

## Lecture 9A • 10/14/11

{topics for exam #1}

bonding and anti-bonding; what the difference between a sigma and a pi bond is; SMOGs; single, double, and triple bonds; sp<sup>3</sup>, sp<sup>2</sup>, sp systems; positively-charged, negatively-charged, radical molecules; nomenclature of alkanes, haloalkanes, alcohols, no alkenes, no E/Z; cis and trans for cyclic compounds; common names; functional groups; rotomers, conformations of butane, Newmann projections, steric hindrance, staggered, eclipsed, gauche, anti, rotomer energy diagram; cyclic compounds; angle strain; chair and boat forms, axial and equatorial substituents. Vicinal and geminal substituents.

Let's say I have a substituted butane like this, and let's say that I chose my perspective point from this orientation, where I'm going to look along that bond. It's a simpler Newmann projection where we only have four carbons. Let's put the front methyl group where it belongs. If I do have my viewpoint oriented this way, looks like the methyl group is going to be pointed straight down from me. In back, the methyl group is pointed straight up. As a reminder, the one in back, you don't write the line all the way through, because we put this virtual disc between the front and back positions, to help show which is which. On the front, the bromine is pointed out towards you, but if my eye is at this position, it's actually on my right, so bromine will go up here. There's a hydrogen that I didn't write in these but of course it's there, it would be on the left. In the back of the molecule, the chlorine is in the paper but if my viewpoint is here, that means it looks like chlorine is on my lefthand side; there's still an unwritten hydrogen there, so it would be on the right.

This is what cyclohexane looks like from the side – two newmann projections combined.

Chirality; the idea of what a stereocenter; R/S.

To start off the discussion, I've got a couple of simple models. Let me define an arbitrary color system – white, hydrogen; blue, fluorine; green, chlorine; red, bromine. I'm choosing simple substituents because we're going to be revisiting the Cahn-Ingold-Prelog rules, the first one of which is if you're trying to figure out which of a number of substituents is the most important one, you select the one that has the highest atomic number. Since these are just four different atoms, it's going to make it really easy to figure out the priority. Here are two different molecules that have those four substituents on them. What you'll find, if you orient these the right way, is that the molecules that I have are mirror images. Notice how the two chlorines are pointed up and the bromines are pointed out, which means, mirror image wise, the hydrogens and fluorines line up with each other. But this would be very much like if I took my two hands and held them up. They are, for the most part, mirror images. But now look what happens when I try to overlap any two of the substituents. If I take, for example, the hydrogen and the chlorine and I put them on top of each other. These two front ones, though, the fluorine and the bromine, wouldn't overlap. It means they're two distinct molecules. They are mirror images; they are extraordinarily similar, therefore. They would have nearly identical physical properties. Every physical property – melting point, boiling point, density, index of refraction – they'd all be the same – except for one: optical rotation.

This is of huge importance biologically. For example, enzymes work because whatever molecules happen to fit into the sites that are available on that enzyme. If you have one version versus the other, their shapes may not match. For example, in nature, all of the sugars have mirror-image forms, but in most life on the planet, only one of the two forms ends up getting metabolized. Similarly for amino acids: out of all of the critters on the planet, generally there's only one form of amino acid, one of the two mirror images, that ends up being biologically active. As a medicinal example, there was a drug called thalidomide that was used back in the 50's and 60's for morning sickness. Turned out that this drug, when it was produced, accidentally got produced in its mirror image forms: one form helped cure morning sickness, one form caused fetal deformations, a syndrome called flipper babies. It was just a matter of stereochemistry – mirror image molecules. It's not something trivial; it has real-life consequences – stereochemistry: the idea that you can have molecules that have exactly the same structure, but just different three-dimensional arrangement. That's actually one of the types of isomers we saw.

