

# PHARM. ORGANIC CHEMISTRY - III

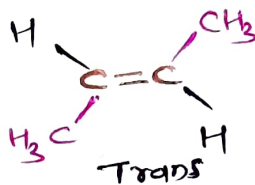
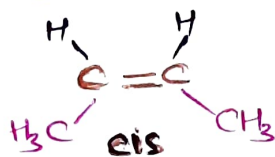
Subject Code: - BP401T & 3414SI

## UNIT I: STEREO CHEMISTRY/ISOMERISM

**ISOMERISM** - The compound having "same molecular formula" but "differ in physiochemical properties", are called Isomers and phenomenon is called Isomerism.

The difference in their properties must be due to different modes of combination or arrangement of atom with in the molecule.

2-Butene



There are two types -

1. Structural Isomerism

2. Stereoisomerism - Configurational & Conformational

1. Structural Isomerism :- Isomerism due to structural differences. When ~~two~~ the isomerism is due to difference in the arrangement of atoms within the molecule, without any reference to space, This phenomenon is called structural isomerism.

" Structural Isomer are compounds that have the same molecular formula but different structural formula.

Types -

- ① chain isomerism - change in the no. of carbon in stem.
- ② Position Isomerism - change in position of functional group
- ③ Functional isomerism - change in functional group
- ④ Metamerism - unequal distribution of carbon atom on either side of functional group
- ⑤ Tautomerism - dynamic equilibrium with each other

2. Stereoisomerism :- When isomerism is caused by the different arrangements of atom or groups in space, is called Stereoisomerism.

" Same Molecular formula but differ in arrangement of atom or group in space"

OR

" Same M.f but differ in configuration"

configuration - refers to 3-dimensional arrangement of atom that characterises a particular compound.

Type - ① Geometrical or Cis-Trans Isomerism

② Optical Isomerism.

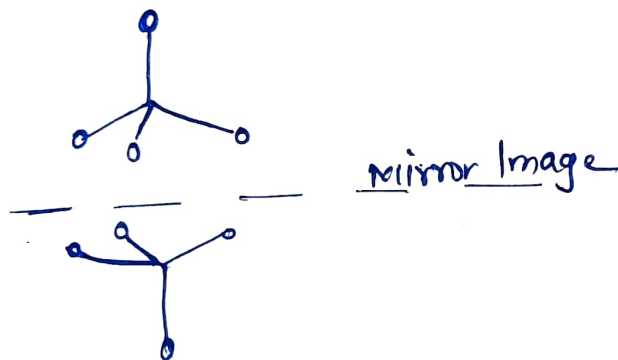
]- Configurational

# OPTICAL ISOMERISM (Stereoisomerism)


↳ Optical Isomers - Same Molecular formula & Same structural formula, & Same physical & chemical properties. They differ in their behaviour towards light (Plane polarized light)

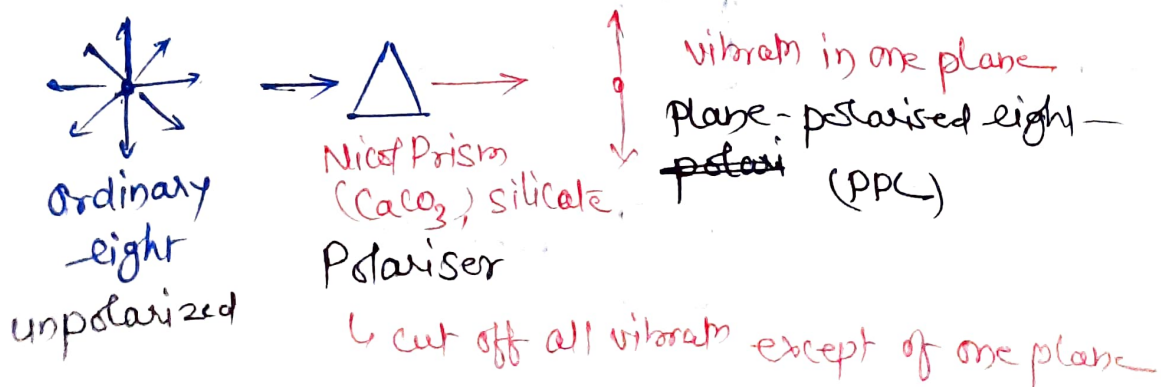
They have ability to rotate plane-polarised light. This property is often referred as optical activity

↳ Except optically active chemical reaction. (otherwise same chemical reaction)



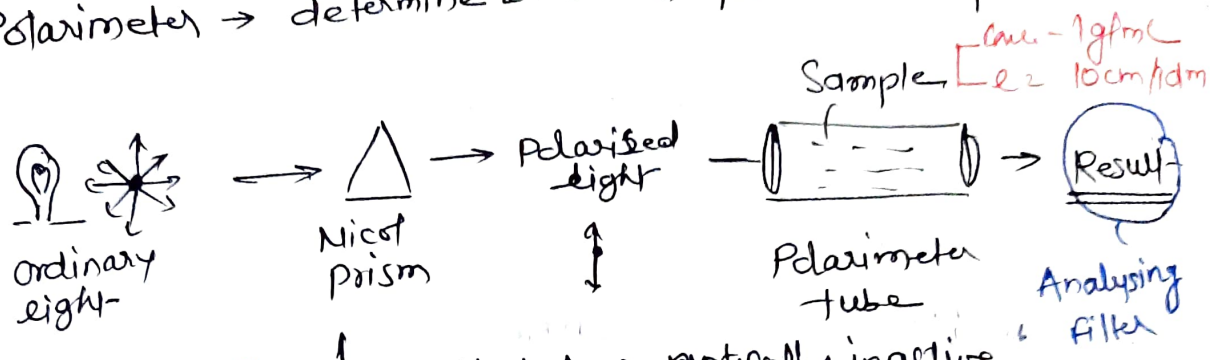
# Nature of Light  $\Rightarrow$  Electromagnetic wave (does not require and media) they require electric & magnetic field.

 = ordinary light = vibrate in diff plane  
2  $\vec{E}$  vibrate in all planes perpendicular to direction of propagation of light

  
Ordinary light unpolarized  $\rightarrow$  Nicol Prism ( $\text{CaCO}_3$ ) silicate Polariser  $\rightarrow$  vibrates in one plane Plane-polarised light - polari (PPL)  
↳ cut off all vibrations except of one plane

Optically Active :- Substance which rotate (clock or Anti clock) plane plane polarised light. This property of a compound is called optical Activity.

# Polarimeter  $\rightarrow$  determine & check optical activity



- Result - ① unaffected  $\rightarrow$  optically inactive
- ② clockwise rotation - optical active  
- Dextrorotatory  $\rightarrow$  (+) Sign
- ③ - Anticlockwise - Levorotatory - (-) Sign
- $\alpha =$  Magnitude of rotation in degree

\* The degree of rotation depends upon the no. of molecules of compound encountered by light along its path

\* Specific Rotation :- is defined as the rotation produced by a solution of length 10 cm and unit concentration (1 gm/ml) for given wavelength of light at the given temp.

$$[\alpha]_D^t = \frac{100\alpha}{lc}$$

$l =$  length of tube decimeter  
 $c =$  no. of gm. in 100ml of soln

\* Specific rotation varies with both the  $\lambda$  & temp.

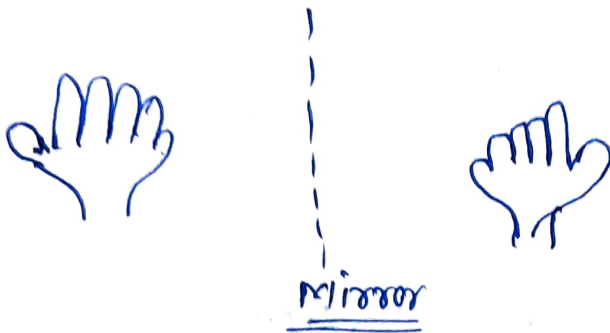
$\alpha = \frac{\theta}{lc}$        $\theta =$  rotation per unit length & unit conc.  
 $\alpha =$  radian. ml/dm.g

!  $\alpha \neq$  optical Active

# How to know  $\rightarrow$  optically Active ??

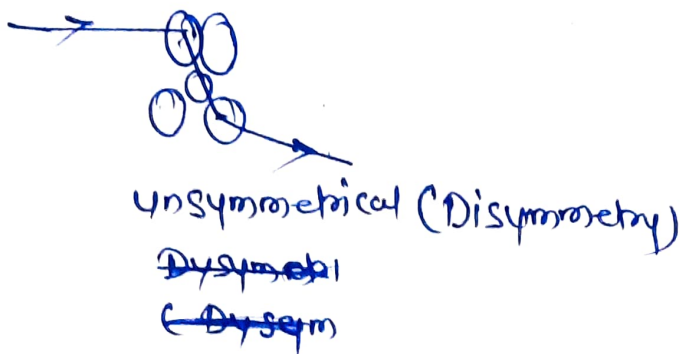
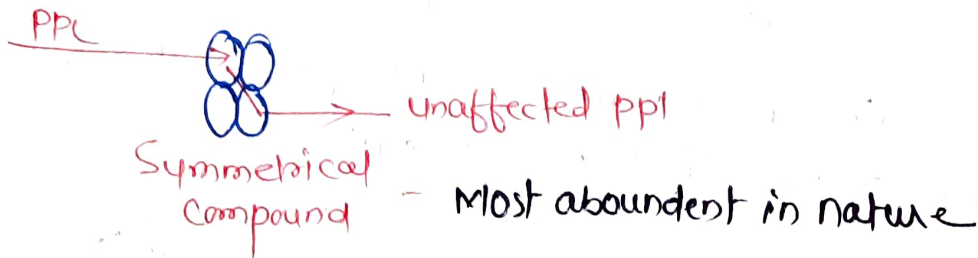
- ✓  $\hookrightarrow$  Dissymmetric compound  $\rightarrow$  OA (Optical Active)
- ✓  $\hookrightarrow$  Chirality compound  $\rightarrow$  OA

chirality - handed



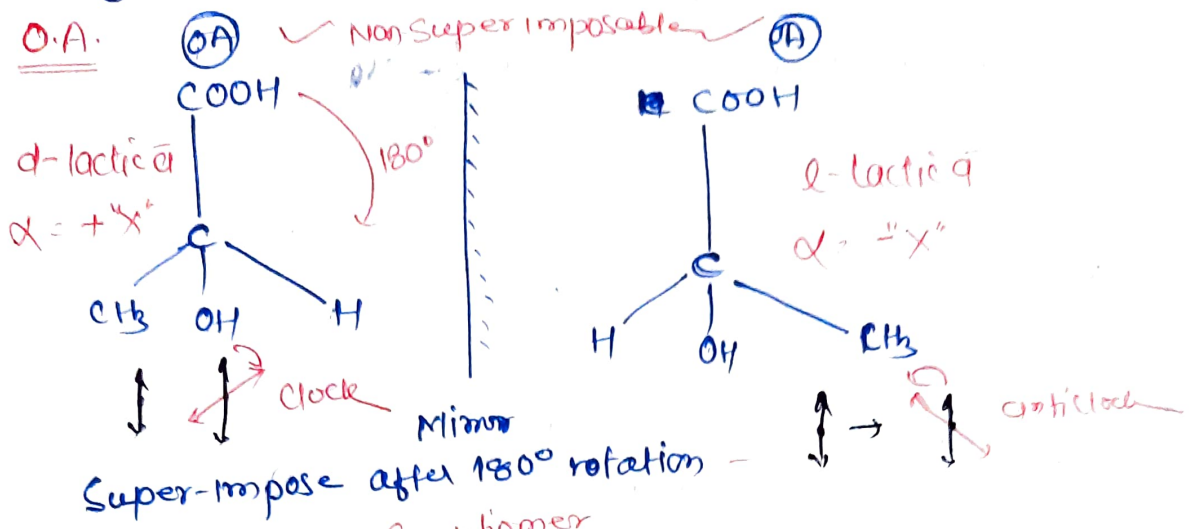
- ✓  $\hookrightarrow$  Non-Superimposable mirror image
- $\hookrightarrow$  Not cover completely

$\rightarrow$  A symmetric object refers to Achiral - OI (Optical Inactive)



#

ex: ① Lactic Acid - 2-hydroxy propan-1-oic acid



⇒ Both pair are Enantiomer

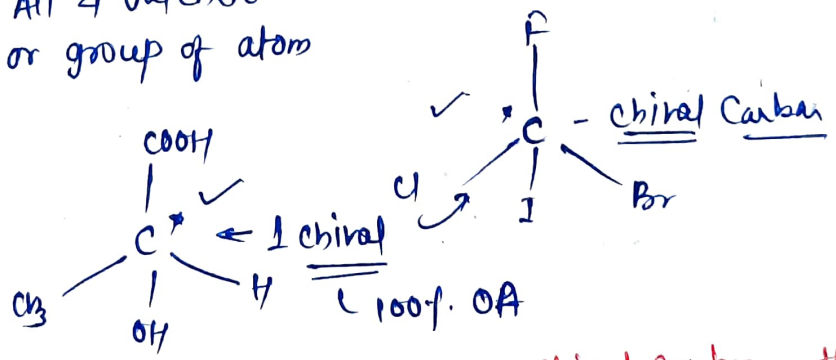
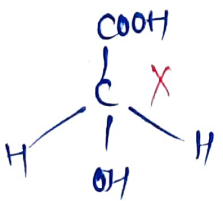
Enantiomer :- pairs of optical isomers, which are non-super imposable mirror images of each other.  
They differ in rotation of PPL. "Enantiomers rotate PPL equally but in opposite direction."

