When you're observing a particular nucleus, if nearby there's some electron-withdrawing group that will pull electron density off of that nucleus that you're observing, that nucleus will be more exposed to the external magnetic field, which causes a greater energy gap between the possible energy states of that nucleus. The larger the energy gap corresponds to a larger energy photon to overcome that gap. Larger energy per photon means higher frequency of radiation. Chemical shift is based on frequency, it just happens to be an expression of frequency that is machine-independent; therefore, you would end up with a greater chemical shift. Having something that's electron withdrawing deshields, exposes the nucleus, causes a larger energy gap, which means you have radiation of a higher frequency and therefore higher chemical shift that would be involved. Chemical shift alone we could relate to different functional groups, because the more electron withdrawing that you have going on, the larger the chemical shift will become. As we, in the future, continue to cover NMR, when we get to different functional groups, we'll talk about how they influence chemical shift.

There are two other pieces of information from a spectrum that we have to worry about. One of them is integration. Then, you might have noticed in the spectra that some of you have taken that instead of just having individual peaks, individual absorbances, sometimes the absorbances occur in a clump. You might have noticed that in the example spectra that you're taking, there's portions of it where it seems like there's four peaks all in a nice little clump, or three peaks in a little clump. We call those quartets and triplets, respectively. That's due to something that's called splitting. We are going to talk about how does it manifest itself and how do we interpret it to be able to determine something about compound structure. We have integration and splitting as two main topics of NMR that we need to get through today.

Let's tackle integration first, because it's the easier one. Integration's related to the fact that, for proton NMR, there's a very good linear correspondance between the strength of the signal that's generated and how many hydrogens that signal is related to. In other words, there's a linear relationship between number of hydrogens and signal strength. When I say that there's a good linear relationship, that means that it really closely matches linear behavior.

Back in the old days of doing NMR spectroscopy, when we didn't have FT-NMR available, when we didn't have the ability to blast a sample with a range of frequencies, we had to do it one at a time. Many times spectrometers had attached to them something called a strip recorder. In the old days [before printers]s, we had these things called strip charts, strip recorders. [vinyl] They're kinda like the tape that comes out of a cash register, where the loop just keeps going and it prints as it's coming out of that. That's how these strip charts used to work. If you were scanning from frequency to frequency to frequency, if you were changing frequency at a constant pace, along with that you would have this plotter – it literally had a pen – that would move back and forth depending on the signal that was being acquired. This roll of paper would keep on rolling and the pen would trace up and down as the signal increased or decreased. If you were scanning at a constant pace as far as your frequency, and if your paper was coming out at a constant pace, it had the end result of making a spectrum. How did you do integration if there were no computers? Once example of the use of integration [in math] is to determine an area under a curve. If you didn't have a computer to determine the area under a curve, how could you? You took one of these graphs and you cut out the paper; you cut out each individual peak, because if the paper had a constant density to it, then what you could do is get the mass of each of those pieces of paper. That ratio would be the ratio of the integrals, because the area is related to mass which, if you have constant density, there's a constant relationship there. So, you would literally cut the piece[s] out, weigh them, and from that get the integrals.

There's days, it's a lot more sophisticated; we have the computer that does it for us. The way it manifests itself is, if you have some compound, on the spectrum that you print out, these tallies, where the numbers are ended up reported up top, those are the integral values; those are the number of hydrogens corresponding to each one of those absorbances. But, the reason I'm bringing up integration is there is a problem with the computer trying to determine what integration is. You had to give the computer information, in fact. I had to calibrate the value of one of the integrals. That's because the NMR spectrometer is reading this signal, but it does not intuitively know how strong of a signal really does match having just one hydrogen or two hydrogens or three hydrogens. Because, imagine this: if you had a set of NMR samples, and each one had a different concentration, if you didn't tell the computer what concentration solution you had, it wouldn't be able to make a correspondance between signal strength and number of hydrogens.

Here's a thought puzzle for you: here are two compounds, two different cyclic ethers. As a side note, one of these is known as a crown ether. You can imagine that the oxygens are like the bottom parts of the crown, and then the carbon chains are the little peaks coming up from them. These crown ethers are important because they're organic compounds that complex, bind to, different types of ions. Different sized compounds prefer attaching to sodium versus potassium versus lithium – extensively-used compounds. On the first of the two compounds, if we ignore stereochemistry, how many different types, unique types of chemically equivalent protons do we have? Just one. Another way I could ask that same question is if I monohalogenated using radical halogenation, how many unique monohalogenated products will I end up with? If I put a chlorine at one carbon versus another versus another versus another, again ignoring stereochemistry, there'd be only one type of compound you'd make. That means there'd only be one signal in the NMR spectrum, so a spectrum for that compound might look just like this.

