4a. Alkanes. Conformational Stereoisomerism. Structural Isomerism.

4a.1 Derivatives of methane.

We can replace one of the H atoms in methane with another atom or group. These atoms or groups are called *heteroatoms*. Examples: Methyl bromide, methyl iodide, methanol, methylamine, methanethiol. Here the central C atom is not quite as perfectly tetrahedral, but for our purposes, it is close enough.

If the H atom is replaced with nothing, we have three possibilities.

- We can remove just the H nucleus and leave behind two electrons -- this gives CH_3^-, with sp^3 hybridization. It has the same structure as ammonia, just one fewer proton (and neutron) in the nucleus in the center.
- We can take away the H nucleus and both electrons. This gives us CH_3^+. The hybridization here? We don't want to waste valuable low-energy s orbital in a hybrid orbital in which there are no electrons. Instead, the valuable s electron is divided equally among the six electrons (three bonds) remaining. Three bonds means three orbitals, one s and two p. That means the third p orbital remains unhybridized. This situation is called sp^2 hybridization. Two p orbitals occupy a plane, so in sp^2 hybridization, the three hybrid orbitals are coplanar. They point 120° apart, to the corners of a triangle. The unhybridized p orbital is perpendicular to this plane.
- What if we take away the H nucleus and *one* electron? We have a situation in which $CH_3\cdot$ (methyl radical) is between sp^2 and sp^3 hybridization. It's a shallow pyramid.

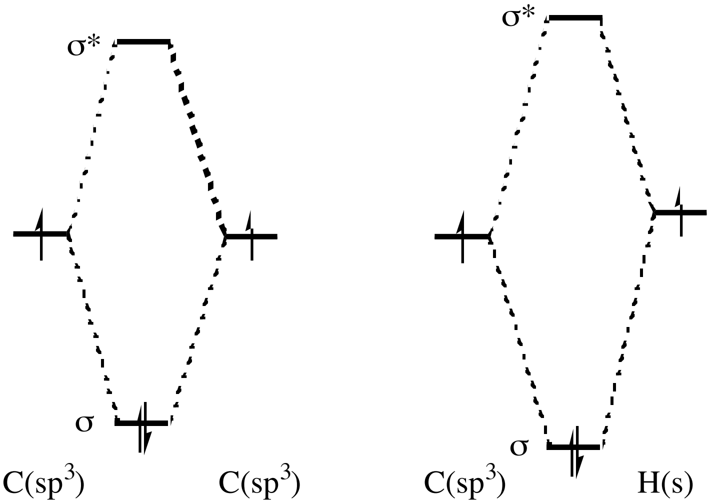
These species are high in energy and don't exist for long.

The word "methyl" also refers to a CH_3– group that is attached to the rest of a molecule. In general, the root "meth-" means "a one-carbon group". The abbreviation Me is often used for CH_3. So MeI is the same as CH_3I.

4a.2 Ethane.

If we replace one of the H atoms in ethane with another CH_3 group, we get a compound that might be called methylmethane, but we call it *ethane*. In ethane, $H_3C–CH_3$, each C atom has four different groups attached, so each one is sp^3-hybridized. Each C-H bond is formed by overlap of a $C(sp^3)$ orbital with a H(s) orbital. The C-C bond is formed by the overlap of a

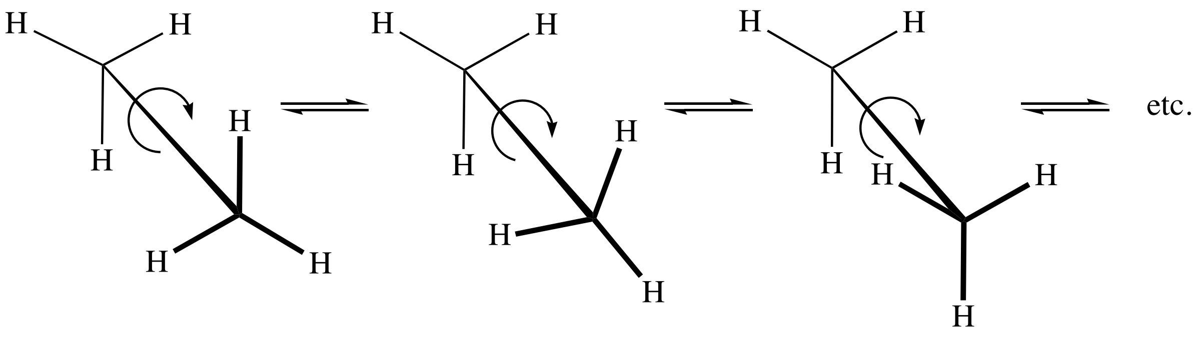
$C(sp^3)$ orbital from each atom. All of these bonds are σ bonds. A σ bond has cylindrical symmetry; if you look down the axis of the bond, it looks like a circle. As you'll see in a bit, not all bonds have that property. We can draw overlap diagrams for C–H and C–C bonds like the one we did for H–H, except, since the two constituent atomic orbitals of the C–H bond have slightly different energies, the diagram for this bond will be slightly lopsided. (A parallelapiped instead of a rhombus.) As in H_2, anti-bonding σ* orbitals are formed along with the bonding σ orbitals. Anti-bonding orbitals are denoted by an asterisk.



It's too much trouble to draw an orbital diagram. Instead, we tend to use just lines to indicate bonds. In the case of ethane, though, even that's a lot (seven bonds). So we use a *condensed* structure, CH_3–CH_3, in which only the most important bond, the C–C bond, is shown.

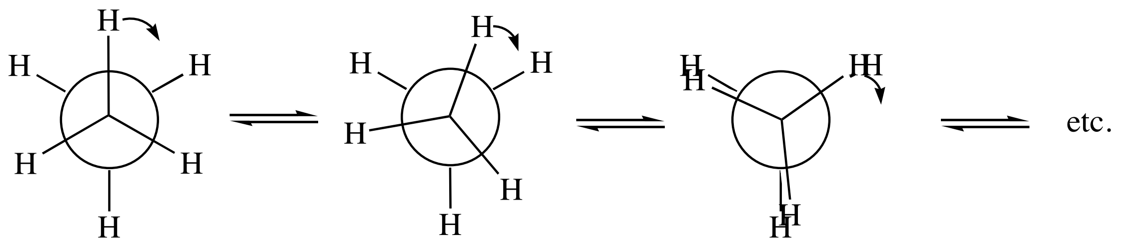
4a.3 Conformational stereoisomers of ethane.

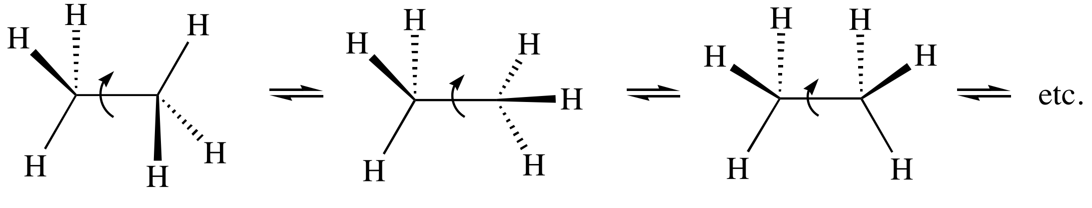
Let's take a closer look at ethane. The C–C σ bond in ethane has cylindrical symmetry, so we can rotate the two CH_3 groups with respect to one another without changing the amount of overlap between the two sp^3 orbitals making up the σ bond. As a result, the rotation is very facile and very fast. This is most obvious if you make a model of ethane.



The three structures above have the same atoms attached to the same atoms, but the shapes of the compounds are different. As a result, they are *stereoisomers*. These particular stereoisomers can be interconverted simply by rotating about σ bonds, so they are called *conformational stereoisomers,* or *conformers* for short. Because the internal dimensions (dihedral angles, H–H distances) of the three conformers above are different, they are *conformational diastereomers*. Conformers usually interconvert so rapidly that they can't be separated from each other. This phenomenon is called *free rotation*.

There are three common ways of drawing different conformers. The *sawhorse projection* is the one that I used above. We call it "sawhorse" because that's what it looks like. Another way of drawing conformers is called the *Newman projection*. In this projection, we look directly down the axis of the C–C σ bond, which is represented as a circle. We can see the proximal C atom, but the distal C atom is obscured by the circle of the σ bond. The bonds to the proximal C atom are fully visible, but the bonds to the distal C atom are partly obscured. The three ethane conformers drawn above are redrawn below as Newman projections. We can also use *perspective drawings* with the wedged/ hashed line formalism to indicate different conformations. These are also shown below.





Problem for home. (1) Draw all eclipsed and staggered conformations of 1-bromo-2-chloroethane. Which of these are stereoisomeric to one another? Which are identical?

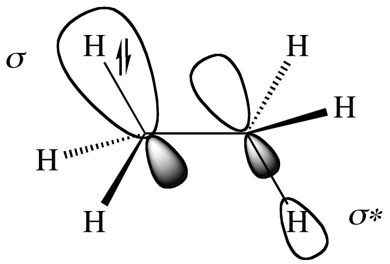
Because the different conformers of ethane are diastereomeric, we can expect that some of them are higher in energy (less stable) than others. This is in fact the case. The first and third conformers that I drew are called the *staggered* and *eclipsed* conformations of ethane. The terms refer to the mutual arrangements of the C–H bonds. The eclipsed conformer is illustrated most dramatically by the Newman projection. The eclipsed conformation is higher in energy than the staggered conformation. The actual difference in energy is 2.9 kcal/mol (12 kJ/mol), which is a small but measurable amount. (At room temperature, every 1.35 kcal/mol difference in energy means a 10-fold difference in ratio.) So rotation about the C–C σ bond is not perfectly free, but passes through an energy barrier of 2.9 kcal/mol every time it passes through the eclipsed conformation. We can draw a graph of energy versus the *dihedral angle* between two C–H bonds. (The dihedral angle of W–X–Y–Z is the angle that we see when we line X and Y up so that one is laying on top of the other, as in a Newman projection. More formally, it is the angle between the line defined by W and X and the plane defined by X, Y, and Z.)

A number of points can be made regarding this graph. First of all, note that the eclipsed conformers represent energy *maxima*. A molecule in the eclipsed conformation is at unstable equilibrium, and it will not remain there for more than one molecular vibration. As a result we say that eclipsed conformers are *transition states* for the interconversion of the staggered conformers.

