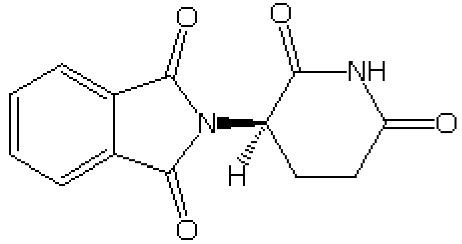
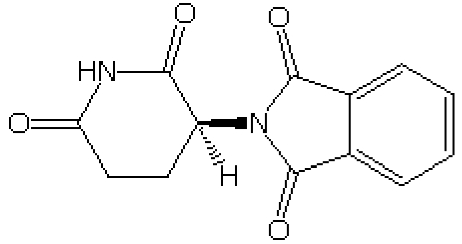
STEREOCHEMISTRY

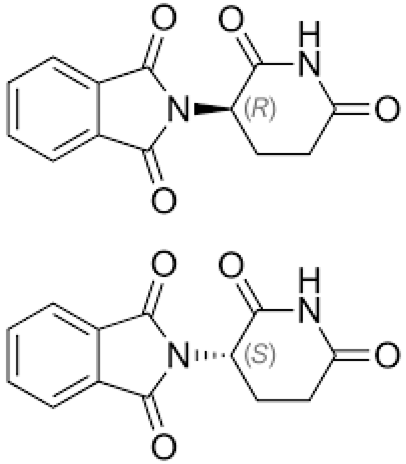
Stereochemistry deals with three dimensional representation of molecule in space. This has sweeping implications in biological systems. For example, most drugs are often composed of a single stereoisomer of a compound. Among stereoisomers one may have positive effects on the body and another stereoisomer may not or could even be toxic. An example of this is the drug thalidomide which was used during the 1950s to suppress the morning sickness. The drug unfortunately, was prescribed as a mixture of stereoisomers, and while one stereoisomer actively worked on controlling morning sickness, the other stereoisomer caused serious birth defects.



(R)-Thalidomide
(sedative)



(S)-Thalidomide
(teratogenic)

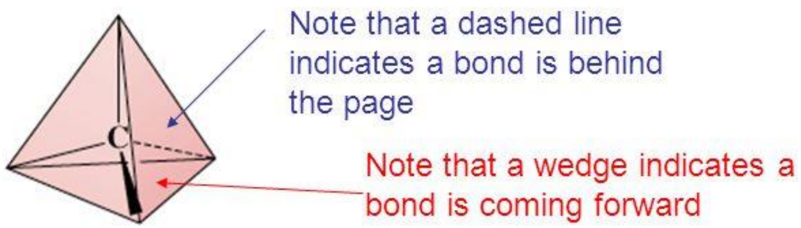


Malformations due to maternal ingestion of thalidomide (Schardein 1982 and Moore 1993).

Carbon is Tetrahedral

- In 1858 Kekulé and Couper independently observed that carbon always has four bonds
- In 1874 van't Hoff and Le Bel proposed that the four bonds of carbon have specific spatial directions
- van't Hoff suggested that the four atoms surround carbon as corners of a tetrahedron

Four tetrahedral *sp*³ orbitals



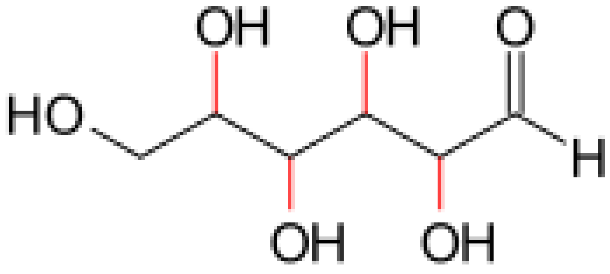
Stereochemistry

The foundations of organic stereochemistry were laid by Jacobus van't Hoff and Joseph Achille Le Bel in 1874.

- **The Greek word stereos means "solid," and stereochemistry refers to chemistry in three dimensions. Isomers that have the same constitution but differ in the spatial arrangement of their atoms are called stereoisomers.**
- **In 1894, William Thomson (Lord Kelvin) defined an object as chiral if it is not superimposable on its mirror image.**

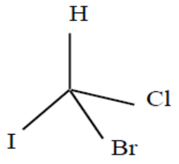
Le Bel–Van 't Hoff rule states that the number of stereoisomers of an organic compound containing no internal planes of symmetry is 2^n, where n represents the number of asymmetric carbon atoms. Joseph Achille Le Bel and Jacobus Henricus van 't Hoff both announced this hypothesis in 1874 and that this accounted for all molecular asymmetry known at the time.

As an example, four of the carbon atoms of the aldohexose class of molecules are asymmetric, therefore the Le Bel–Van 't Hoff rule gives a calculation of $2^4 = 16$ stereoisomers. This is indeed the case: these chemicals are two enantiomers each of eight different diastereomers: allose, altrose, glucose, mannose, gulose, idose, galactose, and talose.

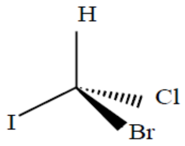


The branch of chemistry which deals with three dimensional structure of molecule and their effect on physical and chemical properties is known as stereochemistry. To represent molecule as three dimensional object we need at least one carbon sp3- hybridized.

Example:



2D drawing Not appropriate for steriochemistry

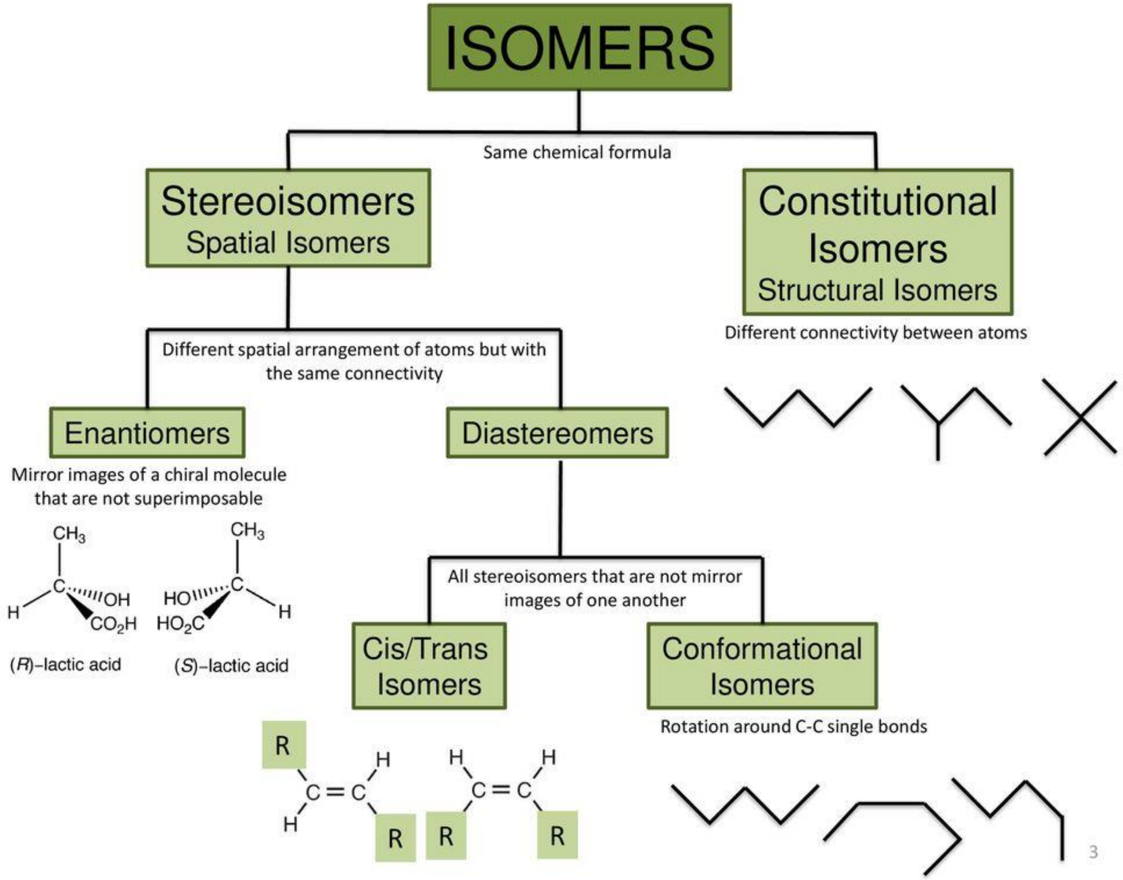


3D drawing appropriate for steriochemistry

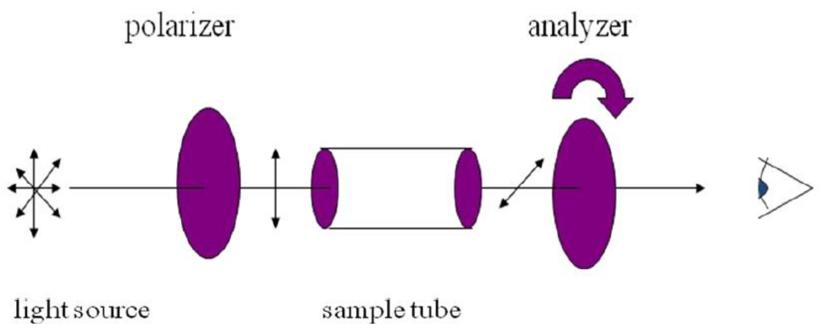
Two stereoisomers that are mirror images are enantiomers. The prefix enantio- designates the mirror-image relationship. Two stereoisomers of the same compound that are not enantiomers are diastereomers. This is a fairly broad definition

ISOMERS AND THEIR CLASSIFICATION

We are already familiar with the concept of isomers: different compounds which have the same molecular formula. Here we will learn to make distinction between various kinds of isomers, especially the stereoisomers.



