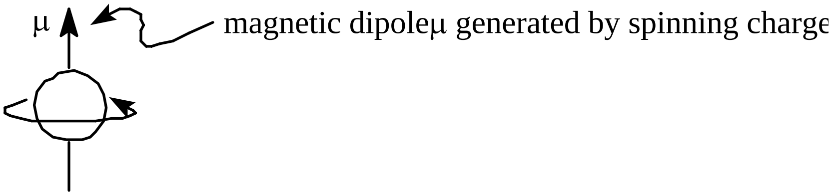
NMR Spectroscopy

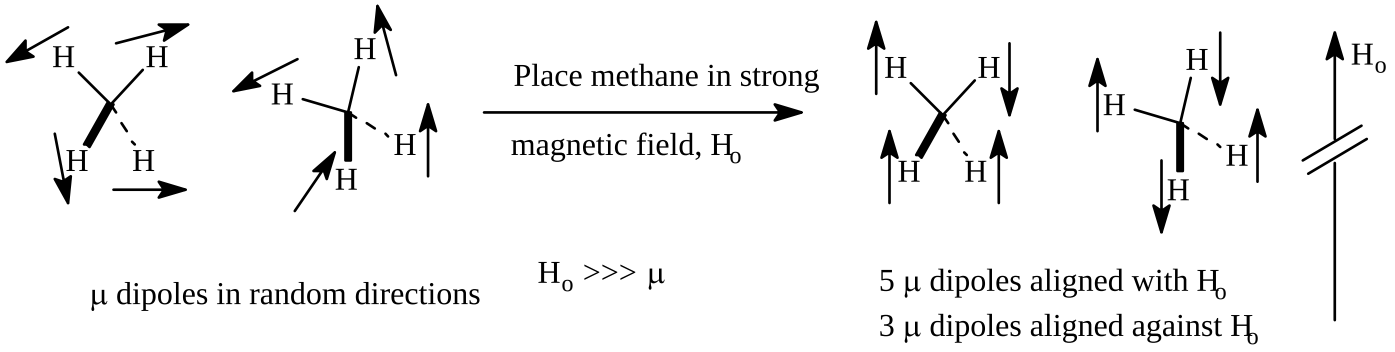
This handout is intended to give you a *practical* understanding of NMR Spectroscopy.

1. Quantum theory allows us to consider each nucleus as a *spinning charge*. Note: we are only considering the **nucleus** of an atom, not the electrons. For hydrogen, the nucleus happens to be a bare proton, symbolized as ^{1}H. (This is different from ^{2}H, deuterium, which has a nucleus containing a proton and a neutron.)

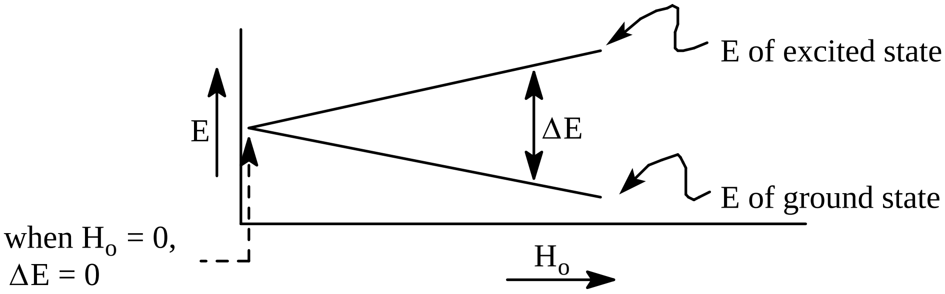
2. Any moving (or spinning) charge creates a magnetic field, or magnetic dipole.



3. Consider methane. Every hydrogen in CH_4 has its own dipole. Normally these dipoles are pointed every which way. However, if you place methane inside an *external magnetic field* H_o, these dipoles will align either with or against H_o. This is a quantum chemical result, that the dipoles μ can have only these two orientations. For NMR to work well, H_o is usually much greater than μ, and slightly more nuclei will align with H_o than against H_o.

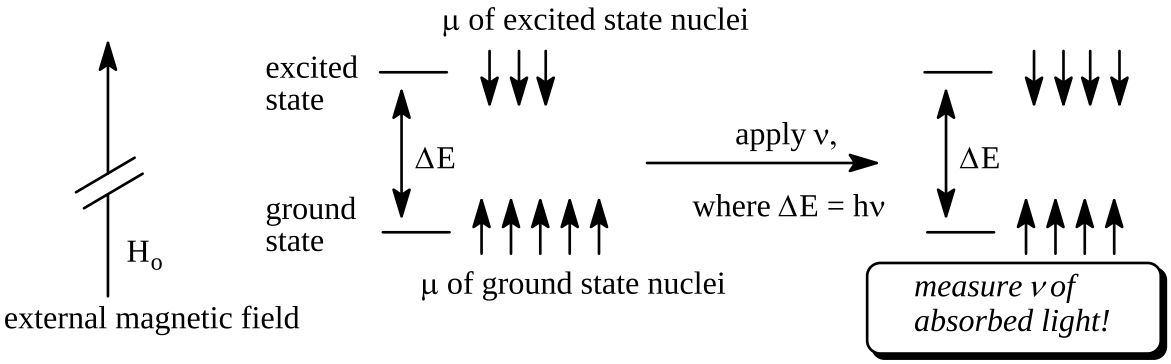


4. The reason that more of the μ dipoles align with H_o is that this is a lower energy (*ground*) state. The dipoles aligned against H_o find themselves in a higher energy (*excited*) state. The difference in energy between these two states *depends upon* H_o. <u>A greater H_o induces a greater ΔE</u>.



5. Now, for any H_O that we use, we can measure ΔE. This is fundamentally what NMR is doing, measuring these ΔE values.

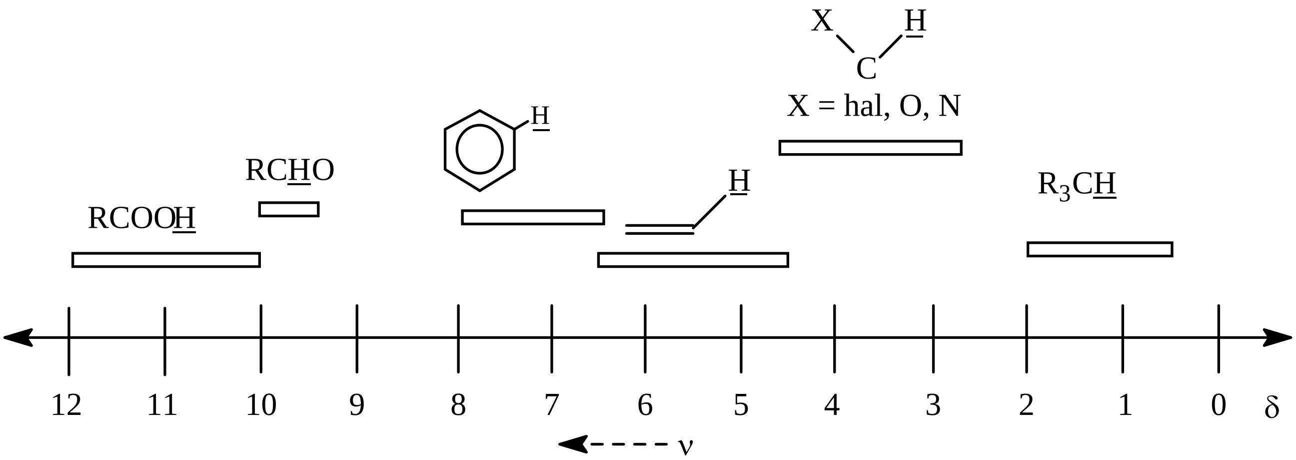
6. How does one measure ΔE? Recall one of the most fundamental physics equations, ΔE = hν. If we irradiate the nuclei with light of the right frequency ν, corresponding to the correct ΔE, we can *induce the ground state nuclei to absorb this energy and jump to the excited state*. This is the principle behind virtually all types of spectroscopy. We can measure ν directly, and this is proportional to ΔE.



