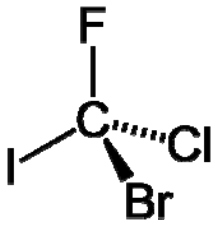
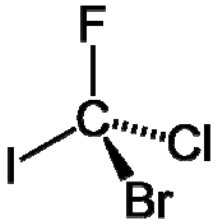
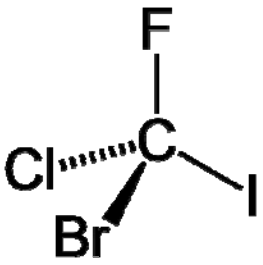
2.4 Enantiomeric Isomers

There is an additional type of isomer that can exist when we have an atom with 4 different groups attached to that atom in tetrahedral geometry. Consider a methane molecule with a fluorine, chlorine, bromine and an iodine atom bonded to it: bromochlorofluoroiodomethane. In wedge and dash notation we have.



If we take the mirror image of this molecule we will have the molecule on the right::





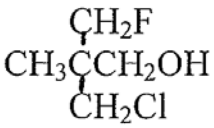
Original mirror image molecule

We might think that these are identical molecules, but if we make the real structures and try to align them we see that we can never line up all the atoms. If we rotate the mirror image molecule to line up the F-C-I atoms we find that the Br atom is now pointing back into the paper (i.e. it is the dashed form) and the Cl atom is pointing out of the plane of the paper towards us (i.e. it is now in the wedge form). No matter how we rotate the mirror image molecule it cannot be aligned with the original. The mirror image **is non-superimposable.**

This is somewhat analogous to taking the mirror image of a right hand glove. The mirror image of a right hand glove is a left hand glove, and although a left hand glove is clearly very similar to a right hand glove, it is not identical.

Non-superimposable mirror image molecules can occur whenever a molecule has one or more C atoms with 4 different groups bonded to it.

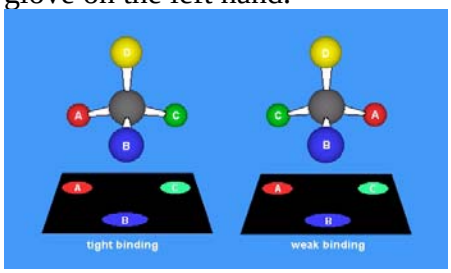
An atom (usually, but not always C) with 4 different **groups** bonded to it is called a **chiral center** or (in older terminology) an **asymmetric C atom**. *(The term chiral is pronounced kiral (rhymes with viral) and comes from chiros-Greek for hand, based on the right and left hand glove analogy. This root also shows up in the word "chiropractor")*
[example]
We have to look at all 4 **groups** attached to a given C to decide whether it is a chiral center. Consider the molecule:



The center C has 4 C atoms attached to it, but it is still a chiral center because each of the C atoms it is bonded to is itself bonded to different atoms.

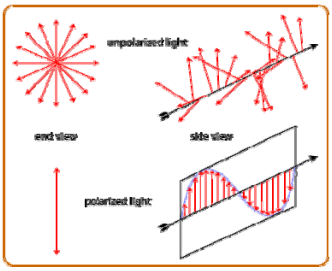
In general a molecule with a chiral center will have non-superimposable mirror image. These mirror image molecules are called **enantiomers** or in older notation **optical isomers.** More generally, molecules which differ only in the direction in which atoms are oriented in 3 dimensional space are called **stereoisomers**. Enantiomers and geometric isomers are two types of stereoisomers.

Enantiomers frequently have substantially different biological activity because they bind to receptors in the body that are also chiral. If one enantiomer molecule binds to complementary chiral binding site on an enzyme, the mirror image of the original molecule will not bind nearly as well, if at all. It would be like trying to put a right hand glove on the left hand.

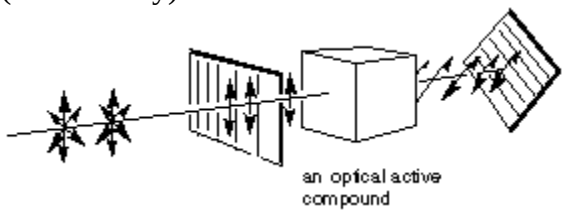


Enzyme Enzyme

Enantiomers also differ in the way they affect polarized light. Ordinary light has light vibrating uniformly in all different planes perpendicular to the direction it is moving. Polarized light is vibrating only in one plane.



