

Stereochemistry, Reaction Mechanism and Synthesis of Drug Molecules.

Introduction:

organic chemistry is based on the relationship between the structure of the molecule and its properties.

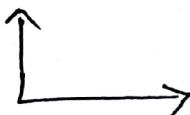
Stereo Chemistry is the branch of chemistry which deals with the structure of molecule in three dimensions and Stereo Isomerism is only a part of this branch of chemistry.

Stereo Chemistry is the study of physical, chemical and biological properties of molecules with respect to spatial arrangements of atoms or groups in a molecule in three dimensions.

- Zero dimensions.

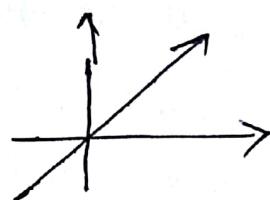
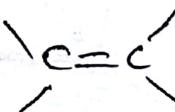
→ one dimension.

Ex: $\text{HC} \equiv \text{CH}$.



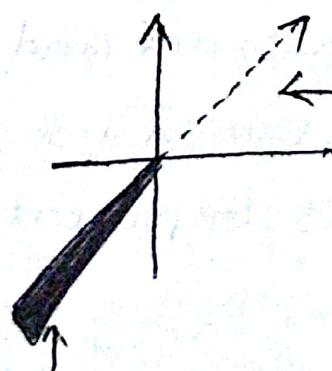
Two dimensions

Ex:



Three dimensions.

Ex:



Away from observer.

In front of the plane

Representation of 3-dimensional structures

Three-dimensional structures are represented in following 2 ways.

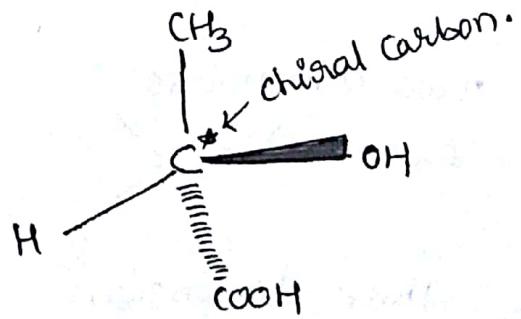
3-dimensional structures can be defined as a representation which completely describes the actual positions of various atoms of a molecule in space is called a spatial formulae (or) Three dimensional i.e. '3D structure'

3-dimensional structures are represented by following ways.

(i) Wedge Representation:

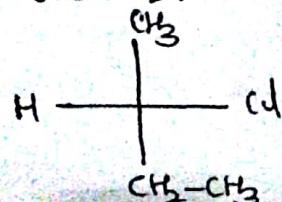
In this method, the four bonds of the chiral carbon are represented by four lines. The - thick line indicates the bond directed towards the eye of the viewer. The normal line indicates the bond that lies in +ve plane of the paper. The dotted lines (---) indicates the bonds behind the plane of the paper.

Ex:



(ii) Fischer Representation:

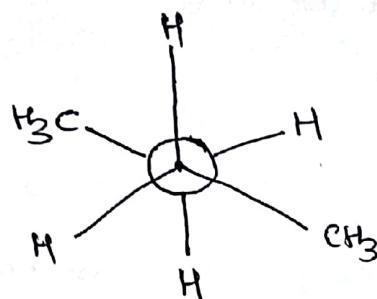
It is a simple method to give planar representation to the enantiomers. The four bonds of the chiral carbon are represented by horizontal and vertical lines. The interaction of the horizontal and vertical lines represents the chiral carbon. The horizontal lines represent bonds directed towards the viewer.



Newman Representation:

③

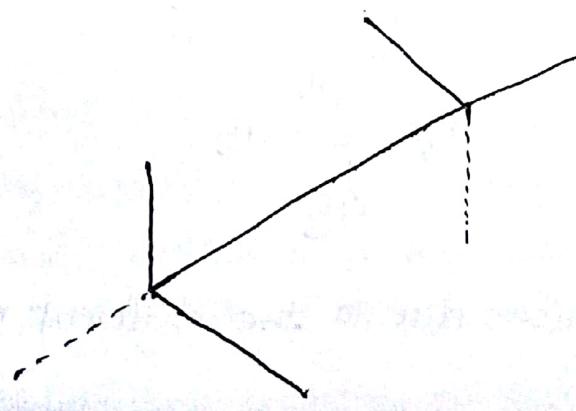
In this method, the nearer carbon is represented by a point. The three atoms or groups attached to this carbon are shown by three points radiating from this point. The other carbon atom which is situated away is represented by a circle. Its three bonds are represented by three lines radiating from the edge of the circle.



(Staggered form) = butane

Saw-horse Representation:

This is a three-dimensions representation. The two carbon atoms under consideration are taken as two points where four lines intersect. The remaining groups are indicated by lines. The bond which is connecting the two carbon atoms under consideration are considered to be in the plane of the paper. The bonds attached to these carbons projects above (or) below this plane. Thick lines represent the atoms (or) groups above the plane while dotted lines represent the atoms (or) groups below the plane.



staggered form.

Types of Isomerism:

(Compounds having same molecular formula but possess different properties (either physical or) chemical (or both) are known as isomers and the phenomenon is known as Isomerism.

Types of Isomerism:

Isomerism is of two types:

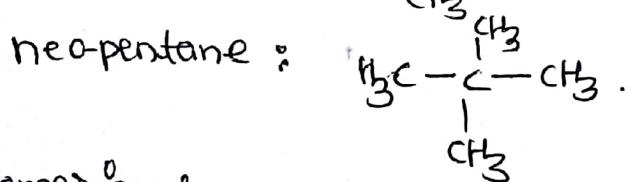
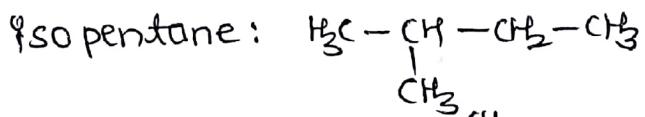
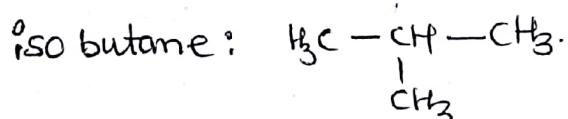
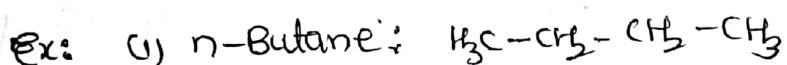
- (a) Structural isomerism
- (b) Stereo isomerism.

Structural Isomerism:

The compounds having same molecular formula but possess different structural arrangement of atoms. This difference may be due to difference in the natures of carbon chain (a) due to the position of the substituent (position isomerism) (b) due to the difference in the nature of the functional group. (functional isomerism).

i) Chain Isomerism:

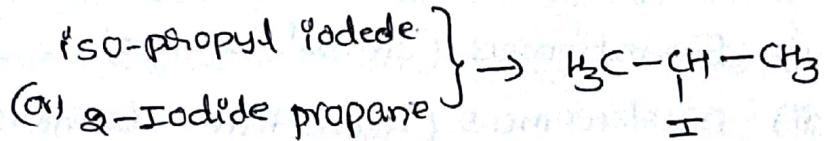
It arises due to the difference in the nature of carbon chain.



ii) Position Isomerism:

It arises due to the difference in the position of the substituent.

Ex: 1) n-propyl iodide : $\text{H}_3\text{C}-\text{CH}_2-\text{CH}_3-\text{I}$



2) 1-butene : $\text{H}_2\text{C}=\text{CH}-\text{CH}_2-\text{CH}_3$

2-butene : $\text{H}_2\text{C}-\text{CH}=\text{CH}-\text{CH}_3$

(iii) Functional Isomerism:

compounds having same molecular formula
but possess different functional groups.

Ex: 1) Ethyl alcohol - $\text{H}_3\text{C}-\text{CH}_2-\text{OH}$

Dimethyl ether - $\text{H}_3\text{C}-\overset{\text{O}}{\underset{|}{\text{C}}}-\text{CH}_3$

2) Propanaldehyde - $\text{H}_3\text{C}-\text{CH}_2-\overset{\text{O}}{\underset{|}{\text{C}}}-\text{H}$

Acetone - $\text{CH}_3-\overset{\text{O}}{\underset{|}{\text{C}}}-\text{CH}_3$.

Stereo Isomerism:

Stereo isomerism is exhibited by the compounds having same structural formula, molecular formula but possess different spatial arrangements of atoms (or) groups. It gives 3-D (or) 3-dimensional structure of a molecule.

Types of Stereo Isomerism

Stereo isomerism can be broadly divided into two classes.

1) configurational isomerism

2) conformational isomerism.

1) Configurational Isomerism:

The stereo isomers which are non-superimposable mirror images of each other and are non-interconvertible by rotation around single bond are known as configurational isomers and the phenomenon is known as configurational isomerism. These isomers can be interconverted only by breaking and making of the bonds.

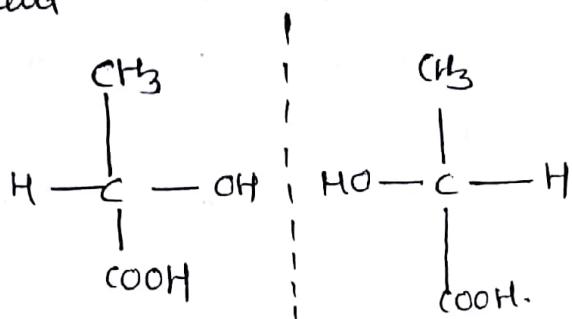
They are 2 types.

- (i) Enantiomers (optical Isomers)
- (ii) Diastereomers (geometrical Isomers),

Enantiomers:

When the two Isomers are the mirror images of each other, they are known as enantiomers (or) optical Isomers.

Ex: Lactic acid



Characteristics of Enantiomers:

- 1) Enantiomers always exists as discrete pairs.
- 2) They are stable, isolable compounds, that differ from one another in 3-dimensional arrangements of atoms (or) groups.
- 3) They cannot be inter converted under ordinary conditions.
- 4) Enantiomers have identical properties in all respect except in their interaction with plane polarized light.
- 5) They have same melting points, density, solubility, colour & reactivity towards acids and bases.
- 6) They differ in the direction in which they rotate plane polarized light. Both Isomers rotate the plane polarized light to exactly the same extent (same angle) but one Isomer rotates the plane polarized light to the right (dextro rotatory) while the other rotates the plane to the left (levo rotatory).
- 7) A mixture of equal amounts of two enantiomers is called racemic mixture which is optically inactive.

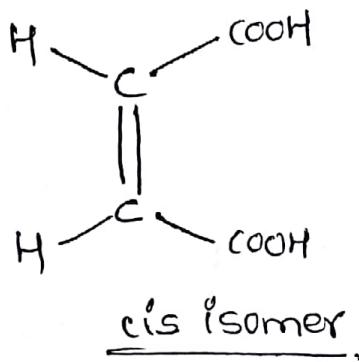
8. Enantiomers can be separated by mechanical separation, bio-chemical separation and complex formation.

Diastereomers:

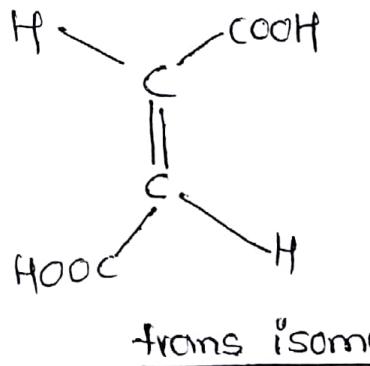
When the configurational isomers are not the mirror images of each other, they are known as diastereomers.

1. The two diastereomers have different properties.
2. They have different melting points, boiling points and solubilities.
3. They have different chemical reactivities towards most of the reagents.
4. They can be separated by fractional distillation, fractional crystallization and chromatography.

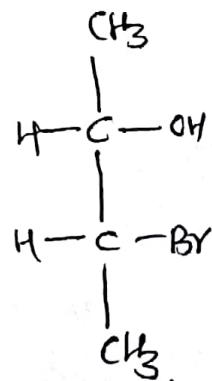
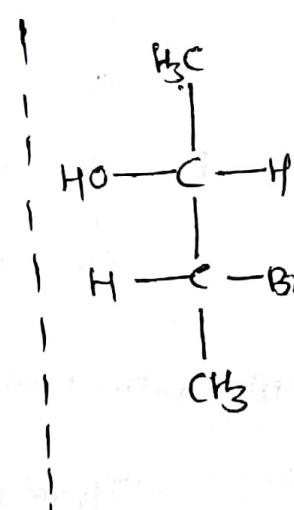
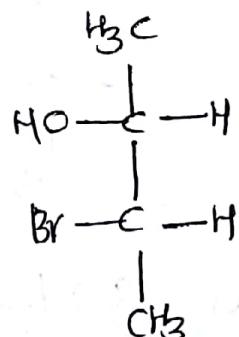
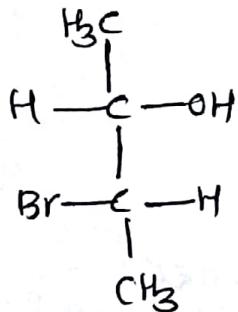
Ex: 1) Maleic acid.



Fumaric acid



2. 3-bromo-2-butanol.



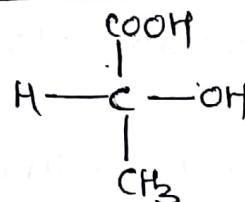
Configurations:

Configuration of a molecule is the spatial arrangement of atoms and groups about a double bond (or) ring and dissymmetric part of molecule.

→ A compound and its derivatives may have the same configuration but different signs of rotations.

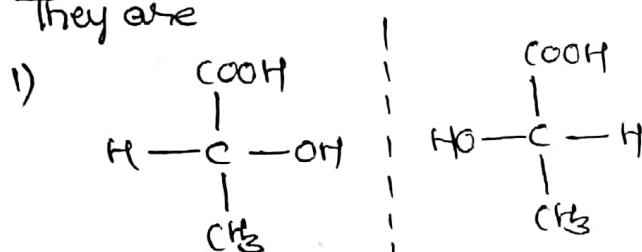
Example:

1) Lactic acid



∴ It has one chiral centre. Therefore it has stereoisomers i.e. = 2 stereoisomers.

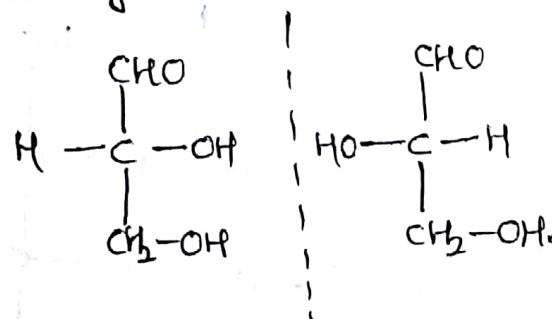
They are



Dextro lactic acid.

Leavo lactic acid.

