5. Stereochemistry.

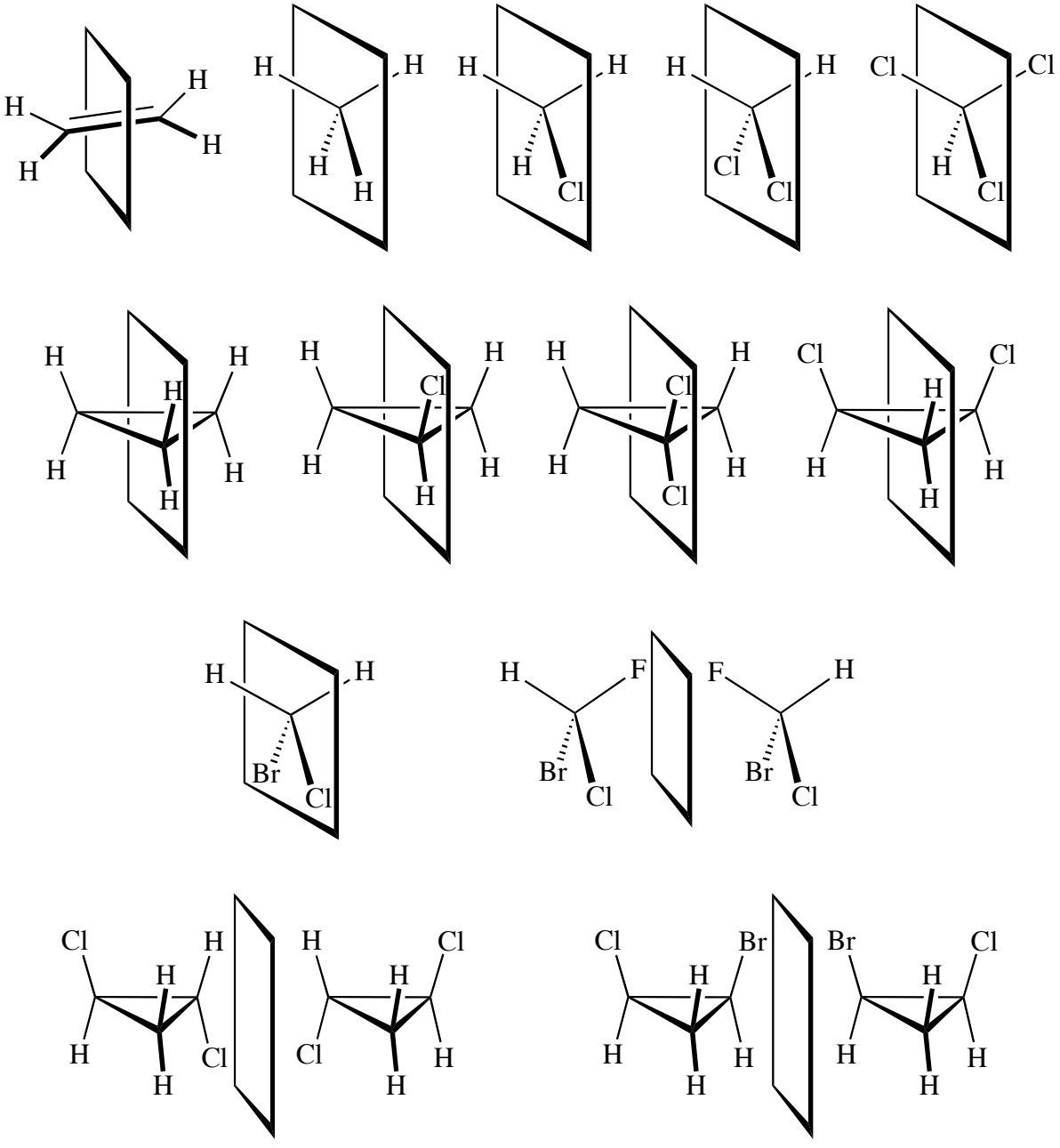
5.1 Enantiomers and Chirality.

We've learned about enantiomers, compounds whose internal dimensions — atom–to–atom connections, bond angles, dihedral angles, interatomic distances — are identical in all respects but whose structures are non-superimposable. We've seen that certain structures are identical to their mirror images, and do not have enantiomers, while other compounds are non-superimposable with their mirror images, and do have enantiomers. There is a particular property of shape, called *chirality,* that allows one to determine whether a compound has an enantiomer or not. A compound that is *not* identical to its mirror image is called a *chiral* compound (from the Greek word for hand). A compound that is identical to its mirror image is said to be *achiral*. Note that "chiral" and "achiral" refer to *structures,* while "enantiomer" refers to the *relationship of one structure to another*. Every structure with a shape is either chiral or achiral, whether it is microscopic like a molecule or macroscopic like a hand, chair, or building. Helices like DNA, screws, and Slinkies are chiral; that's why screws have right-handed or left-handed threads.

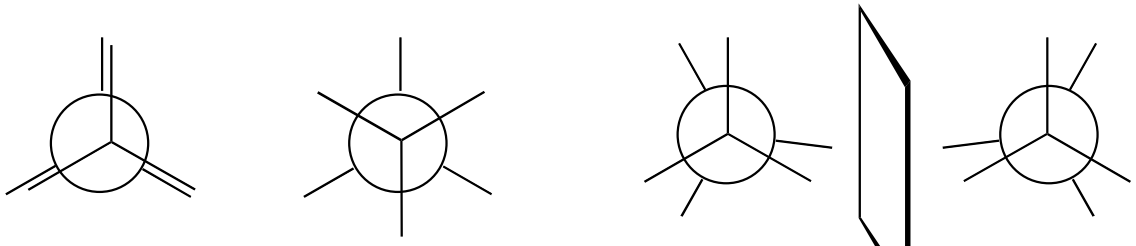
You can tell whether an object is achiral or chiral simply by examining its shape. There is a way of classifying objects according to the symmetry characteristics of their shapes. This is called group theory. We won't go into the details now. At this point, all we need to know is that any object (including a molecule) that has a *plane of symmetry* must be *achiral*. Such an object is *identical* to its mirror image. Almost any object which lacks a plane of symmetry must be *chiral,* i.e. *not identical* to its mirror image. (An object might also be achiral if it has a *center* of symmetry or an *improper axis* of symmetry. Most achiral organic compounds, though, have a plane of symmetry, so we don't need to worry about these other symmetry elements.)

