Lecture 9B • 10/14/11

{review for exam}
bonding, antibonding; sigma and pi bonds; SMOGs; sp3, sp2, sp; single bonds, double bonds, triple bonds; positively-charged carbon, negatively-charged carbon; nomenclature – alkanes, haloalkanes, alcohols, no alkenes; common names of substituents; functional groups; rotomers – butane; steric hinderance; Newmann projections; rotomer energy diagram; staggered, eclipsed, gauche, syn, anti; cyclic compounds, angle strain, cyclohexane – chair, boat, axial, equatorial; steric hinderance; cis an trans; vicinal and geminal.

chirality, stereocenters, R/S

Here I have two molecules – two substituted methanes. We can call the colors different atoms if we want to, but lets say that we have fluorine, chlorine, bromine, and hydrogen. With four substituents on a simple tetrahedral geometry, we end up with two possible situations. Notice that these two molecules are mirror images of each other. If I try to take two of the atoms and overlap them with each other (white and red), we'll see that the two other atoms (blue and green) are not able to overlap with each other. These are non-superimposable mirror-image molecules. This means that they have the same chemical formula and the same essential structure – the same bond formation, just arranged differently in space. They are two distinct compounds. Their physical properties, in this case, because they are mirror images, are all identical, expect for one property – optical rotation.

Why is this so frightfully important? Because shape and form are extremely important biologically. Enzymes, for example, only react with certain molecules that are able to fit into the cavity of an enzyme. Having one form of a molecule versus another means that one might fit that shape and one might not. All sugars, for example, occur in mirror-image forms, but biologically, most critters on the planet only metabolize one of the two forms, and in all life, it is the same form. Similarly, amino acids, there's only one form of amino acids – where there are mirror images possible – that's generally incorporated biologically. A classic example of a medication – thalidomide, which was used as a morning sickness drug. At some point, it was determined that it was causing fetal deformations, a syndrome known as flipper babies. They found out that one form of the molecule was beneficial, it did have that morning sickness curative property; the other mirror image form was the one causing fetal deformations. It was just a matter of one mirror image or the other. There's a practical importance to stereochemistry – the idea that you can have these different three-dimensional configurations. So, it is extremely important when we are learning reactions that we understand how could stereochemistry change during a chemical reaction.

Before we can talk about how it's changing, we need to talk about how it's represented. That's what we're going to focus on today.

That's what chirality is – chirality means handedness, comes from a Greek word meaning hand. Chirality is the fact that two molecules can have identical molecular structure but be mirror images of each other. Sometimes, chirality is called handedness. Just like your left and right hands, they're mirror images – for the most part, yes, maybe your thumbprints are slightly different – so your left handed glove won't fit on your right hand, and vice versa – again this idea of chirality.

Let's draw some example molecules and talk about this structural arrangement. [Color assignment: white, hydrogen; blue, fluorine; green, chlorine; red, bromine] Why am I choosing these atoms for my example? They're the simplest substituents we can have. We've seen a brief introduction to the Cahn-Ingold-Prelog priority rules. What was the first one of those rules? If we had to choose between substituents and say: this one's more important than that one, how do we do that? Higher atomic number. Bromine is higher atomic number than chlorine, which is higher atomic number than fluorine, which is higher atomic number than hydrogen – that's why this is going to be one of the simplest possible organic molecules. Let me take arbitrarily one of these models and let's try to write it down on paper. Our perspective can be anything that we want it do – that's what I mean by arbitrary: I'm just going to decide that let's put the hydrogen in back, where the dash is. The way I'm holding it now, bromine will be pointed out towards you in front, chlorine will be straight up and down in the paper, and fluorine is also going to be in the plane of the paper. Exactly the way that I'm holding this now is exactly the way I'm going to represent this on paper – bromine in front, chlorine up top, fluorine on the right, and then hydrogen in the back.

Let's write it's mirror image. Before I pick the other molecule up and try to visualize it, let's think of ways that we could just create the mirror image on paper. One way that it could be done is to just image that you've got a mirror here and then draw what you see reflected. So on the left, if the fluorine was pointed left, on this other image, we'll point it off to the right. Bromine was pointing right, so we'll have it pointed off to the left. These molecules are known as enantiomers. What would be a good definition for stereoisomers. Same structure, same connectivity, everything's the same, except different orientations, different 3D arrangements. Stereoisomers are molecules with identical molecular structure, identical bond connectivity, but different spatial arrangement. Enantiomers are a subclass of stereoisomers – they are molecules that are specifically mirror images of each other.