2) Glyceraldehyde



(+D) Dextro isomer (L-) Leavo isomer.

There are 2 configurations to represent the molecule.

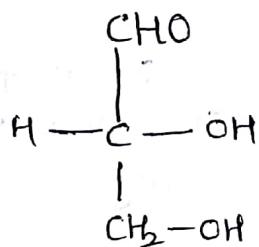
a) Relative Configuration (D, L systems)

b) Absolute Configuration (R, S configurations)

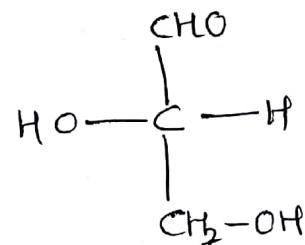
Relative Configuration

In this type actual arrangement of atoms (or) groups in space are studied with reference to a known isomer.

In D & L system, usually glyceraldehyde is used as standard with reference to glyceraldehyde configuration is assigned to isomers.



(+D) Glyceraldehyde



(-L) Glyceraldehyde.

The configuration in which —OH group is on the right is called (+D) glyceraldehyde, while the other which contains —OH group on the left side of the molecule is called L-isomer.

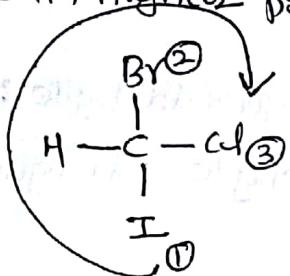
Absolute Configurations ::

Absolute configuration is the three-dimensional arrangement of groups (or) atoms in an asymmetrical molecule. A representation of optical isomers was proposed by Cahn, Ingold, and Prelog.

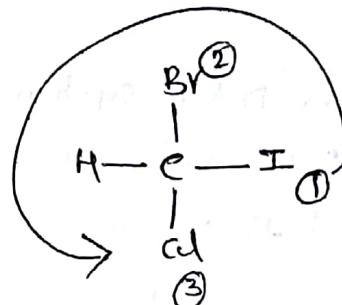
To assign configurational symbols R, S to an organic compound (Optically active compound), sequence rules are proposed. If the sequence is clockwise the configuration is "R" [Rectus is Right] and if the sequence is anti-clockwise, the configuration is "S" [Sinistrors is Left]

The priorities of the groups are determined by the following rules:

- 1). The order of the priority is determined on the basis of the atomic numbers of atoms that are directly attached directly to the chiral carbon. Greater atomic number results in higher priority.



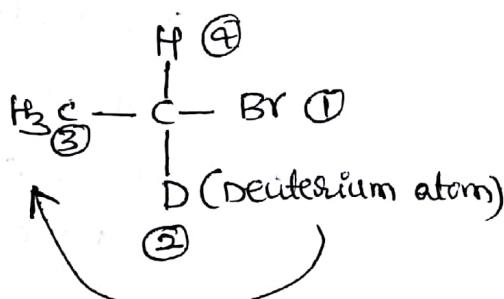
R- configuration.



S- configuration.

- 2) In the presence of two isotopes of some element, the heavier isotope will have higher priority

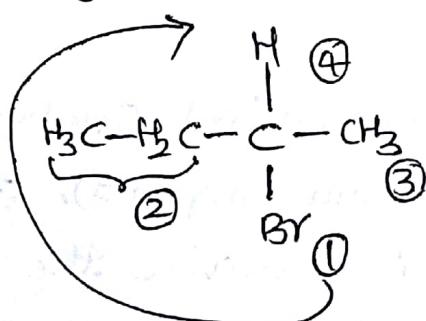
Ex: α-Deutero ethyl bromide.



S- configuration.

- 3) If the two atoms attached to the carbon are the same, rule (1) is not applicable, Priority in such cases is determined by comparing the next atom in the group.

Ex: Secondary butyl bromide.



R- configuration.

NOTE:

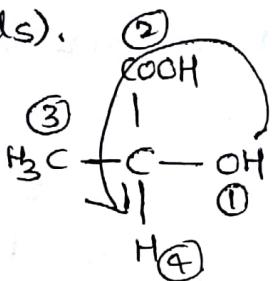
The relative priority of methyl, ethyl groups are taken.

4. If chiral carbon is attached to doubly or triply bonded atom then the atom is considered equivalent to two or three singly bonded atoms in determining priority
 $=, \equiv, \text{C}^{\text{II}}, \text{C}^{\text{EN}}$

In choice of multiple & single bond, multiple bonds gets first preference.

5. i) In the Fischer projection formula, the lowest priority group should be placed at the bottom position (vertically downwards).

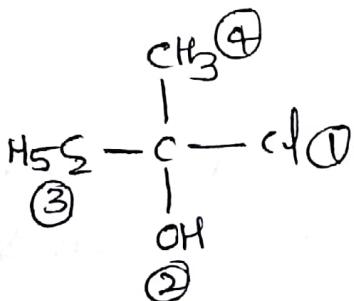
Ex:



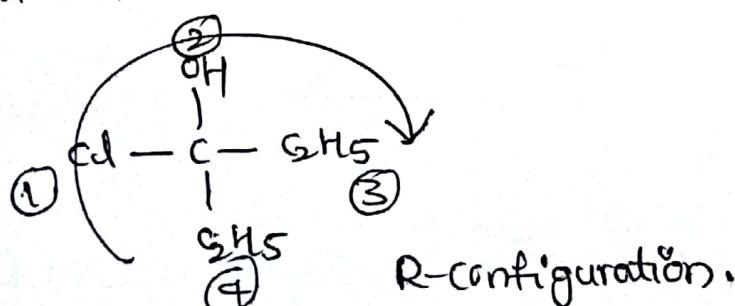
As shown, S-configuration.

Now the molecule is viewed from the opposite side of the lowest priority group i.e. -H atom, and the sequence of the remaining three groups (1, 2, 3) is in clockwise direction thus the molecule has 'R' configuration.

ii) If the molecule, the fourth priority group i.e. -CH₃ group is not placed at the bottom position. Thus, after four (even) interchanges, the new projection of the molecule becomes.



After 4 interchanges the new projection of the above compound



Chirality :-

cheir in greek means hand. Just like our right hand is a non-superimposable mirror image of left hand ie non-superimposable mirror image is called Chiral.

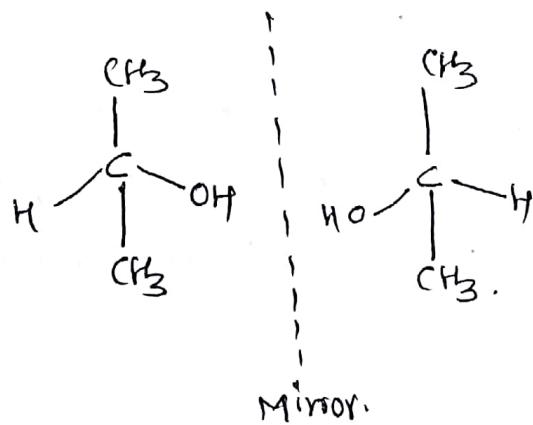
→ planar molecules are achiral and non-planar molecules are chiral.

→ The origin of chirality in organic molecules can be attributed to the tetrahedral nature of the carbon atom.

The tetrahedral carbon atom attached to four different atoms (or) groups is called chiral centre.

→ A pair of enantiomer is always possible for molecules that contain at least one chiral centre. If the tetrahedral atom in the molecule has two (or) more groups attached that are identical, the molecule is superimposable on its mirror image and is chiral.

Example: 2-propanol.



→ A molecule is said to be chiral if it contains

(i) atleast one asymmetric carbon &

(ii) It should not contain any of the elements of symmetry.

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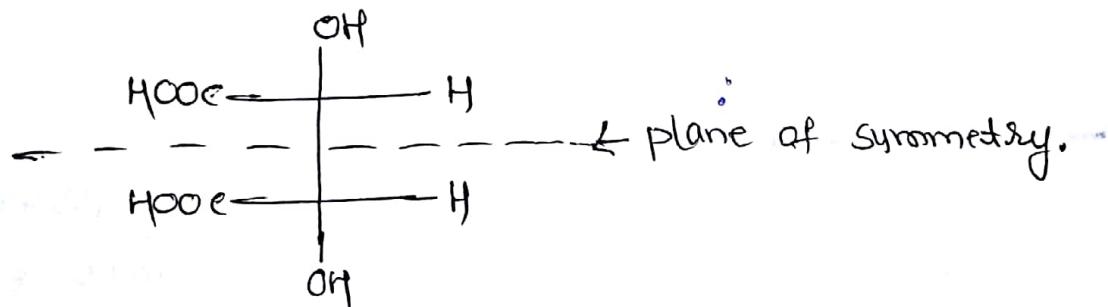
Symmetry Elements:

There are three elements of symmetry

- (i) plane of symmetry
- (ii) centre of symmetry.
- (iii) alternating axis of symmetry.

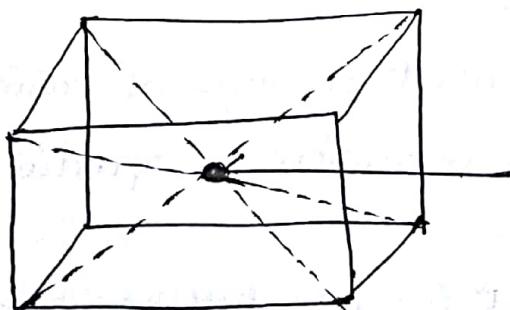
plane of Symmetry:

The plane that divides an object into two identical halves is called plane of symmetry. Each half is the mirror image of the other half. For instance, palm of our hand cannot be divided into two equal halves and hence it does not have a plane of symmetry. Therefore, it is chiral.



centre of Symmetry:

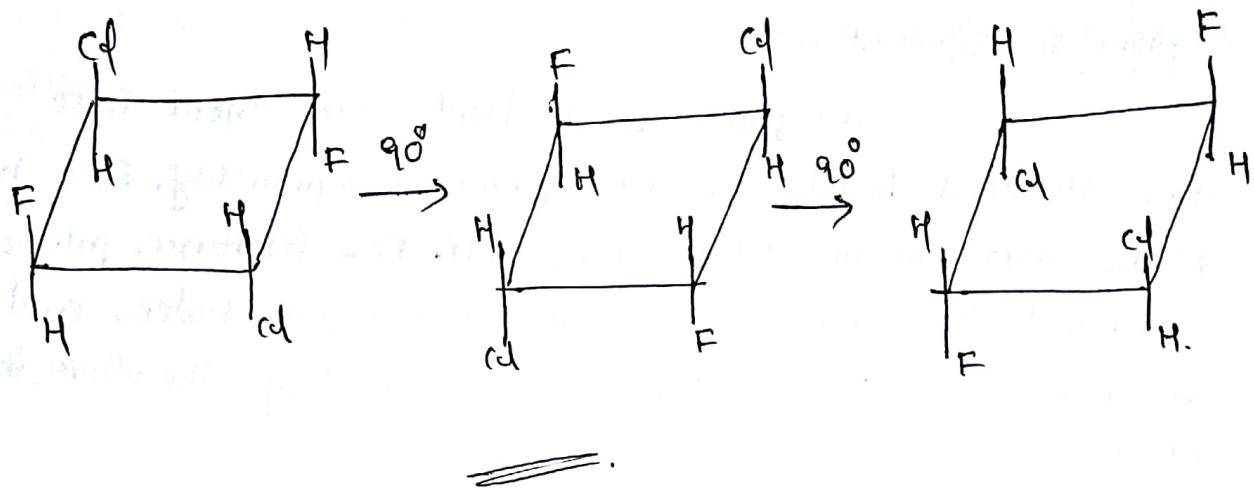
It is a point in a molecule such that if a line is drawn from any atom (or) group to the opposite end through this point the identical group (or) atom is found at the opposite end.



centre of
symmetry

(iii) Alternating axis of symmetry:

If a molecule is rotated by an angle of $\frac{2\pi}{n}$ through an axis followed by reflection across a plane which stands perpendicular to this axis results in an identical structure. This results in an n-fold axis of symmetry of the molecule.



Optical Activity:

The phenomenon of rotating plane polarised light is known as optical activity. The compounds exhibiting this property are known as optically active compounds.

→ In order to exhibit optical activity, the compound must be chiral our left hand is the mirror image of right hand and these two are non-superimposable.

Optical active compounds does not possess any of the element of symmetry.

→ Ordinary light consist of rays of varying wavelengths, vibrating in all possible directions perpendicular to the direction of propagation.

→ When ordinary light is passed through a NICOL prism the vibrations are adjusted in a single plane.

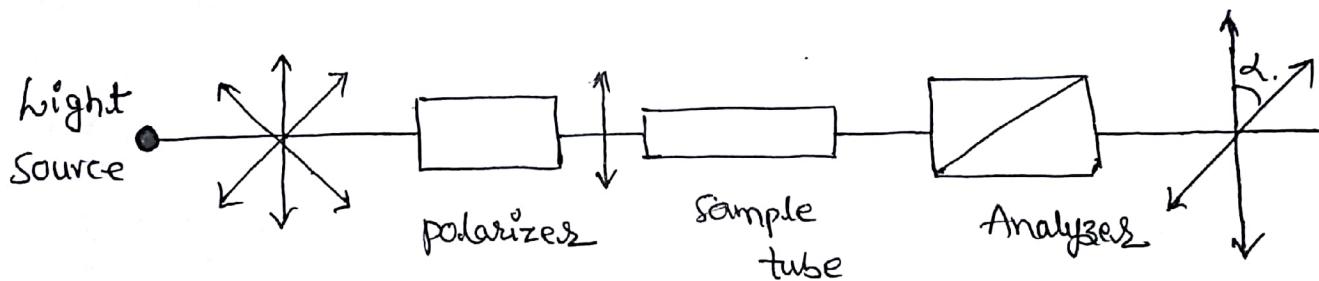
→ The light whose vibrations occur only in one plane is known as plane polarized light. The device that brings polarisation in light is called a polariser.

→ Some substances have the ability to rotate the plane polarised light either clockwise or anticlockwise. These substances are called as optically active substances and the property is called optical activity.

→ The apparatus which measures the extent of rotation of the polarised light is called polarimeter.

→ The angle of rotation depends on a number of factors.

- i) Nature of the substances.
- ii) Wavelength of the light used.
- iii) Concentration of the solution (C) in g/cm^3
- IV) Nature of the solvent.
- V) Length of the path through which polarized light passes.
- VI) Temperature at which the measurements are made.



→ The measurement of optical activity is done in terms of specific rotation which is defined as the rotation produced by a solution of length of 10cm and unit concentration (1g/ml) for the given wavelength of the light at the given temperature.

$$\text{Specific rotation } \alpha = \frac{\alpha_{\text{obs}}}{l \times C}$$

Where α_{D}^{20} is the rotation observed,

d is the length of the solution

c is the number of grams in 1 ml of solutn.

NOTE:

1) If a molecule has only one chiral centre, it is always chiral. However, molecules with two or more chiral centers may be chiral or achiral.

