

## Stereochemistry

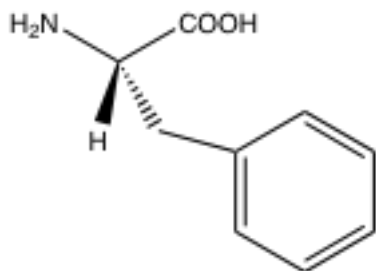
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Videos taken by Ian Eck and Clement Stormes

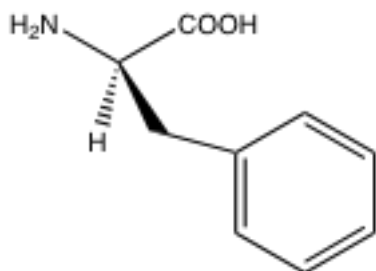
**Chirality and chiral molecules:** Chiral objects be they molecules or macroscopic items are so irregularly shaped (asymmetric) that they are non-superimposable (or noncongruent) on their mirror image. There are many chiral objects in the world. For example, your hands are chiral. Really look at your hands. Each of your individual hands are chiral. This means they are so irregularly shaped that they are non-superimposable (non-congruent, can't occupy the same space) on each other. What does superimposable mean? It means that the objects in question are non-congruent. To test your hands for superimposability or congruency, take your thumb and make it occupy the same space as your other thumb (facing the same direction!). When you do this you will discover that your other four fingers do not line up. This is true of many objects. For example, consider a spiral staircase, a screw, a glove, a shoe, either of your feet, the desks in many classrooms. You are probably chiral overall because your form is probably not perfectly symmetric and even if you do have external "perfection" in terms of symmetry, your internal organs are organized so as to create asymmetry. Therefore, you are not completely superimposable on the mirror image of yourself.

Interestingly, living creatures are comprised of molecules and many of those molecules are organic molecules and many of those organic molecules are chiral. This means the molecule can't be superimposed on its mirror image. This means the two molecules that are mirror images are not the same. Molecules that are the same are congruent. Now superimposing can involve the rotation of bonds, but if it involves the breaking of bonds it is not superimposing. Interestingly, in nature molecules have evolved to be only one of two mirror image forms. This is very important and has great implications in specificity in the communication of molecules.

Consider for example, the amino acid, phenylalanine. Phenylalanine is one of the amino acids commonly found in living systems. In normal living systems, phenylalanine exists as D or L-phenylalanine. The letter designation defines the three dimensional nature of the phenylalanine. The structure of D or L-phenylalanine is given below.



Now consider the structure of D or L -phenylalanine shown below.



What is different about these molecules? They are connected the same way, so they are not constitutional (structural isomers, position isomers). They have the same connectivity, but the only difference is what group is attached the wedge and what group is attached the hash. Ordinarily such a subtle difference would not confer a difference on the molecule. But these two molecules are different. What you should do as a beginning exercise is to build both of these very carefully and attempt to superimpose them. A video demonstrating chirality and superimposability can be found at Stereochemistry 1 and 2:

[Stereochemistry 1: chirality](#)

[Stereochemistry 2: basics of asymmetric!](#)

You should discover that when you try to superimpose one on the other, they will not completely line up. For example, if you get the amino and acid groups to line up perfectly the benzyl and hydrogens will be misaligned. If you line up the benzyl and hydrogens, the amino and carboxylic acid groups will be misaligned. The only way these two compounds can be interconverted is by breaking two bonds. If you take any two sets of bonds, disconnect them and then reconnect them in opposite positions (see video). You will generate the other molecule. The fact that these molecules are not superimposable and are mirror images (try this also set them up so that they are facing each other as in a mirror) indicates that they are isomers of some sort. The sort of isomers they are is rooted in the fact that the molecules each possess an asymmetric carbon. An asymmetric carbon is a carbon with four different groups attached. These four different groups are what create the gross asymmetry or chirality that prevents the molecule from being superimposable on its mirror image. There are other asymmetric centers (called generally stereogenic centers), but this treatise will focus on asymmetric carbons. At the end I will give a few examples of different sorts of asymmetric centers.

Chirality can be complicated, but it is a three-dimensional phenomenon and most chirality that you will encounter will involve one or more asymmetric carbons. You will note as you study natural products such as proteins, carbohydrates, lipids, DNA,

RNA, etc. that they contain many asymmetric carbons. Their irregular shapes make them unique individual molecules capable of interacting (communicating) in unique individual manners with other molecules. This idea is very important for molecules in living systems that need to communicate in very specific ways, as do molecules in flasks.

But before we get to deep into the larger implications of this, let us review the basics. There are molecules that are so irregularly shaped that they are non-superimposable on their mirror images. This mirror image may really exist or it may be just a theoretical molecule generated on paper or using a model. This molecule and its mirror image are different molecules. In principle they could be placed in separate containers and would not normally interconvert. Interconversion involves breaking bonds. Their difference is because they are this irregular shape which is often due to having one or more asymmetric carbons that confer chirality on the molecule. It will make a difference if the groups are oriented oppositely around such a carbon. Since the molecules are different but have the same connectivity they must have a relationship. Their relationship is that of enantiomers. Molecules that are nonsuperimposable stereoisomers are called enantiomers. **All molecules that have one and only one asymmetric carbon are chiral** and in principle can have another molecule with opposite spatial organization and they are enantiomers. This will be repeated, but please note that the term enantiomer is a relationship term. The term chiral is a term that refers to individual molecules. A molecule can be chiral. Two molecules can be enantiomers with respect to each other.

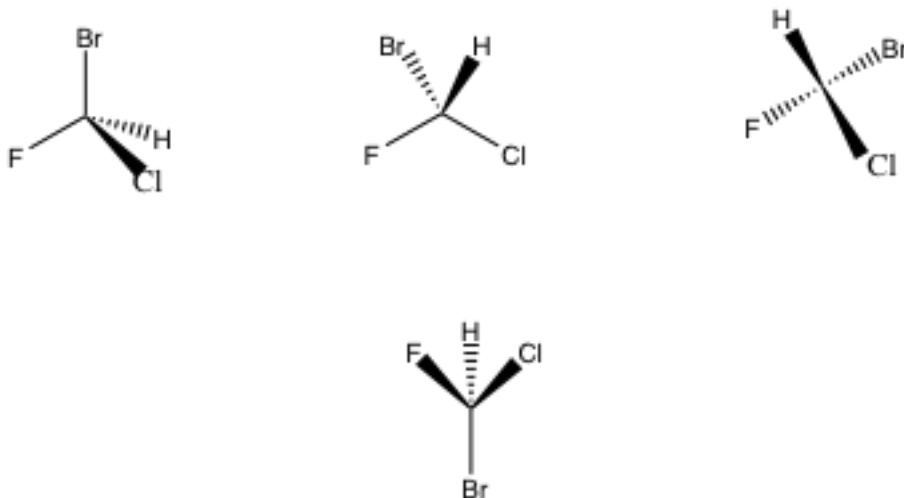
It is very common for students to do a lot of model building when testing to see what the relationship is between molecules that have these seemingly subtle differences. It is very common for students to do a lot of model building when testing to see if a molecule is chiral. This is a very admirable approach and I have nothing against models, but this treatment of stereochemistry is going to train you to work pretty much model free.

When molecules are different as the special stereoisomers called enantiomers are, they need individual names. To name stereoisomers, one uses the Cahn-Ingold-Prelog naming system. You may have already learned this system in regard to Z/E stereoisomerism in alkenes. The use here is very similar, but you will be giving molecules or asymmetric centers rather R/S designations to name them. R stands for rectus and S stands for sinister (sinistra). These designations define the absolute configuration of the center – in other words the precise three-dimensional organization of the groups around the carbon. The way it works is that each of the four different groups around an asymmetric carbon is given a priority number (normally 1-4, where highest priority is number 1). This priority number is based on the first point of difference using atomic number. When the four groups are designate with priority numbers ranging from 1-4, then the lowest priority group (no. 4) is oriented to the back and a circle is traced from priority no. 1 to priority no. 3. If the tracing of this circle is clockwise, assign the center an R (rectus, to the

right) absolute configuration. If it is counterclockwise, assign the center an S (sinister to the left) absolute configuration.

### Stereochemistry 3: Simple Absolute configuration Problem

For a very simple example consider the following molecules. Notice, the molecules have to be drawn with a three-dimensional representation. Later in this text I will

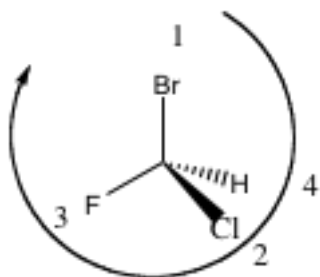


Introduce another manner of representing molecules in three dimensions, however, for now it must be recognized that wedges and hashes have to be used to represent a chiral molecule or a molecules having asymmetric carbons. To understand this, you should think of a tetrahedron as two intersecting **V**s that are perpendicular to each other. If two are in plane, two have to be out of plane. The out of plane groups have to be splayed apart a bit so you can see them, but they are really right in front of each other. It is possible to represent a tetrahedron with none of the groups in plane, in which case, one **V** is coming out and the other going back (third example, above). Finally, it is possible to represent a tetrahedron with one group in plane (the last representation), by having two groups out and one back (it can also be done with two groups back and one out – there are many ways to represent the same structure).

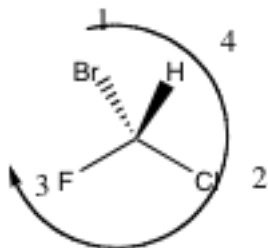
Now, in addition to giving you an idea about how to represent molecules in three dimensions, these representations given above are also an exercise for you to attempt. I would like you to establish the relationships (if any) that exist between pairs of molecules in the group. You might conclude that pairs are the same molecule or they are enantiomers. These are your only options in this set. Why is this (it has to do with the fact that the molecules have the same formula and connectivity)? Now, you may want to make molecules and superimpose them or you may want to try to move these molecules around to test superimposability. If

they superimpose then they are the same, but if they do not, they are enantiomers. **But, I feel a much more efficient and reliable way to arrive at the same information is to assign the absolute configuration to each molecule.**

Since all these molecules have the same four different groups and they are simple groups, applying the Cahn-Ingold-Prelog rules is not too challenging. Bromine will be number one, chlorine number 2 and fluorine number 3 and hydrogen number 4. Normally one might tend to move the molecule in one's mind or build a model and move it and you are welcome to do this, but I want to teach you a little trick. If number 4 (the hydrogen) is a hash, it is back. If it is back, just trace a circle from one to two to three and you will have the absolute configuration. For example with the first structure, the number four is back. Tracing a circle from 1 to 2 to 3 as shown below results in which direction of rotation?



You should be getting rectus or to the right. This is R-bromochlorofluoromethane. Now you will notice in some of the representations (for example the second representation), no. 4 is coming toward you. The arbitrary definition as developed by Cahn, Ingold and Prelog dictates that number four be away from you (remember, nomenclature is arbitrary – they are just a bunch of rules made up by chemists). Now you can envision moving the model (and retaining all the stereochemistry) so that number 4 is in the back, but it is much simpler to just trace the circle from 1 to 2 to 3 and reverse the designation. The reason this works is that when the molecule is oriented backwards all the positions would reverse if you turned the molecule around. Or, as I like to say to my students, picture yourself behind the molecule. If you were behind the molecule (you need to picture yourself standing behind the paper facing it. If you do this with the second compound you will get the same results as if you face it from the front, trace the circle and just reverse the designation. Try it both ways on the second molecule.



Shown is my trick method. Tracing from 1 to 2 to 3 (ignoring 4 in the circle), one comes up with a right hand circle, but number four is not going back, it is coming out, therefore you should reverse the designation from R to S. This is S-bromochlorofluoromethane. Now envision yourself behind the molecule. If you were standing behind the molecule, number four would be pointing away from you. Bromine would be up near your head, pointing toward you and chlorine to your left and fluorine to your right. Can you see that? If you traced standing behind the paper, you would get a sinister circle or S. The molecule is really S.

Now what is the relationship between the first and second molecule – because one is R and one is S they are enantiomers, no further testing is necessary. They are both chiral, but they are different molecules. The R and S designations define their stereochemistry and one does not need to test. As I love to say to my students. What does chiral R see when she looks in the mirror? - Chiral S, of course!

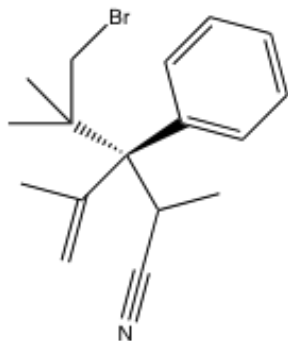
So you don't have to do all the molecular testing. Assignment is a great friend and a great tool, as you will discover. Continue working on the molecules above. Try to understand them by assigning only. You should discover that they are both S.

**Summing up, you can safely conclude that if a molecule has one and only one asymmetric carbon, it is chiral.** I will repeat this because beginners have trouble accepting it is this simple. **If a molecule has one and only one asymmetric carbon, it is definitely chiral.** The four different groups around the asymmetric carbon render it so irregularly shaped that it is nonsuperimposable on its mirror image. The relationship between the molecule in question and its non-superimposable mirror image is that they are stereoisomers. Stereoisomers are compounds that have the same connectivity, but different orientations in space such that they are not congruent. This means they are different molecules and could in principle be placed in different bottles. Their interconversion requires that you break bonds. The naming or defining of the stereochemistry of an asymmetric carbon is the absolute configuration, which is the R or S assignment.

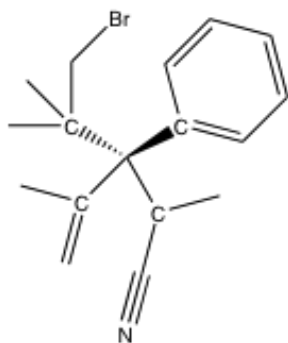
So, are the molecules in the last problem chiral? Yes they are because they possess asymmetric carbons. What are their relationships? Likewise, the relationship can be easily ascertained by just assigning the centers. The first one is R and the last three are S. The relationship between the R and each of the S is that they are non-superimposable mirror images. This means they are enantiomers. The relationship between any two in the last three is that they are the same molecule. With the same connectivity, S is the same as S. What does S see when it looks in the mirror? It sees R. S and R are enantiomers. It is hard for people in the beginning to accept that the assignment is so rich in information.

