Introduction to NMR

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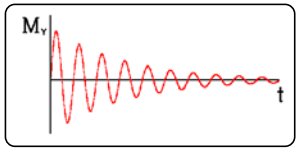
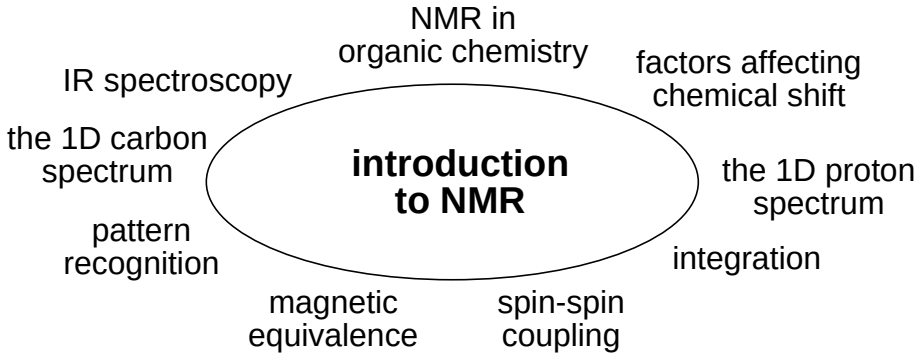
January 24, 2012.



Scope of Lecture



Chem 117

(1) **Prerequisites:** a basic knowledge of organic reactivity and stereochemistry. (*suggested benchmark:* took Chem 17 or Chem 20 and did reasonably well.) You are not assumed to know anything about NMR spectroscopy specifically.

(2) **Organization:** Tues/Thurs, 1-2:30 pm; optional sections on Wednesdays

(3) **Introduction:** The first four lectures will serve as the "NMR Primer" for Chem 135 students. Lecture videos for these will be available on the web for those with scheduling conflicts.

(4) **Evaluation:** problem sets (25%), structural elucidation project (25%), midterm (20%, open book), one final exam (30%, exam period).

Course Outline

(1) NMR Primer (4 lectures)
- how to read a 1D proton and carbon spectrum
- chemical shift and coupling constants
- assigning relative stereochemistry by the nOe, couplings
- spectra of known vs. unknown compounds

(2) Structural Elucidation (7 lectures)
- advanced 1D: APT, DEPT, TOCSY, etc.
- 2D NMR: COSY, HSQC, HMBC, etc.
- analysis of stereochemical data
- how to deal with all this data
- computational approaches: predicting NMR spectra

Midterm (March 9)

(3) Basic NMR Theory (5 lectures)
- the vector model
- the Fourier transform, data acquisition, instrumentation
- relaxation: the nOe, chemical exchange
- composite pulses, solvent suppression

(4) Advanced NMR Theory (7 lectures)
- quantum mechanics of angular momentum, spin
- product operator formalism and density matrix
- spin echoes, *J* modulation, coherence order
- INEPT vs. TOCSY transfer
- workings of COSY, HSQC, HMBC, etc.
- frequency discrimination methods
- pulsed field gradients and phase-cycling

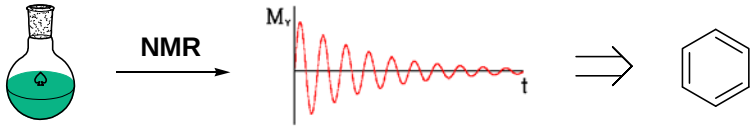
Structural Elucidation Project
Final Exam (Exam Period)

I thank Professors William F. Reynolds (Toronto) and Gene Mazzola (Maryland/FDA) for providing some useful material for this course and helpful guidance.

What Can NMR Do For You?

"A Short History of NMR." Freeman, R. *Chemistry of Heterocyclic Compounds* **1995**, *31*, 1004-1005.

NMR is about 65 years old. I won't say much about the history of it (see above reference), except to say that when it was introduced to organic chemistry, it was a revolution because it allowed chemists to figure out what they were making:



In this course, I will first try to teach you how to interpret the spectra of both very simple and complex organic molecules, but without worrying much about what NMR "is." Then, I will show you some details about what's actually going on in the machine.

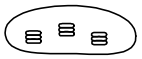
Q: What tasks do I need NMR for?

(1) structural confirmation

A ⟶ B *"Did I really make B and not C?"*
- assigning spectrum of known compound
- assessing purity of a sample

(2) structural elucidation

A ⟶ ? *"Huh? What did my reaction do?"*
- figuring out a completely unknown structure

 ⟶ ? *"What is this weird natural product?"*

(3) mechanistic studies

A $\xrightarrow{k}$ B *"What's the rate of this reaction?"*

A ⟶ [B] ⟶ C *"I want to look at an intermediate!"*

This course is meant to help you in your research.

NMR as a Widget

Trust me when I say the inner workings of NMR are really complicated, and will only hinder your understanding of how to use it at this early stage. So for the next while, I will forego the usual treatment of spins and Larmor frequencies and just treat NMR as a kind of widget or black box:

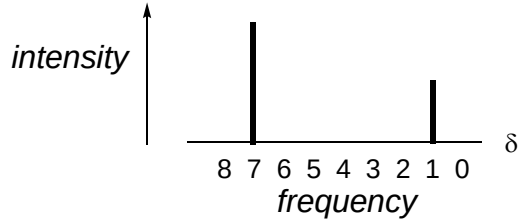
"nuclear magnetic resonance spectroscopy" **NMR spectrum**

If you know what to look for, >99% of the time, the NMR spectrum will tell you everything you need to know, i.e., what's in your sample. If you spend time doing organic chemistry, you will end up taking an NMR spectrum *every day*.

The 1D Proton Spectrum

Organic molecules are made mostly of carbon, *hydrogen*, nitrogen, and oxygen. As it turns out, almost every atom of hydrogen in a molecule (all the protons) emits, under the right conditions, an NMR signal that tell us something about what kind of hydrogen it is and what chemical environment it's in.

In a standard experiment, this is represented as a "one dimensional" spectrum which plots intensity vs. frequency. Here is an idealized cartoon:

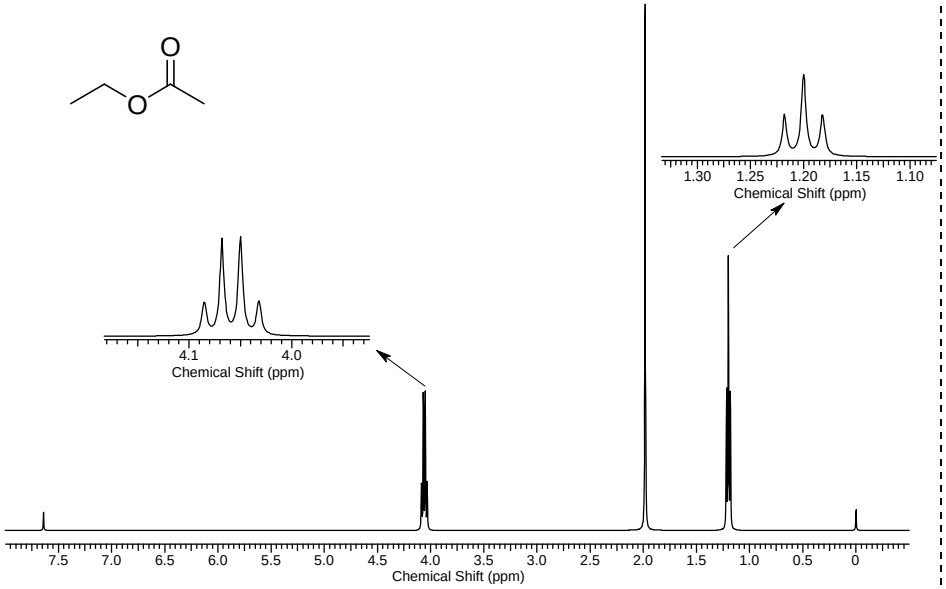


For inscrutable historical reasons, the frequency scale increases from right to left (instead of left to right, as is found in normal graphs). Every signal is called a "peak."

Q: What do all these peaks mean? (This question will occupy a lot of our time.)

The Chemical Shift

Now, I'll show you some spectra, and explain everything by example. Here is a sample that contains ethyl acetate in deuterochloroform ($CDCl_3$), a common NMR solvent:

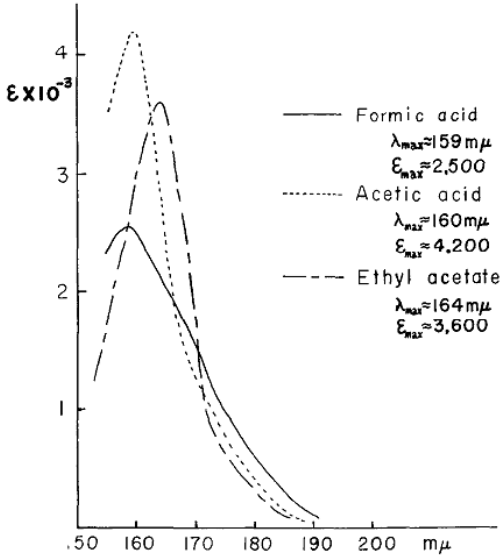


(Actually, this is computer-generated spectrum made with ACD/NMR Predictor v12. But trust me, the real spectra look very similar to this.)

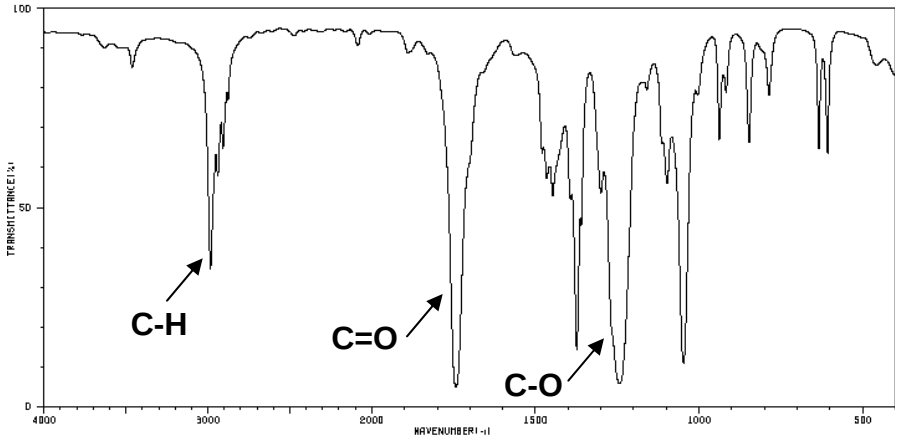
What do you notice about this spectrum?

(1) The peaks are *sharp*. This is a really important advantage that NMR has over other spectroscopies. This has to do with the lifetime of NMR states being relatively long, and through the energy-time uncertainty principle, having small uncertainities in frequency. The states are long because we are dealing with *nuclear* spins, which are relatively slow-moving compared to the electrons. (It's a little odd to think that looking at the *nuclei*, which is not really where a bond "is," still tells us something useful. But it works.)

