Stereochemical Aspects of Organic Molecules:

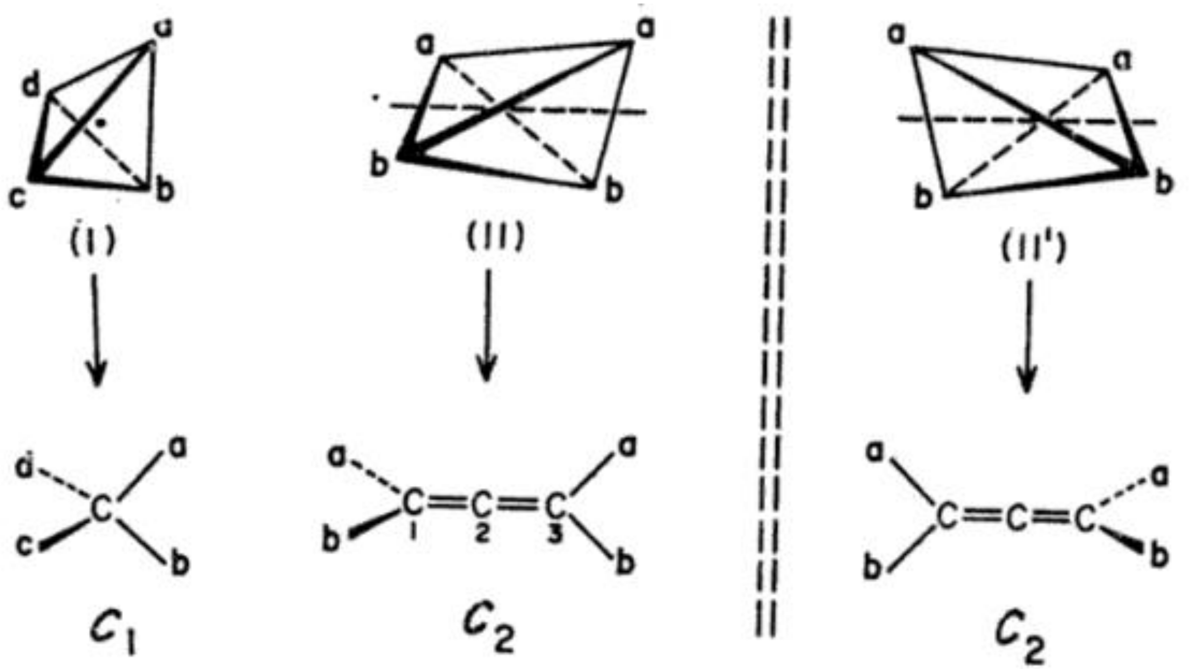
Stereochemistry II

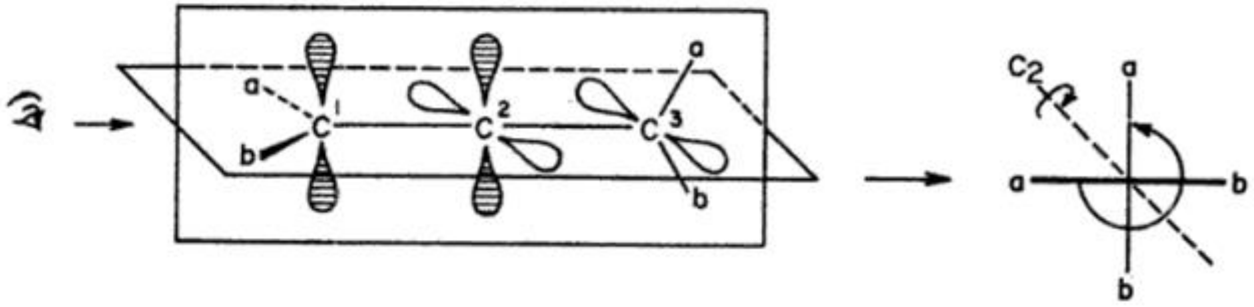
- **Chirality arising out of stereoaxis**: stereoisomerism of substituted cumulenes with even and odd number of double bonds; chiral axis in allenes, spiro compounds, alkylidenecycloalkanes and biphenyls;related configurational descriptors (*R*a/*S*a); atropisomerism; racemisation of chiral biphenyls.

- **Concept of prostereoisomerism**: prostereogenic centre; concept of (*pro*)n-*chirality*: topicity of ligands and faces (elementary idea); *pro-R/pro-S, pro-E/pro-Z* and *Re/Si* descriptors;*pro-r* and *pro-s* descriptors of ligands on propseudoasymmetric centre.

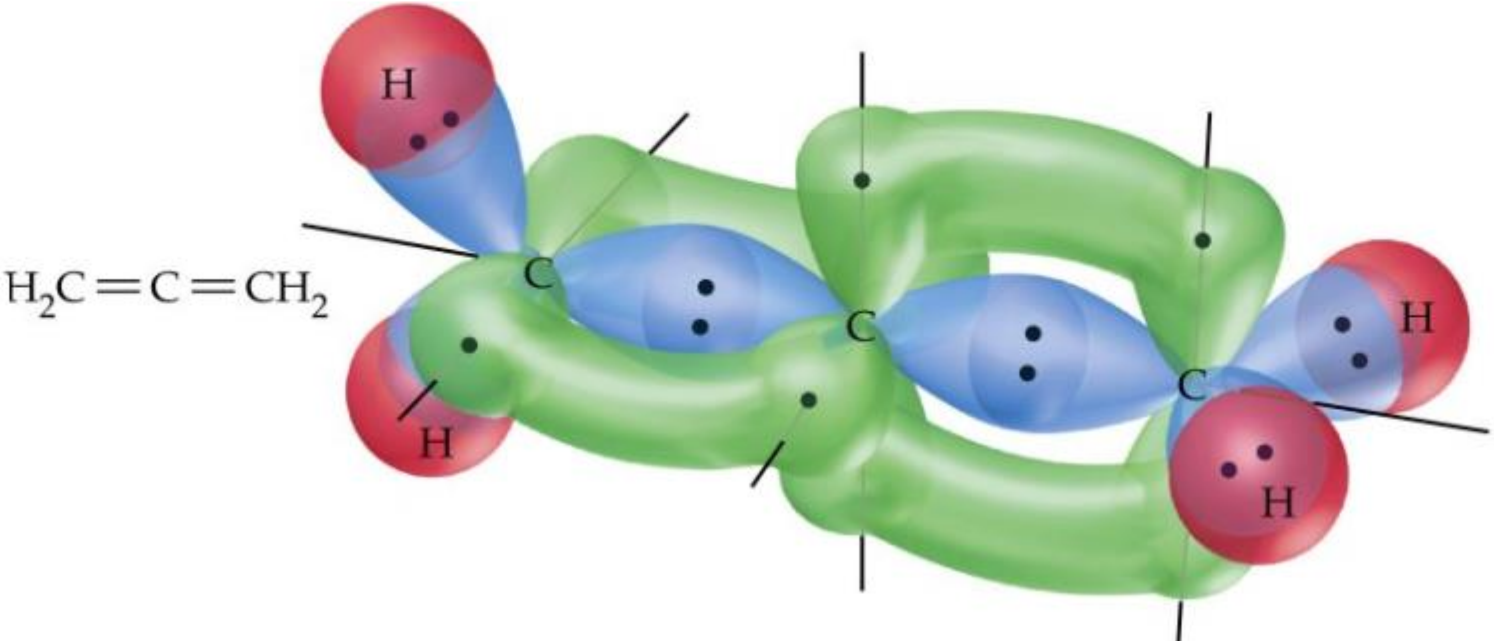
- **Conformation***:* conformational nomenclature: eclipsed, staggered, *gauche*, *syn*and *anti*; dihedral angle, torsion angle; Klyne-Prelog terminology; *P/M* descriptors; energy barrier of rotation, concept of torsional and steric strains; relative stability of conformers on the basis of steric effect, dipole-dipole interaction and H-bonding; *butane gauche* interaction; conformational analysis of ethane, propane, *n*-butane, 2-methylbutane and 2,3-dimethylbutane; haloalkane, 1,2-dihaloalkanes and 1,2-diols (up to four carbons); 1,2-halohydrin; conformation of conjugated systems (*s-cis* and*s-trans*).

Allene system :
Elongated tetrahedron approach:





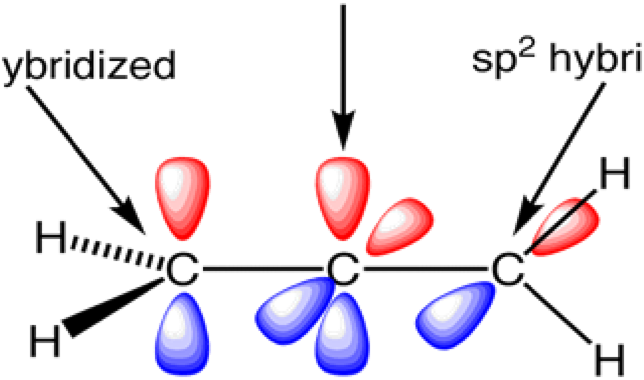
Allene system : Chiral Axis : Presence of C_2 Axis:



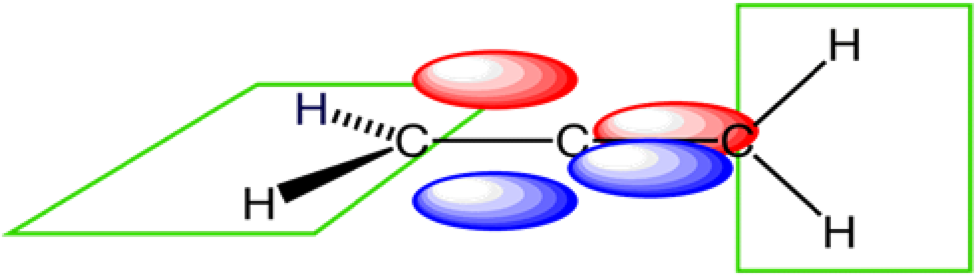
central carbon is sp hybridized

sp^2 hybridized

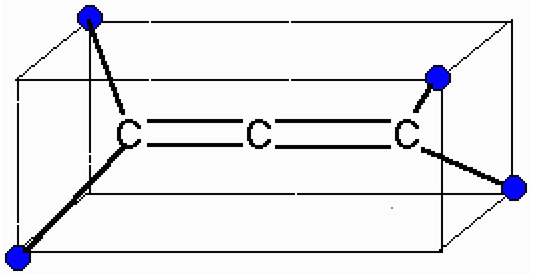
sp^2 hybridized

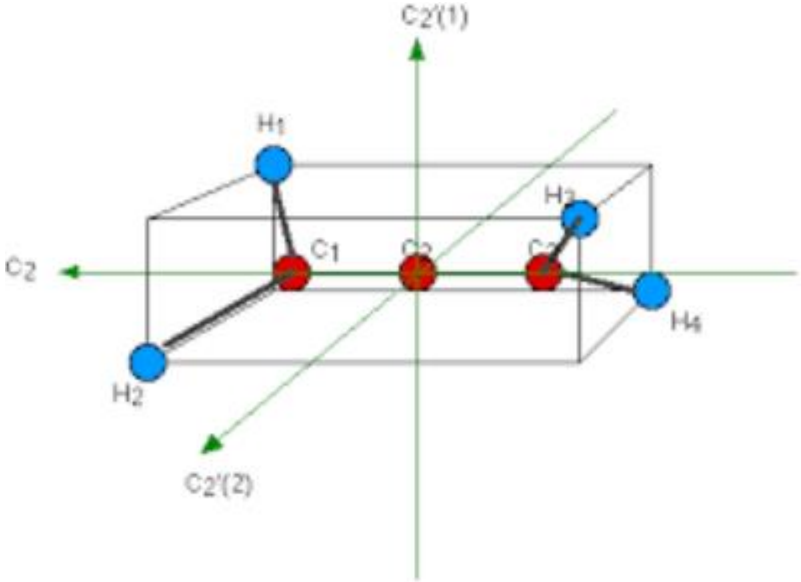


the π bonds formed as a result
of the overlap of the p orbitals
must be at right angles to each other



not only are the two π bonds perpendicular,
but the two methylene groups are too





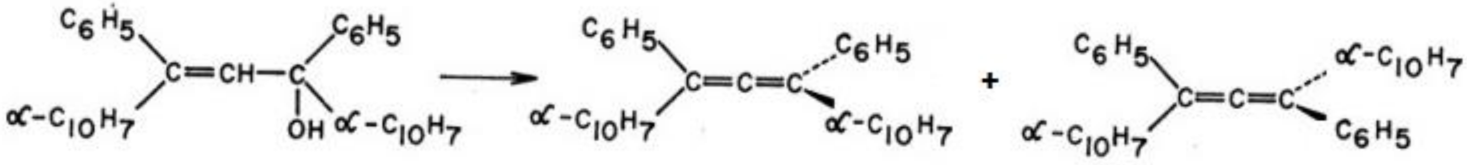
- The terminal methylene groups are perpendicular to each other.

- Of course, apart from C_2, there are two planes of symmetry, each containing one of the terminal methylene groups and passing through the C=C=C, bisecting the opposite <H-C-H angle.

- Therefore, $CH_2=C=CH_2$ is optically inactive and doesn't contain a chiral axis.

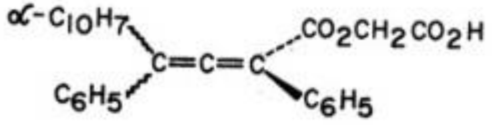
- So, for an allene to be chiral, the substituents of each terminal carbon must be different, i.e. with a general formula C(ab)=C=C(ab) or C(ab)=C=C(cd). Such systems will not have any plane of symmetry and the compound will be chiral due to the presence of a chiral axis.

- The first chiral allene was synthesized as a racemic mixture, by dehydration of a 2-propene-1-ol derivative.



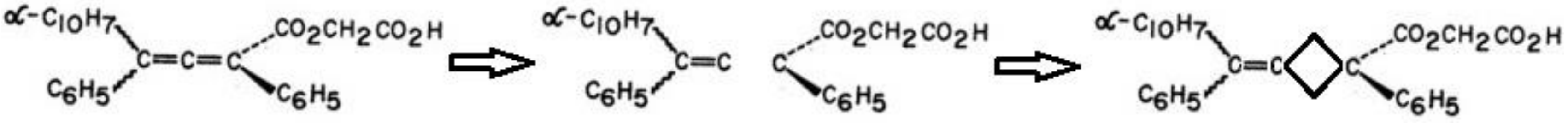
- These could not be separated due to solubility issues in fractional crystallization, due to the absence of suitable solubilizing groups.

- Finally, that problem was solved by introducing an acid functionality and both the enantiomers of the following compound was separated by crystallization.



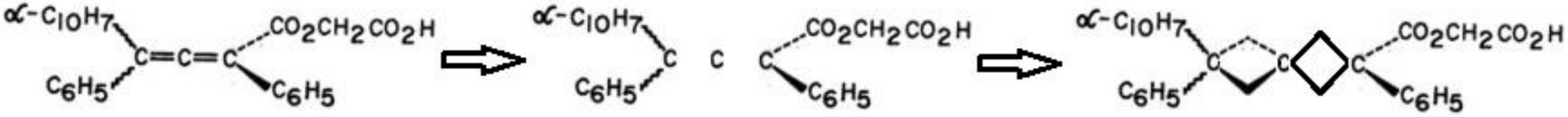
Hemispiranes or alkylidenecycloalkanes:

Of course, if one of the double bond is replaced by a cycloalkane ring, the nature of chirality will be unchanged, as both the terminal methylenes will still be perpendicular. Such systems are called “***Hemispiranes***”, and here the chiral axis proceeds through the C=C, bisecting the ring.



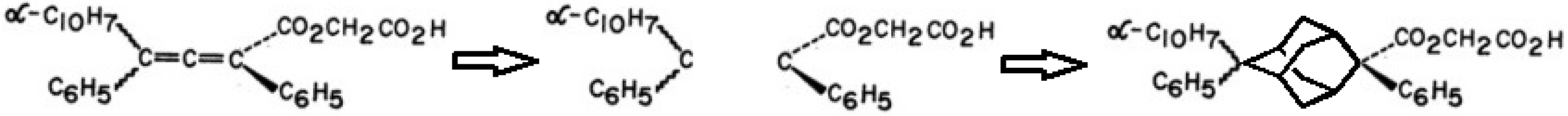
Spiranes:

Similar is the case for spiranes, where both the double bonds of allene is replaced by rings. Here the chiral axis proceeds through the intersection of the rings.