**More on assigning priorities:** The assignment of priorities can become somewhat difficult, but you can quickly master it. See stereochemistry no. Again, the simplest way to explain how to assign priority is by first point of difference, highest atomic number. If the atomic numbers are the same, then atomic mass is used. So one

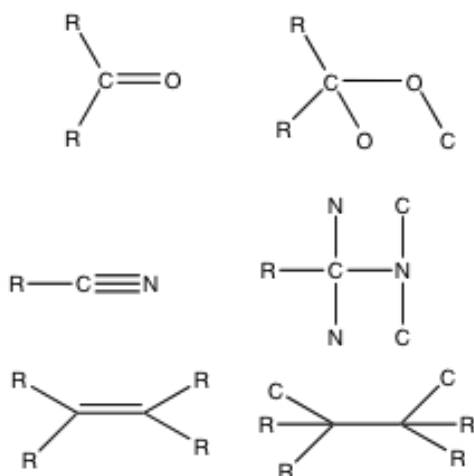
compares level by level and if there is one atom in one group that is higher atomic number than any atom in the other group, it wins or is given higher priority. You will note in the ensuing detailed explanation of a complex example, that one never compares more than three atoms and it is not an addition process. One higher atomic number atom will beat a summation that is higher. Consider the following example.



What we are going to do is compare the groups around the asymmetric carbon atom by atom. Shown below is the first level. The first level is one bond away from the asymmetric carbon. As you can see, at the first level there are four carbons. Notice I am not taking the whole group into account. I am taking it one bond at a time.

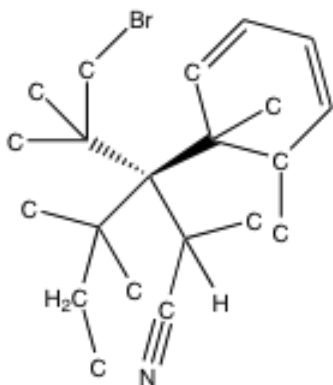


Though this molecule actually has two asymmetric carbons (can you find the other asymmetric carbon, it is chiral – you will soon know why). We will focus on the center drawn in proper, three-dimensional structure. Since there is a complete tie at the first level we have to go to the second level on each group. This is two bonds away. To do this you have to learn how to deal with multiple bonds. Please note that multiple bonds are viewed as though each atom in the multiple bond is bonded to multiple atoms, rather than being in the multiple bond. Please note that this is an arbitrary nomenclature rule and does not represent the molecule chemically. So for example the following groups would be considered as follows.



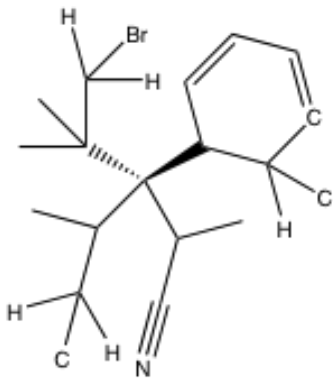
Maybe put some equal signs in.

For example in the first case, it is treated as though the carbon of the carbonyl is bonded to two oxygens and the oxygen of the carbonyl is bonded to a carbon and oxygen. You might have to go out to the oxygen in some cases, but you do not consider that anything else is attached. So let us consider our practice molecule in this way.

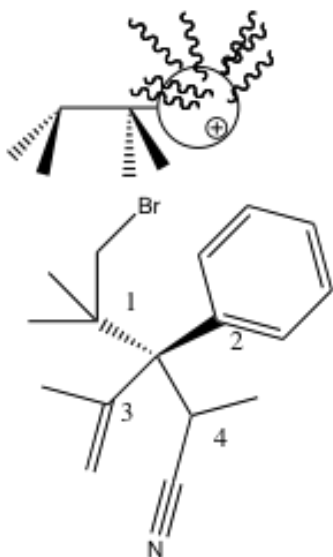


In the above structure, the second level is written in and the multiple bonds are dealt with as above. . So lets look at the second level. In the aromatic ring, the second level is considered to be three carbons. On the chain with the nitrile, the second level is two carbons and a hydrogen. On the chain with the double bond, the second level is three carbons. In the chain with the bromine down the line, the second level is three carbons also. The three carbons are still tied, but the chain with the nitrile is now priority number four. Now lets focus in on the third level on the three groups that have tied so far in our evaluation.





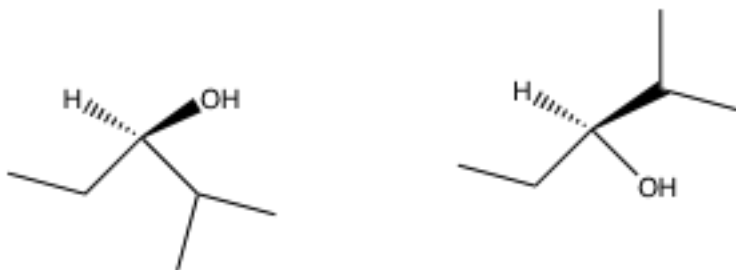
Now, when you go to the third level you have to be careful. In principle you could be comparing nine atoms that are at the same level and if the molecule continued to branch out, you could have many more atoms being considered at the same level. You do not want to compare more than three at a given level, so you want to pick the route of highest priority. On the group with the benzene ring, no matter which direction you pick around the ring, the situation at the third level is the same, so one direction has been chosen arbitrarily. At this level on the benzene ring, there are two carbons and a hydrogen as shown on the lower carbon of the benzene. If you go the other way you obtain the same results. Give it a try. On the group bearing the bromine, you would choose the level three with the bromine. This group has one bromine and two hydrogens at the third level. In the group that really has a double bond though I have drawn in its arbitrary nomenclature form, you should choose the highest priority third level, which is the carbon that is considered to have a carbon and two hydrogens. OK, now we have a difference. What is number one priority? It is the group with the bromine. Bromine is higher atomic number than anything at level three. What group is number two – the benzene because it is considered to have two carbons whereas the group at level three, is considered to have one carbon. Now we have all the priorities and they are written in on the following structure. Let us assign the stereochemistry.



At this point, I want to introduce to super-stereochemistry woman who has wedges and hashes for her arms and legs. Can you make her out above “flying” over the molecule? As you can see she has curly hair blowing in the breezes and a positive charge for an eye. Note the wedges are on her right and hashes on her left. Sometimes, as in this structure, the number four priority group is going neither back nor forward. It is in the plane. In this case, one can build a model or, one can use **super stereochemistry woman**. She is flying (because she has some superpowers in addition to the ability to readily determine stereochemistry) above the molecule so that number four is away. Flying in this manner, priority number 1 is by her left hand, priority number two is by her right hand and number three is down by her feet. Going from left to right to feet, one is obtaining a clockwise rotation for a number four going away, so this asymmetric carbon is “R”.

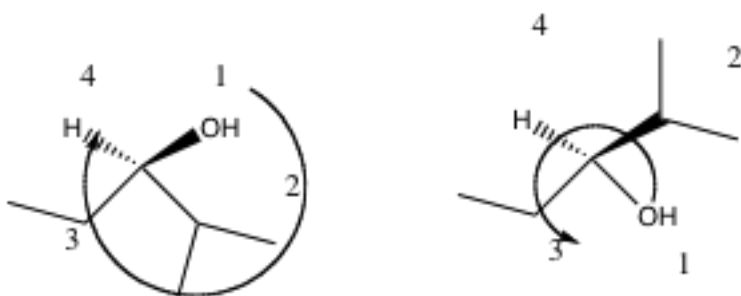
Ah so much work to go through to determine the assignment, but I assure you that problem was a tough one and it will get easier as you go along. Again, it was tough because the number four priority was in the plane, but normally number four is either a wedge or hash, which makes it much easier.

Now consider the following structures for more practice.



First, they are chiral? If so, why? They each have one and only one asymmetric carbon. The asymmetric carbon is the carbon with the OH, H, ethyl and isopropyl attached in each case. Since they each have one and only one asymmetric carbon they are each chiral. There is no doubt about this and no need to test it with a model if you have become a believer.

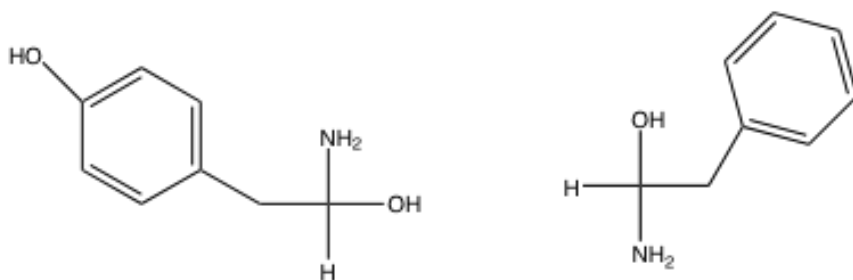
As far as assigning the absolute configuration in each case, at the first level, you should be comparing O vs. C vs. C vs. H. In each case, the H is number 4 priority, the O is number 1 priority and the two C's are two and three priorities. The question is which C is higher priority. To establish this, you have to go one additional level out. On the ethyl, the next level out is a C and two H's. On the isopropyl there are two carbons and one hydrogen at one additional level out. The extra carbon on the isopropyl makes it higher priority. You should stop at this point.



The first molecule has the R configuration and the second, the S configuration. This is because when tracing the circle from 1 to 2 to 3 you are tracing a clockwise rotation in the first case and in the second, you are tracing from 1 to 2 to 3 counterclockwise. Rectus and Sinister, R and S, respectively. Notice in each case, the number four is back so the textbook approach applies.

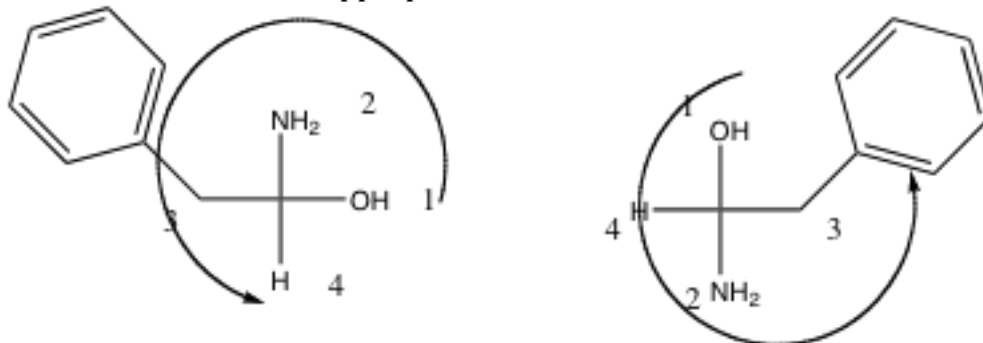
#### [Stereochemistry 4: Simple Assignment of Absolute Configuration using Fischer Projections](#)

There is an alternative method for depicting molecules in three dimensions. It would be good for you at this point to add it to your repertoire. It is a shorthand notation and it is particularly useful when you later need to depict biomolecules, especially sugars. It is called the Fischer representation, after the Nobel Prize winning scientist, Emil Fischer. Consider the following molecule. The intersection of the lines represents an asymmetric carbon. The horizontal lines are interpreted to be wedges and the vertical lines are interpreted as hashes – this is ALWAYS true without exception. **Horizontal lines are wedges and vertical lines are hashes.** If a carbon is drawn in the middle it is no longer a Fischer representation.



In the above representations, the bonds on the horizontal are coming out of the pages (wedges) and the bonds on the vertical are hashes. The great thing about Fischer representations is that you will absolutely never have the lowest priority group sitting in the plane of the paper or image (you saw this problem earlier when we used super-stereochemistry woman). You do not need to use super-stereochemistry woman to solve Fischer absolute configurations. The number four is always going toward you or away from you and this greatly simplifies your life. Now, my first question as it always is refers to the chirality of the molecules. Are these molecules chiral? Your answer should be a resounding yes! RESOUNDING!!! Why? Because there is one and only one asymmetric carbon and all compounds with one and only one asymmetric carbon are chiral. It is so easy. How do you know it is an asymmetric carbon (asymmetric carbons have four different groups and any difference is a difference)? Now let us assign the centers. In the first case, what are the priorities of the groups? It is pretty simple – you can make the decision at the first level of comparison. At the first level, you have O, N, C and H. Their priority numbers based on atomic number are 1, 2, 3, and 4 respectively.

The following shows the prioritization numbers at the correct locations and the circles are traced in the appropriate directions.

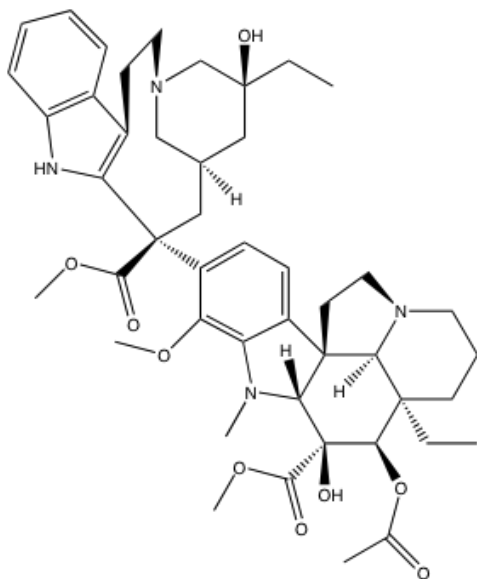


In the first case, the circle is counter-clockwise and the number 4 group is on a hash – going back so therefore it is “S” absolute configuration. In the second case, the circle is also counter clockwise, but the number four priority is going toward you – it is on a horizontal so it is a wedge. Therefore, though it looks “S”, it is really “R”. Remember, you can reverse the designation if the number four is coming toward you or is a hash. It is the equivalent of looking at the molecule from the back. Super-stereochemistry woman can prove this if you have not become a believer.

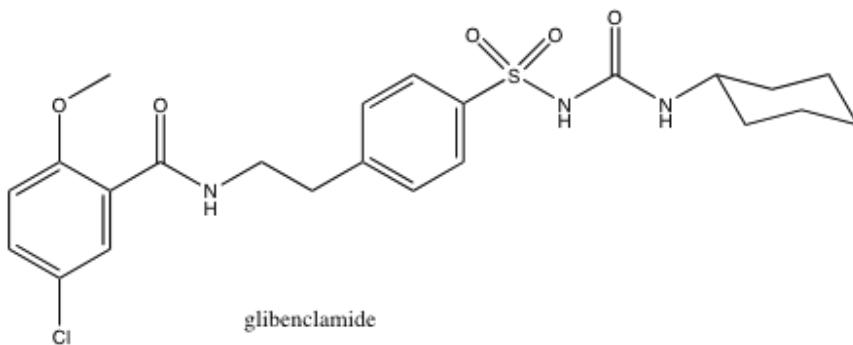
What is the relationship between these two molecules? You do not have to do any manipulation or use models. Since one is R and one is S and they have the same four different groups attached, they are enantiomers (non-superimposable mirror images). The only way they can be interchanged is by breaking two bonds and interchanging the groups. This can be done with any pair and it will result in the other compound.