7. When a nucleus absorbs energy and becomes excited, we call this **resonance**, or is *spin flipping*. Eventually that nucleus will lose its energy and fall back to the ground state. This is called *relaxation*.

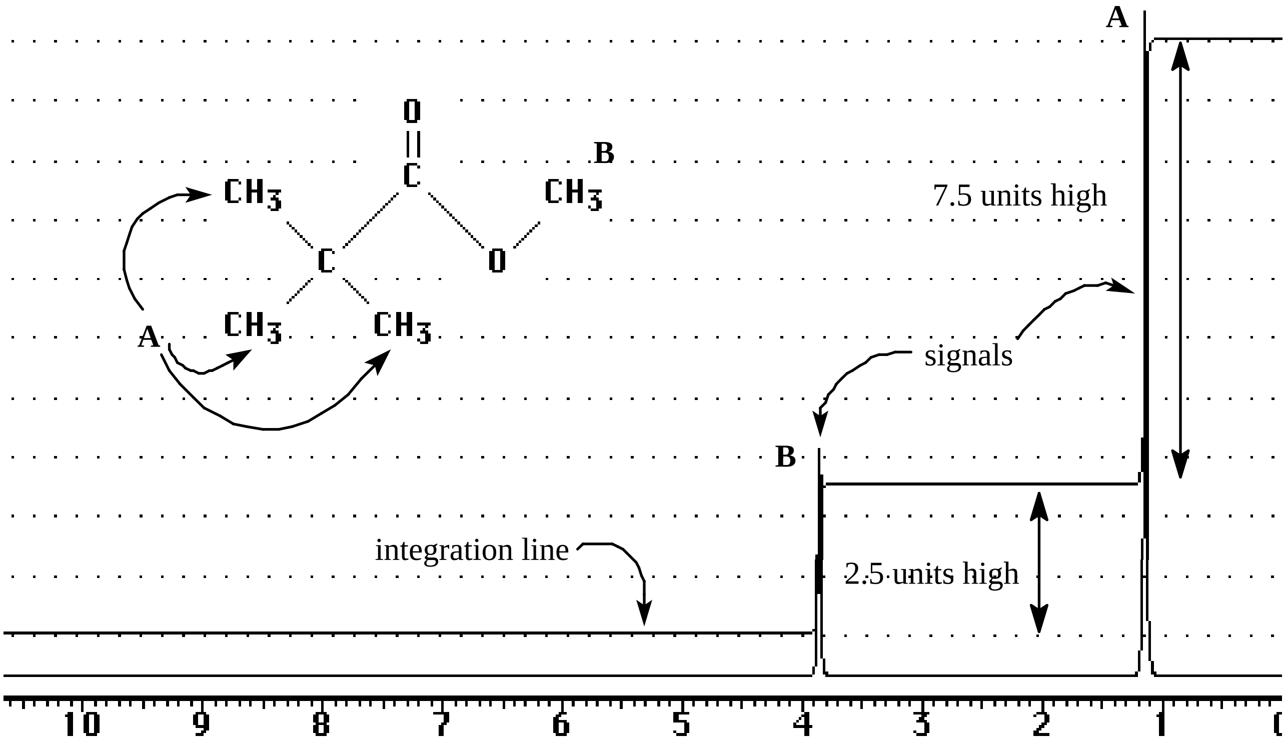
8. Now we know that we can measure ν for CH_4. What good is this? What happens if we measure ν for the ^1H in say, $CHCl_3$? The big question is, will we measure the same ν? The answer is NO! This is *why* NMR is useful. **NMR can distinguish between nuclei that are in different environments.** Once we know the frequency of absorption for CH_4 and for $CHCl_3$, we could then take an unknown sample and find out which one we have by this technique. In fact we could measure ν for lots of molecules, make tables, and compare the measurements of unknown samples with known numbers.

9. Check out a simple table, below.



10. The scale is called the "delta (δ) scale" or the "ppm scale". Basically, ΔE (or ν) increases from right to left. The actual numbers are the **chemical shift** of various nuclei. For instance, typical aromatic hydrogens have a chemical shift around 7 ppm. Notice that the chemical shift of a nucleus depends upon two things: H_O and the environment around the nucleus.

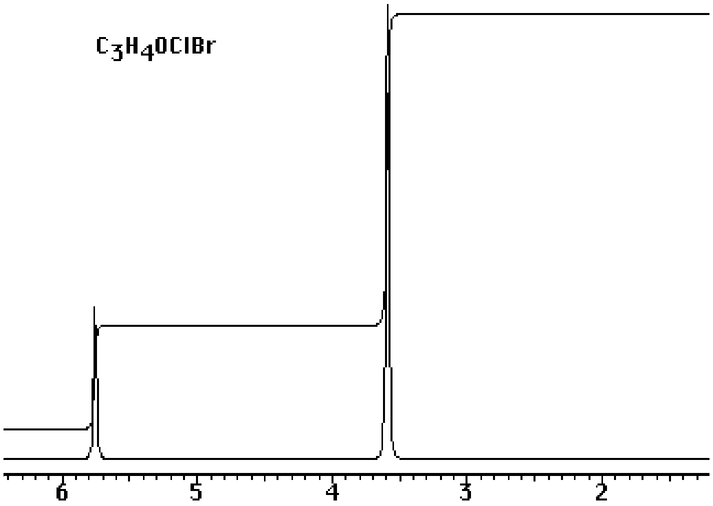
11. What do NMR spectra look like? Consider the molecule methyl formate.

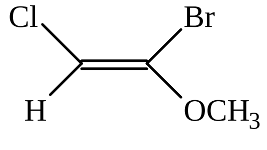


Notice the following pieces of information obtained from this spectrum:

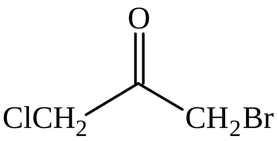
1. **Number of different kinds of hydrogens.** There are two signals, **A** and **B**. Why?
2. **Clues about the environments around these hydrogens.** Where are the two signals? Do they correspond with the table above?
3. **Number of hydrogens in each environment.** There is an *integration line*. The area under a signal is proportional to the number of nuclei it represents. The dotted grid is added to aid in determining the height of the integration line. Is it reasonable that the *ratio* of the areas of signal **A** to signal **B** is 3:1?

12. Hey, let's try to solve a problem!! I have isolated a compound from a strange marine organism. I have previously deduced that I have one of two possible isomeric compounds. Which one do I have, based on the NMR spectrum shown below?



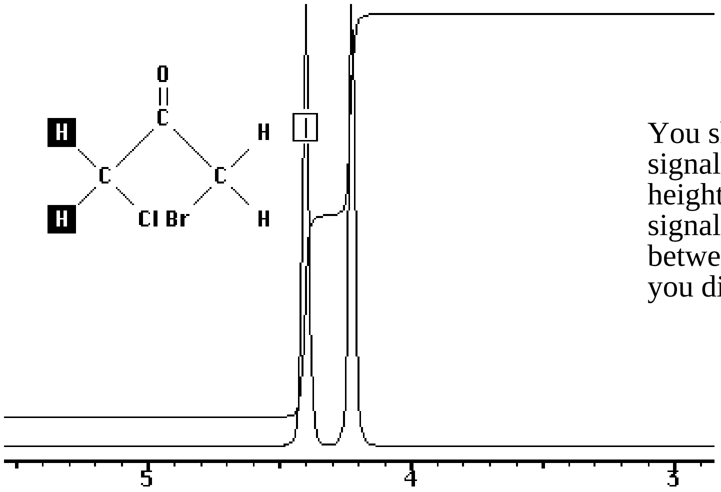


Which one??



You should consider:
1. # of signals
2. position of signals
3. integration

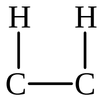
13. What should the NMR spectrum of the *other* compound look like?



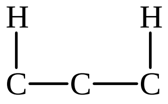
You should have drawn two signals of equal area (equal height). As long as your two signals were in the region between about 2.5-4.5 ppm, you did O.K.!

