

**Stereochemistry:**

**Different types of isomerism; concept of chirality and optical activity (upto two carbon atoms); elements of symmetry [plane ( $\sigma$ ), center (i) and alternating axis ( $S_n$ ) of symmetry]; interconversion of Fischer and Newman representations; threo and erythro, D and L, CIP Rules: R/S (upto 2 chiral carbon atoms), E/Z nomenclature. Conformational analysis of ethane, *n*-butane.**

The stereochemistry is the study of three-dimensional configuration of the atoms that make up molecules and the ways in which the arrangement affects the physical and chemical properties of a molecule.

Stereochemistry is the branch of chemistry that involves “*the study of the different spatial arrangements of atoms in molecules*”.

One of the major problems in organic chemistry is to find out how the atoms are arranged in molecules, i.e., to determine the structure of organic compounds. Each different arrangement of atoms corresponds to a different compound and each compound has own characteristic set of chemical and physical properties. There is definitely a relationship between the molecular structure, i.e., arrangement of atoms or groups of atoms in a molecule and its properties.

Compounds which have the same molecular formula, but different structural formula are called isomers and the compounds having different configuration, i.e., different relative position of atoms or group in space are called stereoisomers. In other words, the molecules that have same atomic connectivity, but different arrangements of their properties is known as **3D** chemistry. In this chapter, we shall deal with different types of structural as well as stereoisomers of organic compounds.

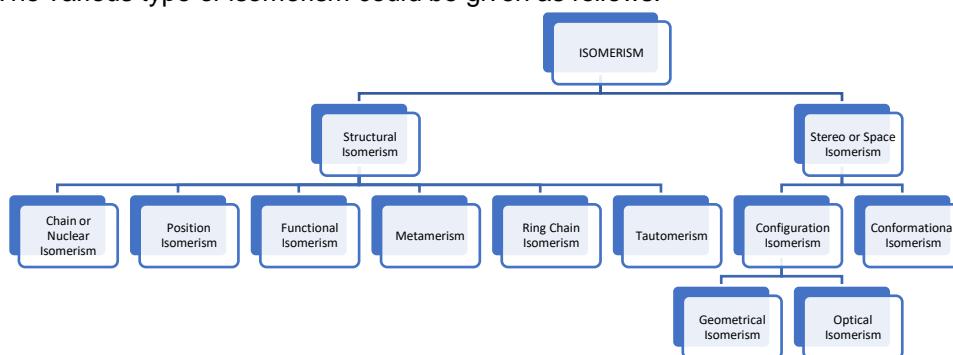
**Isomerism:** In organic chemistry we find numerous organic compounds having same molecular formula but differing in their physical and chemical properties. Such compounds are called isomers and the phenomenon is known as isomerism.

As different compounds possess the same molecular formula, the difference in their physical and chemical properties is attributed to different spatial arrangement of the molecules.

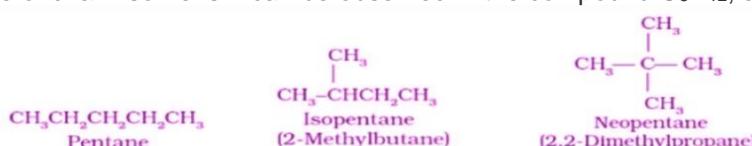
The term isomerism (Greek, *isos* means equal and *meros* means parts) was first used by Berzelius to describe compounds with the same molecular formula but having different physical and chemical properties.

Isomers differ either in their chemical structures or in the spatial arrangement of atoms and groups present in their molecules. The difference in chemical structures gives rise to structural isomerism, whereas different spatial arrangements of atoms or groups give birth to stereoisomerism.

The various type of isomerism could be given as follows:

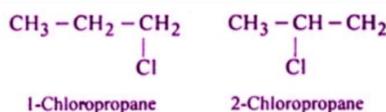
**Chain Isomerism**

- It is also known as skeletal isomerism. The components of these isomers display differently branched structures.
- Commonly, chain isomers differ in the branching of carbon
- An example of chain isomerism can be observed in the compound  $C_5H_{12}$ , as illustrated below.



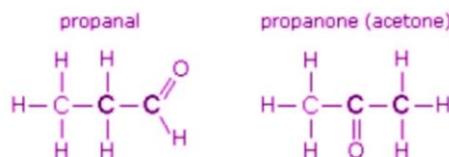
## Position Isomerism

- The positions of the functional groups or substituent atoms are different in position isomers.
- Typically, this isomerism involves the attachment of the functional groups to different carbon atoms in the carbon chain.
- An example of this type of isomerism can be observed in the compounds having the formula  $C_3H_7Cl$ .



## Functional Isomerism

- It is also known as functional group isomerism.
- As the name suggests, it refers to the compounds that have the same chemical formula but different **functional groups** attached to them.
- An example of functional isomerism can be observed in the compound  $C_3H_6O$ .



## Metamerism

- This type of isomerism arises due to the presence of different alkyl chains on each side of the functional group.
- It is a rare type of isomerism and is generally limited to molecules that contain a divalent atom (such as **sulfur** or **oxygen**), surrounded by alkyl groups.
- Example:  $C_4H_{10}O$  can be represented as ethoxyethane ( $C_2H_5OC_2H_5$ ) and methoxy-propane ( $CH_3OC_3H_7$ ).

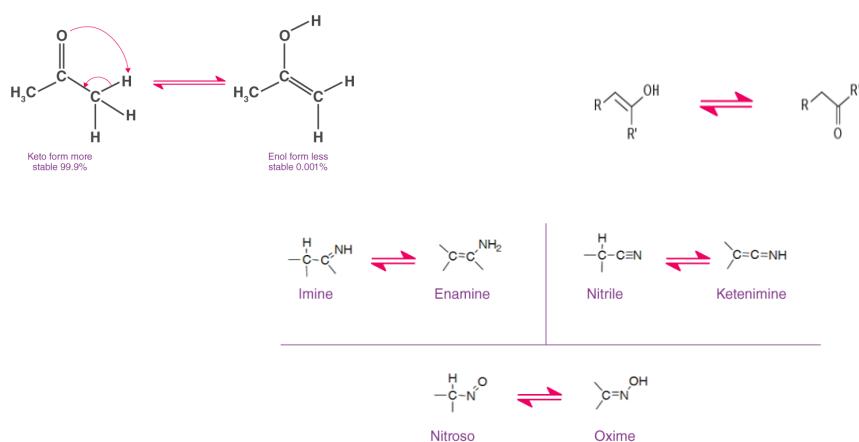
## Ring-Chain Isomerism

- In ring-chain isomerism, one of the isomers has an open-chain structure whereas the other has a ring structure.
- They generally contain a different number of pi bonds.
- A great example of this type of isomerism can be observed in  $C_3H_6$ . Propene and cyclopropane are the resulting isomers, as illustrated below.



## Tautomerism

- A tautomer of a compound refers to the isomer of the compound which only differs in the position of protons and electrons.
- Typically, the tautomer's of a compound exist together in equilibrium and easily interchange.
- It occurs via an intramolecular proton transfer.
- An important example of this phenomenon is Keto-enol tautomerism.



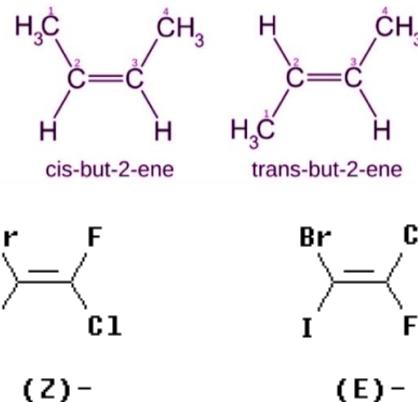
## Stereoisomerism

This type of isomerism arises in compounds having the same chemical formula but different orientations of the atoms belonging to the molecule in three-dimensional space. The compounds that exhibit stereoisomerism are often referred to as stereoisomers. This phenomenon can be further categorized into two subtypes. Both these subtypes are briefly described in this subsection.

### Geometric Isomerism

- It is popularly known as **cis-trans isomerism**.
- These isomers have different spatial arrangements of atoms in three-dimensional space.

An illustration describing the geometric isomerism observed in the acyclic But-2-ene molecule is provided below.

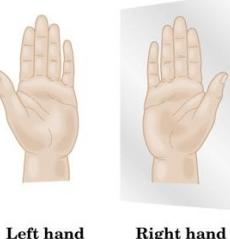


### Optical Isomerism

- Compounds that exhibit optical isomerism feature similar bonds but different spatial arrangements of atoms forming non-superimposable mirror images.
- These optical isomers are also known as enantiomers.
- Enantiomers differ from each other in their optical activities.

Dextro enantiomers rotate the plane of polarized light to the right whereas laevo enantiomers rotate it to the left, as illustrated below.

**Enantiomers:** non-superimposable mirror image isomers. Enantiomers are related to each other much like a right hand is related to a left hand. Enantiomers have identical physical properties, i.e., bp, mp, etc. Chirality (from the Greek word for hand). Enantiomers are said to be *chiral*.

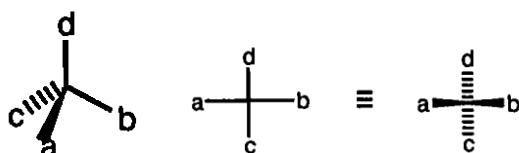


Left hand      Right hand

Molecules are not chiral if they contain a plane of symmetry: a plane that cuts a molecule in half so that one half is the mirror image of the other half. Molecules (or objects) that possess a mirror plane of symmetry are superimposable on their mirror image and are termed *achiral*.

**A carbon with four different groups results in a chiral molecule and is referred to as a *chiral* or *asymmetric* or *stereogenic* center.**

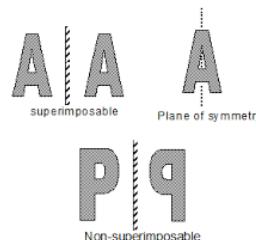
**Chiral Centre:** A carbon atom to which four different group or atoms are attached is called asymmetric carbon atom or chiral center. A molecule a, b, c, d is chiral when  $a \neq b \neq c \neq d$ .



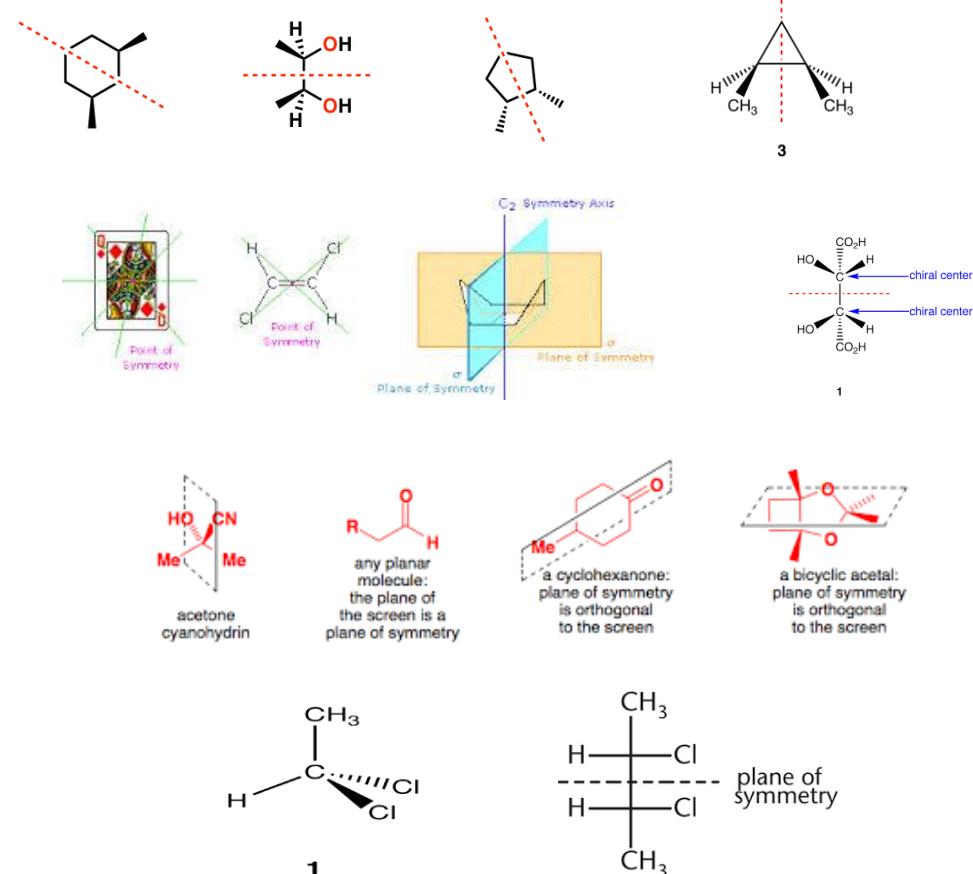
- **Symmetry axis:** an axis around which a rotation by  $360^\circ$  results in a molecule indistinguishable from the original. This is also called an *n*-fold **rotational axis** and abbreviated  $C_n$ . Examples are the  $C_2$  axis in water and the  $C_3$  axis in ammonia. A molecule can have more than one symmetry axis;

the one with the highest  $n$  is called the **principal axis**, and by convention is aligned with the z-axis in a Cartesian coordinate system.

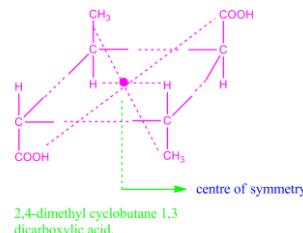
- **Plane of symmetry ( $\sigma$ ):** A plane of symmetry is an imaginary plane that bisects a molecule in such a way that the two halves of the molecule are mirror reflection of each other. A plane of symmetry is equivalent to a one-fold alternating axis of symmetry. It is symbolized by sigma ( $\sigma$ ). Any molecule that has a plane of symmetry will be achiral. A plane of symmetry is two-fold alternating axis of symmetry, through which an identical copy of the original molecule is generated. This is also called a mirror plane and abbreviated  $\sigma$  (sigma = Greek "s", from the German 'Spiegel' meaning mirror). Water has two of them: one in the plane of the molecule itself and one perpendicular to it. A symmetry plane parallel with the principal axis is dubbed *vertical* ( $\sigma_v$ ) and one perpendicular to it *horizontal* ( $\sigma_h$ ). A third type of symmetry plane exists: If a vertical symmetry plane additionally bisects the angle between two 2-fold rotation axes perpendicular to the principal axis, the plane is dubbed *dihedral* ( $\sigma_d$ ). A symmetry plane can also be identified by its Cartesian orientation, e.g., (xz) or (yz).



Planes of symmetry can cut through both atoms and bonds:

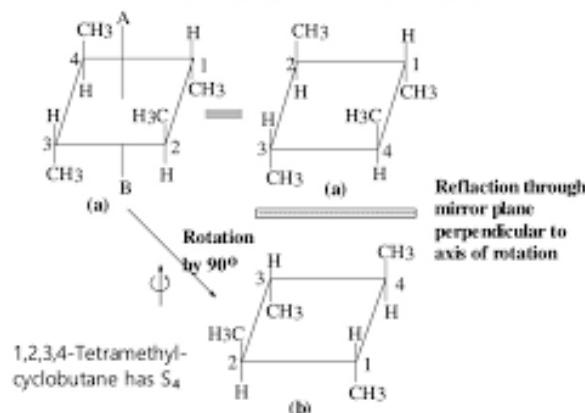


- **Center of symmetry or inversion center (i):** A center of symmetry is a point such that all straight lines drawn through it touch equivalent parts of a molecule at equal distances. A center of symmetry is equivalent to two-fold alternating axis of symmetry. Thus, center of symmetry abbreviated  $i$ . A molecule has a center of symmetry when, for any atom in the molecule, an identical atom exists diametrically opposite this center at an equal distance from it. In other words, a molecule has a center of symmetry when the points  $(x,y,z)$  and  $(-x,-y,-z)$  correspond to identical objects. For example, if there is an oxygen atom in some point  $(x,y,z)$ , then there is an oxygen atom in the point  $(-x,-y,-z)$ . There may or may not be an atom at the inversion center itself. Examples are xenon tetrafluoride where the inversion center is at the Xe atom, and benzene ( $C_6H_6$ ) where the inversion center is at the center of the ring.



