Ashoka Scientific Forum
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Organic Chemistry

TOPIC: STEREOCHEMISTRY

Target IIT-JAM

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SYLLABUS OF STEREOCHEMISTRY

- **Principles of stereochemistry.**
- **Configurational and conformational isomerism in acyclic and cyclic compounds.**
- **Stereochemistry of Allenes , Biphenyls, Spiranes.**
- **Stereogenicity.**
- **Stereoselectivity.**
- **Enantioselectivity.**
- **Diastereoselectivity and Asymmetric induction.**

STEREOCHEMISTRY

"Branch of chemistry which deals with three dimensional structures of molecules and their effects on physical-chemical properties"

Chiral Centre

"A carbon atom bonded tetrahedral to four different substituents in a molecule is termed as chiral centre. It is not necessary all the time that the chiral centre is tetrahedral in shape; trigonal centers are also present in case of alkenes or unsaturated compounds".

Achiral

"Objects and molecules which are superimposable on its mirror image are called achiral or symmetric. A ball is achiral. An internal plane of symmetry is a hypothetical plane which bisects the molecule or object into two equal halves. An object or molecule possessing this internal plane is achiral".

Chirality

"A molecule is said to be chiral if it cannot be superimposable on its mirror image and if it does not possess an alternating axis of symmetry".

When the molecule has a centre of symmetry (i) or a plane of symmetry (σ) then it is said to be achiral.

All molecules which lack all the elements of symmetry but for C_1. Then these molecules are called asymmetric. A carbon atom which has four different groups around it is always asymmetric.

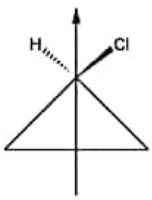
On the other hand when a molecule has only a simple axis of symmetry and no other symmetry elements are present then the molecule is termed as dissymmetric. Thus chiral molecules are dissymmetric.

To find out Chirality

1. Observe if Chiral centre is present or not. If present then the molecule is Chiral and if no Chiral centre than
2. Observe the plane of symmetry
   (i) If plane of symmetry is present – molecule is achiral.
   (ii) If no plane of symmetry – Chiral (allenes).

Examples:-

(i)

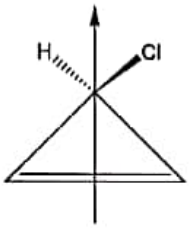


Achiral due to plane of symmetry.

(ii)

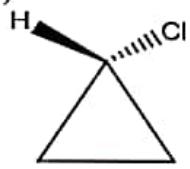
Achiral – Plane of symmetry

(iii)



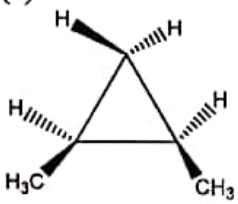
Achiral due to plane of symmetry.

(iv)



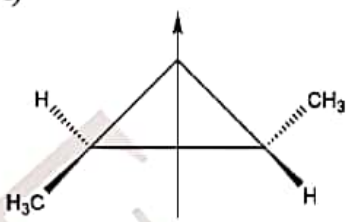
Achiral – Plane of symmetry.

(v)



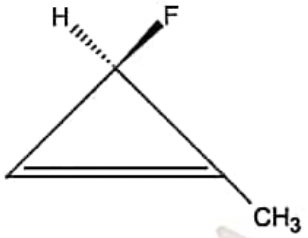
Achiral due to plane of symmetry.

(vi)



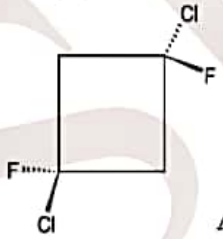
Chiral

(vii)



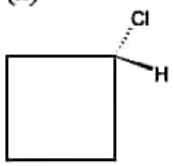
ChiraL =

(ix)



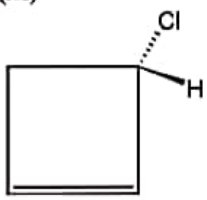
Achiral – centre and plane present

(x)



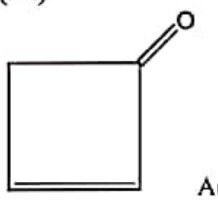
Achiral – Plane of symmetry present

(xi)



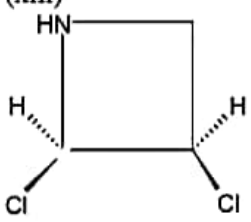
Chiral- no element of symmetry

(xii)



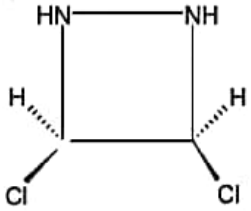
Achiral – no chiral centre is present, plane of symmetry is present i.e. molecular plane is present.

(xiii)



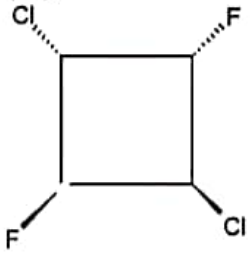
Chiral – no plane , no centre of symmetry

(xiv)



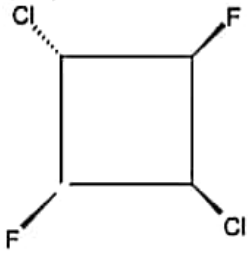
Achiral - presence of plane of symmetry.

(xv)



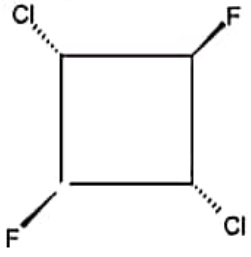
Achiral- centre of symmetry is present.

(xvi)



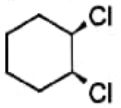
Achiral – plane of symmetry is present

(xvii)



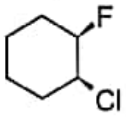
Achiral – plane of symmetry is present

(xviii)



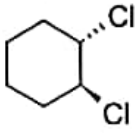
Achiral – plane of symmetry is present

(xix)



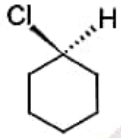
Chiral- no element of symmetry is present

(xx)



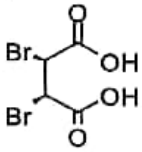
chiral .

(xxi)



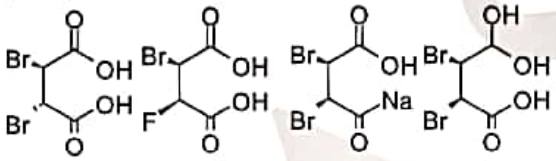
Achiral – plane of symmetry is present.

(xxii)



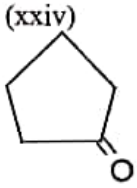
Achiral – plane of symmetry is present. If Br is replaced by any other atom or it is present below the plane then it becomes chiral. If O, OH are replaced then it also becomes chiral.

(xxiii)



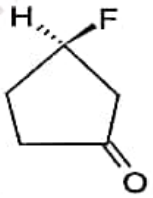
All are chiral- no element of symmetry is present.

(xxiv)



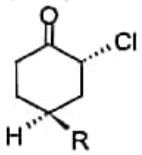
Achiral- plane of symmetry is present.

(xxv)



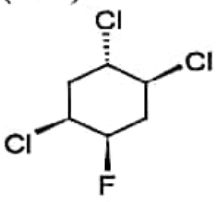
Chiral- no element of symmetry is present

(xxvi)



Chiral

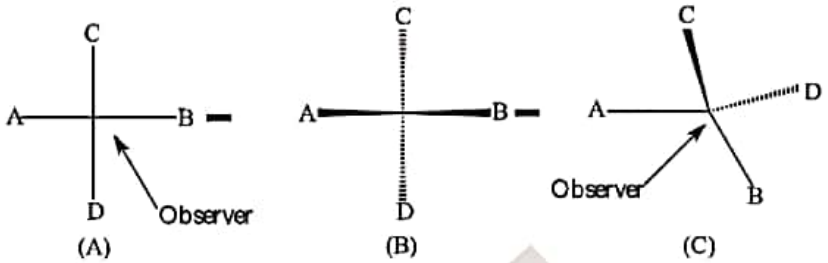
(xxvii)



Chiral

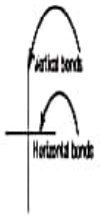
Flying wedge representation (3-D representation)

- ✓ Solid wedge (thick line)- *bond above the plane of paper*
- ✓ Broken wedge (dashed line) – *a bond below the plane of the paper*
- ✓ Continuous lines (solid lines)- *bonds in the plane of the paper*



Fischer projection (2-D representation)

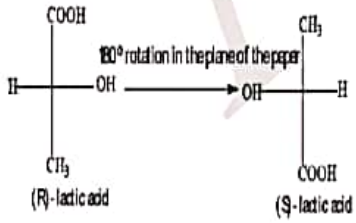
- ✓ Horizontal bonds- *Points towards the observer*
- ✓ Vertical bonds- *Points away from the observer*



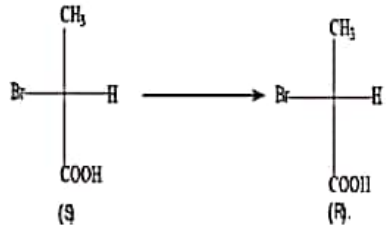
Rules

In order to find out whether the two structures are identical or not these projections can be manipulated only in specific ways. The following rules must be obeyed.

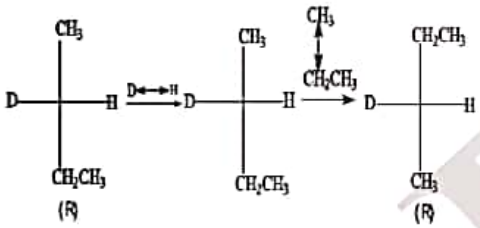
1. For comparison a fischer projection may be rotated 180° in the plane of the paper molecule remains same.



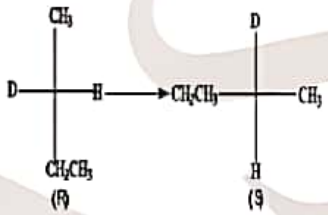
2. One interchange in the fischer projection leads to the enantiomers. configuration at the stereocenter changes from (S) to (R).



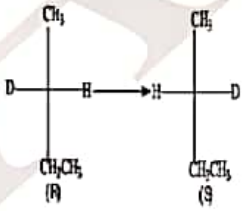
3. Two or any other even number of interchanges of the ligands at the chiral centre don't changes the configuration.



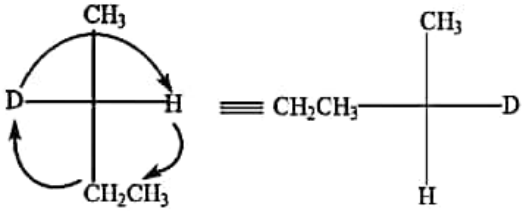
4. A 90° rotation of the fischer projection in the plane of the paper (gives the enantiomeric structures) is not allowed.



5. 180° rotation out of the plane of the paper (gives the enantiomeric structures) is not allowed.



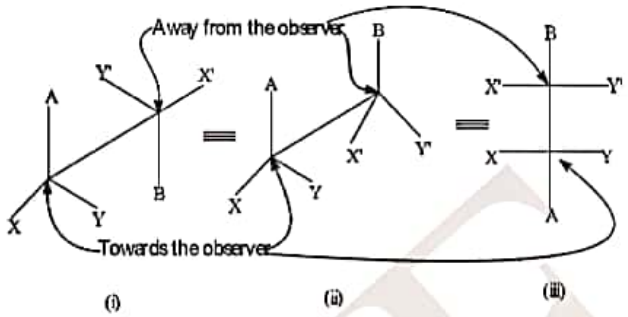
6. Fischer projection can be manipulated by rotating a group of any three ligands in a clockwise or anticlockwise direction, fourth ligand doesn't change its position.



Realistic representation of stereostructures of molecules

***Sawhorse representation*:-**

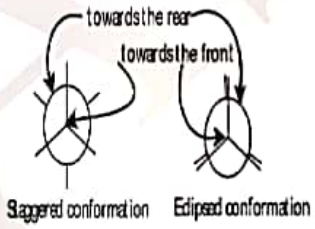
The sawhorse formula indicates the spatial arrangement of all the ligands on two adjacent carbon atoms is represented by a diagonal line usually from lower left to upper right. The left handed bottom end represents the atom nearest to the observer and the right hand top end represents the atom away from the observer. Two of the remaining bonds to the two atoms are drawn vertically and other four at $+120^0$ and-120^0 angles.



i. Staggered conformation(sawhorse representation)
ii. Eclipsed conformation(sawhorse representation)
iii. Fischer projection.

Newman projection formula

The newman projection formula is planar projection formula of the sawhorse formula. Newman projection similar to the sawhorse projection, represents the spatial arrangements of all the ligands on the two carbon atoms. Here a molecule is viewed along the axis of a carbon –carbon bond. The carbon towards the front is represented by a dot (.) and the carbon towards the rear by a circle.

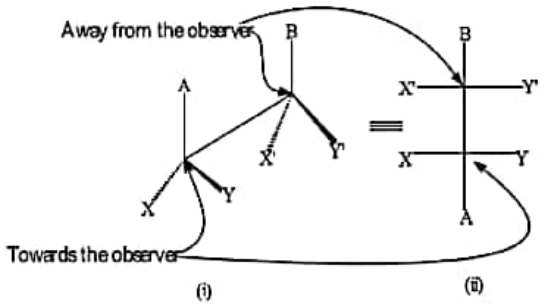


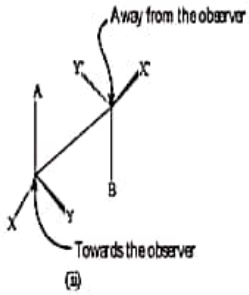
Interconversion of projection and perspective formulae

Conversion of fischer projection into sawhorse and newman formulae.