If we have two different forms, it would be really useful if we could put a label on each form, so that we could clearly communicate which arrangement that we're trying to talk about. This is where another used of the Cahn-Ingold-Prelog priority rules comes in. In fact, this is more the origin of these rules, tackling these different kinds of compounds. If we use these rule, the first rule, which is atomic number takes priority, then let's assign priority patterns to the different substituents. Bromine's most important, so it'd be priority number one; chlorine is second most important, priority two; fluorine is less important, priority three; and then hydrogen is least important. Here's how the system works: when you have a tetrahedral center like this, you visualize or you write the molecule in such a way that the lowest-priority functional group is pointed away from you. That's why, in this example, I chose to put hydrogen in the back – makes an easy first example. Then you look at the arrangement of priorities of the remaining functional groups, the remaining substituents. If, as on the molecule on the left, you go 1, 2, 3 in a counterclockwise direction, that is known as the S form, the S configuration, from sinistrus which means left. The other form, you see the progression of functional groups 1, 2, 3, it's in a clockwise fashion. It's called R for rectus, which means right. These are the R and S configurations of this stereocenter. A stereocenter is a position on the molecule in which stereoisomerization is possible.

What do I mean by that? What if we had two simple substituted methanes8, but let's say each on only has two different substituents on it. On this molecule we have two hydrogens and two other groups, of any kind of group. If you have two substituents on each molecule that are identical, the it's possible always to overlap these two molecules, which means they're not mirror images of each other, any more, they are the same molecule. This molecule, no matter what these two substituents are, at least if we're focusing on this position, it could not exist as stereoisomers. So it's not true that every molecule will have stereoisomer; you have to have an asymmetric carbon, which for a tetrahedral center means that you have to normally have four different substituents attached. A stereocenter is an asymmetric position on a molecule that produces stereoisomers. I defined it this way because technically the carbons in a double bond are asymmetric centers as well, because if you have groups oriented one way versus the other, you could have cis or trans forms (or E or Z). Those are also a form of stereoisomer. A stereocenter, though, is what we're going to refer to in this phenomenon: in tetrahedral geometry, you're going to have two different arrangements.

Can a lone pair count as one of the positions? Yes, in certain situations.

Let's see some examples, then, of determining R and S. Let me start with a simpler one. Ignoring the D that's in front, what would the name of this molecule be, ignoring its configuration? How many carbons are in this molecule? Two. You have a plain line here; that means that the end of the line is a carbon, the beginning of the line is a carbon as well. A two-carbon molecule that has an alcohol functionality: what would the name of the molecule be? Ethanol. The reason I bring this up is I originally told you to always put in a locant to say where the alcohol is located. There is one exception to that, which is for ethanol and methanol, there is only one possible place the –OH group can go; therefore, if you're naming ethanol, you do not have to put in numbers. Ethanol and methanol do require locants (position numbers), since only one substitution pattern is possible. This is a form of ethanol that does have deuterium on it. That deuterium would have the substituent name of deutero.

Coming back to the real question to focus on: is this R or S? Can we simply determine its configuration, simply by looking at what the different substituents are? Let's prioritize the substituents first. Which would be the most important group. Why the –OH? Because it has the highest atomic number of anything attached to the stereocenter. What would be the second-highest priority? The methyl group. Why? Because it's got a carbon. We don't care about the hydrogens attached, because the way the priority rules work, you look at the very first thing that's attached, so we're comparing the oxygen and the carbon, not the fact that there's hydrogens on the oxygen and hydrogens on the carbon. If we do have two of the same atom, two carbons attached, then we go to the next position, which we'll see an example of shortly. Carbon would be the second most important atom. If rule one is that atomic number takes precedence, then rule 1a is that higher mass number takes precedence. Hydrogen and deuterium, they both have atomic number one. But, deuterium has a higher mass number, so it receives the higher priority, which mean that the hydrogen is priority 4.

If we were to look at this the way it is written, and try to figure out its priority order, we would look and say, 1, 2, 3, so looks like it's counterclockwise, which would be S. But it's not. Why? Because we're not visualizing this properly. To practice a bit of visualization: the rule says that you must be observing so that the last important group is pointed away from you. Now I have to imagine that I'm underneath the molecule looking up a the hydrogen. Where is the priority one functional group relative to my viewpoint? It would be to my back an to my left, the way I am standing right now. Priority number two would be in the plane of the paper, so it would be my right; group number three would be the deuterium that's up here on top. If I was to look from that perspective, here's 1, 2, 3, which way I am really rotating? Clockwise. That can be a bit tricky to visualize like that. If you can't see from the paper that this is R, that's the point of the model sets. Or, the other trick, rewrite the molecule, just like we did with rotomers, where on purpose, we were turing by 60°. What could we do to put the hydrogen in back? Put it where the –OH is. If I put it where the –OH is, where's it going to have to go; where's the D therefore going to have to go? Where the hydrogen is. This is a precession of functional groups, a pinwheel, you could say, where you're just spinning around and making a new rotomer, that's all I'm going to do.