- **Alternating axis of symmetry or Rotation-reflection axis of symmetry ( $S_n$ ):** An  $n$  fold alternating axis of symmetry is an axis such that, when the structure passing the axes is rotated around the axis by an angle of  $360/n$  and then reflect across a plane of right angle to the axis another identical structure results. Alternating axis of symmetry an axis around which a rotation by  $360/n$ , followed by a reflection in a plane perpendicular to it, leaves the molecule unchanged. Also called **Rotation-reflection axis of symmetry** and  **$n$ -fold improper rotation axis**, it is abbreviated  $S_n$ . Examples are present in tetrahedral silicon tetrafluoride, with three  $S_4$  axes, and the staggered conformation of ethane with one  $S_6$  axis. An  $S_1$  axis corresponds to a mirror plane  $\sigma$  and an  $S_2$  axis is an inversion center  $i$ . A molecule which has no  $S_n$  axis for any value of  $n$  is a chiral molecule.

#### 4. Alternating or improper axis of symmetry ( $S_n$ )

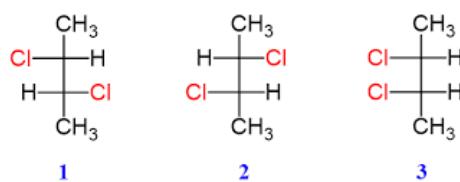


- **Simple axis of symmetry ( $C_n$ ):** An  $n$  fold simple axis of symmetry is an imaginary axis such that when a structure possessing the axis is rotated by an angle of  $360/n$  around the axis, another identical structure results. **Simple axis of symmetry is not related to optical activity.**

#### Simple Axis of Symmetry ( $C_n$ )

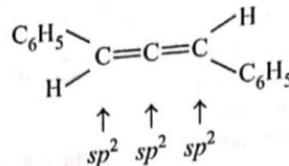
- When a molecule is rotated by an angle  $360/n$  around an axis and arrangement similar to the original is obtained, the molecule is said to possess  $C_n$  axis of symmetry.
- The operation when repeated  $n$  times gives the exact original.
- Proper axis of rotation:  $C_n$   
where
  - $n = 1$ , 360° rotation (Present in every molecule)
  - $n = 2$ , 180° rotation
  - $n = 3$ , 120° rotation
  - $n = 4$ , 90° rotation
  - $n = 6$ , 60° rotation
  - $n = \infty$ , (any) rotation
- Principal axis of rotation,  $C_\infty$ : Highest order of axis present.

- **Identity**, abbreviated to  $E$ , from the German 'Einheit' meaning unity. This symmetry element simply consists of no change: every molecule has this element. While this element seems physically trivial, it must be included in the list of symmetry elements so that they form a mathematical group, whose definition requires inclusion of the identity element. It is so called because it is analogous to multiplying by one (unity). In other words,  $E$  is a property that any object needs to have regardless of its symmetry properties.

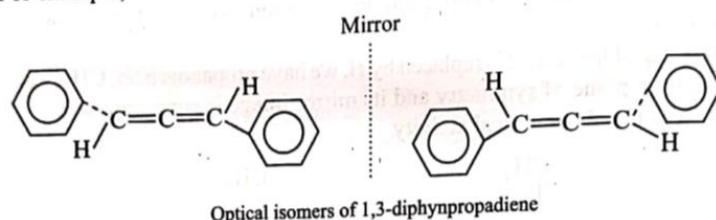


There are some molecules in which there are no asymmetric carbon atoms, yet they exhibit optical activity. The optical activity is due to the chirality of the molecule as a whole. For example, 1,3-diphenyl-propadiene in which various atoms are

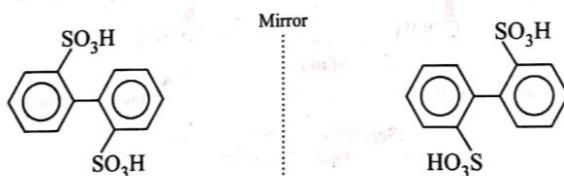
- (i) **Derivatives of allene** like 1,3-diphenyl-propadiene in which various atoms are hybridised as follows:



Moreover C-central atom has two mutually-perpendicular  $p$ -orbitals. The substituents at one end are in a plane, which is perpendicular to that of substituents at the other end. Consequently, the compound exists in two non-superimposable mirror images. For example,



- (ii) **Derivatives of bisphenyl** when the substituents in 2-position are large enough to prevent the rotation about the bond joining the two benzene rings. For example, bisphenyl-2,2-disulphonic acid.



Optical isomers of bisphenyl-2,2-disulphonic acid

Therefore, the presence of an asymmetric carbon or a chiral carbon is not the only criterion for a molecule to exhibit optical activity. A molecule will be optically active provided the entire molecule is achiral. At least one of the following conditions must be fulfilled for a molecule to be optically active: (i) The molecule and its mirror image are not superimposable on each other, (ii) The compounds have only one asymmetric carbon atom, (iii) None of the elements of symmetry is present in the molecule.

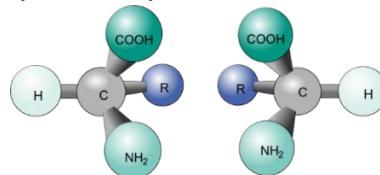
Hence, necessary and sufficient condition for a compound to be optically active is the non-superimposability of the molecule on its mirror image, i.e., chirality.

ASYMMETRIC MOLECULE	DISYMMETRIC MOLECULE
Plane of symmetry ( $\sigma$ ) absent	Plane of symmetry ( $\sigma$ ) absent
Center of symmetry or inversion center (i) absent	Center of symmetry or inversion center (i) absent
Alternating axis of symmetry or Rotation-reflection axis of symmetry ( $S_n$ ) absent	Alternating axis of symmetry or Rotation-reflection axis of symmetry ( $S_n$ ) absent
Simple axis of symmetry ( $C_n$ ) absent	Simple axis of symmetry ( $C_n$ ) present

Operation	Element	Element Construct
Identity, $E$	The object	N/A
Proper rotation, $C_n$	Proper axis, Rotation axis	line
Reflection, $\sigma$	Mirror plane, Reflection plane	plane
Inversion, $i$	Inversion center, Center of symmetry	point
Rotation-reflection Improper rotation, $S_n$	Improper axis, alternating axis	line

An asymmetric carbon atom (chiral carbon) is a carbon atom that is attached to four different types of atoms or groups of atoms.

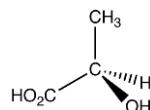
Organic compounds, molecules created around a chain of carbon atom (more commonly known as carbon backbone), play an essential role in the chemistry of life. These molecules derive their importance from the energy they carry, mainly in a form of potential energy between atomic molecules. Since such potential force can be widely affected due to changes in atomic placement, it is important to understand the concept of an isomer, a molecule sharing same atomic make up as another but differing in structural arrangements. This article will be devoted to a specific isomers called stereoisomers and its property of chirality.



Two enantiomers of a tetrahedral complex.

Chirality is based on molecular symmetry. Specifically, a chiral compound can contain no improper axis of rotation ( $S_n$ ), which includes planes of symmetry and inversion centre. Chiral molecules are always dissymmetric (lacking  $S_n$ ) but not always asymmetric (lacking all symmetry elements except the trivial identity). Asymmetric molecules are always chiral.

**Fischer Projection Formula:** Fischer projection or Fischer projection formula is a convention used to depict a stereoformula in two dimensions without destroying the stereochemical information, i.e., absolute configuration, at chiral centres, e.g., (R)-Lactic acid



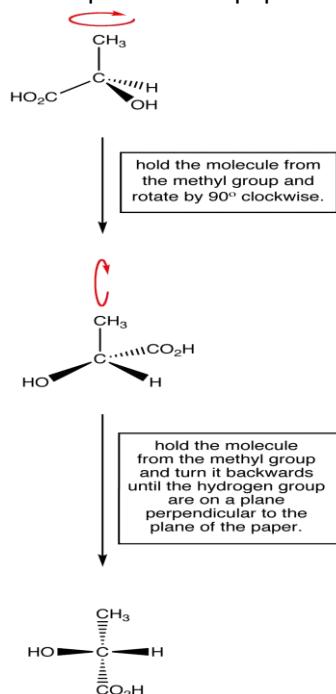
To convert this stereoformula into a Fischer projection use the following procedure:

Step 1: Hold the molecule so that

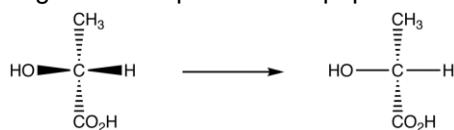
the chiral center is on the plane of the paper,

two bonds are coming out of the plane of the paper and are on a horizontal plane,

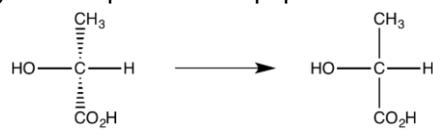
the two remaining bonds are going into the plane of the paper and are on a vertical plane



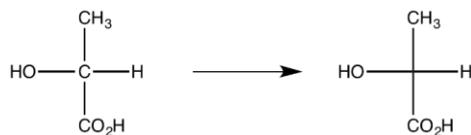
Step 2: Push the two bonds coming out of the plane of the paper onto the plane of the paper.



Step 3: Pull the two bonds going into the plane of the paper onto the plane of the paper.



Step 4: Omit the chiral atom symbol for convenience.



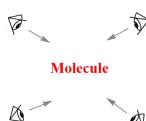
This is the Fischer Projection of (R)-Lactic acid.

### Newman Projection Formulae:

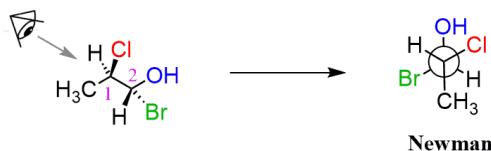
In this notion, the molecule is again viewed by looking down a particular carbon-carbon bond. The front carbon of this bond is represented by a dot, and the back carbon is represented by a large circle. The three remaining bonds are drawn as sticks coming off the dot (or circle), separated by one another by  $120^\circ$ . Just like Sawhorse projection formula, Newman Projection can be drawn such that the groups on the front carbon are staggered ( $60^\circ$  apart) or eclipsed (directly overlapping) with the groups on the back carbon.

For every Newman projection, you need to specify the bond and the direction you are looking at. For example, for our molecule, we can look through the C1-C2 bond (even though it can be through any bond).

The direction is usually shown with an eye symbol:



So, in this case, if we are looking from the top-left, and the carbon in the front is going to be carbon 1 and behind it, we have carbon 2. The corresponding Newman projection would look as follows:

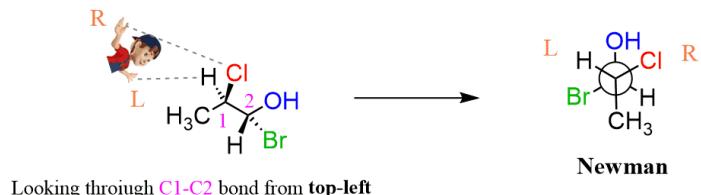


The circle is an imaginary object that is put in between the two carbons so the groups on each carbon are identified clearly in the Newman projection.

How did the groups appear where they are in the Newman projection?

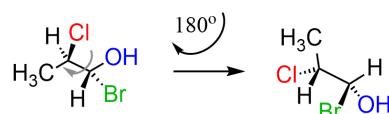
Well, let's replace the simple eye symbol with this fellow. And the reason for this is it is important to see which groups point where i.e., up, down, top-left, top-right, etc.

Here you can see that Cl is on the top right (facing the right hand), H is on the top-left (left hand) and methyl is pointing straight down. And that is all there is to the first carbon:

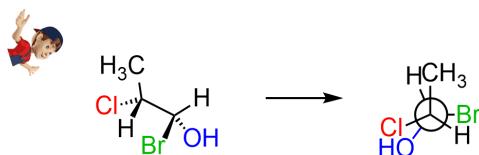


### Staggered and Eclipsed Conformations – Dihedral Angle

Let's take our molecule and do a  $180^\circ$  rotation of the first carbon around the C1-C2 bond:



And now, let's draw the Newman projection still looking from the top-left:

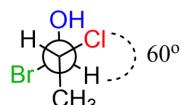


What we notice is that all the groups on the back carbon are exactly behind the ones on the front carbon. They are all aligned. This is called the Eclipsed conformation (cf. Lunar eclipse).

In other words, the angle between each eclipsing group is  $0^\circ$ . The angle between these groups is called Dihedral angle.



Notice that the dihedral angle in all the Newman projections we did before was  $60^\circ$ . It was bisecting the groups on each carbon. All these conformations were staggered conformations – the dihedral angle between all the front and back groups is  $60^\circ$ :

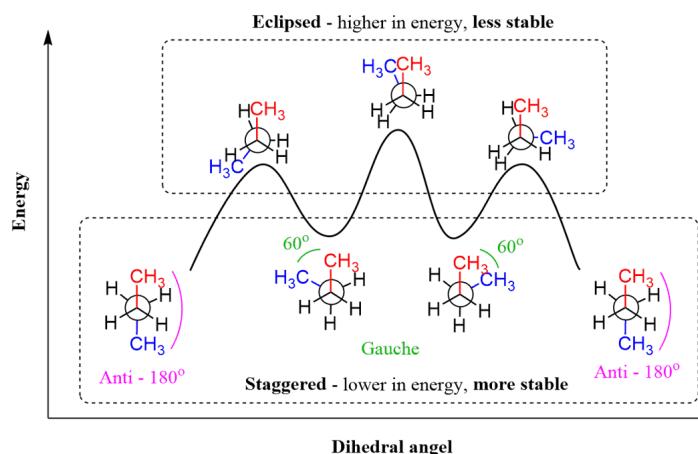


Staggered conformations are more stable than the eclipsed conformations since atoms like space and the closer they come, the more unstable the conformation becomes.

Depending on the dihedral angle between the two larger groups, the staggered conformation can be Anti ( $180^\circ$ ) or Gauche ( $60^\circ$ ). A good example is butane:



Below is the energy diagram of all the staggered and eclipsed conformations of butane. To understand how the transformation from conformation to another occurs, imagine holding the front carbon steady and rotation the back carbon by  $60^\circ$ . Of course, in reality, they both rotate and we only do this to make it easier to visualize. You could also keep the back carbon steady and rotate the front carbon:



The closer you put the large methyl groups the more unstable the conformation becomes. Or, which is the same to say, the greater the distance between the large groups, the more stable the conformation is. Also, the larger the groups, the more unstable the eclipsed and gauche conformations.

Notice that any staggered conformation is more stable than the most stable eclipsed conformation and gauche conformations are less stable than the anti-conformations.

