

4. Stereochemistry.

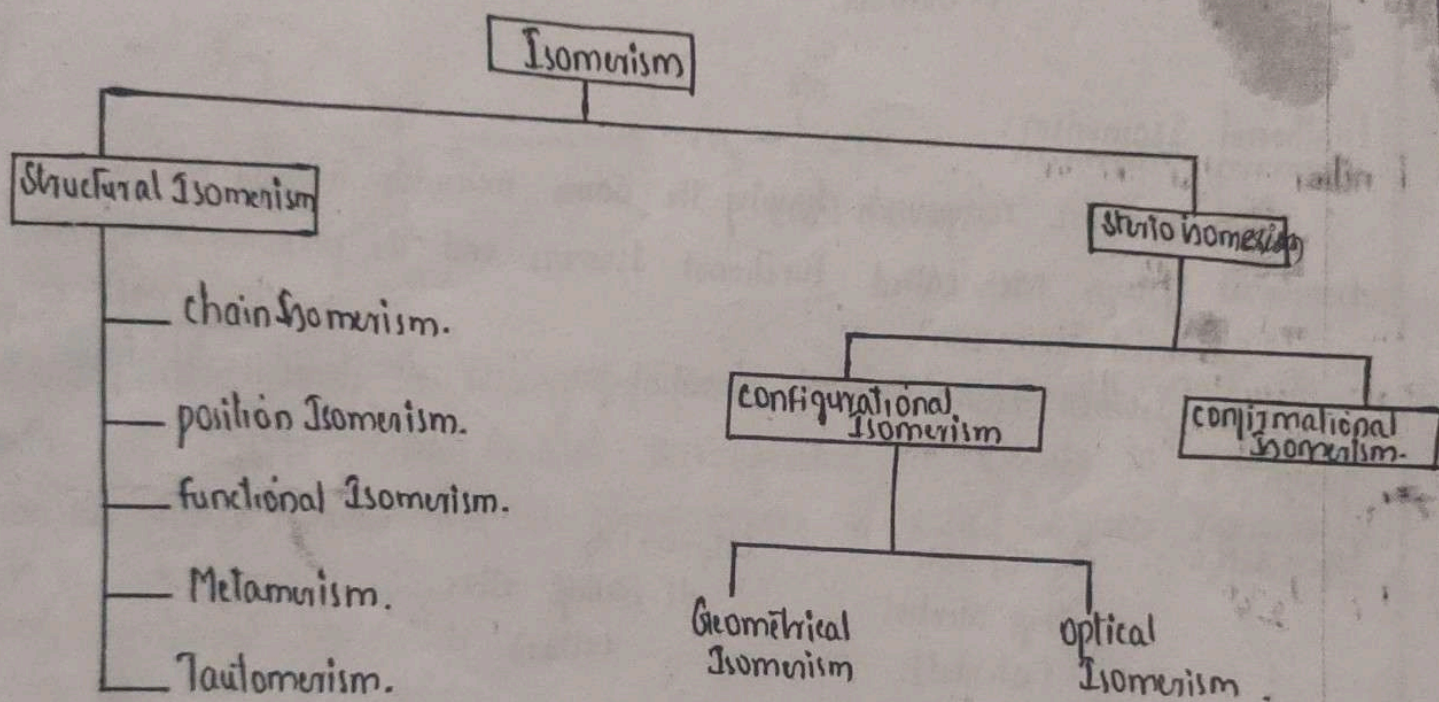
(1)

* Stereochemistry Study the Three dimensional structures of the molecules.

Isomerism:

Existence of two (or) more compounds having same molecular formula but with different properties (physical, chemical (or) both) are called the "Isomers" and the phenomenon is called 'Isomerism'.

Types of Isomerism.



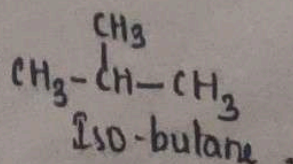
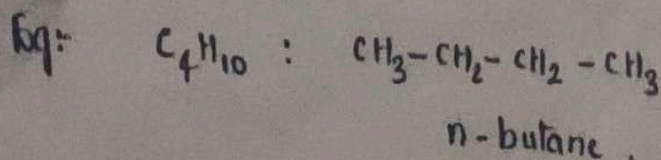
* Structural isomerism:

Two (or) more compounds having the same molecular formula but different structural formula are known as 'Structural Isomerism' and the phenomenon is known as 'Structural Isomerism'.

Structural Isomerism again divided into several types.

* chain Isomerism:

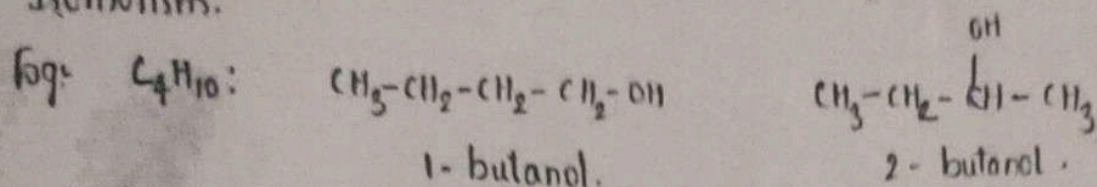
Two (or) more compounds having the same molecular formula but differ in the nature of the carbon chain (straight (or) branched chain) are called chain Isomers and the phenomenon is called chain Isomerism.



Position Isomerism:

Two (or) more compounds having the same molecular formula but differ in the position of substituent atom (or) group (or) unsaturated linkage in the same carbon chain are called "positional isomers" and the phenomenon is called "positional isomerism".

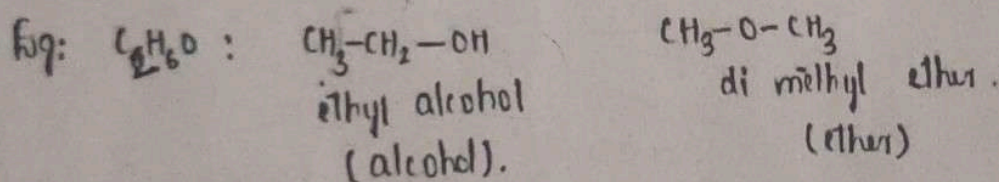
Alkenes, Alkynes, Alkyl halides, Alcohols, Amines etc. all show positional isomerism.



Functional Isomerism:

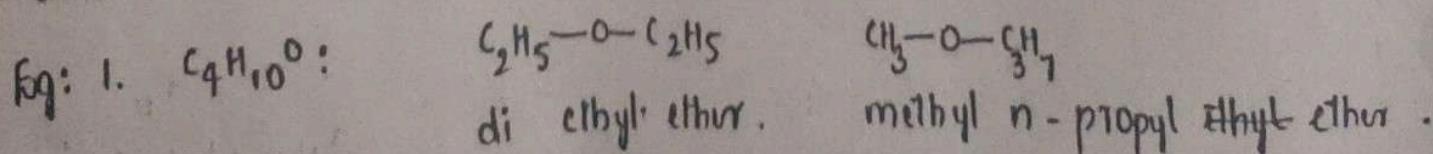
Two or more compounds having the same molecular formula but differ in functional groups are called functional isomers and the phenomenon is called as "functional isomerism".

These isomers have different chemical properties due to different functional groups.



Metamerism:

Two (or) more compounds having the same molecular formula but differ in the nature of alkyl groups attached to the same functional group are called the metamers and the phenomenon is called "metamerism".

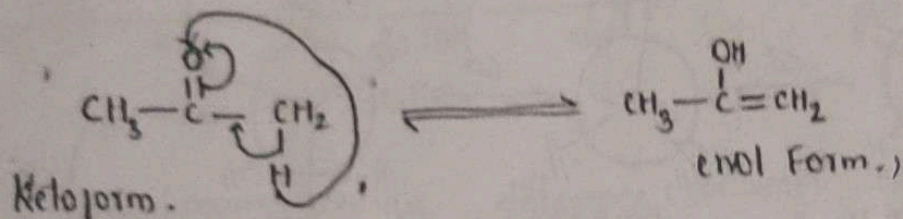


Tautomerism:

Two (or) compounds having the same molecular formula but differ only in the position of hydrogen atom are called Tautomers and the phenomenon is called "Tautomerism".

These two compounds exist in dynamic equilibrium with each other and are easily interconvertible.

Eq:



Stereo Isomerism:

Two (or) more compounds having the same molecular formula and structural formula but differ in the spatial arrangement of atoms or groups are known as Stereo isomers and the phenomenon is called "Stereo isomerism".

It is of two types.

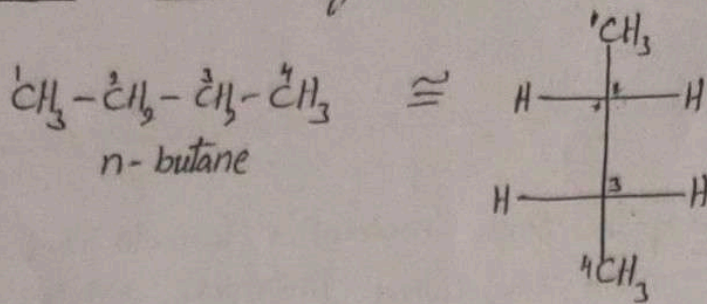
1. conformational Isomerism.
2. Configurational Isomerism.

