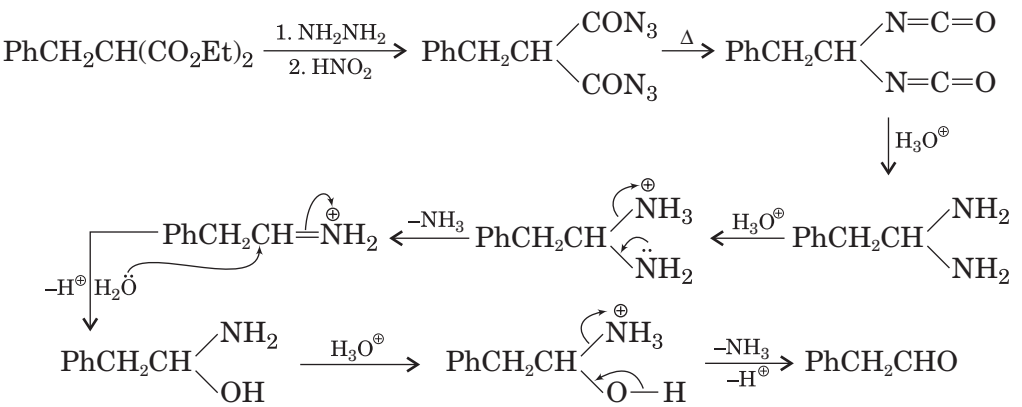
(i) **Synthesis of amines from esters**



(b) 

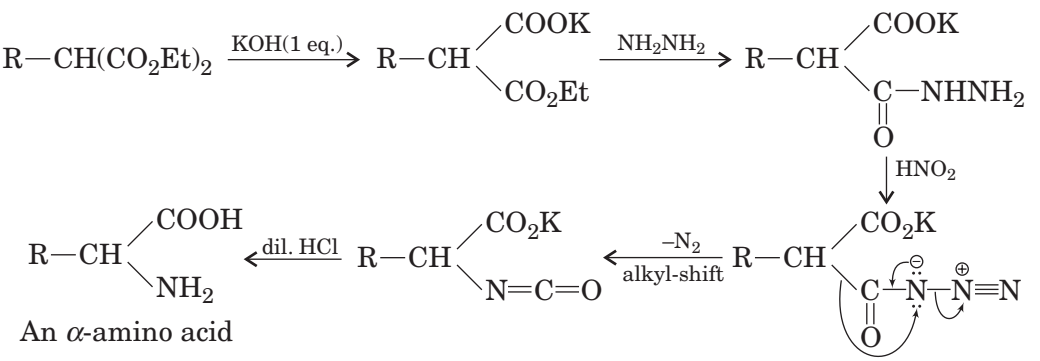
Diethyl adipate Tetramethylenediamine

(ii) **Synthesis of aldehydes from substituted malonic ester**



(iii) **Synthesis of α-amino acids**

This rearrangement is an important method for the synthesis of α-amino acids like glycine, alanine, phenylalanine and valine.

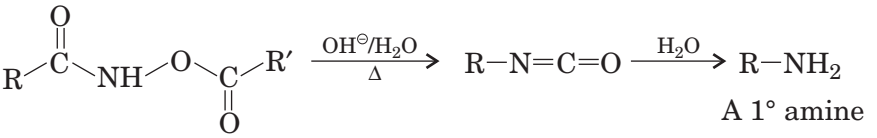


An α-amino acid

(The α-amino acid is glycine, where R = H; alanine, where R = Me, phenylalanine, where R = $-CH_2Ph$ and valine, where R = Me_2CH-.)

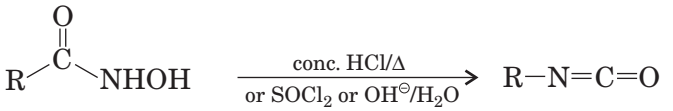
4.1.2.5 Lossen rearrangement

When the *O*-acyl derivatives of hydroxamic acids, RCONHOH, are heated with bases or sometimes even just on heating, isocyanates, RNCO, are obtained. The reaction is called the *Lossen rearrangement*. The isocyanates readily undergo hydrolysis to give 1° amines.



An *O*-ocyl derivative of hydroxamic acid

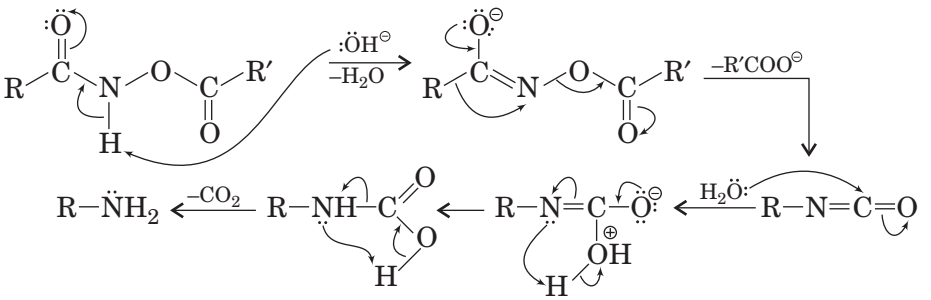
Hydroxamic acids also undergo this rearrangement when treated with mineral acids, $SOCl_2$ or alkali.



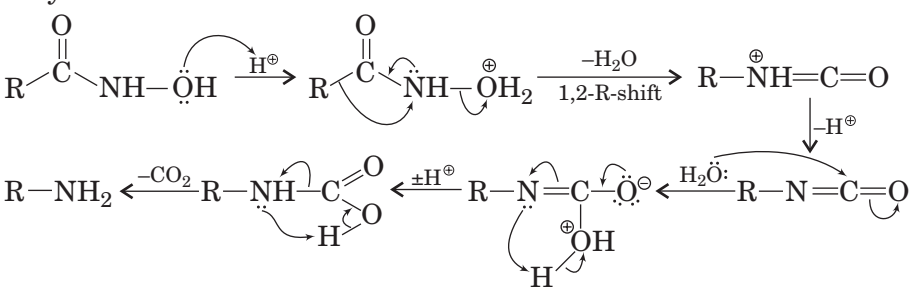
Hydroxamic acid — An isocyanate

The isocyanate undergoes hydrolysis in acidic and alkaline conditions to yield 1° amine.

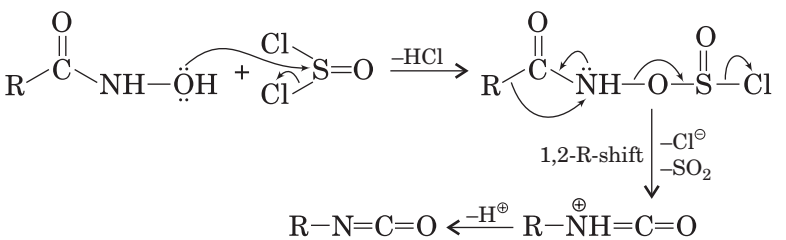
Mechanism of the reaction The mechanism of the reaction involves abstraction of a proton by base to form the corresponding anion followed by its rearrangement, i.e. migration of R from carbon to nitrogen with simultaneous expulsion of $R'COO^{\ominus}$.



(i) The hydroxamic acid reacts with conc. HCl as follows:

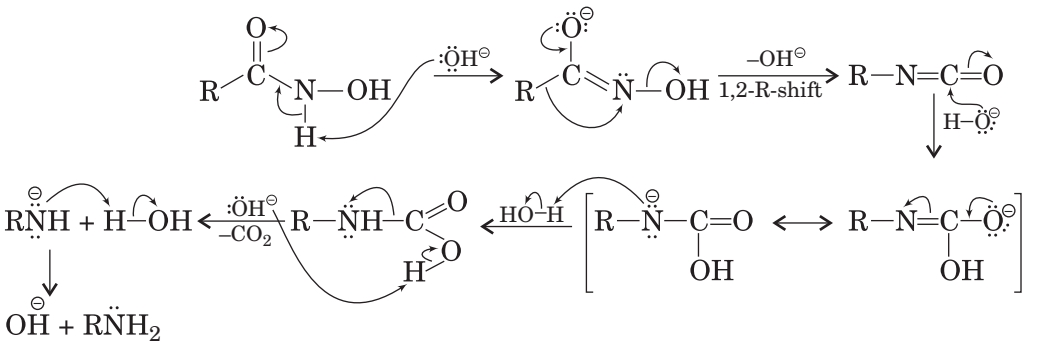


(ii) The hydroxamic acid reacts with $SOCl_2$ as follows:

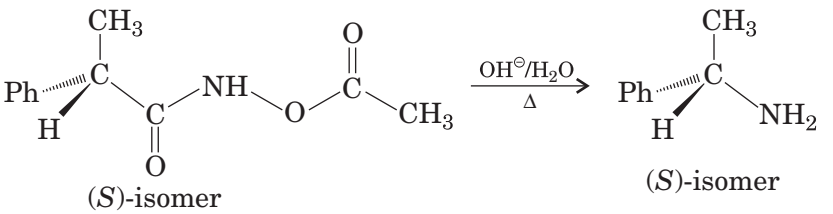


The isocyanate does not undergo hydrolysis in this case.

(iii) The hydroxamic acid reacts with alkali as follows:



Evidence in favour of the mechanism The rearrangement takes place with complete retention of configuration in the migrating chiral alkyl group. For example:

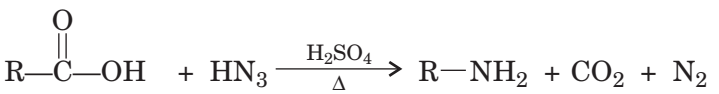


(*S*)-isomer (*S*)-isomer

This observation, therefore, suggests that this rearrangement is an intramolecular concerted process. The migrating group never separates from the rest of the molecule during the rearrangement, otherwise some racemized product would have been obtained.

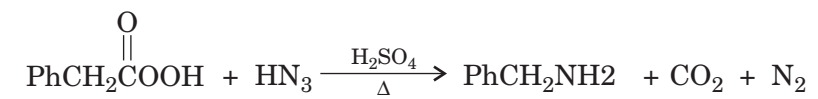
4.1.2.6 Schmidt rearrangement

Conversion of a carboxylic acid to the corresponding primary amine with one less carbon atom by allowing the carboxylic acid to react with hydrozoic acid (HN_3) in the presence of concentrated sulphuric acid is known as the *Schmidt rearrangement* or *Schmidt reaction*.



A carboxylic acid A 1° amine

Example:



Phenylacetic acid Benzylamine

The reaction can be extended to aldehydes and ketones as substrate molecules. An aldehyde gives a mixture of an *N*-alkylated formamide and a nitrile, a symmetrical ketone gives an amide and an unsymmetrical ketone (RCOR′) gives a mixture of two isomeric amides.

$$RCHO + HN_3 \xrightarrow{H_2SO_4} RCN + RNHCHO + N_2$$

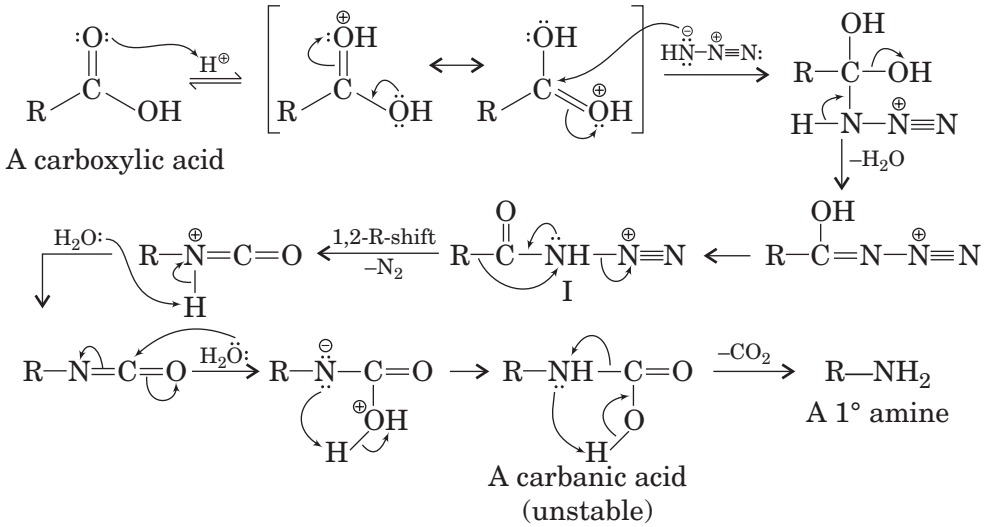
$$RCOR + HN_3 \xrightarrow{H_2SO_4} RCONHR + N_2$$

$$RCOR' + HN_3 \xrightarrow{H_2SO_4} RCONHR' + R'CONHR + N_2$$

The reaction conditions are mild the reagents are easily available and the yields are higher. Hydrazoic acid (toxic and explosive) is usually handled either as a solution in an inert solvent like chloroform or generated *in situ* by adding NaN_3 to the acidic reaction mixture. In the case of carboxylic acids, the best results are obtained from aliphatic acids or from sterically hindered aromatic acids.

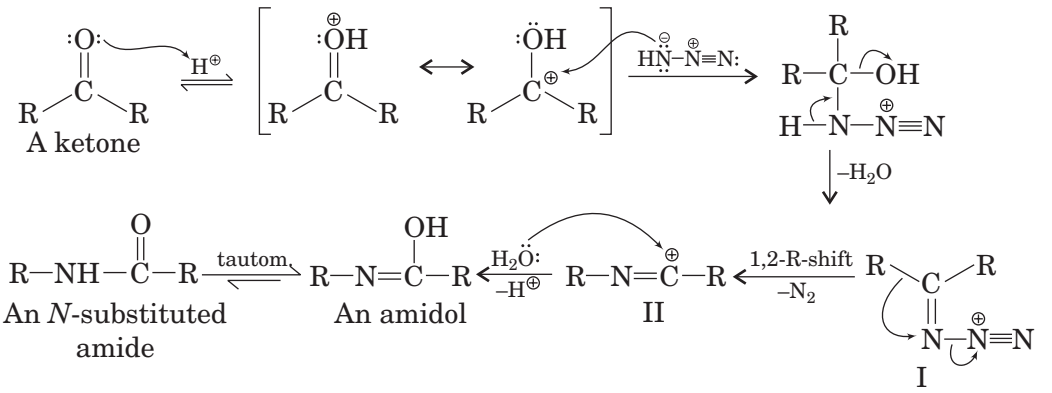
Mechanism of the reaction

(a) The mechanism of the transformation of an acid to a primary amine involves the steps as follows:

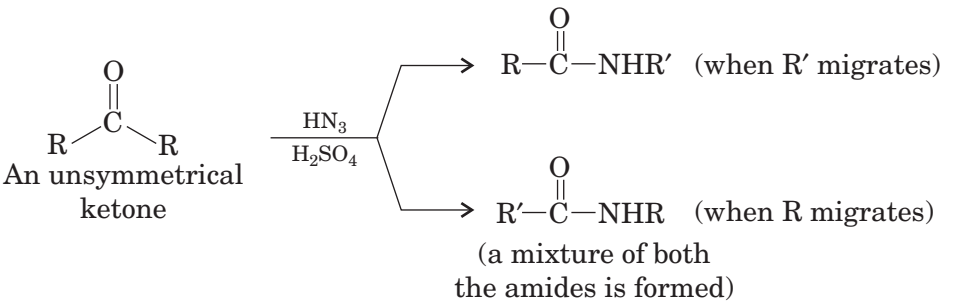


The addition of hydrazoic acid to a protonated carboxylic acid produces a protonated acyl azide (I) which undergoes 1,2-alkyl shift with simultaneous loss of nitrogen to produce, after proton loss, an isocyanate. The isocyanate undergoes hydrolysis under the reaction conditions to yield a primary amine.

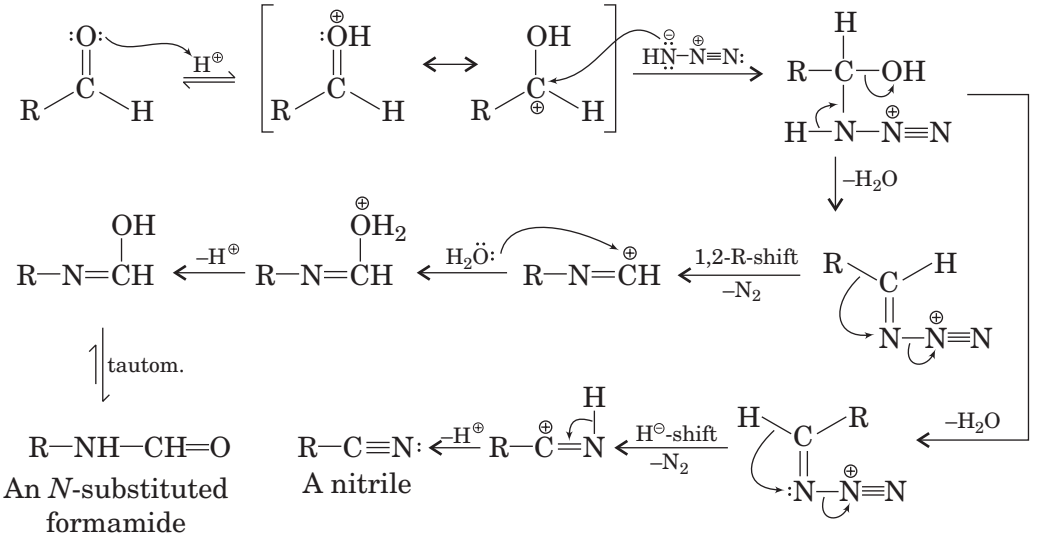
(b) The mechanism of transformation of a ketone to an *N*-substituted amide involves the steps as follows:



Hydrazoic acid adds to the protonated ketone to form, after loss of water, the compound I (similar to protonated oxime) which undergoes migration of the *anti*-group to the diazonium nitrogen with simultaneous loss of nitrogen to yield a nitrilium ion (II). Water adds to the nitrilium ion intermediate to form, after proton loss, an imidol which readily tautomerizes to give an *N*-substituted amide.

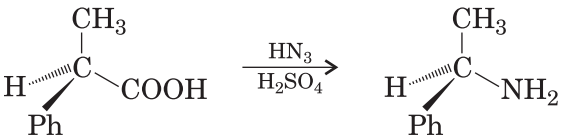


(c) The mechanism of transformation of an aldehyde to an *N*-substituted formamide and a nitrile involves the steps as follows:



The mechanism of formation of the *N*-substituted formamide is similar to that operates in the case of ketones. *Anti*-migration of R takes place to give the formamide. On the other hand, *anti*-migration of H takes place to give the nitrile.

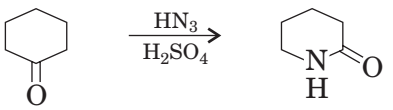
Evidence in favour of the mechanism If the α-carbon of the carboxylic acid is a chiral centre, then its configuration is found to be retained in the amine that is formed. For example:



(*R*)-α-phenylpropanoic acid — α-phenylethylamine

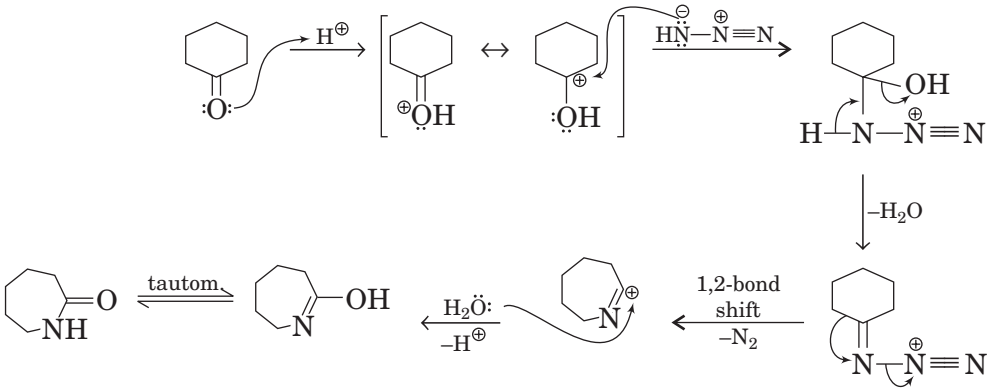
The observation, therefore, suggests that this rearrangement is an intramolecular concerted process. The migrating group never separates from the rest of the molecule during the rearrangement, otherwise some racemized product would have been obtained.

Use of cyclic ketone and sterically hindered carboxylic acids in Schmidt reaction Cyclic ketones undergo ring expansion to give cyclic amides (lactums) when subjected to the Schmidt reaction. Cyclohexanone, for example, produces caprolactam.

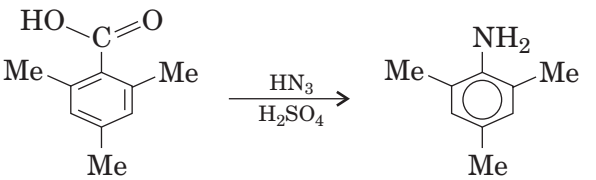


Cyclohexanone — Caprolactam

Mechanism:

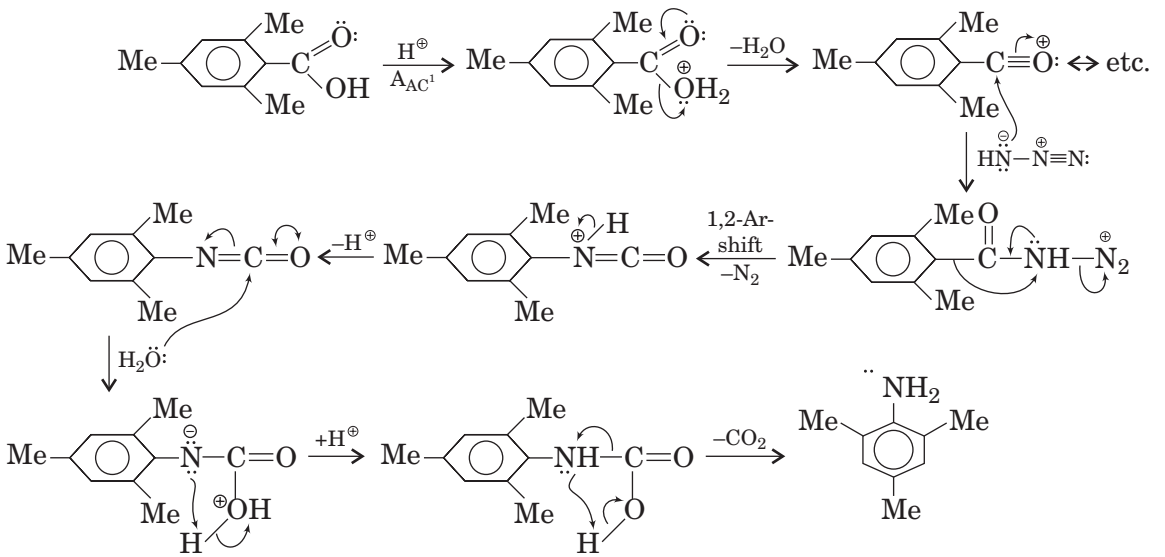


A hindered carboxylic acid like mesitoic acid undergoes Schmidt reaction to give 2,4,6-trimethylaniline through the formation of an acylium ion ($A_{AC}1$ type mechanism).



Mesitoic acid 2,4,6-Trimethylaniline

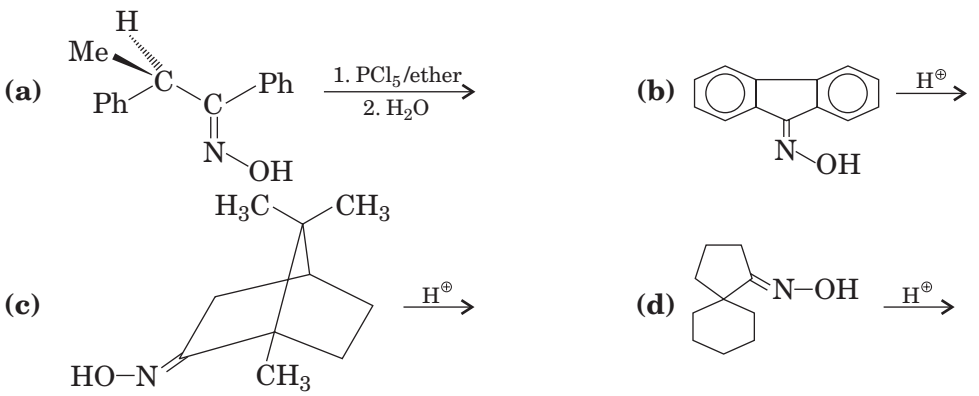
The reaction proceeds through the steps as follows:



A carbamic acid (unstable)

SOLVED PROBLEMS

1. Predict the product and suggest a mechanism for each of the following reactions:

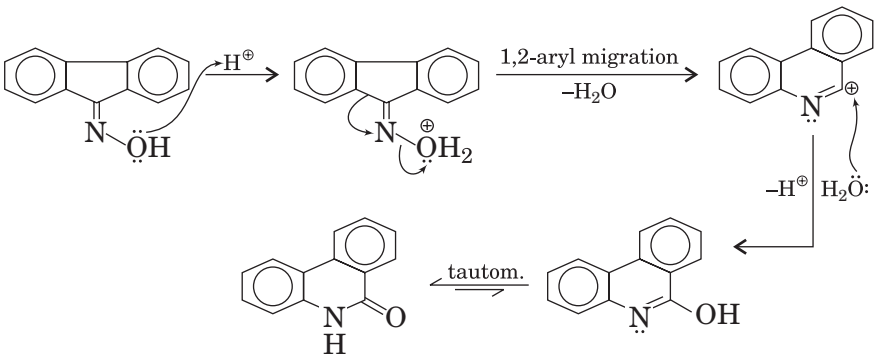


(e) 

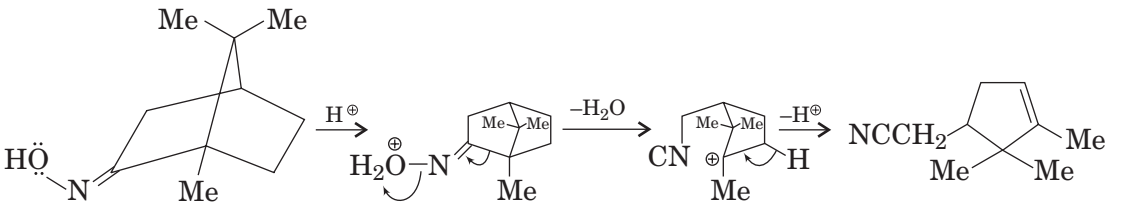
Solution

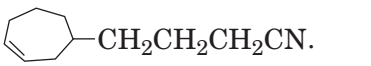
(a) The chiral alkyl group will migrate with retention of configuration to yield an amide. For mechanism see article no. 4.1.2.1.

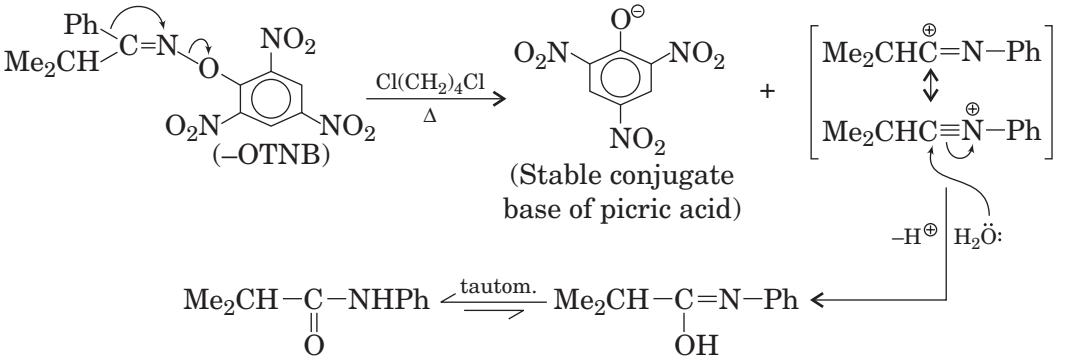
(b) Ring expansion occurs to produce a six-membered lactum.



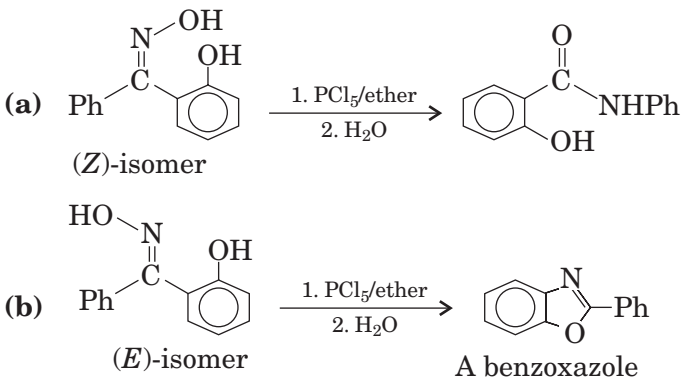
(c) Since there is a tertiary alkyl group *trans* to –OH, a nitrile is obtained by a fragmentation process.



(d) A similar reaction occurs to yield the nitrile 

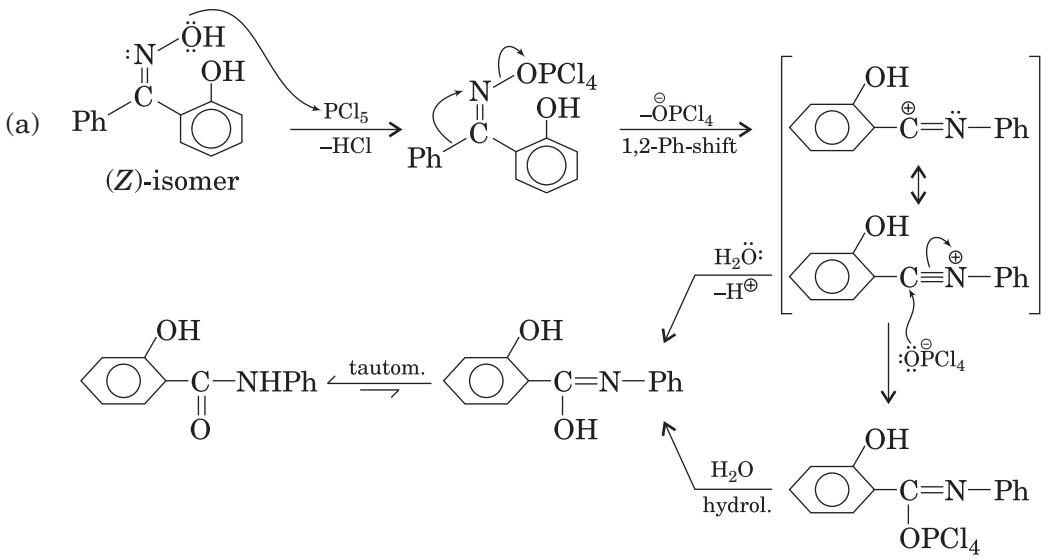
(e) 

2. Explain the following observations:

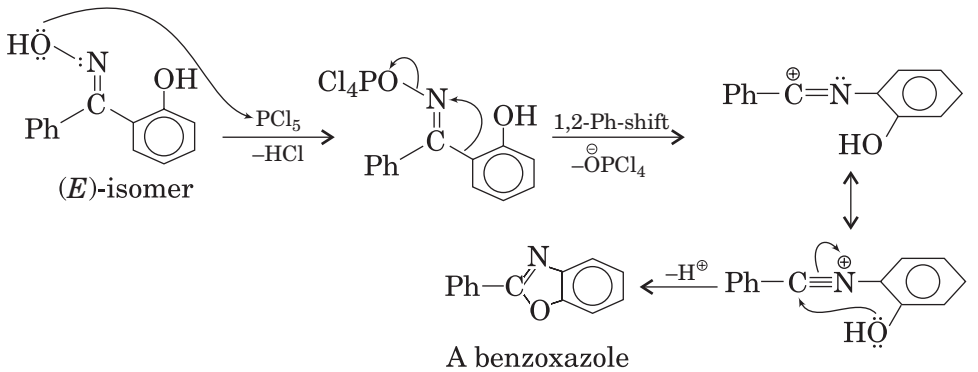


Solution These observations demonstrate the stereospecificity of the Beckmann rearrangement. When phenyl is *trans* to the oxime —OH, it migrates to give an anilide. However, when *o*-hydroxyphenyl is *trans* to —OH, a benzoxazole is obtained by the nucleophilic attack of the *ortho* —OH group on the electrophilic carbon of the nitrilium ion intermediate and this is because the ring —OH is ideally located to bend to the positive carbon.

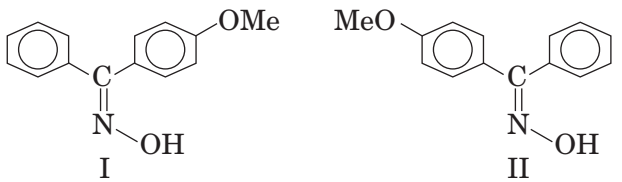
Mechanisms:



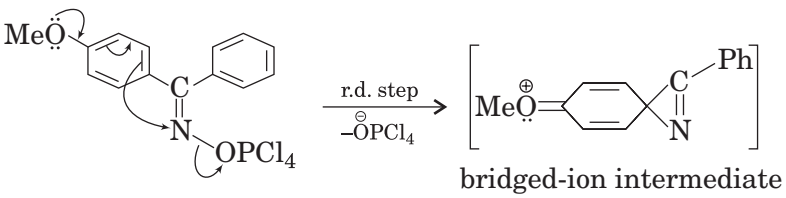
(b)

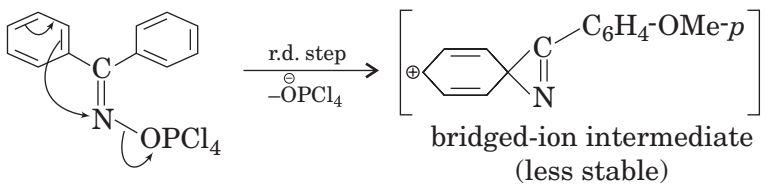


3. Which oxime will undergo the Beckmann rearrangement at a faster rate? Give your reasoning.



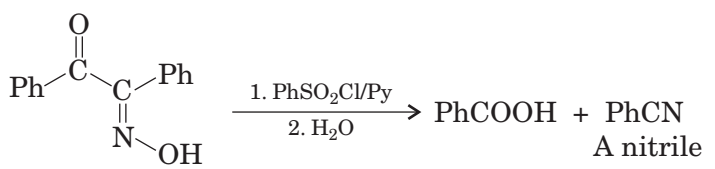
Solution II will undergo the Beckmann rearrangement at a rate faster than I because formation of bridged-ion intermediate is well supported since the migrating aryl group contains an electron-releasing group in the *para*-position.



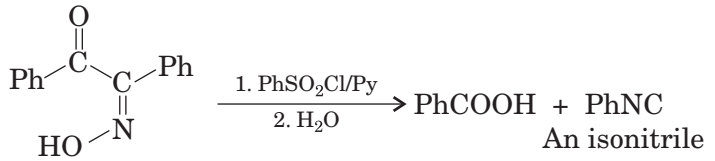


4. Give mechanisms for the following second order Beckmann rearrangements with $PhSO_2Cl/Py$:

(a)

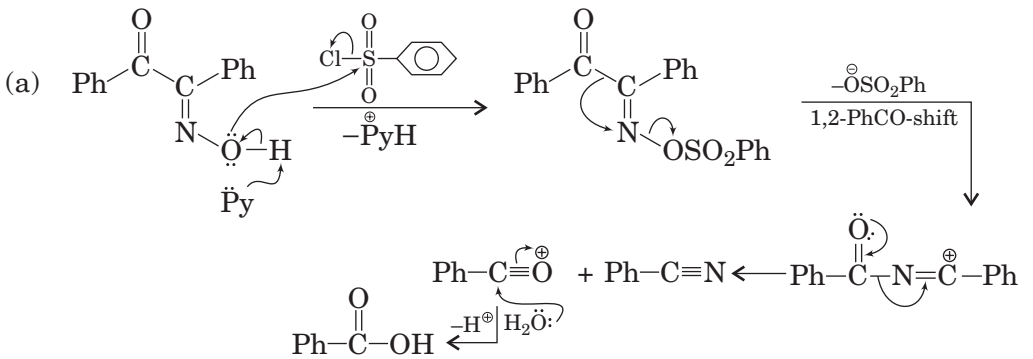


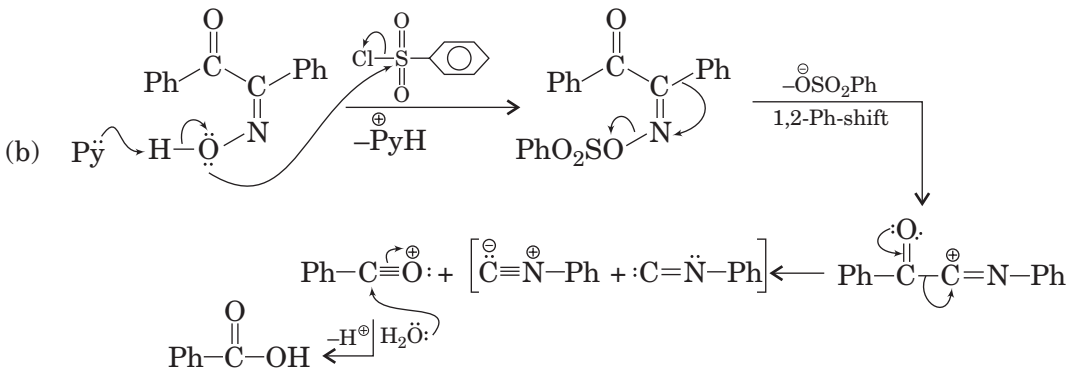
α-Benzilmonoxime

(b) 

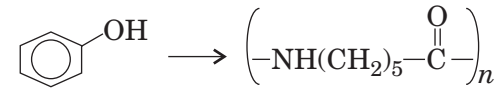
β-Benzilmonoxime

Solution

(a) 

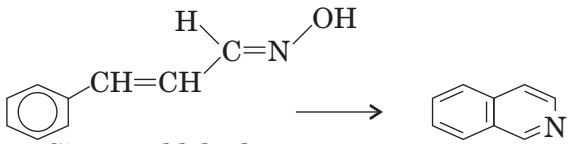
(b) 

5. How would you carry out the following transformation using Beckmann rearrangement?

(a) 

Phenol

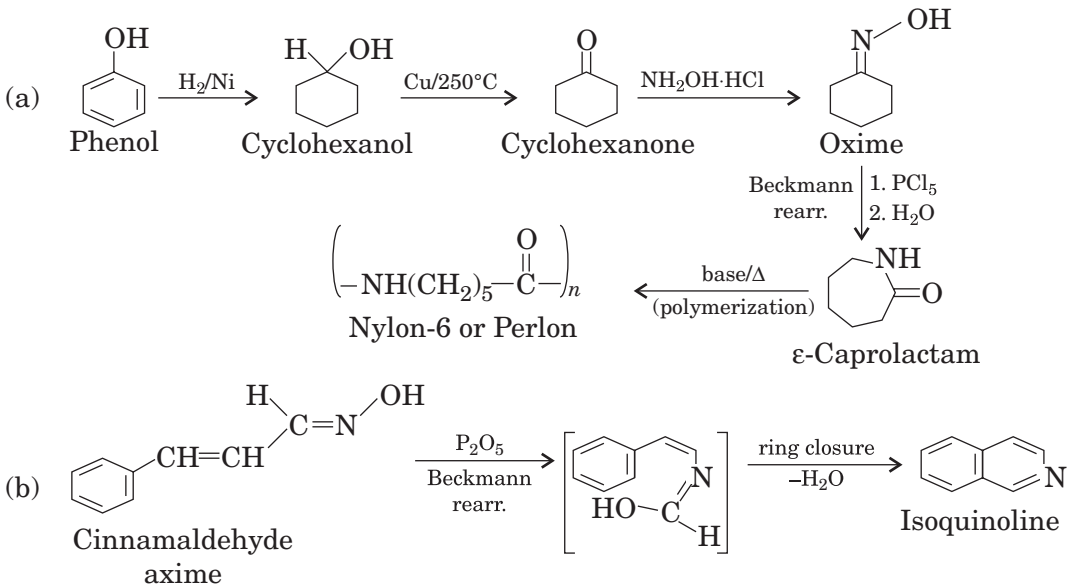
Nylon-6 or Perlon
(a textile polymer)

(b) 

Cinnamaldehyde oxime

Isoquinoline

Solution

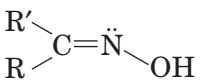


6. How can the configuration of a ketoxime (obtained from an unsymmetrical (ketone) be determined by using the Beckmann rearrangement?

