4. **Stereochemistry and Conformational Analysis of Rings.**

4.1 **Conformational stereoisomers of acyclic alkanes.**

Let's take a closer look at ethane. The C–C σ bond in ethane has cylindrical symmetry, so we can rotate the two CH₃ groups with respect to one another without changing the amount of overlap between the two sp³ 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 $\sigma^*$ orbital of the staggered C–H bond. This \textit{hyperconjugative} interaction helps to delocalize the electrons, lowering their energy. The interaction is better in the staggered conformer, because the big lobe of the $\sigma$ orbital overlaps with the big lobe of the $\sigma^*$ orbital. In the eclipsed conformer, the big lobe of the $\sigma$ orbital overlaps with the small lobe of the $\sigma^*$ orbital.

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 \textit{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.

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).

If we look down the C1–C2 σ bond of butane, 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 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 conformation, two H's are labeled for reference. The H*-C–C–H* dihedral angle of the conformation on the left is somewhere between 0° and 60°, say 30°. In the conformation on the right, the angle is -30°. If you make models of these two conformations, 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!

4.2 Configurational stereoisomers of alkenes.

We saw that the two ends of ethane can rotate with respect to one another with only a small barrier to rotation due to the loss of hyperconjugative stabilization in the eclipsed isomer. Is the same true in ethylene (ethene)? If you look down the C–C axis in ethylene, you will see that each C–H bond on one C has a 180° dihedral angle with a C–H bond on the other C. A 90° rotation about the C–C bond gives a new conformational diastereomer of ethylene, in which no C–H bond has a 180° dihedral angle with another C–H bond. As a result, you might expect that ethylene would be predominantly planar, with a
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small barrier to rotation. In fact, the barrier to rotation in ethylene is very high, about 66 kcal/mol. Why? In the 90° isomer of ethylene, the two p orbitals are perpendicular to each other, so they don't overlap. No overlap, no bond. In other words, rotation about the C=C bond in ethylene breaks the π bond, increasing the energy of the electrons associated with that bond, so it is a very high energy process. Remember that room temperature supplies about 15 kcal/mol of energy. There is no rotation about C=C π bonds at room temperature!

If we replace an H in ethene with CH₃ to get a three-carbon compound with a double bond, we call it propene. Propene has three different kinds of C atoms. Two are sp²-hybridized, and the third is sp³-hybridized. The energy of the C(sp³)–H bond is higher than the energy of the C(sp²)–H bond because the energy of the C(sp³) orbital is higher than the energy of the C(sp²) orbital. We number the C atoms in propene from one end to another. The ends of propene are different, so we can number it in two different ways. We do it so that the atoms of the π bond have the lowest numbers possible.

We can replace one of the H atoms of propene with Cl, to get the skeletal isomers 1-chloropropene, 2-chloropropene, or 3-chloropropene. Actually, there are two kinds of 1-chloropropene. There is the kind where the Cl atom is near the CH₃ group attached to C(2), and there is the kind where the Cl atom is near the H atom attached to C(2). The relationship between these two compounds is that they have the same atom-to-atom connections, but different shapes, so they are stereoisomers. In this particular case, the internal dimensions of the compounds are different (look at the Cl–CH₃ distance and the Cl–C–C–C 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).

*Any alkene in which one C of the C=C bond is attached to two different groups, and the other C is also attached to two different groups, will have two diastereomeric forms.* For alkenes in which each C is attached to one H and one other group, we call these two forms cis and trans. So cis-1-chloropropene is the diastereomer in which the Cl and the CH₃ group are on the same side of the π bond, and trans-1-chloropropene is the diastereomer in which the Cl and the CH₃ group are on opposite sides of the π bond. Remember "cis — same side". In a moment we will see another, more general way of naming the two diastereomers of alkenes.
If we replace a terminal H in propene with a CH\(_3\) group, we generate either 1-butene or 2-butene. (If one replaces the internal H in propene with CH\(_3\), we generate 2-methylpropene, also known as isobutylene.) The number designates the position of the C=C bond in the chain. Not only do 1-butene and 2-butene have their \(\pi\) bond in different locations, but, by necessity, the C–H bonds have also been moved around, so 1-butene and 2-butene are **skeletal isomers**. Just as there are in 1-chloropropene, there are two diastereomers of 2-butene: *cis*-2-butene and *trans*-2-butene. They cannot interconvert by rotation, so they are configurational diastereomers.

The interconversion of cis and trans alkenes requires cleavage of the C=C \(\pi\) bond. This can happen when light of the proper wavelength is absorbed by an alkene, which promotes one electron from the \(\pi\) to the \(\pi^*\) orbital. Because 1/2 bond + 1/2 anti-bond = no bond, there is now no \(\pi\) bond and the molecule is free to rotate about what used to be the \(\pi\) bond. This process is used by nature in vision. 11-*cis*-Retinal is bound to a protein called opsin through exchange of the O of retinal for the N of an amino group of a lysine in the protein. When light enters the eye, the retinal absorbs the light and the *cis* double bond is converted to a trans double bond. This change in shape is detected by proteins which initiate an electrical impulse down the optic nerve to the brain. The all-*trans*-retinal is hydrolyzed away from the opsin, and a new 11-*cis*-retinal is attached. Meanwhile, the all-*trans*-retinal is transported to the back of the eye, where it is converted to the cis form, then transported back to the retina.
A compound XHC=CHY may be classified as cis or trans. But what does one do for a compound like, say, 1-iodo-1-bromo-2-chloro-1-propene? This compound can also exist as two diastereomers, but it's not clear which one is cis and which one is trans. In these cases we use the E/Z nomenclature.