# CHIRAL (ASYMMETRIC) CARBON ATOM

# CHIRAL CENTRE :- #  $sp^3$  hybridized (4 bonds)

↳ All 4 valencies must be satisfied by 4 different atoms or group of atom

100% O.A-X  
(NOT guaranty)



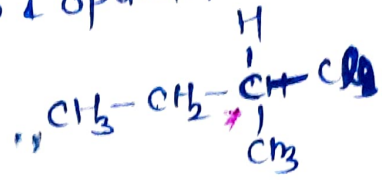
↳ If compound has only one chiral centre, then compound is Optical Active

↳ 1 chiral centre → chirality

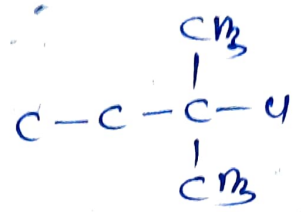
↳ >1 chiral centre → Not Sure Chirality

ex. which has chiral center yes/no & Optical Active or Inactive

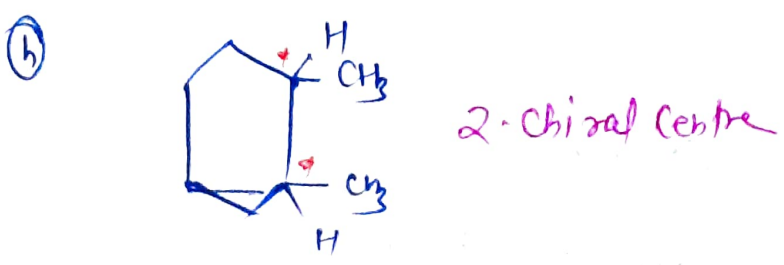
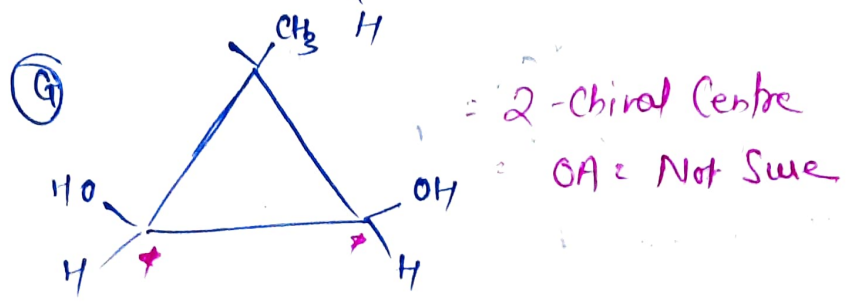
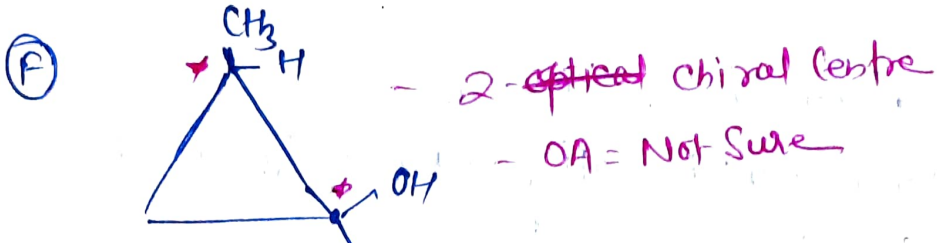
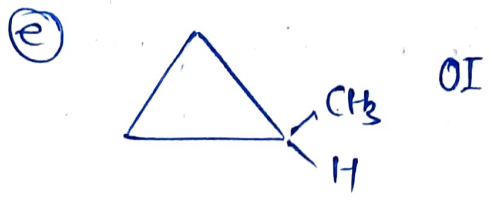
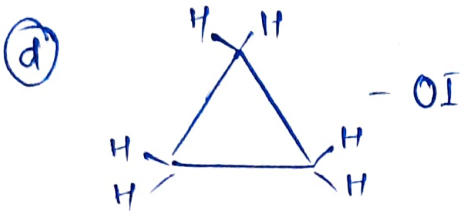
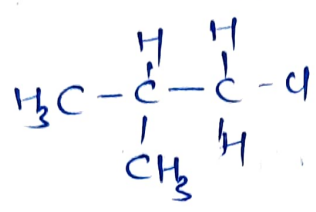
(a) Secondary butyl chloride  
 ✓ O.A.



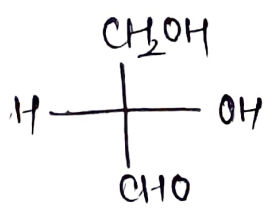
(b) tert-pentyl chloride  
 ✗ OI



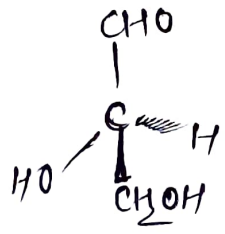
(c) Iso-butyl chloride  
 ✗ OI



# D & L Configuration

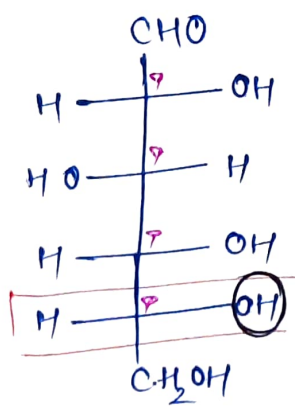


Fischer projection



Wedge & dash

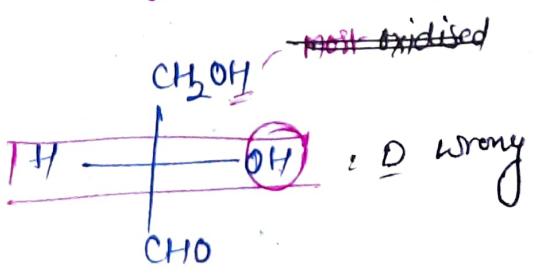
ex



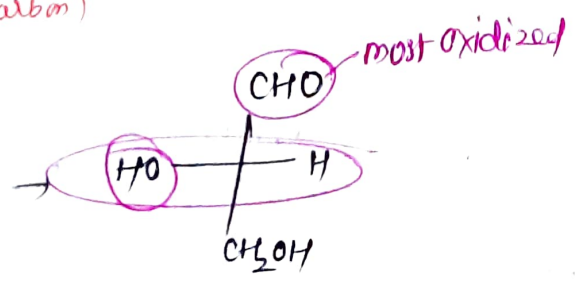
D-glucose

OH = Assign in Right Side = D Configuration  
 -||- Left Side = L-Configuration

Bottom most asymmetric carbon (Chiral carbon)



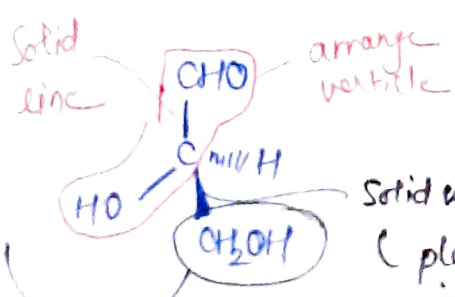
D-glyceraldehyde



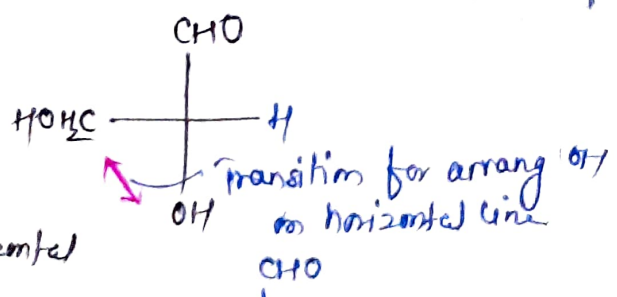
L-glyceraldehyde

(Fischer Project)

- ↳ Groups connected by vertical line are above the plane or towards the reader
- ↳ Horizontal line = below the plane or away the reader



Solid wedge (place on horizontal in left side)



Wedge & dash  
 D Configuration





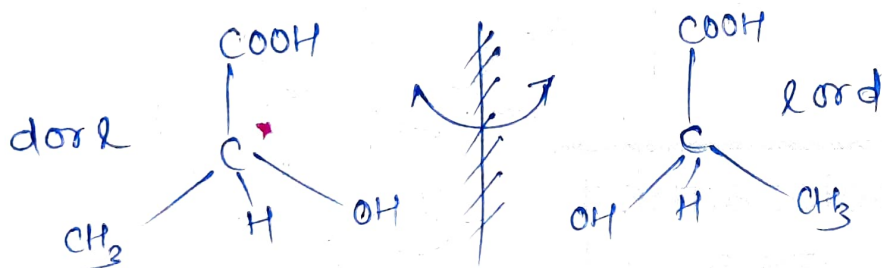
# Enantiomer: - are optical isomers that are non-superimposable mirror image.

# Diastereomers: - are optical isomers that are not mirror images.

# Racemic Mixture - is a mixture of equal parts of enantiomers  
Δ Racemic mixture are optically inactive

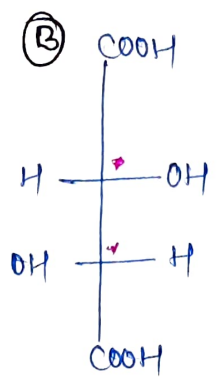
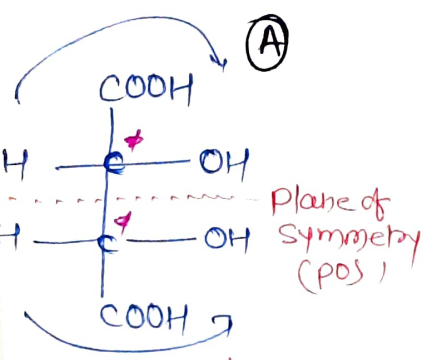
# Meso Compound - is a compound that has more than one asymmetric carbon and that is superimposable on its mirror images. Meso compounds are optically inactive

## ENANTIOMERS

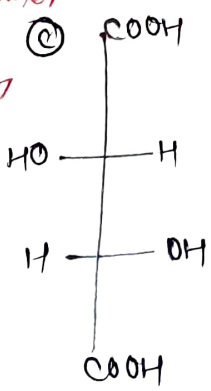


- ↳ Stereoisomers
- ↳ optically active
- ↳ Non-superimposable mirror images
- ↳ They rotate PPL equally in opposite direction
- ↳ They have same physical & chemical properties.
- ↳ If reaction undergoes ~~under~~ with optically active reagent then they will show different chemical reaction.
- ↳ Enantiomers are stable, difficult to separate, & they can not be interconverted under ordinary condition
- ↳ No ~~plane~~ plane of symmetry & Centre of symmetry

Ex. Tartaric Acid - 2 chiral centre



Enantiomer



Racemic mixture (equal (+) & (-))

- 2 chiral Centre
- POS
- Optically Inactive
- Meso-compound

- (+) tartaric acid
- optically Active
- NO-POS
- MP = ~~170~~ 170°C

- (-)-t. acid
- optically active
- NO POS
- MP = 170°C

OI due to internal compensation.

- # Total optical isomer = 3
- # optically Active = 2
- # optically inactive = 1

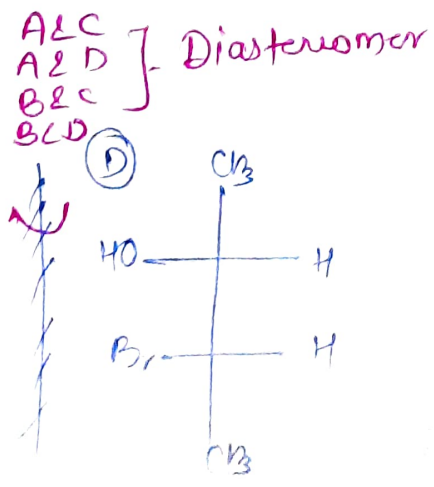
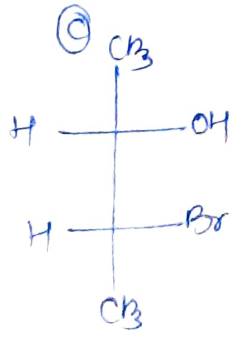
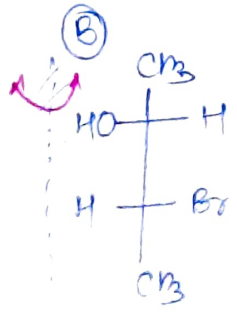
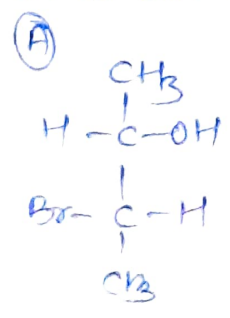
- MP = 143°C
- NO-mirror image (means identical)
- Superimposable

- A, B, C = Stereo isomer
- B & C = Enantiomer
- A & B } stereoisomers
- A & C } Non-mirror image
- Diastereomers

Diastereomers = All geometrical isomers & optical isomer that are non-mirror image are diastereomers

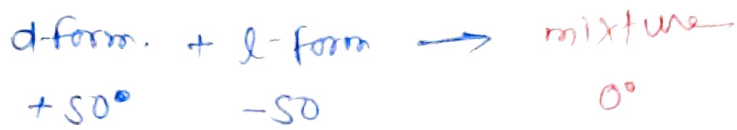
- Non mirror image optical isomers
- \* n-chiral centre = 2<sup>n</sup> stereoisomers
- Different physical property - mp, bp, solubility
- Different chemical Reaction,

ex. 3-bromo-2-butanol

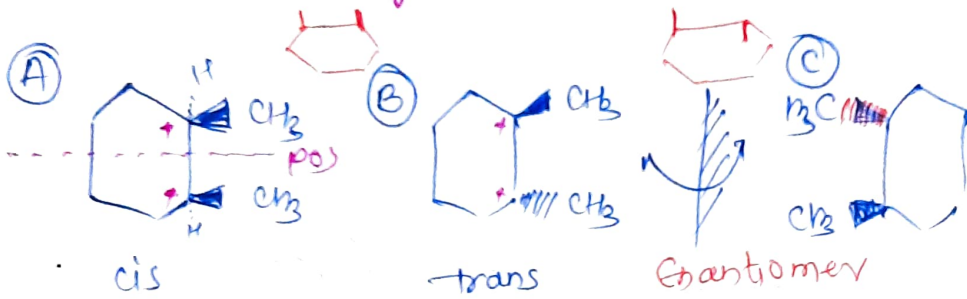


# RACEMIC MIXTURE :-

- ↳ Equal conc of equal quantity of d-form & l form
- ↳ Optically inactive by external compensation.