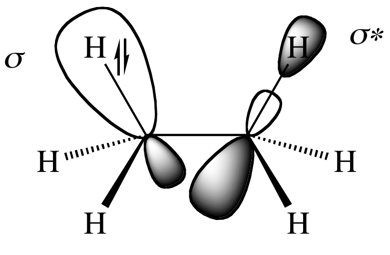
There are two reasons usually given for why the staggered conformer has lower energy.

1. The C–H bonds consist of electrons, and electrons repel one another, so the eclipsed conformation, where the C–H bonds are all aligned, experiences a greater amount of electronic repulsion than the staggered conformation.

2. In the staggered conformation, the orbitals of each C–H bond that contain the bonding electrons overlap better with the antibonding σ* orbital of the staggered C–H bond. This *hyperconjugative* interaction helps to delocalize the electrons, lowering their energy. The interaction is better in the staggered conformer, because the big lobe of the σ orbital overlaps with the big lobe of the σ* orbital. In the eclipsed conformer, the big lobe of the σ orbital overlaps with the small lobe of the σ* orbital.

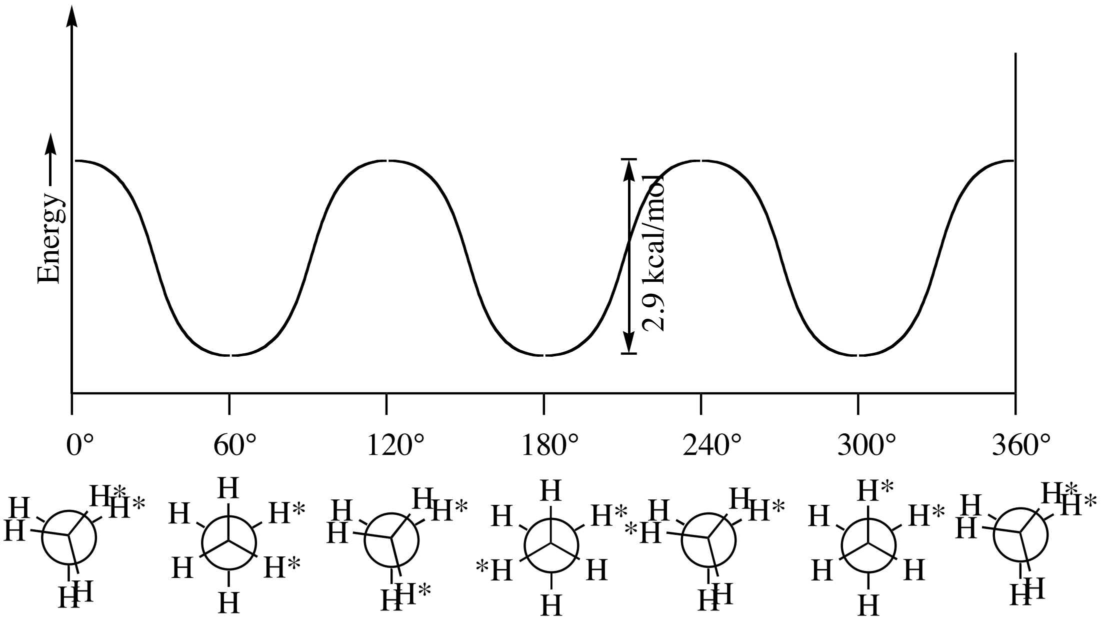


good overlap



poorer overlap

Because there are three eclipsing interactions in each eclipsed conformer, we can divide up the total energy of the eclipsed conformer, 2.9 kcal/mol, into 1.0 kcal/mol for each C–H/ C–H stabilizing interaction. The lack of stabilization in the eclipsed conformer of ethane is called *torsional strain*. We will see soon that there are other kinds of strain that can lead a particular molecule or conformer to have higher than expected energy.



4a.4 Derivatives of ethane.

We can make derivatives of ethane by replacing the H atoms in ethane. If just one of the H atoms in ethane is replaced by a different group, then the C_2H_5 group is called an *ethyl* group. So C_2H_5OH is called *ethyl alcohol*, C_2H_5Cl is called *ethyl chloride*, etc. Another way of naming these compounds is to call them derivatives of ethane. So C_2H_5Br is ethane, but with one bromine replacing a H, so we call it *bromoethane*. By this logic, we might call C_2H_5OH

hydroxyethane. However, the OH group is so important that it is given its own suffix, -ol (as in alcohol). So ethane with one H replaced by the OH group is called *ethanol*.

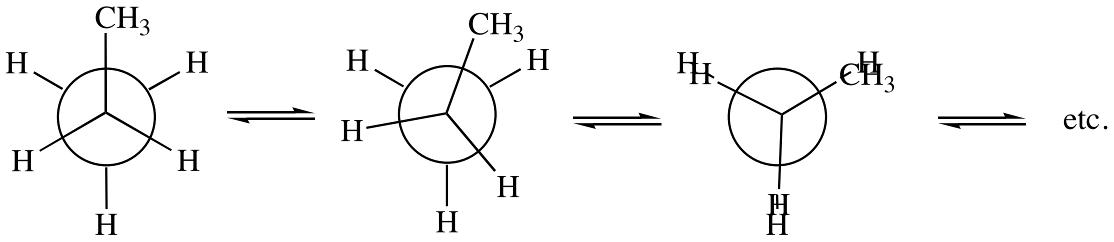
The word "ethyl" also refers to a CH_3– group that is attached to the rest of a molecule. In general, the root "eth-" means "a two-carbon group" (with associated H atoms). The abbreviation Et is often used for CH_3CH_2. So EtOH is the same as CH_3CH_2OH.

Problem for class. What is CH_3OH called?

4a.5 Propane & its derivatives. Skeletal isomerism.

Higher alkanes can be made by replacing more H atoms. Replace one of the H atoms of ethane (it doesn't matter which, they're all equivalent) with another CH_3 group. We now have a three-carbon compound, *propane*.

If we look down one of the C–C bonds of propane, we see that we can have different conformers. There is one kind of staggered conformer, and one kind of eclipsed conformer. The barrier to rotation about the C–C bonds in propane is 3.4 kcal/mol, which is higher than the barrier for ethane (2.9 kcal/mol). The reason is that C is slightly more electronegative than H (2.5 vs. 2.1 on the Pauling scale), so the C–C σ* orbital is slightly lower in energy than the C–H σ* orbital, so the hyperconjugative interaction between the C–H σ bond and the C–C σ* orbital in staggered propane is slightly more favorable than that between the C–H σ bond and the C–H σ* orbital (1.5 kcal/mol vs. 1.0 kcal/mol).



Propane has a property that is not present in ethane or methane. There are two different kinds of C atoms in propane, and there are two different kinds of H atoms. The terminal CH_3 groups in propane (which are indistinguishable, or *equivalent*) are called methyl groups, and the middle CH_2 group is called a *methylene* group. The H atoms on the CH_3 groups are called *primary* (1°), and the H atoms on the methylene group are called *secondary* (2°).

If we want to make a derivative of propane by replacing a H atom with a heteroatom, we now have two different H atoms we can choose from. If we replace a 3° H atom with X, we have a different compound from if we replace the middle H atom. Replacing a 3° H atom gives what are called *propyl* compounds or (old-fashioned) *n-propyl* compounds. Replacing a 2° H atom gives *isopropyl* compounds. So, if X = OH, we have isopropyl alcohol, or isopropanol (rubbing alcohol). The abbreviations Pr and *i*-Pr (or ^{i}Pr, or iPr) are often used for propyl and isopropyl.

Isopropanol and propanol have the same chemical formula, but the atom-to-atom connections are different. They are called *skeletal isomers* (a.k.a. *constitutional isomers*). Skeletal isomers have different properties — taste, smell, melting point, boiling point, everything. They are as different as if their elemental compositions were different. This concept is incredibly important. The different properties of skeletal isomers is one reason why there is such a diversity of organic compounds.

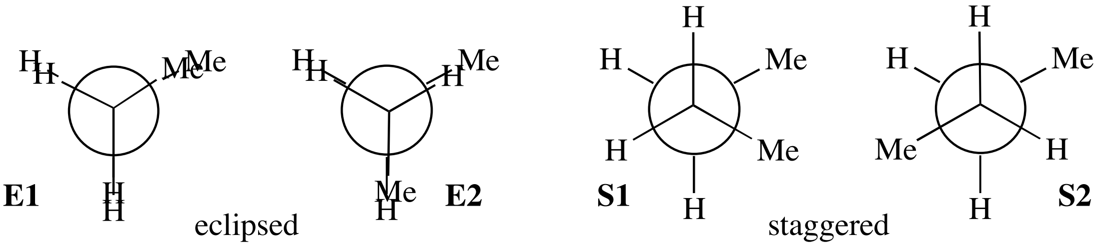
We have already met another kind of isomer. Eclipsed and staggered ethane (or propane) have the same atom-atom-atom connections, but different shapes. They are *stereoisomers*. Skeletal isomers and stereoisomers are the two different kinds of isomers. Stereoisomers can be further subdivided into four types. We have already met *conformational diastereomers*, one of those four types. We will soon meet the other three types.

The root "prop-" means "a three-carbon group with the associated hydrogens".

4a.6 Butane & its derivatives.

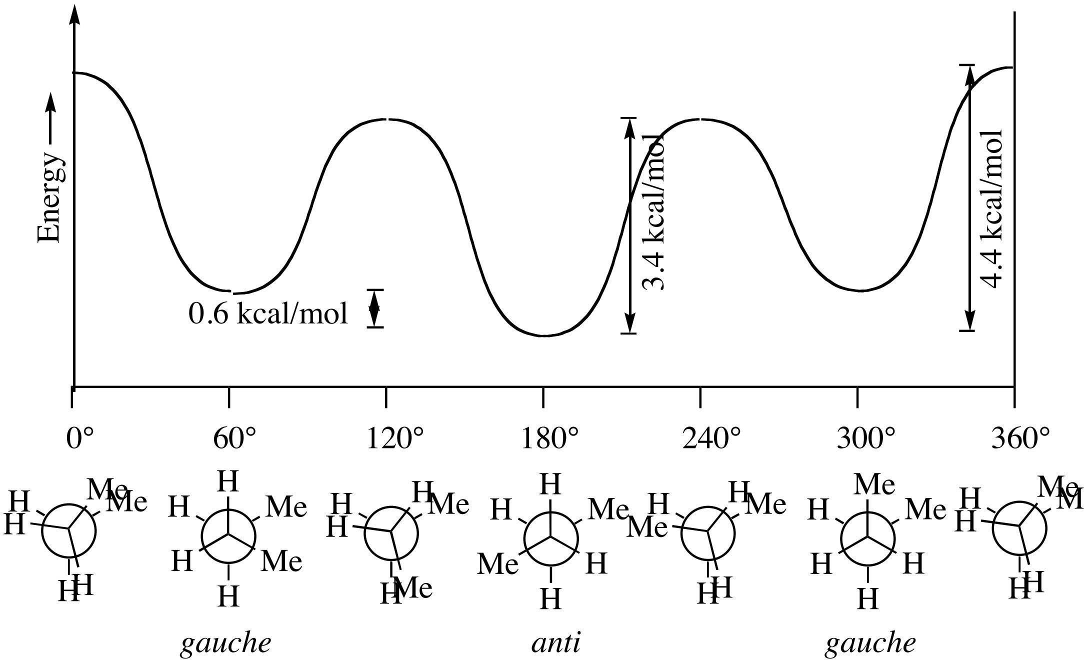
Suppose we want to add one more carbon to propane. We have two different kinds of H we can replace, a methylene H or a methyl H. If we replace the methyl H, we have *butane*. If we replace the methylene H, we have an isomer of butane. This isomer of butane has a common or trivial name, *isobutane*. More systematically, we can think of it as propane with a methyl group on the second carbon, or 2-methylpropane (all one word).

