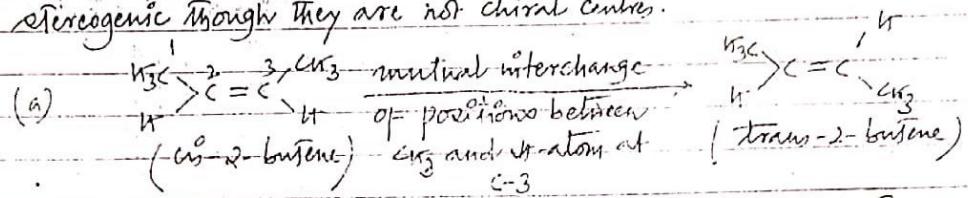


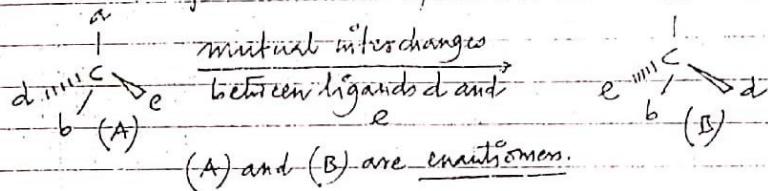
Stereogenic centre \Rightarrow If a new stereoisomer is formed due to mutual position change of two ligands around a particular atom or centre, then that centre will be called, a stereogenic centre.

A stereogenic centre may not be the chiral centre. Stereogenic centre may present in a molecule which doesn't have any chiral centre.

For example, in cis and trans-2-butene, the C-2 and C-3 centres are stereogenic though they are not chiral centres.



(b) In molecules like Cabde, the central carbon atom is stereogenic as well as chiral. Mutual interchange between two ligands in such molecules will produce enantiomers.



Concept of chirotopic and achirotopic centre \Rightarrow In certain molecules, a given type of atom may exhibit more than one type of site symmetry depending on its nature of connectivity within the molecule.

The site symmetry of atoms in molecules falls into two cases, chiral and achiral.

Chirotopicity \Rightarrow Any atom within a molecular framework is said to be chirotopic, if its site symmetry is chiral, i.e. the atom resides in a chiral environment and this phenomenon is said to be chirotopicity.
 If a centre is considered, then it is called a chirotopic centre.

The molecules bearing chirotopic centre need not be as a whole chiral.

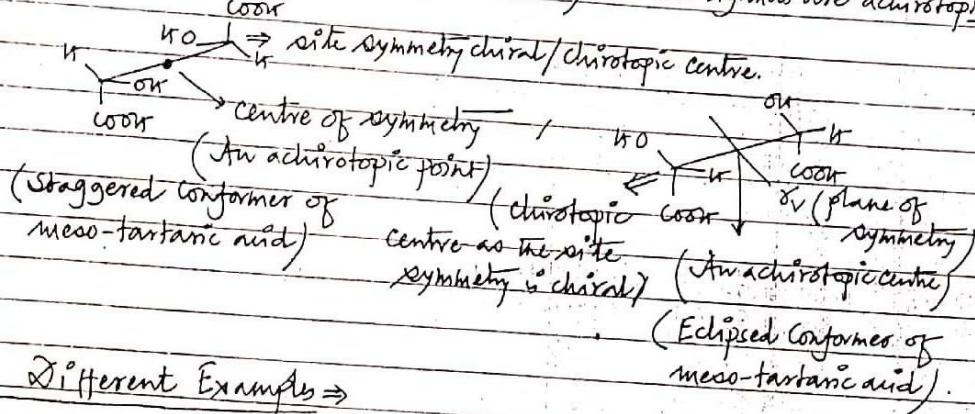
In Lactic acid ($\text{CH}_3\text{-CH(OH)-COOH}$), all ligands are chirotopic, as they reside in chiral environment.

Achirotopicity \Rightarrow An atom is said to be achirotopic, when its site.

Symmetry is achiral i.e. a point or an atom located on a plane of symmetry, or centre of symmetry or at a point where an

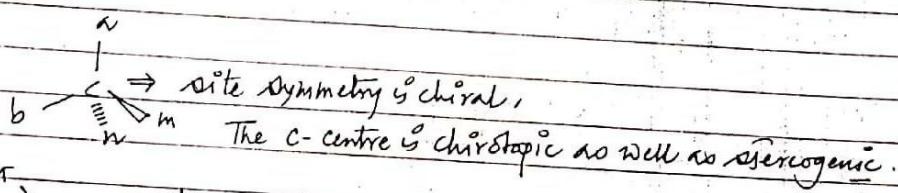
alternating axis of symmetry intersects its reflection plane is achirotopic and this phenomenon is known as achirotopicity.

In propanoic acid ($\text{CH}_3\text{CH}_2\text{COOH}$), all the ligands are achirotopic.

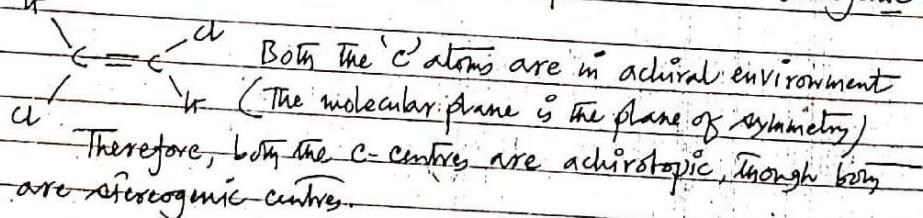


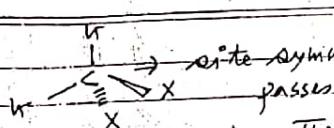
Different Examples \Rightarrow

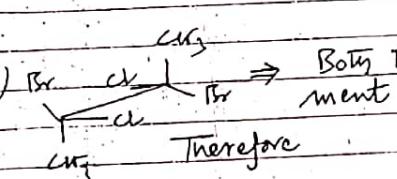
(a)



(b)

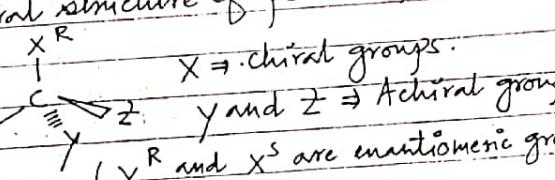


(c)  site symmetry achiral, as plane of symmetry (S) passes through central 'C' atom.
Therefore the C-centre is achirotopic and non-stereogenic.

(d)  Both the chiral centres are in chiral environment through the molecule is achiral.
Therefore

Pseudo-asymmetry \Rightarrow Certain molecules may contain tetrahedral carbon atom which is linked to two constitutionally identical chiral groups and two other different achiral groups.

The chiral groups may or may not have the same absolute configuration. The carbon atom of such a molecule is known as pseudo-asymmetric centre.