1. Conformational isomerism:-

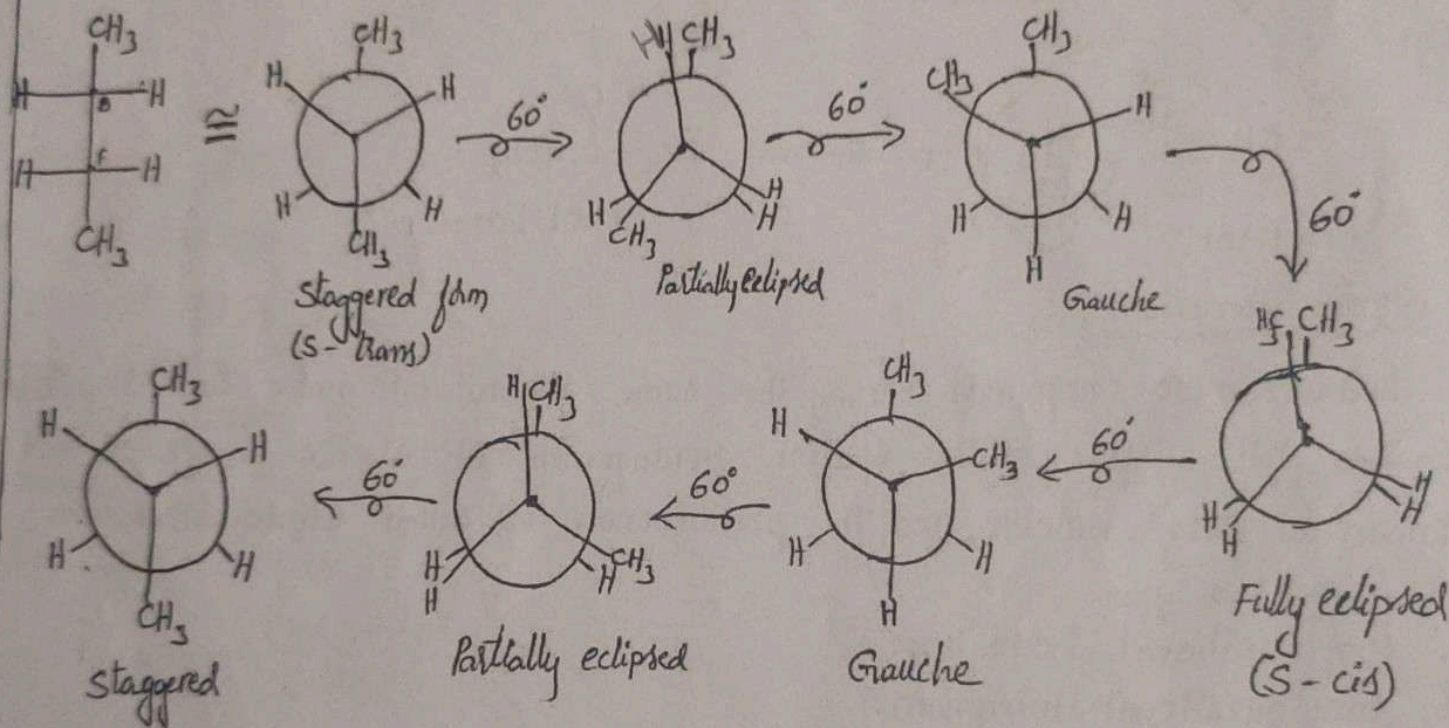
Two (or) more compounds having same molecular formula but differ in the spatial arrangement of atoms (or) groups and are obtained by rotation around C-C single bond are called conformational isomers. (or) This phenomenon is called conformational isomerism.

Ex:- Alkanes, cyclo alkanes.

40 Conformational isomers of n-butane :-



According to "Newman" projection formula, the front carbon represented by a dot (•) & the back carbon as a circle (○)

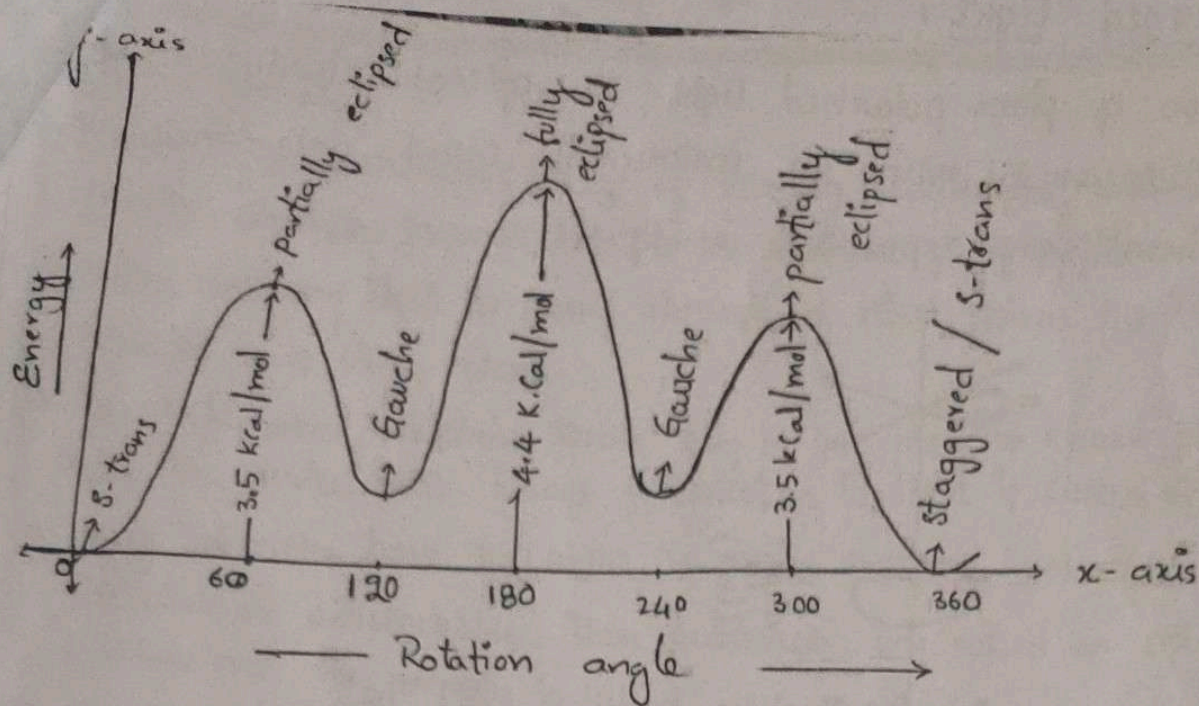


* By rotating carbon atoms around C_2-C_3 bond, different conformations of n-butane are possible. These are represented by "Newmann Projection formula"

* In staggered form, the two methyl groups are arranged by 180° apart. Hence, it is most stable.

* In Gauche form, the methyl groups are arranged by 60° apart. These are less stable than staggered forms, due to the repulsions in between two methyl groups.

* In fully eclipsed form (S-cis), the methyl group is eclipsed over another methyl group. Hence, maximum repulsions arises and it is least stable than all other isomers.



Maximum energy difference between conformations of n-butane is only 4.4 K.Cal/mol. Hence, these conformations are easily converted into one another.

∴ The stability order of different conformations is
 staggered > Gauche > Partially eclipsed > Fully eclipsed (s-cis)

2. Configurational Isomerism:

The Stereo isomers which are non-superimposable and non-convertible by rotation around single bonds are known as configurational isomers and the phenomenon is called configurational isomerism.

The configurational isomers are converted only by breaking and making of bonds.

This isomerism again classified into two types.

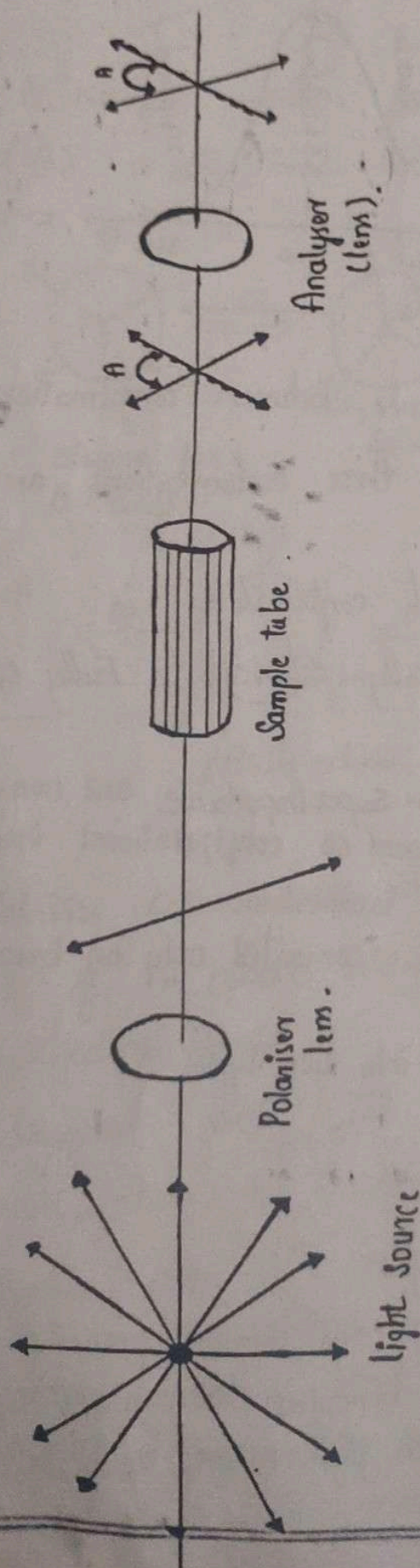
1. Optical Isomerism.
2. Geometrical Isomerism.

