Organic Chemistry

Stereochemistry of Organic Compounds

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Stereochemistry is the chemistry which deals with the different arrangement of atoms or groups in a molecule in space. Stereochemistry plays a very vital role in our day to day life. It has been observed that many living systems, plants and many pharmaceuticals possess or respond to only a particular type of arrangement in a molecule and are found to be stereospecific in nature, for example the double helical form of D.N.A turns in a right handed way, honey suckle winds as a left handed helix. Only one form of sugar plays a unique role in animal metabolism and is the basis of a multimillion dollar fermentation industry. Similarly, only one isomeric form of chloromycetin acts as an antibiotic. Among amino acids, it has been found that only one form of asparagine and one leucine are sweet, and only one of the glutamc acids enhances the flavour of food. Thus stereochemistry and stereospecificity becomes a very important part of our life.

Different arrangements of atoms or groups in a molecule give rise to different forms of the molecule termed as isomers. Molecules which have the same molecular formula but due to difference in their structure or arrangement of atoms or groups in space differ in their properties, physical or chemical, are called isomers. Molecules can exhibit two different types of isomerism:
(1) Structural Isomerism (2) Stereoisomerism

Structural Isomers
Structural Isomers are isomers which have the same molecular formula but differ in their structures. Following is the list of different types of structural isomers:
(a) Position Isomers:
Position Isomers are isomers which show difference in the point of attachment of the functional group to the main carbon chain, for example 1-butanol, $CH_3CH_2CH_2CH_2OH$ and 2-butanol, $CH_3CH(OH)CH_2CH_3$

(***b) Chain Isomers***
Chain Isomers differ in the structure of their chain for example n-butane, $CH_3CH_2CH_2\ CH_3$ and isobutane, $CH_3CH(CH_3)_2$.

(c) Metamerism
Metamers are isomers specially found in the class of ethers. Metamers have different alkyl groups attached on the either side of oxygen in the ether molecule for example methylpropyl ether, $CH_3OCH_2CH_2CH_3$ and diethyl ether, $CH_3CH_2OCH_2CH_3$

(d) Functional Isomers
Functional Isomers are isomers that differ in the functional groups attached to the main carbon chain for example ethylalcohol, CH_3CH_2OH and dimethyl ether, CH_3OCH_3.

Structural isomers show a difference in their physical properties like melting points, boiling points etc. and also in some cases, like functional isomers, show difference in the chemical properties.

Stereoisomers
Stereoisomers are isomers which have the same molecular formula and same structure but differ in the arrangement of atoms or groups in space. Stereoisomers can be classified into the following two types:
Conformational Isomers
Configurational Isomers

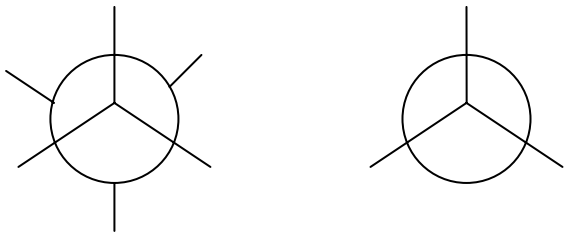
Conformational Isomers

Conformational Isomers are isomers that show different spatial arrangement around a single bond, for exa mple, the ethane molecule is known to exist in a large number of different forms of spatial arrangement. The highest and lowest energy arrangements are known as the eclipsed and the staggered conformational forms. Newman and Sawhorse were the two scientists, who suggested methods for the diagrammatic representation of the different conformational forms. These methods helped in representing the three dimensional molecules in a simple manner.

Newman's Projection Formula

Newman's Projection Formula involves the viewing of the molecule end-on, that is along the bond joining the two carbon atoms. The two carbon atoms joined by the bond are represented as two superimposed circles; however for representation only one circle is drawn. The centre of the circle represents the front carbon atom C_1 whilst the circumference represents the second carbon atom C_2. The line joining the two carbon atoms is not visible. Bonds attached to the C_1 carbon atom i.e. the front carbon atom, are drawn as straight lines from the centre and the bonds attached to C_2, the second carbon atom are drawn as straight lines from the circumference of the circle. The projected angle between each bond is kept as 120^o.

The two forms of the ethane molecule, with the help of Newman's Projection Formula, can be drawn as below in Fig. 1.



Staggered Eclipsed

Fig.1. Ethane

The eclipsed form can be converted into the staggered form and vice versa by rotating the bonds attached to one of the carbon atoms by a 60^o angle. The bonds attached to the second carbon atoms are kept stationary.

In the staggered form, all the bonds attached to the C_1 and C_2 carbon atoms are maximum apart from each other whereas in the eclipsed form, the bonds attached to the two carbon atoms are closest to each other.

Energetically, out of the two forms, the staggered form is the more favored form. In the staggered form, all the bonds are maximally apart from each other, and it therefore has the least amount of stearic strain due to vander Waal repulsion. It also has the minimum repulsion between bond electrons. On the other hand, the bonds are closest to each other in the eclipsed form and it has the highest energy. The strain existing in the eclipsed form is termed as torsional strain. The energy barrier between the two forms in the ethane molecule has been experimentally found to be about 3 kcal/mol. The energy profile for the different conformational forms of ethane can be given as in Fig. 2.

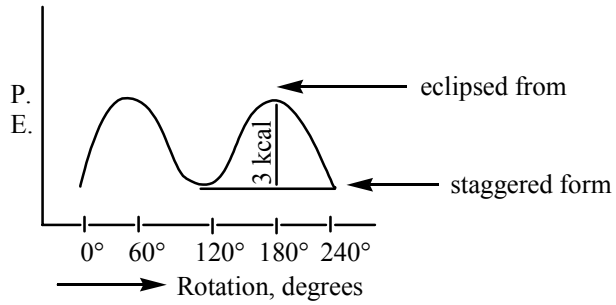


Fig. 2. Energy profile of ethane

Since the energy barrier between the staggered form and the eclipsed form in ethane molecule is very low, just 3 kcal/mol, the conversion of one form to the other form can occur readily. However, at any time most of the molecules of ethane exist in staggered form. The small energy barrier between them makes the isolation of the different conformational forms difficult. The conformational forms lying at the lower energy position in the energy profile graph are termed as conformers.

Conformations around any two adjacent carbon atoms in any molecule can be drawn in a similar manner. Different conformational forms available in a butane molecule, $CH_3CH_2CH_2CH_3$, around carbon atom 2 and 3 can be represented with the help of Newman Projection Formula as shown in Fig. 3.

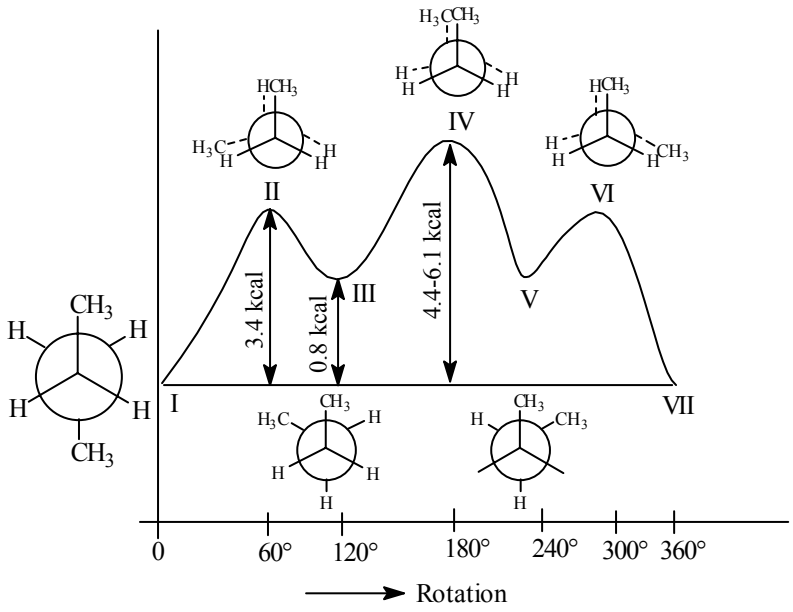


Fig. 3 Different Conformational Forms of n.butane around carbon atom 2 & 3

n-Butane shows the existence of two eclipsed conformational forms II and IV with different energies and two staggered conformational forms I and III having different energies. Staggered forms III and V are mirror image forms of each other and possess the same energy and are known as Gauche form. These are ~0.8 kcal higher in energy than the staggered form I. Eclipsed form II & VI possess the same energy. Stablest conformaton form is I with the lowest energy. Structure I and III are the more stable conformers.

However, in all the molecules, though the different conformational forms differ in their energy contents, the difference is so small that the energy available at ordinary temperature is enough for the conversion of the most stable form into the least stable form. Therefore, the different conformational forms are readily interconvertible and not isolatable.

Sawhorse Projection Formula

In Sawhorse Projection Formula a side view of the molecule is taken. The two carbon atoms are joined by a larger diagonal line which is taken to be on the plane of the paper. The remaining bonds are projected on paper by small lines drawn out from the terminal ends of the diagonal line. The heavy wedged bond projects the bond towards the viewer, the dashed bond projects the bond away form the viewer and the normal bonds lie in the plane of the page. The eclipsed and the staggered conformational form of the Ethane molecule can be represented with the help of Sawhorse Projection Formula as shown in Fig. 4.

Eclipsed Staggered

Fig.4. Conformations of Ethane

Conformational Isomers besides being found in open chain aliphatic compounds are also observed in alicyclic compounds for example in cyclohexane.

The cyclohexane ring, if planar in nature would be unstable as the bond angle around each bond in the planar structure would be 120^{o}, a bond angle value of any hexagon structure. As the bond angle is $109^{o}28'$. for an sp^3 hybridized carbon atom, any deviation from this bond angle value in cyclohexane molecule would result in the instability of the molecule. However, cyclohexane molecule has been found to be stable. Heat of combustion values experimentally determined for cyclohexane molecule has been found to be 936.9 kcal/mol which is similar to the theoretically calculated value for a cyclohexane molecule. Theoretically the heat released, per methylene group, on combustion of any open chain hydrocarbon, to give CO_2 and H_2O is approximately 156.1 kcal/mol.; as cyclohexane shows the same value of the heat released on combustion, per methylene group, the molecule is as stable as any open chain compound.

The stability of the cyclohexane molecule can be explained on the basis that the ring, in order to acquire normal tetrahedral bond angle value, does not remain planar, but gets puckered.

The bonds pucker in a manner that each angle acquires a value of $109^o28'$, that of a normal sp^3 hybridized carbon atom. Puckering results in giving the molecule four different conformational forms: the Chair, the Boat, the Twist and the Half boat form. The following Fig. 5 gives the energy profile of the different conformational forms of the cyclohexane ring.

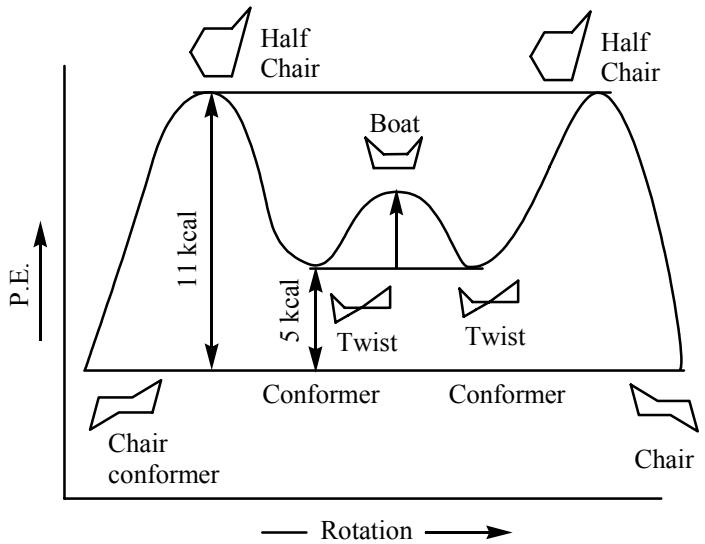
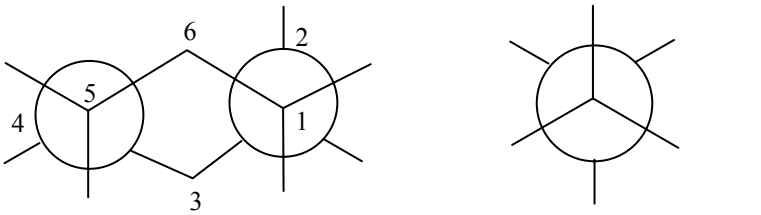


Fig. 5. Energy Graph of Conformations of Cyclohexane

The energy diagram shows that the Chair and the twist forms lie at the energy minima and are the conformers.

