Lecture 10A • 10/19/11

Let's start with the cyclic compound. How many stereocenters are on this molecule? Just one, because the bottom, where there's two methyl groups, since there's two of them, if you flop the position of the two methyl groups, you'd produce exactly the same stereocenter again. Almost anytime we have two or more of the same substituent on one position, it's not going to be a stereocenter. We have the one position here that, yes, is going to be a stereocenter. Why? Because if you go two positions to the clockwise direction, you'd end up with methyl groups, but to get to the same methyl groups, we'd have to go four carbons the other direction. So it's not symmetric, so that means it's a stereocenter. If we're doing it by the first point of difference rule – you go either direction and you'd have the same thing, so you'd have to go out to the next position, which over here there's just hydrogens, down below, we have the methyl groups. Since carbon takes priority over hydrogen, that means that this bottom portion of the ring will be priority one. The top of the ring, two; then deuterium, then hydrogen (same atomic number as deuterium, but lower mass number). Since hydrogen is located in the back, that means we are looking at it at the correct way, so whatever way we see the substituents precessing is the way that we take it. Since it's going to the right like this, that means it is R.

Let's go to the first problem. The righthand position, is that R or S? R. We can know that because oxygen's going to take priority over carbon, so it's more important, then a methyl group versus anything longer than a methyl group – it's not always that it's the longer chain that is more important, but since it's a carbon chain, automatically that means it's going to have more important substituents on it, so that'll be priority number 2. Methyl group will be three; the unwritten hydrogen in the correct position in the back number 4. So yes, it is R. What about the stereocenters closer to the left? First, chloride is going to be the most important substituent, chlorine over carbon. Then, now we do need to use that first point of difference rule. At the point of attachment, I have a carbon versus a carbon. In each one of those position, what do I have attached? A carbon and two hydrogens. Since they have the same priorities, I can't use that position to choose, so I have to go to the next postion out. At the next, position out, what do I have? At the left, I have a carbon and two hydrogens, but on the righthand side, I have an oxygen, carbon, and hydrogen. Since oxygen is more important than carbon, that means the chain on the right is more important. Even though there's two oxygens on the lefthand chain, that doesn't matter; it's where the first point of difference occurs. Having two alcohols is not more important; it's where the first point of difference, which is right here. These look like they are going counterclockwise, so that is an S stereocenter.

The last problem involves the use of phantom atoms. We have a stereocenter – it's definitely a stereocenter because we've got four different things attached: an alkene, an alkyl group, an –OH, and then a hydrogen that's in the back. But how do we decide if an alkene's more important or an alkyl group? We need to have some systematic way to do it. The way to do that is to rewrite using what are called phantom atoms. Sometimes they're called virtual atoms, meaning they're not really there. If I have a double bond, to show that there's a double connection going on explicitly, we rewrite it like this: you make the double bond a single bond, and then you add a mirrored atom that indicates what would have been in that second connection. Carbon oxygen double bond, you rewrite with a carbon oxygen single bond, but then you double the oxygen; you put another oxygen in. Nothing ends up connected to it, so if this double bond was at the end of a molecule, and I had a methyl group, the rest of the structure stays the same, it's just that I've added these extra atoms. From oxygen's perspective, there is nothing else connected to it except carbon, so you leave a single bond to that original carbon, but to show the double-bondedness of that oxygen, you write in this phantom carbon. When determining priorities for double or triple bonds, the bonds are rewritten using multiple single bonds.