We know that ordinary lights are composed of rays of different wavelengths vibrating in all directions perpendicular to the path of its propagation. These vibrations can be made to occur in a single plane by passing ordinary light through the polarizing Nicol prism. Such light whose vibrations occur in only one plane is called plane polarized light



Compounds which rotate the plane of polarized light are called optically active compounds and this property is known as optical activity. Rotation of plane of polarized light can be of two types.

• **Dextrorotatory** : If the compound rotates the plane of polarization to the right(clockwise) it is said to be dextrorotatory (Latin: dexter-right) and is denoted by (+), or 'd'.

• **Laevorotatory** : If the compound rotates the plane of polarization to the left(anticlockwise) it is said to be laevorotatory (Latin: laevus-left) and is denoted by (-) or 'l'

The change in the angle of plane of polarization is known as optical rotation. The optical rotation is detected and measured by an instrument called polarimeter. The measurement of optical activity is reported in terms of specific rotation [α], which is given as,

$[\alpha]_{\lambda}^{t} = \alpha/lc$

[α]= specific rotation

t = temperature of measurement

λ=wavelength of the light used

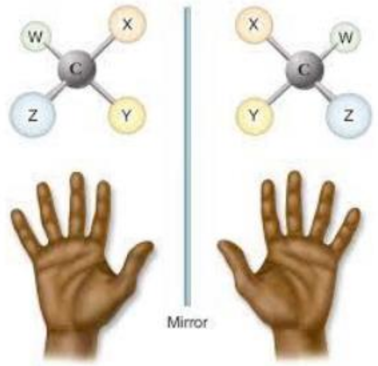
α= observed angle of rotation

l= length of sample tube in decimeter

c=concentration of the sample in g/mL of solution

CHIRALITY

• The term Chiral- The word chiral (Greek word Chier,meaning hand) is used for those objects which have right-handed and left-handed forms, i.e., molecules which have “handedness” and the general property of “handedness” is termed chirality. An object which is not superimposable upon its mirror image is chiral.

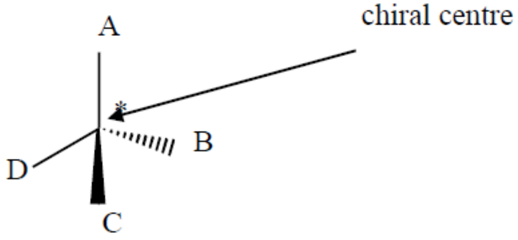


The term Achiral-

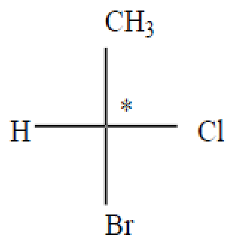
Object and molecules which are superimposable on their mirror images is achiral.

Achiral molecule has internal plane of symmetry, a hypothetical plane which bisects an object or molecule into mirror-reflactive halves. An object or molecule with an internal plane of symmetry is achiral.

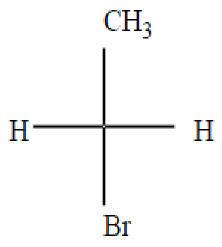
The term Asymmetric center and chiral center- Three terms are used to designate, a carbon atom bonded tetrahedrally to four different substituents in a chiral molecule: Asymmetric atom, chiral center or stereocenter.



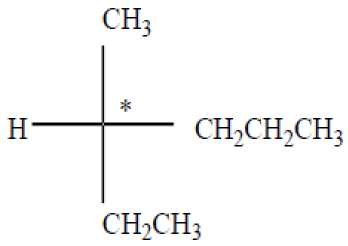
Let us understand chiral and achiral center taking few more examples.



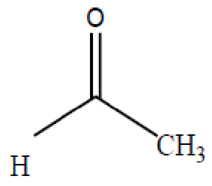
Chiral (asymmetric)
has four different
atoms bonded to
carbon



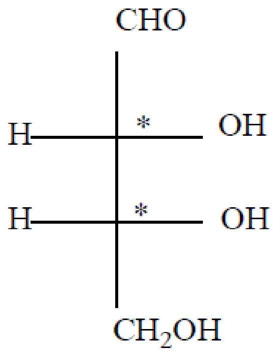
Achiral
does not have
four different
atoms bonded to
the carbon



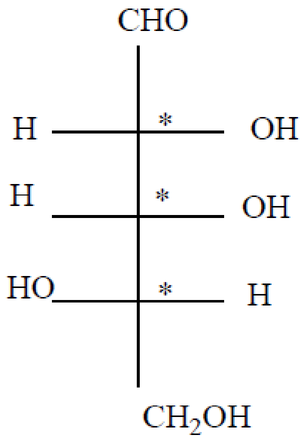
Chiral
has four different
groups bond to
the carbon



Achiral
only has three atoms
bonded to the
carbon



Chiral
with two chiral centre

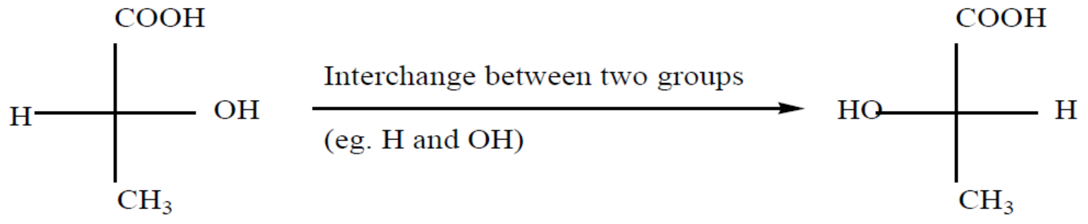


Chiral
with three chiral centre

The term stereogenic center or stereocenter-

A stereogenic center is defined as an atom on which an interchange of any two atoms or groups result in a new stereoisomer, When the new stereoisomers is an enantiomer ,the stereocenter is called chiral center. All stereocenters are not tetrahedral.

Example 1

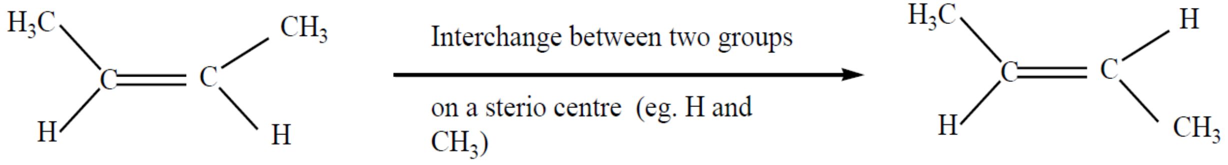


Steriocentre
I

New Sterioisomer
II

First and second are enantiomers (non superimposible mirror images), Hence the steriocentre is a chiral centre

Example-2

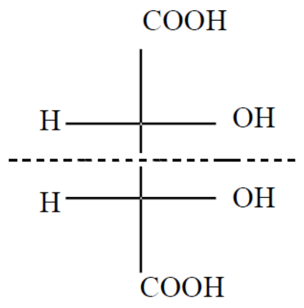


Cis isomer
III

New sterioisomer
IV

III and IV are not enantiomers . they are diasteriomers hence in this case sterio centres are not chiral centres. Also these are not tetrahedral.

Thus, all chiral centres are stereocentres but all stereocentres are not chiral centres. If a molecule contains only one chiral centres it must be chiral. Molecule containing two or more chiral centres may or may not be chiral. For example: meso tartaric acid has two chiral centres but it is achiral.

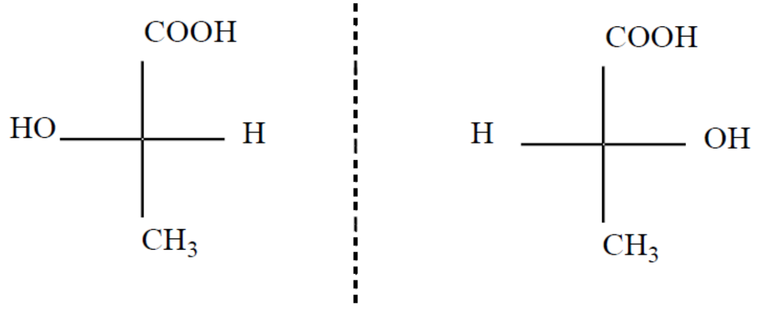


Achiral due to presence of plane of symmetry

D. STEREOISOMERS- Isomers having the same molecular formula but different spatial arrangement of their atoms are known as stereoisomer. They are of following types:

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.