In contrast, ultraviolet-visible (UV-vis) or infrared (IR) spectroscopies deal with short-lived electronic and rotational-vibrational states and relatively broad spectrum. Here are the UV-vis spectra of ethyl acetate, formic acid, and acetic acid (*J Mol Spec* **1964** *13* 1):

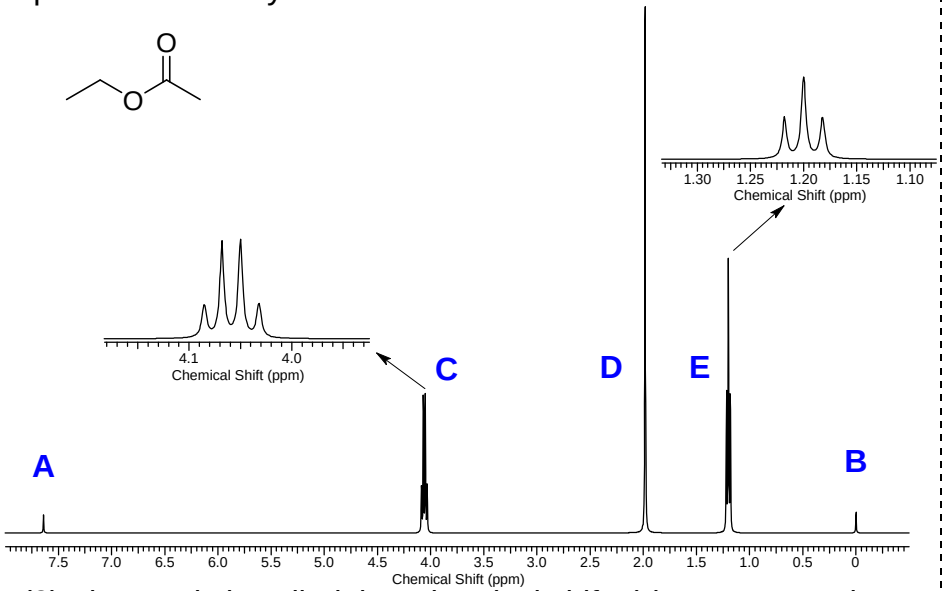


These spectra are *virtually useless* from a structural standpoint: these molecules are quite different, but have practically the same UV-vis spectra. (The position of the maximum can be informative as to the degree of unsaturation, but that's about it.) The IR spectrum of ethyl acetate is more useful (SDBS). In general, IR can identify functional groups:



The Chemical Shift

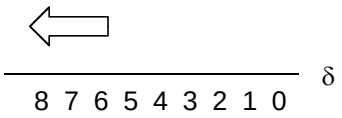
However, the IR spectrum is really, really complicated, and beyond acting as a test for functional groups, is not really suitable for routine structural work. However, the NMR spectrum is readily understandable. Let's take a closer look at it:



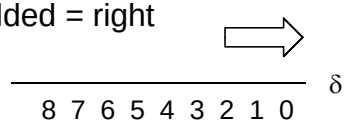
(2) The x-axis is called the "chemical shift" (δ). By convention, the protons in tetramethylsilane are assigned a chemical shift of exactly 0 ppm. Roughly speaking, ***the more electron-poor a proton is, the higher its chemical shift.***

(3) Often we will want to talk about which side of the graph things are going in, so here is some terminology:

downfield, less shielded = left



upfield, more shielded = right



(4) Let's try to identify what everything is in the spectrum. First, signal **A** is chloroform (C**H**Cl_3). The hydrogen in chloroform has three chlorines around it, and so is relatively electron poor. Thus, it has a high chemical shift.

Q: Why is chloroform in the spectrum at all, given that the sample was taken in *deutero*chloroform?
A: Deuteration is never complete in these solvents, merely almost complete (like 99%).

Q: Why use deuterochloroform instead of a regular solvent?
A: If you used chloroform instead, then you would see a giant peak for chloroform, and tiny little peaks for your compound, which would be bad for signal:noise.

Q: Well, can I take the spectrum without solvent (i.e., neat)?
A: You can, but this isn't very convenient for a lot of reasons, the biggest of which is probably that when you're working on developing chemistry, you probably don't have that much sample. The spectrum may also look bad (we'll see why later.)

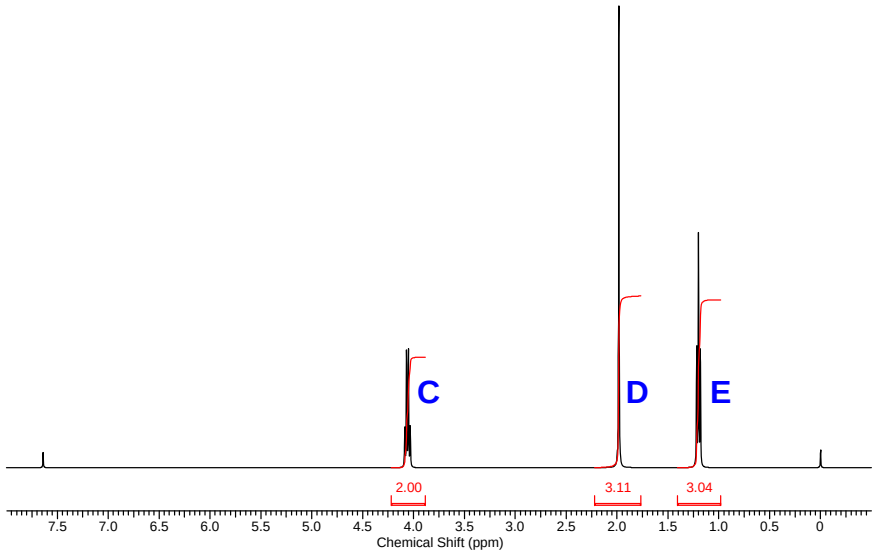
Q: So just how sensitive is NMR?
A: To give you some perspective, it is absolutely routine to get a nice-looking spectrum on 1 mg of material (a few specks on the tip of a spatula, or a very tiny drop of liquid on the end of a Pasteur pipette). However, for routine work, 0.1 mg would be tricky. So NMR is pretty sensitive, but it's nowhere near as sensitive as mass spectrometery.

(5) **B** is tetramethylsilane (Me_4Si). (The methyl groups are undergoing fast rotation, so everything is averaged to one signal.) This is sometimes added to samples for internal referencing, but more often, the x-axis is referenced to residual solvent (i.e., signal **A**.)

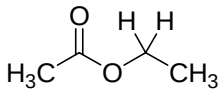
Q: This leaves signals C, D, and E. What do they mean?

The Chemical Shift

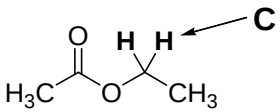
Signals **C**, **D**, and **E** belong to ethyl acetate itself. But which is which?



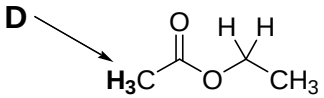
For this discussion, it helps to draw out ethyl acetate explicitly:

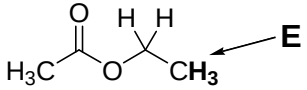


Of these, the hydrogens next to the most electronegative atom, oxygen, are the most downfield:



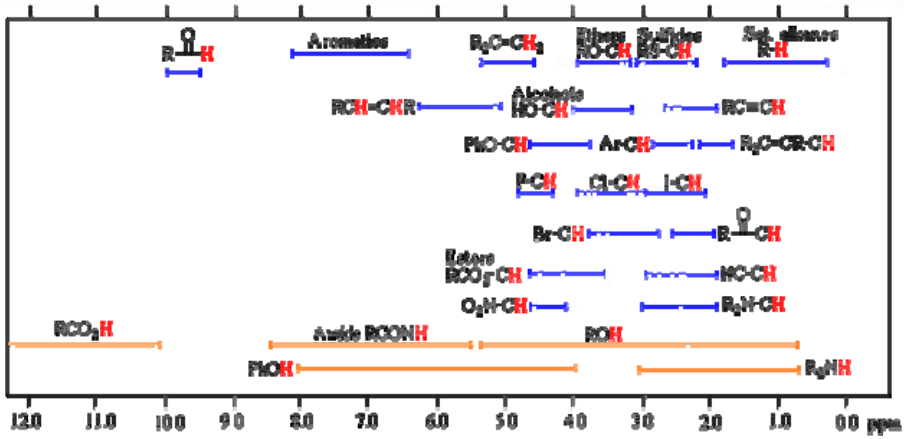
On the same basis, we can assign **D** to the methyl group to the three protons on the methyl group adjacent to the somewhat less electron-withdrawing carbonyl group, and **E** to the methyl part of the ethyl group.





(1) Chemical shifts don't vary a lot from solvent to solvent, with the exception of those that are affected by hydrogen-bonding.

(2) In fact, chemical shifts vary in a way that is very predictable, and people have made tables of what goes where. Here is an example (Dr. William Reusch, MSU):



Memorizing these things is tedious, and I won't make you do it. But as you do more and more problems, you will get to know some of the key numbers.

(3) What are the red lines? These are the **integrals**. The amount of observed signal, as measured by the area under the curve, is proportional to the number of nuclei giving the signal. So the integrals tell you the empirical formula. (There might be some symmetry, so they don't necessarily tell you the molecular formula.)

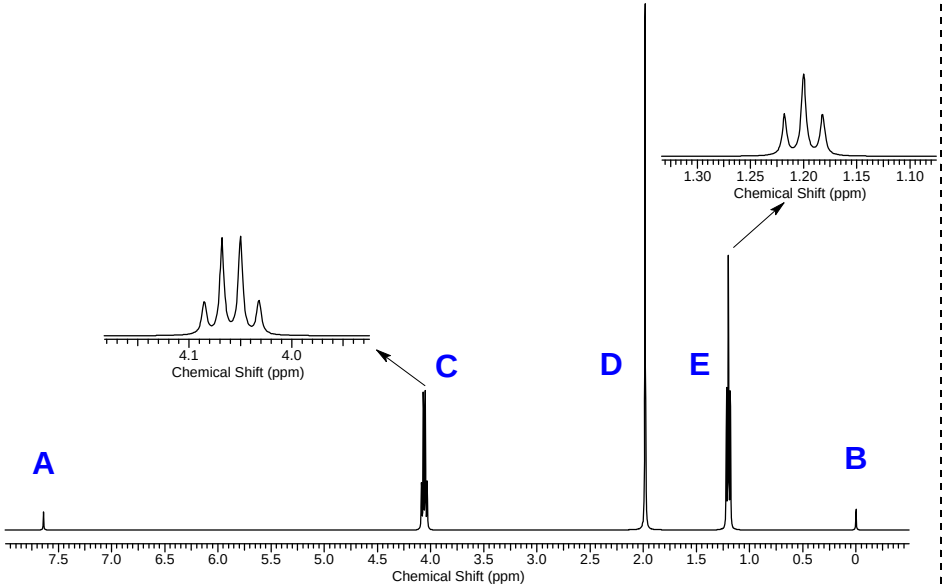
(4) Thus, if we knew the compound was ethyl acetate, then **C** must be the CH_2 group, since it has an integral of 2.

