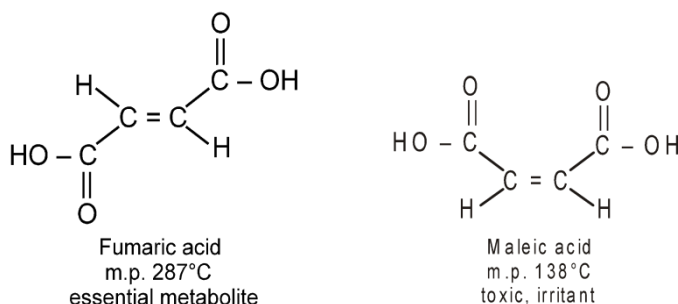


# STEREISOMERISM

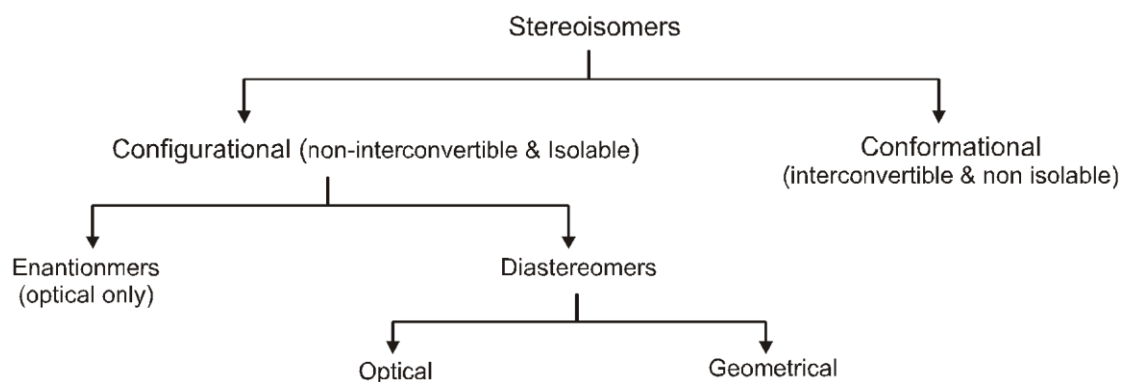
## Introduction :

The particular kind of isomers that are different from each other only in the way the atoms are oriented in space are called stereoisomers. These isomers have same **connectivity** of atoms and groups. Stereoisomers have remarkably different physical, chemical and biological properties.

**Ex.** The two stereoisomers of butenedioic acid are maleic acid and fumaric acid. Fumaric acid is an essential metabolic intermediate in both plants and animals, but maleic acid is toxic and irritating to tissues.



## Classification of Stereoisomers :



## 1. Configurational Isomers :

(I) These isomers differ in the configuration (The spatial arrangement of atoms that characterises a particular stereoisomer is called its configuration).

(II) Configurational isomerism arises due to noninterconvertibility at room temperature. Since these are non interconvertible, therefore can be separated by physical or chemical methods.

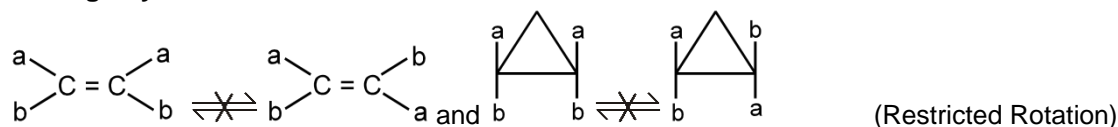
## Section (A) : Geometrical isomerism

**D1** Isomers which possess the same **molecular and structural formula** but differ in the arrangement of atoms or groups in space due to **restricted rotation** are known as geometrical isomers and the phenomenon is known as geometrical isomerism.

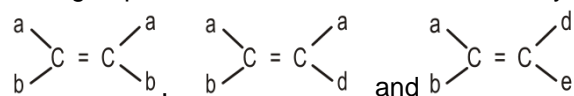
### Conditions of geometrical isomerism :

(I) Geometrical isomerism arises due to the presence of a double bond or a ring structure  
(i.e.  $\text{>C}=\text{C}<$ ,  $\text{>C}=\text{N}-$ ,  $-\text{N}=\text{N}-$  or ring structure)

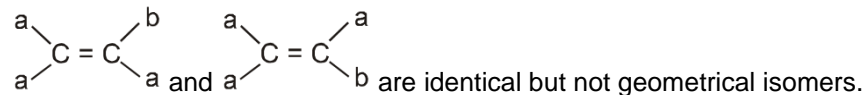
Due to the rigidity of double bond or the ring structure the molecules exist in two or more orientations. This **rigidity to rotation** is described as restricted rotation / hindered rotation / no rotation.



(II) Different groups should be attached at each doubly bonded atom.



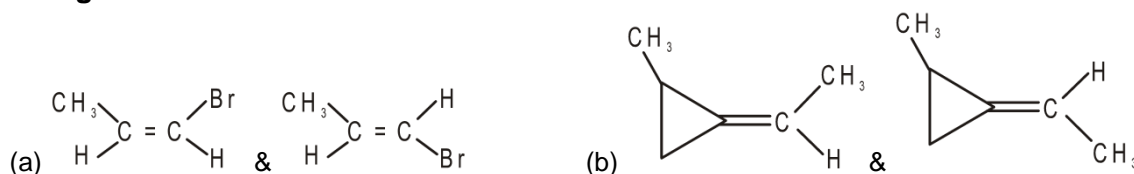
On the other hand, following types of compounds can not show geometrical isomerism :



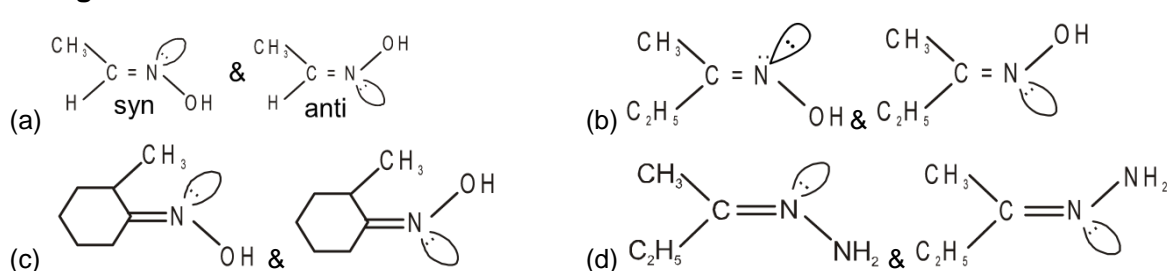
(III) Groups responsible to show geometrical isomerism must be nearly in the same plane.

**Examples of Geometrical isomers :**

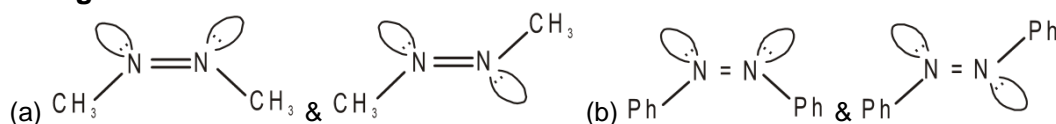
(I) **Along  $C=C$  bond**



(II) **Along  $C=N$  bond**



(III) **Along  $-N=N-$  bond**

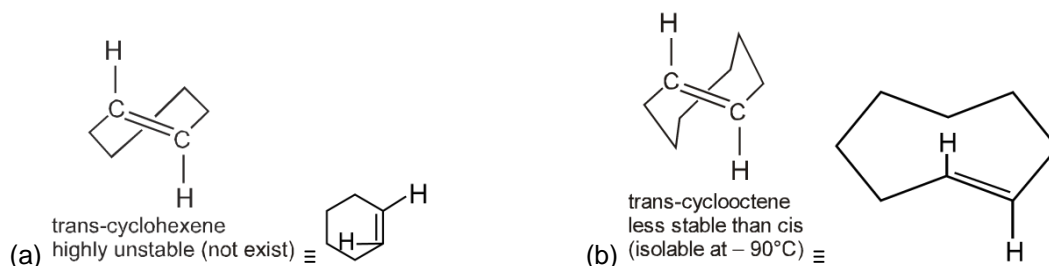


(IV) **Along  $\sigma$  bond in cycloalkanes**



(V) **Along  $C=C$  in ring structures :**

Usually in cycloalkenes double bond has cis configuration. Their trans isomers do not exist due to large angle strain. But if the ring is large enough then the trans stereoisomer is also possible. The **smallest trans cycloalkene** that is stable enough to be isolated & stored is **trans-cyclooctene**.



### Configurational nomenclature in geometrical isomerism :

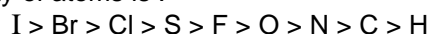
Configuration	Criteria	Remarks
cis / trans	Similarity of groups	If the two similar groups are on same side of restricted bond the configuration is cis otherwise trans.
E/Z	Seniority of groups	If the two senior groups are on same side of restricted bond the configuration is Z (Z = zusammen = together) otherwise E (E = entgegen = opposite).

## Section (B) : CIP rules, E/Z naming & physical properties of geometrical isomers

### Cahn - Ingold - Prelog sequence rules :

For deciding the seniority of groups following (CIP) rules are applied :

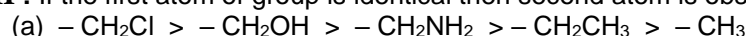
**Rule I :** The group with the first atom having higher atomic number is senior. According to this rule the seniority of atoms is :



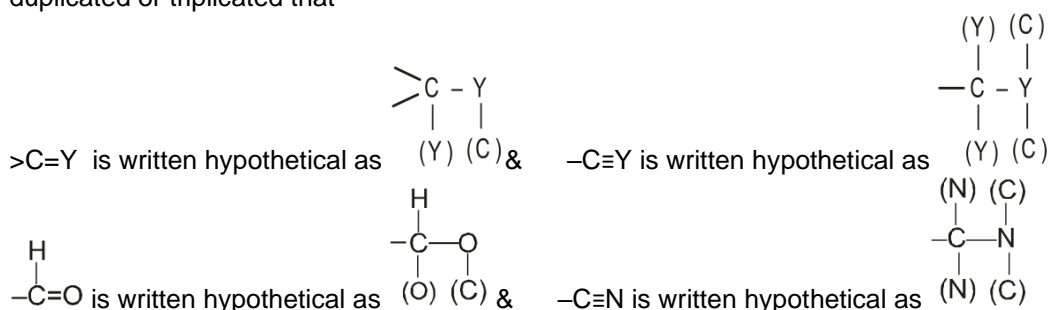
**Rule II :** The higher mass isotope is senior.

Thus (a)  $-T > -D > -H$ . (b)  $-C^{14}H_3 > -C^{12}H_3$

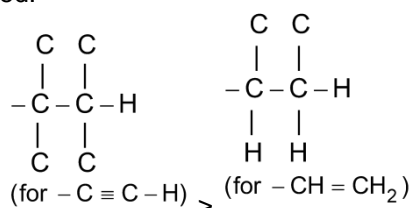
**Rule III :** If the first atom of group is identical then second atom is observed for seniority.



**Rule IV :** Groups containing double or triple bonds are assigned seniority as if both atoms were duplicated or triplicated that

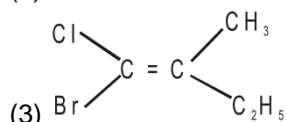
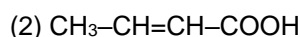
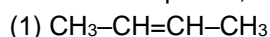


**Ex.** To decide seniority of multiple bonded groups ( $-C\equiv CH$ ,  $-CH=CH_2$ ) their hypothetical equivalents are compared.



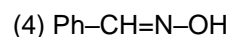
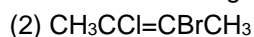
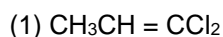
**Rule V :** Bond pair is senior to lone pair.

**Que.** In which compound, Cis-Trans nomenclature cannot be used

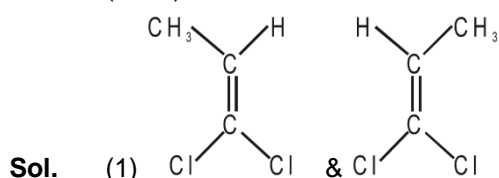


**Ans.** (3)

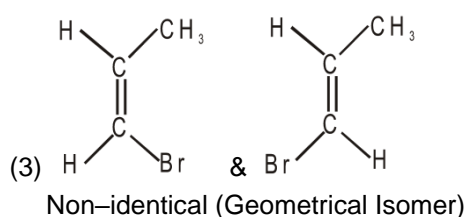
**Que.** Which of the following structures will show geometrical isomerism ?