When we observe the molecule from the bottom of the right side the bond between the adjacent carbon atoms is represented by a diagonal line usually from the lower left to the upper right. The left handed bottom end represents the atom nearest to the observer and the right hand top end represents the atom away from the observer. The atoms which are towards the observer are represented by a solid wedge and those which are away from the observer are represented by dashed lines.

If we want to convert eclipsed form of flying wedge projection into staggered form then hold C_2 atom in hand in its position and rotate the C_3 atom by 180° . The atoms which are towards the observer are away from the observer and the atoms which are away from the observer becomes towards the observer.

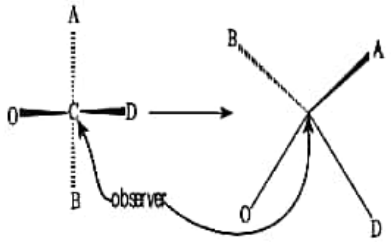




i. Eclipsed conformation (Flying wedge projection).
ii. Eclipsed conformation (Fischer projection).
iii. Staggered conformation (Flying wedge projection).

Fischer projection into flying wedge and vice-versa

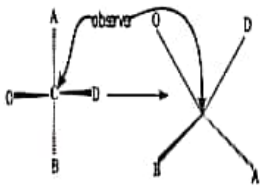
We draw the bonds which are towards the observer by solid wedge and the bonds away from observer by dashed lines. Then the above shown molecule becomes.



We want to convert this molecule into flying wedge projection formula for this hold the atom O and D and starts the process of bending so that a inverted V is formed i.e.^. This inverted v represents the atoms in one

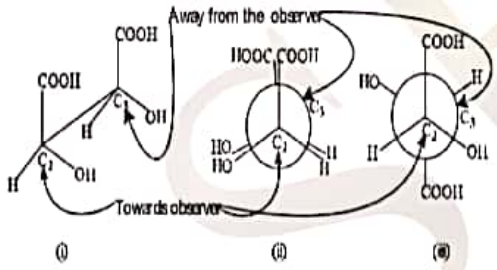
plane. Now draw the B below this plane which is shown below in this formula .The atom shown above is represented by above the plane in flying wedge formula.

We are observing from the bottom of the right side. If we will observe from top of this molecule then we find that



Sawhorse formula into Newman projection formula

We know that the left handed bottom end is towards the observer and right hand top end is away from the observer. We can convert this formula into Newman formula representing the molecule i.e. C_2 which is towards observer by a dot (.) and the atom which is away from the observer that is C_3 by a circle.

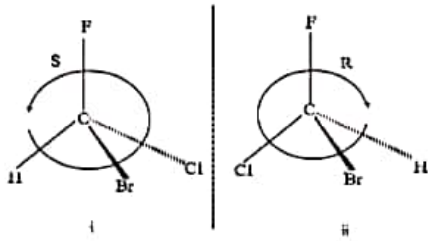


The Newman projection formula is a planar projection of the sawhorse formula. In this molecule we view along the carbon-carbon bond. The carbon atom towards the observer is represented by a dot (.) and the carbon atom away from the observer is represented by a circle. The above shown eclipsed form can be converted into staggered form by a rotation of 180° of one carbon atom only.

Enantiomers

Isomers which are non-superimposable mirror images of each other are called Enantiomers (optical antipodes or enantiomorphs).

The compounds of the type C_{abcd} exist in enantiomeric forms and are described as chiral and the carbon atom with four different substituent is called a stereogenic centre. The phenomenon of enantiomerism is also known as optical isomerism. An important property of the compounds of the type C_{abcd} is that on interchanging any two groups at the stereocenter converts one enantiomer into another.



i- (S) configuration
ii- (R) configuration

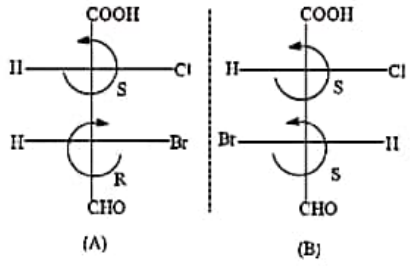
In Enantiomers the configuration at each stereocenter is changed i.e. R changes into S and S changes into R. in the above structure if we replace H with Cl and Br with H then we will get a new enantiomer.

Properties of Enantiomers

1. Each enantiomer of a pair has the same physical and chemical properties in achiral environment.
2. When plane polarized light is passed through the solution of each enantiomer then the plane polarized light is rotated in opposite direction by the same amount.
3. Enantiomers react with achiral reagents at the same rate but with chiral reagents they react with different rate.

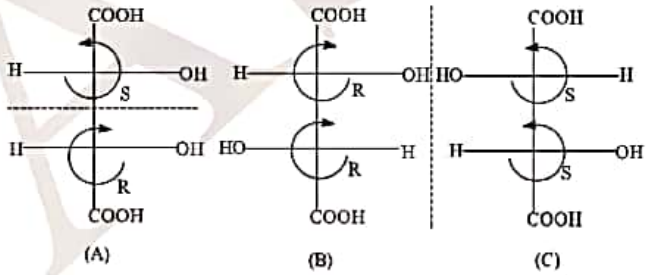
Diastereomers

Stereoisomers which don't have any mirror image relationship are called Diastereomers.



No mirror image relationship

Diastereomers are non-enantiomeric stereoisomers which have two or more stereocenter and differ only in configuration of at least one of them as shown in the above molecule.



(A) (2R,3S)-tartaric acid (meso compound due to internal compensation i.e. plane of symmetry in the molecule)
(B) (2R,3R)-tartaric acid (optically active – no element of symmetry is present).
(C) (2S,3S)- tartaric acid (optically active – no element of symmetry id present)
✓ (A) and (B) , (A) and (C) – Diastereomers (configuration at least one stereocenter is same)
✓ (B) and (C) – Enantiomers.(configuration at both stereocenters are different).

Properties of Diastereomers

1. Diastereomers have different physical properties like melting point, boiling point, solubility, retention times and R_f values.
2. Different rates of reaction even in achiral environments.

3. Diastereomers are not related by symmetry elements such as σ, I and S_n.

Epimers

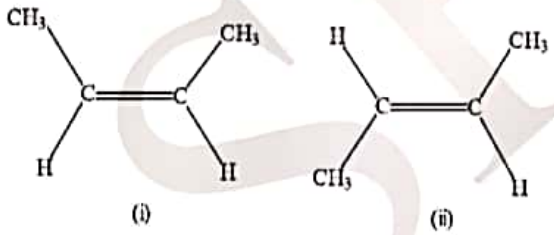
When two Diastereomers differ in the stereochemistry at only one stereocenter then these are called Epimers. The term is quite general. However it is not used for molecules with only two stereocenters. Glucose and mannose are Epimers at C_2.

Anomers

To give a pyranose structure , the OH group at C_5 of open chain form of glucose attacks the aldehyde to form a hemiacetal. A new stereocenters at C_1 is generated and a pair of Diastereomers is formed. These are called Anomers.

Trigonal planar stereocenters

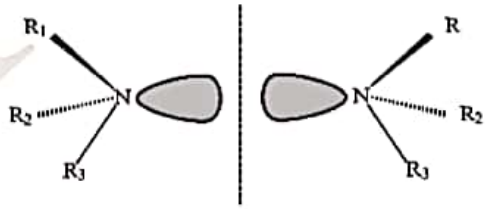
A stereocenter is defined as an atom having groups of suitable nature so that interchange of any two groups will give a stereoisomer. However all stereocenters are not tetrahedral the unsaturated carbon atoms of Cis and trans-2-butene are examples of trigonal planar stereocenters. Since an interchange of groups at these stereocenters gives a stereoisomer.



i. (Z)-2-butene (*groups of higher priority are on the same side*)
ii. (E)-2-butene (*groups of higher priority are on the opp. side*)

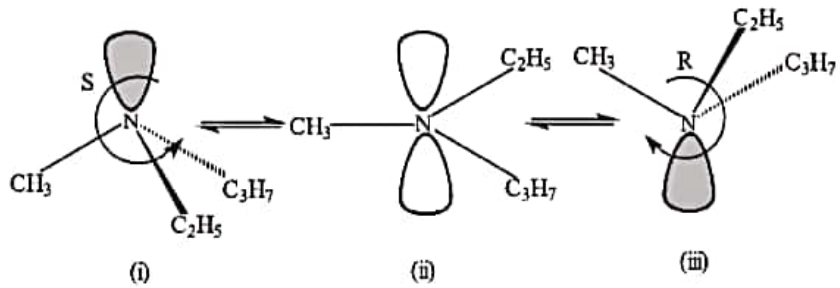
Invertomers

Stereogenic nitrogen and phosphorus.



Chiral amines

Acyclic amines of the type in which the three groups are different and the lone pair on the nitrogen is classed as a formal substituent meets all the requirements of a stereocenter. However no optical activity is observed in amines of this type, even though these are chiral. This is due to very rapid pyramidal inversion (energy barrier to inversion is small ~25 Kj $moli^{-1}$) which interconverts Enantiomers.

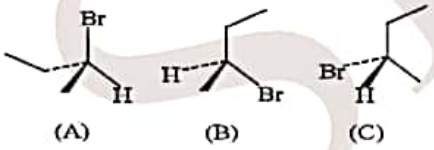


i. (S)-ethylmethylpropylamine (*Sp^3 hybridized state*)
ii. Transition state *(Sp^2 hybridized state*)
iii. (R)- ethylmethylpropylamine (*Sp^3 hybridized state*)

Inversion is slower for third-row elements. Thus phosphines (R_3p) with a high energy barrier ~150 Kj mol^{-1} and sulfoxides ($R_2S{=}O$) can be obtained in optically active form.

Homomers

A molecule may be written in two or more orientations which infact represent the same molecule but at a first sight look different. Such different orientations of the same compound (which are superimposable) are called homomeric.

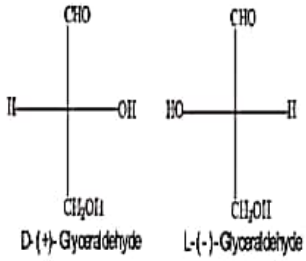


(S)-bromobutane (Homomers)

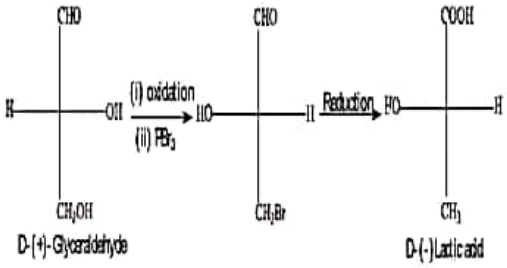
Nomenclature

D,L Nomenclature

The oldest system of nomenclature of enantiomers is D,L system. In this system the configuration of all the compounds were designated with respect to glyceraldehydes the configuration of which was taken as an arbitrary standard by Rosanoff (1906).(+) Glyceraldehyde having the OH group on the right and hydrogen on the left-CHO and-CH_2OH group being on the top and the bottom respectively was arbitrarily given the configurational symbol D. The mirror image compound of (+) Glyceraldehyde was given the configuration L.



Any compound that can be prepared from or converted into D (+) Glyceraldehyde will belong to D-series and the same is true for L-(-)-Glyceraldehyde. There is no change in configuration if a reaction doesn't involve cleavage of a bond to the chiral centre.

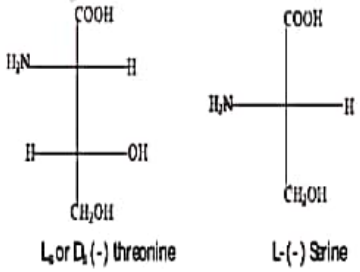


Drawbacks of D,L-nomenclature

(i) It indicated nothing more than relative configurations i.e. there was no way of deciding whether these stereochemical representation reflected reality.
(ii) D,L –nomenclature creates confusion in assigning the configurations to some compounds. Tartaric acid may be assigned L configuration with respect to bottom COOH and may be assigned D configuration with respect to top COOH.

(iii) The D,L system specifies the configurations of only one chiral atom. The configurations at the other chiral centers must be memorized.

(iv) The assignment of configurations to amino acids presented difficulties which resulted in the development of amino acid nomenclature.



R,S-nomenclature (cahn-ingold-prelog nomenclature)

An unambiguous and universally applicable system for specifying the absolute configuration of each chiral centre in a molecule was devised by Cahn et al.

***Rules*:-**

(i) The atom of lowest priority is always away from the observer. If it is toward the observer then the configuration is opposite to that we observe.

(ii) Hydrogen is the lowest priority group when lone pair is absent. When lone pair is present it is given the lowest priority.

(iii) Priorities are assigned on the basis of higher atomic number. If two atoms are isotopes of the same element the isotope of higher mass number has the highest priority.

(iv) If two atom attached to the chiral center are same the priority is decided by applying the sequence rule to the next atoms in the groups and soon.

For examples:-In 2-bromobutanetwo of the atom directly attached to the chiral center are carbon. In CH_3 the second atoms are H, H, H in C_2H_5 they are C, H, H. Since carbon has a higher atomic number so C_2H_5 is preferred over CH_3.

(v) If there is a double or triple bond, both double and triple bond atoms are considered to be duplicated or triplicated.