2) There are some molecules which do not have any chiral center but are still chiral,

Ex: allenes. i.e $\begin{array}{c} a \\ | \\ c=c=c \\ | \\ b \end{array}$.

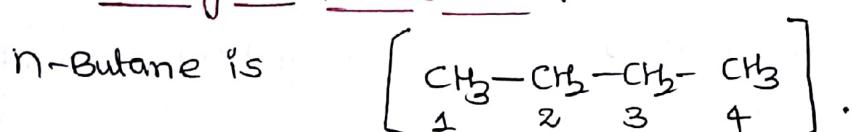
\equiv .

: Conformational Isomerism:

The different spatial arrangements that a molecule can have due to free rotation about C-C single bond are called as conformations.

The stereo isomers which are non-superimposable but are easily interconvertible by rotation about the single bond are known as conformational isomers and the phenomenon is known as conformational isomerism.

Conformation analysis of n-Butane:



In n-butane molecule σ bonding joining the $\Sigma-\text{C}_3$ is cylindrically symmetrical about a line joining the carbon nuclei. Hence the rotation about the $\Sigma-\text{C}_3$ bond requires very less energy.

→ The energy required to rotate the n-Butane molecule about the carbon-carbon bond is called torsional energy. During rotation changes in molecular geometry takes place. It has not only one staggered and eclipsed conformations but a number of other conformations arising due to relative orientation of the two methyl groups. These as follows:

(i) Fully eclipsed conformation

Both the methyl groups are aligned, hence the dihedral angle b/w two methyl groups is 0° .

(ii) Gauche conformation:

This is a staggered form in which the methyl groups are in close proximity with dihedral angle equal to 60° . There are two Gauche conformations possible.

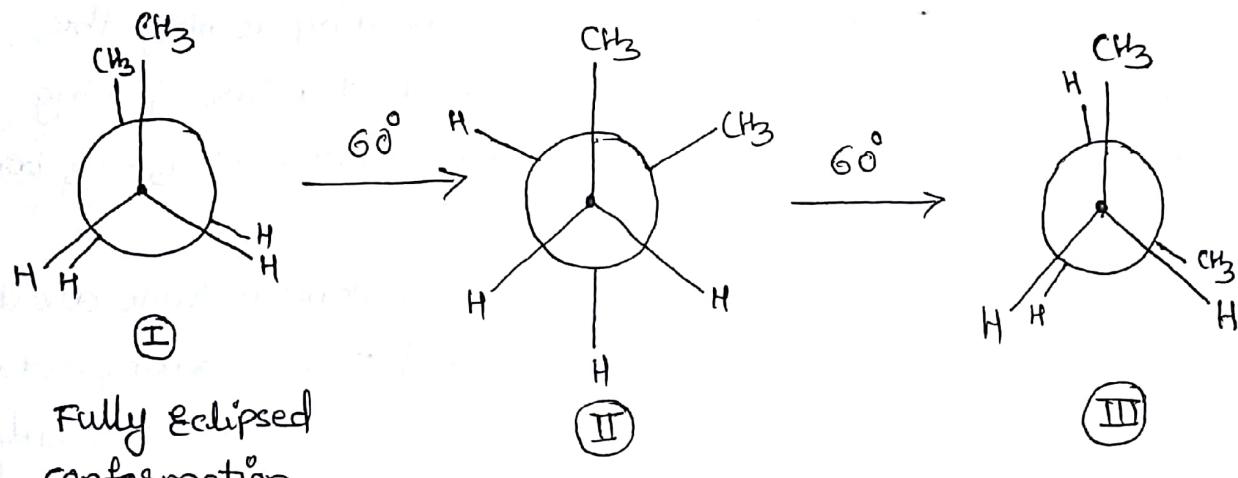
Gauche conformations are free of rotatorial strain. But there is Vander Waals repulsion between the methyl groups and the molecule is less stable because of Vander Waals strain.

Partially eclipsed conformation:

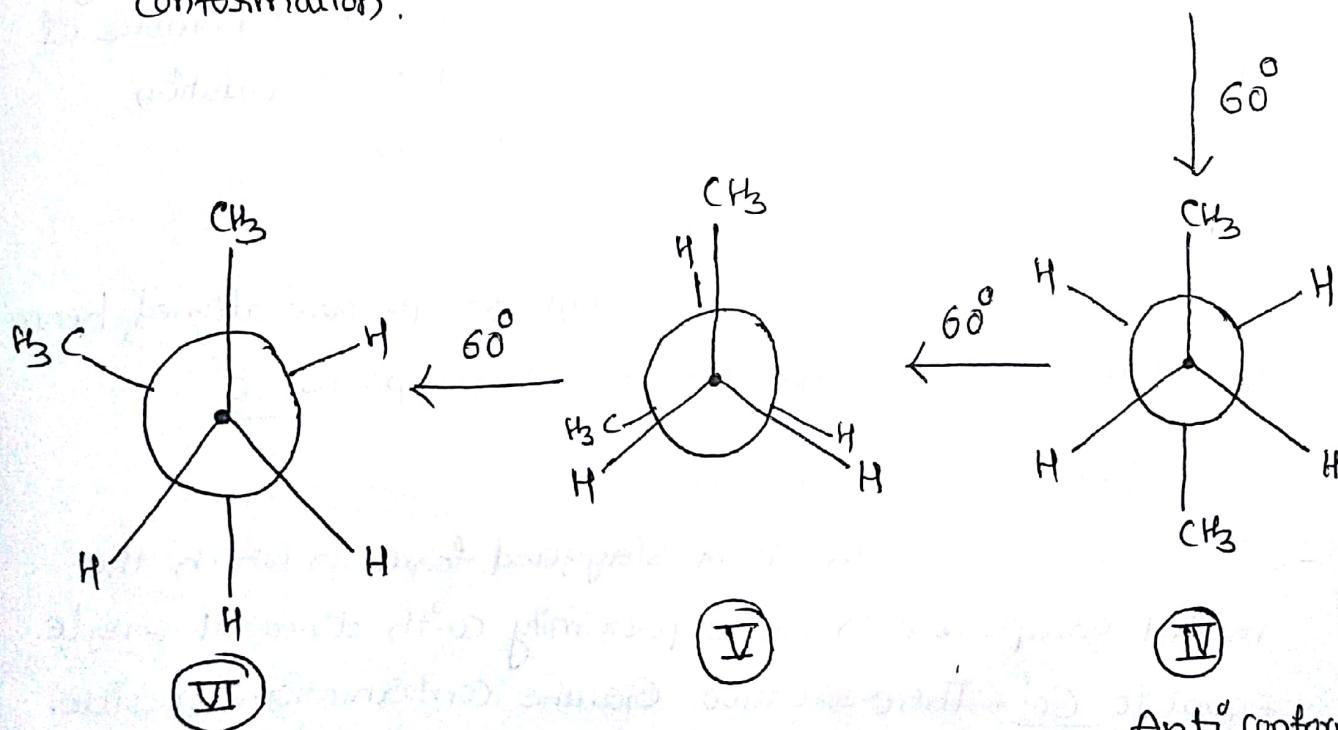
This arises due to further rotation of Gauche conformation on by 60° such that the dihedral angle between two methyl groups becomes 120° .

'Anti' conformation

This is a staggered conformation in which the two methyl groups are away from each other with dihedral angle 180° .



Fully eclipsed conformation.



'Anti' conformation

Conformation ① is \rightarrow Fully eclipsed

④ is \rightarrow Fully staggered (or) anti-form.

③ & ⑤ are \rightarrow Partially eclipsed form

② & ⑥ are \rightarrow Partially staggered (or) Gauche
(or) skew forms.

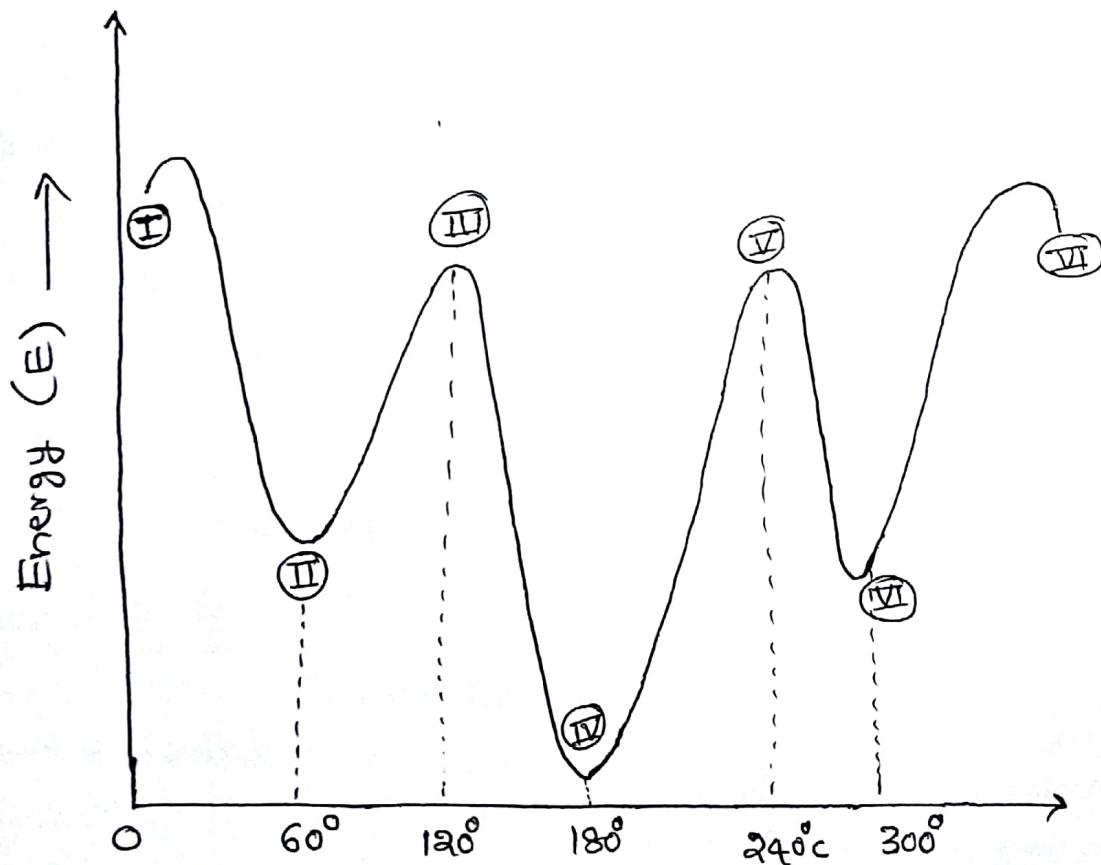
\rightarrow In the case of anti staggered form $\frac{1}{2}$ $\text{CH}_3\text{-H}$ and $\frac{2}{2}$ H-H interactions i.e 6 (six) interactions are possible.

In fully eclipsed form greater steric effects are acting.

\rightarrow In Gauche conformation 1 $\text{CH}_3\text{-CH}_3$, 2 - $\text{CH}_3\text{-H}$, 3 - H-H interactions are present.

\therefore The order of magnitude of interaction is

$\text{CH}_3\text{-CH}_3 > \text{CH}_3\text{-H} > \text{H-H}$. The relative stabilities of all these conformations are shown in the potential energy diagram.



Dihedral angle \longrightarrow
(Potential Energy Diagram of n-butane)

When we observe the above potential energy diagram, the following conclusions can be made.

1. Here, all the three peaks are not present at the same height, one peak is present at a higher height than the other two present at same height.
2. The three valleys are also not present at the same height, Two are present at one height and the third one at lower height.

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Reaction Mechanisms

organic reactions are chemical reactions involving organic compounds. In most of the organic reactions, transformations of reactant to product takes place through some definite steps. An organic reaction mechanism is a detailed description of these steps. A reaction mechanism not only tell us the number of steps involved in the reaction but also gives the information regarding the sequence of breaking and making up bonds.

→ organic reactions involve the fission and formation of covalent bonds. The covalent bond is often represented as '—' and the movement of a pair of \bar{e} s are shown by a 'curved arrow', starting from the atom which gives the pair of electrons to the other atom as shown below where A gives a pair electrons to B,



The movement of single \bar{e} is shown by fish hook arrow (\curvearrowleft) from the atom which gives a single \bar{e} to the other atom which accepts it.

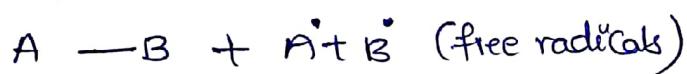
Ex: $\text{A} \begin{array}{c} \curvearrowleft \\ - \end{array} \text{B}$. when A transfer a single electron to B and the covalent bond may be broken.

There are two ways a covalent bond is broken

- a) Homolytic fission
- b) heterolytic fission,

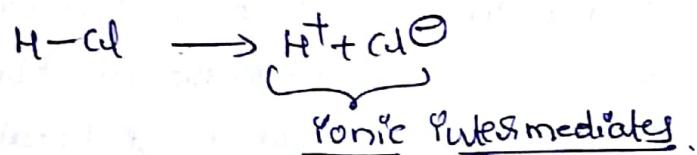
Homolytic fission

Suppose the molecule A-B containing the atoms A and B bonded by a covalent bond may break in such a way that fragment carries one unpaired electron to produce free radicals this type of fission is called homolytic fission.



Heterolytic fission:

When the covalent bonds joining the atoms A and B breaks in such a way that the pair of electrons stays on anyone of the atoms which is electronegative and the other atom is electron deficient. The process is called heterolytic fission producing the ionic intermediates as shown below,



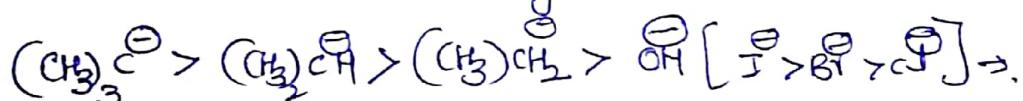
Types of reagents in organic reaction mechanism:

Nucleophiles: A nucleophile (nucleus loving) is an atom or group of atoms that contains an unshared pair of electrons available for reaction, and carry negative charge (-) attack the positively charged centre in group hence called nucleophile.

Ex: 1) Oxygen, nitrogen & sulphur are neutral compounds due to the presence of unshared pair of es.

2) R^{\ominus} , OH^{\ominus} , CN^{\ominus} , NH_3 , H_2O , $\text{R}-\text{OH}$ etc.

The order of nucleophilicity is as follows:



Electrophiles:

Electrophiles (means electron loving) is a reagent that has electron deficiency by a pair of electrons. Electrophiles are also called catenoid reagents and carry +ve charge with incomplete valence shells.

Ex: H^{\oplus} , $\text{H}_3\text{O}^{\oplus}$, NO_2^{\oplus} , BF_3 , ZnCl_2 , AlCl_3 etc.

