CHAPTER

3

Stereochemistry

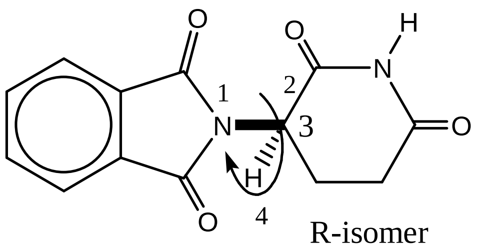
Stereochemistry :

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.

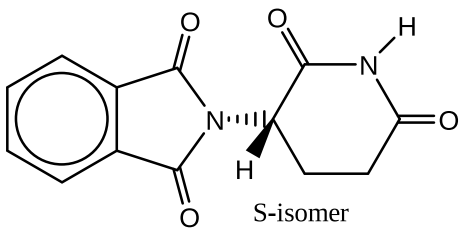
First Stereochemist – Louis Pasteur (1849):

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.



R-isomer

Drug for morning sickness in pregnant women.

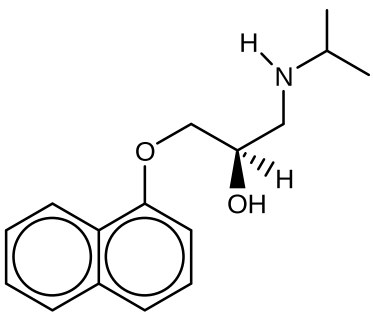


S-isomer

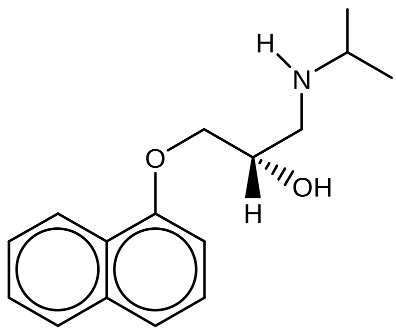
Teratogenic effect

[**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)

SOME TERMINOLOGY

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

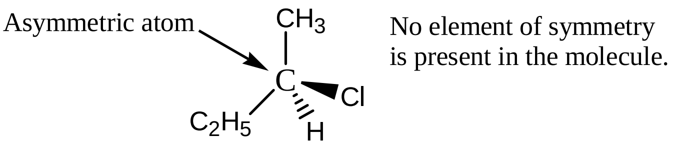
Scalemic: Any non-racemic chiral substance is called *Scalemic*.

- 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.

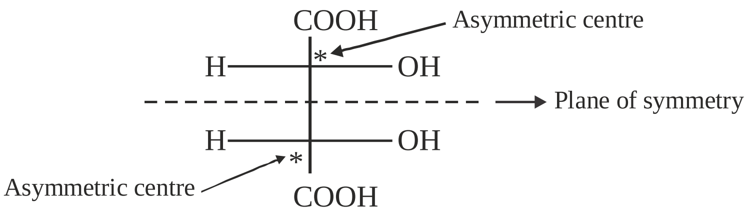
Three terms are used to designate a carbon atom bonded tetrahedrally to four different substituents in a chiral molecule.
(a) Asymmetric atom (*LeBell* & *Vant Hoff* for an atom attached with 4 different groups).
(b) Chiral centre
(c) Stereocentre.

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.

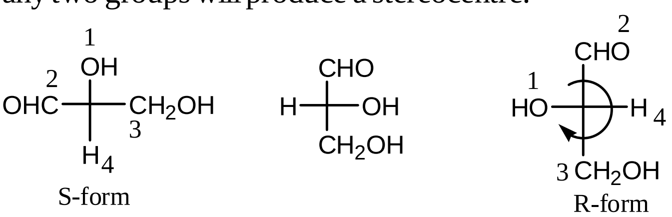


Two asymmetric center but also plane of symmetry.

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

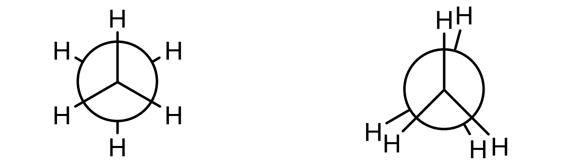
Stereogenic centre or Stereocentre:

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:

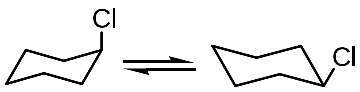


Note: These two are the conformation of ethane arises due to rational possibilites across C–C single bond.

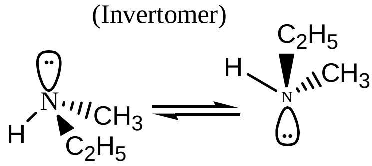
Configuration: Structures that can be interconverted only by breaking one or more bonds have different configuration and they are stereoisomers specifically known as configurational isomers.

Isomers

- Constitutional Isomers
  - → Chain Isomerism
  - → Position Isomerism
  - → Metamerism
  - → Tautomerism
  - → Valence Isomerism
- Stereoisomers
  - Conformational Isomer
    - Rotation about single bond.
    - Amine Inversion (Invertomer)
  - Configurational Isomers



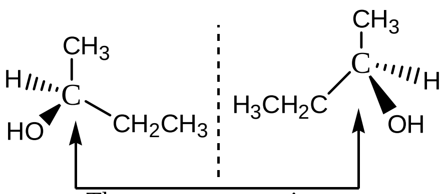
Conformational Isomer (conformers)



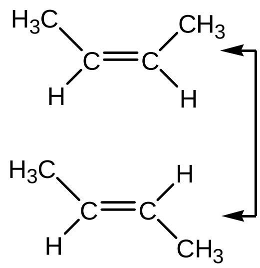
Invertomer (or Umbrella inversion)

Configurational Isomers

- Configurational Enantiomers
- Configurational Diastereomers



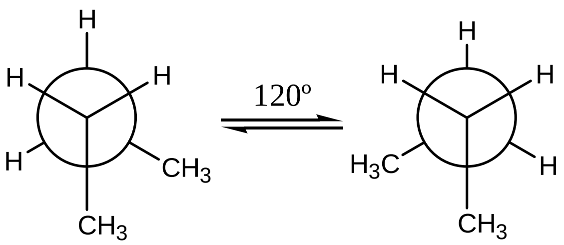
These two are enantiomers



These two are diastereomers

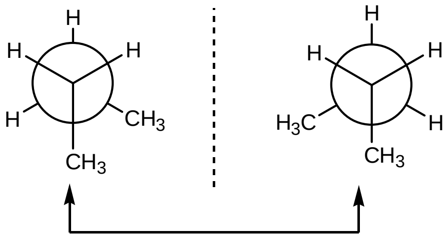
Conformational Isomers

- Conformational enantiomers
- Conformational diastereomers

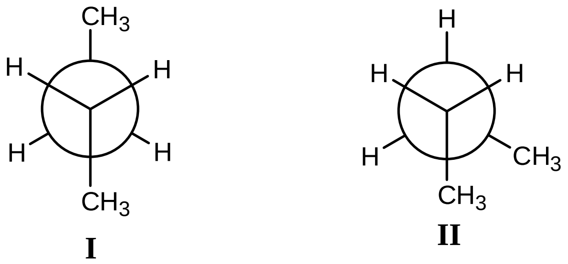


(A) **(S)**

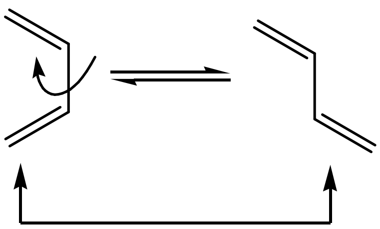
So, (A) and (S) are mirror image of each other as shown below



So, these two are conformational enantiomers

Now, 

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

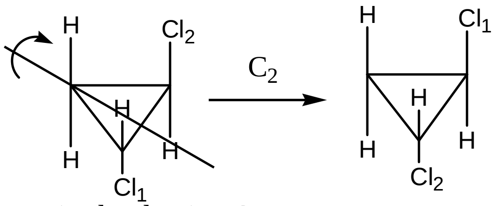


Conformational diastereomers

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

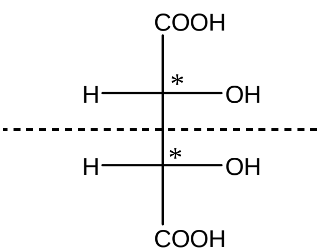
Essential criteria for a molecule to be chiral. There is no any single criterion.

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.

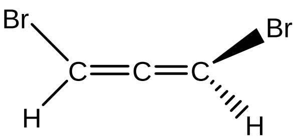
2. The carbon in the molecule should be attacked to four different groups.
It is not a necessary and sufficient condition also because we have an example in which carbon have four different groups but it is still optically inactive.
For example:



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.

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.

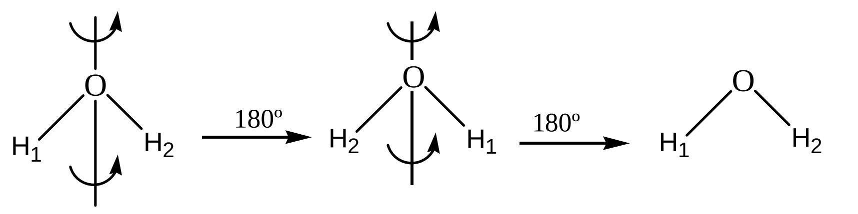
Symmetry element	**Symbol**	**Symmetry operation**
Axis of symmetry	C_n	do C_n
Alternating axis of symmetry	S_n	do S_n
Plane of symmetry	σ	do σ
Point of symmetry or centre of symmetry	i	do i
Identity	E	doing nothing.

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:



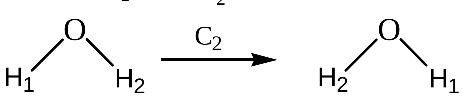
Initial orientation   Equivalent orientation   Identical orientation

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

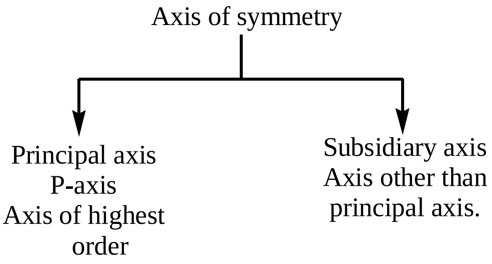
Two things do an axis of symmetry.

Axis of symmetry → Pass
Axis of symmetry → Interchange

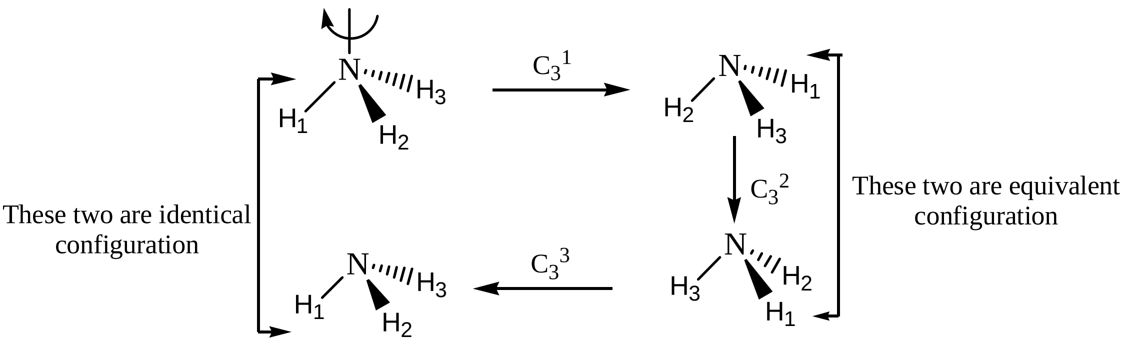
For example in H_2O.



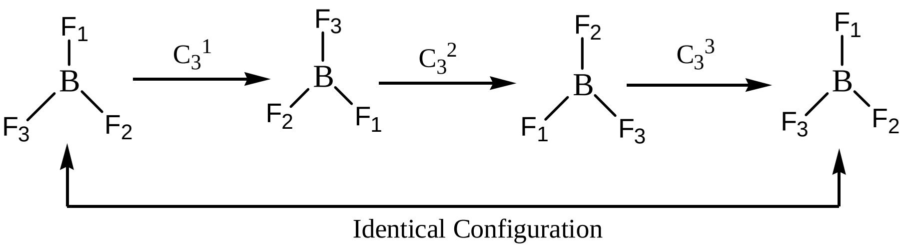
C_2–axis is passing through oxygen atom and interchanging H_1/H_2.



Let us consider another example of NH_3.

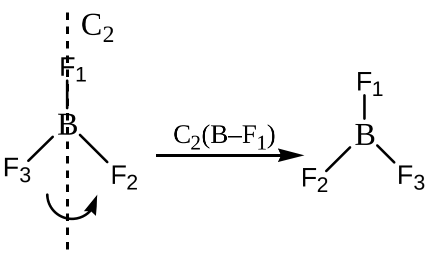


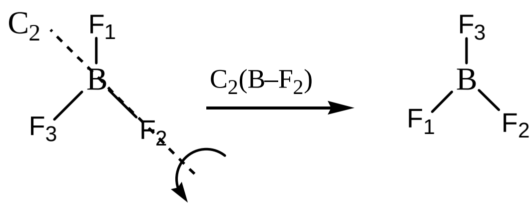
Let us consider an example of BF_3.
In BF_3 one C_3-axis is passing through B-atom which is perpendicular to the molecular plane.

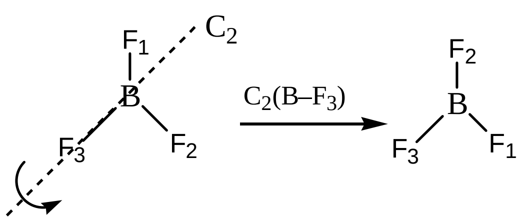


BF_3 molecule has also $3C_2$-axis.
(1) Passing through B—F_1 bond and interchanging F_2/F_3.
(2) Passing through B—F_2 bond and interchanging F_1/F_3.
(3) Passing through B—F_3 bond and interchanging F_1/F_2.

These three C_2-axis can be represented as

(1) 

(2) 

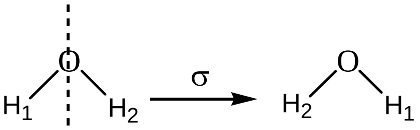
(3) 

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

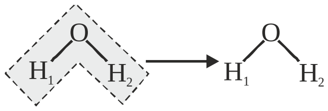
There are two functions of a plane → Bisect, Reflect

For example:

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



(ii) Bisecting all three atoms.

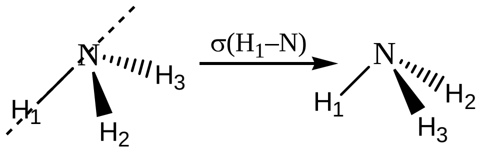


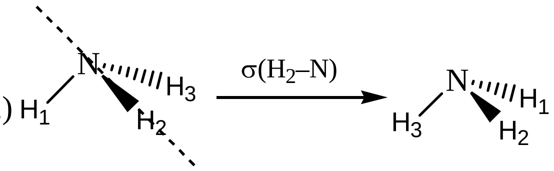
(iii) Ammonia have three plane of symmetry.

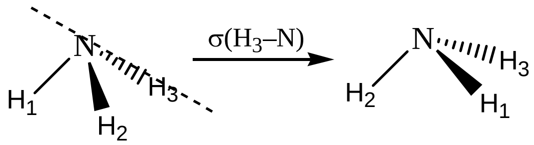
(1) Bisecting H_1–N bond and reflecting H_2/H_3.

(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.

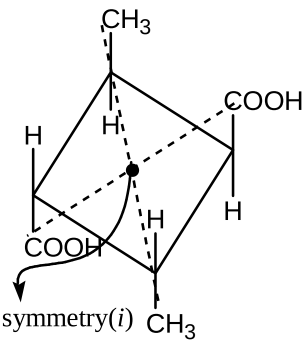
(2) Passing through F_2–B bond and reflecting F_1/F_3.

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

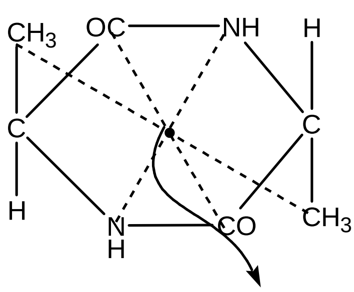
(4) Bisecting all the four atoms viz F_1, F_2, F_3 and B.

(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.



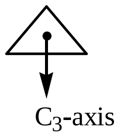
Centre of symmetry(*i*)



Centre of symmetry

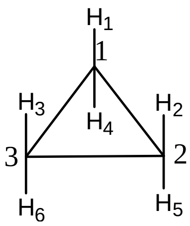
Now, we want to discuss symmetry element of cyclopropane for the purpose of optical activity.

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.

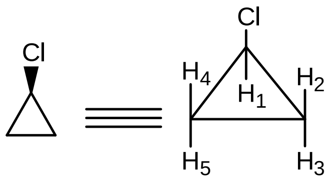
(b) Bisecting $H_1—C_1—H_4$ and reflecting C_2/C_3, H_2/H_3, H_6/H_5.

(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.

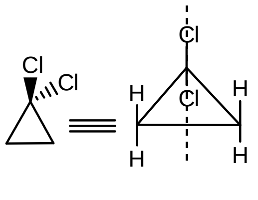
Now, we want to make cyclopropane molecule chiral for this we will have to remove all plane of symmetry from cyclopropane molecule. Because for a molecule to be chiral, plane of symmetry should not be present.

Case I: Mono substituted cyclopropane

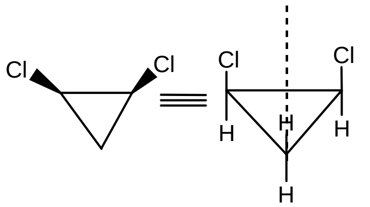


It has plane of symmetry bisecting Cl–C–H_1 and reflecting H_2/H_4 and H_3/H_5. So, this molecule is optically inactive.

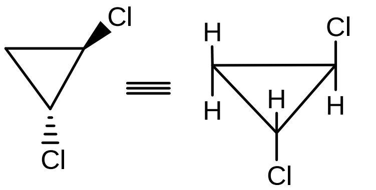
Case II: Homodisubstituted cyclopropane



→ Plane of symmetry
→ Achiral
→ Optically inactive

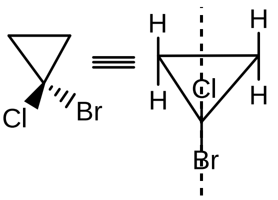


→ Plane of symmetry
→ Achiral
→ Optically inactive

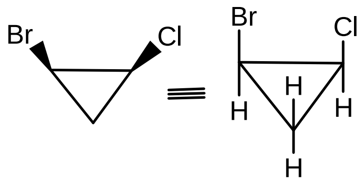


→ No plane of symmetry
→ But C_2-symmetry is present
→ Chiral molecule
→ Optically active.

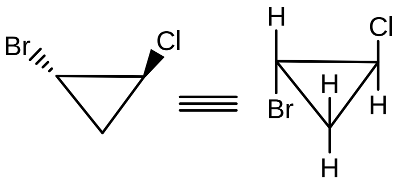
Case III: Heterodisubtituted cyclopropane



→ Plane of symmetry is present
→ Achiral
→ Optically inactive

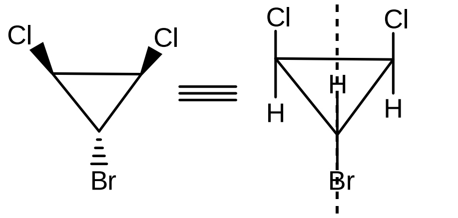


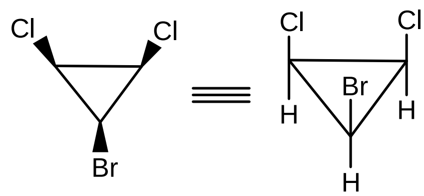
→ No plane of symmetry
→ No axis of symmetry
→ Chiral
→ Optically active



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

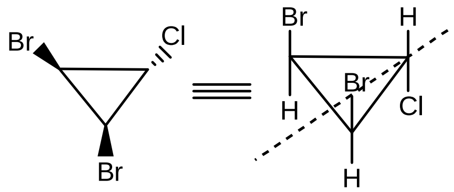
Case - III: Trisubstituted cyclopropane.

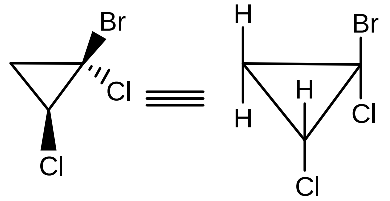




$\rightarrow$ Plane of symmetry present.
$\rightarrow$ Achiral
$\rightarrow$ Optically inactive.

$\rightarrow$ Plane of symmetry is present
$\rightarrow$ Achiral
$\rightarrow$ Optically inactive

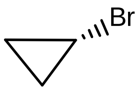
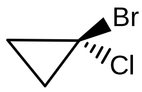
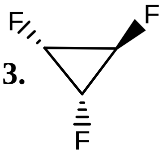
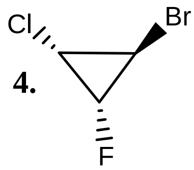




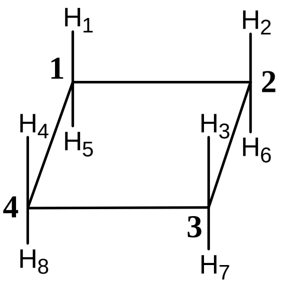
$\rightarrow$ Plane of symmetry present
$\rightarrow$ No axis of symmetry
$\rightarrow$ Achiral

$\rightarrow$ No plane of symmetry
$\rightarrow$ Chiral
$\rightarrow$ Optically active

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

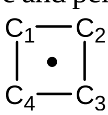
1.  **2.**  **3.**  **4.** 

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

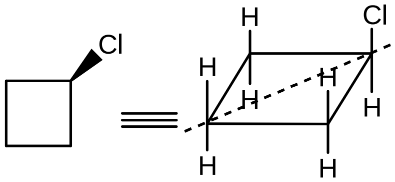
(b) Bisecting H_2–C_2–H_6 and H_4–C_4–H_8 and reflecting H_1/H_3, H_5/H_7.

(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.