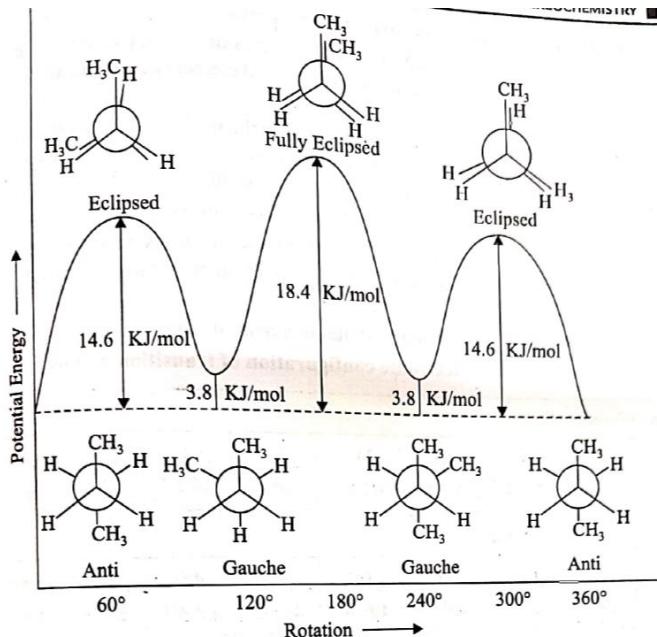
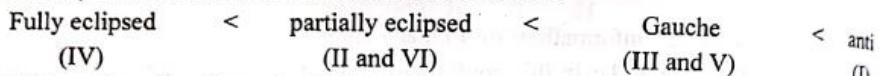


Fig. 10.14 Energy Changes during rotation around the carbon-carbon bond in n-Butane

### Relative Stabilities of Conformations of *n*-Butane

The stability of conformations of *n*-butane is in the order:



- In fully eclipsed conformation IV, there is maximum repulsion between the bonding electrons and bulky methyl group. Repulsion between bonding electrons produces *torsional strain* in the conformation while the crowding together of the bulky methyl group causes *steric or Vander Wall's strain* in the molecule. Due to torsional strain and steric strain, this conformation has maximum energy and minimum stability.
- In the partially eclipsed conformation (II and VI) the repulsive interaction between the bulky methyl group and bonding electrons is less than in fully eclipsed conformation (IV). Thus, *partially eclipsed conformations are more stable than fully eclipsed conformation*.
- In gauche conformation (III and V) there are weak repulsive interactions between two methyl groups as they are 60° apart. In other words, there is a slight Van der Wall's strain but no torsional strain. Thus, *it is more stable than partially eclipsed conformation*.
- In anti conformation (I), the repulsive interaction between the two methyl groups and bonding electrons is minimum because the two methyl groups are maximum distance apart. Thus, *this conformation is free of torsional as well as steric strain*. Hence it is the *most stable conformation*.
- As anti conformation and Gauche conformations have staggered arrangements, they have maximum energy and maximum stability (anti conformation is slightly more stable than Gauche conformation). **These conformations are referred to as conformational isomers.**
- The difference in energy contents between conformations I and IV is about 18.4  $\text{kJ mol}^{-1}$ , between I and II (or VI) is about 14.6.  $\text{kJ mol}^{-1}$  and between I and III or V is only 3.8  $\text{kJ mol}^{-1}$ .
- Maximum energy difference between two conformations is only 18.4  $\text{kJ/mol}$  which is easily provided by colliding molecules at room temperature. Thus various conformations of *n*-butane are inter-convertible and hence cannot be isolated. In other words rotation around carbon-carbon single bond in *n*-butane is almost free. At any time, *n*-Butane at an equilibrium will be mixture of all the possible conformations which contains the highest percentage of the anti conformation(s) and least proportion of the fully eclipsed conformation (IV).

### Relative Stabilities of Conformations of Ethane

It must be pointed out here that rotation around the single bond is *not completely free*. If it were so, the potential energy of different conformations should have been the same. But in actual practice, the potential energy of the molecule changes somewhat with the rotation around C—C single bond. Thus the potential energy of ethane molecule is minimum for staggered conformation and maximum for eclipsed conformation. The difference between the two being  $12.6 \text{ kJ mol}^{-1}$ . In other words, *staggered conformation is the most stable conformation of ethane while eclipsed conformation is the least stable* (Fig. 10.11).

The small energy difference between different conformations is due to the repulsive interactions between the electron clouds of the C—H bonds attached to the central C—C bond. In the staggered conformation of ethane, the electron clouds of these carbon hydrogen bonds are as far apart as possible. But in the eclipsed conformation, the three C—H bonds of one carbon are closest to the three C—H bonds of the other carbon. The repulsive interactions between the electron clouds in this position increase the energy of the molecule and thus decrease its stability.

But the energy difference is not large enough to prevent rotation. Even at ordinary temperature the molecules possess sufficient thermal or kinetic energy to overcome the energy barrier through effective collisions and thus conformations keep on changing from one form to the other. As such it is not possible to separate the different conformations of ethane.

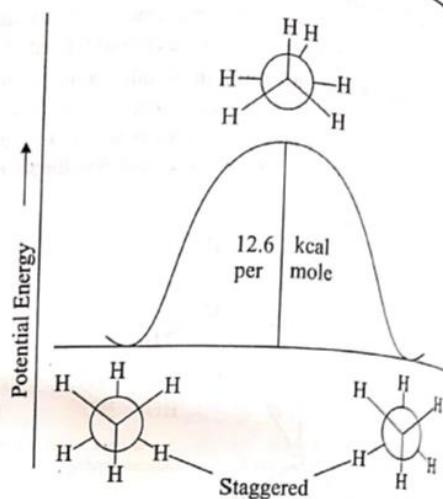


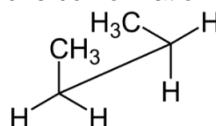
Fig. 10.11 Relative stabilities of conformations of Ethane

**Sawhorse Projection Formula:** Sawhorse projection formulas are used to denote two principal stereocentres. It is a view of a molecule down a particular carbon-carbon bond, with the groups connected to both the front and back carbons are drawn using sticks at  $120^\circ$  angles. Sawhorse Projections can also be drawn so that the groups on the front carbon are staggered ( $60^\circ$  apart) or eclipsed (directly overlapping) with the groups on the back carbon. The overall representation is given below.

A sawhorse projection is similar to a Newman projection, but it shows the carbon-carbon bond that is hidden in a Newman projection.

Just as with Newman projections, you can draw sawhorse projections in eclipsed and staggered conformations.

Below is a sawhorse projection of the gauche conformation of butane.

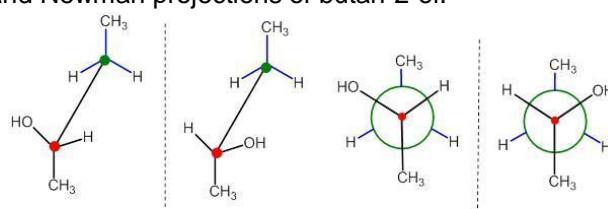


They are called sawhorse projections because the eclipsed conformation looks like a carpenter's sawhorse.



Sawhorse projections are useful for determining if two molecules are enantiomers or diastereomers. They make it easier to see if the structures are mirror images or superimposable.

Here are the sawhorse and Newman projections of butan-2-ol.



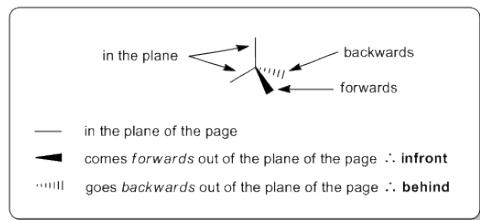
Sawhorse and Newman representations for the 2 enantiomers of 2-Butanol

**Flying Wedge Formula:** A wedge and dash projection is a drawing, a means of representing a molecule in which three types of lines are used in order to represent the three-dimensional structure:

- Solid lines to represent bonds that are in the plane of the paper
- Dashed lines to represent bonds that extend away from the viewer
- Wedge-shaped lines to represent bonds oriented facing the viewer

Although there is no hard-and-fast rule for drawing a wedge and dash structure, most people find it easiest to visualize the three-dimensional shape of a molecule if the pair of bonds in the same plane as the paper is drawn next to each other, and the bonds in front of and behind the plane are also drawn next to each other (as in the example shown).

Although the wedge-and-dash is the most common method of representing molecules in 3D, there are other diagrams you may encounter, including the sawhorse diagram and Newman projections.



## Interconversion of Fischer Projection Formula into Sawhorse Projection and vice-versa:

In this topic, we will be discussing the Interconversions of Fischer Projection Formula into Sawhorse Projection form. Then we will be talking the conversion of Sawhorse Projection into Fischer form.

### (i) Fischer Projection to Sawhorse Projection:

Fischer projection of a compound can be converted into Sawhorse projection; first in the eclipsed form (in Fischer projection the groups on neighbouring carbons are considered to be eclipsing each other), by holding the model in horizontal plane in such a way that the groups on the vertical line point above, and the last numbered chiral carbon faces the viewer. Then, one of the two carbons is rotated by an angle of  $180^\circ$  to get the staggered form (more stable or relaxed form).

For example, Fischer projection of an optically active tartaric acid is converted into staggered Sawhorse projection as shown.

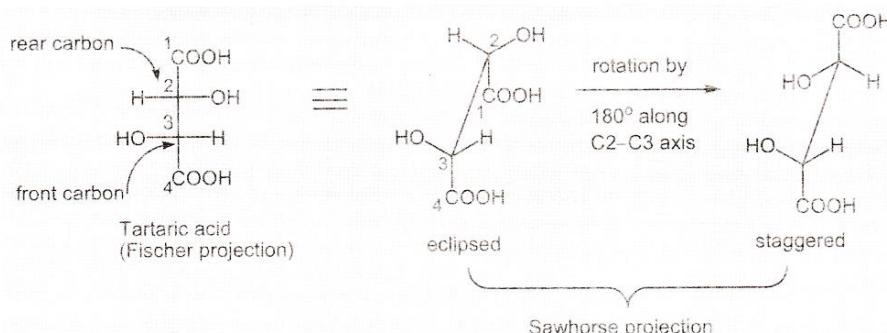


Fig. 2.5: Conversion of Fischer projection into Sawhorse projection

### (ii) Sawhorse Projection to Fischer Projection:

First, the staggered Sawhorse projection is converted to an eclipsed projection. It is then held in the vertical plane in such a manner that the two groups pointing upwards are away from the viewer, i.e. both these groups are shown on the vertical line. Such a conversion for 2,3-dibromobutane is shown.

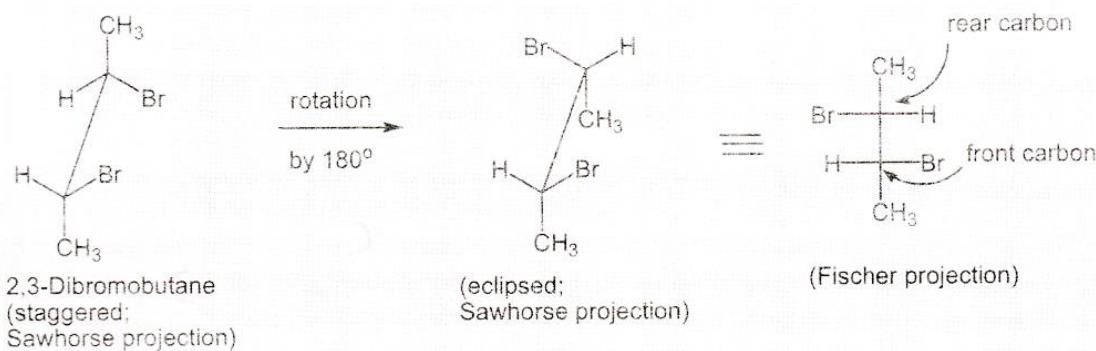


Fig. 2.6: Conversion of Sawhorse projection into Fischer projection

### Interconversion of Sawhorse Projection Formula to Fischer Projection via Newman Projection and vice-versa:

In this topic, we will be discussing the Interconversions of Sawhorse Projection Formula into Newman Projection form followed by Fischer form. Then we will be talking the conversion of Fischer Projection into Newman form followed by Sawhorse Projection.

#### (i) Sawhorse Projection to Newman Projection And then Fischer Projection:

Conversion of Sawhorse projection to Newman projection is quite easy. The molecule is viewed from front carbon (the central C-C bond being invisible) to get the staggered Newman projection. The rear carbon is rotated by  $180^\circ$  to get eclipsed Newman projection. Then, the molecule is held in the vertical plane, i.e. central bond is visible in the vertical plane in such a manner that front carbon is the lowest carbon.

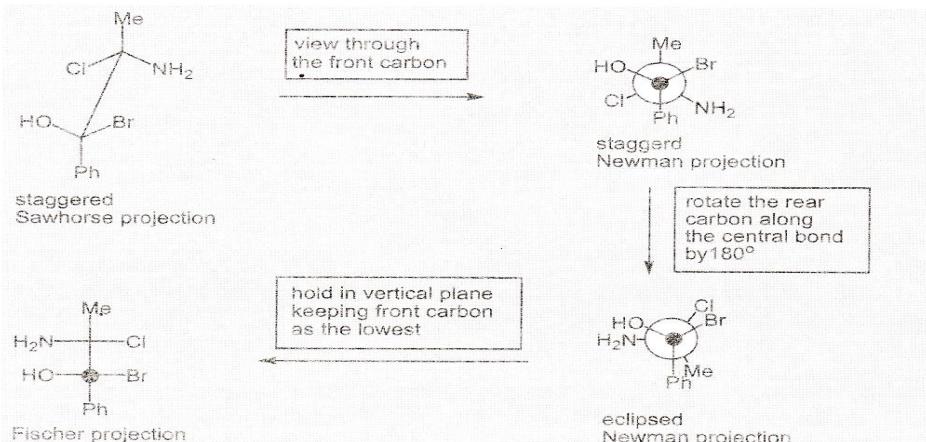


Fig. 2.7: Conversion of Sawhorse projection into Fischer projection via Newman projection

#### (ii) Fischer Projection to Newman Projection and then Sawhorse Projection:

The molecule is viewed through the lowest chiral carbon, which becomes the front carbon, and thus eclipsed Newman projection is drawn. It is then converted into staggered conformation. Finally, the molecule is viewed through the bond connecting the front carbon with rear carbon. Such a conversion of D-erythrose is illustrated in the following scheme.

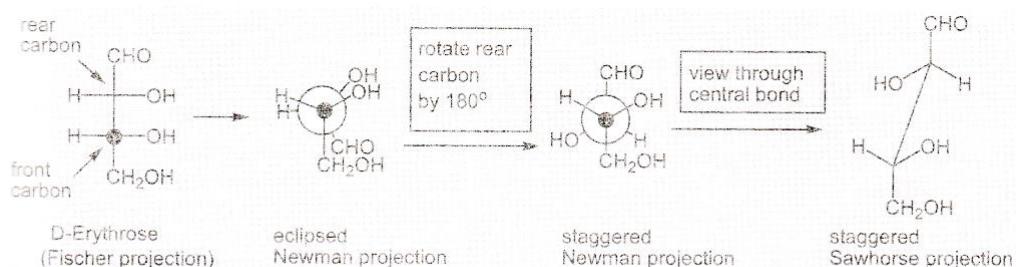


Fig. 2.8: Conversion of Fischer projection into Sawhorse projection via Newman projection

Interconversion of Fischer Projection Formula into Flying Wedge Projection and vice-versa:

In this topic, we will be discussing the Interconversions of Fischer Projection Formula into Flying Wedge Projection form. Then we will be talking the conversion of Flying Wedge Projection into Fischer form.

### (i) Fischer Projection to Flying Wedge Projection:

The vertical bonds in the Fischer projection are drawn in the plane of the paper using simple lines(—). Consequently, horizontal bonds will project above and below the plane ('a' and 'b' in the fig.). Conversion of Fischer projection of one of the enantiomers of  $\alpha$ -bromopropanoic acid into five flying wedge formulae (without changing the configuration) is illustrated in the fig.