### [Stereochemistry 7: Difficult Assignment of Absolute Configuration](#)

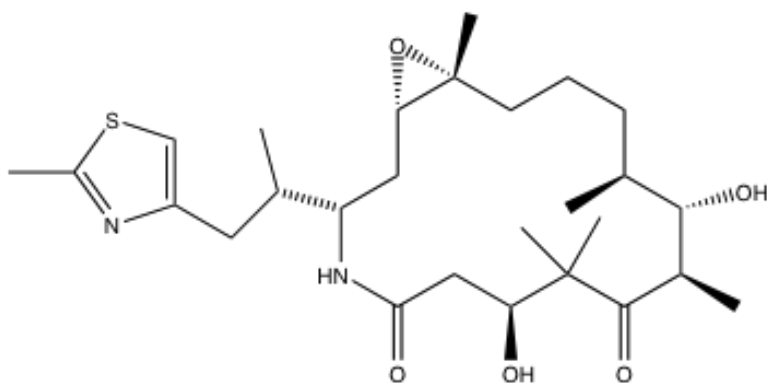
Fischer representations will become increasingly more important as we add more asymmetric atoms into our molecules. Yes, it is true that many compounds have multiple stereocenters. Consider the following natural products and relatives of natural products that are used in treating cancer. Can you find all the asymmetric carbons in the molecules? See if you can find them all in each case.



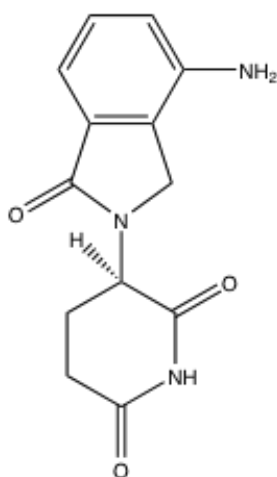
vinblastine



glibenclamide



Ixabepilone



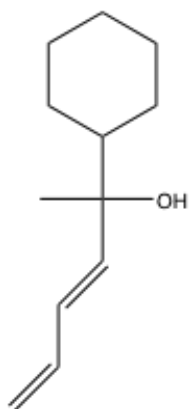
Lenolidamide

Vinblastine (a vinca alkaloid) is a very complex molecule as many compounds that are natural toxins. It has such gross asymmetry that it is safe to assume that really any molecule with more than two carbons or heteroatoms attached is asymmetric. You might also want to note that many double bonds are also stereocenters. This was addressed in class.

A molecule will have a maximum of  $2^n$  stereoisomers where  $n$  is the number of stereocenters – this includes asymmetric carbons, which we have been addressing here, and double bonds that have Z, E potential. Now, it should be noted that this is my own adaptation of this formula, but technically, each carbon that has two different groups on it in a double bond is viewed as a stereocenter (See your text or any text on alkene stereochemistry). However, I find with this small change, students can very easily predict the number of stereoisomers for molecules possessing double bonds and asymmetric carbons. Can you compute the number of stereoisomers in each of the above examples? Lenolidamide only has two total – one R and one S. As mentioned, vinblastine is extremely difficult so you might want to hold off on that one for a while. Glimclamide also only has one asymmetric

carbon. Can you find the asymmetric carbon in glimclamide? Aromatic double bonds don't count when computing the maximum number of stereoisomers, why?

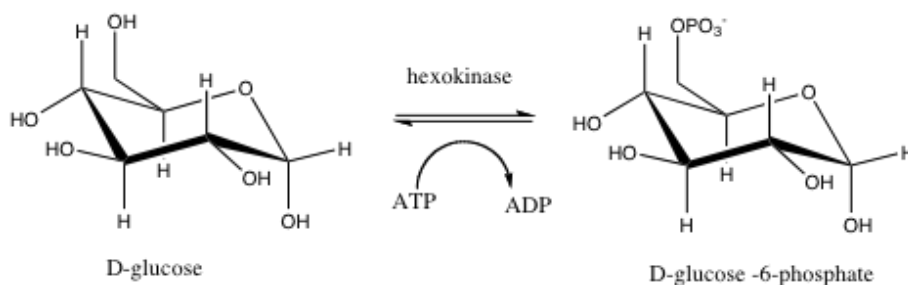
If you are struggling with the above complex examples, consider the following molecule. What is the maximum number of stereoisomers possible? This problem relies on you knowing something about alkene stereochemistry from lecture or your textbook.



In the above molecule, there are a maximum of four stereoisomers. Why? The reason is because there are two stereocenters (using this simplified method defining a stereocenter as a center either an asymmetric carbon or a double bond having Z/E stereochemistry – yes, it is a little more complex than this). Basically, for your purposes a stereocenter is a center with either R, S stereochemistry or Z/E stereochemistry. At the asymmetric carbon bearing the cyclohexyl and the hydroxyl there is the possibility of two stereoisomers, R and S. At the double bond closer to the asymmetric carbon there is the possibility of Z and E stereochemistry. At the double bond at the bottom there is no Z/E because one of the carbons bears two hydrogens. Does this make sense? So this molecule could have a RZ, SZ, RE and SE. Can you draw these stereoisomers? What are their relationships? Which one do I have drawn? You can go to the end of this web book to find the answer to this question.

To digress a bit and start to understand the importance of this topic let us consider the application of stereochemistry to living systems. In living systems, stereochemistry is extremely important. You should think of yourself as a large chemical reactor and in the reactor there are many molecules, many of those molecules are chiral and many have multiple stereocenters. But we have evolved such that we only have one of each possible enantiomer (normally). We have this rich, complex environment filled with a wide variety of chiral molecules having unique, irregular shapes. In spite of the extreme complexity of the system, somehow order is retained (most of the time!!). One would expect if we just dumped a bunch of molecules in a flask to have chaos or maybe an explosion!!! How do the diverse array of biological organic molecules know what to do? Of course

they are mostly organic molecules (proteins, nucleic acids, carbohydrates and lipids are organic compounds and most have more than one asymmetric carbon – they are normally chiral!!!) They have complex shapes due to their many asymmetric carbons and their overall spatial orientations. They only exist in one form and they interact very specifically with other chiral and non-chiral molecules. Think again about your own chirality. Think about a formed glove (like a leather glove). Your right hand will only go comfortably into the right glove. That is a chiral interaction. Think about your shoes – your left foot is more comfortable in your left shoe. Think about shaking hands or even sitting at the typical college desk with an armrest. These are chiral interactions. Left-handed people are not so comfortable in a right-handed desk. Lets face it - you are chiral and you live in a chiral world. Molecules are chiral and they live in a chiral world. Consider Glucose. Glucose exists in two enantiomeric forms. Below I have the structure of natural glucose. It is called D-glucose and it has five asymmetric carbons. L-glucose is the complete mirror image of if D-glucose. All the asymmetric centers are opposite. The first step in the Metabolic process known



As glycolysis is the conversion of glucose into glucose-6-phosphate as shown. It involves an enzyme called hexokinase. Hexokinase is a very large, complex protein comprised of amino acids. The amino acids are chiral and the resulting protein is chiral. It only exists as one of two chiral proteins (made of only one chiral form of the various amino acids) and has a fairly specific interaction with natural D-glucose when it catalyzes the phosphorylation shown above.

What do you think might happen if you fed an organism L-glucose instead? It might not be metabolized because being the mirror image it might not interact properly with the enzyme.

A very interesting protein known as the p-glycoprotein that is embedded in some cells and is responsible for the active transport of certain toxic molecules out of cells (usually for protection from poisons) has been shown to interact with two enantiomers, though the interactions are different. Should this be here????

Hopefully, this discussion has given you some ideas about specificity on a molecular level. This is a discussion that has to be continued as we go along. But you really have to start considering the idea that molecules have the ability to organize themselves (think of lipid bilayers) and do communicate with each other in very



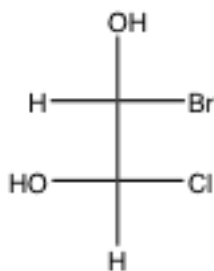
specific ways. Again think of all the molecules in your body and the fact that they know what to do.

Getting back to basics, we want to start working with slightly more complex molecules that have only two stereocenters. Some day we will work our way up to something like vinblastine.

[Stereochemistry 5: YouTube problem demonstrating the assignment of absolute configuration to two centers](#)

[Stereochemistry 6: Part two of the same problem featuring two asymmetric carbons](#)

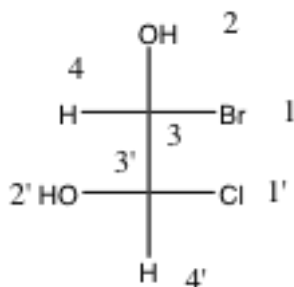
Consider the following molecule drawn in Fischer projection. What if you are asked to draw all the stereoisomers, how would you accomplish this goal? After drawing them, could you assign the absolute configuration of the asymmetric centers? Could you establish the relationships between all pairs of molecules in the set? Would you be able to state whether or not each is chiral? You should have the ability to do this now, but why don't we run through the following structure together.



First, how many asymmetric carbons are there in the structure? It is actually quite obvious in this Fischer projection. There are two asymmetric carbons. If you use the formula given above you would calculate that there are a maximum (note I said maximum – there are cases where there are less) of  $2^n$  stereoisomers where  $n$  is the number of asymmetric carbons in this case. Therefore, one would expect a maximum of 4 stereoisomers.

I think the best way to generate the possible four stereoisomers is to start by assigning the stereocenters in the first structure I drew. It will help us readily generate the three other stereoisomers by realizing what combinations we are missing.

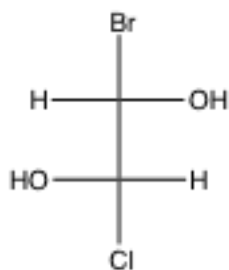
Let us add the priorities to the structure and assign it.



Notice that each center has its own four priorities. I have distinguished these by putting primes on the second set. Notice, that when you are focused on the top asymmetric carbon, you view the bottom asymmetric carbon as just a carbon attached to the first center. The same idea is true for the bottom asymmetric carbon. Getting to work, tracing the circle from priority 1 to 2 to 3 for the top center, you should find you are tracing a counterclockwise circle (do you agree?), however, the number 4 priority group is coming out of the page. Therefore, this center looks “S”, but it is really “R”. The bottom center appears to be “R” and really is “R” – the number 4 group is on a vertical which means it is going into the page as the standard definition dictates. Did you obtain R for both centers? In terms of nomenclature, one would combine the IUPAC and Cahn-Ingold-Prelog systems and the molecule would be named officially 1R, 2R-1-bromo-2-chloro-1, and 2-ethanediol. In terms of absolute configuration, can you come up with the other absolute configurations and the other structures? The other absolute configurations would be the SS, the RS and the SR. Does that make sense to you?

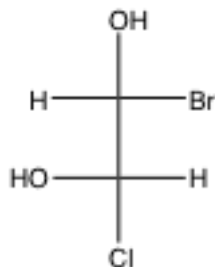
Let’s try to draw them. You can work with our first RR molecule and realize that to generate the opposite configuration you can either switch two groups on the asymmetric carbon in question or you can draw the mirror image of the center (which is the same thing). I am a fan of the switch (i.e., switching two groups).

Therefore, if I want to draw the SS I will simply switch two groups (any two groups) on each asymmetric center as shown below.



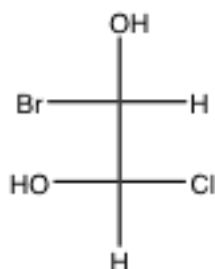
This molecule is definitely the SS. You don’t need to check it, but as a beginner (until you believe in these shortcuts, it is fine to check – of course, it is always fine to check). Next, try to draw the R, S stereoisomer. One way to do this is to merge the R top asymmetric carbon from the first molecule with the S bottom asymmetric center

of the second molecule. You can also accomplish this transformation by simply switching two groups to invert centers. I am going to use the former procedure.



Once again without any further work (provided the work on the first molecule is correct) this is the R, S. Next, generate the S, R. Again, if you feel uneasy about the configuration, just assign it – this will make you start to have faith in the methods we are using to work rapidly and will practice your assigning technique.

The following is one way to draw the S, R stereoisomer.



Again, you can switch any two groups to invert the center (to obtain the opposite absolute configuration at a center).

At this point we now we have all four, the RR, the SS, the RS and the SR molecules. What relationships exist among the molecules? Well, they are definitely stereoisomers since they have the same connectivity, but different absolute configurations (or different spatial orientations). It is important to note that the only molecule that is the same as the RR is the RR – so all the other molecules should be different – meaning they are nonsuperimposable, noncongruent. What do you think RR sees when it looks in the mirror? Of course, it sees SS! And SS is never the same as RR. These are non-superimposable mirror images or more simply said they are enantiomers. Enantiomers always have opposite – completely opposite – all the way through the molecule-absolute configurations and the same connectivity. Considering the remaining molecules, SR is a nonsuperimposable mirror image of RS. RS is what SR sees in the mirror. Though I will give you a method to circumvent this process in the future, it might not be a bad idea to break out your models and make these pairs of molecules and prove to yourself they can't superimpose (noncongruent). Remember, you are allowed to rotate bonds or translate the molecule through space, but you are not allowed to break bonds when

you are attempting superimposability. To superimpose, the molecules have to take up exactly the same space. Exactly the same space, but it can only be achieved by rotating bonds or translating the molecule. You should find in your manipulations that you can't superimpose RR on SS and you can't superimpose SR on RS, but you can set them up so that they look like mirror images.