14. How do we know which hydrogens belong to which signal? We'll discuss this later, but here's a rule you can learn. Nearby electronegative groups shift the signals to the left. Since Cl is more electronegative than Br, the hydrogens nearer the Cl are further to the left. From this, you should deduce that electronegative elements increase ΔE (and ν). Conversely, electropositive elements (i.e. Si) decrease ΔE (and ν).

15. Well, let's make things a bit more complex. It turns out that the examples you have been given were "set up". Look closely, and you'll see that we have no cases where we have carbons bearing hydrogens right next to each other. In other words, we have not yet seen vicinal hydrogens.


$\overset{H}{\overset{|}{C}}-\overset{H}{\overset{|}{C}}$

These are vicinal hydrogens

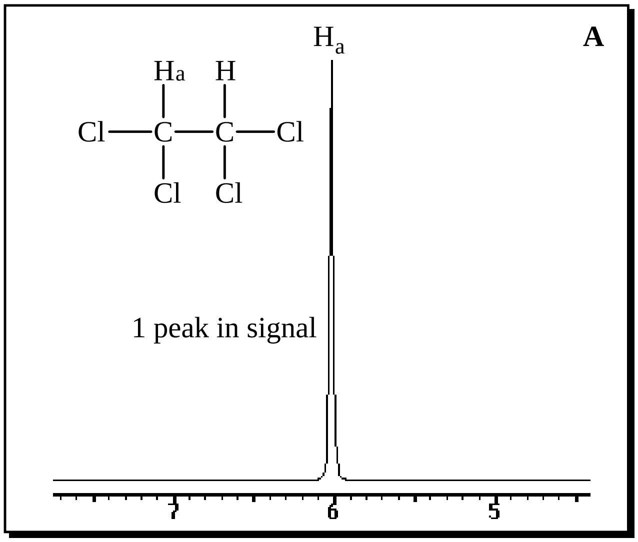

$\overset{H}{\overset{|}{C}}-C-\overset{H}{\overset{|}{C}}$

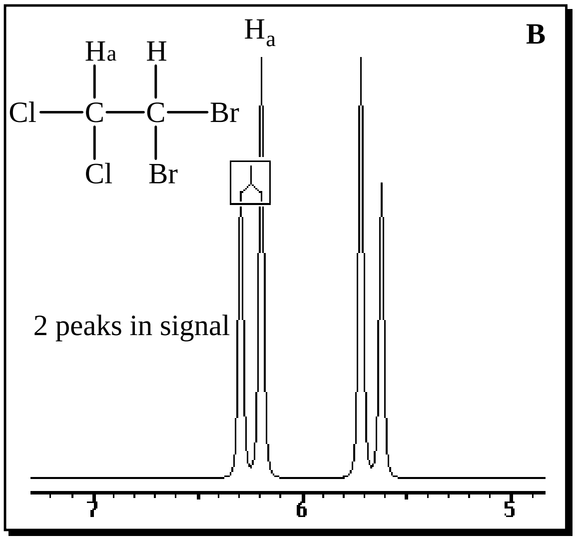
These are *not* vicinal hydrogens

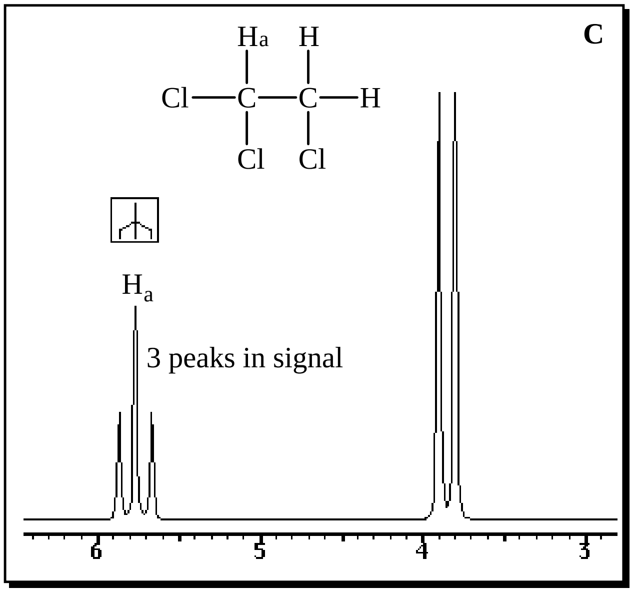
16. So what's the deal with vicinal hydrogens? It turns out that when hydrogens are this close to each other, they will affect each other. How? By causing the signals to split. This is called **coupling**, or *splitting*, and it provides us with really valuable information. Vicinal hydrogens can be coupled.

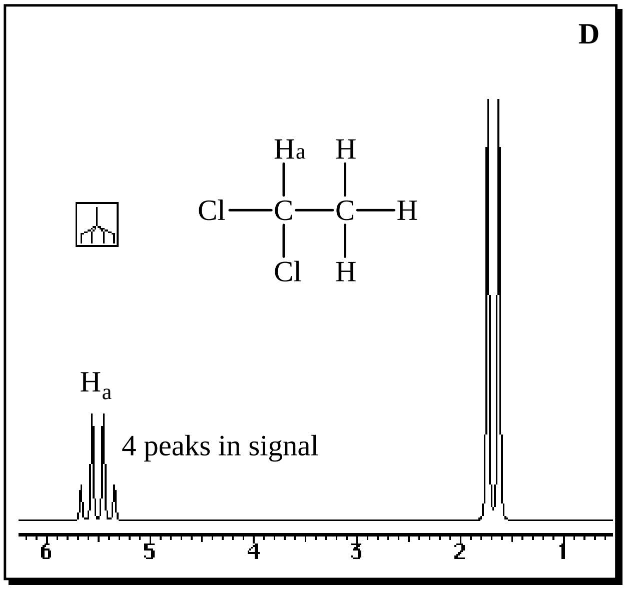
17. Coupling (or splitting) works in a curious way. There are two coupling rules:
    i. *To observe coupling*, the vicinal hydrogens must be in different environments.
    ii. They will split according to the N + 1 Rule.

18. You can only get this by seeing examples. So consider a hydrogen labeled as H_a. Let's allow it to be in a vicinal relationship to some other hydrogens and see what happens. Try to consider the two rules above, and see if you can figure out what the N + 1 Rule is.







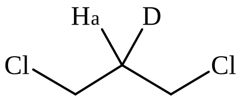


19. Hopefully you've deduced the N + 1 Rule. Let's look at things in more detail. Consider spectrum **A**. In this case all the hydrogens are equivalent, so no coupling is observed. Just one peak. Simple.

20. Skip to spectrum **C**. As expected, H_a is split into a *triplet*. However, the area ratio of the three peaks is not 1:1:1, but 1:2:1. This is always true of a *1st order* triplet. H_a splits the other hydrogens into a *doublet*, with two peaks in an area ratio of 1:1. All 1st order doublets are 1:1.

21. In spectrum **D**, the *quartet* has four peaks in an area ratio of 1:3:3:1. Again, all 1st order quartets are 1:3:3:1.
22. Note: in spectrum **D**, the total integration of the quartet is 1 H. Total integration of the doublet is 3 H.

