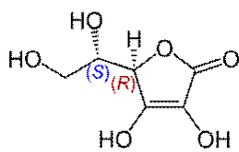
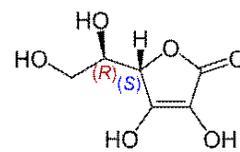


Chapter 5 Lewis Structures and Isomers

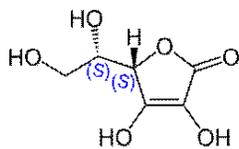
The formula of a compound (e.g., Vitamin C is $C_6H_8O_6$) provides very important and useful information but still insufficient for an understanding of the physical and chemical properties of the compound. The partially condensed Lewis structures of the stereoisomers of ascorbic acid and erythorbic acid to the right gives the chemist additional valuable information. All four of the compounds have the same formula. A glance at the structures might leave the impression that the four structures represent the same molecule. However, as a result of



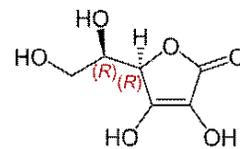
1a



1b

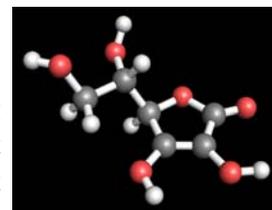


2a



2b

subtle spatial differences indicated by the configuration symbols R and S, each of the molecules has different properties than the others. Only 1a has anti-scorbutic properties (prevents scurvy) although all have strong antioxidant properties. The figures give not only the sequence of bonding but considerable information about the 3-d structure. We will find out later that even subtle details such as whether the OH is up and the H down are all important in determining the properties of ascorbic acid. A good analogy is the way a key fits into a lock. Differences of any kind will prevent the key from working. In many cases, molecules must fit into sites in a protein that are much the same as the way a key fits into a lock. Even for mirror images such as 1a and 1b, only one of the two will fit properly into the protein site.



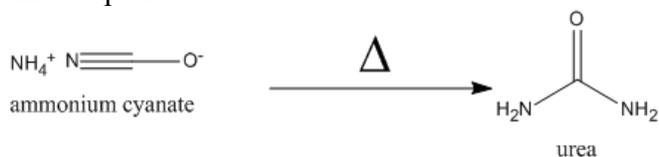
Vitamin C (1a)

For more information on vitamin C, scurvy and mirror images, please visit:

<http://www.history.com/news/hungry-history/ahoy-pass-the-cabbage-preserved-foods-in-the-age-of-exploration>
<http://www.news-medical.net/health/Vitamin-C-History.aspx>
<http://www.sciencelearn.org.nz/Contexts/Food-Function-and-Structure/Timeline>
<http://www.leffingwell.com/download/chirality-pharmacology.pdf>
<http://www.leffingwell.com/chirality.htm>

Chapter 1 contained a quotation by Fredrich Wöhler about the wonders of organic chemistry. Wöhler had performed an experiment that debunked the concept that compounds derived from anything living contained a unique quality then called vitalism. Despite the demise of the vitalism concept almost two centuries ago, some people are still willing to pay more for “natural” vitamin C as they incorrectly think it is different than synthetic vitamin C. The formula and structure determine the properties, not its source. Wöhler’s experiment was important for an additional reason. When Wöhler reacted silver cyanate with ammonium chloride, he found that only with special care could he isolate his desired product, ammonium cyanate (NH_4OCN). Instead the product he found was urea. He also found he could convert ammonium cyanate into urea. This production of an organic substance from inorganic substances eventually led to the demise of the vitalism concept. In addition, the ionic compound, ammonium cyanate, and the product, urea, have the same formula, H_4CN_2O , but different properties. Wöhler’s experiment was one of the first to

demonstrate the concept of isomerism. Two compounds with the same formula but different structures are called isomers and might have considerably different properties. The sequence of bonding and structure are just as important as the formula in determining the properties. There are several types of isomers that will be discussed later in this chapter.



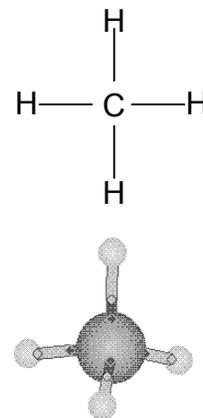
Note: the triangle above the arrow to the left is the uppercase version of the Greek letter delta. This symbol is commonly used to represent heat or energy input.

