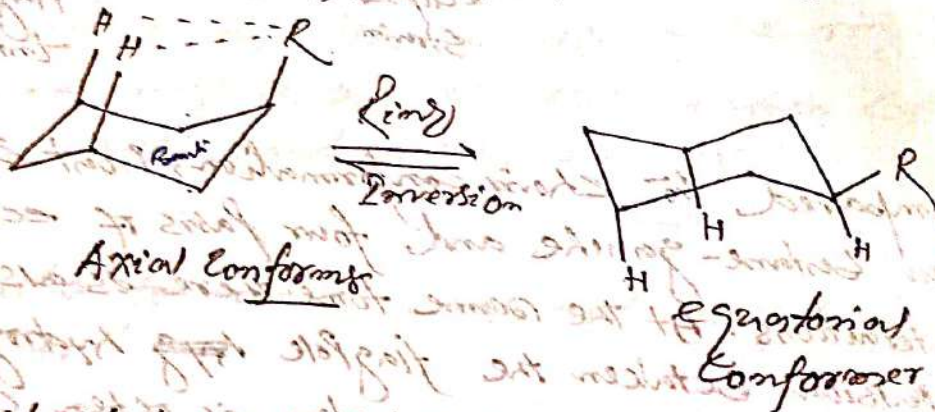


Mono substituted Cyclohexane:

In case of chair conformation of mono substituted cyclohexanes, the equatorial conformation of substituent is more favoured than axial conformation. The preference for an equatorial conformation has been taken as a measure of effective size of the substituent. The effect, a sterically bulky group in the axial position interacts with two hydrogen atoms, also axial, in positions C-3 and C-5, and the conformational equilibrium is displaced towards the equatorial conformation. This type of steric interaction is often called 1,3-diaxial interaction.

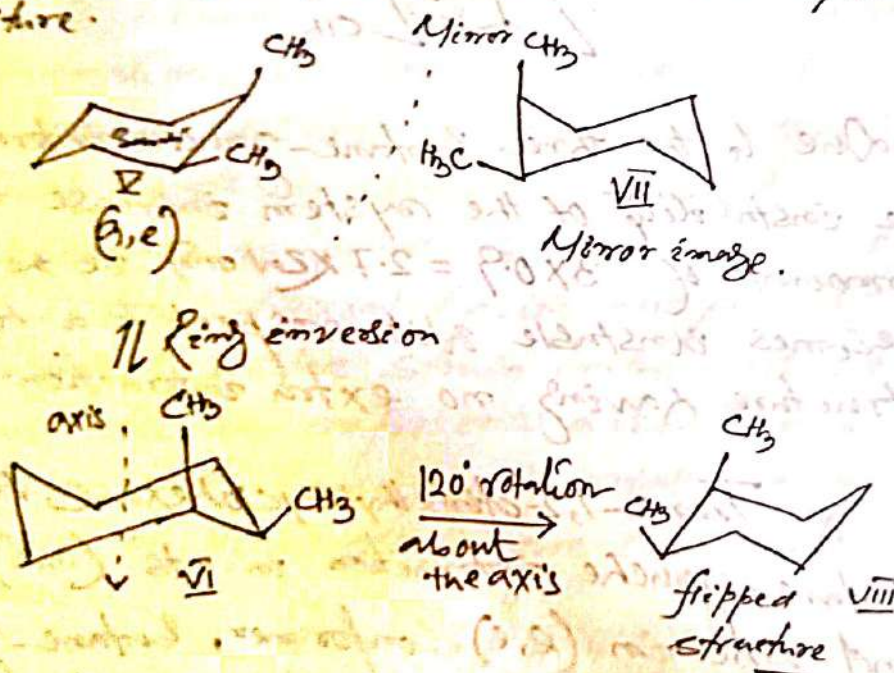


For most of the substituents, the equilibrium between axial and equatorial substituted chair forms is quite rapid at normal conditions and that is why they cannot be separated. However at lower temperature (0°C to -120°C) both forms can be observed separately in the mixture through NMR.

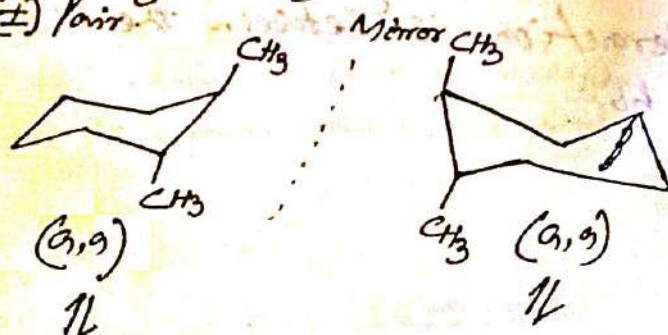
Disubstituted Cyclohexane

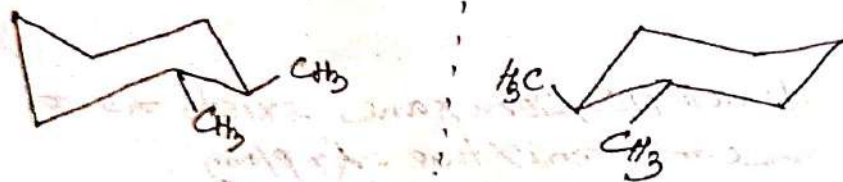
* Cis-1,2-dimethylcyclohexane exists as a non-volatile racemic mixture - by plan

Two constitutionally identical 1,2-dimethylcyclohexanes are Cis-1,2-dimethylcyclohexane and trans-1,2-dimethylcyclohexane. Cis-1,2-dimethylcyclohexane exists in two energetically equivalent chair conformations, namely axial-equatorial (a,e) and equatorial-axial (e,a). The cis isomers represent chiral molecule and belong to C_2 point group. But they are nonresolvable, because one is the non-superimposable mirror image of the other and are readily interconvertible (Potential energy barrier is low) at the ordinary temperature by flipping of one chair conformation into the other. Thus Cis-1,2-dimethylcyclohexane exist as non-volatile racemic mixture.