Stereoisomers are molecules with identical bond connectivity – they're identical in almost every way – but different spatial arrangement. Technically, different forms of a double bond could fall under this case, since that's what the cis and trans forms of the double bond are: same connectivity, just arranging them differently. We're going to focus on molecules that contain what are known as stereocenters. Stereocenters are asymmetric positions on a molecule that produce stereoisomers. What we're really dealing with is this idea of chirality. Chiral comes from the Greek work for "hand": just like if you have your left and your right hands, and you have your glove, your left hand is not going to be able to fit into your right glove. There's a handedness to these molecules. Chirality is, as an example, the fact that two molecules can have identical molecular structures, but be mirror images of each other. That goes with this idea of handedness: is it right-handed or left-handed?

They made unintentionally both forms and either didn't realize that one form was helpful, one form was harmful, or, in their separation process – one thing that we're going to learn is that with enantiomers, mirror-image molecules, because all of their properties are so similar, it can sometimes be difficult to isolate one versus the other.

Do all molecules have stereoisomers? No.

Let's see these simple examples. I've got the two different mirror image forms. I'll choose this one just to start out with randomly. Let's try to represent this on paper. For reasons that will become clear later, I'm going to choose to put the hydrogen in the back, facing away from the viewer, and I'll go ahead and put the fluorine and the bromine in the plane of the paper, so it'll look like this. This is going to make the chlorine come out front. We would have its mirror image molecule, but instead of looking at its mirror image and trying to write it down on paper, let's see if we could just use a little bit of logic. Imagine that we put a mirror plane and we just reflect everything that we see; we're going to make the mirror image doing that. Again, bromine will be pointed straight up, but since hydrogen was pointing to the right at first, in the mirror image, it'll be pointed left. Chlorine was right, now it's left. Fluorine was left, so now it's right.

It would be nice if we had some way we would be able to say that one of these is the left form and one of these was the right form, so if we were trying to communicate to someone else, we didn't have to do it by structure, we could just do it by name. That's where these priority rules are going to come back in, because we'll assign a priority to each substituent. According to that first rule, which substituent would get the highest priority? Bromine, because it has higher atomic number. What would be next? Chlorine, then fluorine, then hydrogen's going to be in back. Now what do we do? We look at which way the groups follow in priority – the one condition is that we have to visualize the system so that the least important group is in the back, which I've done already – that's why I chose to put hydrogen in the back.

For the molecule on the left, which way do the priorities of the groups appear to be following. If you go 1, 2, 3, which direction are they going? They're going clockwise. This is the form that we call R, meaning rectus or right. The other mirror image – should be the opposite if it's a mirror image, and yes it is, we can see that the priorities 1, 2, 3 go in the other direction. That is the S form of the molecule. These are known as the absolute configurations of the molecules. It's an arbitrary system, but it lets us clearly identify one as being left and one as being right.

If you had a flat molecule, that means a mirror plane already exists in it, so you can't have R and S. But, if it was a double bond, you could have E and Z, but that's a different kind of situation. This is going to be for tetrahedral types of structures. Would a lone pair count as one of these things? In some cases, yes, but I'd rather stay with regular, fully-bonded carbon today. Absolute configurations (R & S) – They are determined by orienting the lowest-priority functional group or substituent away from the viewer, then observing the relative order of the remaining substituents.

Let's see another example so we can talk a little bit more about R and S. What would the molecule name be if we didn't care about stereochemistry and we didn't care about the deuterium that's there? What would be the name of the two-carbon alcohol? Ethanol. You don't need a number, because there's one except to naming alcohols. Ethanol and methanol do not require position numbers, or locants. Since only one substitution pattern is possible, if I pick –OH group up and put it on a different carbon, it's still position one. Each atom would be position one automatically, there's no such thing as position two for the –OH group in ethanol; because of that, we just leave the number out.

Now let's figure out what would be the absolute configuration. What's the most important substituent? –OH. Why? Because it's got the higher atomic number. Which would be the next most-important? The methyl. Why? Carbon is there. Then? Rule 1 is highest atomic number takes priority, but rule 1a is that if you can't choose, go with the one with the highest mass number. What is a mass number? Number of protons plus number of neutrons. Deuterium has an extra neutron compared to hydrogen, so deuterium is priority number 3; then, hydrogen is number 4. If we circle the priorities of these groups, what does it look like? But it's not. The way this molecule is drawn, it appears to be in the S configuration, but that is because it is not being visualized correctly; the hydrogen must be oriented away from the viewer. This means I have to establish my visualization point under the molecule, so that I can look up at the hydrogen. If I'm sitting here looking up at the hydrogen, deuterium's back that way, but it's up at my top, then. The –OH group is on my right, kinda pointed down that way, and the methyl group is over here. So, –OH group is there, methyl group, deuterium – from my perspective looking up, which way am I really rotating? Clockwise. It's R. If you're having difficulty seeing that, rewrite the molecule. This is partly why we did rotomers, so we had that practice of moving groups around by just rotating a single bond.