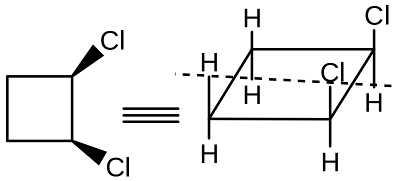
(d) Bisecting C_1–C_2 and C_3–C_4 bond length and reflecting H_1/H_2, H_5/H_6, H_3/H_4, H_8/H_7.

(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.

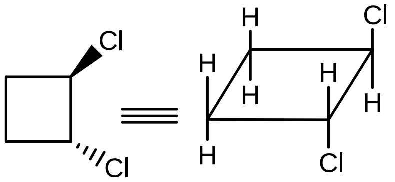
Now, let us consider a case of substituted cyclobutane



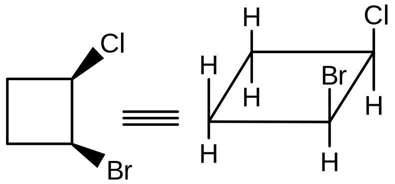
→ Plane of symmetry.
→ Achiral
→ Optically inactive.



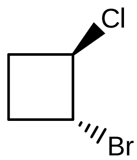
→ Plane of symmetry
→ Achiral
→ Optiacally inactive.



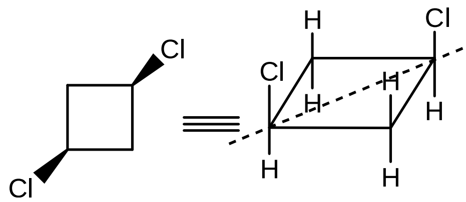
→ No plane of symmetry
→ Chiral
→ Optically active



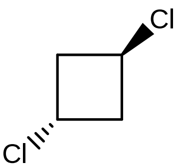
→ No plane of symmetry
→ Chiral
→ Optically active



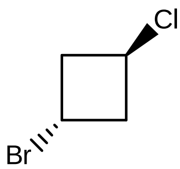
→ No plane of symmetry
→ Optically active



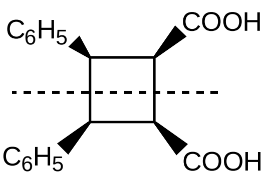
→ Plane of symmetry
→ Optically inactive
→ Achiral molecule.



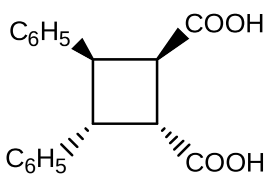
→ Plane of symmetry
→ Optically inactive



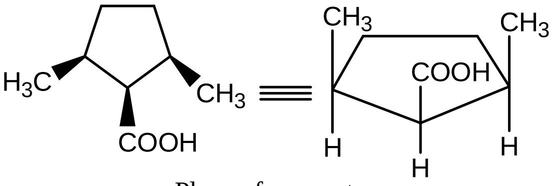
→ Plane of symmetry
→ Optically inactive



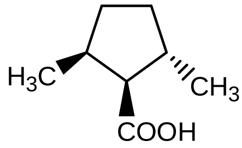
→ Plane of symmetry
→ Optically inactive



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

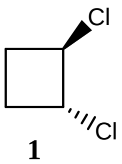


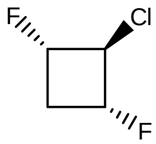
→ Plane of symmetry
→ Achiral molecule
→ Optically inactive.

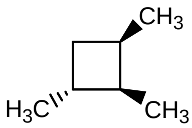


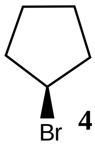
→ No plane of symmetry
→ Chiral molecule
→ Optically active

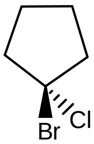
Problem-2: Find out which molecules are/is optically active.

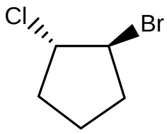

1

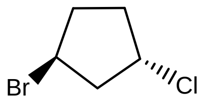

2

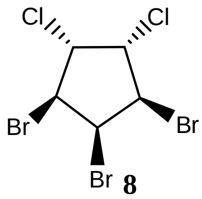

3


4


5


6


7


8

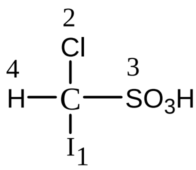
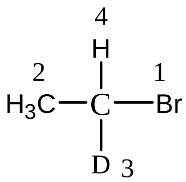
Specification of configuration R/S : Then is absolute configuration of chiral centre Proposed by R.S. Chan, Sir Christopher Ingold, V. Prelog.

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.

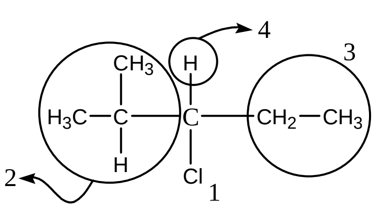
Rule 1: If the four atoms attached to the chiral centre are all different, priority depends on atomic number, with the atom of high atomic number getting higher priority.

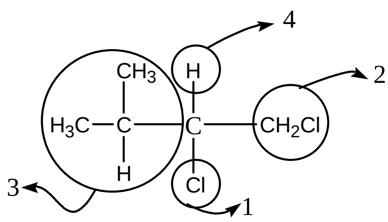
Rule 2: In case of isotope, the atom of higher mass number has the higher priority.
For example among Br, C, D, H priority order is

$$Br > C > D > H.$$

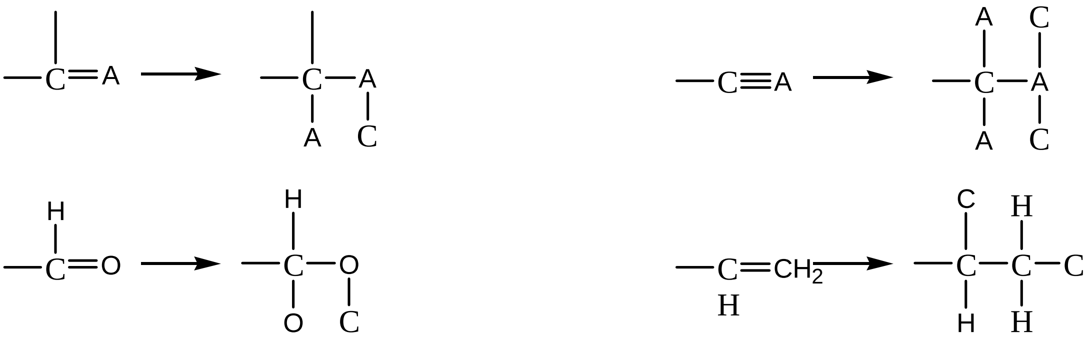
e.g.  

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



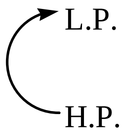


Rule 4: Where there is a double bond or triple bond, both atoms are considered to be duplicated or triplicated.

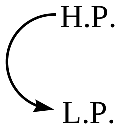


(1) Assign the priority sequence by above mentioned method.
(2) Find out position of the 4th group.
(3) Connect 1→2→3 making a circle.

Case I: If fourth group is below the plane.

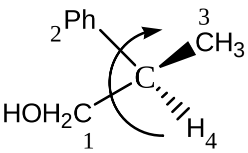


L.P → Low priority group.
H.P → High priority group.

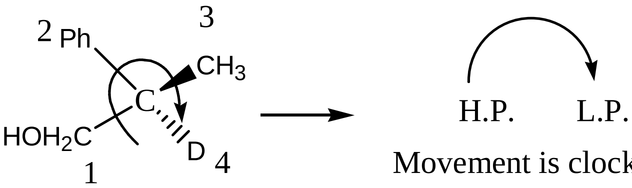


Clockwise → R

Anticlockwise → S



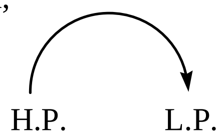
Note: In this case 4th group 'H' is below the plane and rotation is clockwise so, it is 'R'.



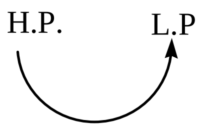
Movement is clockwise
So, it is R.

Case 2: If fourth group is above the plane.

Then,

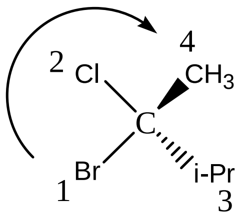


Clockwise movement → S



Anticlockwise movement → R

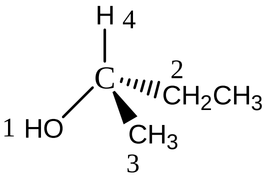
For example:



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

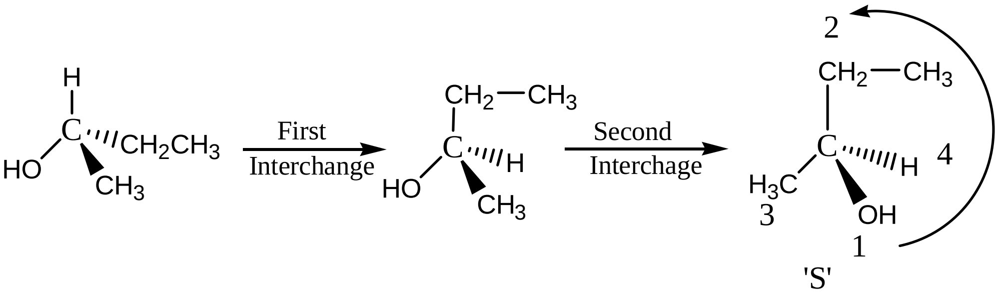
Case III: If the fourth group is on the plane then do double interchange in such a way that the 4th group undergoes below the plane.

For example:

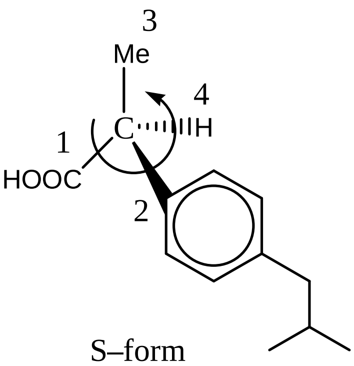


In this case 4^{th} group is on the plane.

Double interchange can be done as

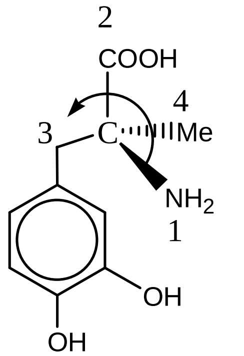


SOLVED PROBLEMS



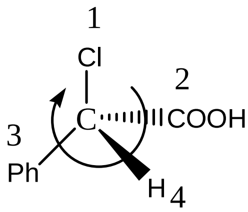
S–form

I



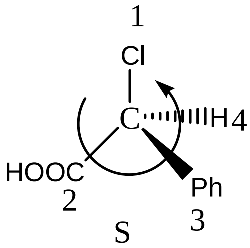
S–Methyl dopa

II



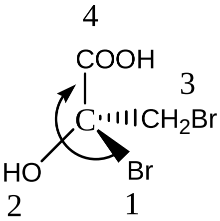
S

III

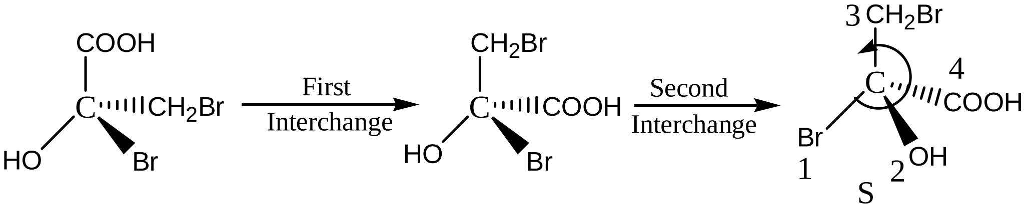


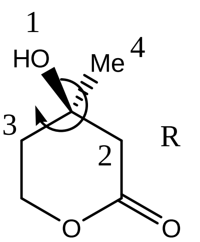
S

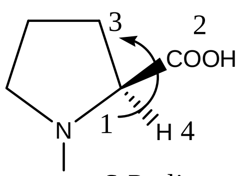
IV



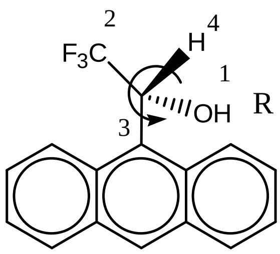
Note: In this case fourth group is on the plane. So, we will have to do double interchange as shown below

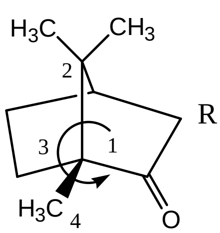






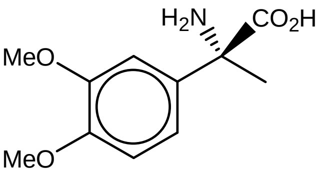
S-Proline

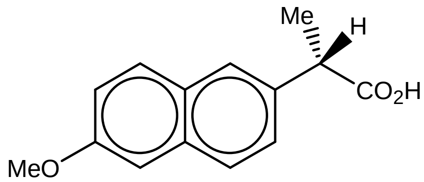


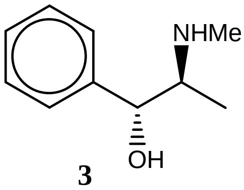


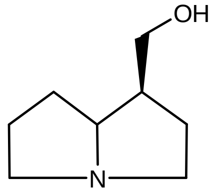
PROBLEMS

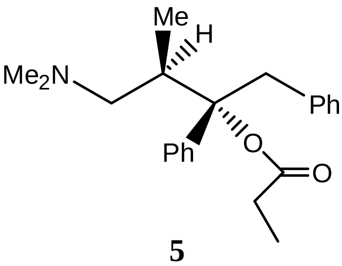
1. Find R/S of the following compounds

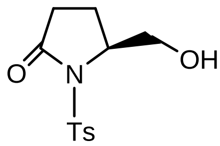

1

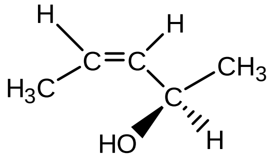

2

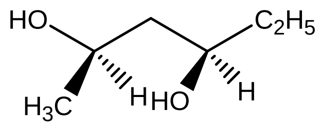

3

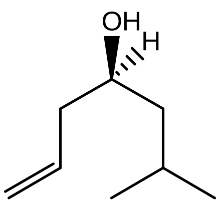

4

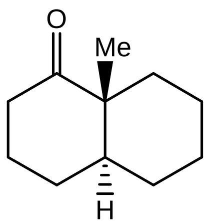

5

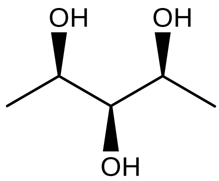

6

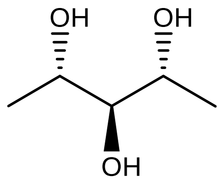

7


8

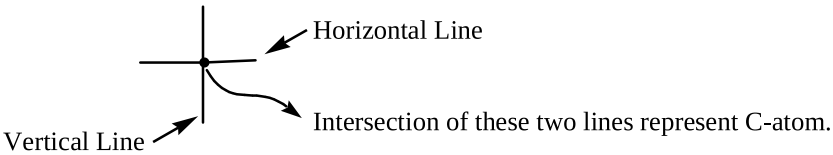

9


10

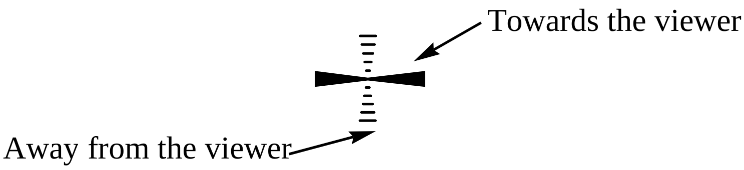

11


12

R/S Nomenclature in Fischer projection.



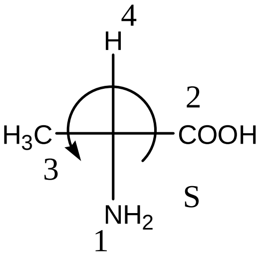
Vertical Line $\rightarrow$ away from the viewer.
Horizontal Line $\rightarrow$ Towards the viewer.

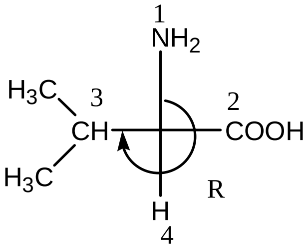


For R/S nomenclature.
Assign priority sequence.
Case I: If fourth group is present on the top or bottom of vertical line then

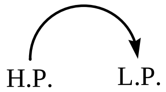
H.P. L.P. $\rightarrow$ Clockwise $\rightarrow$ R   L.P. H.P. $\rightarrow$ Anticlockwise $\rightarrow$ S

For example:

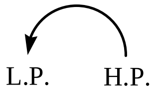




Case II: If 4th group is present on left or right side of the horizontal line then.

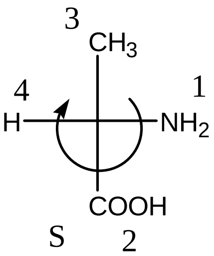


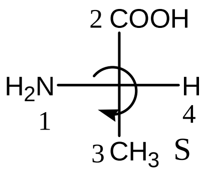
Clockwise → S



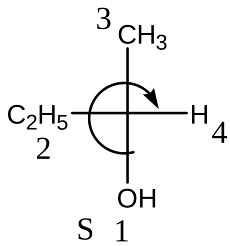
Anticlockwise → R

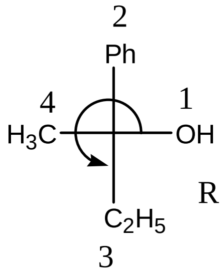
For example:



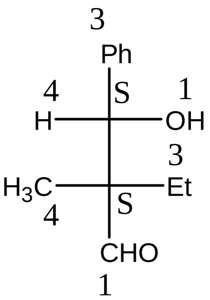


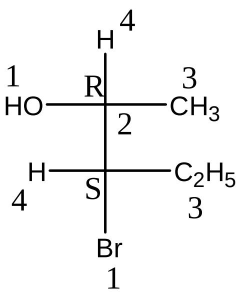
;



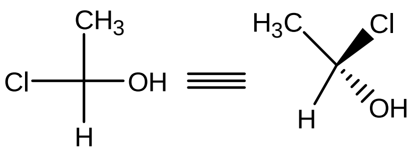


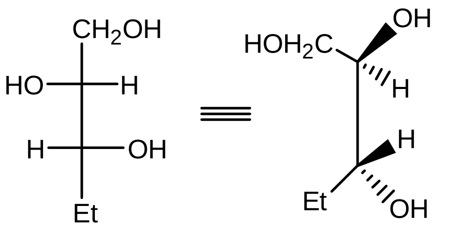
For example:



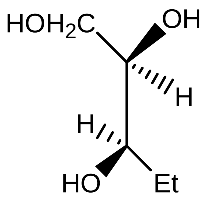


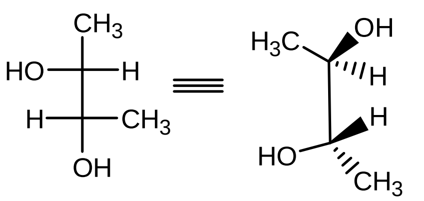
Conversion of Fisher → Wedge.

(i) 

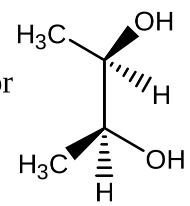
(ii) 

or

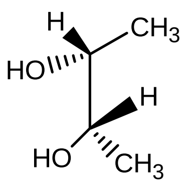


(iii) 

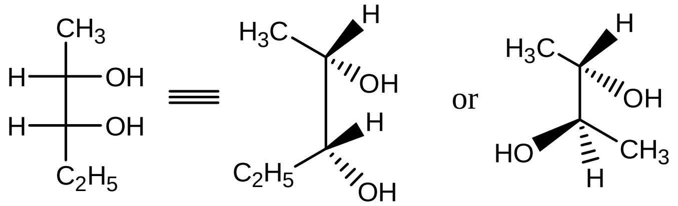
or



or

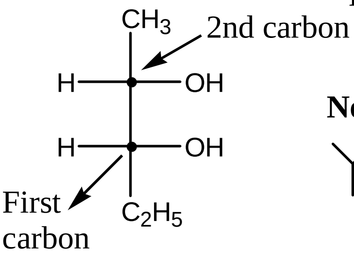


Note: In all conversion, the configuration (R/S) should not be change.

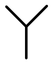


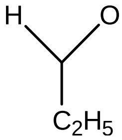
Conversion of fischer to sawhorse.

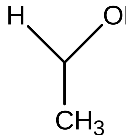
F → W



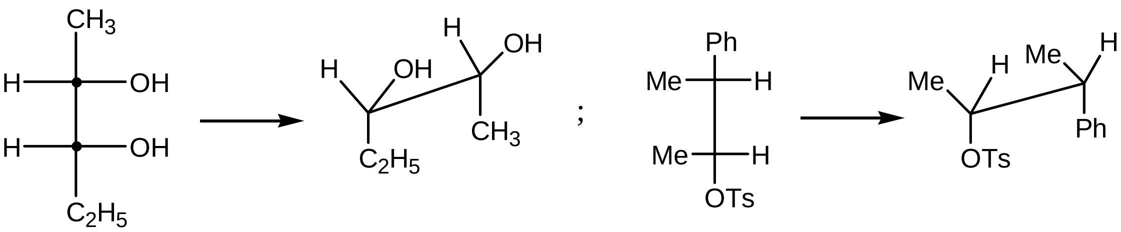
Note: Consider at first carbon shape like

 (Pronounced 'Y')

At first carbon 

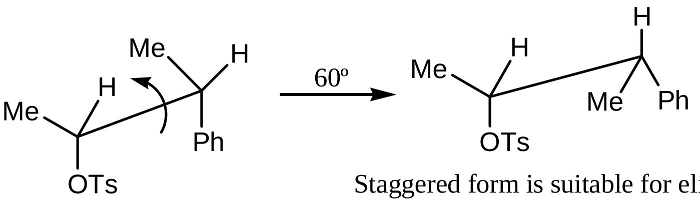
At 2nd carbon 

and then combine these two by a straight line like



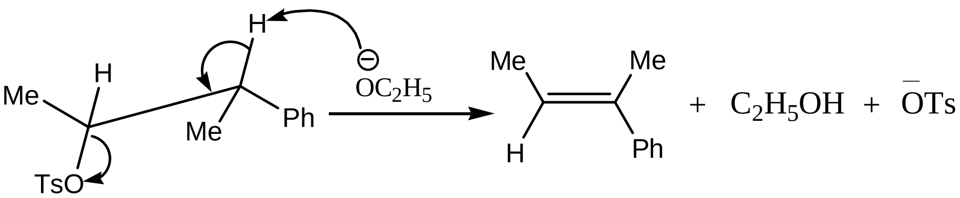
Note: Since Fischer projection is represented in eclipsed form so the resulting sawhorse should also be in eclipsed form if we have need of staggered form we can obtain it by simple rotation.

