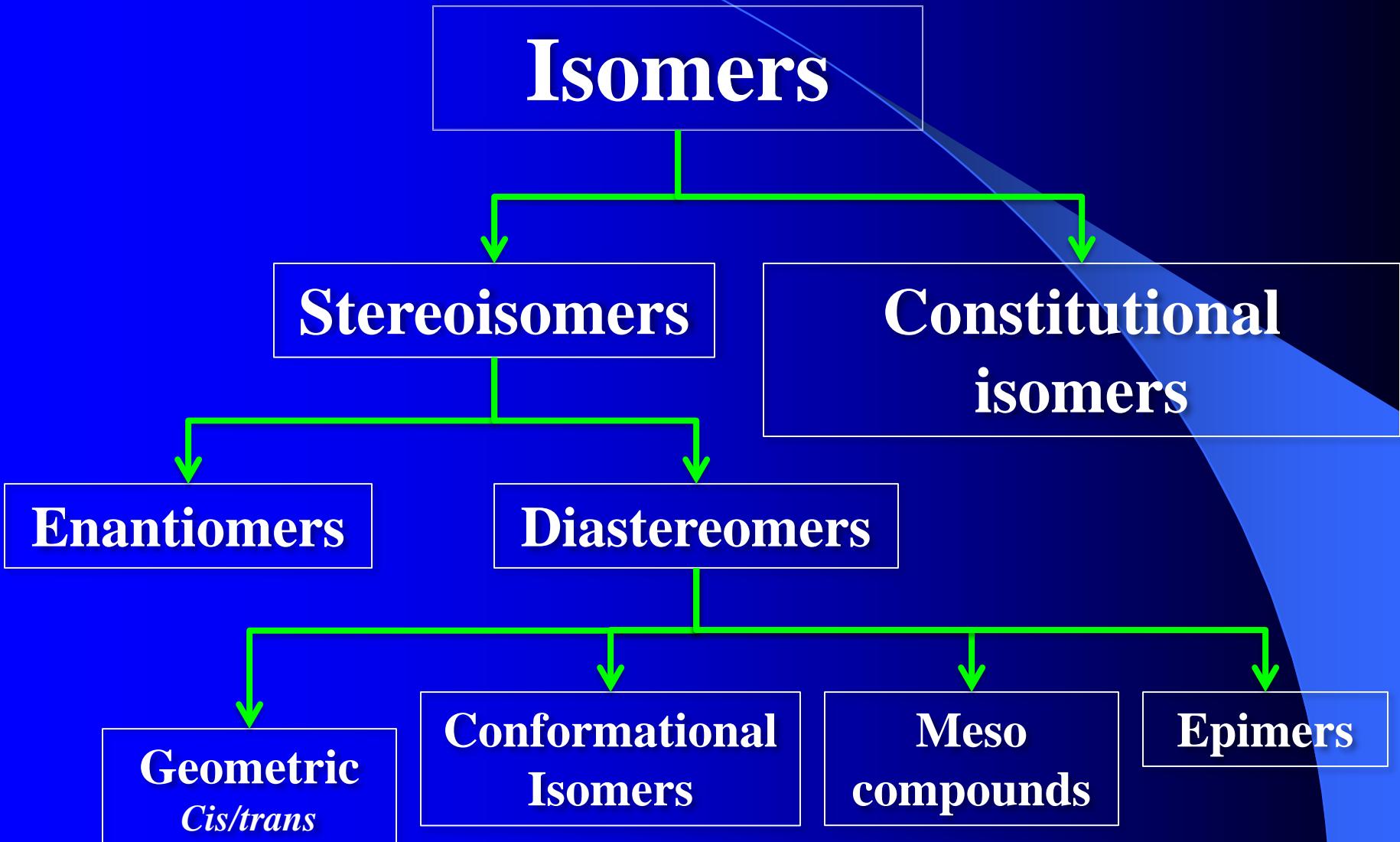


Isomers

Isomers – are compounds that have the same numbers and kinds of atoms but differ in the way the atoms are arranged.

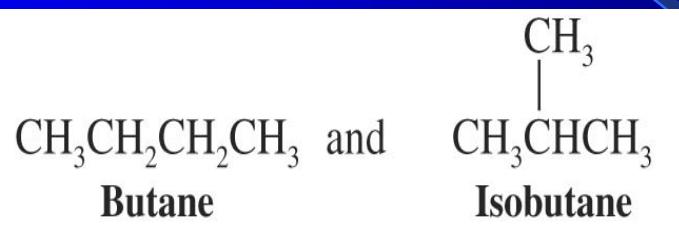
Isomer Organization



Isomers

Constitutional isomers may have

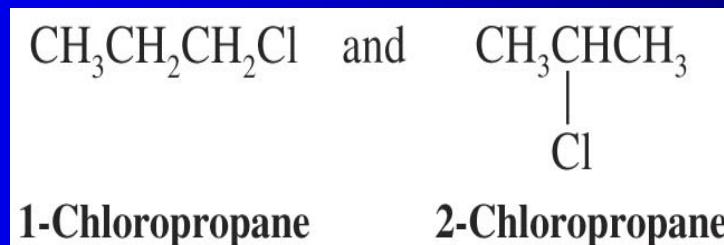
different carbon skeletons (as in isobutane and butane)



different functional groups (as in ethanol and dimethylether)



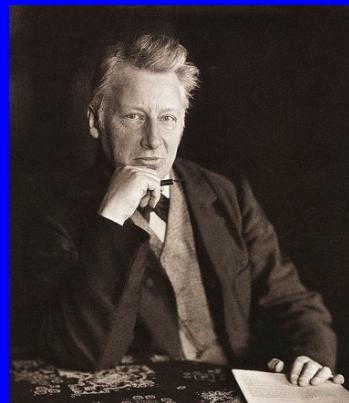
different locations of a functional group along the chain (as in 1-chloropropane and 2-chloropropane).



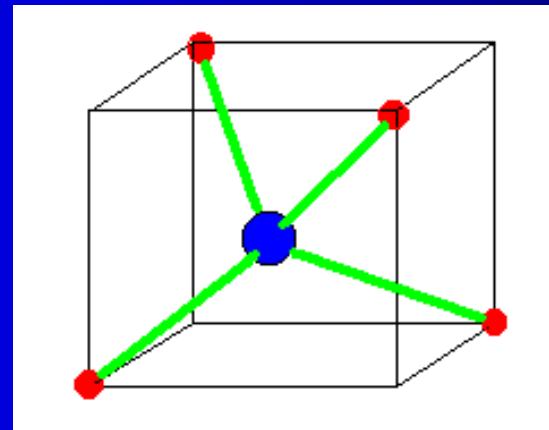
STEREOCHEMISTRY

Introduction:

Stereochemistry is the chemistry of molecules in three dimension.



Jacobus van't Hoff



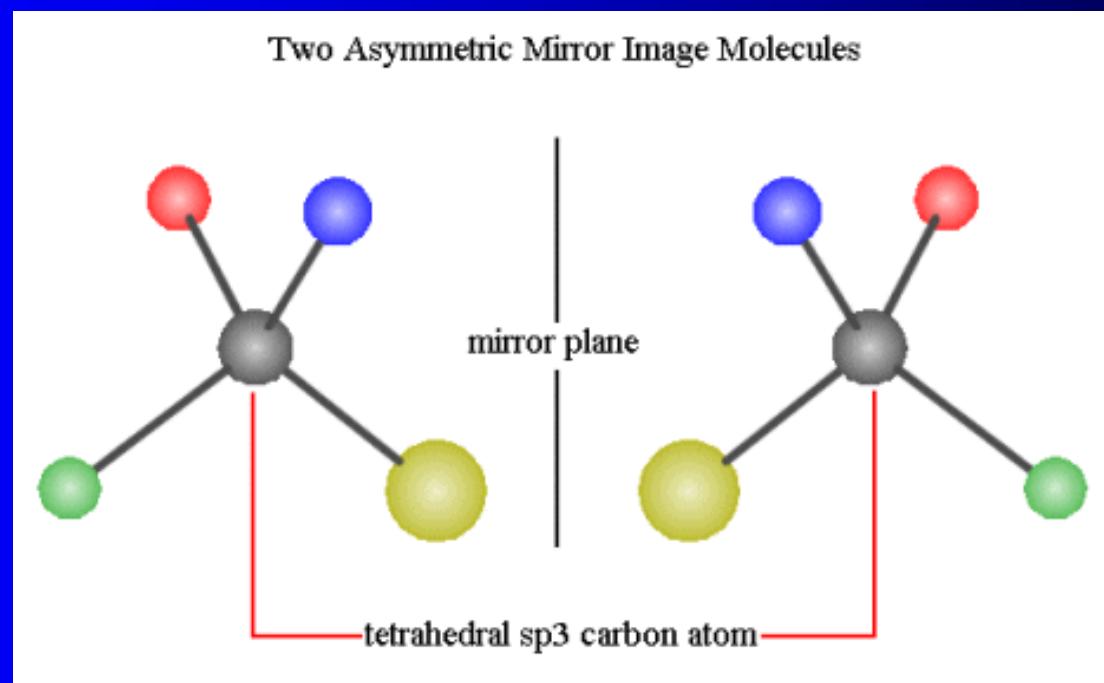
Charles Le Bel

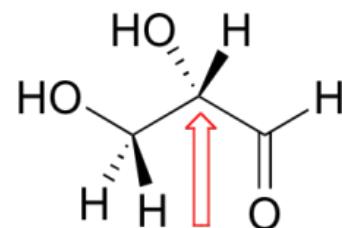
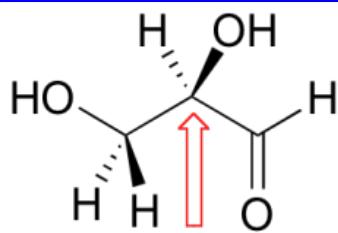
Each one of them independently, proposed (1874) that the four bonds to carbon were directed toward the corners of a tetrahedron.

Jacobus van't Hoff own first Nobel Prize in Chemistry in 1901

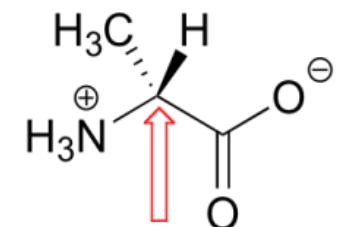
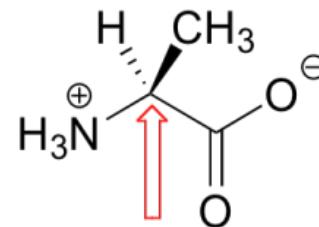
STEREOCHEMISTRY

The consequence of a tetrahedral arrangement of bonds to carbon is that, for the same molecular formula, and for same bonding if two different spatial arrangements are possible then that represents two different compounds.

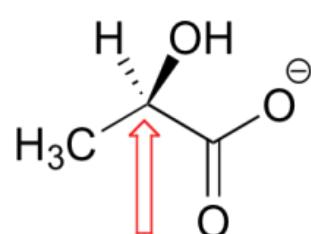
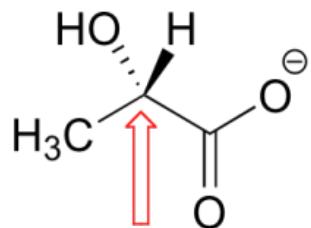




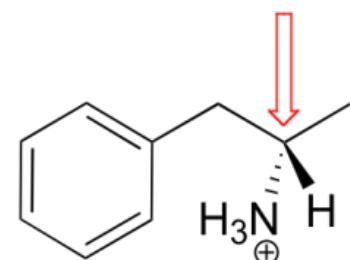
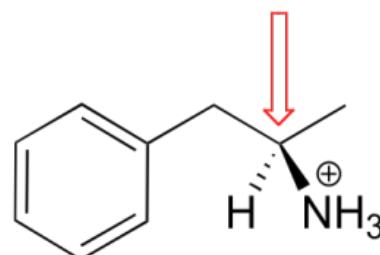
glyceraldehyde



alanine



lactate



amphetamine

Handedness

Stereochemistry of organic molecules can be understood, if we understand the meaning of handedness.

Why?

Because handedness plays a large role in organic chemistry as a consequence of the tetrahedral stereochemistry of sp^3 hybrid carbon.

To understand handedness, let us ask a question to ourselves:

Are we right or left handed?

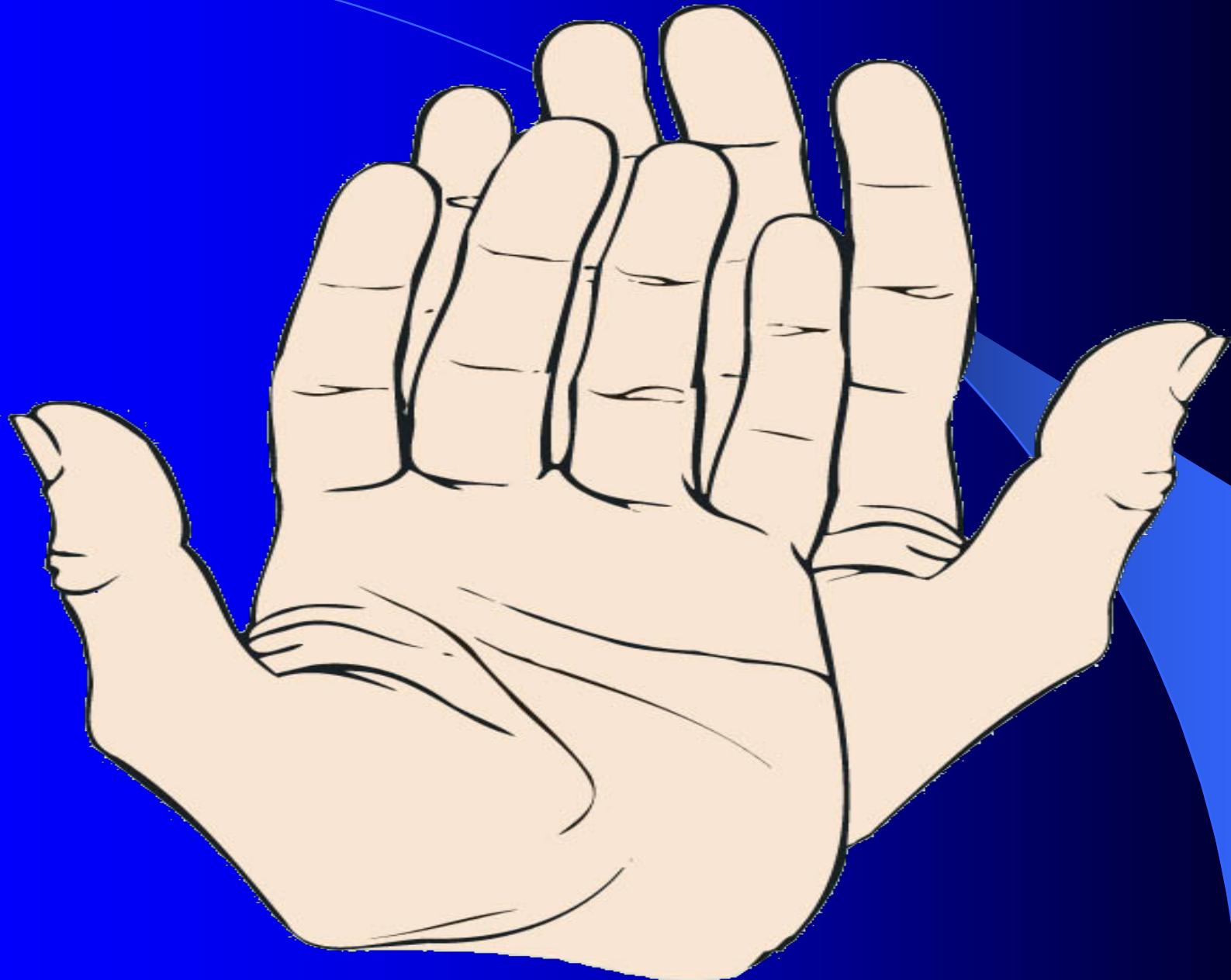
Handedness

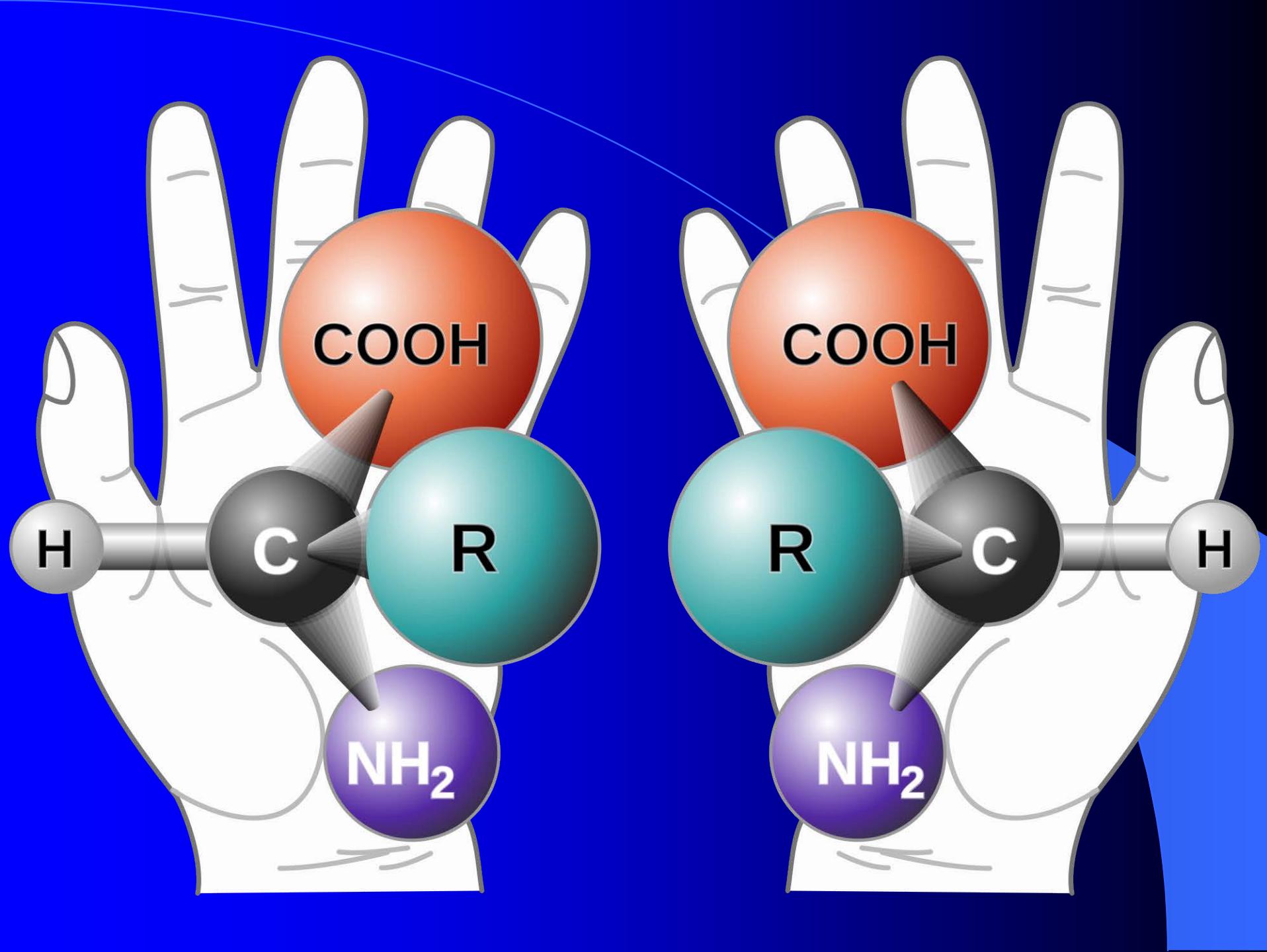
Most of us, though don't often think about it, handedness surprisingly plays a large role in our daily activities.

The way right handed people write is different from the way left handed do.

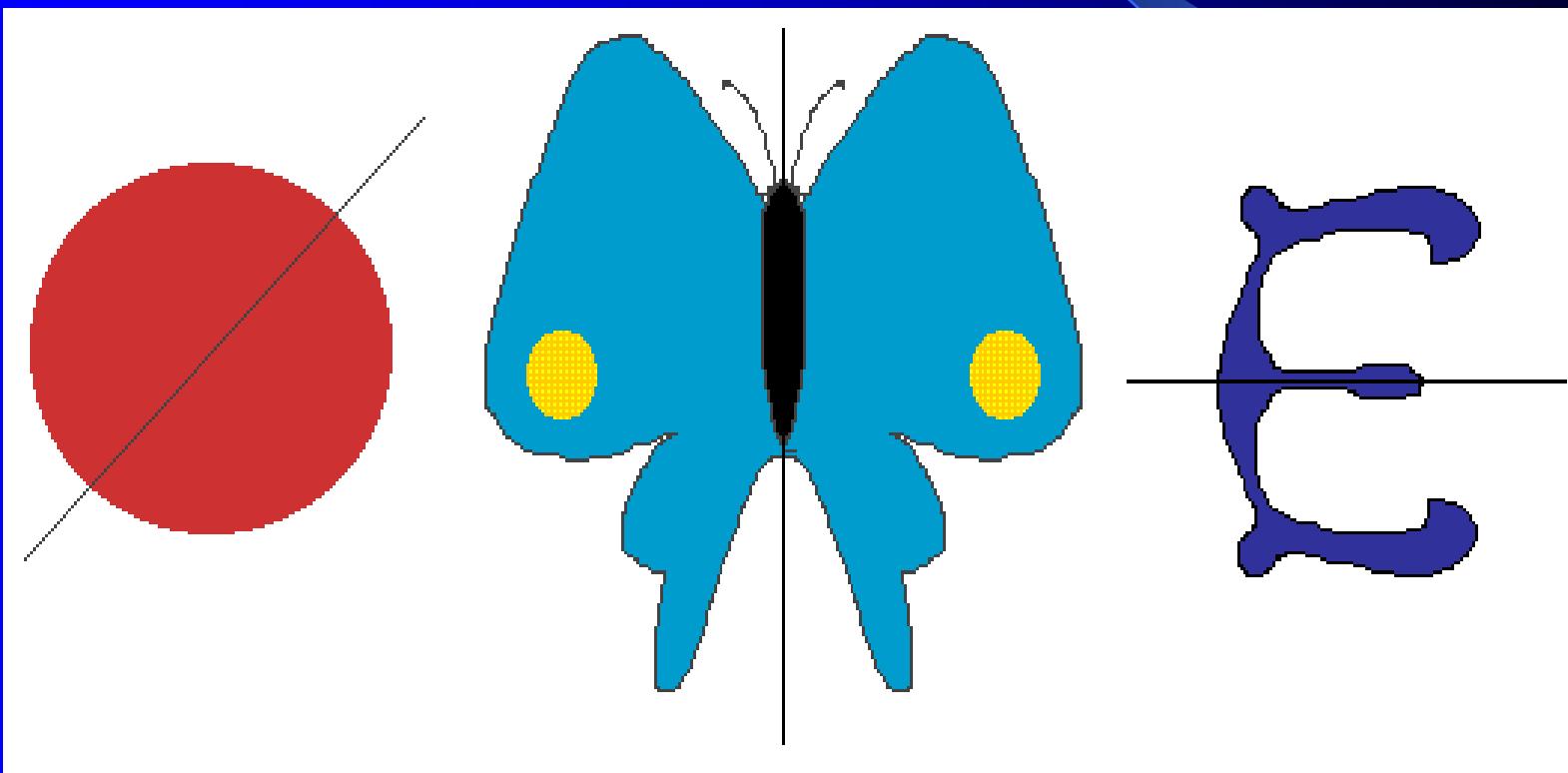
The fundamental reason for this is that our hands are not identical, rather they are mirror images.

Most drugs and most of the molecules in our body, for instance, are handed.





Some examples of symmetry



Handedness

Furthermore, it is molecular handedness that makes possible many of the specific interactions between molecules that are so crucial to biochemistry.

An example can be cited here of (+)-glucose.

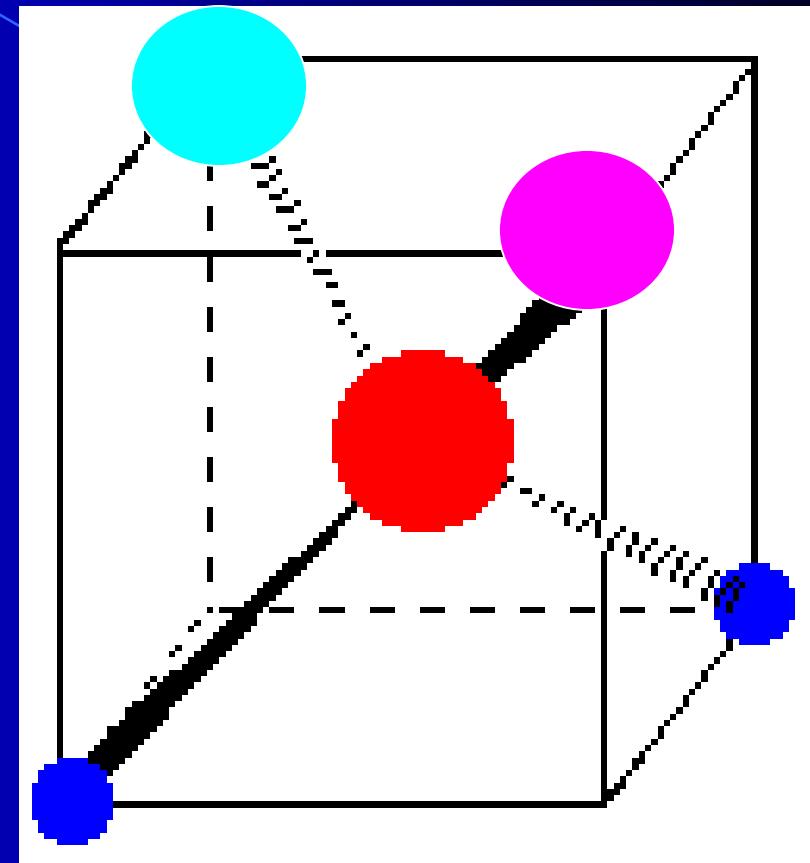
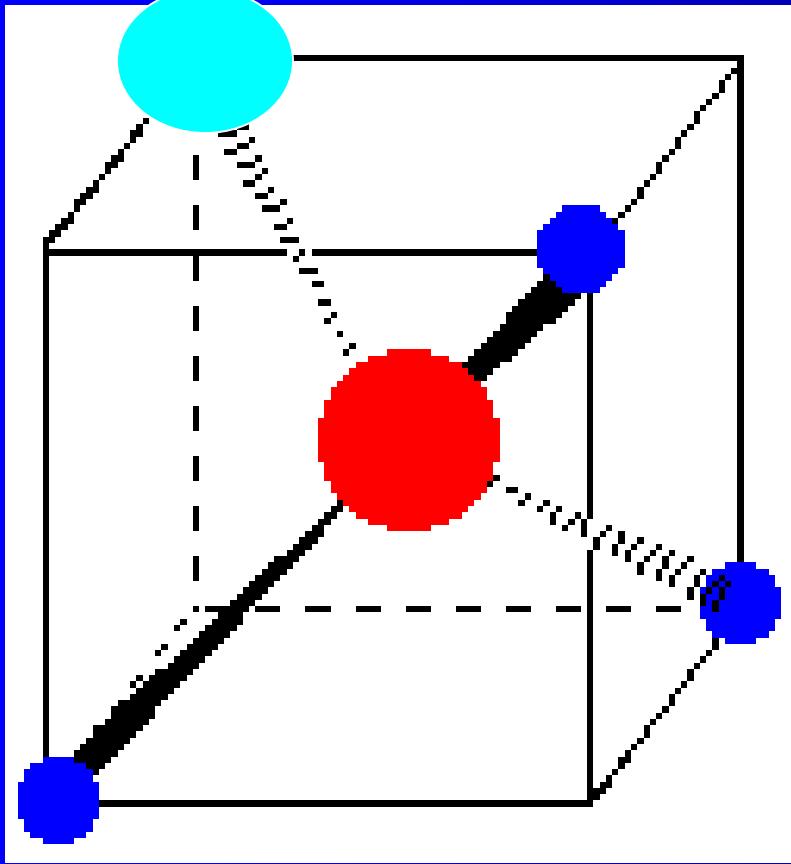
Only (+)-glucose is able to help in animal metabolism, whereas (-)-glucose is unable to participate in the animal metabolism.

Concept development from generalized formulas

Let us consider generalized molecules of the type CH_3X , CH_2XY and CHXYZ .

The CH_3X and CH_2XY molecules are identical to their mirror images and they are not handed.

If we make a model of each molecule and of its mirror image, we can superimpose one on the other.