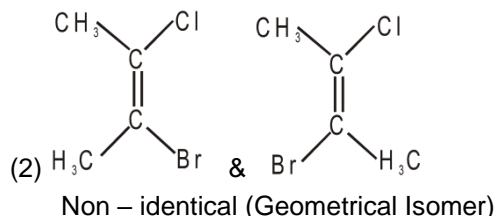
**Ans.** (2,3,4)



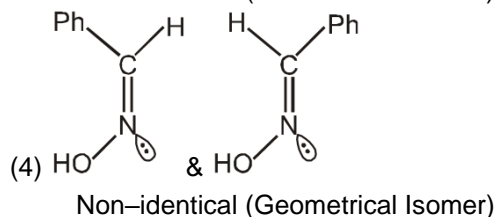
Both are identical



Non-identical (Geometrical Isomer)

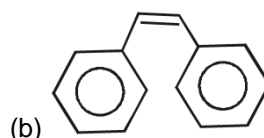
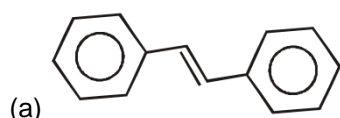


Non-identical (Geometrical Isomer)



Non-identical (Geometrical Isomer)

**Que.** Identify E and Z form of stilbene



**Ans.** (a) E (b) Z

### Physical Properties of Geometrical Isomers :

Physical properties		Remarks
Dipole moment	$I > II$	cis-isomer has resultant of dipoles while in trans isomer dipole moments cancel out
Boiling point	$I > II$	Molecules having higher dipole moment have higher boiling point due to larger intermolecular force of attraction
Solubility (in $\text{H}_2\text{O}$ )	$I > II$	More polar molecules are more soluble in $\text{H}_2\text{O}$ .
Melting point	$II > I$	More symmetric isomers have higher melting points due to better packing in crystalline lattice & trans isomers are more symmetric than cis.
Stability	$II > I$	The molecule having more vander waal strain are less stable. In cis isomer the bulky groups are closer they have larger vander waals strain.

## Section (C) : Chiral carbon and Projection Formula

### Cause of optical activity :

The foundation of modern theory of stereochemistry was laid by Louis Pasteur when he observed two different kind of crystals, which were mirror images of each other. Aqueous solution of both types of crystals showed optical rotation that was equal in magnitude but opposite in direction. Pasteur believed that this difference in optical activity was associated with the three dimensional arrangement of atoms in the two types of crystals.

Later van't Hoff and LeBel proposed that all the four valencies of carbon are directed towards the four corners of regular tetrahedron, and if all the four substituent attached to such a carbon are different the resulting molecule lack symmetry and such a molecule is referred to as asymmetric molecule and **asymmetry** of the molecule is responsible for optical activity in such organic compounds.

### D2 Chirality :

A compound which is non-superimposable to its mirror image is called **chiral** while a compound which is superimposable to its mirror image is called **achiral**.

### D3 Chiral centre :

A compound in which a carbon is attached with four different groups lacks symmetry and is called chiral carbon or asymmetric carbon. It is represented by **C\***.

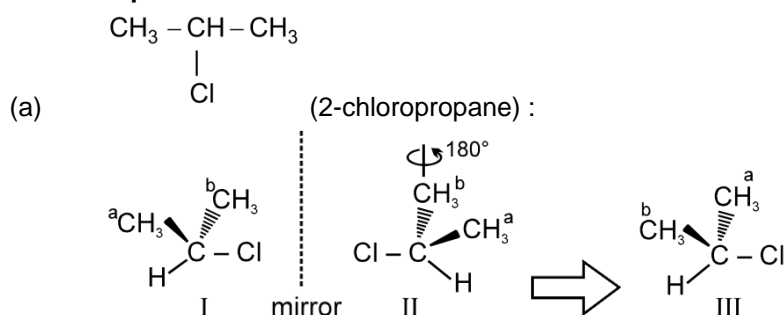
### Asymmetric and dissymmetric compounds :

A molecule which does not possess any element of symmetry (there are all 23 elements of symmetry) is called asymmetric. A molecule which does not possess plane of symmetry, centre of symmetry and alternating axis of symmetry is called dissymmetric.

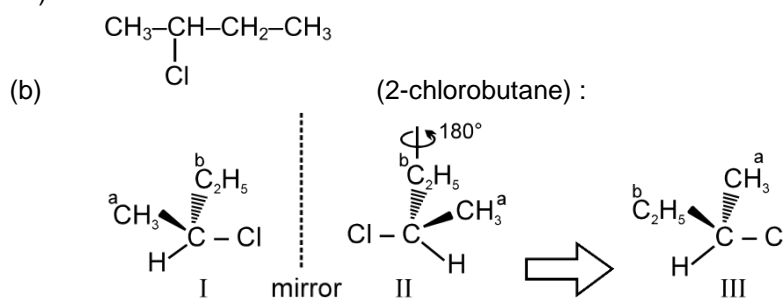
### Condition for optical activity :

The minimum condition for a compound to show optical activity is molecular dissymmetry i.e. absence of plane of symmetry, centre of symmetry and alternating axis of symmetry.

### For Examples :



I has no chiral centre since two groups (a & b) are identical. It is superimposable on its mirror image II ( $\equiv$  III).



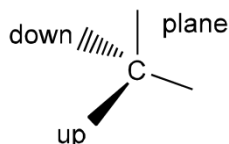
I has one chiral centre it is asymmetric & it is not superimposable to its mirror image II ( $\neq$  III).

The necessary condition for chirality is not just the presence of asymmetric carbon atoms but the dissymmetry of the molecule as a whole.

### Projection formulas in optical isomerism :

#### (I) Wedge-dash projection formula :

It is a convenient way of depicting three dimensional structure in two dimension. In this projection four bonds of a tetrahedral molecule is shown by two lines (in the plane), one wedge (up the plane) and one dash line (down the plane)

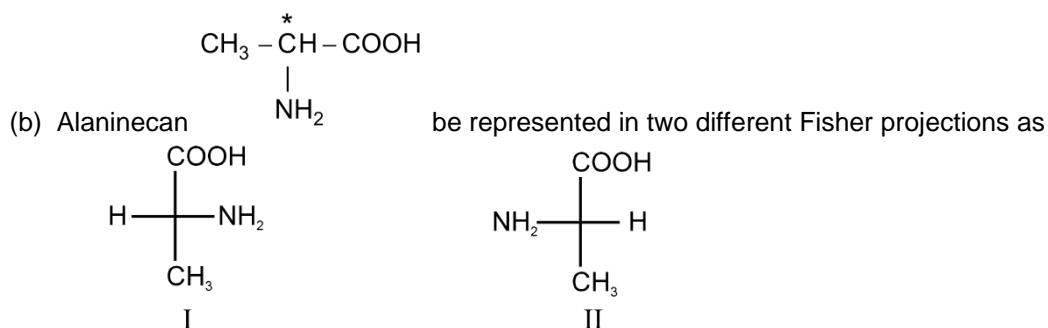
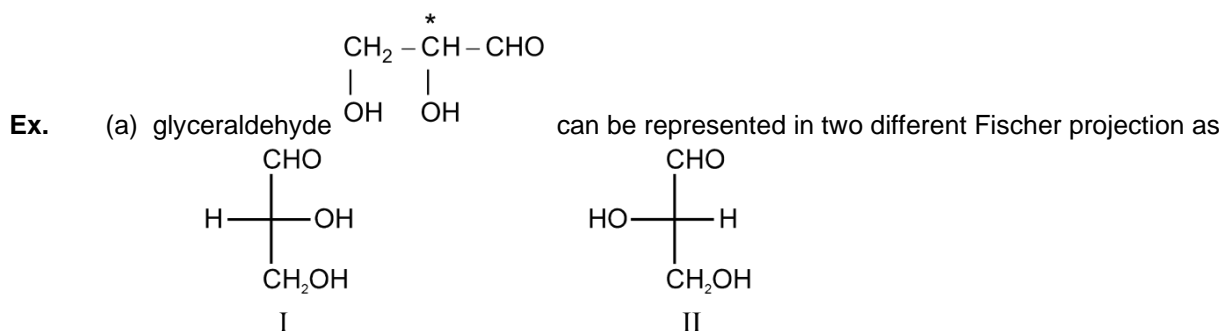


#### (II) Fischer projection formula :

It is also a convenient way of depicting three dimensional structure in two dimension.

##### Rules for writing Fischer projection formula :

- The molecule is drawn in the form of cross (+) with the chiral carbon at the intersection of horizontal & vertical lines.
- On vertical line, main chain is taken with first carbon at the top.
- The horizontal lines represent the bonds directed towards the viewer and vertical lines represent away from the viewer



#### (III) Saw horse projection formula :

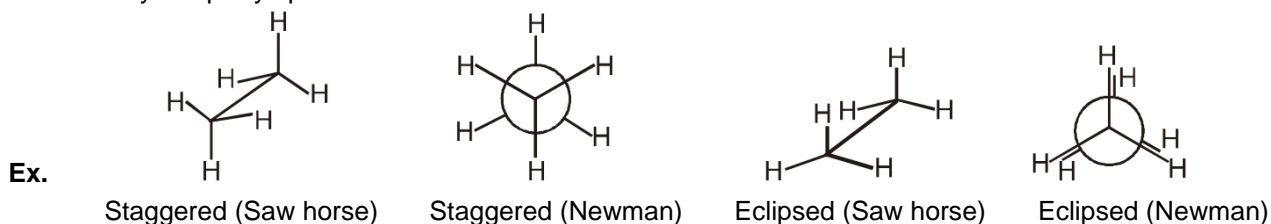
The molecule is viewed slightly from above, from the right and projected on the paper. The bond between the carbon atoms is drawn diagonally. The lower left hand carbon is considered to be towards front and upper right hand side carbon towards back.

#### (IV) Newman projection Formula :

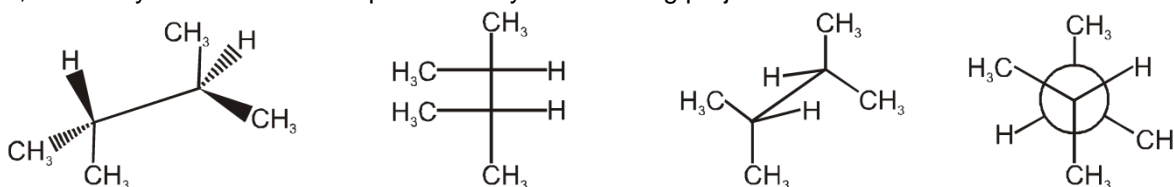
- These projection formulae are obtained by viewing the molecule along the bond joining the two carbon atoms.

(ii) The carbon atoms near the eye is represented by a point and three other atoms/ groups attached to it by 3 equally spaced lines.

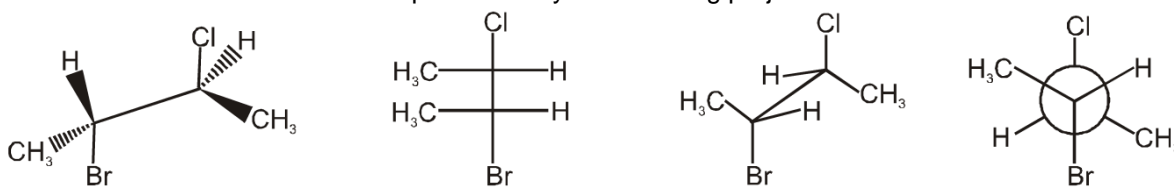
(iii) The carbon atom further from the eye is represented by a circle and three atoms / groups attached to it by 3 equally spaced lines.



Ex. 2,3-Dimethylbutane can be represented by the following projections as follows.



Ex. 2-Bromo-3-chlorobutane can be represented by the following projections as follows.