Let's look at what is a plane of symmetry. First, consider a human being. If we think about the plane going through the center of a person that separates the left and right sides, we can see that the plane relates the two sides as a mirror does. That is, if someone stood to my left and looked toward the plane, that person couldn't tell whether she was seeing my right side in the plane or whether she was seeing a reflection of my left side. This means that the human body is achiral. A broom is achiral. A chair is achiral. The frame of an automobile is achiral. (But the inside is not, because the driver's side has a wheel and the passenger side does not.) All of these objects have planes of symmetry. Now look at your hand. You can't find a plane of symmetry in your hand. Therefore it is chiral. Try to find a plane of symmetry in an extended Slinky™; you won't be able to find one.

How about molecules? The situation here is a little more complicated, because many molecules constantly *change* their shape by rotation about σ bonds. Let's start with compounds that don't undergo rotations about σ bonds. We can certainly say that ethylene is achiral. Same for methane, chloromethane, dichloromethane, and chloroform. Cyclopropane is achiral, and so is chlorocyclopropane, 1,1-dichlorocyclopropane, and *cis*-1,2-dichlorocyclopropane. All these compounds have planes of symmetry. Bromochloromethane is also achiral: it has a plane of symmetry containing the C, Br, and Cl atoms and relating the two H atoms to one another. On the other hand, bromochlorofluoromethane is *chiral*. It has no plane of symmetry, and it is nonsuperimposable with its mirror image. *trans*-1,2-Dichlorocyclopropane is also chiral, as is *cis*-1-bromo-2-chlorocyclopropane.



How about compounds that change their shape? Let's look at ethane first. We have to consider all the different conformers, because different conformers have different shapes, and chirality is a property of shape. Staggered ethane has a plane of symmetry (several, in fact), as does eclipsed ethane. But if we look at a conformation of ethane in between staggered and eclipsed, e.g. by starting with eclipsed ethane and twisting the H–C–C–H dihedral angle 30° in one direction, we find that this conformer has no plane of symmetry. This conformer of ethane is *chiral*. Its nonidentical mirror image is a different conformer of ethane, arrived at by starting with eclipsed ethane and twisting it 30° in the opposite direction. These two enantiomers can interconvert easily by rotation about the C–C σ bond, so they are *conformational enantiomers*.



eclipsed
dihedral angle 0°
achiral

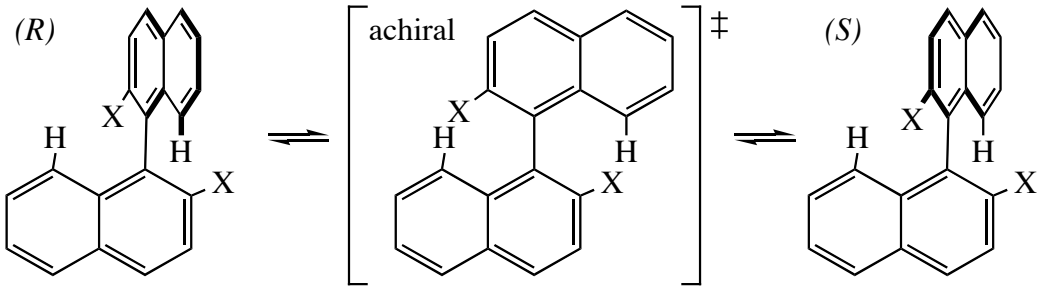
staggered
dihedral angle 60°
achiral

partly staggered
dihedral angle 30°
chiral

partly staggered
dihedral angle –30°
chiral

Almost any compound with more than two or three C atoms has an infinite number of chiral conformers. Even local minima can be chiral; for example, gauche butane. In practice, though, we say that a compound is achiral *if any of its low-energy conformers are achiral*. Ethane's staggered and eclipsed conformers are achiral, so ethane is said to be achiral, even though it has many chiral conformers. In practice you can ignore the H atoms in CH_3, NH_2, and OH groups (but not CH_2 groups!) when you are deciding whether a compound is chiral.

You might ask, how low is "low-energy"? This is a very good question. The answer depends on what time scale we're talking about. If we look at a compound on the time scale of μs, we have a very different sense of "rapid" than if we look at it on the time scale of days. For example, when X = H in the aromatic compound below, the two conformational enantiomers interconvert with a half-life less than seconds. However, when X = OH, the interconversion is slow on a time scale of days, even at very high temperatures. Is the X = H compound chiral or achiral? It depends on whether you're talking about a microsecond or a laboratory time scale! We will use the laboratory time scale, so we would say that the X = H compound is achiral and the X = OH compound is chiral.



Note that the word "chiral" refers to a single object or molecule, while the word "enantiomeric" refers to the *relationship* between two objects or molecules. An object or molecule is chiral if and only if it has an enantiomer. An object or molecule is achiral if and only if it does not have an enantiomer.

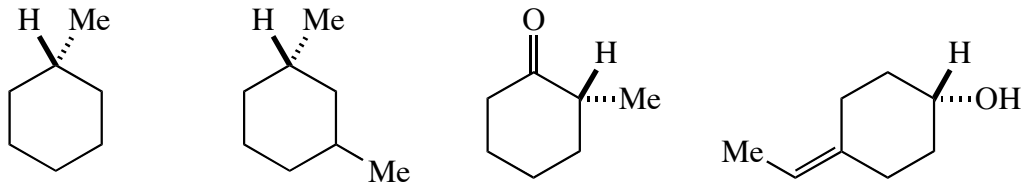
5.2 Stereogenic C Atoms.

Let's look at bromochlorofluoromethane again. This is a chiral compound. Let's do a thought experiment and switch the positions of any two groups attached to C. The compound we obtain is a stereoisomer of what we started with. (In this case, it's an enantiomer.) Any atom with the property that switching two of the attached groups generates a stereoisomer is called *stereogenic*. Both chiral and achiral compounds can have stereogenic atoms (also called stereocenters). For example, *cis*-1,2-dichlorocyclopropane has two stereocenters, C1 and C2. One can switch the H and Cl attached to C1 and obtain a new stereoisomer, and likewise with C2. The mutual orientation of the groups about a stereogenic center is called the *configuration*. If a compound has a stereogenic atom, and all the molecules in a sample of that compound have the stereocenter in the same configuration, the sample is said to be *configurationally pure,* by analogy to enantiopure.

Any C atom with four non-identical groups attached is stereogenic. This is true even when the two groups are nearly the same. For example, in 5-decanol, C5 is attached to OH, H, a straight chain of four C atoms, and a straight chain of five C atoms. Even though the latter two groups are similar, they are different enough that C5 is a stereogenic center. Even C5 in 1-deutero-5-nonanol is stereogenic, because the D atom on one of the Bu groups attached to C5 is sufficient to differentiate it from the other Bu group.

