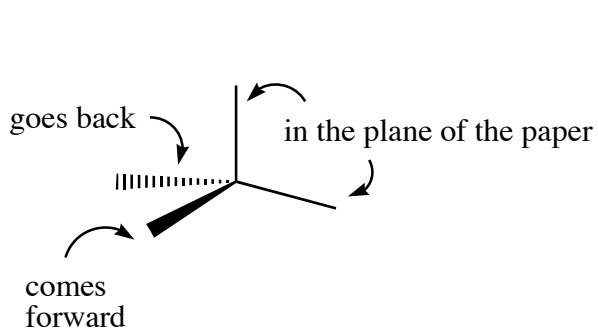


STEREOCHEMISTRY

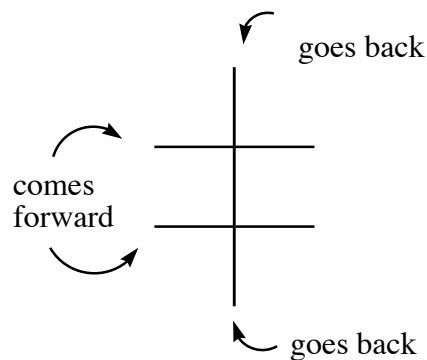
SOME DEFINITIONS WITH EXAMPLES

PRESENTING STEREO STRUCTURES

CHIRAL CENTER REPRESENTATION



DOTTED LINE - WEDGE



FISCHER PROJECTION

STEREISOMERS—ISOMERS THAT ARE DIFFERENT BECAUSE OF THEIR ORIENTATION IN SPACE

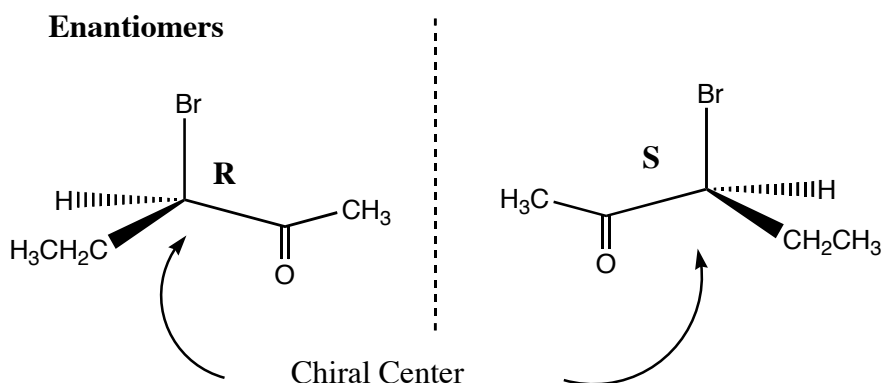
CONFIGURATION—THE EXACT ORIENTATION IN SPACE OF THE ISOMER (CIS, TRANS OR R,S)

CHIRALITY—A PROPERTY OF ISOMERS WHEN THEY ARE NON-SUPERIMPOSABLE (ISOMERS OF OPPOSITE CONFIGURATION)

STEREOGENIC—ANY FEATURE OF A MOLECULE THAT GIVES RISE TO CHIRALITY. A CHIRAL CENTER IS A STEREOGENIC CENTER.

CHIRAL CENTER—A CENTER WITHOUT SYMMETRY. MOST COMMON IT IS A CARBON ATOM WITH FOUR DIFFERENT SUBSTITUENTS.

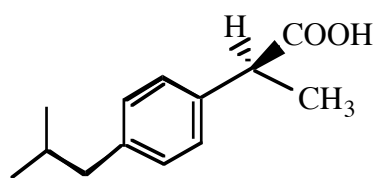
ENANTIOMERS—NON SUPERIMPOSIBLE MIRROR IMAGES



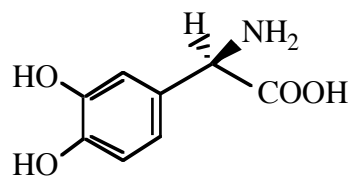
As shown the R and S enantiomers are together as an equal amount in a racemic mixture. They must be separated in order to study their stereochemical properties.

Configurational Isomers-Chirality

Another type of isomerization occurs when a carbon atom is bound to four different substituents. This is called configurational isomerism. Configurational isomers have as their only difference the way they are oriented in space, their three-dimensional arrangement. Although configurational isomers can be difficult to visualize and understand, they are extremely important especially in biological chemistry. For example, the pain reliever Ibuprofen exists as configurational isomers but only one isomer is effective (the S isomer) in treating pain. Also, the drug L-DOPA (L-dopamine) used for treatment of Parkinson's disease is effective only as the L or R isomer in the treatment.



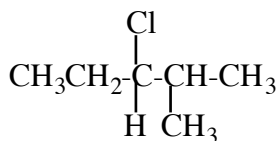
S-Ibuprofen



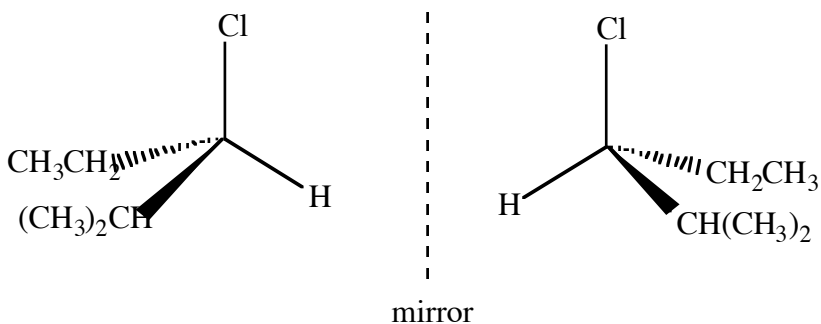
L-DOPA

R-Configuration

In 3-chloro-2-methylpentane, four different substituents are bound to carbon 3; an ethyl group, an isopropyl group, a chlorine atom and a hydrogen atom. When the compound is placed in front of a mirror, it presents a mirror image that is not superimposable on the original structure. This means that there is no way to orient the two structures such that they can be identical. The non superimposable mirror images are called enantiomers, which are configurational isomers. The enantiomers are also called chiral which means they lack symmetry. The word chiral comes from a Greek word **chiros** that means hand. Enantiomers are to each other as your hands are to you, non-superimposable mirror images.



3-chloro-2-methylpentane



Enantiomers are identical in most properties such as melting point, boiling point, **but they are different in the way they react with other chiral molecules and in the way they interact with polarized light.** Their interaction with polarized light is called optical activity.

Optical Activity

PURE ENANTIOMERS (THE R AND S ARE SEPARATED FROM EACH OTHER)

Will rotate plane polarized light (optically active). These experiments involve the use of optical activity studies. Each enantiomer will react differently with another chiral reagent, but there is no difference if the reagent is achiral (not chiral). This is the basis of chemical resolution. R-isomer reacts with S-reagents to yield a compound with R and S centers. (compound 1) S-isomer reacts with S-reagent to yield a compound with S and S centers (Compound 2) Compounds 1 and 2 are stereoisomers but they are not enantiomers, these are diastereomers. Diastereomers have completely different physical properties. Thus they can be separated by crystallization or chromatography. After purification the isomers can be released back in their pure form separated from each other. Compound 1 and Compound 2 are separated by chromatography. Now take pure compound 1 and do a reaction that regenerates the R-isomer. Do the same with compound 2 to get the S-isomer. **This is resolution of an enantiomeric mixture.**

Many natural compounds such as enzymes are not symmetrical. Thus individual enantiomers will react with enzymes to give different results.