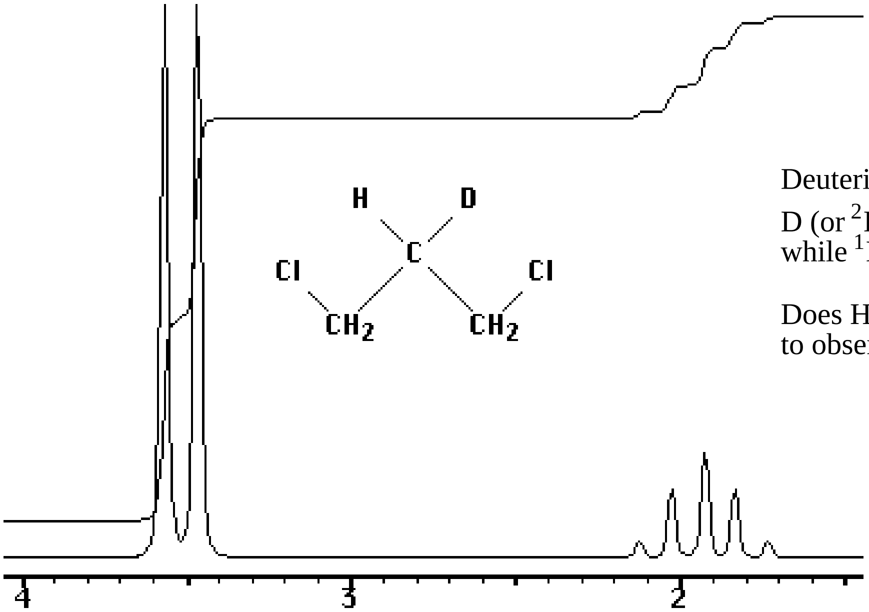
23. Consider the molecule below. How many peaks would you find for H_a? Apply the N + 1 Rule to the number of equivalent neighboring ^{1}H nuclei.



24. Did you guess five peaks? Of course, because their are four equivalent neighboring ^{1}H nuclei. Now the question is, what will be the area ratios of these peaks? Can you predict it? Yes! There is a simple method, and it uses Pascal's triangle. Simply put, Pascal's triangle directly gives you the area ratios for all 1st order *multiplets*, from singlets to doublets to triplets to quartets to quintets to sextets to septets and so on.

1
1 1
1 2 1
1 3 3 1
1 4 6 4 1
.

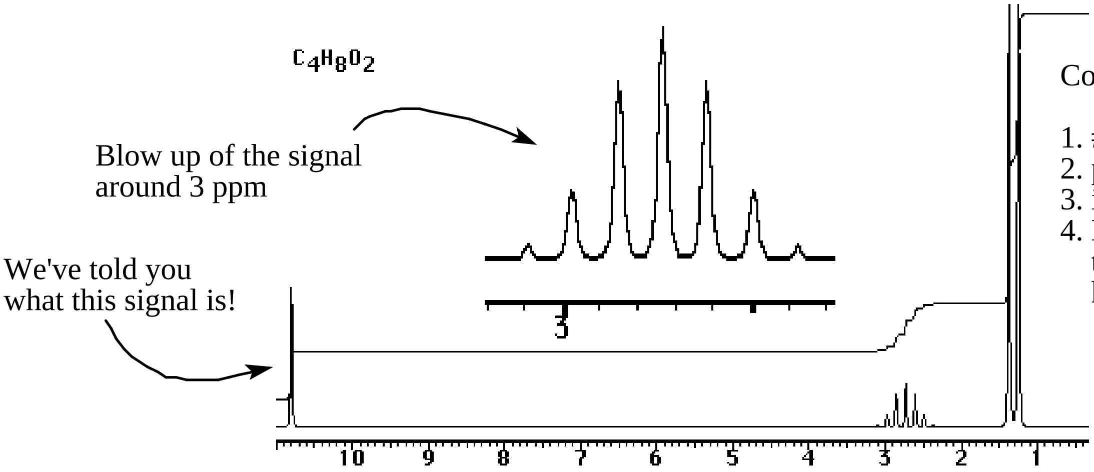
25. From Pascal's triangle, we would guess that a quintet would have area ratios of 1:4:6:4:1. Check the spectrum below. Does Pascal's Triangle hold? Check also the total integration of both signals. Also, why is the doublet to the left of the quintet?



Deuterium and hydrogen are*not* the same.
D (or ^{2}H) has 1 proton and 1 neutron, while ^{1}H has just 1 proton.

Does H couple to D? Yes, but it is difficult to observe, usually.

26. Let's solve another problem. I have an unknown compound with the molecular formula $C_3H_8O_2$. It is a carboxylic acid. What is its structure, based upon the spectrum below? (Note: calculating the degree of unsaturation is helpful.)



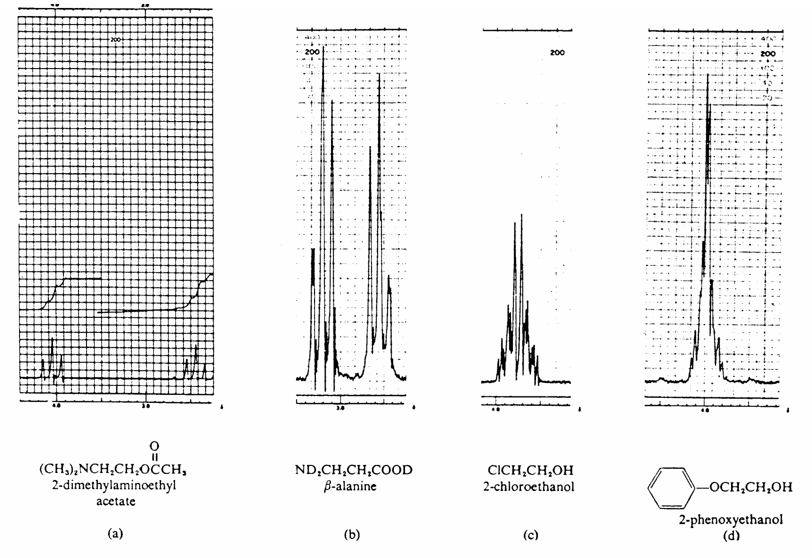
Consider:

1. # of signals
2. position of signals
3. integration
4. N + 1 Rule tells you the number of neighboring hydrogens.

27. Well, did you get it? You now know all the basic rules to elucidate the structures of compounds.

28. There are two more things you need to be aware of: _*2nd order* spectra_ and _coupling to more than one kind of hydrogen_.

29. We saw an example of a 2nd order spectrum. It was spectrum **B** earlier. In this case, you may have noticed that the doublets did not have area ratios of 1:1, as they should have based upon Pascal's Triangle. What's the deal? It turns out that if the chemical shift of coupling hydrogens becomes close, the individual peaks begin to lean toward each other. Strange but true. This is sometimes a problem, because if they lean too much you cannot determine the multiplicity easily. On the other hand, leaning sometimes help you determine which protons are coupled together. Some examples are shown below.



$(CH_3)_2NCH_2CH_2O\overset{O}{\overset{\|}{C}}CH_3$ 2-dimethylaminoethyl acetate (a)

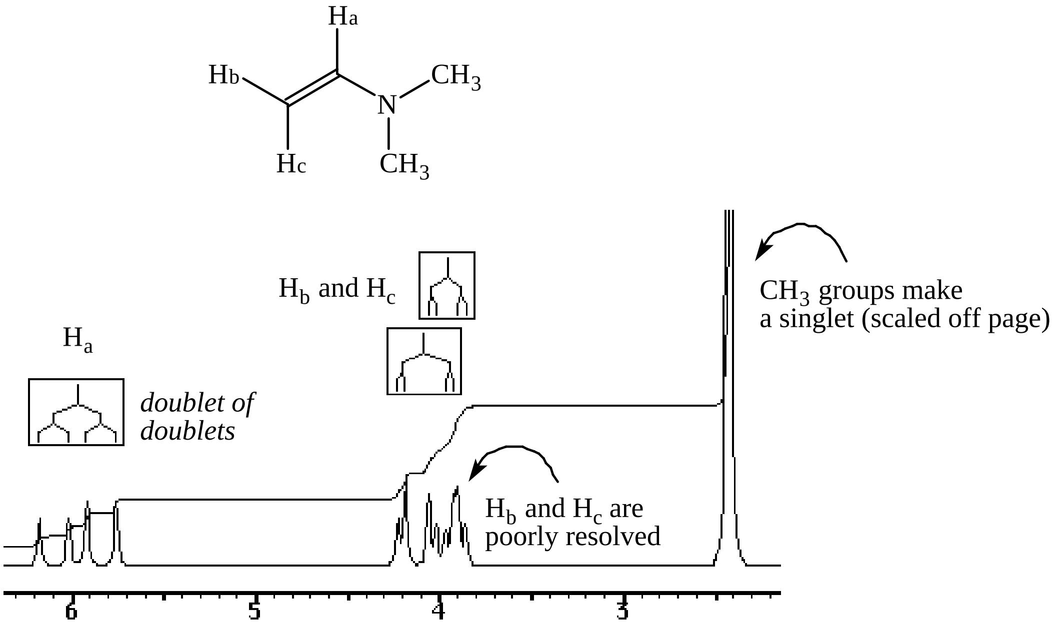
$ND_2CH_2CH_2COOD$ β-alanine (b)

