ORGANIC CHEMISTRY-II

MSc First Year,
Semester-II, PAPER - II

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FOREWORD

Since its establishment in 1976, Acharya Nagarjuna University has been forging ahead in the path of progress and dynamism, offering a variety of courses and research contributions. I am extremely happy that by gaining 'A+' grade from the NAAC in the year 2024, Acharya Nagarjuna University is offering educational opportunities at the UG, PG levels apart from research degrees to students from over 221 affiliated colleges spread over the two districts of Guntur and Prakasam.

The University has also started the Centre for Distance Education in 2003-04 with the aim of taking higher education to the door step of all the sectors of the society. The centre will be a great help to those who cannot join in colleges, those who cannot afford the exorbitant fees as regular students, and even to housewives desirous of pursuing higher studies. Acharya Nagarjuna University has started offering B.Sc., B.A., B.B.A., and B.Com courses at the Degree level and M.A., M.Com., M.Sc., M.B.A., and L.L.M., courses at the PG level from the academic year 2003-2004 onwards.

To facilitate easier understanding by students studying through the distance mode, these self-instruction materials have been prepared by eminent and experienced teachers. The lessons have been drafted with great care and expertise in the stipulated time by these teachers. Constructive ideas and scholarly suggestions are welcome from students and teachers involved respectively. Such ideas will be incorporated for the greater efficacy of this distance mode of education. For clarification of doubts and feedback, weekly classes and contact classes will be arranged at the UG and PG levels respectively.

It is my aim that students getting higher education through the Centre for Distance Education should improve their qualification, have better employment opportunities and in turn be part of country's progress. It is my fond desire that in the years to come, the Centre for Distance Education will go from strength to strength in the form of new courses and by catering to larger number of people. My congratulations to all the Directors, Academic Coordinators, Editors and Lesson-writers of the Centre who have helped in these endeavors.

Prof. K. Gangadhara Rao
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Acharya Nagarjuna University.

M.Sc. CHEMISTRY
SEMESTER-II
2O2CH24: ORGANIC CHEMISTRY-II
SYLLABUS

Learning Objectives:

- To know the general methods of synthesis involving carbon-carbon multiple bonds.
- To know various mechanisms involved in aliphatic and aromatic Nucleophilic/electrophilic substitution reactions.
- To know about various elimination mechanisms in different types of substrates.
- To know the importance of functional group protection in organic synthesis.
- To know the mechanisms involved in various types of named reactions and their applications in organic synthesis.

UNIT-I

General Methods for Synthesis: Addition reactions involving electrophiles (Br_2, HBr HOBr, and H_2O/H_2SO_4); nucleophilic additions (Michael addition, Mannich, and Grignard reactions); Addition to C-C multiple bonds-stereo chemistry of addition, formation and reactions of epoxides, syn and antihydroxylation; hydrogenation (catalytic and Non catalytic).

UNIT-II

Aliphatic Nucleophilic Substitutions: The SN_2, and SN_1: Mechanisms, energy profile diagram and stereochemistry; SNi, mixed SN_1 & SN_2, and SET mechanisms; Factors influencing nucleophilic substitution reactions: Effect of structure, nucleophile, solvent, and leaving group.

The neighbouring group mechanism: Neighbouring group participation by O, N, S, halogens, in nucleophilic substitution reactions. Concept of classical and Non-classical carbocations-participation of Pi and Sigma bonds as neighbouring groups. Anchimeric assistance-steric requirement.

UNIT - III

Aromatic Nucleophilic Substitutions: The SNAr, SNI mechanisms and benzyne mechanism. Reactivity-effect of substrate structure, leaving group and attacking nucleophile. The Von-Ritcher, Sommelet-Hauser and Smiles rearrangements.

Aromatic Electrophillic Substitution reactions -Friedel Crafts Alkylation, Acylation, Halogenations.

UNIT-IV

Elimination and Protecting Groups:

a) Types of elimination (E1, EICB, E2) reactions, mechanisms, stereochemistry and orientation, Hofmann and Saytzeff's rules, Syn elimination versus anti elimination. Competitions between

elimination and substitution.

b) Dehydration, dehydrogenation, decarboxylative elimination, pyrolytic elimination, molecular rearrangement during elimination.

c) Importance of functional group protection in organic Synthesis: Protecting agents for the protection of functional groups- Hydroxyl group, Amino group Carbonyl group and Carboxylic acid group.

UNIT-V

Familiar Named Reactions: Benzoin, Perkin, Cannizaro, Dieckmann and Stobbe condensations; Hofmann, Schmidt, Lossen, Curtius, Clasien, Backmann and Fries rearrangements; Reformatsky, Favoursky, Wittig reaction, Baeyer Villiger reaction and Chichibabiun reaction, Oppenaur oxidation, Clemmensen, Wolff – kishner, Meerwein-Ponndorf-Veriey and Brich reductions.

Reference Books:

l) Advanced organic chemistry - reaction, mechanism and structure, Jerry March, John Wiley.
2) Advanced organic chemistry, F.A.carey and R.J.sundberg, prenum.
3) A guide book to Mechanism in organic chemistry, peter Sykes, Longman.
4) Organic chemistry, I.L.Finar, Vol. I & II, Fifth ed. ELBS, 1975.
5) organic chemistry, Hendrickson, cram and Hammond (Mc Graw - Hill).
6) Stereo Chemistry of carbon compounds _ E.L. Eliel.
7) Modern organic Reactions, H.O.House, Benjamin.
8) An introduction to chemistry of Heterocyclic compounds, R.M.Acheson.
9) Structure and mechanism in organic chemistry, C.K.Ingold, Cornell University hess. l0) Principles of organic synthesis, R.O.C.Norman and J.M.Coxon, Blakie Academic & Professional.
I l) Reaction Mechanism in organic chemistry, S.M.Mukherji and S.p.Sing[Macmillan.

Learning Outcomes:

- Students understand the mode of addition reactions involving addition by electrophile and nucleophiles over unsaturated bonds between carbons
- students understand and apply the substitution and elimination reaction mechanisms at aliphatic and aromatic substrates for various reactions leading to research
- understand how to protect various functional 8troud in organic synthesis and can apply the same to novel molecules useful for research also.
- students understand the mechanisms of studied named reactions and their applications in organic synthesis.
- To learn the molecular rearrangements.

(202CH24)

M. Sc Chemistry :: Organic Chemistry - II

Time: 03 Hours **Max Marks: 70**

Answer all the following questions

Unit-I

1) a) Write the mechanism of bromine addition to an alkene. [4]

or

b) What are epoxides? Give one method of preparation and one reaction.

2) a) Describe syn and anti hydroxylation and hydrogenation of alkenes. [10]

or

b) Explain electrophilic and nucleophilic additions to C=C bonds with examples.

Unit-II

3) a) What is SN_i mechanism? Illustrate with the hydrolysis of tert butyl chloride. [4]

or

b) Discuss SET mechanism in aliphatic substitution.

4) a) Explain the effect of substrate structure, nucleophile, leaving group and solvent on SN_1 and SN_2 reactions. [10]

or

b) Describe neighbouring group participation by O, N, S and halogen with suitable examples.

Unit-III

5) a) What is the SNAr mechanism? State its conditions. [4]

or

b) Discuss Friedel–Crafts alkylation and acylation with mechanisms.

6) a) Explain the mechanism, intermediates and conditions of the benzyne mechanism with two examples. [10]

or

b) Explain Von Richter and Smiles rearrangements.

Unit-IV

7) a) State Hofmann rule with examples. [4]

or

b) Define protecting group. Give one example each for hydroxyl and carbonyl.

8) a) Discuss syn and anti eliminations with suitable examples. [10]

or

b) Describe mechanisms and stereochemistry of E_1, E_2 and E_{1CB} eliminations.

Unit-V

9) a) Write the general reaction and use of the Wittig reaction. [4]

or

b) What is the Reformatsky reaction? Give a simple synthetic application.

10) a) i) Convert benzaldehyde into benzoin.

ii) Convert benzaldehyde into cinnamic acid. [10]

or

b) i) Convert benzamide into aniline.

ii) Convert benzoic acid into aniline via an acyl azide.

CONTENTS

LESSON – 01

GENERAL METHODS OF ORGANIC SYNTHESIS: ADDITION REACTIONS

1.0 OBJECTIVES:

After studying this lesson, the student will be able to:

1. Understand the **nature and importance of addition reactions**.
2. Explain **addition to C=C multiple bonds** in alkenes.
3. Describe **electrophilic and free radical addition mechanisms**.
4. Understand **Markovnikov and Anti-Markovnikov rules**.
5. Explain **stereochemical outcomes** of addition reactions.

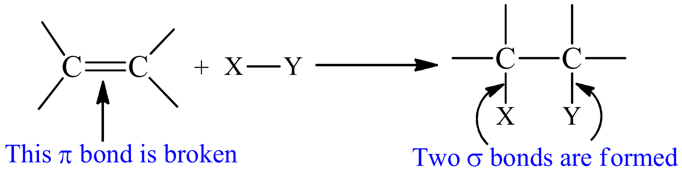
STRUCTURE

1.1 ADDITION TO C-C MULTIPLE BONDS

Addition reaction is one which involves combination of two or more molecules to form a large single molecule with no other products. Addition reaction is common in compounds that have unsaturated C-C bond, like double (alkene) and triple (alkyne) bonds.

Addition to a double or triple bond can take place basically in four ways. Three of these are two-step processes, with initial attack by an electrophile, a nucleophile or a free radical. The second step involves the combination of resulting intermediate with, respectively a negative, a positive or a neutral species. In the fourth type of mechanism, attack at the two carbon atoms of multiple bonds is simultaneous.

A general addition reaction



- In an addition reaction, new groups X and Y are added to the starting material. A π bond is broken and two σ bonds are formed.
- Addition reactions are characteristic of a reaction of π bond. Ions and radicals may add across a multiple bond. Accordingly, these are three types.
- Ionic (electrophilic & nucleophilic) and free radical addition reactions.

1.2 ELECTROPHILIC ADDITION TO CARBON-CARBON DOUBLE BOND:

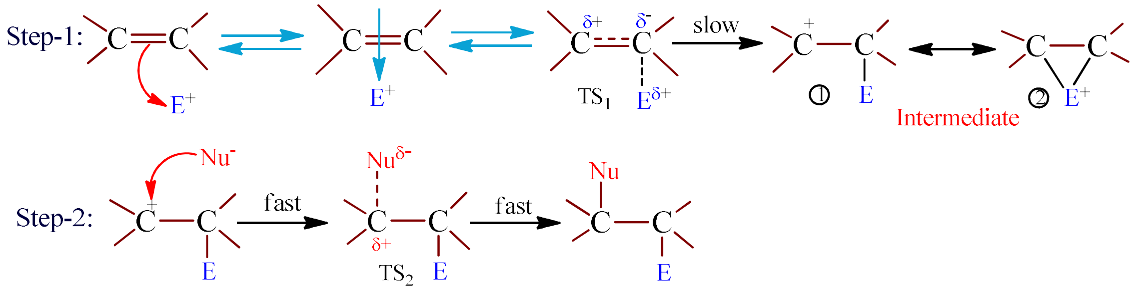
Electrophiles: Proton, Lewis acids such as BF_3, AlX_3, Br_2, Metal ions that contain vacant d orbitals Ag^+, Hg^{++}

Why do alkenes/alkynes undergo addition reaction??

- Conversion of π Bond to 2 σ Bonds is typically energy favored
- "Two σ bonds are more stable (lower in energy) than one σ and one π bond."
- π Electrons are exposed (ABOVE and BELOW sp^2 plane)
- π bonds are good at capturing electrophiles (H^+, Lewis Acids, X_2)
- Metal Ions with vacant orbitals are also good electrophiles

Mechanism:

The reagent E-Nu can be thought of divisible into electrophile E^+ and nucleophile Nu^-



In this mechanism an electrophile approaches the multiple bonds and in the first step forms a bond by converting the π electron pair into a σ pair. Here 'E' need not actually be a positive ion but can be the positive end of a dipole or an induced dipole, with the negative part breaking off either during the first step or shortly later.

The second step is the combination of intermediate 1 or 2 with the nucleophile same as the second step of S_N1 mechanism or S_N2 step respectively. Whether the intermediate is 1 or 2, the mechanism is called electrophilic addition bimolecular (AdE2).

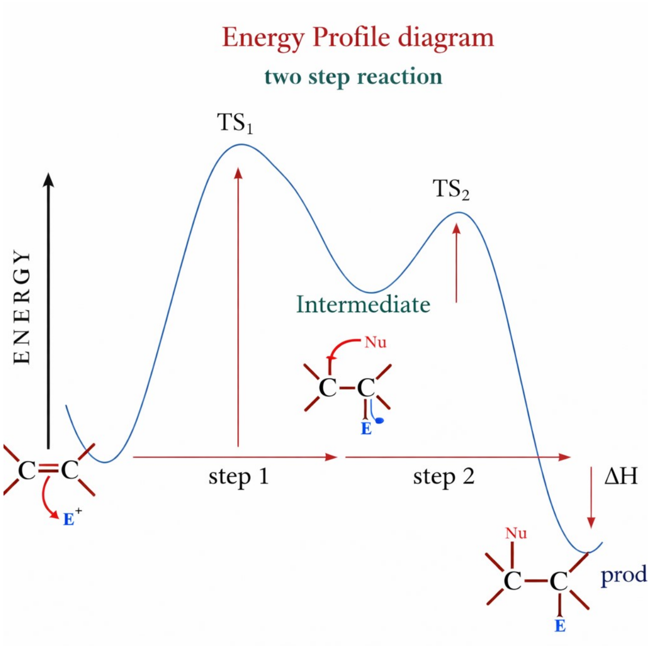


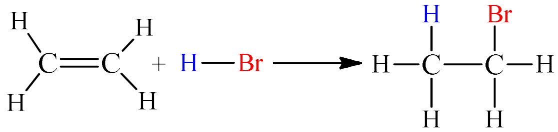
Figure: Energy profile diagram for a two-step electrophilic addition reaction

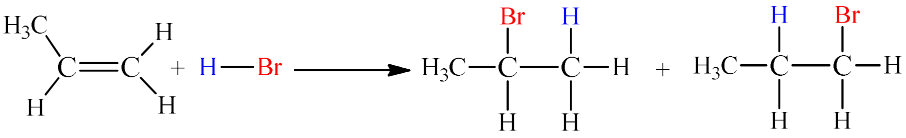
1.3 ADDITION OF HYDROGEN HALIDES TO CARBON-CARBON DOUBLE BOND:

The rate order of hydrogen halides in addition reactions is in the following manner.

HI > HBr > HCl > HF

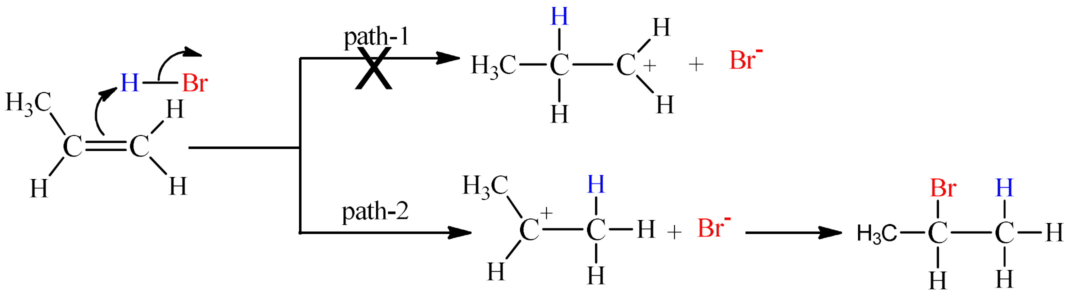
In these addition reactions a carbocation is formed. So, the relative stability of carbocation determines orientation of addition. But in the case of unsymmetrical alkene, HBr can add to the double bond to give two constitutional isomers, but only one is actually formed.





1.4 MARKOVNIKOV'S RULE

It states that the electrophilic addition of HBr across a C=C bond, under polar conditions, the H (of HBr) will add to the carbon of the double bond with the most H's (the least substituent carbon) and the Br will add to the carbon of the double bond that has the most alkyl groups. So, 2-bromopropane is formed predominantly. This can be explained through the following ionic mechanism.



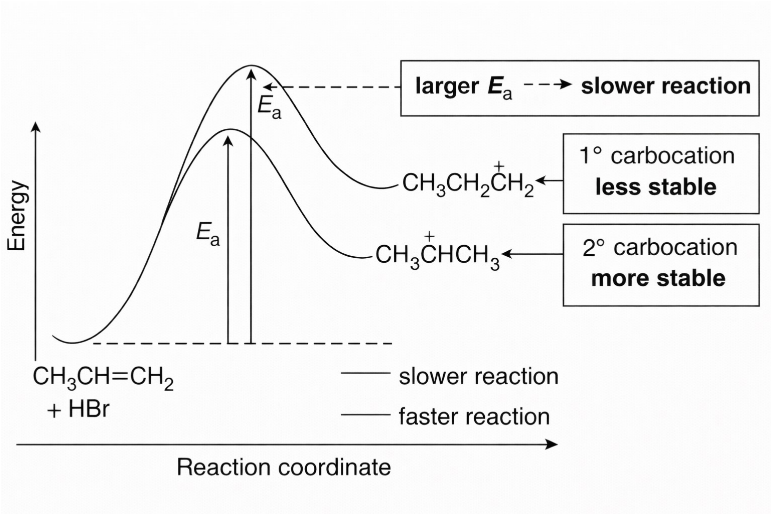
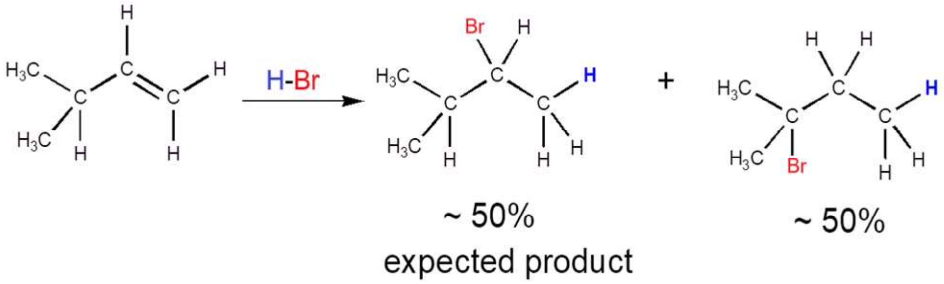
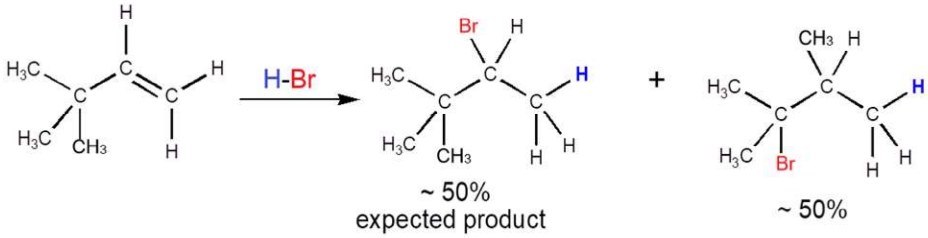


Figure: Energy Profile of HBr addition reaction

Carbocation Rearrangements in Hydrogen Halide Addition to Alkenes - In reactions involving carbocation intermediates, the carbocation may sometimes rearrange if a more stable carbocation can be formed by the rearrangement. These involve hydride and methyl shifts.

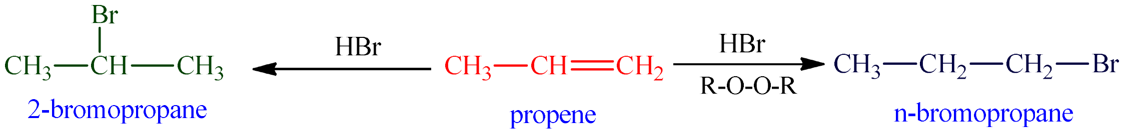




Note that the shifting atom or group moves with its electron pair. A more stable carbocation is formed.

1.5 ANTI-MARKOVNIKOV'S RULE

It has been observed that addition of HBr to propene in the presence of peroxide yields predominenatly 1-bromo propane i.e. the reagent adds on the olefin under this condition in a manner contrary to **Markovnikov's rule.** This phenomenon is known as the peroxide effect or Kharasch effect.



$$\underset{\text{2-bromopropane}}{CH_3-\overset{\overset{Br}{|}}{C}H-CH_3} \xleftarrow{HBr} \underset{\text{propene}}{CH_3-CH=CH_2} \xrightarrow[R\text{-}O\text{-}O\text{-}R]{HBr} \underset{\text{n-bromopropane}}{CH_3-CH_2-CH_2-Br}$$

According this rule, the electrophile adds on the double bonded carbon having less hydrogens (i.e. more substituent carbon) and nucleophile will add to the the carbon of the double bond that has more hydrogen atoms. Hence n-bromopropane is formed majorly. This can be explained on the basis of fact that in the presence of peroxide. The addition takes place via free radical mechanism rather than ionic mechanism.

I. a. $R\text{-}O\text{-}O\text{-}R \xrightarrow{h\nu/\Delta} 2RO^{\bullet}$, b. $RO^{\bullet} + H\text{-}Br \longrightarrow ROH + Br^{\bullet}$

II

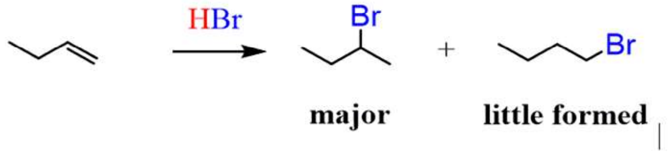
a. $Br^{\bullet} + CH_3\text{—}CH\text{=}CH_2 \longrightarrow CH_3\text{—}\dot{C}H\text{—}CH_2\text{—}Br + CH_3\text{—}\underset{\displaystyle Br}{\underset{|}{CH}}\text{—}\dot{C}H_2$

b. $CH_3\text{—}\dot{C}H\text{—}CH_2\text{—}Br + H\text{-}Br \longrightarrow CH_3\text{—}CH_2\text{—}CH_2\text{—}Br + Br^{\bullet}$

Chain termination occurs by combination of bromine radicals with themselves or with alkyl radicals, or by coupling or disproportionation of alkyl radicals.

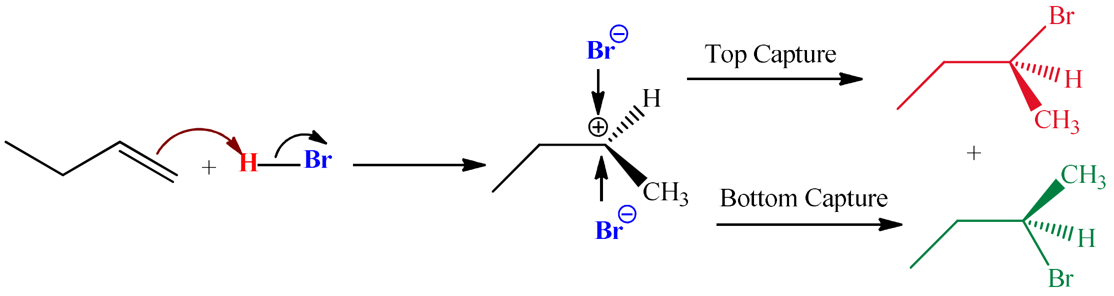
1.6 STEREOCHEMISTRY IN ADDITION REACTION:

In the previous post, we talked about the Markovnikov's rule and learned that **in the addition reaction of HX to an unsymmetrical alkene, the H adds to the carbon that already has the greater number of hydrogen atoms**. Or, looking from the perspective of the X group, we can say that the X atom (or group) adds to the carbon that already has the greater number of carbon atoms.



This is the regiochemistry of the reaction as it shows why one regioisomer (constitutional isomer) is formed preferentially over the other one.

Sometimes the addition to the alkene results in a product with one or two stereo-genic (chirality) centers. The resulting product can be a mixture of stereoisomers which can be enantiomers or diastereomers. Without going too far, let's look at the product in the reaction we just talked about. It has a chirality center and therefore can exist as two enantiomers.



- Notice that the carbon where the '**Br**' had added became a chiral center, therefore we need to address whether it has an *R* or *S* absolute configuration. And the answer is that it actually is a racemic mixture of *R* and *S* enantiomers.

- This is explained by the fact that carbocations are SP^2 hybridized, flat centers (we are talking about the positively charged carbon) and the nucleophilic attack occurs from both sides:
- This attack happens in the same amounts and as a result, a racemic mixture of two enantiomers is obtained.
- To summarize, addition reactions of **alkenes with no stereogenic center** that form a **product with one stereogenic center produce a racemic mixture of enantiomers**.

1.7 SUMMARY:

1) **Addition reactions** involve breaking a π bond and forming two σ bonds.
2) Alkenes undergo addition due to **high reactivity of π electrons**.
3) **Electrophilic addition** proceeds via a **carbocation intermediate**.
4) **Markovnikov's rule** explains regioselectivity in HX addition.
5) **Peroxide effect** leads to **anti-Markovnikov addition of HBr**.
6) Formation of a chiral center often gives a **racemic mixture**.

1.8 SELF-ASSESSMENT QUESTIONS:

1) What is an addition reaction?
2) Why are alkenes reactive toward electrophiles?
3) State Markovnikov's rule.
4) What is the peroxide (Kharasch) effect?
5) What is a carbocation rearrangement?
6) Why do some addition reactions give racemic mixtures?

1.9 TECHNICAL TERMS

1) **Addition reaction** – Reaction involving addition across a multiple bond.
2) **Electrophile** – Electron-deficient species that accepts electrons.
3) **Carbocation** – Positively charged carbon intermediate.
4) **Markovnikov's rule** – Rule predicting regioselectivity of HX addition.
5) **Peroxide effect** – Free-radical addition of HBr opposite to Markovnikov's rule.
6) **Racemic mixture** – Equal mixture of two enantiomers.

1.10 REFERENCE TEXTBOOKS

1) **Morrison and Boyd**, *Organic Chemistry*, Pearson Education.
2) **L. Finar**, *Organic Chemistry, Vol. 1*, Pearson.
3) **T. W. Graham Solomons & C. Fryhle**, *Organic Chemistry*, Wiley.
4) **Peter Sykes**, *A Guidebook to Mechanism in Organic Chemistry*, Pearson.
5) **Clayden, Greeves & Warren**, *Organic Chemistry*, Oxford University Press.
6) **Bahl and Bahl**, *Advanced Organic Chemistry*, S. Chand & Company.

Dr. V. MADHAVA RAO

LESSON – 02

MECHANISM AND STEREOCHEMISTRY OF ALKENE ADDITION REACTIONS

2.0 OBJECTIVES:

After studying this lesson, the student will be able to:

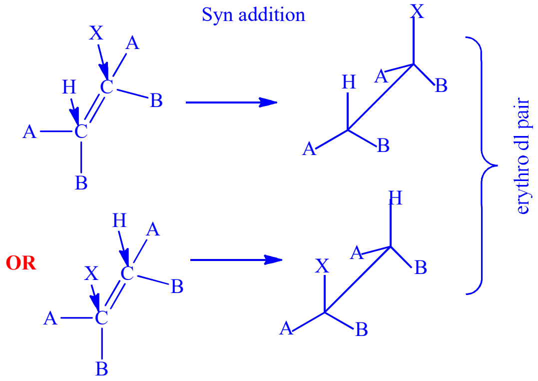
1) **Understand syn and anti-additions** in alkene reactions.
2) **Explain the stereochemical outcome** of addition reactions to cis and trans alkenes.
3) **Describe the mechanism of halogen addition** via halonium ion intermediates.
4) **Explain halohydrin formation** and its regio- and stereochemistry.
5) **Understand acid-catalysed hydration of alkenes** and racemic product formation.

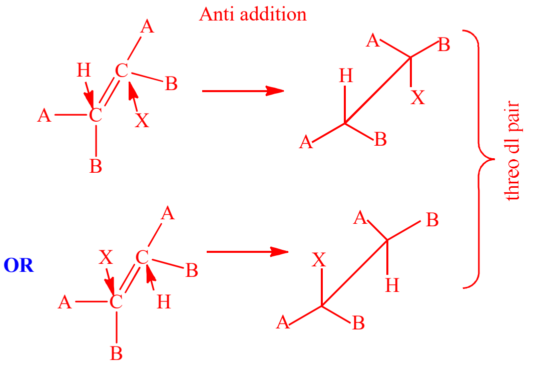
STRUCTURE

2.1 SYN AND ANTI ADDITIONS TO ALKENES

Labeling the addition as “Above” and “Below’ is not scientific and not accurate either as the direction depends on the viewer. **Addition** reactions of **alkenes** will have specific stereochemistry in the finished product. Therefore, a more universal approach is used to describe the stereochemistry of additions to the double bond. When two groups add to the same side of the double bond, it is called a **syn addition** and when they add from different sides, it is an **anti-addition**.

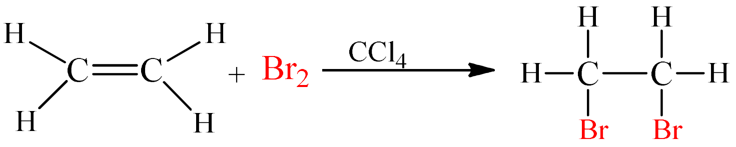
- Addition of H-Br to Alkenes is not Stereo-selective, and gives a roughly equal mixture of “Syn” and “Anti” products.
- Let us consider addition of H-X to the cis and trans isomers of olefin of the form ABC=CBA. We may use the cis olefin as an example. If the addition is syn, the product will be the erythro *dl* pair, because each carbon has 50% chance of being attacked by H^+.
- On the other hand, if the addition is anti, the threo *dl* pair will be formed.
- Of course, the Trans isomer will give the opposite results i.e. the threo pair if the addition is syn and the erythro pair if it is anti.





2.2 ADDITION OF HALOGEN (X_2) TO CARBON-CARBON MULTIPLE BONDS

Most double bonds are easily halogenated with bromine, chlorine or interhalogen compounds. Ethylene reacts with bromine to form ethylene dibromide.



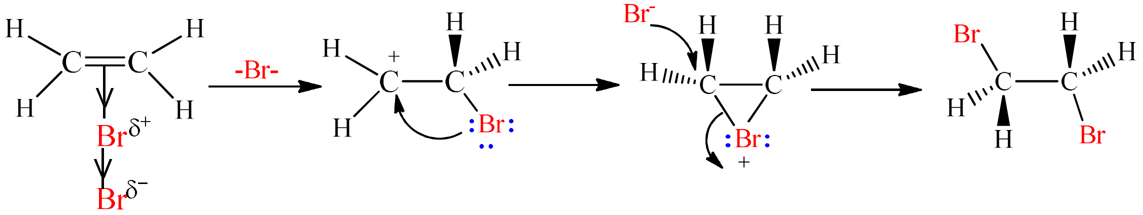
$$H_2C{=}CH_2 + Br_2 \xrightarrow{CCl_4} H\text{-}\underset{Br}{\overset{H}{C}}\text{-}\underset{Br}{\overset{H}{C}}\text{-}H$$

It is not possible to add fluorine directly to alkenes, because the reaction is so exothermic and causing bond fission. Iodination has also been accomplished, but the reaction is slower, however under free radical condition the reaction proceeds more easily. Generally diiodides are unstable and tend to revert to iodine and the olefin.

The above reactions are run in carbon tetrachloride or other solvents non-aqueous / non-alcohol solvents.

Two facts demonstrate that halogenation follows a different mechanism from that of hydrohalogenation or hydration.

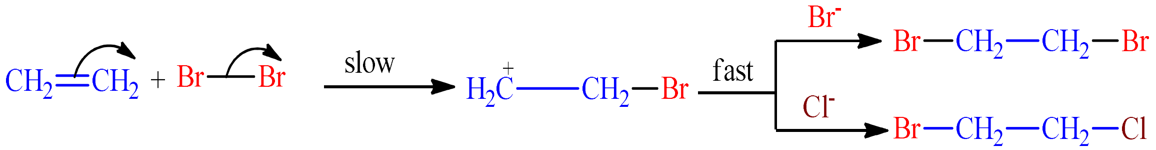
- No rearrangements occur.
- Only anti addition of X_2 is observed.
- These facts suggest that carbocations are not intermediates.



The addition of halogen can take place either by a heterolytic (polar) or a free radical mechanism. The heterolytic mechanism occurs in solution in the absence of light or radicals and is catalyzed by in-organic halides or polar surfaces of reaction vessel. These facts suggest that the reaction occurs by polar mechanism for which consider reaction of ethylene with bromine in aqueous NaCl solution. The products are ethylene dibromide and 1-bromo-2-ethylene, no ethylene dichloride is obtained.

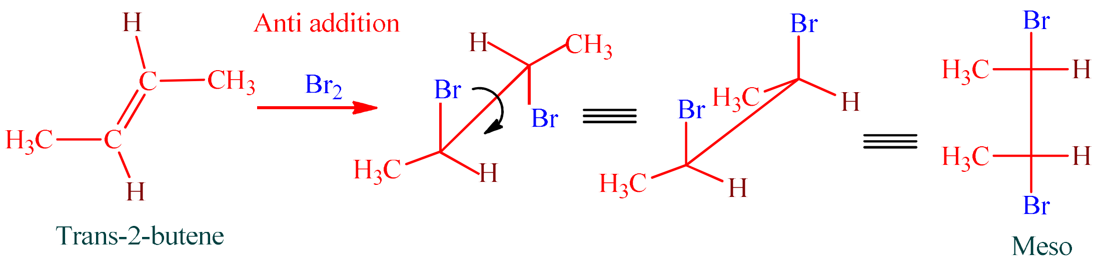
$$CH_2{=}CH_2 + Br_2 \xrightarrow[H_2O]{NaCl} Br{-}CH_2{-}CH_2{-}Br + Br{-}CH_2{-}CH_2{-}Cl$$

This experiment demonstrates that these addition reactions are at least a two-stage process, but does not demonstrate the order of the addition. i.e. whether halogens are electrophilic or nucleophilic reagents. However, with the fact that ethylene does not react with aqueous NaCl in the absence of bromine. This is the strong indication for electrophilic attack by the halogen. A mechanism consistent with these facts is as follows.

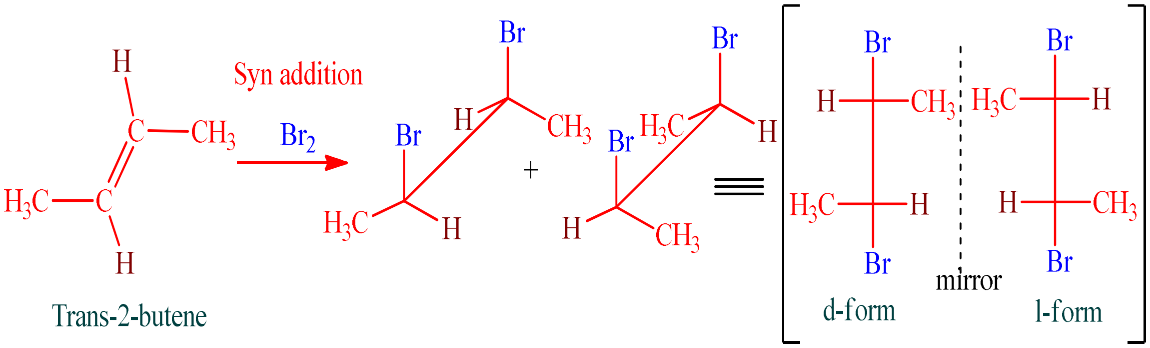


2.3 STEREOCHEMISTRY OF HALOGEN ADDITION TO ALKENES

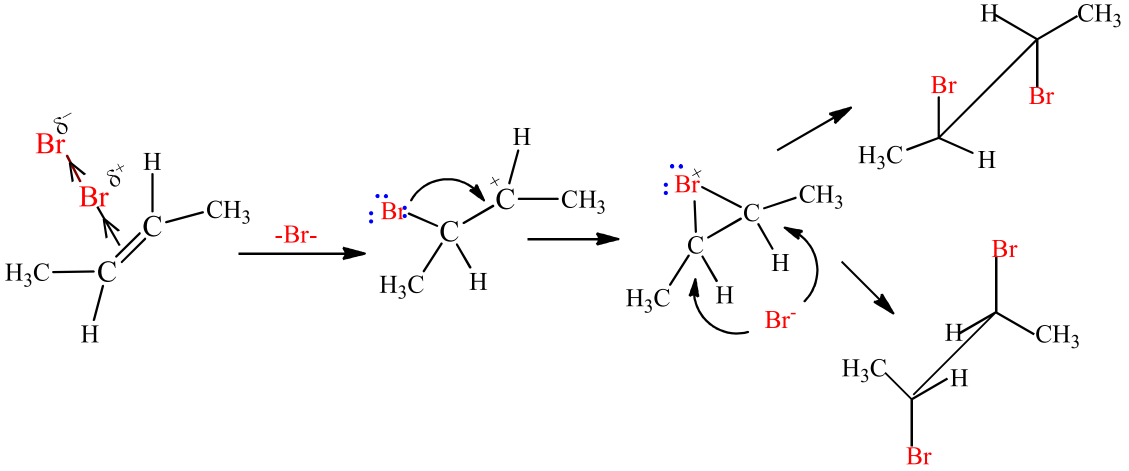
Stereo chemical investigation of halogen addition to alkenes is found in simple alkenes like *Trans* 2-butene with the addition of bromine. The two bromine atoms add on two double bonded carbon atoms from opposite sides of the plane of molecule i.e. Anti-addition.



The product is the symmetrical *meso*-dibromide, whereas if addition had been Syn i.e. both bromine atoms adding from the same side, it would have been the unsymmetrical (±) dibromide.



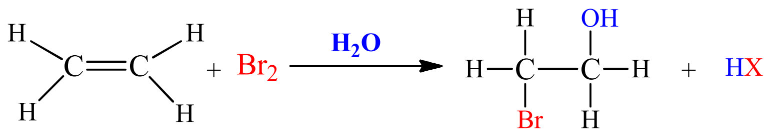
Practically it is observed with trans-2-butene and other acyclic alkenes that the addition is almost completely stereo selective i.e. the addition is 100% Anti. This is true, where it can be explained through the formation of a cyclic bromonium ion which is an alternate canonical form of carbocation. Addition is completed by nucleophilic attack by residual Br^- ion (or other nucleophile like Cl^- or NO_3^- etc.) on either of the original double bonded carbons from the side opposite to the large bromonium ion to yield the *meso* dibromide.



The degree of anti-addition of halogen to alkenes will clearly depends on the cyclic halonium ion intermediate. With increase in the polarity and ion solvating ability of solvent, the anti-product percentage decreases.

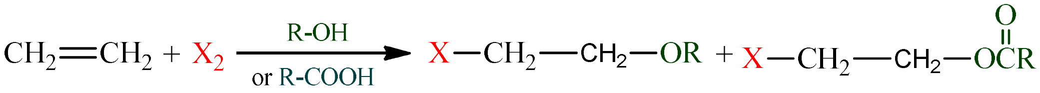
2.4 ADDITION OF HYPOHALOUS ACID (HOX) TO CARBON-CARBON MULTIPLE BONDS

Reaction of alkene with hypohalous acid like HOCl, HOBr etc yields 1,2-haloalcohols, called halohydrins. The reagents (HOCl, HOBr) are often generated in situ by the reaction between water and Cl_2 or Br_2. So, these additions are take place by the reaction of alkene with Br_2/Cl_2 in the presence of water.



The Mechanism of HOX addition is electrophilic with initial attack by a positive halogen end of $\underline{HO \leftarrow X}$ dipole. Following the Markovnikov's rule, the positive halogen goes to the double bonded carbon that has more hydrogens in unsymmetrical alkene. The resulting carbocation reacts with OH^- or H_2O to give the product.

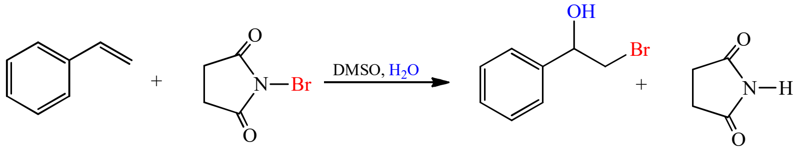
If the substrate is treated with Br_2 or Cl_2 in the presence of alcohol or carboxylic acid as solvent instead of water, it is possible to obtain directly haloalkoxy or halo ester respectively.



$$CH_2{=}CH_2 + X_2 \xrightarrow[\text{or R-COOH}]{\text{R-OH}} X{-}CH_2{-}CH_2{-}OR + X{-}CH_2{-}CH_2{-}O\overset{O}{\overset{\|}{C}}R$$

Hypohalous can also be added to triple bond to give dihalo carbonyl compounds.

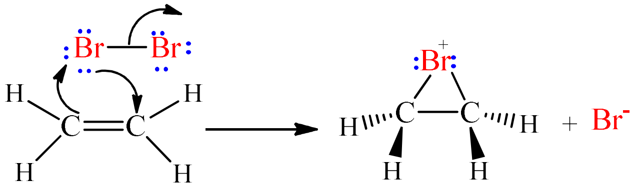
Organic molecules are sparingly soluble in water as solvent. The reaction is often done in a mix of organic solvent and water using N-Bromo succinimide (NBS) as the electrophilic bromine source.



Mechanism:

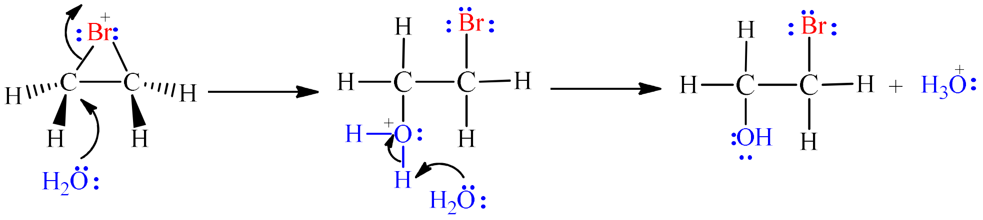
Step-1:

This step is same as for halogen addition to alkene. Two bonds are broken or formed in this step. The electron pair in the *pi* bond and lone pair electrons on the halogen atom are used to form two new C-X bonds. The X-X bond is also cleaved heterolytically, forming X^-. This step is rate determining.



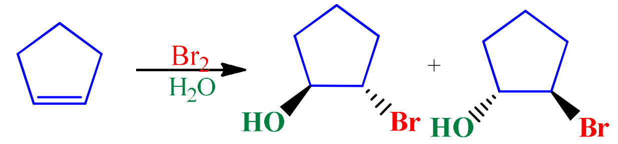
Step-2 & 3:

Nucleophilic attack of H_2O opens the halonium ion ring, forming new C-O bond. Subsequent loss of proton forms a neutral halohydrin.



Anti-Stereochemistry in Halohydrin Formation

Because the bridged halonium ion is opened by backside attack of H_2O, addition of X and OH occurs in an anti-fashion and trans products are formed.



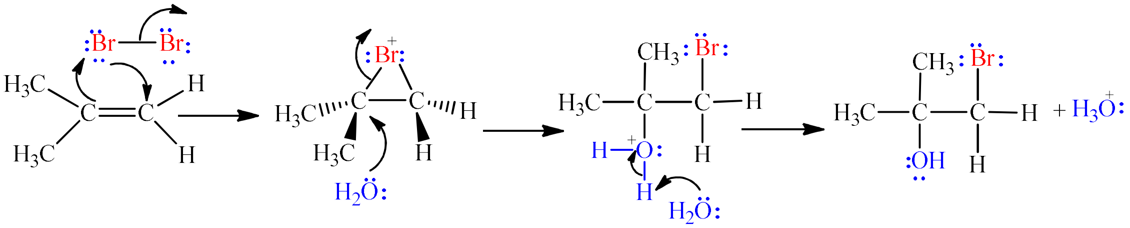
Anti addition of Br & OH

Cyclopentene

Trans Enantiomers

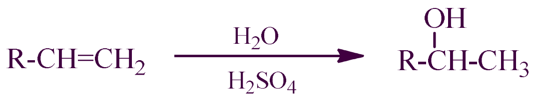
Regiochemistry of Halohydrin Formation:

If alkene is unsymmetrical one, the addition follows Markovnokov's rule. The electrophilic addition takes place at least substituted carbon and nucleophilic attack at more substituted carbon.



2.5 ADDITION OF WATER (H_2O) TO CARBON-CARBON MULTIPLE BONDS:

The addition of H_2O to C=C double bond in the presence of H_2SO_4 is an acid-catalysed hydration reaction that forms an **alcohol**. The reaction follows **Markovnikov's rule,** which states that the hydrogen atom (H) from the water adds to the carbon atom with more hydrogen atoms, and the hydroxyl (OH) group adds to the carbon atom with fewer hydrogen atoms, through the formation of more stable carbocation intermediate.

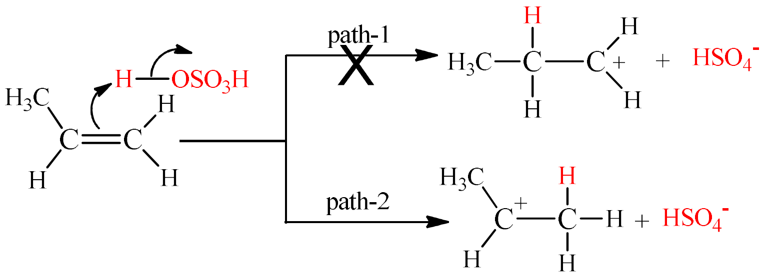


$$\mathrm{R\text{-}CH{=}CH_2} \xrightarrow[H_2SO_4]{H_2O} \mathrm{R\text{-}\overset{OH}{C}H\text{-}CH_3}$$

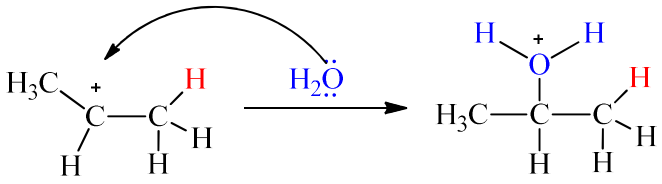
2.5.1 MECHANISM:

i. **Protonation of the alkene**:

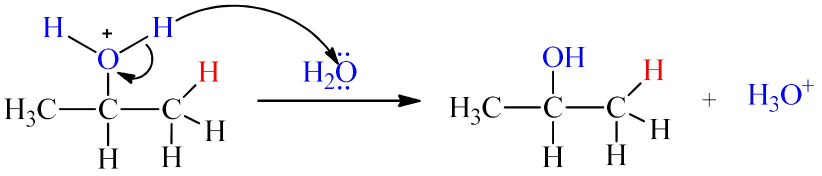
The alkene's double bond attacks a proton (H^+) from the sulphuric acid, forming a carbocation intermediate. The proton adds to the carbon with more hydrogens, leading to a more stable carbocation.



ii. **Nucleophilic attack by water**: A water molecule acts as a nucleophile and attacks the carbocation intermediate.



iii. **De-protonation**: Another water molecule removes a proton from the positively charged oxygen in the intermediate, yielding the neutral alcohol product and regenerating the acid catalyst (H^+).

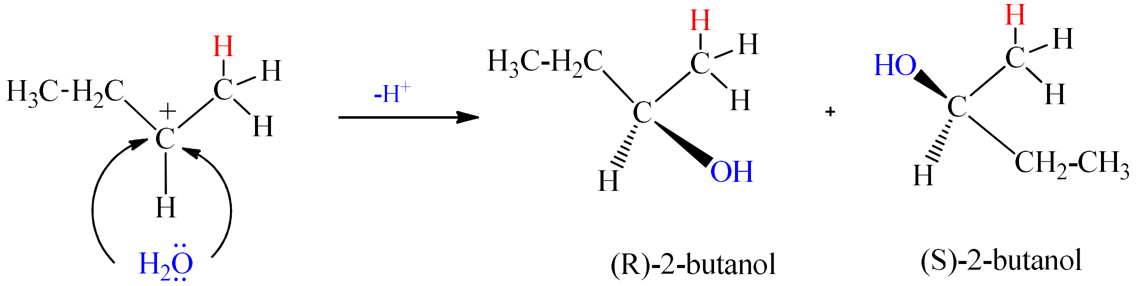


2.5.2 STEREOCHEMISTRY OF HYDRATION:

The addition of H_2O to an alkene in the presence of H_2SO_4 results in a mixture of stereoisomers, because the reaction proceeds through a planar carbocation intermediate, allowing for attack from both faces. The reaction is a two-step process: the acid protonates the alkene and then water attacks the carbocation, following **Markonikov's** rule. Since the carbocation is planar, water can add to either side, leading to a racemic mixture of enantiomers if a new chiral centre is formed.

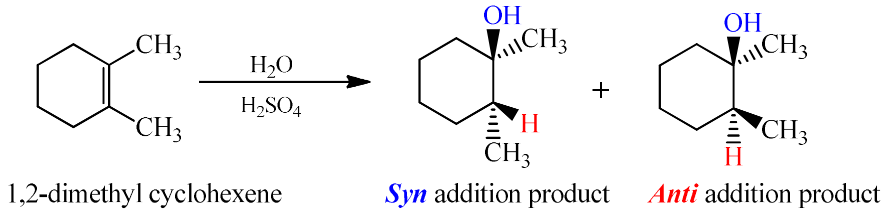
Example:

When 1-butene is reacted with H_2O in the presence of H_2SO_4, the products are a mixture of stereoisomers of 2-butanol. The hydrogen adds to the first carbon, and the OH group adds to the second carbon, but the OH group can be oriented in either direction relative to the rest of the molecule, creating a racemic mixture of (R)-2-butanol and (S)-2-butanol.



Hydration of olefins catalysed by mineral acid is not Stereo selective. The pi bond in alkenes is **flat** and has two faces. So, when addition occurs such that both new bonds to carbon form on the **same** face of the alkene, we call this *syn* addition. When the two bonds are formed on **opposite** faces of the alkene, it is called *anti* addition.