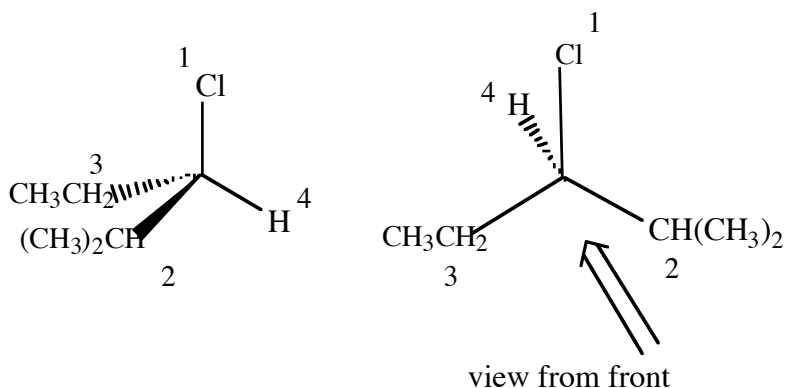
A pure chiral compound, not a mixture of enantiomers, will interact with plane polarized light and cause the plane to rotate to the right (dextrorotatory) or to the left (levorotatory). An equal mixture of enantiomers will not show optical activity because half of the molecules would rotate light to the left while the other half would rotate the light to the right with a net rotation of zero. Thus enantiomers must be separated in order to observe optical activity. **Optical rotation** is an inherent property of an optically active compound and is used as a physical constant for characterization of the compound. Optical rotation depends on the arrangement of atoms or groups around the chiral center—**the configuration**. Optical activity is measured automatically with an instrument called a polarimeter.

Naming Configurational Isomers

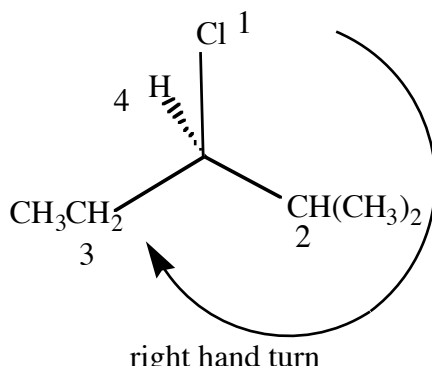
Configurational isomers contain carbon atoms with four different substituents. The carbon atoms are called **stereogenic centers or chiral centers**. A naming system has been devised so that we can distinguish one enantiomer from the other based on the

orientation of those substituents.

The system is called the **Cahn-Ingold-Prelog** method, and it follows several rules. First the substituents on the stereogenic carbon are assigned a priority based on atomic number. Low priority is given to low atomic number. If identical atoms are attached to the stereogenic carbon, then priorities are determined based on the atomic number of the next atom attached. Thus, in 3-chloro-2-methylpentane, the lowest priority goes to hydrogen and the highest priority goes to chlorine (labeled 1). The carbon atoms of ethyl and isopropyl are identical so we go out one atom. Now the ethyl has one carbon (methyl) attached to the CH₂ while the isopropyl has two carbons (methyls) attached to the CH. Thus the isopropyl group gets the higher priority (labeled 2) and the ethyl group gets priority 3. After the priorities are assigned, the molecule must be oriented with the lowest priority group pointing away from the observer.

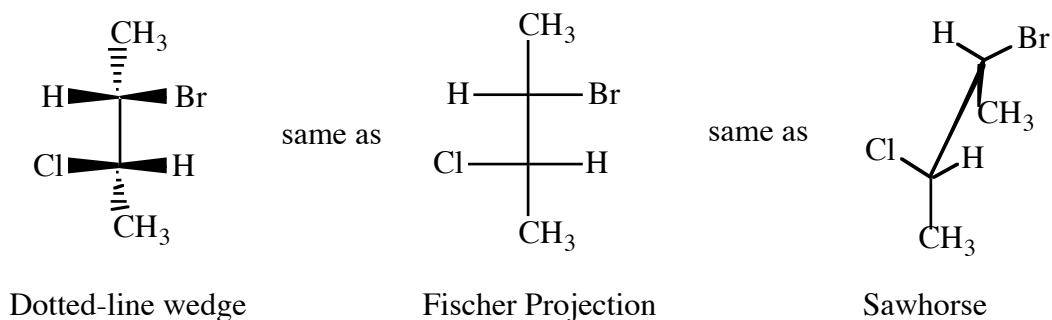


After getting the correct view, draw a circle from priority 1 to 2 to 3. If this circle makes a right hand turn then the configuration is called R. The R comes from the Latin word **rectus**, meaning right. If we draw a circle with a left turn then the configuration is S, meaning left which in Latin is **sinister**. A stereogenic carbon atom thus has two different designations, R or S, depending on the orientation of the substituents. In our molecule the configuration is R, and the complete name of this enantiomer is R-3-chloro-2-methylpentane.



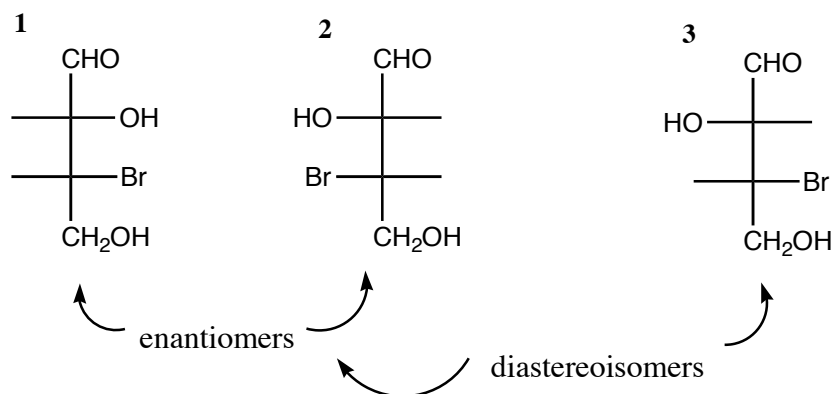
More than One Chiral (Stereogenic) Center

When molecules have more than one stereogenic center, structures such as dotted-line wedge and sawhorse may still be used, but another useful type of structure is the Fischer projection. In the Fischer projection all of the vertical lines go back into the paper and the horizontal bonds come out toward you. You have to remember this method because the structure looks flat. Also the only kind of change you can do to the structure is a rotation of 180° . All of these methods for writing stereochemical structures are important. The Fischer projection is used mostly in the study of carbohydrates.



