Stereochemistry

Conformational Analysis

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Conformational Analysis

Rotations around single bonds gives rise to different Conformations. An infinite number of geometrical arrangements are possible by virtue of rotations around the single bonds in a molecule.

H_2 molecule → only one Conformation

CH_4 → only one Conformation

Rotations around single bonds do not give rise to different geometrical arrangement.

→ Analysis of the energy changes that a molecule undergoes when different groups rotate about the single bonds is called as Conformational analysis.
(Also deals with the reactivity of different conformers)

→ It is important to understand that during rotations, a molecule can adopt different shapes, but the localized arrangement of the atoms remains unchanged That is in saturated hydrocarbons, each C-atom is always tetrahedral before, during and after the rotations.

→ Conformations

Different Conformations are obtained by rotating a molecule about single bonds

Conformers

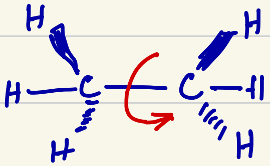
Configuration

In going from Configuration to another, we have to break bonds

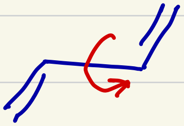
Different Configurations
or
Stereoisomers

Energy barriers to the rotations:

Every molecule Can rotate freely about the Single-bonds, but it needs energy to Carry out the process of rotation. The amount of energy needed to Carry out a rotation varies from one molecule to another.



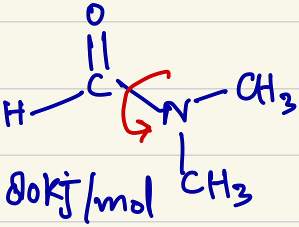
12kJ /mol



30 kJ /mol

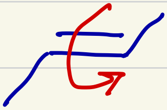
↓

Partial double bond Character

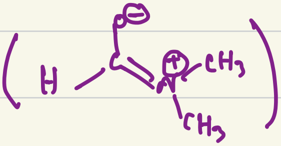


80kJ/mol

Partial double bond character



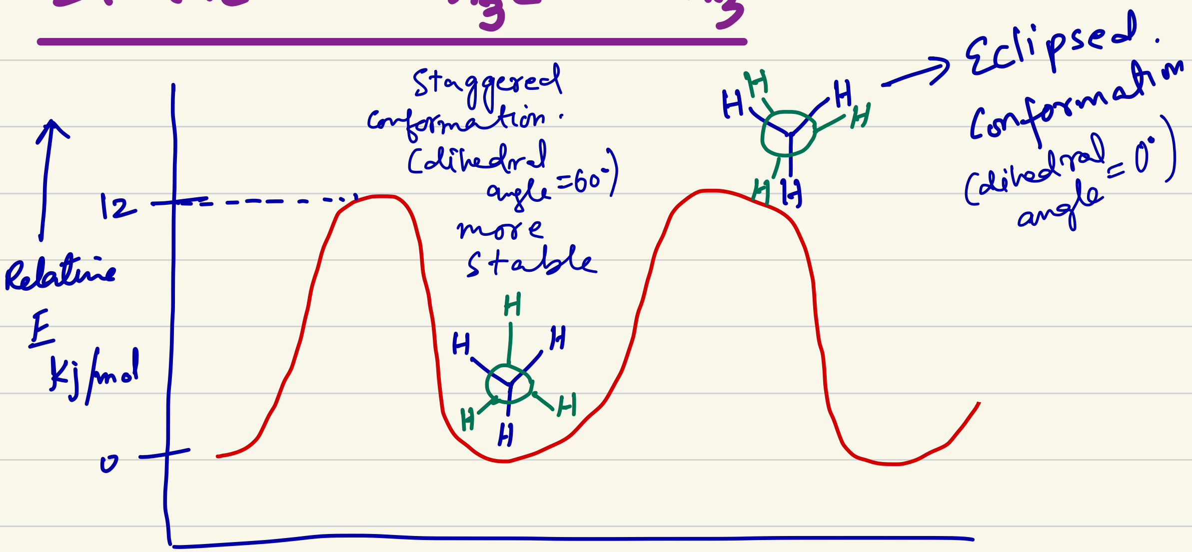
260 kj/mol



→ Beyond a barrier of about 55kJ/mole, the various Conformers of a molecule Can be distinguished by NMR spectroscopy

→ Because of huge energy barrier (260 kj /mol) the E and Z alkenes Can be easily separated.

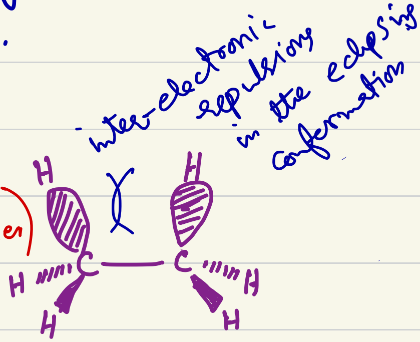
Ethane $H_3C—CH_3$



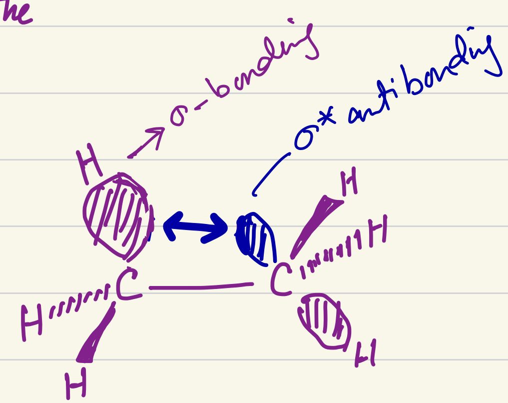
→ Staggered Conformation is 12 Kj/mol more Stable than the Eclipsed Conformation.

→ More stable for two reasons

(i) Repulsion between the filled orbitals of C–H bonds in eclipsed Conformation (Contributes about 10% to Energy barrier)

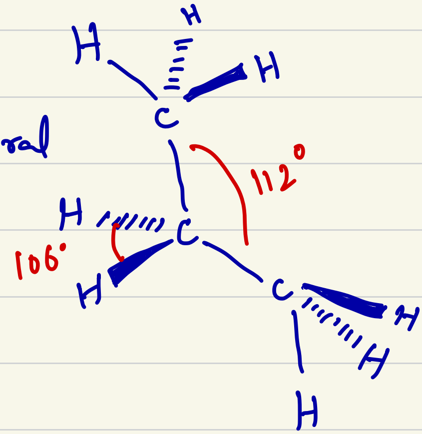


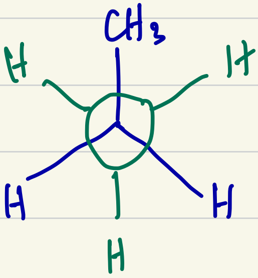
(ii) Stabilizing interaction between the σ-bonding (C–H) orbital with the σ* antibonding orbital on the carbon, in the staggered Conformation. (More important factor)

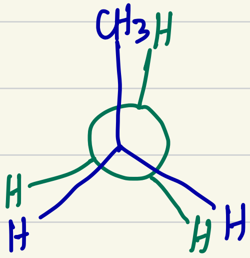


Propane: $CH_3-CH_2-CH_3$

Repulsions between the two C—C bonds Causes the deviation from the tetrahedral bond angle of 109.5°.