It takes practice to spot a stereogenic C atom, especially in cyclic compounds. For example, C1 in methylcyclohexane is nonstereogenic, because the C2-C3-C4 substituent is identical to the C6-C5-C4 substituent. On the other hand, C1 in 1,3-dimethylcyclohexane (either *cis* or *trans*) is stereogenic, because C2-C3 is different from C6-C5 (because C3 has H and Me attached, while C5 has two H's attached). C2 in 2-methylcyclohexanone is also stereogenic, because C1 is different from C3. In 4-

ethylidenecyclohexanol, C1 is stereogenic: C2 and C3 are closer to the Me group on the double bond than C6 and C5.



Problems for home: (2) Identify the stereogenic centers in the following compounds (some may have none). (a) Chlorocyclopropane. (b) 1,1-Dichlorocyclopropane. (c) *cis*-1,2-dichlorocyclopropane. (d) The two enantiomers of *trans*-1,2-dichlorocyclopropane. (e) Bromochloromethane. (f) Bromochlorofluoromethane. (g) Cholesterol.

The presence of a stereogenic center is neither necessary nor sufficient for a compound to be chiral, because chirality is a property of *shape*. Nevertheless, there is a *general coincidence* between the chirality of organic compounds and stereogenicity. It turns out that any compound with *exactly one* stereogenic C atom is chiral (in every conformation!), and the stereoisomer produced by switching two groups is its *configurational enantiomer*. For compounds with more than one stereogenic center, the situation is more complicated; we'll discuss it in more detail momentarily.

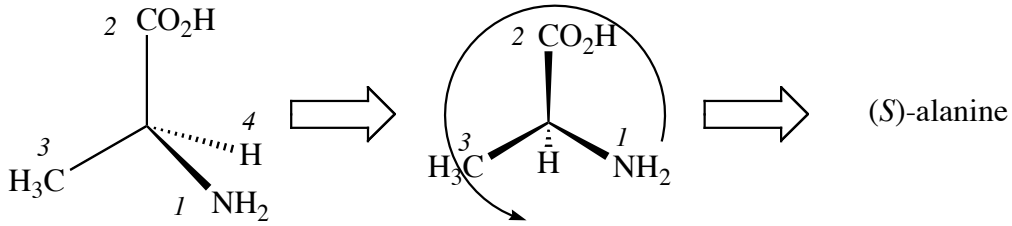
[Because of this general *coincidence* between chirality and the presence of stereogenic C atoms, stereogenic centers are sometimes called "chiral centers." This is *very* bad practice, because it causes confusion between the totally different concepts of chirality and stereogenicity, but unfortunately it's pretty common. Please don't pick up this bad habit.]

5.3 Nomenclature of Stereogenic C Atoms.

A stereogenic C atom can have one of two possible configurations. The system of nomenclature used to designate the configuration about stereogenic C atoms is called the Cahn–Ingold–Prelog (CIP) system. Let's look at natural alanine, one of the essential amino acids. Alanine, like all the amino acids (except glycine, which is achiral), occurs in configurationally pure form in nature. To determine the stereochemical designation for alanine, the first step is to assign *priorities* to the four groups NH_2, CH_3, CO_2H, and H that are attached to the stereogenic center. Priorities are assigned just as they were for alkenes. The order of priority is $NH_2 > CO_2H > CH_3 > H$.

Now we take a view of the stereogenic center such that the three higher priority groups (NH_2, CH_3, CO_2H) are arranged in a triangle coming towards us and the lowest-priority group (H) is pointing directly away from us into the plane of the paper. The three groups in the front will be arranged either in

clockwise or counterclockwise order from highest to lowest priority. If they are arranged *clockwise,* the stereocenter is designated (*R*) (Latin *rectum,* right). If they are arranged *counterclockwise,* the stereocenter is designated (*S*) (Latin *sinestrus,* left). One way to remember these is to think of the triangle as a steering wheel. If you turn the steering wheel counterclockwise from highest to lowest priority, you will turn left, so the stereocenter is (*S*). If you turn the steering wheel clockwise from highest to lowest priority, you will turn right, so the stereocenter is (*R*). In the example at hand, natural alanine has the (*S*) configuration.



This takes practice! There are plenty of problems in the book.

It's sometimes easier to put the lowest priority group in the front than in the back, so here's a trick. If you put the lowest-priority group in the front instead of the back, then the actual configuration is opposite to what it appears to be. For alanine, if you put H in the front, the other groups are arranged clockwise in order of decreasing priority, which seems to indicate *R,* so the actual configuration is *S*.

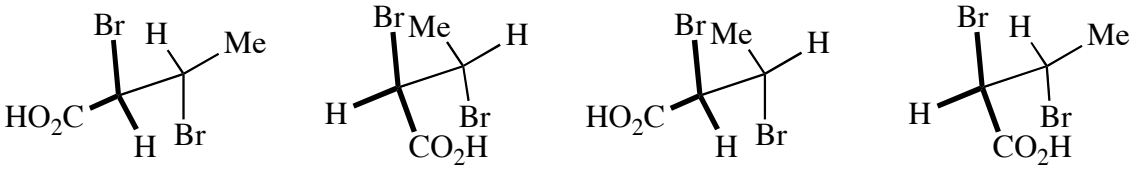
Note that (*R*) and (*S*) have nothing to do with (+) and (–). One indicates the configuration at a stereogenic center; the other indicates an optical property of a chiral compound.

You will sometimes see D and L in front of a compound's name: e.g. L-valine, D-glucose, L-dopa. The letter is usually in a smaller font from the rest of the compound. This is an old-fashioned way of indicating the enantiomer of a compound. D roughly corresponds to *R* and L to *S,* but the correspondence is not exact. In any case, all the naturally occurring amino acids are L, and all the commonly occurring sugars are D. The D and L nomenclature was superseded in the 1950s by the Cahn–Ingold–Prelog system, but it is still used out of habit, mostly by biologists.