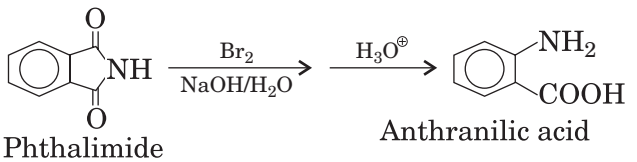
Solution The configuration of ketoxime (RR′C=NOH) can be assigned by studying their Beckmann rearrangement products. In general, the group *anti* to the leaving functionality in the oxime derivative migrates during rearrangement. The product of the reaction (an amide) on hydrolysis yields an amine and a carboxylic acid. Structural analysis of the amine clearly suggests the configuration of the starting oxime, i.e. whether it is (*E*)-diastereoisomer or (*Z*)-diastereoisomer.

$$RR'C=NOH \xrightarrow[\text{Beckmann rearr.}]{H^{\oplus}} RCONHR' \xrightarrow[\text{hydrol.}]{H_3O^{\oplus}} RCOOH + R'NH_2$$

Formation of $R'NH_2$ indicates that the reaction involves migration of the —R′ group to the nitrogen atom. The groups —R′ and —OH are therefore *anti* to each other. Hence, the structure of the oxime is:

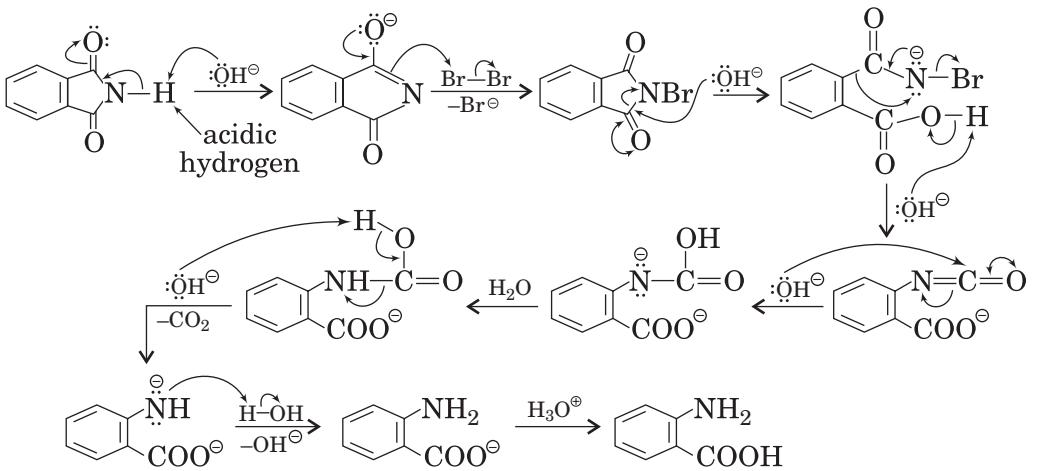


7. A unique reaction where an imide undergoes Hofmann rearrangement to form an amine is the transformation of phthalimide to anthranilic acid.



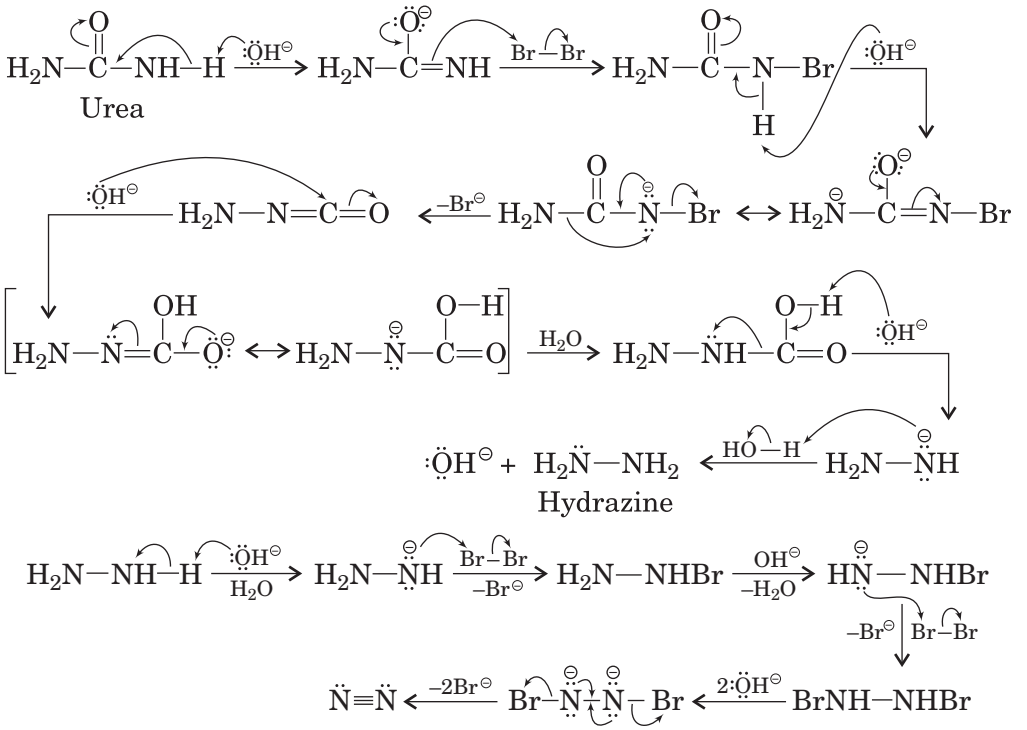
Suggest a mechanism for the reaction.

Solution The mechanism of the reaction involves the steps as follows:



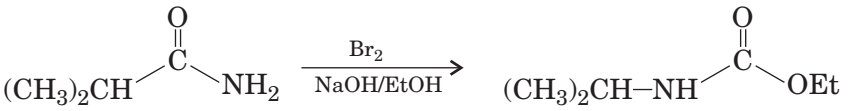
8. When urea (NH_2CONH_2) is treated with excess of Br_2/NaOH solution, it decomposes with the evolution of N_2. Suggest a reasonable mechanism for the reaction.

Solution When urea is treated with excess of alkaline solution Br_2, it undergoes Hofmann rearrangement to yield hydrazine. Hydrazine is then oxidized to nitrogen by excess of alkaline bromine. The mechanism of the reaction involves the steps as follows:



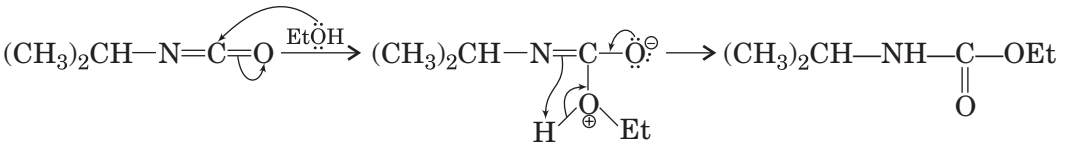
9. What product is expected to be formed when 2-methylpropanamide is subjected to the conditions of the Hofmann rearrangement in ethanol solvent? Give the mechanism of the reaction involved.

Solution When 2-methylpropanamide is subjected to the conditions of the Hofmann rearrangement in ethanol, a carbamate is obtained.

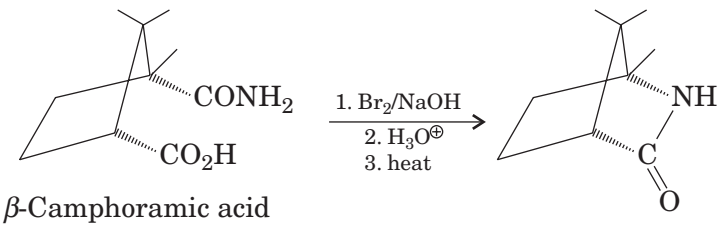


2-Methylpropanamide Ethyl *N*-isopropylcarbamate

2-methylpropanamide reacts with Br_2/NaOH to form the isocyanate $(CH_3)_2CH–N=C=O$ Which reacts with ethanol to yield the carbonate.



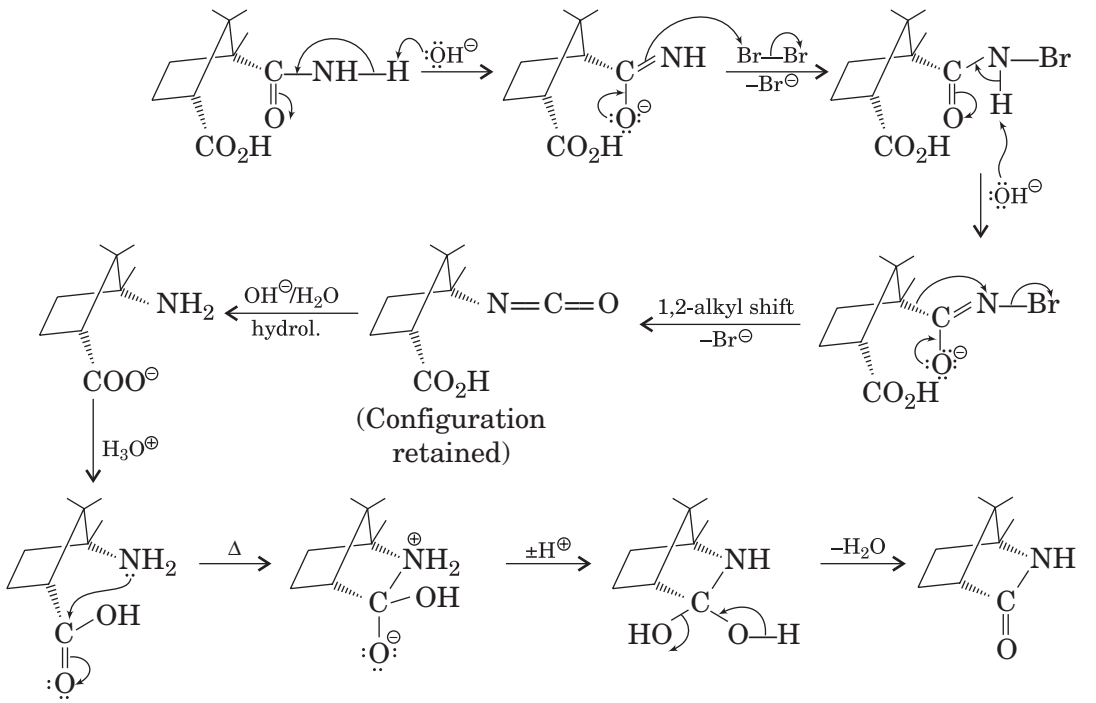
10. Explain the following observation:



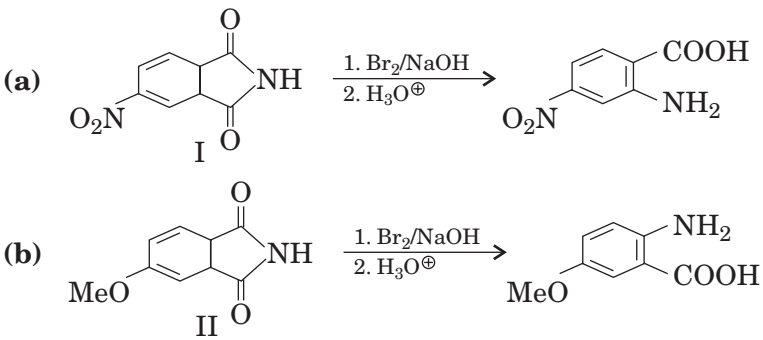
β-Camphoramic acid (both $–CONH_2$ and –COOH groups lie *cis* to each other) A lactam

Solution A lactam can only be formed from the amino acid obtained from *β*-camphoramic acid by the Hofmann rearrangement if the –COOH and $–NH_2$ groups remain *cis* to each other. Since in the starting acid, the –COOH and $–CONH_2$ groups are *cis* to each other, the reaction must have taken place in such a fashion that the $–NH_2$ group occupied the same position that the $–CONH_2$ group occupied in the starting acid. That is, the reaction must have taken place with retention of configuration in the migrating chiral alkyl group. It can only happen if the migrating group never becomes free during the rearrangement. The observation is, therefore, consistent with the fact that the Hofmann rearrangement is an intramolecular process in which the departure of the halide ion and the shift of the migrating group are synchronous.

The mechanism and the stereochemical outcome of the reaction may be shown as follows:

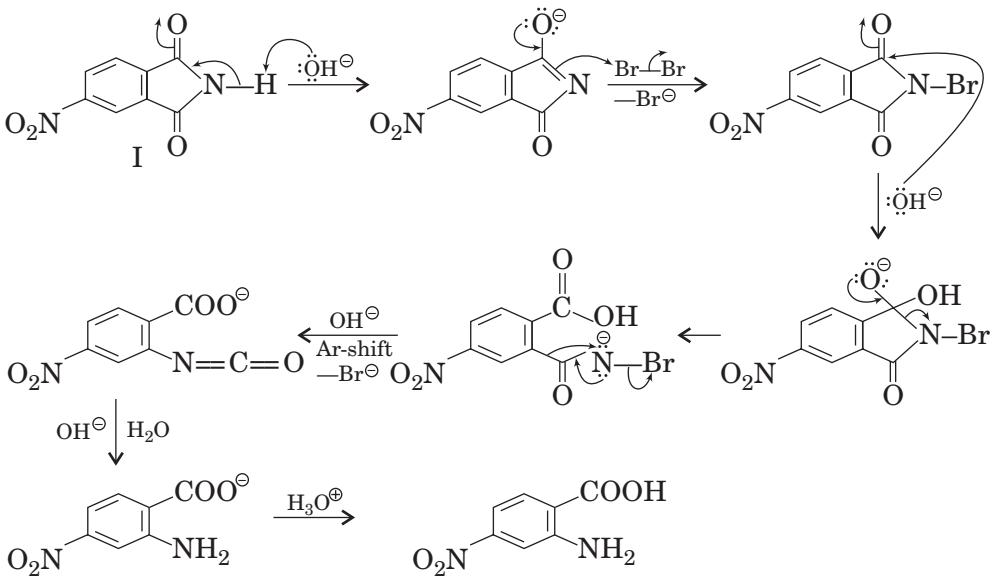


11. Explain the following observations:



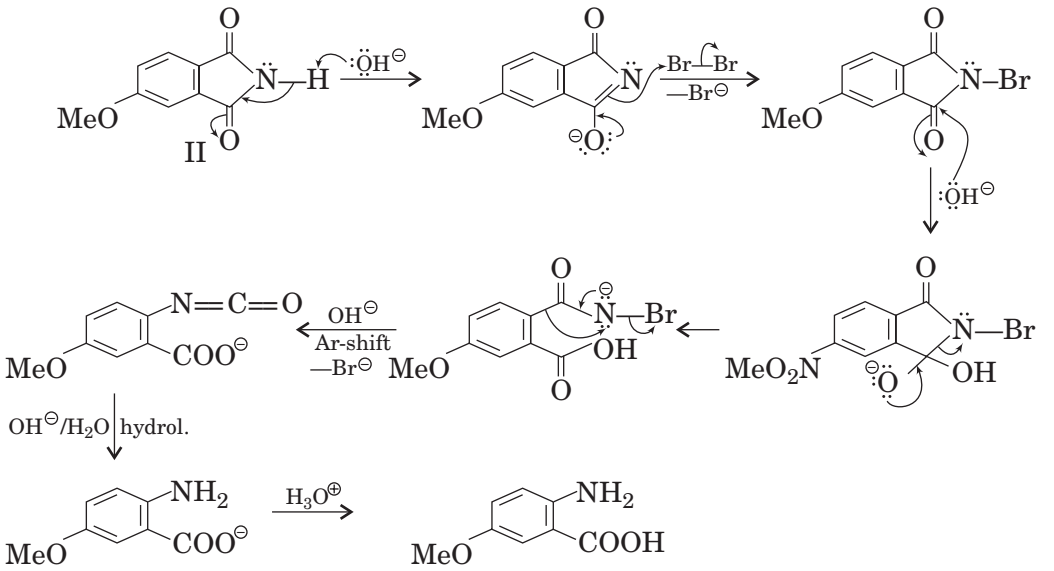
Solution

(a) Since in compound I, the amide carbonyl group *para* to the electron-attracting (–R and –I) —NO_2 group is relatively more positively polarized, it undergoes nucleophilic attack by $OH^{\ominus}$ preferably and as a consequence, this carbonyl group becomes the carboxyl group in the resulting benzoic acid derivative, i.e. the final product in this case is 2-amino-4-nitrobenzoic acid.

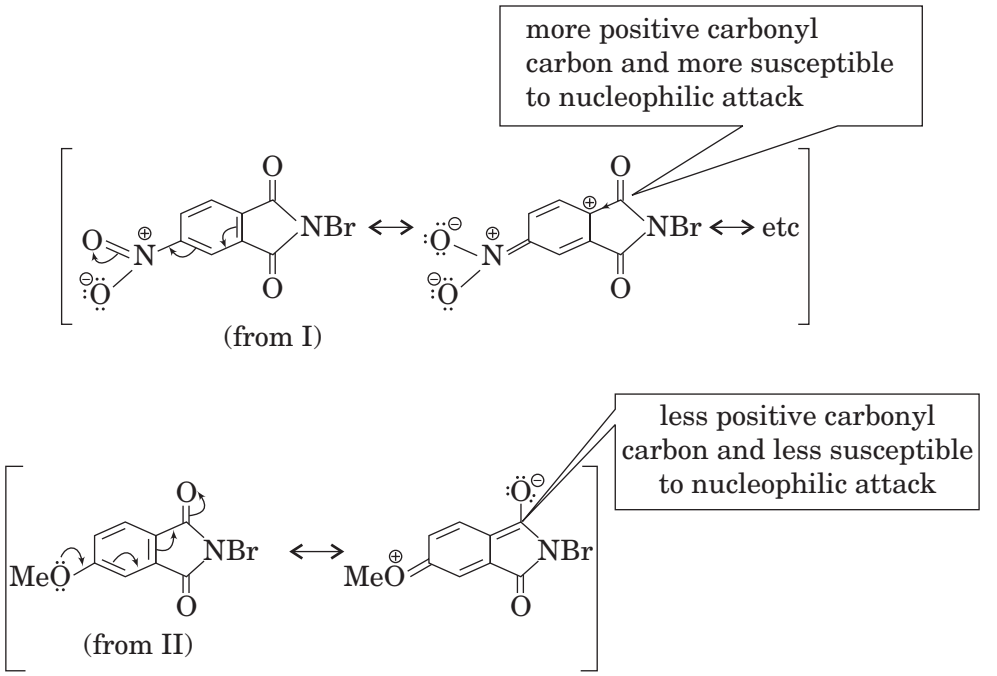


2-Amino-4-nitrobenzoic acid

(b) On the other hand, in compound II, the amide carbonyl *para* to the electron-releasing (+R) –OMe group is relatively less positively polarized. Therefore, the other carbonyl group undergoes nucleophilic attack by $OH^{\ominus}$ instead of its and thus, it becomes the carboxyl group in the resulting benzoic acid derivative. The final product in this case is 2-amino-5-methoxybenzoic acid.



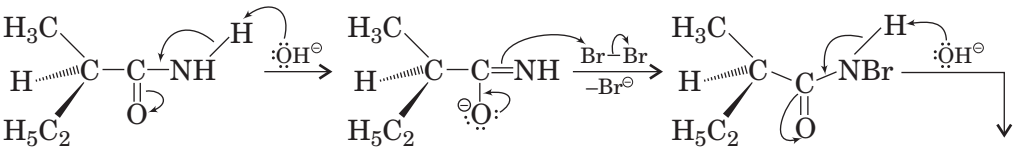
2-Amino-5-methoxybenzoic acid



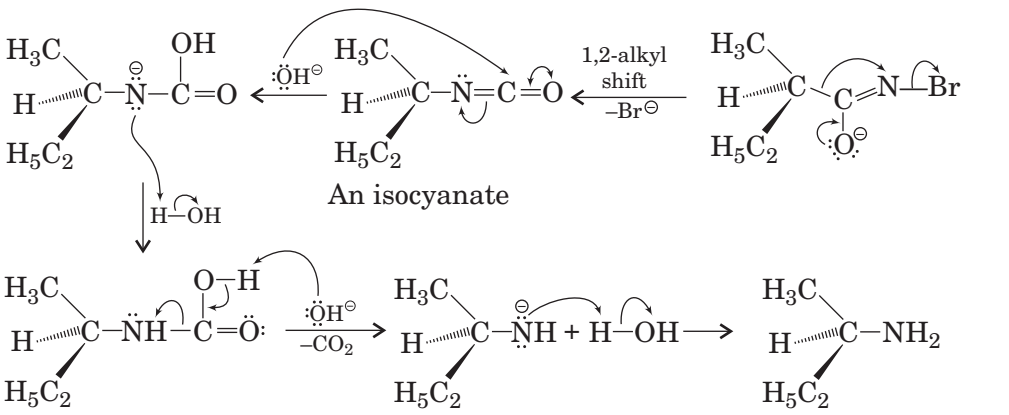
12. When (*R*)-2-methylbutanamide is allowed to react with bromine in a strong aqueous solution of NaOH, the product is an optically active amine. Predict the structure of the expected product and use your knowledge of the reaction mechanism to predict its stereochemistry.

Solution Since the Hofmann rearrangement is an intramolecular concerted process, retention of configuration is expected to be observed when the migrating group is chiral. Therefore, when (*R*)-methylbutanamide is subjected to the Hofmann rearrangement, (*R*)-2-butanamine (an optically active amine) is obtained.

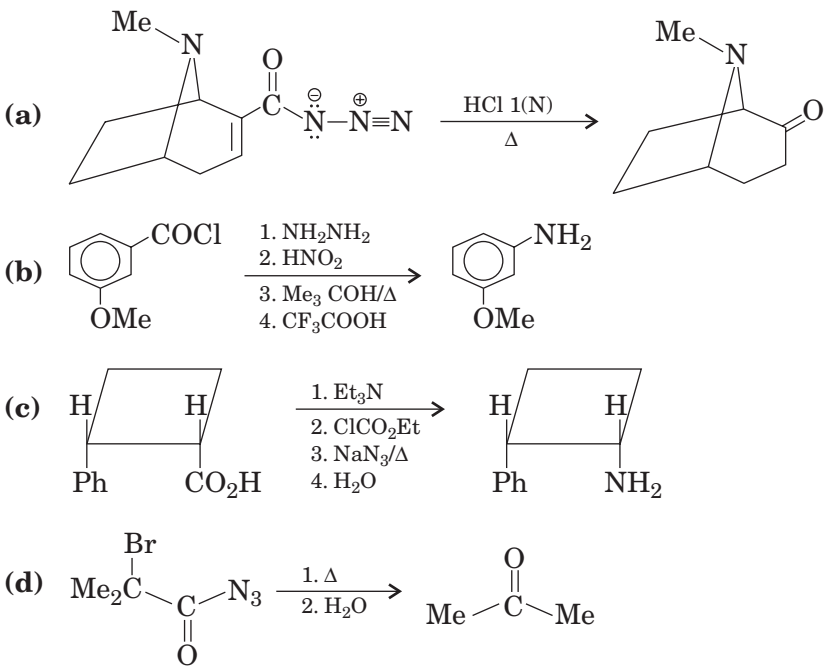
The mechanism and the stereochemical course of the reaction may be shown as follows:



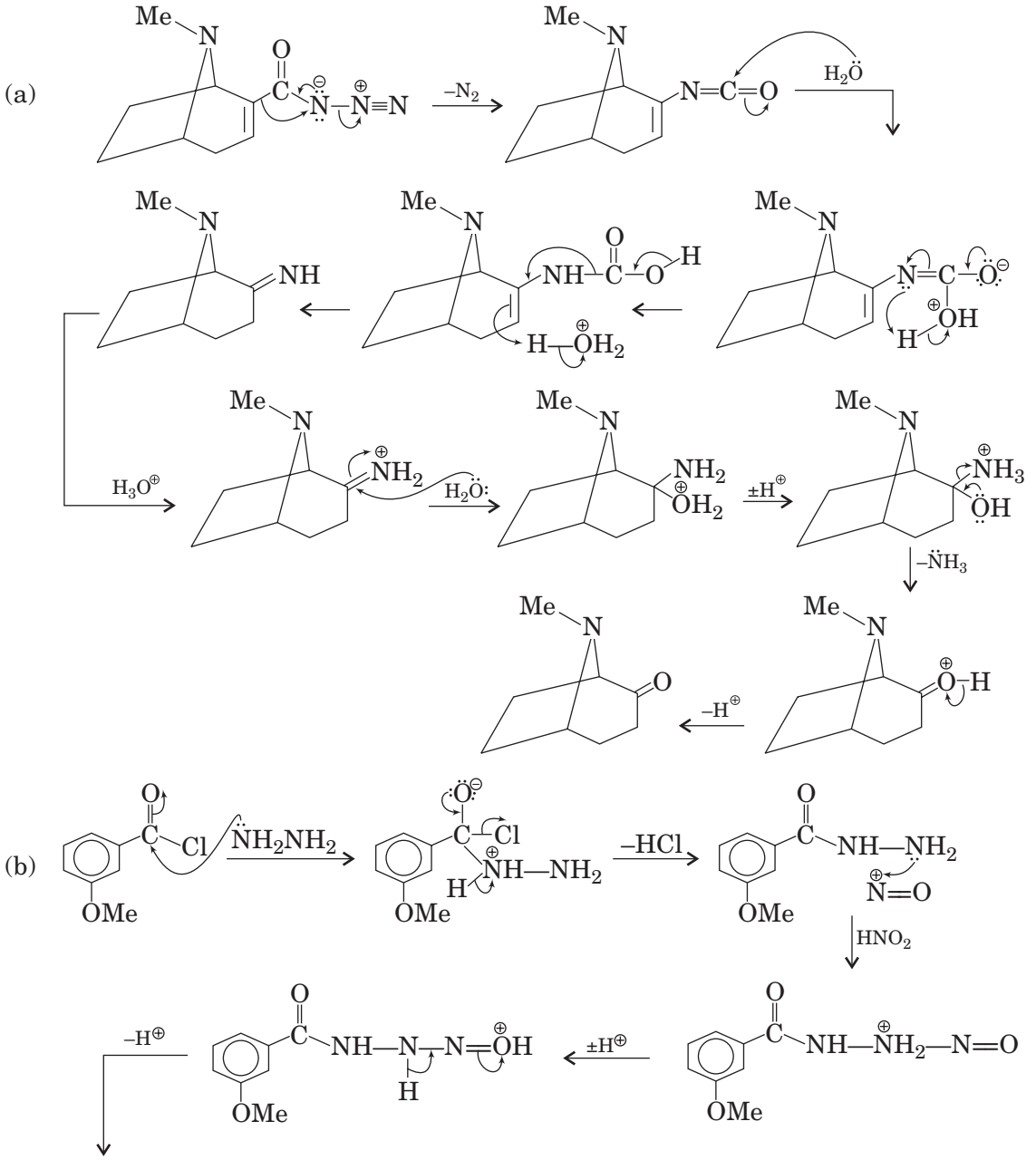
(*R*)-2-Methylbutanamide

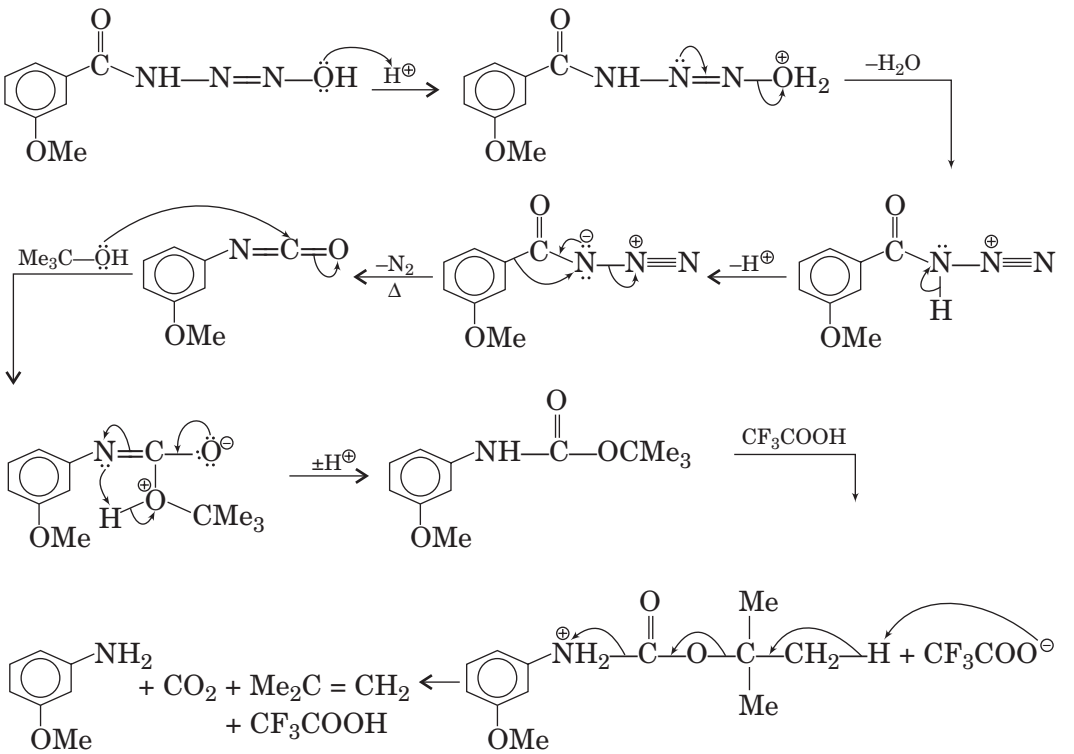


13. Suggest a mechanism for each step of the following conversions:

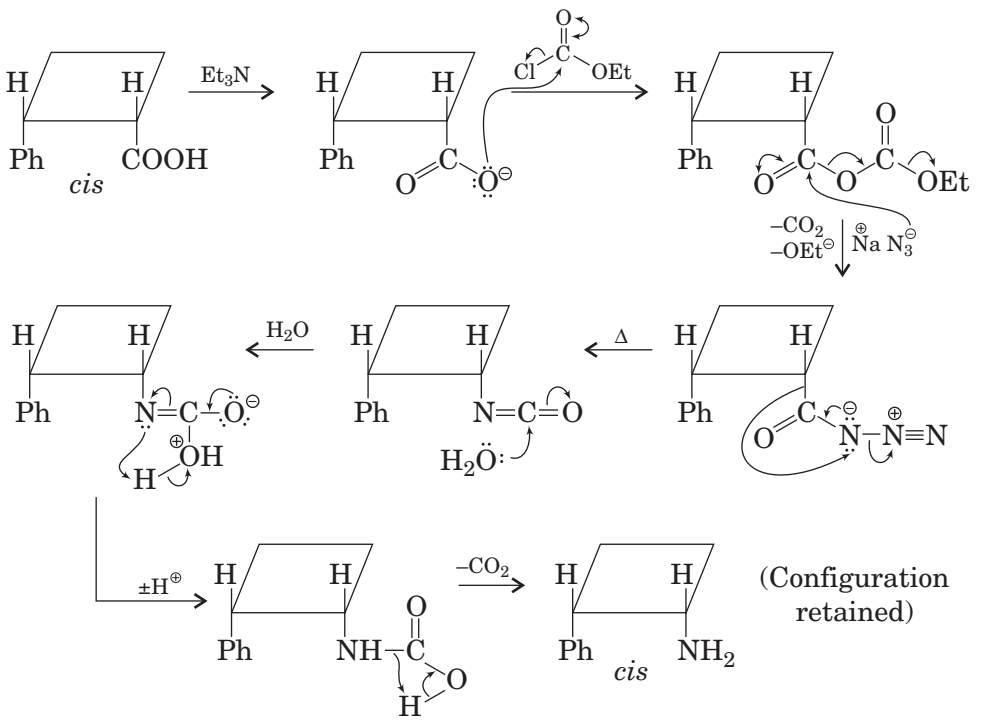


Solution

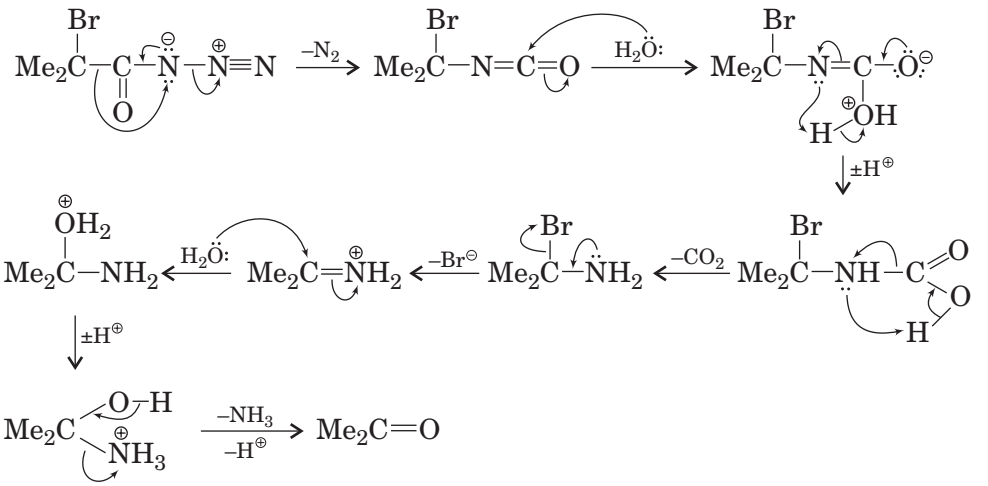

(a)
Me
N
O
C
N
N≡N
–N2
N=C=O
H2Ö
NH
NH—C—O
H
H—OH2
N=C—O
OH
H
H3O⊕
NH2
H2Ö:
NH2
OH2
±H⊕
NH3
OH
–NH3
O
–H⊕
O—H
(b)
O
C
Cl
NH2NH2
O
C
Cl
NH—NH2
H
OMe
–HCl
NH—NH2
N=O
HNO2
–H⊕
NH—N—N=OH
H
±H⊕
NH—NH2—N=O


OMe
NH—N=N—OH
H⊕
NH—N=N—OH2
–H2O
Me3C—OH
N=C=O
–N2
Δ
–H⊕
NH—C—OCMe3
±H⊕
CF3COOH
NH2
+ CO2 + Me2C = CH2
+ CF3COOH
CF3COO⊖
CH2
Me

(c)


Et3N
cis
Ph
COOH
Cl
OEt
–CO2
–OEt⊖
Na N3⊖
H2O
Δ
±H⊕
–CO2
NH2
(Configuration retained)

(d)

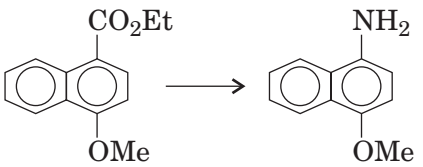


14. Mention the advantage and disadvantage of the Curtius rearrangement over the Hofmann rearrangement.

Solution The advantage of the Curtius rearrangement over the Hofmann rearrangement is that the Curtius reaction can be carried out under mild, neutral conditions and the isocyanate can be isolated if desired. The disadvantage is that some acyl azides in the pure state can detonate without warming, and these should be handled with extreme caution. Amides, in contrast, are much stable and can be handled easily.