Let's rewrite the example we're working on and see how that's applied. So rewriting, everything else in the molecule stays the same, everything that's already a single bond. But here, at this carbon, I'll rewrite it as having a single bond with the next carbon; then, since it's a carbon-carbon double bond, that means each of the carbons gets a phantom carbon atom. How does that help our case? At the first point of attachment, what do we have connected? A carbon and a carbon. Since we can't choose between the two of them, we have to see what's attached at each position. On the position on the left, we have two methyl groups and a hydrogen, so that's [C, C, H]. On the right, we also have [C, C, H]. Notice that we're using that phantom atom, that rewritten atom, as one of the atoms that we count. That's why we do it in this way, so that we can have single bond to single bond comparison, no question how to compare. But we can't decide at this point, because we have [C, C, H] and [C,C, H]. So what do we do? We go along the most important chain on each side. On the left, it doesn't matter which way we go, cause we're going to end up with a methyl group, I can either go along the chain that has two carbons on it, or I could go along the chain that just ends in a carbon. If I'm going along the most important chain, I'm going to go along the chain that has the two carbons. So let's see what we have at these positions. For the methyl group, it's going to be [H, H, H]. Over here, because we have that phantom atom, it's [C, H, H]. That makes the tie-breaker. In this case, even though it only has two carbons, it's going to be more important than the isopropyl group. The means oxygen, priority one, because it's higher [atomic number] than carbon. The double bond, because of this application of phantom atoms, is more important than the isopropyl group, so this is an S stereocenter.

Enantiomers, diastereomers, optical activity, and racemization

I'm going to start with optical activity. Starting with the idea that there is handedness in tetrahedral geometry, that one model will be designated left handed and the other designated right handed. We're going to use the term enantiomers to describe these mirror images. Since they're mirror images, they're identical in every way, except for one physical property, which is this optical activity, more specifically in the form of optical rotation.

Imagine that we have a light source, say some sort of old-fashioned light bulb that gives off light that goes in all directions. Not only does it give light off in all directions, but, even if you're travelling in one direction, there's different ways the waves can be oriented, in terms of their angle. We can pass the light through what's known as a polarizer. A polarizer has got a whole bunch of slits in it that cause light that's wiggling in only one direction to pass through. If you had light that was travelling in a line, maybe it was wiggling this way, maybe it's wiggling this way – all different angles are possible. You pass it through a polarizer, and only one direction of wiggling is going to be let through, because the rest of the angles are blocked by the polarizer itself.

What happens when you pass polarized light through something that is optically active, something that is chiral? Let's say I put a sample in here. Instead of the light wiggling up and down in the plane of the paper as I'm trying to indicate in the first part of this diagram; it'll get twisted. Let's say it was now coming in and out of the paper. What we could do to measure that twist is use another polarizer. Look at the way this diagram is arranged: if light passed through the first polarizer, and let's say it was made to only wiggle straight up and down. If there was not a sample in the middle, and I let that light pass through and hit another polarizer that was at 90° angle, the light might pass through the first polarizer, but won't be able to pass through the second, because it's exactly orthogonal. This is a situation called crossed polarizers. Old version of 3D movies worked on that principle. In fact, even the glasses the use still do something like that. One glass is polarized one way, one glass is polarized the other way. The two images that are being projected, one of those images is being projected with light that is polarized one way to match one of your eyes, and then the other camera is projecting light that's polarized the opposite direction. If you have the right matching polarization, then when you look through the glasses, you'll see that particular image, but the one that's polarized the other direction, you won't be able to see it all. That's how you can have glasses that don't require batteries when you go to the movies because they are projecting these two differently-polarized images.

If you take the older style glasses that were used that were linearly polarized, then if you took one pair of glasses and put them on top of the other and twisted them around, the lens would go light and dark and light and dark as the polarization is lined up, then crossed, then lined up again. This is if there is nothing between the two polarizers. If you have something that twists light in between, then even if you had crossed polarizers, some of that light may have gotten through. If it goes through the first polarizer, it's only travelling one direction, it travels through a compound that twists it, if you have even any component of that new wave that's lined up the right way, the light's going to pass through. You can adjust the angle between the two polarizers and determine the degree of optical rotation. This optical rotation is the one thing that's different between mirror images. If one molecule rotates it clockwise, the other molecule is going to rotate it counterclockwise.