In the example below, the product where C-OH and C-H have added to the same face of the cyclohexane ring ("***syn*-addition**") is formed in about **equal** proportion to the product where C-OH and C-H are formed on opposite faces of the cyclohexane ring ("***anti*-addition**"). Hence Hydration gives roughly equal mixture of ***Syn*** and ***Anti*** addition products.



2.6 SUMMARY:

1) **Syn and anti-additions** describe whether two groups add to the same or opposite faces of a C=C bond.
2) Addition of **HBr to alkenes is not stereoselective**, giving both syn and anti-products.
3) **Halogen addition (X_2)** to alkenes occurs predominantly by **anti-addition** through a **cyclic halonium ion**.
4) **Halohydrin formation (HOX addition)** proceeds by anti-addition and follows **Markovnikov orientation**.
5) **Acid-catalysed hydration of alkenes** occurs via a **carbocation intermediate**.

6) Because carbocations are **planar**, hydration reactions often yield a **racemic mixture of enantiomers**.

2.7 SELF-ASSESSMENT QUESTIONS:

1) What is meant by syn and anti-addition?
2) Why is halogen addition to alkenes anti-stereospecific?
3) What is a halonium ion intermediate?
4) Define halohydrin formation.
5) Why does hydration of alkenes give racemic mixtures?
6) What is the stereochemical outcome of hydration of cycloalkenes?

2.8 TECHNICAL TERMS

1) **Syn addition** – Addition of two groups to the same face of a double bond.
2) **Anti-addition** – Addition of two groups to opposite faces of a double bond.
3) **Halonium ion** – Cyclic intermediate formed during halogen addition to alkenes.
4) **Halohydrin** – 1,2-haloalcohol formed by addition of HOX to an alkene.
5) **Regiochemistry** – Direction in which atoms add to an unsymmetrical double bond.
6) **Racemic mixture** – Equal mixture of two enantiomers.

2.9 REFERENCE TEXTBOOKS

1) **Morrison and Boyd**, *Organic Chemistry*, Pearson Education.
2) **Peter Sykes**, *A Guidebook to Mechanism in Organic Chemistry*, Pearson.
3) **T. W. Graham Solomons & C. Fryhle**, *Organic Chemistry*, Wiley.
4) **I. L. Finar**, *Organic Chemistry, Vol. I*, Pearson.
5) **Clayden, Greeves & Warren**, *Organic Chemistry*, Oxford University Press.

Dr. V. MADHAVA RAO

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LESSON – 03

NUCLEOPHILIC ADDITION REACTIONS OF CARBONYL AND A, B-UNSATURATED COMPOUNDS

3.0 OBJECTIVES:

After studying this lesson, the student will be able to:

1) Understand the **general concept of nucleophilic addition reactions**.
2) Explain the **mechanism and scope of Michael addition reaction**.
3) Describe the **Mannich reaction**, its mechanism under acidic and basic conditions.
4) Understand the **Grignard reaction** as a method for C–C bond formation.
5) Compare the **reactivity of carbonyl compounds** toward nucleophilic addition.
6) Apply **Cram's rule** to predict stereochemical outcomes in carbonyl additions.

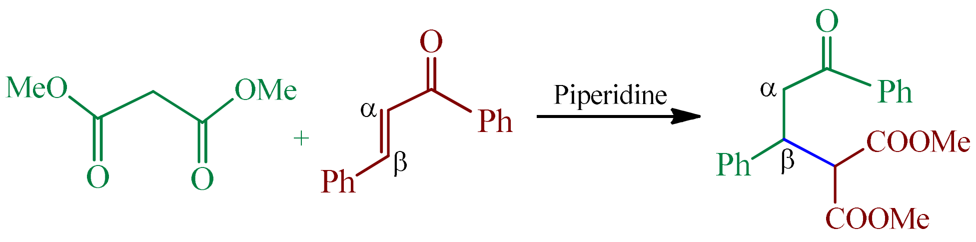
STRUCTURE

3.1 GENERAL INTRODUCTION TO NUCLEOPHILIC ADDITION

Nucleophilic addition reactions involve the attack of an **electron-rich species (nucleophile)** on an **electron-deficient carbon atom**, most commonly the carbon of a **carbonyl group (C=O)** or an **activated carbon–carbon multiple bond**. This initial nucleophilic attack is generally followed by **proton transfer, rearrangement, or substitution steps**, leading to the formation of stable addition products.

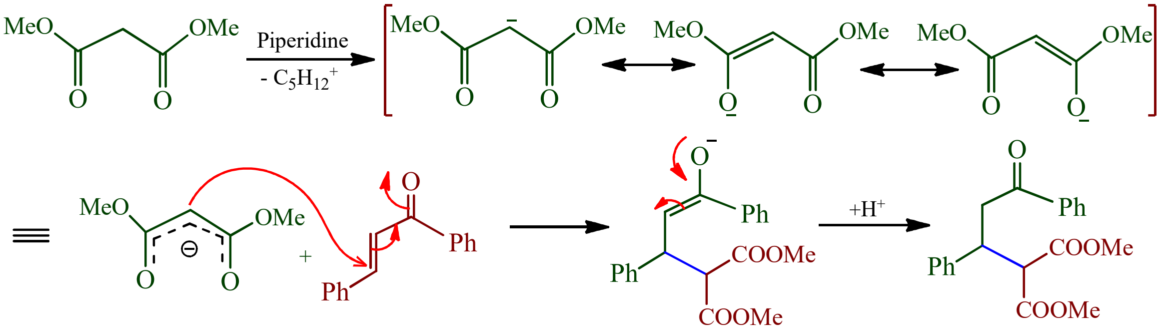
3.2 MICHAEL ADDITION REACTION

The **conjugate addition** of a carbanion, enolate, enamine, or other carbon nucleophile to the β-carbon of an enone, enal, or other α, β-unsaturated compound is called Michael addition reaction. This results in a new carbon-carbon bond at the β-carbon. The **Michael reaction** nucleophile is called the **Michael donor** and electrophile is called the **Michael acceptor.**



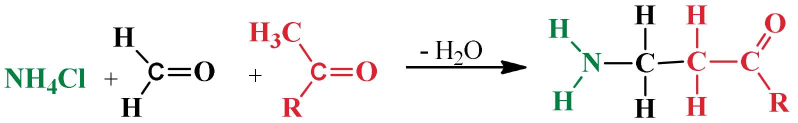
Mechanism:

De-protonation of **di-ketone** by base leads to **carbanion** which stabilized by its electron-withdrawing groups. Three resonance structures can be drawn for this species, two of which have enolate ions. This nucleophile reacts with the electrophilic α,β-unsaturated ketone to form **enolate ion** in a conjugate addition reaction. Proton abstraction from protonated base (or solvent) by the enolate **ion** to **product** is the final step.

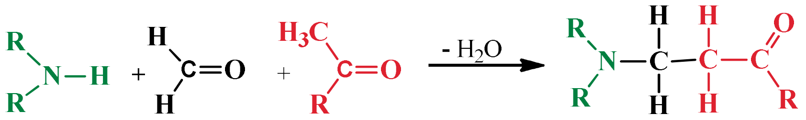


3.3 MANNICH REACTION

The reaction which involves condensation of formaldehyde with ammonia in the form of its salt and a compound containing active hydrogen (carbonyl compounds, nitriles, acetylenes, aliphatic nitro compounds, α-alkyl pyridines or imines etc.) to from a β-amino-carbonyl compound (also known as a Mannich Base) is called Mannich reaction.



In the Mannich reaction, primary or secondary amines are also employed instead of ammonia for the activation of formaldehyde. In that cases n-substituted product is formed.



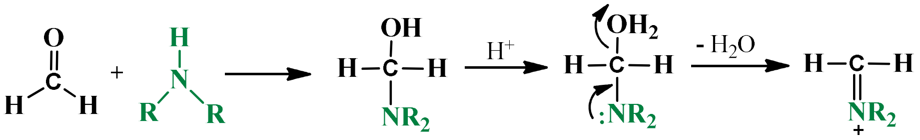
Mechanism:

The reaction proceeds in both media i.e. acidic and basic, hence two mechanisms are proposed to this reaction.

a. Acid catalyzed mechanism: It involves two steps

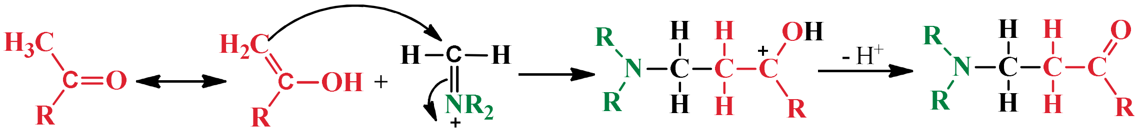
Step – 1

Formaldehyde condenses with amine and forms an addition product.



Step -2

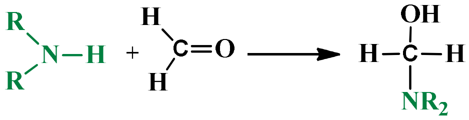
Compound with active hydrogen in enol form attacks the addition product and forms a mannich base.



Base catalyzed mechanism: This mechanism proceeds through three steps.

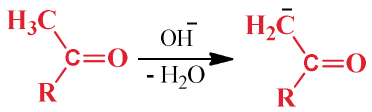
Step-1

Formaldehyde combines with amine and forms addition product.



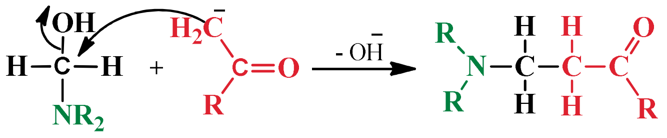
Step – 2

Formation of cabanion in the presence of base.



Step – 3

Carbanion attacks the carbon of addition product and forms mannich base.



3.4 GRIGNARD REACTIONS

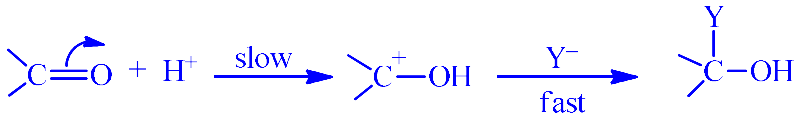
Grignard reactions are a crucial method in organic chemistry for forming new carbon-carbon bonds by reacting Grignard reagents with carbonyl compounds. These reactions are used to synthesize alcohols from aldehydes and ketones, as well as other compounds like carboxylic acids from carbon dioxide and tertiary alcohols from esters. Grignard reagents, which are organ magnesium halides, act as strong nucleophiles that attack the electrophilic carbon in carbonyl groups, followed by an acidic workup to yield the final product.

- The reactions must be carried out under anhydrous conditions to prevent the Grignard reagent from reacting with water, which would destroy it.
- Ethers, like diethyl ether, are used as solvents because they do not have acidic protons, and they also help stabilize the Grignard reagent.

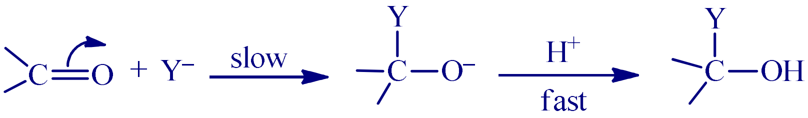
The variation in the electronegativity of carbon and oxygen in C=O group causes migration of π electrons to the more electronegative oxygen atom. So in such cases the bonds strongly polarized.

Thus, the carbonyl group has two active centers, viz a positive center on the carbon atom which can be attacked by nucleophilic reagent, and a negative center on the oxygen atom which will be attacked by electrophilic reagent. So, the addition reaction on a carbonyl group can be theoretically proceeding via two mechanisms.

Mechanism-I:



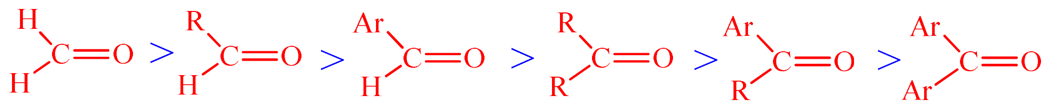
Mechanism-II:



But, since anion is more stable than the cation, the addition to carbonyl group should proceed via mechanism-II, which is further proved by the addition of hydrogen cyanide to carbonyl compounds.

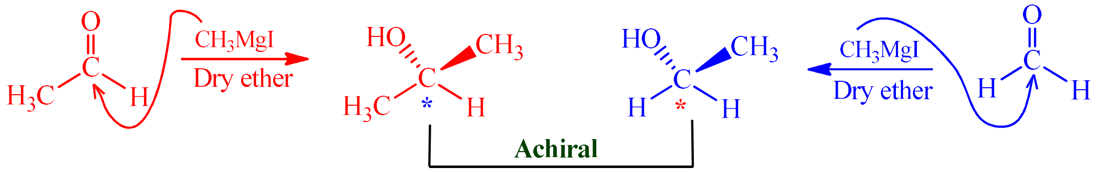
Formaldehyde is more reactive than other aldehydes which intern are more reactive than the ketones. Since the positive charge on the carbonyl carbon can be delocalized over the benzene nucleus in aromatic aldehydes, the latter are less reactive than the aliphatic aldehydes.

The presence of bulky groups in the vicinity of the carbonyl group also retards the addition reactions. The order of reactivity of the carbonyl compounds towards nucleophilic addition is as follows.

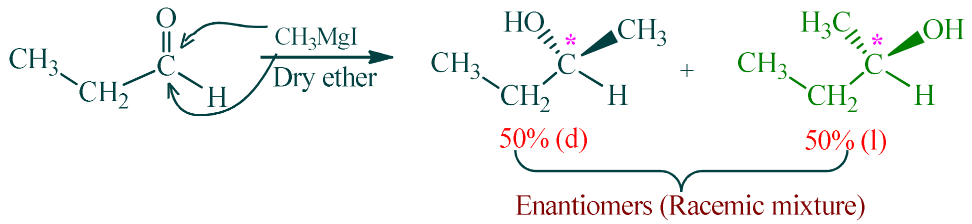


3.5 CRAM'S RULE (STEREOCHEMISTRY IN CARBONYL ADDITION):

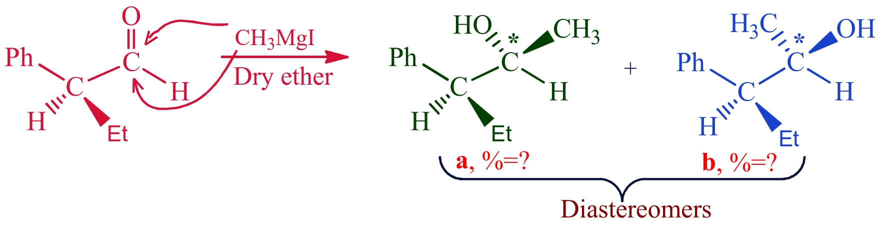
Let us consider the addition of Grignard reagent on formaldehyde or acetaldehyde in dry ether. In this nucleophilic addition reaction, the product is formed with no chiral center. So there is no significance in the addition reaction.



When propionaldehyde is treated with same reagent in dry ether, it yields a product with chiral center which rotates plane polarized light in either direction with same magnitude. So this reaction results in the formation of racemic mixture. Hence this reaction is also insignificant of addition of nucleophile.

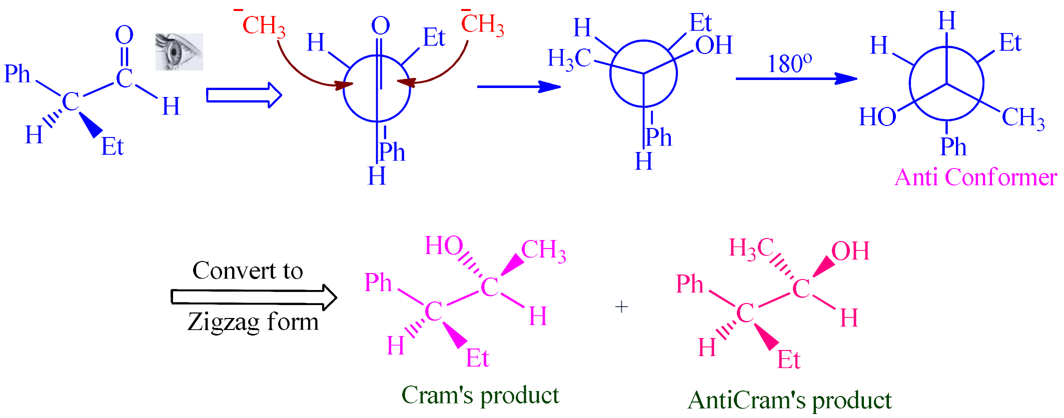


2-Phenybutanaldehyde when treated with methyl magnesium bromide in dry ether, it yields two diastereomers. But the two isomers are not formed in equal amounts as in the case of enantiomers, because here the nucleophilic addition is stereo selective



The formation of ‘a’ or ‘b’ as major product will be decided by Cram’s rule which states the following conditions.

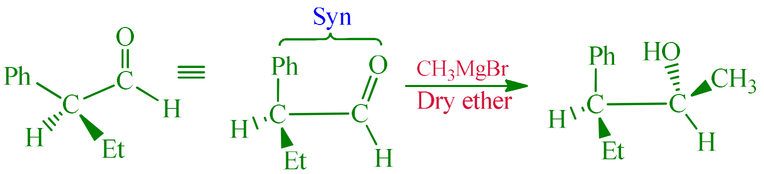
i. There must be chiral center at α-position.
ii. The groups at chiral center should be designate as ‘L’ (large), ‘M’ (medium) and ‘S’ (small).
iii. If the chiral center has group with lone pair electrons, then consider it as large (L) group.
iv. Nucleophilic attack is from less steric hindered side i.e. from the side similar to small group.

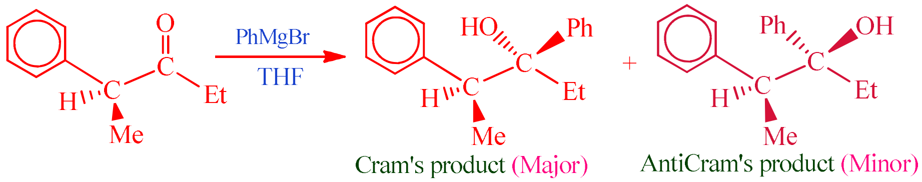


i. Larger group must be anti with respect to carbonyl group.
ii. The carbonyl group should be planked between smaller and medium group.

Attacking of Nu^- from smaller group side gives Cram’s product, from the side of medium group gives Anti Cram’s product, it ‘L’ group is anti to C=O.

The formation of major product can easily be explained in simple way as follows.





i. If the larger group is *Syn* to C=O group, then the attacking of nucleophile takes place the side of medium group.
ii. If the larger group is *Anti* to C=O group, then the attacking of nucleophile takes place the side of smaller group.

3.6 SUMMARY:

1) Nucleophilic addition reactions involve the attack of an electron-rich nucleophile on an electron-deficient carbon, mainly in **carbonyl groups** or **α,β-unsaturated systems**.
2) **Michael addition** is a conjugate (1,4-) addition of stabilized carbanions or related nucleophiles to α, β-unsaturated carbonyl compounds, forming C–C bonds at the β-carbon.
3) **Mannich reaction** is a condensation reaction involving formaldehyde, ammonia or amines, and an active hydrogen compound to yield **β-aminocarbonyl compounds (Mannich bases)**.
4) **Grignard reagents (RMgX)** act as strong nucleophiles and add to carbonyl compounds under anhydrous conditions to form alcohols after acidic work-up.
5) Reactivity toward nucleophilic addition follows the order: **formaldehyde > aliphatic aldehydes > aromatic aldehydes > ketones**, influenced by steric and electronic factors.
6) **Cram's rule** explains stereoselectivity in nucleophilic additions to chiral carbonyl compounds based on steric hindrance and spatial arrangement of substituents.

3.7 TECHNICAL TERMS:

1) **Nucleophile**: An electron-rich species that donates an electron pair.
2) **Carbonyl group**: A functional group containing C=O bond.
3) **Michael donor**: The nucleophile participating in Michael addition.
4) **Michael acceptor**: An α,β-unsaturated compound that accepts the nucleophile.
5) **Enolate ion**: A resonance-stabilized anion formed from carbonyl compounds.
6) **Mannich base**: A β-aminocarbonyl compound formed in Mannich reaction.
7) **Grignard reagent**: Organomagnesium halide (RMgX) used as nucleophile.
8) **Anhydrous conditions**: Reaction conditions free from moisture.
9) **Racemic mixture**: An equimolar mixture of enantiomers.
10) **Diastereomers**: Stereoisomers that are not mirror images.
11) **Cram's product**: Major stereoisomer predicted by Cram's rule.

3.8 SELF-ASSESSMENT QUESTIONS:

1) Define nucleophilic addition reaction with an example.
2) What is Michael addition? Explain the role of Michael donor and acceptor.
3) Describe the mechanism of Michael addition reaction.
4) Explain the Mannich reaction and its significance.
5) Write the acid-catalyzed mechanism of Mannich reaction.
6) What are Grignard reagents? Why must reactions be carried out under anhydrous conditions?
7) Discuss the factors affecting nucleophilic addition to carbonyl compounds.
8) Arrange carbonyl compounds in order of reactivity toward nucleophilic addition.
9) State Cram's rule and its conditions.
10) Differentiate between Cram's product and anti-Cram's product.

3.9 REFERENCE TEXTBOOKS:

1) Morrison, R. T. & Boyd, R. N., **Organic Chemistry**, Pearson Education.
2) Clayden, J., Greeves, N., Warren, S., **Organic Chemistry**, Oxford University Press.
3) Carey, F. A. & Sundberg, R. J., **Advanced Organic Chemistry**, Springer.
4) Solomons, T. W. G., Fryhle, C. B., Snyder, S. A., **Organic Chemistry**, Wiley.
5) March, J., **Advanced Organic Chemistry – Reactions, Mechanisms and Structure**, Wiley.

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LESSON – 04

ADDITION REACTIONS OF ALKENES: EPOXIDATION, HYDROXYLATION, HYDROGENATION AND HYDROBORATION

4.0 OBJECTIVES:

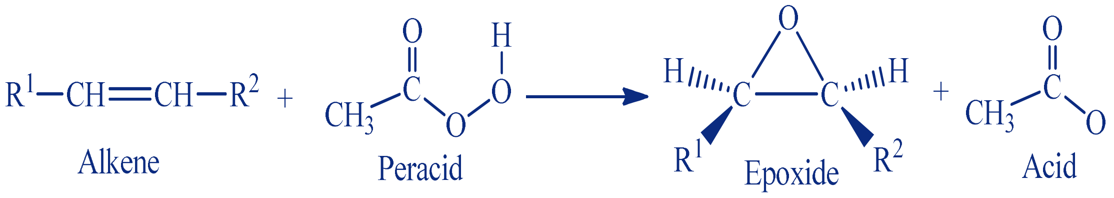
After studying this lesson, the student will be able to:

1) Understand the **formation and structure of epoxides (oxiranes)**.
2) Explain the **methods of preparation of epoxides** and their stereochemistry.
3) Describe the **important reactions of epoxides**.
4) Understand **hydroxylation reactions** and distinguish between syn and anti-additions.
5) Explain **hydrogenation reactions** and the role of catalysts.
6) Understand the **mechanism and applications of hydroboration**.
7) Apply hydroboration reactions for the **synthesis of hydrocarbons, alcohols, and higher alkanes**.

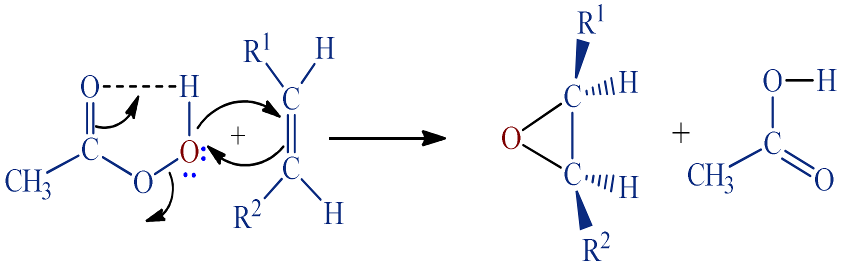
STRUCTURE

4.1 Formation and reactions of Epoxides (Oxiranes):

Three-membered ring, cyclic ethers are known as epoxides or oxiranes. The ring approximates an equilateral triangle, which makes it strained. Hence, these are highly reactive than other ethers. Such compounds are formed by action of per-acids (R-CO_3H) on double of olefin.

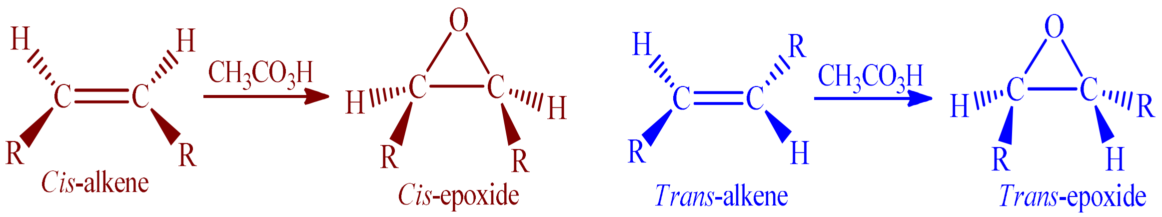


Mechanism:



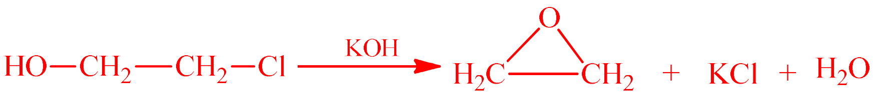
Because both the new C-O bonds are formed on the same side of the alkenes π bond, the geometry of the alkene is reflected in the stereochemistry of the epoxide.

Stereochemistry of the epoxidation of alkenes: syn addition of oxygen. The geometry of the alkene is preserved in the product. *Groups that are trans on the alkene will end up trans on the epoxide product. Groups that are cis on the alkene will end up cis on the epoxide product.*



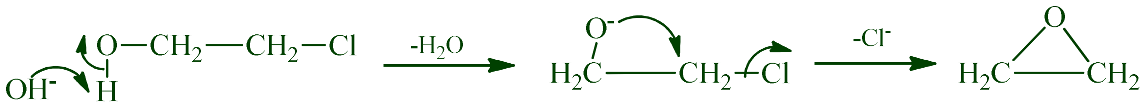
4.1.1 Intramolecular SN^2 substitution:

The compounds halohydrins when treated with strong base (KOH), they can yield epoxides. This method involves dehydro- halogenation. In this case, an alkoxide ion intramolecularly displaces chloride.

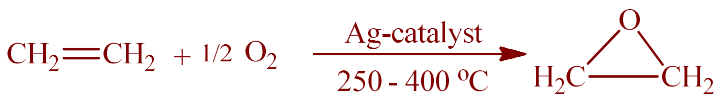


$$HO-CH_2-CH_2-Cl \xrightarrow{KOH} H_2C\overset{O}{-}CH_2 + KCl + H_2O$$

Mechanism:

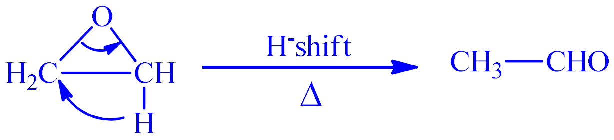


They can also be prepared by the action of oxygen in the presence of silver as catalyst at high temperature.

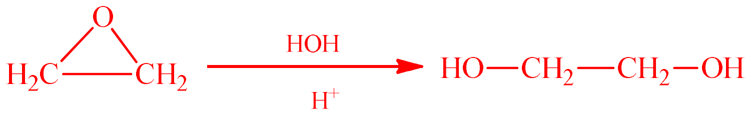


4.2 Reactions of epoxides

1) Ethylene epoxide undergoes molecular rearrangement on heating to form acetaldehyde.

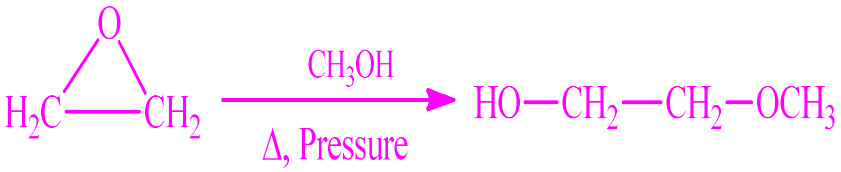


2) Hydrolysis of epoxide in the presence of an acid catalyst generates the glycol.



3) Epoxides are reduced by LiAlH4 to alcohols. Unsymmetrical epoxide giving highly substituted alcohols as main product.

4) Epoxides involve in addition with Alcohols to give monoalkyl ethers of glycols.

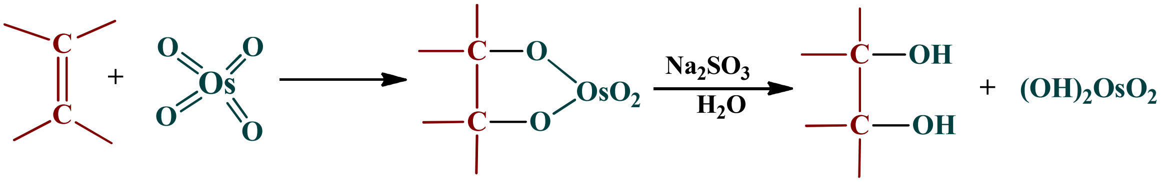


5) They can also add on hydrogen cyanide and yield cyanohydrins.

4.3 Hydroxylation (dihydroxy addition):

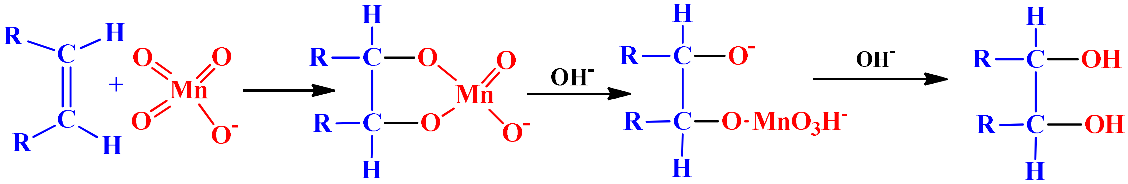
Addition of two -OH groups to alkenes is known as hydroxylation. This reaction results in the formation of 1,2-dihydric alcohols known as glycols. There are many reagents that add two OH groups. Osmium tetroxide, cold alkaline permanganate and per-oxy acids are generally useful for hydroxylation.

When Osmium tetroxide is added to alkene, a cyclic osmium ester is formed as reaction intermediate. It is usually decomposed in solution with sodium sulphite in ethanol or other reagents to yield 1,2-diol or glycol. The chief draw-back of this reaction is that OsO_4 is expensive and highly toxic, so that its use has been limited to small-scale preparations of scares materials.

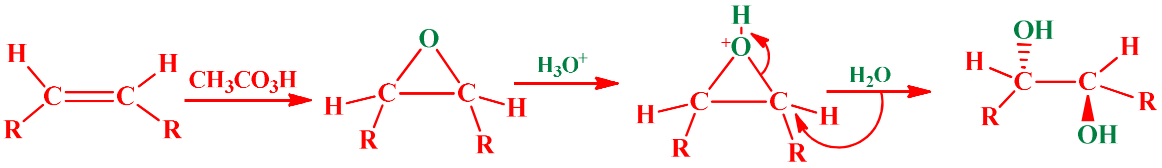


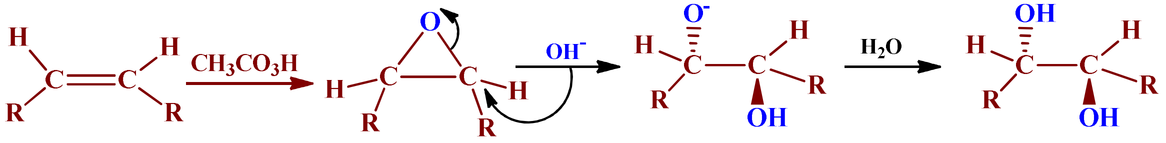
Here the hydroxylation is stereo selectively *Syn* addition.

Alkaline potassium permanganate also effects stereo selective *Syn* addition during hydroxylation. It is used as Bayer's reagent for the identification of unsaturation. This reaction proceeds through the formation of a cyclic permanganate ester. Potassium permanganate is a strong oxidizing agent and can oxidize the glycols that are the products of this reaction. It does so in acid or neutral solution, hence it is not feasible to prepare glycols in this manner. So glycols can be prepared with cold dilute alkaline permanganate.



Per-acids oxidizes alkenes to epoxides by adding an oxygen atom across the double bond. The formed epoxide is more stable and can be isolated. This on further reaction with nucleophile produces 1,2-diol. The epoxide ring can be opened under acid/basic conditions and this is how the **anti-dihydroxylation** is achieved. The acid/base serves as catalyst by converting the oxygen into a better leaving group alcohol.





The osmium tetroxide and alkaline permonganate produces *cis* 1,2-diols by *Syn* addition, whereas peroxides produce *trans* 1,2-diols by *Anti* addition.

4.4 Hydrogenation (catalytic & non-catalytic):

Addition of hydrogen to a carbon-carbon double bond is called “hydrogenation”. The overall effect of such an addition is the reductive removal of the double bond functional group. Regioselectivity is not an issue, since the same group (a hydrogen atom) is bonded to each of the double bond carbons. The simplest source of two hydrogen atoms is molecular hydrogen (H_2), but mixing alkenes with hydrogen does not result in any discernible reaction. Although the overall hydrogenation reaction is exothermic, high activation energy prevents it from taking place under normal conditions. This restriction may be circumvented by the use of a catalyst as shown in the following diagram.

An example of an alkene addition reaction is a process called hydrogenation. In a hydrogenation reaction, two hydrogen atoms are added across the double bond of an alkene, resulting in a saturated alkane. Hydrogenation of a double bond is a thermodynamically favorable reaction because it forms a more stable (lower energy) product. In other words, the energy of the product is lower than the energy of the reactant; thus, it is exothermic (heat is released). The heat released is called the heat of hydrogenation, which is an indicator of

a **molecule’s stability**.

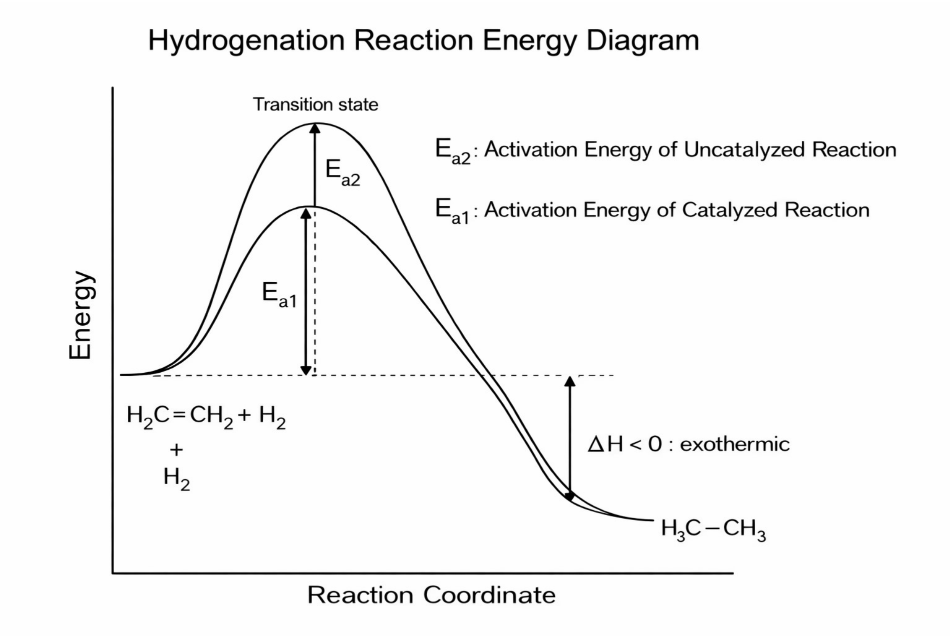
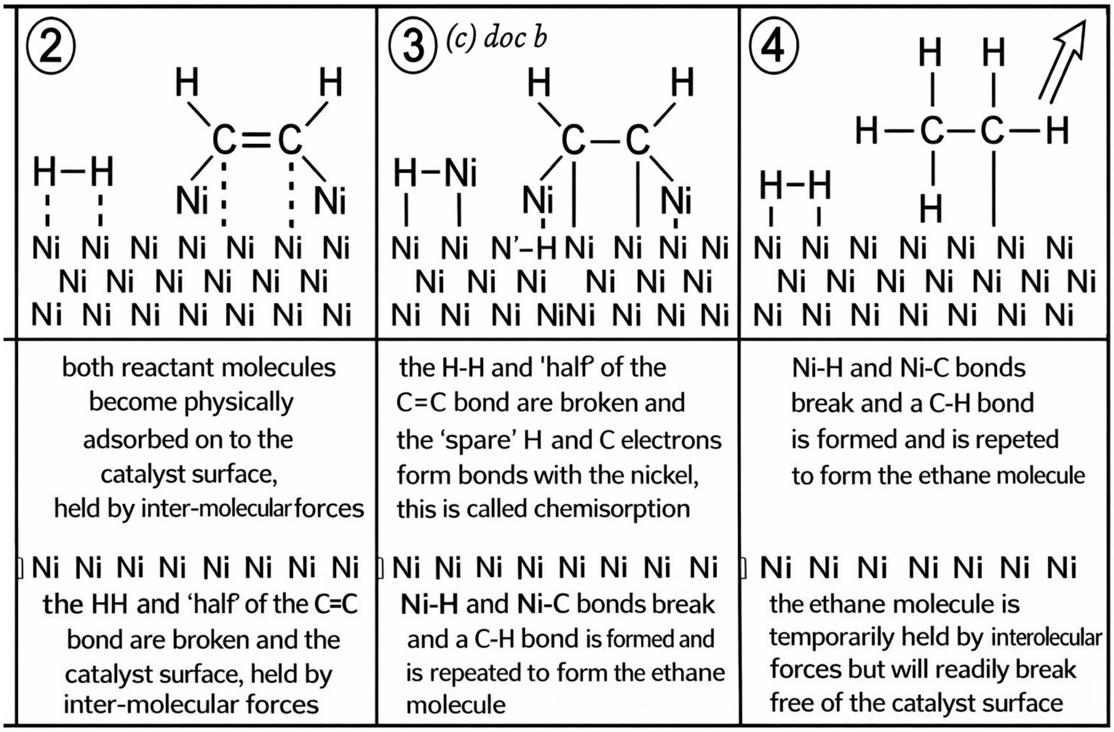


Figure: Energy Diagram of Hydrogenation reaction

Catalysts are substances that change the rate (velocity) of a chemical reaction without being consumed or appearing as part of the product. Catalysts act by lowering the activation energy of reactions, but they do not change the relative potential energy of the reactants and products. Finely divided metals, such as platinum, palladium and nickel, are among the most widely used hydrogenation catalysts.

The function of the catalyst is to lower the activation energy, so that the reaction proceeds rapidly at low temperature (25-150 °C). Finely divided Pt and Pd are effective at room temperature; Nickel on support requires a temperature between 200-300 °C. Raney Nickel is effective at room temperature and atmospheric pressure.

Catalytic hydrogenation takes place in at least two stages, as depicted in the diagram. First, the alkene must be adsorbed on the surface of the catalyst along with some of the hydrogen. Next, two hydrogens shift from the metal surface to the carbons of the double bond, and the resulting saturated hydrocarbon, which is weaklier adsorbed, leaves the catalyst surface.



both reactant molecules become physically adsorbed on to the catalyst surface, held by inter-molecular forces

the H-H and 'half' of the C=C bond are broken and the 'spare' H and C electrons form bonds with the nickel, this is called chemisorption

Ni-H and Ni-C bonds break and a C-H bond is formed and is repeted to form the ethane molecule

the HH and 'half' of the C=C bond are broken and the catalyst surface, held by inter-molecular forces

Ni-H and Ni-C bonds break and a C-H bond is formed and is repeated to form the ethane molecule

the ethane molecule is temporarily held by interolecular forces but will readily break free of the catalyst surface

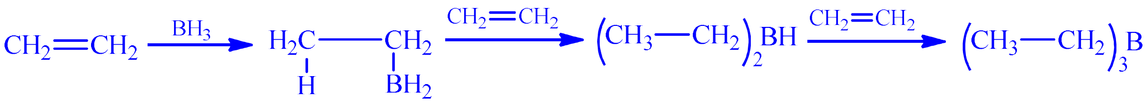
Figure: Catalytic Hydrogenation of Ethene to Ethane

4.5 Hydroboration

Diborane (B_2H_6) readily adds to double bond of olefin at 0-25 °C to form trialkyl borane. This reaction is known as hydroboration.

$$6\ CH_2{=}CH_2 + B_2H_6 \longrightarrow 2\ (CH_3\text{-}CH_2)_3B$$

- Because the alkylborane formed by the reaction with one equivalent of alkene still has two B-H bonds, it can react with two more equivalents of alkene to form a trialkylborane.
- We often draw hydroboration as if addition stopped after one equivalent of alkene reacts with BH_3.
- Instead all three B-H bonds actually react with three equivalents of an alkene to form a trialkylborane.



$$CH_2{=}CH_2 \xrightarrow{BH_3} \underset{H}{H_2C}\text{—}\underset{BH_2}{CH_2} \xrightarrow{CH_2=CH_2} (CH_3\text{—}CH_2)_2BH \xrightarrow{CH_2=CH_2} (CH_3\text{—}CH_2)_3B$$

In the case of an unsymmetrical olefin, the boron atom adds to the carbon having a greater number of hydrogen atoms (i.e. to the least substituted carbon of the double bond) and thus the overall process involves the Anti-markovnikov's rule.

$$\underset{\text{1-butene}}{6\ CH_3\text{-}CH_2\text{-}CH{=}CH_2} + B_2H_6 \longrightarrow \underset{\text{tri-n-butyl borane}}{2\ (CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_2)_3B}$$

The hydroboration reaction is found to be an example of exclusively *cis* addition. This reaction is also proved to be quite general and its importance likes in the fact that the carbon-boron bond in the product can be cleaved by various reagents and converted to a wide variety of useful compounds easily.

4.6 Synthesis of hydrocarbons

When alkyl boranes are treated with a weak aqueous acid, they undergo hydrogenolysis to yield alkanes. This process provides a method for the conversion of alkenes to alkanes without using hydrogen and metal catalyst.

$$\underset{\text{1-butene}}{6\ CH_3\text{-}CH_2\text{-}CH{=}CH_2} + B_2H_6 \longrightarrow \underset{\text{tri-n-butyl borane}}{2\ (CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_2)_3B} \xrightarrow{H_2O/H^+} \underset{\text{n-butane}}{6\ CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_3}$$

4.7 Synthesis of alcohols

Oxidation of alkyl boranes with alkaline hydrogen peroxide provides a general synthesis for primary alcohols. This method involves hydration of alkenes into alcohols according to Anti-Markovnikov's rule.

$$\underset{\text{1-butene}}{6\ CH_3\text{-}CH_2\text{-}CH{=}CH_2} + B_2H_6 \longrightarrow \underset{\text{tri-n-butyl borane}}{2\ (CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_2)_3B} \xrightarrow{H_2O_2/OH^-} \underset{\text{n-butanol}}{6\ CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}OH}$$

4.8 Synthesis of higher alkanes

Treatment of alkylboranes with alkaline silver nitrate solution induces a coupling reaction, and thus affords a route for the synthesis of higher alkanes.

$$\underset{\text{Alkene}}{6\ R\text{-}CH{=}CH_2} + B_2H_6 \longrightarrow \underset{\text{trialkyl borane}}{2\ (R\text{-}CH_2\text{-}CH_2)_3B} \xrightarrow{AgNO_3/OH^-} \underset{\text{Alkane}}{R\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}R}$$

4.9 SUMMARY

1) Epoxides are **three-membered cyclic ethers** with high ring strain and high reactivity.
2) Epoxides are formed by **per-acid oxidation of alkenes** and by **intramolecular SN2 reaction of halohydrins**.
3) Epoxidation occurs by **syn addition**, preserving alkene stereochemistry.
4) Epoxides undergo **rearrangement, hydrolysis, reduction, and nucleophilic ring-opening reactions**.
5) Hydroxylation of alkenes leads to **1,2-diols (glycols)**.
6) **OsO_4 and alkaline $KMnO_4$** give **syn-diols**, while **per-acid followed by ring opening** gives **anti-diols**.
7) Hydrogenation is the **addition of hydrogen to alkenes**, an exothermic reaction requiring a catalyst.
8) **Metal catalysts (Pt, Pd, Ni)** lower activation energy without affecting reaction enthalpy.
9) Hydroboration involves **anti-Markovnikov and syn addition** of boron and hydrogen.
10) Alkyl boranes serve as intermediates for **alkanes, alcohols, and higher alkanes**.

4.10 TECHNICAL TERMS:

1) **Epoxide (Oxirane)**: A three-membered cyclic ether.
2) **Per-acid**: An organic acid containing an extra oxygen used for epoxidation.
3) **Syn addition**: Addition of groups to the same side of a double bond.
4) **Anti-addition**: Addition of groups to opposite sides of a double bond.
5) **Halohydrin**: A compound containing –OH and halogen on adjacent carbons.
6) **Hydroxylation**: Addition of two –OH groups to an alkene.
7) **Glycol**: A 1,2-dihydric alcohol.
8) **Hydrogenation**: Addition of hydrogen across a C=C bond.
9) **Catalyst**: A substance that lowers activation energy without being consumed.
10) **Hydroboration**: Addition of borane to alkenes forming alkyl boranes.
11) **Anti-Markovnikov addition**: Addition where hydrogen attaches to the more substituted carbon.

4.11 SELF-ASSESSMENT QUESTIONS:

1) Define epoxides and explain their reactivity.
2) Describe the mechanism of epoxidation of alkenes.
3) Explain intramolecular SN2 formation of epoxides from halohydrins.
4) Write short notes on reactions of epoxides.
5) What is hydroxylation? Explain syn and anti-hydroxylation.
6) Discuss the role of OsO_4 and $KMnO_4$ in dihydroxylation.
7) Explain catalytic hydrogenation of alkenes.
8) What is the function of a catalyst in hydrogenation?

9) Describe hydroboration and state its stereochemical outcome.
10) Explain the synthesis of alcohols and alkanes using alkyl boranes.

4.12 REFERENCE TEXTBOOKS:

1) Morrison, R. T. & Boyd, R. N., **Organic Chemistry**, Pearson Education.
2) Clayden, J., Greeves, N., Warren, S., **Organic Chemistry**, Oxford University Press.
3) Solomons, T. W. G., Fryhle, C. B., Snyder, S. A., **Organic Chemistry**, Wiley.
4) Carey, F. A. & Sundberg, R. J., **Advanced Organic Chemistry**, Springer.
5) March, J., **Advanced Organic Chemistry – Reactions, Mechanisms and Structure**, Wiley.

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LESSON – 05

ALIPHATIC NUCLEOPHILIC SUBSTITUTION REACTIONS

5.0 OBJECTIVES:

After studying this unit, the learner will be able to:

1) Understand the fundamental concepts of aliphatic nucleophilic substitution reactions.
2) Differentiate clearly between SN_1, SN_2, SN_i, and SET mechanisms.
3) Explain the mechanistic steps, energy profiles, and stereochemical outcomes of SN1 and SN2 reactions.
4) Analyze the effect of substrate structure, nucleophile strength, solvent, and leaving group on reaction pathways.
5) Interpret energy profile diagrams and correlate them with reaction kinetics.
6) Apply theoretical knowledge to predict the reaction mechanism and product formation.

STRUCTURE

5.1 INTRODUCTION TO ALIPHATIC NUCLEOPHILIC SUBSTITUTION REACTIONS

Aliphatic nucleophilic substitution reactions are a fundamental class of organic reactions where a nucleophile replaces a leaving group attached to an aliphatic carbon atom. These reactions are very important because they provide a way to prepare many useful compounds such as alcohols, ethers, amines, and nitriles from alkyl halides.

5.2 MEANING AND DEFINITION OF NUCLEOPHILIC SUBSTITUTION

Nucleophile: A species (ion or molecule) that has a lone pair of electrons and can donate it to an electron-deficient carbon atom. Examples: OH^-, CN^-, NH_3, RO^-.

Leaving group: The atom or group that departs with a pair of electrons. Common examples: Cl^-, Br^-, I^-, and $–OSO_2R$ (tosylate).

General reaction: $R\ \ X + Nu^- \rightarrow R\ \ N$

Here, R–X = alkyl halide (substrate)

Nu^- = nucleophile

X^- = leaving group

5.3 TYPES OF ALIPHATIC NUCLEOPHILIC SUBSTITUTION REACTIONS

A) Nucleophilic Substitution Reactions

These involve the replacement of a leaving group by a nucleophile (a species that donates an electron pair).

a) SN^1 (Unimolecular Nucleophilic Substitution) – takes place in two steps via a carbocation intermediate.

b) SN^2 (Bimolecular Nucleophilic Substitution) – occurs in one step with a simultaneous bond-making and bond-breaking process.

5.3.1. SN^1 (UNIMOLECULAR NUCLEOPHILIC SUBSTITUTION)

The SN^1 reaction stands for Substitution Nucleophilic Unimolecular reaction. It is a type of nucleophilic substitution in which the rate of the reaction depends only on the concentration of the substrate (alkyl halide) and not on the nucleophile.

This reaction is common in compounds that can form stable carbocations, such as tertiary alkyl halides.

Meaning of SN^1

S → Substitution

N → Nucleophilic

1 → Unimolecular (rate depends on one molecule only)

Thus, in an SN1 reaction, the substitution takes place in two steps, and the rate-determining step involves only the substrate.

Mechanism of SN1 Reaction

The SN1 mechanism occurs in two distinct steps:

Step 1: Formation of Carbocation (Slow Step)

The bond between the carbon and the leaving group breaks, forming a carbocation intermediate.

$$R–X \rightarrow R^{+} + X^{-}$$

This step is **slow** and therefore determines the **rate** of the reaction.

