



PHARMA

CHAPTERWISE NOTES

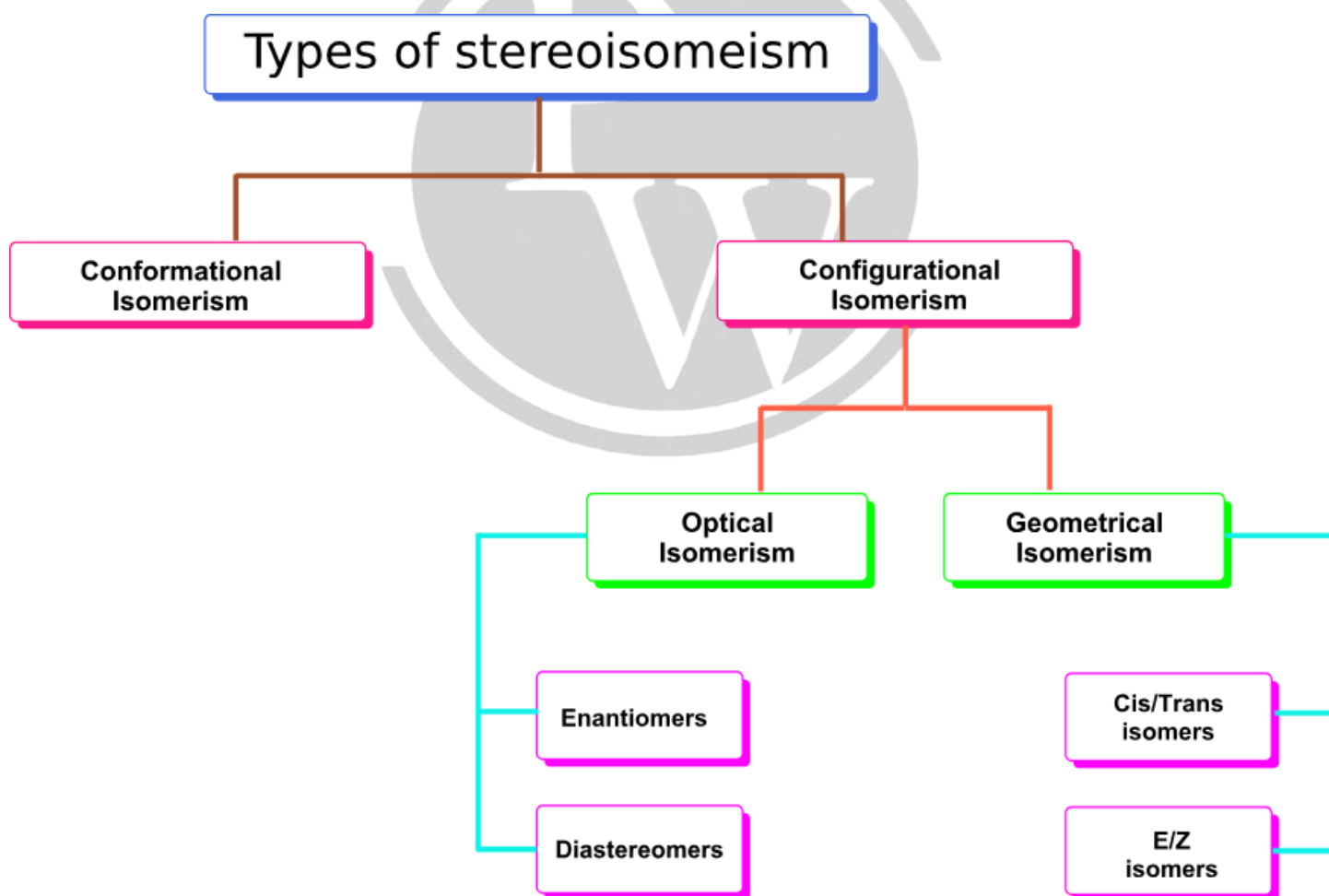
Organic Chemistry

Stereoisomerism

STEREISOMERISM

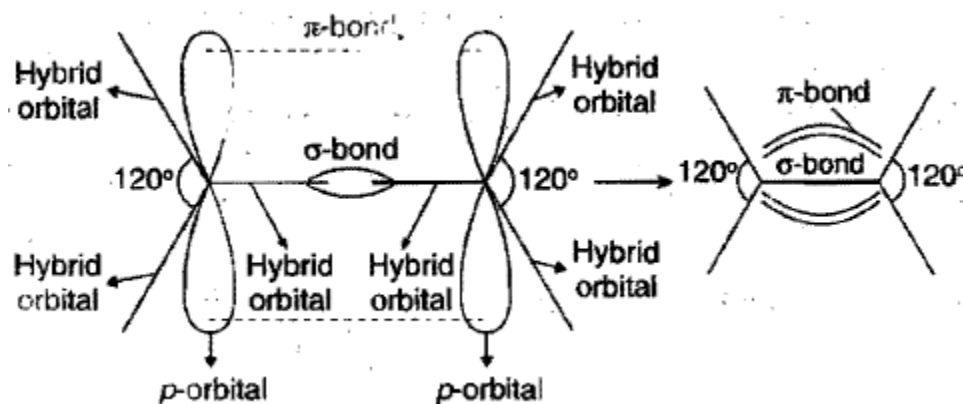
- *It is due to the difference in the relative arrangement of atoms or groups in space.*
- Stereoisomers are compounds having the same molecular and structural formulas but different spatial arrangements of atoms or groups.
- The spatial arrangement of atoms or groups is also referred to as the configuration of the molecule.

