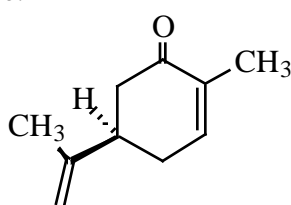


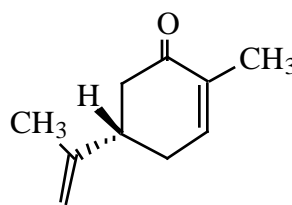
CHAPTER 3

STEREOCHEMISTRY

Many properties of organic compounds are associated with the shape of the molecule. The "two" compounds below are isomers of Carvone, with different orientations of the isopropenyl function. One isomer (the S isomer) has the smell of spearmint whereas the other isomer (the R isomer) has the smell of caraway. The smells are a result of the way the isomers interact with receptors to send signals to the brain. Many reactions, both chemical and biological, show effects of molecular shape.



R-Carvone
Spearmint

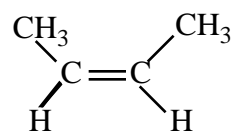


S-Carvone
Caraway

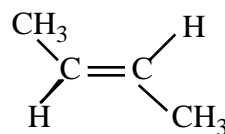
3.1 Geometrical Isomers in Alkenes

The π -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.

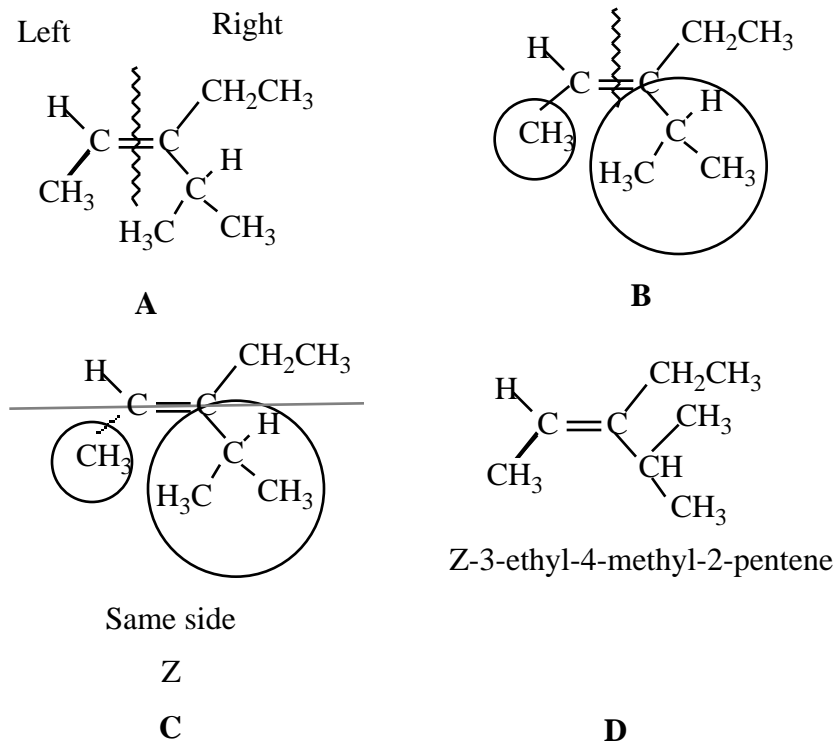


cis- 2-butene



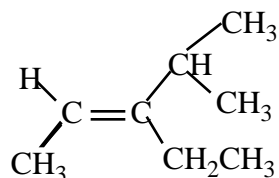
trans- 2-butene

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



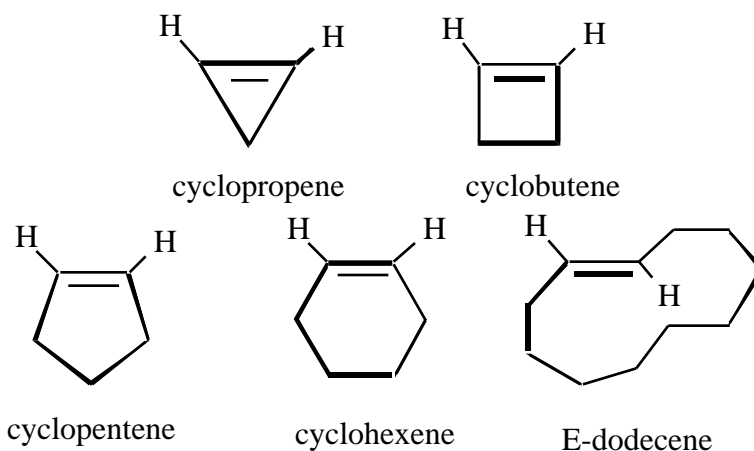
In the E-Z system the geometry is specified by the relative positions of the two **highest priority substituents** on the two carbons of the double bond. The priorities of the substituents are determined by the atomic number with atoms of higher atomic number having higher priority. In the example above, 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.



