

5. Stereochemistry and Conformational Analysis of Rings.

5.1 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*.

5.2 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 B yer in 1885. In fact, von B yer's theory was not correct except for the very smallest rings, and for a very good reason that even von B yer 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 O₂, 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

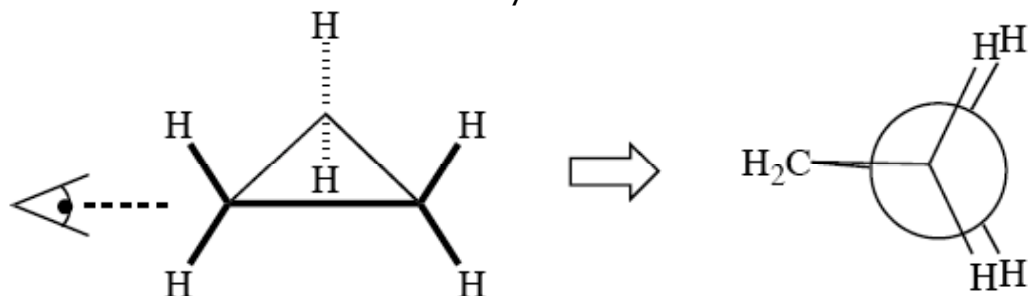
The ring strain starts very high, reaches zero with cyclohexane, increases again to a local maximum at cyclononane, and then decreases to reach zero again with cyclotetradecane.

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.

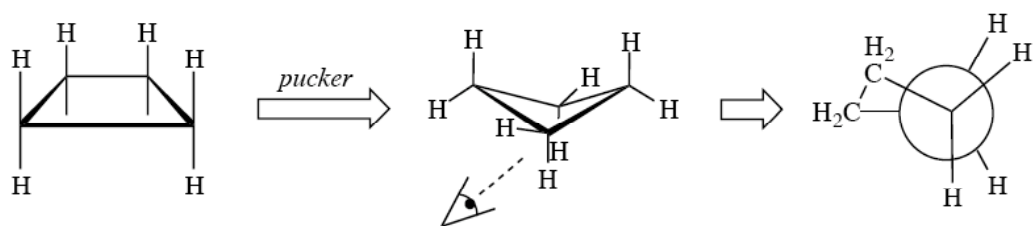
5.3 Conformations of 3- to 5-Membered Rings.

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 sp³ orbitals making up the bond don't meet head-on, so that the bonds are bent (banana bonds, **Jones Fig 5.3**). As a result, cyclopropane is

much more reactive than most cycloalkanes.

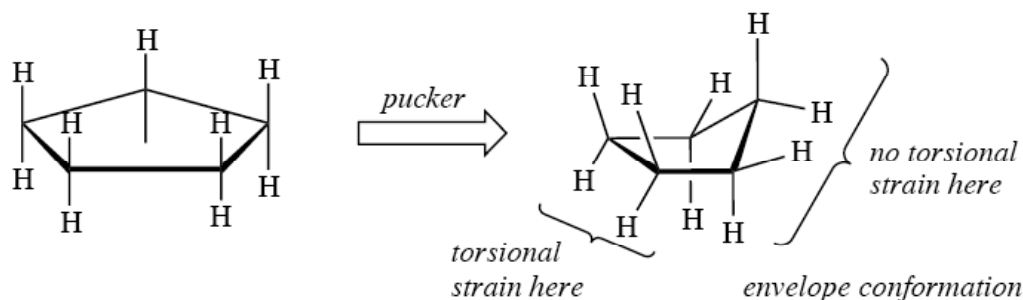


Cyclobutane, on the other hand, puckers a little bit. This makes the bond angles smaller than the planar angle of 90°, increasing the angle strain, but it relieves a lot of torsional strain.



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.

Cyclopentane was predicted to have no angle strain by B  yer. 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 sp³-hybridized C atom in the ring into an sp²-hybridized atom).