Now that we have established the enantiomers, what other relationships exist? What is the relationship of SR to RR or RS to RR or SS? In these evaluations, we discover a new relationship, which is the relationship terms diastereomer. If you compare any other pair in the set, you will discover they are not the same. Again, the only molecule that is exactly the same as RR is RR. The enantiomer of RR is SS. Therefore, we have a situation where the molecules are stereoisomers, meaning they have the same connectivity, but have a different orientation in space. Of course, they are not enantiomers. Molecules that fit this definition are diastereomers. Now you might want to note that the diastereomeric relationship is more distant than the enantiomeric relationship. Isomeric molecules can be related to a human family. Molecules that are structural or constitutional isomers are similar to cousins in a family. Cousins are usually relatively (no pun intended) easy to distinguish. Molecules that are diastereomers are more like siblings (sometimes tougher to distinguish), but enantiomers are like identical twins (often indistinguishable). This analogy is useful when thinking about why we care about the relationships of molecules. Really, why do we care? Is this just of theoretical interest? The relationships of molecules are of great practical importance. For one reason because many molecules that are made by chemists are used in chiral biological systems (e.g. pharmaceuticals) and the wrong stereochemistry in a molecule might bring about the wrong biological response.

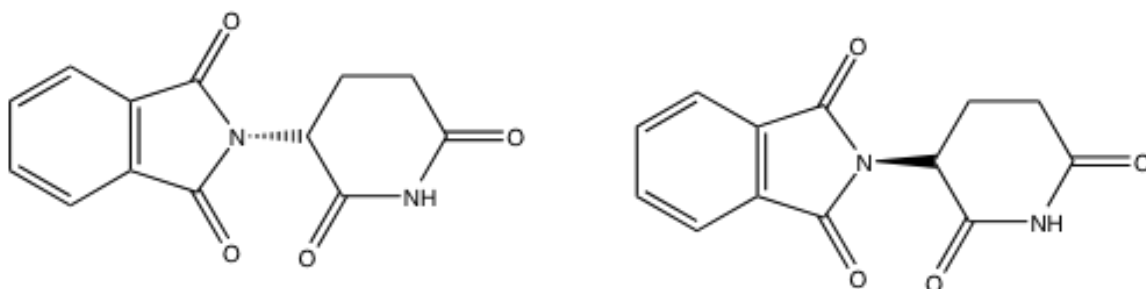
Let us digress again into the biological world. As an example, consider the p-glycoprotein pump that is present in many cell membranes (mentioned earlier), including the endothelial cells that comprise the blood brain barrier. This molecule, which is a large protein that is embedded in the membrane, is chiral. Its chirality is really ultimately derived from the chirality of the individual amino acids and carbohydrates that make up the glycoprotein. The glycoprotein assumes a very specific three-dimensional shape due to different attractions and repulsions in the molecule (and some bonding). This very irregular shape sits in the membrane of the brain barrier with a V shaped pocket facing in toward the inside of the cell (away from the blood stream). Molecules work their way across the endothelial cell but if they have certain shapes and charges they will bind in this pocket. These specific molecules will then be ejected back into the blood stream as the V shaped pocket inverts. This is one of the ways we are able to keep toxins out of our brains and cells in general. Unfortunately, many chemotherapeutic agents used to treat diseases, for example cancer, are toxins and they are ejected from the brain, which is problematic if a patient has a brain tumor or brain metastasis. What is very interesting is a recent discovery that this protein can bind two enantiomers (often such binding sites are more specific and only can bind one of two enantiomers – this is molecular communication). The two enantiomers are little cyclic peptides, but interestingly,

the two peptides are bound in different locations in the molecule. So the chirality of the glycoprotein is such that the interaction is different with the two enantiomeric polypeptides.

Consider the two thalidomides shown below.

One form of thalidomide is an anti-nausea drug; the other is a very potent teratogen (a drug that causes birth defects). This drug was given to women in Europe in the late fifties and many babies were born with missing and malformed limbs. In the middle of the last century organic synthesis was limited such that normally both enantiomers were made in a mixture known as a racemate or racemic mixture that is a fifty-fifty mixture of enantiomers. Enantiomers being identical twins are difficult to physically separate in the laboratory. In the fifties, the teratogenic effect was not known and it was thought that if both forms were administered, they would exhibit only the anti-nausea effect. This was often the assumption, but as shown above enantiomers don't necessarily interact the same way with substrates and this means they may be metabolized differently. It turned out as the biochemistry was discovered in more detail that it did not matter which enantiomeric form was given as a drug as they are interconverted in the human body, ultimately resulting in a racemate (fifty-fifty mixture of enantiomers). It turned out that even if the enantiomers were separated and the "safe" one was administered, half the molecules would convert to the teratogenic form. This is a somewhat rare example and it shows once again (like the p-glycoprotein case above) that no broad generalizations should be made about the metabolism of chiral molecules in living systems. Clearly in a chiral system like the human body, in many cases it does matter which enantiomeric form is used in a medicinal situation? Handedness (chirality) matters in a handed (chiral) environment, as we know from our macroscopic world. As chemists, it is important to know the handedness of what we are making and the way the molecule will interact and react in its applied environment. If the desired molecule can't be made in pure form, one must have a method for separating enantiomers or in general, stereoisomers that might form in the synthesis.

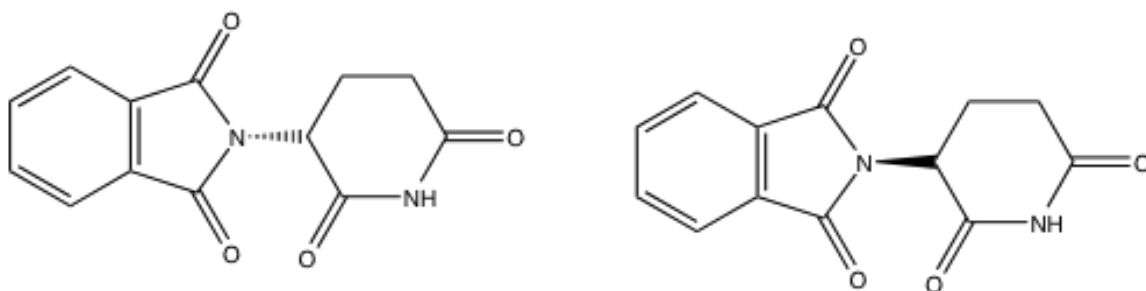
Physical separation is more difficult the closer the relationship is between the molecules. This should make sense as you work in the lab and actually carry out physical separations.



thalidomides

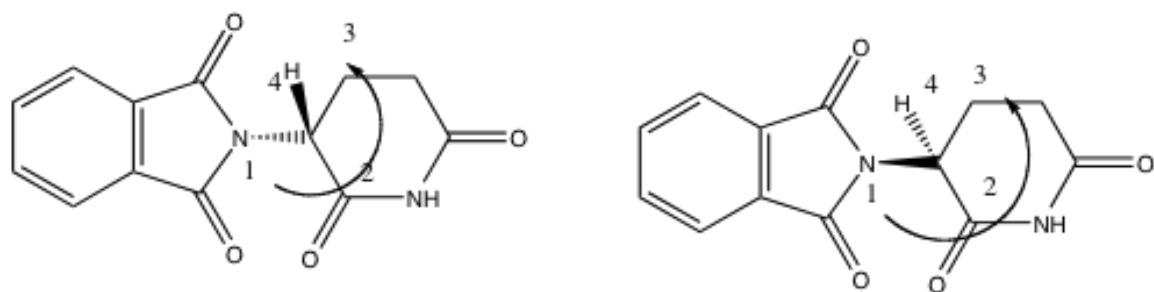
We expect enantiomers to have the same boiling points, melting points, spectra, and the solubilities in achiral environments. This means they really can't be separated by any of the methods you have learned like distillation, extraction, and recrystallization and can't be distinguished by the spectroscopic methods you have learned like NMR or IR in an achiral environment. For example two enantiomers in an achiral solvent like deuteriochloroform will give identical spectra. However, enantiomers can be distinguished from each other in chiral environments. So just as an idea, supposing the NMR of two separated enantiomers was run in the same chiral solvent (one enantiomer of a possible two) and the two enantiomers did not interact with the solvent identically. In this situation, it is possible that the NMR spectra could be slightly different. The thalidomides obviously behave differently in a chiral, biological system (Interact differently with enzymes etc.) In current medicine, thalidomide is used for certain cancers. It is commonly used to treat multiple myeloma. It is dosed as a racemate, but any woman of childbearing years must undergo a pregnancy test and must practice very reliable birth control.

Well I have digressed enough. Let us get back on track and do some more examples. First, as a review reconsider the two thalidomides.



thalidomides

How do you know immediately that they are achiral as individual molecules? What is the absolute configuration of each asymmetric carbon in each molecule? Individually, these molecules are chiral because they each have one and only one asymmetric carbon (one asymmetric atom). It is the carbon next to the carbonyl group in the six membered ring (not the benzene ring – remember, chirality is a three dimensional phenomenon and it normally emanates from a tetrahedral atom (most commonly carbon) with four different groups.) All compounds with only one asymmetric carbon are chiral. The compound on the left has the “R” center and the compound on the right has the “S” center. Note the assignment of absolute configuration (R and S) done below.



thalidomides

As can be seen above, in the left structure when one traces a circle from 1 to 2 to 3, the circle is in a counterclockwise direction, but the number 4 priority group is out of the page. As we demonstrated earlier, one has to reverse the designation. Therefore, it is “R”. Though it looks “S”, it really is “R”. In the second structure, one also obtains a counterclockwise direction, however, the number four-priority group is going back. Therefore this structures appears to be “S”, but really is “R”. What is the relationship between these two molecules? They are enantiomers. They should have the same physical properties, unless they are in a chiral environment. More will be added to this idea as we go along.

Reverting back to the example with two asymmetric carbons shown prior to the biochemical discussion (diversion). We would expect the two sets of enantiomers to have the same physical properties in an achiral environment, but potentially different in a chiral environment (again, think about p-glycoprotein pump, the chiral environment for the two enantiomeric cyclic peptides). However, the other pairs of molecules with diastereomeric relationships should have different physical properties in chiral as well as achiral environments. Sometimes these differences will be very subtle, however, as chemists in the laboratory we can usually separate diastereomers. The diastereomeric relationship is very important. Truly, the separation of enantiomers is not possible without converting the enantiomers into diastereomers somehow. The exclusive synthesis of a single chiral molecule without its enantiomer is impossible unless one creates some sort of diastereomeric relationship – if only in the transition state of a reaction. Enantiomeric transition states have the same energy barriers. So understanding diastereomers and how to make them is extremely important in chiral synthesis. Chiral synthesis is extremely important because we are chiral, we are made of chiral molecules and the treatment of our disease and medical conditions requires chiral molecules that will interact in the correct way to give the proper outcome with our biological chiral molecules.

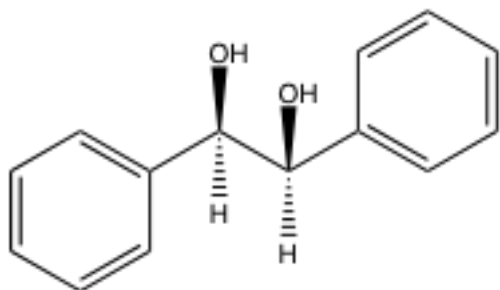
Ah, but I digress again. I hope you are starting to see the importance of chirality. To sum up first example we have studied with two asymmetric carbons, there were the following relationships.

RR with SS enantiomers  
RS with SR enantiomers

RR with RS diastereomers  
RR with SR diastereomers  
SS with SR diastereomers  
SS with RS diastereomers

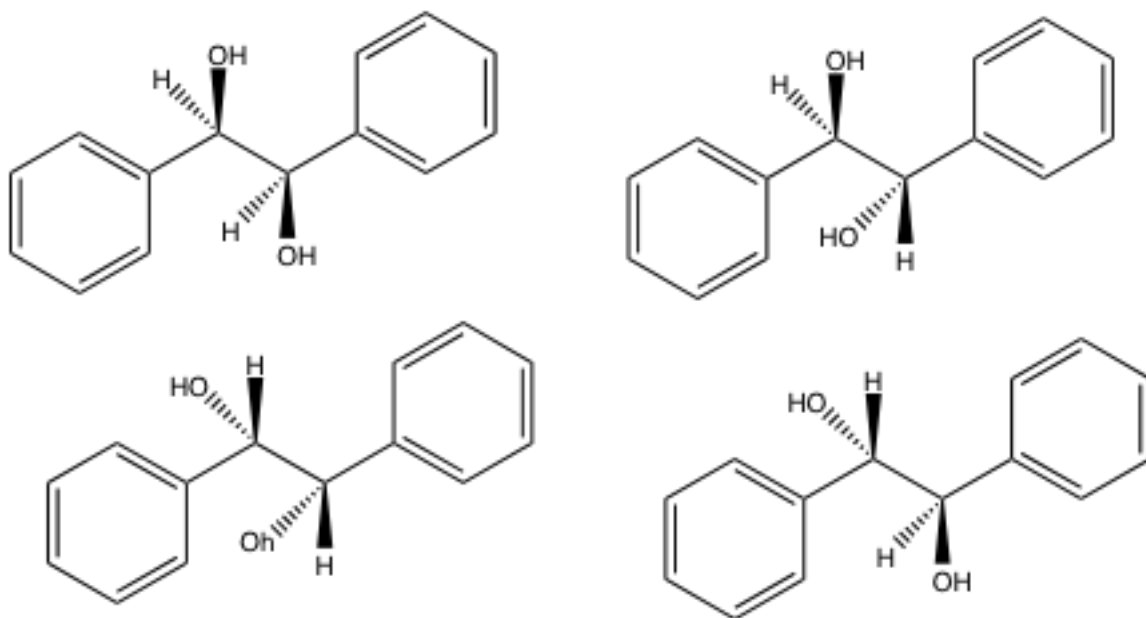
We would expect it to be tough to separate RR and SS and RS vs. SR. We would expect them to behave the same way in an achiral environment, but the other pairs should have different properties in an achiral environment.

Now consider another molecule with two asymmetric carbons and it will be presented in a different manner. I will just give you the name. Consider 2,3-diphenyl-2,3-butanediol. I want you to draw the basic molecule without stereochemistry, draw all the possible stereoisomers, assign all the asymmetric carbons, establish if the individual molecules are chiral and establish all stereochemical relationships. Well, that is a tall order, but this is a very typical problem for an organic chemistry student!!! Notice, this problem is a little different because you have to start from scratch, i.e., I did not give you a starting structure in a stereochemical drawing. At this point you could go in one of two directions. You could draw a Fischer or you could use a wedge and hash drawing, but either way you have to draw a three-dimensional drawing. In your work, try to avoid the following error that many students make in the beginning of organic chemistry.