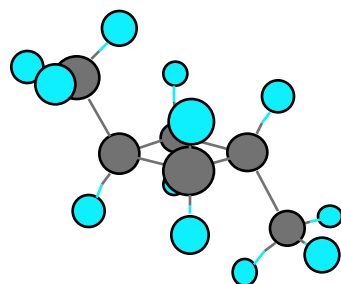
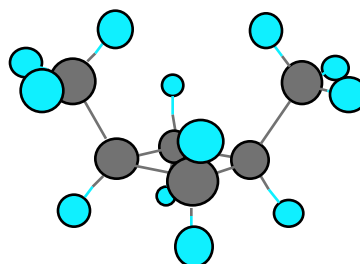
E-isomer

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.

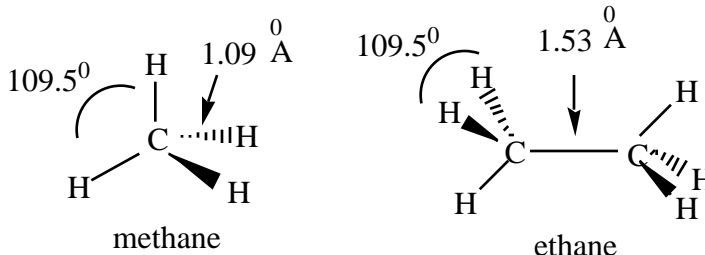


3.2 Geometric Isomers in Cyclic Systems

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 alkanes show cis and trans geometrical isomers. The letters E and Z are not used in cyclic alkanes. The cis and trans isomers of 1,3-dimethylcyclobutane are shown below. .

1,3-dimethylcyclobutane**trans****cis****3.3 Conformational Isomers****3.3a Acyclic Systems (noncyclic)****Ethane**

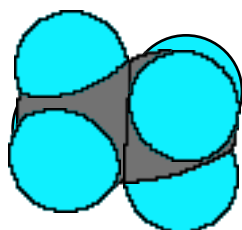
The atoms attached to an alkane carbon arrange such that they are as far apart from each other as possible. This arrangement causes a tetrahedral shape, and is shown below for methane. The length of the carbon-hydrogen bond is 1.09 \AA , and all H-C-H bond angles are 109.5° . Ethane has a C-C bond length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

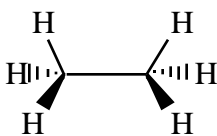
Free rotation around the carbon-carbon bond in ethane leads to many different structures called conformational isomers, or conformers. Two major types of structures occur during the bond rotation: one called eclipsed in which the C-H bonds are directly across from each other, and the other called staggered 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.

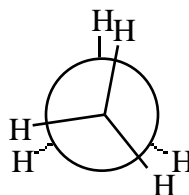


space filling model of
staggered ethane

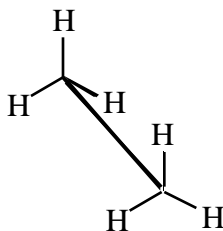
Eclipsed Conformation of Ethane



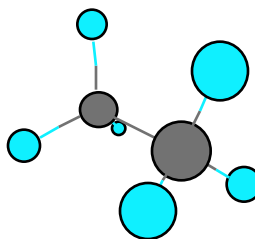
Dotted-line Wedge



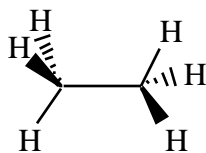
Newman



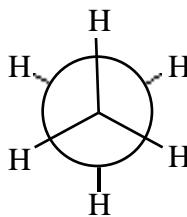
Sawhorse
Staggered Conformation of Ethane