TYPES OF STEREISOMERISM



GEOMETRICAL ISOMERISM

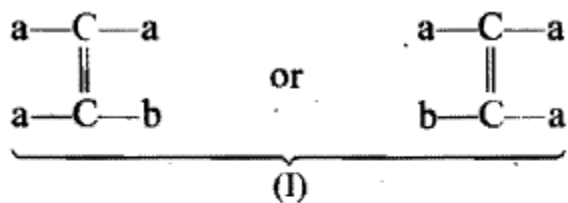
- ❖ *Rotation around the π -bond is not possible.*
- ❖ If any attempt is made to rotate one of the carbon atoms, the lobes of p-orbitals will no longer remain coplanar, i.e., no parallel overlap will be possible and thus, the π -bond will break and it requires the energy of the order of 251 kJ. This is known as **concept of restricted rotation**
- ❖ In other words, the presence of a π -bond makes the position of two carbon atoms rigid, i.e., fixed with respect to each other.



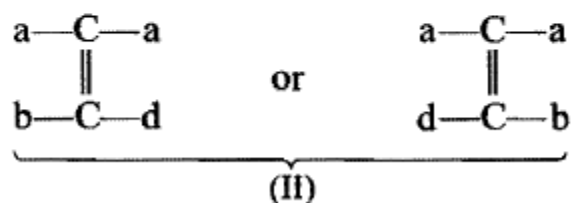
formation of double bond

Note: So, in general, the geometrical isomerism is shown by alkenes or their derivatives in which two different atoms or groups are attached to each carbon containing a double bond and carbon atoms joined by a double bond cannot rotate freely.

1st Case: When two groups attached to a carbon atom are the same, geometrical figures in (I) and (II) will be identical; hence, no geometrical isomers are possible.

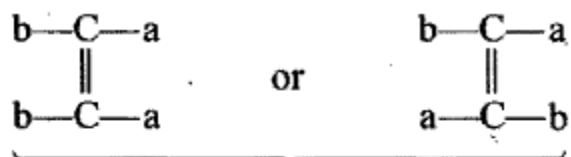


Both the structures are identical

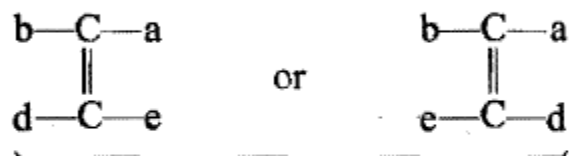


Both the structures are identical

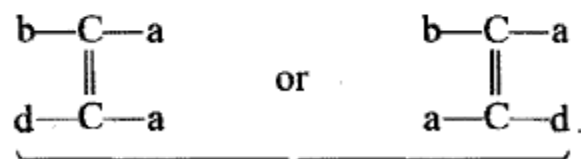
2nd Case: When two groups attached to 3 carbon atom are different, the two geometrical figures [as shown in (III), (IV), and (V)] will be different, and hence, geometrical isomers are possible



(III)
Non-identical



(IV)
Non-identical

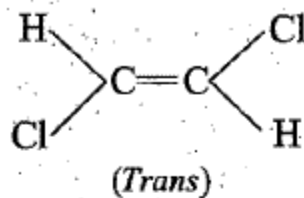
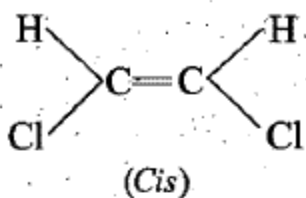


(V)
Non-identical

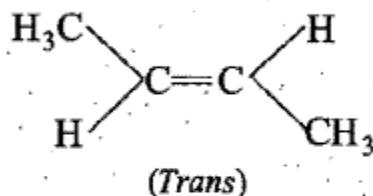
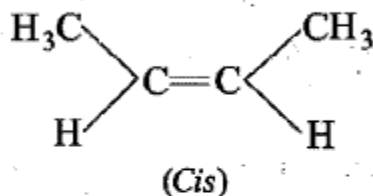
The isomer that has similar groups on the same side of the double-bonded carbon is called a 'cis' isomer (Latin: cis = same side), and the isomer that has similar groups on the opposite side of the double bond is known as a 'trans' isomer (Latin: trans = across).