Q. Find all isomer of 1,2-dimethyl cyclohexane



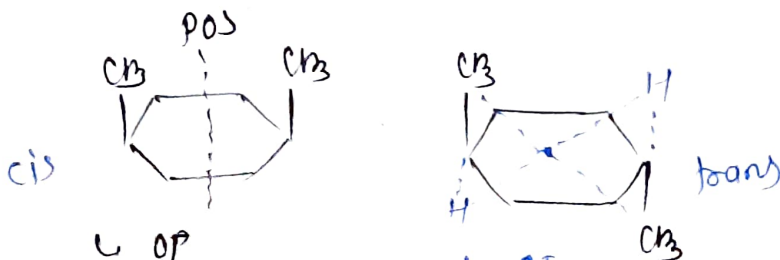
- |                        |                    |
|------------------------|--------------------|
| ↳ 2-chiral Centre      | ↳ 2-chiral Centre  |
| ↳ optically inactive   | ↳ optically Active |
| ↳ POS                  | ↳ NO POS           |
| ↳ <u>Meso-Compound</u> |                    |

- # Total Isomer = 3
- # optically Active = 2
- # optically inactive = 1

- Meso = 1 (A)
- Racemic = 1 (B+C)
- # structure ISO = 3

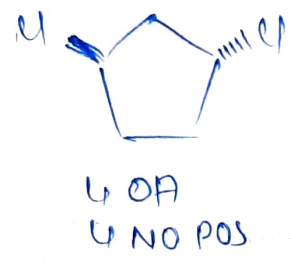
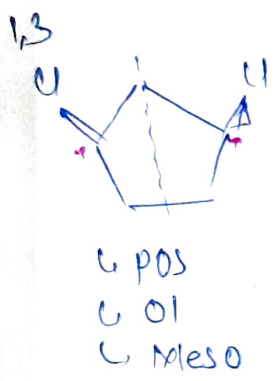
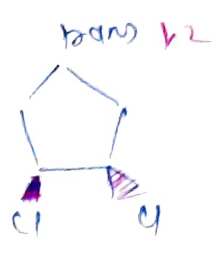
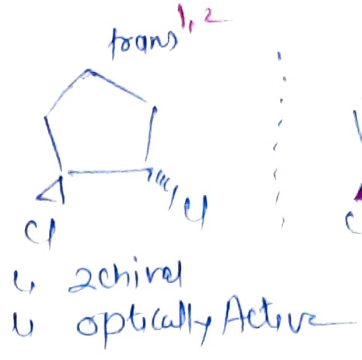
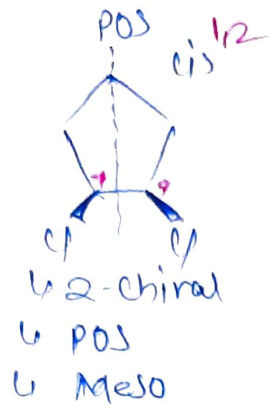
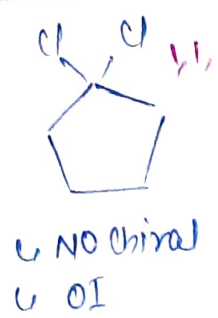
A, B, & C = optical isomer  
 A & B ] = Diastereomers  
 A & C ]  
 B & C = Enantiomers

## 1,4-dimethyl cyclohexane



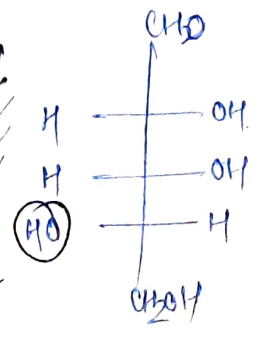
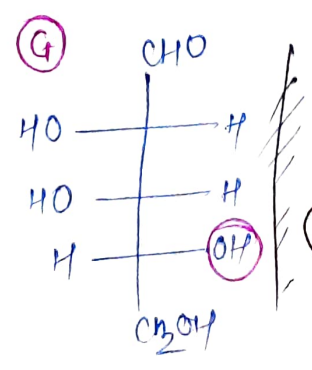
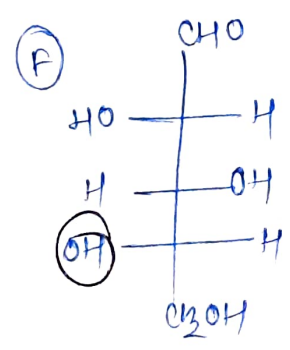
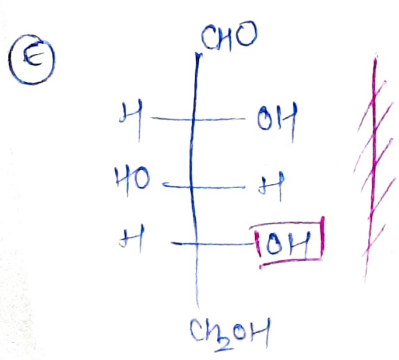
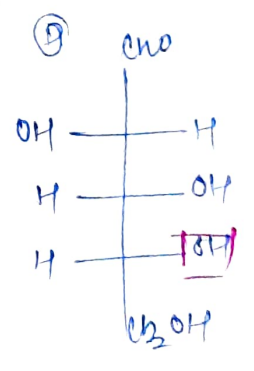
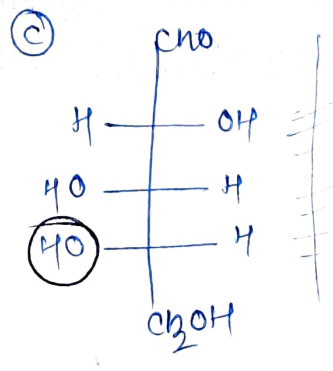
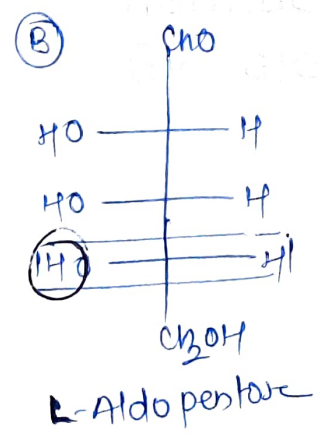
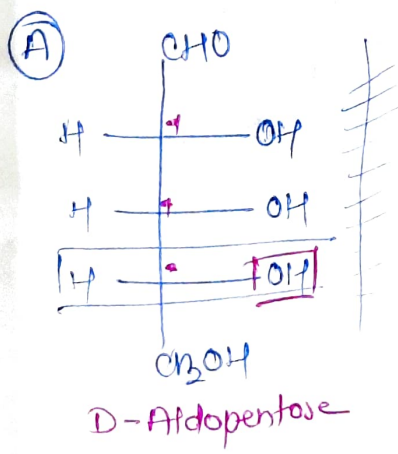
- |                     |   |
|---------------------|---|
| ↳ OP                | ↳ OI                                      |
| ↳ POS               | ↳ COS - opposite direction, same distance |
| ↳ <del>Meso-X</del> | ↳ Same group                              |
| ↳ NO chiral         |   |

# diclora cyclopentane = Answer = 7



Meso = 2  
OA = 4

# Aldo pentose :- 3-chiral centre =  $2^3 = 8$  stereoisomers



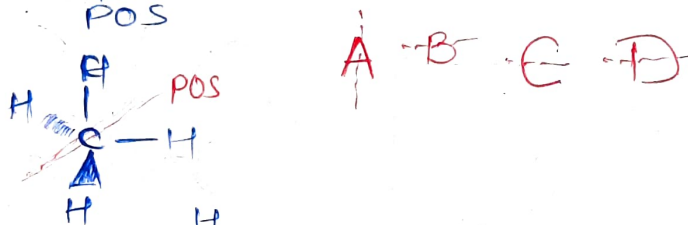
# ELEMENT OF SYMMETRY

- # Optical Activity  $\rightarrow$  Dissymmetry
- $\rightarrow$  Chirality
- $\rightarrow$  Non Superimposable mirror image

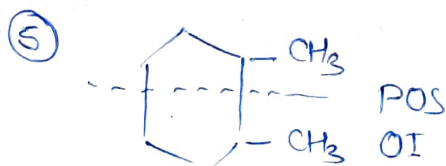
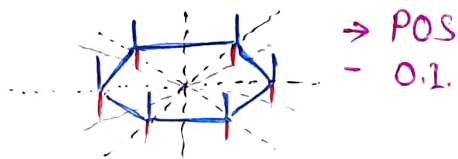
## DISSYMMETRY 1-

- # Compound has ~~NO~~ Centre of Symmetry (COS) - Inversion Centre
- ~~NO~~ Plane of Symmetry (POS) - Mirror Plane
- ~~NO~~ Alternate Axis of Symmetry (AOS)  $\rightarrow$  Improper rotation Axis
- may have ~~Axis~~ Axis of Symmetry

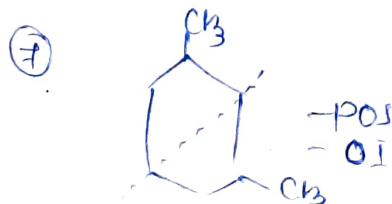
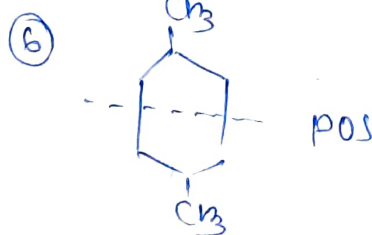
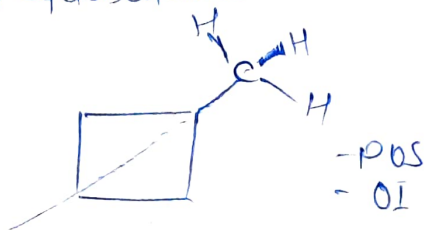
ex. ①  $\text{CH}_4$  = No chirality  
optical inactive  
POS



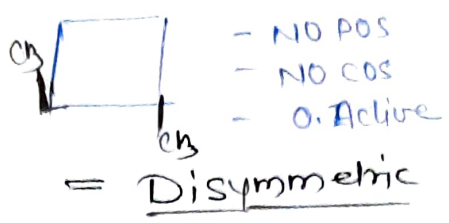
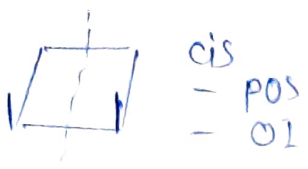
③ Cyclohexane



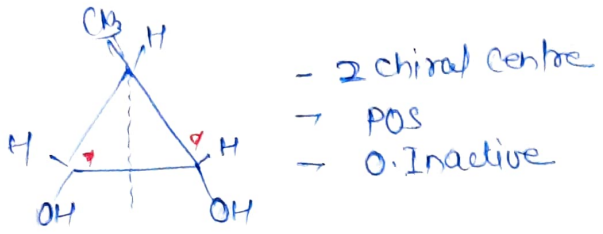
④ methyl cyclobutane



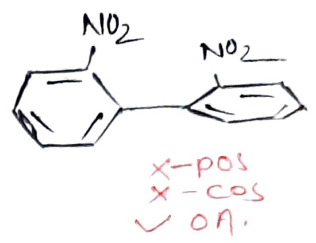
⑧ 1,2-dimethyl cyclobutane



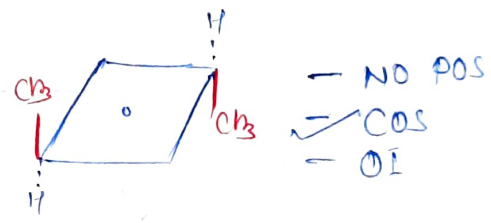
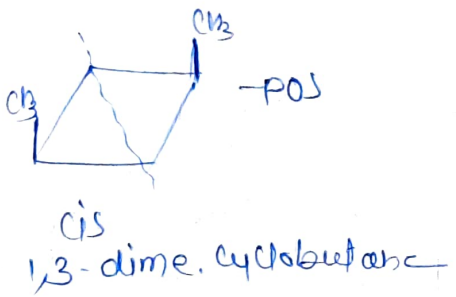
⑨



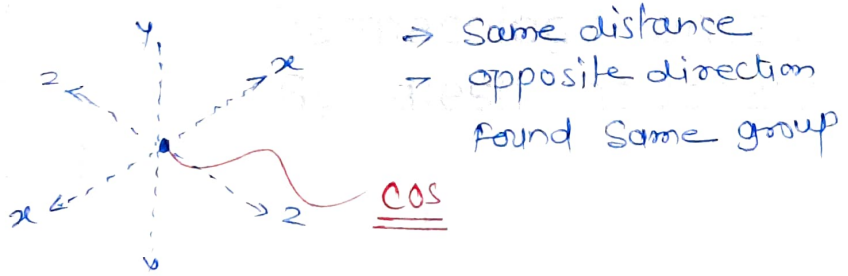
⑩



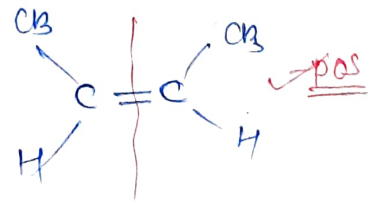
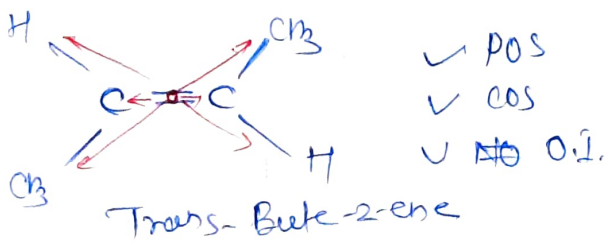
⑪



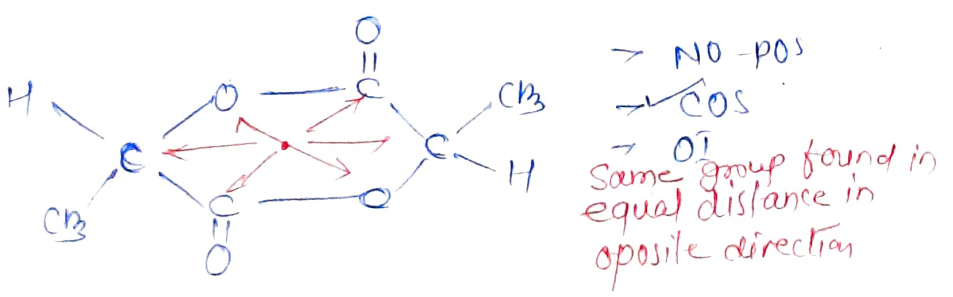
Centre of Symmetry



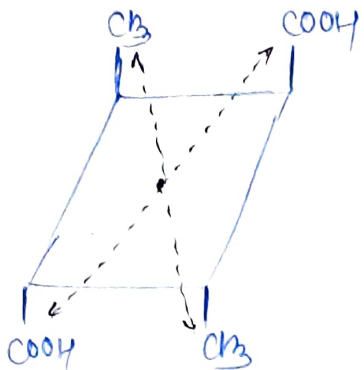
⑫



⑬



3



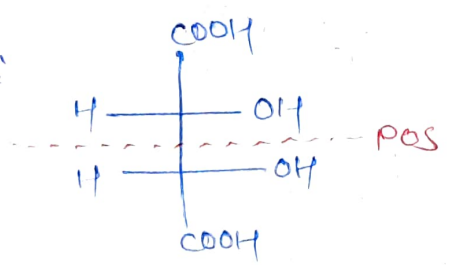
- NO POS  
 ✓ COS!  
 - OI

### 1. Plane of Symmetry (POS) (Mirror plan)

A plane of symmetry is imaginary plane that passes through a molecule such that atom or group on one side of plane form a mirror image of those on the other side.