(5) By convention, in NMR, carbons are designated by how many attached protons there are:

C = "quaternary" carbon	CH = methine
CH_2 = methylene	CH_3 = methyl

Coupling Constants

If you look closely at the peaks of ethyl acetate, you will see that **C** and **E** have some fine structure to them, but **D** doesn't:



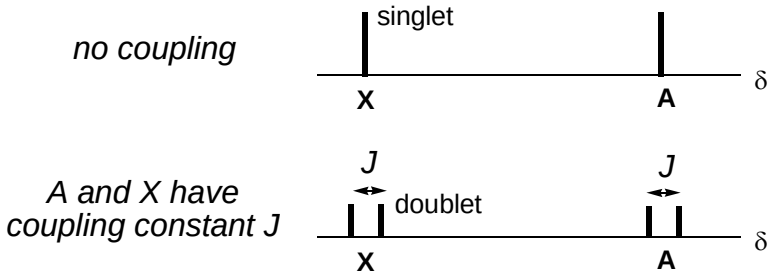
What does this mean? This is called "spin-spin splitting" or "*J* coupling." To understand this, we need a tiny bit of background.

(1) An individual proton can be in the α state or the β state. These spin states have something to do whether the proton's spin moment is aligned with or against the applied magnetic field. The NMR chemical shift is related to the energy difference between these α and β states.

So this means that one proton gives *one* peak. (There aren't two, since NMR measures differences between the energy levels, not the energies of the levels themselves.

(2) If you have two protons which don't interact, then you get two peaks. The frequency of each peak represents the α–β gap for each proton.

(3) However, if the protons are close to each other (as judged by the number of bonds separating them, as opposed to the distance in space between them), then they can interact to give a different, coupled spectrum:



The simplest case, depicted above, is where the interacting protons are quite different in chemical shift. This is denoted by the "AX" nomenclature (as opposed to two things that are close in chemical shift, which would get the "AB" designation).

Now, of course, if A is coupled to X, then X must be coupled to A. The coupling has turned a single peak ("a singlet") for A into two peaks ("a doublet"). ***In general, a proton interacting with n other protons will give multiplet of order n+1.*** Thus, a proton interacting with two other protons will give a triplet, and so forth. ***However, protons with the same chemical shift don't split each other.*** Thus, the protons on a methyl group don't split each other and isolated methyl groups are singlets.

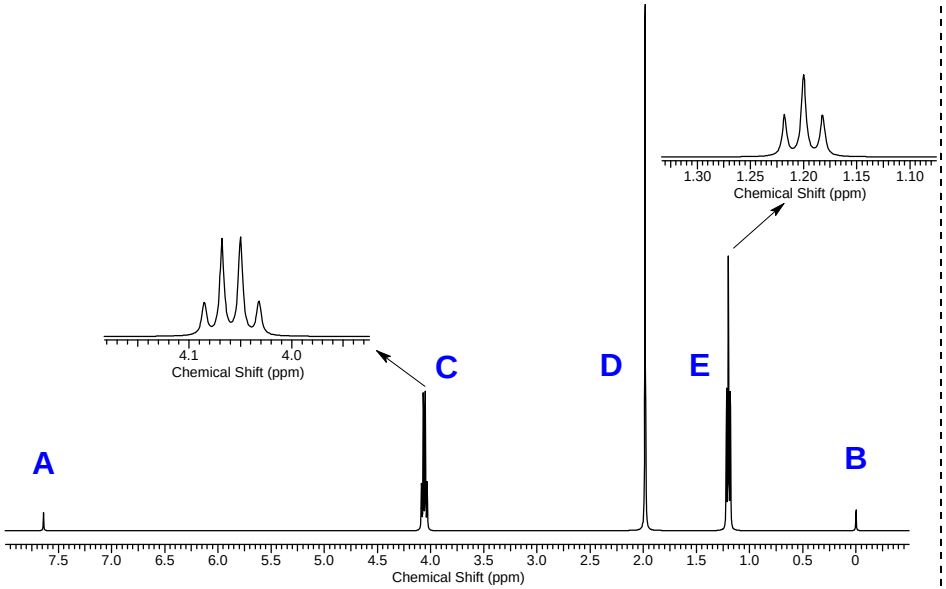
The energy diagrams of how all this occurs are complicated, and would only distract us at this point. For now, I'll just mention that the picture above breaks down if the frequency separation between A and X gets close to the value of *J*.

Q: How do I know if two protons will interact?
A: In general, they'll interact if there's three or fewer bonds between them. (Not always true, but approximately right.)

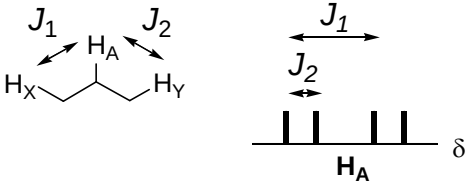
Q: Why does any of this matter?
A: Identifying spin-spin splitting patterns can help us figure out the structure of a molecule.

Coupling Constants

If you look at the spectrum of ethyl acetate again, you can see that the peaks aren't doublets. In fact, they seem to have a variety of shapes:

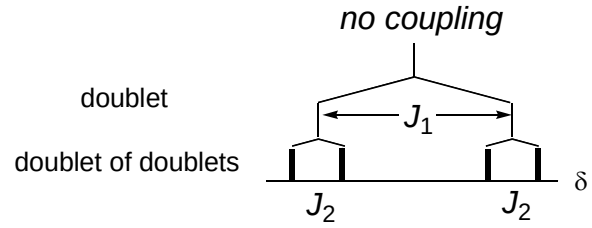


To understand this, imagine a proton A (just any proton A, not the peak **A** above, in case you were confused) is coupled to two other protons, X and Y, with two coupling constants J_1 and J_2, respectively. What spectrum will it give? (In the cartoon of the molecule below, imagine A, X, and Y are the only protons.)

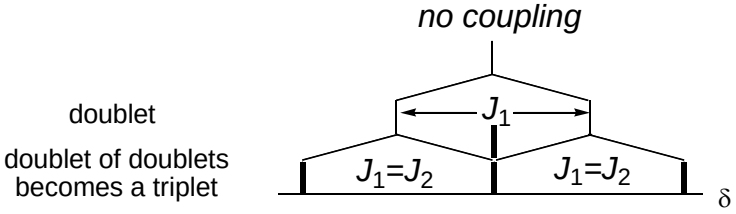


"doublet of doublets"

We can imagine this happening in a step-wise process. First, imagine there's just A and X. That gives a doublet with a coupling of J_1. Then, add in Y. Each peak is doubled again with coupling constant J_2. This can be represented with a "coupling tree diagram":



H_A is still only one proton, so each black stick is merely one quarter of the size it would be without any coupling. But what happens when $J_1 = J_2$?



This puts two black sticks right on top of each other, which just makes one black stick of twice the height.

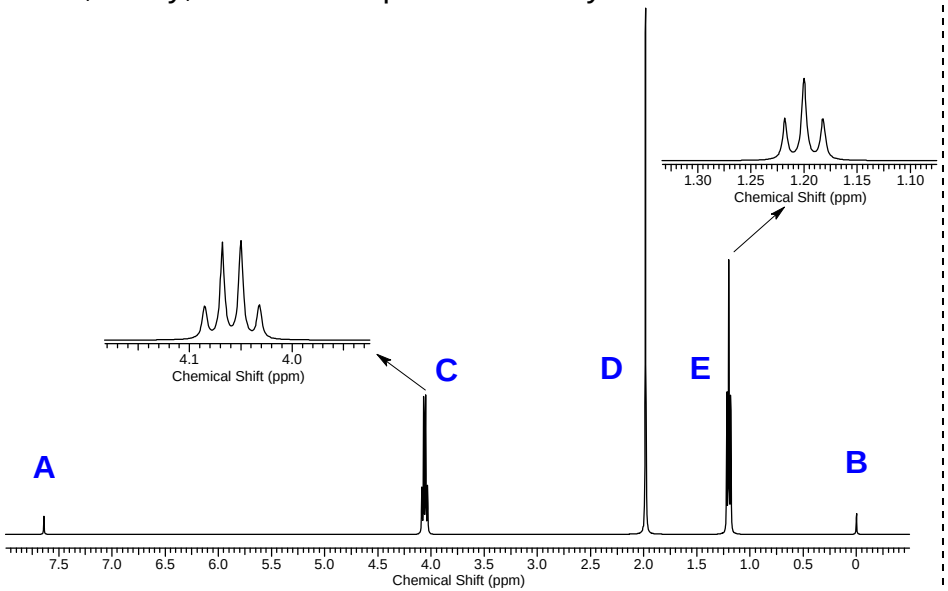
So let me revise what I said before. ***A proton interacting with n other protons gives an n-th order doublet.*** Sometimes, the proton will have the same coupling constant to several protons, in which case, the *n*-th order doublet will become partially degenerate. Degenerate *n*-th order doublets have intensities that follow Pascal's triangle:

```
          1
        1   1
      1   2   1
    1   3   3   1
  1   4   6   4   1
```

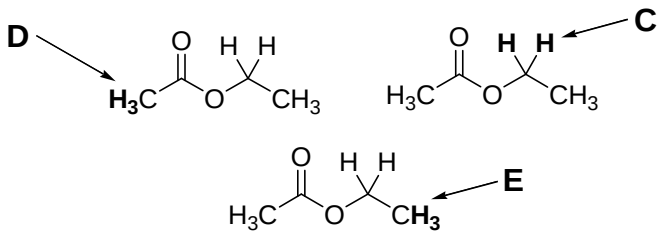
Terms like "triplet" and "quartet" refer to these degenerate *n*-th order doublets. It's possible to have partially degenerate multiplets, like a "doublet of triplets." That would mean a third-order doublet (ie, three coupling constants corresponding to a doublet of doublet of doublets), but where two of the couplings are the same (J_1, J_2=J_1, J_3).

Coupling Constants

Now, finally, back to the spectrum of ethyl acetate:

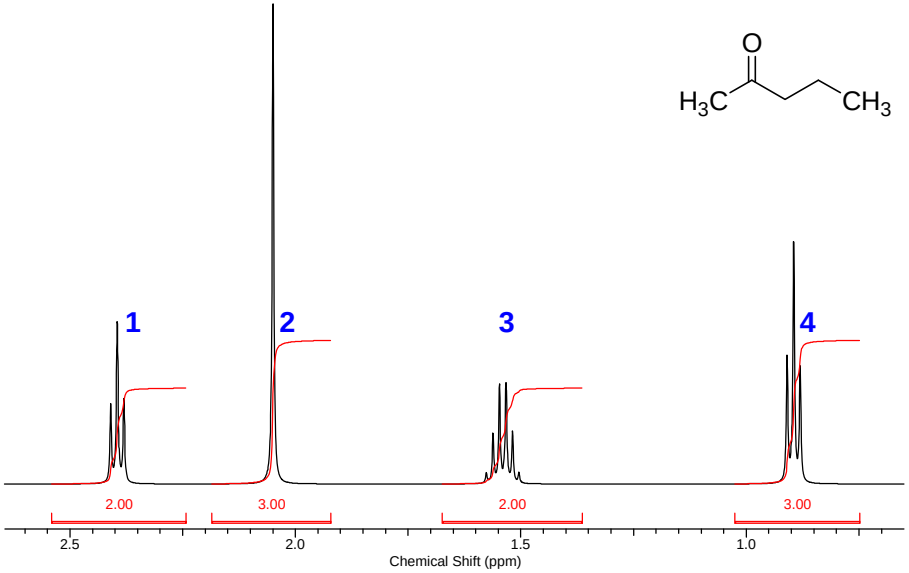


Now, we can see why **D** is a singlet. The methyl group is spinning around very quickly, so all of its protons have the same chemical shift. Therefore, one methyl proton doesn't split another. The nearest protons of a different chemical shift, the methylene **C**, are five bonds away, which is too far to see a significant interaction:



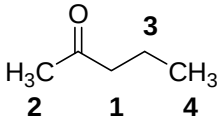
What about the other methyl group (**E**)? It's coupled to two protons (i.e., **C**), so it's a second-order doublet. But it's a triplet because the two coupling constants are the same. Going the other way, **C** looks like a quartet because **C** is coupled to three protons, with all three couplings being the same.