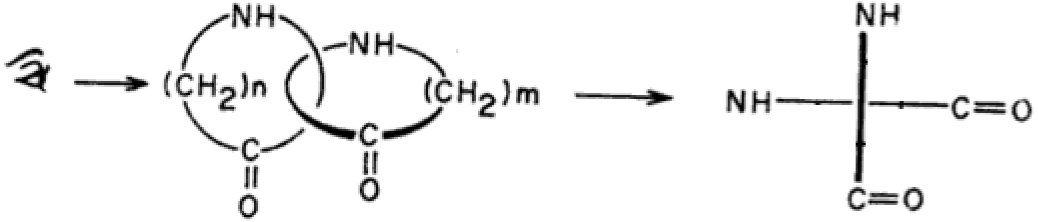
Adamentanes:

An extreme example is the case of adametanes, where C=C=C of allene is replaced by the adamentane core. Here the chiral axis proceeds through the terminal carbons, containing perpendicular methylene bridges.



Catenanes:

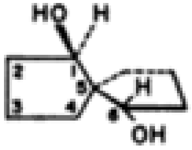
Another interesting class of compounds are Catenanes, where two rings are interlinked and perpendicular to each other.



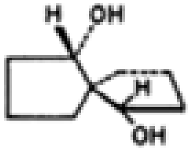
Nomenclature of axially chiral molecules:

- Near groups are given priority over the far groups.
- The near groups are numbered first (1 and 2), applying the nomenclature subrules.
- Then the far groups are numbered (3 and 4), applying the nomenclature subrules again.
- Finally, the clockwise / anticlockwise path from 1-2-3 determines R/S.
- However, it may appear in some spiranes that, the terminal carbons are chiral. But, careful sequencing leads to equal priority of the branches, thereby discards this possibility.
- Again, in some spiranes, there are chiral centers along with chiral axis. In those cases, nomenclature will be done following the CIP rules for chiral centers and not for chiral axis.

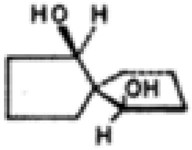
R



1*R*,5*R*,6*S*



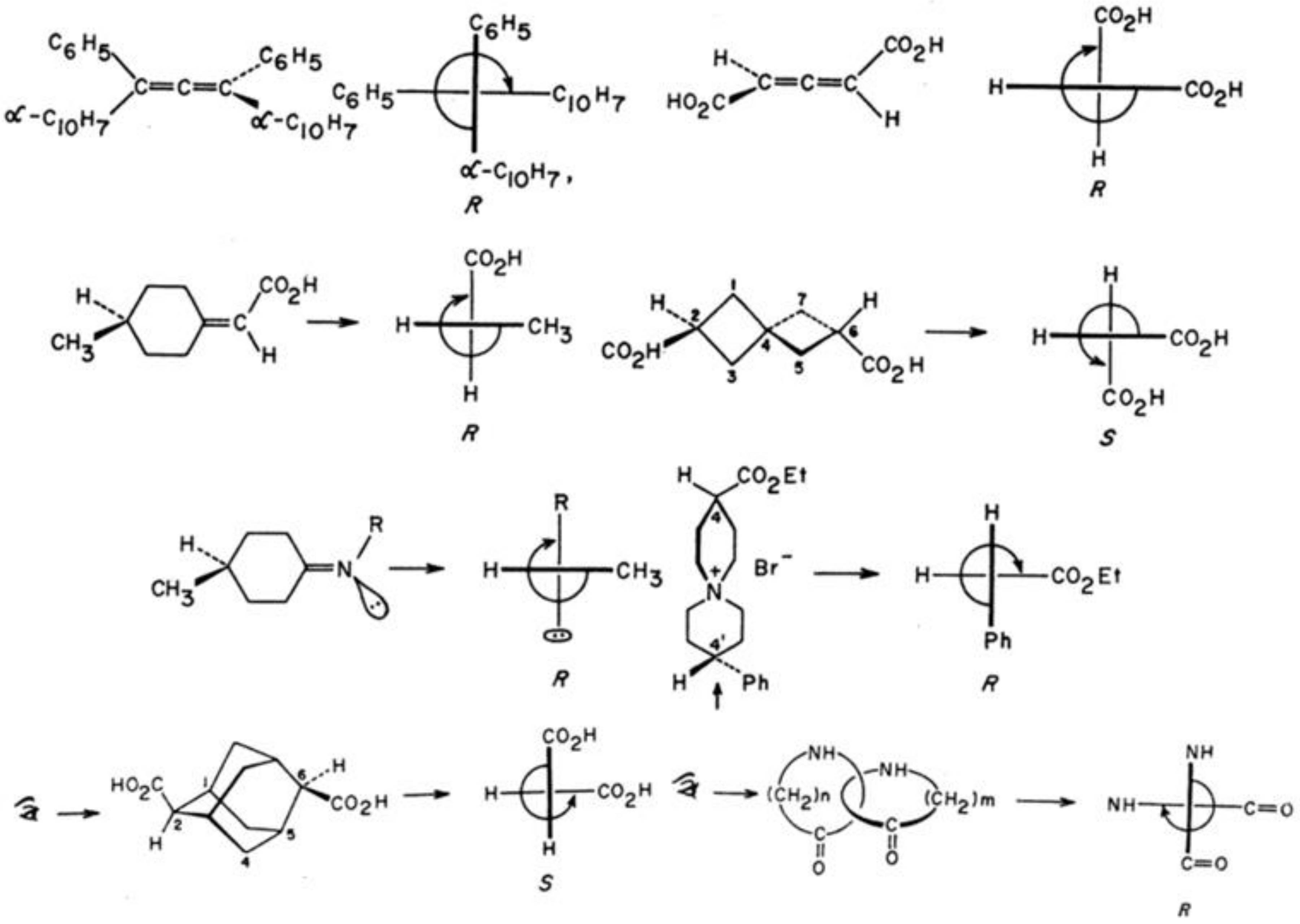
1*S*,5*R*,6*S*



1*R*,5*R*,6*R*

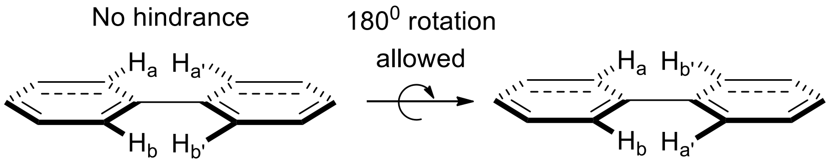
- Note that, the spiral carbon may appear achiral, but due to restricted rotation around the sigma bonds, there are no planes of symmetry, which makes it a chiral center. The situation is analogous to the cyclohexane systems (e.g. cis-1,2-dimethyl cyclohexane).

Some examples of nomenclature of axially chiral molecules:

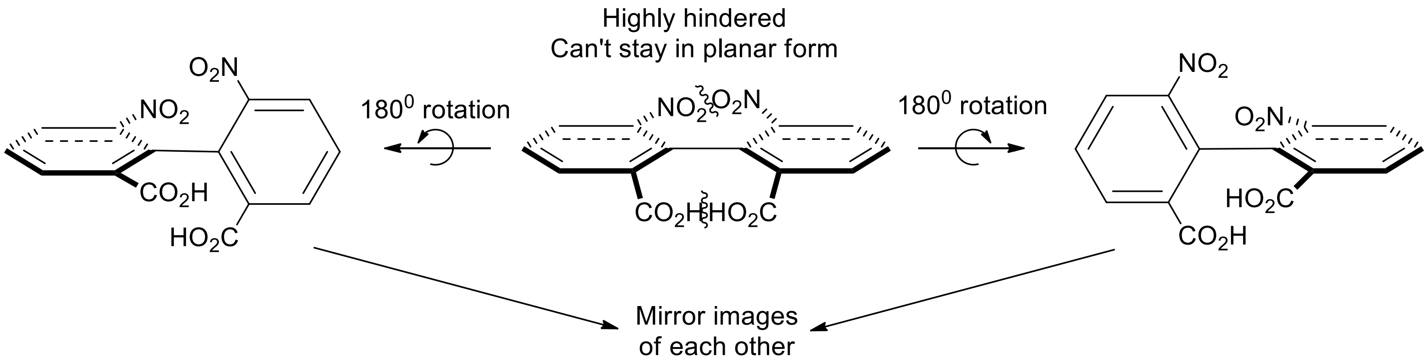


Biphenyls: Atropisomers:

- Rotation around the C-C single bond axis of biphenyl is allowed.



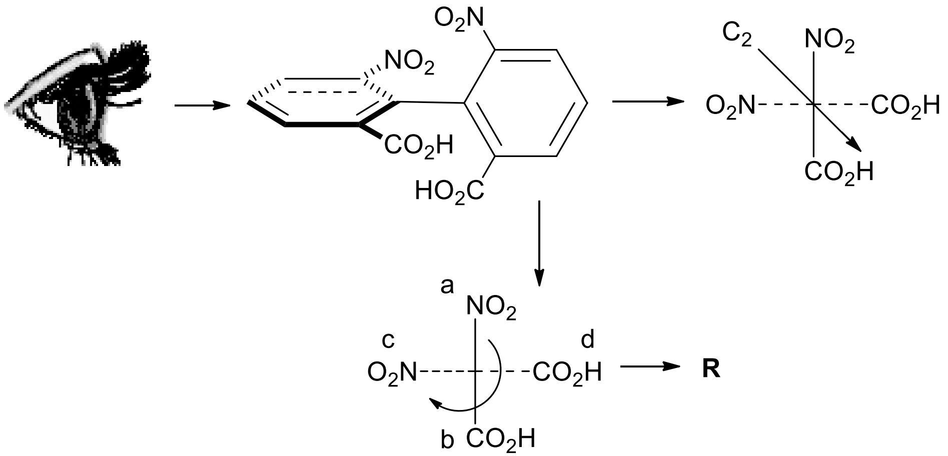
- But, introduction of bulky ortho substituents hinders it, projecting the phenyl groups at ~90^0 to each other, i.e. orthogonal alignment.



- It leads to two possibilities of such orthogonal alignment, which also happens to be mirror images of each other, i.e. enantiomers.

- Thus, we can safely conclude that, restricted rotation around the C-C single bond axis leads to enantiomerism. Therefore, such biphenyls contain a chiral axis (C-C single bond).

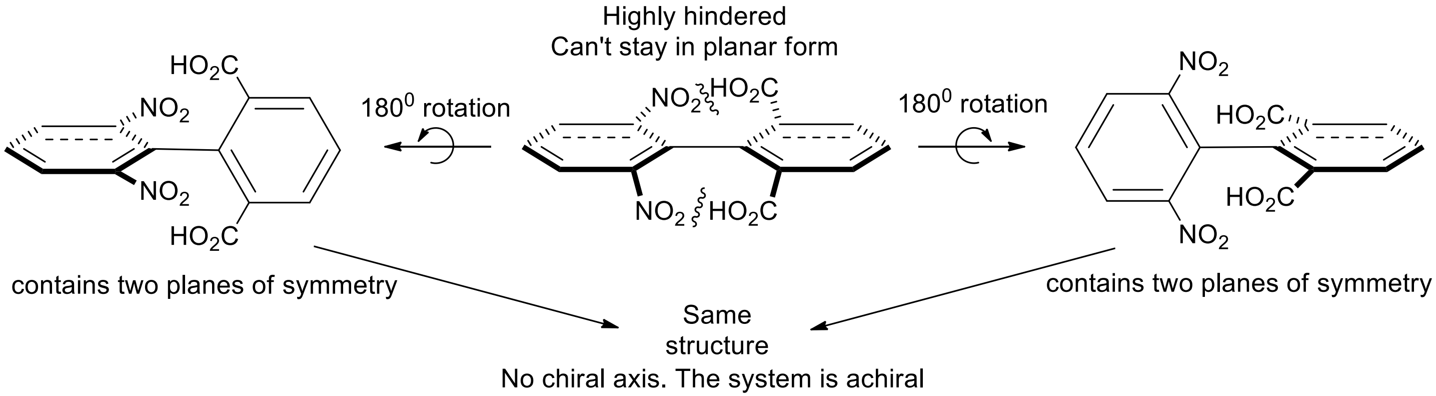
- Also, the molecule contains a C_2. So, the compound is dissymmetric.



- Nomenclature of atropisomers is done in a similar way, like allenes. Here also subrule “0” is applied and near groups are given higher priority over the far groups.

- So, **Atropisomers** are stereoisomers arising because of hindered rotation about a single_bond, where energy differences due to steric strain or other reasons create a barrier to rotation that is high enough to allow for isolation of individual conformers.

- However, if the phenyl rings contain same ortho substituents, although the rotation will still be restricted, but, the compound will have two planes of symmetry, each passing through one phenyl ring and therefore achiral.



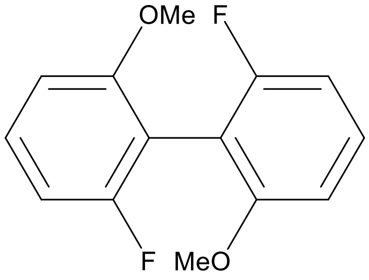
Highly hindered
Can't stay in planar form

contains two planes of symmetry

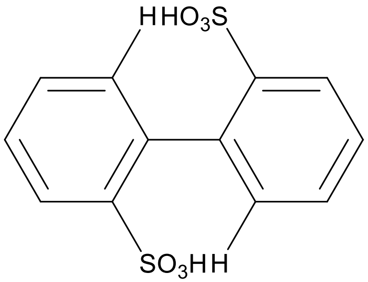
contains two planes of symmetry

Same
structure
No chiral axis. The system is achiral

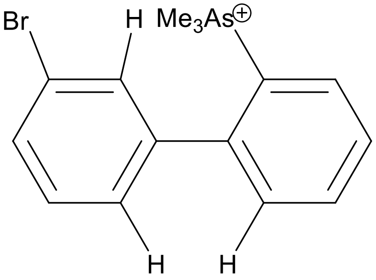
- Atropisomers are detectable by NMR if half lives exceed 10^{-2} sec.
- Atropisomers are isolatable if the half-life is above 1000 sec.



NO ATROPISOMER



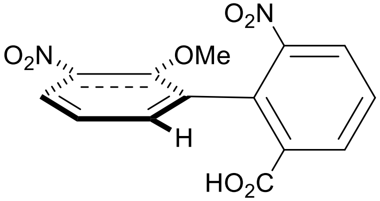
Atropisomerism present



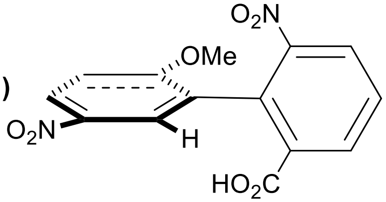
Atropisomerism present

- Since, both methoxy and fluoride are sterically less demanding, the atropisomers of the first compound can not be isolated. But, for the later one, sulphonic acid functionalities themselves create so much overcrowding that, even simple hydrogen on the other ring leads to restricted rotation and exhibits atropisomerism.

- Sometimes, even a single bulky group can also exhibit atropisomerism, like the one containing a bulky –$AsMe_3$ group.

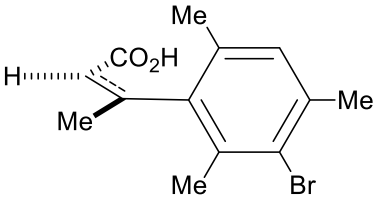


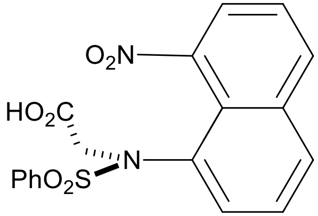
(I)



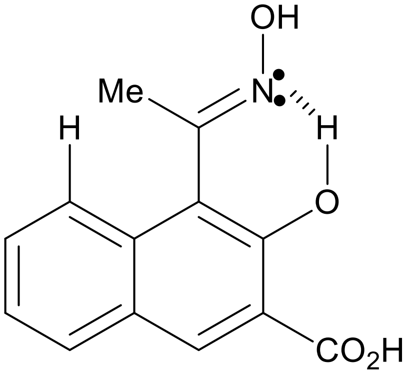
(II)

- In another interesting example, compound-**I** racimizes at a much slower rate than **II**, as buttressing effect of nitro on methoxy in **I**, leads to more hindered rotation than in **II**.

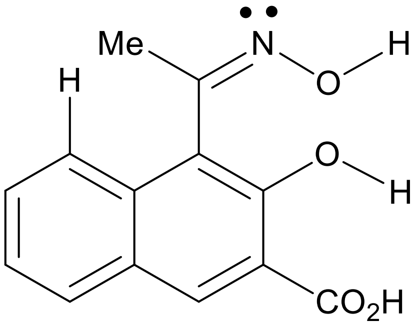




- Sometimes, acyclic molecules also show atropisomerism, due to restricted rotatio around the single bond.