It is use for >2 chiral centre

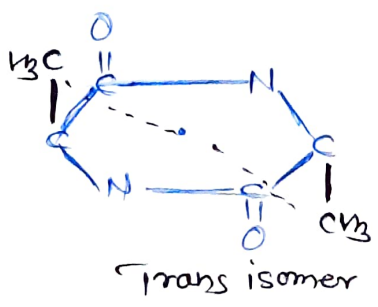
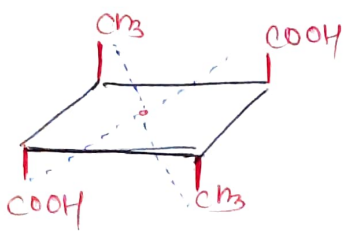
ex:



O.I. due to internal compensation that is rotam of one asym. carbon is cancelled by another asymmetry carbon.

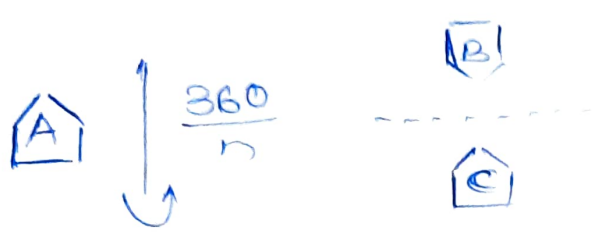
### 2. Centre of Symmetry - Inversion Centre.

A point in a molecule from which lines when drawn on opposite side at equal distance, meet exactly similar atom or group in the molecule



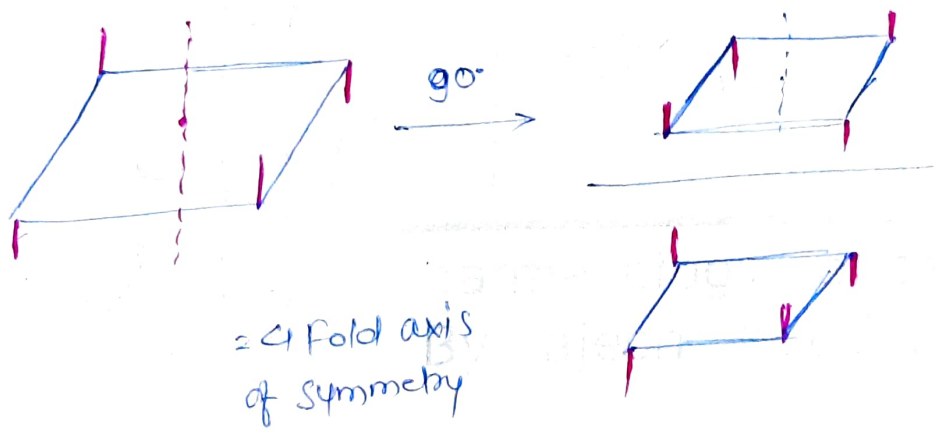
### 3. Alternate Axis of Symmetry (Improper Rotam axis)

A molecule is said to possess an n-fold alternating axis of symmetry if, on rotating through a angle of  $360^\circ$  about the axis & followed by Reflection of the resulting molecule in a plane perpendicular to the axis, then the mirror image is exactly identical to the original molecule



If  $A \equiv C$  then the molecule contains a n-fold axis of symmetry  
 & If  $A \neq C$  the molecule does not contain n-fold axis of symmetry

ex



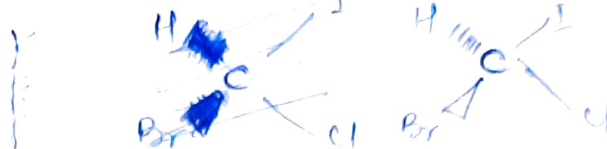
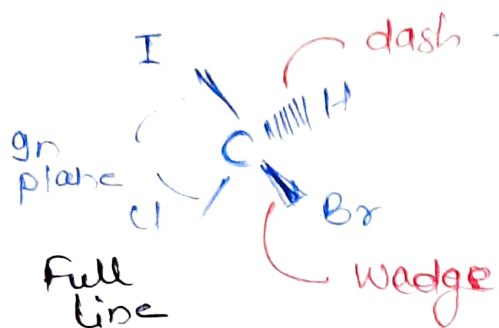


- # Wedges - Dash
- # Fischer - Projection
- # R/S Nomenclature

## WEDGES - DASH

:- 3D Representation

:- For both chiral & achiral carbon formula  
 - Inside of plane & below the plane

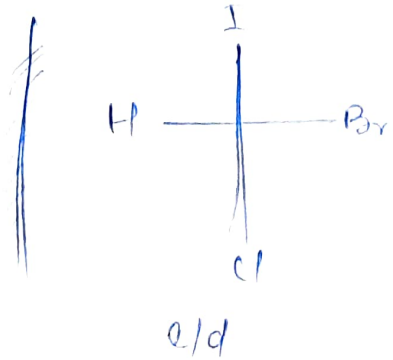
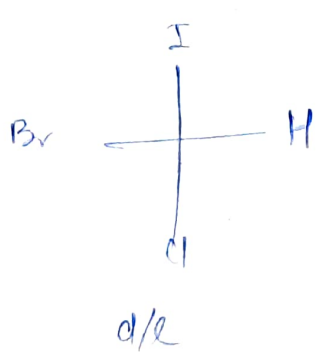
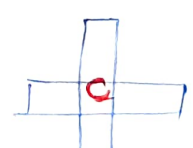
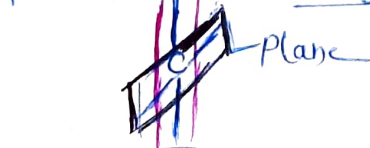
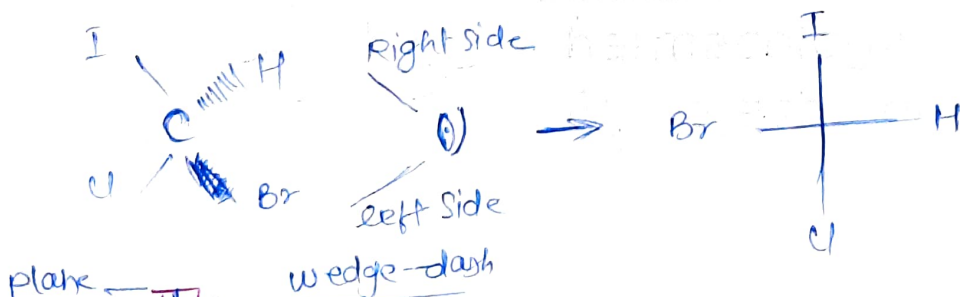
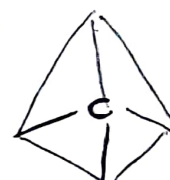
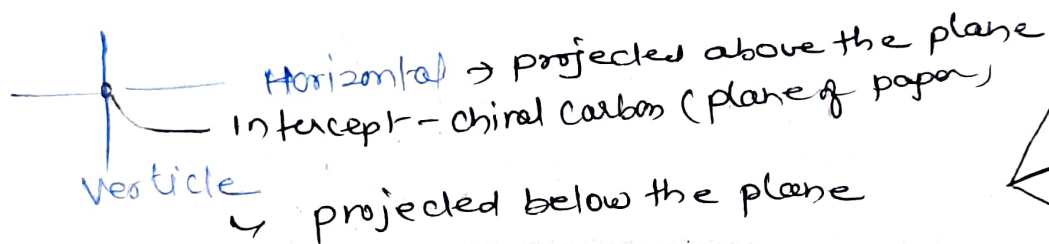


= outside of plane  
 : above the plane

## FISCHER PROJECTION

:- 2-D Representation

:- For ~~both~~ chiral ~~and~~ carbon



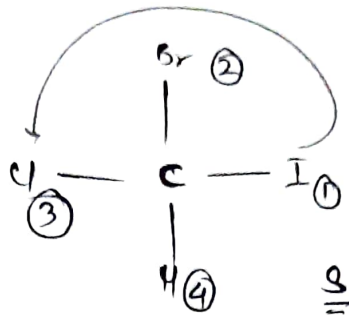
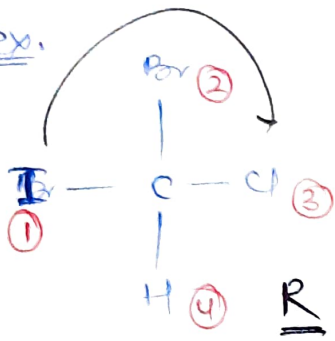
# R-S NOMENCLATURE



# by Fischer projection

# Priority order - CIP Scheme

ex.



Priority order = Set the priority order of different atom or group based on atomic number, those are directly attached to carbon atom.

Cahn

~~Ingold~~ Ingold-Prelog Rule

# Highest atm. no. - 1st priority

# 1 → 2 → 3 (you can cross the 4)

↳ clockwise = **R** = Rectus - Right

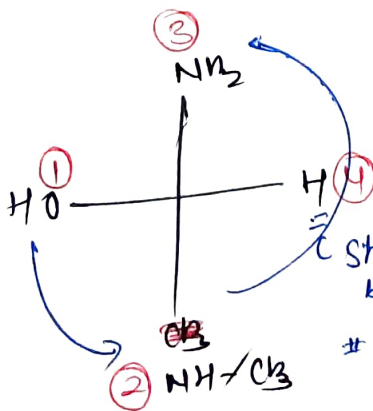
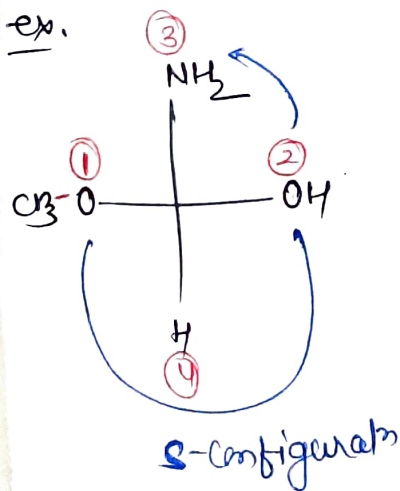
↳ anticlock = **S** = Sinister - Left

Cond<sup>n</sup> -

# Lowest priority should be on vertical bond



ex.



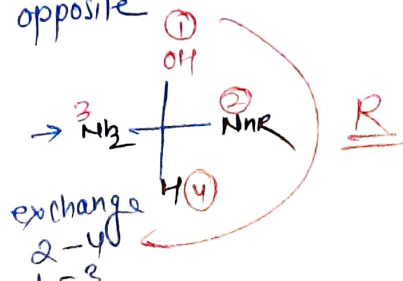
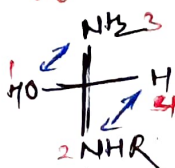
Anticlock = S → R

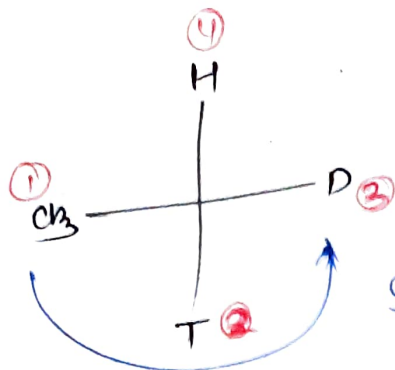
should be vertical

# If not in horizontal then obtained result may be opposite

R-Configuration

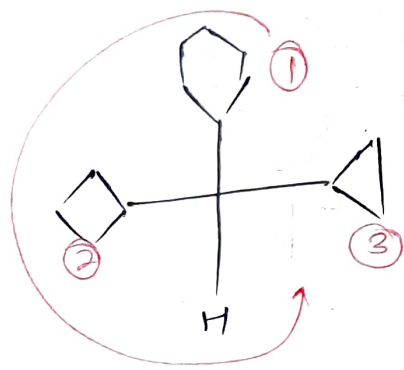
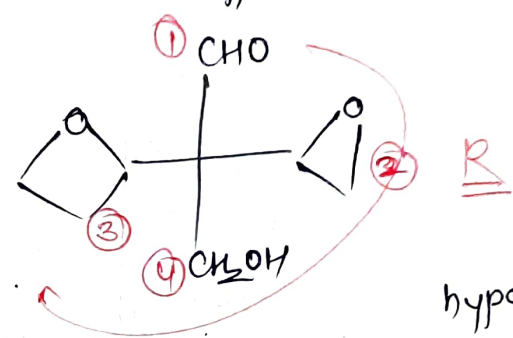
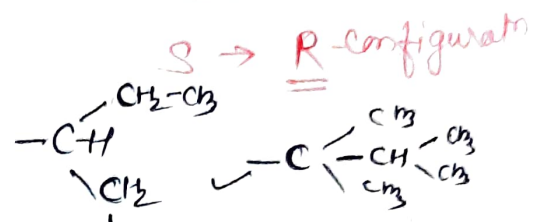
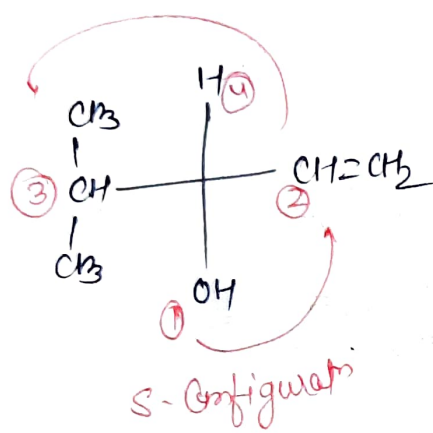
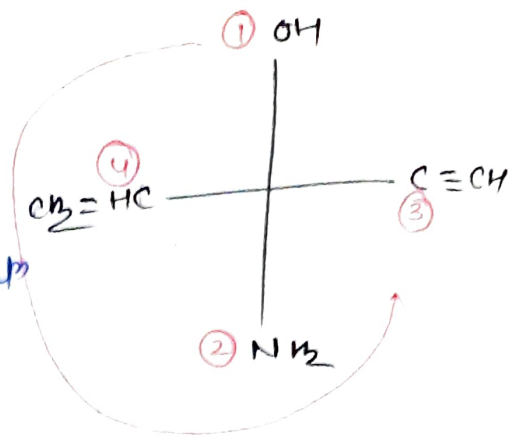
OR