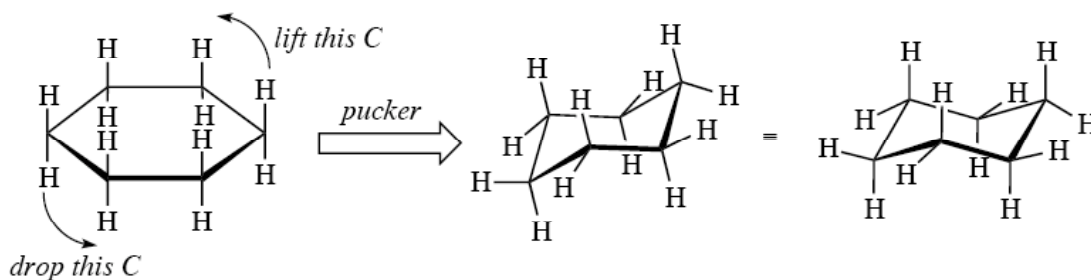


Suppose the different C atoms in the ring are non-identical, i.e. have different substituents. How do we know which C atom in cyclopentane will pucker? The answer is that we would have to look at the different energies of the different diastereomeric conformations, and there would be an equilibrium between 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 cyclohexanes fit a regular and predictable pattern.

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

5.4 Chair Cyclohexane.

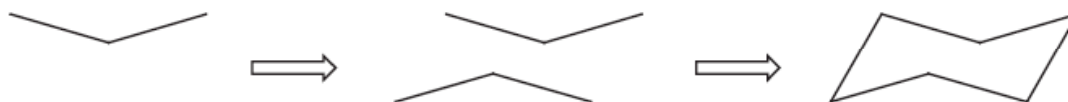
As we saw earlier, cyclohexane is the least strained of all the ring sizes. It has neither angle strain nor torsional strain. This is because it can pucker in such a way that all of the bonds are perfectly staggered, and in this conformation all of the bond angles are 109° ! This conformation is called 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).



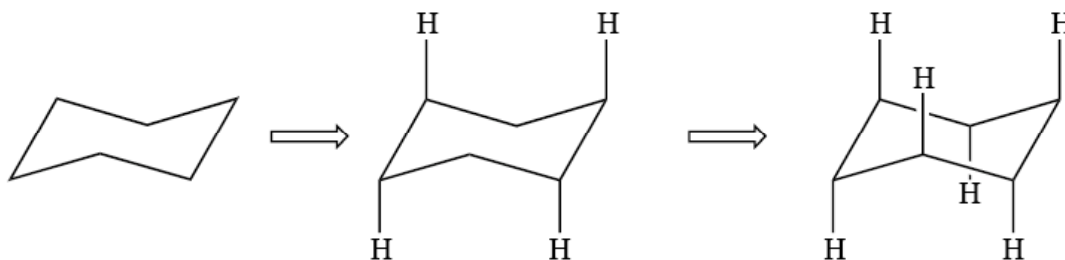
There are two kinds of C–H bonds in cyclohexane. The vertical bonds are called *axial*. The horizontal bonds are called *equatorial*, and they point slightly up or slight down. The six carbons and six equatorial hydrogens form two close planes, while the six axial hydrogens are above and below these 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 (each H_{eq} is parallel to the two C-C bonds one bond away) and gauche to all neighboring C-H bonds. The C1, C3, and C5 axial C-H bonds are parallel to one another.

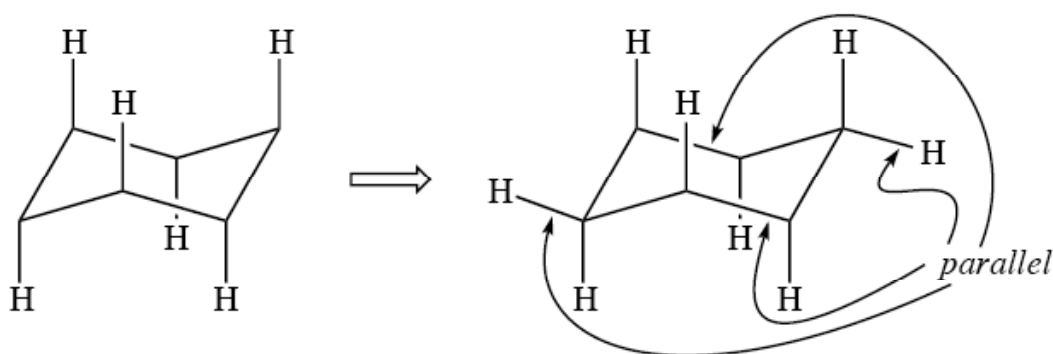
The chair conformation is so important that every student must learn how to draw it properly. Start off with by drawing a shallow V. Then draw the same V but upside-down and offset to the left a little bit. Then connect the ends of the upper and lower V's. You have your chair! The outermost C's are *in* 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.