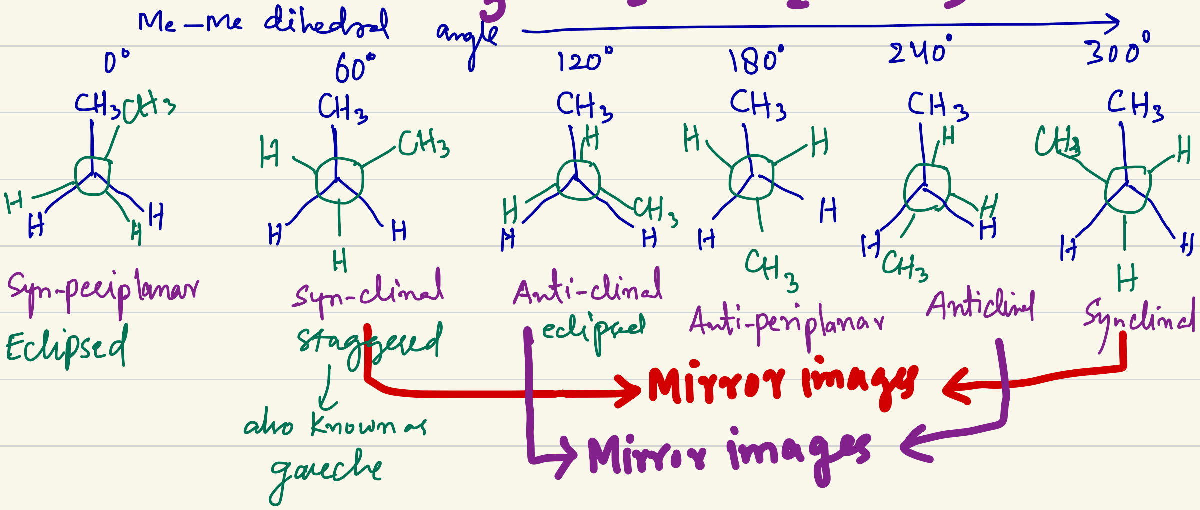


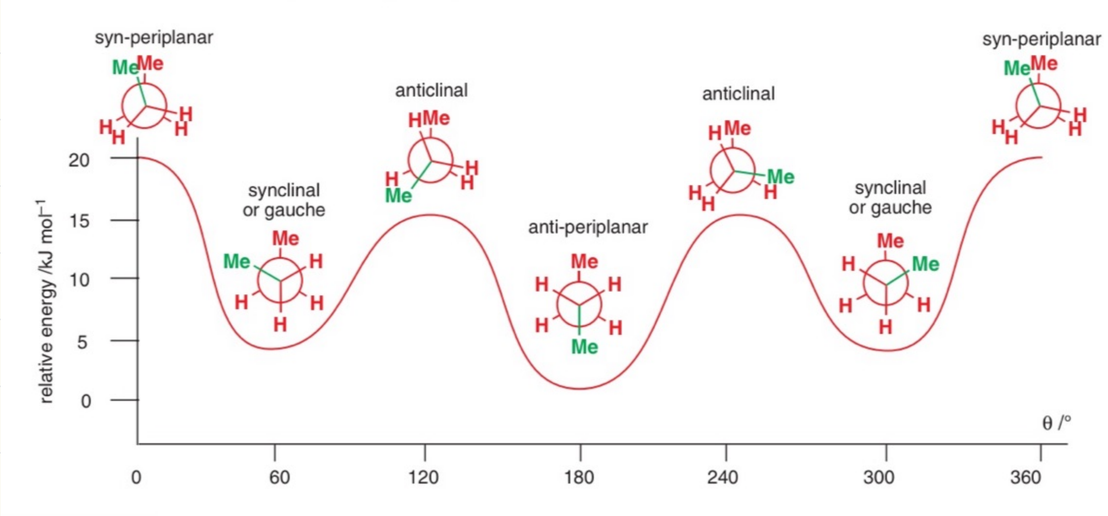


Staggered Conformation is 14 kJ/mol more Stable as Compared to the eclipsed Conformation for the Same reasons as discussed for Ethane.

Butane

$CH_3-CH_2-CH_2-CH_3$





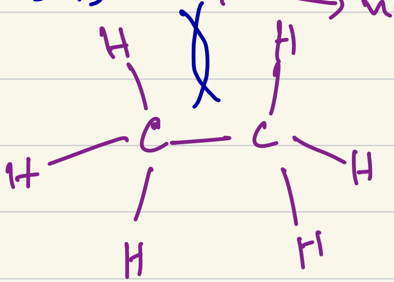
→ Two different eclipsed Conformations. one in which $-CH_3$ and H are eclipsed and the other in which $-CH_3$ & $-CH_3$ are eclipsed (known as partially eclipsed & fully eclipsed respectively).

Different types of strains:

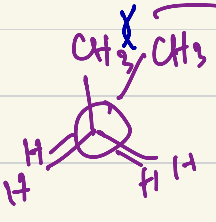
while discussing the conformational analysis, you will come across terms like Steric Strain, Torsional (or pitzer) strain and ring strain. All these types of strains are actually the reasons why some conformations of molecules are stable as compared to others.

Steric Strain:

Repulsions between groups that are not directly bonded to one another (may be separated by 4 or more bonds or may not be boned at all) approach each other too closely to occupy the same space. This repulsion is more for the bulky substituents ($-CH_3$, $-Et$, $-{}^{i}Pr$, $-{}^{t}But$)

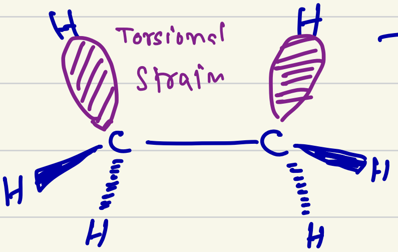


no steric strain as H's are very small



Two $-CH_3$ groups are close enough to experience steric strain. As a result this Syn-periplanar conformation is 20 kJ/mol high in energy as compared to the anti conformer.

Torsional Strain: The origin of torsional strain is the electrostatic repulsions between the electron clouds of two adjacend σ-bonding orbitals that are separated by a single bond.



→ Torsional strain in eclipsed form of ethane is in part responsible for its instability.

Torsional strain only ever exists between atoms separated by three bonds only, like the eclipsed form of ethane.

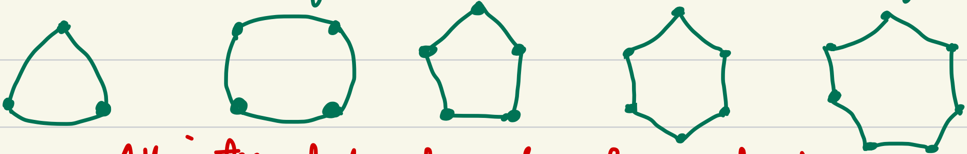
→ The staggered form of ethane has the C–H bonding orbitals as far away from each other as possible at dihedral angles of 60°, 120° and 180° and torsional strain is at a minimum in staggered conformation of ethane.

Ring Strain:

→ Fully saturated Carbocyclic rings have all the C-atoms with sp^3 hybridization and hence would like to have an ideal bond angle of 109.5°. However in planar rings, the internal bond angle is decided by the no. of atoms (size) in the ring.

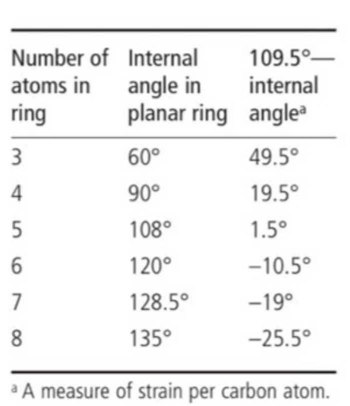
→ Any deviation from the ideal 109.5° bond angle causes strain in these Carbocycles.

→ Planar Carbocycles with all internal bond angles = 109.5°



All internal bond angles forced to be 109.5°

→ Table gives an idea about the deviation of internal ring angles from the ideal bond angle of 109.5° and hence a measure of angle strain per Carbon atom → If the rings are planar.