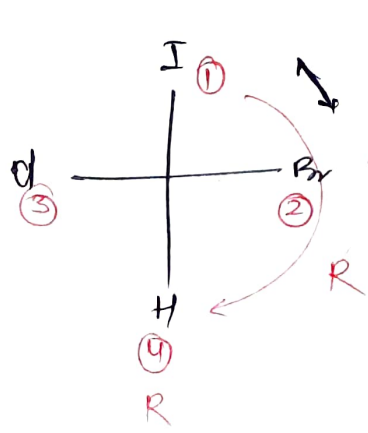
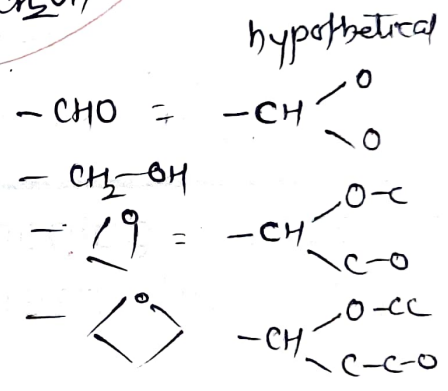


Atomic then Mass

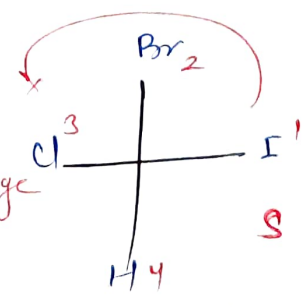
$0^{18} > 0^{17} > 0^{16}$



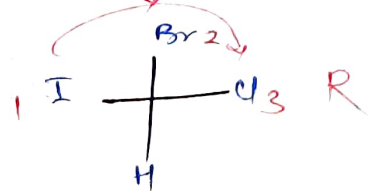
S-Configuration



1st odd interchange



2nd even interchange



# Priority Order Rule

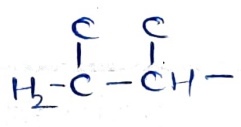
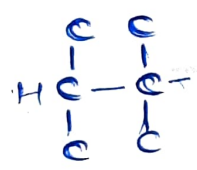
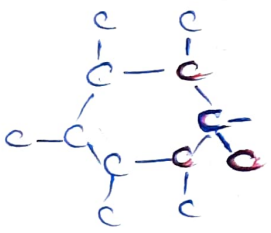
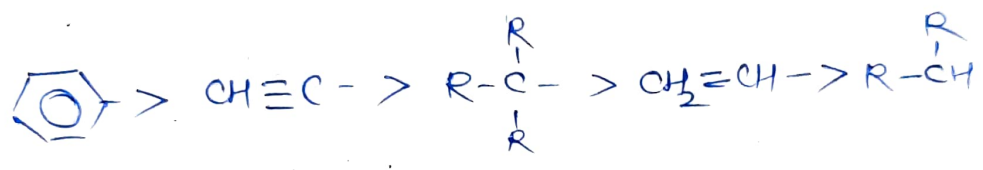
① If attached atom is single, highest atomic no. should give priority



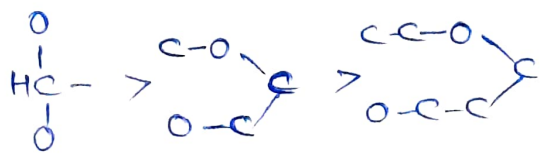
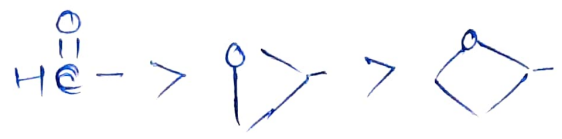
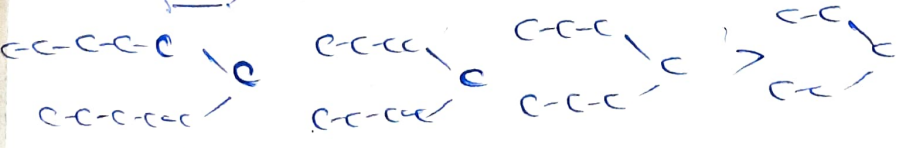
② If attached atom is same then, consider 2nd atom.



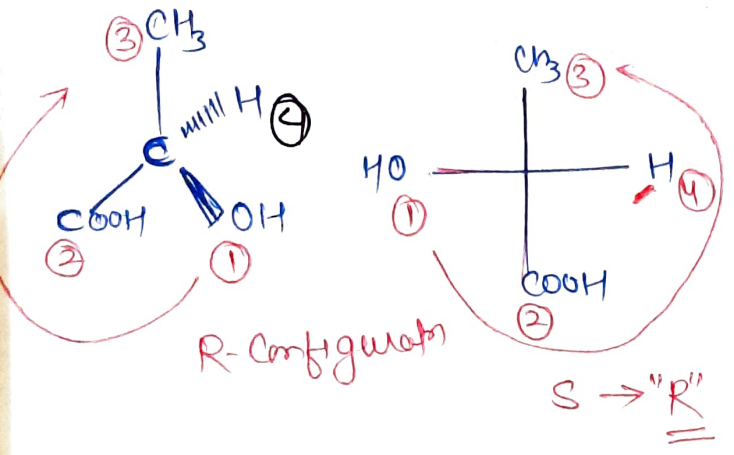
③ If multiple bonded group is attached, a double bond is treated as through each atom of the double bond were bonded to two atoms



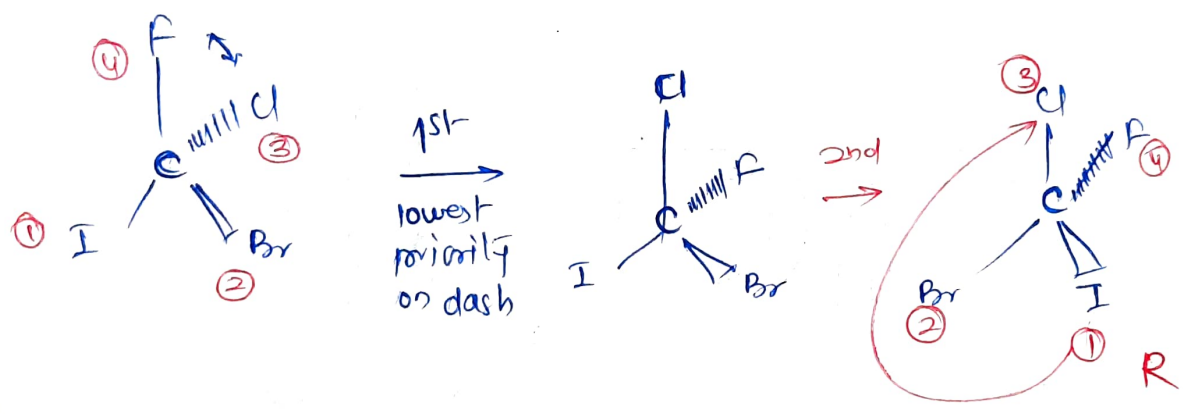
④ If cyclic or heterocyclic atom is attached consider all atom in both side



# # R & S In Wedge & Dash

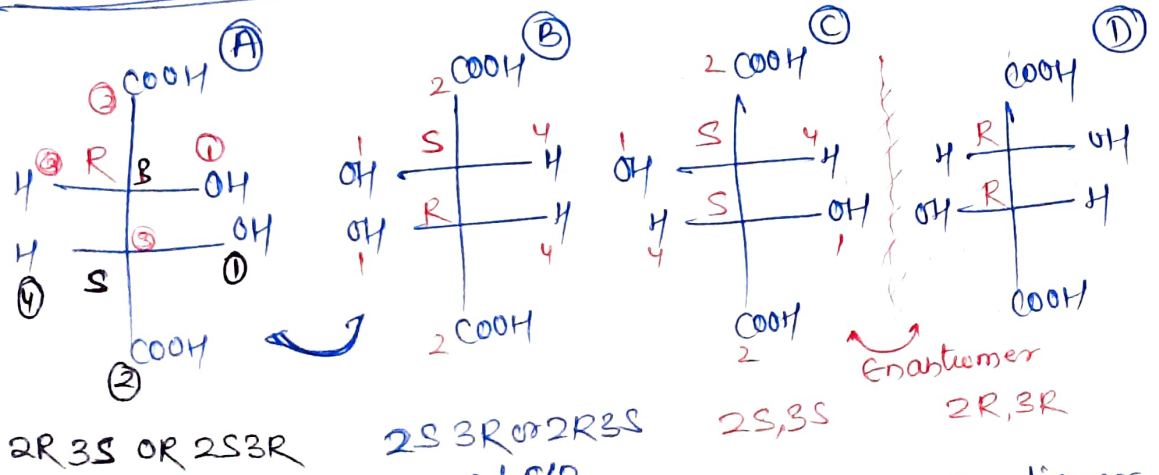


# In wedge-dash, lowest priority should present in dash  
# If not present then two even interchanges



# R-S Nomenclature in →  
↳ 2-chiral centre    ↳ Identical Compound  
↳ Enantiomer        ↳ Diastereomer

## Tartaric Acid



2R,3S OR 2S,3R

2S,3R OR 2R,3S

2S,3S

2R,3R

A & B = Identical  
both are one, O.I.  
meso

A & C/D  
B & D = No mirror image  
= Diastereomer

C & D = Enantiomer

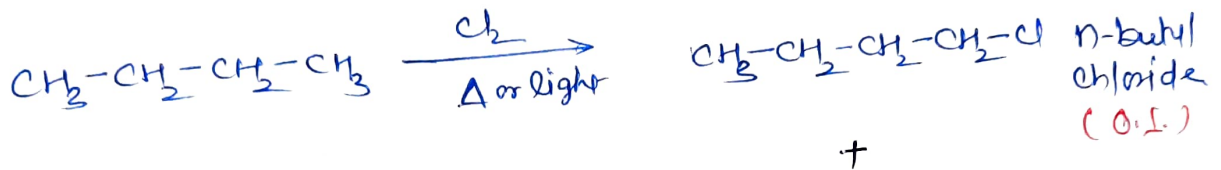
# REACTIONS INVOLVE IN STEREOISOMERS

- Synthetic Reaction :- Generation of Stereoisomer or chiral centre
- Chemical Reaction - 1) with optically active reagent  
2) with optically inactive reagent

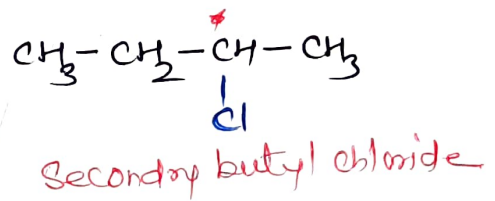
## I. Generation of Chiral Centre, Synthesis & Optical Activity

### = ASYMMETRIC SYNTHESIS

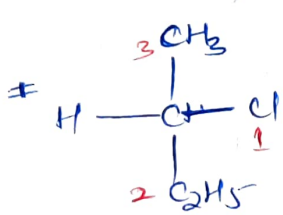
#### ① Chlorination of n-butane



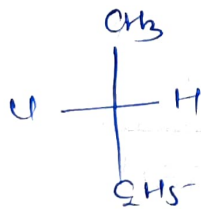
+



two enantiomers



S (+) Sec butyl chloride



R (-) Sec butyl chloride

# Reaction product of chlorination of n-butane → Sec butyl chloride shows no rotation in polarimeter due to equal amount formation of both enantiomers (Racemic mixture)

