

Lab 14A • 03/14/12

[Acylation][reactivity of aluminum trichloride][hella][decomposition of AlCl_3 in water][lab directions – order of addition][need trace of water]
[xylene an activator][lack of byproducts since multiple acylation unlikely][acid goes into water][acylation volcano]

NMR

$\text{C}_4\text{H}_{10}\text{O}$: 3.337, s, 3H; 3.336, t, 2H; 1.59, tq, 2H; 0.93, t, 3H

How many degrees of unsaturation? Zero degrees of unsaturation. There's going to be multiple angles that I work this problem from, so there's different tricks I'm trying to show you. A lot of the tricks end up being combined together in this problem. I'll call the first method a combination of degree of unsaturation and integration. Yes, the degree of unsaturation is zero, which means that it must be an alcohol or an ether.

I want to discuss a little bit about alcohols. There's some other pieces of information that'll be useful for solving problems with alcohols. What happens if you add D_2O to an NMR sample containing an alcohol? The proton attached to an oxygen in an alcohol has a chemical shift of [what is the correct range?]. Why is it that an alcohol can have such a broad range of chemical shifts? We might wonder if there's different interactions that occur with solvents. What is special about that alcohol that would make it more susceptible to that behavior? Why do alcohols have high boiling points? Hydrogen bonding. That's a very pronounced form of dipole-dipole interaction. If you're having hydrogen bonding going on between molecules, though, depending on the exact structure of the molecule, that's going to determine how much hydrogen bonding is going on. If there's any variation in that hydrogen bonding, that's going to change exactly how much electron withdrawing is going on on the carbon the oxygen's attached to, or the hydrogen that is on that oxygen, so that's going to change the chemical shift.

It also is related to the fact that, at room temperature at least, protons undergo very rapid exchange in solution. Alcohols are compounds with pK_a s of 16 through 18, which means they're not terribly acidic, but they have some acidic character. Anytime you have something that's acidic, that means there's an equilibrium between it and its conjugate form. In solution, although it's not favorable for it to be dissociated permanently, rapid association-dissociation of a proton occurs. That has two important consequences: one of them is this D_2O trick. At room temperature, alcohols undergo rapid proton exchange – hops on and off over and over and over again. If you were to add D_2O – a drop, yes, but realize that most NMR samples only have a very small portion of the compound you're looking for in the middle of this solution – if you add sufficient D_2O and there's this constant exchange thing that goes on, statistically you could just outnumber the hydrogens and force the alcohol to become a deuterated equivalent. If D_2O is added to a sample, deuterium exchange can occur, which, if sufficient D_2O is added, can convert an alcohol to its deuterated analog. Deuterium and [protium], even though they're related chemically, they're not related nuclearly – they're two different nuclei, so they're going to be scanned at two very different frequencies. If you're doing proton NMR and you looking for protons, you're not going to see deuteria. What that means is if you had an alcohol peak and then you put D_2O in, it's going to disappear. If you have a compound that you don't know what it is and you add D_2O and a peak disappears, that's strong evidence you have an alcohol and which specific peak corresponds to that alcohol. It's a useful diagnostic trick. Since hydrogen and deuterium are different nuclei – which means they have different magnetogyric constants, which means how much does the spin get spun by being put in a magnetic field, that's what determines the frequency of absorption that occurs – they absorb NMR radiation at different frequencies. When conducting proton NMR, the alcohol peak after exchange disappears.

But there's another consequence as well, that has to deal with what's called the time scale – how quickly does an observation occur, because it's not instantaneous. The sample is bombarded by EM radiation, it absorbs that radiation, there's some delay while that sample decays and the signal is monitored. If, during that acquisition of the signal, proton exchange is going on super rapidly, then splitting won't occur – at least, observable splitting won't occur, cause for splitting to occur, you have to have one neighbor interacting with another. If this neighbor's too busy hopping off and on the whole time, maybe it'll get detected, but you won't see the splitting. That can make a problem complicated, because if you look at an alcohol, the hydrogen on an alcohol, versus a hydrogen on the neighboring carbon (if this is not a tertiary alcohol), those are close enough to each other that they can split. If you're expecting to see splitting, but you don't, that can make a problem a little tough to work. At room temperature, proton exchange is rapid enough that splitting between an alcohol proton and its neighbors will not be observed.

