A Text Book of

PHARMACEUTICAL ORGANIC CHEMISTRY - I

CAREER POINT

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Preface

In the ever-evolving field of pharmaceutical sciences, a thorough understanding of organic chemistry is fundamental to advancing both theoretical knowledge and practical application. It is with this in mind that I present “A Textbook of Pharmaceutical Organic Chemistry - I,” a comprehensive guide designed for students, educators, and professionals in the pharmaceutical and chemical sciences.

This textbook aims to bridge the gap between basic organic chemistry principles and their specific applications within the pharmaceutical industry. It has been meticulously crafted to provide a clear and structured approach to the study of organic compounds, their reactions, and their roles in drug development and formulation.

The content of this book has been organized to facilitate a progressive learning experience. Beginning with foundational concepts, the text advances to more complex topics, always with a focus on relevance to pharmaceutical applications. Key areas covered include the structure and reactivity of organic molecules, reaction mechanisms, and the synthesis of pharmaceutical agents. Each chapter is designed to build on the previous one, ensuring that readers develop a deep and comprehensive understanding of the subject matter.

Throughout this textbook, emphasis is placed on integrating theoretical concepts with practical examples. Detailed illustrations, problem sets, and real-world case studies are included to reinforce learning and illustrate the practical applications of organic chemistry in the pharmaceutical industry. Additionally, the inclusion of review questions and exercises at the end of each chapter aims to enhance comprehension and retention.

The development of this book has been guided by feedback from both students and educators, ensuring that it meets the needs of its audience effectively. It is my hope that this textbook not only serves as an educational resource but also inspires a deeper interest and appreciation for the role of organic chemistry in pharmaceutical sciences.

I would like to extend my sincere gratitude to all those who have contributed to this endeavor, including colleagues, mentors, and students whose insights and suggestions have been invaluable.

Thank you for choosing “A Textbook of Pharmaceutical Organic Chemistry - I.” I trust that it will be a valuable asset in your academic and professional journey.

Book Description

In the ever-evolving field of pharmaceutical sciences, a thorough understanding of organic chemistry is fundamental to advancing both theoretical knowledge and practical application. It is with this in mind that I present “A Textbook of Pharmaceutical Organic Chemistry - I,” a comprehensive guide designed for students, educators, and professionals in the pharmaceutical and chemical sciences.

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Syllabus

PHARMACEUTICAL ORGANIC CHEMISTRY – I

Scope : This subject deals with classification and nomenclature of simple organic compounds, structural isomerism, intermediates forming in reactions, important physical properties, reactions and methods of preparation of these compounds. The syllabus also emphasizes on mechanisms and orientation of reactions.

Objectives : Upon completion of the course the student shall be able to

1. Write the structure, name and the type of isomerism of the organic compound
2. Write the reaction, name the reaction and orientation of reactions
3. Account for reactivity/stability of compounds,
4. Identify/confirm the identification of organic compound

Course Content :

General methods of preparation and reactions of compounds superscripted with asterisk (*) to be explained.

To emphasize on definition, types, classification, principles/mechanisms, applications, examples and differences.

UNIT - I

- **Classification, nomenclature and isomerism :**

  Classification of Organic Compounds

  Common and IUPAC systems of nomenclature of organic compounds (up to 10 Carbons open chain and carbocyclic compounds)

  Structural isomerisms in organic compounds

UNIT - II

- **Alkanes*, Alkenes* and Conjugated dienes* :** SP3 hybridization in alkanes, Halogenation of alkanes, uses of paraffins. Stabilities of alkenes, SP2 hybridization in alkenes.

  E1 and E2 reactions – kinetics, order of reactivity of alkyl halides, rearrangement of carbocations, Saytzeffs orientation and evidences. E1 verses E2 reactions, Factors affecting E1 and E2 reactions. Ozonolysis, electrophilic addition reactions of alkenes, Markownikoff's orientation, free radical addition reactions of alkenes, Anti Markownikoff's orientation.

  Stability of conjugated dienes, Diel-Alder, electrophilic addition, free radical addition reactions of conjugated dienes, allylic rearrangement.

UNIT - III

- **Alkyl halides* :** SN1 and SN2 reactions - kinetics, order of reactivity of alkyl halides, stereochemistry and rearrangement of carbocations.

  SN1 versus SN2 reactions, Factors affecting SN1 and SN2 reactions.

  Structure and uses of ethylchloride, Chloroform, trichloroethylene, tetrachloroethylene, dichloromethane, tetrachloromethane and iodoform.

- **Alcohols* :** Qualitative tests, Structure and uses of Ethyl alcohol, Methyl alcohol, chlorobutanol, Cetosteryl alcohol, Benzyl alcohol, Glycerol, Propylene glycol.

UNIT - IV

- **Carbonyl compounds* (Aldehydes and ketones) :** Nucleophilic addition, Electromeric effect, aldol condensation, Crossed Aldol condensation, Cannizzaro reaction, Crossed Cannizzaro reaction, Benzoin condensation, Perkin condensation, qualitative tests, Structure and uses of Formaldehyde, Paraldehyde, Acetone, Chloral hydrate, Hexamine, Benzaldehyde, Vanilin, Cinnamaldehyde.

UNIT - V

- **Carboxylic acids* :** Acidity of carboxylic acids, effect of substituents on acidity, inductive effect and qualitative tests for carboxylic acids ,amide and ester.

  Structure and Uses of Acetic acid, Lactic acid, Tartaric acid, Citric acid, Succinic acid. Oxalic acid, Salicylic acid, Benzoic acid, Benzyl benzoate, Dimethyl phthalate, Methyl salicylate and Acetyl salicylic acid.

- **Aliphatic amines* :** Basicity, effect of substituent on Basicity. Qualitative test, Structure and uses of Ethanolamine, Ethylenediamine, Amphetamine.

Table of Contents

Editors

Mr. Navnath Sathe, Currently working as an Assistant Professor at Career Point University, Kota, brings 1 years of extensive experience in Pharmaceutical Sciences to his role. He has done Master's of Pharmacy from the Central University of Rajasthan in (Pharmaceutical Chemistry). He is Expertise in Natural Product , In Silico Studies , Synthesis , Nanotechnology , and also qualified national level exam GPAT, NIPER, CUCET. Actively participate in the national and international conferences.

Ms. Ritu Sharma , currently working as an Assistant Professor at Career Point University in Kota, brings 1 year of extensive experience in Pharmaceutical sciences. She has completed Masters of Pharmacy in Pharmacology from Maharishi Arvind College of Pharmacy, Manasarovar, Jaipur. I actively participate in national and international conferences, enriching discussions on pharmaceutical research. Her prolific writing and patent publications in Intellectual Property Rights showcase her commitment to advancing the field.

Ms. Kavita Vijay, currently working as an associate professor at Career Point University in Kota.She had an experience of more than 12 years of teaching in pharmacy colleges and also having industrial experience involved in research activity. Her area of interest is novel and targeted drug delivery systems.I actively participate in national and international conferences, enriching discussions on pharmaceutical research. Her prolific writing and patent publications in Intellectual Property Rights showcase her commitment to advancing the field.

Dr. Rajkumari Thagele is from Bhopal. Her education details include M. Pharm in Pharmaceutics from Barkatullah University Bhopal and Ph. D. In pharmaceutical sciences from RKDF University Bhopal in the year 2009 and 2018 respectively.Currently working as Asso. Prof. School of pharmacy career point university Kota Rajasthan.She had an experience of more than 14 years of teaching in pharmacy colleges and also involved in research activity. Her area of interest is novel and targeted drug delivery systems.I published 13 research and review articles in various international and national journals. Having 4 patents. Attended various International and National conferences along with presentations there. Awardee of two best research papers by Adina institute of pharmaceutical sciences, Sagar and RKDF University Bhopal. Recently awarded by IJRULA, for Best Innovative Researcher in Novel Drug Delivery System.

Mahesh malav.

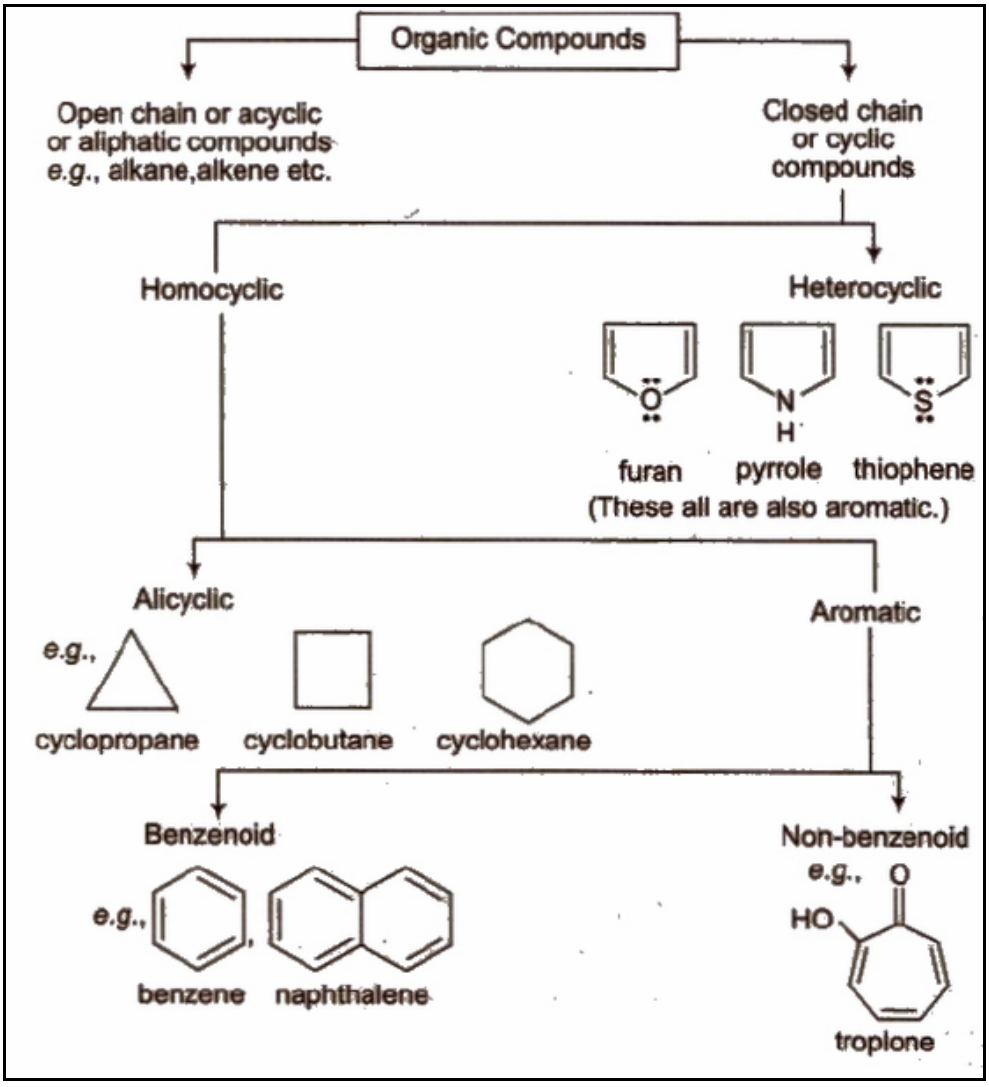
CHAPTER 1

Classification, nomenclature and isomerism

Introduction :

Organic compound, any of a large class of chemical compounds in which one or more atoms of carbon are covalently linked to atoms of other elements, most commonly hydrogen, oxygen, or nitrogen. The few carbon-containing compounds not classified as organic include carbides, carbonates, and cyanides.

Classification of organic compounds :



Acyclic or Open Chain Compounds :

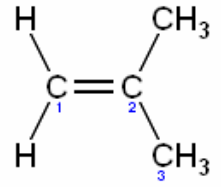
The carbon atoms are present in the form of an open chain.This chain may either be a straight chain or a branched chain. These were initially known as Aliphatic compounds because the compounds of this class were derived from either animal or vegetable fats

- **Straight Chain Compounds:** The carbon skeleton is in the form of a straight chain.

  Examples:

  n-Propane CH3-CH2-CH3

  Propene CH2=CH-CH3



- **Branched Chain Compounds:** The carbon skeleton is in the form of a branched chain. Examples: Isobutylene

Cyclic or Closed Chain Compounds :

They are marked by the presence of one or more closed chains or ring of atoms in their structure. Depending on whether there is a presence of any other atom apart from carbon in the constitution of the ring, they are further classified as:

- Homocyclic or Carbocyclic Compounds
- Heterocyclic Compounds

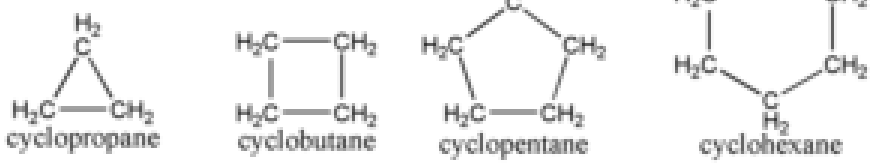
Homocyclic or Carbocyclic Compounds :

The rings in these compounds are entirely made up of carbon atoms. No other atom is present in the ring skeleton.These can be further divided into two sub-classes:

- Alicyclic Compounds
- Aromatic Compounds

Alicyclic Compounds :

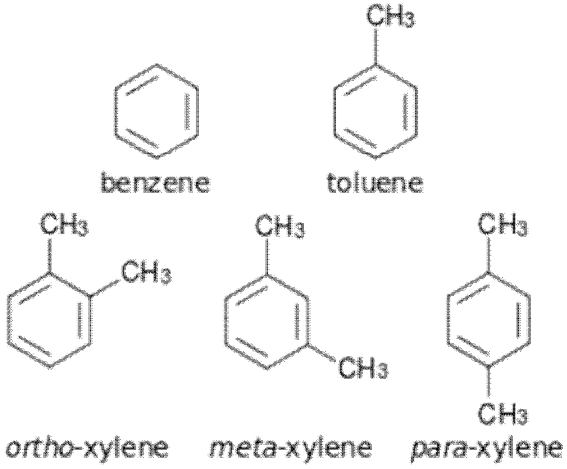
Their name is attributed to their resemblance to Aliphatic compounds in their properties. The examples of this category include cyclopropane, cyclobutane, cyclopentane, cyclohexane, etc.

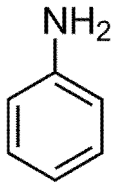


Aromatic Compounds :

These are cyclic unsaturated compounds. They derive their name from the Greek word Aroma which means "fragrant smell" since most of these compounds bear a pleasant smell. These are further classified into two types:

- Benzenoid Aromatic Compounds: They are characterized by the presence of one or more fused or isolated benzene rings as well as their derivatives in their structure. Depending upon the number of benzene rings that are fused together in their structure, they can be further classified as Monocyclic, Bicyclic, Tricyclic.
- Non-Benzenoid aromatic Compounds: They are characterized by the presence of a single benzene ring to which other groups are attached.

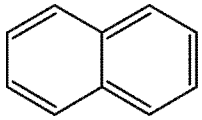




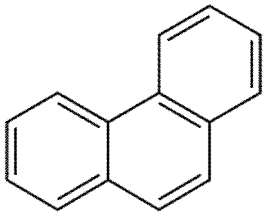
Aniline

Bicyclic and Tricyclic Compounds :

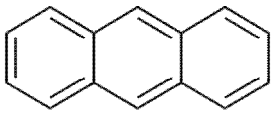
These are characterized by the presence of two or more rings in their structure.Examples include Naphthalene, Phenanthrene as well as Anthracene.



Naphthalene



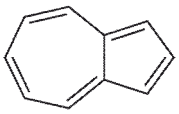
Phenanthrene



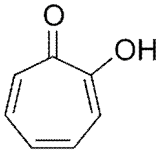
Anthracene

Non-Benzenoid Aromatic Compounds :

Aromatic compounds that contain other highly unsaturated rings in place of the benzene ring are called non-benzenoid aromatic compounds. Examples include



Azulene

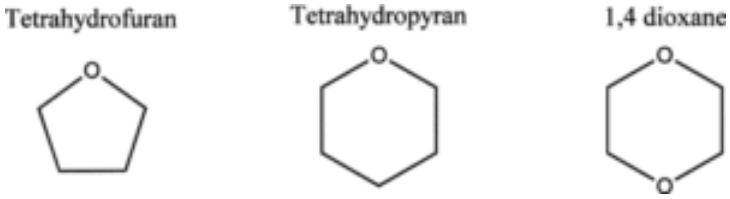


Tropolone

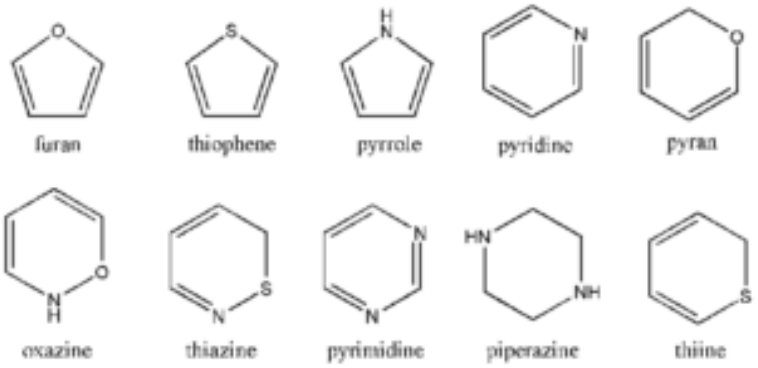
Heterocyclic Compounds :

When one or more heteroatoms such as oxygen, nitrogen, sulphur, boron, silicon etc, are present in the ring such compounds are known as heterocyclic compounds.

- **Alicyclic heterocyclic compounds:** Aliphatic heterocyclic compounds that contain one or more heteroatoms in their rings are called alicyclic heterocyclic compounds.



- Aromatic heterocyclic compounds Aromatic heterocyclic compounds that contain one or more heteroatoms in their ring skeleton are called aromatic heterocyclic compounds.



Nomenclature of Organic compound

Alkanes :

Alkanes are aliphatic hydrocarbons having C—C and C— H σ bonds. They can be categorized as acyclic or cyclic.

Acyclic alkanes have the molecular formula CnH2n+2 (where n = an integer) and contain only linear and branched chains of carbon atoms. They are also called saturated hydrocarbons because they have the maximum number of hydrogen atoms per carbon.

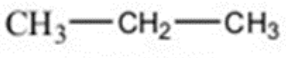
Cycloalkanes contain carbons joined in one or more rings. Because their general formula is CnH2n, they have two fewer H atoms than an acyclic alkane with the same number of carbons.

Nomenclature of alkanes :

The first four members of the series are called by their names i.e, methane, ethane, propane, butane and higher alkanes are derived from the greek prefixes that indicates the carbon atom in the molecule .

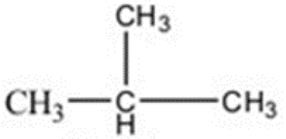
Eg: pentane has 5 carbon atom

The prefix n- is used for those alkanes in which all carbons are in one continuous chain



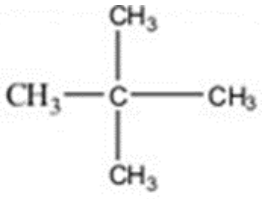
n-propane

Prefix iso is used for those alkanes which have a methyl group attached to the second last carbon atom of a continuous chain.



isobutane

Prefix neo is used for those alkanes which have two methyl groups attached to the second last carbon atom



neo pentane

Alkyl group is formed by removing one hydrogen from an alkane. The suffix of this group is –yl

Non alkyl groups: F-Fluoro, Cl- Chloro, Br- Bromo, I- Iodo, NO2- Nitro, NH2- Amino, OH- Hydroxy.

Parent alkanes

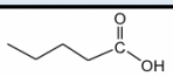
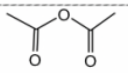
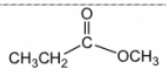
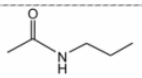
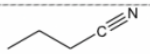
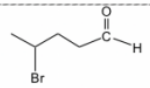
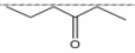
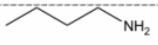
IUPAC Nomenclature :

Alkane Nomenclature: The Rules

Unbranched Alkanes

# C	Name	#C	Name
1	Methane	11	Undecane
2	Ethane	12	Dodecane
3	Propane	13	Tridecane
4	Butane	14	Tetradecane
5	Pentane	15	Pentadecane
6	Hexane	16	Hexadecane
7	Heptane	17	Heptadecane
8	Octane	18	Octadecane
9	Nonane	19	Nonadecane
10	Decane	20	Eicosane

IUPAC Nomenclature :

Functional group	Prefix	Suffix	Examples	Name of Example
carboxylic acid	carboxy	–oic acid –carboxylic acid		pentanoic acid
acid anhydride	—	–oic anhydride –carboxylic anhydride		ethanoic anhydride
carboxylic ester	alkoxycarbonyl	–oate –carboxylate		methyl propanoate
amide	amido	–amide –carboxamide		N-propylethanamide
nitrile	cyano	–nitrile (keep "e") –carbonitrile		butanenitrile
aldehyde	oxo	–al –carbaldehyde		4-bromo-pentanal
ketone	oxo	–one		3-hexanone
alcohol	hydroxy	–ol		3-methyl-2-butanol
amine	amino	–amine		butylamine (common name)
alkene	enyl	–ene		2-pentene
alkyne	ynyl	–yne		1-hexyne
alkyl	yl	–ane		2,2-dimethylbutane

Rules for IUPAC nomenclature :

- Find the longest continuous carbon chain.
- Determine the root name for this parent chain.
- Number the chain in the direction such that the position number of the first substituent is the smaller number.
- If the first substituents from either end have the same number, then number so that the second substituent has the smaller number
- Determine the name and position number of each substituent.
- Indicate the number of identical groups by the prefixes di, tri, tetra, etc.
- Place the position numbers and names of the substituent groups, in alphabetical order, before the root name

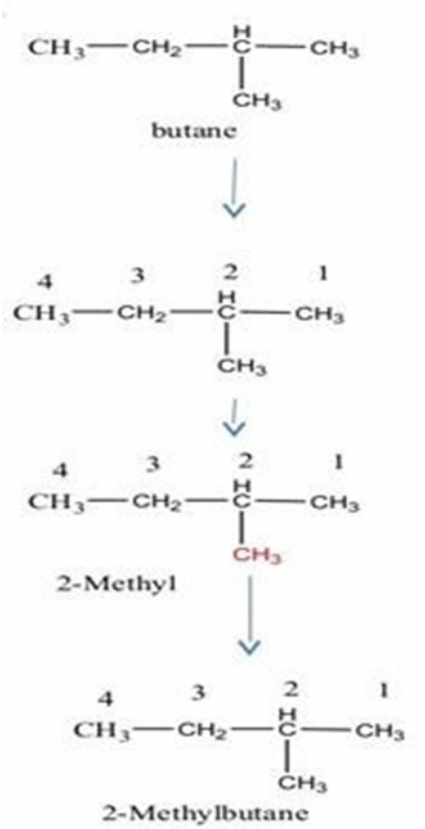
IUPAC Nomenclature of alkanes :

The steps for alkanes= Prefix------Parent------- Suffix.

Rules for nomenclature of alkanes

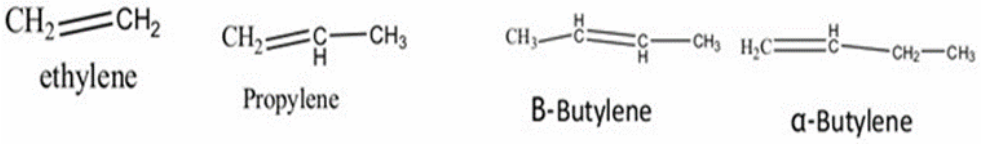
- Name the longest chain- the longest continuous carbon chain is chosen and given a parent name.
- Number the longest chain- the carbon atoms in longest chain are numbered and numbering started from the end where substituent is attached
- Locate and name of substituents- Each substituent is named and position of each substituent is indicated by number.
- Combine the longest chain and substituents- The position and name of substituent are added to the name of the longest chain and written as one word.
- Indicate the number and position of substituents- If the same substituent is present two or more time in the molecule at that time substituent is indicated by prefix di, tri, tetra, penta and location is indicated by separate numbers

If two or more substituents are present, their names are alphabetized and added to the parent alkane



Nomenclature of alkene Common system :

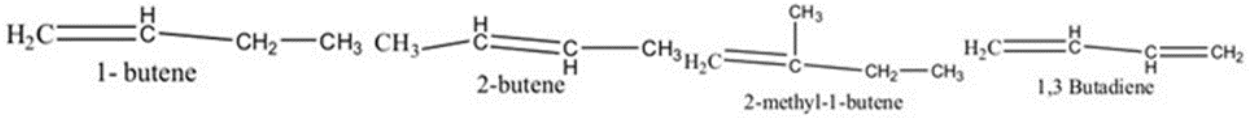
1. The common names of the first four members named by changing –ane to – ylene.
2. The Greek letters are used to distinguish isomers having double bond at the first and second carbon of the chain



IUPAC Nomenclature alkene :

1. The IUPAC names of alkenes are derived from those of the corresponding alkanes by changing the ending –ane to –ene.
2. Select the longest continuous carbon chain that contains the double bond and use this as the parent compound.
3. Number this longest continuous chain so that the double bond has the lowest possible number.
4. To indicate the position of the carbon- carbon double bond, add the number of lower numbered carbon atoms of carbon carbon double bond in front of the alkene name.
5. Side chain and substituents are named as usual and their position is indicated by number to show to which carbon atom they are attached.

6. When there are two or three double bonds in a molecule, the –ane is replaced by –adiene and –atriene.

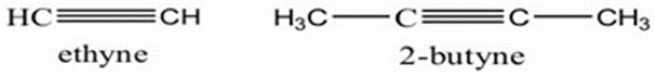


Nomenclature of alkyne :

- **Common system:** acetylene is the common name of for the first member of the series

- **Derived system:** Higher alkynes are regarded as alkyl derivatives of acetylene.

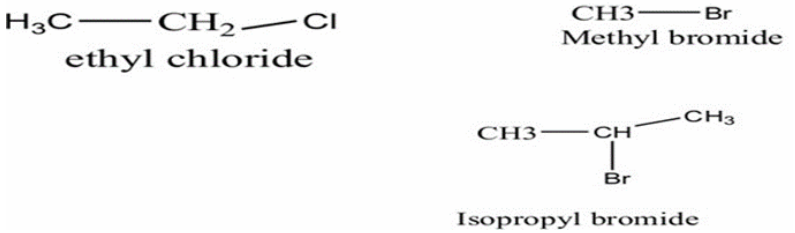
- **IUPAC Nomenclature:** The IUPAC names of alkynes are obtained by dropping the ending –ane of parent alkanes and adding the suffux –yne.



Nomenclature for alkyl halide :

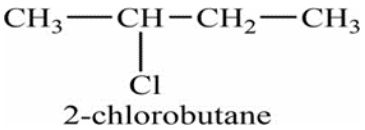
Common system: in this system the alkyl group attached to the halogen atom is named first alkane and then chloride, fluoride and bromide will come.

- Suffix for alkyl halides is –yl halide



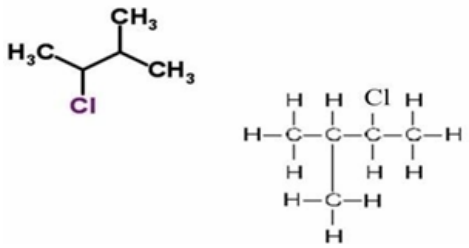
Nomenclature for alkyl halide IUPAC Nomenclature :

- The longest continuous chain of carbon atoms is chosen as the parent. if parent chain has no branching alkyl group, the position of halogen atom is given by a number that corresponds to the carbon atom to which it is attached. The carbon chain is numbered so that the carbon atom bearing the halogen atom has the lowest number.



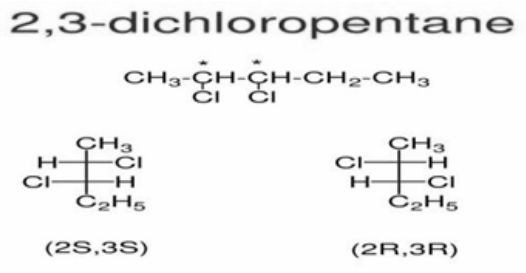
- If the parent chain has branching alkyl group, number the chain from the end near to first substituent. 3. If the compound contains two or more halogen atoms of the same type, they are indicated with prefixes di-, tri-, etc.

2-chloro-3-methylbutane



If the compound contains different substituent's, they are numbered according to their positions on the chain and listed in alphabetical order.

2,3-dichloropentane

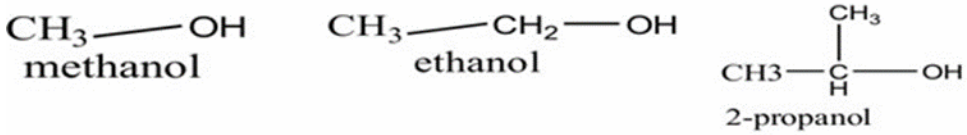


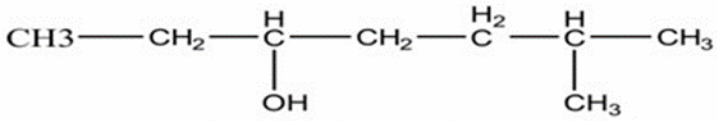
Nomenclature of alcohol :

- **Common system:** In this system alcohols(R-OH) are named as alkyl alcohol.

IUPAC Nomenclature :

- Select the longest continuous carbon chain containing the –OH group.
- Change the name of the alkane corresponding to this chain by dropping the ending –e and adding suffix –ol.
- Number the chain so as to give the carbon carrying the –OH group, the lowest possible number. The position of the -OH group is indicated by this number.
- Indicate the positions of other substituents or multiple bonds by numbers.
- When –OH is part of a higher priority class of compound, it is named as hydroxy.

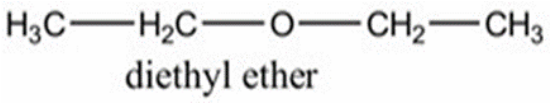




Nomenclature of ethers :

Common system: The two alkyl groups attached to oxygen are named in alphabetical order and word ether is added.

ü If the two alkyl groups are same (R-O-R), the prefix di- is used.



diethyl ether

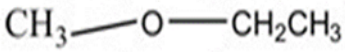
ethyl methyl ether

IUPAC Nomenclature :

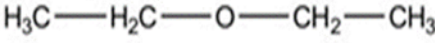
ethers are named as alkoxy alkanes.

The larger alkyl group is considered to be alkanes or parent.

The name of the alkane is prefixed by the name of the alkoxy group and position number.



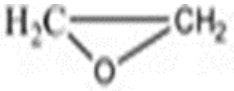
methoxyethane



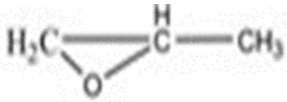
ethoxyethane

Nomenclature of oxiranes :

- **Common system:** usually they alkene epoxide because they are made from alkenes

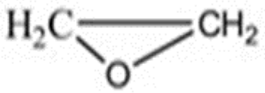


ethylene oxide
(epoxy ethane)

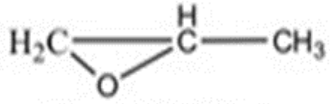


Propylene oxide
(epoxy propane)

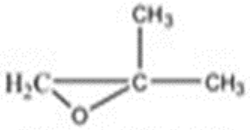
- **IUPAC Nomenclature:** In this system ethylene oxide is called as oxirane and epoxides are named as substituted oxiranes



oxirane



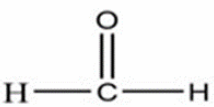
2-methyloxirane



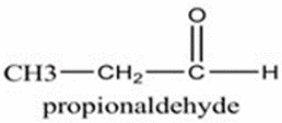
2,2-dimethyloxirane

Nomenclature of aldehyde :

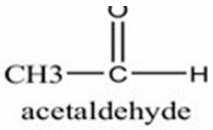
- Common system: The name of simple aldehydes are derived from the common names of corresponding carboxylic acid.
- The characteristic –ic acid ending in the common name of carboxylic acid is dropped and replaced by- aldehyde.
- E.g. one carbon carboxylic acid is formic acid, so the name of the corresponding aldehyde is formaldehyde.



formaldehyde



propionaldehyde



acetaldehyde

IUPAC Nomenclature of aldehyde :

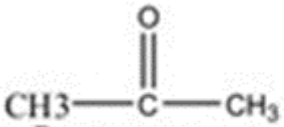
- The IUPAC system of naming aldehyde uses the parent alkane name corresponds to the longest continuous chain containing the aldehyde group.
- The final –e of the alkane name is dropped and replaced by-al.
- The numbering of the longest continuous chain starts with C-1 as the carbon bearing the aldehyde group. 4. The substituents are
- indicated by name and position number.

Nomenclature of ketone

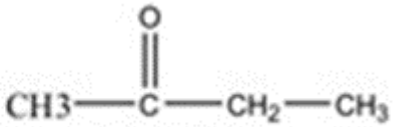
Nomenclature of ketone IUPAC Nomenclature:

ketones are named as dialkyl ketones.

- First member of the series CH3COCH3 is, however, popularly called acetone.
- The common names of unsymmetrical ketones are obtained by naming the alkyl groups as separate words in alphabetic order and adding the third word 'ketone'

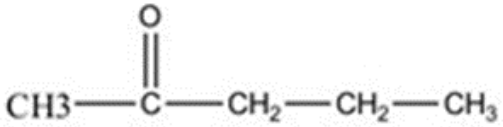


Propanone



Butanone

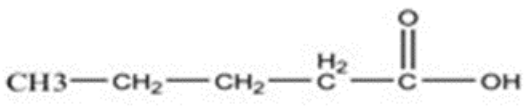
- While naming higher ketones on the IUPAC system, it becomes necessary to assign positional numbers to the carbonyl group.



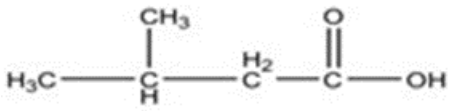
2-pentanone

Nomenclature of carboxylic acid :

- **Common system:** The longest carbon chain containing the carboxylic group is selected and the carboxylic acid is named by replacing the 'e' of the corresponding alkane by '-ic acid'.



Valeric acid

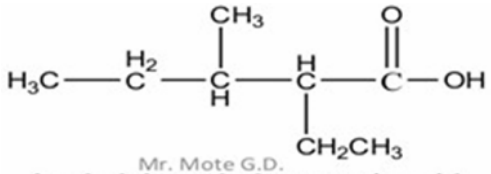


isovaleric acid

IUPAC Nomenclature :

- The longest carbon chain containing the carboxylic group is selected and the carboxylic acid is named by replacing the 'e' of the corresponding alkane by '- oic acid'.

- The selected carbon chain is numbered I, 2, 3, 4 etc to indicate the position of the side- chains attached to it.

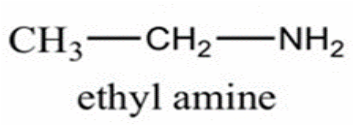


2-ethyl-3-methylpentanoic acid

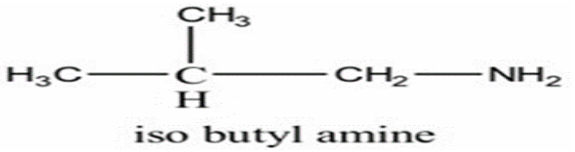
Nomenclature of amine Common system: The longest carbon chain containing the amine group is selected and the amine is named by replacing the 'e' of the corresponding alkane by '- alkylamine'. .

IUPAC Nomenclature: The longest carbon chain containing the amine group is selected and the amine is named by replacing the 'e' of the corresponding alkane by '- amine

The selected carbon chain is numbered I, 2, 3, 4 etc to indicate the position of the side-chains attached to it.



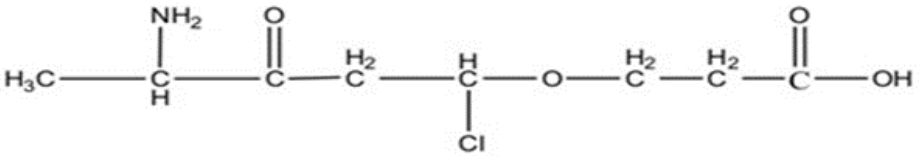
ethyl amine



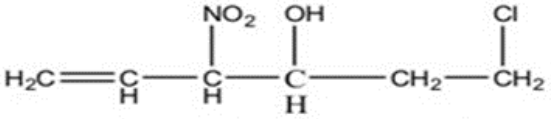
iso butyl amine

Rules for IUPAC nomenclature for polyfunctional group :

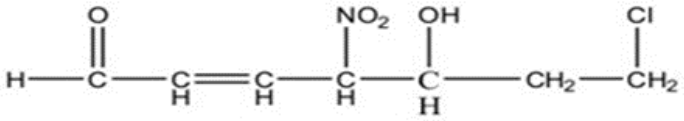
- In naming molecules containing one or more of the functional groups in Group A, the group of highest priority is indicated by suffix; the others are indicated by prefix, with priority equivalent to any other substituents.
- Priority of function group: Carboxylic acid > ester > acyl halide > amide > aldehyde > ketone > alcohol > amine > alkene > alkyne > alkane > ether > alkyl halide > nitro alkane
- Find the highest priority functional group. Determine and name the longest continuous carbon chain that includes this group.
- Number the chain so that the highest priority functional group is assigned the parent chain
- If the carbon chain includes multiple bonds (Group B), replace “ane” with “ene” for an alkene or “yne” for an alkyne. Designate the position of the multiple bond with the number of the first carbon of the multiple bond.
- If the molecule includes Group A functional groups, replace the last “e” with the suffix of the highest priority functional group, and include its position number.
- Indicate all Group C substituents, and Group A functional groups of lower priority, with a prefix. Place the prefixes, with appropriate position numbers, in alphabetical order before the root name.



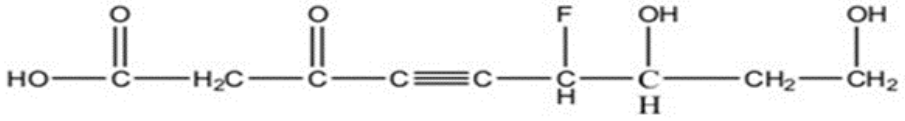
3-(4-amino-1-chloro-3-oxopentyloxy)propanoic acid



1-chloro-4-nitrohex-5-en-3-ol



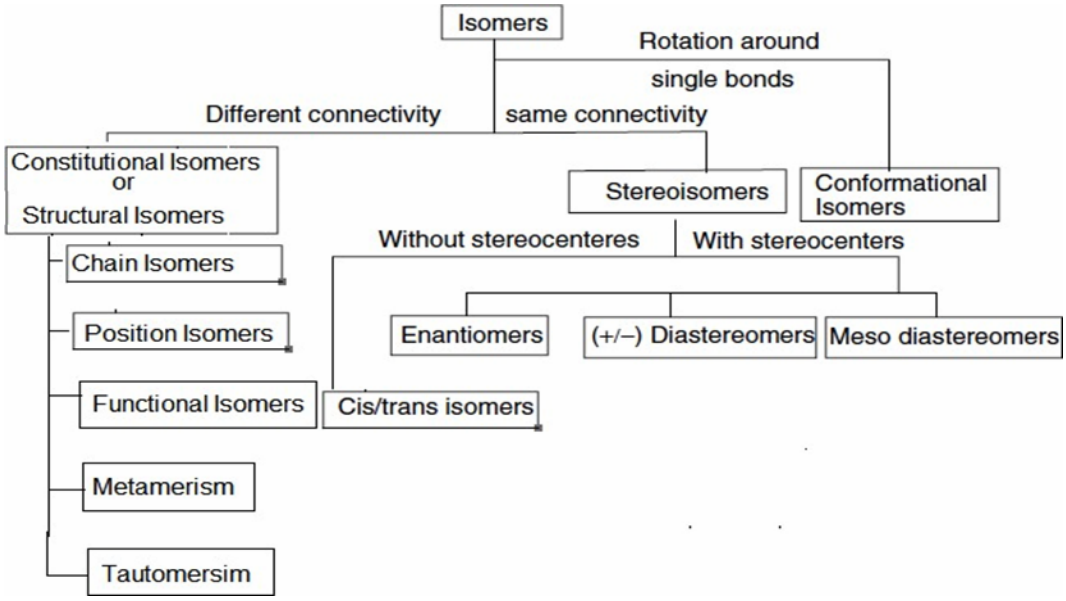
7-chloro-5-hydroxy-4-nitrohept-2-enal



6-fluoro-7,9-dihydroxy-3-oxonon-4-ynoic acid

Structural isomerisms in organic compounds :

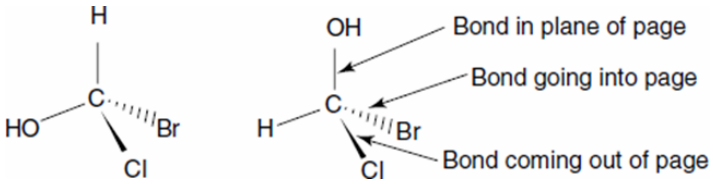
- *Isomers* are compounds that have the same formula but different structures.
- The three main types of isomers are constitutional isomers, conformational isomers and stereoisomers.
- Stereoisomers have the same connectivity but a different spatial orientation. Stereoisomers do not differ from each other as a result of rotation around single (sigma) bonds. They are different compounds.



Connectivity :

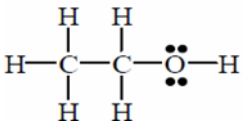
- The term connectivity means all the atoms in a molecule are connected in the same sequence.

- For a molecule containing atoms A, B, and C; one connectivity is A-B–C while A-C-B is a different connectivity. Both have the same connectivity but the atoms have a different orientation in space.