The chair form is the most stable form as the molecule is almost free of angle strain and has minimal amount of torsional strain. All the carbon atoms, adjacent to each other, in the chair form of the molecule are staggered with respect to each other.



Chair form of Cyclohexane Staggered form of Ethane

Fig. 6

The chair form has two types of bonds:

The Axial Bonds
The Equitorial Bonds

If the cyclohexane ring is pulled out and all the carbon atoms come to lie in a plane, the axial bonds would be bonds lying above and below the plane of the carbon ring. The axial bonds 'a' above the plane of the ring would be attached at alternate positions 1, 3 and 5 and below the plane of the ring at alternate positions 2, 4 and 6. The six remaining bonds lie in the plane of the ring and are called equatorial bonds 'e'. The chair form can be flipped. On flipping, the axial bonds get converted into equatorial bonds and equatorial to axial.

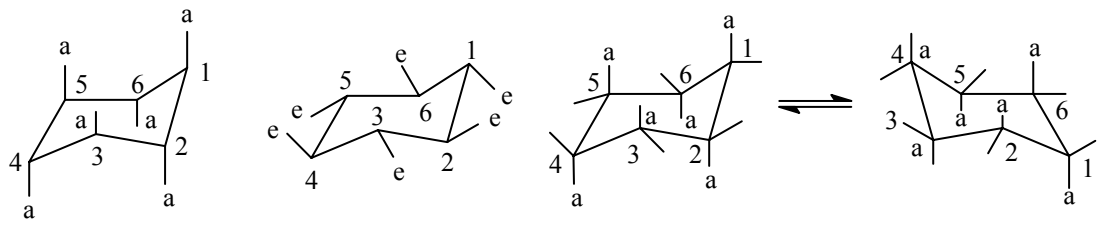


Fig. 7. Axial and Equitorial Bonds in the Chair form of Cyclohexane

The distance between any two axial bonds on the same side of the plane of the cyclohexane ring is 2.3 A^o, which is equal to the sum total of the vander Waals' radii of hydrogen atom, thus the cyclohexane ring is free of vander Waals' repulsion. However, if hydrogen at the axial position on the same side of the plane of the ring is replaced by any other group, then the molecule would become less stable, due to vander Waals' repulsion occurring between the group and the atoms existing on the other axial bonds. A substituent group present in cyclohexane is more stable in the equatorial position.

The boat form is energetically less stable because it has 2 pairs of adjacent carbon atoms 2, 3 and 5, 6 existing in the eclipsed conformational forms.

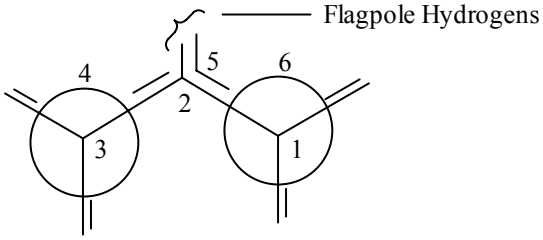


Fig 8. Boat form of Cyclohexane

Existence of the eclipsed conformational forms in the molecule, introduces torstional strain in the molecule and makes the molecule energetically less favourable. Also, the distance between the hydrogens attached to carbon atoms 2 and 5 is (180A^o) less than the sum total of the vander Waals radii of two hydrogen atoms i.e. 2.3A^o.

Twist form, the molecule is energetically closer to the chair form. The twist form is more stable than the boat form as the flag pole hydrogens are still sufficiently apart.

The half chair form is the least stable as the molecule partially acquires a planar structure and hence is subjected to a great amount of angle strain.

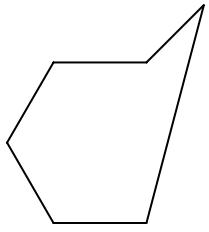


Fig. 9. Half Chair form of Cyclohexane

Configurational Isomers

Configurational Isomers like conformational isomers arise due to the difference in the spatial arrangement of atoms or groups in a molecule. However, the energy difference between

configurational isomers is large and hence one isomeric form cannot be easily converted into the other isomeric form.

Configurational Isomers can be classified into two types:
Optical Isomers
Geometrical Isomers

Optical Isomers

Compounds having the capability of forming non-superimpossible mirror images show optical isomerism. These molecules do not possess any element of symmetry, they are asymmetric as a whole and are termed as Chiral molecules. The non- superimpossible forms of the molecules are called as Enantiomers.

Compounds with one Asymmetric Carbon Atom

A compound in which the carbon atom has all four different groups attached to it is termed as a **Chiral carbon** or a **Stereogenic carbon** or an **Assymetric carbon**. A molecule having one chiral carbon atom or stereogenic carbon atom is asymmetric in nature and forms non-superimpossible mirror images and the molecule is found to be optically active for example 2-butanol, $CH_3CHOHCH_2CH_3$

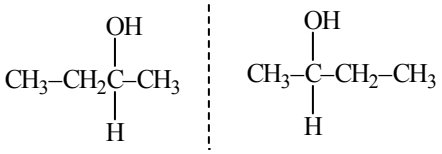


Fig. 10. Enantiomers, nonsuperimpossible Mirror Images

A compound with two similar groups attached to the carbon atom is symmetric in nature and forms superimpossible mirror images for example 2-propanol, $CH_3CHOHCH_3$

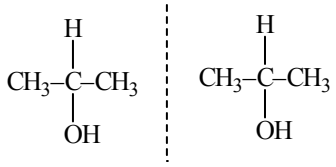


Fig. 11. Symmetric molecule, Superimpossible mirror images

The carbon atom in the symmetric molecule is termed as Chiral carbon atom.

Compounds with more than one Asymmetric Carbon Atom

Compounds can possess more than one stereogenic carbon atom. Study of such molecules shows that the compounds may or may not be optically active. Molecules show optical activity only when the molecule as a whole is asymmetric in nature and does not possess any element of symmetry. Thus the presence of a chiral carbon atom is not the only condition for a molecule to be asymmetric in nature and to show optical activity.
Tartaric acid molecule is a compound possessing two chiral carbon atoms.

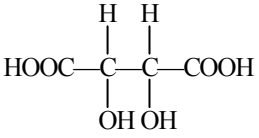


Fig. 12. Tartaric Acid

The groups and atoms attached to the two chiral carbon atoms in the tartaric acid molecule can possibly have two different types of arrangements as shown in structure I and II.

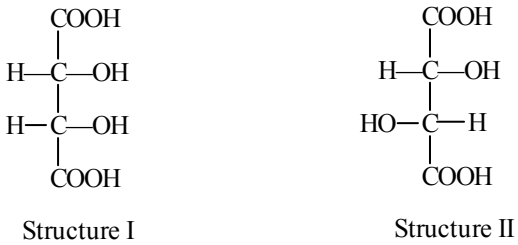


Fig. 13. Tartaric Acid

Structure I shows the presence of both the hydrogens on the same side of the molecule and both the hydroxy groups on the other side. Such a structure is called as the Erythreose type of structure. Structure II has different arrangement with the hydrogen and the hydroxy group on the same side of the molecule. Such a structure is named as the Threose type of structure.

The mirror image forms of structure I are superimposable. To check superimposability of two dimensional structures drawn in this manner you can rotate them but not lift them out of the plane of the paper. Another way is to make three dimensional models of the structure and its mirror image and see if these are identical i.e. superimposable. The molecule has a plane of symmetry structure I is optically inactive and exists in only one form. The two mirror image forms are alike. The molecule is called as an Achiral molecule and is referred to as the Meso form.

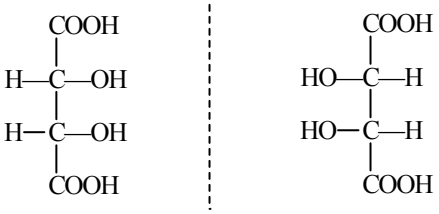


Fig. 14. Optically Inactive, Superimposable Forms

Structure II forms a non superimposable mirror image and can exist in two optically active enantiomeric forms.

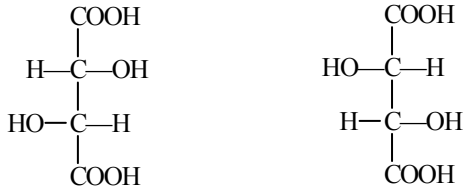


Fig. 15. Enantiomers, Nonsuperimposable optically active mirror images

Structure I is an isomer of structure II but they differ in the spatial arrangement of hydrogen and the hydroxy group and are not mirror image forms of each other. These isomeric forms are termed as **Diastereoisomers**. Molecules of the type $OHC(CHOH)_2CH_2OH$, $CH_3(CHBr)_2CH_3$ can also exist in the Threose and Erythreose type of Diastereoisomeric forms.

Compounds with no Asymmetric Carbon Atom

Allenes are compounds, having the structure as follows:

deC=C=Cab

The two π bonds attached to the centre carbon atom in the alkene are perpendicular to each other as represented in Fig. 16. The geometry of the π bonds causes the groups attached to the end carbon atoms to lie in perpendicular phanes, this makes allenes with different substitutent groups attached to the end carbon atoms form nonsuperimposable mirror images and show optical activities even though they do not have a chiral carbon.

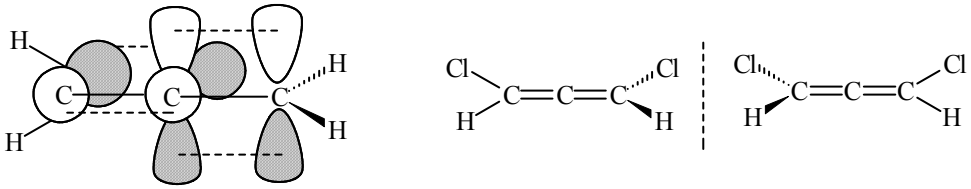


Fig. 16. Structure of Allenes

Biphenyl derivatives can also show optical activity e.g. compounds like 2,2' – dibromono-6,6'-di-iodobiphenyl can exist in two enantiomeric forms as the molecules, due to stearic strain, cannot exist in the planar structural form fig 17.

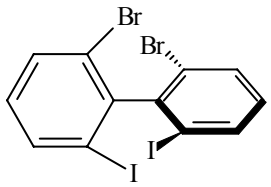


Fig. 17. 2,2' – dibromono-6,6'-di-iodobiphenyl

All compounds that are chiral in nature show optical activity and have the capability of deflecting the plane of plane polarized light whereas the achiral molecules do not show any deflection of the plane of polarized light.

Elements of Symmetry

Molecules that are achiral or stereogenic in nature form non superimposable mirror images and are asymmetric as a whole in nature and would deflect the plane of the plane polarized light. Molecules forming superimposable mirror images are symmetrical in nature and do not deflect the plane of the plane polarized light. These molecules are optically inactive. These symmetrical molecules possess any one of the following types of elements of symmetry:

Plane of Symmetry: A plane of symmetry is defined as that element of symmetry in which the molecule when divided into two equal halves gives one half as the mirror image form of the other half. Due to the presence of the mirror image forms within the molecule, the total deflection of the plane of the plane polarized light is zero. The molecule thus exhibits optical inactivity. This optical inactivity exhibited by the molecule is due to the inherent property of the molecule. Thus the molecule is said to show optical inactivity due to internal compensation. Meso form of the tartaric acid molecule shows optical inactivity due to the presence of the plane of symmetry although it has two chiral carbon atoms.