If we look down the C1–C2 σ bond, we get a picture that is identical to that of propane, except that the Me in propane is replaced by Et. The graph of energy vs. dihedral angle about the C1–C2 bond in butane doesn't look terribly different from propane. The C2–C3 bond is more interesting. We get two staggered conformational diastereomers (**S1** and **S2**) and two eclipsed conformational diastereomers (**E1** and **E2**). In **S2** the two Me groups are as far apart as possible, with a dihedral angle of 180°. It is called the *anti* conformer. In **S1**, the two Me groups are close to one another, with a dihedral angle of 60°. It is called the *gauche* conformer. **S1** is 0.6 kcal/mol higher in energy than **S2**. (The terms “anti” and “gauche” apply only to staggered conformers.) This difference in energy is due to *steric strain,* the strain resulting from the two Me groups trying to occupy approximately the same region of space.



Among the eclipsed conformers, **E1** has two C–H/ C–H interactions and one C–Me/C–Me, and **E2** has one C–H/ C–H and two C–H/ C–Me. Neither has good hyperconjugative interactions, so the difference between them must be due to steric interactions. It turns out that the steric cost of the eclipsed C–Me/ C–Me interaction is 1.0 kcal/mol, considerably worse than the steric interaction in **S1**.

We can draw a graph of energy vs. C–C–C–C dihedral angle as follows.



Again, the eclipsed conformers are transition states, but the energy required to go through one of the eclipsed conformers is appreciably higher than the energy required to go through the other. Also, the gauche conformer is higher in energy than the anti conformer. This doesn't mean that all of the butane in any particular sample exists only in the anti conformation. There is an equilibrium between the anti and gauche conformations, and the equilibrium constant is calculated by:

$$K = e^{(-\Delta G/\, RT)}$$

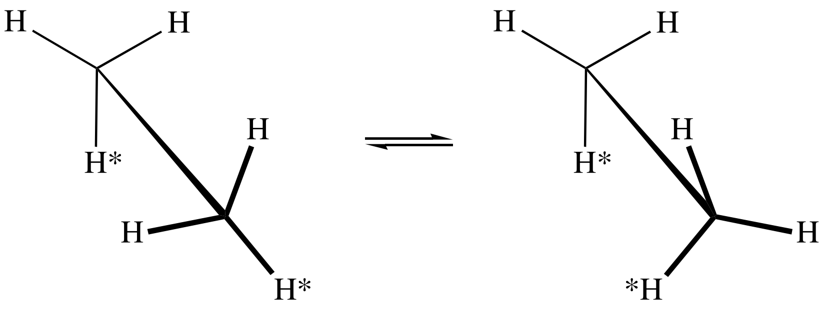
R is the universal gas constant (1.987 cal/mol·K) and T is the temperature at which the measurement is being made (usually room temperature, 295 K). Using this formula we determine that for the anti/ gauche equilibrium, $K = 4.6$ in favor of the anti conformer. So in a given sample of butane, approximately 80% of the material is in the anti conformation and approximately 20% is in the gauche conformation. (Actually, these numbers are not quite right, because we didn’t consider that there are two gauche conformations and only one anti, but it gives us a ballpark estimate.)

For larger alkanes, we can conduct similar analyses. We will see that the lowest energy conformation is the one in which all C–C–C–C dihedral angles are 180°.

Problem. (2) Of the different conformers of 1-bromo-2-chloroethane that you drew earlier, which are anti, and which are gauche?

Let’s look more closely at the two gauche conformers of butane, those with C–C–C–C dihedral angles of 60° and 300°. These two conformers have the same internal dimensions, e.g., the same distances between C1 and C4, the same C–C–C–C dihedral angle, etc. Yet the two compounds are not superimposable. One is the nonsuperimposable mirror image of the other. These two structures are *conformational enantiomers*.

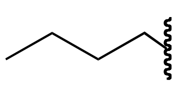
Even ethane has enantiomeric conformers. Two of these conformers are shown below. In each conformer, two H's are labeled for reference. The H*–C–C–H* dihedral angle of the conformer on the left is somewhere between 0° and 60°, say 30°. In the conformer on the right, the angle is - 30°. If you make models of these two conformers, you will see that they are non-identical mirror images of one another. All the internal dimensions (atom-atom distances, dihedral angles, bond angles) are identical, but the two structures are not mutually superimposable.

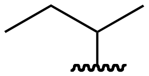


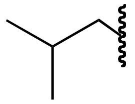
Isomerism summary so far: Two structures with the same formula are isomers (or identical). If they have different atom-to-atom connections, they are *skeletal isomers*. If they have the same atom-to-atom connections, they are *stereoisomers* (or identical). Stereoisomers that can be converted into one another easily by rotating around σ bonds are *conformational stereoisomers*. (We will soon meet the other kind of stereoisomer, the *configurational stereoisomer*.) Stereoisomers that have different internal dimensions (different dihedral angles, atom-to-atom distances, etc.) are *diastereomers*. Stereoisomers that have the same internal dimensions (different dihedral angles, atom-to-atom distances, etc.), but are still not superimposable (because they are mirror images), are *enantiomers*.

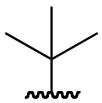
You need to make models to understand these points!

Suppose we want to make a bromo derivative of butane and isobutane? In butane, we have two different kinds of H atoms, 1° and 2°, and in isobutane, we have two different kinds of H atoms, 1° and *tertiary* (3°), so we have four different kinds of bromobutanes. These are called *n*-butyl bromide, *sec*-butyl (or *s*-butyl) bromide, isobutyl bromide, and *tert*-butyl (or *t*-butyl) bromide. The more formal names are 1-bromobutane, 2-bromobutane, 1-bromo-2-methylpropane, and 2-bromo-2-methylpropane. However, the trivial names for the four butyl groups are very, very commonly used. The abbreviations *n*-Bu (or ^{n}Bu), *i*-Bu (or ^{i}Bu, or iBu), *s*-Bu (or ^{s}Bu), and *t*-Bu (or ^{t}Bu) are often used for the four butyl groups. When just Bu is used, it refers to *n*-Bu.


butyl
n-Bu


sec-butyl
s-Bu


isobutyl
i-Bu

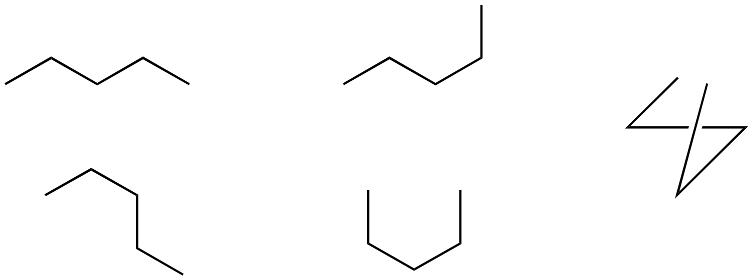

tert-butyl
t-Bu

The root "but-" means "a four-carbon group with the associated hydrogens".

4a.7 Pentane & its derivatives.

From butane and isobutane we generated four different kinds of bromobutanes, so it would seem we can generate four different kinds of pentanes. However, replacing a 2° H in butane with CH_3 gives exactly the same compound as replacing a 1° H in 2-methylpropane! Both replacements give 2-methylbutane, or isopentane. Replacing a 1° H in butane gives pentane, and replacing the 3° H in 2-methylpropane gives 2,2-dimethylpropane, or neopentane.

There are many different ways to draw a compound such as pentane. The mutual orientations of the different lines can change, and the compound is still pentane. The same is true of any other compound. *What matters is the connections between the atoms, not the relative positions of the atoms!*



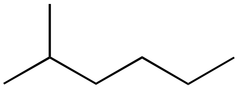
One more point. Methane has the formula CH_4, ethane C_2H_6, propane C_3H_8, butane and isobutane C_4H_{10}, and the three pentanes C_5H_{10}. The formula for any acyclic alkane is C_nH_{2n+2}.

Problem for home. (3) How many bromopentanes are there?

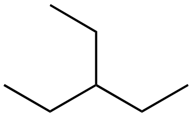
4a.8 Higher alkanes.

We now arrive at one of my least favorite subjects: nomenclature. We have learned about methane, ethane, propane, butane, and pentane. Above pentane, the roots of the names derive from the Greek word for that number: hexane, heptane, octane, nonane, decane, undecane, dodecane, etc. The class of compounds is called *alkanes*. The root of the alkane's name tells you how many C atoms there are; the number of H atoms in an alkane is given by the formula C_nH_{2n+2}.

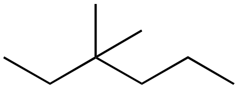
A branched alkane is named as follows. Find the longest straight chain in the molecule. That provides the root of the name. Then describe the substituents on that long chain. If the substituent has one carbon, it is methyl; if two, ethyl, etc. The position of the substituent is described by a number; if there is a choice, the number of the first substituent should be as low as possible. If there is more than one substituent of the same kind, the prefix di-, tri-, etc. is used, and the position of every group must be listed. If there is more than one substituent of different kinds, they are listed alphabetically, and the first substituent in the name should have the lowest number. You can use *i*-Pr, *s*-Bu, *i*-Bu, and *t*-Bu as substituent names.



