CHAPTER

3

Stereochemistry

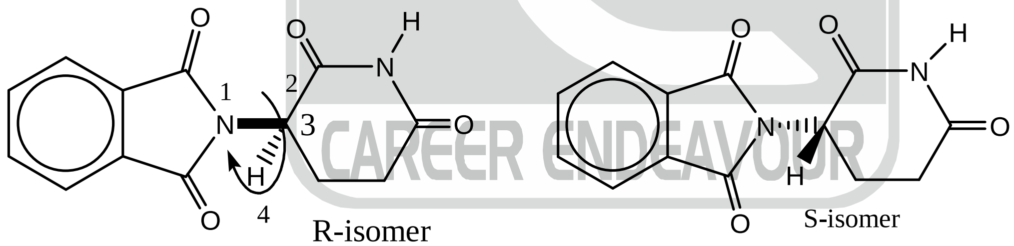
3.1. Introduction :

Stereochemistry : It involves the study of the relative spatial arrangement of atoms within the molecules.

Dynamic stereochemistry: Dynamic stereochemistry is the study of the effect of stereochemistry on the rate of a chemical reaction.

First Stereochemist – Louis Pasteur (1849):

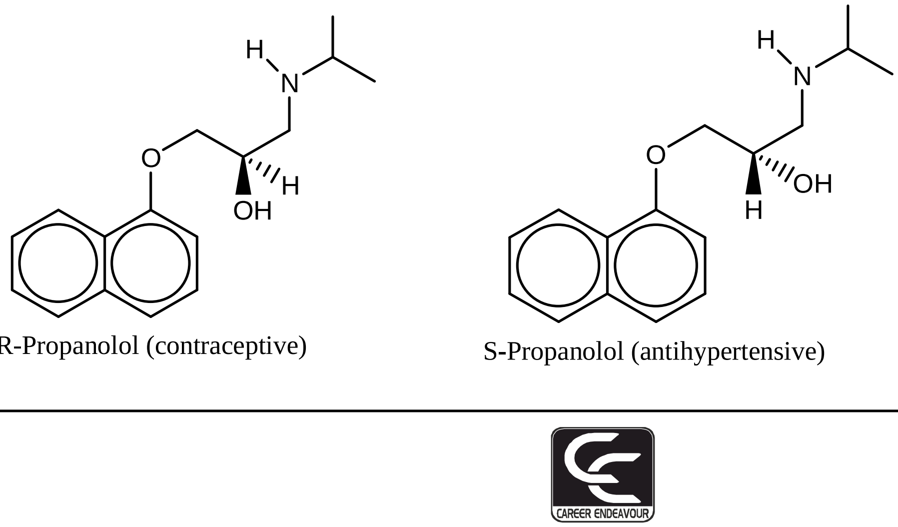
Significance of stereochemistry: One of the most infamous demonstration of the significance of stereochemistry was the ***Thalidomide disaster***. Thalidomide is a drug was first prepared in 1957 in Germany, prescribed for treating morning Sickness in pregnant women. It was discovered that one optical isomer i.e. R-Isomer of the drug was safe whereas the S-isomer had teratogenic effect, causing serious genetic damage to early embryonic growth and development.



Drug for morning sickness in pregnant women. Teratogenic effect

[**Remark:** In human body, Thalidomide undergoes racemization: even if only one of the two stereoisomers is ingested, the other one is produced.]

Now we have another example - Propanolol.



R-Propanolol (contraceptive) S-Propanolol (antihypertensive)

3.2. Basic terminology

Optical activity: The term optical activity derived from the interaction of chiral materials with polarized light.

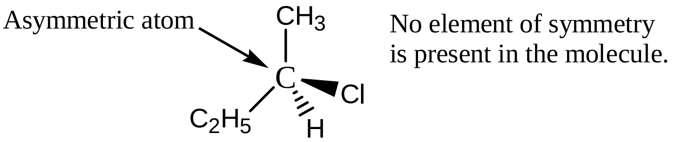
Scalemic: Any non-racemic chiral substance is called *Scalemic*.

- A chiral substance is enantio pure or homochiral when only one of two possible enantiomer is present.
- A chiral substance is enantio enriched or heterochiral when an excess of one enantiomer is present but not the exclusion of the other.

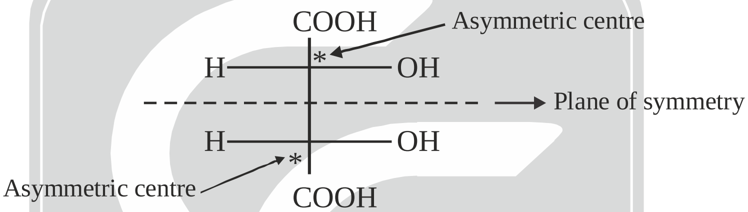
Three terms are used to designate a carbon atom bonded tetrahedrally to four different substituents in a chiral molecule.
(a) Asymmetric atom (*LeBell* & *Vant Hoff* for an atom attached with 4 different groups).
(b) Chiral centre
(c) Stereocentre.

Asymmetric atom:

Compounds with one such atom are truly asymmetric as they lack symmetry. For example



However, there are molecules which also have atoms with four different substituents and which also have various symmetry element including plane of symmetry as in mesotartaric acid.

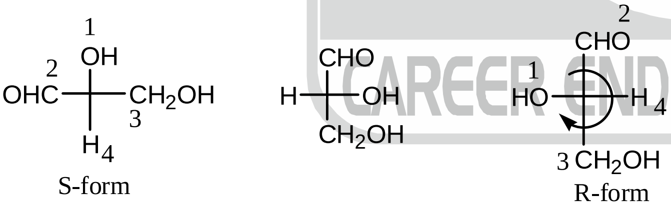


Two asymmetric center but also plane of symmetry.

Chirality is a geometric property which influences and affects all parts of a chiral molecule.

Stereogenic centre or Stereocentre:

A stereogenic centre or in short a stereocentre is an atom having groups of such nature that an interchange of any two groups will produce a stereocentre.

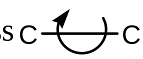


- A carbon atom that is a stereocentre is also called a stereogenic carbon.

Conformation: Structures that can be interconverted simply by rotation about single bonds are conformation of the same molecule.

For example:

Staggered conformation   Eclipsed conformation

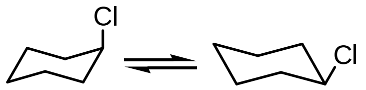
Note: These two are the conformation of ethane arises due to rational possibilites across  single bond.

Configuration: Structures that can be interconverted only by breaking one or more bonds have different configuration and they are stereoisomers specifically known as configurational isomers.