It turns out, that's exactly the same type of spectrum you'd get for this other ether, because it, ignoring stereochemistry, also only has one type of hydrogen. So, how could the computer tell the difference between these two compounds if they're both spectra that generate just one peak? The answer is it can't. Because the computer does not know ahead of time what the integration is, doesn't know that proportionality constant that gets you from the signal to the number of hydrogens, it can't anticipate it, it can't predict it, you have to tell it. In this case, both of these compounds would produce nearly equivalent spectra, only one absorption. Although number of hydrogens is linearly proportional to the signal strength, that proportionality constant is not known unless measured. [when taking an NMR spectrum, the proportionality constant is established by calibrating one of the integrals] Without measurement, the machine would not be able to differentiate these two compounds. [In all problems that you will encounter, you will be given the integral information,] so we're not going to normally encounter this gotcha case. For our purposes, [integration] is just the number of hydrogens present.

Let's get to the tougher topic of splitting, as in splitting headache. Splitting is a phenomenon caused by two non-equivalent hydrogens interacting with each other. [what is the cause]. If you have two protons that are identical protons, they won't, somehow, interfere with each other, but if they're different protons, they do interfere with each other. We'll worry about why after. What happens because of that is the following. Let me give you a concrete compound that we're going to discuss. I have a compound here with exactly two hydrogens on it. One is unique versus the other, because one is substituted on a carbon that has two chlorines attached, the other one is substituted on a carbon that has two bromines attached. They're therefore chemically inequivalent so they'll each have their own unique NMR signal. From what we've discussed so far, we might be able to guestimate what the NMR spectrum's going to look like. Here's our guess: if I have two types of hydrogens, how many NMR signals am I going to generate? Two. Number of types of inequivalent protons is the number of peaks you will get in theory. Which of the two peaks, A or B, corresponding to proton A or proton B, should be further to the left? If the electronegativity trend holds, in terms of its effect on chemical shift, which of the two hydrogen should be located to your left? Ha; why? What causes chemical shift to shift? Shielding and deshielding – whether there's electrons around that nucleus or not. Which element is more electronegative and, therefore, going to cause more deshielding? Chlorine. If chlorine's going to cause more deshielding, that means Ha, which is closer to the chlorine than the bromine, is going to have more electron density pulled away from it, so it's going to be more exposed to the external magnetic field, so it's going to have a higher energy gap, which means larger energy per photon, which means higher frequency, which means higher chemical shift, which means it's to the left. We had that long, drawn out discussion about upfield, downfield, shielded, and deshielded to explain why, historically, left is increasing frequency, backwards from the way we normally write graphs, where stuff normally increases to the right. So, we could guess that Ha has a signal that shows up to the left of Hb. We might also guess, based on our discussion of integration we just had, that they should be relatively the same height, or, if not the same height, then at least the signal should integrate to the same value.

But this is not what we get, because we have this thing called splitting that occurs. The signal that results from A will still be to the left of B, but it will appear as if we're having double vision – there'll be double versions of each of the peaks. What we need to now discuss is why. [ignoring why does it happen, focusing on what happens] Imagine that we're trying to observe proton A, but we know that proton B is over here next door. I've just said a few moments ago that if protons are not equivalent, they somehow interfere with each other. Here is the way that they interfere. Regardless of what A's spin is, because A could be spin up or down relative to that external magnetic field. Remember that whether it's up or down, that's that energy gap that's being accessed by these different frequencies of light. B is doing it's own thing over here, and maybe B is located spin up versus spin down, versus the main magnetic field that the samples in. What if that spin on B is oriented up with the magnetic field, and somehow adds to the magnetic field that A is experiencing. So we're looking at A, but we're talking about the effect that B has. If B's spin aligns with the magnetic field, it effectively is adding to the magnetic field, from the perspective of A. If you add to the magnetic field, you increase the energy gap, which means you increase the chemical shift, which means the peak would move a little bit to your left. The opposite could occur, though: that, if the neighboring spin is spin down, it's going to subtract from that overall magnetic field. If it subtracts from that overall magnetic field, that means the energy gap is going to decrease, which means the peak is going to shift a little bit to your right, and it's going to be lower frequency. Statistically, in solution, both possibilities end up being about 50/50 to occur, so whereas you start with one absorbance initially, because of the interference of this neighboring proton, that actually splits into two. From A's perspective, there's one neighbor B that has the possibility of being up or down. That's why A gets split into two signals. From B's perspective, it's got this one neighbor A that again could be oriented up or down, which is why B's signal ends up getting split. This is splitting, and this is the simplest case of splitting: splitting by just one neighbor.

A neighboring chemically inequivalent proton effectively can add to or subtract from the primary magnetic field, a machine's magnetic field. This causes a corresponding increase or decrease – increase if we're adding to the field, decrease if we're subtracting away from it – in the chemical shift, not of the neighbor, but of the proton being scanned itself. This whole discussion, I could look at B and talk about how A is messing with it, but just to have one point of reference, I'm instead talking about A and how B is messing with it. The neighbor, B, being a non-equivalent hydrogen effectively adds and subtracts to the magnetic field as experienced by proton A. This neighbor, B, therefore can cause an increase or decrease in the chemical shift of the proton being observed, proton A. Statistically, in an entire solution, both possibilities occur with equal probability, so both signals will be generated. When we have a set of peaks like that, where it's two equal sub-peaks, that's called a doublet. We could write what is called a splitting tree to show the formation of this doublet.