We can now look at some common coupling patterns. We now know that a triplet connected to a quartet means an ethyl group. Can you understand this spectrum of methyl propyl ketone?



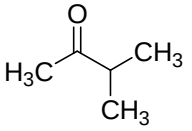
Note that I've labeled the peaks from left to right as 1, 2, 3, ... I'll keep this convention for the rest of the course.

The assignments are:



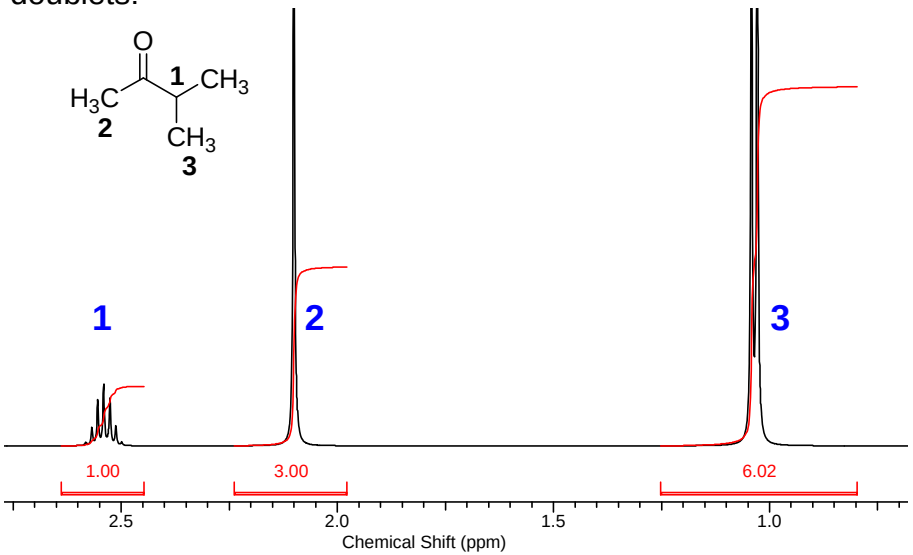
2 is worth three protons and is a singlet, so it's the methyl ketone. **4** is also worth three protons, but is a triplet, so it's a methyl group next to a methylene. **1** is worth *two* protons, and is a triplet, which means it's a methylene next to another methylene. Finally, **3** has a complicated structure because it's next to both **1** *and* **4**.

Q: All right, what splitting do you expect for this molecule?



Coupling Constants

The left hand methyl group, once again, must be a singlet. But what about the isopropyl group? The methine is coupled to six methyl group protons, all of the same averaged chemical shift and coupling, so it appears as a six-fold degenerate doublet, which is a septet. Likewise, the methyl groups appear as doublets:



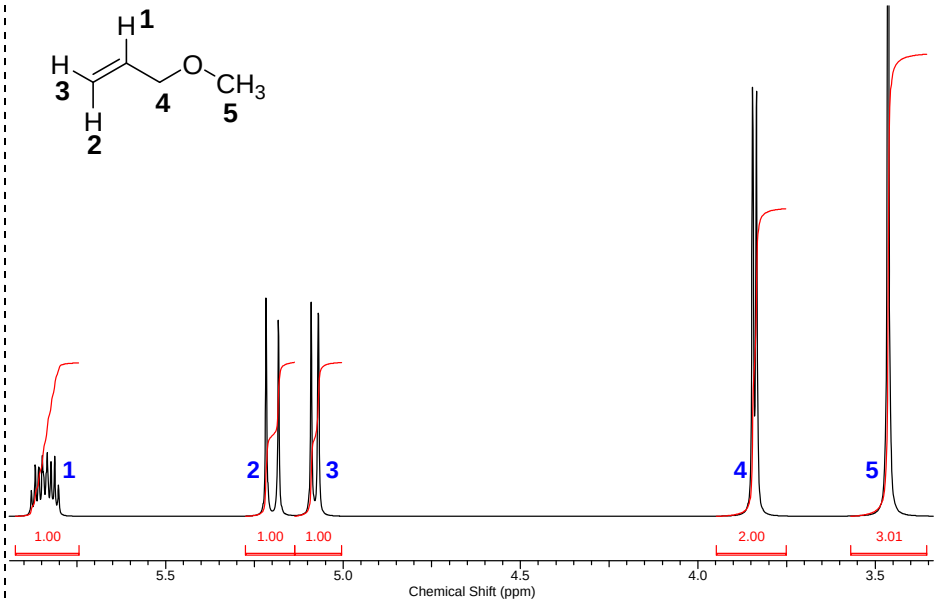
We can apply this thinking in reverse: anytime we see a 6-proton doublet with a septet, that suggests an isopropyl group. Let's assign another example: allyl methyl ether.

You'll need to know this first:

(1) Protons on sp2 carbons have more downfield (larger) shifts. You can think of proton feeling more of the nuclear charge when it has more s-character, and therefore being more electron deficient. Thus, shifts in the 5-6 ppm region often mean an olefin is around.

(2) Protons near oxygen often have shift of 3-4 ppm. This is an inductively electron-withdrawing effect from the oxygen atom.

(3) shifts increase in the order: CH3 < CH2 < CH (largest)



(1) There are two signals in the region near oxygen. From both integrals (2H vs 3H) and electronegativity (CH_2 vs. CH_3), we can distinguish between **4** and **5**.

(2) **1** is a CH while **2** and **3** are CH_2s, so **1** is the most downfield.

(3) **2** is downfield of **3** because anti is a better orientation than syn for σ_{CH} to σ^*_{CH} hyperconjugation

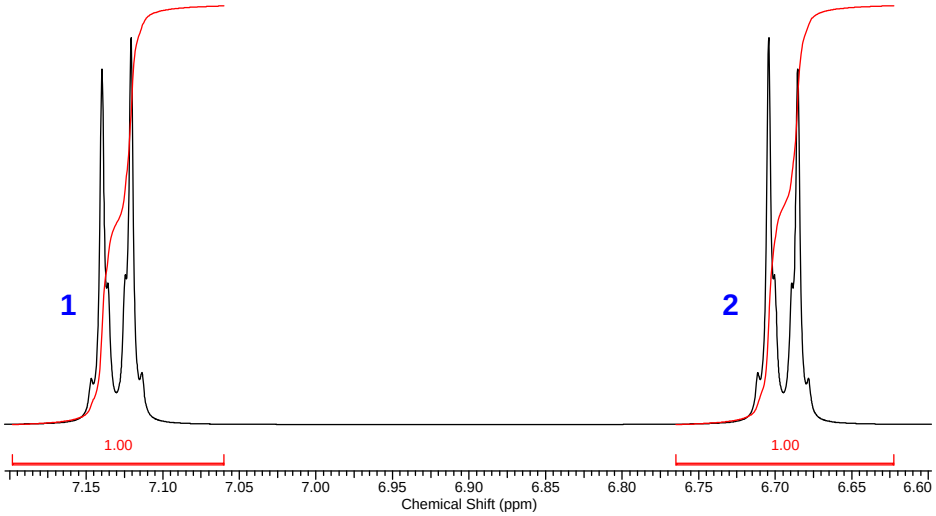
(4) What about the coupling patterns? Certainly, CH_3 **5** is a singlet since it doesn't have any adjacent protons. **4** is a doublet since it has one adjacent proton, **1**. However, **1** has four adjacent protons, which have three unique chemical shifts, so it has a very complicated pattern.

(5) **2** has two adjacent protons: **3** and **1**. So why isn't it a doublet of doublets? It turns out that two bond (geminal) coupling constants for sp2 carbons are very small. So **2** only really sees the coupling to **1** and is a doublet.

Aromatic Substitution Patterns

Let's see if we can use this kind of coupling constant thinking to understand the substitution patterns in aromatic rings. This is the spectrum of a doubly-substituted (Cl, OMe) aromatic ring.

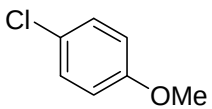
Q: Are the substituents ortho, meta, or para to each other?



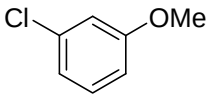
(1) As it turns out, protons on benzene rings are typically in the 7-8 ppm range. The classical picture is that the electrons are "circulating" in the aromatic ring, and this cyclic flow produces an unusually strong magnetic field that reinforces the external field, resulting in a larger chemical shift.

(2) The integrals are 1:1, but this only tells you that there is a 1:1 ratio of protons with those chemical shifts, not the number of protons themselves, which is 2 and 2.

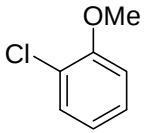
(3) The possibilities are:



para



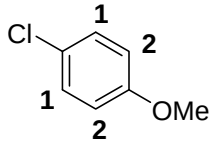
meta



ortho

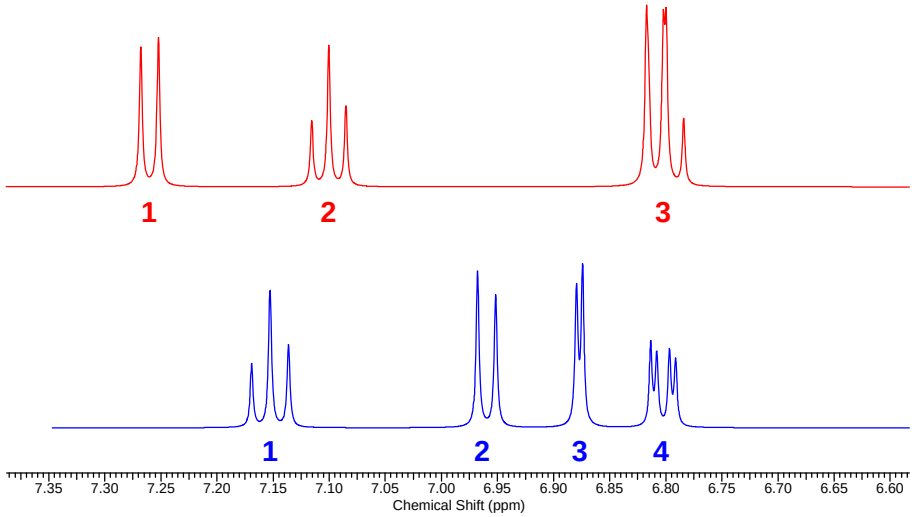
(4) The spectrum is essentially of two doublets. (There is a bit of fine structure from long-range couplings, but we can ignore it.)