* Optical Isomerism.

Compounds which have same physical and chemical properties and differ only in their optical activity (i.e. their behaviour towards plane polarized light) are known as optical isomers and the phenomenon is known as optical isomerism.

Plane polarised light:

The rotation of plane polarised light, the optical activity can be detected and measured using an instrument called polarimeter which is schematically represented in fig 4.8.



Schematic representation of polarimeter.

→ Solid line plane polarised light before rotation.

←---→ Broken line plane polarised light after rotation.

α is the angle of rotation.

Optical activity.

- * Ordinary light consists 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 polarised 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 substance.
 - 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~~ activity is done in terms of specific rotation which is defined as the rotation produced by a solution of length of 10 cm and unit concentration (1 g/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_{obs} is the rotation observed, l is the length of the solution and c is the number of grams in 1 ml of solution,

* Dextro rotatory substances : (+) or (d)

These substances rotate the plane polarised light towards right side.

* Laevo rotatory substances : (-) or (l)

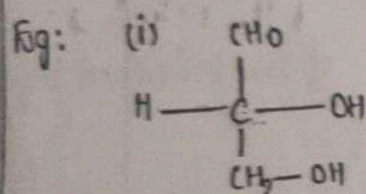
These substances rotate the plane polarised light towards left side.

* Optically inactive substances :-

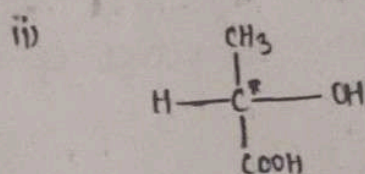
These substances do not rotate the plane polarised light either right side or left side.

* Asymmetric carbon (or) chiral carbon :-

A carbon atom having four different monovalent atoms (or) groups is known as 'asymmetric' or 'chiral carbon'. It is indicated by '*' (Asteric).



Glyceraldehyde



Lactic acid.

Elements of Symmetry:

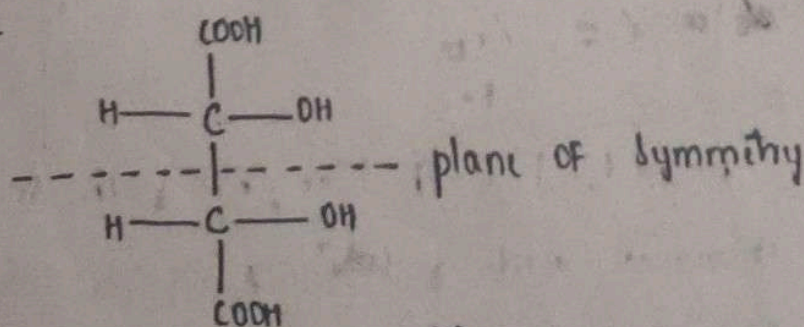
plane of symmetry, center of symmetry and alternating axis of symmetry are the main elements of symmetry.

The absence of these elements of symmetry is an indication for the chirality in a molecule.

Plane of Symmetry:

A plane divides the molecule into two equal halves such that one half of the molecule is a mirror image of the other is called plane of symmetry.

Fig:-

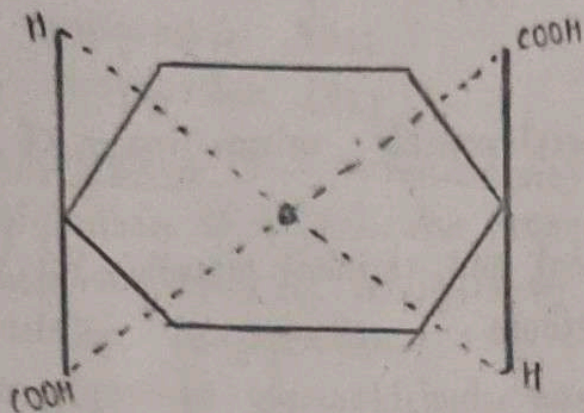


Meso tartaric acid.

Centre of Symmetry:-

A molecule have a centre of symmetry, if all straight lines that can be drawn through the center of the molecule and meet the identical atoms at equal distance from the center.

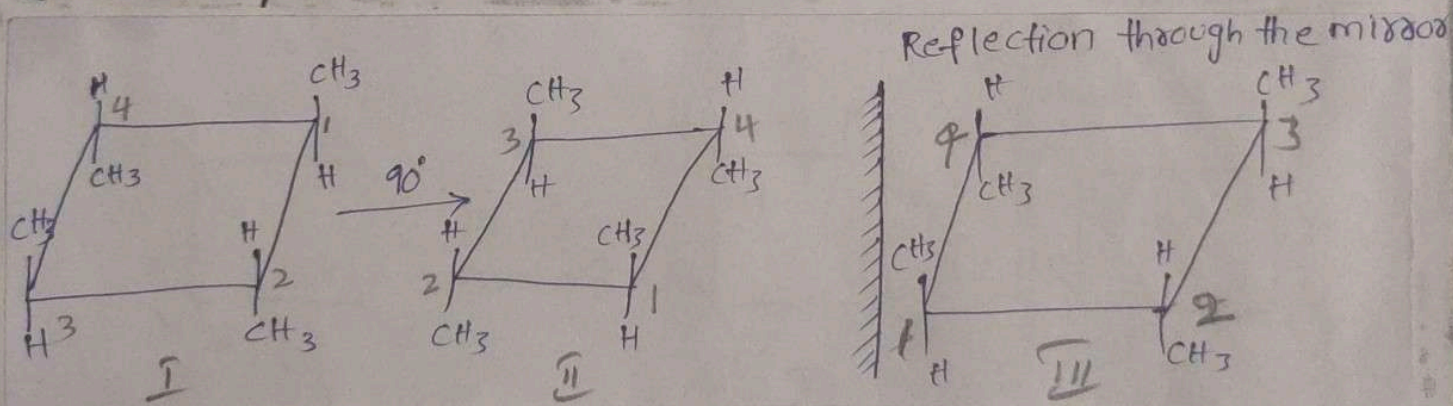
Fig:



Trans-cyclohexane 1,4-dicarboxylic acid.

Alternating axis of Symmetry.

A molecule is said to possess an alternating axis of symmetry, when it is rotated to an angle of $360^\circ/n$ followed by reflection in a plane perpendicular to that axis, an identical structure is obtained.

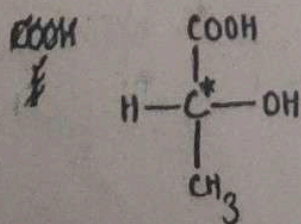


I & III are identical structures

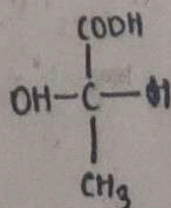
* Asymmetric molecules.

In the absence of elements of symmetry (plane, center, alternating axis of symmetry) a molecule is non-superimposable on its mirror image is called a symmetric (or) chiral molecules.

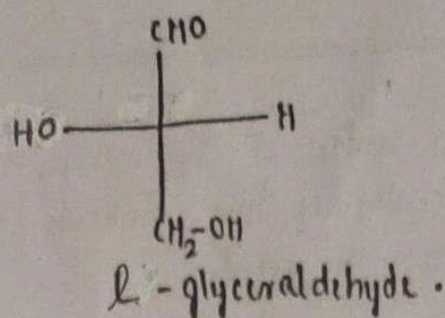
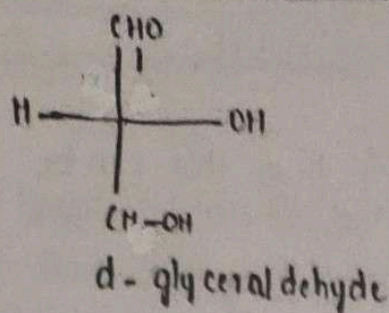
Fig: 1.



D-lactic acid



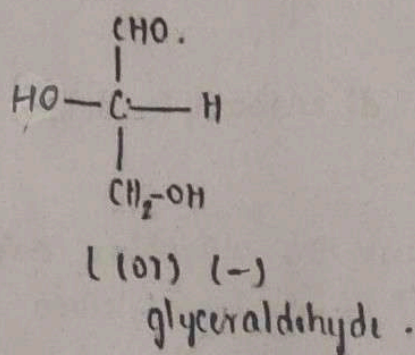
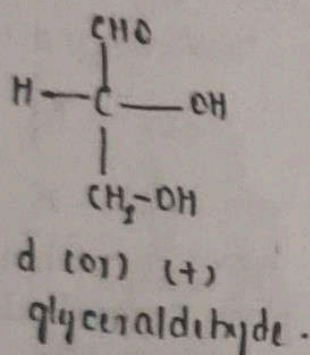
L-lactic acid.