Examples

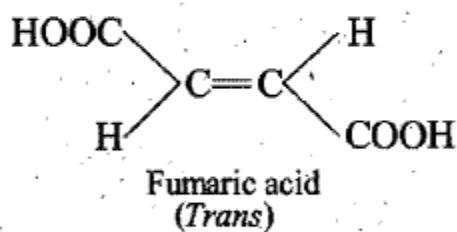
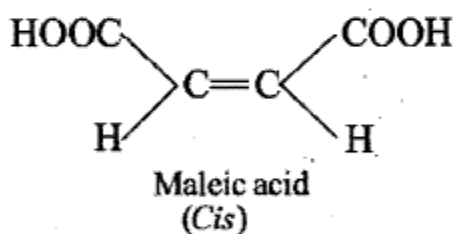
(i) 1,2-Dichloroethene



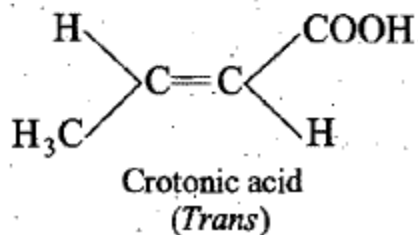
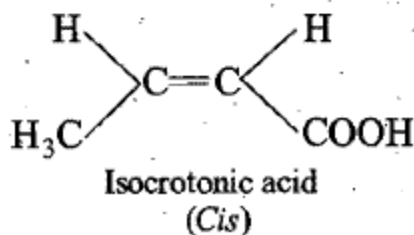
(ii) But-2-ene ($\text{CH}_3\text{CH}=\text{CHCH}_3$)



(iii) Maleic and fumaric acids

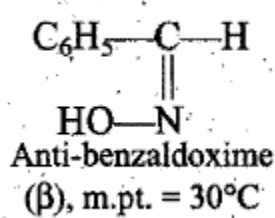
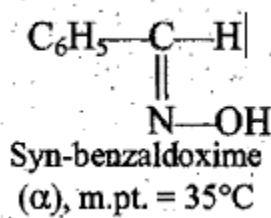


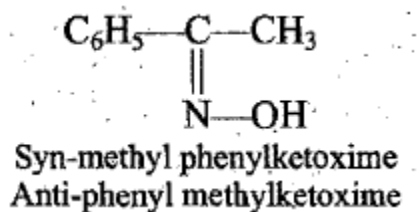
(iv) Crotonic acid and isocrotonic acid



❖ In addition to alkenes, compounds containing C-N (aldoxime and ketoxime) and N=N (azo compounds) bonds also show geometrical isomerism. However, in these cases, ~ 'syn' (for cis) and 'anti' (for trans) are more commonly used.

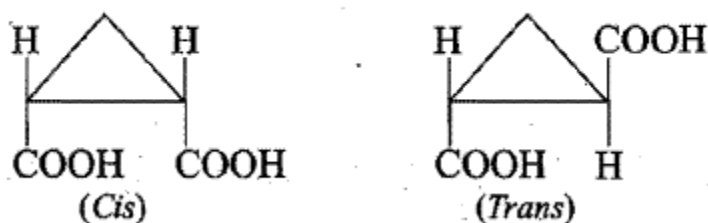
❖ In aldoximes, when -H and -OH groups are on the same side of the double bond, the isomer is known as syn' (analogous to cis) and When these groups are on opposite sides of the double bond, the isomer is known as 'anti' (analogous to trans).





- ❖ Geometrical isomerism is also exhibited by disubstituted cyclic compounds, which may have hindered rotation due to reasons other than the presence of double bonds.
- ❖ Thus, alicyclic compounds, because of their rigid ring structures, also exhibit hindered rotation and geometrical isomerism.

Examples: (i) Cyclopropane 1,2-dicarboxylic acid



E AND Z SYSTEM OF NOMENCLATURE

- 'Cis' and 'trans' designations cannot be used for highly substituted alkenes if four different atoms or groups are attached to the carbon atoms of a double bond.
- In such cases, **the E and Z system of nomenclature is used.**
- This system is based on a priority system developed by Cahn, Ingold, and Prelog.
- In this system, the two atoms or groups attached to each of the doubly bonded carbons are put in order of precedence (priority) on the basis of sequence rules.
- The symbol 'E' is assigned to an isomer in which the atoms or groups of higher precedence are on the opposite side (**E from the German word entgegen, meaning across or opposite**).
- The symbol 'Z' is assigned to an isomer in which the atoms or groups of higher precedence are on the same side (**Z from the German word ,Zusammen,; meaning :together**).