(5) This must be the para compound. There are only two signals because this molecule has a plane of symmetry. The two protons are adjacent, so they split each other and give two doublets. (Actually, this is AA'XX', but we'll see this later.)



para

Here are the spectra of the meta and ortho compounds. Which is which? (This time, symmetry can't help us.)

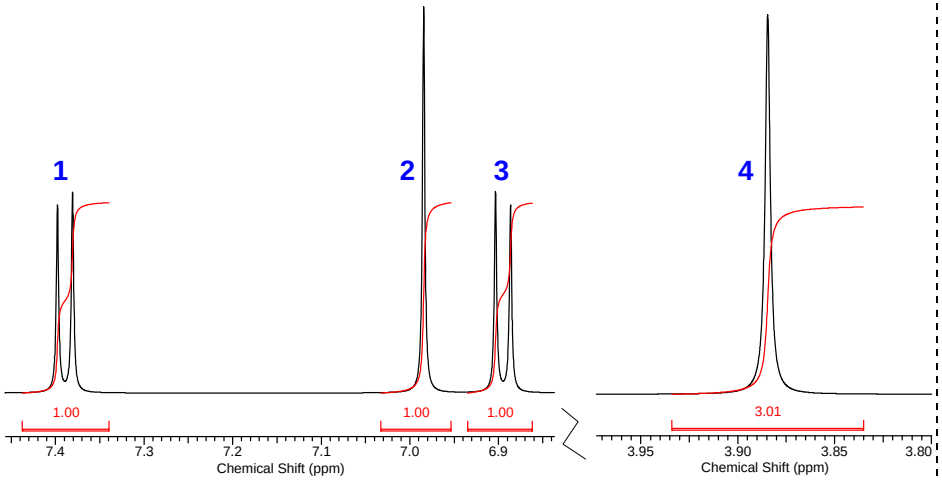


Note that **3** is really two signals on top of each other. It looks like a triplet, but the intensities are all wrong (not 1:2:1).

The key to distinguishing these spectra is to realize that a meta pattern should have a peak that is almost a singlet (**3**). It looks like a doublet, but the coupling constant is small, and comes from a four-bond coupling. So the bottom one is meta.

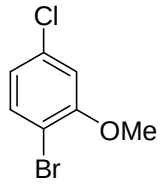
Aromatic Substitution Patterns

The following aromatic compound has the molecular formula C_7H_6OClBr. What is its structure?



In the aromatic region, there are three protons. Two of them are doublets and one of them is a singlet. This means a 1,2,5-substitution pattern. There's a 3H singlet at 3.01 ppm, which means an OMe group.

The molecule is:



Now, you might ask, I know it's 1,2,5-trisubstituted, but which substituent goes where? Is there a trick to that?

No, there isn't. There's no easy way to tell from just this 1D spectrum. You'll need more information. Later, we'll see how 2D NMR spectra can help us in situations like these. You can also predict the NMR spectra of all the possibilities and see which matches best. We'll do that later, too.

Homo-, Enantio-, and Diastereotopic Protons

Two protons will not split each other if they have they are "the same"--i.e., have the same chemical shift. Exactly what "the same" means is complicated, and I defer a full discussion of it to Lecture 3. For now, a pair of protons are:

homotopic if they are related by rotation symmetry and are certain to have the same chemical shift ("isochronous") in any medium (test: replace one proton with a deuterium, and find that it does not produce a chiral center);

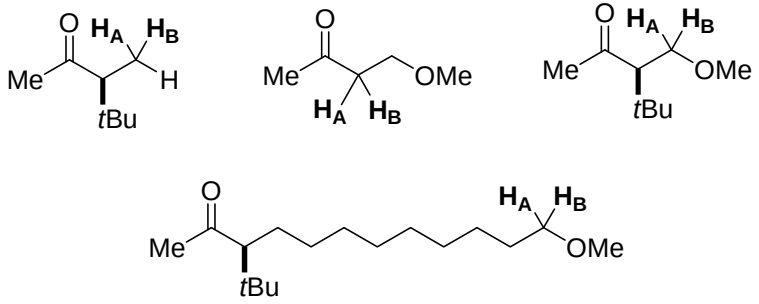
enantiotopic if they are related by reflection symmetry and will be isochronous in achiral or racemic media (test: replace one proton with a deuterium and find that it produces one of a pair of enantiomers);

diasterotopic if they are neither homotopic or enantiotopic and *could* be anisochronous in achiral or racemic media.

Note that (in achiral or racemic media):

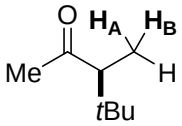
enantiomers have the same NMR spectrum, but **diastereomers** have (potentially) different NMR spectra.

Q: Are these protons equivalent?



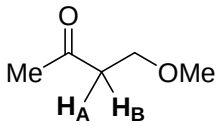
(Assume C-C bond rotation is fast, which it is at any sensible temperature.)

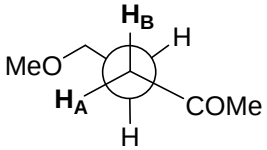
Which Protons are Isochronous?



H_A and H_B are related by rotational symmetry and are homotopic. They are isochoronous.

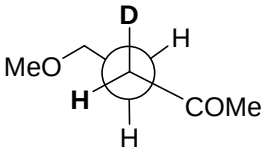
What about the second example?

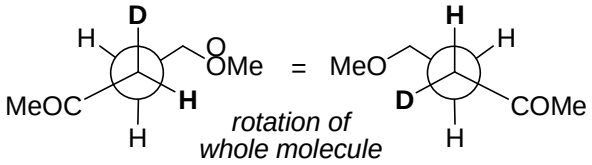




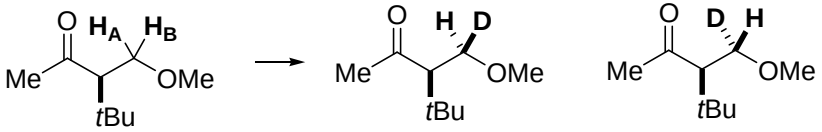
These protons are not related by rotational symmetry!

Replacement of one proton by deuterium will generate an enantiomer. Thus, these protons are enantiotopic and will be isochronous in achiral or racemic media:



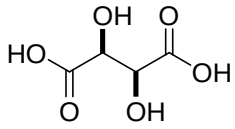


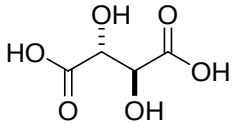
In the third example, there is already a chiral center in the molecule, so replacement by deuterium gives diastereomers, not enantiomers:

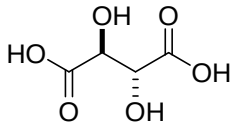


Thus, H_A and H_B will have different chemical shifts (see right panel).

Would these compounds have the same NMR spectrum?

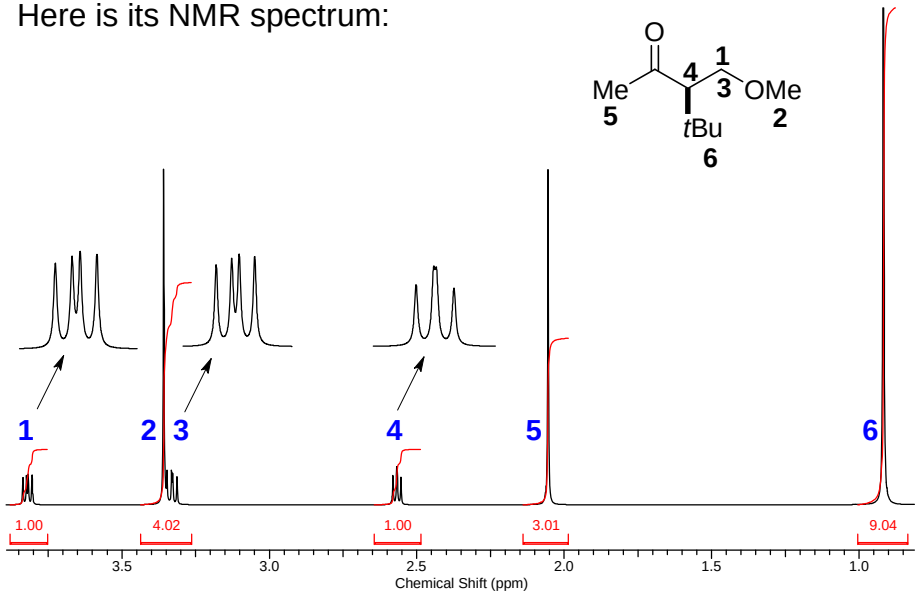






No, the leftmost compound is *meso* and would have a different spectrum than the pair of tartaric acid enantiomers on the right.

Here is its NMR spectrum:

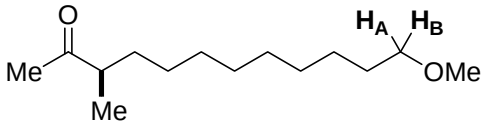


(1) Methylenes adjacent to chiral centers are diastereotopic and have characteristic patterns like these.

(2) The 9H singlet **6** is characteristic of *tert*-butyl group. Signals next to ketones come around 2-2.5 ppm (**5**). Peak **2** is the methyl ether.

(3) Peak **4** is a 1H triplet, since it's coupled to the two protons of the diastereotopic methylene.

(4) Peaks **1** and **3** are considerably separated and are doublets of doublets (they are coupled to each other through their large geminal coupling and to **4** via a vicinal coupling). The couplings are different, so this is not a triplet.



The marked protons *are* diastereotopic in this molecule, but are too far away from the chiral center to experience much of an effect. So they're diastereotopic *in principle*, but won't show it.

Heteronuclear NMR

Organic compounds have a lot of hydrogen, but they also have a lot of carbon, too. So it's fortunate that carbon is a useful NMR nucleus. What determines how useful a nucleus is for NMR?

(1) **Nuclear Spin Moment (I)**

These come in positive, half-integer increments and are specific to a particular nucleus. In general, a nucleus with a spin moment of I has 2I + 1 spin states (α, β, ...). A proton coupled to such a heteronucleus will show 2 I + 1 peaks. Note that these peaks will all have the same height. For example, the carbon in $CDCl_3$ is a 1:1:1 triplet. This is of carbon-13 (I=1/2) to deuterium (I=1); chlorine has I=3/2, but has very broad signals and coupling is not observed to it.

I = 0. The nucleus has no spin, and therefore has no NMR spectrum. It can, however, affect the shifts of neighboring nuclei. Examples: ^{12}C, ^{16}O.

I = 1/2. These are the best NMR nuclei in terms of sharp lines, high sensitivity, and observable homo- and hetero-nuclear couplings. Examples: ^{13}C, ^{19}F

I > 1/2. These are called quadrupolar nuclei. Some of them are useful, and some aren't (see below).

(2) **Gyromagnetic Ratio (γ)**

This essentially a measure of "how magnetic" the nucleus is: how fast the energy difference between the various spin states goes up with an increasingly strong external field. Higher numbers are better. It can be positive or negative. Sensitivity scales as $\gamma^{5/2}$.