The general structure of pseudoasymmetric centre is as follows \Rightarrow 
(The C-centre is the pseudo-asymmetric centre)

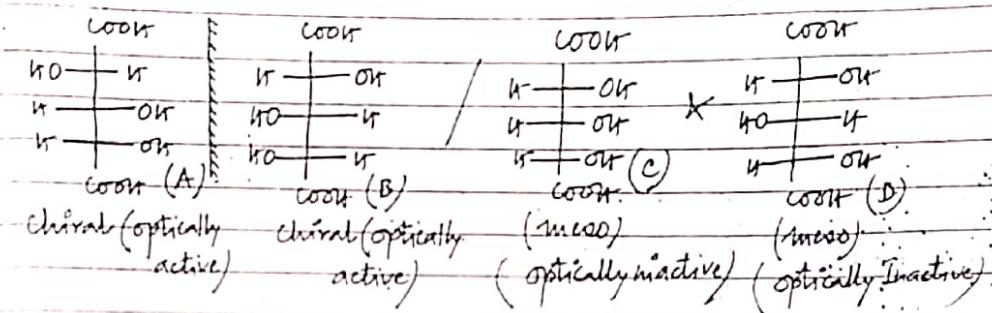
Example of 2,3,4-trihydroxy glutamic acid ($\text{HOOC}-\overset{2}{\text{CH}}(\text{OH})-\overset{3}{\text{CH}}(\text{OH})-\overset{4}{\text{CH}}(\text{OH})-\text{COOH}$) \Rightarrow

The molecule has three chiral centres and the molecule can be divided into two equal and similar halves by a plane passing through the central chiral centre in a specific conformation.

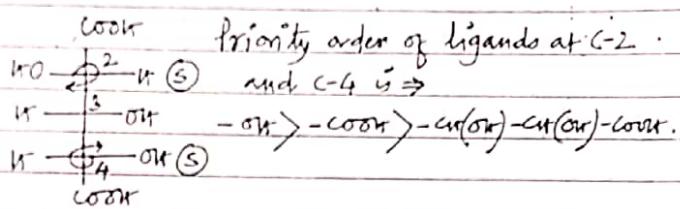
$$\text{No. of optically active isomers} = 2^{n-1} - 2 \quad (\text{where } n=3) \\ = 4 - 2 = 2$$

$$\text{No. of meso compounds} = 2^{(n-1)/2} = 2$$

The four Configurational Isomers are as follows \Rightarrow



In-(A) \Rightarrow



(2S, 4S) -

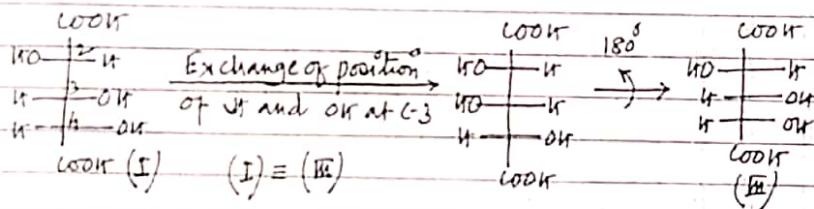
C-2 \Rightarrow Chirotopic and Stereogenic

C-4 \Rightarrow Chirotopic and Stereogenic.

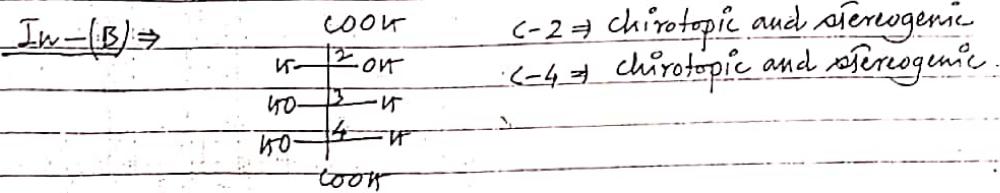
C-3 \Rightarrow The absolute configuration of C-2 and C-4 are (S) and they are homomorphic ligands. Therefore, the C-3 atom is achiral but the compound as a whole is chiral and optically active because it doesn't possess S, I or L in as symmetry elements.

Though C-3 is achiral, it resides in a chiral site symmetry and consequently chirotopic.

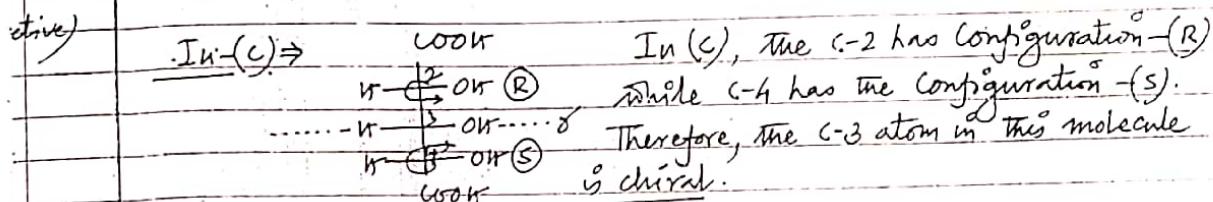
C-3 centre is non-stereogenic because exchange of positions of H and OR or the homomorphic chiral groups doesn't create a new stereo-isomer.



Thus, we see that C-3 centre is chirotopic and non-stereogenic.



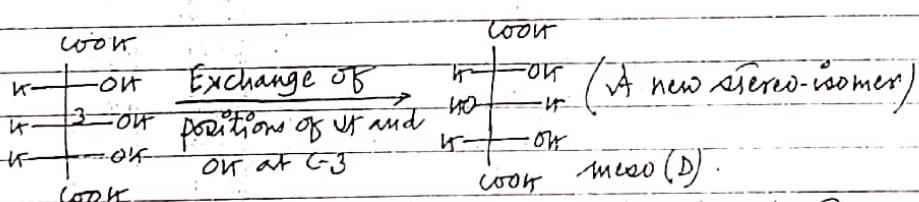
For the same reasons as stated for (A), the C-3 centre in (B) is chirotopic and non-stereogenic.



(Meso) (2R,4S) —

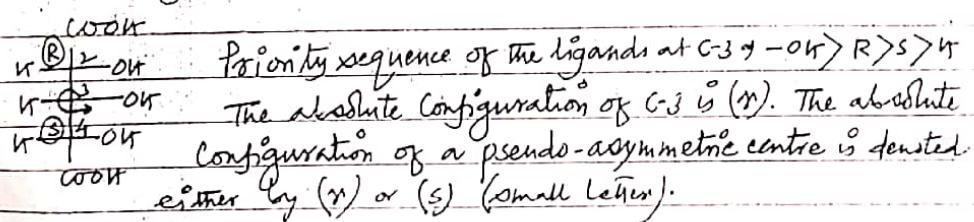
The molecule is optically inactive due to the presence of plane of symmetry (σ), which passes through C-3. Therefore, the C-3 centre resides in an achiral environment i.e. the site symmetry is achiral and hence, the C-3 centre is achirotopic.

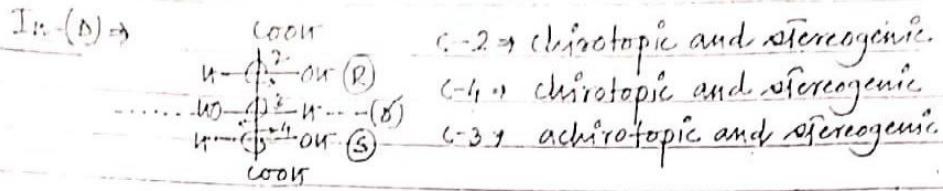
Interchange of position of H and OH gr. on pseudo-asymmetric C-3 centre produces a new stereo-isomer and hence C-3 centre is stereogenic.



Thus, we see that, C-2 \Rightarrow chirotopic and stereogenic
C-4 \Rightarrow chirotopic and stereogenic
C-3 \Rightarrow achirotopic and stereogenic.