* The compound trans-1,2-dimethylcyclohexane exist in two distinct chair conformation i.e. (a,a) and (e,e). Both are chiral having point group C_2 and can exist as a resolvable (\pm) pair.





* Stability of cis- and trans-1,2-dimethylcyclohexane

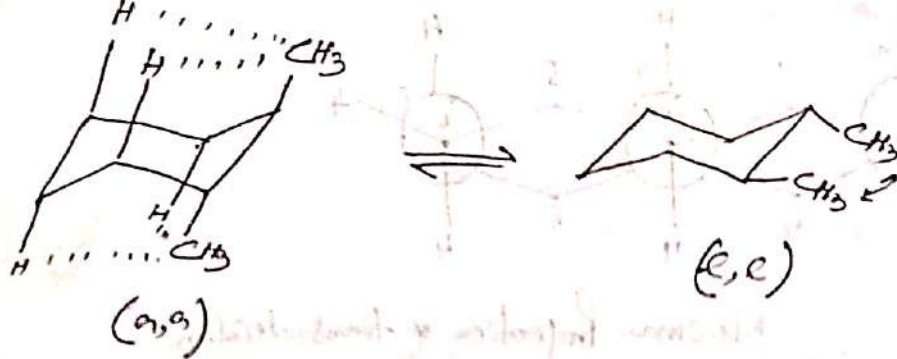
In chair conformation of cis-1,2-dimethylcyclohexane, there are three butane-gauche interactions. These interactions are shown below. Two interactions arise from axial methyl group and syn-axial hydrogen atom at C-3 and C-5 and the other is between the two methyl groups.



Due to the three butane-gauche interactions the instability of the system increase by an amount of $3 \times 0.9 = 2.7 \text{ kcal mol}^{-1}$ i.e. the molecule becomes unstable with respect to a hypothetical structure having no extra interaction.

Trans-1,2-dimethylcyclohexane has four butane-gauche interaction in its (a,e) conformer and one in (e,e) conformer, butane-gauche interaction in (a,e) conformer interactions originate from the two axial methyl group and syn-axial hydrogen atoms. In (e,e) conformer one interaction is between the two equatorial methyl groups.

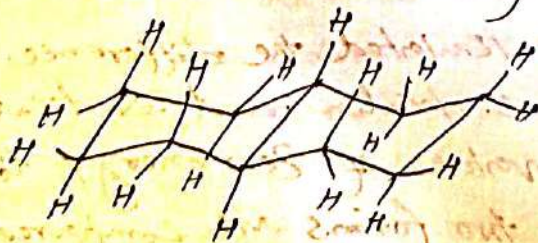




In (a,a) form, the instability increases by an amount $4 \times 0.9 = 3.6$ kcal/mol. The (e,e) conformer is unstable by an amount of 0.9 kcal/mol. Therefore, trans- (e,e) form of 1,2-dimethylcyclohexane is preferred conformation over the trans (a,a) conformation.

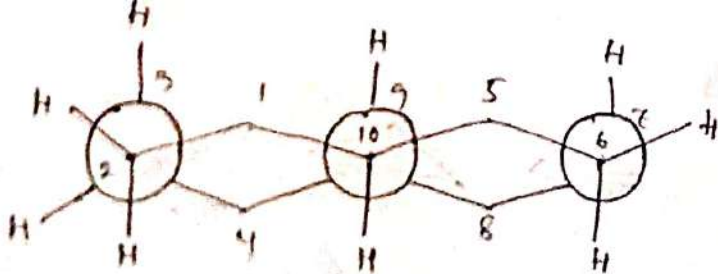
Decalin-System:

Trans-decalin is a rigid two chair conformation where two equatorial bonds are used by one chair form to become locked with another chair. In this conformation, inversion of cyclohexane rings are not possible because in that case the trans-diequatorial bonds on adjacent carbons, by which one cyclohexane is joined to another, will have to become trans-diaxial having anti periplanar orientation resulting excessive strain in the molecule. Therefore, trans-decalin represents a conformationally locked system and consequently axial and equatorial-isomers of trans-decalin are conformationally homogeneous.