Let's say that I have an x-axis here, which is chemical shift, and I have originally a signal for proton A, where I first imagined that it had no interactions with neighbors. But now, we do have this one neighbor B that can add to or subtract from the magnetic field. We say that the magnetic field is pointed up relative to the paper, than we can imagine that the neighbor B could be up or down. That's what's causing the generation of the two peaks. In between the two peaks, the distance of separation that occurs is labeled J and it's known as the coupling constant, which is the extent of splitting between two neighbors. One signal turns into two; that's a doublet.

What happens if there's not just one neighbor? What if there's two of the same neighbor? That's the second example we need to do.

They're interacting in real life. We're enhancing that behavior by causing larger gaps between energy levels than would normally exist in real-life compounds. Right now, we're in a magnetic field, we're in the Earth's magnetic field. Because of that, technically, the hydrogens in us right now are split, in terms of their energy levels. In theory, as radio waves are passing through us, different nuclei are flipping back and forth between different energy states. Those interaction between neighboring hydrogens, therefore, really are happening, we just don't have ourselves suspended in an NMR machine to see it.

If I see a double and I'm looking at one proton, how many hydrogens does that mean it has next door? Just one hydrogen. In real life, if I saw that kind of signal, that would mean next door, there's only one hydrogen, so there otherwise needs to be two other carbons or oxygens or nitrogens or anything else – except hydrogen – next door to what I'm observing. If you then went to observe that one hydrogen, maybe you'd find out some splitting information for neighbors next to it. Then it turns into a puzzle. You know how many hydrogens you are from integration, where you came from; you know by splitting how many hydrogens are next door. If you can put those pieces of information together, you can start with one end of the molecule, move your way along, and solve the puzzle of which neighbors are possible, what would carbon look like in order to generate this kind of signal.

To jump to the end a little bit, let's say that I had three neighbors. That's a methyl group; that's the end of a molecule; I've reached the end. From there, I can then backtrack along the structure and determine the rest of the molecule's structure. That's how we're going to use the splitting information. It'll make a little more sense when you see the example at the end of lecture. Carbons, we don't allow the splitting to occur. Other atoms can split, but we don't observe them, so we're not worried about them. Hydrogen is the easy case because it can only be up or down.

Let's see the second example now. I'll still have a hydrogen labeled Ha with to chlorines as neighbors. But now, on the other carbon, instead of having two bromines, I'll only have one. The same kind of thing happens – these are inequivalent protons, A versus B. Important note: in all of our discussions today, we're going to ignore what having a chiral versus an achiral solvent would cause; don't worry about enantiotopic or diastereotopic protons. That will have an effect, because if you have two protons on the same carbon that are different from each other, they'll split each other. We have two neighbors and one neighbor; they're inequivalent, but two versus the one. The two will split the one, but each hydrogen B will have it's own individual spin that could be up or down, independent of the other B's spin being up or down. That means we really have four possibilities – both Bs up, the first down and the second up, it's equivalent in energy but still a unique case of the first one up and the second one down, or both spins being located down.

Let's rationalize this two different ways, the possible outcome. Let's do the splitting tree second. Think about those four spin possibilities that i had come up with. We have one possibility of both neighbors spins up, and if they're adding to the magnetic field, that means it's going to put the signal generated by it further downfield. Then, we have have spin up and spin down, versus spin down and spin up. If we're talking about probability, those are both unique cases, so you'll get double the number of cases that have that same energy, relative to the first case, or the last case, which is where both of them are spin down. As far as the type of signal that we get generated, within just that signal itself, you'll appear to have an integration of 1:2:1.

Now, let's make the same kind of argument using the splitting tree. If we imagine that we have signal A, where we had no neighbors that it was interacting with, then you'll get just one peak for one type of hydrogen. If we imagine that we introduce one neighbor that causes a split – the degree of split we can measure or is expressed by this constant J. That's if we had one neighbor, the case that we described up above. But now, let's say that the second B gets involved. After tackling what happens with just one B, both of those signals we just generated now would have a different interaction with the second neighbor B, so each of those peaks is split again. But, since it's the same neighbor that we're talking about, it's the same amount of splitting that's going to occur. In other words, that same constant J is going to apply to this next split as it did for the first one. What's that going to mean, that two of the peaks from the two different splits are going to end up recombining and aligning with each other, being the same. Of couse, each one aslo splits off in its own direction, but notice we therefore created the same 1:2:1 pattern by having two neighbors. This, what we generated, is called a triplet. A doublet is making two peaks from one; a triplet, with this pattern of 1:2:1, is what you get when you have two neighbors – a set of three peaks.

Let's see the next case of having a methyl group and what that causes. Third case would be the following. Still have one Ha, but now three totally equivalent Hbs.

In this example, we don't even have to worry about stereochemistry, because those are homotopic protons, they'll always be the same as each other. We're going to end up with four unique energy possibilities this time. Why? Because we have three Hbs, each one of which has its independent spin, so they could be all up, two up, one up, or none of them up, all of them down. They'll end up generating a set of signals with a relative strength of 1:3:3:1. Why? Cause there's 8 eight independent cases of the spins being [up, up, up], [up, up, down], [up, down, up], [up, down, down], [down, up, up], [down, up, down], [down, down, up], and [down, down, down]. [These] are all binary numbers, I just said the numbers zero through seven in binary. Notice, though, that three cases have the same overall energy consequence as each other, so they're all degenerate states, and I have another set of three. This is going to generate an NMR signal with relative integration of 1:3:3:1.