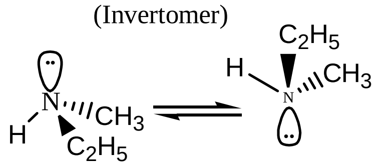
Isomers

Constitutional Isomers
- → Chain Isomerism
- → Position Isomerism
- → Metamerism
- → Tautomerism
- → Valence Isomerism

Stereoisomers
- Conformational Isomer
  - Rotation about single bond.
  - Amine Inversion (Invertomer)
- Configurational Isomers

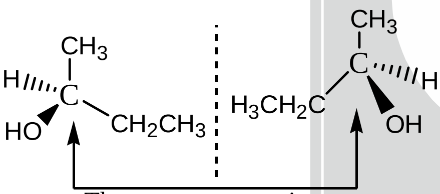


Conformational Isomer (conformers)

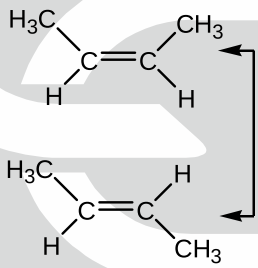


Invertomer (or Umbrella inversion)

Configurational Isomers
- Configurational Enantiomers
- Configurational Diastereomers

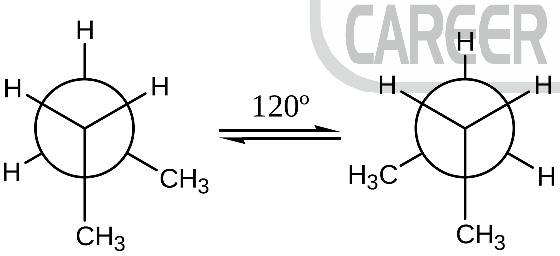


These two are enantiomers



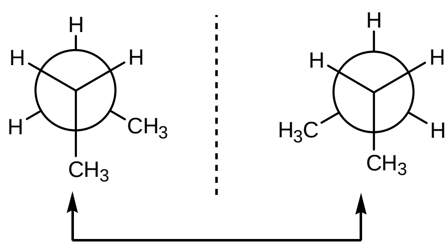
These two are diastereomers

Conformational Isomers
- Conformational enantiomers
- Conformational diastereomers



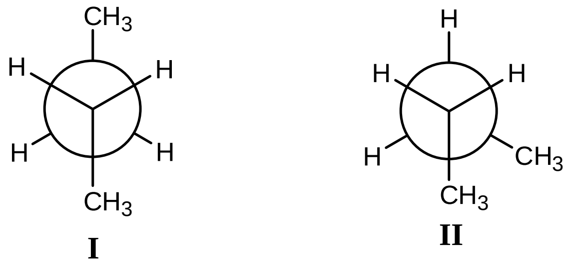
(A) **(S)**

So, (A) and (S) are mirror image of each other as shown below

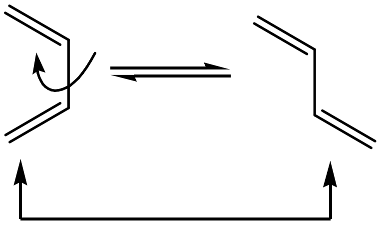


So, these two are conformational enantiomers

Now,



Since, I and II are not mirror image to each other so these two are conformational diasteromers.

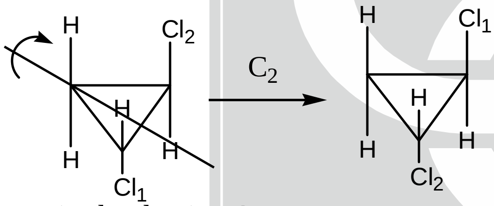


Conformational diastereomers

Structures that are not superimpossible on their mirror image, and can therefore exist as two enantiomers are called chiral.

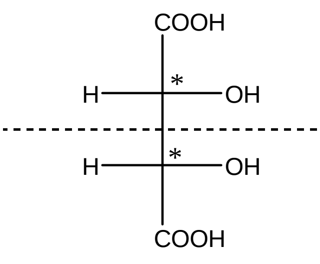
Essential criteria for a molecule to be chiral. There is no any single criterion.

1. There must be lack of element of symmetry.
   Note: It is not necessary and sufficient condition because there are some set of molecules which have some element of symmetry still they are optically active. For example.



Optically active but having C_2-symmetry.

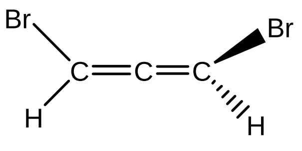
2. The carbon in the molecule should be attacked to four different groups.
   It is not a necessary and sufficient condition also because we have an example in which carbon have four different groups but it is still optically inactive.
   For example:



Two asymmetric centre but still optically in active owing to plane of symmetry.

On the other hand we have also an example in which there is not any chiral centre but still molecule is optically active.

For example: Properly substituted allene.



Not any chiral centre but still it is optically active.

Remrak: This compound is optically active not due to chiral centre but due to chiral axis.

3. There should be an absence of plane of symmetry.

3.3. Symmetry element :

A symmetry element is a geometrical entity such as a line, a plane, or a point with respect to which one or more symmetry operations may be carried out.

Symmetry Operation: A symmetry operation is the movement of a molecule about the symmetry element in such a manner that the resulting configuration of the molecule is indistinguishable from the original molecule. The molecule may assume an equivalent configuration or an identical configuration.

Group Theory: Mathematical study of symmetry is called group theory.

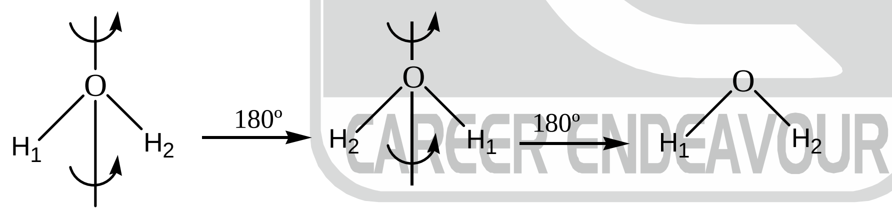
Symmetry element	Symbol	Symmetry operation
Axis of symmetry	C_n	do C_n
Alternating axis of symmetry	S_n	do S_n
Plane of symmetry	σ	do σ
Point of symmetry or centre of symmetry	i	do i
Identity	E	doing nothing.

Various types of elements of symmetry are explained below as:

(A) Axis of symmetry: An imaginary axis passing through the molecule, rotation on which by θ^0 gives an equivalent orientation of molecule. It is denoted by 'n'. Where, n = 1, 2, 3, 4, ...

Orientation: Orientation is three dimensional distribution of atoms and groups of molecule.

For example:



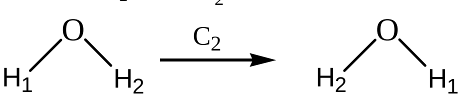
Initial orientation Equivalent orientation Identical orientation

So, the order of axis $C_n = \frac{360^o}{180^o} = 2$ i.e. C_2 (pronounced as C-two)

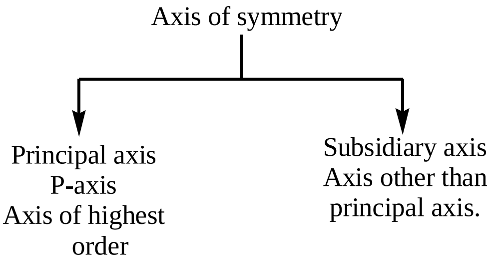
Two things do an axis of symmetry.

Axis of symmetry → Pass
Axis of symmetry → Interchange

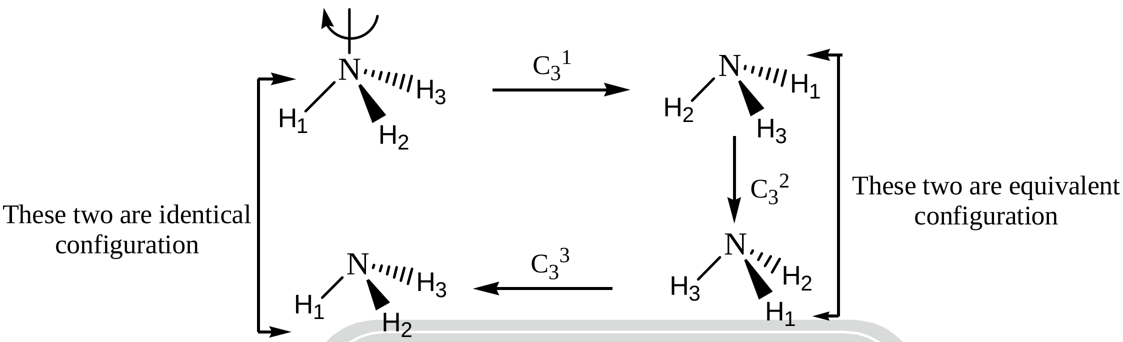
For example in H_2O.