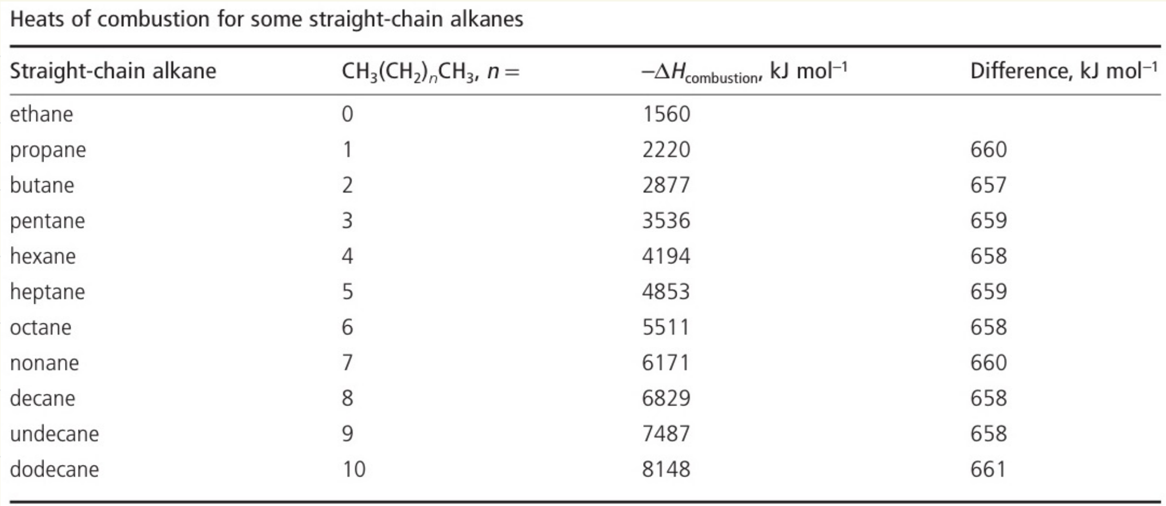


Number of atoms in ring	Internal angle in planar ring	109.5°—internal angle[a]
3	60°	49.5°
4	90°	19.5°
5	108°	1.5°
6	120°	−10.5°
7	128.5°	−19°
8	135°	−25.5°

[a] A measure of strain per carbon atom.

→ Deviation from the ideal angle would certainly be a measure of the ring strain if the rings were planar, however a fully saturated Carbocycle is rarely planar and in order to get an idea about the ring strain in the Carbocycles the way they are, we have to compare them with the acyclic Counterparts.

Ring Strain: A good idea about the strain in the real rings is obtained by looking at their heats of combustion and also the heats of combustion of their straight chain analogues.



Heats of combustion for some straight-chain alkanes

Straight-chain alkane	$CH_3(CH_2)_nCH_3$, $n =$	$-\Delta H_{combustion}$, kJ mol^{-1}	Difference, kJ mol^{-1}
ethane	0	1560	
propane	1	2220	660
butane	2	2877	657
pentane	3	3536	659
hexane	4	4194	658
heptane	5	4853	659
octane	6	5511	658
nonane	7	6171	660
decane	8	6829	658
undecane	9	7487	658
dodecane	10	8148	661

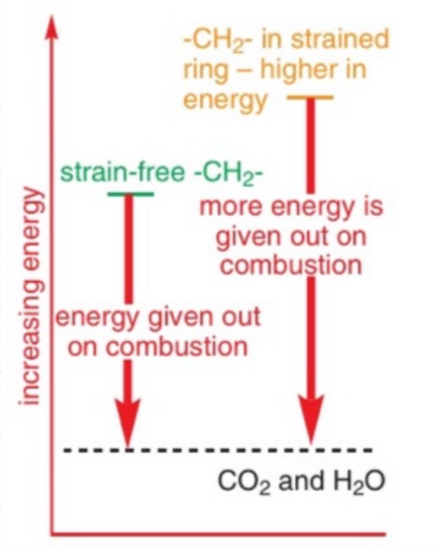
Inorder to get an idea about the ring strain from heats of combustion, we make certain assumptions.

→ Straight chain alkanes are free from any type of strain that exists in cycloalkanes because of their cyclic nature

→ Every successive $-CH_2-$ group contributes an average of 658 kJ of energy to the heats of combustion of alkanes.

→ Since cycloalkanes are merely a multiple of $-CH_2-$ groups, their heats of combustion should be $(n \times 658)$ kJ/mol, where n = no. of $-CH_2-$ groups in the ring.

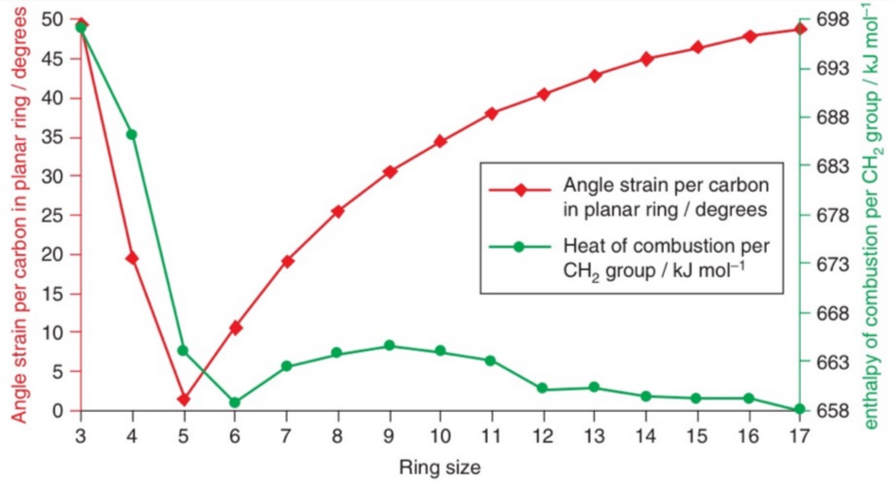
→ If cycloalkanes are strained, they should be unstable and should release more energy per $-CH_2-$ group as heat of Combustion.



→ Now if we plot heat of Combustion per $-CH_2-$ group in cyclo-alkanes and the ring strain as Calculated by the deviations from the ideal bond angle of 109.5°. we get

→ Cyclopropane has the highest strain

→ Strain reaches a minimum value at cyclohexane and not cyclopentane as predicted by the bond angle Calculations.



→ The strain then increases, but not as rapidly as suggested by the bond-angle Calculations. Reaches a maximum at 9 membered ring and then decreases again.

→ After 14 membered rings, the strain remains almost unchanged.

→ For cyclohexane & larger than 14 membered rings the heats of Combustion per $-CH_2-$ group match with the acyclic alkanes and that is 658 kJ per $-CH_2-$ group.

→ Why does the actual ring strain not follow the order predicted by the bond angle calculations?

→ Why is there virtually no ring strain in cyclohexane?

→ Despite having a bond angle very close to the ideal tetrahedral bond angle, why is there still some amount of strain left in cyclopentane?

The answer to these questions is that these cycloalkane rings are not planar.

Larger the ring, easy it is to fold it into a strain free conformation like open chain alkanes.

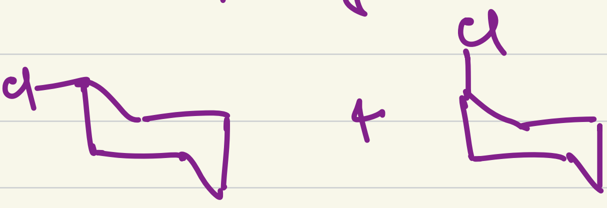
Source: Organic Chemistry
by Clayden, 2nd edn.

Bayer's theory : The Concept of planar rings

cyclopropane & cyclobutane have large deviation from tetrahedral bond angle and hence are unstable as compared to cyclopentane & cyclohexane.

Even cyclohexane has a deviation of 10.9° from tetrahedral bond angle.

1895 E. Sachse proposed that cyclohexane exists in strain free chair and boat forms. The idea was not accepted immediately as it meant that we can have two types of Chlorocyclohexane



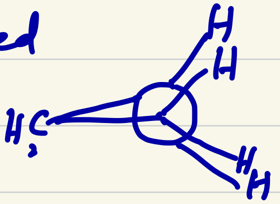
These two can interconvert rapidly.

In 1918, E. Mohr proved definitively that these forms of Chlorocyclohexane indeed exist.