Degree of unsaturation of zero means it's an alcohol or ether. Why an ether? We could make a chemical shift argument, [but] that alcohol peak could have such a wide range that we can't conclusively make the statement off of just chemical shift. You're normally right, but why else. How do I know from integration alone this is not an alcohol? There's only one oxygen, so if it was an alcohol, and all alcohols have one proton only on that oxygen, so if have an alcohol and it's only be a monool, we need an integration of one. There is no integration of one, so it's an ether. An alcohol has to have one hydrogen but only one hydrogen. If we had two alcohols, then we could have a compound that easily integrates to two – ethylene glycol, for example, would have an integration of two on its alcohol protons.

But, we could only have one alcohol, because of the formula we have. Since we don't have an integration of one, we don't have an alcohol. Since there's only one oxygen and no peak integrates to one, the compound is an ether.

There turns out to be only three structures possible. With four carbons and it being an ether, here are the only three possibilities. [From the degree of unsaturation], it must be an alcohol or an ether, and there can't be any rings; it's not a cyclic compound, because cyclization counts as a degree of unsaturation. The first one, what is one of the integration that it's going to have that will prove that it's not the compound described by that spectrum? We have symmetry; we have to methyl groups attached to the same position, which means that these both are going to integrate to six. We have no [integration of] six in this compound, so it's not that compound. Look at diethyl ether – same thing, it's a symmetric molecule. The methyl groups are not attached to the same position, but the whole molecule's symmetric, so they're still equivalent. That means that they're going to integrate to six as well. Without looking at any splitting or chemical shift, we know that it is 1-methoxypropane.

Let's take another approach: let's take the chemical shift approach. [chemical shift info] How does this information help us? If really the low-end cut-off for an alcohol proton really was 4.5, then we don't have an alcohol, cause we don't have a chemical shift that high. What do we know for sure, there are two peaks that have a chemical shift of 3.3 – two different peaks. One of them integrates to three, one of them integrates to two. Five different hydrogens – you can't put five different hydrogens on one carbon, so they have to be at least on two carbons. If we look at the chemical shift chart, 3.5 corresponds to having hydrogen on a carbon next to oxygen. You have to have two carbons; that means we have to have hydrogens on two carbons, both next to the only oxygen in the compound. Two carbons next to an oxygen, that's an ether. If you look at the fact that you have two chemical shifts of three [with integrations greater than one], we know automatically it's an ether. Then we're thrown back in the same situation as method 1. To not completely copy method one, let's take the total number of signals approach this time. If we knew it was an ether, then again we could generate those three possibilities. How many unique types of hydrogens would he have on the first of these compounds? Remember the symmetry. Three. Why? The two methyl groups are equivalent, and then we have this secondary hydrogen, then there is the methyl group at the end. Three signals doesn't match the four that we have. What about diethyl ether? Two, because the molecule's completely symmetric, so we have the methyl groups on either end, and we have two the methylenes (CH₂) equivalent to each other, so we have two signals there. Process of elimination, this last one better give us four signals, and it does, because we have the methyl group at one end, the methylene one closer to the oxygen, the methylene yet more position closer to the oxygen, and then methyl group on the other side of the oxygen. Looking at the chemical shift, [worried about true range of alcohols] I notice that two peaks have that high chemical shift. That by itself may not necessarily mean something; you could have two hydrogens on the same carbon that have different chemical shifts from each other. But, since I have a total integration of five, that meant I had to have two carbons, both of them next to an oxygen, which is how I knew it was an ether, cause there's only one oxygen. From there, I figured out the possible structures [usefulness of writing isomers]. Here are the three possibilities; two of them won't match in terms of number of signals, so the third one's it.