Protium: 26.8 (the highest except for tritium)
Deuterium: 4.1
Carbon-13: 6.7 Carbon-12: 0
Nitrogen-15: -2.7 Nitrogen-14: +1.9

As I mentioned before, the size of couplings depends on the energy level spacing, so couplings to deuterium will be about one-seventh the size of those to proton. The peaks will be shorter, too, since there will be more peaks (D: I=1).

(3) **Electron Spin:** Unpaired electrons have a huge magnetic moment (660 times that of protium) and will cause very efficient "relaxation"--the decay of the NMR signal. So spectra with unpaired electrons are generally useless.

(4) **Electric Quadrupole Moment (Q):** Aside from inherent sensitivity issues, the major prolem with quadrupolar nuclei is that they be a source of efficient relaxation, which gives very broad lines (useless). If they didn't give this relaxation they would still give sharp lines, except there'd be more of them from coupling (since I is bigger). Q measures how bad this relaxation is:

Any I=1/2 Nucleus: 0 (great) Deuterium: 0.3 (good)
Boron-10: I=3, Q=8.4 (bad) Boron-11: I=3/2, Q=4.0 (useful)
Lithium-6: I=1, Q=-0.1 (good) Lithium-7: I=3/2, Q=-4.0 (bad)
Chlorine-35: -8.2 (bad) Chlorine-37: -6.4 (bad)

(5) **Electric Field Gradients at the Nucleus:** For complicated reasons, even if Q is large, a nucleus in a highly symmetrical tetrahedral or octahedral environment can give very sharp lines. The classic example is ammonium ($^{14}NH_4^+$, linewidth 0.1 Hz; Me-$C^{14}N$, linewidth > 50 Hz).

(6) **Natural Abundance**

Obviously, the more of the active NMR nucleus, the better. This is an important reason carbon-13 spectra take much longer to acquire than proton spectra.

Protium: >99%
Carbon-12 (I=0): 98.9%
Carbon-13 (I=1/2): 1.1
Nitrogen-14 (I=1): 99.6%
Nitrogen-15 (I=1/2): 0.37% (useful with isotopic labeling)

source: Prof. Hans Reich, Chem 605 notes

Carbon-13 NMR Spectra

Later, I'll show you more heteronuclear spectra. For now, let's concentrate on carbon-13, which is a very useful NMR nucleus (but not quite as good as proton):

abundance: 1.1% γ: 6.7 **Q**: 0 **I**: 1/2

Nucleus	Relative Sensitivity
^{1}H	1.0
^{13}C	0.016
^{19}F	0.83
^{31}P	0.07

Q: Is there coupling in carbon-13 spectra like there is in proton spectra?
A: Yes, but it's much more complicated than you might think.

Let's consider the possible isotopomers of ethyl iodide. We'll assume hydrogen only exists as protium, but carbon can exist as carbon-12 (99.93%) and carbon-13 (1.07%). Assuming independent probabilities, the possibilities are:

zero ^{13}C: $H_3{}^{12}C–{}^{12}CH_2–I$
$(1-0.0107)^2$ = **97.87%**

one ^{13}C: $H_3{}^{12}C–\mathbf{{}^{13}C}H_2–I$
$(0.0107)(1-0.0107)$ = **1.06%**

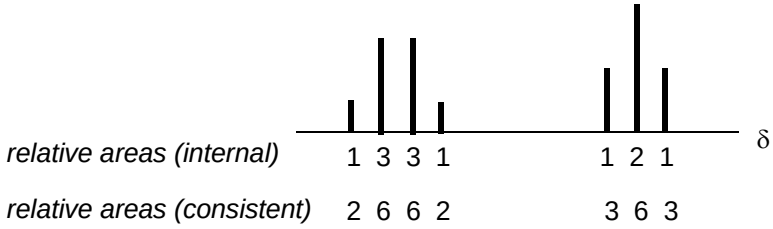
$H_3\mathbf{{}^{13}C}–{}^{13}CH_2–I$
$(1-0.0107)(0.0107)$ = **1.06%**

two ^{13}C: $H_3\mathbf{{}^{13}C}–\mathbf{{}^{13}C}H_2–I$
$(0.0107)^2$ = **0.01%**

(1) In the proton spectrum, the chances that a particular proton will couple to another proton is 100% in this molecule, since all the hydrogen nuclei are NMR-active, spin 1/2 nuclei.

Q: What will the proton spectrum of the most likely (no ^{13}C isotopomer) look like? This is harder than you think it is. What will the areas of all the lines be? How far apart will the lines be?

This cartoon shows the answer, with an exaggerated coupling:



First, the signal next to the iodine is further downfield. It's a quartet, since it's coupled to three equivalent protons on the methyl group. The methyl group is coupled to two equivalent methylene protons, so it's a triplet.

Second, these multiplets are all *n*-fold degenerate, with the same coupling constant corresponding to $^{3}J_{HH}$. The triplet has an internal ratio of 1:2:1 and the quartet has an internal ratio of 1:3:3:1, consistent with Pascal's triangle.

Finally, the ratio of the integrals is 2:3, since this describes a CH_2 and a CH_3. The desired ratios are found by multiplying each set of internal areas by the integrals.

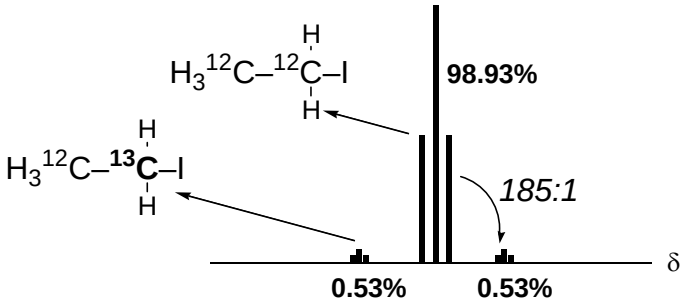
The two ^{13}C isotopomer is very unlikely, so we don't have to worry about it.

Q: But what will the spectrum look like if we include the one ^{13}C isotopomers?

These will add *carbon-13 satellites*.

Carbon-13 NMR Spectra

Considering only the triplet corresponding to the methylene:



How did I arrive at this? 1.07% of the methylenes in the pot will have ^{13}C in them. This will put two spin 1/2 nuclei right next to each other, a proton and a carbon-13. As it turns out, these have quite a large coupling constant: ~140 Hz. So there will be a doublet, about 70 Hz on either side of the central peak. You can see these satellites in many good proton spectra. In fact, it is these satellites that many of the 2D NMR experiments we will talk about later detect. (This analysis has ignored longer range carbon-proton couplings, which also exist, but are a lot smaller.)

Although you can see these in proton spectra, they are small enough that they don't complicate the interpretation of spectra. But now we can think about what the corresponding ^{13}C spectrum will look like. Obviously, the no-^{13}C isotopomer has no ^{13}C spectrum. Since this comprises 97.87% of the total material, this is bad for sensitivity.

As a reminder from the last page:

$H_3{}^{12}C–\mathbf{{}^{13}C}H_2–I$

(0.0107)(1-0.0107) = **1.06%**

$H_3{}^{\mathbf{13}}\mathbf{C}–{}^{13}CH_2–I$

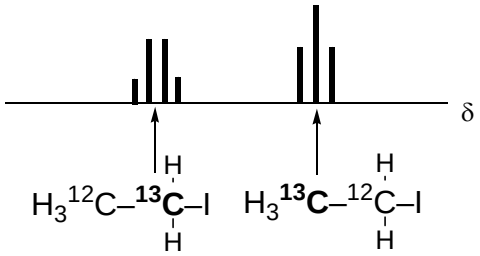
(1-0.0107)(0.0107) = **1.06%**

$H_3{}^{\mathbf{13}}\mathbf{C}–\mathbf{{}^{13}C}H_2–I$

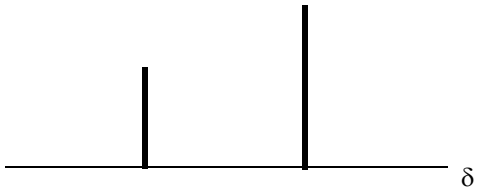
$(0.0107)^2$ = **0.01%**

Unlike the proton spectrum, where proton-proton couplings are common, *carbon-carbon* couplings are very unlikely.

Conversely, *carbon-proton* couplings are assured. This means that instead of two singlets, one observes two multiplets, each with a different coupling constant corresponding to $^1J_{CH}$:



As in the proton spectrum, the methylene is downfield of the methyl group. Now, for a more complicated molecule, you can imagine that this kind of coupling would make the spectrum very complicated and difficult to interpret. As such, it is usual to apply *broadband decoupling* (details later):



(1) Every peak collapses to a singlet to the frequency of the center of the doublet.

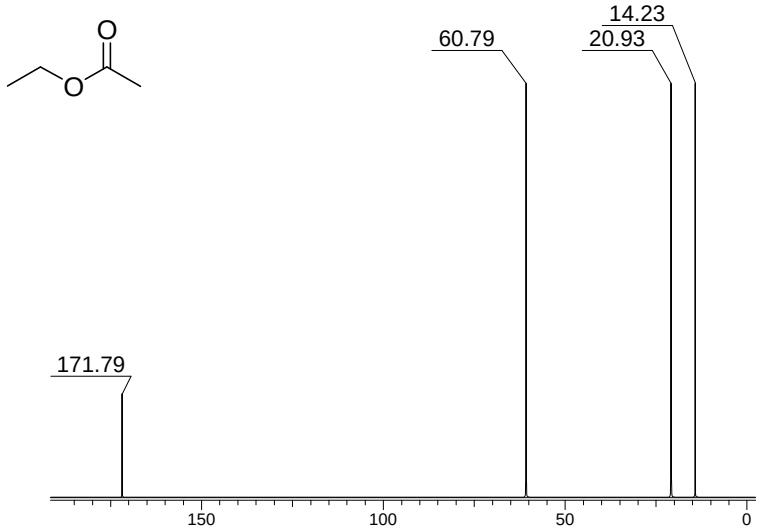
(2) The peaks are *more than* twice as high as before(!), which is good for signal/noise. This is because of the nuclear Overhauser effect (nOe). This basically transfers magnetization from the adjacent protons to the carbon (details later).

(3) Quaternary carbons are not enhanced by the nOe and thus always show up as very small peaks.

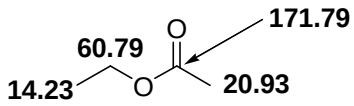
(4) Unless things are done in a special way, the integrals in carbon spectra are *not* quantitative like they are in proton spectra.