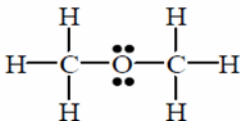


- The same atoms or groups are connected to the central carbon atom. The connectivity is the same, but OH and H are oriented differently in space. To change the positions of H and OH, one would have to break the H-C and HO-C bonds and connect them in the reverse order.
- The two compounds differ in their connectivity: **C–O–C** and **C–C–O**

Ethyl alcohol



Dimethyl ether

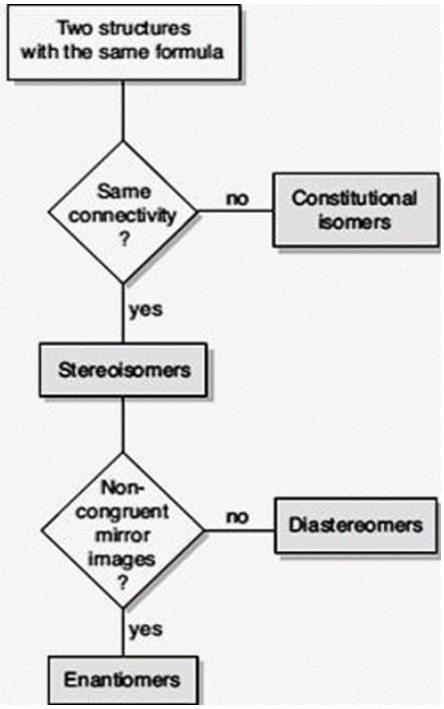


There are two isomeric compounds with molecular formula **C_2H_6O** :

1) **Dimethyl ether:** a gas at room temperature, does not react with sodium.
2) **Ethyl alcohol:** a liquid at room temperature does react with sodium.

Properties of ethyl alcohol and dimethyl ether :

Properties	Ethyl Alcohol (C_2H_6O)	Dimethyl Ether (C_2H_6O)
Boiling point, °C	78.5	–24.9
Melting point, °C	–117.3	–138
Reaction with sodium	Displaces hydrogen	No reaction



Simple flowchart for classifying various kinds of isomers

STRUCTURAL ISOMERISM or CONSTITUTIONAL ISOMERS :

Structural isomers are compounds that have the same molecular formula but different structural formulas.

Types of Structural isomers:

(i) Chain isomerism

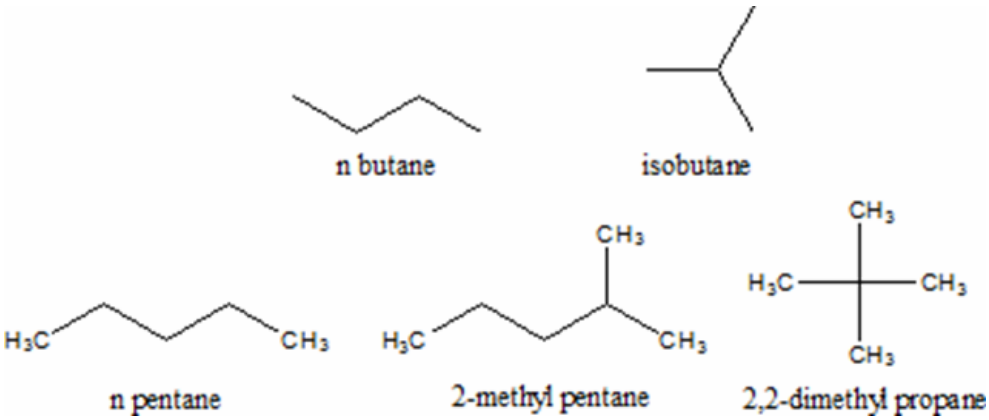
(ii) Position isomerism

(iii) Functional isomerism

(iv) Metamerism

(v) Tautomerism

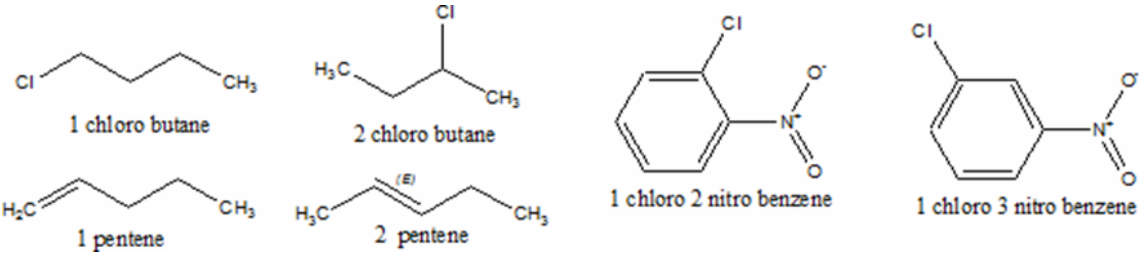
- **Chain isomerism:** It has the same molecular formula but differ in the order in which the carbon atoms are bonded to each other.



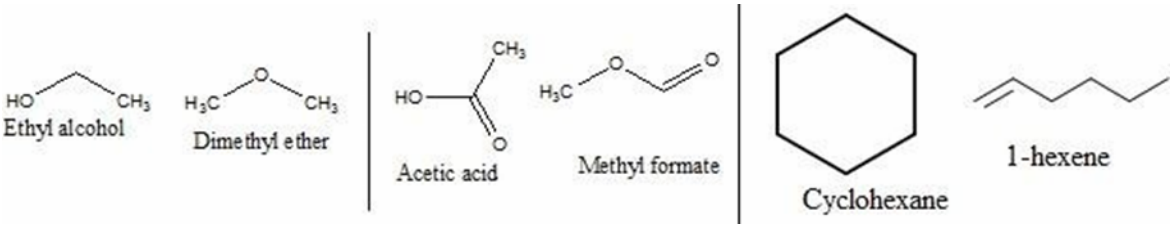
Number of possible chain-isomers for Alkane

Molecular Formula	Possible Number of Constitutional Isomers
C_4H_{10}	2
C_5H_{12}	3
C_6H_{14}	5
C_7H_{16}	9
C_8H_{18}	18
C_9H_{20}	35
$C_{10}H_{22}$	75

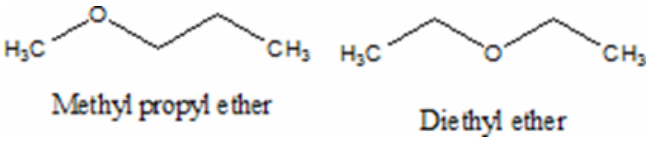
- **Position isomerism:** It has the same molecular formula but differ in the position of a functional group on the carbon chain.



- **Functional isomerism:** It has the same molecular formula but different functional groups.



- **Metamerism:** This type of isomerism is due to the unequal distribution of carbon atoms on either side of the functional group. Members belong to the same homologous series.

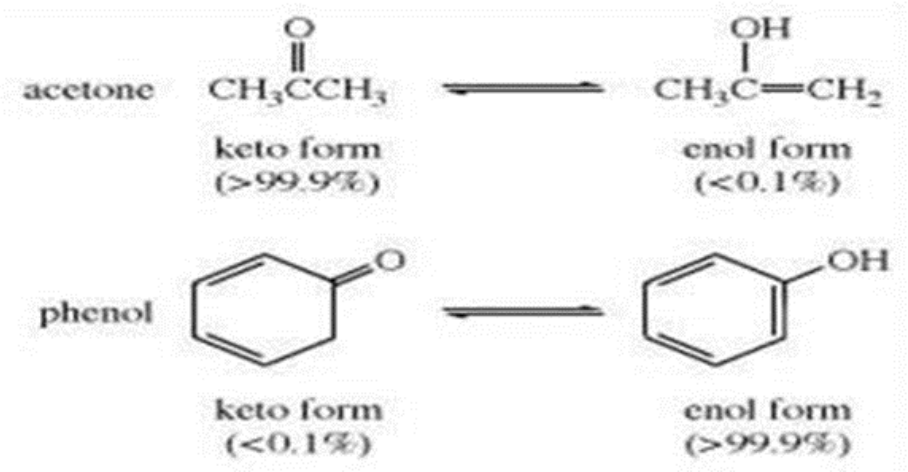


- **Tautomerism:** This is a special type of functional isomerism in which the isomers are in dynamic equilibrium with each other.

Tautomerism

- Tautomers are isomers of a compound which differ only in the position of the protons and electrons. The carbon skeleton of the compound is unchanged. A reaction which involves simple proton transfer in an intramolecular fashion is called tautomerism.
- Sometimes the term tautomerism is also called as desmotropism (In Greek desmos-bond; tropos-turn), since the interconversion of the two forms involves a change of bonds or dynamic isomerism as the two forms are in dynamic equilibrium with each other.
- Other names for tautomerism are kryptomerism, allotropism or merotropy; however, tautomerism is the most widely accepted term.

- There are several types of tautomerism of which keto-enol tautomerism is the most important. In this type, one form (tautomer) exists as a ketone while the other exists as an enol. The two simplest examples are of acetone and phenol. The conversion of a keto form into enol from is known as enolisation.



- The most widely studied example of keto-enol tautomerism is that of **acetoacetic ester** (ethyl acetoacetate).

Why the KETO form is more stable than ENOL: In most keto-enol tautomerisms, the equilibrium lies by far toward the keto form, indicating that the keto form is usually much more stable than the enol form, which can be attributed to the feet that a carbon-oxygen double bond is significantly stronger than a carbon-carbon double bond.

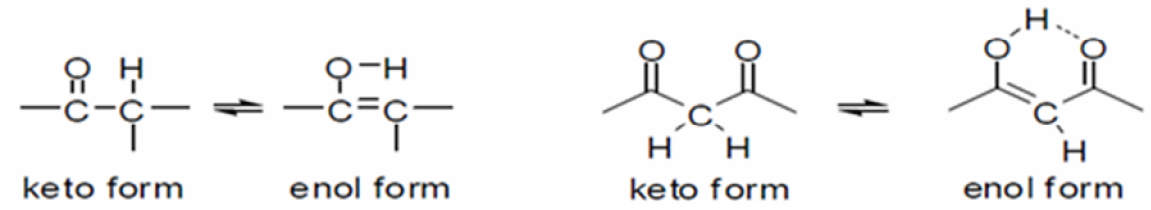
Are Tautomers stereoisomers: No, Tautomers are Structural Isomerism or Constitutional Isomers. Tautomers are two molecules with the same molecular formula but different connectivity - constitutional isomers, in other words - which can interconvert in a rapid equilibrium. The most common tautomeric relationship in organic chemistry is the keto-enol pair.

Types of tautomerism:

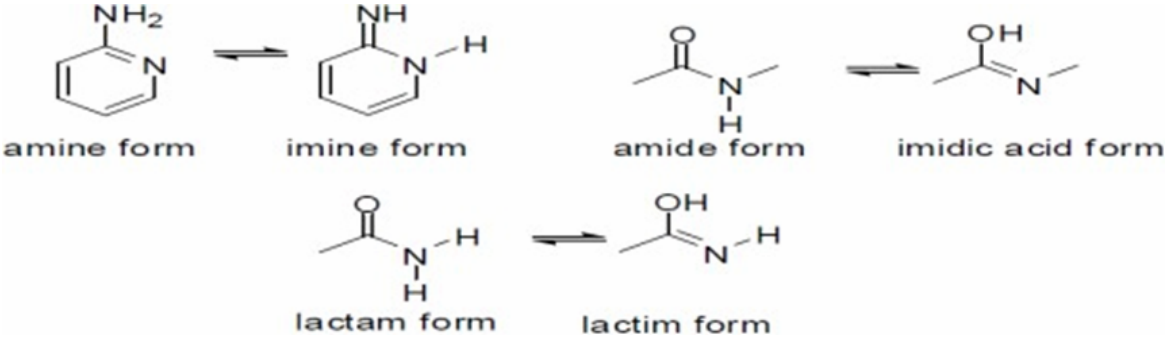
1. Prototropic tautomerism
2. Annular tautomerism
3. Non-prototropic tautomerism
4. Ring-chain tautomerism
5. Valence tautomerism

1) **Prototropic Tautomerism :**

- ***Prototropic tautomerism*** involves the relocation of an **H atom** and a **double bond**.
- One example of prototropic tautomerism is that between **keto** and **enol** forms.
- The **keto tautomer** possesses a **C=O** group, while the **enol form** has a **vinylic alcohol structure**. Increasing acidity of the **α-H** affects this tautomerism, favoringthe **enol form**.
- **Conjugated double bonds** and intramolecular **H-bonds** can also stabilize the **enol form**.

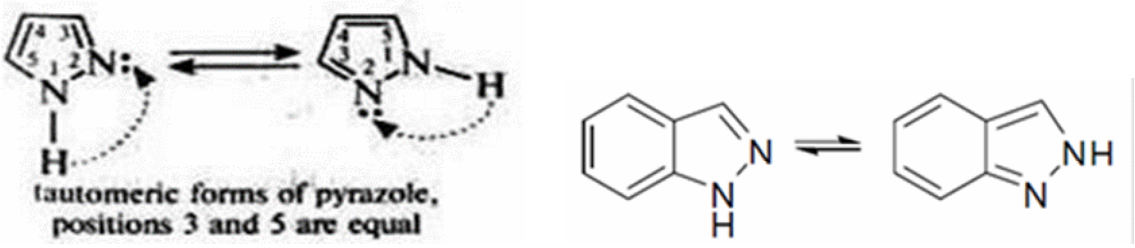


Other types of **prototropic tautomerism** are **amine-imine tautomerism** (e.g. in adenines), amide-imidic acid tautomerism (related to asparagine-linked glycosylation) and, as a special case, lactam-lactim tautomerism (present in uracil and thymine).



2) **Annular Tautomerism :**

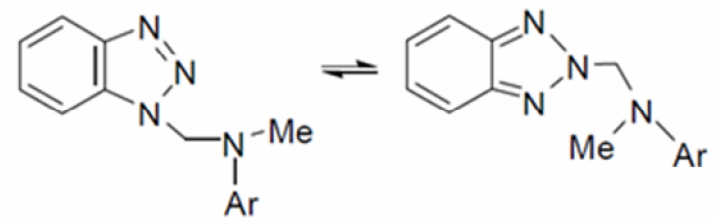
This is a special case of prototropic tautomerism, where an H can occupy two or more possible locations in a heterocyclic system, e.g. imidazole, which can have 1H and 2H tautomers.



1H and 2H tautomers of imidazole

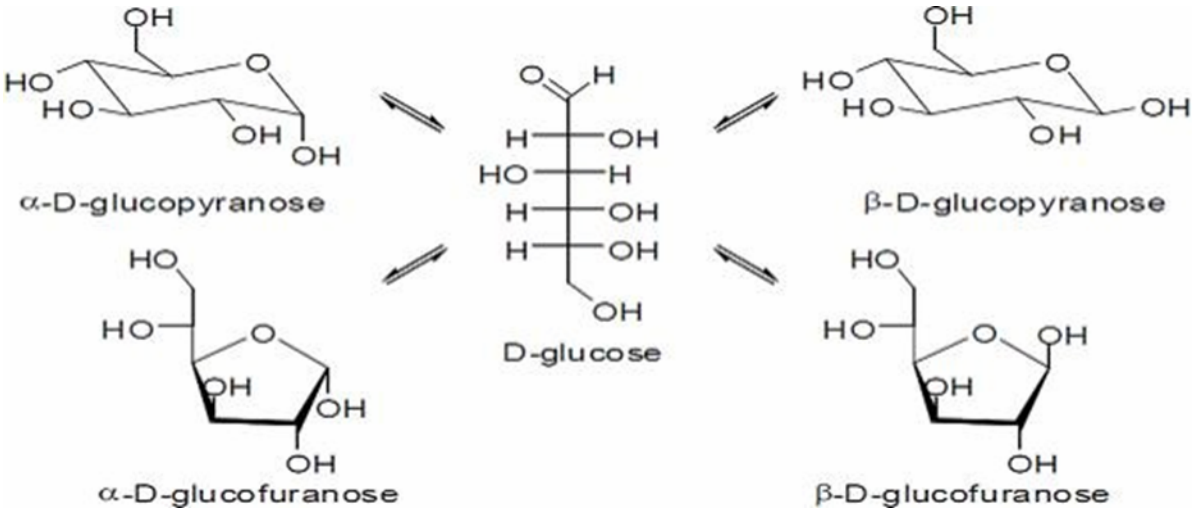
3) **Non-Prototropic Tautomerism :**

Non-prototropic tautomerism involves the relocation of a substituent other than H, e.g. the tautomerism of 1- and 2-(N,N-disubstituted aminomethyl) benzotriazoles.



4) **Ring-Chain Tautomerism :**

- In ring-chain tautomerism, a structural change occurs between an **open-chain** form and a **ring form** through an **H-transfer**.
- This is an important process for monosaccharides such as sugars. Glucose is a well-known example, which can exist in five different tautomeric forms in solution. Ring-chain tautomerism was first discovered by Sir Emil Fischer in the 1890.



5) **Valence Tautomerism :** Valence tautomerism involves the reorganization of bonding electrons, which results in changes in molecular geometry.

1,3,5-cyclo-octatriene ***bicyclo[4.2.0]octa-2,4-diene***

CHAPTER 2

Alkanes, Alkenes and Conjugated dienes

Alkanes, Alkenes and Conjugated dienes :

Alkanes are organic compounds that consist of single-bonded carbon and hydrogen atoms. The formula for *Alkanes is CnH2n+2*, subdivided into three groups – *chain alkanes, cycloalkanes, and the branched alkanes.*

Physical Properties of Alkanes :

- Alkanes are non-polar compounds. The difference in the electronegativities of Carbon and Hydrogen is almost non-existent, hence they have an almost complete absence of polarity.
- Alkanes generally have relatively lower boiling points and melting points. This is because their atoms have weak Van Der Waals force and so the atomic bonds break easily.
- However, as the molecules get bigger the force gets stronger. So more complex alkane has higher boiling and melting points.
- They can exist as solids, liquids and gases in their natural states. Unbranched alkanes usually are gases in their natural state. The examples are methane, ethane etc. The alkanes bigger than hexadecane are all solids.
- Also, they are completely insoluble in water , again due to the weak van der Waal forces.
- However, they are soluble in organic solids. Here the van der Waal forces of alkane break and are replaced by newer van der Waal forces.

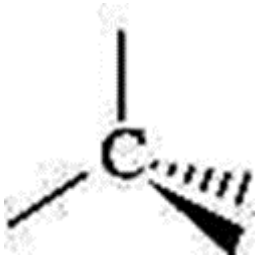
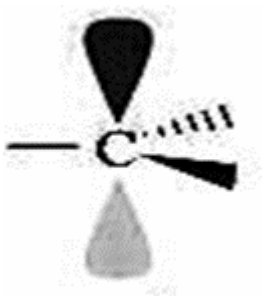
SP^3 hybridization in alkanes :

Hybridization

Hybridization and general principles explain how covalent bonding in organic chemistry is possible.

Hybridization happens when atomic orbitals mix to form a new atomic orbital. The new orbital can hold the same total number of electrons as the old ones. The properties and energy of the new, hybridized orbital are an 'average' of the original unhybridized orbitals.

Types of Hybridization :

Type of hybrid	*sp3 hybridization*	*sp2 hybridization*	*sp hybridization*
Diagram			
Atomic orbitals used	s, p, p, p	s, p, p	s, p
Orbitals Combined	s-orbital + 3 p-orbitals	s-orbital + 2 p-orbitals	s-orbital + 1 p-orbital
Resulting Orbitals	4 sp^3 orbitals (no p-orbitals)	3 sp^2 orbitals + 1 p-orbital	2 sp orbitals + 2 p-orbitals
Number of hybrid orbitals formed	4	3	2
Number of atoms bonded to the C	4	3	2
Geometry	tetrahedral	flat triangular	Linear
Ideal angle	109.5^0	120^0	180^0
Bonds	single bonds	double bonds	triple bonds

Bond Lengths: mostly dependent on atomic size, bond order, and hybridization

Multiple Bonding: Bond length depends strongly on bond order (length: single > double > triple)

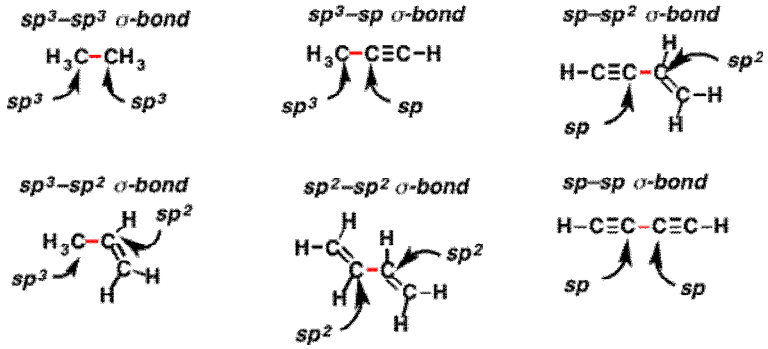
Representative bond lengths:

sp^3–sp^3	154 pm (1.54 Å)
sp^3–sp^2	150 pm (1.50 Å)
sp^3–sp	146 pm (1.46 Å)
sp^2–sp^2	147 pm (1.47 Å)
sp^2–sp	143 pm (1.43 Å)
sp–sp	137 pm (1.37 Å)

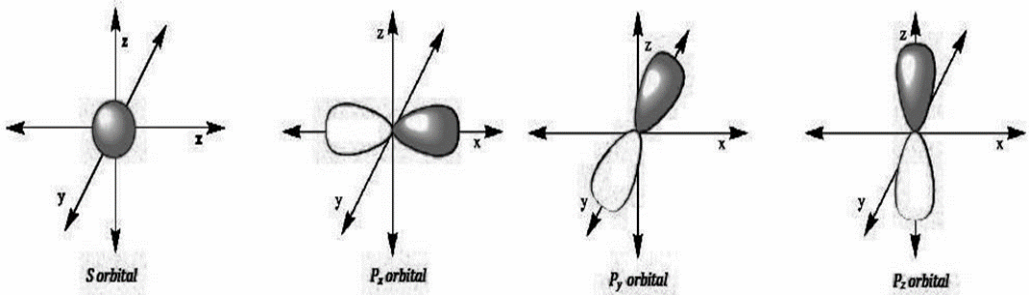
Effect of hybridization on length of single bonds: C–H and C–C bonds shorten slightly with increased s character on carbon.

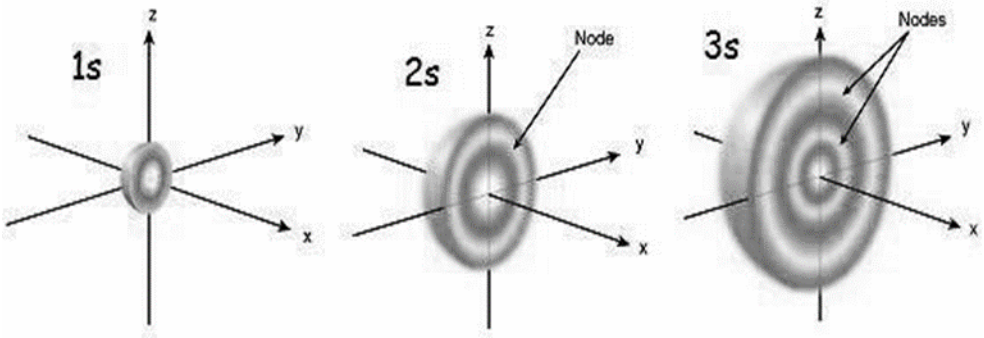
Bond Lengths (Å)					
sp^3	C—H	1.09	sp^3–sp^3	C—C	1.54
sp^2	C—H	1.086	sp^3–sp^2	C—C	1.50
sp	C—H	1.06	sp^3–sp	C—C	1.47

The six types of carbon-carbon σ-bonds

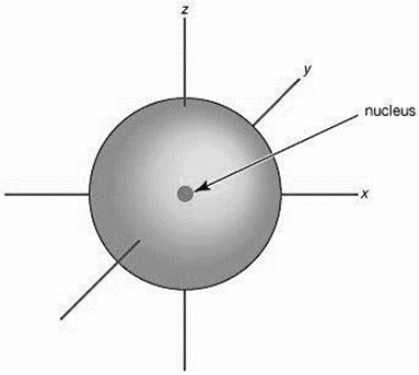


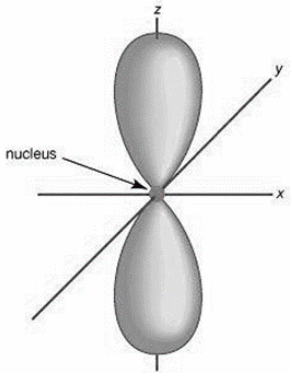
- **Orbital Shapes :**





Cross-section of S-orbitals :





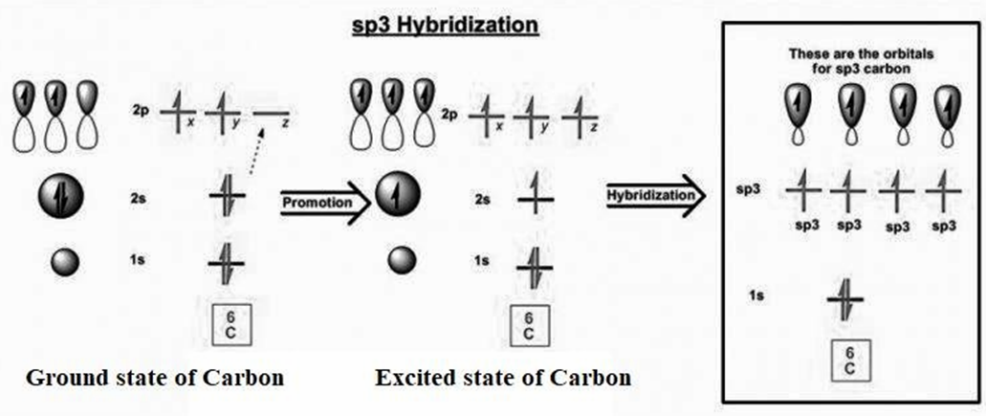
Cross-section of P-orbitals

- **sp^3 Hybridization :**

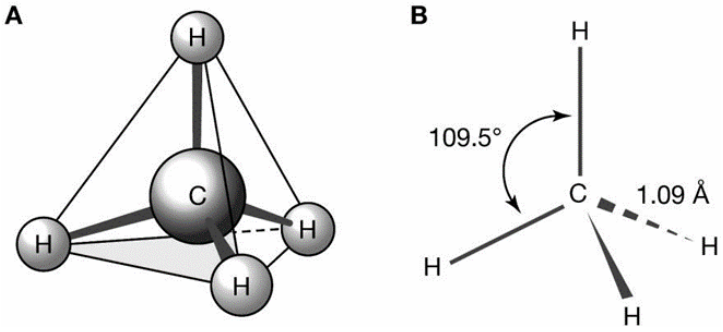
  The process of formation of 4 equivalent orbitals from hybridization or mixing up of one "**S**" and three "**P**" orbitals is known as sp^3 hybridization. sp^3 hybrid orbitals and properties of sigma bonds.

Characteristics :

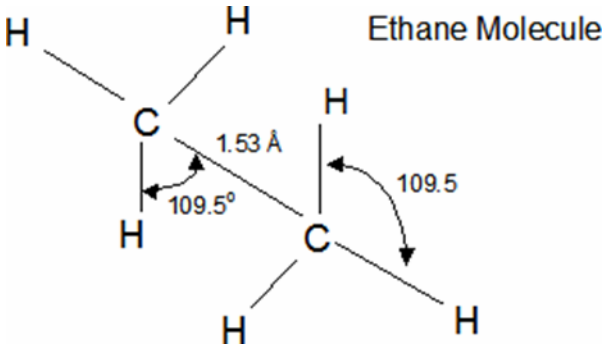
- sp^3 has 25% s and 75% p character
- The 4 sp^3 hybrids point towards the corners of a tetrahedron at 109.5^0 to each other
- Each sp^3 hybrid is involved in a s bond.



- **Bond Angle and Bond Length of Methane :**

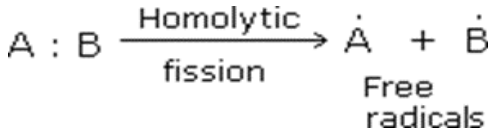


- **Bond Angle and Bond Length of Ethane :**



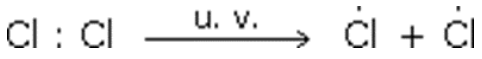
Free Radical :

A free radical may be defined as an atom or group of atoms having an unpaired electron. Free radicals are produced during the homolytic fission of a covalent bond.

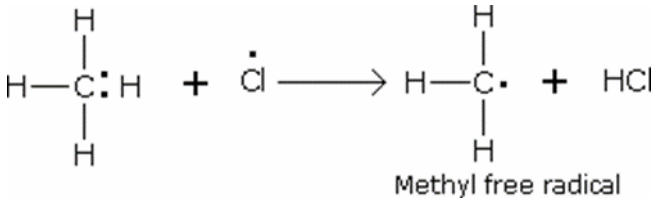


Free radicals are very reactive as they have a strong tendency to pair up their unpaired electron with another electron from wherever available. These pairs are very short lived and occur only as reaction intermediates during reactions.

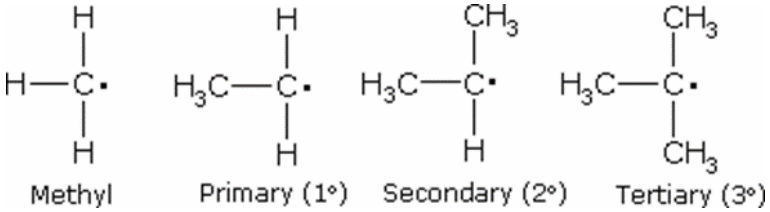
For example, dissociation of chlorine gas in the presence of ultra-violet light produces chlorine free radicals:



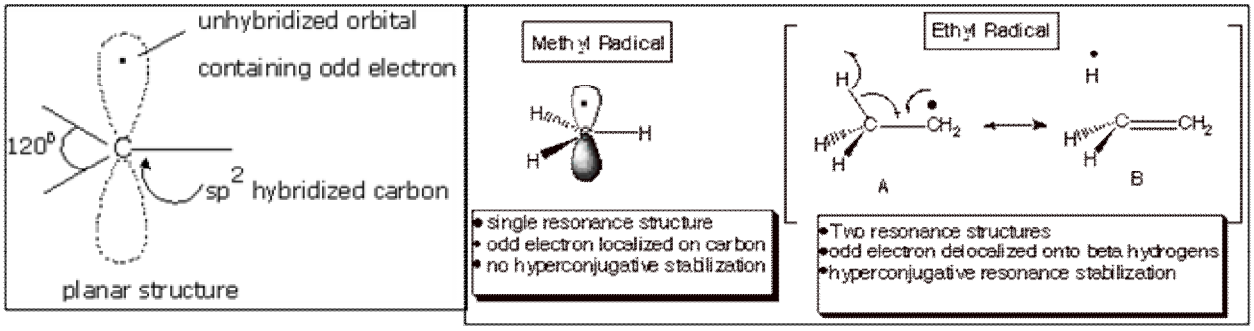
The alkyl free radical may be obtained when free radical chlorine attacks methane



Free radicals may be classified as primary, secondary or tertiary depending upon whether one, two or three carbon atoms are attached to the carbon atom carrying the odd electron:



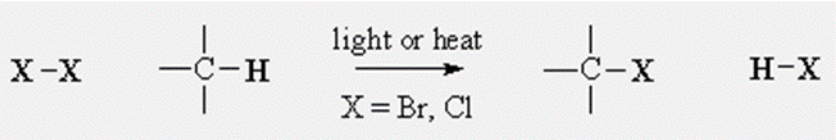
Structure of alkyl free radical*:* The carbon atom in alkyl free radicals involves sp^2 hybridization. Therefore, it has a planar structure. Three hybrid orbitals are used in the formation of three s-bonds with three H atoms or alkyl groups. The unpaired electron is present in unhybridized p orbital



Halogenation of Alkanes :

- The reaction of a halogen with an alkane in the presence of ultraviolet (UV) light or heat leads to the formation of a haloalkane (alkyl halide). An example is the chlorination of methane.

- Radical Halogenation of Alkanes (Reaction type: Free Radical Substitution)



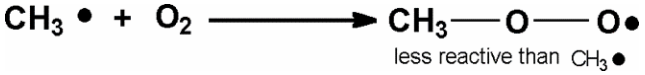
Summary:

- When treated with Br_2 or Cl_2, radical substitution of R-H generates the alkyl halide and HX.
- Alkane R-H relative reactivity order: tertiary > secondary > primary > methyl
- Halogen reactivity $F_2 > Cl_2 > Br_2 > I_2$
- Only chlorination and bromination are useful in the laboratory.
- Bromination is selective for the R-H that gives the most stable radical.
- Chlorination is less selective

Mechanism Of Halogenation	*Radical chain mechanism for reaction of methane with Cl_2*
Initiation Step $X_2 \xrightarrow{uv} X\bullet + X\bullet$ **Propagation Steps** $RH + X\bullet \longrightarrow R\bullet + HX$ $R\bullet + X_2 \longrightarrow RX + X\bullet$ **Termination Steps** $X\bullet + X\bullet \longrightarrow X_2$ $X\bullet + R\bullet \longrightarrow RX$ $R\bullet + R\bullet \longrightarrow R\text{-}R$	• **Chain - initiating steps:** steps in which the chain reaction starts $Cl—Cl \xrightarrow{energy} 2\ Cl\bullet$ • **Chain propagating steps:** steps which keep to the reaction going $Cl\bullet + CH_4 \longrightarrow CH_3\bullet + HCl$ $CH_3\bullet + Cl_2 \longrightarrow CH_3Cl + Cl\bullet$ • **Chain - terminating:** steps which might occur which causes the chain reaction to stop $Cl\bullet + Cl\bullet \longrightarrow Cl_2$ $CH_3\bullet + CH_3 \longrightarrow C_2H_6$ $CH_3\bullet + Cl\bullet \longrightarrow CH_3C$

Inhibitors :

- Inhibitor - a substance which slows down or stops a reaction even though the inhibitor is present in small amounts.
- Inhibition period - time during which the inhibitor lasts.
- Example: If oxygen is present during halogenation, the oxygen slows down the reaction.



- This breaks the cycle (propagating steps) and slows down the reaction.
- When the oxygen molecules are all reacted (inhibition period), the reaction then speeds up.

- **Factors That Affect Free Radical Stability :**

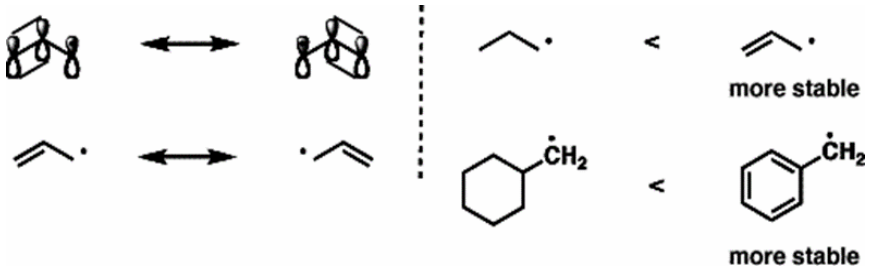
1. Free radicals are electron-deficient species. [Helpful to know: the factors which affect the stability of free radicals are the same which influence the stability of carbocations.] They can be stabilized through donation of electron density by neighbours; for this reason, radical stability increases in the order methyl < primary < secondary < tertiary. [Radicals are also stabilized by adjacent atoms with lone pairs, such as oxygen and nitrogen].

Radical stability increases in the order methyl < primary < secondary < tertiary

Methyl radical **Primary radical** **Secondary radical** **Tertiary radical**

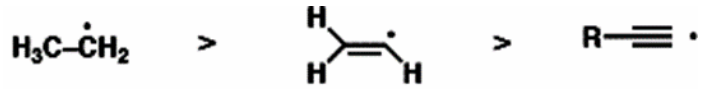
Least stable **Most stable**

A second important factor which stabilizes free radicals is "delocalization" – that is, if the radical can be spread out over two or more carbons. A more familiar way of saying this is that free radicals are stabilized by resonance.



Free radicals decrease in stability as the % of *s-character* in the orbital increases [i.e. as the half-empty orbital becomes closer to the nucleus].

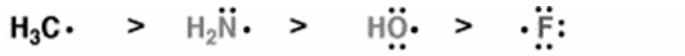
For that reason, free radical stability decreases as the atom goes from $sp^3 > sp^2 > sp$.



most stable ***least stable***

sp^3 **sp^2** **sp**

Across a row of the periodic table, free radicals decrease in stability as the electronegativity increases



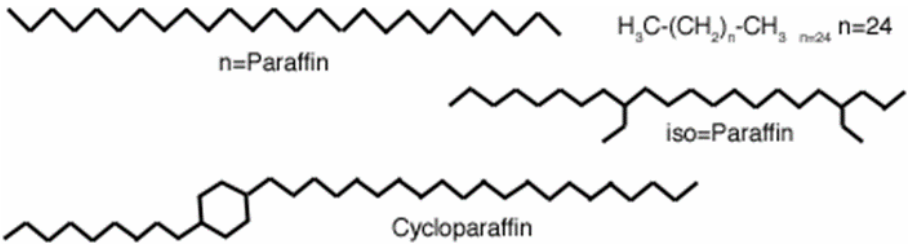
most stable *least stable*

Free radicals increase in stability going down a column of the periodic table, F• < Cl• < Br• < I• since the electron- deficient orbital is spread out over a greater volume.

Paraffin :

- Paraffin"s, more commonly referred to as alkanes, are the chemical family of saturated hydrocarbons.

- The general formula C_nH_{2n+2}, C being a carbon atom, H a hydrogen atom, and „n" an integer.
- The paraffin"s are major constituents of natural gas and petroleum.
- Paraffin"s containing fewer than 5 carbon atoms per molecule are usually gaseous at room temperature, those having 5 to 15 carbon atoms are usually liquids, and the straight-chain paraffins having more than 15 carbon atoms per molecule are solids.
- Branched-chain paraffin"s have a much higher octane number rating than straight-chain paraffin"s and, therefore, are the more desirable constituents of gasoline.
- The hydrocarbons are immiscible with water. All paraffin"s are colourless.
- Paraffin is a strong-smelling liquid which is used as a fuel in heaters, lamps, and engines.



Paraffin wax :

It is also known as American English paraffin, is a white wax obtained from petrol or coal. It is used to make candles and in beauty treatments.

The term "wax" simply refers to saturated hydrocarbons that contain more than 16 carbon atoms in the paraffin series (C_{16}-C_{40}) and are in solid state at room temperature. Chemically, natural waxes are defined as long chain esters, monohydric (one hydroxyl group), or alcohols with long chain fatty acids. The majority of the waxes present in crude oil are considered synthetic paraffin waxes with non-oxidized saturated alkanes.

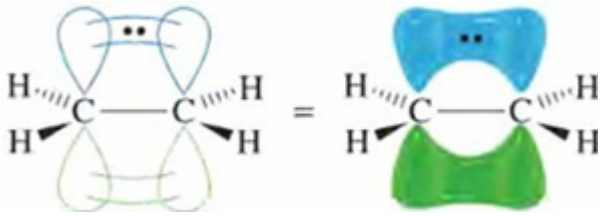
Uses of Paraffin :

- Medicinal liquid paraffin, also known as *paraffinum liquidum*, is a very highly refined mineral oil used in cosmetics and for medical purposes.
- Liquid paraffin has many uses in the medical field. Because liquid paraffin passes through the body's intestinal tract without being absorbed, it can be used as a laxative to limit the amount of water removed from the stool and ease constipation.
- Liquid paraffin is considered to have a limited usefulness as an occasional laxative.
- Liquid paraffin will reveal that this common personal care ingredient is used in many skin products, including creams, lotions, lip balm, soap, and even eczema ointments.
- In burns treatment that involved covering the affected area with a combination of waxes and oils including paraffin wax; this petroleum-derived substance created a barrier for the skin to heal and was seen as a very effective treatment.
- Paraffin wax were developed, the most popular of which was giving hot wax baths to patients suffering from a variety of ailments, in particular rheumatism and joint pain. The wax would be used to soften the skin and the intense heat would soothe the muscles and ready them for massage treatment.

- White soft paraffin with liquid paraffin is used as a barrier cream by providing a layer of oil on the surface of the skin to prevent water evaporating from the skin surface. It is an emollient, sometimes known as skin lubricant. It is used to soothe, smooth and hydrate the skin.

Introduction Alkenes :

Hydrocarbons that contain carbon-carbon double bond are called Alkenes (also called Olefins). Many alkenes are found in plant and animals. It has three sp^2 orbitals that lie in a plane with angles of 120°. One of the carbon–carbon bonds in a double bond is σ-bond, formed by the overlap of a sp^2 orbital of one carbon with a sp^2 orbital of the other carbon. The second carbon–carbon bond in the double bond is formed from side-to-side overlap of the remaining *p*-orbitals of the carbons. These two *p*-orbitals must be parallel to each other to achieve maximum orbital-orbital overlap. Therefore, all six atoms of the double- bond system are in the same plane. Since there is maximum side-to-side overlap, rotation about a double bond does not occur.