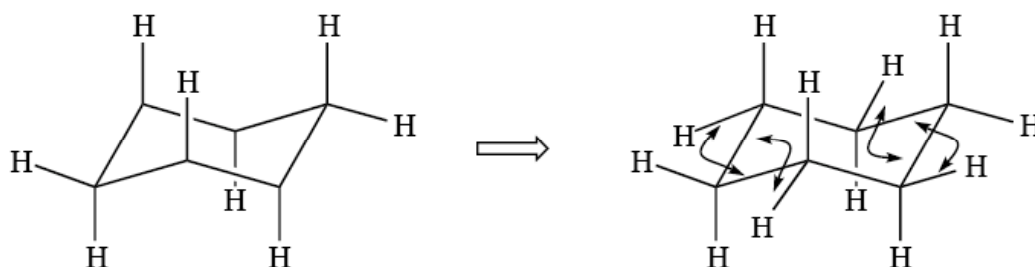
It is equally important to draw the axial and equatorial C-H bonds properly. The two uppermost C's in your drawing have their axial bonds pointing up, and the two bottommost C's have them pointing down. Draw in the axial bonds on the other two C's so that the axial bonds alternate up and down around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

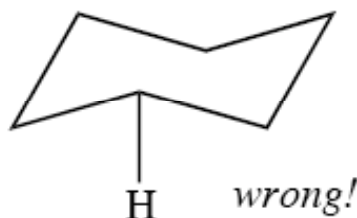
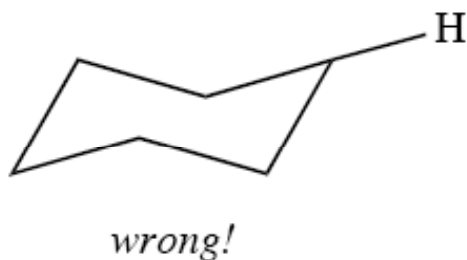


The other equatorial C-H bonds are also parallel to ring bonds, as shown by the arrows. Again, the equatorial bonds on the atoms on the left point to the left, and the equatorial bonds on the atoms on the right point to the right.



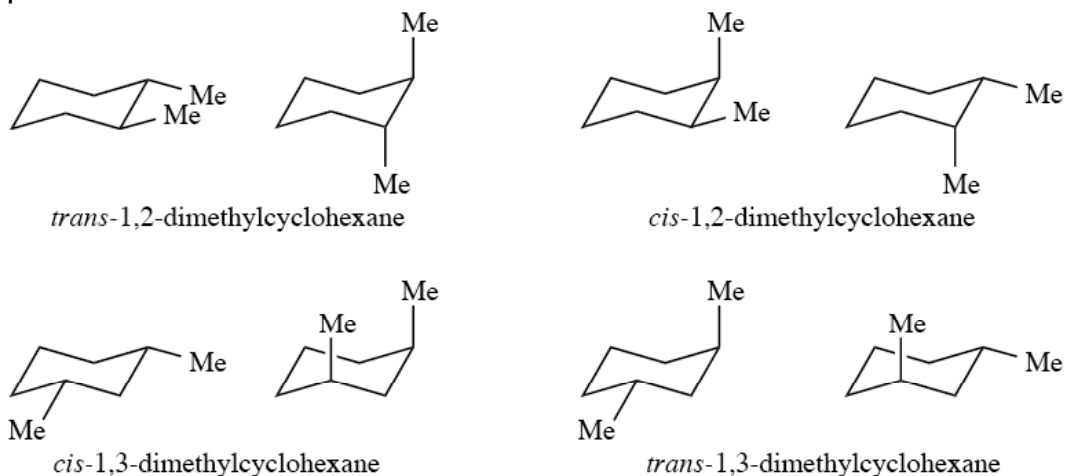
To see how the way we draw the cyclohexane ring corresponds to a projection of the real ring, make a model! The model will also show you how the compound puckers to achieve a conformation in which all bonds are staggered and all angles are 109° . But the *only* way to learn to draw a chair is to *practice*. 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!