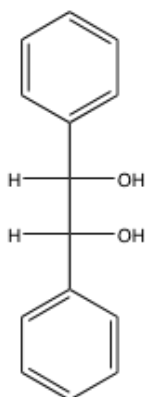


What is wrong with this structure? Think about the spatial orientation of the hydroxyl and the hydrogen on each center. This is not a useful three-dimensional drawing because the hydroxyl and the hydrogen are 180 degrees apart. You can try, but you can't rationally assign absolute configuration to this structure. If you wrote this in an effort to communicate a precise three-dimensional structure, I would not be able to tell what it is. So we would have a total communication breakdown. In showing you the solution of this problem, I am going to take the approach of first solving it using wedge and hash, though I could use Fischer projections. Maybe I will show you that later. The following are the four apparent stereoisomers obtained by drawing every possible spatial orientation. In essence what I have done by just drawing all the permutations of the wedges and hashes is draw the RR, SS, SR and RS as before.



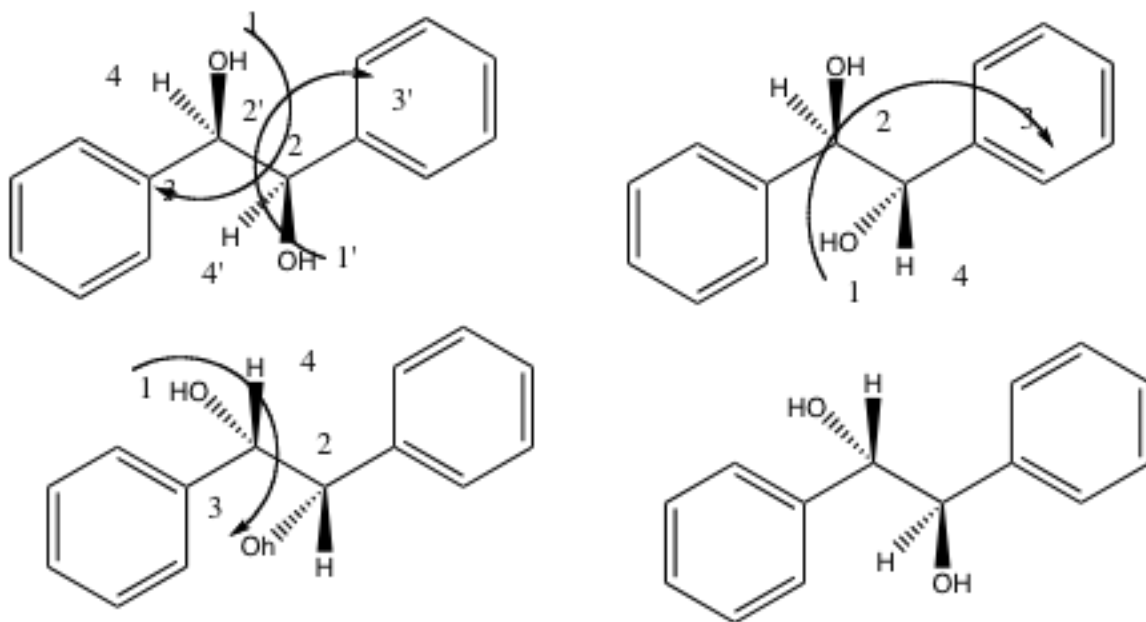


Whew that was a lot of work. Well maybe not. I hope you are seeing that when you assign the very first center, really as long as you know the rules, your work is pretty much done. Now as you will recall the  $2^n$  rule predicts the maximum number of stereoisomers. In this case, even though there are a maximum of four stereoisomers because there are two asymmetric carbons, in this case there are only three stereoisomers. Two that we wrote are the same. Which two are the same? Can you work this out by just manipulating them or making models? After we assign them below you will discover the two that are the same are the *RS* and the *SR*, which are the two structures to the right. In this case the *RS*, *SR* are exactly the same molecule. Why? This set of molecules is very special because the asymmetric carbons have the same four different groups attached. So the *RS* and *SR* molecules are very special because the centers are actually mirror images of each other. These molecules, that have more than one asymmetric center where one is the actual mirror image of the other, have a special name. They are called **meso** compounds. **Meso** compounds are not chiral (achiral). So consider the following drawing of one of the one and only meso as a Fischer representation.



The structure above is the same as the two wedge and hash drawings drawn to the left above. Can you prove it is R/S? In this representation can you see the plane of symmetry in the molecule? Is it starting to make sense that two asymmetric carbons could add up to net symmetry? Can you see that your ability to see the symmetry depends on which conformer is drawn? In molecules that have conformational mobility we are concerned with average symmetry. This will be covered in great detail below. It bears repeating.

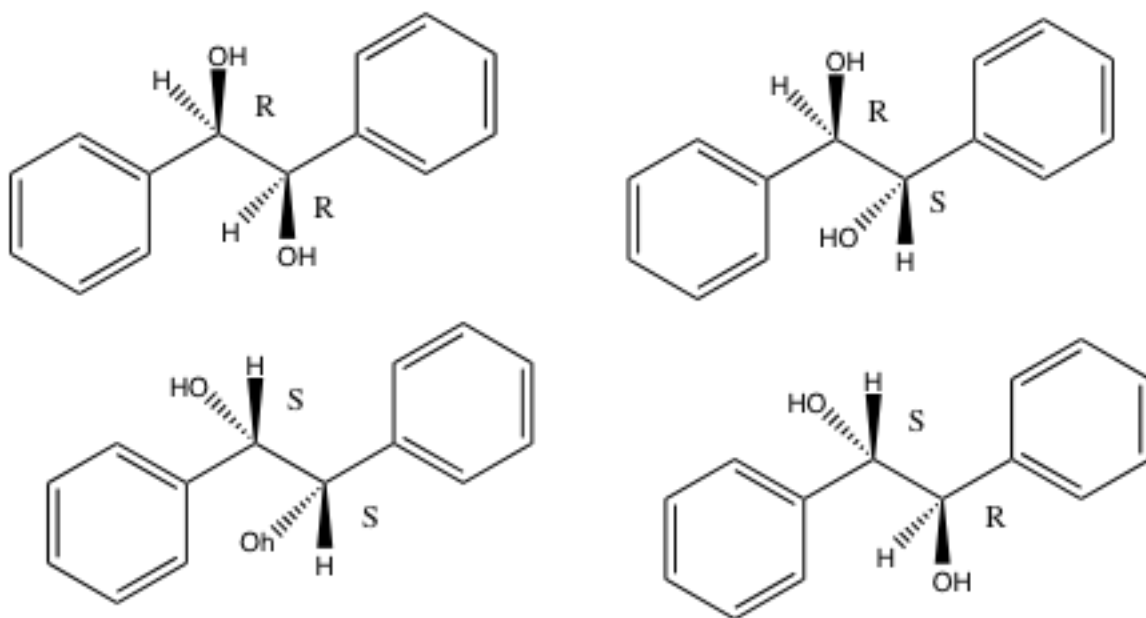
Now let us systematically analyze these structures. Let us start by assigning them.



To make things a little less cluttered, I did not put the priorities and arrows on every carbon. As you have discovered by now I hope, if you do your work really carefully on the first structure, work is much easier on the rest of the structures. Beginning with the structure in the upper left corner, for the left asymmetric carbon – the OH is number 1 priority, the other asymmetric carbon is number 2 priority, the aromatic is number 3 (recall the priority rules given above and how multiple bonds are handled) and the hydrogen is number 4 priority. Note that the asymmetric carbon is number two on each center, in each molecule because at the first level the asymmetric carbon and the aromatic tie – both are carbons, but the other asymmetric has an oxygen on it where the aromatic carbon has three carbons. The single oxygen has higher priority over the three carbons. Priorities are established using first point of difference, level by level as described earlier. Really, now our work is done because we use priorities to figure out what is going on.

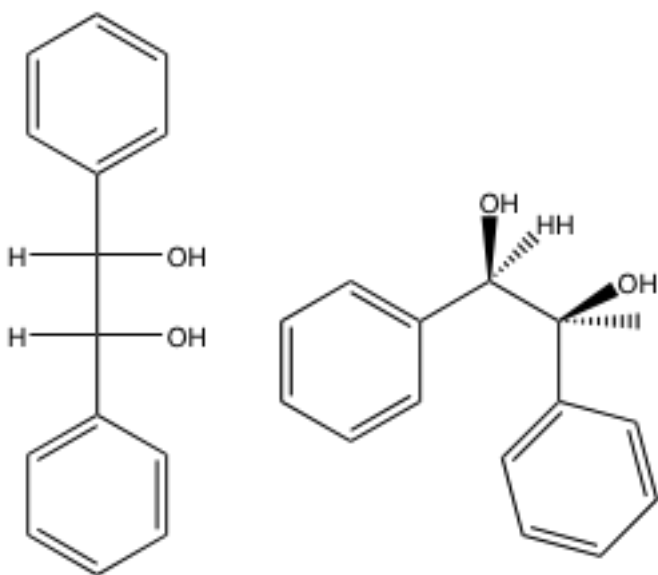
For the first molecule the first center (the one on the left) tracing the circle from 1 to 2 to 3, the circle is clockwise and the same is true for the center on the right. Since

both the number four priority groups are back, both centers look R and are R. For the compound to the right on the top, the centers are R and S, respectively. The left asymmetric carbon is R and the asymmetric carbon to the right is S, so the second compound is RS, the third compound (the one in the lower left) is SS. Again, why is it SS, tracing from priority 1 to priority 2 to priority 3 is clockwise, so they both look R, however, the number 4 is coming out so as we discussed you need to reverse the designation. The compound at the lower right corner is what? The left asymmetric carbon is just like the left center we just did so it looks R, but it is really S. The asymmetric center to the right is the reverse of the last right center we did so it looks R and really is R. I hope this makes sense, but below I have all the centers assigned.



The interesting aspect of this set of molecules is that two of the structures are the same and these two structures are achiral. The two compounds that have this peculiar aspect are the RS and the SR. They are the exact same compound and they are achiral. Therefore, even though the  $2^n$  rule would predict a maximum of four stereoisomers, in this case there are only three and one is achiral. It is very interesting that achirality can occur in a molecule that possesses asymmetric carbons. But, think about it, if you had a perfectly symmetric body, you would be like a meso compound because your hands would be each individually asymmetric but overall one side of your body would be the perfect mirror image of the other. Of course, as I indicated earlier, no one has a perfectly symmetric body so no one is truly meso. By definition again, meso compounds have asymmetric carbons, but have a net plane of symmetry. Now think about what is peculiar about these compounds. Though they have two centers with four different groups, they have the same four different groups so they have the potential for net symmetry. And think about the RS and SR versions of the molecules. Each of these two versions of the same molecules are like enantiomers that are bonded to each other. What does R

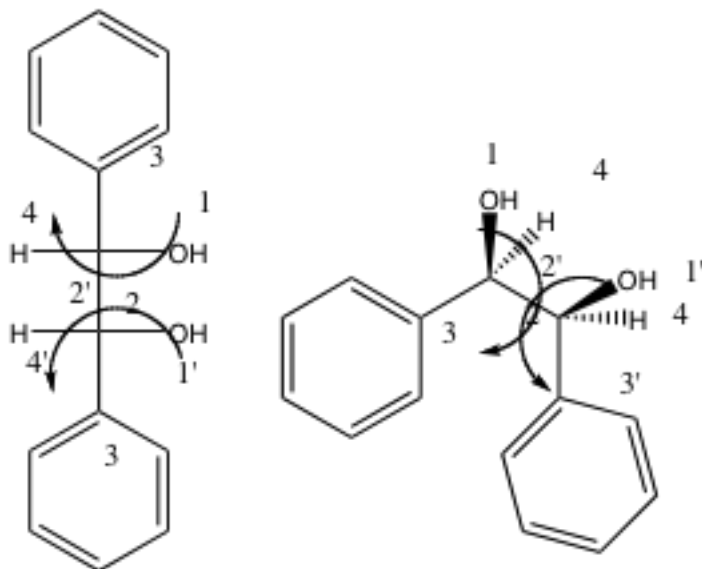
and S mean? R is seeing its mirror image within the meso molecule and vice-versa. Again we have net symmetry in the molecule even though it has asymmetric parts. What matters in terms of chirality is the net, average situation. Remember, molecules have free rotation and they can sit in all sorts of conformations and you can't always see the symmetry. Again a person with perfect body symmetry could assume asymmetric shapes by moving around. The way I have the molecules drawn above you can't see the plane of symmetry or the potential plane of symmetry, but you know it has symmetry because you know when the four groups on the asymmetric groups are the same, R is the mirror image of S. It is by very definition symmetry. Consider the following conformers of the same RS, SR molecules. They are the same and they are the same as the two versions of the RS molecule or the meso molecule drawn above.



The way these molecules are drawn such that the groups are eclipsed (very high energy, but real), you should be able to see the symmetry, the lack of net chirality. Again, molecules that are chiral are nonsuperimposable on their mirror images. In this case, RS is superimposable on SR so it is achiral. The other way to tell is that there is a plane of symmetry in the molecule no matter how it is drawn is to assign the absolute configuration to the stereocenters above. You should discover that in each case one center is R and the other is S. You should also discover that all the molecules written above that are R/S are the same molecule!! They are all achiral and are classed as meso. I know I am being repetitive, but R is the mirror image of S and if a molecule has stereocenters that have the exact same, four different groups on them and one is R and one is S, that is by definition a plane of symmetry. Let me go over the assignments.

[Stereochemistry 6 Part 1, Stereochemistry of Two Asymmetric Carbons, Meso Compounds](#)

## Stereochemistry 6: Part II Stereochemistry of Two Asymmetric Carbons, Meso Compounds



In the first molecule, for the top asymmetric carbon, the circle is traced to the right, but the number four group (the hydrogen) is going out of the paper, so therefore, the center is "S". The lower center in the first structure worked out the same way is "R", therefore, it is SR and by that information and the fact that each center has the same four different groups, you know it is achiral, a meso and it is redundant to write the mirror image as a separate stereoisomer. In the second representation of the same molecule above in each case the number four priority group is going behind the paper so the asymmetric carbon to the left is R and the asymmetric carbon to the right is S. Once again, you would automatically know this is a meso and achiral.

At this point, the following generalizations can be safely made.

All compounds that are simply R or S are chiral. What I am saying here is all compounds with one asymmetric carbon are chiral. If they have the same four different groups attached they are enantiomers.