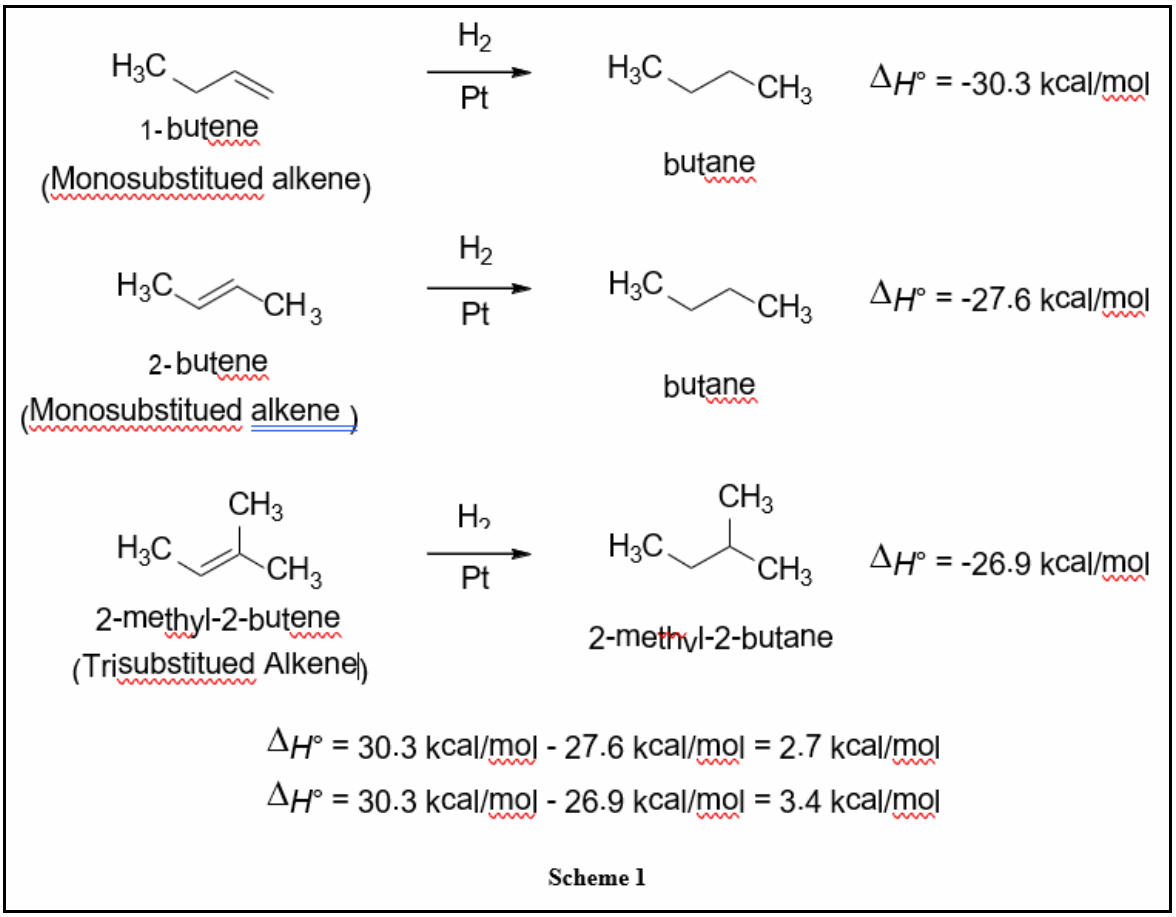
Each C-H σ-bond is formed by the overlap of a sp^2 hybrid orbital of a carbon atom with the 1*s* orbital of a hydrogen atom. The C-H bond length in ethylene is slightly shorter than the C-H bond in ethane because the sp^2 orbital in ethylene has more *s* character that attracts the electrons even more strongly. The C=C bond in ethylene is much shorter than the C-C bond in ethane, partly because the σ-bond of ethylene is formed from sp^2 orbitals and partly because both σ- and π-bonds are attracting the atoms together (Figure 2).

Alkenes are said to be unsaturated because they are capable of adding hydrogen in the presence of a catalyst. An alkane is called saturated because it cannot react with any more hydrogen.

Stability of Alkenes :

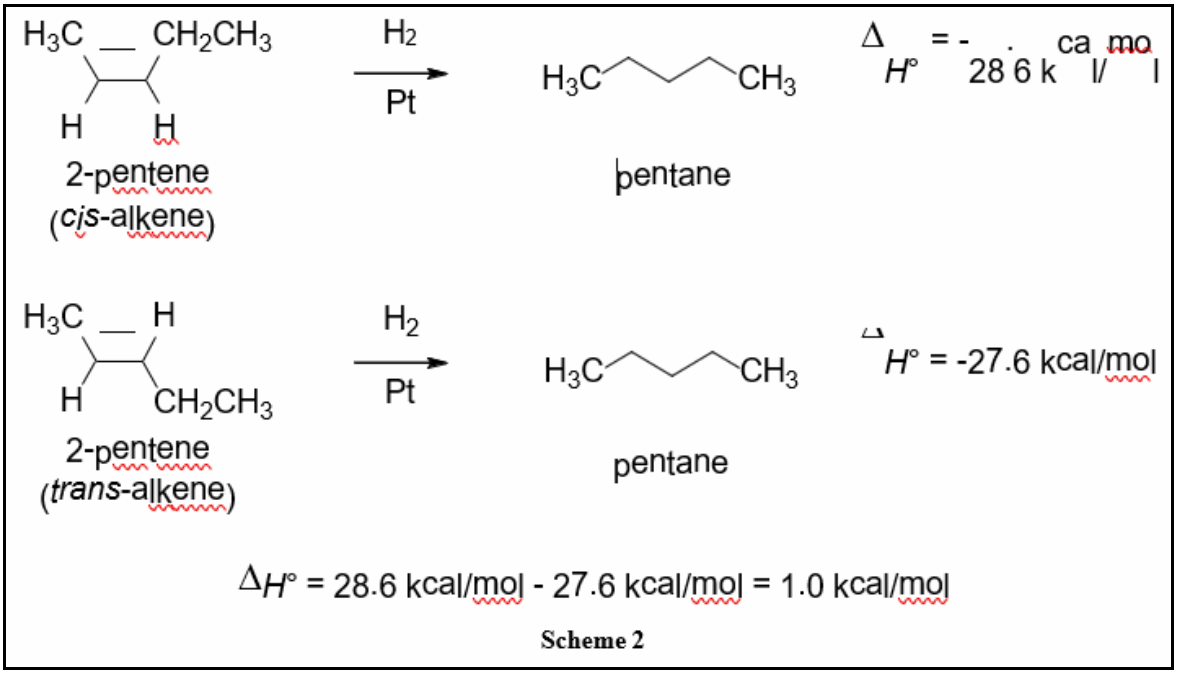
The stability of an alkene depends on its structure. The heat released in a hydrogenation reaction is called the **heat of hydrogenation**. When an alkene is treated with hydrogen in the presence of a platinum catalyst, hydrogen adds to the double bond, reducing the alkene to an alkane. Hydrogenation is exothermic, evolving about 20 to 30 kcal of heat per mole of hydrogen consumed.

The difference in the stabilities of alkenes is the difference in their heats of hydrogenation. While considering the hydrogenation of 1-butene (a monosubstituted alkene), 2-butene (a disubstituted alkene) and 2-methyl-2-butene (a trisubstituted alkene), 2-methyl-2-butene is more stable by 3.4 kcal/mol and 2-butene is stable by 2.7 kcal/mol (Scheme 1). More substituted double bonds are usually more stable. In other words, the alkyl groups attached to the double bonded carbons stabilize the alkene.



Scheme 1

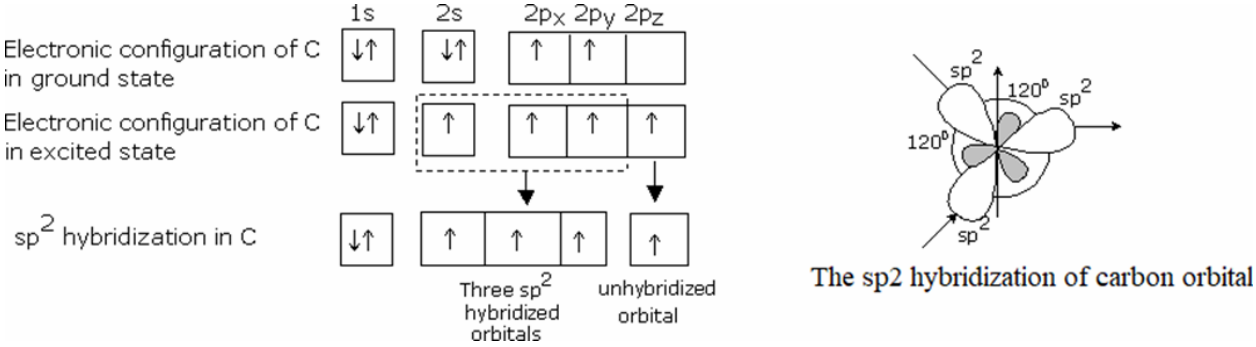
The heats of hydrogenation show that *trans*-isomers are generally more stable than the corresponding *cis*-isomers. Because the alkyl substituents are separated farther in *trans*- isomers than they are in *cis*-isomers. The greater stability of the *trans*-isomer is evident in the following example, which shows that the *trans*-isomer is stable by 1.0 kcal/mol (Scheme 2).



Scheme 2

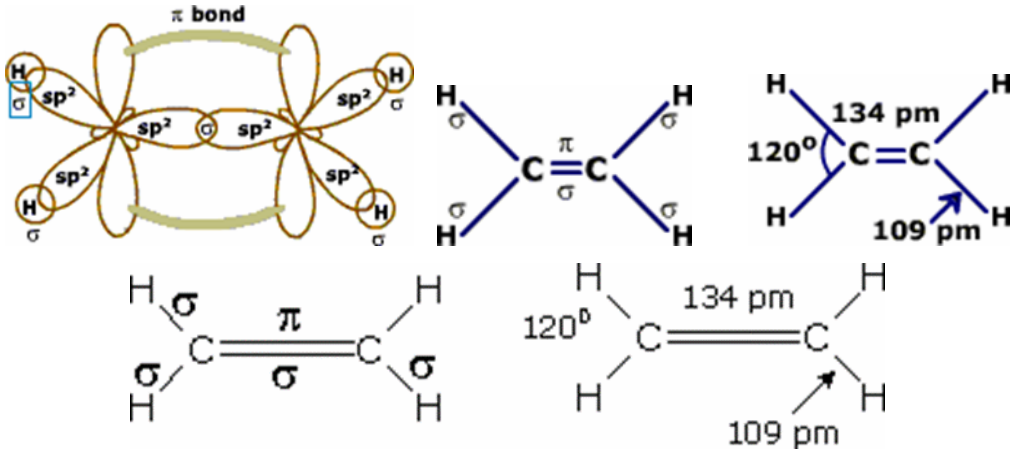
SP^2 hybridization in alkenes : In alkenes, two carbon atoms are bonded through a double bond in the parent chain. The formation of a double bond in alkenes is illustrated below by taking the simplest alkene, ethene, as a typical example.

Ethene can be described by the molecular formula **C2H4**. Each carbon atom in this molecule has three points of attachment and therefore, each carbon atom in ethene is **sp^2 hybridized**.



The sp^2 hybridization of carbon orbital : The three sp^2 hybrid orbitals lie in a plane and are inclined to each other at an angle of 120° (see above figure). One of the p orbitals (say 2pz) on each carbon atom is left unhybridized.

The three sp^2 hybrid orbitals form three sigma (s) bonds: two with H-atoms and one with the adjacent carbon atom. This results in a planar structure. The two partially filled unhybridized p orbitals of the two carbon atoms overlap side-ways to form a pi bond as shown:



Simplified representation of ethene molecule :

Side-ways overlap of unhybridized pz orbitals of the two carbon atoms leading to the formation of a p bond

Therefore, in ethene, the carbon-carbon double bond (=) is a combination of a sigma (s) and a pi bond (p). The simple structural formula of ethene is written as shown above.

Elimination reaction :

Elimination reaction is a type of organic reaction in which two substituents are removed from a molecule in either a one or two-step mechanism.The one-step mechanism is known as the *E2 reaction*, and the two-step mechanism is known as the *E1 reaction*.

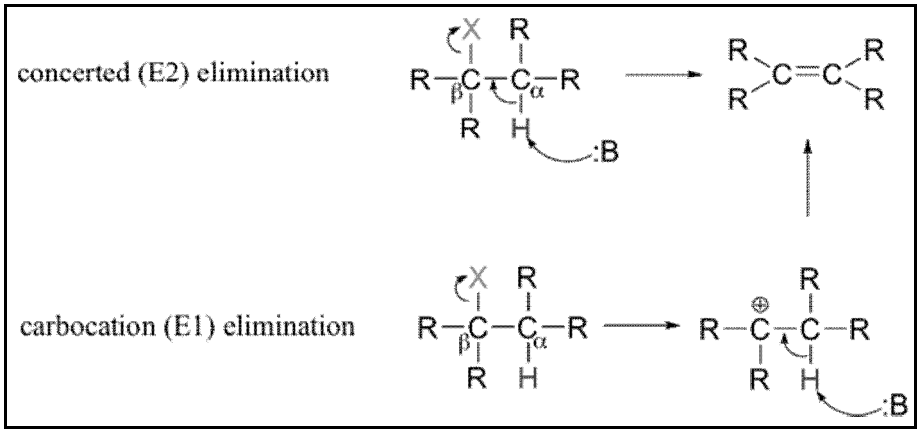
In most organic elimination reactions, at least one hydrogen is lost to form the double bond: the unsaturation of the molecule increases. It is also possible that a molecule undergoes reductive elimination, by which the valence of an atom in the molecule decreases by two, though this is more common in inorganic chemistry.

There are three fundamental events in these elimination reactions:

(i) removal of a proton

(ii) formation of the CC π bond

(iii) breaking of the bond to the leaving group



Characteristics of E1 reaction

1. Unimolecular reaction
2. Two step reaction
3. Carbocation intermediate formed.
4. Reactivity order of RX is 3°>2°>1°
5. No stereospecific.
6. Follow Zaitsev's rule.
7. Polar protic solvent is good because it stabilizes the ionic intermediate.
8. Rate of reaction increases when concentration of substrate increases.
9. Rearrangement may take place.

Characteristics of E2 reaction :

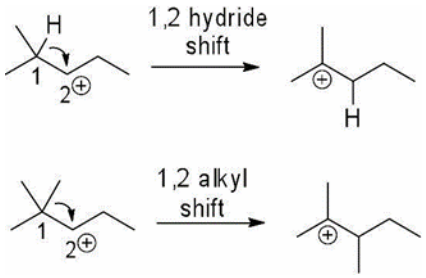
1. Bimolecular reaction.
2. Single step reaction.
3. Hydrogen removes beta carbon.
4. Trans elimination because of low energy consumption.
5. Anti periplanar attack.
6. Polar aprotic solvent best.

7. Phenyl group influences elimination because product alkene is further stabilised by resonance.

8. Reactivity order 3°>2°>1°. No steric effect.

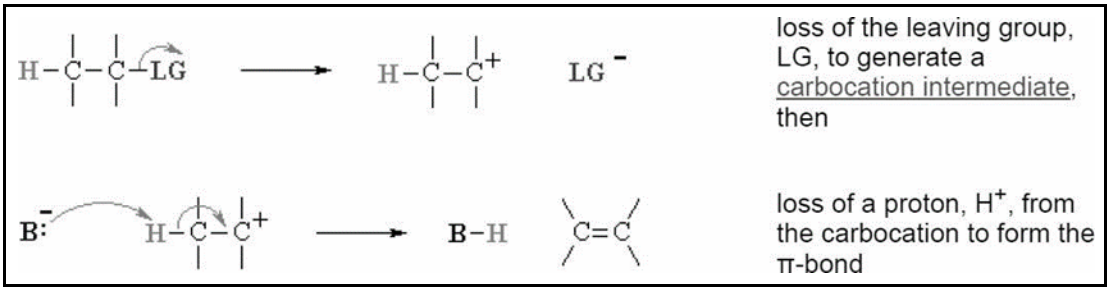
9. Strong nucleophile influence elimination.

10. No intermediate form.



E1 mechanism :

- E1 inicates a elimination, unimolecular reaction, where rate = k [R-LG]. (R-LG = Substrate)



· Reaction influence the reaction pathway:

- E1 mechanistic pathway is most common with:

Good leaving groups

Stable carbocations

Weak bases.

E1 Reactions is Non-stereospecific- follows Zaitsev (Saytseff) Rule

Does NOT occur with primary alkyl halides (leaving groups)

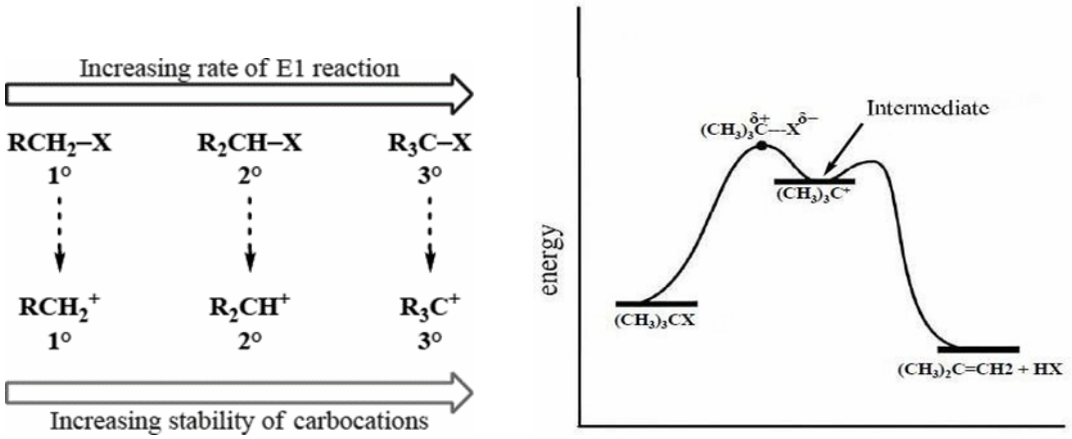
(i) Effect of R-

Reactivity order : $(CH_3)_3C$- > $(CH_3)_2CH$- > CH_3CH_2- > CH_3-

In an E1 reaction, the rate determining step is the loss of the leaving group to form the intermediate carbocation.

The more stable the carbocation is, the easier it is to form, and the faster the E1 reaction.

The rate of an E1 reaction increases as the number of R groups on the carbon with the leaving group increases.



Energy Profile for an E1 Reaction

(i) Leaving Group (LG) : The only event in the rate determining step of the E1 is breaking the C-LG bond. Therefore, there is a very strong dependence on the nature of the leaving group, the better the leaving group, the faster the E1 reaction will be.

In the acid catalysed reactions of alcohols, the -OH is protonated first to give an oxonium ion, providing the much better leaving group, a water molecule.

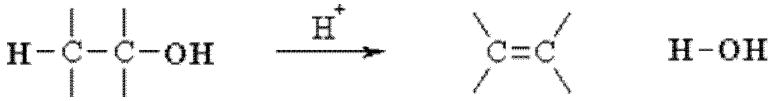
(ii) Base (B) : Since the base is not involved in the rate determining step, the nature of the base is unimportant in an E1 reaction.

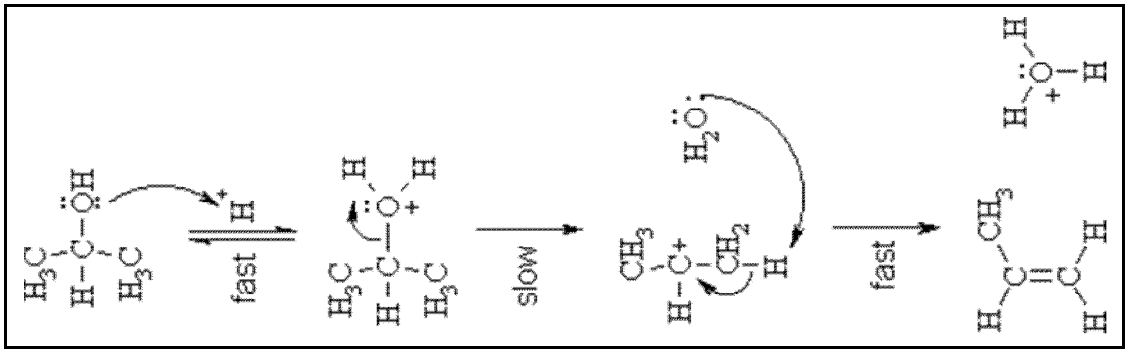
- Favored by weaker bases such as H2O and ROH.

(iii) Type of Solvent :

- Favored by polar protic solvents, which can stabilize the ionic intermediates.

· E1 Mechanism for Alcohols





Step 1 : An acid/base reaction. Protonation of the alcoholic oxygen to make a better leaving group. This step is very fast and reversible. The lone pairs on the oxygen make it a Lewis base.

Step 2 : Cleavage of the C-O bond allows the loss of the good leaving group, a neutral water molecule, to give a carbocation intermediate. This is the rate determining step (bond breaking is endothermic)

Step 3 : An acid/base reaction. Deprotonation by a base (a water molecule) from a C atom adjacent to the carbocation center leads to the creation of the C=C

E2 mechanism :

E2 indicates an elimination, bimolecular reaction, where rate = k [B][R-LG].

This implies that the rate determining step involves an interaction between these two species, the base B, and the organic substrate, R-LG

Removal of the proton, H+, by the base, loss of the leaving group, LG, and formation of the π-bond

Reaction influence the reaction pathway :

- *Kinetics* – Second order
- *Mechanism* – Single step
- Stereospecific (Anti-periplanar geometry preferred, Syn-periplanar geometry possible)0
- Concerted - all bonds form and break at the same time.
- Bimolecular - rate depends on concentration of both base and substrate
- Favoured by strong bases.
- Favored by polar aprotic solvents.
- Better leaving the group leads to faster reaction rates.
- *Identity of R group* – More substituted halides react faster Rate: R3CX > R2CHX > RCH2X

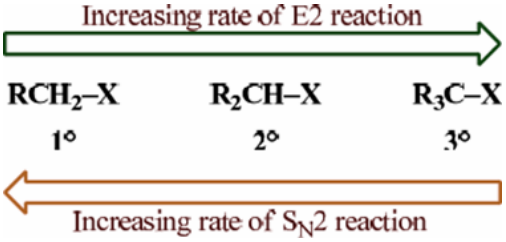
(i) Effects of R :

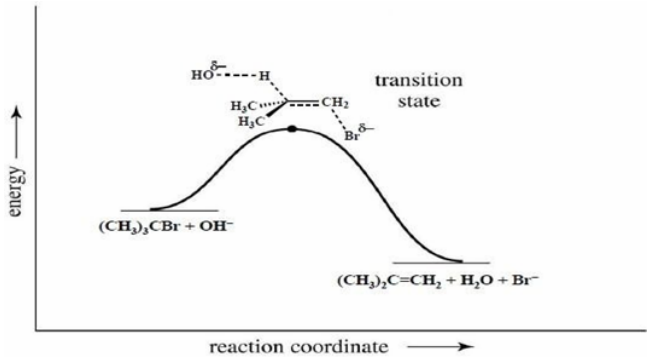
Reactivity order: (CH3)3C- > (CH3)2CH- > CH3CH2- > CH3-

In an E2 reaction, the reaction transforms 2 sp^3 C atoms into sp^2 C atoms. This moves the substituents further apart, decreasing any steric interactions.

So more highly substituted systems undergo E2 eliminations more rapidly. This is the same reactivity trend as seen in E1 reactions.

As the number of R groups on the carbon with the leaving group increases, the rate of the E2 reaction increases.





Energy Profile for an E2 Reaction :

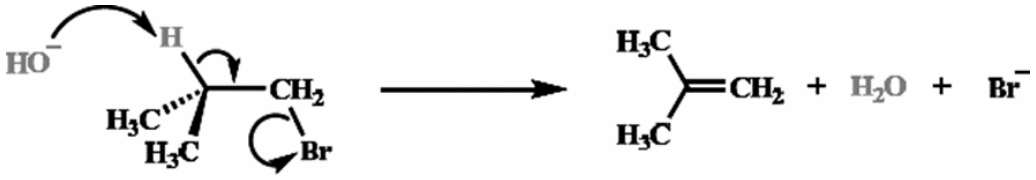
(i) Leaving Group (LG) : The C-LG bond is broken during the rate determining step, so the rate does depend on the nature of the leaving group.

However, if a leaving group is too good, then an E1 reaction may result.

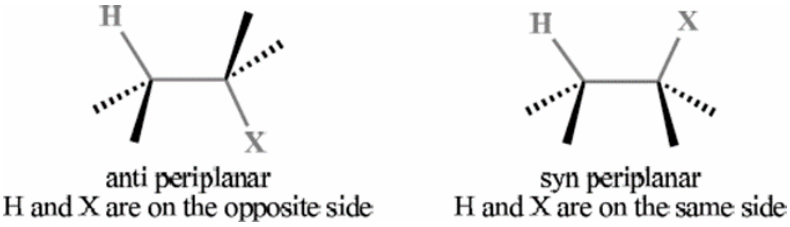
Rate of reaction follows the order Rate of reaction follows the order, R−I > R−Br > R−Cl > R−F

(ii) Base (B) : Stronger bases favor the reaction. Since the base is involved in the rate determining step, the nature of the base is very important in an E2 reaction.

- **E2 Mechanism :**



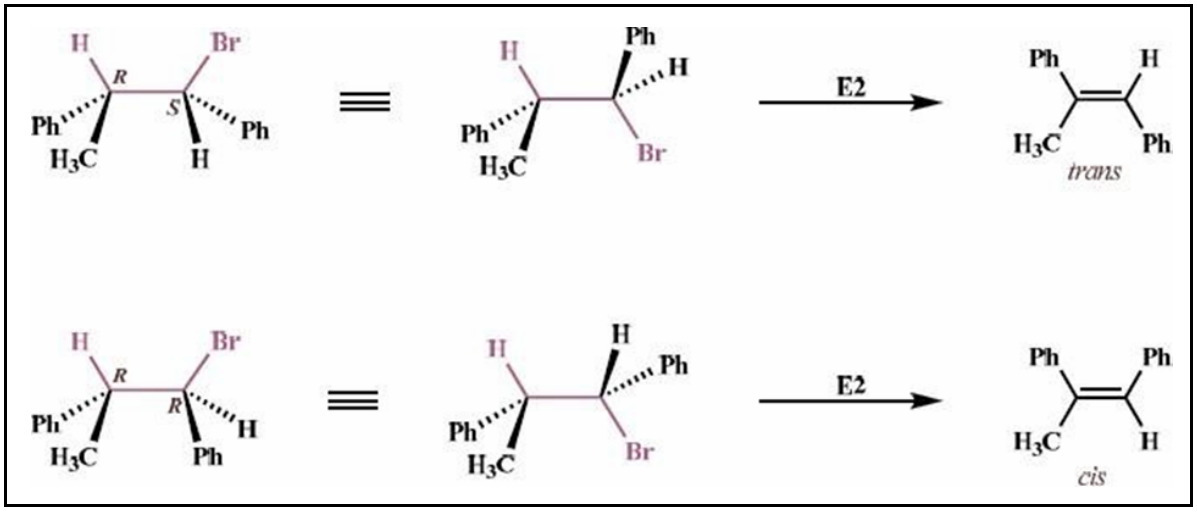
The transition state of an E2 reaction consists of four atoms from the substrate (one hydrogen atom, two carbon atoms, and the leaving group, X) aligned in a plane. There are two ways for the C—H and C—X bonds to be coplanar.



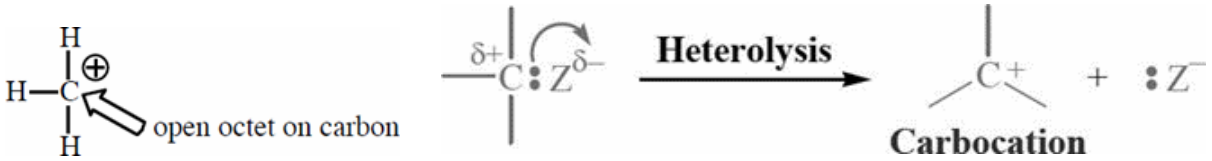
E2 elimination occurs most often in the anti periplanar geometry. This arrangement allows the molecule to react in the lower energy staggered conformation, and allows the incoming base and leaving group to be further away from each other.

The anti periplanar geometry also allows direct interaction between the bonding electrons of the C — H bond and the antibonding orbital of the C —X bond.

Diastereomeric starting compounds yield diastereomeric products after an E2 reaction.



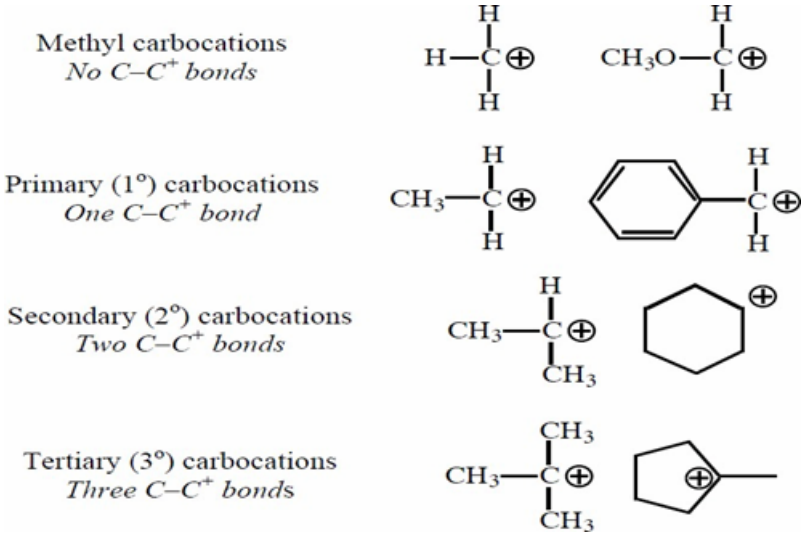
Rearrangement of Carbocations : A carbocation is molecule in which a carbon atom bears three bonds and a positive charge. Carbocations are generally unstable because they do not have eight electrons to satisfy the octet rule. It generate through heterolysis fusion.



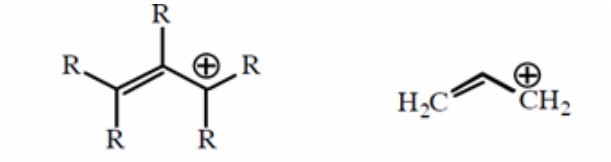
All carbocations were called carbonium ions. Some carbocations may have two or more positive charges, on the same carbon atom or on different atoms; such as the ethylene dication $C2H^{2+}$

The charged carbon atom in a carbocation is a "sextet", i.e. it has only six electrons in its outer valence shell instead of the eight valence electrons that ensure maximum stability (octet rule). Therefore, carbocations are often reactive, seeking to fill the octet of valence electrons as well as regain a neutral charge. One could reasonably assume a carbocation to have sp^3 hybridization with an empty sp^3 orbital giving positive charge. However, the reactivity of a carbocation more closely resembles sp2 hybridization with a trigonal planar molecular geometry. An example is the methyl cation, CH_3^+.

Carbocation Classification : A primary carbocation is one in which there is one carbon group attached to the carbon bearing the positive charge. A secondary carbocation is one in which there are two carbons attached to the carbon bearing the positive charge. Likewise, a tertiary carbocation is one in which there are three carbons attached to the carbon bearing the positive charge.



If the carbon bearing the positive charge is immediately adjacent to a carbon-carbon double bond, the carbocation is termed an allylic carbocation. The simplest case (all R =H) is called the allyl carbocation.



Generic allylic carbocation The allyl carbocation

If the carbon bearing the positive charge is immediately adjacent to a benzene ring, the carbocation is termed a

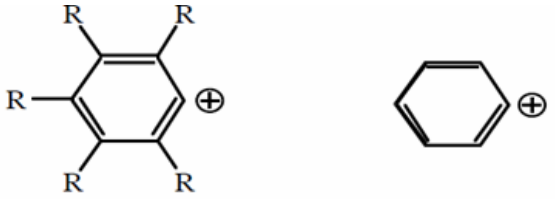
benzylic carbocation. The simplest case is called the benzyl carbocation.

Generic benzylic carbocation The benzyl carbocation

If the carbon bearing the positive charge is part of an alkene, the carbocation is termed a vinylic carbocation. The simplest case is called the vinyl carbocation. Note that the carbon bearing the positive charge has two attachments and thus adopts sp hybridization and linear geometry.

Generic vinylic carbocation The vinyl carbocation

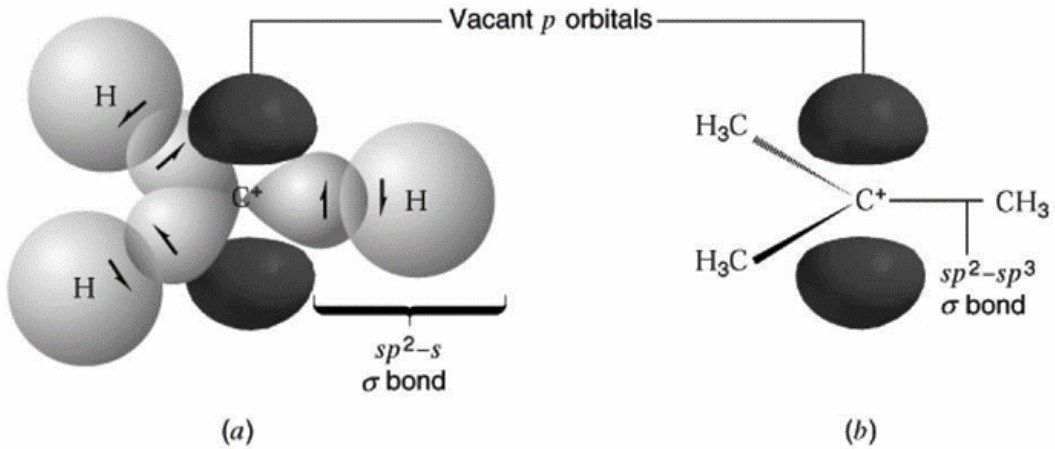
If the carbon bearing the positive charge is part of a benzene ring, the carbocation is termed an aryl carbocation. The simplest case is called the phenyl carbocation.



Generic aryl carbocation The phenyl carbocation

The structure of carbocations :

The structure of carbocations is trigonal planar



(a) A stylized orbital structure of the methyl cation. The bonds are sigma (σ) bonds formed by overlap of the carbon atom's three sp^2 orbitals with 1s orbitals of the hydrogen atoms. The p orbital is vacant.

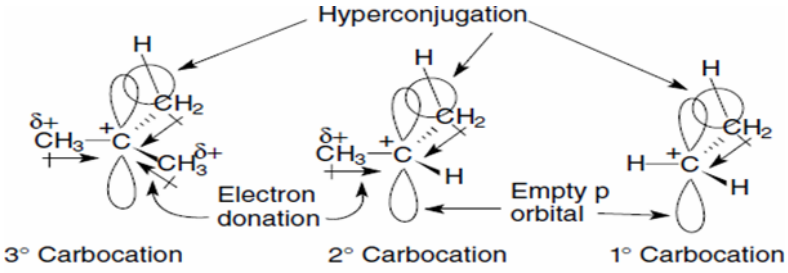
(b) A dashed line-wedge representation of the tert- butyl cation. The bonds between carbon atoms are formed by overlap of sp^3 orbitals of the methyl group with sp^2 orbitals of the central carbon atom.

Factors That Stabilize Carbocations :

Three main structural factors that help to stabilize carbocations.

1. Neighboring carbon atoms.
2. Neighboring carbon-carbon multiple bonds
3. Neighboring atoms with lone pairs.

The order of stability of alkyl-substituted carbocations to be $3^0 > 2^0 > 1^0$. One carbon atom of the carbocation is sp^2 hybridized and contains one unhybridized *p-orbital*. This *p*-orbital contains no electrons. The sp^2 hybridized carbon atom has a formal positive charge.



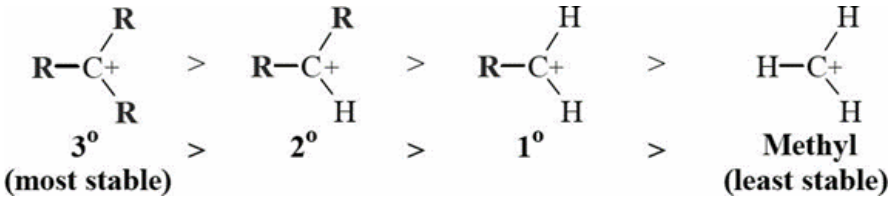
Stabilization of carbocations.

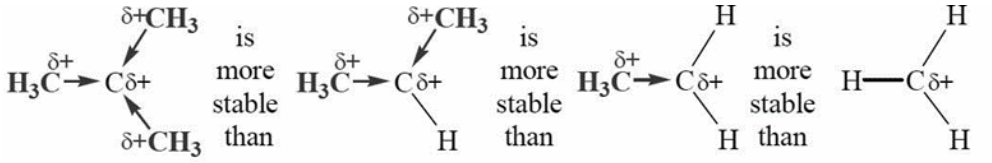
<u>The stability of carbocation through inductive effect</u> :

Ionic species are more stable if the charge can be delocalized (spread out) throughout the molecule. Alkyl groups (such as -CH3) are electron donating. They donate electrons through a single, σ bond. The donation or withdrawal of electrons through a σ bond is called an *inductive effect*.

By donating electrons to the electron-deficient *sp^2 hybridized* carbon atom, the positive charge is delocalized. The full positive charge on the *sp^2 hybridized* carbon atom is decreased somewhat and a small amount of positive charge is transferred to the alkyl groups, increasing the stability of the carbocation species.

The 3^0 carbocation has three methyl groups that donate electrons. The 2^0 carbocation has two methyl groups that donate electrons. The 1^0 carbocation has only one methyl group that donates electrons. The greater the number of electron-donating groups, the greater the stability of the carbocation.





tert-Butyl cation (3°) (most stable) | Isopropyl cation (2°) | Ethyl cation (1°) | Methyl cation (least stable)

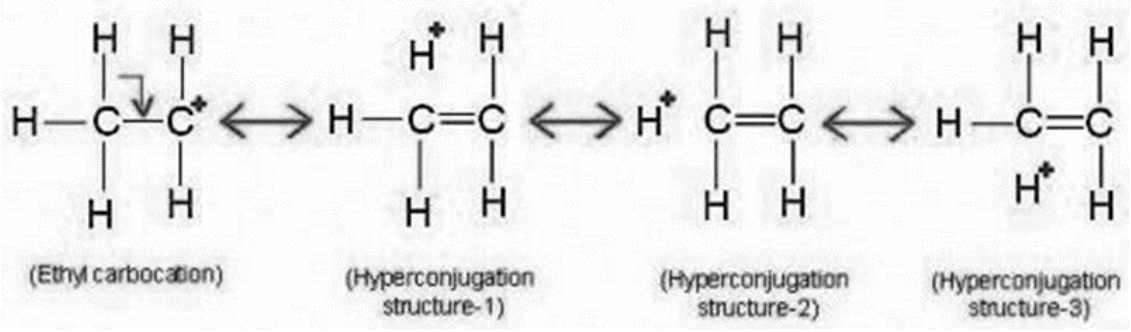
Electron Donating Group:
stabilizes a carbocation

Electron Withdrawing Group:
*de*stabilizes a carbocation

The stability of carbocation through hyperconjugation :

Hyper conjugation is a special type of resonance in which delocalization of electrons takes place through overlap between sigma bond orbital and pi-bond orbital or p- orbitals.

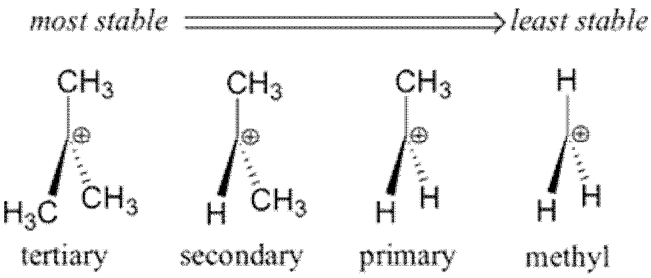
The sp^3-s orbitals containing the bonding electrons in the C-H bond adjacent to the sp^2 hybridized carbon atom can overlap with the unhybridized, empty p-orbital on the sp^2 hybridized carbon atom and share the bonding electrons. Sharing electrons in this manner is called hyperconjugation.

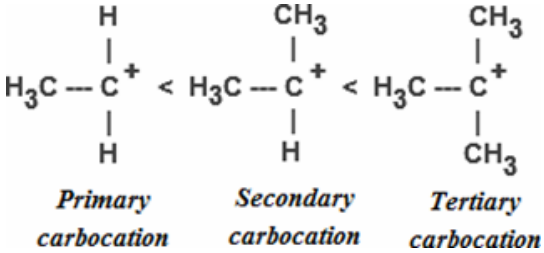


By donating electrons to the electron-deficient sp^2 hybridized carbon atom, the positive charge is delocalized. The full positive charge on the sp^2 hybridized carbon atom is decreased somewhat and a small amount of positive charge is transferred to the alkyl groups, increasing the stability of the carbocation species.

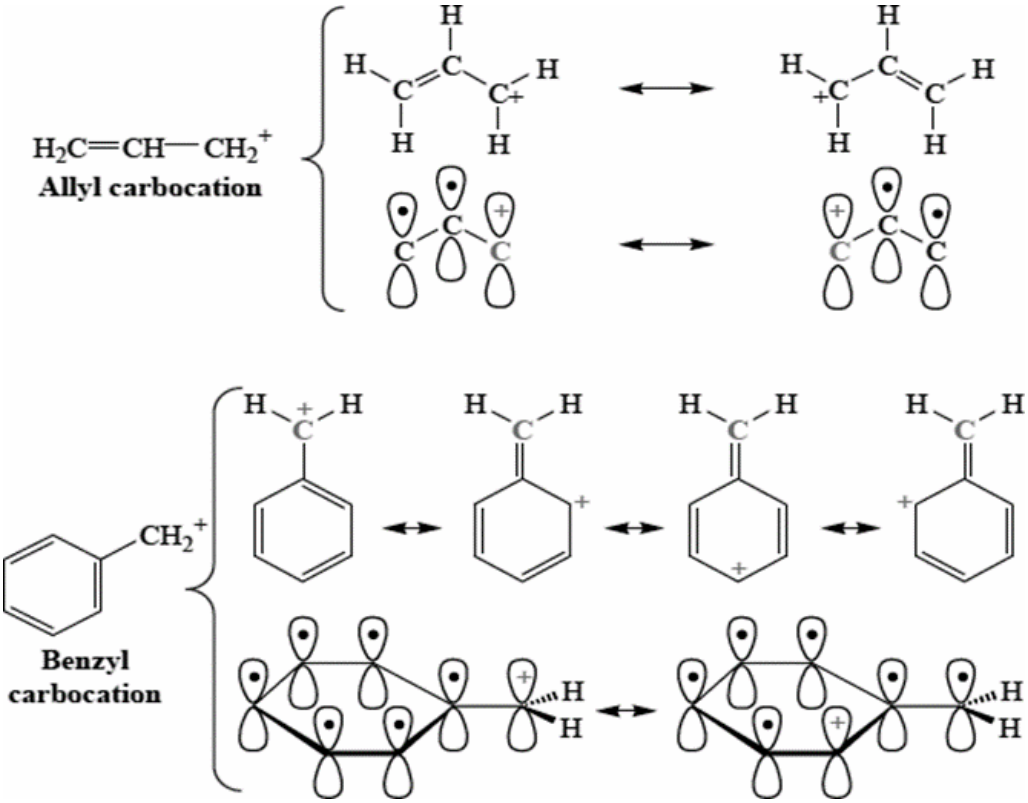
The 3^0 carbocation has nine opportunities (there are nine adjacent C-H bonds) for hyperconjugation; while 1^0 carbocation has only three opportunities (there are three adjacent C-H bonds) for hyperconjugation.