What if we wanted the hydrogen in the back? Put it in the back. Flip it to where the –OH group is. Where do you want me to put the –OH group? Do you want me to switch it with the deuterium or the methyl group? If this is moving, one of these other positions have to give. You're going to hold on to one bond and just twist the molecule around. If the hydrogen goes where the –OH group is, the –OH group goes where the methyl group is, that means the methyl group has to come up to where the hydrogen is. Let me rewrite this. We originally had it like this, but I'm going to precess the groups – grab onto one, spin the others. When you spin, that means three of them automatically move. Any time you rotate three groups, you keep the same stereocenter. I now have priorities 1, 2, 3: it is R.

What if we didn't move the methyl? What if we moved the deuterium instead? Let's write that possibility. The hydrogen, we're still going to throw in back; the -OH group we're going to put where the deuterium was; that means the deuterium has to go where the hydrogen was, and the methyl group stays the same. But it's still priorities 1, 2, 3: it's still R. If you can't visualize, rewrite.

Now that we have the configuration, let's make the name. This molecule is (R) .... remember the order: stereodescriptors, locants, substituents, parent names, and generally after that, functional groups. Here's our stereodescriptor: it's R. We have a deuterium that's substituted at the 1 position. The name for deuterium is deutero. It's ethanol; remember we don't need the 1 for the -ol, cause for ethanol it's understood. Let's see another example so we can get some more practice at R and S.

First, let me draw this up and ask you a question. How many stereocenters does that molecule have? A carbon is usually a stereocenter if it has four unique substituents. If two [or more] substituents are the same, it's like you've got a mirror plane straight through the molecule, which means if I take two molecules which initially might appear to be different, just rotate them around, they're really the same. Any time a mirror plane goes through a molecule, where it can go through that position is not a stereocenter. Look back at the example and answer the question now: how many stereocenters are there on that molecule? Only one. I tried to trick you because I put the dash here, but you've got one methyl group then another, so there's really a mirror plane through that carbon, which means that carbon is not a stereocenter. You could put the methyl group as a wedge instead of a dash, and it'd have exactly the same structure. But over here, we have a deuterium, a hydrogen, an isobutyl, and a methyl – four different things, that means it is a stereocenter. The one on the right is not a stereocenter since two substituents are identical. The one on the left is a stereocenter since the substituents are all unique.

How many stereocenter are there on this next example molecule. Only one, right? Cause on the right side is the same trick with the methyl groups. This time I happened to use plain lines, but just because I used plain does not mean there is not a stereocenter. Sometimes we may not know the configuration or we don't care about the configuration, so for simplicity sake we just use plain lines. Wedges [or dashes] don't mean you have one, plain lines don't mean you don't have one. But since these are both methyl groups, this is not a stereocenter. The one place where we do have a butyl, an isopropyl, a hydrogen, and a chlorine – four different substituents, we have a stereocenter. Is this R or S? We stuck, because we know the first rule, which is that higher atomic number is higher priority. Between the isopropyl and the butyl, which one is more important? The isopropyl, because the second rule is this: if priority cannot be established at the first point of attachment, then you keep progressing along the molecule until you reach the first point of difference. If priority cannot be determined by the first point of attachment, it is determined by the first point of difference. At that stereocenter – by the way, sometimes the fact a stereocenter is there is designated by a star. Not in general, when you're just writing a molecule structure you wouldn't do it, but when you're discussing stereochemistry, to highlight it's there, sometimes you put a star in.