SEQUENCE RULES

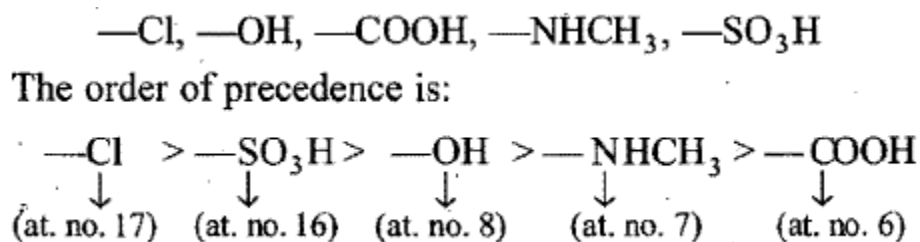
The following rules are followed for deciding the precedence order of the atoms or groups.

(1) **Higher priority is assigned to the atoms of higher atomic number.** For example, the order of precedence in the following atoms, H, Cl, I, and Br, is

I (at. no. 53) > Br (at. no. 35) > Cl (at. no. 17) > H (at. no. 1)

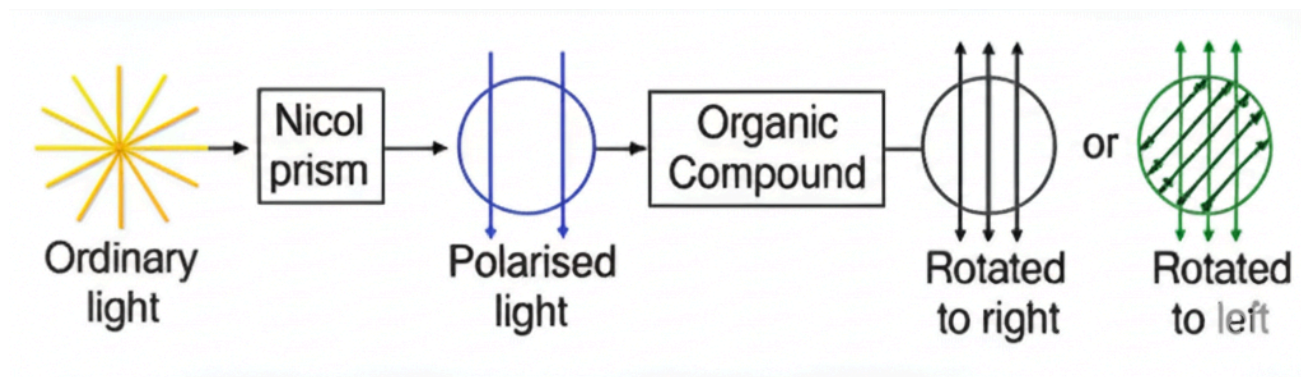
(2) If isotopes of the same element are attached, the isotope with higher mass number is given higher precedence. For example, deuterium (tD) is assigned higher priority in comparison to hydrogen (H).

(3) In the groups, the order of precedence is also decided on the basis of the atomic number of the first atom of the group. For example, in the following set,



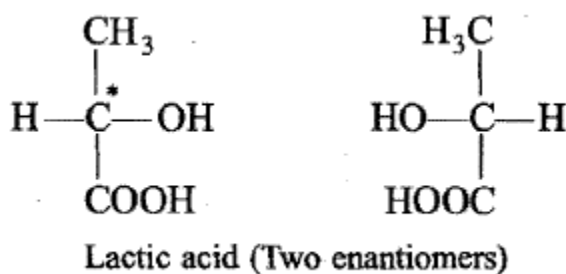
OPTICAL ISOMERISM

- ❖ Compounds having similar physical and chemical properties, differing only in their behavior towards polarized light, are called optical isomers and this phenomenon is called optical isomerism
- ❖ Majority of compounds don't rotate the plane of polarized light
- ❖ The optical activity within a compound is measured by the polarimeter
- ❖ Whenever the beam of polarized light is being passed through individual molecules, its plane gets rotated by a minute amount because of the interaction with the charged particles. Out of which, the direction and amount of rotation differ with the orientation of the specific molecule within the beam.
- ❖ Whenever the solution of the optically active material is mounted within the polarimeter, then the beam of the polarized light is being rotated clockwise [dextrorotatory] or anti-clockwise [levorotatory]



ENANTIOMERS

- ❖ *Enantiomers bears same physical properties but differs in direction of rotation of the plane of polarized light*
- ❖ These enantiomers might rotate the light to the same extent
- ❖ These enantiomers exhibit identical melting points, densities, solubilities, colors, and reactivities.
- ❖ **The molecular dissymmetry or chirality, is a necessary condition for the existence of enantiomers**

