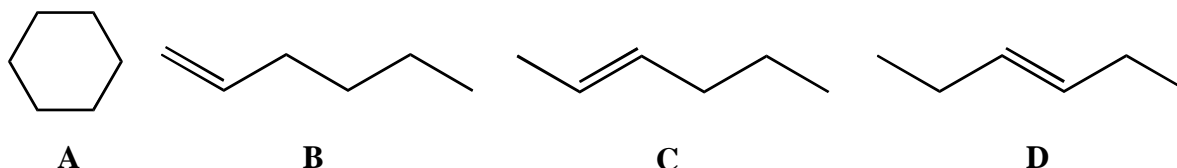


Chapter 17 – Stereoisomerism

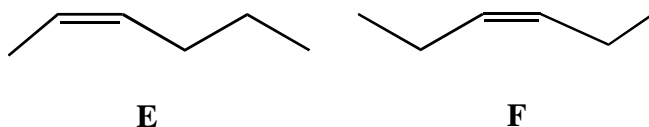
We have already encountered isomers in the organic chemistry chapters. For example in Chapter 12, Unsaturated Hydrocarbons, we say that alkenes can exhibit *cis/trans* isomerism. We will briefly review constitutional isomerism, then stereoisomerism as it applies to alkenes. Most of the chapter is devoted to a different type of stereoisomerism that has an immense impact on biochemical systems.

17.1 Types of Isomerism

Constitutional isomerism occurs when the atoms in a molecule can be rearranged such that different atoms are bound to one another (i.e. the atom connectivity is not the same). For example the following are some of the constitutional isomers of C_6H_{12} :



In contrast, in stereoisomers the same atoms are bound to one another, but their orientation in space differs. We have already seen one type of stereoisomer, the *cis/trans* orientation around a double bond (Chapter 12). Now compounds **C** and **D** have *cis* isomers as well.



What relationship are these molecules to the first 4 (and to each other)? Molecule **E** is a constitutional isomer of molecules **A**, **B**, **D**, and **F** (but not **C**). Molecule **F** is a constitutional isomer of molecules **A**, **B**, **C**, and **F** (but not **D**). Molecules **C** and **E** are stereoisomers as are molecules **D** and **F**. Thus, **C** and **E** are constitutional isomers of **A**, **B**, **D**, and **F** because the

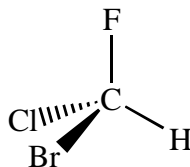
double bond is located in a different place. **C** and **E** are stereoisomers because the (identical) groups attached to the double bond are arranged in a different way. Stereoisomers can also occur in molecules possessing only single bonds. These isomers are the subject of the next section.

17.2 Molecular Chirality

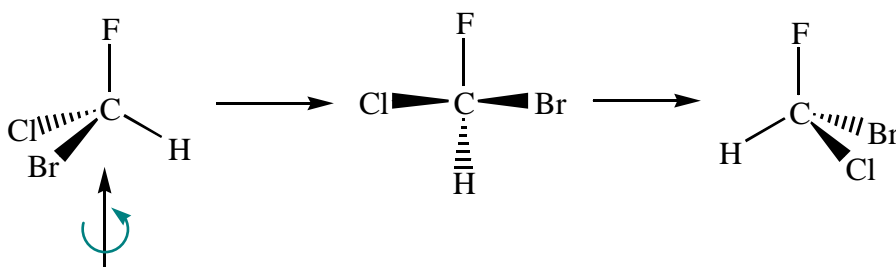
The remaining isomers we will discuss are a type of stereoisomer that incorporate a structural feature that is surprising at first. Typically only one molecule can be built (imagine using a modeling kit where a molecule would be built like using Tinker Toys®) if the atom connectivity is predetermined. Molecules for which stereoisomers are possible have more than one structure that can be drawn, however. Here, the spatial arrangement of those atoms makes a difference. In a molecule such as methane, CH₄, the placement of the hydrogen atoms around the carbon doesn't matter because they are identical. In fact, as long as any two (or more) of the groups bound to carbon are the same, the way they are connected doesn't matter. The situation changes if all four groups are different.