(vi) Priority of cis alkene is higher than trans alkene.

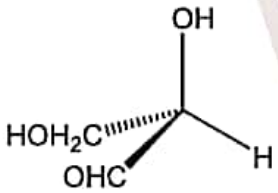
Comparison between D,L and R,S nomenclature

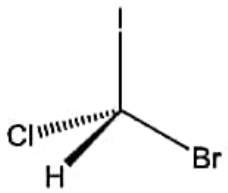
The D,L systems of nomenclature is for the nomenclature of relative configuration where as the R,S system is for the nomenclature of absolute configuration. There is no relation between these two systems of nomenclature and sign of rotation. All the D compounds may not have R and all the L compounds may not have S configurations.

Problems based on, GATE, IISC, BARC, DRDO. IIT-JAM

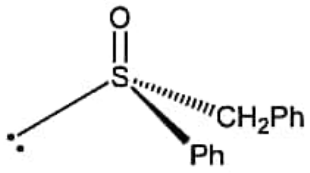
Q.1. Solve the following problems for R-S configuration.

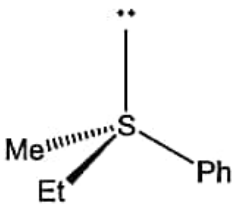
(i) (ii)



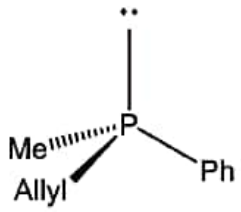


(ii) (iii)

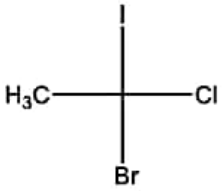




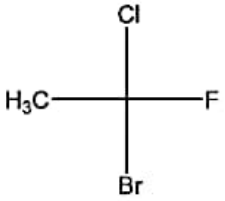
(v)



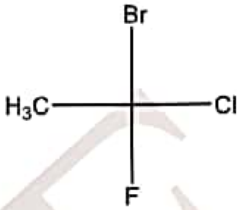
(vi)



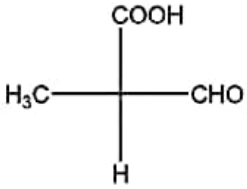
(vii)



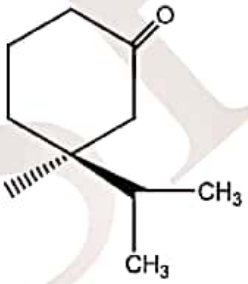
(viii)



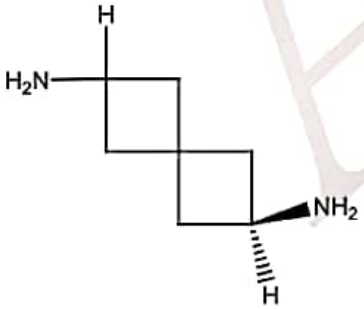
(ix)



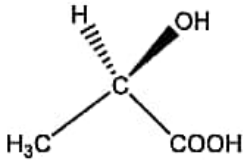
(x)



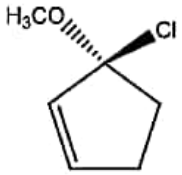
(xi)



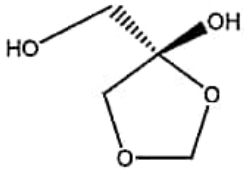
(xii)



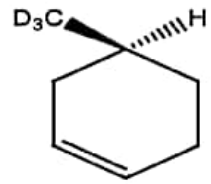
(xiii)



(xiv)

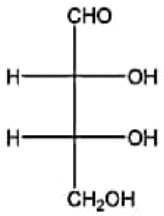


(xv)

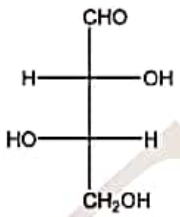


Q.2. Draw the sawhorse and Newman's formula from the given Fischer's formula.

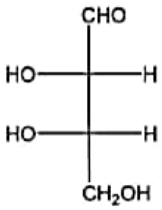
(i)



(ii)

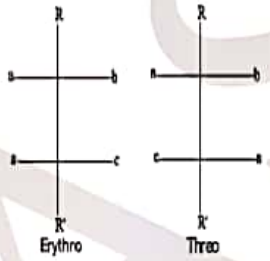


(iii)

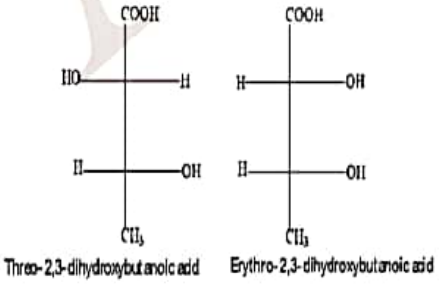


Erythro and threo nomenclature

Erythro and threo nomenclature is for naming the pairs of enantiomers of the type R-cab-cab-R'. An enantiomer of the one pair is the diastereomeric with that of the other pair. This nomenclature is based on aldotetroses, erthrose and threose which exist as two enantiomeric pairs.



The Erythro isomer has similar groups at two adjacent chiral centers on the same side of the Fischer projection, while the threo isomer has the corresponding groups on opposite sides of the Fischer projection.



In the above nomenclature

a=a
b=c or b≠c
R≠R'

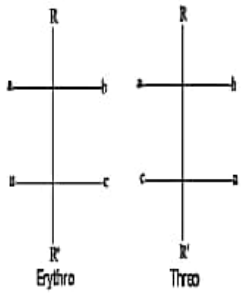
Comparison between Erythro-threo and Meso-dl pair

For Erythro and threo nomenclature.

X must be equal to X

Y may or may not be equal to Y.

A should not be equal to B.

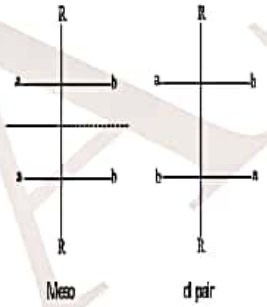


For Meso and dl pair

X must be equal to X

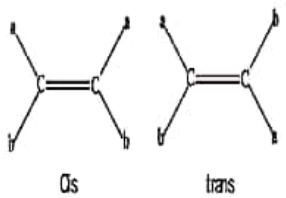
Y must be equal to Y

A must be equal to A



Cis-trans nomenclature for geometrical isomers

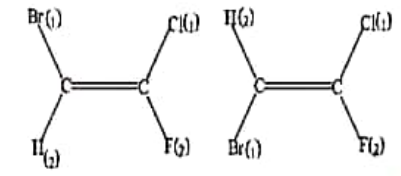
Compounds of the type **abC=Cab** can exist in the following two forms due to frozen rotation about C-C bond.

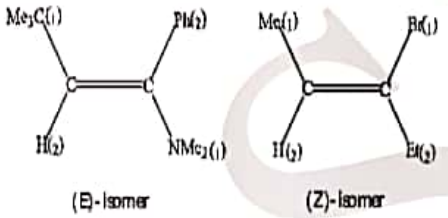


The isomers in which the identical groups are on the same side of the double bond is called Cis and the isomer in which the identical groups are on the opposite sides is called trans. This type of nomenclature can use only when two or three types of ligands are attached around the double bond._

E-Z nomenclature for geometrical isomers

This nomenclature of geometric isomers is more general and can be applied to all the compounds. E-Z is based on the cahn-ingold-prelog system. In the E-Z system the group of highest priority on each carbon atom is identified by using the sequence rules. If highest priority groups are on the same side of the double bond, the configuration is Z (zusammen=together) and if they are on the opposite sides the configuration is (entegegen=opposite).





Optically activity in the absence of a chiral carbon

There are many cases where the Chirality is not because of the presence of one or more chiral centers, but it is because of the presence of other elements of Chirality.

Molecules belonging to following category are chiral without chiral

(i) Allenes

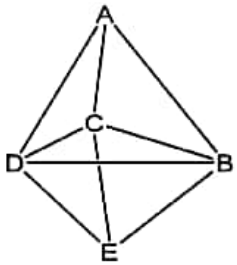
(ii) Spiranes

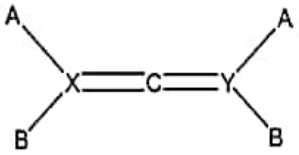
(iii) Biphenyls

(iv) Cyclohexanes

Optical activity due to a chiral axis:-

When four ligands attached to the central atom C are located on the corners of a regular tetrahedron, C is a chiral center of the molecule and is replaced by linear grouping of e.g. C-C or C=C=C. The tetrahedron becomes elongated i.e. extended along the axis of grouping to produce a chiral axis XY.

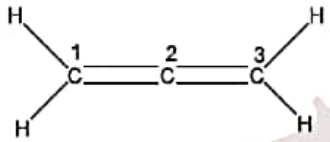




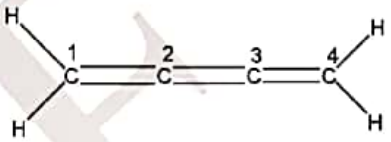
The minimum condition for Chirality of a elongated tetrahedron is that **A** should be different from **B**. i.e. pair of ligands at X end of the axis and pair of ligands at Y end of the axis are each constituted by different ligands.

Stereochemistry of Allenes:-

When three or more adjacent carbon atoms in a molecule are bonded by double bonds, the compound is called cumulene or is said to have cumulative double bonds. Allene is the simplest cumulene



C1 & C2 are perpendicular

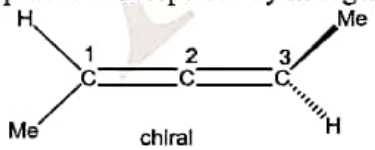


C1 & C4 are parallel

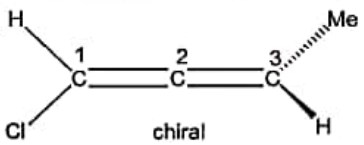
The spatial arrangement of the cumulative double bond in allene is such that its terminal methylene groups are ⊥ to each other. This is easily understandable because the two terminal carbon atoms in allene are in Sp^2 and the central carbon atom is in Sp hybrid state, thus central carbon forms two π bonds which are ⊥ to each other.

Thus allenes of the type:- abC=C=Cab (a≠b) are chiral.

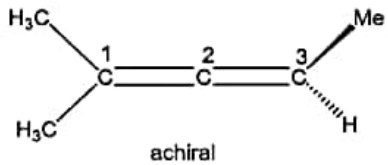
- In allenes if double bonds are even there are two ⊥ planes. If there is no plane of symmetry than molecule is chiral. If there is any plane of symmetry (then the molecule is achiral).
- If cumulene has odd no of double bonds, then it is achiral due to molecular plane of symmetry or it shows geometrical isomerism.
- A 2-fold rotational axis is present in allene when a=a and b=b
- Since the replacement of a double bond in allene by a ring does not alter the basic geometry of the molecule.
- Compound where Sp^2 carbon is replaced by nitrogen have also been obtained as enantiomers.



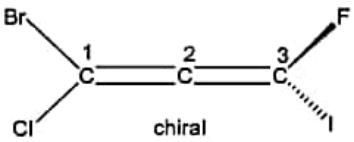
chiral



chiral

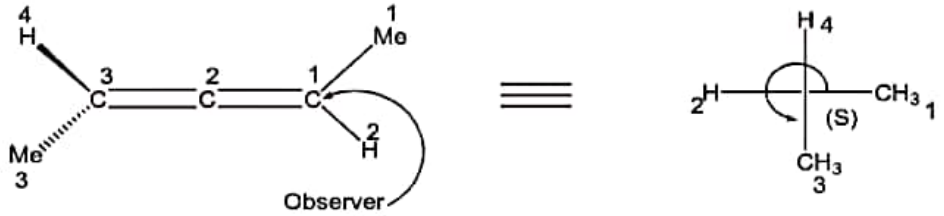


achiral



chiral

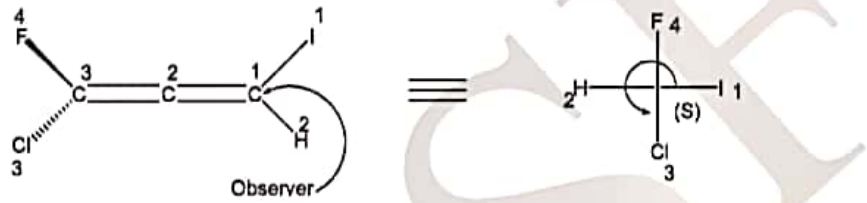
R-S configuration for allenes



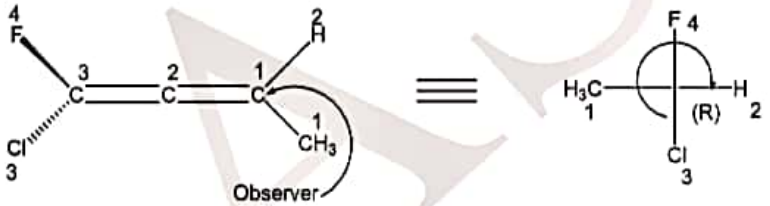
Molecule is viewed from the point which is in plane. Substituents at this site are given priority 1 and 2 according to CIP Rule and thus other end is cited in the same way. Above shown figure shows how to assign configuration to allenes.