Since the sequence of bonding and the 3d structure of molecules is critical for an understanding of the properties of a compound, a method for depicting molecules on a 2d piece of paper had to be developed. Earlier, the use of Lewis structures to provide information on the outer orbital electrons was discussed. With the application of more guidelines, the Lewis structure method is also applied to molecules. In its complete, partially condensed or condensed forms in texts, Lewis structures are ubiquitous in the field of chemistry.

Lewis structure guidelines

1. Complete Lewis structures will show the total number (valence) of electrons present in the molecule. This is determined by adding the **American group numbers** of each element present. For instance, formaldehyde (CH_2O) has $4 + 2(1) + 6$ valence electrons for a total of 12 electrons. Acetic acid with the formula $\text{C}_2\text{H}_4\text{O}_2$ has $2(4) + 4(1) + 2(6)$ for a total of 24 electrons. For ions, this total must be modified by adding in 1 electron for each negative charge and subtracting 1 for each positive charge. The ion sulfate (SO_4^{2-}) would have $6 + 4(6) + 2$ for a total of 32 electrons and ammonium (NH_4^+) would have $5 + 4(1) - 1$ for a total of 8 electrons.
2. Arrange the atoms in the correct sequence or sequences if there is more than one logical sequence. Often the most symmetric form is correct. For polyatomic ions, the atom listed first (e.g. S in SO_4^{2-}) is usually the central atom (an atom attached to two or more atoms).
3.
 - a. Connect each of the atoms with a line or one bond.
 - b. Distribute the remaining electrons in pairs (subtract two each from the total for each bond already inserted) around the external atoms (the ones attached to the central atom) attempting to complete each atom's octet. Remember that the octet (duet for hydrogen) should never be exceeded for atoms through the second period and should only be exceeded for atoms beyond the second period when the atom is a central atom. If electrons still remain, attempt to fill the octets of central atoms or even exceed the octets for atoms beyond the second period.
 - c. If central atoms are short of achieving an octet, move electron pairs from external atoms to form multiple bonds between the external atom and the central atom in an attempt to provide all atoms with an octet (or, for atoms beyond the second period the octet might be exceeded).
 - d. Visually inspect the resulting structure and decide if it is consistent with other structures you have seen (generalities are difficult but the following are usually true):
 - hydrogen has one bond
 - carbon has four bonds (except for carbon monoxide, cyanide ion and unstable species)
 - halogens have one bond unless the halogen is a central atom
 - oxygen usually has two bonds except for polyatomic ions
 - nitrogen usually has three bonds unless the nitrogen is the central atom

4. Just as important as the sequence and multiplicity of bonds is a consideration of the spatial arrangement or geometry of the atoms. With only a very few exceptions, the spatial arrangement can be ascertained by application of a theory such as VSEPR (valence shell electron pair repulsion). As the VSEPR indicates, the theory is based on the concept that particles with like charges repel each other. As a result of the repulsion, groups of electrons (electrons in bonds and in non-bonded orbitals), orient themselves as far apart as possible about a central atom. Two groups of electrons are farthest apart when they are on opposite sides of a central atom on a straight line (180° degrees apart). Three groups are farthest apart when they are in a plane 120° apart. To maximize the distance between four groups, the electrons are oriented in a 3D tetrahedral arrangement with an angle of 109.5° between the orbitals. See the figure to the right for methane (CH_4). The table below summarizes the theories.

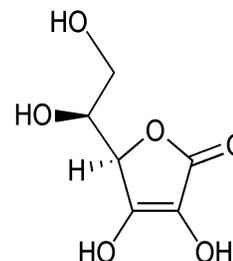


<u>groups¹ of electrons around central atom</u>	<u>electronic shape²</u>	<u>bond angles</u>
2	linear	180°
3	planar	120°
4	tetrahedral	109.47°

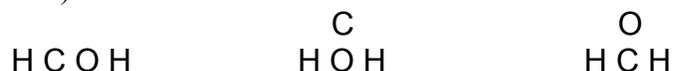
¹The number of groups of electrons is equal to the sum of the number of neighbor atoms and nonbonded electron pairs.

²Be sure to distinguish electronic shape from molecular shape. If one or more of the groups of electrons are nonbonded pairs, the molecule needs to be described by the relative positions of the atoms; not by the shapes of the electronic orbitals.

5. Partially condensed and condensed Lewis structures often leave out non-bonded electrons and bonds to hydrogens (methane is written CH_4 and the lines for the bonds are not included) and even leave out hydrogens completely. Carbons are sometimes indicated by a connection of two bonds and the C for carbon is understood and left out. For example, in the Vitamin C structure to the right, the bonds from oxygen to hydrogen are not indicated with a line, three hydrogens are left out as are the C's for all of the carbons.