Step 2: Attack of Nucleophile (Fast Step)

The nucleophile then attacks the carbocation to form the substituted product.

$$R^{+} + Nu^{-} \rightarrow R–Nu$$

Overall Reaction: $R–X + Nu \rightarrow R–N$

Example: Hydrolysis of tert-Butyl Bromide

$$(CH_3)_3C–Br + H_2O \rightarrow (CH_3)_3C–OH + H^{+} + Br^{-}$$

Step 1: Formation of Carbocation (Slow Step – Rate-Determining)

The C–Br bond undergoes heterolytic cleavage, resulting in the formation of a tert-butyl carbocation and a bromide ion. This bond breaks because bromine acts as an excellent leaving group. The generated carbocation, $(CH_3)_3C^+$, is tertiary and gains significant stability from the +I (inductive) effect of the three methyl groups attached to it.

$$(CH_3)_3C\text{–}Br \xrightarrow{\text{slow}} (CH_3)_3C^+ + Br^-$$

Step 2: Attack of Water Molecule (Fast Step)

The nucleophile (H_2O) attacks the positively charged carbon atom of the carbocation as water donates a lone pair of electrons to it, forming an oxonium ion

$$(CH_3)_3C^+ + H_2O \xrightarrow{\text{fast}} (CH_3)_3C\text{–}OH_2^+$$

Step 3: Deprotonation

The oxonium ion loses a proton (H^+) to form the final alcohol product. The released proton regenerates a neutral water molecule or hydronium ion in the solution, and the final product obtained is tert-butyl alcohol

$$(CH_3)_3C\text{–}OH_2^+ \rightarrow (CH_3)_3C\text{–}OH + H^+$$

Overall reaction $(CH_3)_3C\text{–}Br + H_2O \rightarrow (CH_3)_3C\text{–}OH + H^+$

Energy Profile Diagram for SN1 Reaction

The energy profile of an SN1 reaction shows two distinct steps:

Step-1 The C–X bond breaks heterolytically to form a carbocation and a leavinggroup. This step requires high activation energy.

Step 2 – Nucleophilic Attack (Fast Step):

The nucleophile attacks the carbocation to form the final product. This step has a lower activation energy.

Energy profile diagram for S_N1

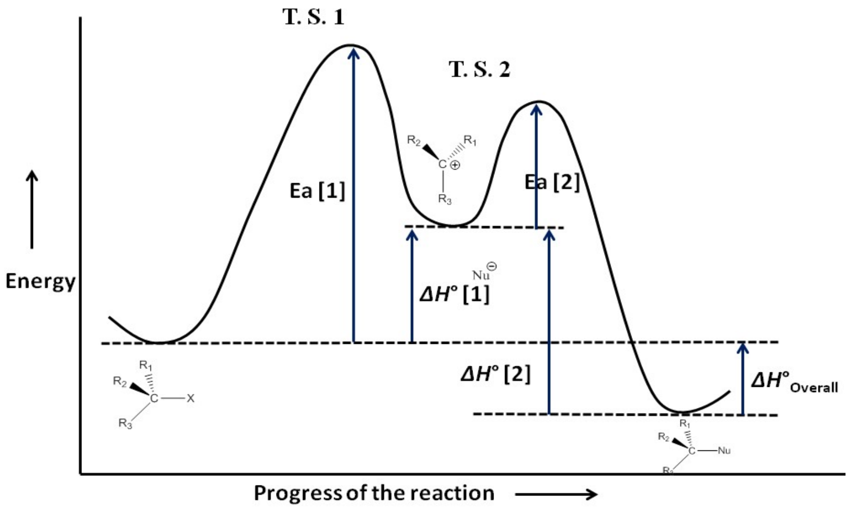
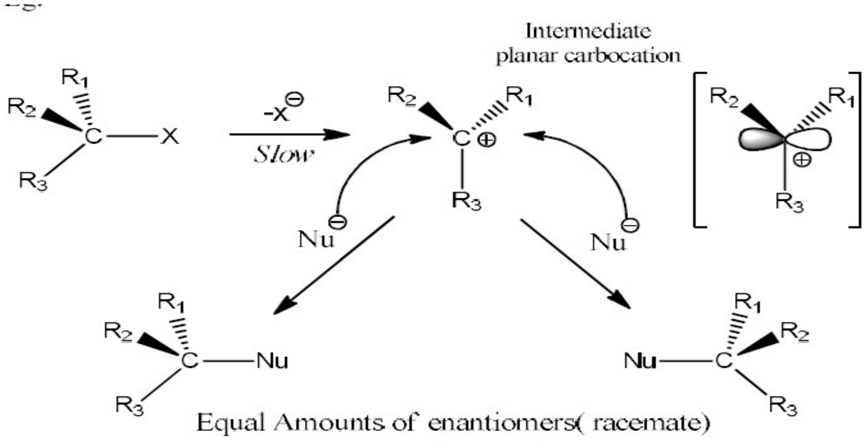


Diagram Description:

- The **y-axis** represents energy, and the **x-axis** represents reaction progress.
- The **first peak** corresponds to the transition state for carbocation formation.
- The **valley** between the two peaks shows the **carbocation intermediate**.
- The **second, smaller peak** represents the nucleophilic attack.
- The reaction ends with the **product** at a lower energy level than the reactants.

Stereochemistry of SN1 Reaction

The carbocation formed in the SN1 reaction is **planar (sp² hybridized)**. Because of this planar structure, the **nucleophile can attack from either side** with equal probability. Attack from both sides produces a **racemic mixture** (equal amounts of R and S enantiomers) if the substrate carbon is chiral.



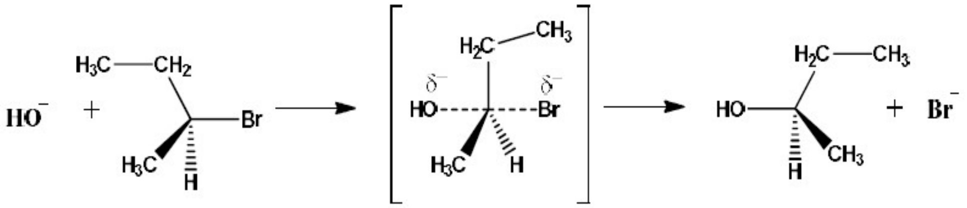
5.3.2 S_N^2 REACTION (BIMOLECULAR NUCLEOPHILIC SUBSTITUTION)

The S_N^2 reaction is a bimolecular nucleophilic substitution reaction. In this reaction, a nucleophile attacks the electrophilic carbon and at the same time, the leavinggroup departs. It takes place in one single step, and both the nucleophile and the substrate are involved in the rate-determining step.

$$\text{Rate} = k[\text{Alkyl halide}][\text{Nucleophile}]$$

Mechanism

The nucleophile attacks the carbon atom bearing the leaving group from the opposite side (backside attack). As the new bond between the nucleophile and carbon forms, the old C–X bond breaks at the same time. There isno intermediate, only a single transition state.



Stereochemistry

- The central carbon is **sp³ hybridized** before and after the reaction.
- During the reaction, it passes through a **planar transition state**.
- The nucleophile attacks from the **backside**, opposite the leaving group. This happens because the leaving group blocks the front side and the backside attack allows better overlap between orbitals.
- This results in **inversion of configuration**, known as **Walden inversion**.
- If the substrate is **chiral**, the product will have the **opposite configuration**.

Transition State of SN^2:

The original starting material was sp3 hybridized but notethat the transition state resembles sp2 hybridization (turned on its side – with thenucleophile, OH, and the group that's leaving, Br, where the perpendicular p orbitalmight once sit). It is this planar geometry and the need to put the other groupsthrough the inversion into this "planar"state that defines what alkyl halides canundergo the SN2 reaction.

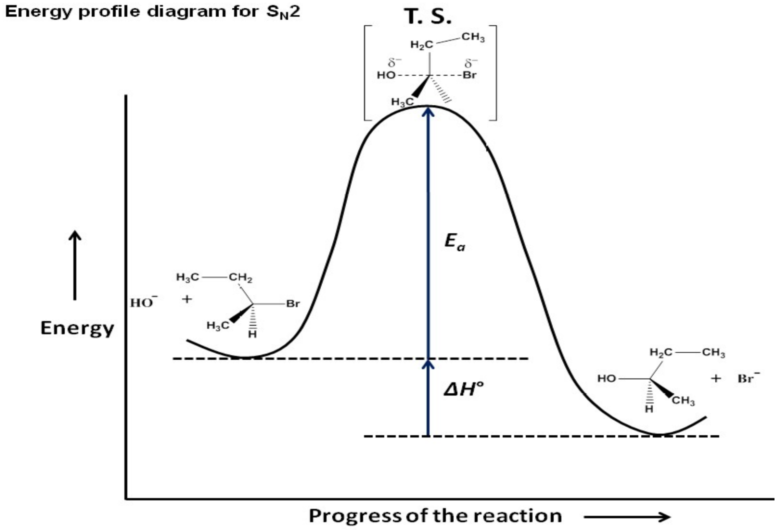
In an SN^2 reaction, a chiral center inverts its configuration (S becomes R or vice versa), while non-chiral centers also undergo inversion though it isn't observable.

Energy profile diagram of SN2 reaction

The energy profile diagram of an SN2 reaction shows how energy changes during the reaction. It is a one-step process with only one transition state. At first, the reactants the alkyl halide and nucleophilehave lower energy. As the reaction begins, the nucleophile attacks the carbon from the backside while the leaving group starts to leave, causing the energy to rise.

At the top of the curve is the transition state, where both the old and new bonds are partially formed. This state has the highest energy and is very unstable. The activation energy (Ea) is the energy needed to reach this point.

After the transition state, the energy drops as the products form, which are more stable than the reactants. The overall energy change (ΔH°) is usually negative, meaning the SN2 reaction is generally exothermic, releasing energy.



5.4 COMPARISON BETWEEN SN1 AND SN2 REACTIONS

Feature	SN1 Reaction	SN2 Reaction
Meaning	Substitution Nucleophilic Unimolecular	SubstitutionNucleophilic Bimolecular
Mechanism	Two-stepprocess (carbocationintermediate formed)	One-step process (simultaneous bond breaking and forming)
Rate Equation	Rate = k [R–X]	Rate = k [R–X][Nu^-]
Rate-Determining Step	Formation of carbocation	Attack of nucleophile and departure of leaving group (together)
Molecularity	Unimolecular	Bimolecular

Substrate Reactivity	3° > 2° > 1° > CH_3X	CH_3X > 1° > 2° > 3°
Carbocation Formation	Yes	No
Stereochemistry	Racemization (mixture of R and S)	Inversion of configuration (Walden inversion)
Type of Solvent	Polar protic (e.g., water, alcohol)	Polaraprotic (e.g., acetone, DMSO)
Nucleophile Strength	Weak nucleophile sufficient	Strong nucleophile required
Leaving Group	Good leaving group important	Good leaving group important
Example	Hydrolysis of tert-butyl bromide	Reaction of methyl bromide with hydroxide ion

5.5 MIXED SN1 AND SN2 REACTIONS

Some reactions under a given set of conditions proceed via the SN2 mechanism, while others follow the SN1 mechanism. However, in certain cases, it is difficult to clearly determine the mechanistic pathway, as such reactions do not strictly follow either a pure SN1 or a pure SN2 mechanism. To explain the behavior of these reactions, several theories were proposed. One such explanation was given by **Sneen**, known as the Intermediate Ion-Pair Mechanism Theory.

According to this theory, both SN1 and SN2 reactions can be described by a common ion-pair mechanism. In this mechanism, the formation of the ion pair (rate constant k_1) is the rate-determining step in an SN1 reaction, whereas the destruction of the ion pair (rate constant k_2) is the rate-determining step in an SN2 reaction.

When the rates of ion-pair formation and destruction are of the same order of magnitude, the reaction exhibits borderline behavior and is said to follow a mixed or simultaneous SN1–SN2 mechanism

5.6 INTRODUCTION TO S_N^I MECHANISM

The S_N^i mechanism stands for Substitution Nucleophilic Internal. It is a special type of nucleophilic substitution reaction in which the nucleophile attacks from the same side as the leaving group — hence the term *internal substitution*.

This mechanism is commonly observed in the conversion of alcohols to alkyl halides using reagents like thionyl chloride ($SOCl_2$), thionyl bromide ($SOBr_2$), or phosphorus halides in the presence of a base (like pyridine).

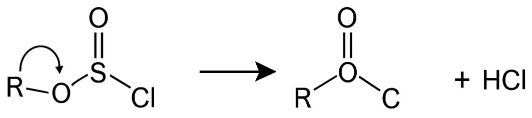
Unlike the SN1 and SN2 mechanisms, the S_{Ni} mechanism proceeds through the formation of an intimate ion pair (not a free carbocation) and leads to retention of configuration at the reacting carbon atom.

Mechanism of SN^{i}Reaction

Example: $R–OH + SOCl_2 \rightarrow R–Cl + SO_2$

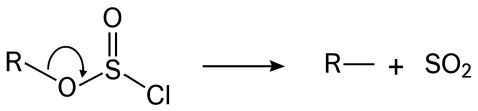
Step 1: Formation of alkyl chlorosulfite intermediate

The alcohol reacts with thionyl chloride to form alkyl chlorosulfite (RO–SOCl).



Step 2: Internal substitution SN^i

The lone pair on the chlorine atom in the same molecule attacks the carbon atom bonded to oxygen.At the same time, the –OSO group leaves, producing R–Cl and releasing SO_2 gas



This internal attack causes retention of configuration at the carbon center, because the nucleophile approaches from the same side as the leaving group.

5.7 SET MECHANISM

In some nucleophilic substitution reactions, radicals or radical ions are involved instead of purely ionic intermediates. The first step in such reactions involves the transfer of a single electron from the nucleophile to the substrate, leading to the formation of a radical anion.

The mechanism in which this type of electron transfer occurs is known as the Single Electron Transfer (SET) mechanism.

In the second step, the radical anion undergoes cleavage, forming products either through reaction with a neutral radical ($Nu\cdot$) or a nucleophilic ion (Nu^-), depending on the reaction conditions.

Thus, the SET pathway represents a non-classical nucleophilic substitution mechanism involving electron transfer and radical intermediates.

Example: Reaction of Sodium Naphthalide with Alkyl Halide

$$R–X + Na^{+}[C_{10}H_{8}]^{-} \rightarrow R\cdot + X^{-} + [C_{10}H_{8}]$$

Step1:

A single electron is transferred from sodium naphthalide (the nucleophile) to the alkyl halide (R–X), forming a radical anion:

$$R–X + e^{-} \rightarrow [R–X]^{\cdot -}$$

Step2:

The radical anion undergoes bond cleavage to give an alkyl radical (R·) and a halide ion (X^-).

Step3:

The alkyl radical then reacts with another electron donor (or another molecule) to form the final product, often an alkane or coupled product.

$$2R\cdot \rightarrow R–R$$

5.8 SUMMARY

Aliphatic nucleophilic substitution reactions play a crucial role in organic synthesis by enabling the replacement of a leaving group with a nucleophile. These reactions primarily occur through SN^1 and SN^2 mechanisms, depending on substrate structure, nucleophile strength, solvent nature, and stability of intermediates.

The SN^1 mechanism proceeds through a carbocation intermediate and results in racemization due to planar geometry, whereas the SN^2 mechanism occurs in a single step with backside attack, leading to inversion of configuration. Energy profile diagrams clearly explain the energy requirements and transition states involved in both mechanisms.

In addition to classical mechanisms, **mixed SN^1–SN^2 behavior**, **SN^i reactions**, and **SET mechanisms** highlight the complexity and diversity of substitution reactions. Understanding these mechanisms helps in predicting reaction outcomes and selecting suitable reaction conditions in organic synthesis.

5.9 SELF-ASSESSMENT QUESTIONS

1) Define nucleophilic substitution reaction with an example.
2) Explain the mechanism of the SN1 reaction with a neat diagram.
3) Why do tertiary alkyl halides favor SN1 reactions?
4) Describe the SN2 mechanism and explain why inversion of configuration occurs.
5) Compare SN1 and SN2 reactions based on kinetics, stereochemistry, and solvent effects.
6) What is meant by racemization? How does it occur in SN1 reactions?
7) Explain the concept of the SNi mechanism with an example.
8) What is the SET mechanism? How does it differ from SN1 and SN2 mechanisms?
9) Draw and explain the energy profile diagrams of SN1 and SN2 reactions.
10) Predict the mechanism for a given alkyl halide under specified conditions.

5.10 TECHNICAL TERMS

1) **Nucleophile** – An electron-rich species that donates an electron pair.
2) **Leaving Group** – An atom or group that departs with a pair of electrons.
3) **Carbocation** – A positively charged carbon intermediate.
4) **Transition State** – A high-energy unstable arrangement during a reaction.
5) **Activation Energy** – Minimum energy required for a reaction to occur.
6) **Racemization** – Formation of equal amounts of enantiomers.
7) **Walden Inversion** – Inversion of configuration during SN2 reactions.
8) **Ion Pair** – Closely associated charged species formed during reaction.
9) **SNi Mechanism** – Substitution Nucleophilic Internal mechanism with retention of configuration.
10) **SET Mechanism** – Single Electron Transfer mechanism involving radicals.

5.11 REFERENCE BOOKS

1) Morrison, R. T., & Boyd, R. N., *Organic Chemistry*, Pearson Education.
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LESSON – 06

FACTORS INFLUENCING NUCLEOPHILIC SUBSTITUTION REACTIONS

6.0 OBJECTIVES

1) To understand the factors influencing nucleophilic substitution reactions
2) To explain how substrate structure affects SN1 and SN2 reactions.
3) To study the role of nucleophile strength and leaving group ability in substitution reactions.
4) To understand the effect of solvent and temperature on reaction rate.
5) To differentiate between factors affecting SN1 and SN2 mechanisms.
6) To apply these concepts to predict reaction rate and mechanism.

STRUCTURE

6.1 INTRODUCTION TO FACTORS INFLUENCING NUCLEOPHILIC SUBSTITUTION REACTIONS

Nucleophilic substitution reactions are among the most important types of organic reactions, where a nucleophile replaces a leaving group in a substrate. The rate and mechanism of these reactions — whether they proceed by SN1, SN2, or a mixed pathway depend on several factors that affect the stability of intermediates, the strength of the nucleophile, and the reactivity of the substrate.

These factors determine how easily the nucleophile can attack the substrate and how readily the leaving group departs.
The major factors influencing nucleophilic substitution reactions include:

1) Nature of the substrate (alkyl halide type)
2) Strength and concentration of the nucleophile
3) Nature of the leaving group
4) Solvent effects
5) Temperature and reaction conditions

Understanding these factors helps in predicting the reaction rate, mechanism, and product formation in nucleophilic substitution processes.

6.2 FACTORS AFFECTING SN1 REACTIONS

Some of the factor which can affect the SN^1 reaction are given below:

6.2.1 NATURE OF SUBSTRATE:

For an SN1 reaction, the reactant should be capable of forming a stable carbocation intermediate. The rate of the SN^1 reaction depends on the stability of this carbocation. Hence, the reactivity order of alkyl halides in SN1 reactions follows the stability of their corresponding carbocations.

Stability of carbocation: $(CH3)_3C^+ > (CH3)_2CH^+ > CH_3CH_2^+ > CH3^+$

6.2.2 NATURE OF LEAVING GROUP:

The efficiency of the SN^1 reaction depends on how easily the leaving group can depart with its electron pair. A good leaving group stabilizes the negative charge formed after leaving, which increases the reaction rate.

Order of leaving group ability: $I \; > Br \; > Cl \; > F$

Example: $(CH_3)_3CBr > (CH$

Tert-butyl bromide reacts faster than tert-butyl chloride because bromide ion (Br^-) leaves more easily than chloride ion (Cl^-).

6.2.3 SOLVENT EFFECT:

Polar protic solvents, such as water and alcohols, stabilize both the carbo cation intermediate and the leaving group through solvation. This stabilization favors the SN1 mechanism and increases the reaction rate.

Rate: Polar protic solvents > Non-polar solvents

Example:

Ethanol or water increases the rate of the SN^1 reaction compared to non-polar solvents like hexane.

6.2.4 TEMPERATURE:

An increase in temperature provides the necessary energy to break the C–X bond, thereby increasing the rate of the SN1 reaction.

Example: The hydrolysis of tert-butyl bromide in water occurs faster at highertemperatures.

6.2.5 CARBOCATION STABILITY (RESONANCE/INDUCTIVE EFFECTS):

Carbocations that are stabilized by resonance or inductive effects form more easily, which increases the rate of the SN1 reaction. Greater carbocation stability leads to faster reaction rates.

Stability order: Allyl or Benzyl carbocation > Tertiary > Secondary > Primary > Methyl

6.3 FACTORS INFLUENCING SN^2 REACTION

6.3.1 STRENGTH OF NUCLEOPHILE:

The SN^2 reaction rate depends directly on how strong the nucleophile is. A strong nucleophile donates its electron pair quickly to the carbon atom, speeding up the reaction. Negatively charged nucleophiles are generally stronger than neutral ones.

Example:

Hydroxide ion (OH^-) reacts faster than water (H_2O) with alkyl halides because it is more reactive.

6.3.2 NATURE OF SUBSTRATE (ALKYL HALIDE):

The reactivity of the substrate depends on steric hindrance around the carbon atom. The more crowded the carbon, the slower the reaction. The order of reactivity is:

Methyl halide > Primary (1°) > Secondary (2°) > Tertiary (3°).

Tertiary halides rarely undergo SN2 reactions because the nucleophile cannot easily approach the central carbon.

Example: Methyl bromide reacts faster than isopropyl bromide.

6.3.3 LEAVING GROUP:

A good leaving group helps the reaction proceed faster by leaving easily with the bonding electrons. The better the leaving group, the more stable it is after departure.
The order of leaving group ability is:

$$\mathbf{I^{-} > Br^{-} > Cl^{-} > F^{-}}.$$

Example: Methyl iodide (CH_3I) reacts faster than methyl bromide (CH_3Br).

6.3.4 SOLVENT EFFECT:

SN2 reactions are favored in polar aprotic solvents because these solvents do not strongly solvate anions, keeping the nucleophile free and reactive. Common polar aprotic solvents are acetone, dimethyl sulfoxide (DMSO), dimethylformamide (DMF).

Example: The reaction of CH_3Br with CN^- is much faster in DMSO than in water.

6.3.5 TEMPERATURE:

Higher temperature increases the kinetic energy of molecules, leading to more frequent and effective collisions between the nucleophile and substrate, thus increasing the rate of reaction.

Example: The substitution of bromoethane by hydroxide ion (OH^-) proceeds faster at higher temperatures.

6.4 SUMMARY

Nucleophilic substitution reactions are strongly influenced by several factors that determine the reaction rate and mechanism. In **SN1 reactions**, the stability of the carbocation intermediate plays a crucial role. Tertiary carbocations react faster due to greater stability, while polar protic solvents enhance the reaction by stabilizing ions. A good leaving group and higher temperature further accelerate the reaction.

In **SN2 reactions**, the strength of the nucleophile and steric hindrance around the substrate are key controlling factors. Less substituted substrates favor SN2 reactions, while polar aprotic solvents increase nucleophilicity. Strong nucleophiles and good leaving groups significantly enhance the reaction rate.

Understanding these factors helps in predicting whether a reaction will proceed via SN1 or SN2 mechanism and allows better control over reaction conditions in organic synthesis.

6.5 SELF-ASSESSMENT QUESTIONS

1) What are the main factors influencing nucleophilic substitution reactions?
2) Explain the effect of substrate structure on SN1 reactions.
3) Why do tertiary alkyl halides favor SN1 reactions?
4) Discuss the role of solvents in SN1 reactions with examples.
5) Explain how nucleophile strength affects the SN2 reaction rate.
6) Why are tertiary alkyl halides unsuitable for SN2 reactions?
7) Explain the effect of leaving group ability on SN1 and SN2 reactions.
8) How does temperature influence nucleophilic substitution reactions?
9) Compare the factors affecting SN1 and SN2 reactions.

6.6 TECHNICAL TERMS

1) **Nucleophile** – A species that donates an electron pair to form a bond.
2) **Leaving Group** – An atom or group that departs with the bonding electron pair.
3) **Carbocation** – A positively charged carbon species formed during SN1 reactions.
4) **Polar Protic Solvent** – A solvent capable of hydrogen bonding (e.g., water, alcohols).
5) **Polar Aprotic Solvent** – A solvent lacking acidic hydrogen but capable of dissolving ions (e.g., DMSO, DMF).
6) **Steric Hindrance** – Resistance to reaction due to bulky groups around a reactive site.
7) **Inductive Effect** – Electron-withdrawing or electron-donating effect transmitted through sigma bonds.
8) **Resonance Stabilization** – Delocalization of charge through π-bond systems.

6.7 REFERENCE BOOKS

1) Morrison, R. T. & Boyd, R. N., *Organic Chemistry*, Pearson Education.
2) Solomons, T. W. G., Fryhle, C. B., & Snyder, S. A., *Organic Chemistry*, Wiley.
3) McMurry, J., *Organic Chemistry*, Cengage Learning.
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LESSON – 07

NEIGHBORING GROUP PARTICIPATION (OR ANCHIMERIC ASSISTANCE)

7.0 OBJECTIVES

1) To understand the concept of neighboring group participation (NGP).
2) To explain how anchimeric assistance affects reaction rate and stereochemistry.
3) To study the mechanism of NGP involving nitrogen, oxygen, sulfur, and halogens.
4) To understand the formation and role of cyclic intermediates in NGP reactions.
5) To explain why reactions involving neighboring group participation show retention of configuration.
6) To analyze the structural and steric requirements necessary for anchimeric assistance.

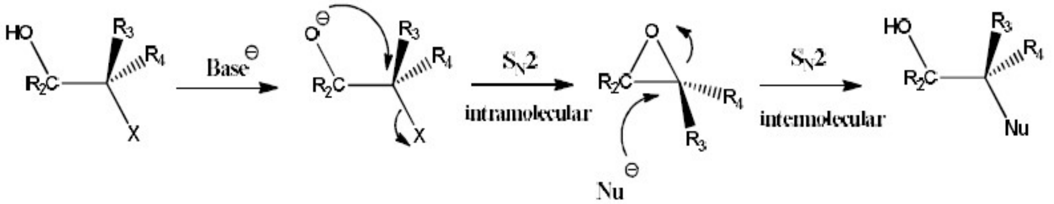
STRUCTURE

7.1 INTRODUCTION TO NEIGHBORING GROUP PARTICIPATION

Two consecutive (successive) SN2 reactions can lead to the overall retention of configuration at a chiral centre. This occurs when a neighboring group within the same molecule acts as a nucleophile in one of the substitution steps.

In such cases, the first SN2 reaction is intramolecular, where the neighboring group attacks the electrophilic carbon atom within the same molecule to form a cyclic intermediate.

This step involves inversion of configuration. The second SN2 reaction is intermolecular, where an external nucleophile attacks the cyclic intermediate, leading to a second inversion of configuration. Since two inversions occur successively, the overall configuration is retained.



The neighboring group, being part of the same molecule, is readily available for a favorable intramolecular attack. Consequently, these reactions are faster than ordinary intermolecular nucleophilic substitution reactions. Such reactions are termed anchimerically assisted reactions, and the phenomenon is known as anchimeric assistance or neighboring group participation (NGP).

These reactions generally follow a first-order rate law:

Rate = k [substrate]

During anchimeric assistance, the cyclic intermediates formed may sometimes be unsymmetrical, creating possibilities for rearrangements, which can lead to the formation of multiple substitution products.

When neighboring group participation is operative:

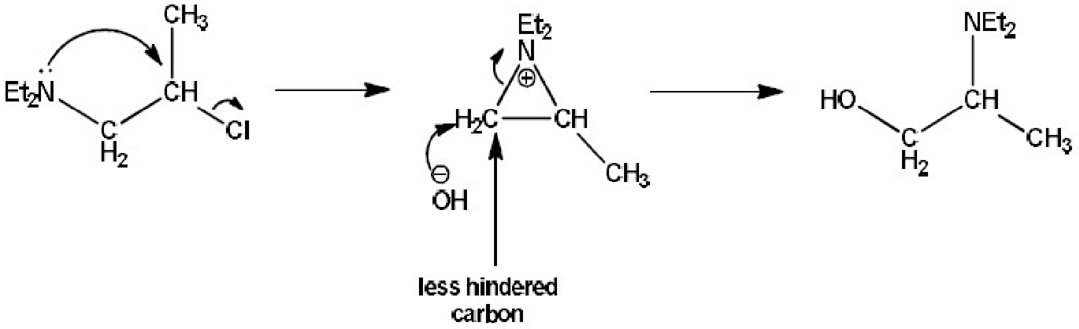
- The reaction rate is significantly enhanced.
- The stereochemical outcome may appear abnormal or unexpected when compared with a normal SN2 reaction.

7.2 NEIGHBORING GROUP PARTICIPATION BY NITROGEN

7.2.1 FORMATION OF AZIRIDINIUM ION

In certain nucleophilic substitution reactions**,** nitrogen can act as a neighboring group due to the presence of a lone pair of electrons on the nitrogen atom. This participation leads to the formation of a three-membered cyclic intermediate, known as an **aziridinium ion**, which facilitates the overall substitution process.

Example:



7.2.2 MECHANISM AND STEREOCHEMICAL OUTCOME

- The lone pair on nitrogen (in the diethylamino group, $–NEt_2$) attacks the adjacent carbon atom bearing the leaving group (Cl), resulting in the intramolecular displacement of the halide ion.This forms a cyclic aziridinium ion intermediate, in which nitrogen is positively charged.
- The hydroxide ion (OH^-), acting as an external nucleophile, attacks the less hindered carbon of the aziridinium ring.This ring-opening reaction produces the substitution product.
- The final product is formed with overall retention of configuration, since two consecutive SN2-type inversions occur (one during ring formation and another during ring opening).

Key Features:

- The reaction proceeds faster due to the intramolecular nature of the first step.
- The intermediate aziridinium ion is stabilized by the nitrogen atom's ability to delocalize positive charge.
- The hydroxide ion preferentially attacks the less sterically hindered carbon, leading to a regioselective product.
- This process is often referred to as an aza-Payne rearrangement, a typical example of anchimeric assistance by nitrogen.

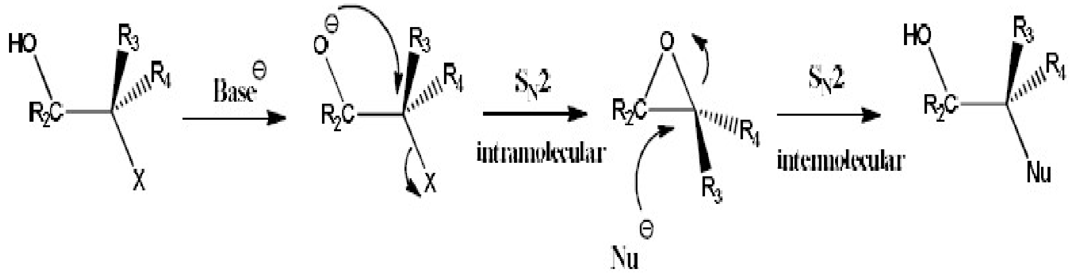
7.3 NEIGHBORING GROUP PARTICIPATION (NGP) BY OXYGEN

7.3.1 FORMATION OF OXONIUM (EPOXIDE) INTERMEDIATE

Oxygen is one of the most common heteroatoms that participates as a neighboring group in nucleophilic substitution reactions.Due to the presence of lone pairs of electrons**,** oxygen can intramolecularly attack an adjacent carbon atom, forming a cyclic intermediate that accelerates the reaction and influences the stereochemical outcome.

The figure illustrates the mechanism of NGP by oxygen, often seen in β-hydroxy alkyl halides **or** β-alkoxy alkyl halides, where oxygen assists in substitution by forming an oxonium ion (epoxide) intermediate.

Example:



7.3.2 MECHANISM AND RETENTION OF CONFIGURATION

Step 1: Formation of Alkoxide Ion

A **base** abstract a proton from the hydroxyl group (–OH), generating an alkoxide ion **(–O⁻)**. This alkoxide oxygen now becomes a strong intramolecular nucleophile.

Step 2: Intramolecular SN2 Attack

The negatively charged oxygen atom attacks the adjacent carbon atom that bears the leaving group (X). This intramolecular nucleophilic substitution (SN2) leads to the displacement of X⁻ and the formation of a three-membered cyclic oxonium ion, commonly known as an epoxide intermediate**.** This step involves inversion of configuration at the reacting carbon centre.

STEP 3: INTERMOLECULAR SN2 ATTACK (RING OPENING)

An external nucleophile (Nu⁻)**,** such as a hydroxide or halide ion, attacks the less hindered carbon atom of the epoxide ring in another SN2 reaction, resulting in ring opening. This step again proceeds with inversion of configuration, leading to the overall retention of configuration in the final product.

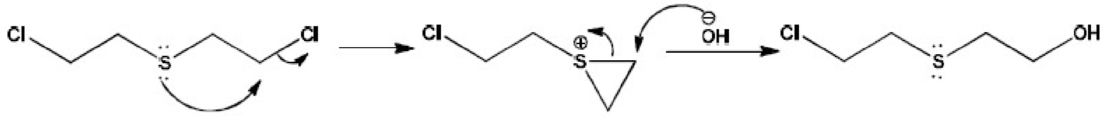
Key Features of NGP by Oxygen

1) Oxygen acts as a neighboring nucleophile through its lone pair.
2) Reaction proceeds via a cyclic oxonium ion (epoxide) intermediate.
3) Reaction rate is significantly enhanced due to intramolecular attack.
4) Two SN2 steps lead to overall retention of configuration.
5) Found commonly in β-hydroxy and β-alkoxy alkyl halides.

7.4 NEIGHBORING GROUP PARTICIPATION BY SULFUR

In this reaction, sulfur acts as a neighboring group through its lone pair of electrons. The sulfur atom donates its lone pair to the adjacent carbon attached to the leaving group (Cl), forming a three-membered cyclic sulfonium ion intermediate through an intramolecular SN2 attack.

In the next step, an external nucleophile such as hydroxide ion (OH^-) attacks the less hindered carbon of the sulfonium ring, opening it to give the substitution product. Since both steps occur via SN2 mechanisms, two inversions take place, resulting in an overall retention of configuration.



Hence, sulfur acts as an effective neighboring group due to its high polarizability and ability to stabilize the transition state, making the reaction faster than normal intermolecular nucleophilic substitutions.

7.5 NEIGHBORING GROUP PARTICIPATION BY HALOGENS

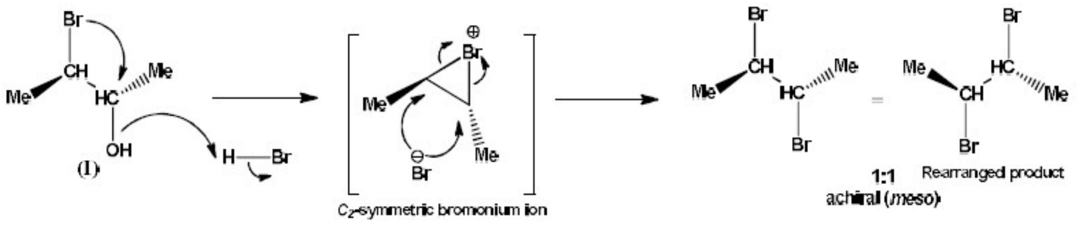
In this reaction, halogens such as chlorine, bromine, or iodine can act as neighboring groups through the participation of their lone pairs. The halogen atom donates a lone pair to the adjacent carbon bearing the leaving group, forming a three-membered cyclic halonium ion intermediate via an intramolecular SN2-type mechanism.

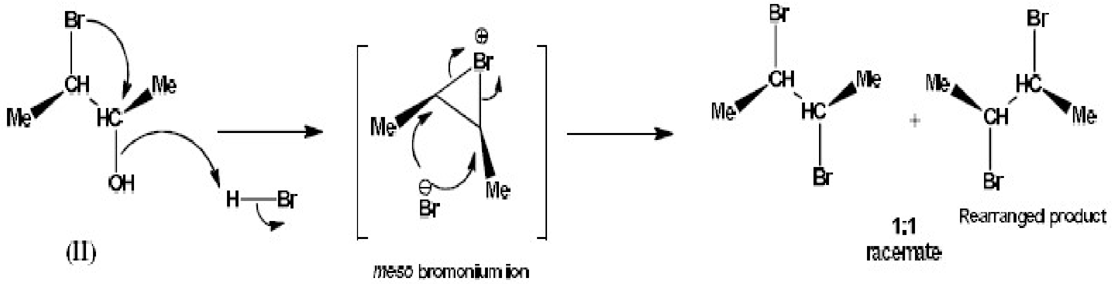
In the next step, an external nucleophile such as hydroxide ion (OH^-) attacks the less hindered carbon of the halonium ion, opening the ring and forming the substitution product. As both steps involve SN2 mechanisms, two inversions occur, resulting in an overall retention of configuration at the reactive center.

Hence, halogens act as neighboring groups by stabilizing the transition state through halonium ion formation. The reactivity order is **I > Br > Cl**, depending on the stability of the cyclic intermediate.

Example: Optically active *erythro*-3 bromo-2- butanol (I) reacts with HBr with retention of

configuration to give meso-product while *threo*-3 bromo-2-butanol (II) give an equimolar mixture of *R, R* and *S, S* enantiomers i.e. racemic mixture.





7.6 STERIC REQUIREMENTS FOR ANCHIMERIC ASSISTANCE (NGP)

7.6.1 PROXIMITY OF THE NEIGHBORING GROUP:

The assisting group must be close enough to the reaction center (usually on the α- or β-carbon) so that it can overlap its orbitals with the developing carbocation or the antibonding orbital of the leaving group.

7.6.2 PROPER ALIGNMENT (GEOMETRY):

The group should be positioned anti-periplanar or syn-periplanar to the leaving group, allowing effective orbital overlap during the transition state or intermediate formation (such as a cyclic intermediate).

7.6.3 SMALL RING FORMATION:

Formation of a 3- or 5-membered cyclic intermediate is most favorable because these rings are least strained and form easily during anchimeric assistance.

7.6.4 NO BULKY SUBSTITUENTS NEARBY:

Steric hindrance near the reacting center should be minimal; bulky groups can prevent the neighboring group from approaching and assisting the reaction.

7.6.5 FLEXIBLE STRUCTURE:

The molecule should be flexible enough to adopt the required conformation for neighboring group participation.

7.7 SUMMARY:

Neighboring group participation (NGP), also known as anchimeric assistance, is a phenomenon in which a group within the same molecule assists a nucleophilic substitution reaction through intramolecular interaction. This assistance leads to the formation of cyclic intermediates such as aziridinium, oxonium, sulfonium, or halonium ions.

NGP significantly increases the reaction rate compared to ordinary SN2 reactions and often results in **retention of configuration** due to two consecutive inversions. Nitrogen, oxygen, sulfur, and halogens can act as neighboring groups depending on their ability to donate lone pair electrons.

The effectiveness of anchimeric assistance depends on structural factors such as proximity, orientation, flexibility, and minimal steric hindrance. Understanding NGP helps explain unexpected stereochemical outcomes and reaction acceleration in many organic reactions.

7.8 SELF-ASSESSMENT QUESTIONS:

1) What is neighboring group participation?
2) Explain how anchimeric assistance increases the reaction rate.
3) Describe the mechanism of neighboring group participation by nitrogen with an example.
4) Explain how oxygen participates as a neighboring group.
5) Why does anchimeric assistance lead to retention of configuration?
6) Describe the role of sulfur in neighboring group participation.
7) Explain how halogens participate as neighboring groups.
8) What structural factors are necessary for effective anchimeric assistance?
9) Why are three-membered ring intermediates commonly formed during neighboring group participation?

7.9 TECHNICAL TERMS:

1) **Neighboring Group Participation (NGP)** – Intramolecular assistance provided by a neighboring group during a substitution reaction, increasing the reaction rate.
2) **Anchimeric Assistance** – Rate enhancement caused by the participation of a neighboring group in the reaction mechanism.
3) **Aziridinium Ion** – A three-membered cyclic intermediate formed when nitrogen participates as a neighboring group.
4) **Oxonium Ion** – A positively charged oxygen-containing cyclic intermediate formed during oxygen participation.
5) **Sulfonium Ion** – A sulfur-containing cyclic intermediate formed during sulfur participation in nucleophilic substitution.
6) **Halonium Ion** – A cyclic intermediate formed when halogens participate as neighboring groups.
7) **Intramolecular Reaction** – A chemical reaction occurring within the same molecule.

8) **Retention of Configuration** – Preservation of the original stereochemical arrangement due to two consecutive inversions.
9) **Steric Hindrance** – Resistance to reaction caused by bulky groups near the reactive center.
10) **Anchimeric Effect** – The stabilizing influence of a neighboring group on a reaction intermediate or transition state.

7.9 REFERENCES:

1) Morrison, R. T. & Boyd, R. N., *Organic Chemistry*, Pearson Education.
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LESSON – 08

CONCEPT OF CLASSICAL AND NON-CLASSICAL CARBOCATIONS

8.0 OBJECTIVES

1) To understand the concept of classical and non-classical carbocations.
2) To differentiate between classical and non-classical carbocations based on structure and stability.
3) To study the role of hyperconjugation, inductive effect, and resonance in stabilizing carbocations.
4) To understand neighboring group participation through π and σ bonds.
5) To explain the formation of bridged intermediates in non-classical carbocations.
6) To analyze the effect of carbocation stability on reaction rate and mechanism.

STRUCTURE

8.1 INTRODUCTION TO CARBOCATIONS

Carbocations are positively charged carbon species that act as key intermediates in many organic reactions such as SN1**,** E1, and rearrangements. Depending on how the positive charge is stabilized, carbocations are broadly classified into classical and non-classical types.

8.2 CLASSICAL CARBOCATIONS

A classical carbocation is the conventional type where the positive charge is localized on a single carbon atom. The carbon carrying the positive charge is sp^2 hybridized and has a planar structure with an empty p-orbital perpendicular to the molecular plane.

- Structure: The positive charge resides entirely on one carbon atom.
- Geometry: Trigonal planar (bond angle ~120°).
- Stability order:
  Tertiary (3°) > Secondary (2°) > Primary (1°) > Methyl

- Stabilization factors:

  a. Hyperconjugation
  b. Inductive effect
  c. Resonance (if possible)

Example:

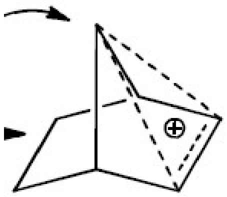
(CH3)3C$^+$— the tert-butyl carbocation, where the positive charge is localized on one carbon atom.

8.3 NON-CLASSICAL CARBOCATIONS

A non-classical carbocation is a delocalized structure in which the positive charge is shared by two or more atoms through bridged or delocalized bonding. It arises when a neighboring atom or bond donates electron density to stabilize the positive center, often forming a three-center two-electron bond.

- Structure: Delocalized or bridged; positive charge spread over two or more atoms.
- Geometry: Non-planar (due to bridge formation).
- Example:

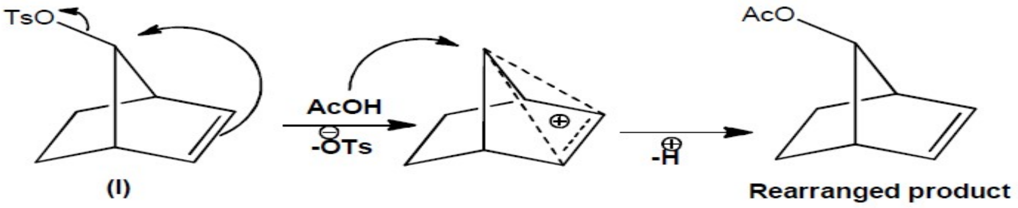
  a. Norbornyl cation (2-norbornyl carbocation) is the best-known example, where the positive charge is delocalized over a three-center bond involving two carbon atoms and one bridging hydrogen

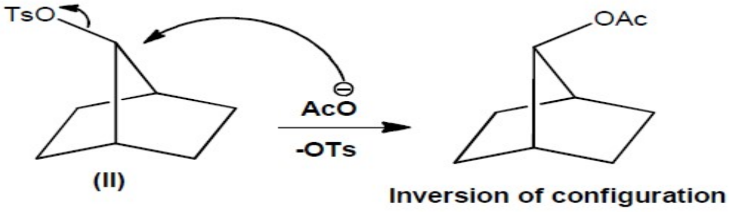


8.4 NEIGHBORING GROUP PARTICIPATION BY Π AND Σ BONDS

8.4.1 C=C (Π) AS A NEIGHBORING GROUP

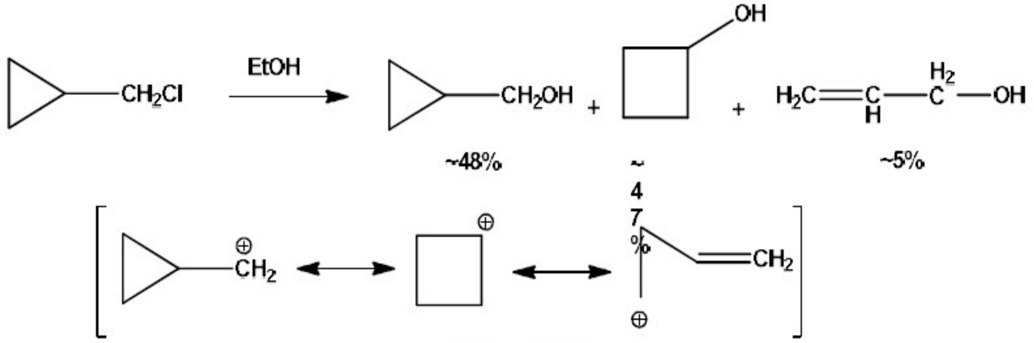
The rate of acetolysis of **7-**norbornenyl tosylate (I) is significantly higher than that of its saturated analogue, 7-norbornyl tosylate (II)**.** In this reaction, compound (I) yields the product with retention of configuration, whereas compound (II) gives the product with inversion of configuration. This clearly indicates the participation of the C=C (π) bond as a neighboring group. In such cases, the π-bond of the double bond interacts with the adjacent positively charged carbon (reaction center) during the reaction, leading to the formation of a non-classical carbocation **or** bridged ion intermediate. This stabilization by the π bond enhances the reaction rate and influences the stereochemical outcome.





8.4.2 NEIGHBORING GROUP PARTICIPATION BY Σ BONDS:

The rate of solvolysis of the cyclopropylmethyl system is exceptionally high due to the participation of σ bonds. During the reaction, the σ bond of the cyclopropane ring interacts with the positively charged carbon center, leading to the formation of **a** symmetrical cation that is stabilized from both sides. This delocalization of charge enhances the stability of the intermediate and increases the likelihood of rearrangement, resulting in the formation of various products.



The observed products include cyclopropylmethyl**,** cyclobutyl, and homoallyl compounds, providing clear evidence for the involvement of σ-bond participation in the reaction mechanism

8.5 SUMMARY

Carbocations are positively charged carbon intermediates commonly formed in organic reactions such as SN1, E1, and rearrangement reactions. Based on charge distribution, they are classified into **classical** and **non-classical carbocations**.

Classical carbocations possess a localized positive charge on a single sp^2-hybridized carbon atom with trigonal planar geometry. Their stability increases with alkyl substitution due to hyperconjugation, inductive effect, and resonance.

Non-classical carbocations exhibit delocalized positive charge shared between two or more atoms through bridged bonding, often involving three-center two-electron bonds. The norbornyl cation is a classic example.

Neighboring group participation by π and σ bonds plays a significant role in stabilizing carbocation intermediates, enhancing reaction rates and influencing stereochemistry. π-bond participation occurs through double bonds, while σ-bond participation is observed in strained systems such as cyclopropylmethyl carbocations.

8.6 SELF-ASSESSMENT QUESTIONS

1) What are carbocations? Explain their role in organic reactions.
2) Define classical carbocations and describe their structure and geometry.
3) Explain the stability order of classical carbocations.
4) What are non-classical carbocations? How do they differ from classical carbocations?
5) Describe the structure of the norbornyl carbocation.
6) Explain π-bond participation with a suitable example.
7) Discuss σ-bond participation in cyclopropyl methyl systems.
8) How does neighboring group participation affect reaction rate and stereochemistry?

8.7 TECHNICAL TERMS

1) **Carbocation** – A positively charged carbon species
2) **Classical carbocation** – Carbocation with localized positive charge
3) **Non-classical carbocation** – Carbocation with delocalized/bridged charge
4) **Hyperconjugation** – Stabilization by overlap of σ bonds with empty p-orbital
5) **Inductive effect** – Electron-donating or withdrawing effect through σ bonds
6) **Resonance** – Delocalization of electrons through π systems
7) **Three-center two-electron bond** – Bond involving three atoms sharing two electrons
8) **Neighboring group participation** – Stabilization of reaction intermediate by adjacent group
9) **Solvolysis** – Reaction of a compound with solvent
10) **Retention and inversion of configuration** – Stereochemical outcomes of reactions

8.8 REFERENCE BOOKS

1) Morrison, R. T. and Boyd, R. N., **Organic Chemistry**, Pearson Education
2) Solomons, T. W. G., Fryhle, C. B., and Snyder, S. A., **Organic Chemistry**, Wiley
3) Carey, F. A. and Sundberg, R. J., **Advanced Organic Chemistry**, Springer
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Mr. E. RAMANJANEYULU

LESSON – 09

AROMATIC NUCLEOPHILIC SUBSTITUTION

9.0 OBJECTIVES

After studying this chapter, the student will be able to:

1) Understand the nature and scope of aromatic nucleophilic substitution reactions.
2) Explain why nucleophilic substitution in aromatic systems is generally difficult.
3) Describe the conditions that favor aromatic nucleophilic substitution.
4) Explain various mechanisms involved in aromatic nucleophilic substitution reactions.
5) Understand the SNAr, SN1, Benzyne, and SRN$_1$ mechanisms with evidences.
6) Correlate structure, substituent effects, and reaction conditions with reaction pathways.