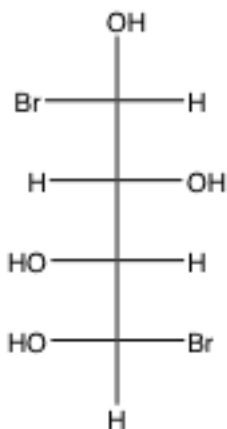
All compounds that are RR or RRR or RRRR or RRRR..... etc. are chiral.

All compounds that are SS or SSS or SSSS or SSSS..... are chiral.

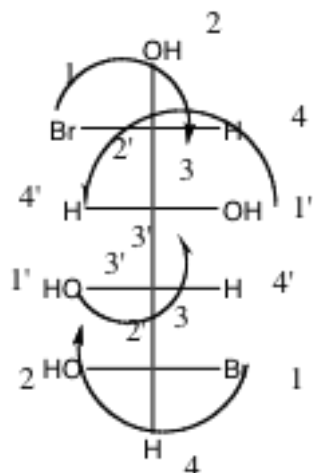
All compounds that are some mixture of these assignments are chiral except meso compounds.

For example, all compounds that are RS or SR are chiral, except mesos. We can now safely say that **all compounds that have asymmetric carbons are chiral except meso compounds.**

How are mesos recognized? Meso compounds have the same four different compounds attached to each asymmetric carbon and the asymmetric carbons on one side of the molecule have the opposite absolute configuration than the asymmetric carbons on the other side of the molecule. If there are two asymmetric carbons, one would have to be R and the other S. If there are four asymmetric carbons one side might have two S and the other two R. Consider the following compound.



This compound has four asymmetric carbons and has the potential to be chiral. Now one way to deal with this compound is to build it and play with it. You could try to rotate it until you could see (or not see) a plane of symmetry or you could draw its mirror image and try to superimpose this mirror image on the one I have drawn. You would be allowed to manipulate the molecule provided you did not break bonds. The problem with most organic chemistry books on this subject is that they create an over dependence on models and a bit of confusion as to what method should be used. What I suggest is to almost exclusively utilize assignment. If you assign the absolute configurations of the centers, you will know immediately if the molecule is chiral. Why is it that this molecule has the potential to be a meso (it may not be a meso)? It has the potential to be a meso compound because the four stereocenters from top to bottom have the potential to be mirror images, i.e., the top center has the same four groups as the bottom center and the two middle centers have the same four different groups. What would be an example of a meso? Well there are several, but one would be the RRSS compound. What would be another? So let's figure out which stereoisomer we are dealing with above and whether or not it is chiral.



I used 1, 2, 3, and 4 on the topmost and bottommost asymmetric carbons and 1', 2', 3' and 4' on the middle two asymmetric carbons to represent the priorities. I know it is crowded but by now you should be able to assign the absolute configurations pretty well.

For this molecule, I obtained, SRRR working from the top asymmetric carbon to the bottom asymmetric carbon. Is this compound chiral? Resoundingly yes! Is this compound a meso compound? No! How do you know with great confidence, using no models and no manipulating. **You know this because all compounds with asymmetric carbons are chiral except meso compounds.** Compounds having the potential for meso have the same groups on potentially reflecting centers and they have opposite absolute configurations. In this case the last center is not the mirror reflection of the first so it has to be chiral. This means that there is another molecule that is the enantiomer of the SRRR. What is it? Can you draw it? It is the RSSS. Is the RRRR chiral? Can you draw it? If it is chiral can you draw its enantiomer? What is the maximum number of stereoisomers for this set. Can you draw them all, assign all the asymmetric centers, identify all meso compounds and establish their relationships.

There are theoretically a maximum of 16 stereoisomers, but some are mesos, so there are fewer in reality.

Summing up they are.....

1. RRRR
2. SSSS
3. RSRS = SRSR
4. RSSS
5. SRRR
6. RSSR = SRRS
7. SSRR = RRSS
8. RSRR

9. SRSS
10. RRSR
11. SSRS
12. RRRS
13. SSSR

What are the relationships that exist among these molecules. Can you draw all the structures?

1 and 2, 4 and 5, 8 and 9, 10 and 11, 12 and 13 are enantiomers.

The two versions written at 3 are the same and are meso compounds.

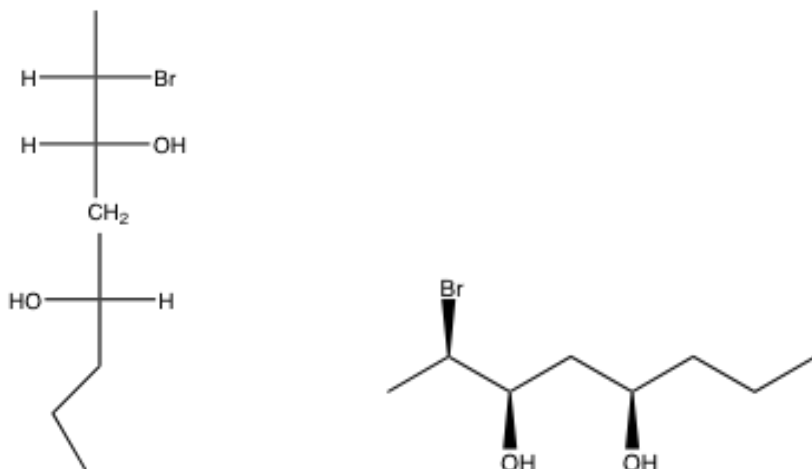
The same is true for combinations 6 and 7.

What is the relationship of the meso with any of the other compounds? They are not mirror images and they are not the same, therefore, they are diastereomers. All other relationships are diastereomeric.

For example, RSRR has a diastereomeric relationship when compared with SSSR.

Supposing you are faced with drawing a specific stereoisomer like 2R, 3S, 5R-2-bromo-3,5-octanediol. My suggestion is that you just slap down any stereochemical version and then edit it. This means draw the correct connectivity, but do not worry about the wedges or hashes. This is my style of writing and this is my method with drawing stereoisomers. Don't be afraid, just draw a stereoisomer, don't even think about it (live dangerously). Remember, every time you set a stereo center, you have a 50:50 chance of getting it right and those are pretty good odds.

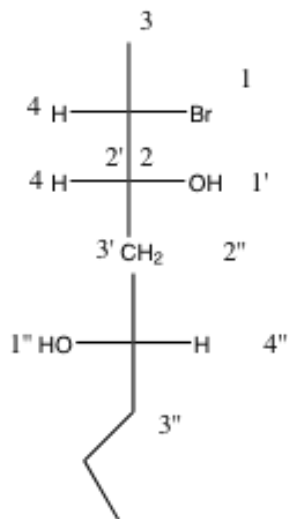
Below I am drawing two structures corresponding to the above name without putting thought into the stereochemistry. One is a Fischer representation and one is a wedge and hash drawing.



These molecules have the same connectivity, but they are not necessarily the same stereoisomers or necessarily the correct or desired stereochemistry. They may

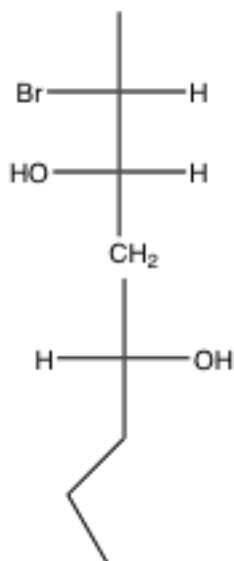


require editing. Whether editing is needed will be ascertained by our good friend, assignment. Editing consists of inverting asymmetric carbons (switching two groups) where necessary.



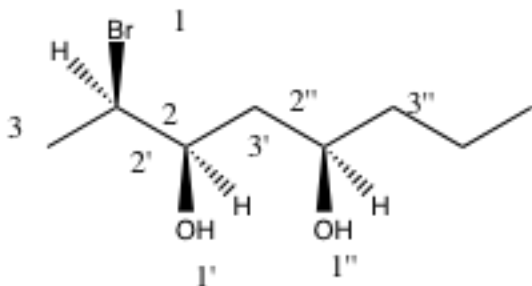
Working from top to bottom, the top asymmetric carbon, tracing from priority 1 to 2 to 3, one has a clockwise rotation, but the designation has to be reversed because the number four priority is going out of the page. Therefore, the top center looks R, but is really S. Using the same process for the next asymmetric carbon, one obtains what appears to be a counterclockwise rotation in going from priority 1' to 2' to 3', but again, no. 4 priority is coming out of the page. Therefore, this asymmetric carbon appears to be S, but is really R. For the last center you should obtain with an asymmetric carbon that appears to be R, but is really S. So what did we draw with the Fischer prior to editing? We drew the exact opposite of what we wanted. We drew the 2S, 3R, 5S!!!! No big deal!!!! This is easily remedied.

I will rapidly correct the structure by inverting all the centers. How are centers inverted? By switching any two groups on any center. In this case we need to switch two groups on each center. Voila!!



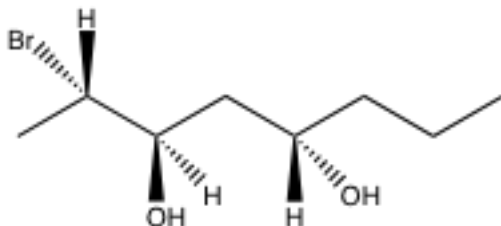
This compound is the desired compound. Check it by assigning the absolute configuration of each asymmetric carbon again. I guarantee it is correct. The relationship of this compound with the Fischer I originally drew is that they are enantiomers. What does RSR see when it looks in the mirror? Of course, it sees SRS.

Now let us consider the second drawing, drawn quickly without consideration of stereochemistry.



For the first asymmetric carbon to the left, when tracing the circle from priority 1 to 2 to 3, one obtains the R absolute configuration and it is really R because the number four priority is going back. For the next asymmetric carbon, tracing from priority 1' to 2' to 3', one obtains R and it is R because number four is going back. Going a little more rapidly now that you are getting the hang of things the last asymmetric carbon is R.

Once again, I rapidly wrote down the wrong compound, but it is no big deal because I can easily edit it by inverting centers. Again, I want the S,R,S, so the second center is correct, but the other two require inversion. Inversion is accomplished by switching any two groups on the centers requiring change. The S, R, S compound is shown below.



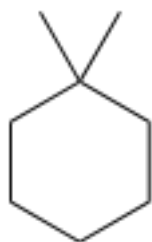
This compound is the desired S, R, S compound and is identical to my corrected Fisher, though it may not look the same due to conformational differences. To gain faith in the methodology, you could build models of both and attempt superimposition through bond rotation. I can assure you they will superimpose, but give it a try. Of course this exercise is generally unnecessary. If the absolute configuration is the same for the centers and the connectivity is the same, they are the same compound. There is only one 2-S, 3-R, 5-S-2-bromo-3,5-octanediol, but there are an infinite number of conformers.

What is the relationship of the above S, R, S compound to the mistakenly drawn R, R, R compound? They are not the same because to be the same they would have to have the same absolute configurations at corresponding asymmetric carbons. They are not enantiomers because the enantiomer of RRR is SSS, etc. They are stereoisomers, but not enantiomers, therefore they are diastereomers.

But relationships aside, don't lose track of the goal here. The goal was to draw a specific chiral organic compound. What we have demonstrated is that this can be accomplished either by using a Fisher or a wedge/hash drawing. It is acceptable to simply draw a stereoisomer, assign it and then switch groups until you have the desired compound. You can conceive the entire stereochemistry before you begin, but this is harder for most people.

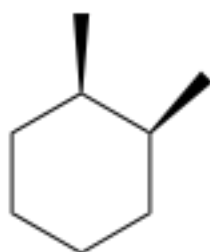
### **Stereochemistry of Ring Compounds**

It is also important to consider the stereochemistry of rings. Rings are really no different than straight chain compounds, but they do not lend themselves well to Fischer representations and conformations are taken more seriously. Let us start by considering all the dimethyl cyclohexanes. Let us draw the structures of 1,1-dimethylcyclohexane, 1,2-dimethyl cyclohexane, 1,3-dimethyl cyclohexane and 1,4-dimethyl cyclohexane. This exercise will help you to begin to understand the stereochemistry of rings. Of course, cyclohexanes are the rings most heavily studied at this level and are the most ubiquitous in natural products.

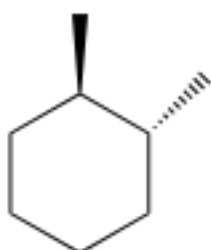


1,1-dimethyl  
cyclohexane

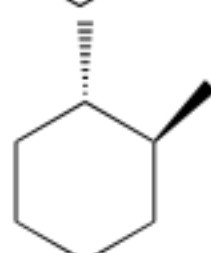
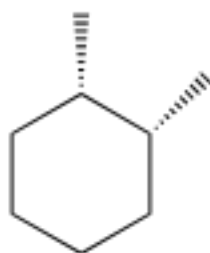
1,1-dimethylcyclohexane is not chiral because it has no asymmetric carbons. Therefore, I will not represent it in a three dimensional drawing, though it can be done.



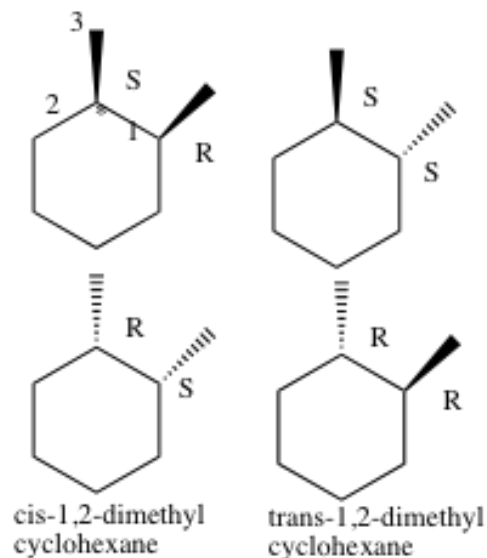
cis-1,2-dimethyl  
cyclohexane



trans-1,2-dimethyl  
cyclohexane



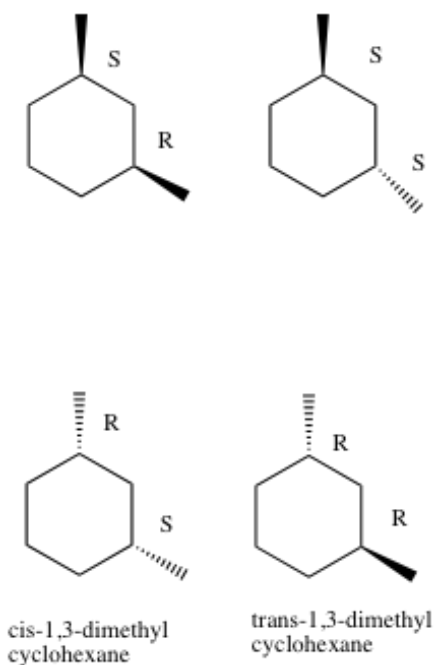
If you analyze the cis-1,2-dimethylcyclohexane structural drawings, you will discover they are superimposable. But even without the analysis with the models, you will discover that these drawings meet the requirements to be a meso compound. Why? The compounds have asymmetric carbons, but they have the exact same four different groups attached to them and one center is R and the other is S as shown below. On the other hand the trans compounds are different, nonsuperimposable and are enantiomers as shown in the assignments below.