Your book chooses to look at an amino acid because it is relevant to this course, but I'm going to use an example that might be a little easier to visualize. The book uses abbreviations to simplify its example and the graphics are quite nice. If you can see how this works using the book's graphics you may be able to skip the explanation given here.

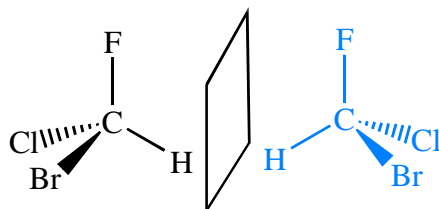
Consider bromochlorofluoromethane, CHBrClF:



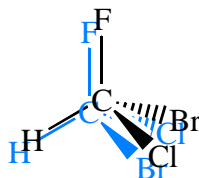
The position to which each atom is attached matters here. Let's look at why. In the next set of figures we will rotate the molecule 180° about the C-F bond. That is the C-F will not change. Remember the H, C, & F atoms begin in the plane of the paper. The Br leans out toward you and the Cl is pressed in behind the paper. In the middle picture C & F are still in the plane of the paper, but H has moved behind the paper, and Cl & Br point out of the paper towards you. In the final picture, H, C, & F are back in the plane in the paper, but now Cl points out towards you and Br back away from you (the reverse of the beginning picture).



Now let's take the first view of the molecule and take its mirror image:



The final thing we need to do is see if we can superimpose a molecule of the initial molecule (in black) on its mirror image (in light blue). Clearly, the molecule as written to the left of the mirror in the previous figure won't work, but what about the molecule that was rotated? It would look like this:

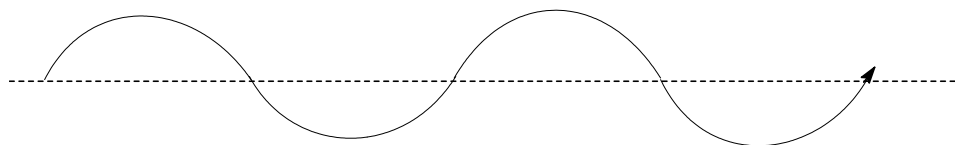


As you can see, the best we can do is get 2 of the 4 atoms bound to carbon to line up with each other. The other two will always be in mirror positions. These structures are called enantiomers

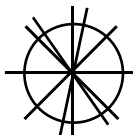
and are related as non-superimposable mirror images. All stereoisomers that are not enantiomers are diastereomers. Figure 17.2 (p. 502) and the blue text in the margin of that paper may be helpful here.

So why does this matter (as opposed to being simply a chemical oddity)? There are only two differences between these isomers: they rotate the plane of polarized light by exactly equal amounts but in opposite directions, and they react with other enantiomers differently. In all other respects they are indistinguishable. Because the mirror images of methanol (CH_3OH) are identical, they would react with it identically. Enantiomers have the same color, boil at the same temperature, and have the same density. Nevertheless, it is important to remember that they are different molecules. Interestingly, they may or may not have the same odor. Can you guess why (or why not)? We will now examine each of these properties and their significance.

What is plane polarized light and what do we mean by rotating it? Imagine a light wave like the one shown below.



Now when you turn on a light bulb or when a star shines there are large numbers of these light waves coming out. Either they are all in the same plane (e.g. this paper) or they aren't. It turns out they aren't. Let's assume for now the "plane" is simply the plane of this sheet of paper and the first light wave we look at is traveling down the dotted line that is in the center of the light wave shown above. If we add a light wave, it will be out of this plane, perhaps perpendicular. The next would probably add at a different angle, maybe 30° . If you could stand behind the source and see all of the different light waves coming out, what you'd see is light coming out at every angle. e.g. For six light waves we might see:



Plane polarized light is light that has passed through a special filter. A blue light filter allows only blue light to pass through it. All other wavelengths are absorbed. A polarized light filter consists of a set of slits all lined up with one another so the light that passes through all lies in the same plane. If the light is out of the plane it gets absorbed. Try this analogy. Imagine light waves $\frac{1}{2}$ inch high and as thin as a human hair. Now imagine a comb as the polarizing filter. If the light wave lines up with the slits in the comb it gets through. If it comes in at an angle, it hits the slats and can't get through. A polarizing filter works like this.