Enantiomers differ in the way they affect polarized light that passes through them. When polarized light passes through a pure enantiomer, one enantiomer will rotate the plane of vibration (not the direction of the light!) to the right (+)(dextrorotatory), while the other mirror image will rotate the polarized plane of vibration an equal amount to the left (-) (levorotatory).



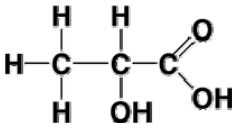
http://www.youtube.com/watch?v=QgA6L2n476Y

Two common notations besides + and - are used to distinguish between the two forms of optical isomers. In an older (but very common) notation D (for dextro) and L (for levo) are used to designate the two enantiomeric forms. In the other system the prefixes R(for rectus) and S (for sinister)are used to designate the two enantiomeric forms. The explanation of both notations is somewhat complex and will be omitted, but you should know that if you see the symbols +/-, D/L, dextro/levo or R/S in front of a chemical name, it means you working with one of 2 enantiomers. You do NOT have to figure out which structure is which in the R/S, D/L prefix system.

Practice Identifying the chiral centers (asymmetric Cs)

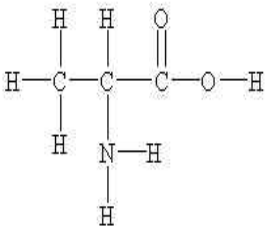
a)

Lactic Acid



We can check each of the three C atoms for chirality. Starting from left to right, the first C is clearly not chiral because it has three H atoms bonded to it. The second C atom *is* chiral because it has a methyl group, an OH group, a carboxylic acid group and a H bonded to it. Hence it is chiral. The last C is not chiral because it has only three groups bonded to it. Hence there is one chiral atom, the central C atom and there are + and -, or D and L (or R and S) forms for lactic acid. You do not have to decide which is which. The lactic acid that builds up in animal muscles is actually the pure L or + form. Bacterial cultures (such as that found in yogurt) produce primarily, but not exclusively the L isomer.

b)

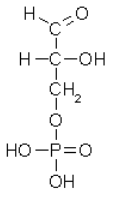


Alanine—a common amino acid

(Circle the amine and carboxylic acid groups.)

Likewise the first C (going from left to right) cannot be chiral because it has 3 H atoms; the middle C atom IS chiral because it has 4 different groups (a CH_3, an NH_2, a H and a CO_2H). The third C is not chiral because it only has 3 groups around it). Alanine can exists in two enantiomeric forms, most commonly referred to as the D and L forms. In general, the L form of amino acids are the most common and are the ones exclusively used to make proteins. D enantiomeric amino acids are found occasionally, such as in the amino acids found in bacterial cell walls.

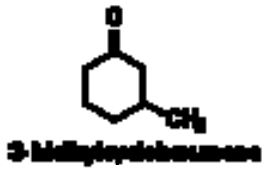
c)Glyceraldehyde-3-phosphate



Fischer
open-chain

This molecule is present vertically rather than horizontally, but that should not cause too much problem. Hopefully you reach the conclusion that the middle C is the only chiral center. The D-enantiomer of this molecule is made when glucose is metabolized. *Label the aldehyde functional group.*

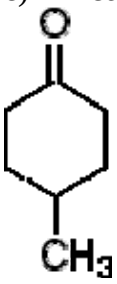
d)



This molecule gets a little trickier and it will probably be useful to draw the complete structure. You should reach the conclusion that the C of the carbonyl group cannot be chiral, nor can any of the other C atoms in the ring except the C bonded to the methyl group. That C is however bonded to 4 different groups: a methyl group and to the ring (twice, but from two different directions) and to a H atom (which is not explicitly shown in this shorthand notation). However the bonding clockwise around the ring is

$CH_2CH_2CH_2C{=}O$ and in the other direction it is $-CH_2C{=}O$. Those bonds are different and hence 3-methylcyclohexanone exists as two enantiomers.

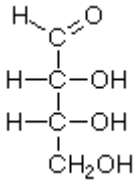
e) **4-methylcyclohexanone**



4-methylcyclohexanone

If you look at the structure of 4- methylcyclohexanone, you should see that the C bonded to the methyl group is symmetrically bonded within the 6-membered ring, so that it is NOT chiral.