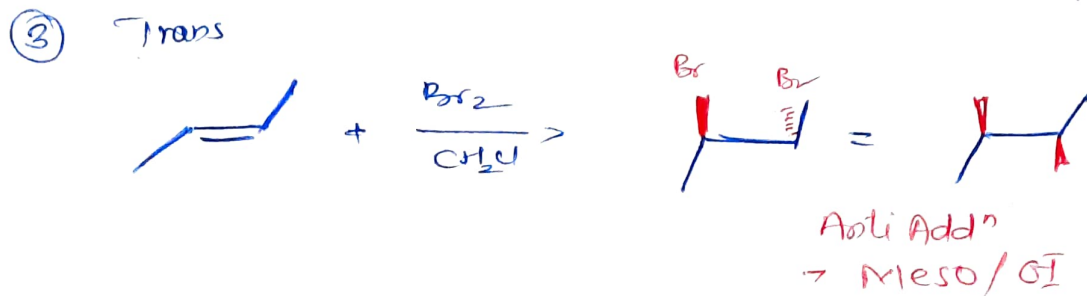
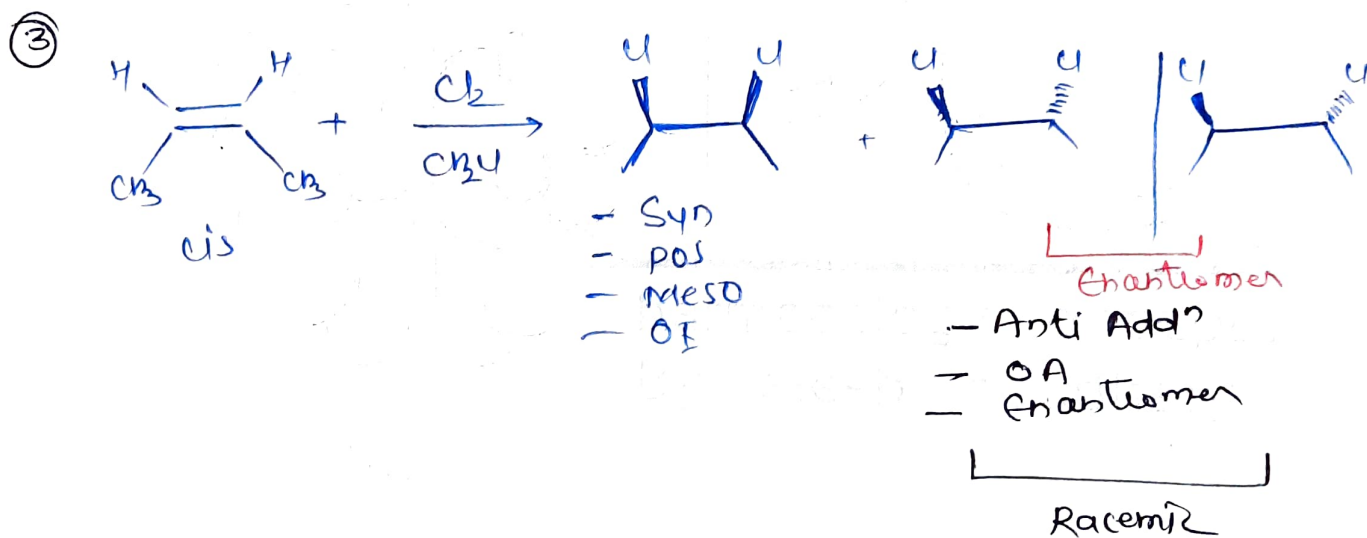
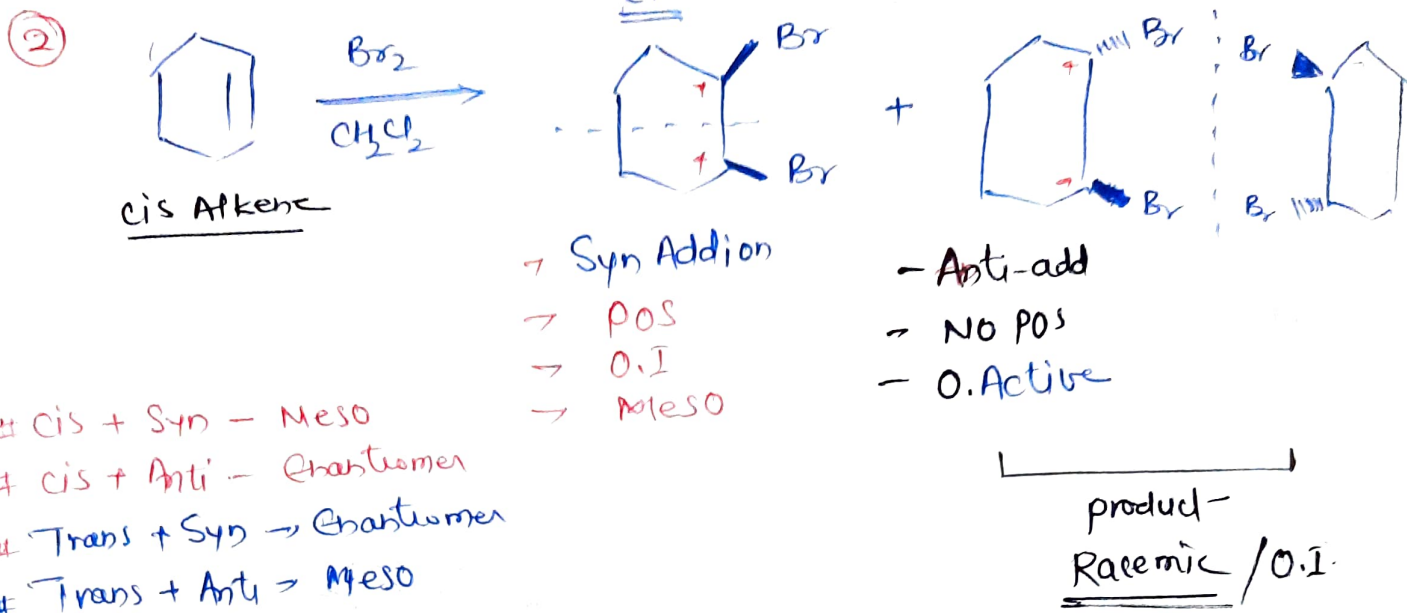
# Need to be Resolved the Racemic mixture → Specific Method

# Conclusion → Reaction product of achiral or optically inactive compounds, obtain a optical inactive product (may be racemic)

# Synthesis of chiral molecule from achiral reactants always yield the racemic modification

# Racemic mixture can't be separated by an ordinary method like fractional distillation or recrystallization due to identical solubility & boiling point

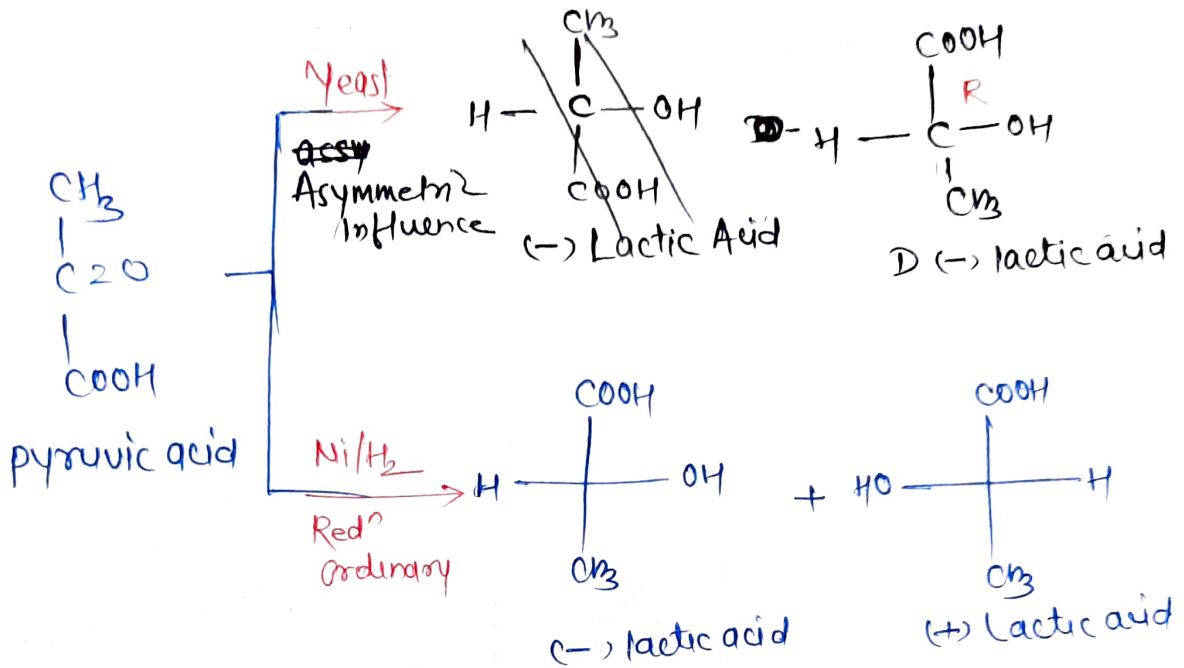
# II: Reaction of Chiral Molecule



# II REACTION INVOLVE INVOLVE IN CHIRAL MOLECULE

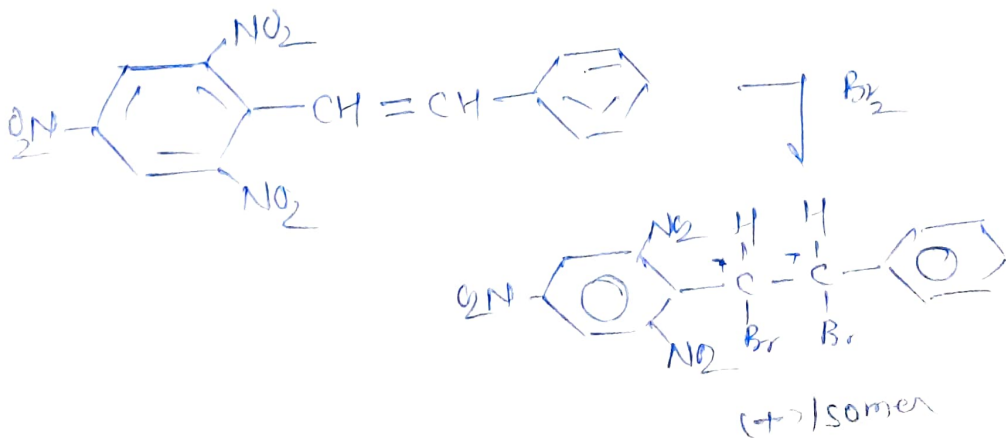


# of asymmetric synthesis carried out under the asymmetric influence of a suitable optically active reagent, then only one optically active isomer (+ or -) is formed.



# Asymmetric Synthesis — A reaction, in which one or more stereoisomers (Enantiomers or Diastereomers) are produced from an optically inactive substrate with or without using Chas.

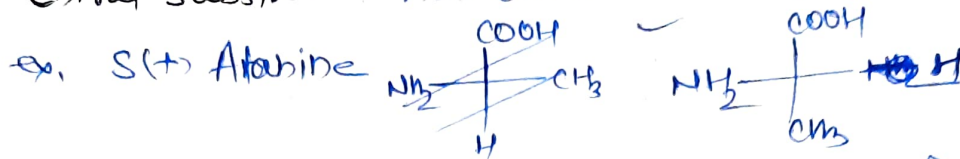
Type 1 - Absolute Asymmetric Synthesis :- Synthesis of a optically active product from optically inactive substance without using enantiomer.



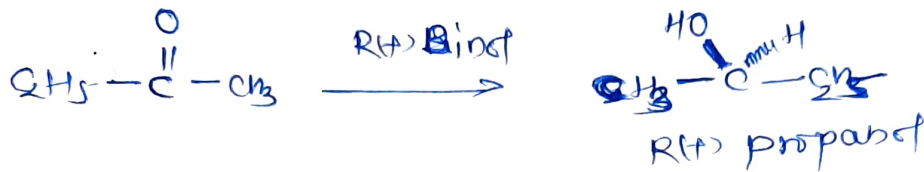


② Partial Asymmetric Synthesis - is synthesis of optically active product from optically inactive substrate by using enantiomer

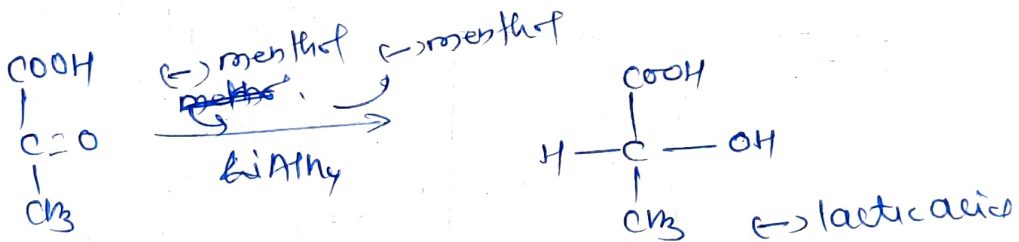
(a) Chiral Substrate - has chiral centre adjacent to reaction site



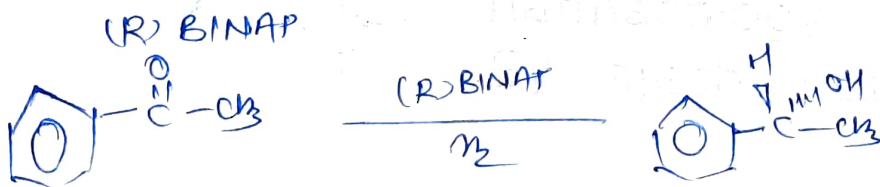
(b) Chiral Reagent - remove or add enantiotopic proton



(c) Chiral Auxiliary - join to substrate & remove to form product



(d) Chiral catalyst



## II REACTION INVOLVE IN CHIRAL MOLECULES



- # As we know that Achiral reaction of achiral substance produces a Racemic mixture (Racemate).
- # Configuration of a particular enantiomer can be determined directly by a special kind of X-ray diffraction, which was first applied in 1951 by Bijvoet to (+) tartaric acid.
- # There are Three major Reaction; -
  - ① Inversion :- change in property  $R \rightarrow S$  or  $(+) \rightarrow (-)$
  - ② Racemisation :- change in Activity Active  $\rightarrow$  Inactive
  - ③ ~~Retain~~ Retention :- Retention is same  $R \rightarrow R$  or  $S \rightarrow S$

### 1) INVERSION (WALDEN INVERSION)

↳ After attachment of new group or atom to the ~~as~~ chiral centre or chiral carbon atom, the new configuration of the chiral compound may be opposite to that of original

