

## Lab 12B • 11/10/11

### Chemical equivalency

We have this molecule 2-methylbutane. We talked about substituting one hydrogen with one halogen. The question came up: how many different kinds of products would we get. Another way of asking that question is: how many unique types of hydrogens are there? We already say that there are four products – ignoring stereochemistry; let me label the different hydrogens on here. We identified that there is a hydrogen on the tertiary carbon, hydrogen on the secondary, and then there were two different primaries. The methyl groups attached to the tertiary position, those we ended up saying were equivalent, because regardless of whether you replace one versus the other you got exactly the same compound out. Those two primary positions, though, were different from this other primary position; if we had substituted, we would end up with a unique compound. If you're looking at two different hydrogens and trying to determine whether or not they're exactly the same or not, if you look at the neighbors to those hydrogens and then the neighbors to that position, and then the neighbors to that position, and then you go across the entire molecule, and if from either of those two hydrogens you encounter exactly the same structure, then they have exactly the same neighbors, they're exactly in the same chemical environment. Why are we talking about this relative to NMR? Because, other than coincidentally two different hydrogens just happen to have the same chemical shift, in principle each different type of hydrogen is going to have its own unique NMR signal. That's why we worry about chemical equivalency; each type of hydrogen is going to have its own unique NMR signal. If the chemical environment around two atoms is identical, meaning that the two atoms have exactly the same neighbors throughout the structure of the molecule, those two atoms are called chemically equivalent. The reason this is important is because a unique NMR signal is generated for each type of chemically inequivalent atom.

Let's look at another relatively simple example molecule just to explore this idea of having similar neighbors. This will look much like the first example molecule that I gave you, where I've got again two methyl groups attached to a tertiary position, and I have that same structural motif on both sides of the molecule. But, would you say the two methyl groups on the lefthand side are chemically equivalent to the two groups on the righthand side? No; why not? Because even though this methyl group is attached to a tertiary position, which is the same as the bottom methyl group, so we could say that these two are the same as each other, and if you look over here you do again see two methyl groups attached to a tertiary position, but what's the next neighbor over? From the lefthand side, we have a position that itself is a tertiary carbon; from the righthand side we encounter a secondary position. It's not just that it's secondary versus tertiary, it's what are exactly the substituents at each one of those positions. If we were to move from left to right versus right to left, we would see two different structures, so the lefthand side and righthand side of the molecule are not equivalent to each other. Another way to say it is if you again think of the chlorination reaction that we learned. If we put chlorine on one of the methyl groups on the left, it would be a different product than putting the chlorine on the right. How many total different types of hydrogens – ignoring stereochemistry – do we have on this molecule? Seven: the two types of hydrogens on the left would be equivalent; they're joined to a common center, that tertiary hydrogen would be its own; next door, we have a different tertiary hydrogen; up above have another methyl group, different from the methyl groups we had initially; we have this one secondary position that's unique; we have this last tertiary position; and then since they're both hooked to the same point, the two methyl groups next door are the same as each other. We've got seven different types of hydrogens.

Let's look at stereochemistry, cause it does turn out that stereochemistry matters. Let's take, for example, butan-2-ol. How many unique types of hydrogens do you think exist on this molecule? 3? 4? 5? Would you say that the lefthand side and the righthand side of the molecule are equivalent to each other? No, because the lefthand side is only one position away from the –OH group; the righthand side is two positions away, so even though they're primaries, it doesn't matter; they're different from each other. Here's one type of hydrogen; here's a second type of hydrogen. Please note that for all of these that I've labeled so far, there may be more than one hydrogen on that position, but so far, I have not differentiated between the different hydrogens located at one position. What about the hydrogen on the oxygen itself? That counts. It may be on oxygen, but it is a hydrogen, so it's going to be its own unique type. We then have the secondary position, so a fourth. Realize that where the alcohol is, there is one more hydrogen there, so we could identify five different hydrogens. But there aren't five, there's six, because the two at this position are not equivalent to each other. In order to understand why, let me draw a rotamer of this molecule. The bond between where the alcohol is and the secondary carbon, I'm going to rotate around that bond. I'll leave off the labels for most of the hydrogens, but I'll specifically draw two of them: the ones next door to where the alcohol group is.