Absolute Configuration of C-3 centre =





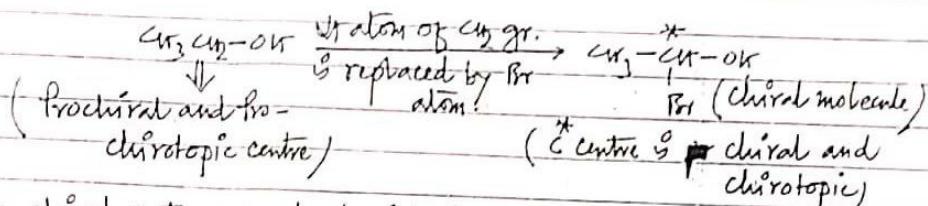
(A)

(meso) The absolute configuration of C-3 $\xrightarrow{(S)}$.

Prochiral centre \Rightarrow A centre is said to be prochiral in which replacement of a single ligand leads to a chiral centre.

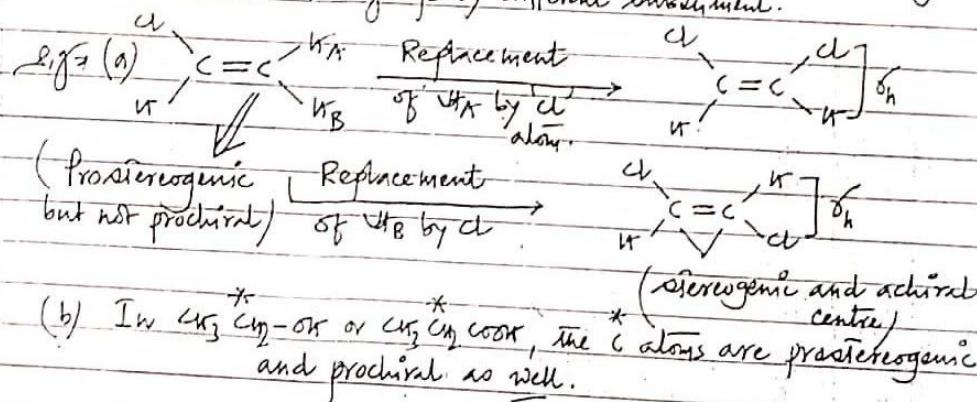
(B)

Examp In $\text{C}_2\text{H}_5\text{CH}_2\text{OH}$, the C-1 atom represents a prochiral centre, because replacement of one of the H atoms by a non-equivalent ligand say Br, will convert the centre into a chiral centre.



The chiral centre can also be introduced by an addition reaction to compounds like $\text{R}'>\text{C=O}$ and $\text{R}'>\text{C=NH}$. In such cases, $>\text{C=O}$ and $>\text{C=NH}$ groups are said to have prochiral faces.

Prostereogenic centre \Rightarrow A centre, bearing identical atoms or groups which can be converted into a stereogenic centre by replacing one of the identical atoms or groups by different substituent.



Homotopic ligands (atoms/groups) \Rightarrow

- (A) From symmetry point of view \Rightarrow Homotopic ligands in a molecule are those whose positions can be interchanged by rotation about proper axis of symmetry (C_n). Where ($n > 1$).
- (B) From substitution point of view \Rightarrow Two or more identical atoms or groups in a molecule are homotopic, if replacement of each in turn by a new ligand, gives the same product.

Example \Rightarrow (i) $NR_3 \rightarrow$ Three 'R' atoms of NR_3 are homotopic (interchangeable by C_3 operation).

(ii) $CH_3 \rightarrow$ Four 'H' atoms are homotopic (interchangeable by C_3 -operations).

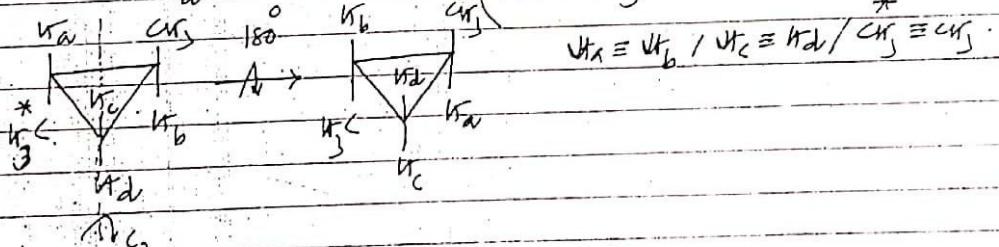
(iii) $R>C< R \rightarrow$ Four 'R' atoms are homotopic (interchangeable by C_2 operations)

(iv) $CH_3-OR ; CH_3-COOH \rightarrow$ Three methyl 'H' atoms are homotopic (interchangeable by C_3 -operation)

(v) $\begin{array}{c} R \\ | \\ C=C \\ | \\ R \\ \text{or} \\ R \\ | \\ R \end{array} \rightarrow$ 2 'R' and 2 'C' atoms are homotopic (interchangeable by C_2 -operation)

(vi) $\begin{array}{c} Br \\ | \\ Br-CR_3 \\ | \\ Br \\ \text{or} \\ Br \\ | \\ Br \end{array} \Rightarrow (Br_a \& Br_b), 2 CR_3, 2 Br, (Br_c \& Br_d)$
are homotopic.

(vii) $\begin{array}{c} R_a | CR_3 \\ | \\ R_b \\ \text{or} \\ R_b | CR_3 \\ | \\ R_a \end{array} \xrightarrow{180^\circ} \begin{array}{c} R_b | CR_3 \\ | \\ R_a \\ \text{or} \\ R_a | CR_3 \\ | \\ R_b \end{array} \xrightarrow{*} \begin{array}{c} R_a | CR_3 \\ | \\ R_b \\ \text{or} \\ R_b | CR_3 \\ | \\ R_a \end{array}$ (Interchangeable by C_2 operation)



Mesotopic ligands (atoms/groups) \Rightarrow Enantiotopic atoms/groups

(v)

(A) Enantiomeric point of view: A pair of ligands in a molecule is said to be enantiotopic when they are interchangeable by σ (plane of sym.) i (centre of sym) or S_n (alternating axis of sym) operations.

(B) From substitution point of view Two identical ligands attached to a centre are said to be enantiomeric, if replacement of each in turn by a different achiral ligand gives enantiomers.

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Example (i) H_A and H_B are enantiotopic (i.e., H_A and H_B are interconvertible by S_i -operation).

H_A $\xrightarrow{S_i}$ I $\xrightarrow{S_i}$ H_B

replacement of H_A by I atom \rightarrow H_B $\xrightarrow{S_i}$ I (S)

↓ replacement of H_B by I atom.

$\text{I} \xrightarrow{S_i} \text{H}_A$ (R)

Thus, we see that, H_A and H_B are enantiotopic.

ii) $\text{CH}_3\text{CH}_2\text{OH}$, $\text{CH}_3\text{CH}_2\text{COOH}$ is Two up atoms of ethanol and propanoic acid are neutralised.

(B)

iii)  These two W atoms are enantiomeric.