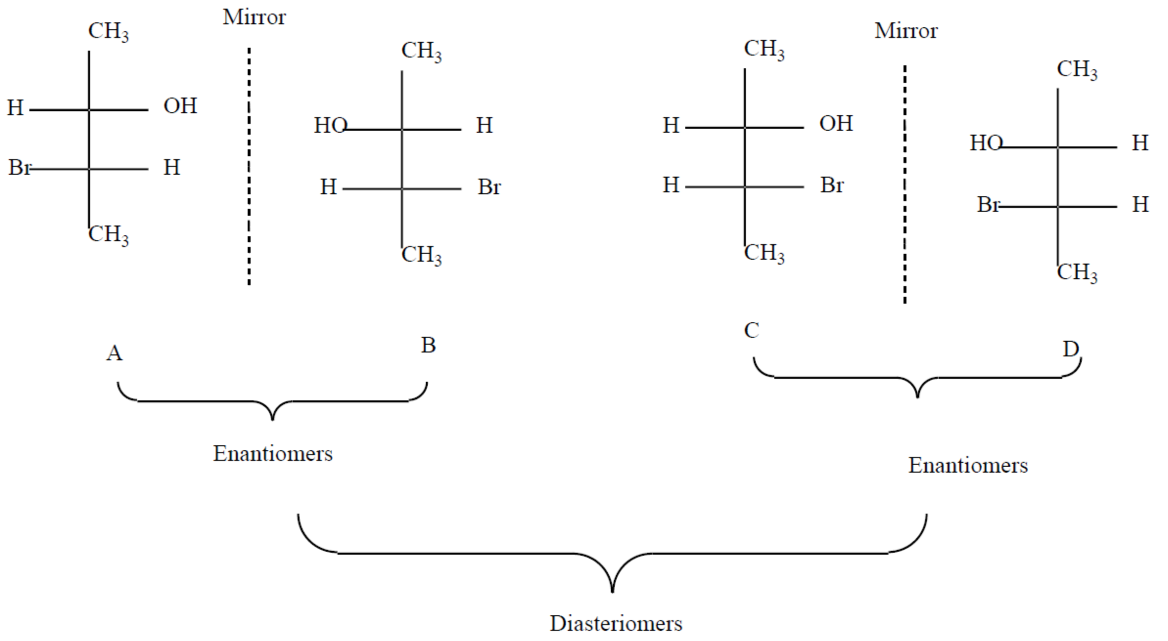
Eg.



Two isomers of Lactic acid

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

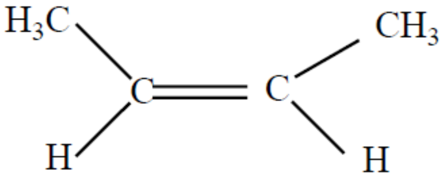
Example.



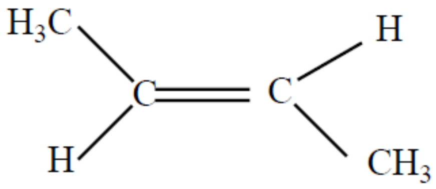
Geometrical Isomers:

Geometrical isomers occurs as a result of restricted rotation about a carbon-carbon bond. This is also called cis-trans isomerism.

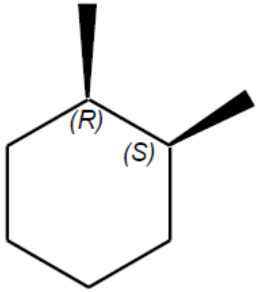
This isomerism exhibited by variety of compounds such as compound containing double bond C=C, C=N, N=N, compound containing cyclic structure or compound containing restricted rotation due to steric hindrance.



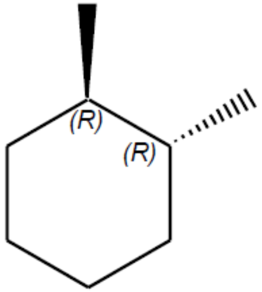
Cis isomer



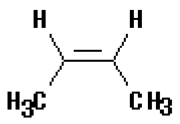
Trans isomer



Cis isomer

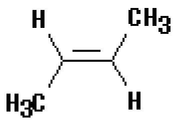


Trans isomer



cis-2-butene

(Z)-2-butene



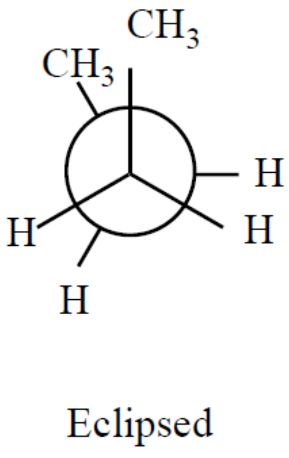
trans-2-butene

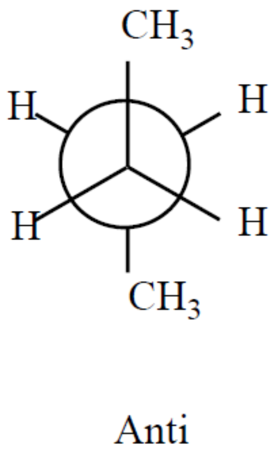
(E)-2-butene

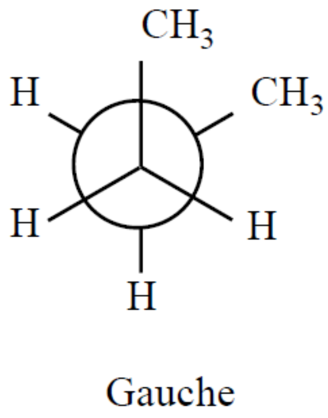
The traditional system for naming the geometric isomers of an alkene, in which the same groups are arranged differently, is to name them as cis or trans. However, it is easy to find examples where the cis-trans system is not easily applied. IUPAC has a more complete system for naming alkene isomers. 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. These 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.

Conformational isomers: Conformational isomers are the isomers that can be converted into one another by rotation around a single bond.
Example: eclipsed, gauche and anti butane are all conformational isomers of one another.(eclipsed means that identical groups are all directly in line with one another, gauche means that identical groups are 60 degree from one another and anti means that identical groups are 180 degree from one another.)







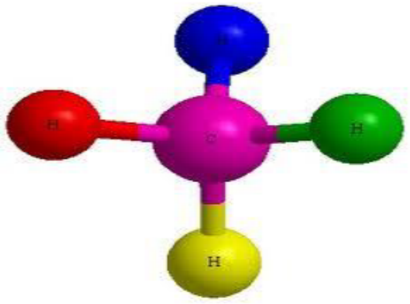
These molecules can be interconverted by rotating around the central carbon-carbon single bond.

REPRESENTATION OF THREE DIMENSIONAL MOLECULES

FLYING-WEDGE OR WEDGE-DASH PROJECTION

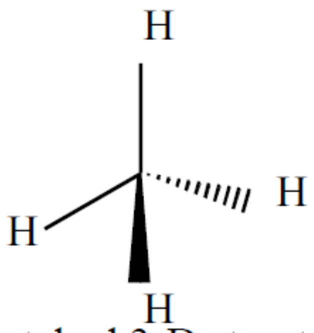
The Flying-Wedge Projection is the most widely used three dimensional representation of a molecule on a two dimensional surface (paper). This kind of representation is usually done for molecule containing chiral centre. In this type of representation three types of lines are used.