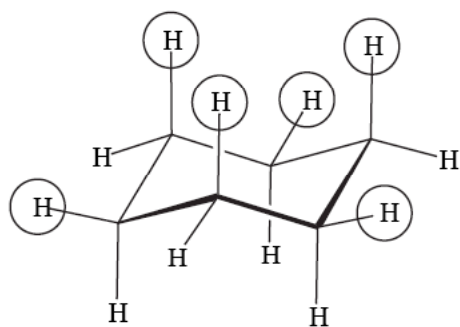


The terms axial/ equatorial and *cis*/ *trans* describe unrelated properties of substituents. Two substituents that are *cis* are always on the same

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*.



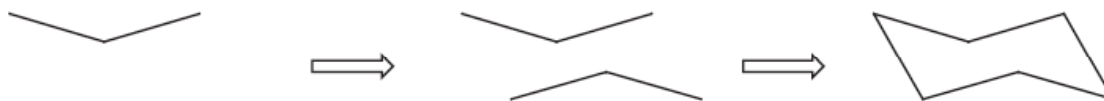
One way to look at a cyclohexane ring in a chair conformation and immediately see which groups are *cis* and which are *trans* is to do the following. Circle the equatorial group on C1. The group *cis* to this one on C2 is axial; circle it. The group *cis* to these on C3 is equatorial; circle it too. 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*.



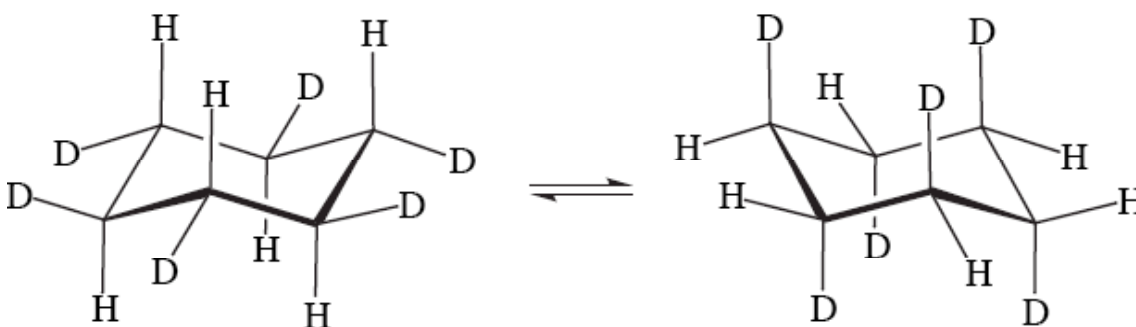
All circled groups are *cis*.
 All uncircled groups are *cis*.
 All circled groups are *trans* to all uncircled groups.

Any cyclohexane ring can theoretically exist in two different chair conformations. The interconversion of one with the other is called a

