Lecture note- 2

Organic Chemistry CHE 502

STEREOCHEMISTRY

DEPARTMENT OF CHEMISTRY

UTTARAKHAND OPEN UNIVERSITY

UNIT 4: STEREOCHEMISTRY 1

CONTENTS

4.1 OBJECTIVES

In this unit learner will be able to:

- Depict various types of isomerism exhibited by organic compounds and their representation
- Analyze the three dimensional depictions of organic compounds and their two dimensional representations.

- Learn Stereogenicity, chirality, enantiomerism, diastereomerism, their relative and absolute configurations
- Learn about the various stereo chemical descriptors such as (cis-trans, E/Z, D/L, d/l, erythro/threo, R/S and syn/anti) given to organic molecules differ
- Describe the stereochemistry of various rigid and complex molecules like spiranes, adamentanes, catenanes, cyclophanes etc.

4.2 INTRODUCTION

In undergraduate level chemistry course we have learn about the fundamental concepts of isomerism and stereochemistry. Isomerism and stereochemistry provides the information about the different kind of depictions for organic compounds with similar structural formulas. Chemical compounds are represented by specific structural formulas. These chemical formulas were first organized by three scientists Kekule, Couper and Butlerov in 1874. The three dimensional representation of depiction of organic molecules were independently suggested by J H van't Hoff and J A LeBel. J H van't Hoff was honored by Nobel Prize for his work in 1901; he was the first recipient of Nobel Prize in Chemistry.

4.3 ISOMERISM

The word isomerism originated from Greek word *isomer* (*iso*= equal; *mers* = part). When two or more organic compounds having similar molecular formula but exhibit differences in their chemical and/or physical properties are called isomers, and the phenomenon is known as isomerism. However, the stereochemistry of an organic compound can be defined as the chemistry of that compound in space and as a function of molecular geometry.

Generally isomerism can be divided in to two categories;

a. Structural (constitutional) Isomerism

b. Stereo (configurational) Isomerism

4.4 STRUCTURAL (CONSTITUTIONAL) ISOMERISM

Structural isomerism is also known as *'constitutional isomerism'*. Structural isomerism arises when a molecule can be represented in to two or more than two different structures. The difference in structure is due to the difference in the arrangement of atoms within the molecules, irrespective of their position in space. In other words, structural isomers are compounds those have identical molecular formulae but different structural formulae; and the phenomenon is called structural isomerism.

Examples 1: Structural isomer of Butane (C_4H_{10}) and Bromobutane (C_4H_9Br)

C_4H_{10} **Butane**

$CH_3CH_2CH_2CH_3$ ***n*-Butane**

CH_3CHCH_3 (with CH_3 branch) **Isobutane**

C_4H_9Br **Bromobutane**

$CH_3CH_2CH_2CH_2Br$ **1-Bromobutane**

$CH_3CHCH_2CH_3$ (with Br) **2-Bromobutane**

Structural isomerism can also be subdivided in to five types.

1) Chain Isomerism
2) Functional Isomerism
3) Position Isomerism

4) Metamerism

5) Tautomerism

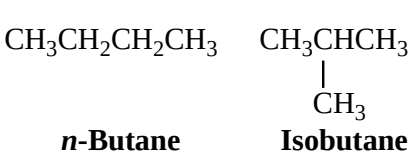
1) Chain Isomerism:

Chain isomers are those isomers having difference in the order in which the carbon atoms are bonded to each other. In other words chain isomers have variable amounts of branching along the hydrocarbon chain.

☞ *If you observe two or more than two molecules having similar molecular formulae, but difference in their hydrocarbon chain length, you should recognize them as chain isomers of each other.*

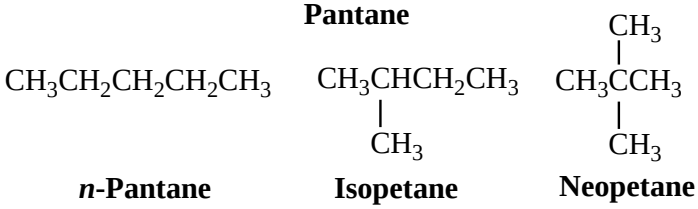
Example 2: Chain isomers of Butane (A) and Pentane (B)

A) C_4H_{10} **Butane**



***n*-Butane** **Isobutane**

B) C_5H_{12} **Pantane**



***n*-Pantane** **Isopetane** **Neopetane**

2) Functional Isomerism:

Two or more than two molecules those having the same molecular formulae but have different functional groups are called functional isomers and the phenomenon is termed as functional isomerism.

☞*If you observe two or more than two molecules having same molecular formulae, but difference in their functional groups, you should understand that these are functional isomers of each other.*

Example 3: Ethyl alcohol and Dimethyl ether

Ethyl alcohol **Dimethyl ether**

Example 4: *n*-Butyl alcohol and Diethyl ether

***n*-Butayl alcohol** **Diethyl ether**

3) Position Isomerism:

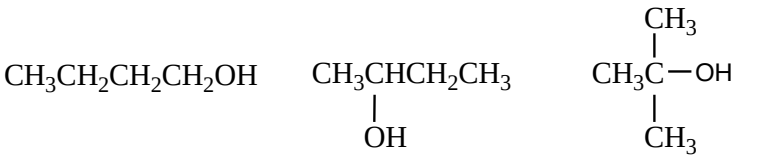
Two or more than two molecules those having same molecular formulae but having difference in the position of functional group on the carbon chain are called position isomers and the phenomenon is called as position isomerism.

☞ *If you observe two or more than two molecules having same molecular formulae, but difference in their functional groups, you should understand that these are functional isomers of each other.*

Example 5: 1-Butene and 2-Butene

1-Butene **2-Butene**

Example 6:1-Butyl alcohol, 2-Butyl alcohol and *t*-Butyl alcohol



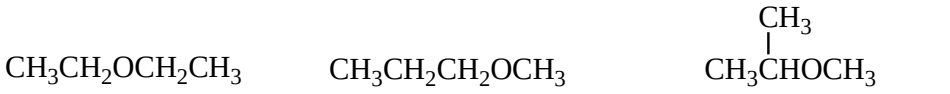
1-Butyl alcohol **2-Butyl alcohol** ***t*-Butyl alcohol**

4) Metamerism:

Two or more than two molecules those having same molecular formulae and functional group but having difference in the distribution of carbon atoms on either side of functional group are called metamers and the phenomenon is called the metamerism.

☞*When you see two or more than two molecule with identical molecular formulae but while structural representation you observe there is a difference in the alkyl group attached to same functional group you should understand these molecules are metamers of each other.*

Example 7: Diethyl ether, Methylpropyl ether and isopropyl methyl ether



Diethyl ether **Methyl propyl ether** **Isopropyl methylether**

Example 8: Diethyl amine, Methylpropyl amine and isopropyl methyl amine

Diethyl amine **Methyl propyl amine** **Isopropyl methylamine**

5) **Tautomerism:**

This is a special kind of isomerism where both the isomers are interconvertible and always exist in a dynamic equilibrium to each other. Due to their interconversion change in functional group takes place that gives two different isomers of an organic compound. This phenomenon is called Tautomerism.

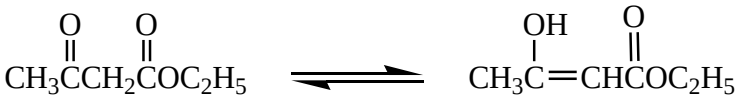
☞*When you observe two different isomeric forms of an organic compound are rapidly interconvertible to each other you should recognize them as tautomer of each other.*

Remember: *Tautomers are not the resonance structure of same compound*

Example 9: Acetone exists in taotomeric equilibrium with Prop-1-en-2-ol

Acetone (keto form) <99% ⇌ **Prop-1-ene-2-ol (enol form) >1%**

Example 10: Tautomeric forms of Ethyl acetoacetate under taotomeric equilibrium



(keto form) 93% ⇌ **(enol form) 7%**

4.5 STEREO (or CONFIGURATIONAL) ISOMERISM

Stereoisomerism is arises due to the difference in arrangement (configuration) of atoms or groups in space. When two or more than two isomers have the same structural formulae but having difference in the arrangement (configuration) of atoms in space are called stereo isomer and the phenomenon is called stereo isomerism.

Stereo isomerism can be further classified as

i. Geometrical or *cis-trans* isomerism
ii. Optical isomerism

4.5.1 GEOMETRICAL ISOMERISM:

Geometrical isomerism is generally observed in alkenes and cyclic compounds due to their restricted rotation around carbon- carbon bond. The rotation about a double bond in alkene or about a single bond in a cyclic/ring like compound is restricted. Double bonded system consists of a σ (sigma) and a π (pi) bond perpendicular to each other. It is not possible to rotate the

molecule about carbon-carbon bond. The rotation will break the π bond as a result the molecule will lose its identity. In some cased the rotation about single bond is also restricted due to steric hindrance. Geometrical isomerism is shown by various groups of compounds the major class of compounds that exhibit geometrical isomerism are classified as:

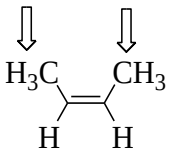
i. Compounds having double bond;

C=C, C=N, N=N

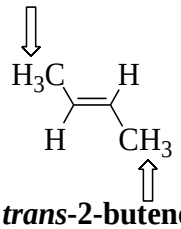
For example *cis*- and *trans*-2-butene have same connection of bond and molecular formulae.

☞ *If you observe two similar groups are on the same side of C=C bond this is called cis- isomer; whereas, if two similar groups are on opposite side of C=C bond this is known as trans- isomer.*

Example 1: *cis*- and *trans*- isomerism in 2-butene



***cis*-2-butene**



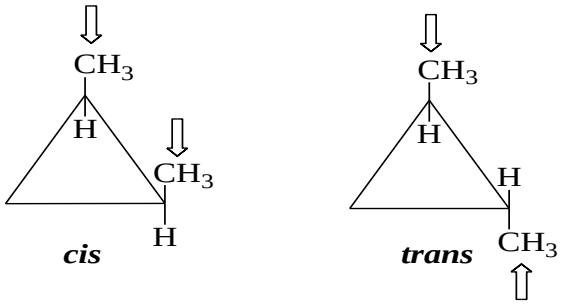
***trans*-2-butene**

☞ *You can understand that due to the presence of one σ (sigma) and one π (pi) bond in carbon–carbon double bond, rotation around C=C bond is not possible. The restricted rotation around C=C bond is responsible for geometrical isomerism in alkenes.*

ii. Cyclic compounds like homocyclic, heterocyclic and fused-ring systems

You can easily observe that rotation around C-C bond is also not possible in cyclic compounds as the rotation would break the bonds and break the ring. Thus Geometrical isomerism is also possible in cyclic compounds.

Example 2: *cis*- and *trans*- isomers of 1,2-dimethylcyclopropane



Conditions for geometrical isomerism:

Following two conditions are necessary for any compounds to show geometrical isomerism

a) There should be restricted (not allowed) rotation about a bond in a molecule.
b) Both substituent/atoms on each carbon about which rotation is not allowed should (restricted) be different.

☞ ***Remember*****:** *Geometrical isomers are non-mirror image of each other hence they are called diastereomers. Therefore their physical and chemical properties are different.*

☞ *Triple bonded molecules do not exhibit any kind of stereoisomerism because such molecule shows cylindrical symmetry.*

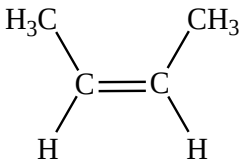
E & Z system of nomenclature for geometrical isomers:

We have already discussed about the *cis*- and *trans*- nomenclature of geometrical isomerism. The *cis*- and *trans*- nomenclature is the oldest and most fundamental nomenclature system for geometrical isomerism. The *cis*- and *trans*- nomenclature system is applicable only for those geometrical isomers in which at least one identical atoms/groups is bonded with each double bonded carbon. If both the identical groups/atoms are on same side of double bond the isomer is called as *cis*- isomer; whereas, if both identical groups/atoms are on opposite side of the double bond the isomer is called as *trans*- isomer (see example 1 of this unit).

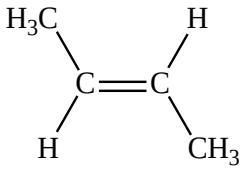
The *cis*- and *trans*- nomenclature method is limited to the molecule in which identical groups/atoms are attached to double bonded carbon. If all the atoms/groups on double bonded carbon are different then the configuration of such molecule could not be assigned as *cis*- and *trans*- nomenclature. A more general nomenclature (*i.e.* E/Z nomenclature) was introduced which was based on *Cahn-Ingold-Prelog* system. In E/Z system the configuration is specified by

the relative positions of two highest priority groups/atoms on the two carbons of the double bond.

Let us understand the *E/Z* nomenclature system by considering an example which we have already discussed in the beginning of this Unit (example 1).



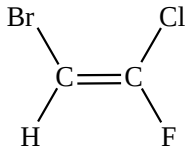
***cis*-2-butene**



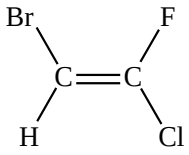
***trans*-2-butene**

You can easily identify which one is *cis*- isomer and which one is *trans*- just by looking the position of similar atoms/groups. It is a simple and visual way of telling the two isomers apart. *So why do we need an alternative system?*

Now consider one another example in which we will change all the atoms/groups in above example by replacing one CH_3- by Br, other CH_3- by Cl, and one H- by F. Now try to predict the nomenclature of these two isomers of **2-bromo-1-chloro-1-fluoroethene (I and II)**. ***Could you name these isomers using cis- and trans- nomenclature?*** The simplest answer is '**NO'**.

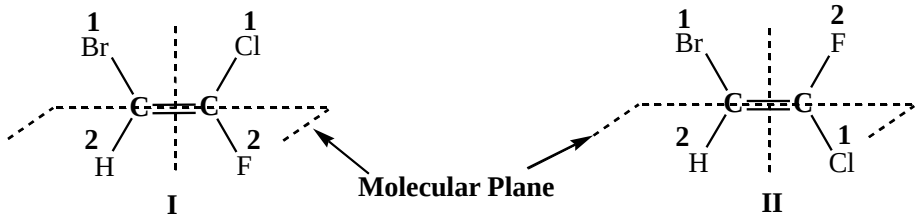


I

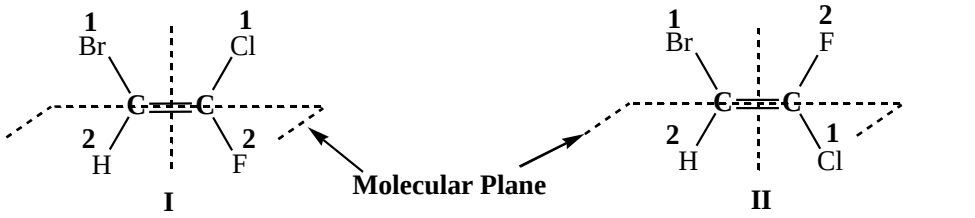


II

Because all four atoms attached to the carbon-carbon double bond are different, therefore it is not so simple that you can predict them as *cis*- and *trans*- to each other. The E/Z system of nomenclature provides the most appropriate solution to above problem. This system is based on the priority of the attached atoms/groups on each double bonded carbon. The priority of the atoms/groups can be assigned as per the 'Sequence Rule' or 'CIP Rule' given by Cahn-Ingold-Prelog. We have discussed the detail about 'Sequence Rule' in later part of this Unit. Now assign priority to atoms/groups attached to each double bonded carbon in above example.

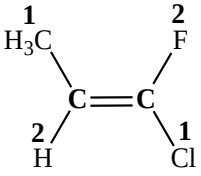


We can easily observe that the both higher priority atoms/groups on each double bonded carbon of isomer **I** are on same side; whereas, the higher priority atoms/groups on each double bonded carbon of isomer **II** are on opposite side. If the two groups with the higher priorities are on the same side of the double bond, such isomer is designated as the (*Z*)- isomer. So you would write it as (*Z*)-name of compound. The symbol *Z* comes from a German word *ZUSAMMEN*, which means together. If the two groups with the higher priorities are on opposite sides of the double bond, then such isomer is designated as (*E*)- isomer. *E* comes from the German *ENTGEGEN*, which means opposite. Thus in given example the isomer **I** is having both higher priority groups/atoms are on same side of double bond, hence it is *Z*- isomer; whereas, the isomer **II** is having both higher priority groups/atoms are on opposite side of the double bond, hence it is *E*-isomer.

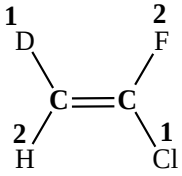


(*Z*)-2-bromo-1-chloro-1-fluoroethene **(*E*)-2-bromo-1-chloro-1-fluoroethene**

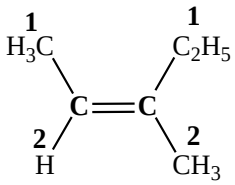
Example 10: Some other examples of geometrical isomers with *E* and *Z* configuration



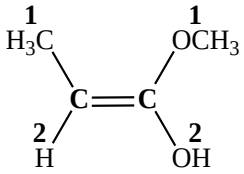
(*E*)-1-chloro-1-fluoroprop-1-ene



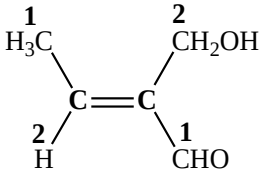
(*E*)-Deuterated1-chloro-1-fluoroprop-1-ene



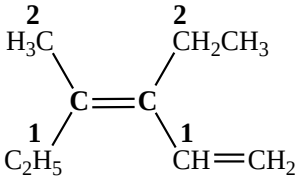
(*Z*)-3-methylpent-2-ene



(*Z*)-1-methoxyprop-1-en-1-ol



(*E*)-2-(hydroxymethyl)but-2-enal



(*Z*)-3-ethyl-4-methylhexa-1,3-diene

Geometrical isomerism in oximes and cyclic compounds:

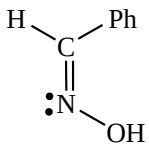
Nitrogen containing compounds like >C=N- as well as –N=N- bond also exhibit geometrical isomerism. The important classes of compounds that exhibit geometrical isomerism due to >C=N- bond are:

(a) Oximes

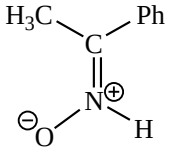
(b) Nitrones

(c) Semicarbazones

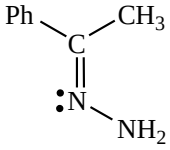
(d) Hydrazones



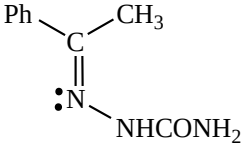
(*Z*)-benzaldehyde oxime



(*E*)-nitrone



(*E*)-1-(1-phenylethylidene) hydrazine



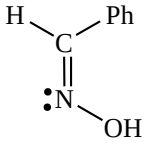
(*E*)-1-(1-phenylethylidene) semicarbazide

Oximes are the most common compounds among all above classes. Both carbon and nitrogen atom in oxime are sp^2 hybridized the C=N bond of oxime consists a sigma (σ) and a pi (π) bond. Therefore, there is no free rotation possible around C=N bond; hence, oximes of aldehyde and

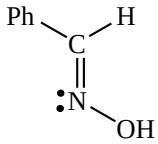
ketones (unsymmetrical) exhibit geometrical isomerism. The configuration of such compounds is also based on priority of the groups/atoms attached to the double bonded carbon and nitrogen. Lone pair of the nitrogen always considered to be the lowest priority group. The priority of the groups/atoms is assigned as per the sequence rule which we have already discussed in Unit 4. If the higher priority groups/atom on double bonded carbon and nitrogen are on same side of the double bond the isomer is considered as *Z*- isomer, whereas if the higher priority groups/atoms are on opposite side the isomer is considered as *E*- isomer.

Example 11:E/Z isomerism is shown by i) benzaldoxime, ii) ethylmethylketoxime and iii) methylphenylketoxime

i)

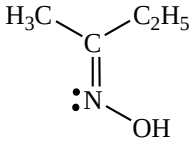


(*Z*)-benzaldehyde oxime

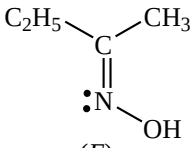


(*E*)-benzaldehyde oxime

ii)

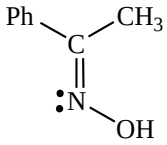


(*Z*)-ethylmethyl ketoxime

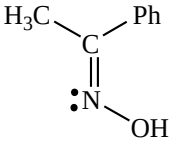


(*E*)-ethylmethyl ketoxime

iii)



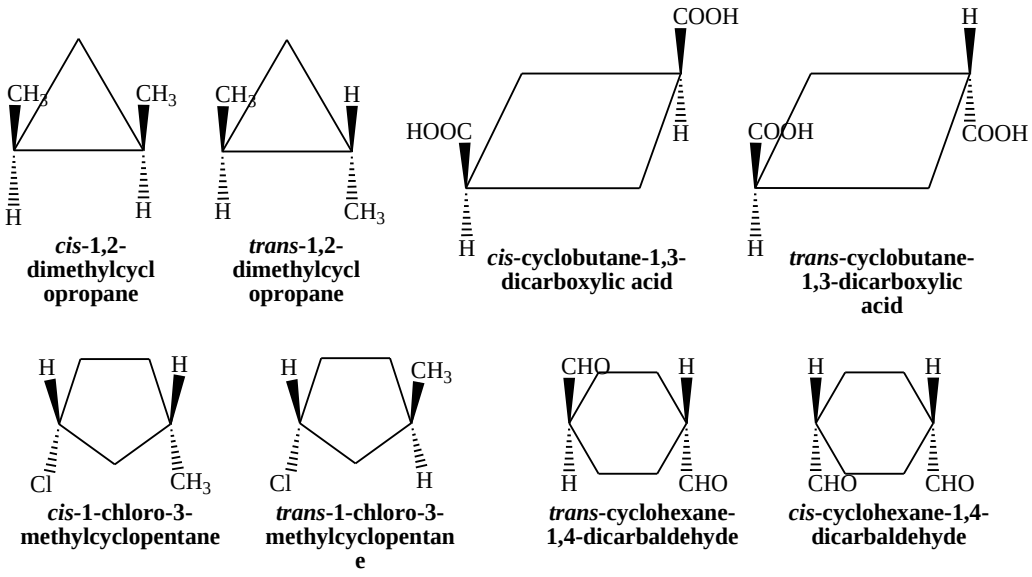
(*E*)-acetophenone oxime



(*Z*)-acetophenone oxime

We have already discussed that the geometrical isomerism is usually arises due to restricted rotation about a bond. Since, there is no rotation possible about the carbon-carbon bond in a cyclic compound or cycloalkanes like cyclopropane, cyclobutane, cyclopantane, cyclohexane, etc. Hence, such molecule also exhibit geometrical isomerism, and can be designated as *cis*- and *trans*- isomer. In a disubstituted cycloalkanes, where the two atoms/groups are bonded on different carbons, can be represented in to two geometrical isomers. The isomer in which the two atoms/groups are located on the same side of the ring is called *cis*-isomer; whereas, the isomer in which the two atoms/groups are located on the opposite side of the ring is called *trans*-isomer.

Example 12: Geometrical isomers of disubstituted cyclopropane, cyclobutane, cyclopantane and cyclohexane.



4.5.2 OPTICAL (CONFIGURATIONAL) ISOMERISM:

Optical isomerism is another class of *stereoisomerism*. The organic compounds that exhibit optical isomerism must have a unique ability to rotate the plane polarized light either towards left or towards right hand directions. This unique ability is generally known as optical activity. Optical activity of any compound is measured by analyzing the sample in an instrument called **Polarimeter.** A solution of known concentration of optically active compound is when exposed to the beam of plane polarized light, the beam of plane polarized light is rotated through a certain number of degrees, either to the clockwise (right) direction or anti-clockwise (left) direction. The compound which rotates the plane polarized light towards clockwise direction is called to be **dextrorotatory** (represented by +); whereas, the compound which rotates the plane polarized light towards anti-clockwise direction is called to be **levorotatory** (represented by -). Figure 1 shows the schematic representation of polarimeter.