Let's do the most systematic method that we've done in any of the problems to date – purely on the basis of splitting. We have one peak that is a singlet that integrates to three. What does it mean to be a singlet? No neighbors, no hydrogen neighbors. There's only a limited number of ways we could achieve that. We did see in a ketone example where, because the carbonyl itself, when it's a ketone, has no hydrogens on it, that it prevents either group on either side with splitting with each other. A singlet that has an integration of three often indicates there is a methyl group with blocked splitting. I could come up with an example that might not be so. If I had some wildly symmetric molecule, you could end up with three different positions all with the same hydrogen, all with singlets. To prove there is such a critter: in this example, the three hydrogens would integrate to three and be a singlet, so this is not always true. But, most of the time, when [you have] a singlet that integrates to three, it's a methyl group blocked from splitting. What does that mean structurally? It means we could have something like this: we could have a quaternary carbon. Or, we could have a methyl ether, cause the oxygen has no hydrogens. Who cares what the R group is, the oxygen no hydrogens, so the methyl group attached to the oxygen isn't going to be split. We have an oxygen in this problem, and integration of three means methyl group, so we could easily guess, then, that it would be a methyl ether. But let's say that this was a large molecule and we had lots of other peaks, so we didn't want to make any direct prognostication based just off that, what might be that R group; so, let's start with one of the other peaks.

We have a triplet that integrates to three. Again, things that integrate to three, especially on [small] molecules, means methyl groups. But what does it mean if I have a triplet that integrates to three? I've got a methyl group – that's what the integration tells me. What does the triplet tell me? That there are two hydrogen neighbors on the next position over. Why did I want to start with the methyl group? Why do I have this fixation on methyl groups? Cause it's the end of a molecule. [If you have ever worked jigsaw puzzles as a kid,] you know once you've got that corner piece, you were all excited because you knew there were two directions, at least, that you were going to be able to build off it. This is what's going on here: we're starting with one piece of information that we think we can get our hands around and then build from there. I started with the methyl group, now I move one position over. That's what the triplet tells me. Now let's go back to the spectral information. How many peaks do I have that have an integration of two? Only two peaks, so these hydrogens must be corresponding to one of those two peaks. Which one? What's the splitting going to be for the blue hydrogens? You've got three neighbors; what do three neighbors cause? A quartet. So this has to have a quartet. There's only one peak that integrates to 2 that has a quartet; it's a triplet of quartets. That's what this peak has to be. I started with the methyl group.

I knew from the methyl group's splitting that my neighbor had two hydrogens, which also means the next thing along has to be either a carbon on an oxygen. I know that much just from one peak. But now let's move one peak over. I'm on a peak that has only two hydrogens. Is there something that integrates to two? Yes: one that's a triplet, one that's a triplet of quartets. If I just came from my methyl group neighbor over here that has three hydrogens, that means I have to have a quartet, so the only possible peak that that two set of hydrogens corresponds to is the triplet of quartets.

The quartet comes from the fact that we have the methyl group neighbor. The integration of two is because that's the peak that we're talking about. But what else do we have? A triplet. What does that mean? There's two more neighbors that are not equivalent to the first three, because if all five of these hydrogens involved were equivalent, we'd have a hexet. The triplet means two different neighbors. There's only one other peak that has an integration of two; what is its splitting? Triplet. The integration of two is because we're on that particular methylene. What does the triplet mean? Two neighbors. We already know which two neighbors: the blue ones. But if we have no other splitting, that means there's no neighbors on the other side. I started with a triplet, I knew from that there were two neighbors. The two neighbors were a triplet of quartets, which quartet matches the fact that I just came from a methyl group, and the triplet tells me I've got two more neighbors on this side. That peak itself is just a triplet, which reflects the fact that I've got two neighbors on this side, but because it's only a triplet, that means I've got nothing over here, except a quaternary carbon – which can't exist because I've already used three of the carbons up – or, the oxygen. Since, from above, I already guessed that this was a methyl ether, that means the compound is this. This is purely an argument by splitting.