5.4 Compounds with More than One Stereogenic Center.

Now let's consider what happens when compounds have more than one stereogenic center. Consider 2,3-dibromobutanoic acid. This compound has two stereogenic centers, so four stereoisomers are possible. These are the (*2S,3R*), (*2R,3S*), (*2S,3S*), and (*2R,3R*) stereoisomers. We can call these **T,** *ent*-**T, E,** and *ent*-**E.** Compounds **T** and *ent*-**T** are enantiomers of one another: they have at least one conformation in which they are non-superimposable mirror images. Likewise, compounds **E** and *ent*-**E**

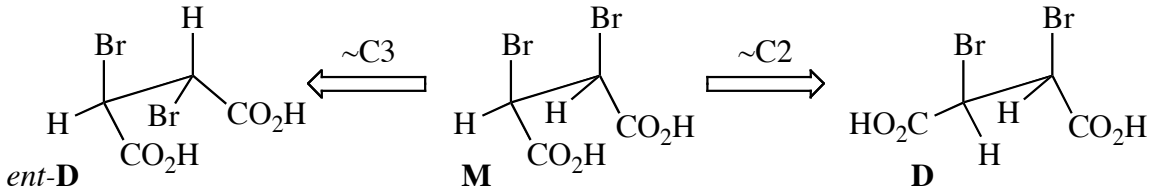
are enantiomers. What is the relationship between **T** and **E?** Well, **T** has the absolute (*R*) configuration at C3, while **E** has the (*S*) configuration there. These compounds cannot be interconverted by rotation about σ bonds, because no matter how much they undergo rotation, the configuration at C3 doesn't change. **T** and **E** *always* have different shapes no matter what their conformation. The *only way* they can be interconverted is by switching the configuration at C3. Since this requires bond-breaking, **T** and **E** are *configurational diastereomers*.



T *ent*-**T** **E** *ent*-**E**

If two stereoisomers differ in configuration at *some* but not *all* of their stereocenters, then they are *configurational diastereomers* (or just diastereomers for short). If they differ in configuration at *all* of their stereocenters, then they are usually *configurational enantiomers*.

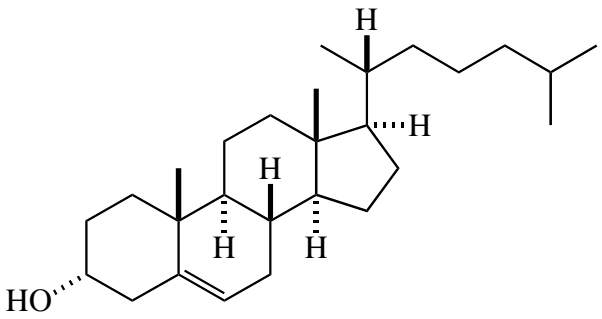
A compound can have more than one stereogenic center and be achiral. This occurs when the compound has a plane of symmetry. For example, (*2S,3R*)-2,3-dibromobutanedioic acid, **M,** has two stereogenic centers and is achiral. If we switch two of the groups about C2 in **M** we get (*2R,3R*)-2,3-dibromobutanedioic acid, **D,** which is chiral. If we switch two of the groups about C3 in **M** we get (*2S,3S*)-2,3-dibromobutanedioic acid, *ent*-**D,** which is also chiral and which is the enantiomer of **D.** Compounds like **M** that have stereogenic centers and are achiral are called *meso* compounds. There's nothing mysterious about meso compounds; they just happen to have a plane of symmetry. At least some of the diastereomers of meso compounds are chiral.



ent-**D** **M** **D**

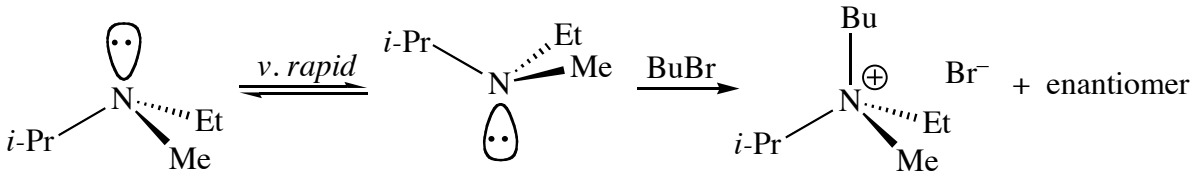
There are many compounds that have more than two stereogenic centers. For example, cholesterol has eight stereogenic centers. Switching any of the two groups about any of the stereogenic centers in cholesterol generates a diastereomer of cholesterol. (In animals, though, only one diastereomer of cholesterol is synthesized. This is because only the natural diastereomer of cholesterol has the physical properties necessary for its biological functions. Remember, different diastereomers have different chemical properties.) A compound with n stereogenic centers has exactly 2^n configurational

stereoisomers, unless some of its diastereomers are meso compounds; then it has fewer than 2^n configurational stereoisomers.



5.5 Other Stereogenic Atoms.

Other sp^3-hybridized atoms with four different groups attached are stereogenic. For example, the compound Ph(Me)Si(H)Cl has a stereogenic Si atom. How about N? Remember that in R_3N, the N atom is sp^3-hybridized. Could we say that the fourth "group" attached to N is its lone pair, and therefore that the N is stereogenic? In principle, yes, but in practice, the two enantiomers of a compound like *i*-Pr(Me)NEt interconvert so rapidly by *lone pair inversion* (like an umbrella) that the enantiomers can't be separated. If we alkylate *i*-Pr(Me)NEt with a compound like BuBr, though, we obtain a compound that has no lone pair to invert, and so in these kinds of compounds N *is* stereogenic.



Lone pair inversion in most N compounds occurs as rapidly as rotation about σ bonds. We must therefore update our definition of conformers: Conformers can be interconverted by rotating about σ bonds *or by N lone pair inversion*.

Problem for home. (3) In the transition state for N inversion, what is the hybridization of N? Compare the bond angles in the transition state to those in the ground states. How might you slow down N inversion?

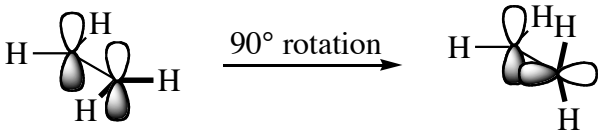
Lone pair inversion occurs very slowly for trivalent P and S^+, so these atoms are stereogenic. (E.g.: MeP(Et)Ph, $PhS^+(O^-)Me$.) The lone pairs in these compounds always have lowest priority. Other atoms such as O, divalent S, B, and the halogens are almost never stereogenic. If you take inorganic chemistry, you will learn about penta- and hexavalent stereogenic atoms, too.

5.6 Definitions of the Four Types of Stereoisomers, Again.

As we have already said, conformational stereoisomers can be interconverted by rotation about σ bonds or by N lone pair inversions, whereas configurational stereoisomers can be interconverted only by breaking bonds. An alternative definition of configurational stereoisomers is as follows: *Configurational stereoisomers have the same atom–to–atom connections but differ in their configurations at some or all of their stereocenters*. Configurational diastereomers differ in their configurations at *some but not all* of their stereocenters, and configurational enantiomers differ in their configurations at *all* of their stereocenters. Structures that have the same atom-to-atom connections and the same configuration at all of their stereocenters may be conformational stereoisomers or may be identical, but they are not configurational stereoisomers.