STRUCTURE

9.1 INTRODUCTION TO AROMATIC NUCLEOPHILIC SUBSTITUTION:

In aromatic nucleophilic substitution reactions, a hydrogen atom or a substituent on an aromatic ring is replaced by a nucleophile. The direct reaction of a nucleophile with a benzene ring is rare due to the high stability of the aromatic π-system.

However, such reactions can occur in the presence of a catalyst or under drastic conditions such as high temperature or high pressure. The reaction is particularly favored when strongly electron-withdrawing groups (e.g., $-NO_2$) are present at the ortho or para positions of the aryl halide. These groups decrease the electron density on the ring through their –R (resonance withdrawal) or –I (inductive withdrawal) effects, thereby activating the ring toward nucleophilic attack.

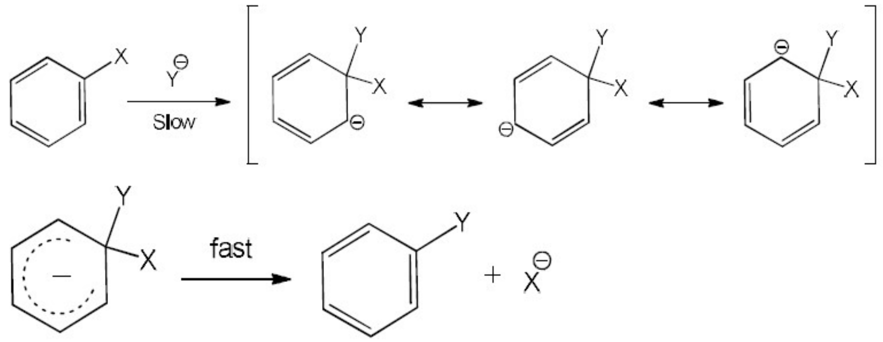
Aromatic nucleophilic substitution can proceed through the following four main mechanisms:

- SNAr mechanism (Addition–Elimination)
- SN1 mechanism
- Benzyne mechanism (Elimination–Addition)
- SRN1 mechanism (Radical mechanism)

9.2 S_NAr MECHANISM

The most important mechanism for aromatic nucleophilic substitution is the SNAr mechanism, which proceeds in two main steps:

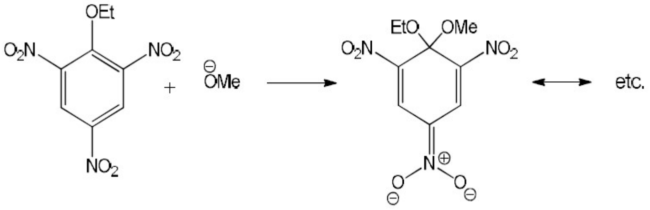
- **Addition Step**:The nucleophile attacks the ipso carbon (the carbon bearing the leaving group) of the aromatic ring. This attack temporarily disrupts the aromaticity, leading to the formation of a resonance-stabilized carbanion intermediate, known as the Meisenheimer complex.
- **Elimination Step**:In the second step, the leaving group departs from the intermediate, and aromaticity is restored, yielding the substituted aromatic compound.



9.2.2 EVIDENCES IN SUPPORT OF THE SNAR MECHANISM

a) Isolation of the Intermediate (Meisenheimer Complex):

The most convincing evidence for the SNAr (addition–elimination) mechanism is the isolation of the intermediate species. In the reaction between ethyl picrate and methoxide ion, a stable intermediate, known as a Meisenheimer complex (or Meisenheimer–Jackson salt), has been isolated and characterized. This confirms that the reaction proceeds through the formation of a carbanion intermediate, which is resonance-stabilized by the electron-withdrawing nitro groups present on the aromatic ring.



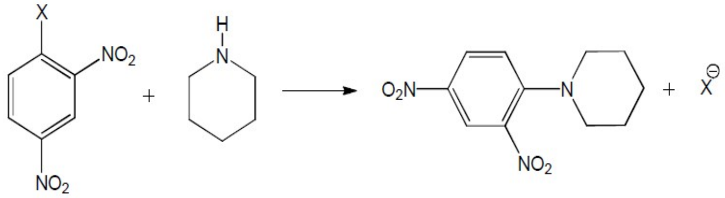
b) Effect of Leaving Group on Reaction Rate

In the reaction of a dinitro-substituted aromatic compound with piperidine**,** when the substituent **X** was Cl, Br, I, SOPh, SO_2Ph, **or** p-nitrophenoxy**,** the reaction rates differed only by **a** factor of about 5**.**

This observation indicates that the Ar–X bond is not broken in the rate-determining step**,** because if bond cleavage were rate-determining, the rates would vary much more significantly with different leaving groups.

However, when **X = F**, the reaction rate increased dramatically — the relative rate was about 3300 times higher than that for **X = I.**

This shows that fluorine acts as the best leaving group in aromatic nucleophilic substitution reactions, which is opposite to its behavior in SN1 and SN2 mechanisms (where fluorine is the poorest leaving group**).**



c) Effect of Electron-Withdrawing Substituents

The rate of aromatic nucleophilic substitution increases greatly when electron-withdrawing groups (EWGs) such as –NO_2**,** –CN, or –COOR are present, especially at the ortho and para positions to the leaving group.

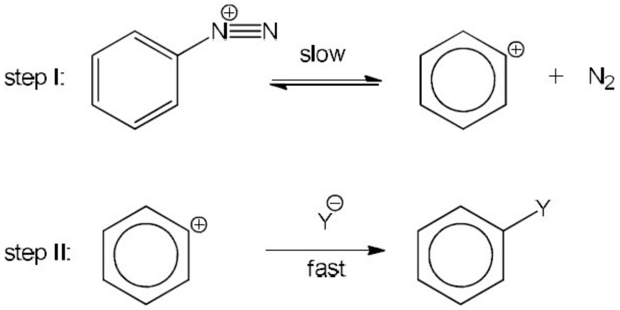
These substituents stabilize the negatively charged Meisenheimer intermediate formed during the nucleophilic attack by delocalizing the negative charge through resonance or inductive effects.In contrast, electron-donating groups (EDGs) like –OH**,** –OCH_3**, or** –NH_2 decrease the rate of reaction, as they destabilize the carbanion intermediate.

9.3 S_N1 MECHANISM

The S_N1 mechanism for aryl halides and aryl sulfonates is very rare because the formation of an aryl carbocation is highly unstable due to the loss of aromaticity.

However, this mechanism has been observed in certain aryl triflates, where both ortho positions are occupied by bulky substituents such as tert-butyl ($–C(CH_3)_3$) **or** silyl groups ($–SiR_3$). These bulky groups help to stabilize the carbocation through hyperconjugation **or** inductive effects, making the SN1 pathway possible.

The S_N1 mechanism also plays an important role in reactions involving aromatic diazonium salts, where the loss of N_2 gas generates a highly reactive aryl cation intermediate that readily undergoes nucleophilic substitution.



9.3.1 EVIDENCES IN SUPPORT OF THE SN1 MECHANISM

a) **First-Order Kinetics:**
The rate of reaction **is** first order with respect to the diazonium salt and independent of the nucleophile concentration (Y)**.**
This indicates that the rate-determining step involves only the aryl diazonium ion, not the nucleophile.

b) Independence from Added Halide Salts:
When high concentrations of halide salts are added, the product formed is the corresponding aryl halide, but the reaction rate remains unchanged.This shows that the formation of the aryl cation (not the attack by nucleophile) is the slow, rate-determining step**.**

c) **Effect of Ring Substituents:**

The influence of substituents on the aromatic ring on the reaction rate supports aunimolecular rate-determining cleavage.Electron-donating groups accelerate the reaction (by stabilizing the aryl cation), while electron-withdrawing groups retard it.

d) Reversible Cleavage of the Diazonium Group:

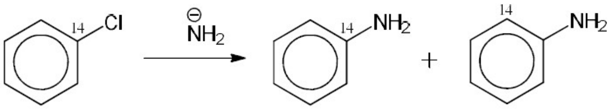
Experimental evidence shows that when $Ar^{15}N≡N$ (diazonium compound labeled with nitrogen-15) is used, the recovered starting material contains both $Ar^{15}N≡N$ and $ArN≡N$**.** This indicates that the N_2 group dissociates and then recombines reversibly, confirming that cleavage of the Ar–N_2 bond is the first, reversible, and rate-determining step in the S_N1 mechanism.

9.4 BENZYNE MECHANISM

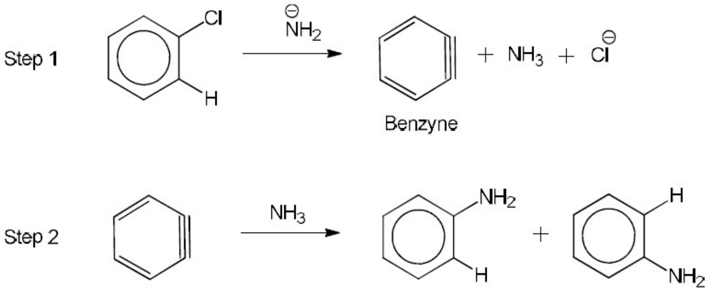
Aryl halides without electron-withdrawing (activating) groups can still undergo aromatic nucleophilic substitution when treated with a very strong base such as sodium amide ($NaNH_2$) **or** potassium amide (KNH_2) in liquid ammonia.

A unique feature of this reaction is that the incoming nucleophile does not always attach at the same position as the leaving group. This occurs due to the formation of a highly reactive intermediate known as benzyne, which is symmetrical and possesses an extra π bond within the aromatic ring.

Hence, the reaction proceeds by the Benzyne mechanism, also called the elimination–addition mechanism.



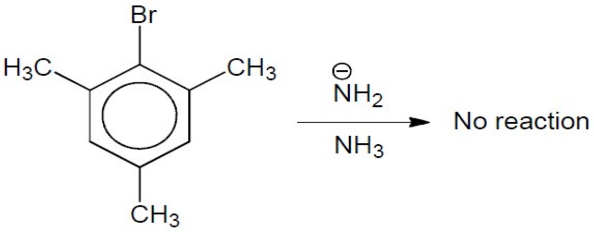
Mechanism



9.4.1 EVIDENCES IN SUPPORT OF THE BENZYNE MECHANISM:

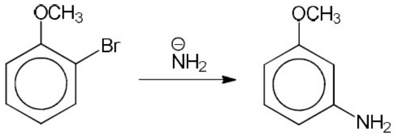
a) Aryl halides containing no hydrogen at the ortho position to the halogen do not react under similar conditions.

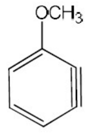
This shows that the presence of an ortho-hydrogen is essential for the reaction to occur, as it is required for the formation of the benzyne intermediate. The base abstracts this ortho-hydrogen, leading to elimination of the halide ion and generation of the benzyne



b) The reaction of **^{14}C-chlorobenzene** with a strong base (like $NaNH_2$ in liquid ammonia) gives almost equal amounts of ^{14}C-1-aniline and ^{14}C-2-aniline**.** This indicates that the substitution can occur at both ortho and para positions with respect to the original halogen atom.Such behavior can be explained only if a symmetrical intermediate (benzyne) is formed, in which both positions are equivalent for nucleophilic attack.

c) The aromatic nucleophilic substitution reactions that lead to substitution at a position different from where the leaving group was originally located are known as cine substitutions.For example, when ortho-bromoanisole is treated with a strong base, it gives meta-aminoanisole as the only product. This happens because the benzyne intermediate formed is unsymmetrical due to the presence of the electron-donating methoxy group (-OCH_3)**,** which directs the nucleophile to the meta position**.** This supports the benzyne mechanism, showing that substitution can occur at a different position through an intermediate benzyne.

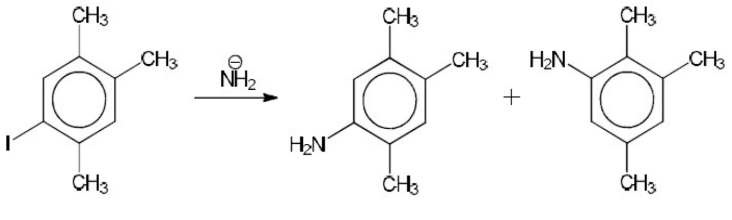




Unsymmetrical benzyne intermediate

9.5 THE S_RN^1 MECHANISM

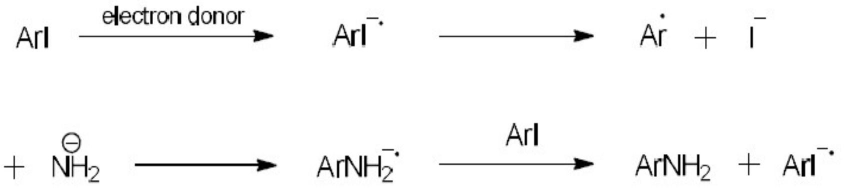
When 5-iodo-1,2,4-trimethylbenzene (1) is treated with KNH_2 in liquid ammonia, it yields two products (2 and 3) in the ratio 0.63 : 1**.** The reaction occurs even though the substrate is unactivated**,** requiring a very strong base (KNH_2).Moreover, both normal and cine substitutions are observed, indicating that substitution can occur at more than one position. These features an unactivated aryl halide, a strong base, and the formation of multiple positional isomers strongly support the formation of a benzyne intermediate, confirming that the reaction proceeds through the benzyne mechanism.



1 **2** **3**

If the benzyne mechanism alone were operating, the 6-iodo isomer of 1 should have produced the same product ratio as the 5-iodo isomer. However, experimentally, the 5-iodo isomer gives products in the ratio 0.63 : 1**,** while the 6-iodo isomer gives 5.9 : 1.Interestingly, the chloro and bromo analogs show a ratio of 1.46 : 1, consistent with the benzyne mechanism, suggesting that another mechanism may also be operating in the iodo case.

To explain this deviation, it has been proposed that**,** in addition to the benzyne mechanism, a free radical chain mechanism called the S_RN^1 mechanism is also taking place. In this mechanism, the last step produces aryl iodide radical ions ($ArI^{\bullet -}$)**,** and the process continues as a chain reaction.The reaction is initiated by solvated electrons generated from KNH_2 in liquid ammonia, which act as the electron donors to start the radical pathway.



9.5.1 EVIDENCES IN SUPPORT OF THE SRN$_1$ MECHANISM:

- Addition of potassium metal (a strong source of solvated electrons in liquid ammonia) completely suppressed cine substitution. This shows that the presence of extra solvated electrons favors the radical pathway and interferes with the benzyne route**.**
- Addition of radical scavengers (substances that trap free radicals**)** changed the product ratio (9:10) to values much closer to 1.46: 1. This suggests that when free radicals are removed, the reaction proceeds mainly via the benzyne mechanism, confirming that radicals play a key role in the SRN$_1$ mechanism**.**
- Formation of 1,2,4-trimethylbenzene among the reaction products**.**This compound can be formed by hydrogen abstraction from the solvent (NH_3) by an aryl radical (Ar·) intermediate, providing direct evidence for the involvement of free radicals in the reaction.

9.6 SUMMARY

- Aromatic nucleophilic substitution reactions involve the replacement of a hydrogen atom or substituent on an aromatic ring by a nucleophile. Due to the high stability of the aromatic π-system, such reactions are less common than aliphatic nucleophilic substitutions and usually require activating groups, strong bases, or special conditions.
- The most important mechanism is the **SNAr (addition–elimination) mechanism**, which proceeds through a resonance-stabilized Meisenheimer complex and is favored by strong electron-withdrawing groups at ortho or para positions.
- The **SN1 mechanism** is rare in aromatic systems due to instability of aryl carbocations but occurs in diazonium salts and sterically hindered aryl triflates.
- The **Benzyne mechanism** operates under strong basic conditions and involves a highly reactive benzyne intermediate, explaining cine substitutions.
- In some cases, especially with aryl iodides, a **free radical chain mechanism (SRN^1)** also operates, supported by radical-based experimental evidences.

9.7 SELF-ASSESSMENT QUESTIONS

1) Why is nucleophilic substitution difficult in aromatic compounds?
2) Explain the SNAr mechanism with evidences.
3) What is a Meisenheimer complex? How is it stabilized?
4) Why does fluorine act as a better leaving group in SNAr reactions?
5) Discuss the SN1 mechanism in aromatic nucleophilic substitution.
6) Explain the benzyne mechanism with suitable examples.
7) What is cine substitution? How does it support the benzyne mechanism?
8) Explain the SRN_1 mechanism with experimental evidences.
9) Distinguish between SNAr and benzyne mechanisms.

9.8 TECHNICAL TERMS

1) **Aromatic nucleophilic substitution** – Replacement of an atom or group on an aromatic ring by a nucleophile.
2) **SNAr mechanism** – Aromatic substitution occurring by addition of a nucleophile followed by elimination of the leaving group.
3) **Meisenheimer complex** – A negatively charged intermediate formed during SNAr reactions.
4) **Electron-withdrawing group (EWG)** – A substituent that pulls electron density from the aromatic ring and increases reaction rate.
5) **Electron-donating group (EDG)** – A substituent that pushes electron density into the aromatic ring and decreases reaction rate.
6) **Ipso carbon** – The aromatic carbon atom bonded to the leaving group.
7) **Aryl carbocation** – A positively charged aromatic carbon species formed in rare SN1 reactions.
8) **Benzyne intermediate** – A highly reactive intermediate formed under strong basic conditions in aromatic substitution.
9) **Cine substitution** – Substitution occurring at a position different from the original leaving group.
10) **SRN_1 mechanism** – Aromatic substitution mechanism proceeding through free radical intermediates.
11) **Solvated electrons** – Free electrons stabilized by solvent molecules, especially in liquid ammonia.
12) **Radical scavenger** – A substance that reacts with and removes free radicals from the reaction system.

9.9 REFERENCE BOOKS

1) Morrison, R. T. and Boyd, R. N., **Organic Chemistry**, Pearson
2) Solomons, T. W. G., Fryhle, C. B., and Snyder, S. A., **Organic Chemistry**, Wiley
3) Carey, F. A. and Sundberg, R. J., **Advanced Organic Chemistry**, Springer
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Prof. D. RAMACHANDRAN

LESSON – 10

EFFECT OF SUBSTRATE STRUCTURE, LEAVING GROUP AND ATTACKING NUCLEOPHILE ON THE REACTIVITY

10.0 OBJECTIVES

After studying this chapter, the student will be able to:

1) Understand how substrate structure affects aromatic nucleophilic substitution reactions.
2) Explain the role of electron-withdrawing and electron-donating groups on reactivity.
3) Describe the influence of leaving groups in aromatic nucleophilic substitution.
4) Understand the effect of the nature and strength of the attacking nucleophile.
5) Correlate reaction mechanism (SNAr or benzyne) with reactivity trends.

STRUCTURE

10.1 EFFECT OF SUBSTRATE STRUCTURE

The structure of the substrate greatly influences its reactivity in aromatic nucleophilic substitution reactions. In a typical aromatic ring, there are several hydrogens (usually four or five) that could potentially participate or influence the substitution process.

For reactions proceeding through the SNAr (nucleophilic aromatic substitution) mechanism, the presence of electron-withdrawing groups (EWGs) such as $–NO_2$, –CN, $–CF_3$, especially at the ortho and para positions to the leaving group, increases the reaction rate. These groups stabilize the negatively charged intermediate (Meisenheimer complex) formed during the reaction.

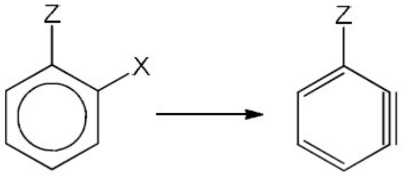
On the other hand, electron-donating groups (EDGs) reduce reactivity by destabilizing this intermediate. Nitrogen-containing groups are particularly activating, especially when quaternized, and tend to influence substitution at the α and γ positions.

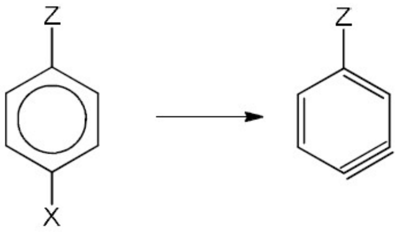
A detailed order of activating and deactivating groups can be found in *March's Advanced Organic Chemistry* (M. Smith and J. March). Among the activating groups, $–NO_2$ is the most commonly used, and typical reactive substrates include 2,4-dinitrophenyl halides and 2,4,6-

trinitrophenyl halides. In contrast, unsubstituted benzene rings or those lacking activating groups are generally unreactive toward SNAr reactions.

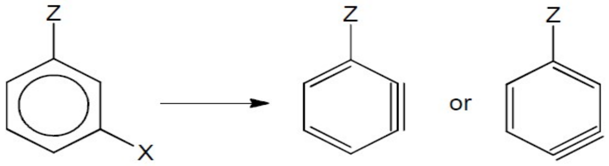
For reactions proceeding through the benzyne (aryne) mechanism, two major factors influence the position of the incoming group:

1) The direction in which the benzyne forms, which depends on the availability of an ortho hydrogen for elimination.
2) When substituents are present ortho or para to the leaving group, the site of benzyne formation becomes fixed, leaving no alternative position for nucleophilic attack.



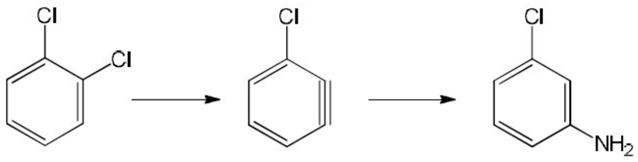


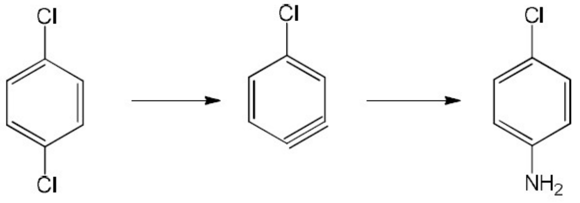
3) When a *meta* group is present, the aryne can form in two different ways

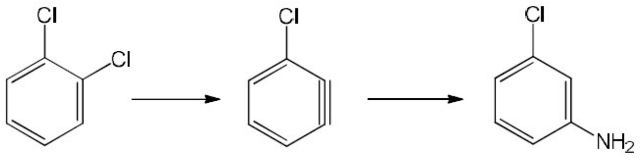


In such cases, the more acidic hydrogen is removed. If Z is an electron-attracting group it favours removal of the *ortho* hydrogen while an electron-donating group (Z) favours removal of the *para* hydrogen.

The second factor is that the aryne, once formed, can be attacked at two positions.The most favoured position for nucleophilic attack is the one that leads to the more stable carbanion intermediate. It can be illustrated by the reaction of the three dichlorobenzenes with alkali-*meta*l amides to give the predicted products as shown below. In each case, the predicted product was found to be the major one.







10.2 THE EFFECT OF THE LEAVING GROUP

The nature of the leaving group plays a very important role in determining the rate and feasibility of aromatic nucleophilic substitution reactions. Many leaving groups that are commonly involved in aliphatic nucleophilic substitution reactions—such as halides, sulfate, sulfonates, and quaternary ammonium groups (NR_3^+)—are also effective leaving groups in aromatic systems.

However, aromatic nucleophilic substitution reactions show some unique features that distinguish them from aliphatic substitutions. Certain groups like **$-NO_2$, –OR, –OAr, $-SO_2R$, and –SR**, which are normally poor leaving groups in aliphatic nucleophilic substitution, behave as **good leaving groups in aromatic substitution reactions**. This unusual behavior is mainly due to the stabilization of reaction intermediates by the aromatic ring and electron-withdrawing substituents.

One of the most striking observations in aromatic nucleophilic substitution is that **nitro group ($-NO_2$) acts as an efficient leaving group**. This is because the nitro group can strongly withdraw electron density from the ring and stabilize the negative charge developed during the reaction. As a result, its departure becomes favorable in aromatic systems.

The **order of leaving group ability** in aromatic nucleophilic substitution reactions is given below:

$$\mathbf{F > NO_2 > OTs > SOPh > Cl, Br, I > N_3 > NR_3^+ > OAr > OR > SR > NH_2}$$

This order is quite different from that observed in aliphatic nucleophilic substitution reactions. For example, **fluorine**, which is usually the poorest leaving group in aliphatic SN1 and

SN2 reactions, becomes the **best leaving group in aromatic substitution**. This is because fluorine's strong –I effect stabilizes the negatively charged Meisenheimer intermediate in SNAr reactions.

It is important to note that the **leaving group ability is not fixed** and **depends strongly on the nature of the attacking nucleophile**. Strong nucleophiles can displace even relatively poor leaving groups, while weaker nucleophiles require highly activated leaving groups. Therefore, the effectiveness of a leaving group in aromatic nucleophilic substitution is influenced by both its intrinsic ability to depart and the strength of the nucleophile involved.

In summary, aromatic nucleophilic substitution reactions display distinctive leaving group behavior, where even traditionally poor leaving groups can participate effectively due to the stabilizing effects of the aromatic system and reaction intermediates.

10.3 THE EFFECT OF THE ATTACKING NUCLEOPHILE

The nature and strength of the attacking nucleophile play a significant role in determining the rate of aromatic nucleophilic substitution reactions. Unlike aliphatic substitution reactions, nucleophilicity in aromatic systems depends on several factors such as the **structure of the substrate**, the **reaction mechanism involved (SNAr or benzyne)**, the **solvent**, and the **reaction conditions**. Therefore, it is not possible to define a single, fixed nucleophilicity order applicable to all reactions.

In general, **strongly basic and negatively charged nucleophiles** show higher reactivity in aromatic nucleophilic substitution reactions. Nucleophiles that can effectively donate an electron pair or participate in single-electron transfer processes react more rapidly.

An **approximate order of nucleophilicity** observed in aromatic nucleophilic substitution reactions is given below:

$$^{-}\mathrm{NH2} > \mathrm{Ph3C}^{-} > \mathrm{PhNH}^{-} \text{ (aryne mechanism)} > \mathrm{ArS}^{-} > \mathrm{RO} > \mathrm{R2NH} > \mathrm{ArO}^{-} >$$

$$\mathrm{OH}^{-} > \mathrm{ArNH2} > \mathrm{NH3} > \mathrm{I}^{-} > \mathrm{Br}^{-} > \mathrm{Cl}^{-} > \mathrm{H2O} > \mathrm{ROH}$$

This order indicates that:

- **Amide ion (NH_2^-)** is one of the strongest nucleophiles due to its high basicity and negative charge.
- **Carbanions** such as triphenylmethyl anion (Ph_3C^-) are highly reactive nucleophiles.
- **Anilide ions ($PhNH^-$)** are particularly effective in reactions proceeding through the **aryne (benzyne) mechanism**.
- **Sulfur-based nucleophiles (ArS^-)** are stronger than oxygen-based nucleophiles due to their higher polarizability.
- **Neutral nucleophiles** such as ammonia and water are much weaker compared to charged species.
- **Halide ions** show decreasing nucleophilicity in the order $I^- > Br^- > Cl^-$.

- **Alcohols (ROH)** are the weakest nucleophiles due to lack of charge and strong solvation.

Thus, the reactivity of the attacking nucleophile greatly influences the rate and outcome of aromatic nucleophilic substitution reactions, and stronger nucleophiles generally lead to faster reactions under suitable conditions.

10.4 SUMMARY

The reactivity of aromatic nucleophilic substitution reactions is strongly influenced by the structure of the substrate, the nature of the leaving group, and the strength of the attacking nucleophile.

Substrate structure plays a crucial role, especially in SNAr reactions, where electron-withdrawing groups such as $-NO_2$ at ortho or para positions stabilize the Meisenheimer complex and increase reaction rate. Electron-donating groups reduce reactivity by destabilizing this intermediate. In benzyne mechanism, the position of substituents controls aryne formation and the site of nucleophilic attack.

Leaving group ability in aromatic systems differs from aliphatic substitutions. Fluorine and nitro groups act as excellent leaving groups due to their strong electron-withdrawing nature. The leaving group order depends on the reaction conditions and nucleophile used.

The attacking nucleophile also affects reactivity. Strong nucleophiles such as amide ions react faster, while weaker nucleophiles show lower reactivity. Nucleophilicity depends on solvent, substrate, and reaction mechanism.

10.5 SELF-ASSESSMENT QUESTIONS

1) Explain the effect of substrate structure on SNAr reactions.
2) Why do electron-withdrawing groups increase aromatic nucleophilic substitution reactivity?
3) How do electron-donating groups affect reaction rate?
4) Explain the role of substrate structure in the benzyne mechanism.
5) Discuss the order of leaving group ability in aromatic nucleophilic substitution.
6) Why does fluorine act as a good leaving group in aromatic substitution?
7) Explain the effect of attacking nucleophile on reaction rate.
8) Compare nucleophilicity trends in different reaction conditions.

10.6 TECHNICAL TERMS

1) **Substrate structure** – The arrangement of atoms and substituents in the aromatic compound affecting reactivity.
2) **Electron-withdrawing group (EWG)** – A group that pulls electrons from the ring and increases reactivity.
3) **Electron-donating group (EDG)** – A group that donates electrons to the ring and decreases reactivity.

4) **Meisenheimer complex** – A negatively charged intermediate formed in SNAr reactions.
5) **Leaving group** – An atom or group that departs with an electron pair during substitution.
6) **Benzyne (aryne)** – A highly reactive intermediate formed under strong basic conditions.
7) **Nucleophile** – An electron-rich species that attacks the substrate.
8) **Nucleophilicity** – Ability of a nucleophile to donate electrons.
9) **Reaction reactivity** – The speed at which a chemical reaction occurs.
10) **Ortho / para directing groups** – Substituents that influence substitution positions on aromatic rings.

10.7 REFERENCE BOOKS

1) Morrison, R. T. and Boyd, R. N., **Organic Chemistry**, Pearson
2) Solomons, T. W. G., Fryhle, C. B., and Snyder, S. A., **Organic Chemistry**, Wiley
3) Carey, F. A. and Sundberg, R. J., **Advanced Organic Chemistry**, Springer
4) March, J., **Advanced Organic Chemistry**, Wiley
5) Clayden, J., Greeves, N., and Warren, S., **Organic Chemistry**, Oxford University Press

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LESSON - 11

THE VON RICHTER, SOMMELIER-HAUSER, AND SMILES REARRANGEMENTS

11.0 OBJECTIVES

After studying this unit, the learner will be able to:

1) Understand the concept of **aromatic rearrangement reactions**.
2) Explain the **mechanisms** of the Von Richter, Sommelet–Hauser, and Smiles rearrangements.
3) Identify the **reaction conditions and reagents** required for each rearrangement.
4) Distinguish between different rearrangements based on **substrates, intermediates, and products**.
5) Apply these rearrangements in **problem-solving and reaction prediction**.
6) Appreciate the **synthetic and mechanistic importance** of aromatic rearrangements in organic chemistry

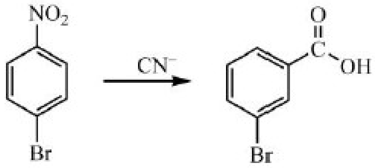
STRUCTURE

11.1 VON RICHTER REACTION

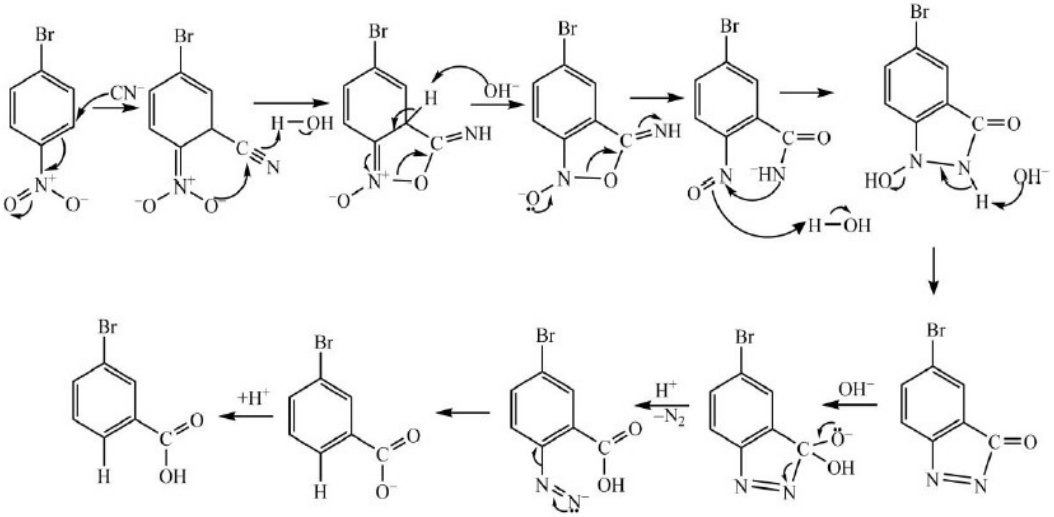
The von Richter reaction may simply be defined as the chemical transformation where aromatic nitro compounds react with KCN in aqueous ethanol to yield cine substitution product by a carboxyl group.

This reaction was invented by a German chemist Victor von Richter in 1871; and therefore, it is also named after him; and It is practically unimportant because of low yield and by-products formation.

Example: The conversion of p-bromonitrobenzene into m-bromobenzoic acid.



Mechanism: The most widely accepted mechanism for the von Richter reaction was given by Rosenblum in 1960 when he employed 15N labeling experiments.



In the first step, the carbon ortho to the nitro group is attacked by cyanide; which is followed by ring-closing through nucleophilic invasion at the cyano group; finally resulting in the rearomatization of the imidate intermediate. The opening of the cycle via nitrogen-oxygen bond-breaking gives rise to an ortho-nitroso benzamide that recyclizes to yield a compound with a nitrogen-nitrogen bond. The elimination of H2O results in a cyclic azoketone, which undergoes nucleophilic invasion by OH− to result in a tetrahedral intermediate. This intermediate breakdowns with the removal of the azo group to give an aryldiazene with an o-carboxylate group, which squeezes out dinitrogen gas to be able to have the anionic form of the benzoic acid.

Evidence Supporting the Above Mechanism (Rewritten)

- **Nitrogen gas (N_2)** is obtained as a major product of the reaction. This clearly indicates that an **N–N bond is formed** at some stage during the reaction.
- **Compound (46)** is a stable species. Therefore, it should be possible to **synthesize it independently** and subject it to the conditions of the **Von Richter rearrangement**. When this was carried out, the **expected products were obtained**, supporting its role as an intermediate.
- When the reaction is performed in **$H_2{}^{18}O$** in the presence of **CN^-**, **half of the oxygen atoms in the product are isotopically labeled**. This demonstrates that **one oxygen atom**

of the carboxyl group originates from the nitro group, while the **other comes from the solvent**, as proposed by the mechanism.

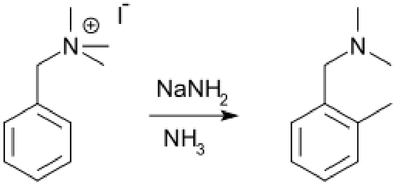
- When the reaction is conducted in the presence of **D_2O/C_2H_5OD**, the resulting **carboxylic acid contains deuterium** at the position originally occupied by the **NO_2 group**. This observation confirms the **formation of the proposed intermediate species**.

11.2 SOMMELET-HAUSER REARRANGEMENT

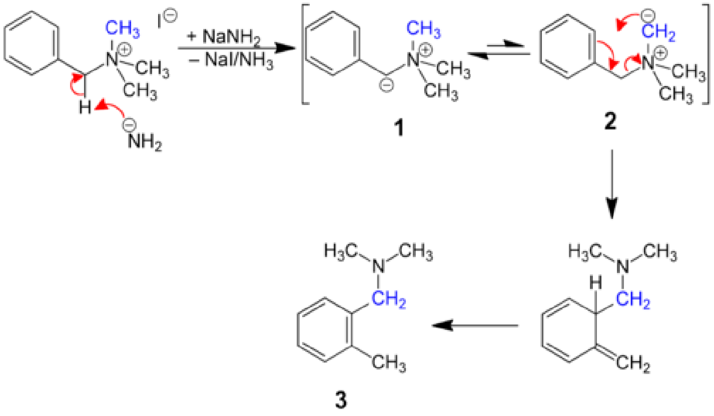
The Sommelet-Hauser rearrangement may simply be defined as the rearrangement reaction of certain benzyl quaternary ammonium salts where the reagent used is sodium amide (or alkali amide) and the reaction results in the N,N-dialkylbenzylamine with a new alkyl substituent in the aromatic o-position.

Now because the final product is a benzylic tertiary amine, it can further undergo alkylation followed by reoccurring rearrangement, and then repeating the process until the blockage of o-site.

Example: The common type of this type of rearrangement is benzyltrimethylammonium iodide that rearranges in the presence of NaNH2 to give the o-methyl derivative of N, N-dimethylbenzylamine.

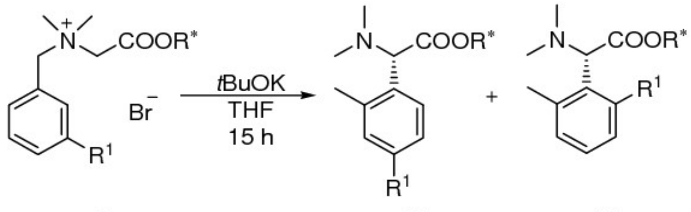


The benzylic methylene proton is acidic and deprotonation takes place to produce the benzylic ylide (**1**). This ylide is in equilibrium with a second ylide that is formed by deprotonation of one of the ammonium methyl groups (**2**). Though the second ylide is present in much smaller amounts, it undergoes a **2,3-sigmatropic rearrangement** because it is more reactive than the first one and subsequent aromatization to form the final product (**3**)



APPLICATIONS:

1)



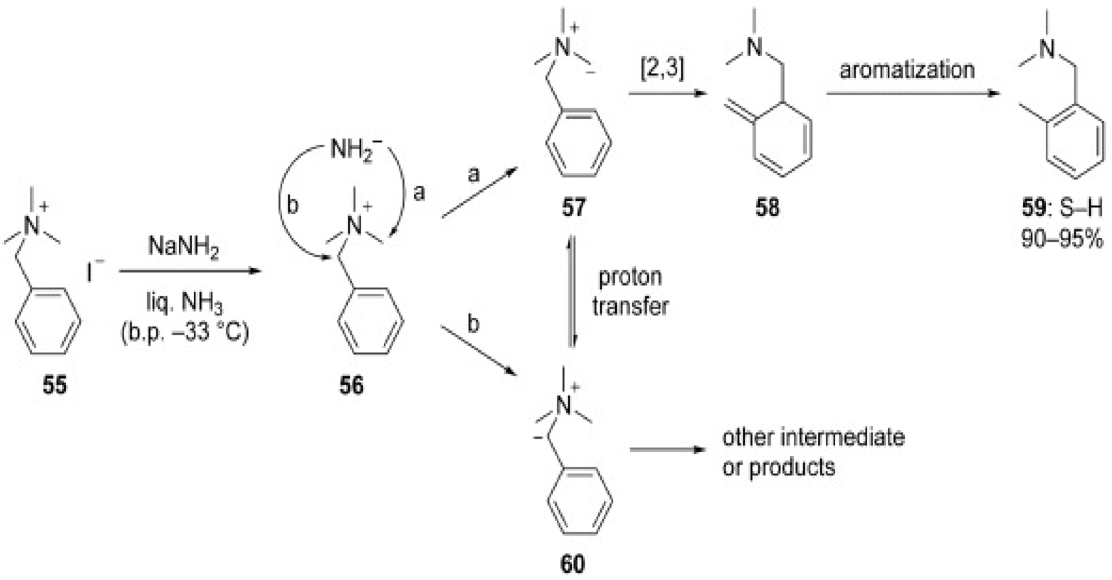
9 **10** **11**

[R* = (–)-8-phenylmenthyl]

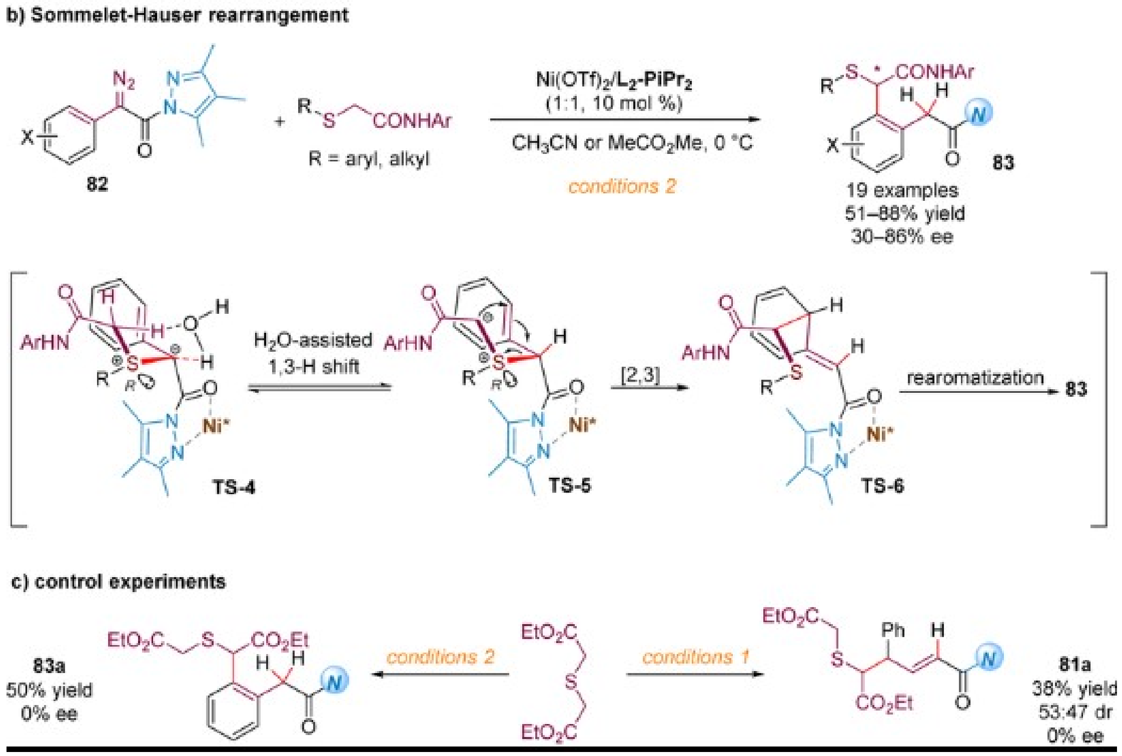
Entry	R^1		T [°C]	Yield[b] (Dr)[c] **10**	Yield[b] (Dr)[c] **11**
1	CN	**a**	–60	63 (>98:2)	6 (>98:2)
2	CF_3	**b**	–60	20[d] (>98:2)	0
3	CF_3	**b**	–40	90 (>98:2)	0

[a] All reactions were performed using **9** (0.20-0.30 mmol), *t*BuOK

2)

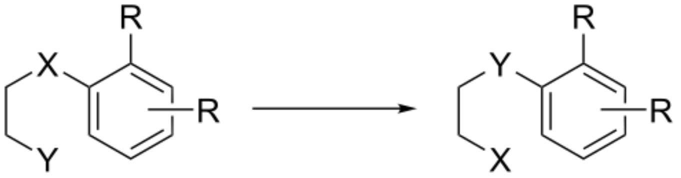


3)



11.3 SMILES REARRANGEMENT

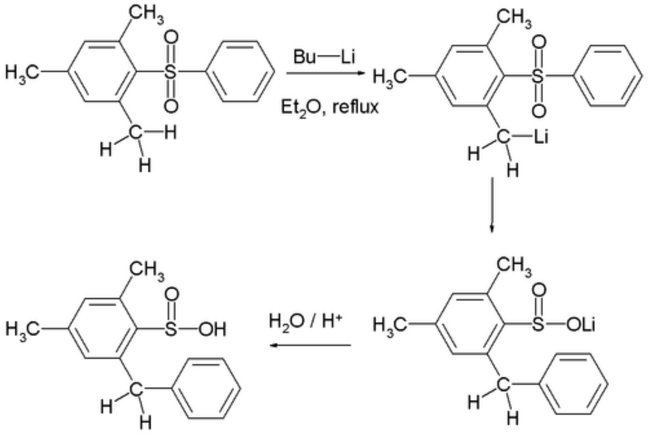
In organic chemistry, the **Smiles rearrangement** is an organic reaction and a rearrangement reaction named after British chemist Samuel Smiles. It is an intramolecular, nucleophilic aromatic substitution of the type:



where X in the arene compound can be a sulfone, a sulfide, an ether or any substituent capable of dislodging from the arene carrying a negative charge. The terminal functional group in the chain end Y is able to act as a strong nucleophile for instance an alcohol, amine or thiol.

As in other nucleophilic aromatic substitutions the arene requires activation by an electron-withdrawing group preferably in the aromatic ortho position.

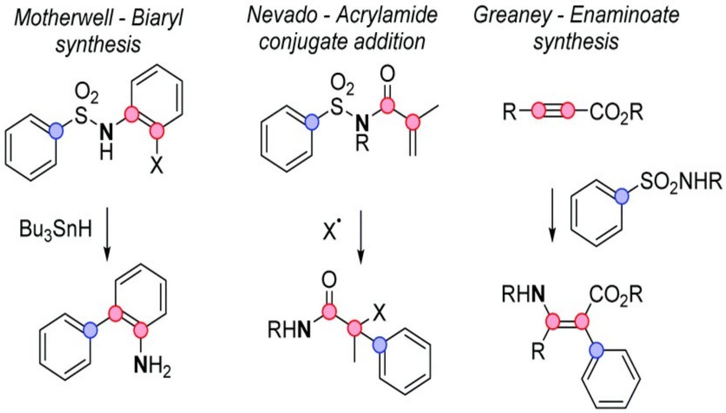
In one modification called the **Truce–Smiles rearrangement** the incoming nucleophile is sufficiently strong that the arene does not require this additional activation, for example when the nucleophile is an organolithium. This reaction is exemplified by the conversion of an aryl sulfone into a sulfinic acid by action of *n*-butyllithium:



Applications:

1. Desulfonylative Smiles

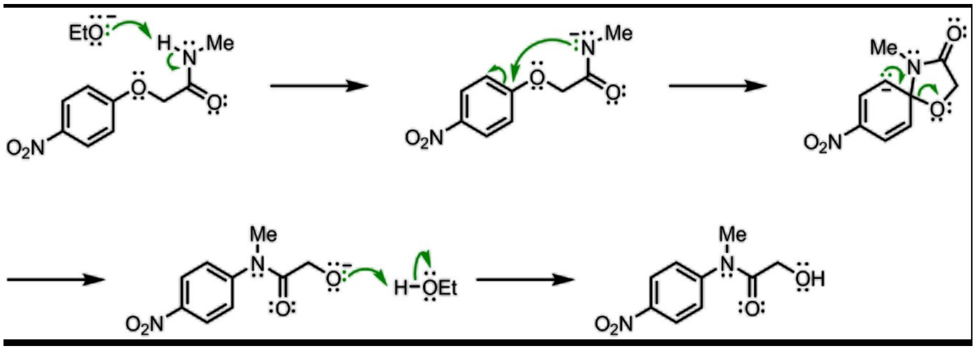
2. Representative substrate classes - Csp^2 and Csp common


Motherwell - Biaryl synthesis

Nevado - Acrylamide conjugate addition

Greaney - Enaminoate synthesis

3)



11.4 SUMMARY

The Von Richter, Sommelet–Hauser, and Smiles rearrangements are important **aromatic rearrangement reactions** involving nucleophilic processes.

1) The **Von Richter reaction** involves the transformation of **aromatic nitro compounds** into **benzoic acids** using cyanide ion, proceeding through complex nitrogen-containing intermediates and supported by isotopic labeling evidence.
2) The **Sommelet–Hauser rearrangement** is a **base-induced rearrangement of benzyl quaternary ammonium salts**, proceeding via **ylide intermediates**, leading predominantly to **ortho-substituted benzylamines**.
3) The **Smiles rearrangement** is an **intramolecular nucleophilic aromatic substitution**, requiring activation by electron-withdrawing groups and proceeding through a **Meisenheimer complex**. Its modified version, the **Truce–Smiles rearrangement**, operates even without ring activation.

Together, these rearrangements highlight the **diverse reactivity of aromatic systems** under nucleophilic conditions and are valuable tools in **synthetic and mechanistic organic chemistry**.

11.5 SELF-ASSESSMENT QUESTIONS

1) What reagent is used in the Von Richter reaction?
2) Name the intermediate formed in the Sommelet–Hauser rearrangement.
3) What type of reaction is the Smiles rearrangement?
4) Which rearrangement involves the formation of nitrogen gas?
5) Explain why the Von Richter reaction is of limited practical importance.
6) Describe the role of ylides in the Sommelet–Hauser rearrangement.
7) Why are electron-withdrawing groups necessary in the Smiles rearrangement?
8) What is the Truce–Smiles rearrangement?
9) Discuss the mechanism of the Von Richter reaction with suitable experimental evidence.
10) Explain the Sommelet–Hauser rearrangement with a suitable example and mechanism.

11) Describe the Smiles rearrangement and explain its applications.
12) Compare the Sommelet–Hauser and Smiles rearrangements with respect to mechanism, conditions, and products.

11.6 TECHNICAL TERMS

1) **Rearrangement Reaction** – A reaction involving migration of atoms or groups within a molecule.
2) **Cine Substitution** – Substitution occurring at a position adjacent to the leaving group.
3) **Ylide** – A neutral molecule with adjacent positive and negative charges.
4) **Meisenheimer Complex** – A σ-complex intermediate in nucleophilic aromatic substitution.
5) **Electron-Withdrawing Group** – A substituent that stabilizes negative charge by inductive or resonance effects.
6) **Sigmatropic Rearrangement** – A concerted migration of a σ-bond.
7) **Intramolecular Reaction** – A reaction occurring within the same molecule.

