Lecture 10B • 10/20/11

How many stereocenters are there on that [middle] molecule? How many places does it look like there may be the possibility of having stereocenters on the molecule? You might be led to think there's two because you see dashes and wedges on two positions, but remember that any time that you have two or more of the same substituent on one position, that means that at least, locally, you could draw a mirror plane through that position, which means that that position itself is not a stereocenter. The bottom of the molecule, where you have the two methyl groups – not a stereocenter. But up top, the way we can figure out if it's a stereocenter or not is to figure out if you do have four unique kinds of attachments. We have a hydrogen and deuterium which are different from each other, then we have the ring itself. But the ring, at that position, is not symmetric. If you were to go clockwise from the deuterium, it's just two positions away to get to that methyl group, but from the other direction, four positions away. That means that there's a difference between the chains. Remember how the priority rules work, where first it's atomic number, and then there's a subrule where, if you can't determine between atomic number, then you look at mass number. That's how me make deuterium more important than hydrogen. If you can't determine the priorities from the first place that you're looking at, from the position right at the stereocenter, then you've got to go one more position out. Following that logic, going one position away either direction, you get the same thing – a carbon that's got two hydrogens and then more of the ring. But go one more position out, then you get to the methyl groups first going clockwise. That's going to make that part of the ring priority number one, the other part of the ring priority number two because carbon is more important than any form of hydrogen. Deuterium is a higher mass number than hydrogen, so it's priority number 3; hydrogen itself is priority 4, and it's already oriented in the back of the plane, which is the way that you're supposed to orient it when you're visualizing whether it's R or S. Since the substituents are arranged in a clockwise order, this is R.

Let's go back to the first molecule; how many stereocenters on this one? Two. The righthand steretocenter, we have [O, C, C, H] that are attached. Oxygen, higher atomic number, so it's going to be priority number one; then, it's not automatically the longest chain that matters, but if you consider that you have just a methyl group, just one carbon sticking out there, or you have a carbon chain of any longer length, that's going to automatically take precedence over a methyl group. So, the longer carbon chain is priority two, methyl group number 3, hydrogen again oriented for proper visualization, in the back. We again have the substituents ordered in clockwise fashion, so that stereocenter is again R. Let me rewrite the molecule so I don't clutter this up any more than I have, o we can do the other stereocenter. It's not exactly a trick problem, but you might have been tempted to say, this chain has two alcohols on it, so it must be more important than the chain that's only got one alcohol on it. But that's not how the priority rule works – you look at each atom as you go one step further and further away from the stereocenter, until you find the first place that there's something different.

If we do look at that first position away from the chlorine, we have carbon and carbon. On the lefthand carbon, attached to it is [C, H, H]; on the righthand side, it is [C, H, H] that attached. Remember that when we're listing these priorities, I don't refer back to where I came from, cause that's going to be the same for everything that's attache to it. Since I can't tell a priority difference between these two, they're both [C, H, H], I've got to go one more position, out, and I follow the most important substituents from that position, which in this case if carbon. I'll go one more position out. On the lefthand side, I have attached another carbon and two hydrogens, but on the righthand side, I have [O, C, H]. Because that oxygen happens first, even though there's only one oxygen, it happens earlier in the chain, so according to the first point of difference, we now are going to give that righthand chain the higher priority. So, chlorine's higher priority because it's higher atomic number, the chain with the closer oxygen is priority #2, the chain that happens to have more oxygens but they're further away, that's priority three; hydrogen's in back. This is S.

I'll sometimes write molecules that have stereocenters but I write with plain lines. In those case, you wouldn't be able to tell if it's R or S, and often, if you're writing the structure in that way, it's on purpose. You either don't know whether it's R or S that you're dealing with, or it doesn't matter that it's R or S that you're dealing with.