(I)



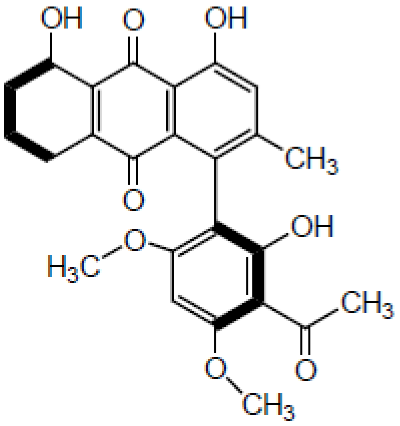
(II)

- Another interesting set of examples are these two diastereoisomeric oximes. Here, **I** doesn't show atropisomerism but, **II** does.

- In **I**, hydrogen bonding stabilizes the molecule and in order to have that H-bonding, the molecule attains a planar 6-membered arrangement.

- But, in **II**, no H-bonding is possible in planar 6-membered arrangement. So, in order to stabilize the molecule through H-bonding between the hydroxyl groups, the molecule must attain a non-planar arrangement and leads to atropisomerism.

Vancomycin is naturally occurring atropisomer

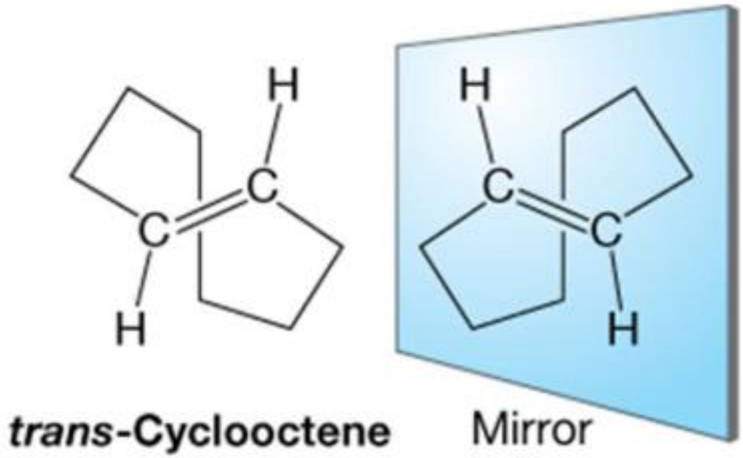


Used against bacterial infections

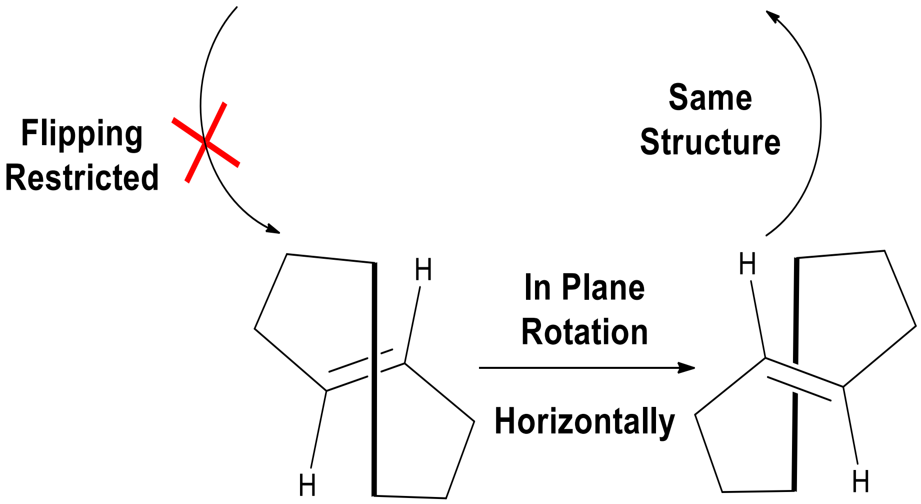
(also known as drug of last resort)

Chirality Without Stereocenters

Chiral Plane: Alkenes:



Flipping of the 6-membered methylene chain below and above the alkene plane is hindered by the alkene hydrogens and therefore, the mirror images are non-convertable to each other and therefore resolvable.

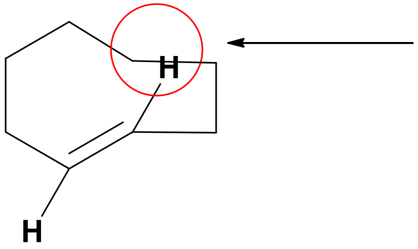


Flipping Restricted

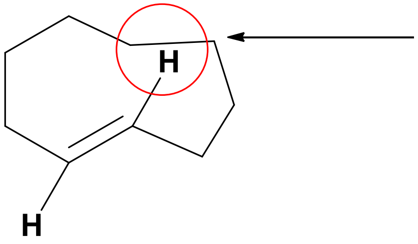
Same Structure

In Plane Rotation

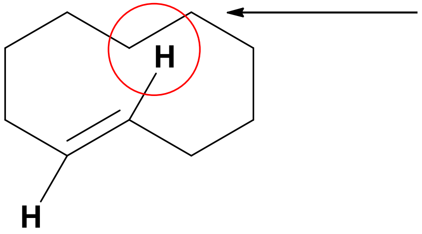
Horizontally



Flipping is highly Hindered, therefore, enantiomers could be isolated

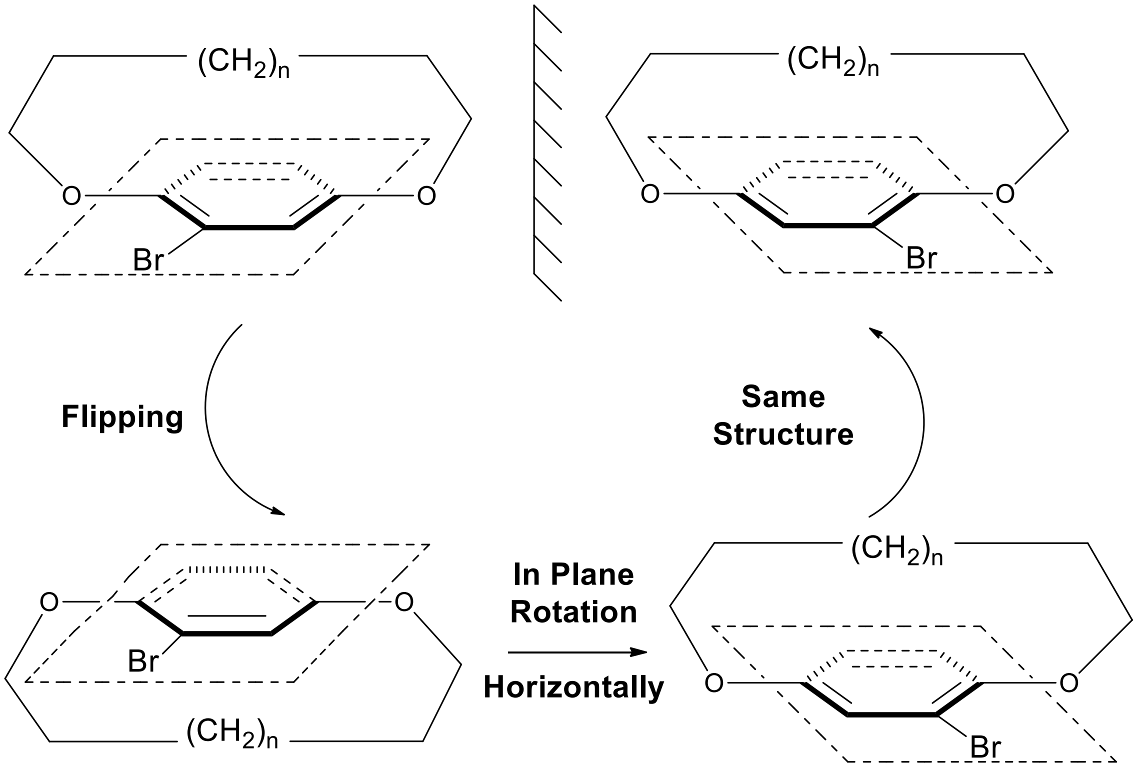


Flipping is less Hindered, therefore, enantiomers couldn't be isolated; but at very low temperature, - 80^{0}C, such flipping could be restricted and enantiomers could be isolated



No hindrance, therefore, enantiomers couldn't be isolated, even at very low temperature.

Chiral Plane: Ansa compounds:



Flipping

Same Structure

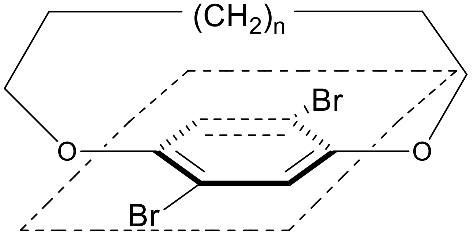
In Plane Rotation

Horizontally

n = 6, Flipping Restricted; chiral molecule

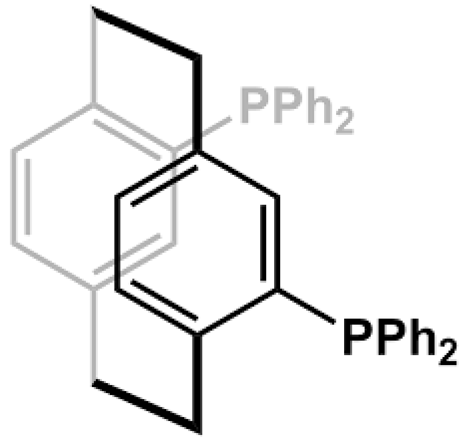
n = 7, Flipping less Restricted; chiral molecule, but enatiomers interconvert

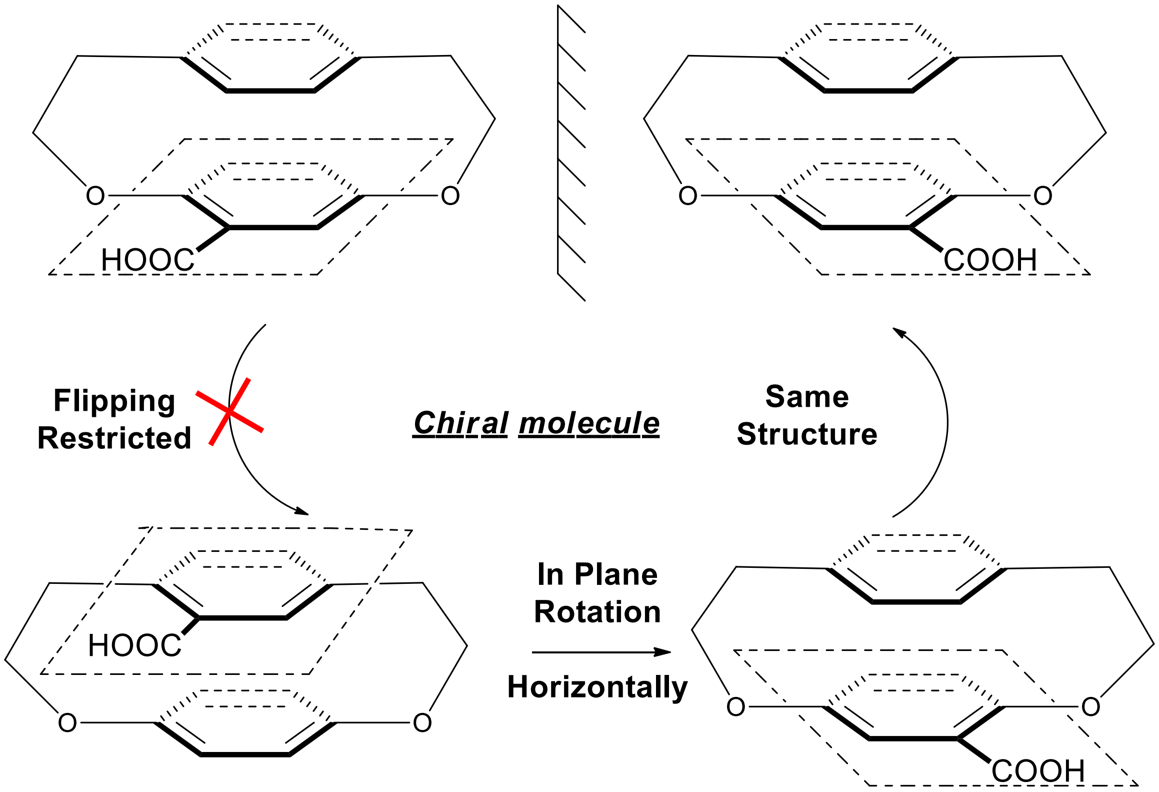
n = 8, Flipping not Restricted, no chirality present.



Even for n = 8, Flipping is Restricted; chiral molecule.

Chiral Plane: Cyclophanes:





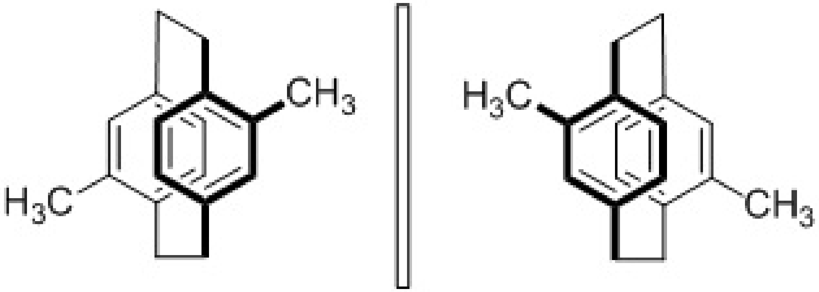
Flipping Restricted

Chiral molecule

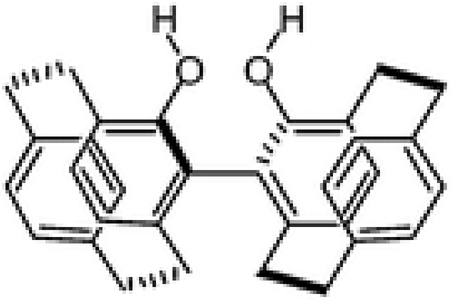
Same Structure

In Plane Rotation

Horizontally

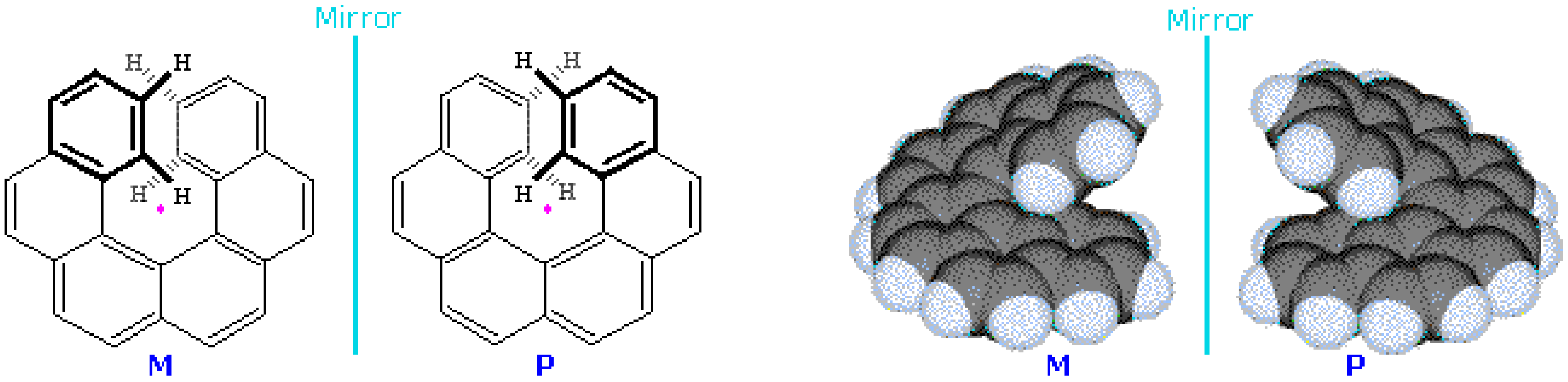


[2,2]-paracyclophane



Chirality Without Stereocenters

Helicity: Generally arises due to molecular overcrowding.



Enantiomeric Configurations of Hexahelicene

***P/M* descriptors:** *Helicity* arises from molecular overcrowding.

- In order to assign the nomenclature, we simply need to examine that, whether the helix is showing a clockwise or anticlockwise orientation, when we move along it's axis from any one of it's ends, towards the other.

- If it's clockwise, then we assign "**P**" (Plus) and if it's anticlockwise, then we assign "**M**" (Minus).