11.7 REFERENCE TEXT BOOKS

1) **Organic Chemistry** – Morrison & Boyd
2) **Advanced Organic Chemistry** – Jerry March / Carey & Sundberg
3) **Organic Chemistry** – Solomons, Fryhle & Snyder
4) **A Guidebook to Mechanism in Organic Chemistry** – Peter Sykes
5) **Advanced Organic Chemistry** – Bahl & Bahl

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LESSON – 12

AROMATIC ELECTROPHILIC SUBSTITUTION

12.0 OBJECTIVES

After studying this unit, the learner will be able to:

1) Understand the nature of **aromatic electrophilic substitution reactions**.
2) Explain why aromatic compounds prefer **electrophilic substitution over addition**.
3) Describe the **arenium ion (σ-complex) mechanism**.
4) Analyze the **experimental evidence** supporting the arenium ion mechanism.
5) Explain the mechanisms of **Friedel–Crafts alkylation and acylation**.
6) Identify the **applications and limitations** of Friedel–Crafts reactions.
7) Understand the **mechanism and reactivity trends** in aromatic halogenation.
8) Apply mechanistic knowledge to **predict products and reaction behavior**

STRUCTURE

12.1 AROMATIC ELECTROPHILIC SUBSTITUTION

12.1.1 INTRODUCTION

The majority of substitution reactions involving aliphatic carbon atoms are nucleophilic substitution reactions. However, in aromatic systems, the situation is reversed. The aromatic ring acts as a Lewis base due to the delocalization of π-electrons above and below the plane of the ring. As a result, aromatic compounds generally undergo electrophilic substitution reactions.

In these reactions, the electrophile (a positively charged ion or the positive end of a dipole) attacks the aromatic ring, while the leaving group departs without its electrons.

12.1.2 ARENIUM ION MECHANISM

The electrophilic substitution reactions proceed s in two main steps:

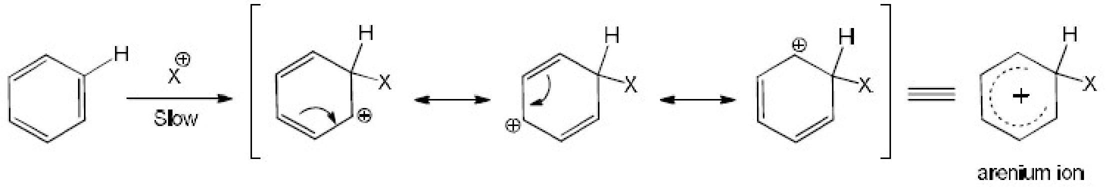
1) Formation of the σ-complex (arenium ion)
2) Restoration of aromaticity by loss of a proton

STEP-1:

Aromatic electrophilic substitution reactions proceed through a single mechanism known as the arenium ion mechanism (also called the Wheland intermediate or σ-complex mechanism).

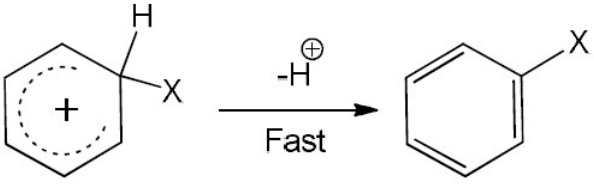
In this mechanism, an electrophile is first generated from the reagent or the reaction mixture. This electrophile is then attacked by the π-electrons of the aromatic ring in the first step, leading to the formation of a new C–X bond (where *X* is the electrophile) and the conversion of one aromatic carbon from sp^2 to sp^3 hybridization.

The resulting positively charged intermediate is called an arenium ion. This intermediate is resonance-stabilized, as the positive charge is delocalized over the ring. However, it is still highly reactive and unstable because the aromaticity of the ring is temporarily lost.



STEP 2:

In the second step**, a** proton (H^+) is lost from the carbon adjacent to the positively charged center. This regenerates the aromatic system, resulting in the formation of the substituted aromatic product.



12.1.3 EVIDENCE FOR THE ARENIUM ION MECHANISM

There are mainly two types of evidence supporting the arenium ion mechanism in aromatic electrophilic substitution reactions.

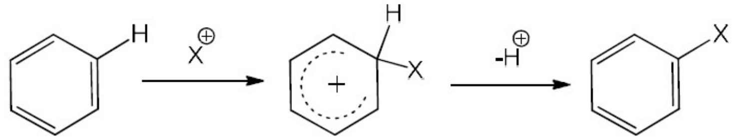
a). Isotope Effect

If the proton were to depart before the electrophile attacks (as in the SE_1 mechanism), or if both processes occurred simultaneously, there would be a significant isotope effect. In such cases, deuterated substrates (compounds in which hydrogen is replaced by deuterium) would undergo substitution more slowly than non-deuterated compounds, because the C–H (or C–D) bond breaking would occur in the rate-determining step.

However, in the arenium ion mechanism, the C–H bond is not broken in the rate-determining step. Therefore, no isotope effect should be observed.

As expected, experimental results especially from nitration reactions showed no measurable isotope effect, confirming that aromatic electrophilic substitution proceeds through a two-step mechanism, and that the loss of hydrogen is not the rate-determining step.

For cases where hydrogen acts as the leaving group, the arenium ion mechanism can be summarized as follows:

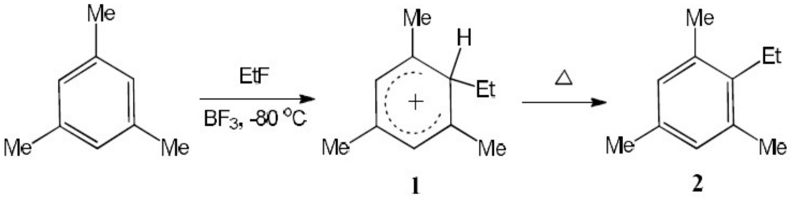


b). Isolation of Arenium Ion Intermediates

A very strong piece of evidence supporting the arenium ion mechanism comes from the isolation of arenium ion intermediates in several reactions.

For example, the arenium ion (1) has been successfully isolated as a solid (m.p. –15 °C) in certain aromatic substitution reactions. When this isolated intermediate was heated, it decomposed to give the normal substitution product (2).

This observation clearly confirms the existence of the arenium ion as a real, isolable intermediate in the aromatic electrophilic substitution process.



12.2 FRIEDEL–CRAFTS ALKYLATION

The Friedel–Crafts alkylation reaction is an important aromatic electrophilic substitution reaction in which an alkyl group is introduced into an aromatic ring by the action of an alkyl halide in the presence of a Lewis acid catalyst, such as $AlCl_3$, $FeCl_3$, **or** BF_3

$$C_6H_6 + CH_3CH_2Cl \xrightarrow[80\ ^\circ C]{\text{Anhydrous } AlCl_3} \underset{\text{Ethyl benzene}}{C_6H_5CH_2CH_3} + HCl$$

A wide variety of aromatic compounds can undergo Friedel–Crafts reactions, including hydrocarbons, aryl halides, polyhydric phenols, amines, aldehydes, quinones, and certain heterocyclic compounds.

The most commonly used Lewis acid catalyst **is** anhydrous aluminium chloride ($AlCl_3$), which usually provides a good yield of the desired product. However, several other catalysts have also been employed, including proton acids such as HF, H_2SO_4, H_3PO_4, and mixed acid systems like HF–BF_3.

The **order of catalytic reactivity** for some common Lewis acids is:

AlBr3 > AlCl3 > FeCl3 > SbCl5 > SnCl4 > BCl3, BF3,

Alkylating agents may be Alkyl halides, olefins, aliphatic alcohols, esters, and ethers.

- For active halides, weaker catalysts (e.g., $ZnCl_2$) are sufficient.
- For less reactive halides, stronger catalysts (e.g., $AlCl_3$) are required.

The **solvents** typically used in Friedel–Crafts reactions include nitrobenzene, carbon disulfide (CS_2), ether, petroleum ether, **and** methylene chloride (CH_2Cl_2).

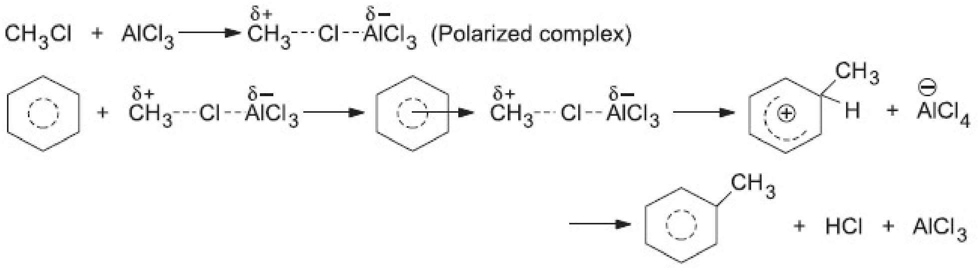
Mechanism

The exact mechanism of the Friedel–Crafts alkylation reaction is not completely understood. The alkylating reagent most commonly used is an alkyl halide. The primary role of the Lewis acid catalyst (such as $AlCl_3$) is to generate a real or potential carbocation, which acts as the electrophile in the attack on the aromatic ring.

In cases where the alkyl halide is tertiary, the corresponding tertiary carbocation is relatively stable, and it is therefore believed that a true carbocation is the actual attacking species responsible for the electrophilic substitution.

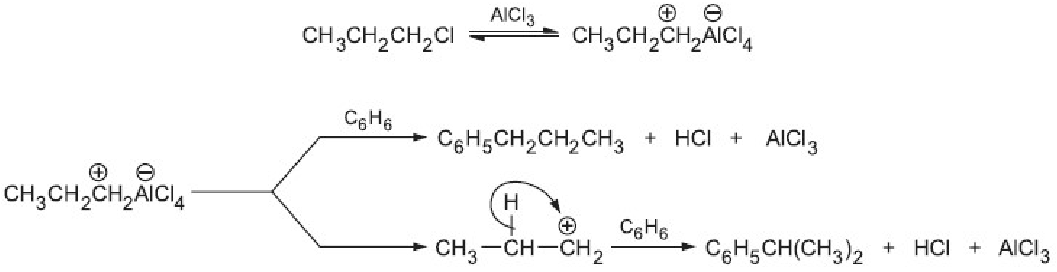
$$R_3CX + AlCl_3 \longrightarrow R_3\overset{\oplus}{C} + \overset{\ominus}{X}AlCl_3$$

However, primary and secondary carbocations are relatively unstable. Hence it is suggested that with 1° or 2° halides, a polarized complex with a potential carbocation is the attacking species.



$$CH_3Cl + AlCl_3 \longrightarrow \overset{\delta+}{CH_3}\text{---}Cl\text{--}\overset{\delta-}{AlCl_3} \text{ (Polarized complex)}$$

It is, however, not certain whether a polarized complex or a free carbocation attacks. For example,*n*-propyl chloride reacts with benzene to form both *n*-propyl benzene and isopropyl benzene. This indicatesthat an *n*-propyl carbocation is first formed which may then either attack the benzene ring or rearrange by1, 2-hydride shift to form a greater stable isopropyl carbocation (2°) before attack.

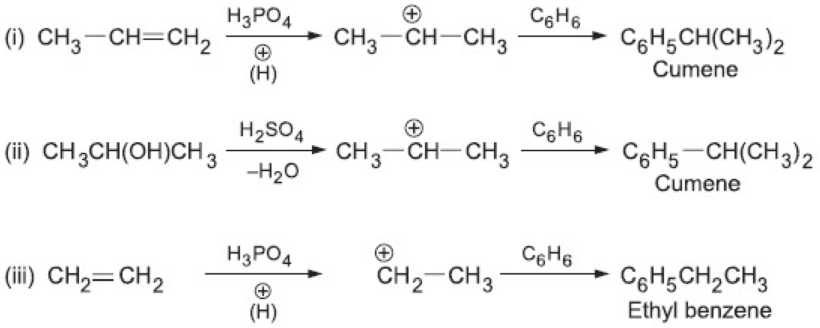


$$CH_3CH_2CH_2Cl \underset{}{\overset{AlCl_3}{\rightleftharpoons}} CH_3CH_2\overset{\oplus}{C}H_2\overset{\ominus}{AlCl_4}$$

$$CH_3CH_2\overset{\oplus}{C}H_2\overset{\ominus}{AlCl_4} \xrightarrow{C_6H_6} C_6H_5CH_2CH_2CH_3 + HCl + AlCl_3$$

$$CH_3CH_2\overset{\oplus}{C}H_2\overset{\ominus}{AlCl_4} \longrightarrow CH_3-\overset{H}{C}H-\overset{\oplus}{C}H_2 \xrightarrow{C_6H_6} C_6H_5CH(CH_3)_2 + HCl + AlCl_3$$

Besides alkyl halides, the alkylating agents may be aliphatic alcohols, alkenes, ethers and esters also.These in the presence of acidic catalysts, such as H2SO4,H3PO4,HF, HF– BF3, etc., afford carbocations for the electrophilic attack on the ring.



$$\text{(i) } CH_3-CH=CH_2 \xrightarrow[\overset{\oplus}{(H)}]{H_3PO_4} CH_3-\overset{\oplus}{C}H-CH_3 \xrightarrow{C_6H_6} \underset{\text{Cumene}}{C_6H_5CH(CH_3)_2}$$

$$\text{(ii) } CH_3CH(OH)CH_3 \xrightarrow[-H_2O]{H_2SO_4} CH_3-\overset{\oplus}{C}H-CH_3 \xrightarrow{C_6H_6} \underset{\text{Cumene}}{C_6H_5-CH(CH_3)_2}$$

$$\text{(iii) } CH_2=CH_2 \xrightarrow[\overset{\oplus}{(H)}]{H_3PO_4} \overset{\oplus}{C}H_2-CH_3 \xrightarrow{C_6H_6} \underset{\text{Ethyl benzene}}{C_6H_5CH_2CH_3}$$

For alkyl halides the reactivity order is F> Cl > Br > I. Hence, $FCH_2CH_2CH_2Cl$ reacts with benzene to give $C_6H_5CH_2CH_2CH_2Cl$ in the presence of BF_3. Benzene rings with substituted haloalkyl groups have important synthetic applications.

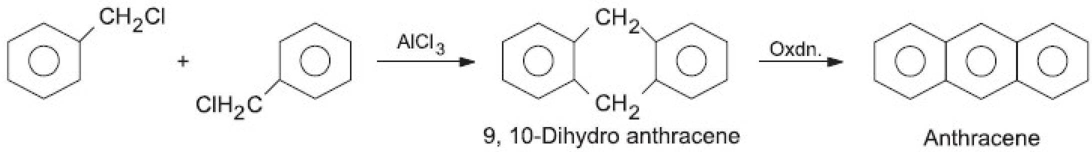
Applications

The reaction is very useful for the synthesis of many classes of organic compounds

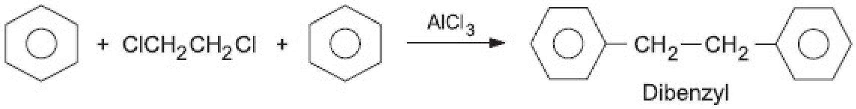
(i) $$C_6H_6 + C_6H_5CH_2Cl \xrightarrow{AlCl_3} \underset{\text{Diphenyl methane}}{C_6H_5CH_2C_6H_5}$$

(ii) $$3C_6H_6 + CHCl_3 \xrightarrow{AlCl_3} \underset{\text{Triphenyl methane}}{(C_6H_5)_3CH} + 3HCl$$

(iii)



(iv)



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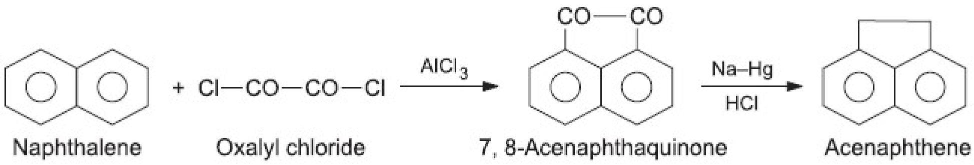
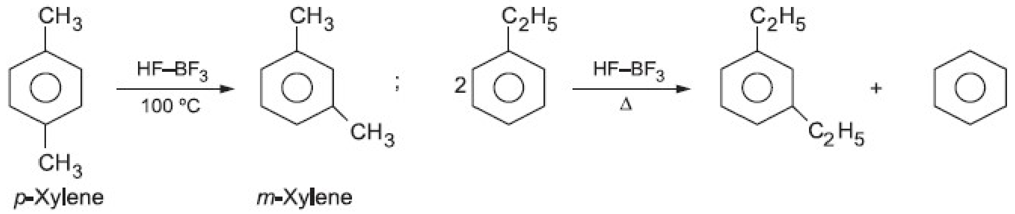


Limitations

(a) Polyalkylation Since the alkyl groups are activating, di- and poly-alkylations are generally observed. To minimize polyalkylation, a large excess of the aromatic compound may be used.

(b) Rearrangement Alkylation is frequently accompanied by rearrangement of the entering group.

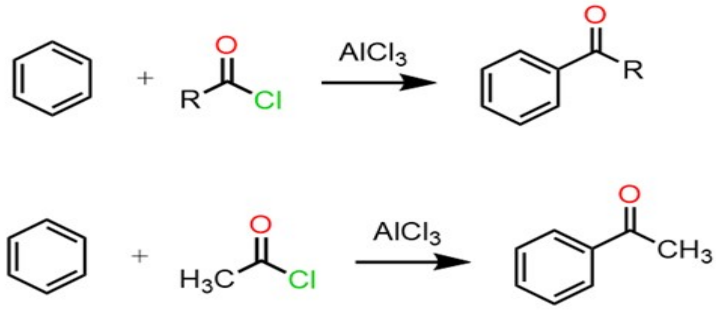
(c) Isomerization In the presence of excess catalyst and at high temperature, isomerization and disproportionation result.



(d) Effect on the reactivity of the substrates: Electron-withdrawing groups inhibit the reaction while activatinggroups, such as OH, OR, NH2, etc., react with the catalyst to retard the reaction. Naphthalene andheterocyclic compounds are very reactive and react with the catalyst. Naphthalene gives poor yield andheterocyclic compounds are not alkylated.

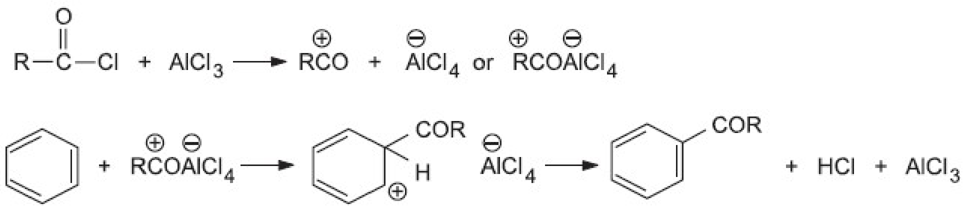
12.3 FRIEDEL–CRAFTS ACYLATION

Friedel–Crafts acylation is an electrophilic aromatic substitution reaction in which an aromatic compound reacts with an acyl halide (RCOCl) or acid anhydride (RCO–O–COR′) in the presence of a Lewis acid catalyst (such as $AlCl_3$ or $FeCl_3$) to form an aryl ketone (aromatic ketone).This reaction introduces an **acyl group (–COR)** into the aromatic ring.



The acylating reagents are acid chlorides or acid anhydrides. Depending on conditions probably two mechanisms operate.

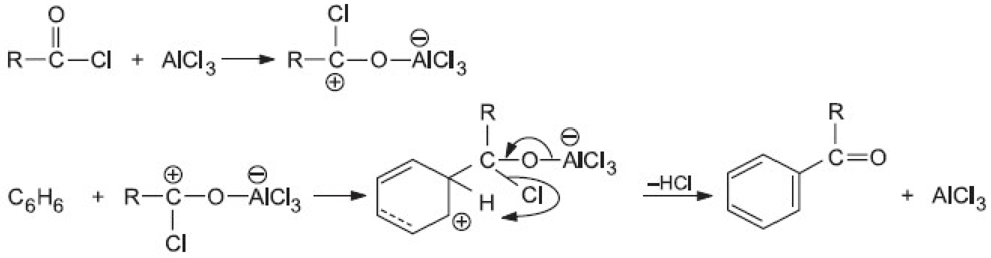
(i) Generation of the attacking species which may be a free acyl cation or an ion pair



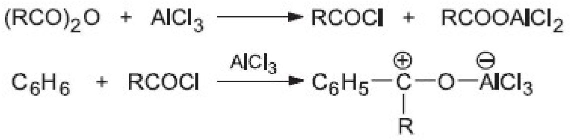
$$R-\overset{\overset{O}{\|}}{C}-Cl + AlCl_3 \longrightarrow \overset{\oplus}{RCO} + \overset{\ominus}{AlCl_4} \text{ or } \overset{\oplus\ \ \ominus}{RCOAlCl_4}$$

With sterically hindered acyl halides the attacking species may be the acyl cation.

(ii) Generation of 1 : 1 complex for the electrophilic attack



In either case, one mole of the catalyst remains complexed with the carbonyl oxygen of the ketone formed. Hence, a little more than one mole of the catalyst is required per mole of the reagent for acylation withacyl halides. When acid anhydride is the reagent, slightly more than two moles of the catalyst is required. Thisis because one mole of the catalyst is used up in liberating acyl halide and another mole for complexing with the product, ketone.



$$(RCO)_2O + AlCl_3 \longrightarrow RCOCl + RCOOAlCl_2$$

$$C_6H_6 + RCOCl \xrightarrow{AlCl_3} C_6H_5-\underset{\displaystyle R}{\overset{\oplus}{C}}-O-\overset{\ominus}{A}lCl_3$$

The product, ketone is liberated with ice-cold dilute acid.

Aromatic rings having activating groups, such as alkyl, alkoxy, halogen, acetamido, etc., are easily acylated. For reasons of steric factors, acylation mainly occurs at the para position. Many heterocyclic compounds undergo acylation with good yield. Metadirecting groups inhibit acylation. Hence, nitrobenzene isthe favoured solvent for acylation.

Acylation differs from alkylation in the following;

a) Acylation unlike alkylation is performed in solvents, such as nitrobenzene, carbon disulphide,
b) petroleum ether, methylene chloride, etc.
c) Acylation requires more catalyst than alkylation for complexing with the carbonyl oxygen of the reagent.
d) Since acyl group is deactivating unlike alkyl group, a monosubstituted product is always obtained.
e) In acylation rearrangement in the substituent is not observed.

This fact has been utilized for preparing long-chain substituted arenes without rearrangement

$$C_6H_6 + CH_3CH_2COCl \xrightarrow{AlCl_3} C_6H_5COCH_2CH_3 \xrightarrow[HCl]{Na-Hg} C_6H_5CH_2CH_2CH_3$$

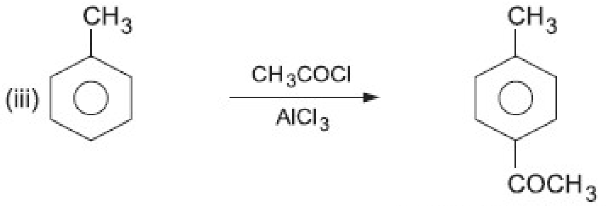
n-Propyl benzene

Applications

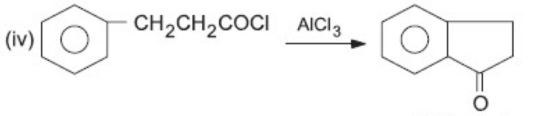
(i) $$C_6H_6 + RCOCl \xrightarrow[PhNO_2]{AlCl_3} C_6H_5COR + HCl$$

(ii) $$C_6H_6 + C_6H_5CH_2COCl \xrightarrow[CS_2]{AlCl_3} C_6H_5COCH_2C_6H_5$$

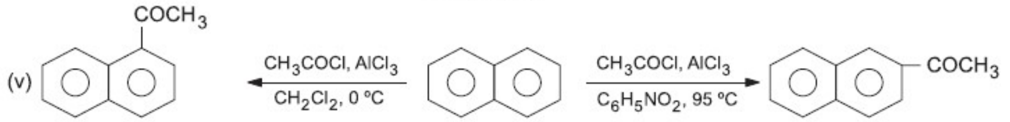
Benzyl phenyl ketone



p-Tolyl methyl ketone



1-Hydrindone



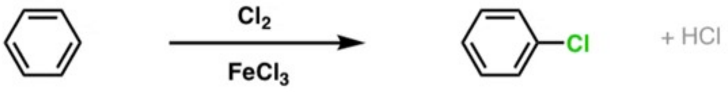
1-Naphthyl methyl ketone

2-Naphthyl methyl ketone

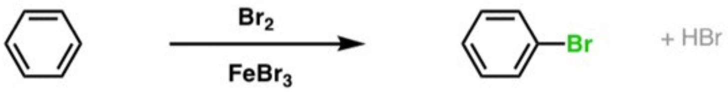
12.4 HALOGENATION

Halogenation of benzene is the replacement of one hydrogen atom of the benzene ring by a halogen atom (Cl, Br, etc.) in the presence of a **Lewis acid catalyst** such as $FeCl_3$, $FeBr_3$, or $AlCl_3$.

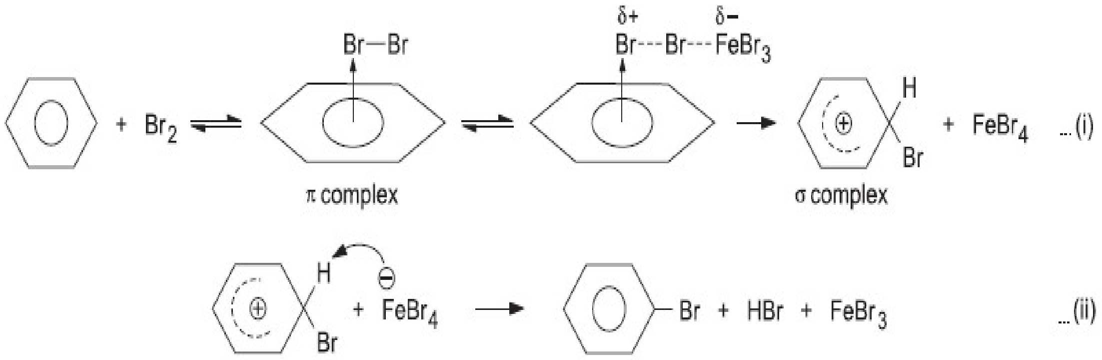
Chlorination:



Bromination:



Free halogens can attack activated benzene rings but a Lewis acid catalyst is required for the benzene ring. It is suggested that probably benzene first forms a **π-complex** with the halogen molecule, e.g., Br_2. The Lewis acid ($FeBr_3$) then polarizes the Br–Br bond and helps in the formation of a **σ-complex** between the benzene carbon and the electrophilic end of the polarized bromine by removing the incipient bromide ion. Subsequent abstraction of hydrogen in the second step completes the reaction.



The order of reactivity of the halogens is $\mathbf{F_2 > Cl_2 > Br_2 > I_2}$. Fluorine is too reactive for practical use. Under ordinary conditions, iodination fails. In the presence of $\mathbf{HNO_3}$, direct iodination has been affected. The attacking electrophile $\mathbf{I^+}$ is produced by HNO_3.

12.5 SUMMARY

- Aromatic electrophilic substitution reactions are characteristic reactions of aromatic compounds due to the **high stability of the aromatic ring**. In these reactions, the aromatic ring acts as a **Lewis base**, attacking electrophiles generated in the reaction medium.
- All electrophilic substitution reactions proceed through a **common arenium ion mechanism**, involving the formation of a resonance-stabilized σ-complex followed by loss of a proton to restore aromaticity. Strong experimental support for this mechanism comes from **isotope effect studies** and **isolation of arenium ion intermediates**.

- The **Friedel–Crafts alkylation** introduces alkyl groups into aromatic rings using alkyl halides and Lewis acids but suffers from limitations such as **polyalkylation and rearrangements**. In contrast, **Friedel–Crafts acylation** introduces acyl groups, avoids rearrangements, and yields only monosubstituted products.
- **Halogenation reactions** require Lewis acid catalysts to generate the active electrophile, and the reactivity of halogens follows a definite trend. Together, these reactions form the foundation for understanding **substitution chemistry of aromatic compounds**.

12.6 SELF-ASSESSMENT QUESTIONS

1) Why do aromatic compounds prefer substitution reactions over addition reactions?
2) What is an arenium ion?
3) Name two Lewis acid catalysts used in Friedel–Crafts reactions.
4) Which step restores aromaticity in electrophilic substitution?
5) Explain the arenium ion mechanism.
6) Discuss the isotope effect as evidence for the arenium ion mechanism.
7) Why does Friedel–Crafts alkylation lead to polyalkylation?
8) Why is nitrobenzene a suitable solvent for Friedel–Crafts acylation?
9) Describe the mechanism of aromatic electrophilic substitution with evidence.
10) Explain Friedel–Crafts alkylation with mechanism, applications, and limitations.
11) Discuss Friedel–Crafts acylation and compare it with alkylation.
12) Explain the mechanism of halogenation of benzene and discuss reactivity trends.

12.7 TECHNICAL TERMS (GLOSSARY)

1) **Electrophile** – Electron-deficient species that accepts an electron pair
2) **Arenium Ion (σ-Complex)** – Resonance-stabilized carbocation intermediate
3) **Lewis Acid** – Electron pair acceptor
4) **Isotope Effect** – Change in reaction rate due to isotopic substitution
5) **Polyalkylation** – Introduction of more than one alkyl group
6) **Carbocation** – Positively charged carbon species
7) **Aromaticity** – Special stability due to delocalized π-electrons

12.8 REFERENCE TEXT BOOKS

1) **Organic Chemistry** – Morrison & Boyd
2) **Organic Chemistry** – Solomons, Fryhle & Snyder
3) **Advanced Organic Chemistry** – Jerry March
4) **A Guidebook to Mechanism in Organic Chemistry** – Peter Sykes
5) **Advanced Organic Chemistry** – Carey & Sundberg

Prof. D. RAMACHANDRAN

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LESSON – 13

ELIMINATION REACTIONS AND THEIR MECHANISMS (E_1, E_2 AND E_{1CB})

13.0 OBJECTIVES:

After studying this lesson, the student will be able to:

1) Understand the **concept and classification of elimination reactions**.
2) Distinguish between **α-, β- and γ-elimination reactions**.
3) Explain the **mechanisms of E_2, E_1 and E_{1CB} elimination reactions**.
4) Understand the **kinetics and molecularity** of different elimination pathways.
5) Describe the **stereochemical requirements** of E_2 and E_1 reactions.
6) Explain **regioselectivity** in elimination reactions using **Saytzeff (Zaitsev) rule**.
7) Analyze the **factors influencing the rate of elimination reactions**.

STRUCTURE

13.1 ELIMINATION REACTIONS

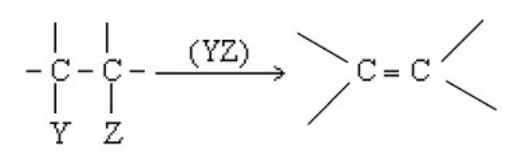
Removal of two atoms or two groups or one atom and one group from a molecule is known as elimination reaction.

In elimination reactions the leaving group is removed as a nucleophile and is called a nucleofuge. The following are examples of leaving groups:

$$X \text{ (halogens)}, \mathrm{OH}, \mathrm{O}R, \overset{\oplus}{\mathrm{N}}_2, \mathrm{N}_3, \mathrm{H}_2\overset{\oplus}{\mathrm{O}}, R_3\overset{\oplus}{\mathrm{N}}, R_2\overset{\oplus}{\mathrm{S}}$$

Elimination reactions are generally endothermic and take place on heating.

Elimination reactions are an important class of reactions which are widely used in the preparation of alkenes. In these reactions a piece of molecule is eliminated from adjacent carbon atoms of the reactant to form a double bond between them.



Such elimination reactions are called 1, 2 – elimination or –elimination reaction. Also known are 1, 1 – elimination and 1, 3 – elimination reaction, but less commonly. Depending upon the molecule eliminated the names of the reactions are given.

- The eliminated molecule is HX, it is called dehydrohalogenation.
- The eliminated molecule is X_2, it is called dehalogenation.
- The eliminated molecule is H_2O, it is called dehydration.
- The eliminated molecule is H_2, it is called dehydrogenation.

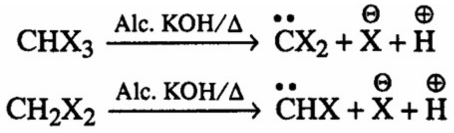
13.2 TYPES OF ELIMINATION REACTIONS

Elimination reactions can be classified into two categories:

- α – elimination or 1,1 – Elimination reactions
- β – elimination or 1,2 – Elimination reactions
- γ – elimination or 1,3 – Elimination reactions

13.2.1 A – ELIMINATION:

A reaction in which both the groups or atoms are removed from the same carbon of the molecule is called α – elimination reaction. It is also known as 1,1-elimination.



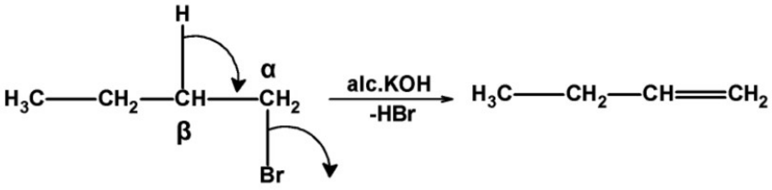
$$CHX_3 \xrightarrow{\text{Alc. KOH/}\Delta} \overset{\bullet\bullet}{C}X_2 + \overset{\ominus}{X} + \overset{\oplus}{H}$$

$$CH_2X_2 \xrightarrow{\text{Alc. KOH/}\Delta} \overset{\bullet\bullet}{C}HX + \overset{\ominus}{X} + \overset{\oplus}{H}$$

Product of the reaction are halocarbenes or dihalocarbenes. Carbenes are key intermediates in a wide variety of chemical and photochemical reactions.

13.2.2 B – ELIMINATION:

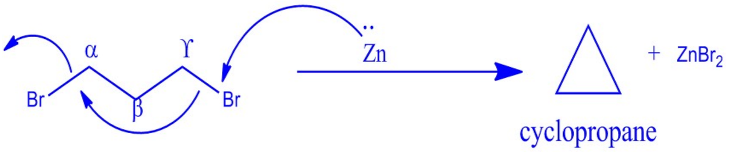
A β-elimination reaction in which atoms or groups are removed from adjacent carbon atoms (the α- and β-carbons), resulting in the formation of a double bond between them. It is also known as 1,2 – elimination.



1-Bromo butane **1-Butene**

13.2.3Γ – ELIMINATION:

A gamma elimination reaction is a type of elimination reaction where the leaving groups or substituents are removed from the gamma (γ) position relative to a reference atom or functional group in the molecule.



1,3 dibromo propane

13.3 TYPES OF Β – ELIMINATION REACTIONS

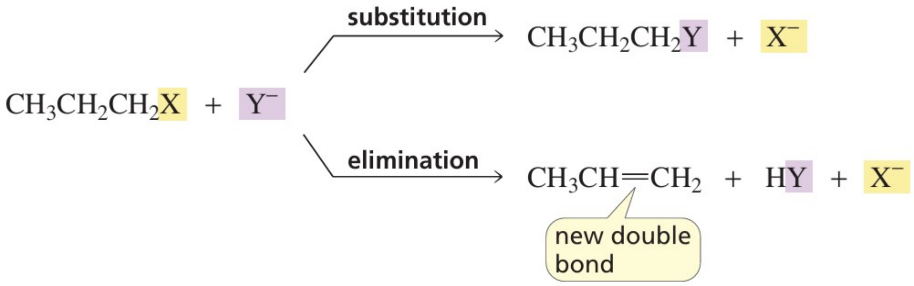
β-eliminations can be further subdivided into three categories depending upon the mechanistic pathway. The important aspect is to establish the number of molecules taking part in the elimination step (molecularity of the reaction).

The types of β-eliminations are

i. E_2 reaction (Bimolecular Elimination reaction)
ii. E_1 reaction (Unimolecular Elimination reaction)
iii. E_{1cb} reaction (Unimolecular Conjugate base reaction)

Elimination Reactions of Alkyl Halides:

In addition to undergoing nucleophilic substitution reactions, alkyl halides also undergo elimination reactions. In an elimination reaction, atoms or groups are removed from a reactant.



Notice that when an alkyl halide undergoes an elimination reaction, the halogen (X) is removed from one carbon and a hydrogen is removed from an adjacent carbon. A double bond is formed between the two carbons from which the atoms are eliminated. Therefore, the product of an elimination reaction is an alkene.

13.4 THE E_2 REACTION

An E_2 elimination is a one-step, bimolecular organic reaction where a proton and a leaving group are removed simultaneously to form a double bond. *where "E" stands for elimination and "2" stands for bimolecular.* It is a second-order reaction. because its rate depends on the concentration of both the substrate and the base. This reaction requires a strong base and a specific stereochemical arrangement called anti-periplanar, where the hydrogen and the leaving group are in opposite planes.

For an example of E_2 reaction, Dehydrobromination of isopropyl bromide caused by the strong base sodium ethoxide (NaOEt) to yield propene is a typical example of E_2 reaction, i.e., a reaction which proceeds through the E_2 mechanism.

$$\mathrm{Et\ddot{\underset{..}{O}}:^{\ominus}} + \underset{\text{Isopropyl bromide}}{\mathrm{(CH_3)_2CHBr}} \xrightarrow{\mathrm{EtOH}} \underset{\text{Propene (79\%)}}{\mathrm{CH_3CH{=}CH_2}} + \mathrm{EtOH} + \mathrm{:\ddot{\underset{..}{Br}}:^{\ominus}}$$

13.4.1 KINETICS OF E_2 REACTION

The E_2 reaction exhibits second-order kinetics.

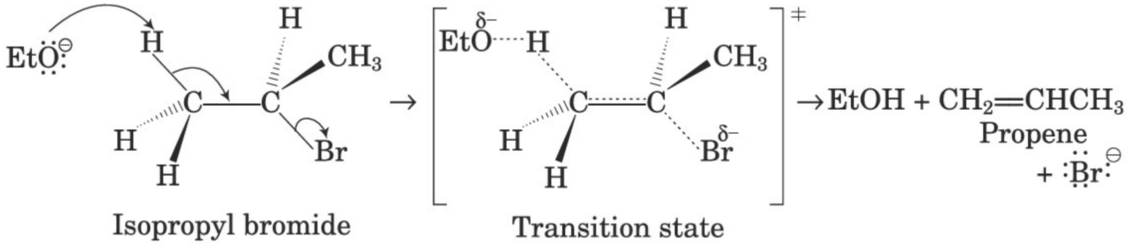
$$\text{Rate} = k\left[\mathrm{(CH_3)_2CHBr}\right][\mathrm{Et\ddot{\underset{..}{O}}:^{\ominus}}]$$

The rate of elimination thus depends on the concentration of both the substrate and the base. Therefore, the reaction is bimolecular, i.e., the substrate and the base are involved in the transition state of the rate-determining step.

13.4.2 MECHANISM OF E_2 REACTION

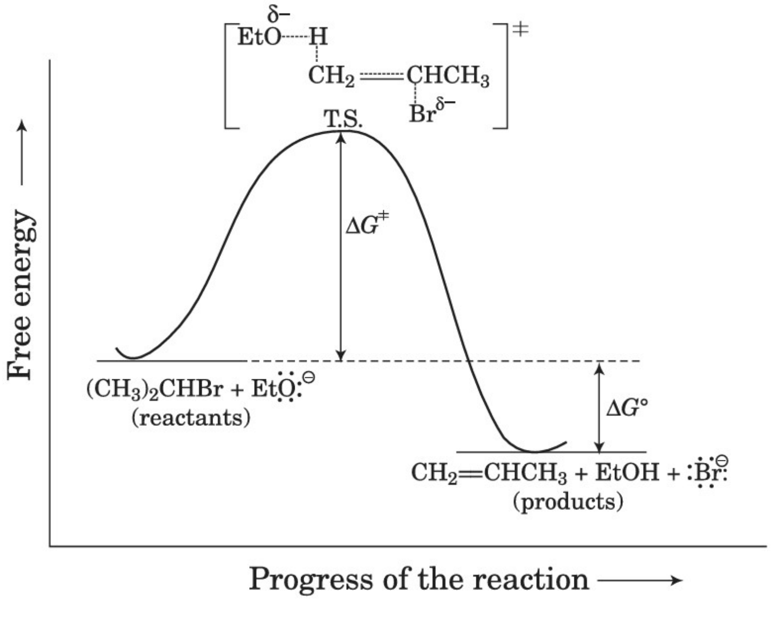
The most straight-forward explanation for the observed second-order kinetics is a concerted reaction, i.e., bond breaking and bond making occur simultaneously. The mechanism of this reaction is designated as E2 (E stands for elimination and 2 stands for bimolecular) because the two reactants (the substrate and the base) are involved in the transition state of the rate-determining step (the only step).

In the E2 reaction, the base (EtO $^-$) abstracts a proton from the β-carbon of the isopropyl bromide and simultaneously the leaving group (Br $^-$) departs from the a-carbon with the formation of a double bond. The electron pair in the β C — H bond forms the new π bond and the leaving group Br $^-$ comes off with the electron pair in the C — Br bond. Thus, it is a concerted elimination, i.e., a one-step process which passes through a single transition state. In the transition state, there is a partially formed O — H bond, a partly broken H — C bond, a partly formed C = C bond and a partly broken C — Br bond. The process can be represented as follows:



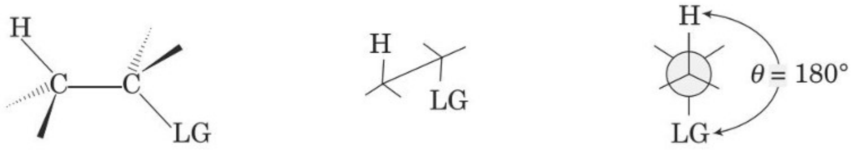
Entropy favours the products of an E_2 reaction because two molecules of starting material are formed from three molecules of product.

The energy profile diagram for this E_2 reaction is as follows:



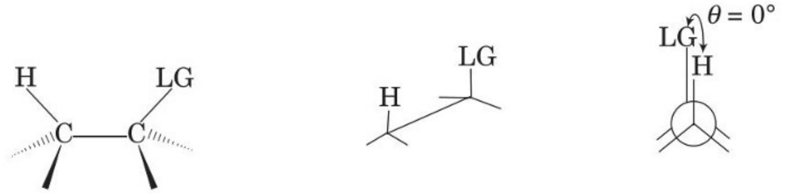
13.4.3 STEREOCHEMISTRY OF E_2 REACTION

There is a stereo electronic requirement of an E_2 process and the requirement is that the groups to be eliminated should be anti-periplanar (i.e., conformationally trans to one another with a dihedral angle of 180°) and not syn-periplanar (i.e., conformationally cis to one another with a dihedral angle of 0°).



Flying wedge projection Sawhorse projection Newman projection

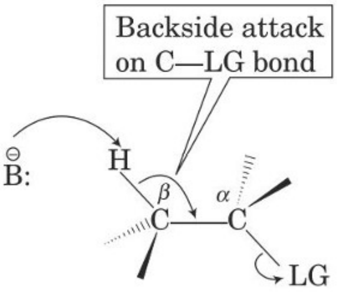
Anti-periplanar conformation
(more favourable for E2 reaction)



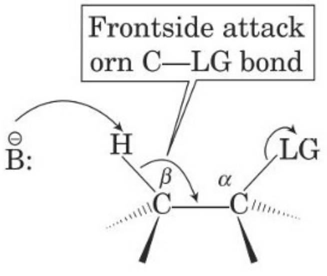
Flying wedge projection Sawhorse projection Newman projection

Syn-periplanar conformation
(less favourable for E2 reaction)

Unlike syn geometry the anti-geometry allows the β C — H bonding electrons to displace the leaving group from the backside. Like S_N^2 this familiar backside attack is energetically advantageous from the electronic point of view.



Anti-elimination
(through *anti*
conformation)

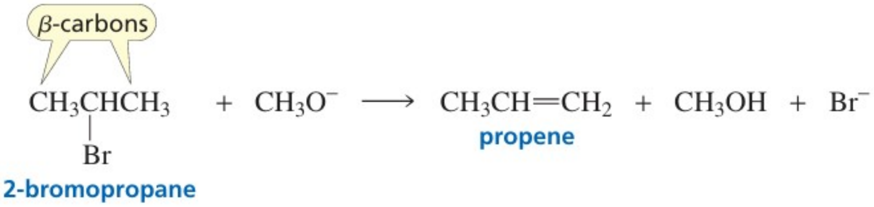


Syn-elimination
(through eclipsed
conformation)

The attacking base and the leaving group remain far apart from each other in anti geometry but not in syn geometry and, therefore, the steric interactions are minimized.

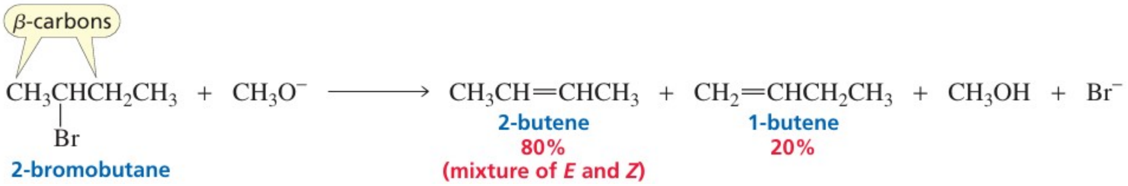
13.4.4 AN E2 REACTION IS REGIOSELECTIVE

An alkyl halide such as 2-bromopropane has two ß-carbons from which a proton can be removed in an E_2 reaction. Because the two ß-carbons are identical, the proton can be removed equally easily from either one.



$$CH_3\underset{\substack{|\\ Br}}{C}HCH_3 + CH_3O^- \longrightarrow CH_3CH{=}CH_2 + CH_3OH + Br^-$$

In contrast, 2-bromobutane has two structurally different ß-carbons from which a proton can be removed. Therefore, when this alkyl halide reacts with a base, two elimination products are formed: 2-butene (80%) and 1-butene (20%). Thus, this E2 reaction is regioselective because more of one constitutional isomer is formed than of the other.

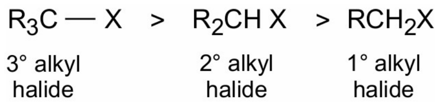


$$CH_3\underset{\substack{|\\ Br}}{C}HCH_2CH_3 + CH_3O^- \longrightarrow CH_3CH{=}CHCH_3 + CH_2{=}CHCH_2CH_3 + CH_3OH + Br^-$$

13.4.5 FACTORS INFLUENCING E_2 REACTION RATE

i. The effect of substrate structure on rate:

In E2 reactions, as the number of alkyl group on the carbon atom having the leaving group increases, the rate of reaction increases. Thus, 3° alkyl halides are more reactive than 2° alkyl halides, which in turn are more reactive than the 1° alkyl halide.



$$R_3C-X > R_2CH\,X > RCH_2X$$

ii. The effect of base on rate:

The rate of E_2 reaction also depends on the strength of the base. The rate increases as the strength of the base increases. Normally in E_2 reactions, the base used are ^-OH or ^-OR. However, two other string bases like DBN, DBU are also used.

iii. The effect of leaving group on rate:

Because the bond to the leaving group is partially broken in the transition state, the better the leaving group the higher the rate of the E_2 reaction.

The order of reactivity of the alkyl halides is $R — F < R — Cl < R — Br < R — I$.

iv. The effect of solvent on rate:

The E_2 reactions are favoured by a decrease in the polarity of the solvent because the charge in the E_2 transition state is considerably dispersed. In fact, polar aprotic solvents increase the rate of E_2 reactions. For example, Polar aprotic solvents like DMSO, DMF, THF, acetone etc., are increases the rate of the reaction.

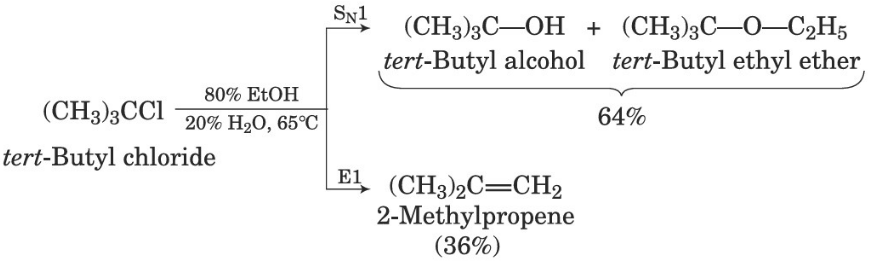
v. The effect of temperature on rate:

The rate of E_2 reaction increases with rise in temperature. The number of particles increases in E_2 reactions and so, E_2 reactions have the more favourable entropy term.

13.5 THE E_1 REACTION

The second kind of elimination reaction that alkyl halides can undergo is an E_1 reaction, where "E" stands for elimination and "1" stands for unimolecular.

For an example of E_1 reaction, when tert-butyl chloride is treated with 80 percent aqueous ethanol at 65°C, 36 percent 2-methylpropene is obtained by unimolecular elimination (E_1) and 64 percent tert-butyl alcohol and tert-butyl ethyl ether by unimolecular substitution (S_N ^{1}).