5.7 Stereochemistry 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? 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 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!



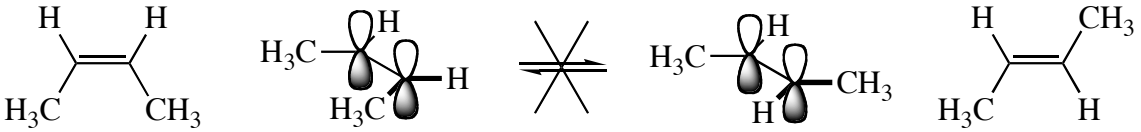
p orbitals overlap p orbitals don't overlap

If we replace an H in ethene with CH_3 to get a three-carbon compound with a double bond, we call it *propene*. Propene has three different kinds of C atoms. Two are sp^2-hybridized, and the third is sp^3-hybridized. The energy of the C(sp^3)–H bond is higher than the energy of the C(sp^2)–H bond because the energy of the C(sp^3) orbital is higher than the energy of the C(sp^2) 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 CH_3 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*. They are stereoisomers that have different internal dimensions, so they are *diastereomers*. Because rotation to interconvert one diastereomer into the other is a high-energy process, requiring cleavage of a π bond, they are *configurational diastereomers*. (In the past, isomers such as these have been called double-bond isomers or geometric isomers.)

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 CH_3 group are on the same side of the π bond, and *trans*-1-chloropropene is the diastereomer in which the Cl and the CH_3 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.

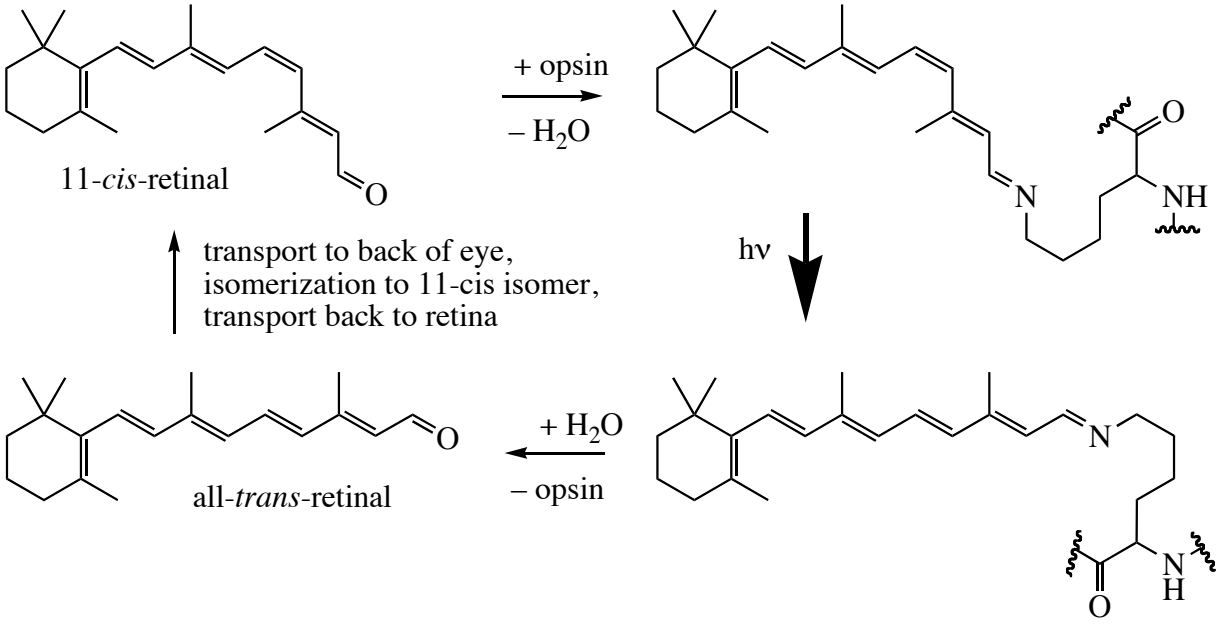
If we replace a terminal H in propene with a CH_3 group, we generate either 1-butene or 2-butene. (If one replaces the internal H in propene with CH_3, we generate 2-methylpropene, also known as isobutylene.) The number designates the position of the C=C bond in the chain. Not only do 1-butene and 2-butene have their π 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.



cis alkene *trans* alkene

Because switching two groups attached to the double-bond C atoms in a cis or trans alkene generates a new steroisomer, we can say that each double-bond C atom is stereogenic. However, the 2^n rule for counting stereoisomers does not apply. Instead, there are only 2 stereoisomers for each *pair* of stereogenic C atoms participating in the double bond, so the total number of stereoisomers is $2^{(n\,/\,2)}$ where n is the number of sp^2 stereocenters. If a compound has both sp^3 stereocenters and sp^2 stereocenters, the formula is $2^{m\,+\,(n\,/\,2)}$, where m is the number of sp^3 stereocenters and n is the number of sp^2 stereocenters.

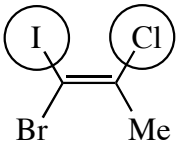
The interconversion of cis and trans alkenes requires cleavage of the C=C π bond. This can happen when light of the proper wavelength is absorbed by an alkene, which promotes one electron from the π to the π* orbital. Because 1/2 bond + 1/2 anti-bond = no bond, there is now no π bond and the molecule is free to rotate about what used to be the π 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 electical 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.



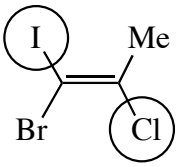
Higher alkenes are named as you would expect. The root designates the number of C atoms in the longest chain containing the double bond, the suffix "ene" designates an alkene, the number preceding the root designates the position of the double bond in the chain, and any prefixes designate substituents. An alkane with two double bonds is called a diene, one with three is called a triene, etc., and more than one number is used before the root to designate the position of the double bonds: e.g., 1,3-butadiene or 1,4-cyclohexadiene. A cycloalkene is named so that the C's of the π bond are 1 and 2 and so that the first substituent has as low a number as possible. All cycloalkenes up to 8-membered rings must be cis, so we don't need to indicate whether they are cis or trans in their name. (Try to make a model of *trans*-cyclohexene!) Larger cycloalkenes, however, must be so designated: e.g., *trans*- or *cis*-cyclodecene.

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.