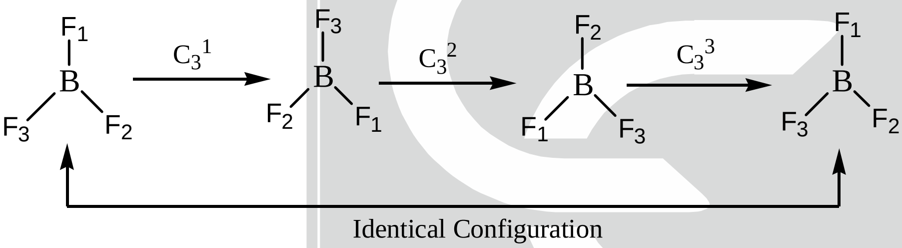
C_2–axis is passing through oxygen atom and interchanging H_1/H_2.



Let us consider another example of NH_3.

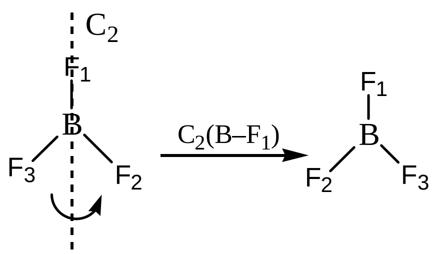


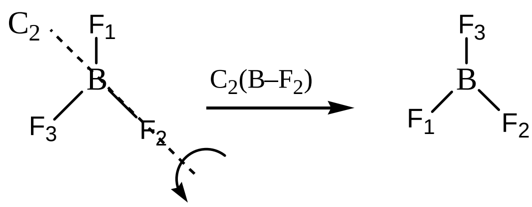
Let us consider an example of BF_3.
In BF_3 one C_3-axis is passing through B-atom which is perpendicular to the molecular plane.

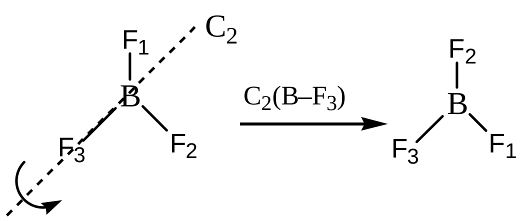


BF_3 molecule has also $3C_2$-axis.
(1) Passing through B—F_1 bond and interchanging F_2/F_3.
(2) Passing through B—F_2 bond and interchanging F_1/F_3.
(3) Passing through B—F_3 bond and interchanging F_1/F_2.

These three C_2-axis can be represented as

(1) 

(2) 

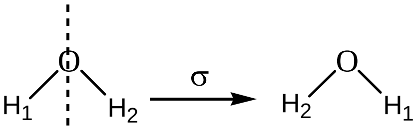
(3) 

(B) Plane of symmetry: Imaginary plane passing through a molecule which can bisect the molecule into two mirror image halves.

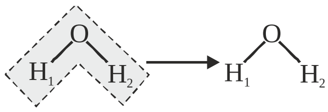
There are two functions of a plane → Bisect / Reflect

For example:

(i) bisecting oxygen atom and reflecting H_1/H_2.



(ii) Bisecting all three atoms.

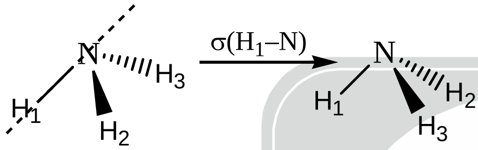


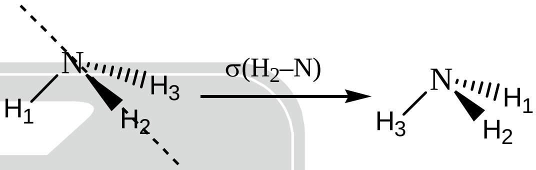
(iii) Ammonia have three plane of symmetry.

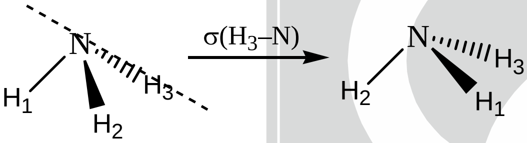
(1) Bisecting H_1–N bond and reflecting H_2/H_3.

(2) Bisecting H_2–N bond and reflecting H_1/H_3.

(3) Bisecting H_3–N bond and reflecting H_1/H_2.

(1) 

(2) 

(3) 

(iv) BF_3 is four plane of symmetry.

(1) Passing through F_1–B bond and reflecting F_2/F_3.

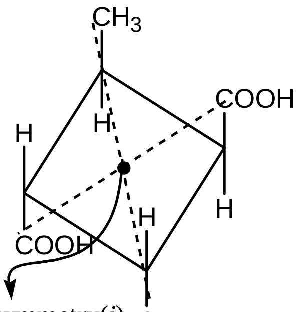
(2) Passing through F_2–B bond and reflecting F_1/F_3.

(3) Passing through F_3–B bond and reflecting F_1/F_2.

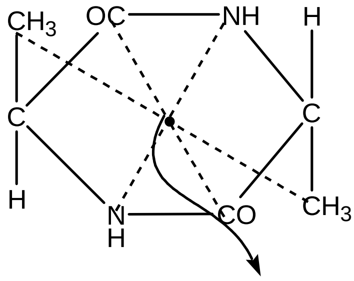
(4) Bisecting all the four atoms viz F_1, F_2, F_3 and B.

(C) Centre of symmetry: A centre of symmetry is a point from which lines, when drawn on one side and produced an equal distance on the other side, will meet identical point in the molecule.

For example: 2, 4-dimethylcyclobutane–1, 3-dicarboxylic acid.



Centre of symmetry(*i*)

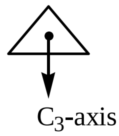


Centre of symmetry

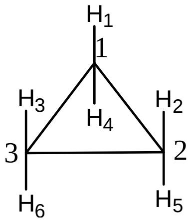
Now, we want to discuss symmetry element of cyclopropane for the purpose of optical activity.

Cyclopropane have one C_3 axis and three C_2 axis and four plane of symmetry.

1. C_3-axis is passing through centre of triangle and perpendicular to all the three C_2-axis.



2. $3C_2$-axis.



(a) Passing through C_1 and interchanging C_2/C_3 or H_1/H_4, H_5/H_3 and H_2/H_6.

(b) Passing through C_2 and interchanging C_1/C_3 or H_2/H_5, H_1/H_6, H_3/H_4.

(c) Passing through C_3 and interchanging C_1/C_2 or H_3/H_6, H_1/H_5 and H_2/H_4.

3. **4 plane of symmetry.**

(a) Bisecting $H_3-C_3-H_6$ and reflecting C_1/C_2, H_1/H_2 and H_4/H_5.

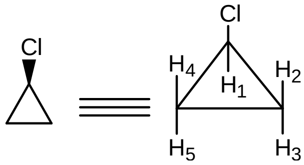
(b) Bisecting $H_1-C_1-H_4$ and reflecting C_2/C_3, H_2/H_3, H_6/H_5.

(c) Bisecting $H_2-C_2-H_5$ and reflecting C_1/C_3, H_1/H_3, H_4/H_6.

(d) Bisecting C_1, C_2 and C_3 and reflecting H_2/H_5, H_1/H_4 and H_3/H_6.