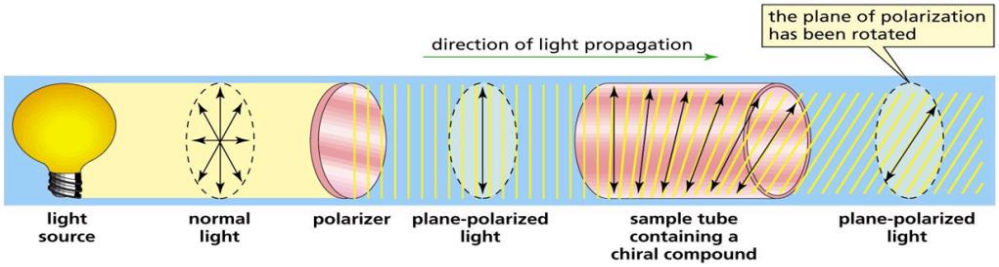


Figure 1. Schematic representation of simple polarimeter

- ☞ *The degree of rotation depends upon the number of the molecules of the compounds falls in the path of beam. To compare the rotating power of different optically active compounds, the specific rotation of each compound is calculated and then comparison should be made.*
- ☞ *Specific rotation is defined as the degree of rotation offered for the given wavelength of plane polarized light at given temperature by a solution of 1g/mL concentration is filled in a 10 cm length sample cell. Specific rotation is represented by* $[\alpha]_{\lambda}^{t}$ *and can be calculated as*

$$[\alpha]_{\lambda}^{t} = \frac{100\alpha}{lc}$$

Where α is observed angle of rotation; t is the temperature of during experiment; λ is the wavelength of light used; l is the length of the tube in decimeter; and c is the concentration of the compounds per 100 mL of solution.

i. <u>Remember:</u>

Optically active compounds always exist in two isomeric forms which rotates the plane polarized light by equal degrees in opposite directions. The optical isomer which rotates the plane polarized light towards right (clockwise direction) is known as Dextrorotatory Isomer or (+)*-isomer, whereas, the optical isomer which rotates the plane polarized light towards left (anticlockwise direction) is known as Levorotatory Isomer or* (-)*-isomer.*

4.6 ELEMENTS OF SYMMETRY

All optically active molecules/object are chiral and they exhibit enantiomerism (Figure 2). A chiral molecule is that which cannot be superimposed on its mirror image; however, both the non-super imposable isomers are called enantiomers. We will learn more about chirality and enantiomerism in separate section of this unit.

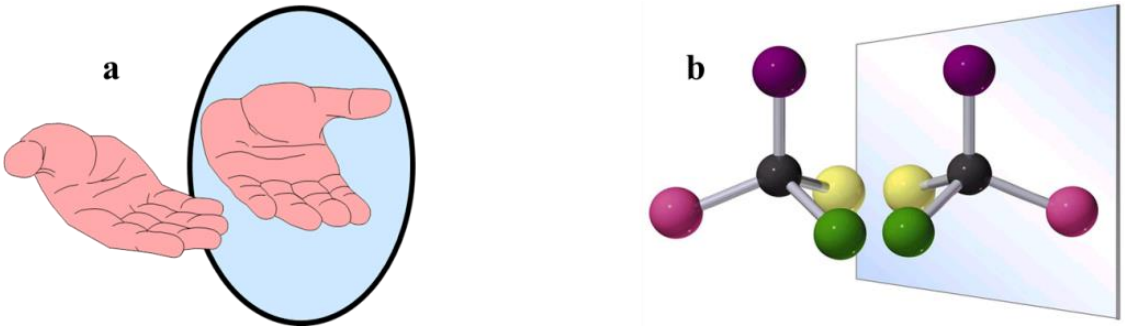


Figure 2. (**a**) Non super imposable mirror image relationship of right and left hands. (**b**) Ball and stick model of tetravalent chiral carbon atom.

Elements of symmetry are a simple tool to identify whether a molecule is chiral or not. The necessary condition for optically active molecule to be chiral is that, the molecule should not possess any kind of symmetry elements. The elements of symmetry are generally categorized as follows:

(i) Simple axis of symmetry (C_n)

(ii) Plane of symmetry (σ)

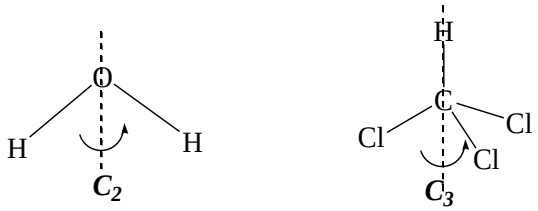
(iii) Centre of symmetry (C_i)

(iv) Alternating axis of symmetry (S_n)

(i) Simple axis of symmetry (C_n):

When a rotation of 360°/n (where n is any integer like 1,2,3…etc.) around the axis of a molecule or object is applied, and the rotated form thus obtained is non-differentiable from the original, then the molecule/object is known to have a *simple axis of symmetry*. It is represented by C_n.

Example 13: Water molecule has C_2 (two fold axis of symmetry) whereas chloroform has C_3 axis of symmetry.

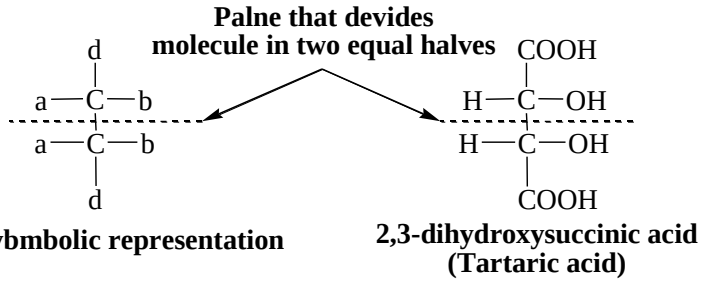


☞ *From above example you can easily understand that if you rotate the water molecule by 180° (i.e. 360°/2=180°) along its molecular axis you will get the identical (non-differentiable) form of water molecule, hence water molecule has two fold of symmetry. Similarly, if you rotate the chloroform molecule by 120° (i.e. 360°/3=120°) along its molecular axis you will get the identical (non-differentiable) form of chloroform molecule, hence chloroform molecule has three fold of symmetry.*

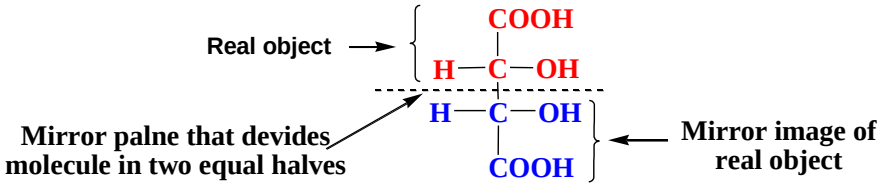
(ii) Plane of symmetry (σ):

It is defined as 'when a plane that devised a molecule or object in to two equal halves which are related to object and mirror image is known as *plane of symmetry*. It is represented by σ.

Example 14: Plane of symmetry in Tartaric acid



☞*From above example you can easily understand that if we put a mirror plane/reflection plane exactly at the centre axis of the molecule/object; you will found that the mirror image thus obtained is the complementary of the original and both will give us the appearance of complete molecule/object.*

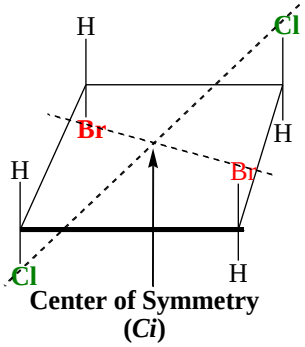


2,3-dihydroxysuccinic acid
(Tartaric acid)

(iii) Centre of symmetry (C_i):

A molecule has a centre of symmetry when, for any atom in the molecule, an identical atom exists diametrically (diagonally) opposite to this centre and at equal distance from it.

Example 15: An isomer of 1,3-dichloro-2,4-dibromocyclobutane has a centre of symmetry

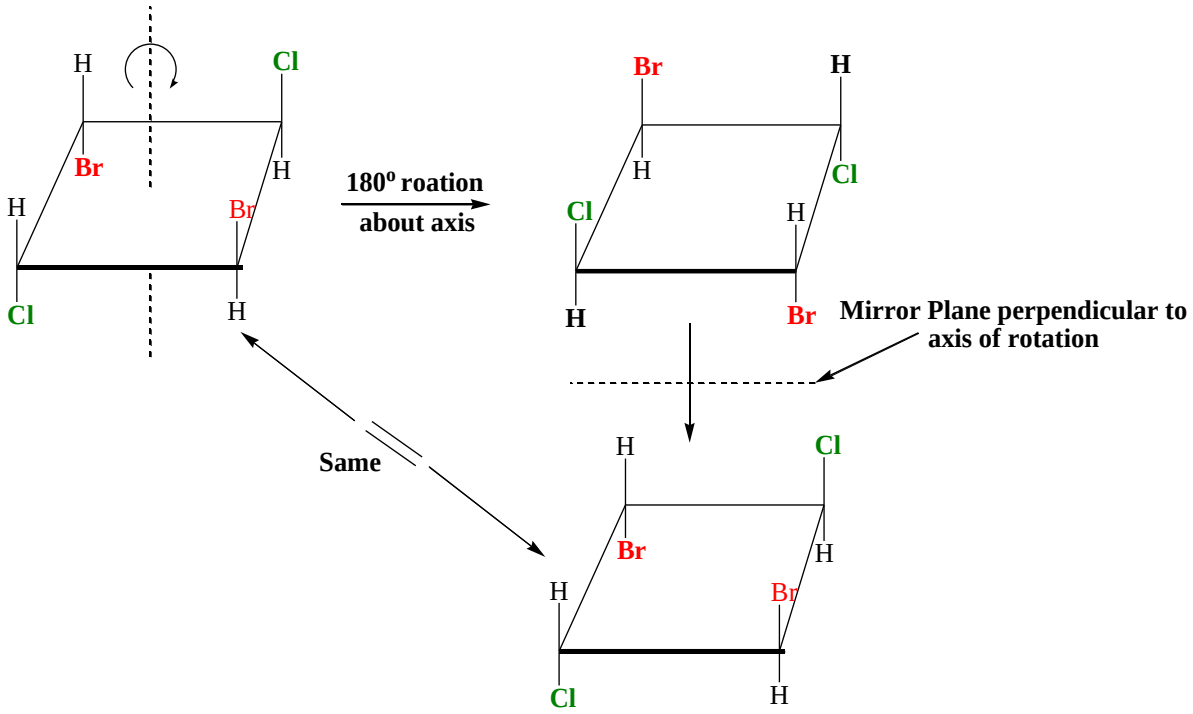


☞*From above example you may understand that all the identical atoms are situated diagonally and at equal distance from the centre. This is called centre of symmetry.*

(iv) Alternating axis of symmetry (S_n):

An alternate axis of symmetry is defined as, when a molecule is rotated by 360°/n degrees about its axis and then a reflection plane is placed exactly at perpendicular to the axis, and the reflection of the molecule thus obtained is identical to the original. It is represented by S_n.

Example 16. An isomer of 1,3-dichloro-2,4-dibromocyclobutane has a 2 fold alternate axis of symmetry

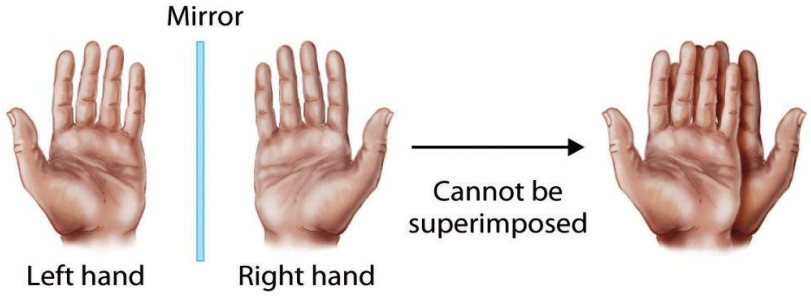


MOLECULAR CHIRALITY, ENANTIOMERISM:

The necessary condition for a molecule to have optical isomerism is that molecule should not have any kind of symmetry elements present in it, in other words the molecule should be dissymmetric. Such molecules are called '*Chiral'* and the property is called '*molecular chirality*'. Optically active chiral molecules which are non-super imposable on their mirror images are called '*enantiomers'* and the phenomenon is known as '*enantiomerism'*. To exhibit optical isomerism an organic compound must have at least one asymmetric carbon atom. An asymmetric carbon atom is that which is bonded to four different atoms or groups.

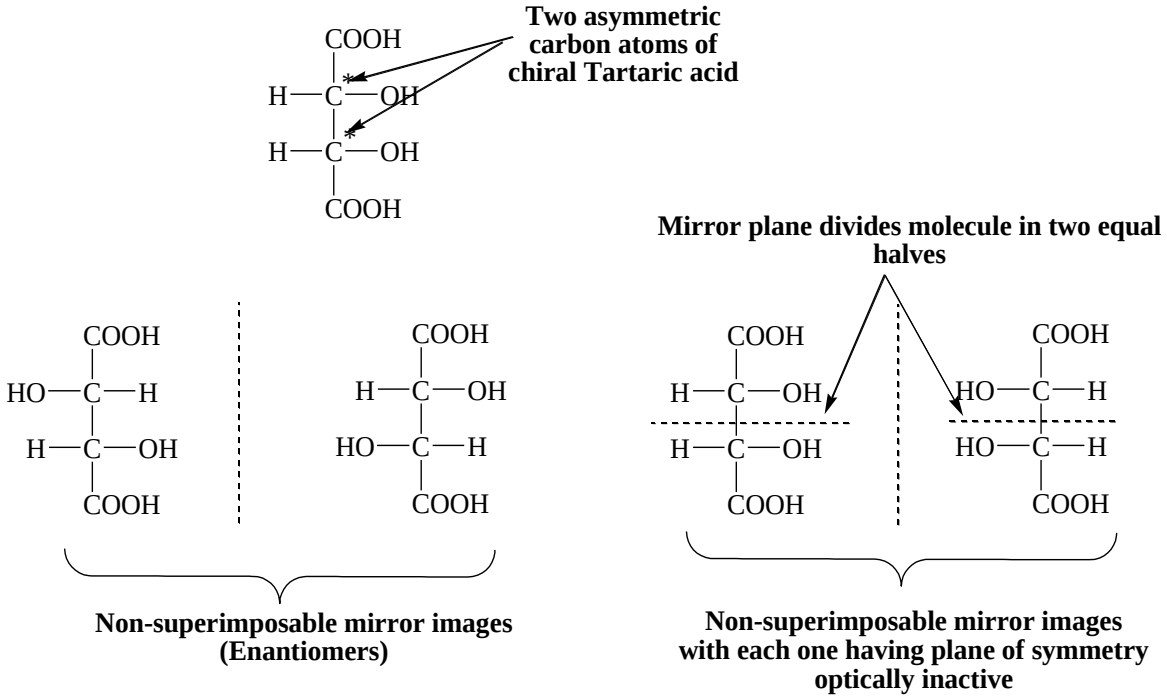
☞*We can easily understand the chirality by comparing our hands (left hand and right hand). Our left hand and right hand are the best example of non-super imposable mirror image of each other. Each hand is therefore considered as chiral.*

ii. Remember: *Our left hand and right hand are non-super imposable mirror image of each other each one of them is chiral.*



iii. Remember: *Chirality is the necessary and sufficient condition for the existence of enantiomers.*

Example 17. Tartaric acid has two asymmetric carbon and it exists in four forms, out of them two form are optically active and two are optically inactive.



4.7 *STEREOGENIC CENTRE (STEREOGENICITY)*

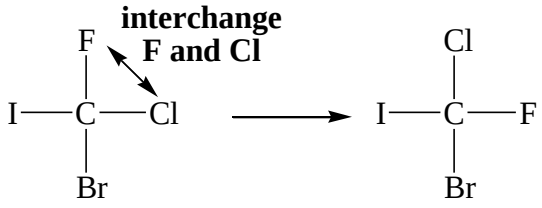
As we discussed in previous section that if a molecule contains one carbon atom which is directly bonded with four different groups or atoms, and the molecule do not have any kind of symmetry element present in it, such molecule is called asymmetric or chiral.

When the interchange of the position of two directly bonded groups or atoms of a centre carbon atom results a new stereoisomer, such chiral centre is called stereo centre or stereogenic centre and the property is called stereogenicity.

If the new stereoisomer is a non-super imposable mirror image of the original molecule such carbon centre is called chiral carbon centre.

iv. Remember: All the chiral centers are stereogenic centers but all stereogenic centers are not chiral centre.

Example 18: Bromochlorofluoroidomethane exhibits chiral carbon centre



Interchange of F and Cl results non-superimposable stereoisomers

4.7.1 OPTICAL ACTIVITY (ENANTIOMERISM):

It is already known to you (from section 4.5) that the optical activity is an ability of a chiral molecule to rotate the plane of plane-polarized light either towards left or right direction. The rotation is measured by an instrument called Polarimeter. When a beam of plane polarized light passes through a sample that can rotate the plane polarized light, the light appears to dim because it no longer passes straight through the polarizing filters. The amount of rotation is quantified as the number of degrees that the analyzing lens must be rotated to observe the no dimming of light appears. Optical rotation can be measured by using the following formulae

$$[\alpha]_{\lambda}^{t} = \frac{100\alpha}{lc}$$

Where α is observed angle of rotation; t is the temperature of during experiment; λ is the wavelength of light used; l is the length of the tube in decimeter; and c is the concentration of the compounds per 100 mL of solution.

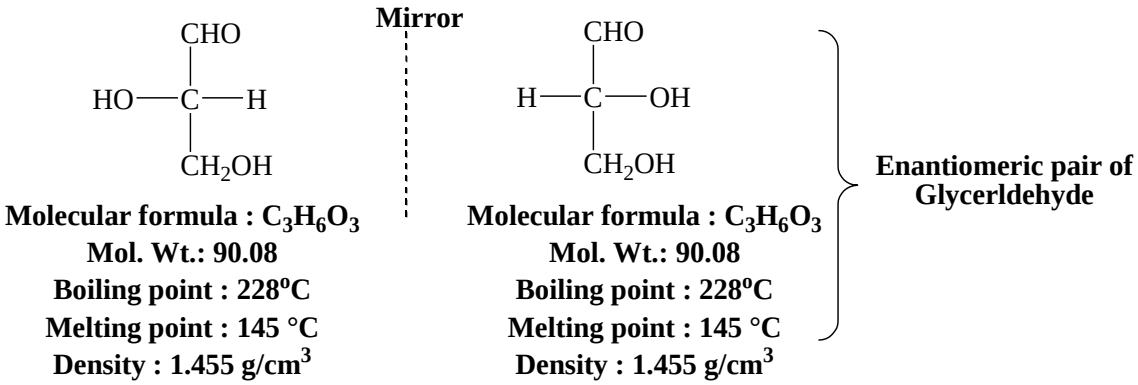
Optically active chiral compounds that are non-super imposable mirror image of each other are called enantiomers.

4.7.2 Properties of enantiomers:

The main properties of enantiomers are given as follow

- Enantiomers always exist in pair
- Enantiomers are non-super imposable mirror image to each other
- Enantiomers have same physical properties (like boiling point, melting point, solubility, density, viscosity, refractive index etc.)and chemical properties in achiral environment
- Each enantiomers have opposite behavior with respect to plane polarized light, if one of them will rotate the plane polarized light towards right hand direction then definitely the other will rotate the plane polarized light towards left hand direction.
- Each enantiomers shows the same chemical reactivity with achiral reagent; however they have different reactivity with chiral reagent.

Example 19: Glyceraldehyde molecule is a chiral molecule. It has a pair of enantiomers with same physical properties except their behavior towards plane polarized light



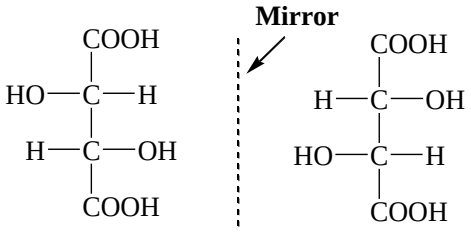
☞*You can see that the glyceraldehyde molecule can exists in two enantiomeric forms which differ only in the arrangement of bonded atoms around the centre chiral carbon. The physical properties (like molecular formula, molecular weight, melting point, boiling point and density etc.) of both the isomers are same. But if one isomer will rotate the plane polarized light towards right hand direction (dextrorotatory) then the other one will rotate the plane polarized light towards left hand direction (levorotatory).*

4.7.3 CHIRAL AND ACHIRAL MOLECULES WITH TWO STEREOGENIC CENTRES:

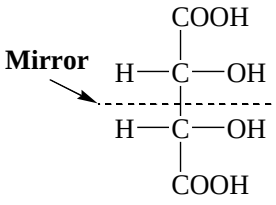
As we have discussed earlier in this unit *(sec. 4.6)* that chiral molecules are those in which the centre carbon atom is bonded directly through four different atoms/groups and do not have any kind of symmetry element present in it and the molecule has non-super imposable mirror image. However, those molecule in which centre carbon atom is directly bonded through four different atoms of groups and it satisfied any kind of symmetry elements are called achiral molecule. Achiral molecules have super imposable mirror images.

Let us consider the stereoisomers of Tartaric acid which has two stereo centers with identical atoms/groups attached to both the stereo centers. The tartaric acid have two stereo centers and can have four stereoisomers out of which two stereoisomers are non-super imposable mirror image of each other called enantiomers and chiral; and rest two are identical to each other and also have plane of symmetry hence it can be divided in to two equal halves, therefore are achiral.

Example 20: Tartaric acid has two stereo centers with three stereoisomers (two are chiral and one achiral stereoisomer)



Chiral Tartaric acid

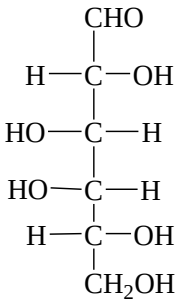


Achiral Tartaric acid

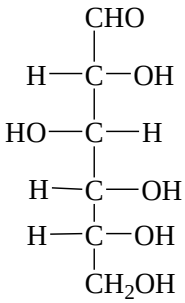
4.7.4 DIASTEREOMERS:

Diastereomers are those stereoisomers that are not mirror image of each other, in other words you can understand the diastereomers are stereoisomers that are not enantiomers. Diastereomers are non-enantiomeric stereoisomers with two or more stereo centers. The pair of stereoisomer that differs in the arrangement of atoms/groups bonded with at least one stereo centre is called diastereomers.

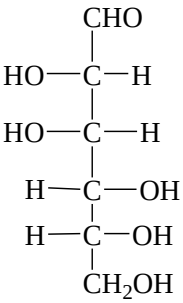
Example 21: D-Galactose, D-Glucose and D-Mannose are the non-mirror image stereoisomer of each other. Therefore are called diastereomers.



D-Galactose

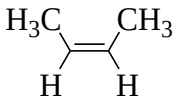


D-Glucose

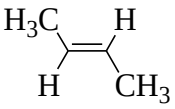


D-Mannose

Example 22: *cis*- and *trans*-2-butenes are non-mirror image stereoisomers of each other hence are called diastereomers.



***cis*-2-butene**



***trans*-2-butene**

4.7.5 PROPERTIES OF DIASTEREOMERS:

The main properties of diastereomers are given as follows:

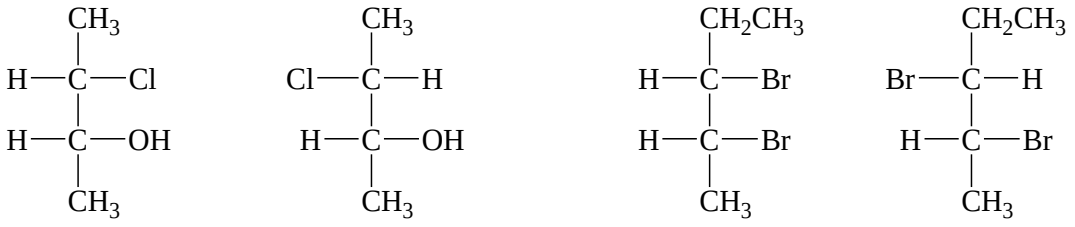
- All the stereoisomers except enantiomers are diastereomers.
- Diastereomers have different physical properties like boiling point, melting point, density, solubility, density, viscosity, refractive index etc.
- Diastereomers have different chemical properties like rates of reactions, reactivity even in achiral reaction medium.
- This difference in physical and chemical properties of diastereomers is very useful in the separation of enantiomers from their mixture.

4.7.6 ERYTHRO (*SYN*) AND THREO (*ANTI*) DIASTEREOMERS:

Threo and *erythro* nomenclature method is designated by organic chemists to assign appropriate name to diastereomers. The *threo* and *erythro* naming is given only to those diastereomers having two adjacent stereocentres. The nomenclature is applicable to these diastereomers if there are two common atoms/groups bonded to each adjacent stereo centre. In other words the terms *erythro* and *threo* are generally applied only to those molecules which do not have symmetric ends. However, when the ends are symmetric then instead of *erythro* and *threo* the *meso* and *dl* nomenclature is preferred. We will discuss separately about *meso* and *dl* in this unit.

If the similar groups/atoms on adjacent stereocentres of diastereomer are on same (*syn*) side it is designated as *erythro*, whereas if the similar groups/atoms on adjacent stereocentres of diastereomer are on opposite (*anti*) side the diastereomer is designated as *threo.*

Example 23: You can easily understand the erythro and threo nomenclature by taking examples of 3-bromo-2-butanol and 2,3-dibromo pentane.