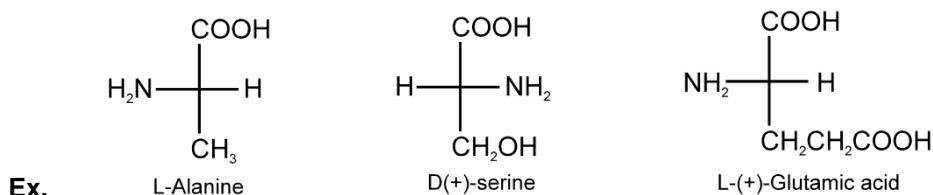


All the presentations have identical configurations

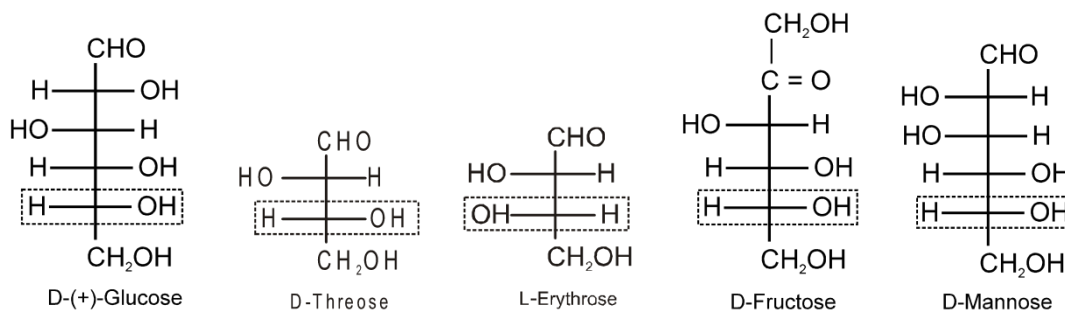
## Section (D) : Configurational nomenclature in optical isomers

### (I) D-L System (Relative configuration) :

This method is used to relate the configuration of sugars and amino acids by the help of enantiomers of glyceraldehyde. The configuration of (+)-glyceraldehyde has been assigned as D and the compounds with the same relative configuration are also assigned as D, & those with (-) glyceraldehyde are assigned as L.



Sugars have several asymmetric carbons. A sugar whose highest numbered chiral centre (the penultimate carbon) has the same configuration as D-(+)-glyceraldehyde (– OH group on right side) is designated as a D-sugar, one whose highest numbered chiral centre has the same configuration as L-glyceraldehyde is designated as an L-sugar.

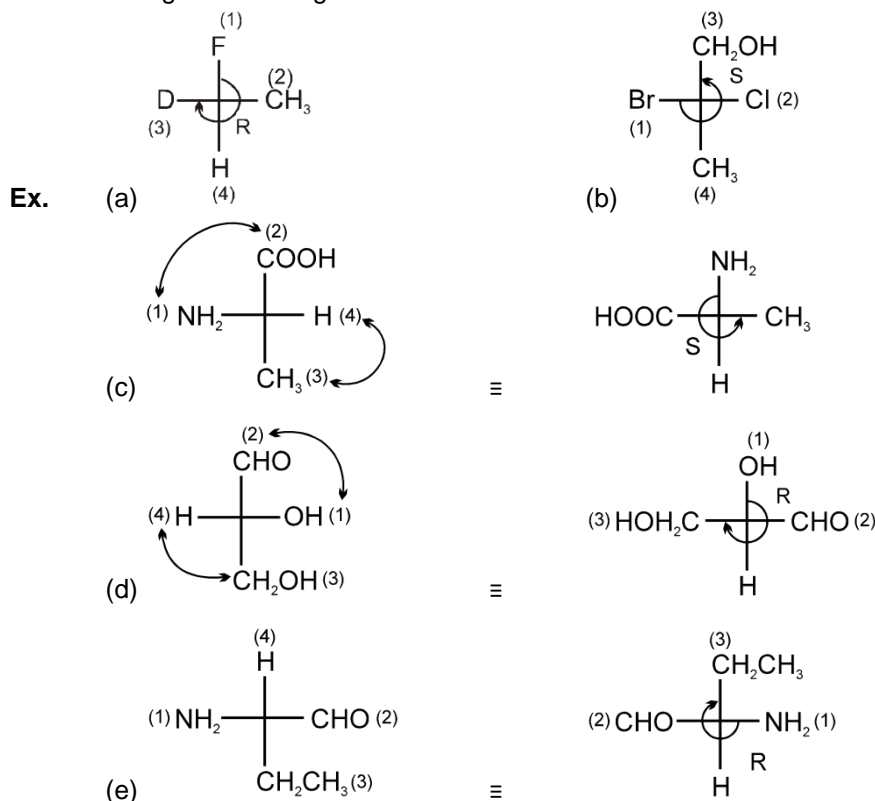


## (II) R and S configurations in Fischer projection : (Absolute configuration)

**Step I :** The priorities of groups which are attached with the asymmetric C-atom are assigned by CIP rule.

**Step II :** The lowest priority group is brought to the bottom of Fischer projection by two or even simultaneous exchanges.

**Step III :** Then an arrow is drawn from first priority group to second priority group to third priority group. If the arrow is clockwise the configuration assigned to the projection is **R** & If it is anticlockwise the configuration assigned is **S**.



## (III) R and S configurations in wedge-dash formula : (Absolute configuration)

Step 1 : Decide the priority of groups by sequence rule.

Step 2 : Bring the lowest prior group to dash by even simultaneous exchanges.

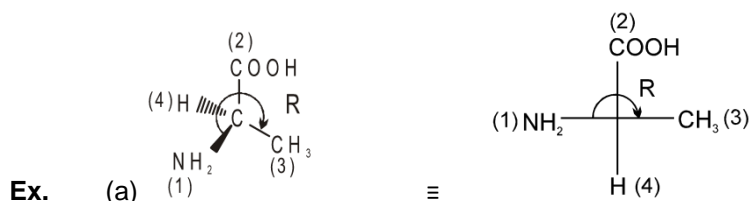
Step 3 : Draw an arrow from first prior group to second prior group till third prior group.

Step 4 : If the direction of arrow is clockwise the configuration is R and if anticlockwise it is S.

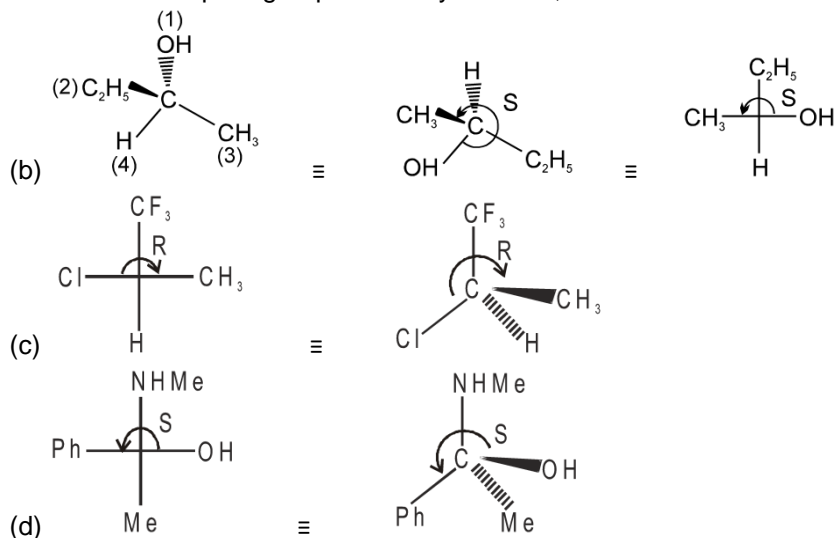
**Converting a wedge-dash formula into Fischer projection formula :**

~~Draw the Fischer projection formula having equivalent configuration to the wedge-dash formula~~





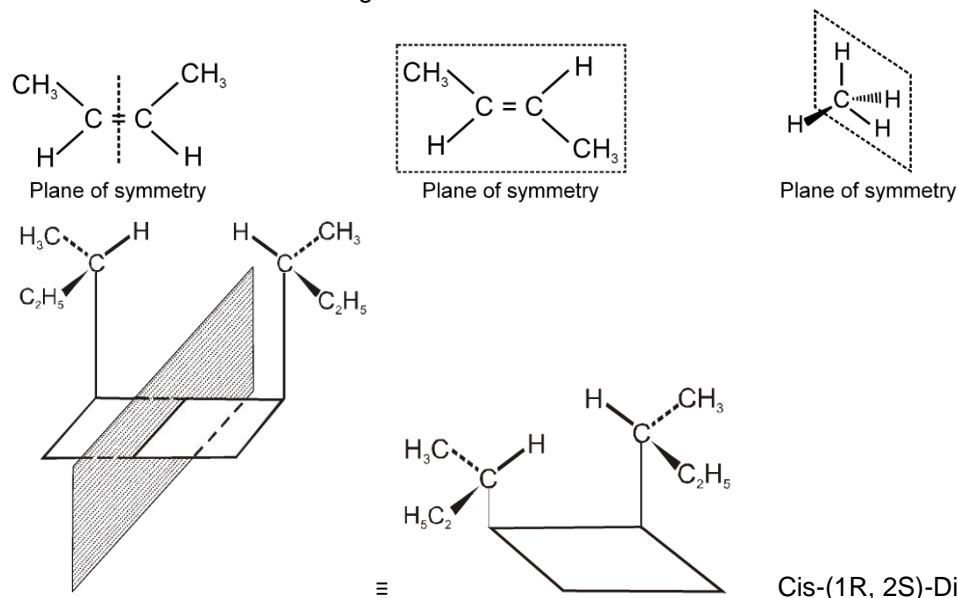
Here the lowest prior group is already on dash, there is no need for exchanges.



## Section (E) : Element of Symmetries (POS, COS, AOS)

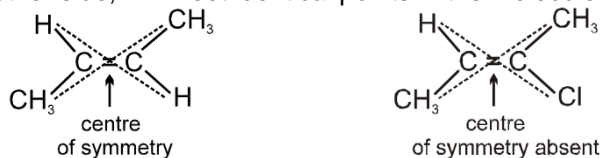
### D4 Plane of symmetry ( $\sigma$ ) :

It is an imaginary plane which bisects the molecule in two equal halves in such a way that each half of the molecule is the mirror image of the other half.



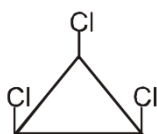
### D5 Centre of symmetry (i) :

A centre of symmetry is a point from which lines, when drawn on one side and produced an equal distance on the other side, will meet identical points in the molecule.

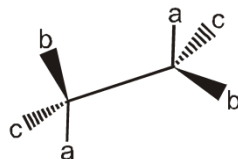


**D6 Axis of symmetry ( $C_n$ ) :**

Axis of symmetry is a line about which the molecule can be rotated by  $360^\circ/n$  and thereby produce a molecule indistinguishable from the original molecule.



$C_3$  axis of symmetry

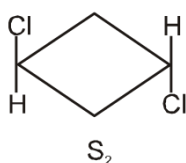


$C_2$  axis of symmetry

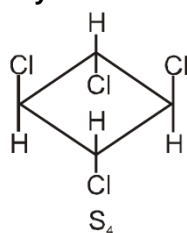
**D7 Alternating axis of symmetry ( $S_n$ ) :**

A molecule possess an  $n$ -fold alternating axis of symmetry if when rotated through an angle of  $360^\circ/n$  about this axis and then followed by reflection in plane perpendicular to the axis ; the molecule is indistinguishable from the original molecule.

It is also called **Improper axis of symmetry**



$S_2$



$S_4$

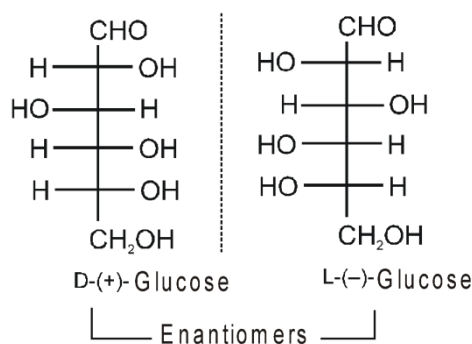
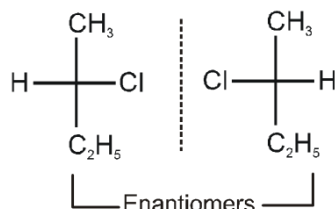
**Section (F) : Definition & properties of Enantiomers, Diastereomers & Meso compounds**

**D8 Enantiomers :**

Stereoisomers which are non-superimposable mirror images of each other are called enantiomers.

Ex. (a) 2-Chlorobutane :

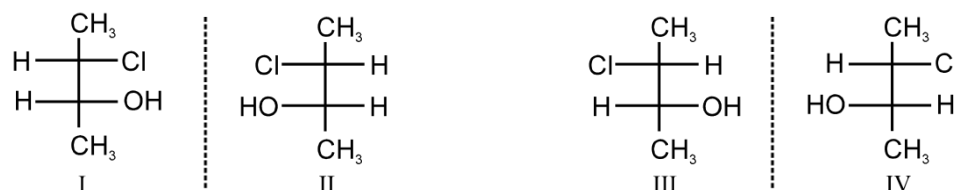
(b) Glucose :



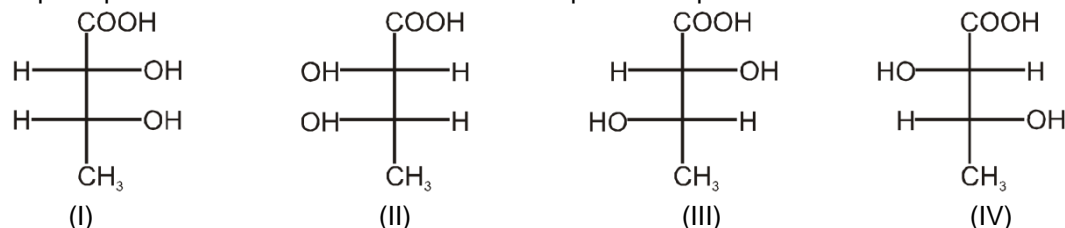
**D9 Optical diastereomers :**

The optical isomers which are neither mirror image nor superimposable to each other are called **diastereomers**. Diastereomers have different physical and chemical properties and they can be easily separated by physical methods.