Now, upon seeing this molecule, can you think of any rational explanation for why the two hydrogens on that secondary center might not be the same as each other? It's not steric hindrance; in terms of NMR, what's going to be more important? The electron-withdrawing effect of that oxygen. You have one hydrogen that's pointed the same direction that the oxygen is, which means, to a small degree, it's going to be closer to that oxygen. You then have another hydrogen that's on the same carbon, so it's still near the oxygen, so it's still definitely going to have that inductive effect, but it's pointed the opposite way of that oxygen. Since you have those two slightly different interactions, that means that they're two different hydrogens.

If we didn't have that stereocenter there, then you'd have equal interaction between the two hydrogens, but we do have the stereocenter, so it's different. So we have the interaction of where they're on the same side as each other, versus having them on opposite sides from each other. The interactions between the two indicated hydrogens with the -OH group are different, since the two hydrogens are slightly different distances from the -OH group; therefore, the hydrogens are chemically inequivalent. If it rotates, it's still going to have one hydrogen closer than the other. Yes, that amount of interaction changes as it spins, but it's still asymmetric, the interaction.

In this particular case, the term that's used to describe this phenomenon .... to explain where the term comes from, let me show you this first. If we took the original alcohol and if we introduced some new group at that secondary position. Don't worry at all about what this chemical reaction might be, because this is not saying a chemical reaction is going on; what we're really trying to grapple with is a geometric issue. The fact that if you replaced one or the other of the hydrogens at that position with some other functional group that you would generate diastereomers, then this relationship, this effect here, this type of hydrogens, are called diastereotopic hydrogens. If, by replacing one hydrogen versus another with an arbitrary functional group diastereomers are generated, the hydrogens are known as diastereotopic. When we have hydrogens of that sort, they're going to be chemically inequivalent to each other, not matter what might be surrounding them. Diastereotopic protons are always chemically inequivalent. It may happen that the difference in interaction may not be that much, so there will be times where maybe we won't see two different hydrogens. However, alcohols, since that oxygen is very electron withdrawing, usually do have this very pronounced effect of making the two hydrogens not equivalent to each other.

If we had this term diastereotopic, it might be logical to wonder is there such a thing as enantiotopic protons – meaning, if you replace one versus another proton, if you make enantiomers, would that have any effect on chemical equivalency? Let's take a look at that. First, let's define that stereochemical relationship. We'll use the molecule butane. I've got this term "magic" in there trying to say we don't care what kind of reaction, because there isn't a reaction going on; we care stereochemically about the fact that if we replaced one hydrogen or another at one of these secondary positions, we could generate a set of enantiomers. If, by replacing one hydrogen versus another with an arbitrary functional group enantiomers are formed, they hydrogens are known as enantiotopic.

You do not have to have chirality to end up with a chiral molecule.

Let's take butane; I'll show two of its hydrogens. Let's say that it's in a solution with a chiral solvent. Let's say we had a snapshot in time where this exact interaction, the way that I've drawn it, is occurring. The hydrogen that I've drawn with a wedge would be closer to the -OH group; the hydrogen I've drawn with a dash would be closer to the hydrogen – on a different molecule. Of course, as soon as that molecule moved away, that interaction would disappear. For anything that's achiral, there would be no difference as far as it interacting with the front and back; but if we do put in a chiral material, then that difference occurs. That means that if you have an achiral solvent, enantiotopic protons are going to be chemically equivalent, but if you have a chiral solvent that you put it in, then enantiotopic protons will be chemically inequivalent. That means that the number of signals that are going to be generated depends on which NMR solvent that you use. It's quite the exception, not the rule, that you would use chiral NMR solvents. Generally, we're going to classify enantiotopic protons as equivalent, but quite technically, put them into a chiral environment and they become different from each other. [separation of enantiomers] What could be done is to do something exactly like this where you take your enantiomer and not just have this kind of interaction but actually bind it somehow to another chiral molecule. If you associated two different stereocenters with each other, you've now made diastereomers, which do have different physical properties and can be separated. Enantiotopic protons are chemically equivalent in achiral environments but chemically inequivalent in chiral environments.