Can I make the same argument using a splitting tree? The answer is yes. I again start out with one peak, that splits into by one neighbor. Throw another neighbor in there, we get splitting again. Throw another neighbor in there, we get splitting again. Notice that the second time we split, we ended up with this central case that has double the intensity. When that splits, it's going to end up overlapping with yet another one from up top and end up, therefore, with triple intensity. We again show the peak pattern of 1:3:3:1.

You might start seeing a pattern develop. What pattern is this? Pascal's triangle. How can you generate it? Each row below is created by looking up above it and adding up what's in between; you're adding the two numbers and that you see immediately above. Notice that here I had 1 + 2 than ended up adding up to being three. Down below here, I have 1 + 3 that adds up to 4; 3 + 3 that adds up to 6; 3 + 1 that again adds up to 4. Then, you put ones on either side. Where does this show up? Curiously enough, the way that you might have seen this originally is from just good old polynomial expansion. (x + y) to the first power is 1x + 1y. (x + y) to the second power is 1x^2 + 2xy + 1y^2. (x + y)^3 is 1x^3 + 3x^2y + 3xy^2 + 1y^3. Let x = spin up; let y = spin down. The numbers corresponding to the spin combinations exactly match the numbers that you get from polynomial expansion. Just one of those whacky coincidences. It's important to realize that math is a language that we use to describe the universe with; that language can be used in more than one place. It can be used for polynomials; it also exactly expresses what's going on with these spins interacting with each other.

What's the point? In general, there's something called the (n + 1) rule, which works like this. If you're observing a proton that has n number of neighbors, add one to that and that's how many peaks the proton you're scanning is going to be split into. If you look at the case where it had one neighbor, it made a doublet. If you look at the case where you had two neighbors, it made a triplet. When we had three neighbors, it made a quartet. This is only the first presentation of splitting, because we're only worried about one neighbor. What if you're a tertiary carbon, has one hydrogen on it, and you've got three different neighbors? Each one will split differently with different splitting constants. You can end up with a doublet that the doublet gets split into its own triplet, which then gets split into another multiplet. You can get a group of several dozen peaks that all have a particular pattern. They might be, for example, doubles of triplets or quartets, 24 different peaks. For right now, we've got this generalized (n + 1) rule that when observing a proton that has n neighbors, a multiplet – that's the general term for singlet, doublet, triplet, quartet, quintet, hextet, heptet, all the different possible outcomes – we generalize that with the word multiplet. When observing a proton that has n neighbors, a multiplet with n + 1 peaks will be generated, if all neighbors are equivalent – or nearly equivalent. That's because, in real life, you may have three different neighbors, but maybe they're so close to each other that you can't detect them easily by NMR, not without more advanced techniques. If they all act as if they're equivalent neighbors, then the (n + 1) rule will still apply.

This compound has the formula C2H5Br. We'll discuss the information that you can get from a chemical formula. What kinds of peaks do you see here? On the lefthand side, what kind of peak does that first peak appear to be? A quartet, because we've got low, high, high, low; that tall peak is about three times, roughly, the height of either one of the side peaks. How many hydrogens would that correspond to, then, as far as being a neighbor? How many neighboring hydrogens would cause that quartet? Three – (n + 1) rule: three neighbors split into four peaks. How many hydrogens are represented by this signal that I'm pointing at? You don't know. You could figure it out from the formula that I mentioned a moment ago, but until we come up with that proportionality constant, the fact that it's not shown here on the graph means we could not figure it out. But, let's see how in this one case we could, because what kind of peak does it appear that we have over here on the right? A triplet – again, the top peak is roughly double the height of either of the side peaks. How many hydrogens would have been responsible for causing that? Two. So if you have three hydrogens and two hydrogens, that's five, which is the total number of hydrogens in the formula, which is how we know that that is going to integrate to 2 versus 3 – backwards from the fact that it's split by three or by two. The integration doesn't depend on the neighbors; it depends on how many protons you really have. But, the number of splits that you have depends on what's neighboring it.

Let's take that information. If I have a peak that is split into a quartet, that means that next door is a methyl group, so CH3 over here. If the compound is C2H5Br, there's only two more hydrogens left, which could be associated with this peak. If you only have two hydrogens, that would cause the methyl group to be split into a triplet, which it is. Then, if we have bromine as the functional group, then it would be on the carbon that only had the two hydrogens; then, that carbon will be shifted further to the left, which is it. This is the compound bromoethane. So this carbon, with three hydrogens on it, is split by two neighbors into a triplet.

This carbon, which has three hydrogens as a neighbor, is split into a quartet because of those three neighboring hydrogens. The position that was split into that quartet has a bromine on it, which is why it is further left in terms of chemical shift.