First we need to assign priorities to the four groups attached to the double bond. Look at the atomic numbers of the two atoms attached to each C of the double bond. One C has I and Br attached: I has higher priority. The other C has C and Cl attached: Cl has higher priority. (It is helpful to circle the higher-priority group attached to each C.) If the two high-priority groups are on the same side of the double bond, the compound is "zusammen" (German for together), or Z; if they are on opposite sides, the compound is "entgegen" (German for against), or E. To help you remember the difference between E and Z, consider that "entgegen," "against," and "opposite" all begin with vowels, and "zusammen," "together," and "same side" all begin with consonants. In the name of the compound, the E or Z follows immediately after the number indicating the position of the double bond.

If the two atoms directly attached to a C are the same, one looks for the first difference between the groups attached to each of those atoms to determine which is higher priority. For example, in the compound below, C2 is attached to C1 and C6: no difference. C1 is attached to O, O, and O (the double bond to O is counted as two O atoms); C7 is attached to S, H, and H. The heaviest atom attached to C6 is heavier than the heaviest atom attached to C1, so C6 has higher priority. Similarly, C3 is attached to C4 and C7: no difference. C4 is attached to C5, C9, and H; C7 is attached to C8, H, and H. The heaviest atom attached to C4 is the same as the heaviest atom attached to C7, but the second-heaviest atom attached to C4 is heavier than the second-heaviest atom attached to C7, so C4 has higher priority. The two high-priority groups, C4 and C6, are against one another, so the isomer is E.

Each C atom in an alkene that can have E and Z isomers is stereogenic, because switching the position of two groups attached to the alkene C atom generates a stereoisomer. When counting the number of
stereoisomers that a compound has, it is useful to think of the entire alkene unit as being a single stereogenic unit. For example, 3-penten-2-ol has two stereogenic units — one alkene and one tetrahedral stereocenter — so it has four stereoisomers: (R,E), (R,Z), (S,E), and (S,Z).

4.3 Cycloalkane stereoisomerism.

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–wedge 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 nonsuperimposable mirror images.

![Diagram of cis-1,2-dibromocyclopropane and trans-1,2-dibromocyclopropane](image.png)

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.

The concept of diastereomers extends to cyclic compounds with any number of ring atoms. A *cyclic compound consists of two or more diastereomers if at least two C or N⁺ atoms in the ring bear two different substituents*. For example, 4-hydroxyproline consists of two diastereomers, *cis*-4-hydroxyproline and *trans*-4-hydroxyproline, because one C in the proline ring bears H and CO₂H, and another bears H and OH. The trans diastereomer is incorporated into the protein collagen; the cis diastereomer is not.
The requirement that there be at least two C atoms bearing two different substituents means that you consider only sp\(^3\)-hybridized C atoms when looking for the possibility of diastereomers in cyclic compounds.

Many monosaccharides (simple sugars) are diastereomers of one another. It’s easiest to see in the sugars’ cyclic forms, which are called furanoses when they are five-membered rings and pyranoses when they are six-membered rings. (We’ll see later that sugars can exist in interconverting cyclic and acyclic forms.) β-D-Ribofuranose and β-D-xylofuranose are diastereomers, differing from one another in the orientation of a single OH group at C(2) of the ring. RNA contains only ribose and no xylose at all. The most common form of glucose, β-D-glucopyranose, differs from α-D-glucopyranose (another form of glucose), β-D-mannopyranose (a form of mannose), and β-D-galactopyranose (a form of galactose) by the orientation of a single OH group at C(1), C(2), and C(4), respectively, so all these compounds are diastereomers of one another. Glucose, mannose, and galactose have very different chemical and biological behaviors because they are diastereomers.
Both cellulose and starch are made up of repeating D-glucopyranose units. The difference between cellulose and starch is that cellulose is made up of repeating β-D-glucopyranose units (in which the C(1)O group is cis to the CH$_2$OH group), whereas starch is made up of repeating α-D-glucopyranose units (in which the C(1)O group is trans to the CH$_2$OH group). As you know, starch and cellulose have very different physical, chemical, and biological properties. We’ll see soon how their different physical properties can be explained by their shapes.

Cholesterol, with its four rings and many substituents, has many diastereomers.

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.
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**Problem.** (3) Which of the cyclic skeletal isomers of C$_5$H$_{10}$ and C$_6$H$_{12}$ have *cis* and *trans* isomers? Draw them using the hashed/ wedged line convention.

### 4.4 Ring size and energy.

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 $180^\circ - \frac{360^\circ}{n}$. The calculated bond angles are shown for polygons from a triangle to a decagon.