For example:

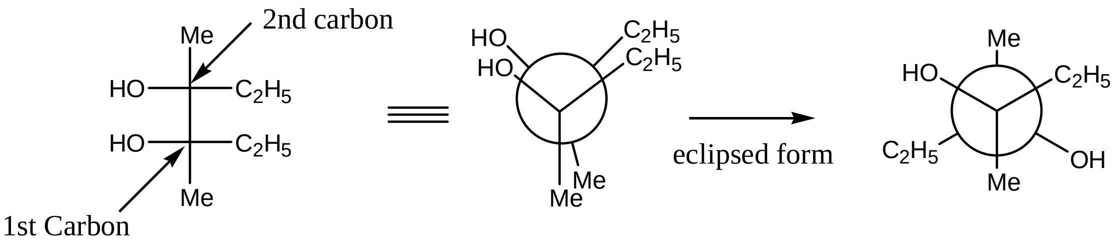


Eclipsed form

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

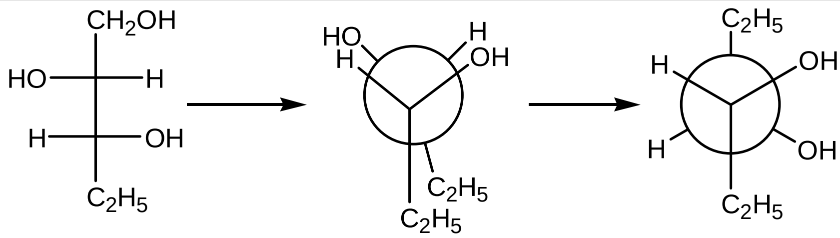


Conversion of Fischer to Newmann:

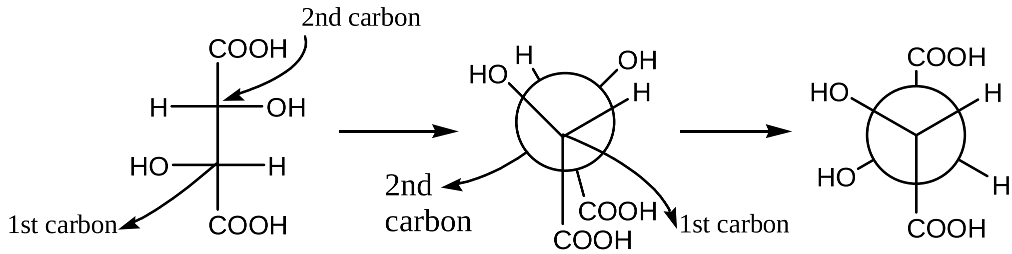


Staggered form

eclipsed form

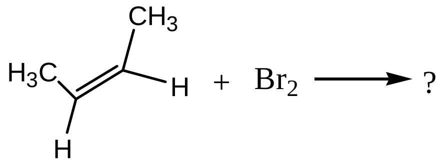


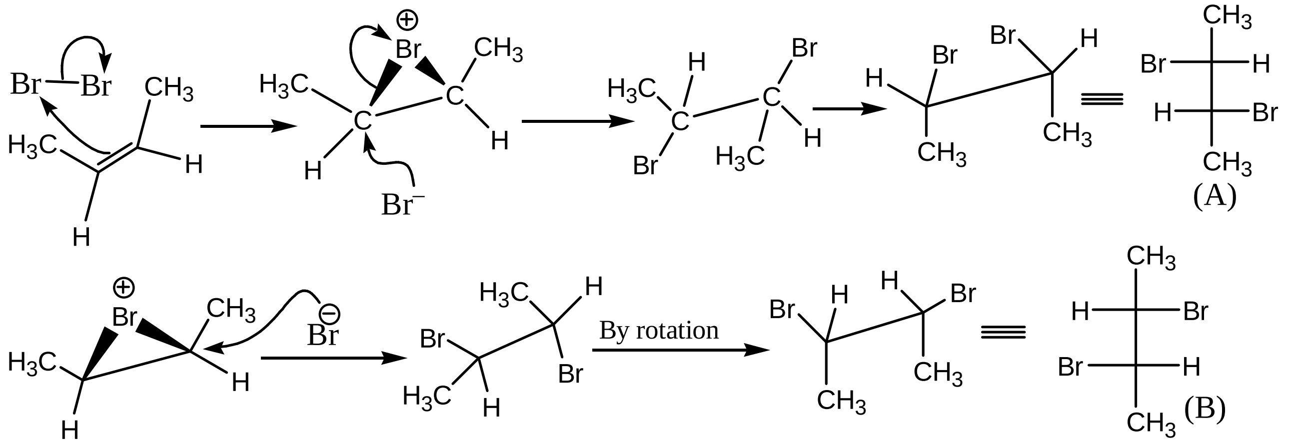
Eclipsed form



How we can apply these interconversion into reaction mechanism.

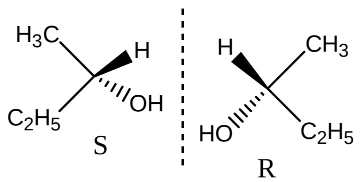
Let us consider addition of Br_2 on cis-2-butene.

2. 



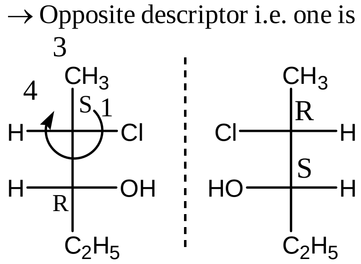
So, A and B are non superimposable mirror image to each other and hence They are enantiomers.

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.



(A) (B)

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

In A

C_2 — S

C_3 — R

In B

C_2 — R

C_3 — S

So, these two are enantiomer

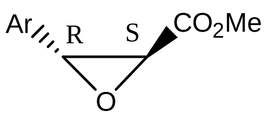
Properties of enantiomer:

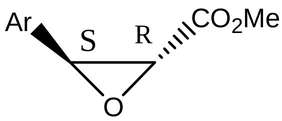
1. All physical properties such as M.P., refractive index, vapour pressure, relative density, NMR spectrum, IR spectrum are same except direction of optical rotation. (Magnitude is same but direction is opposite).
2. All the chemical properties of enantiomers towards achiral reagent are always identical.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

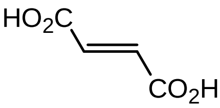
Diastereoisomers:

Diastereomers are the strereoisomers that are not enantiomers.

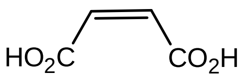
Some important points regarding the diastereoisomers.

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:



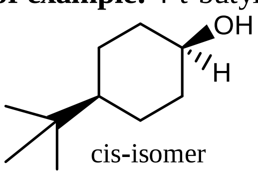
Fumaric acid
m.p. 299-300ºC



Maleic acid
m.p. 140–142ºC

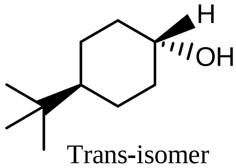
Note: geometrical isomers (i.e. cis and trans isomers) are always diastereoIsomers. A similar stereoisomers can exist in cyclic compounds.

For example: 4-t-butyl cyclohexanol.



cis-isomer

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

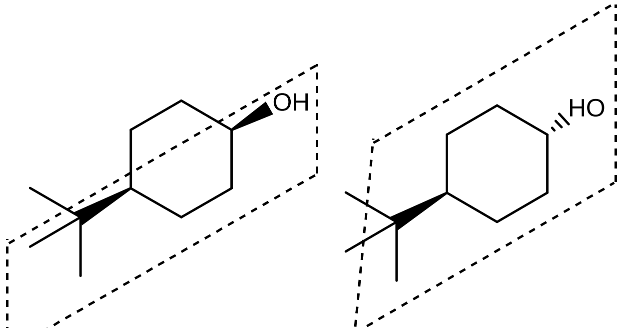


Trans-isomer
m.p. 80-81ºC

So, these two stereoisomers are called diastereomers.

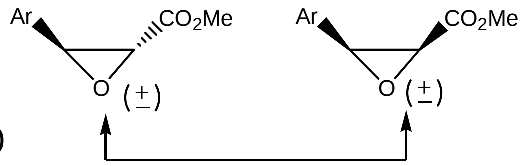
Note: Diastereoisomers can be chiral or achiral.

(i)



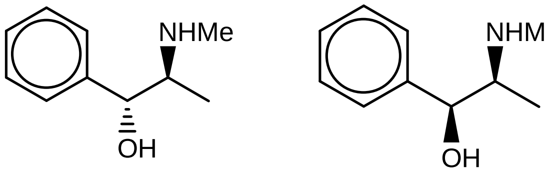
Plane of symmetry present   Plane of symmetry

(ii)



These two diastereoisomers are chiral because plane of symmetry is not present.

So, achiral diastereoisomers.

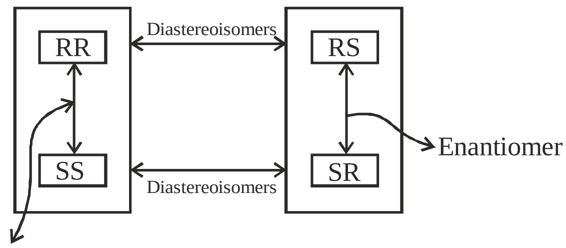


Ephedrine   Pseudoephedrine

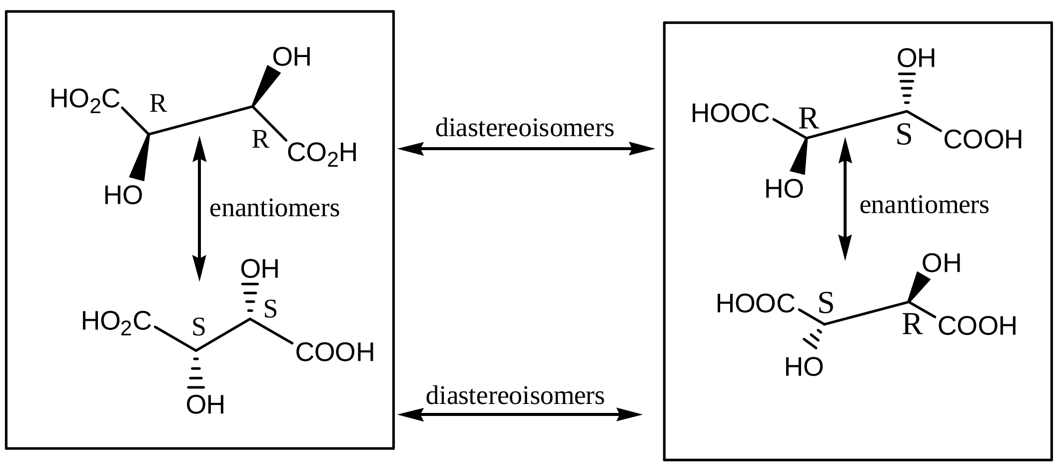
These two are diastereomers.

Remark: The diasteroisomers are different compounds with different names (For example ephedrine and pseudoephedrine) and different properties, while the pair of enantiomers are the same compound and differ only in the direction in which they rotate plane polarized light.

In summary if we have compound having two chiral centre each one R/S then



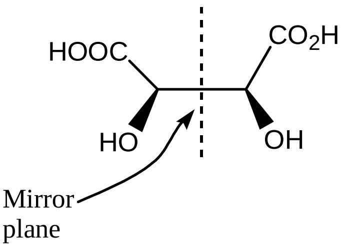
For example:

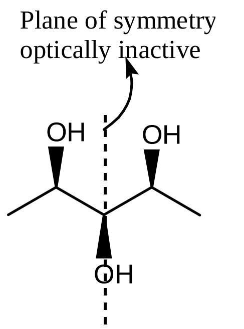


Meso Compounds:

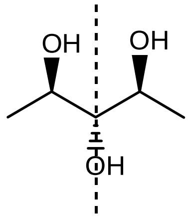
Compounds that contain stereogenic centres but achiral are called meso compounds. This means that there is a plane of symmetry with R stereochemistry on one side and 'S' stereochemistry on the other.

For example:

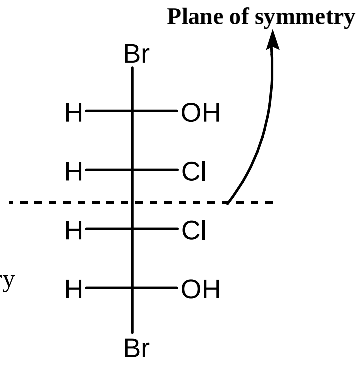




→ So Meso compound
→ Optically inactive

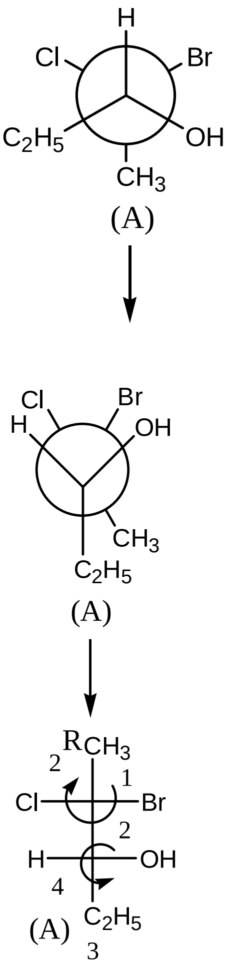


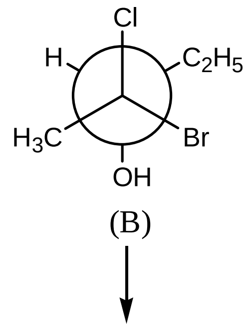
→ Plane of symmetry
→ Achiral
→Meso Compound

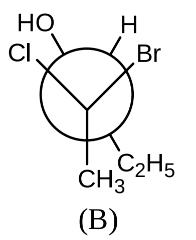


Meso Compound

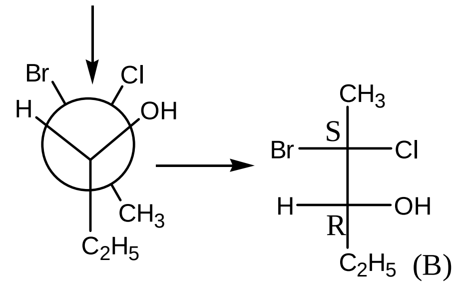
Conversion of Newmann into Fischer and relation between two compounds.



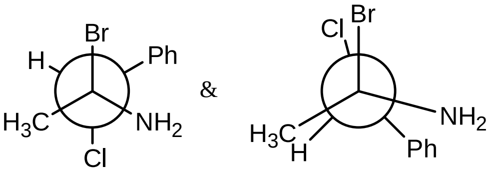




Since, in (B) C_2H_5 group is attached with back carbon and we want to bring it at front carbon so we will have to rotate it by 180º.

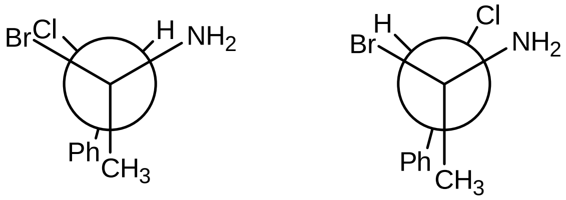


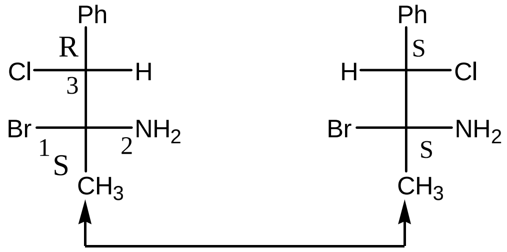
So, A and B are diastereomers.



(A) (B)

What is the relation between A and B.

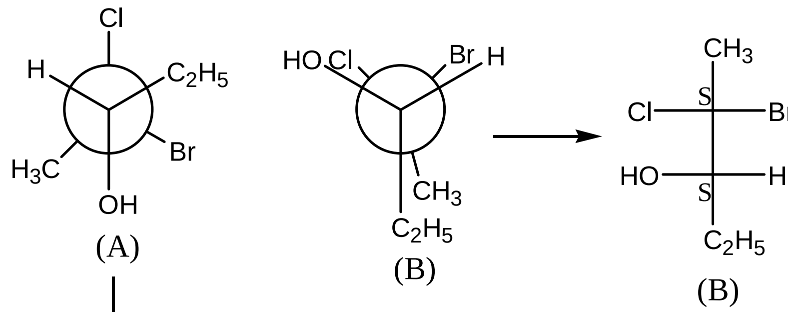
(i) 

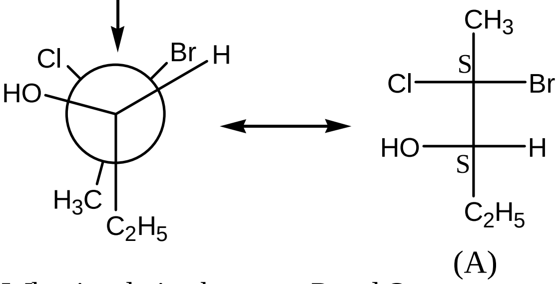
(ii) 

So, these two are diastereomers

PROBLEMS

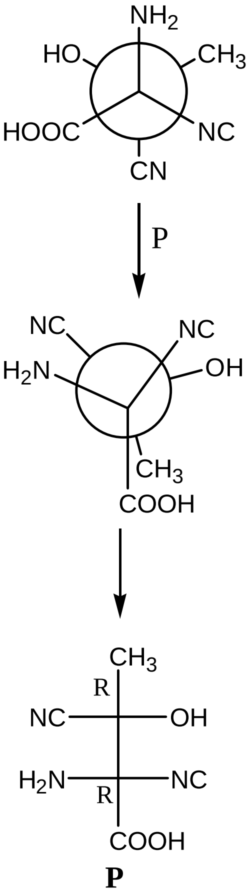
1. What is the relation between A and B.

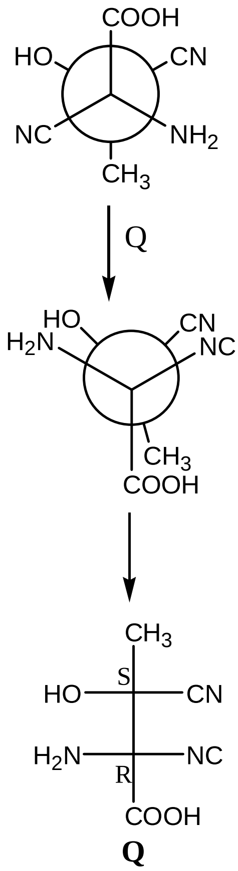




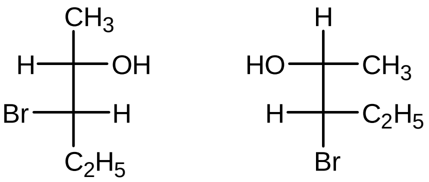
So, A and B are identical.

What is relation between P and Q.



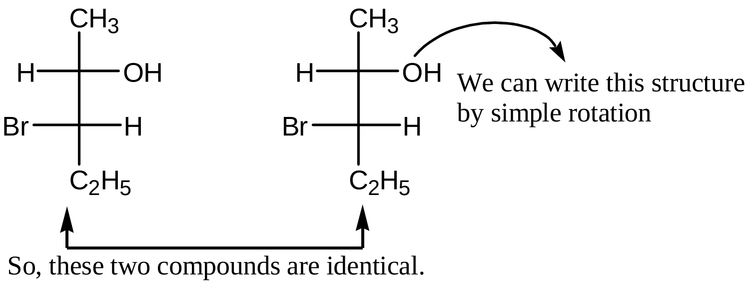


So, P and Q are diastereomer.

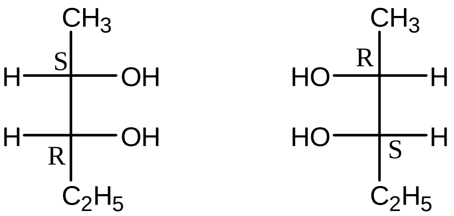
2. 

The molecules represented by the above two structures are

(a) Identical (b) Enantiomers (c) Diastereomers (d) Epimer



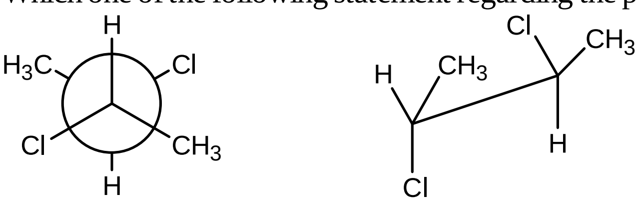
3. The following two compounds are



(a) Enantiomers (b) Diastereomers (c) Identical (d) epimer.

Soln. (a)

4. Which one of the following statement regarding the projections shown below is true?

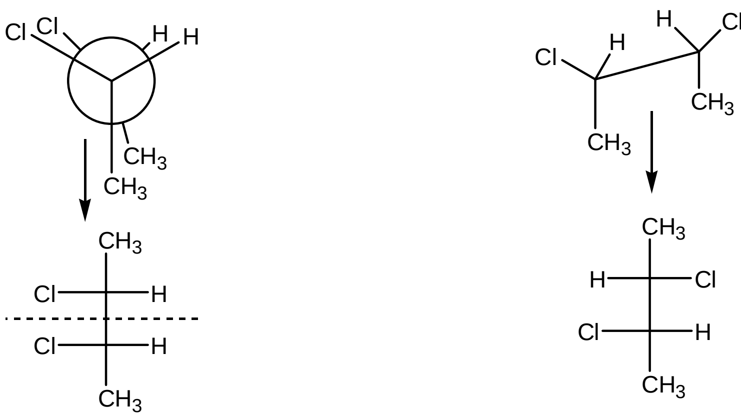


(A) **(B)**

(a) A and B represent the same configuration. (b) Both A and B are optically active

(c) B is optically active. (d) A is optically active

Soln.