Ex. Let us consider the stereoisomers of 3-chlorobutan-2-ol



There are 4 stereoisomers of 3-chlorobutan-2-ol. In which (I & II) & (III & IV) are enantiomeric pairs. (I & III) or (I & IV) or (II & III) or (II & IV) all the isomers in each pair are neither mirror image nor superimposable to each other. Therefore these pairs are optical diastereomers.



There are 4 stereoisomers of 2,3-Dihydroxybutanoic acid. In which (I & II) & (III & IV) are enantiomeric pairs. (I & III) or (I & IV) or (II & III) or (II & IV) all the isomers in each pair are neither mirror image nor superimposable to each other. Therefore these pairs are optical diastereomers.

### Properties of Enantiomers & Diastereomers :

	Properties	Enantiomers	Diastereomers
(1)	Molecular formula	Same	Same
(2)	Structural formula	Same	Same
(3)	Stereochemical formula (structure formula with orientation)	Different	Different
(4)	Dipole moment	Same	Different
(5)	Physical properties (m.p., b.p., density, solubility, refractive index etc.)	Same	Different
(6)	Specific rotation	Different sign but same magnitude	Different
(7)	<b>Chemical properties</b>		
	(a) with optically inactive compound	Same	Different
	(b) with optically active compound	Different	Different

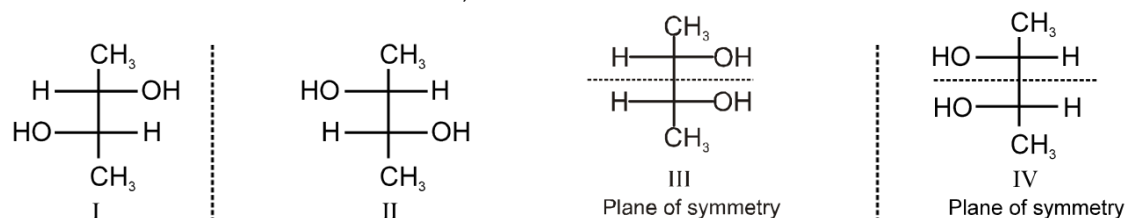
### D10 Meso compound :

An optically inactive molecule whose at least one diastereomer is optically active.

\* Mirror image of meso compound is superimposable over each other & nonresolvable.

\* Molecule contains chiral centres & symmetry but optically inactive.

**Ex.** Let us consider the stereoisomers of 2, 3-Butanediol

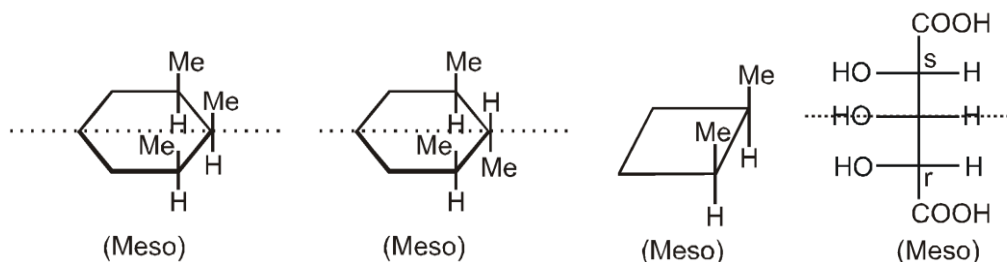


In all the possible isomers I & II are enantiomers but III & IV are not enantiomers since they have plane of symmetry and are superimposable to each other.

**Note :** All symmetrical compounds are superimposable to their mirror images.

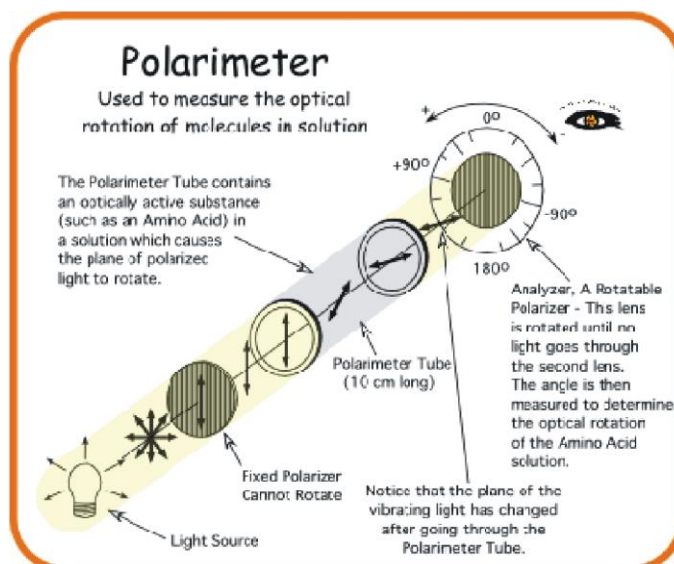
Thus III & IV are identical & meso compounds.

Thus total stereoisomers of 2, 3-butanediol is 3. Two enantiomers and one meso isomer.



### Section (G) : Plane polarized light, specific rotation, observed rotation, optical purity and enantiomeric excess

- (I) **Optical activity & plane-polarised light** : Ordinary light is an electromagnetic wave, which has oscillation in all the directions perpendicular to the path of propagation. When ordinary light is passed through Nicol prism it has all its oscillations in the same plane and is called plane-polarised light.
- D11 Certain compounds rotate the plane of polarised light in a characteristic way when it is passed through their solutions. These compounds are referred to as **optically active compounds**. The angle of rotation can be measured by an instrument called polarimeter.
- (II) **Dextrorotatory compounds** : If the substance rotates plane-polarised light to the right ( i.e. in clockwise direction) then it is called dextrorotatory & indicated by 'd' or (+).
- (III) **laevorotatory compounds** : If light is rotated towards left (i.e. in anticlockwise direction) then substance is said to be laevorotatory and indicated by 'l' or (-).



- D12 **Specific rotation ( $\alpha$ )** : Specific rotation is the number of degrees of rotation observed if a 1-dm (10-cm) tube is used and the compound has concentration 1 gm/mL. Thus specific rotation  $[\alpha]$  is

$$[\alpha]_t^\lambda = \frac{\theta}{l \times C}$$

- $[\alpha]$  = Specific rotation ;  $\theta$  = observed angle of rotation (degree)  
 $l$  = Pathlength (dm) ;  $C$  = concentration (gm/ml)  
 $\lambda$  = wavelength (nm) ;  $t$  = temperature (25°C)

**Note :-** Specific rotation of a compound is **independent** of the length of tube and concentration of the solution.

**Optical purity :**

Sometimes we deal with mixture that is neither optically pure nor racemic mixture. In these cases we specify the optical purity of the mixture. It is defined as the ratio of its rotation to the rotation of pure enantiomer.

$$\text{Optical purity} = \frac{\text{observed optical rotation}}{\text{optical rotation of pure enantiomer}} \times 100$$

**Ex.** If we have some 2-butanol with observed rotation of + 9.72, we compare this rotation with + 13.5 rotation of the pure (+) enantiomer.

$$\text{optical purity} = \frac{9.72}{13.5} \times 100 = 72\%.$$

That means 72% is pure (+) 2-Butanol and 28% is racemic ( $\pm$  mixture)

Total (+) isomer = 72 + 14 = 86%, (–) isomer = 14%

**Enantiomeric excess :**

To compute the enantiomeric excess of a mixture we calculate the excess of predominant enantiomer as a percentage of the entire mixture. The calculation of enantiomeric excess gives the same result as the calculation of optical purity.

$$\therefore \text{Optical purity} = \text{Enantiomeric excess} = \frac{|d - \ell|}{d + \ell} \times 100 = \frac{\text{excess of one enantiomer over other}}{\text{entire mixture}} \times 100$$

Thus for above example optical purity = enantiomeric excess =  $d - \ell = 72\%$  &  $d + \ell = 100\%$

so,  $2d = 172 \Rightarrow d = 86\%$  &  $\ell = 14\%$  (composition of mixture)

**Ex.** Cholesterol, when isolated from natural sources, is obtained as a single enantiomer. The observed rotation  $\alpha$  of a 0.3 g sample of cholesterol in 15 mL of chloroform solution contained in a 10 cm polarimeter tube is  $-0.78^\circ$ . Calculate the specific rotation of cholesterol. A sample of synthetic cholesterol was prepared consisting entirely of (+) -cholesterol. This synthetic (+)- cholesterol was mixed with some natural (–)-cholesterol. The mixture had a specific rotation  $[\alpha]_D^{20}$  of  $-13^\circ$ . What fraction of the mixture was (+)-cholesterol ?

**Sol.** Specific rotation,  $[\alpha]_D^{20} = \frac{\theta}{\ell \times C} = \frac{-0.78}{1 \times \frac{0.3}{15}} = -39^\circ$

$$\text{Enantiomeric excess} = \frac{\text{observed optical rotation}}{\text{optical rotation of pure enantiomer}} \times 100 = \frac{-13^\circ}{-39^\circ} \times 100 = 33.3\%.$$

Therefore (+)-cholesterol is of 33.3 % and (–)-cholesterol is of 66.6 % in the mixture.

**Section (H) : Racemic mixture & optical resolution****D13 Racemic mixture :**

**A mixture of equal amounts of enantiomers is called a racemic mixture or racemic modification.**

A racemic modification is always **optically inactive** when enantiomers are mixed together, the rotation caused by a molecule of one enantiomer is exactly cancelled by an equal and opposite rotation caused by a molecule of its enantiomer.

The prefix ( $\pm$ ) is used to specify the racemic nature of the particular sample.

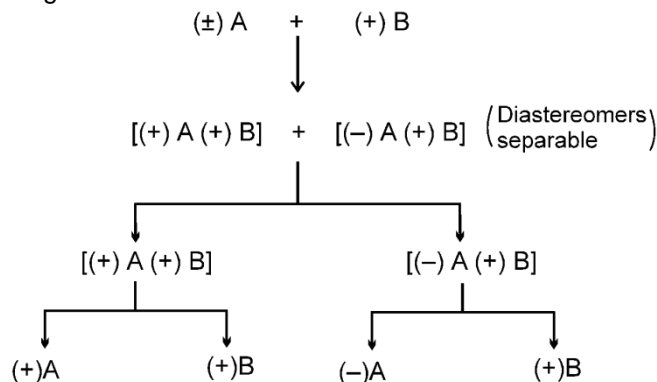
e.g. ( $\pm$ ) Lactic acid, or ( $d + \ell$ ) Lactic acid.

### Optical resolution (Reaction of chiral molecules with optically active reagent) :

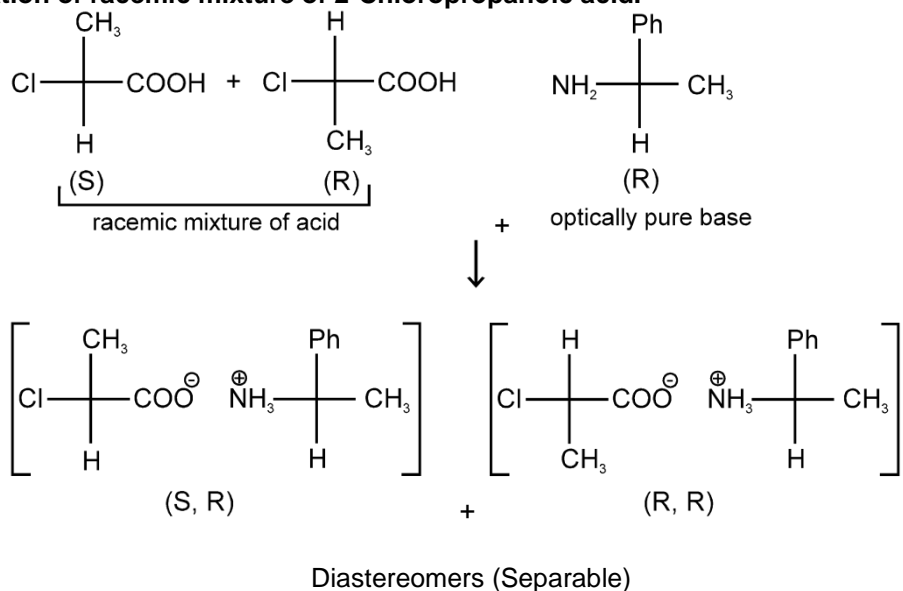
Resolution refers to the method of separating a racemic mixture into its enantiomeric constituents.