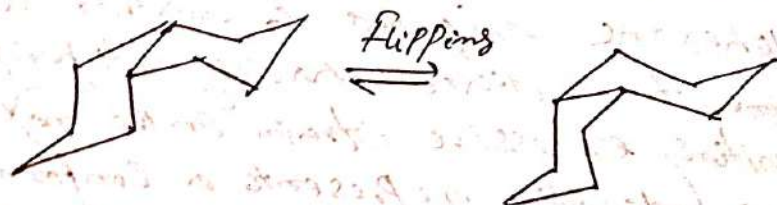
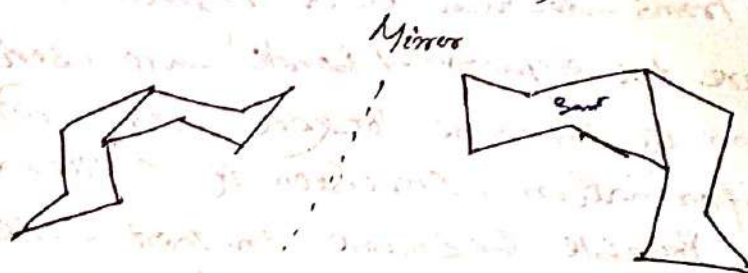
Trans decalin

Trans-decalin is achiral. Newman Projection formula of trans-decalin can be drawn as follows:



Newman projection of trans-decalin

In cis-decalin, one chair form of cyclohexane is fused to another chair-cyclohexane where an axial and an equatorial bonds on adjacent carbon of a chair-form are used for fusion with the other. This two chair form of cis-decalin is not rigid like trans-decalin. cis-decalin can be flipped in which both the chair forms undergo inversion to form another cis-decalin.



* Why trans-decalin is more stable than cis-decalin.

Johnson has calculated the difference in energy between the trans-decalin and cis-decalin assigning (arbitrarily) a value of zero energy to the trans-isomer. When two forms are compared, it is found that trans-form has 12 skew interactions and 3 staggered and 15 skew. Thus cis-decalin has three additional skew (sawtooth gauche interactions). These interactions may be shown as follows:



Additional gauche interactions in:
 $C_2-C_1-C_9-C_8$
 $C_4-C_{10}-C_5-C_6$
 $C_4-C_{10}-C_9-C_8$

The difference of energy is due to three gauche-interactions i.e. $3 \times 3.87 = 10.11 \text{ kJ/mol}$. Thus trans decalin is more stable than cis-decalin.

* Conformation of Cyclohexanone:

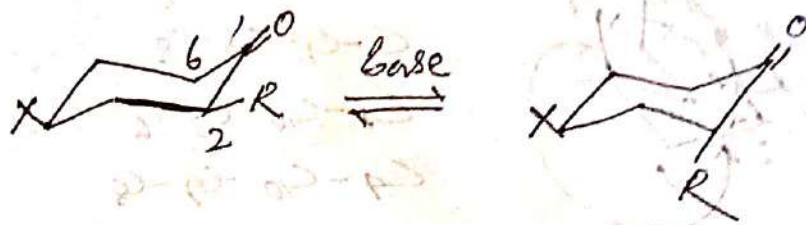
It is observed that when an sp² carbon atom is introduced in cyclohexane, the chair conformation is not very much disturbed. For this reason, cyclohexanone having an exocyclic C=O bond attached to cyclohexane ring exist almost entirely (90%) in the chair form and the chair form easily interconvertible.

Back



2-alkyl ketone effect:

In cyclohexanone, the equatorial hydrogen atoms at C-2 and C-6 are partially eclipsed with the C=O group and if either of them is replaced by an alkyl group, the interaction between it and the carbonyl oxygen may destabilise the equatorial conformer and the energy barrier between the axial and equatorial conformations also decreases in comparison to that in cyclohexane. 2-alkylated cyclohexanones undergo facile epimerisation and the equilibrium prefers axial isomer.



When $R = \text{Me}$, the value of $-\Delta G^\circ$ is almost zero. This is because of the fact that $-\text{CH}_3$ does not produce any serious steric problem. Moreover there is an attractive interaction between $\text{C}=\text{O}$ and a group, as observed in the conformational study in propanal. The $-\Delta G^\circ$ value gradually increases when $R = \text{Et}$, $R = \text{iPr}$. When $R = \text{t-Bu}$, the major exists in twist boat conformation in which $\text{t-Bu/C}=\text{O}$ eclipsing is avoided.

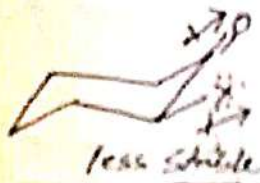


2-t-Butyl Cyclohexanone twist boat conformation

α -Haloketone effect:

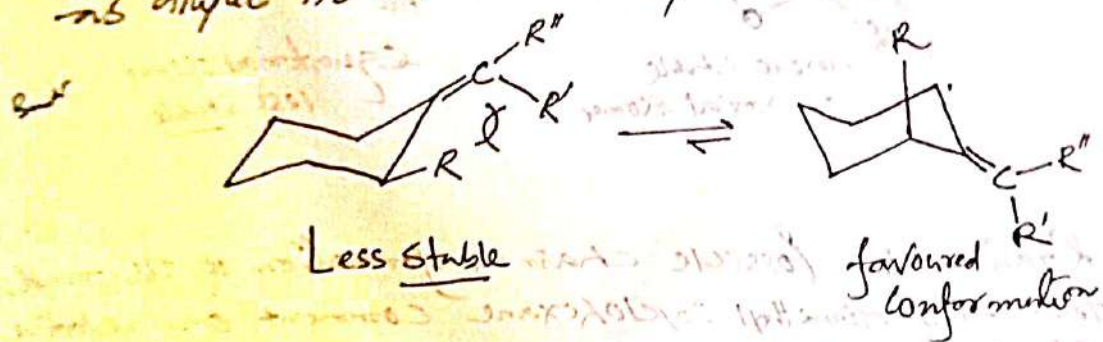
Conformational study of α -halocyclohexanones reveals that conformation with axial halogen atom is more stable than that of equatorial halogen. This phenomenon is called haloketone effect and is closely related in character to the anomeric effect.