* Enantiomers

Optical isomers which are non-superimposable mirror images of each other are called "Enantiomers".

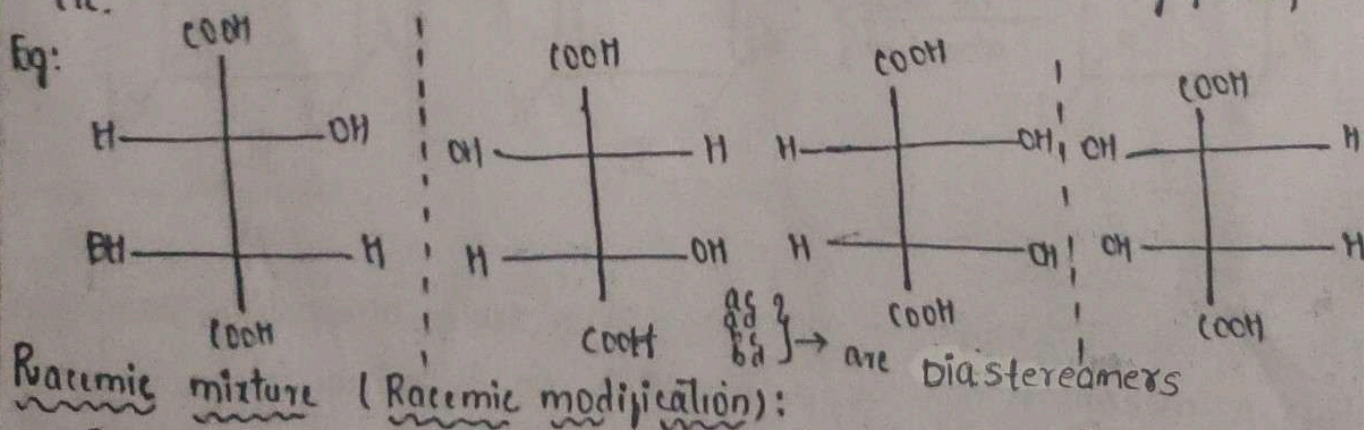
The enantiomers have identical physical and chemical properties but rotate the plane polarised light in opposite directions.



* Disastercomers :-

Optical isomers of a compound which are not mirror images and non superimposable are called ~~as~~ 'Diastereomers'.

Diastereomers differ in physical properties like melting point, solubility etc.



Racemic mixture (Racemic modification):

Equimolar mixture of dextro and leavo forms called Racemic mixture, It is denoted by 'dl' (or) '±' (or) 'r' (or) 'I'. It is optically inactive i.e. it does not rotate the plane polarised light.

Configuration.

The arrangement of atoms (or) groups around the asymmetric carbon atom is known as configuration. For studying the configuration of organic compounds, two systems are developed.

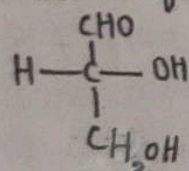
1. Relative configuration (DL)
2. Absolute configuration (RS)

Relative configuration (DL: nomenclature)

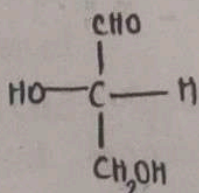
The configuration of a particular compound is assumed and taken as standard and based on this, the configuration of other compounds are studied. This is called relative configuration.

The configuration glyceraldehyde was taken as standard. The configuration of all compounds were studied with respect to glyceraldehyde.

Glyceraldehyde having the -OH group on the right and hydrogen atom on the left, -CHO group at the top and -CH₂OH at the bottom was given the configuration symbol 'D'. The mirror image of D-glyceraldehyde was given the configuration symbol 'L'.



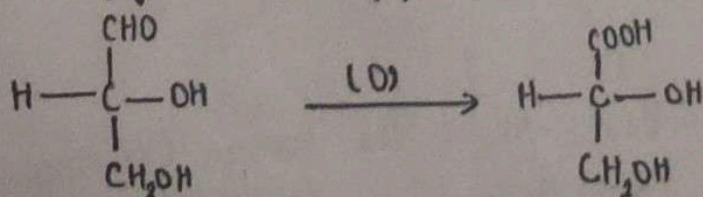
D-(+)-glyceraldehyde



L-(-) glyceraldehyde

Any compound can be prepared from D-Form (or) converted into D-glyceraldehyde belongs D-series. Similarly any compound can be prepared from L-Form (or) converted into L-glyceraldehyde belongs to L-series.

Eg: D-glyceraldehyde can be converted into glyceric acid by oxidation. Thus the configuration of glyceric acid obtained must be D-glyceraldehyde.



D-glyceraldehyde

D-glyceric acid

Absolute configuration: (R,S nomenclature).

R_s notation is indicates the absolute configuration of the compounds. It was proposed by Cahn, Ingold and Prelog. This system is based on the three dimensional structure of the compound. In this system two system are involved.

Step: I

In this step, ~~four~~ atoms (or) groups of priority is to be determined by sequence rules.

Sequence rule: 1

If the four atoms attached to the asymmetric carbon atom, the priority of atoms is determined based on the atomic number.

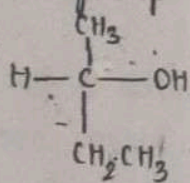
Eg: CHBrCl [Bromo chloro Ido methane].

Order of priority is $I > Br > Cl > H$.

Sequence rule: 2

If two (or) more atoms directly attached to asymmetric carbon atom have the same atomic number, the priority may be determined by comparing the next atom in the group.

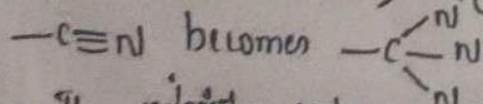
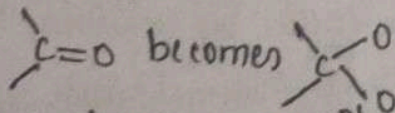
Eg: 2-butanol



Order of priority is $-\text{OH} > \text{CH}_2\text{CH}_3 > -\text{CH}_3 > -\text{H}$
 $[-\text{CH}_3 (C, H, H) - \text{CH}_2\text{CH}_3 (C, C, H)]$.

Sequence rule: 3

A double (or) triple bonded atom is considered equivalent to two (or) three atoms.



Eg: The priority order of $(-\text{CHO}) - \overset{\text{H}}{\underset{\text{H}}{\text{C}}}=\text{O}$ and $-\text{CH}_2\text{OH}$ The former (having C, O, O, H). ~~the third~~ gets higher priority order than $-\text{CH}_2\text{OH}$ (having C, O, H, H). The third atom in $-\text{CHO}$ is 'O' (Atomic no 8) while it is H (atomic no. 1) in $-\text{CH}_2\text{OH}$.

Step: III.

After deciding the priority, the molecule is arranged with the group of least priority away from us and the arrangement of other groups are examined. If the priority decreases from left to right (clock wise direction), the molecule is said to have R-configuration. If the priority decreases from right to left (anti clock wise direction) it has S-configuration.

Geometrical Isomerism.

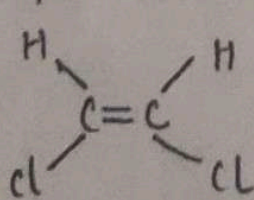
The isomers which contain same molecular formula but differ in the special arrangement of the groups around the double bond are known as 'Geometrical isomers' and the phenomenon is known as 'Geometrical Isomerism'.

It is due to restricted rotation around the double bond. This isomerism is shown by alkenes and their derivatives.

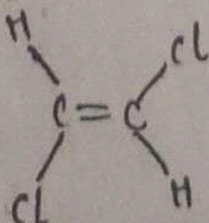
Conditions for Geometrical Isomerism:

- * The molecule must contain $C=C$.
- * The two groups present on each carbon must be different.
- * One group must be common on both the carbon atoms (or) all the groups may be different.
- * So $abc = cab$, $abc = cad$, type of alkenes (or) derivatives of alkenes only exhibit geometrical isomerism.
- * In similar groups present on the same side of the double bond, it is known as 'Cis-isomers'.
- * If similar groups present on the opposite side of the double bond, it is known as 'Trans-isomers'.

Fig: 1. 1, 2 dichloro ethene.

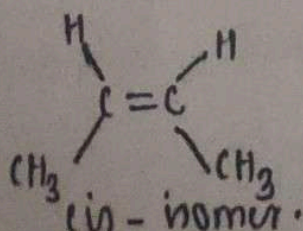


Cis-isomer

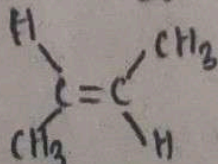


Trans isomer.

Fig: 2 2-Butene ($CH_3-CH=CH-CH_3$)



Cis-isomer.



Trans-isomer.

Organic reactions and synthesis of a drug molecule :-

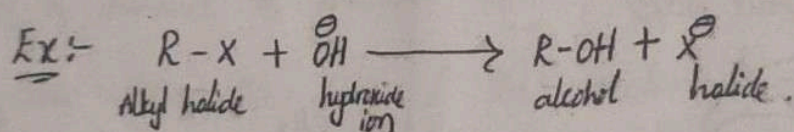
Organic reactions are chemical reactions involving organic compounds.

* Organic reactions can be classified into the following categories

- * Substitution reactions
- * Addition reactions
- * Elimination reactions
- * Oxidation - Reduction reactions
- * Rearrangement reactions.