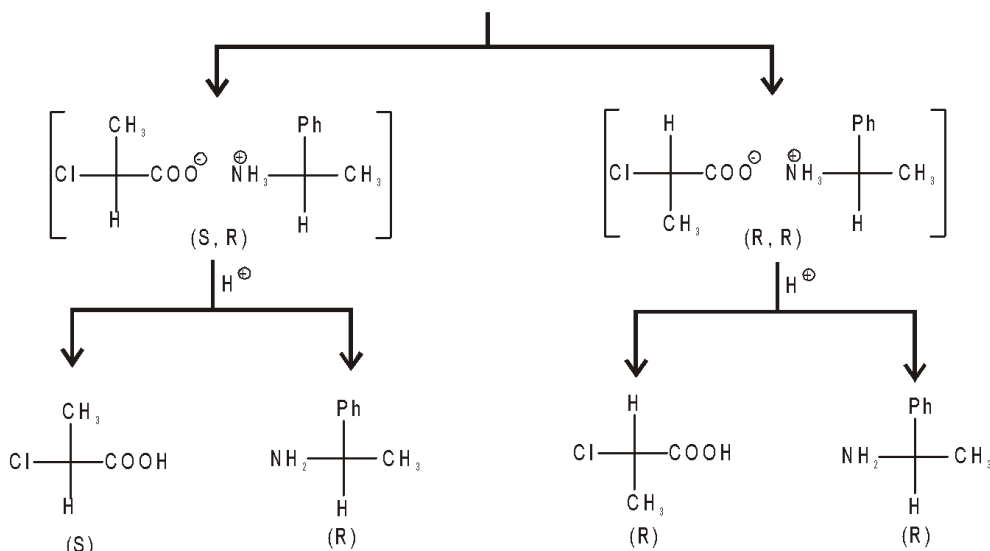
**Method :** A racemic mixture is allowed to react with another optically pure compound. This changes a racemic mixture into a mixture of diastereomers which have different melting and boiling point and solubilities. These can be separated from one another by conventional method of separation of compounds. The separated diastereomers is then broken down to give pure enantiomers.

Suppose a racemic mixture ( $\pm$ ) A is to be separated. It is reacted with an optically pure compound (+) B. Thus the schematic diagram for resolution will be.



Ex. Separation of racemic mixture of 2-Chloropropanoic acid.

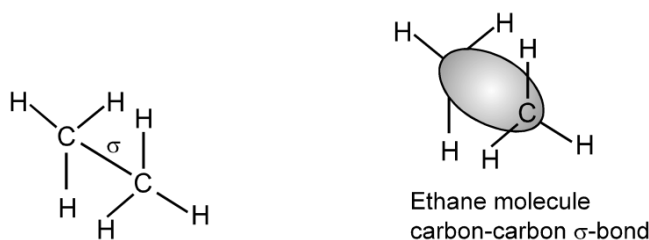




## Section (I) : Conformations, strains and stability

### 2. Conformations :

**Free rotation :** For defining free rotation let us consider the bonding in ethane.



We find that the  $\sigma$ -bond joining the carbon atoms is cylindrically symmetrical about the line joining the two carbon nuclei ; if the energy does not differ much in different arrangements the molecule can rotate about this carbon-carbon  $\sigma$  bond, we describe this freedom to change by saying that there is free rotation about the carbon-carbon single bond.

#### D14 Conformations :

Different arrangements of atoms that can be converted into one another by rotation about single bonds are called conformations.

#### D15 Conformers :

There are infinite arrangement (conformations) which arise due to free rotation around carbon-carbon  $\sigma$  bond, **out of them different conformations corresponding to energy minima are called conformers** . The conformational isomerism arises due to free rotation along a bond.

**Note :** (i) Conformers are also called as **rotamers or conformational isomers**.

(ii) It may be remembered that in all the conformations, the bond angles and the bond lengths remain the same.

#### Configuration vs Conformation :

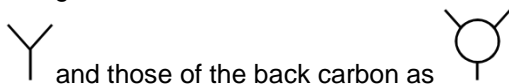
Configuration is the spatial arrangement of molecule without considering the internal forces acting on the molecule whereas conformation is the spatial arrangement of the molecule when all the internal forces are taken into account. In this more restricted sense, the term conformation is used to designate different spatial arrangements arising by twisting or rotation of bonds of a given configuration.

#### Newman projection :

For conformational analysis, a special type of structural formula is convenient to use which is called newman projection formula and another type is a sawhorse formula.



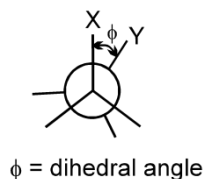
To write newman projection formula we imagine ourselves taking a view from one carbon atom directly along the selected bond axis to the next atom. The front carbon and its other bonds are represented as



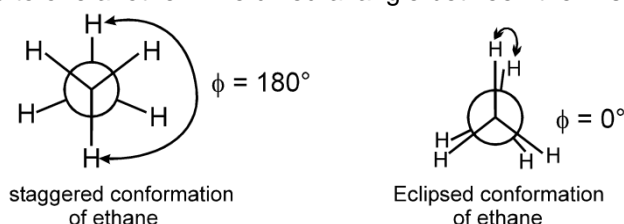


**Dihedral angle :**

The angle between C–X and C–Y in X–C–C–Y when it is visualised along C–C bond.

**Staggered, eclipsed and skew conformations :**

- (I) The **staggered conformation** of a molecule is that conformation where the dihedral angle between the bonds at each atom of carbon-carbon bond is  $60^\circ$ ,  $180^\circ$ ,  $300^\circ$ .
- (II) In the **eclipsed conformation** the atoms bonded to carbons at each end of carbon-carbon bond are directly opposite to one another. The dihedral angle between them is  $0^\circ$ ,  $120^\circ$ ,  $240^\circ$ .



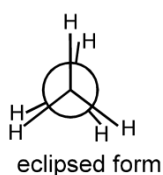
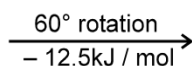
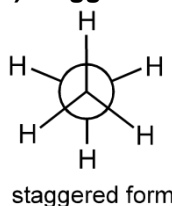
- (III) **Skew conformation** : All conformations other than staggered or eclipsed are skew conformations.

**Factors affecting stability of conformations :**

- (I) **Angle strain** : Any deviation from "normal" bond angles are accompanied by angle strain. It is normally present in the cyclic structures but absent in the acyclic structures.
- (II) **Torsional strain** : Any pair of tetrahedral carbons attached to each other tend to have their bonds staggered for minimum repulsion between their bonds. Any deviation from the staggered conformation are accompanied by torsional strain . It is also known as **Pitzer strain** or **Eclipsing strain**.
- (III) **van der Waals strain** : Non bonded atoms or groups that just touch each other i.e. they are about as far apart as the sum of their van der Waals radii, if brought any closer together they repel each other. Such crowding together is accompanied by van der Waals strain.

**Section (J) : Conformational analysis of Ethane, Propane, Butane and substituted butane****Conformational analysis of ethane :**

Ethane molecule contains a carbon-carbon  $\sigma$  bond and each carbon is further attached to 3 H-atoms. It exists in two extreme conformations i.e.

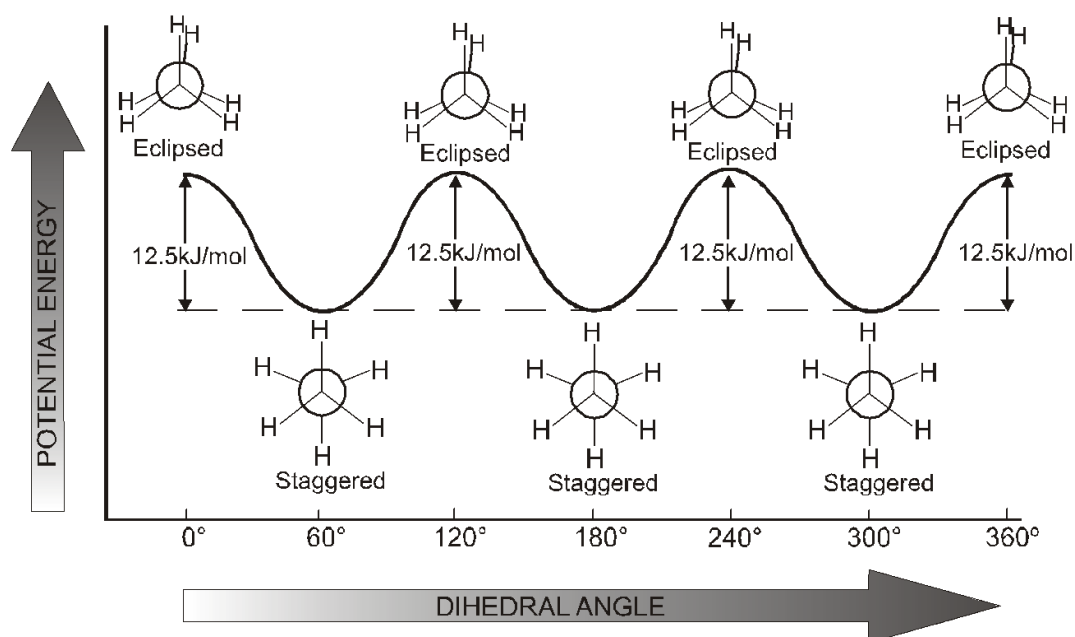
**(i) eclipsed conformation****(ii) staggered conformation**

The potential energy barrier between the two conformations of ethane is about 12.5 kJ/mol.

The potential energy of ethane molecule is at a minimum for the staggered conformation, increase with rotation and reaches a maximum at the eclipsed conformation. Most ethane molecules naturally exist in

the most stable staggered conformation. **There are only three energy minima**, that is ethane has only **three conformers**. Since they are indistinguishable and degenerate.

### Energy profile of Eclipsed and Staggered forms of ethane



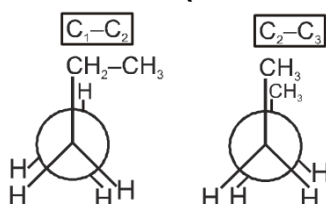
**Stability order** : Staggered > Eclipsed.

### Conformational analysis of propane ( $\text{CH}_3\text{--CH}_2\text{--CH}_3$ ) :

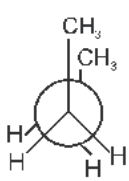
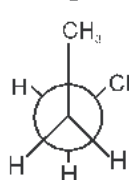
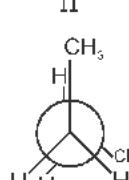
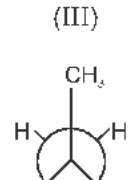
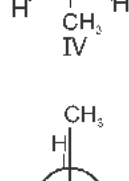
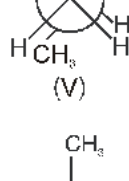
$\text{CH}_3\text{--CH}_2\text{--CH}_3$	Torsional Strain	Vander Waal strain	Stability
(a)	maximum	Zero	Staggered > Eclipsed
(b)	Zero	Zero	

Potential energy diagram of propane is exactly same as ethane but energy barrier is slightly more than ethane.