13.5.1 KINETICS OF E_1 REACTION

The E1 reaction exhibits first-order kinetics and obeys the following rate law:

$$\text{Rate} = k[(CH_3)_3\,Cl]$$

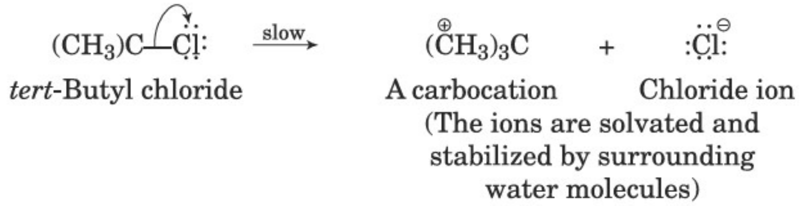
Like the $S_N{}^1$ mechanism, the kinetics suggests that the mechanism of this elimination reaction involves more than one step, and that the slow step is unimolecular, involving only the alkyl halide.

13.5.2 MECHANISM OF E_1 REACTION

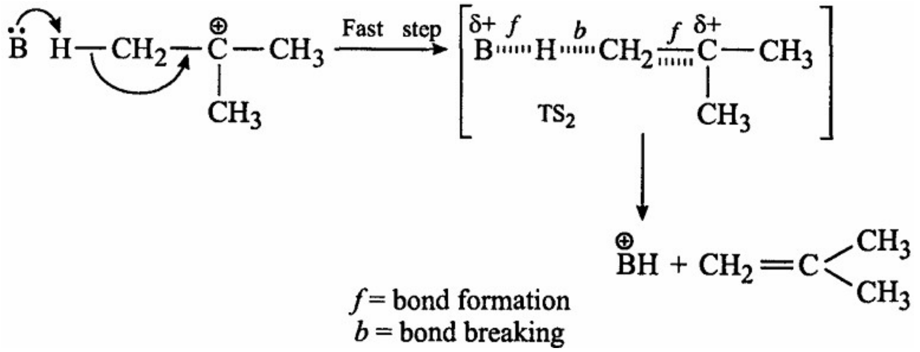
The most straightforward explanation for the observed first-order kinetics is a two-step reaction in which the bond to the leaving group breaks followed by the pi bond is formed. The mechanism of this reaction is designated as E_1 (E stands for Elimination and 1 stands for unimolecular) because only one reactant (the substrate) is involved in the transition state of the rate-determining step.

The E_1 mechanism of the formation of 2-methylpropene form tert-butyl chloride involves the following two steps:

Step 1: Formation of carbocation intermediate



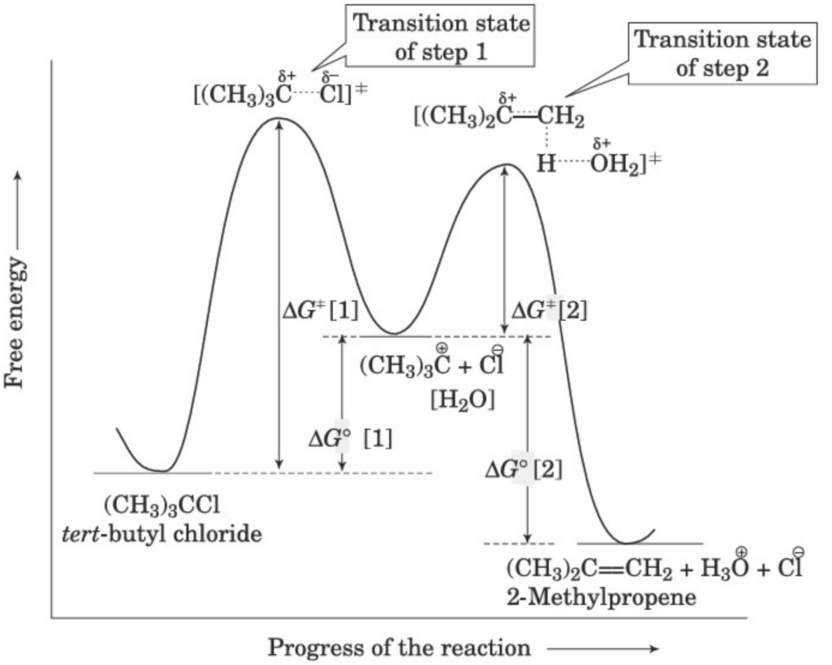
Step 2: Removal of proton by base



In the first step, tert-butyl chloride slowly dissociates under the influence of solvent forces to form tert-butyl cation (a stable 3° carbocation) and chloride ion. It is the rate-determining step of the reaction and it is the same first step as the $S_N{}^1$.

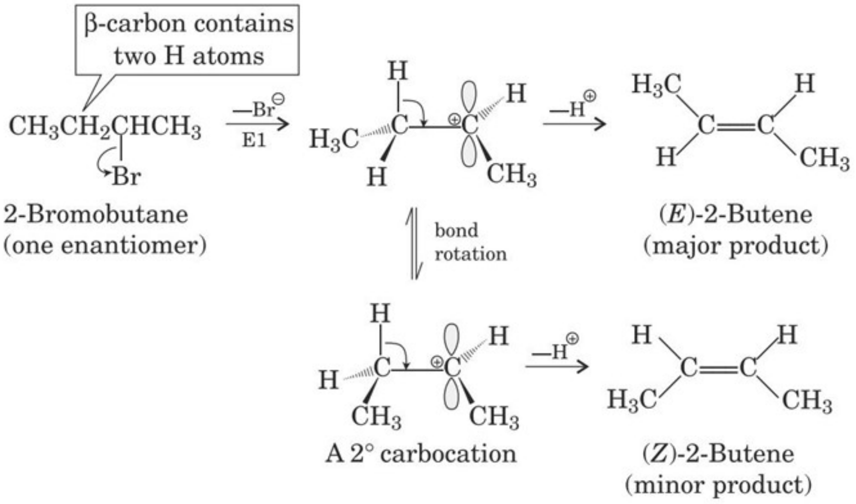
In the second step, the solvent H_2O (or Cl^-) acts as a base and removes a proton from a carbon adjacent to the positive carbon of the carbocation (α ß - carbon) to form the alkene.

The energy profile diagram for this E_1 reaction is as follows:



13.5.3 STEREOCHEMISTRY OF E_1 REACTION

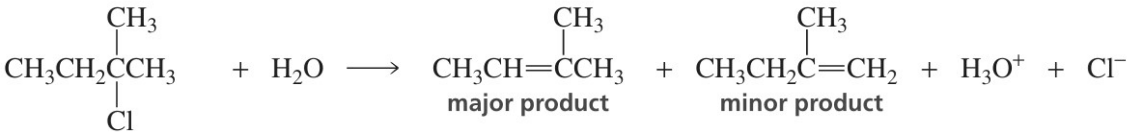
The carbocation formed in the first step of an E1 reaction is planar. This means that the electrons from a departing proton can move towards the positively charged carbon from either side. Therefore, both syn- and anti-elimination can take place. Because both syn and anti-elimination can occur, an E1 reaction forms both the E and Z products regard- less whether the b-carbon atom from which the proton is removed is bonded to one or two hydrogens. The major product is the one with the bulkiest groups on opposite sides of the double bond because this alkene is thermodynamically more stable. For example:



It is to be noted that an E2 reaction forms the E and Z products only if the β-carbon from which the proton is expelled is bonded to two hydrogens. If it contains only one hydrogen, only one product is obtained because anti-elimination takes place. The configuration of the product then depends on the configuration of the substrate.

13.5.4THE E1 REACTION IS REGIOSELECTIVE

When more than one alkene can be formed, the E1 reaction, like the E2 reaction, is regioselective. And, like an E2 reaction, the major product is the more stable alkene.



$$CH_3CH_2\underset{Cl}{\overset{CH_3}{C}}CH_3 + H_2O \longrightarrow CH_3CH{=}\overset{CH_3}{C}CH_3 + CH_3CH_2\overset{CH_3}{C}{=}CH_2 + H_3O^+ + Cl^-$$

The more stable alkene is the major product because its greater stability causes the transition state leading to its formation to be more stable. Therefore, it is formed more rapidly. Notice that the more stable alkene is formed by removing the hydrogen from the ß – carbon bonded to the fewest hydrogens, in accordance with Zaitsev's rule or Saytzeff rule.

13.5.5FACTORS INFLUENCING E_1 REACTION RATE

i. The effect of substrate structure on rate:

The order of reactivity is primary < secondary < tertiary and this is because the stability of the carbocations formed in the rate-determining step increases on going from primary to tertiary due to +I and hyper conjugative effects.

ii. The effect of the base on rate:

Since the base is not involved in the rate determining step of the E_1 reaction, therefore, the E_1 reaction rate does not depend on base concentrations. Weak bases like H_2O and EtOH favor E_1 reactions.

iii. The effect of the leaving group on rate:

Since a better leaving group causes facile ionization in the rate-determining step, the more the leaving ability of a group increases the more the E1 reaction is favoured.

The order of reactivity of the alkyl halides is R — F < R — Cl < R — Br < R — I.

iv. The effect of solvent on rate:

Since E_1 reactions involve an ionic intermediate, the carbocation, the rate of the E_1 reaction increases with increasing polarity of the solvent. Polar solvents of poor nucleophilicity favour E_1 reactions.

v. The effect of temperature:

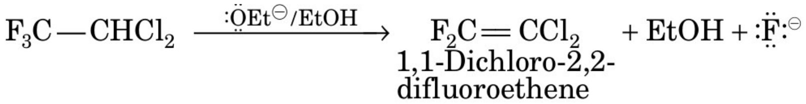
The rate of E_1 reaction increases with rise in temperature. The number of particles increases in E_1 reactions and so, E_1 reactions have the more favourable entropy term.

13.6 THE E_{1CB} REACTION

There is third mechanism of ß – elimination reactions. This begins with the rapid loss of a proton to a base. Loss of this proton leads to a formation of a carbanion. The carbanion is then converted to, an alkene. Conversion of carbanion to alkene is slow step and hence the rate determining step. Since this reaction proceeds through the conjugate base of the starting material, this elimination is abbreviated as E_{1CB} (elimination unimolecular conjugate base).

Example of E_{1CB} Reaction

Base-promoted dehydrofluorination of 2,2-dichloro-1,1,1-trifluoroethane proceeds by the E_{1CB} mechanism.



$$F_3C{-}CHCl_2 \xrightarrow{:\ddot{O}Et^{\ominus}/EtOH} \underset{\text{1,1-Dichloro-2,2-difluoroethene}}{F_2C{=}CCl_2} + EtOH + :\ddot{\underset{..}{F}}:^{\ominus}$$

13.6.1 KINETICS OF E_{1CB} REACTION:

The E_{1CB} reaction exhibits second-order kinetics (first order in the substrate and first order in the base) and obeys the following rate law (same as E_2):

$$\text{Rate} = k[F_3CCHCl_2]\ [OEt^{\ominus}]$$

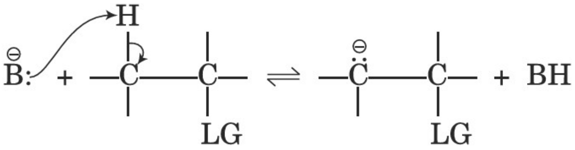
13.6.2 MECHANISM OF E_{1CB} REACTION:

Although the E_{1CB} mechanism is the least common of the elimination pathways, it provides a reasonable extension of the elimination mechanism that is not related to substitution. This is, in fact, a base-promoted unimolecular reaction taking place through the formation of the conjugate base (CB) of the substrate. The mechanism is designated as E_{1CB} (Elimination Unimolecular conjugate Base) because it is the conjugate base of the substrate that gives up the leaving group and the conjugate base is the only species involved in the rate-determining step of the reaction (i.e., unimolecular).

An E_{1CB} reaction proceeds through the following two steps:

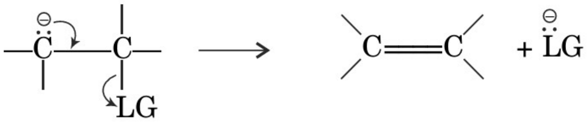
Step 1:

The base abstracts the most acidic ß – hydrogen atom from the substrate to form an intermediate carbanion. This step is fast and reversible.



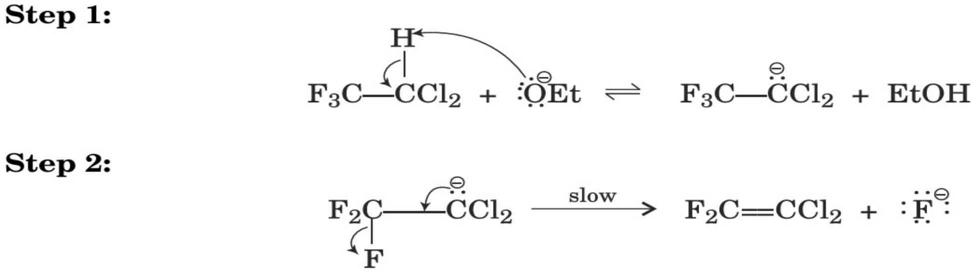
Step 2:

The carbanion loses the leaving group to form the alkene product. This step is slow (rate determining).



13.6.3 THE NATURE OF THE SUBSTRATE:

Substrates containing acidic ß – hydrogens (groups like $-NO_2$, –CHO, –COR, –CN, –COOR, $-SO_2Ar$ etc. should present at ß – Carbon) and poor leaving groups like ^-F, ^-Cl, ^-SePh, ^-OPh, ^-OH, etc. are very prone to react by the E_{1CB} mechanism. In the given example, the halogens enhance the acidity of the ß – hydrogen atom and fluoride ion (F^-) is a poor leaving group. The reaction occurs as follows:



However, unlike E_1 elimination, the intermediate in E_1 elimination and the intermediate is E_{1CB} elimination is a carbanion, not a carbocation.

13.7 SUMMARY

1) Elimination reactions involve the **removal of two atoms or groups** from a molecule to form a **double bond**, commonly producing alkenes.
2) Based on the position of eliminated groups, eliminations are classified as **α (1,1), β (1,2), and γ (1,3) eliminations**.
3) **β-Elimination** is the most important type and proceeds through **E2, E1, or E1CB mechanisms**.
4) **E2 reaction** is a **concerted, bimolecular process** requiring a strong base and **anti-periplanar geometry**.
5) **E1 reaction** proceeds via a **carbocation intermediate**, follows **first-order kinetics**, and often competes with SN1 reactions.

6) **E1CB reaction** involves formation of a **carbanion (conjugate base)** and occurs when the leaving group is poor and the β-hydrogen is acidic.
7) Elimination reactions are generally **endothermic**, favored by **high temperature**, and show **regioselectivity**, yielding more stable alkenes as major products.
8) These reactions are widely used in **alkene synthesis** and form an essential part of reaction mechanism studies.

13.8 TECHNICAL TERMS

1) **Elimination reaction**: Removal of atoms or groups leading to formation of a double bond.
2) **Nucleofuge**: A leaving group that departs as a nucleophile.
3) **α-Elimination**: Removal of two groups from the same carbon atom.
4) **β-Elimination**: Removal of groups from adjacent carbon atoms.
5) **E2 reaction**: One-step, bimolecular elimination reaction.
6) **E1 reaction**: Two-step, unimolecular elimination reaction via carbocation.
7) **E1CB reaction**: Elimination via conjugate base (carbanion) intermediate.
8) **Anti-periplanar**: Geometry where leaving group and hydrogen are opposite (180°).
9) **Regioselectivity**: Preference for formation of one constitutional isomer.
10) **Saytzeff (Zaitsev) rule**: More substituted alkene is the major product.

13.9 SELF-ASSESSMENT QUESTIONS

1) Define elimination reactions with suitable examples.
2) Classify elimination reactions based on the position of eliminated groups.
3) Explain the mechanism of E2 reaction.
4) Discuss the kinetics and stereochemistry of E2 elimination.
5) Describe the mechanism of E1 reaction.
6) Why does E1 reaction compete with SN1 reaction?
7) What is E1CB reaction? Explain its mechanism.
8) Compare E1, E2 and E1CB reactions.
9) Explain the factors influencing the rate of E2 reactions.
10) Discuss regioselectivity in elimination reactions with examples.

13.10 REFERENCE TEXTBOOKS

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Prof. D. RAMACHANDRAN

LESSON – 14

ORIENTATION AND STEREOCHEMISTRY IN ELIMINATION REACTIONS

14.0 OBJECTIVES:

After studying this lesson, the student will be able to:

1) Understand the **orientation of elimination reactions**.
2) Apply **Saytzeff's (Zaitsev's) rule** to predict major elimination products.
3) Explain the **Hofmann rule** and conditions favoring Hofmann elimination.
4) Distinguish between **Saytzeff and Hofmann products**.
5) Understand the role of **base size, leaving group nature, and substrate structure**.
6) Differentiate between **syn and anti-elimination**.
7) Analyze **competition between elimination and substitution reactions**.
8) Predict reaction pathways among **SN_1, SN_2, E_1, and E_2 mechanisms**.

STRUCTURE

14.1 ORIENTATION IN ELIMINATION REACTIONS

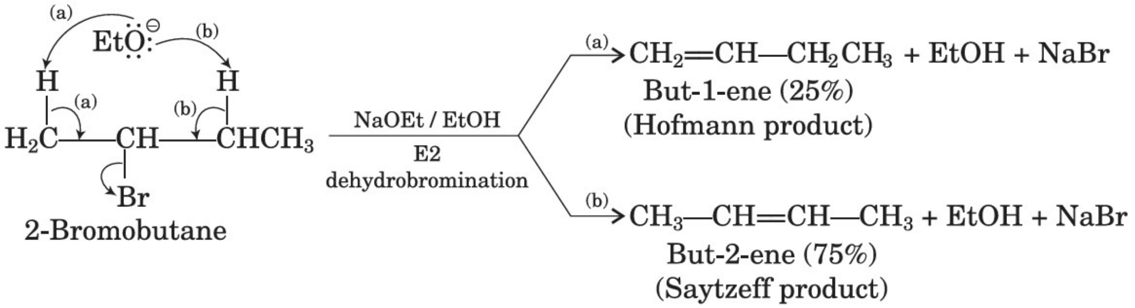
If a substrate has different types of ß – hydrogens then it will give more than one product. Major product of the reaction can be known by two empirical rules. The **Hofmann** and the **Saytzeff** rules, govern the orientation of elimination of these reactions.

14.2 SAYTZEFF'S (OR ZAITSEV'S) RULE

According to this rule, major product is the most substituted alkene, i.e., the most stable alkene. Thus, the major product is obtained by elimination of H^+ from that ß-carbon which has the least number of hydrogens. Product of the reaction in this case is known as Saytzeff product.

This rule states that neutral substrates possessing two different types of ß – hydrogens yield predominantly the more substituted alkene.

For example, when 2-bromobutane is treated with NaOEt in EtOH, it undergoes E_2 dehydrobromination following the Saytzeff rule because it produces 75% of the more substituted alkene (but-2-ene) and 25% of the less substituted alkene, (but-1-ene).

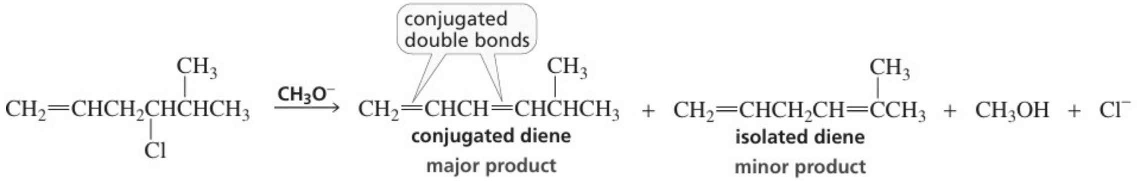


The predominant formation of Saytzeff product can be explained as follows:

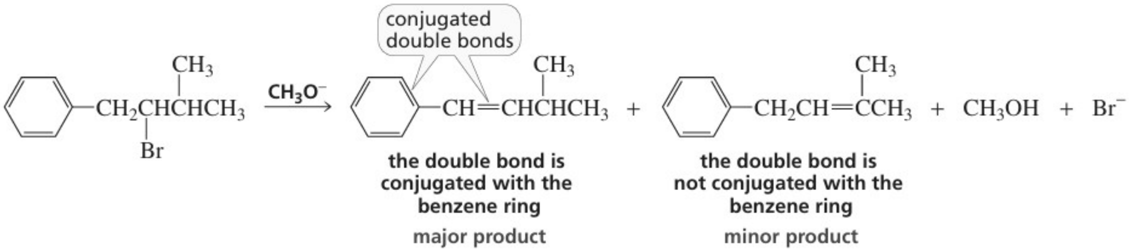
Neutral substrates (except fluorides) undergo ideal E_2 elimination reaction in which both the C — H and C — LG bonds are being broken and the carbon–carbon double bond is being formed simultaneously. For this reason, the transition state possesses considerable double bond character. Therefore, any effect that stabilizes the product alkene also stabilizes the transition state. ***Because of hyperconjugation effect, the stability of a double bond increases progressively with increase in the number of alkyl groups bonded to it, i.e., with increase in the number of α-H atoms.*** The disubstituted alkene, but-2-ene (with six hyperconjugable α-H atoms) is, therefore, thermodynamically more stable than the monosubstituted alkene, but-1-ene (with only two hyperconjugable α-H atoms) and so, but-2-ene is formed more rapidly through the transition state of lower energy than but-1-ene, i.e., the reaction produces the more substituted alkene but-2-ene predominantly.

The more substituted alkene, however, is not always the more stable alkene, and in such cases, Saytzeff rule cannot be used to predict the major product.

For example, in each of the following reactions, the major product is the alkene with conjugated double bonds because it is the more stable alkene, even though it is not the more substituted alkene.



$$CH_2{=}CHCH_2\underset{Cl}{C}H\overset{CH_3}{C}HCH_3 \xrightarrow{CH_3O^-} CH_2{=}CHCH{=}CH\overset{CH_3}{C}HCH_3 + CH_2{=}CHCH_2CH{=}\overset{CH_3}{C}CH_3 + CH_3OH + Cl^-$$



Therefore, if the alkyl halide has a double bond or a benzene ring, do not use Zaitsev's rule to predict the major product of an elimination reaction.

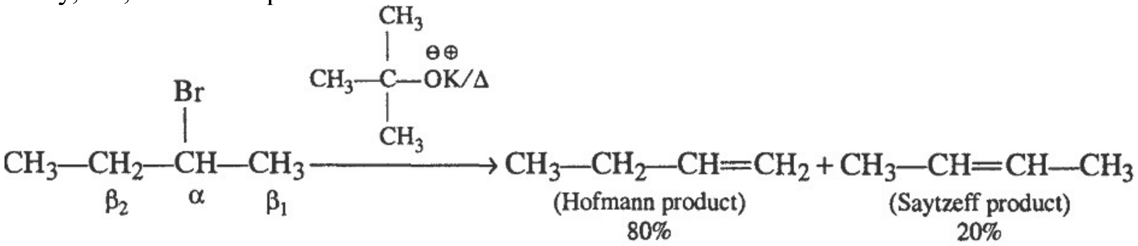
14.3 THE HOFMANN RULE

According to this rule major product is always least substituted alkene, i.e., the least stable alkene. Thus, the major product is formed from ß – carbon which has maximum number of hydrogens. Product of the reaction in this case is known as Hofmann product.

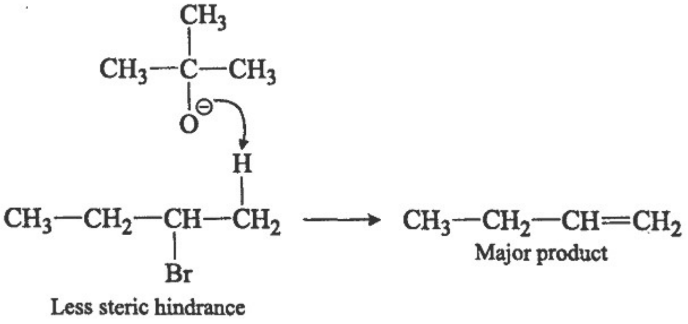
In almost all E_2 reactions product formation takes place by Saytzeff rule. *Only in four cases product formation takes place by Hofmann Rule.*

i. Size of attacking base:

Primary and sec-alkyl halides give Hofmann elimination when the size of the base is bulky, i.e., sodium or potassium ter-butoxide.


$$\underset{\beta_2}{CH_3-CH_2}-\underset{\alpha}{\overset{Br}{CH}}-\underset{\beta_1}{CH_3} \xrightarrow{(CH_3)_3C\overset{\ominus\oplus}{O}K/\Delta} \underset{\substack{\text{(Hofmann product)}\\ 80\%}}{CH_3-CH_2-CH=CH_2} + \underset{\substack{\text{(Saytzeff product)}\\ 20\%}}{CH_3-CH=CH-CH_3}$$

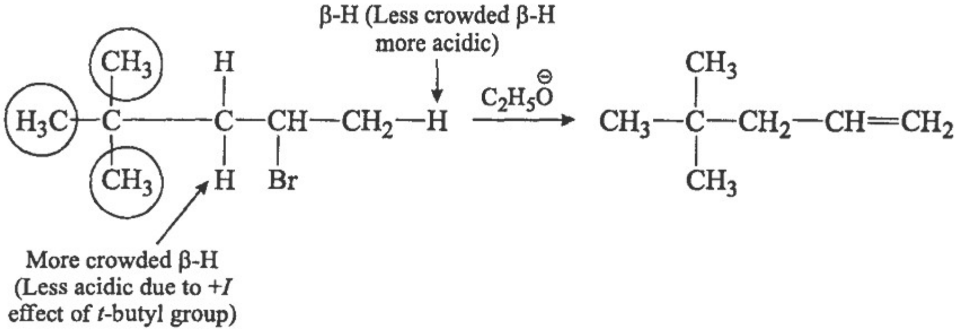
Due to steric hindrance, bulky bases favour the removal of β-hydrogens from the least substituted carbon adjacent to the leaving group.



This favours the formation of the less substituted alkene, called the Hofmann product, instead of the thermodynamically more stable, more substituted alkene (Saytzeff product).

ii. Bulkiness of groups surrounding the leaving group:

The hindered β-hydrogen (i.e., γ - carbon is quaternary) yields the less substituted alkene in E_2 reaction even with a small base like the ethoxide ion.

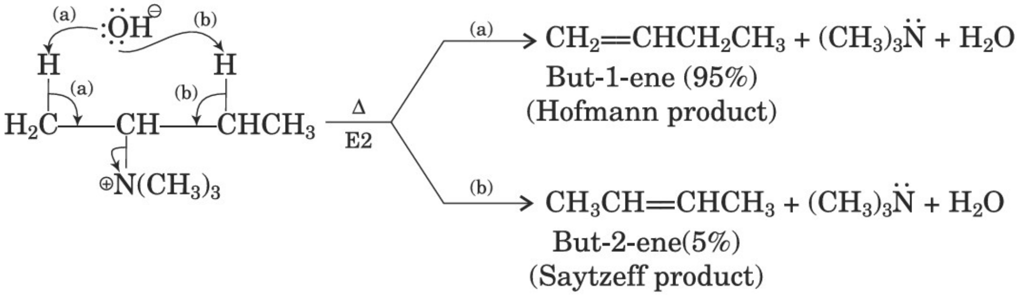


Above two factors decide whether the orientation of elimination will follow Saytzeff rule or Hofmann rule.

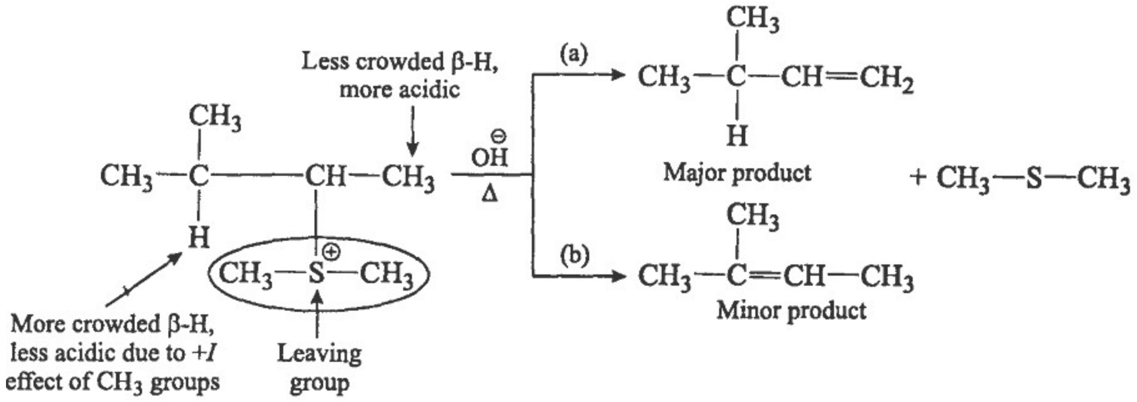
iii. Bulky leaving groups:

The most common type of bulky leaving groups which lead to Hofmann products. The charged groups are generally bulkier than the neutral ones.

If the eliminations are carried out with charged substrates. i.e., Substrates containing charged leaving group (e.g., – $^+N(CH_3)_3$, – $^+SMe_2$, etc.) undergo E_2 elimination reaction leads to the formation of less substituted alkenes as major product.



The abstraction of ß – H by base thus takes place preferentially form the methyl group because this leads to the formation of a more stable (lower energy) carbanion(1°)-like transition state. The reaction thus produces a predominance of the less substituted alkene but-1-ene.

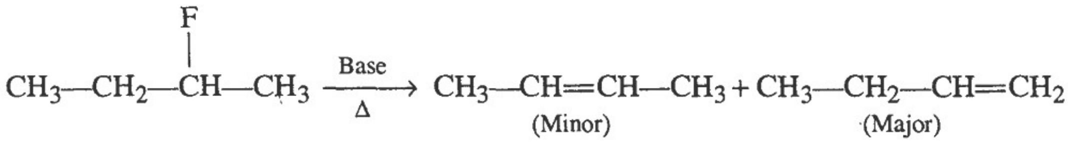


The formation of the less substituted terminal alkene may also be explained in terms of steric effect.

iv. Poor Leaving Groups:

The presence of poor leaving groups, e.g., $-F^-$, $-^+NR_3$ and $-^+SR_2$ leads to the formation of Hofmann product.

Dehydrohalogenation of alkyl halides when leaving group is very poor, e.g., alkyl fluoride (primary or secondary)



$$CH_3-CH_2-\overset{\overset{\large F}{|}}{C}H-CH_3 \xrightarrow[\Delta]{\text{Base}} \underset{\text{(Minor)}}{CH_3-CH=CH-CH_3} + \underset{\text{(Major)}}{CH_3-CH_2-CH=CH_2}$$

In general, in the case of substrates with $-F^-$, $-^+NR_3$ and $-^+SR_2$ leaving groups, the acidity of the eliminating hydrogen governs the orientation. The most acidic hydrogen is preferably removed to give the major product.

Note:

i) In E_1 reactions, product formation always takes place by Saytzeff rule.

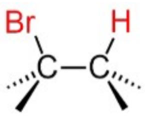
ii) In E_{1CB} reactions, product formation always takes place by Hofmann rule.

iii) In E_2 reaction, product formation takes place by Saytzeff as well as Hofmann rule.

14.4 SYN ELIMINATION VERSUS ANTI ELIMINATION

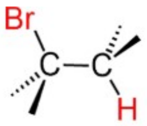
Syn and anti-elimination are two types of E_2 elimination reactions, differing in the relative orientation of the departing leaving group and the hydrogen atom being removed.

Feature	Anti-Elimination	Syn Elimination
Orientation	The hydrogen atom and the leaving group are on opposite sides of the C-C bond (anti-periplanar).	The hydrogen atom and the leaving group are on the same side of the C-C bond (syn-periplanar).
E_2 Reaction	The preferred and most common mode of reactivity for E_2 reactions.	Less common but can occur under specific conditions.
Mechanism	Occurs through a cyclic transition state where the base, hydrogen, and leaving group are all on opposite sides of the bond being broken.	Occurs through a cyclic transition state where the base, hydrogen, and leaving group are all on the same side of the bond.
Result	Typically forms an alkene.	Typically forms an alkene.



***syn* periplanar**

β-H and Br on the same side.

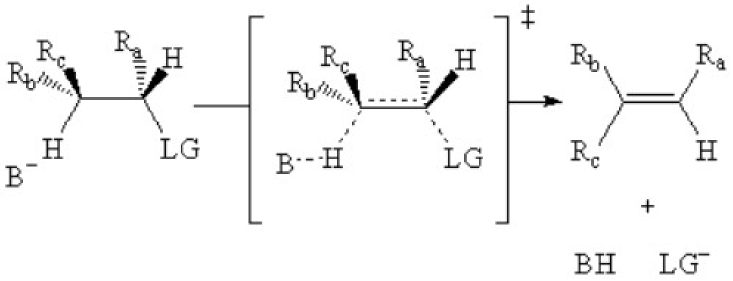


***anti* periplanar**

β-H and Br on opposite sides.

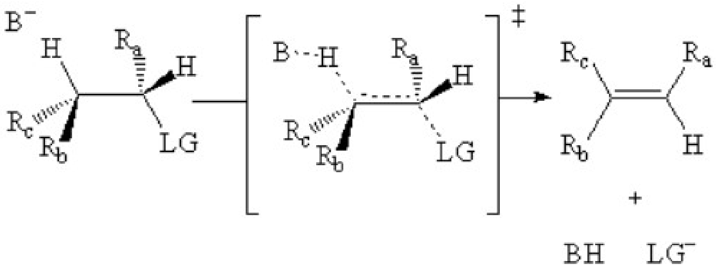
14.4.1 SYN ELIMINATION:

In syn elimination, the base attacks the β-hydrogen on the *same* side as the leaving group.



14.4.2 ANTI-ELIMINATION:

In anti-elimination, the base attacks the β-hydrogen on the *opposite* side of the leaving group.



14.5 COMPETITIONS BETWEEN ELIMINATION AND SUBSTITUTION:

Elimination–substitution competition is controlled by a small set of variables: substrate, nucleophile/base, solvent, temperature, and leaving group. Each combination biases the system toward one or more of SN_1, SN_2, E_1, or E_2 pathways, often giving mixtures but with a predictable major product.

Step 1: Classify the Substrate

- Methyl (CH_3–X): Only SN_2; no β-H for E_2 and no stable carbocation for SN_1/E_1.
- Primary (1°): Almost always SN_2 with good nucleophiles; E_2 appears only with strong bulky bases (e.g. t-BuO^-).
- Secondary (2°): Genuine four-way competition; conditions decide between SN_1, SN_2, E_1, E_2.
- Tertiary (3°): SN_2 essentially shut down; strong base → E_2, weak base/nucleophile in polar protic solvent → SN_1/E_1 mixture.

Step 2: Nature of the Nucleophile/Base

- Strong nucleophile, weak base (e.g. I^-, Br^-, RS^-, N_3^-, CN^-):
  - 1°: predominantly SN_2.
  - 2°: SN_2 vs SN_1; elimination only minor unless temperature high or base strength non-negligible.
- Strong base and strong nucleophile (e.g. OH^-, RO^-):
  - 1°: SN_2 major, E_2 minor (unless very hot).
  - 2°: Significant SN_2/E_2 competition.
  - 3°: E_2 dominates (SN_2 blocked sterically).
- Strong, bulky base (e.g. t-BuO^-, LDA):
  - 1°, 2°, 3°: E_2 strongly favored; Hofmann or less substituted alkene often forms due to steric effects.
- Weak nucleophile/weak base (e.g. H_2O, ROH):
  - 2°, 3° in polar protic solvent: SN_1 + E_1 mixture; increasing temperature shifts toward E_1 (more alkene).

- Concentration of the attacking species also matters: higher concentration favors bimolecular SN_2/E_2 versus unimolecular SN_1/E_1.

Step 3: Solvent and Temperature

- Polar protic solvents (water, alcohols): Stabilize carbocations and anions; favor SN_1/E_1 when nucleophile/base is weak; also help SN_1/E_1 at 2° and 3° centers.
- Polar aprotic solvents (DMSO, DMF, acetone, acetonitrile): Enhance nucleophilicity of anions and favor SN_2 (and sometimes E_2 if the anion is a strong base).
- Temperature: Because elimination increases entropy (2 molecules → 2 but with formation of a π-bond and loosening of organization), raising temperature tips the equilibrium toward E_1/E_2 relative to SN_1/SN_2.
- Practically: "heat + base" is a red flag for an elimination-favored set of conditions, especially with 2°/3° substrates.

Step 4: Mechanistic Pairings and Typical Competitions

- SN_2 vs E_2 (bimolecular pair):

  - Common with 1° and 2° substrates in presence of strong bases/nucleophiles.
  - Less steric bulk and lower temperature favor SN_2; bulkier base and higher temperature push E_2.
- SN_1 vs E_1 (unimolecular pair):
  - Share the same carbocation intermediate and rate-determining step, so they usually occur together.
  - More substituted carbocations and higher temperature increase alkene fraction (E_1).

14.6 SUMMARY

1) When a substrate has more than one type of β-hydrogen, elimination reactions can give **more than one alkene**, and the **major product orientation** is governed by empirical rules.
2) **Saytzeff's rule** states that the **more substituted (more stable) alkene** is formed as the major product in most elimination reactions.
3) The preference for Saytzeff product is explained by **hyperconjugation and alkene stability**.
4) **Hofmann rule** predicts formation of the **least substituted alkene** as the major product under special conditions
5) **E1 reactions** always follow Saytzeff rule, while **E1CB reactions** follow Hofmann rule.
6) In **E2 reactions**, both Saytzeff and Hofmann orientations are possible depending on reaction conditions.
7) **Anti-elimination (anti-periplanar)** is the preferred and most common pathway in E2 reactions.
8) Elimination and substitution reactions often **compete**, and the outcome depends on **substrate, base/nucleophile, solvent, and temperature**.

14.7 TECHNICAL TERMS

1) **Orientation of elimination**: Direction in which β-hydrogen is removed during elimination.
2) **Saytzeff (Zaitsev) rule**: Major product is the more substituted alkene.
3) **Hofmann rule**: Major product is the least substituted alkene.
4) **Saytzeff product**: More substituted alkene formed in elimination.
5) **Hofmann product**: Less substituted alkene formed in elimination.
6) **β-Hydrogen**: Hydrogen atom on the β-carbon relative to leaving group.
7) **Syn elimination**: Removal of hydrogen and leaving group from same side.
8) **Anti-elimination**: Removal of hydrogen and leaving group from opposite sides.
9) **Anti-periplanar**: Geometry with 180° dihedral angle between C–H and C–LG bonds.
10) **Elimination–substitution competition**: Competition between SN and E pathways.

14.8 SELF-ASSESSMENT QUESTIONS

1) What is meant by orientation in elimination reactions?
2) State Saytzeff's rule with an example.
3) Explain why Saytzeff product is generally more stable.
4) Define Hofmann rule and Hofmann product.
5) List conditions under which Hofmann elimination is favored.
6) Differentiate between Saytzeff and Hofmann eliminations.
7) Explain syn and anti-elimination.
8) Why is anti-elimination preferred in E2 reactions?
9) Discuss elimination–substitution competition.
10) How do base, solvent, and temperature influence elimination reactions?

14.9 REFERENCE TEXTBOOKS

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Prof. D. RAMACHANDRAN

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LESSON – 15

ELIMINATION REACTIONS: DEHYDRATION, DEHYDROGENATION, PYROLYTIC ELIMINATIONS AND MOLECULAR REARRANGEMENTS

15.0 OBJECTIVES:

After studying this lesson, the student will be able to:

1) Understand the **nature and classification of elimination reactions**.
2) Explain **dehydration of alcohols** and the role of E_1 and E_2 mechanisms.
3) Describe **dehydrogenation elimination** and its industrial significance.
4) Understand **pyrolytic eliminations (E_i reactions)**.
5) Explain **molecular rearrangements during elimination**.
6) Analyze **hydride and alkyl shifts** and their effect on product formation.

STRUCTURE

15.1 DEHYDRATION

Dehydration is an elimination reaction in which an alcohol loses a molecule of water to give an alkene, usually under acidic conditions and heat. It is a typical example of β-elimination because the – OH and the hydrogen removed come from adjacent carbon atoms.

Basic concept

- **Dehydration of alcohols:**

$$R–CH_2-CH(OH)-R' \rightarrow R–CH = CH–R' + H_2O.$$

- A strong acid (commonly conc. H_2SO_4 or H_3PO_4) and heat are used to convert the poor leaving group – OH into a good leaving group (water).
- The reaction gives an alkene and is favoured at higher temperature, so it is classified as an elimination reaction rather than substitution.

15.1.1 ORDER OF REACTIVITY AND ZAITSEV RULE

- Ease of dehydration: $3^\circ > 2^\circ > 1^\circ$, because more substituted carbocations (or alkene-like transition states) are more stable.
- When more than one alkene is possible, the major product is usually the more substituted alkene (Zaitsev's rule).
- Thus, secondary and especially tertiary alcohols often give internal, more highly substituted double bonds as the main products.

15.1.2 MECHANISM FOR SECONDARY AND TERTIARY ALCOHOLS (E1)

For most $2^\circ$and 3°alcohols, dehydration follows an E_1 mechanism in acid. The steps are:

- Protonation of the hydroxyl group:

  $R-CH\ (OH)-R' + H^+ \rightarrow R-CH\ (OH_2^+)-R'$ (makes water a good leaving group).

- Loss of water to form a carbocation:

  $R-CH\ (OH_2^+)-R' \rightarrow R-C^+H-R' + H_2O.$

- Deprotonation of a β-hydrogen by the conjugate base (e.g. HSO_4^-) to form the C=C bond (alkene).

Because a carbocation is formed, rearrangements (hydride or alkyl shifts) are common, sometimes giving more substituted alkenes than expected from the starting structure.

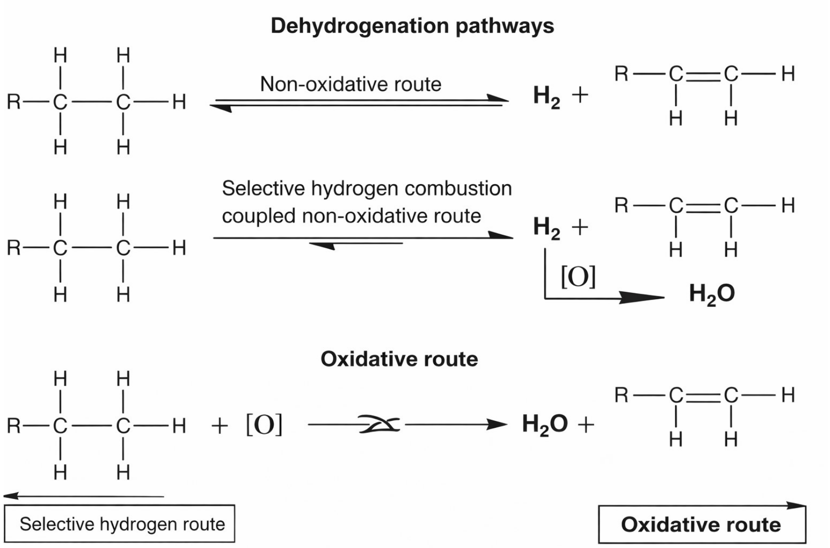
15.1.3 MECHANISM FOR PRIMARY ALCOHOLS (E_2-LIKE)

- Primary alcohols are difficult to dehydrate via E_1 because the primary carbocation would be very unstable.
- Their dehydration usually occurs by a concerted E_2-type pathway: protonation of $-OH$ followed by simultaneous loss of water and removal of a β-hydrogen in one step to form the alkene.
- Stronger heating is generally required for primary alcohols compared with secondary and tertiary alcohols.

15.2 DEHYDROGENATION ELIMINATION

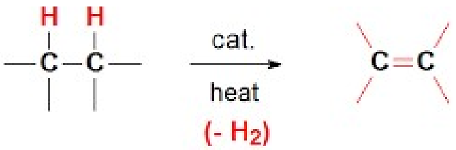
Dehydrogenation is an elimination reaction where a molecule loses H_2 to form a more unsaturated product like an alkene from an alkane or a carbonyl from an alcohol.

- Endothermic process requiring high temperature and catalysts (e.g., metal oxides like Cr_2O_3/Al_2O_3).
- Types: catalytic (alkanes → alkenes), oxidative (with O_2), functional-group (alcohols → carbonyls).



Mechanism:

often redox-based (hydride + proton removal from adjacent carbons), akin to β-elimination.



Importance

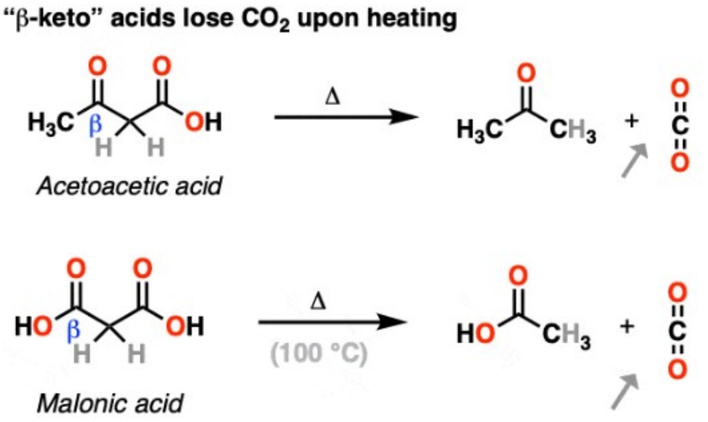
- Industrial: propane → propene, ethylbenzene → styrene for polymers.
- Complements dehydration (loses H_2O) by increasing unsaturation via H_2 loss.

15.3 DECARBOXYLATIVE ELIMINATION

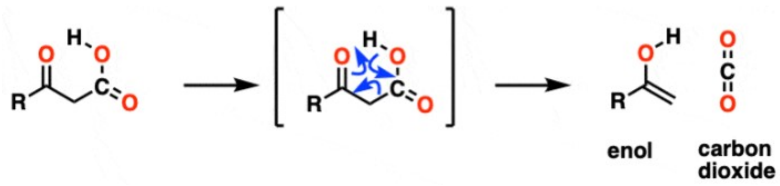
Decarboxylative elimination is an elimination reaction where a carboxyl group (-COOH) is removed from a molecule as carbon dioxide (CO_2), producing a less substituted hydrocarbon or unsaturated product. It involves breaking a carbon-carbon bond adjacent to the carboxyl group, often accompanied by the formation of a new double bond.

15.3.1 MECHANISM HIGHLIGHTS

- The reaction commonly proceeds through a concerted cyclic transition state involving a six-membered ring, where the C-C bond breaks as CO_2 is released simultaneously with the formation of a C = C bond.
- β-Keto acids and malonic acid derivatives undergo decarboxylation readily due to resonance stabilization of the intermediate enolate.



- Decarboxylation passes through a cyclic, concerted cyclic transition state that results in the formation of an enol intermediate



- The process is typically heat-induced or catalysed by bases like soda lime or enzymes in biological systems.
- It can be seen as a 1,2-elimination where the loss of CO_2 "kicks off" the adjacent bond to form the unsaturated product.

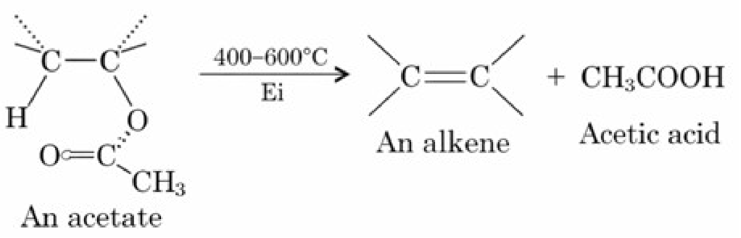
15.4 PYROLYTIC ELIMINATIONS (OR THERMAL ELIMINATIONS) OR CYCLIC ELIMINATIONS

Thermal elimination is given by a small family of organic compounds like acetates, xanthates and amine oxides.

In this elimination, product formation takes place via formation of ***intramolecular cyclic TS*** hence no carbon skeleton rearrangement occurs. Thus, elimination is ***always syn elimination***. This elimination takes place in gaseous state. This elimination ***does not involve acid or base as catalyst.***

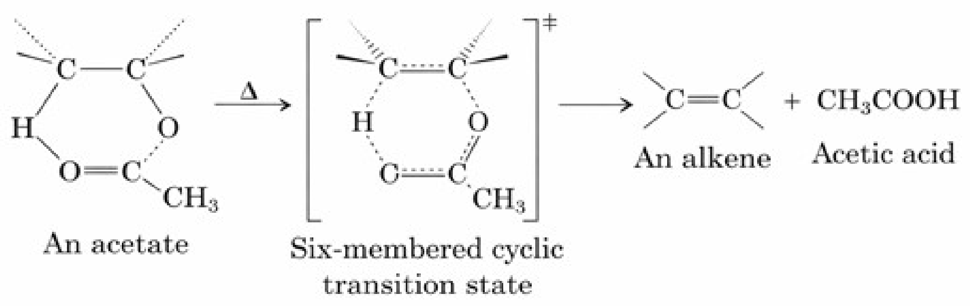
In thermal elimination, product formation always takes place by Hofmann rule.

15.4.1 PYROLYSIS OF ACETATES:



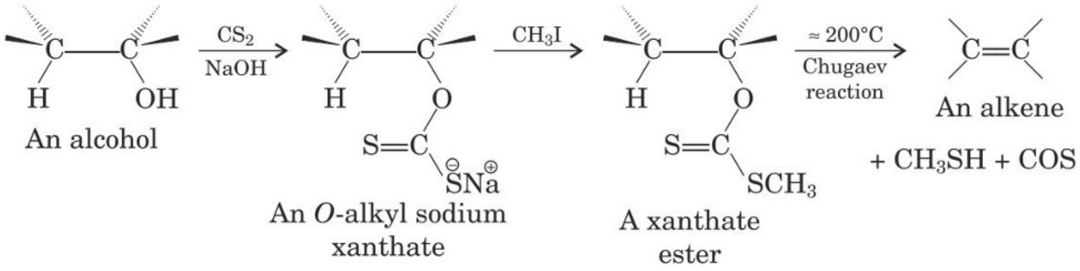
The pyrolytic elimination of an acetate containing at least one ß - H atom proceeds concertedly through a six-membered cyclic transition state. The cyclic pathway required a syn-coplanar arrangement of the departing groups and so, the reaction is a highly stereoselective syn-elimination.