Problems:-

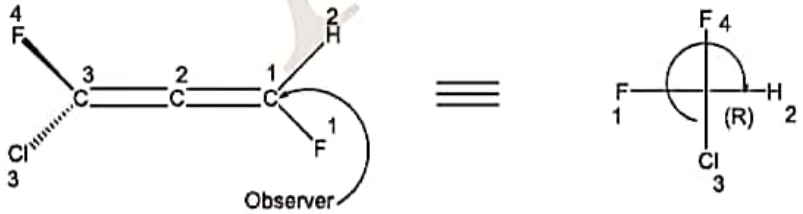
(i)



(ii)

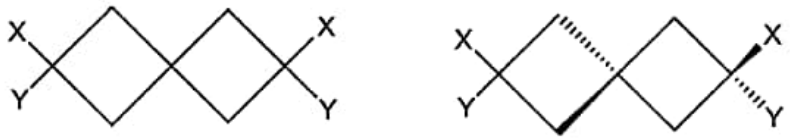


(iii)



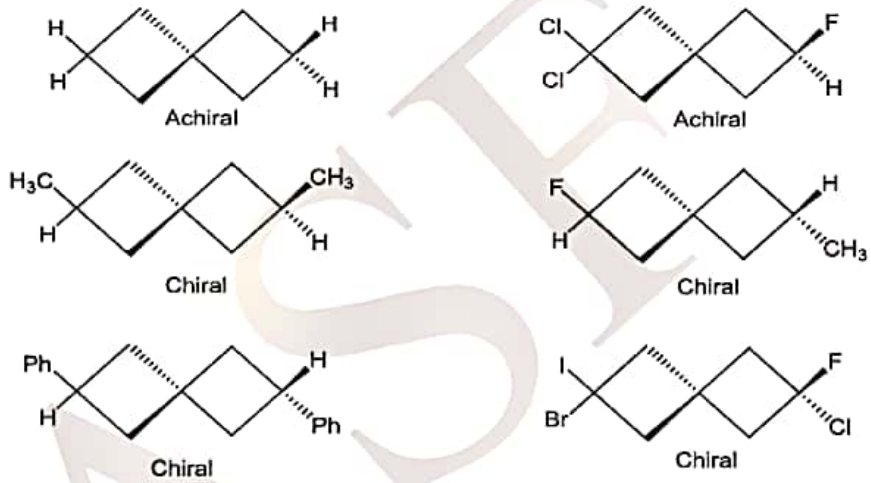
Stereochemistry of Spirane :-

If both the double bonds in allenes are replaced by a ring systems, the resulting molecules are known as spiranes or Spiro compounds.

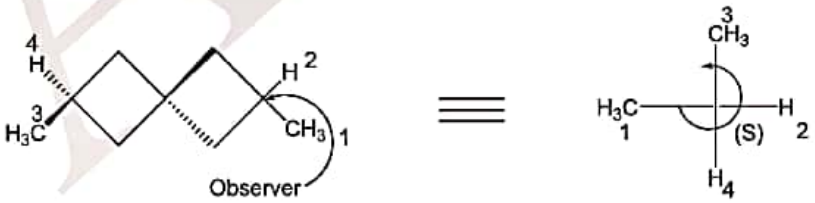


For Chirality X≠Y

If X=Y – plane of symmetry is present and molecule becomes achiral.



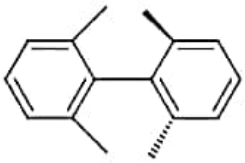
R-S configuration in case of spiranes:-



Molecule is viewed from the point which is in plane. Substituents at this site are given priority 1 and 2 according to CIP Rule and thus other end is cited in the same way. Above shown figure shows how to assign configuration to spiranes.

Stereochemistry of biphenyls:-

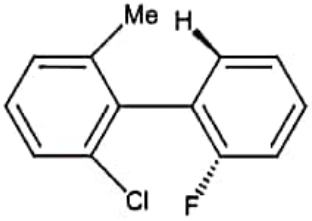
In the crystals, both benzene rings lie in the same plane. However, in solution and vapour phase the two rings are twisted with respect to each other by an angle 45^0 due to steric interactions between the 2,2' and 6,6' pairs of hydrogen's. These interactions effects are further enhanced by ortho substituent's larger than hydrogen so that

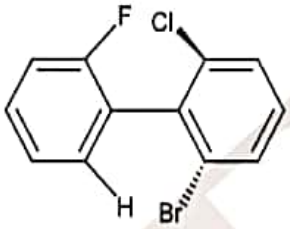


The rotation about the bond linking the two phenyl rings doesn't occur due to steric strain (hindrance) between the bulky ortho substituent's.

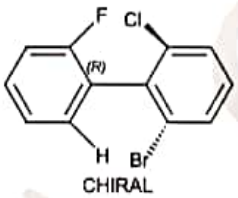
Biphenyls show enantiomerism when following two conditions are satisfied

- Each ring must be unsymmetrically substituted.

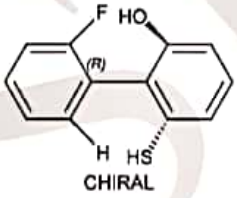




- Both rings must be substituted in ortho positions (minimum number of substituent's should be two, one substituent in each ring) and the substituent must have a large size.



CHIRAL



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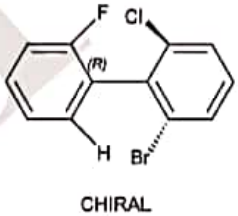
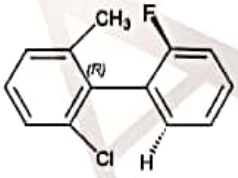


CHIRAL



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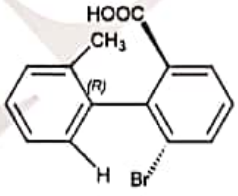
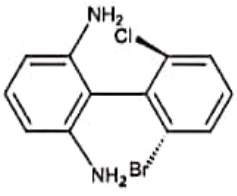
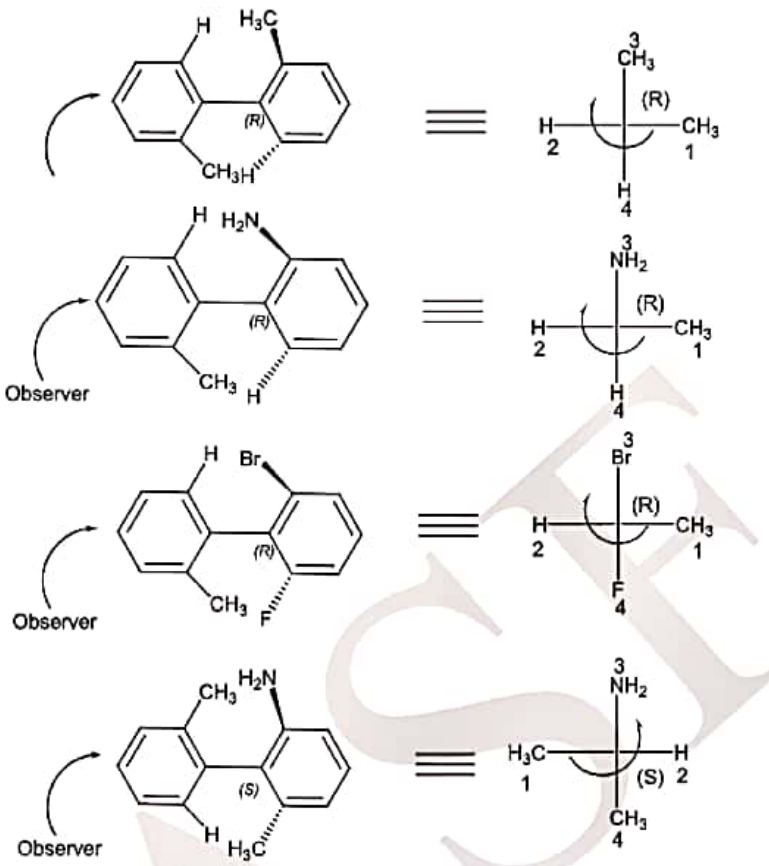


CHIRAL



ACHIRAL

R-S configuration of biphenyls



Conformational analysis

The different spatial arrangements of atoms in a molecule which are readily interconvertible by rotation about single bonds are called conformations; if not conformation. The term conformation and configuration are related to energy barrier for Interconversion of different spatial arrangements of atoms in a molecule.

(i) For conformation energy barrier for conversion of different spatial arrangements is >0.6 and <16 kcal/mole
(ii) For configuration energy barrier for conversion of different spatial arrangements is ≥16 kcal/mole.

The study if the existence of preferred conformations in a molecules and the relating of physical and chemical properties of a molecule to its preferred conformation is known as conformational analysis.

Conformation of acyclic systems

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

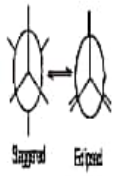
Eclipsed conformation:-A conformation with a 0° torsional angle is known as eclipsed conformation.

Conformation of ethane

When an ethane molecule rotates about its carbon-carbon single bond, two extreme conformations can result

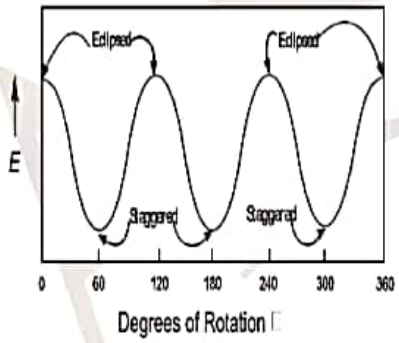
1. Staggered conformation
2. Eclipsed conformation

An infinite number of conformations between these two conformations are also possible.



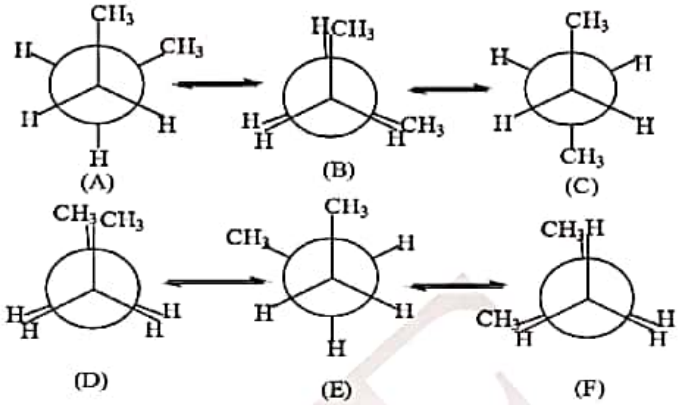
The electron in a carbon-Hydrogen bond will repel the electrons in another Carbon-hydrogen bond if the bonds get too close to each other. Therefore, the staggered conformation is the most stable conformation because the carbon-Hydrogen bonds are as far away from each other as possible. The eclipsed conformation is the least stable because the carbon Hydrogen bonds are closest. The distance between hydrogen nuclei is 2.55 Å in staggered and 2.29 Å in eclipsed conformation

The rotational energy barrier in ethane is 2.9 kcal. The extra energy of the eclipsed conformation is due to the repulsion felt by bonding electrons of one substituent as they pass close to the bonding electrons of the other substituent. The energy barrier for ethane is 2.9 kcal which is more than the free energy for rotation i.e. ~0.6 kcal and less than restricted rotation i.e. 16 kcal at room temperature. So at the room temperature we can't get the conformation of ethane.



Conformation of n-butane:-

Butane may be treated as a derivative of ethane where one hydrogen on each carbon is replaced by a methyl group. The conformation of butane will be symmetrical only if the rotation will be about C_2-C_3 bond.



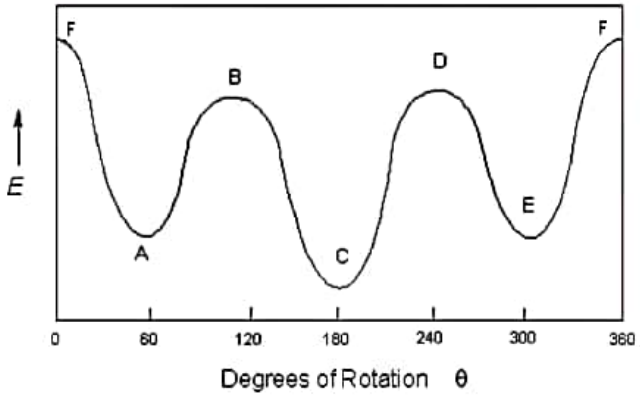
Butane has three conformations which are staggered (A, C, E). (C) in which the two methyl groups are as far apart as possible is more stable than the other two staggered conformations (A) and (E). The most stable of the staggered is called anti conformation and other two conformations are called gauche conformation.

In the anti conformation the larger substituents are opposite to each other, in the gauche conformer, they are adjacent. The two gauche conformers have the same energy barrier but each is 0.9 kcal/mole less stable than the anti conformation.

Anti and gauche conformers do not have the same energy because of steric strain. Steric strain is the strain put on a molecule when its atoms or groups are large in size and due to this they are too close to each other, which cause repulsion between the atoms or groups.

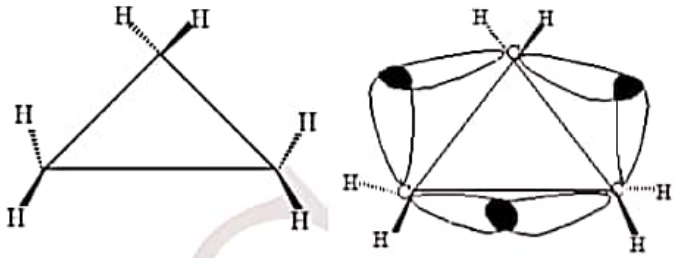
All other eclipsed conformation has torsional and steric strain. The (F) conformation is much unstable because the two methyl groups eclipsed each other and cause much steric strain.