Exercises

(iv) CH_3
 $\text{H} \quad \text{C}=\text{O}$ \rightarrow Two 'H' atoms are enantiotopic. (interchangeable by δ -operation)

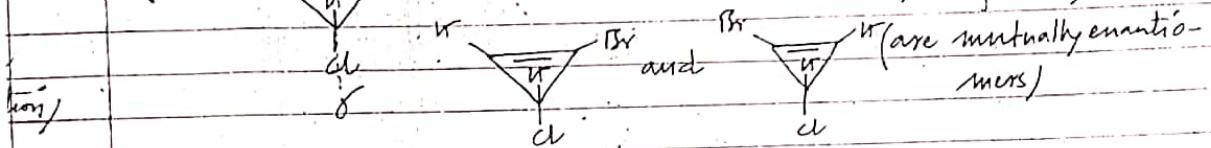
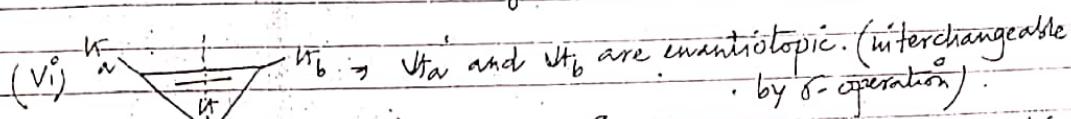
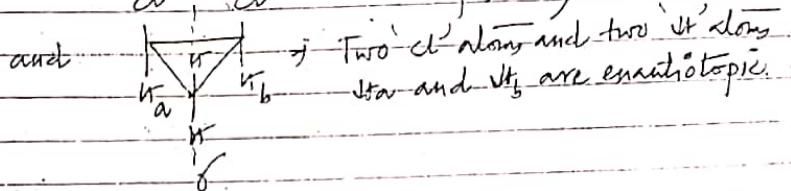
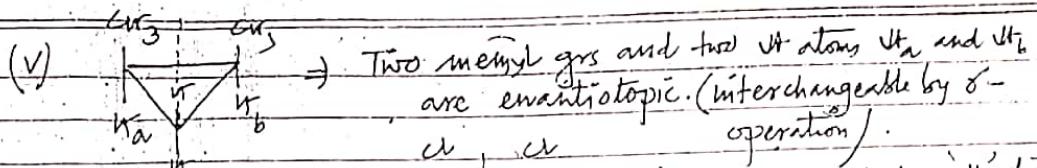
-cl?

(Meas. distance = 2,3-diol) $\text{Br}-\text{CH}_2-\text{CH}_2-\text{OH}$ (A)

 (Meas. distance = 1,3-diol) $\text{Br}-\text{CH}_2-\text{CH}(\text{OH})-\text{CH}_2-\text{Br}$ ((A) ends (B))

 (Meas. distance = 1,3-diol) $\text{Br}-\text{CH}_2-\text{CH}(\text{OH})-\text{CH}_2-\text{Br}$ ((A) ends (B))

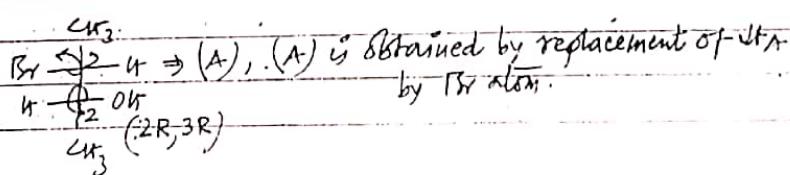
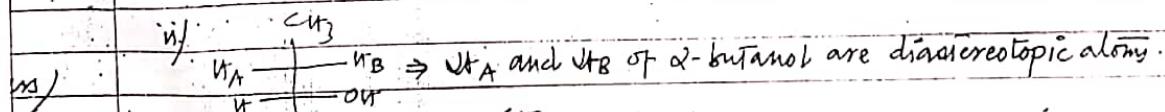
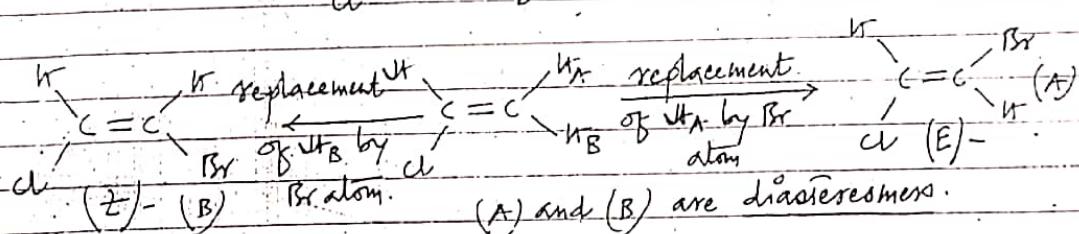
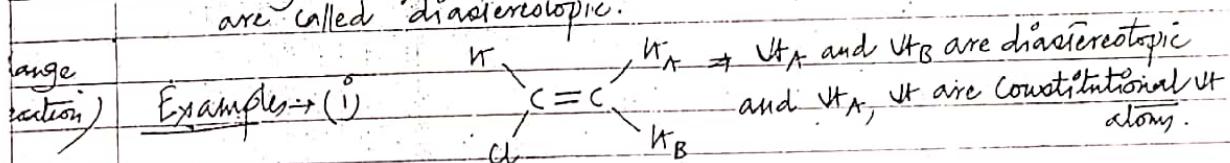
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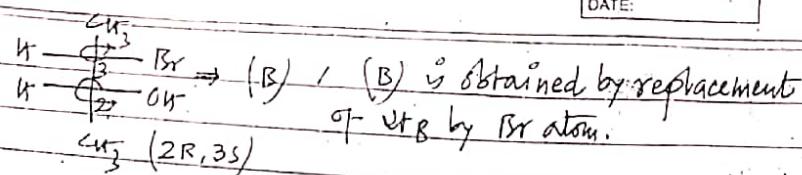


Diaxioptopic ligands (atoms/groups) \Rightarrow

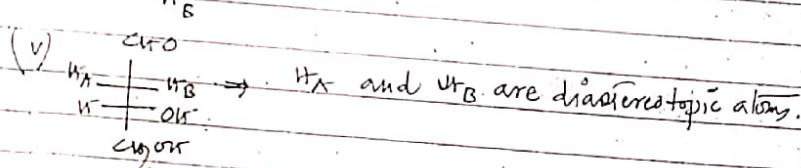
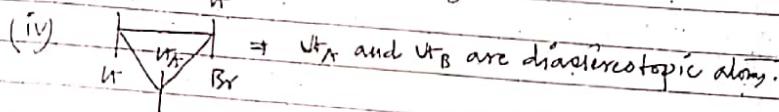
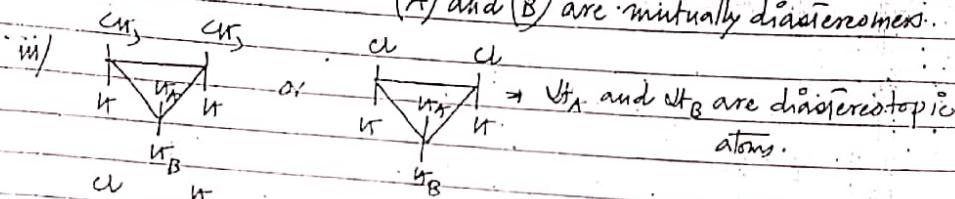
(A) From symmetry point of view \Rightarrow Diaxioptopic atoms or groups can not be interchanged by symmetry operations such as C_n , S_n , i or σ_{h} .