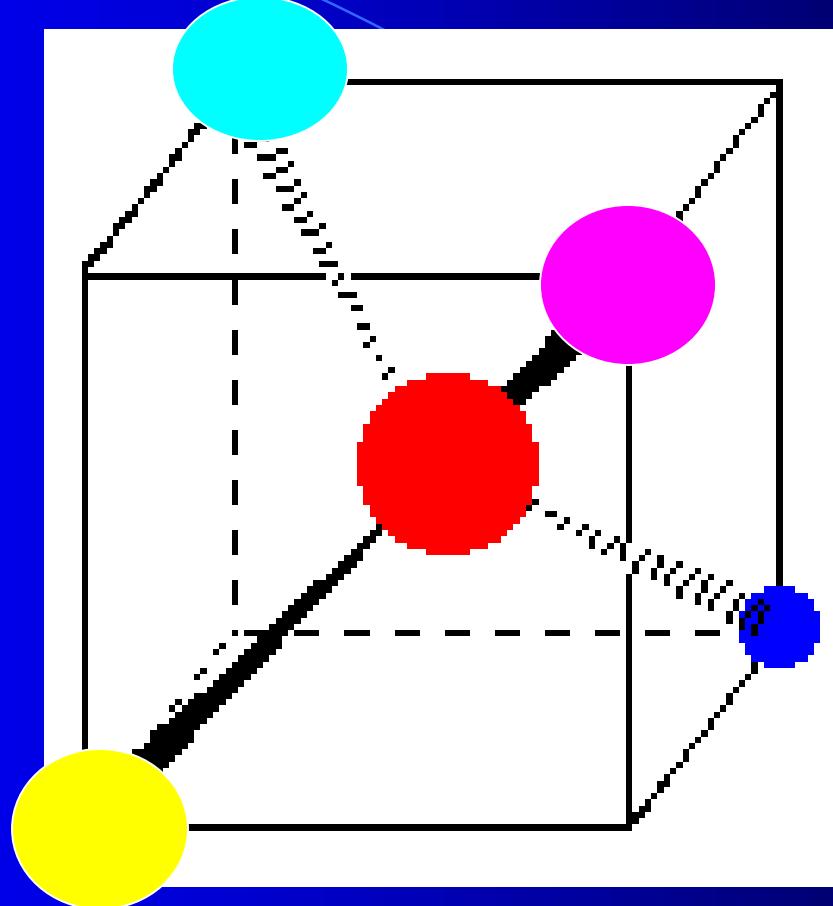


Concept development from generalized formulas

Unlike the CH_3X and CH_2XY molecules, the CHXYZ molecule is not identical to its mirror image.

We can not superimpose a model of the CHXYZ molecule on a model of its mirror image for the same reason that we can not superimpose a left hand on a right hand.

One might get two of the substituents superimposed, ‘X’ and ‘Y’ for example, but ‘H’ and ‘Z’ would be reversed and vice-versa.

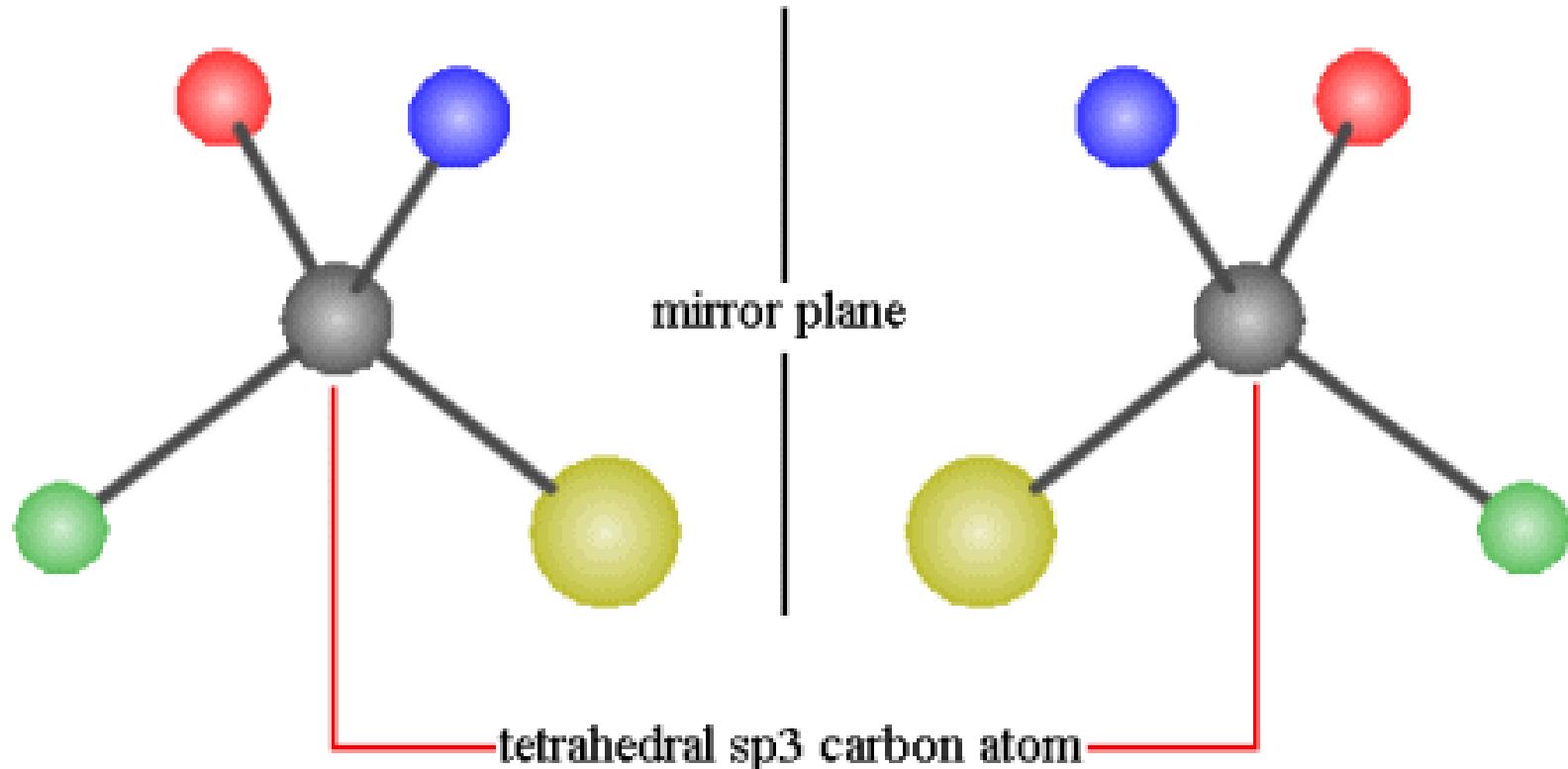


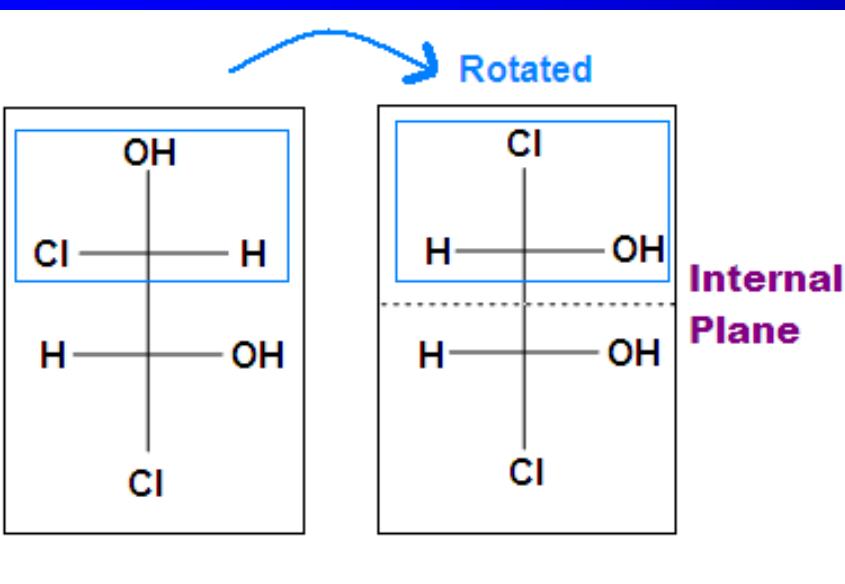
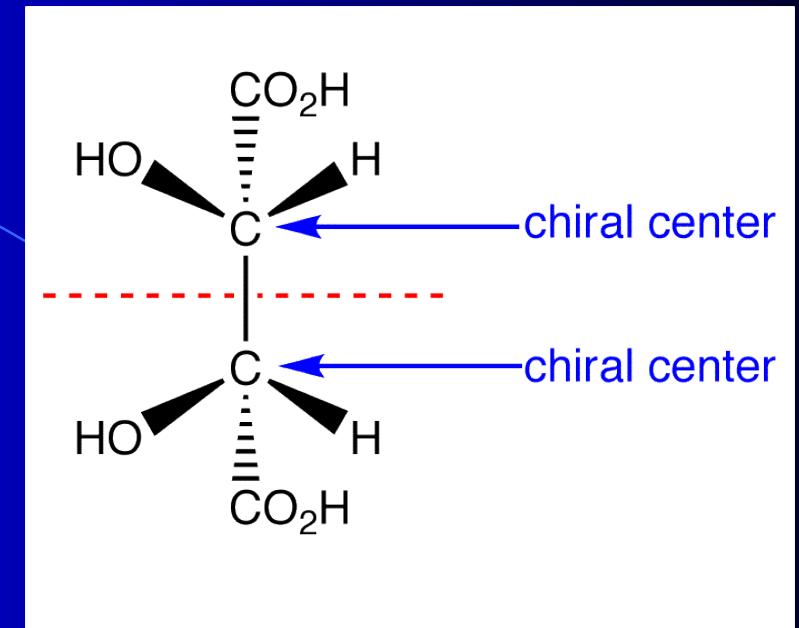
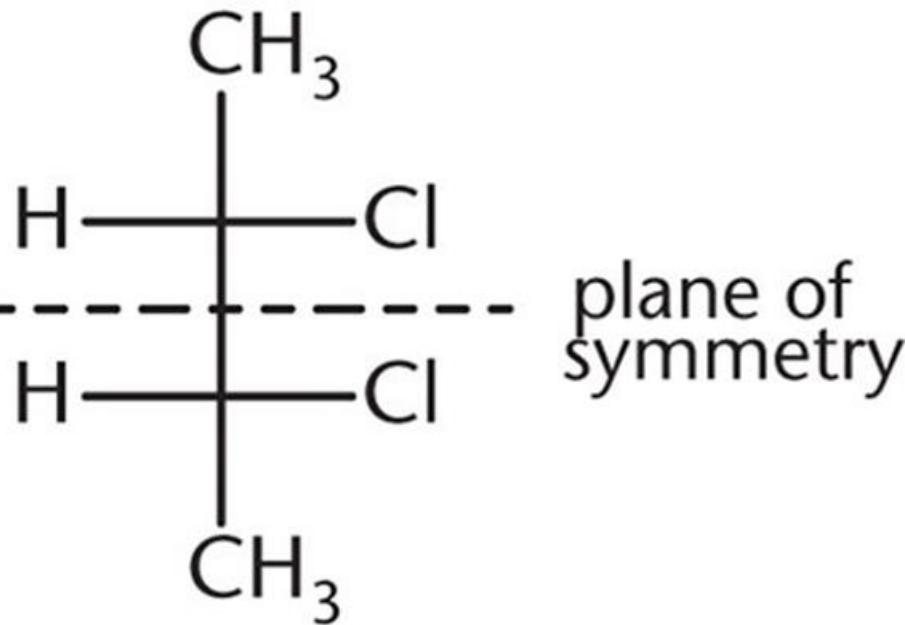
Concept development from generalized formulas

Enantiomers are related to each other as a right hand is related to a left hand and result whenever a tetrahedral carbon is bonded to four different substituents.

A molecule is **not chiral** (ky-ral, from the Greek cheir, “hand”) if it **contains a plane of symmetry** (plane that cuts through the middle of an object or molecule in such a way that one half of it is a mirror image of the other half)

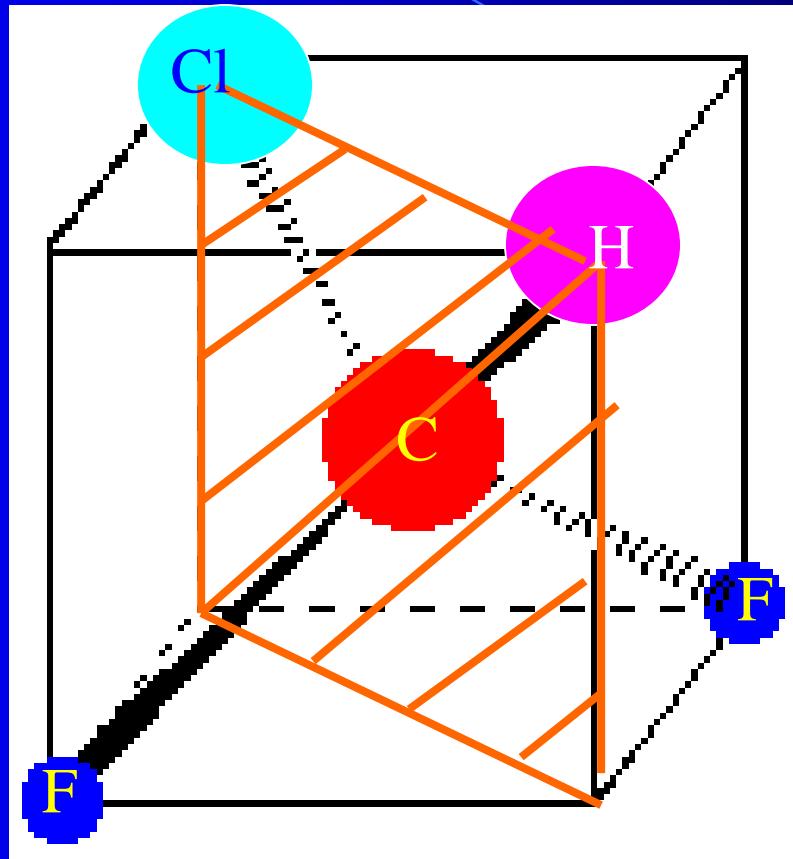
Two Asymmetric Mirror Image Molecules

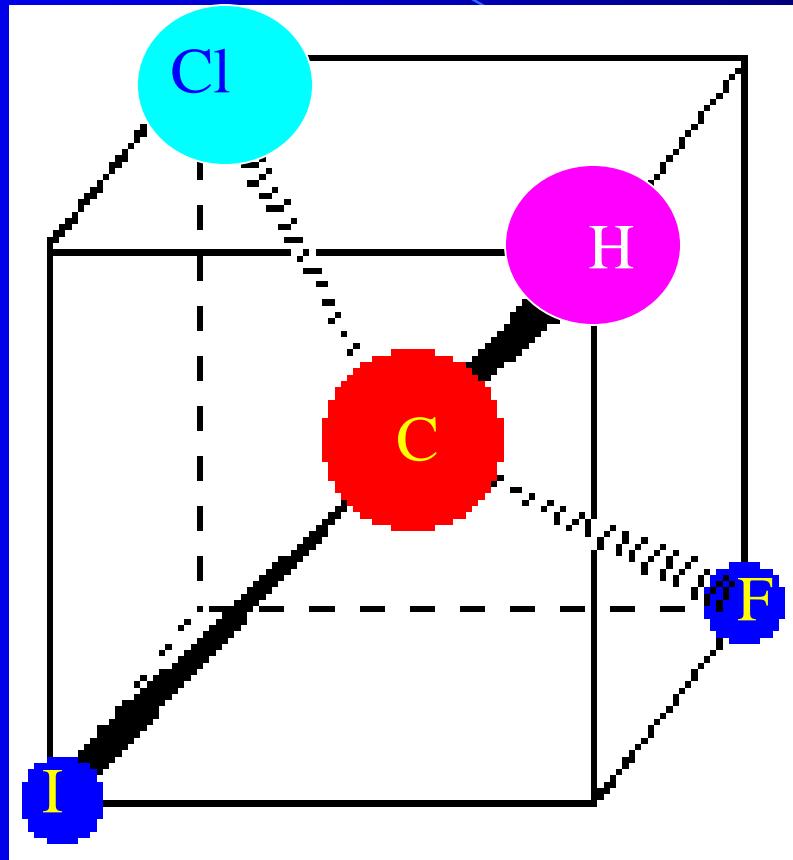




**Internally compensated compounds
meso compounds**





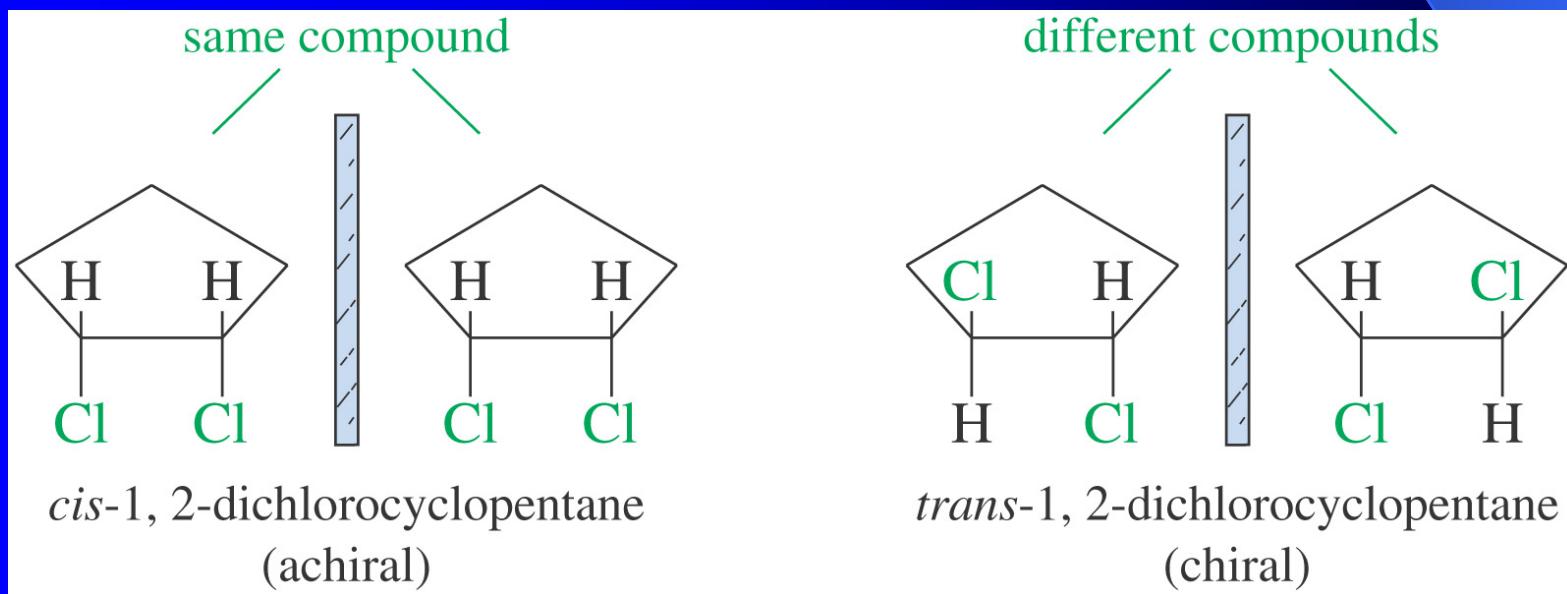


Chirality in Molecules

The *cis* isomer is achiral.

The *trans* isomer is chiral.

Enantiomers: nonsuperimposable mirror images, different molecules.



Concept development from generalized formulas

A hand, however, has no plane of symmetry.

One “half” of a hand is not a mirror image of the other “half”.

Chirality is the property of the entire molecule, whereas a stereocenter (also called as chiral center or stereogenic center) is a structural feature within the molecule that gives rise to the chirality.

Fischer's Projections

How do we represent a three dimensional molecule on to a two dimensional plane i.e. blackboard or paper?

By, Wedge-and-dash drawing or
by Fischer's projection formula

We will concentrate in our discussions on molecular representation by Fischer's formula mainly.

Fischer's Projections

How is Fischer's formula drawn?

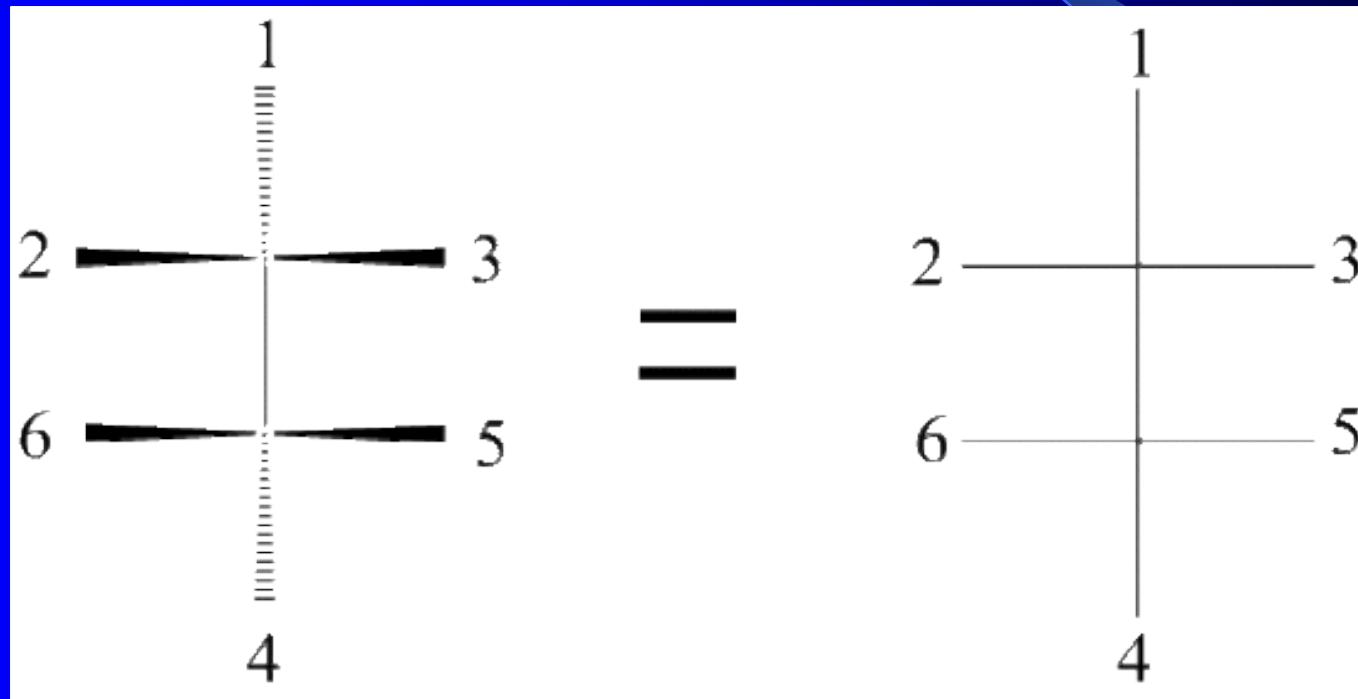
We draw two lines (one vertical and one/(two or more) horizontal line(s)) depending upon the number of stereocenter/(s) in the molecule.

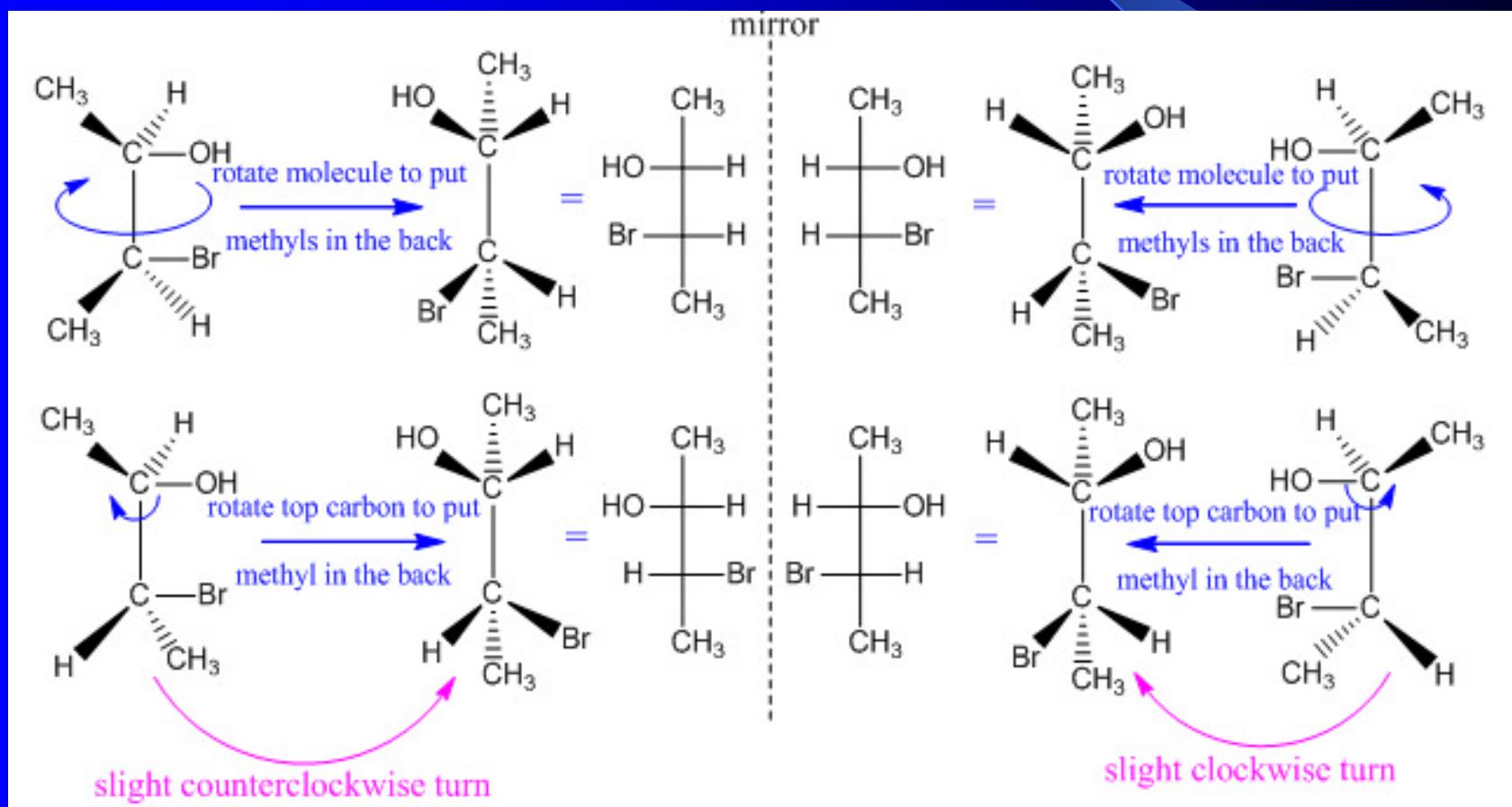
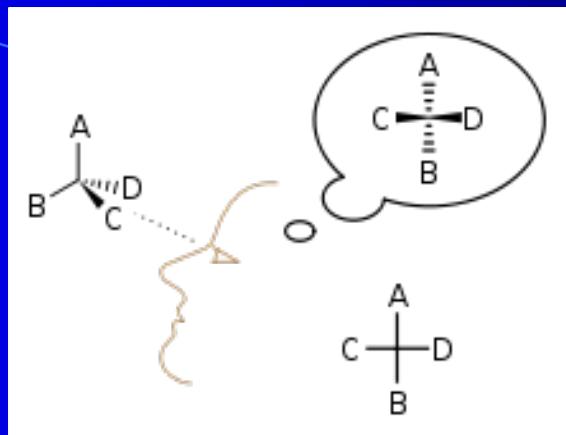
The point of intersection of these lines is considered as representing the stereocenter.

This formula can be drawn only for molecules with stereocenter.

Fischer's Projections

How is Fischer's formula drawn?