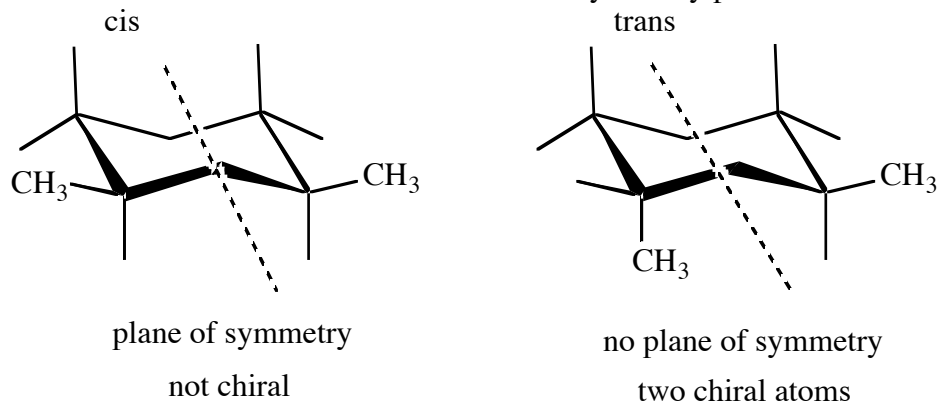
(2S, 3S)-2-bromo-3-chlorobutane

Many compounds that contain more than one chiral center are stereoisomers that are not enantiomers. In this case they are called diastereoisomers. While enantiomers have all of the same properties except for their interaction with other chiral substances and with polarized light, diastereomers are completely different in physical properties (different solubility, different mp, different chromatography, different spectra). The compounds 1 and 2 below are enantiomers as they are non-superimposable mirror images, but compound 3 is not an enantiomer of 1 or 2. Thus 1 and 3, and 2 and 3 are diastereomers.

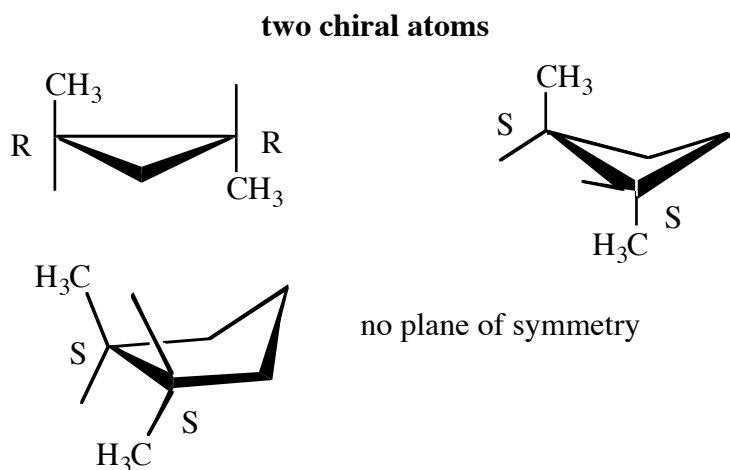


Chirality in Cyclic Systems

Stereogenic centers may also exist in cyclic systems. The cyclic structure must be tested for a plane of symmetry, and if one is present the molecule is not chiral. It is an achiral molecule designated as *meso*. The example below with cis and trans 1,3-dimethylcyclohexane shows that the cis isomer contains a plane of symmetry and is achiral. The trans isomer is chiral as it contains no symmetry planes.



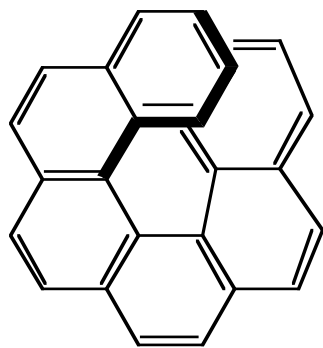
Several other trans-dimethyl-cyclopropane, -cyclobutane, and -cyclopentane chiral rings are shown below. All of the cis isomers are achiral.



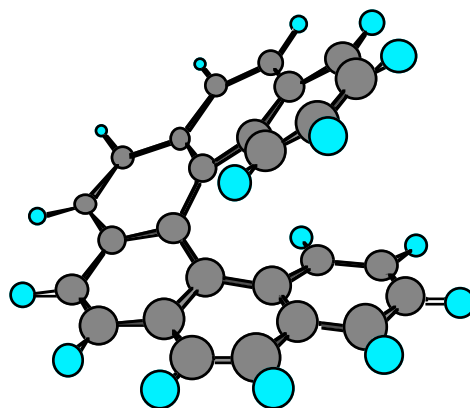
Chiral Systems without Chiral Centers

Ring systems do not have to contain a chiral center to be chiral. Certain molecular distortions cause ring systems to lose their symmetry and show chirality. The

molecule hexahelicene, synthesized by M. S. Newman, is chiral and can be resolved into enantiomers that show optical activity. The chirality in the molecule occurs because the rings are distorted to avoid bumping into each other. The computerized structure on the right shows the shape of the molecule.

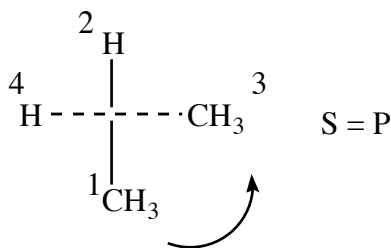
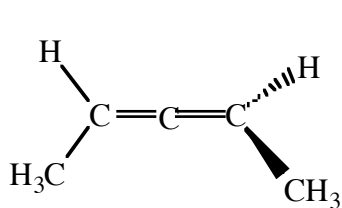


hexahelicene
optically active

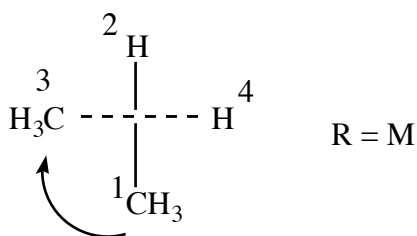
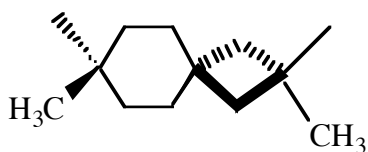


A number of compounds exist that contain two perpendicular planes of which neither has a plane of symmetry. Several examples are shown below.

Allene



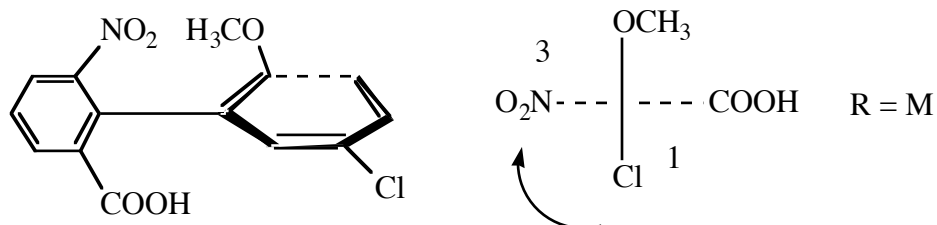
Spiro



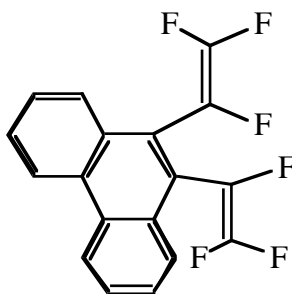
Biraryls compounds contain perpendicular rings because the ortho substituents prevent rotation around the bond joining the rings. The compounds can be made racemic

by heating and the free energy required is in the range of 10 - 50 kcal/mole depending on the substituents. The isomerization caused by restricted rotation of a carbon-carbon bond is called atropisomerism.