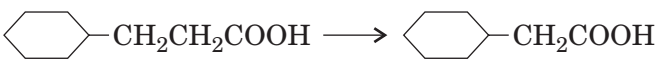
15. Carry out the following transformations by using the Curtius rearrangement in one of the steps:

(a)

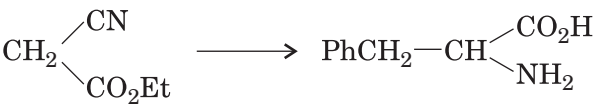


(b) Ph CH(OH)COOH ⟶ Ph CHO

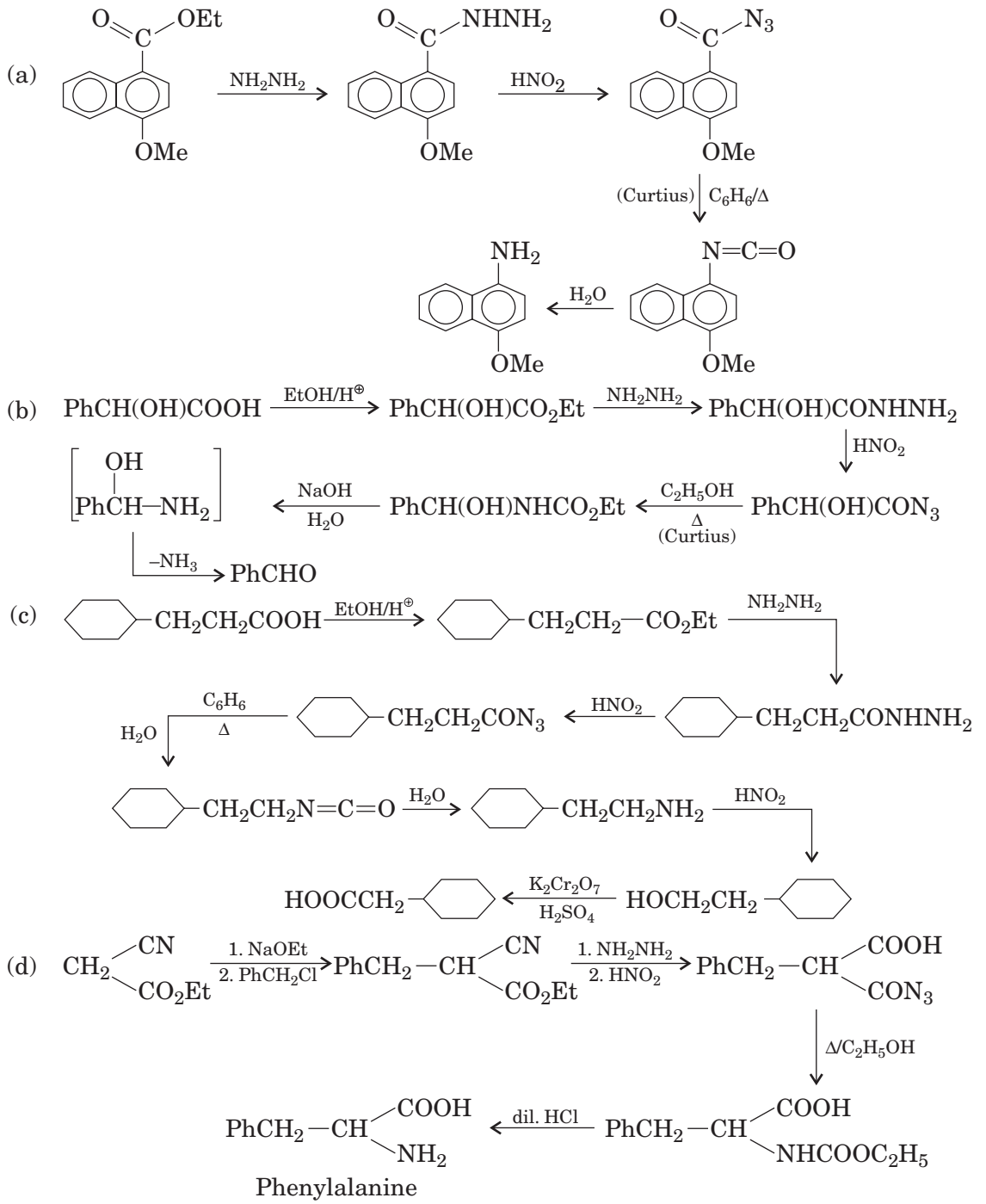
(c)



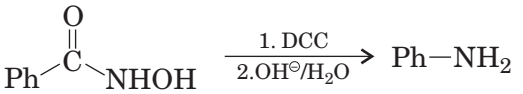
(d)

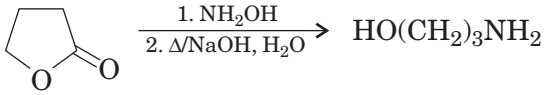


Solution

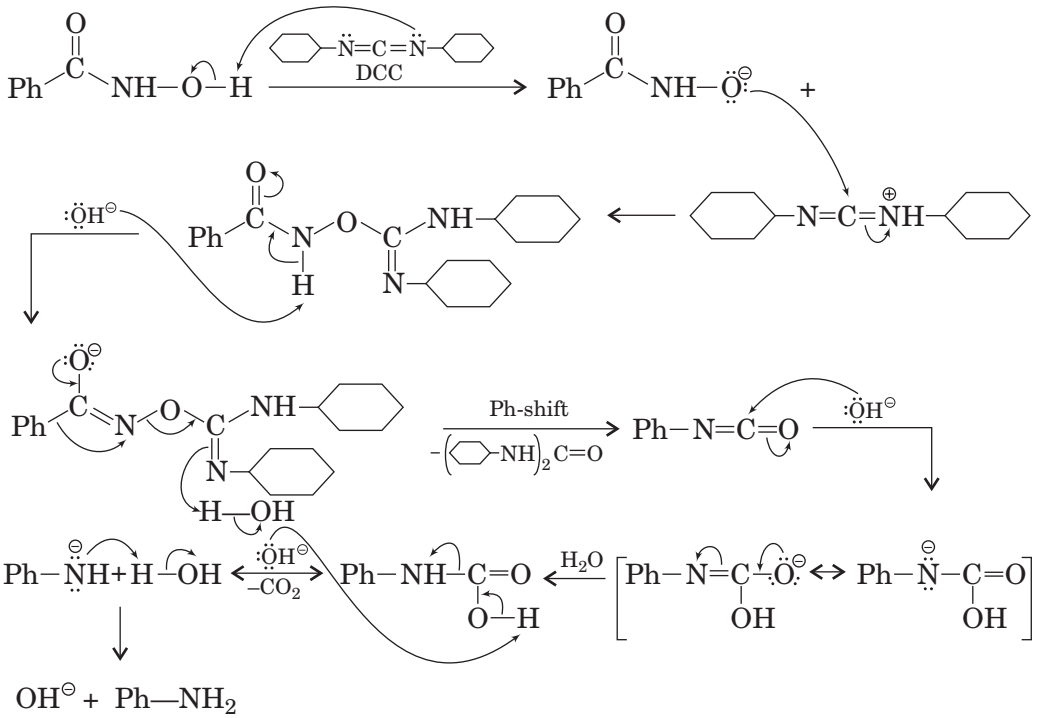

(a)
NH2NH2
HNO2
(Curtius) C6H6/Δ
H2O
(b) PhCH(OH)COOH EtOH/H⊕ PhCH(OH)CO2Et NH2NH2 PhCH(OH)CONHNH2
HNO2
NaOH H2O
C2H5OH Δ (Curtius)
–NH3 PhCHO
(c)
EtOH/H⊕
NH2NH2
HNO2
C6H6 Δ H2O
H2O
HNO2
K2Cr2O7 H2SO4
(d)
1. NaOEt 2. PhCH2Cl
1. NH2NH2 2. HNO2
Δ/C2H5OH
dil. HCl
Phenylalanine

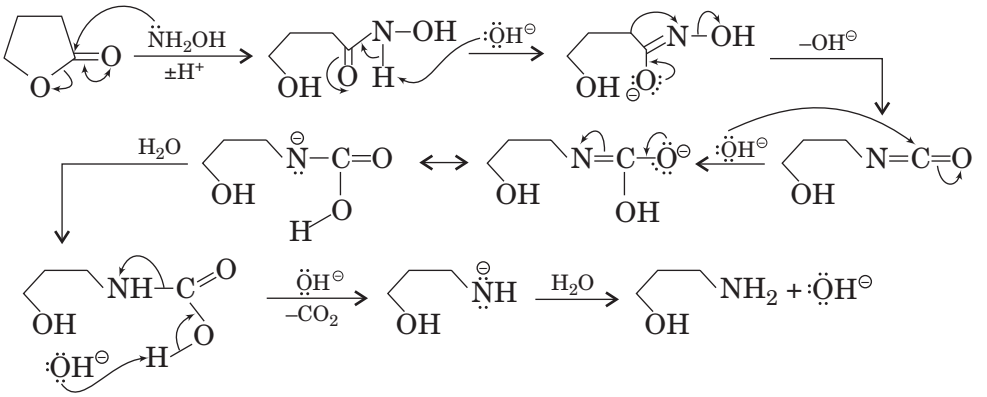
16. Provide reasonable mechanism for each of the following reactions (Lossen rearrangements):

(a) 

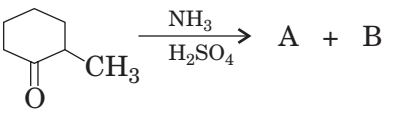
(b) 

Solution

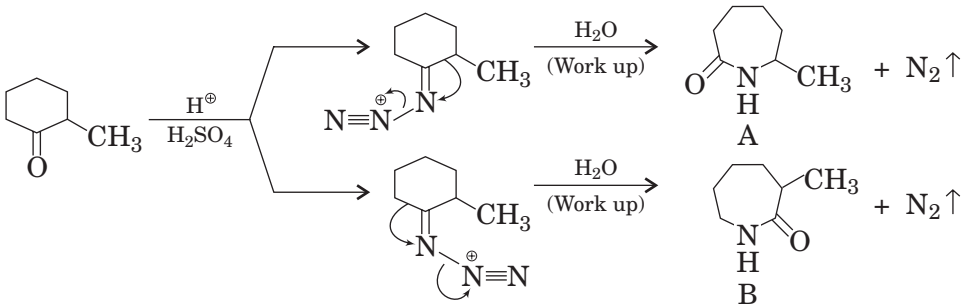
(a) 

(b) 

17. Predict the products and suggest a reasonable mechanism for the following reaction (Schmidt rearrangement):

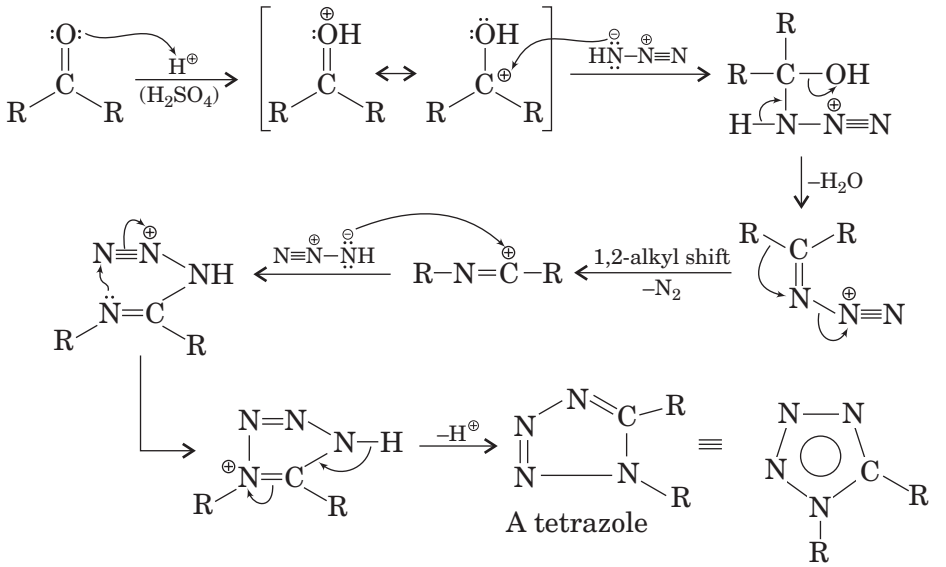


Solution 2-Methylcyclohexanone (an unsymmetrical cyclic ketone) undergoes the Schmidt rearrangement to give two isomeric lactams (A and B) as a result of migration of two different ring bonds to nitrogen.

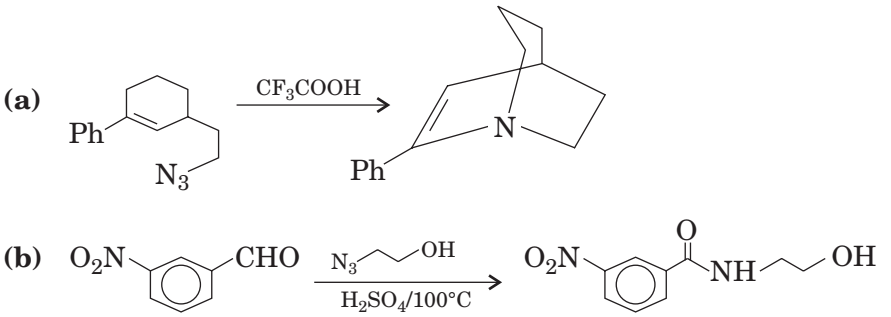


18. When an excess of hydrazoic acid is used during the Schmidt rearrangement involving a ketone, then a tetrazole derivative is obtained in good yield. Explain its formation by a suitable mechanism.

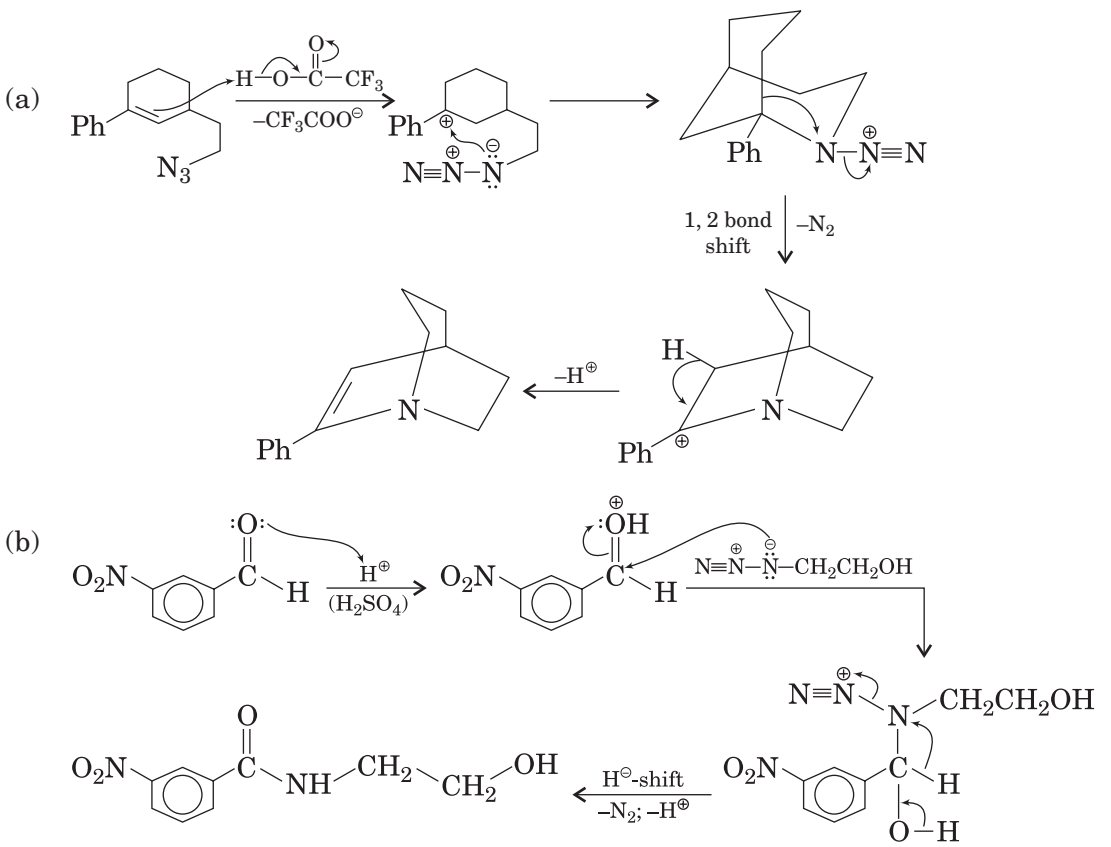
Solution The intermediate nitrilium ion reacts with hydrazoic acid (present in excess) to form a tetrazole derivative. Instead of expulsion of N_2, an intramolecular cyclization takes place to give the product. The mechanism of the reaction is as follows:



19. Suggest a mechanism for each of the following reactions (Schmidt reactions):

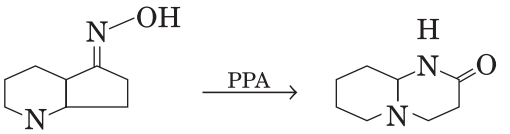


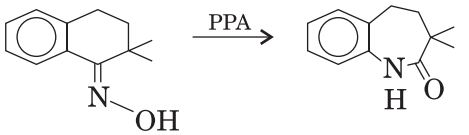
Solution

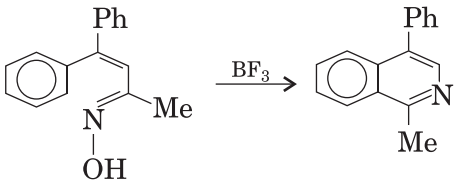


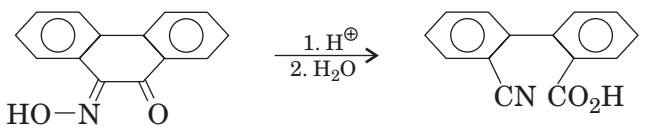
Study Problems

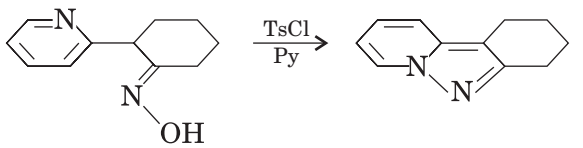
1. Write an arrow formalism mechanism for each of the following reactions:

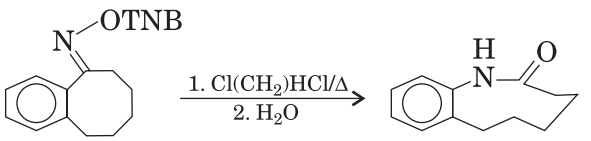
(a) 

(b) 

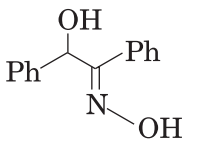
(c) 

(d) 

(e) 

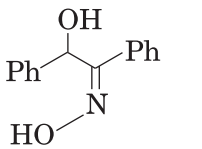
(f) 

2. Provide a suitable mechanism for the following second-order Beckmann rearrangements with $PhSO_2Cl/Py$:

(a) 

α-Benzoin oxime

$\longrightarrow$ PhCHO + PhCN
A nitrile

(b) 

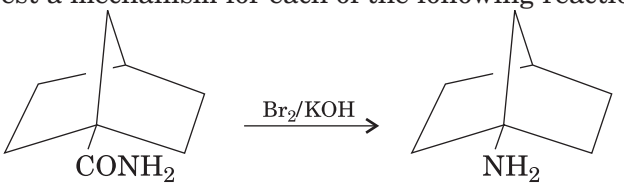
β-Benzoin oxime

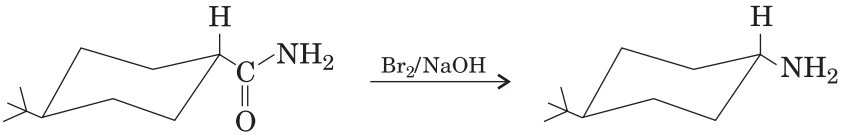
$\longrightarrow$ PhCHO + PhNC
An isonitrile

3. $A(C_{14}H_{13}NO_2) \xrightarrow[2.\ H_2O]{1.\ PCl_5/ether} B(C_{14}H_{13}NO_2) \xrightarrow{H_3O^{\oplus}} p\text{-}CH_3OC_6H_4COOH + PhNH_2$

Identify A and B in this reaction sequence.

4. Suggest a mechanism for each of the following reactions:

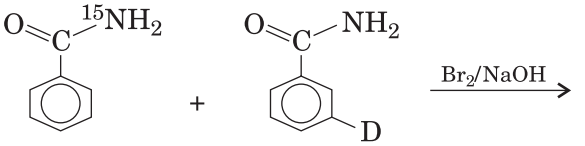
(a) 

(b) 

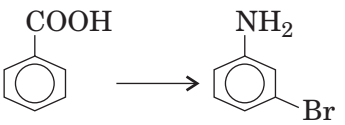
5. Predict the stereochemical outcome of the following reaction and explain:

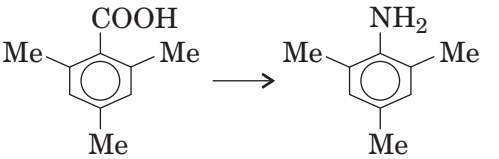
(*S*)-2-Phenylpropanamide $\xrightarrow{Br_2/NaOH}$

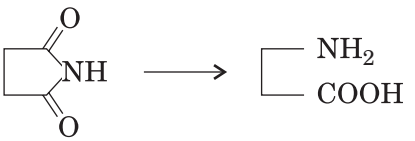
6. Predict the products expected to be formed when the Hofmann rearrangement is carried out with a mixture of the following two amides. Give your reasoning.

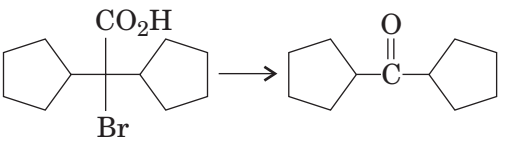


7. How would you carry out the following conversions using the Hofmann rearrangement:

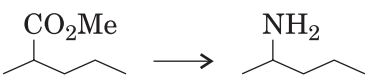
(a) 

(b) 

(c) 

(d) 

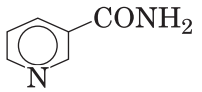
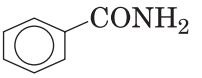
(e) $(CH_3)_2\overset{\overset{OH}{|}}{C}-COOH \longrightarrow CH_3-\overset{\overset{O}{\|}}{C}-CH_3$

(f) 

8. Which one of each of the following pairs will undergo the Hofmann rearrangement at a rate faster than the other and why?

(a) $PhCONH_2$ or p-$MeOC_6H_4CH_2CONH_2$

(b) $PhCH_2CONH_2$ or $PhCONH_2$

(c)  or 

9. A carboxylic acid can be converted to a primary amine (with one less carbon atom) by using the following reaction sequence:

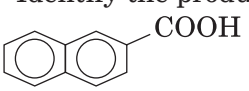
$$R\text{–}COOH \xrightarrow[\text{or } PCl_5]{SOCl_2} R\text{–}COCl \xrightarrow{NH_3} RCONH_2 \xrightarrow{Br_2/NaOH} RNH_2$$

A primary amine obtained by this process is identified as (*S*)-3-methyl-3-hexanamine. Draw three-dimensional structures for all the four compounds involved in this reaction sequence and designate them as (*R*) or (*S*).

10. Predict the products formed when the following amides are treated with alkaline bromide water:

(a) $Ph(CH_2)_3\,CONH_2$ (b) $H_2NCO(CH_2)_4CONH_2$ (c) 

11. Identify the products A, B, C, D and E in the following reaction sequence:

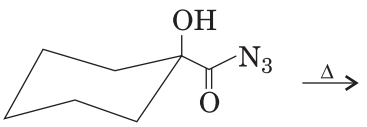
 $\xrightarrow{SOCl_2}$ A $\xrightarrow{NH_2NH_2}$ B $\xrightarrow{HNO_2}$ C $\xrightarrow[Me_3COH]{\Delta}$ D $\xrightarrow{CF_3COOH}$ E

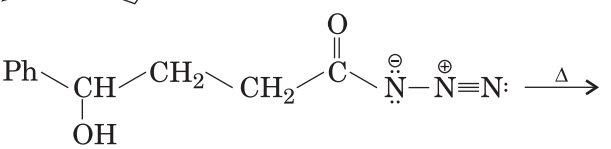
12. Which one of the following azides will undergo the Curtius rearrangement at a faster rate and why?

p-$MeOC_6H_4CON_3$ or $PhCON_3$

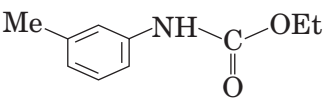
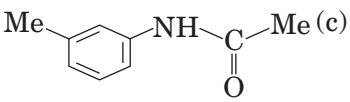
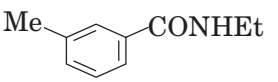
13. How can glycine be synthesized from diethyl malonate using the Curtius rearrangement?

14. Predict the product and suggest a mechanism for each of the following reactions:

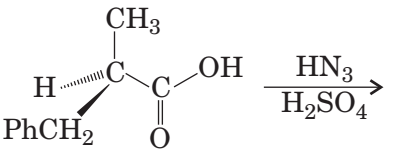
(a) 

(b) 

15. How would you synthesize the following compounds starting from 3-methylbenzoic acid using the Schmidt reaction?

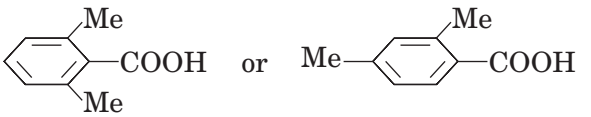
(a)  (b)  (c) 

16. Predict the product of the following reaction and give your reasoning:



17. Predict the products expected to be obtained when butanone is subjected to Schmidt rearrangement. Give mechanism and necessary explanation for the formation of these products.

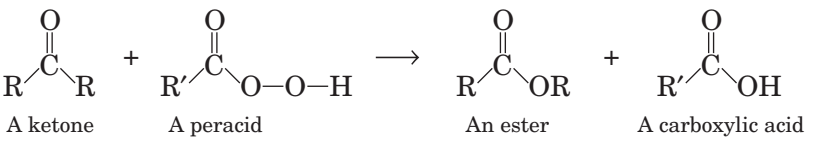
18. Which one of the following two carboxylic acids will undergo the Schmidt rearrangement at a faster rate than the other and why?



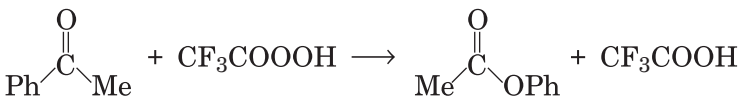
4.1.3 Nucleophilic Rearrangements to Electron-Deficient Oxygen

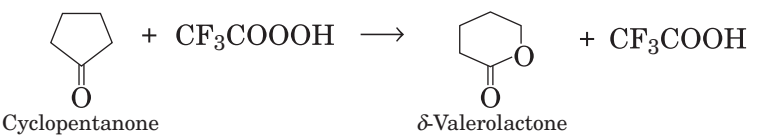
4.1.3.1 Baeyer–Villiger oxidation

The oxidation of ketones to esters and of cyclic ketones to lactones by treatment with peroxy acids such as trifluoroperacetic acid, *m*-chloroperbenzoic acid, perbenzoic acid, peracetic acid, etc. is called the *Baeyer–Villiger oxidation*.



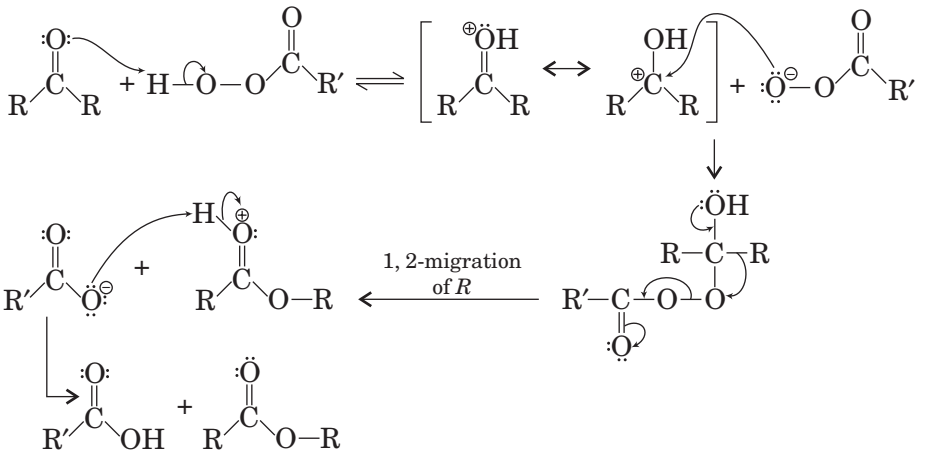
Examples:





Other reagents like $K_2S_2O_8$–H_2SO_4 and H_2O_2–BF_3–Et_2O are also used in this reaction. The reaction is basically an insertion of an oxygen atom to a C–C σ-bond which is attached with a carbonyl carbon and involves migration of a group from carbon to electron-deficient oxygen.

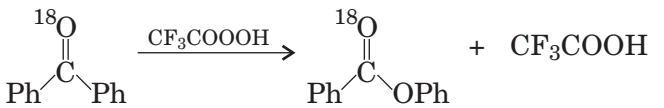
Mechanism of the reaction The mechanism of the reaction involves the steps as follows:



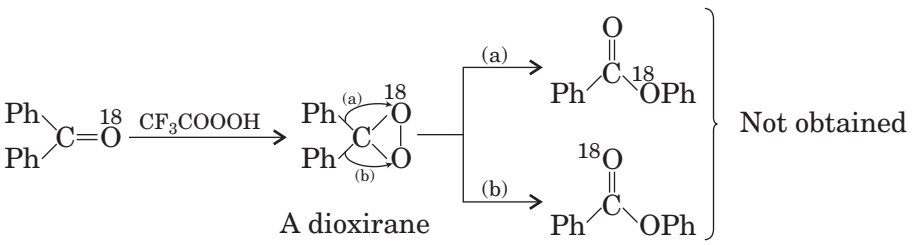
In the first step, the ketone undergoes protonation by the peroxy acid. In the second step, nucleophilic attack on the carbonyl carbon by the conjugate base of the peroxy acid occurs to form a tetrahedral intermediate (the so-called *Criegee intermediate*). In the next step, the intermediate undergoes rearrangement involving migration of an alkyl group from carbon to electron-deficient oxygen with concomitant loss of a carboxylate ion. This is the rate-determining step of the reaction. In the fourth and final steps, proton transfer occurs to form an ester (from the ketone) and a carboxylic acid (from the peroxy acid).

Evidence in favour of the mechanism The important evidences in favour of the mechanism of Baeyer–Villiger oxidation are as follows:

(i) When a labelled ketone with ^{18}O is subjected to the Baeyer–Villiger oxidation, the resulting ester is found to contain ^{18}O.



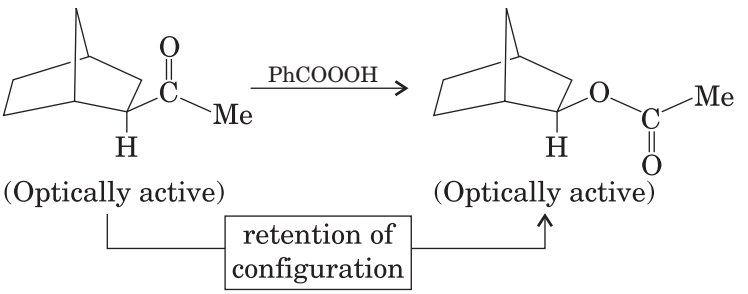
This observation supports the proposed mechanism involving the Criegee intermediate and not a dioxirane intermediate because there is no scrambling of the ^{18}O label in the product ester.



(ii) That the concerted step is the rate-determining step is supported by the following facts: (a) an electron-attracting group in the R′COOO-group increases the rate of

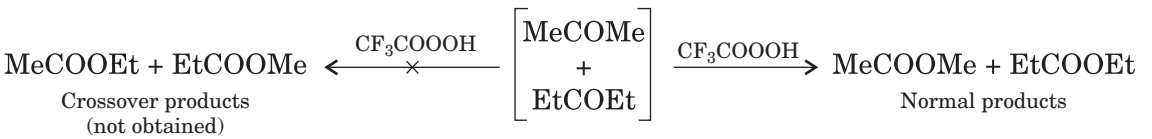
the reaction and (b) an electron-donating group in the migrating alkyl group also increases the rate of the reaction.

(iii) Retention of configuration occurs in a chiral migrating group. For example:



The observation suggests that the migrating group never separates from the rest of the molecules during shifting, otherwise a racemic product would have been obtained because of pyramidal inversion of free carbanion. Therefore, it is an intramolecular concerted rearrangement.

(iv) When two different ketones are allowed to undergo the Baeyer–Villiger oxidation simultaneously in the same solution, no crossover product is obtained. For example:



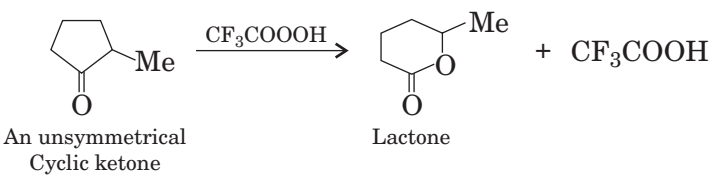
From this crossover experiment, it also becomes evident that the migrating group does not become detached from the remainder of the molecule, i.e. the rearrangement is intramolecular in nature.

Characetristic features

1. For unsymmetrical ketones, the group that is better supplier of electrons actually migrates preferably. The order of preference is 3° alkyl > 2° alkyl > benzyl ~ phenyl > 1° alkyl > cyclopropyl > methyl. The migrating preference in aromatic ketones decreases in the following order for the same reason, i.e. the migrating ability increases with electron-donation and decreases with electron-withdrawal.

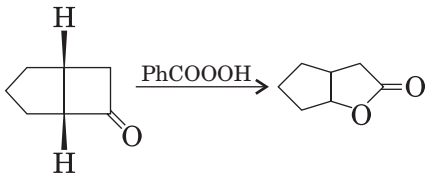


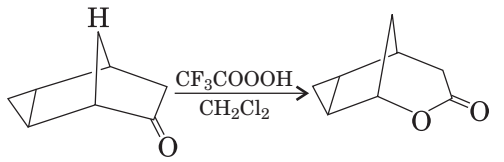
2. In the case of an unsymmetrical cyclic ketone, the C–C σ-bond with more substituted α-carbon usually migrates. For example:

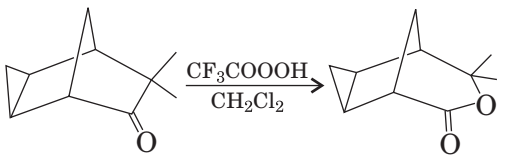


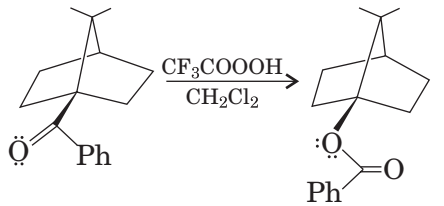
3. The reactivity of peracids can be ranked as follows: CF_3COOOH > monopermaleic acid > nonoperphthalic acid > 3,5-dinitroperbenzoic acid > *m*-chloroperbenzoic acid (*m*-CPBA) > perbenzoic acid > peracetic acid.
4. Baeyer–Villiger oxidation tolerates the presence of many functional groups in the ketone molecule used as a substrate. These groups include $-NO_2$, halogens, –OH, olefinic double bond, etc. Even α, β-unsaturated ketones undergo this reaction without affecting the C═C bond.

A few more examples of Baeyer–Villiger Oxidation

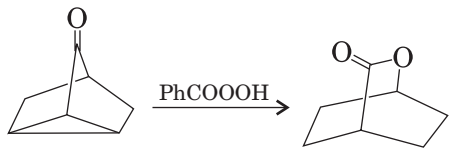
(i) 

(ii) 

(iii) 

(iv) 

(v) $Me_2CHCOMe \xrightarrow{m\text{-CPBA}} MeCOOCHMe_2$

(vi) 

Applications Some important applications of Baeyer–Villiger oxidation are as follows:

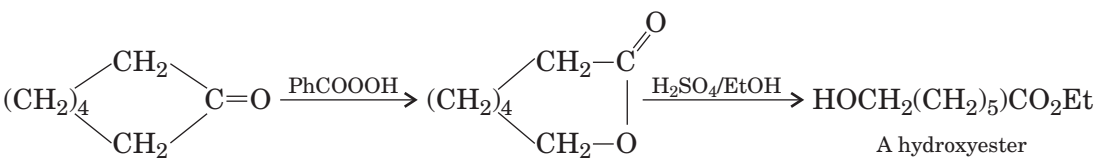
(i) Esters can be prepared from ketones, which are normally very difficult to oxidize without degrading the structure to smaller molecules.

(ii) The reaction provides a method for preparing carboxylic acids by hydrolyzing the resulting ester.

(iii) Identification of the starting ketone is possible by identifying the acid and alcohol obtained by hydrolyzing the product ester.

(iv) The reaction provides a means of preparing alcohols (ROH) and phenols (ArOH) by the hydrolysis of acetate esters obtained from methyl ketones (a methyl group has a low migratory aptitude).

(v) Long-chain hydroxyesters can be prepared from large ring-size ketones by using this reaction. For example:

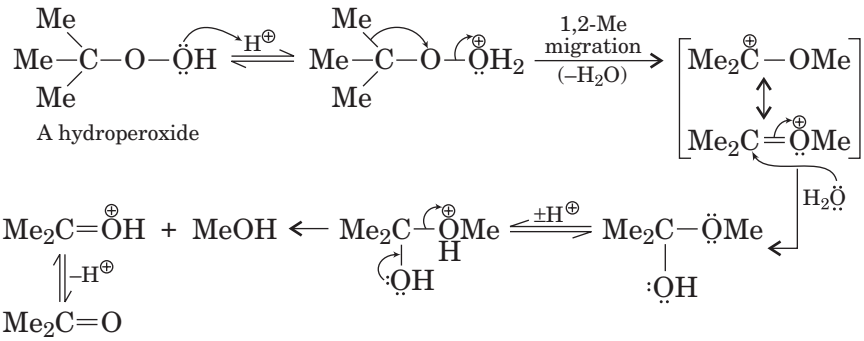


Cycloheptanone

A hydroxyester

4.1.3.2 Hydroperoxide rearrangements

When a hydroperoxide (a compound containing the structural unit C–O–O–H) is treated with Bronsted or Lewis acid, it undergoes cleavage of the peroxide bond along with concomitant 1,2-migration of a neighbouring substituent from carbon to oxygen. As a result of this, a carbocation is obtained, which undergoes hydration to form a hemiacetal. The hemiacetal is then hydrolyzed under this aqueous acid condition to yield the corresponding carbonyl compound. For example:

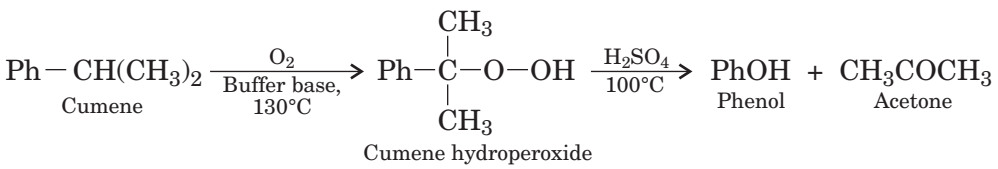


The ease of migration of the alkyl groups is 3° alkyl > 2° alkyl > 1° alkyl > CH_3.

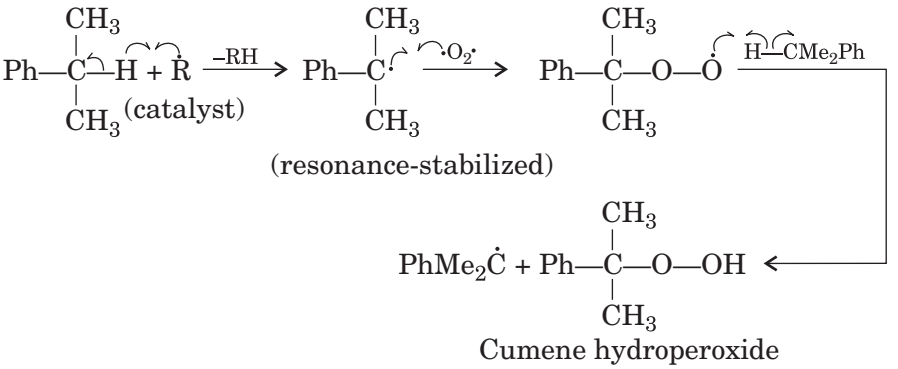
It is very difficult to isolate hydroperoxides, which are very unstable in nature. So, in practice, the reaction is performed by treating alcohols with H_2O_2 in the presence of acid.

$$R_2CHOH \xrightarrow{H_2O_2/H^{\oplus}} RCHO + ROH$$

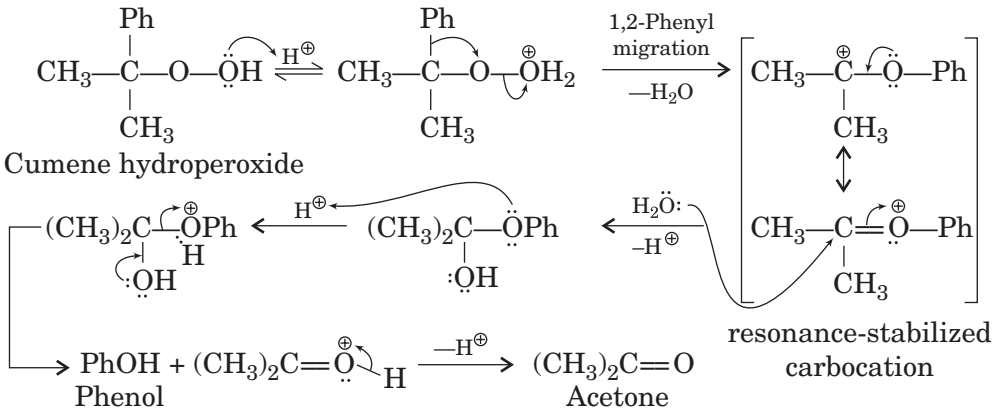
Autoxidation of cumene followed by acid-catalyzed decomposition of the intermediate hydroperoxide constitutes a method for the industrial preparation of phenol and acetone.



(i) Mechanism of autooxidation: The free radical (Ṙ) obtained from the impurities by photolysis causes C–H bond cleavage to form a resonance-stabilized free radical (a benzyl radical). The resulting radical then reacts with aerial oxygen (which is diradical in nature) to form a peroxide radical, which takes up a hydrogen atom from a new cumene molecule to yield cumene hydroperoxide and a benzyl radical.



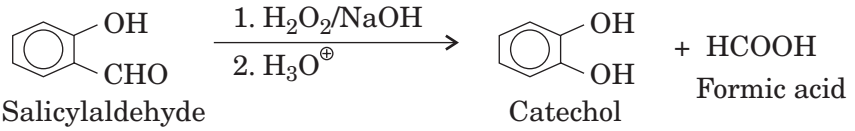
(ii) Mechanism of acid-catalyzed hydrolysis of cumene hydroperoxide:



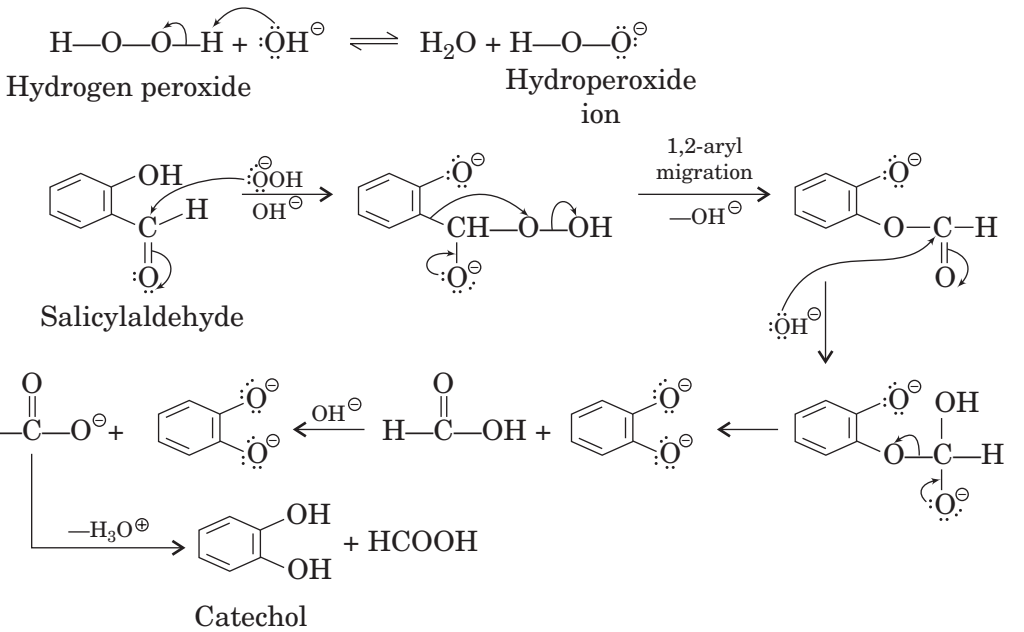
The conjugate acid of the hydroperoxide undergoes loss of water with simultaneous migration of the Ph group with greater migratory aptitude to form a resonance-stabilized carbocation. Water adds to the carbocation to form a hemi-acetal, which undergoes ready hydrolysis under the acidic reaction conditions to yield phenol and acetone.

4.1.3.3 Dakin reaction

Aromatic aldehydes or ketones having an –OH or $–NH_2$ group at the *ortho*- or *para*-position can be converted to the corresponding phenols by treatment with alkaline hydrogen peroxide followed by hydrolysis. This reaction is known as the *Dakin reaction* or *Dakin oxidation*. Salicylaldehyde, for example, can be converted to catechol by this reaction.