Conformations of Cycloalkanes:

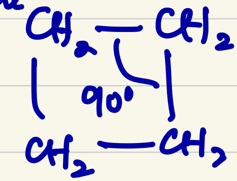
(i) Cyclopropane: It has the highest ring strain as the C–C–C bond angles are fixed at 60° & deviate from the tetrahedral bond angle by 49.5°.

The C–H bonds are all eclipsed as C–C bond rotation is not possible.

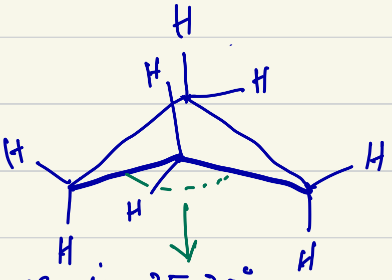


Because of these two strains, the heat of combustion per $-CH_2-$ group is highest.

(ii) Cyclobutane: In planar cyclobutane internal angles are 90° but that would put all the C–H bonds in eclipsed conformation.

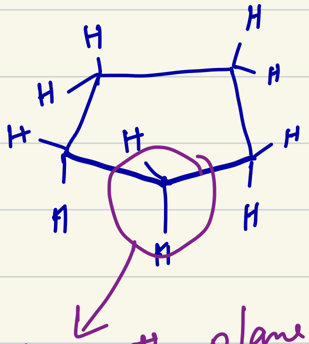


In order to reduce the C–H eclipsing interactions cyclobutane adopts a non-planar conformation that reduces the bond angles even further. The final shape is determined by a balance between the angle strain and eclipsing interactions.

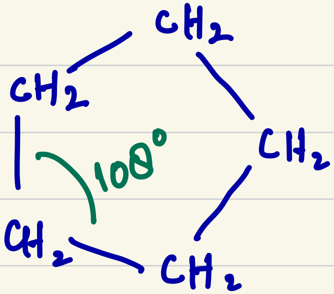


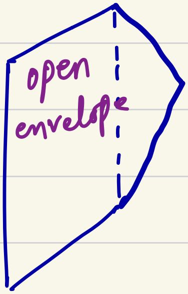
The dihedral angle b/w the two ring planes is 25-30°

(iii) Cyclopentane: Even though Cyclopentane has almost no angle strain, but in a planar structure all the C–H bonds would be eclipsed with one-another. To reduce the C–H eclipsing interactions cyclopentane adopts an open envelope type shape in which one of the $-CH_2-$ groups is out of the plane of the ring.



above the plane $-CH_2-$





This deformation of the ring moves throughout the ring in such a manner that at any given point of time, only one $-CH_2-$ group is out of the plane.

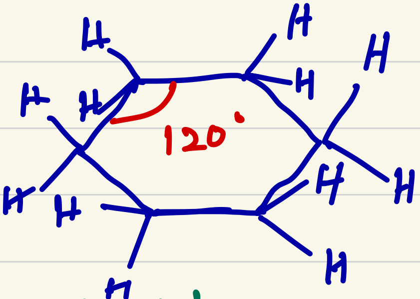
Because of this non-planar structure the bond angle decreases (Causing increase in angle strain), but the minium energy shape is decided by a balance of ring strain and C–H eclipsing interactions.

(iv) Cyclohexane: The C—C—C bond angle in an open chain $-CH_2-CH_2-CH_2-$ unit = 112.5°.

A planar cyclohexane has a bond angle of 120° & hence angle strain (120 − 112.5 = 7.5°) It also has all the C—H bonds eclipsed

Angle Strain = 7.5° (10.5° if we consider the tetrahedral bond angle 109.5°)

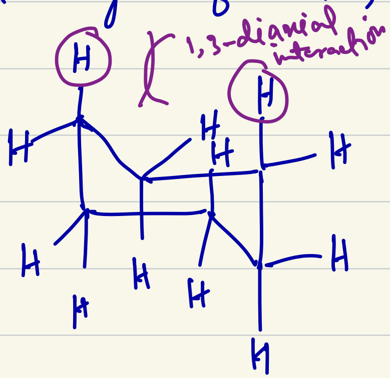
All C–H bonds eclipsed.

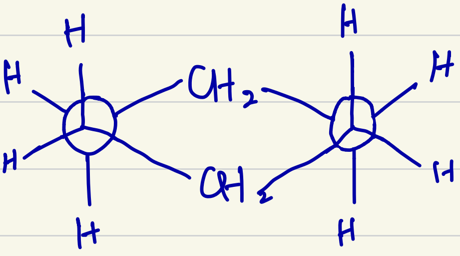


However from the heats of combustion we see that there is virtually no strain in cyclohexane.

When we try to make a model of cyclohexane with all the bond angles equal to the tetrahedral bond angle of 109.5°, we get two conformations;

(i) Chair Conformation

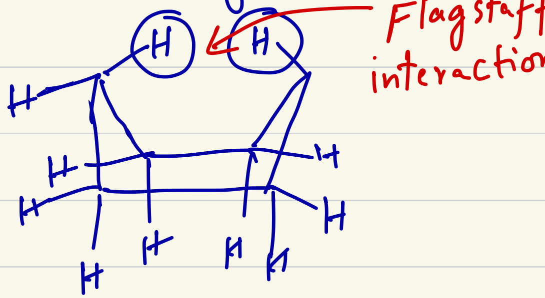


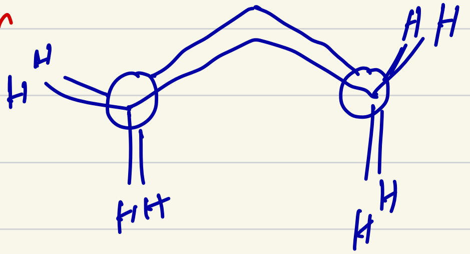


All the bond angles are 109.5°

All the C—H bonds are staggered.