$ClCH_2CH_2OH$ 2-chloroethanol (c)

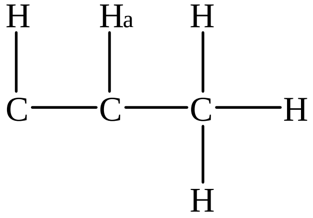
$—OCH_2CH_2OH$ 2-phenoxyethanol (d)

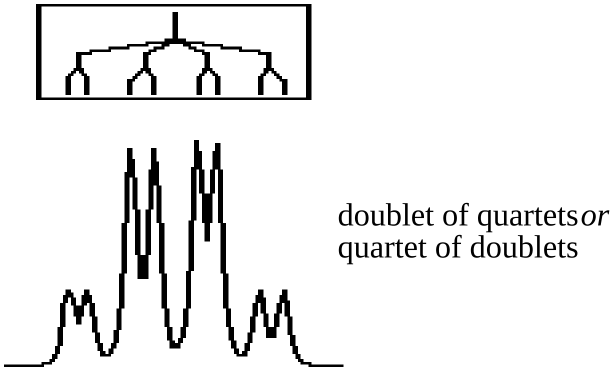
Progressive distortions as AA'XX' → AA'BB' in $Z-CH_2-CH_2Y$. 60 MHz.

30. Coupling to more than one kind of nuclei. This is the most complex case, but it can be figured out quite rationally. Consider the molecule on the next page. Look at H_a. What is it's multiplicity? A triplet? NO. It is *not* coupled to two *equivalent* hydrogens, so it will not be a triplet. Well then, is it a doublet? Still the answer is no. The way to consider this is to _look at each coupling individually, and add them together_.



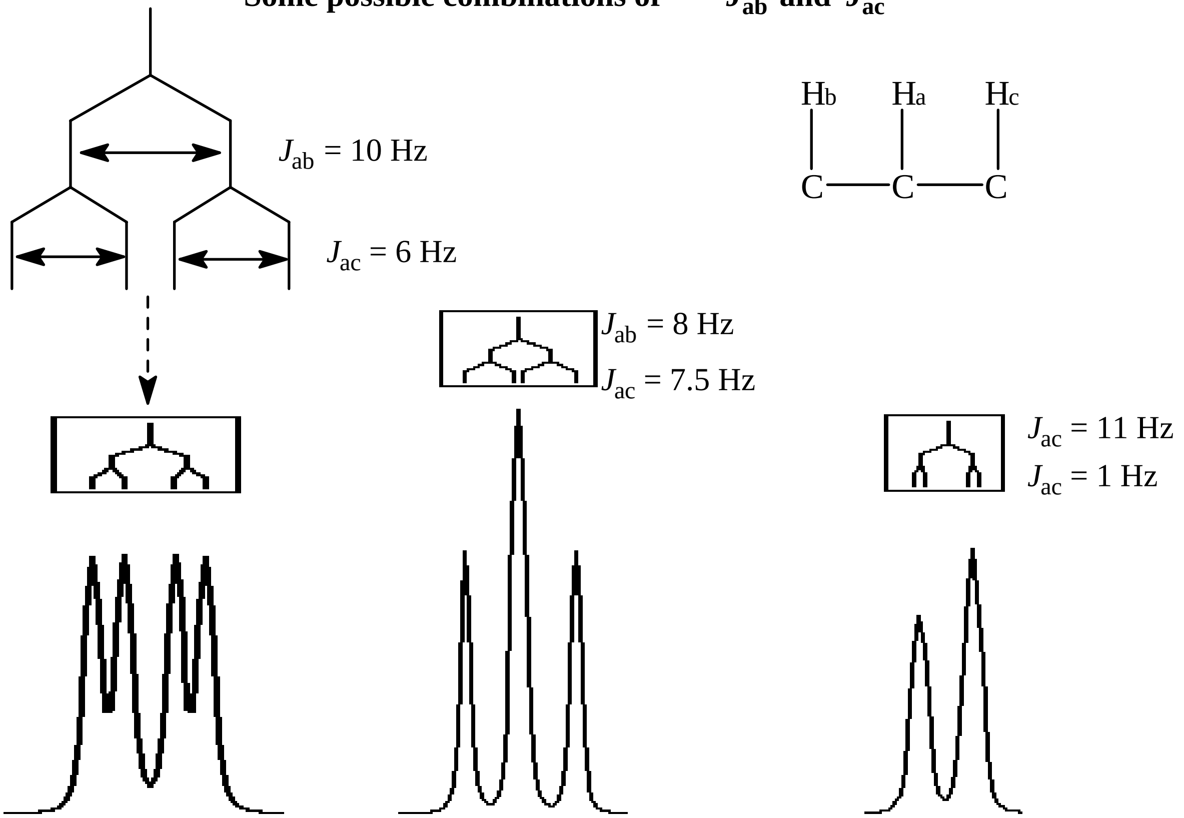
31. Let's do another one. Do you understand why the signal for H_a has eight peaks in the following case?





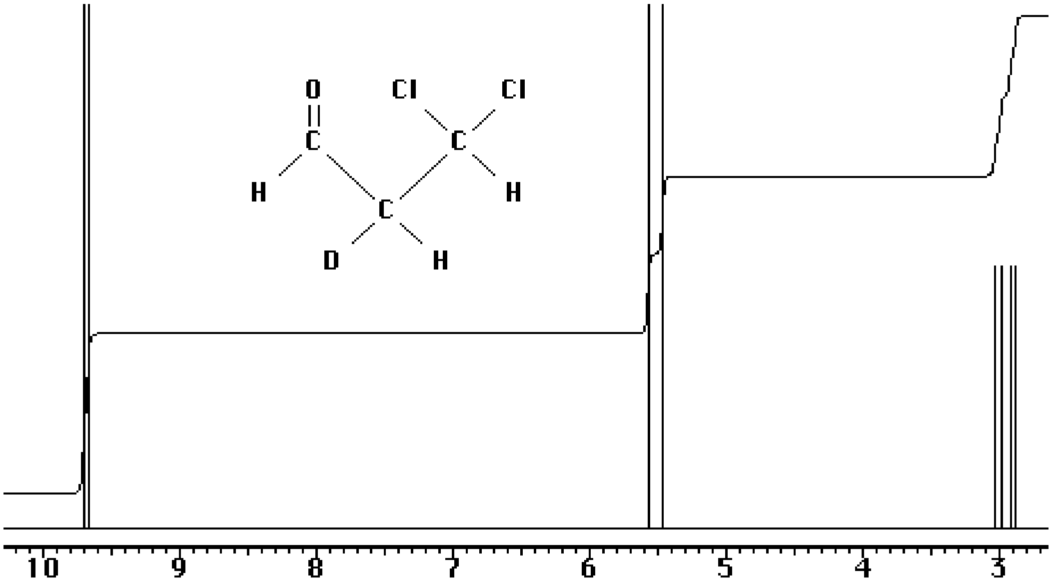
32. The distance between peaks in a doublet, triplet, or any multiplet can be measured in Hertz. This distance is called the coupling constant and is designated as *J*. In the example below, on the left, you can see that the two coupling constants are different, resulting in a doublet of doublets. One thing you must watch out for is this: what happens if the spacing between the two sets of couplings are the almost equal? Or what happens if one coupling constant is very small? The total number of peaks will change. For example, a doublet of doublets has three extreme outcomes, as shown below. Notice that what appears to be a triplet or a doublet may really be a doublet of doublets. This can, of course, fool you!