- A solid wedge or thick line ( ) - it represents bond projection towards the observer or above the plane of paper.
- A continuous line or ordinary line ( ) - it represents bond in the plane of paper.
- A dashed wedge or broken line ( ) - it represents bond projection away from the observer or below the plane of paper. Example:- CH_4 (methane)



"Ball and stick" model

of 3-D structure of methane

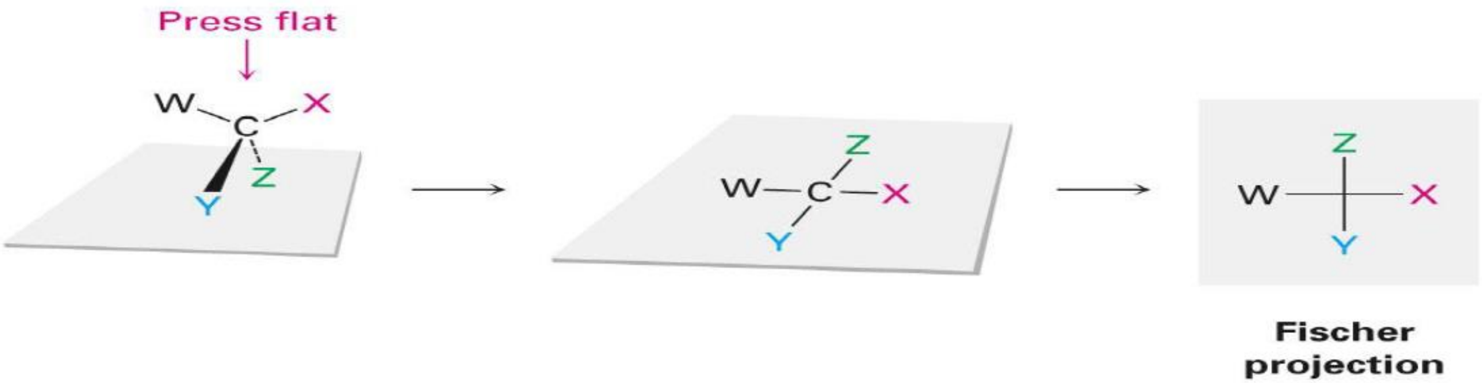


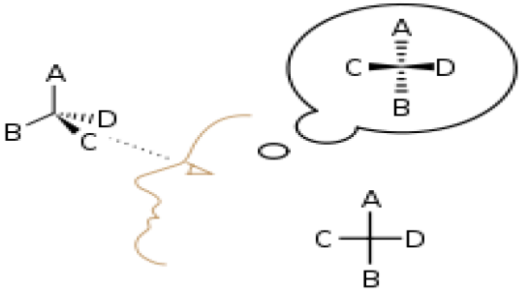
sketched 3-D structural

formula of methane

FISCHER PROJECTION

Fischer projection provide an easy way to draw three dimensional molecule on two dimensional paper and all the bonds are drawn as solid lines around asymmetric carbon atom.





The Fischer rules for showing the arrangement around asymmetric carbon.

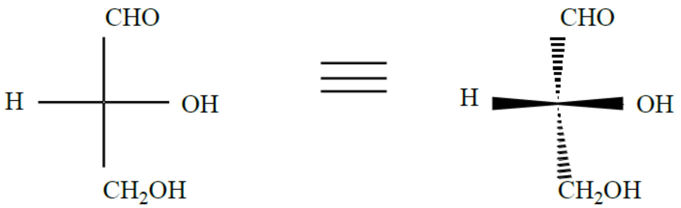
• The carbon chain of the compound is projected vertically, with the most oxidized carbon at the top or place the carbon number one at the top (as defined by nomenclature rule).

• The chiral carbon atom lies in the plane of the paper and usually omitted. The intersection of cross lines represents asymmetric carbon.

• The horizontal bonds attached to the chiral carbon are considered to be above the plane of paper or point towards the observer.

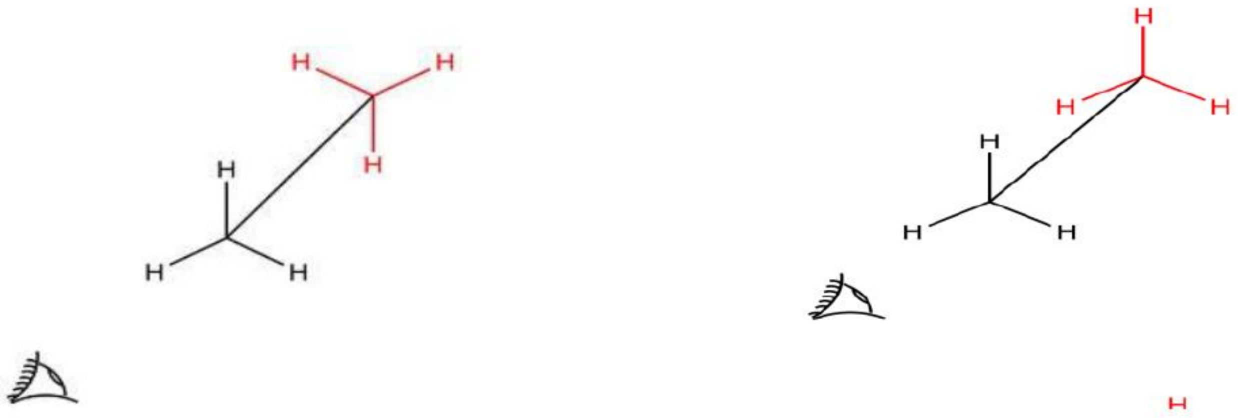
• The vertical bonds attached to the chiral carbon are considered to be below the plane of paper or point away from the observer.

Example: glyceraldehyde

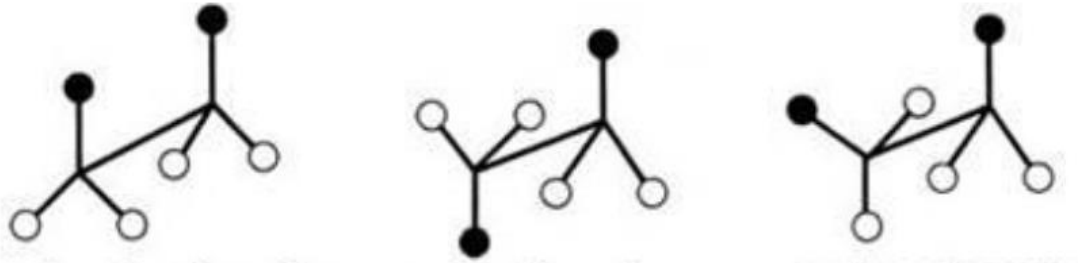


SAWHORSE FORMULA

The sawhorse formula indicates the arrangement of all the atoms or groups on two adjacent carbon atoms. The bonds between the two carbon atoms are drawn diagonally and of relatively greater length for the sake of clarity. The lower left hand carbon is taken as the front carbon or towards the observer and the upper right hand carbon as the back carbon or away from the observer. e.g. ethane



Anti conformation eclipsed conformation



eclipsed conformation anti conformation gauche conformation

● = methyl group

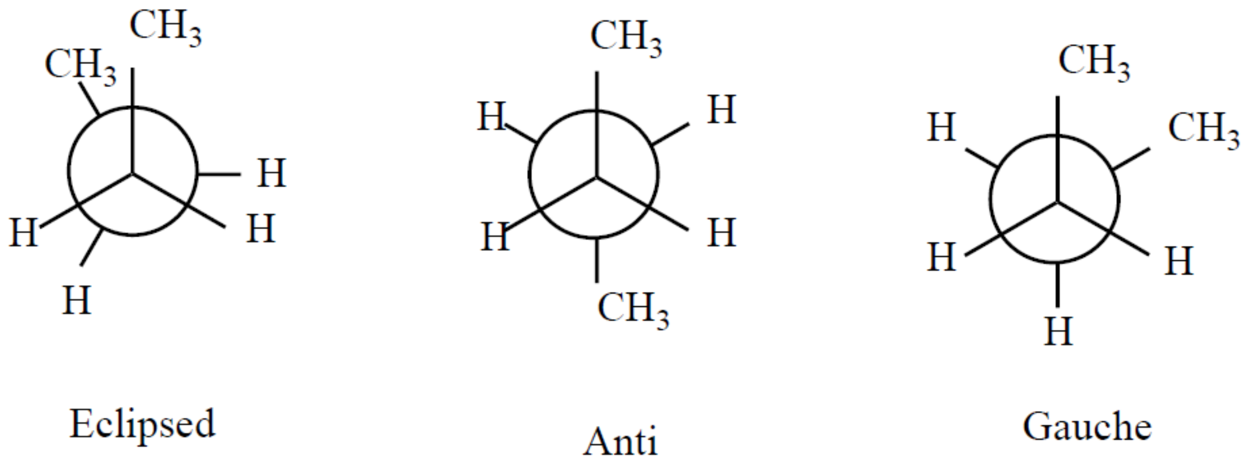
All parallel bonds in sawhorse formula are eclipsed and all anti parallel bonds are opposite or scattered.

Gauche representation is that in which bulky groups are nearer to each other at 60 deg angles.

NEWMAN PROJECTION

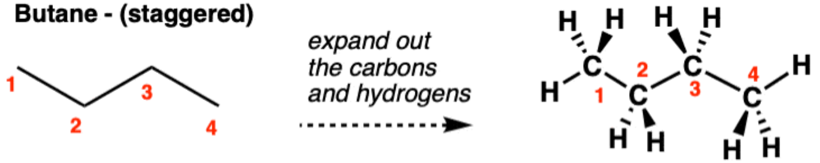
Newman devised a very simple method of projecting three dimensional formulas on two dimensional paper which are known as Newman projection.

- In these formulae the molecule is viewed from the front or along the axis of a carbon-carbon bond.
- The carbon nearer to the eye is represented by a point and the carbon atom towards the rear by circle.
- The three atoms or groups on the carbon atoms are shown as being bonded to dot or circle by an angle of 120 deg to each other.
- In Newman formula all parallel bonds are eclipsed or all anti parallel or opposite bonds are staggered.