At that star, I have a carbon and a carbon that are connected. Since they're both carbons, I can't decide which one's more important. For each of these positions, I then find out what's attached to them. What's attached, other than the stereocenter we came from, to the carbon on the left? A carbon and two hydrogens. I list those in descending order. What's attached to the other position? Two carbons and a hydrogen. So, carbon versus carbon, that's the same. I move to the next position. Hydrogen versus carbon: carbon is more important than hydrogen. That makes isopropyl, the smaller substituent, more important than butyl. The size of the substituent does determine priority, it's by following these first point of difference rules. The isopropyl group is more important than the butyl group due to higher atomic number at the first point of difference. Now that we have that established, we can say the chlorine is priority one; the isopropyl is priority two; the butyl is priority three; don't forget the hydrogen, which is priority four. It is written in the back, though, so we can read this directly. Is this R or S? It's S. It's 1, 2, 3 going in a counterclockwise direction, meaning that's the S configuration. We're doing it correctly because hydrogen's in back. What would the rest of the name be? 3-chloro-2-methylheptane. If you look at the molecule again, ignore the stereochemistry, make it flat, it doesn't matter which way you go, the longest chain is seven carbons. The center of the chain is numbered one, so the methyl group occurs at 2, and the chloro group occurs at 3. It is S, which we throw at the front of the name.

Our final example for today: how many stereocenters? Two. Left one: R or S? It is R. How do we determine that? If we look at the stereocenter itself and go to the next position out, those are both carbons. Since they're both carbons, we can't decide at that position which one's more important, so we have to see what's attached. On the left carbon, we have [C, H, H] attached, on the right carbon, we have [C, H, H] attached. Since all of those match, we still can't make the decision, so what's the rule say? Keep on going until you find the first point of difference. So, you follow the most important substituent on both of those chains, the one that has the carbon, and you see what is attached at the next position out. On the left, it's [H, H, H], and on the right, it's [O, C, H]. Since the oxygen on the right takes priority over the one on the left that's just hydrogen, the more complex group with the oxygen gets higher priority. It's not just cause it has an oxygen. If we put the oxygen one more position away, then maybe the priority wouldn't change (not in this example, but otherwise). That's because at the first point of difference, there is an oxygen there, and that's what makes the righthand group more important. Oxygen is automatically number one; the more complex group is number two; the simpler groups is number three; remember there's a hydrogen and it's pointed towards us. Since it's pointed towards us, instead of rewriting it, why not flip the answer that we see? This appears to be S, but because it's pointed towards us, we know it's R.

That's a quick trick that's perfectly legitimate to use, since sometimes rewriting and visualizing a molecule takes a while. Since H is in front, visualize the stereocenter as is, then invert the answer. Since it appears S, it's really R.

The other stereocenter is easier to determine. What is it's configuration? R. Oxygen is more important. We have a carbon and a carbon, but the methyl group has nothing else, the other one has something attached, so automatically it's more important. This time, the hydrogen is in back, the way it's supposed to be. If we look at which way the groups are rotating, it's clockwise, and so it is R. How do we name this molecule? Before, the Rs and Ss didn't have numbers, because if you only have one stereocenter that you need to name, you automatically know where that name is referring to, so you leave the number out. Since we have two stereocenters, even though they happen to have the same configuration, you're still going to tell where each one is. That means I'm going to put (2R, 4R). Why 2 and 4? Because one of the -OH groups is closer to one side than the other of the molecule, so we have stereocenters at the 2 and 4 positions. We have no substituents, so we'll name that it's got six carbons. It's a diol, so I'll put an e in. Since it's got more than two carbons and it's got functional groups, I've got to say where they are located - 2,4-diol. The other way you could write this is (2R, 4R)-2,4-hexanediol - put the numbers out in front. Number of carbons comes before functional group endings. Think of an alkene like butene: the ene comes after the but. If you had two double bonds like this, this would be buta-1,3-diene.