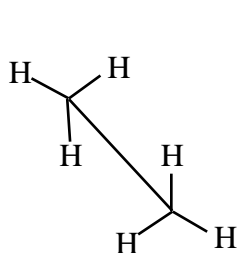
ball and stick



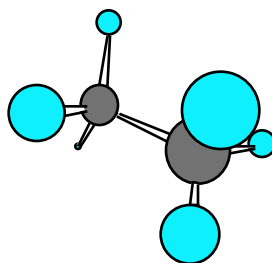
Dotted-line Wedge



Newman



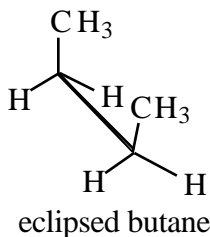
Sawhorse



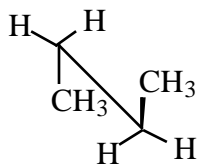
ball and stick

Butane

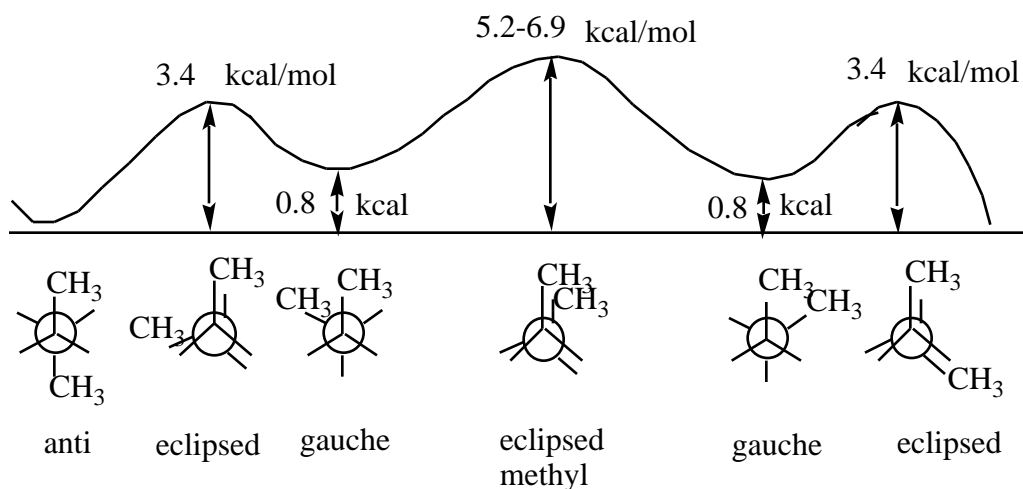
Rotation by 60° of the bond between carbon two and carbon three in butane gives rise to several conformational isomers. The most stable conformation occurs in a staggered structure in which the methyls are opposite each other, called the **anti** conformation. Rotation of the bond in the anti conformation 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.



eclipsed butane



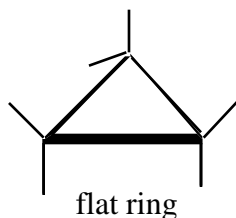
anti butane



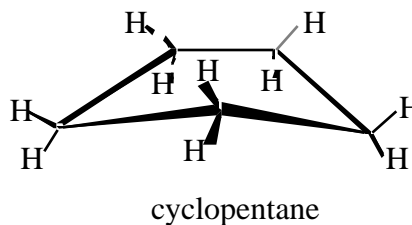
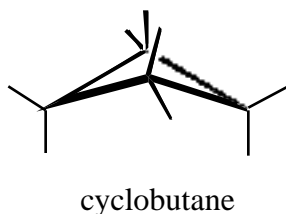
3.3b Conformational Isomers in Ring Systems

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.

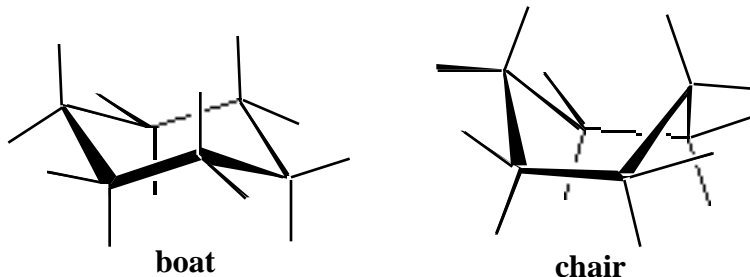


Cyclobutane rings contain a slight pucker and their internal bond angles are 90° . Thus a strain energy of 26 kcal/mol exists in cyclobutane. Cyclopentane has a shape of an envelope and the internal bond angles are 108° . Thus cyclopentane does not contain significant strain energy.