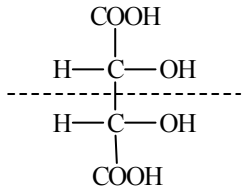


Fig. 18. Meso form of Tartaric Acid

The optically active form of tartaric acid molecule, Structure II Fig. 9, possess no element of symmetry.

Centre of Symmetry: Centre of Symmetry is the element of symmetry in which, a line, when drawn from any group of this molecule, passing through a point at the centre of the molecule, meets an identical group, when extended to an equal distance, beyond the centre point. For example trans – 1,4-Dimethyl Cyclohexane.

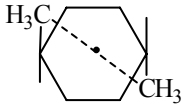


Fig. 19. 1,4-Dimethyl Cyclohexane, Centre of Symmetry

2,4 Dimethyl Cyclobutane 1,3 Dicarboxylic acid also shows optical inactivity due to the presence of the centre of symmetry.

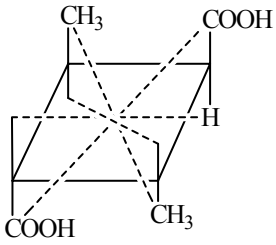


Fig. 20. 2,4 Dimethyl Cyclobutane 1,3 Dicarboxylic Acid

Axis of Symmetry: A molecule possesses an axis of symmetry if on rotating the molecule, by certain angle, around the axis passing through the centre the molecule results in an arrangement similar to the arrangement in the molecule before rotation for example 1,2,3,4 – tetramethyl cyclobutane Structure III has a four fold axis of symmetry. The rotation of the molecule by an angle of 90o about the axisXY (axis passes through the centre of the molecule and is perpendicular to the plane of the molecule) results in giving the structure IV, a mirror image of structure III.

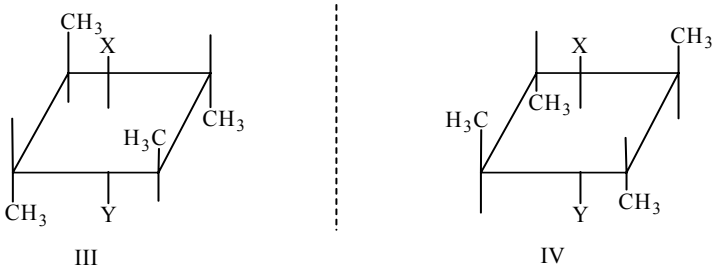


Fig. 21. Axis of symmetry – Rotation of 90^o, 1,2,3,4 –Tetramethylcyclobutane

Properties of Enantiomers

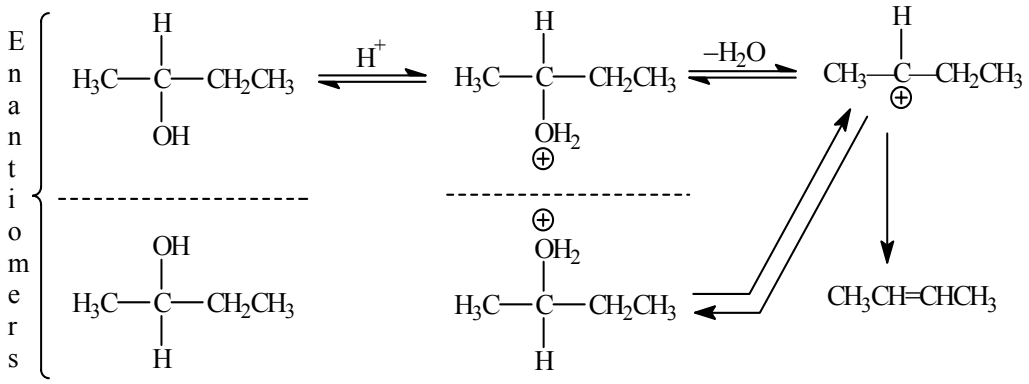
Enantionmers show similarity in most of their physical properties like melting points, boiling points, refractive index, etc. These properties are dependent on the intermolecular forces working between the molecules. The mirror image forms have the same type of intermolecular forces working between the molecules, as a result, they show similarity in their physical properties.

However, the difference in the properties of the two enantiomeric forms, show up, in two different ways.

(a) Reactivity of the Enantiomers with other optically active, chiral molecules.
(b) Deflection of the plane of the plane polarized light.

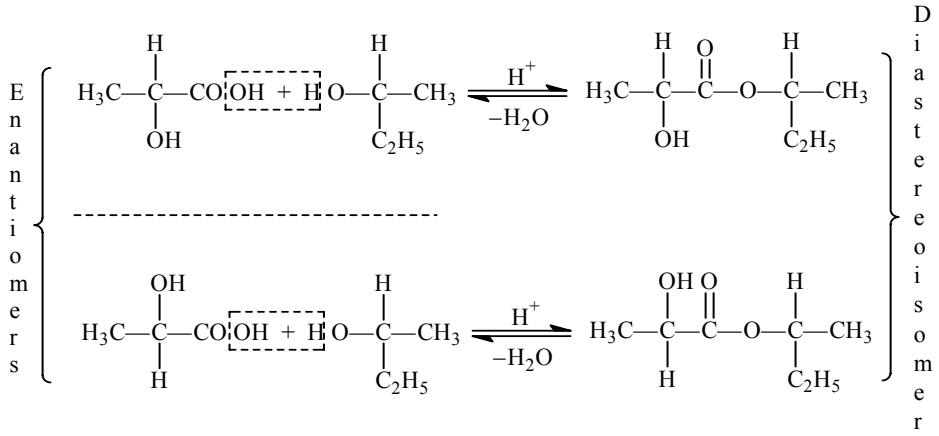
Reactivity of the Enantiomers with other optically active compound: Reactivity of the optically active, enantiomeric forms, of the molecules, with another optically active compound differs. Optically active enantiomeric forms of a molecule react with the same rate with an optically inactive compound.

The enantiomeric forms of optically active 2-Butanol when made to react with an achiral molecule like H_2SO_4 acid show no difference in the rates of their reaction. The product, from both the enantiomeric forms, will be the same 2-butene. The reaction will proceed as follows:



Attack by the proton on the two enantiomeric forms will result in the transitional state which again would be mirror image forms of each other. The energy content of the mirror image forms of the transitional states would be the same; hence the rate of reaction of H_2SO_4 with the two enantiomeric forms would also be the same.

Optically active enantiomeric forms of a molecule show difference in rate on reacting with one of the enantiomeric forms of another optically active chiral compound. The difference in the rate of reaction is observed as the two transition states and the products, obtained by the reaction of the enantiomers of the optically active reactant, are not mirror image forms of each other. Since the transitional states obtained during the course of reaction are different, the energy content possessed by the transitional states would also be different and therefore the rates of reaction would also differ. The reaction rates are so different that in some cases the reaction with one isomer does not take place at all. This can be exemplified by the following reaction.



One enantiomeric form of 2-butanol reacts with the mirror image forms of the Lactic acid molecule. The Esters obtained after the reaction with the two enantiomeric forms of the acid are not mirror images of each other. They are disastereoisomers and the energy content of the two forms would differ. The transitional state of the two diastereoisomeric forms hence would also differ in their energy content. Thus the two esters would be formed at different ratios. If only one equivalent of the alcohol is used one diasteriomeric ester would be formed in excess compared to the other ester.

*Deflection of the plane polarized light:*Enantiomers have the property of deflecting the plane of plane polarized light in equal but in opposite directions to an equal extent. If one enantiomeric form deflects it to the left the other mirror image form deflects it to an equal extent but towards the right.

Plane polarized light: Light is an electromagnetic phenomenon. A beam of light consists of two mutually perpendicular oscillating fields, an oscillating electric field and an oscillating magnetic field.

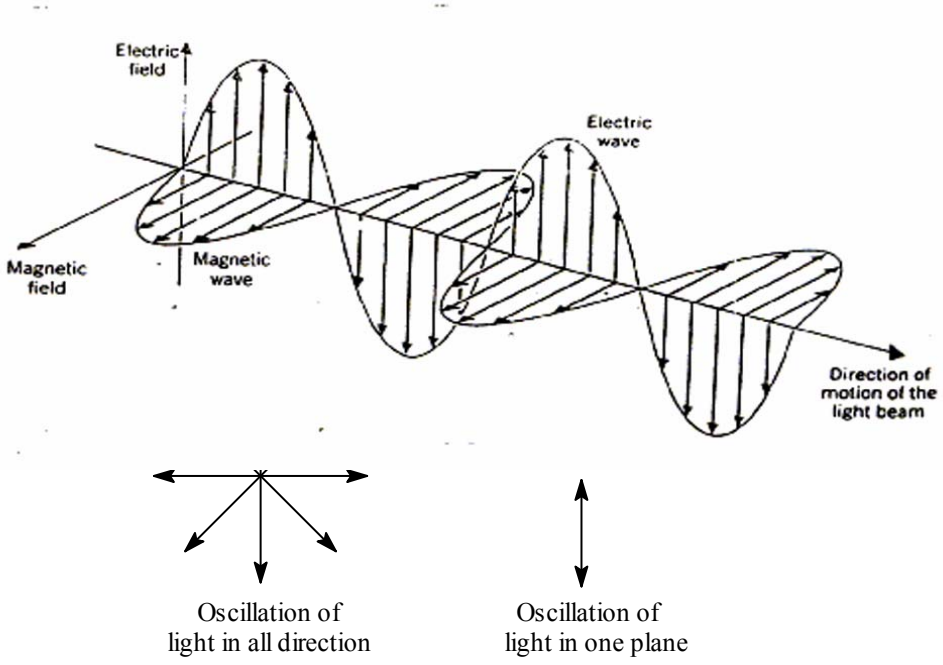


Fig. 22. Plane Polarized Light

The above diagram shows the oscillation of the electric and the magnetic field in only one plane. However the oscillation of both the electric and the magnetic field of an ordinary light can occur in all possible planes perpendicular to the direction of the propagation of light. When a beam of ordinary light is made to pass through a polarizer, the polarizer interacts in a manner that the light that emerges out oscillates in only one plane. Such a light is called plane polarized light.

Polarimeter: Polarimeter is the device used to measure the effect of an optically active compound on the plane polarized light. The principal working parts of the polarimeter are:

- A light source (usually a sodium lamp)
- A polarizer – A Nicolm Prism
- A tube for holding the optically active substance (or solution) in the light of the beam
- An analyzer – another polarizer – a Nicolm Prism.
- A scale for measuring the number of degrees that the plane of the plane polarized light has been rotated.