(A) (B)

'A' is optically inactive due to presence of plane of symmetry. **(Correct answer is (a))**

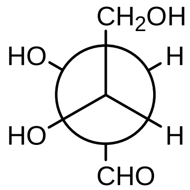
5. Match **List-I** with **List-II** and select the correct answer using the code given below the lists.

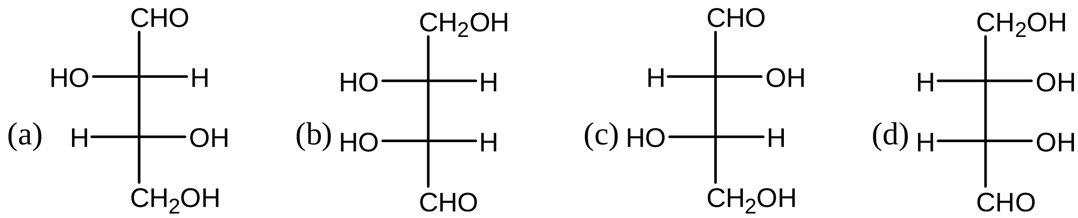
List-I	**List-II**
A. Meso compounds	1. An equimolar mixture of enantiomer
B. Enantiomers	2. Stereoisomers that are not mirror images
C. Diastereoisomers	3. Non-superimposable mirror images
D. Racemate	4. An optically inactive compound whose molecules are achiral even though they contain chiral centre.

	A	B	C	D
(a)	3	4	1	2
(b)	3	4	2	1
(c)	4	3	1	2
(d)	4	3	2	1

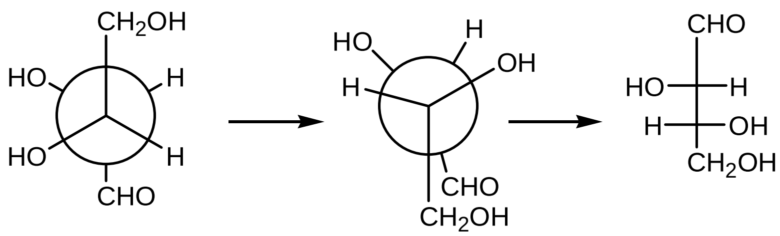
Soln. **(d)**

6. What is the correct Fischer Projection formula for the compound represented by the following Newmann Projection?



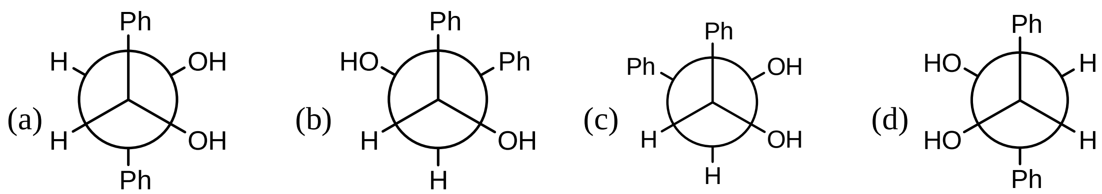


Soln.

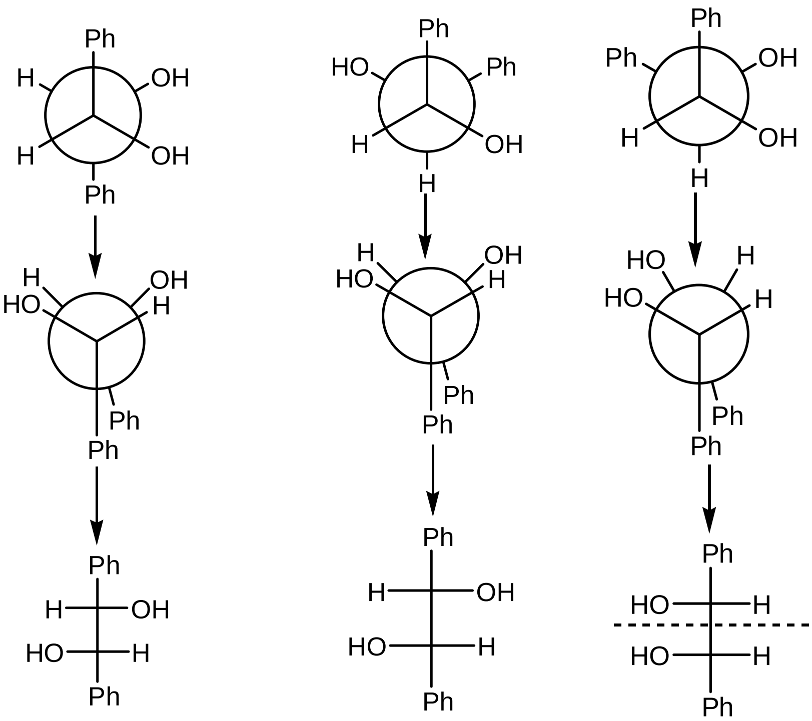


Correct answer is (a)

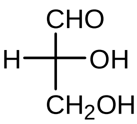
7. Which one of the following Newmann projection formulae correctly represents a meso structure?



Soln.



‘c’ has plane of symmetry so, it correctly represents a meso compound.

8. 

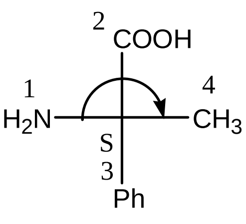
Which is the correct order of priority of groups attached to the chiral carbon in the compound given above while as assigning R or ‘S’ configuration.

(a) HO > CHO > CH_2OH > H (b) H > CH_2OH > CHO > OH

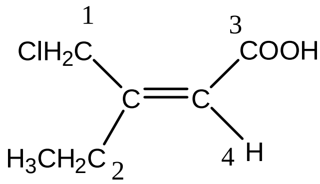
(c) CHO > OH > CH_2OH > H (d) CH_2OH > CHO > OH > H

Soln. (a)

9. Which one is the correct configurational assignment (in terms of CIP principle) for each of the compound listed below?



I

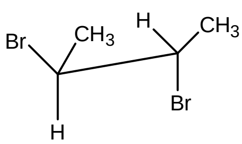
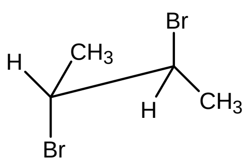
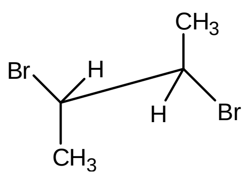


II

(a) I-R, II-S (b) I-S, II-E (c) I-L, II-S (d) I-S, II-Z

Soln. **(d)**

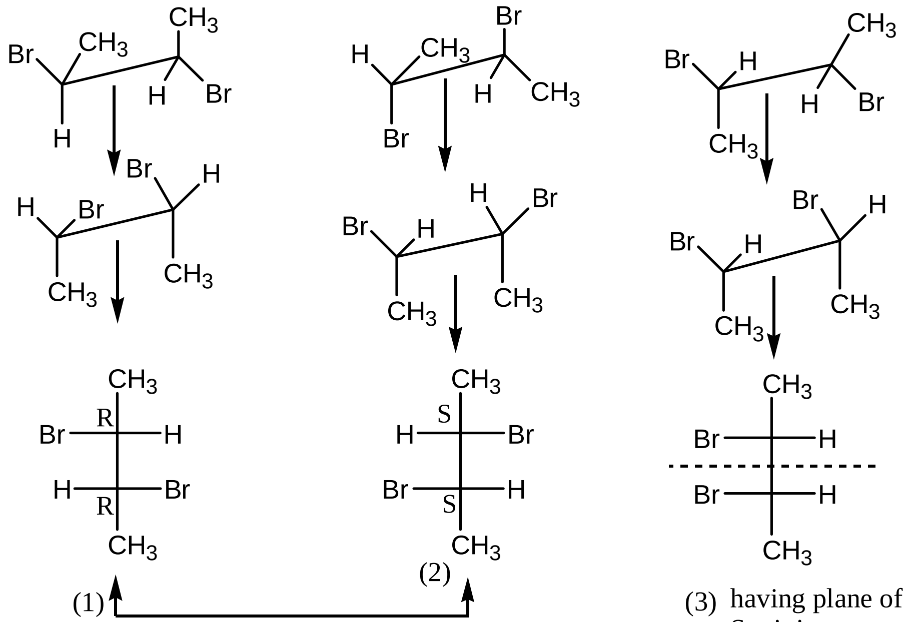
10. Consider the following configuration of 2, 3-dibromobutane.

(1)  (2)  (3) 

Which one of the following is the correct answer?

(a) Conformation (1) is the meso-form while (2) and (3) are an enantiomeric pair.
(b) Conformation (2) is the meso-form while (1) and (3) are an enantiomeric pair.
(c) Conformation (3) is the meso form while (1) and (2) are an enantiomeric pair.
(d) Conformation (1) and (2) are identical and (3) is the meso-form.

Soln.

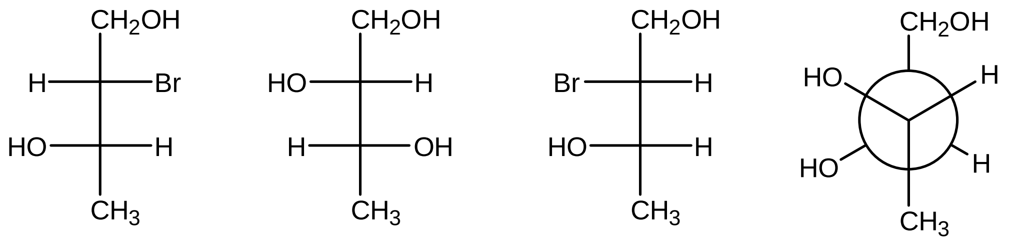


(1) (2) So, these two compounds are enantiomers

(3) having plane of symmetry So, it is a meso compound.

So, the correct statement is conformation (3) is the meso while (1) and (2) are an enantiomeric pair.

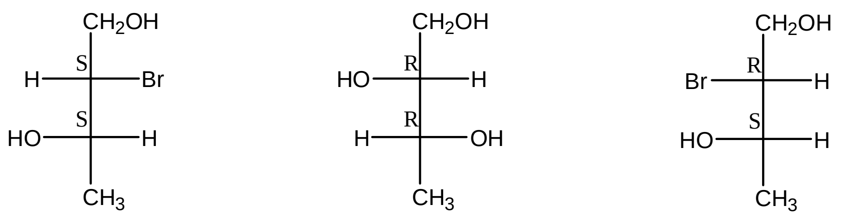
11. Consider the following statements regarding the given projections.



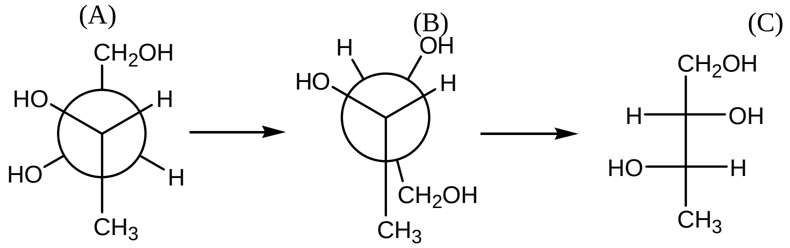
(A) (B) (C) (D)

(1) (A) and (C) are diastereoisomers.
(2) (D) is the Newmann projectoin of (B).
(3) (B) may be named as thereo-1, 2, 3-butanetriol.
Which of the above statements are correct?
(a) 1, 2 & 3 (b) 1 & 2 (c) 2 & 3 (d) 1 & 3.

Soln.

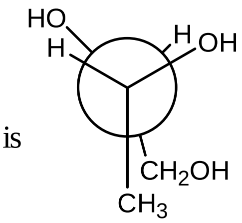


(A) (B) (C)



(D)

So, A and C $\rightarrow$ are diastereomers.
D is not the Newmann projection of B.

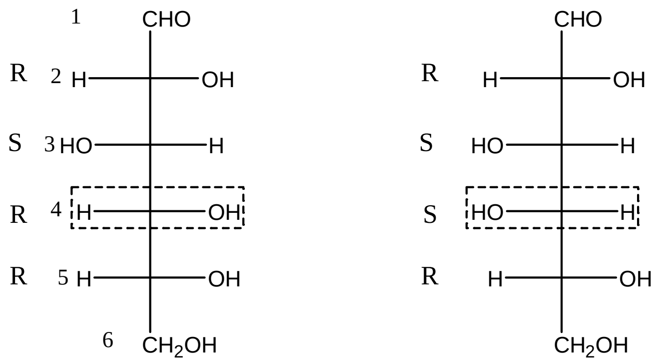
The Newmann projection of 'B' is 

Soln. (d).

Epimers

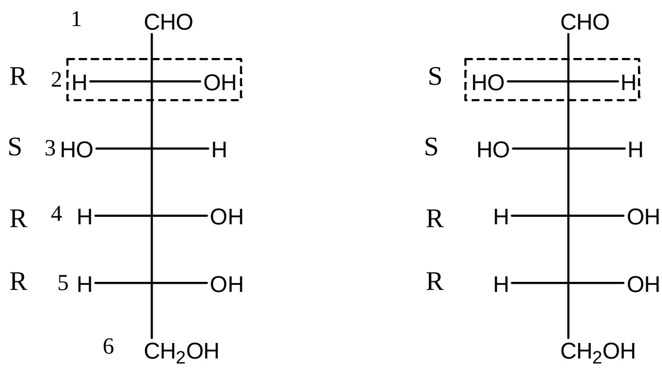
Epimers are the diastereomers, differ in the stereochemistry at only one stereocentre.

The term can be applied only to the chiral compound having more than two chiral center.
For example glucose and glactose have difference in configuration at C_4 so they are epimers at C_4.

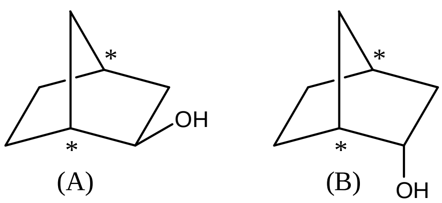


Glucose Glactose

Similarly glucose and mannose have change in configuration at C_2 so they are epimers at C_2.



Glucose Mannose

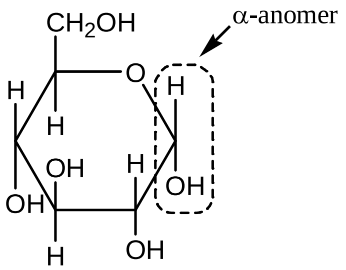


(A) (B)

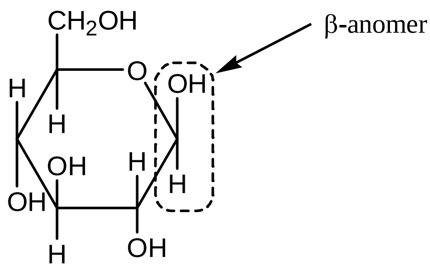
Compound (A) and (B) are epimeric pair.

Anomers:

Anomers are the diastereomers (in the case of a monosaccharide) which differ in the configuration at C_1 are called anomers.



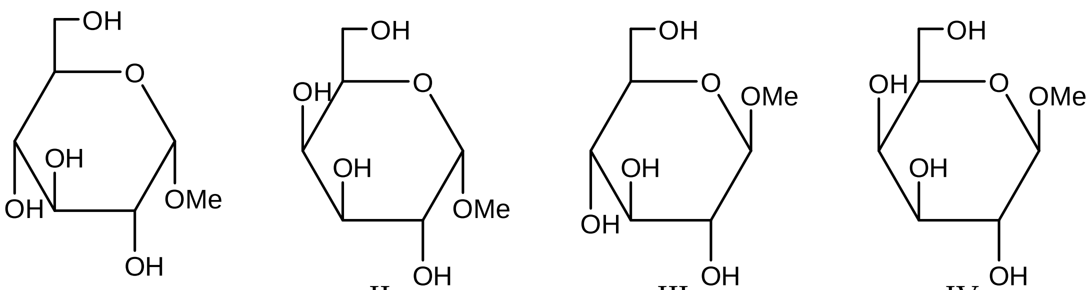
α-D-glucose



β-D-glucose

PROBLEMS

1. Identify the correct set of stereochemical relationship amongst the following monosaccharides I-IV.



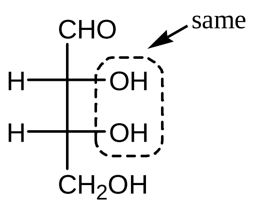
I II III IV

(a) I and II are anomers; III and IV are epimers.
(b) I and III are epimer; II and IV are anomers.
(c) I and II are epimers; III and IV are anomers.
(d) I and III are anomers; I and II are epimers.

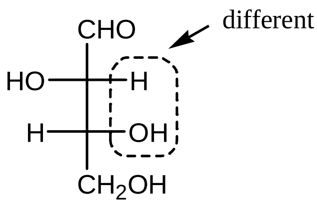
Soln. **(d).**

Threo and Erythro nomenclature

Threo and Erythro nomenclature are based on sugar chemistry.



D(–) erythrose



D(–) threose

- Erythrose and threose are diastereomers.
- A molecule with two adjacent stereocentres, when there are two groups which are common to each carbon while third is different i.e. $C_{abx} – C_{aby}$ gives rise to erythro and threo diastereomer.

Procedure for finding erythro and threo diastereomers.

Step I: Find out the group or atom which is not common on two adjacent asymmetric centre.

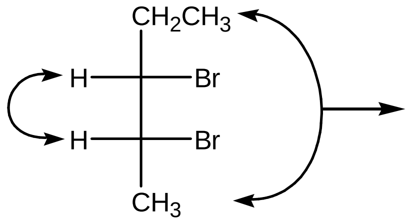
Step II: Placed this different group on top and bottom position of vertical line in Fischer projection formula.

Step III: And arrange the rest group or atoms around horizontal position of Fischer projection.

Case I: If two similar group are on the **same side** then it is called **erythro**.

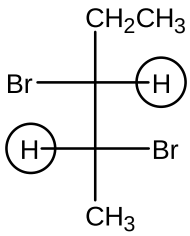
Case II: If two similar group on the **opposite side** then it is called **threo**.

For example:



These two are different group on the two asymmetric carbon placed at top and bottom.

These two H, atoms are projected in same side so, it is erythro



In this structure the two similar group viz H and Br are opposite so, it is threo.

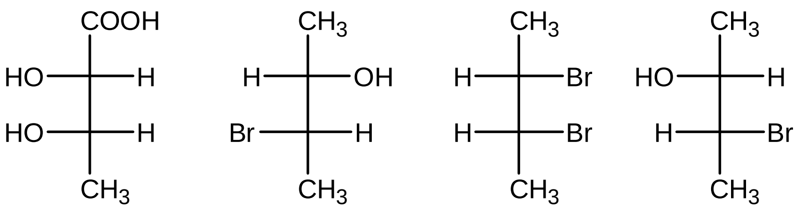
Note: The terms erythro and threo are generally applied only to those molecules which do not have symmetric ends.

In summary, condition for erythro and threo nomenclature:

(1) Two asymmetric carbon should be there

(2) On two asymmetric carbon, two of the groups are the same and the third is different.

2. Consider the following statements about the Fischer projection A — D.



(A) (B) (C) (D)

(1) A and B are erythro forms while C and D are threo forms.

(2) There must be two assymetric carbon

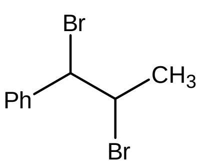
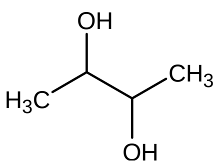
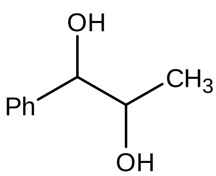
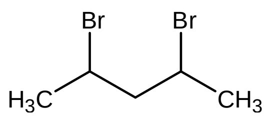
(3) C is a meso form while B and D are dL form.

(4) A and B are meso-form while C and D are diastereomers which of the above statements are correct?

(a) 1, 2 and 4 (b) 2, 3 and 4 (c) 3 (d) 2 and 4

Soln. (c)

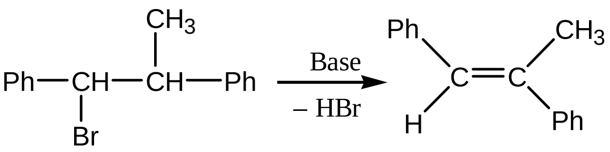
3. Which of the following compounds can be represented as threo and erythro isomers?

(1)  (2)  (3)  (d) 

(a) 1 & 2 (b) 1 & 3 (c) 1 & 4 (d) 2 & 4

Soln. (b) Hint– Condition for erythro and threo are $C_{abx} - C_{aby}$.

4. Consider the following statements. In the elimination reaction.



(1) Of the various stereoisomers of the reactant, only stereoisomers of proper geometry, that is antiperiplanar conformation will undergo this elimination reaction.

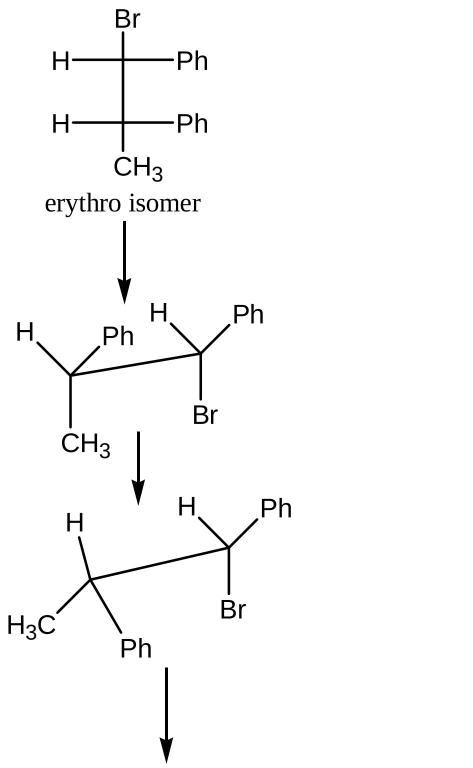
(2) Erythro isomer will undergo elimination reaction at a faster rate.