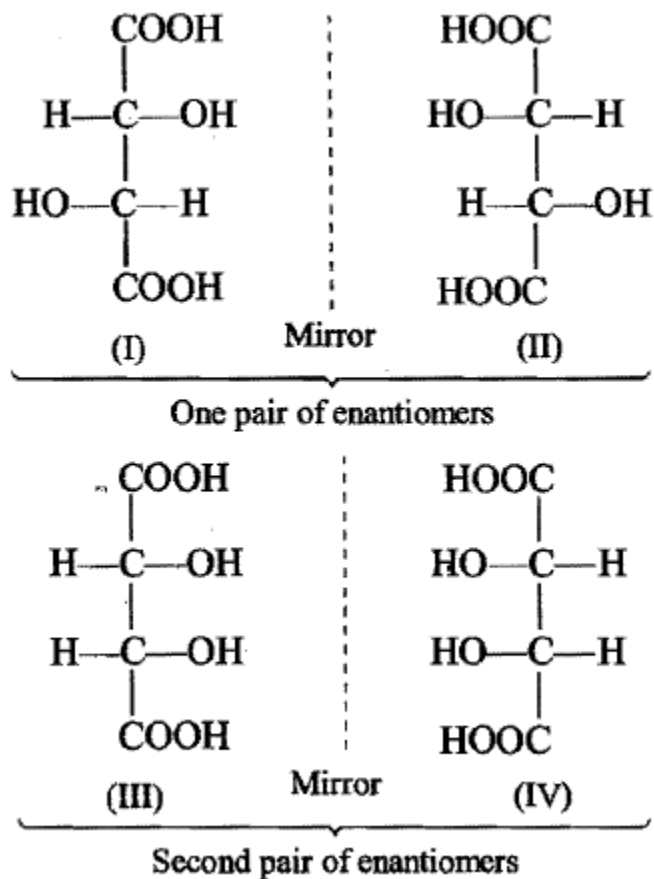


CHIRALITY CENTRE

A carbon atom that is bonded to four different atoms or groups in the molecule is called Chiral carbon or stereo centre or Stereogenic centre or an asymmetric carbon atom (Chirality centre).

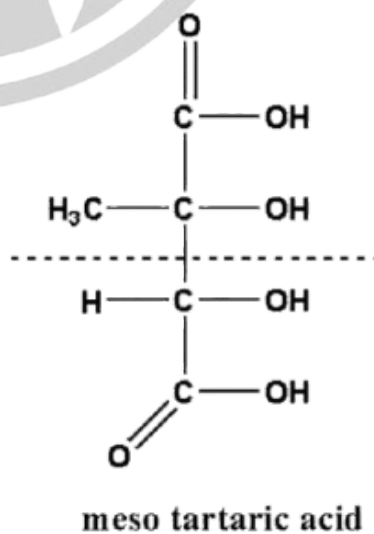
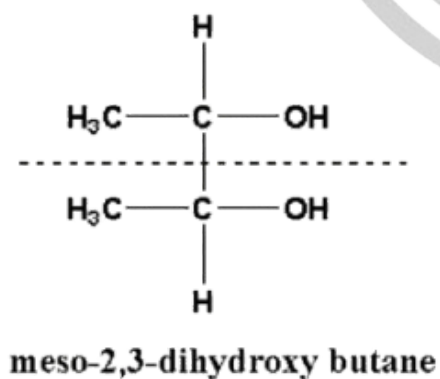
DIASTEREOMERS

A compound containing one asymmetric carbon atom exists in two stereoisomers, which are known as enantiomers and are mirror images of each other. As the number of asymmetric carbon atoms increases, the number of stereoisomers also increases. For example, a compound having two asymmetric carbon atoms can have four stereoisomers, as shown below in the case of tartaric acid:



MESO COMPOUNDS

- ★ Those compounds containing 2 or more chiral carbon atoms, followed by the plane of symmetry, are termed "meso compounds".



- ★ These molecules exhibit a plane of symmetry dividing them into 2 chiral carbon atoms, where one half is the mirror image of the other, but both these molecules are optically inactive.

- ★ In the case of tartaric acid, 2 chiral carbons are present and the number of optical isomers is 4, but the number becomes 3 since 1 molecule exhibits the plane of symmetry.

ELEMENT OF SYMMETRY

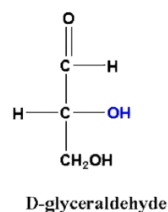
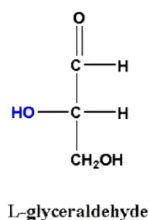
- ★ It is referred to as the point of reference around which the symmetry occurs
- ★ In specific elements, these might be mirror planes, axes of rotation, or centers of inversion.
- ★ A plane of symmetry is that plane which divides an object into symmetrical halves.

CHIRAL AND ACHIRAL MOLECULES

- The chiral molecule refers to the molecule that is non-superimposable, also known as chirality
- Those molecules that are superimposable are called achiral molecules.
- The carbon atoms linked to 4 varied groups are referred to as the asymmetric carbon.
- In stereoisomerism, isotopes of the specific atom behave as different groups.

D AND L SYSTEM OF NOMENCLATURE

- This system of convention is being employed to differentiate enantiomers of chiral monosaccharides and chiral alpha amino acids on the basis of Fischer projection in a particular orientation.
- D and L forms of the sugar rely upon the orientation of H and OH about the carbon atom adjacent to the terminal primary alcohol carbon, indicating whether the sugar belongs to the D or L series.
- The D and L notation is based upon glyceraldehyde
- When the hydroxyl group is present on the right side, then it is a D-isomer, while on the left side, it is called an L-isomer.