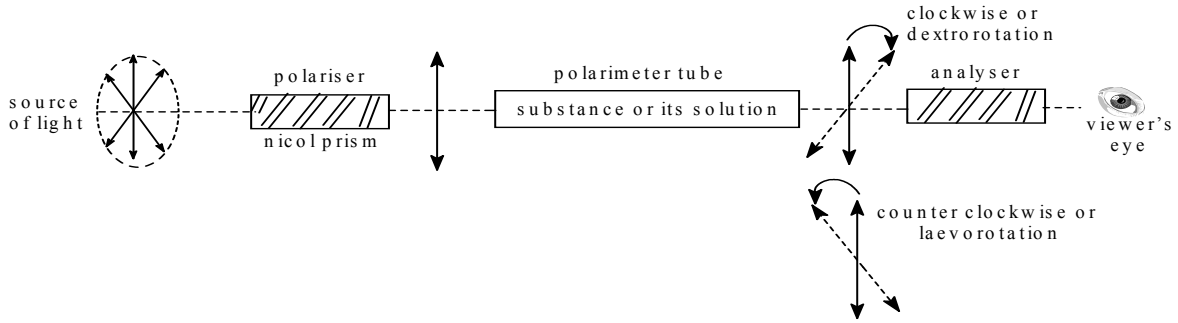


Fig. 23. Polarimeter

The study of the optical activity of the substance is done through the scale end. The light from the lamp passess first through the polarizer, then the tube, then the analyzer and finally reaches our eyes. When the light rays passing the two Nicolm prisms are vibrating in the same plane, the maximum amount of light reaches the eye. When an optically active compound is kept inside the tube the polarized light after passing through the substance gets deflected and vibrates in a different plane. Now, to receive the maximum amount of light again, the scale is adjusted and rotated. If the scale is to be rotated to the right, the plane of the plane polarized light after passing through the optically active compound has been deflected to the right. The enantiomeric form which deflects the plane of the plane polarized light to the right or clockwise direction is called as **Dextro-rotatory**. The enantiomeric form which deflects the light to the left or anticlockwise direction is called as **Leveorotatory**.

Specific Rotation: Specific rotation is the number of degrees of rotation observed if a 1-dm (10 cm) tube is used and the compound being examined is present to the extent of 1 gm/ml. The number of degrees that the plane of polarization is rotated as the light passes through a solution of an optically active compound depends on the number of chiral molecules that it encounters. Calculation of specific rotation can be done with the help of the following equation:

$$[\alpha] = \frac{\alpha}{Cl}$$

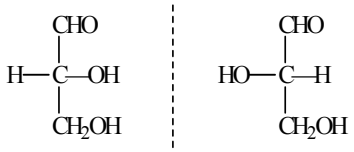
Where $[\alpha]$ = the specific rotation

α = the observed rotation
C = concentration of the solution in gram per mililitre
l = the length of the tube in decimeter (1dm = 1cm)

Specific rotation also depends on the temperature and the wave length of the light employed. Thus if D-line of a sodium lamp (λ – 589.6 m) was used for a light at a temperature 25°C then to express the specific rotation value, these values are to be indicated as $[\alpha]^{D}_{25}$.

Relative Configuration

Rosanoff (1906) was the first scientist, who tried to give names to the different optically active configurational forms of the molecule. He arbitrarily chose Glyceraldehyde for naming the enantiomeric forms. Rosanoff represented the glyceraldehyde molecule in a specific manner, following the convention set up by Fischer (1809) for the structural representation of a carbohydrate molecule. According to the convention established by Fischer, the carbon chain was represented on the vertical line drawn on a plane piece of paper. The groups attached to the carbon chain were represented on the horizontal line. The carbonyl group belonging to the carbohydrate was placed at the top of the vertical line. Glyceraldehyde molecule was considered as the first member of the carbohydrate series and Rosanoff represented the Glyceraldehyde molecule like any other carbohydrate. The two forms of the Glyceraldehyde molecule were thus represented as follows:



Structure V Structure VI

Structure V deflected the plane of the plane polarized light to the right i.e. showed dextrorotation and was assigned 'D' as the name of its configurational form; Structure VI deflected the light towards the left i.e. showed leoveorotaiton and was assigned 'L' as the name to its configurational form.

Before 1951 the configurations assigned to all chiral molecules were relative, related to each other by chemical reactions. For example the configuration of (-) Lactic acid could be related to D(+) Glyceraldehyde molecule through the following sequence of reactions. No bond attached to the chiral carbon atom breaks, at any point of time, during the sequence of reactions.

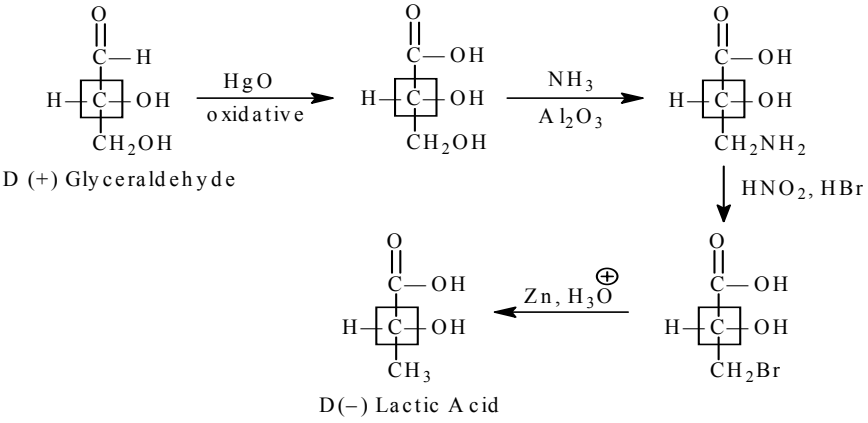


Fig. 24. Conversion of D(+) Glyceraldehydto D(-) Lactic Acid

As the above sequence of reactions does not involve any cleavage of bond at the chiral carbon atom, the configuration at the chiral carbon atom remains unchanged and hence the resultant Lactic acid can be assigned the same configuration 'D' as that of the starting Glyceraldehyde molecule. The example, however emphasizes that the molecules having the same configuration need not deflect the plane polarized light in the same direction. The starting Glyceraldehyde molecule showed dextrorotation but the resultant Lactic acid molecule was Leaveorotatory.

However, to establish the absolute configuration of a molecule Bijuot et al (1951) took the help of X Ray analysis. He chose the molecule Sodium Rubidium Tartarate for his studies. He also further confirmed and supported, the arbitrarily suggested relative configurational forms of the Glyceraldehyde molecule by Rosanoff.

Absolute Configuration

Cahn, Ingold and Prelog helped in introducing a new system for assigning the configurational form to the molecule. The system replaced the DL system. This system, adopted by IUPAC, is called the RS convention or the sequence rule system.

In the sequence rule system, the four atoms or groups directly attached to the asymmetric carbon atom, are to be ranked and to be placed in a priority order. Use of the following rules was made to decide the priority order of the groups attached to the asymmetric carbon atom.

(1) Of the four atoms directly attached to the asymmetric carbon atom, the atom with the highest atomic number was given the highest priority and the atom with the lowest atomic number the lowest priority. For example in compound like 1-chloroethanol, $CH_3CHCl(OH)$. The four atoms through which the groups attached to the asymmetric carbon atom. Since the priority order of the atomic numbers of the atoms involved are O>Cl>C>H the priority order given to the four groups would be –OH>-CL>-CH_3>-H.

(2) In case, the molecule has more than one group, having the same atom through which the groups are attached to the asymmetric carbon atom, then to decide the priority order between the groups the next atoms attached to the first atom are taken into consideration. For example in 2-butanol, $CH_3CHOHC_2H_5$, the four different groups attached are –CH_3, -C_2H_5, -OH and H. The highest priority group would be –OH and the lowest priority group would be H. As both the groups –CH_3 and –C_2H_5, are attached to the asymmetric carbon atom through carbon therefore to decide the priority between these two the next atoms attached in the groups are to be taken into consideration. In –CH_3 the next atoms are hydrogen whereas in –C_2H_5 the next atoms are one carbon and two hydrogens; therefore the priority goes to the ethyl group.

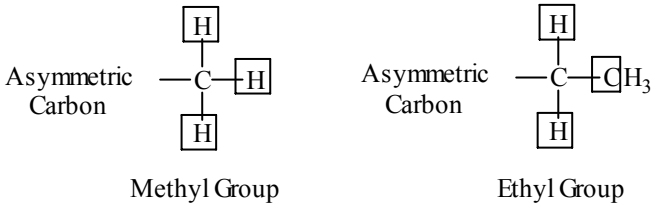


Fig. 25

If the decision cannot be based on the second atoms present attached to the group, third atoms in the group are considered for example in 3-hexanol, CH_3 CH_2CH_2 $CHOH.CH_2CH_3$ the propyl group will get priority over the ethyl group.

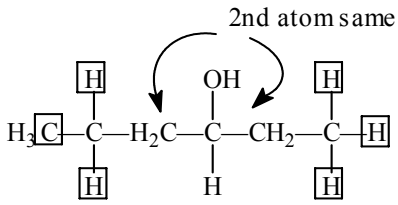


Fig. 26. 3-Hexanol

Thus in 3-Hexanol the priority order of the groups would be –OH, -C_3H_7, -C_2H_5 and H.

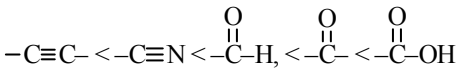
(3) In order to decide priority for groups having double or triple bonds instead of considering presence of a single double bond or a single triple bond, each bond is duplicated in case of a double bond and triplicated for a triple bond. For example, a triple bond would be considered as follows:

Fig. 27.

And a double bond would be considered as follows:

Fig. 28.

Therefore in a compound like 3-Methyl-pent-1-en-4-yne CH_2=CHCH(CH_3)C=CH the groups attached are –CH_3, -C=CH, -CH=CH_2. Hydrogen is the lowest priority group. All the other groups are attached to the chiral carbon atom through carbon, however in the acetylenic group, the second atoms attached are three carbon whereas in the ethylenic group the second atoms attached are two carbons and methyl has three hydrogens attached as second atoms. Therefore, the priority order would be –C=CH>CH=CH_2>-CH_3 and H.
According to the rule suggested above the priority order of some groups with unsaturated bonds can be arranged as follows:



(4) In case the molecule has two isotopes of the same element attached to the asymmetric carbon atom, higher priority is given to the heavier isotope. For example deuetrium would get priority over hydrogen and C^{13} would set priority over C^{12}.

To apply the sequence rule on a molecule, the molecule is viewed in a manner so that the lowest priority group is placed furthest from the eye. The rest three groups are placed facing the eye as in Fig. 29.

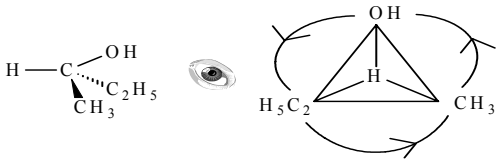


Fig. 29

To determine the priority order an arrow is drawn starting from the highest priority order group moving to the next and then to the next to complete a circle. If the arrow moves in the clockwise direction, the label given to the configuration of the molecule is 'R'; if the arrows move in the anticlockwise direction the configuration assigned to the molecule is S.

Fischers Plane Projection Diagram

Conventionally, the tetrahedral from of the molecule is represented on paper with the help of a dashed wedge line formula. The tetrahedral molecule is held in a manner that out of the four bonds, one bond projects towards the viewer, the other away from the viewer and the rest two lie on the plane of the paper. A heavy wedged bond is drawn to represent the bond towards the viewer, a dashed bond projects the bond away from the viewer and the normal bonds drawn are the bonds lying on the plane of the paper.

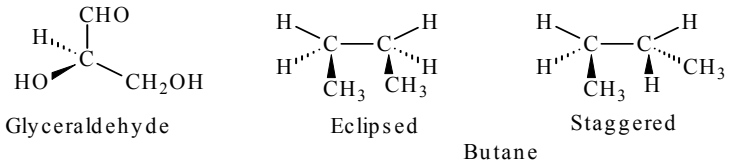


Fig. 30. Dash – Wedged Line Formula

Fischer suggested the plane projection formula to be able to represent the three dimensional structure of the molecule on a paper or a check board, a two dimensional surface in a simpler manner.

Fischer suggested the tilting of the tetrahedral form of the molecule in a manner that if the chiral carbon atom is held on a line drawn on the paper, two groups would lie above the plane of paper and the other two groups would lie below the plane of paper. Structure VIII.