Types of organic reaction Mechanisms :

The organic compounds undergo five kinds of reactions namely

- Substitution
- Addition
- Elimination
- Molecular rearrangement
- Molecular reactions.

a) Substitution Reaction:

Substitution reaction is a reaction in which an atom or group replaces another atom (or) group present in a compound without causing a change in the structure of that compound then this reaction is called substitution reactions.

i) Nucleophilic Substitution Reaction:

When nucleophile attacks the carbon atom bearing a group to be replaced called leaving group then this substitution reaction is called nucleophilic substitution reaction.

→ Nucleophilic substitution reactions are an important class of reactions that allow the interconversion of functional groups.

Nucleophilic substitution are 2 types

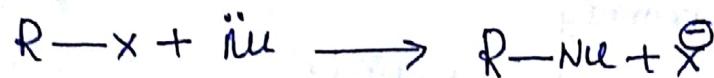
- S_N^1 Mechanism
- S_N^2 Mechanism,

S_N^1 mechanism:

The term S_N^1 unimolecular nucleophilic substitution reaction is used because the rate determining step involves only one molecule.

S_N^1 involves heterolysis to form the carbocation as an intermediate.

→ In S_N^1 reaction the rate of the reaction depends only on the concentration of the substrate and is independent of concentration of nucleophile.



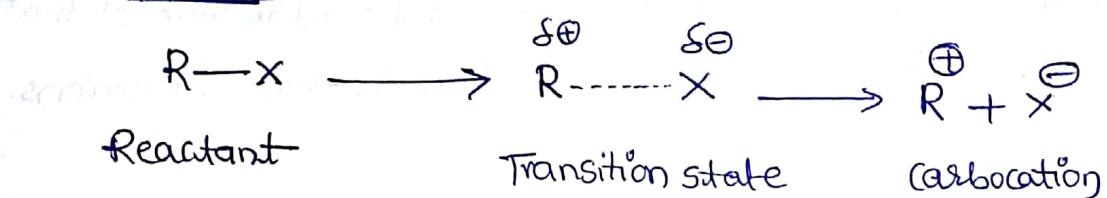
$$\therefore \text{Rate of the reaction} = k[R-X]$$

Mechanism:

From kinetics it has been found that rate is proportional to only concentration of substrate. To fit into kinetic data, a two step mechanism has been proposed.

First step involves ionization of the substrate forming an intermediate carbocation.

i.e STEP-I:



→ This is a slow step i.e rate controlling (O) step determining rate.

STEP-II

The second step involves the attack of nucleophile to the electron deficient i.e 'carbocation' to form the product.

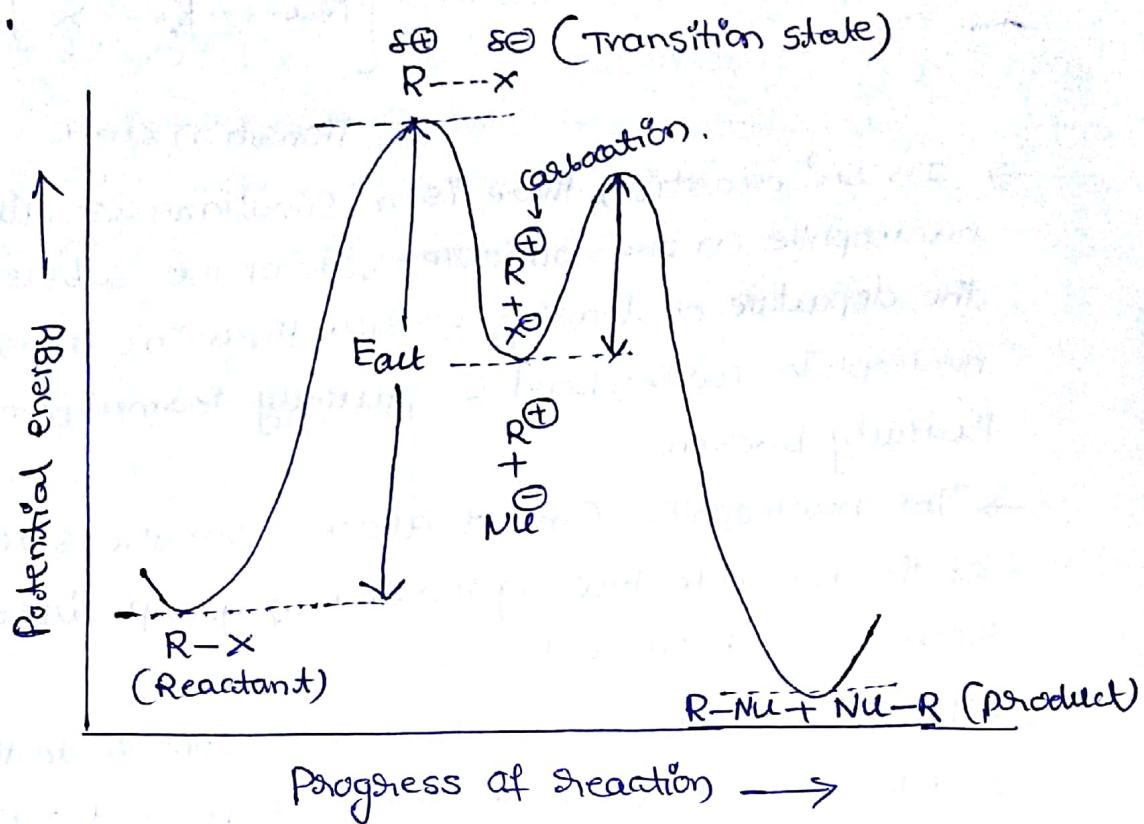


50% 50%

Recemic mixture of
products.

→ The second step is the fast step

→ The energy profile diagram of S_N^2 reaction is shown below.



S_N^2 Mechanism:

S_N^2 indicates a Substitution, Nucleophilic bimolecular reaction with the expression for rate as

$$\text{Rate} = k [Nu] [R-X]$$

which shows the rate determining step involves an interaction between two species, the nucleophile and the organic substrate.

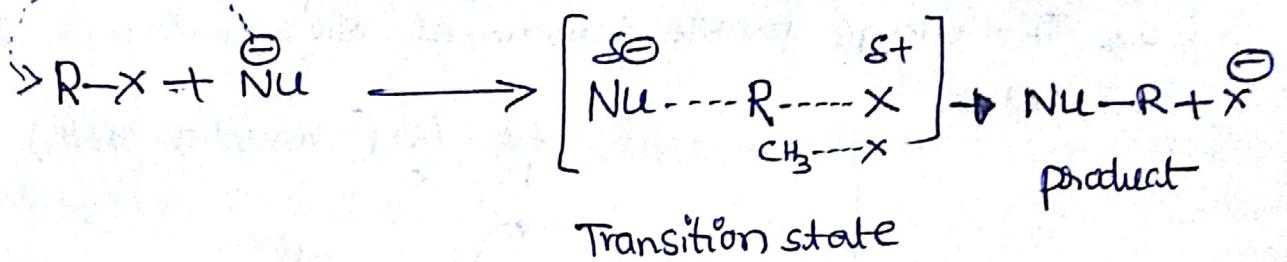
→ S_N^2 reactions follows second order kinetics, nucleophilic reagent Nu attacks the back side of reactant and complete inversion of configuration takes place.



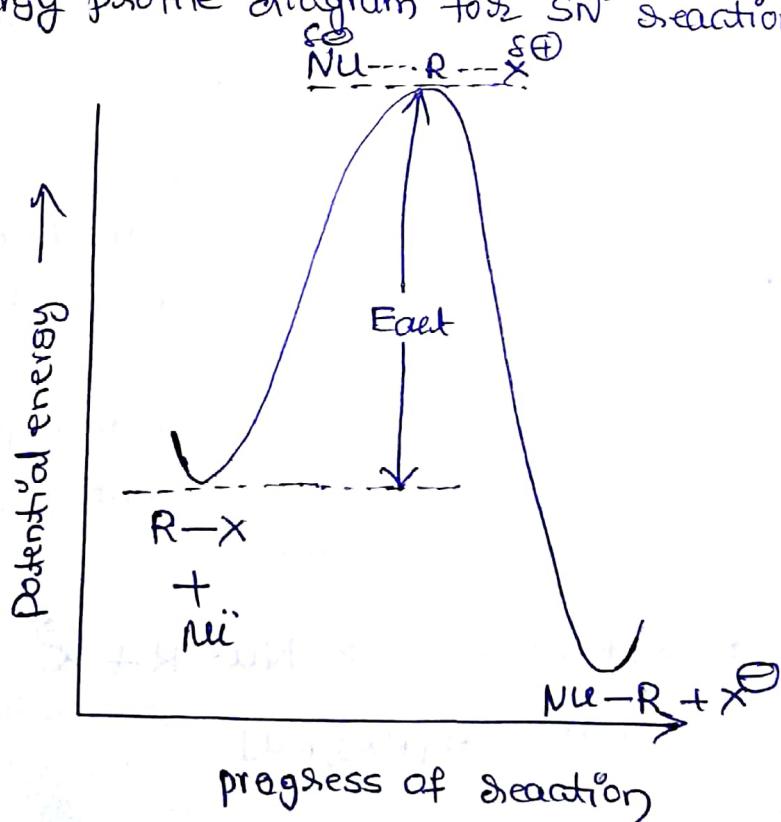
$$\therefore \text{Rate} = k [Rx][Nu]$$

Mechanism:

→ As no intermediate involved in S_N^2 reaction is single step reaction.



- In S_N^2 reaction, there is a simultaneous attack by the nucleophile on the opposite side of the substrate followed by the departure of leaving group. Hence in transition state the nucleophile carbon bond is partially formed and $C-X$ bond is partially broken.
- The nucleophile cannot attack from the side opposite to the of the molecule bearing the leaving group due to electrostatic repulsion and steric factors.
- Thus the attack will be from side opposite to the leaving group and the substitution reaction will proceed with inversion of configuration.
- The energy profile diagram for S_N^2 reaction is shown below.



→ Steric hindrance around the central carbon atom plays a significant role in the rate of S_N^2 reaction. The reactivity towards S_N^2 mechanism decreases with increase in number of substituents on the carbon bearing the leaving group.

→ The reactivity in S_N^2 mechanism,



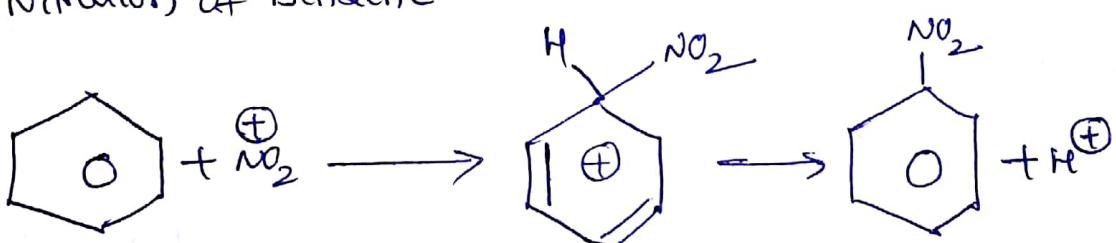
→ In the reactant and product, the central carbon atom is tetrahedral and in the transition state it is bonded to five atoms (or) groups.

∴

(ii) Electrophilic Substitution:

The attacking species is an electrophile and the leaving group departs without its bonding electrons. This type of substitution occurs mainly in Aromatic systems where the high electron density attracts electrophiles.

Ex: Nitration of benzene



(iii) Free radical Substitution:

Free radical substitutions are initiated by radicals in the gas phase (or) in the non-polar solvents.

Example: Chlorination of methane.



Addition Reactions:

The reaction in which two substances combine to form a single compound is called as addition reaction without elimination of any atom (or) group.

→ Addition reactions occur in compounds containing multiple bonds.
Ex: C=O , C=N , C\equiv C , C=C

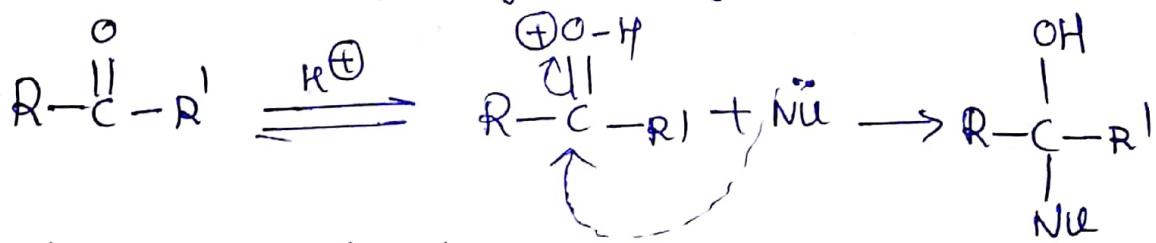
→ The addition reactions are 3 types.

- 1) Nucleophilic addition
- 2) Electrophilic addition
- 3) Free radical addition.

Nucleophilic addition Reaction:

Nucleophile reagent reacts with the reactants having carbonyl group C=O in this type of reaction become exposed for the attack of electron rich species nucleophiles.

→ Nucleophilic addition to carbonyl compounds is catalysed in presence of acid because the protonated carbonyl group undergoes nucleophilic attack more readily because oxygen can take electrons without acquiring a negative charge.



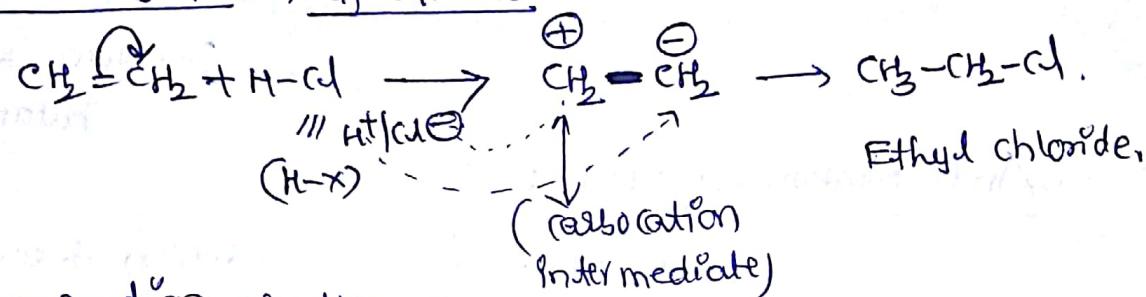
→ Aldehydes more reactive towards nucleophilic addition than ketones because a ketone contains a second alkyl or aryl group and hence causes crowding. An alkyl group also releases electrons and thus destabilizes the transition state by intensifying the negative charge developing on oxygen.