(B) From Substitution point of view \Rightarrow If replacement of two identical ligands by different ligand gives diastereomers, then the ligands are called diaxioptopic.



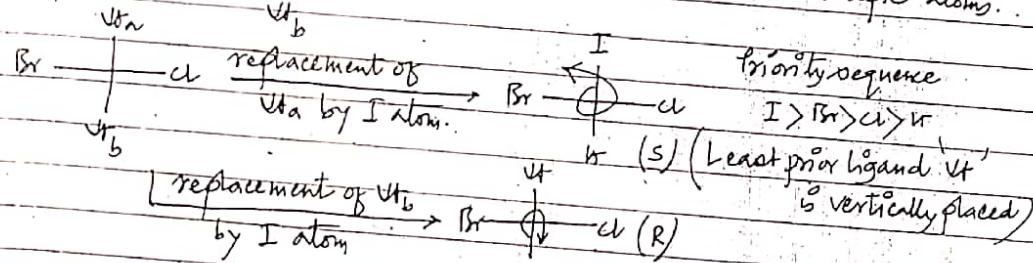


(A) and (B) are mutually diastereomers.



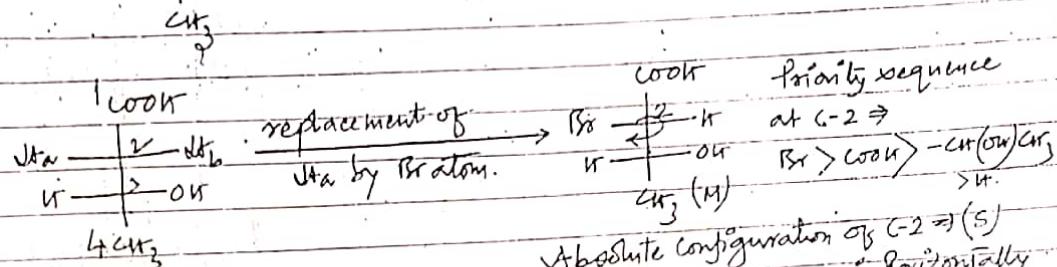
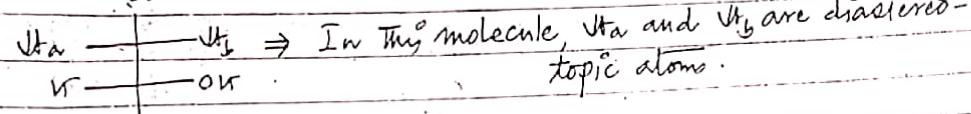
Pro-R and Pro-S Designation \Rightarrow Enantiotopic or Diastereotopic ligands on a pro-chiral centre in a molecule, is designated as Pro-R and Pro-S, if replacement of one of them by a non-equivalent achiral ligand with higher priority than the other converts the pro-chiral centre into a chiral centre with R and S absolute configuration.

Example → 1. $\text{Br} - \text{Cl} \Rightarrow$ Stere, H_{a} and H_{b} are enantiotopic atoms.

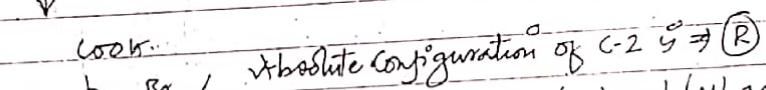


Thus, we see that, H_{a} is Pro-S while H_{b} is Pro-R atoms.

2. soon



replacement of H_b by Br atom.



Thus, we see that, (M) and (N) are mutually enantiomers and the atom C_b is pro-S while the atom C_b is pro-R.

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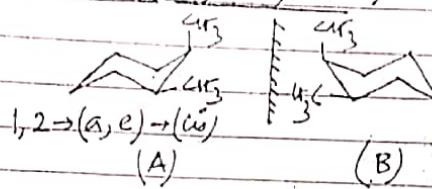
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Conformational Analysis of Cyclohexane derivatives

(四)

(I) 1,2-Dimethyl Cyclohexanes ⇒

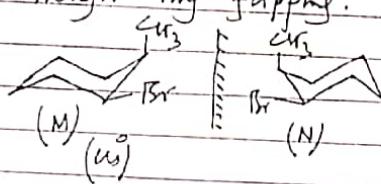


(A) and (B) can not be called meso Compound because these two constitute a non-resolvable enantiomeric pair through ring inversion or flipping.

(a) (A) and (B) are conformational enantiomers. (A) and (B) are individually chiral molecules. But these two are readily interconvertible. (A) can be converted into (B) by ring flipping and vice-versa.

(b) Thus cis-1,2-dimethyl Cyclohexane exists as a racemic mixture and it is impossible to have its optically active sample (either (A) or (B)). (a)
 (A) and (B) maintain a conformational equilibrium between them at room-temp and these two can not be separated (resolved). (b) (c)

(II) If two substituents be different at C-1 and C-2, two conformers (for e.g.) will be chiral and one can not get converted to other through ring flipping.



(M) and (N) both are chiral
and these two are not
interconvertible at room temp

(iii) If the six-membered ring is flat (planar), 1,2-dimethyl Cyclohexane will have a plane of symmetry (σ) and such a molecule will be achiral (optically inactive).

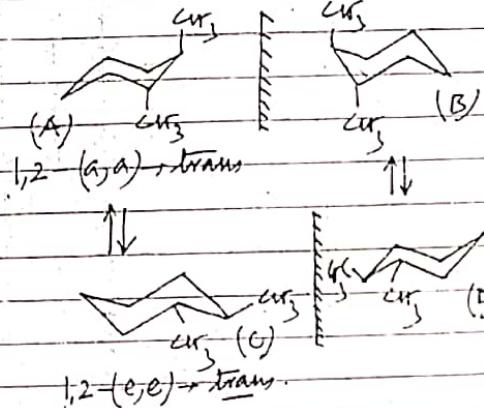


 \Rightarrow planar-1,2-dimethylcyclohexane (w°) achiral.

(VI)

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(IV) Trans-1,2-dimethyl Cyclohexane ⇒



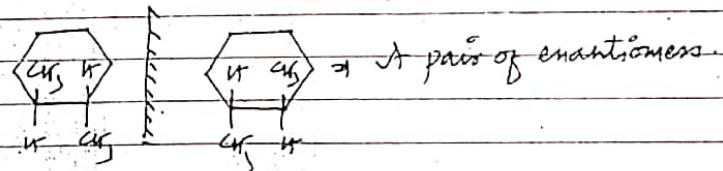
(a) (A) and (B) make an enantiomeric pair while (C) and (D) also make an enantiomeric pair.

(b) Both the trans forms i.e. (a,a) and (e,e) are chiral.

(c) (A) and (c) are conformational diastereomers and diastereomeric relationship is true for (B) and (D).

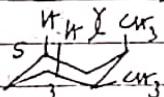
(d) (A) and (B) are non-interconvertible through ring inversion and therefore (A) and (B) can be separated (resolved). The same thing is true for (C) and (D).

(IV) In planar conformation of trans-1,2-dimethyl Cyclohexane, it has no δ , i or Sw and therefore it is a chiral molecule and has a pair of enantiomers.



(vi) Conformational stability of 1,2-dimethyl Cyclohexanes \Rightarrow

(A) cis-1,2-dimethyl Cyclohexane \Rightarrow

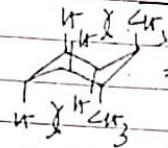


 This compound faces three gauche-butane interactions (steric and repulsive).