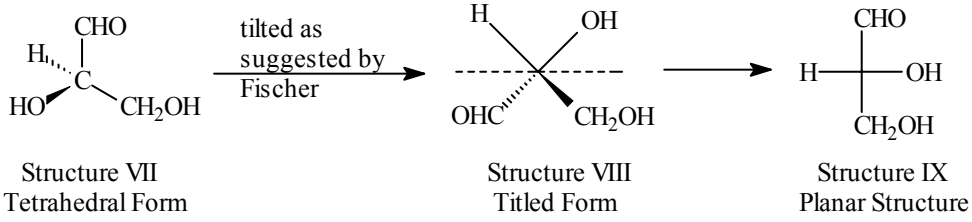


Fig. 31. Glyceraldehyde

Fischer then represented the tilted form of the molecule on a cross with the groups above the plane of paper represented on horizontal line of the cross and the groups lying below the plane of paper in the tilted form of the molecule are represented on the vertical line of the cross. Out of the two groups lying below the plane of paper the group away from the viewer is placed at the upper end of the vertical line and the group towards the viewer on the lower end of the vertical line, as in structure IX.

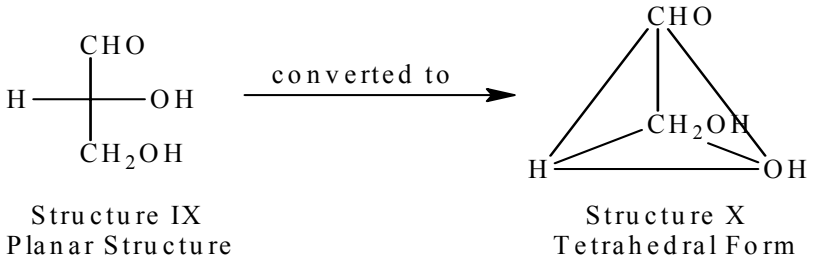
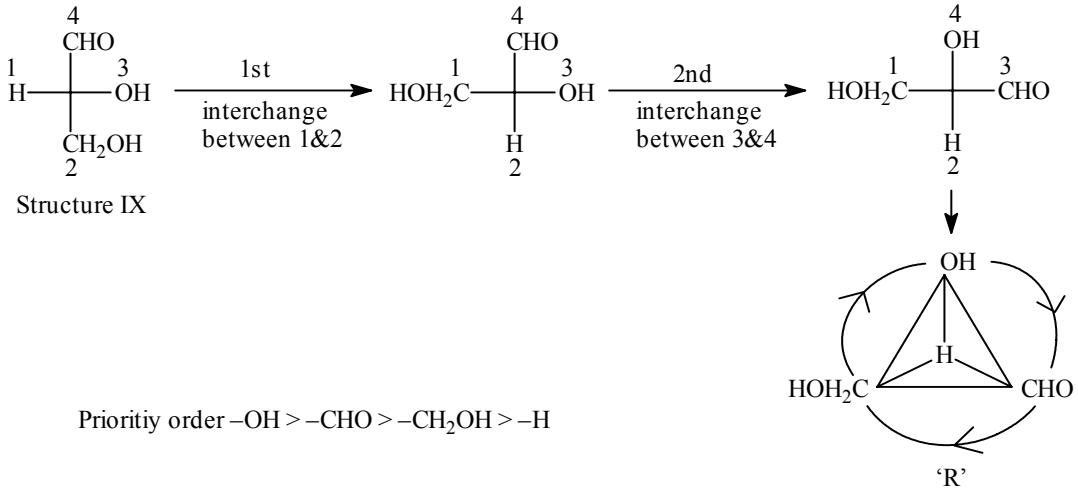


Fig. 32. Fischer's Plane Projection Diagram

Conversion of the plane projection diagram of the Glyceraldehydes molecule, structure IX, back to the tetrahedral form structure X places the $-CH_2OH$ furthest away from the eye. To work out the 'R' and 'S' configuration of the molecule, the lowest priority group should occupy position, furthest from the eye. Therefore, to get hydrogen in the position occupied by $-CH_2OH$ group interchange of the positions of the groups are required. Fischer suggested some rules to be followed whilst interchanging the position of the groups. The rules are as follows:

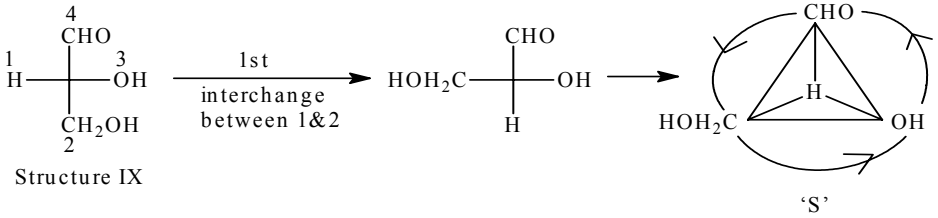
(1) One interchange of a pair of substituent group will result in the change of configuration of the molecule. One enantiomeric form would get converted to the other enantiomeric form of the molecule, if one interchange of a pair of substituent group is done.
(2) Two interchange of two pairs of substituent groups result in no change in the enantiomeric form. The configuration of the molecule is retained.

For example to work out the configurational form of the Glyceraldehydes molecule structure IX interchange has to be done such that the H occupies the position farthest from the eye i.e. it should occupy the position of the $-CH_2OH$ group. Two interchange(s) of two pairs of substituent groups would be required to retain the configuration. Interchange of groups at positions 1 and 2, and 3 and 4 would place the hydrogen in a position furthest from the eye.



Now to assign the configurational form to the molecule an arrow is to be drawn starting from the highest priority order group –OH, going to the next –CHO and then to the next i.e. $-CH_2OH$. Thus the configuration form of Glyceraldehyde molecule structure IX is 'R'.

However, if only one interchange of just a pair of substituent groups is carried out in the Glyceraldehydes molecule structure IX, then the configuration of the molecule changes to 'S'.



Fischer also suggested that the comparison between two Fischer's Plane Projection Diagram may be made by rotating one projection through 180° within the plane of the paper about an axis perpendicular to the paper. It would result in giving the same molecule. Rotation of Fischer's projection by 90° or 270° will lead to an enantiomeric mirror image form.

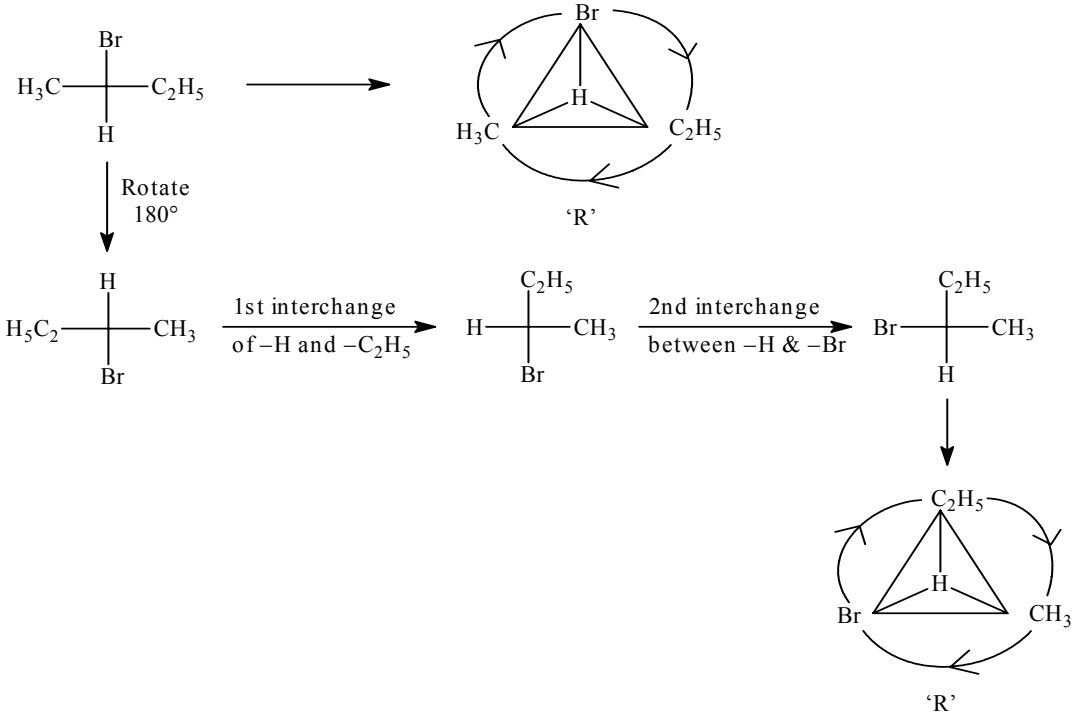


Fig. 33. 180° Rotation of Fischer's Plane Projection Diagram

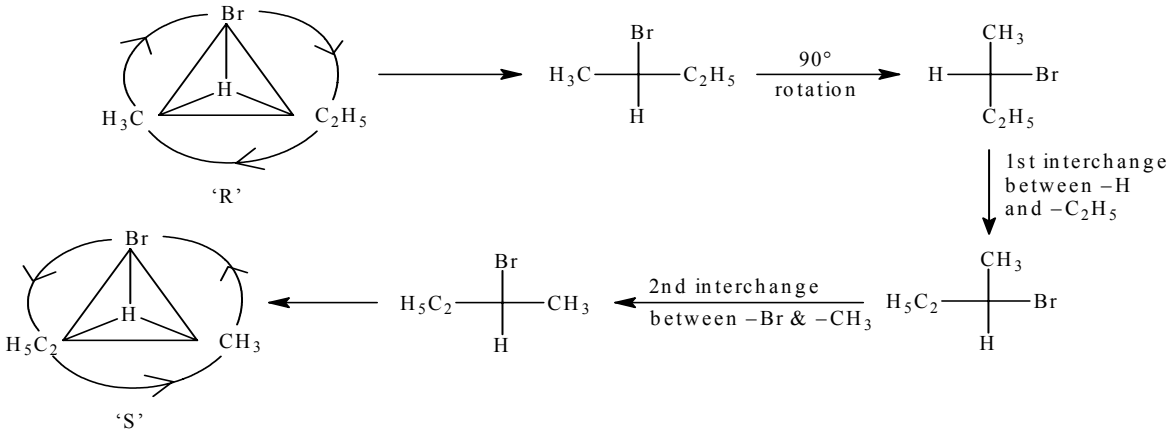


Fig. 34. 90° Rotation of Fischer's Plane Projection Diagram

Molecules with more than one Chiral Atom: Fischer's projection diagram of a molecule with more than one chiral carbon atom always represents the eclipsed conformational form of the molecule. The Fischer's Plane Projection Diagram and the Newman's Projection Diagram of the erythreose molecule can be represented as:

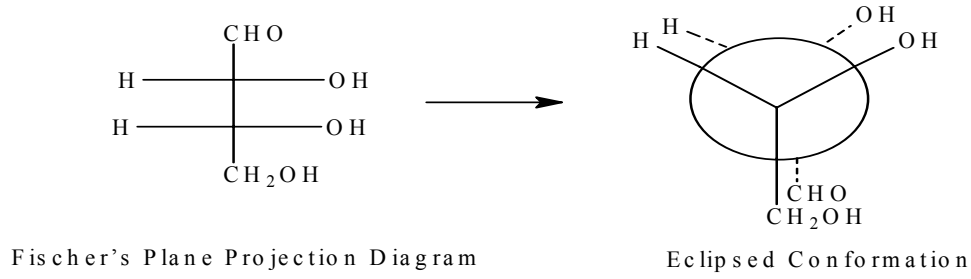
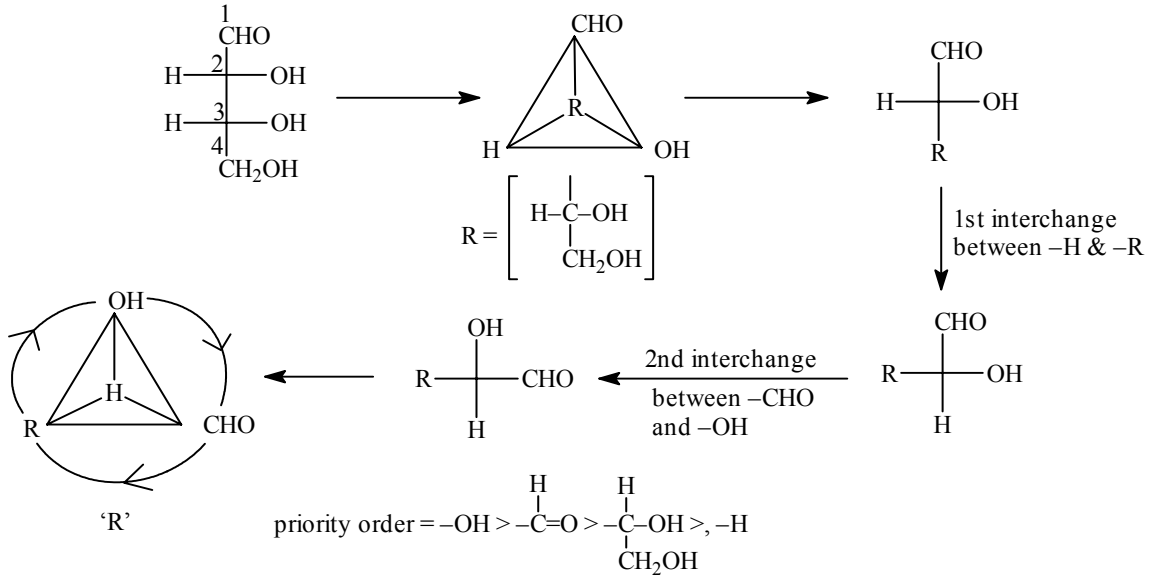


Fig. 35. Erythreose

The horizontal lines on the Fischer's Plane Projection Formula are lines above the plane of paper. The vertical lines represent groups lying below the plane of paper. The configuration of each of the asymmetric carbon atoms is worked out separately. For working out the configuration of carbon atom C_2, the steps adopted are as follows:



For working out the configuration at C_3, the steps adopted are as follows:

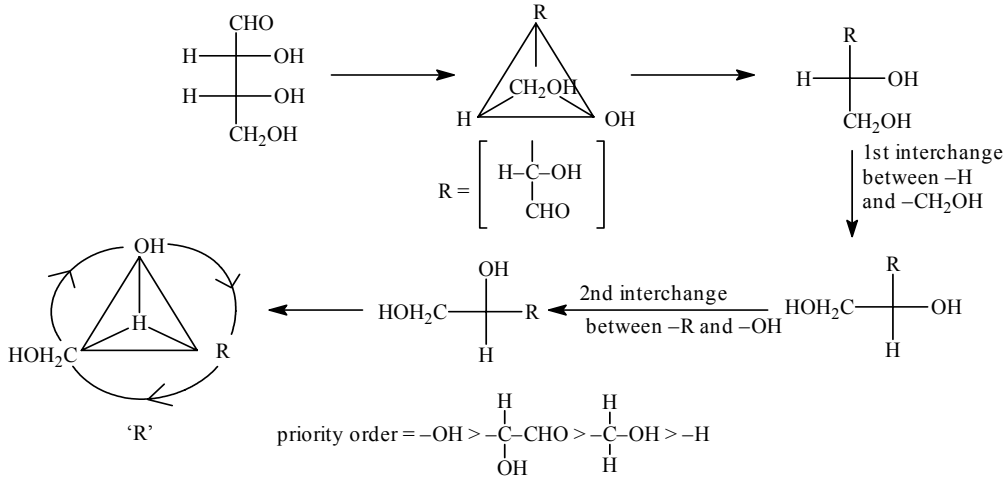


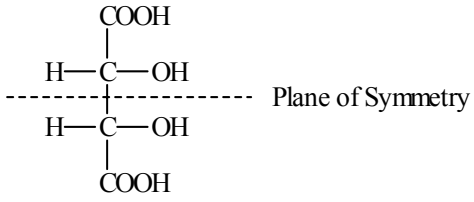
Fig. 36. Configuration of C_2 and C_3 in Erythreose

Thus the configuration of both the asymmetric carbon atom in the erythreose molecule works out to be 'R'.

Optical inactivity in compounds having Chiral Carbon Atoms

Compounds possessing chiral carbon atoms can show optical inactivity. This can be due to two reasons:

(1) Due to internal compensation: Such compounds are called as Meso Compounds. In the meso form of the molecule, one half of the molecule is the mirror image of the other half ;thus if one half of the molecule deflects the light towards the right, the other half would deflect it, to the same extent, towards the left. Therefore no deflection of the light would be observed. The zero deflection is being observed because of the intrinsic property of the molecule.



Meso Form of Tartaric Acid.

(2) Due to external compensation: Optical inactivity due to external compensation is observed when the two enantiomers are present in equal quantities. This mixture is termed as a racemix mixture. The optical inactivity is not due to the intrinsic property of the molecule. These molecules can be resolved and separated out in its optically active enantiomeric forms.

Resolution of Racemix Mixture

Resolution is the method adopted for separating the enantiomers, the two mirror image forms, from the racemix mixture. Three simple methods were suggested by Loius Pasteur.

Mechanical Separation: In this method the crystals are separated mechanically, by hand. This separation can be achieved only when the crystals of the two enantiomeric forms are well defined and enantiomorphoces in nature. Loius separated crystals of ammonium sodium tartarate by this method. This method is now of historical importance only.

Biochemical Separation: Some bacteria or mould when introduced into a dilute solution of a racemix modification grows by destroying one enantiomeric form faster than the other e.g. Penicillium glaucum (a mould) when grown in a solution of Ammonium sodium tartarate Racemate, attacks the 'D'-form leaving the 'L' form.

By means of salt formation: This method is based on the principle that reaction of the racemic modification with another optically compound a mixture of diastereoisomeric products.

The racemic mixture of an acid when made to react with an optically active base would gives two diastereoisomeric salts.

$$(D_{acid} + L_{acid}) + 2D_{base} \longrightarrow D_{acid} + D_{base}) + (L_{acid} + D_{base})$$

Salt Salt

Any differnce in the physical properties, like solubility, boiling point of the two diastereoisomeric can be used to separate them. Similarly, racemic aldehydes and ketones may be resolved by reacting with an optically active hydrazine.

Geometrical Isomers

Geometrical Isomers are isomers which arise due to the different spatial arrangement of atoms or groups around a double bond, or in cyclic compounds. The different spatial arrangemenst arise in these molecules as one form cannot be readily converted into the other form without the breakage of a bond. For example 2-butene can exist in the following two forms, the cis and the trans form. The cis form has identical groups lying on the same side of the double bond whereas the trans form has identical groups lying on opposite side of the double bond.

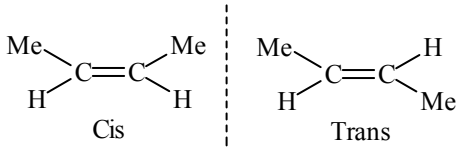


Fig. 37. Geometrical Isomers of 2-Butene

Disubstituted cyclic compounds can also exist in two different forms.

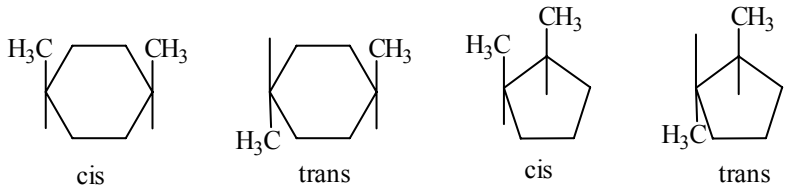


Fig. 38. Geometrical Isomers of Cyclohexane and Cyclopentane

E & Z system of Normenclature of the Geometrical Isomers

In an unsaturated open chain molecules if, the carbon atoms carrying the double bonds have just two different groups attached to it, they can easily be classified as the cis and trans isomers. However, carbon atoms holding double bonds can have all four different groups attached to it for example 2-chloropentene, $CH_3ClC{=}CHC_2H_5$. The nomenclature cis and trans would not be able to give the exact dispositions of the groups for such compounds. The compounds are then named with the help of E & Z nomenclature. The E & Z system is based on the sequence rule applied for naming the optical isomers. The groups are arranged as according to their priority order. Out of the two groups, attached to any one of the two carbon atoms holding the double bond, the group having atoms with higher atomic number gets priority. If the higher priority group belonging to both the carbon atoms held by the double bond, lie on the same side of the double bond, the molecule gets the configuration 'Z' but if the higher priority order groups lies on the opposite sides of the double bond, then the configuration assigned to the molecule is E.

Fig. 39. 3-Bromobut-2-ene

In 3-Bromobut-2-ene molecule, the groups attached to C_2 carbon are Me and H showing the priority order of -Me>H. The groups attached to C_3 carbon atom are –Br and –Eth and their order of priority would be –Br>-Eth. Since in structure X both the higher priority groups are on the same side of the double bond, therefore the configuration assigned to the molecule

would be ‘Z’. In structure XI the two higher priority order groups are on the opposite sides, hence the molecule would be expressed as having the configuration ‘E’.

The following molecules could be assigned the configurational forms ‘Z’ & ‘E’ on similar grounds.

‘Z’ ‘E’

Priority order $-C_6H_5 > -H$

And $-COOH > -CH_3$

Naming the compounds however, becomes a bit confusing when the double bond holding carbon atoms have only three different groups attached to them. The following are the examples:

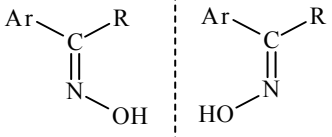
‘Z’ (trans in text) ‘E’ (cis in text)

‘E’ (cis in text) ‘Z’ (trans in text)

Geometrical isomers are also observed in aldoximes, ketoximes, diazo and azo compounds having – C=N bond or –N=N- bond.

Hantzsch and Werner (1890) suggested that compounds with double bonds involving nitrogen have the capability of showing geometrical isomerism. An assumption was made that there is no free rotation around the double bond therefore the molecules could exist in the following isomeric forms.

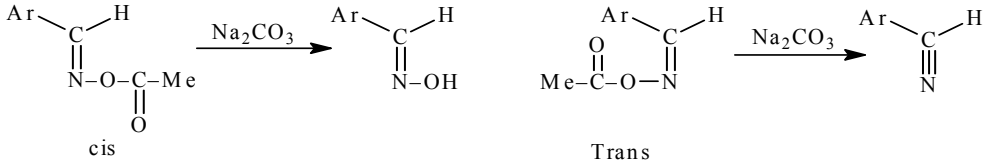
Syn (cis or Z) Anti (trans or E)



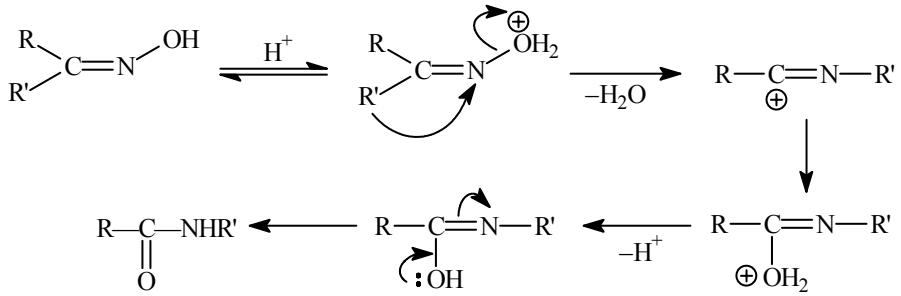
Structure XII Structure XIII

Fig. 40. Geometrical Isomeric forms of Aldoximes

The aldoxime structure (XII) & (XIII) are designated as syn (or cis) hydroxyl and anti (or trans) hydroxyl with reference to hydrogen. The fact that, both aldoximes and ketoximes exist in two geometrical forms, was established with the help of reactions. The two isomeric aldoximes could be distinguished from each other by the behaviour of their acetyl derivatives towards aqueous carbonate. The cis form gives back the oxime whereas the trans form gets converted into a cyanide.