Anti(C) > **gauche** (A, E) > **eclipsed** (B, D) > **fully eclipsed** (f).



Cyclopropanes

1. The molecule of cyclopropane is planar
2. Its bond angle is 60°(C-C-C).
3. Bent bond between C-C atoms.
4. It has been suggested that in cyclopropane , carbon uses Sp^3 orbital's for (C-H) (which are short and stronger) but it uses orbital's having greater p-character for the formation of C-C bonds (Sp^4 to Sp^5)
5. The greater p-character (Sp^4 to Sp^5) makes these orbital's larger in size and consequently the C-C bond in cyclopropane is longer than the C-H bond.
6. The orbital's (used for C-C bonds) are capable of bending and their overlap gives bent bonds (also called banana bond) the bending of orbital's permits their weak overlap only thereby making the ring unstable.
7. Because of bending of orbital's a considerable part of the overlapping orbitals is protruded outside the ring and hence becomes susceptible to the attack of electrophile reagents.

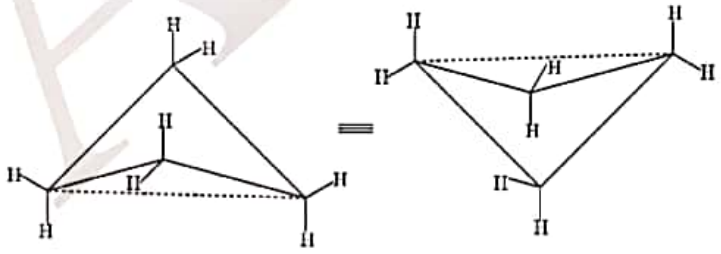


Cyclobutane

1. Bond angle 90° (less angular strain as compare to cyclopropane).

2. Four strained bonds are present rather than three.

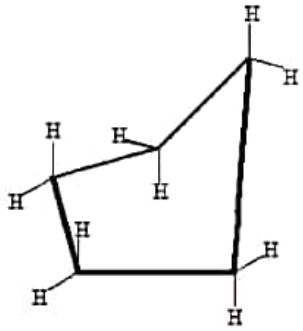
3. Eight pairs of eclipsed hydrogen's are rather than six in cyclopropane.So, total ring strain in the two compounds is almost the same.



Folding of a methylene group in Cyclobutane.

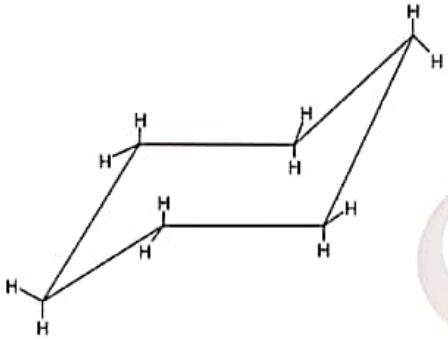
Cyclopentane

1.Planar Cyclopentane ring, the interior C-C-C bond angle of 108° approaches the normal tetrahedral angle of 109°28'. So, expected free from angle strain.
2. All hydrogen's are eclipsed. So, there is a torsional strain.
Actually, Cyclopentane exists in "Envelope" shape. By doing this the ring is relieved of considerable torsional strain at the expense of a little angle strain.



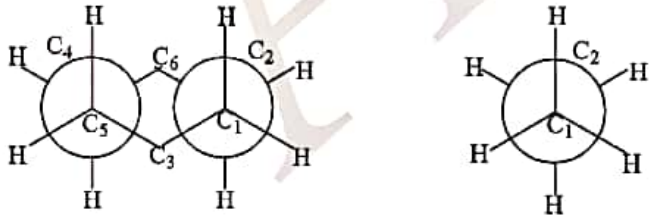
Cyclohexane and its derivative

A. Chair conformation of cyclohexane



This conformation of cyclohexane resembles a chair and hence is called chair form.

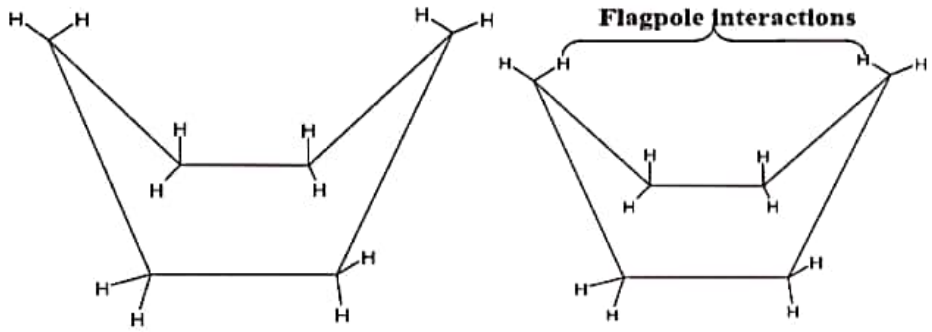
1. This conformation is free from angle strain.
2. The close resemblance of the chair conformation of cyclohexane with the staggered conformation of ethane can be well appreciated from the following diagrams..



Resemblance between chair conformation of cyclohexane and ethane in staggered form.

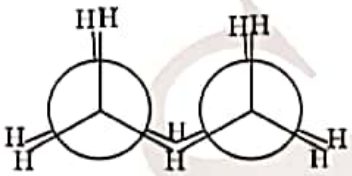
1. The chair form of cyclohexane represents the staggered conformation and hence it is free from torsional strain.
2. The chair form, therefore lies at the energy minimum and is the most stable conformation of cyclohexane and of almost all its derivatives.

B. Boat conformation of cyclohexane



If we flip up the lower end of the model of the chair form we will get the boat conformation

1. It is obvious that these results from rotation about single bonds, hence we are indeed dealing with the conformation of cyclohexane.
2. If we sight the model of the boat conformation from the front side, we find the hydrogen's on two sets of C-C bonds in perfectly eclipsed conformation



Boat conformation of cyclohexane

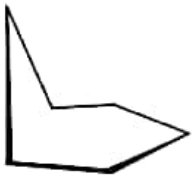
1. The boat conformation of cyclohexane is expected to have considerable torsional strain ~ approximately equivalent to the two eclipsed ethane molecules (2*3=6 kcal/mole). The result however indicates the boat conformation to be less stable than the chair form by about 7.1 kcal/mole. It leads to the conclusion that beside torsional strain, some other factor is also contributing to the boat conformation.
2. If we look closely at the model of the boat conformation from the front side, it is found that the two hydrogen's are very close to each other. These hydrogen's are called flagpole hydrogen's. It has been found that the flagpole hydrogen's lie only 1.83 A^0 apart, considerably closer than the sum of their Vander Waals radii. This leads to the development of Vander Waals repulsion between two flagpole hydrogen's. The combined effects of torsional strain and Vander walls repulsion between flagpole hydrogen's make the boat conformation considerably less stable then the chair conformation.

C. Twist boat conformation of cyclohexane

1. If we twist the two flagpole hydrogen's in the model of the boat conformation of cyclohexane in the opposite direction a new conformation results, which is known as twist-boat conformation.

2. The hydrogen's on two sets of C-C bonds are not in perfectly eclipsed positions, which relieves the torsional-strain considerably. The distance between flagpole hydrogen's also increases, as a result of which the Vander Waals repulsion between them decreases. The twist boat conformation is therefore more stable than the boat conformation.

D. Half-chair conformation of cyclohexane



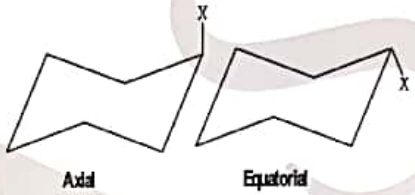
1. If we flip the lower end of chair form then new conformation results known as half chair. In it H atoms of adjacent carbon atoms are fully eclipsed.

2. In half chair there is angular strain. So , half chair conformation is less stable.

***Stability order*:-**

Chair > Half chair > Twist boat > Boat

Conformational free energy



The two diastereomeric chair forms are of unequal energy and so are differently populated, the equilibrium constant K being given by the equation:-

$\Delta G^0 = -RT \ln K$

ΔG^0 is the difference of free energy between the Equatorial and axial conformers and $-\Delta G^0$ is known as conformational free energy of the substituent. (Sometimes known as A value).

It determines the equatorial preference of the substituent in the substituted cyclohexane. The conformational free energies ($-\Delta G^0$ values) of a number of common substituent are given below-

Substituent	$-\Delta G^0$	Substituent	$-\Delta G^0$
F	0.63	COOH	5.65
Cl	1.80	COOMe	5.32
Br	1.59	CH_3	7.50
I	1.80	C_2H_5	8.10
CN	0.71	$CHMe_2$	9.00
OH	2.18[a],3.65[b]	CMe_3	20.00
OCH_3	2.51	C_6H_5	12.60
OC_2H_5	2.96		

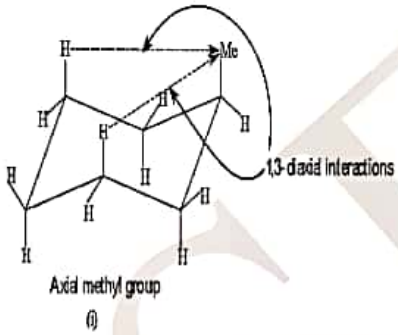
$OCOCH_3$	2.51		
NH_2	5.03[a],6.70[b]		
No_2	4.60		

*a=aprotic solvent

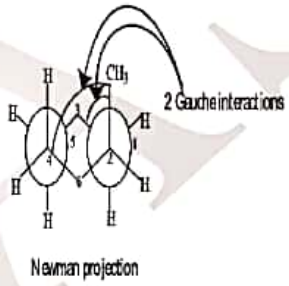
b= protic solvent.

Monosubstituted cyclohexane:-

1.When methyl group is axial it is sufficiently closer to the Syn axial Hydrogen's to undergo 1,3-diaxial interactions and is repelled by them (This is another example of trans-annular strain)

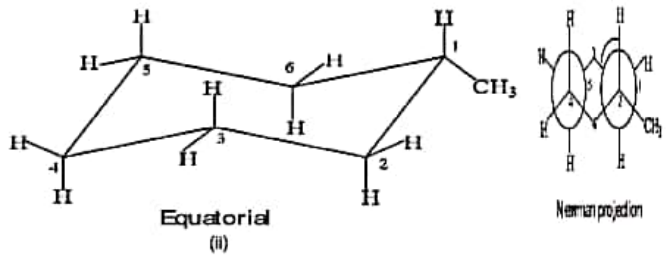


2.This 1, 3-diaxial interaction is similar to that in gauche conformation of butane. The axial methyl group in methyl cyclohexane is thus gauche to two ring carbons and when in equatorial positions it is anti to same nuclei.



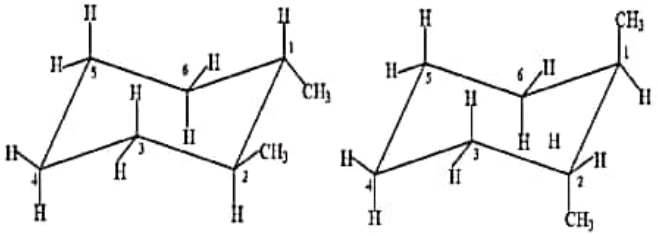
3.When methyl group is equatorial, there are no 1, 3-diaxial interaction.
4.Equatorial methyl group don't show any gauche butane like interactions.

Monosubstituted cyclohexane exists in two non-equivalent diastereomeric chair conformations.

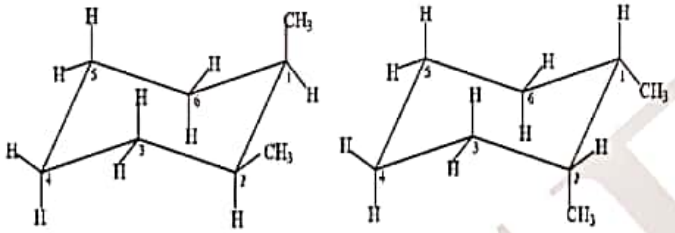


(I) is less stable than (ii) because of the presence of 1, 3-diaxial interactions.

Disubstituted cyclohexane



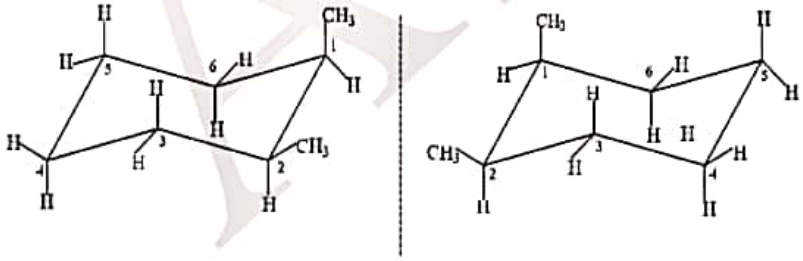
(A) Transisomers (B)



(C) Cisisomers (D)

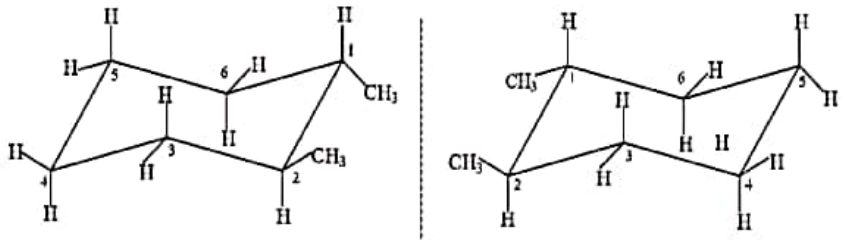
***Stability*:- A > C=D > B**

Enantiomerism in 1, 2-dimethyl cyclohexane: - In 1, 2-dimethylcyclohexane two chiral centers are present and hence can have more than four stereoisomers but actually it has only three. The Cis-1, 2-dimethylcyclohexane molecule is not superimposable on its mirror image but the molecule and its mirror image are readily interconvertible by flipping one chair conformation into another. Hence these are conformational enantiomers. There is a rapid Interconversion at room temperature.