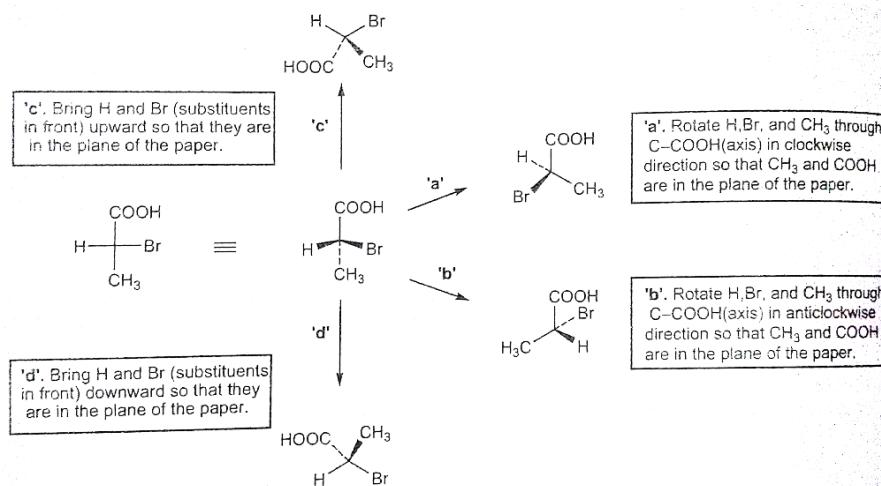
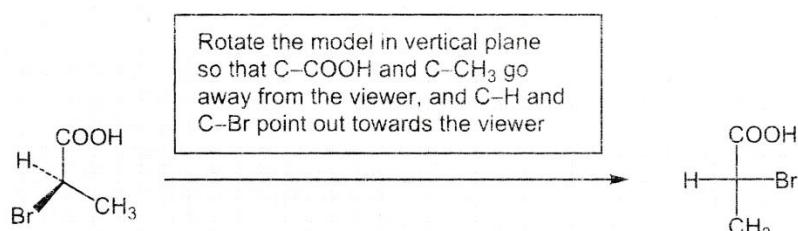


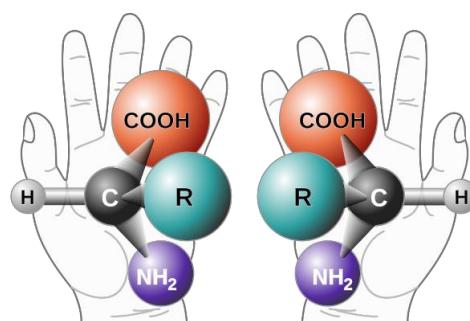
Fig. 2.9: Conversion of Fischer projection into flying wedge projections

### (ii) Flying Wedge Projection to Fischer Projection:

The molecule is rotated (in the vertical plane) in such a way that the bonds shown in the plane of the paper go away from the viewer, and are vertical.



In chemistry, a molecule or ion is called chiral if it cannot be superposed on its mirror image by any combination of rotations and translations. This geometric property is called chirality. The terms are derived from Ancient Greek  $\chi\epsilon\pi$  (cheir), meaning "hand"; which is the canonical example of an object with this property.



Chirality is based on molecular symmetry. Specifically, a chiral compound can contain no improper axis of rotation ( $S_n$ ), which includes planes of symmetry and inversion center. Chiral molecules are always dissymmetric (lacking  $S_n$ ) but not always asymmetric (lacking all symmetry elements except the trivial identity). Asymmetric molecules are always chiral.

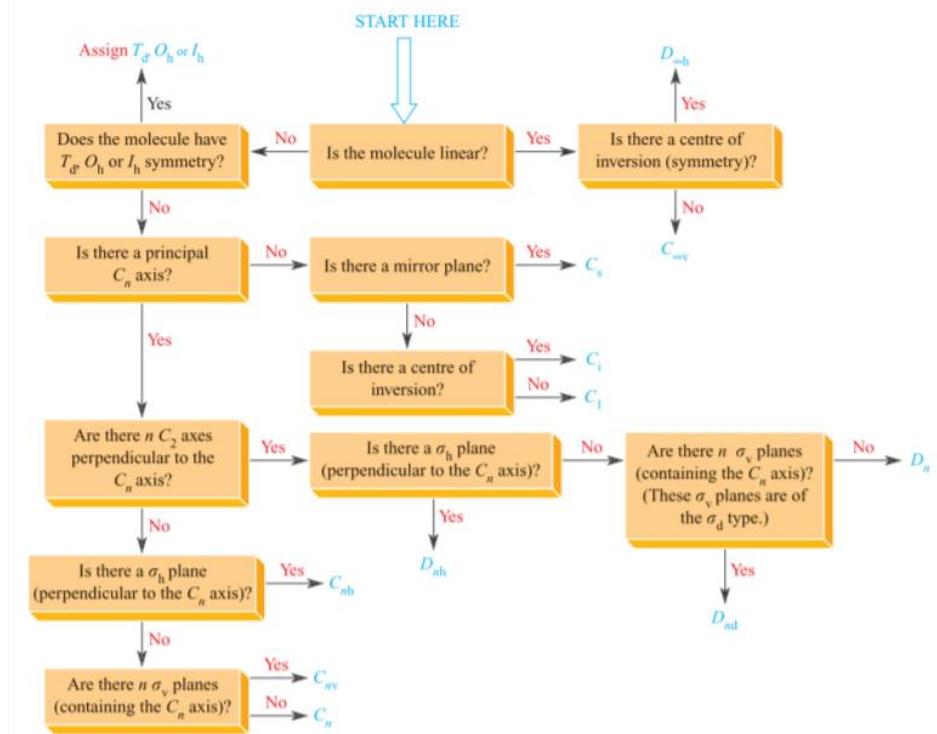
An object is said to be chiral when it is not superimposable on its mirror image. 'Chirality' is derived from the Greek word for hand. A chiral molecule is distinguishable from its mirror image just like the left hand is distinguishable from the right hand. The two isomers related this way are called enantiomers.

Molecules which do not possess any symmetry elements other than the C1 axis are said to be asymmetric. Molecules which have one or more proper rotation axes ( $C_n$ ,  $n > 1$ ), but no improper rotation axes ( $S_n$ ) are said to be dissymmetric. All asymmetric and dissymmetric molecules will be chiral. In other words, the absence of  $S_n$  is the necessary and sufficient condition for chirality. (Note that  $S_1$  is the same as a mirror plane, and  $S_2$  is the same as the inversion center.) How do you understand this requirement?

Chirality arises in organic chemistry mainly through asymmetric centers. There are also many examples of compounds which do not belong to this category.

A symmetry element is an imaginary geometrical construct about which a symmetry operation is performed. In other words, symmetry elements are a point, line or plane about which a symmetry operation is carried out.

A symmetry operation is an operation performed on an object which leaves it in a configuration that is indistinguishable from, and superimposable on, the original configuration. In other words, a symmetry operation is a movement of an object about a symmetry element such that the object's orientation and position before and after the operation are indistinguishable.



**Centre of Chirality** - A molecule containing a carbon with four different groups results in a chiral molecule, and the carbon is referred to as a chiral, or asymmetric, or stereogenic centre.

### Symmetry Designations

Term	Alternating axis	Simple axis	Optical activity
Symmetric	Present <sup>a</sup>	May or may not be present	Inactive
Dissymmetric	Absent	May or may not be present	Usually active
Asymmetric	Absent	Absent	Usually active

#### 10.4.1 Optical Isomerism

It has been observed that certain compounds resemble one another in their chemical properties as well as in most of their physical properties but they differ in their behaviour towards the action of plane polarised light. Such compounds are called *optically active* and this phenomenon is called *optical activity*. Compounds, which rotate the plane polarised light towards the right are said to be *dextro-rotatory* and are represented as *d* or  $(+)$  form, whereas those which rotate it to the left are called *laevo-rotatory* represented as *l* or  $(-)$  form. These isomers are said to show optical isomerism. Before proceeding further, it is important to understand the terms **polarised light** and **optical activity**.

**Polarised Light:** An ordinary ray of light consists of electromagnetic waves and its vibrations taking place in all planes perpendicular to the direction in which it travels. *Monochromatic light*, on the other hand, consists of waves of one wave length. Even such a ray has its vibrations in all the planes.

When if a ray of monochromatic light is passed through a Nicol prism, the wave motion of emergent light is restricted to only one plane. Such a beam of light which has vibration only in one plane is called plane polarized light or unidirectional light. The Nicol prism used to obtain plane polarized light is called a *polarizer* (Fig. 10.1).

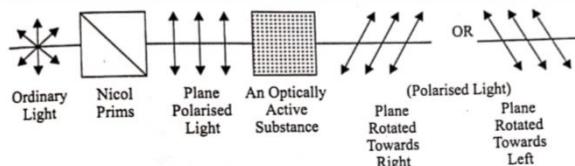


Fig. 10.1 Polarization of light

**Optical Activity:** When the plane polarized light is allowed to fall on another Nicol prism with its axis parallel to the first Nicol prism, the plane polarized light passes through it without undergoing any deviation. The first Nicol prism is known as *polarizer* and the second Nicol prism is known as *analyzer*. If the axis of analyzer is kept at right angle to polarizer complete darkness appears due to total internal reflection (Fig. 10.2).

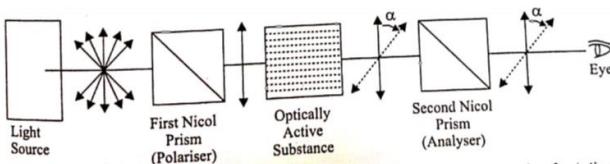


Fig. 10.2 Representation of polarimeter (the dotted lines indicate the angle of rotation)

The arrangement of polarizer and analyzer with their axis perpendicular to each other is used to study the behaviour of solutions of organic compound towards plane polarized light. For this purpose a polarimeter tube containing solution of organic compound is placed between the two Nicol prisms. If some light appears, it indicates that organic compound has rotated plane polarized light through a certain angle. Such compounds which can rotate the plane polarized light through a certain angle are known as *optically active compounds*. The property by virtue of which the organic compounds can rotate the plane polarized light is known as *optical activity*.

The angle through which plane polarized light is rotated by an optically active compound is known as angle of rotation. It can be represented by alpha ( $\alpha$ ) and it can be determined with the help of an instrument called Polarimeter.

The angle of rotation depends upon the following factors:

- |  |                               |
|--|-------------------------------|
| (i) Nature of the compound                                       | (ii) Nature of Solvent        |
| (iii) Concentration of solution                                  | (iv) Wavelength of light used |
| (v) Length of the solution column through which the light passes |                               |
| (vi) Temperature   |                               |

The rotatory power of a given solution is usually expressed as *specific rotation*, which can be defined as the angle of rotation ( $\alpha$ ) produced by one decimetre length of solution having one gram of the substance per millilitre. The measurement of rotation is carried out at temperature T using sodium light (the D lines).

● **Specific rotation:**

The specific rotation symbolised as  $[\alpha]$ , may be defined as the rotation in degrees brought about by a pure transparent liquid or a solution containing 1g of an optically active substance per mL of solution, placed in a 1 decimetre polarimeter tube.

Specific rotation is related to observed rotation by the following equation.

$$[\alpha]_t^{\circ}C = \frac{100 \times \alpha}{l \times c} \quad \text{----- equation 3.1}$$

$$\text{Specific rotation} = \frac{100 \times \text{observed angle of rotation } \theta}{\text{Length of decimeters} \times \left[ \begin{array}{l} \text{grams of substances present} \\ \text{in 100 mL of solution} \end{array} \right]}$$

$$[\alpha]_D = \frac{100 \times \theta}{l \times C}$$

where,  $\lambda$  = wave length of polarised light (generally yellow line of sodium vapour light ( $\lambda = 5893 \text{ nm}$  is used))

$t^{\circ}C$  = experimental temperature,

$\alpha$  = observed angle of rotation in degrees

$l$  = length of solution in dm = length of the polarimeter tube in dm

$c$  = concentration of the solution g/100 mL

When pure transparent liquid (neat liquid) is taken,

the expression used is,

$$[\alpha]_t^{\circ}C = \frac{\alpha}{l \times d} \quad \text{--- eq. 3.2}$$

where,  $d$  = density of the liquid in g/mL and other symbols have the same meaning as before. Optical activity is not a colligative property.

Since optical property of stereoisomers is associated with chirality, measurement of optical property is called *Chiroptical method*. Other Chiroptical methods are ORD (optical rotations dispersion) and CD (circular dichroism). These are discussed in short later in this Chapter.

● **Molecular rotation or Molar rotation:**

$$[\Phi]_t^{\circ}C = \frac{[\alpha] \times M}{100} \quad \text{----- equation 3.3}$$

Where,  $[\Phi]$  = molar rotation

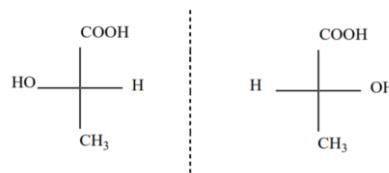
$[\alpha]$  = specific rotation

$M$  = molar mass of the substance

For a substance of molecular weight 100, molar and specific rotations are the same.

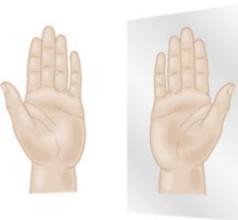
The sign and magnitude of  $[\alpha]$  are functions of variables, ( $t^{\circ}$ ,  $l$ ,  $c$ ) as well as the nature of solvent and temperature of measurement. Normally, temperature and wavelength ( $\lambda$ ) of the plane polarised light used are shown in the symbol, i.e.,  $[\alpha]_t^{\circ}C$ . If the solvent is not water then it must be mentioned. Observed rotation has the unit *degree* but the unit of specific rotation is *degree cm<sup>2</sup>g<sup>-1</sup>* but this is not usually shown. Expressing specific rotation in degree only is incorrect, although it is done conventionally. Under a given set of conditions the specific rotation of any substance is constant and the value may often be used as criterion for identification of optically active compounds.

**Enantiomers:** Stereoisomers which are non-superimposable mirror images of each other are called enantiomers. Chirality is necessary and sufficient condition for existence of enantiomers. These always exist as discrete pairs.



Two isomers of Lactic acid

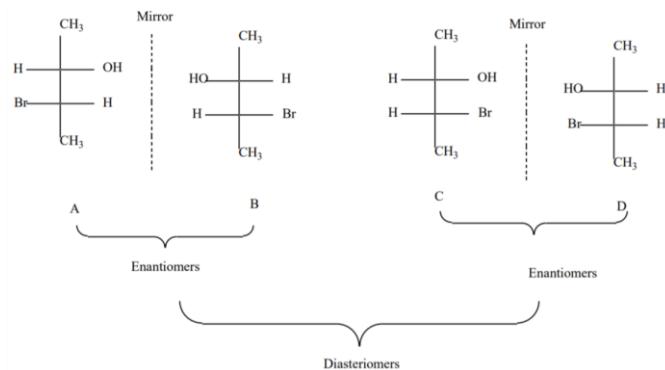
Enantiomers are related to each other much like a right hand is related to a left hand. Enantiomers have identical physical properties, i.e., bp, mp, etc. Chirality (from the Greek word for hand). Enantiomers are said to be chiral.



Left hand

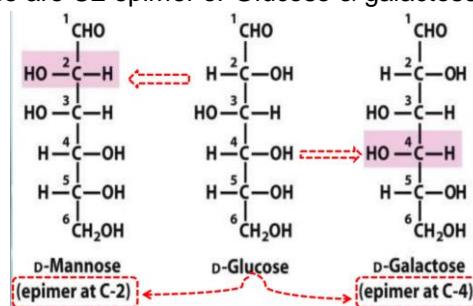
Right hand

**Diastereomers:** Stereoisomers that are not mirror images of each other are called diastereomers.



**Epimers:** If two stereoisomers differ in configuration around only one asymmetric carbon atom they are defined as epimers of each other.

Examples: Glucose & mannose are C2 epimer or Glucose & galactose are C4 epimer.