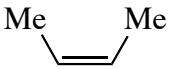
First we need to assign *priorities* to the four groups attached to the double bond. Look at the atomic numbers of the two *atoms* attached to each C of the double bond. One C has I and Br attached: I has higher priority. The other C has C and Cl attached: Cl has higher priority. (It is helpful to circle 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.



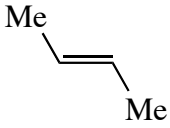
the *Z* isomer



the *E* isomer

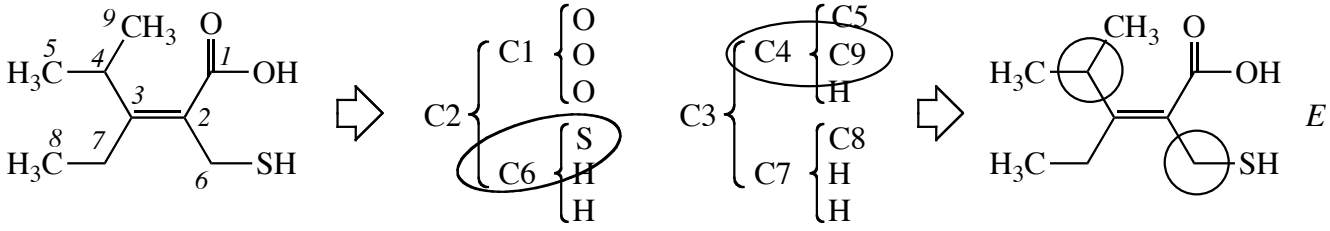


2*Z*-butene



2*E*-butene

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).

The easier way to determine whether an alkene is E or Z is to draw it in a chemical drawing program such as ChemDraw or MarvinJS and then let the program figure out the configuration for you.

5.8 Optical Activity and Enantiomeric Purity.

A beam of light consists of waves that oscillate perpendicular to the plane of the beam. Normally, the waves oscillate in all planes perpendicular to the beam; this is called unpolarized light. If the light is passed through a polarizer, though, the beam of light is altered so that the waves making up the light oscillate only in one plane. This kind of light is called *plane-polarized light*. A chiral compound interacts with plane-polarized light in such a way that the plane of light is *rotated* in one direction or another. This phenomenon is called *optical activity*. A sample of a compound is said to be *optically active* if it rotates the plane of plane-polarized light. Note that optical activity is a bulk phenomenon: it is measured on a sample of a compound as light passes through it, so one is dealing with a large collection of molecules.

Compounds that rotate plane-polarized light to the right are called *dextrorotatory* and are indicated by (+) in front of their names, e.g. (+)-tartaric acid. Compounds that rotate plane-polarized light to the left are called *levorotatory* and are indicated by (–) in front of their names. The angle by which light is rotated depends on the compound and its concentration, path length (the length of solution or crystal through which the light must pass), solvent, wavelength of light, and temperature. It is conventional to use the yellow light emitted by sodium, the D line, to measure the optical activity of a compound at room temperature (21 °C), although any wavelength and any temperature may be used. The *specific rotation*, $[\alpha]^{T}_{\lambda}$, of any compound is defined as follows:

$$[\alpha]^{T}_{\lambda} = \alpha / \ell \cdot c$$

where α is the measured rotation, T is the temperature (in °C), λ is the wavelength (in nm), ℓ is the path length (in dm, Lord knows why), and c is the concentration of the chiral compound in solution (in g/ 100 mL; if the compound is neat, i.e. not in solution, c = 1). The specific rotation is a physical characteristic of a chiral compound, like boiling point or color. Specific rotations are usually measured at 589 nm, a particular emission wavelength of sodium called the D line, and at room temperature, so usually one sees reported $[\alpha]^{21}_{D}$. Specific rotations are usually reported as follows: "$[\alpha]^{21}_{D}$= +44° (c = 1.0, ethanol)." The specific rotation is an immutable characteristic of a compound, just like its melting point and its IR spectrum.

A sample of one enantiomer of a compound will rotate the plane of plane-polarized light in the *opposite* direction from a sample of the other enantiomer of the same compound. A sample of a compound that

exists as a 1:1 mixture of enantiomers, a *racemic mixture*, is optically inactive, because half of the molecules rotate light in one direction, and the other half rotate light in the other direction, so the net result is no rotation at all. A sample of an achiral compound is also optically inactive. Only samples of chiral compounds in which one enantiomer is in excess rotate plane-polarized light. Such a sample is called *enantiomerically pure* or *enantiopure* if it consists of only one enantiomer. It is called *enantiomerically enriched* or *enantioenriched* if it consists of both enantiomers, but one predominates. The *enantiomeric excess* (ee) of a compound is defined as:

$$ee = (er - 1) / (er + 1)$$

where er is the ratio of the two enantiomers. The ee is expressed as a percentage. A racemic mixture has an ee of 0%, a 7:1 mixture of enantiomers has an ee of 75%, and an enantiopure compound has 100% ee.

A sample of a compound that is enantioenriched rotates polarized light with smaller α than a sample of the same compound that is enantiopure. This is because the minor enantiomer rotates light in an opposite direction from the major enantiomer, so the net rotation is less than if only one enantiomer were present. Suppose one has a sample of a compound, and one wants to determine its ee. If the specific rotation $[\alpha]$ for the compound in enantiopure form is known, then the ee of your sample can be determined using the formula:

$$ee = [\alpha_{\text{your sample}}] / [\alpha_{\text{enantiopure}}]$$

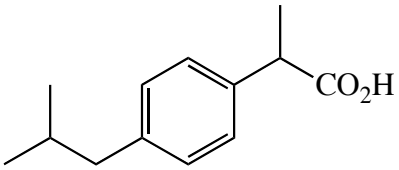
where $[\alpha_{\text{your sample}}]$ is the specific rotation of your sample, and $[\alpha_{\text{enantiopure}}]$ is the specific rotation of a sample of enantiopure compound. Racemic compounds are optically inactive, and this formula gives their ee as 0%, as expected.

5.9 Resolution and Asymmetric Synthesis.

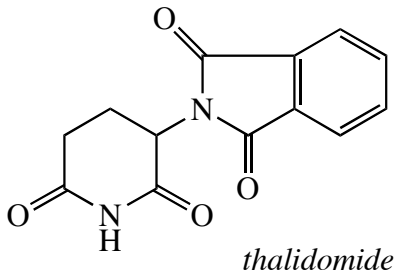
The two enantiomers of a compound have identical physical properties in almost all respects. They have identical melting points, boiling points, solubilities, acidities, and spectroscopic characteristics. There are only two ways in which two enantiomers differ in their properties: in their interaction with other chiral compounds, and in their interaction with plane-polarized light. (We will talk about the latter in a moment.) The difference in interaction of two enantiomers with a chiral compound is akin to the difference between the interaction of your *left* hand with a *left* glove and the interaction of your *right* hand with a *left* glove. It is also the same as the way that an (*R,R*) compound differs from an *(R,S*)

compound. Chemically, this means that two enantiomers of a compound will have different behaviors when they interact with another chiral, enantiopure compound.