At this point, I am assuming you have some facility with the assignment, but rings are a little different. The way you deal with a ring is that you view one half of the ring as one substituent and the other half of the ring as another substituent. So as an example, on the first asymmetric carbon to the left on the first structure, the right hand side of the ring receives number one priority, the left hand side of the ring number two priority and the methyl number three priority. The hydrogen, which is pointing to the back here, is number 4 priority. You have probably noticed, I have stopped bothering drawing in each hydrogen and writing it in as the lowest priority group. Why is the right side of the ring number 1 priority? This is because at the first point of comparison we have C vs. C vs. C vs. H (the one that is not drawn in). Comparing these three carbons, the carbon to the right is attached to two carbons and a hydrogen. The carbon to the left is attached to one carbon and two hydrogens, whereas the methyl is attached to three hydrogens. Does this make Tracing the circle from the right to the left to the methyl at the top, you should obtain a counterclockwise direction of rotation and since the number four priority is indeed going back, the assignment is S. Similar assignments can be done for all the asymmetric carbon.

One concludes after completing the assignments, that the cis compounds in this case are indeed the same. They meet the requirements of meso compounds. They have multiple asymmetric carbons. The carbons have the same four different groups attached and one is R and one is S. These factors define the symmetry. Once again, it is as though you have two enantiomers bonded to each other. The two trans compounds are not the same. One is RR and one is SS. Without any manipulation of models one can confidently state that each individual compound is chiral and that they are not the same and they are enantiomers. As we stated earlier, all RR and all SS compounds are chiral. All SR and all RS compounds are chiral except meso compounds. In this case we happen to have a meso compound. Please note that the second drawing of the cis compound is redundant.

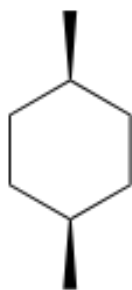
Now let us consider the 1,3-dimethylcyclohexanes. Similar to the last example, there is only one cis-1,3-dimethylcyclohexane. If you translate one you will discover you can flip it over and superimpose it. But we don't need to do this. All you have to do is assign it. The cis representations meet the requirements of being meso compounds. They have multiple stereogenic centers that have the same four different groups and one is R and one is S as shown below. Did you obtain the same assignments as shown with the structures below?



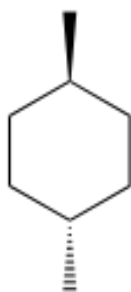
Let's review by going over the left center on the first structure. If I were to assign the left center on the first structure, the right side of the ring would be priority one, the left side of the ring would be priority two, and the methyl, priority 3. The hydrogen is going back and not drawn in because you are so sophisticated at this point. Therefore, tracing from right to left to up, you should obtain a counterclockwise tracing of a circle, and with the hydrogen going back into the page, the center is therefore S. Why is the left side of the ring, number one priority? By now you should be able to work it out. Briefly, priorities one, two and three tie at the first comparison. They are all carbons. At the second level priorities one and two tie because they are both connected to one carbon and two hydrogens. Working out one more level, the right side of the ring has more branching and is therefore higher priority.

Analyzing this set of molecules, the RR, SS pair are each chiral and are enantiomers. The RS, SR pair are not a pair with a relationship, they are the same molecule. They are the meso. The single meso compound has a diastereomeric relationship with either the RR or the SS.

Finally, let us consider trans-1,4-dimethylcyclohexane shown below.



cis-1,4-dimethyl  
cyclohexane



trans-1,4-dimethyl  
cyclohexane

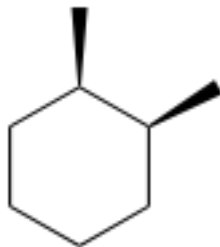
These compounds fall into a completely different category. They do not have asymmetric carbons. If you analyze either carbon bearing a methyl (the most likely to be asymmetric), you discover that both sides of the ring are identical so the sides are identical groups. When we enter this world of chirality, we start to think everything is chiral, but it is not true. There are many molecules that are not chiral. Think of benzene or ethanol. Though living systems are filled with chiral molecules, many molecules you will deal with routinely are not chiral. At least most that you have encountered thus far have been achiral. Not having asymmetric carbons and having such an obvious plane of symmetry, the 1,4-dimethylcyclohexane molecules are achiral so there is no assignment possible and no value in drawing the mirror image. Comparing the cis- and the trans- we discover they are not the same, they are not superimposable. Interconversion requires breaking bonds. These are conventional cis/ trans isomers and they are locked in by the restricted rotation of the ring. What is their relationship? They are not the same and they are obviously not enantiomers. As I like to say when cis- looks in the mirror it does not see trans!!! So basically, they have the same connectivity but different spatial orientation only interconvertible by bonds being broken. This makes the compounds diastereomers. All cis trans stereoisomers can be described as diastereomers., including those involving double bonds.

Now when you study your textbook (and you are encouraged to study your textbook), you will read that cyclohexane rings should be analyzed in a chair form. It should be noted is that all compounds should be analyzed this way not just cyclohexanes. But I maintain to answer the basic answer of chirality, it is better to analyze the compound flat. Again this is how compounds are analyzed, they are not analyzed as percentages of certain conformers. So as an example, consider cis-1,2-dimethyl cyclohexane. Above, we said that it is achiral because it has a plane of symmetry in the flat structure or you could say it has two asymmetric carbons with the same four different groups attached and one is S and one is R. But in reality the molecule exists in puckered conformers. More than 99 percent of the molecules are in the two chair formations as shown below.



There are of course other conformers, but one way to argue the lack of net chirality is to consider each conformer individually and consider its chirality.

Each conformer is chiral. That is it has a chiral shape. If you look at the first structure it is cis and if you flattened it, it would be the structure I showed earlier.



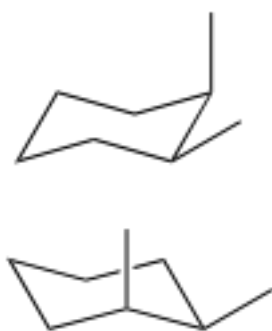
But again, in reality it is in conformers. If you held the conformer on the right locked as it is you would discover that the shape is chiral, i.e., it is nonsuperimposable on its mirror image. Now this requires that you hold the conformation steady. In this exercise you are not allowed to rotate bonds, which means you are not allowed to flip the chair. What we are saying is the shape is chiral. By the way, lots of shapes are chiral. If I were perfectly symmetric, I would be like a meso because my hands and feet are chiral but they are mirror reflections of each other so there is no net symmetry. However, if I stick one of my legs out or arms out, I assume a chiral shape and that shape is nonsuperimposable on its mirror image. Of course, I can quickly reassume my meso shape. What matters for molecules is the average symmetry. For a perfectly symmetrical person, when they straighten up they will assume their average symmetry, but in the course of a day, the perfectly symmetric person assumes many chiral shapes.



So the true explanation for the chirality or lack of chirality in a molecule truly emanates from an analysis of the percentages of all the conformers and whether they cancel each other out.

In this case the conformer on the left is non superimposable on the conformer on the right. If you pick it up and try to superimpose it on the conformer on the left, it will not sit down become congruent with the other structure. Remember you can not rotate the bonds. Do not do this. If you start rotation, you will be able to superimpose it.

So consider the following. If I pick up the structure and move it around a bit so that I have two of the methyls lined up conformationally, you will see that it does not superimpose.



The way I have these two structures sitting the equatorial methyl groups can sit down on each other, but you can see that the axial methyls are in opposite positions. One is in the front and one is in the back.

These are what are called conformational stereoisomers. They are conformers that are non superimposable mirror images provided the chair is not flipped or the bonds are not rotated.

Must do a movie on this. Movie must contain some discussion on this.

Maybe have links into the movie in the document.

So the true explanation of the lack of net chirality is that the two major forms and the minor forms form equal quantities of enantiomeric pairs and they cancel each other out.



In a group of 1,2-dimethylcyclohexane, there is fifty percent of the left conformer and fifty percent of the right conformer and together they make a conformational racemate, have no net rotation.

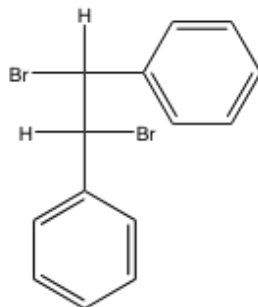
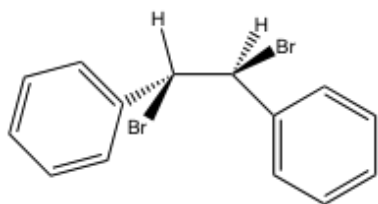
But truthfully, this level of thinking has little practical use. In the laboratory what matters are molecules that are different on a configurational level. These molecules interconvert at room temperature and therefore cannot be placed in separate bottles.

Now much is made of rings in textbooks and they come off as being special in regard to conformational stereochemistry, but the truth is all molecules have conformers that have a chiral shape and that could be considered in this way and it is true of all straight chain meso compounds we have looked at before. For example consider the following compounds in the shapes they are in.

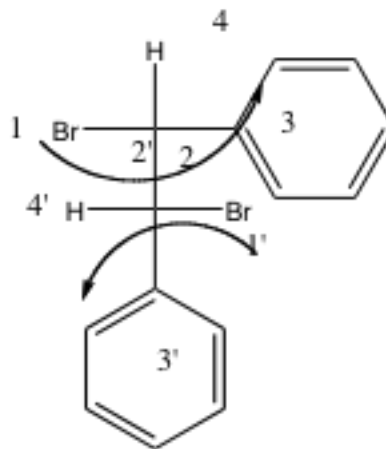
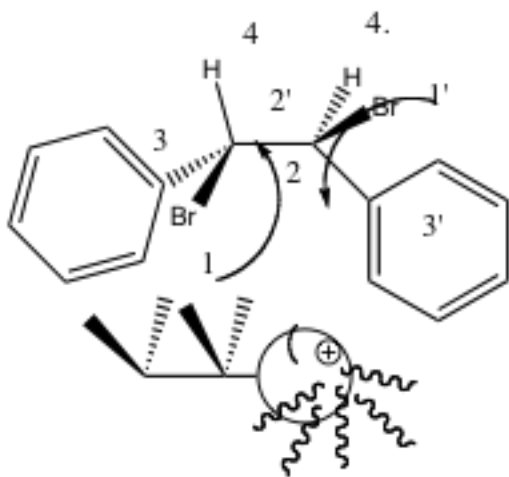


These are two representations of butane. Butane is not considered to be a chiral compound. So it is not chiral from a configurational standpoint. Why would you say it is not chiral because it does not contain asymmetric carbons, more generally it does not possess the right types of stereogenic centers to confirm configurational chirality on the molecule. The best way to say it, is that the butane on the right can be superimposed on the butane on the left using bond rotations. But taken on a conformational level, the butane on the left is not superimposable on the butane on the right if the conformers are held steady. When the butane on the left looks in the mirror, it does not see the butane on the right, so therefore, they are not conformational enantiomers as in the last case, they are conformational diastereomers because they are not the same, not nonsuperimposable mirror images. Again are these molecules really different. No, not in the normal sense. They cannot be placed in separate bottles.

Consider the following molecules.



Are these molecules chiral or do they at least have the potential to be chiral? What is their relationship? Now based on what you have learned you can easily ascertain whether they are REALLY chiral in the configurational sense. You should ask yourself if they possess asymmetric carbons. Which they both do. Then you should decide whether they have the potential to be meso in which case they would not be chiral. In each case they do because they have the same four different groups attached to each asymmetric carbon. Since they both have the same groups attached and in any case, the best way to resolve the problem is to assign the stereochemistry of each center. As shown below.



In the first structure, the carbon on the left has to be viewed underneath or above to assign. So if I was laying under the molecule (see super-chiral woman shown above), the hydrogen would be away, the bromine to my left, the number two group up by my head and the phenyl to my right. Tracing the circle, super chiral woman would obtain an R direction. The center to the right is more conventional because the number four group is going back, so tracing the circle from 1' to 2' to 3' the circle is counter clockwise and is S. So this compound is an R, S compound and is therefore meso and achiral. Notice, you only need super chiral woman if you have the number four priority group in the plane of the paper.

Now let us look at the compound to the right. It is a Fischer projection and super chiral woman is never needed for a Fischer projection because remember the advantage of a Fischer is that all groups are either out or back (wedges or hashes). On the top center, tracing from 1 to 2 to 3 one obtains a counter clockwise circle which does not need to be reversed as the number 4 priority group is going behind the paper. Therefore, the top carbon is S. On the bottom carbon, one traces from 1 to 2 to three and it looks counterclockwise, but the absolute configuration needs to be reversed because number four priority is in the wrong orientation, coming forward. So this compound is S, R and therefore is also a meso.

The point I am trying to make is these two mesos are not really any less special than the two interconverting chair compounds. These two straight chain compounds do not look the same upon quick observation because they are in different conformations. Think about it, Fischer projections are always eclipsed. Always. The projection to the left is a staggered projection. The way they are drawn they are not directly superimposable. Are they really the same, yes, in the sense of chemistry these structures are the same compound. They are the meso in two different rotomers or conformers. They rapidly interchange at room temperature. But if one really analyzed them on a conformational level, not allowing the rotation of bonds, these two forms would not be super imposable.

It is also true that the staggered form does not see the Fischer in the mirror. These two shapes are chiral (in the transient sense), but they are not conformational enantiomers. They are conformational diastereomers. Anything that is not superimposable, has the same connectivity and is not a mirror image falls in the diastereomer category, one way or the other.