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<th>Polygon</th>
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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:

<table>
<thead>
<tr>
<th>Ring size</th>
<th>Ring strain (kcal/mol)</th>
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<th>Ring strain (kcal/mol)</th>
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<td>12</td>
<td>14</td>
<td>0</td>
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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°.

Naturally occurring cyclic compounds most often have five- and six-membered rings.

4.5 Conformations of 3- to 5-Membered Rings.

Let's now look at the conformations of specific cycloalkanes in detail.

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

### 4.6 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!

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. For example, we drew two conformations for each of four dimethycyclohexane isomers earlier. Each pair of conformations can interconvert through a ring flip. The two conformations of trans-1,2-dimethycyclohexane are conformational diastereomers (because their internal dimensions (e.g., Me–Me distance) are different), as are the two conformations of cis-1,3-dimethycyclohexane. But the two conformations of cis-1,2-dimethycyclohexane are conformational enantiomers, and the two conformations of trans-1,3-dimethycyclohexane are identical.

**Problem for home.** (5) Draw trans-1,4-dimethycyclohexane 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 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\(_2\)H 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.

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.

**4.7 Conformations of hexapyranoses. Anomeric effect.**

We discussed earlier that the six-carbon sugars D-glucose, D-mannose, and D-galactose were commonly in the form of six-membered rings, and that these six-membered rings are diastereomers of one another. If we look at these compounds in their chair conformations, we see that β-D-glucopyranose has all
substituents on the six-membered ring in equatorial positions, whereas \( \alpha \)-D-glucopyranose, \( \beta \)-D-mannopyranose, and \( \beta \)-D-galactopyranose each have one equatorial OH group.

\[
\begin{align*}
\text{\( \beta \)-D-glucopyranose} & \quad \text{\( \alpha \)-D-glucopyranose} & \quad \text{\( \beta \)-D-mannopyranose} & \quad \text{\( \beta \)-D-galactopyranose} \\
\text{HO-} & \quad \text{HO-} & \quad \text{HO-} & \quad \text{HO-} \\
\text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\text{1,2,4} & \quad \text{1,2,4} & \quad \text{1,2,4} & \quad \text{1,2,4} \\
\text{OH} & \quad \text{OH} & \quad \text{OH} & \quad \text{OH} \\
\text{HO} & \quad \text{HO} & \quad \text{HO} & \quad \text{HO} \\
\text{HO} & \quad \text{HO} & \quad \text{HO} & \quad \text{HO} \\
\text{HO} & \quad \text{HO} & \quad \text{HO} & \quad \text{HO}
\end{align*}
\]

It’s also easier now to understand why cellulose and starch have such different physical properties. In cellulose, all ring C–O bonds are equatorial, causing the polymer to have a very flat shape, which allows individual polymer molecules to nestle against one another very tightly, making them hard to break apart and digest. By contrast, in starch, the bond joining C(1) of each glucose molecule to O(4) of the next glucose molecule is axial, causing the polymer to have more of a zigzag or ladder shape, which makes it less prone to form tough fibers.
If you ask whether starch or cellulose is higher in energy, you might expect to hear that starch is higher in energy because it has axial C–O bonds, whereas cellulose does not. However, it turns out that when a ring C–OR bond is adjacent to a ring O, the axial orientation of the OR group is lower in energy. This effect, called the *anomeric effect*, can be explained by hyperconjugation. Electronegative elements such as O have low-energy atomic orbitals, and that low energy is reflected in MOs (both σ and σ*) that are constructed from those AOs. In fact, the energy of the σ* orbital associated with the C–OR bond is low enough that it can interact with nonbonding orbitals such as the ones containing the ring O atom’s lone pairs. When the OR group is axial, the filled sp³ orbital containing the ring O atom’s axial lone pair is nicely aligned with the empty σ* orbital associated with the axial C–O bond; this favorable interaction of a filled and an empty orbital is not present when the OR group is equatorial. The combination of the small steric bulk of an O atom (which reduces 1,3-diaxial interactions) and the favorable energy of the anomeric effect together make the axial (or α) orientation adjacent to the O lower in energy than the equatorial (or β) orientation. Note that the anomeric effect applies only to the C atom adjacent to the ring O and only when the group attached to that C atom is O (or another electronegative element).

![Diagram of anomeric effect](image)

**4.8 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.
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?

4.9 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.
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-methylcyclohexane. (e,f) cis- and trans-1,4-Dimethylcyclohexane. (g,h) cis- and trans-decalin.

\[
\begin{array}{c}
\text{chiral} \\
\text{Me} \\
\end{array} \rightarrow \begin{array}{c}
\text{achiral} \\
\text{Me} \\
\end{array} \uparrow \rightarrow \begin{array}{c}
\text{chiral} \\
\text{Me} \\
\end{array}
\]

**4.10 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 –CH₂CH₂– 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 CH₂CH₂ group is insufficiently long to bridge them. trans-Decalin is said to be conformationally locked because it can't undergo a ring flip.

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 change 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 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)