Newman



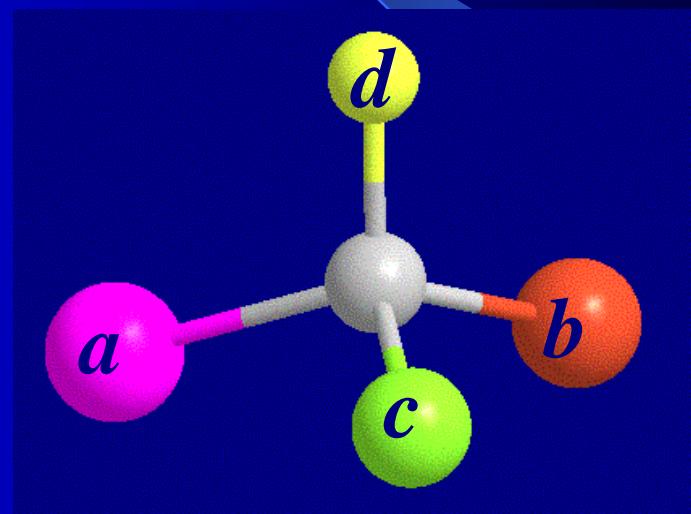
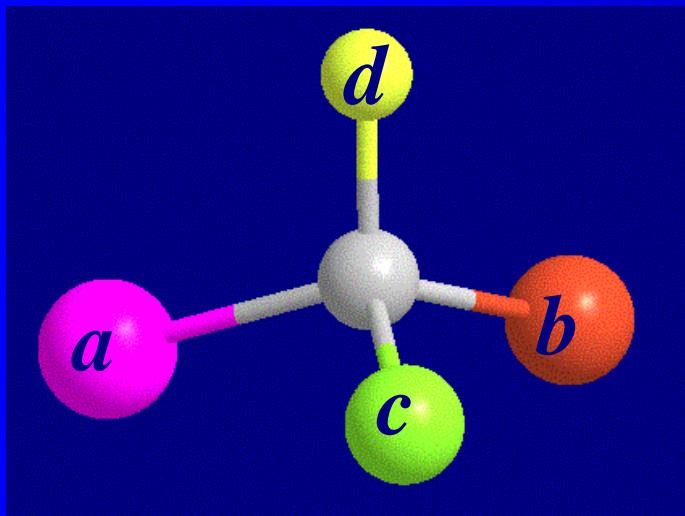
Sawhorse



Stereoisomerism: Resulting from *single center of chirality*

Stereochemical designation: (CIP nomenclature)

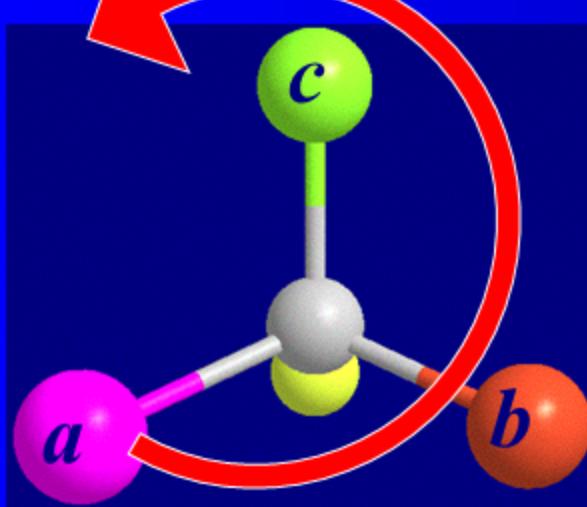
❖ *Priority order = a>b>c>d*



❖ Chiral center is viewed with a,b,c pointing towards the observer and d pointing away

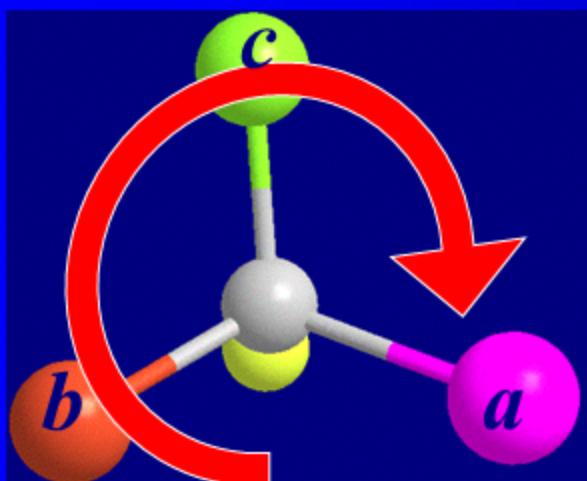
Stereoisomerism: Resulting from *single center of chirality*

Stereochemical designation: (CIP nomenclature)



When the path *a* to *b* to *c* gives a counterclockwise course: S

S = *sinister (Latin) or left*



When the path *a* to *b* to *c* gives a clockwise course:

R = *rectus (Latin) or right*

Stereoisomerism: Resulting from *single* center of chirality

Stereochemical designation: CIP nomenclature)

- ❖ How to assign? Apply sub-rules
- ❖ 1st Sequence rule: atoms are arranged in an order of preference that decreases with decreasing atomic number

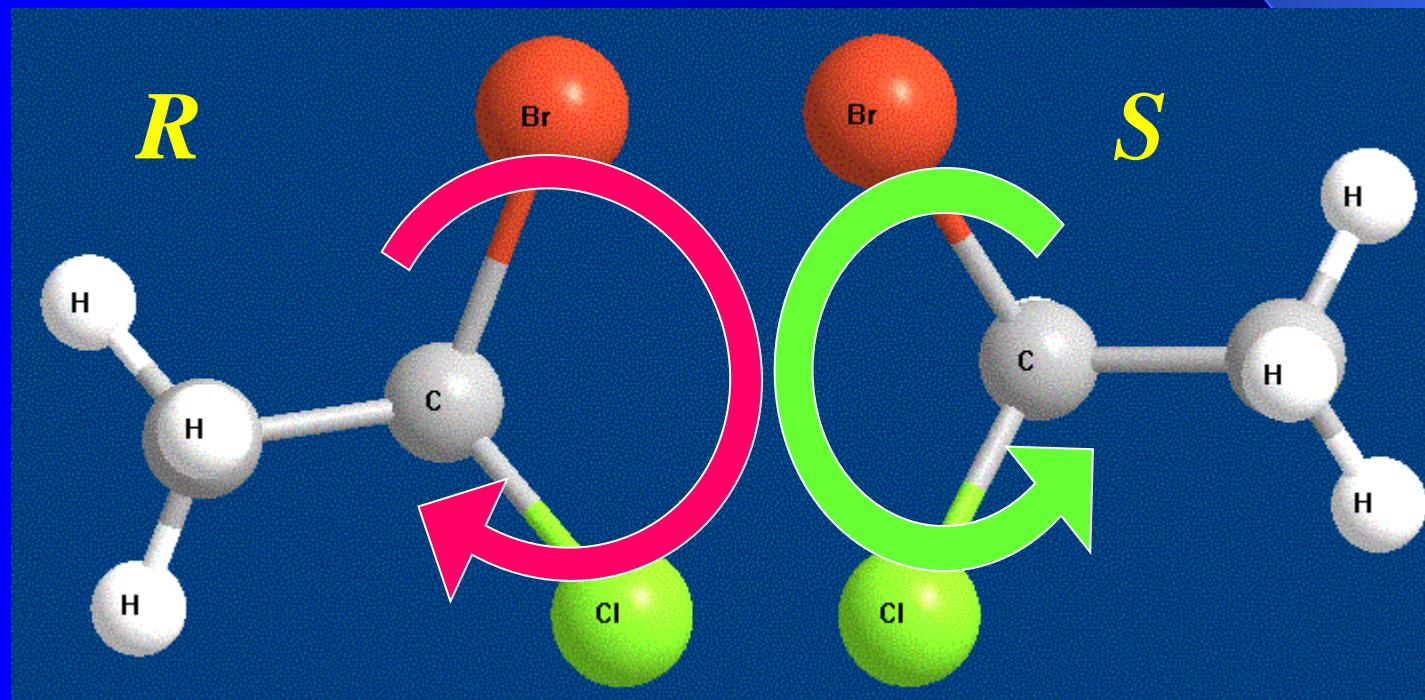
Representative atoms:

I>Br>Cl>S>P>F>O>N>C>H; free electron pair is considered as phantom atom with at. No. as 0

Stereoisomerism: Resulting from *single center of chirality*

Stereochemical designation: CIP nomenclature)

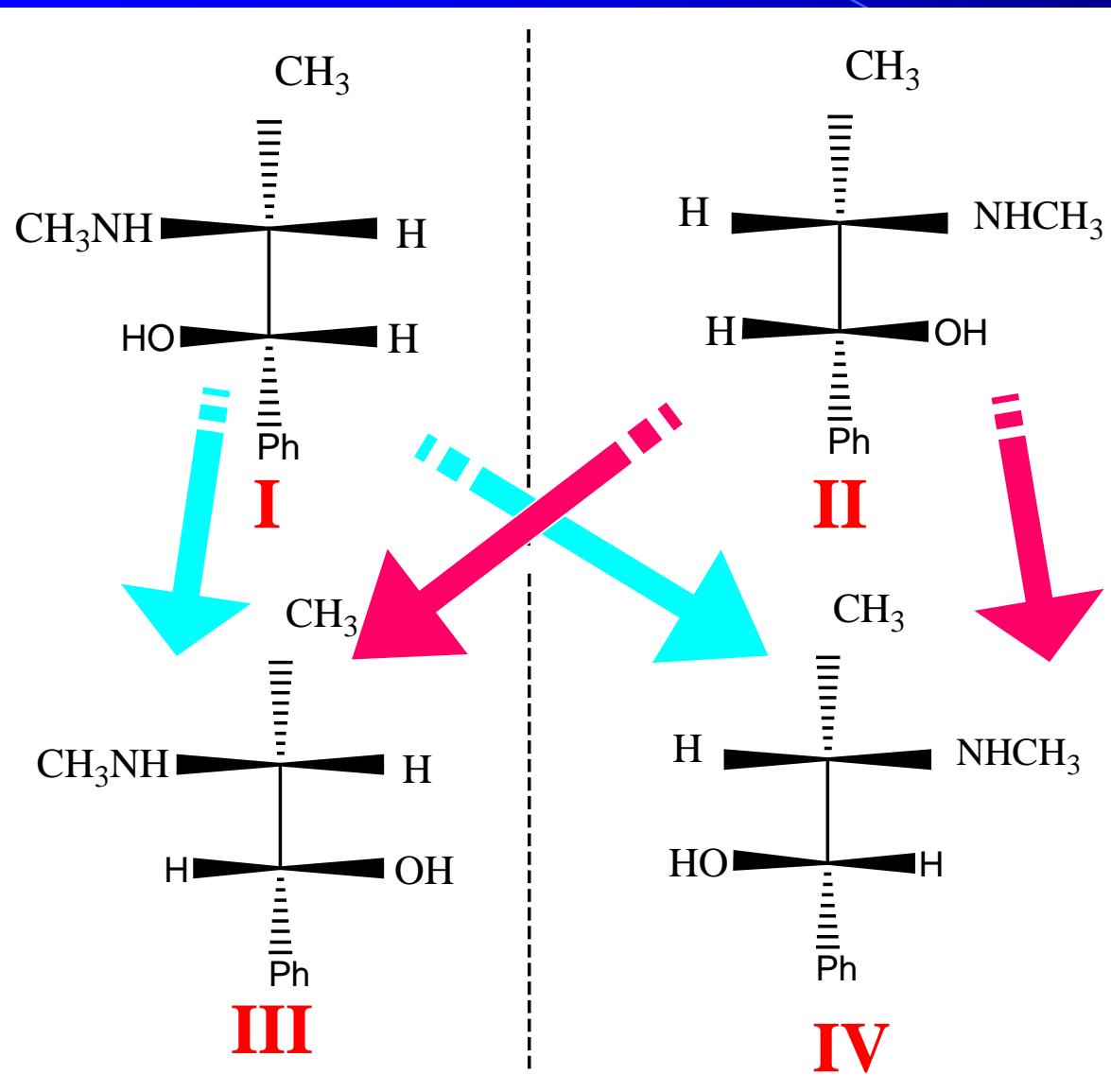
- ❖ Use of 1st Sequence rule: 1-bromo-1-chloro-ethane
- ❖ Br>Cl>C>H



Stereoisomerism: Resulting from **multiple** center of chirality

- ❖ Acyclic molecules with n **nonidentical** centers of chirality gives 2^n stereoisomers which are enantiomeric *in pairs*
- ❖ Applies to only molecules with **nonidentical** centers of chirality (so called constitutionally **unsymmetric** molecules)
- ❖ Constitutionally symmetric molecules have fewer than 2^n stereoisomers

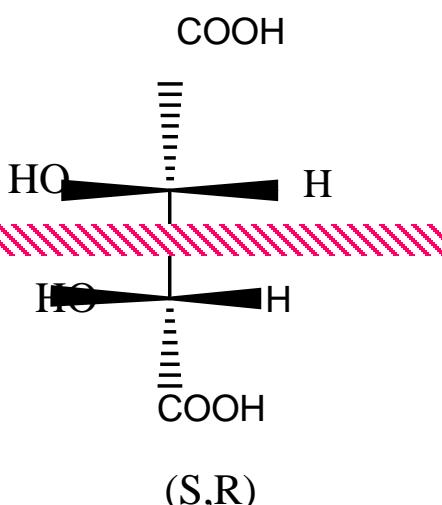
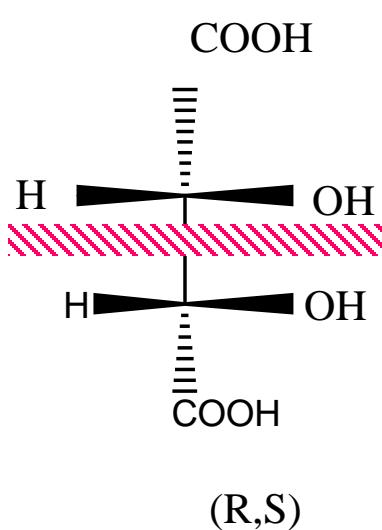
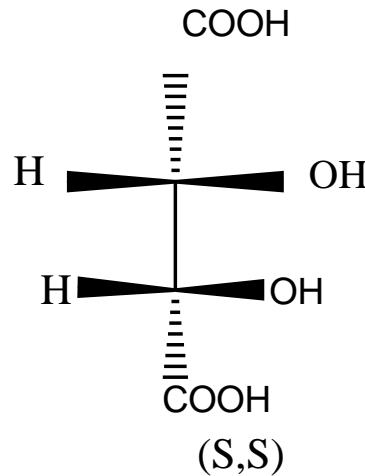
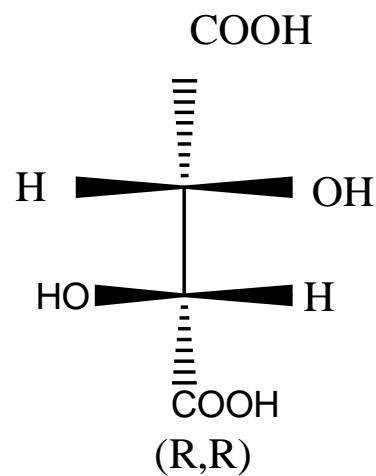
Stereoisomerism: Resulting from two non-identical center of chirality



What are the stereochemical relations between any molecule of upper pair and that of lower pair?

Diastereomeric

Stereoisomerism: Resulting from two identical centers of chirality

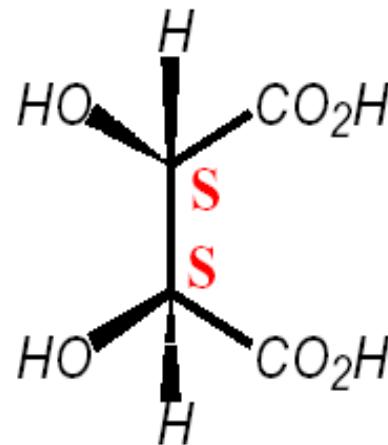


The dextrorotatory form is (R,R), levorotatory form is (S,S)

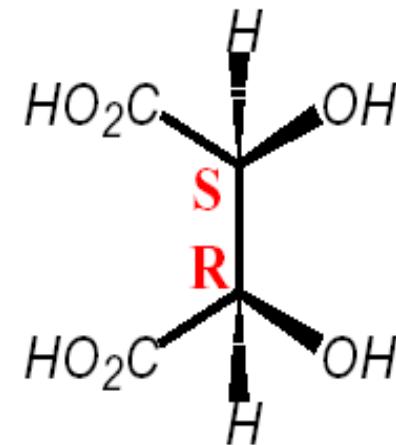
Symmetry plane bisecting the molecule () forbids the chirality

-meso form

Diastereomers: have different chemical and physical properties in any type of environment.



(S,S)-Tartaric Acid



Mesotartaric Acid

[α] _D	- 12.7	0 (achiral)
Melting p. (°C)	171-174	146-148
Density (g/cm ³)	1.7598	1.660
Solubility in H ₂ O	139	125

Optical activity, plane polarized light

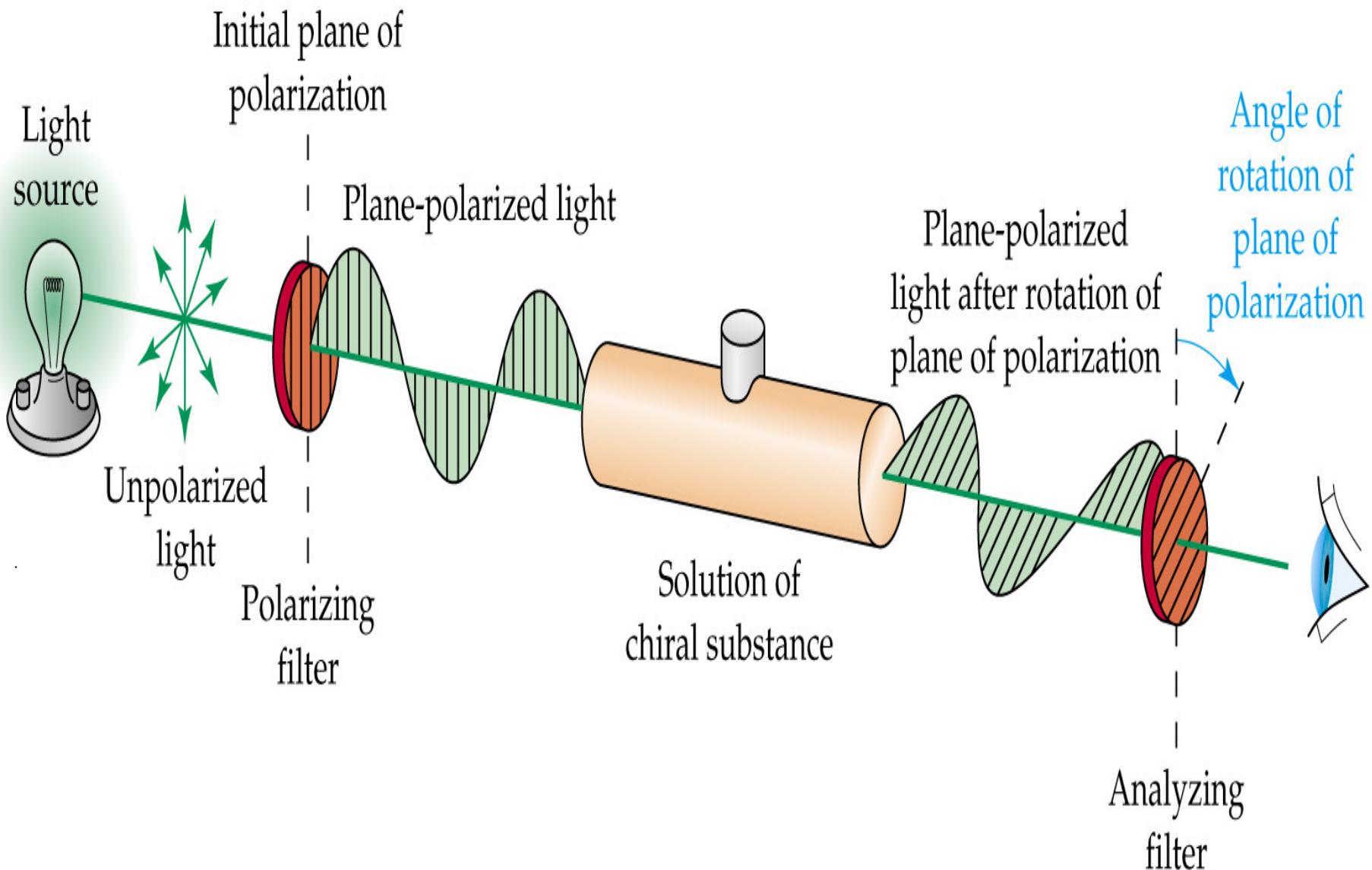
Crime story:

Muscarine from mushroom Amanita Muscaria is a poison

Light possesses certain properties that are best understood by considering it to be a wave phenomenon in which the vibrations occur at right angles to the direction in which the light travels.

There are infinite number of planes passing through the line of propagation, and ordinary light is vibrating in all these planes.

Optical activity, plane polarized light

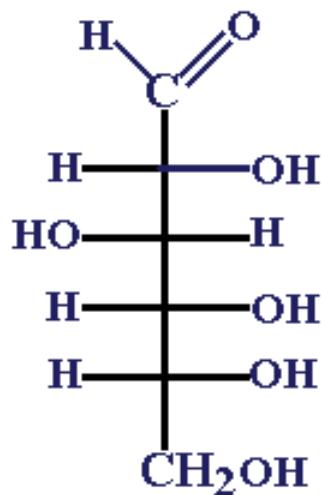
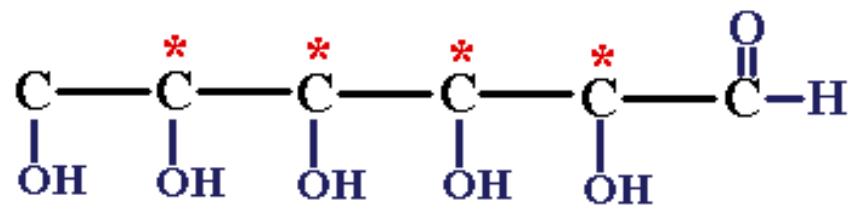


Optical activity, plane polarized light

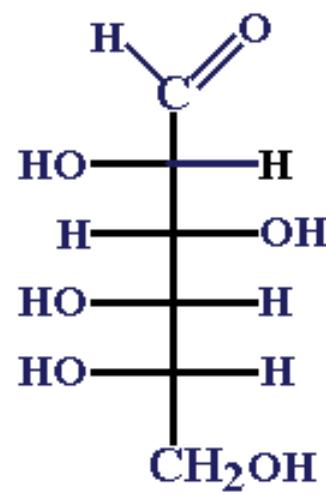
Plane polarized light is light whose vibrations take place in only one of these possible planes.

Ordinary light is turned into plane polarized light by passing it through a prism made up of the material known as Polaroid or more traditionally through pieces of calcite (a crystalline form of CaCO_3) so arranged as to constitute Nicol prism.

An optically active substance is one that rotates the plane of polarized light.



D-Glucose



L-Glucose

Optical activity, plane polarized light

If the rotation of the plane is in clockwise direction the substance is said to be dextrorotatory and if it is counterclockwise then substance is said to be laevorotatory.

The optical activity of a compound is determined by an instrument called Polarimeter.

Racemic forms

An equimolar mixture of two enantiomers is called a racemic form (either a racemate or a racemic mixture).

It does not show any rotation of plane polarized light.

It is designated as (\pm).

Racemic forms and enantiomeric excess

A sample of an optically active substance that consists of a single enantiomer is said to be enantiomerically pure.

Racemic forms

Enantiomeric excess (ee) is defined as :

(Moles of one enantiomer - Moles of other enantiomer) × 100

$$\% \text{ ee} = \frac{\text{(Moles of one enantiomer - Moles of other enantiomer) } \times 100}{\text{Total moles of both enantiomers}}$$

Can be calculated from optical rotations as:

$$\% \text{ ee} = \frac{\text{(Observed specific rotation) } \times 100}{\text{specific rotation of the pure enantiomer}}$$

Racemic forms

If observed specific rotation of an enantiomeric solution is $+6.76^{\circ}$ and specific rotation of the pure enantiomeric solution is $+13.52^{\circ}$ then

$$\% \text{ ee} = \frac{+6.76^{\circ} \times 100}{+13.52^{\circ}} = 50 \text{ \%}$$

What does this 50% mean?

It means, 50% of the mixture consists of the (+) enantiomer (the excess) and the other 50% consists of the racemic form.

Consider that (S)-2-bromobutane has a specific rotation of +23.1°

(R)-2-bromobutane has a specific rotation of -23.1°. What is the optical purity of a mixture, of (R)- and (S)-2-bromobutane, whose specific rotation was found to be -9.2°? Which isomer is dominant ?

The negative sign tells indicates that the R enantiomer is the dominant one.

$$\begin{aligned}\text{Optical purity, \%} &= \\ 100 \times [\alpha]_{\text{mixture}} / [\alpha]_{\text{pure sample}} &= 100 (-9.2) / -23.1^\circ \\ &= 40\% \text{ } this \text{ } indicates \text{ } a \text{ } 40\% \text{ } excess \text{ } of \text{ } R \\ &\text{over S!}\end{aligned}$$

Resolution of enantiomers

- A racemic acid can be treated with an optically active base and converted to diastereomers.
- Diastereomers can be separated by crystallisation, distillation etc.
- Treat the individual diastereomers with a mild acid and get the separated enantiomers (+) and (-)

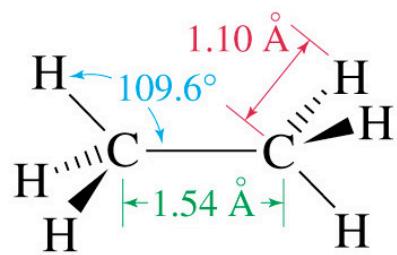
Conformational Analysis

Newman Projections

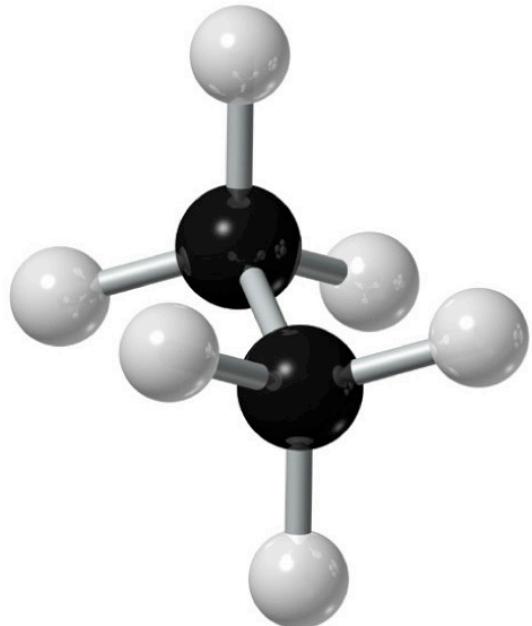
Ring Strain

Cyclohexane Conformations

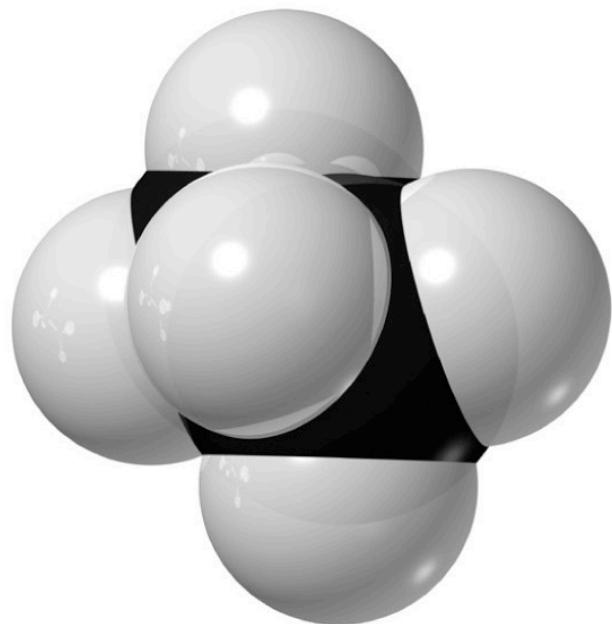
Views of Ethane



ethane

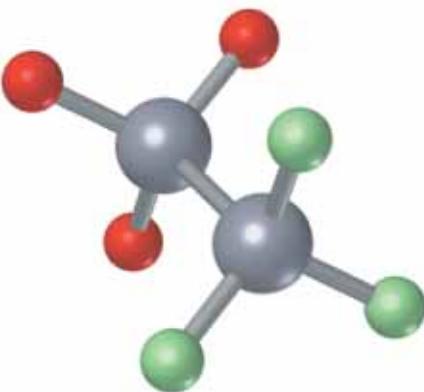


ethane

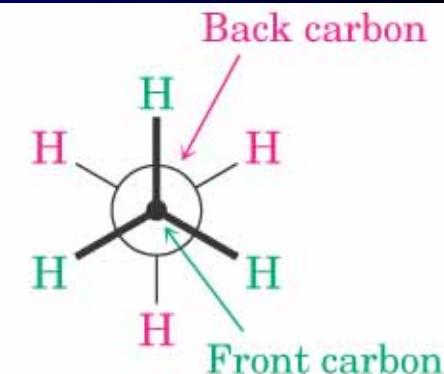
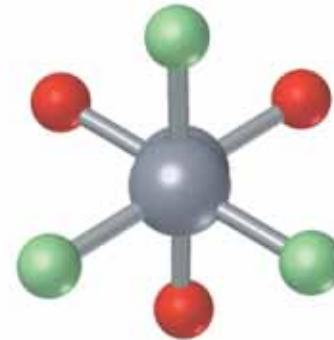
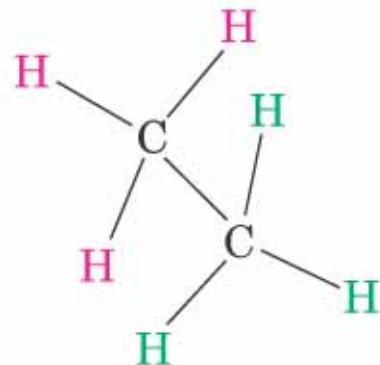


ethane

The Newman Projection



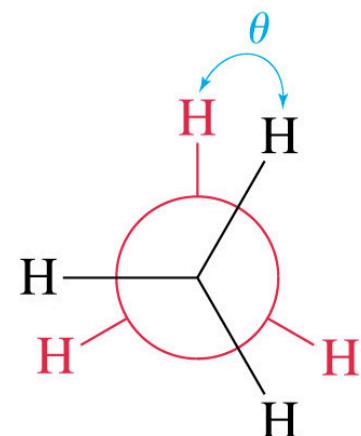
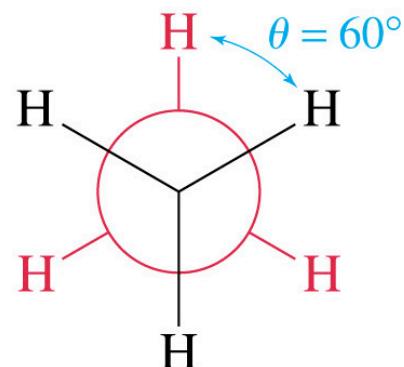
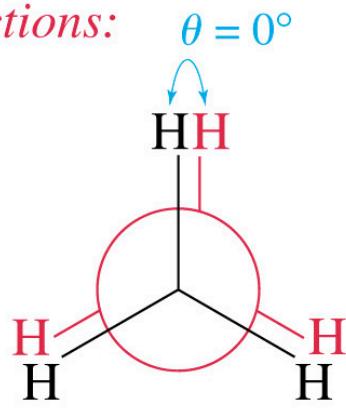
Sawhorse
representation