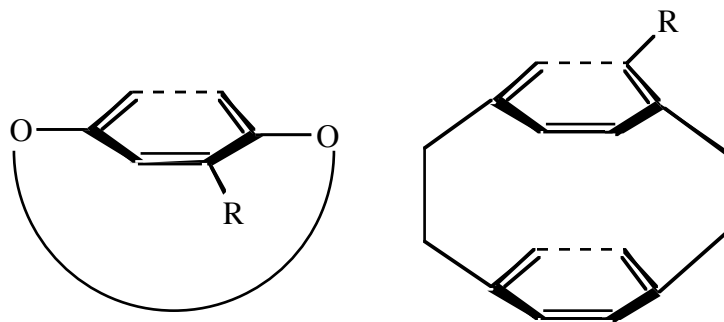
Biphenyl



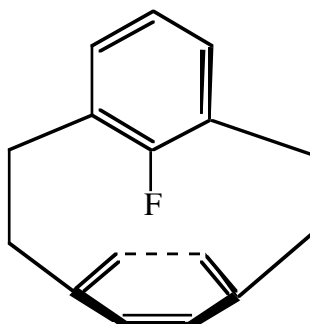
Atropisomerism is also observed in the perfluorovinyl compound below because the close proximity of the vinyl groups restricts free rotation of the groups. Chiral isomers can be isolated and have an energy difference for interconversion of 15.1 kcal / mol.



Restricted rotation in the compounds below also give rise to dissymmetric planes of symmetry, and chiral isomers can be resolved.



The cyclophane below shows much more restricted rotation when the R is a fluorine atom than when the R is a hydrogen atom. Ring flipping in the hydrogen compound occurs 10^{11} times faster than in the fluorine compound. This also shows that F is larger than H.



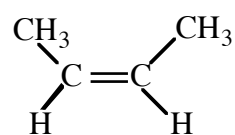
ALKENES ARE DIASTERIOISOMERS.

Cis and trans or EZ isomers of alkenes are stereoisomers. Since they are not mirror images they are diastereoisomers..

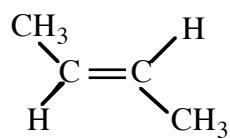
Geometrical Isomers in Alkenes

The p-bond in an alkene does not permit rotation, thus all of the atoms attached directly to the alkene lie in a plane. Groups attached to the alkene could be positioned on the same side of the alkene or on opposite sides of the alkene. Such compounds are different in chemical and physical properties as well as in their geometry, and are called geometrical isomers. In 2-butene the methyl groups can be located on the same side or on the opposite side of the double bond, giving rise to two geometrical isomers.

The isomer with the methyl groups on the same side is called the cis isomer, while the isomer with the groups located on opposite sides is called the trans isomer. Trans isomers of compounds are usually more stable than cis isomers.

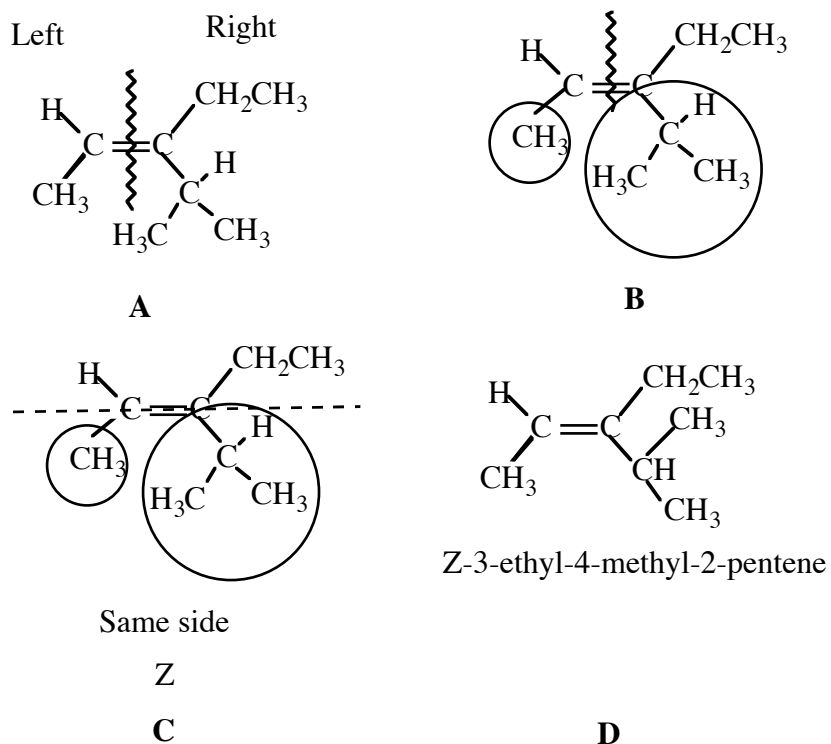


cis- 2-butene



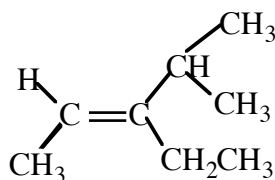
trans- 2-butene

Except for very simple alkenes with hydrogen atoms on each carbon of the alkene, the designations of cis and trans for alkenes are replaced by a system that uses E and Z designations.



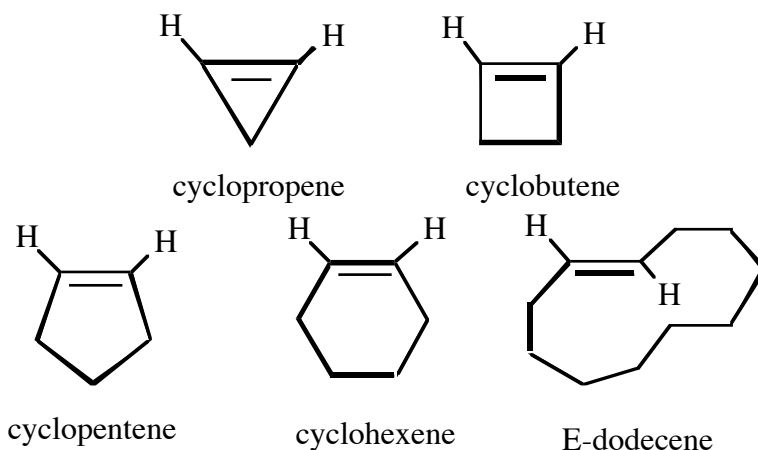
In the E-Z system the geometry is specified by the relative positions of the two **highest priority substituents** on the two carbons of the double bond. The priorities of the substituents are determined by the atomic number with atoms of higher atomic number having higher priority. In the example above, the molecule is divided into left and right sides. The group of higher priority on the left side is determined. The left side has a methyl and a hydrogen attached. The carbon atom of the methyl group has a higher atomic number than hydrogen and is given the higher priority (circled in B). On the right side the two groups are ethyl and isopropyl. The carbon atoms have the same atomic number but the isopropyl group has three carbons attached to the alkene carbon whereas the ethyl group has two carbons attached. Thus the isopropyl group has higher priority (circled in B). Next in structure C a determination is made to locate the two priority groups relative to a horizontal plane. If the two groups are on the same side of the horizontal line then the isomer is designated Z. If the two priority groups were on opposite sides of the horizontal line, the isomer would be designated E. The Z comes

from the German word *zusammen*, meaning same, while the E comes from the German word *entgegen*, meaning opposite. In the final name of the compound the letter designating the geometry, in this case Z, is written preceding the name of the compound (D). The structure of the E isomer is shown below.