(ii) Boat Conformation

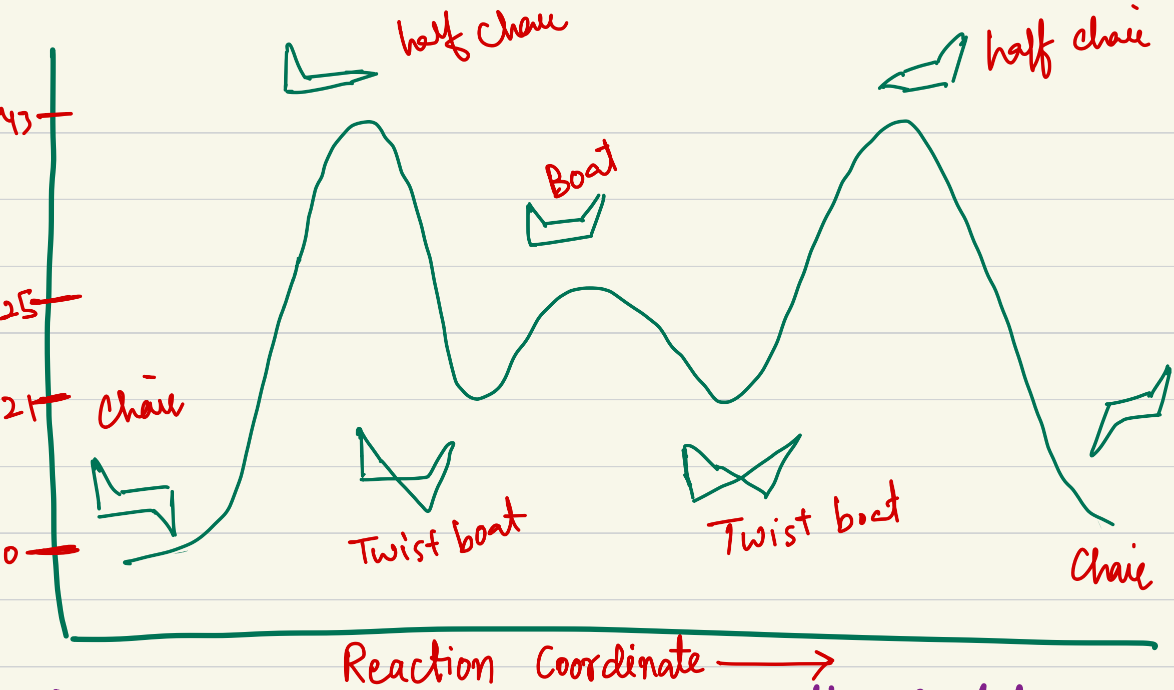




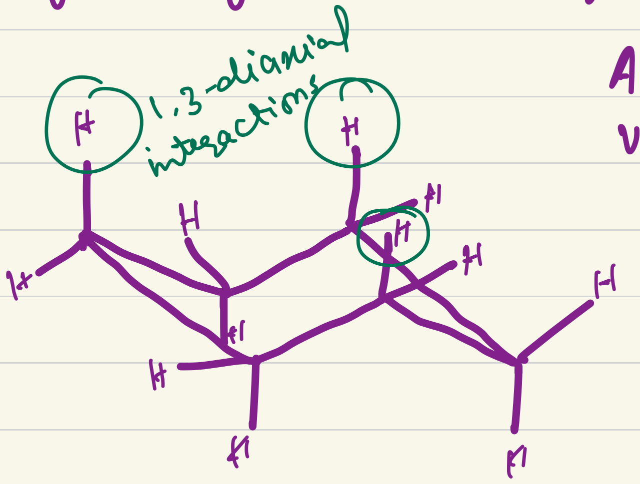
Flagstaff interaction (Steric repulsions between the C_1 & C_4 hydrogens) and the eclipsing C—H interactions makes the boat conformation about 25 kj/mol higher in energy as compared to the chair conformation.

There is another low energy conformation for cyclohexane known as the twisted boat conformation that is achieved when the eclipsing C—H interactions in the boat form are relieved. Twist boat is about 4 kj/mol lower in energy as compared to the boat conformation.

Also on going from chair to boat form, a very high energy (43 kj/mol from chair) conformer called half chair is obtained. It is the least stable conformation for cyclohexane.



Ring Flipping of the chair form of the cyclohexane.

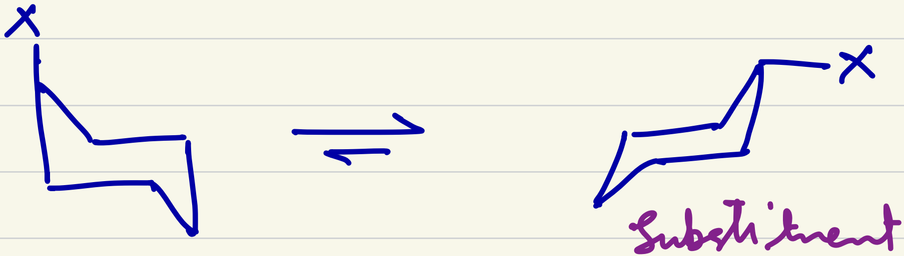


Axial H are either vertically up or down

Equitorial H are side-ways up or down.

Monosubstituted Cyclohexanes

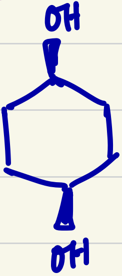
In monosubstituted cyclohexanes, the substituent can either be axial or equitorial and these two forms are in rapid equilibrium with each other. However the form where the substituent is equitorial is more stable as compared to the one where it is axial

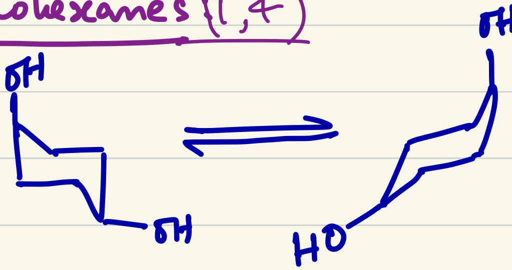


Substituent axial

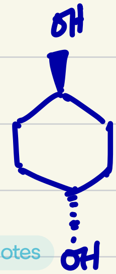
Substituent equitorial (more stable)

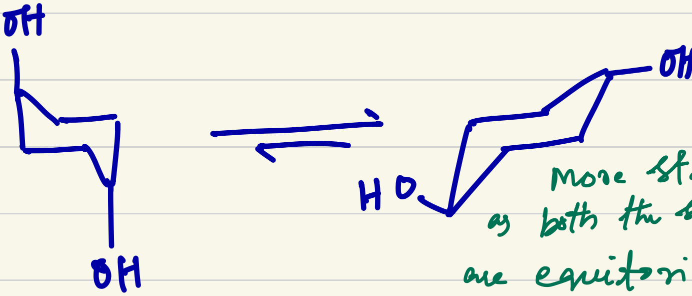
Disubstituted Cyclohexanes (1,4)



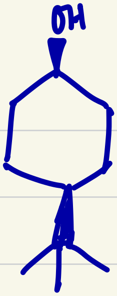


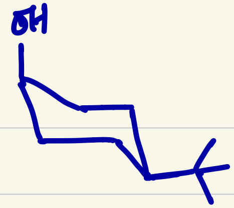
→ Both are equally stable



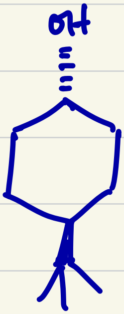


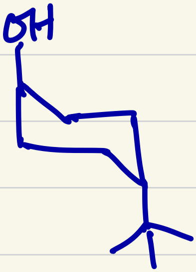
More stable as both the substituents are equitorial.



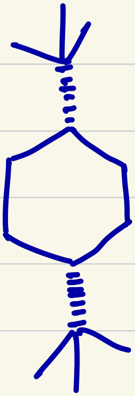


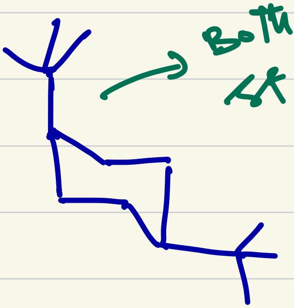
More stable as the largest substituent is equitorial



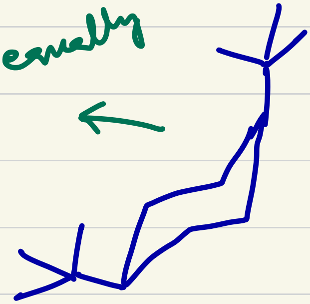


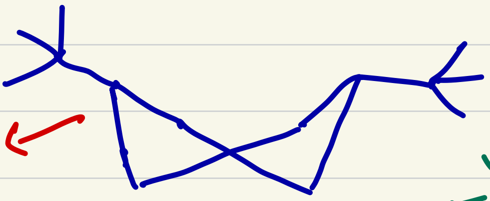
More stable as both the substituents are equitorial.





Both are equally stable



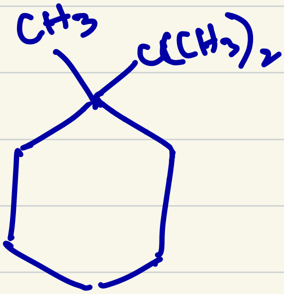


locked in twisted boat as in this both the substituents are equitorial.

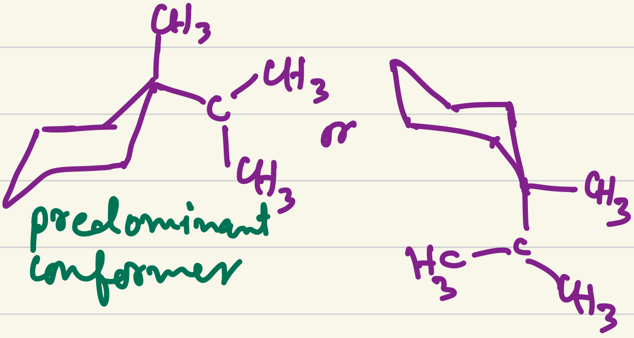
←

Twist boat is more stable than the chair form.