Some possible combinations of J_{ab} and J_{ac}

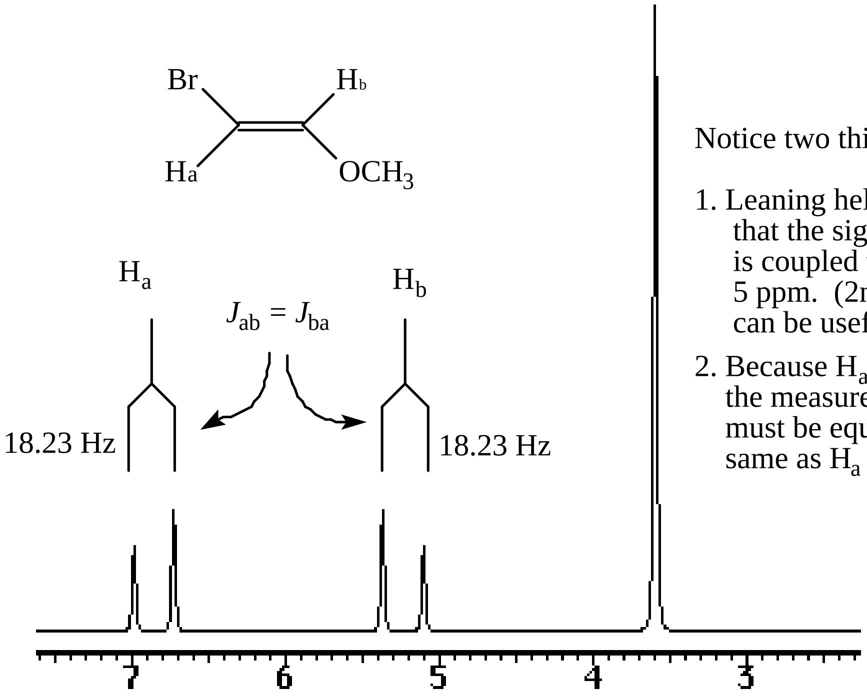


33. Coupling constants are generally not greater than about 20 Hz. They are a measure of the "intensity" of coupling between hydrogens. They are extremely useful to the advanced organic chemist!

34. Let's take some time to look at some example spectra and analyze them. Ask yourself the following:
    1. Are the **number of signals** correct? Could overlapping signals be a problem?
    2. Do the **positions of the signals** make sense? (Use table!)
    3. Is the **integration** correct?
    4. Can the **coupling** (splitting) be understood? Can you make a splitting diagram?

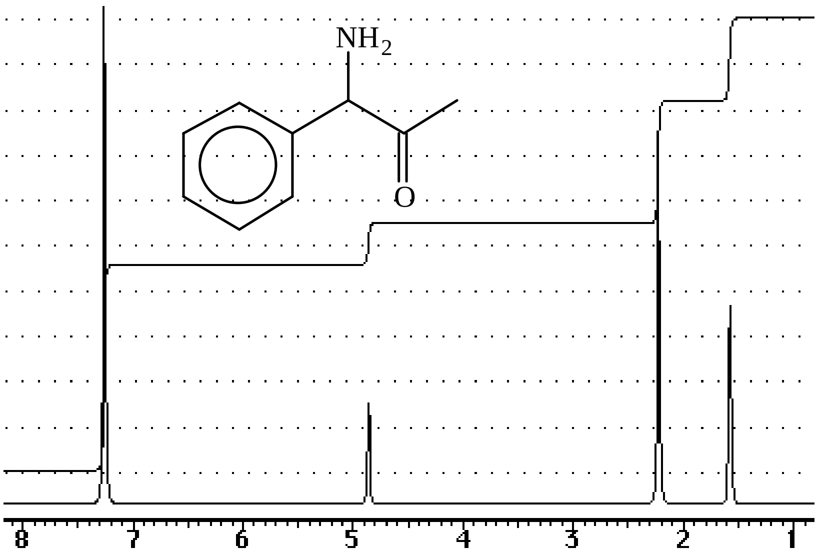


For this one I have presented a "line spectrum". Each line represents a peak.



Notice two things:

1. Leaning helps show visually that the signal near 7 ppm is coupled to the signal near 5 ppm. (2nd order effects can be useful.)
2. Because H_a is coupled to H_b, the measured coupling constants must be equal. (H_b splits H_a the same as H_a splits H_b.)

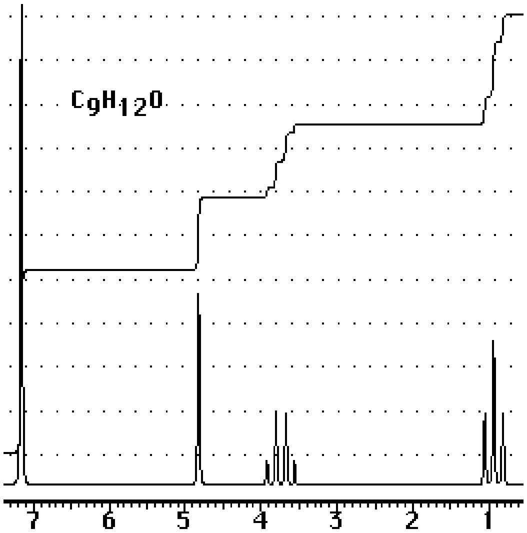


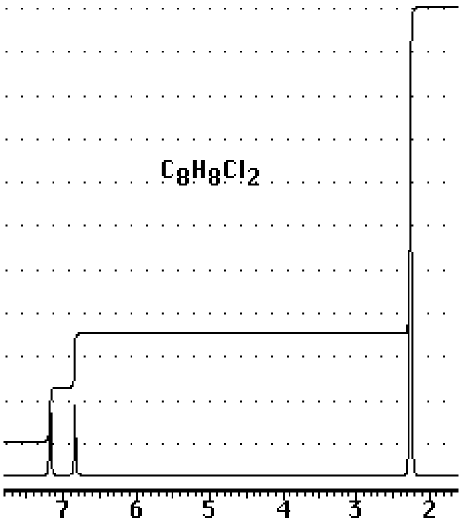
Can you assign hydrogens to each signal? How do you know where the NH_2 hydrogens are located?

Is it strange that all the aromatic hydrogens form only one signal? What's happening here?

Should the signal at about 5ppm be a singlet? What does this say about the ability of amino hydrogens to couple?

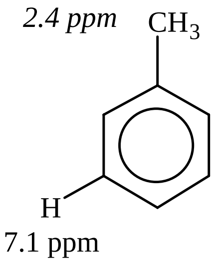
35. Here are some practice problems. Propose structures consistent with the MF and ^{1}H NMR data.

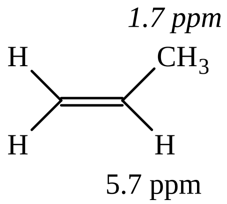


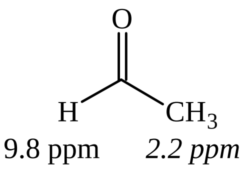


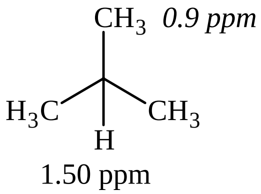
(Answers on last page.)

36. **Anisotropy**. Do you remember that we have learned one rule for trying to predict the approximate chemical shift for a proton? (It has to do with electronegativity.) Compare methyl and methine chemical shifts of the first three compounds with the last compound, 2-methylpropane. Notice that in the unsaturated compounds, both methyl and methine protons are shifted to the left? Why is this?