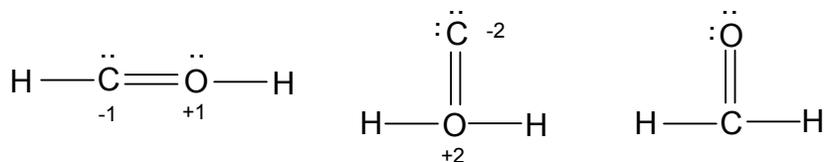


To illustrate the use of the preceding guidelines, the procedure will be applied to a couple of examples. Consider the molecule formaldehyde, CH_2O . First, determine the correct number of electrons that should show in the final structure which is $4 + 2 + 6 = 12$. Now we must consider the sequence of bonding. Three possible choices are (other possibilities can be eliminated because they require two bonds to hydrogen which except for some unusual boron compounds should be absolutely avoided):



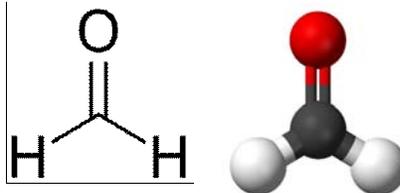
As symmetrical choices are often favored, the first structure could be eliminated because it has lower symmetry than the other two. We will leave it in for this discussion and continue by inserting the three single bonds ($6 e^-$) and adding the remaining $6 e^-$ to the external atoms (C and O respectively for the second and third structures) or $6 e^-$ to the C and O of the first structure. To satisfy the octet rule in each structure, one non-bonded electron pair is moved from the external atom

in the second and third structure to form a double bond with the central atom. For the first structure, the second non-bonded electron pair on either the C or O is moved between the two atoms to form a double bond.

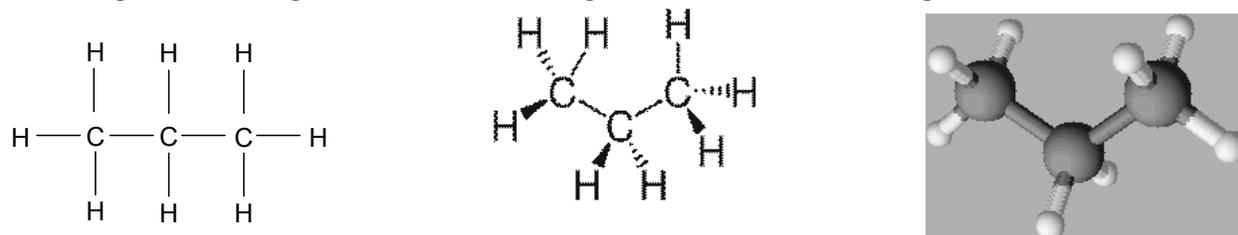


The three structures are technically correct Lewis structures for CH_2O but only one is a correct model for formaldehyde. The charges indicated above are called formal charges. Formal charges will not be used in this course but the goal would be to minimize formal charges. Clearly using this criteria, the third and correct structure on the right would be selected.

Now let's look at the geometry of formaldehyde. For the formaldehyde molecule drawn earlier, there are 3 groups of electrons around the central carbon. Notice the double bond counts as 1 group of electrons and not 2! Focus on the shape around each atom and do not look at the oxygen when determining the shape around carbon. The 3 groups result in a prediction that the atoms around carbon are 120° apart in a plane.



The compound propane (C_3H_8) is often used for heating rural homes. Since hydrogen can only have one bond, using the guidelines there is only one way to connect the atoms. The figure should show $3(4) + 8(1) = 20$ electrons. Since each bond represents 2 electrons and 10 bonds are necessary to connect the atoms, all of the electrons are used and the structure is complete. Since each carbon has four groups, the four bonds around each carbon must have a tetrahedral arrangement. Recognize that the bonds when written on a 2d piece of paper are often represented as having 90° bond angles but should be recognized as tetrahedral configurations.

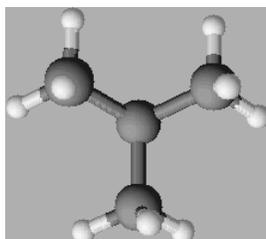
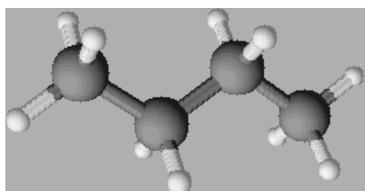
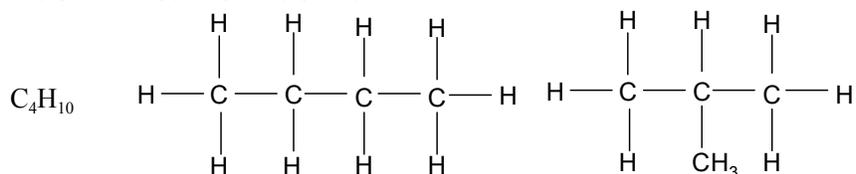