You can prove this to yourself. Go to a store that sells polarized sunglasses. Take two pairs and put one on. Look at the ceiling lights. Now take the other pair and line them up so they're just like the first. Look through both pairs at the lights. Slowly rotate the second pair. At first you won't notice much difference, but suddenly it will begin getting a lot darker very quickly. By time you have rotated the glasses 90° no light whatsoever will get through. If you keep going to 180° you'll get back to where you began because the slits will line back up. At 90° all of the light getting through the first filter is perpendicular to the second and gets completely absorbed. Your book shows pictures on these topics on p. 509-510. Now back to chemistry.

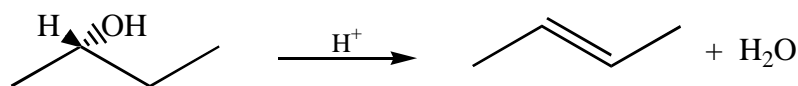
We all know light interacts with matter. The most obvious types of examples are that you can't see through a brick wall and that a car steering wheel gets warm on a sunny day, but there are more subtle and relevant examples. Take a smooth, clear (and preferably colorless) dinner glass and fill it with water. Hold it up to a light bulb at an angle and look at the light through the water. Now slowly lower the glass. You can see how the water bends the light waves as the surface of the water passes between your eyes and the light. In a similar fashion, some

molecules twist light waves. Thus they may strike the molecule in one plane (say 0°) and come out at a different angle (say 27°). This value is called the optical rotation. With ordinary light this makes no difference because, since all angles come in and all are rotated by the same amount, we can't tell a difference. If the light is polarized though, we can measure the rotation because the light strikes the molecule at only one angle.

Now for a few definitions. Optically active molecules are those that rotate the plane of polarized light. Molecules that exhibit optical activity are said to be chiral. Molecules that don't are achiral. The word chiral comes from the Greek word for hand. Your hands are (for all practical purposes) mirror images of one another, but can't be superimposed on each other. Although other optically active structures are possible, the only time you will encounter chirality is in molecules possessing tetrahedral carbons with 4 different groups attached. Remember that any carbon with four different groups attached is chiral.

This property of optically active molecules was discovered in 1815 by Jean-Baptiste Biot, but remained an unexplained curiosity until a very famous experiment by Louis Pasteur in 1848. He had just received his Ph.D. and wanted to learn about crystallography. To do this he decided to learn by repeating an experiment that someone before him did. In the experiment he grew crystals of sodium ammonium tartrate (a by-product of the winemaking process). Unlike the first experimenter he noticed under a magnifying glass that crystals could be divided into two groups, each crystal in the first group the non-superimposable mirror image of a crystal in the second. Their optical rotations were equal in size, but opposite in sign. In 1874, the Dutch chemist Jacobus Van't Hoff and the French chemist Joseph-Achille LeBel independently closed the loop by proposing tetrahedral carbon atoms to account for this and other chemical phenomena.

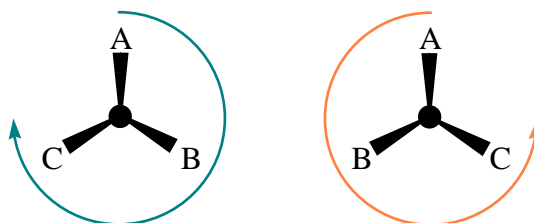
Now we will turn our attention to the chemical properties of chiral molecules. As was mentioned earlier, enantiomers of chiral molecules react with achiral molecules identically. When we discuss this we are assuming the reaction occurs at the chiral carbon. There are two possibilities. The first is that the product can't be chiral. For example, imagine an alcohol with a chiral carbon, say 2-butanol. If it is dehydrated to an alkene, the alkene doesn't have a chiral center so the fact that the acid catalyst isn't chiral doesn't make any difference.



So why do chiral molecules react with other chiral molecules differently? Enzymes are, perhaps, the easiest chiral molecules to explain. Typically an enzyme is a huge molecule with a relatively rigid structure. It has numerous chiral centers within it. Usually the substrate molecule must either enter a pocket or bind to the surface for a reaction to occur. If the shape of the molecule doesn't line up with the shape of the pocket or surface, it can't bind. If it can't bind, it won't react. Your book has a nice illustration that shows this on p. 504. To use an analogy, your hands are (to a first approximation) chiral. Let them be enantiomers. Now a glove is like an enzyme. It will interact correctly with only one of the two hands.