2

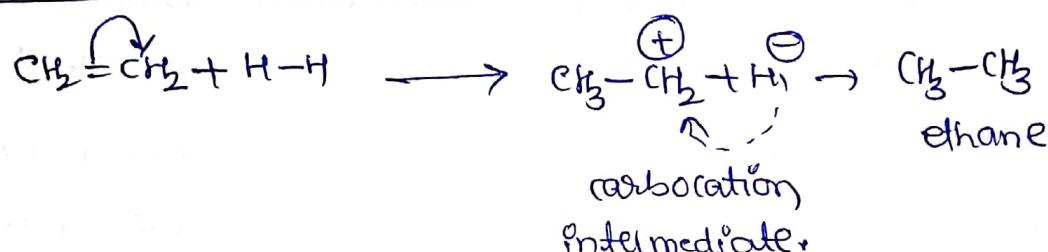
Electrophilic addition reaction:

Electrophilic addition reactions can be defined as the chemical reactions in which electrophile + is added to an electron rich carbon atom, specially alkenes containing C=C and gets attached to the double bonded carbon.

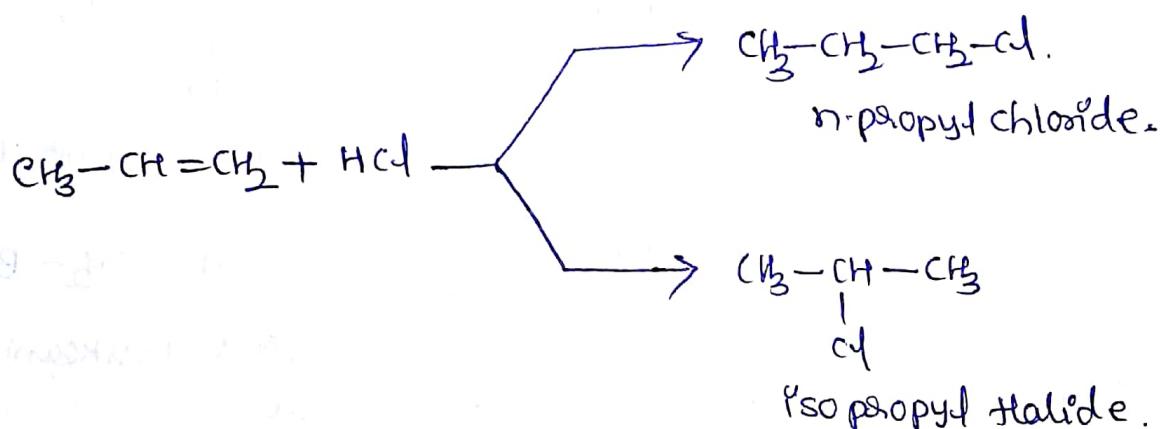
Eg: 1) Hydrohalogenation of alkenes:



2) Hydrogenation of alkenes:

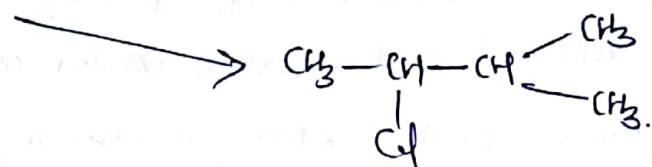
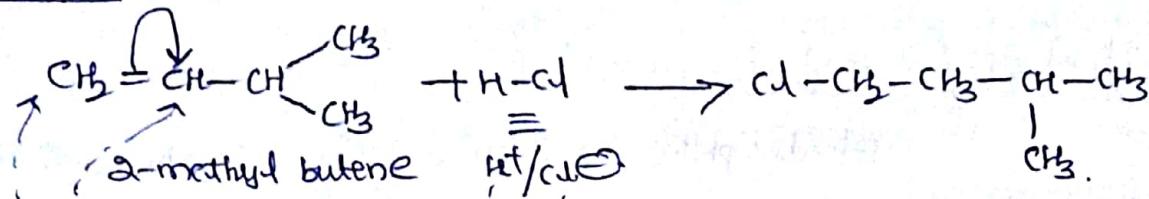


If HX (i.e. $\text{HCl}, \text{HBr}, \text{HI}$) adds on to a symmetrical olefin, only one product is obtained. But when HX is added to unsymmetrical olefin, different alkyl halides are produced.



In such cases, the addition of HX to olefin (unsymmetrical) is governed by "Markownikoff's rule". According to this rule the negative part of the molecule attaches to that carbon of the double bond which bears least number of hydrogen atoms. In the above case *isopropyl halide* will be the main product.

examples:

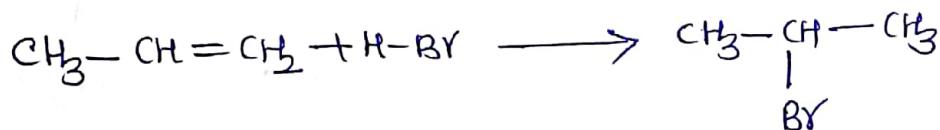


3-chloro-2-methyl butane.

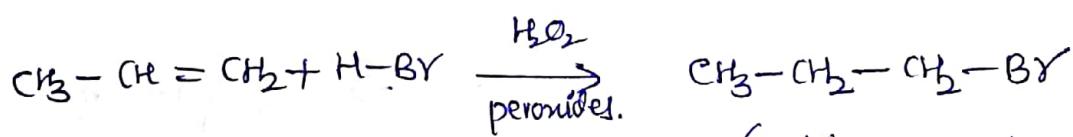
Anti' Markonikoff's Rule:

Anti' Markonikoff's addition describes the regiochemistry where the substituent is bonded to a less substituted carbon, rather than the more substituted carbon.

Anti' Markonikoff's addition is an addition reaction of an electrophile ($\text{H}^{\oplus}\text{X}^{\ominus}$) to an alkene (or) alkyne where the hydrogen atom of HX is bonded to the carbon atom that had the more number of hydrogen atoms.



(Markonikoff's rule)



(Anti' Markonikoff's rule)

Conditions for Anti' Markonikoff's rule

- 1) This Anti' Markonikoff's rule reaction occurs only in the presence of HBr not in presence of HI & HCl .
- 2) There must be peroxide for initiation usually H_2O_2 is used.
The reaction in presence of peroxide and KI (or) HCl cannot take place.

Grignard addition reactions on Carbonyl Compounds:

The Grignard reaction named after Victor Grignard who proposed the mechanism and awarded Nobel prize (1912) is an organometallic chemical reaction in which alkyl, vinyl or aryl Magnesium halides (Grignard reagents) added to a carbonyl group in an aldehydes & ketones. This is a very important reaction for the formation of carbon-carbon bonds.

This reaction can be used for synthesis of all types of alcohols i.e primary, secondary and tertiary alcohols.

Grignard reagent is $[R-Mg-X]$

Here $R \rightarrow$ alkyl group.

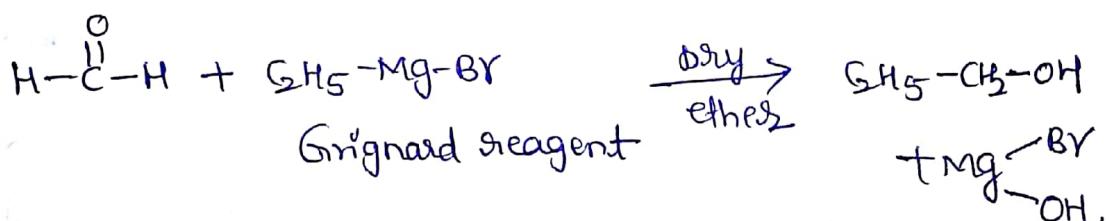
$Mg \rightarrow$ Metal

$X \rightarrow$ Halogen atom.

(F, Cl, Br, I) etc.

Primary alcohol:

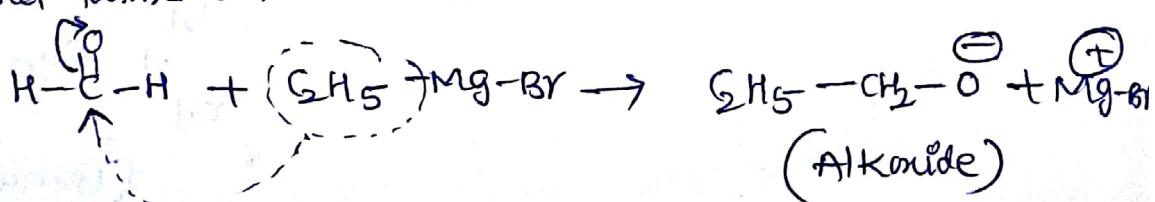
Ethyl magnesium bromide reacts with $H-\overset{\text{O}}{\underset{\text{H}}{\text{C}}}-H$ (Formaldehyde) to form 1-propanol i.e primary alcohol.



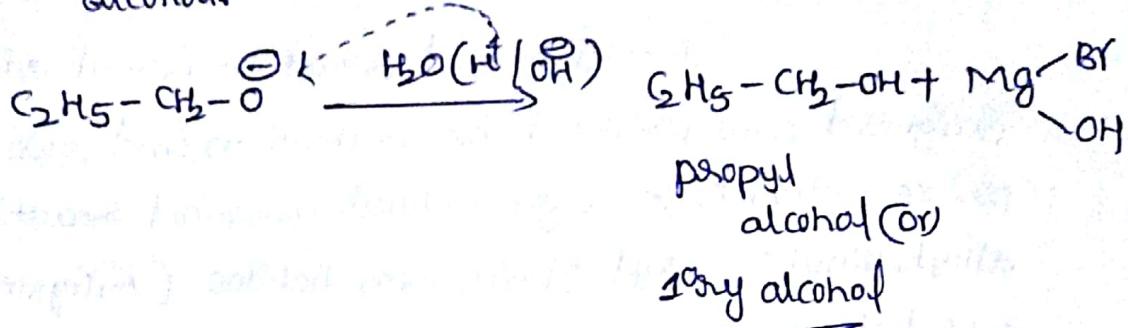
Mechanism:

Step-1:

The nucleophile (CH_3^-) or R^- attacks the carbonyl carbon. cleavage of π -bond between C-O bond takes place and forms an alkoxide.

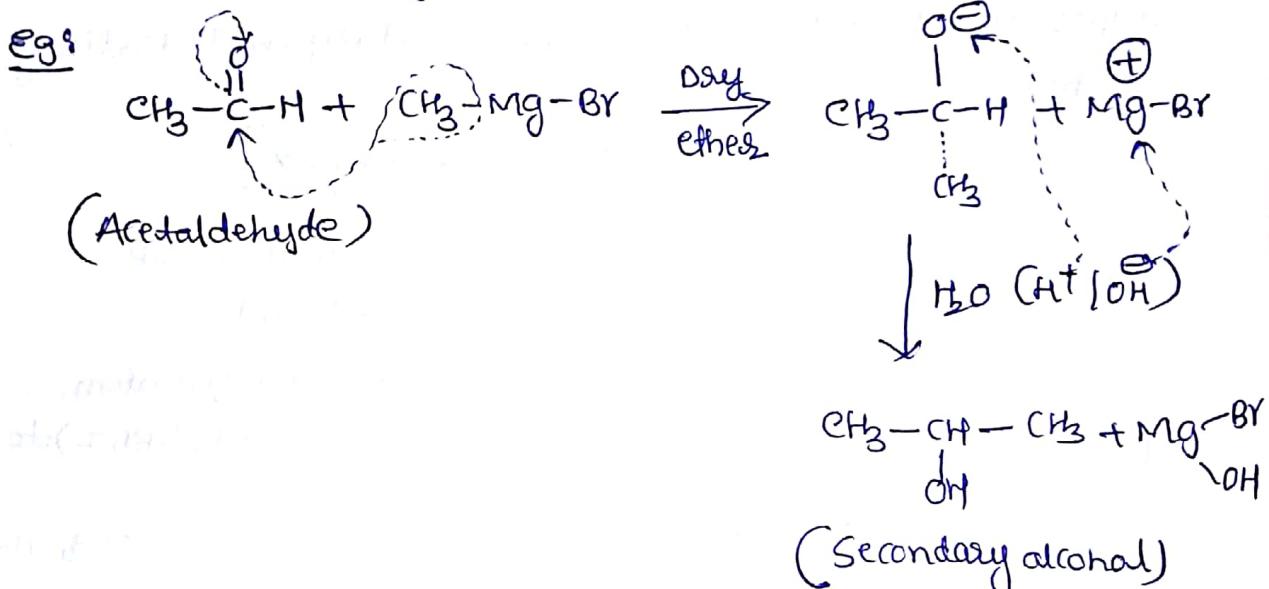


Step-II: protonation of alkoxide by H_2O and forms an alcohol.



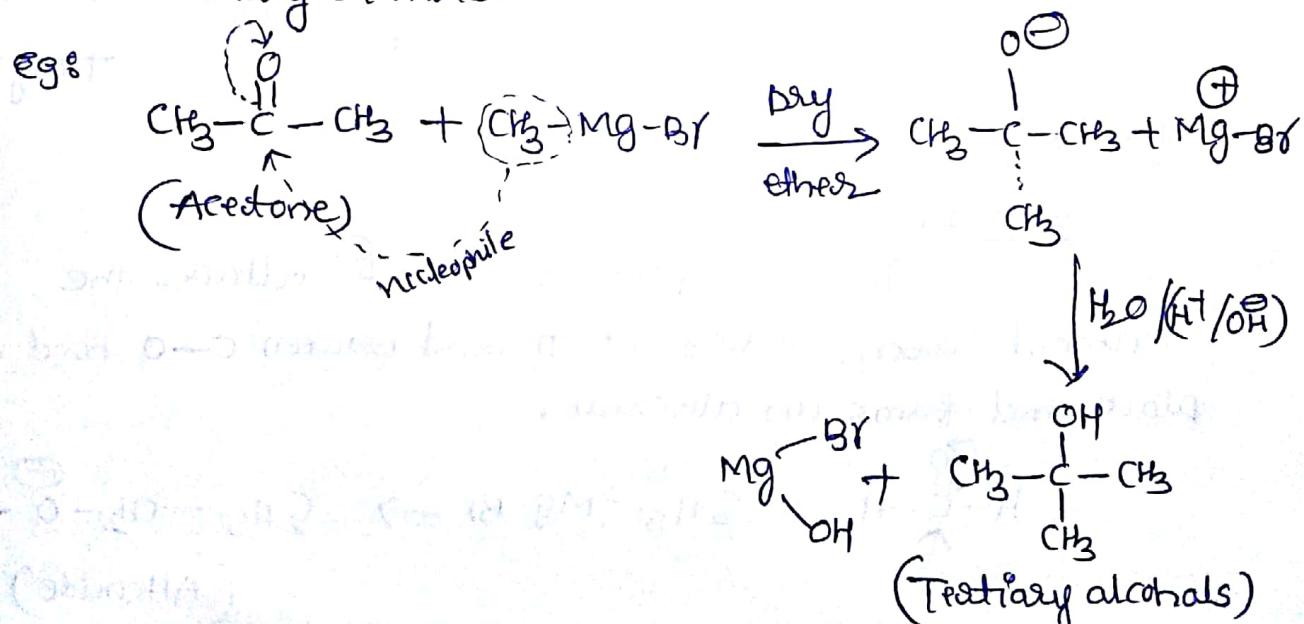
Secondary alcohols:

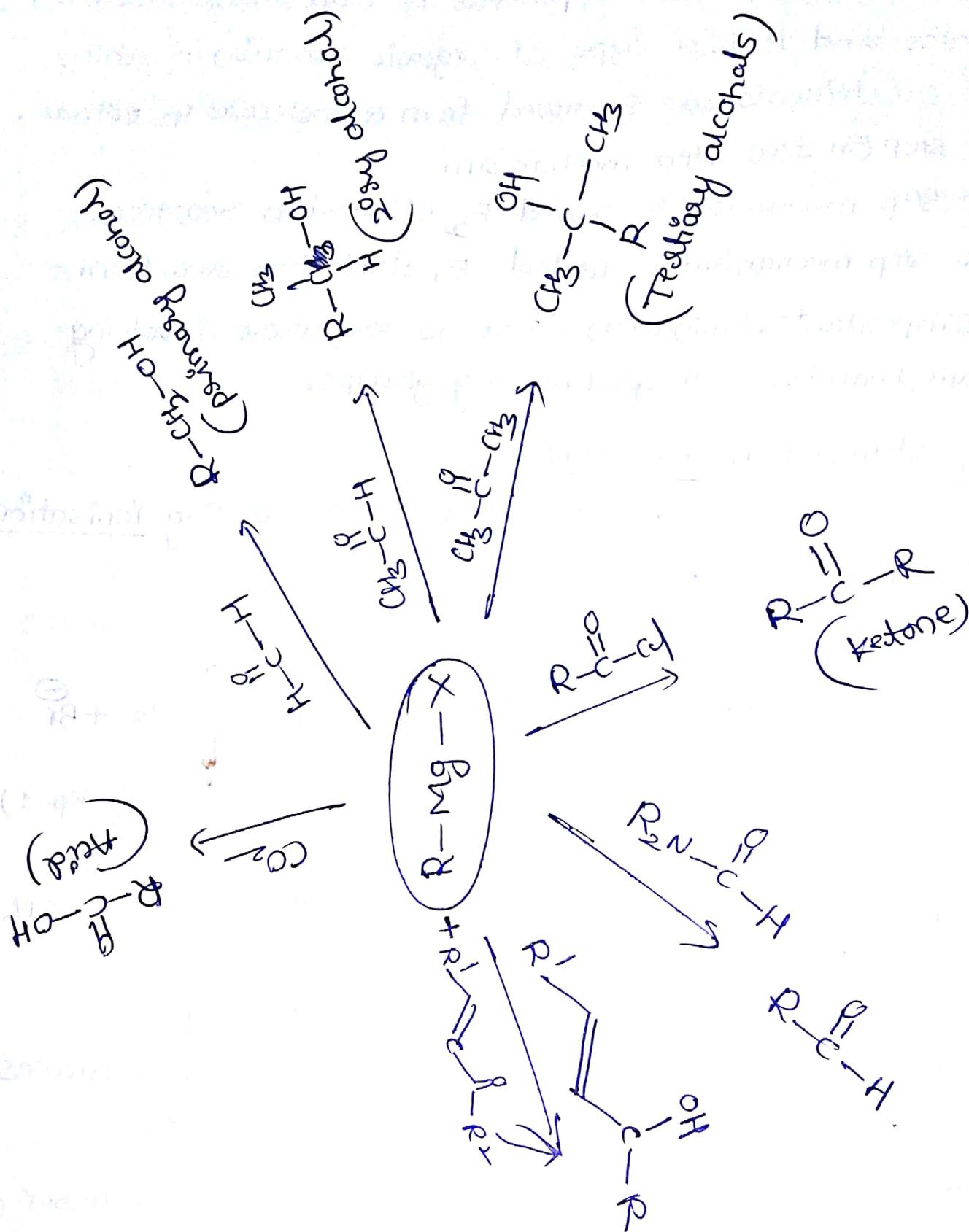
Grignard reagent reacts with other aldehydes & it forms secondary alcohols.



Tertiary alcohols:

Grignard reagent reacts with ketones & it forms tertiary alcohols.





Elimination Reactions:

Elimination process is opposite to addition process and it is a type of organic reaction in which two substituents are removed from a molecule in either one step or two step mechanism.

One step mechanism is called E_1 elimination reaction.

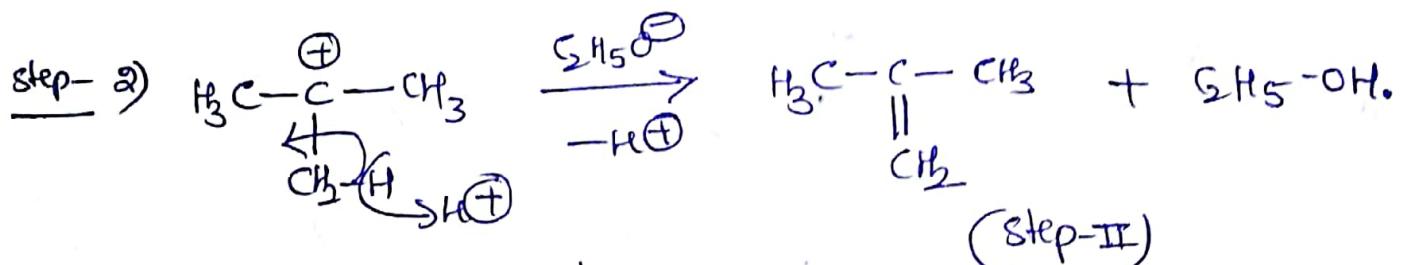
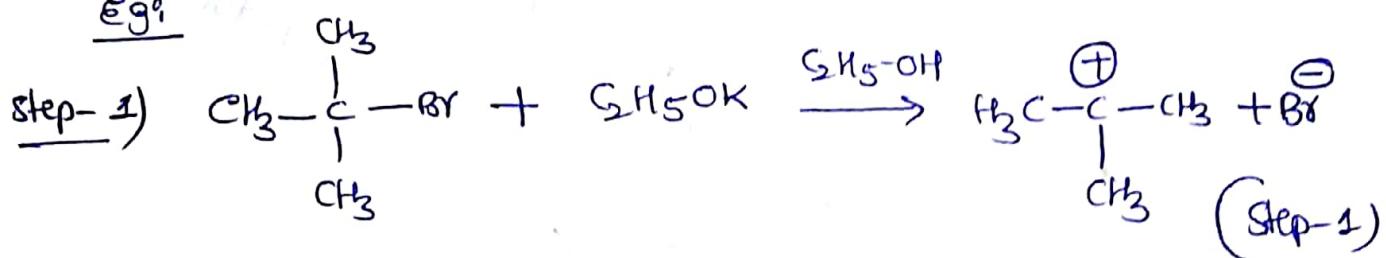
Two step mechanism is called E_2 elimination reaction.

→ Important elimination reactions are those involving alkyl halides with good leaving groups.

E_1 elimination reaction:

It is a two step process involving ionisation and deprotonation.

Eg:-



→ Highly substituted alkyl groups on carbon increases the rate of reaction because of the inductive effect.

→ The stability of Carbo cation increases as the number of methyl groups on the carbon increases.

→ E_1 elimination increases with increasing temperature.

E_2 elimination reaction:

E_2 -mechanism is a bimolecular mechanism and one step mechanism in which C-H and C-X bond break to form a double bond (π bond).

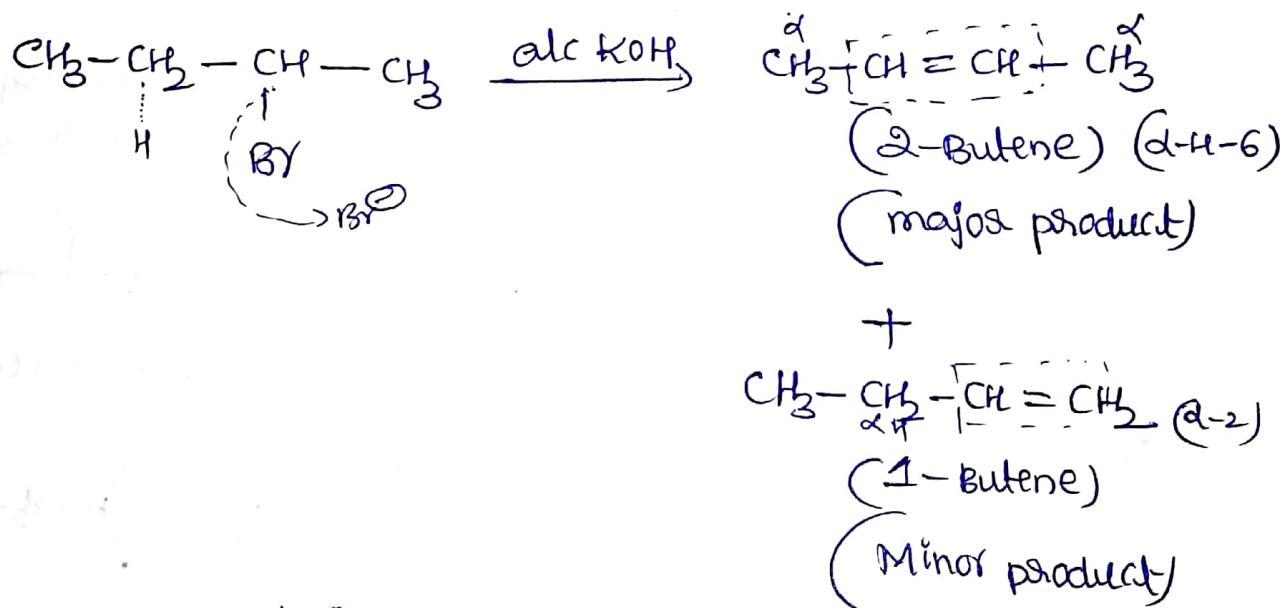
→ E_2 mechanism goes by single step with a single transition state.

→ The rate of reaction is second order because it is influenced by both the alkyl halide & base.

→ In dehydrohalogenation the hydrogen atom from β -carbon is lost.

Saytzeff rule:

During dehydration more substituted alkene is formed as a major product since greater the substitution at double bond greater is the stability of alkene.



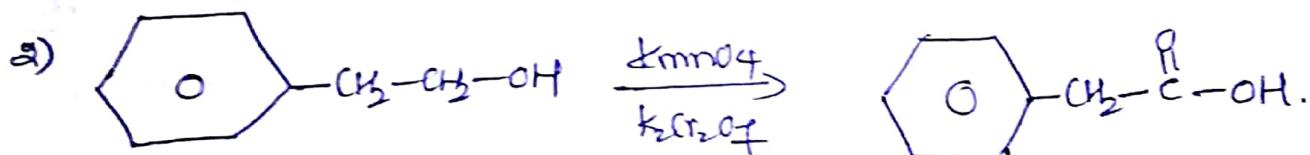
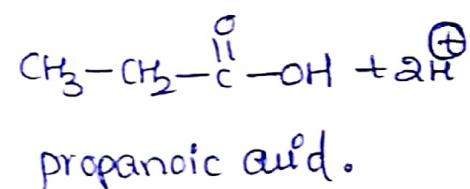
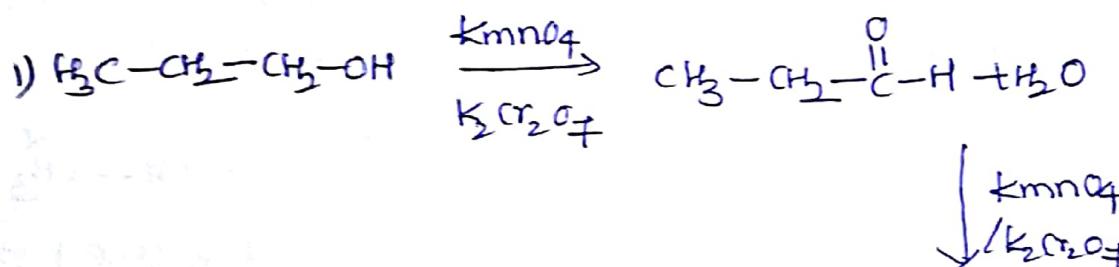
→ If any product is containing more α -Hydrogens and that compound is said to be Saytzeff compound (or) Major compound.

Oxidation of alcohols by using $KMnO_4$ and Chromic acid (H_2CrO_4)

- The oxidation reactions are very important reactions in organic chemistry.
- $KMnO_4$ oxidation occurs in base, H_2CrO_4 (chromic acid) occurs in acid.
- Alcohols may be oxidized to give aldehydes, ketones & carboxylic acids.

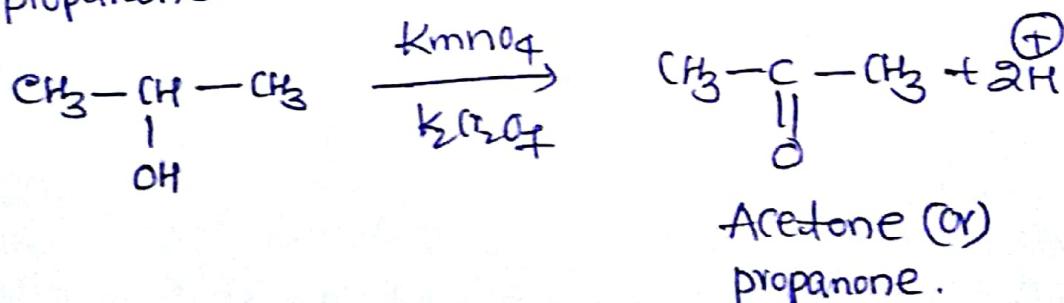
Primary alcohols:

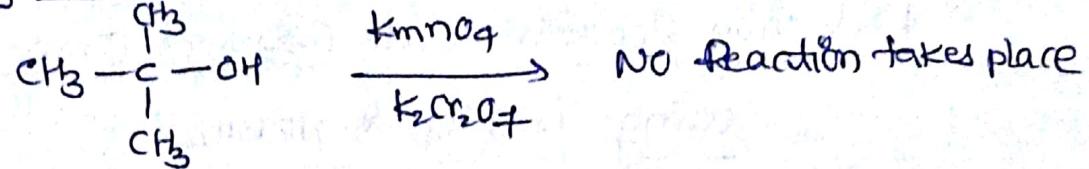
1- propanol reacts with $KMnO_4$ in presence of $K_2Cr_2O_7$ gives propanal and further oxidized to propanoic acid.



Secondary alcohols:

2- propanol reacts with $KMnO_4$ in presence of $K_2Cr_2O_7$ gives propanone.