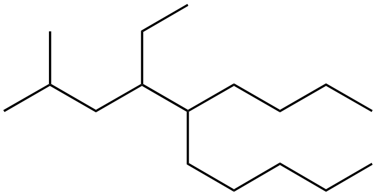
2-methylhexane



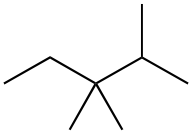
3-ethylpentane



3,3-dimethylhexane



5-butyl-4-ethyl-2-methyldecane



2,3,3-trimethylpentane

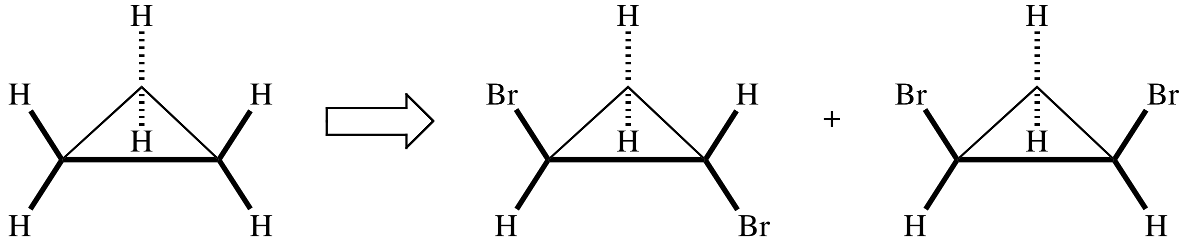
I do not expect you to name compounds. I do expect you to be able to draw a compound that I name.

4a.9 Cycloalkanes.

Let's take pentane and remove one H from each of the terminal C atoms. Then let's join the terminal two C atoms. The structure we have now has the formula C_5H_{10}. We call it *cyclopentane*. In fact, we can make cyclic alkanes of any size. A three-membered ring is cyclopropane, a four-membered ring is cyclobutane, a six-membered ring is cyclohexane, etc. The number of H atoms in a cycloalkane is given by the formula C_nH_{2n}.

When we have a cycloalkane with a single substituent, for example a fluorine atom on a six-membered ring, we call it fluorocyclohexane. No number is needed, because the ring has no beginning and no end. We can have alkyl substituents on an alkane: for example, isopropylcyclopropane. If we have more than one substituent, the alphabetically first substituent is at position 1, and the other substituent is numbered relative to the first one and as low as possible: for example, 1-fluoro-3-iodocyclooctane (not 1-fluoro-5-iodocyclooctane).

Let's look at cyclopropane from the side. The three C atoms are in a plane; three H atoms, one on each atom, point up, and three point down. Let's change one of the H atoms on one C to a Br group, and let's change another H atom on another C to a Br group. We get 1,2-dibromocyclopropane. There are two different kinds of 1,2-dibromocyclopropane that we can get, though. In one of them the two Br groups are on the same side of the ring; in the other, they are on opposite sides of the ring. These two compounds have different *shapes*. The only way to convert one of them into the other is to break a bond. Because they have different shapes, they have different properties. For example, the one with the two Br atoms on the same side of the ring has a much larger dipole moment than the other. The one with the two Br atoms on opposite sides is much thicker than the other.



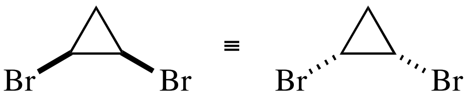
Here again we have stereoisomers, because the atom-to-atom connections are the same, but the structures are not identical. In this particular case, the internal dimensions of the compounds are different (look at the Br–Br distance and the Br–C–C–Br dihedral angle), so the compounds are *diastereomers*. However, these compounds are not conformational diastereomers, because they can't be interconverted by rotations without breaking covalent bonds. As a result, they are called *configurational diastereomers* (our third kind of stereoisomer).

Configurational diastereomers have different melting and boiling points, different reactivities, different spectral behavior ...; in short, they are completely different chemical entities. If you could separate conformational diastereomers, the same would be true of them; however, conformational diastereomers usually interconvert so rapidly on the time scale in which we operate that we can't separate them and examine their properties. As a result, we don't usually think of conformational diastereomers as being different compounds. In fact, if someone uses the word "diastereomer" without specifying conformational or configurational, you should assume that they mean configurational diastereomer. (See my online stereochemical glossary.)

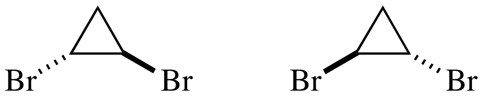
Two groups that reside on the same side of a ring are called *cis*. Two groups that reside on opposite faces of a ring are called *trans*. The two compounds above would be called *trans*-1,2-dibromocyclopropane and *cis*-1,2-dibromocyclopropane.

Any time you have at least two C atoms, each of which has two non-identical groups attached, in a ring of any size, you can have *cis–trans* isomers.

We used the hashed–wedged line convention to denote cis–trans isomers. E.g., for 1,2-dibromocyclopropane, we write the following. (Some people use dashed lines instead of hashed lines, but dashed lines can have several different meanings, so hashed lines are better.) Note that the doubly wedged and doubly hashed structures that are drawn for the *cis* isomer are *identical;* if we pick one up out of the plane of the paper, flip it over, and put it back down, we get the other. This is not true of the two *trans* structures that are drawn; these represent examples of the fourth class of stereoisomers, *configurational enantiomers*. Enantiomers are *nonsuperimposable mirror images* of one another. One pair of enantiomers that is very familiar to you is your hands. Your left hand is an enantiomer of your right hand. The two feature the same shape, the same pinkie-to-thumb distance, etc., but they are non-superimposable mirror images.



cis-1,2-dibromocyclopropane



trans-1,2-dibromocyclopropane

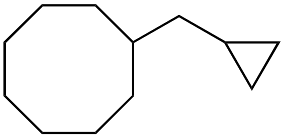
Diastereomers have different internal dimensions, i.e. dihedral angles and distances between nonbonded atoms — for example, the two Br atoms in *cis*-1,2-dibromocyclopropane are closer than they are in *trans*-1,2-dibromocyclopropane — while enantiomers have *identical* internal dimensions. Enantiomers have identical energies, whereas diastereomers differ in energy. Some compounds don't have enantiomers; for example, *cis*-1,2-dibromocyclopropane is *identical* to its mirror image. We will talk about enantiomers in much greater detail soon.

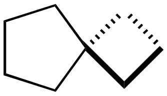
You must make models to understand the concept of stereoisomerism of cycloalkanes!

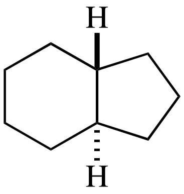
Note well that if I use the term "isomers," I could be referring to any kind of isomer: constitutional isomer, stereoisomer, diastereomer, or enantiomer.

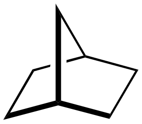
Problem. (3) Which of the cyclic skeletal isomers of C_5H_{10} and C_6H_{12} have *cis* and *trans* isomers? Draw them using the hashed/ wedged line convention.

Many organic compounds have more than one ring. A compound can rings that are isolated, spiro, fused, or bridged, depending on whether they share 0, 1, 2, or >2 atoms. Any alkane with *m* rings in it has the formula $C_nH_{2(n-m+1)}$.









4b. Stereochemistry and Conformational Analysis of Rings.

4b.1 Summary of Isomerism so far.

Two compounds that have identical formulae but are not identical either in shape or bonding are called *isomers*. Isomers can be classified as *skeletal isomers* or *stereoisomers,* depending on whether they have *different* or *identical* atom-to-atom connectivities, respectively.

There are four kinds of stereoisomers. If two stereoisomers have different internal dimensions (atom-to-atom distances, dihedral angles, thickness, dipole moment), *and* they can only be interconverted by breaking σ or π bonds, then they are *configurational diastereomers*. If two stereoisomers have different internal dimensions (atom-to-atom distances, dihedral angles, thickness, dipole moment), *and* they can be interconverted by free rotation about σ bonds, then they are *conformational diastereomers*. If two stereoisomers have identical internal dimensions, i.e. are nonsuperimposable mirror images of one another, *and* they can only be interconverted by breaking σ or π bonds, then they are *configurational enantiomers*. If two stereoisomers have identical internal dimensions, i.e. are nonsuperimposable mirror images of one another, *and* they can be interconverted by free rotation about σ bonds, then they are *conformational enantiomers*.

4b.2 Conformations of Cycloalkanes.

Let's think about cycloalkanes now. The hybridization of the C atoms in all of the cycloalkanes we've seen so far is sp^3, so the ideal bond angles should be 109°. If we consider three sp^3-hybridized C atoms in a ring, though, we see that the C–C–C bond angles must be 60°, since we have an equilateral triangle. So the ideal bond angles of 109° are forced to deform to angles of 60°. We would expect that this would make the compound higher in energy. In fact it does. The extra energy is said to be due to *angle strain*.

We can continue up the ladder to cyclobutane, cyclopentane, and the like. For a polygon of n sides, the ideal angle is calculated to be 180 – 360/n. The calculated bond angles are shown for polygons from a triangle to a decagon.

Polygon	Internal angle	Polygon	Internal angle	Polygon	Internal angle
3	60	7	129	11	147
4	90	8	135	12	150
5	108	9	140	13	152
6	120	10	144	14	154

We would guess from this table that the cycloalkane with the least angle strain would be cyclopentane, and that the amount of angle strain in a compound would steadily increase after that. This was the theory proposed by Adolf von Bäyer in 1885. In fact, von Bäyer's theory was not correct except for the very smallest rings, and for a very good reason that even von Bäyer should have been able to see. Cycloalkanes (except for cyclopropane) are not planar compounds! In fact, like acyclic alkanes, they can bend and twist about their C–C bonds in order to minimize their energy.

We can actually calculate the amount of *ring strain* in various cycloalkanes by burning them with O_2, measuring the amount of energy released, and comparing this energy with the amount of energy released by an acyclic alkane. We get a table that looks like the following:

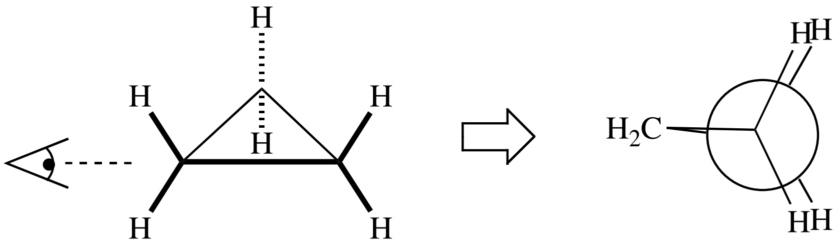
Ring size	Ring strain (kcal/mol)	Ring size	Ring strain (kcal/mol)	Ring size	Ring strain (kcal/mol)
3	28	7	6	11	11
4	26	8	10	12	2
5	7	9	13	13	5
6	0	10	12	14	0

The ring strain starts very high, reaches zero with cyclohexane, increases again to a local maximum at cyclononane, and then decreases to reach zero again with cyclotetradecane.