Energy Profile Diagram of butane

Butane - (staggered)

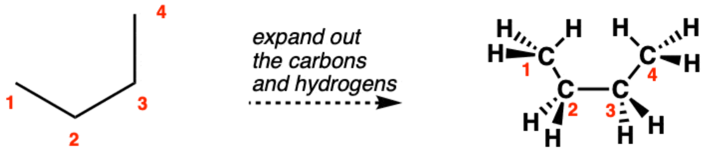


Line drawing

Structural formula

drawn with staggered conformations along each of the three C-C bonds

Butane (eclipsed)

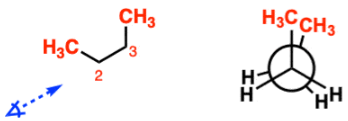


Line drawing

Structural formula

drawn with eclipsed conformations along each of the three C-C bonds

Eclipsed



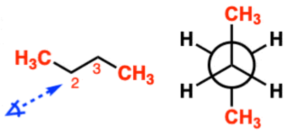
Highest-energy conformation of butane

Front groups **eclipsed** with respect to back groups

CH_3 groups are ***syn*** (dihedral angle 0°)

Strain energy about **5.0 kcal/mol** above that of the staggered conformation (at right)

Staggered

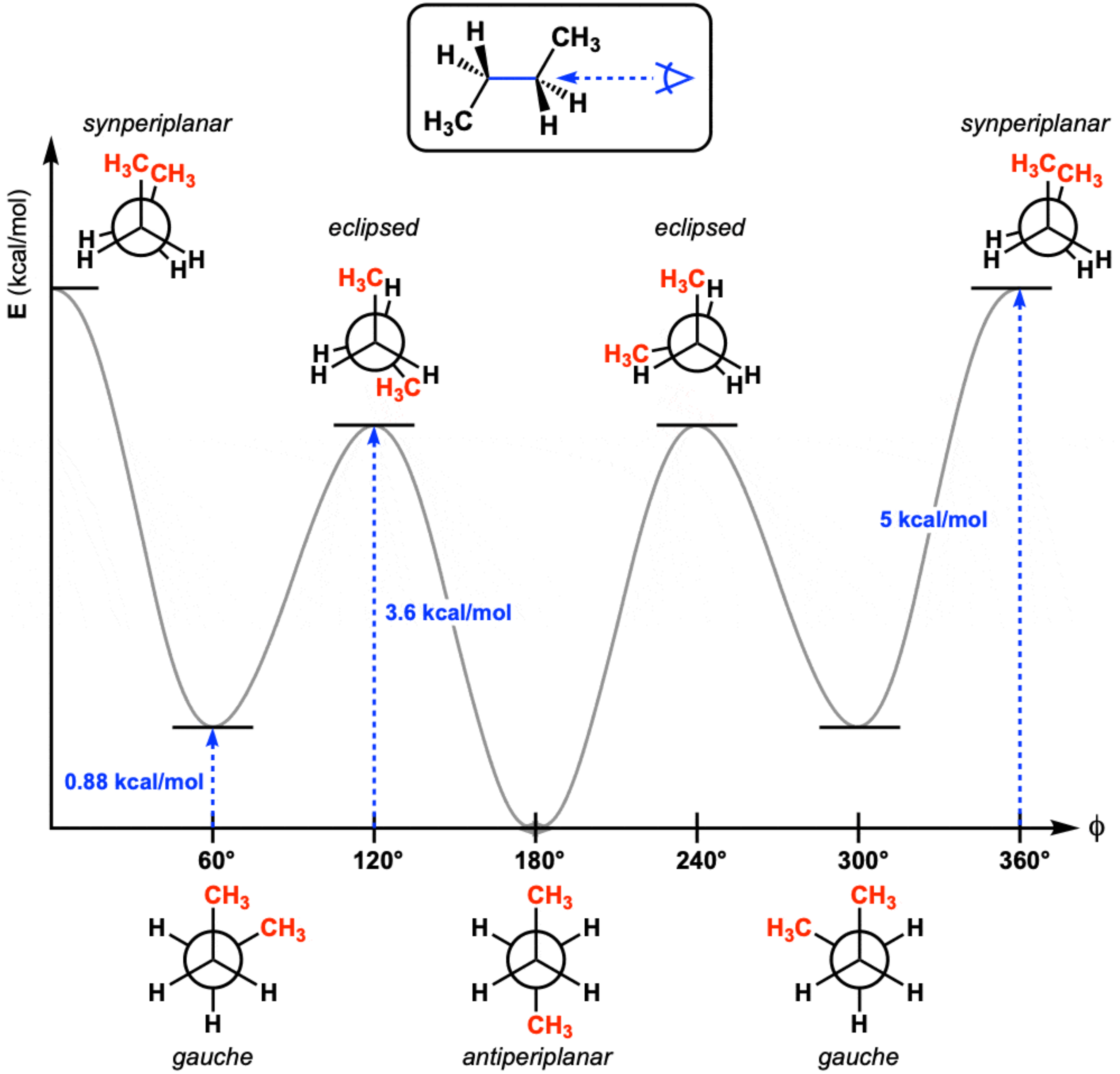


Lowest energy conformation of butane

Front groups **staggered** with respect to back groups

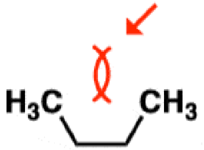
CH_3 groups are ***anti*** (dihedral angle 180°)

Energy minimum

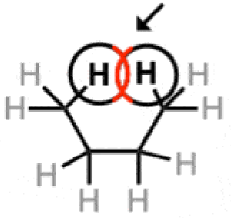


The Eclipsed Conformation Of Butane Is Strongly Disfavored Due To Repulsion Between The Methyl Groups

Often use this symbol to mean, "steric repulsion"…

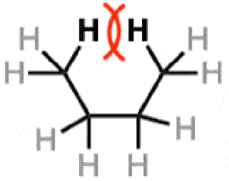


…which means the hydrogens of the methyl groups are in close contact…*



**about 2.9 Angstroms between CH_3 groups in this conformation*

…leading to a (destabilizing) repulsion between their electron clouds



The result is that the C-C bond is lengthened and the bond angles distort, resulting in strain

A "Price List" For Some Steric Interactions

H–H eclipsing interaction: **1.0 kcal/mol**

CH_3–H eclipsing interaction: **1.4 kcal/mol**

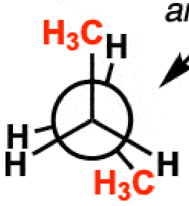
CH_3–CH_3 eclipsing interaction: **3.0 kcal/mol**

Can use these values to estimate the "costs" of various conformations!

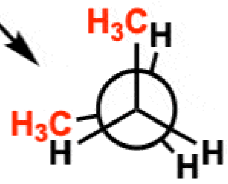
This repulsion between methyl groups is often called the "CH_3-CH_3 **eclipsing** interaction"

Two more "eclipsed" conformations: An Example Of Using The "Price List"

dihedral angle 120°



dihedral angle 240° (or –120°)



	Cost
H–H	1.0
H–CH_3	1.4
CH_3–CH_3	3.0

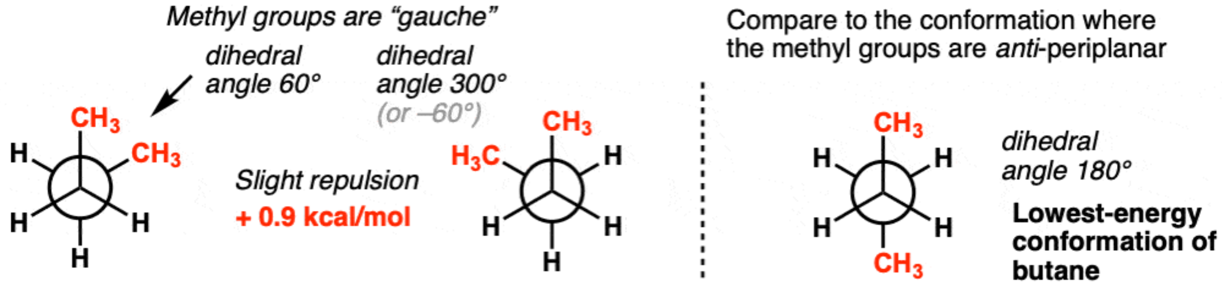
We can use the values from the "price list" to estimate the energies of these two conformations

Two CH_3–H eclipsing interactions (each **1.4** kcal/mol)

One H–H eclipsing interaction (**1.0** kcal/mol)

Total: 3.8 kcal/mol (Actual value: 3.6 kcal/mol, so this is a good estimate!)