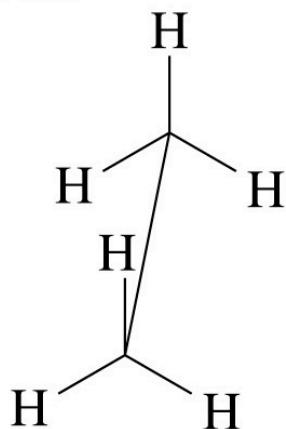
Newman
projection

Rotational Conformations of Ethane

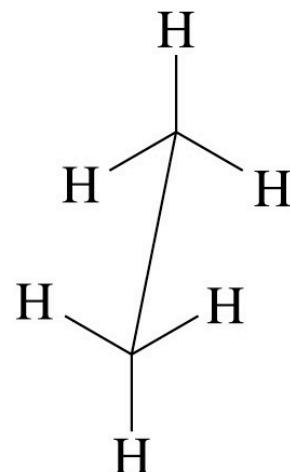
Newman projections:



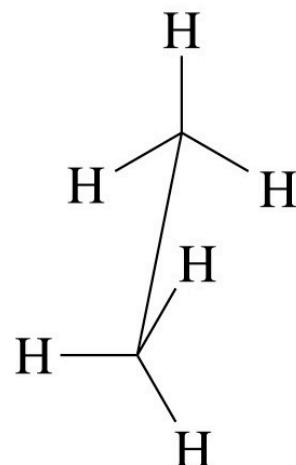
Sawhorse structures:



eclipsed, $\theta = 0^\circ$



staggered, $\theta = 60^\circ$

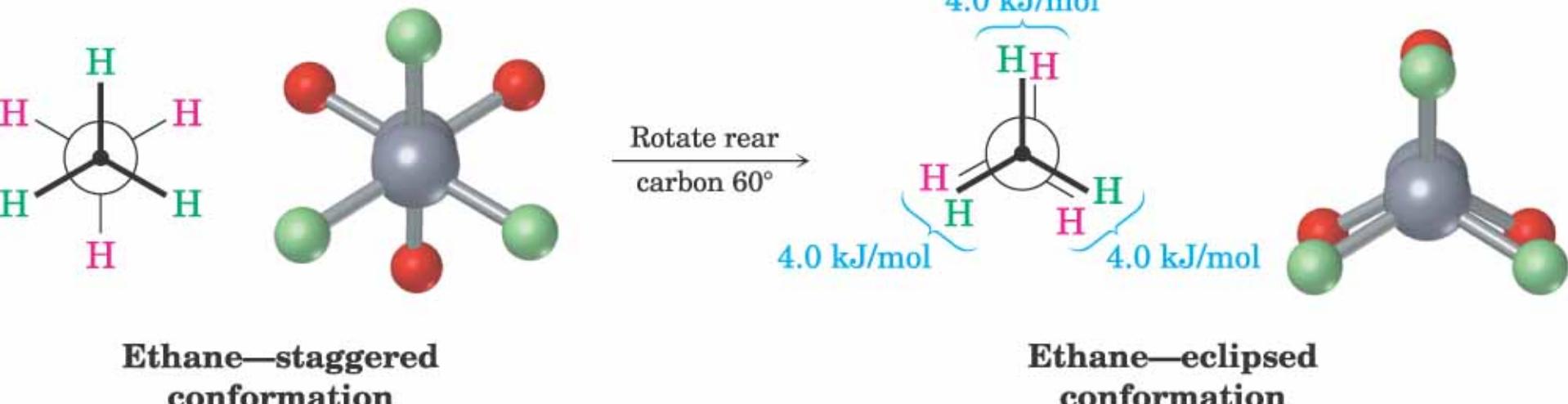


skew, $\theta = \text{anything else}$

Definitions

- **Conformations** - Different spatial arrangements that a molecule can adopt due to rotation about sigma bonds.
- **Staggered** - A low energy conformation where the bonds on adjacent atoms bisect each other (60° dihedral angle), maximizing the separation.
- **Eclipsed** - A high energy conformation where the bonds on adjacent atoms are aligned with each other (0° dihedral angle).

60° Rotation Causes Torsional or Eclipsing Strain



©2004 Thomson - Brooks/Cole

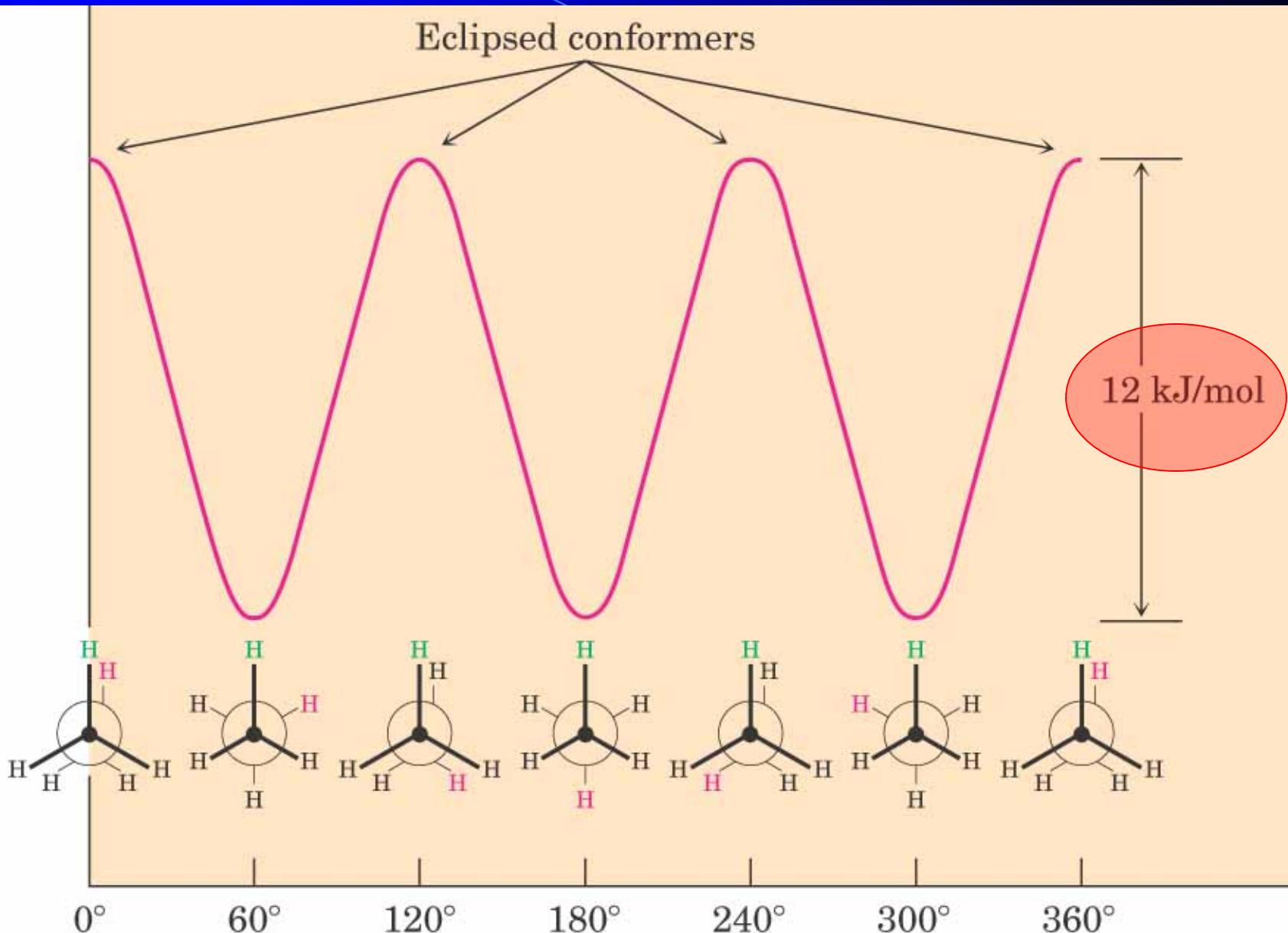
Types of Strain

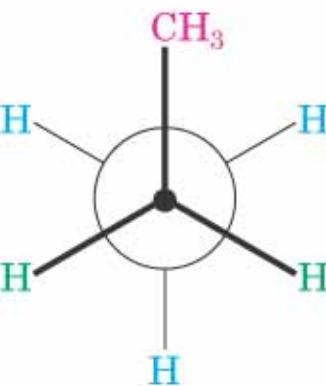
- **Steric** - Destabilization due to the repulsion between the electron clouds of atoms or groups. Groups try to occupy some common space.
- **Torsional** - Destabilization due to the repulsion between pairs of bonds caused by the electrostatic repulsion of the electrons in the bonds. Groups are eclipsed.
- **Angle** - Destabilization due to distortion of a bond angle from it's optimum value caused by the electrostatic repulsion of the electrons in the bonds.
e.g. cyclopropane

Definitions

- **Anti** - Description given to two substituents attached to adjacent atoms when their bonds are at 180° with respect to each other.
- **Syn** - Description given to two substituents attached to adjacent atoms when their bonds are at 0° with respect to each other.
- **Gauche** - Description given to two substituents attached to adjacent atoms when their bonds are at 60° with respect to each other.

Potential energy diagram of Ethane



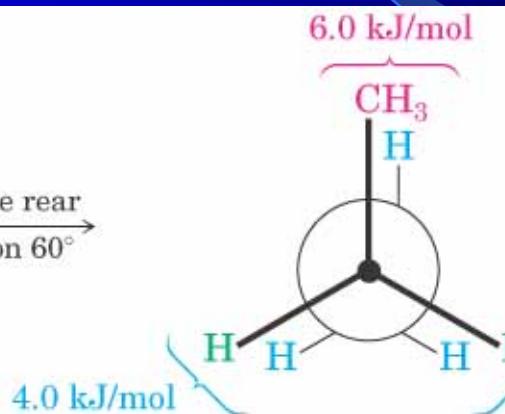


Staggered propane

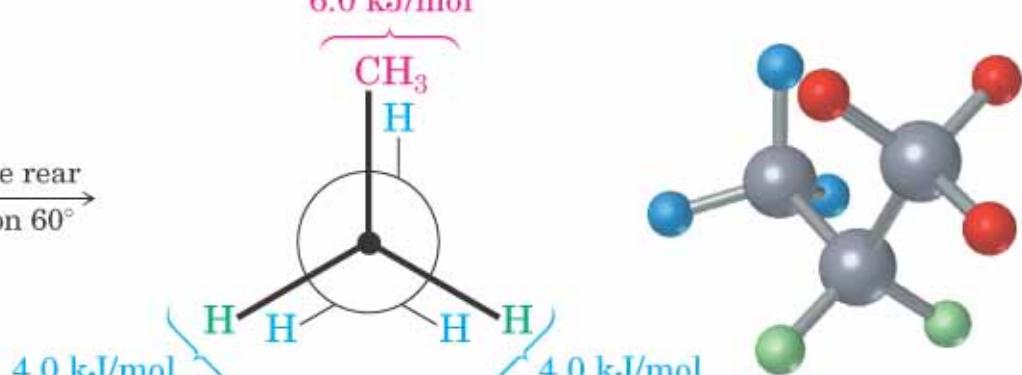
© 2004 Thomson/Brooks Cole



Rotate rear
carbon 60°



Eclipsed propane

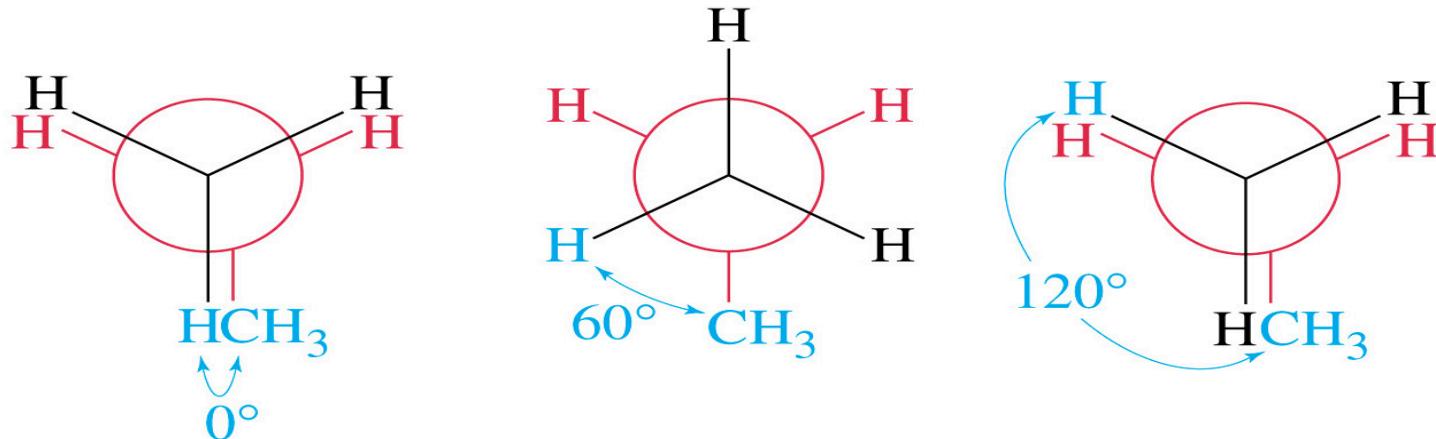
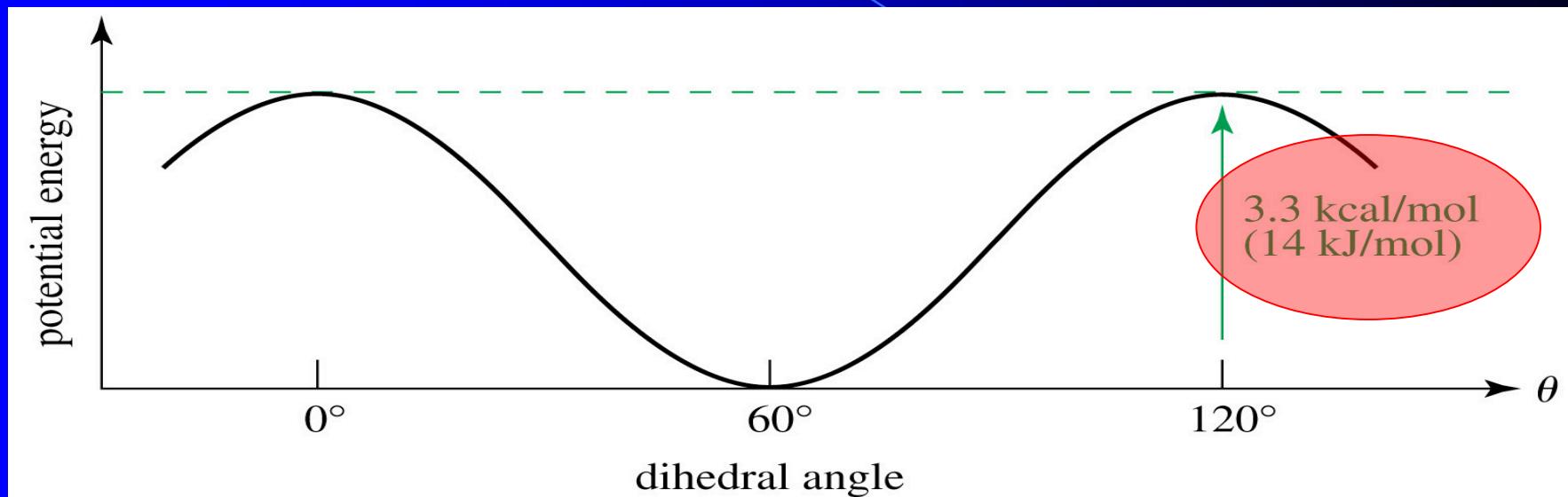


6.0 kJ/mol

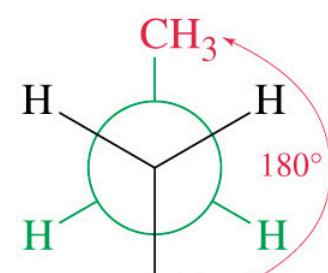
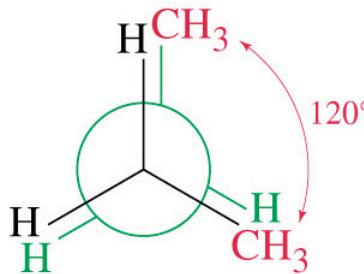
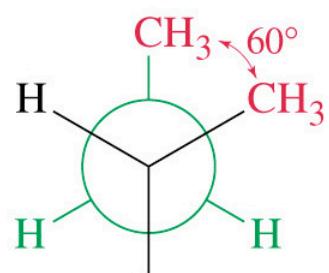
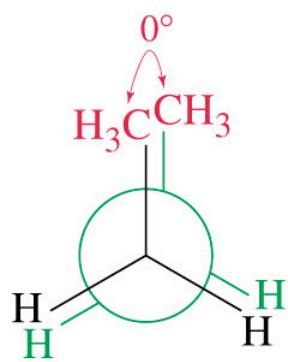
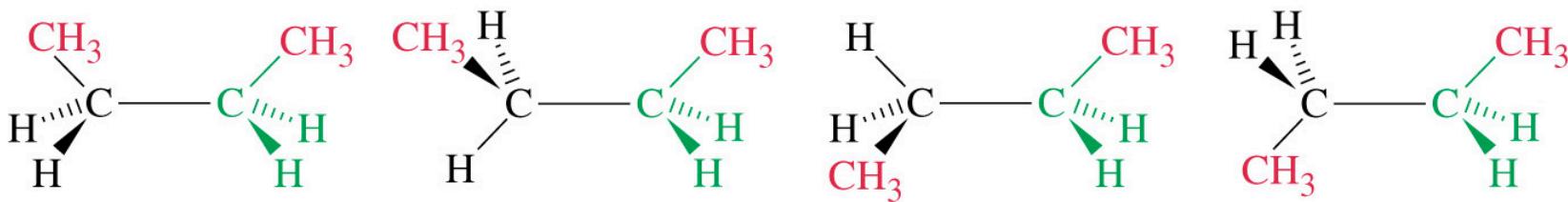
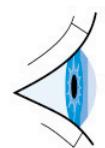
4.0 kJ/mol

4.0 kJ/mol

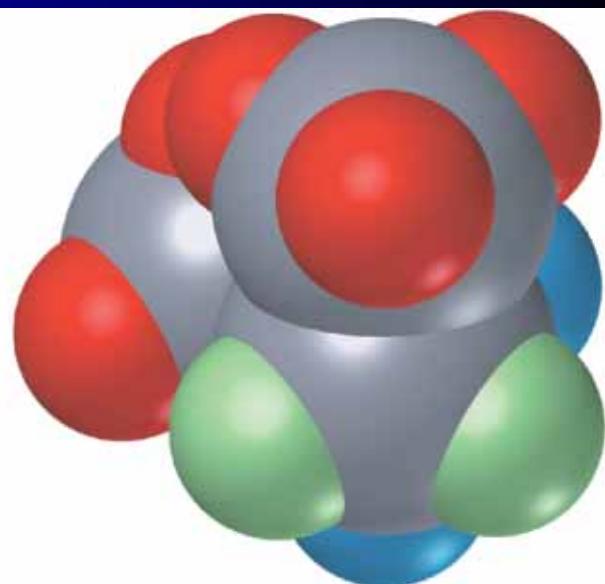
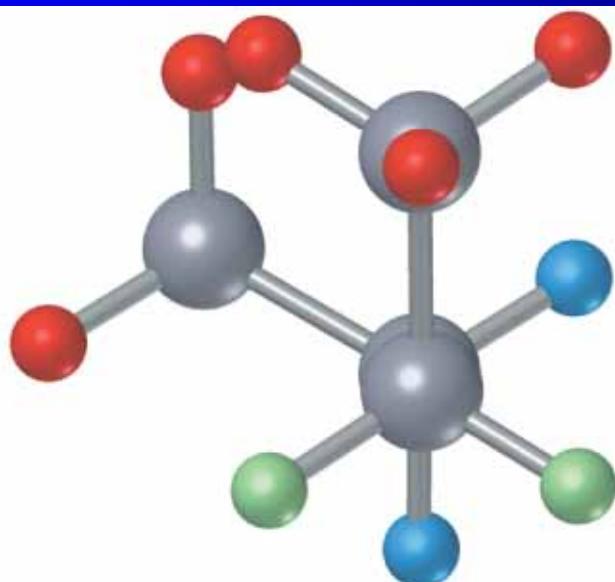
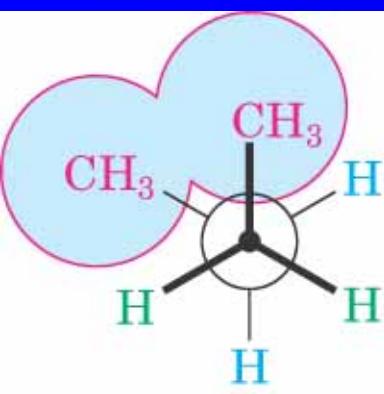
Propane Conformations: Larger Barrier to Rotation



Butane Conformations (C_2 - C_3)

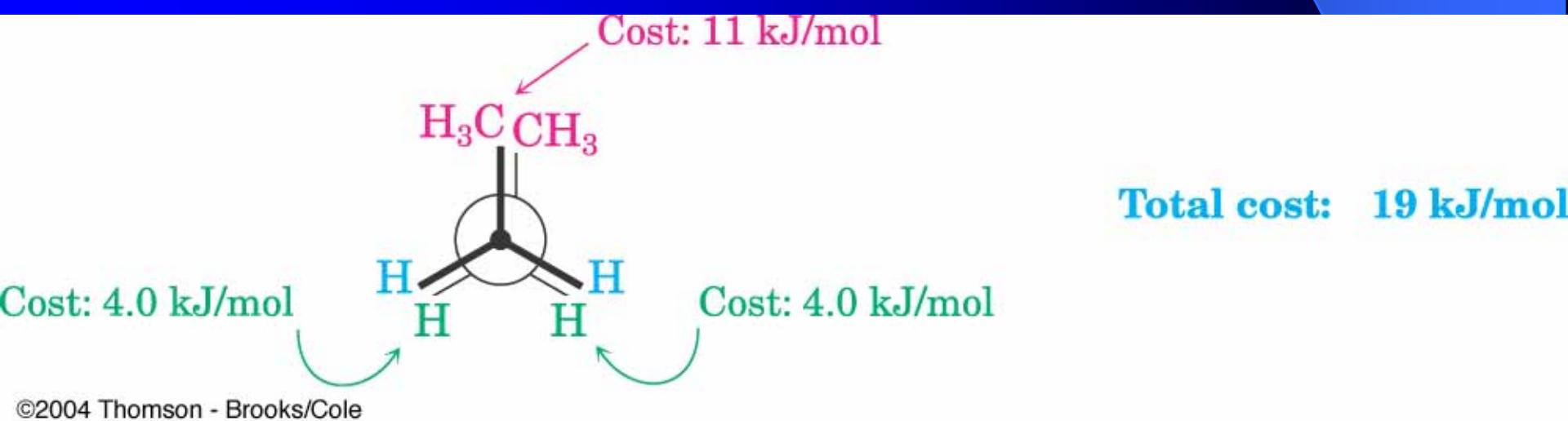


Gauche Interaction in Butane



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2 Different Eclipsed Conformations



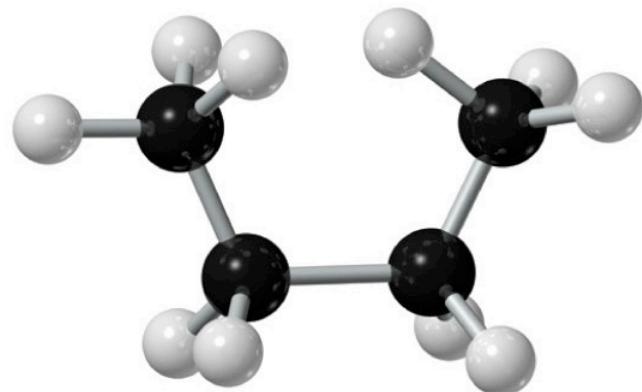
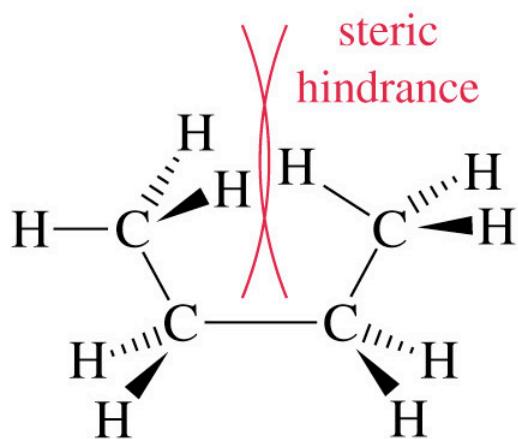
Strain Energy can be Quantified

TABLE 4.1 Energy Costs for Interactions in Alkane Conformers

Interaction	Cause	Energy cost (kJ/mol) (kcal/mol)	
H \leftrightarrow H eclipsed	Torsional strain	4.0	1.0
H \leftrightarrow CH ₃ eclipsed	Mostly torsional strain	6.0	1.4
CH ₃ \leftrightarrow CH ₃ eclipsed	Torsional plus steric strain	11.0	2.6
CH ₃ \leftrightarrow CH ₃ gauche	Steric strain	3.8	0.9