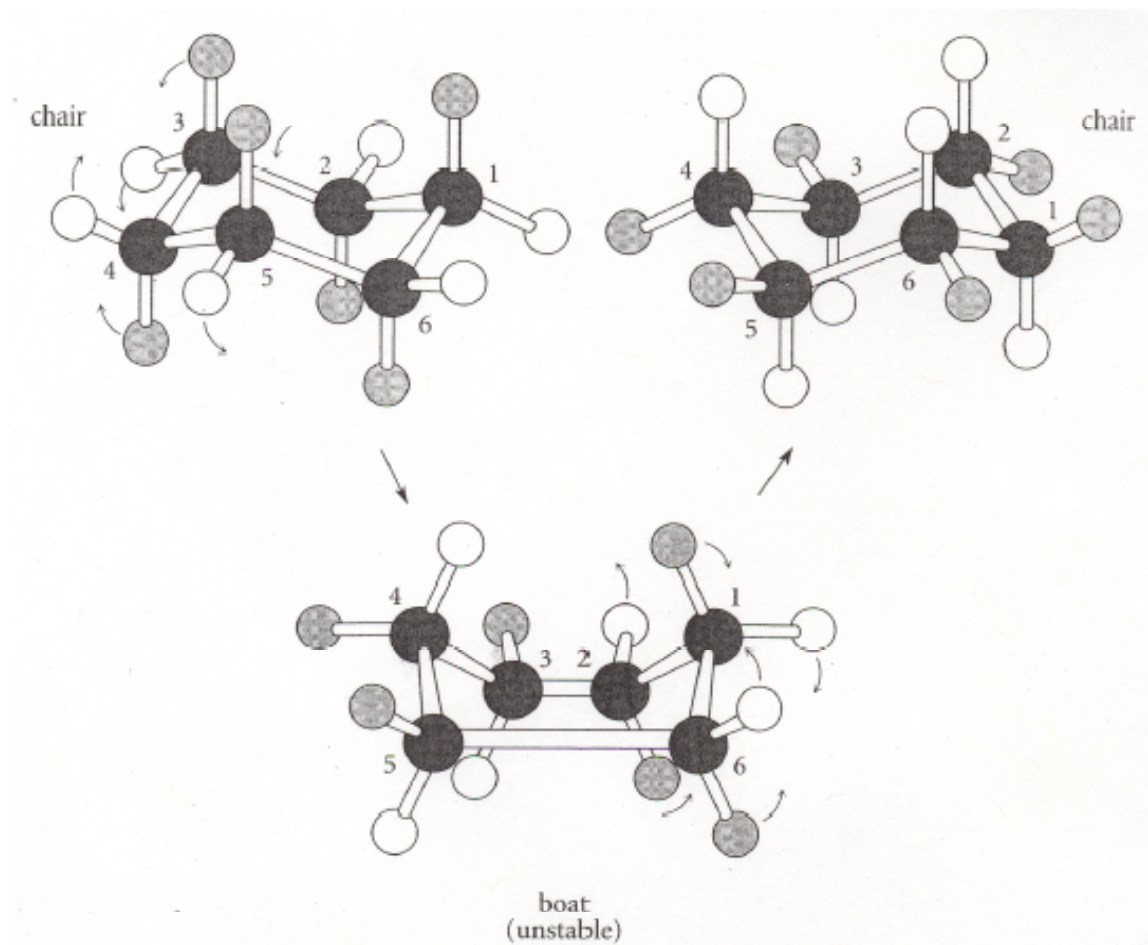
ring flip. The flipped chair is drawn similarly to the first chair that we drew, except that the upside-down V is offset to the right, rather than to the left.



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.