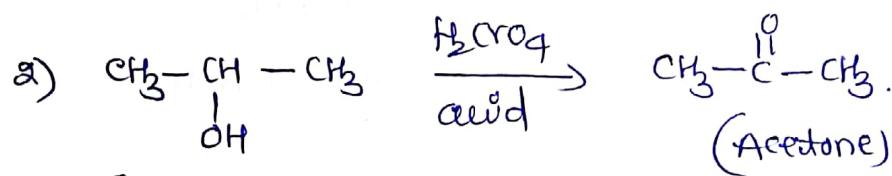
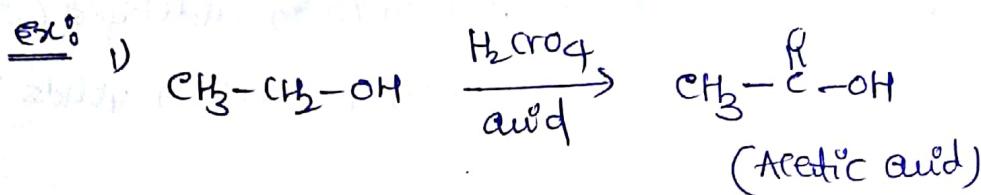


Tertiary alcohols:Oxidation by Chromic acid (H_2CrO_4):

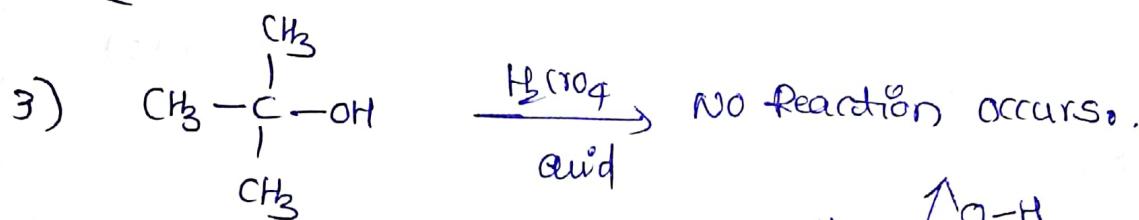
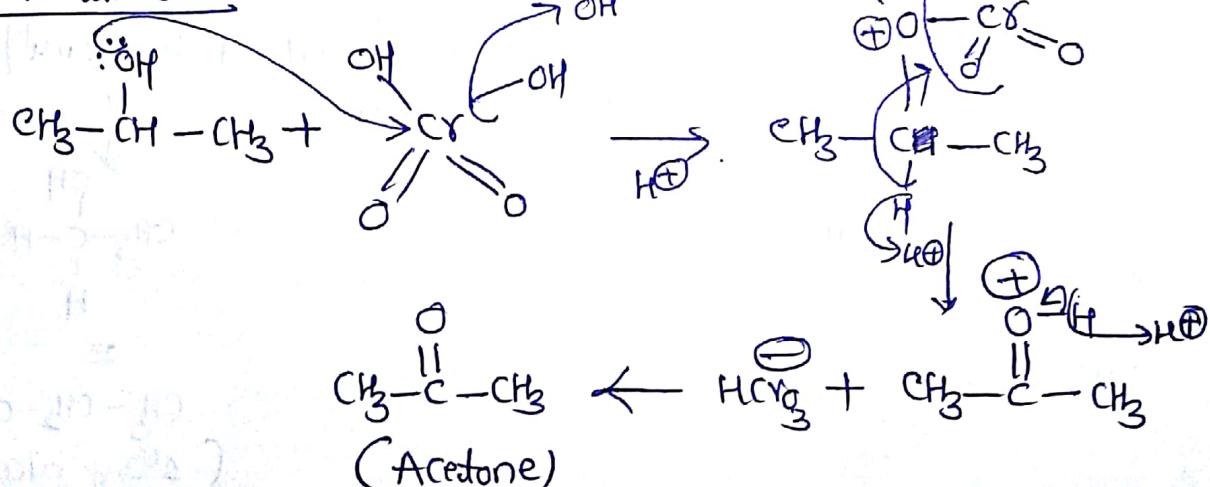
This is also called Jones oxidation is carried out by Jones reagent which is prepared by dissolving chromium trioxide (Cr_2O_3) in aqueous sulphuric acid that produces a reddish solution of chromic acid H_2CrO_4 .

→ The chromic acid oxidises primary alcohols to a carboxylic acid.

→ The chromic acid oxidises secondary alcohols to ketone.



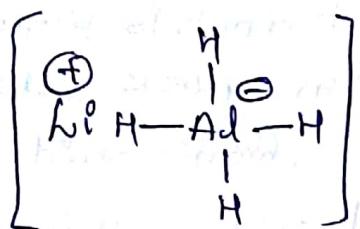
(Primary alcohols)

Mechanism:

Reduction Reactions of Carbonyl Compounds by using LiAlH_4 & NaBH_4

→ Reduction Reactions of carbonyl compounds by "LiAlH₄"

The structure of LiAlH₄ is as follows.

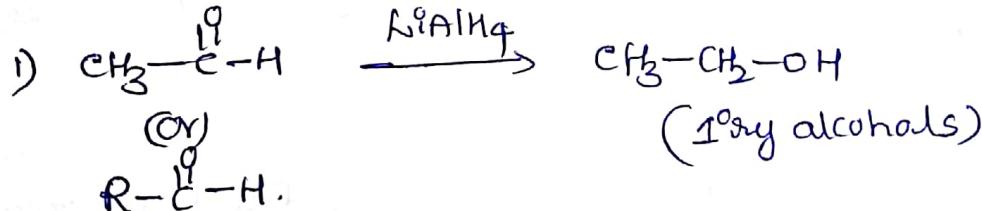


→ The Al-H bond of LiAlH₄ is more polar making LiAlH₄ a strong reducing agent.

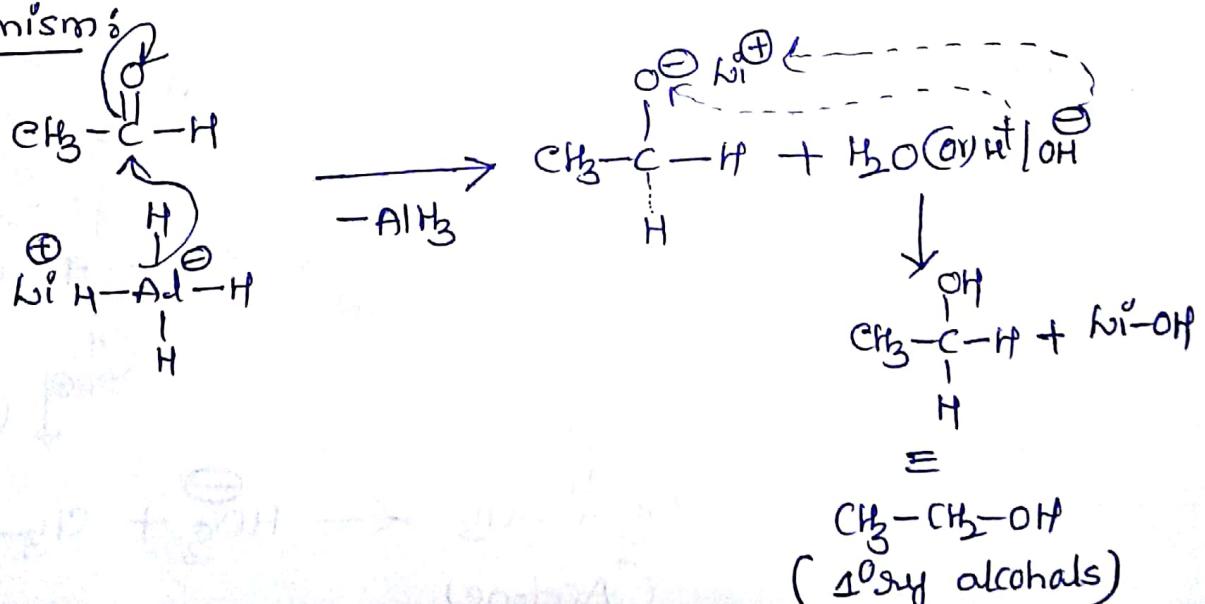
→ The addition of a hydride (H^-) ion to an aldehyde (or) ketone gives alkoxide anion which on protonation yields the corresponding alcohols.

- * Aldehydes produce primary alcohols
- * Ketones produce secondary alcohols.

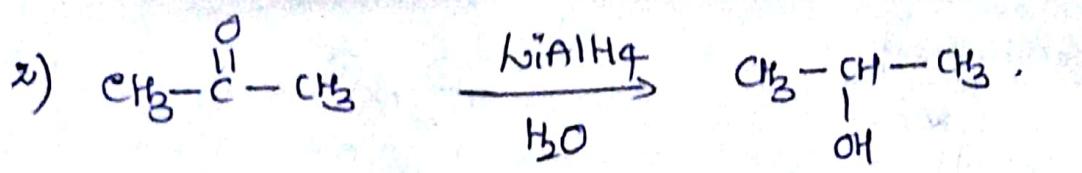
Eg:



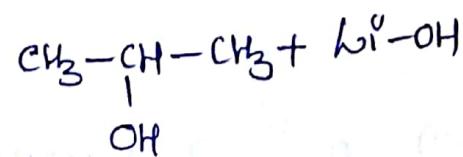
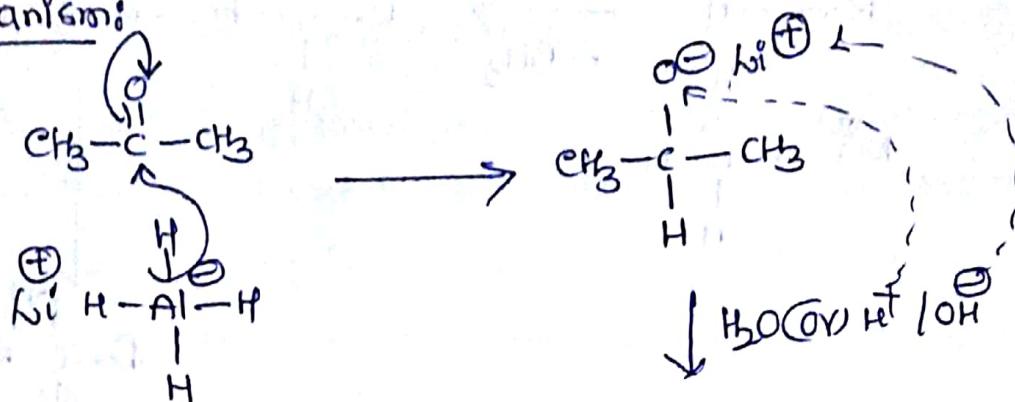
Mechanism:



(Primary alcohols)



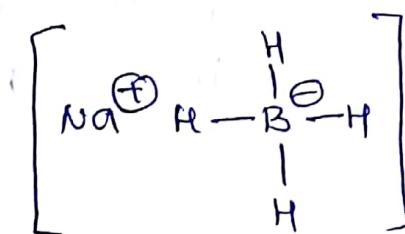
Mechanism:



(2° xy alcohols).

Reduction reactions of Carbonyl Compounds by NaBH_4

The structure of NaBH_4 is as follows.

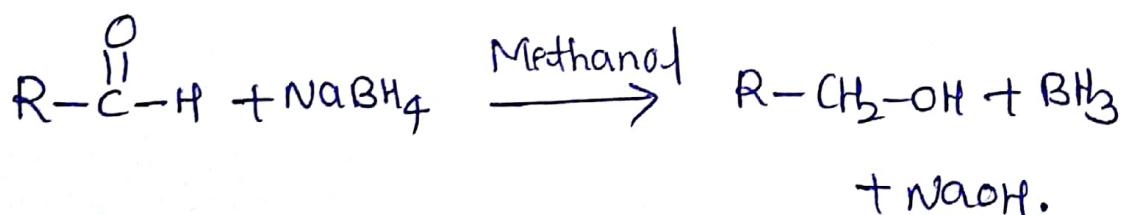


NaBH_4 is sodium Borohydride, B is more electronegative than Al. During the reduction of sodium borohydride methanol is used as solvent with both as hydrolising agent.

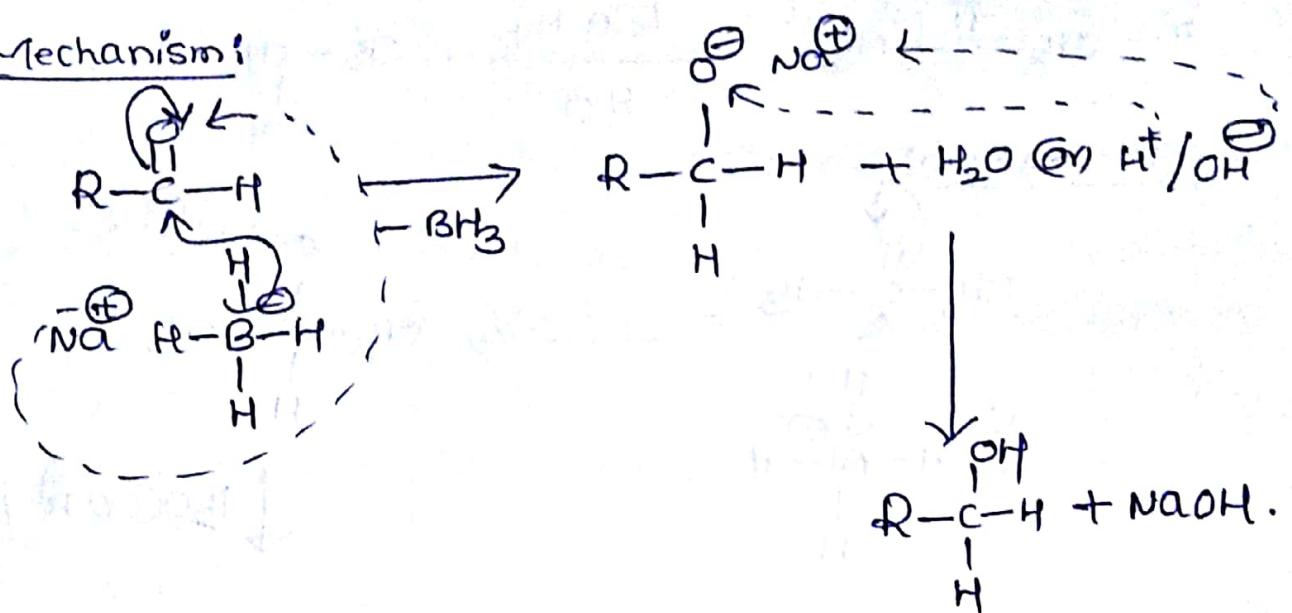
→ Aldehydes undergo reduction with NaBH_4 and produces primary alcohols.

→ Ketones undergo reduction with NaBH_4 and produces secondary alcohols.