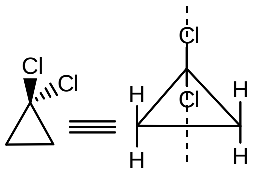
Now, we want to make cyclopropane molecule chiral for this we will have to remove all plane of symmetry from cyclopropane molecule. Because for a molecule to be chiral, plane of symmetry should not be present.

Case I: Mono substituted cyclopropane

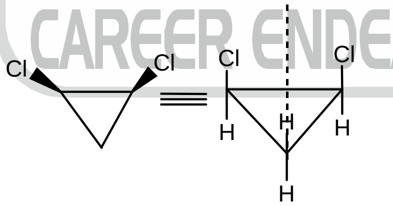


It has plane of symmetry bisecting Cl–C–H_1 and reflecting H_2/H_4 and H_3/H_5. So, this molecule is optically inactive.

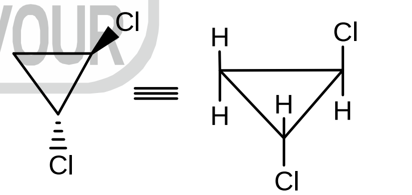
Case II: Homodisubstituted cyclopropane



→ Plane of symmetry
→ Achiral
→ Optically inactive
→ C_2-symmetry is present

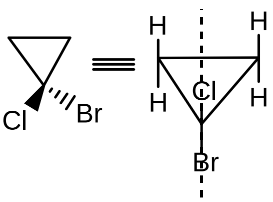


→ Plane of symmetry
→ Achiral
→ Optically inactive

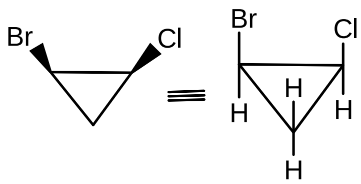


→ No plane of symmetry
→ But C_2-symmetry is present
→ Chiral molecule
→ Optically active.

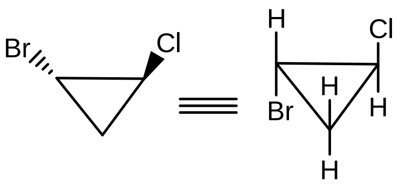
Case III: Heterodisubtituted cyclopropane



→ Plane of symmetry is present
→ Achiral
→ Optically inactive

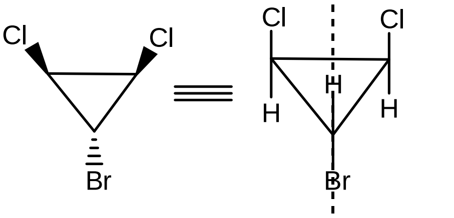


→ No plane of symmetry
→ No axis of symmetry
→ Chiral
→ Optically active

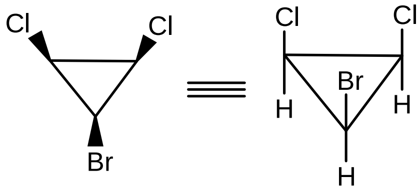


→ No plane of symmetry
→ No axis of symmetry
→ Chiral
→ Optically active

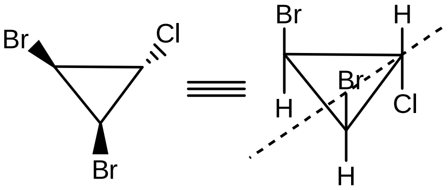
Case - III: Trisubstituted cyclopropane.



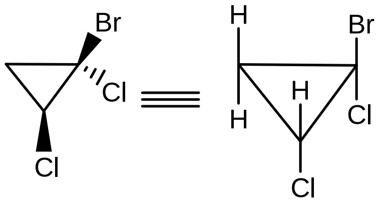
→ Plane of symmetry present.
→ Achiral
→ Optically inactive.



→ Plane of symmetry is present
→ Achiral
→ Optically inactive

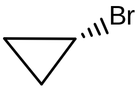
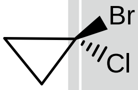
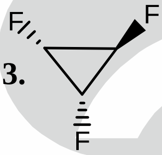
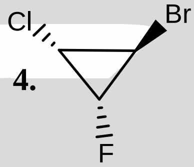


→ Plane of symmetry present
→ No axis of symmetry
→ Achiral

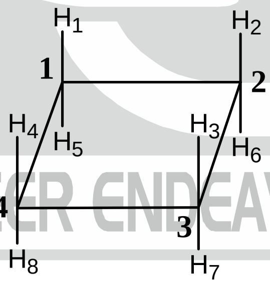


→ No plane of symmetry
→ Chiral
→ Optically active

Problem: Find out which of the following molecule is optically active.

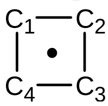
1.  **2.**  **3.**  **4.** 

Symmetry properties of cyclobutane.



Cyclopropane have one C_4-axis and $4C_2$'s axis, $4\sigma_v$'s and one σ_h.

1. C_4-axis passing through centre of square and perpendicular to C_2' s axis.



2. $4C_2$'s axis.

(a) Passing through C_1 and C_3 and interchanging C_2/C_4, H_1/H_5, H_3/H_7, H_4/H_6, H_2/H_8.

(b) Passing through C_2 and C_4 and interchanging C_1 and C_3. H_4/H_8, H_2/H_6, H_1/H_7, H_5/H_3.

(c) Passing through C_1–C_4 and C_2–C_3 and interchanging H_3/H_6, H_2/H_7, H_1/H_8, H_4/H_5.

(d) Passing through C_1–C_2 and C_3–C_4 and interchanging. H_4/H_7, H_3/H_8, H_1/H_6, H_2/H_5.

4 σ_v' s

(a) Bisecting H_1–C_1–H_5 and H_3–C_3–H_7 and reflecting H_2/H_4, H_6/H_8

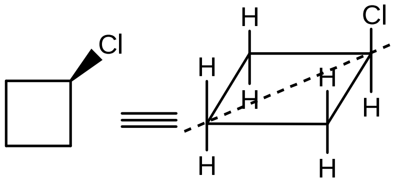
(b) Bisecting H_2–C_2–H_6 and H_4–C_4–H_8 and reflecting H_1/H_3, H_5/H_7.

(c) Bisecting C_2–C_3 and C_1–C_4 bond length and reflecting H_2/H_3, H_6/H_7, H_1/H_4, H_5/H_8.

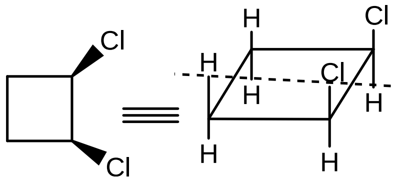
(d) Bisecting C_1–C_2 and C_3–C_4 bond length and reflecting H_1/H_2, H_5/H_6, H_3/H_4, H_8/H_7.

(e) Bisecting C_1, C_2, C_3 & C_4 and reflecting H_1/H_5, H_2/H_6, H_3/H_7 and H_4/H_8.

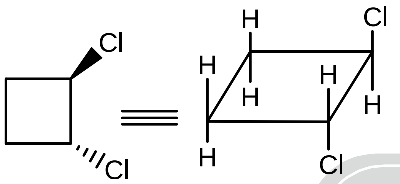
Now, let us consider a case of substituted cyclobutane



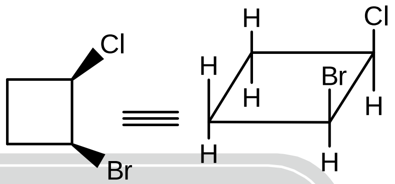
→ Plane of symmetry.
→ Achiral
→ Optically inactive.



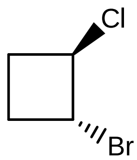
→ Plane of symmetry
→ Achiral
→ Optiacally inactive.