E-isomer

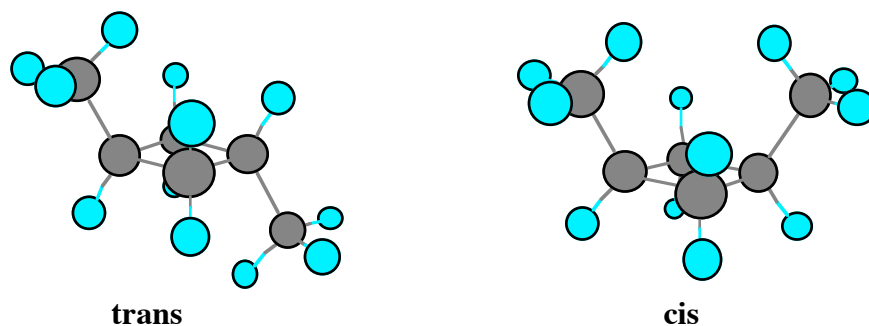
Cyclic alkenes with 3 - 7 atoms in the ring are fixed in the cis or Z structure. A trans or E configuration for a double bond can exist in cyclic compounds but a large ring is necessary or the strain in the compound is very high.



Geometric Isomers in Cyclic Systems

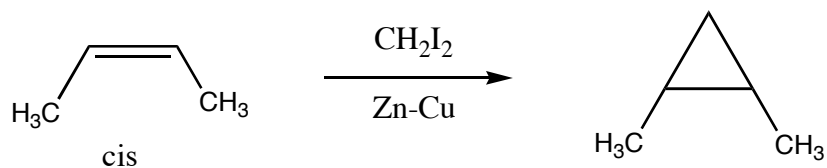
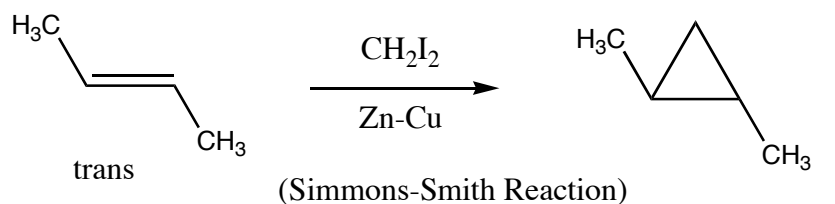
Substituents attached to a ring system will either be on the same side of the ring or on the opposite side of the ring. Thus, cyclic alkenes show cis and trans geometrical isomers. The letters E and Z are not used in cyclic alkenes. The cis and trans isomers of 1,3-dimethylcyclobutane are shown below. .

1,3-dimethylcyclobutane



STEREOSPECIFIC REACTIONS

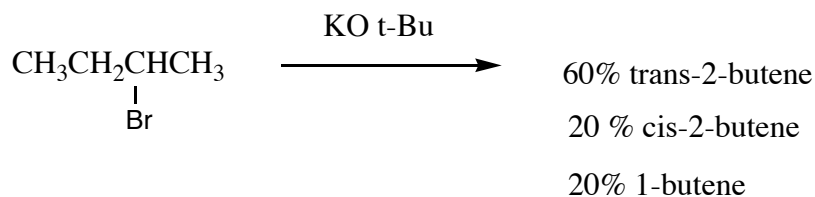
Some reactions give only one stereoisomer as the product. If the reactions starting material has two stereoisomers (such as cis and trans) and each material gives only one stereoisomer as a product of the reaction, then it is called stereospecific. *But both stereoisomeric starting materials must be used in the reaction.* The Simmons Smith reaction shown is a stereospecific reaction.



STEREOSELECTIVE REACTION

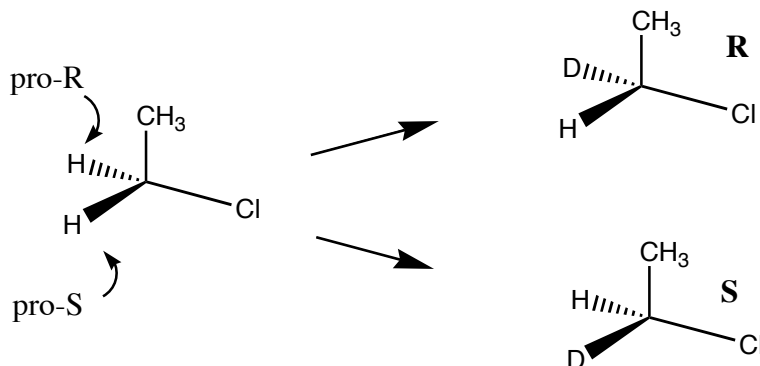
A reaction that has the possibility of forming more than one stereoisomer, but actually forms one isomer more than any other is stereoselective. There does not need to be a comparison with another starting material.

This E2 reaction give more trans than cis, and is stereoselective.

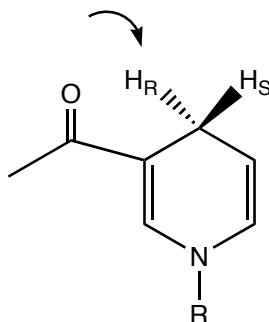


PROCHIRALITY

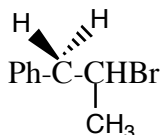
If a compound that is not chiral (achiral) could become chiral by replacement of an atom, then the compound is prochiral. Replacement of the H atoms in the compound below would lead to a chiral R and S mixture. When the H atom is replaced by D and the chiral compound is R, then the H atom is called pro-R. When the H atom is replaced by D and the chiral compound is S, then the H atom is called pro-S. It is a simple matter on paper to change a H to a D and determine the chirality of the new molecule.



When there is only one prochiral center present the attached H atoms are called enantiotropic. They are identical except in their reaction with chiral substances. When NADH is oxidized by enzyme catalysis, only the pro R hydrogen is used.

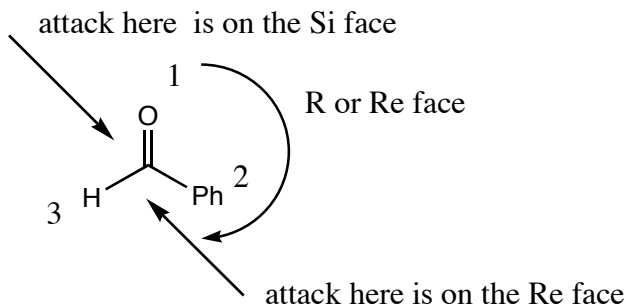


In cases where exchange of a hydrogen would lead to diastereoisomers the hydrogens are called diastereotropic. Diastereotropic hydrogens are different in many ways, but importantly is that they are not equivalent in a ^1H NMR spectrum. Thus in the compound below the methylene protons are not equivalent and thus have different chemical shifts and undergo splitting with each other as well as with the methine hydrogen.



Re and Si faces of a C=O group.