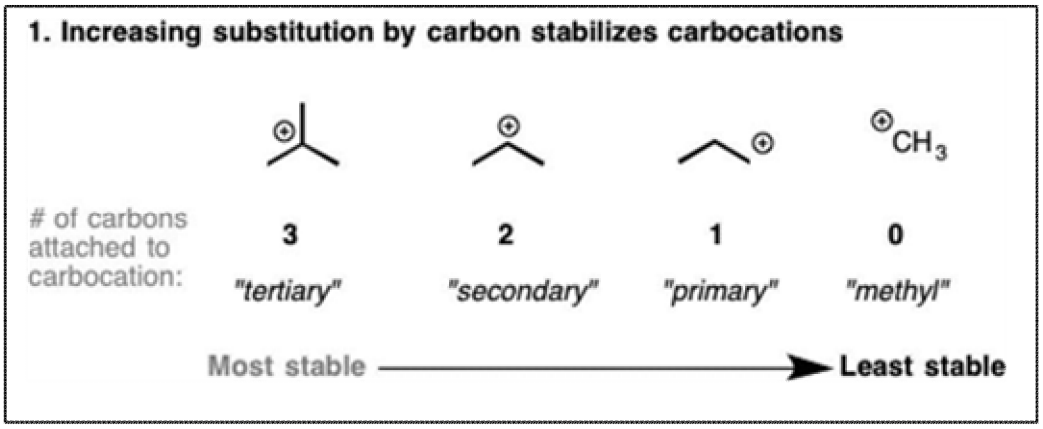
Primary < Secondary < Tertiary carbocation :





The stability of allylic and benzylic carbocations: delocalization :





Carbocation Formation :

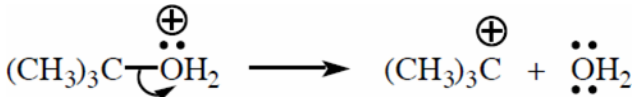
Even though carbocations can be found in many organic reaction mechanisms, most carbocations are formed by one of only two basic mechanism steps: ionization of a carbon - leaving group bond or electrophilic addition to a π bond.

1. **Ionization of a Carbon - Leaving Group Bond :** When a bond between a carbon atom and a leaving group ionizes, the leaving group accepts the pair of electrons that used to be shared in the covalent bond. This may leave the carbon atom with an open octet, resulting in a carbocation.

   The ionization is indicated with a curved arrow starting at the bond and pointing to the leaving group atom that accepts the electron pair.

Better leaving groups or formation of a more stable carbocation result in lower activation energy and faster ionization.

Carbocation formation by ionization of a leaving group occurs in many organic reactions such as the SN1 and E1 mechanisms.

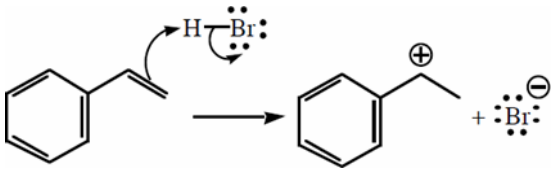


1. **Electrophilic Addition to a π Bond :**

When an electrophile attacks a π bond, the π electron pair may form a new σ bond to the electron-deficient atom of the electrophile. (Not all additions to π bonds involve electrophiles or carbocations.)

The other π bond carbon no longer shares the π electron pair, resulting in a carbocation.

Electrophilic addition to a π bond occurs in many reactions of alkenes, alkynes and benzene rings. Note every addition reaction forms a carbocation, for example, catalytic hydrogenation or ozonolysis.



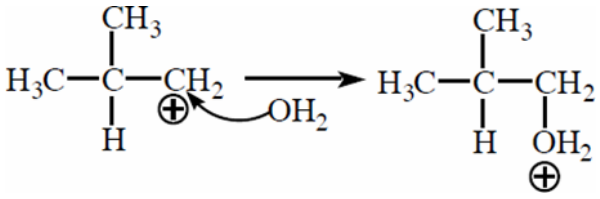
Three Fates of a Carbocation :

Generally, carbocations are unstable due to their open octets and positive charges. Thus, their reactions will be strongly influenced by filling the octet of the carbon bearing the positive charge, or at least making this positive charge more stable.

There are three common mechanism pathways (or fates) by which carbocations may achieve this stability. These fates are (a) capture a nucleophile; (b) loses a proton to form a π bond, and (c) rearrange.

1. **Capture a nucleophile :** The carbocation is electrophilic because it has a positive charge and (in most cases) a carbon atom with an open octet.

The positive charge is neutralized when an electron pair is accepted and a new covalent bond is formed. By definition, a species that donates a pair of electrons to form a new covalent bond is a nucleophile. Because carbocations are very reactive, even weak nucleophiles such as water can be captured with ease.

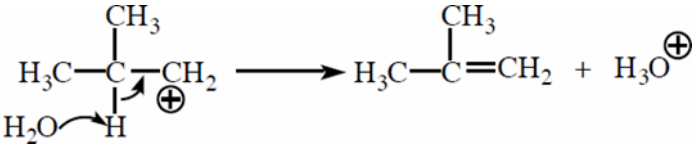


1. **Lose a proton to form a π bond :**

Accepting an electron pair from an adjacent bond to a hydrogen atom neutralizes the positive charge or fills the open octet and forms a new π bond. (The carbocation carbon now has four bonds and a full octet, so its formal charge is zero.)

The hydrogen atom must be removed by a base, but because carbocations are generally very reactive species and very strongly driven to dispose of the positive charge even a weak base such as water or iodide ion can accomplish this deprotonation.

When carbocation deprotonation can lead to more than one product, the more stable product is major.

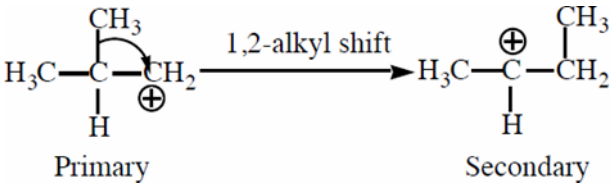


1. **Rearrangement :** The bonding electrons of a carbocation may shift between adjacent atoms to form a more stable carbocation.

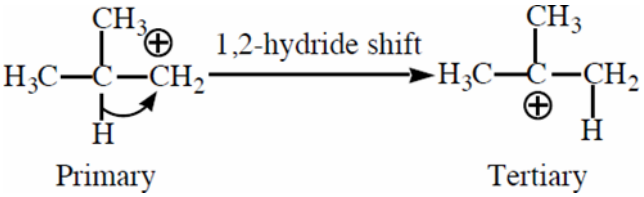
   For example, rearrangement will occur if a secondary carbocation can be formed from a primary carbocation because a secondary carbocation is more stable than the primary carbocation.

   There can be two types of rearrangements.

(i) Shift of an alkyl group is called a 1,2-alkyl shift.



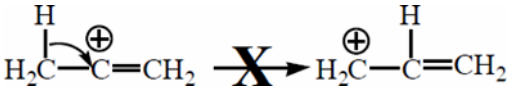
(i) Shift of a hydrogen atom is called a 1,2-hydride shift. Hydride ion = H^-



Of these two examples, hydride shift leads to a tertiary carbocation whereas alkyl shift leads to a secondary carbocation. Because a tertiary carbocation is more stable than a secondary carbocation, the hydride shift is favored in preference to the alkyl shift.

Any C–H or C–C bond adjacent to a carbocation may shift (including C–C bonds that are part of a ring), but only C–C and C–H bonds can migrate during carbocation rearrangement.

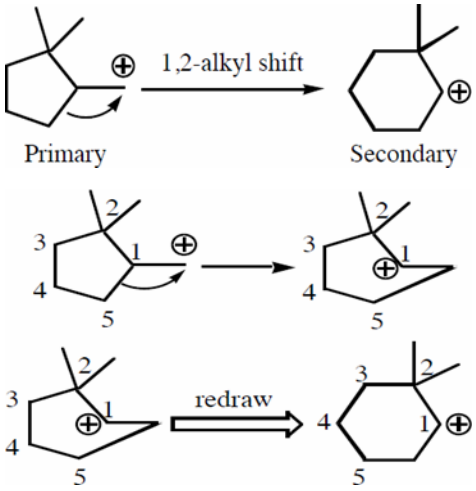
Vinylic carbocations generally do not rearrange, even if they can become more stable. For example, the rearrangement shown below does not occur, even though a secondary carbocation would rearrange to become a more stable allylic carbocation (primary with resonance).



(*This resistance to rearrangement is probably due to orbital alignment restrictions during the rearrangement transition state.*)

Rearrangement Causing a Change in Ring Size :

Rearrangement may lead to a change in ring size. For example



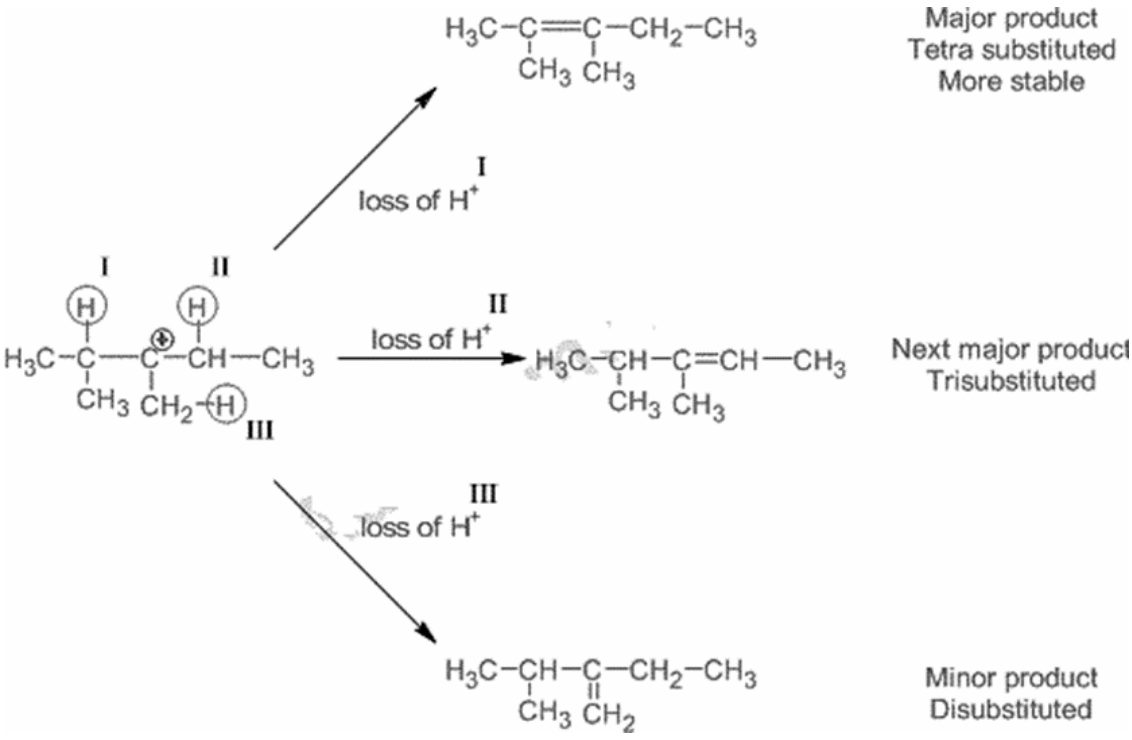
Saytzeff's Rule :

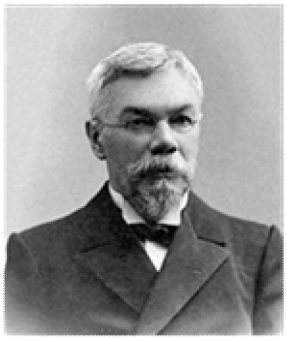
Saytzeff's rule (or Zaitsev's rule, Saytzev rule) is an empirical rule for predicting the favored alkene product(s) in elimination reactions.

This reaction was predicted by Russian chemist *Sir Alexander Zaitsev*.

Saytzeffs rule states that when alternatives exist hydrogen is preferentially eliminated from the carbon atom with fewer number of hydrogen atoms.

Saytzeff Rule implies that base-induced eliminations (E2) will lead predominantly to the olefin in which the double bond is more highly substituted, i.e. that the product distribution will be controlled by thermodynamics.





Sir Aleksander Mikhaylovich Zeitsev, also spelled as Saytzeff and Saytzev (2 July 1841 – 1 September 1910), was a Russian chemist from Kazan. He worked on organic compounds and proposed Zaitsev's rule, which predicts the product composition of an

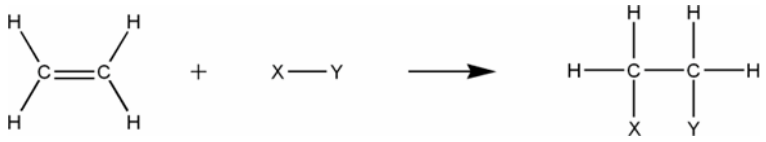
A neutron walks into a restaurant and ordersa couple of sodas. As she is about to leave, she asks the waiter how much she owes. The

Teacher: Describe hydrogen
Student: It is a prostitute element*Teacher:* Who taught you that?

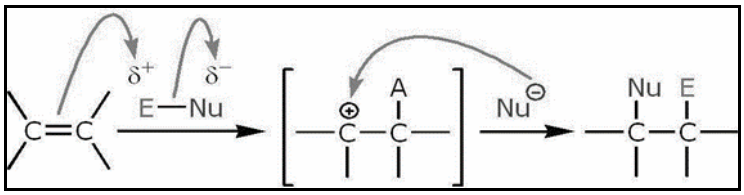
Electrophilic Addition Reactions of Alkenes :

Electrophilic addition reaction is an addition reaction where, in a chemical compound, **a π bond** is broken and **two new σ bonds** are formed.

The substrate of an electrophilic addition reaction must have a double bond or triple bond.

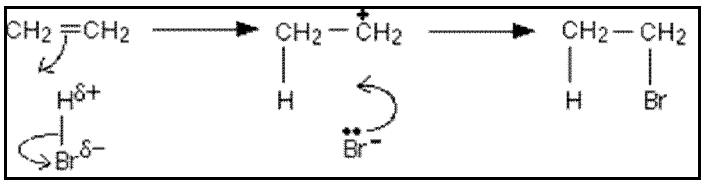


Electrophilic addition to alkenes takes the following general form:

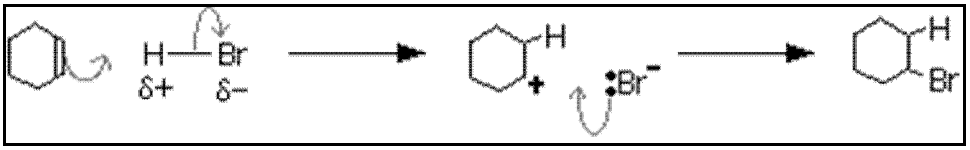


Electrophilic addition reaction between symmetrical alkenes and the hydrogen halides

The reactions of electrophilic addition with ethene and HBr:



The reactions of electrophilic addition with cyclohexene and HBr:



Electrophilic addition reactions involving the other hydrogen halides :

Hydrogen chloride and the other hydrogen halides add on in exactly the same way. For example, hydrogen chloride adds to ethene to make Chloroethane:

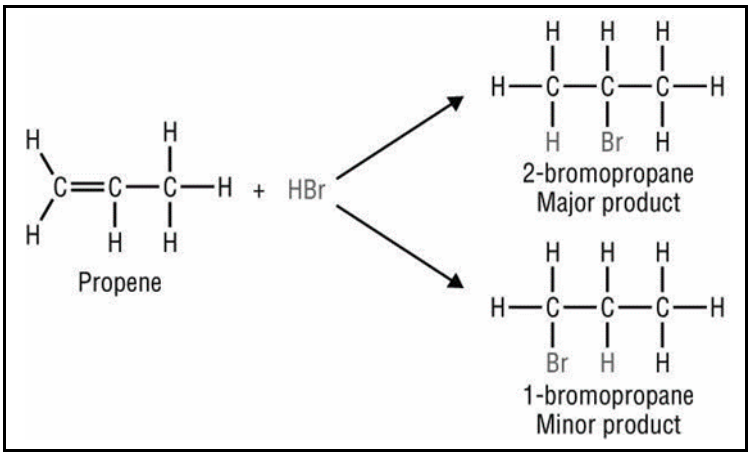
$$CH_2{=}CH_2 + HCl \longrightarrow CH_3CH_2Cl$$

The only difference is in how fast the reactions happen with the different hydrogen halides. The rate of reaction increases as you go from HF to HCl to HBr to HI.

The reason for this is that as the halogen atoms get bigger, the strength of the hydrogen-halogen bond falls. Bond strengths (measured in **kilojoules per mole**) are:

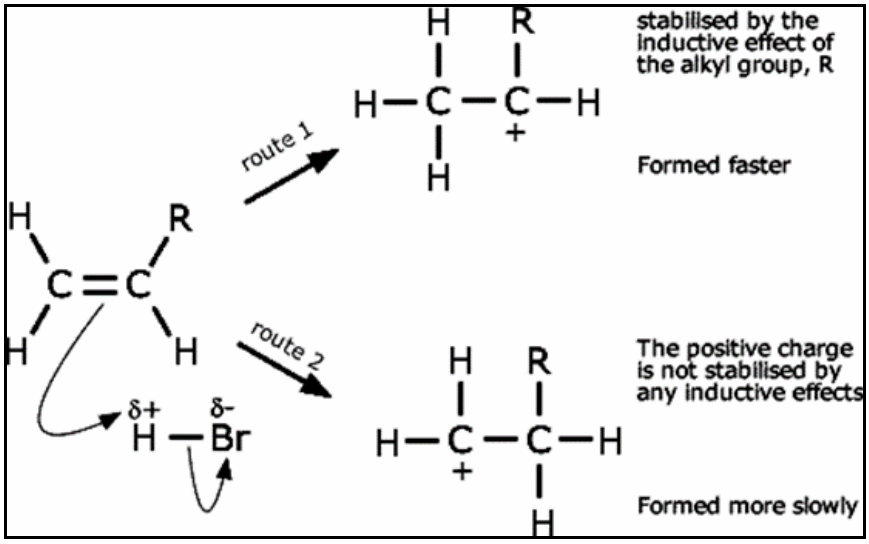
Electrophilic addition reaction between unsymmetrical alkenes and the hydrogen halides :

The reactions of electrophilic addition with Propene and HBr:



Markownikoff's rule :

The rule states that with the addition of a protic acid HX to an asymmetric alkene, the acid hydrogen (H) becomes attached to the carbon with more hydrogen substituents, and the halides (X) group becomes attached to the carbon with more alkyl substituents. Alternatively, the rule can be stated that the hydrogen atom is added to the carbon with the greatest number of hydrogen atoms while the X component is added to the carbon with the least number of hydrogen atoms

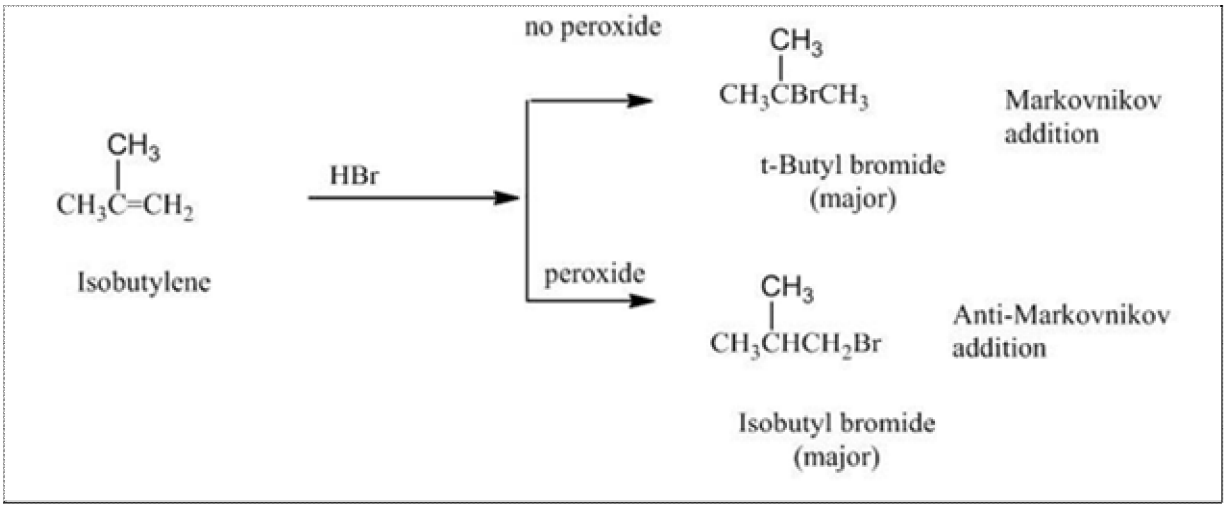


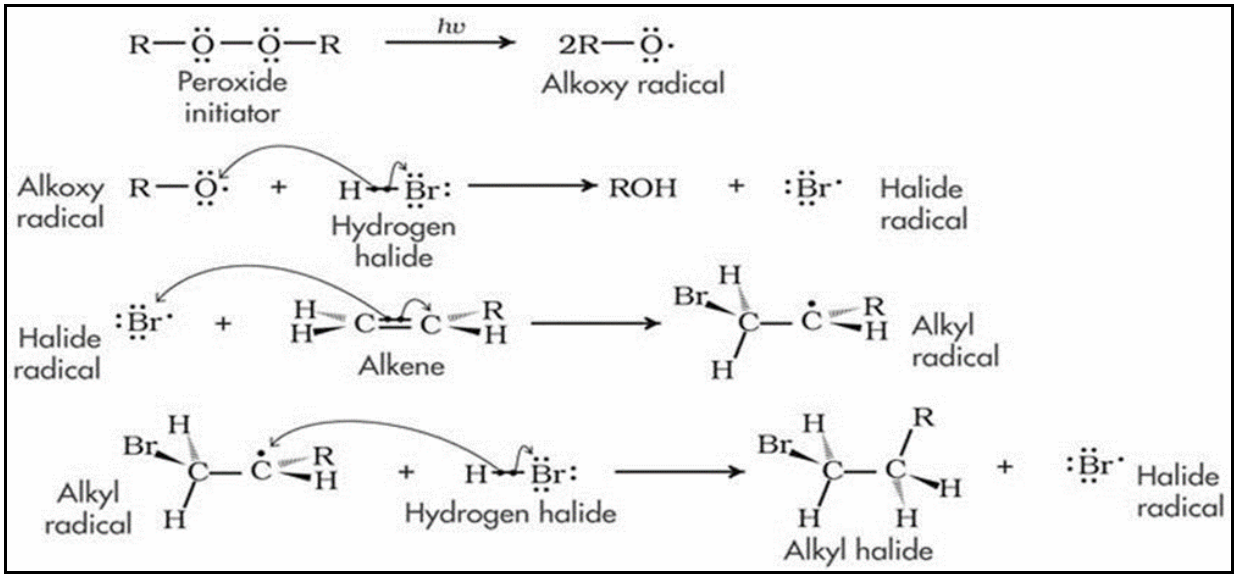
Reason :

- The top one has two alkyl groups (the CH3 and the R group) that can push electrons towards it, stabilizing the positive charge.
- It will form quite easily.
- The bottom carbocation only has one alkyl group to stabilize it so forms less well.
- So, since the first carbocation forms in preference the Hydrogen atom on the H-Br will mostly end up on the left-hand Carbon atom in the alkene - and will only sometimes end up on the middle one.
- And the Br atom is more likely to end up in the middle rather than on the left-hand Carbon atom.
- Alkyl groups pushing electrons is known as the Alkyl Inductive Effect.

Anti- Markownikoff's rule (free radical addition reactions of alkenes)

- In an addition reaction of a generic electrophile HX to an alkene or alkyne, the hydrogen atom of HX becomes bonded to the carbon atom that had the least number of hydrogen atoms in the starting alkene or alkyne.
- In the presence of Peroxide for H-Br, the reaction will always yield the **Anti-Markovnikov product**.
- Anti Markovnikov addition reaction is found to follow a free radical mechanism. The peroxide compound involved helps in the generation of free radicals.
- Generation of free radical through homolytic cleavage of peroxide compound.
- Attack of generated free radical on hydrogen halide to form halide radical through homolysis
- Attack of generated halide radical on alkene molecule to form alkyl radical through homolysis.
- Attack of generated alkyl radical on hydrogen halide to form alkyl halide through homolytic cleavage of hydrogen halide bond





Diene

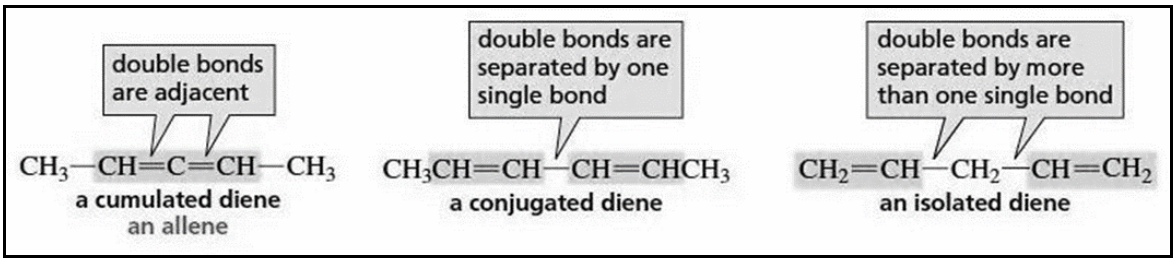
An unsaturated hydrocarbon containing two double bonds between carbon atoms.

Dienes can be divided into three classes, depending on the relative location of the double bonds:

(i) Cumulated dienes have the double bonds sharing a common atom as in a group of compounds called allenes.

(ii) **Conjugated dienes** have conjugated double bonds separated by one single bond.

(iii) **Unconjugated dienes** have the double bonds separated by two or more single bonds. They are usually less stable than isomeric conjugated dienes. This can also be known as an **isolated diene**.

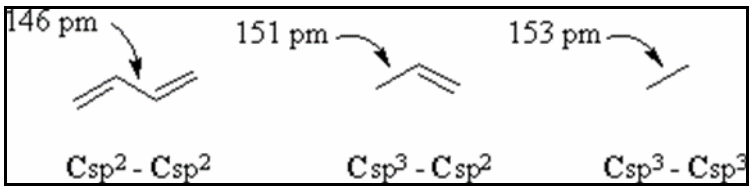


Isolated Dienes :

The bonding in isolated dienes is the same as that in alkenes.

- **Conjugated Dienes :** The C-C single bond between conjugated double bonds is shorter than a typical alkane C-C.

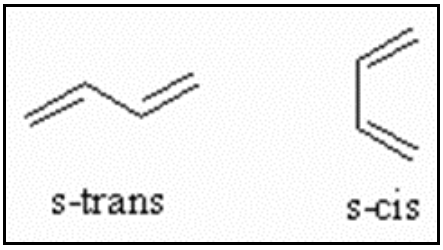
  This is due to the difference is the hybridisation of the **C atoms** involved (check the % **s character**) and the conjugation of the **two π bonds**.



Two conformations of conjugated dienes are important, **s-cis** and **s-trans**, as for 1,3-butadiene.

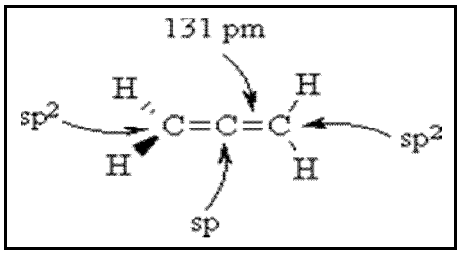
The "**s**" refers to rotation about a σ bond.

Stability of conjugated dienes: The **s-trans** conformation of 1,3-butadiene is about 12 kJ/mol (2.8 kcal/mol) more stable than the **s-cis** due to the unfavourable steric interaction of substituents at **C1** and **C4**

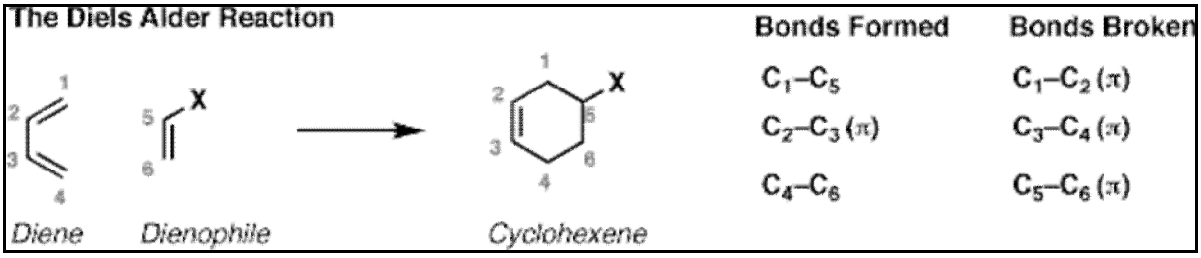


Cumulated Dienes :

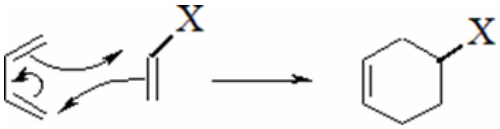
- Like the triple bond unit of an alkyne, the C=C=C unit of allenes are linear.
- The central **sp hybridised C** atom.
- The C=C bonds in allenes are slightly shorter (131 pm) than those in a typical alkene C=C (134 pm)
- Allenes are non-planar. Note the perpendicular nature of the **C-H bonds**.

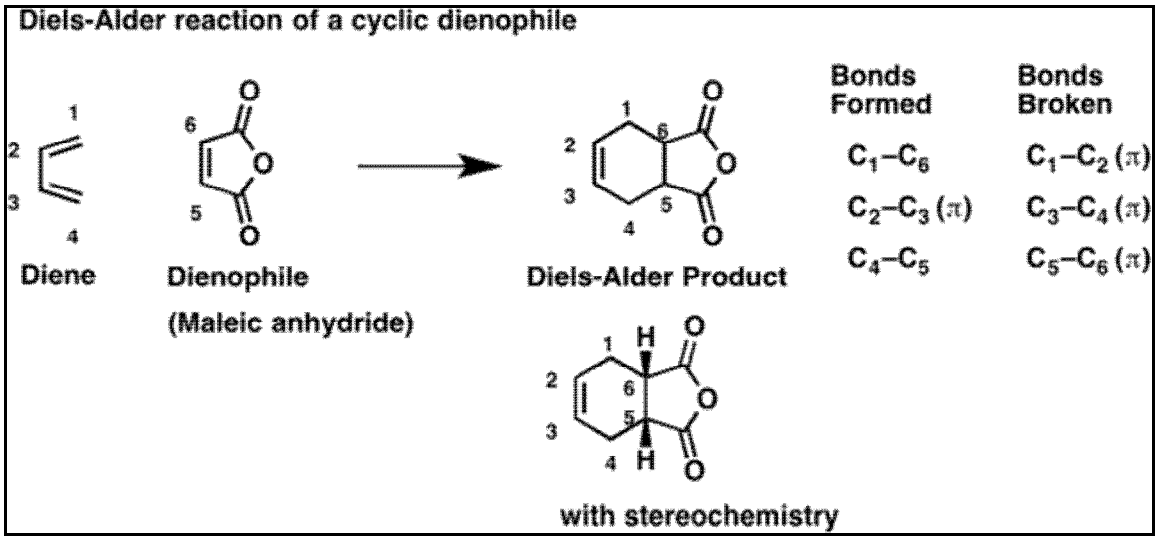


Diels-Alder Reaction : The Diels Alder reaction converts a **diene** (an unsaturated hydrocarbon containing two double bonds between carbon atoms.) and an alkene (**usually electron-poor, called a —dienophile**") into a six-membered ring containing an alkene (cyclohexene).

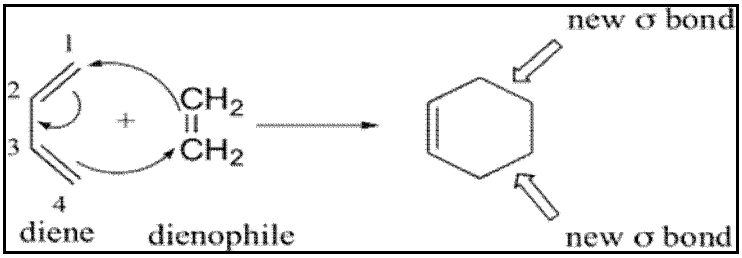


Mechanism :

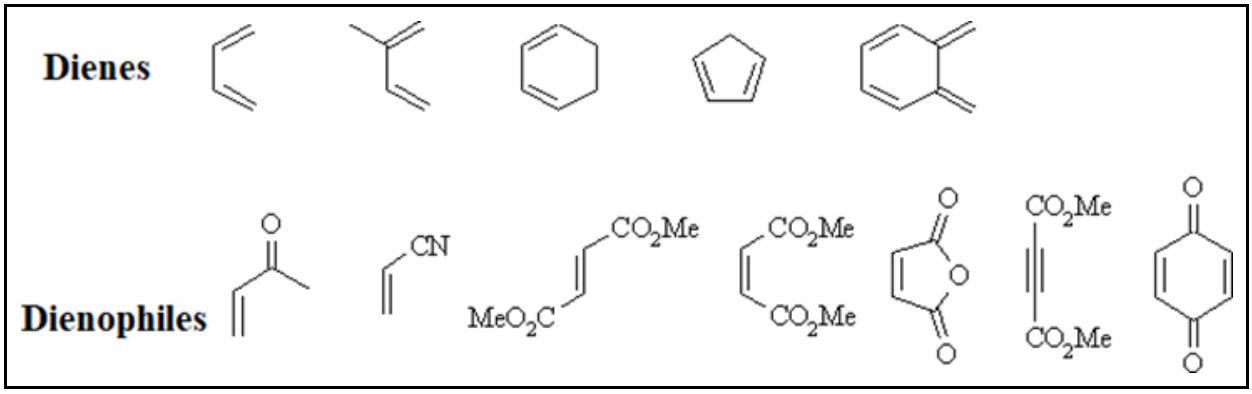




Diels Alder reaction usually thermodynamically favourable due to the conversion of **2 π-bonds** into **2 new stronger σ-bonds**

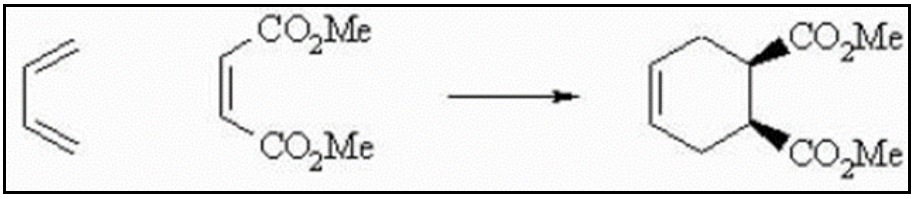


The normal Diels-Alder reaction is favoured by electron withdrawing groups on the electrophilic dienophile and by electron donating groups on the nucleophilic diene.

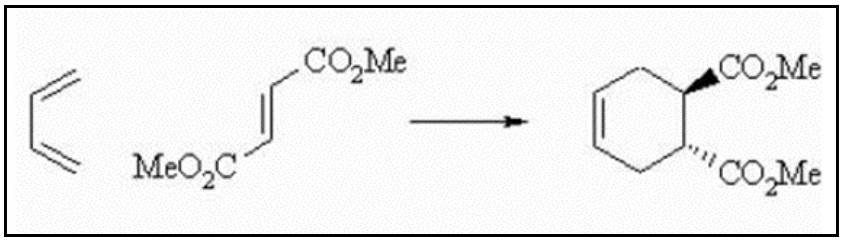


The Diels-Alder reaction is stereospecific :

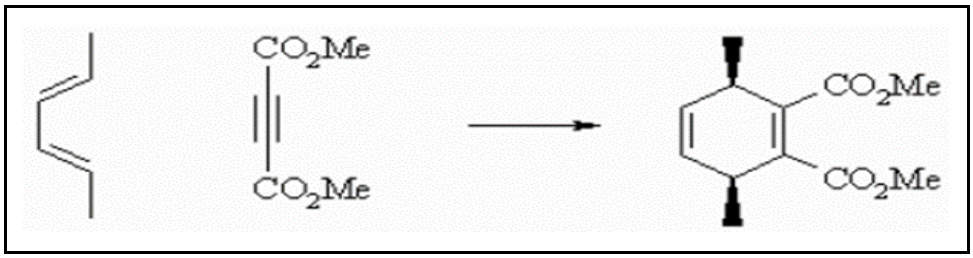
A***cis*-dienophile** gives ***cis*** substituents in the product



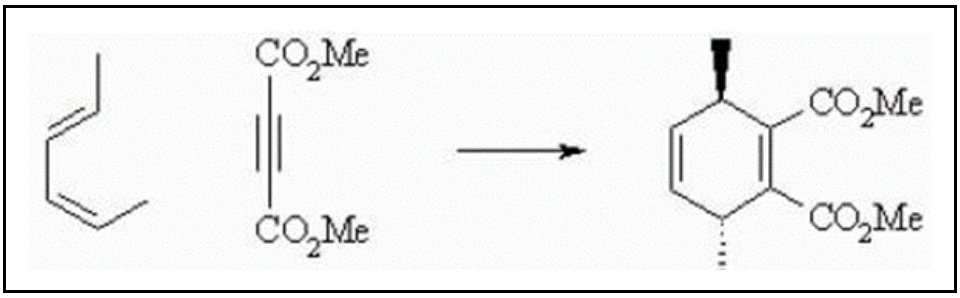
a ***trans*-dienophile** gives ***trans***-substituents in the product



If the **diene** substituents have the same stereochemistry (here they are both E), then both **diene** substituents end up on the same face of the product

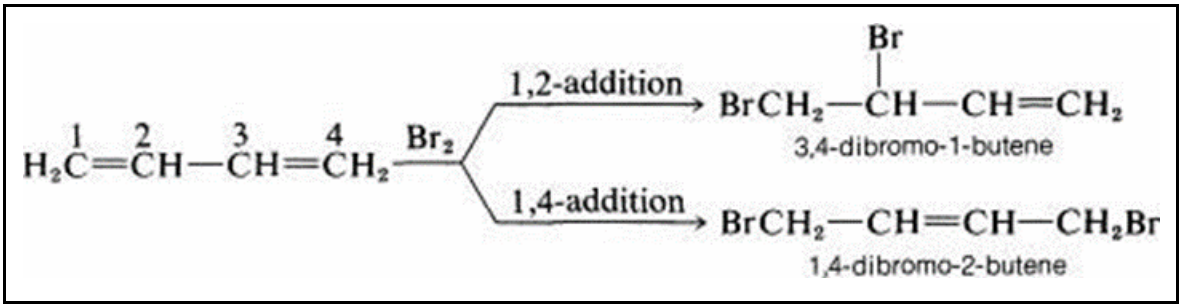


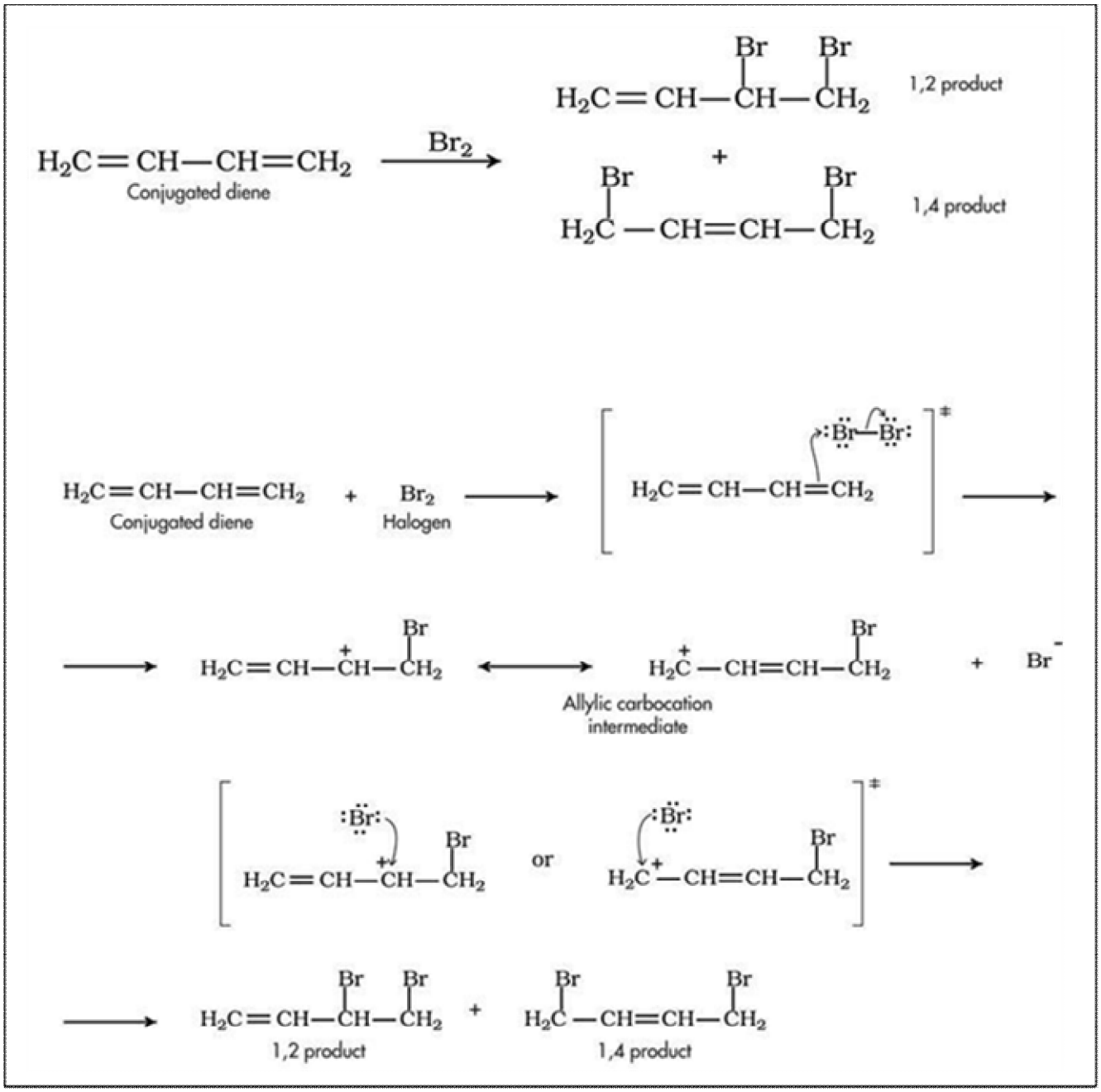
If the **diene** substituents have opposite stereochemistry (here one is E and one Z), then the **diene** substituents end up on opposite faces of the product



Electrophilic addition reactions of conjugated dienes :

- Dienes with electrophilic reagents like halo acids give electrophilic addition reaction.
- Conjugated dienes undergo addition reactions in a similar manner to simple alkenes, but two modes of addition are possible.
- Consider the reaction of **1,3-butadiene**.