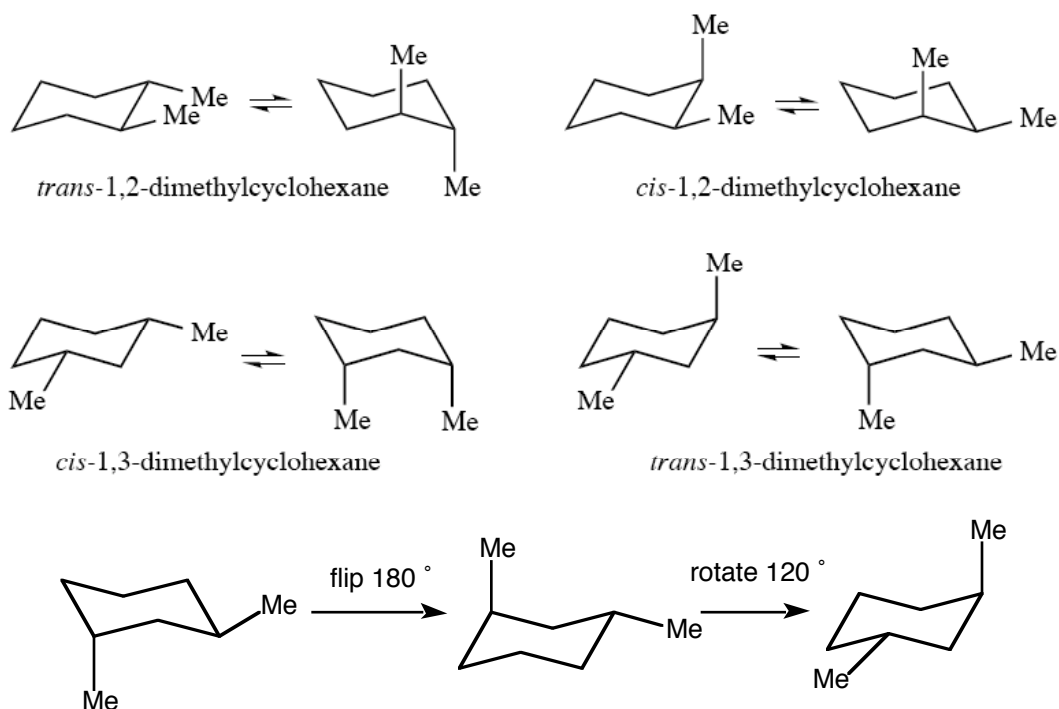


The two chair conformations of a substituted cyclohexane are sometimes stereoisomeric. They may be **conformational enantiomers, conformational diastereomers, or identical structures**. We call the stereoisomeric pairs "conformational" and not "configurational" because the chair flip is a special kind of rotation about C-C σ bonds.



Interconversion of the two chair conformations of cyclohexane (the chair flip). The colored arrows show how the atoms move in each step.

Remember, 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.



Problem (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.

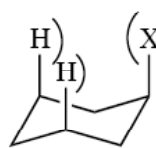
A monosubstituted cyclohexane such as methylcyclohexane has two low-energy diastereomeric conformers, one in which the substituent is axial and one in which it is equatorial. The axial conformer is *almost always* less stable than the equatorial conformer. This is because in the axial conformer there 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.



The difference in free energy (ΔG°) 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 similar 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 [Remember $\Delta G^\circ = -RT \ln K$ hence the equilibrium constant is calculated by: $K = e^{(-\Delta G^\circ / RT)}$ where 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)].

The investigation of molecular conformations and their relative energies is called **conformational analysis**. 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.

	Strain of one		Strain of one		Strain of one	
	X	1,3-diaxial interaction	X	1,3-diaxial interaction	X	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>i</i> -Pr	1.1	CN	0.1
	OH	0.5	<i>t</i> -Bu	2.7		

You can calculate the proportion of each monosubstituted cyclohexane that exists in the axial or equatorial conformation by plugging the energy of two 1,3-diaxial interactions into the formula: $K = e^{(-\Delta G^\circ / RT)}$ [where 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)].

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 ($4 \times 0.9 = 3.6$ 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 $2 \times 0.9 + 3.7 = 5.5$ kcal/mol. This is a very large difference in energy.

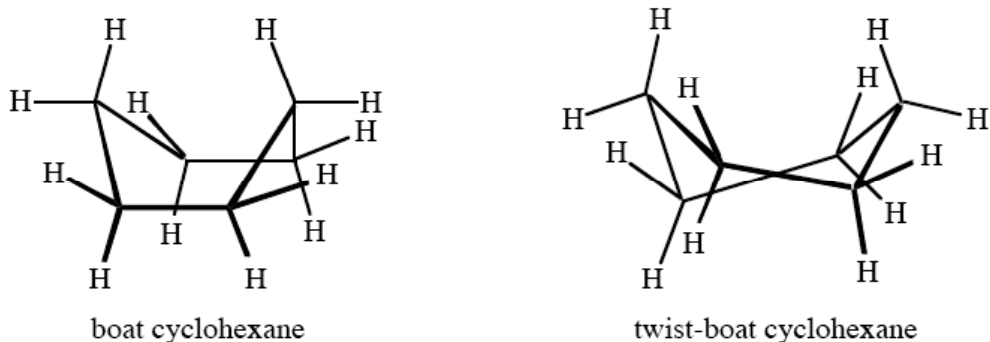
Problems for home. (7) Calculate the proportion of *cis*-1,3-dimethylcyclohexane that exists in the diaxial conformation. (8) Compare the steric energies of the chair conformers of *trans*-1,3-dimethylcyclohexane and determine which (if either) is stabler.