Erythro ***Threo*** ***Erythro*** ***Threo***

3-Chloro-2-butanol **2,3-Dibromopentane**

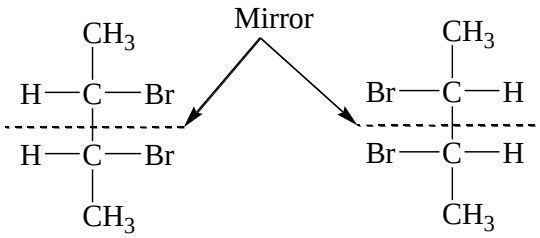
☞*You can see if both the hydrogen atom on two adjacent stereocentres of 3-chloro-2butanol lies on same (syn) side the isomer is called erythro, whereas, when both the hydrogen atoms on two adjacent stereocentres of 3-chloro-2butanol lies on opposite (anti) side the isomer is called threo. Similarly you can find the same observation with 2,3-dibromopentane and designate the isomers as erythro and threo.*

☞*You must also remember that the each erythro and threo stereo isomer can have their non-super imposable mirror image (enantiomers). Thus there will be always one enantiomeric pair of erythro and one enantiomeric pair of threo stereoisomer exists for a stereoisomer with two similar atoms on adjacent stereocentres.*

4.7.7 *MESO* COMPOUNDS:

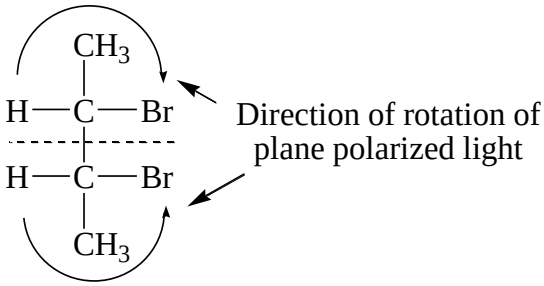
A compound with two or more carbon stereo centre but also having a plane of symmetry is called *meso* compounds. All the carbon centers have four different atoms/groups but the compound can be divided in to two equal halves which are super imposable mirror image.

Example 24: 2,3-dibromobutane have two stereocentres, but the molecule have two symmetric ends therefore it can be divided in to two equal halves. In other words the molecule have plane of symmetry.

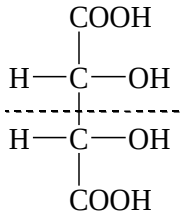


2,3-Dibromobutane

☞*We can see that even the 2,3-dibromobutane have non super imposable mirror image but this molecule have an internal plane of symmetry hence this molecule is optically inactive or achiral. This molecule will not be able to rotate the plane polarized light in any direction. If one half of the molecule will rotate the plane polarized light towards right hand direction with some degrees; the other half will rotate the plane polarized light towards left hand direction with same degrees of rotation. Thus the net rotation of the plane polarized light is zero. Such molecules are called meso compounds.*



Example 25: Another example of meso compound is one of the stereo isomeric forms of Tartaric acid (2, 3-dihydroxysuccinic acid). The molecule is optically inactive because it has internal plane of symmetry.



meso-Tartaric acid

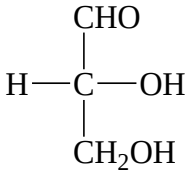
4.8 RELATIVE AND ABSOLUTE CONFIGURATION

Relative and absolute configuration of a compound discusses about the spatial arrangement of atoms/groups around the centre chiral atom. Relative configuration is a comparison of the spatial

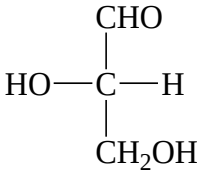
arrangement of attached atoms/groups of two different chiral centers. Relative configuration is a geometrical property which do not changes on reflection; whereas, the absolute configuration is the precise arrangement of atoms in three dimensional space. The *D/L* system is usually known as relative configuration whereas, the *R/S* stereo descriptor or nomenclature system for chiral molecules is known as absolute configuration. The absolute configuration is a topographic property which changes on reflection.

4.8.1 *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 $–CH_2OH$ 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*.



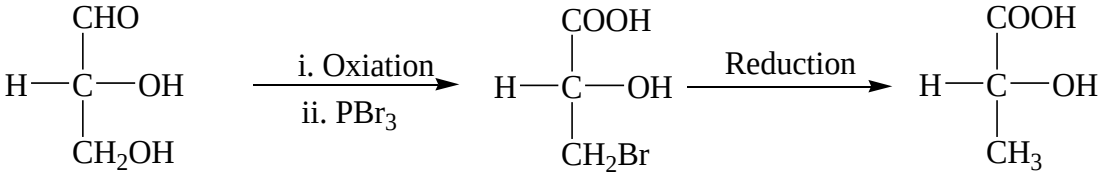
***D*-(+)-glyceraldehyde**



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



***D*-(+)-glyceraldehyde** ***D*-(+)-Lactic acid**

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 pe prepared or converted from the glyceraldehyde.*
- *It is limited to only one chiral atom.*

4.8.2 *R/S* NOMENCLATURE:

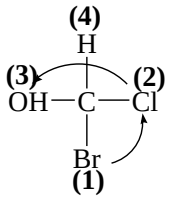
Since you have been noted from the above discussion on D/L configuration, there are several drawbacks associated with the D/L nomenclature system. Hence a definite and universally applicable nomenclature system was needed to specifying the absolute configuration of each chiral centre in a molecule. Cahn and coworkers (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 deceasing 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.

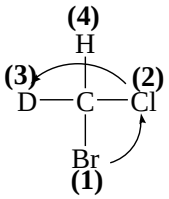
4.8.3 SEQUENCE RULE:

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.



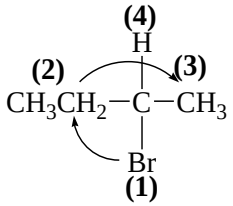
Bromochloromethanol
1-2-3 order is anticlockwise
the configuration is *S*



Deuterio bromochloromethane
1-2-3 order is anticlockwise
the configuration is *S*

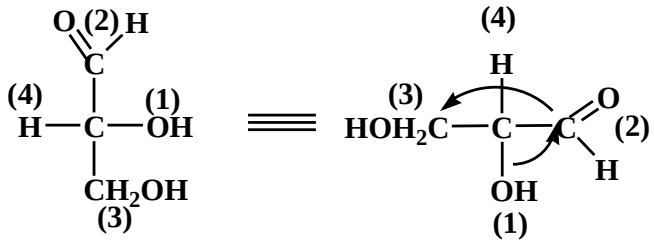
Deuterium (D) is an isotope of Hydrogen with mass number 2 hence get higher priority than H

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.



2-bromobutane
1-2-3 order is clockwise
configuration is *R*

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.

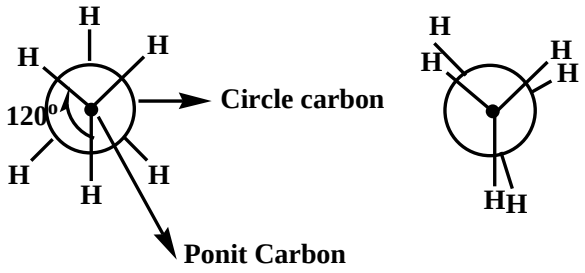


2,3-dihydroxypropanal
1-2-3 order is anticlockwise
configuration is *S*

4.9 NEWMAN AND SAWHORSE PROJECTION FORMULA

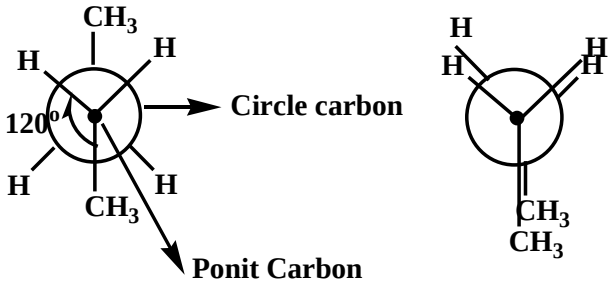
The different spatial arrangements of atoms in a molecule which is readily interconvertible by rotation about single bonds are called ***conformations***. The study of various preferred conformations of a molecule and the correlation of physical and chemical properties to the most preferred conformer is called conformational analysis. Due to rapid interchange of the spatial positions of groups/atoms these conformers are non-separable under normal conditions. Since, different conformations arises because of the rotation about single bonds, hence, they are also called the rotamers. The conformational and configurational isomerisms are related to energy barrier for interconversions of different spatial arrangements of atoms in a molecule. If the energy barrier for interconversion of different spatial arrangements is between 0.6 kcal/mol-16.0 kcal/mol; it result the conformational isomers or conformers; whereas, if this energy barrier is more than or equal to 16 kcal/mol than the configurational isomers are obtained.

The Newman representation formula: Newman Projections are used mainly for determining conformational relationships. Recall that, conformers are molecules that can be converted into one another by a rotation around a single bond. Newman Projections are also useful when studying a reaction involving prochiral molecules that have a double bond, in which the addition of a new group creates a new stereocenter.In this notation, you are actually viewing a molecule by looking down a particular carbon-carbon bond. The Newman representation formula is a planar representation of the sawhorse formula. The molecule is viewed along the axis of a carbon-carbon bond. The carbon atom in front of the viewer is represented by a dot (●), whereas the carbon atom away to the viewer is represented by circle. The rest of the atoms/groups are located on each carbon atoms at +120° or -120° angles to each other as shown below:



Newman representation formula of ethane

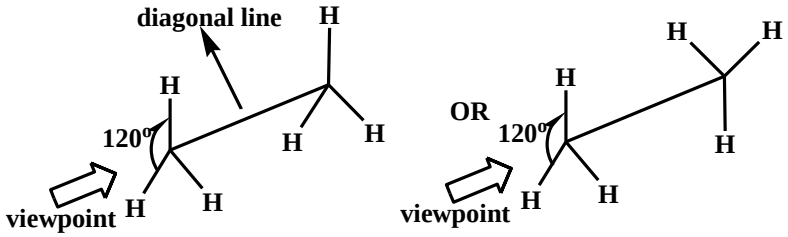
Addition of more carbons makes Newman Projections more complicated. For example, Newman Projections can be made for butane, such that it's eclipsed, gauche, and anti-conformations can be seen. (Recall that these three forms of butane are conformational isomers of one another.) In this case, the front dot represents the second carbon in the butane chain, and the back circle represents the third carbon in the butane chain. The Newman Projection condenses the bond between these two carbons.



Newman representation formula of butane

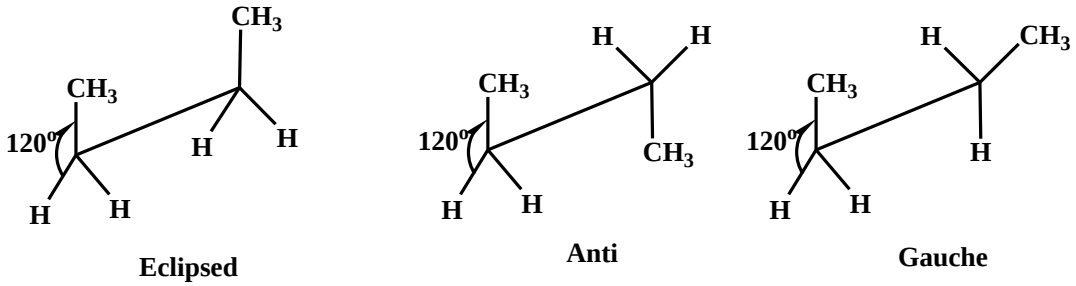
The Sawhorse representation formula: Sawhorse Projections are very similar to Newman Projections, but are used more often because the carbon-carbon bond that is compressed in a Newman Projection is fully drawn out in a Sawhorse Projection. When properly laid-out, Sawhorse Projections are useful for determining enantiomeric or diastereomeric relationships between two molecules, because the mirror image or superimposibility relationships are clearer. Like with Newman Projections, a Sawhorse Projection is a view of a molecule down a particular carbon-carbon bond, and groups connected to both the front and back carbons are drawn using sticks at 120 degree angles. Sawhorse Projections can also be drawn so that the groups on the front carbon are staggered (60 degrees apart) or eclipsed (directly overlapping) with the groups on the back carbon. Below are two Sawhorse Projections of ethane. The structure on the left is

staggered, and the structure on the right is eclipsed. These are the simplest Sawhorse Projections because they have only two carbons, and all of the groups on the front and back carbons are identical. The sawhorse representation formula is the spatial arrangement of all the atoms/groups on two adjacent carbon atoms. The bond between adjacent carbon atoms is represented by a diagonal line and rest of the atoms are located on each carbon at +120° or -120° angles to each other. The sawhorse representation is shown as:



Sawhorse representation formula of ethane

Addition of more carbons makes Sawhorse Projections slightly more complicated. Similar to Newman Projections, Sawhorse Projections can also be made for butane, such that it's eclipsed, gauche, and anti-conformations can be seen. (Recall that these three forms of butane are conformational isomers of one another).



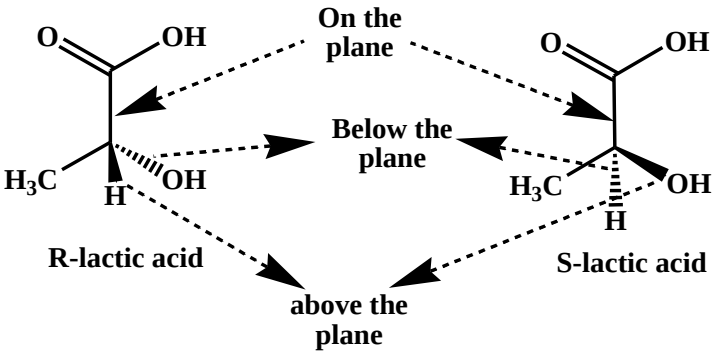
Sawhorse representation formula of butane

4.10 FISCHER AND FLYING WEDGE FORMULA

The sp^3 hybridized tetrahedral carbon is three dimensional in nature. Generally it is very difficult to represent a three dimensional structure in a two dimensional plane paper. There are many methods have been developed for two dimensional representation of a three dimensional

structure. Out of them the flying-wedge and Fischer representation methods are most commonly used for two dimensional representation of a three dimensional structure.

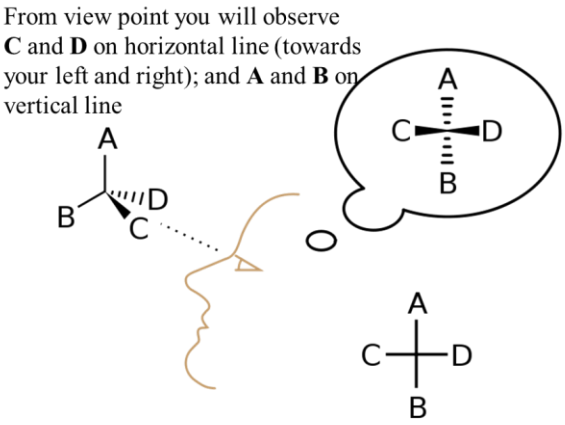
The flying-wedge: This is the most commonly used model for the two dimensional representation of a three dimensional molecule. In this model the bonds are presented in continuous, solid thick and dashed lines. A solid this line represents a bond projecting above the plane of the paper; it is considered that the bond with solid thick line is pointing towards observer. A dashed line represents a bond below the plane of the paper; it is considered that the bond with dashed line is pointing away to the observer. The bonds with continuous lines represent the bonds in the plane of paper. Let us consider an example of *R*-Lactic acid and *S*-Lactic acid.



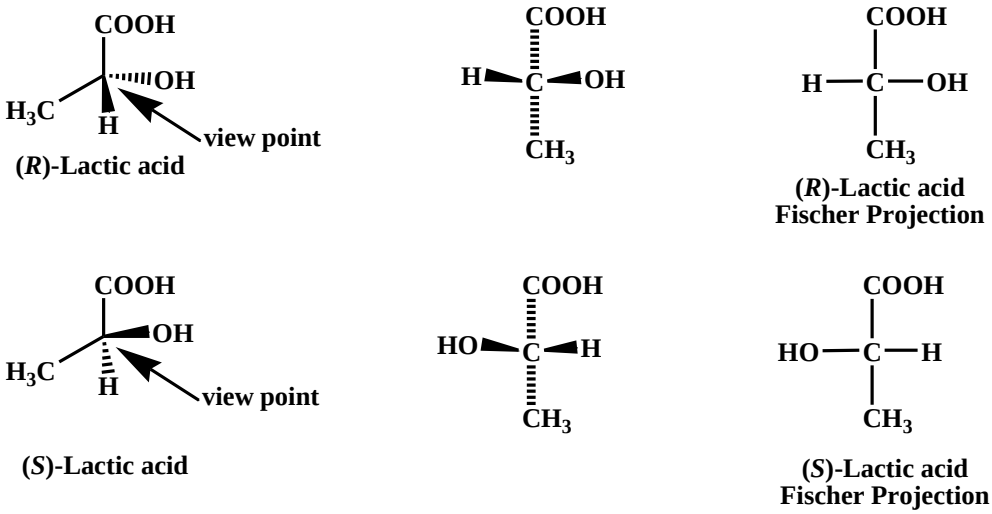
Flying-wedge representation of *R*- and *S*-Lactic acid

Fischer projection formula: It is a simplification of flying-wedge representation, in Fischer projection formula all bonds are drawn as solid lines in a plane paper. Fischer Projections are used often in drawing sugars and hydrocarbons, because the carbon backbone is drawn as a straight vertical line, making them very easy to draw. When properly laid-out, Fischer Projections are useful for determining enantiomeric or diastereomeric relationships between two molecules, because the mirror image relationship is very clear. In a Fischer Projection, each place where the horizontal and vertical lines cross represents a carbon. The vertical lines are actually oriented away from you (similar to dashes in the Wedge-Dash Notation) and the horizontal lines are oriented toward you (similar to wedges in the Wedge-Dash Notation).

Fischer projection is not as demonstrative as flying –wedge representation. It does not represent the actual shape of the molecule. Usually the Fischer projection formula is drawn so that the longest carbon chain in the molecule is vertical with the highly oxidized group on the top.



Let us consider an example for conversion of flying-wedge formula to Fischer projection formula for *R*- and *S*- Lactic acid.



Conversion of flying wedge to Fischer projection formula for Lactic acid

4.11 RACEMIC MIXTURE (RACEMATES)

A Racemic mixture is an equimolar mixture of a pair of enantiomers. The racemic mixture or racemates are optically inactive due to mutual or external compensation of two enantiomeric constituents. Racemic mixture in liquid and vapor phase shows physical properties (like boiling points, density, refractive index etc.) identical to those of pure enantiomers. However, the solid phase enantiomeric mixtures have some properties different from the pure enantiomers.

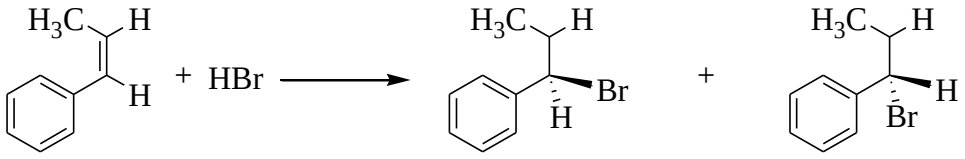
i. ***Remember:*** *Racemic mixture is not a meso compound; since both are optically inactive. The racemic mixture is an equimolar mixture of two enantiomers whereas meso is a*

single compound. Meso compounds are optically inactive because of the internal compensation; however, the racemic mixtures (racemates) are optically inactive because of the external compensation.

You might have aware with that the enantiomerically pure compounds are of great importance in chemical and pharmaceutical areas. But during the synthesis of optically active compounds using achiral reaction condition and achiral reagents, it always gives racemic mixture (racemates). Therefore to obtain the pure enantiomers we must have to separate the racemic mixture in to corresponding pure enantiomers. Thus, the separation process of a racemic mixture in to its pure individual enantiomeric constituents is called resolution of racemic mixtures (resolution of enantiomers).Since enantiomers have identical physical properties(like solubility, boiling point, melting point, density, refractive index etc.),therefore, they cannot be separated by common physical techniques such as direct crystallization, distillation or basic chromatography. There are four general methods that are extensively being used for the resolution of racemic mixtures.

- **i.** Mechanical separation (crystallization method) method
- **ii.** Diastereomer formation method
- **iii.** Chromatographic method
- **iv.** Biochemical/enzymatic methods

Example 27: The addition of HBr on *beta*-Methyl styrene gives an equimolar mixture of enantiomers.



beta-Methyl styrene

50% *S* enantiomer

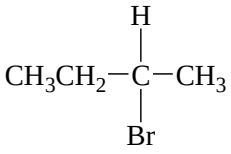
50% *R* enantiomer

4.12 QUASI-ENANTIOMERS

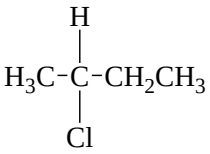
Quasi enantiomers are defined as, two different chemical compounds those are closely related to the sense of chirality. Although chemically different, they are sterically similar (isosteric) and are still able to form a racemic crystalline phase. One of the compound have a property to rotate the plane polarized light towards left hand direction; whereas, the other have a tendency to rotate the

plane polarized light towards right hand direction. The first quasi-enantiomeric pair was studied by Pasteur in 1853.

Example 28: (*R*)-2-bromobutane is a quasi-enantiomer of (*S*)-2-chlorobutane.



(R)-2-Bromobutane

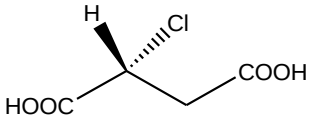


(S)-2-Chlorobutane

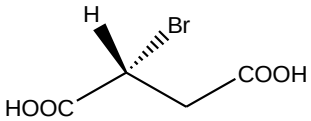
4.13 QUASI-RACEMATE

Quasi-racemate is defined as a 1:1 mixture of quasi-enantiomers that may form a compound, a eutectic mixture, or a solid solution and shows typical compound behaviour in the phase diagram.

Example 29: Equimolar mixture of (+)-Chlorosuccinic acid and (+)-Bromosuccinic acid form a quasi-racemate and shows eutectic behaviour similar to that of a conglomerate.



(*R*)-2-chlorosuccinic acid



(*R*)-2-bromosuccinic acid

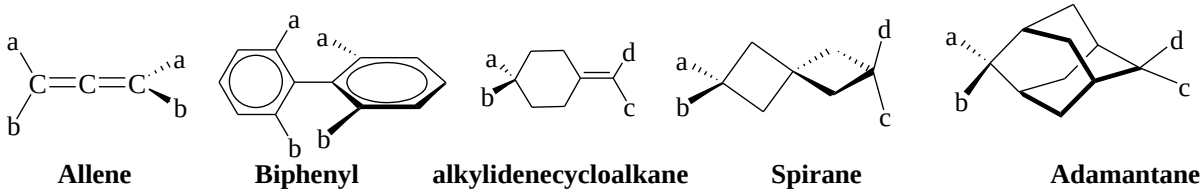
4.14 STEREOCHEMISTRY OF ALLENES, SPIRANES; BIPHENYLS, ANSA COMPOUNDS CYCLOPHANES AND RELATED COMPOUNDS

In above sections of this unit we have discussed about the compounds containing one or more stereocentres and their chirality is specified at these centres. However, there are a class of compounds with nonsuperimposable mirror images it is not possible to identify a stereocentre, then to predict the stereochemistry of such compounds it becomes necessary to focus our attention on other aspects of the molecule. Thus, the presence of stereocentre is not a necessary and sufficient condition for molecular dissymmetry. The overall chirality of a molecule can be

categorised in to three elements; i) stereocentres; ii) stereoaxes; and iii) stereoplanes, one other element of chirality is still there and called helicity.

Chirality due to axes (Axial chirality): Such type of chirality is produced in a molecule when there is no chiral centre present in the molecule. As discussed, in order to produce chirality it is not necessary for all of the substituents to be different. However, it is sufficient to have each substituent different from its nearest neighbour.

When four atoms/groups attached to a central atom are located on the corners of tetrahedron the central atom is termed as chiral centre. If the chiral centre is replaced by a linear grouping like C-C or C=C=C, the tetrahedron geometry get extended along the axis of the grouping and thus generates a chiral axis. Depending on the nature of groups attached with the carbon atoms, some examples of molecules with chiral axis are allenes, biphenyls, alkylidenecycloalkanes, spiranes, adamentanes etc.; are shown below (Figure 3).



Allene **Biphenyl** **alkylidenecycloalkane** **Spirane** **Adamantane**

Figure: 3 examples of molecules with chiral axis are allenes, biphenyls, alkylidenecycloalkanes, spiranes and adamentane

Allenes: Allenes are compounds with two or more double bonds side-by-side. Such bonds are called *cumulated double bonds.* The central carbon of allene forms two sigma bonds and two pi bonds. The central carbon is *sp*-hybridized and the two terminal carbons are sp^2-hybridized. The two π-bonds attached to the central carbon are perpendicular to each other. The geometry of the π-bonds causes the groups attached to the end carbon atoms to lie in perpendicular planes (Figure 4). The bond angle formed by the three carbons is 180°, indicating linear geometry for the carbons of allene.