Addition of certain reagent (Grignard, hydride) to a carbonyl group often gives rise to a chiral center. The carbonyl function can be designated as Re (R) or Si (S) by the same rules used for chiral centers (high priority to low priority). Then the carbonyl group is considered have a Re face and a Si face for stereochemical considerations.

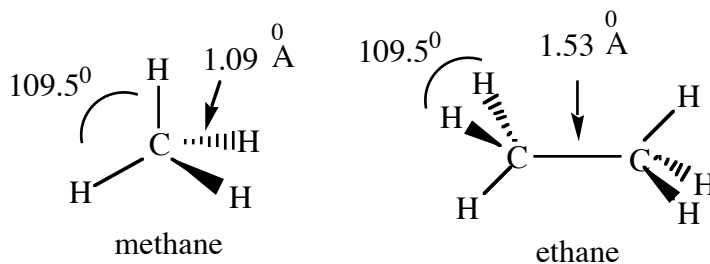


Conformational Isomers

Acyclic Systems (non-cyclic)

Ethane

The atoms attached to an alkane carbon arrange such that they are as far apart from each other as possible. This arrangement causes a tetrahedral shape, and is shown below for methane. The length of the carbon-hydrogen bond is 1.09 Å, and all H-C-H bond angles are 109.5°. Ethane has a C-C bond length of 1.53 Å and the bond angles are all 109.5°.

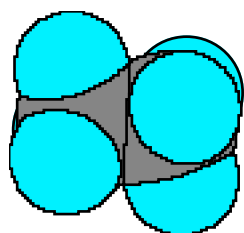


The structures shown for methane and ethane use dotted-line wedge formulae. In this representation the dark bonds are visualized as coming toward the reader, while the dotted lines go away from the reader. The straight bonds are in the plane of the page.

Free rotation around the carbon-carbon bond in ethane leads to many different structures called conformational isomers, or conformers. Two major types of structures occur during the bond rotation: one called eclipsed in which the C-H bonds are directly across from each other, and the other called staggered in which the C-H bonds are lined up between each other. The staggered conformation is more stable by 3 kcal/mol than the

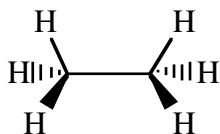
eclipsed one.

The conformations are shown in four different common representations; the sawhorse structure, the dotted-line wedge structure, the Newman projection and a computer generated ball and stick model. Each type of structure allows a different perspective on the molecule. The Newman projection is viewed on a line from the front carbon to the back carbon. The front carbon is not written but is located at the intersection of the three bonds to hydrogen. The big circle represents the back carbon with the three hydrogens tilting back.

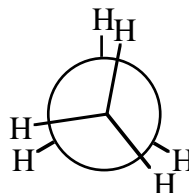


space filling model of staggered ethane

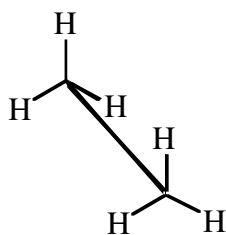
Eclipsed Conformation of Ethane



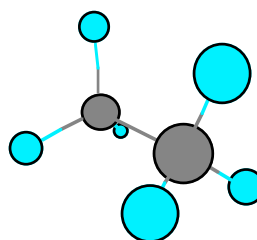
Dotted-line Wedge



Newman

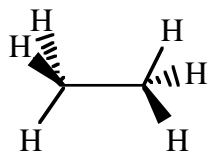


Sawhorse

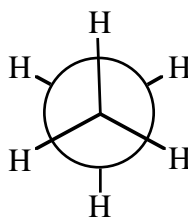


ball and stick

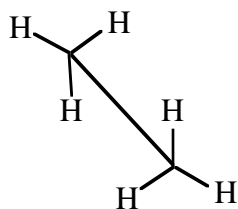
Staggered Conformation of Ethane



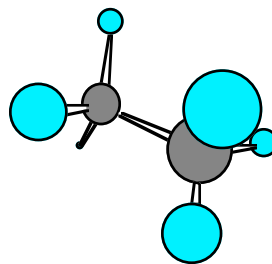
Dotted-line Wedge



Newman



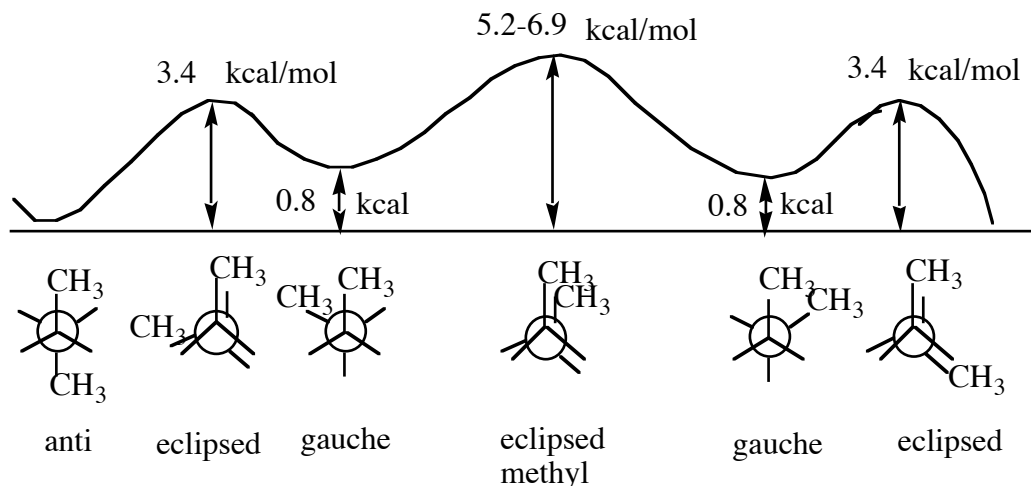
Sawhorse



ball and stick

Butane

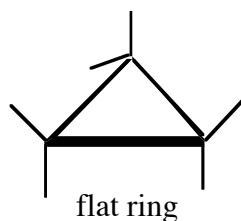
Rotation by 60° of the bond between carbon two and carbon three in butane gives rise to several conformational isomers. The most stable conformation occurs in a staggered structure in which the methyls are opposite each other, called the **anti** conformation. Rotation of the bond in the anti conformation 60° leads to an **eclipsed** conformation. Continued rotation leads to a staggered conformation in which the methyl groups are close to each other, called the **gauche** conformation. Further rotation gives the least stable conformation in which the hydrogens are eclipsed and the methyls are also eclipsed, called the eclipsed methyl conformation. Staggered conformations are always more stable than eclipsed conformations, and structures with crowding of the methyl groups are less stable.



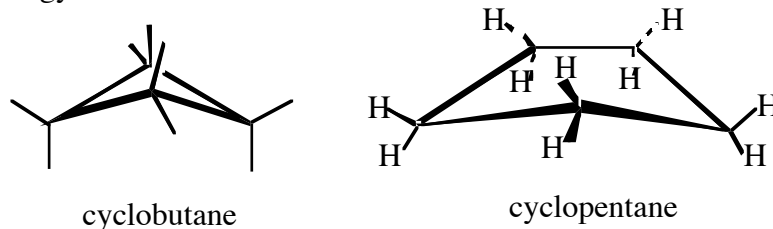
Conformational Isomers in Ring Systems

Cyclopropane, Cyclobutane and Cyclopentane

The three-membered ring in cyclopropane contains bond angles of 60° instead of the normal 109.5° . The large deformation of bond angles results in considerable strain in the molecule. On combustion, molecules with strain in their bond angles produce a higher amount of heat, called strain energy. The strain energy in cyclopropane is about 27 kcal/mol.