What about the last case with the double bond? We have to rewrite it somehow. Everything that we've done so far is comparing things that have single bonds. There is a systematic way to handle that double bond. It is using what are called phantom or virtual atoms. As a simple example, let's take this aldehyde. What you do is you look at one atom that's on the double bond, and you see what it's double bound to. To show that it's go this double connection, rewrite it as a single bond, but then make a new single bond to a copy of that same atom. The carbon is double-bonded to oxygen. You show the bond to oxygen, but then you write another oxygen in. From oxygen's perspective, it's connected to carbon, so we've got that bond back to carbon; but to show it's really got a double connection, you put another carbon on there. So you're doubling the bond, again, from each atom's perspective. Those extra atoms I've written in are these virtual or phantom atoms. When determining the priorities of double or triple bonds, rewrite them using the phantom atoms, to then determine which one has that highest first difference point. When determining priorities of double or triple bonds, the bonds are rewritten as multiple single bonds, using phantom atoms.

So, rewriting, everything that's already a single bond stays exactly the same. The carbon-carbon double bond, we rewrite with a single bond. All of the other atoms that might have been there are still there.

Then, on the lefthand carbon, since it was double bonded to carbon, you write in an extra carbon; now you show that it had two connections. On the righthand carbon, because it was connected to a carbon, you're also going to put one of those doubling atoms in. Now let's look at priorities. From the stereocenter, you go the first position out and, we can't make a determination there what's most important, because on the lefthand side, we have the two methyl groups, so there's two different carbons attached, which means there's a hydrogen left over. On the righthand side, now that we've rewritten that double bond, it also shows two carbons attached; one of them's a phantom atom, but that's fine, then another one's a real carbon. So we still have [C, C, H] priority, so from that position, still, we can't figure out the priority. So we go one more position out. When we go one more position out, now either direction we go, it's the same, so it doesn't matter which way I go. It's a methyl group, which means we only have [H, H, H] attached. But on the righthand side, when you have to go one more position out, you always follow the most important chain. We have carbon with a carbon attached, versus just the phantom atom carbon. Since this chain is longer, it's going to have higher priority, so we follow it. At that position, it's not [H, H, H]; because of that phantom atom, it's [C, H, H]. Now we've found the first point of difference. Carbon is more important than hydrogen, so the double bond, even though it's only two carbons, has higher priority than the isopropyl group. So, back to the original structure: oxygen, priority one; double bond, priority two; isopropyl, number three; hydrogen, still correctly oriented in the back. These go counter clockwise, so this is S.

Optical activity, stereoisomers, enantiomers, diastereomers, meso, racemization

Optical activity

Enantiomers, these are molecules that are non-superimposable mirror images of each other. If you have a methyl group and you put four different substituents on: the halogens and a hydrogen, because there is tetrahedral geometry, there are two unique ways you can orient it, kinda like your left and right hand. Because these molecules are just mirror images, all of their physical properties are identical to each other, except for one critical property, which is the fact that opposite molecules will rotate plane-polarized light in opposite directions. Imagine this setup. Imagine that we have a light source, say an old-style bulb which is going to give off light in all directions. On top of giving off light in all directions, along the path that it's travelling, it may oscillator horizontally, it may oscillate vertically, it may oscillate at some other angle, or it can have a circular oscillation that occurs. Light travelling in all of these different directions, we can then organize in some fashion by using what is known as a polarizer. Notice that I've written these lines on the polarizer vertically. If you pass light through it, then only light that is oscillating vertically will be able to pass through.

Imagine that we let it keep on going until it hit another polarizer. Let's say that that second polarizer was oriented perpendicularly to the first one, and we observe what ever comes light. If light were travelling in only one direction, oscillating up and down, and you tried to pass it through a polarizer that was crossed with it, that was orthogonal to it, none of the light's gonna make it through. This is related to the technology used to make 3D films that don't require the goggles. What you have are the two different panes of the glasses being oppositely polarized. The modern version is not linear polarization like this, but we could pretend it was for the sake of discussion. Imagine that one eye had polarization so that it was vertical, one eye had polarization so that it was horizontal. You'd project two images on the screen, using a light source that it was itself polarized these different ways. If you project light that is vertically polarized, but you look through your glasses, the one that is horizontally polarized, you won't see it; but the other eye that has the correct orientation will see it. That way, the two different images, one of each only reaches one eye, and that's how you see in 3D. If you take these style of glasses, take two of them, put them on top of each other, if you twist 90°, they'll go black; if you twist another 90°, it goes clear again, and back and forth, because of this crossed-polarization effect.