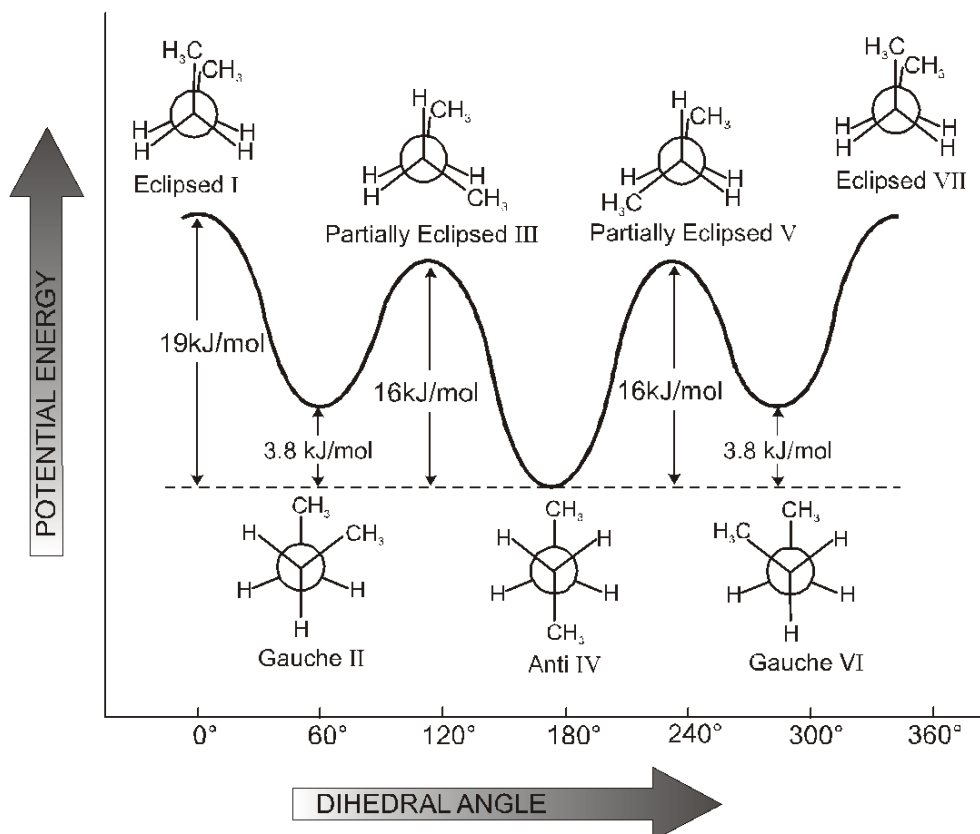
### Conformational analysis of butane ( $\text{CH}_3\text{--CH}_2\text{--CH}_2\text{--CH}_3$ ) :



Ethyl group -hydrogen atom repulsion is less than methyl-methyl repulsion. So draw the newman between C<sub>2</sub> - C<sub>3</sub> for detailed analysis.

CH <sub>3</sub> – CH <sub>2</sub> – CH <sub>2</sub> – CH <sub>3</sub>	Torstional Strain	Vander Waal strain	Stability/energy
<p>(a)  Fully eclipsed I</p> <p>(b)  Gauche form II</p> <p>(c)  Partially eclipsed (III)</p> <p>(d)  Anti form IV</p> <p>(e)  Partially eclipsed (V)</p> <p>(f)  Gauche form VI</p>	<p>Maximum</p> <p>Absent</p> <p>Maximum</p> <p>Absent</p> <p>Maximum</p> <p>Absent</p>	<p>Maximum</p> <p>Present between two CH<sub>3</sub> group</p> <p>Present between CH<sub>3</sub> and H group</p> <p>Absent</p> <p>Present between CH<sub>3</sub> and H group</p> <p>Present between CH<sub>3</sub> and H group</p>	<p><b>Stability order: Anti &gt; Gauche &gt; Partial eclipsed &gt; Eclipsed</b></p> <p><b>Energy order: Anti &lt; Gauche &lt; Partial eclipsed &lt; Eclipsed</b></p>

Energy profile of conformations of butane :



The stability order will be : Anti > Gauche > Partially eclipsed > Fully eclipsed.

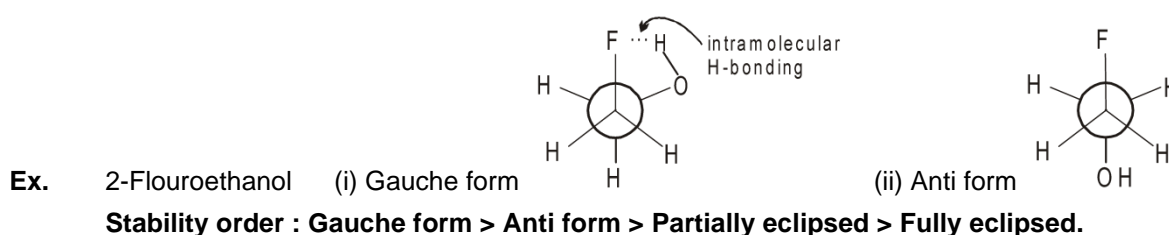
n-Butane exists as **three conformers** one anti (IV) and two gauche (II & VI). The gauche conformers II and VI are mirror images of each other and hence are **conformational enantiomers**. Gauche conformations (II & VI) and anti conformation (IV) are not mirror images of each other and hence are **conformational diastereomers**.

n-Butane spends the greater part of its time as the anti conformer, and divides the smaller part equally between the two gauche conformers. As a result of the rapid inter-conversion these conformers **can't be separated**.

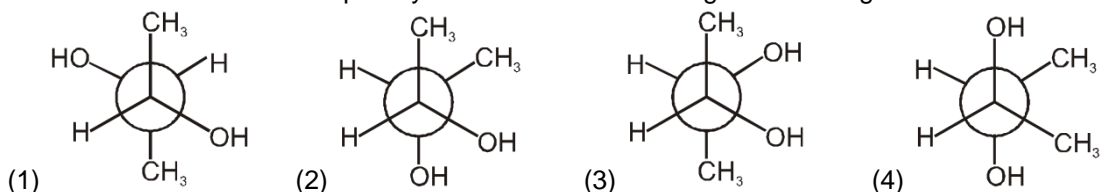
## Section (K) : Conformational analysis of compound having intramolecular H-bonding.

### Case of intramolecular hydrogen bonding :

In case of  $G-CH_2-CH_2-OH$ , where  $G = -OH, -NH_2, -F, -NR_2, -NO_2, -COOH, -CHO$  the Gauche form is more stable than the anti form due to intramolecular hydrogen bonding



**Que.** Which is the most stable & optically active conformer among the following ?

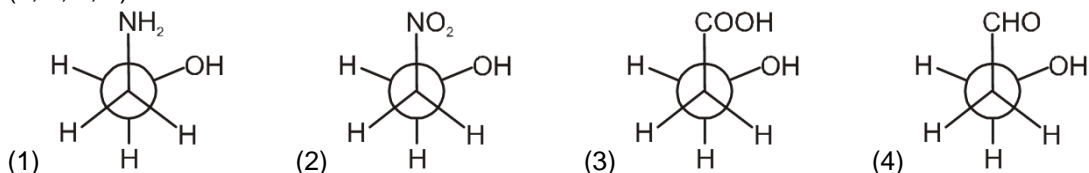


**Sol.** Structure (3) is optically active & most stable due to hydrogen bonding.

**Que.** In which of the following molecules Gauche form is more stable than their anti form?

- (1) 2-Aminoethanol (2) 2-Nitroethanol  
(3) 3-Hydroxypropanoic acid (4) 3-Hydroxypropanal

**Ans.** (1, 2, 3, 4)

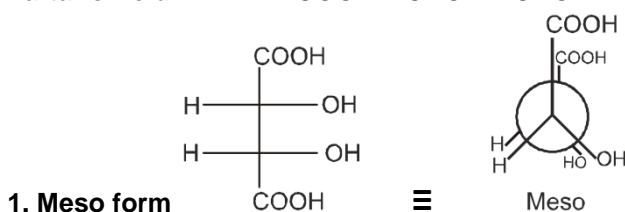


**Sol.**

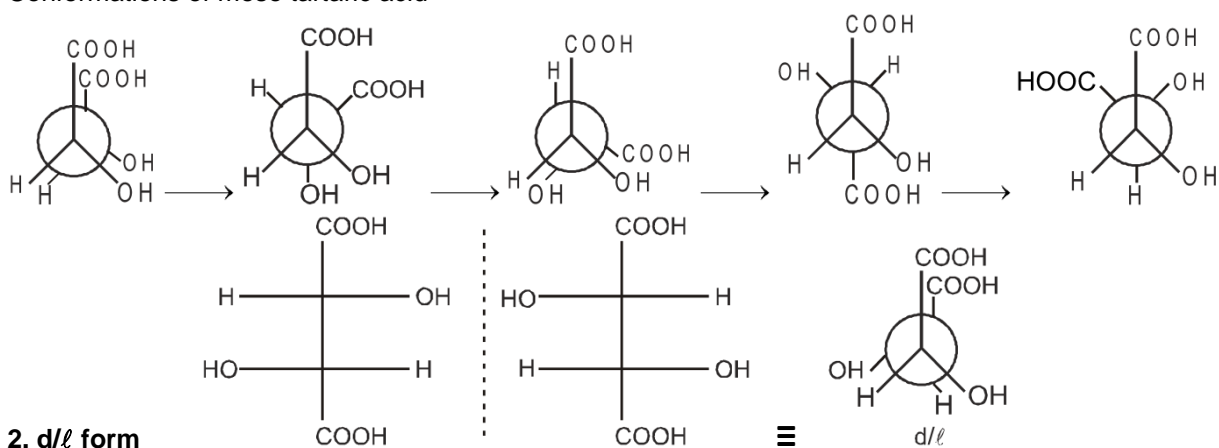
**(V) Interconversion of projection formulae :**

**Tartaric Acid :**  $\text{COOH} - \text{CHOH} - \text{CHOH} - \text{COOH}$

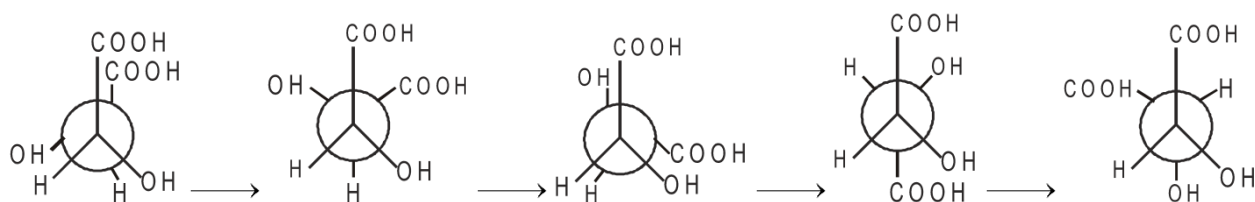
**no. of Stereoisomers : 3**



**Ex.** Conformations of meso tartaric acid



**Ex.** Conformational isomers of optical active (d/l) tartaric acid.



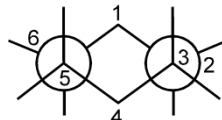
## Section (L) : Conformational analysis of cyclohexane

### (I) Chair form :

The most stable conformation of cyclohexane ring is the chair conformation. It is the staggered form of cyclohexane. In this non-planar structure the C–C bonds angles are close to  $109.5^\circ$ . This conformation is free from all the strains (like angle strain and torsional strain.)

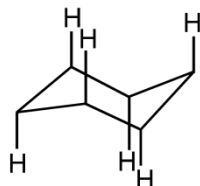


chair conformation

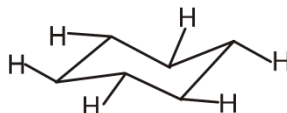


chair form (all staggered bonds)

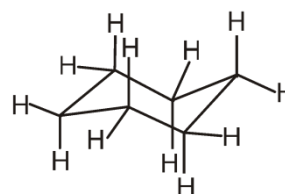
### Axial and equatorial bonds in chair form of cyclohexane :



Axial C – H bonds



Equatorial C – H bonds

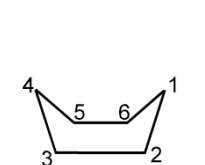


Axial &amp; equatorial bonds together

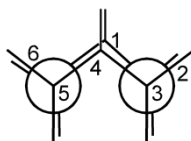
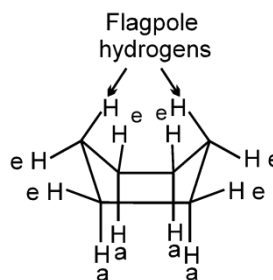
The 12 hydrogen atoms of chair conformation of cyclohexane can be divided into two groups. Six of the hydrogens called axial hydrogens, hence their bonds parallel to a vertical axis that passes through the rings centre. These axial bonds are directed up & down on adjacent carbons. The second set of six hydrogens called equatorial hydrogens which are located approximately along the equator of the molecule.

### (II) Boat form :

Another conformation which is known as boat conformation has exactly eclipsed conformations. Boat form is the transition state of two chair form.