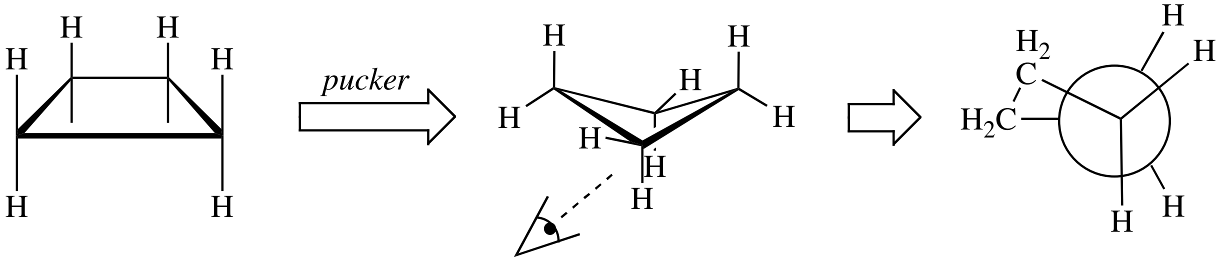
Why do we observe this pattern? We have already seen that small rings have a considerable amount of angle strain. There are two other sources of strain that are possible in cyclic compounds. Just as we saw in the acyclic alkanes, cycloalkanes can experience torsional strain and steric strain if the dihedral angles are not perfectly staggered and if non-bonding groups are forced to come close to each other in space. Thus, ring strain incorporates several sources of strain: angle strain, torsional strain, and steric strain. In fact, the strain in rings of six C atoms or more is due entirely to torsional and steric strain and not at all to angle strain, as these rings can bend and pucker to make the bond angles equal to 109°. Let's now look at the conformations of specific cycloalkanes in detail.

4b.3 Conformations of 3- to 5-Membered Rings.

The smallest ring is cyclopropane. Since three points define a plane, cyclopropane is necessarily a planar compound (considering just the C atoms). If we look at a Newman projection along one of the C–C bonds, we see that the C–H bonds are perfectly eclipsed. Thus cyclopropane, in addition to its angle strain, has a lot of torsional strain. The angle strain in cyclopropane is so bad that the two sp^3 orbitals making up the bond don't meet head-on, so that the bonds are bent (banana bonds). As a result, cyclopropane is much more reactive than most cycloalkanes.



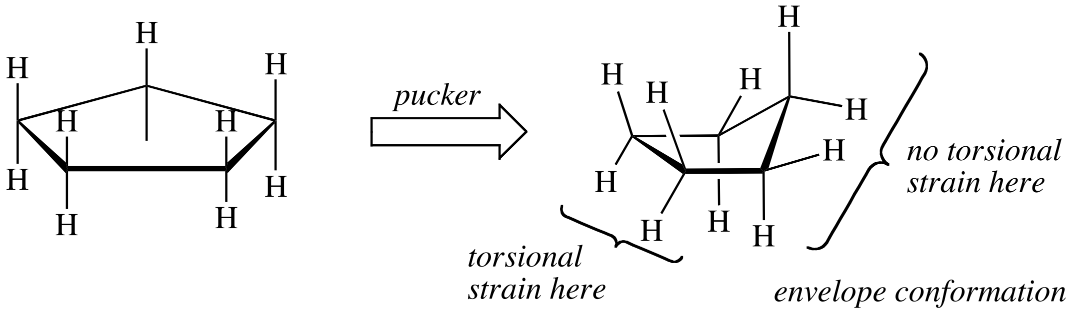
Cyclobutane, on the other hand, puckers a little bit. This makes the bond angles smaller than the planar angle of 90°, increasing the angle strain, but it relieves a lot of torsional strain.



Note how in the puckered conformation of cyclobutane there are two different kinds of C–H bond and hence two different kinds of H atom. There are those C–H bonds that are nearly anti to other C–H bonds, and there are those C–H bonds that are nearly anti to C–C bonds. We will see that this has great significance for cyclohexane rings.

Problem for home. (3) Draw the different conformers possible for methylcyclobutane (two). Predict which ones are most stable.

Cyclopentane was predicted to have no angle strain by Bäyer. If cyclopentane were planar, though, it would have a tremendous amount of torsional strain from all of the aligned C–H bonds. As a result, cyclopentane adopts a puckered conformation. This increases its angle strain a little bit but relieves a lot of the torsional strain. There are two puckered conformations of cyclopentane, one in which three atoms are coplanar and one in which four atoms are coplanar. The latter is called the *envelope* conformation, because it looks like an envelope. Even in the envelope conformation, cyclopentane has some torsional strain, and compounds with five-membered rings tend to react in ways that decrease the torsional strain (i.e., by converting an sp^3-hybridized C atom in the ring into an sp^2-hybridized atom).

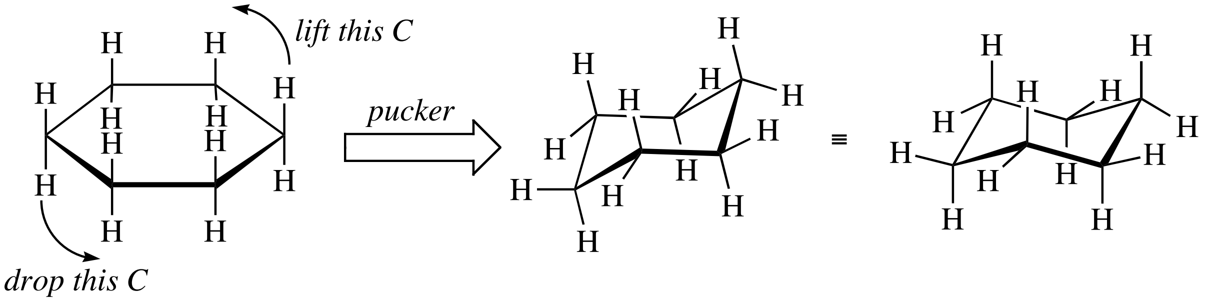


Suppose the different C atoms in the ring are non-identical, i.e. have different substituents. How do we know which C atom in cyclopentane will pucker? The answer is that we would have to look at the different energies of the different diastereomeric conformations, and there would be an equilibrium between them. It is very difficult to predict which of the conformers of, for example, methylcyclopentane is most stable. The energies of the different conformers are in fact very close. We will shortly see that the energies of the conformers of substituted cyclo*hex*anes fit a regular and predictable pattern.

Problem for home. (4) Draw the different conformers possible for methylcyclopentane (six). Predict which ones would be most stable.

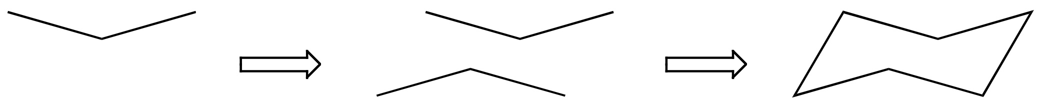
4b.4 Chair Cyclohexane.

As we saw earlier, cyclohexane is the least strained of all the ring sizes. It has neither angle strain nor torsional strain. This is because it can pucker in such a way that all of the bonds are perfectly staggered, and in this conformation all of the bond angles are 109°! This conformation is called the *chair* conformation of cyclohexane, so-called because it looks like a lounge chair. In the chair, C1, C2, C4, and C5 are coplanar (the C1–C2 and C3–C4 bonds are parallel), while C3 is above the plane and C6 is below the plane (or vice versa).

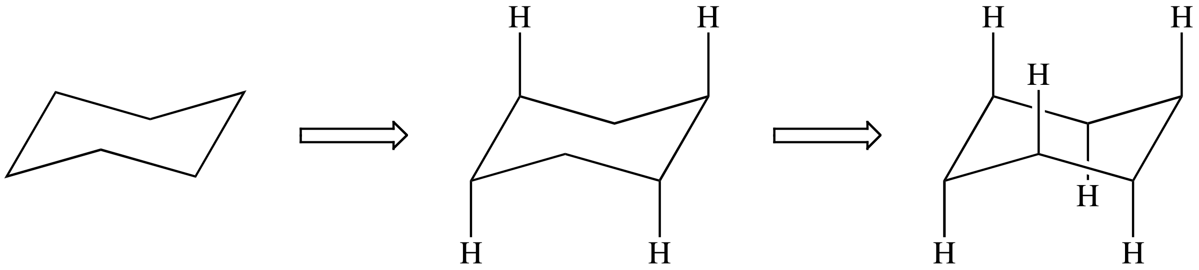


There are two kinds of C–H bonds in cyclohexane. The vertical bonds are called *axial*. The more-or-less horizontal bonds are called *equatorial*. The six carbons and six equatorial hydrogens form two close planes, while the six axial hydrogens are above and below these planes. Axial C–H bonds are anti to other axial C–H bonds and gauche to equatorial C–H bonds and ring bonds. Equatorial C–H bonds are anti to ring bonds and gauche to all neighboring C–H bonds. The C1, C3, and C5 axial C–H bonds are parallel to one another.

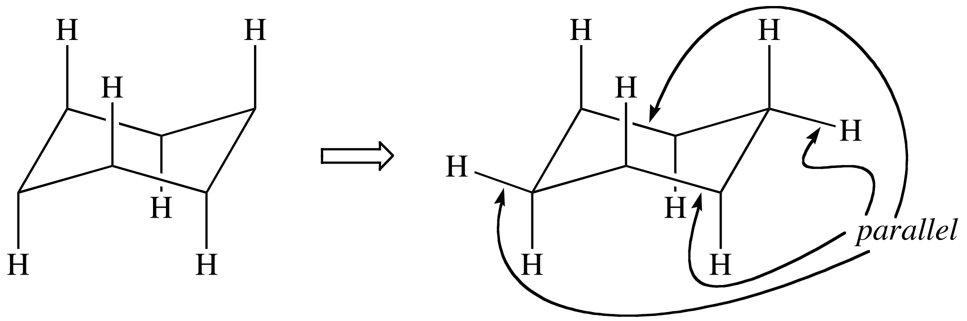
The chair conformation is so important that every student must learn how to draw it properly. Start off with by drawing a shallow V. Then draw the same V but upside-down and offset to the left a little bit. Then connect the ends of the upper and lower V's. You have your chair! The outermost C's are *in* the plane of the paper. The two C's on the lower right are *in front of* the plane of the paper, and the two C's on the upper left are *behind* the plane of the paper. You could use wedged and hashed lines to show this, but most people don't.