Assignment: predict the most stable Conformation for the following 1,2-disubstituted Cyclohexanes. (Use models in the tutorials to do it)

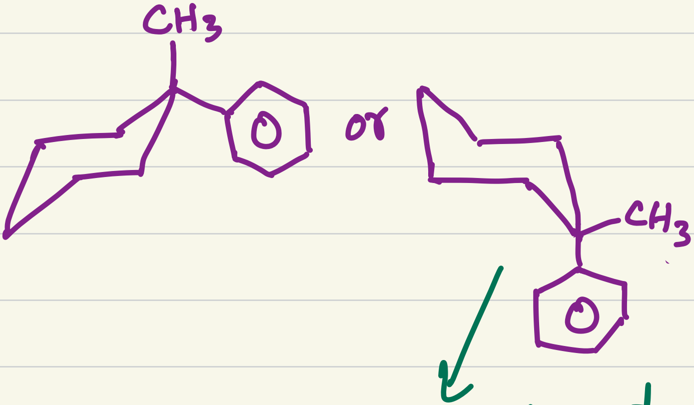


1,1-disubstituted



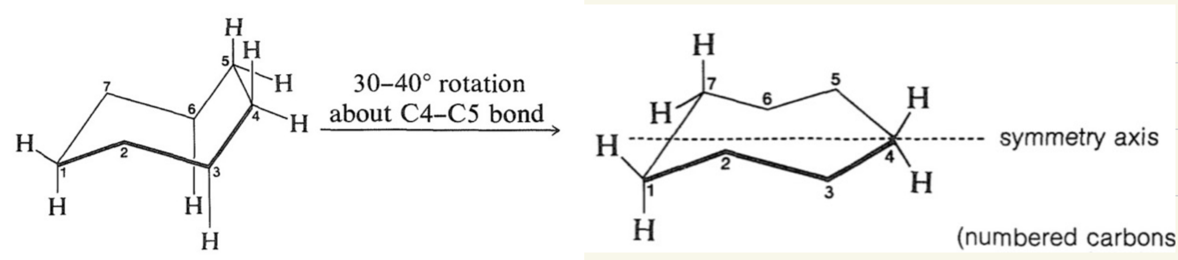
predominant conformer

1,1-disubstituted.



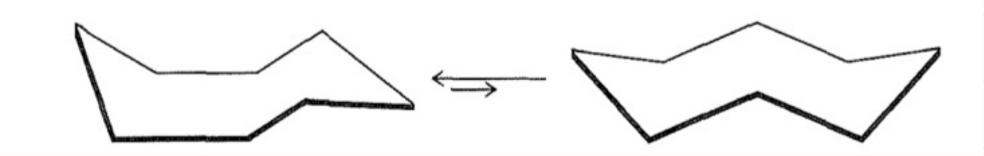
predominant because phenyl is planar and adopts an orientation in which it is able to avoid the 1,3-diaxial interactions.

(v) Cycloheptane: The chair form has eclipsed Hydrogens at C_4 and C_5. This is relieved by rotation about C_4-C_5 bond to give the



twisted chair form as shown.

(vi) Cyclooctane: The most favoured conformation for cyclooctane is boat-chair which is in equilibrium with the crown form.



Boat-chair Crown

cyclohexane with one sp^2 Carbon :

Introduction of an sp^2 Carbon atom causes many changes in a cyclohexane system;

(i) Flattening of the ring in the viscinity of the sp^2 Carbon

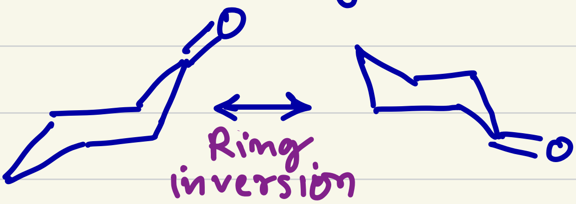
(ii) Increase in one angle

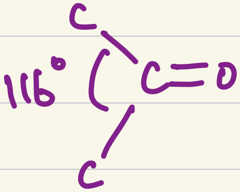
(iii) Decrease in a torsional angle causing an increase in the torsional strain.

Over all there is an increase in the energy.

Example: cyclohexanone

The combined effect of all the three factors for cyclohexanone makes it to exist exclusively as the chair conformation

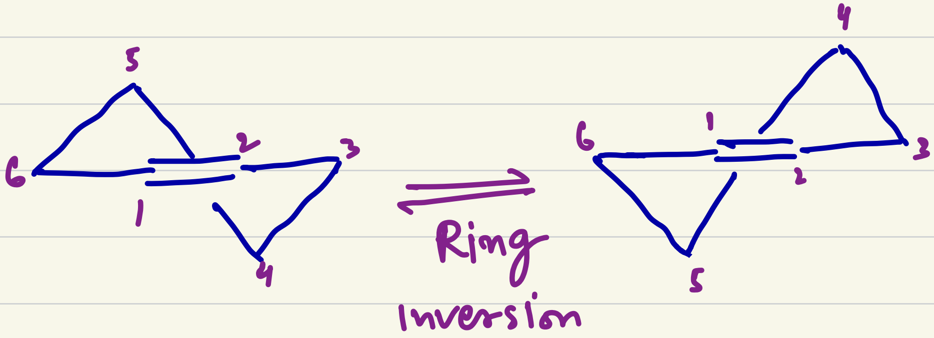




Because cyclohexanone is higher in energy than cyclohexane, the activation barrier for the ring inversion is considerably lower in cyclohexanone as compared to cyclohexane.

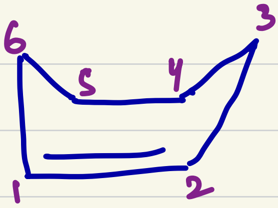
Cyclohexane with two sp² Carbon atoms: Cyclohexene

Cyclohexene by x-ray crystallography and electron diffraction data has been shown to predominantly exist as half chair as shown below



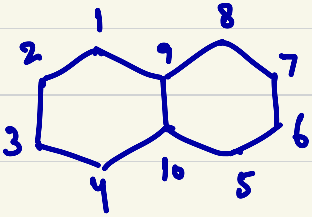
→ Cyclohexene ring is Considerably flattened near the C—C=C—C System.

→ The interconversion of the two half chair forms occurs through the boat Conformation shown below



Fused ring systems: Decalins & Decalones

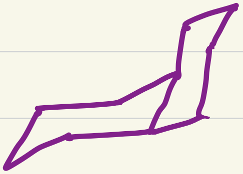
Bicyclo[4,4,0]decane (Decalin)



Decalin is the fused ring system of two cyclohexanes

→ There are two ways to join two cyclohexane chairs.

Trans-decalin



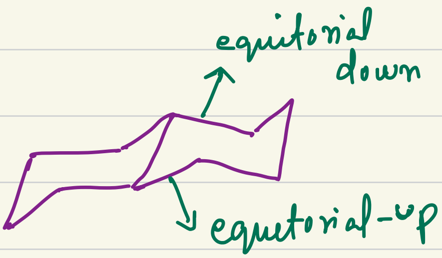
cis-decalin

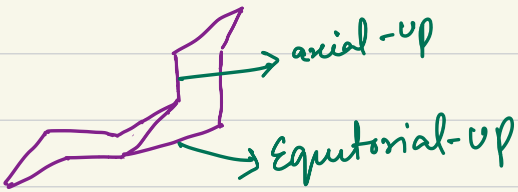
The two ring junctions are on the opposite sides of the molecule

→ Two rings are joined through the equitorial bonds

→ The two ring junctions are on the same side of the molecule

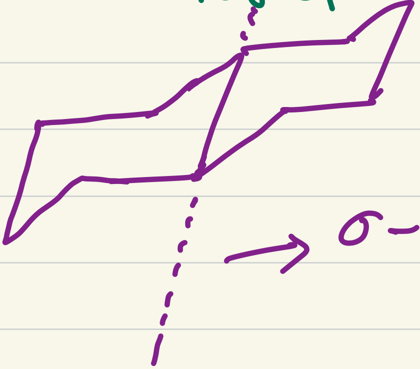
→ The two rings are joined at two points one axial & one equitorials





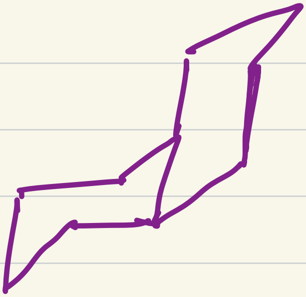
Ring inversion is possible only in cis-decalin & not in the trans decalin!!! Why? (Clayden 2nd Ed. page-379)

Trans-decalin is achiral as it has a σ-plane of symmetry passing through the Common bond



trans decalin

Cis-decalin on the other hand is chiral but due to rapid interconversion Cannot be resolved into the (+) & (−) enantiomers.