NMR Solvents

Could you think of any restriction that you would need in place on the type of NMR solvent that you would use in order for it to be a viable NMR solvent? Can you think of some ideas of things that would be bad NMR solvents? If they have lots of hydrogens on them, which means almost any laboratory solvent. You take something like acetone or ethyl acetate, any normal solvent, and it's going to be loaded with hydrogens, which as the solvent – that means the major component of this mixture that you make – your compound's signal will just get totally smothered by the signal from the solvent itself. If you had a particularly sensitive NMR machine, you might be able to see it though the solvent, but it'll be this tiny signal versus this gargantuan signal that you get from the solvent, if it hydrogens. So, what would you guess, then, we would need to do to make a solvent that would be useful as an NMR solvent? What if we use hydrogen's bigger brother, deuterium? Because, way back at the beginning of this NMR [discussion], we talked about a couple of factors that directly affect the energy gap that forms on a compound['s nucleus]. One of those factors was the main magnetic field itself, but one of the other factors was also the identity of the nucleus – whether it is hydrogen versus chlorine versus this versus that. Deuterium is a different nucleus than hydrogen, so deuterium is going to show up in an entirely different region of the spectrum than hydrogen will. So, if you put deuterium on a molecule, as far as proton NMR, it makes the deuterium invisible. What we do is use deuterated solvents.

Since normal – which means protium-containing solvents (protium is 1H) – since normal solvents would effectively flood the signal of any compound dissolved in it, deuterated solvents are used in NMR spectroscopy. By far the most common of which is deuterated chloroform, $CDCl_3$, which is sometimes called chloroform-d, showing that the hydrogen that had been on chloroform has been replaced by deuterium. Why is this particular solvent used? There are a wide range of compounds that are soluble in chloroform, and deuterated chloroform is, by comparison, inexpensive to produce. It still requires a source of deuterium, which that, in itself, may not be cheap, but to make deuterated chloroform – not difficult compared to other solvents. What are some other common solvents if something won't dissolve in chloroform? The more-common ones are things like acetone-d6; if it was something that was water-soluble, D_2O, which has the common name of heavy water. [can you drink D_2O? No you shouldn't. Isotope effect, a kinetic effect.] Chloroform is actually one of a general class of compounds from chloroform, fluoroform, bromoform, and iodoform, all of which are methane where everything except one hydrogen has been replaced by that halogen [haloforms].

Even though I said a moment ago we don't normally use solvents with hydrogens in them, that is, in fact, what we [often] do, to a small degree. In other words, instead of having a solvent that's 100% replaced with deuterium, sometimes we'll use 99+%. 99+ means better than 99, but not as good as 100. Why does that 1% or less difference matter? Productionwise, in anything, if you had to make something that's 100% pure versus 99% pure, that last little bit requires an awful lot of effect. Besides that – which means cost – why else might it actually be a good thing that we let a little residual non-deuterated solvent through? Solvent, being the major component of that mixture, they're going to have fairly reproducible behavior, regardless of what the sample is that you prepare and regardless of what machine that you put it in. So, the chemical shift that you would get from a solvent's peak is gonna show up at pretty much the same place, no matter what sample that you have. So it becomes a little bit like a secondary calibration standard, that little bit of signal that's left over. You might notice that down in the 7 range, around 7.2, you get a little bitty tiny peak there [when using chloroform that has some residual hydrogen on it as a solvent]. Chloroform has a chemical shift of delta 7.26 [although this value fluctuates very slightly depending on the source]. If you allow a little bit of regular chloroform to slip through, you could use that to calibrate your spectrum, especially if you don't go through the effort to get solvent that has TMS in it. In other words, if you didn't have any reference, and you just did your spectrum, you wouldn't know where zero is supposed to be; you would just hope that if the machine was well-calibrated, it's where it's supposed to be. But, if you wanted to make sure, you'd need to refer to something. Sometimes you use NMR solvents that have TMS in them, but that's not even necessarily required, as long as you have 99% deuterated solvent that lets a little bit of non-deuterated solvent through, cause then that, itself, can be used as the reference.

Although 100% deuterated solvents can be used, often, 99+% deuterated solvents are used instead, partly because they can be significantly less expensive, but, in addition to that, it's because the non-deuterated signal can be used to calibrate the chemical shift on an NMR spectrum. Even with this, sometimes you'll still add TMS, just if you want to make absolutely sure you've at least got your zero reference correct. Sometimes TMS is added to an NMR solvent regardless of the level of hydrogen depletion – meaning, regardless of whether you go through the exhaustive effort of making sure it's 100% deuterated or not. Sometimes TMS is added as a primary calibration standard.

In integration, you sometimes can add TMS as a quantitative standard. Sometimes TMS is added not just for chemical shift purposes, but if you know the exact concentration of TMS, then when you scan that sample, you could take the strength of the signal that you've acquired and directly equate that to the number of moles of TMS hydrogens that are present.

If you then make a carefully calculated concentration of your target compound, the one that you want to analyze, and you know it's concentration at the same time you know TMS's concentration, then, because TMS is there for you to determine that proportionality constant, you can then determine exactly how many hydrogens are on a particular compound. That's a side use of TMS [quantitative].