The "Gauche" Interaction: Not All "Staggered" Conformations Are Equal

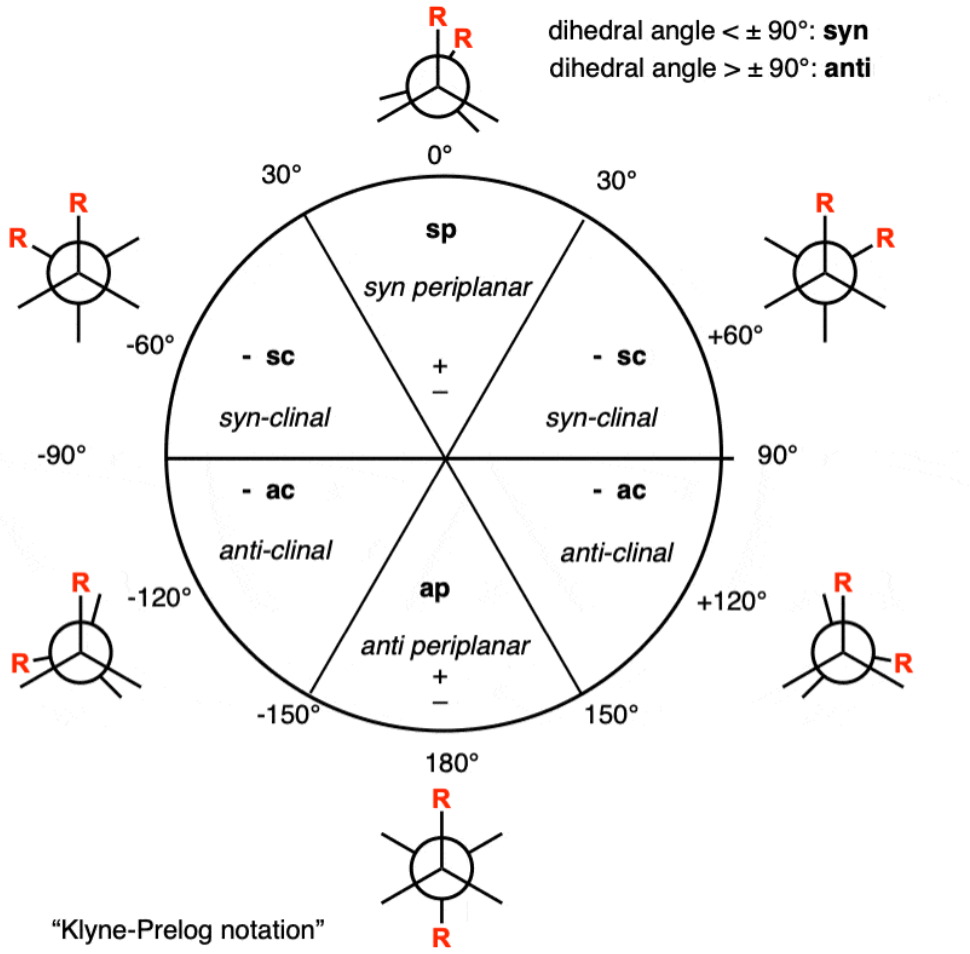


Even through the two adjacent carbons are staggered, there is still a small repulsion between the two methyl groups when they are separated by 60°. This is known as the "**gauche**" (awkward) interaction

The gauche interaction "costs" about **0.9 kcal/mol** relative to the staggered conformation where the two methyl groups are *anti*-periplanar

syn vs anti, periplanar vs clinal

dihedral angle < ± 90°: **syn**
dihedral angle > ± 90°: **anti**



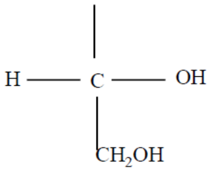
Dihedral angle	Designation	Dihedral angle	Designation
0 ± 30°	± syn periplanar	180 ± 30°	± anti periplanar
+60° ± 30°	+ syn-clinal	-120° ± 30°	- anti-clinal
120 ± 30°	+ anti-clinal	-60 ± 30°	- syn-clinal

NOMENCLATURE OF OPTICAL ISOMERS

D, L SYSTEM OF NOMENCLATURE

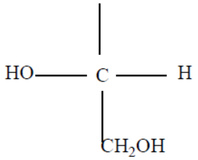
This nomenclature is mainly used in sugar chemistry or optically active polyhydric carbonyl compounds. This is a relative nomenclature because all the configurations described with respect to glyceraldehydes.

All sugars whose Fischer projection formula shows the OH group on the right hand side of the chiral atom belong to the D-series.



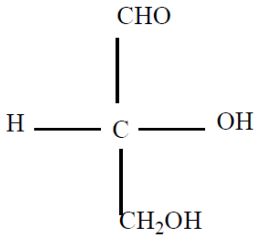
D-series.

Similarly, if OH is on the left hand side, then the sugar belongs to the L-series.

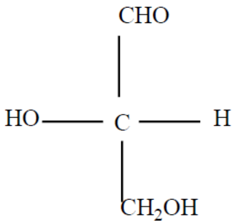


L-series

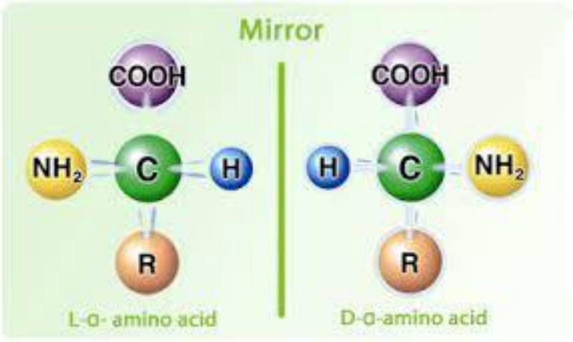
Examples:

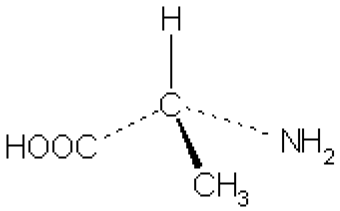


D(+) glyceraldehyde

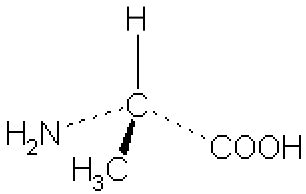


L(-) glyceraldehydes





D-Amino acid



L-amino acid

It must be noted that there is no relation between sign of rotation and (+, - or d,l) and configuration (D and L) of enentiomer.

- Any compound that can be prepared from, or converted in to D(+) glyceraldehydes will belong to D-series and similarly any compound that can be prepared from, or converted in to L(-) glyceraldehydes will belongs to the L-series.

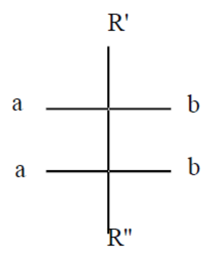
ERYTHRO AND THREO SYSTEM OF NOMENCLATURE

This nomenclature is mainly used only in those compounds which have only two chiral carbons and the following structures:

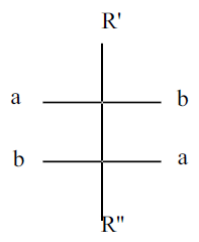
R’-Cab-Cab-R’’ or R’-Cab-Cbc-R’’

i.e. out of six substituent on two asymmetric carbons, at least one should be same in both the carbons.

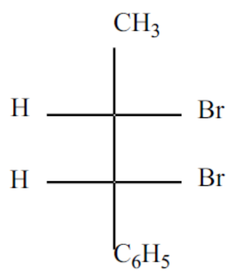
When two like groups in fisher projection formula are drawn on the same side of vertical line, the isomer is called erythro form; if these are placed on the opposite sides the isomer is said to be threo form.



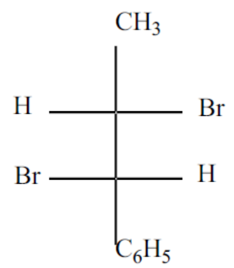
erythro form



threo form

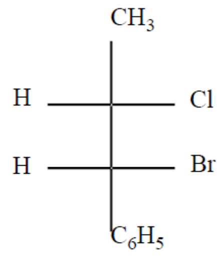


erythro form

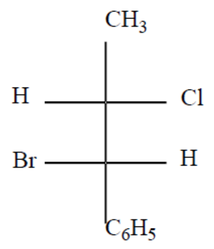


threo form

Following are some examples of *threo* and *erythro* form.



erythro form



threo form

R.S. NOMENCLATURE

The order of rearrangement of four groups around a chiral carbon is called the absolute configuration around that atom. System which indicates absolute configuration was given by three chemists R.S. Cahn, C.K. Ingold and V. Prelog. This system is known as (R) and (S) system or the Cahn-Ingold Prelog system.