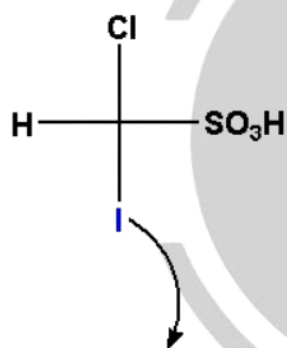
- The majority of monosaccharides occurring within the mammals are D-sugars
- The presence of the asymmetric carbon atom contributes to the optical activity
- When the plane of the polarized light is passed through the solution of an optical isomer, it will rotate clockwise or counterclockwise.
- Since the rotation does not depend upon the stereochemistry of the sugar

Note: D-tagatose is the epimer of D-fructose inverted at C-4

SEQUENCE RULES

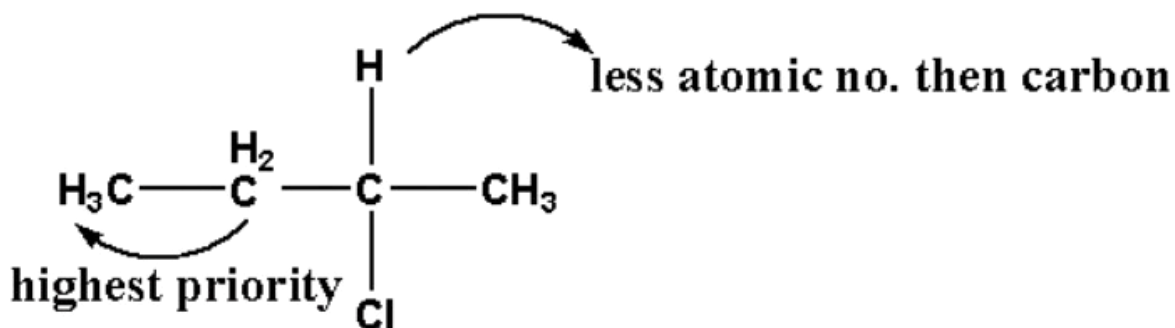
- If all 4 atoms linked to the carbon are different, then priority is given on the basis of atomic number, i.e., the atom with the greater atomic number gets priority, but if 2 atoms are the isotopes of the same element, then the atom with the greater mass number is given the priority.

Chloriodomethanesulfonic acid



- In case the relative priority of 2 groups can't be decided, then it might be determined by the comparison of next atoms present within the group, i.e., *if 2 atoms linked to the chiral center are identical, then we perform the comparison of the atoms being attached to each of first atoms*

sec-Butyl chloride



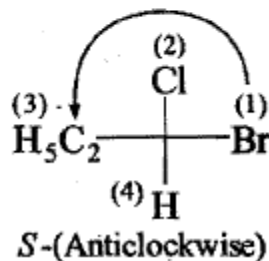
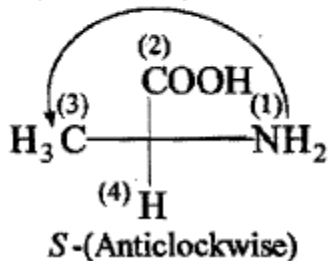
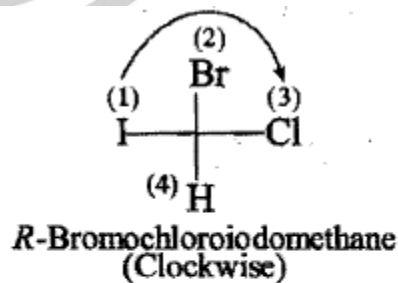
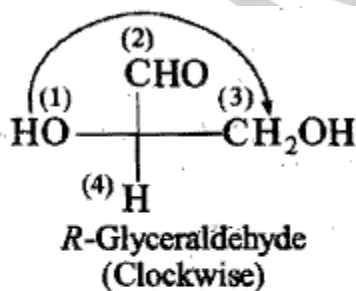
R AND S SYSTEM OF NOMENCLATURE

Assigning of R and S configurations from Fischer projections containing one chirality centre.

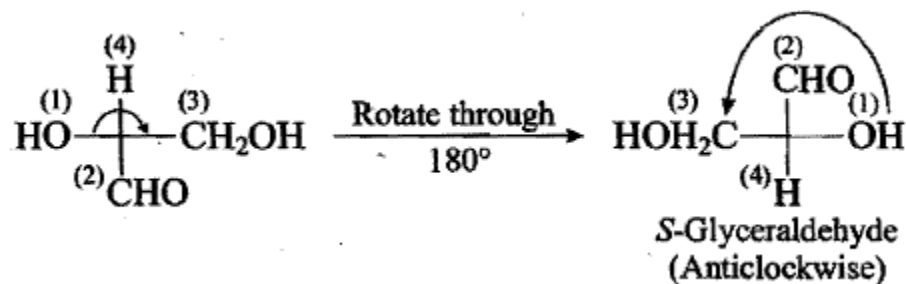
Step 1. Assign priorities to the four atoms or groups attached to chiral centre in the usual way.