Let's go back to the last case. What if we have the same chiral alcohol, but look at the methyl group that is at the end of the molecule next to the stereocenter. Yes, one hydrogen versus another on that methyl group might have different interaction, but in this case, if you were to twist that methyl group around, each hydrogen would eventually have that same interaction. Another way of saying it is because we have three hydrogens on that methyl group, if you were to replace one of them with any arbitrary functional group, it would not generate a stereocenter, because you'd still have two hydrogens left. Because of that, no matter what you do, you would not be able to generate a different interaction. In the case of halogenation, for example, if you monohalogenated that methyl position, there would only be one product that would result. Hydrogens that like that that no matter which one you replace you get the same thing out again, those are called homotopic protons, meaning that they're exactly the same as each other. In this example, we're focusing on the methyl group. No matter which of the hydrogens at the end of this molecule [is] replaced, the exact same product would result; no new stereocenter is formed. Therefore, these hydrogens are always equivalent to each other; the term for that is homotopic. Homotopic protons are always chemically equivalent.

There's one last example for today that I want to give for chemical equivalency; that involves the molecule cyclohexane. How many different types of hydrogens do we have on cyclohexane? Two – axial versus equatorial. Axial, you would have diaxial interactions, which would make that slightly different than the equatorial position. But at room temperature, you would see only one signal. Why? Because of the ring flip, because of what's called the time scale issue.

This comes up in different forms of spectroscopy: if what you're trying to observe is fast than what the machine can measure, then you're not going to be able to observe whatever it is that you're trying to observe. In this case, we have two different hydrogens; they are definitely chemically inequivalent, but at room temperature, the rate at which this structure inverts, the rate at which this ring flip occurs is fast enough that the signal generated ends up getting averaged out. If I drew some just quickie little spectra, where chemical shift of zero is on the right, chemical shift increases to the left, intensity's my y-axis, and let's say I was at room temperature, I'd only get one NMR signal. As I cooled this off, went to 0 °C then -50 °C, -100 °C, as you cool off, you'll slow down a little bit, so maybe at first the peak, instead of being nice and sharp, will start to broaden. Cool it off even further, you'll start to see that peak resolve into two. Cool it off enough, where there is no longer any kind of ring flip, and those two signals will finally separate from each other. So cold enough, no ring flip, you see the two of them. Too warm, the ring flip's too rapid, the machine's not able to scan that, averages out to one signal. Cool it off to where there's not enough thermal energy that you could overcome the barrier for rotation – because really a ring flip is just a series of rotomers – so cool off enough, we don't really have the energy for rotation around a bond, you won't change equatorial and axial, you'll get the two signals. At room temperature, ring flips occur rapidly enough that the signals of the two types of hydrogens become averaged together. Far below room temperature, ring flips no longer occur, so the two types of hydrogens can be distinguished. It's not that at room temperature that the hydrogens become equivalent, we just are unable to tell that they're not equivalent, and you'll only see it at below room temperature.

[integrals] It's actually not the height that matters, it's the area under the curve. Generally, if you have two hydrogens that are really similar to each other, their heights themselves will be the same, but it's actually the area under the curve that matters and, for proton NMR, if you do it correctly, there's a linear relationship between area and number of hydrogens. We're going to come across this term integral, [one application of which is] to find the area under a curve. The more hydrogens that you have, the more signal that you're going to generate, so the large area under the curve. We can make a linear correspondence between area, as detected, and the number of hydrogens.

---

#### Chemical equivalency

If the chemical environment around two atoms is identical – meaning that the two atoms have exactly the same neighbors through[out] the structure of a molecule – those atoms are called chemically equivalent. A unique NMR signal is generated for each unique (chemically inequivalent) type of atom.

The interactions between the two indicated hydrogens with the OH group are different, since the two hydrogens are slightly different distances from the OH group. ∴ The hydrogens are chemically inequivalent.

If, by replacing one hydrogen versus another with an arbitrary functional group, diastereomers are generated, the hydrogens are known as diastereotopic. Diastereotopic protons are always chemically inequivalent.

If, by replacing one hydrogen versus another with an arbitrary group, enantiomers are formed, the hydrogens are known as enantiotopic. Enantiotopic protons are chemically equivalent in achiral environments, but chemically inequivalent in chiral environments.

No matter which of the hydrogens at the end of this molecule are replaced, the exact same product would result (no stereocenter is formed). Therefore these hydrogens are entirely equivalent → homotopic. Homotopic protons are always chemically equivalent.

@ RT, ring flips occur rapidly enough that the signal of the two types [of] hydrogens become averaged together. Far below RT, ring flips no longer occur, so the two types of hydrogens can be distinguished.

---

#### Structures

Identical to those from lecture 12A (11/09/11)