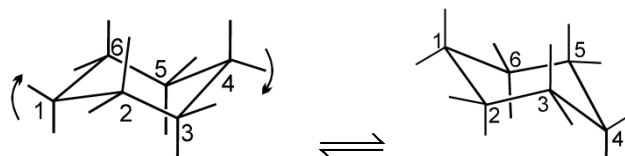
Boat conformation

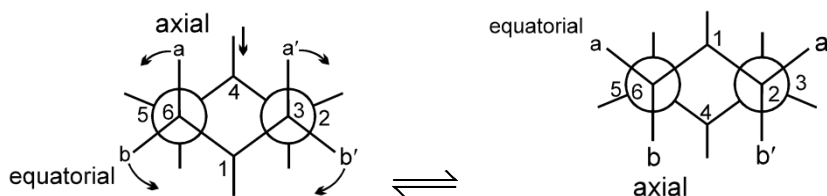
Boat conformation  
(all eclipsed bonds)

In boat form of cyclohexane **6 hydrogens are equatorial, 4 hydrogens are axial** and **two hydrogens are flagpoles**. It is an **unstable conformation** of cyclohexane due to **torsional strain** among axial hydrogens and due to **van der waals strain** caused by crowding between the "flagpole" hydrogens.

### Conformational inversion (Ring flipping) in cyclohexane :

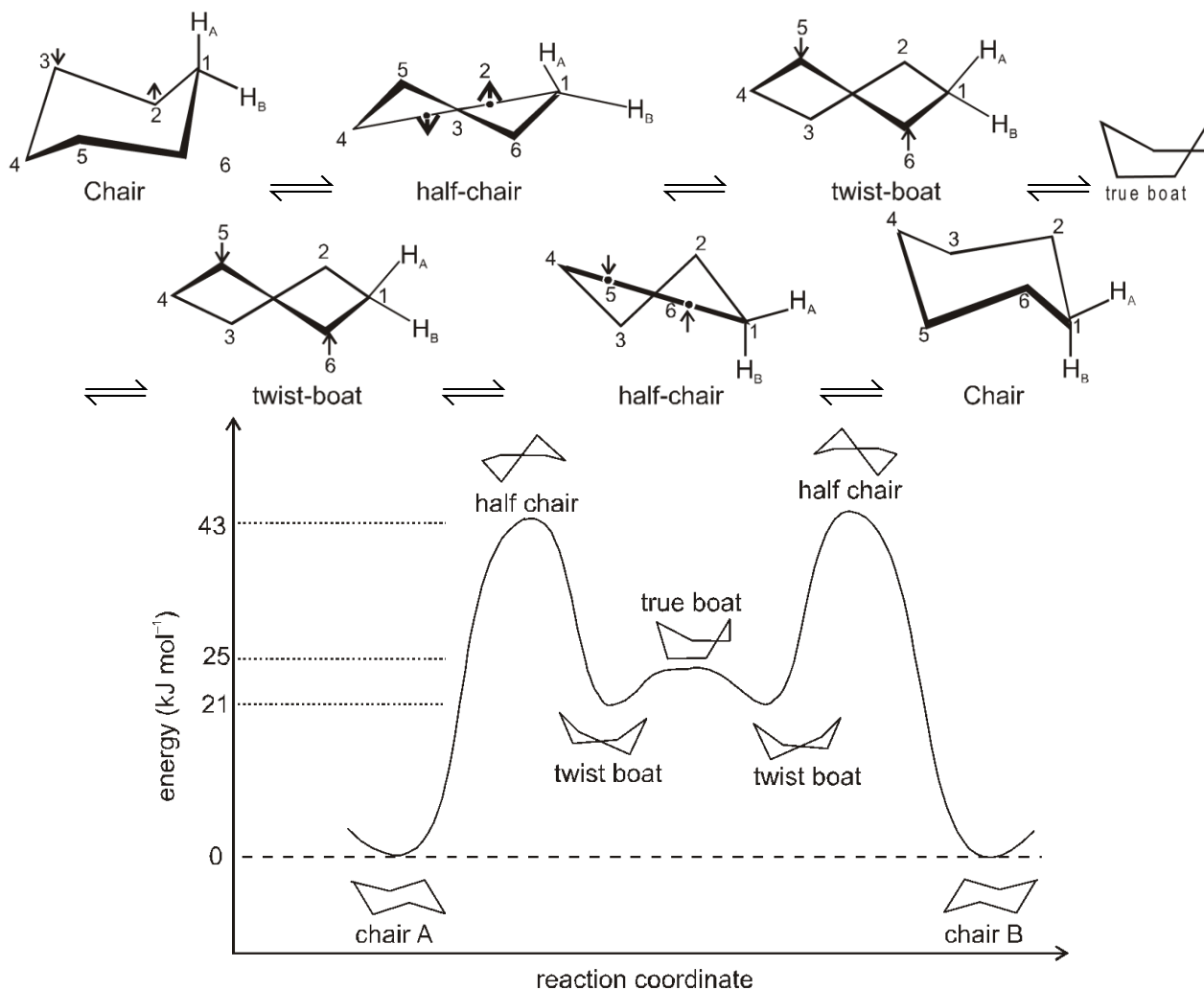
Like alkanes cyclohexane too is conformationally mobile. Through a process known as ring inversion, chair-chair interconversion, or more simply ring flipping one chair conformation is converted to another chair through the half chair, twist boat and boat form.





By ring flipping all axial bonds convert to equatorial and vice-versa. The activation energy for cyclohexane ring inversion is 45 kJ/mol. It is a very rapid process with a half-life of about  $10^{-5}$  sec. at  $25^\circ\text{C}$ .

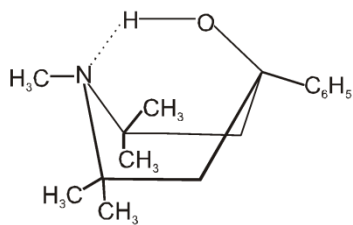
### The relative energy profile of various conformations of cyclohexane



Because of the greater stability of the chair form, more than 99% of the molecules are estimated to be in a chair conformation of any given moment.

**Note :** (a) Twist boat form of cyclohexane is **chiral**.

(b) Some molecules due to intramolecular hydrogen bond stabilization exist in **boat form** rather than chair form.

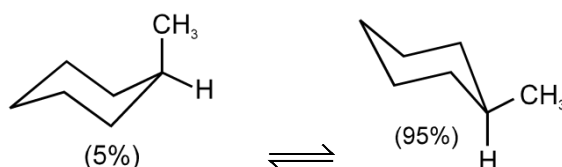


Ex.

1,2,2,6,6-Pentamethyl-4-hydroxyl-4-phenyl piperidine

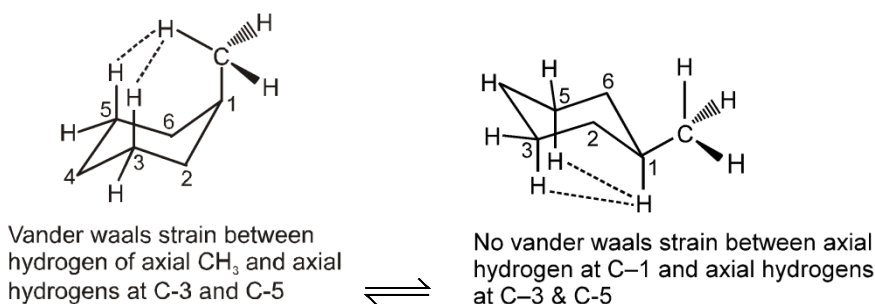
### Conformational analysis of monosubstituted cyclohexanes :

In ring inversion in methylcyclohexane the two chair conformations are not equivalent. In one chair the methyl group is axial; in the other it is equatorial. At room temperature 95% of the methylcyclohexane exist in **equatorial** methyl group whereas only 5% of the molecule have an **axial** methyl group.

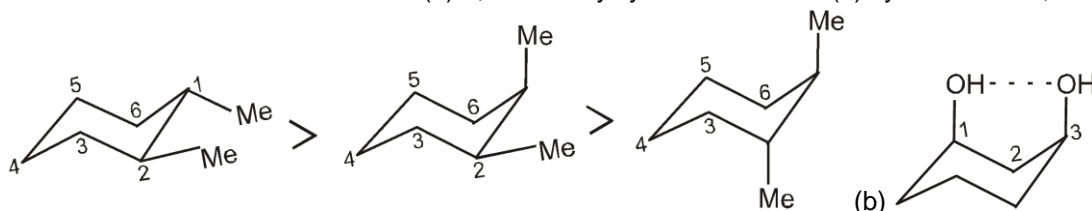


### 1, 3-diaxial repulsion :

A methyl group is less crowded when it is equatorial than when it is axial. The distance between the axial methyl groups at C-1 and two hydrogens at C-3 & C-5 is less than the sum of their vander waal radii which causes vander waal strain in the axial conformation. This type of crowding is called 1, 3-diaxial repulsions. When the methyl group is equatorial, it experience no significant crowding.

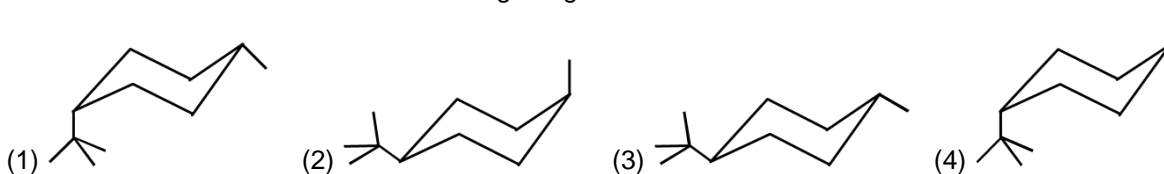


**Que.** Draw the most stable conformation of (a) 1, 2-dimethylcyclohexane. (b) cyclohexane-1, 3-diol



**Ans.** (a)

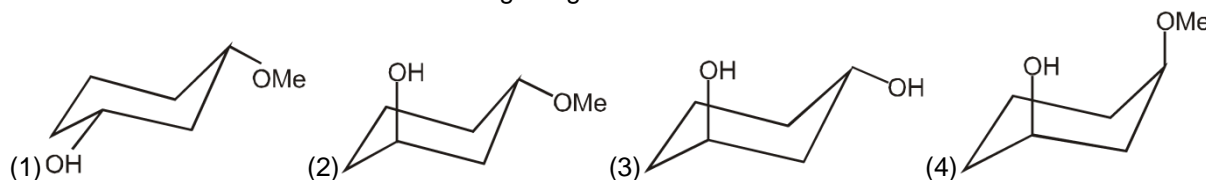
**Que.** Which is the most stable conformer among the given conformers ?



**Sol.** Conformer (3) is most stable.



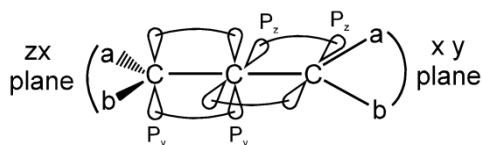
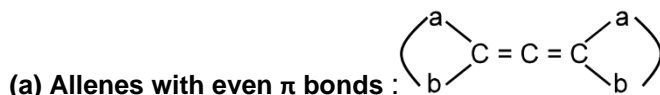
**Que.** Which is the most stable conformer among the given conformers ?



**Sol.** Conformer (4) is most stable due to hydrogen bonding.

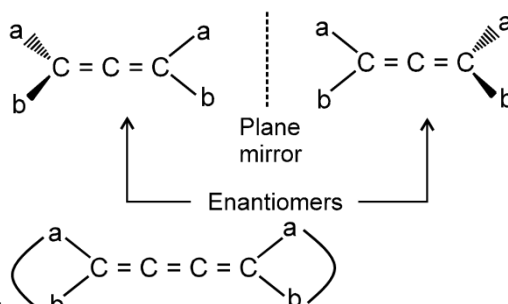
#### 4. Optical activity without asymmetric carbon

##### (I) Case of allene :

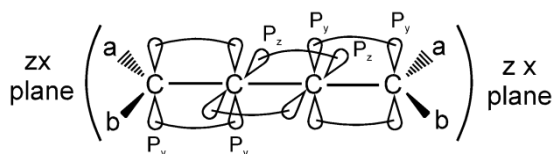


the orbital diagram of this structure will be

Since the groups at the end of allene are in perpendicular plane, it will not show geometrical isomerism. The molecule lacks centre of symmetry as well as plane of symmetry. Overall the structure has molecular dissymmetry which is the sufficient condition for optical activity. The molecule will exist in two enantiomeric forms.

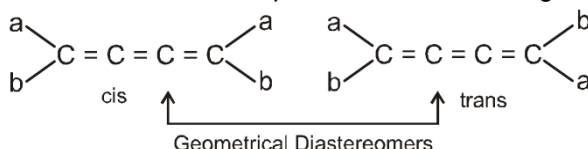


##### (b) Allenes with odd $\pi$ bonds :



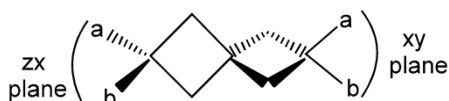
the orbital diagram of this structure will be

The groups at the end of allene structure lie in same plane (ZX plane). Therefore it will have a plane of symmetry (ZX plane). The molecules lacks molecular dissymmetry & it will not show optical activity and optical isomerism. But the compound will exist in two geometrical diastereomeric forms.