Conformational Language

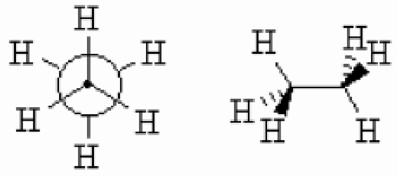
Conformations - Different spatial arrangments that a molecule can adopt due to rotation about sigma bonds. Conformations are the different shapes that a molecule can attain without breaking any covalent bonds.

Conformers - Contracted version of conformational isomers.

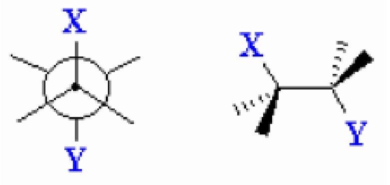
Rotamers - Alternative expression for conformational isomers.

Conformational isomers - Structures that can be interconverted by rotation about σ bonds.

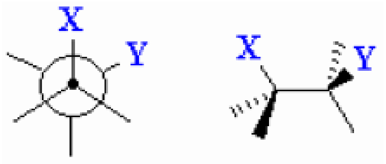
Staggered - A low energy conformation where the bonds on adjacent atoms bisect the bond angle, maximising the separation.



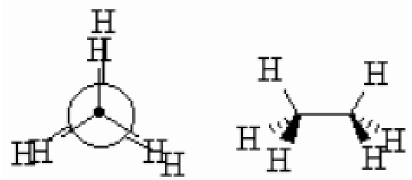
Anti - Description given to two substitutents attached to adjacent atoms when their bonds are at 180° with respect to each other.



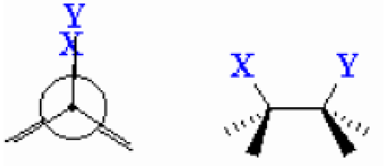
Gauche - Description given to two substitutents attached to adjacent atoms when their bonds are at 60° with respect to each other.



Eclipsed - A high energy conformation where the bonds on adjacent atoms are aligned with each other.

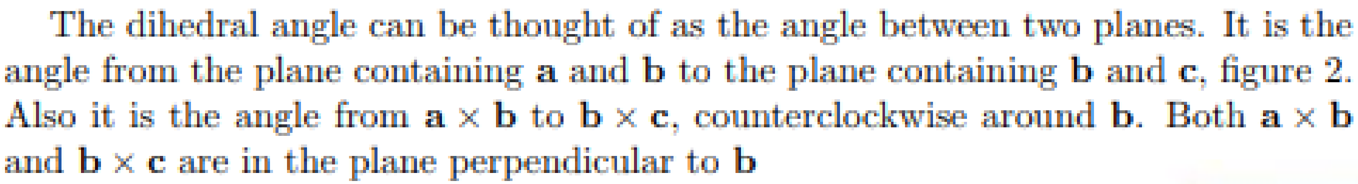


Syn - Description given to two substitutents attached to adjacent atoms when their bonds are at 0° with respect to each other.

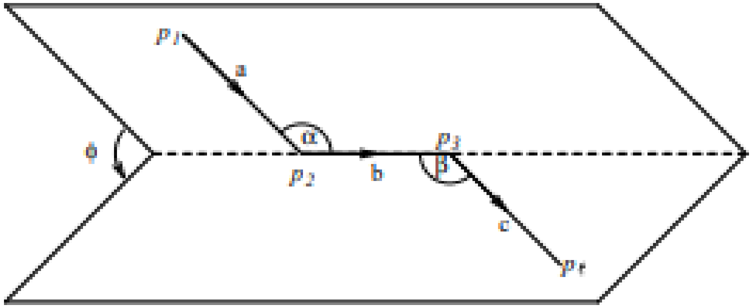


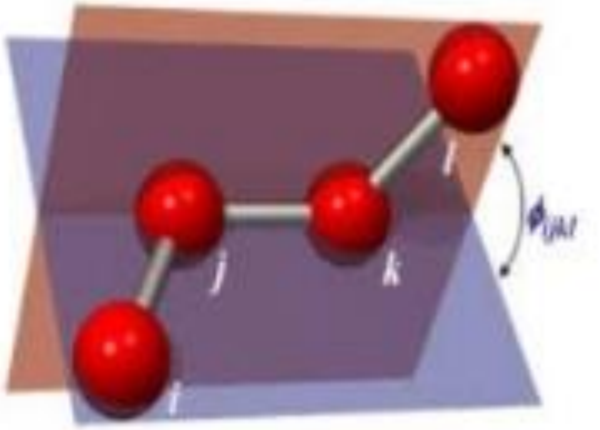
Angle and strain

Dihedral angle vs. Torsion angle

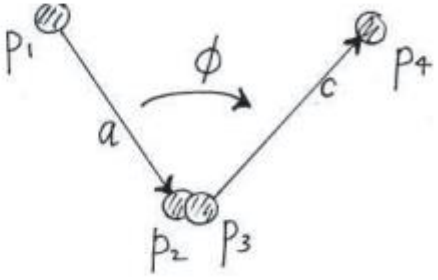


The dihedral angle can be thought of as the angle between two planes. It is the angle from the plane containing **a** and **b** to the plane containing **b** and **c**, figure 2. Also it is the angle from $\mathbf{a} \times \mathbf{b}$ to $\mathbf{b} \times \mathbf{c}$, counterclockwise around **b**. Both $\mathbf{a} \times \mathbf{b}$ and $\mathbf{b} \times \mathbf{c}$ are in the plane perpendicular to **b**





Torsional angle is basically the angle between projections of “a” and “c” on the plane, Perpendicular to P_2-P_3 bond

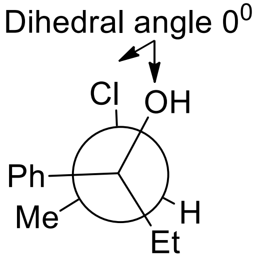


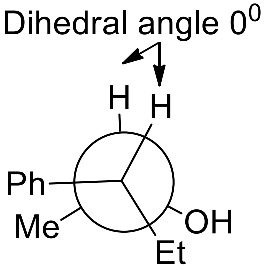
<u>Rules for identification of Dihedral angle:</u>

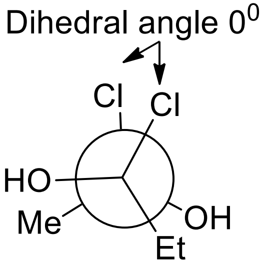
- When all the substituents of both the front and back carbons are different, the angle between highest priority groups (of both carbons), according to the sequence rule, is considered as the dihedral angle.

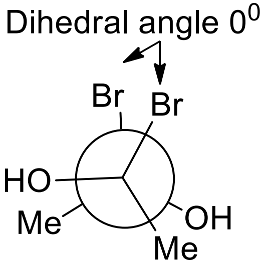
- When there is only one common substituent between the front and back carbons, the angle between the common groups (of both carbons), is considered as the dihedral angle.

- When there are two or three common substituents between the front and back carbons, the angle between the highest priority common groups (of both carbons), is considered as the dihedral angle.



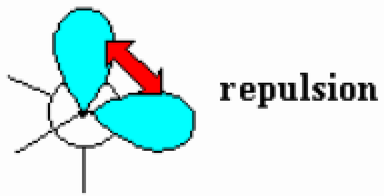




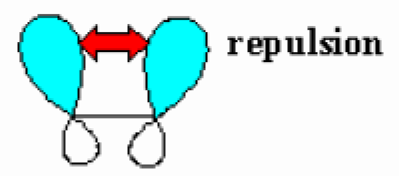


Strain - Energy associated with a system due to its geometry.

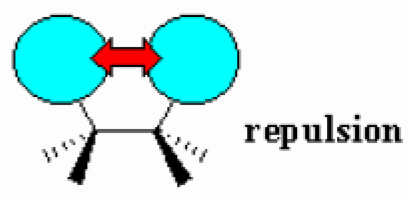
Angle strain / Bond Angle strain - Destabilisation caused by the electrostatic repulsion of the electrons in the Bonds, due to distortion of a bond angle from its optimum value.



Torsional strain / Torsional angle strain - Destabilisation due to the repulsion between pairs of bonds caused by the electrostatic repulsion of the electrons in the bonds.

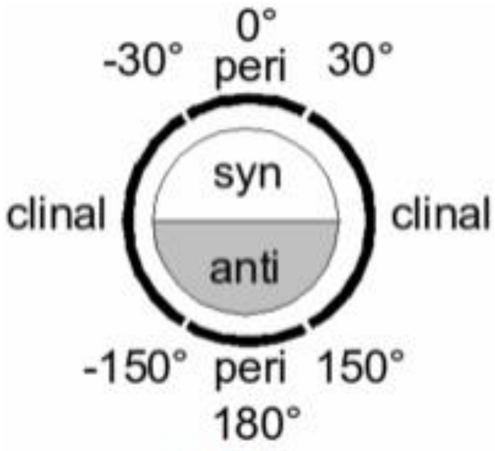


Van der Waals strain - Destabilisation due to the repulsion between the electron clouds of atoms or groups. Also known as Van der Waals repulsion. This occurs when atoms or groups are too close.



Steric strain - A composite of the strains (angle, torsional, Van der Waals) within a molecule.

Klyne-Prelog terminology



syn/anti peri/clinal

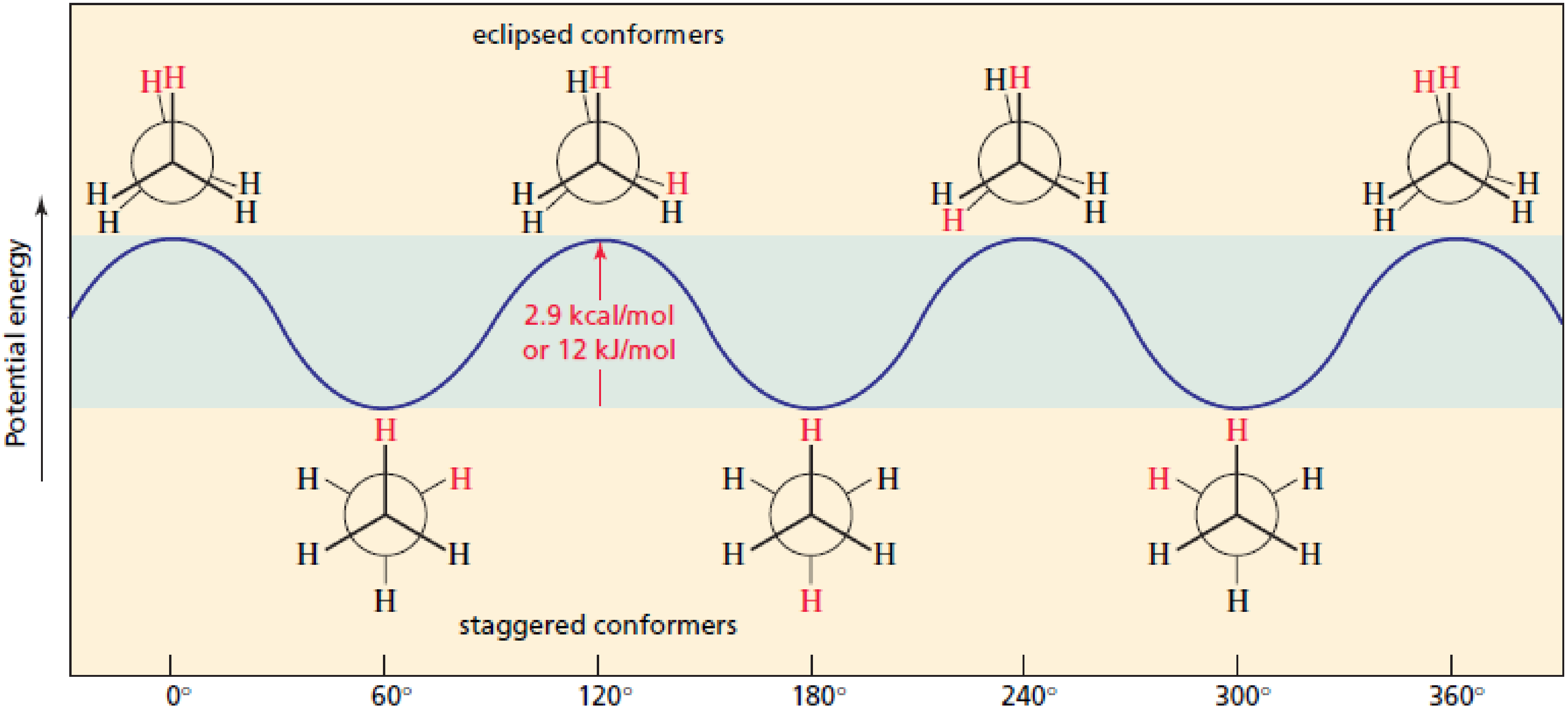
Many definitions that describe a specific conformer (IUPAC Gold Book) exist, developed by William Klyne and Vladimir Prelog, constituting their Klyne–Prelog system of nomenclature:

- a torsion angle of ±60° is called **gauche** [6]
- a torsion angle between 0° and ± 90° is called **syn** (s)
- a torsion angle between ± 90° and 180° is called **anti** (a)
- a torsion angle between 30° and 150° or between –30° and –150° is called **clinal**
- a torsion angle between 0° and 30° or 150° and 180° is called **periplanar** (p)
- a torsion angle between 0° to 30° is called **synperiplanar** or **syn-** or **cis-conformation** (sp)
- a torsion angle between 30° to 90° and –30° to –90° is called **synclinal** or **gauche** or **skew** (sc)[7]
- a torsion angle between 90° to 150°, and –90° to –150° is called **anticlinal** (ac)
- a torsion angle between ± 150° to 180° is called **antiperiplanar** or **anti** or **trans** (ap).

Energy barrier of rotation and *Conformational analysis*

- ***Conformational analysis*** is the process of relating conformation to the properties and reactivity of molecules.

Conformational analysis of Ethane:



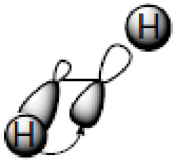
- Eclipsed conformation represents maximum energy and staggered, the minimum. Two staggered conformers interconvert at te rate of 6×10^9 s^{-1} at 25^0C, by crossing an energy barrier of 2.9 kcal/mol.

Origin of the Energy barrier of rotation:

- The barrier is the result of destabilizing factor(s) in the eclipsed conformation as well as stabilizing factor(s) in the staggered one.

- Analysis of the van der Waals radii show that the hydrogens do not come close enough in eclipsed form to account for the barrier to rotation.

- Calculations from computational studies concluded that, hyperconjugation (σ-σ^* delocalization) contributes nearly 5 kcal/mol of stabilization to the staggered conformation, whereas electron-electron repulsion destabilized the eclipsed conformation by 2 kcal/mol. However, these two factors, which favor the staggered conformation, are partially canceled by the fact that, repulsions in eclipsed form leads to adjustments in bond lengths and bond angles to minimize repulsive interactions. These deformations affect the shapes and energies of the orbitals. When the effects of molecular relaxation are incorporated into the analysis, the conclusion reached is that delocalization (hyperconjugation) is the principal factor favoring the staggered conformation. This leads to the overall rotational barrier, 2.9 kcal/mol.



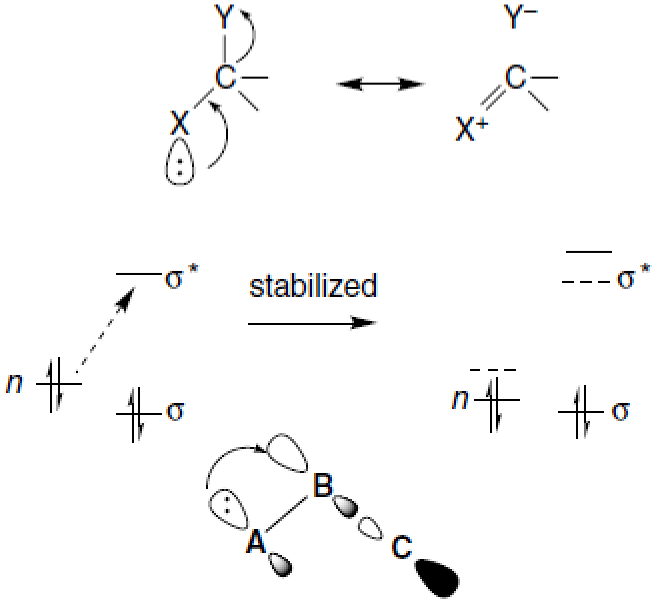
hyperconjugation
in *anti* conformation

- So, the barrier is an intrinsic property of the bonds and independent of substituent size, and called the ***torsional barrier***. This arises because of the bonding electron cloud repulsion and σ-σ^* delocalization between the adjacent bonds, while undergoing rotation along the C-C bond.