But what if the light did not just pass straight through. What if we had some sort of optically active compound, so we put in the middle here some kind of sample. Linearly polarized light is exactly what I've descried here, where you have it oscillating in just one direction, and as it passes through something that's chiral, something that does have handedness, that light will twist, either clockwise or counterclockwise. When it comes out again, it will be oscillating in some other direction, which I'm trying to show with a slanted plane, showing that it's now at an angle. The is the property of optical rotation, which is how much twist occurs as light passes through the sample. The further that the light passes through the sample, the more that it's going to twist. There is a quantity known as specific rotation that takes into account pathlength. I'm more concerner that you just know what the physical property of optical rotation is. You can use a setup like this to measure it, though. You get the crossed polarizers and, again, if there was not rotation, you should see dark if you have the polarizers crossed. If you had a chiral sample in between, you are going to have light that makes it through. You adjust the angle of the polarizers until you do make it go dark again. That's the extent of the rotation. Optical rotation is a twisting of plane-polarized light caused by chiral materials. A clockwise rotation is given a + sign; a counterclockwise rotation is given a – sign.

Coming back to enantiomers. If you do have molecules that are mirror images, they'll have equal and opposite optical rotation. Sometimes, when you see the names of compounds, instead of referring R and S, they'll refer to + and –, particularly for biological molecules. Limonene, for example, a molecule that's found in lemons and limes, there's a plus version that has one kind of scent and a minus version. They're just enantiomers of each other, but they're quoted and listed and discussed as their + and – optical rotations.

Let's say I had a molecule with just one stereocenter, and let's say that stereocenter was in the R configuration. You cannot, without some sort of sophisticated computer molecule, be able to determine whether that molecule is going to have + or − rotation. R and S are just a convention that we've come up with to be able to name molecules, but R and S themselves have no physical meaning. There is no connection between R and S, as a concept, and + and −, as a concept. The only connection would be is if you had a molecule with just one stereocenter: if it happened to be R, and if it happened to be +, then when you make the opposite, which means you're going to make an S stereocenter, because it's the mirror image, it's going to be − rotation. R and S are opposites, + and − are opposites, but R is not equated with + or −, S is not equated with + or −. The way we name it, and the way it acts physically, have absolutely no connection with each other. There is no connection between R and S and + and −, except that mirror molecules have opposite rotation.

If you have a mirrored molecule, then everything on the original molecule that's an R is going to be an S when you take it's mirror image. Everything that's an S is going to be an R. Mirror molecules, in which R and S are reversed, have opposite optical rotation.

Historically, we couldn't determine if something was R or S. That's a very important moment in carbohydrate chemistry. Emil Fischer made a guess. He guessed that glyceraldehyde, in one form, it's + form, had an R configuration. Because the physical properties are identical, and they didn't have the kind of crystallographic techniques that we have now to really determine what the structure of the molecule is, he just had to guess what it was. He was able by inference to determine the relative structure, the relative stereocenters on a whole bunch of molecules. He knew whether they were + or − rotation, so when chemists describe them, they quoted them as the + or −. In 1951, they finally got a crystal structure of a chiral molecule that they knew the optical rotation of, so then they knew that R meant + for that one molecule. Every other molecule that they could make from that first molecule, they could have determined that he guessed right. But if he had guessed wrong, in 1951, the configuration of every molecule known would have been reversed.

I'd like you to try to write down the structure of (S)-butan-2-ol. There's not one way to write it, there's at least four, four simple ways, then there's even variations on that. Notice I didn't use a number in front of the R or S. That's because if you only have one stereocenter, you don't need the number, because if you knew enough about structure to write the structure down, you'd recognize there's only one place you need to worry about. It's butanol. It's a four-carbon compound. The alcohol is on position two. You have to make sure that you write it so that, if you use a wedge, for example, is that going to give you the rotation direction that you want – yes, if you put it on the correct position. The way I've drawn it, really there's only two choices. Whether it is on the middle carbon towards the left or the right, either place I put the –OH group would have to have a dash, the way that I've done the zigzag. To verify that, we note that oxygen is priority one; anything longer than a methyl is two; methyl is three; and hydrogen is four, but it's pointed at us, which means whatever we view has to be inverted. It looks like it's R, but it's really S. But what if I did my zigzag like this instead, effectively the mirror image. Then when you answered it, you could have answered it using a wedge. For all four of those structure, you'd also then have the possible rotomers you could draw. It was convenient to write all of the carbons in the plane of the paper, but not necessary to. You could have put the –OH group in the plane of the paper, but then either part of the carbon chain would have to have a wedge or a dash....