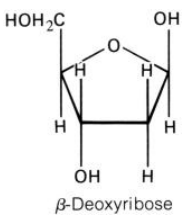
f)erythrose



Erythrose

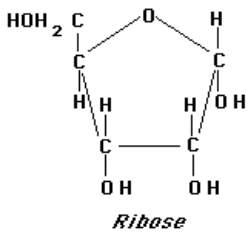
In the molecule erythrose, the aldehyde C cannot be chiral because it does not have four different groups. The next C has a H, OH, C=O, and $CHOHCH_2OH$ group bonded to it. The third C has a H, OH, CH_2OH, and CHOHC=O bonded two it. There are 4 different groups on both of the middle C atoms, so they are both chiral. The fourth C has two hydrogens bonded to it so it is not chiral. Multiple chiral atoms in a single molecule are in fact very common in biological molecules. They do make for a quite complex brew of **stereoisomers** that is beyond this text. Although we will identify chiral centers in molecules, we will not try to look at the complexities that result in molecules with multiple chiral centers.

Label chiral centers in the molecules below with a *.



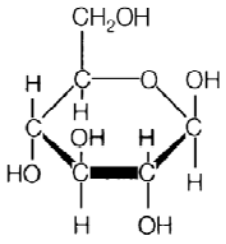
β-Deoxyribose

deoxyribose



Ribose

ribose



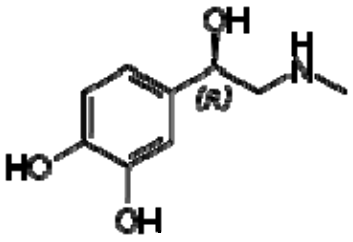
Glucose

Enzymes produce only 1 enantiomer of any possible pair, but synthetic organic chemists often produce a mixture of both enantiomers. A mixture of both enantiomers is called a **racemic mixture.** This is particularly important when drug molecules are synthesized. These drugs generally bind to **chiral receptors** and as a result one enantiomer usually binds the desired site better than the other, as we saw with DES in the previous chapter.

Pharmaceutical chemists have developed increasingly sophisticated drug syntheses that allow them to make pure enantiomers rather than racemic mixtures and newer drugs on the market are often pure enantiomers.

Some Medically important examples of enantiomers:

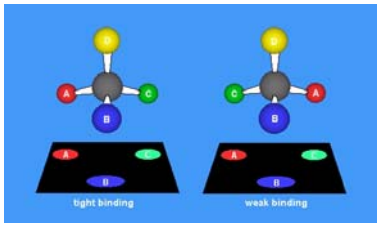
1)Epinephrine(adrenaline)



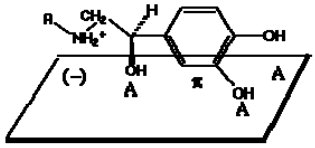
Epinephrine(adrenaline) How do the two differ in structure?

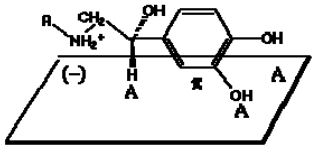
Epinephrine (adrenaline) acts as a neurotransmitter or hormone which binds to several different kinds of **adrenergic** receptors in the body and cause a large variety of physiological effects. The best known effect is the "fight or flight" phenomenon or "adrenaline rush" which increases heart rate and blood pressure. Epinephrine is used as a drug for the treatment of anaphylactic shock where it increases heart rate and blood pressure. It is commonly added to local anesthetic injections to promote vasoconstriction at the injection site, thereby reducing the amount of local anesthetic that gets into the blood stream.

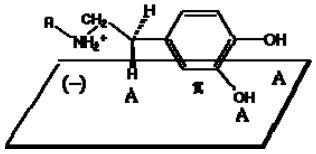
Epinephrine contains a chiral center in its structure. Can you find it? The naturally occurring form in organisms is the (D) R (-) enantiomer. When epinephrine is used as a drug, the routine organic synthesis results in a **racemic mixture**. The (+) S enantiomer does not typically bind as well to adrenergic receptors nor produce as much activity but its presence in the racemic mixture doesn't appear to be a clinical problem either. Organic chemists are getting better at synthesizing pure enantiomers in mass quantities and commercial epinephrine is now typically the pure D enantiomer.



The diagram A below shows that the D enantiomer of epinephrine binds to 3 **A** sites aligned on the plane to attract the polar OH groups. In B, the L isomer only binds the two OH on the ring, and hence binding is not as good. In C, dopamine does not have any OH group at the first A site on the left and it also does not bind as well.

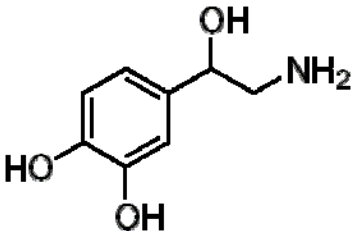






dopamine

2)Norepinephrine



Norepinephrine is another important neurotransmitter in the body.