Two syn-^o-dialix between axial methyl and axial CH₃ and 5 H atoms and the remaining one between two methyl grs.

Therefore, the instability factor is $\Rightarrow 3 \times 0.9 = 2.7 \text{ K.cal mol}^{-1}$

(B) (a,a)-trans-1,2-dimethyl Cyclohexane \Rightarrow

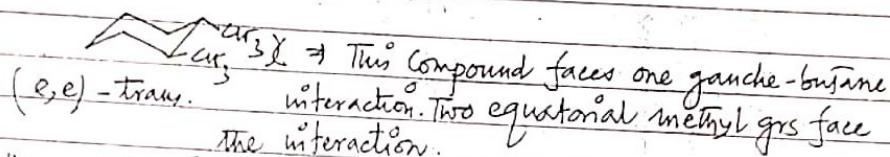


\Rightarrow This Compound faces four butane-gauche interactions.

(a,a)-trans. The butane-gauche interactions arise from two axial methyl grs and syn-axial hydrogen-atoms.

Therefore, the instability factor is $\Rightarrow 4 \times 0.9 = 3.6 \text{ K.cal mol}^{-1}$

(C) (e,e)-trans-1,2-dimethyl Cyclohexane \Rightarrow



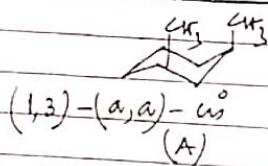
\Rightarrow This Compound faces one gauche-butane interaction. Two equatorial methyl grs face the interaction.

Here, the instability factor is $\Rightarrow 0.9 \text{ K.cal mol}^{-1}$

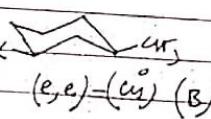
Thus, we see the stability order as $\Rightarrow (e,e)\text{-trans} > (a,e)\text{-cis} > (a,a)\text{-trans}$
(most stable)

1,3-Dimethyl Cyclohexanes \Rightarrow

cis-1,3-dimethyl Cyclohexane \Rightarrow



(1,3)-(a,a)-cis
(A)



(e,e)-(cis) (B)

(a)

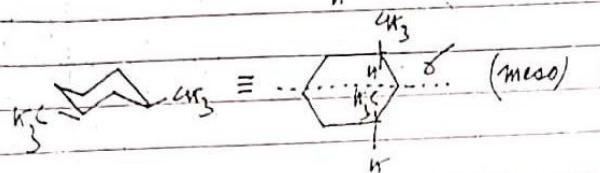
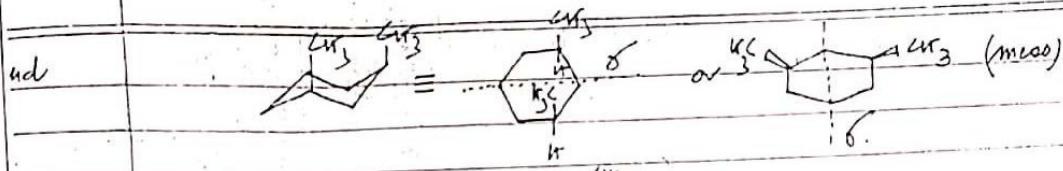
(b)

(c)

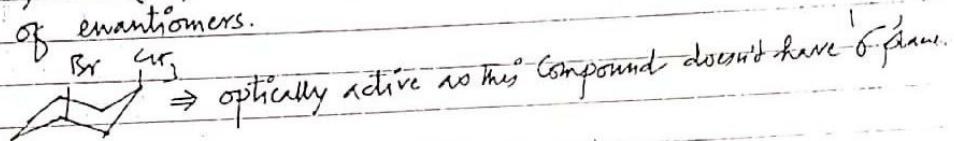
(a) (A) and (B) are Conformational isomers i.e interconvertible by ring inversion.

(b) Both (A) and (B) are meso compounds, as they possess plane of symmetry (S) and thus obviously achiral.

(d)

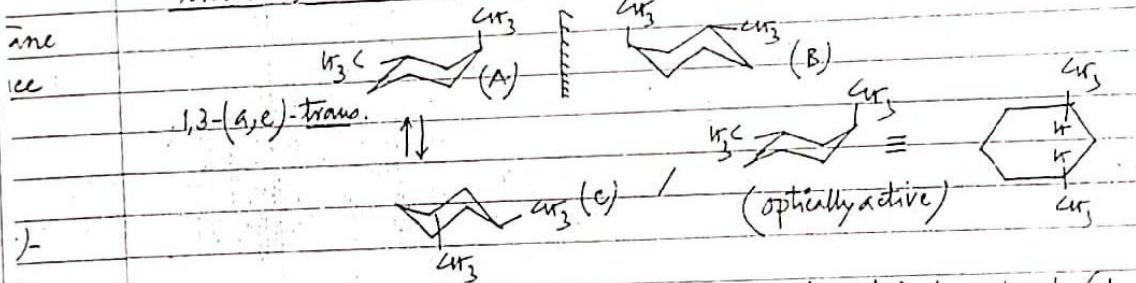


(c) When the substituents are different both the cis -form i.e. (a,a) and (e,e) are chiral and each one can exist as a pair of enantiomers.



cis \rightarrow chiral, doesn't possess σ plane.

trans-1,3-dimethyl Cyclohexane \Rightarrow

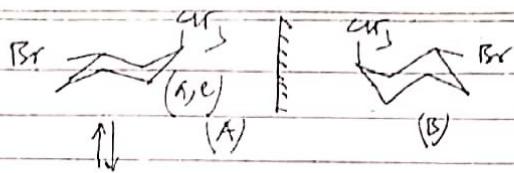


(a) The trans-1,3-dimethyl Cyclohexane is a chiral molecule (doesn't have σ). Two enantiomers (A) and (B) are resolvable.

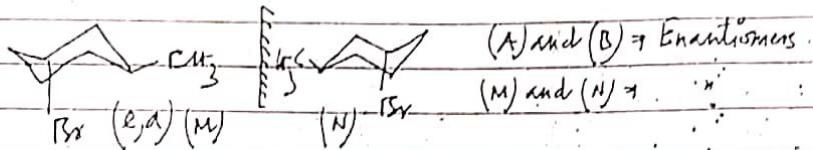
(b) (A) and (B) \Rightarrow Enantiomers / (A) and (C) \neq Topomers (Isomers)
 (B) and (C) \neq Enantiomers.

(c) (a,a)- cis and (a,e)- $trans$ are mutually diastereomers.
 and (e,e)- cis and (a,e)- $trans$ are mutually diastereomers.

(d) When the substituents are different (a,e) and (e,a) forms are non-identical and each one can exist as a pair of enantiomers and thus in total, four configurational isomers are possible.



(A) \neq (M) and (A) \neq (N).



Conformational stability \Rightarrow

(A)
 This compound faces two butane-gauche interactions (between axial CH_3 gr. and the axial 3H atom) and one 1,3-syn-di-axial interaction between two axial CH_3 grs.

$$\text{Therefore, the instability factor } S = 2 \times 0.9 + 3 \cdot 6 (\text{CH}_3 - \text{CH}_3 \text{ syn-di-axial}) \\ = 5.4 \text{ Kcal mol}^{-1}$$

(B)
 In this compound two methyl grs are at equatorial position and thus face no butane-gauche interaction.