enantiomers – this is one class of stereoisomers. This is one of the classic definitions: these are non-superimposable mirror images. One relationship between enantiomers is that everything that's R on one version is S on the other. Another way to define enantiomers is that all stereocenters are inverted; R is reversed with S. Let's say we had a relatively simple molecule. Is the stereocenter on the left R or S? Oxygen, priority 1; carbon with bromine and carbon, priority two; carbon with just carbon, priority three; those go counterclockwise, so yes, it is S. How about the other stereocenter? Bromine, priority 1; carbon with oxygen and carbon, two; carbon with just carbon, three. So 1, 2, 3, it looks like it's S, but which way is the hydrogen pointed? It's pointed out towards you, so it looks like it's S, but because it's backwards, it's actually R. Let's write the mirror image. The way that I wrote the mirror image on is image that I put a mirror on the piece of paper and just reflect one side to the other. If you're in a hurry, there's an easier way to do it: flip all of the wedges and dashes around. If you check the configurations, what used to be S is now R, and R is now S. All physical properties of enantiomers are identical except optical rotation. This makes it hugely difficult with deal with enantiomers when you do a chemical reaction. You make a product that, let's say, is a 50/50 mix of enantiomers. Since the boiling point's the same, density's the same, polarity's the same, everything's the same, it's tricky to get them apart. There are strategies you can use to isolate those compounds.

Let's go to the next class of stereoisomers – diastereomers. Enantiomers and diastereomers are stereoisomers, which means that all of the bond connectivity is exactly the same, it's just whether it is a wedge or a dash that's different, that's the only difference. Enantiomers are where all of the stereocenters are inverted, so you have mirror images. Diastereomers are everything else. They're non-superimposable non-mirror images, which means that some, but not all, stereocenters are inverted. Imagine we had a compound like this, with three fluorines on it. If I chose to flip two of them, it wouldn't be a mirror image, but it would be a stereoisomer, but not all of the Rs and Ss are inverted, so it's a diastereomer. Since not all of the stereocenters are inverted, that means the physical properties are very likely – and normally are – different. They're not mirror molecules, they're totally different molecules, in some sense. Diastereomers have different physical properties.

There's a subset of diastereomers that you'll encounter frequently in carbohydrate chemistry, sugar chemistry; that's a type of diastereomer known as an epimer. It is a subset of diastereomer in which only one stereocenter has changed. We could imagine even a simple alkane, where out of four stereocenters, only one of them changes. It's still a diastereomer, but the term epimer refers to the fact that one one position switched. There's a subset of epimer known an anomer. You might have heard of the alpha and beta configurations of sugars. This is something that exists only when sugars are in cyclic form. At that point when they become cyclic, a new stereocenter is created. Once we get there, we'll figure out that the circle can be closed one of two different ways, gives you two different stereoisomers, but the rest of the molecule is the same. That's a special case called an anomer, which is a subclass of epimer.

Let's continue with the topic: is it chiral. I wanted to show you this molecule. This is a molecule that does have stereocenters. The lefthand stereocenter, R or S? R. The other one? S. Notice what that means, though, in this specific case. Both carbons, both stereocenters, have exactly the same substituents attache to it. They're in mirror image orientation. That means that the whole molecule itself has an internal mirror plane. You may not be able to see it the way it's drawn; in fact, this is a very class trick question, this particular molecule. If you were to rotate the middle bond, like we were making a rotomer, we would more plainly see that the molecule has an internal mirror plane, which means if you tried to make the mirror image of it – and we did it by imagining that there was a mirror on the paper itself – we're going to get exactly the same molecule out again. This is a molecule that doesn't have enantiomers, because the mirror image is itself. This is a special case, know as meso. Meso is a molecule that has stereocenters, but is not chiral. When you ask the question: is it chiral? That mens, is there handedness. Are there multiple versions of this molecule that can exist. With this particular set of configurations, no, there is no mirror image that is different; the mirror image is the same as itself. Instead of saying not chiral, we usually say achiral. Meso refers to a molecule that has stereocenters, but is achiral. This occurs because there is an internal mirror plane of symmetry. Meso molecules will not be optically active, because the direction that one of those stereocenters twists light is going to be exactly balanced by its mirror image stereocenter on the same molecule. Meso compounds are optically inactive, since the optical rotation caused by one stereocenter is exactly balanced by the mirror stereocenter.