In case of aromatic ketoximes the trans form undergoes Beckman's Rearrangement Reaction when treated with reagents like phosphoroces pentachloride, sulphuric acid, polyphosphoric acid, etc. Cis form of the molecule does not show this reaction. In Beckman's Rearrangement the migrating groups always approaches the nitrogen atom on the side opposite to the oxygen atom. The mechanism of the reaction can be given as follows:



The cis (syn) and the trans (anti) form of the ketoximes are designated with reference to one group in particular.

In case of the azo compound syn is the nomenclature given to the molecule with both the groups on the same side of the double bond anti when the two groups are on the opposite sides.

Properties of Geometrical Isomers

The trans geometrical isomeric forms are more stable than the cis forms. The cis forms are subjected to a greater stearic strain thus making the molecule, energetically, the less favourable one. In general the physical properties of the geometrical isomers could be explained with the help of Auwa's Skita Rule. According to this rule all the physical properties like density, refractive index, solubility dipole moment, heat of combustion and dissociation constant (if the molecule is an acid) of the cis form generally shows a higher value than the trans form, however the m. pt of the trans form is higher than cis. Table (I) shows the comparative data of some compounds.

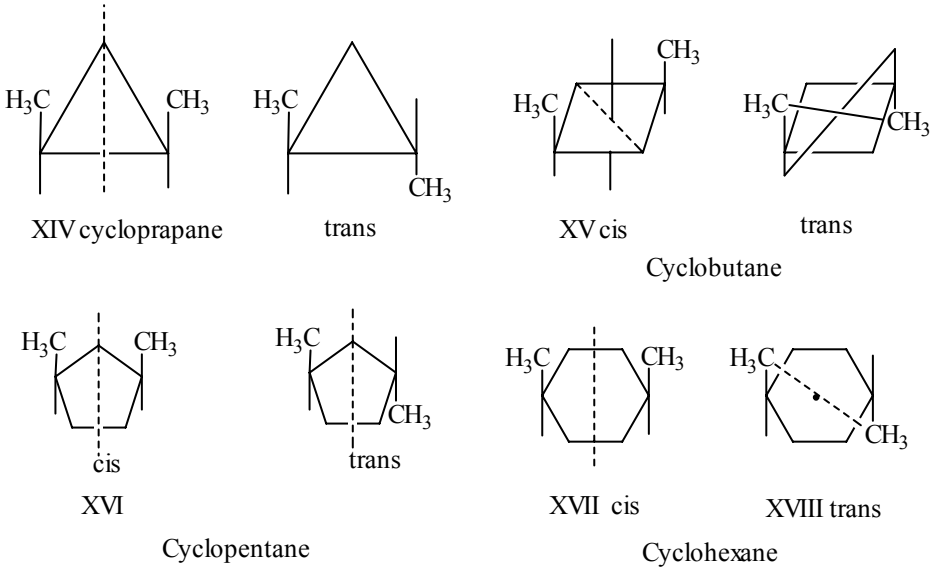
Table I. Dipole moments and m.p. of dihaloethylenes

x	cis		trans	
	μ	m.p.	μ	m.p.
Cl	1.85D	–80°C	OD	–50°C
Br	1.35D	–53°C	OD	–6.5°C
I	0.75D	–14°C	OD	72°C

The difference in values of the physical properties can be explained on the basis of the structure of the cis and the trans form. The molecules of the trans form, being more symmetrical are more closely packed with greater amount of intermolecular forces working as a result the melting point of the trans form is higher than the cis form. However the dipole moment of the trans form is lower than the cis form as the bond moments of each bond gets cancelled in the trans form but in the cis form the bond moments add up. Higher polarity in the cis form results in the other physical properties also showing higher values.

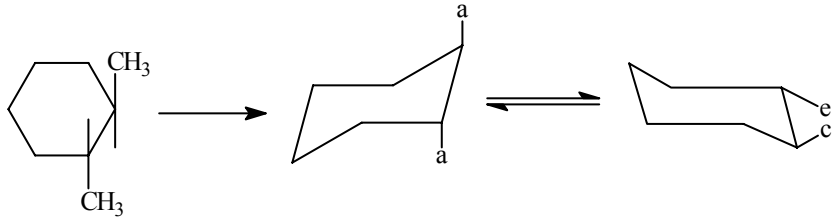
Alicyclic Compounds

Disubstituted alicyclic compounds like alkenes can also show geometrical isomerism as the carbon atoms involved in the ring are trapped in the cyclic structure and are not free to rotate. Thus all disubstituted cyclo alkanes for example cyclopropane, cyclobutane, cyclopentane, cyclohexane, etc. can show geometrical isomerism.



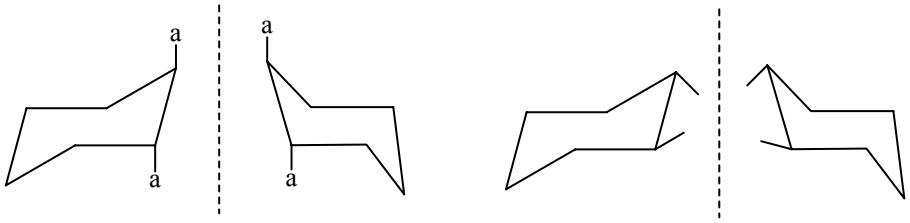
Interestingly some of these cycloalkanes besides showing geometrical isomerism are also capable of showing optical isomerism. This can be explained on the basis of the chiral carbon atoms present in the molecule. Structure XIV, XV, XVI, XVII and XVIII have a symmetry element present in the molecule and therefore loose their optical activity.

Cyclohexane shows special dispositions of groups in the molecule as the molecule is puckered and has two types of bonds present attached to it, the axial and the equatorial bonds. The cis and trans forms of the 1,2; 1,3; and1,4 disubstituted cyclohexane can be given as follows:



The 1,2 trans dimethyl cyclohexane can have the methyl groups existing at the axial-axial positions which on flipping will occupy the equatorial equatorial positions. The two forms are readily interchangeable but are not mirror image forms of each other, therefore they form

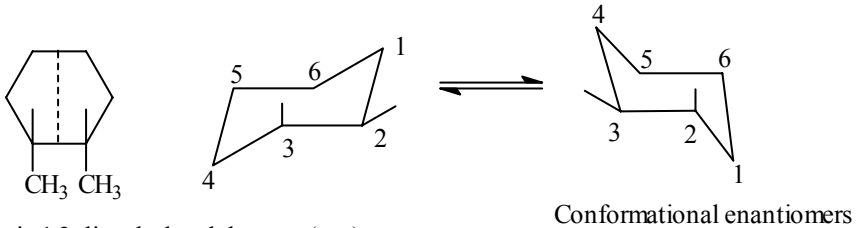
conformational diastereoisomers. Each conformational form a, a and e, e form nonsuperimposable images i.e. exist as configurational enantiomers and would show optical activity.



a,a(Configuration enantiomers)

e,e (Configurational enantiomers)

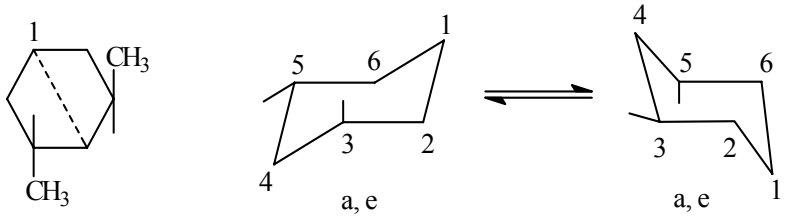
1,2-trans dimethylcyclohexane



cis 1,2-dimethylcyclohexane (a, e)

Conformational enantiomers (nonsuperimpossible mirror images obtained on flipping)

The cis 1,2 dimethyl cyclohexane can have methyl groups existing at axial and equatorial bonds. The two forms obtained on flipping are mirror image forms and hence are termed as conformational enantiomers. This molecule also has a plane of symmetry and hence the molecule will show optical inactivity.

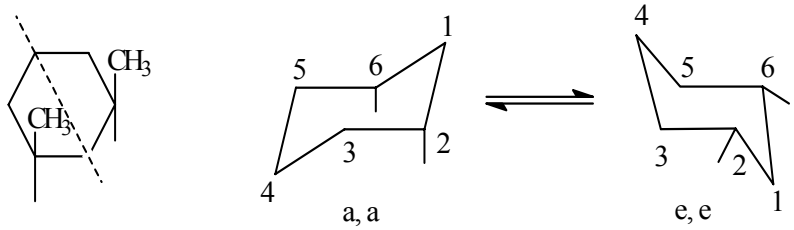


No element of symmetry

1,3-transdimethylcyclohexane

Configurational Enantiomers
Nonsuperimpossible mirror images
(one conformer)

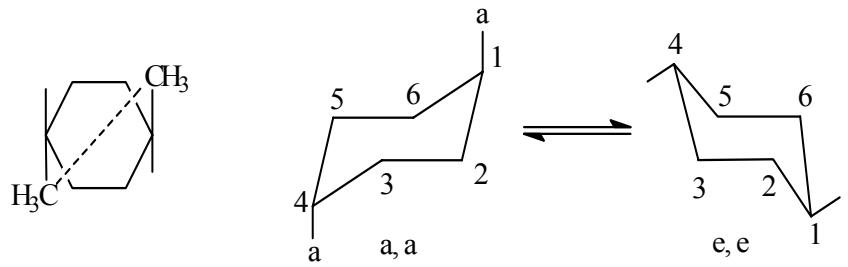
The trans 1,3 dimethyl cyclohexane can have methyl groups existing at axial and equatorial bonds. The molecule is optically active and exist in enantiomeric form. The molecule has just one conformer.



Plane of symmetry
Non resoluable
Meso form

Conformational Diastereoisomers
1,3 cis-dimethylcyclohexane

Cis 1,3 dimethylcyclohexane has methyl group at a, a or on flipping at e, e position they form conformational diastereoisomer. The molecule has a plane of symmetry and forms superimpossible mirror images.

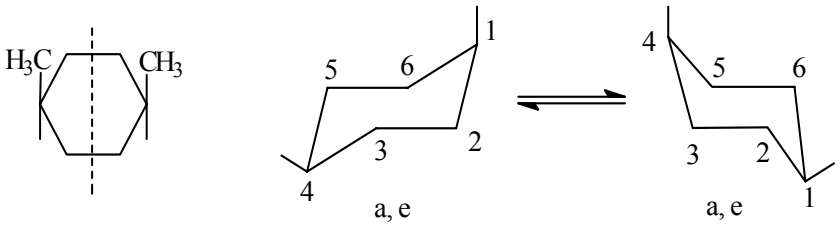


Centre of symmetry
superimposible
Mirror images

Conformational Diastereoisomers

1,4-trans-dimethylcyclohexane

Trans 1,3 dimethylcyclohexane has methyl groups at axial-axial or on flipping at equatorial – equatorial position. The two forms are conformational diastereoisomer. The molecule possess centre of symmetry and forms superimpossible mirror images and would be optically inactive.