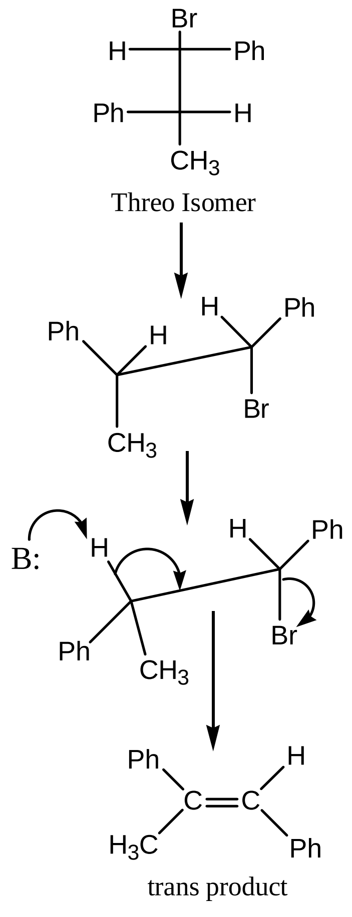
(3) The threo isomer will form the trans olefin of these statements.

(a) 1, 2 & 3 are correct (b) 2 & 3 are correct

(c) 1 & 3 are correct (d) 1 & 2 are correct.

Soln.





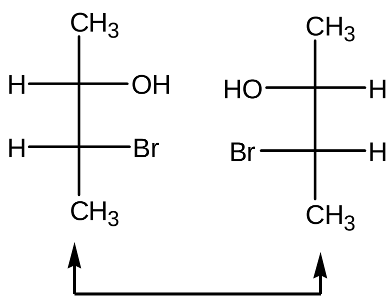
Rate of elimination will not be faster because the two bulky Ph group projected in the same direction causes steri chindrance and will increase the activation energy of this conformation.

Correct answer is (c)

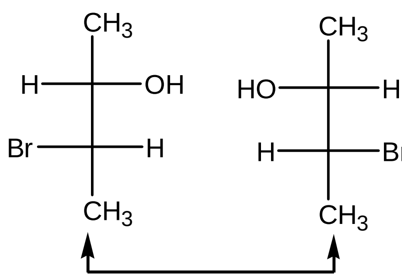
5. Find out the stereoisomers of 3-bromo-2-butanol

Soln. 3-bromo-2-butanol have two asymmetric centre. So, the total number of stereoisomers = $2^2 = 4$

These are



Erythro enantiomers



Threo enantiomers

(A) Optically activity in biphenyls

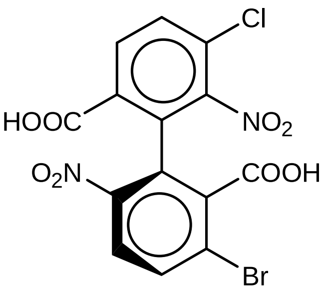
Two conditions are necessary for biphenyl compounds to exhibit optical activity.

(i) Neither ring have a vertical plane of symmetry.

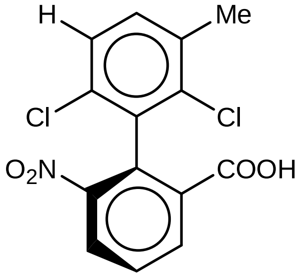
(ii) The substituents in ortho position must have a large size.

Note: There is no chiral centre in Biphenyl, it is the molecule as a whole which is chiral, due to restricted rotation. The chirality due to restricted rotation arround C–C single bond in biphenyl is known as atropisomers.

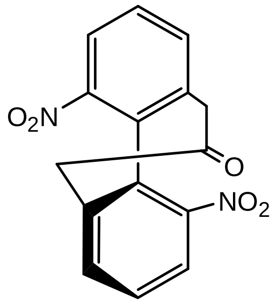
Remark: If H, F and – OCH_3 group are present on ortho position of biphenyl then rotation of the ring will not be prevent. Because the volume of these groups are too small to prevent the rotation about the single bond.



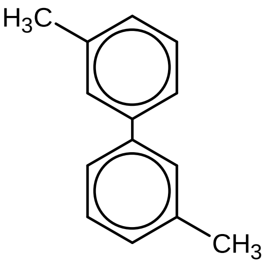
→ Properly substituted
→ Restricted rotation
→ So optically active



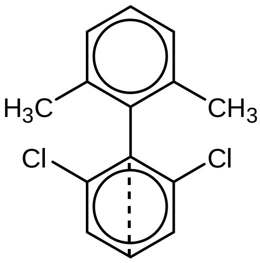
→ Properly substituted
→ Restricted rotation
→ So optically active



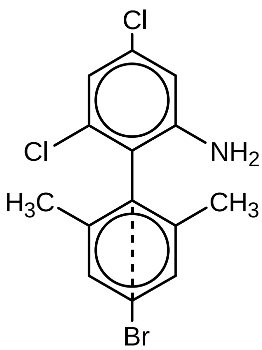
→ Properly substituted
→ Restricted rotation
→ So optically active



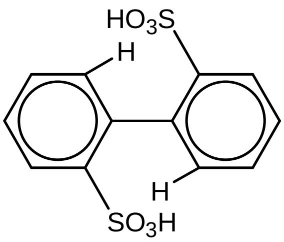
→ Properly substituted
→ Not restricted rotation
→ So optically inactive



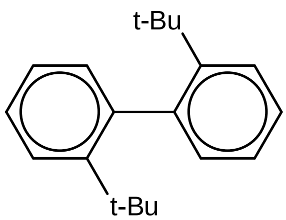
→ Not properly substituted
→ Restricted rotation
→ Optically inactive



→Achiral (restricted rotation
→But not properly substituted)
→ Optically inactive

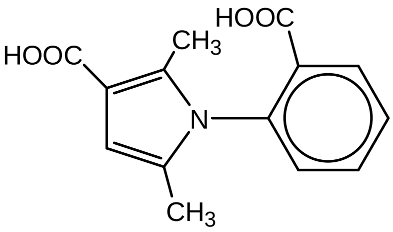


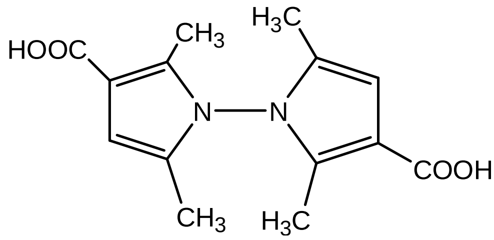
Optically active

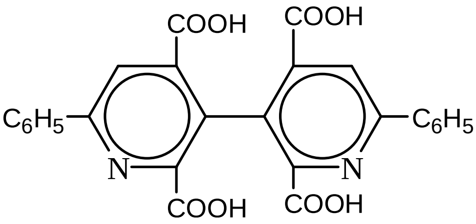


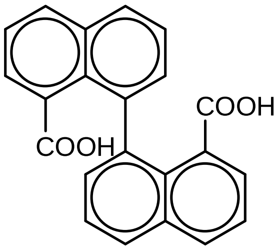
Optically active
t-Bu is bulky

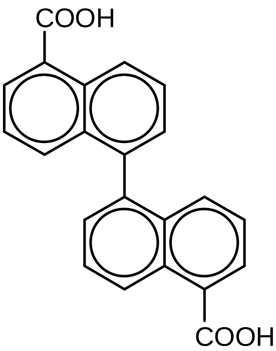
Some more examples of biphenyl type compounds are as follows:

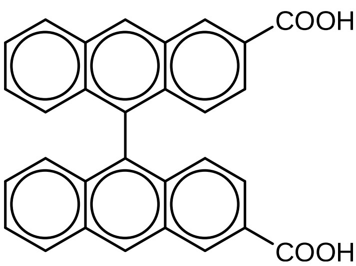
(1)


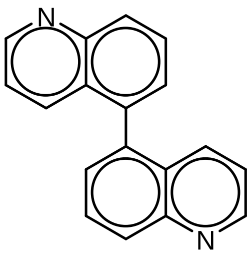
(2)


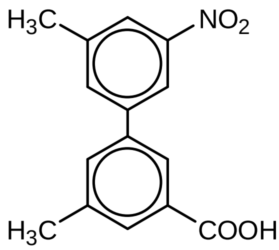
(3)


(4)


(5)


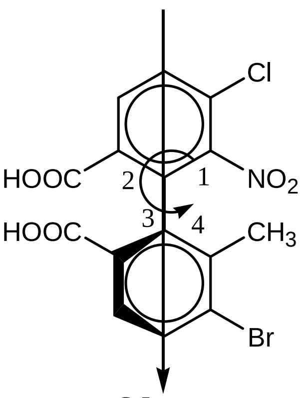
(6)


(7)


(8)


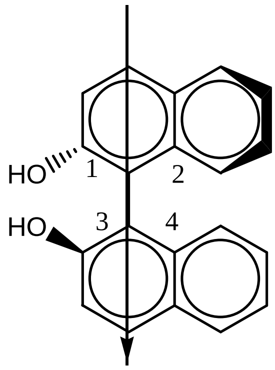
Properly substituted but not ristricted rotation.So, optically inactive.

R/S in Biphenyl:

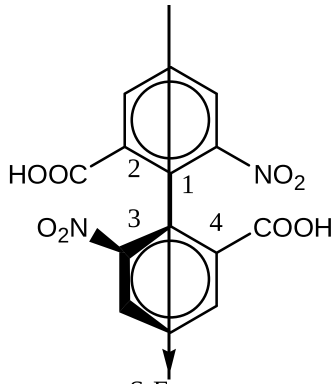


S-Isomer

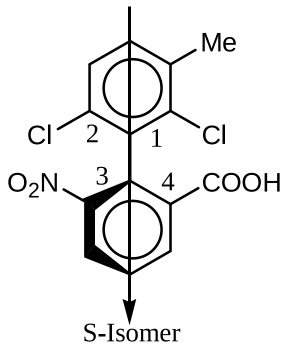
Put the head of the arrow on which side where configuration of the ring is defined in the problem and then assign priority sequence as per CIP rule.



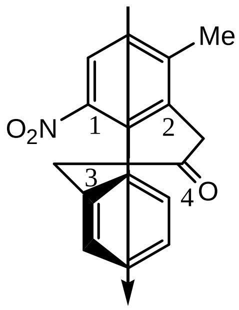
R-Isomer



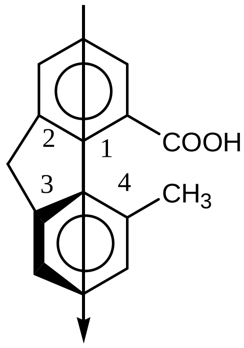
S-Form



S-Isomer



R



S-Isomer

(B) Chirality in Allenes

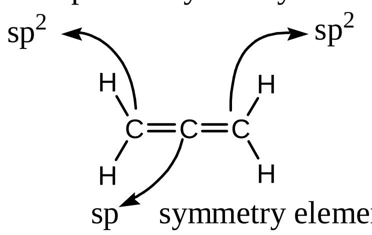
Allenes are chiral due to chiral axis.

Essential criteria for chirality of allene.

(1) Proper substitution

(2) Number of double bond should be even.

Properly substituted means that terminal carbon of allene should have two different groups, so that it deprive from plane of symmetry.

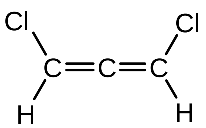


symmetry element

$3C_2$'S

$2\ \sigma v$

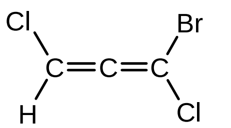
Problem-1:

(1) 

→ Number of double bond = even

→ Properly substituted

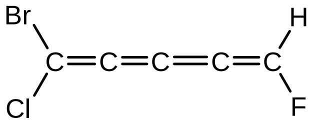
→ So it is chiral

(2) 

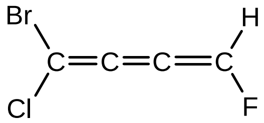
→ Number of double bond = even

→ Properly substituted.

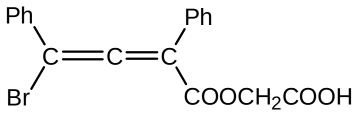
→ So it is chiral.

(3) 

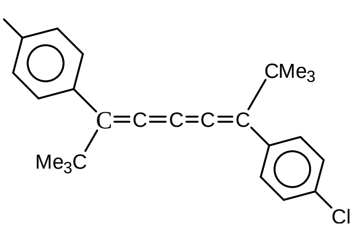
→ Number of double bond = even
→ Properly substituted
→ So, it is chiral.

(4) 

→ Number of double bond = odd
→ Properly substituted
→ Achiral, optically inactive.

(5) 

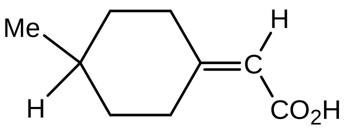
→ Number of double bond = even
→ Properly substituted
→ Chiral, optically active.

(6) 

→ Number of double bond = even
→ Properly substituted
→ Chiral, Optically active.

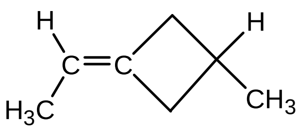
Note: One of the double bond of allene may be replaced by a four, five & six membered ring and the general shape of the allene molecule is retained.

For such a system. Optically activity arises if **Number of doubled bond + ring = even** and criteria for properly substitution is same.



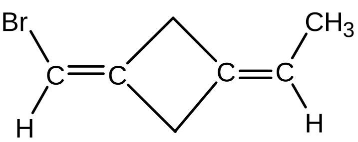
→ 1 double bond + one ring = 2 = even
→ Properly substituted
→ Chiral and hence optically active.

Problem-2:

(1) 

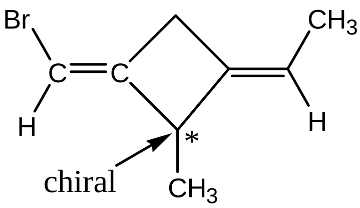
chiral

→ 1 double bond + 1 ring = even
→ Properly substituted
→ Chiral, optically active.

(2) 

→ 2 double bond + 1 ring = odd
→ Properly substituted
→ Achiral, optically inactive.

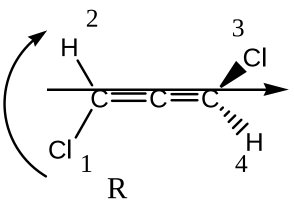
Problem-3:



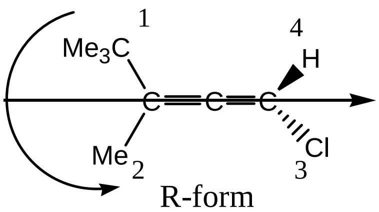
chiral
centre

→ 2 double bond + 1 ring = odd
→ Properly substituted
→ It is chiral, due to chiral centre but not chiral axis.

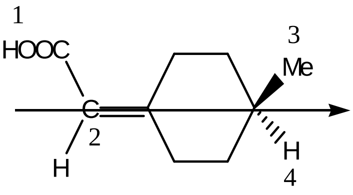
R/S in allene.

(1) 

R

(2) 

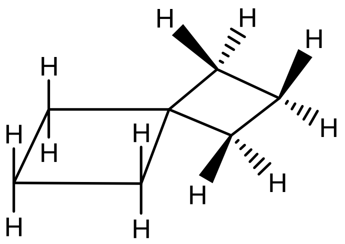
R-form

(3) 

S-Form

(C) Optical Activity in Spirane:

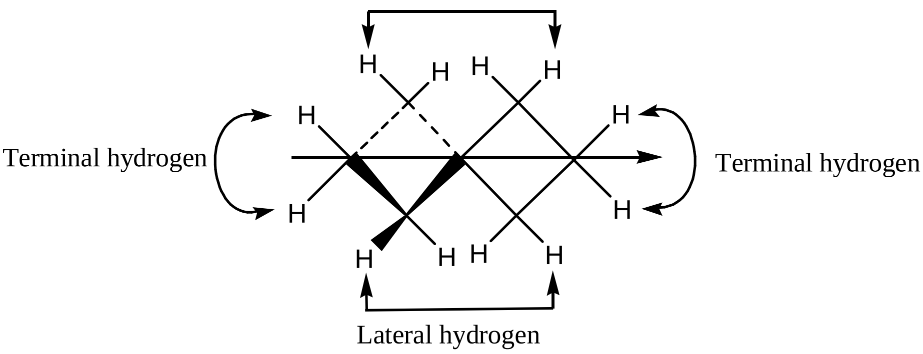
• If both double bonds in allene are replaced by ring system, the resulting molecules are spiranes.

• 

Examinations of these formulae show that the two rings are perpendicular to each other, and hence suitable substitution will produce molecules with no element of symmetry, thereby giving rise to optically active forms.

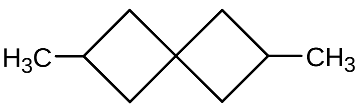
Essential criteria for chirality due to chiral axis.

1. Even number of ring in spiro compound (Odd number of spiro carbon)
2. Proper substitution at only terminal H.
   Spirane has two types of hydrogen
   (1) Lateral (2) Terminal.

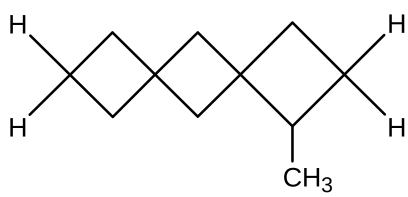


4H's are terminal, 8H's are lateral.

- Chirality due to chiral centre can be generated in any spirane compound (even or odd number of ring) by substitution at lateral hydrogen (Plane of symmetry should not be there).
- Chirality due to chiral axis can be generated in spiranes having even numbers of rings by proper substitution.

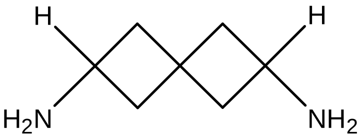


chiral



→ Number of rings = even
→ Properly substituted
→ Chiral due to chiral axis.

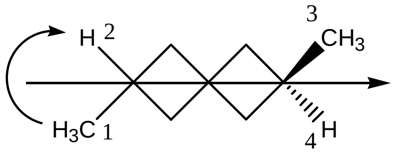
→ Number of rings = odd
→ Not properly substituted
→ But chiral due to chiral centre not due to axis.

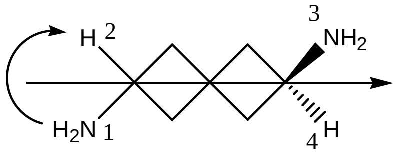


→ Number of rings = even
→ Properly substituted
→ Chiral, due to chiral axis.

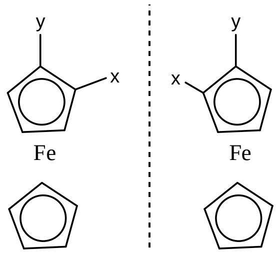
R/S nomenclature in spirane

Similar to allene and biphenyl.

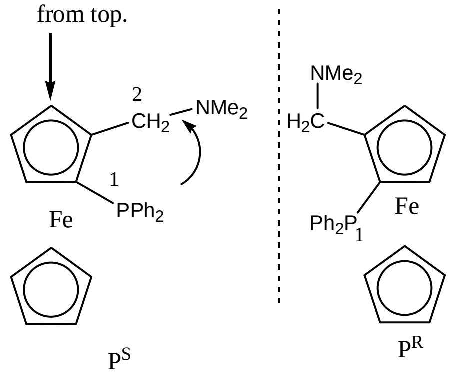




Planar Chirality:

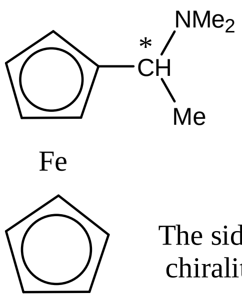


• Specific type of chirality known as planar chirality.
• Chirality can not be removed it is permanent.



P^S → This 'P' stand for planar.

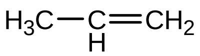
Note:

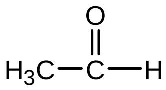


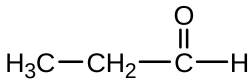
The side chain has a chiral centre such type of chirality is called lateral chirality.

Conformational Analysis

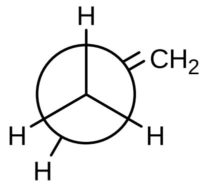
Conformation studies of unsaturated compounds and compounds containing the oxo group have led to some unexpected results. For example, microwave spectroscopy has shown that the preferred conformation of propene and acetaldehyde are the eclipsed forms and NMR spectroscopy has shown that the predominant conformation of propionaldehyde is the one in which methyl group and oxygen atom are eclipsed. The reason for these observation is uncertain.



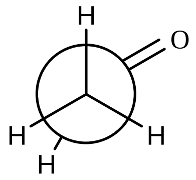




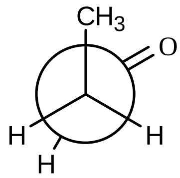
Propionaldehyde



Propene



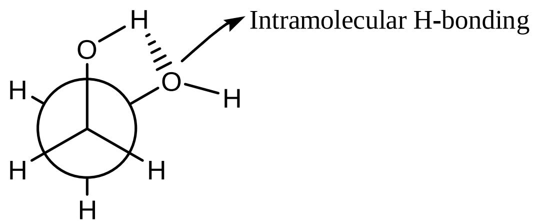
Acetaldehyde



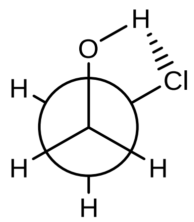
Propionaldehyde

Remark: Molecule such as ethylene chlorohydrin or ethylene glycol, intramolecular hydrogen bonding is possible in the skew form but not in the staggered form, due to this intramolecular H-bonding the molecule is stabilised by about 20-29 kJ/mol and this is enough to make the skew form more stable than the staggered form.

Evidences–I.R. spectroscopy has shown that the skew form predominates.



Gauche form of ethylene diol



Gauche form of ethylene chlorohydrine

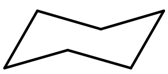
Method used to investigate the conformation of molecules.
- Thermodynamic calculation
- Dipole moment.
- X-ray and electron diffraction
- IR and UV spectroscopy
- Chemical method.
- NMR spectroscopy

Conformational Analysis of Cyclohexane

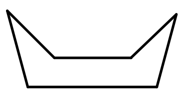
Factor affecting the stability of conformations
(1) **Angle strain:** Any deviation from normal bond angle
(2) **Torsional strain:** Any deviation from the staggered arrangement.
(3) **Vander waals strain(Steric Strain):**
Any two atoms (or group) that are not bonded to each other can interact in several ways depending on
(a) Their size (b) Polarity (c) How closely they are brought together.

These non bonded interaction can be either repulsive or attractive, and the result can be either destabilization or stabilization of the conformation.
Bayer suggested (incorrectly) there should be certain amount of strain in cyclohexane.