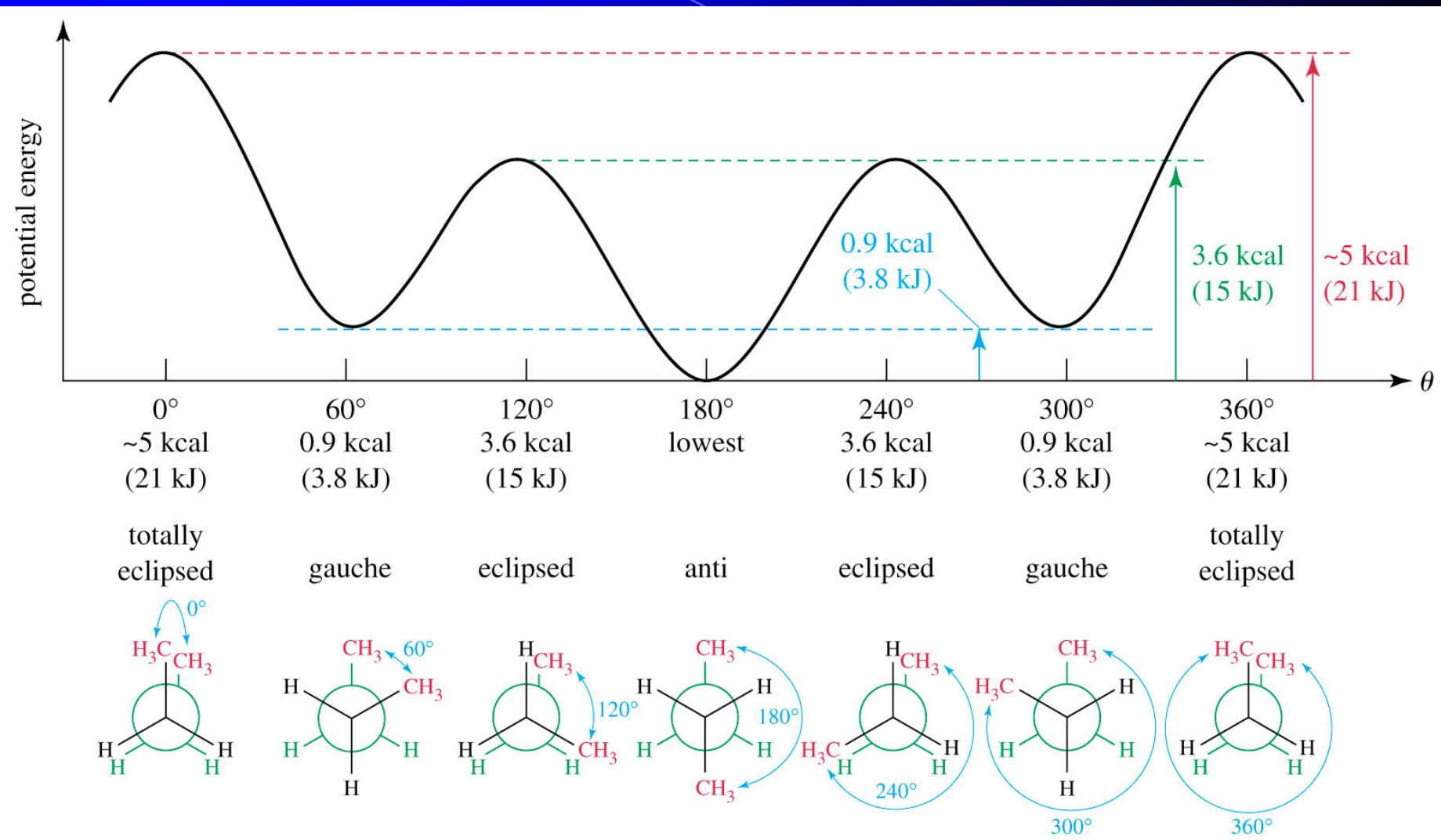
©2004 Thomson - Brooks/Cole

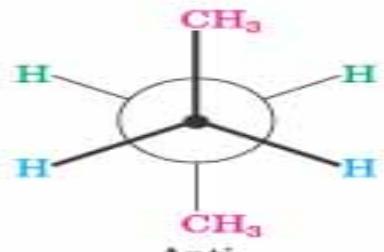
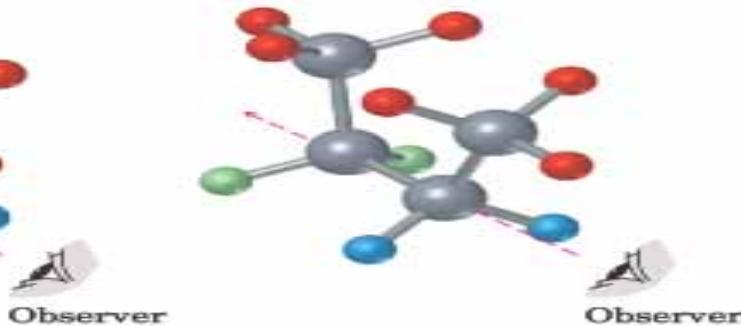
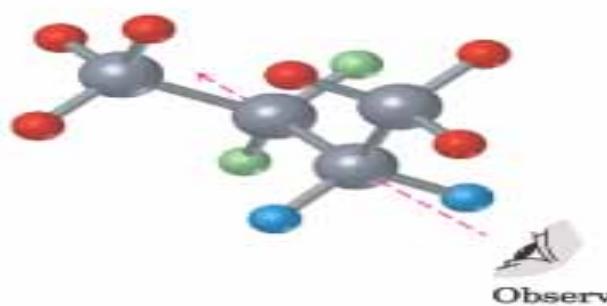
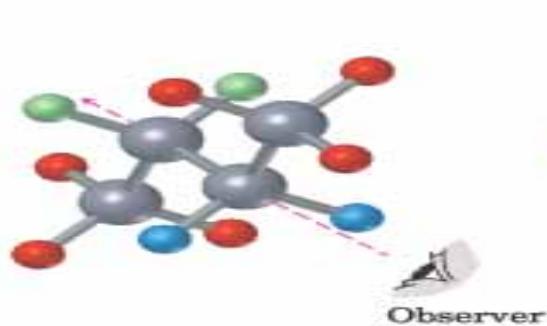
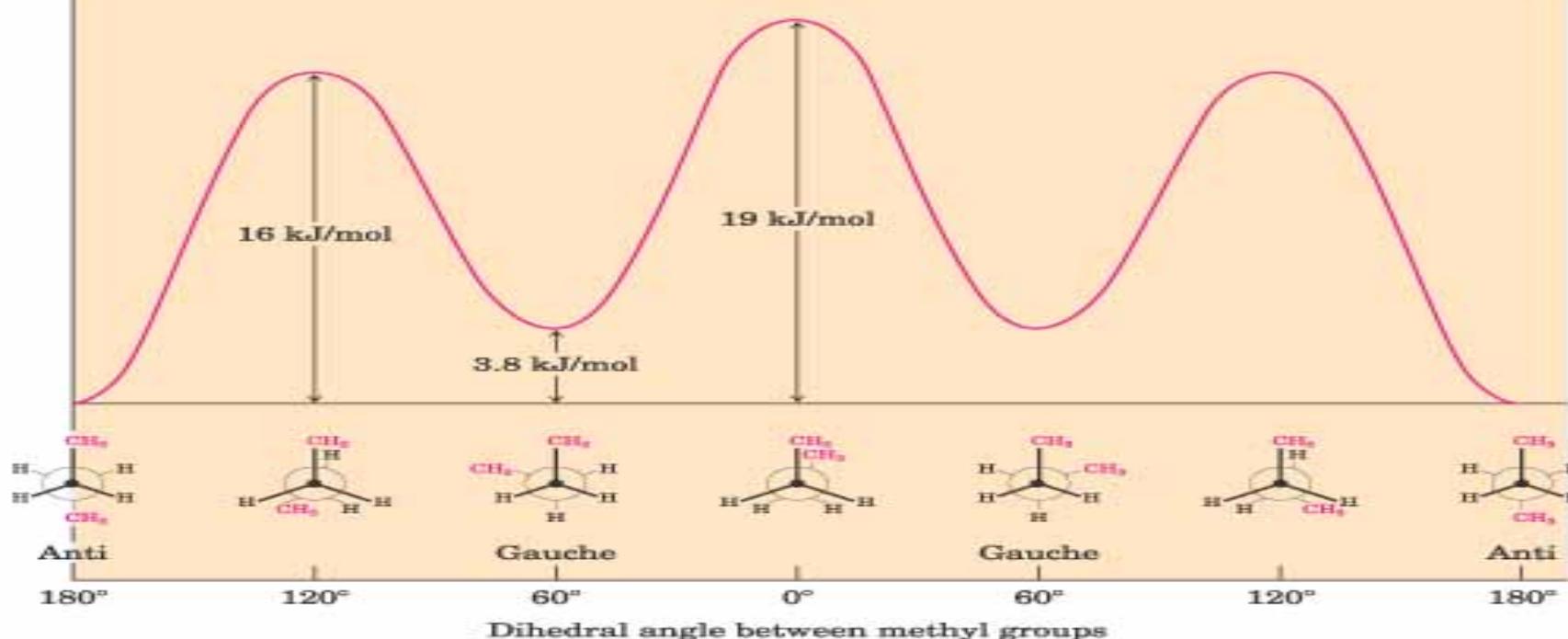
Butane has Steric and Torsional Strain When Eclipsed



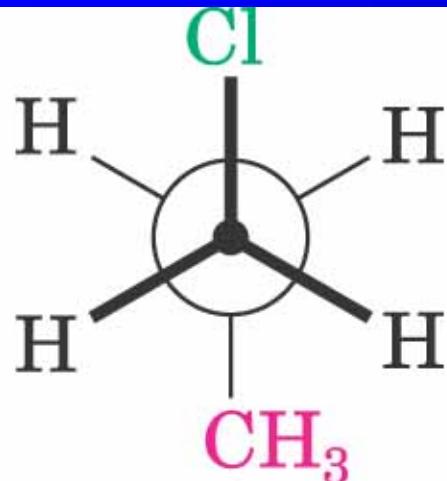
Totally eclipsed conformation of butane

PE Diagram for Butane

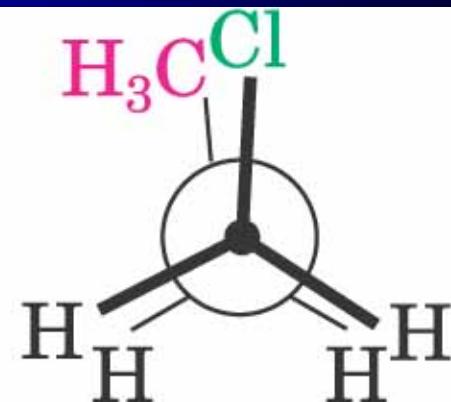




1-Chloropropane

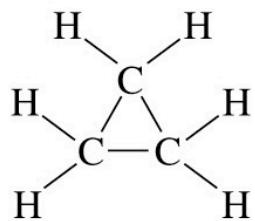


Most stable (staggered)



Least stable (eclipsed)

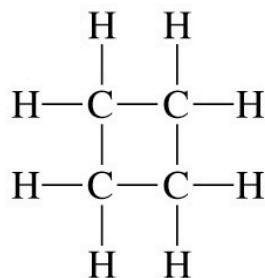
Saturated Cyclic Compounds



or



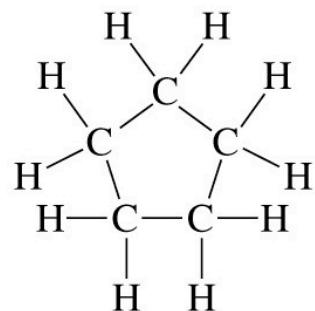
cyclopropane
 C_3H_6



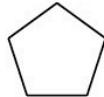
or



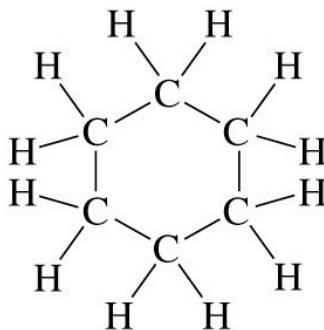
cyclobutane
 C_4H_8



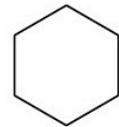
or



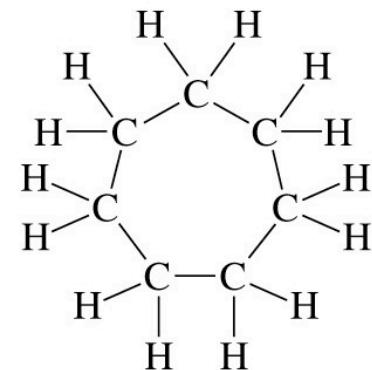
cyclopentane
 C_5H_{10}



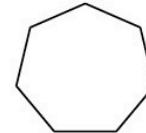
or



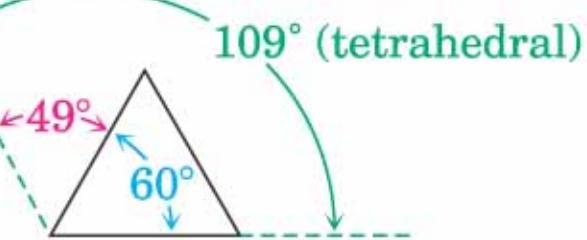
cyclohexane
 C_6H_{12}



or

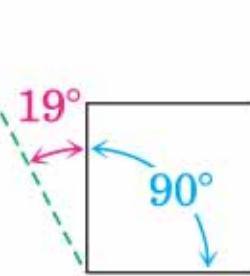


cycloheptane
 C_7H_{14}

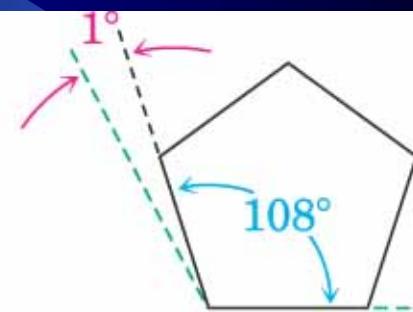


Cyclopropane

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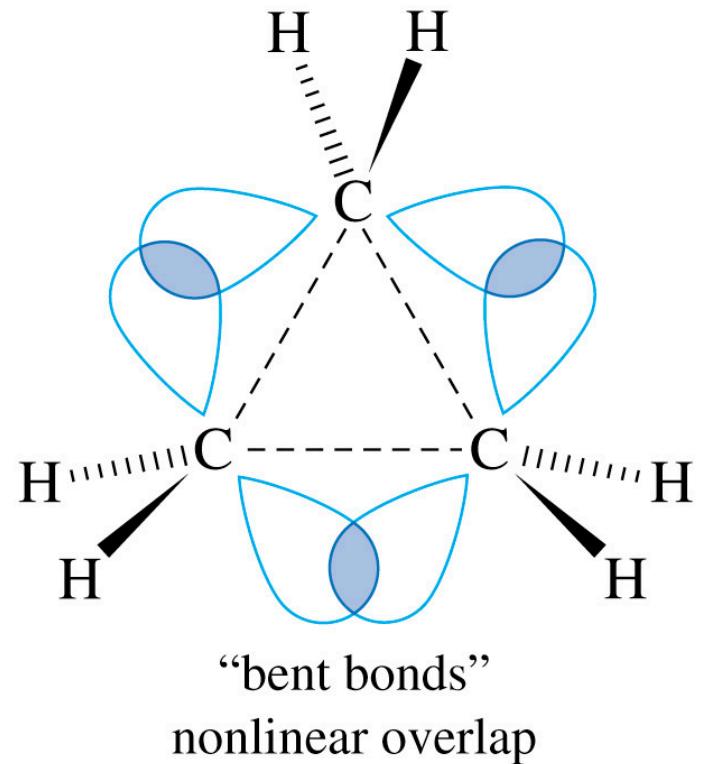
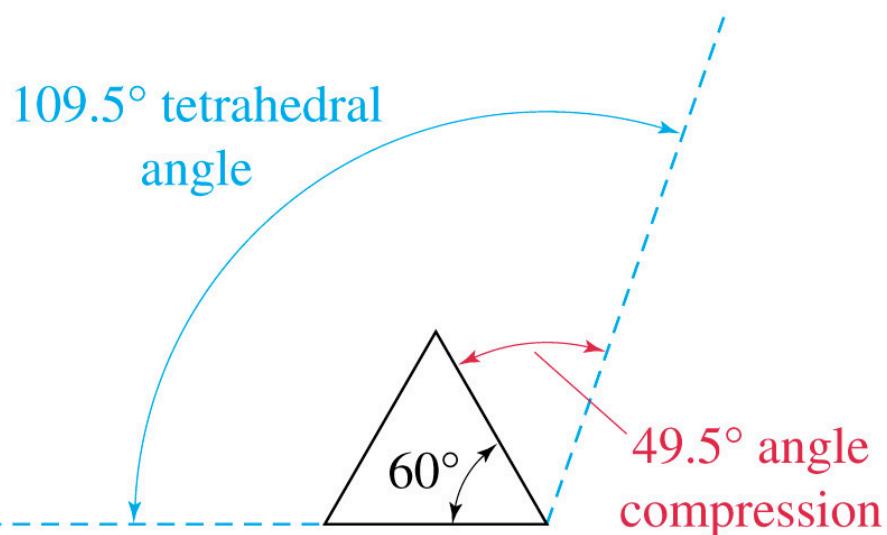
Cyclobutane



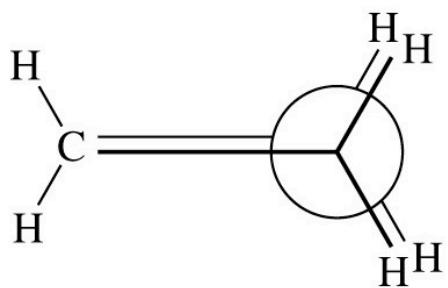
Cyclopentane

Cyclopropane

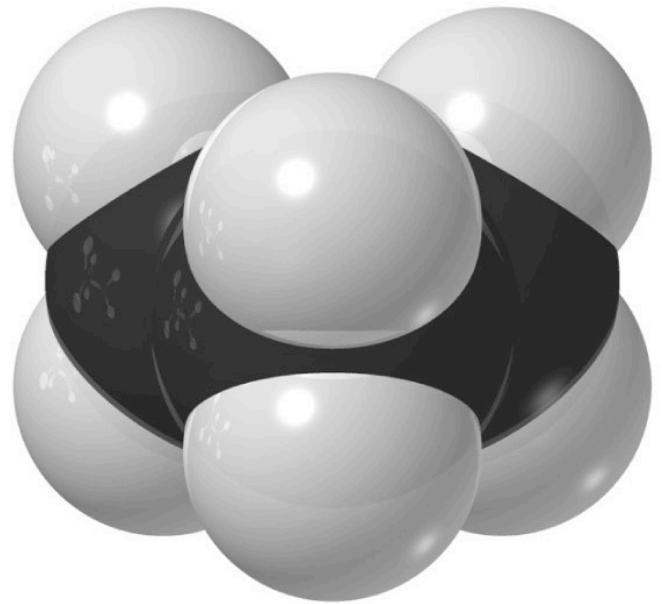
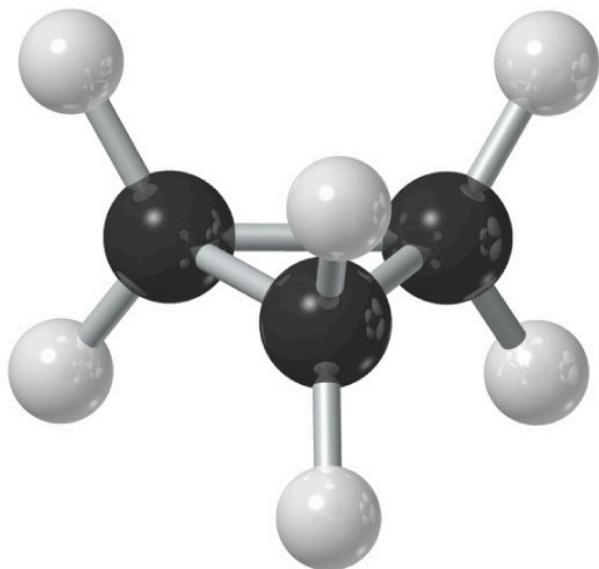
Angle and Torsional Strain



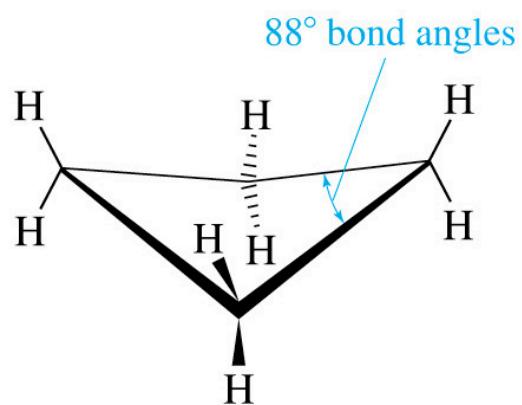
All Dihedral Angles = 0°



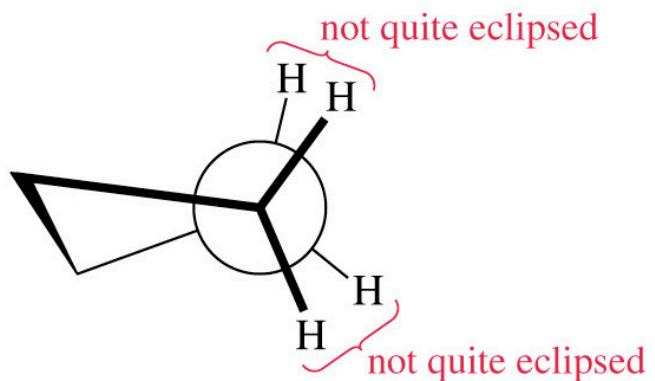
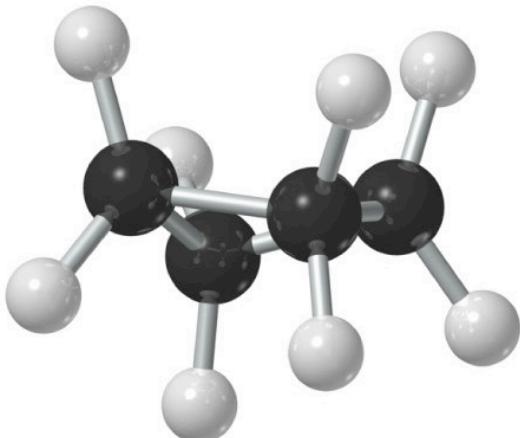
Newman projection
of cyclopropane



Cyclobutane is not Planar

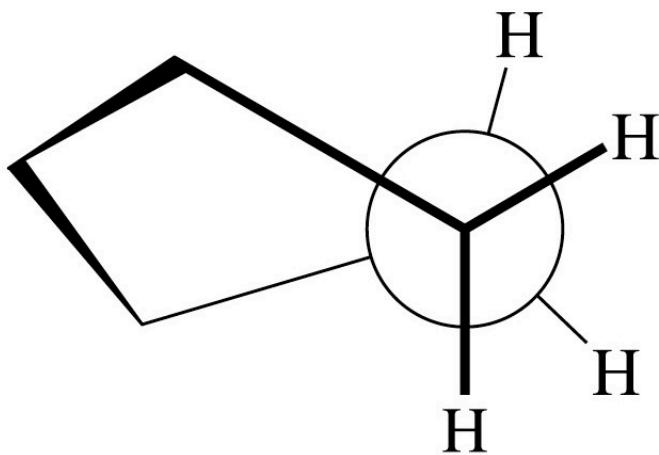
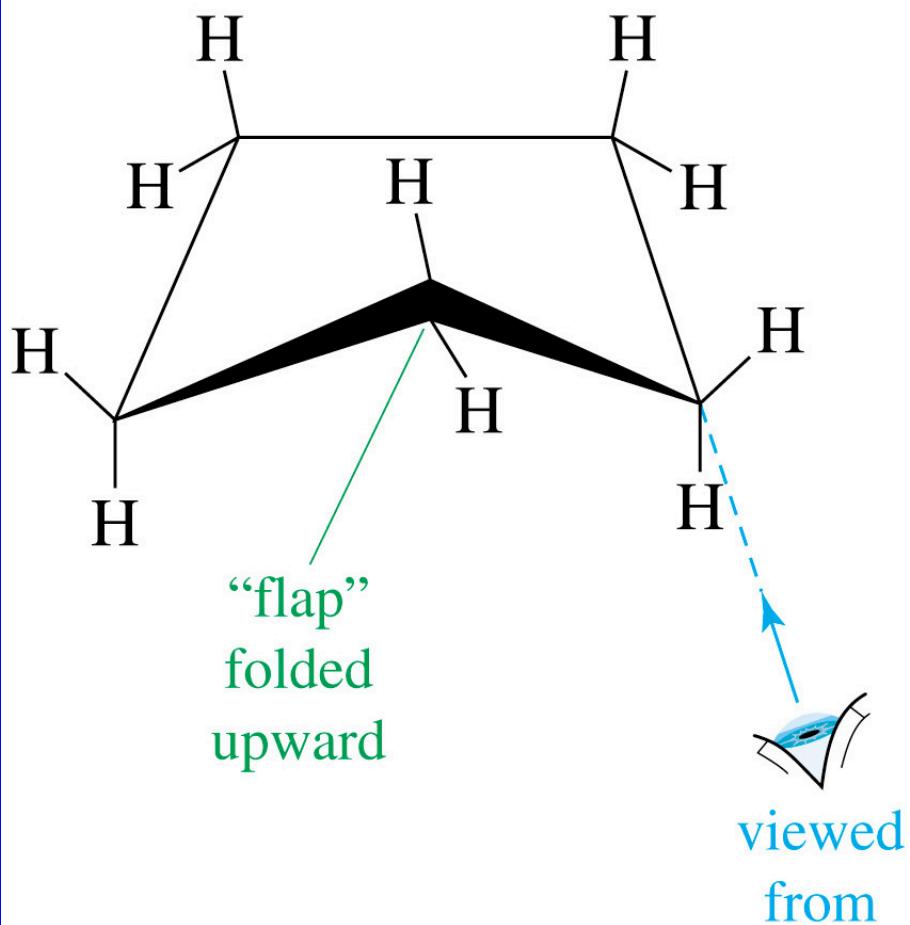


slightly folded conformation



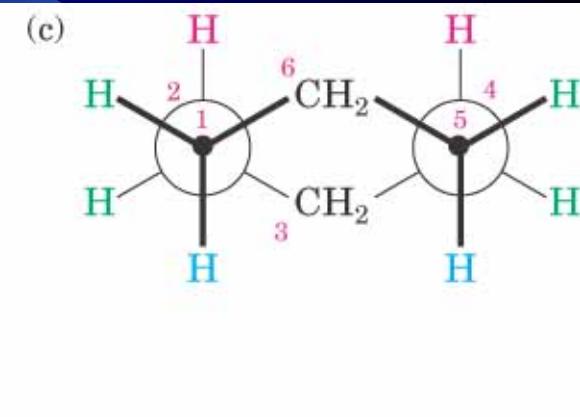
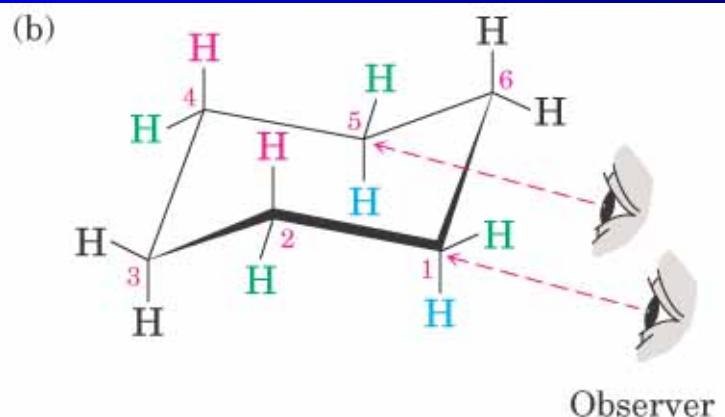
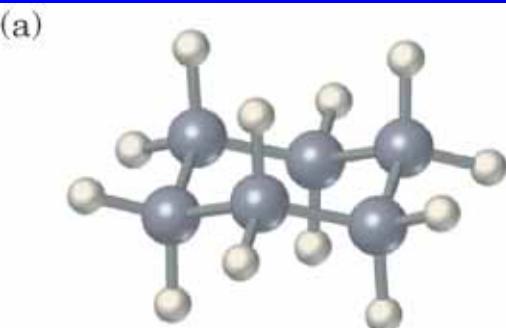
Newman projection of one bond