[Can something have] five neighbors [total]? No; you never will have a hexet – except, in real life, what can happen is if you have two different sets of neighbors, but their coupling constants differ by one percent, then when you run the compound, you're going to see a hexet. That's why it's called the $n + 1$ rule, cause $n + 1$ works even if you have multiple neighbors that are different, if their coupling constants are the same.

C8H8: 7.1 - 7.5, m, 5H; 6.692, dd, 1H, $J = 7$ Hz, $J = 12$ Hz; 5.737, dd, 1H, $J = 2$ Hz, $J = 12$ Hz; 5.225, dd, 1H, $J = 2$ Hz, $J = 7$ Hz
[multiplet, meaning that the splitting pattern is so complicated, it can't be determined, or we don't care what it is and it's easier to say multiplet]

[that should be an interesting red flag right there: how can something integrate to 5?]

[alkenes have a more sophisticated NMR signature than some other functional groups; we actually care about the details of the structure because we can tell from it what kind of alkene we have]

How many degrees of unsaturation? 5. Chemical shift greater than 7. What functional group must I have? Benzene. Degree of unsaturation of 4 [or more] does not automatically mean benzene, but in combination with that high chemical shift, it's hard to think of a functional group otherwise that would give us that combination. Integration of 5 – how could you have a symmetric compound with three and two? You can have an integration of five – there's your integration of five. That's called a crown ether, because if you have a really vivid imagination [chemists sniffing solvents], five oxygens that are like the seat of the crown, and then these groups coming off of it – these are chelators, meaning they like to associate with particular ions. Depending on exactly the structure of your [crown ether], the number of oxygens, and whether they are oxygens, sulfurs, or nitrogens, they tend to preferentially bind to particular ions. If you were to shape these types of systems more carefully – vaguely make them planar, make some aromatic structure around it, put a nitrogen on it and call it a porphyrin group – we end up with hemoglobin. Hemoglobin has an iron center on it that also binds to heteroatoms that are in a cyclic arrangement. Crown ethers are hugely important compounds – if nothing else because it lets you take an organic molecule and bind it to something ionic, so if you have a mixed-phase aqueous/organic reaction, you can bring reagents across the phases.

In this problem, if we know we have benzene, how do we get an integration of five? If you only have one substituent on the benzene ring. Given that that consumes four of the degrees of unsaturation, we only have two carbons left, and there's one more degree of unsaturation – the compound is styrene. I didn't even look at the rest of the information. We're going to figure out, of the remaining absorbances, which one is which one of these protons. There's three different protons on the alkene; which one is which? Why is it that I listed this with chemical shift of something through something? Because in this case, once we know that it's a monosubstituted benzene, who cares what the splitting pattern is. Every monosubstituted benzene's going to have the same theoretical splitting pattern. It changes, depending on what the substituent is, exactly the nature of that pattern, but since we don't care about it, that's why we're lazy and say: multiplet. That's also why we're lazy and say that those five hydrogens integrate to 5. They're not chemically equivalent; there are three different hydrogens there. But if we're not bothering to distinguish the splitting patterns from each other, and all we care about's the structure of the compound, we lump it together and say there's 5 benzene hydrogens. We don't do this for every functional group, but it's very common for benzene to be lazy and simplified.

But we do have three other hydrogens; let me mark those off here. I'm going to give you some information that helps determine what kind of hydrogen is which. There are three spatial interactions occurring here. First, can we accept that the hydrogens that I circled in green and red are not the same as each other? They may be on the same carbon, but they're not at all in the same chemical environment. Why? Is there any bond rotation that could occur without a chemical reaction that would let you flip the two hydrogens? No; it's a pi bond. If you tried to flip, the whole compound spins, unless you break the pi bond.