Let me summarize this physical property and how it can be measured. Optical rotation is a physical property of chiral compounds in which plane-polarized light, light oscillating in only one direction, is twisted as it passes through the compound. Molecules that are mirror images of each other will have equal but opposite optical rotation, one clockwise versus counterclockwise. Clockwise, to the right, we ascribe that as having a positive optical rotation. Counterclockwise, we say, has a negative rotation. You'll even see the names of compounds quoted sometimes not with R and S, or this + or –. Limonene, there's a + version, which means if you pass light through it it rotates to the right, and there's a minus version. There is no connection between R and S and + and –, except that mirror molecules have opposite rotation. If I write any random molecule down in its R configuration, you do not know if it has + or – [optical] rotation; it has to be measured. Unlesss you have some sort of super sophisticated computer model, there's no way to tell from the structure if it is going to be plus or minus. If you did have a compound that only has one stereocenter, and that stereocenter happens to be R, and that R configuration happens to cause positive rotation, if it happens to be +, then, when you make the mirror image, which would make the S form, it would be –, but only because it's the opposite. Once you know what one is, you can predict what the other is. But if I just say, "is it + or – ", and all you see is a structure on paper, you can't answer that question, because it depends on the physical structure of the molecule as to whether it is + or –.

If you have multiple sterocenters, one may twist one direction, one may twist another. You're going to have an overall optical activity for the entire molecule. What if we start out with a chiral solution, and we do a chemical reaction that ends up where there's no optical rotation. {Sn1} If you have 50% of the molecules that twist light one way and 50% the other, they cancel each other out.

Light can rotate multiple times as it passes through. There's something called specific rotation that takes into account the path length that you travel through. This value that we normally report covers that fact and specifies that you're looking over a specific difference.

A molecule doesn't know it's R or S, it's our label. If I said butan-2-ol, you could ask me which one, R or S? If I say R, you'd know by the convention how to be able to write it down on paper. What if I tell you to write down the molecule (S)-butan-2-ol? The absolute configuration is the idea that we can put this (S) and long as you know how to handle the convention, you'd be able to come up with the right molecule. Turns out there are multiple answers. If I had my alcohol pointed up from this position, is it going to be a wedge or a dash? A dash. It looks R, but remember that the hydrogen's actually pointed towards you, so you have to reverse whatever you see, so as the way I wrote it currently, it's S. But what if I had written it pointed down instead? You just rotate 180° around on paper, you get the same molecule. Still has to be pointed away so it looks R but is really S. But what I had my zigzags the other direction, like this? Now it would be a wedge, so it could be S, or I could have written it like this. All four of these are correct answers.

Let's get to some of these stereochemical relationships.

Enantiomers. These are the classic non-superimposable mirror images. Since they're mirror images, that means all stereocenters are inverted. If I take some random molecule, put in some functional groups, and assign R and S them, on the left we have S, on he right R. Oxygen, 1; carbon with bromine and carbon, 2; carbon with just carbon, 3; hydrogen in the back; that is S. Bromine, oxygen with carbon, 2; carbon with just carbon, 3; it looks S, but the hydrogen's pointed towards me, so I have to reverse it, R. If I make the mirror image, I've got two choices: I could just draw everything backwards, but a simpler way to do it would be flip all of the wedges and the dashes. That's exactly what you can't do when you're drawing ring-flip structures on cyclohexane, because it makes the mirror image. Here, I want to make the mirror image, so I really did just flip the wedges and the dashes. This, the alcohol now has an R configuration, and the bromide position now has an S configuration. These are enantiomers; they're mirror images. All physical properties of enantiomers are identical except optical rotation.

Let's see the next type of stereoisomer – the diastereomer, which is a non-superimposable, non-mirror image. We would say that some of the stereocenters, but not all, are inverted. Here I have three fluorines. If I changed two of them, but I don't change all of them, then they're stereoisomers; they have different 3D configurations. But they don't have a special relationship with each other because they're not mirror images. Since you're not mirroring the molecule, it's going to have different physical properties. Diastereomers have different physical properties. Much more easily separated. They have the same formula, all of the bonds are to the same atoms, same connectivity. The only difference is where it's pointing in 3D; is it a dash or a wedge. Because they have exactly the same formula [and connectivity], they're stereoisomers. A diastereomer is only a diastereomer if it is a stereoisomer. It's not just any two molecules that are hooked up differently; they have to be stereoisomers. If they're not mirror images, they're diastereomers.