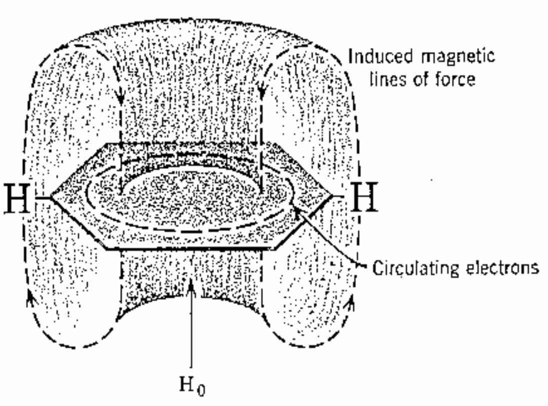


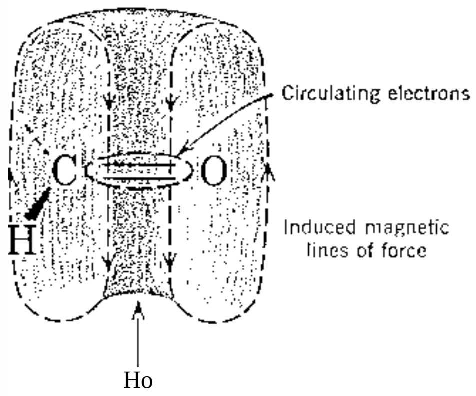






37. The shifts above are due to a phenomenon called **anisotropy**. It is caused by circulating electrons in π-systems and is pictured below. The circulating π-electrons create their own magnetic field, *that reinforces the applied magnetic field, H_o*. Thus, you've learned a second rule. Protons near double bonds or aromatics are shifted to the left. Protons *on* double bonds are shifted the most. This rule does not hold for triple bonds, although triple bonds do exhibit anisotropy.





38. A couple of practical details. Your sample compound must be placed inside an NMR tube, a glass tube with an inner diameter of about 2 mm. It is maybe 15 cm long. This tube will be placed inside the magnet. Your sample must be about 3 cm high in this tube, and must be liquid, or dissolved in a liquid solvent. This creates some problems because if your material is liquid, you may not have enough, and if it solid, you need to dissolve it in a solvent.

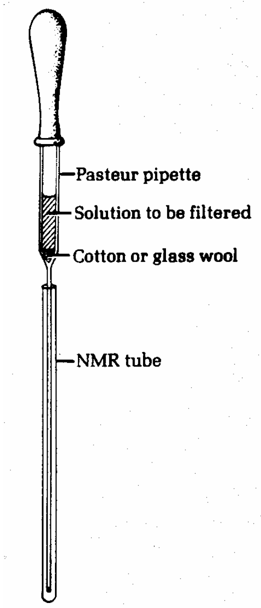
39. What types of solvents do you use? Imagine this. What if you use, say, hexane as a solvent? What would that do to your spectrum? You'd have a spectrum of hexane! So, you cannot use solvents that contain hydrogens. What else is left? One good solvent is CCl_4. However, there aren't many other good solvents with no hydrogens, so chemists have come up with a trickier solution. Use **deuterated solvents**! One popular deuterated solvent is $CDCl_3$. Others include benzene-d_6 (C_6D_6), CD_2Cl_2, CD_3OD, D_2O, and DMSO-d_6. Deuterium actually is NMR active, but it takes a completely different frequency to achieve resonance than does hydrogen. Most deuterated solvents are not 100% deuterated (costs too much), but are usually 98-99% deuterated. So often you will see a tiny signal for the non-deuterated solvent. For instance, you will see a small signal at 7.2 ppm when using $CDCl_3$, which is due to a little $CHCl_3$.

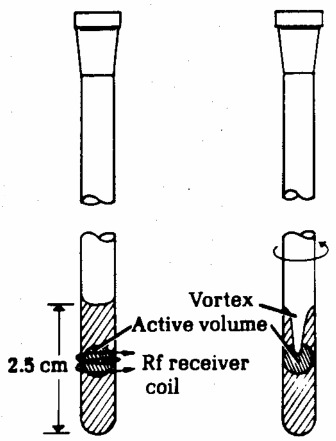
40. TMS is tetramethylsilane. This is the **internal reference** most often used in ^{1}H NMR spectroscopy. It is a liquid and you simply add a drop to your sample tube. When measuring an NMR spectrum, it is not convenient to actually try and determine the frequency of resonance ν exactly. Rather, we set the protons in TMS to 0.00 ppm, and determine all other chemical shifts relative to TMS. Reasons why TMS is so useful include:
    i. it is inert
    ii. it dissolves well in organic solvents (it *isn't* useful in D_2O)
    iii. it has a low boiling point, so can be easily removed
    iv. it gives only one signal, and the signal is out of the way (to the right of most other signals)
    v. it is cheap

(Answers: Left one is $PhCH_2OCH_2CH_3$. Right one is 1,5-dichloro-2,4-dimethylbenzene.)

Running An NMR Spectrum

A typical ^{1}H-NMR sample in a low-field spectrometer is 0.3-0.5 ml of a 10-20% solution of a nonviscous liquid in a proton free solvent contained in a 5-mm-diameter 18-cm-long glass tube. Less sample (5 mg) and more solvent (0.5 ml) are required in high-field spectrometers. The NMR sample tubes are expensive and delicate.





Deuterochloroform ($CDCl_3$) is one of the most widely used solvents in NMR. It dissolves a wide range of compounds. Residual protons in the $CDCl_3$ will always give a peak at 7.27 ppm. Chemical shifts of protons are measured relative to the sharp peak of protons in tetramethylsilane (TMS) (taken as 0.00 ppm). Stock solutions of 0.05-3% TMS in $CDCl_3$ are useful for preparing routine samples.

A wide variety of deuterated solvents are commercially available, for example, deuteroacetone (CD_3COCD_3), deuterodimethylsulfoxide (CD_3SOCD_3), and deuterobenzene (C_6D_6), although they are expensive.

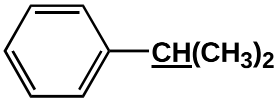
Solid impurities in the NMR sample will cause a very erratic spectrum. These can be removed by filtration of a sample through a tightly packed wad of glass wool in a Pasteur pipette.

The usual NMR sample has a volume of 0.3-1.0 ml, even though the volume sensed by the spectrometer is smaller. In order to average the magnetic fields produced by the spectrometer in the sample, the sample is spun by an air tribune at 20-40 rpm while taking the spectrum. Too rapid spinning or an insufficient amount of sample will cause the vortex produced by the spinning to penetrate to active volume, giving erratic, nonreproducible spectra. The sample tube is filled to a depth of 2.5-3 cm.

1) How many signals would each compound give in its ^{1}H-NMR spectrum? Explain why. Draw structure and show all different types of protons for each compound.

   a) Ethane
   b) Propane
   c) Butane
   d) *tert*-Butyl methyl ether
   e) 2,3-Dimethyl-2-butene
   f) (Z)-2-Butene
   g) (E)-2-Butene
   h) *sec*-Butyl alcohol
   i) 4-Nitrotoluene
   j) *cis*-1,2-Dimethylcyclopropane

2) What splitting pattern in the ^{1}H nmr spectrum would you expect for the hydrogen atom(s) underlined in the compounds shown below? Explain your answer briefly for each compound
   <u>Your choices are:</u> **s** singlet **d** doublet **t** triplet **q** quartet **m** multiplet. Enter the appropriate letter in the answer box to the right of each formula.