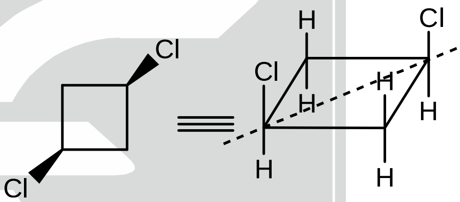
→ No plane of symmetry
→ Chiral
→ Optically active



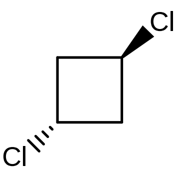
→ No plane of symmetry
→ Chiral
→ Optically active



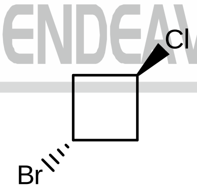
→ No plane of symmetry
→ Optically active



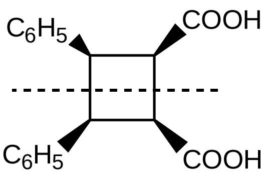
→ Plane of symmetry
→ Optically inactive
→ Achiral molecule.



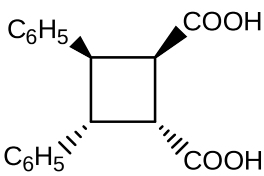
→ Plane of symmetry
→ Optically inactive



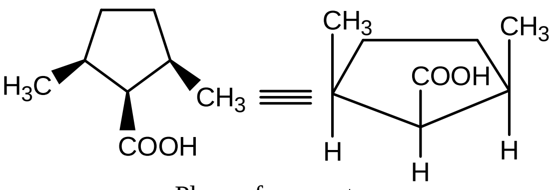
→ Plane of symmetry
→ Optically inactive



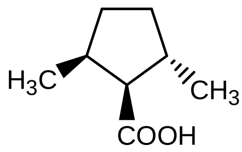
→ Plane of symmetry
→ Optically inactive



→ No plane of symmetry
→ Optically active
→ Chiral molecule.

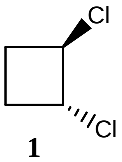


→ Plane of symmetry
→ Achiral molecule
→ Optically inactive.



→ No plane of symmetry
→ Chiral molecule
→ Optically active

Problem-2: Find out which molecules are/is optically active.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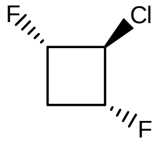
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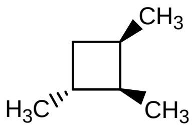
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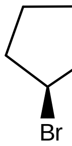
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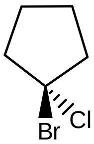
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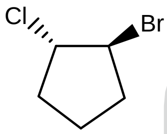
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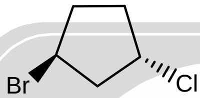
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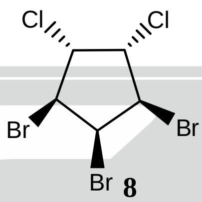

8

3.4. Specification of configuration R/S :

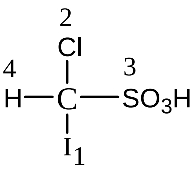
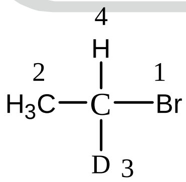
Then is absolute configuration of chiral centre Proposed by R.S. Chan, Sir Christopher Ingold, V. Prelog.

Sequence rule: Priority to the four atoms or groups of atoms attached to the chiral centre can be determined in accordance with sequence rule which are as follows.

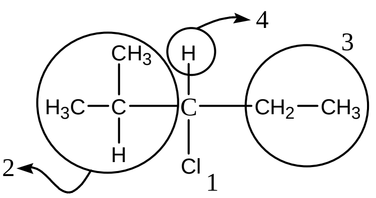
Rule 1: If the four atoms attached to the chiral centre are all different, priority depends on atomic number, with the atom of high atomic number getting higher priority.

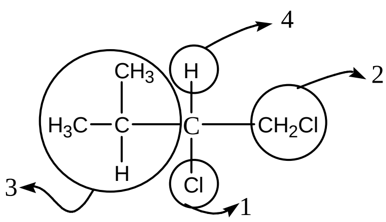
Rule 2: In case of isotope, the atom of higher mass number has the higher priority.
For example among Br, C, D, H priority order is

Br > C > D > H.

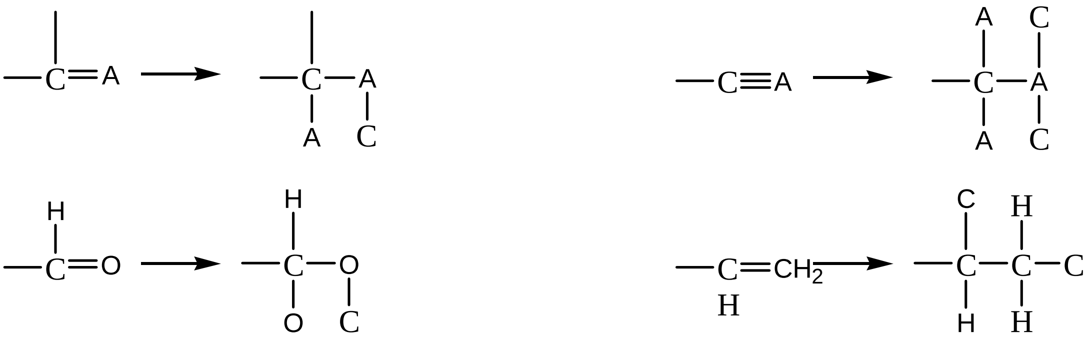
e.g.  

Rule 3: If the relative priority of two groups cannot be decided by rule mentioned above, then look for next atoms.



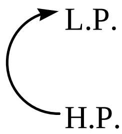


Rule 4: Where there is a double bond or triple bond, both atoms are considered to be duplicated or triplicated.

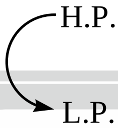


(1) Assign the priority sequence by above mentioned method.
(2) Find out position of the 4th group.
(3) Connect 1→2→3 making a circle.

Case I: If fourth group is below the plane.

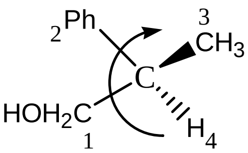


L.P → Low priority group.
H.P → High priority group.

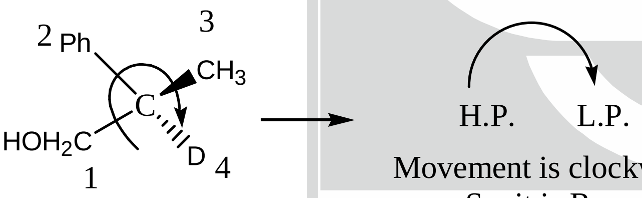


Clockwise → R

Anticlockwise → S



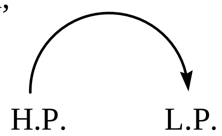
Note: In this case 4th group 'H' is below the plane and rotation is clockwise so, it is 'R'.

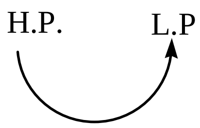


Movement is clockwise
So, it is R.

Case 2: If fourth group is above the plane.

Then,

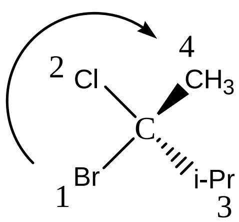




Clockwise movement → S

Anticlockwise movement → R

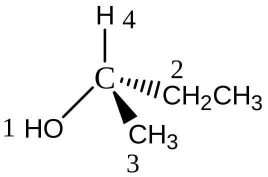
For example:



Note: In this case 4th group is above the plane,
So, clockwise movement gives 'S'.