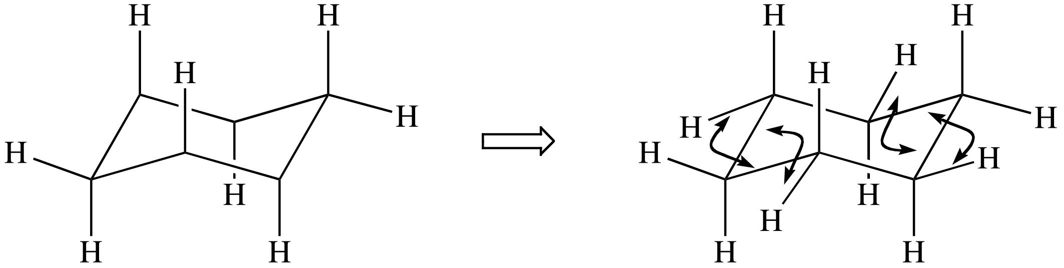
It is equally important to draw the axial and equatorial C–H bonds properly. The two uppermost C's in your drawing have their axial bonds pointing up, and the two bottommost C's have them pointing down. Draw in the axial bonds on the other two C's so that the axial bonds alternate up and down around the ring.



The equatorial C–H bonds are drawn so that they are parallel to the C–C bonds to which they are anti. Draw the equatorial bonds of the two outermost C's first. The equatorial bond on the leftmost atom points to the left, and the equatorial bond on the rightmost atom points to the right. These bonds should be parallel to one another and to two ring C–C bonds. When you have drawn them, the outermost C's should look like ordinary tetrahedral C's, with the two C–H bonds *in* the plane of the paper and the two ring bonds going into and out of the plane of the paper.

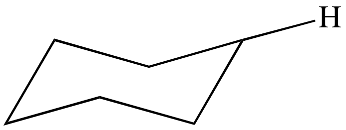


The other equatorial C–H bonds are also parallel to ring bonds, as shown by the arrows. Again, the equatorial bonds on the atoms on the left point to the left, and the equatorial bonds on the atoms on the right point to the right.

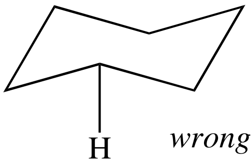


To see how the way we draw the cyclohexane ring corresponds to a projection of the real ring, make a model! The model will also show you how the compound puckers to achieve a conformation in which all bonds are staggered and all angles are 109°. But the *only* way to learn to draw a chair is to *practice*. If you cannot draw a chair properly, then you cannot communicate properly, and this will lead to reduced scores on exams.

Common errors: to draw a substituent incorrectly by making it neither axial nor equatorial. Make sure you point the axial substituents on the four central C's in the right direction!

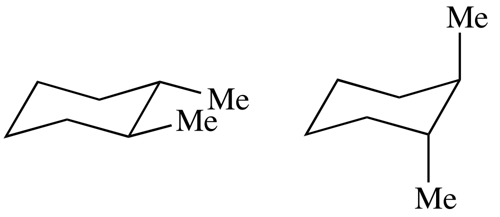


wrong!

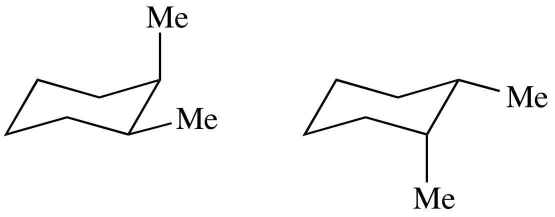


wrong!

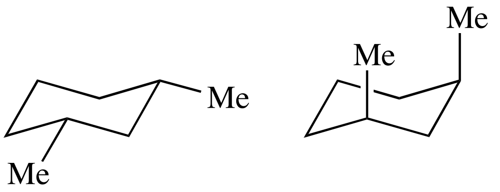
The terms axial/ equatorial and *cis*/ *trans* describe unrelated properties of substituents. Two substituents that are *cis* are always on the same side of the ring, but one may be axial and the other equatorial, both may be axial, or both may be equatorial. For example, *trans*-1,2-dimethylcyclohexane has both Me groups axial or both equatorial, while *trans*-1,3-dimethylcyclohexane has one Me group axial and one equatorial. Similarly, *cis*-1,2-dimethylcyclohexane has one Me group axial and one equatorial, while *cis*-1,3-dimethylcyclohexane has both Me groups axial or both equatorial. Axial and equatorial are dependent on the *conformations* of a compound, while *cis* and *trans* are dependent on its *constitution*.



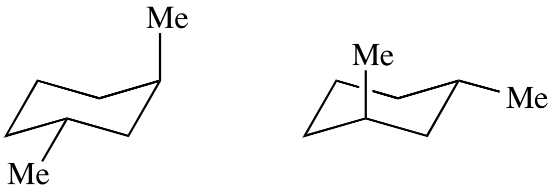
trans-1,2-dimethylcyclohexane



cis-1,2-dimethylcyclohexane

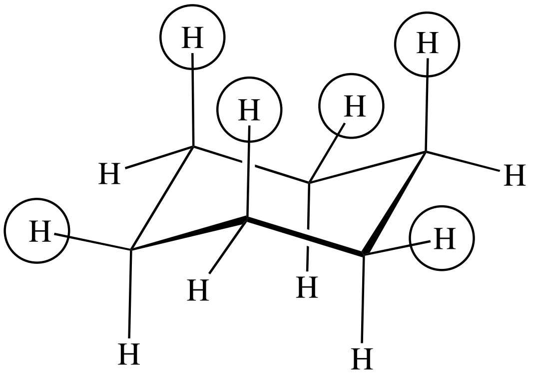


cis-1,3-dimethylcyclohexane



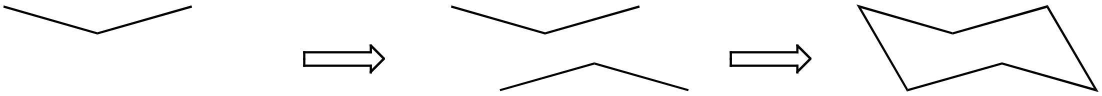
trans-1,3-dimethylcyclohexane

One way to look at a cyclohexane ring in a chair conformation and immediately see which groups are *cis* and which are *trans* is to do the following. Circle the equatorial group on C1. The group *cis* to this one on C2 is axial; circle it. The group *cis* to these on C3 is equatorial; circle it too. And so on around the ring. When you have finished, you will have circled one set of substituents, all of which are *cis* to one another. The substituents that remain uncircled are all *cis* to one another, too. Any circled substituent is *trans* to any uncircled substituent. Now you can see at a glance which substituents on any two C atoms in the ring are *cis* and which are *trans*.

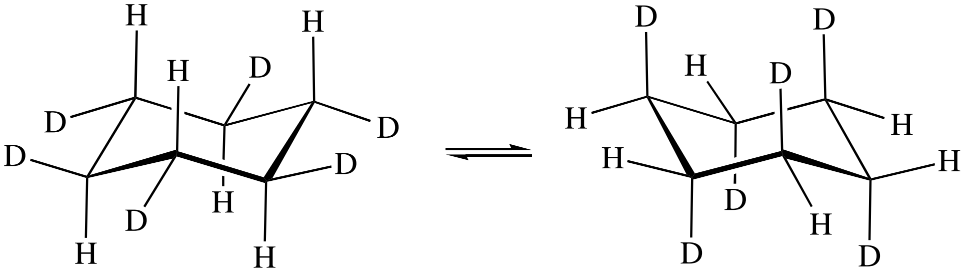


All circled groups are *cis*.
All uncircled groups are *cis*.
All circled groups are *trans* to all uncircled groups.

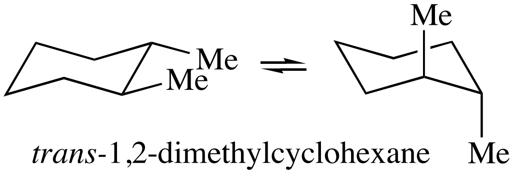
Any cyclohexane ring can theoretically exist in two different chair conformations. The interconversion of one with the other is called a *ring flip*. The flipped chair is drawn similarly to the first chair that we drew, except that the upside-down V is offset to the right, rather than to the left.



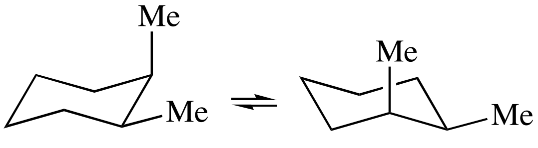
When a cyclohexane ring flips from one chair to the other, *all the axial substituents become equatorial, and all the equatorial substituents become axial,* but the *cis-trans* relationships of substituents don't change. Consider the structures below. The compound on the left has six deuterium atoms that are all equatorial. Each D is *trans* to the D on the neighboring C. This conformer can undergo a ring flip to give a new, diastereomeric conformer in which all D's are axial. In the new conformer, though, each D is *still trans* to the D on the neighboring C.



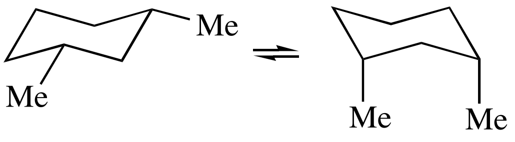
The two chair conformations of a substituted cyclohexane are sometimes stereoisomeric. They may be conformational enantiomers, conformational diastereomers, or identical structures. We call the stereoisomeric pairs "conformational" and not "configurational" because the chair flip is a special kind of rotation about C–C σ bonds. For example, we drew two conformations for each of four dimethylcyclohexane isomers earlier. Each pair of conformations can interconvert through a ring flip. The two conformations of *trans*-1,2-dimethylcyclohexane are conformational diastereomers (because their internal dimensions (e.g., Me–Me distance) are different), as are the two conformations of *cis*-1,3-dimethylcyclohexane. But the two conformations of *cis*-1,2-dimethylcyclohexane are conformational enantiomers, and the two conformations of *trans*-1,3-dimethylcyclohexane are identical.