Rotational Barriers of Heteroatom containing Compounds:

- Hyperconjugation is enhanced in certain systems containing heteroatoms. If one atom with an unshared electron pair is a particularly good electron donor and another a good σ^* acceptor, the n → σ^* contribution should be enhanced. This is represented by a charged, ***"no-bond"*** resonance structure.

- This is also known as ***"Heteroatom hyperconjugation"*** and can also be expressed in MO terms. The ***n***, ***σ***, and ***σ**** orbitals are involved, as depicted below. If the ***A*** atom is the donor and ***C*** the acceptor, the MO perturbation indicates a stabilization of the ***n*** orbital ***A*** by partial population of the ***σ**** orbital of ***B–C***.



- This stereoelectronic interaction has a preference for an *anti* relationship between the donor electron pair and the acceptor σ^* orbital. Such hyperconjugative stabilization is expected to have at least three interrelated consequences: (1) altered bond lengths; (2) enhanced polarity, as represented by the charged resonance structure; and (3) an energetic preference for the conformation that optimizes hyperconjugation.

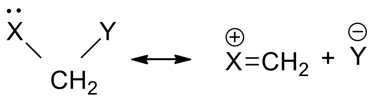
- The n→σ^* interaction becomes more profound in carbon atoms having two heteroatoms.

- σ* acceptor capacity increases with electronegativity, i.e., in the order C<N <O<F.

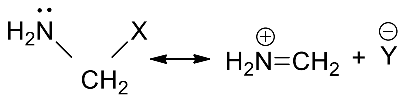
- However, acceptor σ* capacity also increases going down the periodic table for the halogens, F < Cl < Br < I, probably due to the lower energy of the σ* orbitals with the heavier elements.

- Donor ability also increases going down the periodic table. This trend indicates that *softness* (polarizability) is a factor in hyperconjugation.

Computational analysis on the amount of expected stabilization:



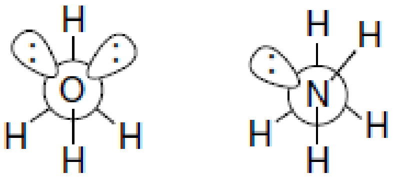
	Y(acceptor)		
X(donor)	NH_2	OH	F
NH_2	10.6	12.7	17.6
OH		17.4	16.2
F			13.9



X	kcal/mol
H	8.07
F	20.49
Cl	22.55
Br	29.87

Rotational energy barrier:

Heteroatom compounds	Barrier (kcal/mol)
CH_3-NH_2[c]	2.0
CH_3-NHCH_3[c]	3.0
$CH_3-N(CH_3)_2$[c]	4.4
CH_3-OH[d]	1.1
CH_3-OCH_3[d]	4.6

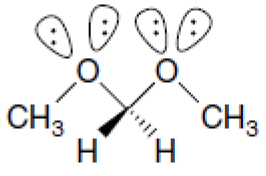


- Also, on going from ethane to methylamine to methanol, the rotational barrier decrease from 2.9 to 2.0 to 1.1 kcal/mol.

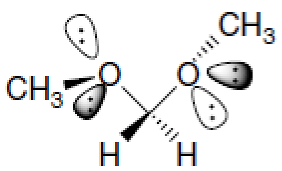
- The barriers in methyl amine and methanol are determined by the extent of stabilization by hyperconjugation in the ***anti*** conformer, which is partially cancelled by other factors, as discussed earlier.

- Regular decrease in the rotational barrier from ethane to methylamine to methanol can be explained by the decreases in hyperconjugative stabilization, due to the decrease in number of hyperconjugative hydrogen in ***anti*** conformer from ethane to methyl amine to methanol (3 to 2 to 1), and less effective n → σ^* contribution (***n*** of O is energetically lower than σ of C-H, leading to energy mismatch).

- Of course, introduction of methyl groups at the heteroatom center introduces new Me/H eclipsing strains in the system, thereby gradually distabilizing the eclipsed conformer, with the introduction of every methyl group. Therefore, it increases the rotational energy barrier, as evident from the above table.

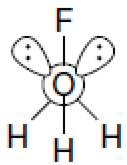


anti, anti

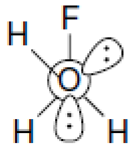


gauche, gauche

- Dimethoxymethane prefers a conformation that allows alignment of an unshared pair on each oxygen (donor) with a C–O σ^* orbital on the other. This condition is metin the conformation labeled *gauche*, *gauche*. In contrast, the extended hydrocarbon-like *anti*, *anti* conformation does not permit this alignment

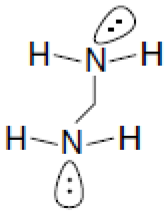


anti



gauche

- Fluoromethanol shows a preference for the *gauche* conformation.

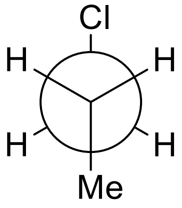


preferred *gauche* conformation for diaminomethane

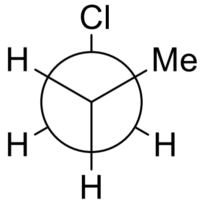
- For diaminomethane, there is a small preference for the gauche, gauche conformation.

Haloalkanes and 1,2-dihaloalkanes:

- Rotational energy barrier of haloalkanes of type CH_3-CH_2-X are comparable in magnitude (3.4-3.6 kcal/mol). Here the effect of increasing size of the halogens is counterbalanced by the effect of increase in bond length from C-F to C-I.

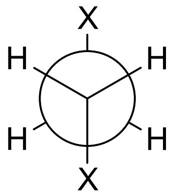


Anti

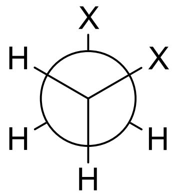


gauche (more stable)

- Interestingly, in liquid and gaseous state gauche conformer of the n-propyl halide is more stable than the anti conformer, probably due to dominating van der Waals attractive force between Me/Cl, originating from electrostatic attractions, over the repulsive force.



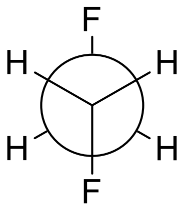
Anti



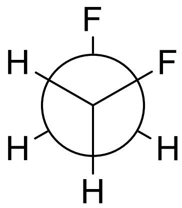
gauche

73% (X=Cl)	27%	Gaseous state
85% (X=Br)	15%	
50% (X=Cl)	50%	Liquid state
65% (X=Br)	35%	

- In gaseous state, the anti conformer of 1,2-Dihaloalkanes predominates over the gauche, due to absence of steric and dipolar repulsion between the halogen substituents. But, such destabilizing factors were reduced in liquid state and in polar solvents, due to solvation, leading to increase in amount of gauche conformer in the system.



Anti



gauche (more stable)

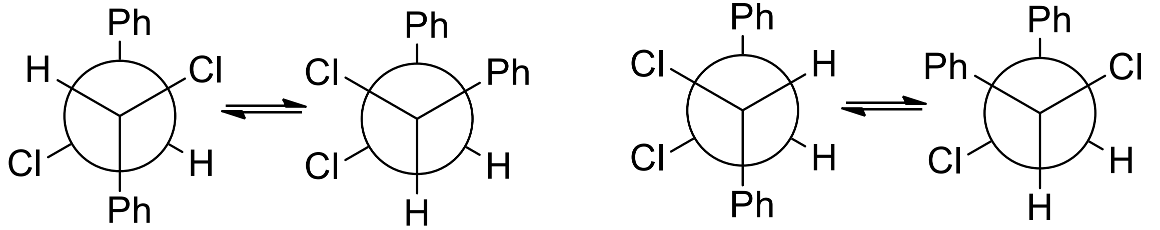
- However, for 1,2-difluoroalkanes, the gauche conformer is always more stable than the anti conformer, due to dominating stabilizing interaction between σ-C-H and σ^*-C-F over the dipolar F/F repulsion, which in not possible in anti conformer. This is known as "Gauche Effect".

- Note that, the gauche conformers of 1,2-Dichloro/bromoalkanes have a net dipole moment, whereas that of anti conformer is zero and the actual dipole moments of 1,2-Dichloro and bromoalkanes are found to be 1.00 D and 1.12 D, respectively, which proves that, there are sufficient amounts of gauche conformers in the system. This amount increases with temperature, as evident by the increase in their dipole moment with temperature.

- Another interesting example is stilbene dichloride. Here the the prerfered conformation of meso variety has –Cl groups, anti to each other, leading to low dipole moment of overall sample. But, the prefered conformation of active variety contins –Cl groups at gauche orientation, leading to a substatial value of dipole moment of the overall sample. Thus, meso and active varities of stilbene dichlorides can be distinguished easily, just by dipole moment consideration.

Meso Variety

Active variety



More stable

Less stable

More stable

Less stable

Overall dipole moment = 1.27 D

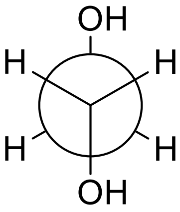
Overall dipole moment = 2.75 D

<u>1,2-diols, 1,2-halohydrin:</u>

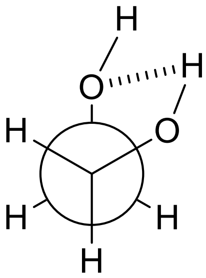
- 1,2-Diols show strong preference for gauche coformer, where strong intramolecular H-bonding predominates the distabilising OH/OH dipolar repulsion. Thus, IR in CCl_4 shows strong peak at 3612 cm^{-1} for H-bonded –OH , along with the peak at 3644 cm^{-1} for free –OH of ethylene glycol.

- Due to the same reason, 1,2-ethylene glycol possesses high dipole moment.

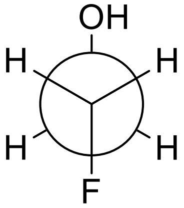
- Similarly, in 2-substituted ethanols of type Z-CH_2-CH_2-OH, the gauche conformer always predominates. (Z = OH, NH_2, F, Cl, Br, OMe, NHMe, NMe_2).



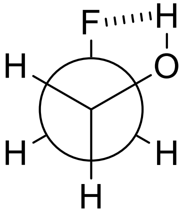
Anti



gauche (more stable)



Anti

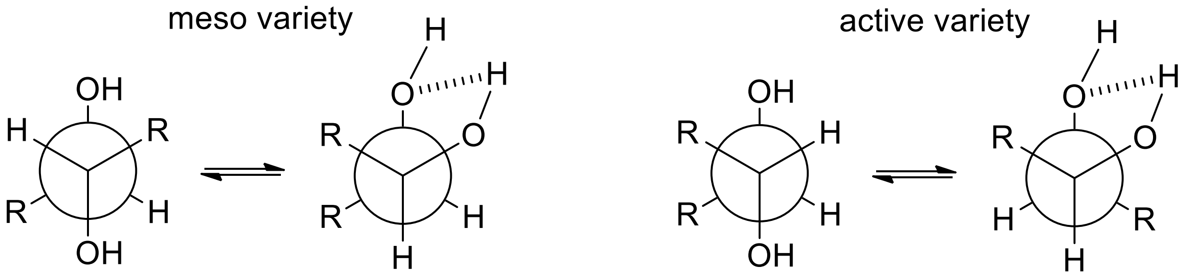


gauche (more stable)

- With increase in bulkness of –R, the hydroxyl groups tend to bend away from –R groups in all conformers of both meso and active variety, leading to stronger H-bonding. Thus, difference in IR stretching frequency between H-bonded –OH group and non-H-bonded –OH group increases for both meso and active variety. This effect is more in active variety.

- But, for meso variety, repulsion between R/R also increases with increase in bulkness of –R. Therefore, although the difference in IR stretching frequency increases, "**I**" becomes more and more preferred, leading to weak or no signal for H-bonded –OH groups in IR.

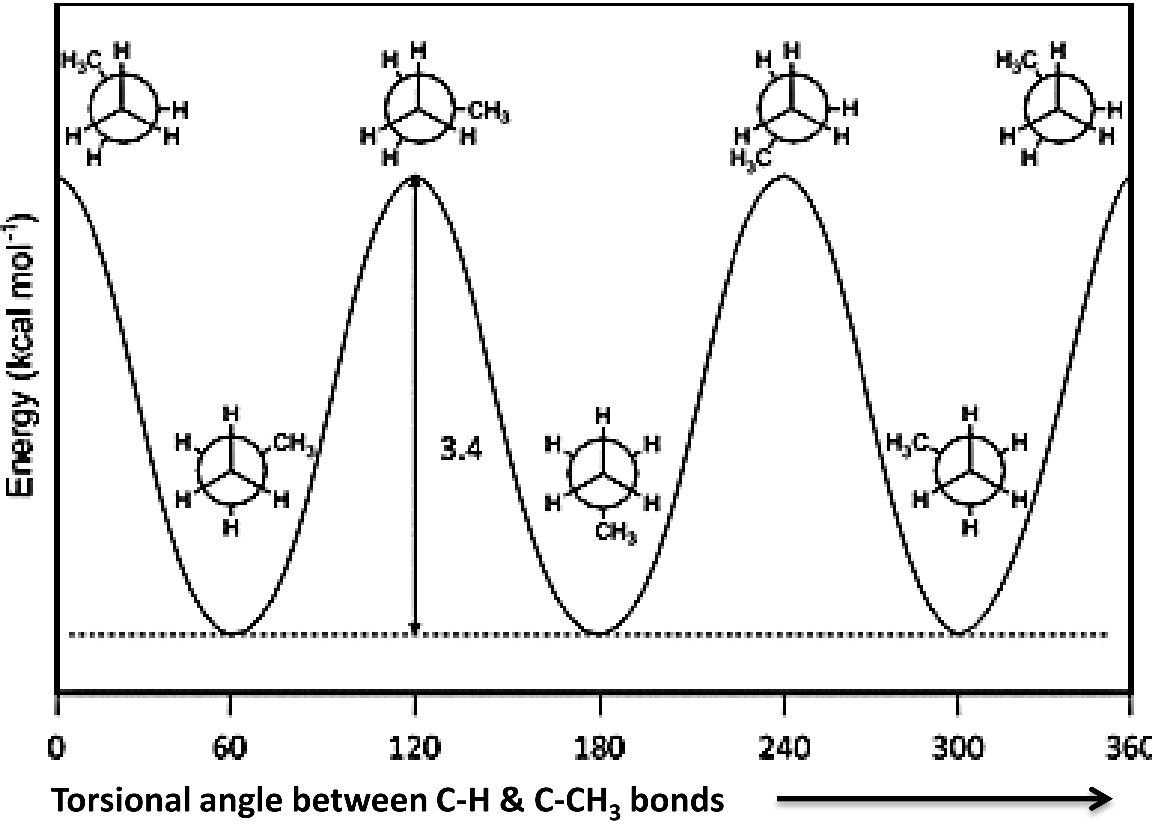
- For, active variety, repulsion between R/R also increases with increase in bulkness of –R. Therefore, "**IV**" becomes more and more preferred, leading to stronger signal for H-bonded –OH groups in IR, which leads to higher frequency difference between H-bonded –OH group and non-H-bonded –OH group.