In short, diastereomers that differ in configuration at only one of the several stereogenic centers are known as epimers.

Enantiomeric molecules are always non-superimposable mirror images of each other. The non-superimposability of mirror images invariably arises due to chiral nature of the molecules. A molecule is termed as chiral if it has no plane of symmetry and is, therefore, non-superimposable on its mirror image. The chirality (i.e., the property of existing as non-superimposable mirror images) is the fundamental and only condition of enantiomerism.

#### Characteristics of Enantiomers:

- They have identical physical properties such as melting points, boiling points, densities, solubilities, refractive indices. The only difference lies in the direction of rotation of plane polarised light, although the magnitude of specific rotation is the same.
- They have identical chemical properties except in reactions with other optically active compounds. For example, the ordinary chemical reactions of (+) lactic acid are exactly like those of (-) lactic acid. There may be a difference, however, in the rates of reactions at which two enantiomers react with some other optically active compound. For instance, the rate of esterification of (+) lactic acid with (+) sec. butyl alcohol [ $\text{CH}_3\text{CH}_2\text{CH}(\text{OH})\text{CH}_3$ ] would be different from the rate of esterification of (-) lactic acid with the same alcohol.
- They have different biological properties. In contrast to physical and usual chemical properties, enantiomers are quite different in their biological properties. For example, (+) sugar plays an important role in animal metabolism whereas (-) sugar is not metabolized at all. Similarly, (+) tartaric acid is readily consumed by the mould *penicillium glaucum* while (-) tartaric acid is not.
- When equal quantities of enantiomers are mixed together it results in the formation of an optically inactive form called racemic modification or racemic mixture or racemate. The racemic modification is distinguished by using the prefix  $(\pm)$  before the name of the compound. For example, if equal quantities of (+) lactic acid and (-) lactic acid are mixed with each other, we get racemic or  $(\pm)$  lactic acid which is optically inactive.

Diastereomers are stereoisomers of a substance which are neither mirror images of each other nor superimposable.

#### Characteristics of Diastereomers:

- They show similar, but non identical, chemical properties. In the reactions of two diastereomers with a given reagent, the rates of reactions are generally different.
- They have different physical properties, such as melting points, boiling points, densities, solubilities, refractive indices. Even specific rotations are different: this does not, of course, apply

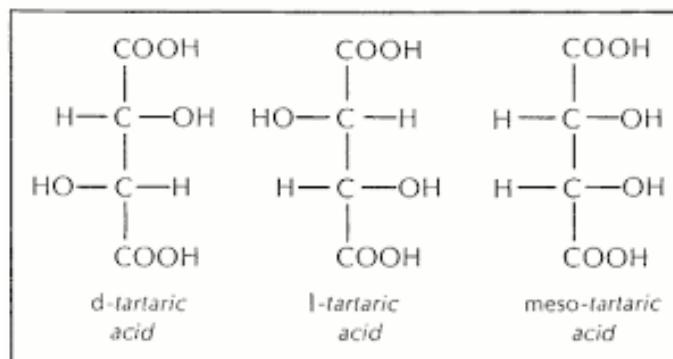
to diastereomers which are geometrical isomers since such diastereomers are not optically active.

- (iii) On account of differences in physical properties, they can be rather easily separated through fractional crystallization, fractional distillation, chromatography, etc.

**Internal Compensation:** it has been stated that meso compounds are optically inactive because their molecules are not chiral even, they contain two (or more) chiral centers. For example, it is clear from the structural formula of meso-tartaric acid that the top half of the structure is the mirror image of the bottom half. As such the optical activity due to one chiral center is counter balanced by the optical activity due to one chiral center is counter balanced by the optical activity due to the other and the compound is optically inactive. The compensation of optical activity due to one half of a molecule by the other half is known as internal compensation and the molecule is said to be internally compensated. An internally compensated molecule is permanently inactive.

**External Compensation:** in a racemic mixture equimolar mixture of two enantiomers, say (+) and (-) lactic acids are present. The molecules of one enantiomer would be present in a quantity equal to those of other enantiomer. This means that rotation of plane polarized light by each isomer would be equal in magnitude and opposite in sign i.e., direction. Therefore, extra cancellation of all rotation would take place and the equimolar mixture would be optically inactive. The cancellation of rotation of one enantiomer by the other in equimolar mixture of the two enantiomers is known as external compensation and the racemic mixture is said to be externally compensated.

It may be pointed out that if the two enantiomers are not mixed in equimolar quantities, the rotation caused by one enantiomer is not exactly cancelled by the other. As such this mixture still exhibits some optically activity. The direction of rotation corresponds to that of enantiomer present in larger quantity but the specific rotation is lesser. In this way partial compensation takes place and the mixture formed is said to be partially racemized.



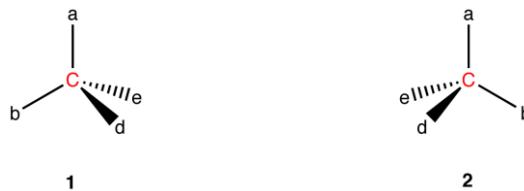
### Number of Stereoisomerism: Systems Involving 1/2/3-Chiral Centre(S) (AA, AB, ABA and ABC Types).

	Nature of molecule	Optically active isomers	Meso isomers or Optically inactive isomers
1. AB or ABC type	Contains 'n' different chiral centers and the molecule cannot be divided into two equal and similar halves in any possible conformation.	$2^n$	None
2. AA type	Contains an even number 'n' no of chiral centers, but the molecule can be divided into two mirror image halves in one of the possible conformations.	$2^{(n-1)}$	$2^{(n-2)/2}$
3. AAA or ABA type	Contains an odd number 'n' no of chiral centers, and the molecule can be divided into two mirror image halves by a plane passing through the central chiral center in one of the possible conformations.	$2^{(n-1)} - 2^{(n-1)/2}$	$2^{(n-1)/2}$

The **relative configuration** of a chiral molecule is its configuration in relation to another chiral molecule (often through chemical interconversion). We can use the

relative configuration to determine whether molecules are enantiomers, diastereomers, or the same molecule. On the other hand, the absolute conformation of a chiral molecule describes the exact spatial arrangement of these atoms or groups, independent of other molecules. Relative configuration refers to D/L, or more elaborately, assigning configuration in reference to a standard molecule (glyceraldehyde, most commonly).

The **absolute configuration** at a chiral centre in a molecule is a time-independent and unambiguous symbolic description of the spatial arrangement of ligands (groups) bonded to the chiral center.



The chiral centres in 1 and 2 bear the same ligands: a, b, d and e. However, 1 and 2 are not superimposable on each other, meaning that the arrangement of ligands around the chiral centre in 1 and in 2 is different. 1 and 2 are mirror images of each other, meaning that the arrangement of ligands around the chiral centre in 1 is the exact opposite of that in 2. Chiral centres in 1 and 2 are said to have opposite absolute configurations.

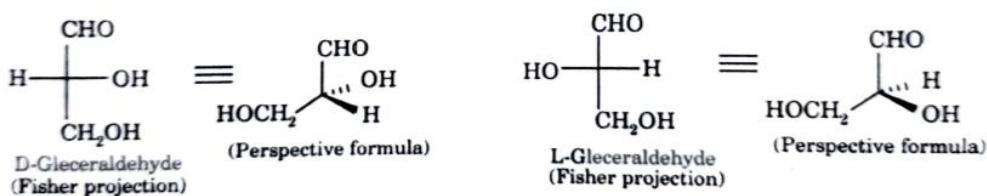
According to R/S convention, if the absolute configuration at the chiral centre in 1 is R, that at the chiral centre in 2 is S or vice versa.

• **D, L - system of designation:**

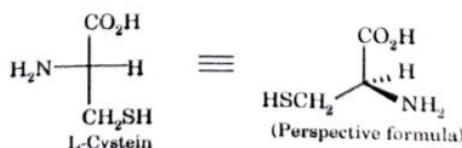
The relationship between the configurations of two chiral molecules is the basis of this system. When two such molecules can be chemically interconverted (at least in principle) without breaking any bonds to the chiral centre, they are said to have the same relative configuration independent of the direction of rotation of the plane-polarised light.

The simplest and oldest system of nomenclature of optical isomers having chiral centres is D,L-system, introduced by German chemist Emil Fischer, who worked extensively with carbohydrates.

The compound glyceraldehyde, supposed to be the smallest possible carbohydrate molecule, has the constitutional formula  $\text{HOCH}_2\text{CH}(\text{OH})\text{CHO}$ . This molecule was chosen by Fischer as the standard for defining configurations of molecule with chiral centres. Glyceraldehyde with one chiral centre has a pair of enantiomers. The enantiomer that rotates plane polarised light clockwise (+) was arbitrarily labelled D-enantiomer, and the other enantiomer became L. Fisher drew the projection formulas of D- and L-Glyceraldehyde as given below.



Any other molecule containing a single chiral centre was to be assigned as D or L by imagining a resemblance between the ligands on its chiral centre and those in glyceraldehydes, i.e. the enantiomer having the "same" groups in the same place, as D-glyceraldehyde, becomes 'D' and its mirror image is 'L'. Thus, for example, the naturally occurring form of the amino acid cysteine was labelled L-enantiomer.



### 3.14. Absolute configuration: *R, S* - system of nomenclature :

D, L-system of assigning configurational nomenclature is based on some reference compounds but due to its shortcomings, another system, which is more generalised, was developed by Cahn, Ingold and Prelog (CIP) to designate the configurations of stereoisomers having chiral centres. It is often called 'chirality rule'. The method has also been extended to compounds having chiral axes and chiral planes. This system is commonly called *R, S*-system and since this type of specifying configurations is independent of any reference compound, the system is often termed 'Absolute configuration' assignment.

Cahn-Ingold-Prelog system is also extended to specify achiral planar diastereoisomers. This has been discussed separately in another Chapter.

#### • Method of assigning *R, S* - notations:

The CIP system is based on rules and a strict hierarchical order of decisions until a single stereodescriptor can be used to describe a given configuration. For tetrahedral stereogenic atoms having four different atoms or groups, the chirality rule is based on the arrangement of these atoms or groups, including chain and rings, in an order of precedence, often referred to as an order of priority.

For assigning *R, S*-nomenclature to any chiral centre of a molecule, certain procedures are to be followed. They are:

1. Identify the number of chiral centres in the molecule.

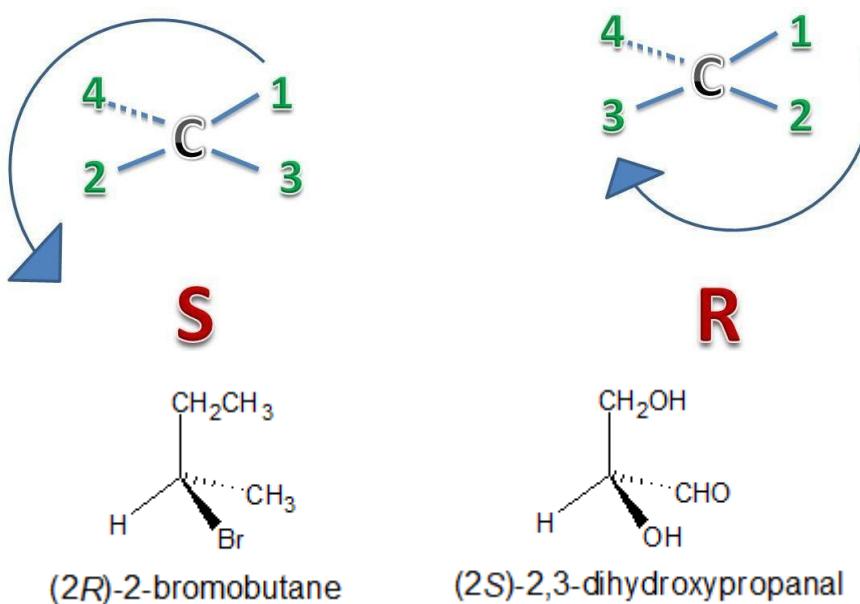
2. Identify the four different atoms or groups attached to each of these chiral centres. Assign to each of the substituents on a chiral centre a priority symbol 1, 2, 3, 4 or a, b, c, d based on sequence rules (discussed latter), such that decreasing order of priority is  $1 > 2 > 3 > 4$  or  $a > b > c > d$ , where ' $>$ ' denotes 'has priority over'. The name 'ligand' should not be used for atoms or groups in case of organic molecules.

3. The molecule is then viewed from the position remotest from the lowest priority group and a hypothetical path is drawn moving from 1 to 2 and then to 3 ( $1 \rightarrow 2 \rightarrow 3$ ) or  $a \rightarrow b \rightarrow c$ .

If this path traces a clockwise path, then the stereocentre is said to have *R* configuration (*R* from *rectus*, *Latin* for right). If the said path traces a counterclockwise path, then the stereocentre is said to have *S* configuration (*S* from *Sinister*, *Latin* for left). This has been illustrated in the diagram in the next page.

The designation (*R*)- or (*S*)- is written in italics within parentheses followed by a hyphen before the name of the compound, preceded when necessary by the appropriate locants for the chiral centres. The method is also extended to torsional stereoisomers and allenes having chiral axis. This has been discussed in the appropriate part of this book.

It is to be noted that when a molecule contains a single chiral centre then a pair of enantiomers is possible. One of them is *R*-isomer and its mirror image is *S*-isomer. For example, in case of lactic acid,  $\text{CH}_3\text{CHOHCOOH}$ , we can name them as (*R*)-lactic acid and (*S*)-lactic acid. But when there is more than one chiral centre then each of them should be assigned *R, S*-stereochemical descriptors separately. This has been discussed later.



### Sequence rules or standard subrules

- (0) Nearer end of an axis or a plane precedes the farther end (proximity rule).
- (1) Higher atomic number precedes lower, e.g., S > F > O > N > C > H.
- (2) Higher atomic mass number precedes lower, e.g., T > D > H.
- (3) Cis precedes trans; and Z precedes E.<sup>†</sup>
- (4) Like pair R,R or S,S precedes unlike pair R,S or S,R; M,M or P,P precedes M,P or P,M; R,M or S,P precedes R,P or S,M; M,R or P,S precedes M,S or P,R; and r precedes s.
- (5) R precedes S; and M precedes P.

For the majority of compounds, only subrules (1) and (2) are important; the other subrules apply only to special cases. Subrule (0) is applicable to axial and planar chirality to be discussed in Chapter 5. Subrule (1) needs further elaboration which is done in the following paragraphs:

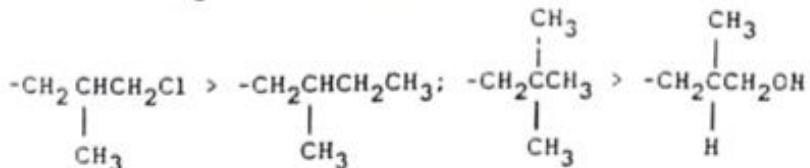
1. Atoms directly attached to the central chiral atom must be sequenced first according to subrule (1). If the priority still remains undecided for some of the ligands, one passes over to the next atom in the ligands and the exploration continues until a decision is reached on the basis of the subrules. The following examples illustrate the point :



(Decision is reached at the italicised atoms)

It may be noted that subrule (2) must not be used until subrule (1) is completely exhausted; thus  $-\text{CH}_2\text{CH}_2\text{CH}_3 > -\text{CD}_2\text{CH}_3$  because propyl > ethyl (subrule 1); but  $-\text{CH}_2\text{CD}_2\text{CH}_3 > -\text{CH}_2\text{CH}_2\text{CH}_3$  (subrule 2).