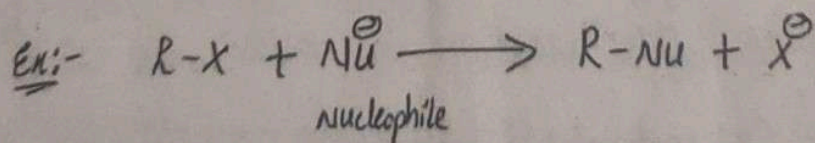
Substitution reaction :-

Substitution reaction is a reaction in which an atom (or) group in a molecule is replaced by another atom (or) group.



Nucleophilic substitution reaction :-

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



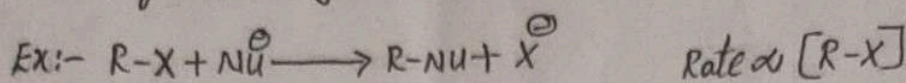
Where X^{\ominus} - leaving group
 Nu^{\ominus} - Nucleophile.

Nucleophilic substitution reactions again classified into two types.

- 1) S_N1 - Uni molecular nucleophilic substitution reaction.
- 2) S_N2 - Bi molecular nucleophilic substitution reaction.

SN¹ - Reaction :- Unimolecular nucleophilic substitution reaction

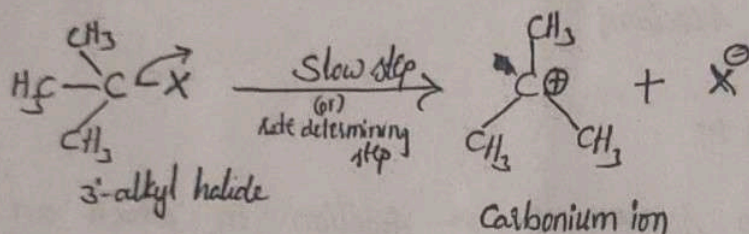
In this reaction, the rate of reaction depends only on concentration of the alkyl halide and



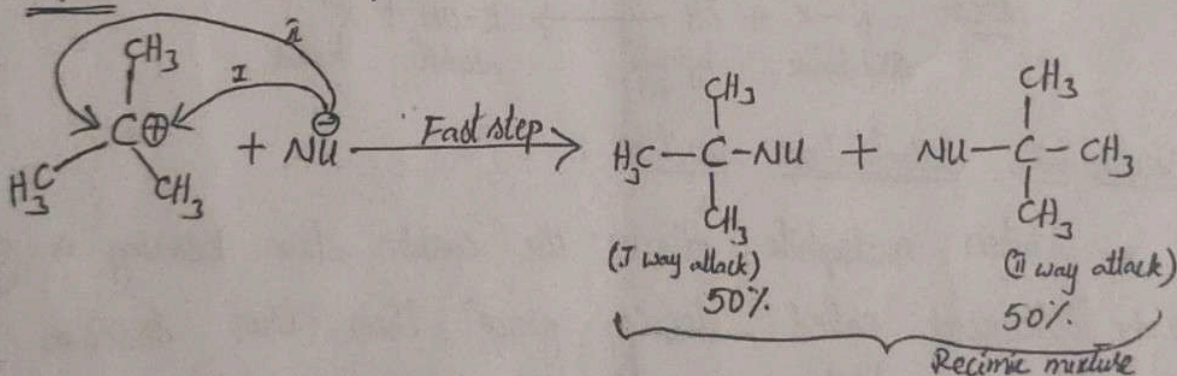
Reaction mechanism :-

- * Reaction mechanism of this reaction follows two step mechanism
- * 3° & 2° alkyl halides will participate in reaction.

Step - I :- (slow step)



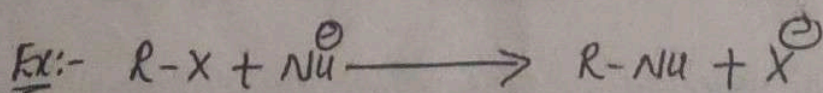
Step - II :- (Fast step)



In rate determining step (slow step), only one reactant (alkyl halide) participated. Hence this reaction is called as "SN¹" reaction.

SN² reaction :- (Bi molecular nucleophilic substitution reaction)

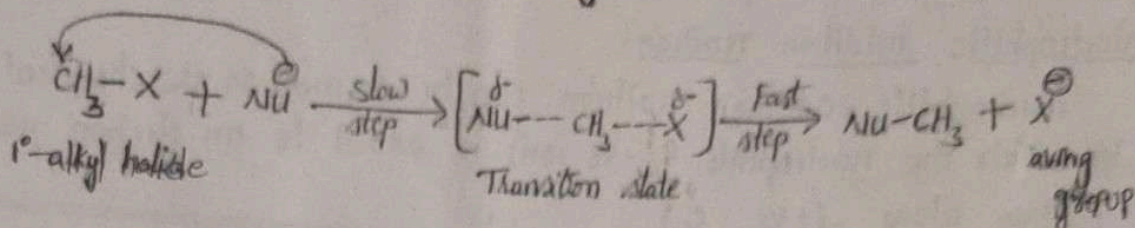
In this reaction, the rate of reaction depends on both i.e. concentration of the alkyl halide and also the nucleophile.



$$\therefore \text{Rate} \propto [R-X][\text{Nu}^-]$$

Reaction mechanism:-

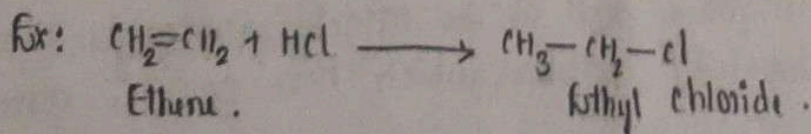
- * It follows one single step mechanism
- * In this reaction 1° & 2° alkyl halides will participate



- * In this rxn mechanism, there is a simultaneous attack by the nucleophile on the opposite side of the alkyl halide followed by the departure of leaving group. Hence in transition state, the new nucleophile-carbon bond is partially formed and C-X bond is partially broken.
- * Due to electrostatic repulsions, the nucleophile will attack the carbon from opposite side to the leaving group. Hence inversion of product is formed.
- * In slow step, the rate of the reaction is depending on both i.e. alkyl halide concentration & Nu^- concentration, so SN^2_{rxn}
 $\therefore R \propto [\text{R-X}][\text{Nu}^-]$

Addition Reactions:

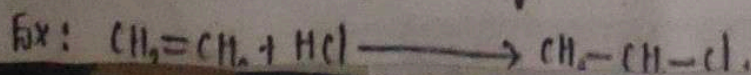
- * An addition reaction occurs when two (or) more reactants combine together and form a single (compound). This product will contain all the atoms that were present in the ^{product} reactions.
- * Addition reactions occur with unsaturated compounds.



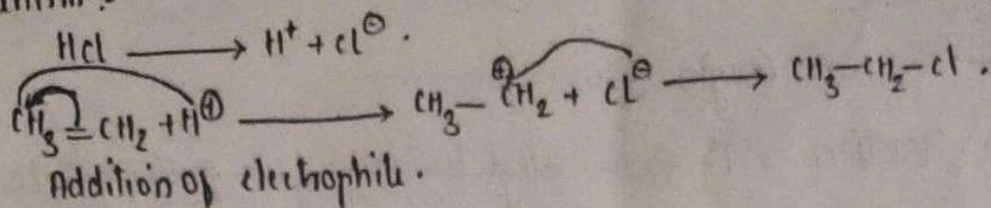
Electrophile in addition reaction:

Electrophile addition reactions can be defined as the chemical reactions in which the electrophile (+ve ion) is added to an electron rich carbon atom (-ve rxn)

Ex: Addition of hydrohalogenation



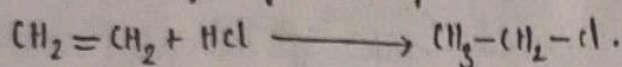
Mechanism:-



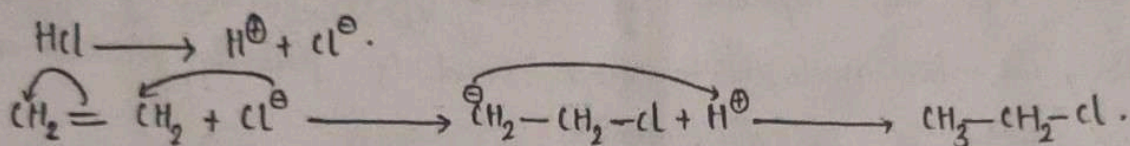
Nucleophilic addition reaction:

Nucleophilic addition reactions can be defined as the chemical reactions in which the nucleophile (-ve ion) is added to an electron poor carbon atom (+ve C).

Ex: Addition of hydrohalogenation.