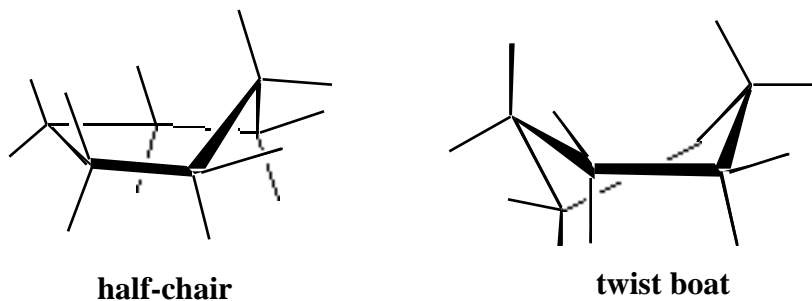


Cyclohexane

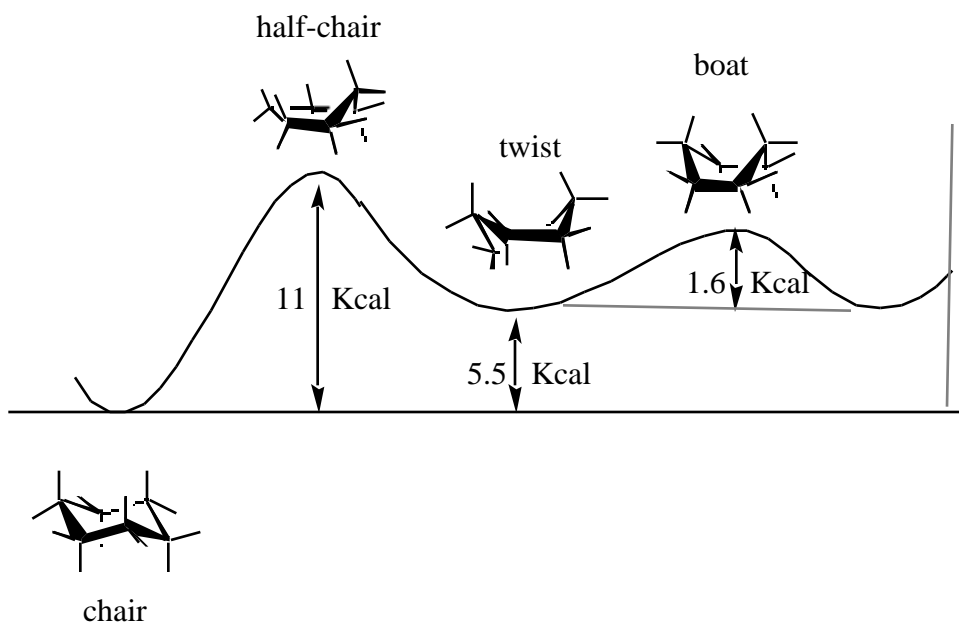
The cyclic six membered ring is the most commonly found ring system in organic chemicals. In both nature and in the laboratory, chemical reactions produce six membered rings with ease. Cyclohexane is not strained, and it contains important conformations. The most stable and most important conformation 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.

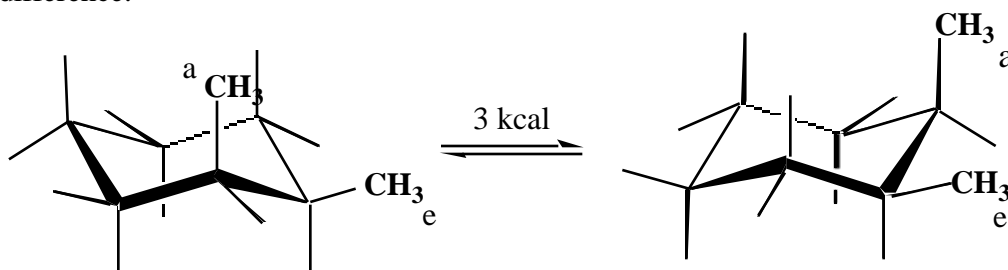


The chair form of cyclohexane is flexible, and may be flipped into other chair forms. The outer bonds, called equatorial bonds, flip into vertical bonds, called axial bonds. Thus in cyclohexane the axial and equatorial bonds interchange when the molecule flips from one chair form to another. A portion 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.

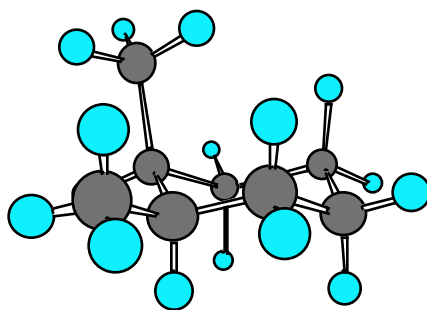


When the cyclohexane ring contains substituents, the chair forms that result from the conformational flipping can be of different energy. The more stable **conformational isomer, also called a conformer**, is the one usually with the least crowding of substituents. Equatorial substituents are the least 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.