2. In case a ligand bifurcates, one must proceed along the branch providing the highest precedence until a difference is encountered. The decision must be made at the *earliest* opportunity and once made, cannot be changed from consideration of substituents farther along the chain. These points are illustrated below:



3. When the central atom is a part of a ring system, each branch is followed until a decision is reached as shown in Figure 4.7a below (see Prelog and Helmchen 1982 for complicated cases):

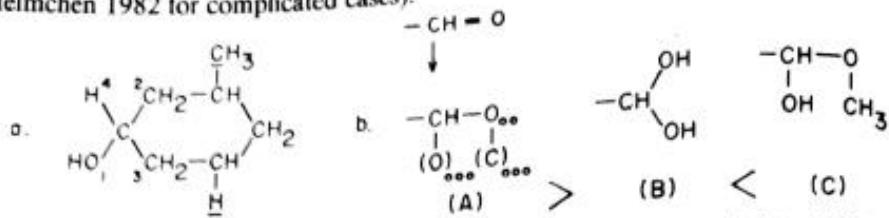


Figure 4.7 (a) Priority sequence in ring system; (b) aldehyde versus hydrated aldehyde versus hemiacetal

4. In the case of atoms with multiple linkages, the atom to which they are multiply bonded must be duplicated or triplicated as the case may be at both ends of the multiple bond. The duplicate atoms are put into parenthesis and except for hydrogen are made up (complemented) to ligancy four with phantom atoms of atomic number zero. Thus the representation of the aldehyde group,  $-\text{CHO}$  is shown (Figure 4.7b) along with its hydrated form and hemiacetal for comparison. From the structures (A), (B), and (C), it is clear that  $-\text{CHO}$  has preference over the hydrated form (B) but the hemiacetal (C) has preference over the aldehyde (A). The last point illustrates the utility of the phantom atom which has lower priority than hydrogen. In the following illustrations, (Figure 4.8) the phantom atoms are omitted.

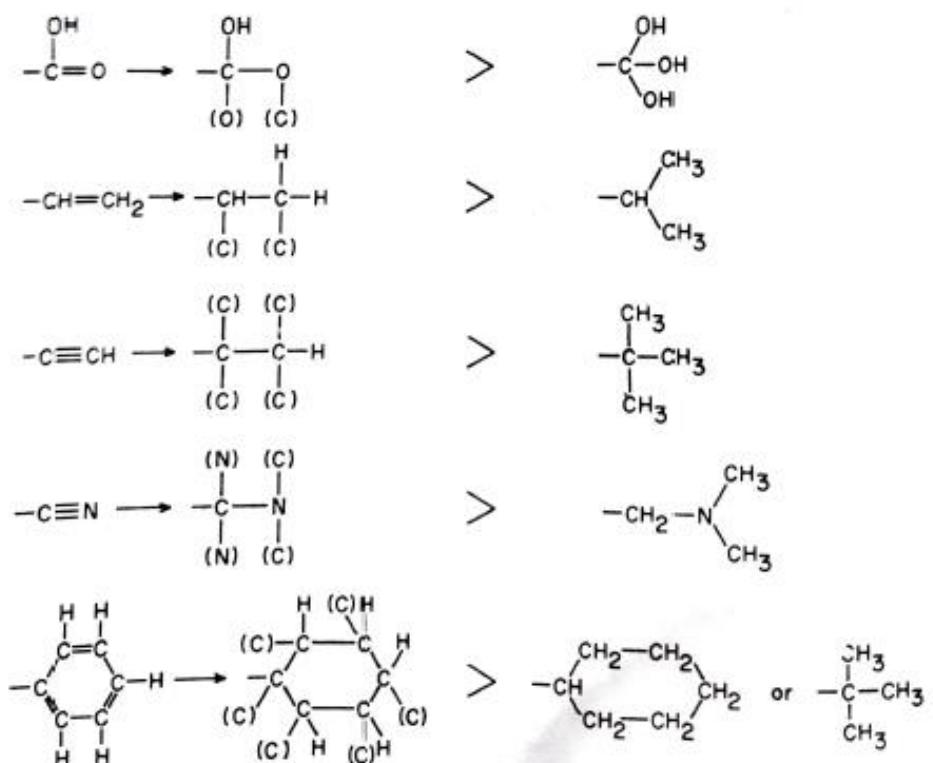
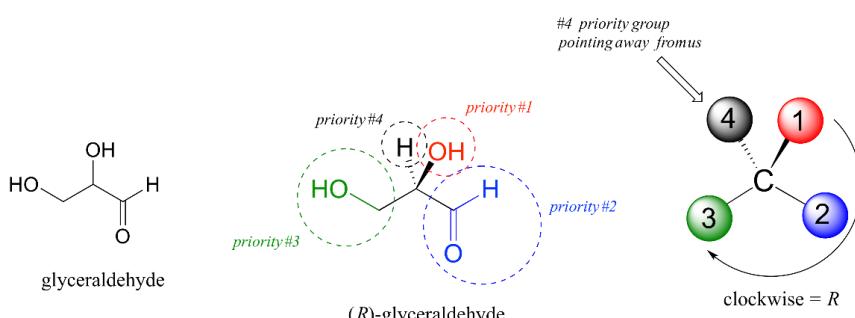


Figure 4.8 Priority sequence of some common groups

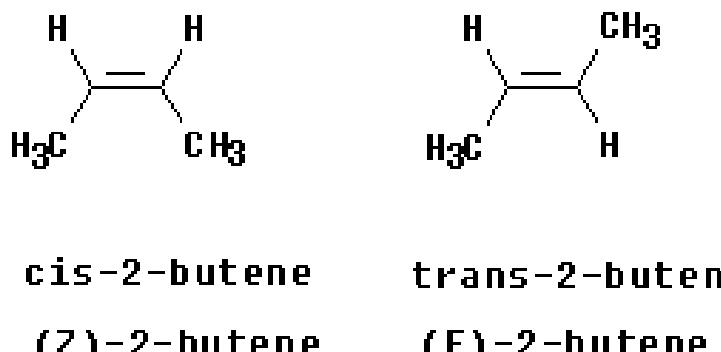
### Assigning R/S configuration to glyceraldehyde:



## E/Z nomenclature

The traditional system for naming the geometric isomers of an alkene, in which the same groups are arranged differently, is to name them as cis or trans. However, it is easy to find examples where the cis-trans system is not easily applied. IUPAC has a more complete system for naming alkene isomers. The R-S system is based on a set of "priority rules", which allow you to rank any groups. The rigorous IUPAC system for naming alkene isomers, called the E-Z system, is based on the same priority rules. The priority rules are often called the Cahn-Ingold-Prelog (CIP) rules, after the chemists who developed the system.

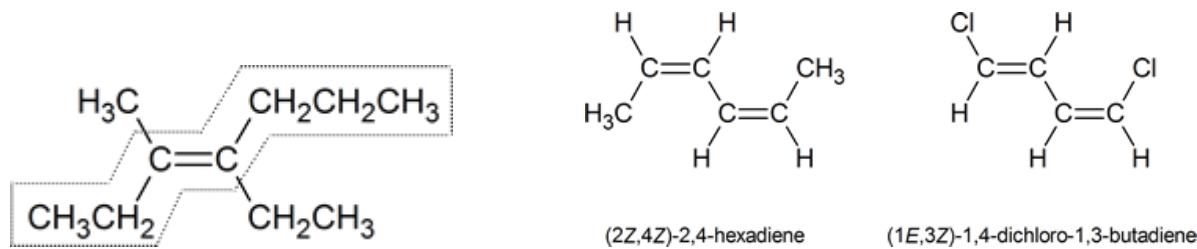
The general strategy of the E-Z system is to analyze the two groups at each end of the double bond. At each end, rank the two groups, using the CIP priority rules, discussed in Ch 15. Then, see whether the higher priority group at one end of the double bond and the higher priority group at the other end of the double bond are on the **same** side (Z, from German zusammen = together) or on **opposite** sides (E, from German entgegen = opposite) of the double bond.



Example 7.5.1: Butene

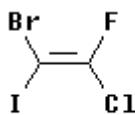
The Figure above shows the two isomers of 2-butene. You should recognize them as cis and trans. Let's analyze them to see whether they are E or Z. Start with the left-hand structure (the cis isomer). On C2 (the left end of the double bond), the two atoms attached to the double bond are C and H. By the CIP priority rules, C is higher priority than H (higher atomic number). Now look at C3 (the right end of the double bond). Similarly, the atoms are C and H, with C being higher priority. We see that the higher priority group is "down" at C2 and "down" at C3. Since the two priority groups are both on the **same** side of the double bond ("down", in this case), they are zusammen = together. Therefore, this is (Z)-2-butene.

Now look at the right-hand structure (the trans isomer). In this case, the priority group is "down" on the left end of the double bond and "up" on the right end of the double bond. Since the two priority groups are on **opposite** sides of the double bond, they are entgegen = opposite. Therefore, this is (E)-2-butene.

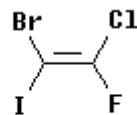


4-ethyl-3methyl-*trans*-3-heptene.

The following figure shows two isomers of an alkene with four different groups on the double bond, 1-bromo-2-chloro-2-fluoro-1-iodoethene.

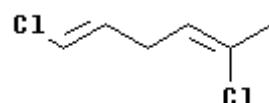
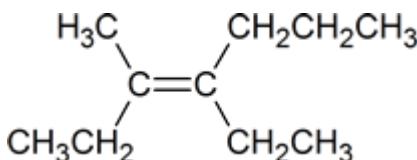
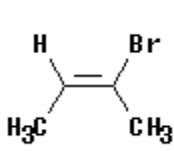


(Z)-

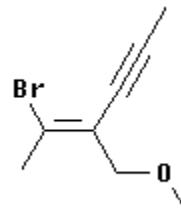
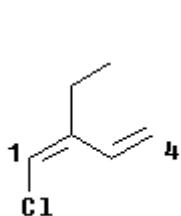


(E)-

It should be apparent that the two structures shown are distinct chemicals. However, it is impossible to name them as cis or trans. On the other hand, the E-Z system works fine... Consider the left-hand structure. On C1 (the left end of the double bond), the two atoms attached to the double bond are Br and I. By the CIP priority rules, I is higher priority than Br (higher atomic number). Now look at C2. The atoms are Cl and F, with Cl being higher priority. We see that the higher priority group is "down" at C1 and "down" at C2. Since the two priority groups are both on the **same** side of the double bond ("down", in this case), they are zusammen = together. Therefore, this is the (Z) isomer. Similarly, the right-hand structure is (E).



(1E,4Z)-1,5-dichloro-1,4-hexadiene.

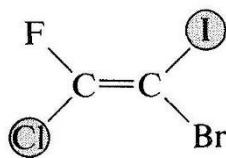


This is 1-chloro-2-ethyl-1,3-butadiene

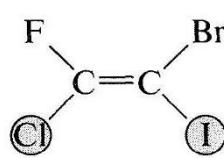
To illustrate this, consider the molecule at the left. Is the double bond here E or Z? At the left end of the double bond, Br > C. But the right end of the double bond requires a careful analysis.

At the right-hand end, the first atom attached to the double bond is a C at each position. A tie, so we look at what is attached to this first C. For the upper C, it is CCC (since the triple bond counts three times). For the lower C, it is OHH -- listed in order from high priority atom to low. OHH is higher priority than CCC, because of the first atom in the list. That is, the O of the lower group beats the C of the upper group. In other words, the O is the highest priority atom of any in this comparison; thus, the O "wins". Therefore, the high priority groups are "up" on the left end (the -Br) and "down" on the right end (the -CH<sub>2</sub>-O-CH<sub>3</sub>). This means that the isomer shown is opposite = entgegen = E. And what is the name? The "name" feature of Chem Sketch says it is (2E)-2-(1-bromoethylidene) pent-3-ynyl methyl ether.

Examination of the two configurations shows that the two priority groups- one on each end- are either on the same side of the double bond or on opposite sides:

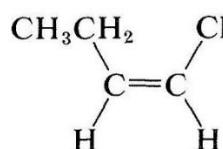


priority groups  
on opposite sides  
E configuration

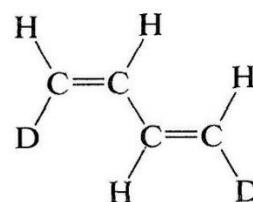


priority groups  
on same side  
Z configuration

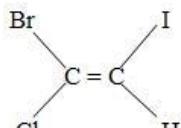
The Z isomer is designated as the isomer in which the top priority groups are on the same side (Z is taken from the German word zusammen- together). The E isomer has these groups on opposite sides (E, German for entgegen across). Two further examples show how the nomenclature is used:



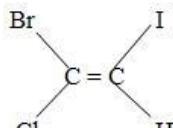
(Z)-1-chloro-1-butene



(1Z,3E)-1,3-butadiene-1,4-d<sub>2</sub>



Z form



E- form

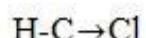
Although Cl atom present on opposite side but according to sequence rule it is Z form.

Determination of the configuration of geometrical isomers

(i) Physical methods:- Generally trans-isomer had high m.p. and low b.p. than cis isomer.

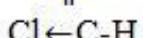
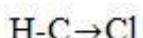
(ii) Solubility of cis isomer is more. For example, solubility of maleic acid is 3.0 g/100 mL of water at 293 K and solubility of fumaric acid is 0.7 g in 100 mL of water at 293 K

(iii) Dipole moment measurement:- the trans isomers are symmetrical and hence will have zero or low dipole moment as compared to the cis.  $\mu = 0$



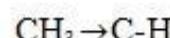
(Cis)

$$\mu = 1.85 \text{ D}$$



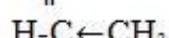
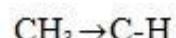
(trans)

$$\mu = 0.0 \text{ D}$$



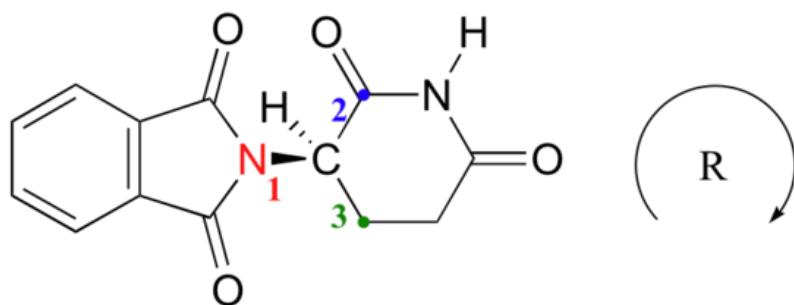
(Cis)

$$\mu = 0.4 \text{ D}$$

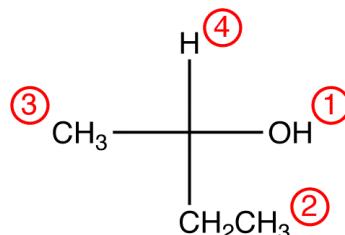
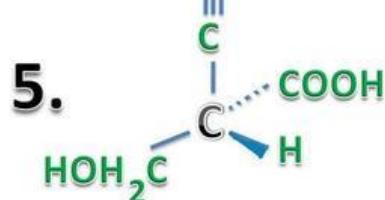
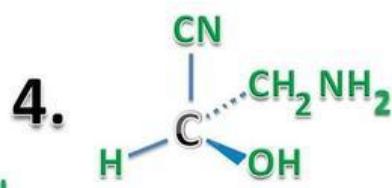
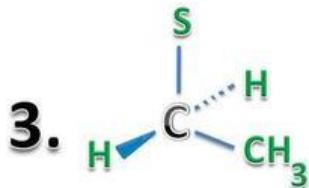
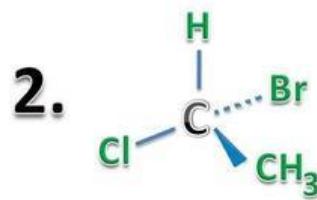
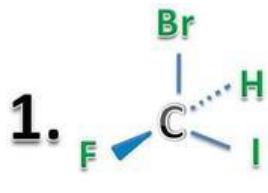


(trans)

$$\mu = 0$$



(R)-thalidomide



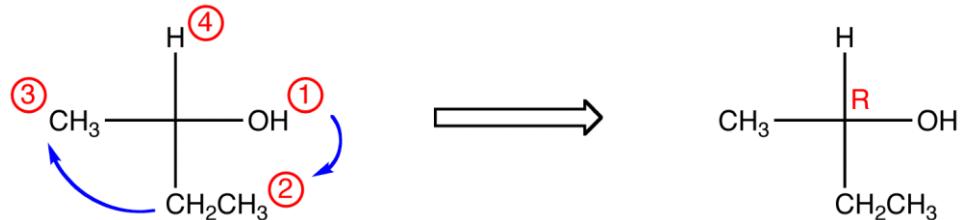
Step 2 - vertical option

If the lowest priority ligand is on a Vertical bond, then it is pointing away from the viewer.