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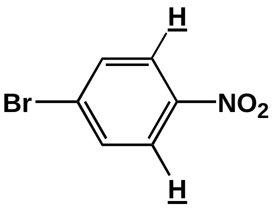

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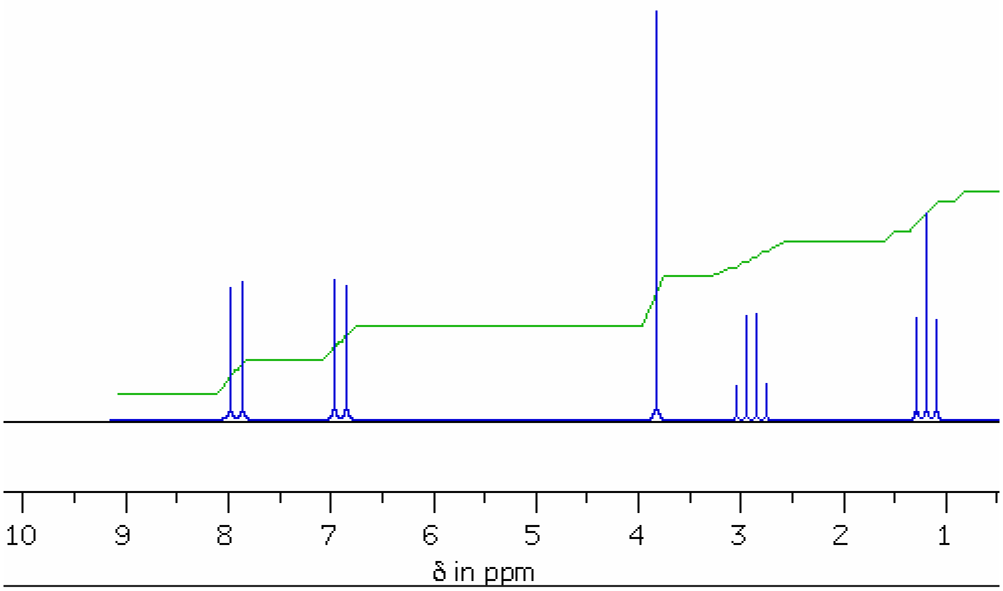
$Br-C\underline{H_2}-N(CH_3)_2$ ☐

3) Please answer the questions about the NMR spectrum presented below of a compound with the molecular formula $C_{10}H_{12}O_2$:



a) What is the multiplicity of the highest field signal from this sample? ____________

b) What structural feature is suggested by the singlet at 3.8 ppm? Circle your choice.

CH_3-C=O -CH_2- -O-H -O-CH_3 C-CH_3 C=C-H

c) From the multiplet line separations (coupling constants-J), which of the other signal is coupled to the quartet at 2.9 ppm?_____________

d) Using the integrator trace and the formula of the sample, assign a whole number ratio to the protons as follows:

7.9 ppm ____ : 6.9 ppm _____ : 3.8 ppm _____ : 2.9 ppm ______ :
1.2 ppm ______

4) Listed here are ^{1}H-NMR absorption peaks for several compounds. Propose a structure that is consistent with each set of data. (In some cases characteristic IR absorptions are given as well.). Explain your answer by assigning the protons to designated peaks and interpreting the IR data.

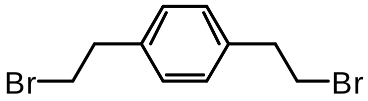
a) $C_4H_{10}O$ ^{1}H-NMR spectrum: singlet at δ 1.28 (9H), singlet at δ 1.35 (1H)

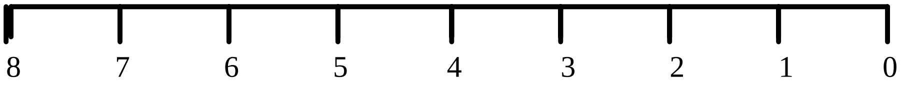
b) C_4H_8O ^{1}H-NMR spectrum: triplet at δ 1.05 (3H), singlet at δ 2.13 (3H), quartet at δ 2.47 (2H). IR spectrum: strong peak near 1720 cm^{-1}.

c) $C_4H_7BrO_2$ ^{1}H-NMR spectrum: triplet at δ 1.08 (3H), multiplet at δ 2.07 (2H), triplet at δ 4.23 (1H), singlet at δ 10.97 (1H). IR spectrum: broad peak in 2500-3000 cm^{-1} region and a peak at 1715 cm^{-1}.

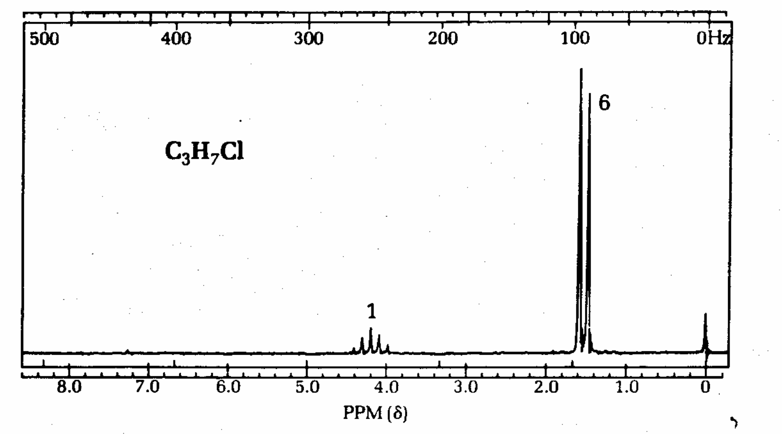
d) A $C_8H_4N_2$ compound shows a sharp infrared absorption at 2230 cm^{-1}. It's ^{1}H NMR spectrum has a singlet at δ 7.6 ppm. The ^{13}C NMR spectrum shows three signals at δ132, 119 and 117 ppm (This means there are 3 types of carbons). Suggest a structure for this compound.

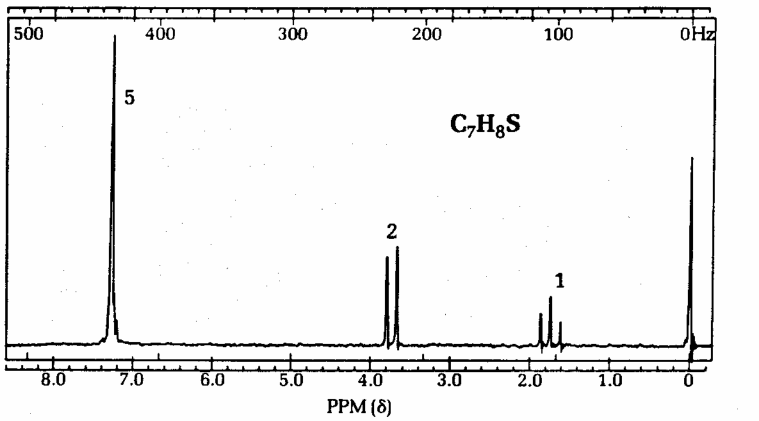
5) Please sketch the NMR spectrum of the structure below using the scale provided. Do not worry about the right chemical shift values, however show the relative positions of the peaks and their multiplicities.

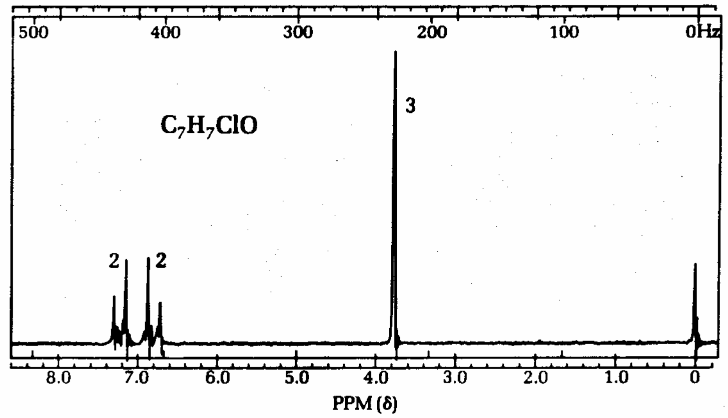




6) Please propose a structure consistent with each of the NMR spectra below (Explain how you come up with these structures). The numbers adjacent to peaks refer to relative peak integrations.







7) Interpret the NMR spectra (^{1}H, ^{13}C, and DEPT) of the sample you prepared at the end of the Techniques lab. For the ^{1}H NMR spectrum, prepare a table with chemical shifts, integrations, peak assignments, etc., as shown in the lab manual introductory material. Be sure to include a structure of the compound with your table, and make sure that you have clearly indicated which peak belongs to each proton/set of equivalent protons in the structure. For the ^{13}C NMR spectrum, prepare a similar table of chemical shift and peak assignments. Use the DEPT spectrum to assist in assigning the ^{13}C peaks.