Let me write the four (three) diastereomers of a molecule like this that has two –OH groups. Ignoring what relationships do exist, we could choose to write the molecule such that the –OH groups are wedges, or the one on the right could be a dash, or the one on the left could be a dash, or we could make both of them dashes. Going from left to right, or up and down, the relationship between these two molecules would be diastereomers, because between each one, only one stereocenters flips. In fact, these all could be called epimers as well, since epimers are a subset of diastereomers. If we look at the upper-left and lower-righthand corners, if they are both wedges or both dashes, if you made the model for both of those, you'd find out they're the same molecule, because there's this internal plane of symmetry. It's really not two different molecules, it's just that we've written the same molecule two different ways. The other pair, though, they really are images; if you made the models for the other two corners and tried to overlap them, you wouldn't be able to; these are enantiomers.

What you're talking about is a case like this. This molecule is meso, because there's an internal plane of symmetry. It happens to pass through one of the stereocenters itself. But, is that center position a stereocenter or not? Because if a mirror plane passes though it, you could say it's not a stereocenter, except that what if I drew its cousin molecule, like this, that also has an internal mirror plane. You could also make an argument that that middle stereocenter is not a stereocenter, and yet these are two distinct molecules if you did flip the configuration of that center. That is what is known as a pseudostereocenter. We assign r and s to its configurations.

This is a unique set of relationship that you'd only have if you have a mirror plane through the molecule. If you had something like this, then no matter which way the –OH group and the –Br group are oriented, it's always going to be chiral, because there's never a mirror plane. You could have one center R and one center S, but because you have different substituents, they don't exactly cancel each other out across the molecule. If you did the same thing where you drew both wedge, one dash, the other dash, both of them dash, those would be four unique molecules. In that case you could say that there's two pairs of enantiomers that are diastereomers of each other.

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When determining priorities of double or triple bonds, the bonds are rewritten as multiple single bonds using phantom atoms. enantiomers, diastereomers, optical activity, racemization, meso

Optical rotation – twisting of plane-polarized light caused by chiral materials. clockwise (+); counterclockwise (–).
*Molecules that are mirror images will have equal and opposite optical rotation.
*There is no connection between R/S and +/–, except that mirror molecules (in which R & S are reversed) have opposite optical rotation.

enantiomers – non-superimposable mirror images. All stereocenters are inverted (R <—> S). All physical properties are identical except optical rotation.
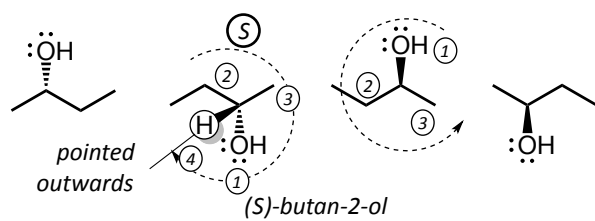
diastereomers – non-superimposable non-mirror images. Some, but not all, stereocenters are inverted. Diastereomers have different physical properties.

epimer – subset of a diastereomer in which only one stereocenter has changed.
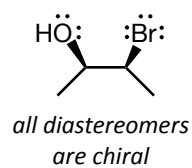
meso – a molecule that has stereocenters but is achiral. This occurs because there is an internal mirror plane of symmetry. Meso compounds are optically inactive since the optical rotation caused by one stereocenter is exactly balanced by the mirror stereocenter.

Structures *(remaining structures identical to lecture 10A)*

10/20/11 lec • 1

:ÖH

pointed
outwards

(S)

②
③
Ⓗ :ÖH
④
①

(S)-butan-2-ol

:ÖH ①
②
③

:ÖH

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HÖ: :Br:

*all diastereomers
are chiral*

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:ÖH :ÖH

:ÖH

:ÖH :ÖH

:ÖH