There's a subset of diastereiomer called an epimer. It is a subset of diastereomer in which only one configuration is different. So this pair of molecules are diastereomers; they're not mirror images. But, they are stereoisomers. It's a special kind of diastereomer, though, where only one position has changed between the two molecules, so this is an example of an epimer. This term frequently appears in the context of carbohydrate chemistry. We're going to learn about a special subset of epimer called an anomer, which you only see in sugars – the alpha and beta forms of a sugar.

These will be our three kinds of relationships: enantiomers, diastereomers, and then a subset, epimer.

There is one more relationship, which is not a relationship between molecules, but a special case that addresses this question: is it chiral? What do I mean by that? Chiral means that you have molecules that are non-superimposable mirror images. What about a case like this? Is this molecule chiral? No. Why? If we make a rotomer out of this, if we twist the single bond, then we're going to end up with the two –OH groups pointed the same way. That means that we now have an internal mirror plane. The left –OH group, R or S? R. That automatically means the one on the right is going to be S, because the two halves of the molecule are just mirror images. If the two halves are identical, think about this: one of those stereocenters is going to cause one form of optical activity; it's going to cause light to rotate one direction. The other half of the molecule is going to cause the light to rotate back exactly the same amount the other way, because it's a mirror image of the molecule in it's own self. What would happen if you made the mirror image of this molecule? It's the same. A meso compound, which is what this is called, is a compound that has stereocenters, but because it has a plane of symmetry, is not chiral, or achiral. This occurs because there is an internal plane of symmetry, which causes the optical rotation of one half of the molecule to cancel the effect of the other half. In other words, no optical rotation. Meso is not a form, it's not a relationship between stereoisomers. In fact, because of the fact that it's meso, if I asked you to write it's enantiomer, you'd have to say there is no enantiomer for this molecule, because the mirror image is itself.

However, there are diastereomers of this molecule. One classic presentation is to do the following: to draw the four possibilities. Between any two molecules that are right next to each other, these are diastereomers. Why? Because only one of the two stereocenters is being changed. If you had anything different than all of them, that means they're not mirror images, that means they're diastereomers. For the molecule on the lower-left and upper-right, they are enantiomers. If you determine their R & S, you'd figure out they're reversed from each other. But then these other two, the upper-left and lower-right, are the same, because they're meso.

Turns out that if you take this alkyl halide and react it with water and heat, we're going to get two products. This alkyl halide reacts with water, forms two products. If you form the two products in exactly equal proportions, then each molecule individually is chiral, but the solution won't be. One molecule will turn light one direction, the other molecule will turn light the other direction. It's not like what the meso case was. Meso is when the molecule itself cancels its own optical rotation internally. If enantiomers are present in equal amounts, then the solution is called racemic, which comes from a root word meaning a bunch of grapes, because some of the early discoveries that were made in stereochemistry came from tartaric acid, which is a compound that comes from grapes.

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

Optical rotation – a physical property of chiral compounds in which plane-polarized light (light oscillating in only one direction) is twisted as it passes through the compounds.
*Molecules that are mirror images will have equal but opposite optical rotation – clockwise (+) versus counterclockwise (–).
*There is no connection between R/S and +/–, except that mirror molecules have opposite rotation.

enantiomers – non-superimposable mirror images. All stereocenters are inverted. All physical properties are identical except optical rotation.

diastereomers – non-superimposable non-mirror images. Some stereocenters, but not all, are inverted. Diastereomers have different physical properties.

epimer – subset of a diastereomer in which only one configuration is different.

meso – a molecule that has stereocenters but is achiral. This occurs because there is an internal mirror plane of symmetry which causes the optical rotation of one half of the molecule to cancel the effect of the other half (no optical rotation).

If enantiomers are present in equal quantities, the solution is called racemic.