Which is the major product formed predominantly 1,2 or 1,4?

The formation of product will depend on

(i) Stability of carbocation : The addition of proton occurs as per the **Markovnikov rule**; the stable carbocation will be formed at the more substituted carbon atom.

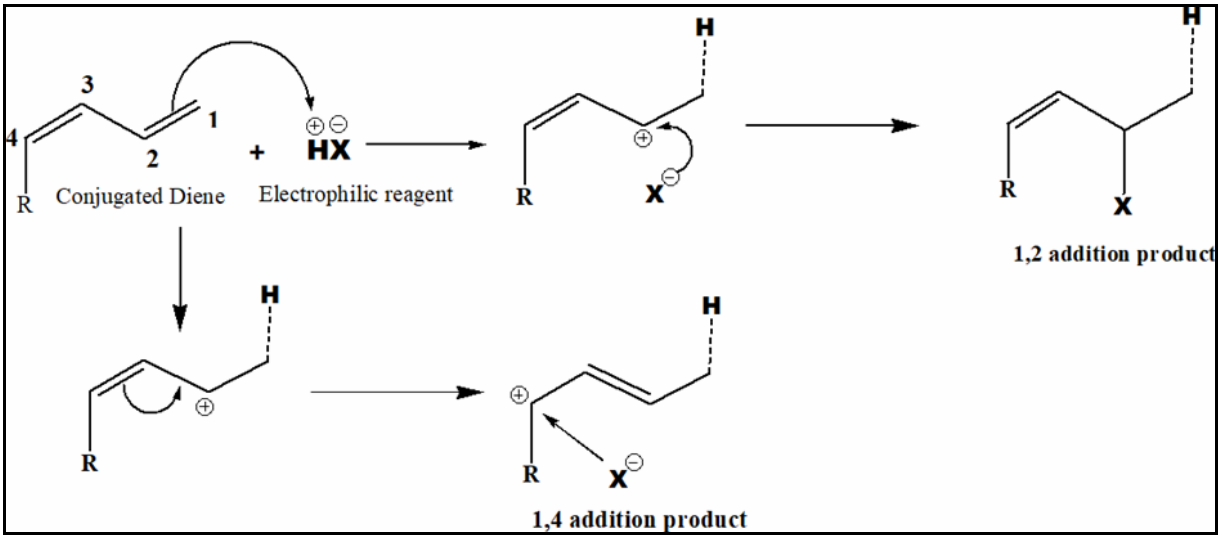
(ii) Rate of reaction : The energy of activation for the formation of 1,2 product is lower and hence formed faster. However, equilibrium is less favored.

1,4 product require higher activation energy but favors equilibrium.

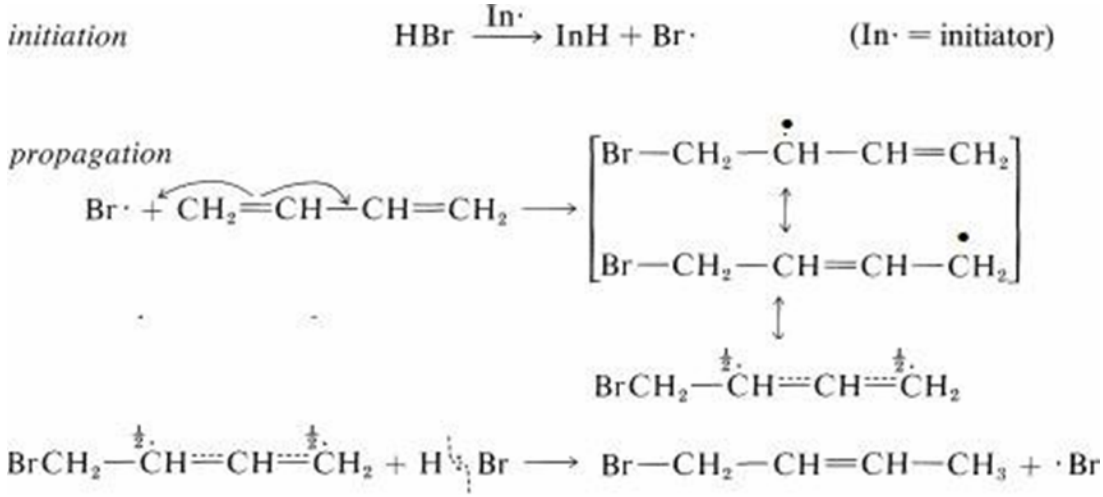
(iv) Reaction temperature : Kinetic product is the product which appears first in reaction but the stable product is the thermodynamic product.

1,2 product is formed first at lower temperature but rearranges to 1,4 product at high temperature or on standing for some time even at low temperature.

(v) Reagent: Use of milder condition gives mixture of products , use of excess of reagent result in 1,4 product.

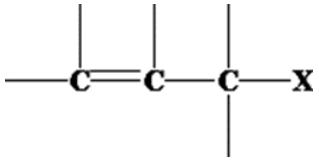


Free radical addition reactions of conjugated dienes : Conjugated dienes also undergo addition reactions by radical-chain mechanisms. Here, the addition product almost always is the 1,4 adduct. Thus radical addition of hydrogen bromide to 1,3-butadiene gives l-bromo-2-butene.



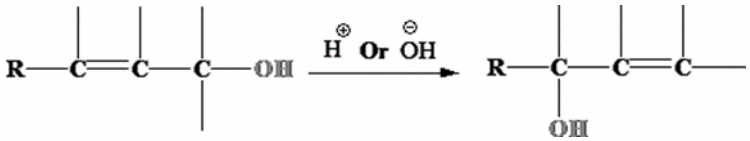
Allylic Rearrangement :

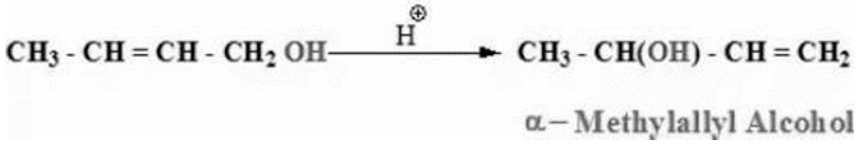
Allylic compounds are those which have a functional group on a carbon atom α to an olefinic bond, e.g.,

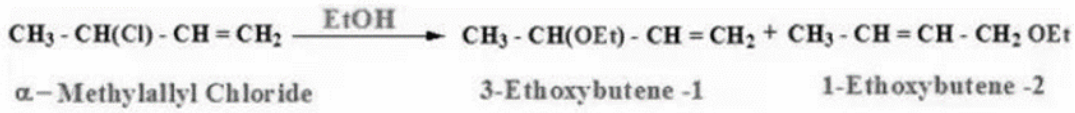


Alkenes are also called Olefins because they form oily liquids on reaction with chlorine gas. An alkene consists of at least one double bond. This double bond is known as the **olefinic bond**.

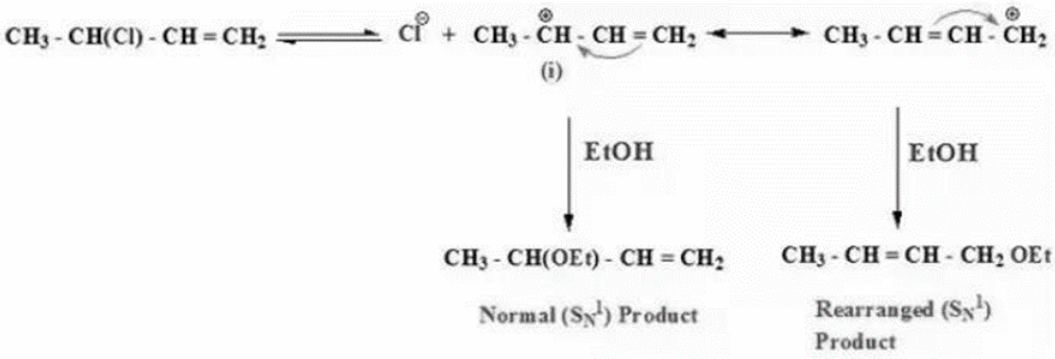
The double bond (and the functional group) in these compounds undergo acid or base catalyzed migration to form a new compound.







Mechanism: Allylic rearrangement is observed generally in nucleophilic substitution reactions which may be SN1 or S_N2 type.



Ozonolysis : Ozonolysis is an organic reaction where the unsaturated bonds of alkenes, alkynes, or azo compounds are cleaved with ozone.

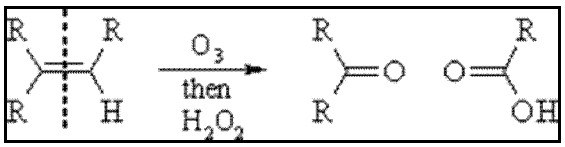
Alkenes and alkynes form organic compounds in which the multiple carbon–carbon bond has been replaced by a carbonyl group while **azo** compounds form **nitrosamines**.

Reaction type: Electrophilic Addition.

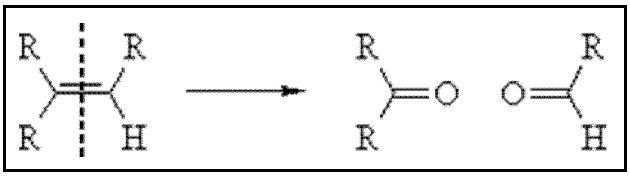
Reagents: ozone followed by :

a reducing work-up, either Zn in acetic acid or dimethyl sulfide, (CH3)2S an oxidising work-up, usually H2O2 (under these conditions, carboxylic acids are obtained instead of aldehydes)

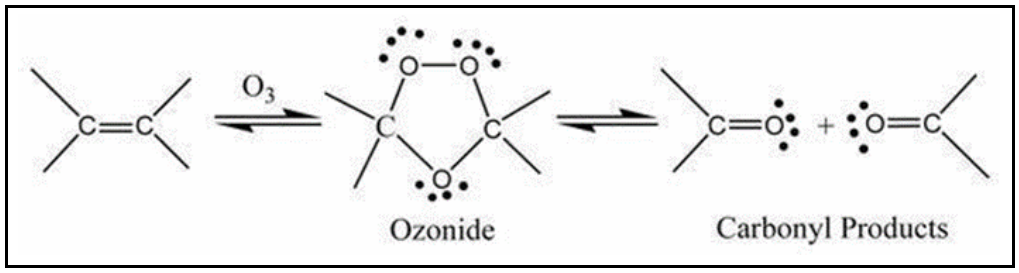
OXIDATIVE work-up :



REDUCTIVE work-up :

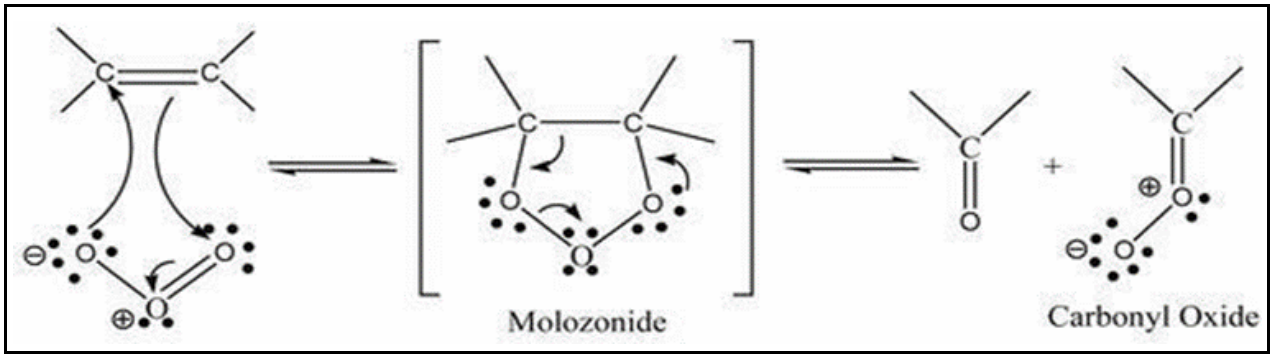


Reaction "

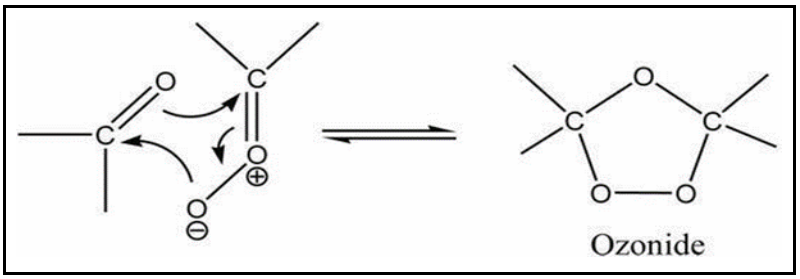


Reaction Mechanism :

Step 1: The first step in the mechanism of ozonolysis is the initial **electrophilic addition** of **ozone** to the **Carbon- Carbon double bond**, which then forms the **molozonide intermediate**. Due to the unstable **molozonide** molecule, it continues further with the reaction and breaks apart to form a carbonyl and a carbonyl oxide molecule.



Step 2: The carbonyl and the **carbonyl oxide (zwitterions)** rearranges itself and reforms to create the **stable ozonide** intermediate. A reductive workup could then be performed to convert the **ozonide** molecule into the **desired carbonyl products**.

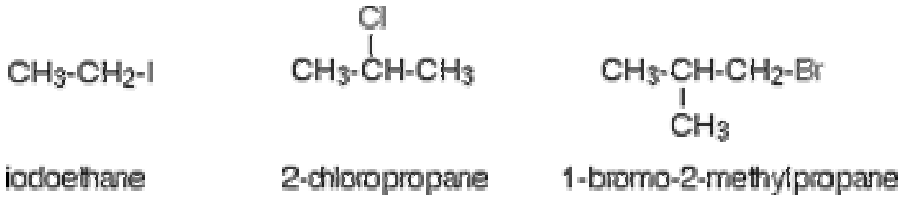


CHAPTER 3

Alkyl halides (Haloalkanes)

Introduction :

Alkyl halides are also known as haloalkanes. Alkyl halides are compounds in which one or more hydrogen atoms in an alkane have been replaced by halogen atoms (fluorine, chlorine, bromine or iodine). We will only look at compounds containing one halogen atom like the compounds below.



(1) Nomenclature of alkyl halides : Generally, alkyl halides are named based on both the substitutive nomenclature and radicofunctional nomenclature haloalkane, haloarene (substitutive nomenclature) alkyl halide, aryl halide (radicofunctional nomenclature)

In substitutive nomenclature, "halogen" is to be used exclusively as a prefix. Mixed use of two methods of nomenclatures should be avoided.

Example

[Example] CH3CH2CH2Cl

1-chloropropane (substitutive) propyl chloride (radicofunctional) propane chloride (error; mixed use)

[Example] CH3CHClCH3

2-chloropropane (substitutive) isopropyl chloride (radicofunctional)

[Example] BrCH2CH2Br

1,2-dibromoethane (substitutive) ethylene dibromide (radicofunctional) ethane dibromide (error; mixed use)

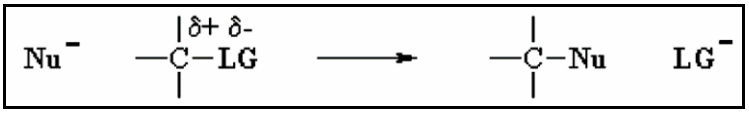
[Example] CH2=CHCl]

chloroethylene (substitutive) vinyl chloride (radicofunctional)

Name*	Structural formula	melting point (°C)	boiling point (°C)
methyl chloride (chloromethane)	CH3Cl	-97.72	-23.76
methyl bromide (bromomethane)	CH3Br	-93.66	3.56
methyl iodide (iodomethane)	CH3I	-66.45	42.8
methylene chloride	CH2Cl2	-96.8	40.21
(dichloromethane)			
chloroform** (trichloromethane)	CHCl3	-63.5	61.2
carbon tetrachloride**	CCl4	-28.6	76.74
(tetrachloromethane)			
ethylidene dichloride	CH3CHCl2	-96.7	57.3
(1,1-dichloroethane)			
1,2-dichloroethane	ClCH2CH2Cl	-35.3	83.38
vinyl chloride (1-chloroethylene)	CH2=CHCl	-150.7	-13.70
vinylidene chloride	CH2=CCl2	-122.1	31.7
(1,1-dichloroethylene)			
benzyl chloride	C6H5CH2Cl	-39.2	179.3-179.4
((chloromethyl)benzene)***			

Nucleophilic Substitution Reaction:

Overall a nucleophilic substitution can be represented as follows:



There are two fundamental events in a nucleophilic substitution reaction:

i. formation of the new σ bond to the nucleophile

ii. breaking of the σ bond to the leaving group

Depending on the relative timing of these events, three different mechanisms are possible:

i. Bond breaking to form a carbocation proceeds the formation of the new bond: **S_N1 reaction**

ii. Simultaneous bond formation and bond breaking: **S_N2 reaction**

iii. **S_Ni** or **Substitution Nucleophilic internal**: It stands for a specific but not often encountered nucleophilic aliphatic substitution reaction mechanism. A typical representative organic reaction displaying this mechanism is the chlorination of alcohols with thionyl chloride, or the decomposition of alkyl chloroformates, the main feature is retention of stereo chemical configuration.

Bonding in the halogen-alkanes : Halogen-alkanes (also known as halo-alkanes or alkyl halides) are compounds containing a halogen atom (fluorine, chlorine, bromine or iodine) joined to one or more carbon atoms in a chain.

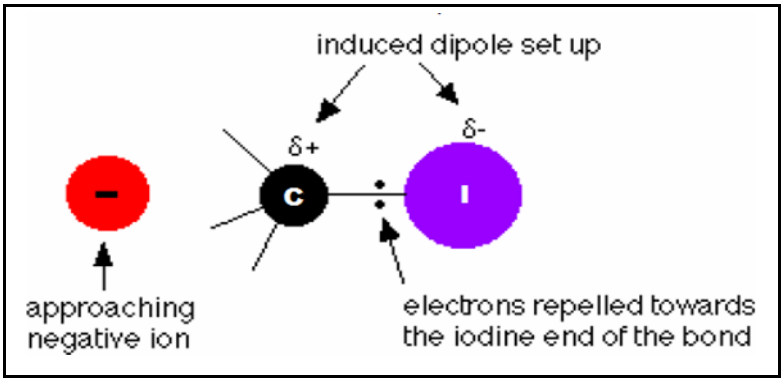
The interesting thing about these compounds is the carbon-halogen bond, and all the nucleophilic substitution reactions of the halogen alkanes involve breaking that bond

The polarity of the carbon-halogen bonds : With the exception of iodine, all of the halogens are more electronegative than carbon.

Electronegativity values				
C=2.5	F=4.0	Cl=3.0	Br=2.8	I=2.5

That means that the electron pair in the carbon-halogen bond will be dragged towards the halogen end, leaving the halogen slightly negative (d-) and the carbon slightly positive (d+) except in the carbon-iodine case.

Although the **carbon-iodine bond** doesn't have a permanent dipole, the bond is very easily polarised by anything approaching it. Imagine a negative ion approaching the bond from the far side of the carbon atom:



The fairly small polarity of the carbon-iodine bond will be increased by the same effect

The strengths of the carbon-halogen bonds

Strength of various bond (KJ/mol)	
C-H	413
C-F	467
C-Cl	346
C-Br	290
C-I	228

In all of these **nucleophilic substitution** reactions, the **carbon-halogen bond** has to be broken at some point during the reaction. The harder it is to break, the slower the reaction will be.

The **carbon-fluorine bond** is very strong (stronger than **C-H**) and isn't easily broken. It doesn't matter that the **carbon-fluorine bond** has the greatest polarity, the strength of the bond is much more important in determining its reactivity, Therefore expect ***fluoro-alkanes*** to be very unreactive and they are.

In the other halogeno-alkanes, the bonds get weaker as you go from ***chlorine*** to ***bromine*** to ***iodine***.

That means that ***chloro-alkanes*** react most slowly, ***bromo-alkanes*** react faster, and ***iodo-alkanes*** react faster still: ***Rates of reaction***: **R-Cl < R-Br < R-I**

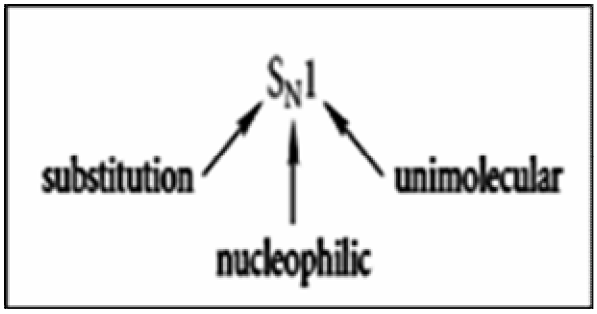
Nucleophilic Aliphatic Substitution :

S_N1 Reaction : The S_N1 reaction is a substitution reaction in organic chemistry. "SN" stands for nucleophilic substitution and the "1" represents the fact that the rate determining step is unimolecular.

Thus, the rate equation is often shown as having first order dependence on electrophile and zero order dependence on nucleophile.

- In S_N1 reaction, substitution at Sp^3 carbon in which a Carbon-Leaving group bond ionizes to form a carbocation intermediate before the Carbon-Nucleophile bond is formed.

  Making faster S_N1 reaction: Use a better leaving group, create a more stable carbocation by increasing number of carbon groups on Sp^3 carbon, or add resonance to structure. Remember that resonance from one pi bonds outweighs stability from one alkyl group (ex: tertiary without resonance is slower than secondary with resonance).



S_N1 reaction is:

- Non-stereospecific (attack by nucleophile occurs from both sides)
- Non-concerted - has carbocation intermediate
- Unimolecular - rate depends on concentration of only the substrate.

Substrate for S_N1 reaction:

- Best if tertiary or conjugated (benzylic or allylic) carbocation can be formed as leaving group departs
- never primary

Formation of carbonium ion :

- Reactivity of an alkyl halide depends chiefly upon how stable a carbonium ion it can form.
- In ***S_N1 reactions*** the order of reactivity of alkyl halides is **Allyl**, **benzyl $>3^0>2^0>1^0>CH_3X$**.
- **3^0 alkyl halides** undergo **S_N1 reaction** very fast because of the high stability of 3^0 carbocations.

Nucleophile character in S_N1 reaction:

- Best if more reactive (i.e. more anionic or more basic)

Leaving Group nature:

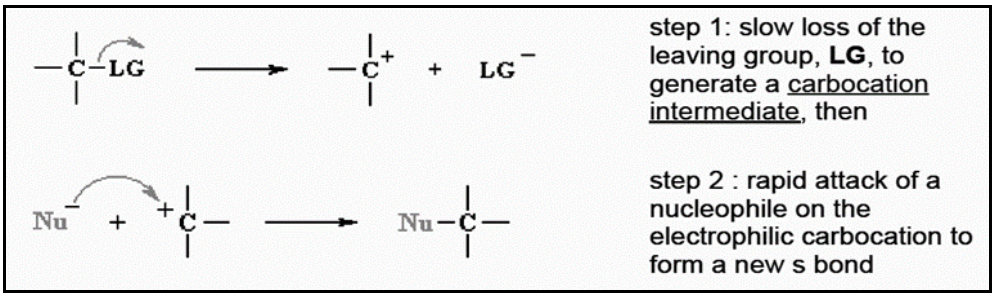
- Best if more stable (i.e. can support negative charge well)
- Examples: **TsO-** (very good) > $\mathbf{I^-}$ > $\mathbf{Br^-}$ > $\mathbf{Cl^-}$ > $\mathbf{F^-}$ (poor)

  However, tertiary or allylic **ROH** or **ROR'** can be reactive under strongly acidic conditions to replace **OH**

Solvent used in S_N1 reaction:

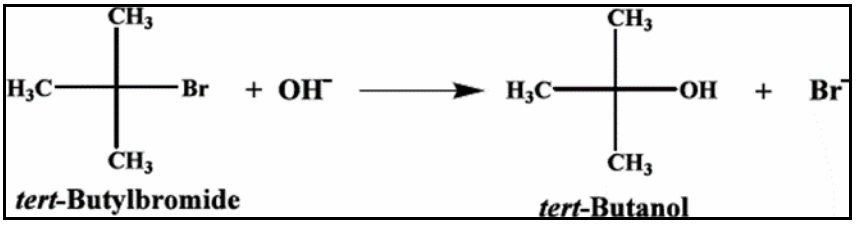
Protic solvents used in S_N1 reaction because formation of carbocation intermediate is the rate determining step. Since for the formation of stable intermediate carbocation a highly polar solvent is required. The negative part of the polar protic solvent interacts with the highly positive part and minimises the energy and makes it stable.

S_N1 Reaction mechanism:



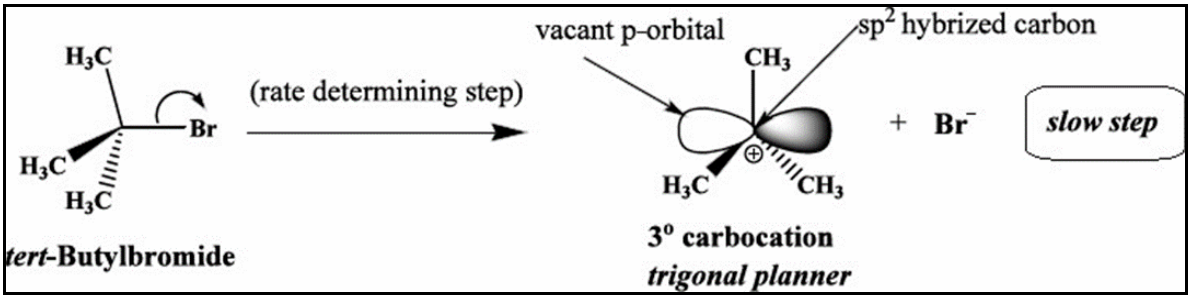
For example: The reaction between ***tert*-butylbromide** and **aqueous sodium hydroxide ion** to give

***tert*-butyl alcohol and bromide ion** follows **S_N1 mechanism**.



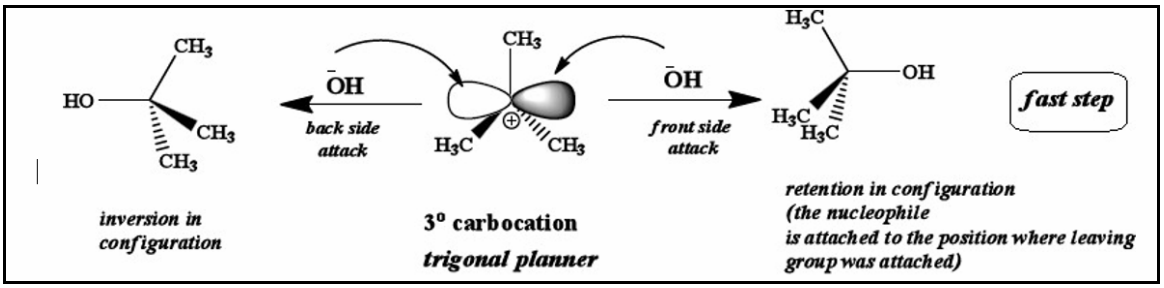
In the first step :

The Carbon-Halogen (C-Br) bond of the substrates slowly breaks by heterolytic fission (halogen departs with the shared pairs of electrons) forming a carbocation. This is the slowest step and hence is the rate determining step. The formed carbocation has trigonal plannar structure.



In the second step :

The nucleophile rapidly attacks the free carbocation giving the product. The nucleophile can attack the carbocation from either sides of the plane giving racemized product (with inversion and retention configuration).

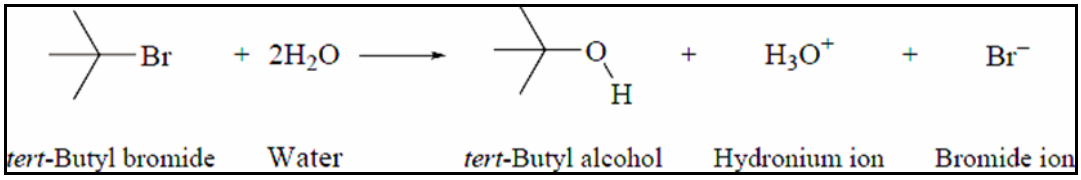


Rate of S_N1 reaction:

- Rate of ***S_N1 reaction*** follow ***first-order rate law***.
- According to the **kinetics of reactions**, their rate depends only on the **substrate's concentration [S]**:

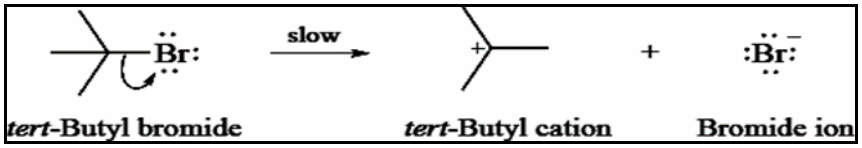
Reaction rate a [S]

- As for example: hydrolysis of *tert*-butyl bromide

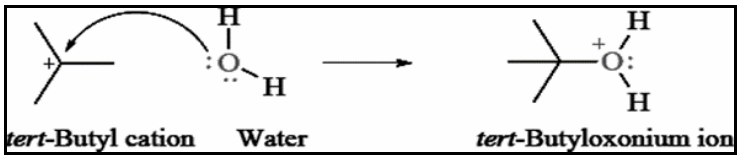


The overall reaction Mechanism :

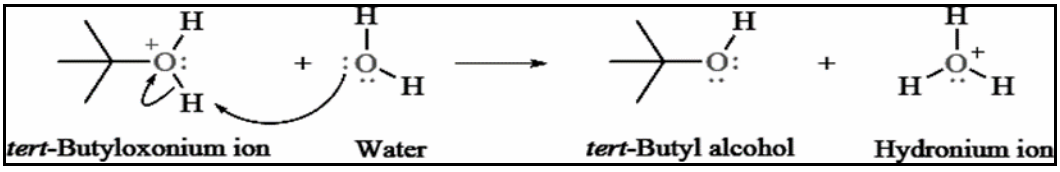
Step 1 : The alkyl halide dissociates to a *carbocation* and a *halide ion*.

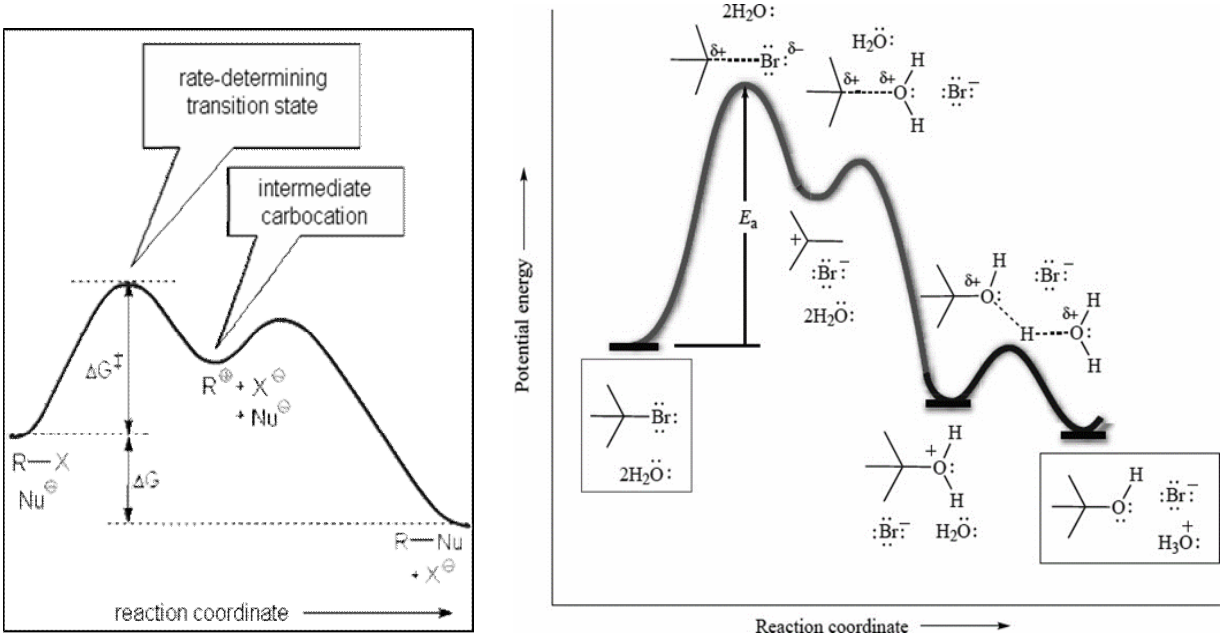


Step 2 : The carbocation formed in step 1 reacts rapidly with water, which acts as a nucleophile. This step completes the nucleophilic substitution stage of the mechanism and yields an *alkyloxonium ion*.



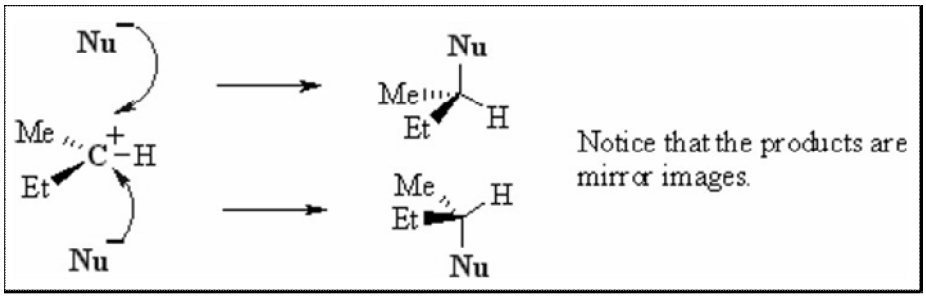
Step 3 : This step is a fast acid–base reaction that follows the nucleophilic substitution. Water acts as a base to remove a proton from the *alkyloxonium ion* to give the observed product of the reaction, *tert-butyl alcohol*

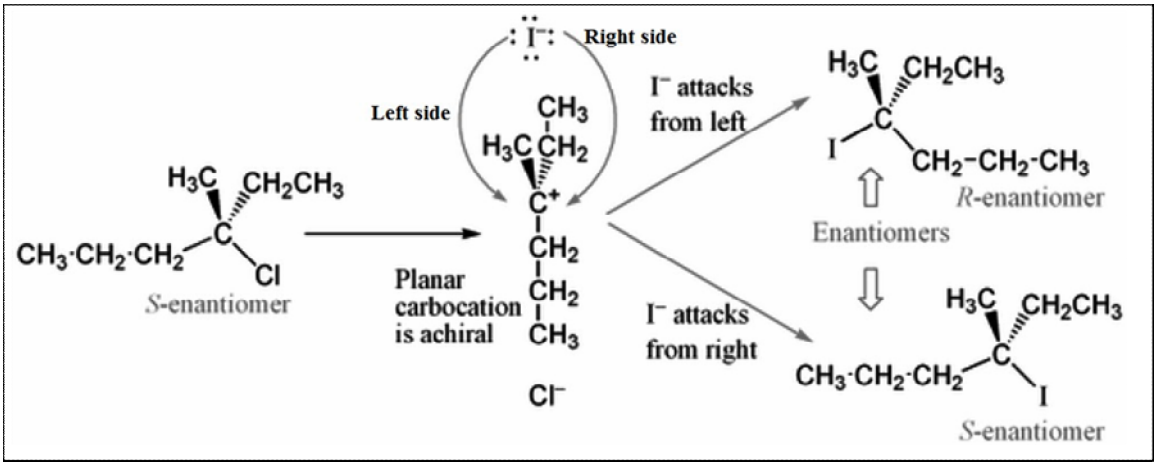


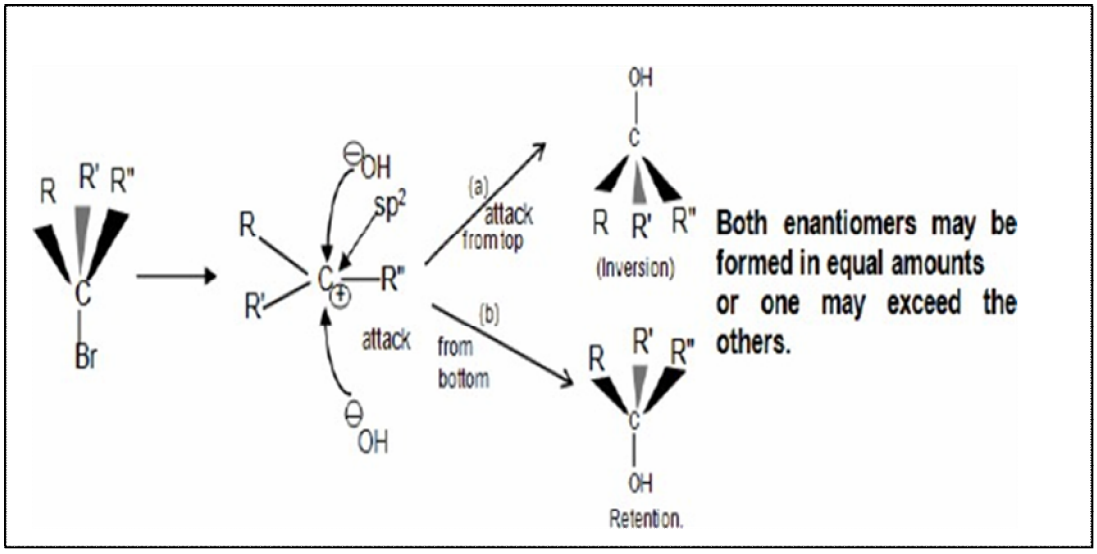


Stereochemistry in S_N1 reaction:

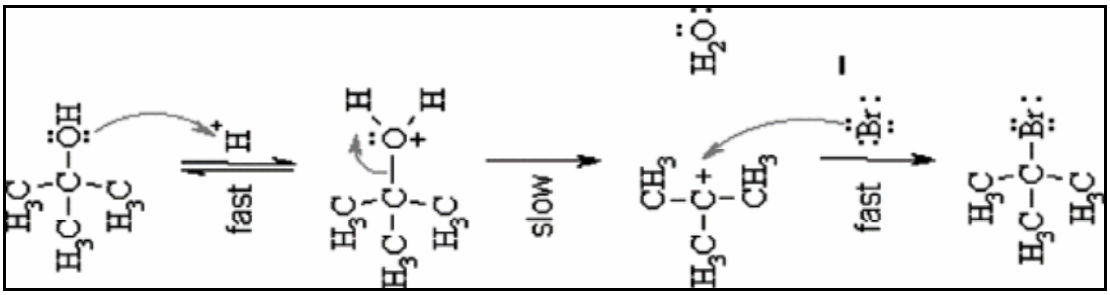
- In **S_N1 reaction**, the nucleophile attacks the <u>planar **carbocation**</u>. Since there is an equally probability of attack on each face there will be a loss of stereochemistry at the reactive center as both products will be observed.
- **S_N1 reaction** proceeds with racemization though may not be complete.







S_N1 mechanism for reaction of alcohols with HBr



Step 1 : An acid/base reaction. Protonation of the alcoholic oxygen to make a better leaving group. This step is very fast and reversible. The lone pairs on the oxygen make it a Lewis base.

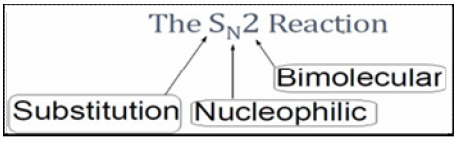
Step 2 : Cleavage of the CO bond allows the loss of the good leaving group, a neutral water molecule, to give a carbocation intermediate. This is the rate determining step (bond breaking is endothermic)

Step 3 : Attack of the nucleophilic bromide ion on the electrophilic carbocation creates the alkyl bromide.

S_N2 Reaction :

S_N2 reaction stands for Substitution Nucleophilic Bimolecular Reaction.

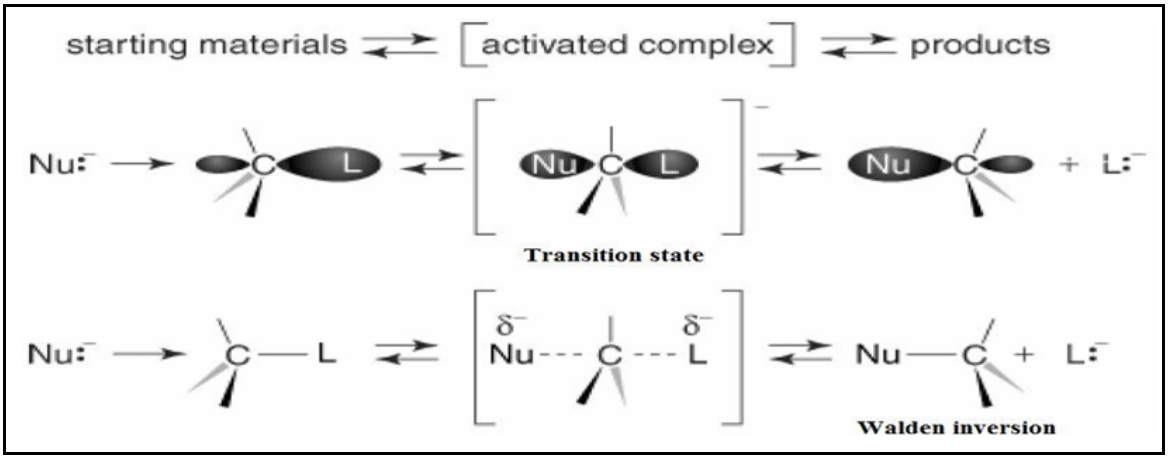
In this mechanism, one bond is broken and one bond is formed synchronously, i.e., in one step.