The axial preference of halogen atom has been explained on the basis of dipole-dipole repulsive interaction present in equatorial isomer where the $\text{C}=\text{O}$ and $\text{C}-\text{X}$ are almost parallel. The dipole-dipole interaction is supported by the fact that equatorial isomer has increased stability in polar solvents.



A^{1,3} Strain

In alkylidene cyclohexanes $C=C$ group in cyclohexane is replaced by $C=C R' R''$. It is found that there is no appreciable change in the chair conformation of cyclohexane due to this structural modification. In the equatorial conformation, the allylic reagent is near to equator so that R' and R'' are almost eclipsed, giving rise to 1,3-diaxial type strong steric interaction and therefore, an exocyclic $C=C$ bears an equatorial substituents on the adjacent position. This interaction is specifically called as allylic 1,3-strain and symbolised as $A^{1,3}$ strain.



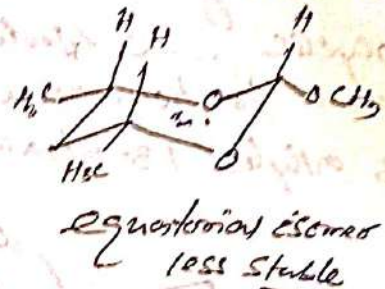
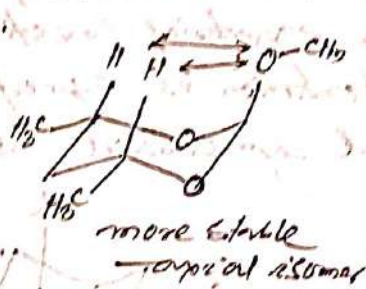
Conformation of Cyclohexene: A^{1,2} strain:

The introduction of a double bond within the cyclohexane ring greatly alters the geometry of the ring. The most stable conformation of cyclohexene is half chair form. In this form one can easily distinguish between the axial and equatorial linkages for homoallylic carbon atom C-4 and C-5. The axial and equatorial character is less marked for allylic positions, which are therefore, designated pseudo-axial and pseudo-equatorial. C-1, C-2, C-3 and C-6 carbon atoms and two vinylic carbon atoms are in one plane. C-4 and C-5 atoms are disposed alternately up and down with respect to this plane.



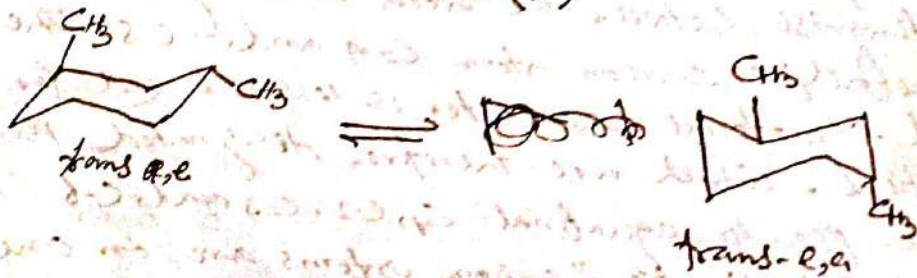
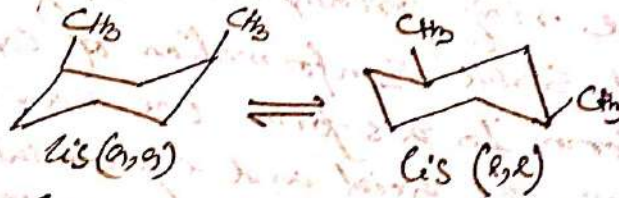
1,3-dioxane: Double anomeric effect:

Like tetrahydrofuran, 1,3-dioxane is also found to have stable chair conformations. In case of 2-methoxy-1,3-dioxane, axial methoxy isomer is found to be very much preferred over the equatorial isomer, although the former has strong e_1 -diaxial interaction. The greater stability of axial isomer has been attributed to the double anomeric effect.



* Draw all the possible chair conformations of cis and trans-1,3-dimethyl cyclohexane. Comment on relative stability. Are the compounds resolvable?

Ans cis- and trans-1,3-dimethyl cyclohexane have chair conformations as shown below:



Cis-isomer has (aa) and (ee) - diastereoisomerism. The (aa) form has two butane-gauche and one CH_3/CH_3 syn-diaxial interactions and therefore very unstable. The (ee) form has no interaction and therefore, most stable. The trans form has only one conformation i.e. (ae) or (ea). The trans form has ~~only~~ butane-gauche interaction and therefore, energy increases by an amount of ~~1.8 kcal/mole~~ 1.8 kcal/mole .

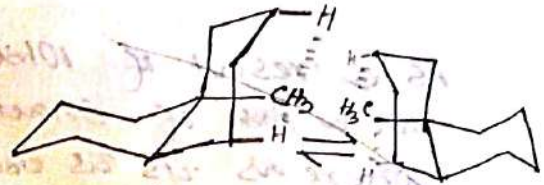
The cis-form are achiral having plane of symmetry. The trans form is chiral and therefore, can exist as enantiomeric form.