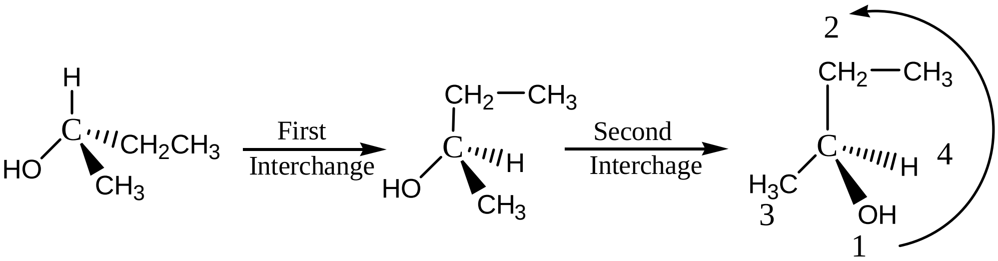
Case III: If the fourth group is on the plane then do double interchange in such a way that the 4th group undergoes below the plane.

For example:



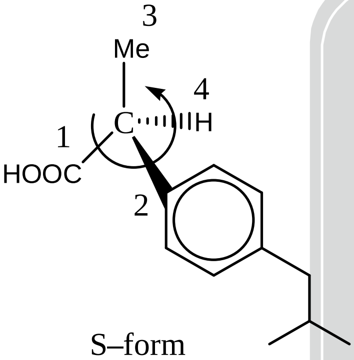
In this case 4^{th} group is on the plane.

Double interchange can be done as



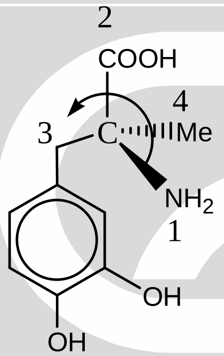
'S'

PROBLEMS



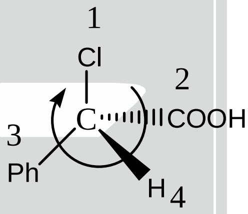
S–form

I



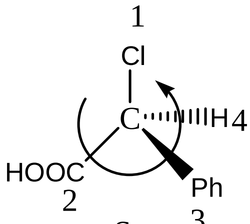
S–Methyl dopa

II



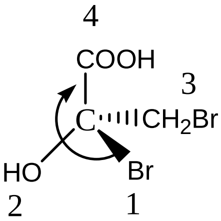
S

III

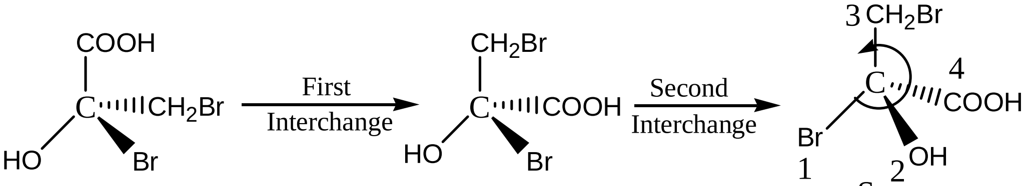


S

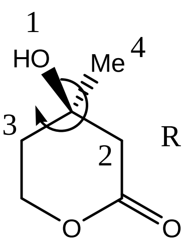
IV



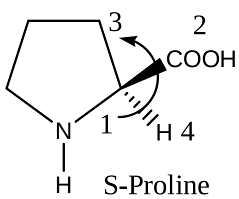
Note: In this case fourth group is on the plane. So, we will have to do double interchange as shown below



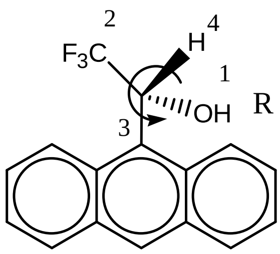
S



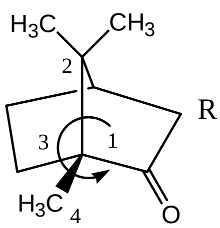
R



S-Proline



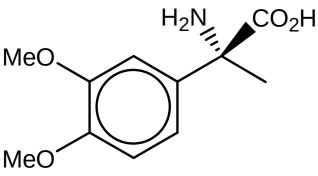
R



R

PROBLEMS

1. Find R/S of the following compounds



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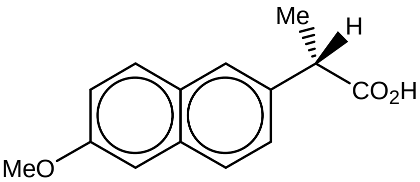

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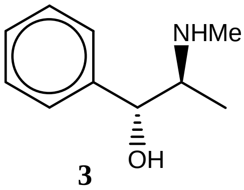

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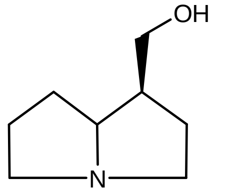

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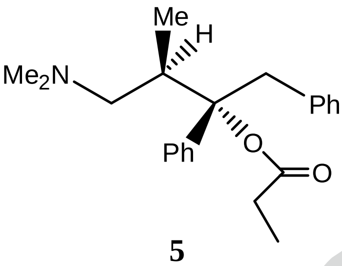

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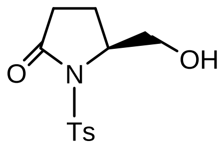

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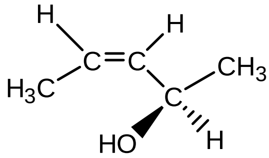

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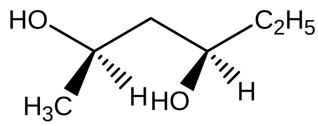

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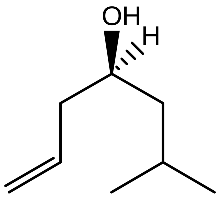

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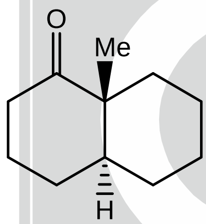

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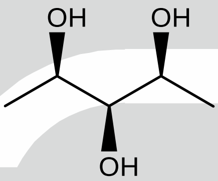

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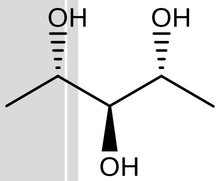
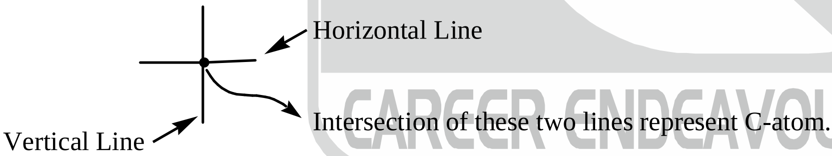
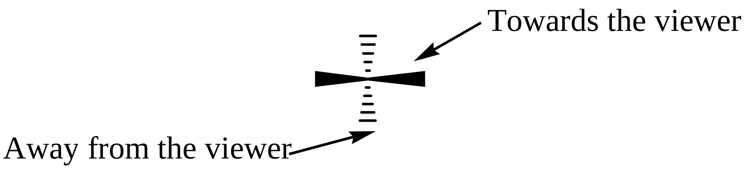


12

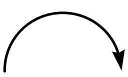
R/S Nomenclature in Fischer projection.

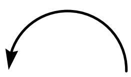


Vertical Line $\rightarrow$ away from the viewer.
Horizontal Line $\rightarrow$ Towards the viewer.