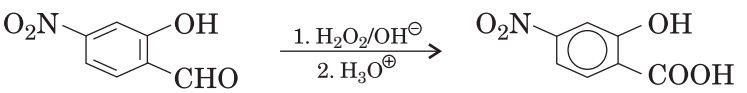


Mechanism of the reaction The mechanism of the reaction involves the steps as follows:

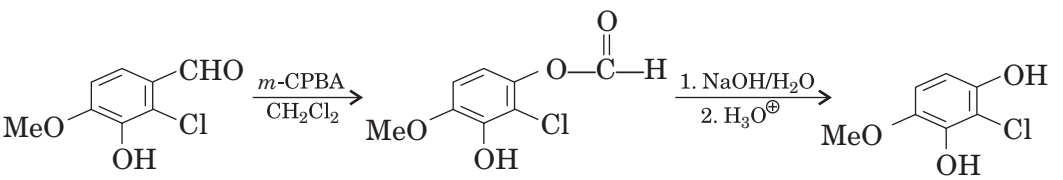


Characteristic features

1. The reaction is facilitated by the –OH or $–NH_2$ group at *ortho*- or *para*-position because these groups increase the electron density, thereby making the 1,2-shift of the aryl group easy.
2. When strong electron-attracting group is present at the *ortho*- or *para*-position, then instead of aryl shift, hydride shift occurs preferably to yield an aromatic acid as the major product. For example:

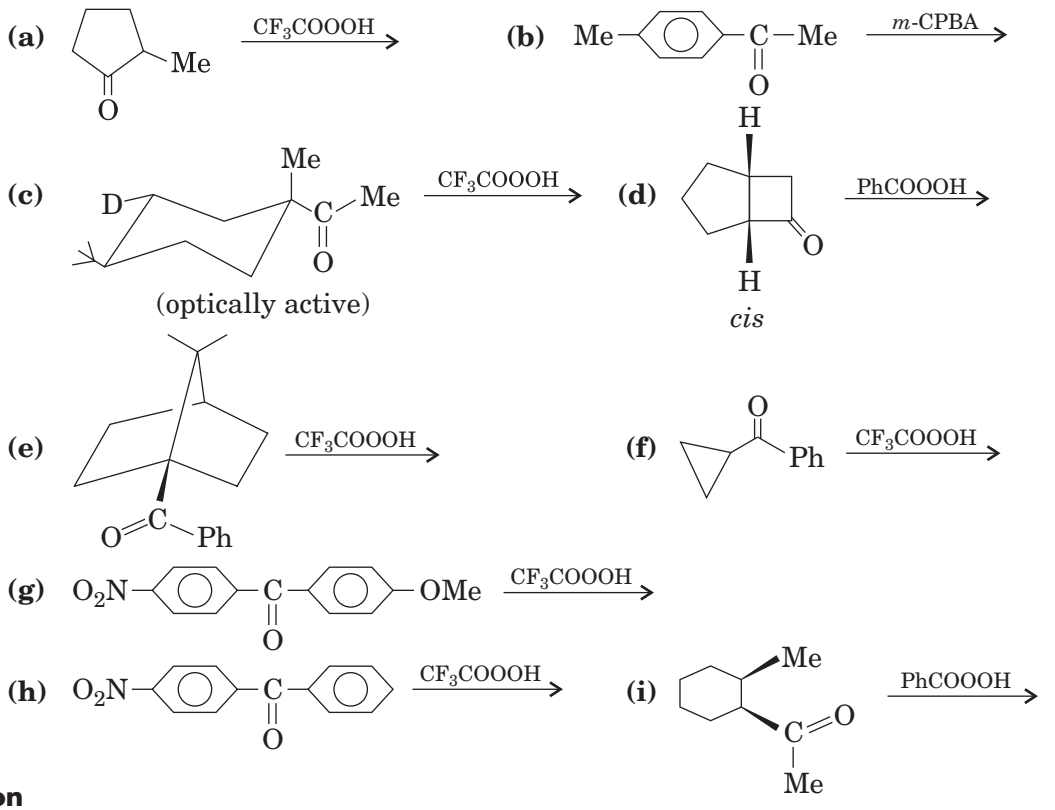


3. Dakin reaction can also be carried out with *m*-chloroperbenzoic acid (*m*-CPBA). For example:



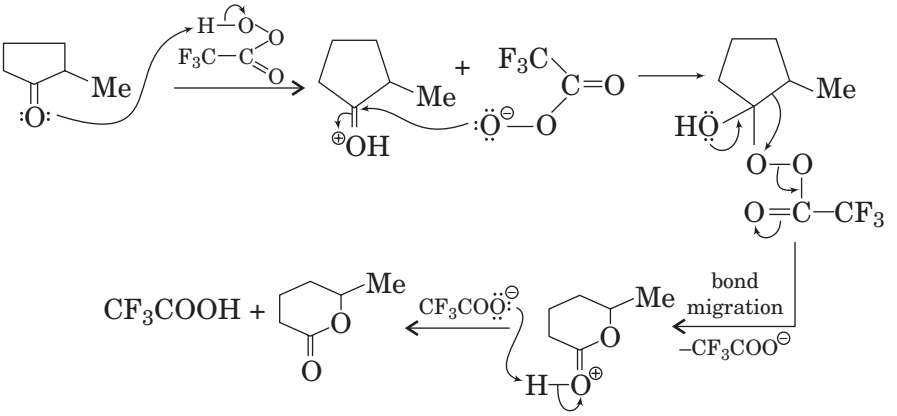
SOLVED PROBLEMS

1. Predict the product and suggest a reasonable mechanism for each of the following reactions (Baeyer–Villiger oxidation):



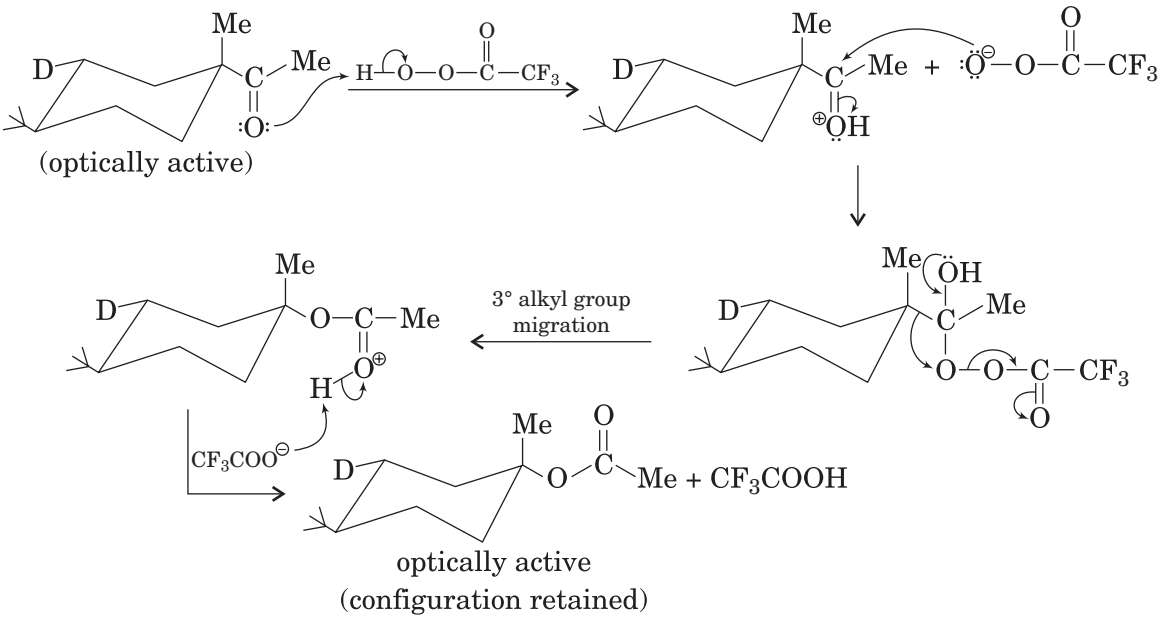
Solution

(a) In unsymmetrical cyclic ketone, the bond with more substituted α-carbon usually migrates. Therefore, the mechanism of the reaction leading to the expected lactone is as follows:

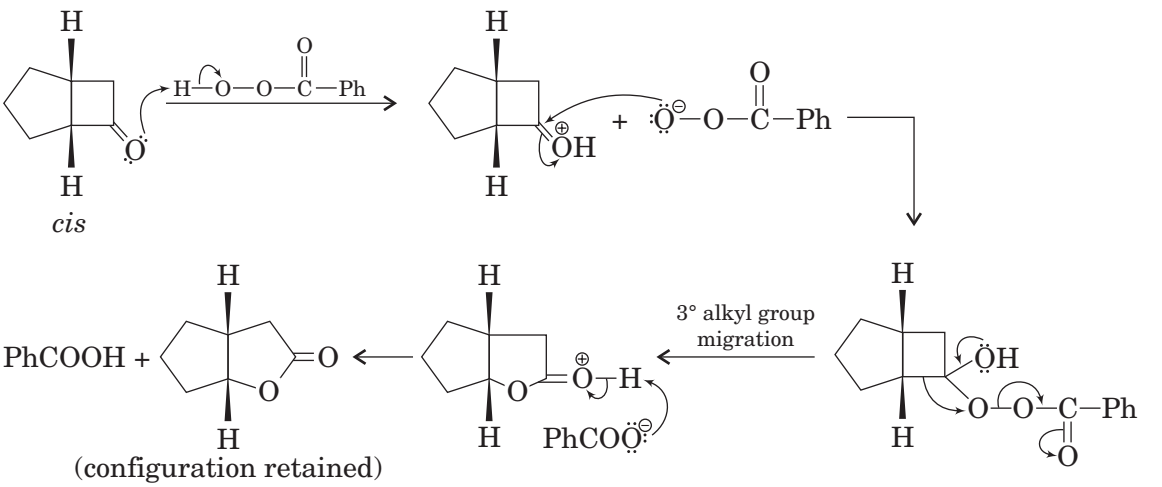


(b) [**Hint:** Since the aryl group has greater migratory aptitude than the methyl group, it will migrate preferably to give the acetate ester p-MeC_6H_4OCOMe. For Mechanism see article no. 4.1.3.1.]

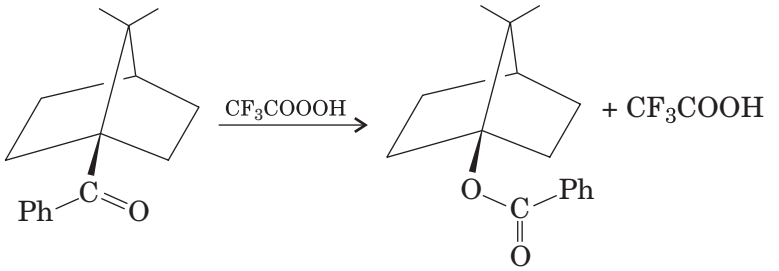
(c) Since the rearrangement is intramolecular in nature, retention of configuration of the chirality centre is observed. The resulting ester is optically active (almost 100% optically pure). The chiral carbon migrates because it (a 3° alkyl group) has greater migratory aptitude than methyl.



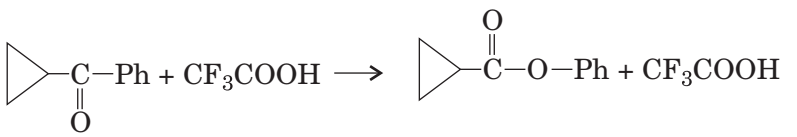
(d) The chiral 3° alkyl group migrates with retention of configuration and as a consequence, a *cis* product is obtained from the *cis*-starting compound.



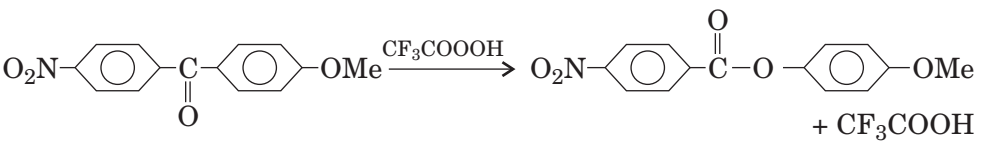
(e) [**Hint:** A 3° alkyl group migrates to give a lactone because it has greater migratory aptitude than the phenyl group.]



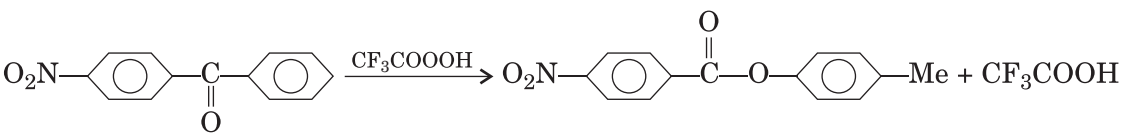
(f) [**Hint:** Phenyl group has greater migratory aptitude than the cyclopropyl group. So, it migrates to give the corresponding ester.]



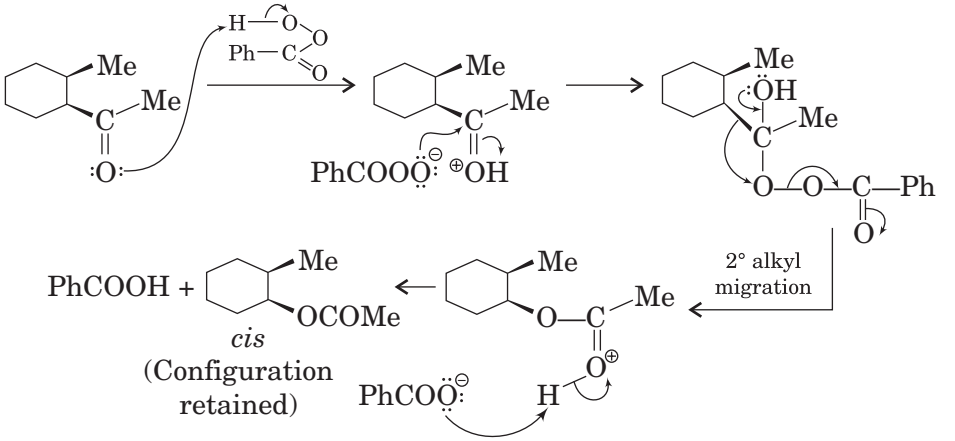
(g) [**Hint:** Due to the presence of an electron-releasing (+R) –OMe group at the *para*-position,  OMe has greater migratory aptitude than the  NO_2 group containing an electron-attracting (–R plus–I)–NO_2 group at a similar position. Therefore, the former aryl group, i.e., the *p*-anisyl group will migrate to give the corresponding ester.



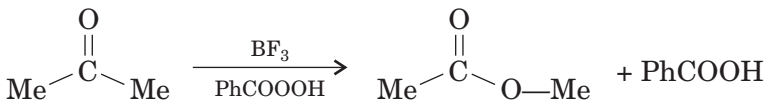
(h) [**Hint:** Due to the presence of an electron-withdrawing (–R plus–I) –NO_2 group, the *p*-nitrophenyl group has lower migratory aptitude than the phenyl group. As a consequence, the phenyl group migrates to give the corresponding ester.



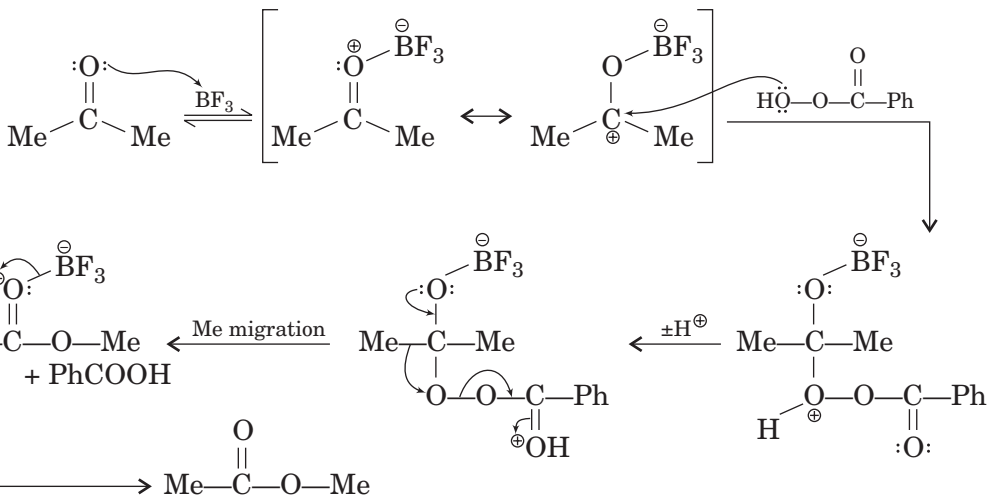
(i) The chiral 2°alkyl group migrates preferably with retention of configuration and because of this *cis*-ester is obtained from *cis*-starting ketone.



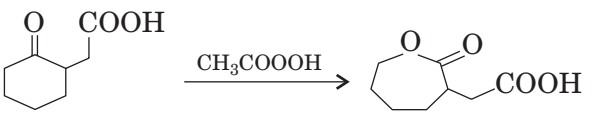
2. Provide a reasonable mechanism for the following reaction:



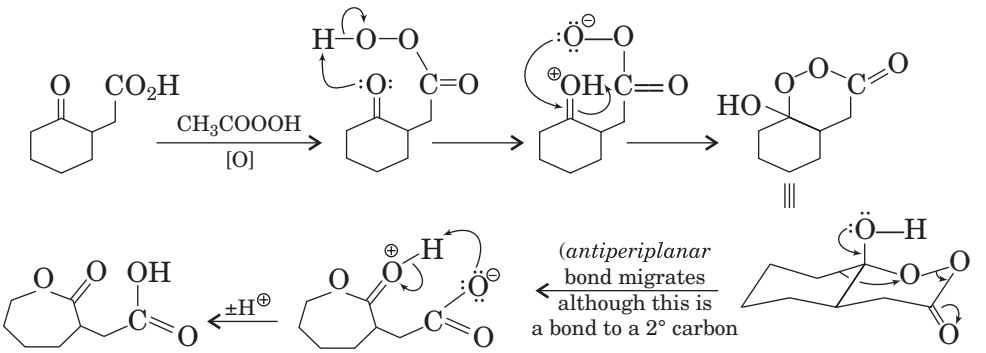
Solution The Lewis acid (BF_3) catalysed mechanism of the reaction may be outlined as follows:



3. Write an arrow formalism mechanism for the following reaction (an intramolecular Baeyer–Villiger oxidation):

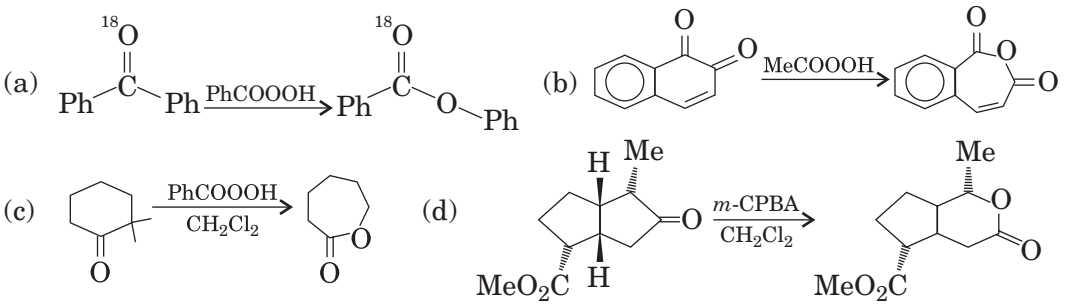


Solution Peracetic acid oxidises the ketoacid to 2-ketocyclohexylperacetic acid which then undergoes the Baeyer–Villiger oxidation to give the corresponding lactone.

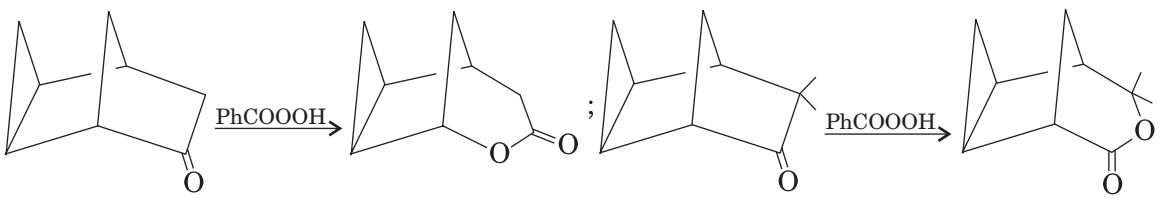


Study Problems

1. Postulate a reasonable mechanism for each of the following reactions (Baeyer–Villiger oxidations) and give your reasoning:



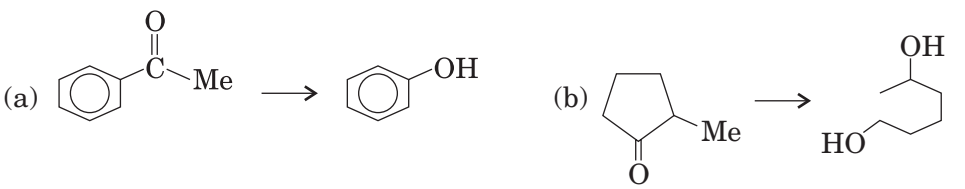
2. Explain the following observations:

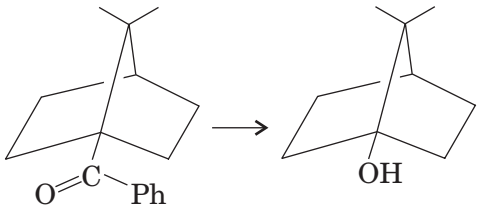


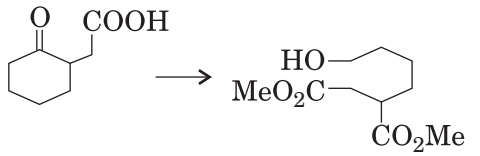
3. Predict the product (with *R*/*S* designation) for the following reaction and give your reasoning:

$$(S)\text{-PhMeCHCO}_2\text{Me} \xrightarrow{\text{CF}_3\text{COOOH}}$$

4. How would you carry out the following transformations using the Baeyer–Villiger oxidation in one of the steps:



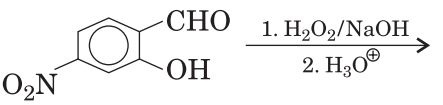
(c) 

(d) 

[**Hint:** (a) CF_3COOOH followed by acidic hydrolysis; (b) CF_3CO_3H followed by reduction with $LiAlH_4$; (c) CF_3CO_3H followed by alkaline hydrolysis; (d) CH_3CO_3H followed by $MeOH/H_3O^{\oplus}$.]

5. How would you convert benzene to phenol through the formation of cumene hydroperoxide?

6. Predict the product of the following reaction and give your reasoning:



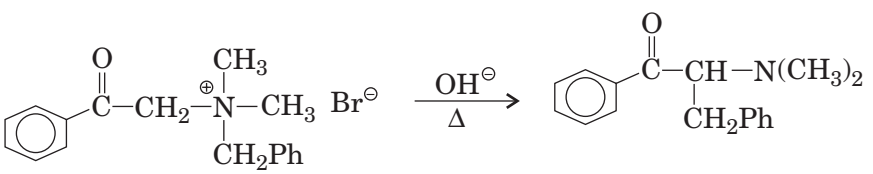
[**Hint:** Due to the presence of an electron-attracting $–NO_2$ group at the *para*-position, hydride shift occurs preferentially instead of aryl shift.]

4.1.4 Electrophilic Rearrangements

An electrophilic rearrangement involves the migration of a group without its electron pair from a heteroatom such as N, O and S to an electron-rich carbon. Although these rearrangements are less common but not rare. A few of them are discussed below:

4.1.4.1 Stevens rearrangement

When a quaternary ammonium salt bearing an electron-withdrawing group (e.g. aryl, heteroaryl, RCO–, $–CO_2R$, –CN, etc.) on one of the carbons attached to nitrogen is heated with a strong base (such as $NaNH_2$, NaOR, PhLi, Me_3COK, NaH, NaOH, etc.) a rearranged tertiary amine is obtained. This reaction is called the *Stevens rearrangement*. This is illustrated by the rearrangement of phenacylbenzyldimethylammonium bromide (I) to α-dimethylamino-β-phenylpropiophenone (II).

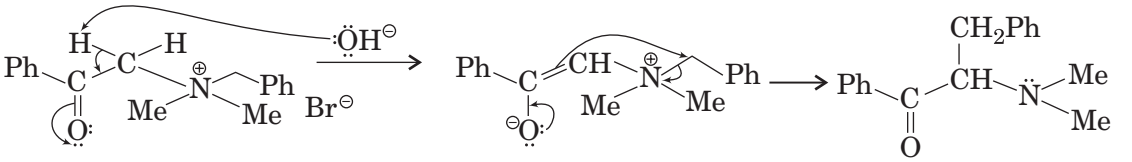


I II

Mechanism of the reaction Crossover experiments showed that the mechanism of Stevens rearrangement is intramolecular. This was further established by the fact that an optically active substrate (e.g. dimethylphenacyl-1-phenylethylammonium bromide)

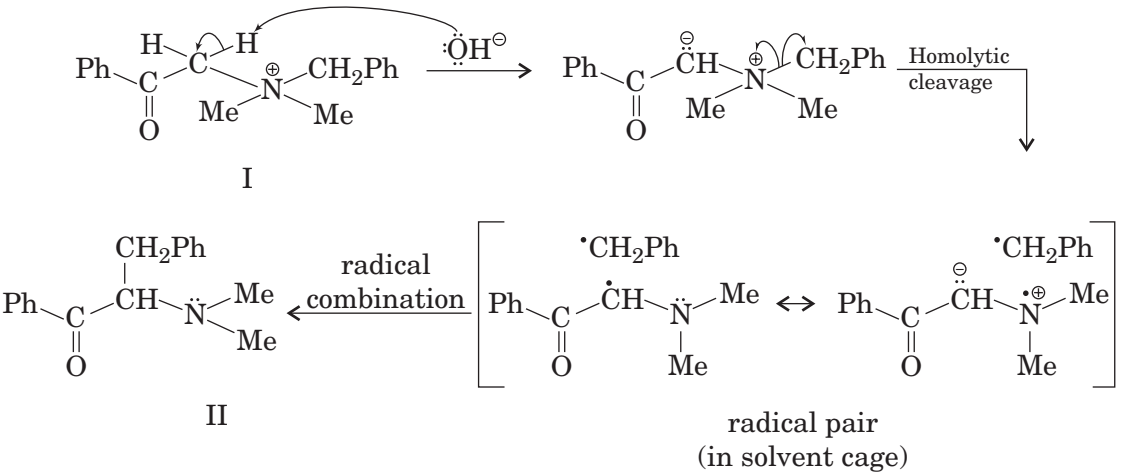
is found to rearrange with 97% retention of configuration. From these observations, it has been suggested that the rearrangement proceeds through a concerted mechanism involving an intramolecular nucleophilic substitution (S_Ni).

Concerted mechanism:



However, a concerted rearrangement shown above would not be an allowed reaction according to orbital symmetry rules, i.e. it is a symmetry-forbidden process. Such observations, therefore, rule out a concerted mechanism, and a radical-pair mechanism is proposed.

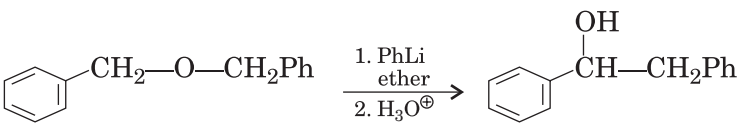
Radical-pair mechanism:



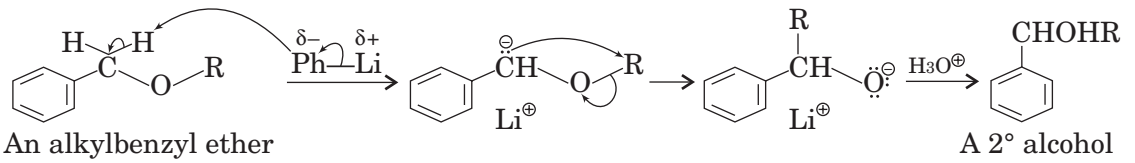
I II

4.1.4.2 Wittig rearrangement

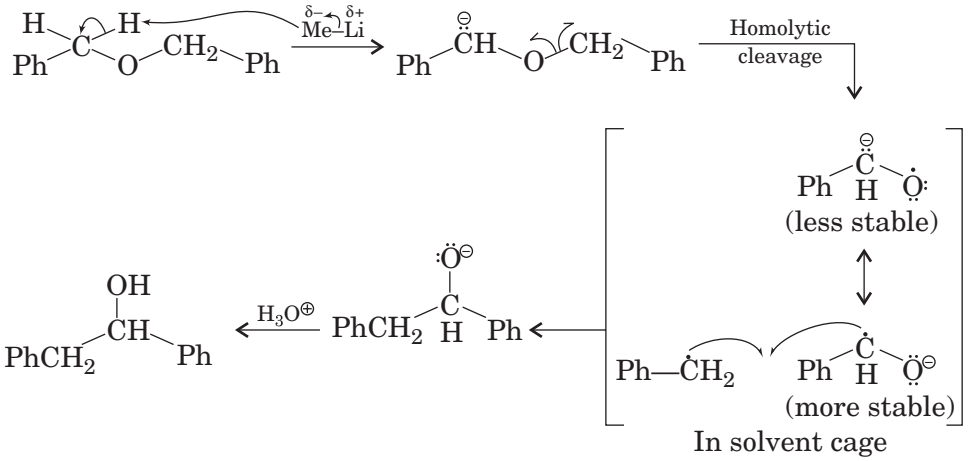
The rearrangement of alkylbenzyl and related ethers induced by strong bases results in formation of carbinols. Here, the migration of carbon group occurs from oxygen to carbon. The reaction is called the *Wittig rearrangement*. For example, when dibenzyl ether is treated with phenyl lithium, 1,2-diphenylethanol is obtained.



Mechanism of the reaction No single mechanistic pathway appears to be applicable to this type of rearrangement and a particular path followed depends very much on the starting material. The earliest proposal was an intramolecular displacement similar to the Stevens rearrangement.



There is enough evidence to support the radical pair mechanism for the Wittig rearrangement where the migrating group is alkyl or aryl.

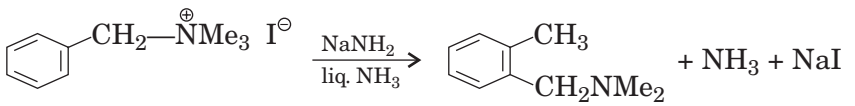


The radical route is also supported by the migrating aptitude of the groups which parallels the order of free radical stability.

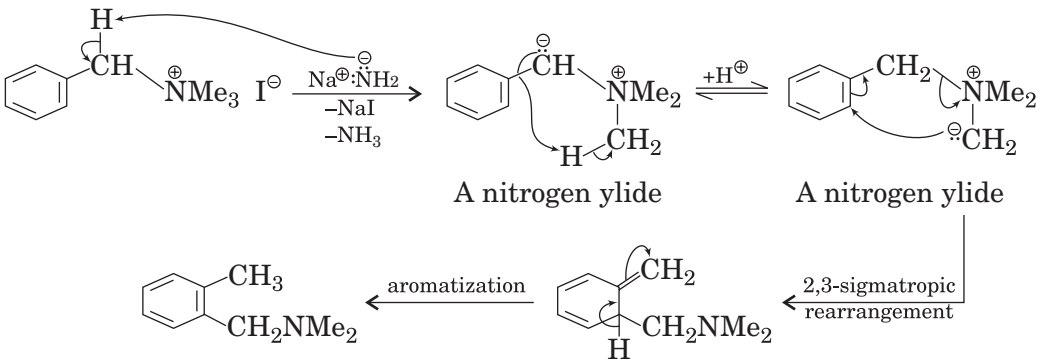
$$\text{R = allyl} \sim \text{benzyl} > \text{methyl} > \text{ethyl} > \text{isopropyl} > \text{phenyl}$$

4.1.4.3 Sommelet–Hauser rearrangement

When benzyl trialkylammonium salts are heated with strong base, like alkali metal amide, benzyl dialkylamines are produced. This reaction is called the *Sommelet–Hauser rearrangement*. For example:

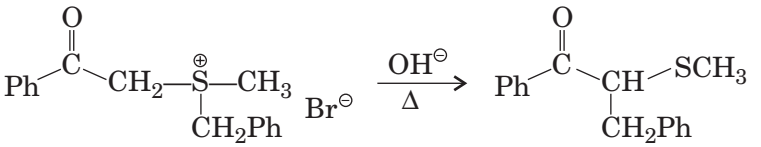


Mechanism of the reaction A nitrogen ylide is formed first by abstraction of a benzylic proton by base. The ylide then undergoes [2, 3]-sigmatropic rearrangement to form an intermediate carbocyclic ring system with an exocyclic double bond. Subsequent aromatization leads to the formation of a rearranged benzylic amine. The course of the reaction may be shown as follows:

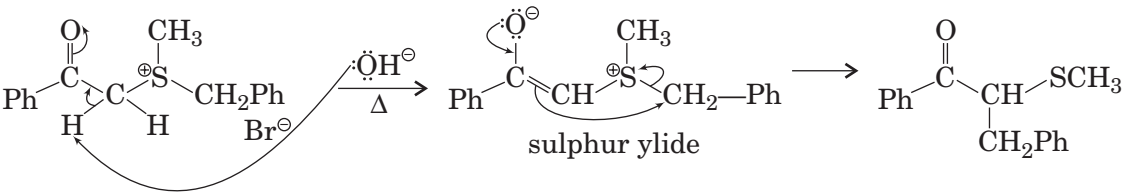


SOLVED PROBLEMS

1. A variant of the Stevens rearrangement is the rearrangement of sulphur ylides. Suggest a mechanism for the following reaction:



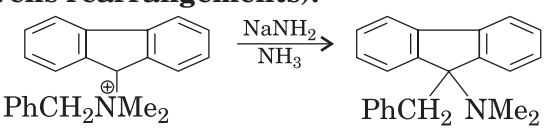
Solution This rearrangement involving an electrophilic 1,2-shift preceds as follows:



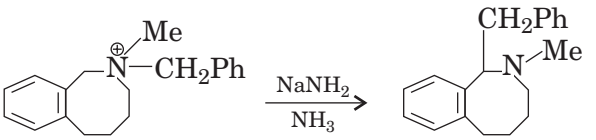
A sulphonium salt

2. Provide an arrow formalism mechanism for each of the following reactions (Stevens rearrangements):

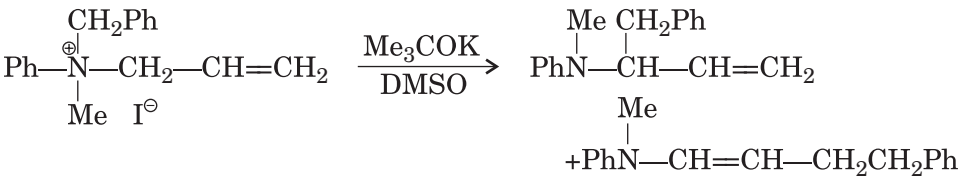
(a)



(b)

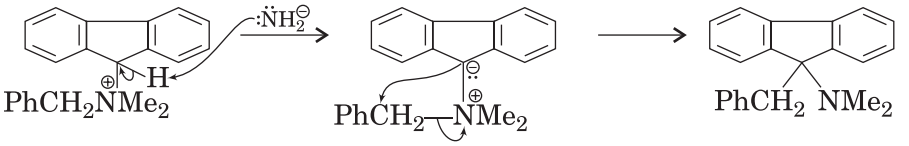


(c)



Solution

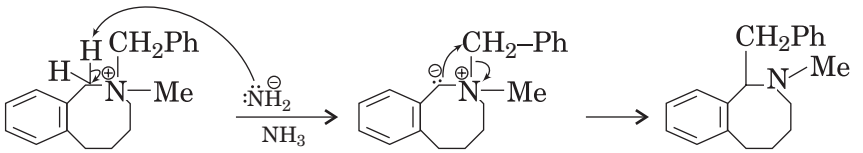
(a)



A nitrogen ylide

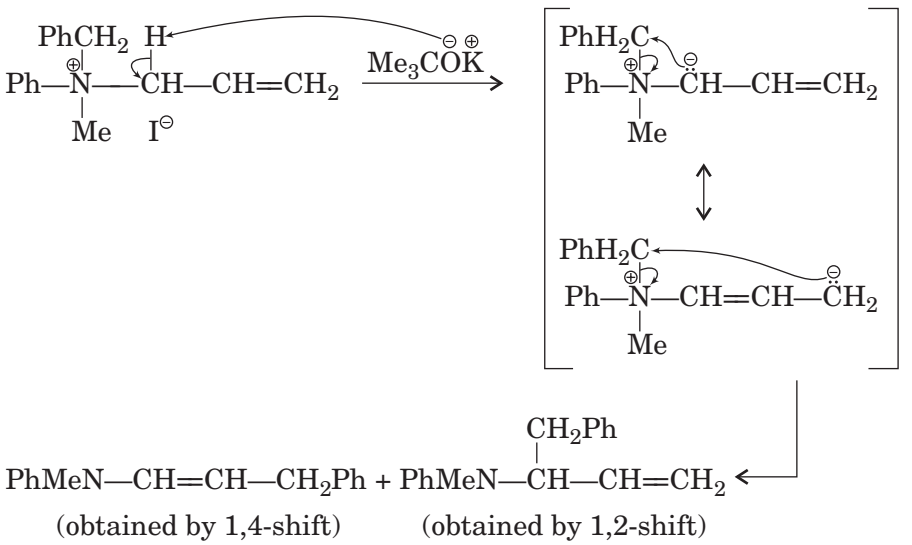
The base abstracts a proton (which is acidic because the conjugate base is an aromatic cyclopentadienyl anion system) to form a nitrogen ylide which then rearranges to give the product.

(b)



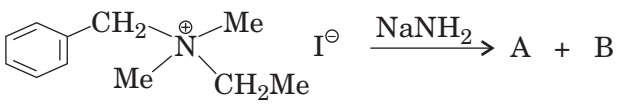
A nitrogen ylide

(c) Allylbenzylmethylphenylammonium iodide under Stevens conditions yields a 1,2-rearranged product along with a 1,4-rearranged product.

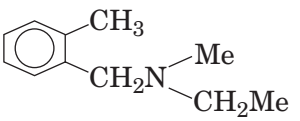


(obtained by 1,4-shift) (obtained by 1,2-shift)

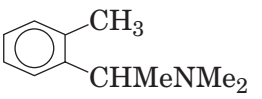
3. Predict the products of the following reaction and give mechanisms for their formation:



Solution [**Hint:** Since nitrogen contains two non-identical groups, two products (A and B) are obtained in this Sommelet–Hauser rearrangement and this is due to formation of two nitrogen ylides by transfering proton from –Me and –CH_2Me groups.