The simplest saturated (no double bonds) hydrocarbons (carbon and hydrogen containing compounds) form a series:

name	methane	ethane	propane	butane	pentane	hexane	heptane	octane	nonane	decane
formula	CH_4	C_2H_6	C_3H_8	C_4H_{10}	C_5H_{12}	C_6H_{14}	C_7H_{16}	C_8H_{18}	C_9H_{20}	$\text{C}_{10}\text{H}_{22}$
# isomers	1	1	1	2	3	5	9	18	35	75

Up through propane, there is only one way to attach the atoms together. For butane, a new situation is encountered. When the next carbon is added to propane, it could be added to one of the two ends. Butane is the result when the carbons are linked in a row. However, it is also possible to link the

4th carbon to the middle carbon. This forms 2-methylpropane commonly named isobutane. The structures below show the two options. Because they have the same formula but different structures, they are called structural isomers. As you can see, the boiling and melting points of the two isomers are similar but not the same.

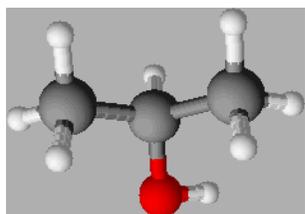


b.p. -0.5°C
m.p. -138.3°C

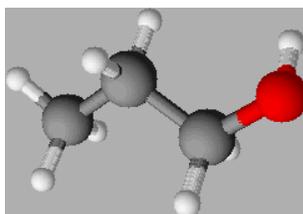
-11.7°C
 -159.6°C

The table above includes the number of possible structural isomers. Notice how the number of possibilities is increasing rapidly and really accelerates after 10 carbons. For $\text{C}_{15}\text{H}_{32}$, $\text{C}_{20}\text{H}_{42}$, $\text{C}_{30}\text{H}_{62}$ and $\text{C}_{40}\text{H}_{82}$, the number of possible isomers are 4347, 366,319, 4,111,846,763 and 62,491,178,805,831 respectively. The number of possible isomers is one of the reasons that an entire field of chemistry is devoted to the chemistry of one element, carbon. To date, tens of millions of compounds have been registered but over 4 billion could exist just with the formula $\text{C}_{30}\text{H}_{62}$.

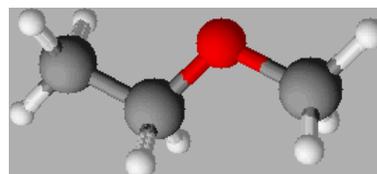
Another example of structural isomers that in this case are sometimes called positional isomers occurs with the first three carbon alcohol ($\text{C}_3\text{H}_8\text{O}$). One of these isomers is familiar to you as it is the alcoholic component of rubbing alcohol, $\text{CH}_3\text{CH}(\text{OH})\text{CH}_3$. The group that makes the compound an alcohol, OH, is attached to the central carbon. The alcohol goes by several names including isopropyl alcohol, isopropanol and 2-propanol. The hydroxy group could also be attached to one of the terminal carbons giving *n*-propanol or 1-propanol ($\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}$). To be complete, there is one more isomer of $\text{C}_3\text{H}_8\text{O}$ but it is an ether rather than an alcohol.



isopropyl alcohol

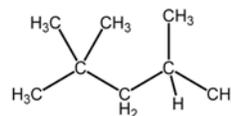


1- propanol



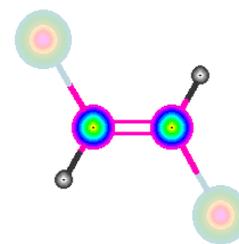
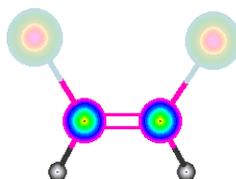
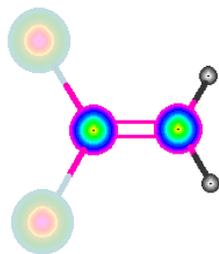
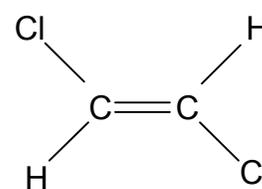
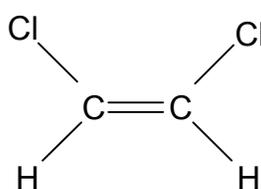
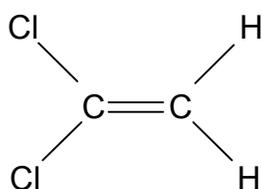
ethyl methyl ether

You have heard of the octane rating of gasoline. Octane has the formula C_8H_{18} and has 18 structural isomers. The rating on gasoline is based on the isomer 2,2,4-trimethylpentane which has been assigned an octane rating of 100. *n*-Heptane has a rating of 0. An 87 octane rating would have the knocking equivalent of 87% 2,2,4-trimethylpentane and 13% heptane. Gasoline is actually a mixture of many compounds and might not contain much octane at all.