* What changes are observed in the mixture of butane-gauche interactions when a methyl group is introduced at one of the bridge-head carbon atoms of trans and cis-decalin.

Ans: Introduction of a methyl group at one of the bridge head carbon atoms of trans and cis-decalins gives rise to additional butane-gauche interactions. The number of such interaction is four in trans-isomer and five in cis-isomer. Before the introduction of the methyl group, trans isomer was free from any gauche interaction and cis had three. Therefore, introduction of a methyl group, the energy difference between trans and cis-decalins decreases.



trans isomer
 four butane
 gauche
 interactions



five butane-gauche
 interactions

cis-isomer

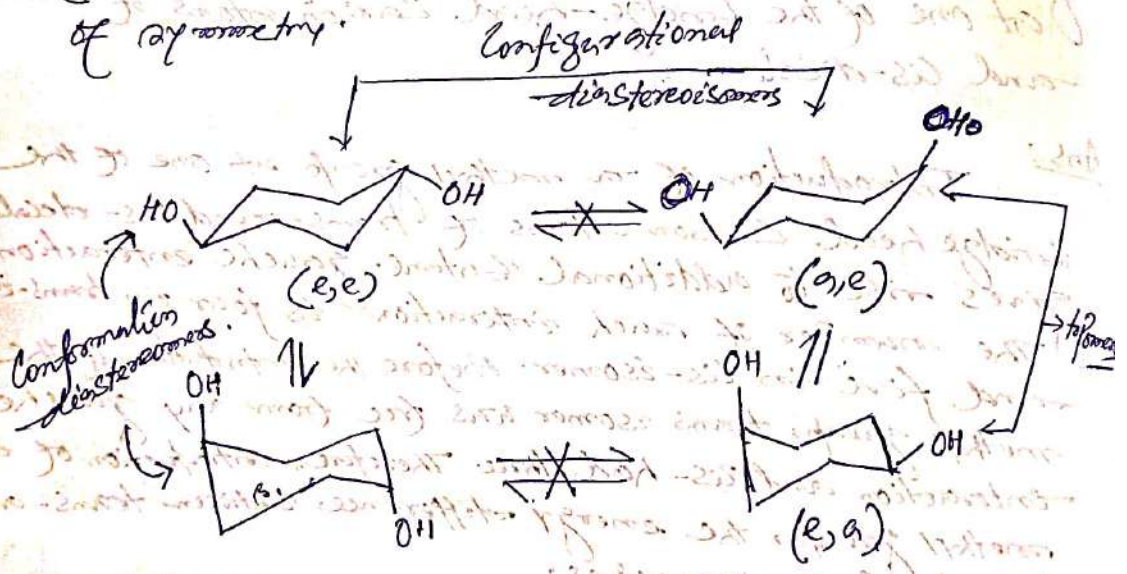
*

Trans-1,4-cyclohexane diol exist as a pair of inactive conformational diastereoisomers whereas its cis-isomers exist as a single inactive isomer.

Ans

Possible isomers of 1,4-dihydroxy cyclohexane are cis- and trans-. cis-isomer exists as two equivalent topomeric (a,e) and (e,a) forms. Trans isomers can have diastereoisomeric (e,e) and (a,a) forms, but they are conformational diastereoisomers.

1,4-disubstituted cyclohexane are always achiral irrespective of the nature of substituent (achiral) because all of them have vertical plane of symmetry.

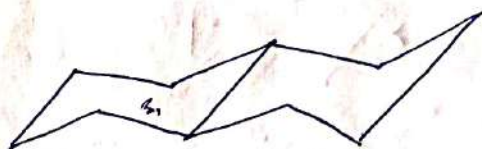


As a result of which trans-1,4-cyclohexane diol exist as a pair of inactive conformational diastereoisomers whereas its cis isomers exist as a single inactive isomer.

* Cis-decalin is flexible whereas trans-decalin is rigid. Explain.

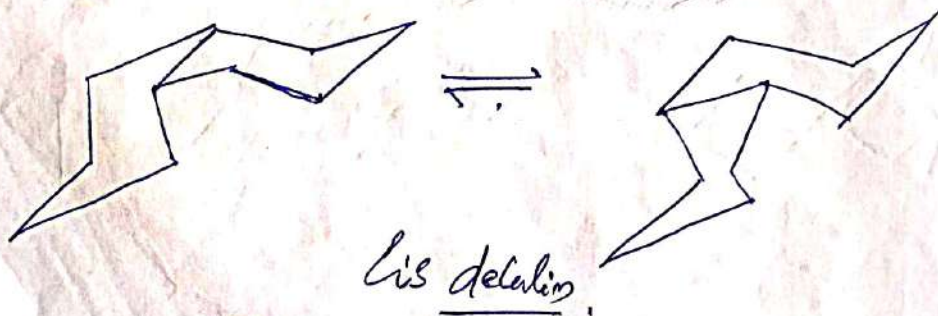
Ans

Trans-decalin is a rigid two-chair conformation where two-equatorial bonds are used by one-chair form to become locked with another chair. In this conformation, inversion of cyclohexane rings are not possible because in that case the trans-diequatorial bonds on adjacent carbons, by which one cyclohexane is joined to another, will have to become trans-diaxial having anti-periplanar orientation resulting excessive strain in the molecule. Therefore trans-decalin represents a conformationally locked system.