The stereochemical course and the mechanism of this intramolecular E_2 reaction may be shown as follows:



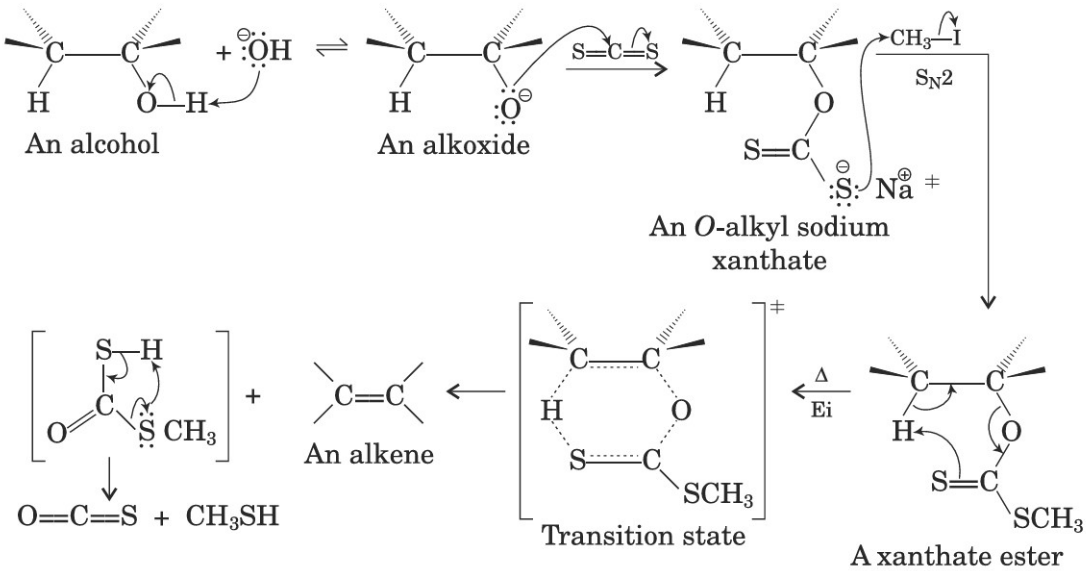
15.4.2 PYROLYSIS OF XANTHATES (CHUGAEV REACTION):

Pyrolysis of xanthates to alkenes is known as the **Chugaev** reaction. The following reaction sequence involving the Chugaev reaction is an indirect method of dehydration of alcohols.



In the reaction sequence, the alcohol is first converted to the corresponding alkoxide ion by the action of alkali. The alkoxide then reacts with carbon disulphide to yield O-alkyl sodium xanthate. The O-alkyl sodium xanthate subsequently reacts with methyl iodide by an SN_2 mechanism to form a xanthate ester.

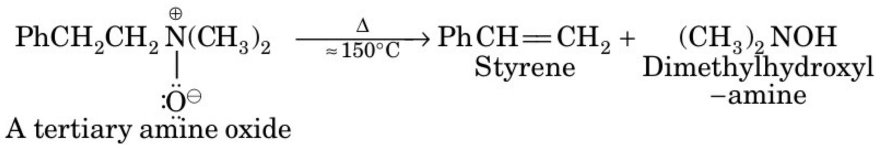
The xanthate ester then undergoes pyrolytic elimination (E_i elimination), a concerted reaction that proceeds through a six-membered cyclic transition state to yield an alkene. The reaction exhibits higher degree of syn stereoselectivity.



15.4.3 PYROLYSIS OF TERTIARY AMINE OXIDES:

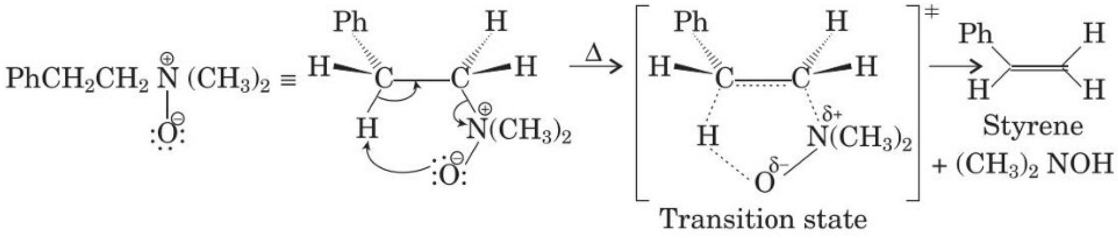
When tertiary amine oxides containing at least one ß-H atom are heated, they undergo decomposition to yield an alkene and a dialkylhydroxylamine. This is called Cope elimination reaction.

For example:



$$PhCH_2CH_2\overset{\oplus}{N}(CH_3)_2(\text{–}\ddot{O}^{\ominus}) \xrightarrow[\approx 150^\circ C]{\Delta} PhCH{=}CH_2 + (CH_3)_2NOH$$

In this E_i reaction, the negatively charged oxygen of the amine oxide is the base that removes a proton from the b-carbon. The reaction proceeds through a planar five-membered cyclic transition state. The mechanism of the reaction requires the departing groups to be syn-coplanar and in fact, the reaction exhibits the greatest degree of syn stereoselectivity of any of the E_i reactions.



Also, pyrolytic eliminations of sulfoxides and selenoxides are thermal, intramolecular syn eliminations (E_i mechanism) that convert these chalcogen oxides into alkenes through a cyclic transition state, without the need for an external base. They are among the most useful stereospecific methods for forming C=C bonds, with selenoxide elimination generally occurring under milder conditions than sulfoxide elimination.

15.5 MOLECULAR REARRANGEMENT DURING ELIMINATION

Molecular rearrangement during elimination refers to the **intramolecular migration of atoms or groups**, such as a **hydride ion or an alkyl group**, within a molecule **before or during the elimination step**. This migration alters the carbon framework and leads to the formation of **rearranged products**.

Such rearrangements are a **distinct feature of E1 elimination reactions** and are **absent in E2 eliminations**, owing to fundamental differences in their mechanisms.

Why Molecular Rearrangement Occurs

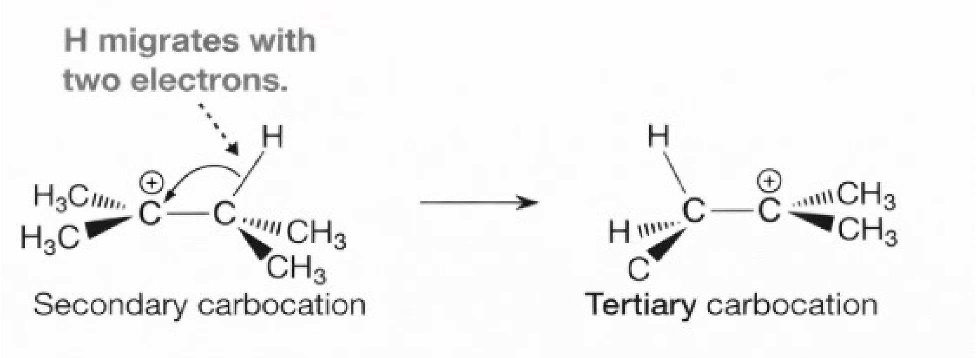
- **E1 elimination reactions proceed through a carbocation intermediate** formed by ionization of the leaving group.
- Carbocations are **highly reactive and electron-deficient** species.
- If a **more stable carbocation** can be generated by structural rearrangement, the molecule undergoes such a change **before the elimination of a proton**.
- Rearrangement lowers the **activation energy** and increases the overall stability of the reaction pathway.

Order of carbocation stability: 3° > 2° > 1° > methyl

15.5.1 TYPES OF MOLECULAR REARRANGEMENTS

A. Hydride Shift (1,2-Hydride Shift)

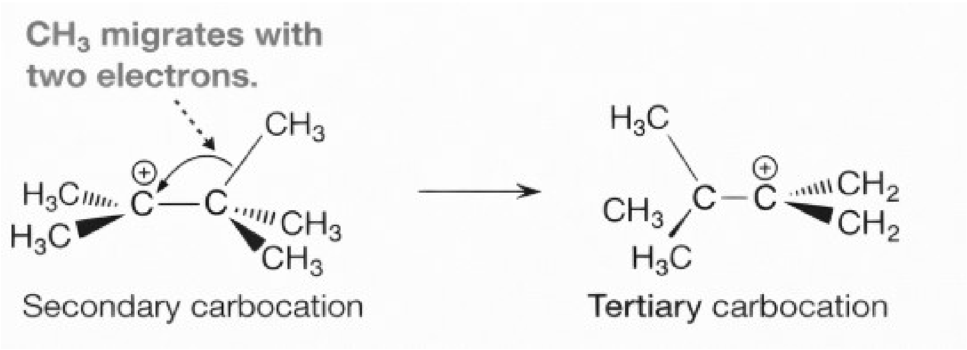
- Involves the migration of a **hydride ion (H^-)** from an adjacent carbon atom to the positively charged carbon.
- Occurs when the shift results in the formation of a **more stable carbocation**.
- This is the **most common type** of rearrangement due to the small size and high mobility of hydride ions.



Result: Conversion of a secondary carbocation into a tertiary carbocation.

B. Alkyl Shift (1,2-Alkyl Shift)

- Involves the migration of an **alkyl group** (commonly a methyl group) from an adjacent carbon.
- Takes place when hydride shift is not possible or less favorable.
- Leads to the formation of a **more substituted and stabilized carbocation**.



Result: Structural reorganization of the carbon skeleton.

Effect on Elimination Products

Molecular rearrangement during elimination can lead to:

- Formation of an **alkene different from that predicted** based on the original substrate.
- Production of a **more substituted and thermodynamically more stable alkene**.
- Generation of **unexpected or rearranged products**, particularly in E_1 reactions.

As a consequence, the **final alkene structure may not directly correspond to the original carbon skeleton** of the reactant.

15.6 SUMMARY:

- Elimination reactions involve the **removal of atoms or groups** to form a **double bond**.
- **Dehydration of alcohols** leads to alkene formation; secondary and tertiary alcohols follow an **E1 mechanism**, while primary alcohols follow an **E2-like mechanism**.
- **Dehydrogenation elimination** involves loss of H_2 under high temperature and catalysts, forming unsaturated compounds.
- **Pyrolytic (Ei) eliminations** occur through **syn elimination** via cyclic transition states and follow the **Hofmann rule**.
- Important pyrolytic reactions include **Chugaev and Cope eliminations**.
- **Molecular rearrangements** (hydride and alkyl shifts) occur in **E1 eliminations** due to carbocation intermediates.
- Rearrangements generally yield **more substituted and more stable alkenes**.

15.7 TECHNICAL TERMS:

1) **Elimination reaction**: Reaction forming a double bond by loss of atoms/groups.
2) **Dehydration**: Elimination of water from alcohols.
3) **Dehydrogenation**: Removal of molecular hydrogen.
4) **β-Elimination**: Elimination from adjacent carbon atoms.
5) **Pyrolytic elimination (E_i)**: Thermal syn elimination via cyclic transition state.
6) **Carbocation**: Positively charged carbon intermediate.
7) **Hydride shift**: Migration of H^- to stabilize a carbocation.
8) **Alkyl shift**: Migration of an alkyl group to form a more stable carbocation.
9) **Zaitsev rule**: Formation of the more substituted alkene.
10) **Hofmann rule**: Formation of the least substituted alkene.

15.8 SELF-ASSESSMENT QUESTIONS:

1) Define elimination reactions with examples.
2) Explain dehydration of alcohols and their mechanisms.
3) Distinguish between E1 and E2 eliminations.

4) What is dehydrogenation elimination?
5) Explain pyrolytic eliminations.
6) What is molecular rearrangement during elimination?
7) Explain hydride shift and alkyl shift.
8) How do rearrangements affect elimination products?

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Dr. P. BHARATH

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LESSON – 16

FUNCTIONAL GROUP PROTECTION STRATEGIES IN ORGANIC SYNTHESIS

16.0 OBJECTIVES

After studying this lesson, the student will be able to:

1) **Understand the need for functional group protection** in multistep organic synthesis.
2) **Explain the concept of protection–reaction–deprotection strategy**.
3) **Identify ideal characteristics of a protecting group**.
4) **Describe protection methods for hydroxyl, amino, carbonyl, and carboxylic acid groups**.
5) **Understand formation and cleavage of common protecting groups**.
6) **Appreciate the role of protecting groups in complex molecule synthesis**.

STRUCTURE

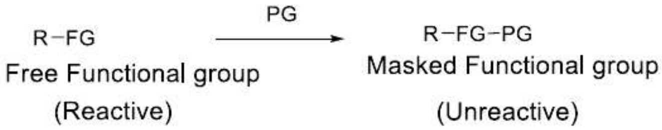
16.1 IMPORTANCE OF FUNCTIONAL GROUP PROTECTION IN ORGANIC SYNTHESIS

In **multistep organic synthesis**, target molecules frequently contain **two or more functional groups with different chemical reactivities**. During a specific transformation, a functional group that is not intended to react may **interfere, react competitively, or undergo degradation**, resulting in **poor selectivity, low yield, or undesired by-products**.

To overcome these difficulties, chemists employ the strategy of **functional group protection**. In this approach, a reactive functional group is **temporarily converted into a chemically inert derivative** using an appropriate **protecting group**. Once the desired transformation has been successfully carried out at another site in the molecule, the protecting group is **selectively removed (deprotected)** under mild conditions to regenerate the original functional group.

Thus, **protection–reaction–deprotection** constitutes a fundamental sequence in modern organic synthesis.

A good protecting group should be such that:



Theory and Importance of Functional Group Protection

Protection and deprotection play a **central role in organic synthesis**, particularly when selective reactions are required in **polyfunctional molecules**. Many reagents do not discriminate between similar functional groups.

For example, in a molecule containing both an **ester and a ketone**, if a reducing agent is used to reduce the ester group, the ketone group may also be reduced unintentionally. To avoid such complications, the **ketone must first be protected**, allowing selective reaction at the ester group.

Importance of Functional Group Protection

- Ensures **chemoselectivity**, allowing reaction at a specific functional group while others remain inactive.
- Prevents **undesired side reactions**, such as over-reaction, rearrangement, or decomposition.
- Facilitates the **stepwise construction of complex molecules** with multiple reactive sites.
- Plays a vital role in the synthesis of **natural products, pharmaceuticals, peptides, carbohydrates, and nucleosides**.
- Enhances **reaction yield, purity, and reproducibility** in multistep synthetic sequences.
- Enables the use of **strong reagents or harsh reaction conditions** that would otherwise damage sensitive functional groups.

Criteria for an Ideal Protecting Group

A good protecting group should satisfy the following requirements:

i. **Selective introduction**

It should be **readily and selectively introduced** onto the desired functional group in a polyfunctional molecule.

ii. **Stability during synthesis**

It should be **stable and resistant** to the reagents and conditions used in subsequent reaction steps.

iii. **Ease of removal**

It should be **easily removable (deprotected)** when its protective role is no longer required.

iv. **Selective deprotection**

Deprotection should occur under **mild conditions** without affecting other functional groups present in the molecule.

v. **High efficiency**

Both protection and deprotection steps should proceed in **high yield**.

vi. **Structural integrity**

It should not significantly alter the **stereochemistry or overall structure** of the molecule.

Functional Groups Commonly Requiring Protection

In organic synthesis, functional groups that are **highly reactive toward nucleophilic or electrophilic reagents** often require protection to achieve selectivity. These include:

- Hydroxyl groups (–OH)
- Amino groups ($-NH_2$)
- Carbonyl groups (>C=O)
- Carboxylic acid groups (–COOH)

Masking these groups with suitable protecting agents allows controlled and selective transformations in complex synthetic pathways.

Functional group protection is a **fundamental and indispensable strategy in modern organic synthesis**. It provides **control, selectivity, and flexibility** in designing multistep reaction sequences. A thorough understanding of protecting group chemistry is therefore essential for the synthesis of **structurally complex and biologically important molecules**.

16.2 PROTECTION OF HYDROXYL GROUP (–OH)

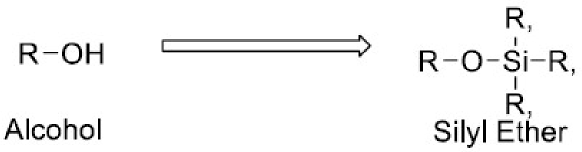
Alcohols are reactive functional groups due to their **nucleophilicity and acidity**. The most commonly used protecting groups for alcohols are **ether-type protecting groups**, as ethers are among the least reactive organic functional groups.

The ether protecting groups of alcohols can be grouped in the following categories:

Types of Ether Protecting Groups

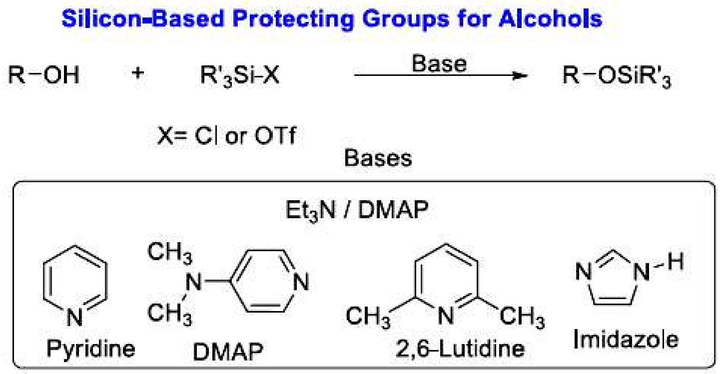
The ether protecting groups for alcohols can be broadly classified as:

(a) **Silyl Ether Protecting Groups**



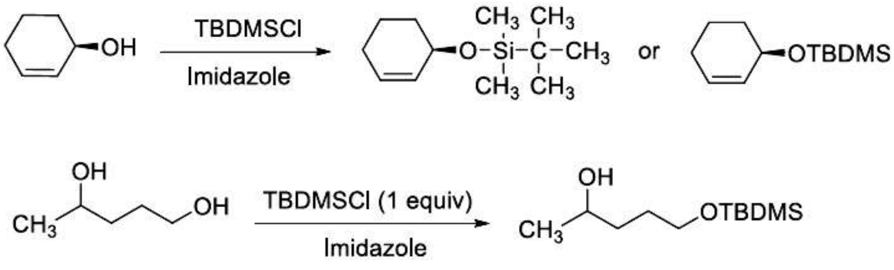
(b) **Acetal Protecting Groups**

Formation:

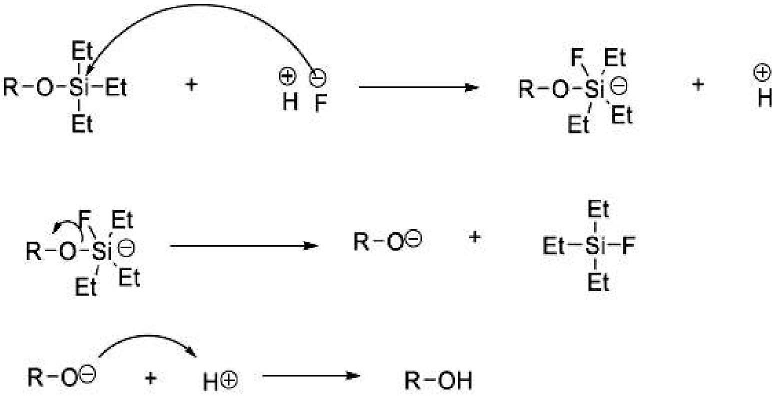


Tert-Butyldimethylsilyl ethers (TBDMS)

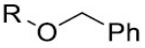
Example



Deprotection of Silicon-Based Protecting Groups

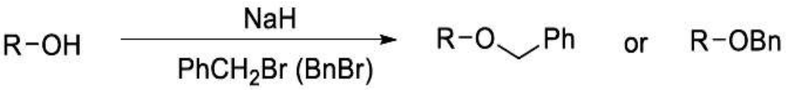


Rarely are alkyl ethers used as protecting groups for alcohols, but benzyl ethers are special.



Benzyl ether
(Bn)

Formation



Cleavage

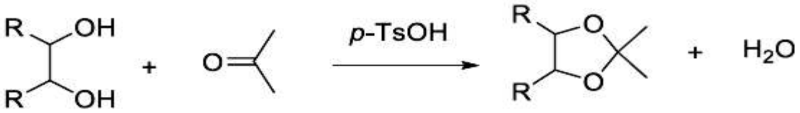
Hydrogenolysis is selectively used to cleave
benzyl ether protecting groups

$$R-OCH_2Ph \xrightarrow[Pd/C]{H_2} R-OH + PhCH_3$$

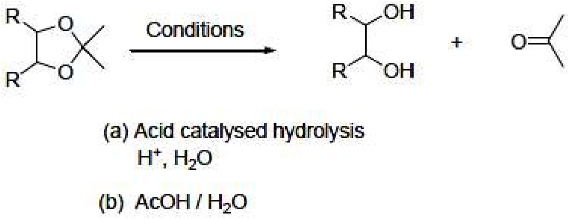
Cyclic Acetal Protecting Groups

Acetonide protecting groups are commonly employed for **1,2-diols**, forming stable cyclic acetals.

Formation: Reaction of diols with acetone under acidic conditions.

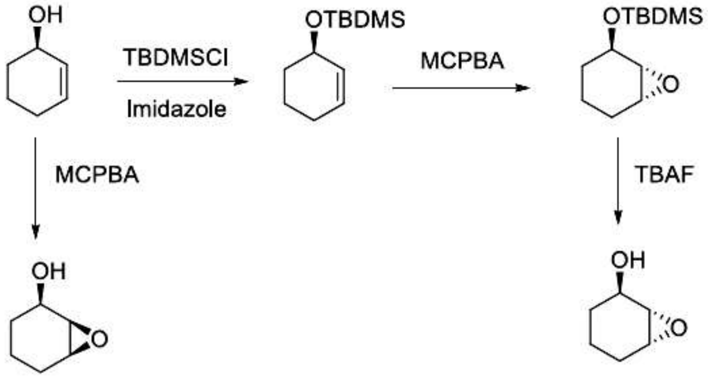


Cleavage: Acid-catalysed hydrolysis regenerates the diol.

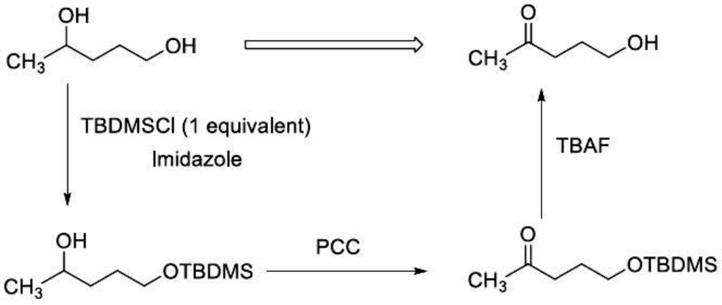


Synthetic Applications of Silyl Protecting Groups

- The bulkiness of TBDMS and TBDPS ether protecting groups can be used to advantage to suppress hydrogen-bonding to the oxygen restricting any incoming reagents to approach from the least hindered side of the molecule.



- The bulkiness of TBDMS and TBDPS ether protecting groups can also be exploited in incorporating the protecting group on less sterically encumbered primary hydroxyl groups selectively using sub-molar amounts of the silyl chloride.

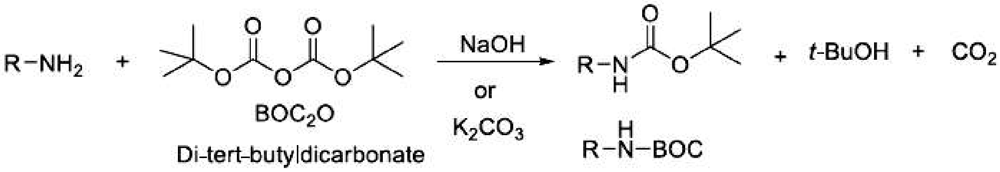


16.3 PROTECTION OF AMINO GROUP

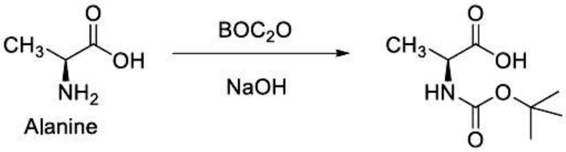
Amino groups are **highly nucleophilic and basic**, often interfering with alkylation, acylation, and oxidation reactions.

***Tert*-Butyloxycarbonyl Protecting Group (BOC)**

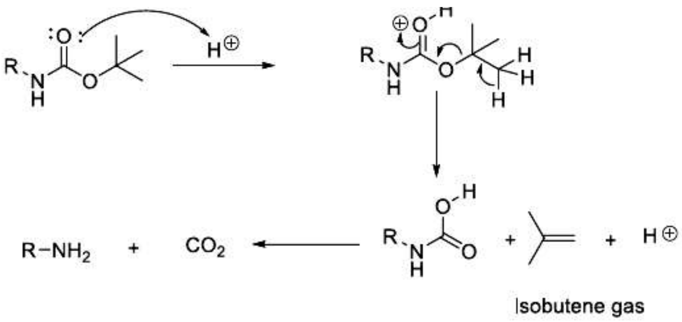
Formation: Reaction of amines with BOC anhydride in the presence of a base.



Example

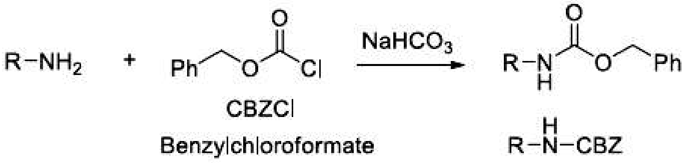


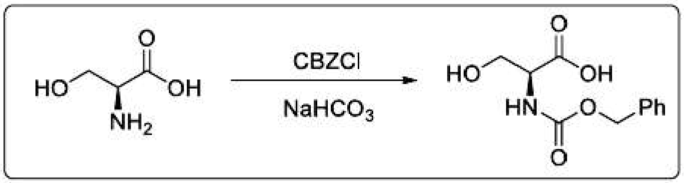
Cleavage: Removal under acidic conditions.



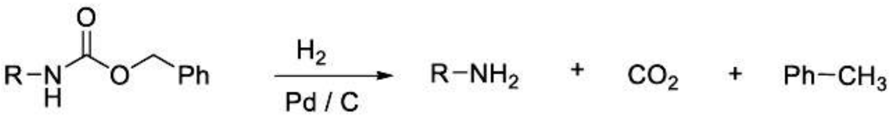
Benzyloxy carbonyl Protecting Group (CBZ)

Formation: Reaction of amines with benzyl chloroformate.





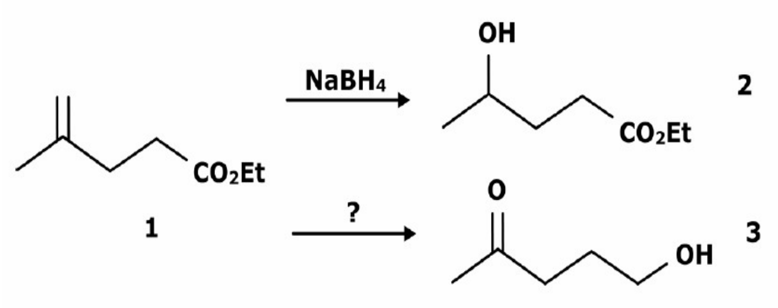
Cleavage: Removed by catalytic hydrogenolysis.



16.4 PROTECTION OF CARBONYL GROUP

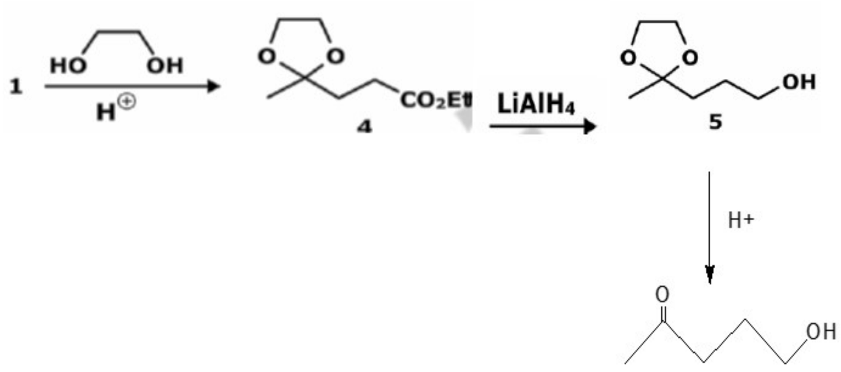
Acetal and Ketal Protecting Groups:

The protecting groups allow the masking of a particular functional group where a specified reaction is not to be performed. The protection is required as it interferes with another reaction. Let us take the example of reduction of the keto-ester **1** to the alcohol **2** with a nucleophilic reagent such as $NaBH_4$ that attacks only the more electrophilic ketone. In order to make alcohol **3** by the reduction of ester, it is important to protect the ketone as an acetal **4** that allows the reduction of the ester with the more nucleophilic $LiAlH_4$.



Formation of Acetals and Ketals

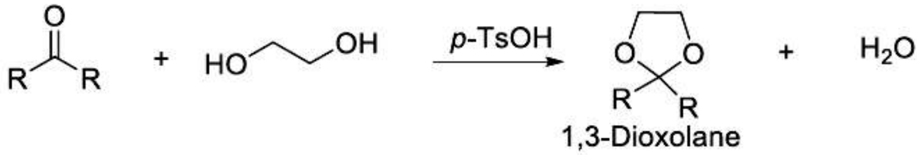
Carbonyl compounds react with diols under acidic conditions to form cyclic acetals or ketals.



Formation of Acetals and Ketals

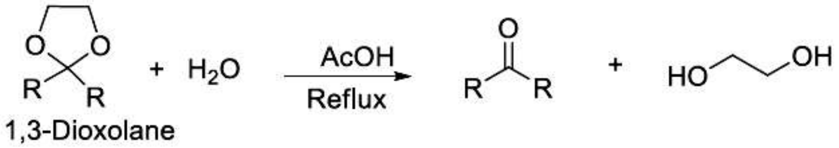
Carbonyl compounds react with diols under acidic conditions to form cyclic acetals or ketals.

Formation



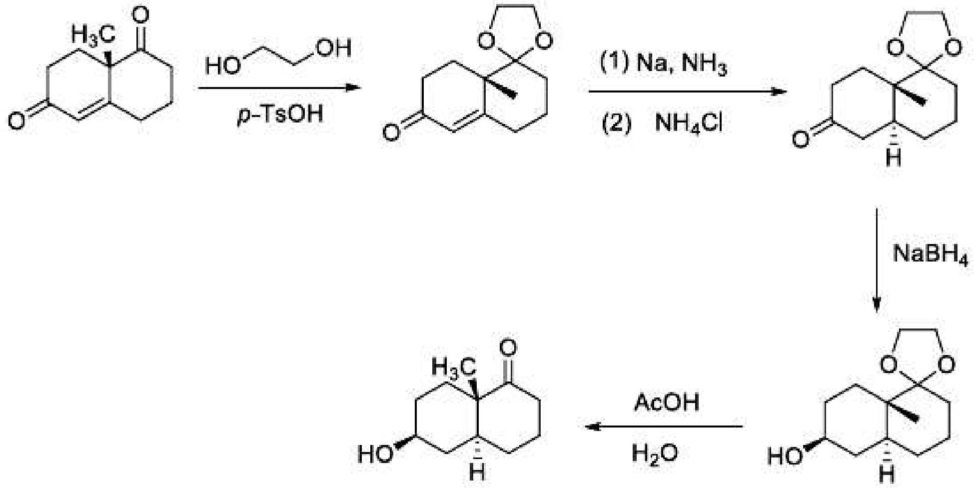
Cleavage

Acid catalysed hydrolysis (dilute HCl or AcOH / H_2O or TFA/ H_2O or *p* - TsOH in acetone) can be used.



Synthetic Applications of the Acetal Protecting Group

- The **Wieland–Miescher ketone** is a key intermediate in the synthesis of natural and synthetic steroids.
- In **α, β-unsaturated ketones**, resonance stabilization reduces electrophilicity, making them less reactive toward nucleophiles than isolated ketones.



16.5 PROTECTION OF CARBOXYLIC GROUPS

Carboxylic acids are **highly reactive functional groups** due to the presence of both an **acidic proton** and an **electrophilic carbonyl carbon**. In multistep organic synthesis, the –COOH group can interfere with reactions by undergoing **acid–base reactions, nucleophilic acyl substitution, or salt formation with bases**. Therefore, carboxylic acids are commonly protected to achieve **chemoselectivity and controlled reactivity**.

The most widely used protecting groups for carboxylic acids are **esters**, although **amides and hydrazides** may also be employed when greater stability is required.

Esters as protecting group for carboxylic acid.

Formation: Esterification using alcohols under acidic conditions.

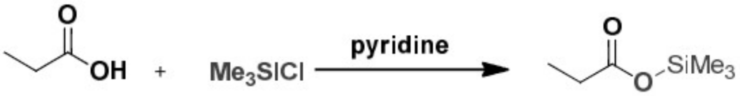
$$\mathrm{RCOOH} + \mathrm{PhCH_2OH} \xrightarrow[\mathrm{Et_2O}]{\mathrm{DCC}} \mathrm{RCOOCH_2Ph}$$

Cleavage: Hydrolysis under acidic or basic conditions.

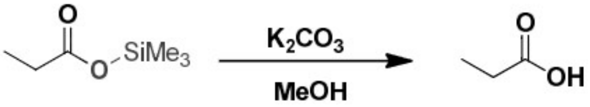
$$\mathrm{RCOOCH_2Ph} \xrightarrow{\mathrm{H_2\,/\,Pd\text{-}C}} \mathrm{RCOOH} + \mathrm{CH_3Ph}$$

Protection of carboxylic groups using silyl ester:

Formation: Reaction of carboxylic acids with silyl reagents.



Cleavage: Removal under mild acidic or fluoride ion conditions.



Importance of Carboxylic Acid Protection

- Prevents acid–base reactions with reagents or catalysts
- Avoids unwanted nucleophilic substitution at the acyl carbon
- Enables selective reactions at other functional groups
- Essential in **peptide synthesis, pharmaceutical chemistry, and natural product synthesis**

16.6 SUMMARY

1) **Functional group protection** is essential when multiple reactive groups are present in a molecule.
2) Protection involves **temporary masking of a functional group** to achieve chemoselectivity.
3) An **ideal protecting group** should be easy to introduce, stable during reactions, and easily removable.
4) **Hydroxyl groups** are commonly protected as **ethers, silyl ethers, and acetals**.
5) **Amino groups** are protected using **BOC and CBZ groups**.
6) **Carbonyl groups** are protected as **acetals or ketals** under acidic conditions.
7) **Carboxylic acids** are usually protected as **esters or silyl esters**.
8) Protecting group chemistry is vital in **pharmaceuticals, natural products, peptides, and carbohydrates**.

16.7 SELF-ASSESSMENT QUESTIONS

1) Why is functional group protection necessary in organic synthesis?
2) What is meant by protection–reaction–deprotection sequence?
3) List the criteria for an ideal protecting group.
4) How are hydroxyl groups commonly protected?
5) Explain BOC and CBZ protecting groups for amines.
6) Why are carbonyl groups protected as acetals or ketals?
7) How are carboxylic acids protected in multistep synthesis?
8) Mention applications of protecting groups in organic synthesis.

16.8 TECHNICAL TERMS

1) **Protecting group** – A temporary modification that masks a reactive functional group.
2) **Deprotection** – Removal of a protecting group to regenerate the original functionality.
3) **Chemoselectivity** – Selective reaction of one functional group in the presence of others.
4) **Silyl ether** – A silicon-based ether used to protect hydroxyl groups.
5) **BOC group** – Acid-labile protecting group for amines (tert-butyloxycarbonyl).
6) **CBZ group** – Hydrogenolysis-removable protecting group for amines.
7) **Acetal/Ketal** – Carbonyl protecting groups formed by reaction with diols.
8) **Ester protecting group** – Temporary protection of carboxylic acids as esters.

16.9 REFERENCE TEXTBOOKS

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2) **Peter G. M. Wuts**, *Greene's Protective Groups in Organic Synthesis*, Wiley.
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LESSON – 17

NAMED CONDENSATION REACTIONS OF ALDEHYDES AND ESTERS

17.0 OBJECTIVES:

After studying this lesson, the student will be able to:

1) Understand the **concept and significance of named reactions** in organic chemistry.
2) Explain the **mechanism and applications of Benzoin condensation**.
3) Describe the **Perkin reaction** for synthesis of α, β-unsaturated aromatic acids.
4) Understand the **Cannizzaro reaction** and its kinetic features.
5) Explain the **Dieckmann reaction** as an intramolecular Claisen condensation.
6) Describe the **Stobbe condensation** and its synthetic importance.
7) Compare different **condensation reactions involving aldehydes and esters**.

STRUCTURE

17.1 INTRODUCTION

Named reactions in organic chemistry are chemical reactions that have been given a specific name, typically after the scientists who discovered or developed them. This naming convention acts as a form of simplification, allowing chemists to describe complex transformations without needing to detail all the properties of a specific reaction.

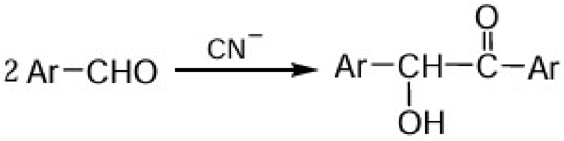
These reactions are a fundamental part of organic chemistry, providing a convenient way to discuss chemical processes and predict the products of a reaction. Each named reaction has a unique and well-defined set of conditions and products. They are crucial tools in synthesis, enabling the creation of a vast array of complex and useful molecules, including pharmaceuticals, polymers, and dyes.

There are hundreds of named reactions, but some of the most common and familiar ones as follows.

17.2 BENZOIN CONDENSATION

Condensation of aromatic aldehyde in presence of CN^- ion to give condensation products called benzoin, is known as Benzoin Condensation.

Reaction

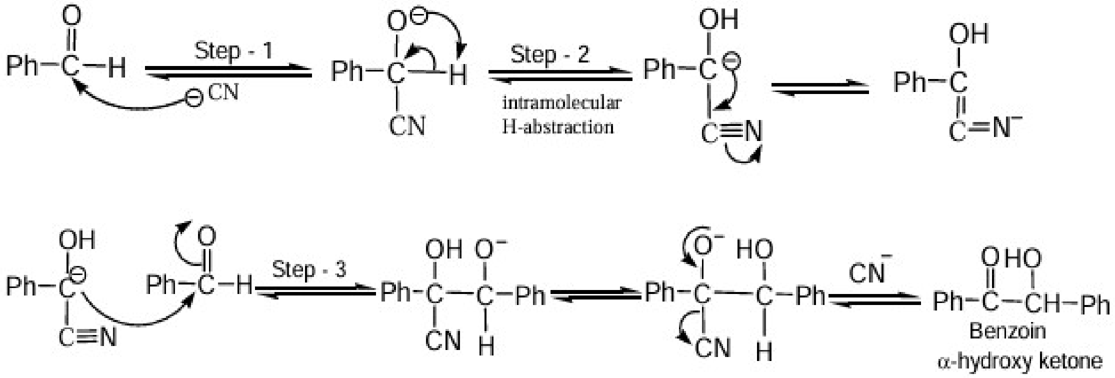


$$2\,Ar-CHO \xrightarrow{CN^-} Ar-\underset{OH}{\underset{|}{CH}}-\overset{O}{\overset{\|}{C}}-Ar$$

When Ar = Ph, it is called benzoin rate law $r = K\,[ArCHO]^2\,[CN]^-$

The reaction involves attack of CN^- ion on the carbonyl carbon but in this reaction instead of H– transfer (as that of Cannizzaro reaction) it is now a carbanion addition of the one aromatic aldehyde to the carbonyl carbon of the other aromatic aldehyde. The reaction is of 3rd order.

Mechanism



The benzoin condensation and its product have several applications in chemistry:

It is a fundamental method for creating carbon-carbon bonds and synthesizing heterocyclic compounds. And also used in the production of new monomers and polymers.

17.3 PERKIN REACTION

The Perkin reaction is an organic condensation reaction that synthesizes an α, β-unsaturated aromatic acid from an aromatic aldehyde and an aliphatic acid anhydride in the presence of sodium acetate.

The reaction is a type of aldol condensation and is widely used to prepare cinnamic acid and its derivatives.

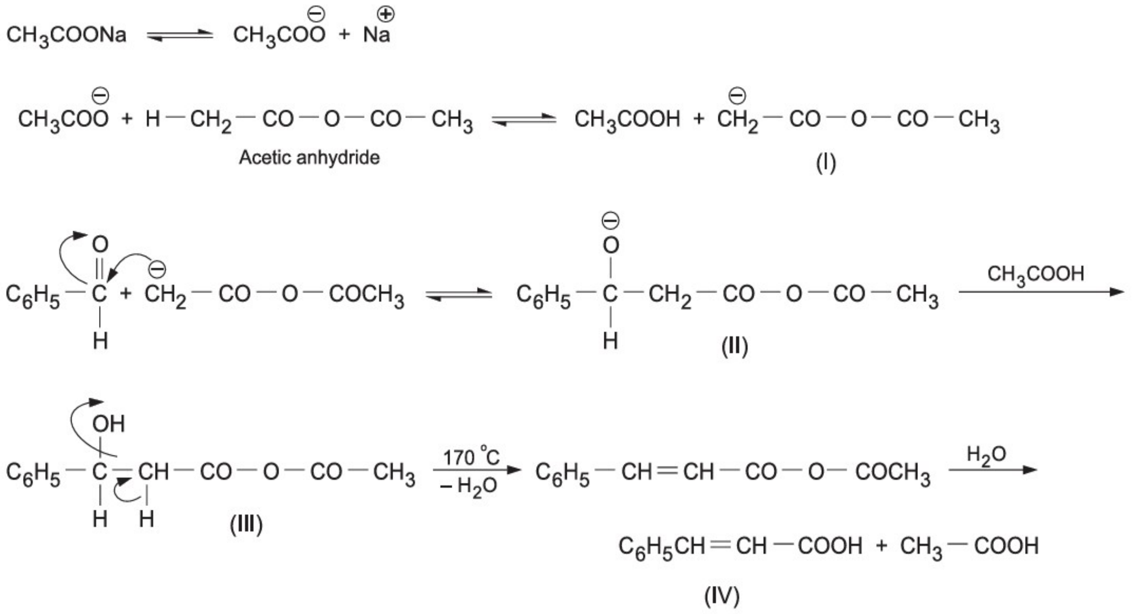
Reaction

$$C_6H_5CHO + (CH_3CO)_2O \xrightarrow[170-180\,^{\circ}C,\ 5\ h]{AcONa} C_6H_5-CH=CH-COOH + CH_3COOH$$

Cinnamic acid

The Perkin reaction mechanism involves the base-catalysed formation of an enolate ion from an acid anhydride, which then attacks an aromatic aldehyde to form a tetrahedral intermediate. This intermediate undergoes elimination and hydrolysis steps to yield an α, β-unsaturated aromatic acid such as cinnamic acid (IV)

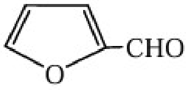
Mechanism



The Perkin reaction is a valuable tool in organic synthesis for creating carbon-carbon bonds and producing specific unsaturated acids.

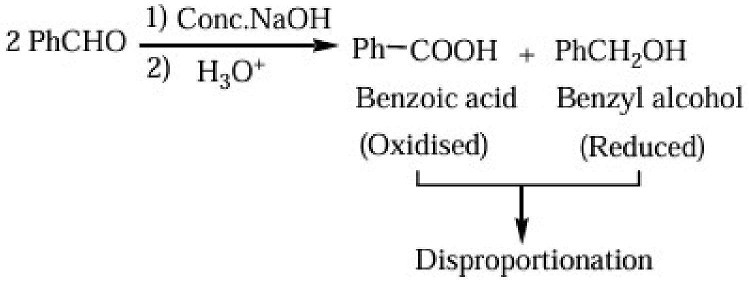
17.4 CANNIZZARO REACTION

Under the influence of strong and conc. base, aldehyde which has no α-H (non enolazable) undergoes self-oxidation reduction reaction (disproportionation) to produce corresponding alcohol and acid. This is known as Cannizzaro reaction.

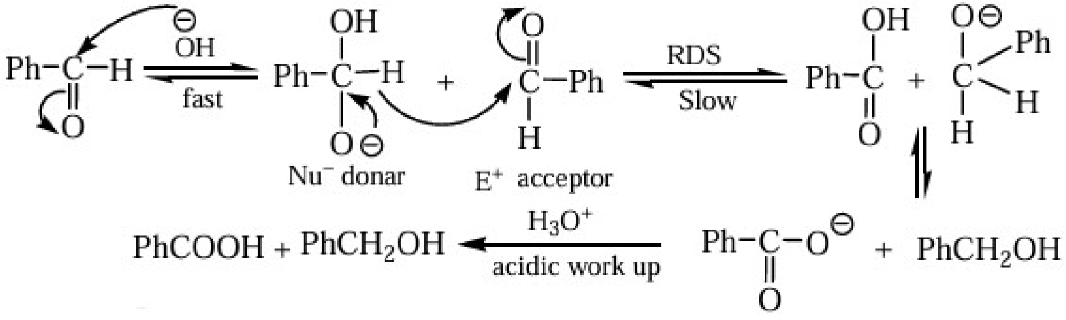
e.g. Aldehyde - HCHO, PhCHO, R_3C– CHO, 

Aldehydes which have α-H undergo aldol reaction much faster than the Cannizzaro reaction.

Reaction



Mechanism: The mechanism involves intermolecular hydride transfer



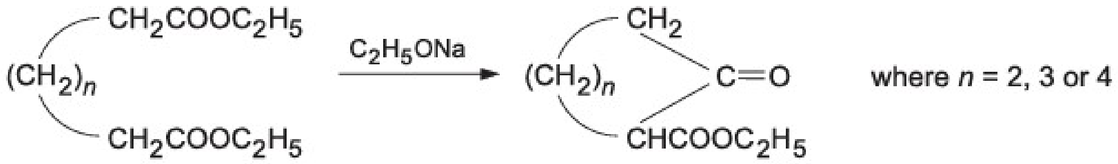
Rate = $K[PhCHO]^2 [OH^-]$ 3rd order reaction

Cannizzaro reaction is a third order reaction.

17.6 DIECKMANN REACTION

Intramolecular Claisen condensation in dibasic acid esters is called Dieckmann reaction. The resulting products are invariably cyclic-ketone derivatives. The condensing bases may be sodium, sodium ethoxide, sodium hydride, potassium t-butoxide, etc.

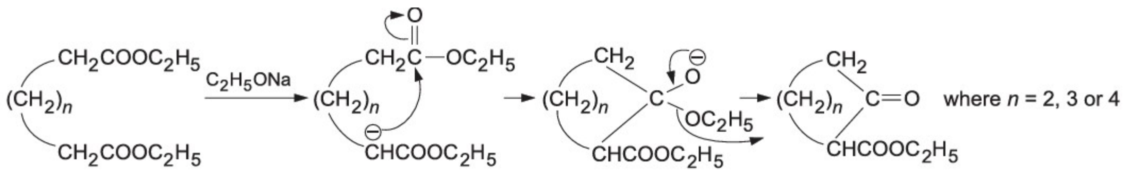
Reaction



The reaction best proceeds with dibasicacid esters having 6, 7 or 8 carbon atoms which give stable rings with 5, 6, or 7 carbons. Yields for rings of 9 to 12 carbons are very low. High-dilution technique is used for the formation of large-size rings.

The mechanism of the reaction is similar to that of Claisen condensation. The base abstracts a proton from one of the-carbons. The resulting carbanion then attacks the carbonyl carbon of the other ester group. Subsequent expulsion of the alkoxide ion gives the cyclic ketone derivative.

Mechanism

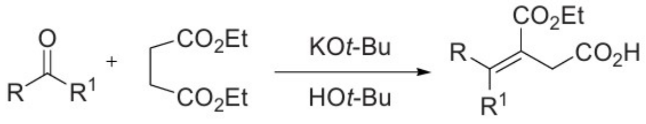


The compound on hydrolysis and decarboxylation gives cyclic ketone.

17.7 STOBBE CONDENSATION

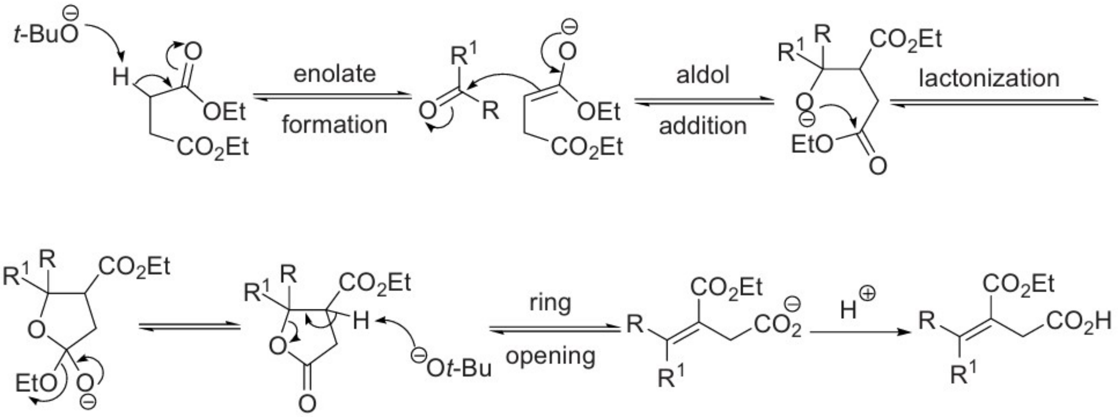
The condensation of aldehyde or ketone with succinic ester in the presence of basic catalyst like sodium hydroxide or potassium tertiary butoxide to form alkylidene succinic acid is known as stobbe condensation.