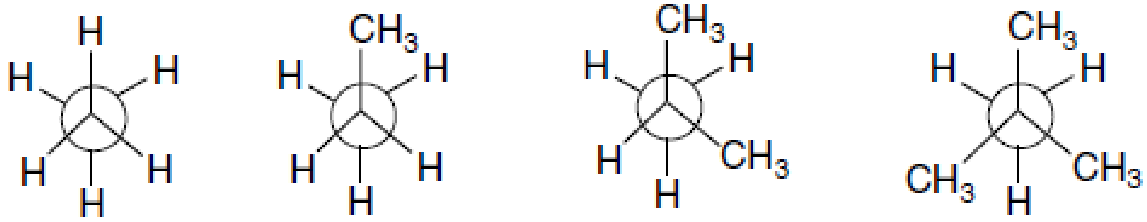


I II III IV

R =	H	Me	-CHMe$_2$	-CMe$_3$
Meso	32	42	55 (very weak peak for H-bonded -OH)	No extra peak for H-bonded -OH
Active	32	49	81	94

Conformational analysis of Propane:



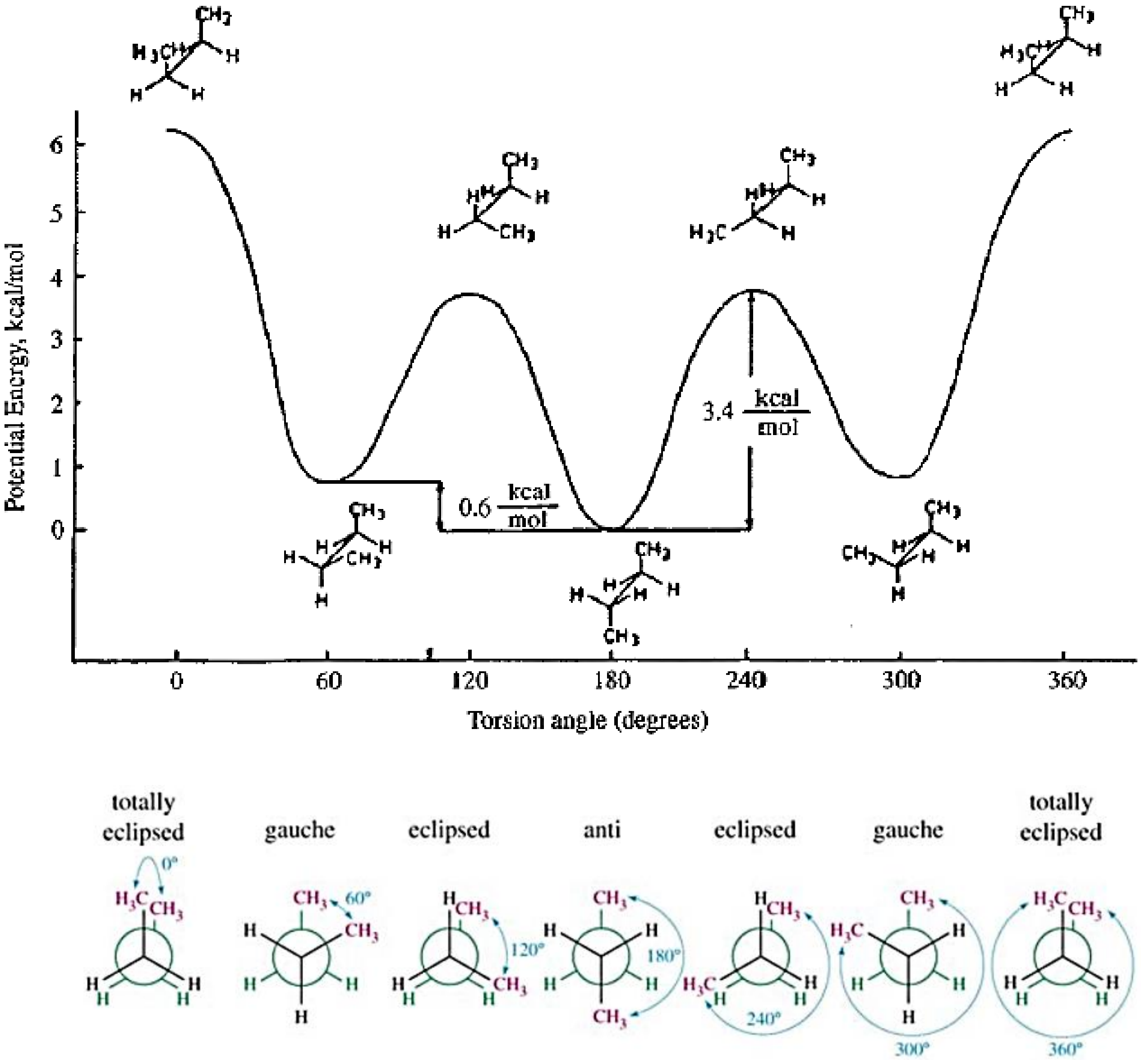


~2.9 kcal/mol **~3.4 kcal/mol** **~3.9 kcal/mol** **~4.7 kcal/mol**

Rotational barrier increases by ~ 0.5 kacl/mol in each case, with the introduction of each methyl group at C-2

- The shape of the profile is similar to that of ethane.
- Here, one hydrogen is replaced by a methyl group, which increases the barrier only to ~ 3.4 kcal/mol.
- Thus, van der Waal's repulsion is also not very significant in proane and the rotational barrier is mainly arising out of the torsional strain and the value of eclipsing Me/H strain is ~ (3.4-2.9) Kcal/mol ~ 0.5 Kcal/mol
- Incorporation of more methyl groups in C-2, inceases the rotational barrier by ~ 0.5 kacl/mol per methyl group.
- However, the energy profile diagram of all these alkanes will still have the same shape and only the magnitude of maxima and minima will be different.

Conformational analysis of n-butane: The gauche butane interaction:



- Of course, the situation will be complicated when methyl group is incorporated at both C-1 and C-2, i.e. the case of n-butane.

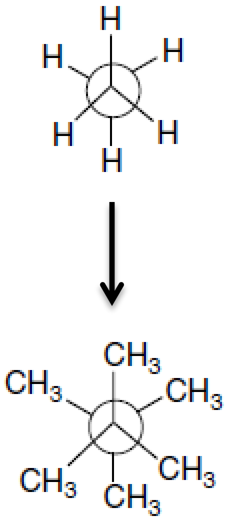
- Here, the interplay between the torsional barrier and nonbonded (van der Waals) interactions will become more vivid.

- The two *gauche* conformers are raised in energy relative to the *anti* by an energy increment resulting from the van der Waals repulsion between the two methyl groups at 60° angle and the value is about 0.6 kcal/mol. This is known as ***Gauche Butane Interaction***.

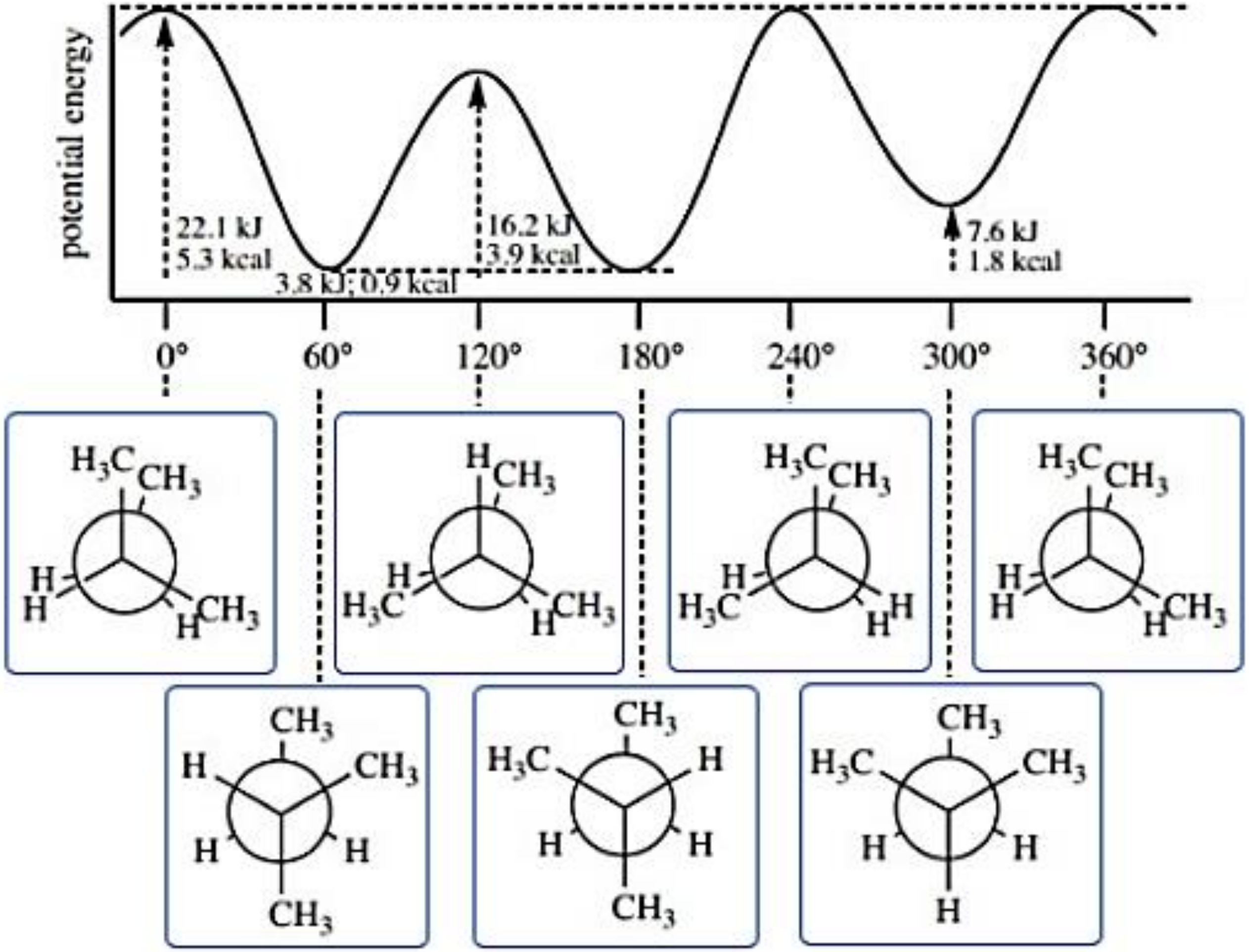
- All eclipsed conformations incorporate 2.8 kcal/mol of torsional strain relative to the staggered conformations, just as in ethane, along with either Me/H or Me/Me eclipsing van der Waals strains.

- Of course, here the energy barrier means barrier between most stable ***anti*** and least stable ***totally eclipsed*** conformer, as all the conformations can only be seen, only when the largest barrier is overcame.

- For n-butane, the energy barrier is ~ 4.7 Kcal/mol, leading to Me/Me eclipsing strain ~ (4.7 – 2.9) Kcal/mol ~ 1.8 Kcal/mol. This value suggests that, 2,2,3,3-tetramethylbutane, in which there are three methyl-methyl eclipsing interactions, the barrier will be ~ (1.8 x 3) Kcal/mol ~ 5.4 Kcal/mol higher than ethane. The experimental value of the rotational energy barrier of 2,2,3,3-tetramethylbutane is ~ 8.4 Kcal/mol.

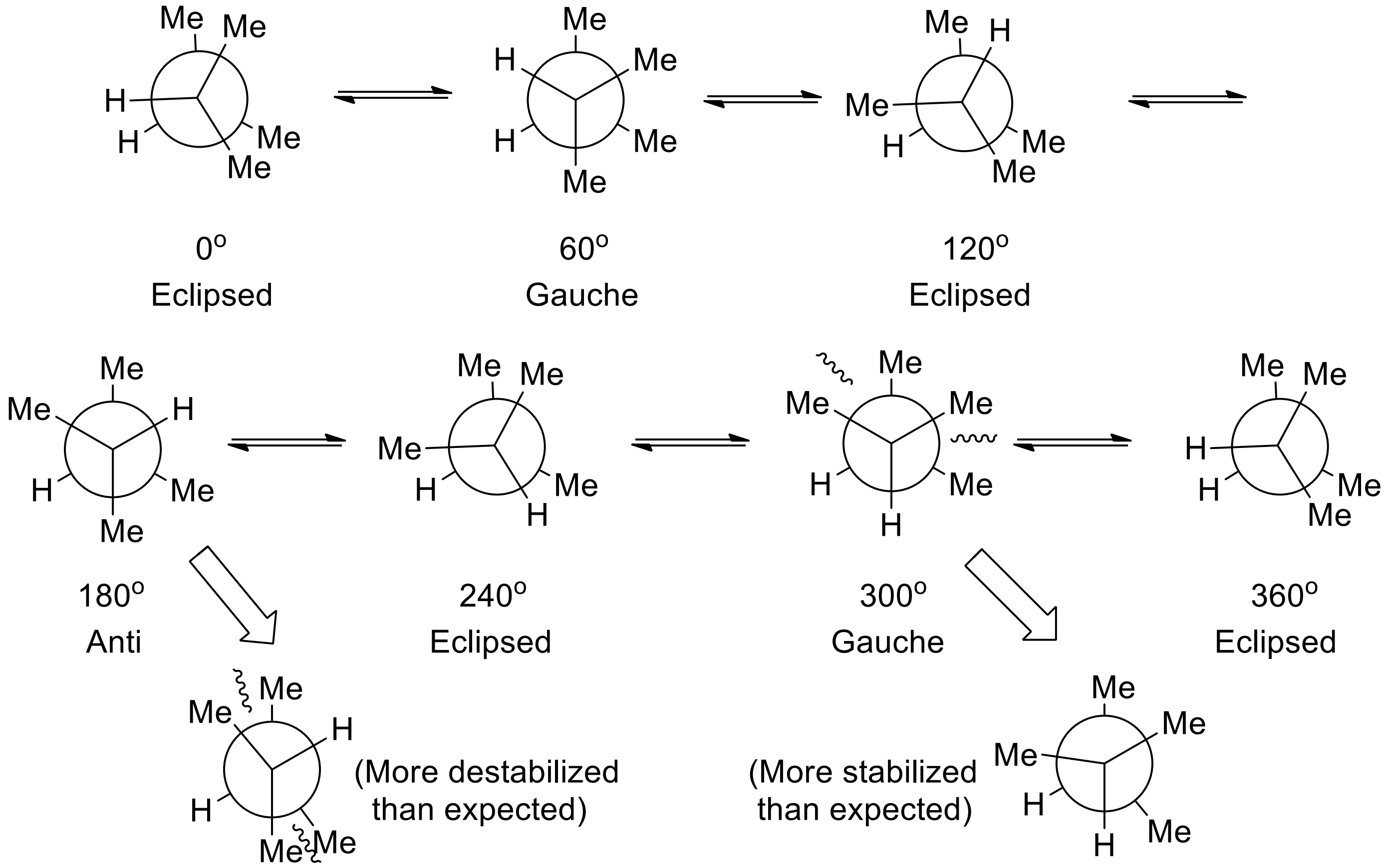


Conformational analysis of 2-methylbutane:



- In case of 2-methylbutane, the energy barrier is expected to be ~ [0.5 (for one Me/H eclipsing interaction) + 1.8 (for one Me/Me eclipsing interaction)] Kcal/mol, i.e. ~ 2.3 Kcal/mol higher than ethane. The experimental energy barrier is ~ 5.3 Kcal/mol.

Conformational analysis of 2,3-dimethylbutane:



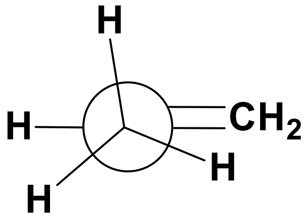
- Interestingly, both gauche and anti forms are equally stable, although the anti conformer is expected to be more stable, due to less Me/Me interaction.

- Higher <Me-C-Me (114^0, as compared to 109^0 in n-butane) is the key factor here, which makes the gauche conformer more stable than expected and makes the anti conformer less stable than expected. As a result both gauche and anti forms become equally stable.

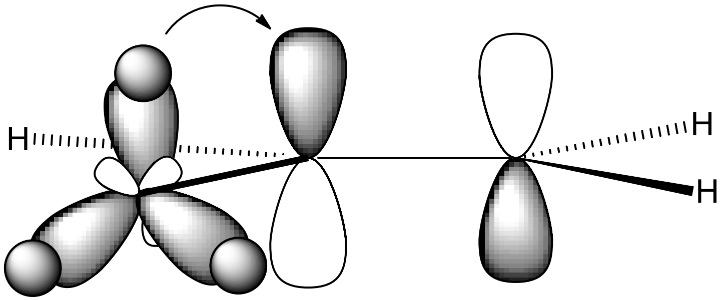
Conformational analysis alkenes and conjugated dienes:
Propene:

- Overall, the methyl substituent of propene has an stabilizing effect of 2.7 kcal/mol on the double bond, as evident from the less negative heat of hydrogenation compared to ethene, due to hyperconjugation.

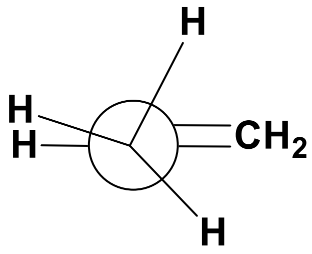
- Computational studies also show significant shortening of the C_2-C_3 bond.



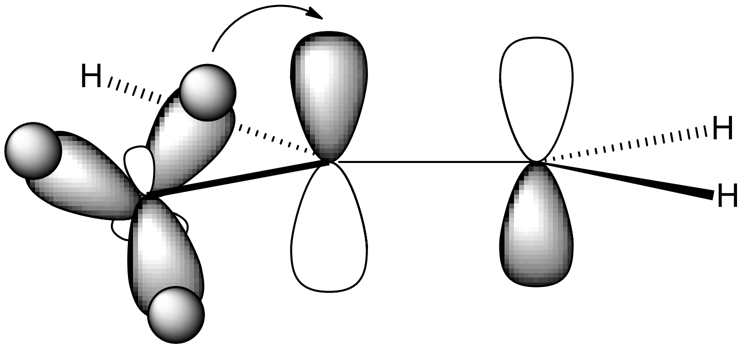
Eclipsed



* Almost parallelly alligned * Effective bonding interaction



Bisected



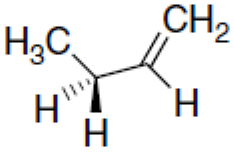
* Not properly alligned * Less effective bonding interaction

- There are two families of conformations available to terminal alkenes: ***eclipsed*** and ***bisected*** conformations.