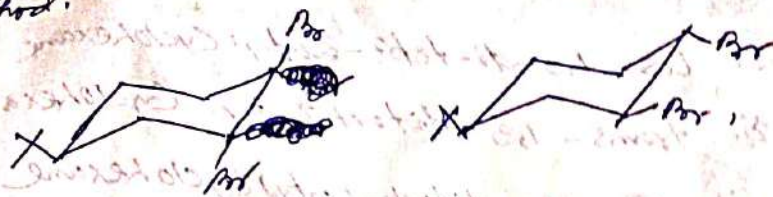
Trans-decalin

In cis-decalin, one chair form of cyclohexane is fused to another chair-cyclohexane where an axial and an equatorial bonds on adjacent of a chair-form are used for fusion with the other conformation of cis-decalin. This two-chair conformation of cis-decalin is not rigid like trans-decalin. Cis-decalin can be flipped in which either the chair forms undergo inversion to form another cis-decalin.



Cis-decalin

* How can you easily distinguish the following two cyclohexane derivatives by physical or chemical method.



2. Write down the preferred conformer(s) of the following compounds with reason:

i. trans-1,3-di-*n*-butylcyclohexane

ii. cis-9-methyl decalin.

3. Explain 2-halo ketone effect in cyclohexanone

4. Among cis and trans-decalin, which of them represent a chiral molecule? Is that compound resolvable give reason.

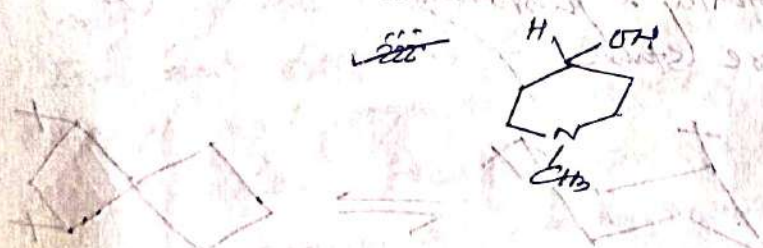
5. cis-1,2-cyclohexane diol is a pair of conformational isomers, where as its trans isomer exists as a pair of configurational enantiomers, each of which exists as a pair of conformational diastereomers. Explain the observation.

6. Why Bayer strain is not applicable to bicyclic compounds?

7. Indicate the preferred conformation of each of the following compounds:

i. trans-1,3-dimethylcyclohexane

ii. 1-methyl-1-phenylcyclohexane



* Draw the structure of stable conformation of the following compound with reasons.

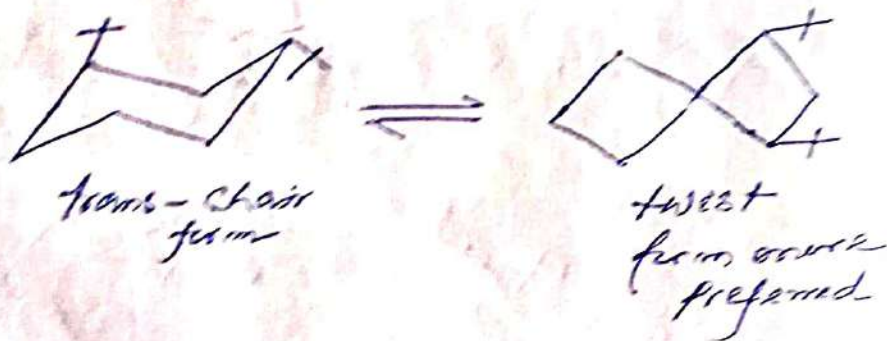
- i. cis-1,3-di-tert-butylcyclohexane
- ii. trans-1,3-di-tert-butylcyclohexane
- iii. cis-1,4-di-tert-butylcyclohexane
- iv. trans-1,4-di-tert-butylcyclohexane

Ans,

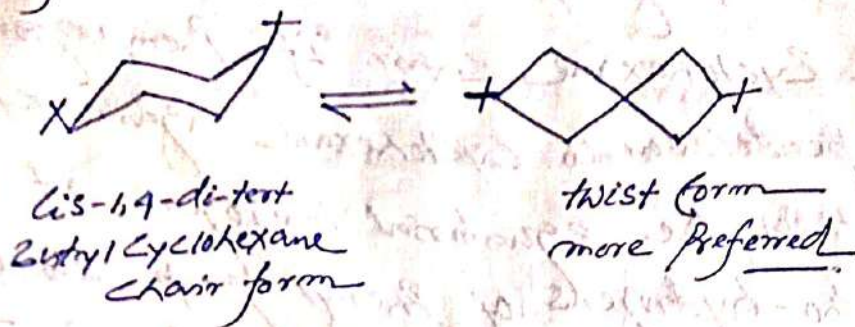
i. The cis-1,3-di-tert-butylcyclohexane exists in normal diequatorial chair conformation. There is no equatorial or axial gauche interaction in this compound. Therefore, the molecule is stable in this form.



ii. The trans-1,3-di-tert-butylcyclohexane exists in an equilibrium mixture of chair and twist forms. In chair form one tert-butyl group is in axial position having a conformational energy of 4.8 kcal/mol. This is very close to the energy difference between the chair and twist conformations of cyclohexane. In twist form tert-butyl groups are essentially equatorial. The twist form is slightly more stable.



iii) The *cis*-1,4-di-*tert*-butylcyclohexane also exist as an equilibrium mixture of chair and twist form. The twist form has some predominance over the chair form.