Reaction



The mechanism starts with base-induced enolate formation from the succinic ester, which undergoes aldol-type addition to the carbonyl compound, followed by intramolecular cyclization to a γ-lactone intermediate. This intermediate subsequently opens and rearranges to yield the final α, β-unsaturated half-ester product after acid work-up. The reaction is notable for producing a half-ester and acid group in one molecule and has applications in synthesizing complex intermediates in organic synthesis.

Mechanism



17.8 SUMMARY

1) Named reactions simplify the discussion of complex organic transformations and are vital tools in synthetic chemistry.
2) **Benzoin condensation** involves CN^--catalyzed coupling of aromatic aldehydes to form benzoin through carbanion addition.
3) **Perkin reaction** is a base-catalyzed condensation of aromatic aldehydes with acid anhydrides producing α, β-unsaturated aromatic acids such as cinnamic acid.
4) **Cannizzaro reaction** is a disproportionation reaction of non-enolizable aldehydes in strong base, yielding alcohol and acid.
5) **Dieckmann reaction** is an intramolecular Claisen condensation of dibasic esters producing cyclic ketones.
6) **Stobbe condensation** involves aldehydes or ketones reacting with succinic esters to give α, β-unsaturated half-esters.
7) These reactions are widely applied in **C–C bond formation**, synthesis of cyclic compounds, polymers, and intermediates for pharmaceuticals.

17.9 TECHNICAL TERMS

1) **Named reaction**: A chemical reaction identified by the name of its discoverer.
2) **Condensation reaction**: A reaction involving bond formation with elimination of a small molecule.
3) **Benzoin**: α-Hydroxy ketone formed in benzoin condensation.

4) **Cyanide ion (CN^-)**: Catalyst used in benzoin condensation.
5) **Perkin reaction**: Aldol-type condensation forming α, β-unsaturated acids.
6) **Cannizzaro reaction**: Base-induced disproportionation of non-enolizable aldehydes.
7) **Dieckmann reaction**: Intramolecular Claisen condensation forming cyclic ketones.
8) **Stobbe condensation**: Reaction of carbonyl compounds with succinic ester forming half-esters.
9) **Enolate ion**: Resonance-stabilized anion formed from carbonyl compounds.
10) **Disproportionation**: Simultaneous oxidation and reduction in the same reaction.

17.10 SELF-ASSESSMENT QUESTIONS

1) What are named reactions and why are they important in organic chemistry?
2) Define Benzoin condensation and explain its mechanism.
3) What is the role of CN^- ion in Benzoin condensation?
4) Describe the Perkin reaction and its applications.
5) Explain the Cannizzaro reaction with suitable example.
6) Why do aldehydes with α-hydrogen not undergo Cannizzaro reaction readily?
7) Describe the mechanism of the Dieckmann reaction.
8) What factors favor ring formation in Dieckmann condensation?
9) Explain the Stobbe condensation reaction.
10) Compare Benzoin condensation and Cannizzaro reaction.

17.11 REFERENCE TEXTBOOKS

1. Morrison, R. T. & Boyd, R. N., **Organic Chemistry**, Pearson Education.
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LESSON – 18

REARRANGEMENT REACTIONS IN ORGANIC CHEMISTRY

18.0 OBJECTIVES:

After studying this lesson, the student will be able to:

1) Understand the **concept and significance of rearrangement reactions** in organic chemistry.
2) Explain the **mechanism and applications of Hofmann rearrangement**.
3) Describe the **Schmidt reaction** for the synthesis of amines and amides.
4) Understand the **Lossen rearrangement** and the role of hydroxamic acids.
5) Explain the **Curtius rearrangement** and its synthetic importance.
6) Describe the **Claisen rearrangement** as a sigmatropic rearrangement.
7) Explain the **Beckmann rearrangement** and its industrial applications.
8) Compare different **rearrangement reactions involving migration of groups**.

STRUCTURE

18.1 HOFMANN REARRANGEMENT

The reaction involves the conversion of an amide into a primary amine with one carbon less, by the action of alkaline hypohalite (NaOH solution + Br_2 or Cl_2). The overall reaction is

Reaction

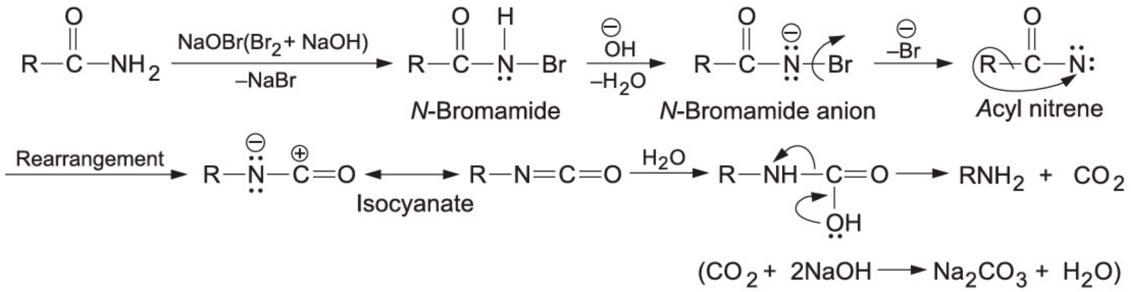
$$\mathrm{RCONH_2 + Br_2 + 4NaOH \longrightarrow RNH_2 + 2NaBr + Na_2CO_3 + 2H_2O}$$

where R may be aliphatic, aromatic or heterocyclic.

The mechanism has been suggested on the basis of the intermediates isolated during the course of reaction.

In the presence of bromine and a strong base (like NaOH), the amide first forms an N-bromoamide intermediate. This undergoes rearrangement where the alkyl or aryl group migrates from the carbonyl carbon to nitrogen, forming an isocyanate intermediate. Water then hydrolyzes this isocyanate to give a primary amine and carbon dioxide.

Mechanism



This reaction is widely used for producing primary amines free from contamination by secondary or tertiary amines.

18.2 SCHMIDT REACTION

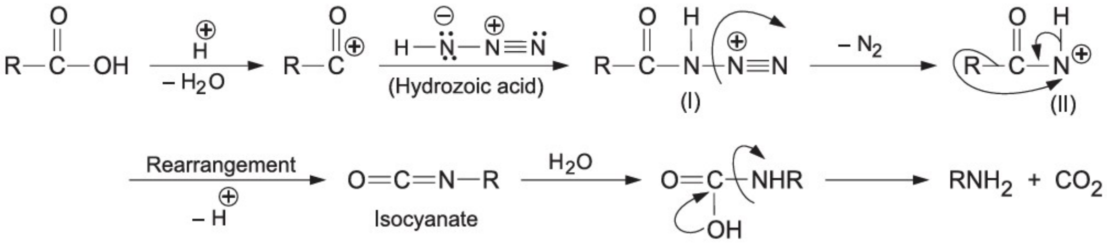
Carboxylic acids and hydrazoic acid react in the presence of sulphuric acid to give amines. This reaction is known as Schmidt reaction.

Reaction

$$RCOOH + N_3H \xrightarrow{H_2SO_4} RNH_2 + CO_2 + N_2$$

For carboxylic acids, the reaction proceeds via formation of an acylium ion, reaction with hydrazoic acid to form an acyl azide intermediate, then rearrangement and hydrolysis to produce the amine. With ketones, the azide adds to the protonated carbonyl to form an intermediate that rearranges to an amide.

Mechanism

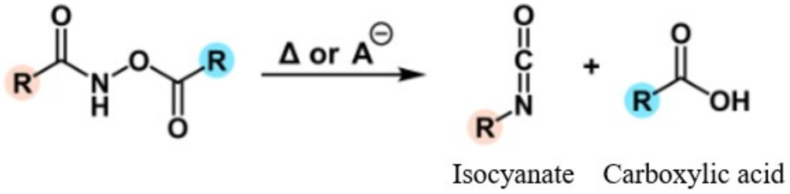


This reaction is valuable for synthesizing amines and amides through nitrogen insertion adjacent to carbonyl groups.

18.3 LOSSEN REARRANGEMENT

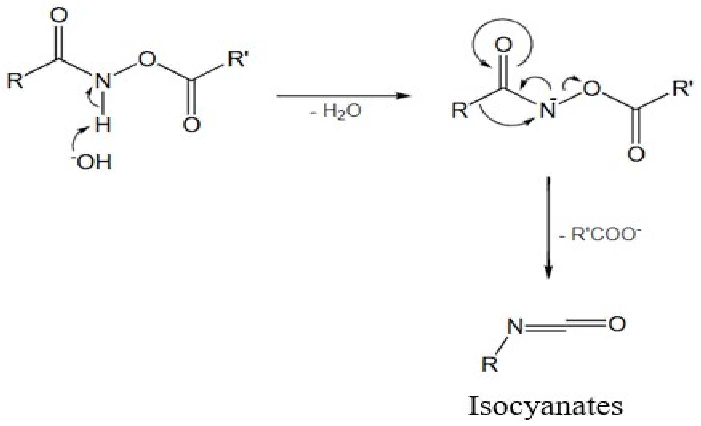
The Lossen rearrangement is the conversion of an acyl hydroxamate to an isocyanate and carboxylic acid side product.

Reaction



The mechanism involves deprotonation of the hydroxamic acid nitrogen, followed by a concerted 1,3-shift where the alkyl or aryl group migrates from the carbonyl carbon to the nitrogen, breaking the N–O bond and generating the isocyanate.

Mechanism



The isocyanate can be used further to generate ureas in the presence of amines or generate amines in the presence of H_2O.

18.4 CURTIUS REARRANGEMENT

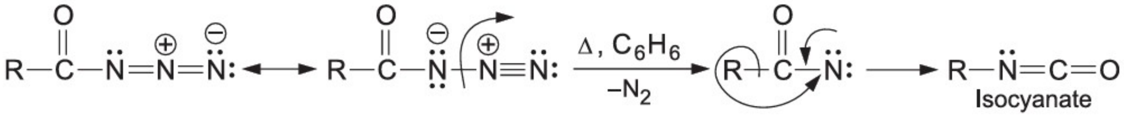
The Curtius rearrangement is a thermal decomposition reaction of an acyl azide that produces an isocyanate with the loss of nitrogen gas (N_2).

Reaction6

$$RCON_3 \xrightarrow{\Delta} R{-}N{=}C{=}O \; + \; N_2$$

The reaction proceeds via a concerted mechanism where the alkyl or aryl group migrates from the acyl carbon to nitrogen simultaneously with nitrogen loss, retaining stereochemistry of the migrating group.

Mechanism

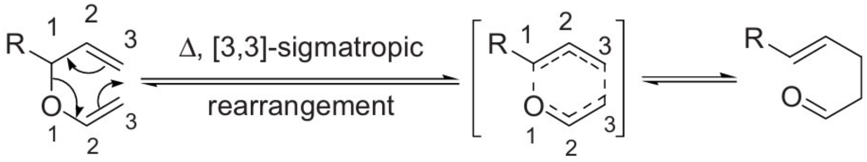


The isocyanate intermediate formed can be further transformed by nucleophiles such as water, alcohols, or amines to yield primary amines, carbamates, or urea derivatives. This rearrangement is valuable for synthesizing various nitrogen-containing compounds and is mechanistically similar to the Schmidt and Hofmann rearrangements.

18.5 CLAISEN REARRANGEMENT

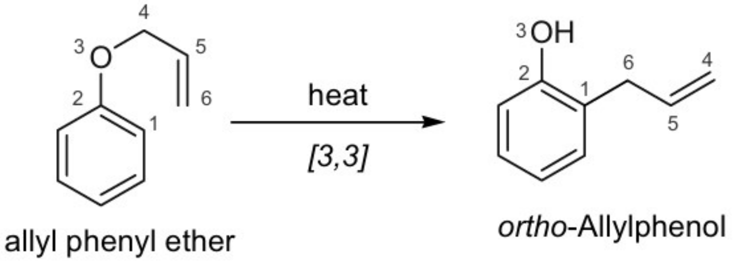
The thermal [3,3]-sigmatropic rearrangement of allyl vinyl ethers to the corresponding γ,δ-unsaturated carbonyl compounds are called the Claisen rearrangement.

Reaction



The core of the Claisen rearrangement is a concerted, intramolecular process that proceeds through a six-membered, chair-like transition state.

Mechanism



This rearrangement is widely employed for constructing C–C bonds in organic synthesis with high regio- and stereoselectivity.

18.6 BECKMANN REARRANGEMENT

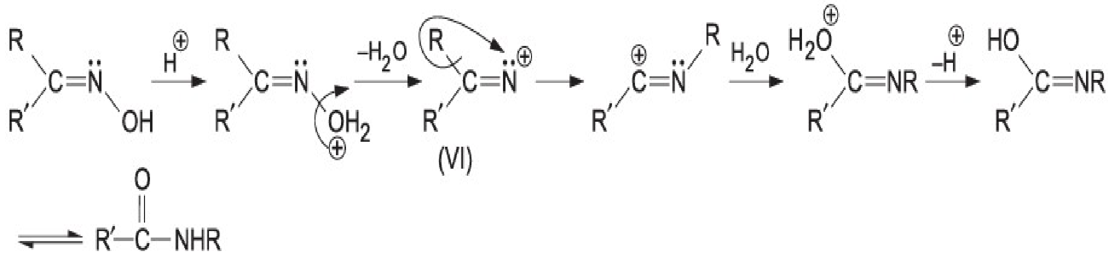
The Beckmann rearrangement is an acid-catalyzed reaction that converts an oxime (derived from a ketone or aldehyde) into an N-substituted amide.

Reaction

$$RR'C{=}NOH \xrightarrow{\overset{\oplus}{H}} RCONHR' \quad \text{or} \quad R'CONHR$$

The mechanism starts with protonation of the oxime's hydroxyl group, making it a better leaving group. Then, the substituent anti (trans) to the hydroxyl migrates from carbon to nitrogen as the N–O bond breaks, forming a nitrilium ion intermediate. Water attacks this intermediate, leading to an imidic acid, which tautomerizes to the stable amide product.

Mechanism



This rearrangement is widely applied in organic synthesis and industrial production of lactams like ε-caprolactam for nylon manufacturing.

18.7 SUMMARY

1) Rearrangement reactions involve **migration of atoms or groups within a molecule**, leading to structural reorganization.
2) **Hofmann rearrangement** converts amides into primary amines with one carbon less via an isocyanate intermediate.
3) **Schmidt reaction** involves the reaction of carboxylic acids or ketones with hydrazoic acid to form amines or amides.
4) **Lossen rearrangement** converts acyl hydroxamates into isocyanates, which further yield amines or ureas.
5) **Curtius rearrangement** involves thermal decomposition of acyl azides to isocyanates with nitrogen loss.
6) **Claisen rearrangement** is a [3,3]-sigmatropic rearrangement producing γ,δ-unsaturated carbonyl compounds.
7) **Beckmann rearrangement** converts oximes into amides and is industrially important in lactam synthesis.
8) These rearrangements are essential tools in **nitrogen insertion, carbon skeleton modification, and heterocycle synthesis**.

18.8 TECHNICAL TERMS

1) **Rearrangement reaction**: A reaction involving migration of atoms or groups within a molecule.
2) **Hofmann rearrangement**: Conversion of amides to primary amines with loss of one carbon.
3) **Isocyanate**: Reactive intermediate containing –N=C=O group.
4) **Schmidt reaction**: Reaction of carboxylic acids or ketones with hydrazoic acid.
5) **Lossen rearrangement**: Rearrangement of acyl hydroxamates to isocyanates.
6) **Curtius rearrangement**: Thermal rearrangement of acyl azides to isocyanates.
7) **Sigmatropic rearrangement**: Concerted migration involving σ-bond movement.
8) **Claisen rearrangement**: [3,3]-sigmatropic rearrangement of allyl vinyl ethers.
9) **Beckmann rearrangement**: Acid-catalyzed conversion of oximes to amides.
10) **Nitrilium ion**: Reactive cationic intermediate formed in Beckmann rearrangement.

18.9 SELF-ASSESSMENT QUESTIONS

1) What are rearrangement reactions? Explain their importance.
2) Describe the mechanism of Hofmann rearrangement.
3) Explain the Schmidt reaction with suitable examples.
4) What is Lossen rearrangement? Describe its mechanism.
5) Explain the Curtius rearrangement and its applications.
6) Describe the Claisen rearrangement with mechanism.
7) Explain the Beckmann rearrangement and its industrial significance.
8) Compare Hofmann, Curtius, and Schmidt rearrangements.

9) What is the role of isocyanate intermediates in rearrangement reactions?
10) Discuss the stereochemical aspects of Claisen rearrangement.

18.10 REFERENCE TEXTBOOKS

1) Morrison, R. T. & Boyd, R. N., **Organic Chemistry**, Pearson Education.
2) Clayden, J., Greeves, N., Warren, S., **Organic Chemistry**, Oxford University Press.
3) Carey, F. A. & Sundberg, R. J., **Advanced Organic Chemistry**, Springer.
4) Solomons, T. W. G., Fryhle, C. B., Snyder, S. A., **Organic Chemistry**, Wiley.
5) March, J., **Advanced Organic Chemistry: Reactions, Mechanisms and Structure**, Wiley.
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8) **V. K. Ahluwalia & R. Aggarwal**, *Organic Synthesis: Special Techniques*, Narosa Publishing House.
9) **S. N. Sanyal**, *Reactions, Rearrangements and Reagents*, Wiley Eastern.

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LESSON – 19

ADVANCED CARBONYL TRANSFORMATIONS AND REARRANGEMENT REACTIONS

19.0 OBJECTIVES:

After studying this lesson, the student will be able to:

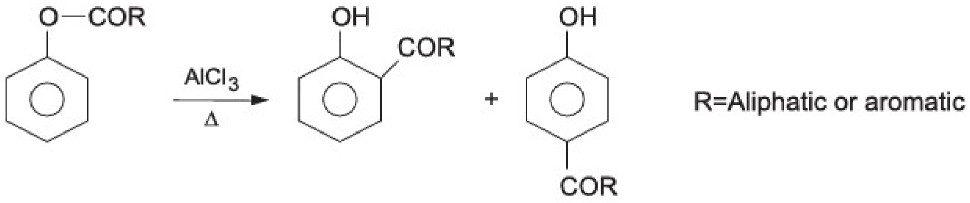
1) Understand the **principles and mechanisms of rearrangement and carbonyl reactions**.
2) Explain the **Fries rearrangement** and its regioselectivity.
3) Describe the **Reformatsky reaction** for C–C bond formation.
4) Understand the **Favorskii rearrangement** and its role in ring contraction.
5) Explain the **Wittig reaction** for carbonyl-to-alkene conversion.
6) Describe the **Baeyer–Villiger oxidation** and ring expansion reactions.
7) Understand the **Chichibabin reaction** as a nucleophilic aromatic substitution.
8) Apply these reactions in **synthetic and industrial organic chemistry**.

STRUCTURE

19.1 FRIES REARRANGEMENT

The Fries rearrangement is an organic reaction in which an aryl ester is converted into hydroxy aryl ketones (ortho and para isomers) using a Lewis acid catalyst like aluminium chloride ($AlCl_3$).

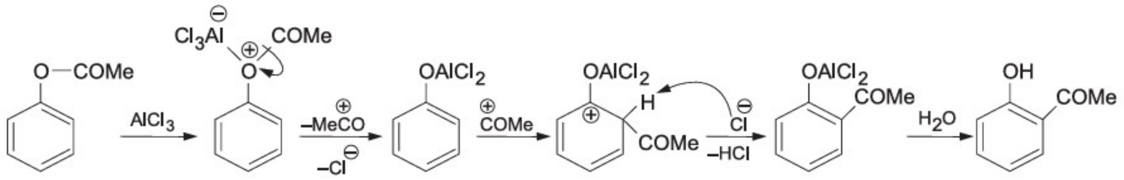
Reaction



A mixture of ortho- and para-isomers is obtained. Electron-withdrawing groups in the substrate retard the reaction as in the case of Friedel–Crafts reaction. In general, low temperature favours the para-product and high temperature favours the ortho-product.

At first, $AlCl_3$ complexes with the oxygen of the phenoxy group from which the acylium ion is generated. The acylium ion then attacks the benzene ring as in the case of Friedel–Crafts reaction.

Mechanism



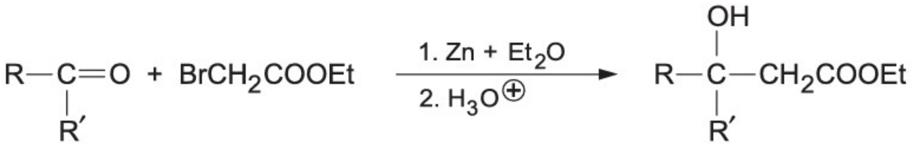
Similar attack at *p*-position gives the para-isomer.

Fries rearrangement is useful for synthesizing hydroxy aryl ketones, which are important intermediates in pharmaceuticals and fine chemicals.

19.2 REFORMATSKY REACTION

The Reformatsky reaction is an organic reaction where an α-haloester reacts with an aldehyde or ketone in the presence of metallic zinc to produce β-hydroxy esters.

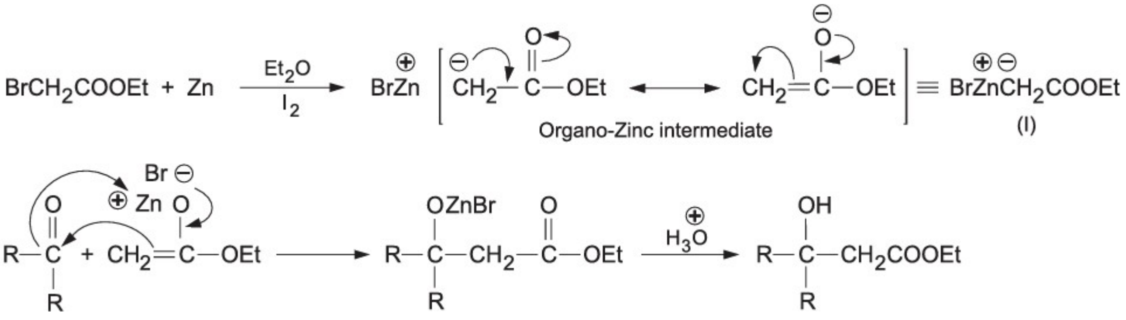
Reaction



$$\underset{\displaystyle R'}{R-\overset{}{C}=O} + BrCH_2COOEt \xrightarrow[2.\ H_3O^{\oplus}]{1.\ Zn\ +\ Et_2O} R-\underset{\displaystyle R'}{\overset{\displaystyle OH}{C}}-CH_2COOEt$$

The mechanism starts with zinc inserting into the carbon-halogen bond of the α-haloester to form a zinc enolate intermediate. This intermediate then coordinates with the carbonyl oxygen of the aldehyde or ketone, enabling nucleophilic addition that creates a new carbon-carbon bond. After acid work-up, the reaction yields β-hydroxy ester products.

Mechanism

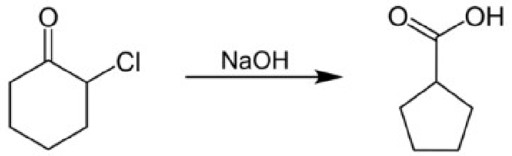


The Reformatsky reaction is valuable because it allows C–C bond formation under mild conditions, tolerates steric hindrance, and isolates useful β-hydroxy esters for further synthesis. It is widely used in natural product and pharmaceutical synthesis.

19.3 FAVORSKII REARRANGEMENT

The Favorskii rearrangement is a base-catalyzed reaction involving α-halo ketones or cyclopropanones, leading to carboxylic acids or their derivatives.

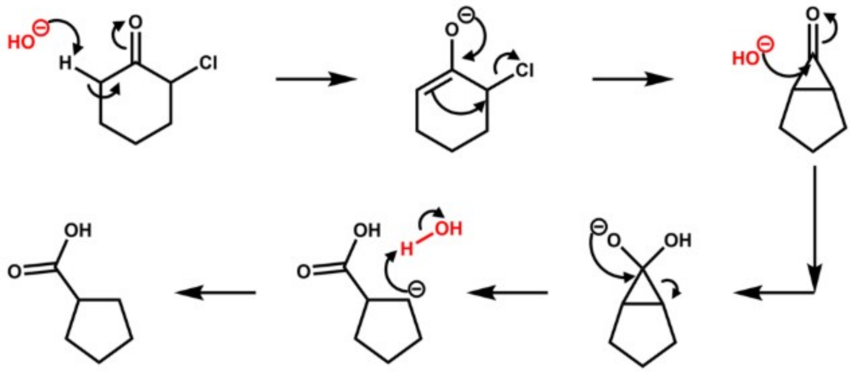
Reaction



The reaction mechanism is thought to involve the formation of an enolate on the side of the ketone away from the chlorine atom. This enolate cyclizes to a cyclopropenone intermediate which is then attacked by the hydroxide nucleophile. Its formation can otherwise be viewed as a 2-electron electrocyclization of a 1,3-dipole, which can be captured in Diels Alder reactions. The cyclopropanone intermediate is opened to yield the more stable carbanion, which is quickly protonated.

PTO

Mechanism

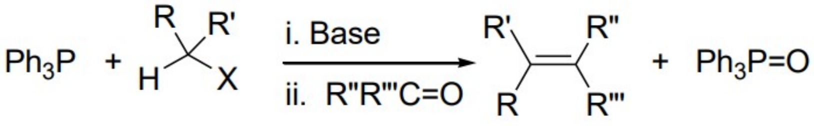


The reaction is especially useful for ring contraction in cyclic ketones and has applications in synthesizing complex molecules, including strained ring systems like cubane.

19.4 WITTIG REACTION

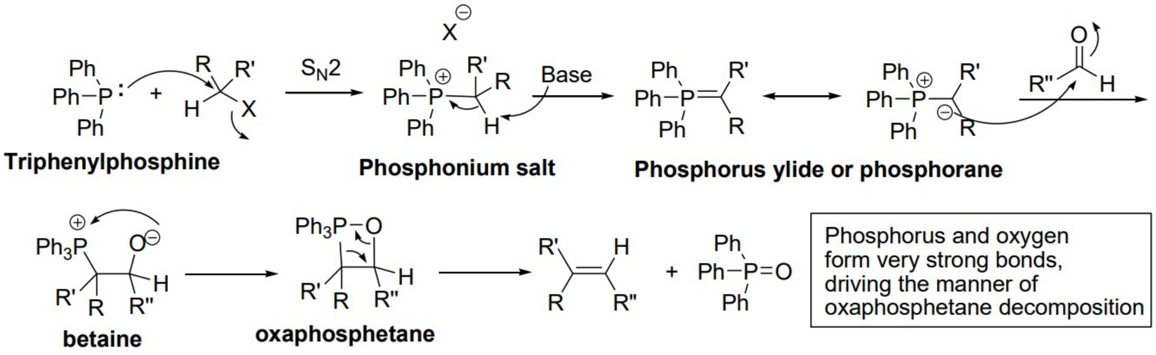
The Wittig Reaction is a fundamental organic chemistry transformation that converts aldehydes or ketones into alkenes by reacting them with a Wittig reagent—typically a triphenyl phosphonium ylide.

Reaction



The Wittig Reaction involves the attack of a negatively charged carbon in an ylide on the carbonyl carbon of an aldehyde or ketone, forming a betaine intermediate. This intermediate then cyclizes into a four-membered ring called oxaphosphetane. Finally, the ring breaks down to produce an alkene and triphenylphosphine oxide as a byproduct. This reaction effectively converts carbonyl groups into alkenes with the formation of a carbon-carbon double bond.

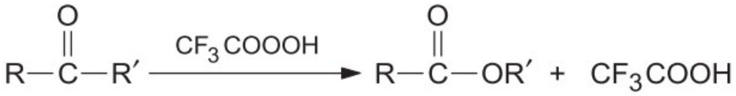
Mechanism



19.5 BAEYER VILLIGER REACTION

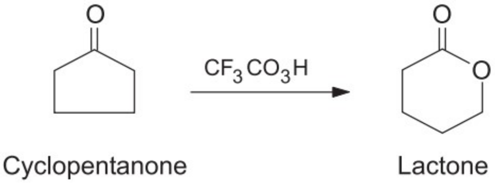
The Baeyer-Villiger reaction is an organic oxidation process that converts a ketone into an ester or a cyclic ketone into a lactone (a cyclic ester). This transformation is typically achieved using a peroxyacid, such as m-chloroperoxybenzoic acid (mCPBA), or other peroxides as the oxidizing agent. The overall reaction involves the insertion of an oxygen atom next to the carbonyl group.

Reaction



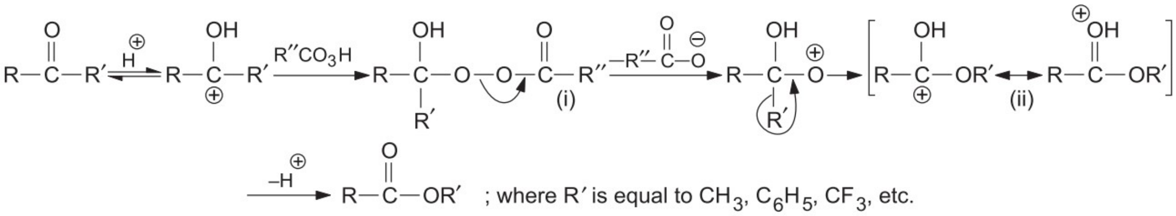
$$R-\overset{\overset{\displaystyle O}{\|}}{C}-R' \xrightarrow{CF_3COOOH} R-\overset{\overset{\displaystyle O}{\|}}{C}-OR' + CF_3COOH$$

Cyclic ketones are converted to lactones with ring expansion.



Nucleophilic attack of the peracid on the protonated ketone gives an intermediate peroxide (i). The peroxide then undergoes loss of carboxylate anion and migration of a group from carbon to electron deficient oxygen to yield the protonated ester (ii). Finally, the loss of proton gives the ester.

Mechanism

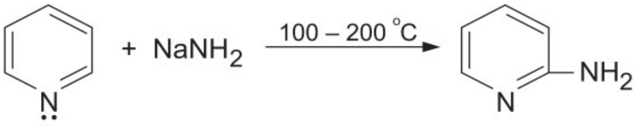


The Baeyer-Villiger reaction is a vital synthetic tool that efficiently converts ketones into valuable esters and lactones, which are essential for creating pharmaceuticals and natural products.

19.6 CHICHIBABIN REACTION

The Chichibabin reaction is a nucleophilic aromatic substitution where pyridine reacts with sodium amide to form 2-aminopyridine by replacing a hydrogen atom with an amino group, proceeding via an addition-elimination mechanism involving a Meisenheimer intermediate and hydride ion elimination.

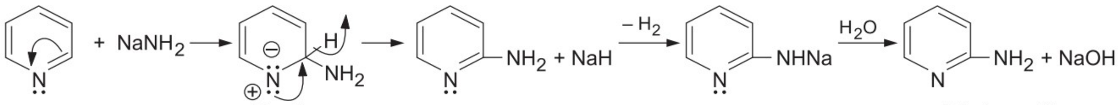
Reaction



2-Aminopyridine

Mechanism:

The Chichibabin reaction mechanism involves the nucleophilic attack of the amide ion (NH2−) on the 2-position of the pyridine ring, forming a negatively charged σ-adduct (Meisenheimer intermediate) which temporarily disrupts aromaticity. Electrons are then pushed back to restore aromaticity by forming a C=N bond and ejecting a hydride ion (H−), which subsequently abstracts a proton to form hydrogen gas. This results in the formation of 2-aminopyridine after an acidic workup step.



2-Aminopyridine

Aminated heterocyclic compounds like 2-aminopyridine, which are key intermediates in the production of pharmaceuticals, agrochemicals, and dyes, enabling functionalization of aromatic nitrogen-containing rings that are otherwise difficult to modify.

19.7 SUMMARY

1) **Fries rearrangement** converts aryl esters into hydroxy aryl ketones using Lewis acid catalysts, yielding ortho and para isomers.
2) **Reformatsky reaction** involves α-haloesters reacting with carbonyl compounds in the presence of zinc to form β-hydroxy esters.
3) **Favorskii rearrangement** is a base-catalyzed rearrangement of α-halo ketones leading to carboxylic acids or derivatives, often with ring contraction.
4) **Wittig reaction** converts aldehydes or ketones into alkenes using phosphonium ylides via oxaphosphetane intermediates.
5) **Baeyer–Villiger reaction** oxidizes ketones to esters or cyclic ketones to lactones through oxygen insertion.
6) **Chichibabin reaction** introduces an amino group into pyridine via nucleophilic aromatic substitution.
7) These reactions are widely used in the synthesis of **pharmaceuticals, agrochemicals, polymers, and fine chemicals**.

19.8 TECHNICAL TERMS

1) **Fries rearrangement**: Lewis acid-catalyzed conversion of aryl esters to hydroxy aryl ketones.
2) **Reformatsky reaction**: Zinc-mediated coupling of α-haloesters with carbonyl compounds.
3) **β-Hydroxy ester**: Product formed in Reformatsky reaction.
4) **Favorskii rearrangement**: Base-induced rearrangement of α-halo ketones.
5) **Wittig reagent (ylide)**: Phosphonium compound used to convert carbonyls to alkenes.
6) **Oxaphosphetane**: Four-membered intermediate in Wittig reaction.
7) **Baeyer–Villiger oxidation**: Peracid oxidation converting ketones to esters or lactones.
8) **Lactone**: Cyclic ester formed from cyclic ketones.
9) **Chichibabin reaction**: Amination of pyridine using sodium amide.
10) **Meisenheimer intermediate**: σ-complex formed in nucleophilic aromatic substitution.

19.9 SELF-ASSESSMENT QUESTIONS

1) Define Fries rearrangement and discuss its regioselectivity.
2) Explain the mechanism of the Reformatsky reaction.
3) What is the synthetic importance of β-hydroxy esters?
4) Describe the mechanism of Favorskii rearrangement.
5) Explain the Wittig reaction with mechanism.
6) What is Baeyer–Villiger oxidation? Explain ring expansion.
7) Describe the mechanism of the Chichibabin reaction.
8) Compare Fries rearrangement and Friedel–Crafts acylation.
9) Discuss the applications of Wittig reaction in synthesis.
10) Explain the role of peracids in Baeyer–Villiger reaction.

19.10 REFERENCE TEXTBOOKS

1) Morrison, R. T. & Boyd, R. N., **Organic Chemistry**, Pearson Education.
2) Clayden, J., Greeves, N., Warren, S., **Organic Chemistry**, Oxford University Press.
3) Carey, F. A. & Sundberg, R. J., **Advanced Organic Chemistry**, Springer.
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5) March, J., **Advanced Organic Chemistry: Reactions, Mechanisms and Structure**, Wiley.
6) **S. Mukherjee & S. P. Singh**, *Reaction Mechanism in Organic Chemistry*, Macmillan India.
7) **R. T. Morrison & R. N. Boyd (Indian Edition)**, *Organic Chemistry*, Pearson India.
8) **V. K. Ahluwalia & R. Aggarwal**, *Organic Synthesis: Special Techniques*, Narosa Publishing House.
9) **S. N. Sanyal**, *Reactions, Rearrangements and Reagents*, Wiley Eastern.

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LESSON – 20

REDOX TRANSFORMATIONS IN CARBONYL COMPOUNDS AND AROMATIC SYSTEMS

20.0 OBJECTIVES

After studying this lesson, the student will be able to:

1) Understand the **importance of oxidation and reduction reactions** in organic synthesis.
2) Explain the **principle and mechanism of Oppenauer oxidation**.
3) Describe the **Clemmensen reduction** and its applicability under acidic conditions.
4) Explain the **Wolff–Kishner reduction** for carbonyl group removal under basic conditions.
5) Understand the **Meerwein–Ponndorf–Verley (MPV) reduction** and its reversibility.
6) Describe the **Birch reduction** and its role in partial reduction of aromatic rings.
7) Compare different **redox methods based on reaction conditions and selectivity**.
8) Apply these reactions in **multistep synthesis, pharmaceuticals, and natural product chemistry**.

STRUCTURE

20.1 INTRODUCTION

Redox reactions form a cornerstone of organic synthesis, enabling the controlled interconversion of functional groups and fine adjustment of molecular frameworks. Among these, oxidation and reduction reactions of carbonyl compounds and aromatic systems are especially significant because they allow chemists to selectively increase or decrease the oxidation level of organic molecules without disturbing other sensitive functionalities.

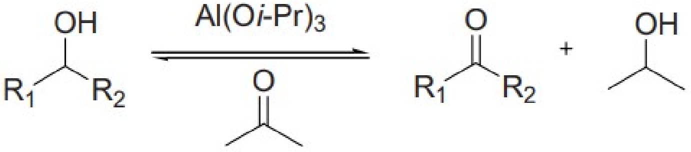
This lesson focuses on a group of classical and widely used redox reactions, including **Oppenauer oxidation**, **Clemmensen reduction**, **Wolff–Kishner reduction**, **Meerwein–Ponndorf–Verley reduction**, and **Birch reduction**. These reactions illustrate different mechanistic pathways—hydride transfer, metal-mediated reduction, base-induced nitrogen extrusion, and single-electron transfer—each suited to specific substrates and reaction conditions.

Together, these transformations provide powerful and complementary strategies for converting alcohols to carbonyl compounds, carbonyl groups to hydrocarbons or alcohols, and aromatic rings to partially reduced systems. Their selectivity, mechanistic diversity, and broad applicability make them indispensable tools in multistep synthesis, pharmaceutical chemistry, and the construction of complex natural products.

20.2 OPPENAUR OXIDATION

Oppenauer oxidation is a chemoselective organic reaction that oxidizes secondary alcohols to their corresponding ketones using an aluminium alkoxide catalyst (such as aluminium isopropoxide or aluminium tert-butoxide) and a ketone, typically acetone, as the hydride acceptor.

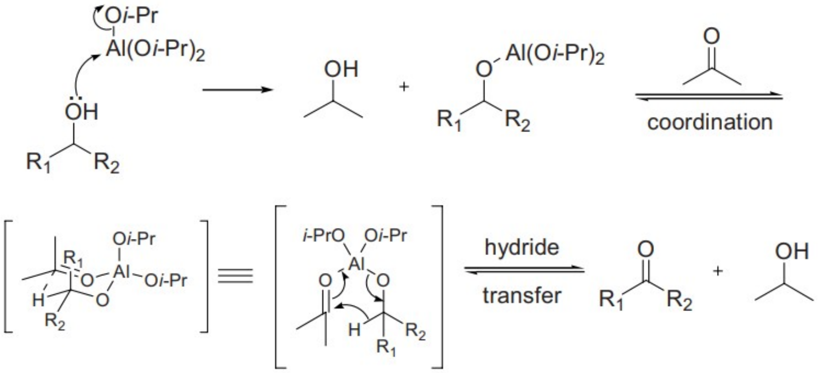
Reaction



The reaction is the reverse of Meerwein–Ponndorf–Verley reduction.

The mechanism involves the alcohol coordinating to the aluminium catalyst, followed by the formation of a six-membered cyclic transition state with the ketone. In this state, a hydride ion is transferred from the α-carbon of the alcohol to the ketone's carbonyl carbon. This transfer oxidizes the alcohol to a ketone and reduces the ketone to a secondary alcohol, typically isopropanol. The catalyst is then regenerated.

Mechanism

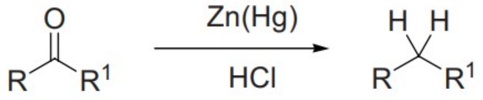


This reaction is the reverse of the Meerwein-Ponndorf-Verley reduction and is favored for its mild conditions, selectivity for secondary alcohols, and use of relatively non-toxic reagents. It is commonly applied in the synthesis of complex molecules such as steroids and natural products.

20.3 CLEMMENSEN REDUCTION

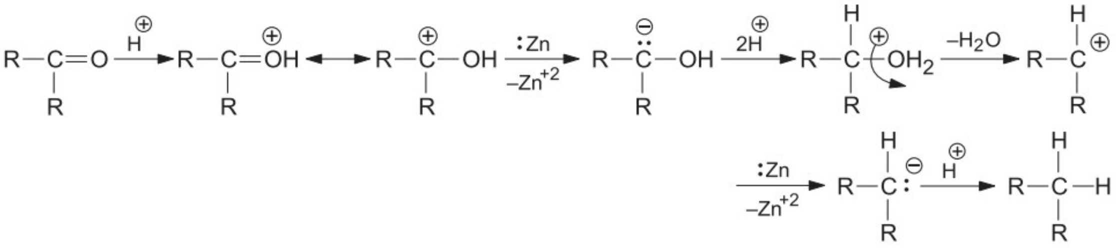
Clemmensen reduction is an organic chemical reaction used to reduce aldehydes and ketones to alkanes. It involves treating the carbonyl compound with zinc amalgam (zinc treated with mercury, Zn(Hg)) and concentrated hydrochloric acid (HCl).

Reaction



Nakabayaski has suggested a mechanism on the assumption that the reduction under acid condition involves protonated carbonyl group to which electrons are transferred from the metal.

Mechanism

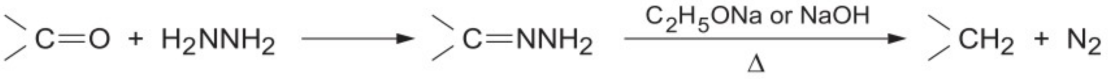


This reaction is valuable in organic synthesis for preparing hydrocarbons, pharmaceuticals, dyes, and fragrances under strongly acidic conditions.

20.4 WOLFF-KISHNER REDUCTION

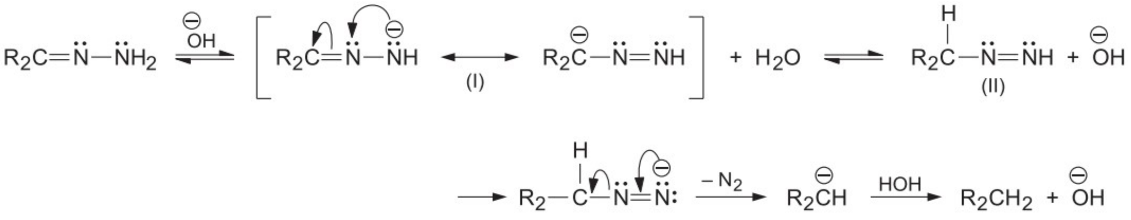
The Wolff-Kishner reduction is a classic organic reaction used to convert carbonyl groups (such as those in aldehydes and ketones) into methylene groups (*Effectively reducing the carbonyl compound to a hydrocarbon)* by heating their hydrozones, semicarbazones or azines in the presence of strong base such as C_2H_5ONa or NaOH.

Reaction



First step involves the formation of the anion of the hydrazone (I) which is protonated at the carbonyl carbon to form a substituted diimine (II). This is followed by simultaneous loss of nitrogen and formation of hydrocarbon. (Compounds of the type (II) are unstable and decompose to hydrocarbon and nitrogen probably through carbanion or free radical mechanism.) During the course of reduction, semicarbazones and azines are first converted to hydrazones before reduction.

Mechanism



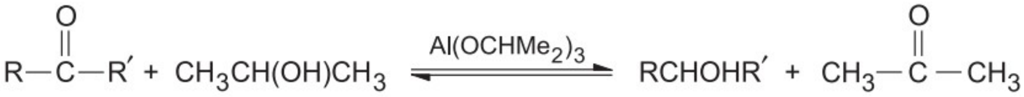
Frequently used in multi-step syntheses to remove carbonyl groups after their utility is exhausted in earlier steps.

20.5 MEERWEIN–PONNDORF–VERLEY REDUCTION

The reaction involves the reduction of aldehydes or ketones to alcohols by treatment with aluminium isopropoxide in excess of isopropyl alcohol.

The reaction is reversible. The reverse reaction, called Oppenauer oxidation.

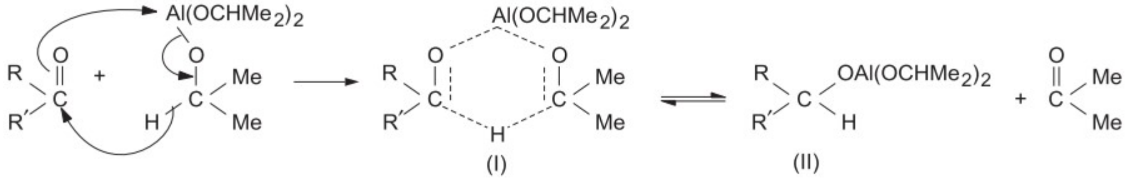
Reaction



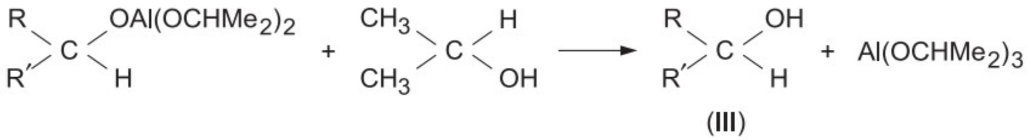
$$R-\overset{\overset{O}{\|}}{C}-R' + CH_3CH(OH)CH_3 \xrightleftharpoons{Al(OCHMe_2)_3} RCHOHR' + CH_3-\overset{\overset{O}{\|}}{C}-CH_3$$

Mechanism

The reaction probably involves a cyclic transition state (I) in which a hydride ion from the -CH bond of the alkoxide migrates to the carbonyl carbon of the ketone to yield the mixed alkoxide (II)



An excess of isopropyl alcohol is used so that it exchanges with the mixed alkoxide (II) to liberate the reduced ketone (III), i.e., the desired alcohol.

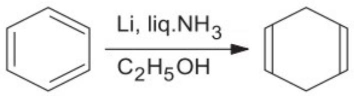


It is useful in pharmaceutical synthesis, biomass conversion, and fine chemical production using environmentally friendly aluminium alkoxide catalysis.

20.6 BIRCH REDUCTION

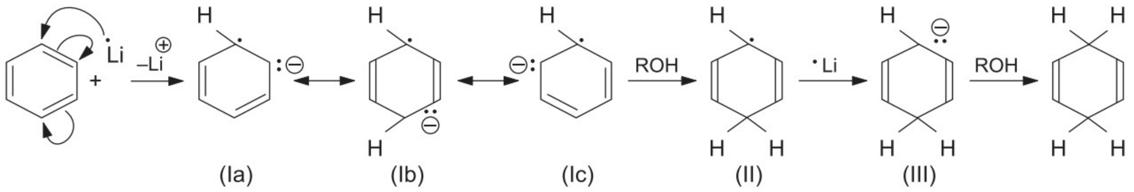
The Birch reduction is an important organic reaction where aromatic rings, such as benzene, are partially reduced to form 1,4-cyclohexadienes using alkali metals (sodium, lithium, or potassium), liquid ammonia, and a proton source (typically an alcohol).

Reaction



The accepted mechanism of reduction involves the following sequential steps: The metal transfers one electron to the benzene ring to produce a resonance-stabilized anion radical (Ia–Ic) which accepts a proton from the alcohol to form a radical (II). The addition of an electron from the metal to the radical produces an anion (III) which subsequently takes up a proton from the alcohol to give the dihydro product.

Mechanism



The Birch reduction remains a classic method for dearomatization and selective reduction in organic synthesis, particularly useful for complex molecule construction.

20.7 SUMMARY

1) Redox reactions enable controlled **interconversion of alcohols, carbonyl compounds, hydrocarbons, and aromatic systems**.
2) **Oppenauer oxidation** selectively oxidizes secondary alcohols to ketones using aluminium alkoxides and a ketone hydride acceptor.
3) **Clemmensen reduction** converts aldehydes and ketones to hydrocarbons using Zn (Hg)/HCl under strongly acidic conditions.
4) **Wolff–Kishner reduction** removes carbonyl groups via hydrazone formation followed by base-induced nitrogen extrusion.
5) **Meerwein–Ponndorf–Verley reduction** reduces carbonyl compounds to alcohols through hydride transfer using aluminium isopropoxide.
6) **Birch reduction** partially reduces aromatic rings to 1,4-cyclohexadienes via single-electron transfer in liquid ammonia.
7) These reactions offer **complementary strategies** depending on substrate sensitivity and reaction environment.

20.8 TECHNICAL TERMS

1) **Redox reaction**: A chemical reaction involving oxidation and reduction.
2) **Oppenauer oxidation**: Oxidation of secondary alcohols to ketones using aluminium alkoxide.
3) **Meerwein–Ponndorf–Verley reduction**: Aluminium alkoxide-mediated reduction of carbonyl compounds to alcohols.
4) **Clemmensen reduction**: Acidic reduction of carbonyl compounds to hydrocarbons using Zn(Hg)/HCl.
5) **Wolff–Kishner reduction**: Base-induced conversion of carbonyl compounds to hydrocarbons via hydrazones.
6) **Hydride transfer**: Migration of a hydride ion (H^-) between molecules.
7) **Isocyanate**: (Not applicable here, but often compared in redox contexts—omit in answers if needed.)
8) **Birch reduction**: Partial reduction of aromatic rings using alkali metals in liquid ammonia.
9) **Dearomatization**: Loss of aromatic character during reduction.
10) **Chemoselectivity**: Preferential reaction of one functional group in the presence of others.

20.9 SELF-ASSESSMENT QUESTIONS

1) What are redox reactions and why are they important in organic synthesis?
2) Explain the mechanism of Oppenauer oxidation.
3) Why is Oppenauer oxidation considered the reverse of MPV reduction?
4) Describe the Clemmensen reduction and its reaction conditions.
5) Explain the Wolff–Kishner reduction with mechanism.
6) Compare Clemmensen and Wolff–Kishner reductions.
7) Describe the mechanism of Meerwein–Ponndorf–Verley reduction.
8) What is Birch reduction? Explain its mechanism.

9) Why is Birch reduction called a partial reduction?
10) Discuss the applications of redox reactions in pharmaceutical synthesis.

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