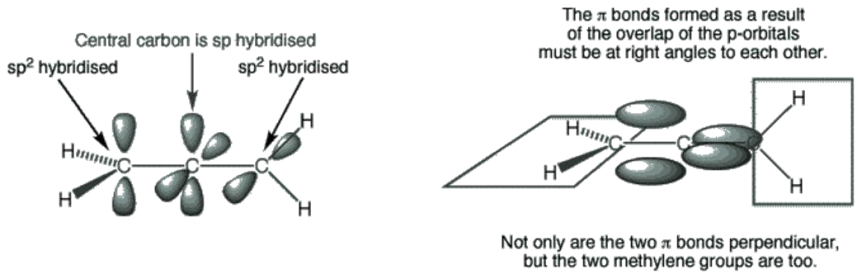
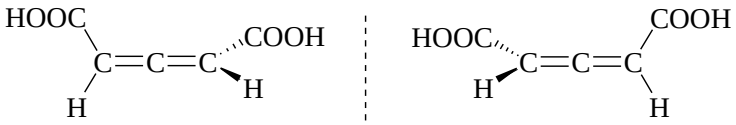


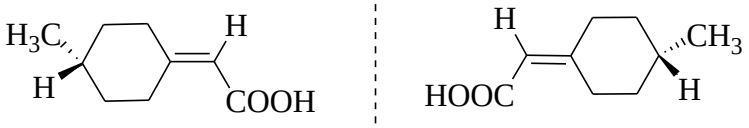
Figure 4: Planar depiction of allene molecule

Stereochemistry of Allenes: When three or more adjacent carbon atoms in a molecule are bonded by double bonds, the compounds is called cumulene or said to have cumulative double bonds. Allene is the simplest example of this class. Allenes are chiral and they have nonsuperimposable mirror images and exist as enantiomers although they have no chiral centre.



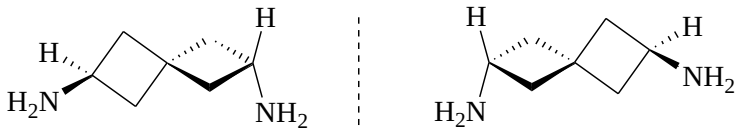
Nonsuperimposable Mirror images
(Enantiomeric Pair)

Stereochemistry of Alkylidenecycloalkanes: The replacement of double bonds in allene by a cycloalkane ring gives the alkylidenecycloalkane; such replacement does not change the basic geometry of the molecule. The suitably substituted alkylidenecycloalkanes also exhibit enantiomerism. The enantiomerism in such compounds is also due to the presence of chiral axis. For example, 4-methylcyclohexyldene acetic acid has been resolved into two enantiomers.



4-methylcyclohexyldene acetic acid

Stereochemistry of Spiranes: When both the double bonds in allenes are replaced with the ring system the resulting compounds are known as *spiranes* or *spiro* compounds. The conditions for chirality in spiranes are similar to those of allenes. The two rings of spiranes are perpendicular to each other; therefore, proper substitution on the terminal carbon will make the molecule chiral and thus exhibit enantiomerism. The chirality in the spiranes is also due to the presence of chiral axis. For example, Diaminospiroheptane can be resolved in to its enantiomers.

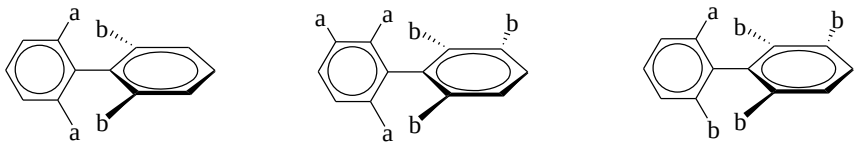


Diaminospiroheptane

Stereochemistry of Biphenyls: Stereoisomers obtained due to the restricted rotation about carbon-carbon single bond are called atropisomers and the phenomenon is called atropisomerism. Such compounds also have the chirality due to the axis. Suitably substituted biphenyls exhibit enantiomerism due to the presence of chiral axis. This enantiomerism arises due to atropisomerism *i.e.* restricted rotation around C-C bond between two phenyl rings. This steric hindrance of substituents at *ortho*- position of the each ring is responsible for such restricted rotation. To maintain the maximum stability, molecule orients itself in such a manner so that both the *ortho*- substituted phenyl rings lie in different plane.

Biphenyl shows the enantiomerism when the molecule has the following properties.

a) Each ring must be unsymmetrically substituted. Each of the rings should not contain any kind of symmetry element.



I **II** **III**

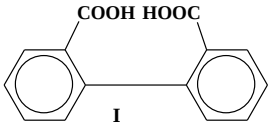
nonresolvable Biphenyl (optically inactive due to plane of symmetry)

resolvable Biphenyls (optically active due to absence of symmetry elements)

b) Suitable substitution (at least one substitution) at *ortho*- position must be there at each rings.

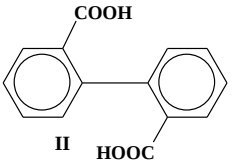
c) *othro*- substituents must be larger in size (-Cl, -Br, -I, -COOH, $-NO_2$, $-NHCOCH_3$, $-SO_3H$, -R groups etc.).

The smaller groups at *othro*- position make the compounds planar in nature and thus do not exhibit atropisomerism.



I

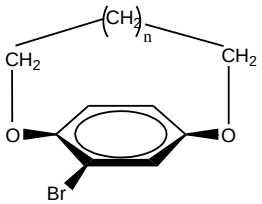
nonresolvable Biphenyl (optically inactive due to plane of symmetry)



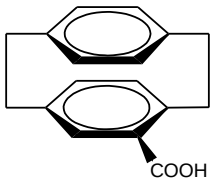
II

nonresolvable Biphenyl (optically inactive due to centre of symmetry)

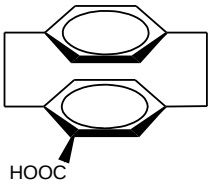
Chirality due to Plane (Planar Chirality): Chirality shown by a molecule due to the asymmetry in molecular plane is called chirality due to plane. The chirality is particularly due to the out of the plane arrangement of atoms or groups in the molecule with respect to reference plane, hence called chiral plane. The most important example of the molecule with chiral plane is cyclophanes. Other examples are trans-cyclooctene, bridged annulenes and metallocenes etc.



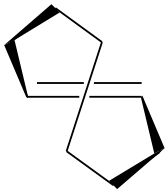
Polymethylene ether of hydroquinone



paracyclophane (*S*)-



paracyclophane (*R*)-



***trans*-cyclooctene**

The polymethylene bridge is perpendicular to the plane of the benzene ring; the substituent Br restricts the rotation of the benzene nucleus inside the methyl bridge, that makes the molecule chiral. Similarly the simple paracyclophane can be resolved because the benzene ring cannot rotate in such a way that the carboxylic passes through the acyclic ring. The plane of both the aromatic rings is approximately parallel to each other. Similarly the *trans*-cyclooctene also exhibits the chirality due to the presence of chiral plane.

4.15 SUMMARY

- The stereochemistry, determines many chemical, physical and biochemical properties of the compounds.

- The types of stereo-chemical situations are divided into classes called geometrical isomers, conformational isomers and configurational isomers.
- All of the isomers are studied as a way to understand the shapes and properties of organic compounds.
- Alkenes and cyclic compounds display geometrical isomers.
- In alkenes, geometrical isomers are labeled as *cis*- or *trans*- for the longest chain in the alkene, or as *E* and *Z* for substituents of higher priority attached to the alkene.
- Cyclic alkanes are designated only as *cis*- or *trans*-.
- Stereochemistry is all about the 3Dimensional spatial aspects of chemistry.
- Molecules that differ only in the arrangement of bonds in 3Dimensional space are called "stereoisomers"
- Many objects (including molecules) are non-differentiable from their mirror images, but other objects, such as your left and right hands, are differentiable. An object that has a non-superimposable mirror image is said to be "chiral" (Greek = "handedness") and one that has a superimposable mirror image is called "achiral".
- Pairs of molecules that are non-superimposable mirror images of each other are called "enantiomers"
- The most common type of "chirality" is observed when a carbon atom has four different groups attached to it. This carbon atom is then described as a chiral or asymmetric or stereogenic center. This later term can also be contracted to a stereocenter.
- Enantiomers have the same chemical and physical properties (melting points, boiling points, heat of combustion etc.), except for their interaction with plane polarized light or with other chiral molecules (reagents, solvents, catalysts, etc). (Think about how your feet feel if you put them in the wrong shoes).
- Diastereomers are stereoisomers that are not enantiomers.
- The differing interaction with plane polarized light gives rise to optical activity. Enantiomers cause the plane of polarized light to rotate in opposite directions, but to the same extent (clockwise = +ve, counterclockwise = -ve). This can be measured using a polarimeter. An achiral molecule is optically inactive.

- A 50:50 mixture of a pair of enantiomers is called a racemic mixture. This is optically inactive since the rotations produced by each of the enantiomers must cancel each other out.
- If there is more of one enantiomer than the other, then the optical purity of a sample can be determined by measuring the rotation and comparing it to that of a pure enantiomer. This can be used to establish the enantiomeric excess (ee) of the mixture.
- Despite what one may observe, most molecules are not 2D objects, they are 3D as a result of the spatial arrangement of the atoms, groups and bonds. The interaction of molecules (reactions) which occur as the result of collisions between these 3D objects in 3D spacecan therefore also have 3D requirements and characteristics. Stereochemistry is all about the 3D properties of molecules and reactions.

4.16 TERMINAL QUESTION

1. What do you understand by Isomerism? Give its types.
2. What is chirality? Explain the necessary condition for a molecule to be chiral.
3. What do you understand by optical activity? How is it measured?
4. What are enantiomers and diastereomers?
5. What are symmetry elements? How they affect optical isomerism?
6. Explain relative and absolute configuration.
7. What is racemization?

4.17 ANSWERS

Ans.1. When two or more compounds having the same molecular formula but difference in their chemical and/or physical properties are called isomers and the phenomenon is known as isomerism. Isomerism has following types:

a. Structural (constitutional) Isomerism
b. Stereo (configurational) Isomerism

Ans. 2. An organic compound with four different atoms/groups attached to center carbon and have non-superimposable mirror image is called chiral compound and the phenomenon is called

chirality. The presence of four different atoms/groups attached to center carbon and absence of any kind of element of symmetry are the necessary condition for a molecule to be chiral.

Ans. 3. The tendency of an organic compound to rotate the plane polarized light towards left or right hand direction is called optical activity. Optical activity of any compound is measured by analyzing the sample in an instrument called **Polarimeter.** A solution of known concentration of optically active compound is when exposed to the beam of plane polarized light, the beam of plane polarized light is rotated through a certain number of degrees, either to the clockwise (right) direction or anti-clockwise (left) direction. The compound which rotates the plane polarized light towards clockwise direction is called to be **dextrorotatory** (represented by +);whereas, the compound which rotates the plane polarized light towards anti-clockwise direction is called to be **levorotatory** (represented by -).

Ans. 4. Optically active chiral compounds that are non-superimposable mirror image of each other are called enantiomers. Whereas, optically active compounds which are non-mirror image of each other are called diastereomers.

Ans. 5. Elements of symmetry are a simple tool to identify whether a molecule is chiral or not. The necessary condition for optically active molecule to be chiral is that, the molecule should not possess any kind of symmetry elements. The elements of symmetry are generally categorized as follows:

(i) Simple axis of symmetry (C_n)
(ii) Plane of symmetry (σ)
(iii) Centre of symmetry (C_i)
(iv) Alternating axis of symmetry (S_n)

Optically active compound should not have any kind of symmetry elements.

Ans.6. Relative and absolute configuration of a compound discusses about the spatial arrangement of atoms/groups around the centre chiral atom. Relative configuration is a comparison of the spatial arrangement of attached atoms/groupsof two different chiral centres. Relative configuration is a geometrical property which do not changes on reflection. The absolute configuration is the precise arrangement of atoms in space. The *D/L* system is usually known as relative configuration whereas, the *R/S* stereo descriptor or nomenclature system for

chiral molecules is known as absolute configuration. The absolute configuration is a topographic property which changes on reflection.

Ans.7. The process of conversion of an optically active compound in to the racemic mixture/racemate is called *racemization*. The racemization process may take place under the influence of temperature, light or chemical reagents.

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UNIT 5: STEREOCHEMISTRY-II

CONTENTS

5.1 OBJECTIVES

In this unit learner will be able to

- Define prochiral property of an achiral molecule
- Differentiate between two similar atoms or groups attached with a prochiral center
- Learn about the homotopic, heterotopic, enantiotopic and diastereotopic ligands and faces
- Define stereospecific and stereoselective synthesis
- Learn about the principle of asymmetric synthesis
- Learn about the various conformations of cyclohexanes and decalins
- Know about the stereochemistry of compounds containing N, P and S

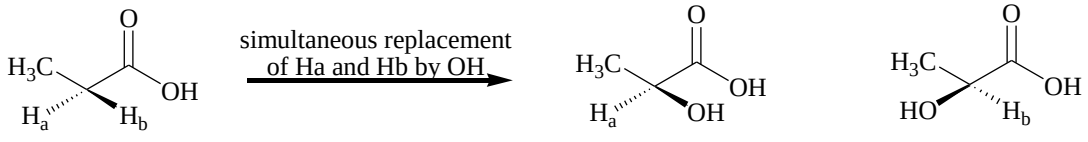
5.2 INTRODUCTION

Stereochemistry is a sub-discipline of chemistry that involves the study of the relative spatial arrangement of atoms. The study of stereochemistry focuses on stereoisomers, which by definition have the same molecular formula and sequence of bonded atoms (constitution), but differ in the three-dimensional orientations of their atoms in space. For this reason, it is also known as 3D chemistry-the prefix "*stereo*-" means "*three-dimensionality*". Stereochemistry includes methods for determining and describing these relationships; the effect on the physical or biological properties these relationships impart upon the molecules in question, and the manner in which these relationships influence the reactivity of the molecules in question (dynamic stereochemistry). Thus stereochemistry is all about the 3D properties of molecules and reactions and has its own language and terms that need to be appreciated.

5.3 *TOPOCITY*

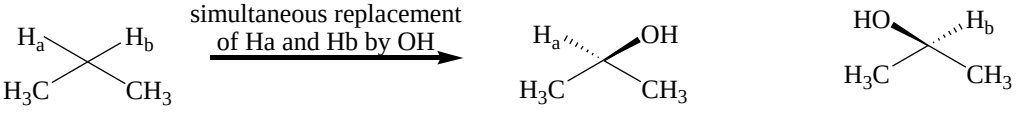
Stereo-chemical relationships between individual atoms or groups within a single molecule can be defined in terms of topicity. Thus, two atoms equated by a mirror reflection of the molecule are enantiotopic and two atoms in equivalent environments (i.e., the methylene protons in n-propane) are homotopic. Two protons placed in diastereomeric positions by a mirror reflection are in diastereotopic environments.

Examples 1: Propane has homotopic ligands; however, propionic acid has enantiotopic ligands



Propionic acid
(prochiral molecule H_a and H_b are enantiotopic)

Both the compounds are enantiomer



Propane H_a and H_b are homotopic

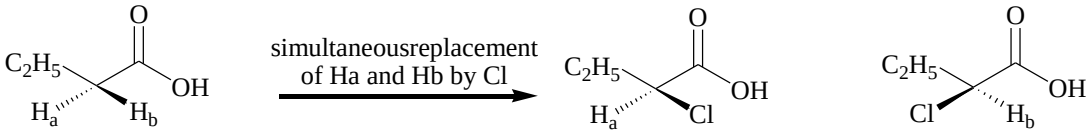
Both the compounds are identical

5.3.1 PROCHIRAL CENTER AND PROCHIRAL MOLECULE:

As we discussed in Unit 4 (Stereochemistry I) of this module; a tetrahedrally bonded atom with four different atoms or groups (**Cabcd**) is called a chiral molecule. However, a tetrahedrally bonded atom with two identical atoms or groups (**Cabbc**) is called an achiral molecule.

If replacement of one of the identical groups in an achiral molecule of type **Cabbc** with a different group when gives an asymmetric molecule then the achiral center is called prochiral center and the molecule is called prochiral molecule. This property is called prochirality.

Example 2: Propionic acid is a prochiral molecule with centre carbon atom as prochiral centre. Replacement of one of the hydrogen atom by a different group gives the optically active compound.



Butanoic acid
(prochiral molecule H_a and H_b are enantiotopic)

Both the compounds are enantiomer

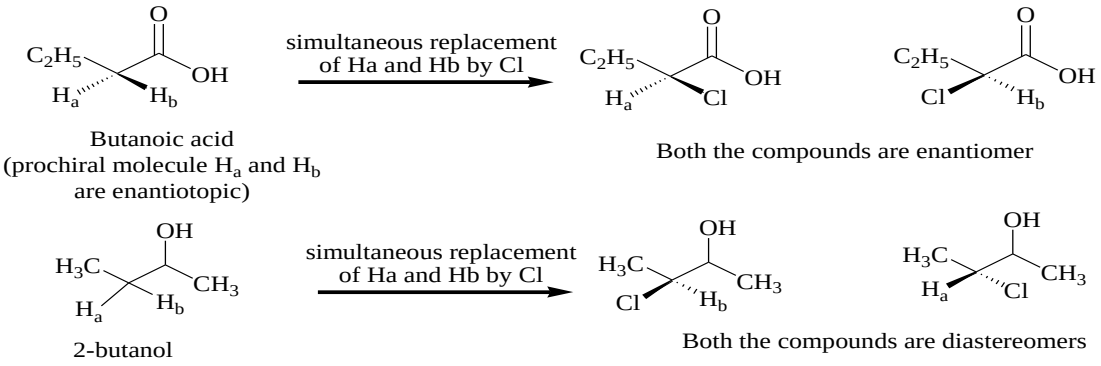
5.3.2 HOMOMORPHIC LIGANDS:

Two apparently identical atoms/groups of a prochiral centre are called homomorphic atoms/groups. These are also known as homomorphic ligands. Homomorphic is a Greek name where *homos* meaning similar and *morphe* meaning form. Thus two homomorphic ligands are indistinguishable during their isolation. Two hydrogen atoms of Propionic acid are apparently identical groups *i.e.* H atoms of methylene group are called homomorphic atoms or ligands.

5.3.2 STEREOHETEROTOPIC LIGANDS:

Consider two molecules, Butanoic acid in which two identical hydrogen atoms attached with methylene carbon, and 2-butanol in which two identical hydrogen atoms of methylene carbon. Replacement of any one of the homomorphic ligands in butanoic acid will give a pair of enantiomer; however, replacement of any one of the homomorphic ligands in 2-butanol will give the formation of two diastereomers. Since enantiomers and diastereomers are stereoisomers therefore the homomorphic groups or ligands are also called stereoheterotopic groups or ligands.

Example 3: Stereoheterotopic ligands (H_a and H_b) of **butanoic acid** and **2-butanol**. Simultaneous replacement of H_a and H_b in both the compounds leads the formation stereoisomers.



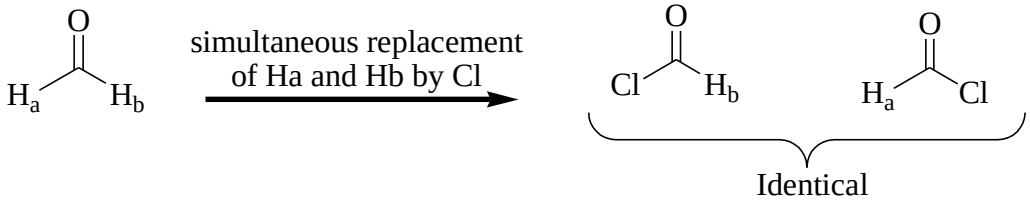
5.3.4 PROCHIRALITY:

It is the property of some molecules due to which these molecules can be converted in to stereoisomers (enantiomers or diastereomers) by replacing one of the identical atoms or groups by a different atom or group. It is also known as '*prostereoisomerism'* more specifically. If the replacement of such atoms or groups leads the formation of enantiomer the atoms or groups are called enantiotopic; whereas, if such replacement lead the formation of diastereomers the atoms or groups are termed as diastereotopic.

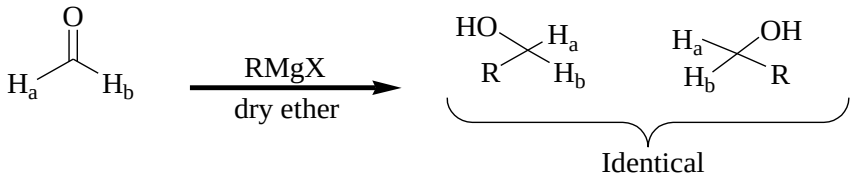
5.3.5 HOMOTOPIC LIGANDS AND FACES:

When replacement of two H atom in a methylene carbon of a molecule generates two identical compounds instead of stereoisomers, these two hydrogen atoms are called homotopic ligands.

Example 4: Let us consider the case of formaldehyde, the two hydrogen atoms of formaldehyde when replaced with a different atom or group generates two identical compounds hence both the hydrogen atom of formaldehyde molecules are homotopic atoms or homotopic groups.

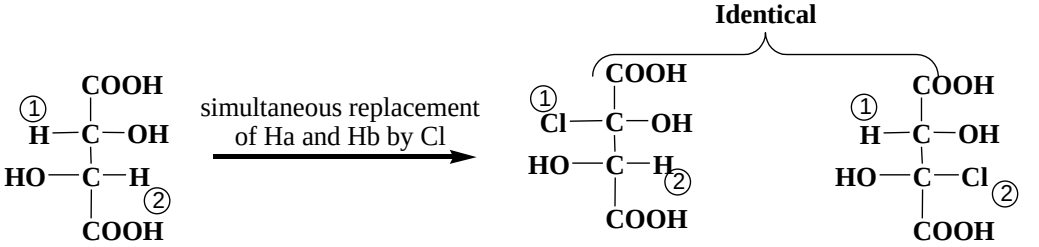


Example 5: Similarly there is no way to differentiate between the two faces of formaldehyde molecule. The addition of Grignard reagent RMgX to either faces gives the identical compound ethanol. Hence, two faces of formaldehyde are also homotopic faces.



Substitution/addition and symmetry are the two key criteria to determine the topicity of homomorphic ligands and faces. Two homomorphic ligands are called homotopic if replacement of each one of them by another atom or group leads to the identical structure. Thus we can consider three hydrogen atom of acetic acid as homotopic hydrogen, similarly three hydrogen of toluene are also called homotopic hydrogen, because replacement of each one of them will lead the same structure.

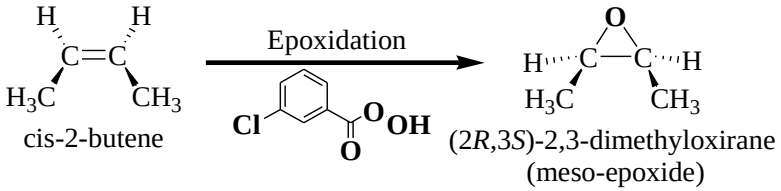
Example 6: In (2*R*,3*R*)-2,3-dihydroxytartaric acid two homotopic hydrogen atoms are present; replacement of each one of them by a different atom gives identical compounds.



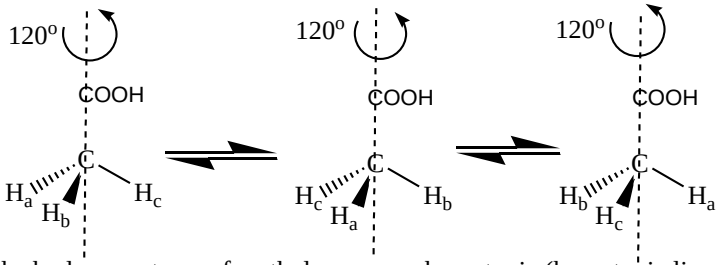
***(2R,3R)* 2,3-Dihydroxytartaric acid**

(2*S*)-2-chloro-2,3-dihydroxysuccinic acid

Example 7: In a double bonded compound like cis-2-butene, two faces of double bond are homotopic since addition on either faces gives the same product. The epoxidation of double bond on either face gives meso product [(*2R,3S*)-2,3-dimethyloxirane].

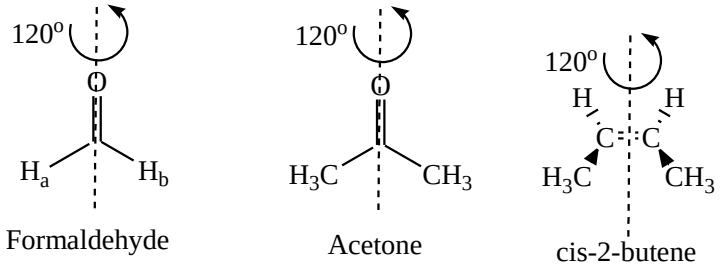


Homotopic ligands and faces can also be determined by employing symmetry operations on the molecule. Let us consider an example of acetic acid, in which all three hydrogen atom of methyl group are homotopic. Two successive rotation of methyl group around its C_3 axis (with the rotation angle of 120°) allow each hydrogen atom to occupy the position of either of the other two hydrogen atoms without effecting any structural changes. As we know that hydrogen atom of methyl group interchanges their position rapidly in 3 dimensional planes, due to this rapid interchange of hydrogen atoms of methyl group leads the formation of indistinguishable structure, that's why these hydrogen atoms are called homotopic hydrogen (homotopic ligands).