[structural elucidation using NMR and IR together]

From the molecular formula, you can determine something called the degree of unsaturation. The term 'saturated' we used in one sense earlier on in the quarter – the maximum number of hydrogens, given the number of carbons present. That actually is the correct definition of unsaturation. I might have used a looser, not quite technically correct version when I referred to compounds being saturated as only having single bonds and unsaturated compounds having double bonds and triple bonds. That's the way that the term unsaturated is generally used if you're talking about fats. Saturated fats as more harmful that unsaturated fats because unsaturated fats do have alkenes, alkenes that can undergo electrophilic additions or other reactions that simple alkanes do not undergo. So if you have this big, fat molecule floating through your bloodstream and you've got some way for it to be split up, then it more easily passes through the blood stream, doesn't accumulate, doesn't cause the problems that, we know as humans, eating too much fat can cause. More correctly, it's not just whether or not there are double bonds or triple bonds present, it's how many hydrogens there are present, relative to the number of carbons.

Unsaturation would be having few than the maximum number of hydrogens possible given that number of carbons; saturated [would be] a compound that contains the maximum number of hydrogens possible given the number of carbons present. Let's just see a couple of simple examples that will verify the following statement: that the number of hydrogens possible is equal to twice the number of carbons plus two. That's quite easy to observe in a straight-chain, non-branched [saturated] hydrocarbon – hexane, for example. If you were to draw in the hydrogens on hexane, then each position has, at a minimum, two hydrogens. In fact, the carbons that are not the ends each have exactly two hydrogens. What is the common name that I gave in class for the structural feature of having a carbon with two hydrogens on it? Methylene. There's an alternate name for dichloromethane – methylene chloride. The -ene part of the name comes from the fact that it has two connections; it's divalent. If it's got two connections, it can only have two hydrogens, so that's why methylene is the common name for a CH_2 group. Each methylene means two hydrogens, but at the end, the methyls, you've got two hydrogens, plus one more, you could say, from the fact that you're at the end of the molecule. Since each end has that on extra hydrogen, that's why the rule is that you take two times the number of carbons and add two.

What if you didn't have a straight-chain compound? What if you had something that was branched? The rule still works. If we take an isomer of pentane – isopentane – how many methyl groups do we have? Three methyl groups, so three time three. How many tertiary carbons do we have? One, which has one hydrogen on it. We have one secondary carbon that has two hydrogens on it that adds up to 12. How many carbons are there? 5. 5 x 2 = 10 + 2 = 12. You could arrive at this kind of compound if you took a straight-chain alkane and just move a methylene group over one position and swap it with a hydrogen, and you keep doing that until you end up with your branched compound.

But what happens if you make a ring? Cyclohexane, for example, only has the formula C_6H_{12}, not 14. Why? Because, effectively, to take hexane and close it up into a ring compound, you're going to have to take off one hydrogen from either end; that's how the new carbon-carbon bond would be able to form – if the hydrogens were not there. That means, technically, a ring counts as a degree of unsaturation. If we compare that to hexene, both of those are C_6H_{12}. A ring and a double bond each count as one degree of unsaturation. Why's it one degree when there's two hydrogens missing? Because two hydrogens is the minimum number of hydrogens you can take away to create a new bond. If you only took one hydrogen off of one end or the other, you'd have a radical, and that'd be the end of it. So, take two hydrogens off and that's one degree of unsaturation. What if you had a triple bond? If you had pentyne, for example? That's C_5H_8; that represents two pairs of hydrogens missing. C5: 5 x 2 = 10 + 2 = 12, which is what we should have if we have a saturated five-carbon compound. We only have eight, so that means there's four hydrogens missing. So, a triple bond counts as two degrees of unsaturation.

Of course, if all we knew was that there are two degrees of unsaturation, we could say it's a triple bond, but we could also say it's two rings, or two double bonds, or a ring and a double bond. You might think: what's the point? Well, if you found, based on the chemical formula, that you have only one degree of unsaturation, and you found from your IR that you have a carbonyl, which is a carbon-oxygen double bond, then even if you know there's an oxygen present, you know there's no alcohol present. If you formula only has one oxygen, and it's in that carbonyl, which is the only double bond, then you know the rest of your structure won't contain rings, won't contain double or triple bonds. You can put pieces of information together like that and more quickly figure out a compound's structure. That's the one use of knowing degree of unsaturation.

The only complicating factor I need to introduce is how do we get to a formula for calculating degree of unsaturation. I'm saying that if a pair of hydrogens is missing, then that's one degree of unsaturation. In fact, the degree of unsaturation formula, you could write as this: number of hydrogens based on the number of carbons minus number of hydrogens present, that whole thing divided by true.

What I said is a true statement, but we're not done talking about how many hydrogens should be there, because all we've done so far is look at hydrocarbons. What if we had heteroatoms there, things besides carbon and hydrogen. How would they or would they not affect the hydrogen count?