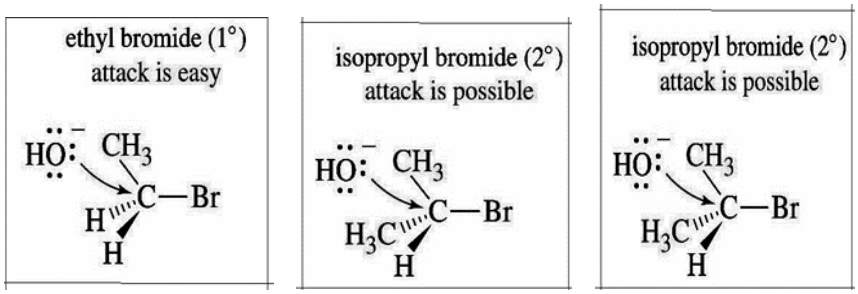
The **S_N2 mechanism** begins when an electron pair of the nucleophile attacks the back lobe of the leaving group. Carbon in the resulting complex is **trigonal bipyramidal** in shape. With the loss of the leaving group, the carbon atom again assumes a **pyramidal** shape; however, its configuration is inverted.

In an **S_N2 reaction**, **Nucleophile** attacks opposite side of the **leaving group**. This occurs because the nucleophilic attack is always on the back lobe (antibonding orbital) of the carbon atom acting as the nucleus. The bond between **nucleophile (Nu)** and **carbon (C)** forms at the exact same time that the bond between **carbon** and **Leaving Group (L)** breaks. In other words, **Nu-C** bond formation and **C-Leaving Group** bond breakage happen simultaneously. In the **transition state**, the carbon is partially attached to both.

S_N2 mechanisms always proceed via rearward attack of the nucleophile on the substrate. This process results in the inversion of the relative configuration, going from starting material to product. This inversion is often called the ***Walden inversion.***



Steric hindrance: S_N2 reactions require a rearward attack on the carbon bonded to the leaving group. If a large number of groups are bonded to the same carbon that bears the leaving group, the nucleophile's attack should be hindered and the rate of the reaction slowed. This phenomenon is called **steric hindrance**. The larger and bulkier the group(s), the greater the **steric hindrance** and the slower the rate of reaction.

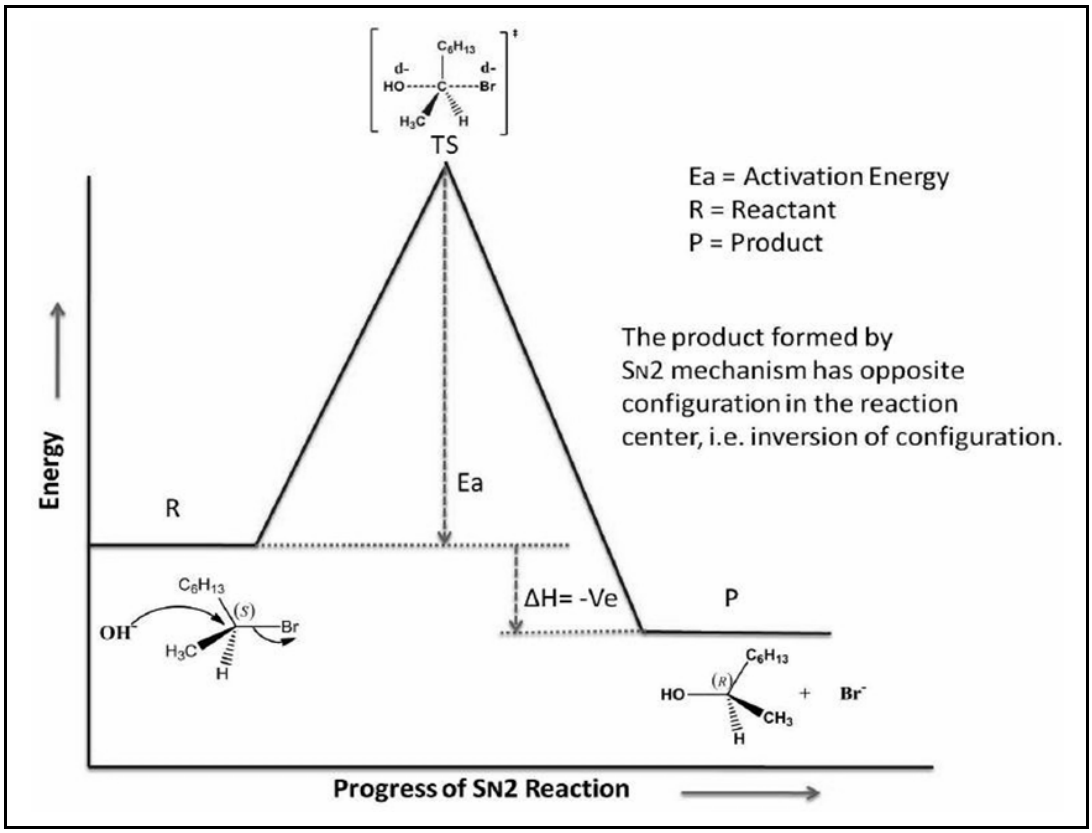


Effect of Steric Hindrance upon Rates of S_N2 Reaction	
Alkyl Group	***Relative Rate of Substitution***
$-CH_3$ (small group)	30
$-CH_2CH_3$ (large group)	1
$-CH(CH_3)_2$ (bulky group)	0.03
$-C(CH_3)_3$ (very bulky group)	0

S_N2 reactions give good yields on **1^0** (primary) alkyl halides, moderate yields on **2^0**(secondary) alkyl halides, and poor to no yields on **3^0** (tertiary) alkyl halides.

The Rate of S_N2 Reaction :

- The rate of the reaction depends on the concentration of both the ***Substrate*** **[S]** and the ***Nucleophile*** **[Nu]** and the reaction is of second order and is represented as S_N2. ***Rate*** a ***[Substrate] [Nucleophile]***
- *S_N2 Mechanism*: a substitution at an sp3 carbon in which the nucleophile-carbon bond formation and the leaving group-carbon bond breakage occur at the same time.
- Transition state: highest point of an energy structure on a reaction profile graph for any mechanism step
- S_N2 reactions are bimolecular, meaning the rate-determining step involves the nucleophile and the starting molecule (electrophile).
- For an S_N2 reaction, the rate-determining step occurs when the nucleophile attacks the sp3 carbon and the leaving group leaves. As depicted on the graph to the right, the energy barrier of the transition state of the nucleophile carbon bond formation and the carbon-leaving group bond scission must be overcome for the reaction to occur.

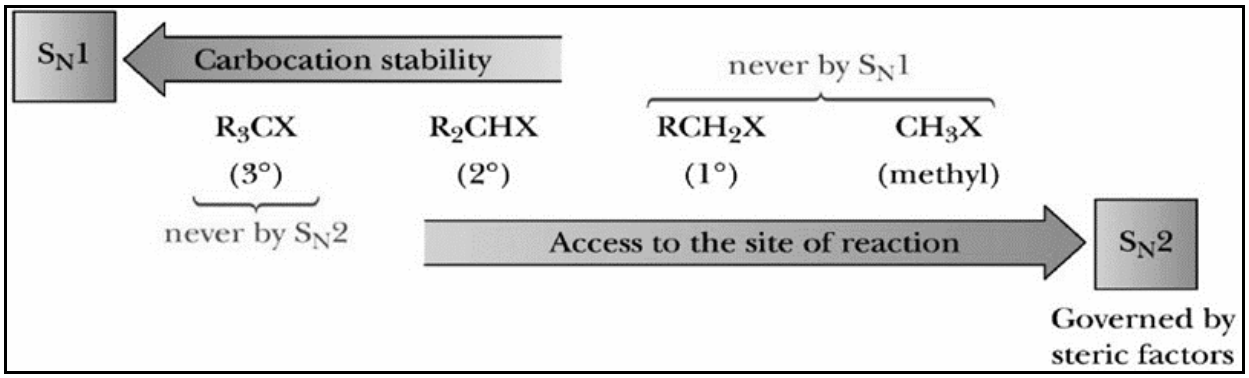


Factors affecting the rates of S_N2 reactions:

<u>Structure of Substrate :</u>

- In S_N2 reaction the substrate plays the most important part in determining the rate of the reaction.
- This is because the nucleophile attacks from the back of the substrate, thus breaking the carbon leaving group bond and forming the carbon nucleophile bond. Therefore, to maximise the rate of the S_N2 reaction, the back of the substrate must be as unhindered as possible.

- Overall, this means that **methyl** and **primary substrates** react the fastest, followed by **secondary substrates**.
- Tertiary substrates do not participate in SN2 reactions, because of steric hindrance



The Nature of the Nucleophile :

- For **S_N2 reaction** in solution there are some principles that govern the effect of nucleophile on the rate.
- A nucleophile with a negative charge is always more powerful than its conjugate acid. Thus **OH^-** is more powerful than H_2O, **NH_2^-** is more powerful than **NH_3**, **CH_3O^-** is more powerful than **CH_3OH**, etc.
- In comparing nucleophiles whose attacking atom is in the same row of the periodic table, nucleophilicity is approximately in order of basicity as following:

$$\mathbf{NH_2^- > RO^- > OH^- > NH_3 > F^- > H_2O\ R_3C^- > R_2N^- > RO^- > F^-}$$

- Going down the periodic table, nucleophilicity increases, though basicity decreases. Thus the usual order of halide nucleophilicity is: **$I^- > Br^- > Cl^- > F^-$**
- So, a strong/anionic nucleophile always favours S_N2 manner of nucleophilic substitution.

Effect of Solvent :

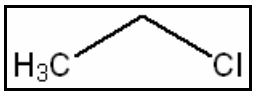
- Polar aprotic solvent (without OH) favors **S_N2**.
- For example polar aprotic solvents are **acetone**, **dimethylsulfoxide**, **N,N'-dimethylformamide**, etc.
- In **S_N2 reaction**, freer the nucleophile, faster is the reaction.
- The stronger the solvation of the nucleophile, the greater the energy required to remove the nucleophile from its solvation cage to reach the transition state, and hence lower is the rate of the S_N2 reaction.
- For example when NaOH is added to aprotic solvent like acetone or dimethyl sulfoxide, sodium is solvated by the solvent whereas OH^- is not. Thus the nucleophile is free and can easily attack the positively charged carbon for S_N2.
- In polar protic solvent both the sodium and hydroxide ions are strongly solvated and more energy is needed to free the nucleophile from the solvent cage to carry out S_N2.

Comparison of S_N1 and S_N2

Points	S_N1	S_N2
Steps	Two steps	One step
Molecularity	Unimolecular, only substrate is involved in rate determining step	Bimolecular, both substrate and nucleophile are involved in the reaction
Kinetics and rate	First order	Second order
Stereochemistry	Racemisation or partial racemization favouring product with inverted configuration	Complete inversion
Effect of substrate structure on rate	Stability of carbocation: Tertiary > secondary > primary > methyl	Steric hindrance decreases the rate of reaction: Methyl > primary > secondary > tertiary
Effect of solvents on rate	Polar protic solvents like water favours S_N1.	Polar aprotic solvent (without OH) favours S_N2, like acetone, DMSO
Nucleophilicity and concentration of nucleophiles	Weak nucleophiles of low concentration too can make the reaction to occur	Stong nucleophles of high concentration increases the rate
Leaving group effect	Weakly basic and highly polarizable group increase the rate	Weakly basic and highly polarizable group increases the rate.
Reaction intermediate	carbocation	None
Competition Reaction	E1 (Elimination Unimolecular) and rearrangement	E2 (Elimination Bimolecular)

Structure and uses

Ethyl Chloride

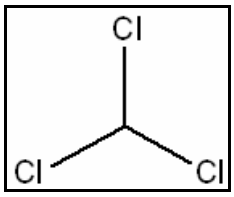


Uses :

- The major use of Chloroethane was to produce tetraethyllead (TEL: It is a petro-fuel additive), an anti-knock
- Chloroethane has been used as a refrigerant, an aerosol spray propellant, an anesthetic, and a blowing agent for foam packaging.
- In dentistry, Chloroethane is used as one of the means of diagnosing a 'dead tooth', i.e. one in which the pulp has

- died. A small amount of the substance is placed on the suspect tooth using a cotton wad. Chloroethane's low boiling point creates a localized chilling effect. If the tooth is still alive this should be sensed by the patient as mild discomfort that subsides when the wad is removed.
- Chloroethane is not classifiable as to its carcinogenicity to humans, but toxic over-exposure starts at 9% to 12% concentrations, the heart rate drops.

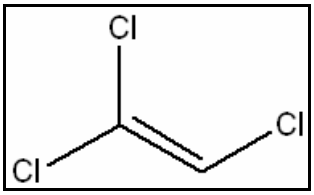
Chloroform :



Uses :

- The hydrogen attached to carbon in chloroform participates in hydrogen bonding. Worldwide, chloroform is also used in pesticide formulations, as a solvent for fats, oils, rubber, waxes, gutta-percha, and resins, as a cleansing agent, grain fumigant, in fire extinguishers, and in the rubber industry..
- Chloroform is also used to extract and purify penicillin.
- Chloroform used for extraction and purification of Alkaloids.
- Chloroform was popular as an **anesthetic** from the mid-1800s to around 1900, but it was found to cause death from
- paralysis. It also depresses most of the body's other organs, including the blood vessels, liver, pancreas, and kidneys. It is toxic to the liver. Oxygen-gas mixtures (oxygen with nitrous oxide, for example) regained use in anesthesia after 1900, and chloroform was replaced by safer compounds after about 1940.
- Chloroform gives relieve the pain of childbirth.
- Although chloroform did carry some risk of heart failure, it was more pleasant to take and more powerful than
- ether. Queen Victoria's anesthetist, an inhaler to regulate the amount of chloroform administered to a patient so that patient felt no pain but remained conscious.

Trichloroethylene :

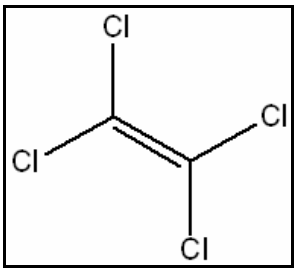


Uses :

- The main use of trichloroethylene is in the vapor degreasing of metal parts.
- Trichloroethylene is also used as an extraction solvent for greases, oils, fats, waxes, and tars, a chemical intermediate in the production of other chemicals, and as a refrigerant.

- Trichloroethylene is used in consumer products such as typewriter correction fluids, paint removers/strippers, adhesives, spot removers, and rug-cleaning fluids.
- Trichloroethylene was used in the past as a general anesthetic.

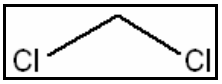
Tetrachloroethylene :



Uses :

- Tetrachloroethylene is used primarily as a cleaning solvent and as a chemical precursor for fluorocarbons.
- It is an anthelmintic, used chiefly in the treatment of hookworm infestation.
- Used in transformers, paint removers, inks, adhesive formulations, paper coatings and leather treatments as an insulating fluid and cooling gas in aerosol formulations.
- Chlorinated hydrocarbons are a crucial solvent and chemical intermediate in the manufacture of chlorofluorocarbons

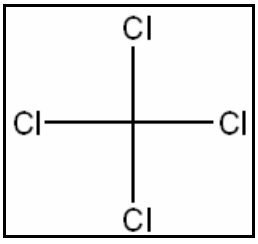
Dichloromethane :



Uses :

- DCM's volatility and ability to dissolve a wide range of organic compounds makes it a useful solvent for many chemical processes.
- It is widely used as a paint stripper and a degreaser.
- In the food industry, it has been used to decaffeinate coffee and tea as well as to prepare extracts of hops and other flavorings. Its volatility has led to its use as an aerosol spray propellant and as a blowing agent for polyurethane foams.

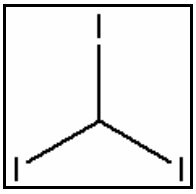
Tetrachloromethane :



Uses :

- Carbon tetrachloride was used to produce the chlorofluorocarbon refrigerants **R-11** (trichlorofluoromethane) and **R-12** (dichlorodifluoromethane).
- Carbon tetrachloride has also been used in the detection of neutrinos.
- Use of carbon tetrachloride in determination of oil has been replaced by various other solvents, such as tetrachloroethylene. Because it has no **C-H** bonds, carbon tetrachloride does not easily undergo free-radical reactions. It is a useful solvent for halogenations.
- Carbon tetrachloride was widely used as a dry cleaning solvent, as a refrigerant, and in lava lamps.
- Carbon tetrachloride is one of the most potent hepatotoxins (toxic to the liver), so much so that it is widely used in scientific research to evaluate Hepatoprotective agents.
- Under high temperatures in air, it forms poisonous phosgene

Iodoform :



Uses :

- The compound finds small-scale use as a disinfectant.
- It was used in medicine as a healing and antiseptic dressing for wounds and sores.
- It is the active ingredient in many ear powders for dogs and cats, along with zinc oxide and propanoic acid, which are used to prevent infection and facilitate removal of ear hair.

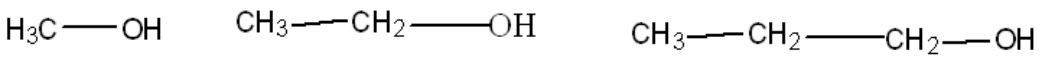
CHAPTER 4

Alcohol

An alcohol is an organic compound with a hydroxyl (OH) functional group on an aliphatic carbon atom. Because OH is the functional group of all alcohols, we often represent alcohols by the general formula ROH, where R is an alkyl group. Alcohols are common in nature. Most people are familiar with ethyl alcohol (ethanol), the active ingredient in alcoholic beverages, but this compound is only one of a family of organic compounds known as alcohols. The family also includes such familiar substances as cholesterol and carbohydrates. Methanol (CH3OH) and ethanol (CH3CH2OH) are the first two members of the homologous series of alcohols.

Nomenclature of Alcohols :

Alcohols with one to four carbon atoms are frequently called by common names, in which the name of the alkyl group is followed by the word *alcohol*:



Structural formula of methyl alcohol, ethyl alcohol, propyl alcohol

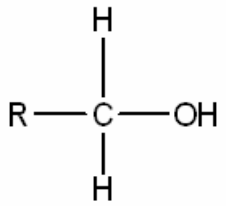
According to the International Union of Pure and Applied Chemistry (IUPAC), alcohols are named by changing the ending of the parent alkane name to *-ol*. Here are some basic IUPAC rules for naming alcohols:

1. The longest continuous chain (LCC) of carbon atoms containing the OH group is taken as the parent compound—an alkane with the same number of carbon atoms. The chain is numbered from the end nearest the OH group.
2. The number that indicates the position of the OH group is prefixed to the name of the parent hydrocarbon, and the *-e* ending of the parent alkane is replaced by the suffix *-ol*. (In cyclic alcohols, the carbon atom bearing the OH group is designated C1, but the 1 is not used in the name.) Substituents are named and numbered as in alkanes.
3. If more than one OH group appears in the same molecule (polyhydroxy alcohols), suffixes such as *-diol* and *-triol* are used. In these cases, the *-e* ending of the parent alkane is retained.

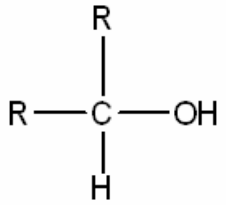
Classification of Alcohols :

Some of the properties of alcohols depend on the number of carbon atoms attached to the specific carbon atom that is attached to the OH group. Alcohols can be grouped into three classes on this basis.

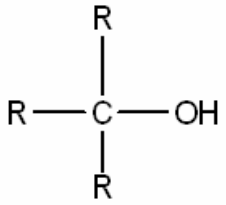
A primary (1°) alcohol is one in which the carbon atom (in red) with the OH group is attached to *one* other carbon atom (in blue). Its general formula is RCH2OH.



A secondary (2°) alcohol is one in which the carbon atom (in red) with the OH group is attached to *two* other carbon atoms (in blue). Its general formula is R2CHOH.



A tertiary (3°) alcohol is one in which the carbon atom (in red) with the OH group is attached to *three* other carbon atoms (in blue). Its general formula is R3COH.



Methods of preparation of alcohols :

1) **Hydration of Alkenes:** Alkenes on treatment with concentrated sulphuric acid and followed by subsequent hydrolysis of intermediate (alkyl hydrogen sulphates) alcohols are produced. This is one of the best method and basic method for producing alcohols on large scale in industries.

$CH_2=CH_2 + OH\text{-}SO_2\text{-}OH \longrightarrow$ CH3-CH2-OSO3H

Ethene — Ethyl hydrogen sulphate

CH3-CH2-OSO3H + H2O $\longrightarrow$ $CH_3\text{-}CH_2\text{-}OH$

Ethyl hydrogen sulphate — Ethyl Alcohol

2) **Hydrolysis of Alkyl halides:** Alcohols can be prepared by the addition of dilute aqueous solution of sodium or potassium hydroxide to alkyl halides.

R-X + NaOH $\longrightarrow$ R-OH + NaX

Alkyl halide — Alcohol

CH3-CH2-CH2Cl + NaOH $\longrightarrow$ CH3-CH2-CH2OH + NaCl

Propyl Chloride — Propyl alcohol

3) **Hydrolysis of carboxylic esters:** Alcohols can be prepared by the addition of dilute solution of an alkali or mineral acid to ester.

$$RCOOR + H_2O \longrightarrow R\text{-}COOH + ROH$$

Ester Acid Alcohol

4) **Reduction of carbonyl compounds:** Carbonyl compounds, carboxylic acids, esters on reduction with appropriate reducing agents, alcohols can be prepared.

Reduction of aldehydes

5) **Fermentation of carbohydrates:** Molasses on fermentation in the presence of yeast produces ethyl alcohol. Molasses is the mother liquor left after the crystallization of sugar.

$$C12H22O11 + H2O \longrightarrow C6H12O6 + C6H12O6$$

Sugar Glucose Fructose

Physical properties:

1) **State:** Lower alcohols are colorless volatile liquids while higher alcohols are solids. Methyl alcohol is a nerve poison, very small intake also causes blindness.

2) **Solubility:** Lower alcohols are soluble in water, solubility of alcohols in water is due to the hydrogen bonding. Solubility of alcohols decreases with increase in molar mass.

3) **Boiling points:** Alcohols have higher boiling points compared to alkanes because of hydrogen bonding existing between alcohol and water molecules.

Chemical Properties:

Chemical properties of alcohols can be studied in three ways

1. Reactions involving cleavage of O-H bond
2. Reactions involving cleavage of C-O bond
3. Reactions involving unshared electrons of oxygen.

Reactions involving cleavage of O-H bond:

1. **Acidic nature:** Alcohols behave as weak acids. Alcohols acidic strength is less than that of water.

$$ROH \longrightarrow RO^- + H^+$$

Alcohol Alkoxide

2) **Action with alkali metals:** Alcohol reacts with alkali metals and liberates hydrogen.

$$ROH + Na \longrightarrow RONa + 1/2H_2$$

3) **Action with metal hydride** : Alcohol form metal alkoxide on the reaction with metal hydride

$$ROH + NaH \longrightarrow RONa + H2$$

4) **Esterification:** Esters are formed when alcohols react with acid chlorides.

$$RCOCl + HOR1 \rightleftharpoons RCOOR1 + HCl$$

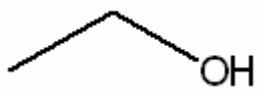
5) **Reaction with Grignard reagent:** Alcohols form alkanes on reaction with Grignard reagent.

$$C2H5OH + CH3Mg\ Br \longrightarrow CH4 + C2H5OMgBr$$

Ethyl alcohol — Methane

Structure and uses :

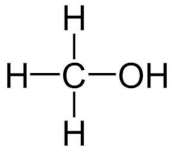
Ethyl alcohol



Uses :

- Antibacterial hand sanitizer gels and medical wipes contain ethanol as one of the ingredients.
- In addition to killing most bacteria and fungi, ethanol kills many viruses by denaturing their proteins. Ethanol can be used as an antidote to poisoning from methanol and ethylene glycol.
- The stomach secretes more acid when ethanol is consumed. Alcohol is a depressant that affects the nervous system. Mood can be lifted, euphoria can be felt, anxiety can be reduced.
- The most common uses of ethanol are in motor fuels and fuel additives. Alcohol is a good general-purpose solvent because it is miscible with water. Chemicals containing this compound can be found in paints, tinctures, markers, mouthwashes, perfumes, and deodorants.

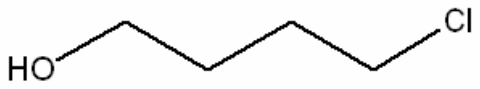
Methyl alcohol :



Uses :

- The commercial production of ethanol uses Methanol as an alcohol denaturant to prevent factory workers from accessing ethanol.
- Synthesis of methanol can be based on heterogeneous catalysts such as zeolites, which are capable of catalyzing condensation reactions. Methanol can function as a source of gasoline, olefins, and other high-level aromatic compounds.
- When methanol is thermally decomposed, carbon dioxide and water are released, making it a suitable fuel for automobiles. The combustion engine of cars uses carbon dioxide as a source of thermal energy.
- As a fuel source, methanol was often used in stove-based cooking appliances.
- The de-staining agent methanol is used to remove dyes originally added to the gel to detect proteins or nucleic acids during polyacrylamide gel electrophoresis (PAGE).
- The perfume industry also uses methanol as a component. Many pharmaceutical reactions take place in methanol.

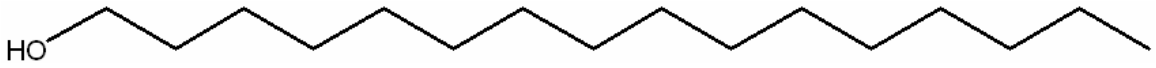
Chlorobutanol :



Uses :

- In conjunction with clove oil, applied topically to provide dental analgesia.
- Sedative and hypnotic properties are provided by chlorobutanol.
- Antiseptic, anti-microbial, and local anesthetic purposes of chlorobutanol in pharmaceuticals.
- This preservative is used in injections, eye drops, mouthwashes, salves, creams, ointments, and cosmetics at a concentration of 0.5%.

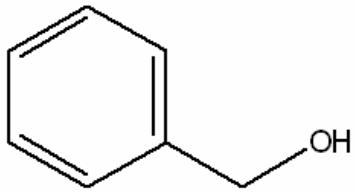
Cetostearyl alcohol :



Uses :

- Used in cosmetics as an opacifier or emollient in shampoos, or as a thickener or emulsifier in creams and lotions. Some "liquid pool covers" contain it as an active ingredient.
- They are also used as lubricants for nuts and bolts.
- This surfactant can be used as an emulsion stabilizer, opacifier, foam booster, and viscosity increaser in both aqueous and nonaqueous solutions. A feeling of emolliency is imparted to the skin with emulsions made of water-in-oil and water-in-oil, as well as anhydrous formulations.

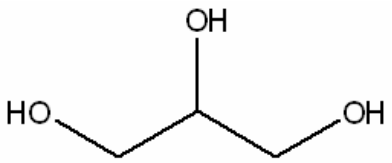
Benzyl alcohol :



Uses :

- emulsions made of water-in-oil and water-in-oil, as well as anhydrous formulations.
- This solvent of choice is used for ink, wax, shellac, paint, lacquer, and epoxy resins.
- E-liquids containing this additive are also used in e-cigarettes to enhance the flavor. According to the U.S. FDA,
- benzyl alcohol in a concentration of 5% can be used as a treatment for head lice in adults and children older than six months. Wool, nylon, and leather can be dyed with it since it is a dye solvent.
- Furthermore, it is used as an insect repellent and a photographic developer.
- At low concentrations, benzyl alcohol is useful as a preservative in cosmetics, intravenous medications, and topical medications because of its bacteriostatic property.

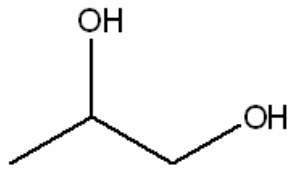
Glycerol :



Uses :

- Glycerol's ability to kill bacteria and viruses makes it a widely used treatment for burns and wounds.
- Glycerol may also be used to measure liver damage. The food industry also uses glycerol to sweeten foods.
- It is one of the ingredients of glycerine soap. As a humectant, glycerol is often used in pharmaceutical, cosmetic, and medical preparations to provide smoothness, lubrication, and hydration.

Propylene glycol :



Uses :

- The liquid form of Propylene glycol is used for absorbing water.
- Polyester compounds are also made with propylene glycol, as well as de-icing solutions.
- The chemical, food, and pharmaceutical industries use propylene glycol in antifreeze when it may contact food in the event of a leak. In addition to coffee beverages, liquid sweeteners, ice cream, whipping cream, and soda, propylene glycol is used in various edible products.
- In many pharmaceutical formulations, including oral, injectable, and topical, propylene glycol is used as a solvent.

CHAPTER 5

Carbonyl compounds (Aldehydes and ketones)

Introduction :

A carbonyl compound is a type of organic compound that contains a carbon-oxygen double bond (C=O) functional group. For example Aldehydes, Ketones and Carboxylic Acids.

This functional group consists of a carbon atom bonded to an oxygen atom by a double bond. The carbon atom in the carbonyl group is often referred to as the carbonyl carbon, and the oxygen atom is referred to as the carbonyl oxygen.

Here's a brief overview of some important types of carbonyl compounds with common examples of organic carbonyl compounds:

1. **Aldehydes:** Aldehydes have the carbonyl group bonded to at least one hydrogen atom. The general formula for an aldehyde is RCHO, where R represents an alkyl or aryl group.

   Example- Formaldehyde (HCHO), Acetaldehyde (CH_3CHO)

2. **Ketones:** Ketones have the carbonyl group bonded to two carbon atoms. The general formula for a ketone is RCOR', where R and R' represent alkyl or aryl groups.

   Example- Acetone (CH_3COCH_3), Butanone ($CH_3COCH_2CH_3$)

3. **Carboxylic acids:** Carboxylic acids have a carbonyl group and a hydroxyl group (OH) bonded to the same carbon atom. The general formula for a carboxylic acid is RCOOH.

   Example- Formic acid (HCOOH), Acetic acid (CH_3COOH), Propionic acid (CH_3CH_2COOH)

4. **Esters:** Esters have a carbonyl group bonded to an oxygen atom and an alkyl or aryl group. The general formula for an ester is RCOOR', where R and R' represent alkyl or aryl groups.

   Example- Methyl acetate (CH_3COOCH_3), Ethyl acetate ($CH_3COOCH_2CH_3$)

5. **Amides:** Amides have a carbonyl group bonded to a nitrogen atom and one or more alkyl or aryl groups. The general formula for an amide is RCONR'R", where R, R', and R" represent alkyl or aryl groups.

   Example- Acetamide (CH_3CONH_2), N-Methylacetamide ($CH_3CONHCH_3$)

Physical Properties of Carbonyl Compounds :

1. **Polarity:** Carbonyl compounds are polar due to the difference in electronegativity between the carbon and oxygen atoms in the carbonyl group (C=O). Oxygen's greater electronegativity results in a partial negative charge (δ-) on the oxygen atom and a partial positive charge (δ+) on the carbon atom, making carbonyl compounds prone to hydrogen bonding and dipole-dipole interactions.

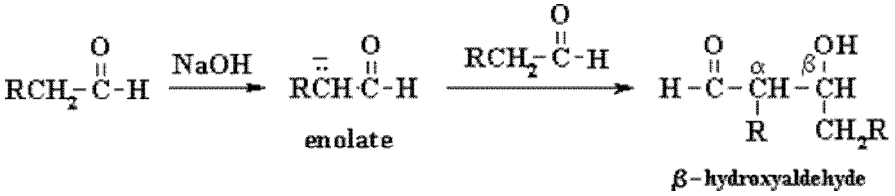
2. **Solubility:** Carbonyl compounds show varying solubility in water based on size and functional groups. Smaller ones like formaldehyde and acetone can form hydrogen bonds with water, making them somewhat soluble. However, as chain length increases or nonpolar groups are present, solubility decreases. They are generally more soluble in organic solvents like ethanol or acetone.
3. **Chemical Reactivity:** Carbonyl compounds are highly reactive due to the polar C=O bond, undergoing various reactions like nucleophilic addition, oxidation, reduction, and condensation. They react with nucleophiles, oxidizing agents, and reducing agents, leading to diverse chemical transformations.
4. **Physical State:** Carbonyl compounds exist as colorless liquids at room temperature, but some may be solids or gases depending on molecular weight and structure.
5. **Odor:** Carbonyl compounds often have distinctive odors; for instance, formaldehyde has a pungent odor, acetone smells fruity, and vanillin imparts a pleasant aroma similar to vanilla.

Aldol condensation Reaction :

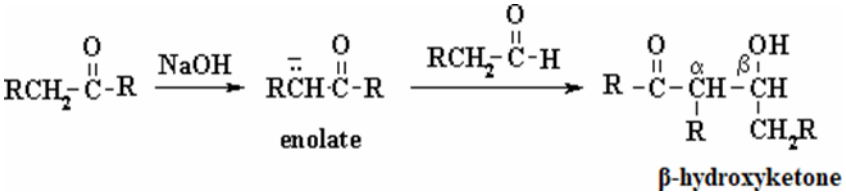
An Aldol Condensation is a condensation reaction in organic chemistry in which an enol or an enolate ion reacts with a carbonyl compound to form a β-hydroxyaldehyde or β-hydroxyketone, followed by dehydration to give a conjugated enone.

Discovered independently by the Russian chemist *Alexander Borodin* in 1869[4] and by the French chemist *Charles-Adolphe Wurtz* in 1872,

The Aldol Reaction of Aldehydes :



The Aldol Reaction of Ketones :



Reaction type:

Nucleophilic addition

Summary:

Reagents: commonly a base such as NaOH or KOH is added to the aldehyde.

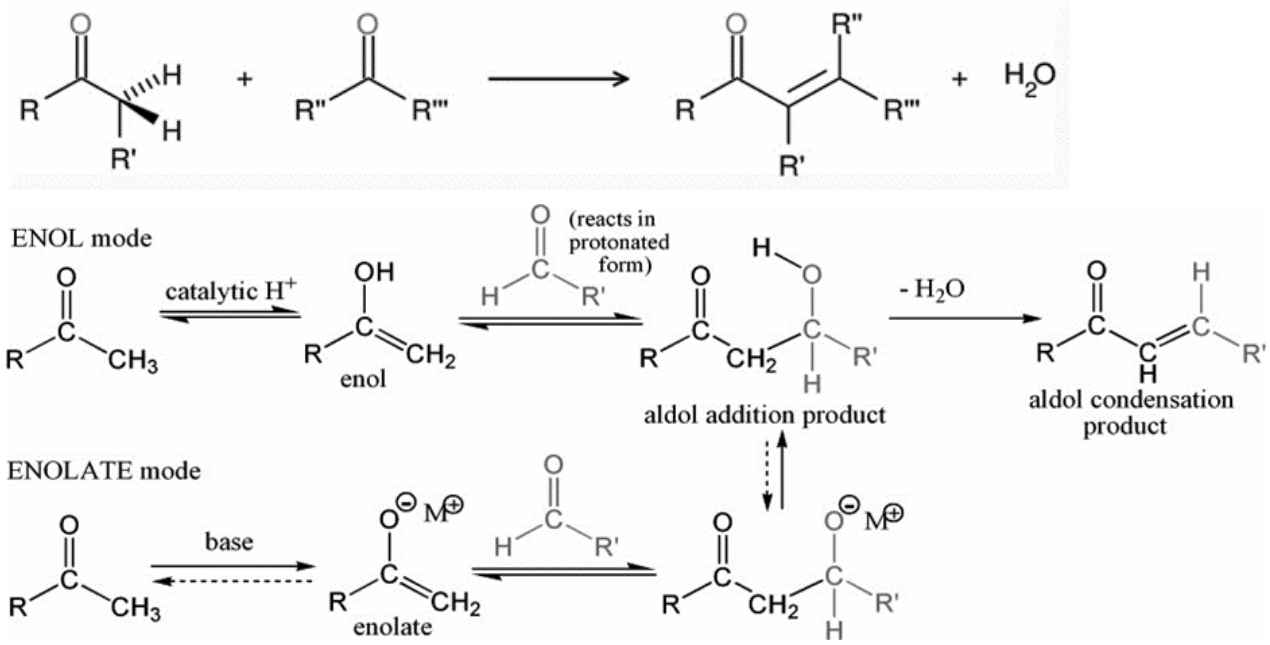
The reaction involves an aldehyde enolate reacting with another molecule of the aldehyde.

Remember **enolates are good nucleophiles** and **carbonyl C are good electrophiles.**

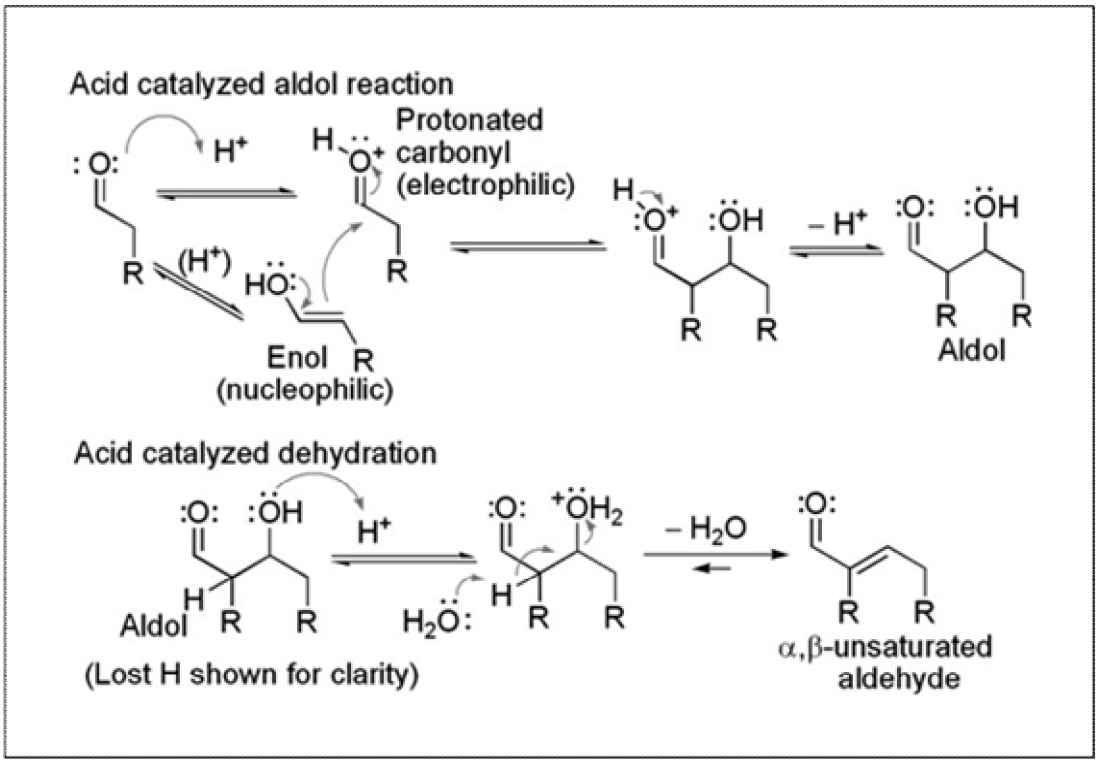
Since the pK_a of an aldehyde is close to that of NaOH, both enolate and aldehyde are present simultaneously.

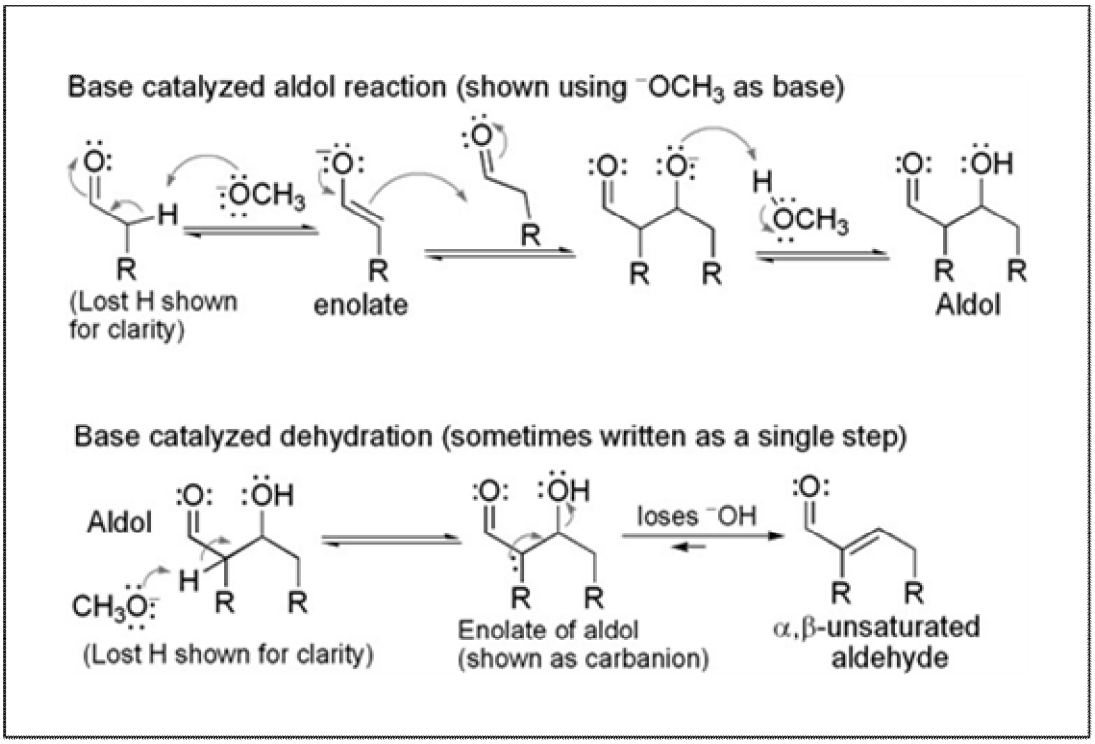
The products of these reactions are β-hydroxyaldehydes or **ald**ehyde-alcoh**ols** = **aldols**.