Living organisms are made up of chiral, enantiomerically pure compounds. For example, most amino acids in the proteins of all living organisms have the absolute (*S*) configuration, and most sugars have the D configuration. A living organism is like a left glove, then, and so the two enantiomers of any racemic compound that an organism ingests may have totally different biological properties. For example, the pain reliever ibuprofen is a chiral compound. The (*S*) enantiomer is more potent than the (*R*) enantiomer by about three-fold, but this is not a very big difference, so the compound is marketed as a racemic mixture (for now). On the other hand, the situation is very different for thalidomide, a chiral compound which was marketed in the early 1960's. The dextrorotatory enantiomer of thalidomide cures morning sickness, the intended therapeutic effect. The levorotatory enantiomer is a potent teratogen (causes birth defects). Unfortunately, thalidomide was sold as a racemic mixture, and as a result a lot of severely deformed children were born in Europe. (The drug wasn't marketed in the US because the FDA had vigilantly noticed some neurological side effects and had refused approval.)

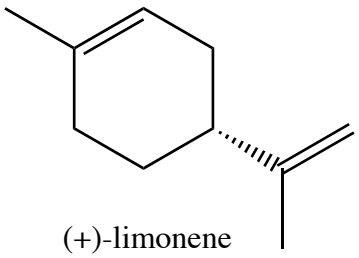


ibuprofen

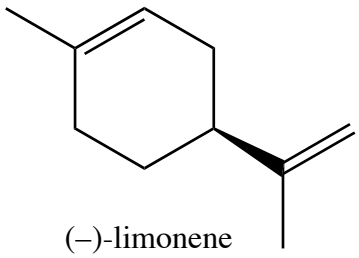


thalidomide

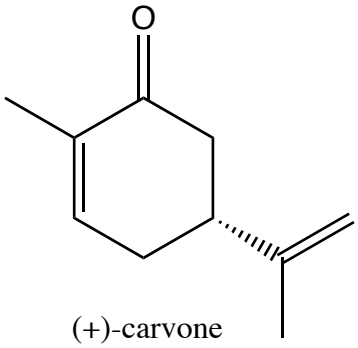
Limonene and carvone are less dramatic examples of this phenomenon. The two enantiomers of limonene are found in different plants in nature; one enantiomer smells like oranges, and the other smells like lemons. Similarly, one enantiomer of carvone is found in spearmint, and the other is found in dill and carraway seeds. Again, the two enantiomers of each pair have different interactions with the smell and taste receptor proteins, themselves chiral objects, in your nose and mouth.



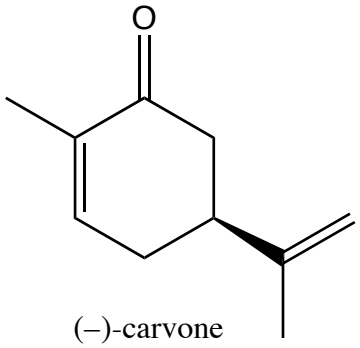
(+)-limonene
orange smell



(–)-limonene
lemon smell



(+)-carvone
spearmint



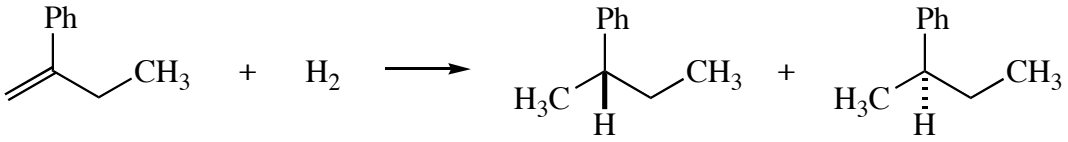
(–)-carvone
dill/caraway

The process of separating a racemic mixture into its enantiomers, *resolution,* can be effected by temporarily attaching a chiral, enantiopure reagent to the two enantiomers in the racemic mixture. This results in the formation of two diastereomers. For example, a carboxylic acid will react with an amine, a good base, to give a salt. If the carboxylic acid is chiral and racemic (*R* and *S*)and the amine is chiral and enantiopure (say, *R* only), two diastereomeric salts (*RR* and *SR*) will be obtained. The diastereomeric salts have different properties such as solubility, so one can be selectively crystallized. Now one enantiomer is a solid and the other is a liquid, so filtration will separate them. The amine can be removed from either enantiomer by extraction with aqueous HCl, completing the separation.

Two enantiomers can also be separated by chromatography on a chiral support. You may remember paper chromatography from high school, where ink on a piece of filter paper is separated into its colors. If the two enantiomers are placed on a piece of "filter paper" made up of a chiral material, one enantiomer will move faster than the other. This separation method is useful as an analytical technique for very small amounts of material, but it is usually too expensive to do on a large scale.

Optically inactive starting materials always give optically inactive products in chemical reactions. For example, 2-phenyl-1-butene reacts with H_2 (in the presence of a catalyst) to give 2-phenyl-1-butane. The product is chiral; since the starting materials are achiral, the product *must* be racemic, i.e. a 1:1 mixture of enantiomers must be formed. This is a fundamental statistical result of the huge number of molecules that are involved in the reaction. The H_2 has an equal probability of attacking the top or the bottom of the alkene, and so there is an equal probability of forming the (+) or the (–) enantiomer. If you multiply this by 10^{23} or so events, you can see why a 1:1 mixture is obtained. Likewise, if a

racemic compound is allowed to react with an achiral or a racemic compound, then the product(s) must be either achiral or racemic. Only when one of the starting materials is chiral *and* enantioenriched or enantiopure is it possible to obtain enantioenriched or enantiopure product.