Step 2. As per the priority rules, the atom (H) or group of lowest priority is to be brought vertically (upward or downward) in the Fischer projection and directed away from the viewer Nnw. determine the direction of rotation while going from 1 to 2 to 3 of remaining three groups and assign R or S configuration. This step is carried out differently in the following ways:

1. When an atom or group of lowest priority is at the bottom of the vertical line.

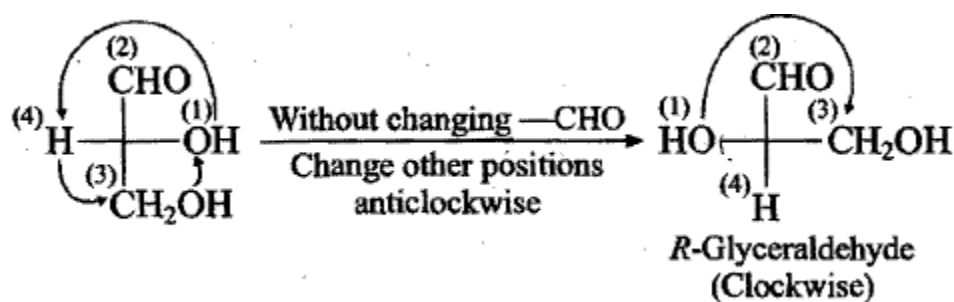


2. When an atom or group of lowest priority is at the top of the the vertical line. In such a case rotate the entire molecule through 180° so that the atoms or groups of lowest priority come at the bottom



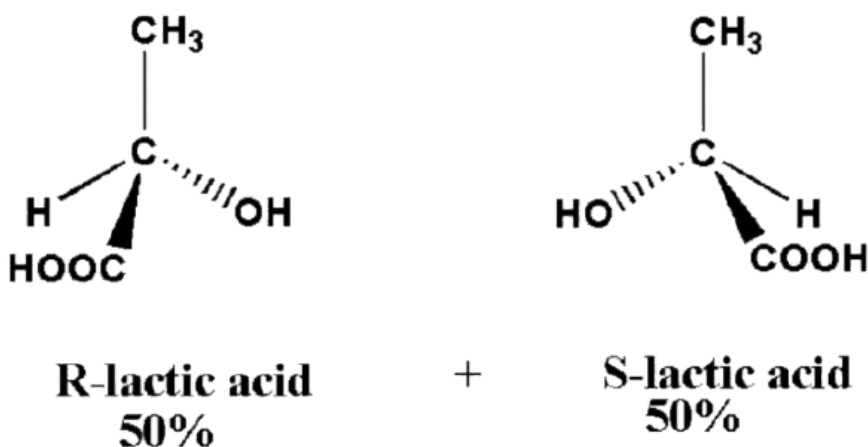
3. **When an atom or group of lowest priority appears at the left-hand side on the horizontal line.**

Then, without changing the position at the top of the vertical line, change the positions of other atoms or groups in an anticlockwise direction until the group of lowest priority comes to the bottom of the vertical line.



RACEMIC MIXTURE

- ❖ The racemic mixture refers to 1:1 mixture of 2 enantiomers
- ❖ Irrespective of the number of molecules, it is said to be racemic if an equal number of enantiomers are present.
- ❖ These induce a net optical rotation of plane-polarized light due to the presence of an equimolar mixture of both enantiomers of opposite rotations.



RESOLUTION OF RACEMIC MIXTURES

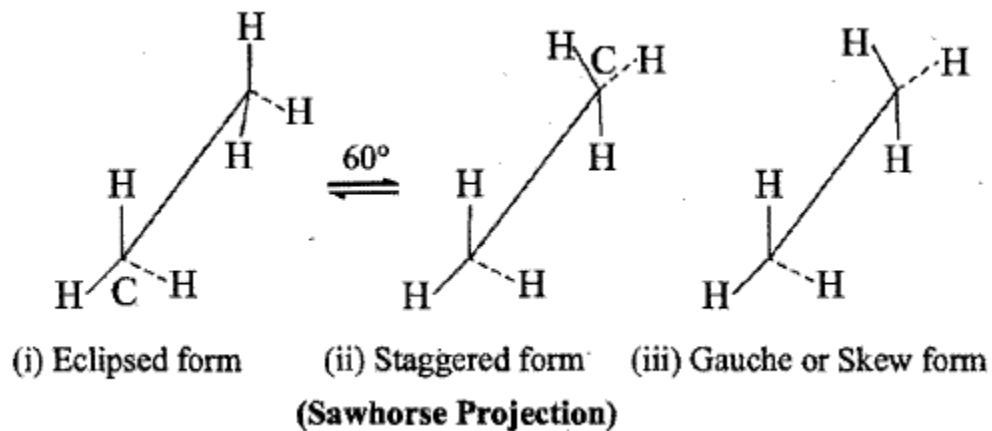
- The process of separating the racemic mixture into individual pure enantiomers is termed resolution.
- As we know that the enantiomers have same physical properties, so these can't be resolved using physical techniques, i.e., direct crystallization, distillation, or basic chromatography
- The main obstacle while separating the racemic mixture is that D or (+) L or (-) exhibits same physical and chemical properties
- So for d and l forms, methods for resolution are
 - a) **Mechanical separation:** *If the d- and l-forms of a substance exist in well-defined crystalline forms, the separation can be done by 'hand picking' with the help of a magnifying lens and a pair of tweezers. For example, the d- and l-forms of sodium ammonium tartrate can be separated by this method.*
 - b) **Biochemical separation:** *This type of separation usually employs the use of microorganisms. When bacteria is added to the solution of d or l forms, then these degrade any of the optically active forms relatively faster as compared to others.*
 - c) **Chemical separation:** *This is considered the best method of resolution. In this, the racemic mixture is combined with another optically active compound and these can be separated by fractional crystallization.*