As observed with ascorbic acid, it is also possible to have isomers even when the sequence of bonding is the same. When two or more structures can be drawn that differ spatially and can not be superimposed by rotation around single bonds, the compounds are isomers. Another way of putting it is that the isomers are not superimposable and cannot interconvert at room temperature. The general name for isomers that differ spatially but have the same bonding sequence is stereoisomers. Geometric isomerism is one type of stereoisomerism. While single bonds rotate very quickly at room temperature (very roughly about 100 billion times/sec.), double bonds do not rotate at room temperature. To do so requires breaking of one of the two bonds and this process requires considerable energy input such as heating to a very high temperature or absorption of visible or ultraviolet light.

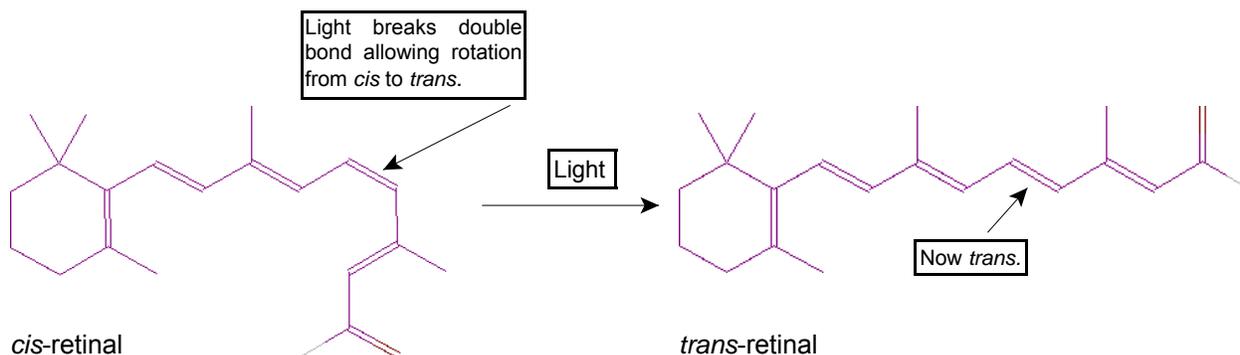
Consider the formula $C_2H_2Cl_2$. It is possible to draw three acceptable Lewis structures for this formula that correspond to the compounds 1,1-dichloroethene, *cis*-1,2-dichloroethene and *trans*-1,2-dichloroethene.



	1,1-dichloroethene	<i>cis</i> -1,2-dichloroethene	<i>trans</i> -1,2-dichloroethene.
b.p.	37°C	60°C	48°C
m.p.	-122°C	-80°C	-50°C
density	1.218 g/mL	1.284 g/mL	1.257 g/mL

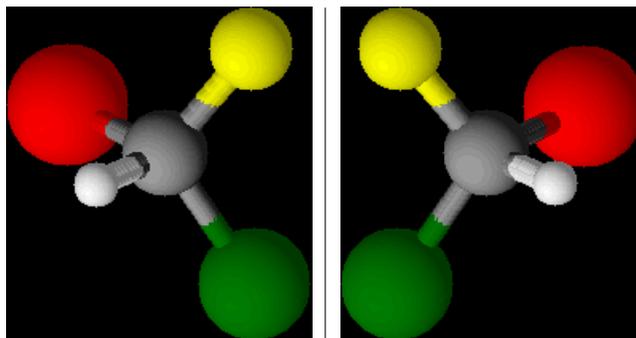
The three possible **isomers** exist and as can be observed from the data above, have different properties. This demonstrates the fact that the spatial arrangement of the atoms has significant effects on the physical properties of the molecule. The first isomer (1,1-dichloroethene) has a different sequence of bonding than the other two and is a structural isomer of the other two. The second and third isomers have the same sequence of bonding but are spatially different. Because they differ in geometry, they are called geometric isomers or stereoisomers. Notice that because of the presence of the double bond, rotation from the *cis* to the *trans* is not possible unless substantial energy input is provided. The absorption of light by rhodopsin (*cis*-retinal + scotopsin) in the eye causes a *cis* - *trans* isomerization that leads to the nerve impulse that is sent to the brain and results in vision.