At the end of the day, these conformational stereoisomers do not matter much. At the end of the day we are organic chemists. Organic chemists do a lot of things, but principle among them is making molecules. When molecules are made they have to be separated. As described earlier in this document, the handedness of a molecule is very important to its activity and toxicity in living systems. When we make molecules in the lab we are very concerned with what we are making, what are the contaminants involved and we are very concerned with contaminants that are stereoisomers. The removal of contaminants involves different separation techniques that you are learning in lab, distillation, extraction, recrystallization, chromatography etc. It is true that the farther apart in relationship and of course structure, molecules are, the more different their physical properties and normally, the easier they are to separate. So molecules with no relationship should be the easiest, then structural or constitutional isomers (like cousins), then diastereomers (the siblings) and finally enantiomers (twins)

In principle, enantiomers have different physical properties such as boiling point, melting point, solubility, spectra etc. Sometimes the properties of diastereomers are dramatically different (consider the two trans-cinnamic acid dibomides you prepare in the lab, these have drastically different melting points) or they can be

very close. But in principle diastereomeric compounds can be separated by conventional techniques such as distillation, recrystallization, extraction, and chromatography and can be distinguished by normal spectroscopic techniques such as infrared spectroscopy and nuclear magnetic resonance spectroscopy.

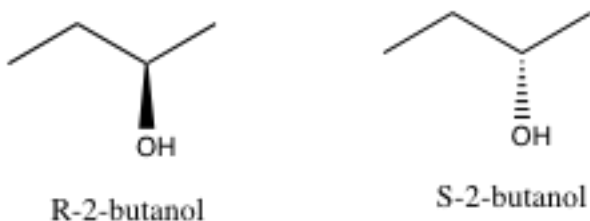
On the other hand, enantiomers are rough to separate. In an achiral world, they have the same boiling point, melting point, solubility and spectra. In an achiral world chirality has no meaning. In a handed world made up of only one of a pair or pairs of enantiomers (such as a living system) they interact differently, like you with a left handed glove. They even react at different rates.

In a chiral environment, enantiomers can exhibit different physical properties and reactivities. One of the properties that is highly focused on and it is tremendously interesting, though perhaps not so practically useful in daily lab life is the physical property, optical rotation. Optical rotation is the ability of molecules to rotate plane polarized light (light that has been placed through a polarizer so that all but one oscillating plane has been removed.) It has been long known that molecules that are enantiomers have equal and opposite optical rotations. All chiral molecules when pure exhibit this property. It is true that all chiral molecules have this property, but only enantiomers have equal and opposite rotations. So two diastereomers may have optical rotations because they are individually chiral, but the magnitude and direction of the optical rotation will not have a relationship. Every chiral molecule will have a rotation and each chiral molecule in principle, would have an enantiomer with an opposite rotation.

So please consider 2-butanol.

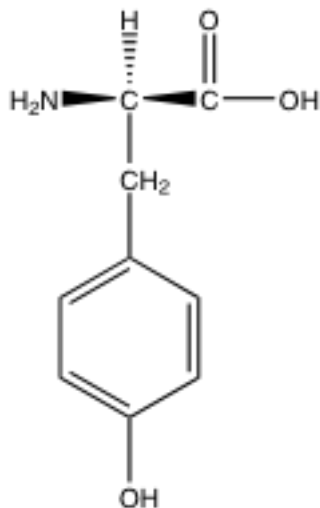


As shown, there are two, 2-butanol. They are each chiral and the one on the left is the enantiomer of the one on the right. You could easily prove this just using your recognition of the asymmetric carbons and assigning them.

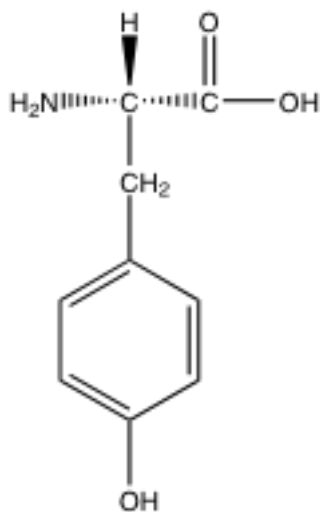


Now these two compounds have equal and opposite rotations. R-2-butanol has specific optical rotation of -13.52 degrees and S-2-butanol has a specific optical rotation of +13.52 degrees. I will explain optical rotation on a more physical basis

in a few paragraphs, but first consider the next pair of molecules. R-tyrosine and S-tyrosine.



The above compound is R-tyrosine and R-tyrosine is unnatural tyrosine (though I believe it is found in some decaying bacteria). R-tyrosine has a specific optical rotation of +10.9 degrees. The following is the natural amino acid (it is one of the twenty amino acids typically found in living systems and that are the monomers for proteins). S-tyrosine has an optical rotation of -10.9 degrees.



S-(-)-tyrosine

Though I have yet to explain optical rotation, a few things become apparent upon looking at just a few optical rotations. It is not obvious what causes the magnitude of the rotation (though it is somehow related to the structure) and even more interestingly, there is no correlation between the absolute configuration and the

direction of rotation. Remember, absolute configuration, i.e., R and S assignment is an arbitrary nomenclature set up by Cahn, Ingold and Prelog. The tracing of the circle to the right or left refers to the very arbitrary way the priority system was designed. Optical rotation is a physical property measured in the lab and it is independent of this arbitrary system. There is another system used by biologists for certain molecules called the D and L system, mainly used for sugars and amino acids. This often causes more confusion because when people refer to the positive rotation, they say the rotation is levorotary (to the left) or dextrorotary (to the right) and people like to translate this little d and l which refers to the property known as optical rotation with the big D and L system which is just another arbitrary nomenclature system that describes the three dimensional orientation of the groups (like R and S). Of course, the idea of a physical property rotating left or right can be sort of confusing with the idea of tracing a circle left or write when assigning R and S. It is important to try to understand the difference and try to keep them straight as you study and utilize stereochemistry as organic chemists.

So let us discuss optical rotation in more detail. As stated previously, it happens when these chiral molecules are in their enantiomerically pure form, they rotate plane polarized light either clockwise or counter clockwise. What is plane polarized light? Plane polarized light is ordinary light that has been passed through a polarizer (sort of like Polaroid sun glasses). One can think of ordinary light as being comprised of an infinite number of perpendicular oscillating electrical and magnetic fields. By oscillation, we mean that the electrical fields are constantly and regularly switching their dipole from negative positive to positive negative. This would be happening at some frequency. Similarly, the magnetic fields would be changing from "north" - "south" to "south" - "north" at some frequency as diagramed below in the following URL.

After passing through the polarizer, only one oscillating plane remains. When this plane encounters a sample with net chirality, it rotates. So basically there is a light source, it passes through a polarizer, then the polarized light passes through sample of some length and concentration. If the sample contains net chirality, the plane polarized light will be rotated some degrees from the original position. The operator of the polarimeter will rotate a moveable polarizer at the other end to "find" the rotated plane polarized light. The rotation in some way relates to the interaction of the chiral molecules that have an asymmetric electrical density with the plane polarized light. The truth is the reason this property exists is because light is chiral. Plane polarized light consists of two forms that are rotating, sort of corkscrewing, in opposite directions. They are two helical forms of light that are meeting in the middle to form the plane. These two helical forms of light are enantiomeric in nature, but individually each is chiral. Once again, it is like your right and left hands encountering a right handed glove. So here we have a right and left form of light encountering a right or left handed form of a molecule. When the left handed light interacts it is different than the interaction with the right handed form. Think of it this way, a left handed molecule with left handed light versus a left handed molecule with right handed light is a diastereomeric relationship – a more

distant relationship. It is thought that one form of light slows down more than the other from the interaction and the resolution of the helices occurs in a different plane. Please see the associated YouTube where I explain this in a more dynamic manner. Truthfully though, this phenomenon is not totally understood and as stated earlier, it is not known exactly what causes the magnitude or direction of rotation for a particular enantiomer. The absolute configuration once linked with a specific rotation of a certain direction can be used to help identify and to verify the absolute configuration, but only after it has been determined using some other method (e.g., x-ray crystallography or chemical conversion into another known molecule of known stereochemistry).

## Polarimeter

Light source--> polarizer---> sample in long tube---> moveable polarizer ----> human being

As indicated earlier, the rotation is expressed as a **specific rotation**. The specific rotation is expressed in equation form as follows:

$[\alpha]_D = \frac{\text{observed rotation (degrees)}}{(\text{cell length in dm})(\text{sample concentration g/mL})}$

If the liquid is a pure liquid it is expressed in density units, which are also g/mL.

The rotation has to be expressed this way because the more molecules the plane polarized light encounters, the more it rotates. So if the concentration of the sample is doubled, the observed rotation is doubled. If the cell is half as long, the observed rotation is cut in half. By correcting for these two factors, the values are standardized and can be compared with the literature. There is also a slight dependence on temperature and there is dependence on the wavelength of electromagnetic radiation used, though the wavelength is typically the D line of sodium.

## Stereochemistry 8: Optical Rotation Problem

Please see the associated video, but supposing one had a sample of sucrose dissolved in water having the concentration of 0.5 g/mL and the sample was placed in a cell that is 0.5 decimeter long. One measures the optical rotation of this sample using the D line of sodium at around room temperature and obtains a value of  $-25^\circ$ . What does this mean? This means that the sample rotated the plane polarized light by  $25^\circ$  in a negative direction. But truthfully this could be  $\pm 180^\circ$  of this or  $\pm 360^\circ$  of this rotation. Realize it is a plane and the plane can line up at  $\pm n180^\circ$ . Can you devise an experiment where you could determine real magnitude and direction of rotation? Think about measuring more than one sample at different concentrations or path lengths. Suppose you think the rotation is  $+25^\circ$ , but you realize that the rotation could also be  $+205^\circ$  or it could be  $-155^\circ$  or  $180^\circ$  more or less, etc. If the sample is really  $+25^\circ$  and you halve the concentration, then the rotation should be half according to the equation given above. At half concentration, the observed rotation should become exactly  $12.5^\circ$ . If on the other hand the



rotation is really  $-155^\circ$ , the diluted rotation should be  $-78.5^\circ$  and this a significantly different position on the dial.

Suppose you do establish the observed rotation for the solution of sucrose is  $25^\circ$ . From this number you would want to calculate the specific rotation by dividing by the concentration of the solution in grams/mL and the cell length. Supposing this solution is 0.5 g/mL (the solution would be aqueous in this case) and the cell length is 2 cm. the specific rotation  $[\alpha] = 25^\circ / 0.5(2)$  which gives a specific rotation of  $25^\circ$ . This number can now be compared to literature values to get a sense of the sample. If one peruses the literature, one can find a literature specific rotation for sucrose in water. The literature value for the specific rotation natural sucrose (sucrose exists as one of two enantiomers in nature, structure shown below) is  $+66.47^\circ$ . This rotation is the specific rotation for pure sucrose of the chirality shown below in water at about room temperature. So what does our value of  $25^\circ$  mean? The specific rotation obtained is considerably lower than the value given. Assuming all the material dissolved in water and placed in the polarimetry tube is sucrose, one would assume that the sample is contaminated with the enantiomer of natural sucrose. One could take a ratio of the experimental value and divide it by the literature value to determine the optical purity.

**Optical purity = experimental specific rotation/literature specific rotation X 100**

In this case

**Optical purity =  $25^\circ / 66.47^\circ \times 100 = 37.6$  percent**

The way this would be interpreted if the sample is truly all sucrose is that the sample contains 37.6 percent of the molecule shown and the rest of the sample is a racemic mixture. Meaning, the other 62.4 percent of the sample is half the molecule shown and half the mirror image or enantiomer of the molecule shown (shown below).

Perhaps this is not obvious yet, but a racemic mixture or racemate would have zero optical rotation. Again, a racemate is a 50:50 mixture of the two enantiomers. This is because they rotate plane polarized light in equal and opposite directions. Of course, achiral molecules also do not have rotations. It should be noted that diastereomers have different rotations, but not opposite rotations. Achiral molecules include the special molecules discussed earlier that are called meso compounds.

So this sample could very well be a racemic mixture, with a 37 percent excess of the natural sugar + enantiomer. This means the sample is really 68.7 percent the natural sucrose and 31.2 percent of the unnatural, enantiomeric stereoisomer.

In nature, sucrose is one hundred percent the natural isomer shown and most compounds in nature are enantiomerically pure and therefore, if isolated optically pure.

Of course, other factors could result in a low or high optical rotation. Contamination with other chiral molecules with other rotations or even contamination with other compounds without rotations (how would this effect rotation given it would increase the mass). Obviously, if one is going to study a compound by optical rotation, one has to have established the purity of the sample in terms of general structure (connectivity and general stereochemistry).

This of course has some value in identification in that if one has an established compound and is isolating it or synthesizing it one can use the direction and magnitude of rotation to determine purity and the stereochemistry.

But again, it can't be emphasized enough that if a new compound is isolated and it is established it has a rotation, the only thing it tells one is that there are chiral compounds in the sample. The absolute stereochemistry has to be determined by independent means. As shown above, compounds that are both R can have opposite rotations.

It is extremely important to understand the significance of all this. Why is it important to know stereochemistry? It is extremely important. To me it is one of the most important areas of chemistry. Why do shapes of molecules matter because we have evolved as system of molecules that communicate with each other through shape, charge, size, etc. There are many reasons this is an important and interesting area, but something to consider is the pharmaceutical area. When drugs are designed their purpose is normally to interact with some substrate to induce some change. It could be to block an enzyme and make it non functional. Say it is some enzyme that makes cancer grow like thymidilate syntase. You might be able to develop a drug that binds the enzyme and prevents the process needed for Cancer.

## **Glossary**

**Chiral:** molecules or any objects that are sufficiently asymmetric such that they are non-superimposable on their mirror images. Molecules that are chiral at least in principle have an enantiomer. Chiral molecules lack planes and points of symmetry. This term refers to individual objects or molecules.

**Chirality:** The state of being chiral

**Stereoisomers.** Molecules that have the same connectivity, but groups having different spatial orientations.

Enantiomers: stereoisomers that are nonsuperimposable mirror images.

Diastereomers: Stereoisomers that are not mirror images.

Meso compounds: Molecules that have the asymmetric centers but have a net plane of symmetry

Optical Rotation: The ability of a substance to rotate plane polarized light

Plane Polarized Light: Light that has been passed through a polarizer, removing all oscillating planes except one.

Racemate or Racemic Mixture: a fifty-fifty mixture of enantiomers having no optical rotation