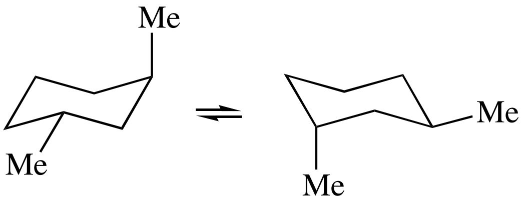
trans-1,2-dimethylcyclohexane



cis-1,2-dimethylcyclohexane



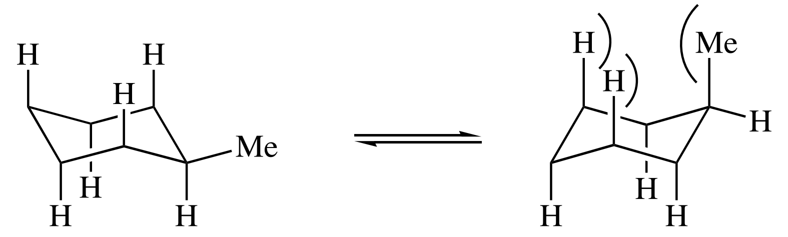
cis-1,3-dimethylcyclohexane



trans-1,3-dimethylcyclohexane

Problem for home. (5) Draw *trans*-1,4-dimethylcyclohexane in its two chair conformations, and determine whether the two chairs are identical, conformational enantiomers, or conformational diastereomers. Then do the same for the *cis* isomer.

A monosubstituted cyclohexane such as methylcyclohexane has two low-energy diastereomeric conformers, one in which the substituent is axial and one in which it is equatorial. The axial conformer is *almost always* less stable than the equatorial conformer. This is because in the axial conformer there is a steric interaction between the axial Me group on C1 and the axial H's on C3 and C5. These are called *1,3-diaxial interactions*. In the equatorial conformer, the only 1,3-diaxial interactions occur between H atoms, which are smaller. We indicate only 1,3-diaxial interactions by using parentheses to show where the groups are bumping into one another.



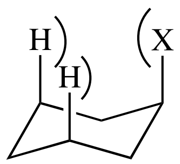
equatorial
only H–H 1,3-diaxial interactions

axial
two Me-H 1,3-diaxial interactions

The difference in energy between the axial and equatorial conformers of methylcyclohexane is 1.8 kcal/mol. Because we have two 1,3-diaxial interactions between Me and H, this makes 0.9 kcal/mol difference in energy for each one. We've already seen that 0.9 kcal/mol is the difference in energy between the gauche and anti conformers of butane. The numbers are the same because the strain originates from the same source. The axial Me on C1 is in a gauche relationship with C3 and C5 of the ring. When it is in an anti relationship, i.e. equatorial, no steric strain is observed.

Problem for home. (6) Calculate the ratio of axial to equatorial methylcyclohexane that is present at room temperature.

Different groups show different energy differences between the axial and equatorial conformers. The differences in energy represent a measure of the *steric bulk* of the substituents. Substituents with sp^3-hybridized C attached to the ring have more steric bulk than sp^2-hybridized substituents of comparable size, and these are in turn larger than sp-hybridized groups. Single atoms have very little steric bulk. The CO_2H group is smaller than the Ph group because the C–O bonds are shorter than the C–C bonds. Note that there is not a big increase in bulk from Me to Et to *i*-Pr, but that there is then a big jump with *t*-Bu. In fact, the *t*-Bu group is so large that a cyclohexane ring will do anything in order to put it in an equatorial position.



X	Strain of *one* 1,3-diaxial interaction	X	Strain of *one* 1,3-diaxial interaction	X	Strain of *one* 1,3-diaxial interaction
F	0.12	Me	0.9	Ph (C_6H_5)	1.5
Cl	0.25	Et	0.95	CO_2H	0.7
Br	0.25	*i*-Pr	1.1	CN	0.1
OH	0.5	*t*-Bu	2.7		

You can calculate the proportion of each substituted cyclohexane that exists in the axial or equatorial conformation by plugging the energy of *two* 1,3-diaxial interactions into the formula we had earlier.

The situation becomes more complicated when we consider disubstituted cyclohexanes. We need to compare the sum of the energy of *all* of the interactions in one conformer with that for the other conformer. For example, let's look at *trans*-1,2-dimethylcyclohexane. It can exist as a diequatorial conformer or a diaxial conformer. The diequatorial conformer has one gauche interaction (0.9 kcal/mol) between the Me groups and no 1,3-diaxial interactions other than H/H. The diaxial conformer has four Me/H 1,3-diaxial interactions (4 x 0.9 = 3.6 kcal/mol) but no gauche interactions. (To see the gauche interactions, look at a Newman projection down the C1-C2 bond.) We conclude that the diaxial conformer is 2.7 kcal/mol less stable than the diequatorial conformer.

Let’s look at *cis*-1,2-dimethylcyclohexane. One conformer has two 1,3-diaxial interactions and one gauche interaction between the two Me groups. The other has the same. We conclude that they are exactly equal in energy. In fact, these two conformers constitute one example of a pair of *conformational enantiomers*.

Let’s look at *cis*-1,3-dimethylcyclohexane. The diequatorial conformer has no gauche interactions and no 1,3-diaxial interactions. The diaxial conformer, though, has two Me/ H 1,3-diaxial interactions and one Me/ Me 1,3-diaxial interaction. The Me/ Me diaxial interaction, as you might imagine, is much more severe than the Me/ H diaxial interaction. The Me/ H diaxial interactions cost 0.9 kcal/mol each, but the Me/ Me diaxial interaction costs 3.7 kcal/mol. The difference in energy between the two conformers is then 2 x 0.9 + 3.7 = 5.5 kcal/mol. This is a very large difference in energy.

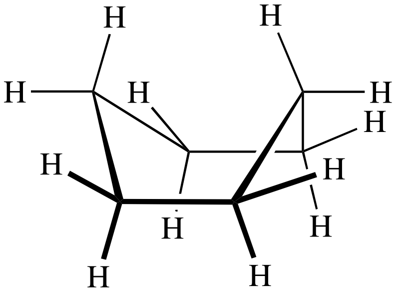
Problems for home. (7) Calculate the proportion of *cis*-1,3-dimethylcyclohexane that exists in the diaxial conformation. (8) Compare the steric energies of the chair conformers of*trans*-1,3-dimethylcyclohexane and determine which (if either) is stabler.

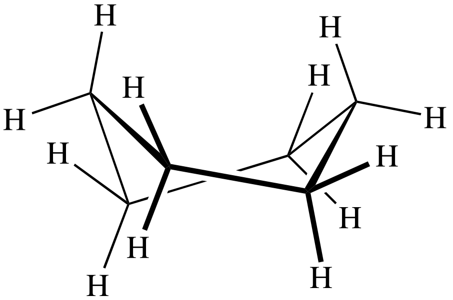
If a cyclohexane is substituted with more than one group, the stablest conformer is usually the one in which the largest group (as measured by the difference in steric strain in going from axial to equatorial) is equatorial. This is especially true for disubstituted cyclohexanes.

Problems for class. (Practice drawing conformations.) (9) Draw the more stable conformer of the following compounds. (a) *cis*-1-Chloro-4-ethylcyclohexane. (b) Menthol, or *trans*-2-isopropyl-*cis*-5-methylcyclohexanol. (c) *trans*-3-Isopropylcyclohexanamine.

4b.5 Boat and Twist-boat Cyclohexane.

There are other conformations of cyclohexane besides the chair conformations. The boat conformation of cyclohexane is also free of angle strain. In this conformation, instead of C1 and C4 being above and below the plane formed by C2, C3, C5, and C6, both are above the plane. The boat conformation of unsubstituted cyclohexane is about 7.0 kcal/mol higher in energy than the chair conformation. This is due to torsional strain among the four pairs of hydrogens on C2, C3, C5, and C6, and also due to a *flagpole* interaction between the H's on C1 and C4 that are pointing towards one another. Some of this strain can be relieved by twisting around the C2–C3 and the C5–C6 bonds to achieve what is called the *twist-boat* conformation. The twist-boat is only 5.5 kcal/mol higher in energy than the chair, still a considerable amount of energy but not as high as the boat.


boat cyclohexane


twist-boat cyclohexane

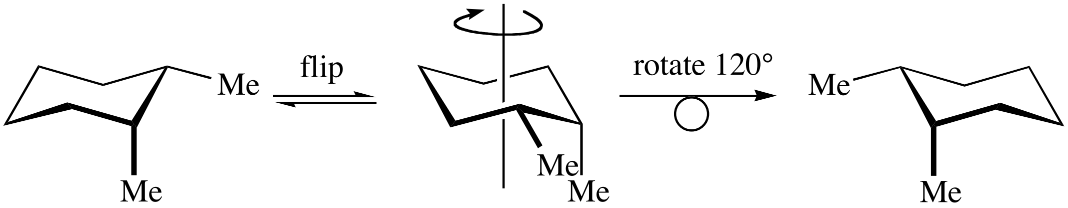
In fact, the boat is a transition state on the way from the chair to the twist-boat. The twist-boat is an intermediate between the two flipped forms of the chair. The energy of the boat above the chair, 7.0 kcal/mol, represents the energy barrier through which cyclohexane must pass before it can flip from one chair conformation to the other.

Remember that the twist-boat conformation is higher than the chair by 5.5 kcal/mol only for unsubstituted cyclohexane; appropriate substituents can raise the energy of the chair relative to the twist-boat until the twist-boat is more stable than the chair.

Problem for home. (10) How many different diastereomeric boat conformers of methylcyclohexane are there?

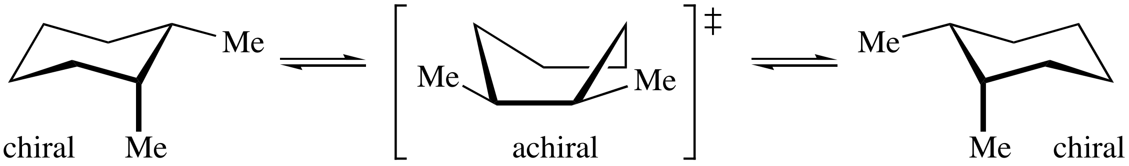
4b.6 Chirality of Cyclohexanes.