Let's compare three pairs of molecules: ethane with ethanol. I'm going to write the hydrogens in on one of the carbons of ethane to show whether or not it's different from the number of hydrogens on ethanol. We'll also do the same comparison with ethanamine, so put a nitrogen there instead, and we'll also do a comparison with a [halide]. Since it doesn't matter which hydrogen it is, I'll just represent it by X. Notice that the oxygen effectively just inserts in the middle of a carbon-hydrogen bond. It doesn't add or subtract to the number of hydrogens that would need to be there to make it a neutral, non-charged, non-ionic compound. That's because oxygen, like the other chalcogens, is divalent; it only wants to have two bonds. SInce it doesn't change the number of bonds by putting the oxygen there, no extra hydrogens or no fewer hydrogens are present. Oxygen and sulfur, the two main chalcogens that we have in organic compounds, do not affect the hydrogen count because they're divalent.

But look at the nitrogen. The nitrogen, in order to be neutral, has this extra hydrogen on it, because nitrogen and the other pnictogens tend to be trivalent. So, nitrogen and phosphorus, if they're there, you have to add one to whatever number you think the number of hydrogens should be. In fact, if you count this up, three on the methyl group over here, four on this other side – you have seven hydrogens. So, two carbons time two is four, plus two is 6, but because of the nitrogen there, we have seven. NItrogen and phosphorus add to the hydrogen count because they are trivalent. Valence means have control; trivalent means three bonds therefore.

The last case would be the opposite situation, for halogens. Notice that the halogen takes the place of the hydrogen, because halogens, in normal organic compounds, are monovalent. Halogens do not have to be monovalent. If you have, for example, the iodate ion, that ion is trivalent, but in standard alkyl halides, the halogens are only monovalent, so they take the place of the hydrogen, so we have to reduce the hydrogen count. Halogens subtract from the hydrogen count because they are monovalent.

Taking these three pieces of information, and incorporating into the formula we had earlier, I'll say our new adjusted formula is that the degree of unsaturation is equal to 2C + 2, that's the base number of hydrogens that we would have assuming the number of carbons. We're then going to add the number of nitrogens, cause each one has an extra hydrogen, and we're going to subtract the number of halogens. Then, subtract the number of hydrogens that really are present, and divide the whole thing by two. Once we do start to work through structures and solve for compounds, we'll practice doing degree of unsaturation and we'll see how it's useful.

Gas chromatography

Let me show you the general outline of what a gas chromatograph looks like. You have an injector port that is connected to a column. We call it a column even if it's not a real upright tube of some sorts. By extension, we take what is called a column, which we use in column chromatography, and just make a really long, extended[, and flexible] version of that; by parallel, that's why we call this a column. That column is wrapped around inside an oven. Eventually, that comes out at a detector. What is that column really made of? Generally, the outside of the column is metal to have some structural support. On the inside of the column is your separatory material or stationary phase. Along with the stationary phase, you'll have a gas tank that's hooked up to the machine that will be responsible for pushing your compounds through this column. [vaporized, volatilized] You need something to push that vapor through; that's called a carrier gas, literally something that carries the sample through the machine.

The stationary phase, that's what causes the separation of the compounds as the compounds are forced through the column. In gas chromatography, a liquid sample is injected into a port which is heated, causing the sample to be vaporized upon injection. That sample then passes into the column, which is also heating inside an oven to ensure that the sample remains a gas, or, if the liquid does briefly recondense, it would easily re-evaporate again. A carrier gas, which is an inert gas, a non-reactive gas, generally nitrogen, helium, or argon. That is used to help push the samples through the column. You have the sample and the carrier gas that are passing through the metal tube that's coated on the inside with your separatory material, your stationary phase. This combination of the carrier gas and the sample acts as the mobile phase.

As the sample passes through the column, then on the basis of, generally, polarity, but sometimes, depending on your application, size or boiling point itself, the compounds will be separated. Higher boiling point compound take more energy to reevaporate, so on that basis they would move more slowly through the machine. Even ignoring boiling point, though, if we go back to the same way that compounds were separated in TLC, on the basis of polarity, if we had the inside of this column coated with something that was really polar, and if we passed a non-polar compound through it, it would pass through pretty easily. If you had something that was polar instead, it would end up interacting with the column, move through the column more slowly. Primarily, on the basis of polarity, but also sometimes boiling point, the compounds will travel at different speeds through the column and then eventually be detected by the detector.

As the sample mixture passes through the column, the components of the mixture will be separated on the basis of polarity and/or boiling point. As the compounds pass through the column, they'll eventually be registered, detected by the detector.

This is the simple way of describing GC. The injector port is heated; the oven is generally heated; and then the detector is usually heated as well to make sure the compounds are still volatile as they're passing over the detector. In [more] complicated forms of GC, you might have different temperatures for each one of those stations, and those temperatures would be established by practice; if you had a particular application in mind that you knew that better separation resulted by having those different temperatures, that's why you'd use them. Sometimes, if you have a wide range of compounds that you're analyzing, you might actually have what's called a temperature profile or a temperature ramp, meaning that the oven heats at a certain rate over a certain period of time, generally increasing the temperature, so that compounds, the more sluggish compounds, can start coming through more and more easily.