Trace the three highest-priority ligands starting at the highest-priority ligand (① → ② → ③) in the direction that will give a Very correct answer.

direction of ① → ② → ③	absolute configuration
clockwise	R
counterclockwise	S

In the compound below, the movement is clockwise indicating an R-configuration. The complete IUPAC name for this compound is (R)-butan-2-ol.



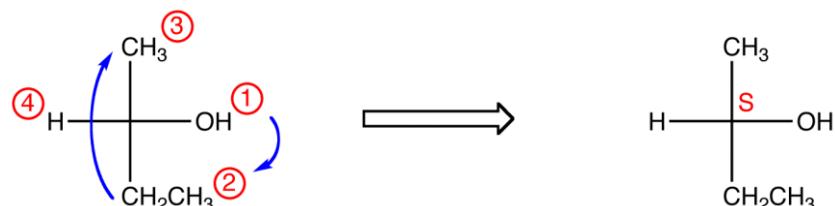
Step 2 - horizontal option

If the lowest-priority ligand is on a Horizontal bond, then it is pointing toward the viewer.

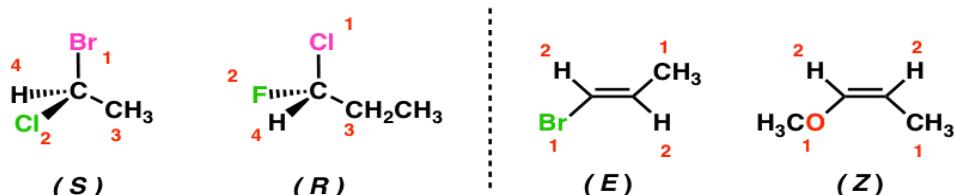
Trace the three highest-priority ligands starting at the highest-priority ligand (① → ② → ③) in the direction that will give a Horribly wrong answer. Note in the table below that the configurations are reversed from the first example.

direction of ① → ② → ③	absolute configuration
clockwise	S
counterclockwise	R

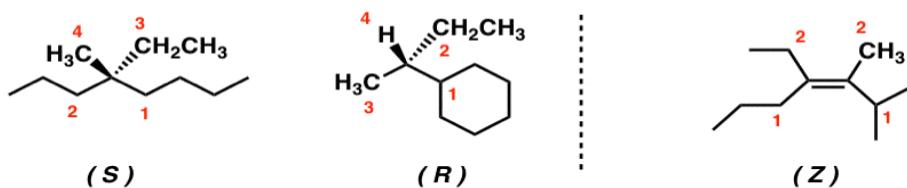
In the compound below, the movement is clockwise (R) which is Horribly wrong, so the actual configuration is S. The complete IUPAC name for this compound is (S)-butan-2-ol.



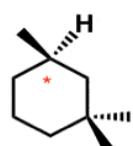
**Determining C/P priorities when different atoms are directly attached to the stereocenter is relatively straightforward**



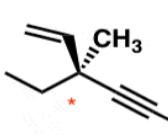
**In cases where identical atoms are attached, breaking "ties" is pretty straightforward in many cases**



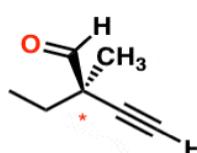
**Complications: How Do We Assign Priorities In These Situations?**



Chiral centers in rings



Molecules with multiple bonds

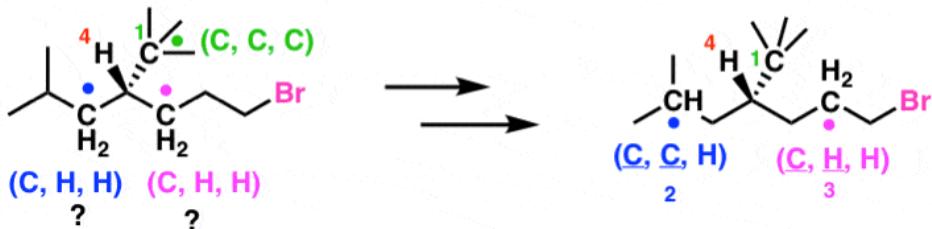


Isotopes?

## Priority is Determined At The First Point of Difference

Draw dots on all the carbons directly attached to the chiral center, and then write out the 3 atoms attached.

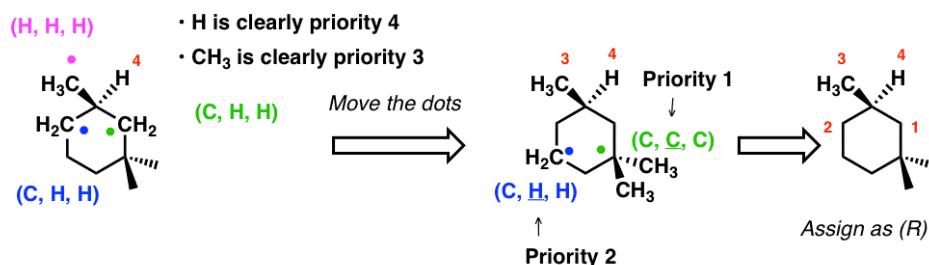
Moving the dots outward, we see that the isopropyl group has priority #2



By doing this we see that the *t*-butyl group is priority #1

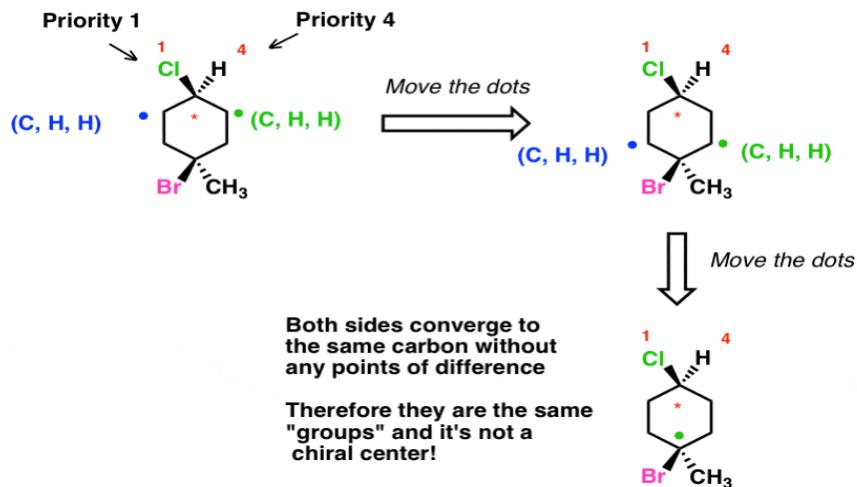
Note that the Br is too far along the chain to make a difference!

## Determining R/S in a ring

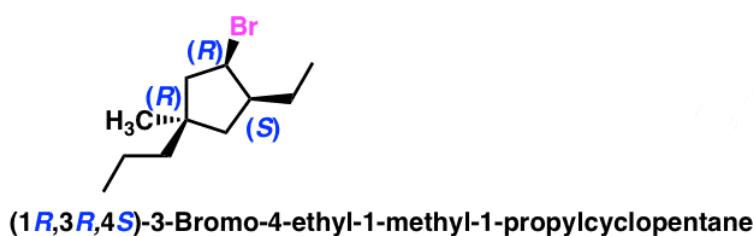


It's really no different than a chain: just keep moving the dots around the ring until a point of difference is found.

What about R/S for the starred atom ( \* ) in this case?

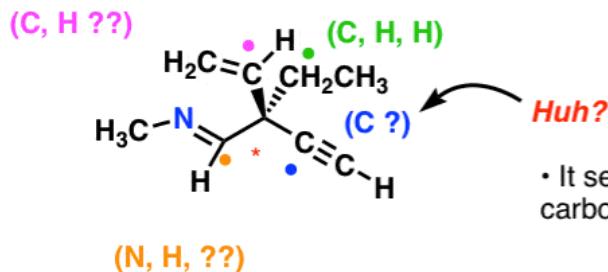


**Molecules with multiple chiral centers follow the exact same process**



## How should we deal with multiple bonds?

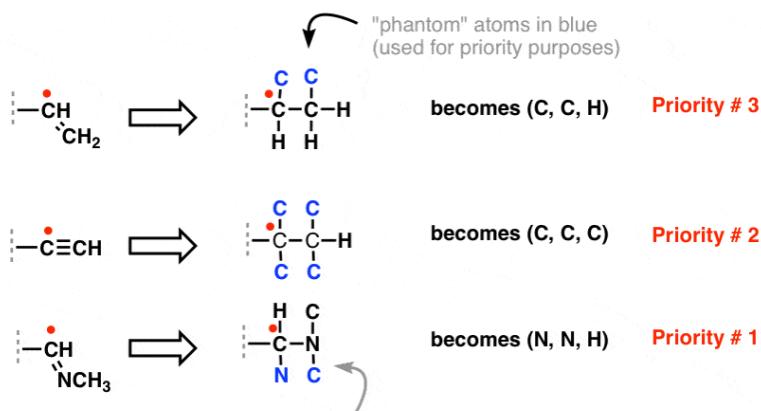
New rules appear justified - it seems weird to rank an alkyl group as "higher priority" than an alkene or alkyne



- It seems weird to treat an alkyne carbon as just "C" for priority purposes

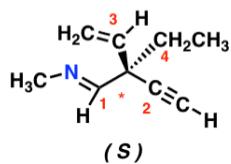
New rule: Expand out multiple bonds with "Phantom atoms"

In order to properly compare, we "expand out" all multiple bonds and treat them as single bonds attached to "phantom atoms" (in blue)

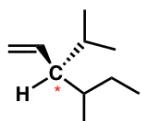


Note that the process of assigning "phantom atoms" to the nitrogen involves looking "backwards" towards the chiral center. This is the only case we ever do this!

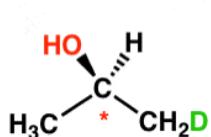
According to this system, we then get the following priorities:



Exercise: assign R/S to this chiral center



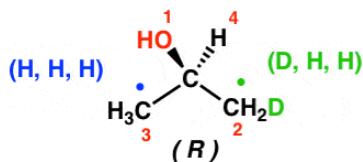
What about isotopes? Do they count? Is this carbon chiral?



D = deuterium (heavy isotope of hydrogen)  
(1 proton, 1 neutron)

Isotopes are assigned priority based on atomic mass

D > H



Note that tritium (T), with 1 proton and 2 neutrons would rank even higher than deuterium (D)

How are these molecules related?



Metamerism: this type of isomerism is due to unequal distance of C-atoms on either side of \*\*\* group in compound of molecules belonging to same class.

### OPTICALLY ACTIVE COMPOUND

The compounds that can rotate the plane polarised light are optically active compounds. A beam of ordinary light, there is electric and magnetic field vibrating at  $90^{\circ}$  with each other and direction of propagation in every plane. The same is true for monochromatic light.

#### Elements of symmetry

- i) Rotational axis of symmetry:
- ii) Plane of symmetry:
- iii) Centre of symmetry:
- iv) Alternating axis of symmetry:

We can classify molecules as

- i) Disymmetric:
- ii) Assymmetric:

### Number of Stereoisomerism: Systems Involving 1/2/3-Chiral Centre(S) (AA, AB, ABA and ABC Types).

	Nature of molecule	Optically active isomers	Meso isomers or optically inactive isomers
1. AB or ABC type	Contains 'n' different chiral centers and the molecule cannot be divided into two equal and similar halves in any possible conformation.	$2^n$	None
2. AA type	Contains an even number 'n' no of chiral centers, but the molecule can be divided into two mirror image halves in one of the possible conformations.	$2^{(n-1)}$	$2^{(n-2)/2}$
3. AAA or ABA type	Contains an odd number 'n' no of chiral centers, and the molecule can be divided into two mirror image halves by a plane passing through the central chiral center in one of the possible conformations.	$2^{(n-1)} - 2^{(n-1)/2}$	$2^{(n-1)/2}$

## MESO COMPOUND

When a set of diastereoisomers is found to be optically inactive in spite of presence of presence of multiple chiral centres then molecule is said to be a meso compound. Meso compound is found to have different physical and chemical properties than its optically active isomers.

Meso compound is optically inactive due to internal compensation. The meaning of internal compensation is that molecule can be divided into two equal halves. If one half rotates in clockwise direction, then another half rotates in anticlockwise direction. So, net optical rotation is zero. Molecule is **optically inactive**.

Presence or absence of chiral carbon is not essential criteria for optical activity. But absence of  $i$ ,  $\sigma$ ,  $S_n$  are the necessary condition for optical activity.

## RACEMIC MIXTURE / RACEMIC MODIFICATION

Equimolecular mixture of a pair of enantiomers independent of whether it is crystalline / liquid / gaseous.

Racemic mixture is optically inactive due to external compensation.

Since, racemic modification is a mixture, it can be separated into pure enantiomers.

The process is known as resolution. Racemisation is the process of producing a racemic modification starting from either of the pure enantiomers.

From thermodynamic point of view, it is a spontaneous process.

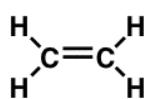
## OPTICALLY ACTIVE COMPOUND WITHOUT CHIRAL CENTER

Chiral centre is not present into the molecule, but **Axial chirality OR Molecular chirality** is present into the molecule. Therefore, the molecules are optically active.

## OPTICAL ACTIVITY IN ALLEN SYSTEM

### Allenes are “Cumulated” Dienes

Alkenes contain both sigma [  $\sigma$  ] bonding formed through “head-on” orbital overlap [i.e. “single bonds”] and also pi [  $\pi$  ] bonding where orbitals have “side-on” overlap [i.e. “multiple bonds”]



Ethene  
(an alkene)

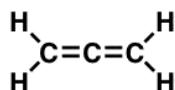


Bonding in ethene  
showing sigma bonds (in black)  
and the  $\pi$  bond formed by  
overlapping p orbitals (dashed line)

Alkenes like ethylene are flat [planar]. The p orbitals are at 90 degrees to this planar structure. If you've ever used graphite lubricant, you might know it's slippery because graphite is made up of layered sheets of flat, pi-bonded carbon, and the sheets have very little friction between each layer. Graphene is the same idea, only it's a single layer.

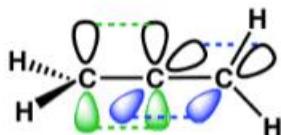
We extend a second double bond directly adjacent to the first one.

Allene - a "cumulated" diene



This molecule is called allene, called cumulenes, so named because the double bonds are cumulative (consecutive).

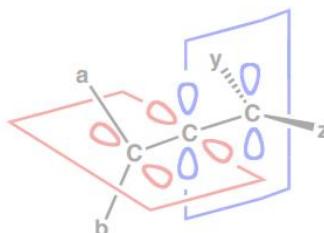
### Allene is NOT planar!