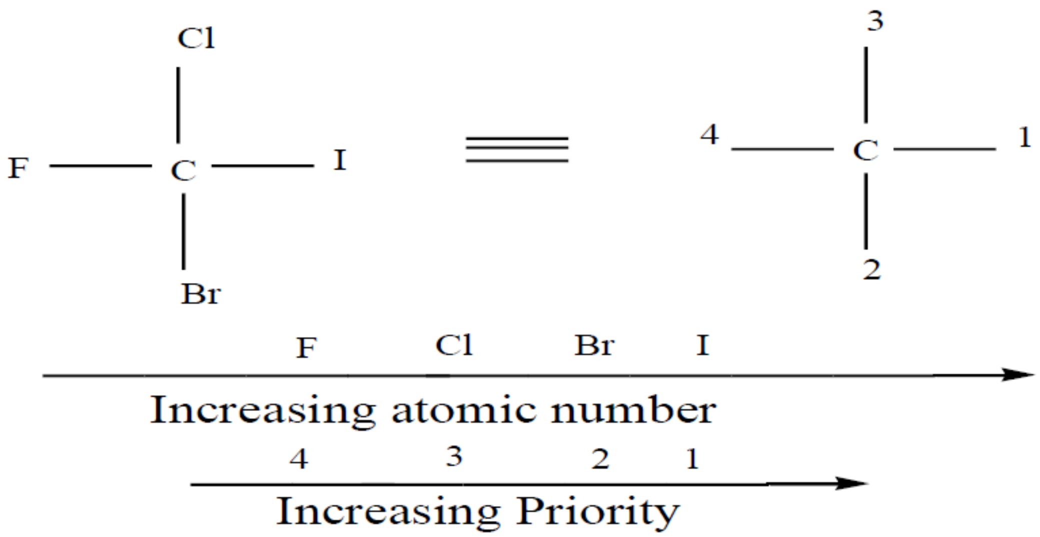
The letter (R) comes from the Latin rectus (means right) while (S) comes from the Latin sinister (means left). Any Chiral carbon atoms have either an (R) configuration or a (S) configuration. Therefore one enantiomer is (R) and the other is (S). A recemic mixture may be designated as (RS), meaning a mixture of the two.

The R, S nomenclature involves two steps:

Step I: The four ligands (atom or groups) attached to the chiral centre are assigned a sequence of priority according to sequence rules.

Rule 1: If all the four atoms directly attached to the chiral carbon are different, priority depends on their atomic number. The atom having highest atomic number gets the highest priority, i.e., (1).The atom with lowest atomic number is given lowest priority, i.e. (2), the group with next higher atomic number is given the next higher priority (3) and so on.

For example:



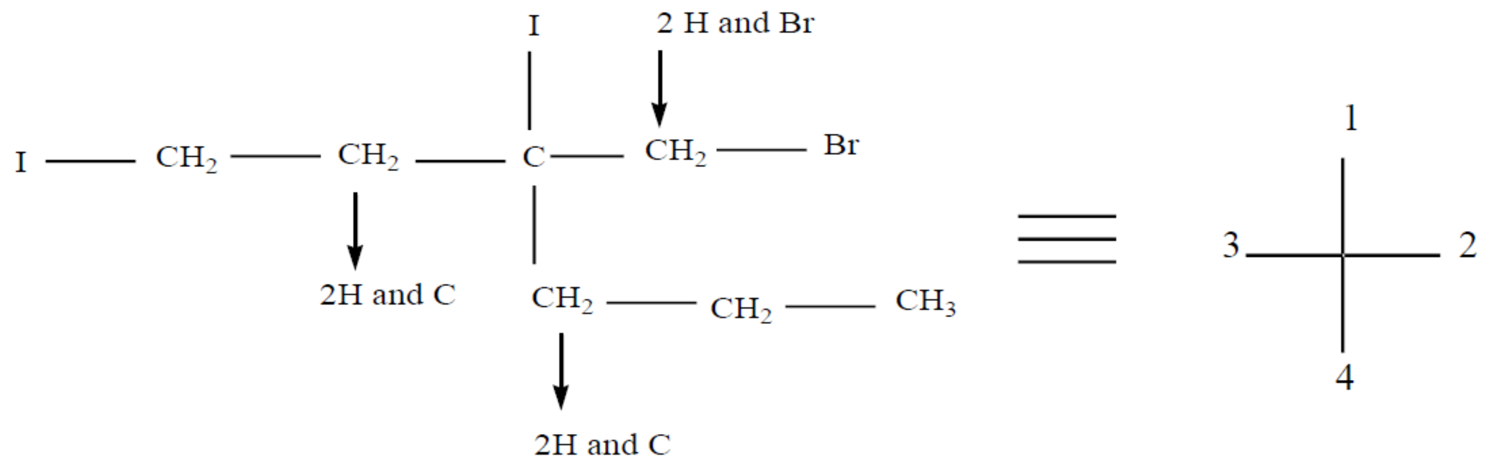
Rule 2: if two or more than two isotopes of the same element are present, the isotope of higher mass receives the higher priority.

$$_1H^1 \qquad _1H^2 \qquad _1H^3$$

$$\xrightarrow{\hspace{10em}}$$

increasing priority

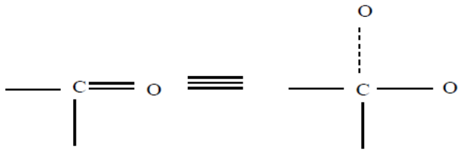
Rule 3: if two or more of the atoms directly bonded to the chiral carbon are identical, the atomic number of the next atom is used for priority assignment. If these atoms also have identical atoms attached to them, priority is determined at the first point of difference along the chain. The atom that has attached to it an atom of higher priority gets the higher priority.

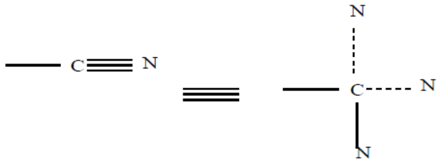


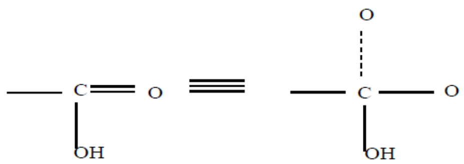
In the above example, the atoms connected directly to the chiral carbon are iodine and three carbons.

- Iodine has the highest priority.
- Connectivity of other three carbons are 2H and Br, 2H and C and 2H and C.
- Bromine has the highest atomic number amongst C, H, Br and thus CH2Br has highest priority among these three groups (i.e. priority number 2).
- The remaining two carbon are still identical (C and 2H) connected to the second carbon of these groups are 2H and I and 2H and C. Iodine has highest priority.
- Amongst these atoms, so that-CH2-CH2-I is next in priority list and CH2-CH2-CH3 has the last priority.

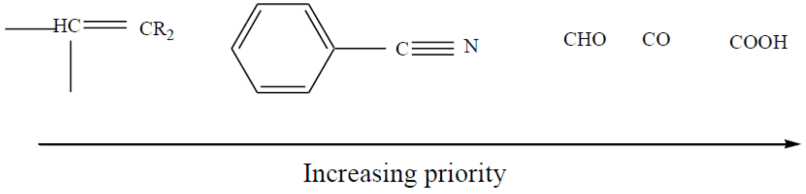
Rule 4: If a double or a triple bond is linked to chiral centre, the involved electrons are duplicated or triplicated respectively.





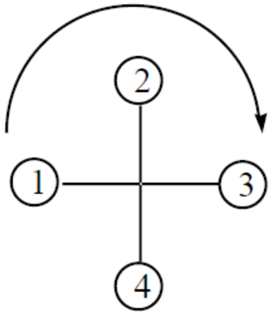


- By this rule, we obtain the following priority sequence:



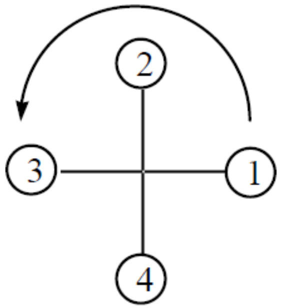
STEP-II: The molecule is then visualised so that the group of lowest priority (4) is directed away from the observer (at this position the lowest priority is at the bottom of the plane). The remaining three groups are in a plane facing the observer. If the eye travels clockwise as we look from the group of highest priority to the group of second and third priority (i.e. 1 2 3 with respect to 4) the configuration is designated R. If arrangement of groups is in anticlockwise direction, the configuration is designated as S.

For example:



Clockwise arrangement of

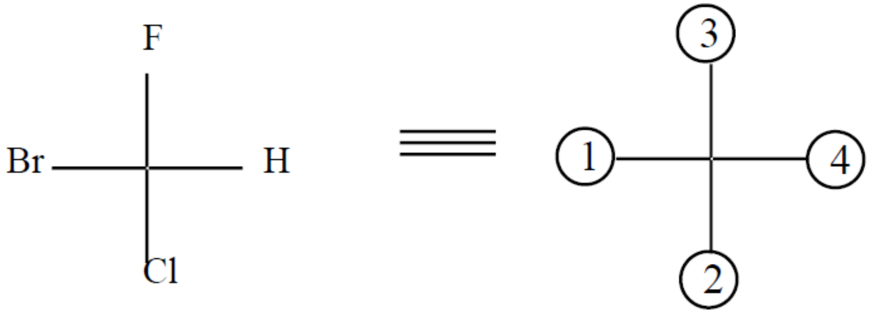
1 2 and 3 ⟶ **R**



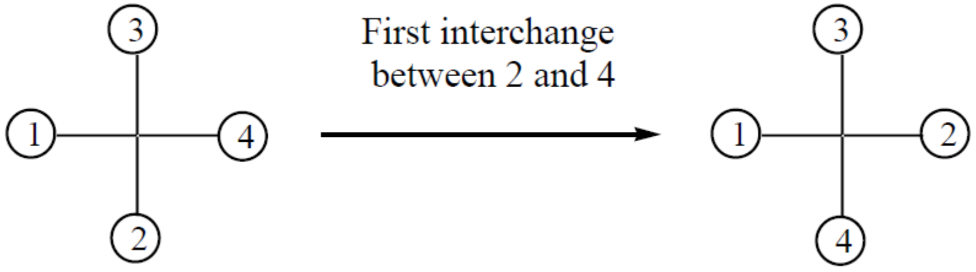
Anticlockwise arrangement of

1 2 and 3 ⟶ **S**

Let us apply the whole sequence to bromochlorofluoromethane.