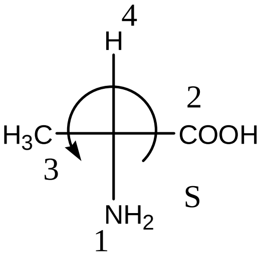


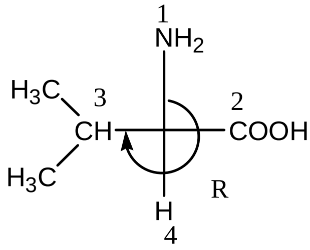
For R/S nomenclature.
Assign priority sequence.
Case I: If fourth group is present on the top or bottom of vertical line then


H.P. L.P. $\rightarrow$ Clockwise $\rightarrow$ R

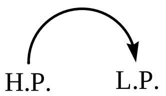

L.P. H.P. $\rightarrow$ Anticlockwise $\rightarrow$ S

For example:

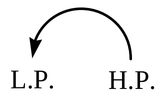




Case II: If 4[th] group is present on left or right side of the horizontal line then.

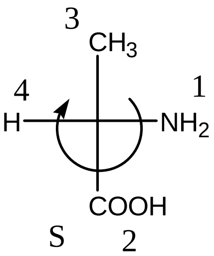


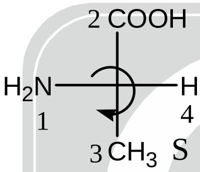
Clockwise → S



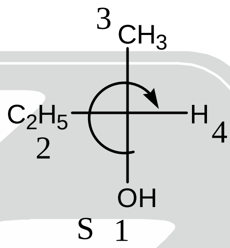
Anticlockwise → R

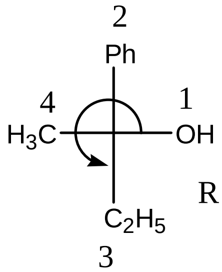
For example:



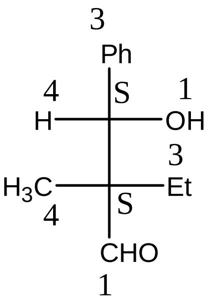


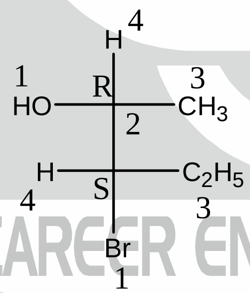
;



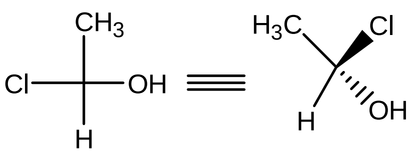


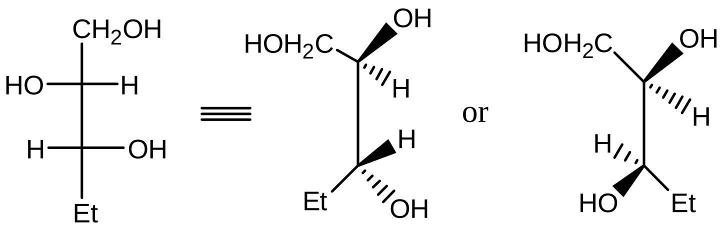
For example:

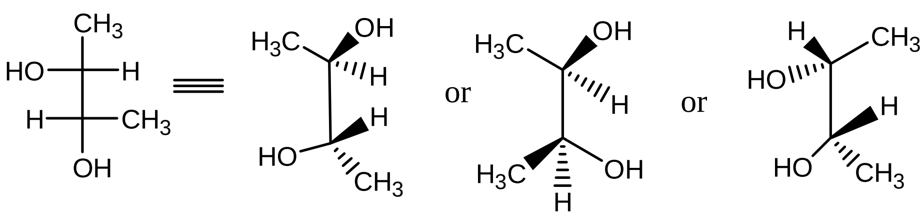




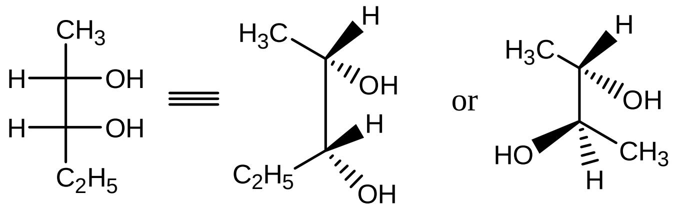
Conversion of Fisher → Wedge.

(i)


(ii)


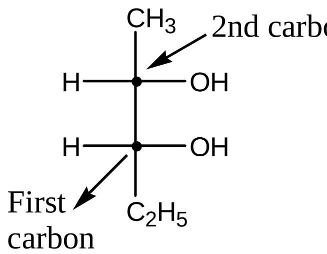
(iii)


Note: In all conversion, the configuration (R/S) should not be change.

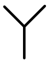


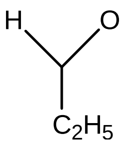
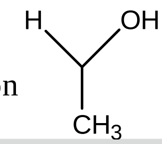
Conversion of fischer to sawhorse.

F → W

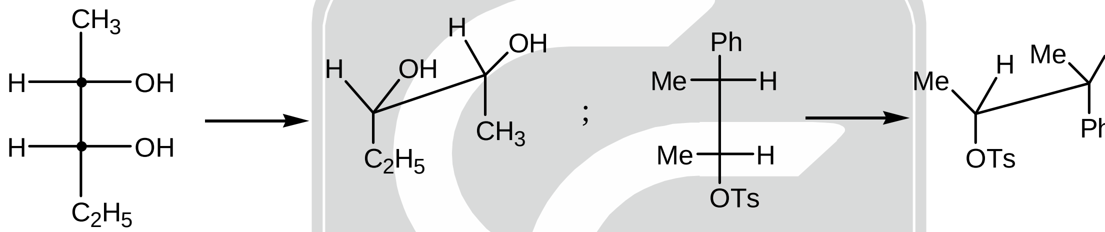


Note: Consider at first carbon shape like

 (Pronounced 'Y')

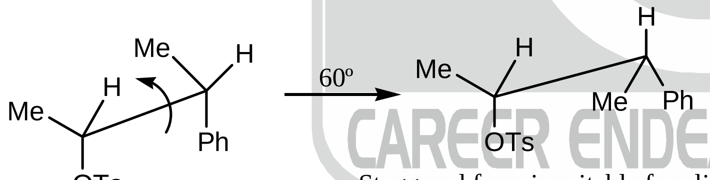
At first carbon  At 2nd carbon 

and then combine these two by a straight line like



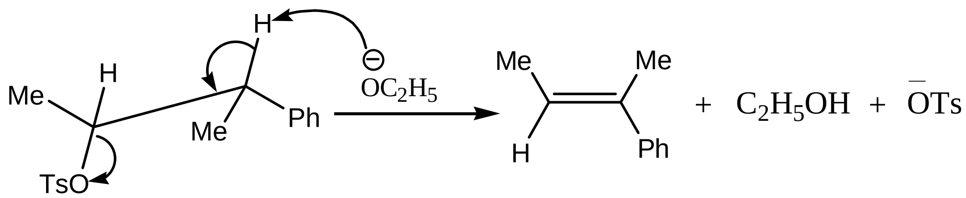
Note: Since Fischer projection is represented in eclipsed form so the resulting sawhorse should also be in eclipsed form if we have need of staggered form we can obtain it by simple rotation.