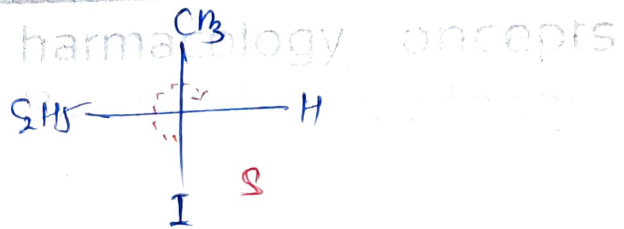
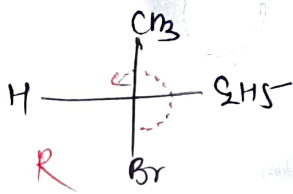
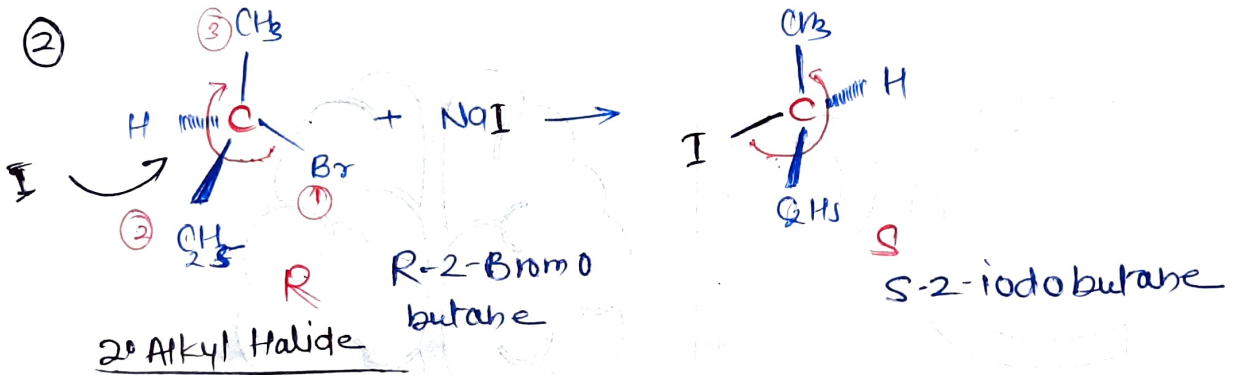
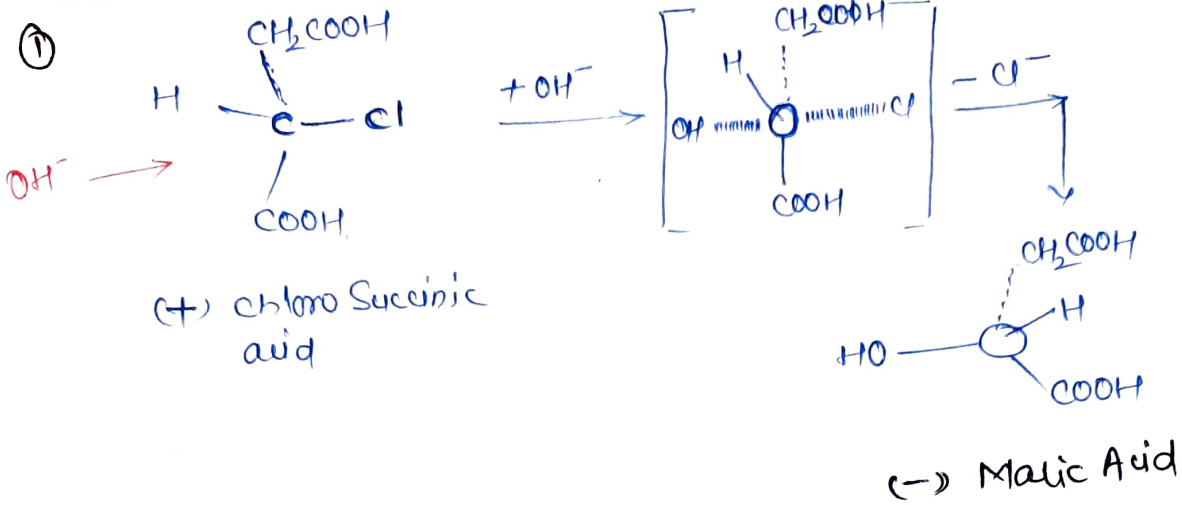


↳ The product looks like a mirror image (enantiomer)

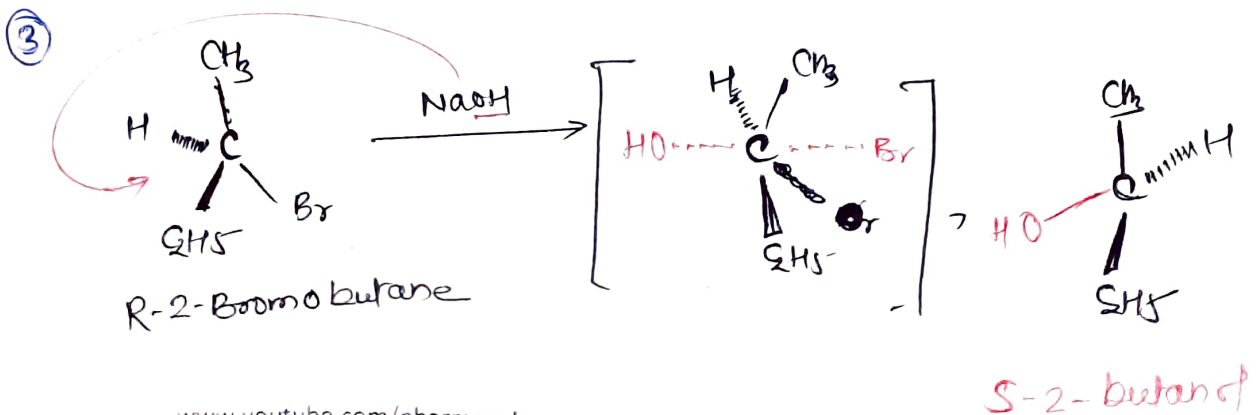
↳ This phenomenon is known as the "Walden Inversion"

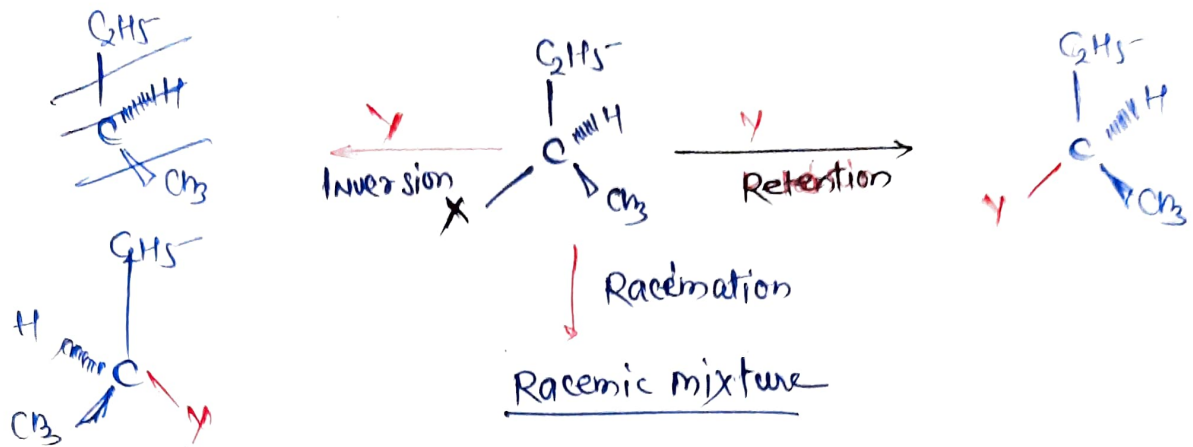
- ★ SN2 Reaction -
  1. Attacking molecule or group approaches to chiral carbon centre from opposite side of replacing group
  2. Formation of an intermediate transition state in which three groups & chiral-C atom lie in one plane
  3. Separation of the group being replaced.

Ex - INVERSION

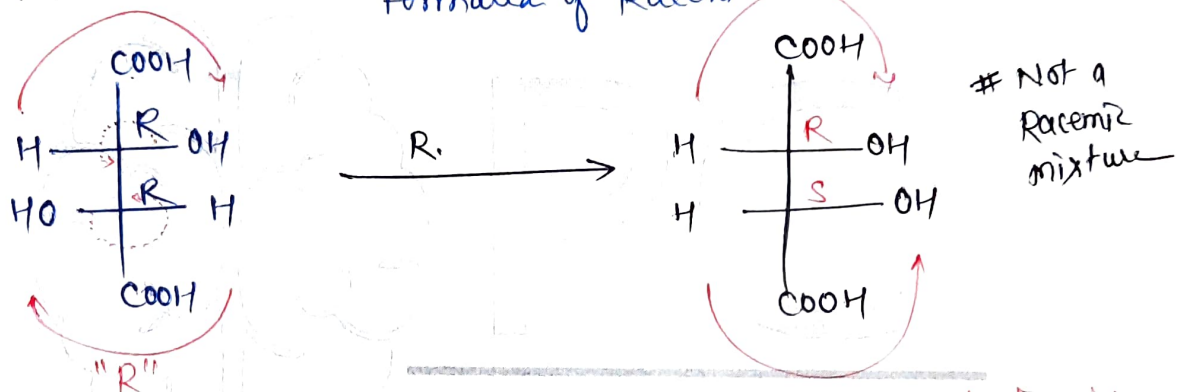


#	3°	2°	1°	methyl
SN1	Good	Yes	X	X
SN2	X	Yes	Good	Good



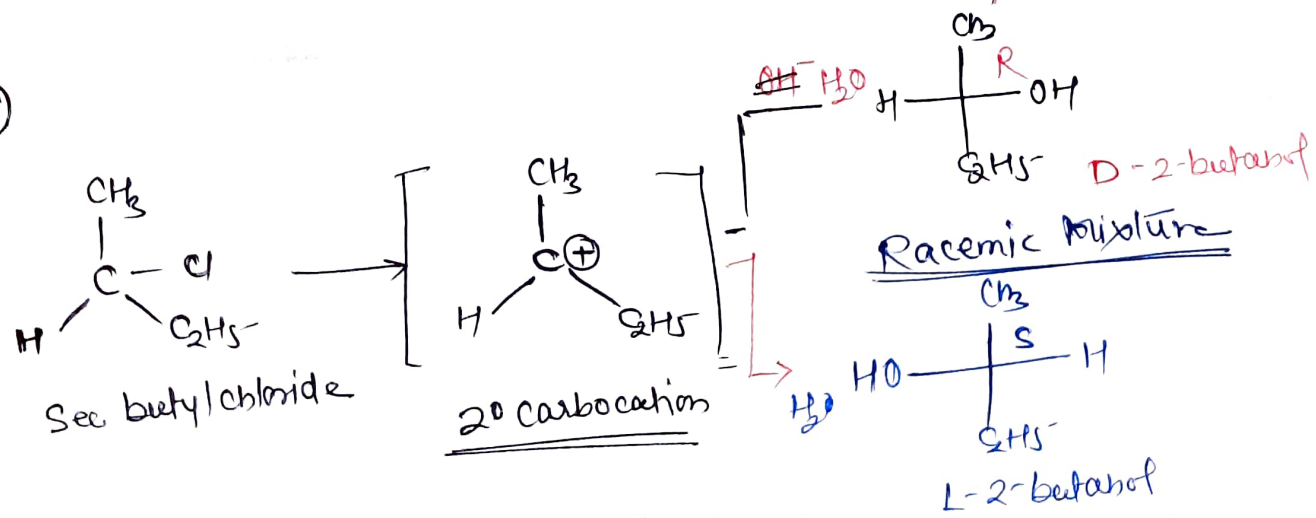


2. Racimisation - Occurs mainly in  $S_N1$  Reaction  
formation of Racemic mixture



2R,3R L(+)-Tartaric acid  $\xrightarrow{R_1}$  RS (±) Tartaric acid  
meso compound

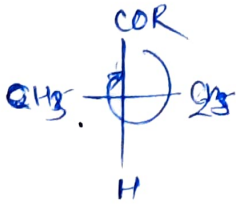
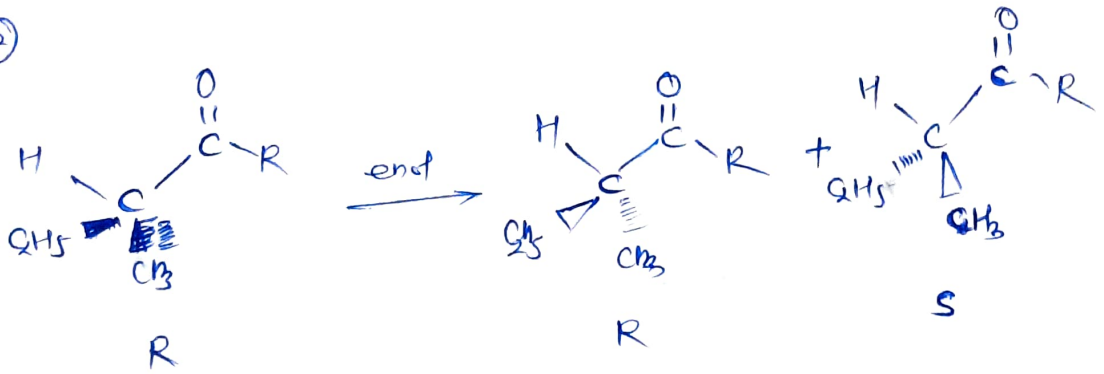
①