All the hydrogen atoms of methyl group are homotopic (homotopic ligands)

Similarly, both the faces of cis-2-butene, formaldehyde and symmetrical ketones are homotopic, hence called homotopic faces.



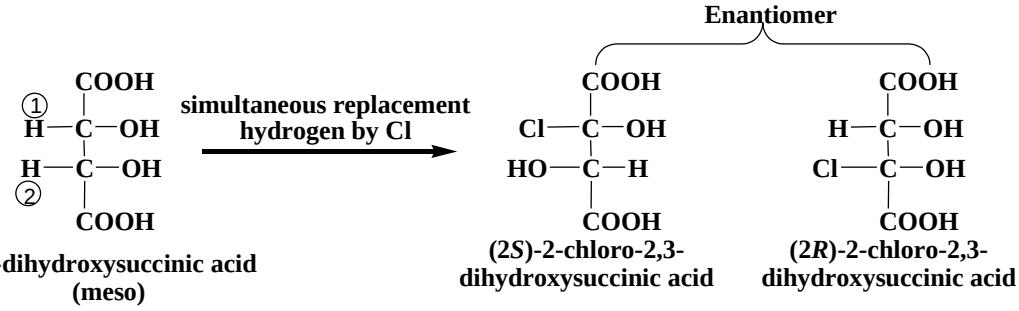
Homotopic Faces

☞ ***Remember:*** *A molecule contains two equivalent atoms/groups they would not be homotopic if the other two groups are different. Such molecules are known as prochiral molecule.*

5.3.6 ENANTIOTOPIC LIGANDS AND FACES:

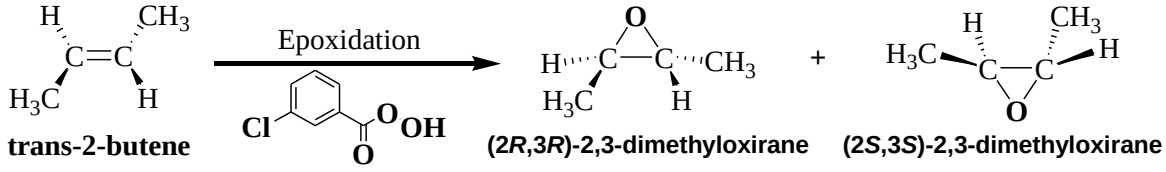
When the replacement of each equivalent atom or groups by a different atom given enantiomeric products, such equivalent atoms or groups are called enantiotopic atoms or enantiotopic ligands.

Example 8: For example, two hydrogen atoms of meso-tartaric acid are enantiotopic since the replacement of each one of them by a different atom or group gives the enantiomeric pair of (*2S*)-2-chloro-2,3-dihydroxysuccinic acid and (*2R*)-2-chloro-2,3-dihydroxysuccinic acid.

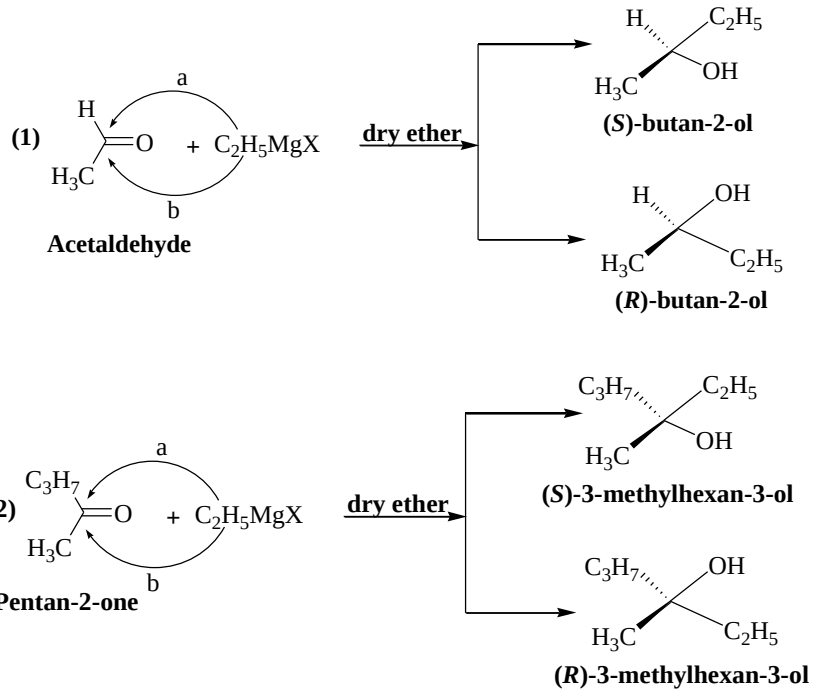


Similarly, when two faces of a double bond gives enantiomers on addition of suitable reagents, such faces are called enantiotopic faces. For example, trans-2-butene and unsymmetrical ketones have enantiotopic faces since they also give enantiomers on addition of suitable reagents.

Example 9: Epoxidation of trans-2-butene on either face of double bonds gives the enantiomeric pair of (*2R,3R*)-2,3-dimethyloxirane and (*2S,3S*)-2,3-dimethyloxirane.



Example 10: Similarly, addition of the Grignard reagent (RMgX; R=C_2H_5) or other organometallic reagents on either faces of unsymmetrical carbonyl compounds gives enantiomers. Hence, faces 'a' and 'b' of acetaldehyde **(1)** and Pentan-2-one **(2)** are called enantiotopic faces.

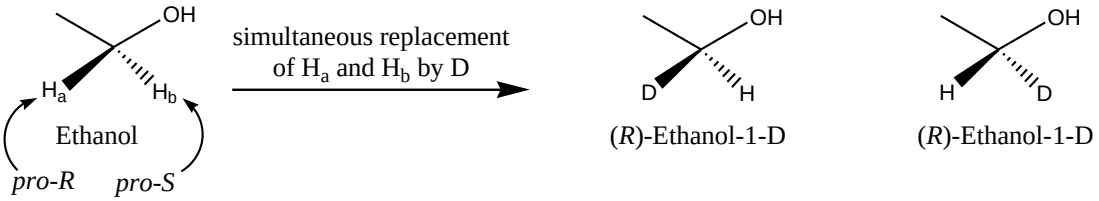


Unlike homotopic ligands and faces, enantiotopic ligands and faces cannot be interchanged by a simple axis of symmetry (C_n). However, they can be interchanged by plane of symmetry, center of symmetry (i) and alternative axis of symmetry (S_n).

5.3.7 NOMENCLATURE OF ENANTIOTOPIC LIGANDS AND FACES:

Naming of enantiotopic ligands and faces is based on the CIP sequence rule by arbitrarily assigning priority to the homomorphic groups/ligands/faces.

Example 11: Let us consider ethanol with two homomorphic ligands (H_a and H_b). If H_a is arbitrarily preferred over H_b in the sequence rule, the priority order of the attached groups at central carbon will be OH>CH_3> H_a> H_b and the hypothetical configuration of the stereocenter will be R, thus H_a is designated as *pro-R* and H_b is designated as *pro-S.* Similarly, if H_b was arbitrarily given higher priority over H_a in that case according to sequence rule priority order would have been OH>CH_3> H_b> H_a and the hypothetical configuration of ethanol would be S, thus H_b is designated as *pro-S* and H_a is designated as *pro-R.* Replacement of H_a by deuterium 'D' gives (*R*)-ethanol-1-*D*, hence, H_a is *pro-R;* similarly, replacement of H_b by D gives (*S*)-ethanol-1-*D*, hence, H_b is *pro-S*.

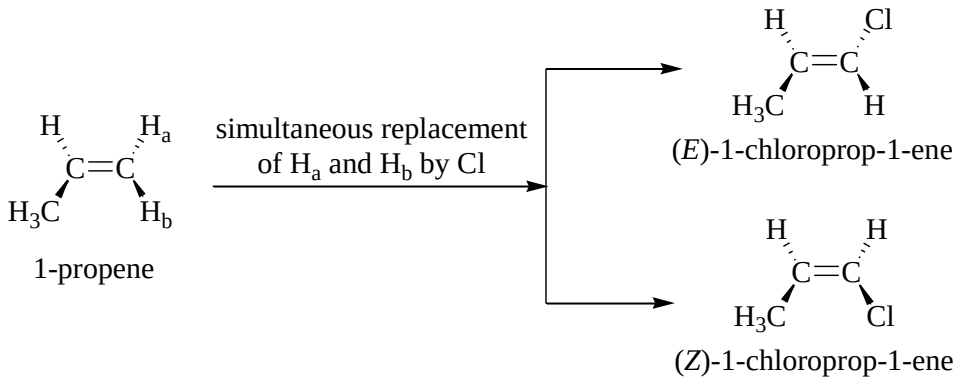


Similalry, two faces of carbonyl carbon are termed as enantiotopic faces. These faces can be designated as *Re*-*Si* nomenclature. The groups around the carbonyl group are given priorities as per CIP sequence rule for R and S nomenclature. While going from the highest priority group to the lowest priority group around the faces of carbonyl group, if the path followed is clockwise the faces is *Re* and if it is anticlockwise, the face is *Si*.

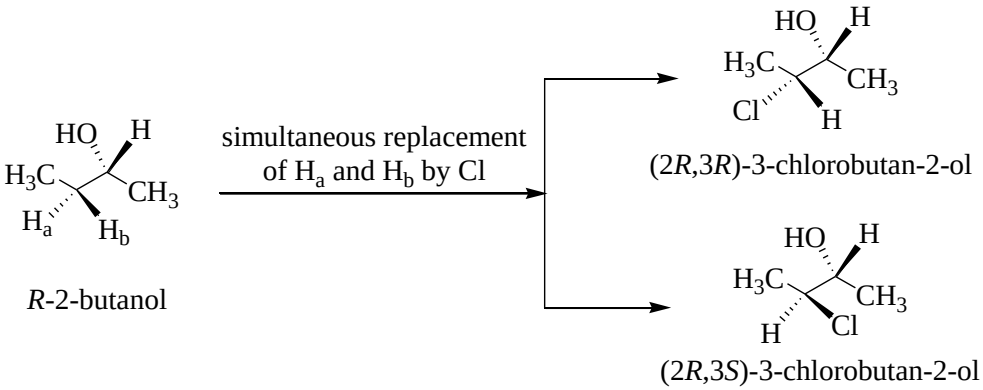
5.3.8 DIASTEREOTOPIC LIGANDS AND FACES:

When the replacement of either of two homomorphic ligands or atoms of a molecule by a different atom generates diastereomers, such homomorphic ligands or atoms are called diastereotopic ligands or atoms.

Example 12: Let us consider an example of propene in which two homomorphic hydrogen are present. Replacement of one of the homomorphic hydrogen with a hetero atom Cl gives *Z*-alkene ((*Z*)-1-chloroprop-1-ene) while replacement of other homomorphic hydrogen atom by Cl generates *E*-alkene ((*E*)-1-chloroprop-1-ene). Both, (*Z*)-1-chloroprop-1-ene and (*E*)-1-chloroprop-1-ene are stereoisomer but non mirror image of each other, hence are called diastereomer. Thus, two hydrogen atoms (*i.e.* H_a and H_b) of 1-propene are diastereotopic.

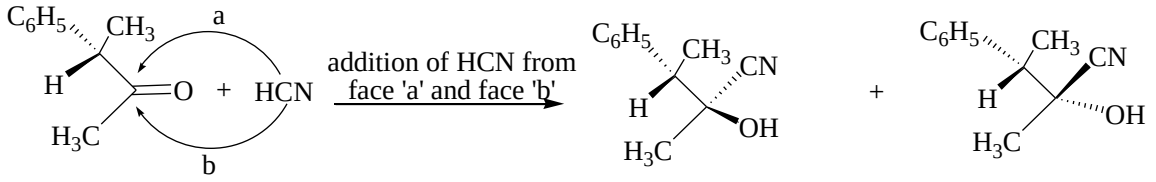


Example 13: Consider another interesting example of *R*-2-butanol with a stereocenter at C1 and two homomorphic hydrogen atoms (H_a and H_b) at C2. Replacement of H_a leads to the formation of (*2R,3R*)-3-chlorobutan-2-ol, and replacement of H_b leads the formation of (*2R,3S*)-3-chlorobutan-2-ol. Therefore, these two products are diastereomers, and the two protons (H_a and H_b) of *R*-2-butanol are diastereotopic.



The two faces of carbonyl group next to a stereocenter are diastereotopic. Since, addition of reagents (like HCN, RMgX, HCl etc.) from either faces gives diastereomers. Thus, two faces of such carbonyl group are termed as diastereotopic faces.

Example 14: For example, let us consider addition of HCN to the either faces of carbonyl group of (*S*)-3-phenylbutan-2-one leads to the formation of, (*2S,3S*)-2-hydroxy-2-methyl-3-phenylbutanenitrile and (*2R,3S*)-2-hydroxy-2-methyl-3-phenylbutanenitrile, a pair of diastereomers.

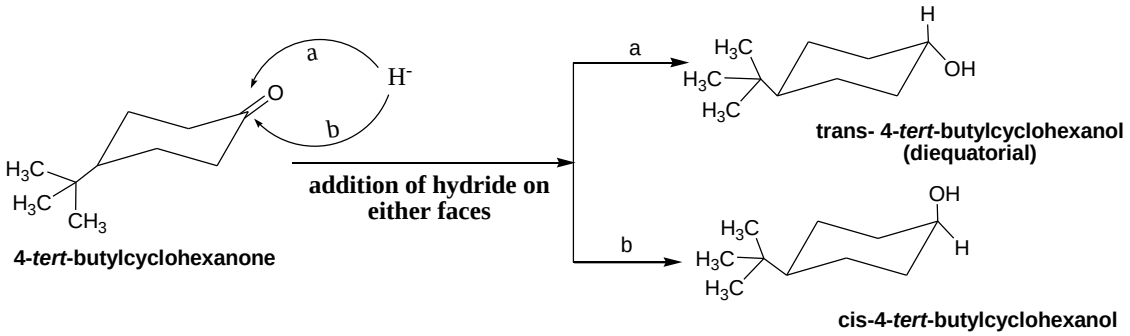


(*S*)-3-phenylbutan-2-one

(2*S*,3*S*)-2-hydroxy-2-methyl-3-phenylbutanenitrile

(2*R*,3*S*)-2-hydroxy-2-methyl-3-phenylbutanenitrile

Example 15: Similarly, consider another example of 4-*t*-butylcyclohexanone in which addition of hydride on either faces of carbonyl group leads the formation of *trans*- and *cis*- 4-*t*-butylcyclohexanol (diastereomers). Thus two faces of 4-*t*-butylcyclohexanone are diastereotopic faces.



4-*tert*-butylcyclohexanone

The addition of hydride on either faces of 4-*t*-butylcyclohexanone gives two diastereomers (achiral) products. Hence, the carbonyl carbon is considered as prostereo center rather than prochiral center.

5.4 *ASYMMETRIC INDUCTION*

Before 1940, the optically active compounds could be obtained in stereoisomerically pure form only by isolation of racemic mixture of optically active compounds from natural products and their subsequent enzymatic resolution. Since, equimolar amount of enantiomers (racemic mixture) is obtained when a prochiral molecule undergoes reaction in the absence of chiral environment. As we know the physical and chemical properties of enantiomers are always same in the absence of a chiral environment. However, enantiomers have entirely different reactivities in biological system.

Asymmetric induction is a stereo chemical transformation (reaction) that results the preferential formation of one enantiomer or diastereomer over other in the presence of a chiral substrate, reagent, catalyst or environment. This is also known as asymmetric synthesis. The chiral agent must play an active part in the asymmetric induction. Such chiral agent has an important role in the formation of transition state.

The direct synthesis of an optically active substance from optically inactive compound with or without the use of any optically active compound is called asymmetric synthesis. In general asymmetric synthesis can also be defined as *the synthesis which converts a prochiral unit in to a chiral unit and formation of unequal amount of stereoisomers.*

5.4.1 PRINCIPLE OF ASYMMETRIC SYNTHESIS:

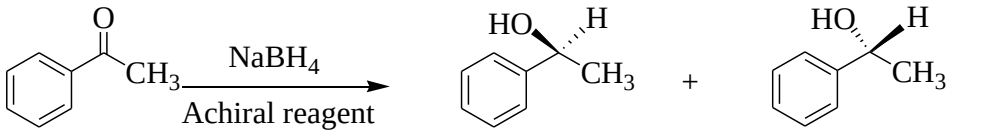
There are three principle of asymmetric synthesis

a) The substrate molecule must be prochiral *i.e.* the substrate must have either enantiotopic or diastereotopic ligands or faces.

b) There must be presence of chirality in the reaction/asymmetric transformation for the preferential formation of one stereoisomer over the other. Either the substrate, or the reagent, or the solvent, or the catalyst must be enantiomerically pure.

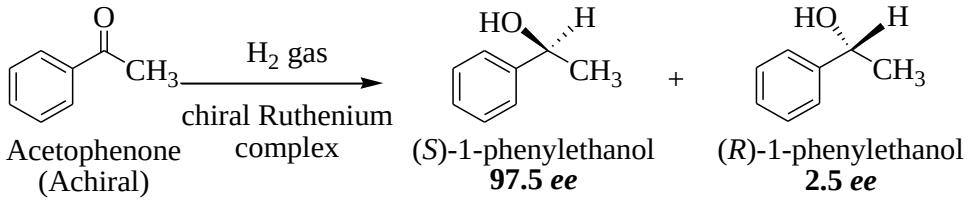
c) The chiral agent must play an important role in the reaction and must involve in the formation of two diastereomeric transition states.

Example 16: Let us consider hydrogenation of Acetphenone by sodiumborohydride ($NaBH_4$). Since, both the reagent and substrate are achiral (optically inactive) and also the reaction takes place in the medium of methanol (achiral), hence, equal amount of (*R*)-1-phenylethanol and (*S*)-1-phenylethanol (racemic mixture) is formed.



Acetophenone (Achiral) | (*S*)-1-phenylethanol 50% | (*R*)-1-phenylethanol 50%

Example 17: However, when the above reaction is allowed to proceed in the presence of a chiral reagent the (*S*)-1-phenylethanol is formed preferentially over (*R*)-1-phenylethanol.

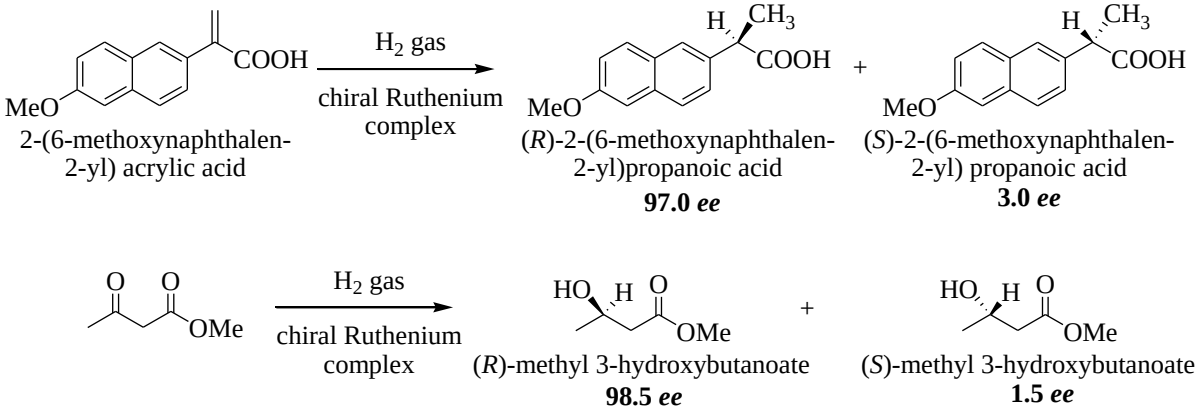


Acetophenone (Achiral)

(*S*)-1-phenylethanol **97.5 *ee***

(*R*)-1-phenylethanol **2.5 *ee***

Some more example of asymmetric synthesis in presence of chiral reagents is shown in figure 1.



2-(6-methoxynaphthalen-2-yl) acrylic acid

(*R*)-2-(6-methoxynaphthalen-2-yl)propanoic acid **97.0 *ee***

(*S*)-2-(6-methoxynaphthalen-2-yl) propanoic acid **3.0 *ee***

(*R*)-methyl 3-hydroxybutanoate **98.5 *ee***

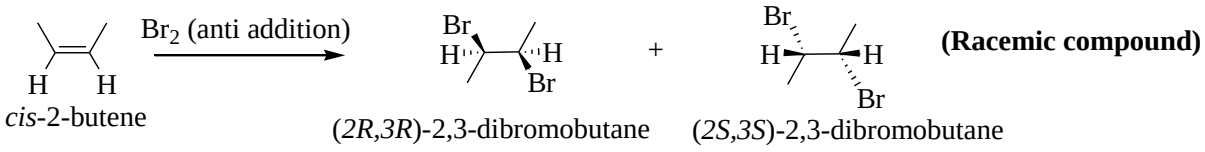
(*S*)-methyl 3-hydroxybutanoate **1.5 *ee***

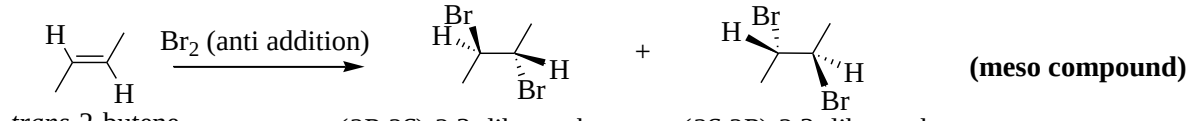
Figure 1: Examples of asymmetric synthesis

5.4.2 STEREOSPECIFIC AND STEREOSELECTIVE REACTIONS:

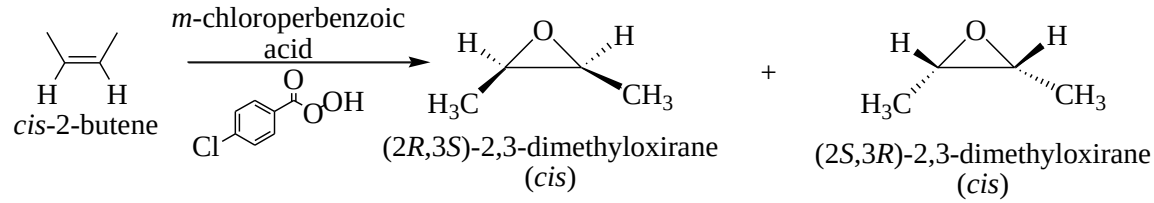
Stereospecific reactions: Stereospecific reactions or synthesis are those reactions in which a particular stereoisomer reacts with given reagent to give one specific stereoisomer of the product. This property is called stereospecificity. Thus each individual stereoisomeric substrate under stereospecific synthesis gives a different isomer of the product.

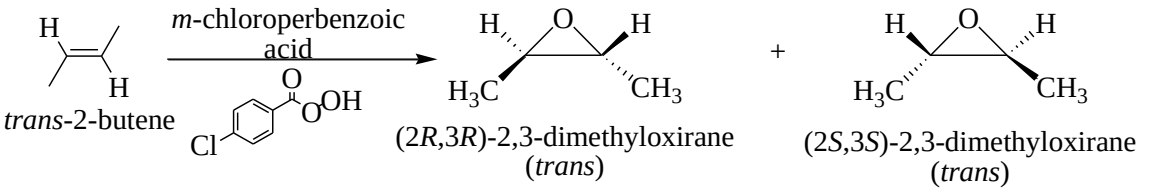
Example 17: For example, *anti* addition of bromine to *cis*-2-butene gives racemic mixture of 2,3-dibromobutane, while the *anti* addition of bromine to *trans*-2-butene gives meso-2,3-dibromobutane. These kinds of reactions are called stereospecific because different stereoisomeric substrate leads different stereoisomeric products.



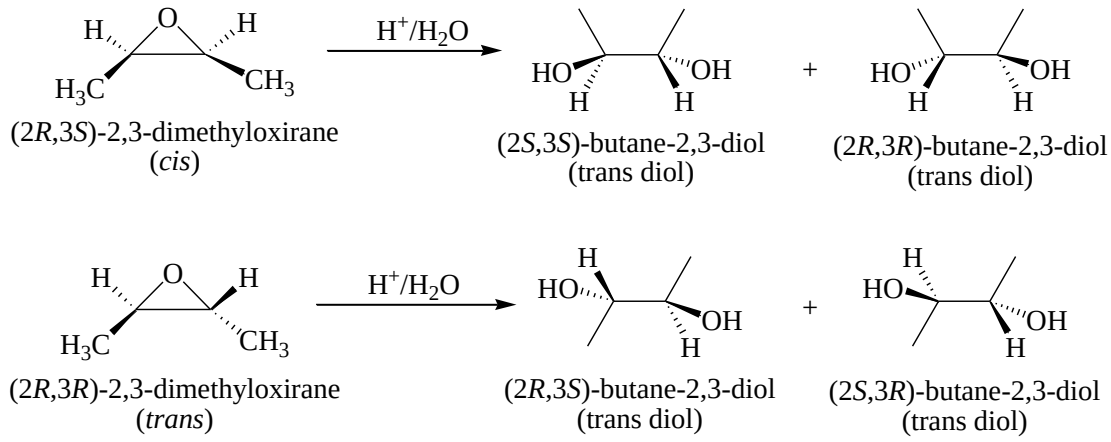


Similarly, *syn* addition of peroxyacid to cis- and trans- alkenes gives stereospecific reaction. **Example 18**: For example, *syn* addition of *meta*-chloroperbenzoic acid (*m*-CPBA) to cis-2-butene gives cis-2-dimethyloxirane [(2*R*,3*S*)-2,3-dimethyloxirane], while *syn* addition of *meta*-chloroperbenzoic acid (*m*-CPBA) to trans-2-butene gives trans-2,3-dimethyloxirane [(2*R*,3*R*)-2,3-dimethyloxirane]. Thus the reaction is stereospecific.