The detector: how does the detection process occur? There are different types of detectors. One is an optical detector, where you might be scanning at a particular wavelength, something along the lines of IR or UV-Vis. Another way that's commonly used, though, is have a flame detection sensor, where you have a thin, heated wire that the samples are passing over. That heated wire will have an electric current pass through it, and the amount of current it measures depends on the resistance that it encounters. As a compound floats past that detector, it's going to slightly interfere with its resistance, which will slightly change the electric signal that's generated. The information that you get out looks like this, which is not a spectrum, really, cause we're not using different frequencies of light to analyze the compound. Instead, we're measuring retention time, which is the time it takes for a compound to travel from the injection port to the detector. The other axis is intensity, which is related to the quantity observed. If more sample is passing over that detector at one moment, then that detector's going to make a stronger signal.

You might end up with something like this. Each peak corresponds to a different compound that came off of it at a different time. Retention time is kinda like the Rf factor. In TLC, we had a fixed distance that everything was travelling, or a better way of expressing that, a fixed time for the solvent to start at the bottom and go all the way up. We measured the relative distance of each compound compared to that solvent front. In this case, everything flushes through eventually. It's not like you stop and say where'd the solvent get through. No. The whole sample passes through. How much time it takes to pass through, that's what important in this case. The identity of a compound can be established by its retention time. The quantity of the compound can be determined by the integral of the curve.

_____

Integration – For 1H-NMR, there is a good linear relationship between the strength of an NMR signal generated and the # of hydrogens involved.

Both of these compounds would produce nearly equivalent spectra (only one absorption). Although # of hydrogens is linearly proportional to signal strength, that proportionality constant can only be determined by measurement. Without that constant, these two compounds could not be distinguished.

Splitting – Caused by two non-equivalent hydrogens interacting with each other.

A neighboring (B) non-equivalent hydrogen can effectively add to or subtract from the machine's primary magnetic field as experience[d] by A. This neighbor (B) therefore can cause an increase or decrease in the chemical shift of the proton being observed. Statistically, both possibilities occur with equal probability, so both peaks are generated –> doublet

*Assume achiral solvents for all examples

n + 1 rule – when observing a proton that has 'n' neighbors, a multiplet with n + 1 peaks will be generated (if all neighbors are equivalent *or nearly equivalent*.)

NMR solvents

Since "normal" (protium {1H}-containing) solvents would effectively flood the signal of any compound dissolved in them, deuterated solvents are used in NMR spectroscopy.

Although 100% [isotopically-replaced] solvents can be used, often 99+% deuterated solvents are used instead, partly because they can be significantly less expensive, but also because the residual non-deuterated solvent signal can be used to calibrate the chemical shift of an NMR spectrum.

Sometimes TMS is added to an NMR solvent (regardless of the level of hydrogen depletion) as a primary calibration standard.

Degree of unsaturation

Saturated – a compound that contains the maximum number of hydrogens possible, given the number of carbons present.

#H = 2C + 2; 3 x 3 + 1 + 2 = 12

A ring an a double bond each count as one degree of unsaturation.

A triple bond counts as two degrees of unsaturation.

D.O.U. = (# of H based on # C) - (# of hydrogens present) / 2

Oxygen (and sulfur) do not affect the hydrogen count because they are divalent.

Nitrogen (and phosphorus) add to the hydrogen count because they are trivalent.

Halogens subtract from the hydrogen count because they are monovalent.

D.O.U. = ([2C + 2] + N - X - H) / 2

Gas chromatography

In GC, a liquid sample is injected into a port which is heat[ed], causing the sample to be vaporized upon injection. The sample then passes through a column that is also heated to ensure the sample remains vaporized. A carrier gas (an inert gas, usually N2, He, or Ar) is used to help push the sample through the column (mobile phase). As the sample mixture passes through the column the components of the mixture will be separated on the basis of polarity and/or boiling point. As the compounds successfully pass through the column, they will then be detected.

The identity of a compound can be determined by its retention time. The quantity of the compound can be determined by the peak area.
retention time –> time it takes for a compound to travel from the injection port to the detector.

Structures

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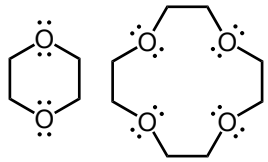

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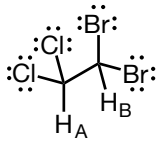

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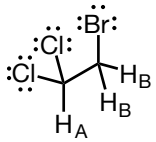

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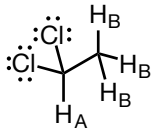

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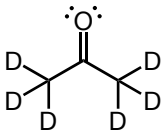
$CDCl_3$



chloroform-*d*

$\delta = 7.26$

acetone-d_6

D_2O

"heavy water"

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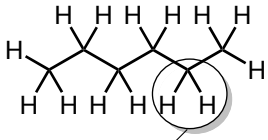
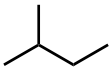


methylene



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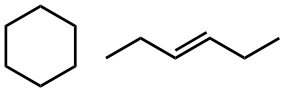

C_6H_{12} (*2H* "*missing*")

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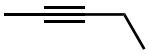

C_5H_8 (*4H* "*missing*")

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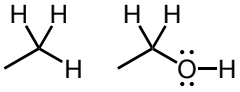

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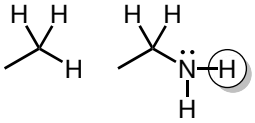

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