Aldol condensation reactions :



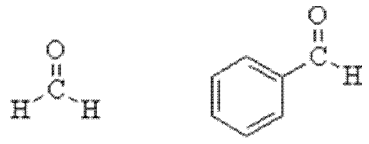
The mechanism of aldol condensation reaction of a ALDEHYDE





Crossed Aldol Condensation Reaction :

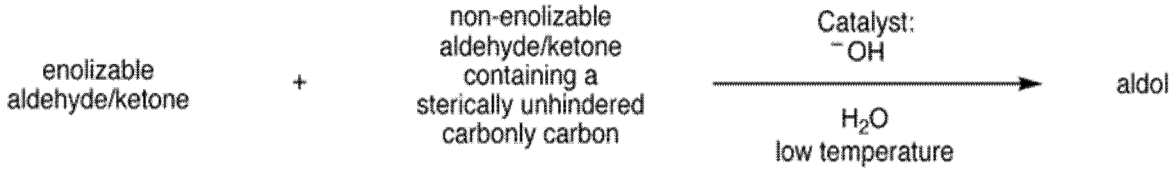
The process is also known as Mixed Aldol Condensation and occurs during the combination of two different molecules that contain carbonyl groups. Generally, such a reaction is only practical if no α-hydrogens are present in one of the compounds. This way, only one nucleophile is formed and only a single enol or enolate is generated.



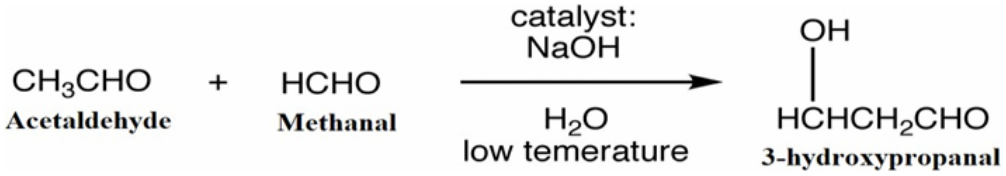
methanal benzaldehyde

Neither of these aldehydes has α-hydrogens and therefore they cannot form an enolate.

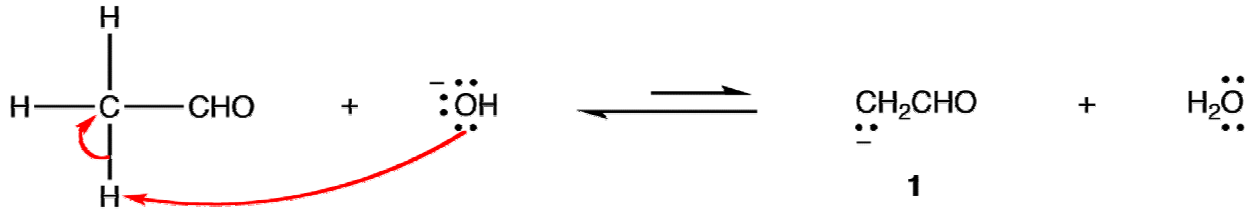
General representation of Aldol reaction



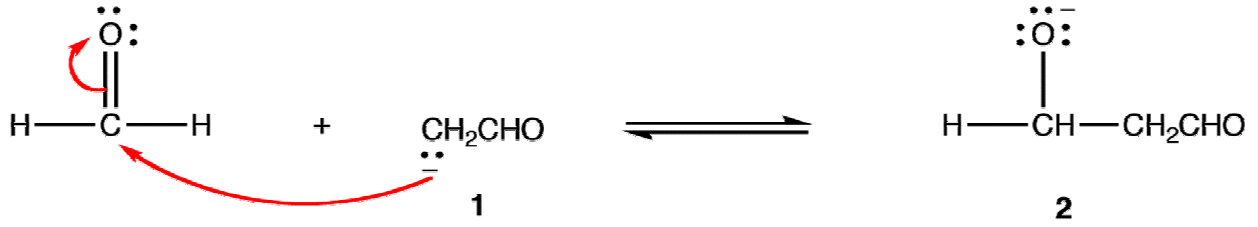
Reaction Mechanism :



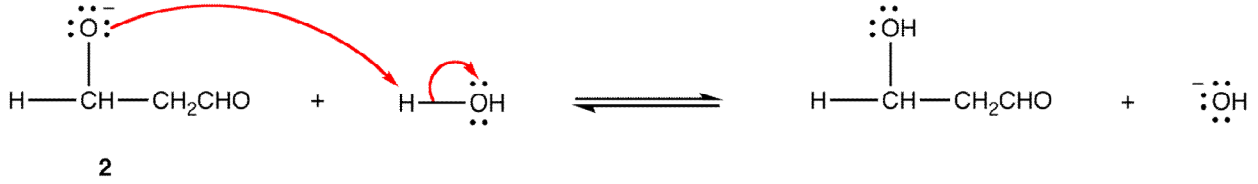
Step 1: The hydroxide ion deprotanates the enolizable aldehyde reversibly.



Step 2: Enolate ion 1 preferentially adds to the non-enolizable aldehyde, which has the Sterically less hindered and, therefore, more accessible carbonyl carbon.



Step 3: Alkoxide ion 2 is protonated by water.

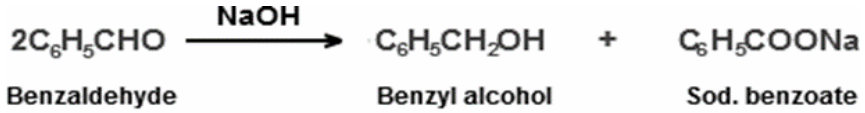


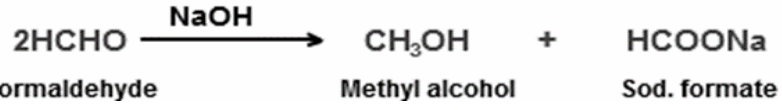
Cannizzaro reaction :

The Cannizzaro reaction, named after its discoverer *Stanislao Cannizzaro*.

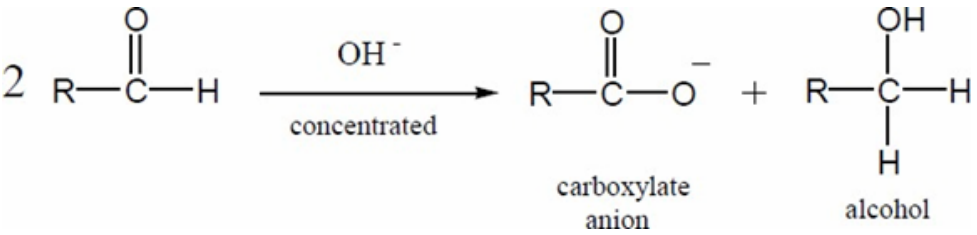
The disproportionation (self-redox) of aldehydes lacking αα-hydrogen atoms in presence of strong base to form salt of an acid and a primary alcohol is known as **Cannizzaro reaction**.

Thus, **aromatic aldehydes, formaldehydes, trialkyl acetaldehyde, heterocyclic aldehydes** undergo **Cannizaro reaction**.

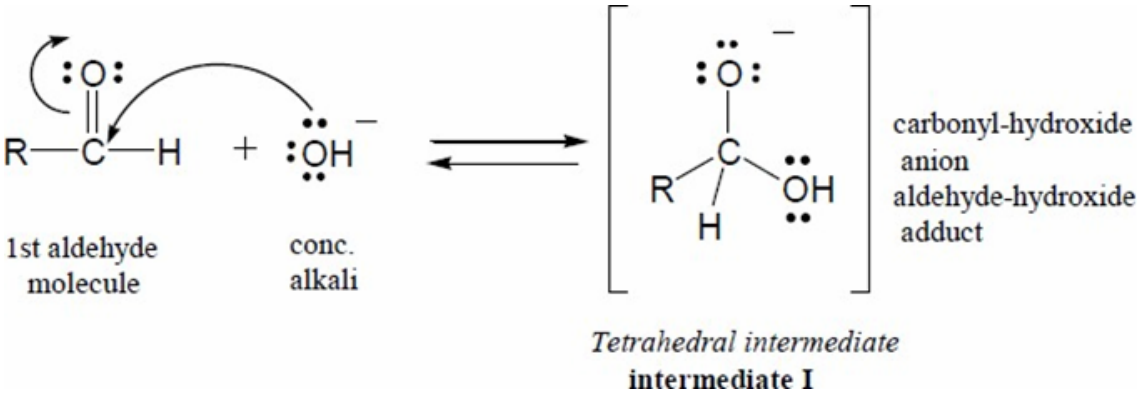




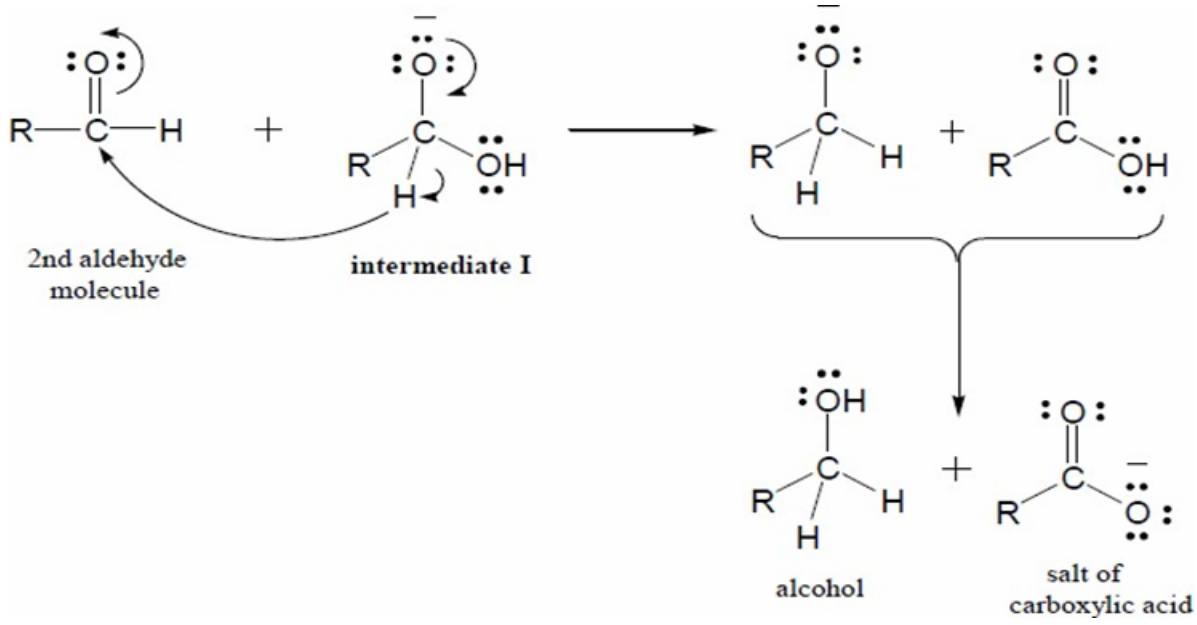
Reaction Mechanism :



Step I: *Nucleophilic addition* of an OH - ion to the 1st aldehyde molecule gives a tetrahedral intermediate I.



Step II: *Hydride shift:* The tetrahedral intermediate I, expels a hydride ion "as a leaving group" and is thereby oxidized. A second aldehyde molecule accepts the hydride ion in another nucleophilic addition step and is thereby reduced.

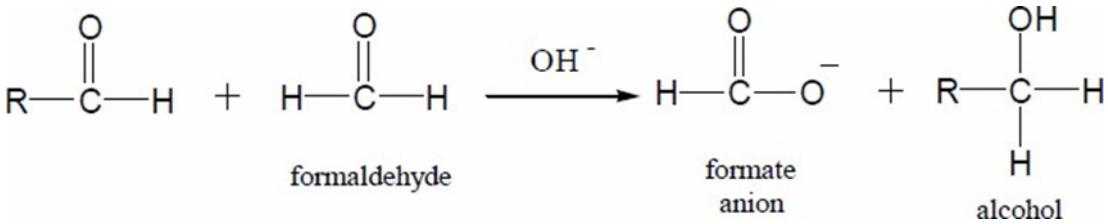


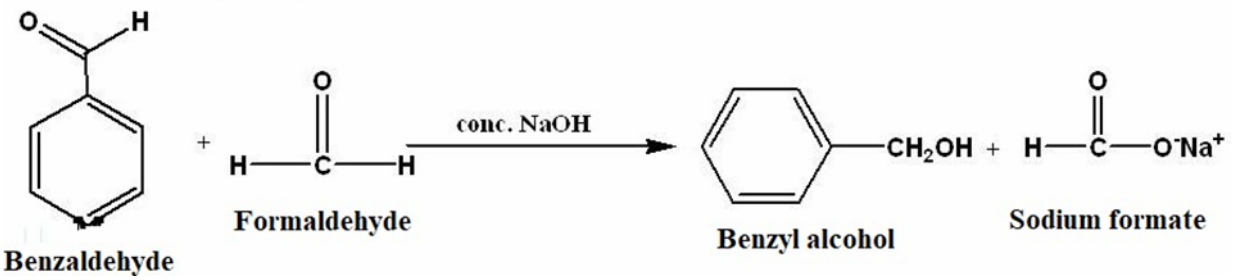
Crossed Cannizzaro Reaction :

In general, a mixture of aldehydes undergoes a Cannizzaro reaction to yield all possible products.

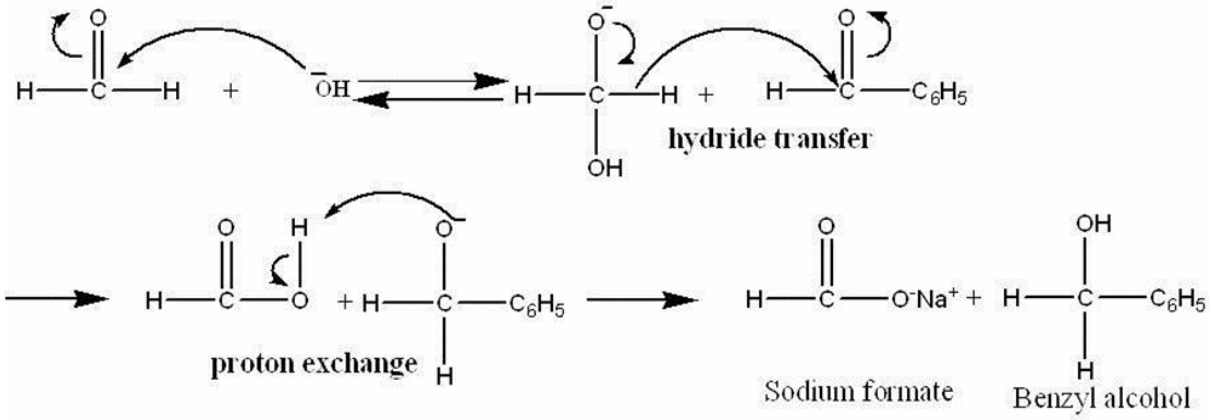
If one of the aldehydes is formaldehyde, the reaction yields almost exclusively salt of formic acid and the alcohol corresponding to the other aldehyde. Such a reaction is called a **Crossed Cannizzaro Reaction**.

If two different aldehyde having no a-Hydrogen, it is called **Crossed Cannizzaro Reaction.**





Reaction Mechanism :



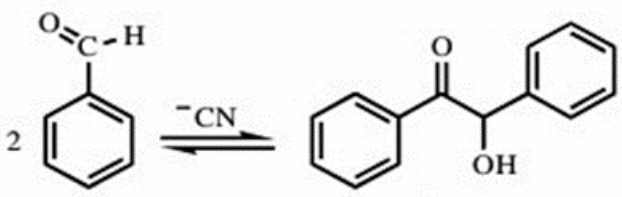
Benzoin condensation :

Benzoin Condensation is an important reaction in which carbon-carbon bond is formed when two molecules of aldehydes (particularly benzaldehyde) reacts with each other to form a condensed product called **Benzoin**.

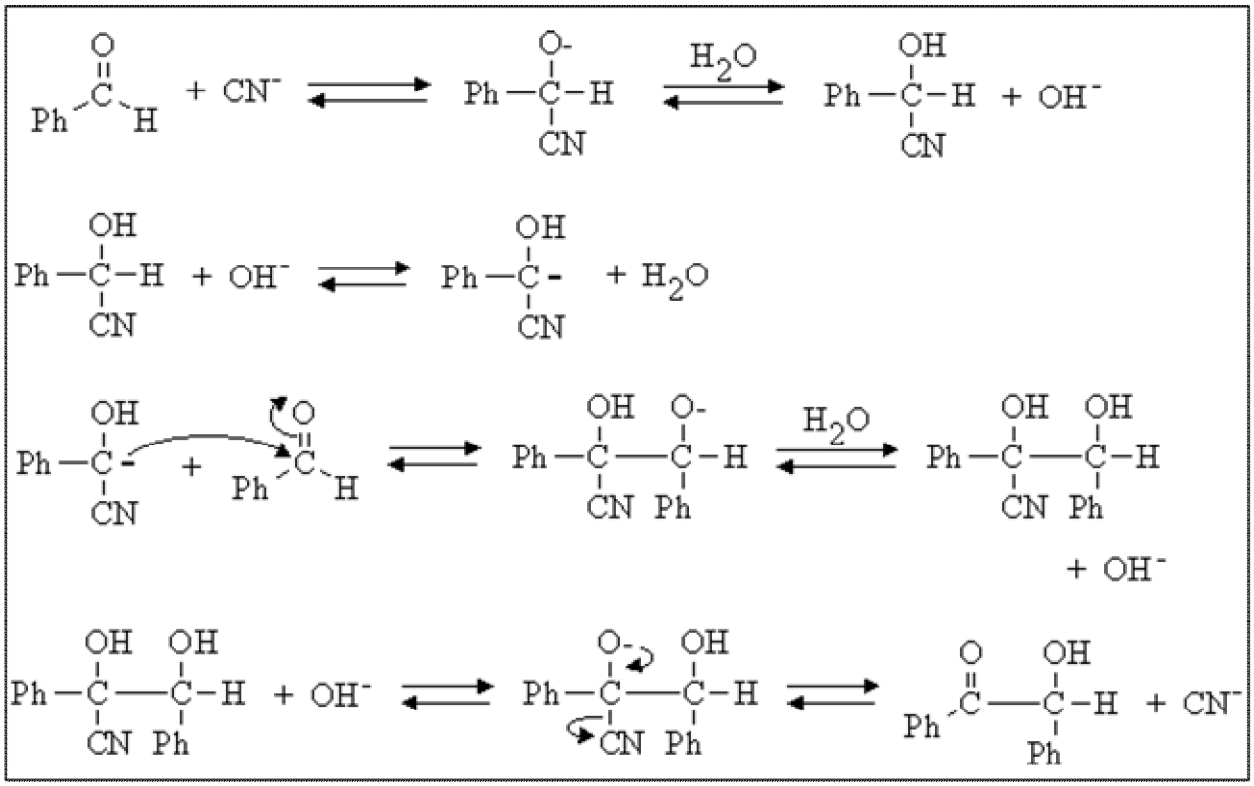
This reaction is named after ***Friederich Woehler*** and ***Justus von Liebig*** in 1832.

This reaction is catalyzed by **cyanide ions**.

- When 2 moles of aromatic aldehydes react in the presence of KCN, an alpha hydroxyl ketone is obtained



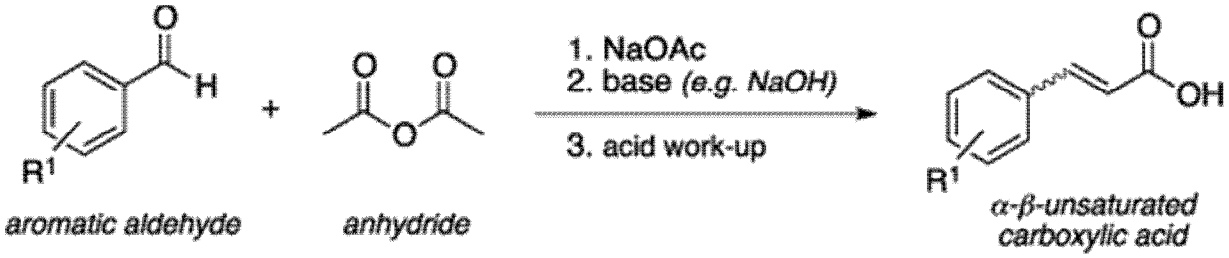
Reaction Mechanism :

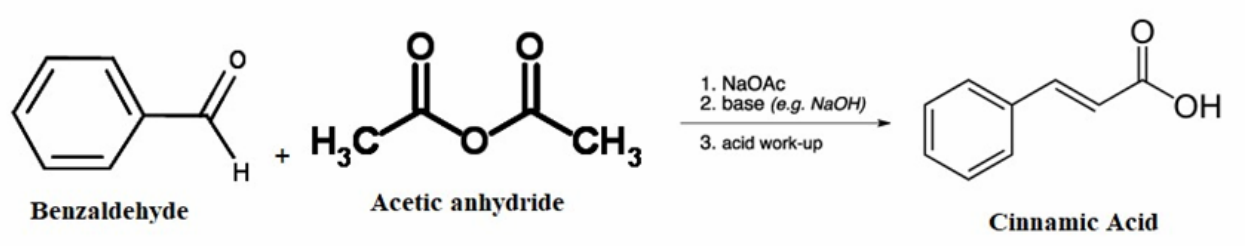


Perkin condensation :

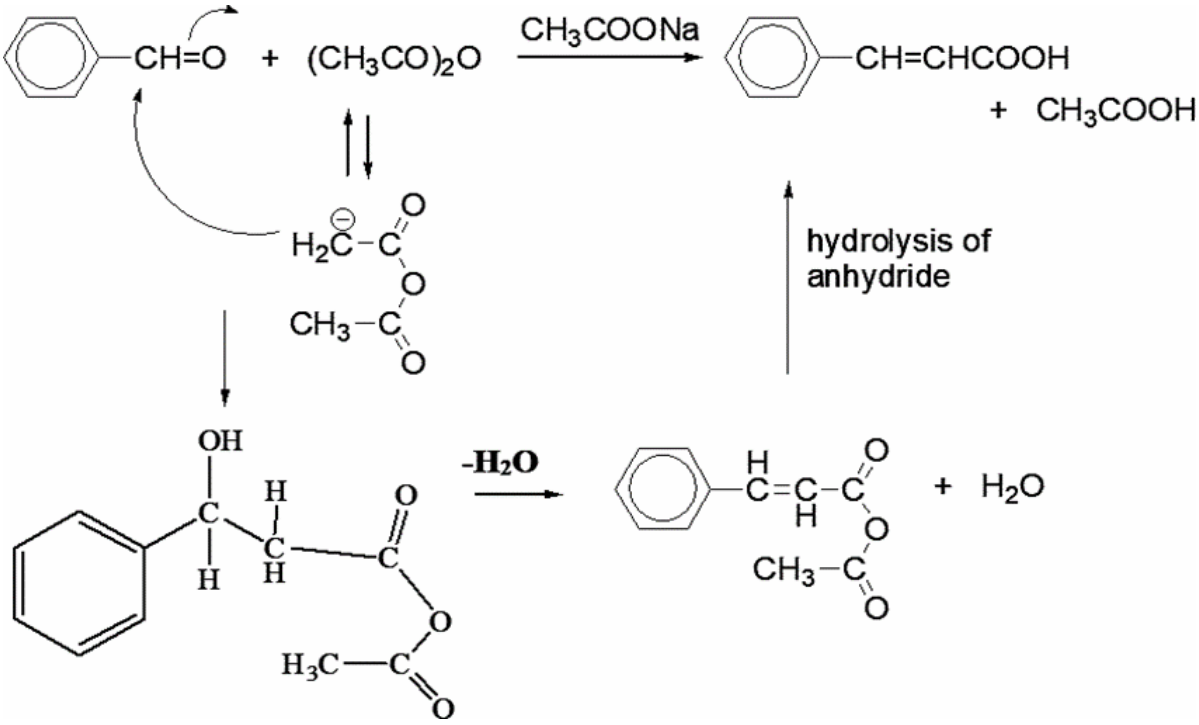
The Perkin reaction is an organic reaction used to convert an aromatic aldehyde and an anhydride to anα,β-unsaturated carboxylic acid using sodium acetate, a base, and an acid work-up.

The Perkin reaction is an organic reaction developed by ***Sir William Henry Perkin*** that is used to make **cinnamic acids**.



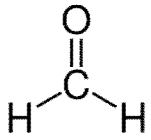


Reaction Mechanism :



Structure and uses :

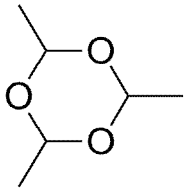
Formaldehyde :



Uses :

- Used in the production of resins, principally urea -formaldehyde and phenol-formaldehyde, which are used to make cores and moulds for foundries.
- Used in agriculture and medicine where it is used as a disinfectant, fungicide, fumigant and preservative.
- Formaldehyde is used to produce a wide array of products, particularly building materials.

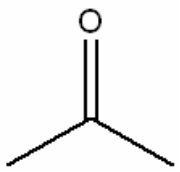
Paraldehyde :



Uses :

- Paraldehyde is used to treat certain convulsive disorders.
- It also has been used in the treatment of alcoholism and in the treatment of nervous and mental conditions to calm or relax patients who are nervous or tense and to produce sleep.
- This medicine has generally been replaced by safer and more effective medicines for the treatment of alcoholism and in the treatment of nervous and mental conditions.

Acetone :



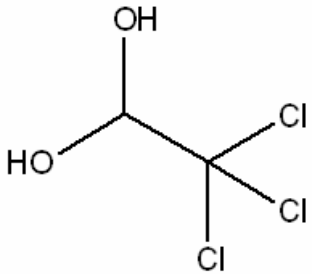
Uses :

- It is used as a solvent for synthetic fibres and plastics
- It is used as a precursor for methyl methacrylate
- It is used to prepare metal before painting
- It is used in pharmaceutical industries in some drugs
- It is volatile and hence used in the laboratory to rinse lab glassware
- It is used as a drying agent
- It is used in the defatting process
- It is used in cosmetics such as nail polish remover

It is used in the treatment of acne

Chloral hydrate :

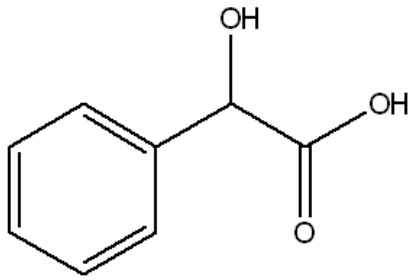
Structure :



Uses :

- As a sedative and hypnotic
- Chloral hydrate can also serve as a precursor for other chemicals.
- A key component of Hoyer's mounting medium (used for observing organisms through a microscope mounted on slides) and a clearing agent of chitin (and fibers) have also been found to be useful.

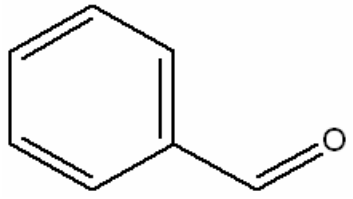
Hexamine :



Uses :

- The mandelic acid salt is used for urinary tract infection treatments, and it decomposes at an acidic pH to produce ammonia, and formaldehyde, which is bactericidal, which the mandelic acid adds to this effect. The use of this compound was temporarily reduced in the late 1990s, because of the adverse effects, specifically because of the chemically-induced hemorrhagic cystitis in the case of overdose.
- Hexamine is considered to be suitable for the long-term prophylactic urinary tract infection treatments. Hexamine should not be used in chronic kidney disease presence. Hexamine is used in the treatment of concomitant odor and excessive sweating.
- Since the mandelic acid salt (which is a generic methenamine mandelate, USP) is used for urinary tract infection treatments, it decomposes at an acidic pH to produce ammonia, and formaldehyde is bactericidal; which the mandelic acid adds to this effect. Typically, urinary acidity is ensured by co-administering ammonium chloride or vitamin C (otherwise an ascorbic acid).
- This compound's usage had temporarily been reduced in the late 1990s because of the adverse effects, specifically chemically-induced hemorrhagic cystitis in the case of overdose. However, currently, its use has been re-approved due to the prevalence of antibiotic resistance to drugs, which are more commonly used. This drug is especially suitable for long-term prophylactic urinary tract infection treatments because the bacteria do not develop resistance to formaldehyde. Also, it should not be used in chronic kidney disease presence.
- In the form of spray and creams, hexamine is successfully used for the treatment of concomitant odor and excessive sweating with the medical citation.

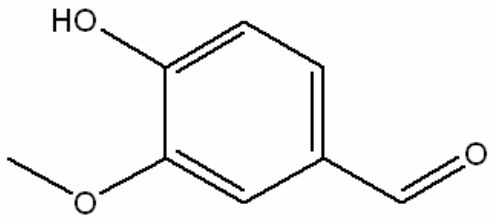
Benzaldehyde :



Uses :

- The most common use of benzaldehyde is to provide almond flavouring to items. It is used in food and beverages to provide the scent of almonds. Various scented products also use benzaldehyde as an additive for having a distinct odour.
- The industrial usage of benzaldehyde is that it acts as an intermediate in the production of several organic compounds. It is a precursor to various chemical additives, plastics, and pharmaceutical products.
- Another significant use of the odour of benzaldehyde is as a bee repellent. It is used to draw the bees away from a honeycomb in order to extract the honey from these structures.
- Some cosmetic products and personal care products also contain benzaldehyde.
- Benzaldehyde is also used in the production of dyes (acridine and aniline dyes), soaps, and perfumes.
- It is also used in cakes and baked goods as almond extract. Benzaldehyde is also used in additives like antibacterial and antifungal preservatives.
- It is an intermediary product in the formation of compounds like cinnamic acid, benzoic acid, etc.
- It is used as a solvent for oils, resins, ethers, etc

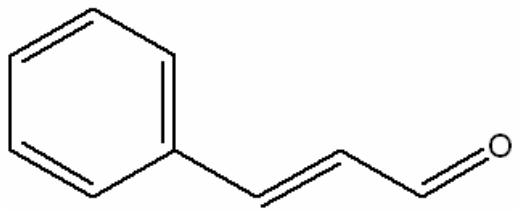
Vanillin :



Uses :

- The largest use of vanillin is as a flavoring, usually in Sweet foods. The ice cream and chocolate industries together comprise 75% of the market for vanillin as a flavoring, with smaller amounts being used in confections and baked goods.
- Vanillin is also used in the fragrance industry, in perfumes, and to mask unpleasant odors or tastes in medicines, livestock fodder, and cleaning products. It is also used in the flavor industry, as a very important key note for many different flavors, especially creamy profiles such as cream soda.
- Additionally, vanillin can be used as a general-purpose stain for visualizing spots on thin-layer chromatography plates. This stain yields a range of colors for these different components.
- Vanillin-HCl staining can be used to visualize the localisation of tannins in cells.
- Vanillin is becoming a popular choice for the development of bio-based plastics

Cinnamaldehyde :



Uses :

therapeutic uses : Many of the health benefits of Cinnamon and its effect on metabolism is due to the presence of Cinnamaldehyde in it. It helps to fight against tooth decay and bad breath and so the herb of Cinnamon is used for enhancing oral health. The antifungal and antibacterial property of Cinnamaldehyde helps to reduce infections.

As an anti-bacterial and anti-fungal agent : Cinnamaldehyde exhibit anti-microbial activity. The antimicrobial nature of Cinnamaldehyde was proved by the study conducted at the University of Illinois, Chicago. It had been found that Cinnamaldehyde prevents above 50% of the bacterial growth in the oral cavity. It is especially effective for preventing the growth of bacteria and other pathogens in the tongue.

Anti-diabetic property : Since the primordial times, Cinnamon has been used to treat diabetes in China and in India. The anti-diabetic nature of Cinnamon is due to the presence of cinnamaldehyde. According to a study conducted on the streptozotocin(STZ) induced male diabetic wistar rats, it had been found that by administering Cinnamaldehyde at different doses, it had considerably reduced the plasma glucose level and simultaneously increased the plasma insulin level.

As a flavoring agent : Cinnamaldehyde is mainly added to foods and medicines to enhance its quality in terms of aroma and taste. It is used as a flavoring agent in liquid refreshments, ice-creams, chewing gums and candy. It is also used in perfumes to recreate the magic of fruity and interesting fragrance ranges.

Insecticide and Mosquito repellent : Cinnamaldehyde is an effective animal repellent, which is used to repel animals like cats and dogs. It is also used as an efficient insecticide for mosquitoes. It had been found that about half of Aedes aegypti mosquito larvae are killed by an amount of 29 ppm of cinnamaldehyde in 24 hours.

CHAPTER 6

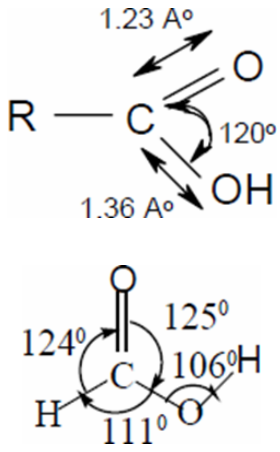
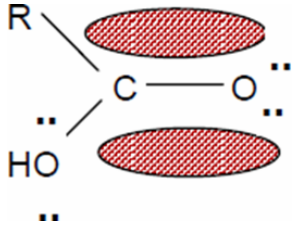
Carboxylic acids

The carboxyl functional group is represented as –COOH and is the end product of alcohol oxidation.

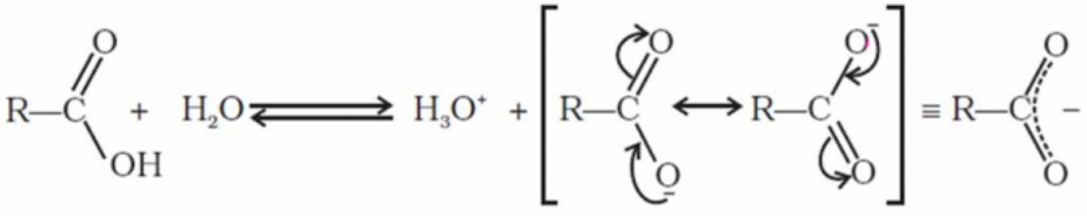
The term carboxylic acid is little special in the sense that it represents two functional groups; first a carbonyl group and second hydroxyl group. One can say that in the carboxyl group a hydroxyl group is bonded to a carbonyl (>C = O) group. It is often represented as CO2H or COOH.

Carboxylic acids have been found to constitute one of the most frequently encountered classes of organic compounds. A large number of natural products are either carboxylic acid derivatives or are derived from them.

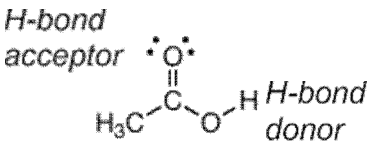
The structure of the most stable conformation of formic acid is shown below. The entire molecule is approximately planar. The sp2 hybrid carbonyl carbon atom is planar, with nearly trigonal bond angles. The O-H bond also lies in this plane, eclipsed with the C=O bond.

Molecular Structure of carboxylic acid	***Orbital diagram of carboxylic acid***
	

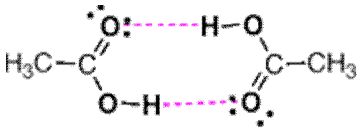
Carboxylic acids dissociation water to form *carboxylate ion* and *hydronium ion*. The carboxylate ion formed is stabilized through resonance by effective delocalization of the negative charge.



Carboxylic acids exist as hydrogen bonded dimers.



acetic acid



Acidity of Carboxylic Acids :

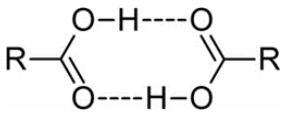
Carboxylic acids act as both hydrogen bond acceptors, due to the carbonyl group, and hydrogen bond donors, due to the hydroxyl group.

As a result, they often participate in hydrogen bonding.

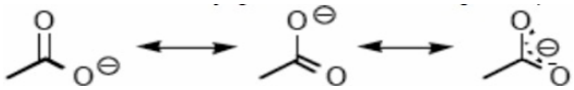
Carboxylic acids usually exist as **dimeric pairs** in nonpolar media because of their tendency to **"*self associate*."** This tendency to hydrogen bond gives them increased stability as well as higher boiling points relative to the acid in aqueous solution.

Carboxylic acids are polar molecules; They tend to be soluble in water, but as the alkyl chain gets longer, their solubility decreases due to the increasing hydrophobic nature of the carbon chain.

Carboxylic acids are characterized as weak acids, meaning that they do not fully dissociate to produce **H+** cations in a neutral aqueous solution.



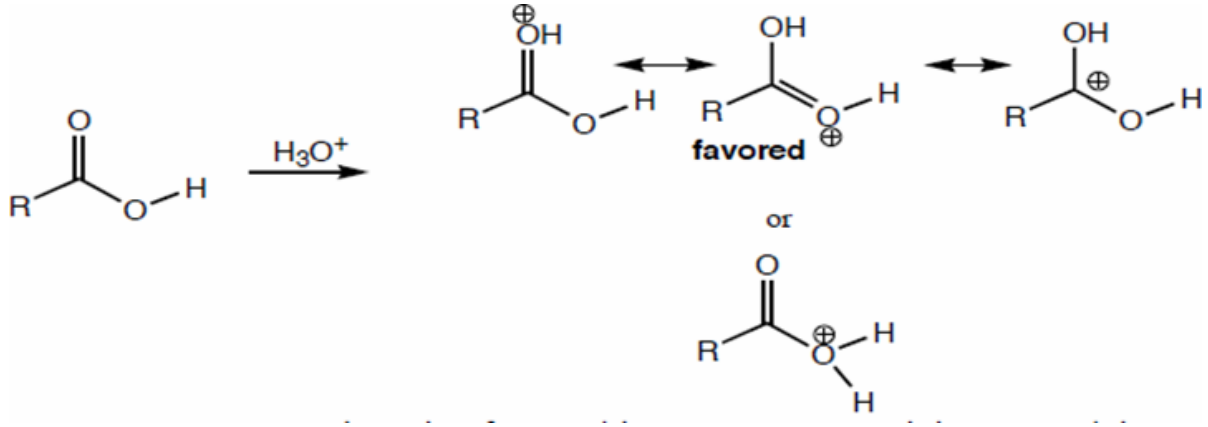
Carboxylic acids have one property that distinguishes them from most other organic compounds – they're acidic. Now not as acidic as fuming sulfuric acid, but still pretty darned acidic. The acidity of these compounds arises from the resonance stabilization of the conjugate base (bond lengths equalize):



Carboxylic acids undergo hydrogen bonding much like alcohols. However, in a carboxylic acid you have both a hydrogen bond donor and acceptor in the same molecule. These acids thus form highly stable dimers (as shown below). For small acids (e.g. acetic acid) this dimer cannot even be broken down by distillation

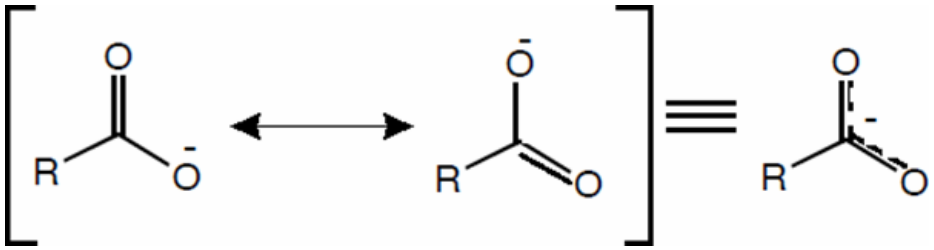
The acidity of these compounds can be modified by changing the substituents on the alkyl portion of the acid. Electron withdrawing groups make the molecule more acidic (by stabilizing the negative charge on the conjugate base), while electron-donating groups make it less acidic, by destabilizing that same charge.

Protonation :

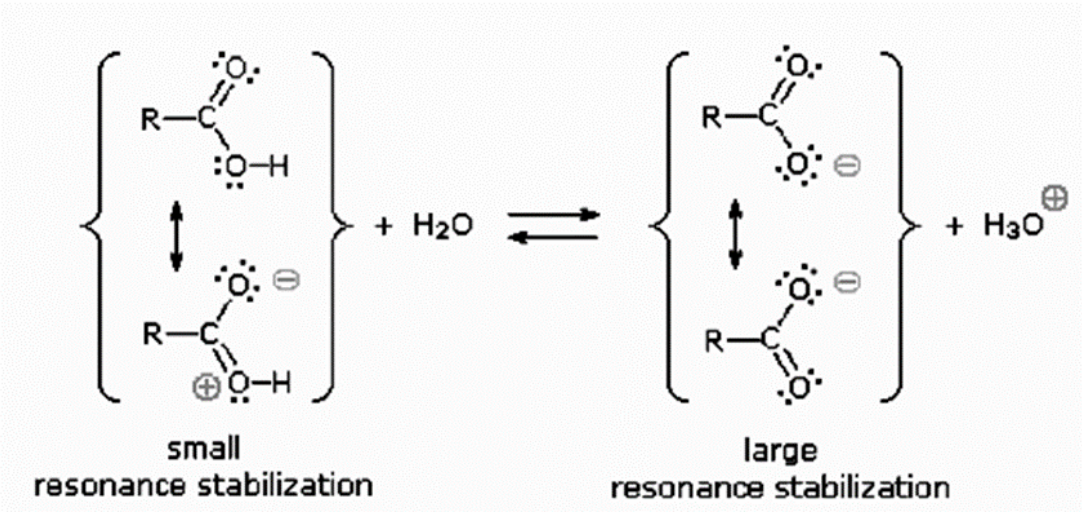


Factor that determine the strength of an acid :

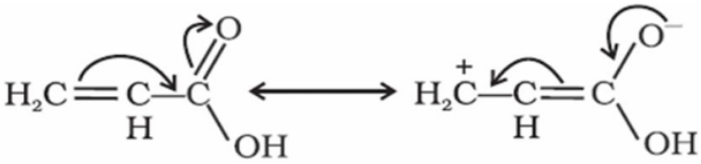
Resonance Stabilization:



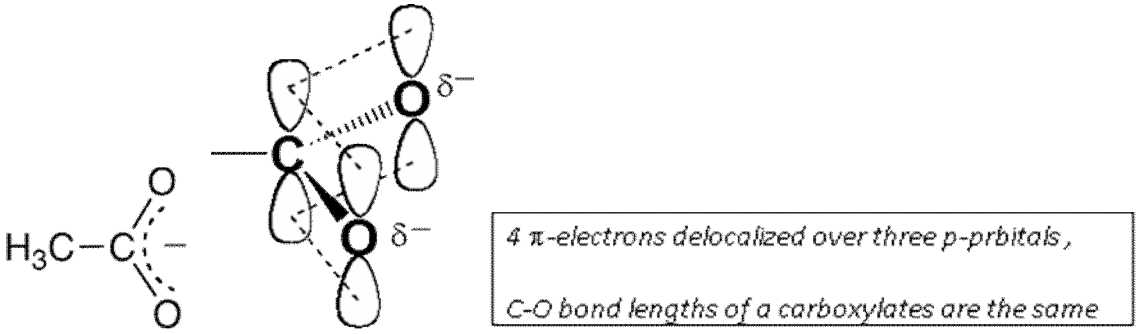
- The Ethanoate ion is strongly stabilized by two equivalent resonance structures.
- Both the carboxyl group and the carboxylate anion are stabilized by resonance, but the stabilization of the anion is much greater than that of the neutral function. In the carboxylate anion the two contributing structures have equal weight in the hybrid, and the C–O bonds are of equal length (between a double and a single bond). This stabilization leads to a markedly increased acidity.