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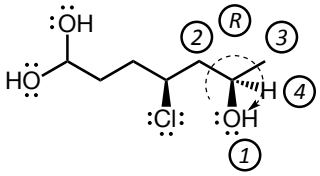

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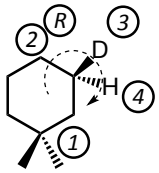

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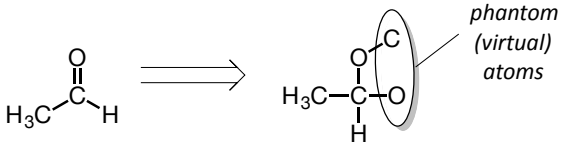

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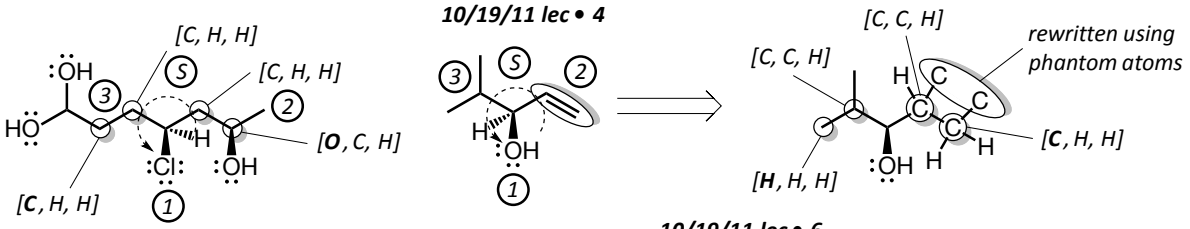

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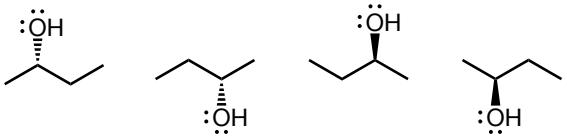

(S)-butan-2-ol

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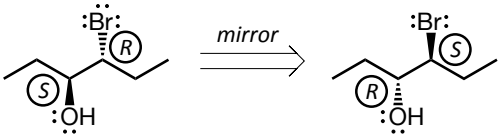

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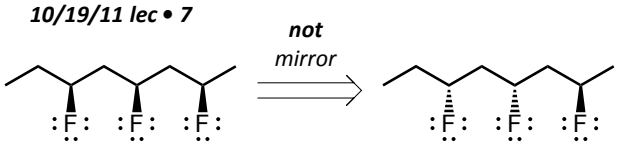

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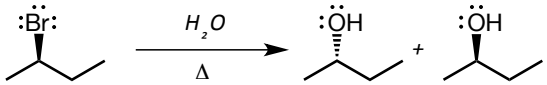

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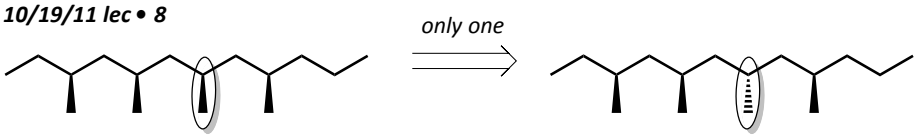

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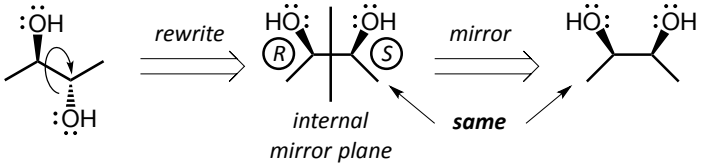
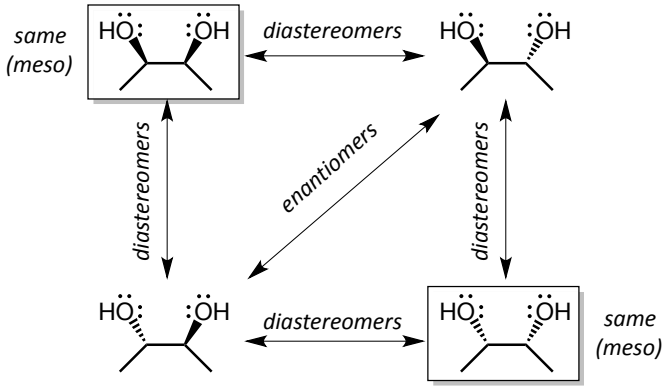
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