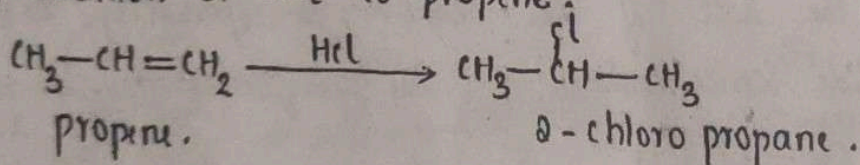
Mechanism:



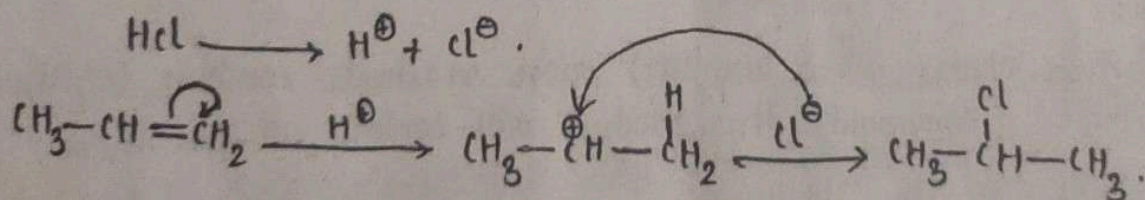
Markownikoff's rule:

According to this rule the negative part of the attacking reagent attaches to the double bonded (unsaturated) carbon, which has lesser number of hydrogen atoms.

Ex: Addition of HCl to propene.



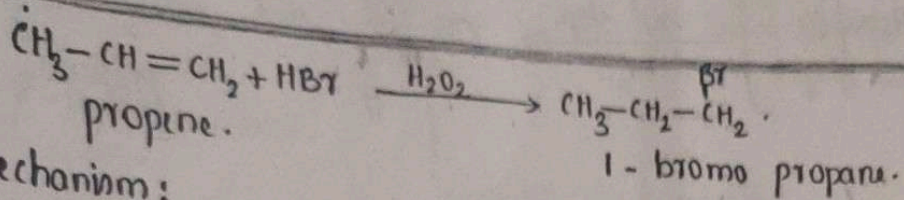
Mechanism:



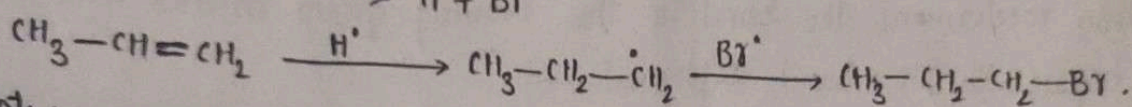
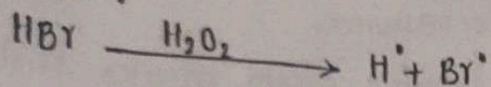
Anti-markownikoff's rule.

According to this rule the negative part of the attacking reagent attaches to the double bonded (unsaturated) carbon, which has greater number of hydrogen atoms.

Ex: Addition of HBr to propene in the presence of peroxides.



Mechanism:



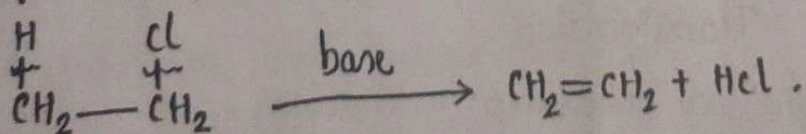
Note:-

- * In presence of peroxides addition of HBr takes place exactly opposite of markownikoff's rule.
- * The anti-markownikoff's addition occurs due to the presence of peroxides and is called peroxide effect.

Elimination reactions:

Elimination process is opposite to addition process, and in which ~~there are~~ two substituents are removed from a molecule in either one step or two step mechanism to form unsaturated compound.

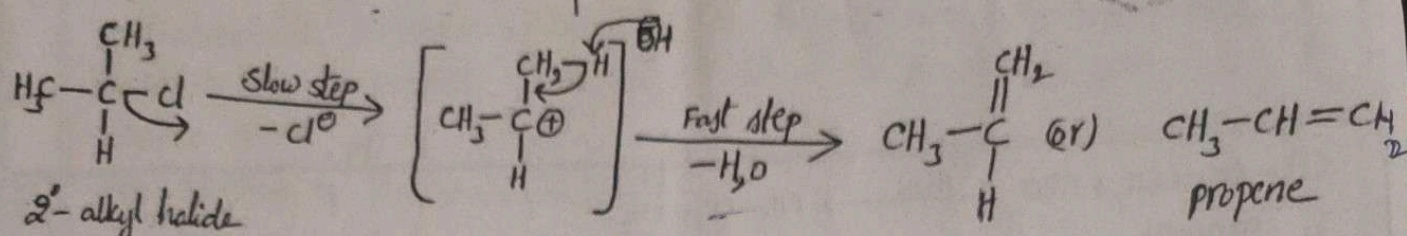
Ex: Dehydrohalogenation of alkyl halide.



Ethyl chloride

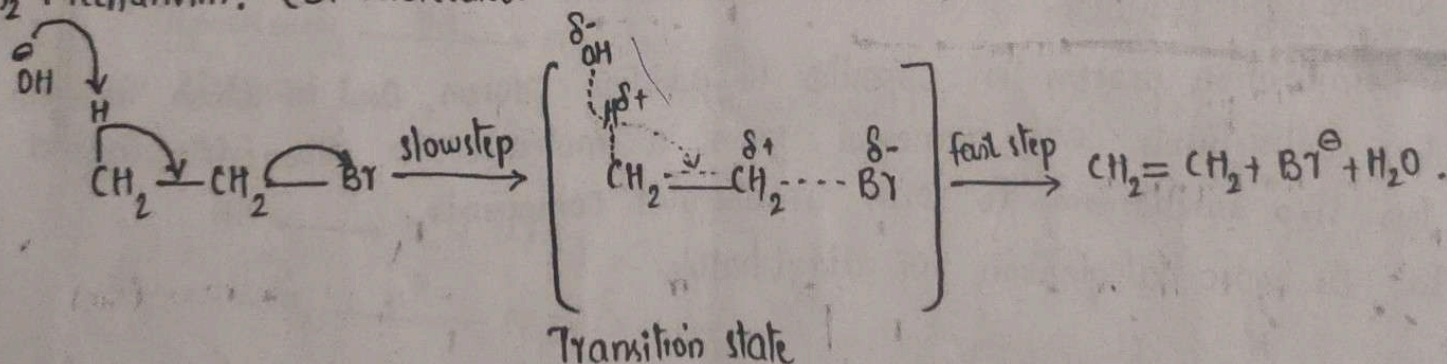
If the reaction is occurred in a two step process is called E_1 mechanism and if occurred in one step-process is called E_2 mechanism.

E_1 Mechanism: (uni molecular Elimination reaction).



- * The E_1 reaction proceeds via a two-step mechanism.
 - * In this reaction mechanism the bond to the leaving group breaks first (In 1st step) before the π -bond is formed.
 - * The slow step is also called as rate determining step. In this step only alkyl halide is involving.
- $\therefore \text{Rate} \propto [\text{Alkyl halide}]$.

E_2 Mechanism: (Bi molecular Elimination reaction).

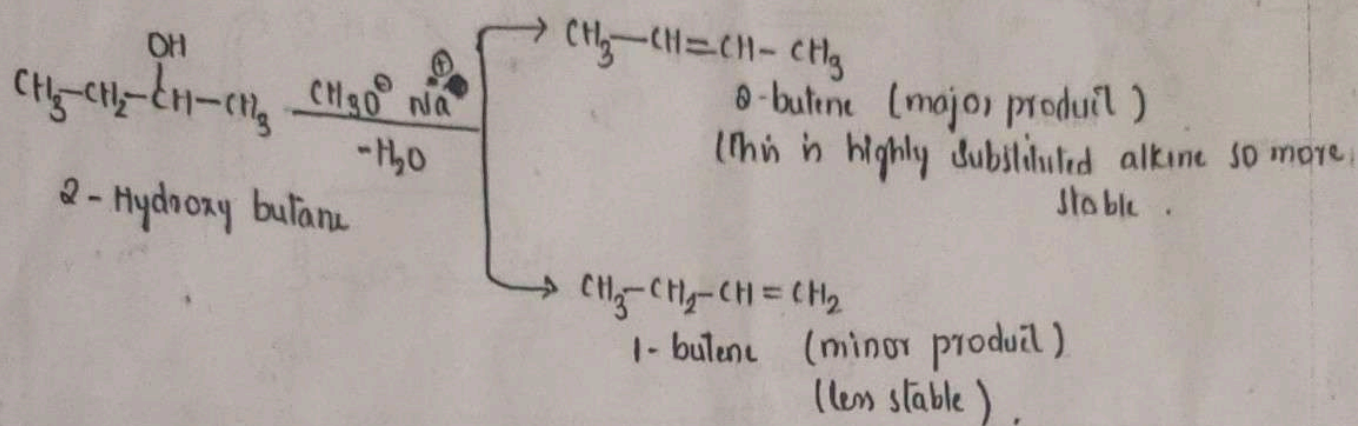


- The E_2 reaction proceeds via a one-step mechanism.
- Rate depends on concentration of both base and substrate.
- All bonds are forming and breaking at same time (in Transition state).
- $\text{Rate} \propto [\text{alkyl halide}][\text{base}]$.

and Zaitsev's (or) Saytzeff's (or) Saytzev's rule.