Two most stable form of cyclohexane are as follows:



Chair form

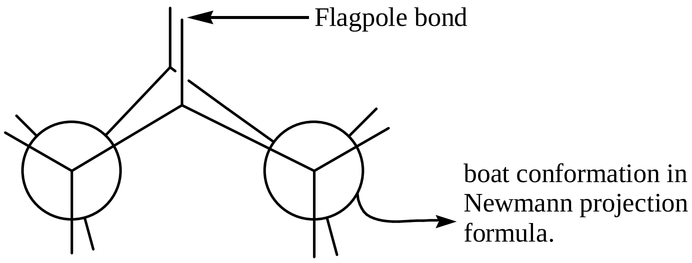


Boat form

Chair form is more stable than that of boat form due to following fact.

Chair form	Boat form
(1) No angle strain	(1) No angle strain
(2) No torsional strain	(2) Torsional strain is present.
(3) No flagpole interaction	(3) Flagpole interaction is present (vander waal strain)
(4) No any eclipsed ethane condition	(4) Two eclipsed ethane condition (will creat torsional strain)

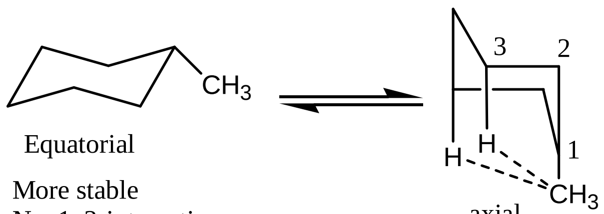
Conclusion: The boat conformation is less stable than the chair conformation.



Potential energy relationship among conformation of cyclohexane.

Stability order: Chair > twist boat > boat > half chair

Mono substituted cyclohexane:

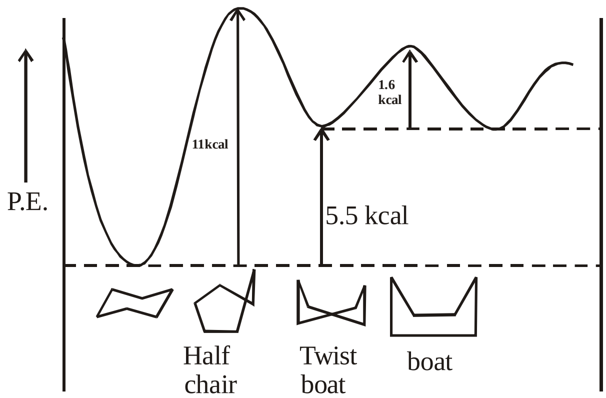


Equatorial

More stable
No. 1, 3-interaction

axial

Less stable due to
1, 3-interaction



Remark: Except for '**H**', a given atom or group has more room in an equatorial positions than the axial position. Most molecule (about 99% at room temperature) exist in the conformation with methyl in uncrowded equatorial position.

Disubstituted cyclohexane:

1, 2-disubstituted cyclohexane

→ Homo disubstituted

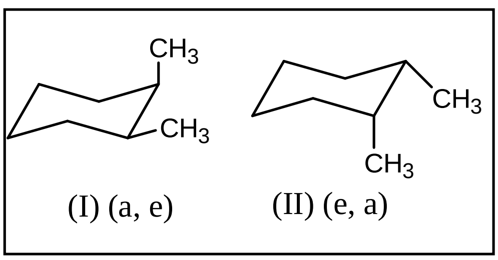
→ Hetero disubstituted cyclohexane.

Cis and trans relationship in disubstituted cyclohexane can be understood as

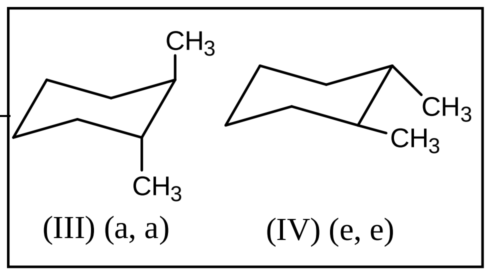
1, 2-disubstituted cyclohexane.	1, 4-disubstituted cyclohexane.	1, 3-disubstituted cyclohexane.
Cis — (a, e) or (e, a)	Cis — (a, e) or (e, a)	Cis — (a, a) or (e, e)
Trans — (a, a) or (e, e)	Trans — (a, a) or (e, e)	Trans — (a, e) or (e, e)

Let us consider an example of 1, 2-disubstituted cyclohexane.

Cis–



Trans–

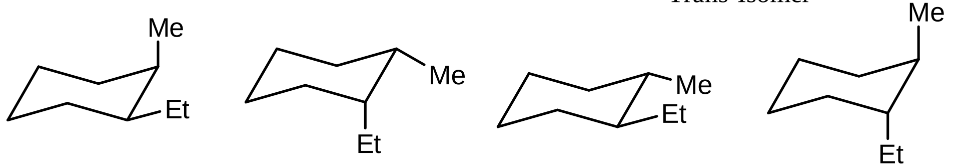


I & II are degenerate because both have one 1, 3-interaction.
III & IV are non degenerate
III is least stable because in this case both methyl group is placed at axial position and suffer 1, 3-interaction.

So, the stability order is IV >I > II > III

1, 2-disubstituted cyclohexanes with two different substituents.
Let us consider an example of 1-ethyl-2-methyl cyclohexane.

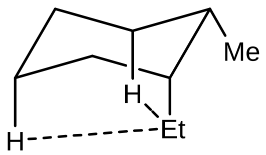
Cis-isomer Trans-Isomer



(1) (a, e) (2) (e, a) (3) (e, e) (4) (a, a)

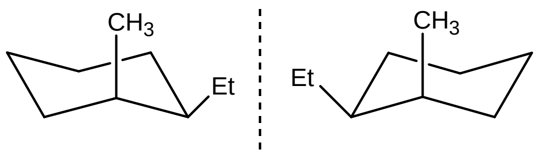
1 and 2 are non degenerate.

Remark: Energy of conformation (2) will greater than that of (1) because, the bulky ethyl group is at axial position which suffer more 1,3-interaction.

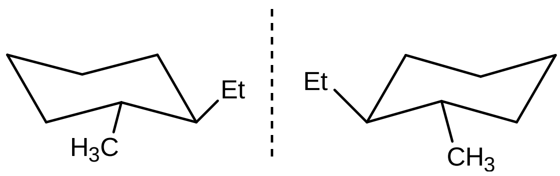


3 and 4 are also non degenerate, out of these two conformations, (4) has maximum energy because both, methyl and ethyl are placed at axial position where they suffer severe 1, 3-interaction.
So, overall stability order is 3 > 1 > 2 > 4.

Optical activity:



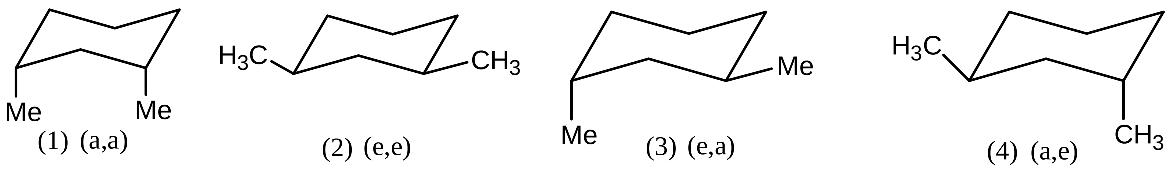
A pair of enantiomer



A pair of enantiomer

1, 3-disubstituted cyclohexanes (1, 3-dimethyl cyclohexane)

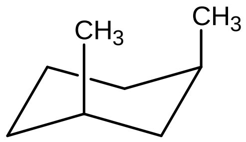
Cis-1, 3-dimethyl cyclohexane. Trans-1, 3-dimethyl cyclohexane.



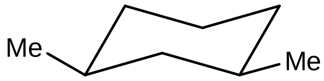
(1) (a,a) (2) (e,e) (3) (e,a) (4) (a,e)

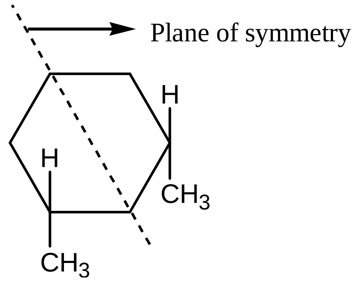
3 and 4 are degenerate.
1 and 2 are non degenerate.
Energy order 1 > 3 ~ 4 > 2.
Stability order 2 > 3 ~ 4 > 1

Note: In Cis-1, 3-dimethyl cyclohexane, plane of symmetry is present in both (a, a) or (e, e) conformation.



(a, a)

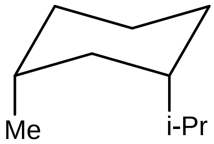




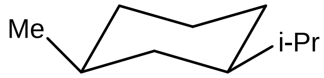
However, trans 1, 3-dimethyl cyclohexane, does not have a plane of symmetry and exist as a pair of enantiomers.

Let us consider the case of 1-isopropyl-3-methyl cyclohexane.

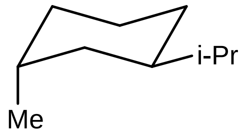
cis-1-isopropyl-3-methyl cyclohexane. trans-isoprophyl-3-methyl cyclohexane.



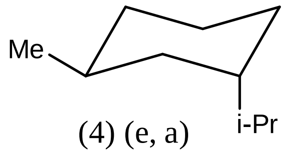
(1) (a, a)



(2) (e,e)



(3) (a, e)



(4) (e, a)

1 and 2 are nondegenerate.

3 and 4 are non degenerate.

Stability order:

2 > 3 > 4 > 1

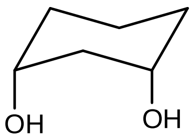
1 → Both group at axial position

4 → Bulkier group (i-Pr) at axial position.

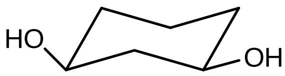
2 → Both group at equitorial position

Let us consider an example of 1,3-dihydroxy cyclohexane.

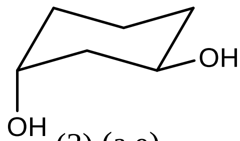
Cis-1,3-dihydroxy cyclohexane. trans-1, 3-dihydroxycyclohexane.



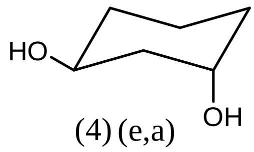
(1) (a, a)



(2) (e,e)



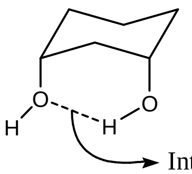
(3) (a,e)



(4) (e,a)

Stability order 1 > 2 > 3 ~ 4

Conformer (1) is more stable than that of (2) because of the fact that in case of (1) intramolecular H-bonding is possible.



Intramolecular H-bonding.

PROBLEMS

1. From which conformation of cis-1, 3-cyclohexane dicarboxylic acid anhydride will be form.

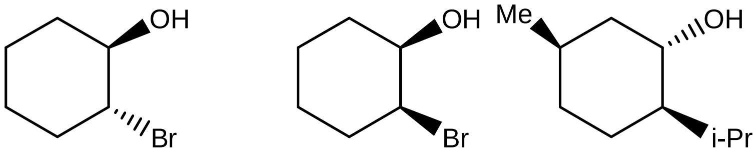
Soln. Cis-cyclohexane-1, 3-dicarboxylic acid diequatorial conformer (More stable)

Δ Cis-cyclohexane 1, 3-dicarboxylic acid diaxial conformer(Less stable)

Anhydride

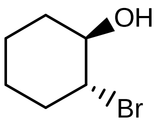
Remark: The –COOH grop in (A) are far apart for anhydride formation. Ring flip to give (S) brings them with in reacting distance.

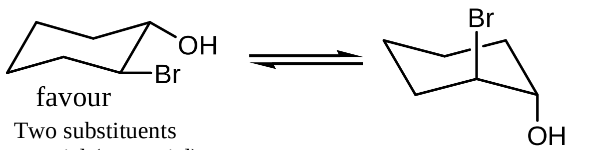
2. Draw the favoured conformation of following compounds



(1) (2)

Soln. (1)



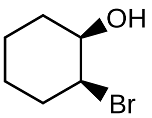


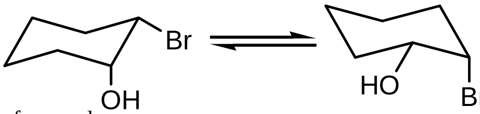
favour

Two substituents equatorial (non-axial)

No substituents equatorial two (axial).

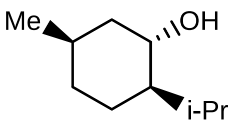
(2)



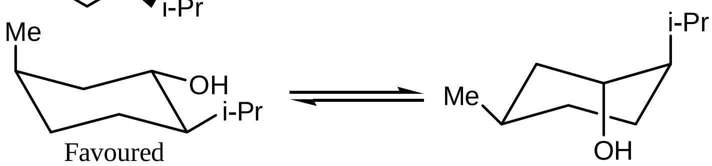


Since Br > OH (in size)

favoured



(3)



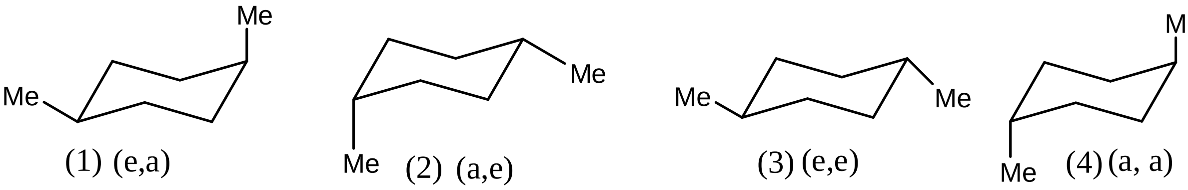
Favoured

Two substituents equatorial one axial.

One substituent equatorial two axial.

1, 4-disubstituted cyclohexane: Let us consider an example f 1, 4-dimethyl cyclohexane.

Cis-1, 4-dimethylcyclohexane. trans-1, 4-dimethylcyclohexane.

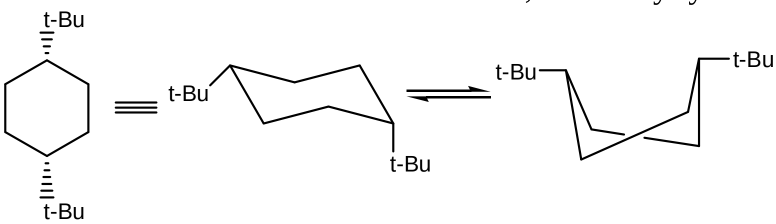


Stability order: 1 > 1 ~ 2 > 4.

SOLVED PROBLEMS

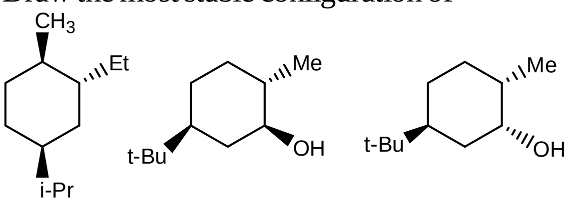
1. Draw the most stable conformation of cis-1, 4-di t-butylcyclohexane.

Soln.

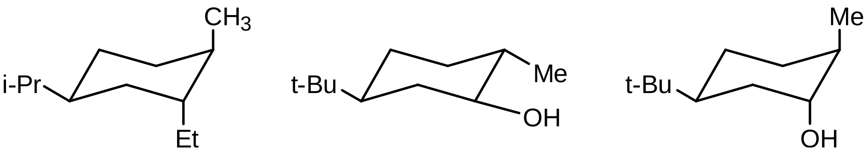


Remark: An axial t-butyl group is very unfavourable form. In Cis-1,4-di-t-butyl cyclohexane, one t-butyl group would be forced axial if the compound existed in a chair conformation, to avoid this, the compound prefers to pucker into a twist boat so that the two large groups can both be in equatorial positions (or Pseudoequatorial, since this is not a chair).

2. Draw the most stable configuration of

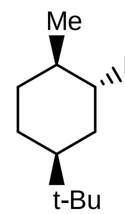


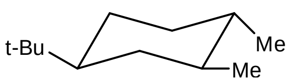
Soln.

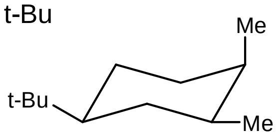


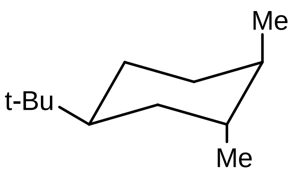
Remark: The bulky t-butyl group is particularly prone to occupy an equatorial position if other substituents are considerably smaller than t-butyl, the molecule is virtually locked in a single conformation. The one with an equatorial t-butyl group. t-butyl group has been widely used as a holding group to permit the study of physical and chemical properties associated with a purely axial or purely equatorial substituent.

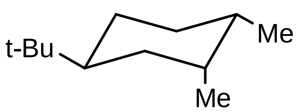
3. The most stable conformation of the following compound is:

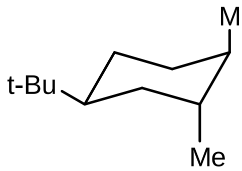


(a) 

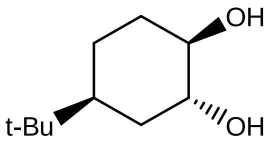
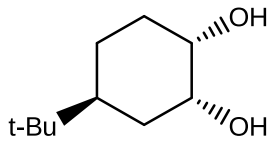
(b) 

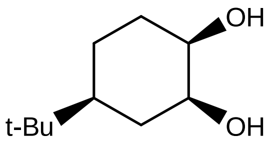
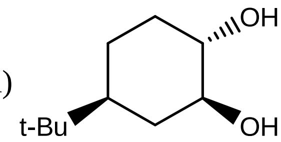
(c) 

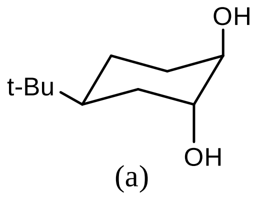
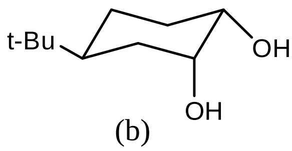
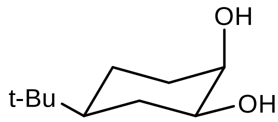
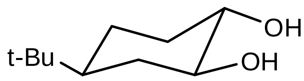
(d) 

Ans.  . Because t-butyl group is locking group.

4. The favoured vicinal diols shown below only three are cleaved by HIO_4. The diol which is not cleaved HIO_4 is:

(a)  (b) 

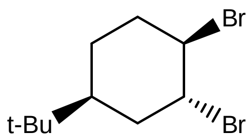
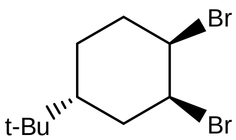
(c)  (d) 

Soln.    

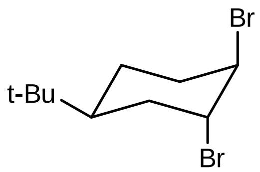
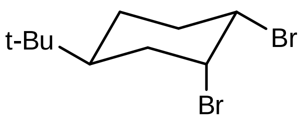
(a) (b) (c) (d)

(a) Because in this case the two-OH groups are diaxial, so there is more distance between two OH groups and hence will not interact with HIO_4 effectively.

5. Accouts for the fact that only one of the following compounds A and B give the expected elimination product with KI acetone.

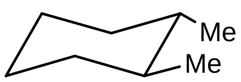
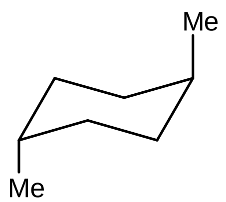
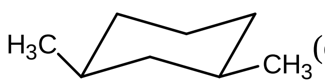
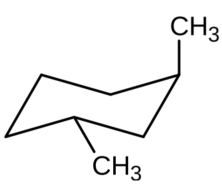
(A) (B)

Soln.  

(A) (B)

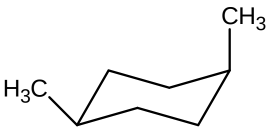
(A) will give the expected elimination product with KI in acetone because for E2-elimination. The two departing group should be placed at diaxial position (or antiperiplanar) such requirement is only fulfilled by compound (A).

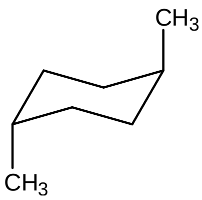
6. Which of the following is a cis-isomer?

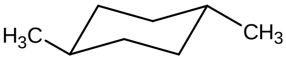
(a)  (b)  (c)  (d) 

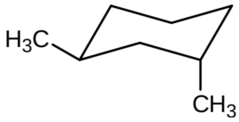
Soln. **(c)** Because in case of 1, 3-disubstituted cyclohexane cis means (e, e) or (a, a).

7. The stable form of trans-1,4-dimethyl-cyclohexane is represented as

(a) 

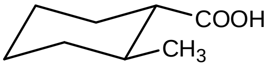
(b) 

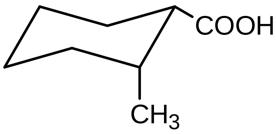
(c) 

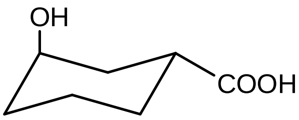
(d) 

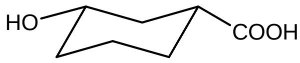
Soln. (c) because both groups are at equatorial position.

8. Identify the hydroxycyclohexane carboxylic acid, which upon heating readily gives a bicyclic lactone

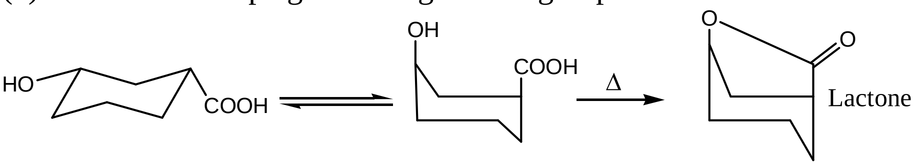
(a) 

(b) 

(c) 

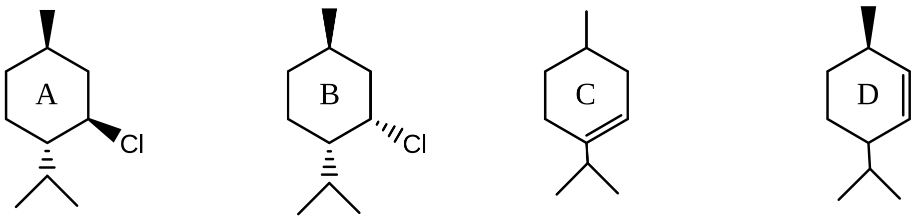
(d) 

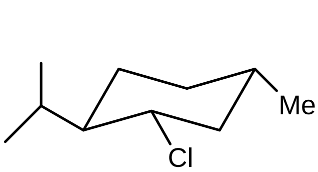
Soln. (d) Because after filiping of the ring the two groups OH and COOH come nearer to each other.