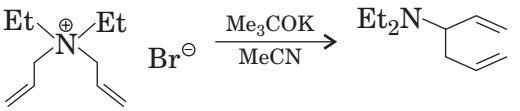
A

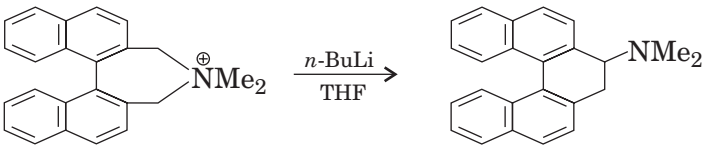


B

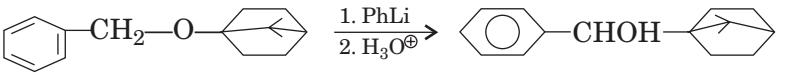
Study Problems

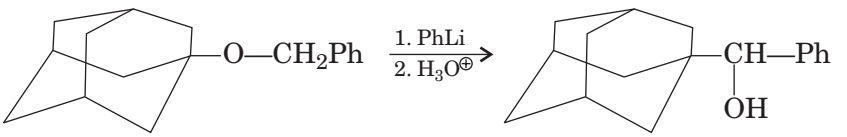
1. Write down the mechanism of the following Stevens rearrangements:

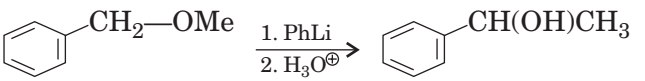
(a) 

(b) 

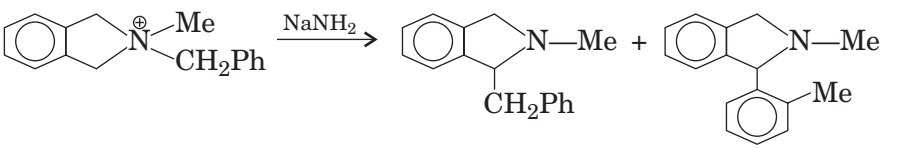
2. Give a reasonable mechanism for each of the following reactions (Wittig rearrangements):

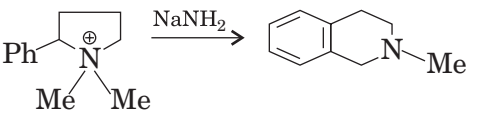
(a) 

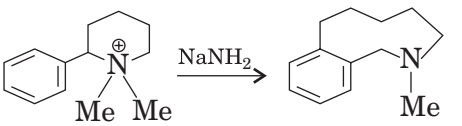
(b) 

(c) 

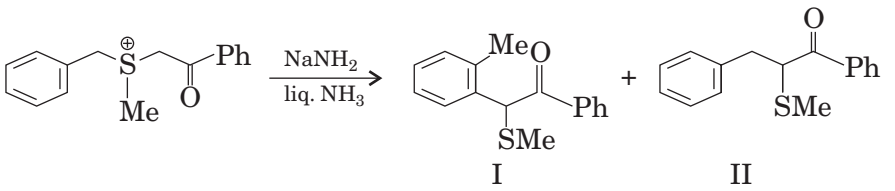
3. Suggest a mechanism for each of the following reactions (Sommelet–Hauser rearrangements):

(a) 

(b) 

(c) 

4. Explain the formation of the two products:



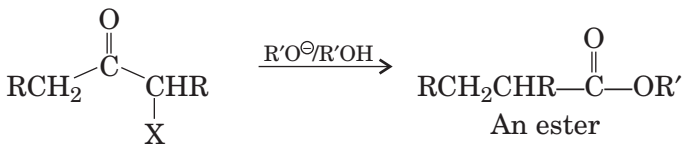
I II

[**Hint:** I is the Sommelet–Hauser rearrangement product (favoured at lower temperature and II is the Stevens rearrangement product (favoured at higher temperature).]

4.2 NON-1,2-REARRANGEMENTS

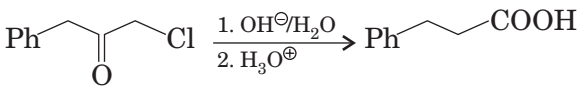
4.2.1 Favorskii Rearrangement

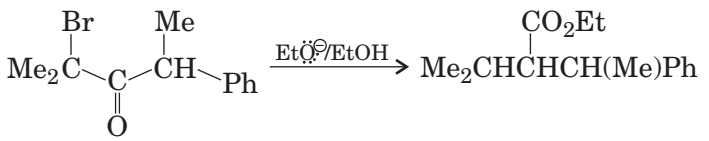
When acyclic or cyclic α-haloketones (chloro, bromo or iodo) containing at least one α'-hydrogen atom are treated with alkoxide base, they undergo skeletal reorganization to produce esters. Hydroxide and amine base lead to the formation of carboxylic acid (salt) and amide, respectively. This nucleophilic rearrangement is known as the *Favorskii rearrangement*.

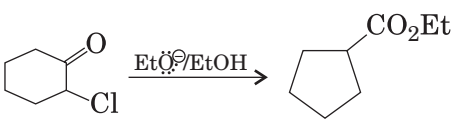


An α-haloketone An ester

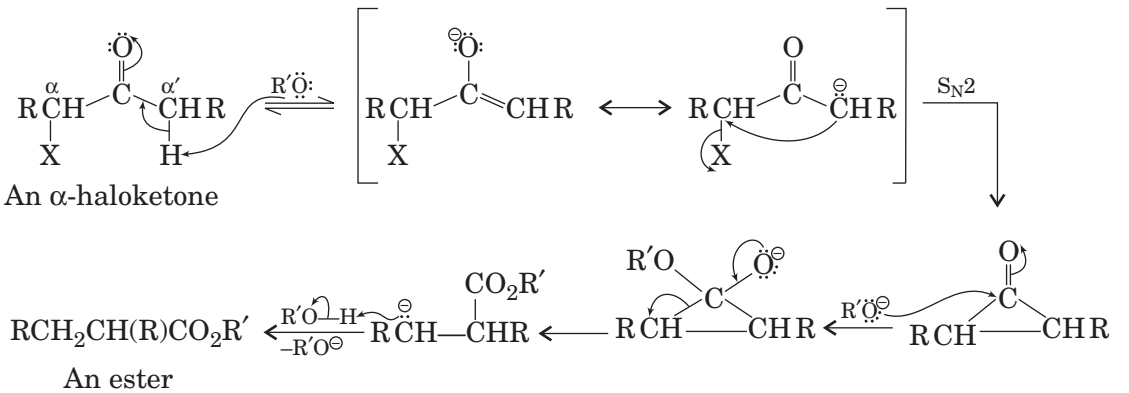
Examples:

(i) 

(ii) 

(iii) 

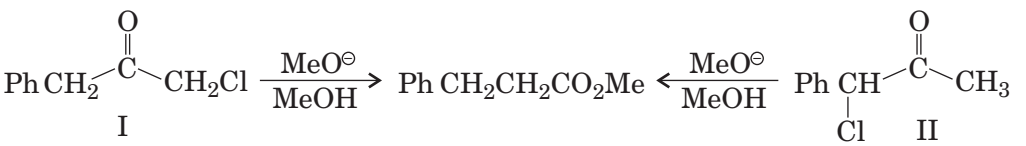
Mechanism of the reaction The mechanism of the reaction involves the steps as follows:



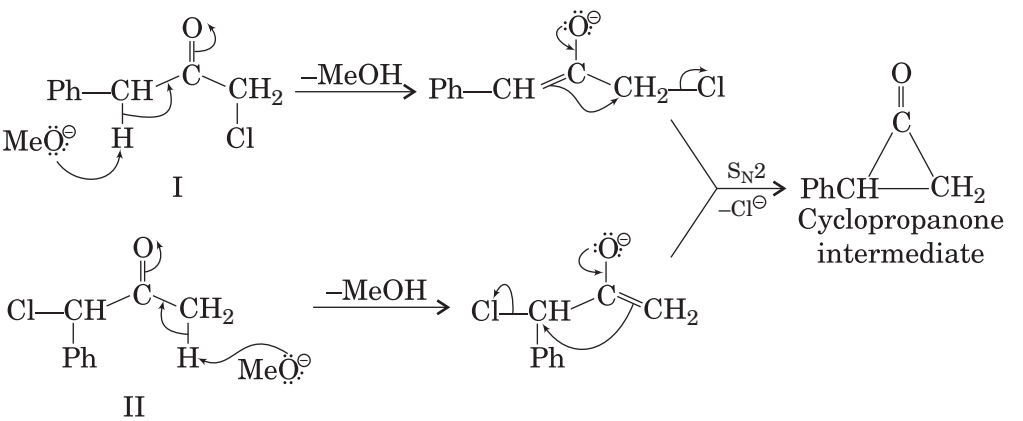
In the first step, base abstracts an α'-H atom to form an enolate ion. In the second step, intramolecular displacement (S_N2) of halogen by the α'-carbanion occurs to form a symmetrical cyclopropanone intermediate. In the next step, the unstable cyclopropanone intermediate undergoes a base-induced ring opening to form a carbanion (the more stable carbanion in the case of an unsymmetrical cyclopropanone intermediate). In the fourth and final step, the carbanion takes up a proton from the solvent R′OH to form an ester.

Evidence in favour of the mechanism There are a number of evidence in support of this mechanism. These are as follows:

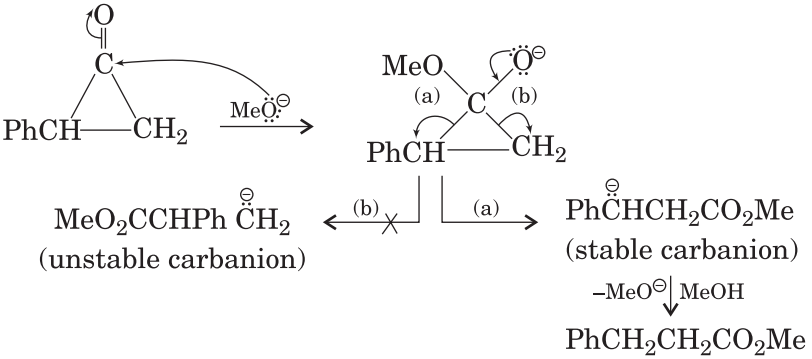
1. When the following two isomeric α-haloketones (I and II) are subjected to the Favorskii rearrangement separately, the same methyl ester is obtained



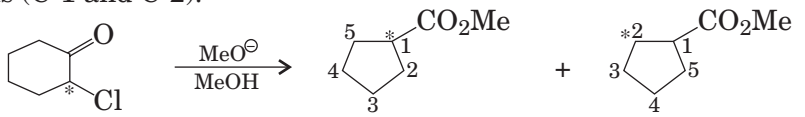
This observation leads to the conclusion that a common cyclopropanone intermediate must be involved in this rearrangement.



The cyclopropanone intermediate then undergoes base induced ring opening to give the stable carbanion. The carbanion abstracts a proton from the solvent MeOH to give the product ester.

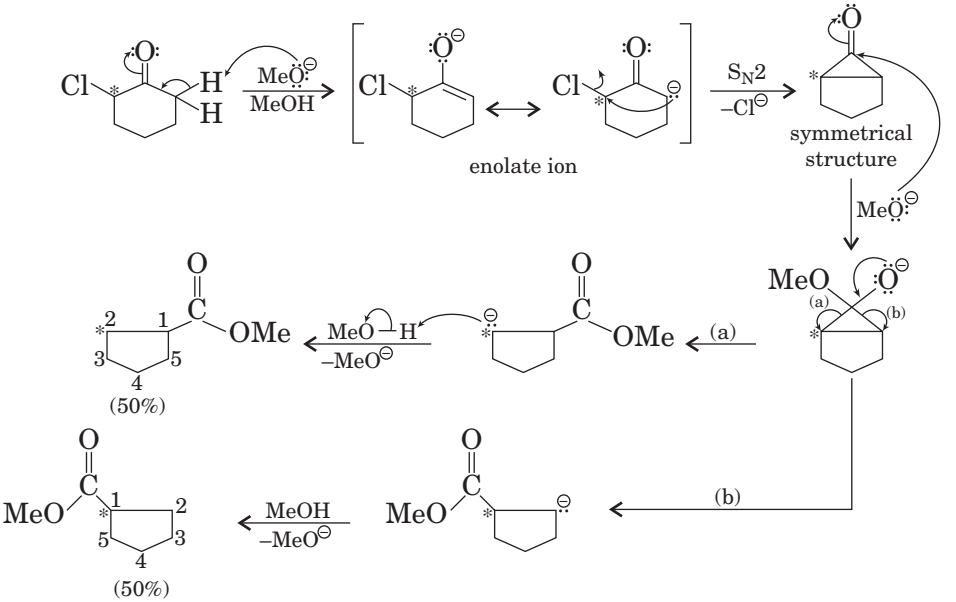


2. Direct support for the involvement of such a cyclopropanone intermediate are from the ^{14}C-labelling studies. When 2-chlorocyclohexane-2-^{14}C is subjected to the Favorskii conditions, the ^{14}C isotope has been found to be distributed between the two carbons (C-1 and C-2).

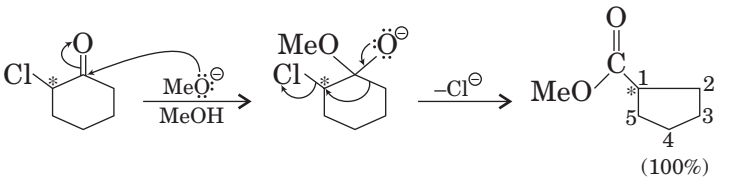


2-Chlorocyclohexanone-2-^{14}C (* = ^{14}C) (50%) (50%)

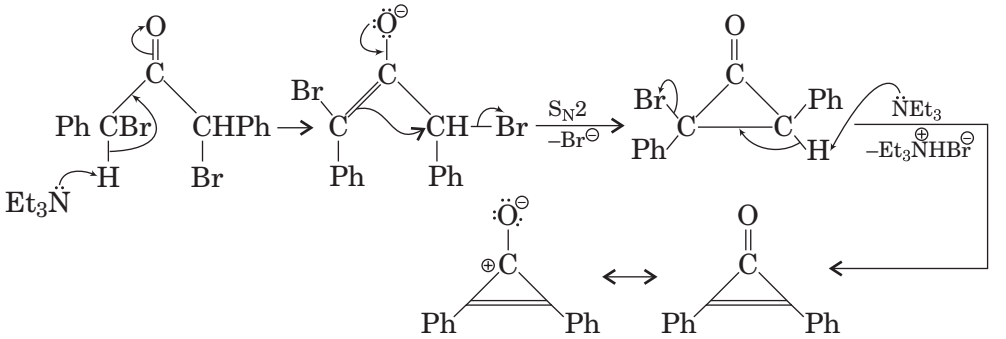
This result is in keeping with the fact that a symmetrical cyclopropanone intermediate, which can open in either direction with equal facility, is involved in the reaction.



If the direct bond migration was involved, we should have got the product containing 100% of the label on C-1.

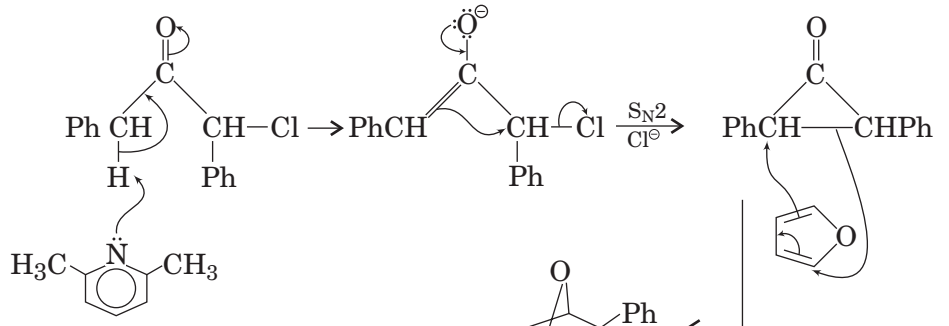


3. A more direct evidence for the involvement of a cyclopropanone intermediate in Favorskii rearrangement is provided by the isolation of a stable cyclopropenone derivative from the reaction between 1,3-dibromo-1,3-diphenylpropanone and triethylamine.



(Isolable because it is a stable aromatic system)

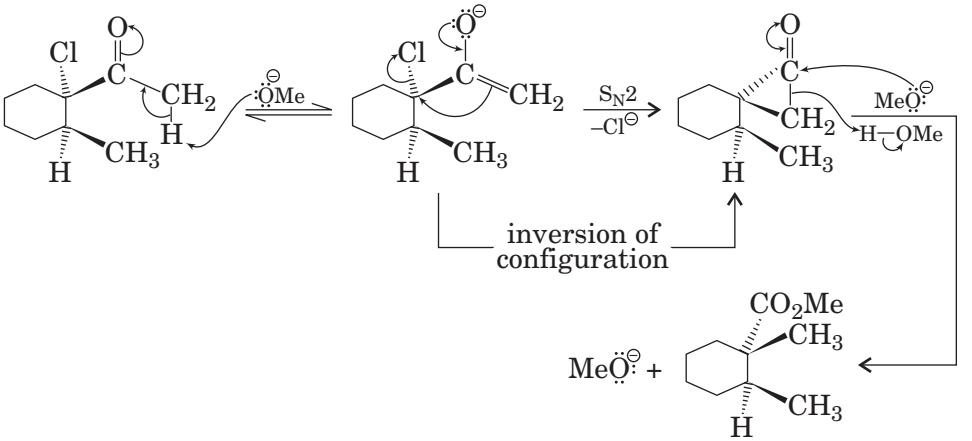
4. The cyclopropanone derivative can also be trapped as Diels–Alder adduct. For example, when the following chloroketone is treated with the base (2,6-dimethylpyridine in the presence of furan (a diene), a Diels–Alder adduct is obtained. This observation, therefore, suggests that the Favorskii rearrangement must proceed through the formation of a cyclopropanone intermediate. It is to be noted that this trapping is possible due to quasi double bond character of a three-membered carbocyclic ring which can act as a dienophile.



2,6-Dimethylpyridine

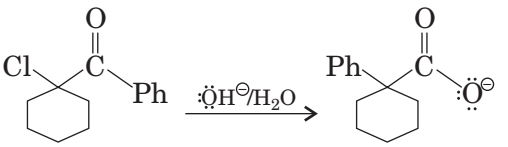
Diels–Alder adduct

Stereochemical aspects of the Favorskii rearrangement Since the Favorskii rearrangement involves an internal S_N2 type displacement of halide ion from the α-carbon, an inversion of configuration at the centre containing the halogen atom is expected. In actual practice, an inversion of configuration has been observed and, therefore, the reaction is considered to be a stereospecific process. For example:

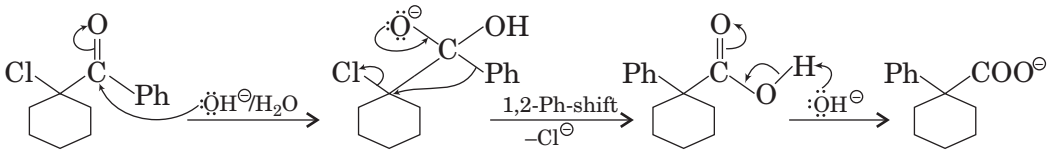


In a low polar solvent like 1,2-dimethoxyethane, the yield is about 90%. The degree of sterospecificity thus depends on solvent polarity.

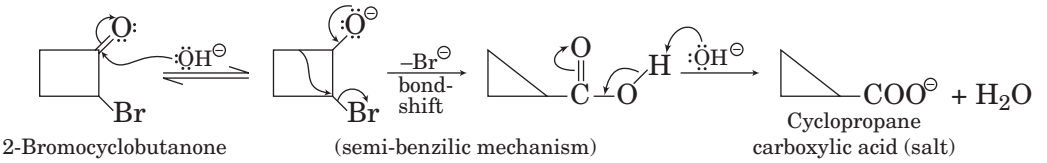
Favorskii rearrangement involving semi-benzilic mechanism It has also been observed that α-haloketones with no α'-H atom still undergo this reaction to yield the same type of rearranged product. This is usually called the quasi-Favorskii rearrangement which proceeds through semi-benzilic like mechanism. For example, the base-catalyzed rearrangement of α-chlorocyclohexyl phenyl ketone yields 1-phenyl-1-cyclohexanecarboxylic acid (salt) when treated with alkali.



This reaction obviously cannot take place by the cyclopropanone mechanism. An alternative pathway (similar to the benzilic acid rearrangement) has been proposed. This may be shown as follows:



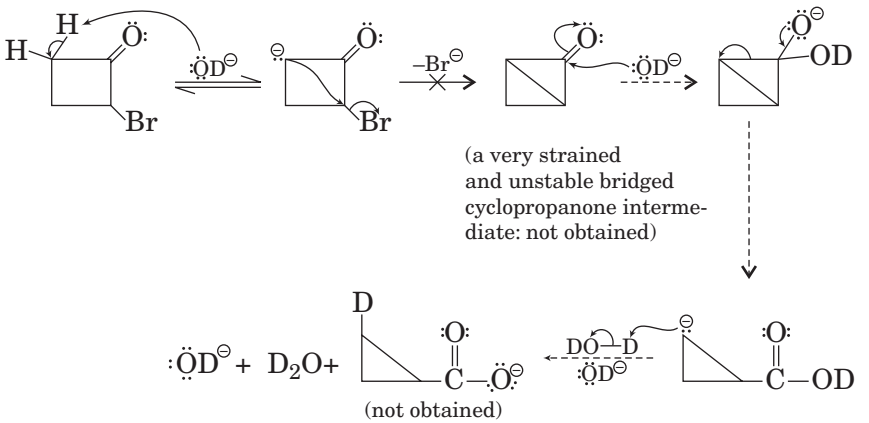
Destabilization caused by the severe angle strain in the cyclopropanone intermediate sometimes change the course of the Favorskii rearrangement and yield products analogous to the Favorskii product in a different way, i.e. by a semi-benzilic mechanism. A unique example is the reaction of 2-bromocyclobutanone with alkali to yield cyclobutane carboxylic acid (salt).



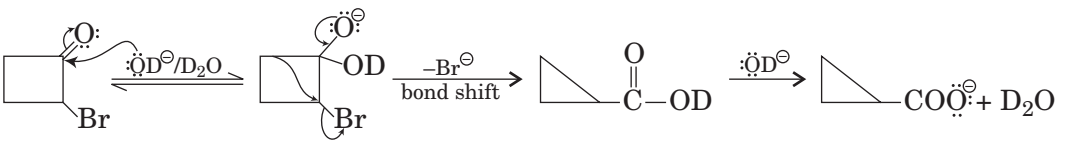
2-Bromocyclobutanone (semi-benzilic mechanism)

When the reaction is carried out with $NaOD/D_2O$, no deuterium has been found to be incorporated at the α-position of the product cyclopropanecarboxylic acid (salt). This observation, therefore, suggests that in this case the semi-benzilic mechanism is the actual mechanism which operates and that is because in such a mechanism, there is no scope of incorporation of deuterium on the α-carbon of the product.

Cyclopropanone mechanism (not operates):

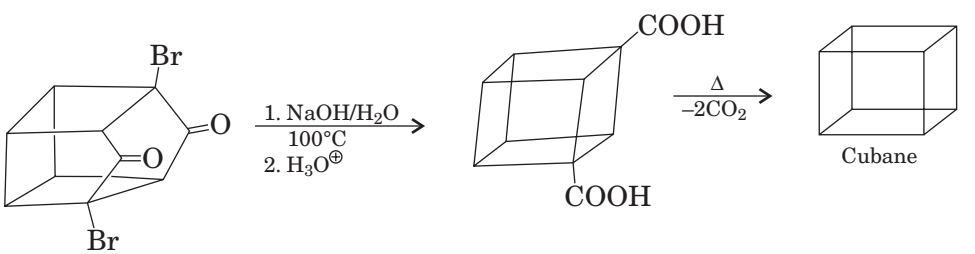


Semi-benzilic mechanism (operates):

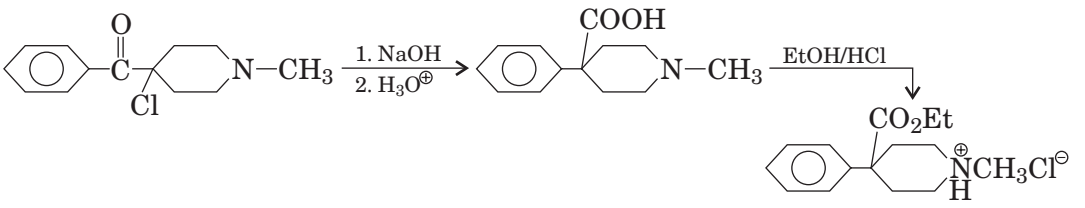


Applications

(a) The most extensive use of the Favorskii rearrangement is to carry out the ring contractions. An important example is the synthesis of cubane *via* a double Favorskii rearrangement as shown below:

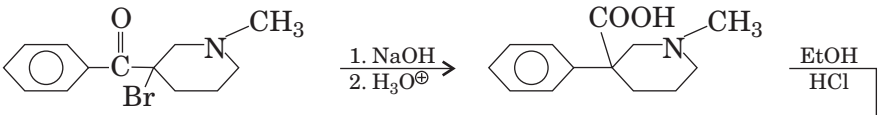


(b) The analgesic demerol (ethyl 1-methyl-4-phenyl-4-piperidine carboxylate) can be prepared by quasi-Favorskii rearrangement from 4-chloro-1-methyl-4-benzoylpiperidine having no α-H.

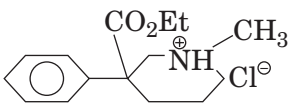


Demerol
(as hydrochloride salt)

Similarly, β-pethidine can be prepared from 3-bromo-1-methyl-3-benzoylpiperidine carboxlic using the same sequence of reactions.

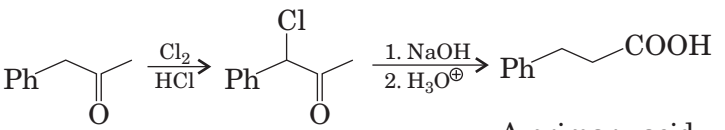


3-Bromo-1-methyl-3-benzoyl piperidine

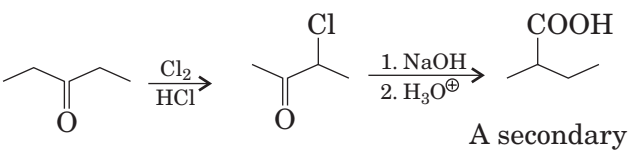


β-Pethidine
(as hydrochloride salt)

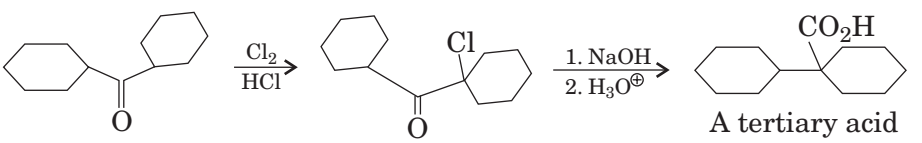
(c) Favorskii rearrangement can be used to synthesize primary, secondary and tertiary acids (or esters) with the same number of carbon atoms as the starting ketone.



A primary acid



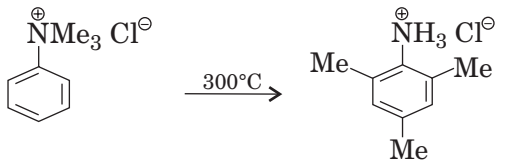
A secondary acid



A tertiary acid

4.2.2 Hofmann–Martius Rearrangement

When the hydrochloride (or hydrobromide) salts of *N*-alkylanilines are strongly heated (200–300°C), they undergo rearrangement in which the alkyl group migrates preferentially from nitrogen to the *para* carbon atom (or if it is occupied then to the *ortho* carbon). This reaction is known as the *Hofmann–Martius rearrangement*. For example:

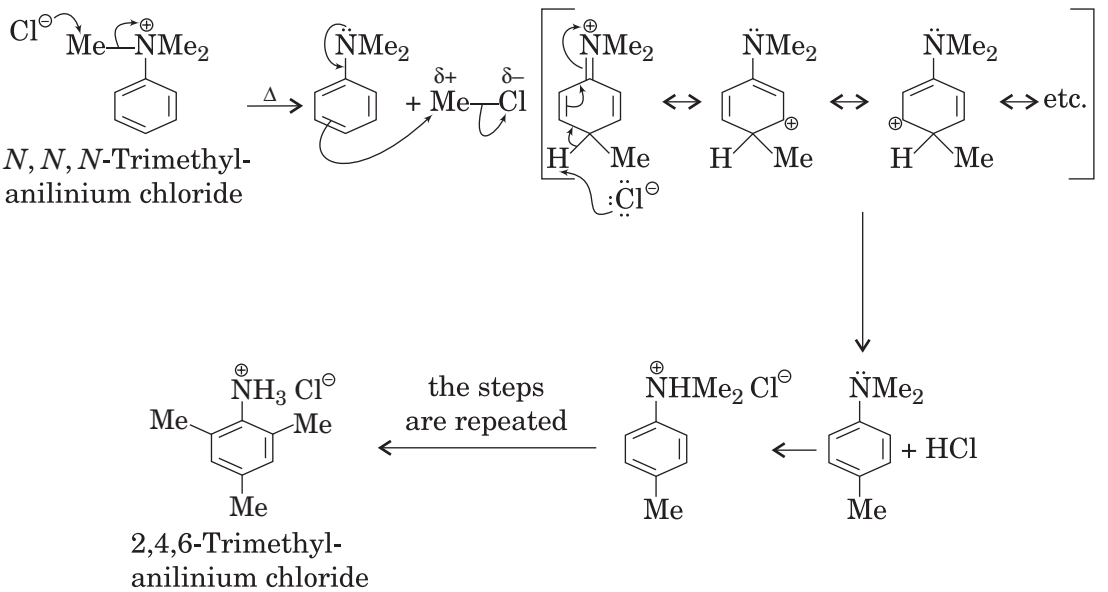


N, *N*, *N*-Trimethyl-anilinium chloride

2,4,6-Trimethyl-anilinium chloride

This rearrangement has a wide range of application for the synthesis of mesitylene derivatives.

Mechanism of the reaction The reaction involving intermolecular mechanism proceeds through the steps as follows:



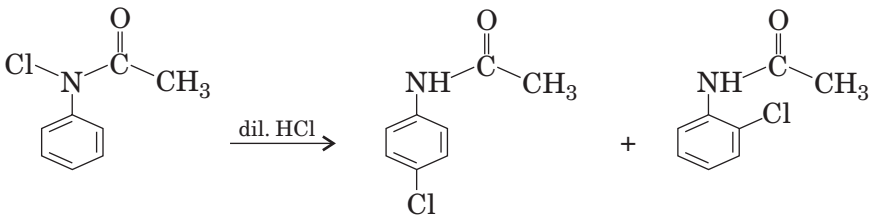
N, *N*, *N*-Trimethyl-anilinium chloride

2,4,6-Trimethyl-anilinium chloride

In the first step, the hydrochloride salt of *N*,*N*,*N*–trimethylaniline decomposes to give *N*,*N*-dimethylaniline and methyl chloride by an S_N2 process. In the next step, electrophilic attack at the *para*-position of the aniline molecule by the positive end of $\overset{\delta+}{C}H_3 - \overset{\delta-}{Cl}$ dipole occurs to form a σ-complex. In the third step, the σ-complex undergoes aromatization to give the hydrochloride salt of *N*,*N*,4-trimethylaniline. The reaction is repeated to give 2, 4, 6-trimethylanilinium chloride.

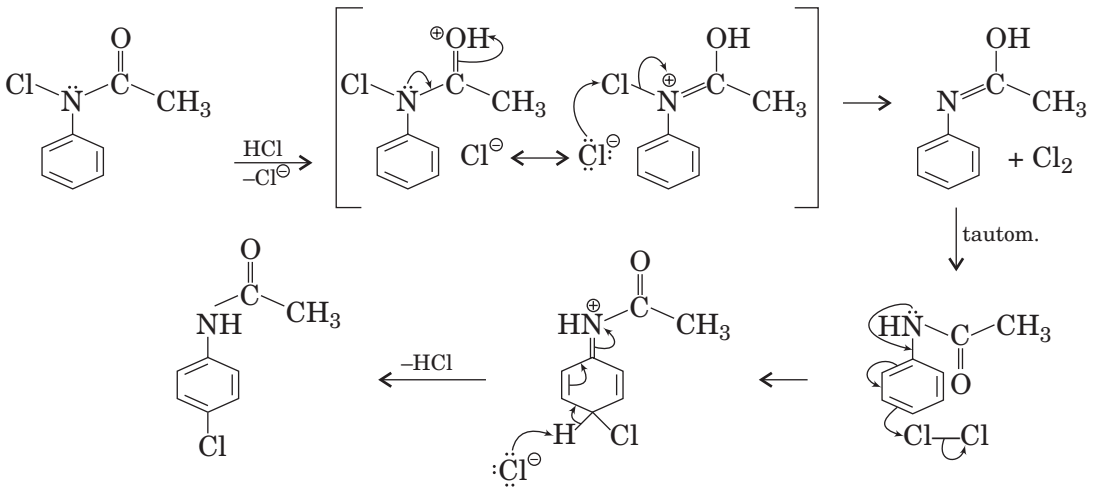
4.2.3 Orton Rearrangement

When *N*-chloroacetanilide is treated with HCl, it is converted into *p*-chloroacetanide as the main product and a small amount of *o*-product. This reaction, which involves migration of halogen from nitrogen to ring carbon, is called the *Orton rearrangement*.



N-Chloroacetanilide *p*-Chloroacetanilide (major) *o*-Chloroacetanilide (minor)

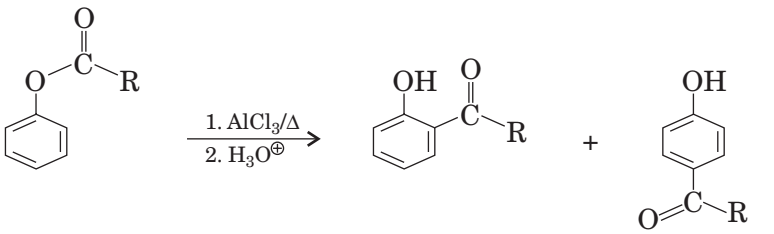
Mechanism of the reaction The mechanism of the reaction (an aromatic electrophilic substitution through rearrangement) involves the steps as follows:



This rearrangement is intermolecular and the chlorine molecule formed by attack of $Cl^{\ominus}$ on the positively polarized chlorine acts as an electrophile. The presence of free chlorine is detected. This observation proves the mechanism.

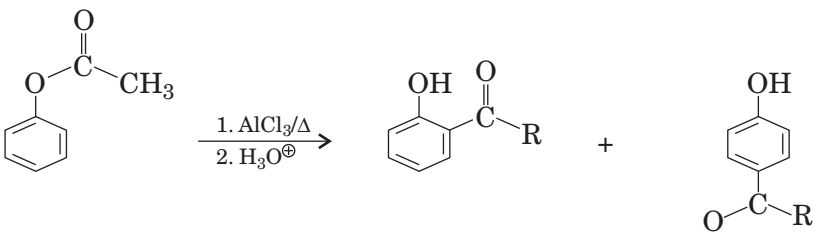
4.2.4 Fries Rearrangement

When phenolic esters are heated in the presence of anhydrous aluminium chloride (a Lewis acid), they undergo a rearrangement reaction involving migration of an acyl (RCO–) group from oxygen to ring carbon to yield, after hydrolysis, a mixture of both *ortho*- and *para*-acylphenols. This rearrangement is known as the *Fries rearrangement*.



A phenolic ester (R = alkyl or aryl) | An *o*-acylphenol | A *p*-acylphenol

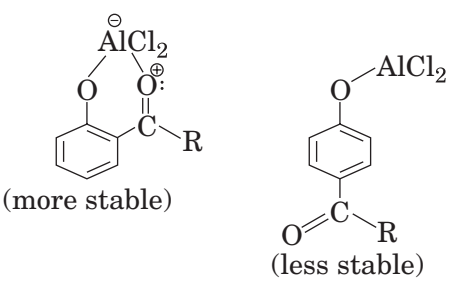
Example:



Phenyl acetate | *o*-Hydroxyaceto-phenone | *p*-hydroxyaceto-phenone

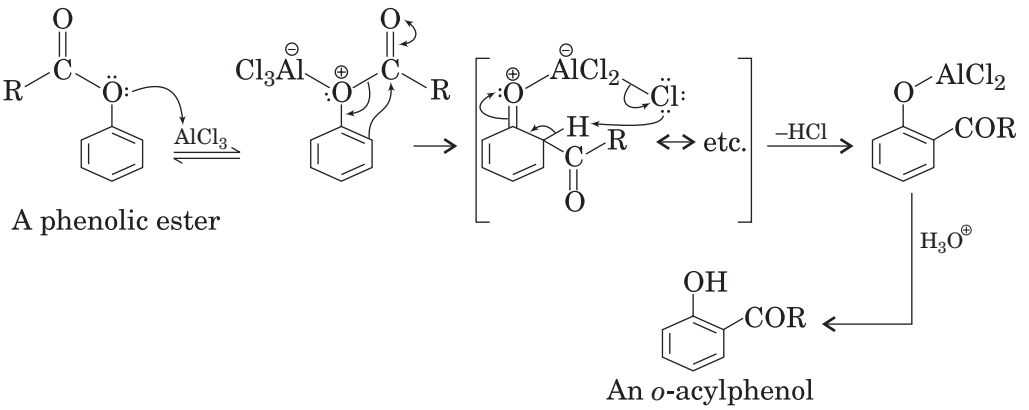
The relative amount of each isomeric hydroxyketone depends mainly upon the temperature of the reaction. The initially formed aluminium phenoxide that produces the *o*-acylphenol on hydrolysis is thermodynamically more stable due to chelation and predominates at higher temperature (>160°). On the other hand, the corresponding *p*-alkoxide is the kinetic product and is formed at lower temperature (<60°C). The mixture of *o*- and *p*-acylphenols can be separated by steam distillation because the intramolecularly hydrogen bonded *ortho*-isomer has greater volatility.

Other Lewis acids like $AlBr_3$, BF_3, etc. are also used in solvents like carbon disulphide, nitrobenzene, etc. Bronsted acids like HF, $HClO_4$ and PPA can also be used as a catalyst.

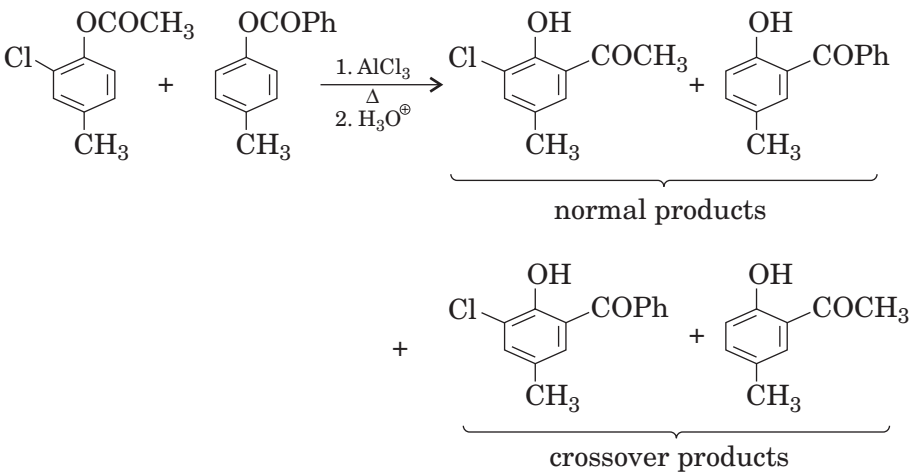


Mechanism of the reaction There is evidence of both intramolecular and intermolecular mechanisms. The rearrangement is, therefore, best regarded as a combination of the two mechanisms occurring simultaneously.

Intramolecular mechanism: Formation of the *o*-isomer can be explained by intramolecular mechanism. In this case, the initially formed complex undergoes intramolecular electrophilic substitution at the *o*-position to yield, after hydrolysis, the *o*-acyl phenol.



Intermolecular mechanism: In this case, the acyl group may migrate as an electrophile is supported by crossover experiments. When the mixture of the following two phenolic esters, for example, is subjected to the Fries rearrangement, four products are obtained (two normal products plus two crossover products).



Formation of *ortho*-rearranged crossover products confirms that free acylium ion $(R—C\equiv\overset{\oplus}{O}:)$ is involved in the reaction and, therefore, the reaction is intramolecular in nature.