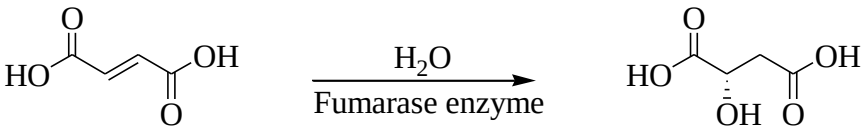
Example 19: Another example of stereospecific reaction is also considered as the ring opening freactions of oxirans (epoxides). Hydrolysis of epoxides (oxiranes) obtained by the *syn* addition of peroxyacid to *cis*- and *trans*- alkenes leads to the formation *trans*- diols (diols = dihydroxy compounds) in which both the vicinal hydroxy groups are trans to each other.



Stereoselective reactions: Stereoselective reactions or synthesis are those reactions in which one stereoisomer (or one pair of enantiomers) is formed predominantly or exclusively out of several possible stereoisomers. This property is called stereoselectivity. In such reactions one stereoisomer is formed more rapidly than other, thus one stereoisomer forms in excess in the resulting mixture of the products. For every stereoselective reaction there is more than one mechanistic path by which reaction may proceed; however, it is observed that the reaction proceeds either via the most favorable path (for which rate of reaction is fast *i.e.* kinetic control) or via the path that gives the most stable stereoisomer as the major product (*i.e.* thermodynamic control). The stereoselective reactions/synthesis or the stereoselectivity can be further subdivided in to two categories, a) enantioselective reactions/synthesis or enantioselectivity, b) diastereoselective reactions/synthesis or diastereoselectivity.

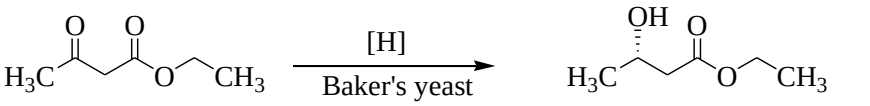
a) **Enantioselective reactions or enantioselectivity:** Enantioselective reactions are defined as the reactions or processes in which one of the enantiomer forms predominantly over the other. This property is known as enantioselectivity. Enantioselectivity is achieved when a stereoselective reaction is performed in the presence of using a chiral environment (*i.e.* either a chiral substrate, or a chiral reagent, or a chiral catalyst, or a chiral solvent).

Example 20: For example, Fumaric acid when hydrolyzed in presence of Fumarase (a chiral enzyme) gives (*S*)-2-hydroxysuccinic acid exclusively.

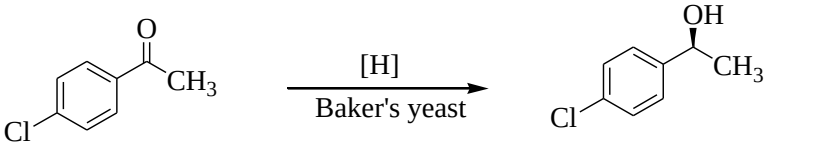


fumaric acid (S)-2-hydroxysuccinic acid

Example 21: Similalry, reduction of carbonyl group by Baker's yeast exclusively leads to the formation of *S*- enantiomer. Examples of reduction of carbonyl groups by baker's yeast are shown below.

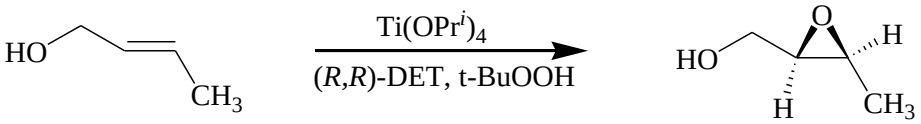


ethyl 3-oxobutanoate (*S*)-ethyl 3-hydroxybutanoate

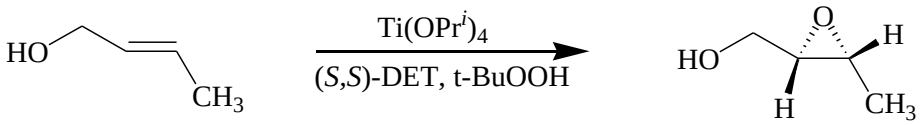


1-(4-chlorophenyl) ethanone (*S*)-1-(4-chlorophenyl)ethanol

The Sharpless epoxidation of allylic alcohol in presence of titanium tetraisopropoxide, *t*-butylhydroperoxide and enantiomerically pure diethyltartrate (DET) gives enantiomerically pure epoxide. The stereochemistry of product depends on the stereochemistry of diethyltartrate. The diethyltartrate is readily available in its enantiomerically pure forms (*i.e.* *R*,*R* and *S*,*S*). (*R*,*R*)-diethyltartrate (DET) gives (*S*,*S*)- epoxide, whereas, (*S*,*S*)-diethyltartrate (DET) gives (*R*,*R*)-epoxide.



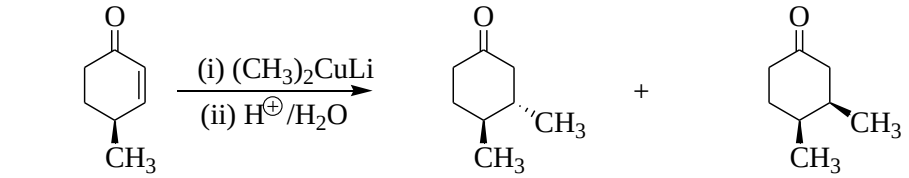
(*E*)-but-2-en-1-ol ((2*S*,3*S*)-3-methyloxiran-2-yl)methanol



(*E*)-but-2-en-1-ol ((2*R*,3*R*)-3-methyloxiran-2-yl)methanol

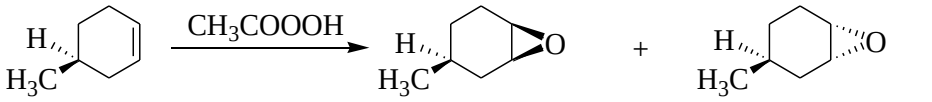
b) **Diastereoselective reactions or diastereoselectivity:** Diastereoselective reactions are defined as the reactions or processes in which one of the diastereomer forms predominantly or exclusively over the other. This property is known as diastereoselectivity. Diastereoselectivity is usually achieved through in the presence of steric hindrance.

Example 22: Let us consider the conjugate addition of lithium dimethylcuprate [$(CH_3)_2CuLi$] to 4-methylcyclohexenone. In this reaction cuprate reagent has equal possibilities to react from the either faces of the 4-methylcyclohexenone; however, the bulky cuprate reagent prefers to approach from the less hindered face (*i.e.* opposite to the methyl group) of the 4-methylcyclohexenone. As a result one diastereoisomer (*i.e. trans*- product: methyl groups are *trans*- to each other) out of two possible diastereoisomers forms in excess. Thus, this reaction is called diastereoselective reaction.



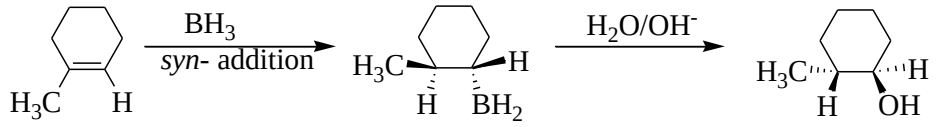
(*S*)-4-methylcyclohex-2-enone | (3*S*,4*S*)-3,4-dimethyl cyclohexanone (98%) | (3*R*,4*S*)-3,4-dimethyl cyclohexanone (2%)

Example 23: Another example of diastereoselective reaction/synthesis is the epoxidation of cyclic alkenes with peroxyacids. In such reactions the epoxidation also takes place from the less hindered face. Epoxidation of 4-methylcyclohexene by peroxyacetic acid gives 80% addition product from the less hindered face (*i.e.* opposite to the methyl group) and 20% addition product from the more hindered face (*i.e.* from the face of methyl group).



(*S*)-4-methyl cyclohex-1-ene | *cis*-epoxide 20% | *trans*- epoxide 80%

Example 24: Similarly, synthesis of alcohols from alkenes by the hydroboration-oxidation is another class of example of diastereoselective reactions. Hydroboration-oxidation of 1-methylcyclohexene gives the *trans*- product as the major product.



1-methylcyclohex-1-ene

(1*R*,2*R*)-2-methylcyclohexanol
(*trans product*)

5.4 ENANTIOMERIC EXCESS (*ee*):

It is a measurement of optical purity of a chiral substances formed in an asymmetric synthesis. It reflects the degree to which a mixture of enantiomer contains one enantiomer in greater amounts than the other. A racemic mixture has an *ee* of 0%, while a single and pure enantiomer has an *ee* of 100%. A sample with 70% of one enantiomer and 30% of the other has an *ee* of 40% (70% − 30%). Enantiomeric excess can be determined by the following mathematical expression.

$$\text{Enantiomeric excess (\% ee)} = \frac{[R] - [S]}{[R] + [S]} \times 100$$

5.5 *DIASTEREOMERIC EXCESS (de)*

It is the measurement of % excess formation of one of the diastereomers over the other in an asymmetric synthesis. It reflects the degree to which a mixture of diastereomer contains one diastereomers in greater amounts than the other. Diastereomeric excess can be determined by the following mathematical expression.

$$\text{Diastereomeric excess (\% } de\text{)} = \frac{[D_1] - [D_2]}{[D_1] + [D_2]} \times 100$$

5.6 *CRAM'S RULE*

Diastereoselectivity of nucleophilic addition on carbon-oxygen double bond of aldehyde and ketones containing an asymmetric α carbon is explained by D. J. Cram and co-workers. According to this the formation of the *major* product was correctly predicted by a model in which the largest group was eclipsed with the other carbonyl substituent. This empirical relationship became known as *Cram's rule*. Since, during nucleophilic addition on symmetrical sp^2 carbonyl carbon, the nucleophile has equal possibilities to give addition on carbonyl carbon from either faces. However, when α-carbon of sp^2 carbonyl carbon is asymmetric, the nucleophile

would experience more steric hindrance from one side, leading to unequal synthesis of the two diastereomers. The Cram's rule predicts the formation of major product based on most stable conformation of carbonyl compound. Following points may be considered during the prediction of the most stable conformation of carbonyl compound:

- The existing asymmetric center would have a Small, Medium and Large group, denoted **S, M** and **L** respectively (Fig 2).
- In the reactive conformation, the carbonyl group would orient itself in such a way that it will rest between the Small group and the Medium group.
- The attacking nucleophile would prefer to attack from the side of the small group, resulting in the predominant formation of one diastereomer in the product.

As shown in figure 2 path A is preferred over path B.

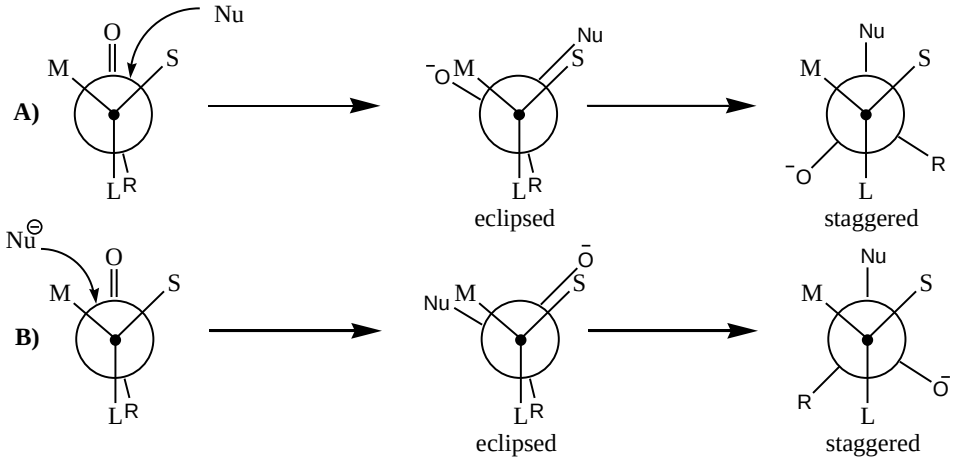


Figure 2: Schematic representation of Cram's rule

For example, the reduction of α-phenylpropionaldehyde ($PhCH(CH_3)CHO$) with Grignard reagent yields the erythro diastereomer as the major product according to Cram's rule, where (*S*=H, *M*=Me, *L*=Ph) [Fig 3(1)]. Similarly, reaction of HCN with 2-methylbutanal to form cyanohydrins with diastereoselectively and the major product will be erythro diastereomer [Fig 3(2)].

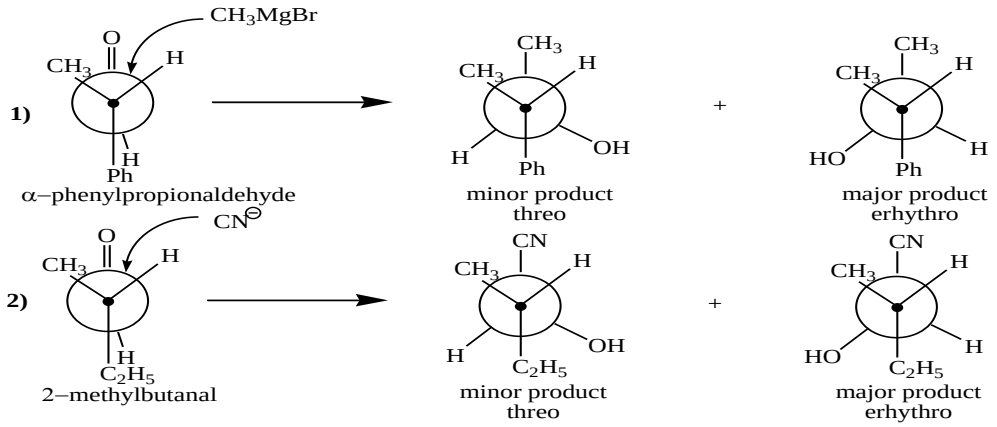
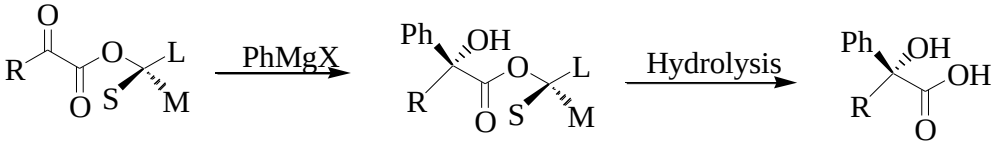


Figure 3: Examples of Cram's rule

5.7 *PRELOG'S RULE*

Prelog's rule is an extension of Cram's hypothesis of reactive conformation to nucleophilic addition on chiral esters of □-ketoesters (pyruvates) and was reported in 1953. It is generally the addition of Grignard reagent to chiral pyruvates to form chiral alcohols. The rule has been applied for asymmetric synthesis of α-hydroxyacids and for assigning the configuration of secondary and tertiary alcohols. The *anti* configurational arrangement of the two α-carbonyl moieties could be rationalized. The negative end of these dipoles would prefer to be as far as possible. The attack from the side of the small (S) group is an extension of Cram's Rules. The asymmetric induction in such reaction is not very effective due to the large distance between the reaction center and the asymmetric center inducing asymmetry at the developing chiral center.

Example 25: Reaction of pyruvates with Grignard reagent (extension of Cram's rule)



5.8 *CONFORMATIONAL ANALYSIS OF ALKANES*

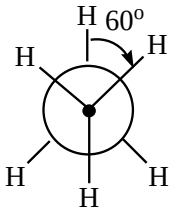
The different spatial arrangements of atoms in a molecule which is readily interconvertible by rotation about single bonds are called ***conformations***. The study of various preferred

conformations of a molecule and the correlation of physical and chemical properties to the most preferred conformer is called conformational analysis. Due to rapid interchange of the spatial positions of groups/atoms these conformers are non-separable under normal conditions. Since, different conformations arises because of the rotation about single bonds, hence, they are also called the rotamers. The conformational and configurational isomerisms are related to energy barrier for interconversions of different spatial arrangements of atoms in a molecule. If the energy barrier for interconversion of different spatial arrangements is between 0.6 kcal/mol-16.0 kcal/mol; it result the conformational isomers or conformers; whereas, if this energy barrier is more than or equal to 16 kcal/mol than the configurational isomers are obtained.

5.8.1 CONFORMATIONAL ANALYSIS OF ETHANE:

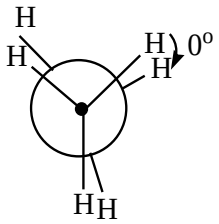
When ethane molecule rotates around carbon-carbon single bond, two extreme conformations (one is highly stable and other is highly unstable) are obtained. The highly stable conformation of ethane is called '*staggered conformation*' and the highly unstable conformation of ethane is called '*eclipsed conformation*'. In between these two extreme conformations (*i.e.* staggered and eclipsed), an infinite number of conformations are also possible.

Staggered conformation: A conformation with a 60° dihedral angle is known as staggered conformation. The angle between the atoms attached to the front and rear carbon atom is called dihedral angle.



Staggered conformation

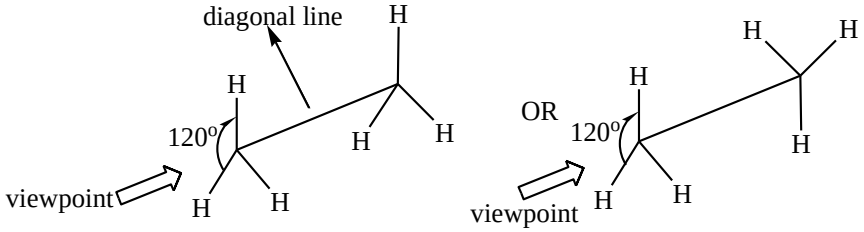
Eclipsed conformation: A conformation with a 0° dihedral angle is known as eclipsed conformation.



Eclipsed conformation

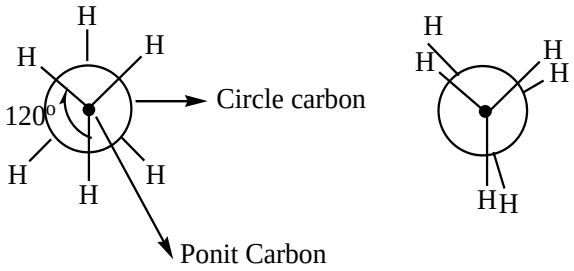
In staggered conformation the atoms are located at maximum possible distance from each other hence they are in their most relaxed spatial arrangement thus the staggered conformation is considered as the most stable conformation; whereas, in eclipsed conformation the atoms are located at minimum distance, hence due to repulsion between the atoms the eclipsed conformation is considered as the least stable (high energy) conformation. There are two methods for the representation of staggered and eclipsed conformations, **a**) the Sawhorse representation formula and, **b**) the Newman representation formula.

a) **The Sawhorse representation formula:** In sawhorse representation formula the spatial arrangement of all the atoms/groups on two adjacent carbon atoms. The bond between adjacent carbon atoms is represented by a diagonal line and rest of the atoms are located on each carbon at +120° or -120° angles to each other. The sawhorse representation is shown as:



Sawhorse representation formula

b) The Newman representation formula is a planar representation of the sawhorse formula. The molecule is viewed along the axis of a carbon-carbon bond. The carbon atom in front of the viewer is represented by a dot (●), whereas the carbon atom away to the viewer is represented by circle. The rest of the atoms/groups are located on each carbon atoms at +120° or -120° angles to each other as shown below:



Newman representation formula

The different conformations of ethane are not equally stable. The staggered form in which the hydrogen atoms are 'perfectly staggered' (dihedral angle is 60°) is the most stable conformation. This is because, in this conformation the all carbon hydrogen (C-H) bonds are located at maximum possible distance to each other, and hence they feel minimum repulsive energy from each other. In eclipsed conformation of ethane, the hydrogen atoms attached to each carbon are directly opposing to each other. This result the minimum separation of the atoms or groups, and hence they feel maximum repulsive energy from each other. The eclipsed conformation therefore, of highest energy and has the lowest stability. A graph plot for the energy profile for various conformations of ethane is shown on figure 4. The relative stability of various conformations of ethane is

Staggered >> Eclipsed

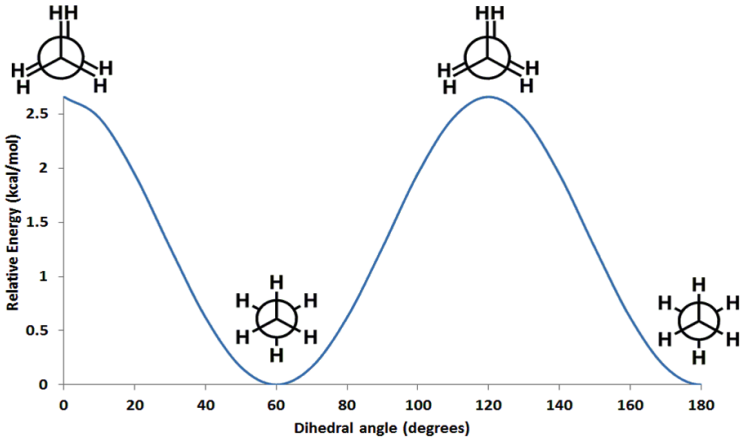


Figure 4: Energy profile diagram of conformational isomer of ethane

5.8.2 CONFORMATIONAL ANALYSIS OF *N*-BUTANE:

n-Butane (C_4H_{10}) has three carbon-carbon single bonds (Figure 5); therefore the molecule can rotate about each of them. The rotation about C2 and C3 bond will provide the symmetrical conformations. To study the conformational analysis of *n*-butane, we must consider it as a derivative of ethane molecule, where one hydrogen at each carbon of ethane is replaced by methyl group ($-CH_3$).

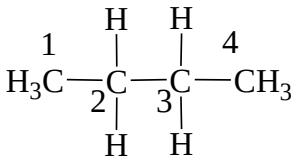


Figure 5: Butane molecule

Various conformation of *n*-butane can be obtained by rotation about C2 and C3 bond are shown in figure 6:

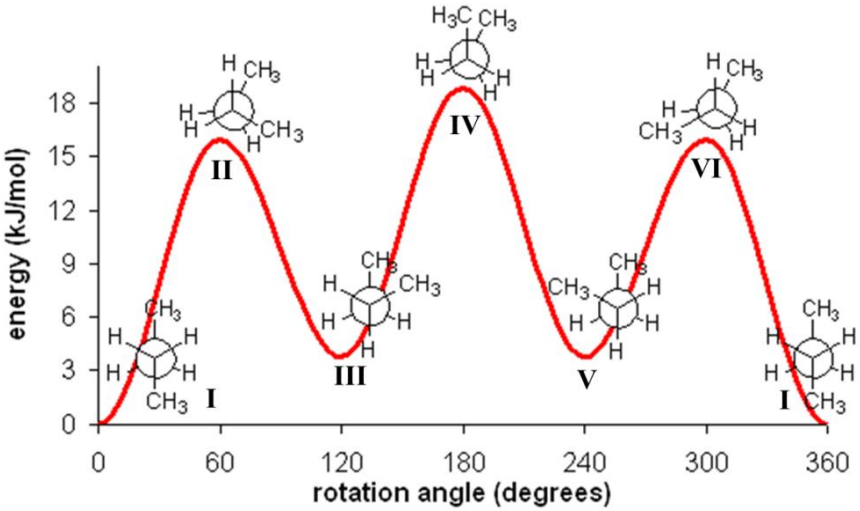


Figure 6: Energy profile diagram of conformational isomer of *n*-butane

From figure 3, we can see that *n*-butane has three staggered conformations (**I, III** and **V**). Conformer **I**, in which two methyl groups are as far as possible, and hence is more stable than other two staggered conformers (*i.e.* **III** and **V**), because conformer **I**, has minimum repulsive energy. As you can see from figure 3; in conformer **I,** both the methyl groups are located opposite to each other. The most stable conformer of *n*-butane, in which both the methyl groups are located opposite to each other is called the *anti-conformer*, whereas other two staggered conformers (*i.e.* **III** and **V**) are called *gauche conformer*. Due to difference in steric strain

(repulsion between dihedral atoms/groups) the repulsive energy of *anti* and *gauche* conformers are also different. Three eclipsed conforms (**II**, **IV** and **VI** in figure 6) are also exits for *n*-butane, in which the dihedral atoms/groups are in front of each other (*i.e.* dihedral angle is 0°). The fully eclipsed conformer **IV,** in which the two methyl groups are closest to each other, has maximum steric strain; hence it is of higher energy than the other eclipsed conformers (**II** and **VI)**.Thus the relative stabilities of the six conformers of *n*-butane in their decreasing order is given as follows:

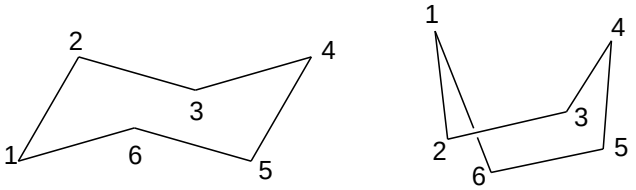
Anti > Gauche > Eclipsed > Fully eclipsed

I **III and V** **IV** **II and VI**

5.8.3 CONFORMATION OF CYCLOHEXANE:

It is known to you that in cycloalkane, all the ring carbons are sp^3 hybridized, hence must have tetrahedral geometry with all bond angles of 109.5°. But to sustain its cyclic structure the cycloalkane could not be able to maintain the bond angle of 109.5°. As a result there is a deviation from the normal tetrahedral bond angle. This deviation leads the development of strain in the molecule. Thus the cycloalkanes exhibit angle strain, due to which cycloalkanes are not as stable as their non-cyclic homolog. To minimize the angle strain the structure of cycloalkane is keep on changing from one cyclic form to another which are readily interconvertible by rotation about single bond. This is the reason why cyclohexane and larger rings are non-planar.