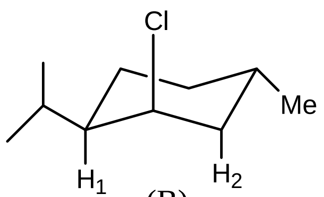
No one conformation will give this geometry.

9. Menthyl chloride (A) and neomenthyl chloride (B) both react with base to lose a molecule of HCl by E_2 mechanism. The products are regio isomers (C) and (D). Identify which product is formed from which starting compound. Also mention starting compound (A) or (B) which will react faster. Give reasons for your answer.



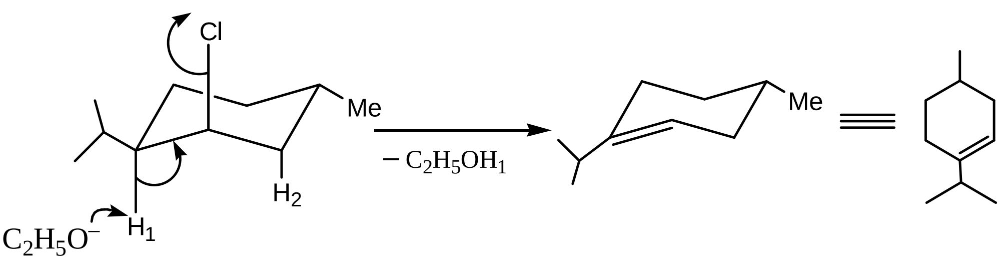
Soln. 

(A)

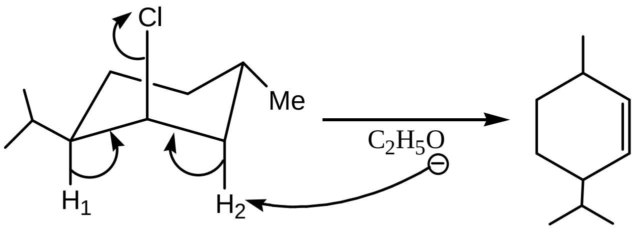


(B)

In case of (B) for elimination of HCl with base Cl have diaxial relationship with H_1 and H_2 which is the demand of E_2 elimination.

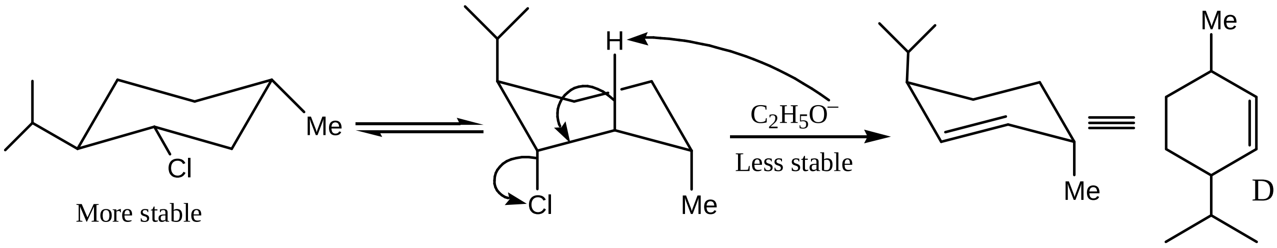


If proton H_2 will remove by base such as:



This product will also obtain but more highly alkylated product (C) will be formed.

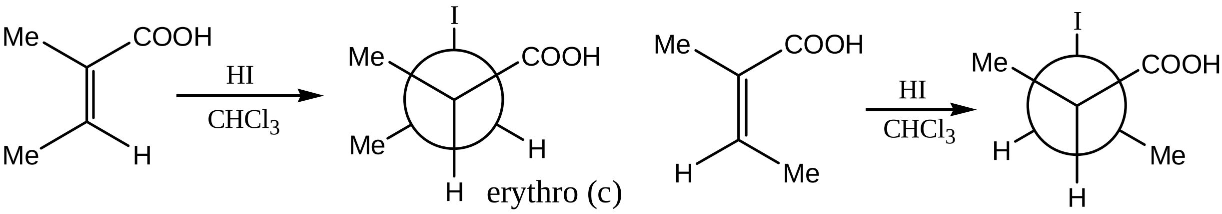
In the chair conformation (A) Cl–atom is equatorially placed and we know for E_2 elimination. The two departing group should be antiperiplanar, on this demand the conformation flip will occur such as



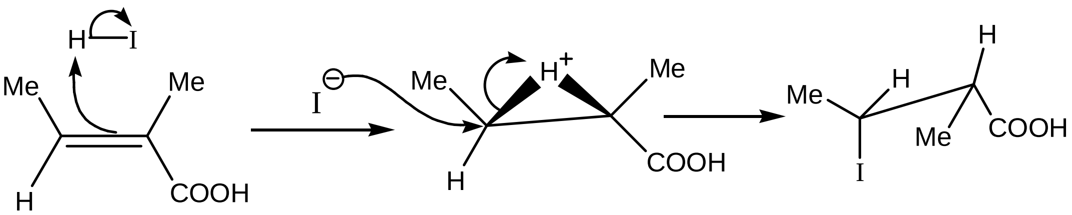
So,

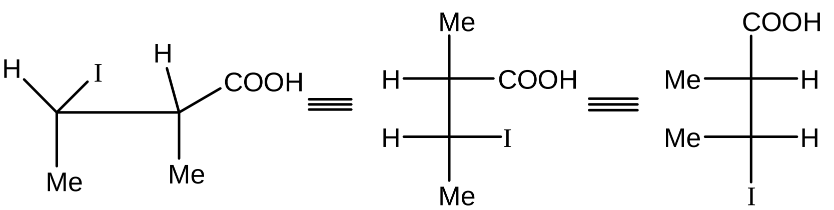
Rate of elimination of (B) is faster than that of A because elimination of (A) occur from high activation energy conformation.

10. How would you explain the addition of HI to *tiglic acid* (A) and *angelic acid* (B) to give stereospecifically the erythro and threo-β-Iodo acid, (c) and (d) respectively instead of a mixture of both the acids (c and d) in each case?

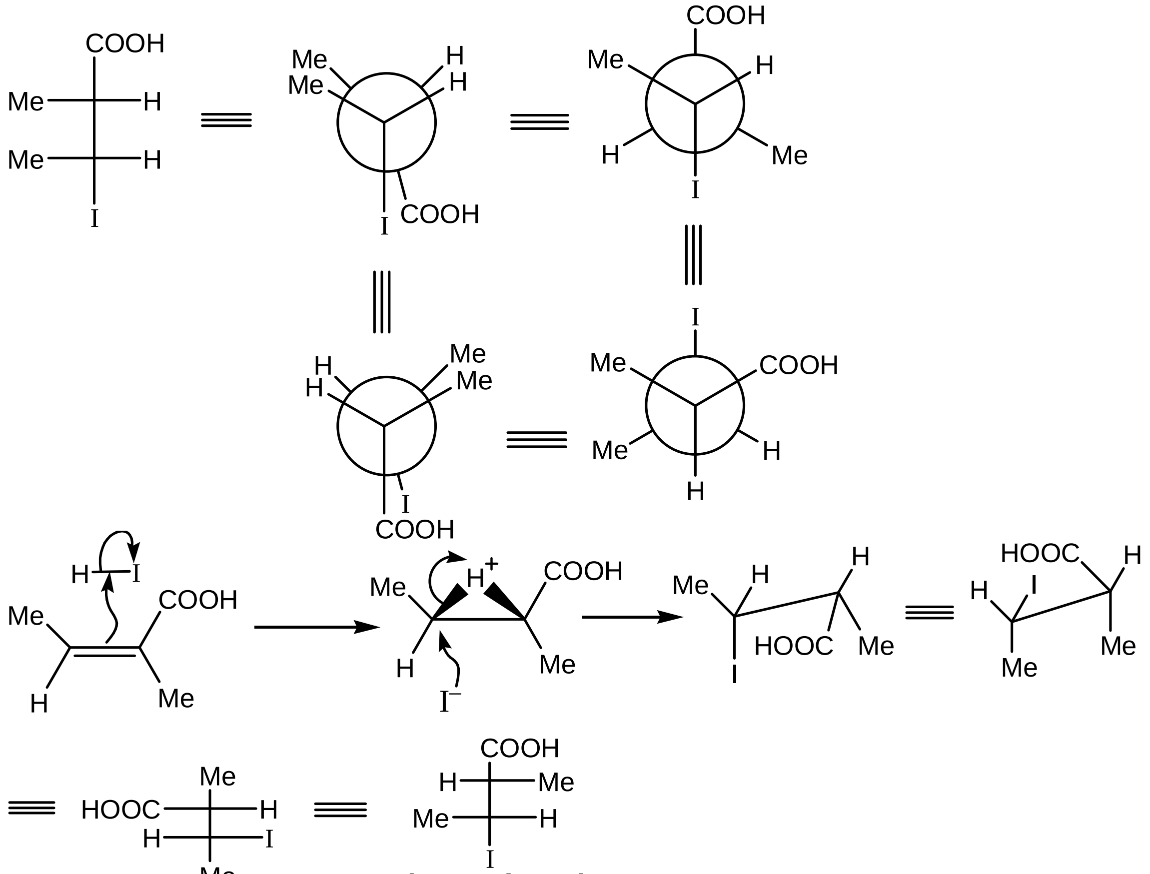


Soln.





erythro product



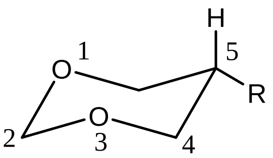
threo product only

Conformation in six membered rings containing hetero atoms

In six membered ring containing hetero atoms, the basic principles are the same i.e. there are chair, twist and boat forms, axial and equatorial groups etc, but in certain compounds a number of new factors enter the picture.

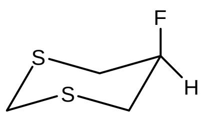
For example:

In 5-alkyl-substituted 1, 3-dioxane, the 5-substitutent has a much smaller preference for the equatorial position than in cyclohexane derivatives.

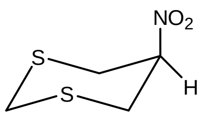


This indicate that lone pairs on the oxygen have a smaller steric requirement than the C–H bonds in the corresponding cyclohexane derivatives.

Similar behaviour is found in the 1, 3-dithiane with certain nonalkyl substitution (eq, F, NO_2, SOMe, $\overset{+}{N}Me_3$) the axial positions is actually preferred.

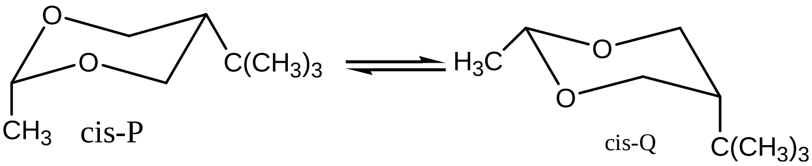


Preferred form

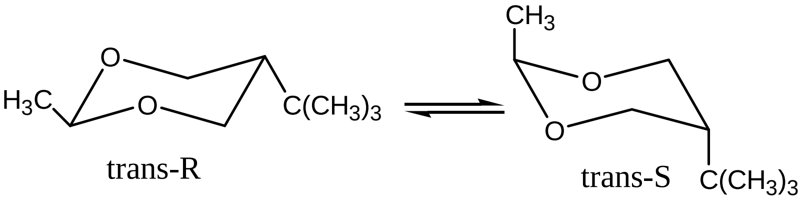


Preferred form

11. Cis–and trans–2–methyl –5-tbutyl–1, 3-dioxane each can exist as two conformers as shown below.



cis-P cis-Q



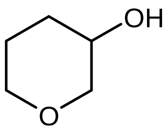
The preferred conformations for the cis and trans–compounds will be

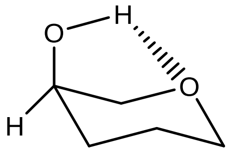
(a) P, R (b) Q, S (c) P, S (d) Q, R

Soln. **(b)**

Hints: In Q the bulky group (t-butyl) does not suffer 1, 3-interaction because carbon is replaced by oxygen.

Conclusion: In heterocyclic rings the steric repulsion for axial substituents are reduced due to the replacement of methylene groups of cyclohexane by oxygen or nitrogen.

12. Draw the most stable conformation of 

Soln. 

The presence of an oxygen atom in the ring allows hydrogen bonding that can stablize hydroxyl groups in the axial position.

Specific Rotation

Specific rotation as optical rotation of I gm/mL concentrated solution when path length 10 cm (1 dm) at particular wavelength (*l*) of light.

$$[\alpha] = \frac{\alpha}{c.\ell}$$

Note: Most $[\alpha]$ values are quoted as $[\alpha]_D$ (where the D indicates the wavelength of 589 nm, the D line of a sodium lamp) or $[\alpha]_D^{20}$, the 20 indicating $20^o C$.

Enantiomeric Excess

Enantiomeric excess or e e is a measure for how much f one enantiomer is present compared to the other.

For example, in a sample with 40% e e in R, the remaining 60% is racemic with 30% of R and 30% of S so that the total amount of R is 40% + 30% = 70%.

$$\% \text{ optically purity} = \frac{[\alpha]_{obs}}{[\alpha]_{max}} \times 100$$

assuming a linear relationship between $[\alpha]$ and concentration, which is true for most cases. The optical purity is equal to percent excess of one enantiomer over the other

So,

$$\text{Optical purity} = \text{percent enantiomeric excess} = \frac{[R]-[S]}{[R]+[S]} \times 100 = \%R - \%S$$

$$\boxed{\text{Optical rotation} = \frac{e\,e}{100} \times \text{specific rotation}}$$

13. 20 mg mandelic acid was dissolved in 1 cm^3 of ethanol and the solution placed in a 10 cm long polarimeter cell. An optical rotation α of –4.35°C was measured (that is, 4.35° to the left) at 20°C with light of wavelength 589 nn. What is the specific rotation of the acid?

Soln. $[\alpha]_D^{20} = \frac{\alpha}{c \times \ell}$

Since, $\alpha = -4.35^o$

$c = 28 \text{ mg / cm}^3$ $\qquad \ell = 10 \text{ cm} = 1 \text{ dm}$

$c = 28 \times 10^{-3} \text{ g / cm}^3$

$c = 0.028 \text{ g / cm}^3$

So, $[\alpha]_D^{20} = \frac{\alpha}{c \times \ell} = \frac{-4.35}{0.028 \times 1} = -155.4$

So, the specific rotation of mandolic acid = –155.4°.

14. Calculate the optical rotation from the given data

sp = 20°

D = 90%

L = 10%

Soln. e e = 90% – 10%

e e = 80%

So, Optical rotation $= \frac{80}{100} \times 20 = 16$

$$\boxed{\text{e e} = \frac{\text{Optical rotation}}{\text{specific rotation}} \times 100}$$

15. Calculate enantiomeric excess from the given data

sp rotation = 20°

optical rotation = 18°

Soln. $\text{e e} = \frac{18}{20} \times 100$

e e = 90%

Since, $\% \text{ of } d + \% \ \ell = 100$

$\% \text{ of } d - \% \ \ell = 90 = \text{e e}$

So, $\% \text{ of } 2d = 190$

$\therefore \text{ of } d = \frac{190}{2} = 95\% \ \& \ \% \ \ell = 5\%$

Optical activity of compounds having symmetric carbon

Case I: If the molecule has no plane of symmetry and molecule has 'n' asymmetric carbon atoms then–

Number of optically active forms = 2^n = a

Number of enantiomeric pair = a/2

Number of racemic mixture = a/2

Number of meso form = 0

Case II: If the molecule has plane of symmetry, then the number of configuration isomers depend on the number of asymmetric carbon atoms.

(1) When compound has even number of asymmetric carbon atoms i.e. n = 2, 4, 6, ...

(a) Number of optically active forms = a = 2^{n-1}.

(b) Number of enantiomeric pairs = a/2

(c) Number of racemic mixture = a/2

(d) Number of meso forms = $m = 2^{\frac{n}{2}-1}$.

(e) Total number of configurational isomer = a + m

For example:

$$HOOC-\overset{*}{C}H(OH)-\overset{*}{C}H(OH)-COOH$$

n=2

Number of optical isomer $= a = 2^{n-1} = 2$

Number of meso form $= m = 2^{n/2-1} = 2^{2/2-1} = 1^o = 1$

Total number of configurational isomers = 2+1=3

Let us consider another example

$$Ph-\overset{*}{C}HCl-\overset{*}{C}HCl-\overset{*}{C}HCl-\overset{*}{C}HCl-Ph$$

n= 4

$a = 2^{4-1} = 2^3 = 8$

$m = 2^{(n/2)-1} = 2^{4/2-1} = 2^{2-1} = 2^1 = 2$

So, the total number of configurational isomers $= 8 + 2 = 10$

Case III: When compound has odd number of asymmetric carbon atoms and plane of symmetry i.e. n = 3, 5, 7, 9, 11...........

(a) Number of optically active forms

$$a = 2^{n-1} - 2^{(n-1)/2}$$

(b) Number of enantiomeric pair = a/2

(c) Number of racemic mixture = a/2

(d) Number of meso forms = m = $2^{(n-1)/2}$

(e) Total number of configurational isomers = a + m.

For example:

$$HOH_2C-\overset{*}{C}HOH-\overset{*}{C}HOH-\overset{*}{C}HOH-CH_2OH$$

n=3

$a = 2^{n-1} - 2^{(n-1)/2} = 2^{3-1} - 2^{3-1/2} = 2^2 - 2^1 = 2 \times 2 - 2 = 4 - 2 = 2$

$m = 2^{(n-1)/2}$

$m = 2^{3-1/2} = 2^1 = 2$

Hence total number of configurational isomers = 2 + 2 = 4

Number of Geometrical Isomers in Polyenes

(a) When compound has 'n' doube bonds and ends of polyene are different, the number of geometrical isomers = 2^n.

where n = Number of double bonds.

$Ph-CH=CH-CH=CH-CH=CH-CH=CH-Cl$

$n = 4$

(b) When the ends of polyene are same

Case I: When number of double bond is even.

Then the number of geometrical isomers.

$$2^{n-1} + 2^{n/2-1}$$

Let us consider another example

$$Cl-CH=CH-CH=CH-CH=CH-CH=CH-Cl$$

$n = 4$

Number of geometrical isomers $= 2^{n-1} + 2^{n/2-1} = 2^3 + 2^1 = 8 + 2 = 10$

Case II: When the number of double bonds are odd

Number of geometrical isomer $= 2^{n-1} + 2^{n-1/2}$

$$Ph-CH=CH-CH=CH-CH=CH-Ph$$

Number of geometrical isomers $= 2^2 + 2^{\frac{3-1}{2}} = 2^2 + 2^1 = 4 + 2 = 6$

Topocity :

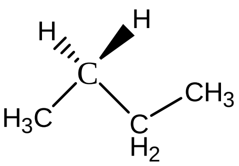
Topocity is the strereochemical relationship of substituents relative to the structure to which theyare attached, depending on the relationship, such groups can be heterotopic, homotopic enantiotopic, or diastereotopic.

Homotopic:

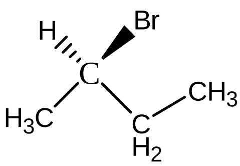
- Homotopic atom, are always identical in any environment.
- Homotopic NMR - active nuclei have the same chemical shift in an NMR spectrum.

eq– CH_4 all 4H's are potential. So homotopic with one another.

Enantiotopic:

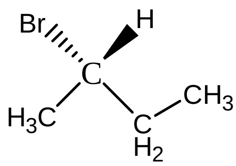


Butane



R-2–bromobutane

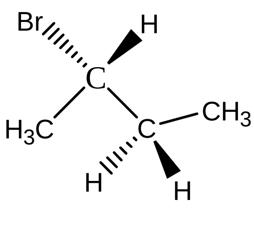
+



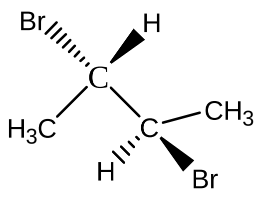
(S)–2–bromo butane

- Enantiotopic groups are identical and indistinguishable except in chiral environment
- Enantiotopic pairs of NMR active nuclei are also indistinguishable by NMR and produce a single signal..........

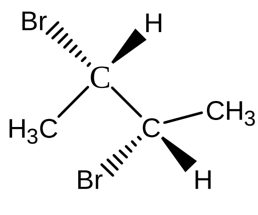
Diastereotopic groups are often, but not always identical group attached to the same atom in a molecule containing at least one chiral centre.



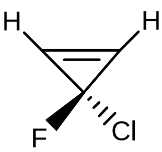
(S)–2–bromobutane



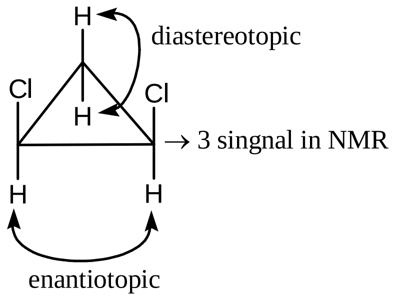
(2S,3R)–2,3–dibromobutane

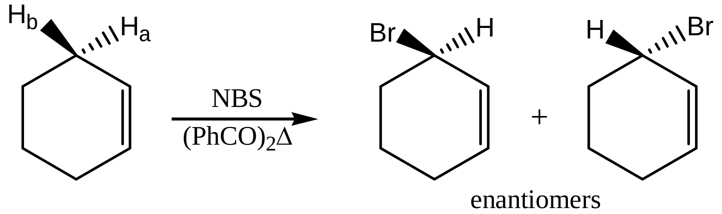


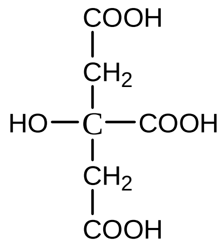
(2S,3S), –2, 3–dibromobutane



$\longrightarrow$ enantiotopic face

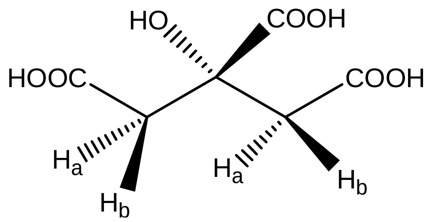






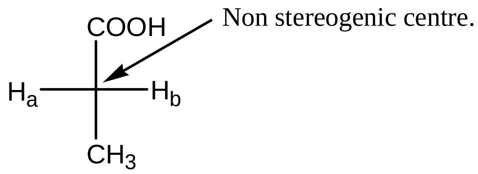
Citric acid

Citric acid has the prochiral centre the two chain CH_2COOH are enantiotopic.
This is an interesting example where enantiotopic and diastereotopic H', co-exist.