Cyclopentane

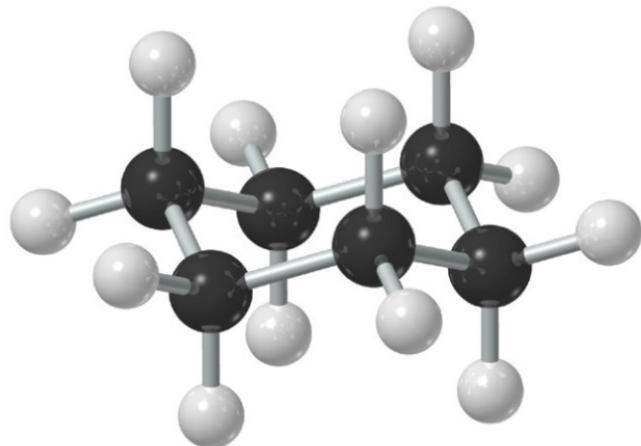


Newman projection
showing relief of
eclipsing of bonds

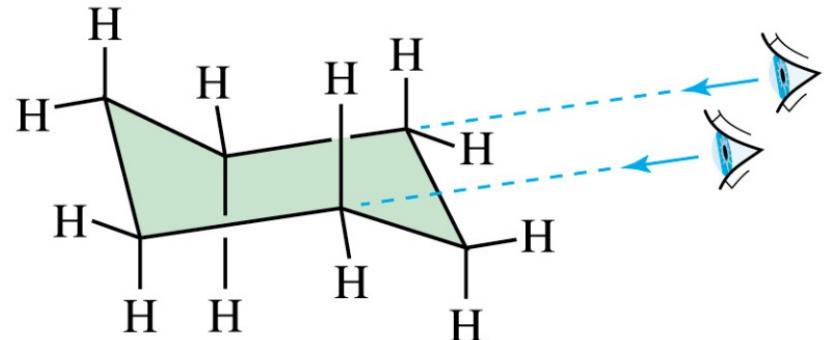
Cyclohexane



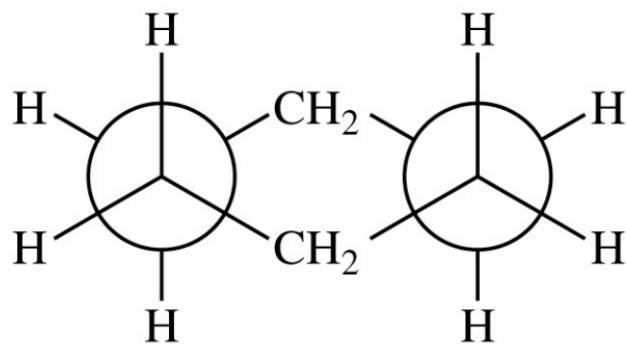
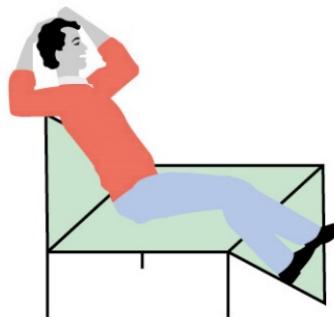
Chair Conformation



chair conformation

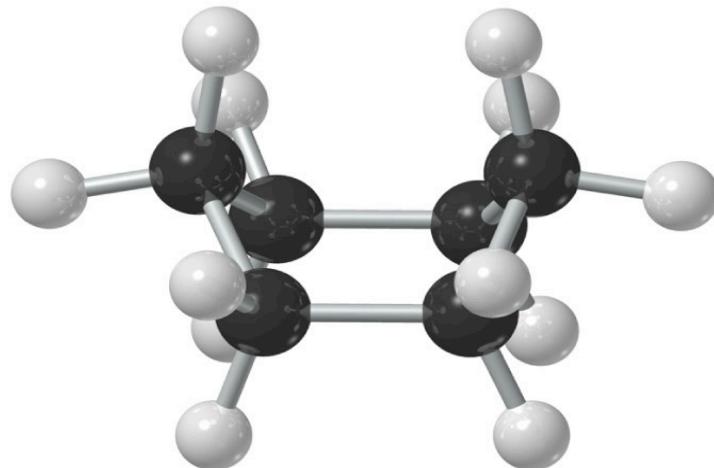


viewed along the “seat” bonds

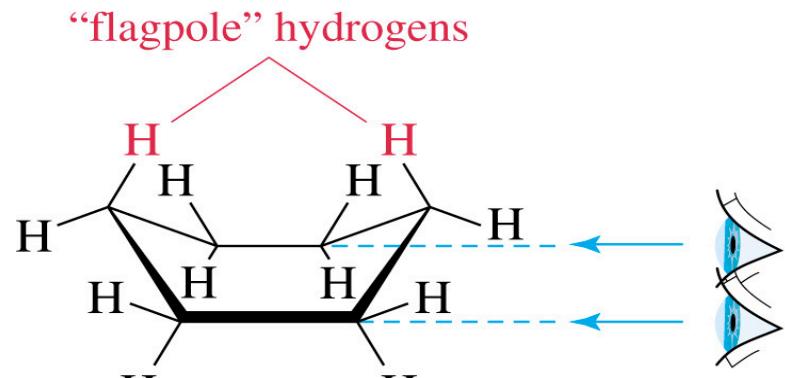


Newman projection

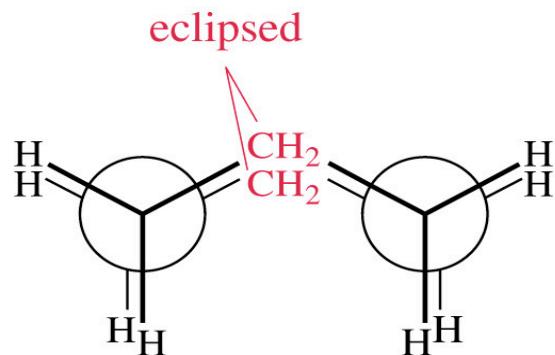
Boat Conformation



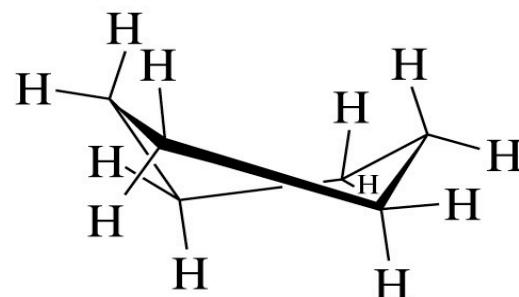
boat conformation



symmetrical boat

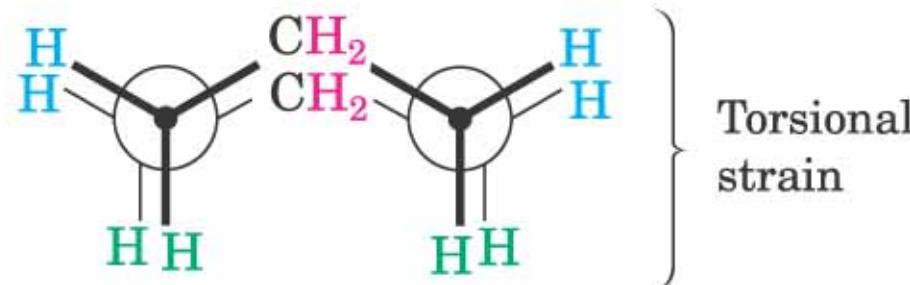
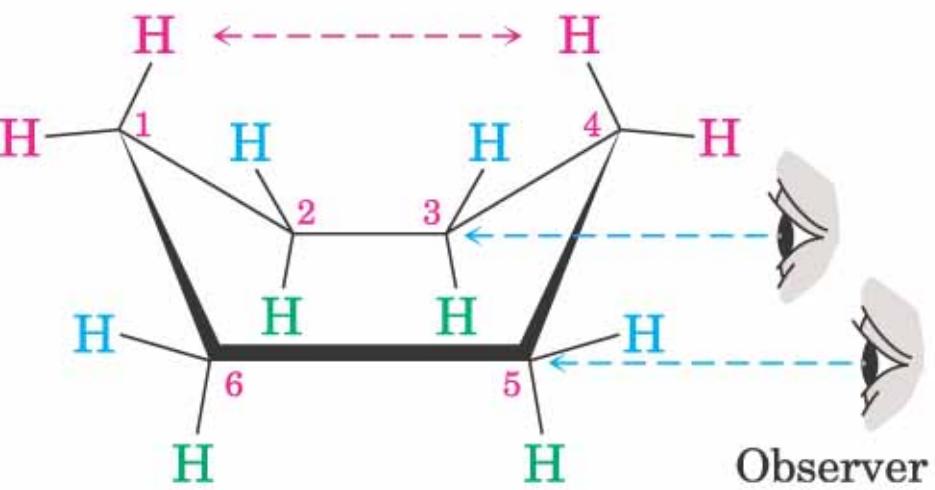


Newman projection



"twist" boat

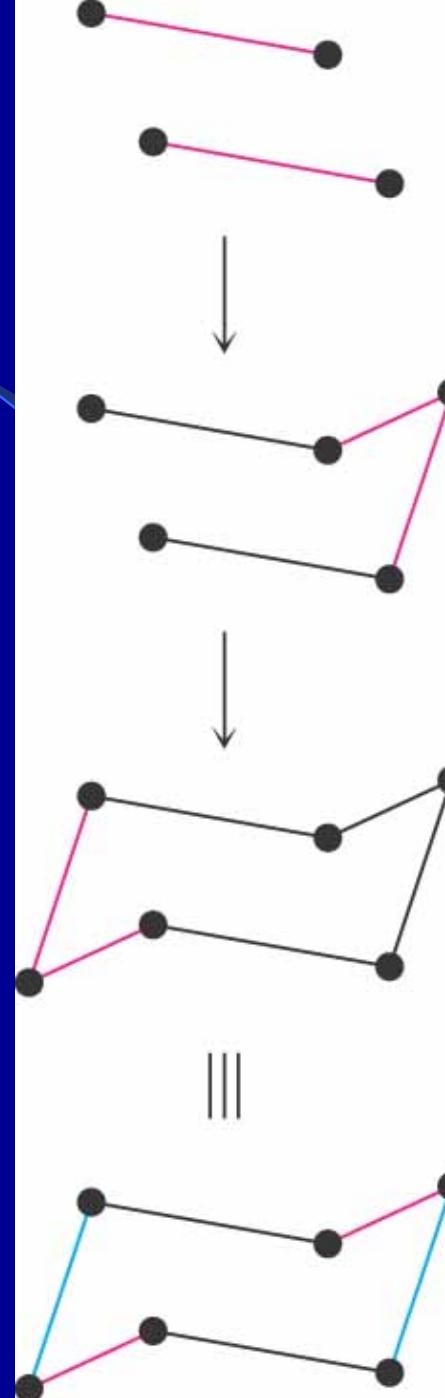
Steric strain of hydrogens at C1 and C4



Torsional strain

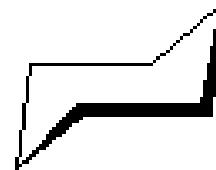
How to Draw a Chair Conformation

all opposite bonds
are parallel

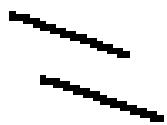




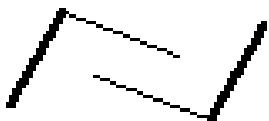
adding "wedges" helps show the 3D structure



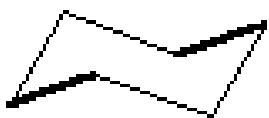
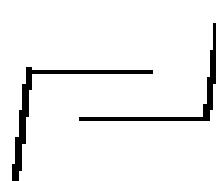
The chair can be obtained by drawing opposite sides as 3 sets of parallel lines



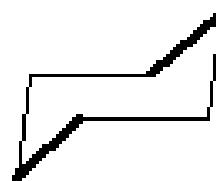
First draw the sides of the middle portion



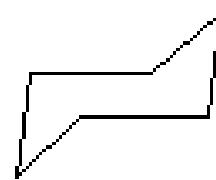
Next draw in the first half of each end



Finally complete the two ends

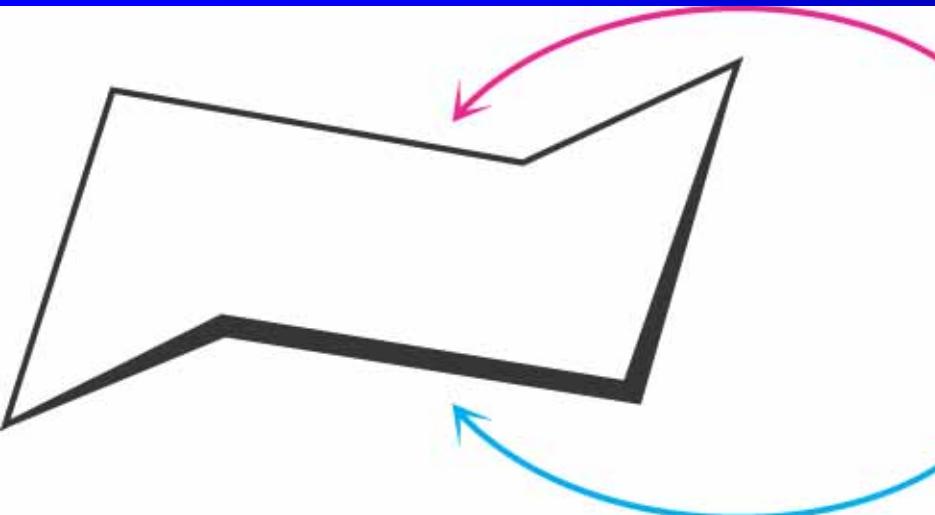


Done !



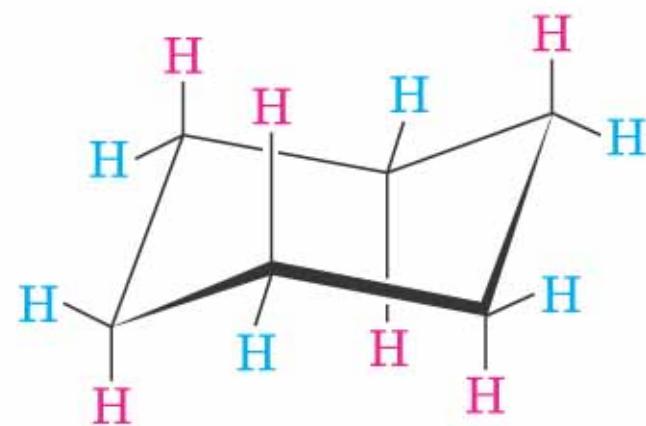
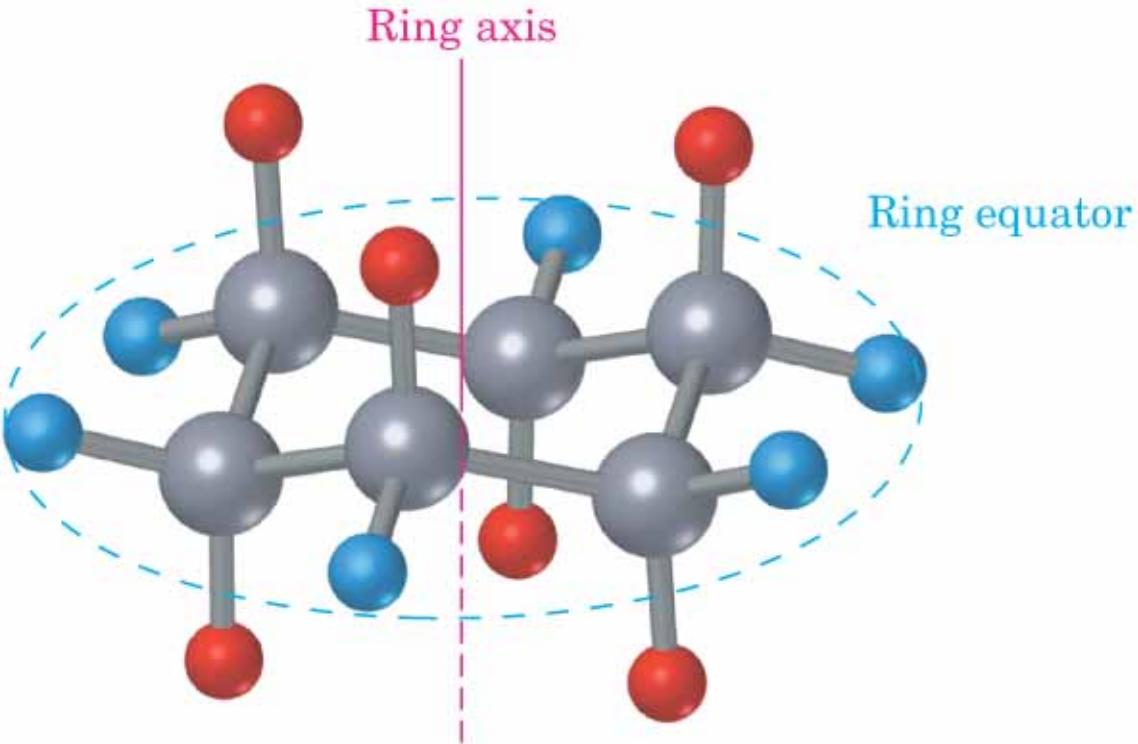
angled

horizontal



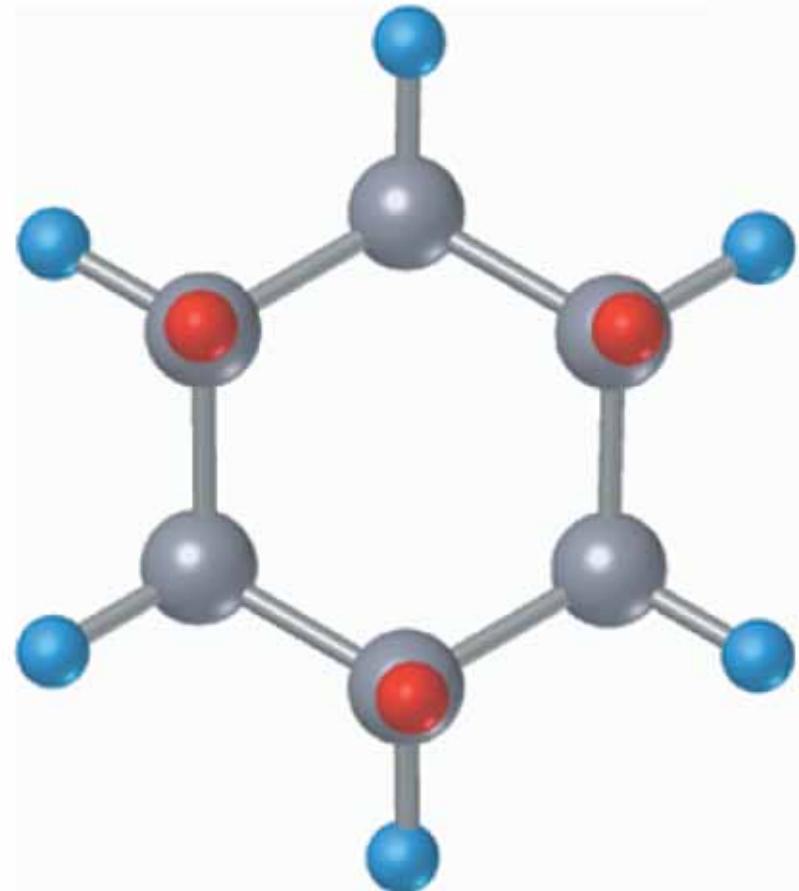
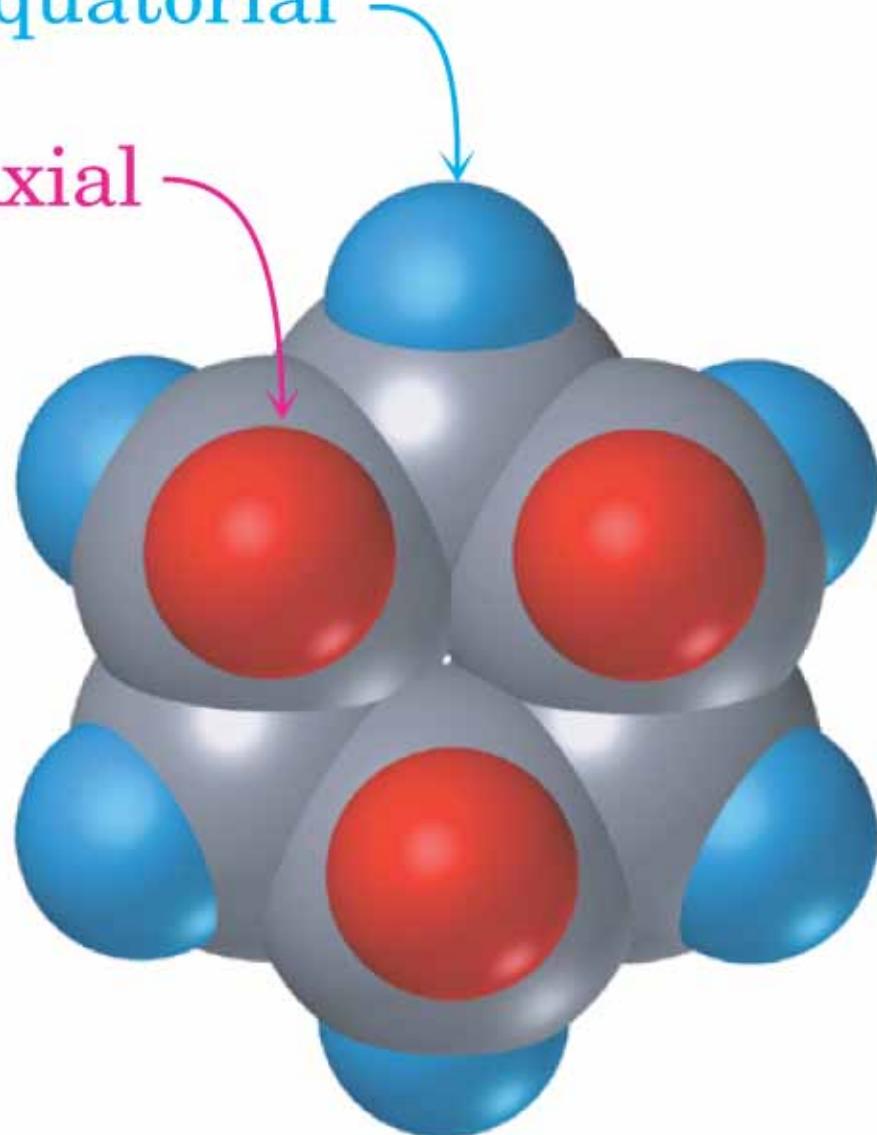
This bond is in back.

This bond is in front.



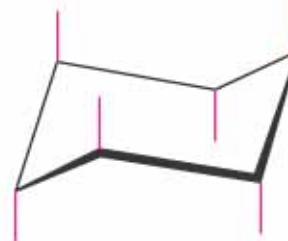
Equatorial

Axial

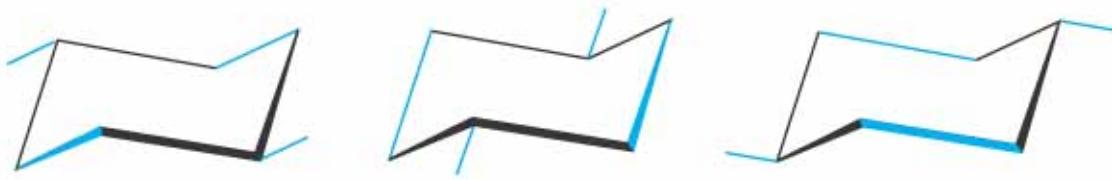


Axial bonds and Equatorial bonds

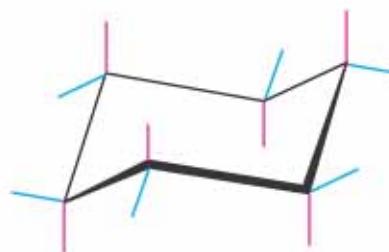
Axial bonds: The six axial bonds, one on each carbon, are parallel and alternate up–down.

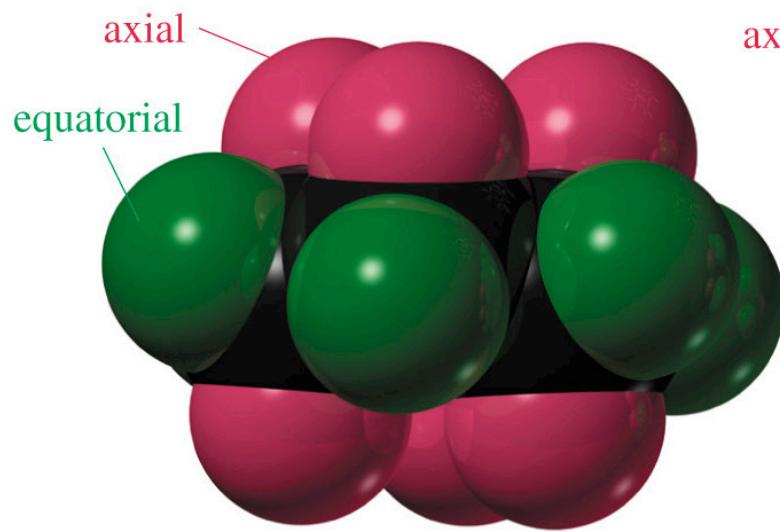
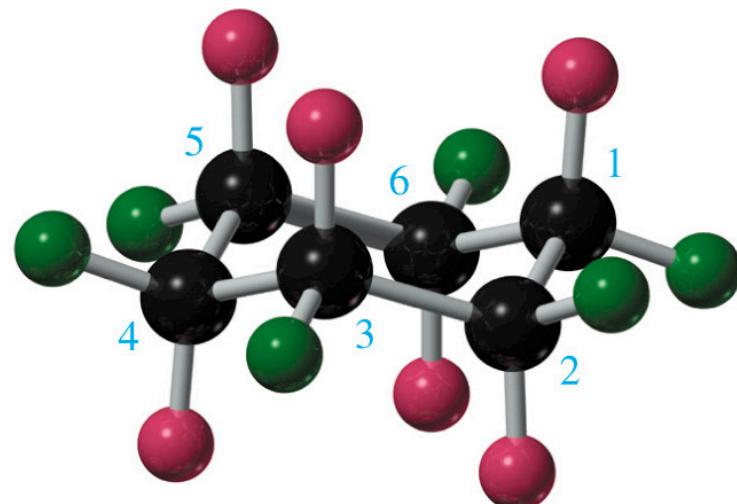
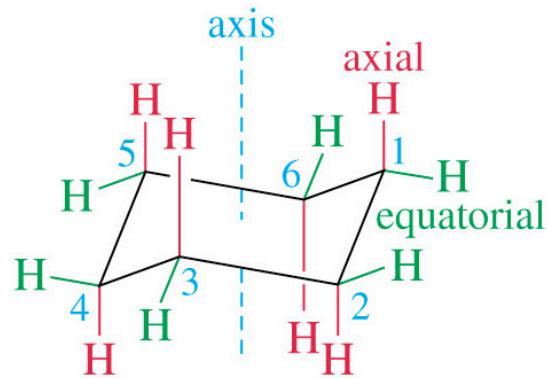


Equatorial bonds: The six equatorial bonds, one on each carbon, come in three sets of two parallel lines. Each set is also parallel to two ring bonds. Equatorial bonds alternate between sides around the ring.

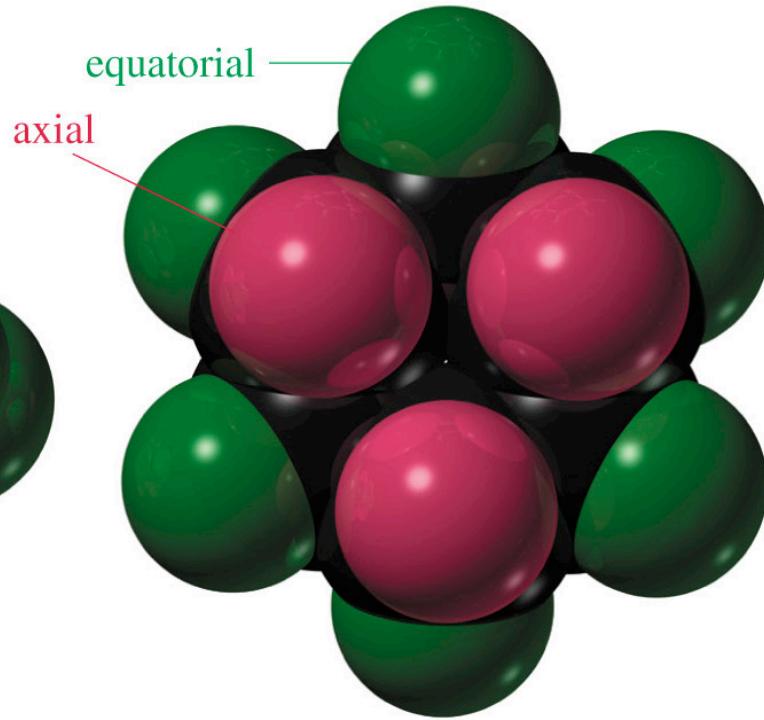


Completed cyclohexane



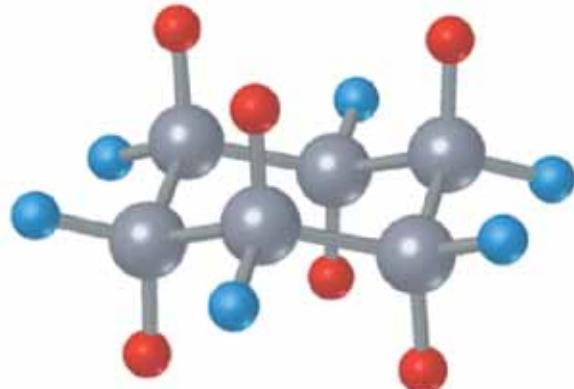


seen from the side

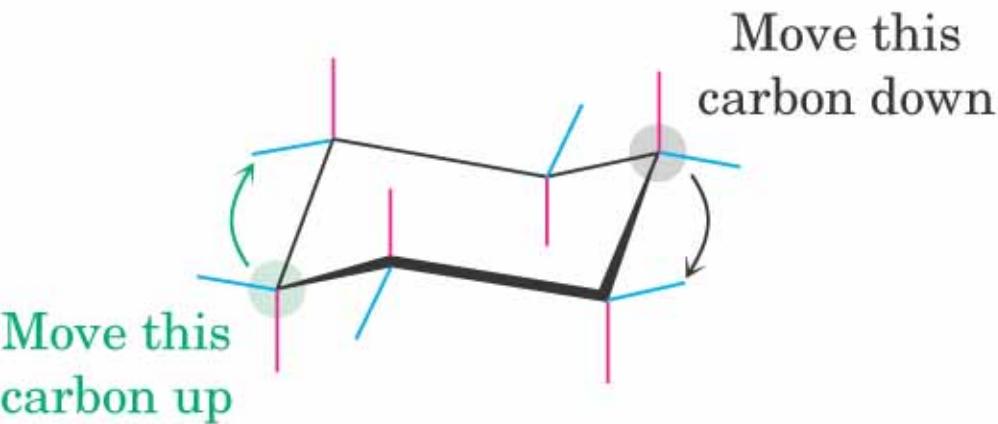
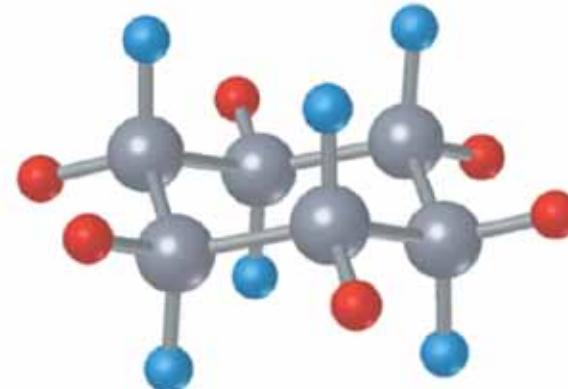


seen from above

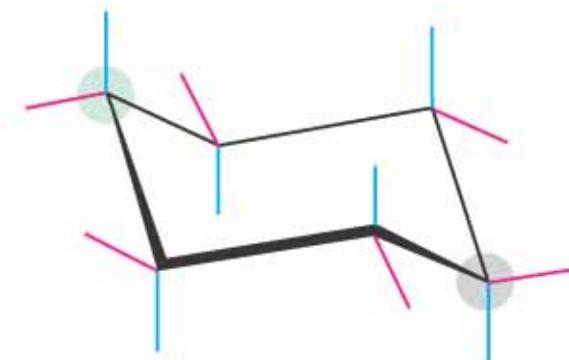
Rings can Flip from one Chair Conformation to Another