P5-1. For the following formulas, write the structures of the isomers of each one. a. C_5H_{12} b. $C_4H_{10}O$ c. C_4H_8
d. $C_2H_4Cl_2$



Another extremely important type of stereoisomerism occurs whenever a molecule has a carbon bonded to four different groups. To emphasize the importance of this situation, many of the molecules vital for life including amino acids and sugars have carbons with four different groups. These carbons are said to be stereogenic. To understand this type of stereoisomerism requires that the molecules be visualized in 3 dimensions. It is only then that the spatial differences can be understood. The best way to convince yourself of this phenomenon is to use molecular models. Attach four different colored atoms to the central carbon in a tetrahedral configuration.

Now make a second model in an identical way. Rotate one of the models to determine if it is superimposable on the first model. Half of the time it will be but the other half of the time it will be impossible to make them superimposable. If your models were superimposable, switch any two of the atoms. Now you should find that the models are not superimposable but instead are mirror images. Non-superimposable mirror images are said to

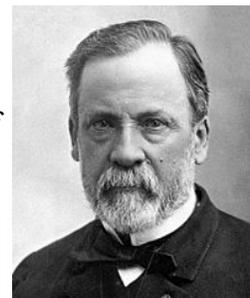


be chiral (have handedness). The mirror images are called enantiomers. Except for two properties, enantiomers have the same physical and chemical properties. Melting points, boiling points and densities are identical. On the other hand, Louis Pasteur discovered that enantiomers rotate the plane of polarized light in equal but opposite directions.



Jean-Baptiste Biot

Experiments demonstrating that some molecules rotate the plane of polarized light were performed early in the 19th century by Jean-Baptiste Biot and others. One of Biot's key experiments was a "successful" attempt to show the rotation is not limited to solids and liquids. He obtained permission to use an old church. He installed a 30 meter long tube that he tried to fill with turpentine vapor by heating the turpentine with a furnace. He succeeded in observing rotation of plane polarized light in this system but an explosion occurred and the church burned down.

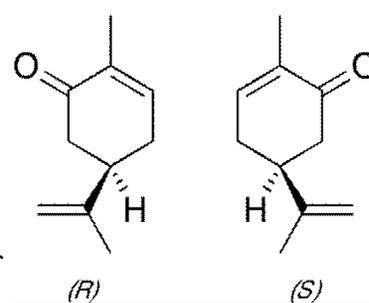


Louis Pasteur

You are strongly encouraged to visit the first site below and at least one of the other sites to gain a better background on stereochemistry.

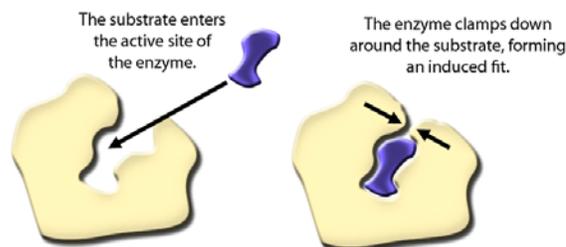
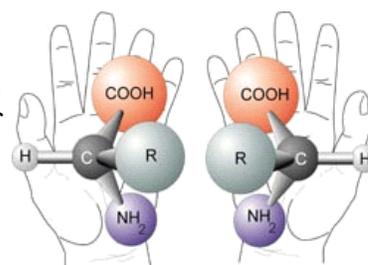
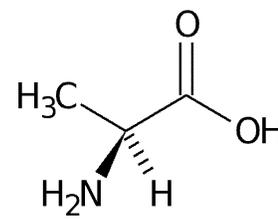
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<http://faculty.concordia.ca/muchall/chem325/LC-History.pdf>
<http://www.leffingwell.com/download/chirality-pharmacology.pdf>
<http://www.leffingwell.com/chirality.htm>

The interaction of molecules containing stereogenic carbons with polarized light is useful for determining which enantiomer is present and its purity. But more importantly, the second way enantiomers differ from each other is the way enantiomers interact with enantiomers of other molecules and with enantiomeric sites in proteins. In the image above of the carbon with different colored balls, imagine that instead of being the mirror image, the figure on the right is a receptor site. The left figure then matches the colors or fits. However, if the receptor was the mirror image, there would not be any way rotation could result in the matching of more than two colors. The key does not fit the lock and will not work. One example that you might have experienced involves the molecules responsible for the smells of spearmint and caraway. 90% of the population can easily distinguish these odors. The compounds causing the odors are mirror images. Thus the receptors in your nose must have two different kinds of receptor sites. The spearmint fits into one and caraway into the other. Since many of the important molecules in everything living are chiral, the behavioral differences of enantiomers is very significant.