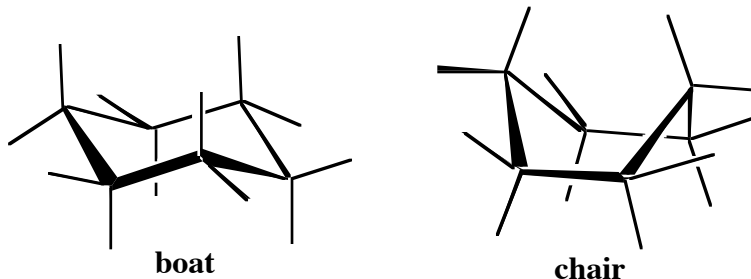
Cyclobutane rings contain a slight pucker and their internal bond angles are 90° . Thus a strain energy of 26 kcal/mol exists in cyclobutane. Cyclopentane has a shape of an envelope and the internal bond angles are 108° . Thus cyclopentane does not contain significant strain energy.



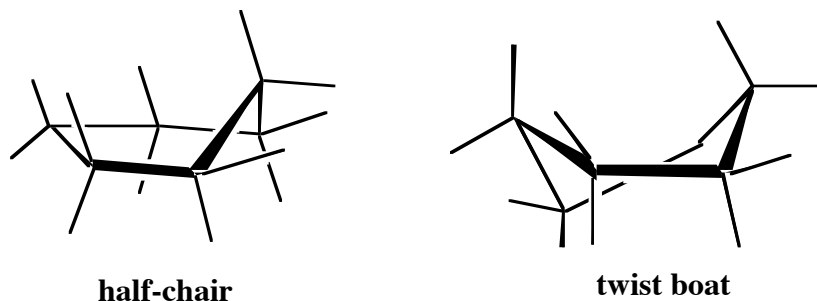
Cyclohexane

The cyclic six membered ring is the most commonly found ring system in organic chemicals. In both nature and in the laboratory, chemical reactions produce six

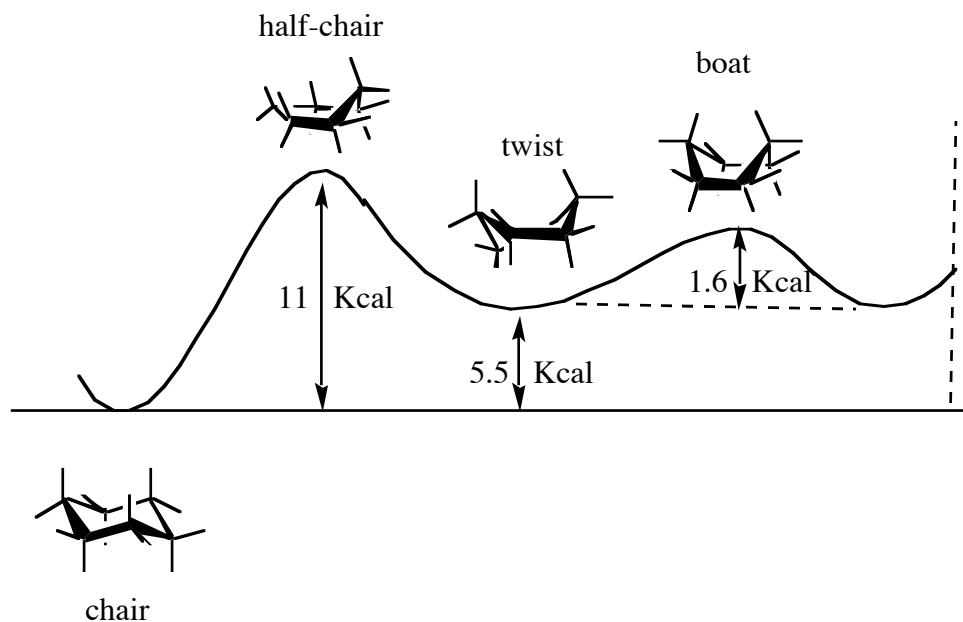
membered rings with ease. Cyclohexane is not strained, and it contains important conformations. The most stable and most important conformation of cyclohexane is the **chair** conformation shown below. An unstable conformation of cyclohexane is the **boat** conformation which is 7.1 kcal/mol higher in energy than the chair form.



The boat and chair conformations are interconvertible by passing through some very unstable high energy structures called the **half-chair** and the **twist-boat** conformations.

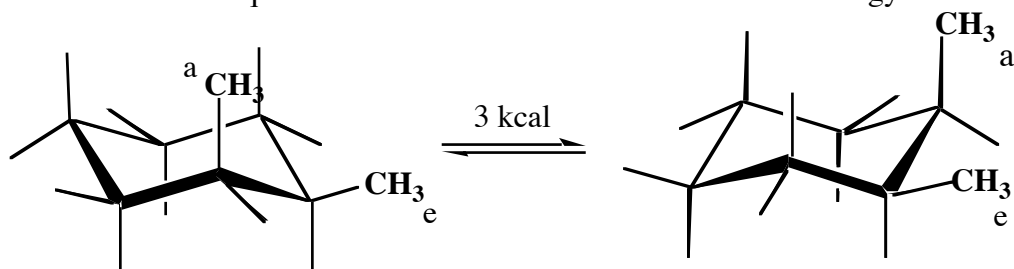


The chair form of cyclohexane is flexible, and may be flipped into other chair forms. The outer bonds, called equatorial bonds, flip into vertical bonds, called axial bonds. Thus in cyclohexane the axial and equatorial bonds interchange when the molecule flips from one chair form to another. A portion of the conformational energy diagram for cyclohexane is shown below. In the completed diagram the final stable structure is another cyclohexane ring with the axial and equatorial substituents interchanged.



When the cyclohexane ring contains substituents, the chair forms that result from the conformational flipping can be of different energy. The more stable **conformational isomer, also called a conformer**, is the one usually with the least crowding of substituents. Equatorial substituents are the least crowded and the more stable structures are the ones that contain more equatorial substituents. Examples with dimethyl cyclohexane isomers show the favored isomer in the equilibrium.

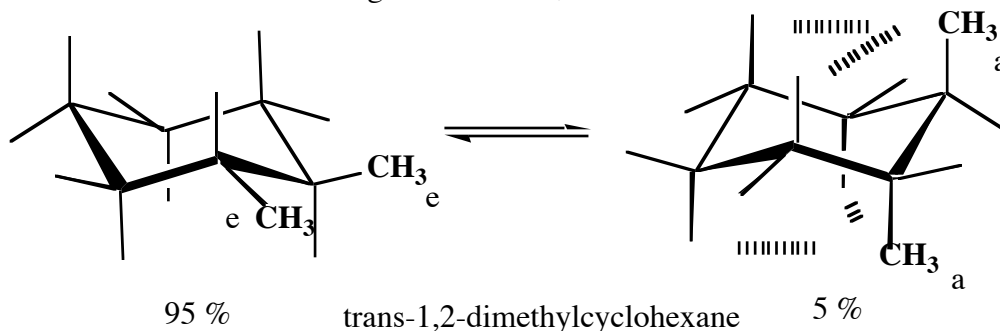
Cis-1,2-dimethylcyclohexane can interconvert to another conformation, but the new conformation is identical with the starting structure because one methyl is axial while the other is equatorial in each structure. Thus there is no energy difference.