Axial-equatorial cis-1, 2-dimethylcyclohexane

The trans-1, 2-dimethylcyclohexane molecule and its mirror image are not superimposable, hence constitute an enantiomeric pair. These are not interconvertible by flipping one chair form into another. On flipping the equatorial is converted into axial. The two isomers are known as configurational isomers. Each isomer is optically active and mixture is resolvable.



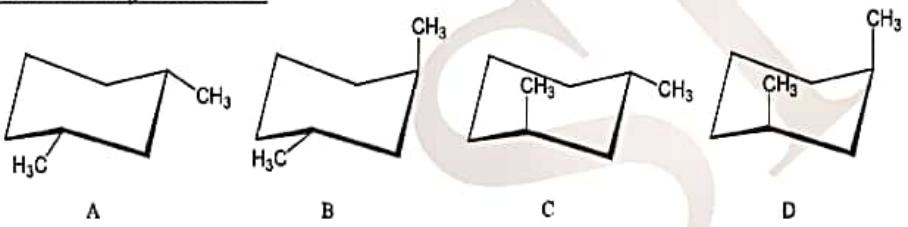
Trans -1, 2-dimethylcyclohexane

In summary 1, 2-dimethylcyclohexane exists as a pair of Diastereomers, the Cis and trans isomers. The Cis isomer exists as a pair of conformational enantiomer, whereas the trans isomer exists as a pair of configuration Diastereomers.

Chirality and optically activity

All 1, 2-disubstitutedcyclohexanes are achiral due to presence of plane of symmetry and two fold rotational axis hence all are optically inactive.

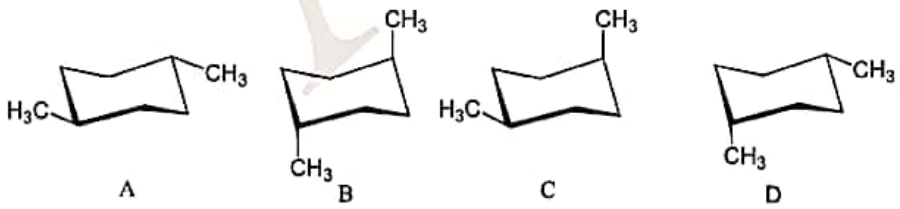
1, 3-disubstitutedcyclohexane



Stability: *- A>C=B>D*

1, 3-dimethylcyclohexane has two chiral centers, and can have four stereoisomers (2^2=4). Actually there are only three, the cis-1, 3-dimethylcyclohexane has a plane of symmetry and is achiral. Trans isomer has a twofold rotational axis hence it is also achiral. If different substituents are present all will be chiral.

1, 4-disubstututedcyclohexane



Stability: - A > C = D > B

In 1, 4-dimethylcyclohexane it does not have any chiral centre. It exists as Cis and Trans Diastereomers. Neither Cis nor Trans form is chiral because both have a plane of symmetry.

Chirality:- All are chiral due to the plane of symmetry

If different substituent's then all 1, 4-disubstituted will be chiral.

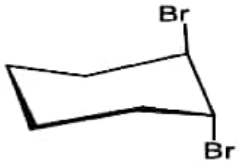
Factors affecting stability of cyclohexane derivatives

1. Steric strain **α** *1/ stability*

2. Torisonal strain **α** *1/ stability*

3. Dipole moment:- If μ> 0 less stable, If μ=0 more stable

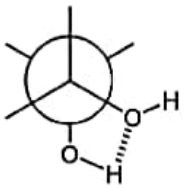
If electronegative group is present then 1,2-diaxial is more stable than 1,2-diequatorial due to dipole-dipole repulsions.



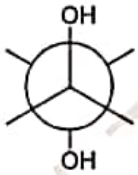
μ=0 more stable

μ> 0 less stable

4. Hydrogen bonding:- *In cases where hydrogen bonding is possible, gauche form is more stable than the staggered form as in case of ethylene glycol.*



Hydrogen bonding (more stable)



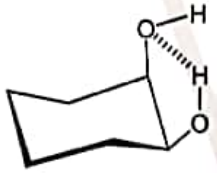
No Hydrogen bonding (less stable)

Stable conformations of cyclohexandiols

A. 1,4-diol :-

Stable in boat form H-bonding possible

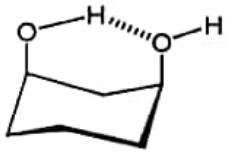
B. 1,2-diols:-



Most stable preferable H-bonding

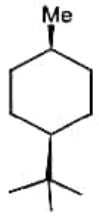
Less stable due to steric repulsion

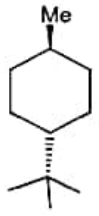
C. 1,3-diols:-

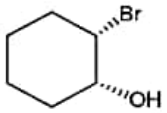


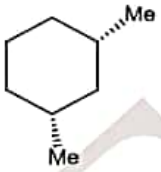
Most stable due to hydrogen bonding

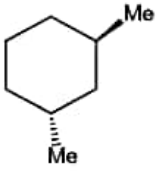
Problem:- *Draw the most stable chair conformation of following cyclohexanes.*

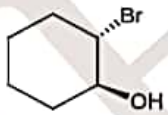
(i) 

(ii) 

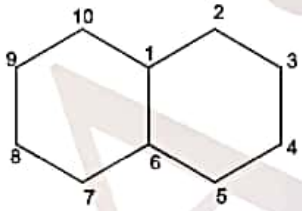
(iii) 

(iv) 

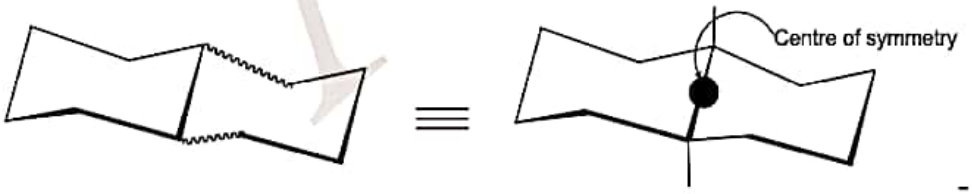
(v) 

(vi) 

Decalins- bicyclo[4,4,0]decane



Trans- decalin



Trans decalin is obtained by fusion between two equatorial bonds of cyclohexanes with 4 carbon system. In this two hydrogen atoms on the bridge head carbon are opposite to each other. Achiral, more stable due to diequatorial type structure.

Cis-decalin

When one axial and one equatorial bond of cyclohexanes ring are used for fusing 4 carbon chain system a decalin molecule results which has two hydrogen on the same side of bridgehead carbon.

Less stable, Non-bonding interactions

(i) Less stable due to non-bonding interactions

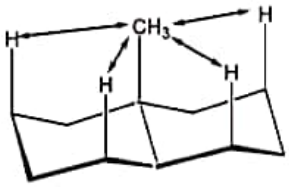
(ii) No plane of symmetry

(iii) Molecule is chiral

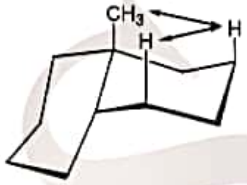
Cis- and trans- isomers are conformational isomers. Energy of trans decalin is 25 kj/mol lesser than cis decalins

Stability

Trans decalins are generally more stable. If 1 position of decalin is substituted by Me- group then stability is reversed



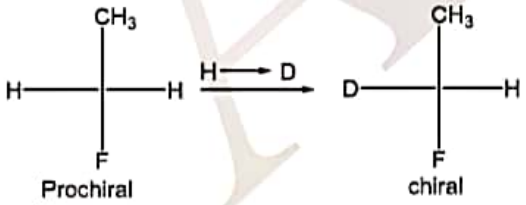
4-diaxial Interactions ,less stable



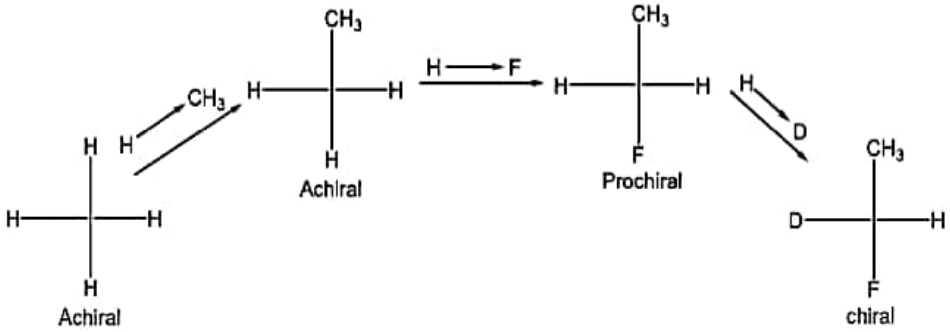
2-diaxial Interactions, more stable

Prochirality :-

Before chirality changing one of two same group by another group except two groups present, molecule is said to have prochirality or molecule is prochiral.



Prochiral chiral

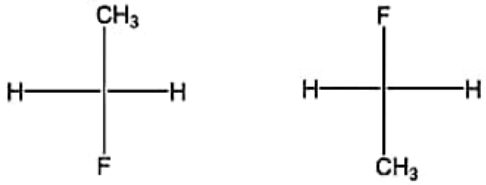


Achiral Achiral Prochiral chiral

A molecule in which carbon is joined by different types of groups called prochiral molecule.

Homomer :-

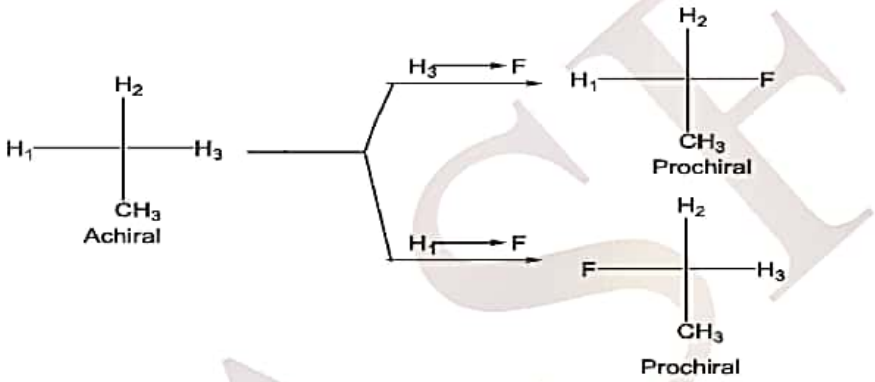
The molecule which are same but appears different are called homomers.



Homomers are generally prochiral molecules. Homomers are equivalent structure of the same molecule.

Homotopic ligands:-

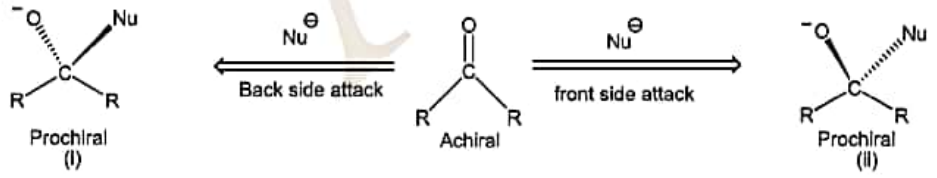
Two ligands in an achiral molecules if on replacement yields homomer then they are termed as homotopic ligands.



In the above shown figure H_1, H_2, H_3 are homotopic ligands. These ligands are exchanged with the help of simple rotational axis of any fold.

Homotopic faces:-

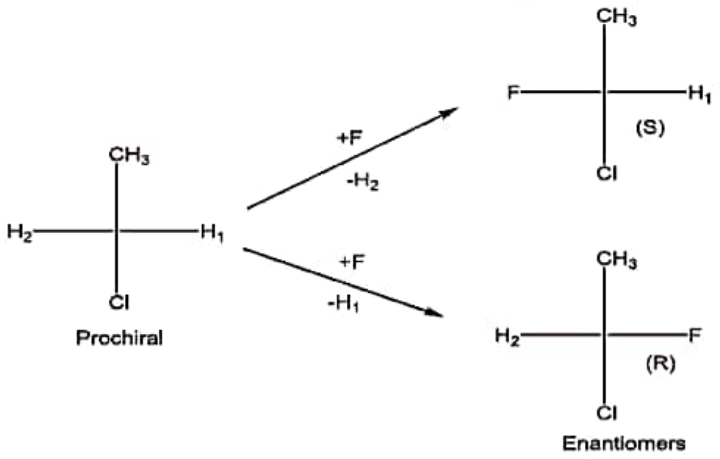
Two faces in an achiral molecule are homotopic faces if attack from each side yields homomer.



In the above shown figure i & ii are homomers so both the faces of the given compound are homotopic faces .