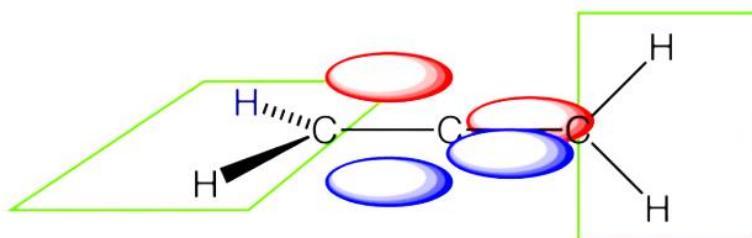
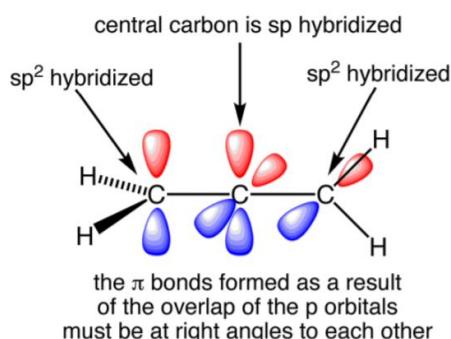
Bonus Q - what is the hybridization of that central carbon atom?

Note that the pi bonds are oriented 90° to each other - as are the C–H bond framework on the end carbons

The central carbon is  $sp$  hybridised, and the end carbons are  $sp^2$ .



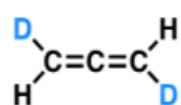
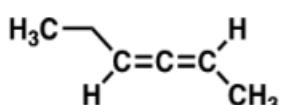
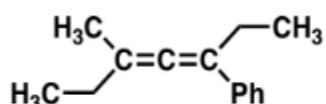
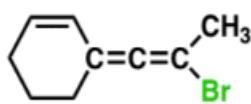
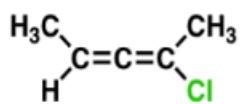
Orthogonal Bonding



not only are the two  $\pi$  bonds perpendicular, but the two methylene groups are too

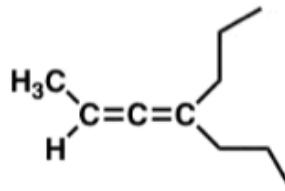
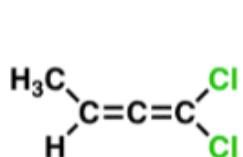
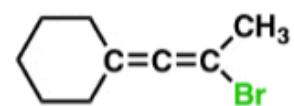
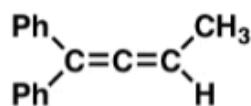
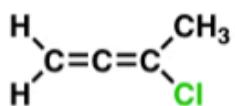
If either of those ends is attached to two identical substituents, it is achiral – because it will have a mirror plane.

### Chiral allenes



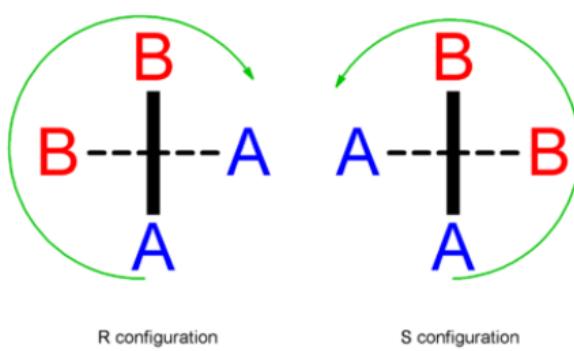
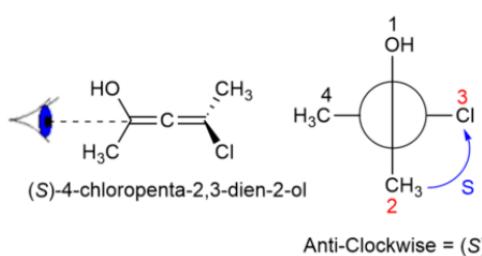
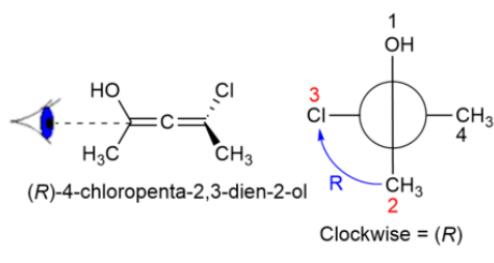
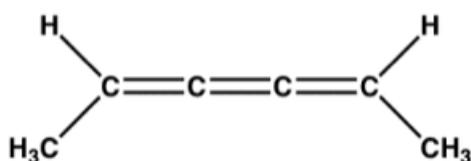
If neither of the ends are attached to two identical substituents, then it is chiral.

### Achiral allenes



If either of those ends is attached to two identical substituents, it is achiral – because it will have a mirror plane.

**Is this molecule optically active? Or is this a chiral molecule?**



Allene can be of **four** types

Allene will be optically active (OA) if each terminal carbon contains different groups.

### OPTICAL ACTIVITY IN SPIRANES SYSTEM

Two C=C of the allenes are replaced by cycloalkyl groups.

### OPTICAL ACTIVITY IN ALKYLIDENS SYSTEM

One C=C and a cyclohexyl ring is known as alkylidene cycloalkane.

### OPTICAL ACTIVITY IN BIPHENYLS SYSTEM

To avoid steric repulsion Ph-Ph,  $\sigma$ -bond rotates. So that one Ph is perpendicular to other. Such compounds are optically active (OA) if  $G_1 \neq G_2$  &  $G_3 \neq G_4$

### CONFIGURATION:

i) RELATIVE CONFIGURATION: D/L System

ii) ABSOLUTE CONFIGURATION: R-S System

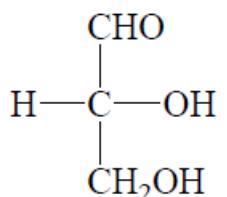
### D/L NOMENCLATURE:

The D/L nomenclature is the oldest nomenclature system for enantiomers. In this nomenclature system the configuration of all the compounds were given with respect

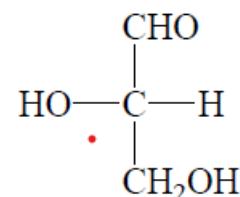
to glyceraldehyde molecule, where the configuration of glyceraldehyde molecule is taken as an arbitrary standard. According to this nomenclature if in glyceraldehyde molecule the  $-\text{OH}$  group on right and  $-\text{H}$  on left, the  $-\text{CHO}$  and  $-\text{CH}_2\text{OH}$  groups being on top and bottom, respectively the molecule is designated as (+) Glyceraldehyde and it was arbitrary given the configuration symbol D. The mirror image of this compound (-) glyceraldehyde was given the configuration L.

## D/L NOMENCLATURE:

The D/L nomenclature is the oldest nomenclature system for enantiomers. In this nomenclature system the configuration of all the compounds were given with respect to glyceraldehyde molecule, where the configuration of glyceraldehyde molecule is taken as an arbitrary standard. According to this nomenclature if in glyceraldehyde molecule the –OH group on right and –H on left, the –CHO and –CH<sub>2</sub>OH groups being on top and bottom, respectively the molecule is designated as (+) Glyceraldehyde and it was arbitrary given the configuration symbol D. The mirror image of this compound (-) glyceraldehyde was given the configuration L.



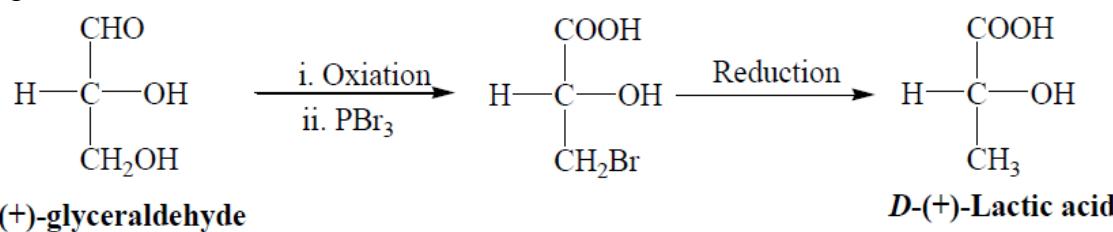
### *D*-(+)-glyceraldehyde



### *L*-(+)-glyceraldehyde

Any compound that can be prepared, or converted in to D-(+)-glyceraldehyde will belong to D series (relative configuration), whereas, any compound that can be prepared, or converted in to L-(+)-glyceraldehyde will belong to L series.

Example: Lactic acid obtained from D-(+)-glyceraldehyde and hence assigned D configuration



## Remember:

- There is no correlation between the D and L designation and the sign of rotation. D form of isomer may be levorotatory, and L form of isomer may be dextrorotatory and vice versa.
  - The D/L nomenclature is limited to the compound that can be prepared or converted from the glyceraldehyde.
  - It is limited to only one chiral atom.

## R/S NOMENCLATURE:

Since you have been noted from the above discussion on D/L configuration, there are several drawbacks associated with the D/L nomenclature system. Hence a definite and universally applicable nomenclature system was needed to specifying the absolute configuration of each chiral centre in a molecule. Cahn and co-workers (1956, 1966) have proposed a new and universally applicable nomenclature pattern for the determination of absolute configuration of any chiral molecule. This is known as the R/S system or Cahn-Ingold-Prelog (CIP) nomenclature. It involves following two steps.

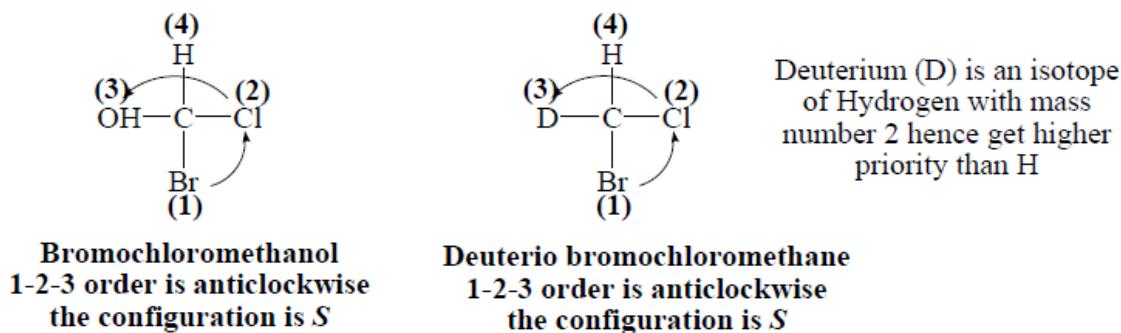
- ❖ In first step we need to assign the priority to the four different atoms/groups attached to a chiral centre.

- ❖ Priorities to the groups/atoms can be assigned as per the sequence rule.
- ❖ After assigning the priority to the atoms/groups attached to the chiral centre, the molecule is oriented in such a way that the lowest priority group is directed away to the observer.
- ❖ Now the arrangement of the remaining atoms/groups is viewed by following decreasing order of priorities from highest priority to lowest priority.
- ❖ While viewing the atoms/groups in their decreasing order if your eyes follow the clockwise direction then the chiral centre will have R configuration; whereas if your eyes follow anticlockwise direction the chiral centre will have S configuration.
- ❖ When a molecule has two or more than two chiral centers then the same process should be followed to assign their configuration.

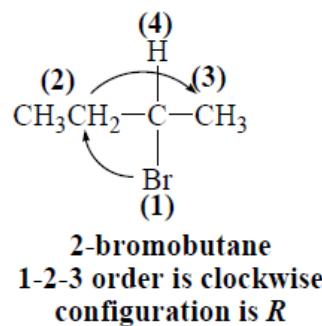
#### SEQUENCE RULE:

To assign the priorities to all four different groups/atoms attached with the chiral centre following sequence rule should be followed. The sequence rule is given by the three scientists Cahn-Ingold-Prelog therefore it is also called the CIP rule. The sequence rules are arbitrary but consistent. The main observations of sequence rules are listed below.

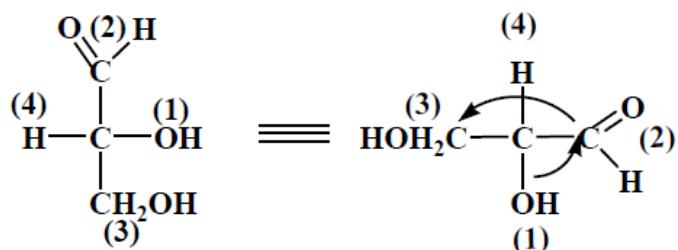
1. If all the atoms directly attached to the chiral centre are different, the sequence of priorities is determined by their atomic number. The atom with higher atomic number is given higher priority. If two atoms are isotopes of same element, the isotope with higher mass number has the higher priority.



2. If two or more atoms attached to the chiral centre having same atomic number, the priorities are assigned by comparing the atomic numbers of the next atoms attached to each group/atom.



3. If the atoms or groups attached to the centre atom are further linked with some other atoms via double and triple bonds. Then the double or triple bonded atoms are considered to be duplicate or triplicate. As per sequence rule the triple bond gets priority over double bond, similarly double bond gets priority over single bond.



2,3-dihydroxypropanal  
1-2-3 order is anticlockwise  
configuration is *S*

This absolute configuration is used to designate the configuration of stereoisomers having chiral centres.

Configuration of stereo isomers are named on the basis of individual chiral centres. For this

1<sup>st</sup> the four groups attached to each chiral centre are identified according to their priorities. These priorities are determined according to rules given by Cahn-Ingold-Prelog which is known as CIP rules.

### CIP RULES

1. Four different groups attached to a chiral centre get their priorities according to atomic no. of atom of each group directly attached to chiral centre.
2. The atom directly attached to chiral carbon such that when two or more atoms are same, then atomic no. of next set of atoms in the unassigned groups are taken in to consideration. This outward exploration is continued until a decision can be made. The priorities are then assigned at the first point of difference.
3. For the purpose of assigning priority double and triple bond are considered as assuming that each such double / triple bond duplicated or triplicated from the both sides of multiple bonds. The duplicated atoms are placed within parenthesis and except H atom and other duplicate atoms are meant tetra liganded by phantom atoms.

**Phantom atoms have lower priorities than H atom?**

(Phantom atoms are those atoms that are placed in order to understand clearly the number of bonds for priority selection in naming and R/S configuration. ... Here, the C=O is represented as 2 single bonds, being equivalent to this double bond. The atoms in brackets like, (C) and (O) are the phantom atoms.)

4. Priority order: -I > -Br > -Cl > -SO<sub>2</sub>R > -SOR > -SR > -SH > -F > -OCOR > -OR > -OH > -NO<sub>2</sub> > -NO > -NHCOR > -NR<sub>2</sub> > -NHR > -NH<sub>2</sub> > -CX<sub>3</sub> > -COX > -COOH > -CONH<sub>2</sub> > -COR > -CHO > -CR<sub>2</sub>OH > -CH(OH)R > -CH<sub>2</sub>OH > -C≡CR > -C<sub>6</sub>H<sub>5</sub> > -C≡CH > -C(R)=CR<sub>2</sub> > -CR<sub>3</sub> > -CHR<sub>2</sub> > -CH<sub>2</sub>R > -CH<sub>3</sub> > -D > -H > lone pair.

## GEOMETRICAL ISOMER / DIASTEREOMER

Due to different attachment of groups on two sides of C=C, C=N, N=N bond the different special arrangement results in the geometrical isomers

**In case of polyenes a long chain alkene having alternating double bond.**



	Nature of molecule	Geometrical Isomers (GI)
1.	If terminal groups are different. Contains 'n' no of double bond. $G_1 \neq G_2$	$2^n$
2. A.	If terminal groups are same. Contains 'n' no of double bond. $G_1 = G_2 = R$ . If n is even.	$2^{(n-1)} + 2^{(n-2)/2}$
2. B.	If terminal groups are same. Contains 'n' no of double bond. $G_1 = G_2 = R$ . If n is odd.	$2^{(n-1)} + 2^{(n-1)/2}$