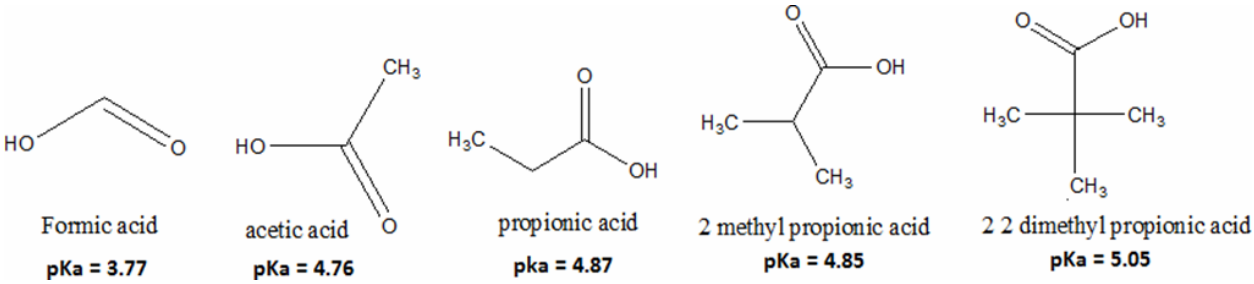
- Due to the resonance effect, phenyl or vinyl groups too, increase the acidity of carboxylic acids in spite of decreasing the acidity due to induction effect.



- Resonance stabilization of the carboxylate ion

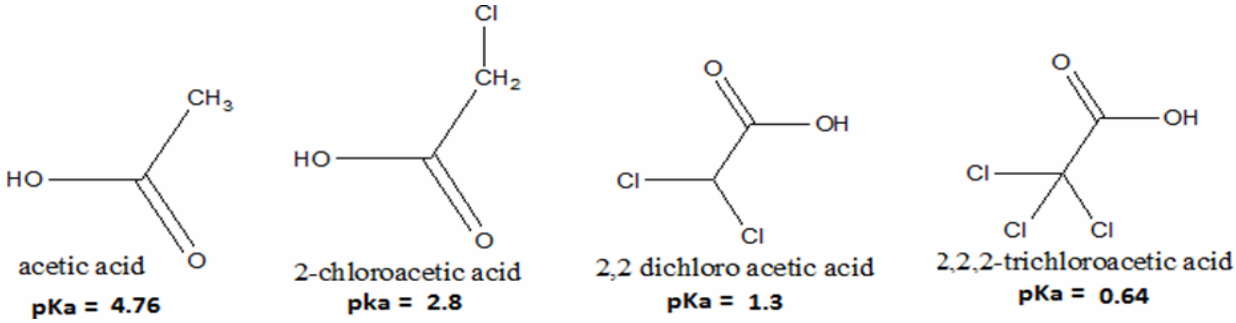


Electron Donating Groups :



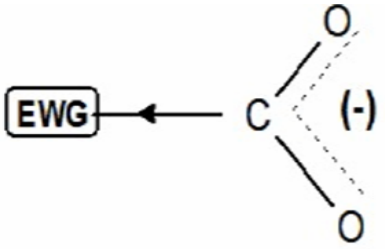
- Alkyl groups are electron donating. They tend to "push" electron away from themselves. This increase the electron density in the O-H bond. The H-atom is more strongly attached to the O-atom. It is less likely to leave. So the acid is weaker.

Electron Withdrawing Groups :

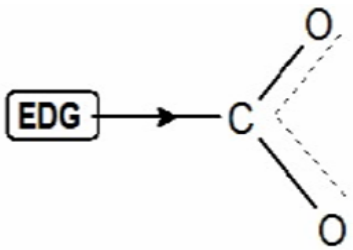


- Electron withdrawing groups increase the acidity of an organic acid.
- An electronegative atom like Cl-atom can pull electron density towards itself. This decrease the electron density in the O-H bond. The H-atom is less strongly attracted to the O-atom. It is more likely to leave, so the acid is stronger.

- The more Cl-atom attach, the stronger the acid becomes.



Electron withdrawing group stabilises the carboxylate ion by dispersing the negative charge and hence increases the acidity of the carboxylic acid



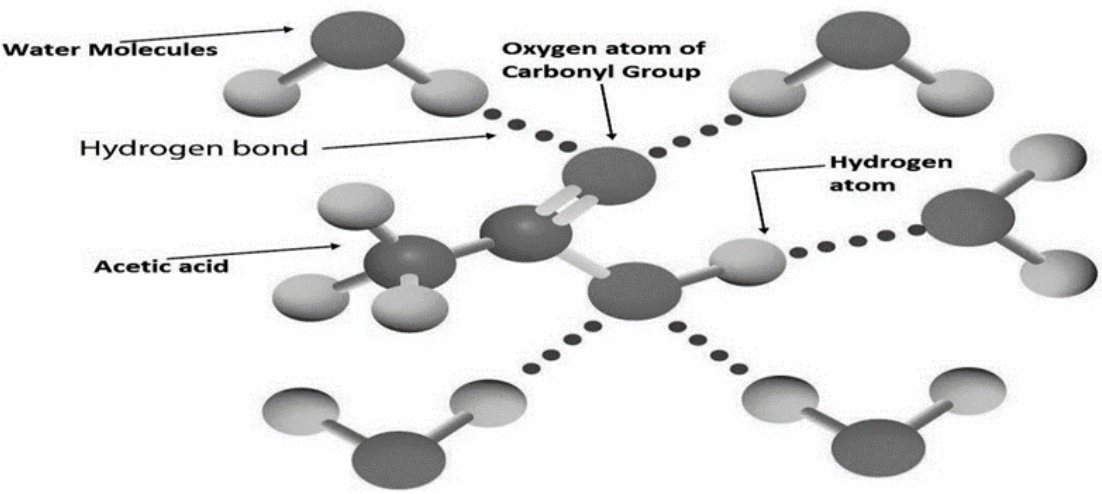
EDG destabilises the carboxylate ion by intensifying the negative charge and hence decreases the acidity of the carboxylic acid

- Atomic radius affect the strength of an acid: Greater the atomic radius, stronger is the acid.
- If the distance between the two nucleuses is more less is the attractive forces between the nucleus and the electrons of the other atom.
- Less the attractive force, less stronger is the bond and if this bond is with the hydrogen then hydrogen is held with less strength, so it can be removed easily.

Solubility & Appearance of Carboxylic Acid :

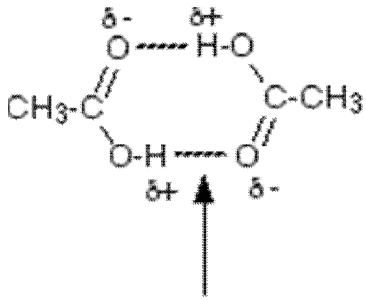
- Many carboxylic acids are colorless liquids with disagreeable odours. The carboxylic acids with 5 to 10 carbon atoms all have “goaty” odours.
- These acids are also produced by the action of skin bacteria on human sebum (skin oils), which accounts for the odour of poorly ventilated locker rooms.
- The acids with more than 10 carbon atoms are wax like solids, and their odour diminishes with increasing molar mass and resultant decreasing volatility.
- Carboxylic acids exhibit strong hydrogen bonding between molecules. They therefore have high boiling points compared to other substances of comparable molar mass.
- The carboxyl group readily engages in hydrogen bonding with water molecules. The acids with one to four carbon atoms are completely miscible with water. Solubility decreases as the carbon chain length increases because dipole forces become less important and dispersion forces become more predominant.
- The solubility of the bigger acids decreases very rapidly with size. This is because the longer **hydrocarbon *"tails"*** of the molecules get between water molecules and break hydrogen bonds. In this case, these broken hydrogen bonds are only replaced by much weaker van der Waals dispersion forces.
- **Hexanoic acid** [CH3(CH2)4COOH] is barely (narrowly) soluble in water (about 1.0 g/100 g of water).

  Palmitic acid [CH3(CH2)14COOH], with its large nonpolar hydrocarbon component, is essentially insoluble in water.



Boiling Points of Carboxylic Acid :

- The boiling points of alcohols are higher than those of alkanes of similar size because the alcohols can form ***hydrogen bonds*** with each other as well as ***van der Waals dispersion forces*** and ***dipole-dipole interactions***.
- Similarly the boiling points of the carboxylic acids are still caused by hydrogen bonding, but operating in a different way.
- In a pure carboxylic acid, hydrogen bonding can occur between two molecules of acid to produce a dimer.



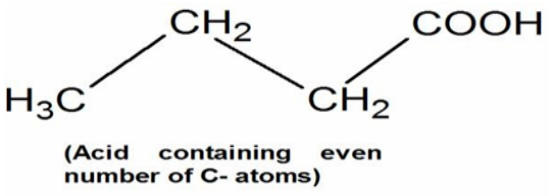
Hydrogen bond between the fairly positive hydrogen atom and a lone pair on the fairly negative oxygen atom.

This immediately doubles the size of the molecule and so increases the *van der Waals dispersion forces*between one of these dimers and its neighbours - resulting in a high boiling point.

Melting Points of Carboxylic Acid :

- In the first ten members of the homologous series, the 'alternation effect' is observed.
- The effect implies that the melting point of an acid with even number of carbon atoms is higher than with odd number of carbon atoms above whereas no such effect is observed in homologues with more than ten carbons.

- The alternation effect is due to the fact that in the carboxylic acids with even number of carbon atoms, the terminal methyl group and carboxylic group are on the opposite side of the zig-zag carbon chain. Hence they fit better in the crystal lattice and it results in stronger intermolecular forces.



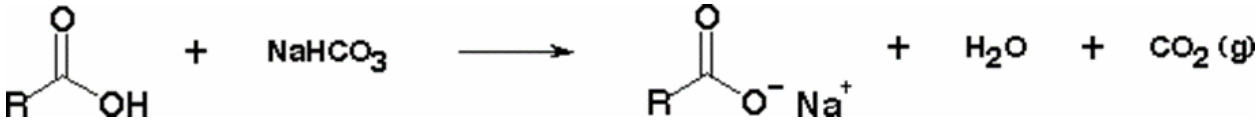
On the other hand, in acids with **odd number of C-atoms**, **the carboxyl and terminal methyl groups** are on the same side of the carbon chain. Hence the molecules fit poorly in the **crystal lattice**, because of their being relatively unsymmetrical. So the intermolecular forces are weak and the melting points are relatively lower.

Qualitative tests for Carboxylic Acids and Amide :

Test for Carboxylic Acids :

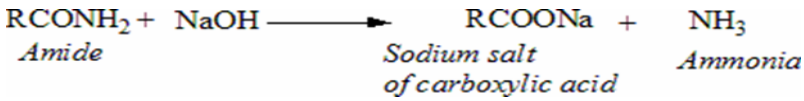
- ***Procedure :*** A few drops or a few crystals of the unknown sample are dissolved in 1mL of methanol and slowly added to 1 mL of a saturated solution of sodium bicarbonate.
- ***Positive Test :*** Evolution of a carbon dioxide gas is a positive test for the presence of the carboxylic acid and certain phenols listed in the Complications section.

Reaction

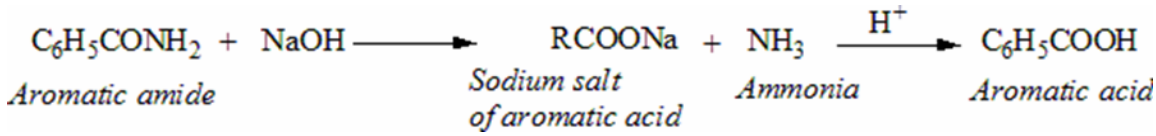


Test for Amides :

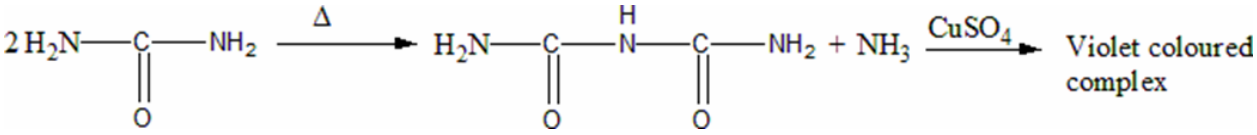
Reaction of NaOH: Amides are decomposed by NaOH to evolve ammonia. The gas can be tested by a moist red litmus paper which is then turned blue



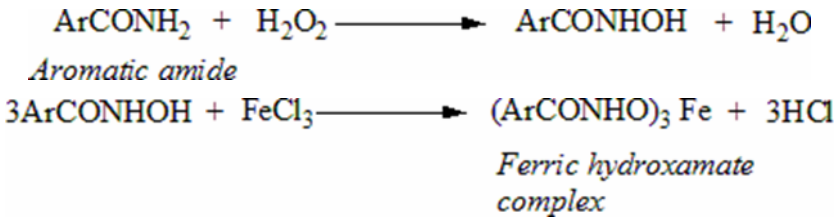
Alkaline hydrolysis of aromatic amides to aromatic acid: The soluble sodium salt of aromatic acid formed from aromatic amides upon hydrolysis is regenerated as white precipitate in acidic medium.

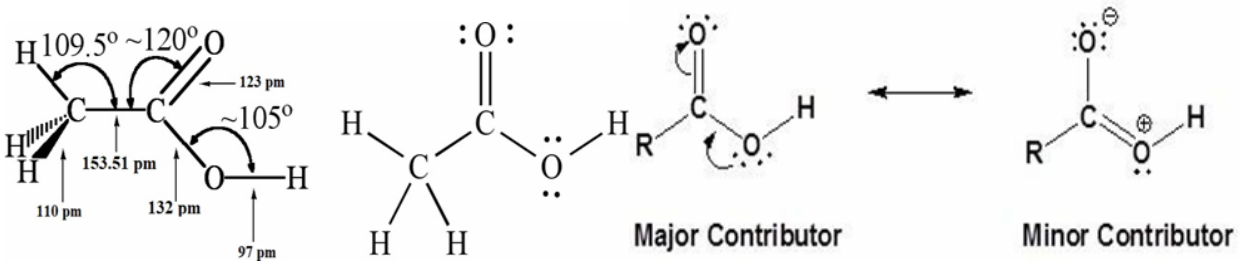


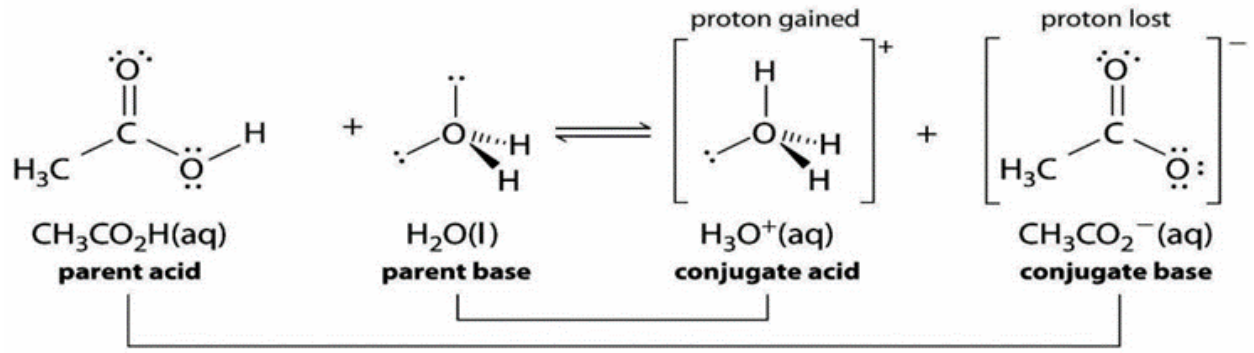
Biuret Reaction for aliphatic diamide: When aliphatic diamide is heated at a temperature above its melting point, ammonia is evolved and crystalline biuret is formed. This biuret in alkaline medium gives a violet colour with a drop of copper sulphate solution.



Hydroxamic acid test for aromatic primary amides: Hydrogen peroxide reacts with aromatic primary amides to form the hydroxamic acid, which then reacts with ferric chloride to form ferric hydroxamate complex having a violet colour.

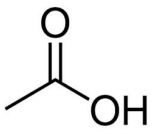






Structure and Uses :

Acetic Acid :



- Acetic acid is a colourless liquid organic compound with the chemical formula CH_3COOH or CH_3CO_2H or $C_2H_4O_2$.
  - When undiluted, it is sometimes called glacial acetic acid.

- Vinegar is roughly 3–9% acetic acid by volume, making acetic acid the main component of vinegar apart from water. Acetic acid has a distinctive sour taste and pungent smell. In addition to household vinegar.

Uses :

- Industrial chemical, used primarily in the production of cellulose acetate for photographic film, polyvinyl acetate for wood glue, and synthetic fibres and fabrics.
- The major esters of acetic acid are commonly used as solvents for inks, paints and coatings.
- In households, diluted acetic acid is often used in descaling agents.
- In the food industry, acetic acid is used as food additive.

Medicinal Uses :

Acetic acid injection into the tumor has been used to treat cancer since the 1800s.

While diluted acetic acid is used in Iontophoresis.

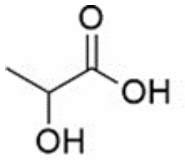
As a treatment for otitis externa.

It is an effective antiseptic when used as a 1% solution, with broad spectrum of activity against streptococci, staphylococci, pseudomonas, enterococci etc.

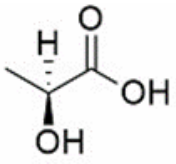
Lactic Acid :

Lactic acid is an organic compound with the formula CH3CH(OH)COOH.

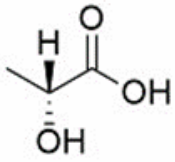
In its solid state, it is white and water-soluble. In its liquid state, it is colorless. It is produced both naturally and synthetically. With a hydroxyl group adjacent to the carboxyl group, lactic acid is classified as an alpha- hydroxy acid (AHA). In the form of its conjugate base called lactate, it plays a role in several biochemical processes.



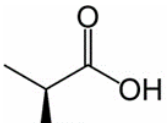
Lactic acid



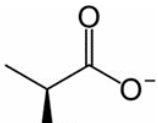
(+)-Lactic acid



(-)-Lactic acid



Lactic acid



Lactate

Uses :

In Pharmaceutical and cosmetic :

- Lactic acid is also employed in pharmaceutical technology to produce water-soluble lactates from otherwise-insoluble active ingredients.
- It is use in topical preparations and cosmetics to adjust acidity and for its disinfectant and keratolytic properties.
- It is also used as buffer.

In Food uses :

- Lactic acid can be used in meat, poultry and fish in the form of sodium or potassium lactate to extend shelf life, control pathogenic bacteria.
- Because of its mild taste, lactic acid is used as an acidity regulator in beverages such as soft drinks and fruit juices.
- Lactic acid is effective in preventing the spoilage of olives, gherkins, pearl onions and other vegetables preserved in brine.
- Lactic acid may be also used as a preservative in salads and dressings, resulting in products with a milder flavour while maintaining microbial stability and safety.

In Detergents :

- It is a good descaler, soap-scum remover, and a registered anti-bacterial agent.

In Mosquito lure :

- Lactic acid, along with ammonium bicarbonate, is used in the Lurex brand mosquito attractant.

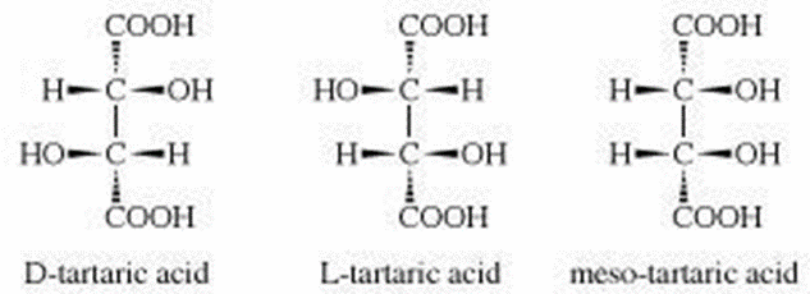
Tartaric Acid :

Tartaric acid is a white crystalline organic acid that occurs naturally in many fruits, most notably in grapes, but also in bananas, tamarinds and citrus.

Its salt, potassium bitartrate, commonly known as cream of tartar.

It is commonly mixed with sodium bicarbonate and is sold as baking powder used as a leavening agent in food preparation.

The acid itself is added to foods as an antioxidant and to impart its distinctive sour taste.



Uses :

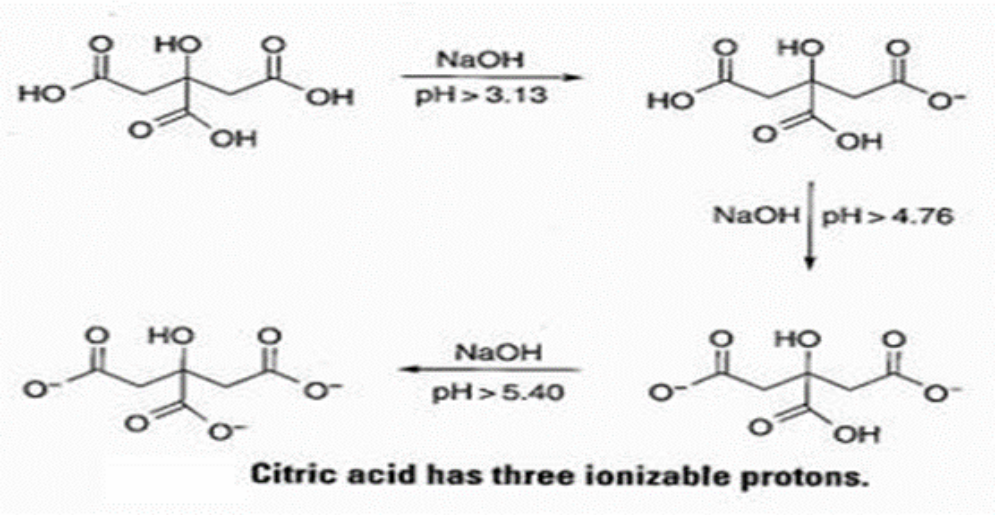
- Tartaric Acid is used for ***Antiscorbutic*** and ***Antiseptic***.
- It has been used in the production of effervescent salts, in combination with citric acid, to improve the taste of oral medications.
- Tartaric acid is a great source of ***antioxidants***.
- Another health benefit of tartaric acid is that it aids digestion and fights ***flatulence***. It improves intestinal absorption as well which will increase the rate at which healthy nutrients flow into your bloodstream.
- One of the most surprising benefits of tartaric acid is that it significantly improves ***glucose intolerance***.

- Salt of Tartaric acid like Potassium sodium tartrate, also known as **Rochelle salt** which is used as ***Saline (Osmotic) Cathartics***.

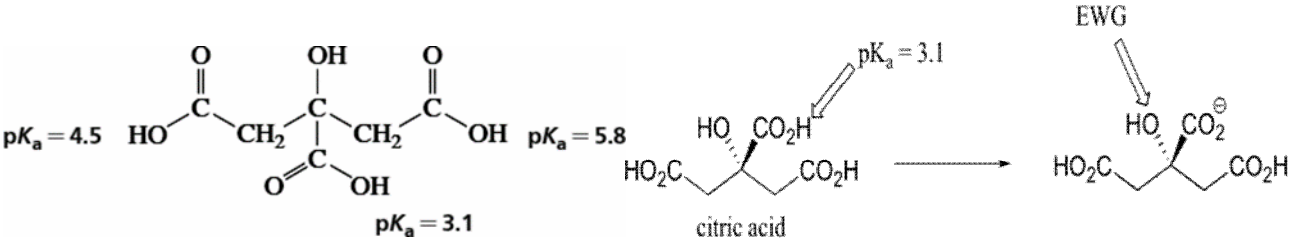
Citric Acid :

Citric acid is a weak organic acid that has the chemical formula C6H8O7

Citric acid is **Polyprotic acids** are capable of donating more than **one proton**



It occurs naturally in citrus fruits. In biochemistry, it is an intermediate in the **Citric Acid Cycle**, which occurs in the metabolism of all aerobic organisms.



In Citric acid the middle acid group that has the lowest pKa. This is because the hydroxyl group also bonded to the middle carbon is electron-withdrawing by induction, and a negative charge associated with a conjugate base will be stabilized to the greatest extent on the middle carboxylate.

Uses :

- Citric acid powder is used as a food preservative, added to beverages and pharmaceutical products and To Prevent Sugar Crystallizing
- It has a tangy taste which makes it as a flavouring ingredient for candy and beverages.
- It is also an antioxidant, which makes it a favourable product to be used in skin care products.
- Citric acid is a type of alpha-hydroxy acid (AHA), making it a good agent to remove dead skin cells and exfoliate the skin.
- It is important for producing energy that keeps you active and healthy and is safe for human consumption.Also, its alkaline nature helps to balance the acid levels in the body.

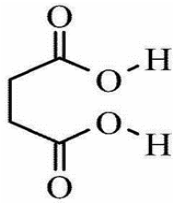
- It is used in the canning process as it helps to maintain a healthy pH balance inside the foods and helps to prevent botulism (a harmful form of food poisoning).
- Citric acid can also be used as a mouth rinse.
- Citric acid combined with other ingredients can make up a very good anti-aging face mask.
- Citric acid has alkalizing properties which help to bind calcium and therefore preventing the formation of kidney stones. It also helps to keep the kidneys in a proper functioning state.

Succinic Acid :

- Succinic acid is a dicarboxylic acid with the chemical formula $(CH_2)_2(CO_2H)_2$.
- The name derives from Latin ***succinum***, meaning ***amber***.
- Succinate can exit the mitochondrial matrix and function in the cytoplasm as well as the extracellular space, changing gene expression patterns.

  As a diprotic acid, succinic acid undergoes two successive deprotonation reactions and The pKa of these processes are 4.3 and 5.6.

Succinic Acid :



Uses :

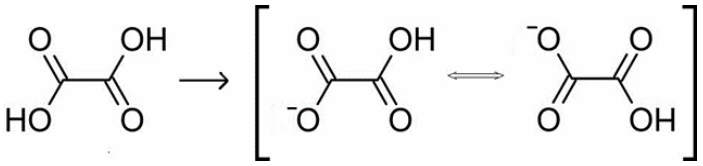
- Succinic acid regulates ***cardiomyocyte***. It means that it's helps the heart pump blood properly. This is good for people suffering from a cardiovascular disorder. Succinic acid has even been known to help prevent heart attacks.
- Succinic acid is used as an acidity regulator and pH regulator in food.
- Succinic Acid can be used as an excipient.
- Succinic Acid can be used as **Masking Buffering** in Cosmetics and personal care products.
- The analgesic properties make succinic acid a great remedy for many ailments. Reducing irritability and preventing menopause, succinic acid has played a key role in healing and providing pain relief.

Oxalic Acid :

Oxalic acid is an organic compound with the formula C2H2O4. It is a colorless crystalline solid that forms a colorless solution in water. Its condensed formula is HOOCCOOH, reflecting its classification as the simplest dicarboxylic acid.

Its acid strength is much greater than that of acetic acid.

Oxalic acid is a reducing agent and its conjugate base, known as oxalate (C2O2−4), is a chelating agent for metal cations. Typically, oxalic acid occurs as the dihydrate with the formula C2H2O4·2H2O.



Uses :

- ***As a Cleaning Agent:*** The oxalic acid is an ideal chemical for cleaning purposes. Its bleach-like qualities make it perfect for sterilizing household items.
- ***For Industrial Uses:*** This acid is sometimes used in mineral processing mechanisms. Its bleaching properties can be used to sterilize equipment in a number of corporate environments. Textile mills and factories use it for bleaching in order to color cloths.

Other Uses :

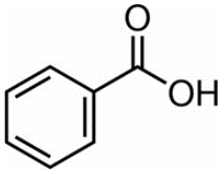
- Aside from bleaching, rust removing, and stain removing, oxalic acid is also used as a reducing agent in developing photographic film.
- It is also used in wastewater treatment as well since oxalic acid can effectively remove calcium from wastewater.
- And lastly, oxalic acid is also used as a grinding agent when polishing marble.

  Medicinal properties: Organic oxalic acid does not present any problem. In its raw form, it is one of the most important minerals needed in the body to maintain tone and peristalsis of the bowel.

  Negative effect: The negative effect of oxalic acid is that it may contribute to kidney stones. Normally, calcium and small amounts of oxalate are present in the urinary tract at the same time, but they remain dissolved and do not cause problems. Apparently, there are times when they bind to form crystals. These crystals can lead to the formation of stones, especially when oxalate is high and urine volume is low.

Benzoic Acid :

- Benzoic acid (C6H5COOH), is a colorless crystalline solid and a simple aromatic carboxylic acid.
- The name is derived from gum benzoin.



Uses :

Medicinal uses :

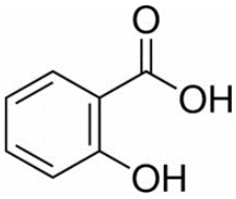
- Benzoic acid is used for the treatment of fungal skin diseases such as tinea, ringworm, and athlete's foot.
- Benzoic acid was used as an expectorant, analgesic, and antiseptic in the early 20th century.

Preservatives: **Benzoic acid and its salts are used as food preservatives**

Salicylic Acid :

Salicylic acid is a lipophilic Monohydroxybenzoic acid, a type of phenolic acid, and a beta hydroxy acid (BHA).

Salicylic acid is a compound obtained from the bark of the white willow (*Salix alba* L.; Family: Salicaceae



Uses :

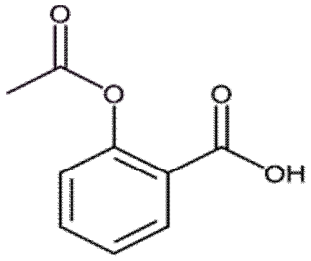
Medical uses of salicylic acid :

- It is also used to treatment of,
- ***Acne*****:** It is a skin condition characterized by red pimples on the skin, especially on the face, due to inflamed or infected sebaceous glands
- ***Psoriasis*****:** It is a skin disease marked by red, itchy, scaly patches.
- ***Seborrheic dermatitis*****:** It is a common skin condition that mainly affects your scalp. It causes scaly patches, red skin and stubborn dandruff. It can also affect oily areas of the body, such as the face, sides of the nose, eyebrows, ears, eyelids and chest.
- ***Eczema*****:** It is an inflammatory condition of the skin characterized by redness, itching, and oozing vesicular lesions which become scaly, crusted, or hardened.
- ***Viral warts*****:** It is typically small, rough and hard growths that are similar in color to the rest of the skin.
- ***Dandruff*****:** scaly white or grayish flakes of dead skin cells especially of the scalp
- ***Ringworm*****:** a contagious itching skin disease occurring in small circular patches, caused by any of a number of fungi and affecting chiefly the scalp or the feet. The commonest form is athlete's foot.
- ***Chemistry:*** Salicylic acid used for synthesis of Aspirin (acetylsalicylic acid).
- ***Other Uses:*** Salicylic acid is used as a food preservative, a bactericidal and an antiseptic.

Acetyl Salicylic Acid :

Aspirin, also known as acetylsalicylic acid (ASA), is a medication used to treat pain, fever, or inflammation.

Aspirin is also known as Nonsteroidal Anti-Inflammatory Drug (NSAID)



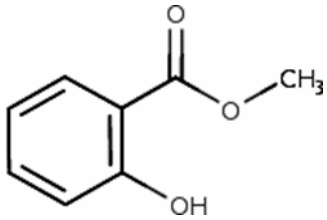
acetylsalicylic acid
(aspirin)

Uses :

- Aspirin is used in the treatment of a number of conditions, including fever, pain, rheumatic fever, and inflammatory diseases, such as rheumatoid arthritis, pericarditis, and Kawasaki disease.
- It is sometimes used to treat or prevent heart attacks, strokes, and chest pain (angina).
- Aspirin is thought to reduce the overall risk of both getting cancer and dying from cancer. This effect is particularly beneficial for colorectal cancer (CRC).

Methyl Salicylate :

- Methyl salicylate (oil of wintergreen or wintergreen oil) is an organic compound with the formula C6H4(OH)(CO2CH3).
- It is the methyl ester of salicylic acid.
- It is a colorless, viscous liquid with a sweet odor.
- It is produced by many species of plants, particularly wintergreens.
- It is also synthetically produced, used as a fragrance, in foods and beverages, and in liniments.



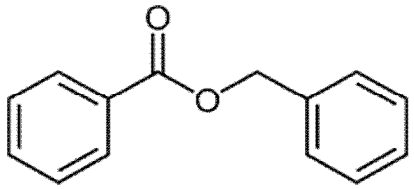
Uses :

- It is used in high concentrations as a rubefacient and analgesic in deep heating liniments
- It is used in low concentrations (0.04% and under) as a flavouring agent in chewing gum and mints.
- Methyl salicylate (oil of wintergreen) is a non-selective COX inhibitor (traditional NSAID), used to treat minor aches and pains of the muscles/joints (e.g., arthritis, backache, sprains).
- Used as Anti-inflammatory agent.
- Used as Analgesic agent.

Benzyl Benzoate :

Benzyl benzoate is a medication and insect repellent.

Benzyl benzoate was first studied medically in 1918. It is on the World Health Organization's List of Essential Medicines.



Uses :

Medical uses of Benzyl benzoate:

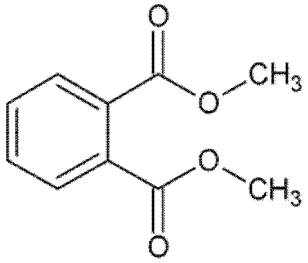
- 25%W/V Benzyl benzoate used for treating Scabies & Pediculosis (lice infestation of any part of the body).
- It has vasodilating and spasmolytic effects and is present in many asthma and whooping cough drugs.
- It is also used as an excipient in some testosterone-replacement medications for treating hypogonadism.

Non-medical uses of Benzyl benzoate:

- It is used as a repellent for chiggers, ticks, and mosquitoes.
- It is also used as a dye carrier, solvent for cellulose derivatives, plasticizer, and fixative in the perfume industry.

Dimethyl Phthalate :

Dimethyl phthalate is a methyl ester of phthalic acid



Uses :

I. Dimethyl phthalate is used as an insect repellent for mosquitoes and flies.

II. It is also an ectoparasiticide and has many other uses, including in solid rocket propellants, and plastics.

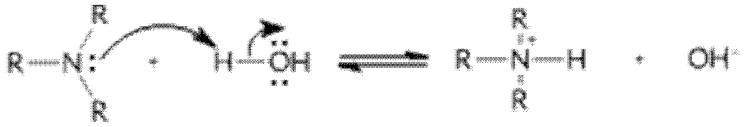
CHAPTER 7

Aliphatic amines

Basicity of Aliphatic Amines :

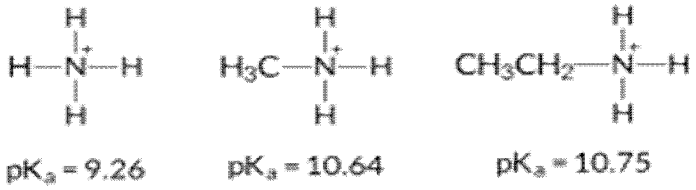
Amines can behave as Brønsted–Lowry bases by accepting a proton from the acid to form corresponding conjugate acids. Due to a lone pair of nonbonding electrons, aliphatic amines can also act as Lewis bases by forming a covalent bond with an electrophile.

To measure the basicity of amines, two conventions are generally used. The first defines *K*b as the basicity constant for the deprotonation reaction of water by the amine, as presented in Figure 1. Conventionally, lower *K*b indicates higher basicity of the amine. For example, ammonia and methylamine have basicity constants of 4.7 and 3.3, respectively.



The deprotonation of water by an amine.

The other convention correlates the basicity of the amines with the acidity of the corresponding conjugate acid. The higher the acidity constant, p*K*a, of the conjugate acid, the higher the basicity of the amine from which the conjugate acid has been formed. For example, as shown in Figure 2, the conjugate acids of ammonia, methylamine, and ethylamine have p*K*a values of 9.26, 10.64, and 10.75, respectively. This indicates the higher basicity of ethylamine, followed by methylamine and ammonia.



The p*K*a values of various amines.

Aliphatic amines are more basic than ammonia due to the electron-releasing ability of the alkyl groups attached to the N atom. The alkyl group stabilizes the conjugate acid by dispersing its positive charge; as a result, enhancing the basicity of amines. It might be anticipated that the tertiary amines, having three alkyl groups, should be more basic than the primary amines having only one alkyl group. However, this is only true in the gas phase, where we see the acidity of the conjugate acids of ammonia, methylamine, dimethylamine, and trimethylamine in the order listed below

[NH4]+ > [MeNH3]+ > [Me2NH2]+ > [Me3NH]+

Therefore, ammonia is the weakest base, and trimethylamine is the strongest base in the gas phase. However, the basicity of amines in the aqueous phase is also influenced by the solvation of the corresponding conjugate acids in water. Therefore, despite having three alkyl groups attached to the N atom, conjugate acids of tertiary amines have only one H atom to be donated for intermolecular H bonding with water. In contrast, conjugate acids of primary amines have three H atoms for intermolecular hydrogen bonding with water. Therefore, the p*K*a values of the conjugate acids of amines in an aqueous solution

$pK_a = 9.21$ $pK_a = 10.62$ $pK_a = 10.64$ $pK_a = 9.76$

The p*K*a values of conjugate acids of amines.

The conjugate acids of secondary amines enjoy an optimal balance of electron-releasing ability of alkyl groups and solvation capability with water.

Ethanolamine

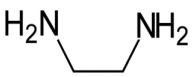
Ethanolamine (2-aminoethanol, monoethanolamine, ETA, or MEA) is an organic chemical compound with the formula $HOCH_2CH_2NH_2$. The molecule is both a primary amine and a primary alcohol (due to a hydroxyl group).

Uses :

1. It is used as feedstock in the production of detergents, emulsifiers, polishes, pharmaceuticals, corrosion inhibitors, chemical intermediates.
2. It is used as a pH regulator in cosmetics.
3. Ethanolamine is often used for Alkalinization of water in steam cycles of power plants, including nuclear power plants with pressurized water reactors.
4. Ethanolamine oleate is used to treat Esophageal Varices (dilated blood vessels inside the tissues lining the esophagus or upper part of the stomach).

Ethylenediamine :

- Ethylenediamine (abbreviated as en when a ligand) is the organic compound with the formula $C_2H_4(NH_2)_2$.
- It is a widely used building block in chemical synthesis. Ethylenediamine readily reacts with moisture in humid air to produce a corrosive, toxic and irritating mist, to which even short exposures can cause serious damage to health.
- Ethylenediamine is the first member of the so-called *polyethylene amines*.



Applications :

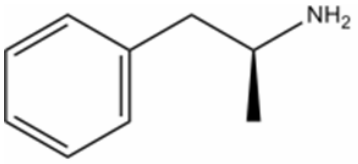
- Ethylenediamine is a most prominent derivative of ethylenediamine is the chelating agent EDTA
- Ethylenediamine is an ingredient in the common bronchodilator drug aminophylline, where it serves to solubilize the active ingredient theophylline.

  Ethylenediamine has also been used in dermatologic preparations.
- It has been used as a urinary acidifier
- Ethylenediamine used for synthesis of first-generation antihistamines drug (piperoxan).
- Ethylenediamine, because it contains two amine groups, is a widely used precursor to various polymers. Condensates derived from formaldehyde are plasticizers. It is widely used in the production of polyurethane fibers.
- It is also used as a corrosion inhibitor in paints and coolants.

Amphetamine :

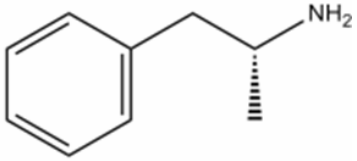
Amphetamine (alpha-methylphenethylamine) is a potent central nervous system (CNS) stimulant that is used in the treatment of attention deficit hyperactivity disorder (ADHD), narcolepsy, and obesity.

Amphetamine was discovered in 1887 and exists as two enantiomers: *levoamphetamine* and *dextroamphetamine*.



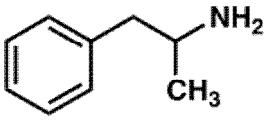
(*S*)-1-phenylpropan-2-amine

(Dextroamphetamine)



(*R*)-1-phenylpropan-2-amine

(Levoamphetamine)



Applications :

- Amphetamine is used to treat Attention Deficit Hyperactivity Disorder (ADHD), Narcolepsy (a sleep disorder), and Obesity.
- Amphetamine is used by some athletes for its psychological and athletic performance-enhancing effects, such as increased endurance and alertness.
- At therapeutic doses, amphetamine causes emotional and cognitive effects such as euphoria, change in desire for sex,