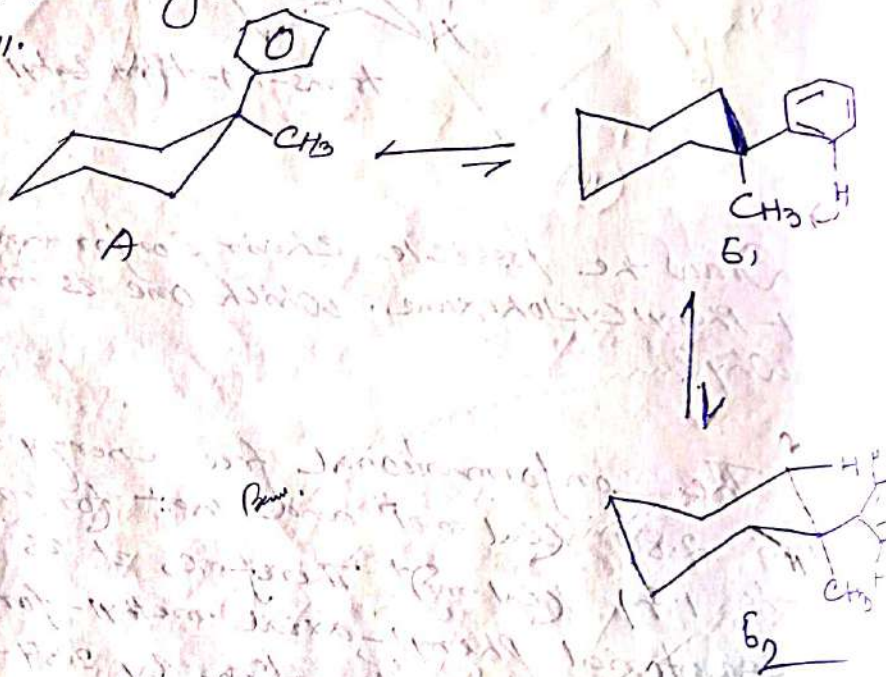
iv) The *trans*-1,4-di-*tert*-butylcyclohexane has the normal chair conformation with diequatorial orientation of *t*-butyl group.



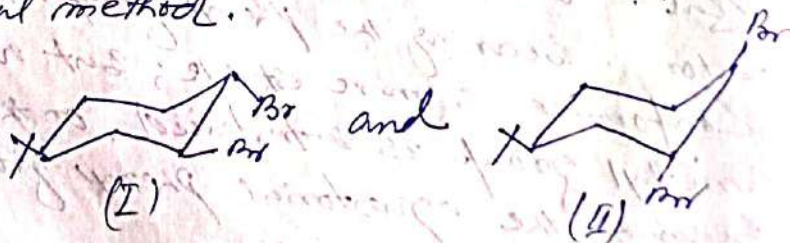
* Draw the possible chair conformations of 1-methyl-1-phenylcyclohexane. Which one is more stable and why?

Ans The conformational free energy of phenyl-group is 2.87 kcal/mol and that for methyl group is 1.74 kcal/mol. Therefore, it is expected that the preferred conformation is axial phenyl, equatorial methyl form (should be preferred conformation by $2.87 - 1.74 = 1.13$ kcal/mol if the conformational energies are additive. In fact, however, conformation 'A' with axial phenyl and equatorial methyl is preferred by 0.32 kcal/mol. When there is no methyl group on the carbon atom bearing the phenyl group, then equatorial conformer is more stable; but when an axial methyl group is introduced on the same carbon bearing the equatorial phenyl group, a series of

Steric interaction develops between the methyl group and one of the ortho-hydrogen atoms of the phenyl group, as shown in E_1 conformation. In E_1 , phenyl group is in the same vertical plane with the cyclohexane chair. If phenyl group is placed perpendicular to cyclohexane, a given steric interaction between the equatorial hydrogens at C-2, C-6 and ortho-hydrogens of phenyl group becomes minimized. This is shown in conformation E_2 . This type of steric interactions are not present in conformation A. Therefore, A is the preferred conformation in this case. The energy barrier between E_1 and E_2 is quite small.



* How can you easily distinguish the following two cyclohexane derivatives by physical or chemical method.