Enantiotopic ligands:-

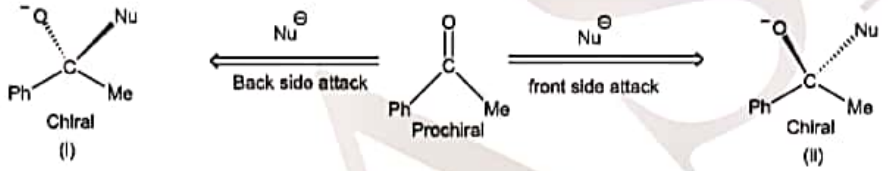
In a prochiral molecule two ligands which are same are called enantiotopic ligands if an alternative interchange of them yields enantiotopic compounds / enantiomers



H_1 and H_2 are enantiotopic ligands. On exchanging these enantiotopic ligands with F it results into the conversion of prochiral molecule into chiral molecules which are non-superimposable mirror images of each other and hence called enantiomers. In this same molecule the hydrogen atoms of methyl group are homotopic because on replacement of each hydrogen with other group we get the same configuration molecule. *These ligands are exchanged with plane of symmetry.*

Enantiotopic faces:-

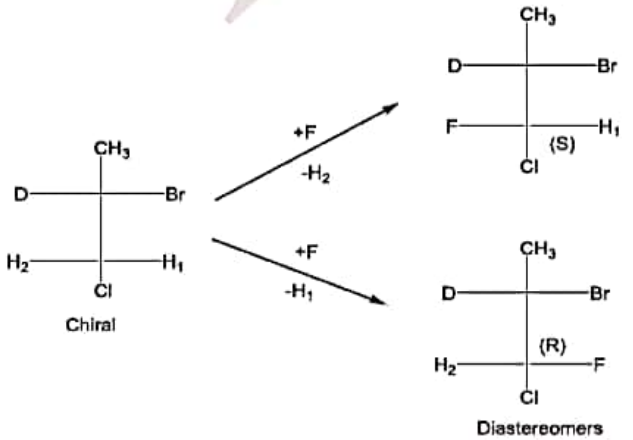
In an achiral molecule if two faces on attack by any group (nucleophile) yields enantiomers then the faces are called enantiotopic faces.



In the above shown figure i & ii are enantiomers so both the faces of the given compound are enantiotopic faces.

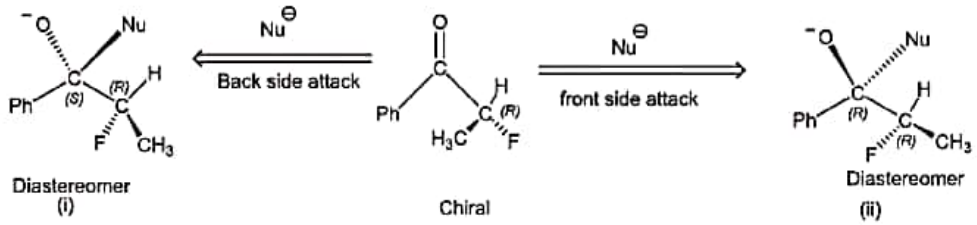
Diastereotopic ligands:-

Two ligands are diastereotopic if alternative replacement of them yields diastereomers. These ligands cant be exchanged by any type of symmetry element



Diastereotopic faces:-

Two faces in a molecule are diastereotopic if attack from these sites yields diastereomers.

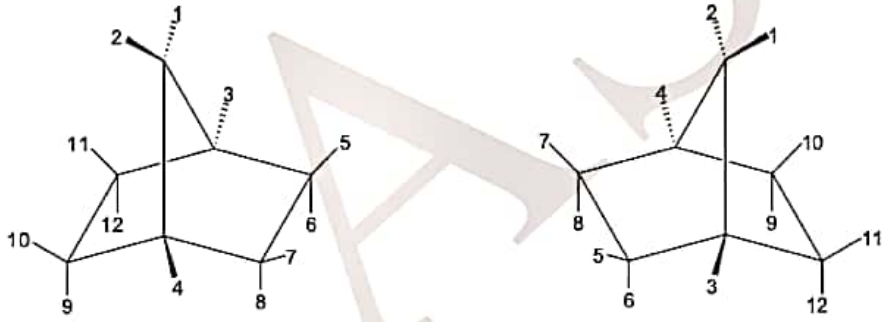


In the above shown figure i & ii are diastereomers so both the faces of the given compound are diastereotopic faces.

Quick tips for exam point of view.

Prochirality relations:-

- Groups or ligands which are interchangeable with any type of simple axis of rotation are homotopic groups or ligands.
- Groups or ligands which are interchangeable with the help of centre of inversion or effected by plane of symmetry are enantiotopic ligands
- Groups or ligands which are not realted with any type of symmetry elements are called diastereotopic ligands.



This is a prochiral molecule. On performing a C_2 operation on the first molecule we will get the second one. Now check for the relationship among groups.

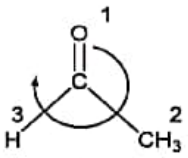
5-6,7-8,9-10,11-12 - Diastereotopic

5-10,6-9,8-12,7-11,1-2,3-4 – Homotopic

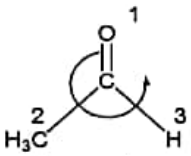
10-11,9-12,8-6,7-5 – Enantiotopic

Nomenclature of faces and ligands

Faces are given Re or Si on the basis of the rules of CIP. Same rules are applied.



clockwise rotation- Re face



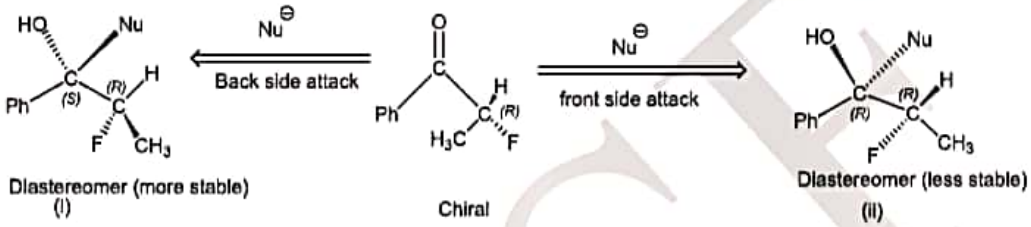
Anti-clockwise rotation- Si face

In the same way we can solve other problems related with nomenclature.

Cram's rule:-

During certain additions to the carbon-oxygen double bond of aldehydes and ketones containing an asymmetric α carbon cram's rule predicts diastereoselectivity i.e. which diastereomer will predominate.

According to this rule the incoming nucleophilic group preferentially attacks on the side of the plane containing the small group.

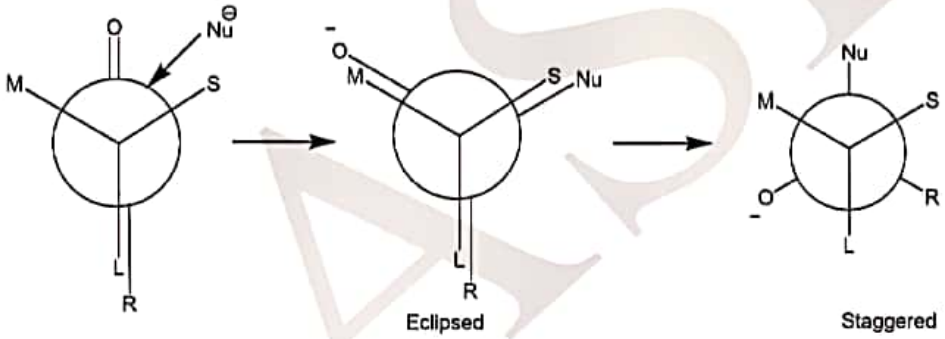


Diastereomer (more stable) (I)

Chiral

Diastereomer (less stable) (II)

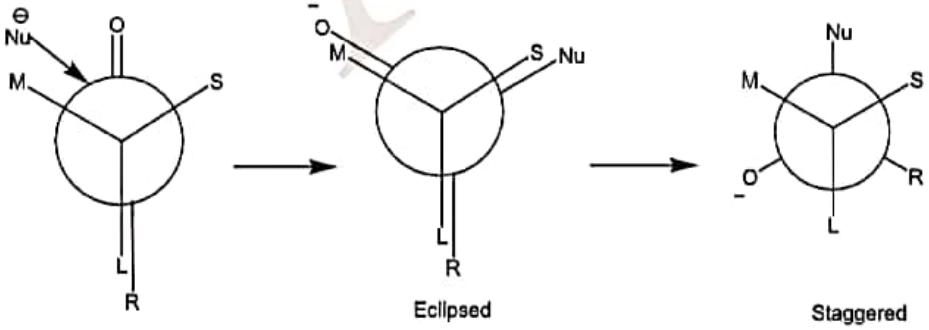
A.



Eclipsed

Staggered

B.



Eclipsed

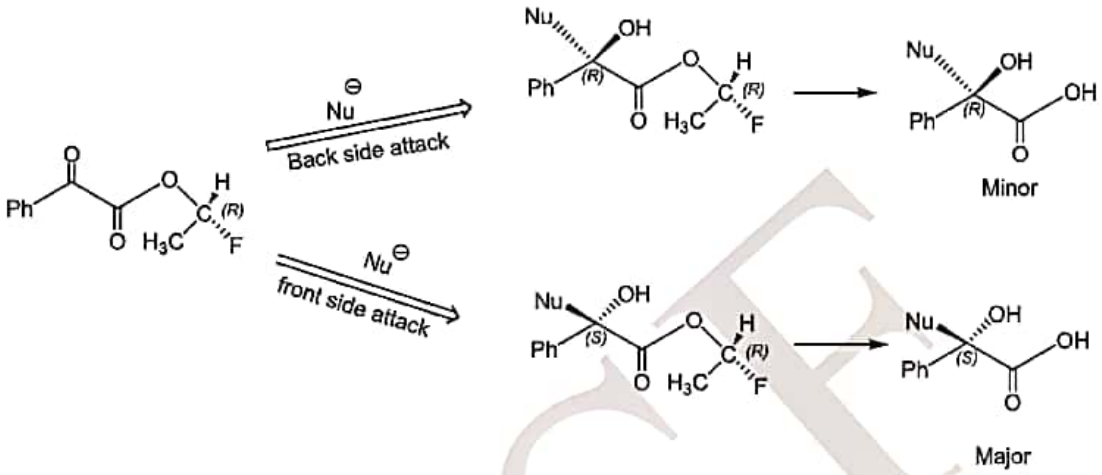
Staggered

By this rule, it can be predicted that the reaction(A) should preffered over (B).

When the size of incoming group increases the extent of diastereoselectivity also increases. As in the above shown example if we increases the size of incoming group i.e. nucleophile from Me<Et<Ph then ratio of the major product formed is also increased.

Prelog rule:-

This rule is applied for α-keto esters. This reaction is enantioselective as one enantiomer is preffered which is formed by attack on α-carbonyl carbon from less hindered site.

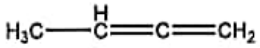


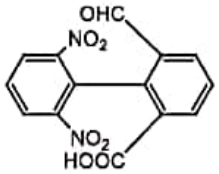
From the above reaction two compounds are formed which are non-superimposable mirror images of each other i.e. enantiomers. According to this rule incoming nucleophile will attack from that side of the plane which contains group of lowest priority.

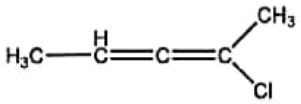
Problems based on, GATE, IISC, BARC, TIFR, IIT-JAM

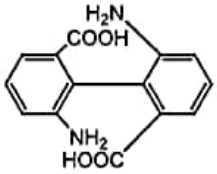
Q.1. Which of the following is/are chiral?

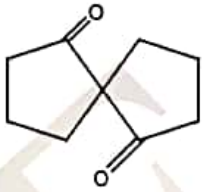
(a) 

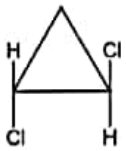
(b) 

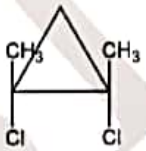
(c) 

(d) 

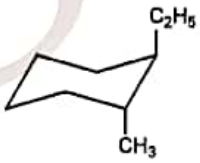
(e) 

(f) 

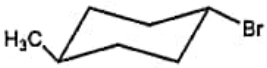
(g) 

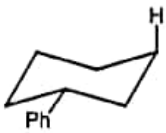
(h) 

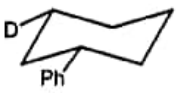
(i) 

(j) 

(k) 

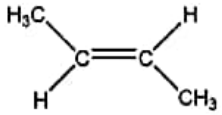
(l) 

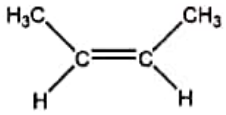
(m) 

(n) 

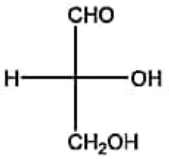
Q.2. Classify the following as Homomers, Enantiomers and Diastereomers.