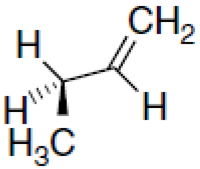
- Eclipsed conformer of propene is more stable than bisected conformer due to more effective hyperconjugation ($\sigma - \pi^*$ bonding interaction).

<u>Higher alkenes and carbonyls:</u>

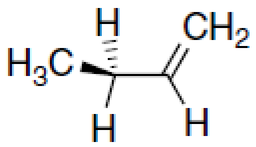
- 4 possible conformations. **A, B** are ***eclipsed*** and **C, D** are ***bisected.***



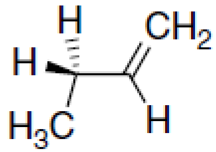
A



B

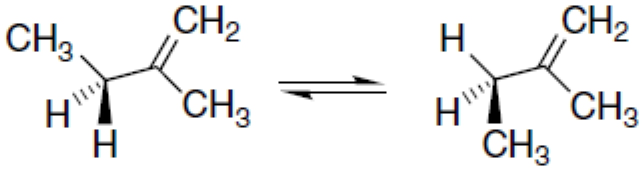


C



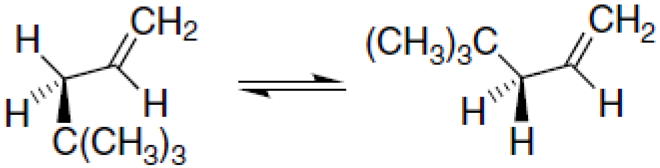
D

- Eclipsed conformers are more stable than bisecteds.
- B is more stable than A.



A-type **B-type**

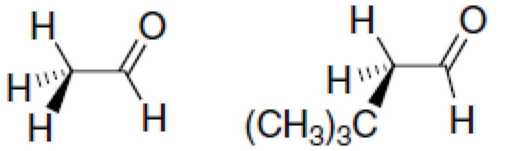
- Further substitution at C-2 makes both **A-type** and **B-type** conformers equally stable, due to additional Me/Me gauche interaction in B-type.



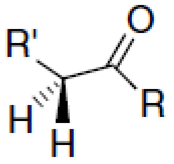
favored **B-type**

disfavored **A-type**

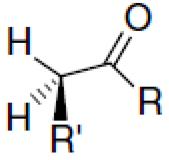
- Increasing the size of the group at C-3, increases the preference for the **B-type** eclipsed conformation, at the expense of **A-type**. 4,4-Dimethyl-1-pentene exists mainly in the hydrogen-eclipsed conformation. This interaction is an example of *1,3-allylic strain.* Carbonyls also show a similar trend.



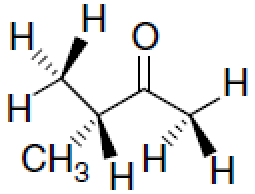
preferred conformations for ethanal and 3, 3-dimethylbutanal



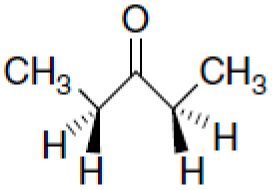
more stable



less stable



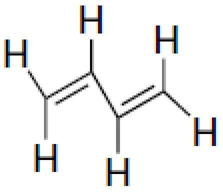
preferred conformation of 3-methyl-2-butanone



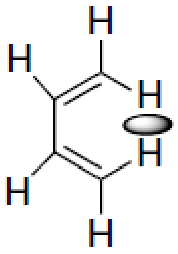
preferred conformation for 3-pentanone

1,3-Dienes:

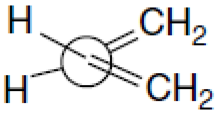
- 1,3-Dienes adopt conformations in which the double bonds are coplanar, so as to permit optimum orbital overlap and electron delocalization.



s-trans

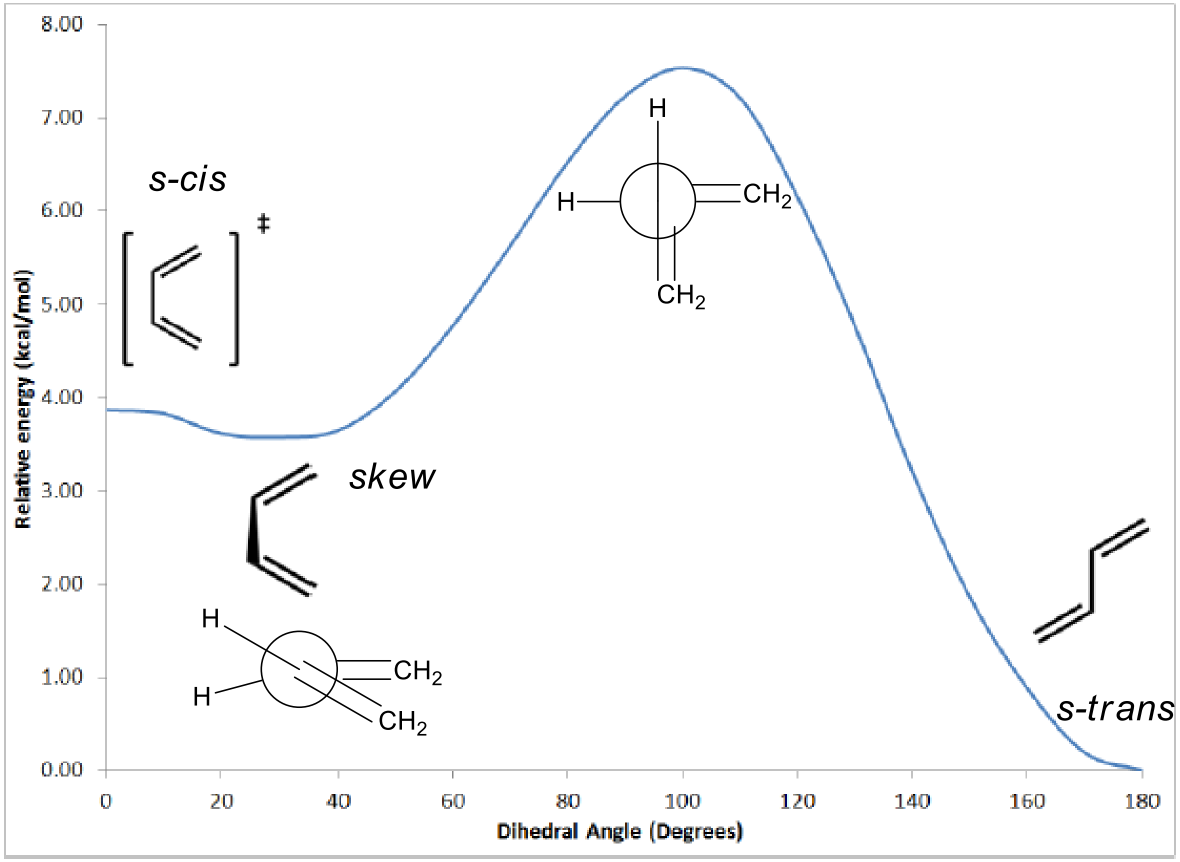


s-cis



skew

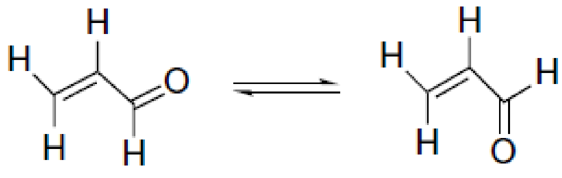
- ***s-trans*** and ***s-cis*** are planar, but ***s-cis*** incorporates a van der Waals repulsion between hydrogens on C-1 and C-4, which is relieved in cisoid but non-planar ***skew*** conformation. Thus, skew is also present in equilibrium with the major conformer.



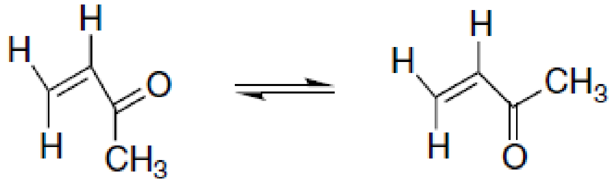
- The barrier for conversion of the skew conformation to the *s-trans* is 3.9 kcal/mol.

- The energy maximum presumably refers to the conformation in which the two bonds are mutually perpendicular.

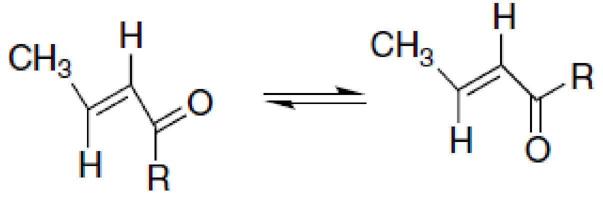
α, β-unsaturated carbonyl compounds:



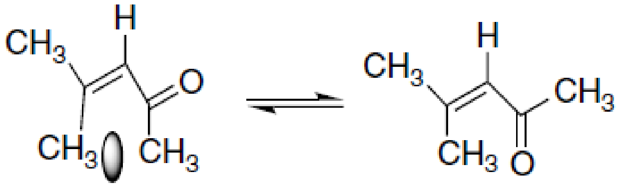
s-trans *s-cis*



s-trans (73%) *s-cis* (27%)



R	*s-trans*	*s-cis*
CH_3	0.7	0.3
C_2H_5	0.55	0.45
$(CH_3)_2CH$	0.3	0.7
$(CH_3)_3C$	0.0	1.0



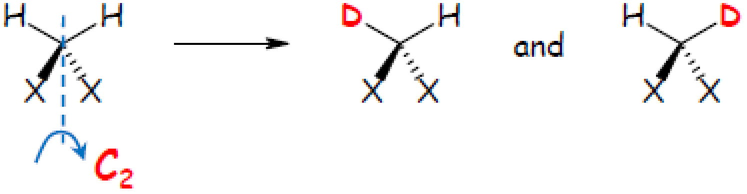
s-trans (28%) *s-cis* (72%)

- The case of ,ß-unsaturated carbonyl compounds is analogous to that of 1,3-dienes.
- Microwave data indicate that the *s-trans* form is the only conformation present in detectable amounts in 2-propenal.
- The equilibrium distribution of *s-trans* and *s-cis* conformations of substituted α, β-unsaturated ketones depends on the extent of van der Waals interaction between the C-1 and the C-4 substituents.
- When larger alkyl groups are substituted for methyl, the ratio of the *s-cis* form progressively increases as the size of the alkyl group increases.
- An unfavorable methyl-methyl interaction destabilizes the *s-trans* conformation of 4-methylpent-3-en-2-one (mesityl oxide) relative to the *s-cis* conformation, and the equilibrium favors the *s-cis* form.

Prostereoisomerism

Topicity of ligands:

A. Homotopic ligands:

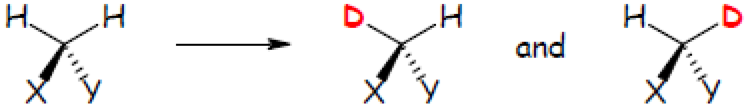


Here, the methylene hydrogens are ***"homotopic"***

- Constitutionally and configurationally equivalent.
- Related through a symmetry axis, C_n (symmetry criterion), i.e. identical groups exchange position with each other by C_n operation.
- Substitution of either ligand, by any hypothetical atom, gives identical compounds (substitution criterion).

B. Heterotopic ligands:

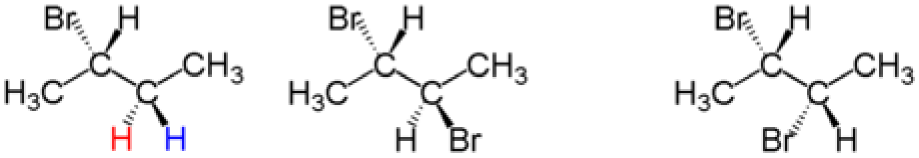
1. enantiotopic:



Here, the methylene hydrogens are ***"enantiotopic"***

- Related through *σ, i* or S_n i.e. identical groups are interchangable through *σ, i* or S_n .
- Substitution gives enantiomers.

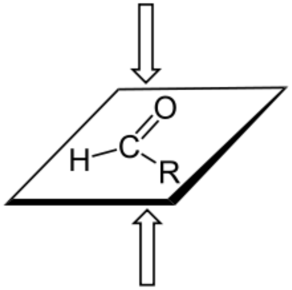
2. diastereotopic:



- Not related by symmetry
- Substitution gives diastereomers

Here, the methylene hydrogens are replaced by –Br, which leads to diastereoisomers. So the methylene hydrogens are ***"Diastereotopic"***

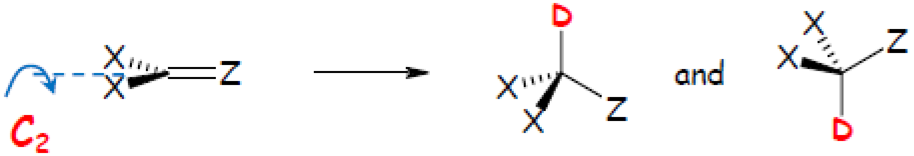
Topicity of faces:



The two faces of a planar molecule

A. Homotopic faces:

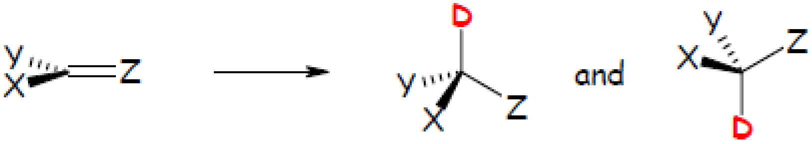
- Related through a symmetry axis, C_n (symmetry criterion), i.e. identical groups exchange position with each other by C_n operation.
- Addition of an hypothetical atom to either face gives identical compounds (addition criterion)



Both the faces, are ***"Homotopic"***

B. Heterotopic faces:

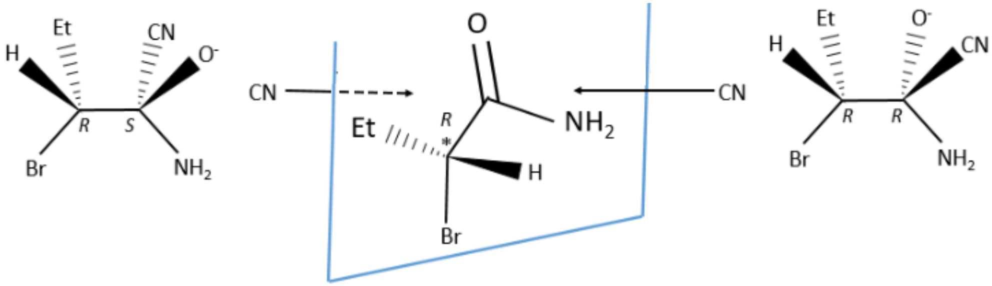
1. enantiotopic:



Both the faces, are ***"Enantiotopic"***

- Related through symmetry plane, σ. i.e. non-identical groups reside on plane of symmetry.
- Addition gives enantiomers.

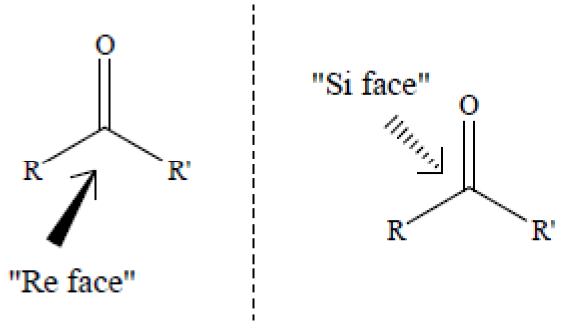
2. Diastereotopic:



- Not related by symmetry.
- Addition gives diastereomers.