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Exam #1 - bonding & antibonding; sigma and pi bonds, SMOGs;  
nomenclature - alkanes, haloalkanes, alcohols, no alkenes; common substituent name  
functional groups - all  
rotomers - Newman projections; steric hinderance, term (syn, anti, gauche, staggered, eclipsed), energy diagram  
cyclic compounds - angle strain  
cyclohexane - chair & boat; axial vs equatorial; cis & trans

chirality; stereocenter; R & S  
white - hydrogen; blue - fluorine; green - chlorine; red - bromine  
stereoisomers - molecules with identical bond connectivity but different spatial arrangement  
stereocenters - asymmetric positions on a molecule that produce stereoisomers  
chirality - the fact that two molecules can have identical molecular structures but be mirror images of each other - handedness

Absolute configurations - R & S - determined by orienting the lowest priority substituent away from the viewer then observing the relative order of the remaining substituents

Ethanol and methanol do not require locants (position numbers) since only one substitution pattern is possible.

1) highest Z (atomic #) takes priority

1a) highest mass # takes priority

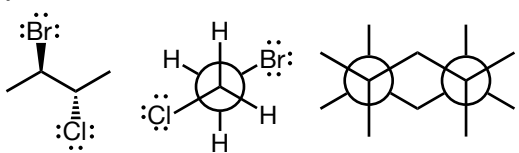
The way the molecule is drawn, it appears to be in the S configuration, but that is because it is not being visualized correct. The H must be oriented away from the viewer.

A carbon is usually a stereocenter if it has four unique substituents.

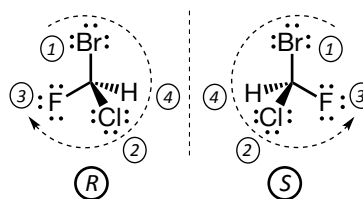
2) if priority cannot be determined by the first point of attachment, it is determined by the first point of difference.

Structures

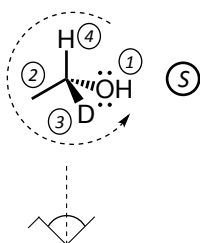
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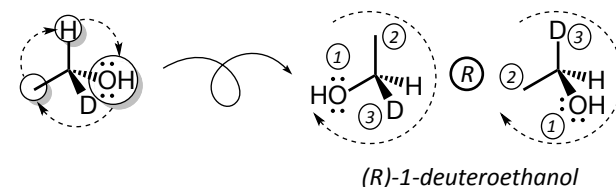
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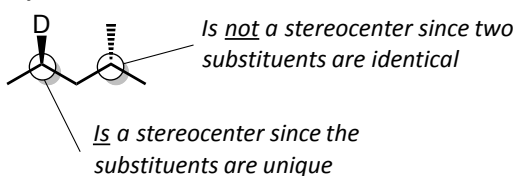
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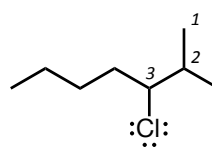
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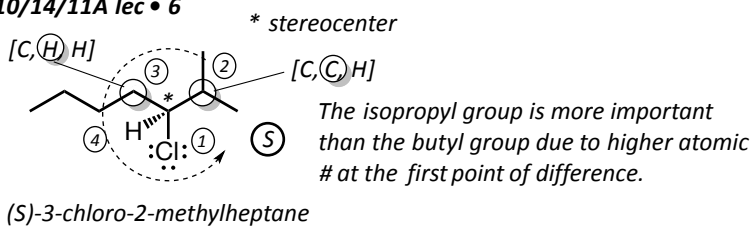
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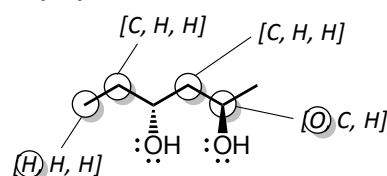
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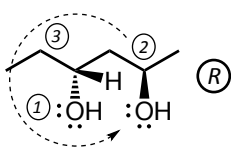
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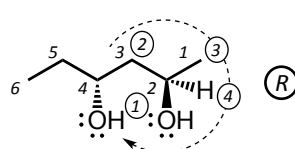


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Since H is in front, visualize the stereocenter as is, then invert the answer: appears S, really R

10/14/11A lec • 10



(2R, 4R)-hexane-2,4-diol