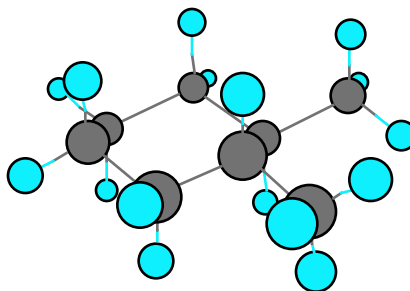
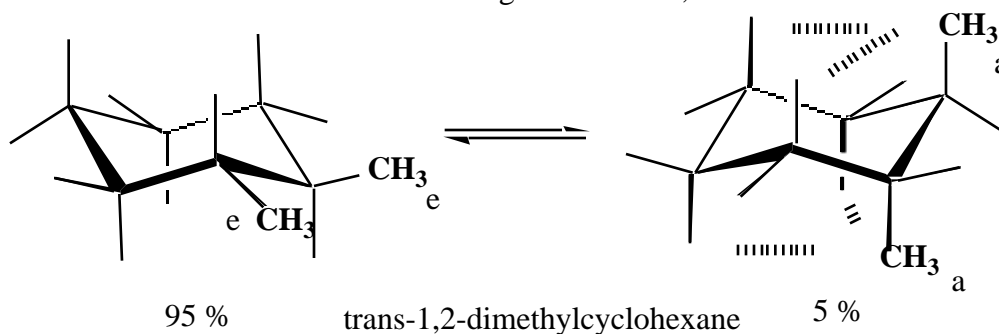
Cis-1,2-dimethylcyclohexane can interconvert to another conformation, but the new conformation is identical with the starting structure because one methyl is axial while the other is equatorial in each structure. Thus there is no energy difference.



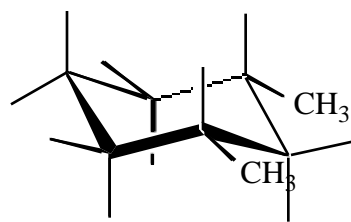
cis-1,2-dimethylcyclohexane



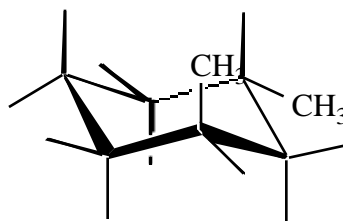
In trans-1,2-dimethylcyclohexane one conformation exists with both methyls equatorial while the other conformer has both methyls axial. The structure with two equatorial methyls is much more stable and represents the major isomer in the equilibrium. The reason for instability in the diaxial isomer is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



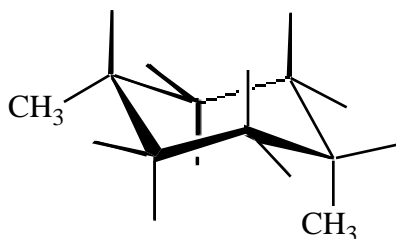
Several other dimethylcyclohexanes are shown below in their more stable conformation. The trans-1,3- and the cis-1,4-dimethyl compounds are the same when they interconvert to the other conformer, thus only one conformer exists.



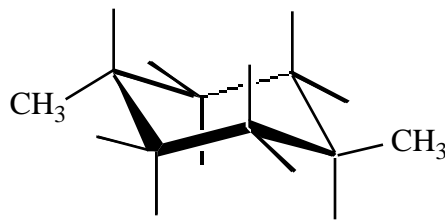
cis-1,3-dimethylcyclohexane
two equatorial methyls



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

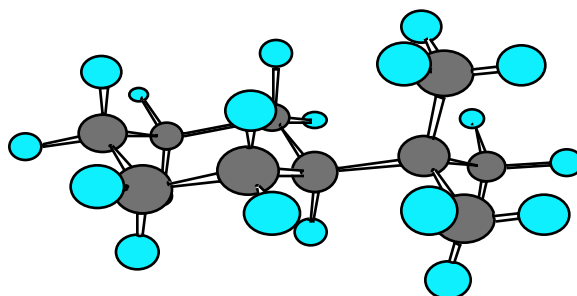


cis-1,4-dimethylcyclohexane
one equatorial and one axial methyl
both conformations are the same



trans-1,4-dimethylcyclohexane
two equatorial methyls

Tertiary-butyl groups are especially bulky and can only exist in the equatorial position as shown the model below.