Therefore, the instability factor for this compound = '0'.

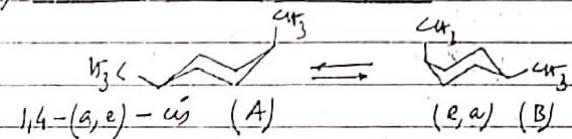
(C)
 In this compound, the axial methyl gr. faces two butane-gauche interactions with axial 3H and 5H atoms.

The instability factor for this compound = $2 \times 0.9 = 1.8 \text{ Kcal mol}^{-1}$.

Thus, we see the stability order $\Rightarrow (e,e)-\text{cis} > (e,e)-\text{trans} > (e,a)-\text{cis}$
 (most stable)

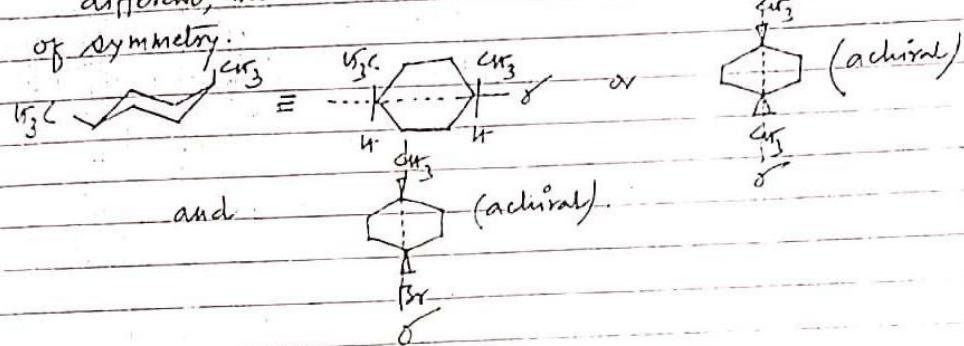
1,4-Dimethyl Cyclohexanes \Rightarrow

(A) $\text{cis}-1,4-\text{Dimethyl Cyclohexane}$ \Rightarrow

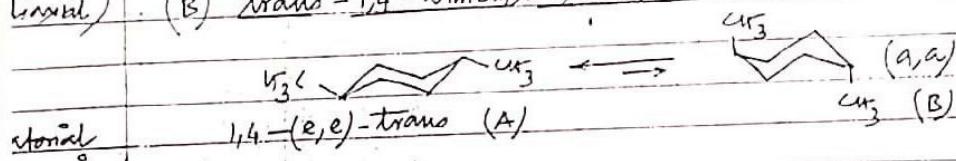


(a) (A) and (B) are topomers (Homomers)

(N) (b) cis-1,4-dimethyl Cyclohexane is an achiral molecule due to the presence of a plane of symmetry. If the two substituents are different, the molecule will be chiral due to the presence of plane of symmetry.



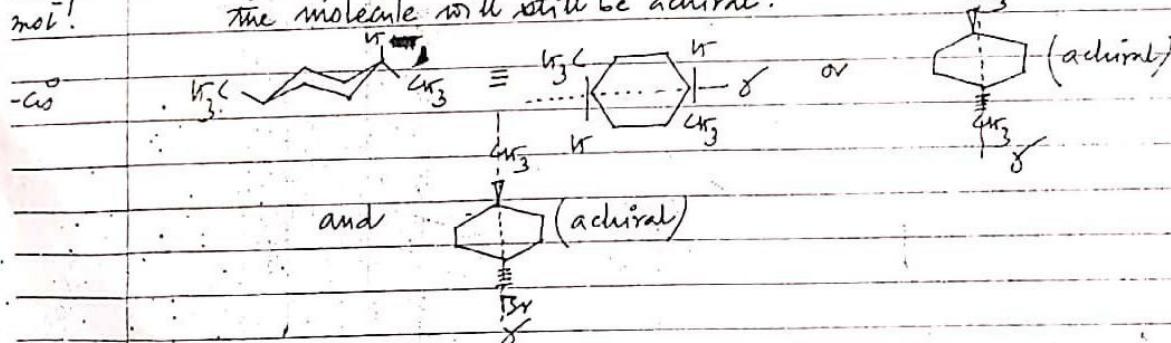
Lewis) (B) trans-1,4-Dimethyl Cyclohexane \Rightarrow



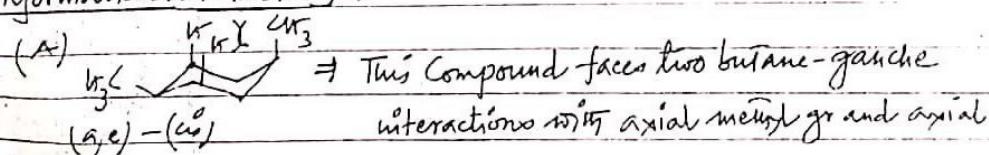
O! (a) (A) and (B) are conformational diastereomers.

(b) (a,e)-cis and (e,e) or (a,a)-trans are mutually configurational diastereomers.

(c) trans-1,4-dimethyl Cyclohexane is also achiral, due to the presence of a plane of symmetry. If the two substituents are different, the molecule will still be achiral.

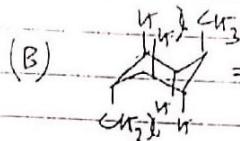


Conformational stability \Rightarrow



3H and 5H atoms.

The instability factor is therefore $\Rightarrow 0.9 \times 2 = 1.8 \text{ K.cal mol}^{-1}$



\Rightarrow This compound faces four butane-gauche interactions.

(a,a)-trans. Therefore, the instability factor is $\Rightarrow 0.9 \times 4 = 3.6 \text{ K.cal mol}^{-1}$

(c)
 \Rightarrow In this compound, no two methyl grs are (e,e)-trans. equatorial, it faces no butane-gauche interactions.

Thus, we get the stability order as \Rightarrow

(e,e)-trans $>$ (a,e) $=$ (e,a)-cis $>$ (a,a)-trans.
 (most stable)

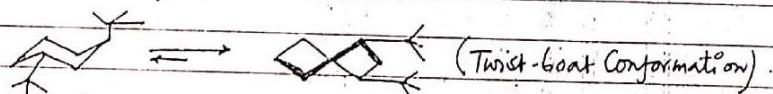
Draw the structure of stable conformation of the following compounds with reason \Rightarrow

1. cis-1,3-di-tertiary butyl Cyclohexane \Rightarrow

\Rightarrow In this Conformer two tertiary butyl grs are 1,3-(e,e)-(cis) equatorially placed and hence don't face butane-gauche or 1,3-syn-diaxial interactions.

It is the most stable Conformer of cis-1,3-di-tertiary butyl Cyclohexane.