For example:

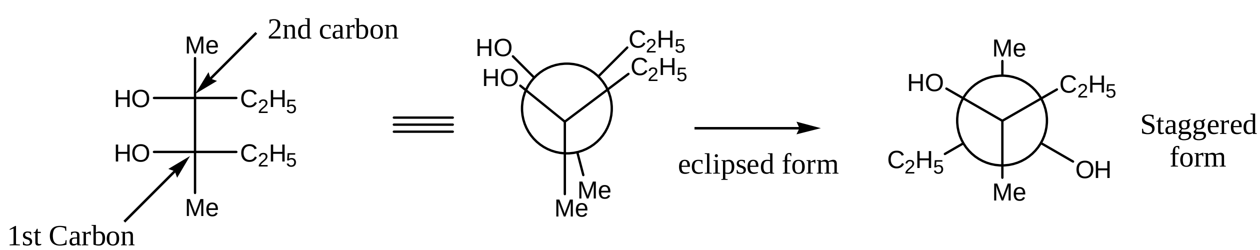


Eclipsed form

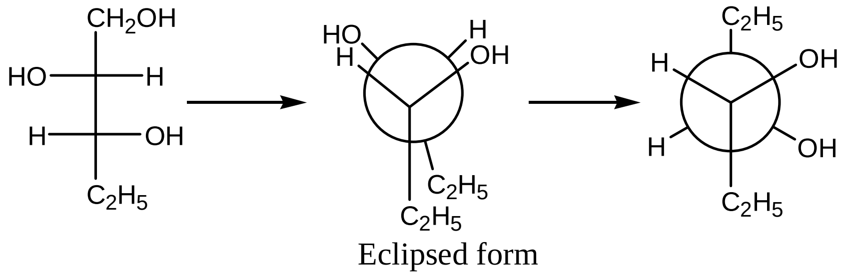
Staggered form is suitable for elimination reaction since, for E_2 elimination, the two departing group should be trans.

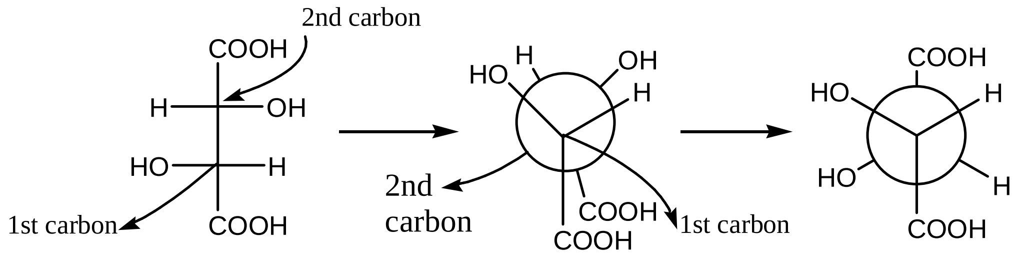


Conversion of Fischer to Newmann:



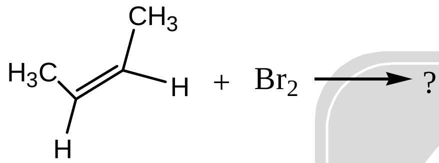
eclipsed form

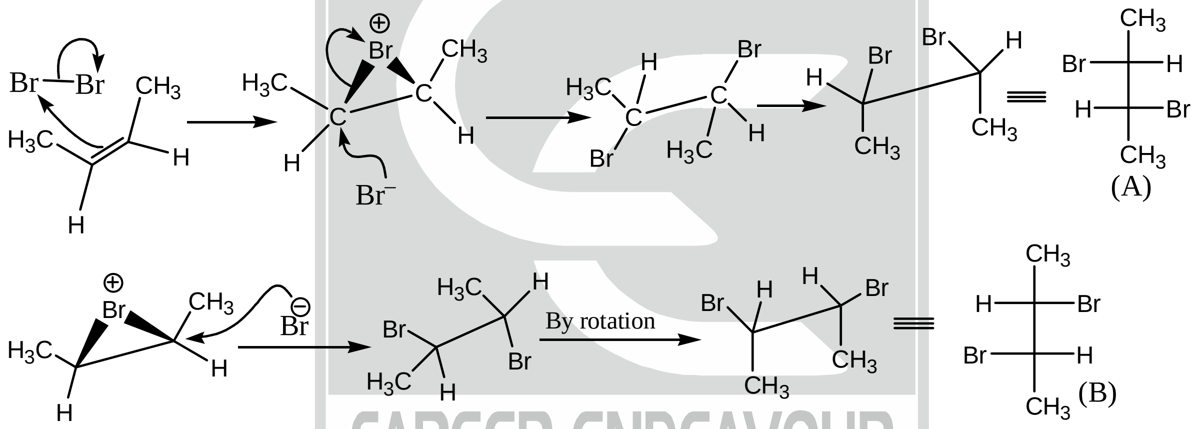




How we can apply these interconversion into reaction mechanism.

Let us consider addition of Br_2 on cis-2-butene.

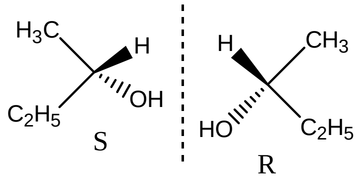
2. 



So, A and B are non superimposable mirror image to each other and hence They are enantiomers.

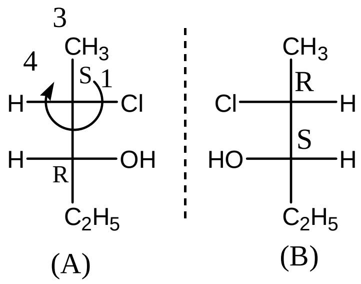
3.5. Enantiomers:

Enantiomers are the stereoisomers which are non superimposable mirror images to each other. So these two steroisomers have opposite descriptor.



→ Non super imposable mirror image.

→ Opposite descriptor i.e. one is R and other is S.



So, in compound 'A' and 'B', the configuration at chiral centre are

In A	In B
C_2 — S	C_2 — R
C_3 — R	C_3 — S

So, these two are enantiomer

Properties of enantiomer:

1. All physical properties such as M.P., refractive index, vapour pressure, relative density, NMR spectrum, IR spectrum are same except direction of optical rotation. (Magnitude is same but direction is opposite).
2. All the chemical properties of enantiomers towards achiral reagent are always identical.
3. The chemical properties of enantiomers will be different in the following condition.

	Reagent	Solvent	Catalyst	Result
1	Chiral	Achiral	Achiral	Difference in rate of reaction.
2	Achiral	Chiral	Achiral	Difference in rate of reaction
3	Achiral	Achiral	Chiral	Difference in rate of reaction

Note: If we run NMR spectrum of enantiomers in chiral solvent then it will be also different.

3. What is the relation between following compound.

So, these two compounds are enantiomer.

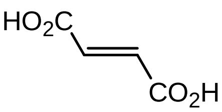
3.6. Diastereoisomers:

Diastereomers are the strereoisomers that are not enantiomers.

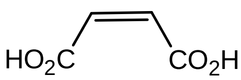
Some important points regarding the diastereoisomers.

1. Diastereomers can arise when structures have more than one stereogenic centre.
2. The magnitude of optical rotation of diastereoisomers are always different but the direction may be same or opposite.
3. The physical properties of diastereomers are always different but difference may be more or less.
4. The chemical properties of diastereomers toward chiral as well as achiral reagent is always different.

Examples of diastereoisomers:



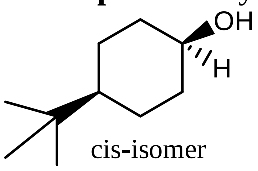
Fumaric acid
m.p. 299-300ºC



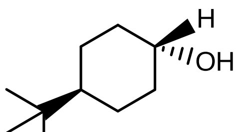
Maleic acid
m.p. 140–142ºC

Note: geometrical isomers (i.e. cis and trans isomers) are always diastereoIsomers. A similar stereoisomers can exist in cyclic compounds.

For example: 4-t-butyl cyclohexanol.



cis-isomer
because –OH and t-Bu group are projected in same direction
m.p. 82-83ºC



Trans-isomer
m.p. 80-81ºC

So, these two stereoisomers are called diastereomers.