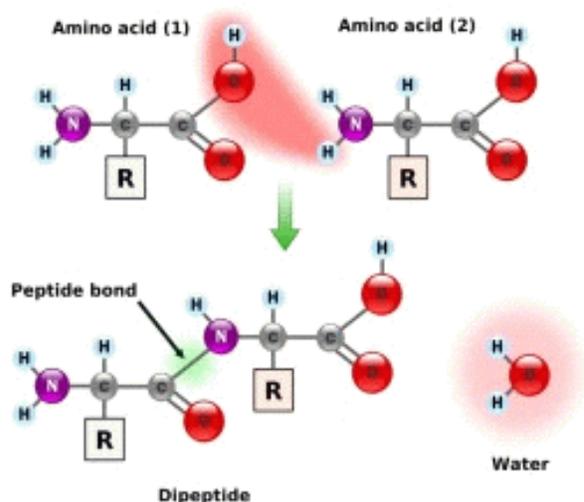


Carvones from Spearmint, Caraway

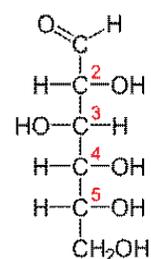
The concept of enantiomers will be developed more by using specific examples. Amino acids have the general formula, $RCH(NH_2)COOH$, where R represents one of 20 different groups commonly found in amino acids and determines the name of the amino acid. The simplest R is a hydrogen and results in the only amino acid (glycine) that does not have four groups on the tetrahedral carbon. As a result, glycine is the only amino acid that does not have enantiomeric forms. In the figure to the above right, the R is a CH_3 (methyl group) and the amino acid is called alanine. The chirality of amino acids is illustrated in the figure to the right. The amino acids are linked together in your body to form proteins and virtually all of the amino acids in anything living on earth have the configuration on the left and are L-amino acids. If you were to consume the mirror image set of amino acids (the D-amino acids), you would starve as your body has receptor sites only for the L amino acids and the D-amino acids would go through your body unmetabolized. Imagine that the blue blob on the right is an L-amino acid. As you can see, it fits the site in the enzyme. However, the mirror image of the blue blob would not fit the site and undergo the reaction that the enzyme catalyzes.



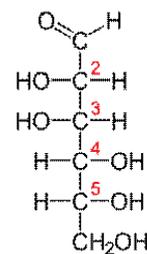
Of the 20 amino acids used by humans to synthesize peptides and proteins, four (alanine, aspartic acid, cysteine, glutamic acid) are synthesized by the human body and do not have to be consumed. An additional seven (arginine, asparagine, glutamine, glycine, proline, serine, tryosine) are considered to be conditionally non-essential as most people synthesize them but some populations do not and therefore must have them in their diets. The remaining nine need to be present in the human diet and are called essential amino acids. If not present in a diet, health consequences can result.



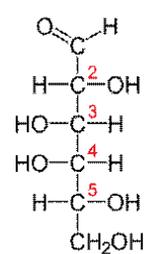
Carbohydrates (so called because the formulas can be written as $C_x(H_2O)_y$ such as glucose [$C_6H_{12}O_6$ or $C_6(H_2O)_6$] have many stereogenic (carbons with four groups attached to them) resulting in many possible stereoisomers. The name carbohydrate is a misnomer as sugars are not hydrated carbons but contain carbons bonded to a hydrogen and a hydroxy group. The open form of glucose is given to the right. Carbons 2, 3, 4 and 5 all have four different groups attached to each carbon. While we are aware that each carbon is tetrahedral, sugars are often written according to the guidelines of Fisher projections. According to the guidelines, the groups on the left and right are coming out of the paper and the top and bottom groups are going back from the paper. Because there are two possible configurations at four carbons, there are 2^4 or 16 possible stereoisomers of glucose. Naturally occurring sugars are D-sugars which means the hydroxy on carbon 5 is on the right. Of the eight D stereoisomers, glucose, mannose and galactose are the most common. Notice that for the three stereoisomers, the OH on carbon 5 is on the right and mannose and galactose differ from glucose only by the position one hydroxy group.