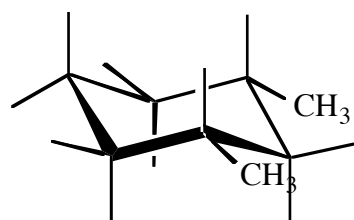
cis-1,2-dimethylcyclohexane

In trans-1,2-dimethylcyclohexane one conformation exists with both methyls equatorial while the other conformer has both methyls axial. The structure with two equatorial methyls is much more stable and represents the major isomer in the equilibrium. The reason for instability in the diaxial isomer is that the methyls become

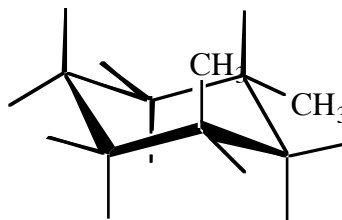
crowded by the hydrogens in other axial positions, as shown by the dotted lines in the diaxial isomer. The crowding is termed a 1,3-diaxial interaction.



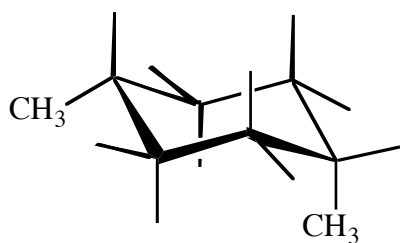
Several other dimethylcyclohexanes are shown below in their more stable conformation. The trans-1,3- and the cis-1,4-dimethyl compounds are the same when they interconvert to the other conformer, thus only one conformer exists.



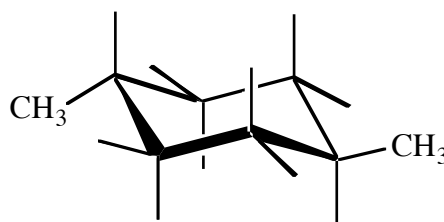
cis-1,3-dimethylcyclohexane
two equatorial methyls



trans-1,3-dimethylcyclohexane
one equatorial and one axial methyl
both conformations are the same



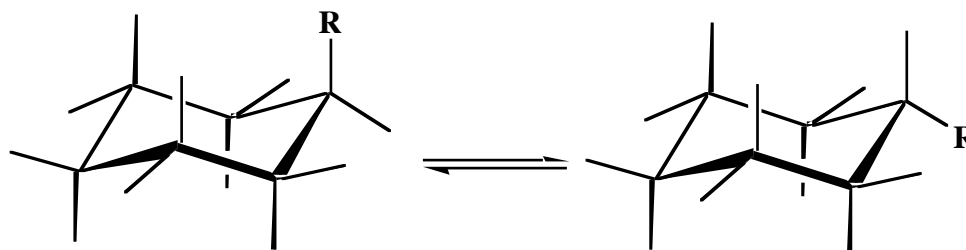
cis-1,4-dimethylcyclohexane
one equatorial and one axial methyl
both conformations are the same



trans-1,4-dimethylcyclohexane
two equatorial methyls

A semiquantitative measure of steric size is given by the A value. The A is

determined from the equilibrium position of the anti-equatorial pair. A is set to equal - ΔG . Thus in a series of similar groups where the cyclohexane to substituent bond lengths are nearly equal and entropy contributions are nearly equal, then the free energy change is attributed to the size of the group. Some A values are listed below.

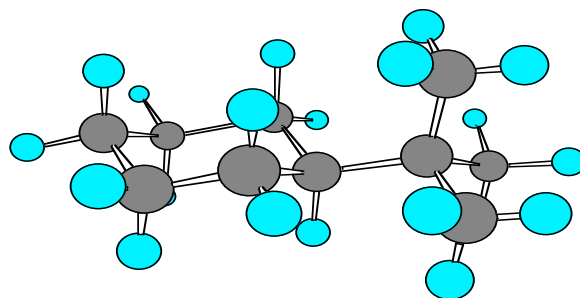


$$A = -\Delta G = RT \ln K$$

| | A | van der Waal | Es | v |
|-------------------------------|-------------|--------------|-------|------|
| OH | 0.6 - 1.0 | 1.52 | +0.69 | |
| F | 0.25 - 0.42 | 1.47 A | +0.78 | |
| H | 0.0 | 1.2 A | +1.24 | |
| CH ₃ | 1.74 | 16.8 | 0.0 | 0.52 |
| Et | 1.8 | | -0.07 | 0.56 |
| Iso-Pr | 2.2 | | -0.47 | 0.76 |
| t-Bu | 4.7 | | -1.24 | 1.24 |
| CF ₃ | 2.4 | 42.6 | -1.16 | 0.91 |
| C ₆ H ₅ | 2.2 | | | |
| OtBu | 0.75 | | | |

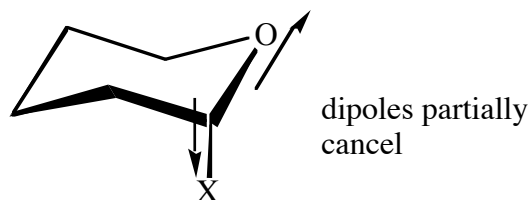
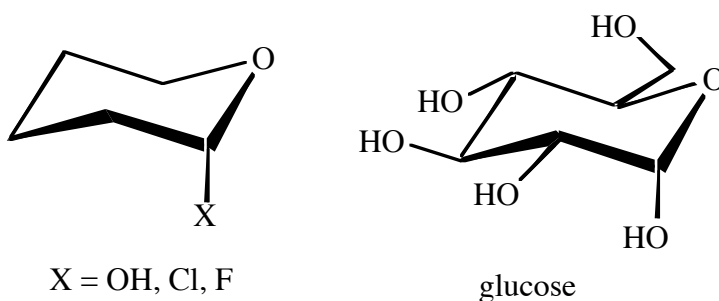
(Es and v from Chambers, Fluorine in Org Chem 2004)

These results contain a value for F that is not representative of the steric size of F. This happens because of the different C-F bond length and contributions from entropy. But for the other substituents we see that CF₃ and iso-Pr are nearly the same and that t-Bu is a very large group. The tert-Bu group is thus confined in cyclohexane to an equatorial position with no ring inversion to the axial isomer.



In some six-membered rings containing oxygen, an alpha substituent, if it is electronegative such as OH, prefers that axial conformation. This is known as the

Anomeric Effect



Anomeric effect and is seen often in carbohydrates such as glucose. The exact reason for this effect is uncertain, but it seems that the dipoles of the electronegative atoms are partially neutralized when the substituent is axial.

When two 1,3 oxygen atoms are present in a six-membered ring substituents in the 5 position often prefer the axial conformation as the 1,3-diaxial repulsions are not present.