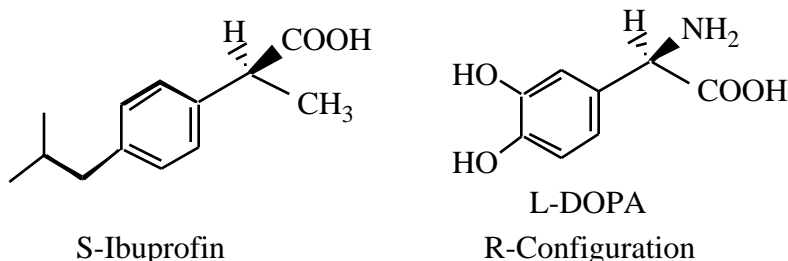


3.4 Configurational Isomers

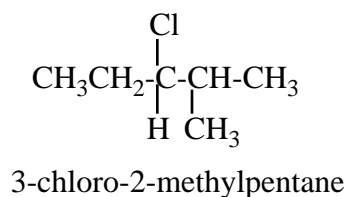
3.4a Chirality

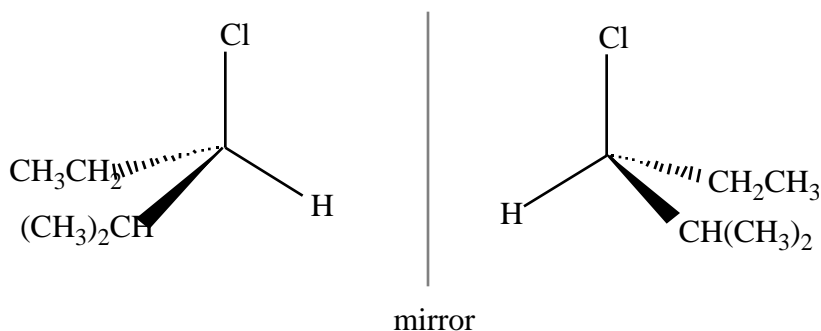
Another type of isomerization occurs when a carbon atom is bound to four different substituents. This is called configurational isomerism. Configurational isomers have as their only difference the way they are oriented in space, their three-dimensional arrangement. Although configurational isomers can 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. (A method for designating configurations is based on carbohydrate chemistry and uses D and L notations referring to the configuration of hydroxyl groups in glyceraldehyde. The details are given in the carbohydrate chapter.)



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.





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.

3.4b Optical Activity

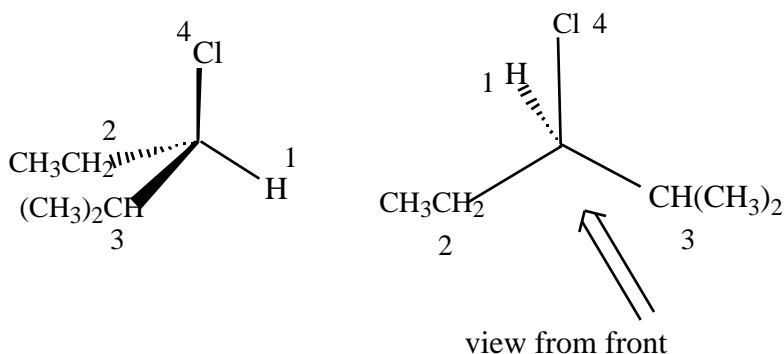
A pure chiral compound, not a mixture of enantiomers, will interact with plane polarized light and cause the plane to rotate to the right (dextrorotatory) or to the left (levorotatory). An equal mixture of enantiomers will not show optical activity because half of the molecules would rotate light to 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.

3.4c Naming Configurational Isomers

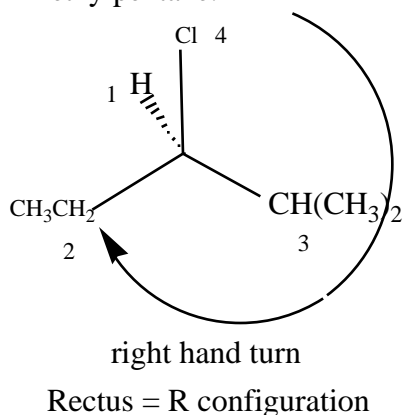
Configurational isomers contain carbon atoms with four different substituents. The carbon atoms are called **stereogenic centers or chiral centers**. A naming system has been devised so that we can distinguish one enantiomer from the other based on the orientation of those substituents.

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. 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 CH_2 while the isopropyl has two carbons (methyls) attached to the CH . Thus the isopropyl group gets the higher priority. After the priorities are assigned, the molecule must be oriented with the lowest priority group pointing away from the observer.