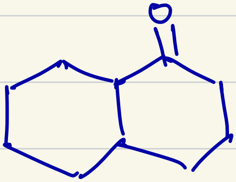


Cis-decalin is chiral but non-resolveable.

Decalones: Trans decalins without a substituent are achiral.
cis-decalins are chiral, but cannot be resolved.

→ Introduction of a single substituent creates 3 chiral centres: Two at the bridgeheads and one at the C-centre where the substituent is attached.

→ Introduction of a carbonyl group makes the two bridgeheads chiral & makes it possible to resolve (+) & (−) isomers in both the cis and trans decalin



1-decalone

The two enantiomers of trans-1-decalone can be resolved as they have a fixed Conformatio and do not undergo ring inversion.

For cis-1-decalone, the (+) & (−) enantiomers are resolveable as the conversion is not as rapid as the normal cis-decalin.

Conformation and Reactivity

When we look at how the energy of a molecule changes with rotations around bonds, we are concerned with conformations that correspond to energy minimum & energy maximum → This stereochemistry is called static stereochemistry

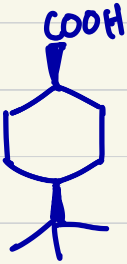
↙

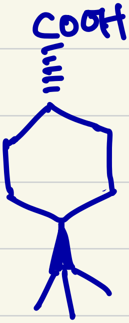
In static stereochemistry, we don't consider the interaction of the molecule with external factors and hence static.

When we take into account, how the conformation of a molecule affects its reactivity towards a particular reaction/process, we are no more concerned only with an isolated molecule. This is known as the dynamic stereochemistry.

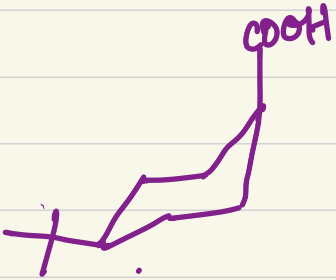
Conformation and Reactivity

Odd Hassel while studying the acidity of the 4-tert butyl cyclohexane carboxylic acids noted that the pKa values were dependent on the orientation of -COOH group, The cis isomer had a larger pKa value as compared to the trans isomer



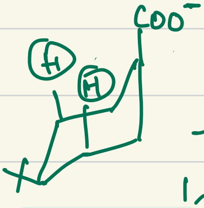


Since the tBu group locks the conformation with it being equatorial, we will have -COOH group either axially up or equatorially down.

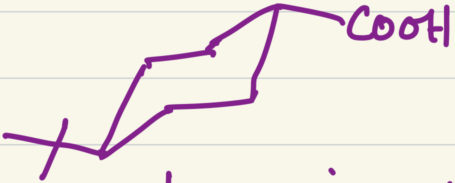


cis isomer

weaker acid because



cannot be easily hydrated because of 1,3-diaxial interaction



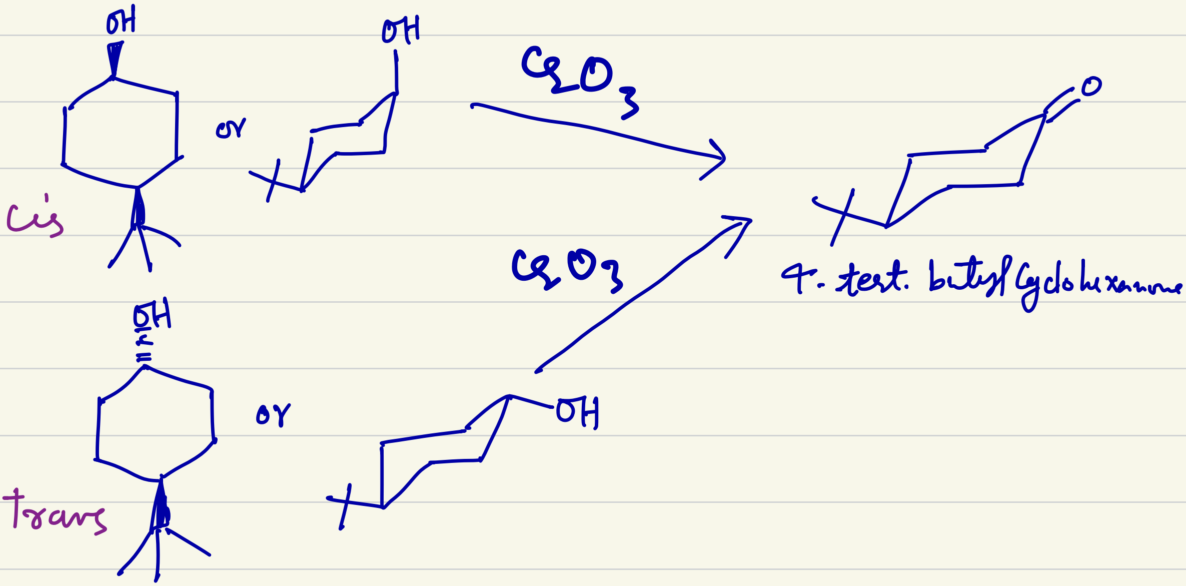
trans isomer

Stronger acid because

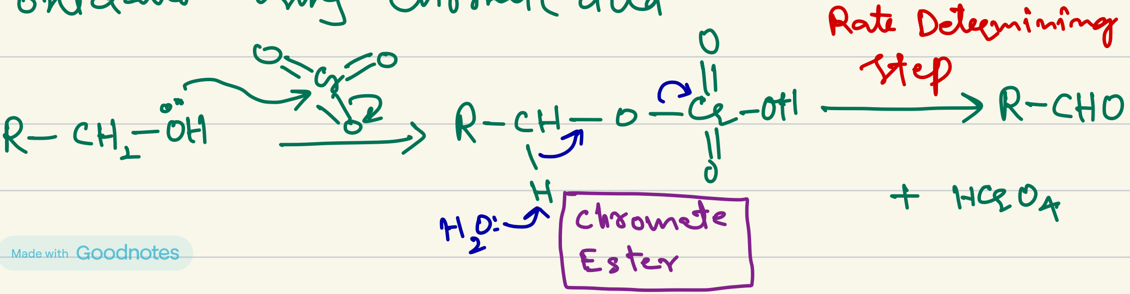
can be easily hydrated & hence stabilized

Oxidation of cis / trans 4-ᵗBu-cyclohexanol

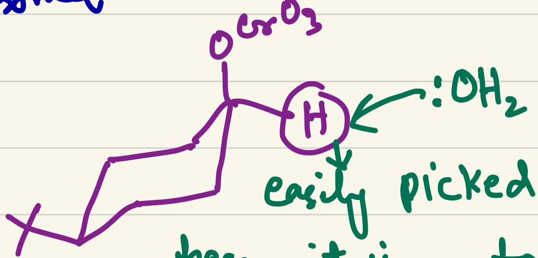
Barton studied the oxidation of 4-ᵗBu-cyclohexanols and found that the cis isomer is more reactive towards the oxidation reaction as compared to the trans isomer



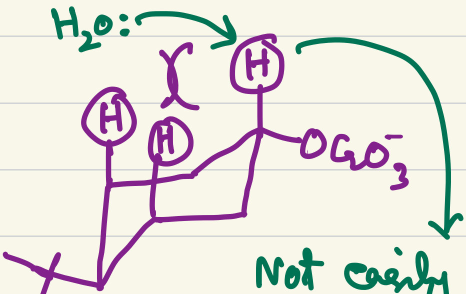
In order to understand how the reactivity is affected by the conformations of this molecule, it is important to look at the mechanism of alcohol oxidation using chromic acid



When we look at the chromate ester intermediate for cis and trans alcohols, Barton proposed that H_2O picks up the equitorial H easily from chromate ester intermediate of the cis-isomer as compared to the axial -H of the trans isomer

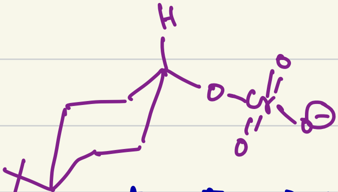


easily picked up because it is equtorial and no steric hindrance for the incoming H_2O molecule.