Cyclohexane exists in two readily interconvertible forms which are called the chair and boat conformations of cyclohexane (Figure 7).



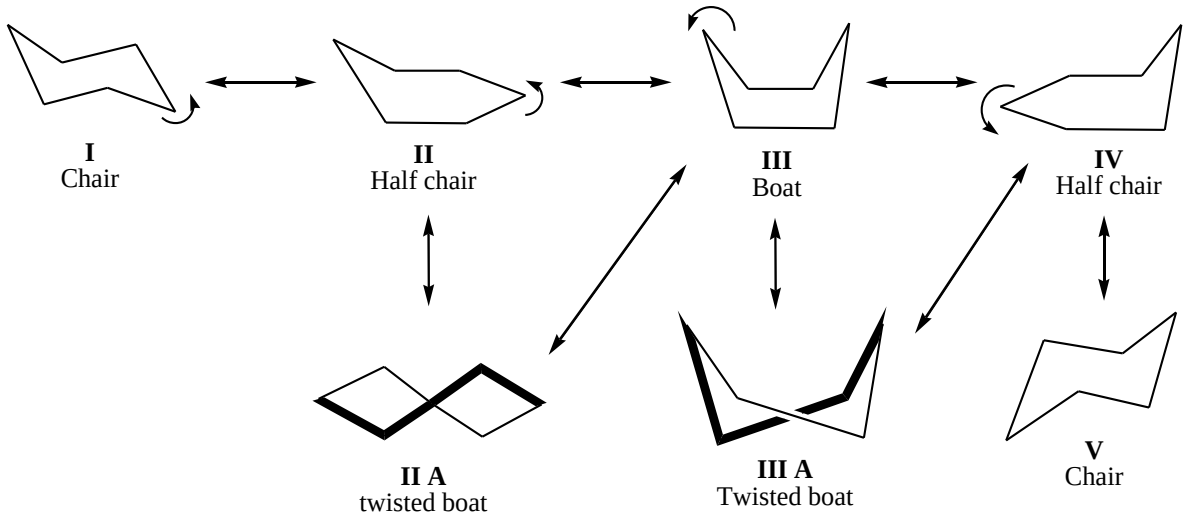
Chair Conformation of cyclohexane

Boat Conformation of cyclohexane

Figure 7: Two readily interconvertible conformations of cyclohexane

Both chair and boat forms are free from angle strain. In chair form carbon C1, C3 and C5 are in one plane and carbon C2, C4 and C6 are in different plane. Similarly, in boat form carbon

C1 and C4 are in one plane and carbon C2, C3, C5 and C6 are in other plane. The interconversions of chair to boat and boat to chair *via* various other intermediate conformations are shown in Figure 8.The chair conformation (**I** and **V scheme 1**) is considered as a rigid conformation of cyclohexane in comparison to boat conformation; because during interconversion from chair to boat conformation, some angular deformations are required. These



angular deformations usually increase the energy barrier for interconversion from chair to boat conformation. Therefore the chair conformation of cyclohexane is the most stable conformation.

Figure 8: Conformational analysis of cyclohexane

Chair form on distortion gives half chair (**II** and **IV figure 8**) conformations which are of highest energy conformations. In comparison to chair conformation, the boat conformation (**III figure 8**) is flexible and can readily distort into many steps to reduce the C-H bond eclipsing. The boat conformation can be interconvertible in to twisted boat (**IIA** and **IIIA figure 8**) conformations, which has comparatively less angular and steric strains. The twisted boat conformations have lower energy than the boat conformation, hence is more stable than boat conformation. At room temperature 99.9% cyclohexane molecules exist in the most stable chair conformation.

The energy profile diagram along with various possible conformations of cyclohexane is shown in figure 9.

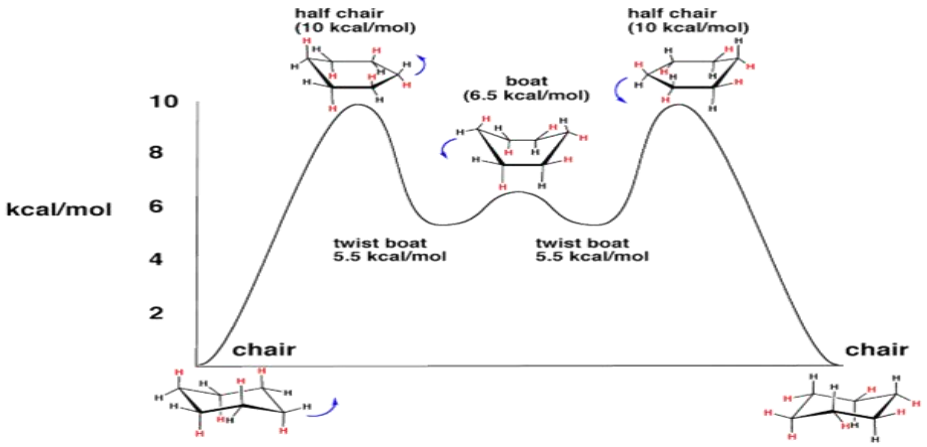
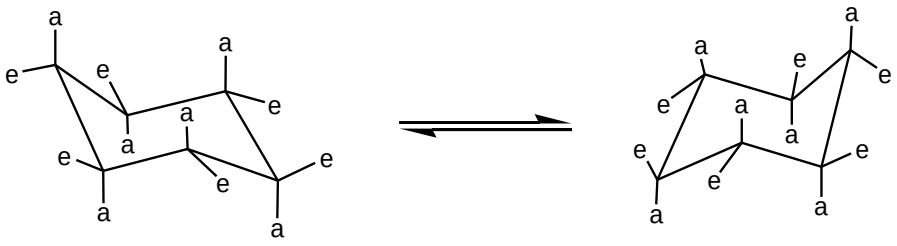


Figure 9: Energy profile diagram of conformation of cyclohexane

5.8.3.1AXIAL AND EQUATORIAL BOND:

In chair conformation of cyclohexane, there are two different positions occupied by the 12 hydrogen atoms of cyclohexane. Out of total 12 Hydrogen atoms of cyclohexane, six hydrogen atoms are located towards perpendicular to average plane of the ring; these perpendicular hydrogen atoms are called axial hydrogens (*a*), and respective bonds are called *axial* bonds. The other six hydrogen atoms are located along with the average plane of the ring; these hydrogens are called *equatorial* hydrogens (*e*), and the respective bonds are called equatorial bond.

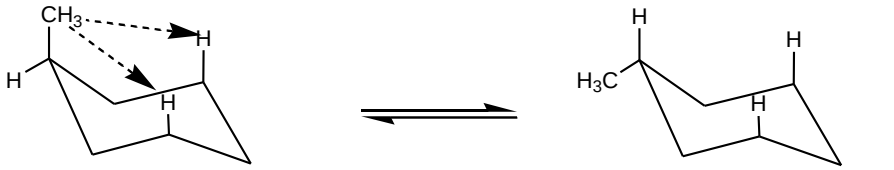


a = axial; e = equatorial

Cyclohexane is rapidly interconvertible (flips) in to its mirror image chair conformations at room temperature. During flipping all the axial hydrogens becomes equatorial and all the equatorial hydrogens becomes axial.The flipping of the cyclohexane is so rapid that it is not possible to differentiate between equatorial and axial hydrogens. These hydrogens can be differentiated at very low temperature (*i.e.* -80°) and analyzed by ^{1}H NMR spectroscopy.

5.8.4 CONFORMATION OF MONO SUBSTITUTED CYCLOHEXANE:

If one hydrogen atom of cyclohexane is replaced by a larger atom or group, the molecule becomes highly hindered. As a result the repulsion between atoms increases. Axial atoms/groups usually face more repulsive interaction in comparison to equatorial atoms/groups. Since three axial atoms/groups are located in one side of the average plane of ring, whereas rest three atoms/groups are located in other side of the average plane of ring. The repulsive interaction experienced by three axial atoms is called *1,3-diaxial interaction.*To minimize the 1,3-diaxial interaction and resulting repulsive energy, the monosubstituted cyclohexane acquires a chair conformation in which the substituents occupies an equatorial position. There are two possible chair conformations for methyl cyclohexane. In one conformation the methyl group located at axial position (**I**), whereas in other conformation the methyl group is located at equatorial position (**II**). When methyl group is at axial position, it has 1,3-diaxial interaction with hydrogen atoms at C3 and C5 carbons due to which the energy of such conformation is very high in comparison to the conformer in which the methyl group is at equatorial position. The conformer with methyl group at equatorial position does not have any kind of 1,3-diaxial interaction hence is more stable.



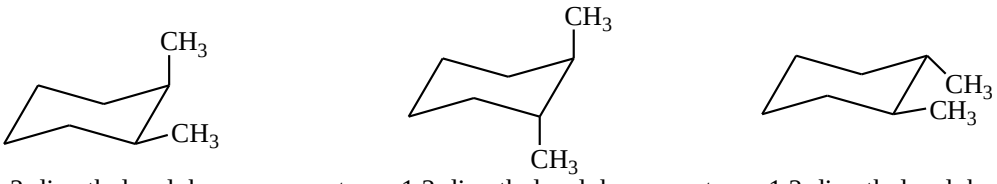
Axial conformer with 1,3-diaxial interaction (I)

Equatorial conformer with no 1,3-diaxial interaction (II)

5.8.5 CONFORMATION OF DISUBSTITUTED CYCLOHEXANES:

Disubstituted cyclohexanes are of three types *viz*. 1,2-; 1,3- and 1,4- with respect to each other. Therefore, the conformational analysis of all three types of disubstituted cyclohexanes is discussed separately in this section. It is also important to note that whether the substituents are either *cis*- or *trans*- to each other. In general, it is observed that in disubstituted cyclohexanes either the chair conformation with both the substituents in equatorial positions will be the preferred conformation, or the conformation with bulkier substituent at equatorial position will be the preferred conformation. Let us consider the disubstituted cyclohexanes containing methyl group as both the substituents.

1,2-Dimethylcyclohexane: For 1,2-dimethylcyclohexane, two isomeric forms (*i.e. cis*- and *trans*-) are possible. The 1,2-dimethylcyclohexane with substituents at one axial and one equatorial positions is known to have a *cis*- configuration, whereas, the 1,2-dimethylcyclohexane with both the substituents at either axial or equatorial positions is known to have a *trans*-configuration. Out of three conformations shown in figure 10, the conformation with diaxial substituent is the least stable conformation of cyclohexane since two axial methyl group causes four 1,3-diaxial interaction (repulsive interaction) between axial methyl group and hydrogen atom.



cis-1,2-dimethylcyclohexane
a,e or *e,a*
(more stable)

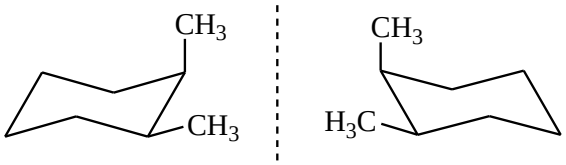
trans-1,2-dimethylcyclohexane
a,a (diaxial)
(least stable)

trans-1,2-dimethylcyclohexane
e,e (diequatorial)
(most stable)

Figure 10: Conformational isomers of 1,2-dimethylcyclohaxane

Whereas, the conformation with diequatorial substituent id the most stable conformation of cyclohexane since there are no 1,3-diaxial interaction between methyl group and hydrogen atom. However, the conformation of 1,2-dimethylcyclohaxane, with one methyl at axial and one methyl at equatorial, causes two 1.3-diaxial interactions hence it is more stable than diaxial conformation and less stable than diequatorial conformation of 1,2-dimethylcyclohaxane. Thus the decreasing order of stability of different conformations of 1,2-dimethylcyclohexane is: *ee>ae~ea>aa*.

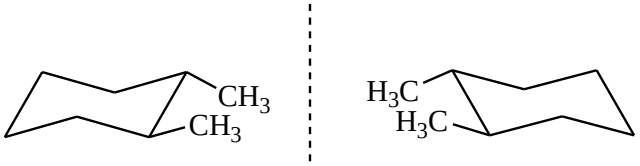
1,2-dimethylcyclohexane shows enantiomerism. It has 2 chiral centers, hence can have four stereoisomers possible, since *cis*-1,2-dimethylcyclohexane is not superimposable on its mirror image but they are readily interconvertible by flipping one chair conformer in to other, hence, only three stereoisomers are exist for 1,2-dimethylcyclohexane (Figure 11). These two readily interconvertible conformers are called conformational enantiomers. It must be noted that the *cis*-1,2-dimethylcyclohexane constitutes a non resolvable racemic mixture, hence it is not a meso compound.



cis-1,2-dimethylcyclohexane
a,e or *e,a*
(readily interconvertible non resolvable racemic mixture)

Figure 11: Interconvertible (racemic mixture) of *cis*-1,2-dimethylcyclohaxane

However, *trans*-1,2-dimethylcyclohexane (*ee*) and its mirror image are non superimposable, hence they constitute an enantiomeric pair. They cannot be interconvertible readily by flipping. On flipping *ee* chair conformer leads the formation of *aa* chair conformer. These two stereoisomers are called configurational enantiomers (Figure 12).



trans-1,2-dimethylcyclohexane
ee
(non interconvertible)

Figure 12: Non-interconvertible (enantiomeric mixture) of *trans*-1,2-dimethylcyclohaxane

1,3-Dimethylcyclohexane: In case of 1,3-Dimethylcyclohexane (molecule with two identical substituents) two *cis*- and one *trans*- chair conformations are possible as shown in figure 13.

cis-1,3-dimethylcyclohexane
a,a (diaxial)
(least stable)

cis-1,3-dimethylcyclohexane
e,e (diequatorial)
(most stable)

trans-1,2-dimethylcyclohexane
a,e or *e,a*

Figure 13: Conformational isomers of 1,3-dimethylcyclohaxane

In the case of 1,3-dimethylcyclohexane the *cis*- stereoisomer (*ee*) is more stable than the trans-stereoisomer (*ae*). Since, *cis*- stereoisomer (*ee*) has no 1,3-diaxial interactions, while, *trans*-stereoisomer (*ae*) has two 1,3-diaxial interactions between hydrogen of cyclohexane and methyl

group. However, another *cis*- stereoisomer (*aa*) of 1,3-dimethylcyclohexane is the least stable stereoisomer due to maximum 1,3-diaxial interactions. The decreasing order of stability of these stereoisomers is: *ee*>*ae*~*ea*>*aa*.

Likewise 1,2-dimethylcyclohexane, 1,3-dimethylcyclohexane has also two chiral centers, hence, it must have four stereoisomers. However, both the conformational isomers of *cis*-1,3-dimethylcyclohexane has plane of symmetry, hence, it is achiral and called meso compound Figure 14. The *trans*-1,3-dimethylcyclohexane does not have plane of symmetry hence it exist in two configurational enantiomeric forms. These two configurational enantiomers are not interconvertible by flipping of the chair forms Figure 14.

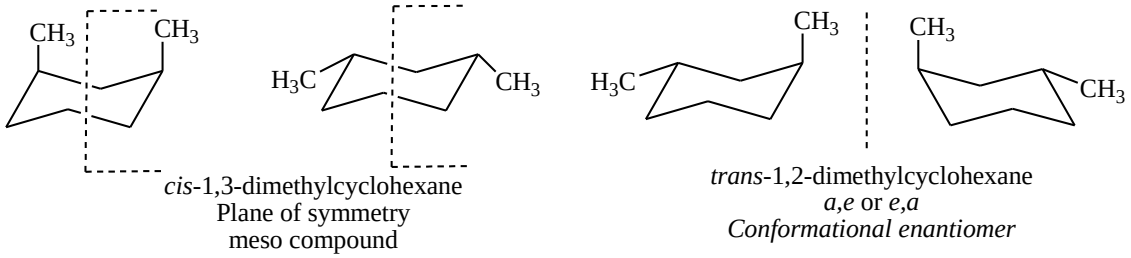


Figure 14: Stereochemistry of 1,3-dimethylcyclohaxane conformations

1,4-Dimethylcyclohexane: Similar to 1,2-Dimethylcyclohexane, 1,4-dimethylcyclohexane have also one *cis*- and two *trans*- conformational isomers are possible, as shown in figure 15.

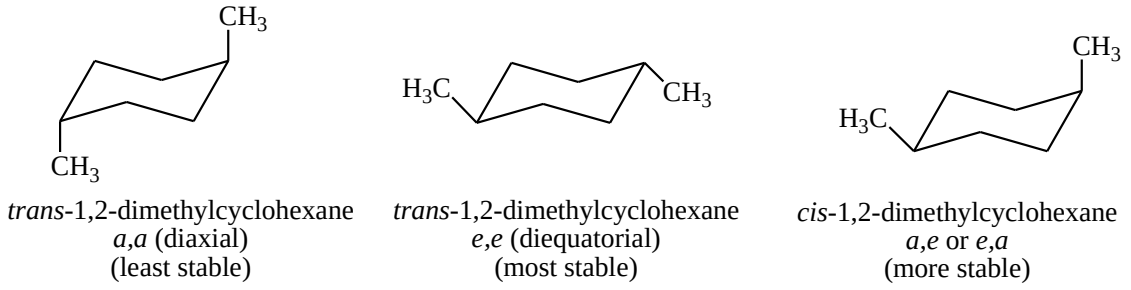
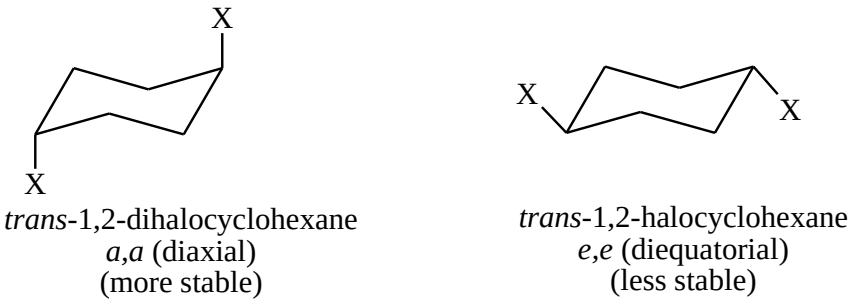


Figure 15: Conformational isomers of 1,4-dimethylcyclohaxane

Due to plane of symmetry in all the isomeric forms of 1,4-dimethylcyclohexane does not have any chiral center. It exists only in *cis*- and *trans*- diastereomers. Neither its *cis*- nor *trans*- diastereomeric forms is chiral.

As we have observed that, if cyclohexane is substituted with alkyl groups diequatorial conformation is the most stable conformation in all types of disubstituted cyclohexanes. However, if the substituents are different than methyl group then the above observation may not be applicable. For example, when methyl groups are replaced with halogens (*i.e.* Cl or Br), the *trans*- conformations (*i.e. ee* and *aa*) of 1,4-dihalocyclohexane are equally populated, and most of the *trans*-1,4-dihalocyclohexane exists predominantly in *aa* conformation due to dipole and gauche interactions Figure 16. Similarly, for 1,2-dihalocyclohexane the *aa* conformation is more stable than *ee* conformation Figure 16. In the case of 1,3-cyclohexnediol, it is observed that the *aa* conformation is found to be more stable than the *ee* conformation due to the stabilization of diaxial conformation by formation of hydrogen bonding between the oxygen atom of one hydroxyl group and hydrogen atom of other hydroxyl group (intramolecular H bonding).

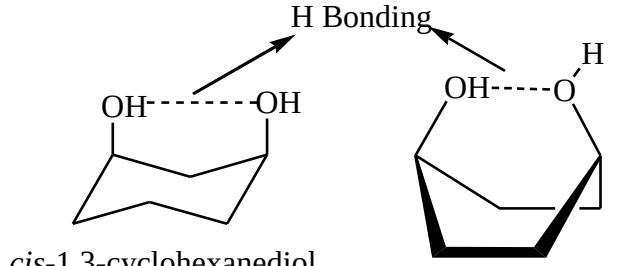


trans-1,2-dihalocyclohexane
a,a (diaxial)
(more stable)

trans-1,2-halocyclohexane
e,e (diequatorial)
(less stable)

Figure 16: Stability of *trans*-1,4-dimethylcyclohexane

In the case of 1,3-cyclohexnediol the preferred conformation is the chair form; while, when the hydroxyl substituent are at 1, 4- position (1,4-cyclohexnediol) then the boat conformation is preferred to stabilize the 1,4-cyclohexnediol via formation of intramolecular hydrogen bonding (Figure 17).



cis-1,3-cyclohexanediol
(chair conformation)
(more stable)

1,4-Cyclohexanediol
boat conformation
(more stable)

Figure 17: Hydrogen bonding in *trans*-1,4-dihydroxycyclohexane

5.8.6 CONFORMATION OF DECALINS:

Decalin is a bicyclic compound. Generally, bicyclo [4,4,0] decane is known as decalin. Two cyclohexane rings are fused together in chair conformation to generate decalin. It exists in two diastereomeric forms (*i.e. cis*- and *trans*-decalins). Decalin is structural analogous to 1,2-disubstituted cyclohexane. When both the cyclohexane rings are fused together in *ea* form the decalin thus formed is called *cis*-decalin. However, when two cyclohexane rings are fused together in *ee* form the decalin thus formed is called *trans*-decalin. The *cis*- and *trans*-decalins are shown in figure 19.

Figure 19: Conformations of decalin

The *trans*-decalin is more stable than *cis*-decalin by 2.7 kcal/mol of energy. Thus *cis*-decalin can be easily converted in to *trans*-decalin but the reverse process is not possible. Due to flexibility in structure of cis-decalin, its ring flipping is possible. Thus cis-decalin exists in two interconvertible conformational isomers Figure 20. In comparison to *cis*-decalin, the *trans*-decalin is a rigid molecule. Due to the presence of two equatorial bonds the ring flipping of *trans*-decalin is not possible.

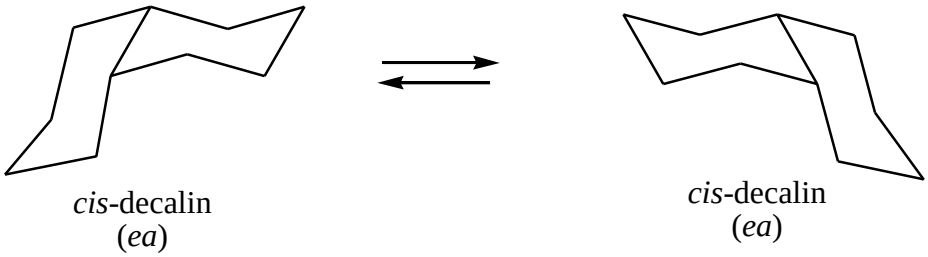
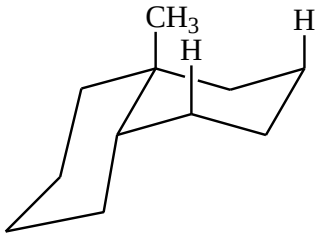
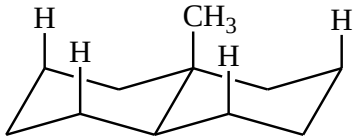


Figure 20: Flipping of *cis*-decalin

The *cis*-decalin is chiral in both the conformation, since, these conformations are non-superimposable mirror image of each other. Hence, *cis*-decalin exists in a conformational enantiomeric pair. On the other hand, the *trans*-decalin due to center of symmetry is achiral. In case of substituted decalins, the substituent located at the fusion point of both the rings. In the case of *cis*-decalin the substituent at fusion point is axial with respect to one ring and equatorial with respect to other ring. On the other hand, in *trans*-decalin the substituent is located at axial position with respect to both the rings (Figure 21). It must be noted that the substituent to the *cis*-decalin is free to adopt the equatorial position.