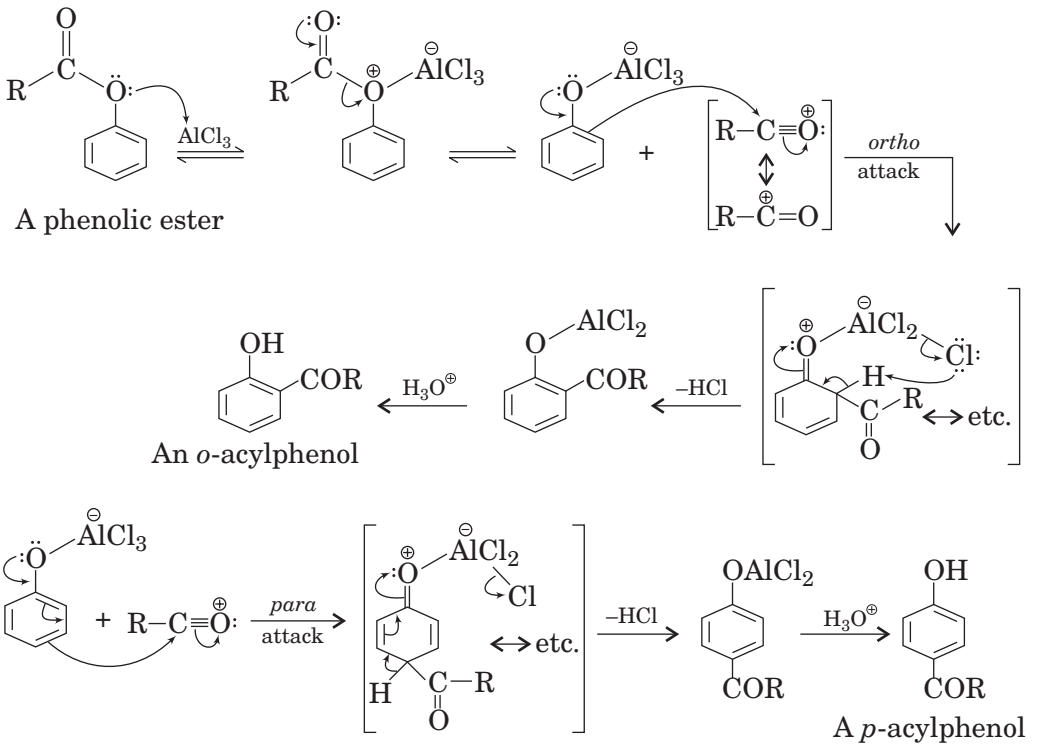
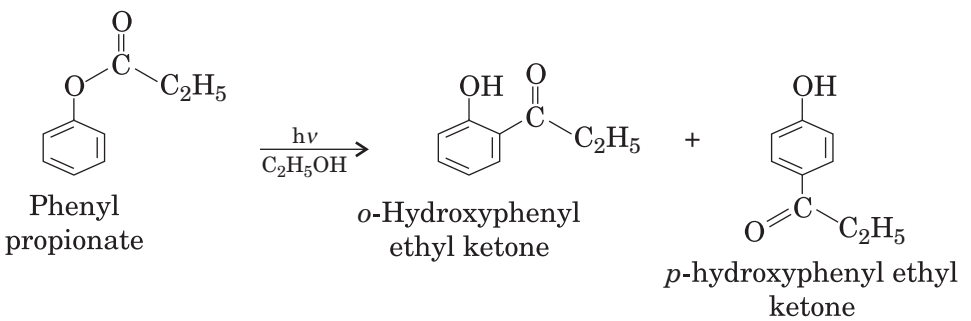
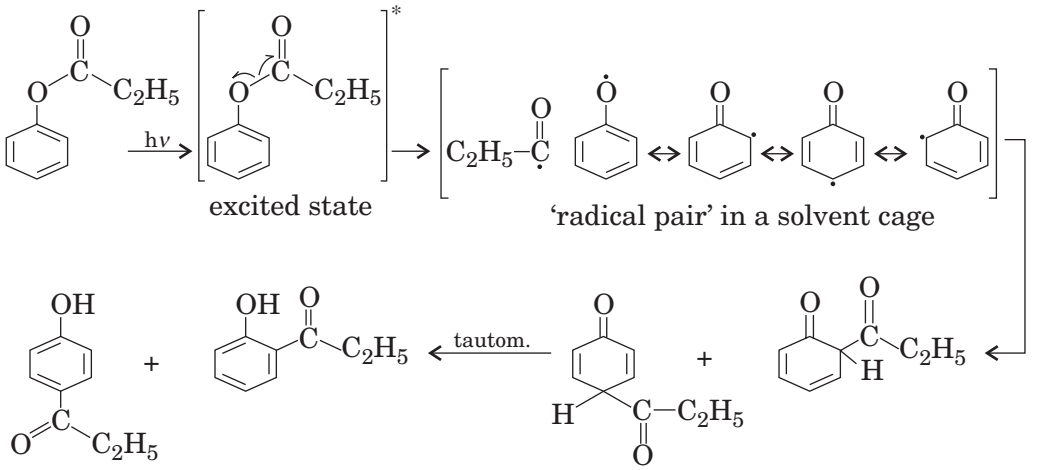


Photo-Fries rearrangement When the Fries rearrangement is carried out in the presence of ultraviolet light, it is called the *photo-Fries rearrangement*. For example:

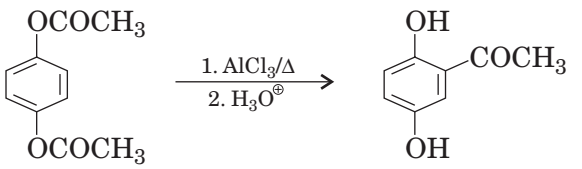


Mechanism: The photo-Fries rearrangement is an intramolecular free-radical process. Photon absorption by the ester results in its dissociation into two radicals within a solvent cage. The radicals then combine before diffusion from the solvent cage to give, after tautomerization, the rearranged acylphenols.



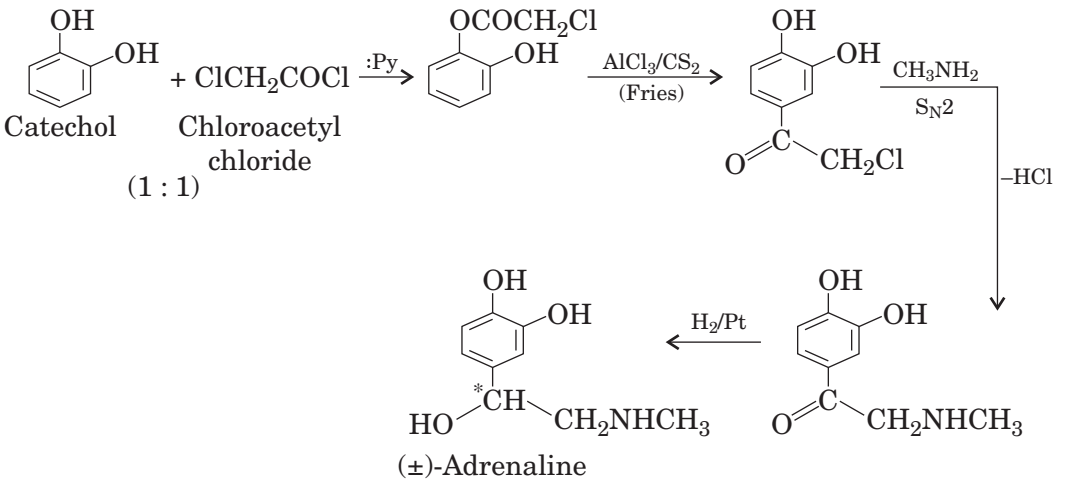
Applications

(i) This rearrangement is a useful synthetic route to phenolic ketones because introduction of an acyl group (RCO–) into a phenolic nucleus by the Friedel-Crafts reaction does not always result in acceptable yields. For example, 2,5-dihydroxyacetophenone, which cannot be prepared by Friedel-Crafts acetylation of hydroquinone, can be prepared from hydroquinone diacetate in good yield.



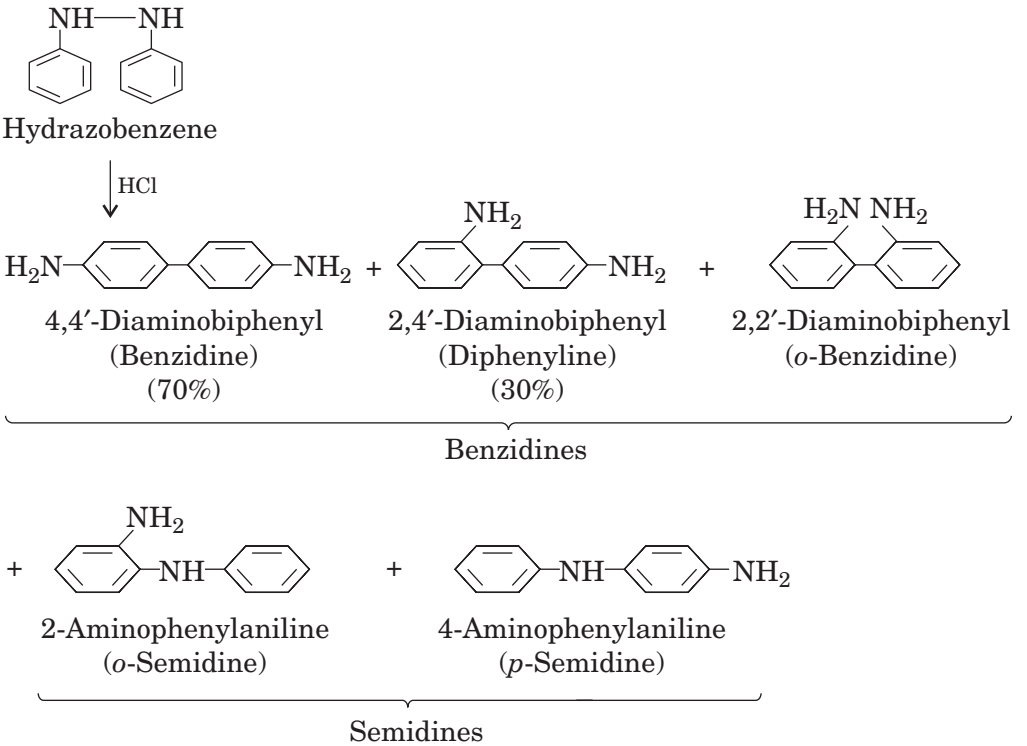
Hydroquinone diacetate — 2,5-Dihydroxyacetophenone

(ii) Adrenaline which is a heart stimulant drug, can be synthesized by using the Fries rearrangement.



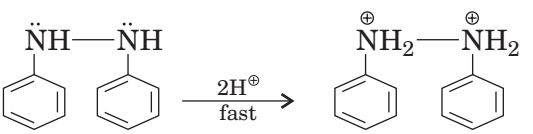
4.2.5 Benzidine Rearrangement

The acid-catalysed rearrangement of hydrazobenzenes to diaminobiaryls (benzidines) and aminoarylamines (semidines) by an intramolecular mechanism is called the *benzidine rearrangement*. When hydrazobenzene, for example, is treated with aqueous or ethanolic hydrochloric or sulphuric acid, it rearranges to give benzidines like 4,4′-diaminobiphenyl (70%), 2,4′-diaminobiphenyl or diphenyline (~30%) and a very small amount of 2,2′-diaminobiphenyl. Two semidines (*o*-semidine and *p*-semidine) are also obtained in smaller amounts.

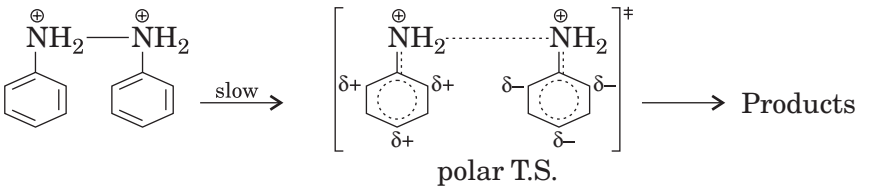


Mechanism of the reaction The mechanism of benzidine rearrangement has been investigated in detail and two mechanisms, namely, the polar transition state mechanism (follows third order kinetics) and the π-complex mechanism (follows second-order kinetics) have been proposed for this rearrangement. The polar transition state mechanism, which accounts for most of the known facts, involves the steps as follows:

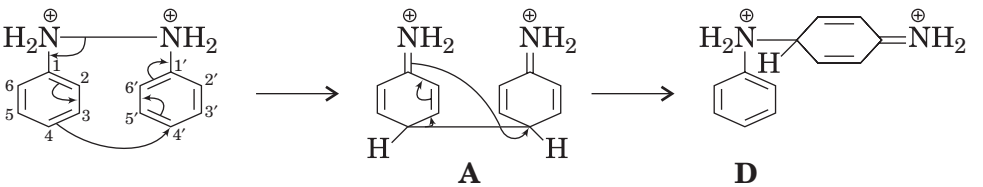
Step 1: Hydrazobenzene takes up two protons from acid to form a dipositive ion.



Step 2: Because of repulsive interaction between the two positive N atoms, the N—N bond cleavage and C—C bond formation occur in a concerted and slow step through a polar transition state. The process is thermodynamically favourable because a C—C bond is stronger than an N—N bond. The rings then link up in 4,4′, 2,4′ or 2,2′ manner to produce the intermediates A, B and C, respectively. The intermediates A and C are further rearranged to produce the intermediates D and E, respectively.

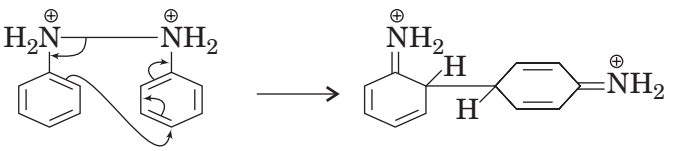


4, 4′-Linking leads to the intermediate A and then to D:



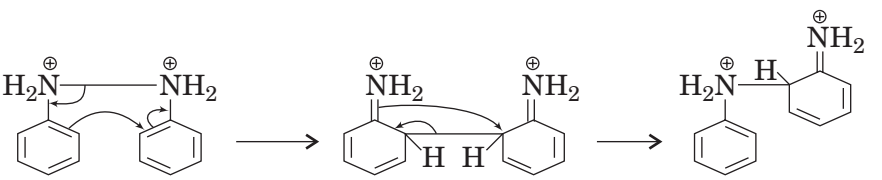
A **D**

2,4′-Linking leads to the intermediate B:



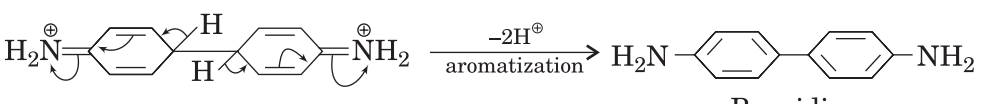
B

2,2′-Linking leads to the intermediate C and then to E:

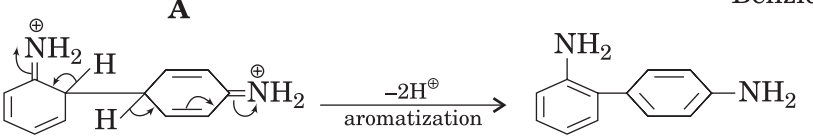


C **E**

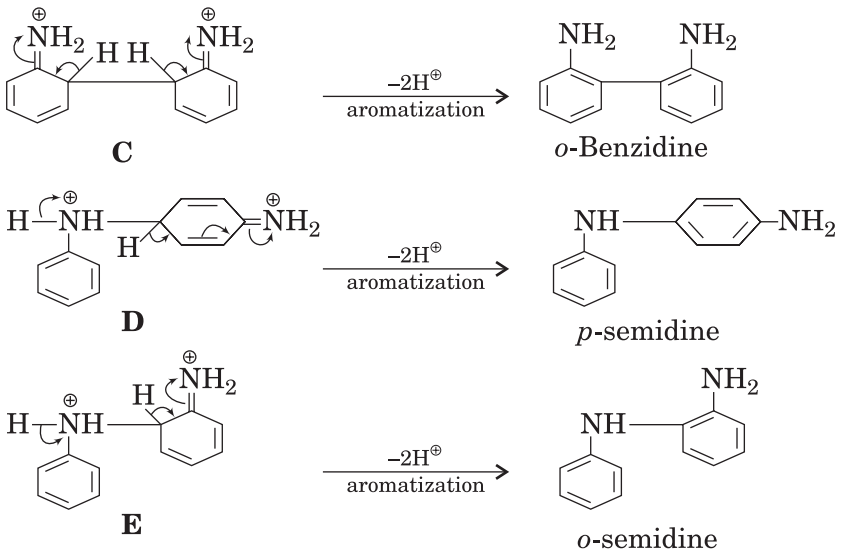
Step 3: Each intermediate eliminates two protons to give the corresponding benzidine or semidine.



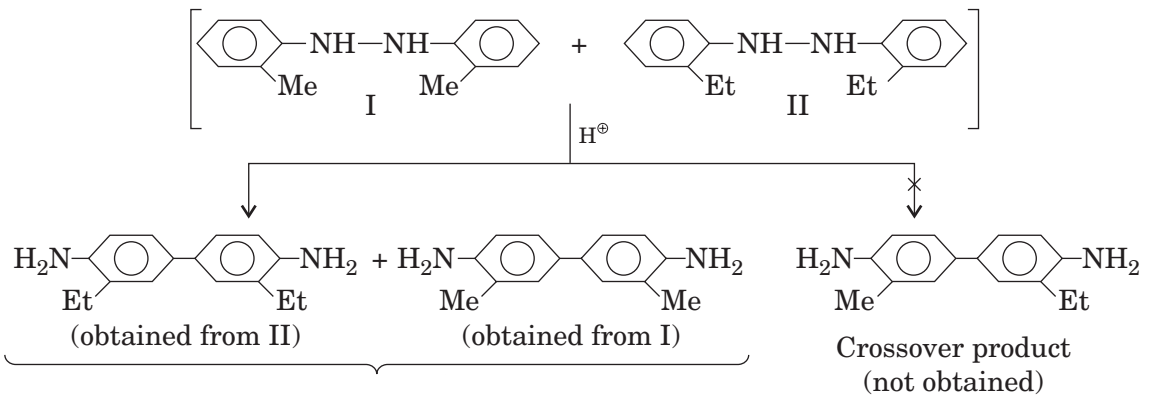
A



B

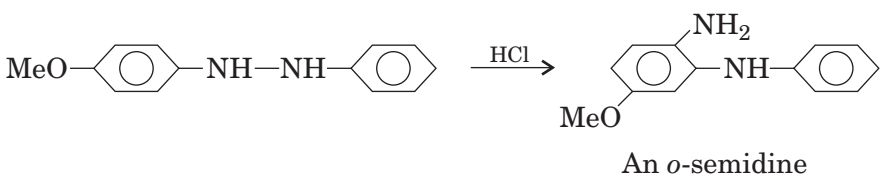


Evidence in favour of intramolecularity of the rearrangement The benzidine rearrangement has been found to be intramolecular in nature because when a mixture of two different hydrobenzenes is subjected to this rearrangement (treated with acid in the same vessel), then no crossover product is obtained. For example:

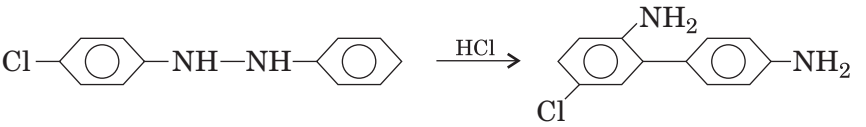


Characteristic features The product composition of this reaction largely depends on the substituents present.

(i) When the *para*-position of a ring of hydrazobenzene is occupied with a +R group like $-OCH_3$, *o*-semidine is found to the major product with a small amount of *para*-semidine. For example:

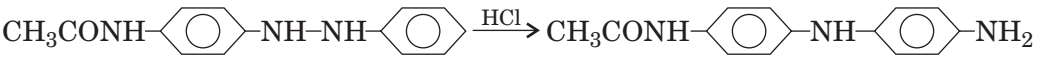


(ii) If the *para*-position is blocked by –I groups like Cl, Br, I or $\overset{\oplus}{\text{H}}\text{NMe}_2$, the product is a diphenyline accompanied by a small amount of an *o*-semidine. For example:



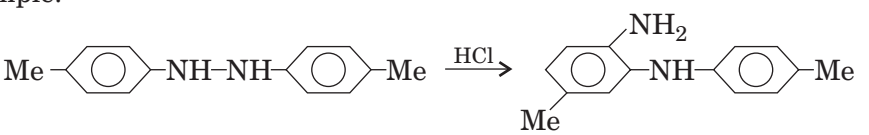
A diphenyline

(iii) If the *para*-position is blocked by $-NH_2$ or $-NHCOCH_3$, the major product is a *p*-semidine. For example:

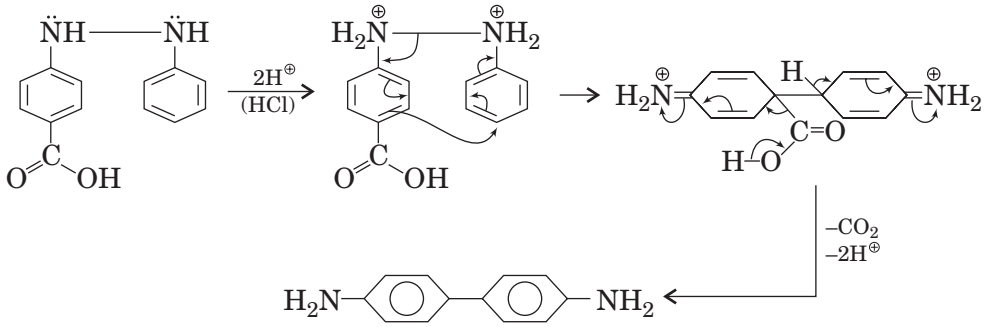


A *p*-semidine

(iv) If both the *para*-positions are substituted, then only an *o*-semidine is obtained. For example:

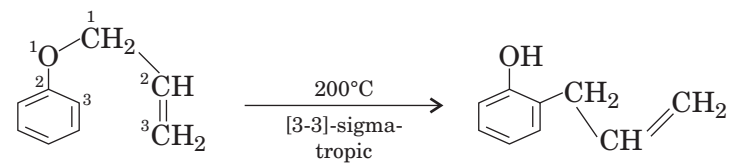


(v) Groups like –COOH, $-SO_3H$, etc. present at the *para* position are eliminated during the course of rearrangement. For example:



4.2.6 Claisen Rearrangement

When allyl aryl ethers are heated, they undergo migration of the allyl group from oxygen to the *ortho* carbon of the aromatic ring. But when both the *ortho*-positions are blocked, migration occurs at the respective *para*-position. This thermal rearrangement which is actually a [3,3] sigmatropic rearrangement is known as the *Claisen rearrangement*. For example, when allyl phenyl ether is heated to 200°C, it rearranges to give *o*-allylphenol.

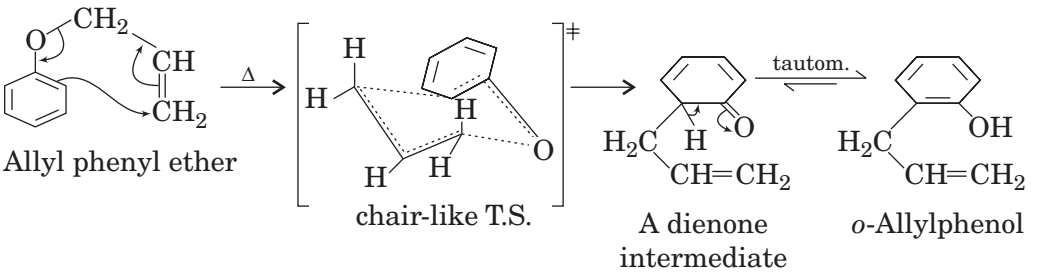


Allyl phenyl ether — *o*-Allylphenol

This is, in fact, a pericyclic reaction which can be well explained by frontier molecular orbital (FMO) approach. Aliphatic ethers are also found to undergo this reaction. For example:



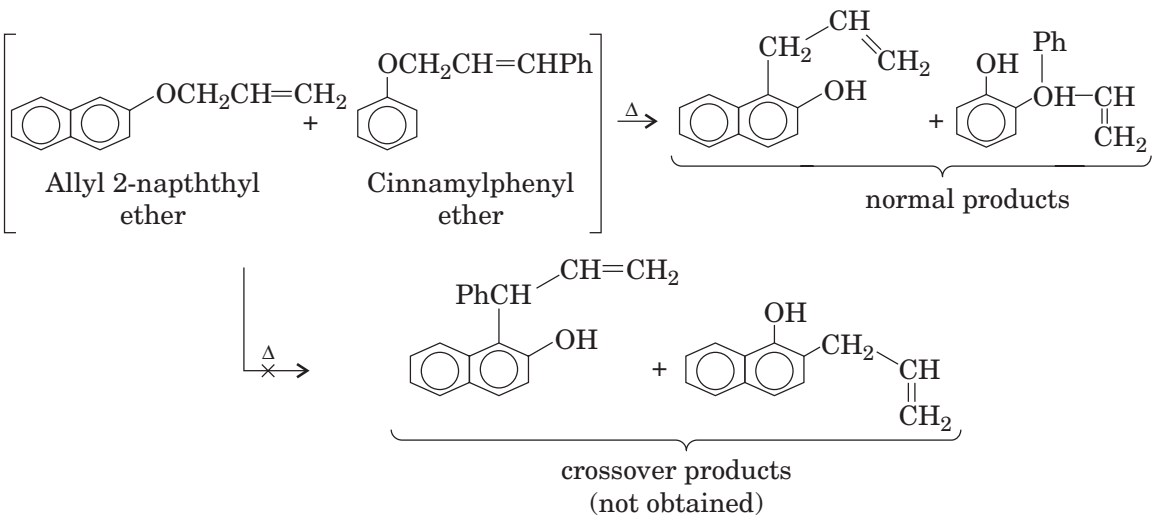
Mechanism of the reaction The Claisen rearrangement is of first order with respect to rate and has large negative entropy of activation ($\Delta S^* = -ve$). This observation is consistent with a cyclic transition state. This reaction actually proceeds through a concerted pathway involving a six-membered cyclic transition state. Formation of bond between the γ-carbon of the allyl group and the *ortho*-carbon of the benzene ring and cleavage of bond between carbon and oxygen takes place simultaneously. The initially formed product is an unstable cyclohexadienone intermediate which readily tautomerizes to give *o*-allyl-phenol. Conformational analysis has shown that the reaction preferably proceeds via a chair-like transition state.



Allyl phenyl ether — chair-like T.S. — A dienone intermediate — *o*-Allylphenol

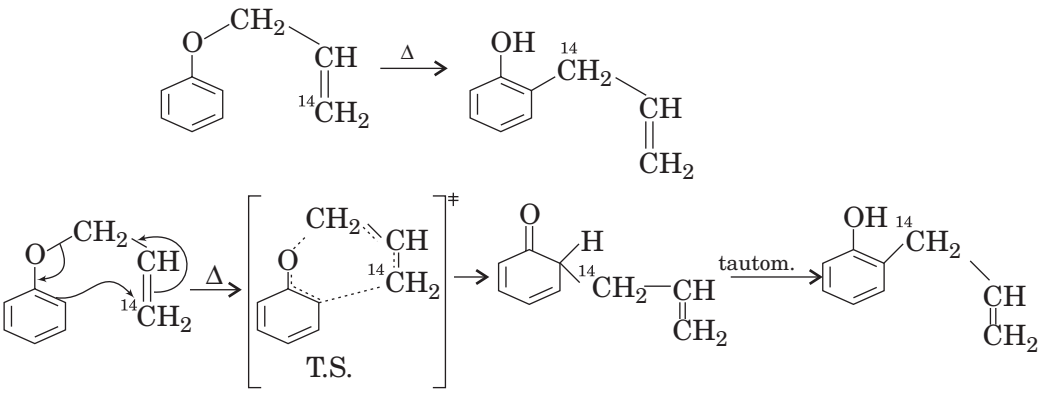
Evidence in favour of the mechanism:

(i) When a mixture of two different ethers are allowed to rearrange simultaneously in the same vessel, no crossover product is obtained. For example:



This observation, therefore, suggests that the rearrangement is intramolecular in nature.

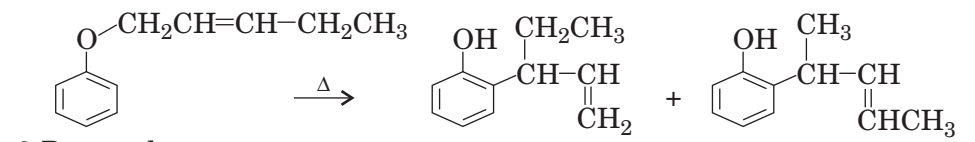
(ii) The intramolecular nature of the rearrangement can also be established by an isotopic labelling experiment. When allyl phenyl ether in which the allyl group is labelled with ^{14}C at the γ-carbon is heated, the rearranged product is found to contain the labelled carbon bonded to the ring. This also strongly suggests that the allyl moiety never gets completely separated from the substrate during rearrangement. That is, the rearrangement is intramolecular in nature.



Characteristic features

(i) The reaction rate has been observed to become greatly influenced by the solvent effect. Trifluoroacetic acid (CF_3COOH) is usually used as a solvent for carrying out the reaction at room temperature.

(ii) Certain aryl allyl ethers with an alkyl or aryl substituent at the γ-carbon atom of the allyl group rearrange to give a mixture of normal *ortho*-Claisen product along with an isomeric *o*-allyl phenol. The second *o*-allylphenol is called *abnormal Claisen product*. For example:

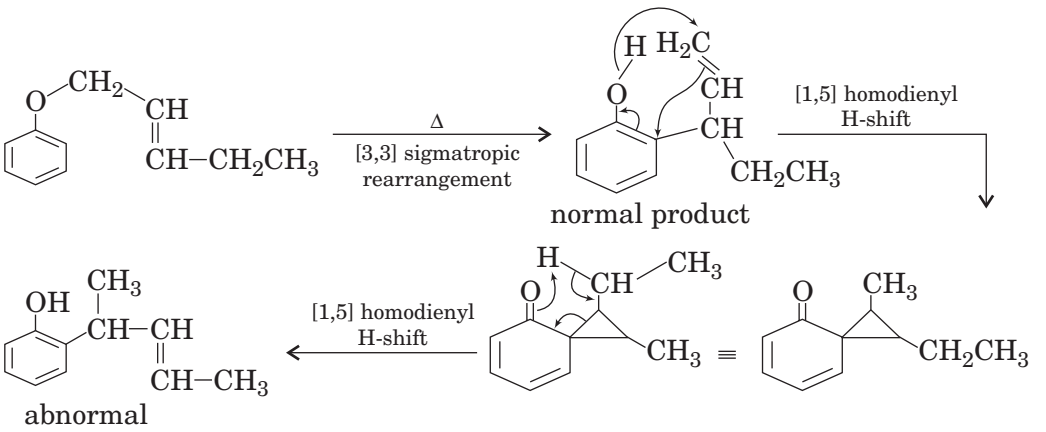


2-Pentenyl phenyl ether

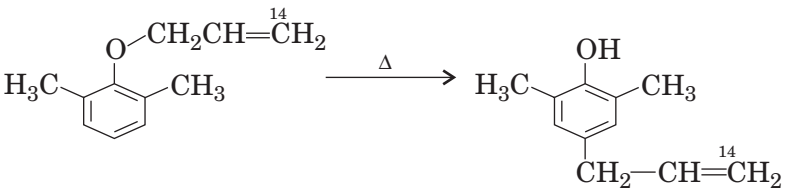
normal product

abnormal product

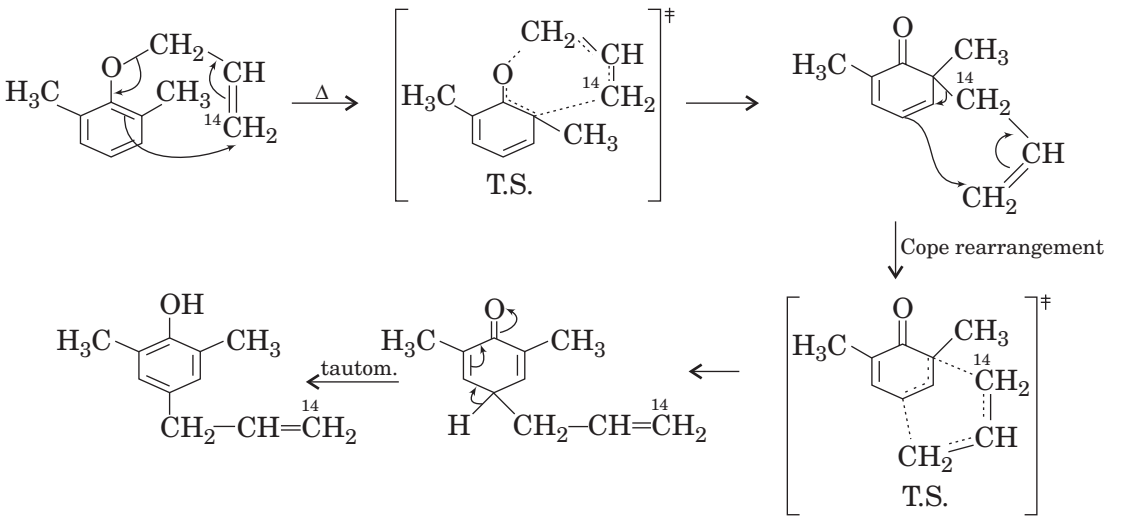
This abnormal product is believed to be formed from the normal product by two successive [1,5]-homodienyl hydrogen shifts. This may be shown as follows:



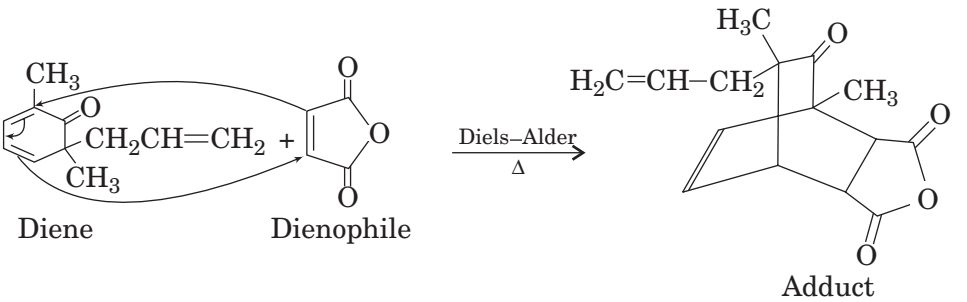
(iii) *para*-Claisen rearrangement: When both the *ortho*-positions of an allyl phenyl ether are blocked then enolization of the *ortho*-dienone does not take place and the dienone undergoes the Cope rearrangement to give *para*-allyl phenol. The allyl chain actually undergoes double inversions to give the *para*-isomer and as a result, the original order of the carbon atoms in the allyl group in allyl phenyl ether is restorted. This has been confirmed by an isotope labelling experiment. For example, in the rearrangement product of the following ^{14}C labelled allyl 2,6-dimethyl phenyl ether, the labelled carbon is not found to be bonded to the ring.



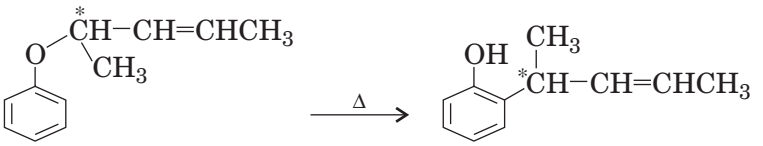
The mechanism of the reaction may be shown as follows:



The second evidence in favour of a two-fold shift is that the intermediate *ortho*-dienone has been trapped as a Diels–Alder adduct using maleic anhydride.

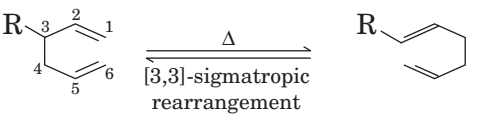


(iv) *Rearrangement of a chiral aryl vinyl ether:* The Claisen rearrangement of a chiral ether in which the α-carbon is a chiral centre leads to an optically active phenol in which the γ-carbon has become asymmetric. It may, therefore, be considered as a special case of asymmetric induction. For example:

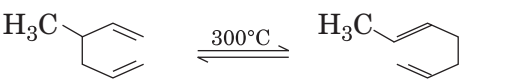


4.2.7 Cope Rearrangement

The thermal [3,3]-sigmatropic rearrangement of 1,5-dienes to the isomeric 1,5-dienes is called the *Cope rearrangement*. The reaction is normally reversible in nature and gives an equilibrium mixture of starting material and product of which the thermodynamically more stable isomer predominates.



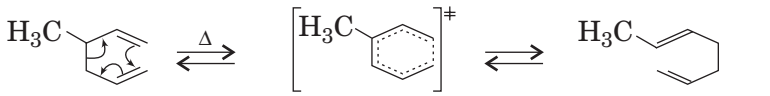
For example, when 3-methyl-1,5-hexadiene is heated, it isomerizes to give 2,6-heptadiene.



The temperature needed to bring about the reaction depends on the nature of the substituent present on C-3 or C-4. A conjugating group R (e.g. acyl, phenyl, etc.) lowers the energy of the transition state and causes the rearrangement to take place at a lower temperature (165–185°C). This is also a pericyclic reaction which can be well explained by the FMO approach.

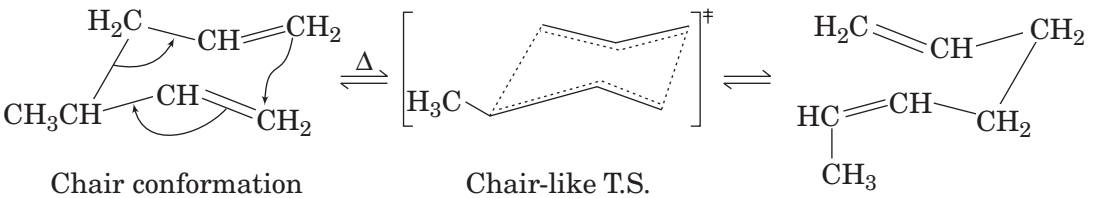
Mechanism of the reaction

The cope rearrangement is a concerted (cleavage of the C-3—C-4 bond is synchronous with the formation of C-1—C-6 bond) intramolecular process involving a six-membered cyclic transition state.

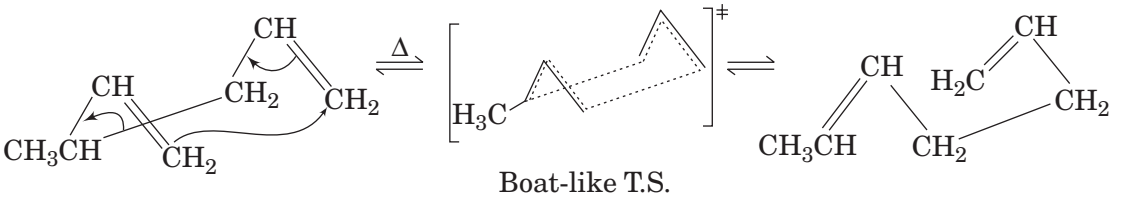


3-Methyl-1,5-hexadiene — T.S. — 2,6-Heptadiene

In fact, the reaction proceeds through a chair-like transition state and not through a boat-like transition state because the former is relatively more stable (~25 kJ/mol) than the latter.



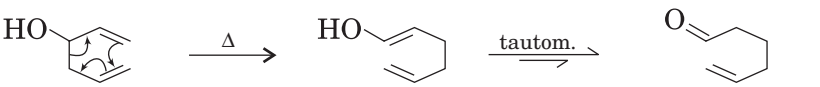
Chair conformation — Chair-like T.S. (more stable)



Boat conformation — Boat-like T.S. (less stable)

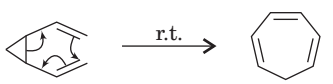
Characteristic features:

(i) *Oxy-Cope rearrangement:* The rearrangement of 1,5-hexadiene with a hydroxyl group at 3-position provides a useful route to unsaturated acyclic or cyclic aldehyde or ketone. This is called *oxy-Cope rearrangement*. For example:



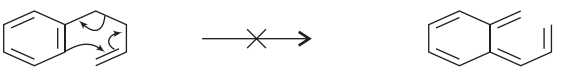
An unsaturated alcohol — Enol intermediate — An aldehyde

(ii) If the C-3—C-4 σ-bond which breaks in the reaction is a part of a small ring, the rearrangement takes place rapidly and at a lower temperature to form a strain free product molecule.