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.

5.5 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 (*van der Waals strain*) 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.



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.

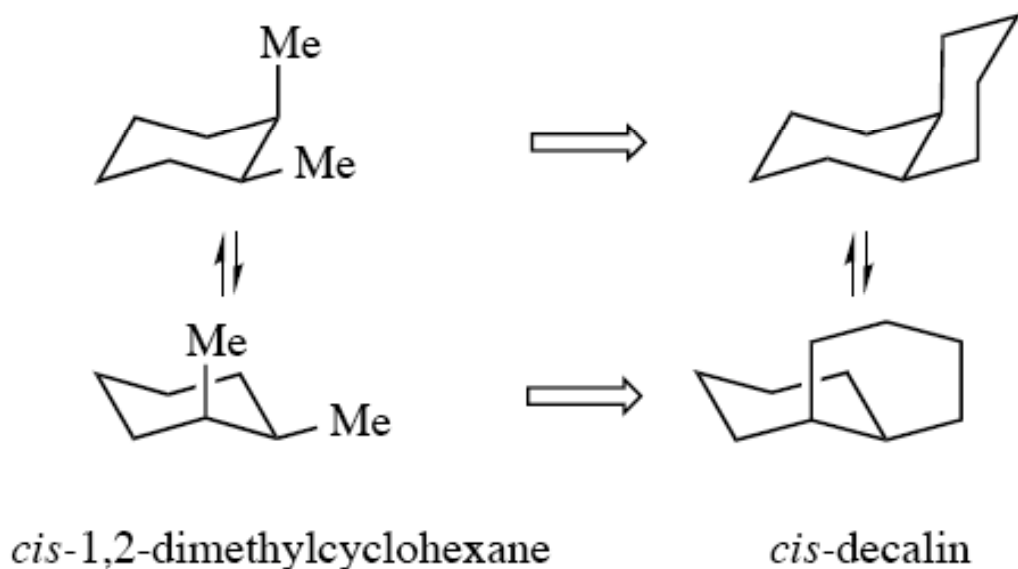


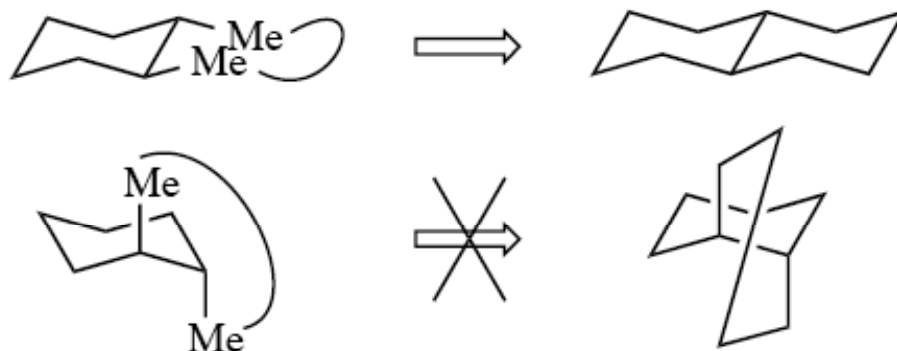
Remember that the twist-boat conformation is higher than the chair by 5.5 kcal/mol only for unsubstituted cyclohexane; appropriate substituents can raise the energy of the chair relative to the twist-boat until the twist-boat is more stable than the chair.

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

5.6 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 $-\text{CH}_2\text{CH}_2-$ 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.