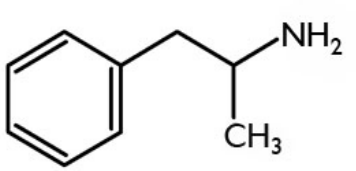
How do the structures of epinephrine and norepinephrine differ? How are they similar? Label any chiral centers in norepinephrine.

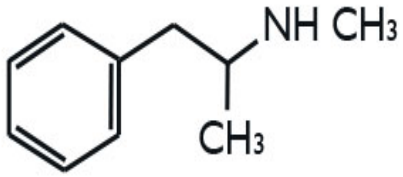
3) **Dopamine**

Dopamine

Dopamine is another neurotransmitter with a large variety of actions on different receptors in the brain. It is involved in regulating motor activity, motivation, and the pleasure response and overproduction of dopamine in the "pleasure center" of the brain can lead to addiction. High dopamine levels in the chemoreceptor trigger zone (CTZ) can cause nausea and vomiting. It has a structure similar to epinephrine and norepinephrine. Does it have a chiral center? Why or why not?

4)Amphetamine (sold as trade name product Adderall) and methamphetamine, formerly used as an appetite suppressant and as a stimulant ("cognitive enhancer")by truck drivers, pilots, and students(!), is currently approved by the FDA for use in treating attention deficit and hyperactivity disorder (ADHD). Methamphetamine has an extra methyl group added to the amine group in amphetamine.





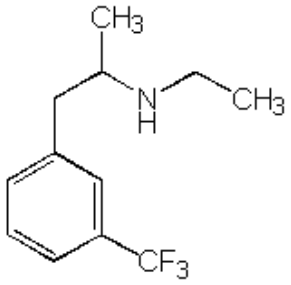
Amphetamine Methamphetamine

As originally marketed, amphetamine contained both D and L isomers, with only the D isomer having significant activity. Increasingly sophisticated organic chemistry techniques have produced the pure D enantiomer which is available in a sustained release form of amphetamine (Adderall).

Methamphetamine has become an "upper" of choice on the street drug circuit because of the huge "high" it causes. This should not be entirely surprising given its similarities to epinephrine. Meth also contains a chiral center.

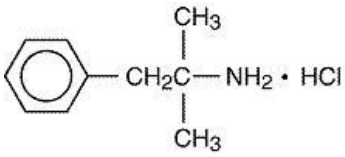
Plant an * by the chiral center of both molecules. Is the chiral center the same C as in epinephrine and norepinephrine?

5) Fenfluramine(Pondimin)



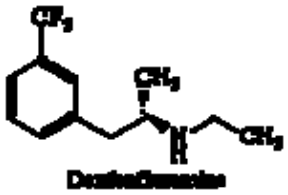
Fenfluramine was a drug that was a very popular appetite suppressant in the late 1980's and early 1990's. As originally marketed, it contained a racemic mixture of both D and L fenfluramine enantiomers. While D-fenfluramine (or dexfenfluramine) suppressed the appetite, its mirror image molecule caused drowsiness.

To counteract the drowsiness, the **racemic** fenfluramine was combined with a drug called **phentermine** a mild "upper", which has been used by itself as a weight loss drug. **Phentermine** stimulates the sympathetic nervous system (fight or flight) to counteract the drowiness caused by L-fenfluramine. The combination was marketed as **fen-phen** and was a huge product in the weight loss industry in the early 1990's. In 1997 reports of heart defects, some of them fatal, in fen-phen patients started being reported to the FDA and in September of 1997 fenfluramine was pulled off the market. Lawsuits started immediately and are still ongoing, with settlements in the billions of dollars.



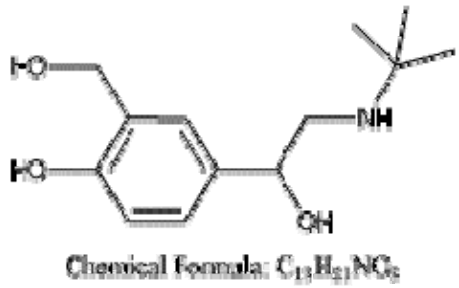
phentermine

As with the case of Adderall, synthetic organic chemists developed a chiral reaction pathway to make pure dexfenfluramine, which was marketed as Redux in 1996, just a year before the revelations about heart valve defects. Redux was associated with heart valve defects just as was the racemic mixture of fenfluramine and was also removed from the market place.