A strained molecule — A strain-free molecule

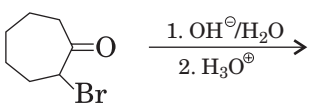
(iii) The Cope rearrangement does not take place when one of the double bonds is a part of an aromatic system. This is because the reaction causes a much higher loss of resonance energy. For example:

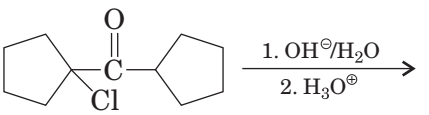


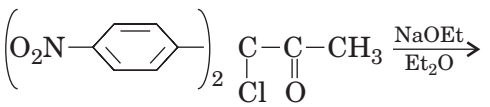
Aromatic system (more stable) — Nonaromatic system (less stable)

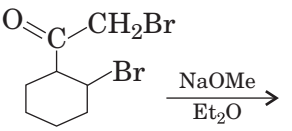
SOLVED PROBLEMS

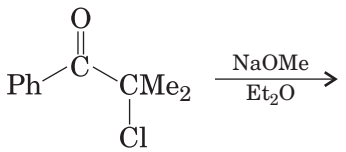
1. Predict the product and suggest a plausible mechanism for each of the following reactions (Favorskii rearrangements):

(a) 

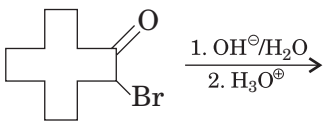
(b) 

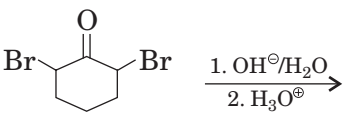
(c) 

(d) 

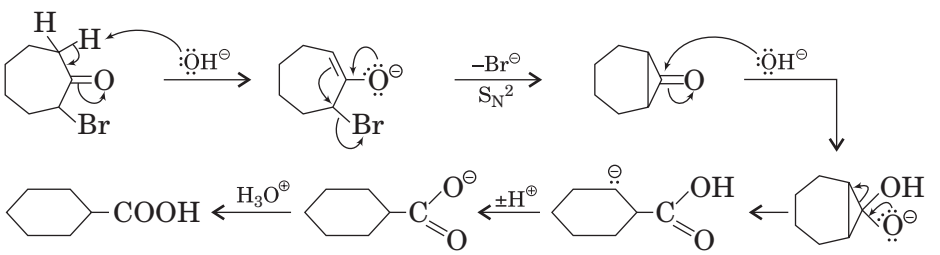
(e) 

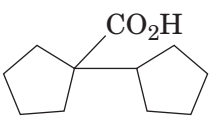
(f) 

(g) 

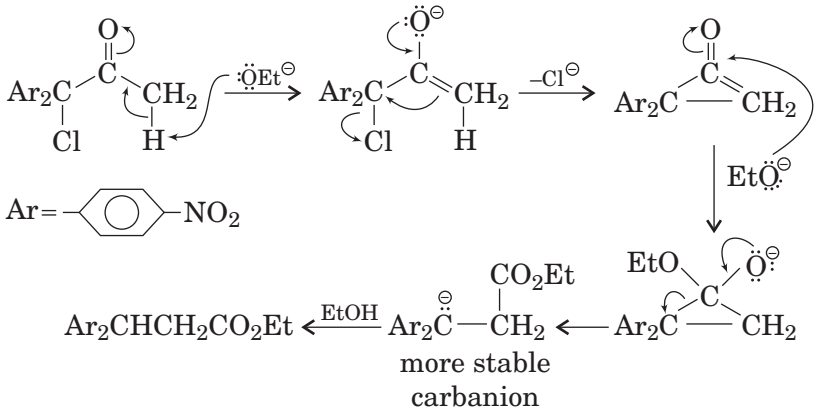
(h) 

Solution

(a) 

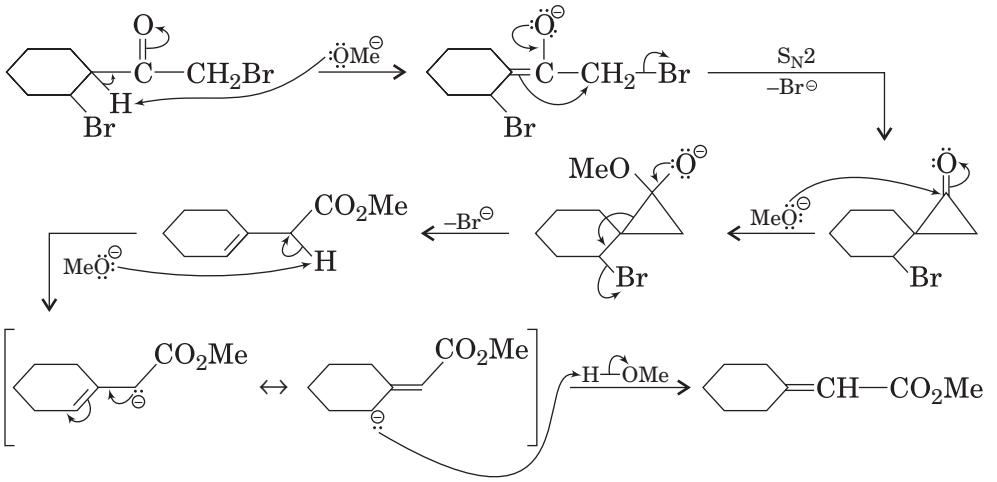
(b) [Hint: The product is  .]

(c)



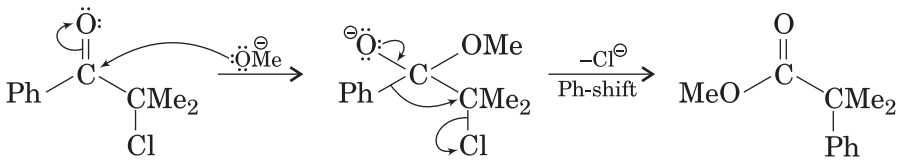
The cyclopropane ring opens in that direction which leads to the formation of a more stable carbanion.

(d)



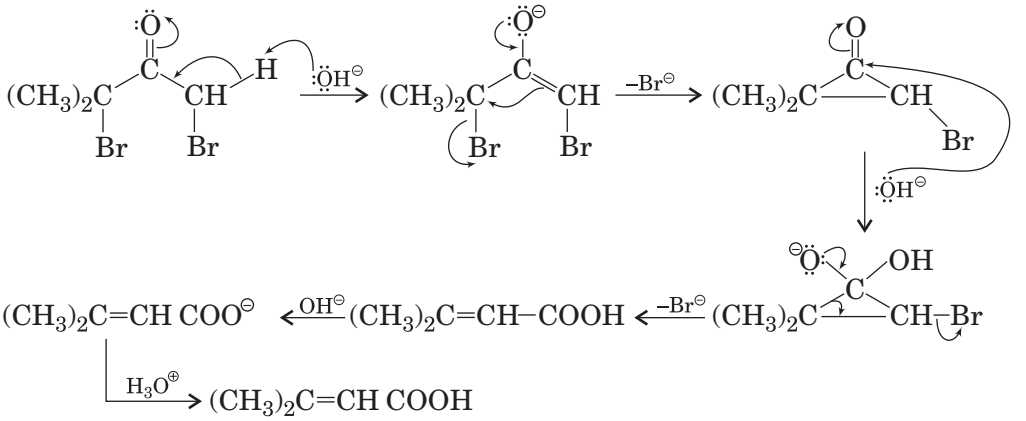
When in a ketone both α- and β'-positions contain halogen atom, then ring opening of the intermediate cyclopropanone becomes almost unidirectional. Due to the presence of Br atom (good leaving group) at the β'-position, the ring opening takes place in such a way that bromine atom is lost with simultaneous formation of a C═C bond. The β, γ-unsaturated ester then isomerizes to the thermodynamically more stable α, β-unsaturated ester.

(e)



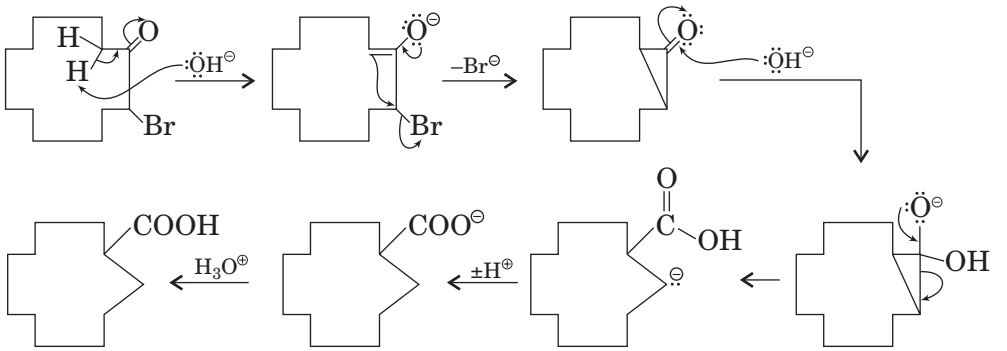
This is a quasi-Favorskii rearrangement, which proceeds through semi-benzilic mechanism.

(f)

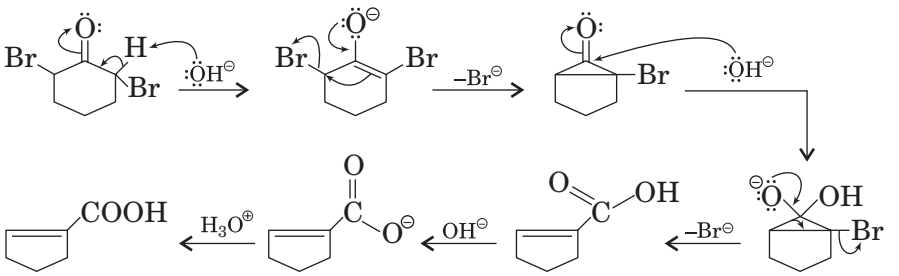


Due to the presence of Br atom at the α'-position, the ring opening takes place in such a way that the bromine atom is lost with simultaneous formation of a double bond.

(g)



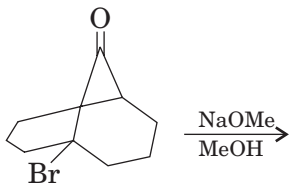
(h)



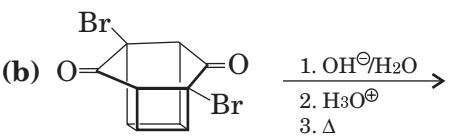
Ring opening, which occurs with expulsion of bromine atom, results in formation of a double bond.

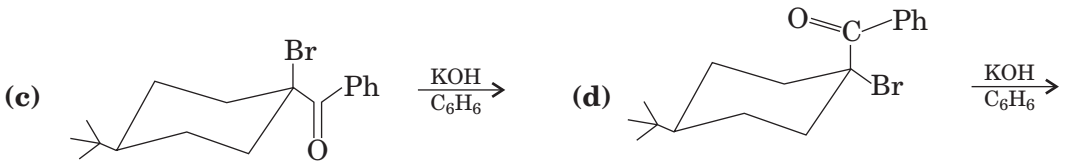
2. Predict the product and give the plausible mechanism involved in each of the following reactions:

(a)

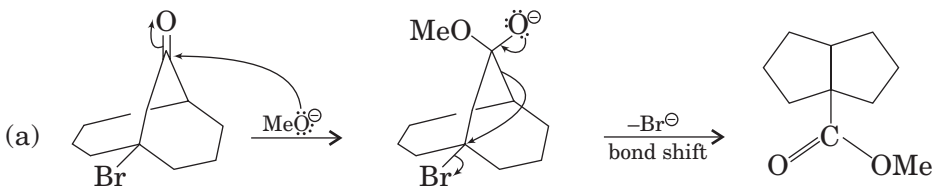


(b)

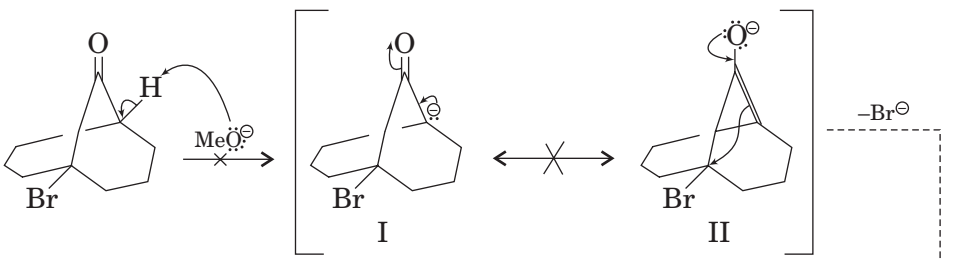




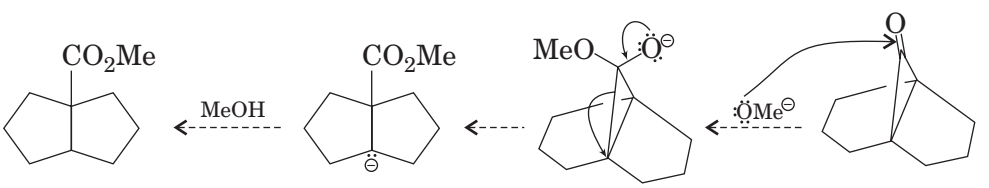
Solution These are all quasi-Favorskii rearrangements which proceed through semi-benzilic mechanism.



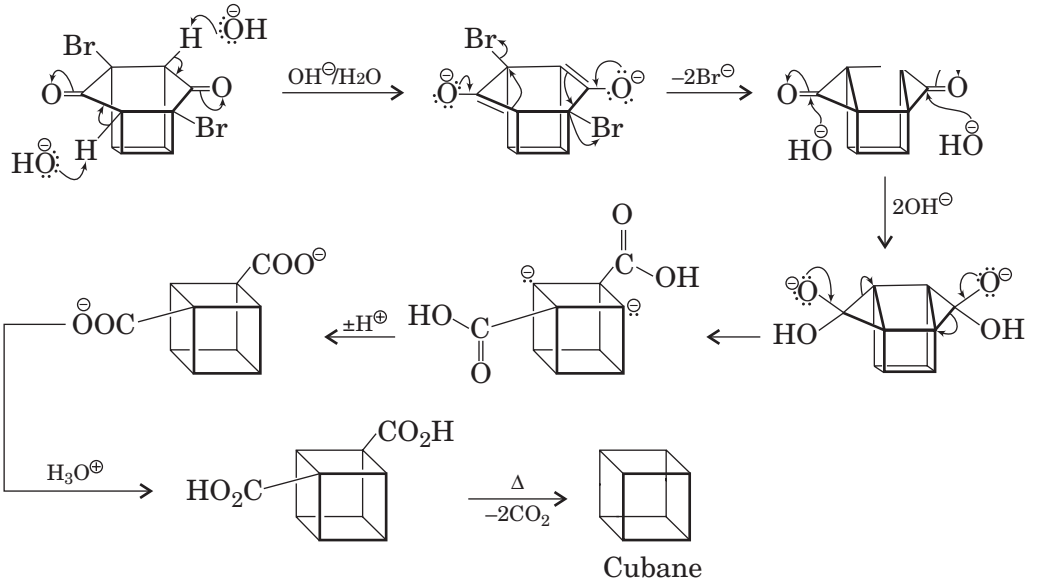
The cyclopropanone mechanism does not operate because an α-carbanion cannot be formed at the bridgehead carbon and this is because the negative charge at that position cannot be resonance-stabilized by the adjacent carbonyl group as it requires formation of a double bond at the bridgehead position (Bredt's rule).



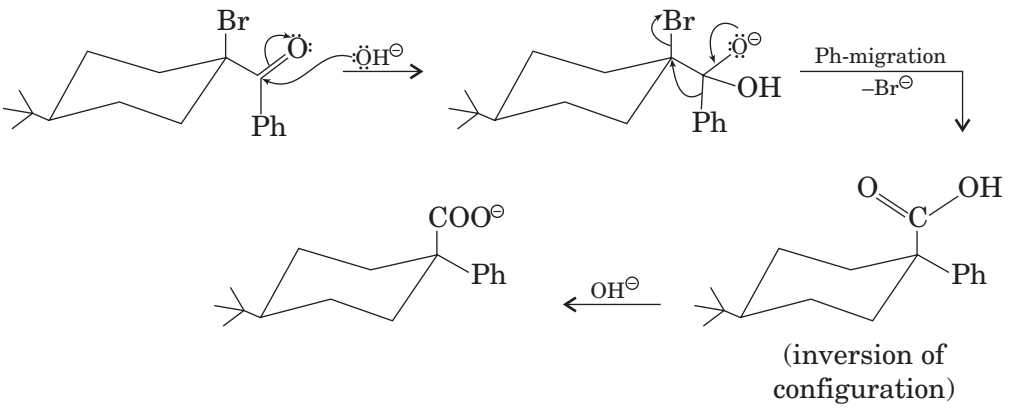
An unstable carbanion
(contribution of structure II is negligible)



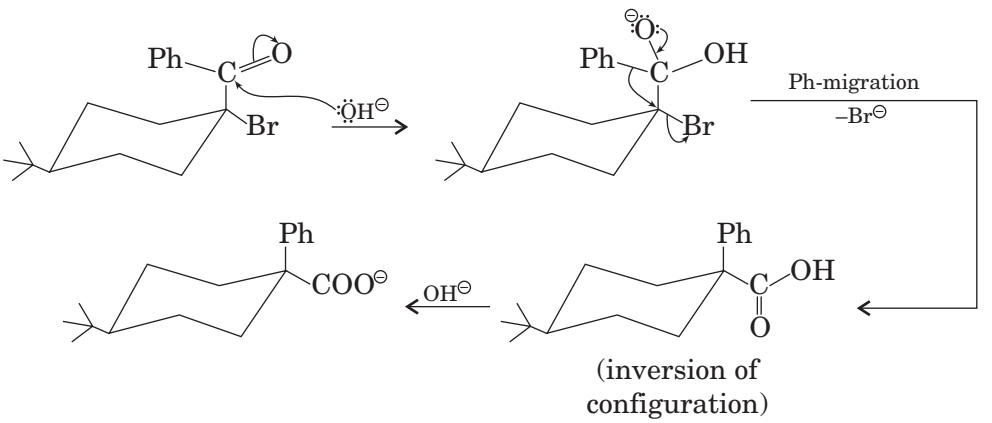
(b) The compound undergoes two Favorskii ring contractions to give, after decarboxylation, cubane.



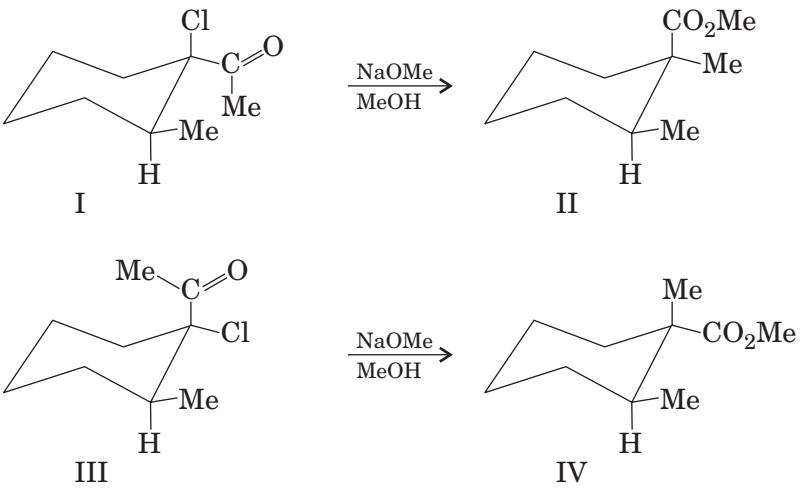
(c)



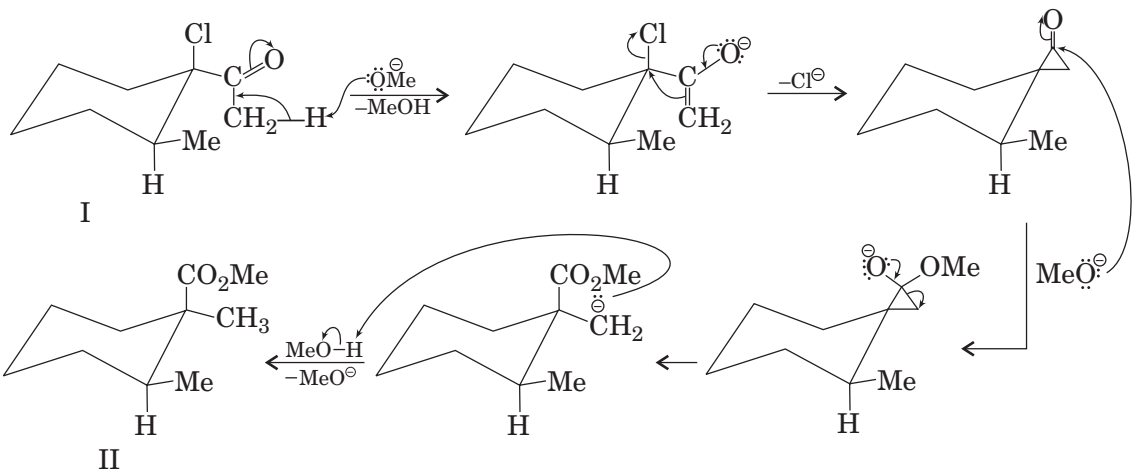
(d)

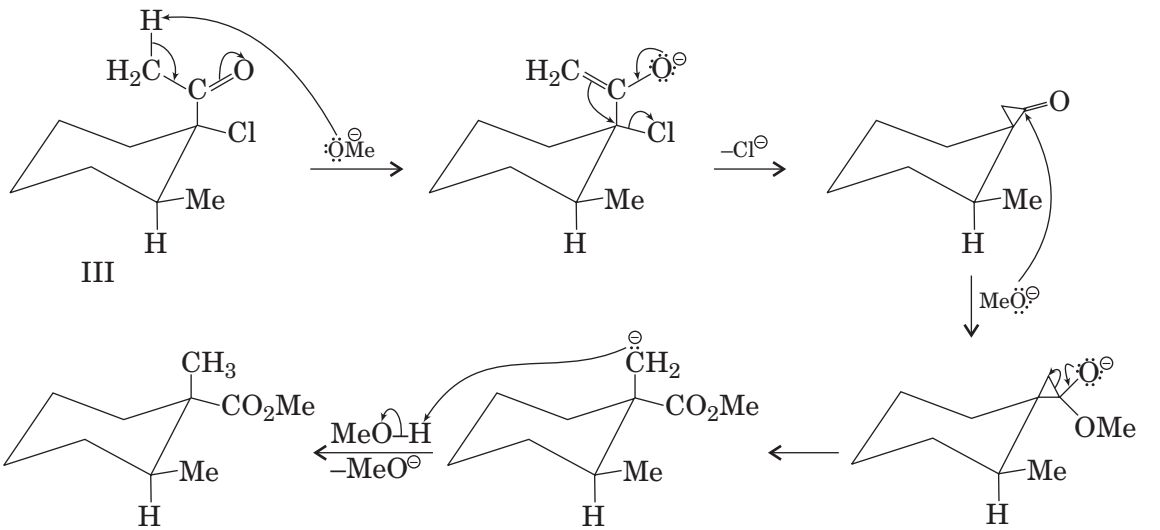


3. Explain the following observations:



Solution The Favorskii rearrangement requires proper stereochemical disposition of the negative carbon and the halogen atom to perform the internal S_N2-displacement of the halide ion. Therefore, the two diastereoisomeric haloketones produce two diastereoisomeric esters when treated with NaOMe in MeOH.

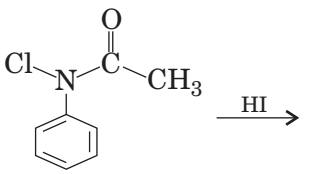




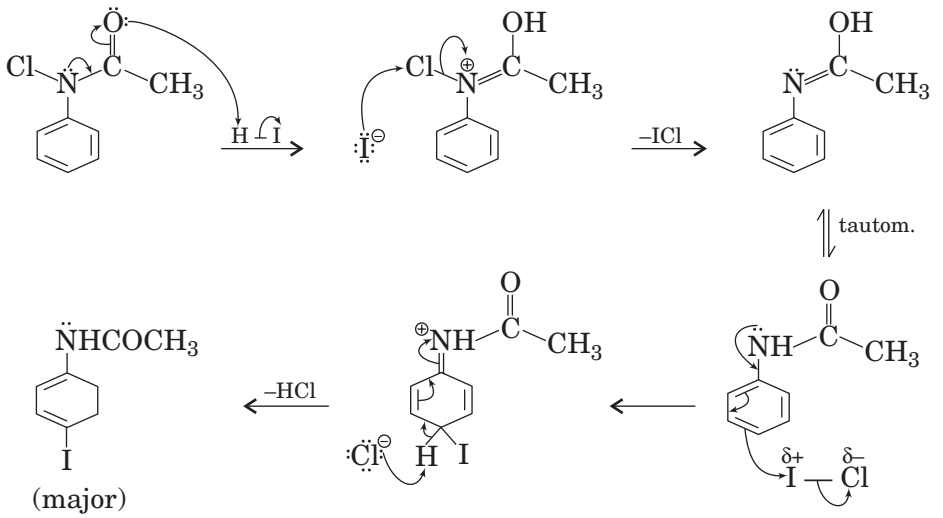
III

IV

4. Predict the product of the following reaction (Orton rearrangement) and give the mechanism for its formation:



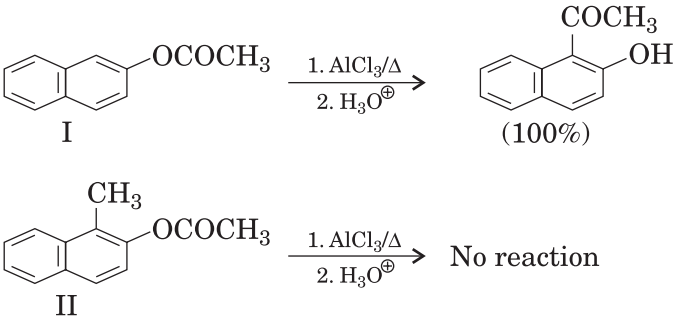
Solution When *N*-chloroacetanilide is treated with HI, *p*-iodoacetaniline is obtained predominantly. The mechanism of the reaction is as follows:



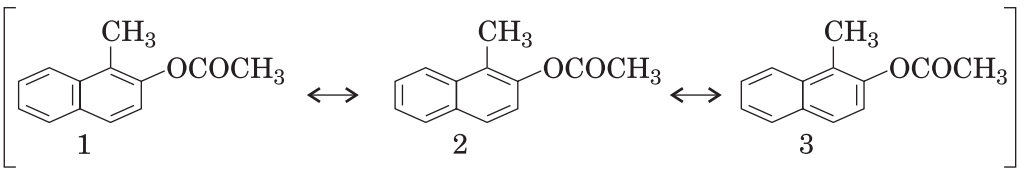
(major)

Due to large size of iodine, steric repulsion at the *ortho*-position is much higher and for this reason, *p*-product is obtained predominantly.

5. Explain the following observations:



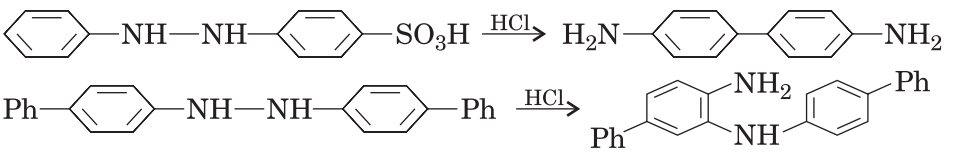
Solution In compound I, the position *para* to $-OCOCH_3$ is blocked by benzene ring substituent. However, the two *o*-positions are open. But C-1 acetylated product is obtained exclusively. In compound II, the C-1 position is blocked by a methyl group, but the acetyl group does not go to the other *ortho*-position, i.e. C-3. These observations can be explained in terms of '*Fries rule*' which states that the most stable form of a polynuclear compound is that in which a maximum number of rings are in the benzenoid form. The compound II may be represented as a hybrid of the following three resonance structures:



Resonance structures of II

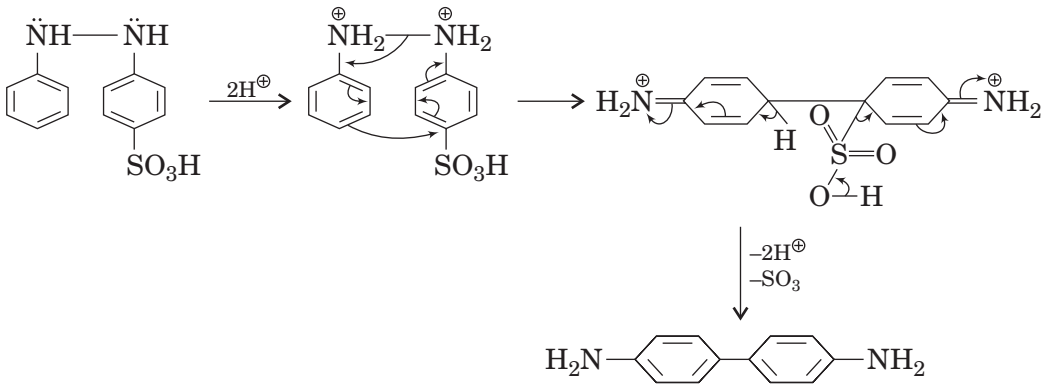
According to the Fries rule, the structure 1 having two benzenoid rings makes a major contribution to the resonance hybrid, i.e. the compound behaves as structure 1. Because of such bond fixation, C-3 is very weakly nucleophilic and does not attack the weakly electrophilic acylium ion ($R\overset{\oplus}{C}O$). It is for this reason, the compound I undergoes the Fries rearrangement to give only the C-1 acylated product and the compound II does not undergo the Fries rearrangement.

6. Suggest a mechanism for each of the following reactions:



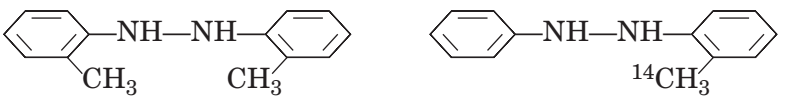
Solution

(a) This hydrozobenzene undergoes benzidine rearrangement along with desulphonation to give benzidine.



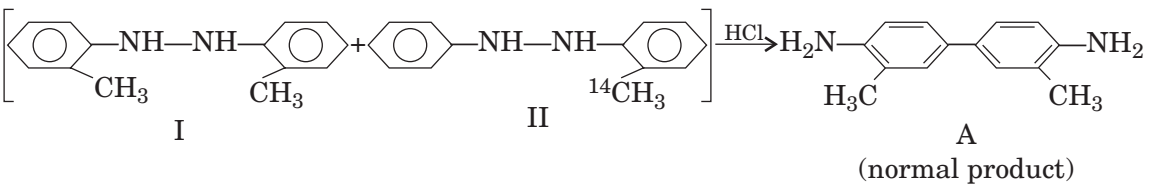
(b) [**Hint:** Since the *para*-positions are blocked, this hydrobenzene leads to the formation of an *o*-semidine as the major product.]

7. How would you prove by a crossover experiment using the following two substrates that the benzidine rearrangement is intramolecular in nature?

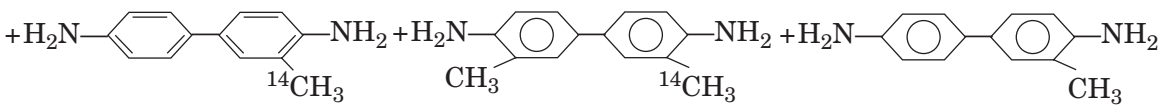


I II

Solution When these two (I and II) hydrobenzenes are subjected to benzidine rearrangement, the normal products expected to be formed are A and B and the crossover products (if the reaction is intermolecular) expected to be formed are C and D.



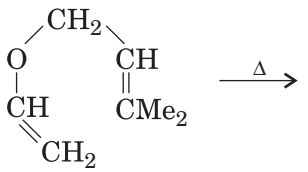
I II A
(normal product)

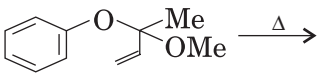


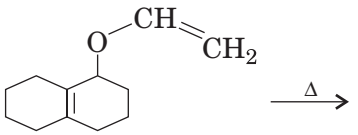
B C D
(normal product) (crossover product) (crossover product)

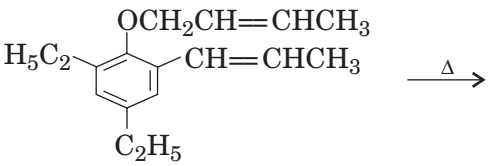
Now, the crossover product C is chemically identical with the normal product A, and D is identical with B. After separation of the reaction products using column chromatography, followed by measurement of the specific activity of each, it has been observed that the specific activity of B is identical with that of II, i.e. no dilution of the ^{14}C label has taken place on rearrangement. Also, it has been found that the rearrangement product A has no trace of ^{14}C label. It thus follows that no crossover product is obtained. This observation, therefore, suggests that this rearrangement is intramolecular in nature.

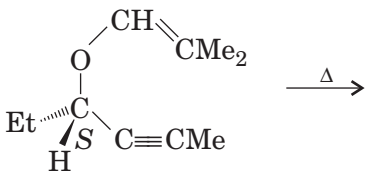
8. Predict the product and suggest a mechanism for each of the following reactions (Claisen rearrangements):

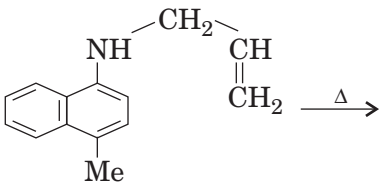
(a) 

(b) 

(c) 

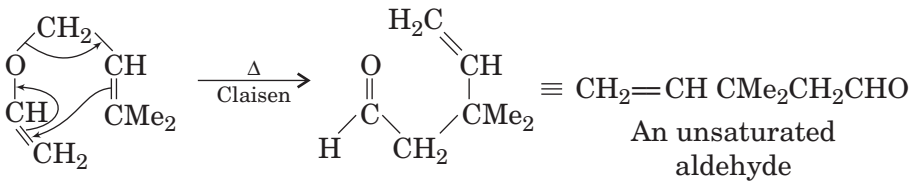
(d) 

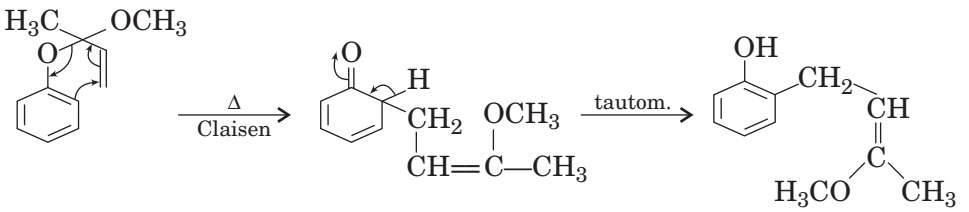
(e) 

(f) 

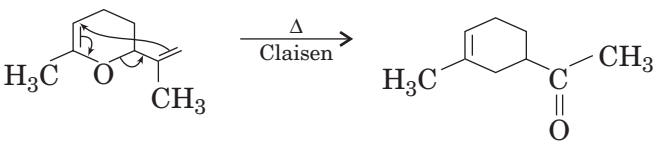
Solution

(a) This allylic vinylic ether undergoes Claisen rearrangement to give an unsaturated aldehyde.

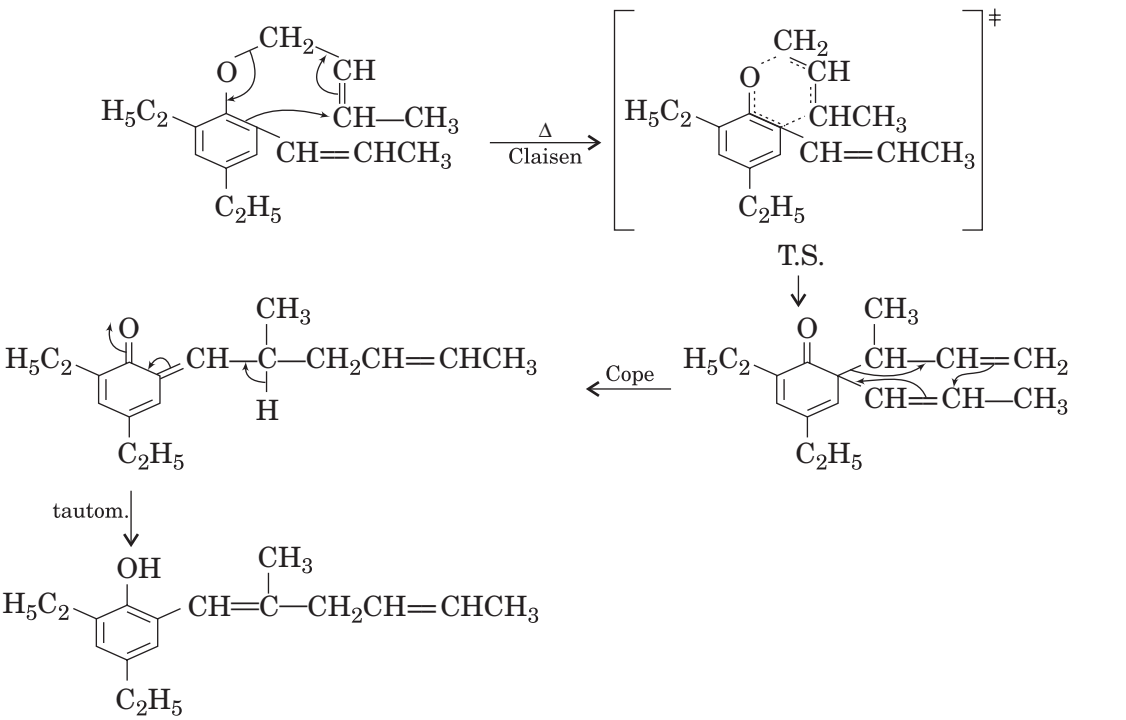


(b) 

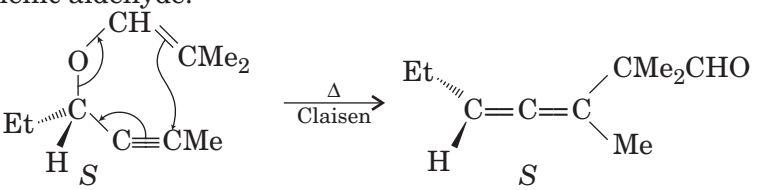
(c) The allylic vinylic ether undergoes Claisen rearrangement to yield an unsaturated ketone.



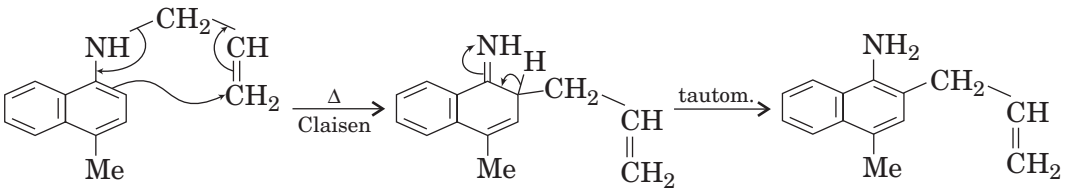
(d) This is a case of Claisen rearrangement followed by Cope to give an *o*-vinylphenol.



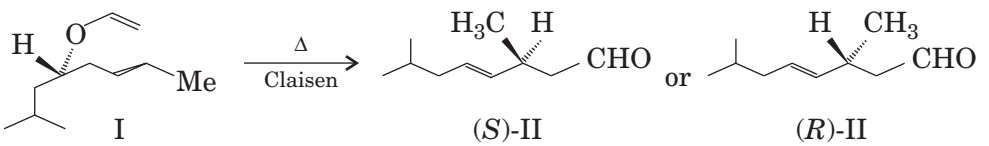
(e) This chiral propargyl vinyl ether undergoes the Claisen rearrangement to yield a chiral allenic aldehyde.



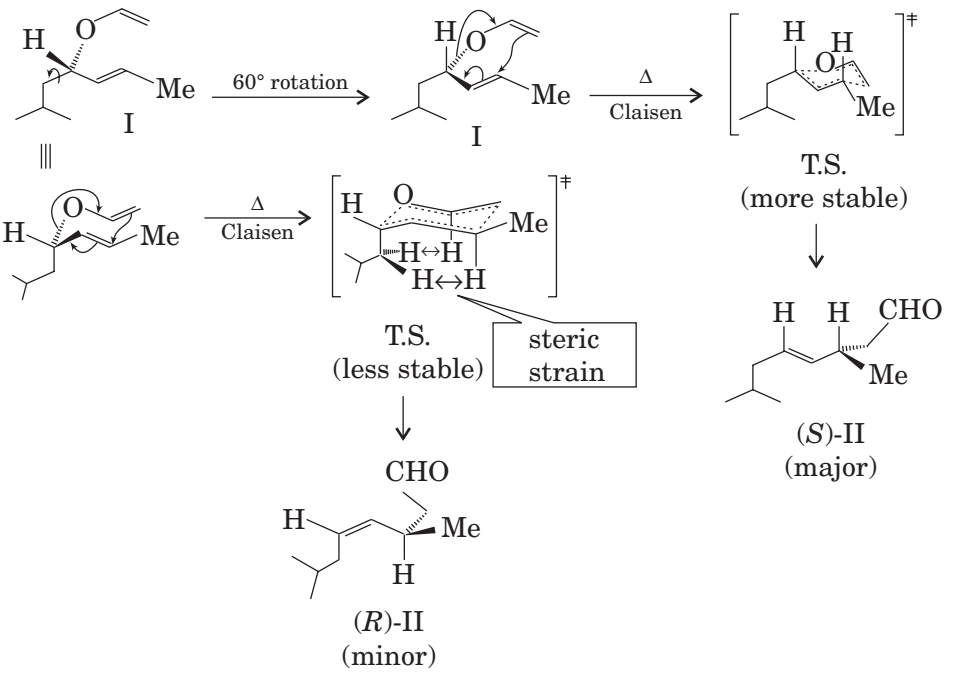
(f)



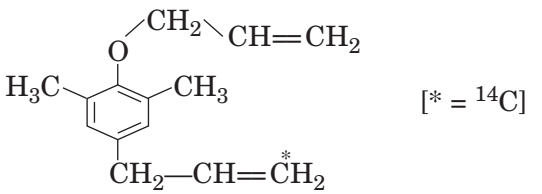
9. When heated, the enol ether I produces one of the two enantiomeric aldehydes (*S*)-II or (*R*)-II as the major product (>96%). Predict by considering the chair-like transition states which enantiomer is the preferred product.