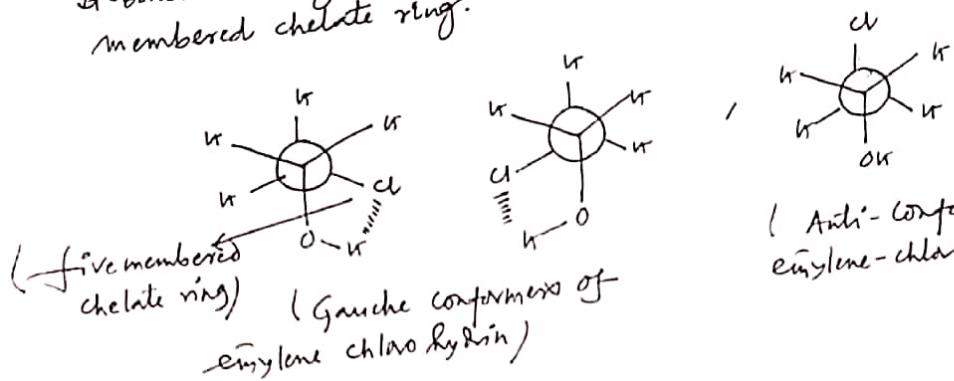
2. trans-1,3-di-tertiary butyl Cyclohexane \Rightarrow



1,3-(a,e)-trans. Trans-1,3-di-tertiary butyl Cyclohexane exists as an equilibrium mixture of chair and twist boat conformations. The twist boat conformation is more stable than the chair conformation.

(2) $\text{HO}-\text{C}_2\text{H}_4-\text{C}_2\text{H}_4-\text{X}$ type comp's (where $\text{X} = \text{Ar}_2, \text{F}, \text{Cl}, \text{Br}, \text{OR}, \text{NR}_2, \text{NR}_2\text{Ar}_2$)

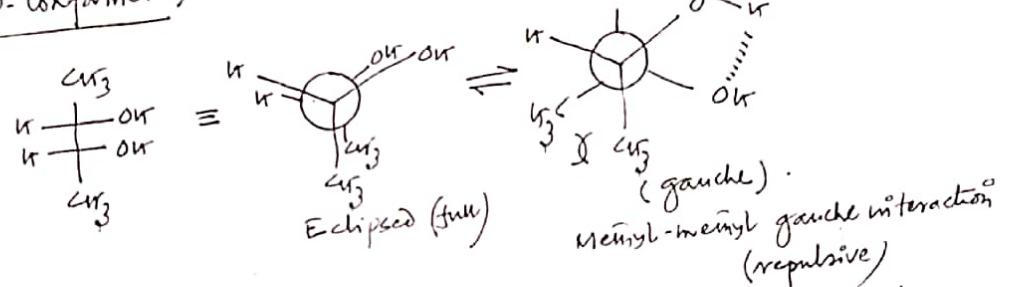
The gauche conformers of such comp's are more stable and preferred conformer over the other conformers due to the formation of intramolecular H-bond in the gauche conformer, which results in formation of a five-membered chelate ring.



(Anti-conformer of ethylene-chloro-hydrin)

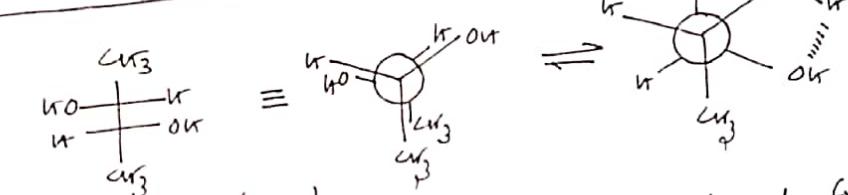
(3) Butane-2,3-diol \Rightarrow

Meso-Conformer \Rightarrow



In meso Conformer, when the two -OH grps are placed in gauche conformation, the bulky methyl grps take up sterically unfavorable gauche position. The repulsive steric interaction between methyl grps makes the intramolecular H-bond in meso, weaker.

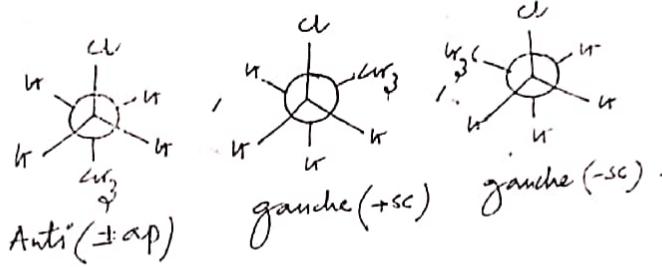
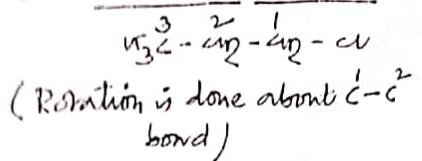
d or l-Conformer \Rightarrow



In case of active d or l form of the diol, when -OH grps are gauche, methyl grps are placed anti and thus in the active form; there is no gauche-interaction between the methyl grps and in this conformer the intramolecular H-bond is stronger than that in the meso form.

Thus, we see that, the d or l-form of butane-2,3-diol is more stable than its meso form.

(4) In Halo-alkanes \Rightarrow

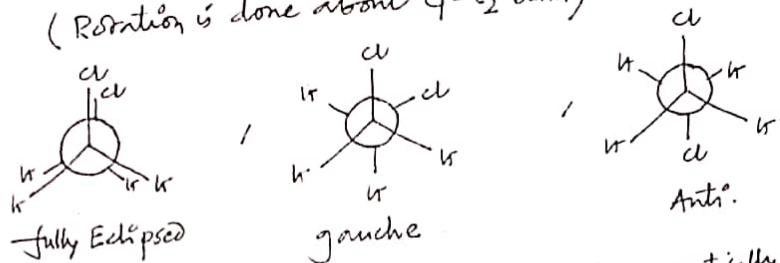


The gauche conformers are more stable than the anti-conformers.

It may be due to the fact that in gauche conformers, the van der waals attractive forces (London force) between methyl and chlorine are more operative than the van der waals repulsive forces (steric).

In anti conformer, the attractive force doesn't operate, as the distance between CH₃ and Cl is sufficiently long.

(5) In $\text{Cl}-\text{C}_2\text{H}_5-\text{C}_2\text{H}_5-\text{Cl}$ and $\text{Br}-\text{C}_2\text{H}_5-\text{C}_2\text{H}_5-\text{Br} \Rightarrow$
(Rotation is done about C-C bond)



1. The fully eclipsed conformer is energetically least favorable, as in this conformer the repulsive steric interaction between two 'Cl' atoms and the dipole-dipole repulsive interaction between two 'C-Cl' bonds are quite strong.

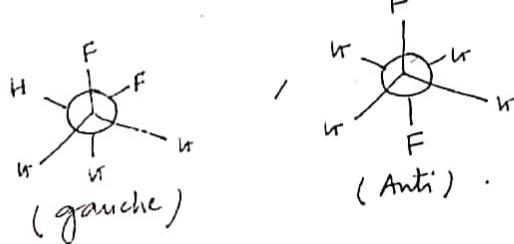
In anti conformer the two 'C-Cl' dipoles are acting in opposite directions (180°), while in the gauche conformer they are acting at angle 60°. Thus, we see that in the anti-conformer steric and dipole-dipole interaction are not operative, while they are operative in the gauche conformer.

Therefore the anti-conformer is more stable than the gauche conformer.

It is seen that both CH₂Cl₂ and Br₂C₂H₅ have finite value of dipole moment ($\mu \neq 0$). Therefore, the gauche conformers which have considerable contribution in conformational equilibrium ($M \neq 0$) have considerable contribution in conformational equilibrium.

(6) In $\text{F}-\text{C}_2\text{H}_5-\text{C}_2\text{H}_5-\text{F} \Rightarrow$

(Rotation is done about C-C bond)



(7)

(II)

Aug

O

Tu

-

Dex