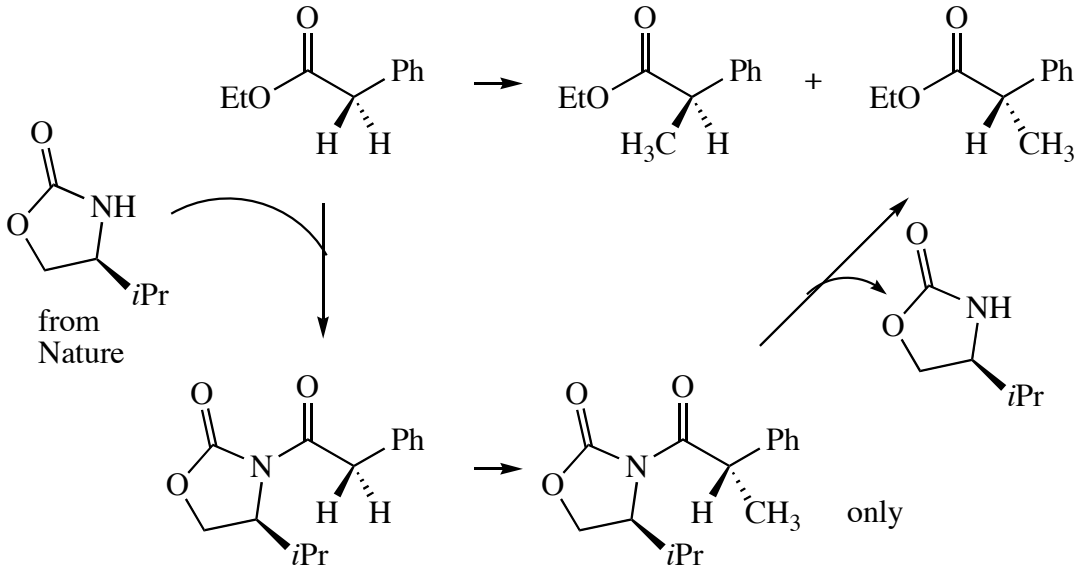


achiral *achiral* *chiral and racemic*

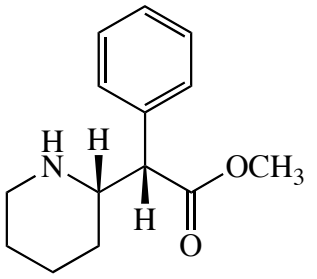
If optically active starting materials are required to make optically active products, where does one get optically active starting materials to begin with? The answer is Nature. Because organisms are made up of chiral, enantiopure molecules, they are able to make chiral, enantiopure compounds. We can extract these compounds from living organisms and use them ourselves.

(Why should all amino acids be left-handed and all sugars be right-handed? Why not the other way around? Good question. No one has the foggiest idea. Much time has been spent hypothesizing why it is the case, but the hypotheses are very difficult to verify experimentally.)

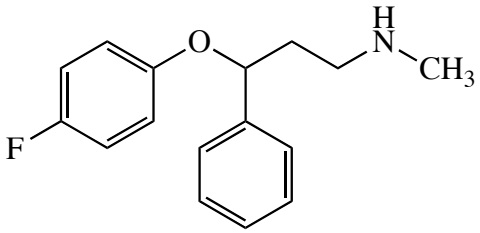
Suppose one wants to make an enantiopure compound. There are two ways to do it: (1) make a racemic mixture and carry out a resolution, or (2) carry out an *asymmetric synthesis*. An asymmetric synthesis uses an optically active starting material isolated from nature and uses its chirality to influence later reactions. For example, one can replace the H next to the carbonyl group of an ester with a CH_3 group. This reaction turns an achiral compound into a chiral one, and hence a racemic mixture is obtained. If, however, one attaches an optically active starting material to the ester (a *chiral auxiliary*), then one can use the asymmetry of the auxiliary to make all the CH_3 group attach to the bottom of the ester and none to the top. When one removes the chiral auxiliary, one is left with an optically active product.



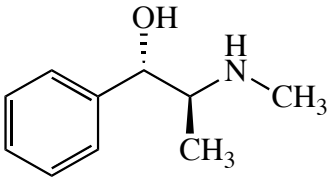
Many older chiral drugs (Prozac®, Ritalin®) are sold as racemic mixtures (Ritalin as a diastereomeric mixture), whereas others (pseudoephedrine) are sold as enantiopure compounds. One of the components of the racemic mixture has the desired biological activity, but the other may or may not have similar or different activity. Some of the side effects of these drugs may be attributed to the presence of the "wrong" enantiomer. So why would the companies that make these drugs sell them as racemic mixtures? It is often very expensive to resolve drugs or to make them in enantiopure form. If the company were to sell enantiopure compound, the cost of the drug would be much higher, and profit would be lower.



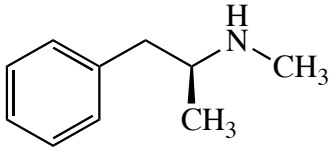
Methylphenidate (Ritalin)



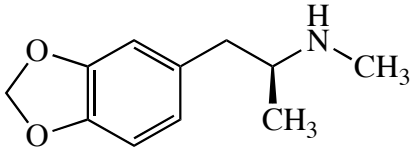
Fluoxetine (Prozac)



Pseudoephedrine

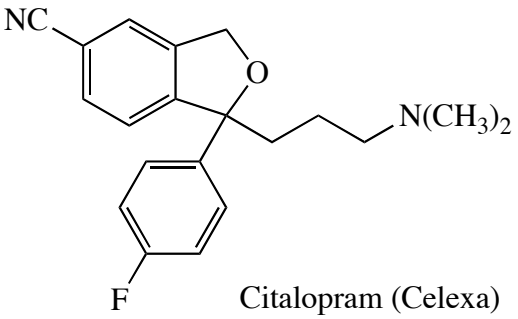


Methamphetamine

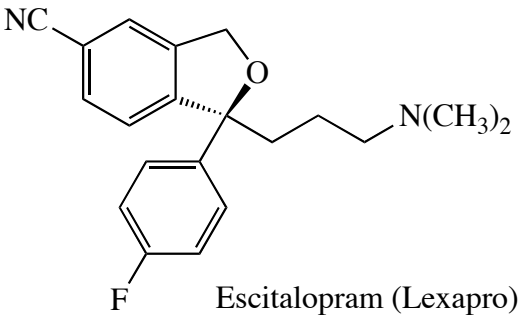


MDMA (Ecstasy)

Nowadays, the technologies of resolution and asymmetric synthesis have advanced to the point that the cost of making enantiopure material is not so great, and the FDA is expressing a strong preference that all medicinal drugs be sold in enantiopure form. One drug that has already made the "racemic switch" is the antidepressant citalopram, sold as Celexa®. Citalopram is a racemic mixture, but only the S enantiomer is biologically active. The S enantiomer, which is called escitalopram, is now sold separately as Lexapro®. As you might expect, the recommended dosage for Lexapro (10 mg/day) is only half that of Celexa (20 mg/day).



Citalopram (Celexa)



Escitalopram (Lexapro)