Now something in the previous paragraph warrants further comment. Molecules can have multiple chiral centers and there are some consequences of this fact. The first is that each additional chiral center potentially doubles the number of stereoisomers. (We will see shortly why we don't always double the number.) To visualize this imagine a carbon atom to which 4 different groups are bound. Call the groups A, B, C, and D. The picture below shows the two different enantiomers with A, B, and C in the plane of the paper, the carbon atom in the center behind the paper, and D is directly behind the carbon atom.

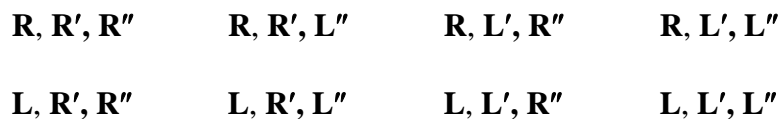
To move from A to B to C in the first enantiomer one moves to the right (clockwise). Lets call this enantiomer **R**. The same movement on the second enantiomer requires moving to the left (counterclockwise). This is enantiomer **L**. As you might imagine one could draw such pictures for any enantiomer.



Thus, for a molecule with two chiral centers one would have two pairs of enantiomers: **R** & **L** and **R'** & **L'**. They could be paired 4 different ways:

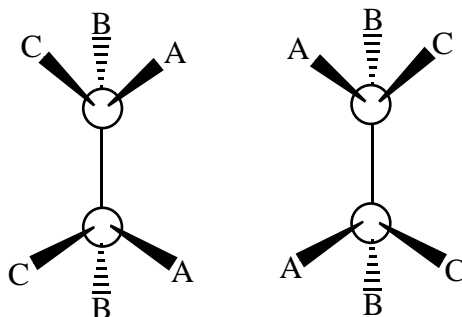


For three chiral centers, there would be three pairs of enantiomers: **R** & **L**, **R'** & **L'**, and **R''** & **L''**. This results in 8 different triplets:



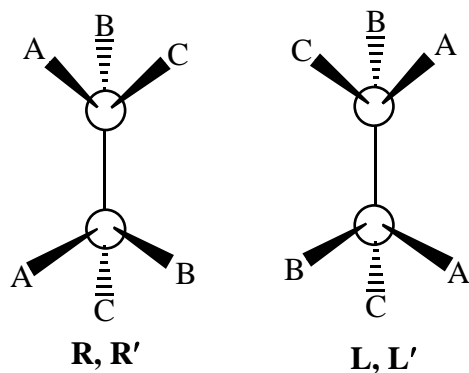
Mathematically, we can say that if there are n chiral centers in a molecule, there will be 2^n stereoisomers.

For the most part this is straightforward, but in one scenario something different happens. When the two chiral centers are identical, pairs of the enantiomers turn out to be identical. This is best seen pictorially.



This molecule, which has two chiral centers, is the mirror image of itself. This type of molecule is said to have a *meso* structure. Meso isomers are not optically active (don't rotate the plane of polarized light). They are composed of different enantiomers however. If you look carefully you may be able to see that the left meso form is **L, R'** (top, bottom), while the right meso form is **R, L'**.

The two other forms of the previous molecule are optically active and are not superimposable. These molecules are enantiomers. Thus this type of molecule has 3 stereoisomers, not the expected 4.



Recall diastereomers are stereoisomers that are not related as mirror images. Thus **L, R'** and **R, L'** are diastereomers of **R, R'** and **L, L'**. The chemical and physical properties of diastereomers are different from one another, although they are usually quite similar. The two exceptions occur when some of the diastereomers are optically active. In that case, the optical rotations may vary widely (e.g. the meso form will always have an optical rotation of zero). Chemically they will react differently with chiral centers.

17.3 Optical Activity

Most of this has already been covered, but there are a few points worth addressing now.

Recall that enantiomers rotate the plane of polarized light by equal amounts, but in opposite directions. This means that a solution containing equal amounts of two enantiomers of the same molecule will not rotate the plane of polarized light. Such a solution is called a racemic mixture. It is optically inactive.

February 2, 2002