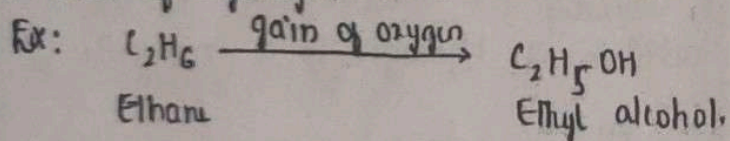
* Zaitsev states that the most highly substituted alkene is the major product in an elimination reaction where more than one alkene can form.

Ex:



Oxidation reactions:

Oxidation can also be defined as the addition of oxygen to a molecule (or) the removal of hydrogen from a molecule.

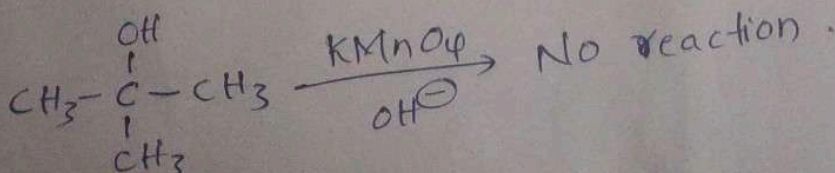
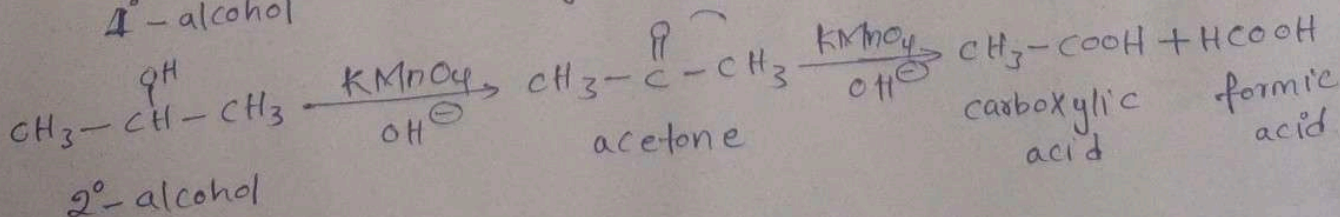
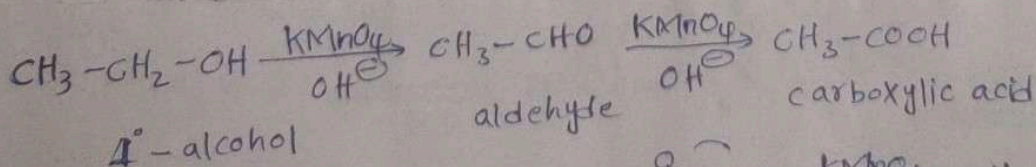


Oxidation of alcohol using KMnO_4 :

potassium permanganate (KMnO_4) is a very strong oxidant able to react with many functional groups, such as alcohol, aldehydes, alkenes.

* KMnO_4 oxidizes alcohols to carbonyl compounds then carboxylic acids.

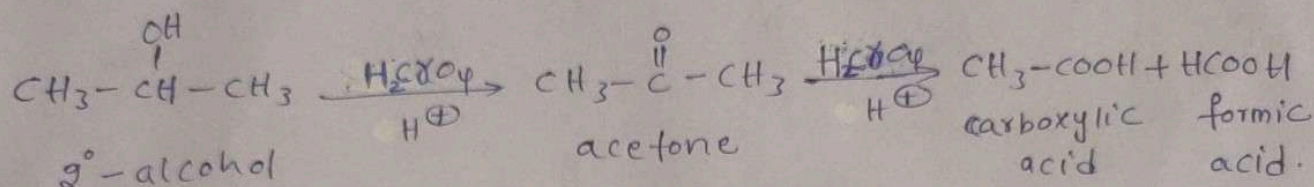
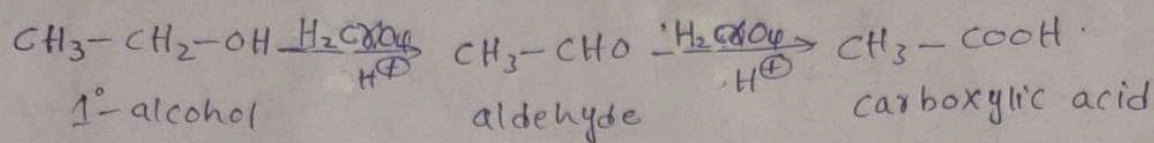
* To promote a greater oxidation speed, oxidation must be performed in strong alkaline conditions using NaOH (or) KOH .



Oxidation of alcohols by using chromic acid (H_2CrO_4) (Jones oxidation)

Jones reagent \rightarrow an aqueous solution of chromic acid (H_2CrO_4).

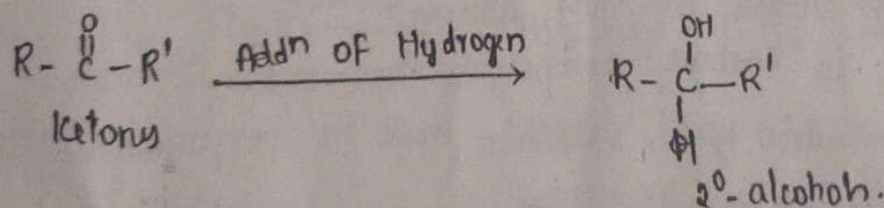
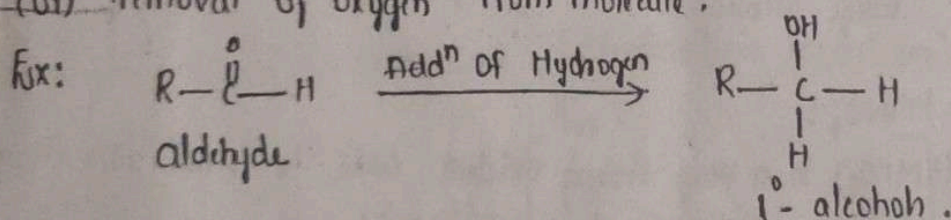
Chromic acid oxidises, alcohols to carbonyl compounds then carboxylic acids.



* H_2CrO_4 oxidation occurs in acid medium, where as ~~chromic~~ $KMnO_4$ oxidation occurs in basic medium.

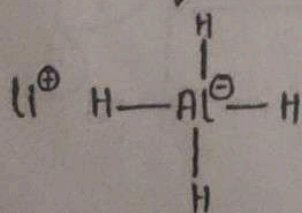
Reduction reactions:

Reduction can also be defined as the addition of Hydrogen to a molecule (or) removal of oxygen from molecule.

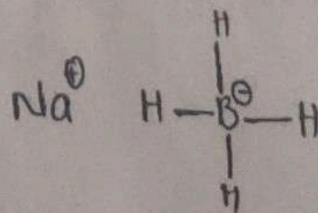


Reduction of carbonyl compounds using $LiAlH_4$ and $NaBH_4$:

The structure of $LiAlH_4$ and $NaBH_4$

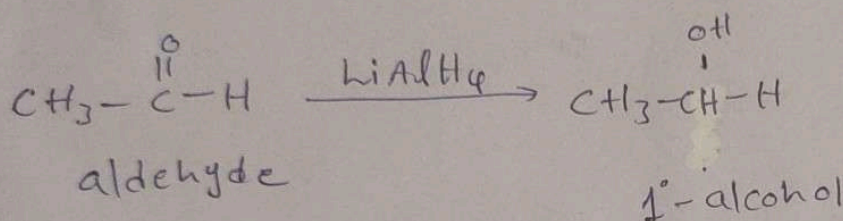
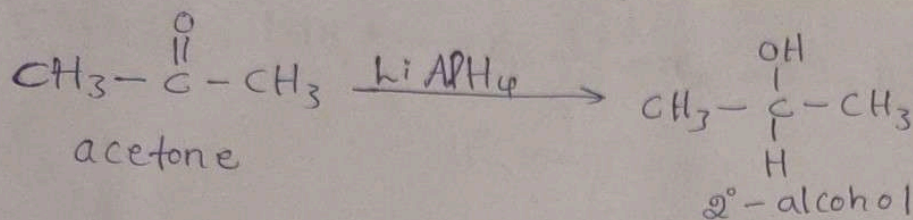


lithium aluminium
hydride.

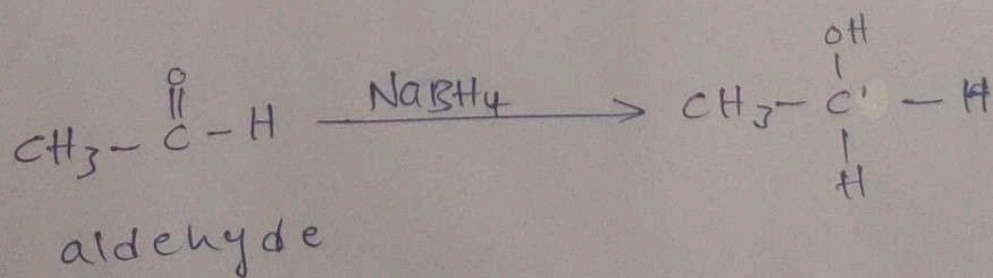
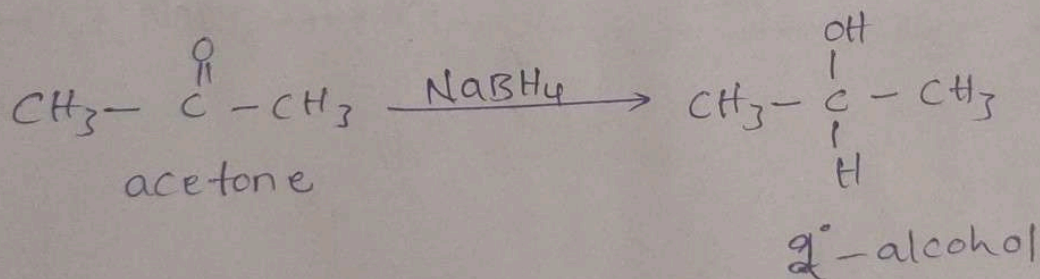


sodium borohydride.