Ring-flip
 \longleftrightarrow



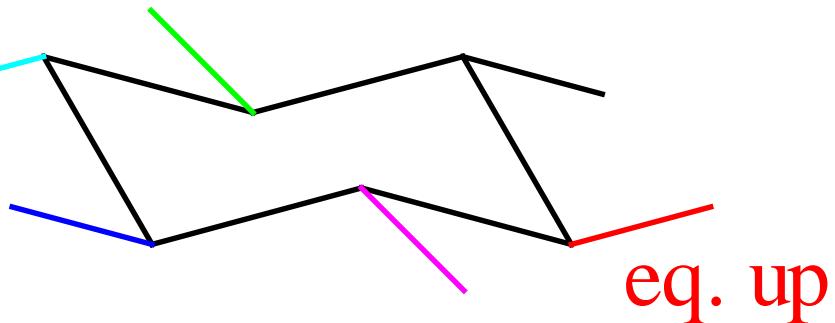
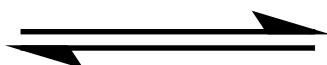
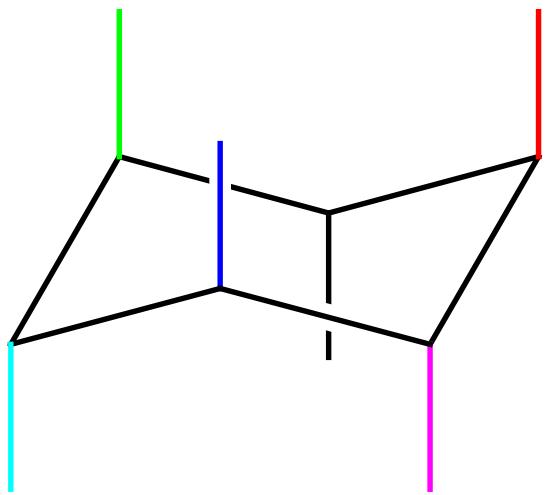
Ring-flip
 \longleftrightarrow



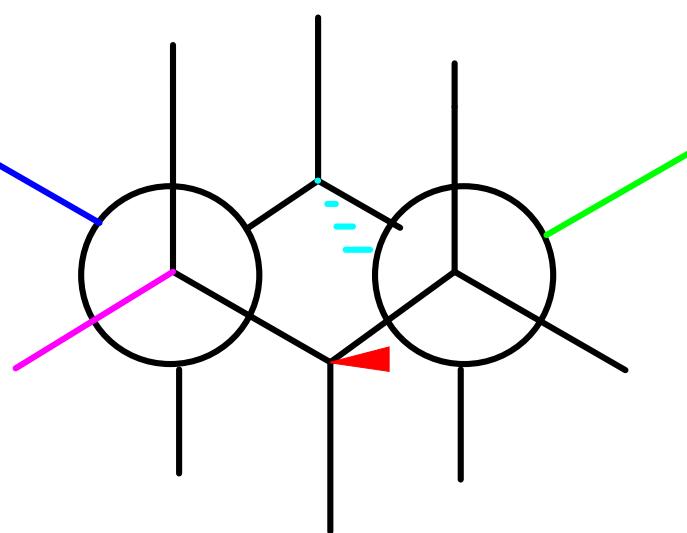
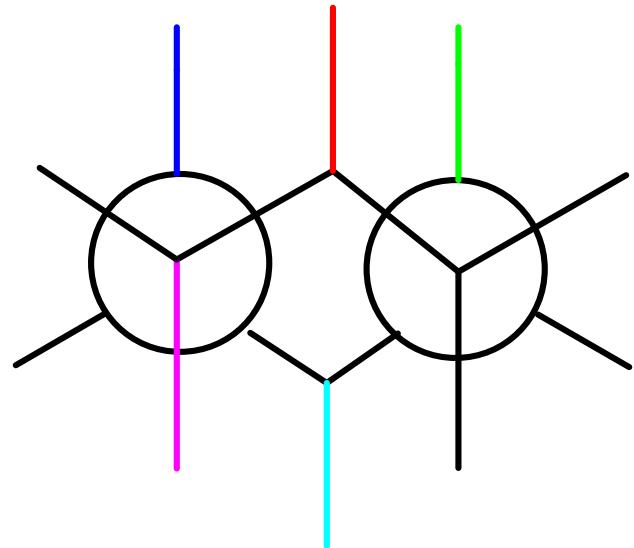
Flipping Chair Conformations

- All axial bonds become equatorial
- All equatorial bonds become axial
- All “up” bonds stay up
- All “down” bonds stay down

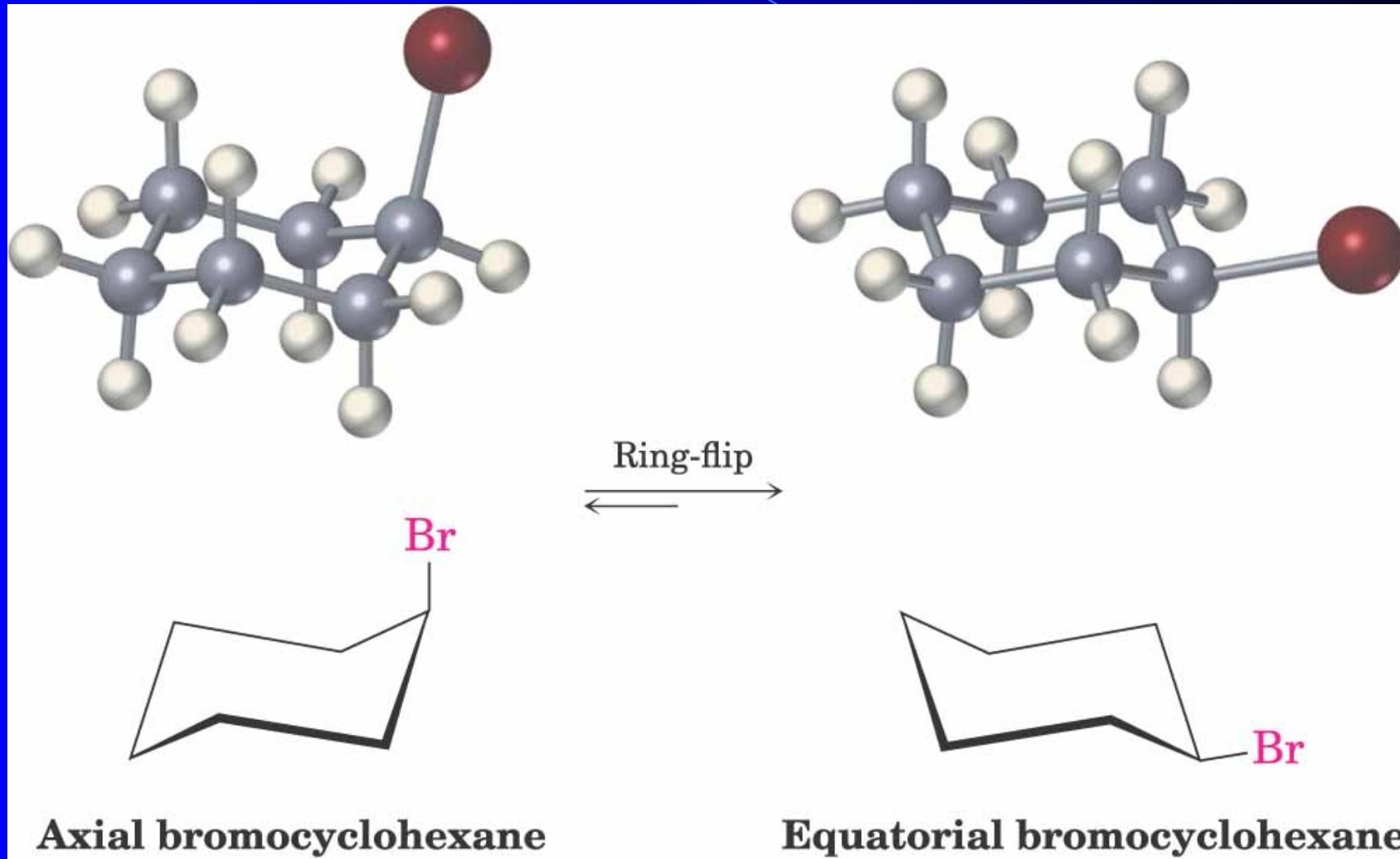
axial up

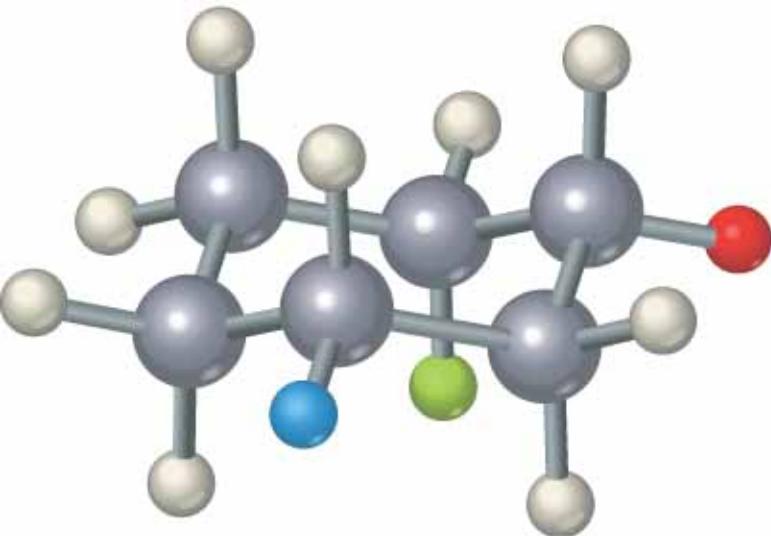


eq. up

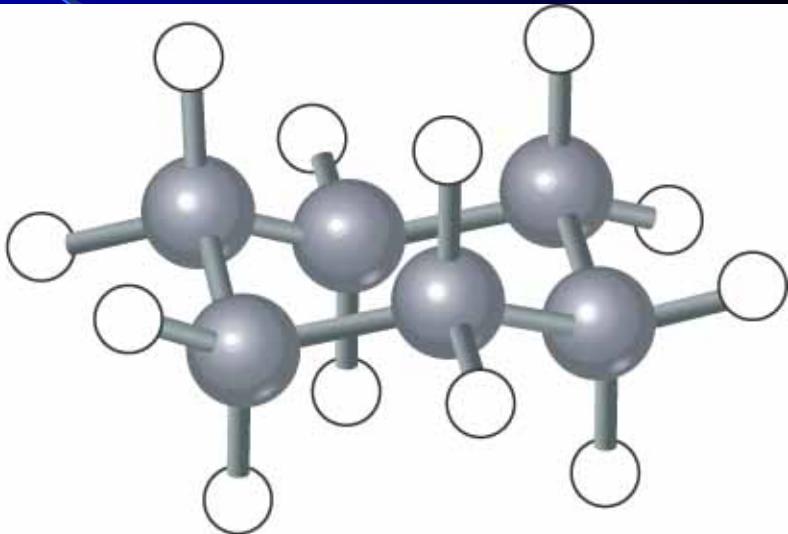


Axial-up becomes Equatorial-up



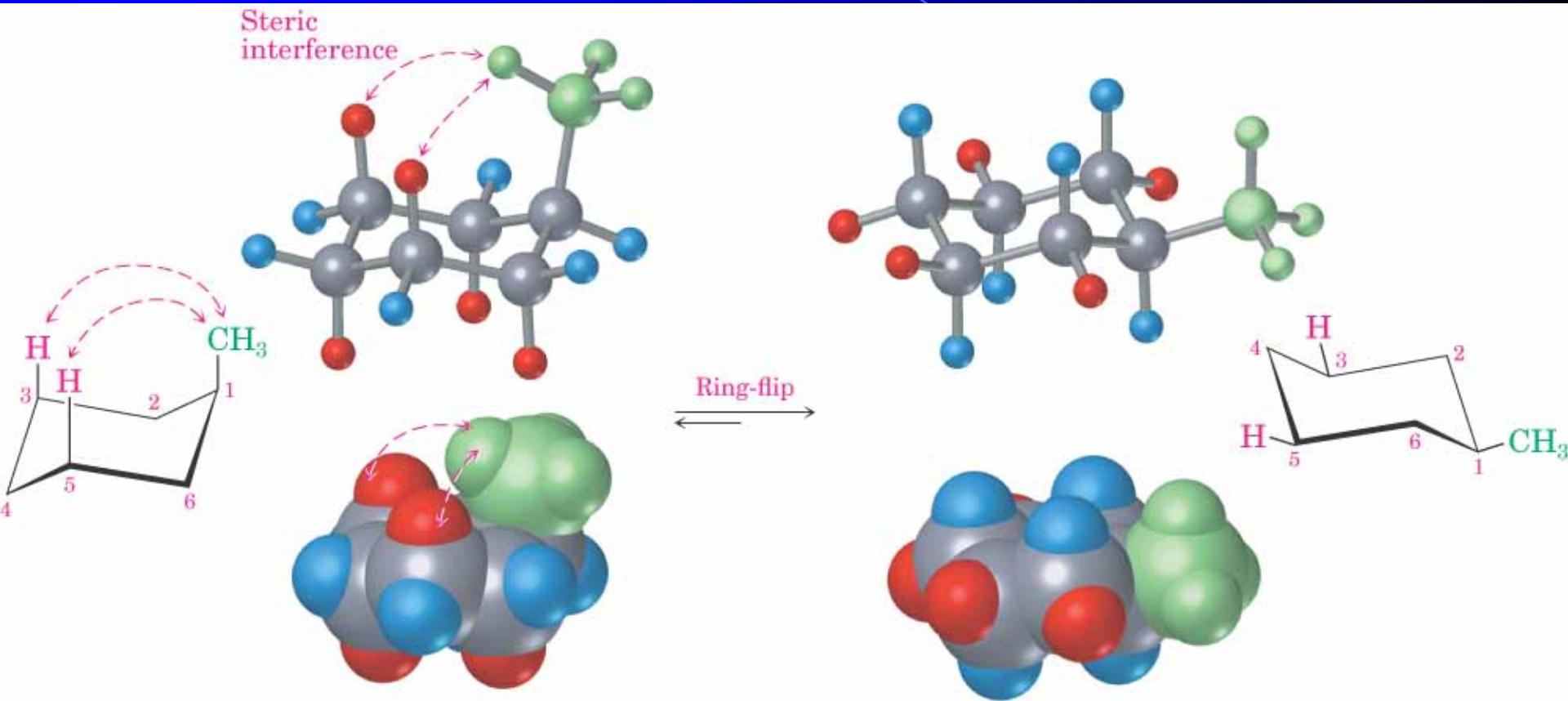


Ring-flip

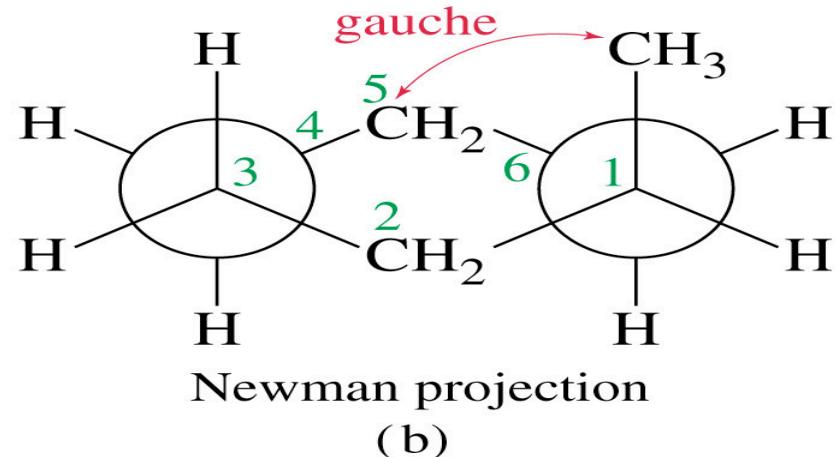
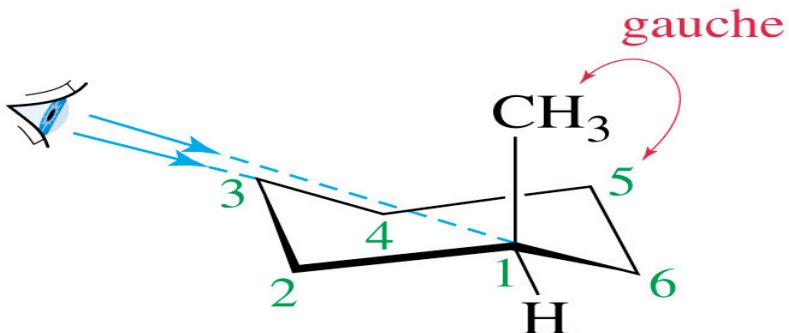
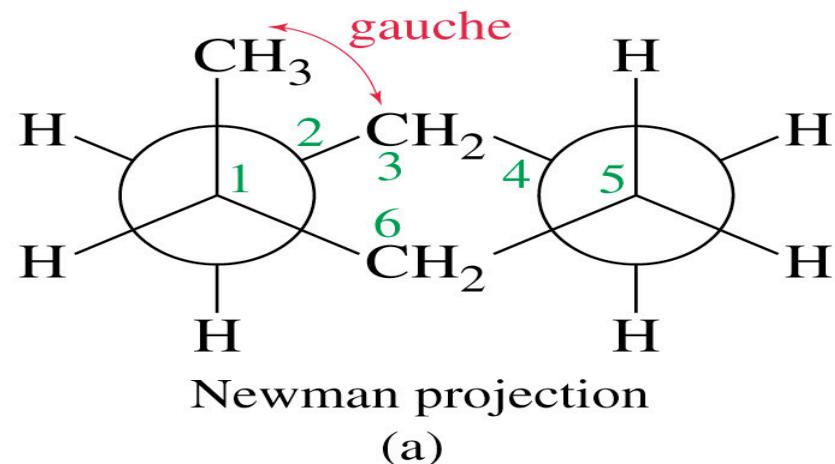
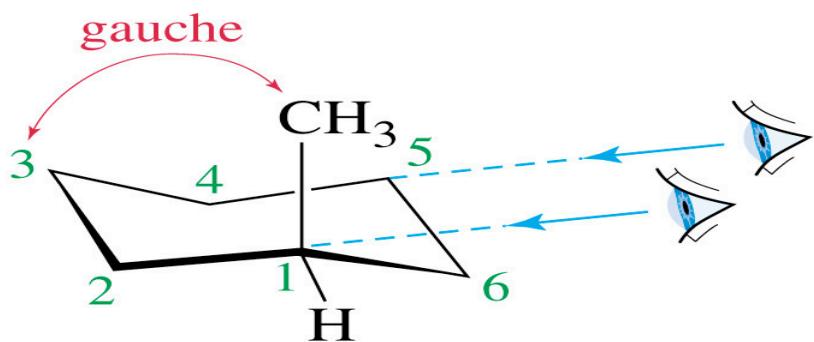


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Equatorial Conformation is Preferred

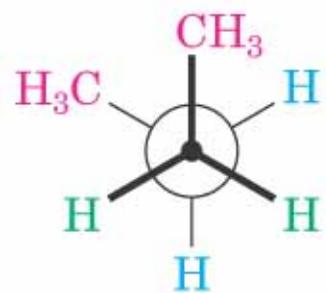


Axial Methyl group is Gauche to C₃ in the ring

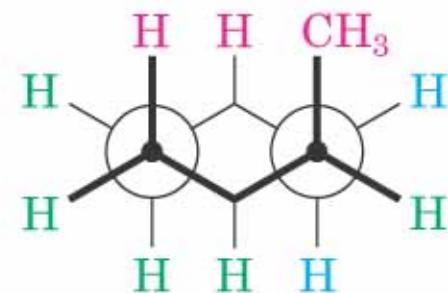
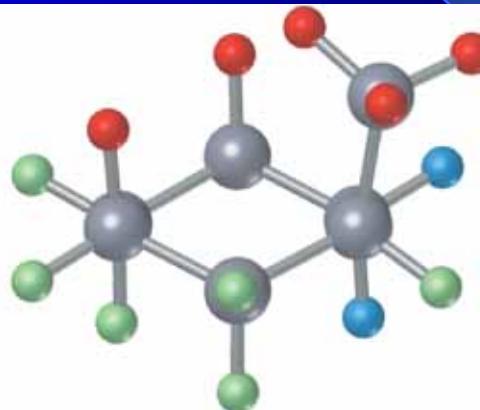
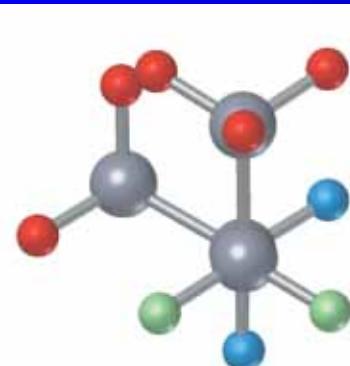


Gauche Interactions are Flagged by Parallel H's

1,3-Diaxial Interactions



Gauche butane
(3.8 kJ/mol strain)



Axial
methylcyclohexane
(7.6 kJ/mol strain)

Equatorial Methyl Group is Anti to C₃ in the ring

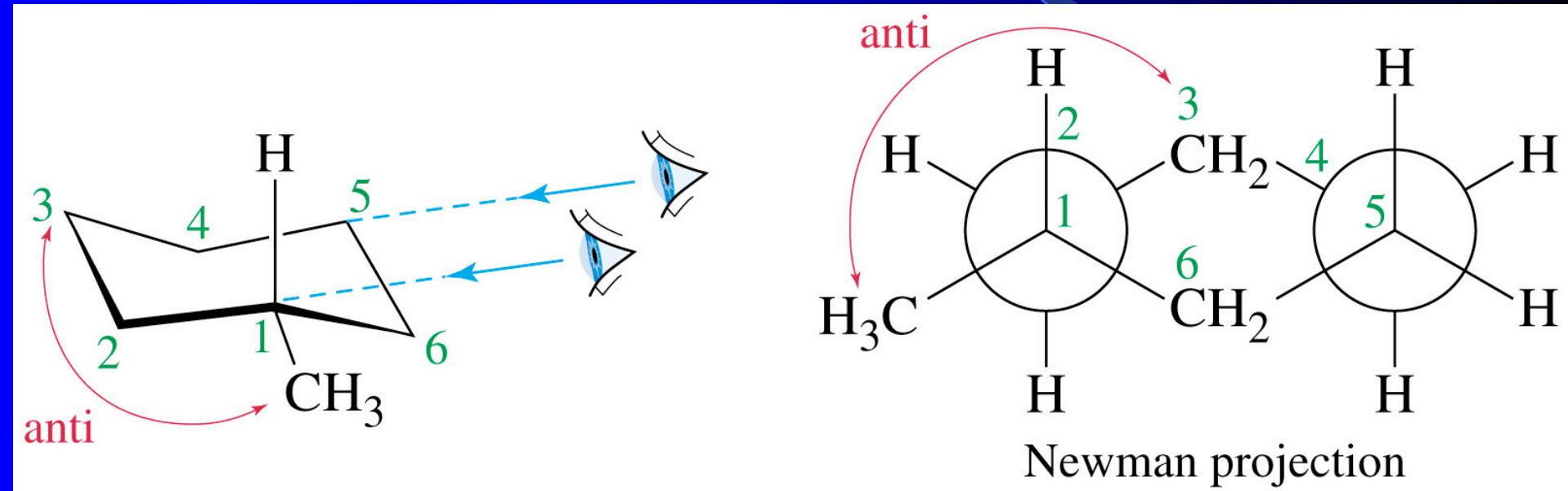
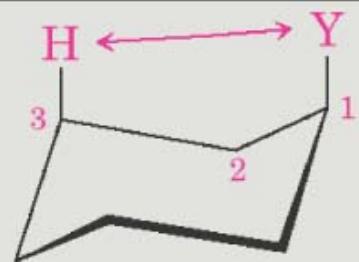
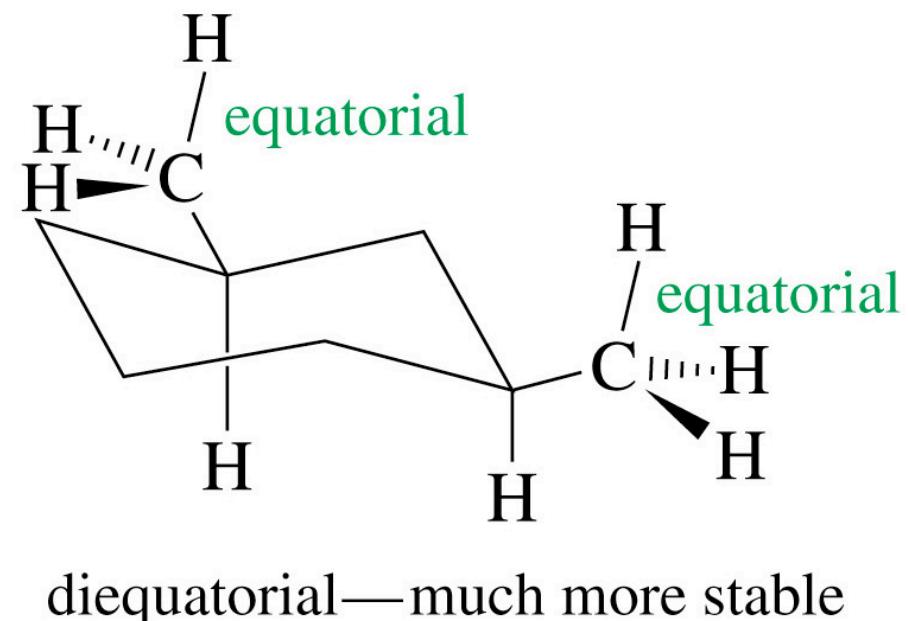
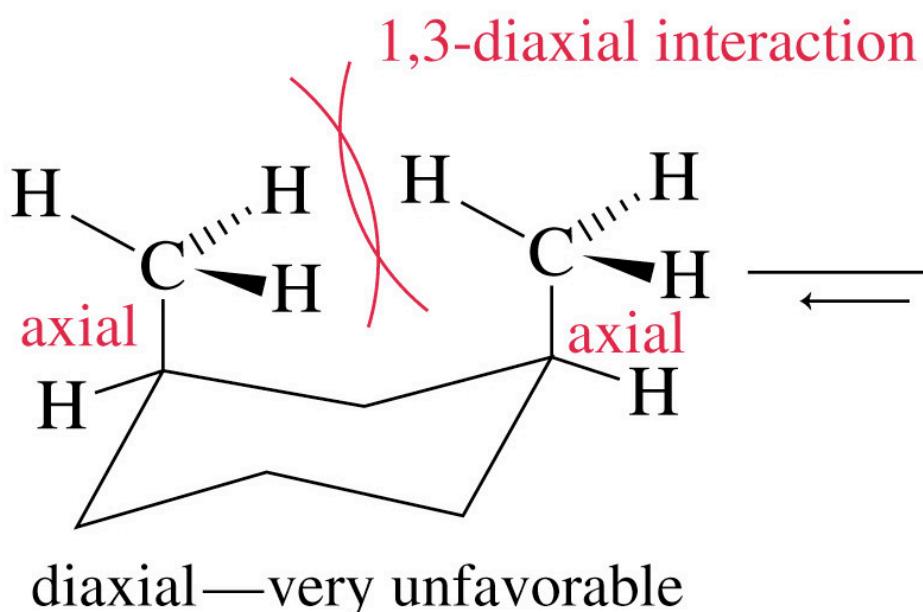


TABLE 4.2 Steric Strain in Monosubstituted Cyclohexanes

Y	Strain of one H-Y 1,3-diaxial interaction	
	(kJ/mol)	(kcal/mol)
-F	0.5	0.12
-Cl	1.0	0.25
-Br	1.0	0.25
-OH	2.1	0.5
-CH ₃	3.8	0.9
-CH ₂ CH ₃	4.0	0.95
-CH(CH ₃) ₂	4.6	1.1
-C(CH ₃) ₃	11.4	2.7
-C ₆ H ₅	6.3	1.5
-CO ₂ H	2.9	0.7
-CN	0.4	0.1