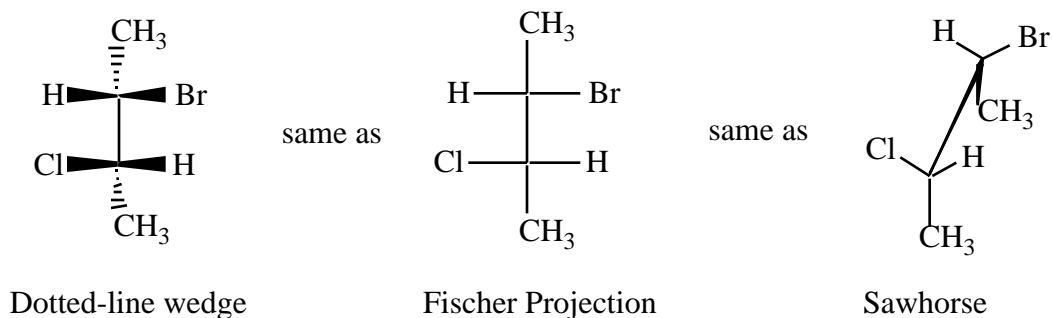
After getting the correct view, draw a circle from priority 4 to 3 to 2. If this circle makes a right hand turn then the configuration is called R. The R comes from the Latin word **rectus**, meaning right. If we draw a circle with a left turn then the configuration is S, meaning left which in Latin 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.



3.4d More than One 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

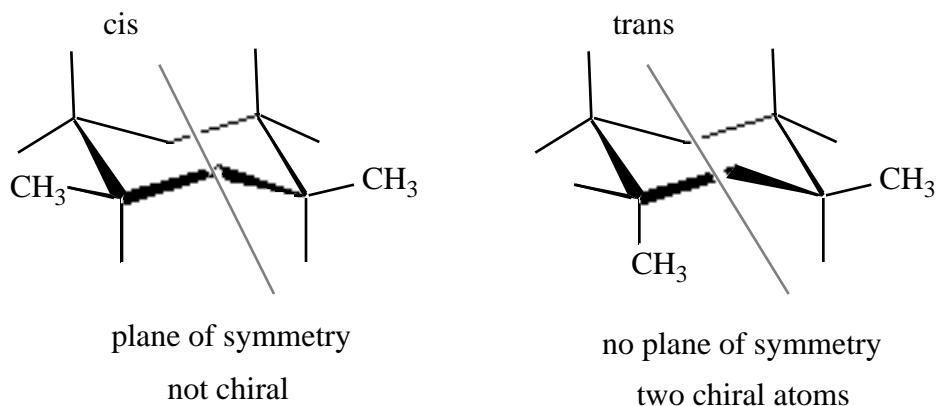
structure is the Fischer projection. In the Fischer projection all of the vertical lines go back into the paper and the horizontal bonds come out toward you. You have to remember this method because the structure looks flat. Also the only kind of change you can do to the structure is a rotation of 180° . 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

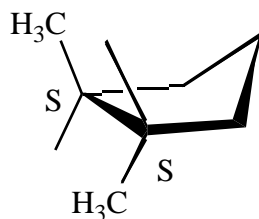
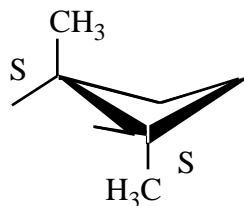
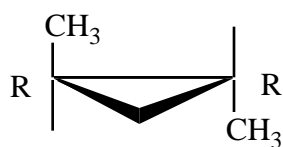
3.4e Chirality in Cyclic Systems

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.



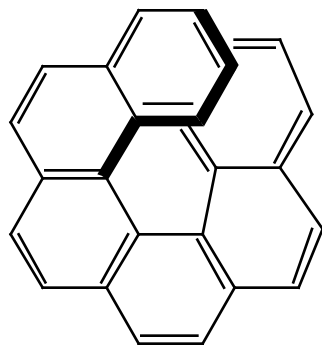
Several other trans-dimethyl-cyclopropane, -cyclobutane, and-cyclopentane chiral rings are shown below. All of the cis isomers are achiral.

two chiral atoms

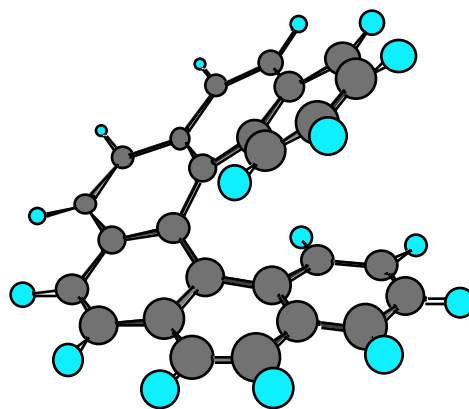


no plane of symmetry

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



3.5 Summary

The geometrical shape of organic substances the stereochemistry, determines many chemical, physical and biochemical properties of the compounds. The types of stereochemical situations are divided into classes called *geometrical isomers*, *conformational isomers* and *configurational isomers*. All of the isomers are studied as a way to understand the shapes and properties of organic compounds.