If they're permanently locked into this configuration, that means the hydrogen that I circled in blue permanently has a cis interaction with the green hydrogen, whereas it instead has a trans interaction with the red hydrogen. Since this is a double bond, they're locked into that configuration. Since they have different interactions, they're different chemical environments, which, as you can see from the spectra, causes two different chemical shifts. On top of that, because the red and the green hydrogens are not the same as each other, we have geminal interaction, twin interaction. For geminal splitting, that usually has a coupling constant between 0 and 3 Hz. [why is it hertz] Cis, that has a coupling constant of 6 - 14 Hz, and trans has a coupling constant of 12 - 18 [Hz]. Yes there is a little bit of overlap between cis and trans.

How does that help in our problem? Coupling constant of 2 [Hz] – geminal splitting. We know which two hydrogens are the geminal ones. Once we know which two are, we know the one that isn't. The one that's neither of the geminals is the one that's circled in blue. What about the remaining two? Coupling constant of 7 Hz vs coupling constant of 12 Hz. There's no way 7 [Hz] can be trans; it has to be cis. The only interaction that could happen that's cis in nature is between the blue and what I've circled in green, so this is the green hydrogen. The trans, that is the greater splitting constant. You might look at that and say: wait, trans, that's further away, so how do you have more interaction further away? What if there's orbital interactions involved, and what if it happens to just be the right geometry in the trans position versus the cis? That is the reason. We therefore are able to distinguish between the three types of hydrogens. Why do we care about any of that? What if we had 2-hexene; that could be cis-2-hexene or trans-2-hexene. With coupling constants, we'd know which one it is. [look up the two]

[Two take-home problem]

C₄H₁₀O – delta 3.337, s, 3H; 3.337, t, 2H; 1.59, tq, 2H; 0.93, t, 3H

C₈H₈ – delta 7.10 – 7.5, m, 5H; 6.692, dd, 1H, J₁ = 7 Hz, J₂ = 12 Hz; 5.737, dd, 1H, J₁ = 2 Hz, J₂ = 12 Hz; 5.225, dd, 1H, J₁ = 2 Hz, J₂ = 7 Hz

Method 1 : D.O.U. & Integration

D.O.U. = 0 → must be an alcohol or ether, no rings. Since there is only one oxygen and no peak integrates to one, the compound is an ether.

Alcohols – At room temperature, alcohols undergo rapid proton exchange (dissociation & reassociation). If D₂O is added to a sample, proton/deuterium exchange can occur, which, if sufficient D₂O is added, can convert an alcohol to its deuterated analog. Since H & D are different nuclei, they absorb NMR radiation @ different frequencies, so when conducting ¹H-NMR the alcohol peak (after exchange) disappears. At RT, proton exchange is rapid enough that splitting between an alcohol proton and its neighbors will not be observed.

Method 2: Chemical shift

This compound has two peaks with d ~ 3.4, which a combined integration > 3. This must mean there are two carbons next to the only oxygen present, so the compound is an ether.

Method : Splitting

A singlet that has an integration of 3 often indicates there is a methyl group with blocked splitting. It is a reasonable guess that the compound is a methyl ether.

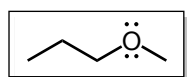
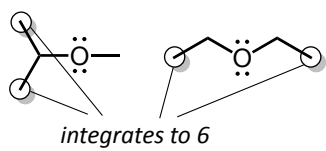
C₈H₈ → 5 D.O.U.

C₅H₈O – delta 6.342, d, 1H, J = 6.2 Hz; 4.664, dt, 1H, J = 6.2 Hz; 3.957, t, 2H; 1.984, dt, 2H; 1.846, tt, 2H

C₆H₁₂ – delta 5.45, dt, 1H, J = 14 Hz; 5.42, dq, 1H, J = 14 Hz; 1.95, dt, 2H; 1.643, d, 3H; 1.360, tq, 2H; 0.885, t, 3H

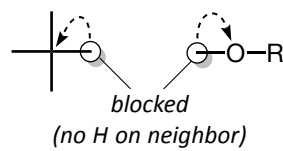
Structures (remaining structures identical to lab 13B)

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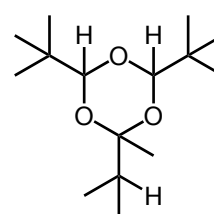


no integral > 3

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