Solution (*S*)-II is expected to be formed as the major product because in this reaction involving chair-like T.S. an unfavourable axial orientation of the bulky *sec*-butyl group is avoided.

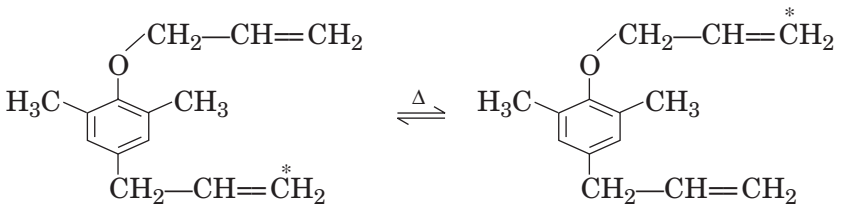


10. What happens when the compound I is heated at 160°C. Explain.

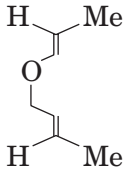


I

Solution Since the two *ortho*-positions and also the *para*-position are occupied in this substrate, none of the dienones can enolize and an equilibrium is set up among the dienones and the ether. As a result, distribution of ^{14}C between its original position and the terminal position of the *o*-allyl group occurs. This observation establishes the reversibility of the cyclic mechanism operating in the Claisen rearrangement.



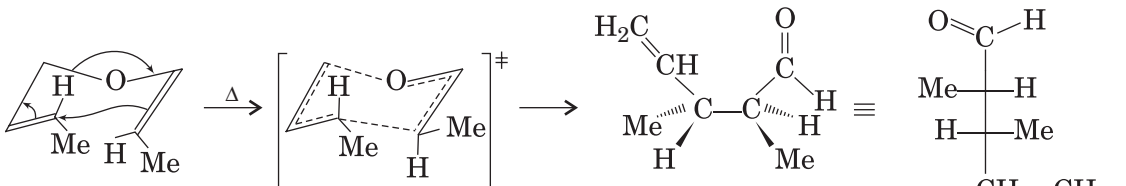
11. Explain why the *threo*-aldehyde is obtained nearly exclusively in the following reaction:



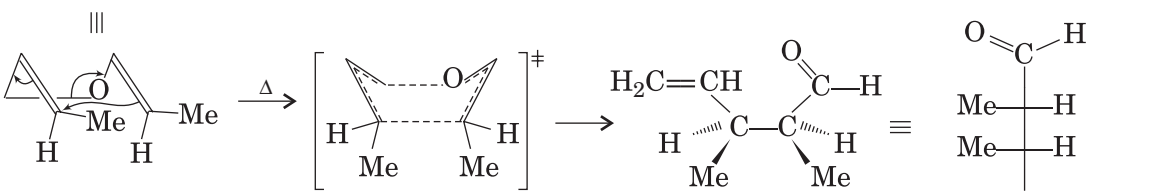
trans, *trans*-Crotyl propenyl ether

$\xrightarrow[\text{Claisen}]{\Delta}$ (±)-threo- and (±)-erythro-$CH_2{=}CH\overset{*}{C}HMe\overset{*}{C}HMeCHO$
(97%) (3%)

Solution Since the ether undergoes the Claisen rearrangement through the relatively more stable chair-like T.S., rather than the boat-like transition state, the *threo*-aldehyde is produced nearly exclusively. The stereochemical course of the reaction may be shown as follows:



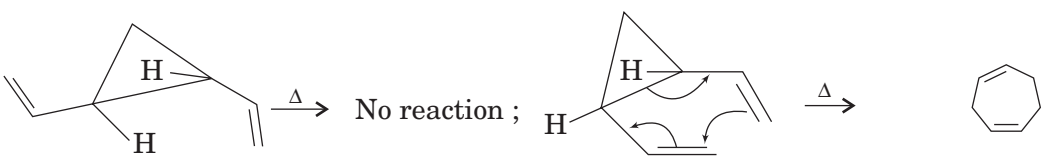
trans, *trans*-Crotyl propenyl ether (chair-like conformation) | Chair-like T.S. (more stable) | *threo*-aldehyde (97%) (one enantiomer)



(boat-like conformation) | Boat-like T.S. (less stable) | *erythro*-aldehyde (3%) (one enantiomer)

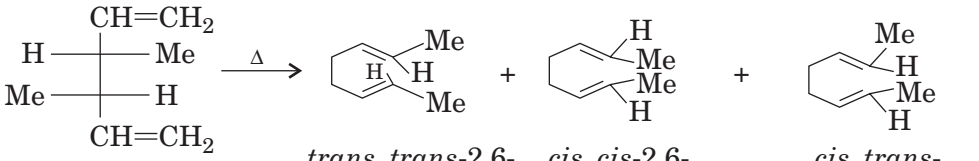
12. *Cis*-1,2-divinylcyclopropane undergoes the Cope rearrangement whereas the *trans*-isomer does not. Explain.

Solution The *trans*-isomer of 1,2-divinylcyclopropane does not undergo the Cope rearrangement because the terminal carbons of the molecule, between which bonding must take place, are too far apart. The *cis*-isomer, on the other hand, undergoes this rearrangement because the terminal carbons are very close to each other.



trans-1,2-Divinylcyclopropane | No reaction ; | *cis*-1,2-Divinylcyclopropane | 1,4-Cycloheptadiene

13. Explain the following observation:



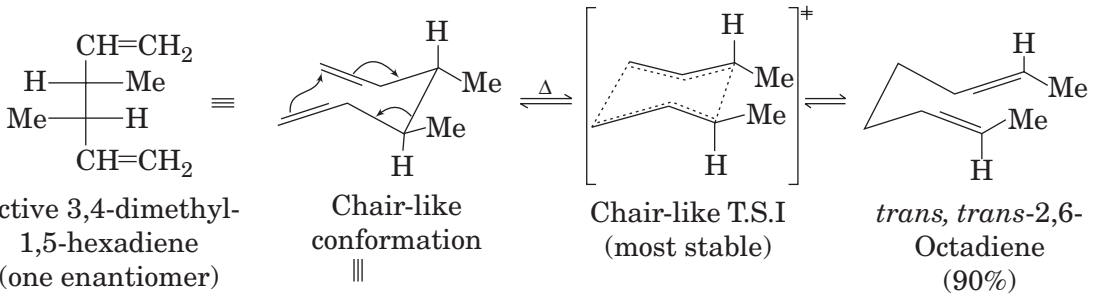
Active 3,4-dimethyl-1,5-hexadiene (one enantiomer)

trans, *trans*-2,6-Octadiene (90%)

cis, *cis*-2,6-Octadiene (9.9%)

cis, *trans*-2,6-Octadiene (0.1%)

Solution Active 3,4-dimethyl-1,5-hexadiene undergoes the Cope rearrangement through more stable chair-like transition state I (in which both the methyl groups are equatorial) to give *trans*, *trans*-2,6-octadiene predominantly (90%) and through the less stable chair-like transition state II (in which both the methyl groups are axial) to give a small amount (9.9%) of the *cis*, *cis*-isomer. A very little amount of the *cis*, *trans*-isomer is obtained through the least stable boat-like transition state III.

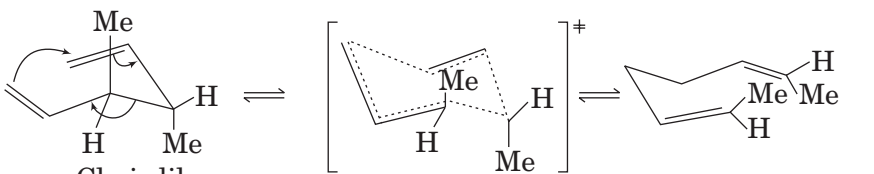


Active 3,4-dimethyl-1,5-hexadiene (one enantiomer)

Chair-like conformation

Chair-like T.S.I (most stable)

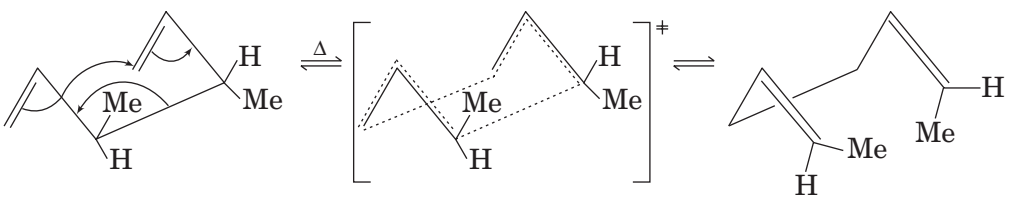
trans, trans-2,6-Octadiene (90%)



Chair-like conformation

Chair-like T.S. II (less stable)

cis,*cis*-2, 6-octadiene (9.9%)



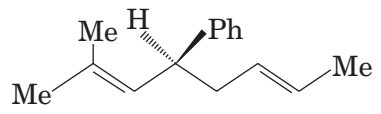
Boat-like conformation

Boat-like T.S. III (least stable)

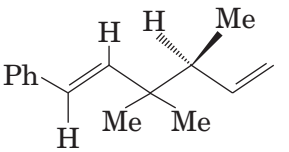
trans, *cis*-2,6-octadiene (0.1%)

14. Explain why (4*S*,6*E*)-2-methyl-4-phenylocta-2,6-diene undergoes the Cope rearrangement to give mainly 3,3,4-trimethyl-1-phenylhexa-1,5-diene when heated at 180°C.

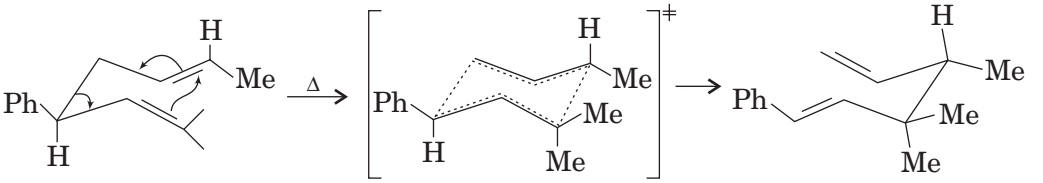
Solution When (4*S*, 6*E*)-2-methyl-4-phenylocta-2,6-diene (a 1,5-diene) is heated at 180°, it undergoes the Cope rearrangement mainly through the more stable chair-like transition state I (in which only one $-CH_3$ group is axial) rather than the less stable chair-like transition state II (in which –Ph and two –Me groups are axial) to yield (1*E*, 4*S*)-3,3,4-trimethyl-1-phenylhexa-1,5-diene as the major product.



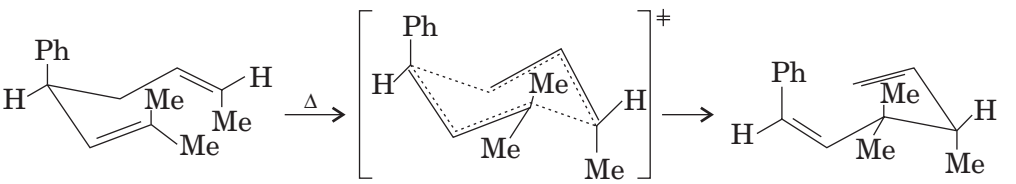
(4*S*,6*E*)-2-Methyl-4-phenylocta-2, 6-diene



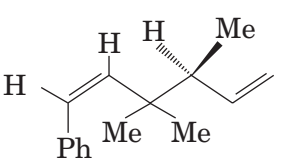
(1*E*, 4*S*)-3,3,4-Trimethyl-1-phenylhexa-1,5-diene (major)



Chiar-like T.S. I (more stable because only one group is axial)



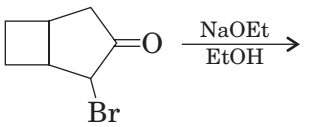
Chair-like T.S. II (less stable because three groups are axial)

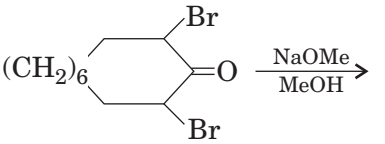


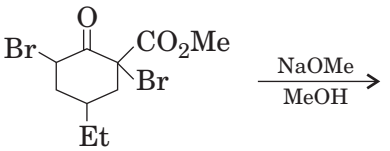
(1*Z*, 4*S*)-3, 3, 4-Trimethyl-1-phenylhexa-1, 5-diene (minor)

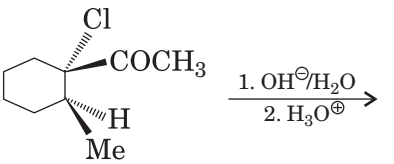
Study Problems

1. Predict the major product and formulate a reasonable mechanism for each of the following reactions (Favorskii rearrangements):

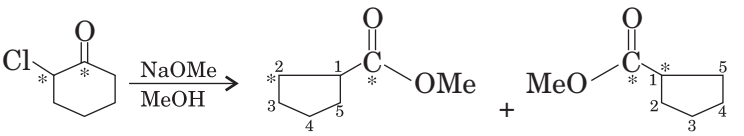
(a) 

(b) 

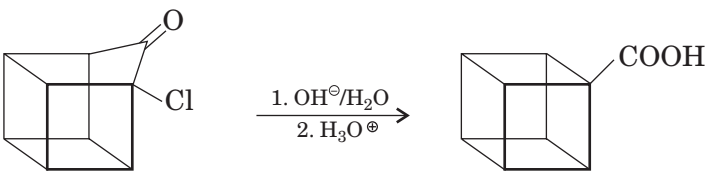
(c) 

(d) 

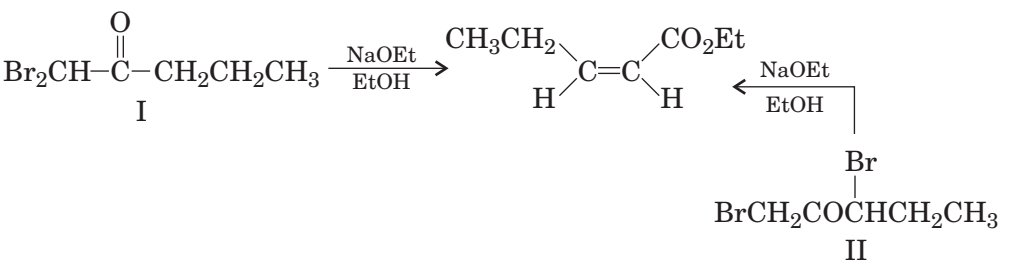
2. Explain the following observation:



3. When treated with alkali, the following haloketone undergoes quasi-Favorskii rearrangement instead of Favorskii rearrangement. Provide a suitable explanation for this observation and give the mechanism involved.

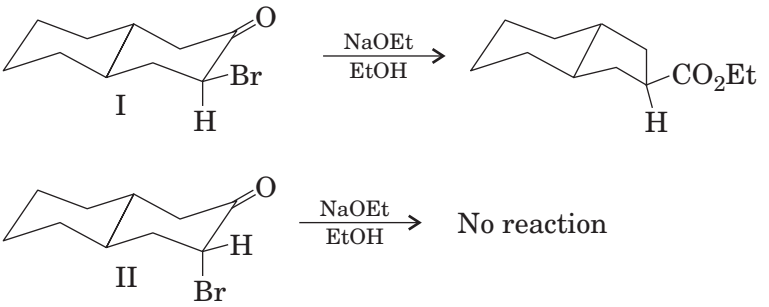


4. Explain the following observations:



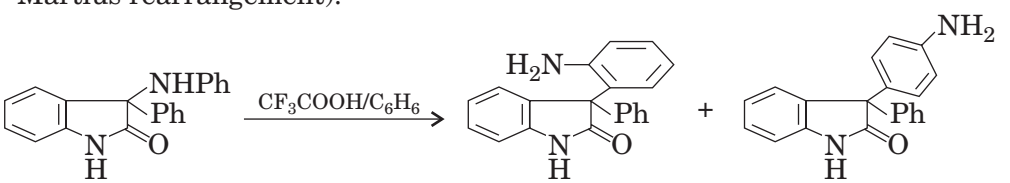
[**Hint:** In the case of II, the stability of the carbanion is to be considered.]

5. Explain why the haloketone I undergoes the Favorskii rearrangement when treated with NaOEt/EtOH but the haloketone II does not.

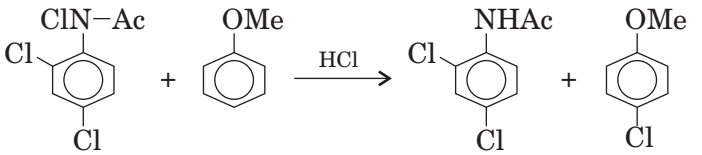


[**Hint:** Since the axial α-H in I is *trans* to the equatorial bromine, the α-carbanion is able to displace bromine from the backside (S_N2). So, the haloketone I undergoes this reaction. On the other hand, the axial α-H in II is *cis* to the axial bromine and due to lack of stereoelectronic requirement, the reaction does not take place.]

6. Provide a suitable mechanism to explain the formation of the products (Hofmann–Martius rearrangement):

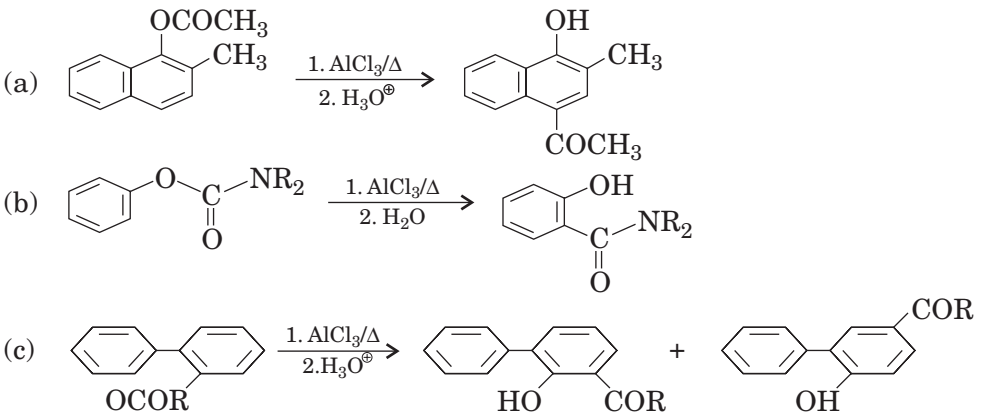


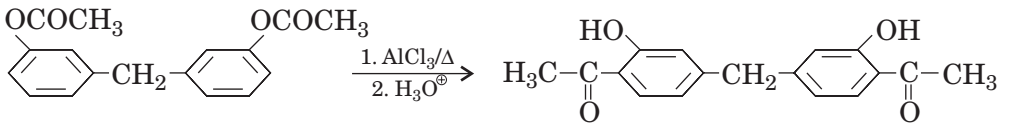
7. Explain the following observation related to the Orton rearrangement:

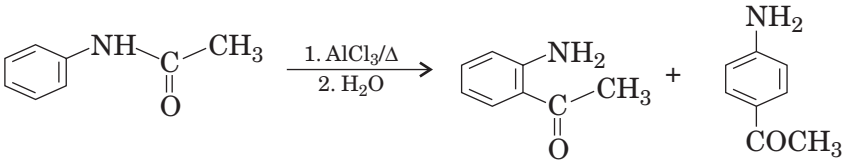


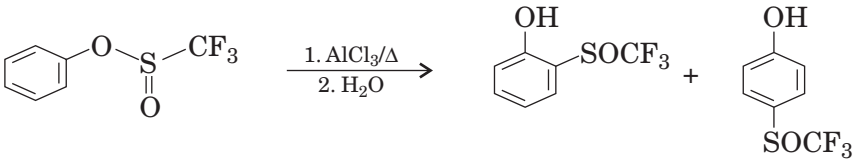
[**Hint:** The Orton rearrangement is intramolecular.]

8. Suggest a reasonable mechanism for each of the following reactions (Fries rearrangements):

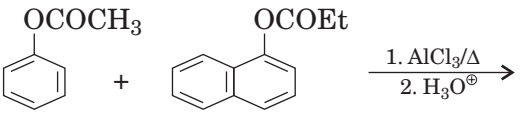


(d) 

(e) 

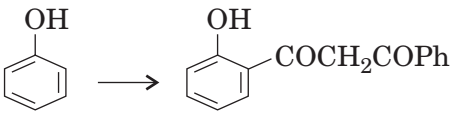
(f) 

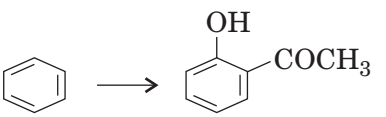
9. Write structures of all possible products expected to be obtained from the following reaction and give your reasoning:

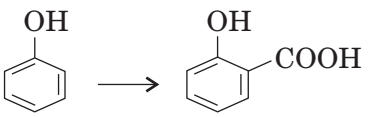


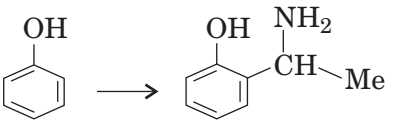
[**Hint:** Two normal plus two crossover products will be obtained as the Fries rearrangement is intermolecular (also intramolecular) in nature.]

10. How would you carry out the following transformations using the Fries rearrangement in any one of the steps?

(a) 

(b) 

(c) 

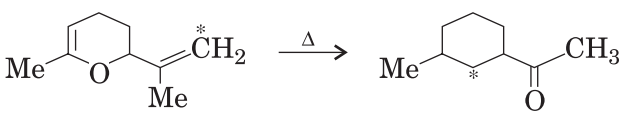
(d) 

11. Predict the products of the following reaction sequence and mention an important use of the compound C:

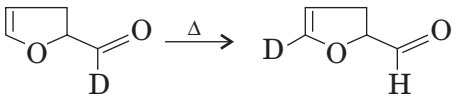
Hydrazobenzene $\xrightarrow{HCl}$ A $\xrightarrow{HNO_2}$ B $\xrightarrow{\text{Naphthionic acid (2 equiv.)}}$ C

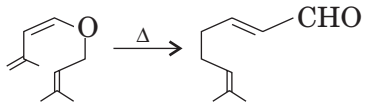
[**Hint:** The compound C is 'Congo red'.]

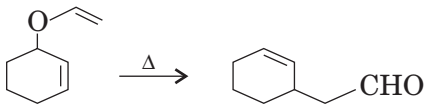
12. Write down a reasonable mechanism for each of the following reactions (Claisen rearrangements):

(a) 

[* = ^{14}C]

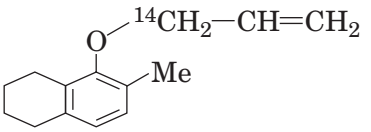
(b) 

(c) 

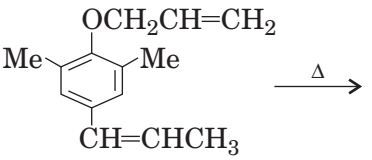
(d) 

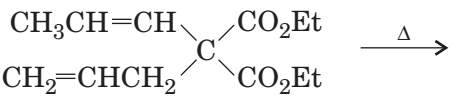
13. Explain why allyl phenyl ether isomerizes to *o*-allyl phenol when heated.

14. Predict the product of the following reaction with plausible mechanistic interpretation:

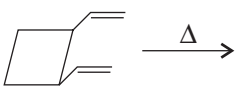


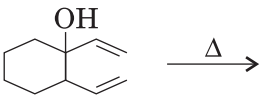
15. Predict the product and suggest a reasonable mechanism for each of the following reactions:

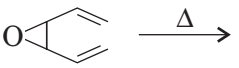
(a) 

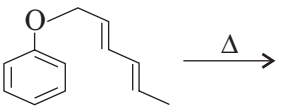
(b) 

16. Predict the products of the following reactions and give plausible mechanisms:

(a) 

(b) 

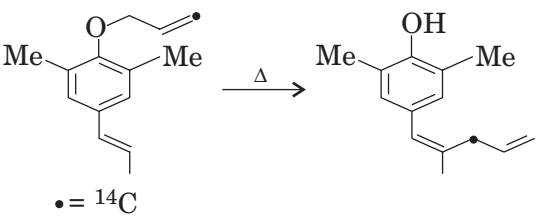
(c) 

(d) 

17. The transition states of the Diels–Alder reaction and the Cope rearrangement are comparable. Why?

[**Hint:** Both of them are aromatic and involve six orbitals and six electrons.]

18. Provide a mechanistic rationalization for the following thermal transformation:



REFERENCES

1. *Molecular Rearrangements*; de Mayo, P., Ed., Inter-science: New York, 1963.
2. C J Collins, "The Pinacol Rearrangement"; *Quart. Revs*. (London), 1960, **14**, 357.
3. F C Whitmore, "The Common Basis of Intramolecular Rearrangements" ; *J Amer. Chem. Soc*. 1962, **54**, 3274.
4. "*Polar Rearrangements*", L M Harwood, Ed., Oxford University Press, New York, (1992).
5. W Lwnoski (Ed.) *Nitrenes*, Interscience Publishers, New York, (1970).
6. A K Banerjee and H E Hwrtado, Tetrahydron, **41**, 3029 (1985).
7. B M Trost and L S Melvin, Sulphur Ylides, Academic Press, New York, (1975).
8. T S Stevens and W E Watts, *Selected Molecular Rearrangements*, van Nostrand Reinhold, London, (1973).
9. A W Johnson, *Ylide Chemistry*, Academic Press, New York, (1966).
10. L M Harwood, Ed., "Polar Rearrangements", Oxford University Press, New York, (1992).
11. S Lang and J A Murphy, *Chem. Soc. Rev*., **35**, 146 (2006).
12. W D Ollis *et al*., *J. Chem. Soc.,* **1**, 1049 (1983).
13. G Mark Loudon, *Organic Chemistry*, Fourth Edition, Oxford University Press.
14. Laurence M Harwood, *Polar Rearrangements*, Oxford University Press.
15. HO House and W F Gilmore, Stereochemistry of Favorskii rearrangement, *J. Am. Chem. Soc.* **1961**, 83, 3980–3985.

INDEX

Index Guide: Alphabetization is by the "word" method, which uses the first term in a compound term; hyphenated terms are treated as one word. Leading numbers, Greek letters, and other descriptors (*E*, *cis*, *tert*, etc.) are ignored unless they alone determine the order.

A

$A_{AC}1$ mechanism 2.298
$A_{AC}2$ mechanism 2.296
$A_{AL}1$ mechanism 2.300
Acetals as protecting groups 2.22
Acetoacetic ester synthesis 2.219, 2.244
Acid-Catalyzed Hydrolysis of Amides 2.317
Acid-catalyzed 4.4
    aldol condensation 2.148
    halogenation at the α-carbon 2.208
Acid-hydrolysis 2.222
Activating groups 3.6
Acyl substitution 2.286
Acyl-oxygen cleavage: 2.294
Acyloin condensation 2.314
Adamantylideneadamantane 1.51
Addition of
    acetylides 2.116
    alcohol to an alkene 1.30
    bromine to cyclohexene 1.54
    carbenes 1.102
    compounds like hydroxylamine 2.86
    diazomethane (CH_2N_2) 2.116
    electrons 2.46
    enolate ions 2.145
    Grignard and other organometallic compounds 2.109
    halogens 1.45
    HX to cumulated dienes 1.10
    hydride ion 2.46
    hydrogen cyanide (HCN) 2.106
    hydrogen halides 1.6
    nitrogen nucleophiles 2.84
    organolithium compounds 2.114
    oxygen nucleophiles: water and alcohols (ROH) 2.11
    primary amines 2.84
    radicals and radical substitution 1.199
    sulphur nucleophiles 2.38
    thiols 2.38
    water 2.11
    ylides 2.118
Adipic acid 2.257
Adrenaline 4.132
Aldol reactions 2.145
Alkylation at the α-carbon of aldehydes and ketones 2.214
Alkylation of
    carboxylic Acids 2.310
    β-dicarbonyl compounds 2.218
Allylic Chlorination and Allylic Bromination 1.207
Ammonolysis 2.313
π- and σ-complex 3.4
Anthracene 3.23
Anti-Hydroxylation of Alkenes by Treating with a Peroxy Acid Followed by Acid- or Base-Catalyzed Hydrolysis 1.122
Anti-Markownikoff's Hydration of alkenes 1.65
Applications of
    bisulphite addition reaction 2.41
    the Haloform reaction 2.213
    the Stobbe condensation 2.159
Arenium ion 3.3

B

Backbone of organic chemistry 2.2
$B_{AC}2$ mechanism 2.295
$B_{AL}1$ mechanism 2.301
$B_{AL}2$ mechanism 2.302
9-BBN and its uses 1.74
Baeyer–Villiger oxidation 4.102
Base-promoted hydrolysis of amides 2.318
Base-promoted halogenation 2.210
Beckmann rearrangement 4.60
Benzenonium ion 3.3
Benzidine rearrangement 4.133
Benzilic acid rearrangement 4.32
Benzoin condensation 2.164
Birch reduction 1.138
Bouveault-Blanc reduction 2.65
Bromination and chlorination of benzene 3.63
Butane-1,2,3,4-tetracarboxylic acid 2.257
Butanone 2.244

C

Cannizzaro reaction 2.57
Carbenoids and the Simmons–Smith reaction 1.108

Chlorosulphonation 3.78
Claisen
condensation 2.227
rearrangement 4.136
Schmidt condensation 2.153
Cleavage of C═C by acidic or alkaline solution of $KMnO_4$ 1.121
Clemmensen reduction 2.68
σ-complex 3.3
Concept of 'umpolung' in benzoin condensation 2.165
Condition for acyl substitution 2.290
Cope rearrangement 4.140
Cope-Knoevenagel reaction 2.177
Cram's rule 2.9
Criegee intermediate 4.103
Crossed
aldol addition 2.151
Cannizzaro reaction 2.59
Claisen condensation 2.232
Crossover experiment 4.62
Crotonic acid 2.248, 2.256
Cubane 4.146
Curtius rearrangement 4.71
Cyanoethylation 1.178
Cyclobutane-1,2-dicarboxylic acid 2.257
Cyclobutanecarboxylic acid 2.256
Cyclohexane-1,4-dicarboxylic acid 2.257
Cyclopentane-1-carboxyl-1-acetic acid 2.257
Cyclopentane-1,1-diacetic acid 2.257
Cyclopentane-1,3-dicarboxylic acid 2.257
Cyclopropanone 2.16
Cyclopropyl methyl ketone 2.244

D

Dakin reaction 4.107
Darzens condensation 2.160
Darzens condensation or Darzens glycidic ester condensation 2.160
Deactivating groups 3.7
Decarboxylation 2.303
Decomposition of ozonides 1.86
Dehydration of amides 2.318
Demjanov rearrangement 4.35
Desulphonation 3.73
Dieckmann condensation 2.231
Diels–Alder reaction 1.149
Dienone–Phenol rearrangement 4.26
Dimedone 2.261
Dimethyldioxirane 1.126
β-Dimethylglutaric acid 2.257
Direct and conjugate addition to *α*, *β*-Unsaturated Aldehydes and Ketones 1.180
Directed aldol reaction 2.154
Disiamylborane (Sia_2BH) 1.71
Doebner condensation 2.178

E

E-selectivity 2.122
Effect of structure on reactivity 2.5
Electrophilic
addition 1.2
aromatic substitution 3.3
rearrangements 4.114
or cationotropic rearrangements 4.2
Equilibrium constant for cyanohydrin formation 2.127
Esterification of carboxylic acids and hydrolysis of esters 2.293
Ethyl 2-methyl-4-oxo-2-cyclohexene carboxylate 2.249
Ethyl-2,5-dimethylpyrrole-3-carboxylate 2.249
Ethyl-3,4-dimethyl-3-carboxylate 2.249
Ethyl-3,5-dimethylpyrrole-2,4-dicarboxylate 2.249

F

Favorskii rearrangement 4.120
Fluorination of benzene 3.66
Formation of
acid anhydrides 2.292
acyl chlorides 2.291
alkyl bromides (the Hunsdiecker reaction) 2.306
amides 2.293
halohydrin 1.52
hemiacetals and acetals 2.16
ketones and primary alcohols 2.302
stable and isolable hydrates 2.14
Free radical rearrangements 4.2
Friedel–Crafts reaction 3.83
Fries rearrangement 4.128

G

Gem-diols 2.11
Generation of carbenes 1.104

H

Haloform reaction 2.211
Halogenation at the α-carbon of aldehydes and ketones 2.208
Heat of hydrogenation 1.135
Hell-Volhard-Zelinsky (HVZ) reaction 2.307
Heptane-2,6-dione 2.247
Heterogenous and homogeneous catalysts 1.146
High dilution technique 2.316
Hofmann
hypobromite reaction or Hofmann degradation 4.66
Martius rearrangement 4.127
rearrangement 4.66
Homologation of ketones by diazomethane 4.28
Horner–Wadsworth–Emmons reaction 2.123
Hydration of
alkenes 1.26
alkynes 1.31
Hydrazine and substituted hydrazines and formation of imine derivatives 2.86
Hydride shift 4.11
Hydroboration-oxidation 1.65
Hydrogenation 1.134

Hydrolysis of
acetals 2.20
esters 2.313
Hydroperoxide rearrangements 4.106
Hydroxylation of alkenes 1.117

I

Indane-1,2,3-trione 2.15
Intramolecular
aldol condensation 2.150
Cannizzaro reaction 2.60
elelctrophilic addition 1.34
rearrangements 4.3
Iodination of benzene 3.66
Ipso-substitution 3.74
Isomerizations of alkylboranes 1.70

K

Ketonic hydrolysis 2.222
Knoevenagel condensation 2.175

L

LAH reduction of comphor 2.71
Limitations in planning grignard of synthesis of
alcohols 2.114
Lossen rearrangement 4.74

M

Mannich
base 2.180
reaction 2.180
Markownikoff's rule 1.7
Mechanism for thioacetal formation 2.38
Mechanism of nucleophilic addition–elimination at the
acyl carbon or nucleophilic acyl substitution
2.286
Meerwein–Ponndorf–Verley (MPV) reduction 2.55
Meta-directing groups 3.7
2-Methylpropanoic acid [$CH_3CH(CH_3)COOH$] 2.255
3-Methylbutanone 2.244
3-Methylpentan-2-one 2.244
β-Methylglutaric acid 2.257
Michael
addition 1.182
retrogression 1.185
Migration of
alkyl group 4.4
aryl group 4.9
C–C σ-bond 4.7
heteroatoms 4.36
Migratory aptitude of the migrating groups 4.15
Mixed benzoin condensation 2.168
Molecular rearrangements 4.1

N

Naphthalene 3.22
Neber rearrangement 4.65
Nitrating agents 3.43
Nitration 3.43
through nitrosation: 3.45
Nitrosation 3.47
Non-1,2-rearrangements 4.120
Nucleophilic
addition 1.178
addition to carbon-oxygen double bond 2.5
carbenes 1.108
or aninotropic rearrangements 4.2
rearrangements to electron deficient carbon 4.3
rearrangements to electron-deficient nitrogen
4.60
rearrangements to electron-deficient oxygen
4.102

O

Oppenauer oxidation 2.74
Orientation in disubstituted benzenes 3.20
Ortho-para directing groups 3.6
Orton rearrangement 4.148
2-Oxobutanoic acid ($CH_3CH_2COCO_2H$) 2.261
4-Oxocyclohexanecarboxylic acid 2.261
5-Oxo-2-hexenoic acid 2.246
5-Oxohexanoic acid 2.246
Oxy-Cope rearrangement 4.141
Oxymercuration-demercuration 1.39
Ozonolysis of Alkenes and Alkynes 1.82

P

Partial rate factor 3.19
Pentaerythritol tetranitrate (PETN) 2.63
Pentane-2,4-dione 1.4
Pentanoic acid 2.248
Performed enolate 2.154
Perkin reaction 2.172
Peroxide effect or Kharasch effect 1.201
Phenylacetic acid ($PhCH_2COOH$) 2.255
Phenylation of EAA 2.252
Phenylpropanone ($PhCH_2COCH_3$) 2.261
Photo-Fries rearrangement 4.131
Pinacol rearrangement 4.12
Pinacolization of ketones 2.67
Preparation of sulphur ylides 2.125
Prevost oxidation 1.125
Principle of microscopic reversibility 2.12
Product development control 2.70
Propane-1,2,3-tricarboxylic acid 2.257
Propanoic acid (CH_3CH_2COOH) 2.255

R

Reaction of
bromine with *cis*- and *trans*-2-butene 1.48
hydrogen bromide with 1, 3-butadiene (kinetic
control versus thermodynamic control of a
chemical reaction) 1.11
Reaction of esters with
Ammonia or amines to form amides 2.313

Grignard reagents 2.313
Reactions of
acid chlorides 2.311
amides 2.317
carboxylic acid anhydrides 2.319
carboxylic acids 2.290
esters 2.313
nitriles 2.320
1,2-rearrangements 4.3, 4.120
Reducing property of Grignard reagents 2.113
Reduction of
carbon–carbon multiple bond with hydrazine 1.141
acid chlorides 2.53
aldehydes and ketones by sodium borohydride 2.50
carbonyl compounds by lithium aluminium 2.47
carboxylic acids 2.51
carboxylic acids, amides and nitriles by borane 1.4
esters and nitriles 2.53
Reductive amination 2.88
Reformatsky reaction 2.169
Regioselective formation of enolates and alkylation of unsymmetrical ketones 2.216
Regioselective reaction 1.9
Retro Diels–Alder reaction 1.160
Retro-Claisen condensation 2.234
Retro-aldol reaction 2.147
Reversibility of
ArS_E2 reaction 3.24
the benzoin condensation 2.166
Robinson annulation 1.192, 2.181
Rule of endo addition 1.156

S

Schmidt rearrangement 4.76
Semipinacol rearrangements 4.21
Solvomercuration–demercuration 1.42
Sommelet–Hauser rearrangement 4.116
Stabilized ylides 2.121
Stereochemical aspect of
aldol addition 2.155
Darzens condensation 2.162
Stereochemistry of nucleophilic addition 2.8
Stereoselectivity
in the Wittig reaction 2.121
of Grignard addition to bicyclic ketones 2.111
Steric approach control 2.70
Stevens rearrangement 4.114
Stobbe condensation 2.157
Stork enamine reaction 2.94
Structure and stability of carbenes 1.103
Structure of the carbonyl group 2.5
Succinic acid 2.248, 2.257
Sulphonation 3.72
Sulphonation of naphthalene (Kinetic control versus thermodynamic control) 3.76
Sulphur-selective Lewis acid 2.45
Syn- and *Anti*-Addition of hydrogen to an alkyne 1.136
Syn-Hydroxylation of alkenes by osmium tetroxide 1.117
Syn-Hydroxylation of alkenes by basic solutions of potassium permanganate ($KMnO_4$) 1.120
Synthesis of
a disubstituted acetic acid 2.224
a monosubstituted acetic acid 2.224
alicyclic carboxylic acids 2.226
carbostyril 2.175
carboxylic acids 2.222
Coumarin 2.174
cycloalkyl methyl ketones 2.221
dicarboxylic acids 2.225
diketones 2.221
disubstituted acetone 2.220
keto acids 2.221
methyl ketones 2.219
monosubstituted acetone 2.219
phenanthrene 2.175
phenylalanine 2.175
substituted acetic acids 2.223
Synthetic applications of aldol reaction 2.149

T

THP ether 2.23
Tetrabutylammonium fluoride 2.189
Tetrahydropyranyl group as a protecting group 2.23
Thermodynamic and kinetic enolates 2.154
Thexylborane 1.80
Thiele acetylation 1.193
Thioacetals in organic synthesis 2.39
Tishchenko reaction 2.64
Trifluoroacetaldehyde (CF_3CHO) 2.15

U

Unstabilized ylides 2.121
Unsymmetrical bromonium ion 1.51
Use of enamines in organic synthesis 2.93

V

van't Hoff factor i 2.299

W

Wagner–Meerwein rearrangement 4.3
Wheland intermediate 3.3
Wilkinson's catalyst 1.146
Wittig
reaction 2.119
reagents and their preparation 2.118
rearrangement 4.115
Wolff rearrangement and Arndt–Eistert synthesis 4.29
Wolff-Kishner reduction 2.89

Z

Z-selectivity 2.122