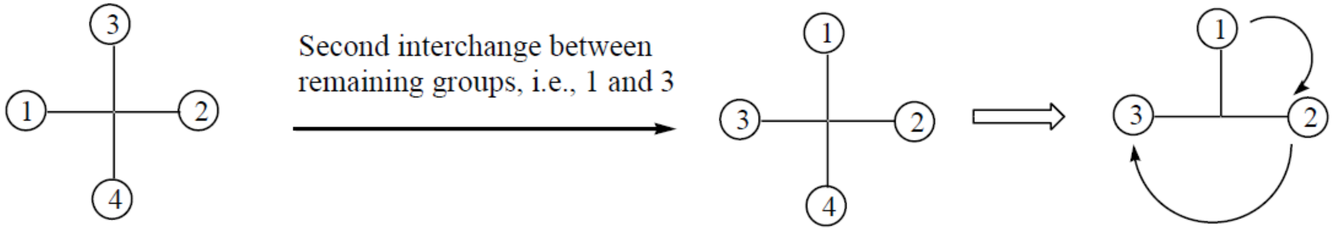


In this Fischer projection, the least priority number is not at the bottom of the plane. In such cases, the Fisher projection formula of the compound is converted in to another equivalent projection formula in such a manner that atom the lowest priority is placed vertically downward. This may be drawn by two interchanges between four priority numbers.
The first interchange involves the two priority numbers, one is the least priority number and the other is the priority number which is present at the bottom of the plane. In the above case, first interchanges will takes place between 2 and 4.



A B

A second inter change creates the original molecule (i.e. A).



B A

arrangement of 1,2 and 3 are clockwise, hence configuration is **R**

Note:-

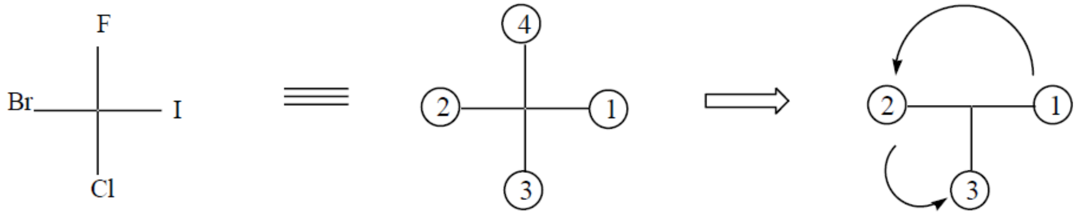
• An odd number of interchange of positions of groups on chiral carbon gives different compound.

• An even number of interchange of positions of groups on chiral carbon gives same compound.

An alternative, simple and most widely accepted procedure used now (Epling,1982) to assign R,S configuration in the case of Fischer projections is as followes:

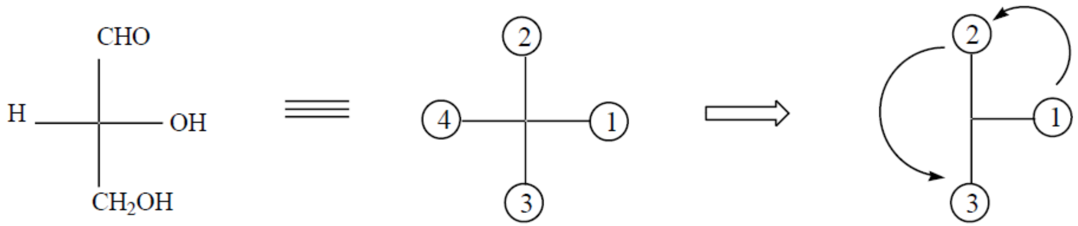
Case-I: R and S nomenclature from Fischer projection formula (Golden rule): If in a Fischer projection, the group of lowest priority (4) is on a vertical line, then the assignment of configuration is R for a clockwise sequence of 1 to 2to 3 and S for anticlockwise sequence.

For example:



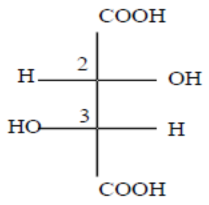
Anticlockwise arrangement
hence S- configuration

However, if the group of lowest priority is on horizontal line, then the assignment of configuration is S for a clockwise sequence of 1 to 2 to 3, and R for the anticlockwise sequence.

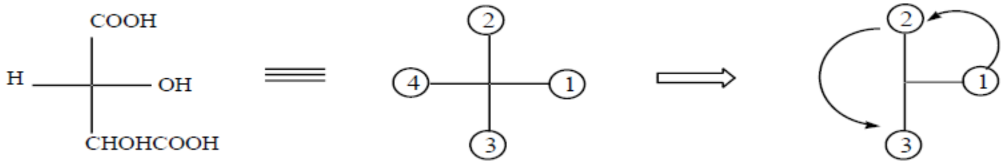


Anticlockwise arrangement
but lowest priority at horizontal
line hence R- configuration

When molecule contain two or more chiral centres, each chiral centre is assigned an R or S configuration according to the sequence and conversion rules. Thus (+) tartaric acid is (2R,3R) (+) tartaric acid.

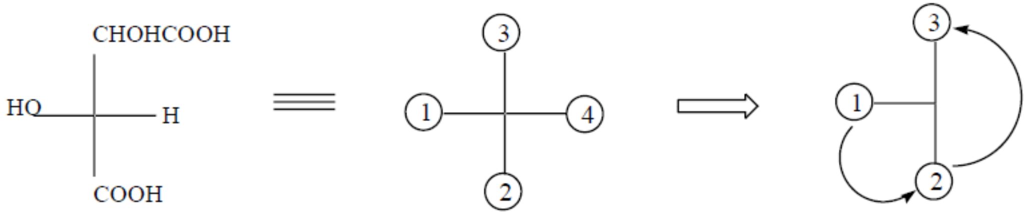


Configuration at chiral carbon - 2.



Anticlockwise arrangement
but lowest priority at horizontal
line hence R- configuration

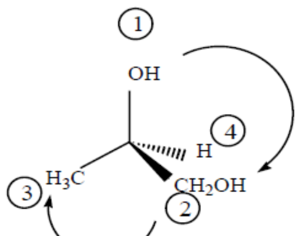
Configuration at chiral carbon - 3.



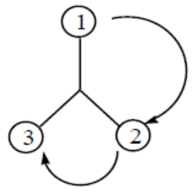
Anticlockwise arrangement
but lowest priority at horizontal
line hence R- configuration

R, S- nomenclature from flying-wedge formula.

- If the group of the lowest priority is away from the observer (i.e., bonded by dashed line) and the priority sequence (1 > 2 > 3) is clockwise, then the configuration is assigned as R. If the priority sequence is anticlockwise then the configuration is S.

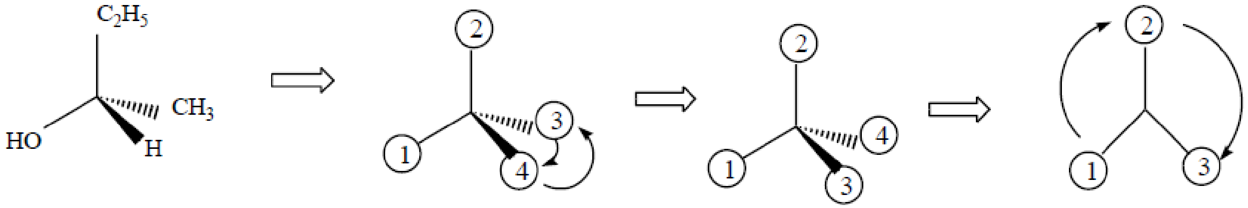


Lowest priority order is on deshed line



Clockwise arrangement thus configuration is R

If the group of lowest priority is not bonded by dashed line then interchange a pair of groups so that the group with the lowest priority is bonded by dashed line. Now see the sequence (1 > 2 > 3), if it is clockwise then the configuration is assigned as S and if anticlockwise R. This is because you have interchanged a pair of groups and now you are determining the configuration of enantiomer of original molecule.



Least priority order is not bonded with deshed line , so interchange the group 3 and 4

This is R configuration, which means that the original compoundI has S configuration