##### (II) Case of spiranes :

A similar case like allenes is observed in spiranes. The spiranes with even rings and different groups at terminal carbons show optical activity & optical isomerism, while the spiranes with odd rings shows geometrical isomerism.

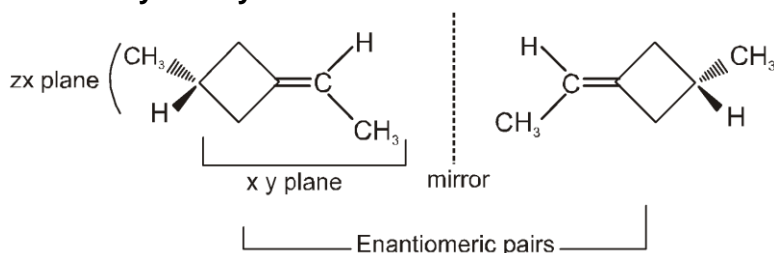


(a) spiranes with even rings :

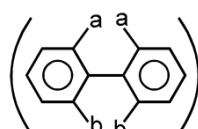
shows optical isomerism

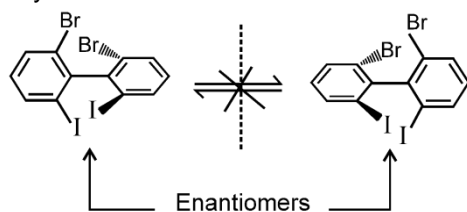
(b) Spiranes with odd rings :  shows geometrical isomerism.

(III) Case of cycloalkylidene :



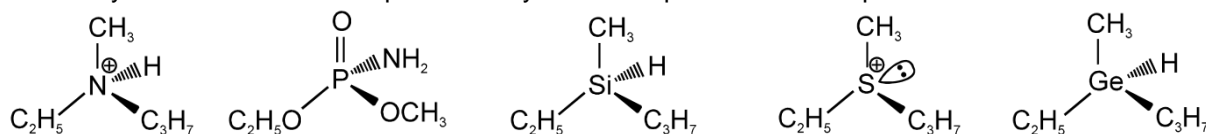
(IV) Case of ortho-ortho-tetrasubstituted biphenyls :

 becomes non-planar at room temperature in order to have minimum electronic repulsion among the substituents. In this orientation (phenyl planes perpendicular to each other) the free rotation of C – C single bond is restricted and molecule shows optical activity due to molecular dissymmetry.



Compounds having chiral centres other than carbon :

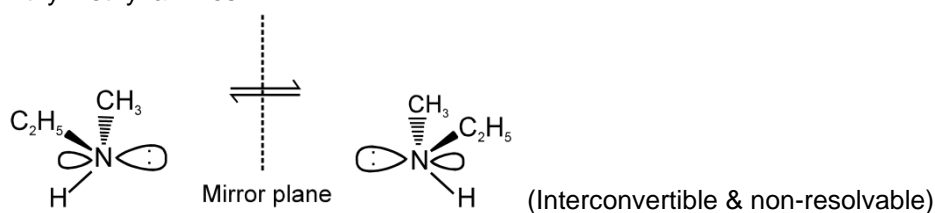
The tetrahedral atom with four different groups attached to it is a stereocentre (chiral centre). Thus when atom like nitrogen, phosphorous, sulphur, silicon, germanium has four different groups attached with them they are chiral and show optical activity & hence optical isomerism possible.



Asymmetric nitrogen : Amine inversion

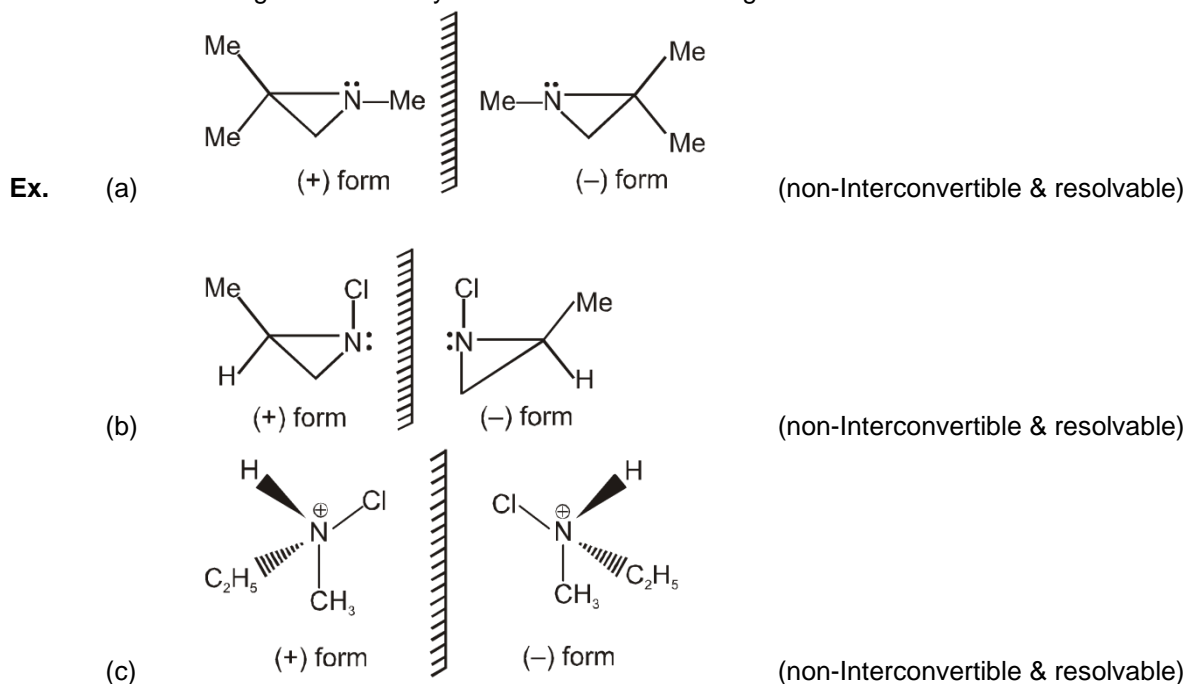
Amine with all different groups attached to N-atom have chiral centre ( $R_1R_2R_3N$ ) as nitrogen atom. Since the geometry of the molecule is tetrahedral it has molecular dissymmetry. It will exist as two enantiomers but the two enantiomers of amines cannot be separated because they rapidly interconvert into each other. Therefore they always exist as racemic mixture hence optically inactive.

Ex. Ethylmethyl amines  $CH_3\dot{N}HC_2H_5$  .



Interconvertible enantiomers are also known as **invertomers** (non resolvable)

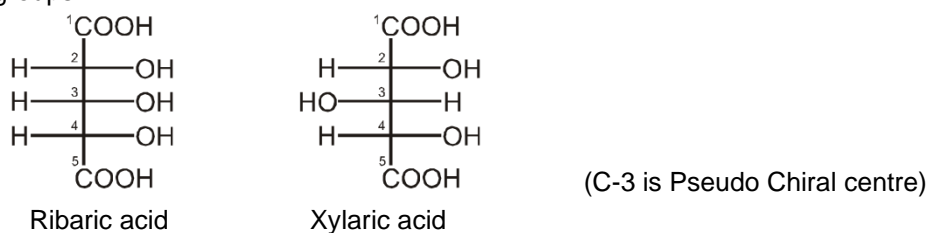
**Note :-** Nitrogen salts and cyclic amines will not undergo amine inversion.



## Section (M) : Calculation of stereoisomers

**D-16 Stereocentre:** Stereocentre is defined as an atom or bond bearing groups of such nature that an interchange of any two group will produce a stereoisomer.

**Note :** **Pseudo Chiral centre** is an atom which is attached to two constitutionally like chiral groups and two other distinct atoms/ groups.



### Number of Stereoisomers :

Number of Stereoisomers (either geometrical or optical or both) can be found by calculating the number of **stereocentres** in the compound.

Nature of compound	No. of Stereoisomers (n=no. of stereocentres)
(I) Compound with dissimilar ends	$2^n$
(II) Compound with similar ends and even stereocentres	$2^{n-1} + 2^{\frac{n}{2}-1}$
(III) Compound with similar ends and odd stereocentres	
(a) If only Geometrical stereocenters are present in the molecule	$2^{n-1} + 2^{\frac{n-1}{2}}$
(b) If only optical stereocenters are present in the molecule	$2^{n-1}$ only

**Note :- (i) Compounds having similar ends with even chiral centres then :**

Enantiomers =  $2^{n-1}$  & meso compounds =  $2^{\frac{n}{2}-1}$ .

(ii) Compounds having similar ends with odd chiral centres then :

Enantiomers =  $2^{n-1} - 2^{\frac{n-1}{2}}$  & meso compounds =  $2^{\frac{n-1}{2}}$ .

Ex. (a)  $\text{CH}_3\text{--CH=CH--CH=CH--C}_2\text{H}_5$  (molecule with dissimilar ends) .

Here  $n = 2$  , So Number of G.I = 4 [ (cis, cis), (trans, trans), (cis, trans), (trans, cis) ]

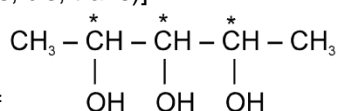
(b)  $\text{CH}_3\text{--CH=CH--CH=CH--CH}_3$  (molecule with similar ends)

Here  $n = 2$  , So Number of G.I = 3, [ (cis, cis), (trans, trans), (cis, trans), (trans, cis) ]

(c)  $\text{CH}_3\text{--CH=CH--CH=CH--CH=CH--CH}_3$  (molecule with similar ends)

Here  $n = 3$ , So Number of G.I = 6

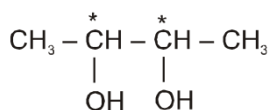
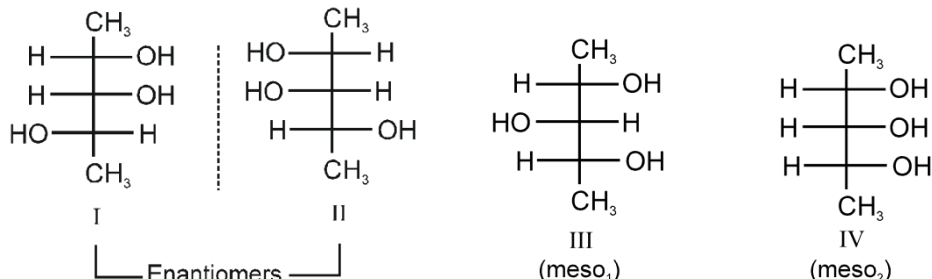
[(cis, cis, trans) = (trans, cis, cis), (cis, trans, trans) = (trans, trans, trans), (cis, cis, cis), (trans, trans, trans), (cis, trans, cis), (trans, cis, trans)]



(d) Let us draw the total stereoisomers of

Sol.  $n = 3$  (odd chiral centres with similar ends.) so,

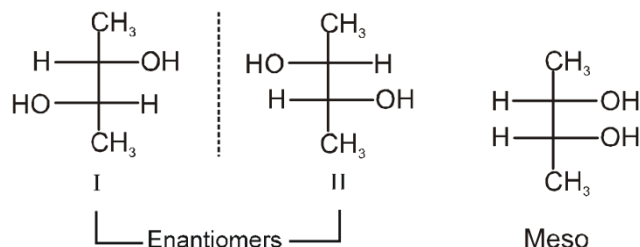
Total stereoisomers =  $2^{3-1} = 2^2 = 4$  (enantiomers =  $2^{n-1} - 2^{\frac{n-1}{2}}$  & meso compounds =  $2^{\frac{n-1}{2}}$  )



(e) Let us draw the total stereoisomers of

Sol.  $n = 2$  (even chiral centres with similar ends.)

so, Total isomers =  $2^{n-1} + 2^{\frac{n}{2}-1}$  (enantiomers =  $2^{n-1}$  & meso compounds =  $2^{\frac{n}{2}-1}$  )



(f) Let us draw the total stereoisomers of  $\text{CH}_3\text{--CH(OH)--CH}_2\text{--CH=CH--Cl}$

Sol. Total stereocentres ( $n$ ) = 1 + 1 = 2 (Molecule with dissimilar ends)

So, total stereoisomers =  $2^2 = 4$  [(R, cis) ; (R, trans) ; (S, cis) ; (S, trans)]

Note : If the starting materials of a reaction are achiral and the products are chiral, then they will be formed as a racemic mixture of two enantiomers.