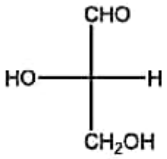
(a)



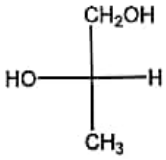


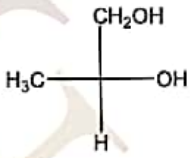
(b)



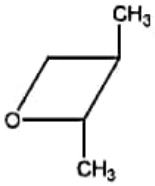


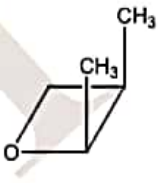
(c)



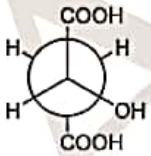


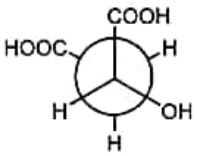
(d)



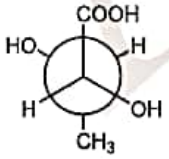


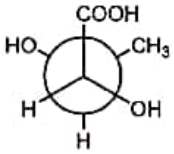
(e)



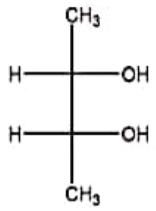


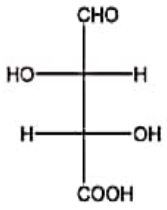
(f)

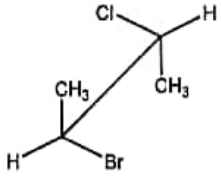


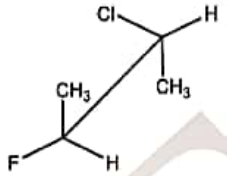


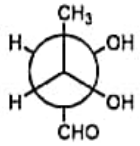
Q.3. Classify the following as Threo, Meso and Erythro compounds.

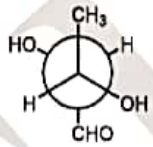
(a) 

(b) 

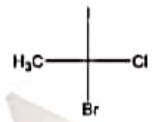
(c) 

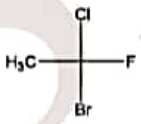
(d) 

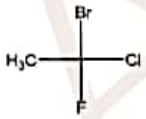
(e) 

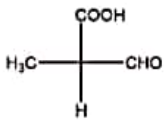
(f) 

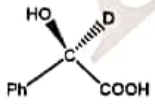
Q.4. Assign (R) & (S) for the following:

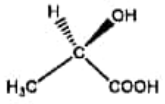
(i) 

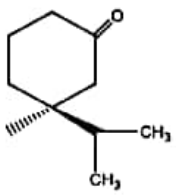
(ii) 

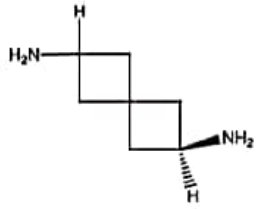
(iii) 

(iv) 

(v) 

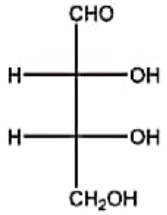
(vi) 

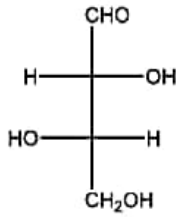
(vii) 

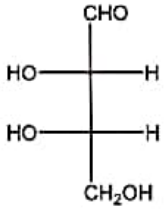
(viii) 

Q.5. Give the Fischer projection for (R) and (S)-2-bromopentane and convert them into "wedge and dotted line representation".

Q.6. Draw the sawhorse and Newman's formula from the given Fischer's formula.

(i) 

(ii) 

(iii) 

Q.7.Draw the preferred conformation of following:-

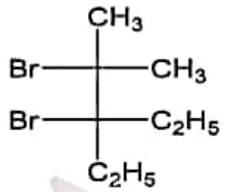
(a) Cis-1,3-cyclohexanediol

(b) 1,4-cyclohexanediol

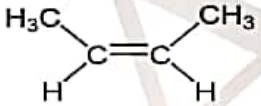
(c) 1,2-dibromoethane

(d) trans-1,4-ditertiarybutyl cyclohexane

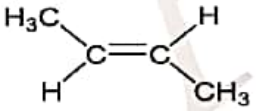
Q.8. Write down the products (A), (B), (C), (D), (E), (F), (G).

(i) 

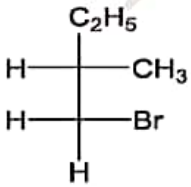
NaI / Acetone 'A'

(ii) 

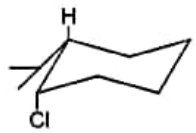
Br_2 'B'

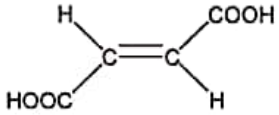
(iii) 

Br_2 'C'

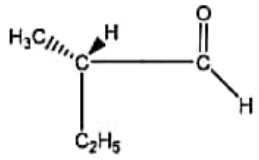
(iv) 

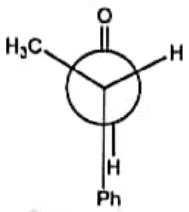
Alc. KOH 'D'

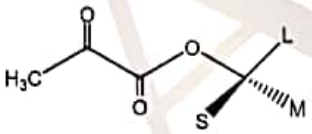
(v)  Alc. NaOH 'E' + 'F'

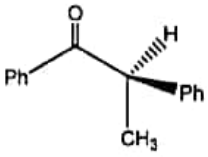
(vi)  Br_2 'G'

Q.9. Write down only major products in the reaction given below with their stereochemistry:-

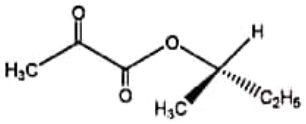
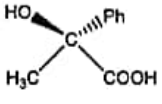
(i)  HCN

(ii)  (a) EtMgX (b) Hydrolysis

(iii)  (a) PhMgX (b) Hydrolysis

(iv)  (a) MeMgX (b) Hydrolysis

Q.10. Give reason for the following reaction:-

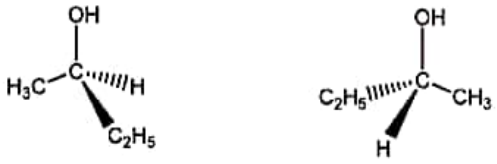
 (a) PhMgX (b) Hydrolysis 

(Major)

Q.11. Assign R/S and indicate stereochemical relationship in the following examples:-

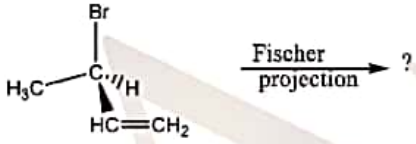
(a)

(b)

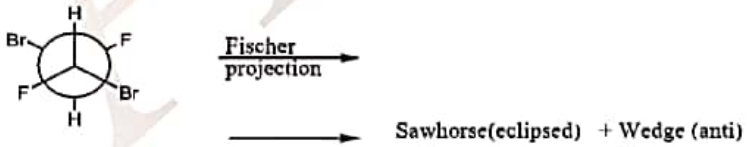


(c)

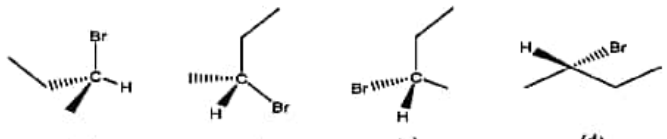
Q.12. Convert

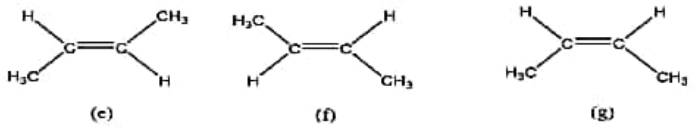


Q.13. Convert

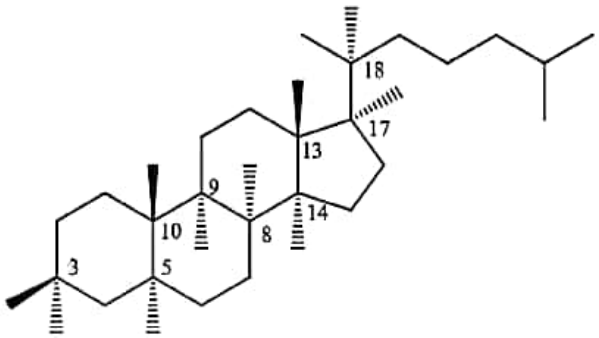


Q.14. Identify Enantiomers, Diastereomers, Homomers in the following compounds:-

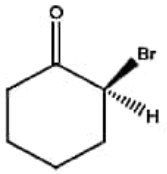


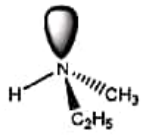


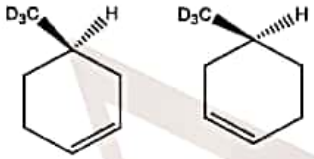
Q.15. Assign absolute configuration (R/S) in followingcompound.

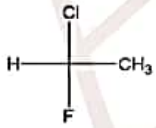


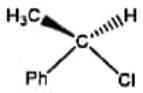
Q.16. Match following.

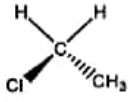
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

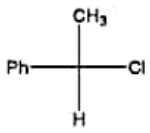
(i) R

(ii) Enantiomers

(iii) S

(iv) Fischer projection

(v) Achiral

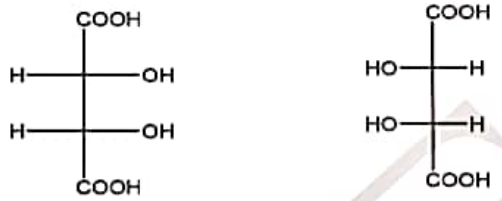
(vi) 

(vii) Homomer

Q.17. Following pairs having relationship as Enantiomerism/ Diastereomerism or Identical.

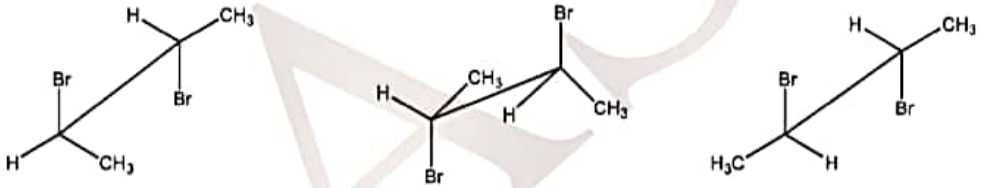
(i)

(ii)



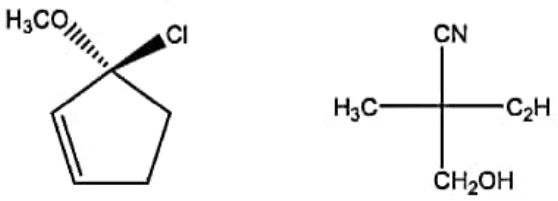
(iii)

Q.18. How are the following conformations of 2,3-dibromobutane related with each other.

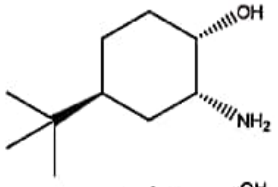


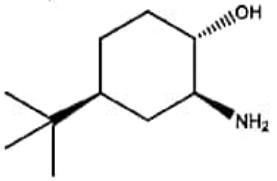
(a) (b) (c)

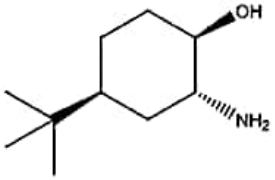
Q.19. Designate the structures below as R/S



Q.20. Write down the products A, B, C, D in the following reactions:-

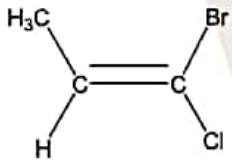
(i)  $\xrightarrow{NaNo_2/HCl}$ A

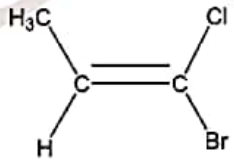
(ii)  $\xrightarrow{NaNo_2/HCl}$ B

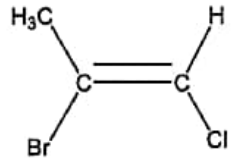
(iii)  $\xrightarrow{NaNo_2/HCl}$ C

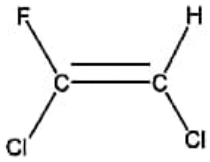
(iv)  $\xrightarrow{NaBH_4}$ D

Q.21. Which of the following is Z-isomer.

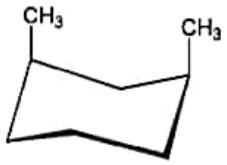
(1) 

(2) 

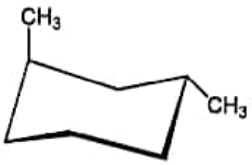
(3) 

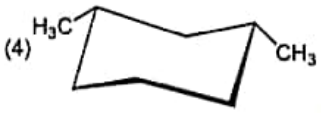
(4) 

Q.22. Most stable conformation of cis 1,3-dimethyl cyclohexane is?

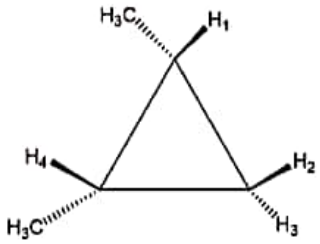
(1) 

(2) 

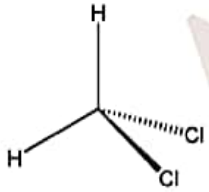
(3) 

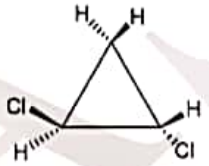
(4) 

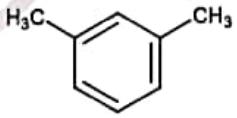
Q.23. Find out the relationship among hydrogens present in this molecule.



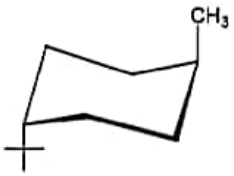
Q.24. Which of the following compounds has two vertical plane of symmetry?

(1) 

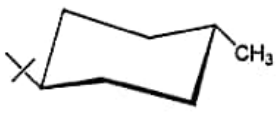
(2) 

(3) 

Q.25. Which of the following conformations are most preferred ?

(1) 

(2) 

(3) 

(4)