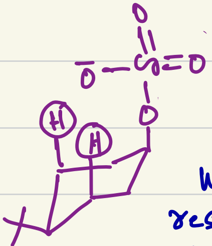


Not easily picked up as the OH_2 molecule faces the other axial-Hs at C3 & C5.

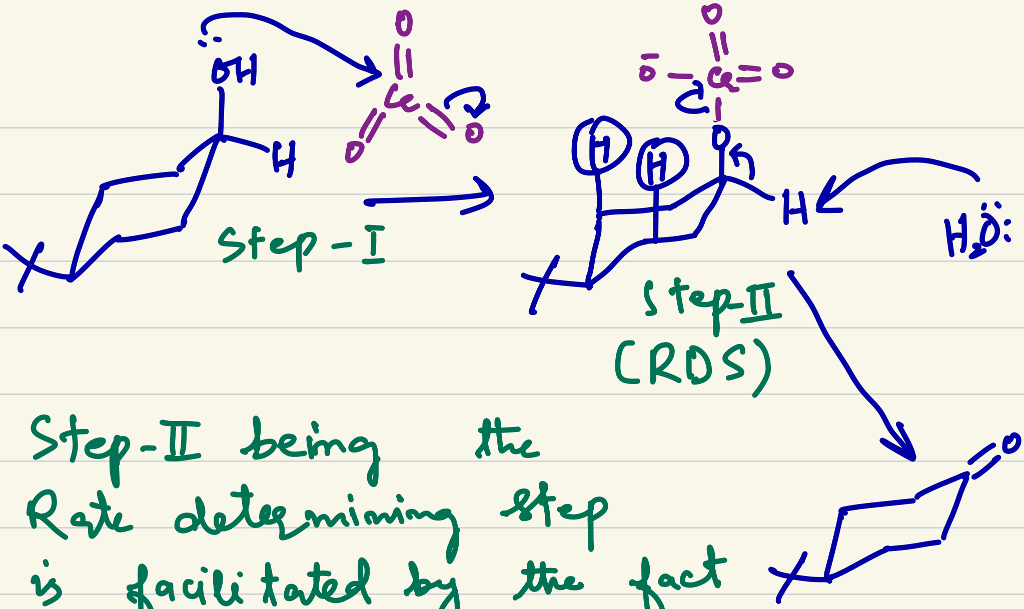
However after studying many similar examples, the real reason was found to be Steric Acceleration.



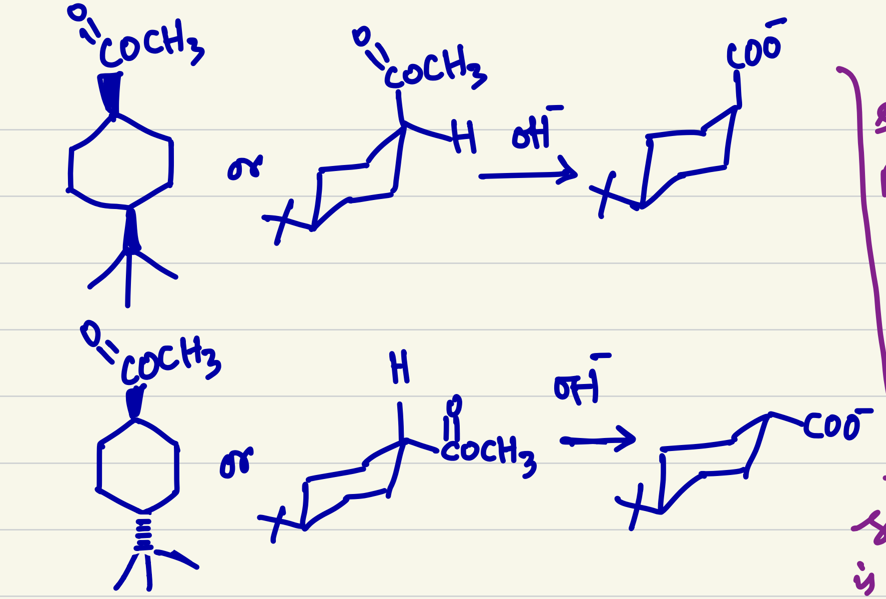
Chromate ester of the trans isomer can be easily stabilized by solvation as the $-OCrO_3^-$ group is away from axial hydrogens



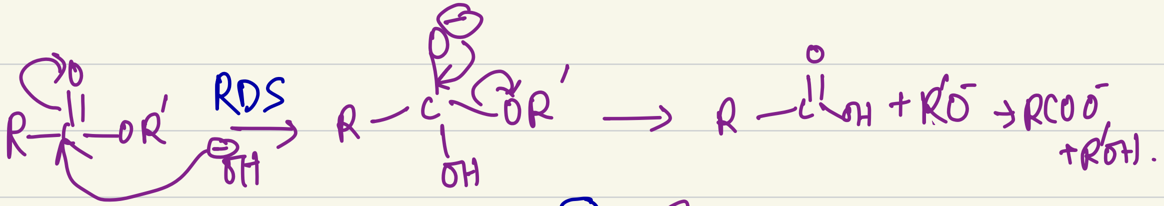
→ Chromate ester of the cis-isomer cannot be easily solvated because of steric hindrance of the solvent molecules with the axial C_3 & C_5 hydrogens. As a result the ester intermediate has a lower barrier with the product. This is an example where presence of steric hindrance increases the rate of a reaction → Steric Acceleration.

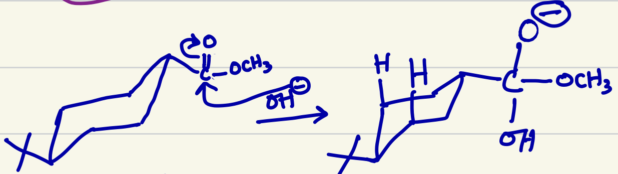


Step-II being the Rate determining step is facilitated by the fact that the chromate ester is sterically very stressed because its solvation is hindered by the diaxial hydrogen atoms. In-order to relieve this stress, the chromate ester goes to the ketone product faster than it would if it was equatorial and not axial.



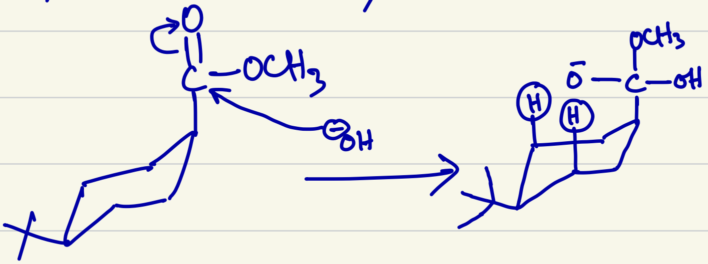
In this saponification Reaction, the trans isomer is more reactive because now the formation of the sterically stressed species is the RDS.





→ No steric stress

→ Formed easily



→ Sterically stressed and hence not formed so easily

Anomeric effect and Conformations of Sugars: ASSIGNMENT

End of Unit-I. Unit Test on 29/04/24