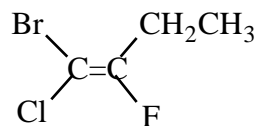
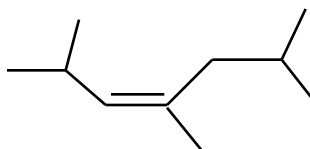
Alkenes and cyclic compounds display *geometrical isomers*. In alkenes, geometrical isomers are labeled as *cis* or *trans* for the longest chain in the alkene, or as *E* and *Z* for substituents of higher priority attached to the alkene. Cyclic alkanes are designated only as *cis* or *trans*.

Rotation around bonds in alkane structures, exemplified in ethane and butane, gives rise to *conformational isomers*. Conformational isomers are drawn with the aid of *dotted-line wedge*, *sawhorse*, and *Newsman projections*, and they are analyzed for internal destabilizing steric interactions. *Anti* conformations are usually the more stable with *gauche* and *eclipsed structures* of higher energy. Analysis of cyclohexane derivatives pays attention to substituents in *axial* and *equatorial positions*, with equatorial substituents being more stable. Cyclohexane interconversions between *chair* forms involve higher energy structures known as *boat*, *twist* and *half-chair structures* that are unstable.

Chiral molecules result from an organic structure *not having a plane of symmetry*. The easiest type of chiral molecule to identify is one with a stereogenic center; *four different substituents on a tetrahedral carbon atom*, but other types of asymmetry are possible. Chiral compounds exist as *enantiomers* that, when obtained free of each other, show a property called *optical activity*. Each enantiomer shows equal *optical rotation* but have opposite signs, and they react differently with other chiral molecules. Compounds with more than one chiral center show both *enantiomers* and *diastereomers*. Diastereomers have completely different chemical and physical properties. Stereogenic carbons are identified in the *Cahn-Ingold-Prelog* system as *R* or *S configurational isomers*. In this system the atoms attached to the stereogenic center are arranged in a priority order based on atomic weight. After proper orientation of the molecule to the viewer, the *R* or *S* designation can be determined. Enantiomers always have one structure of *R* configuration and the mirror image of *S* configuration.

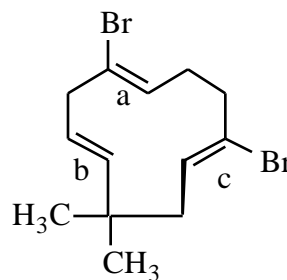
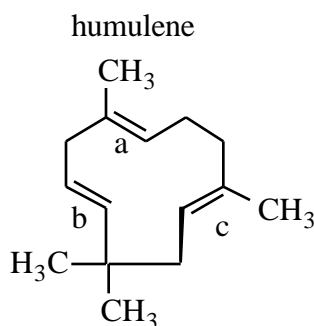
3.6 Problem Set

3.1 Name the two alkenes below and show the alkene configuration by a) cis-trans rules and b) E, Z rules.



3.2 Draw structures for trans-1,3-dibromo- and trans-1,4-dibromocyclohexane and examine the axial-equatorial relationships of the bromine atoms.

3.3 Humulene is a triene found in hops. Label bonds a, b, and c by both cis-trans and EZ rules. If two methyl groups are replaced by Br atoms then the compound on the right occurs. Label the a, b, and c bonds in the dibromo compound also by cis-trans and EZ rules. How did the Br affect the nomenclature?



3.4 Draw structures for a) cis-1-tert-butyl-4-methylcyclohexane and b) cis-1,4-di-tert-butylcyclohexane and determine the structural changes.

3.5 a) Draw Newman projections for the staggered conformations of 1-fluoro-2-chloroethane. b) Draw Newman projections for all of the conformations of 1,2-dichloroethane.

3.6 Draw the structure for the more stable conformation of

a) isopropylcyclohexane

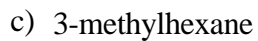
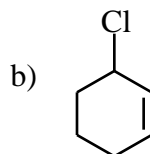
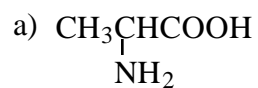
b) cis-1,2-dimethylcyclohexane

c) 1-fluoro-1-bromocyclohexane

d) trans-1,2-dichlorocyclohexane

3.7 Identify the stereogenic center in each compound below and draw with a dotted-

line wedge structure the R isomer.



3.8 The compounds below are all well-know compounds with important biological activity. The S enantiomer is the active substance in each case. Draw the S isomer for each compound.