Methyl substituted *cis*-decalin
There are twor sets of 1,3-diaxial interaction
with axial methyl substituent
(more stable)



Methyl substituted *trans*-decalin
There are four sets of 1,3-diaxial interaction
with axial methyl substituent
(less stable)

Figure 21: Position of substituents on *cis*- and *trans*-decalin

5.9 *STEREOCHEMISTRY OF COMPOUNDS CONTAINING N, P AND S.*

Like tetravalent carbon compounds, the nitrogen, phosphorous and sulphur containing compounds also exhibit stereochemical behaviour. Compounds of N, P and S show both enantiomerism and/or geometrical isomerism. This section deals with the brief discussion on the stereochemistry of compounds of N, P and S.

5.9.1 STEREOCHEMISTRY OF NITROGEN COMPOUNDS:

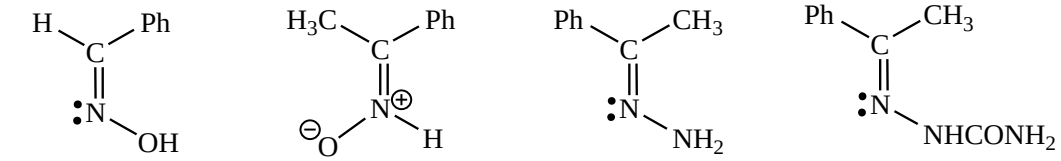
Geometrical isomerism of nitrogen compounds: Nitrogen containing compounds like >C=N- as well as –N=N- bond also exhibit geometrical isomerism. The important classes of compounds that exhibit geometrical isomerism due to >C=N- bond are (Figure 22):

(e) Oximes

(f) Nitrones

(g) Semicarbazones

(h) Hydrazones

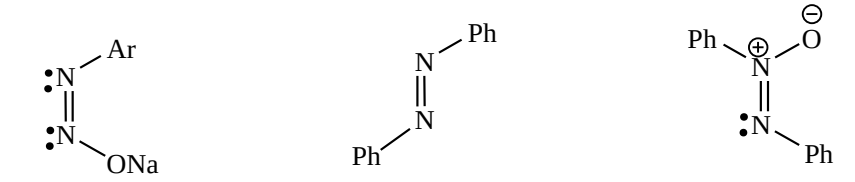


(*Z*)-benzaldehyde oxime | (*E*)-nitrone | (*E*)-1-(1-phenylethylidene) hydrazine | (*E*)-1-(1-phenylethylidene) semicarbazide

Figure 22: Geometrical isomers of compounds having >C=N

Oximes are the most common compounds among all above classes. Both carbon and nitrogen atom in oxime are sp^2 hybridized the C=N bond of oxime consists a sigma (σ) and a pi (π) bond. Therefore, there is no free rotation possible around C=N bond; hence, oximes of aldehyde and ketones (unsymmetrical) exhibit geometrical isomerism.

Some examples of compounds exhibiting geometrical isomerism containing –N=N- are shown in figure 23.

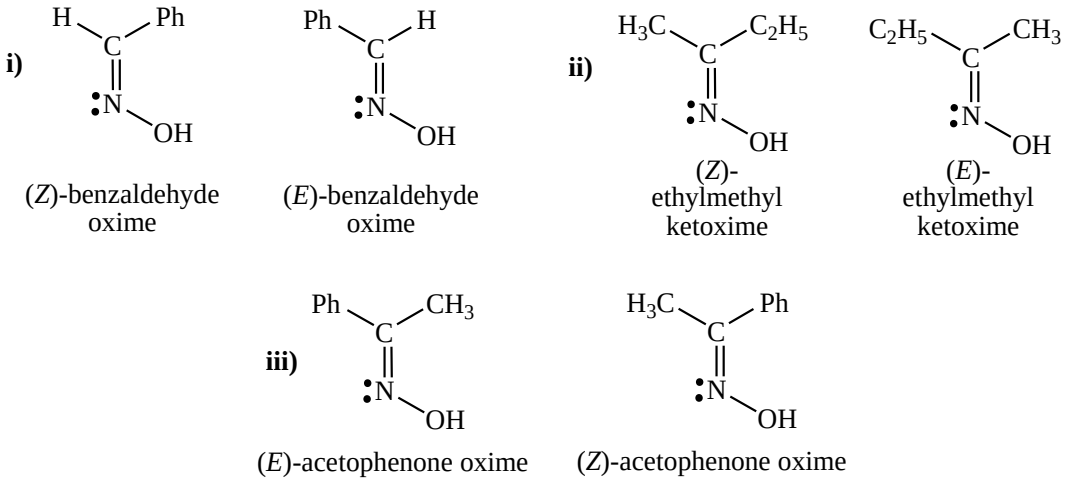


(*Z*)-Diazoate | (*E*)-Azobenzene | (*E*)-Azoxybenzene

Figure 23: Geometrical isomers of compounds having -N=N

The configuration of such compounds is also based on priority of the groups/atoms attached to the double bonded carbon and nitrogen. Lone pair of the nitrogen always considered to be the lowest priority group. The priority of the groups/atoms is assigned as per the sequence rule which we have already discussed in Unit 4. If the higher priority groups/atom on double bonded carbon and nitrogen are on same side of the double bond the isomer is considered as *Z*- isomer, whereas if the higher priority groups/atoms are on opposite side the isomer is considered as *E*-isomer.

Example 26: E/Z isomerism is shown by i) benzaldoxime, ii) ethylmethylketoxime and iii) methylphenylketoxime



Enantiomerism of nitrogen compounds: The tetrahedral concept of carbon has also been successfully extended to nitrogen containing compounds. The only difference in nitrogen compounds is that one of the sp^3 hybridized orbital of nitrogen usually contains a lone pair of electrons which is not involved in bonding. Thus nitrogen containing compound have three ligands and one lone pair in sp^3 orbital. Thus in terms of a chiral center, nitrogen is analogous to carbon. The tertiary amines of with all three different atoms or groups attached with center nitrogen atom have chiral nitrogen, but do not have optical activity. Thus is due to the rapid interconversion of lone pair from one face of the other resulting in rapid racemization Figure 24. The amine interconversion is described as an inversion, such enantiomers are called invertomers.

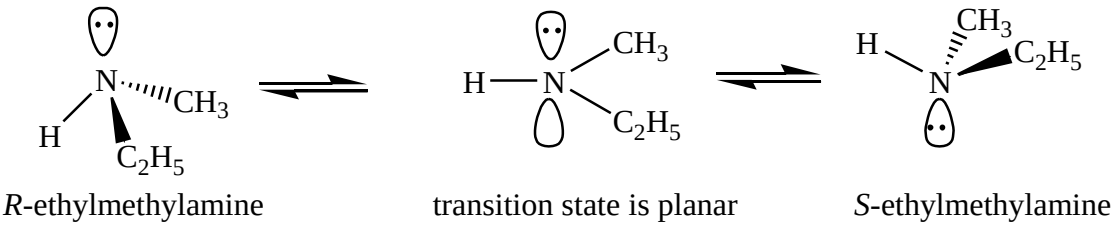


Figure 24: Inversion of lone pair in nitrogen containing compounds

5.9.2 STEREOCHEMISTRY OF COMPOUNDS CONTAINING P:

Phosphorous can also exhibit covalencies of 3, 4 and 5, hence they give rise to more possible configuration than nitrogen. In tetravalent phosphorous compounds the valence deposition is tetrahedral (sp^3 hybridized) in which one sp^3 orbital being occupied by lone pair, whereas, in quinquevalent (pentavalent) phosphorous compounds the valence deposition is trigonal bipyramidal (sp^3d). The following are examples of the various resolvable compounds of phosphorous in its different hybrid states (Figure 26).

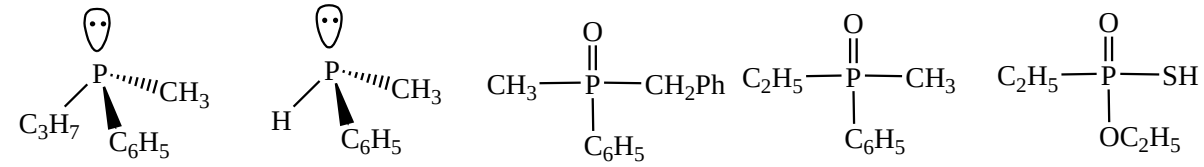


Figure 27: Examples of the various resolvable compounds of phosphorous

5.9.3 STEREOCHEMISTRY OF COMPOUNDS CONTAINING S:

Similar to nitrogen and phosphorous containing compounds, various sulphur containing compounds have also been identified to exhibit enantiomerism. Some common examples are Sulphonium salts, Sulphuris esters, Sulphoxides and Sulphines, Figure 28.

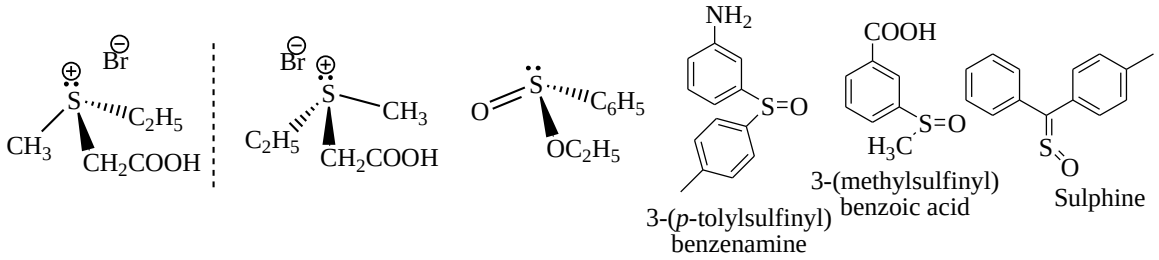


Figure 28: Examples are Sulphonium salts, Sulphuris esters, Sulphoxides and Sulphines

5.10 SUMMARY

The present unit may be summarized as:

- Topicity is the stereo-chemical relationships between individual atoms or groups within a single molecule.

- The property by which the replacement of two similar atoms or groups of a carbon center generates the chirality is called prochirality.
- Two apparently identical atoms/groups of a prochiral centre are called homomorphic atoms/groups.
- If the replacement of two homomorphic ligands generates enantiomers the ligands are called enantiotopic ligands.
- If the replacement of two homomorphic ligands generates diastereomers the ligands are called diastereotopic ligands.
- Stereo chemical transformation (reaction) that results the preferential formation of one enantiomer or diastereomer over other in the presence of a chiral substrate, reagent, catalyst or environment is called asymmetric induction.
- Those reactions in which one stereoisomer (or one pair of enantiomers) is formed predominantly or exclusively out of several possible stereoisomers are called stereoselective reactions.
- The reactions or processes in which one of the enantiomer forms predominantly over the other is called enantioselective reaction.
- The reactions or processes in which one of the diastereomer forms predominantly or exclusively over the other are called diastereoselective reaction.
- Rotation around bonds in alkane structures, exemplified in ethane and butane, gives rise to conformational isomers.
- In the staggered form, the torsional angle between attached groups is at 60^{o}. In the eclipsed form, it is at 0^{o}.
- A staggered conformation of ethane or butane has a lower rotational energy than the eclipsed conformation.
- Anti-conformations are usually the more stable with gauche and eclipsed structures of higher energy.
- Analysis of cyclohexane derivatives pays attention to substituents in axial and equatorial positions, with equatorial substituents being more stable.
- The most stable form of cyclohexane is the chair conformation. In this form, the molecule has both axial and equatorial substituents.

- ❖ Cyclohexane undergoes a chair-boat-chair ring flip in which the axial substituents become equatorial, and vice versa.
- ❖ Interconversions between chair forms involve higher energy structures known as boat, twist and half-chair structures that are unstable.
- ❖ Cyclohexanes with axial substituents are less stable than those with the same substituents equatorial, because of unfavorable interactions among axial substituents.

5.11 TERMINAL QUESTION

Q.1 Define Topicity.

Q.2 What is prochirality?

Q.3 What are enantiotopic ligands and faces?

Q. 4 What do you understand with asymmetric synthesis?

Q. 5 Define configurational and conformational isomers.

Q. 6 Why the geometrical isomers are called diastereomers?

Q. 7 What is cyclization method for determination of configuration of geometrical isomers?

Q. 8 How do you determine the configuration of geometrical isomerism using physical method?

Q. 9 What are staggered and eclipsed conformations of alkanes?

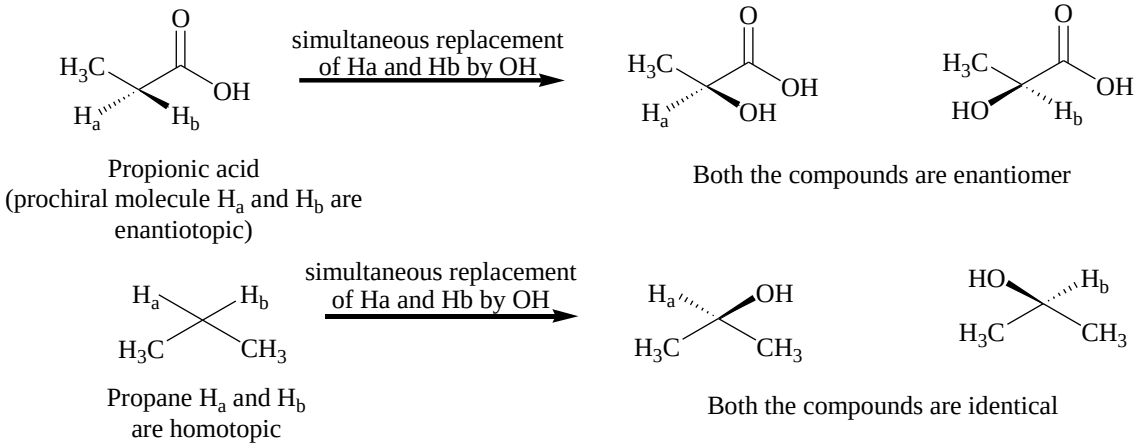
Q. 10 Which conformation of cyclohexane is the most stable and why?

Q. 11 What will be the preferred position for methyl group in the conformation of methyl cyclohexane?

5.12 ANSWERS

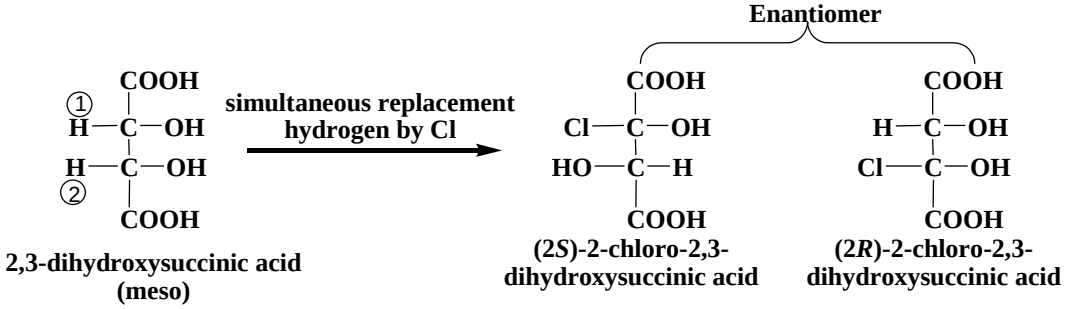
1. Stereo-chemical relationships between individual atoms or groups within a single molecule can be defined in terms of topicity. Thus, two atoms equated by a mirror reflection of the molecule are enantiotopic and two atoms in equivalent environments (i.e., the methylene protons in n-propane) are homotopic. Two protons placed in diastereomeric positions by a mirror reflection are in diastereotopic environments.

   Examples: Propane has homotopic ligands; however, propionic acid has enantiotopic ligands



2. It is the property of some molecules due to which these molecules can be converted in to stereoisomers (enantiomers or diastereomers) by replacing one of the identical atoms or groups by a different atom or group. It is also known as '*prostereoisomerism'* more specifically. If the replacement of such atoms or groups leads the formation of enantiomer the atoms or groups are called enantiotopic; whereas, if such replacement lead the formation of diastereomers the atoms or groups are termed as diastereotopic.
3. When the replacement of each equivalent atom or groups by a different atom given enantiomeric products, such equivalent atoms or groups are called enantiotopic atoms or enantiotopic ligands.

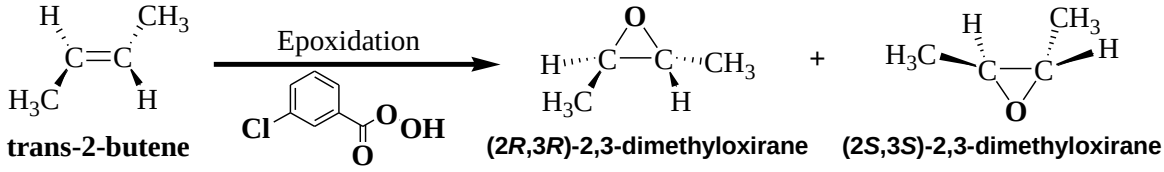
   Example: For example, two hydrogen atoms of meso-tartaric acid are enantiotopic since the replacement of each one of them by a different atom or group gives the enantiomeric pair of (*2S*)-2-chloro-2,3-dihydroxysuccinic acid and (*2R*)-2-chloro-2,3-dihydroxysuccinic acid.



Similarly, when two faces of a double bond gives enantiomers on addition of suitable reagents, such faces are called enantiotopic faces. For example, trans-2-butene and

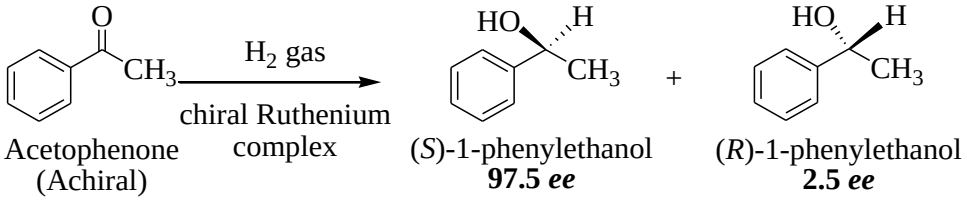
unsymmetrical ketones have enantiotopic faces since they also give enantiomers on addition of suitable reagents.

Example: Epoxidation of trans-2-butene on either face of double bonds gives the enantiomeric pair of (*2R,3R*)-2,3-dimethyloxirane and (*2S,3S*)-2,3-dimethyloxirane.



4. Asymmetric induction is a stereo chemical transformation (reaction) that results the preferential formation of one enantiomer or diastereomer over other in the presence of a chiral substrate, reagent, catalyst or environment. This is also known as asymmetric synthesis.

   Example: Let us consider hydrogenation of Acetphenone by sodiumborohydride ($NaBH_4$). Since, both the reagent and substrate are achiral (optically inactive) and also the reaction takes place in the medium of methanol (achiral), hence, equal amount of (*R*)-1-phenylethanol and (*S*)-1-phenylethanol (racemic mixture) is formed.



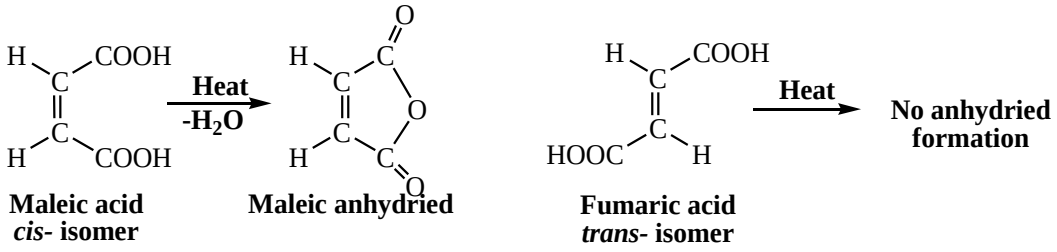
5. The stereoisomerism which is due to the rotation about a single bond is referred to as conformation. Conformers are easily interconvertible and it is difficult to isolate the isomer. On the other hand, when two compounds are different in their configuration, e.g., a pair of enantiomers of bromofluoromethane, or a pair of geometrical isomers, maleic acid and fumaric acid, these are distinguishable compounds, and their isolation is possible

6. Geometrical isomers are non-mirror image of each other hence they are called diastereomers. Therefore their physical and chemical properties are different.

7. Cyclization method**:** Cyclization within a molecule (intramolecular) is usually depends upon the distance of two associating groups of a molecule. In other words if the reacting groups are closer to each other than the intramolecular cyclization takes place more effectively. This principal is also helps to identify the configuration of geometrical isomers.

   Let us take an example of two geometrical isomer of Butenedioic acid (*i.e. Maleic acid and Fumaric acid*) can be differentiated by possibility of formation of anhydride. Maleic acid which is c*i*s- form of Butenedioic acid can only give the respective anhydride on heating; whereas, the trans- form of Butenedioic acid (*i.e.* Fumaric acid) does not give its anhydride on heating. If the Fumaric acid is strongly heated it get converted into Maleic acid.

   Example : Cyclization of Maleic acid to Maleic anhydride. Fumaric acid does not give the anhydride on heating.



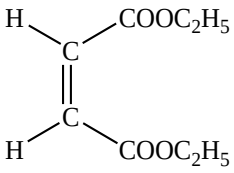
Maleic acid ***cis*- isomer** **Maleic anhydried** **Fumaric acid** ***trans*- isomer**

8. The geometrical isomers are non-mirror image of each other hence are called diastereomers. We have discussed in Unit 4 that diastereomers have different physical and chemical properties. Based on this fact, we can determine the configuration of geometrical isomers by comparing their physical properties. For example the melting point and absorption intensity of the *cis*-isomer are lower than the *trans*-isomer. Similarly the boiling point, solubility, heat of hydrogenation, density, refractive index, dipole moment and dissociation constant of *cis*-isomer is greater than the *trans*-isomer.

   Thus if you have a set of geometrical isomers, then by comparing their above mentioned physical properties you can assign their configuration (means you can identify the *cis*- and *trans*-isomers).

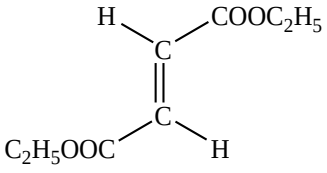
   Example : Diethyl maleate and diethyl fumarate are the *cis*- and *trans*- form to each other. The configuration of these can be determined by comparing their dipole moment.

The dipole moment of diethyl maleate is 2.54D whereas the dipole moment of diethyl fumarate is 2.38D. Based on the fact that the dipole moment of *trans*- form of an isomer is lower than that of *cis*- form, you can easily predict the *cis*- and *trans*- form for diethyl maleate and diethyl fumarate.



diethyl maleate

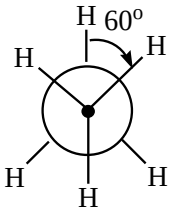
dipole moment = 2.54D



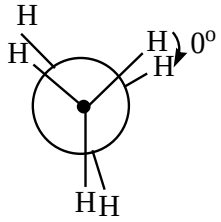
diethyl fumarate

dipole moment = 2.38D

9. Conformation with a 60° dihedral angle is known as staggered conformation. The angle between the atoms attached to the front and rear carbon atom is called dihedral angle.A conformation with a 0° dihedral angle is known as eclipsed conformation.

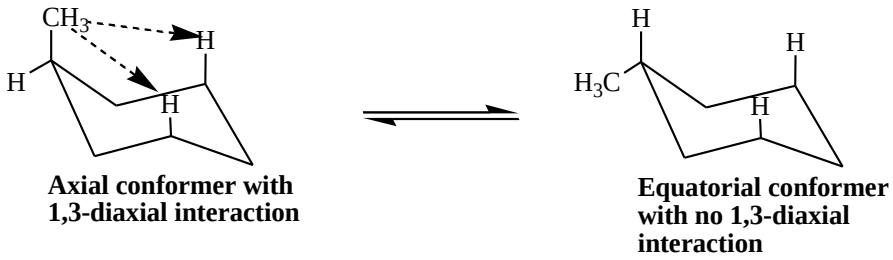


Staggered conformation



Eclipsed conformation

10. The chair conformation is considered as a rigid conformation of cyclohexane in comparison to boat conformation; because during interconversion from chair to boat conformation, some angular deformations are required. These angular deformations usually increase the energy barrier for interconversion from chair to boat conformation. Therefore the chair conformation of cyclohexane is the most stable conformation.
11. There are two possible chair conformations for methyl cyclohexane. In one conformation the methyl group located at axial position, whereas in other conformation the methyl group is located at equatorial position. When methyl group is at axial position, it has 1,3-diaxial interaction with hydrogen atoms at C3 and C5 carbons due to which the energy of such conformation is very high in comparison to the conformer in which the methyl group is at equatorial position. The conformer with methyl group at equatorial position does not have any kind of 1,3-diaxial interaction hence is more stable.



Axial conformer with 1,3-diaxial interaction

Equatorial conformer with no 1,3-diaxial interaction

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