D-Glucose

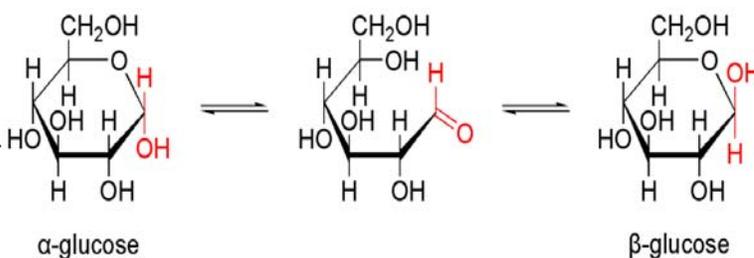


D-Mannose



D-Galactose

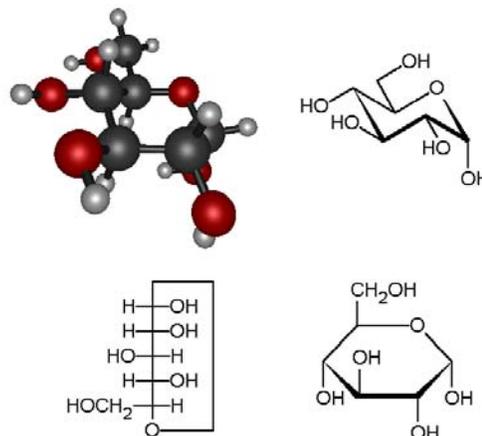
It turns out that the open structures given for the three sugars does not correctly depict the structure of the sugars. The middle structure to the right shows the open form of glucose written in a ring configuration but missing the bond that would complete the ring. Sugars form the bond and exist in the ring form.

 α -glucose β -glucose

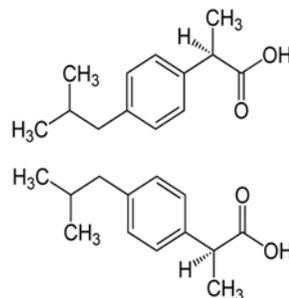
When glucose forms the ring, a 5th stereogenic carbon is created. This means that two forms of glucose can form (the α and β forms) and both are found in nature. If either form is dissolved in water, the ring opens and closes resulting in a mixture of the two forms.

The figure to the right shows 4 different ways to represent α -glucose.

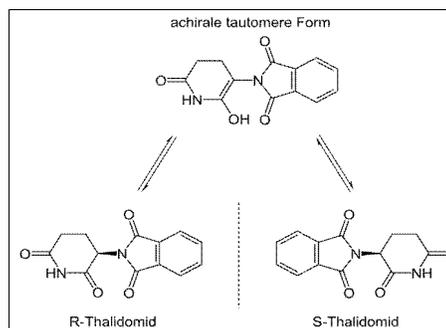
For reasons that are not understood, living things on earth contain essentially only L-amino acids and D-sugars. As a result, reactions in nature use chiral molecules to selectively synthesize more chiral molecules. In the laboratory however, the starting materials are usually not chiral or contain an equal amount of enantiomers (a racemic mixture). Thus laboratory syntheses even when stereogenic carbons are present in the product produce racemic mixtures. Pasteur was able to separate enantiomers using tweezers to separate crystals that contained mirror images of tartaric acid. However, separating enantiomers is generally much more difficult than the experience of Pasteur and can be time consuming and expensive. Often, chiral molecules produced by nature are involved in either the synthesis or resolution process. This can be especially important in the drug industry.



Most of you are familiar with the drug ibuprofen that is the active component of many analgesic products. As seen in the figure to the right, ibuprofen has one stereogenic carbon and therefore has a pair of mirror images. The bottom one [S(+)] has anti-inflammatory properties but the top one does not. Fortunately in this case, the top one is not toxic and does not produce side effects and 60% of it is converted by an enzymatic reaction in the body to the active one. The lab synthesis produces a 50:50 mixture of the two. Because the separation is expensive and the presence of the inactive isomer does not cause problems, the product usually is sold as the racemic mixture. There is some evidence that the pure S(+) form is more effective than the racemic mixture. Therefore there are research efforts underway to find less expensive routes to the S(+) isomer.



Unfortunately, unlike the ibuprofen example, the enantiomer of the effective drug can have undesirable side effects. For these cases, it is necessary to run a stereospecific synthesis or to resolve the racemic mixture to make sure only the desired enantiomer is used. A very interesting and sad story involves the drug thalidomide. Perform an Internet search on this drug, comment on its applications and the issues associated with its stereochemistry.



It was mentioned above that while explanations for nature's selectivity on earth for one set of enantiomers for sugars and amino acids have been published, the level of confidence in these explanations is low. The lack of an explanation is a missing piece of the theory of evolution. Write a paper on this issue that addresses this issue.