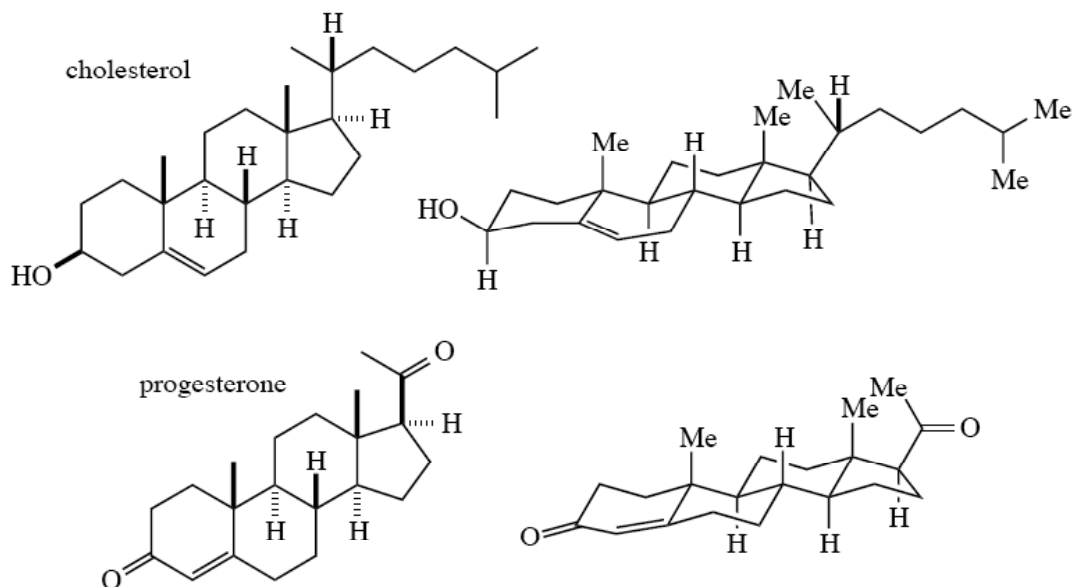


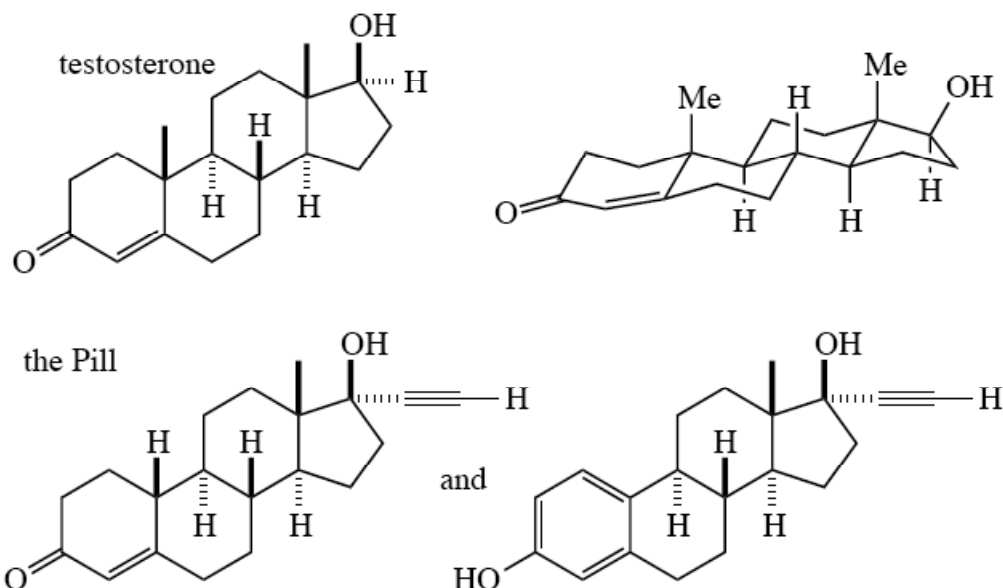


trans-1,2-dimethylcyclohexane

trans-decalin

Steroids consist of several six-membered rings fused together. These are almost always fused like *trans*-decalin is. 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!





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 anti-malarial 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.