Finding Functional Groups

What does all this mean? The carbon spectrum has a very clean appearance. Here it is for ethyl acetate:



In this case, the assignments are simple, and just based on inductive effects:



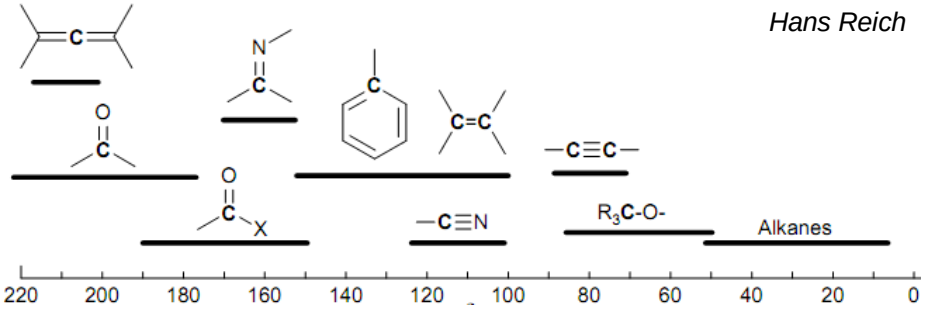
However, you will see that the chemical shift range for carbon is *much* larger than that for carbon. This is common for heteronuclei, and has something to do with what orbitals (p vs. s) are used for bonding (details later). Importantly, inductive effects, in general, are *not* the only factor that matters.

As you can see, the ester carbonyl is distinctively downfield. In general, this downfield region is only occupied by carbonyl carbons.

the good news: Carbon-13 can identify functional groups.

the bad news: It's not as specific as IR. It can't really tell between different kinds of carboxylic acid derivatives:

Hans Reich

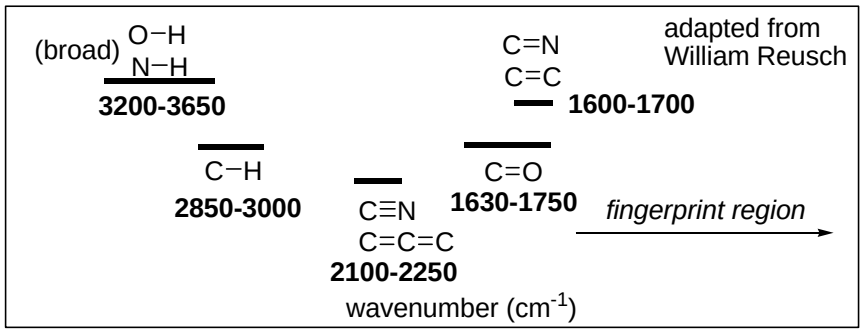


In IR, however, one can be quite specific about which carboxylic acid derivative might be present:

aldehyde (1740-1720 cm^{-1}) *(amides are much weaker--*
ketone (1725-1705) *can you explain this?)*
carboxylic acid (1725-1700)
ester (1750-1730) amide (1630-1695)

There's a bit of overlap, but it's not nearly as bad as in carbon-13.

IR can also give some other useful information. A sketch:



In contrast, the carbon-13 spectrum of any reasonably complex molecule will be almost impossible to interpret without other information. It's more useful for telling you how many unique carbon chemical shifts there are, and maybe something about what kind of unsaturation is in the molecule.

Further talk, at this point, is useless, so let's do a lot of examples.

Problem Solving

You'll see two different kinds of problems:

(1) **Assign a structure:** I give you a structure and some spectra, and you tell me if the structure and the peaks are consistent. If they are, you tell me which peaks correspond to which nuclei. If they aren't, you point out the inconsistencies. In the lab, this is what you would do when you carry material through a synthetic sequence: at each step, you would verify that the reaction had worked.

(2) **Unknown structure:** I give you spectra and a molecular formula, and you tell me what the structure is. Sometimes this means you give me several plausible structures that all fit the data. (Some really terrible mistakes have been made when people got tunnel vision and assumed that there was only one possible structure.) In the lab, this is what you would do if you got an unexpected product. Or, you could envision doing this when isolating potentially new natural products. Usually, this is harder than assignment.

You will need a handy formula for determining how unsaturated a molecule is from its molecular formula. That is, how many molecules of hydrogens you would have to add to the molecule to get back to the alkane oxidation state. This is called the **index of hydrogen deficiency** or the **unsaturation number** of the molecule:

unsaturation number = C + 1 - (H + X - N)/2

where C is the number of carbons, H is the number of hydrogens, X is the number of monovalent atoms (like chlorine), and N is the number of hydrogens.

Rings count as one unit of unsaturation.

Double bonds count as one unit.

Triple bonds count as two units.

(You can work out this formula for yourself by noting that the molecular formula of an alkane is C_nH_{n+2}, and working from there.) Here's benzene, which has a formula of C_6H_6:

U = 6 + 1 - 6/2 = 4

Benzene has one ring and three double bonds, which makes for an unsaturation number of 4, in agreement with the formula. I won't tell you to memorize much, as everything is open-book, both in this class, and when you're pondering at the bench, but this would be useful to know by heart.

These problems were adapted from the questions written by Professor Smith (Notre Dame): http://www.nd.edu/~smithgrp/structure/pbm_table.html. Googling "NMR problems" will return more problems than you could possibly want to ever do.

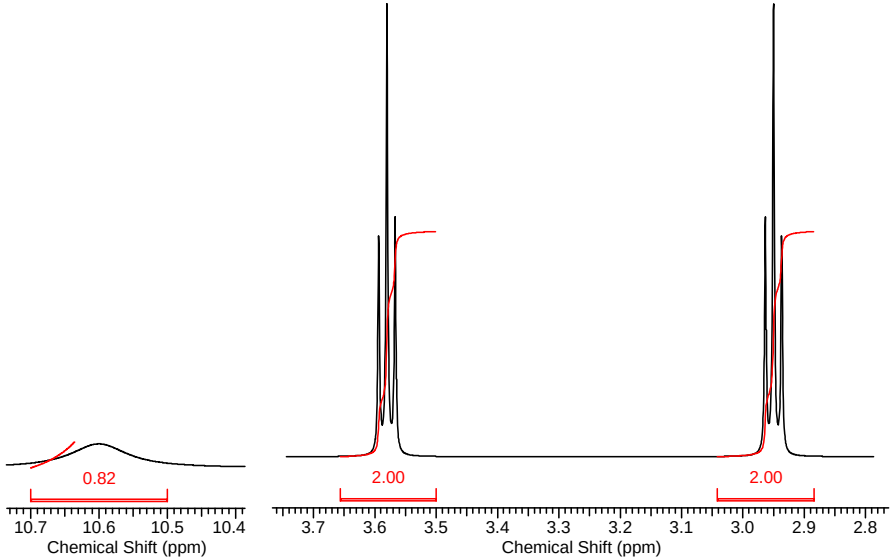
Unknown #1

$C_3H_5BrO_2$

^{13}C NMR: 178.6, 38.6, 24.3

key IR: 3067 (br), 1717 (s)

hint: in both IR and NMR, broad signals are an indication of protons bound to heteronuclei like O or N



Unknown #1

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^{13}C NMR: 178.6, 38.6, 24.3

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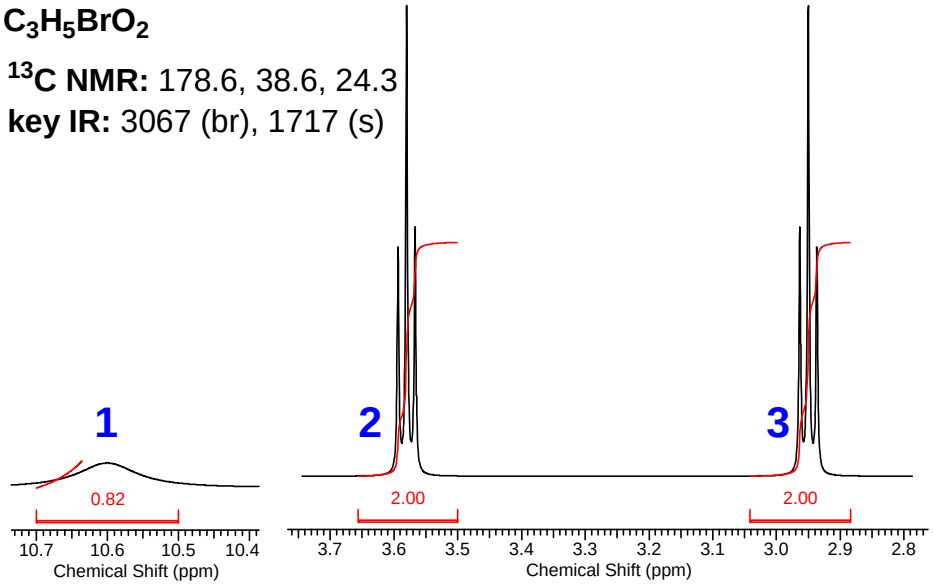


(1) The unsaturation number is 1.

(2) The signal at 178.6 and IR absorption at 1717 indicate a carbonyl group of some kind.

(3) The exchangeable proton indicates a hydrogen bound to a heteroatom. In this case, the only reasonable possibility is an alcohol or a carboxylic acid.

(4) There is no diastereotopic splitting indicative a chiral center. Thus, two reasonable possibilities are:

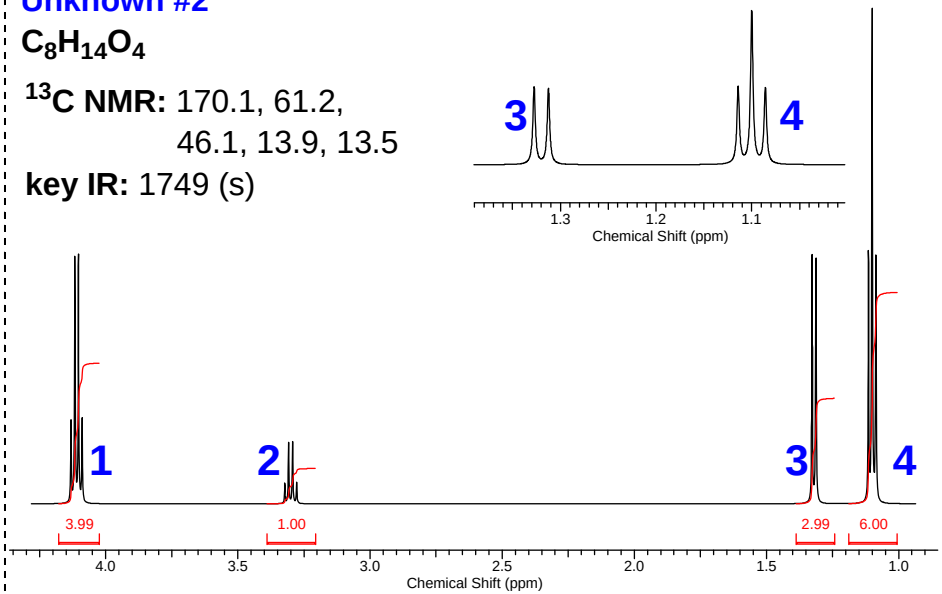
(5) The chemical shifts are more consistent with the alkyl bromide. Alcoholic O-Hs typically appear around 3-4 ppm, while carboxylic acid O-Hs typically appear around 10 ppm. The IR shift of the carbonyl group is also instructive; for reference: acetyl bromide (1811) and acetic acid (1715).

Unknown #2

$C_8H_{14}O_4$

^{13}C NMR: 170.1, 61.2, 46.1, 13.9, 13.5

key IR: 1749 (s)

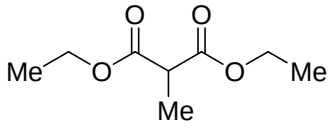


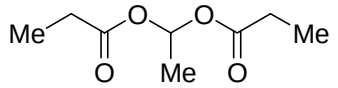
(1) The unsaturation number is 2.