23
 LiAlH_4 is a strong reducing agent because of the Al-H bond of LiAlH_4 is more polar.

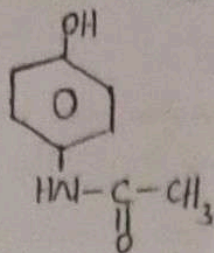


The reaction mechanisms of LiAlH_4 and NaBH_4 are same, but during the reduction of carbonyl compounds in the presence of NaBH_4 methanol is the proton source.



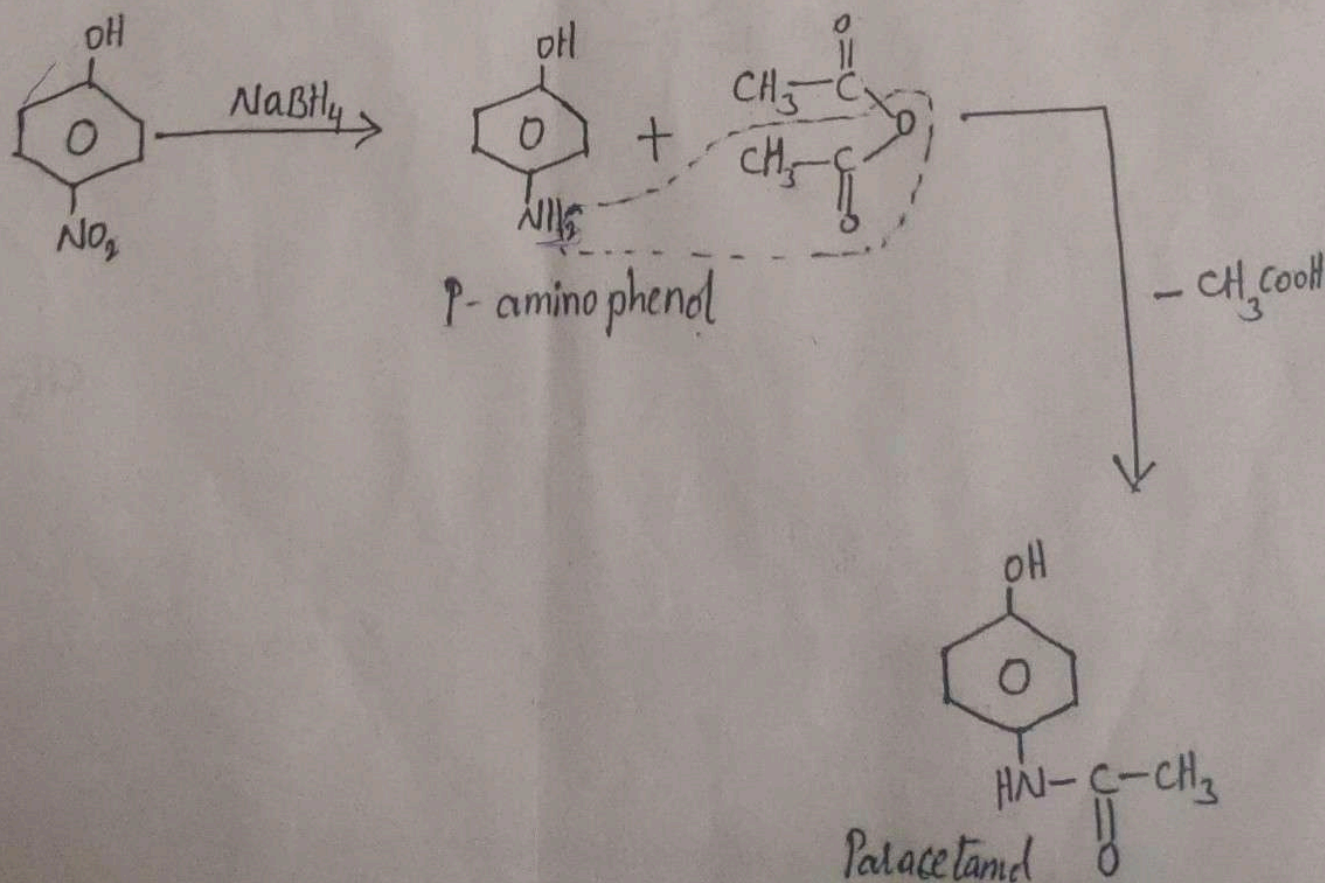
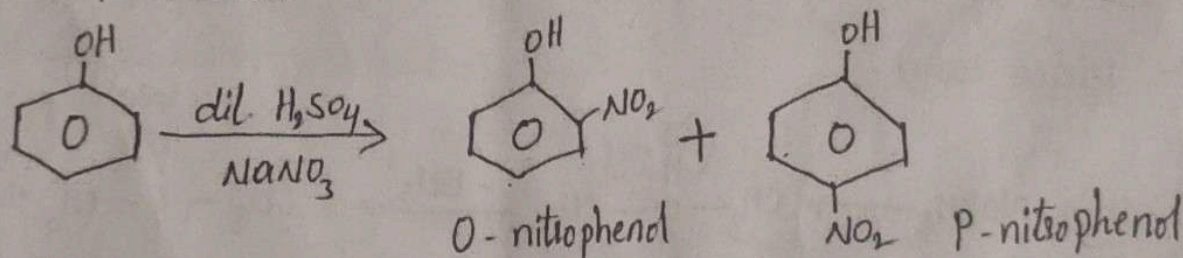
Synthesis of Paracetamol and Aspirin :-

Paracetamol :-



Synthesis :- (Boots method)

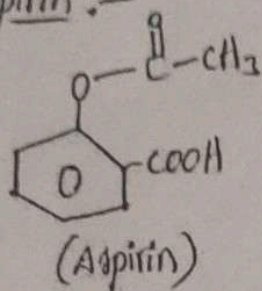
- * Paracetamol is easily prepared by nitrating phenol with sodium-nitrate, which gives two isomers, (O-nitrophenol and P-nitrophenol) were separated by distillation.
- * The nitro group is reduced to amine in the presence of NaBH₄ (Sodium borohydride) producing P-amino-phenol.
- * Thus P-amino phenol reacts with acetic anhydride [(CH₃CO)₂O] to produce Paracetamol.



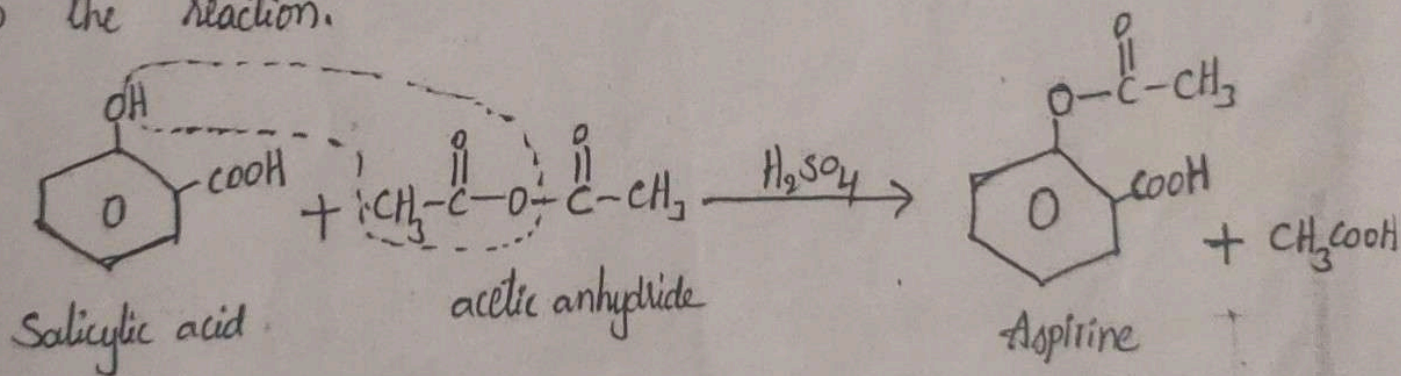
Uses:-

- * Paracetamol is used for reducing fever.
- * It is used for the relief of mild to moderate pain.
- * Some studies state that paracetamol is also used to treat arthritis pain of knee, hand or hips.
- * Some studies show that it is also used in pain of tooth.

Synthesis of Aspirin:-



Salicylic acid is reacted with an excess of acetic anhydride. A small amount of a strong acid is used as a catalyst which speeds up the reaction.



Uses:-

- * It is used to treat pain and fever.
- * Aspirin is also used long-term, at low doses, to help in prevent heart attack, strokes and blood clot.
- * It may be effective at preventing certain types of cancer.