Substituted cyclohexanes may be chiral or achiral in their lowest-energy conformation. For example, both *cis-* and *trans-*1,2-dimethylcyclohexane are chiral in the chair conformations. However, most organic chemists would say that *trans-*1,2-dimethylcyclohexane is chiral, but *cis-*1,2-dimethylcyclohexane is not. The reason is that *cis-*1,2-dimethylcyclohexane rapidly interconverts between its two enantiomer chair conformations.



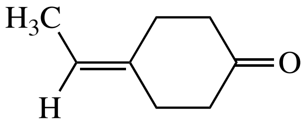
enantiomeric chair conformers of *cis-*1,2-dimethylcyclohexane

In practice, though, we say that a compound is achiral *if any of its low-energy conformers are achiral*. *cis-*1,2-Dimethylcyclohexane has an achiral boat conformation, so it is achiral. In practice, you can look at a *planar* projection of a monocyclic compound to determine whether it is chiral or achiral. If its planar projection is achiral, it is bound to have an achiral ground state or transition state conformation. You must look at planes *perpendicular to* the plane of the paper *and* the plane *of* the paper.

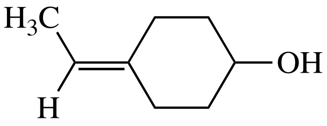


Problems for home: (1) Determine whether the following compounds are chiral on the laboratory time scale. Then determine whether their lowest-energy conformers are chiral. (a) *cis*-1-bromo-2-methylcyclohexane. (b,c) *cis*- and *trans*-1,3-Dimethylcyclohexane. (d) *cis*-1-Chloro-3-methyl-cyclohexane. (e,f) *cis*- and *trans*-1,4-Dimethylcyclohexane. (g,h) *cis*- and *trans*-decalin.

(i)



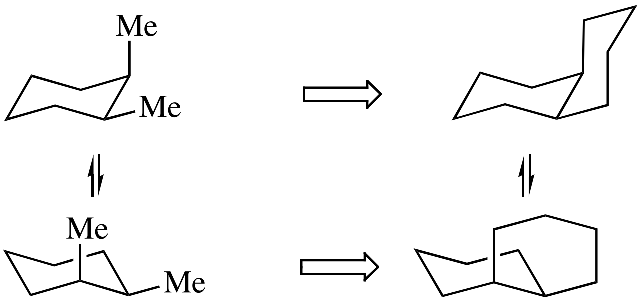
(j)



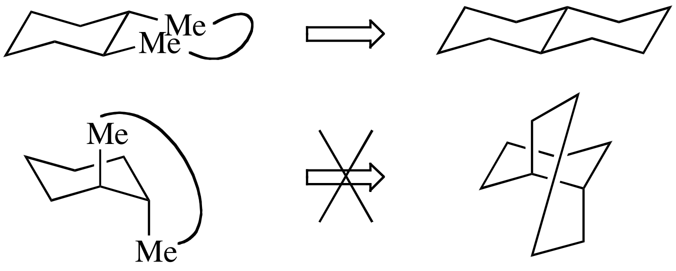
4b.7 Fused and Bridged Rings.

We have already seen the difference between *cis*- and *trans*-1,2-dimethylcyclohexane. Suppose we join the two Me groups together with a –CH_2CH_2– group to make a second ring. The compound we obtain, which has two *fused* cyclohexane rings (two rings that share an edge in common), has the trivial name of decalin, because it has ten carbon atoms. From *cis*- 1,2-dimethylcyclohexane we get *cis*-decalin, and from *trans*-1,2-dimethylcyclohexane we get *trans*-decalin. The two forms of decalin are diastereomers, just like *cis*- and *trans*-1,2-dimethylcyclohexane are.

Like *cis*-1,2-dimethylcyclohexane, *cis*-decalin can exist in two different chair-chair conformations of equal energy. When the decalin is substituted, the different conformations have different energies, because the axial substituents in one chair-chair conformation are equatorial in the other, and vice versa. Unlike *trans*-1,2-dimethylcyclohexane, *trans*-decalin can exist in only one chair-chair conformation. The other conformation is hopelessly strained. To see this, make a model of *trans*-1,2-dimethylcyclohexane and see how far apart the Me groups are and how a CH_2CH_2 group is insufficiently long to bridge them. *trans*-Decalin is said to be *conformationally locked* because it can't undergo a ring flip.



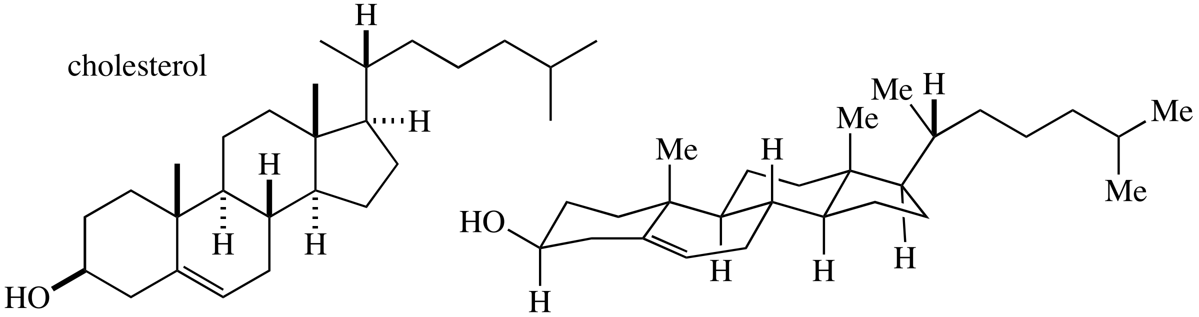
cis-1,2-dimethylcyclohexane *cis*-decalin



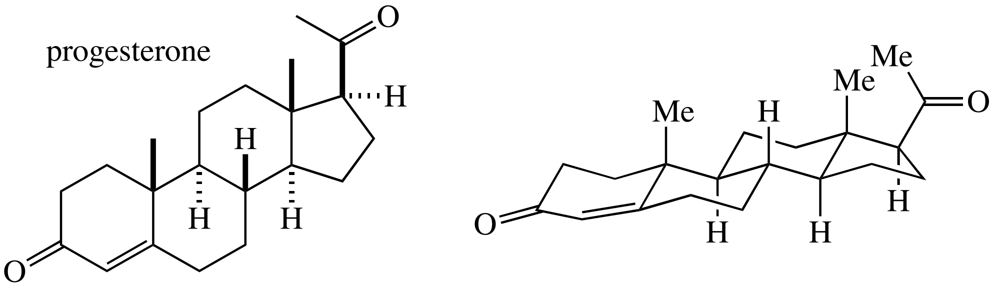
trans-1,2-dimethylcyclohexane *trans*-decalin

Steroids consist of several six-membered rings fused together. These are almost always fused like *trans*-decalin is. You may remember when I drew cholesterol, and I drew wedges to certain Me and H substituents and hashes to others. This was to indicate a particular diastereomer. I can draw a perspective drawing of cholesterol which shows more explicitly how certain groups are *cis* to each other and how some are *trans*. More importantly, the perspective drawing shows how cholesterol is locked into a *trans*-decalin-type conformation. It is conformationally immobile. This is true of steroids in general. Flat and perspective drawings of progesterone and testosterone are shown for comparison. Note how the small change from a ketone to an alcohol at one end of the steroid changes it from a female sex hormone to a male sex hormone! This shows the importance of functional groups in defining the chemistry of a compound. You can also see the dramatic effect of adding an ethynyl group to testosterone: one obtains a birth control medication!

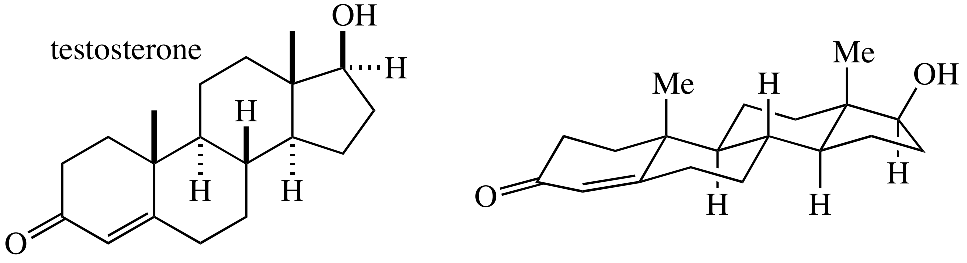
cholesterol



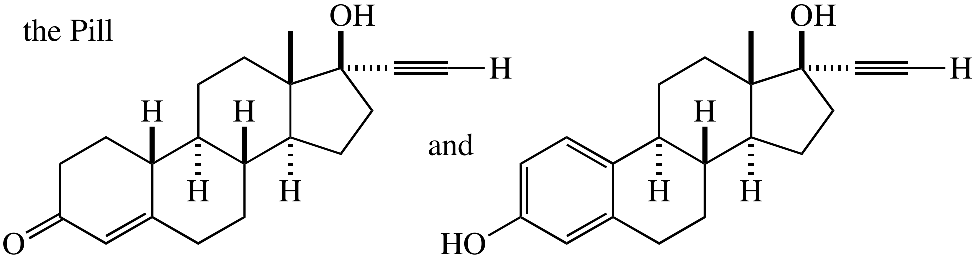
progesterone



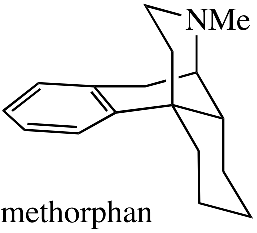
testosterone



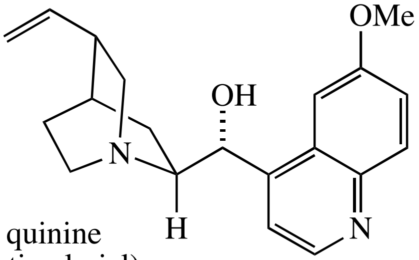
the Pill



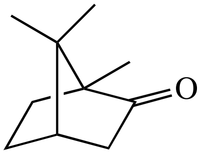
We can also have polycyclic compounds that are bridged. In these compounds, a chain of one or more atoms connects two noncontiguous ring atoms. These compounds can be bicyclic or tricyclic. Examples of compounds that have both bridged rings are dextromethorphan, found in your medicine cabinet as a cough suppressant, quinine, an antimalarial medicine, and camphor, an ointment used in various remedies. Note how dextromethorphan has three cyclohexane rings (one with a N instead of C). Two of these are *cis*-fused, two are *trans*-fused, and two are bridged. There is also a benzene ring fused to one of the cyclohexane rings.



dextromethorphan
(cough suppressant)



quinine
(antimalarial)



camphor
(ointment)