Here, the products are diastereoisomers. So the faces are ***"Diastereotopic"***

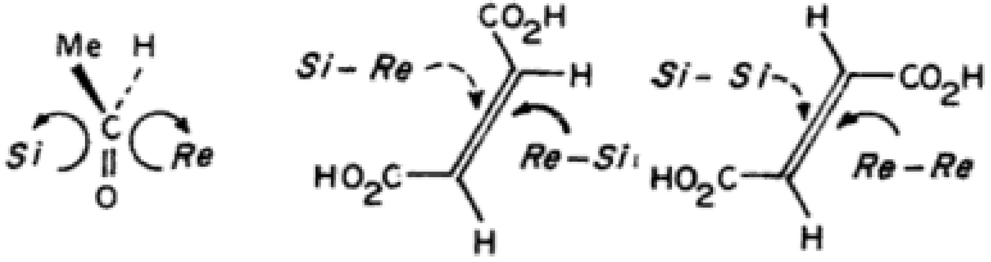
Topicity descriptors: Re/Si:



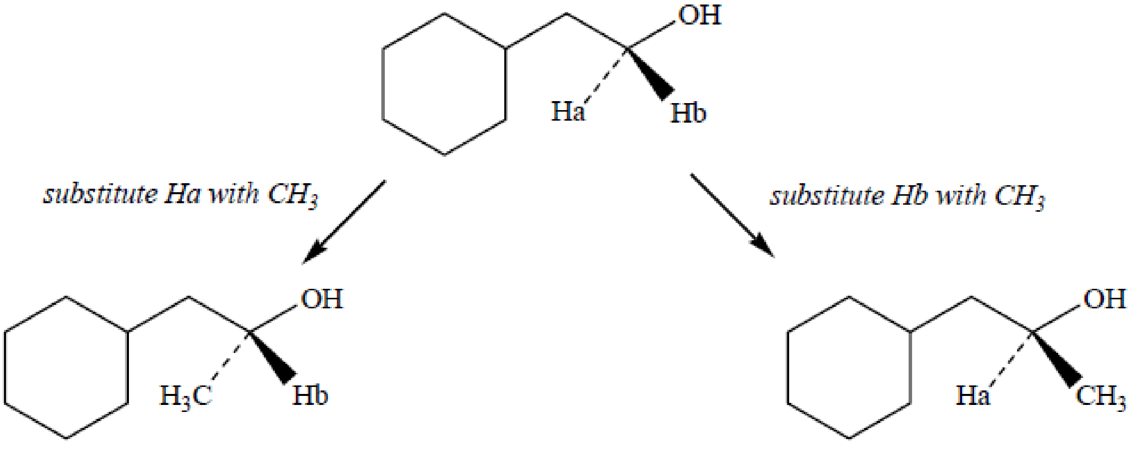
When R' > R

- The carbonyl group has a trigonal planar geometry (sp2). When the priorities of three substituents of the front face of the carbonyl group are oriented in a clockwise fashion (highest --> lowest), front face is called the ***Re-face*** and the back face is referred to as the ***Si-face***.

- *For alkenes, we have to consider both alkene ends.*



Topicity descriptors: pro-R/pro-S:



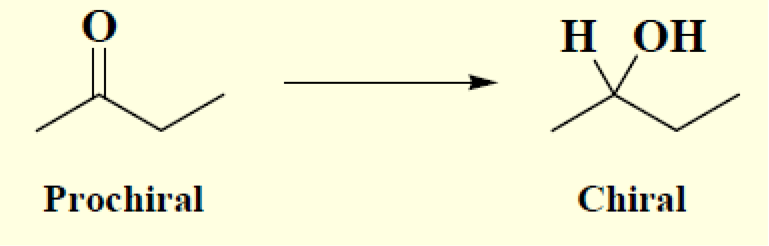
R-configuration

Ha is referred to as "pro-R"

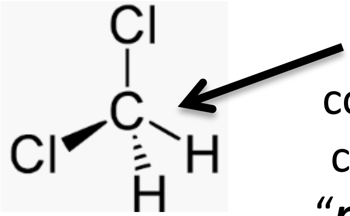
S-configuration

Hb is referred to as "pro-S"

Prochiral , proachiral and prostereogenic centers:

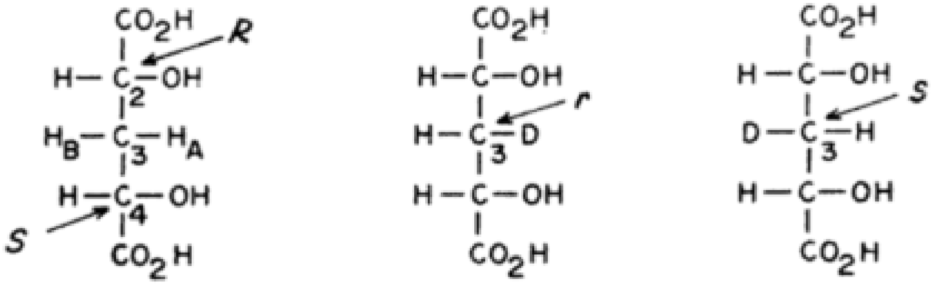


- If the identical groups of an achiral molecule can be made different and eventually the molecule can be turned into a chiral molecule it is "***Prochiral***" and the center, which gets converted into a chiral cenrter, is a "***prochiral center***"
- Here, the carbonyl carbon is a prostereogenic center, because, the interchange of H/OH leads to a new stereoisomers. Therefore, any center in a molecule, which upon a hypothetical one step conversion leads to a *stereogenic center*, is known as a "***prostereogenic center***".
- Of course, similar to sterogenic center / axis / plane, there are prostereogenic center / axis / / plane.
- When, the achiral molecule can't be turned into a chiral molecule, it is "***Proachiral***" and the center, is a "***proachiral center***".



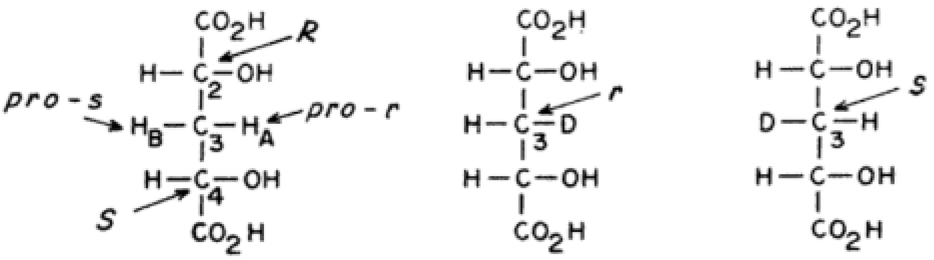
"***Proachiral***" compound and the carbon center, is a "***proachiral center***".

Propseudoasymmetric center:



- Here, the C-3 center is a ***propseudoasymmetric center***, because, replacement of H_a or H_b by –D, turns C-3 into a *pseudoasymmetric center*.

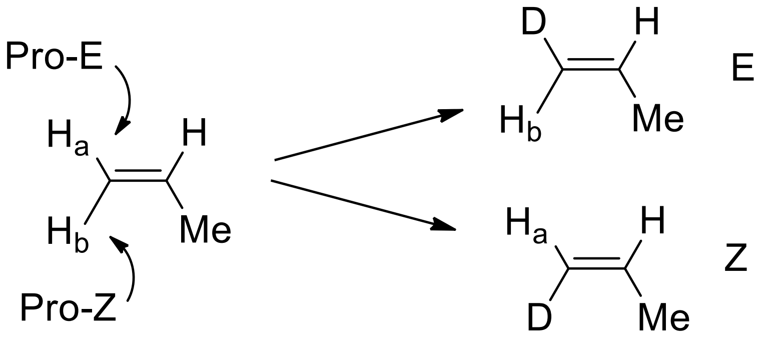
Pro-r/pro-s descriptors of ligands on propseudoasymmetric centre :



Pro-r and pro-s are basically the descriptors of ligands of propseudoasymmetric centers.

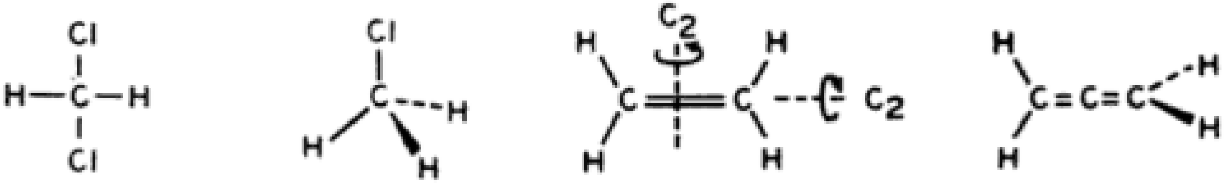
Pro-E/pro-Z:

- *Pro-E and Pro-Z* ligands are found in planar molecules.
- The molecules are the examples of entities having ***prostereogenic***, but ***proachiral centers.***
- Here, the alkene carbons are ***prostereogenic***, but ***proachiral centers.***

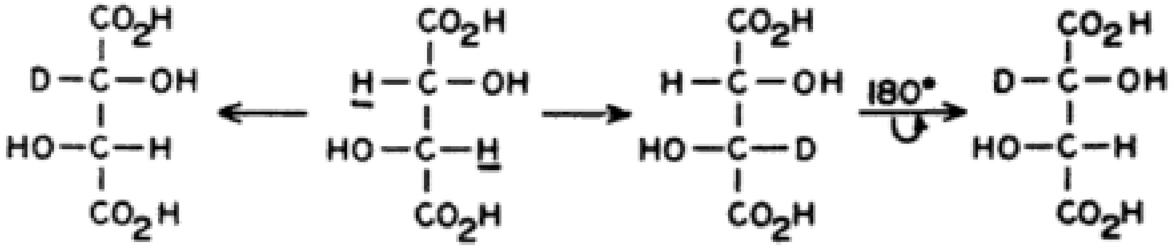


Examples:

- ➢ *All hydrogens are homotopic in following examples:*

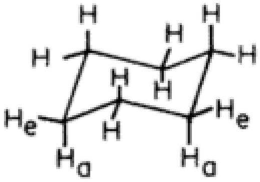


- ➢ *Hydrogens at C-2 and C-3 are homotopic in the following example:*

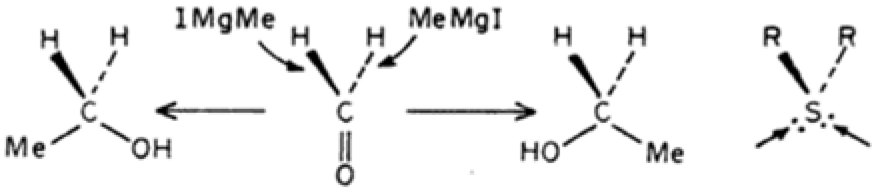


- ➢ *At very low temperature, when fliping of cyclohexane is arrested, the equatorial hydrogens can't get converted to axial hydrogen.*

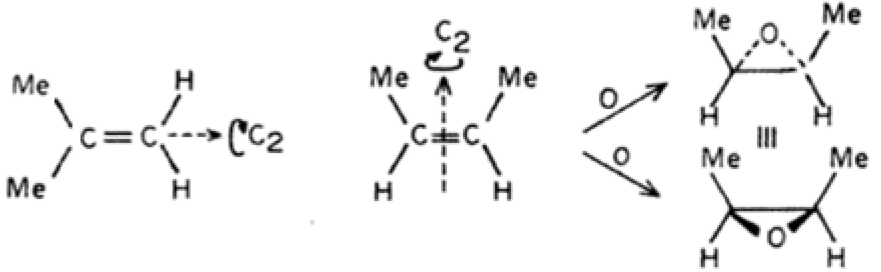
- *So, all 6 equatorial hydrogens describe one set of **homotopic** hydrogens and all six equatorial hydrogens describe another set of **homotopoic** hydrogens.*
- *Relation between members of two sets is **heterotopic**.*



- ➢ *Both faces of formaldehyde are **homotopic**.*
- ➢ *Both faces of dialkylsulfide are **homotopic.** **Alternatively,** both lone pairs or both R-groups are **homotopic**.*

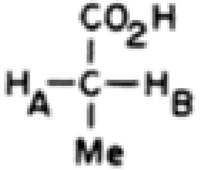


- ➢ *For alkenes, we have to consider addition at both ends. So, following alkenes have homotopic faces.*



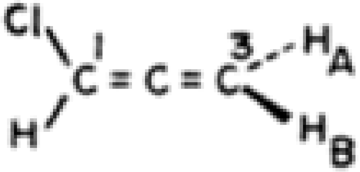
Example of Prostereogenic center:

H_a and H_b are enatiotopic.



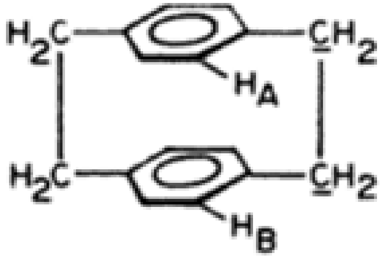
Prostereogenic axis:

H_a and H_b are enatiotopic.

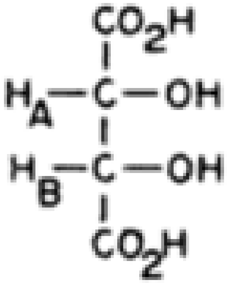


Prostereogenic plane:

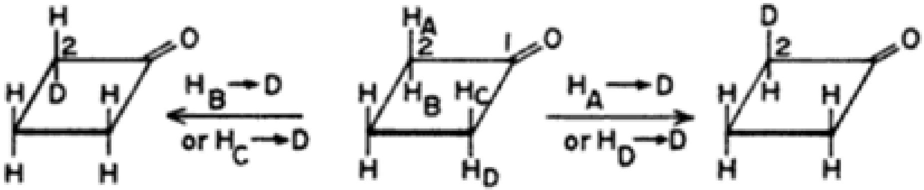
H_a and H_b are enatiotopic.



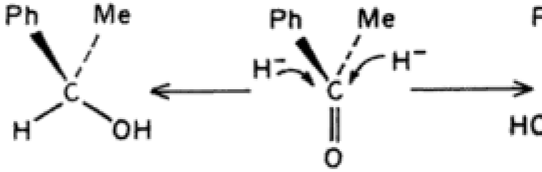
- *H_a and H_b of meso-tartaric acid are enatiotopic*

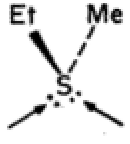


- *H_a / H_d pair and H_c / H_b pair are homotopic, whereas H_a is enantiotopic with H_b and H_c.*

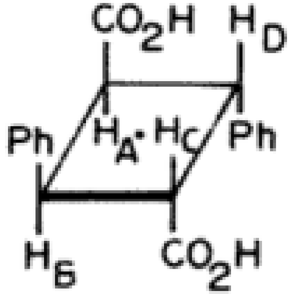


- *Following examples have enantiotopic faces.*

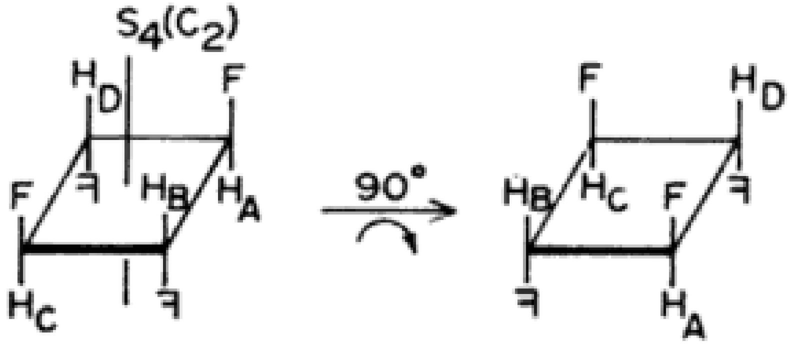




- *In the following example, H_a / H_c, H_b / H_d, 2 Ph and 2 COOH are interchangable by "i". So, they are enantiotopic pairs.*

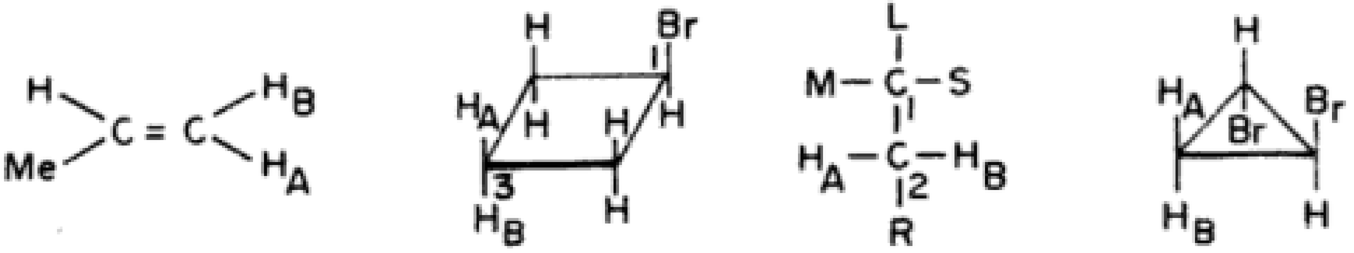


- *In the following example, both H_a and H_c is related to H_b / H_d via S_4. So, both H_a and H_c / bear enantiotopic relation with H_b / H_d .*



- *But, H_a is related to H_c via $C_{2,}$ and H_b is related to H_d via $C_{2,}$ therefore H_a / H_c and H_b / H_d are homotopic pairs.*

- *Following compounds showcase diastero- -topic ligands.*



- *Following are examples of diastereotopic faces.*