CONFORMATIONAL ISOMERISM

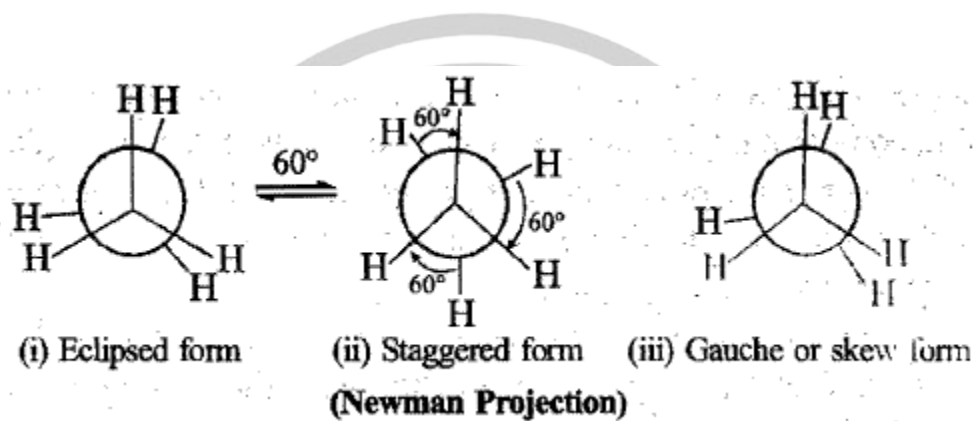
The different arrangements of atoms in space that result from the free rotation of groups about the C--C bond axis are called conformations or conformational isomers, rotational isomers, and the phenomenon is called conformational isomerism

TYPES OF REPRESENTATION OF CONFORMATIONS

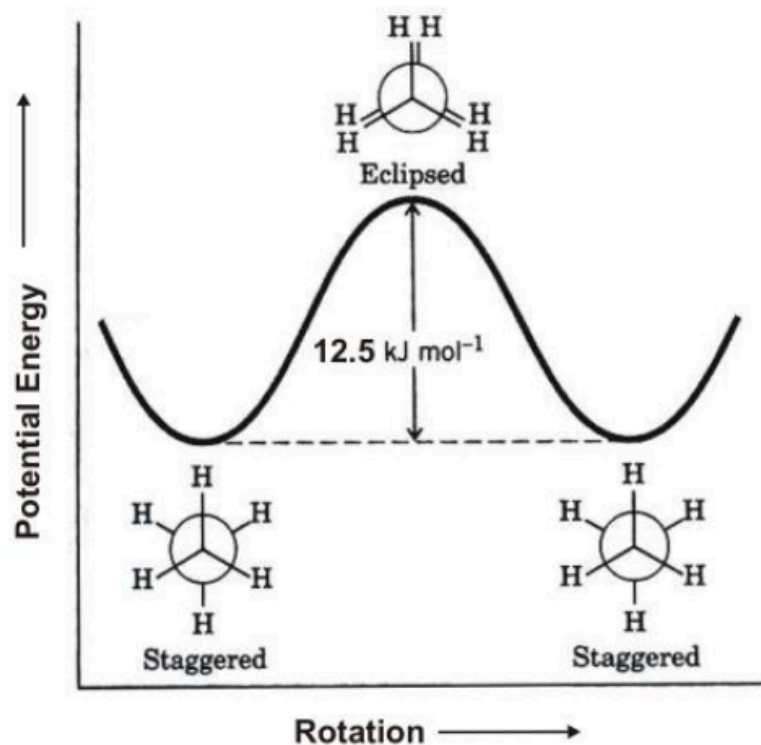
1. Sawhorse Conformations



2. Newman Projections



POTENTIAL ENERGY DIAGRAM



CONFORMATIONS OF BUTANE