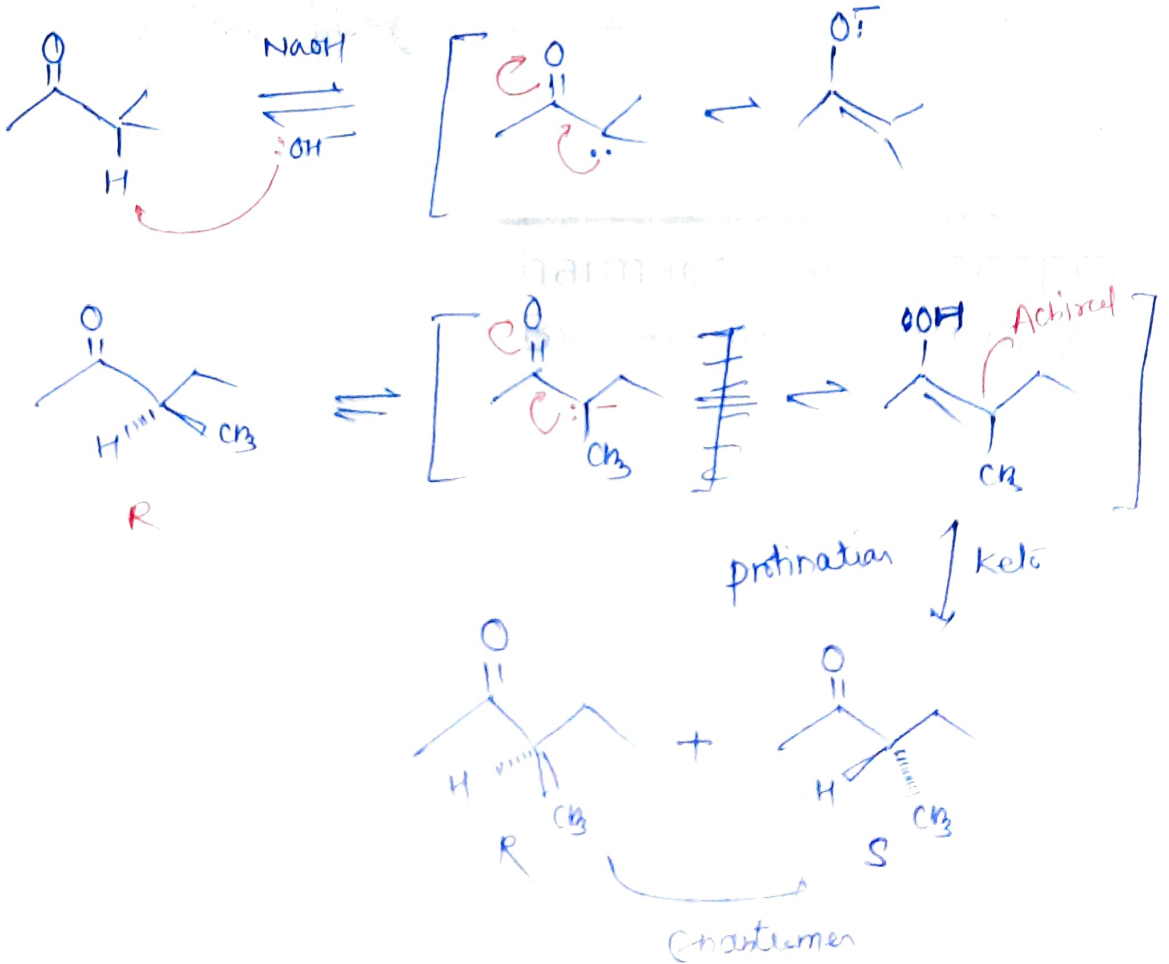
# Process of converting an optically active (d/e) compound into the racemic mixture

At the  $\alpha$  Carbons

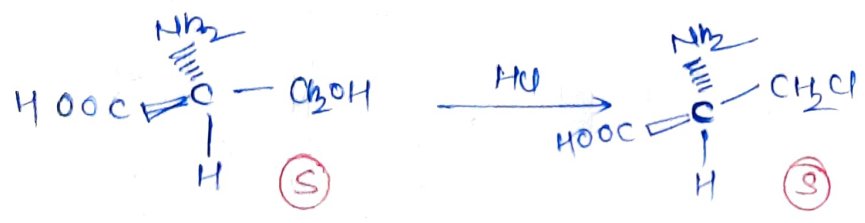
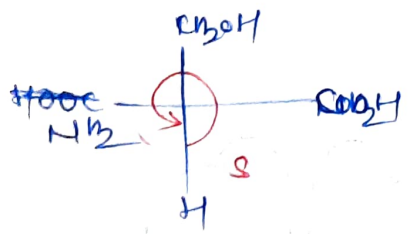
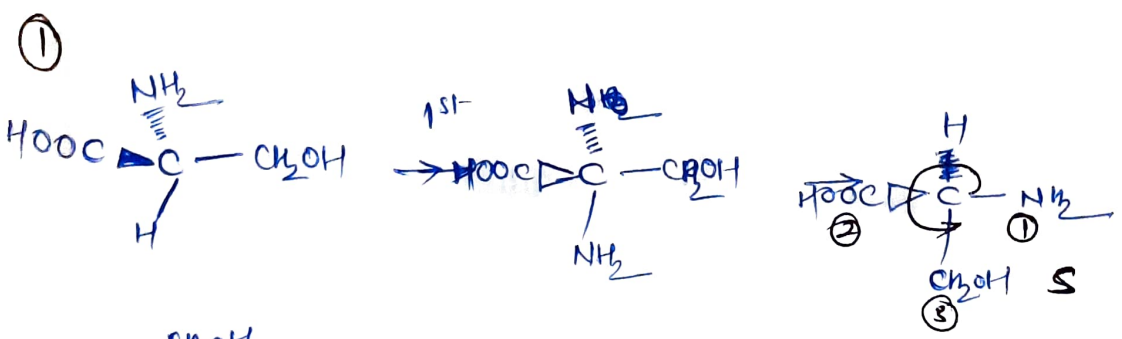
(2)



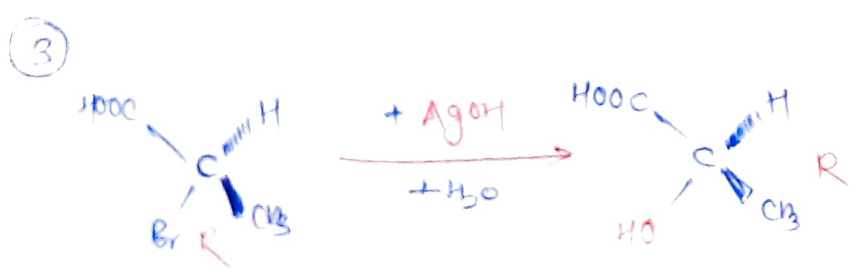
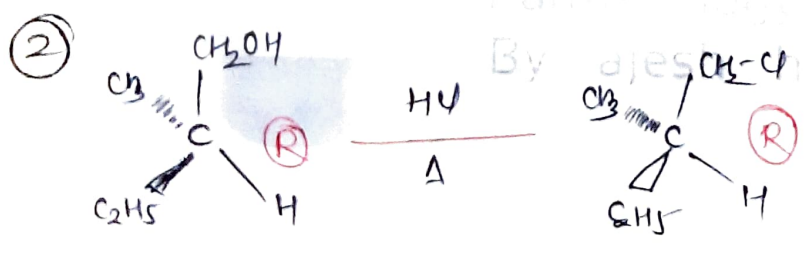
(3)



3. Retention 1-# Not-change in configuration  
# Preferred in SN1 Reaction

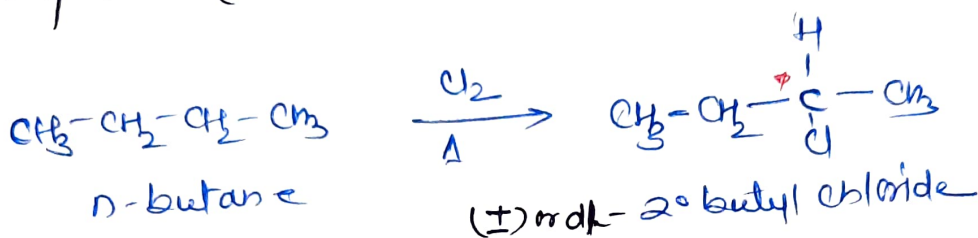


Pharmacology Concepts  
By Rajesh Choudhary



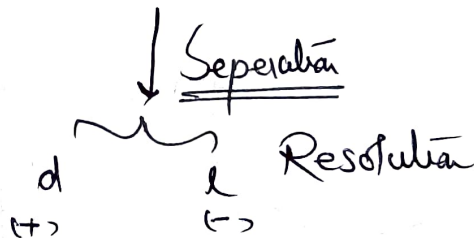
# RESOLUTION OF RACEMIC MIXTURE

- # Synthesis of optical ~~comp~~ active compound from achiral substances produces a mixture of both (+) & (-) isomers in equal amount. Such Racemic mixture needs to be separated.
- # Separation of such racemate into its two optically active components (d & l) is known as Resolution



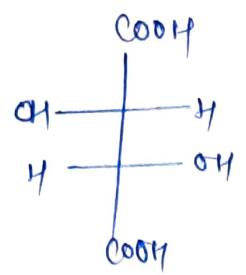
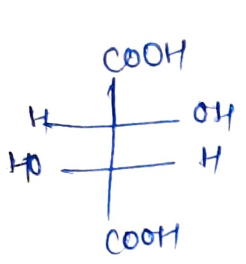
equal amt-  
total opposite

( Racemate )



- Methods
- ① Chemical Resolution
  - ② Biochemical Resolution
  - ③ Mechanical Method
  - ④ Kinetic Method
  - ⑤ Preferential Crystallization by inoculation/Seeding

Racemic Mixture Modification - formation of Racemic Mixture by mixing both enantiomers



50:50  
mix

± Tartaric acid

RR Tartaric Acid

SS Tartaric acid

mp = 168-170

168-170

210-212

$\alpha = -12^\circ$

+12°

0

# differ in physio-chemical properties

① Mechanical Separation or Spontaneous Resolution

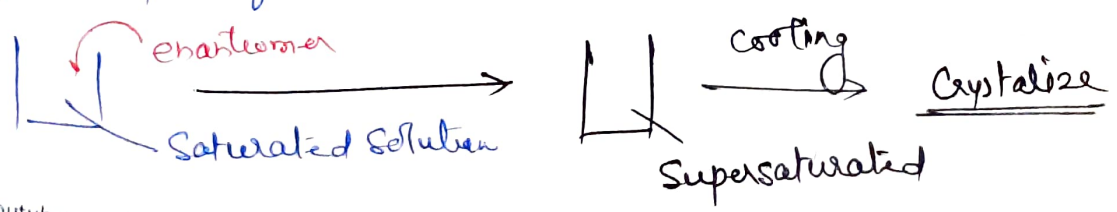
# 1<sup>st</sup> used by "Pasteur" for resolution of Sod. Ammonium tartarate which crystallizes out in the form of racemic mixture below 27°C

# Racemate  $\xrightarrow{<27^\circ\text{C}}$  two different crystal formed with mirror image  
 Separate by Magnifying glass & forceps

disadvantage - laborious method with same crystal structure

② Seeding or Preferential Crystallization.

↳ Seeding of a saturated solution of racemic mixture with pure crystal of one enantiomer.

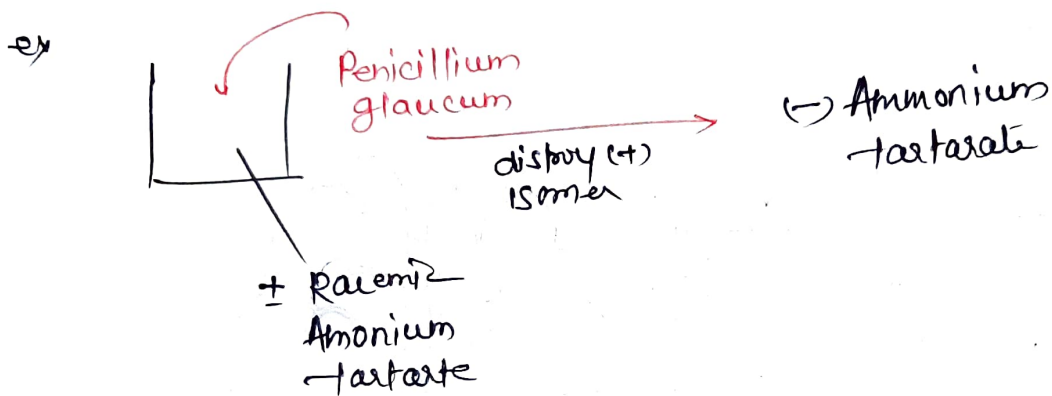




ex. Crystal of (-) asparagine crystallize out ( $\pm$ ) Sod. ammonium tartarate from solution of Racemic modification.

③ Biochemical Method: By using some microorganism like bacteria, yeast, mould, fungi.

When these microorganism are grown in dilute solution of racemic mixture they assimilate one enantiomer rapidly than the others

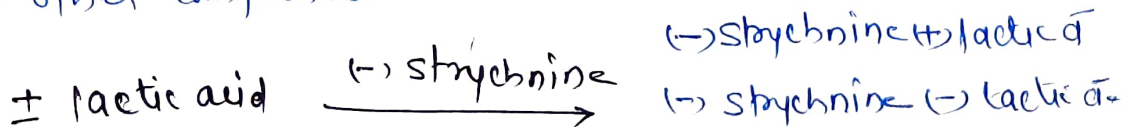


Disadv - ① Half material is lost

② Can not be used if mixture is toxic to microorganism

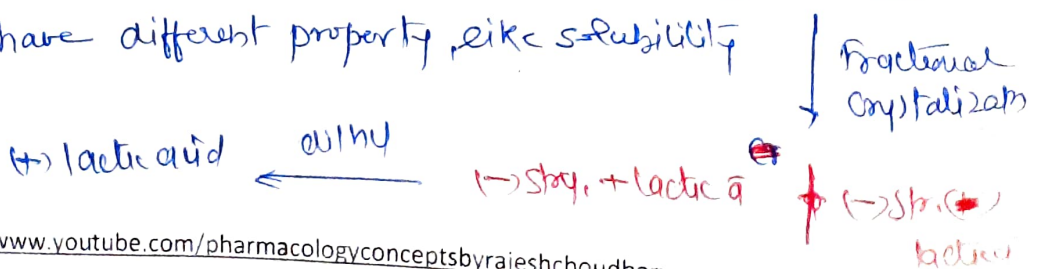
④ Chemical Method (Pasteur 1858)

converting of enantiomers of a racemic mixture to diastereomer by adding of pure enantiomer of other compounds.



diastereomer

Both have different property, like solubility



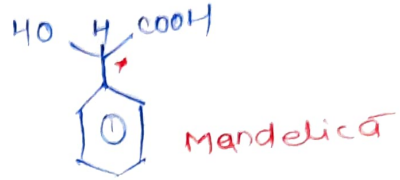
## 5. Kinetic Method



# One enantiomer reacts faster than other with optically active compound.

# e.g. ~~Meth~~ menthol reacts faster with (+) mandelic acid than (-) isomer

# thus it can be separated



harmful by products  
By ajeski chemistry