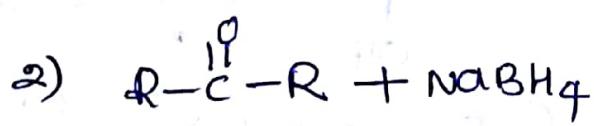
Eg:



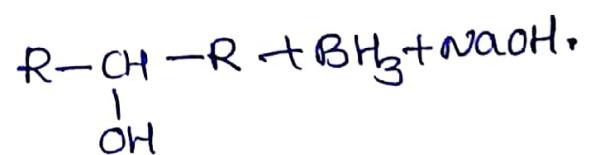
Mechanism:



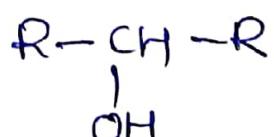
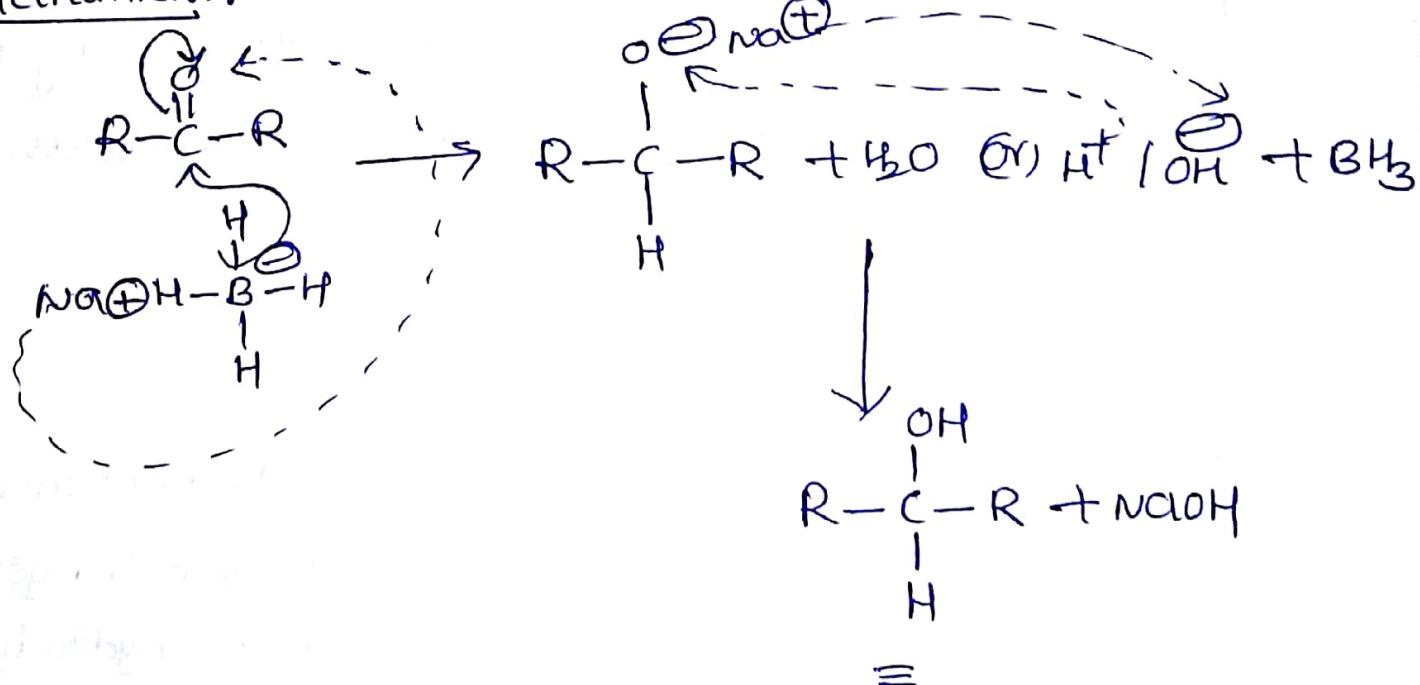
Primary alcohols.



Methanol



Mechanism:

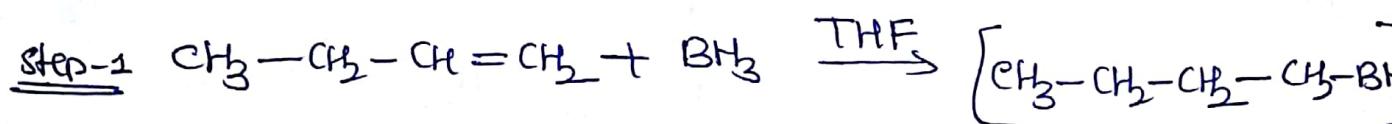


(Secondary alcohols)

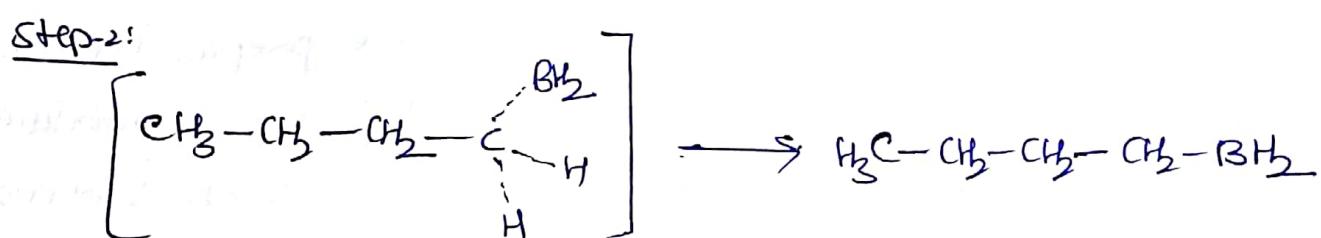
Hydroboration of alkenes

Hydroboration—Oxidation is a two step pathway used to produce alcohols. The reaction proceeds in an anti-Markovnikoff's manner. Where the hydrogen from BH_3 attaches to more substituted carbon and boron attaches to the less substituted carbon in the alkene double bond.

The mechanism of hydroboration of an alkene is given below.

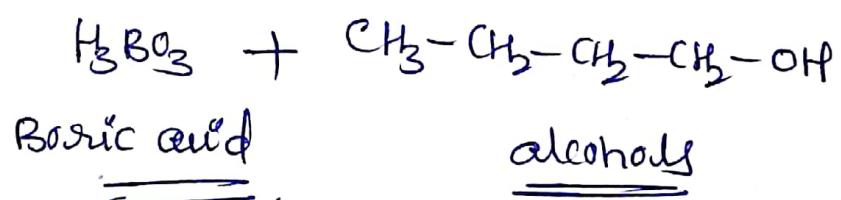
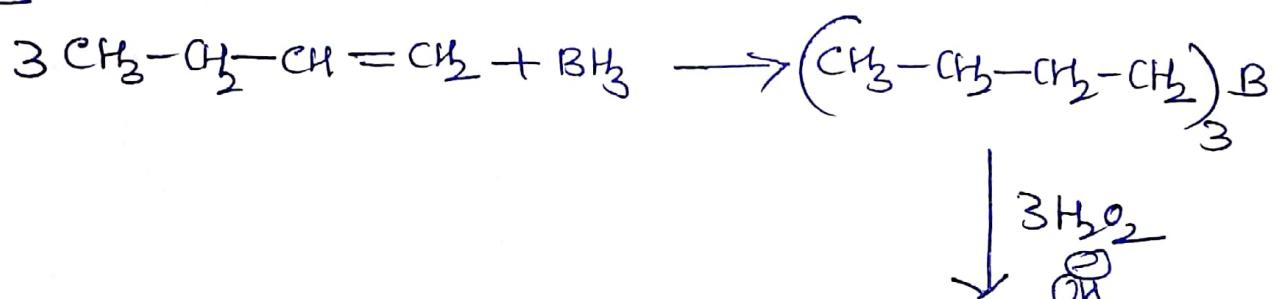


Transition state.



→ NO carbocation formed and no rearrangement takes place.

Eg:

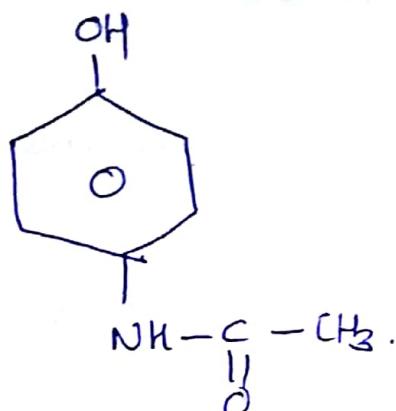


Structure, synthesis and pharmaceutical

Applications of Paracetamol and Aspirin

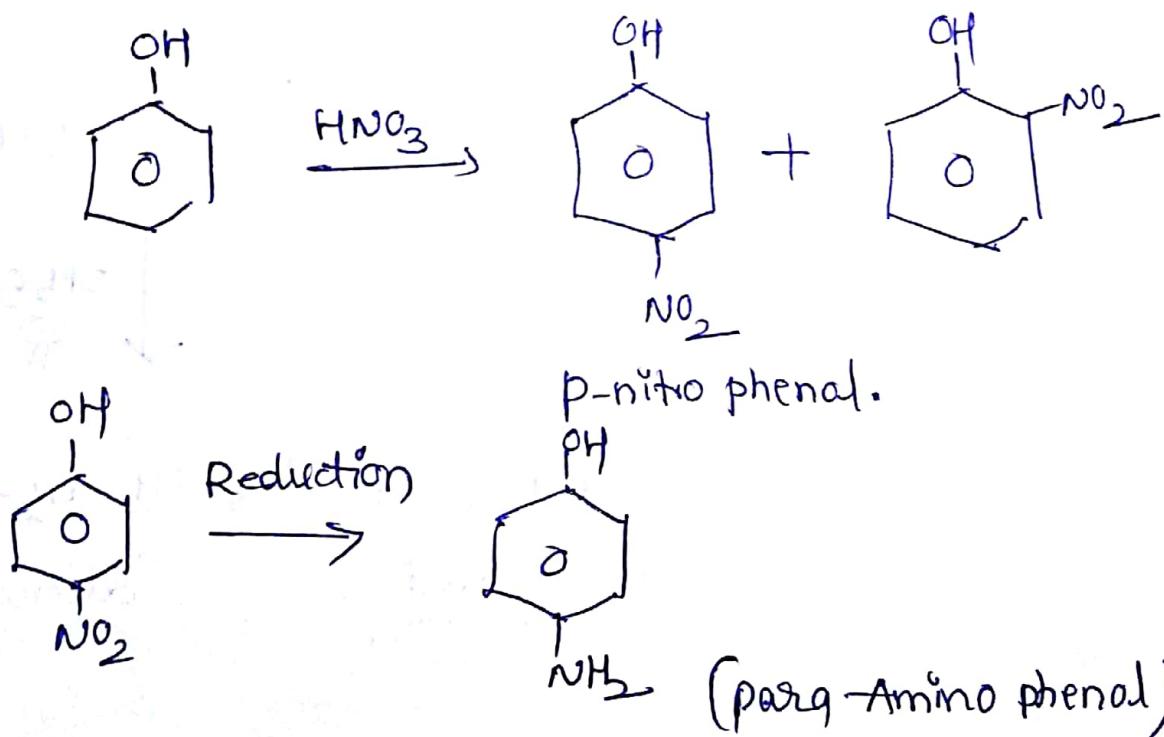
Paracetamol:

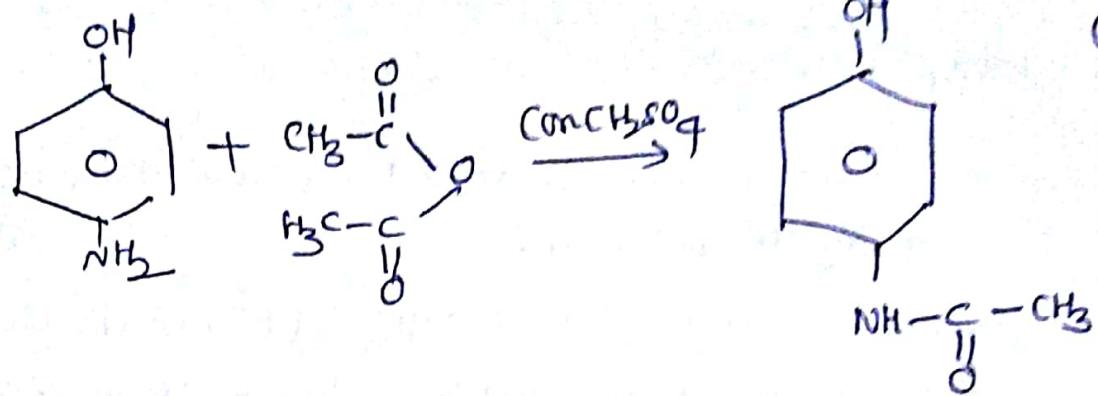
Structure of Paracetamol is as follows.



Synthesis:

The starting material for the preparation of Paracetamol is phenol, which is nitrated to give a mixture of the ortho and para-nitrophenol. The -O- isomers is removed by steam distillation and p-nitro group reduced to p-amino phenol. This is then acetylated to give paracetamol.





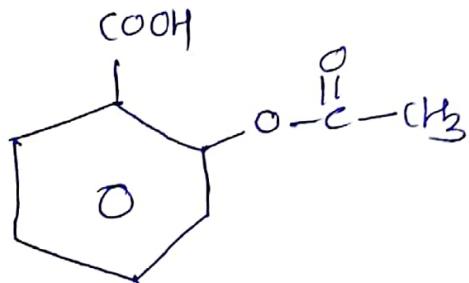
paracetamol

Applications:

- 1) paracetamol is a pain reliever and a fever reliever
- 2) paracetamol is used to treat many conditions such as headache, muscle aches, arthritis, backache, colds.

Aspirin:

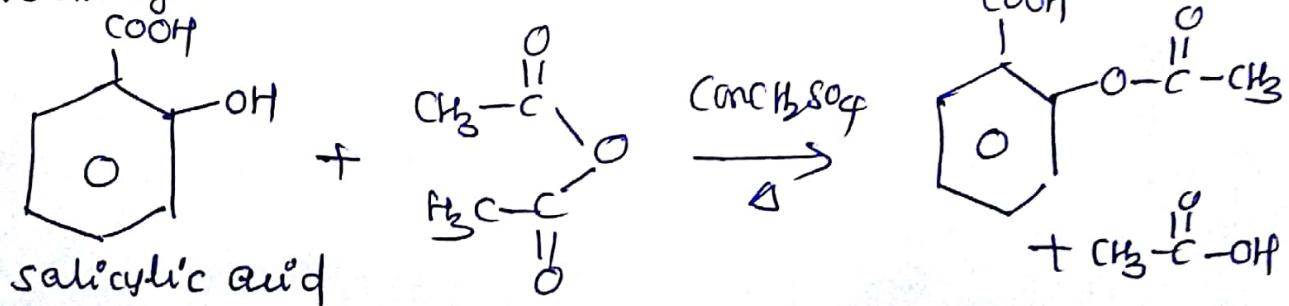
Structure:



Acetyl salicylic acid (or) Aspirin.

Synthesis:

An excess of acetic anhydride is added to an salicylic acid in presence of catalyst FeSO_4 . The mixture is heated to form the aspirin and acetic acid. After the reaction takes place water is added to destroy the excess acetic anhydride.



Applications:

- 1) Aspirin is an antipyretic drug which lowers the body temperature.
- 2) It is a common Analgesic (pain reliever)
- 3) Use in the prevention of heart attack as it has anti-blood clotting action and acts as vaso-dilator.
- 4) It prevents the aggregation of platelets.