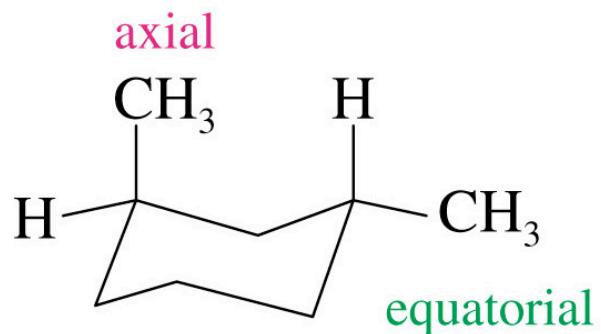


cis 1,3-Dimethylcyclohexane

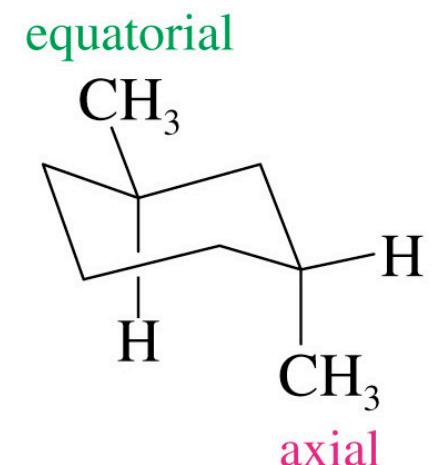


trans 1,3-Dimethylcyclohexane

Chair conformations of trans-1,3-dimethylcyclohexane



same energy



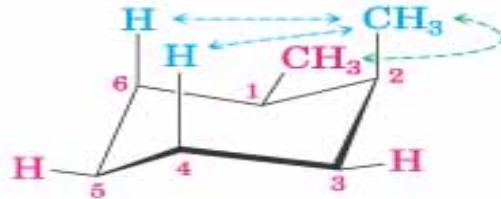
cis-1,2-Dimethylcyclohexane

One gauche interaction (3.8 kJ/mol)
 Two CH₃-H diaxial interactions (7.6 kJ/mol)

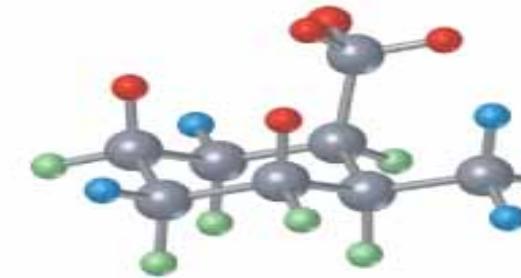
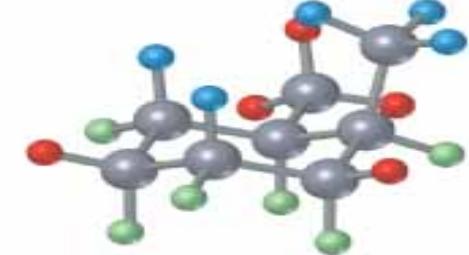
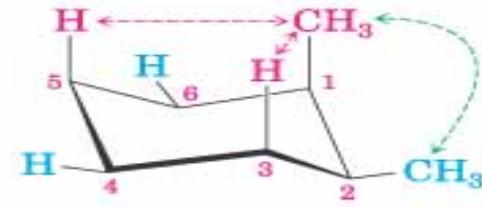
Total strain: 3.8 + 7.6 = 11.4 kJ/mol

One gauche interaction (3.8 kJ/mol)
 Two CH₃-H diaxial interactions (7.6 kJ/mol)

Total strain: 3.8 + 7.6 = 11.4 kJ/mol



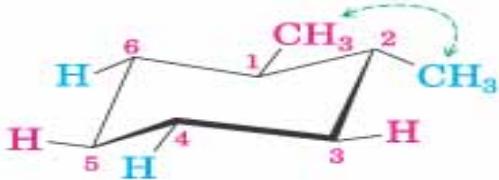
Ring-flip



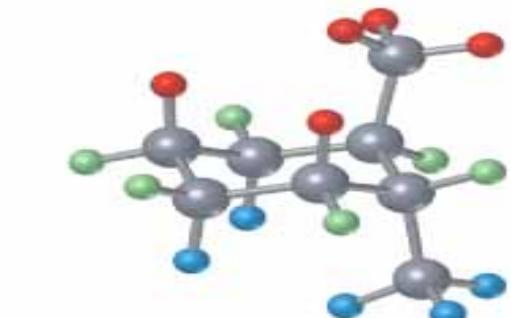
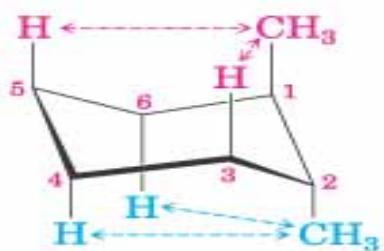
trans-1,2-Dimethylcyclohexane

One gauche interaction (3.8 kJ/mol)

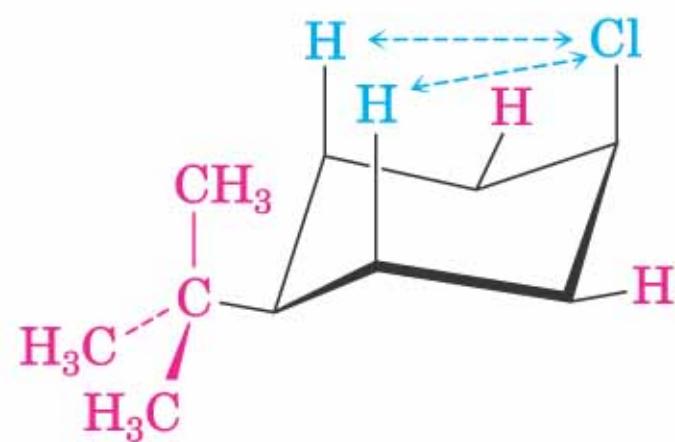
Four CH₃-H diaxial interactions (15.2 kJ/mol)



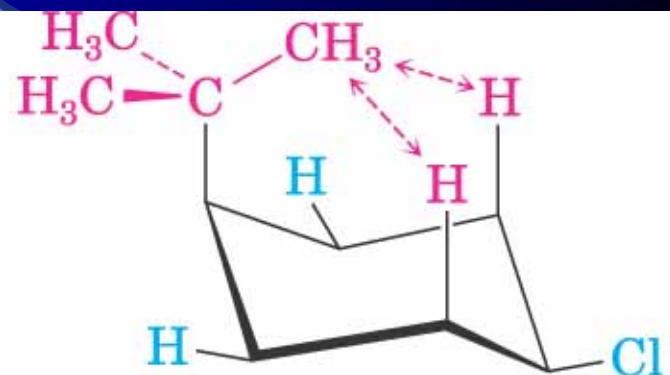
Ring-flip



cis 1-Chloro-4-*t*-butylcyclohexane



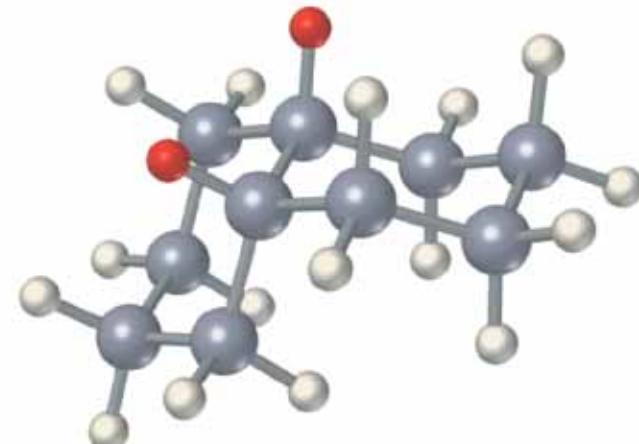
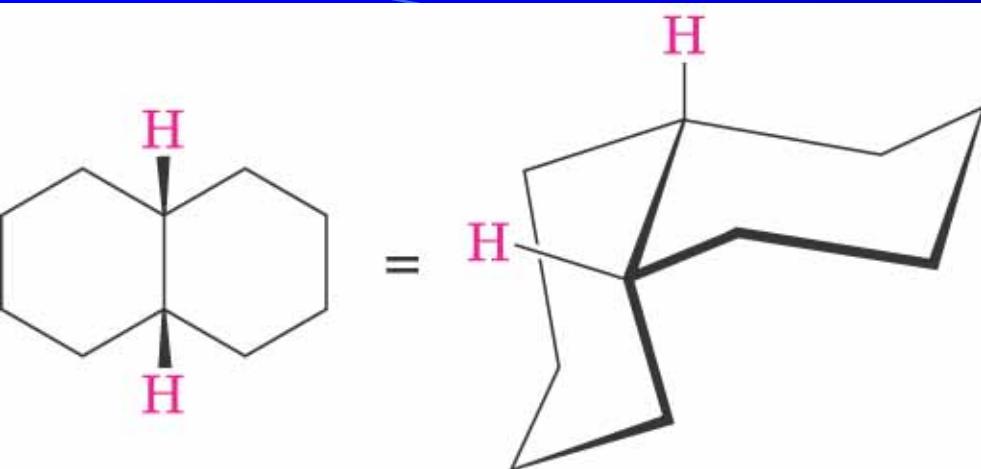
Ring-flip \longleftrightarrow



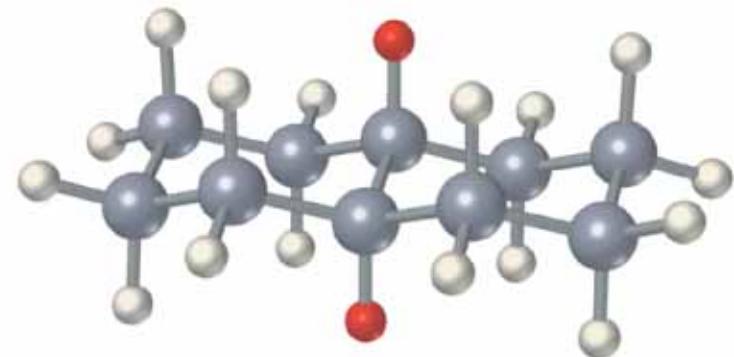
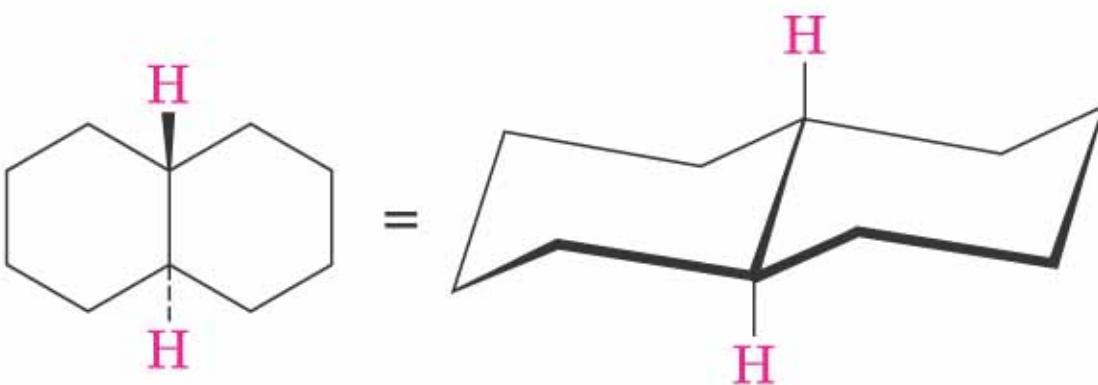
$$2 \times 1.0 = 2.0 \text{ kJ/mol steric strain}$$

$$2 \times 11.4 = 22.8 \text{ kJ/mol steric strain}$$

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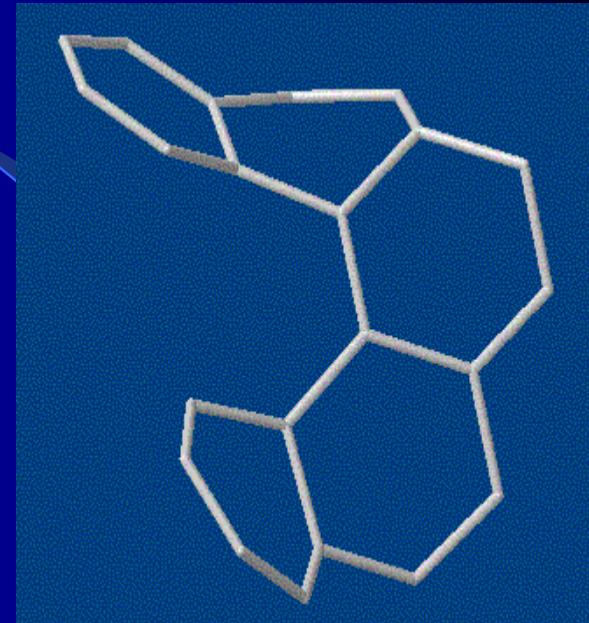
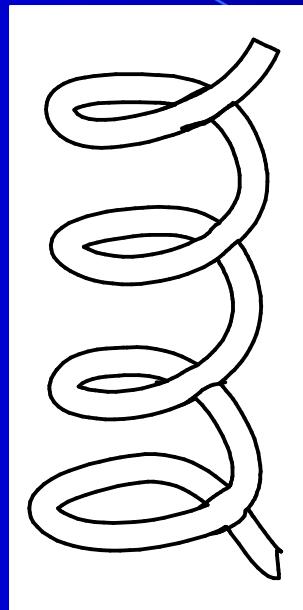
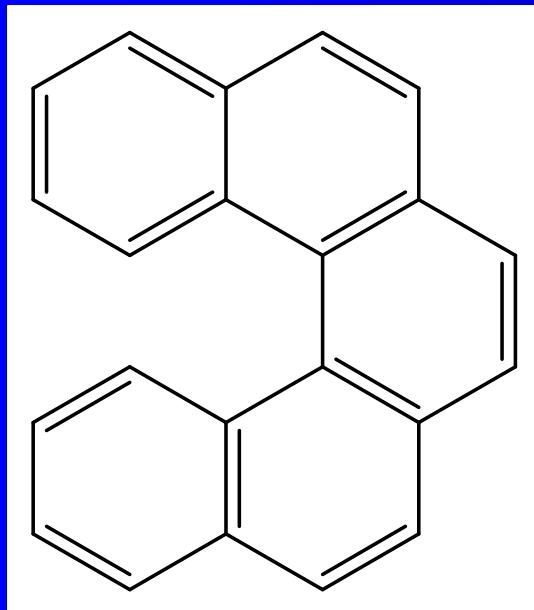


cis-Decalin



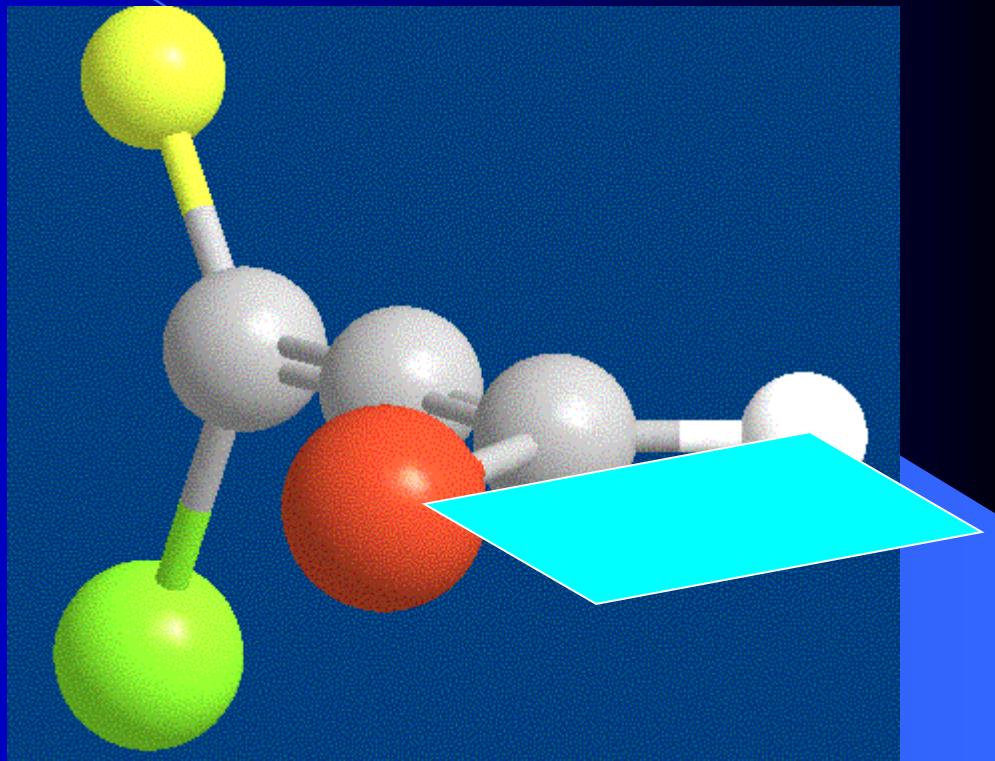
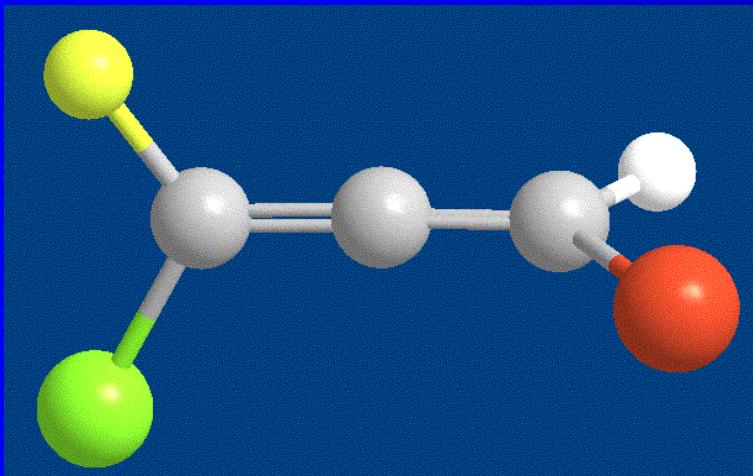
trans-Decalin

Stereoisomerism: Resulting from sources other than center of chirality



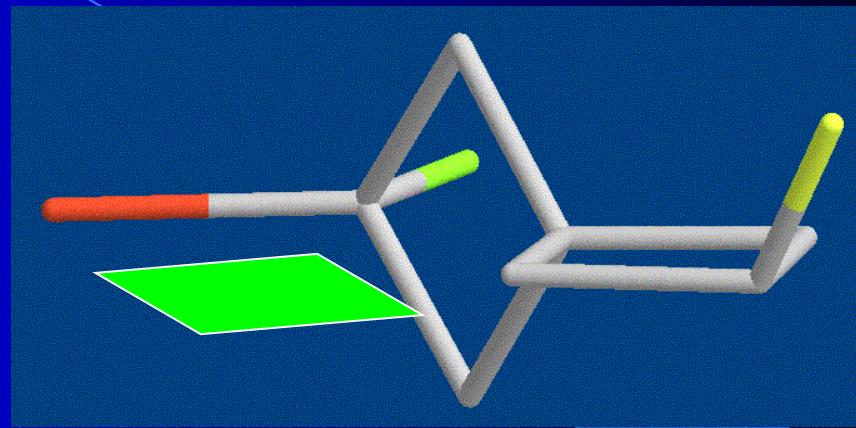
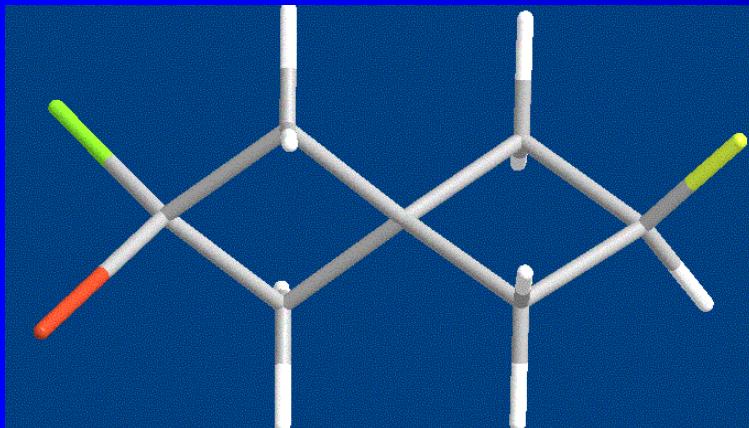
helicenes – due to helical structure

Stereoisomerism: Resulting from sources other than center of chirality

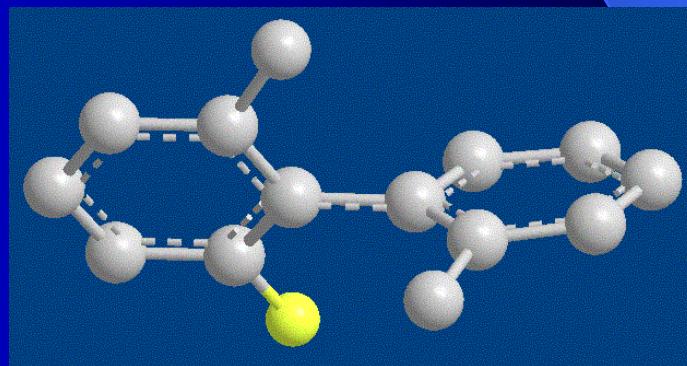
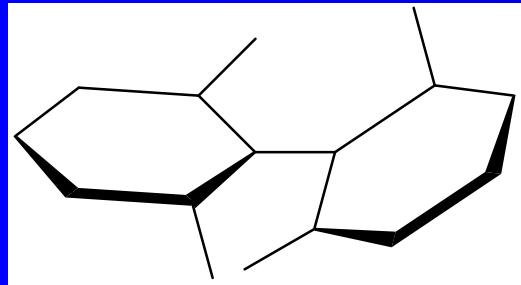


Allenes ($\text{H}_2\text{C}=\text{C}=\text{CH}_2$) : have chiral axis but do not have center

Stereoisomerism: Resulting from sources other than center of chirality

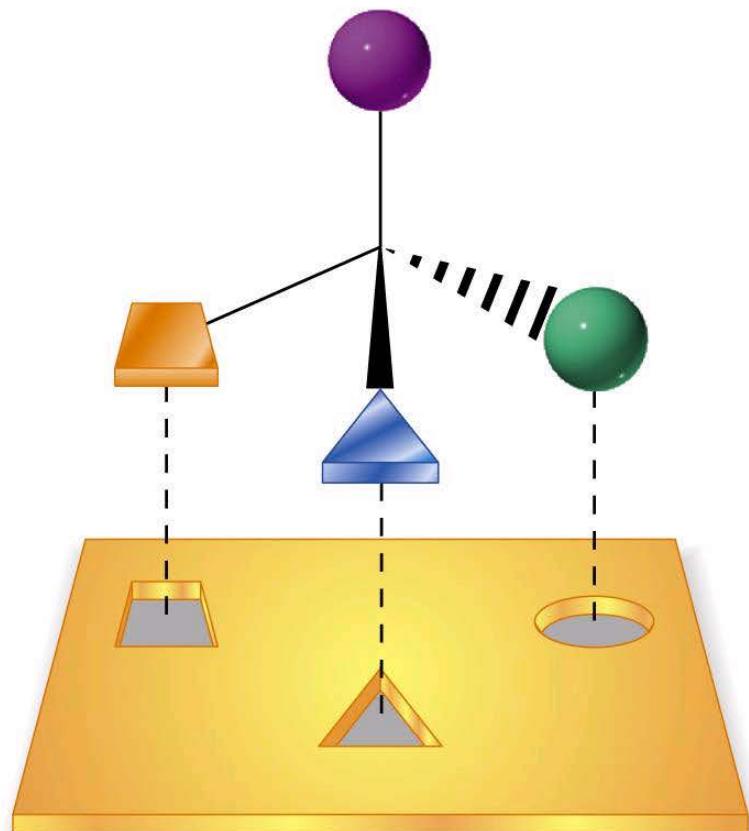


Spiranes – have chiral axis but do not have center

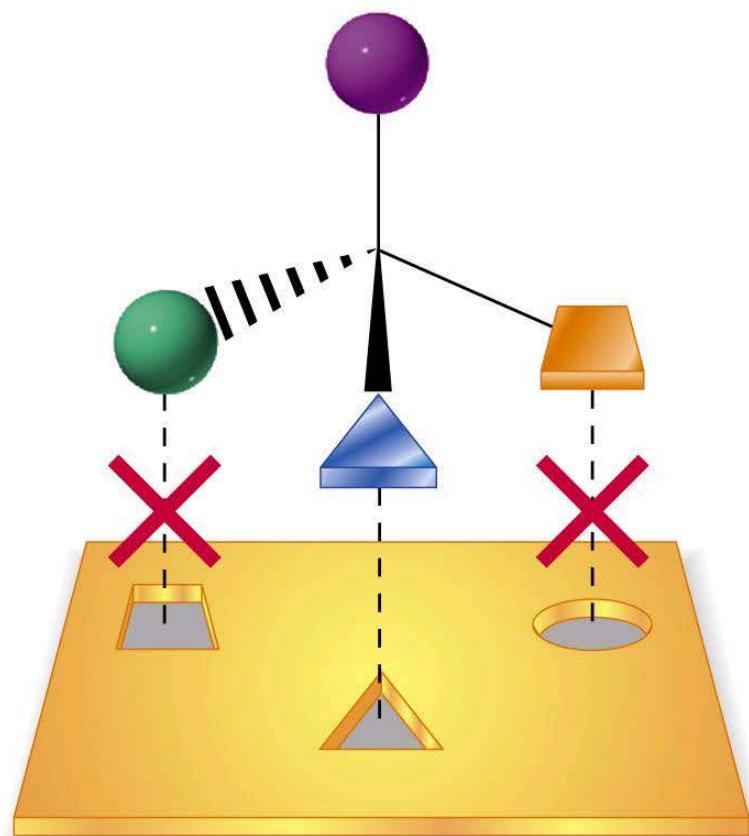


Biphenyls – have chiral axis but do not have center

R enantiomer

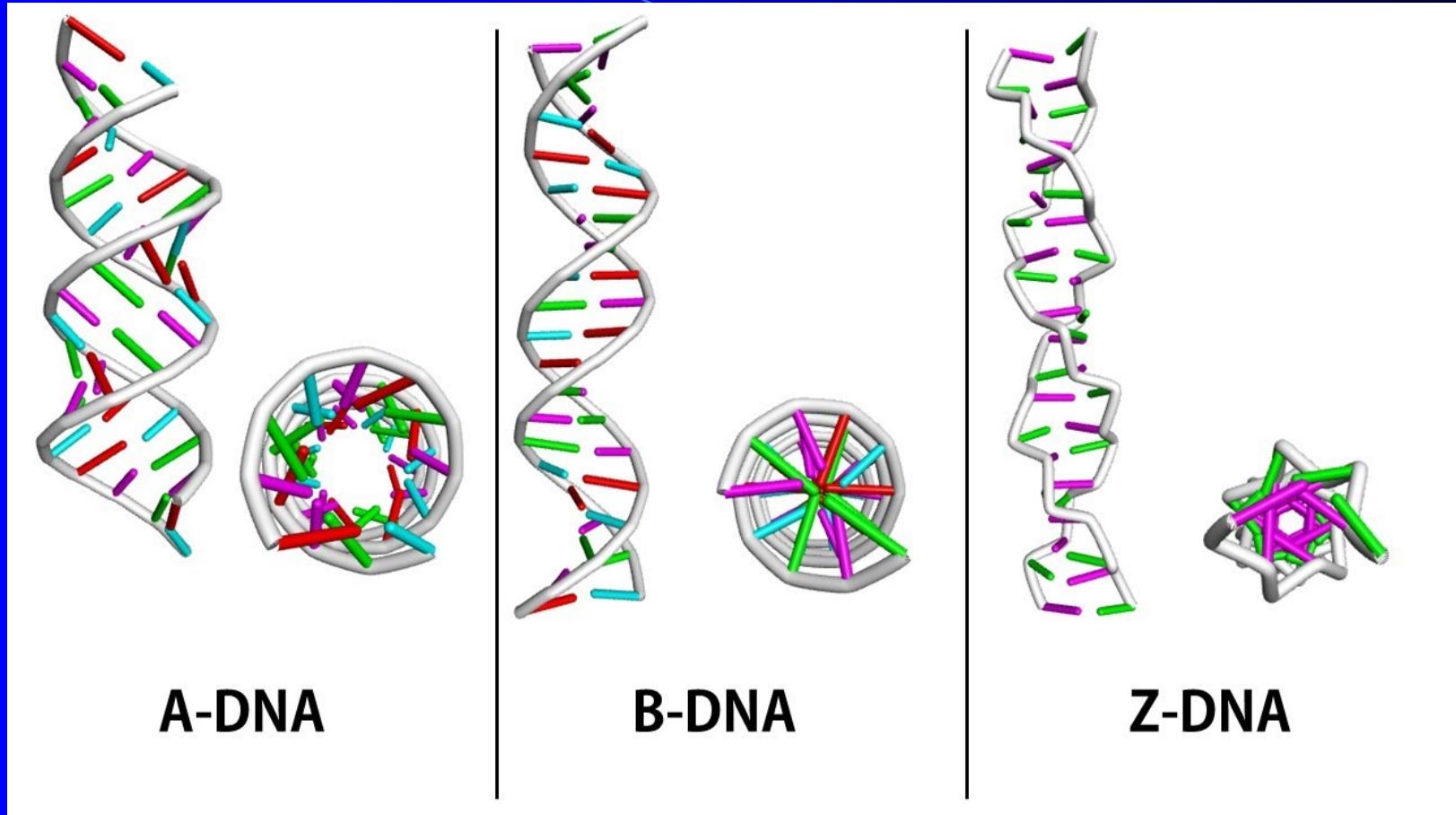


S enantiomer



binding site of the receptor

binding site of the receptor



(+)Daunorubicine binds selectively to right handed B-DNA, - w/ left Z-DNA. Some of conformation turn on or off transcription for a section.