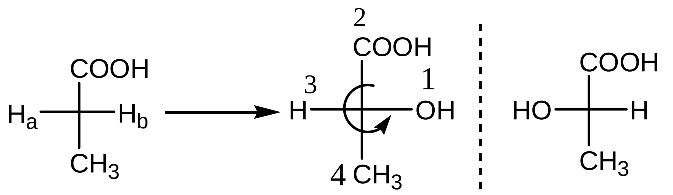


A plane of symmetry perpendicular to the page and passing through the middle carbon make H_a's enantiotopic and H_b's also enantiotopic. No Plane of symmetry can pass between each CH_2 group protons *a* and *b* on each CH_2 group diastereotopic.

Prochirality: Prochirality is the property of certain molecules due to which these can be converted into stereoisomers. (enantiomers or diastereoisomers).



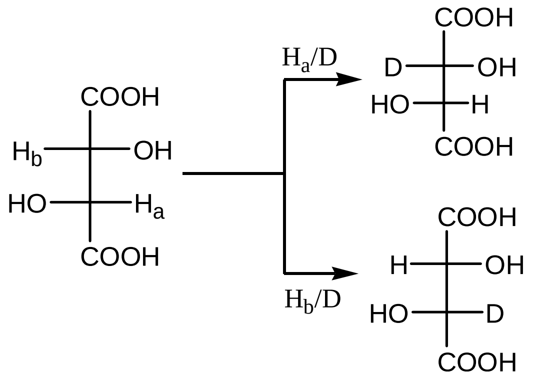
Propionic acid



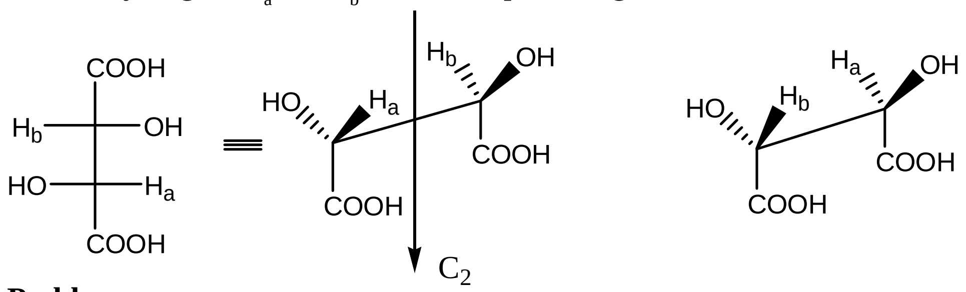
R-lactic acid S-lactic acid

Homotopic ligands and Faces:

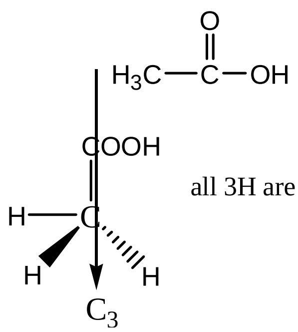
• If the substitution of each one of them by another atom or group leads to the same structure.



So, two hydrogens H_a and H_b are homotopic through rotational around

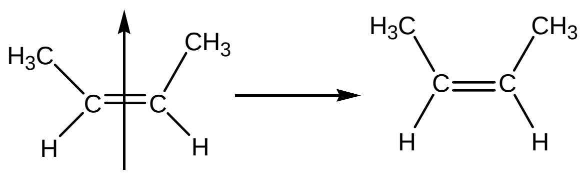


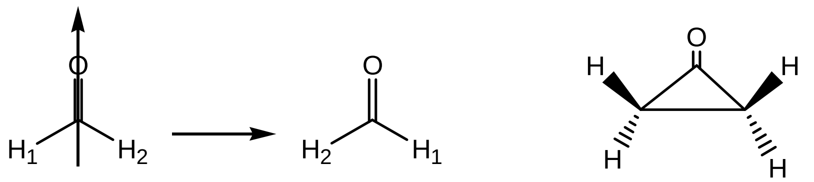
Problem:



all 3H are identicals, so homotopic in nature

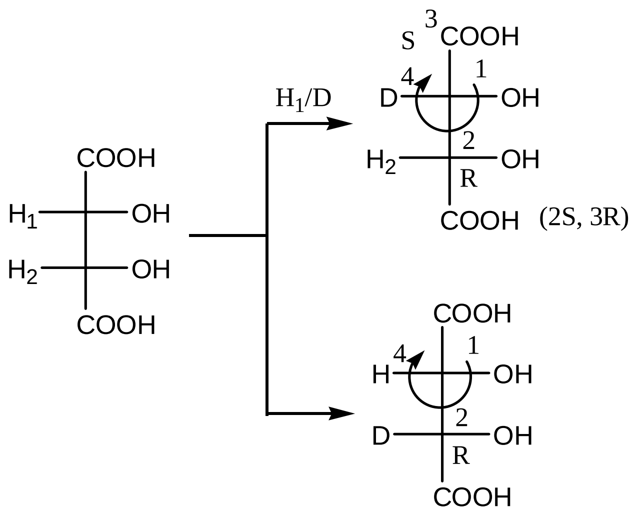
Homotopic face:



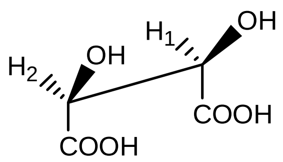


C_2 homotopic face homotopic face

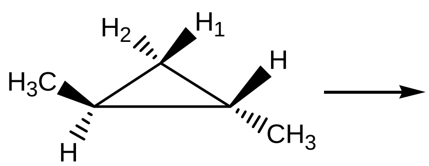
Enantiotopic ligand and faces



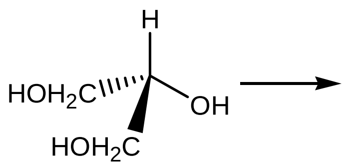
These two are not non super imposable mirror images to each other but still diastereoiomers.



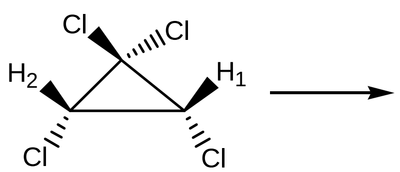
H_1 and H_2 are reflected by a plane
So, these two are enantiomers to each other.



H_1/H_2 are homotropic becaue it is interchanged with C_2-symmetry.

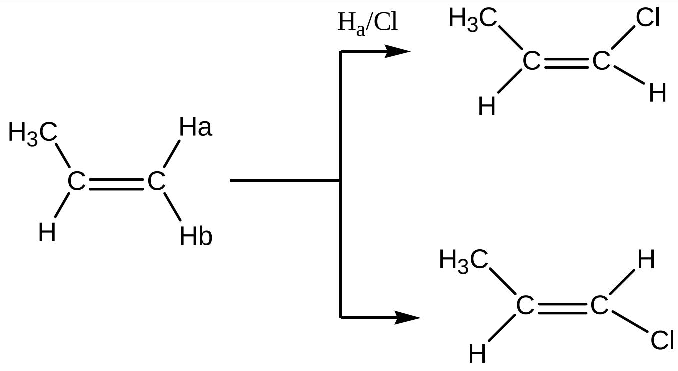


enantiotopic



H_1/H_2 $\rightarrow$ are enantiotopic

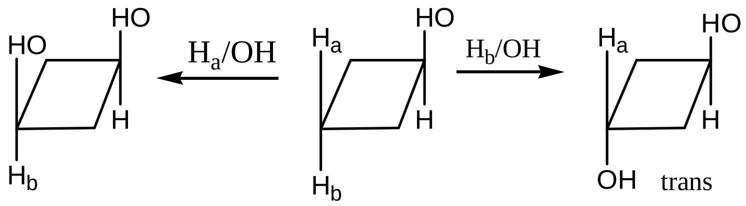
Diastereotopic ligands and faces:



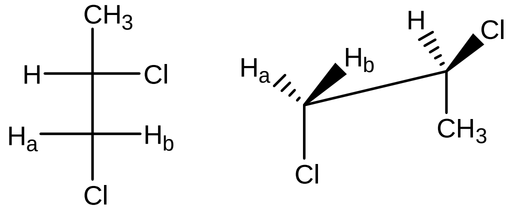
So, these two are diasteroismers

cis(z)

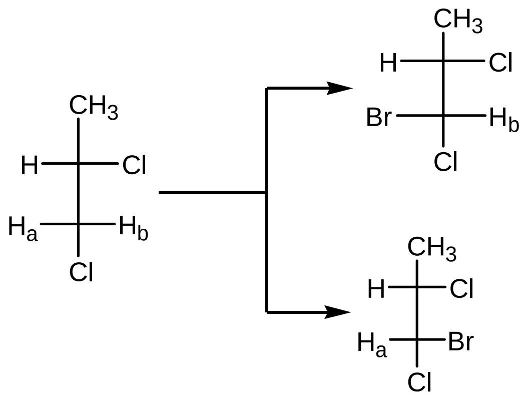
trans (E)



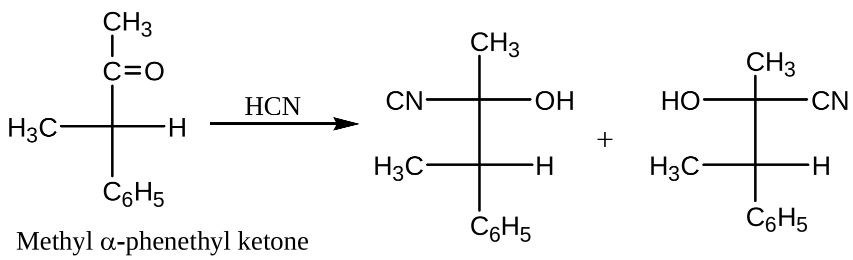
So, H_a and H_b diastereoisomers



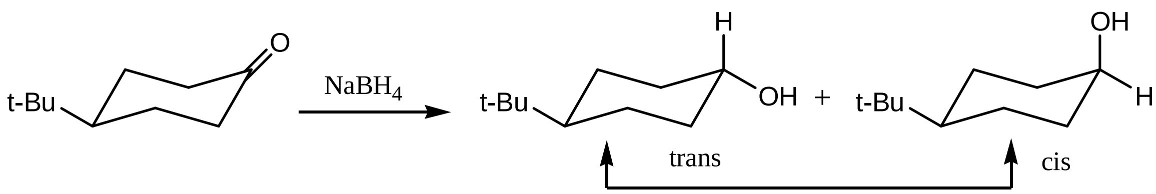
So, H_a and H_b $\rightarrow$ are diastereotopic.



Diastereotopic face:



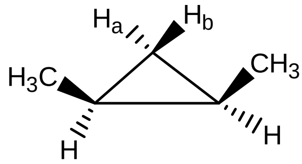
Methyl α-phenethyl ketone



So this face is diasterotopic

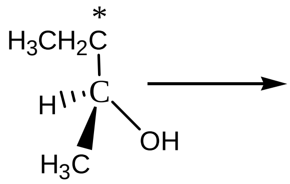
PROBLEMS

1.



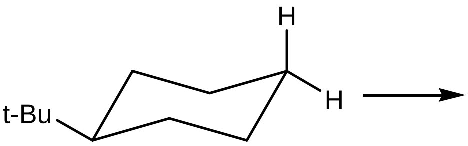
So, H_a/H_b are diasrereoisomers because it is bisected from a plane.

2. (i)

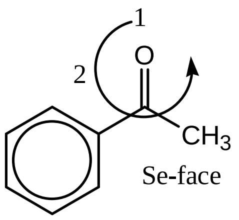


diastereotopic

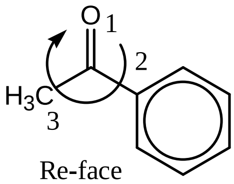
(ii)



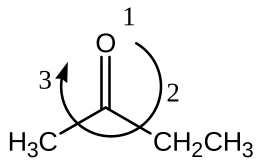
diastereotopic



Se-face

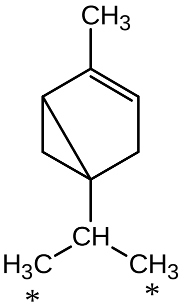


Re-face

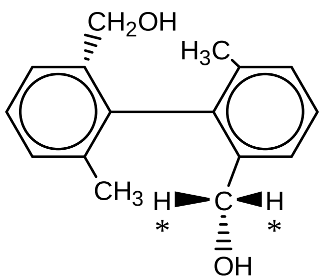


Re-face

3.

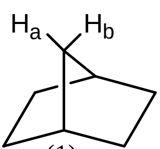


diastereotopic since there is no symmetry and the two methyl group are close to a stereogenic centre.



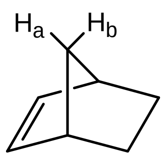
diastereotopic when the rotation of the ring is slow when rotation becomes fast these protons become enantiotopic (average mirrorplane)

4. Indicate H_a and H_b are homotopic, enantiotopic or diastereotopic.

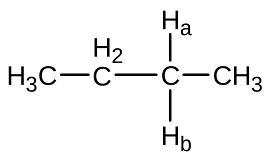


(1)

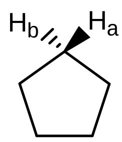
homotopic



diastereotopic replacement test would give syn and anti compounds which are diastereomers.

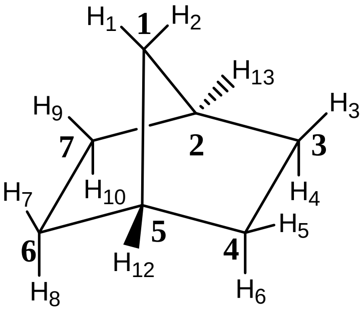


enantiotopic



homotopic

Let us consider an example of norborane system first we want to discuss the symmetry properties of this system.



It has one C_2 axis passing through C_1 and interchanging C_2/C_5, C_3/C_6, C_4/C_7. H_1/H_2, H_{12}/H_{13}, H_3/H_7, H_5/H_9, H_4/H_8, H_6/H_{10}.

So, these protons are identical (as we know the protons which are interchanging with an axis are identical i.e. homotopic protons).
Now, It has two σ_v.

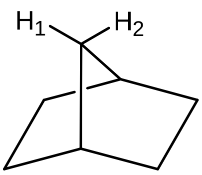
(a) σ_{v1}–bisecting C_1–C_2–C_5, H_{13}, H_{12} reflecting C_3/C_7, C_4/C_6, H_1/H_2, H_3/H_9, H_5/H_7, H_6/H_8, H_4/H_{10}.

(b) σ_{v2}–bisecting C_1, H_1, H_2 and reflecting C_2/C_5, C_3/C_4, C_7/C_6, H_{13}/H_{12}, H_3/H_5, H_4/H_6, H_9/H_7, H_{10}/H_8.

The protons which are reflected with plane are enantiotopic where as those which are bisected with plane are diasterotopic.

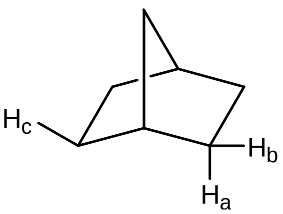
Note: If a protons are interchanging with C_2 axis and also reflected by plane the priority will be given to interhanging by axis and hence it will be homotopic but not enantiotopic.

For example



H_1/H_2 are interchangabe with C_2-axis and also reflected by a plane. So, in this case priority will be given to former not latter and hence H_1/H_2 are homotopic proton.

5. Identify the correct stereochemical relationship amongst the hydrogen atoms H_a, H_b and H_c in the following molecule. **[GATE-2006]**

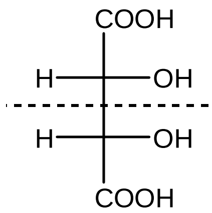


(a) H_a and H_b:enantiotopic (b) H_a and H_b : diastereotopic
(c) H_a and H_c: enantiotopic (d) H_b and H_c : diastereotopic

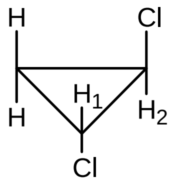
Soln. Since, H_a and H_b do not have direct relationship with any symmetry element. So, we will have to see chemical environment around H_a and H_b since the chemical environment is different viz H_b is exo where as H_a is endo so these protons are diastereotopic.
H_c/H_b are reflected with plane hence it will be enantiotopic.
$H_a/H_c \rightarrow$ diastereotopic

Correct answer is (b)

6. The two H's at C–2 and C–3 in (2R, 3S) tartaric acid.
(a) enantiotopic (b) diastereotopic (c) homotopic (d) constitutionally heterotopic



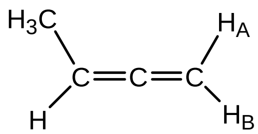
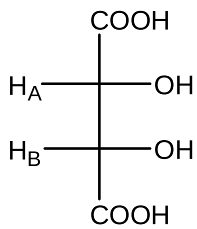
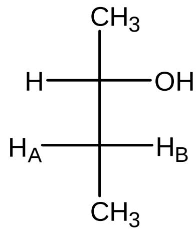
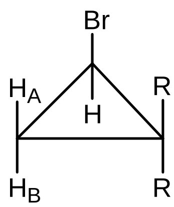
Soln. These two hydrogenes are reflected by a plane.
So, it is enantiotopic.

7. 

The relation between H_1/H_2 are
(a) Homotopic (b) Diastereotopic (c) enantiotopic **CSIR-JRF-2008**

Soln. Since H_1 and H_2 are interchangable with C_2-axis so these two are homotopic.

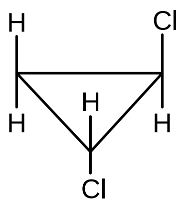
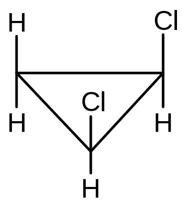
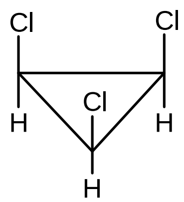
8. Consider the hydrogen atoms labelled as H_A and H_B in the following molecules. [**IAS-2008**]

(1)  (2)  (3)  (4) 

In which of the above are H_A and H_B diastereotopic
(a) 1, 2 and 3 (b) 2, 3 and 4 (c) 1, 3 and 4 (d) 1, 2 and 4

Soln. (b) have plane of symmetry so H_A and H_B are enantiotopic in the case of (3). H_A and H_B are adjacent to the chiral centre so these two protons are diastereotopic while in case of (4) no direct relationship with symmetry element while chemical environment of these two protons are different so these two are diasterotopic.
So, the correct answer is (c)

9. Consider the following molecule S: **[IAS-2007]**
1. trans-1, 2-dichlorocyclo propane.
2. cis-1, 2-dichlorocyclo propane
3. 1, 1, 2-trichlorocyclopropane.
In which of the above molecules is/are the sets(s) of methylene hydrogen(s) diasterotopic?
(a) 1 only (b) 1 and 3 (c) 2 and 3 (d) 2 only

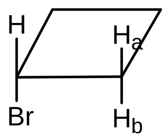
Soln.   

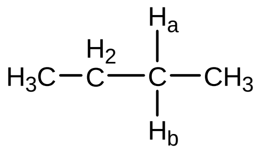
1. **2.** **3.**

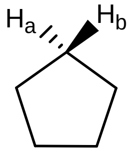
In case of (1) the methylene H's are exchangable with C_2 symmetry so, these two are homotopic while in (2) methylene protons are bisected with a plane so these two are diastereotopic

In case of (3) No methylene protons are present.
So, correct answer is (d).

10. Consider the following compounds.



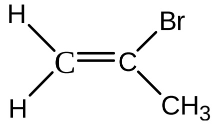




I **II** **III**

Identify H_a and H_b hydrogens in the above compounds.
(a) diastereotopic, enantiotopic, homotopic respectively.
(b) Enantiotopic, diastereotopic, homotopic respectively.
(c) Homotopic, diastereotopic, diastereotopic respectively.
(d) diastereotopic, enantiotopic, diastereotopic respectively.

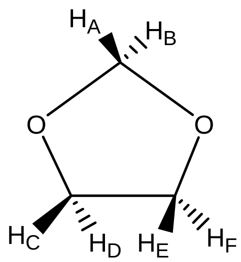
Soln. **(a)**

11. 

[IAS - 2006]

What are the two methylene protons in the above compound called?
(a) Homotopic protons (b) Tautomeric protons
(c) Diastereotopic protons (d) Enantiotopic protons.

Ans. **(c)**

12. 

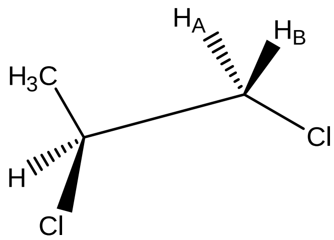
Consider the following statements concerning the features of the protons of the structure given above
1. H_A and H_B are homotopic
2. H_C and H_D are enantiotopic
3. H_E and H_F are diastereotopic
4. H_C and H_E are vicinal and cis.

Which of these statements are correct?
(a) 1 and 2 (b) 2 and 4 (c) 1, 2 and 4 (d) 2, 3 and 4 **[IAS-2003]**

Soln. H_A and H_B are homotopic because they are exchanged with C_2-axis.
H_C and H_D are enantiotopic because they are reflected with a plane.

H_E and H_F are not diastereotopic because they reflected with a plane but not bisected.
So, the correct answer is (c).

13. In the compound [**IAS-2001]**



The two hydrogen atoms marked as the H_A and H_B are
(a) enantiotopic (b) diastereotopic
(c) homotopic (d) anomer.

Soln. (b) because these two methylene protons are adjacent with chiral centre.