Plane of symmetry
superimposible
Mirror image -
Meso form

1,4-cis-dimethylcyclohexane

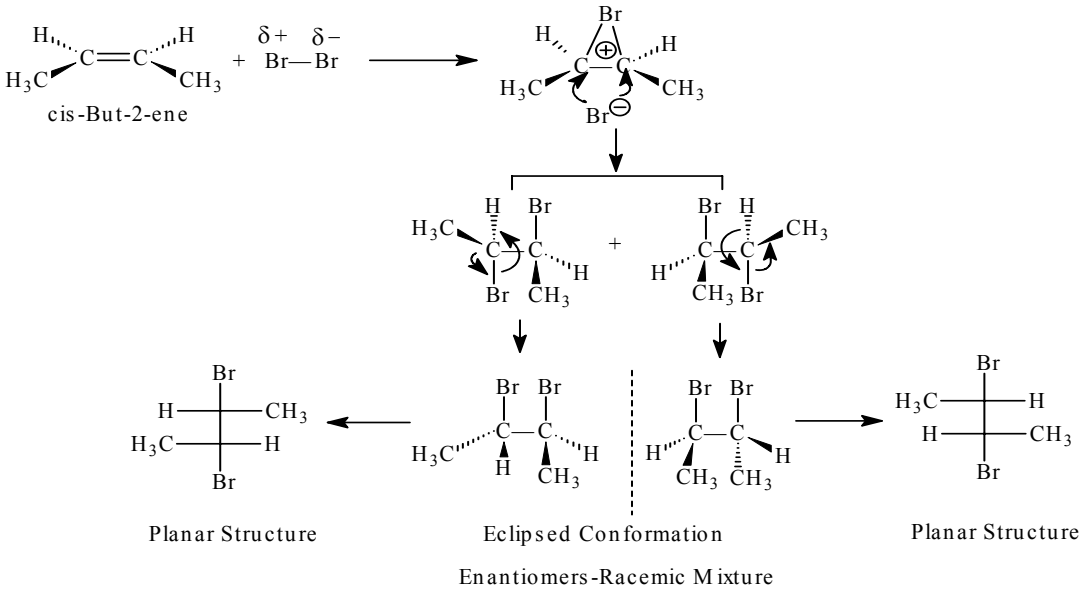
Cis 1,4 dimethylcyclohexane has the methyl groups existing at positions axial and equatorial. On flipping the mirror image form is obtained which are superimposable. They are termed as conformational enantiomers. The molecule has a plane of symmetry and would be optically inactive.

Reactions and their Stereochemistry

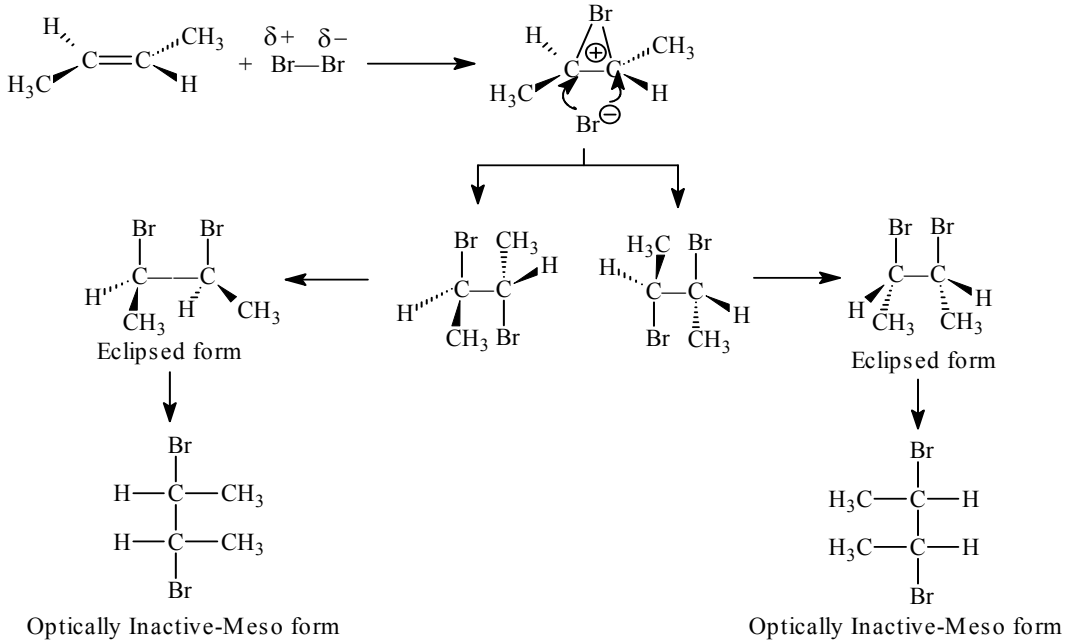
Stereochemistry plays a very important role in number of reactions and their mechanisms. Many reactions have been found to be stereospecific or stereoselective in nature.

Stereospecific Reactions:

Stereospecific Reactions are reactions in which a stereoisomeric form of the molecule reacts in a manner to give only a specific stereoisomeric form of the product, for example, bromine adds up to cis-butene to give exclusively an optically active product.



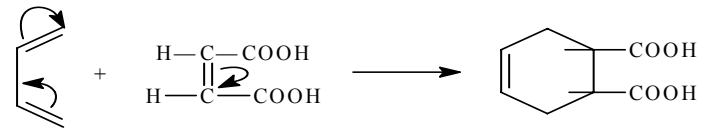
Since equal quantities of both the enantiomers are obtained, the product is a racemix mixture. Br2 would add up to trans-butene in a stereospecific manner to give exclusively an optically inactive meso product.



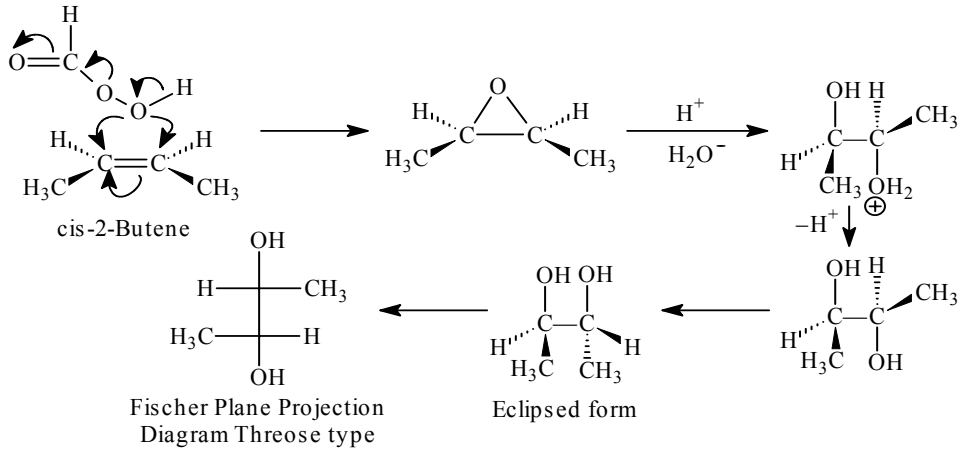
Both Racemic mixture and the meso products thus obtained show optical inactivity but Racemic mixture shows optical inactivity due to external compensation. The product being a mixture of equal quantities of two enentiomers deflection of the plane polarized light becomes zero. Meso form, however, shows optical inactivity due to internal compensation. The molecule has an element of symmetry and forms superimpossible mirror images.

Many addition reactions are stereospecific in character and give stereospecific products e.g. Diel's Alders reaction, addition of peroxides to alkenes.

In Diel's Alders Reaction, the Diene and the Dineophile undergoes a cis addition to give a stereospecifically cis product.



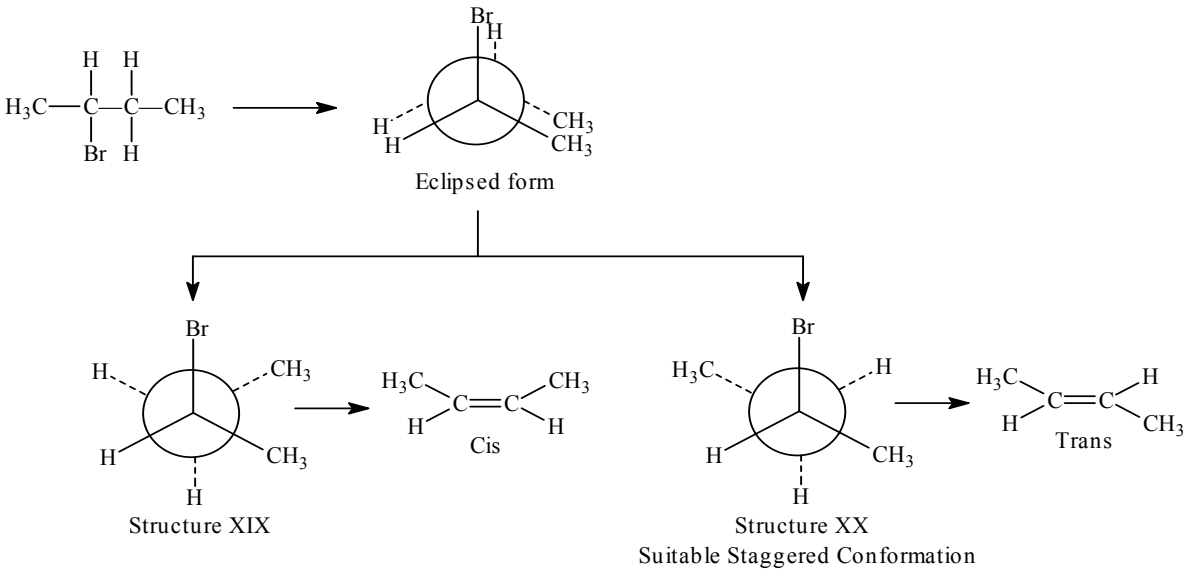
The addition of peroxides to the alkene is a trans addition giving a stereospecifically trans addition product. Cis – 2 – Butene gives Threose type of a product and trans – 2 – Butene gives Frythreosetype of a product.



Stereo Selective Reactions:

Stereo selective Reactions are reactions in which the reactant produces predominantly or exclusively only one stereoisomeric form of the product out of the all the stereoisomeric forms that are possible. For example dehydrohalogenation reaction preferably gives the trans alkene product. The elimination always occurs with the molecule existing in the staggered conformational form with the two out going groups farthest apart from each other. Elimination in 2-bromobutane molecule can be demonstrated in the following manner.

The 2-bromobutane molecule can exist in two possible, suitably, staggered conformational forms Structure XIX & XX. Structure is more suitable conformaitonal form of the molecule, as the stearic strain in the molecule would be less. Therefore the major stereoselective product obtained after elimination from the more stable structure XX would be trans alkene.



Reactions involving inversion retention and racemization
Stereoisomers can undergo reaction involving either inversion of configuration retention of configuration or it may also result in giving a racemized product.

Reactions involving racemization
Unimolecular nucleophilic substitution reaction occurs through the formation of a carbocation A chiral molecule, for example, 3-bromo-3-methylhexane,when subjected to solvolysis reaction undergoes unimolecular nucleophilic substitution reaction through the formation of an achiral carbocation as intermediate. The achiral intermediate in turn gives equal quantities of both the enantiomeric forms or a racemic forms or a racemic mixture as product.

Reactions involving inversion of configuration
Inversion of configuration of an optically active compound can be observed when the molecules undergo biomolecular nucleophilic substitution reaction. 2-chlorobutane on treatment with alkali undergoes biomolecular nucleophilic substitution reaction to give product with inverted configuration.

In the transition state in bimolecular nucleophilic substitution reaction the chiral carbon atom acquires a pentavalent state. The incoming nucleophilie attacks the chiral carbon atom from the side directly opposite to the leaving group, before the bond of the leaving group breaks, resulting in invasion of configuration.

Reactions involving retention of configuration
Retention of configuration of a chiral molecule would occur if in nucleophilic substitution reactions the attacking group links up to the chiral carbon atom from the same side to which the leaving group is attached. Internal nucleophilic substitution results in the formation of a product with retention in configuration, for example, reaction of 2-butanol with thionyl chloride.