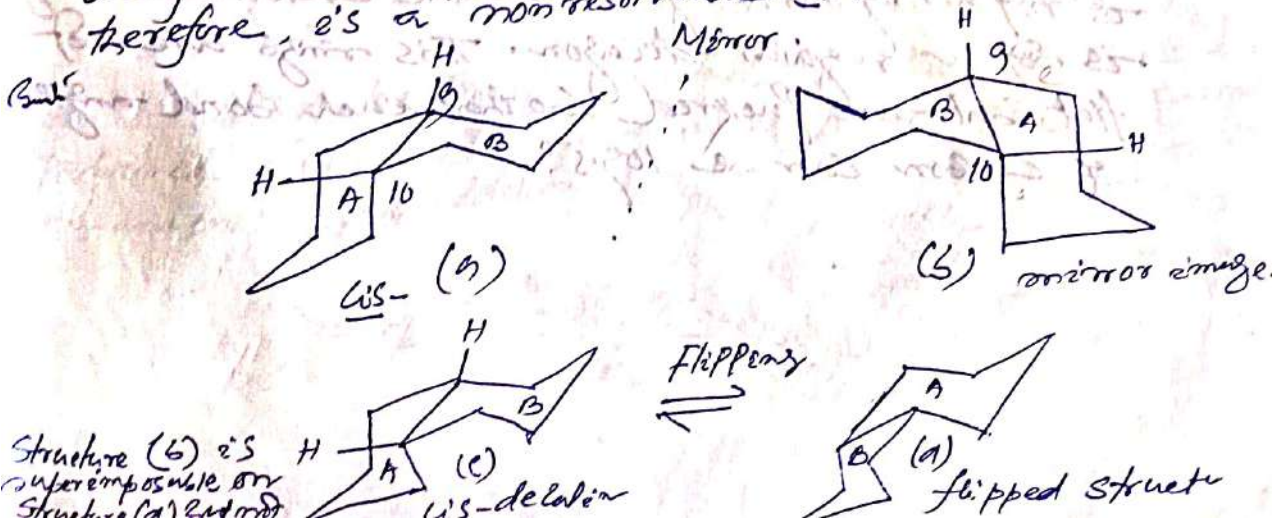
I and II are enantiomeric system due to bulky-CMe₃ group at C-1 position. Therefore, they do not easily undergo ring inversion. In I, C-Br bonds are antiperiplanar and therefore C-Br bond vectors are opposing each other. Consequently, its resultant dipole moment will be low compared to II where C-Br bond vectors are separated by a dihedral angle of 60°. Therefore, these two diastereoisomers can be distinguished from their dipole moment values. In fact, dipole moments of I and II are 1.19 D and 3.3 D respectively.

* Among cis- and trans-decalin which of them represent a chiral molecule? Is that compound resolvable gives reason.

Ans

Trans-decalin has a C₂ axis along with a σ_h perpendicular to C₂ axis. As a result of which, trans-decalin is achiral.

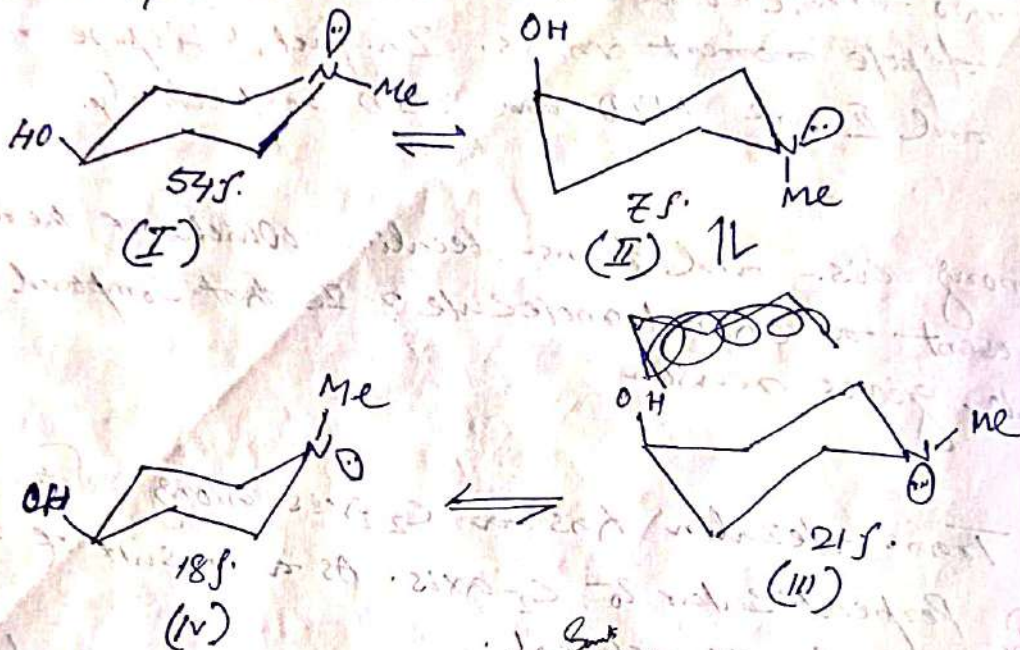
Cis-decalin represents a chiral conformation having only C₂-proper axis passing through the mid-point of the bond joining C₉ and C₁₀. The C₂ proper axis bisects the dihedral angle between the planes containing C-9-H and C-10-H. Since cis-decalin has a point group C₂ (C₂) it represents a chiral molecule but it can not be resolved because flipping of one form always gives its enantiomer. Cis-decalin, therefore, is a non-resolvable (d,l) pair.



Indicate the preferred conformation of



Ans In case of N-methyl-4-hydroxypiperidine, four conformations are possible due to ring inversion and pyramidal inversion.



* Why Bayer strain theory is not applicable to higher ring compound.

Ans This is due to the fact that the angles that Bayer used for each ring were based on the assumption that the ring were flat. For example, the angle of a regular hexagon are 120° , the angles for a regular decagon are 144° . But the cyclohexane ring is not a regular hexagon, and the cyclodecane ring is not a regular decagon. These rings are not flat, but are puckered so that each bond angle of carbon can be 109.5° .