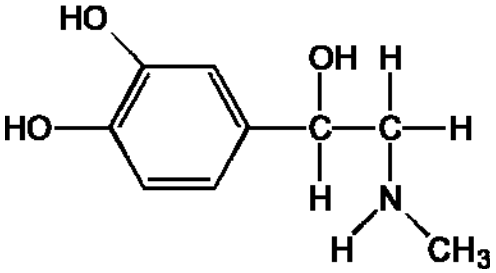


6) Albuterol

Albuterol is a very common asthma medication. Although there are differences, notice the similarities in the structure of albuterol and epinephrine. In fact albuterol acts to activate epinephrine receptors specifically in the lung to cause broncodilation.



Albuterol

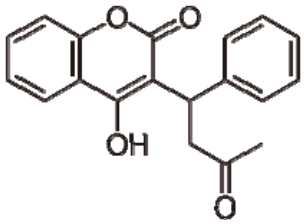


epinephrine

R albuterol (levo albuterol) is the enantiomer which causes bronchodilation desirable in asthmatics. S albuterol (dextro albuterol) appears to be relatively biologically inactive. Label the chiral center in albuterol

The current albuterol on the market is a racemic mixture of + and - albuterol. Pure (-) L albuterol is available as levalbuterol (Xopenex) but has not been found to be better than the racemic mixture by most clinicians and its cost is about six times the racemic mixture.

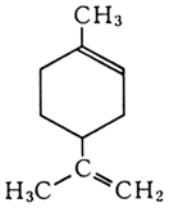
7) Warfarin(Coumadin) is a very common blood anticoagulant. (Warfarin is the generic name; Coumadin is the trade name of a specific manufacturer)



Commercial Coumadin is a racemic mixture of R and S(D and L) enantiomers. Although both enantiomers are anticoagulants, the S isomer is 3-5 times as active as the R isomer. Can you identify the chiral center?

8)Limonene

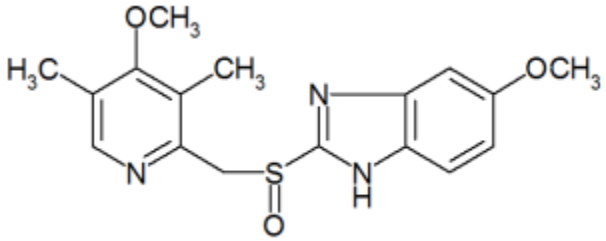
Limonene is one of the molecules responsible for producing the characteristic citrus smell of lemons and oranges. It is a byproduct from the orange juice and lemonade manufacturing and is used to provide the citrus smell in a wide variety of cleaning, degreasing, and cosmetic products.



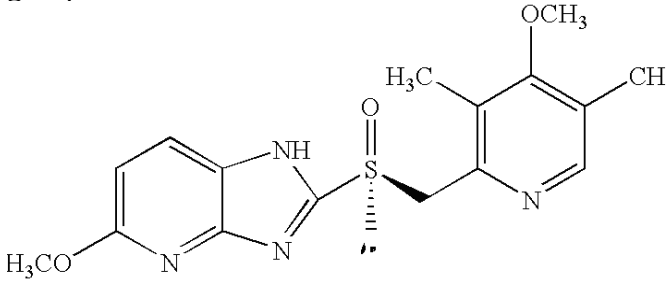
Limonene exists as two enantiomers. Can you find the chiral center?
R (+) limonene is the naturally occurring enantiomer in citrus oil. S (-) limonene has more of a pine resin smell.

9)Omeprazole (Prilosec)

Omeprazole(Prilosec) is a **proton pump inhibitor(PPI)** that shuts down HCl secretion into the stomach and is used for the treatment of ulcers and *GERD(*gastroesophageal reflux disease, heart burn*).* It exists as a racemic mixture. The chiral center is different from the previous examples in that it is the S atom in the structure. This may seem strange because all of our previous examples of chiral centers were C atoms. C is by far the most common **chiral center**, but there are other atoms that can show chirality and this is one example. The next apparent contradiction is that one needs to have 4 different groups on an atom for it to be chiral, and the S atom in omeprazole only has 3 groups bonded to it.



The contradiction is resolved if one looks closer at the actual Lewis dot bonding of the S atom and realizes that there is a non-bonding pair of electrons which is rarely if ever shown when its structure is drawn. This non-bonding pair of electrons constitutes a fourth group around the S atom which causes it to be chiral.



Omeprazole(Prilosec) is the racemic mixture of the two enantiomers. The clever organic chemists at AstraZeneca worked out a synthesis of the pure active S isomer and when the patent on Prilosec ran out, its manufacturer introduced esomeprazole (**Nexium)** which is

the pure biologically active enantiomer of Prilosec and marketed it heavily. The es in omeprazole stands for the prefix S.