Let's say I did exactly that. The hydrogen that I want in back I've put in back. But that means that I rotated it towards the –OH group, which means the –OH group is going to go towards where the deuterium was. The deuterium is therefore going to go where they hydrogen was. I know have my most important group, the –OH group, then the methyl, then the deuterium, and this is twisting to the right, so it is R.

If I move the hydrogen to the –OH, I could move the –OH to either the deuterium or the methyl group; it's arbitrary. I could hold this bond stable and rotate those three groups. Whichever of the ones I choose – in this case I chose the deuterium – that has to be where the –OH goes, because it's therefore going to be the deuterium that moves to the hydrogen. In other words, I could have done this representation as well: put the –OH group where the methyl group was, put the methyl group up top, and leave the deuterium alone. We would still end up with priorities 1, 2, 3, so it would still be R.

Let me go back to the original way that I wrote it so that I could make this cautionary note. With priorities 1, 2, 3, the way it's drawn, it might appear to be S, but that's because it's not being visualized correctly. The hydrogen must be in back.

Since we now have the configuration, let's name the molecule. There are five things that went into a name: stereodescriptors, locants, substituents, the main compound, then functional group endings. We have a sterodescriptor. This is a molecule in the R configuration. We have a deuterium substituent that is on the same carbon as the most important thing on the molecule, the alcohol. That alcohol position gets the position one, therefore. This is 1-deutero.... It's going to have ethan, part of ethane in it, cause that's the parent two-carbon compound, and because it's ethanol, it's an exception, so it doesn't need a number to say where the ol is, so we just throw it in. (R)-1-deuteroethanol.

Any three groups you can rotate, any three. We pick the way that puts the hydrogen in the back to make it easier to visualize. That's why we only really had a couple of choices what to do to benefit us. But, and three groups could rotate, because that would just be rotation about a single bond.

Let's look at one more complicated case. How many stereocenters does this molecule have? Before you answer that question, how many stereocenters does the molecules I just drew have? How many places does it look like I'm trying to get you to say that there's stereocenters? It looks like two, because there's two places with wedges, so there's two places where I'm highlight the three-dimensionality of the molecule. Is the position on the left a stereocenter? What have you got? You've a deuterium, and you've got two different carbons. The problem you're having is what do we do about the different carbons. They're non-equivalent groups, so not even worrying about which one is more important than the other, you could say that's a methyl group, that's an isobutyl group, so they're different from each other; there's four things attached since you've got hydrogen in the back, so that is a stereocenter on the left. But the one on the right, you've got a methyl group and a methyl group – they're both the same substituent. Because they're both the same substituent, that means there is effectively a mirror plane that goes through that carbon. Because of that, you can't make another version of it that is different. You can rotate it around in space, but if you pick the methyl group up and swapped it with a hydrogen, it would not change its configuration, because it doesn't have one. So that molecule only has one stereocenter.

So after that example, we'll come back to the one that's on the left. Just one, because all of the other places on the molecule have enough hydrogens that the hydrogens themselves are identical, so they're not stereocenters, or on the righthand side, it's the same situation. I tried to trick you with the molecule on the right because I wrote it with a wedge, but that would be correct if I was visualizing that half of the molecule. The methyl group would have to be either towards you or away from you if it's a tetrahedral center. But it is misleading; you just have to know that since it's got two of the same substituent, it's not a stereocenter. The molecule on the left, I've shown flat, which does not mean there isn't a stereocenter. There may be times where we don't know the configuration, or we don't care, so we might write a molecule flat even though it has stereoisomers possible. There is only one place here, where we have an isopropyl, a butyl, and a chloro, and a hydrogen – four different things attached. Sometimes, when learning stereochemistry, you'll see structures annotated with asterixes. That asterix is indicating where there are stereocenters.

If we weren't concerned about the stereocenter, how would we name this compound? 3-chloro-2-methylheptane. 7 carbons in the longest chain; two different ways you could write the chain, but they produce the same compound, so it doesn't matter which way you make the chain. The numbering is the lowest from the righthand side. Chloro would be at carbon number three; methyl at carbon number two. The c in chloro goes before the m in methyl. 3-chloro-2-methylheptane. Which is this, R or S? You might get stuck, because the rule is, higher atomic number takes priority. But we have carbon and carbon substituted, so how do we decide which one's more important. You might be tempted to say, the group on the left is bigger, it's got four carbons. Then we have to go to the second rule: if you cannot determine priority where you first substitute something, look at the next position out. There is a systematic way to do it. If I look at what's attached on that righthand substituent, on that carbon we have [C, C, H]. Notice that I've arrange those in order of priority within that atom. On the left, what do I have attached to the carbon that's here, so [C, H, H]. We compare each atom in a row like that, so carbon versus carbon, there's no different. Carbon versus hydrogen, there's a difference. Another way of expressing the second rule is the first point of difference rule, where you walk along the molecule and the first point where something's different than the other, that's where the decision about the importance is made.

Again, over here, because I had two carbons attached, versus over here I only had one carbon attached, the one with two carbons is more important. This groups is more important because it has a higher atomic number at the first point of difference.

Chlorine is number one priority because it wins out over either of the carbons; the isopropyl group has priority two; the butyl group is priority three; don't forget that there's technically a hydrogen in back that's number four. Since it's in back, we can go ahead and visualize it; it is S. The full name of this molecule would be (S)-3-chloro-2-methylheptane.

Let me show you one last example for today. How many stereocenters? 2. Left stereocenter, right stereocenter: what are the configurations? We're still going to need the first point of difference rule, because for the left stereocenter I have a carbon and I have a carbon attached. Let's see what I have attached to those positions. Attached to the left position, I have a methyl group, which means I have [C, H, H] attached to the carbon itself. On the right, I have this more complex group, but the first thing I run into is just [C, H, H]. Those have the same set of substitution patterns, so I can't make the decision, even at that next point out. So what do I do? I follow the most important group, one more step out; I look at what else is attached here. At the left end, all it has attached are hydrogens; on the right, it has an oxygen, a carbon, and a hydrogen attached. Oxygen is more important than hydrogen; the group on the right is most important. So, if I rewrite the molecule to show what's around just that first stereocenter, oxygen, most important, the group with the oxygen is second most important, the ethyl is third, and the unwritten hydrogen is fourth. Because the hydrogen is in front, instead of rewriting it, since it's in front, just flip whatever answer you see. Since hydrogen is in front, visualize the stereocenter as is, then invert the answer. It appears S, because it looks like it's going counterclockwise, which means it's really R.

The right stereocenter, we don't have as difficult a choice: we have an oxygen, a carbon chain that's complex, and just a plain old methyl group. On that other position, they oxygen is most important; the complex group is second; the methyl group is third; they hydrogen is unwritten, it's fourth, but it's in back, so that position is also R. To name this, you have to name the positions of stereocenters if there's more than one of them. So, now I'm going to use numbers to say (2R, 4R). There are no substituents, just functional groups, so I'll name the number of carbons: hexane. I have two alcohols, 2,4-diol.

_____

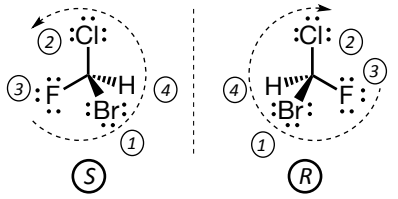
Exam #1 – bonding & antibonding; sigma and pi bonds, SMOGs;
nomenclature – alkanes, haloalkanes, alcohols, no alkenes; common substituent name
functional groups – all
rotomers – Newman projections; steric hinderance, term (syn, anti, gauche, staggered, eclipsed), energy diagram
cyclic compounds – angle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

chirality; stereocenter; R & S
white – hydrogen; blue – fluorine; green – chlorine; red – bromine
enantiomers – stereoisomers that are mirror images of each other
stereoiosmers – molecules with identical bond connectivity but different spatial arrangement
stereocenter – an asymmetric position 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

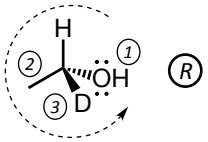
Ethanol and methanol do not require locants (position numbers) since only one substitution pattern is possible.

Structures *(remaining structures identical to lecture 9A)*

10/14/11B lec • 1



10/14/11B lec • 2



The way this molecule is drawn, it <u>appears</u> to be in the S configuration, but that is because it is not being visualized correctly. The hydrogen must be oriented in back.