(2) There are only five unique carbons and four unique protons, suggesting that the molecule is symmetrical.

(3) **3** and **4** are methyl groups. **3** is next to a methine, since it's a doublet. The methine is probably **2**. **4** and **1** have the characteristic signature of an ethoxy group.

(4) Two reasonable possibilities are:





(5) The left hand structure is more consistent with the chemical shifts.

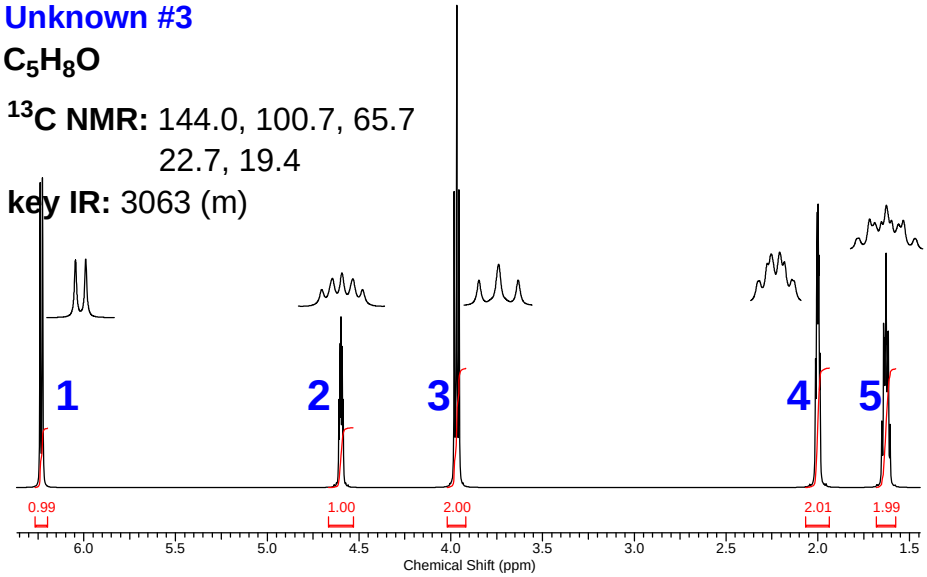
(6) Remember that the structure you propose must make chemical sense. If it looks like a commercial material, that's good. "*If you hear hooves, expect a horse, not a zebra!*"

Unknown #3

C_5H_8O

^{13}C NMR: 144.0, 100.7, 65.7
22.7, 19.4

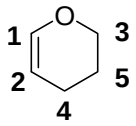
key IR: 3063 (m)



(1) The unsaturation number is 2.

(2) The peak at 3063 cm^{-1} and 100.7/114.0 cm^{-1} suggest the presence of a polarized olefin (i.e., an enol ether). There aren't any more obvious functional groups, suggesting that a ring accounts for the additional unsaturation. This ring must have no methyls. The only possibility is:

(3) This is dihydropyran, a common protecting group reagent. **1** is heavily downfield, since it is both on an olefin and next to an oxygen. There are many complex couplings in the ring methylenes, but **3** is next to the oxygen and is a triplet.



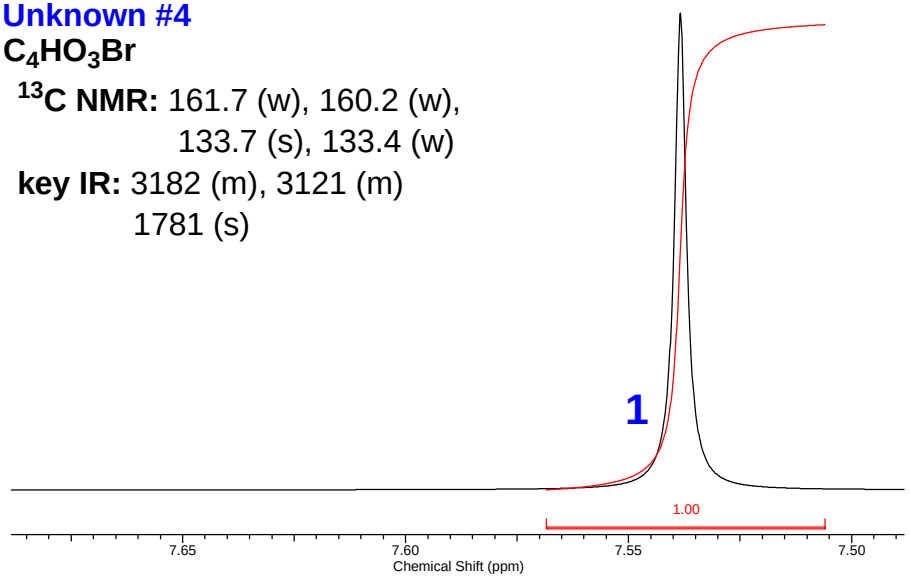
(Allylic protons are downfield of homoallylic ones.)

Unknown #4

C_4HO_3Br

^{13}C NMR: 161.7 (w), 160.2 (w),
133.7 (s), 133.4 (w)

key IR: 3182 (m), 3121 (m)
1781 (s)



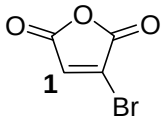
(1) This question is harder. The unsaturation number is 4.

(2) There may be two carbonyl groups in this molecule.

(3) Low intensity ^{13}C NMR peaks are indicative of quaternary carbons, as is the presence of only one proton.

(4) Two carbonyl groups and an olefin mean one ring.

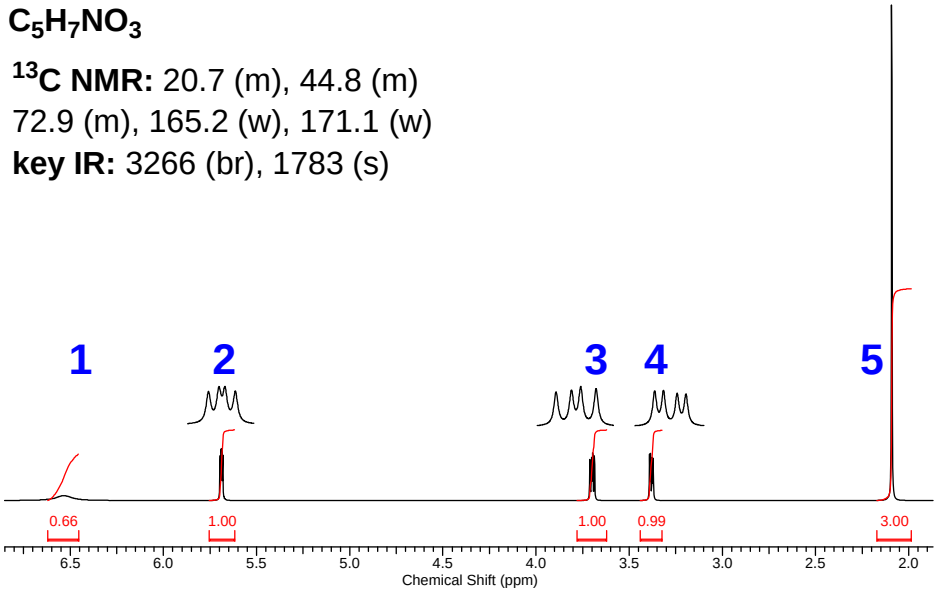
(5) The only reasonable structure is:



Unknown #5

$C_5H_7NO_3$

^{13}C NMR: 20.7 (m), 44.8 (m)
72.9 (m), 165.2 (w), 171.1 (w)
key IR: 3266 (br), 1783 (s)



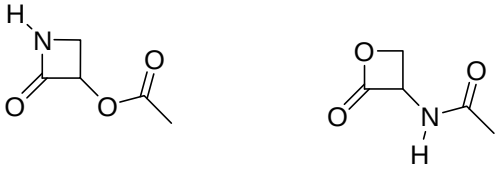
(1) The unsaturation number is 3.

(2) The paired dd appearance of peaks **3** and **4** is characteristic of a methylene adjacent to a chiral center (methine **2**).

(3) The highly downfield nature of **2** suggests it is next to two electronegative groups.

(4) A downfield methyl group suggests an acetate or acetamide.

(5) Two possibilities are:

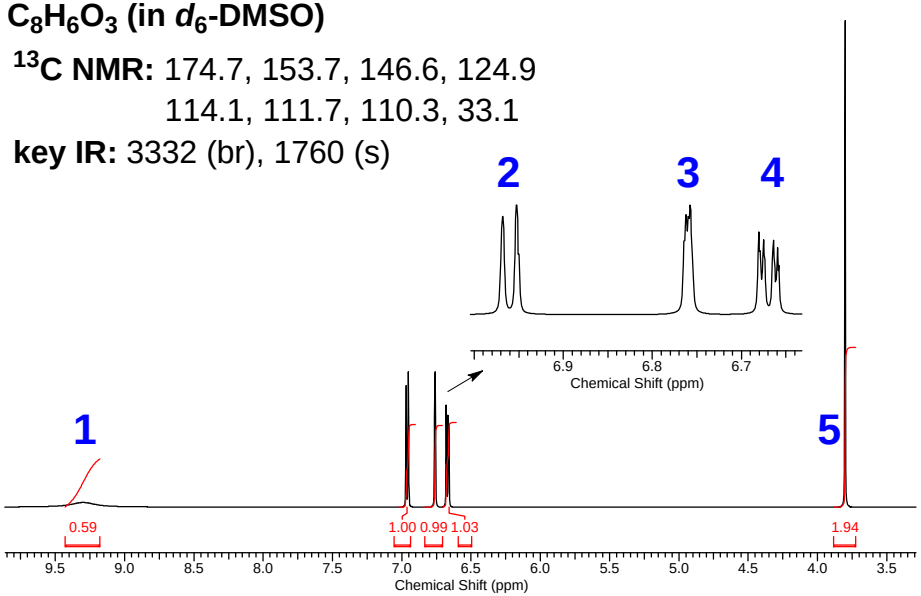


The structure on the left is more likely. No amide rotamers are observed. The shifts of **3** and **4** make more sense if they are next to nitrogen (rather than oxygen).

Unknown #6

$C_8H_6O_3$ (in d_6-DMSO)

^{13}C NMR: 174.7, 153.7, 146.6, 124.9
114.1, 111.7, 110.3, 33.1
key IR: 3332 (br), 1760 (s)

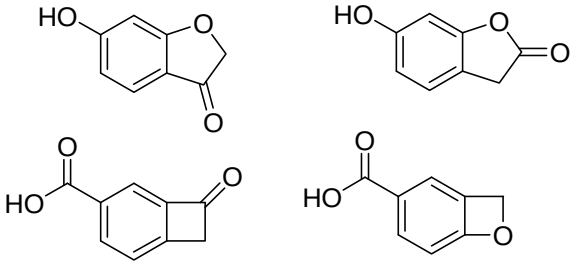


(1) The unsaturation number is 6.

(2) The aromatic pattern is that of a 1,2,5-trisubstituted benzene.

(3) The exchangeable proton is either a phenol, alcohol, or acid.

(4) Here are some possibilities:



(plus versions where the aromatic substituent has moved)

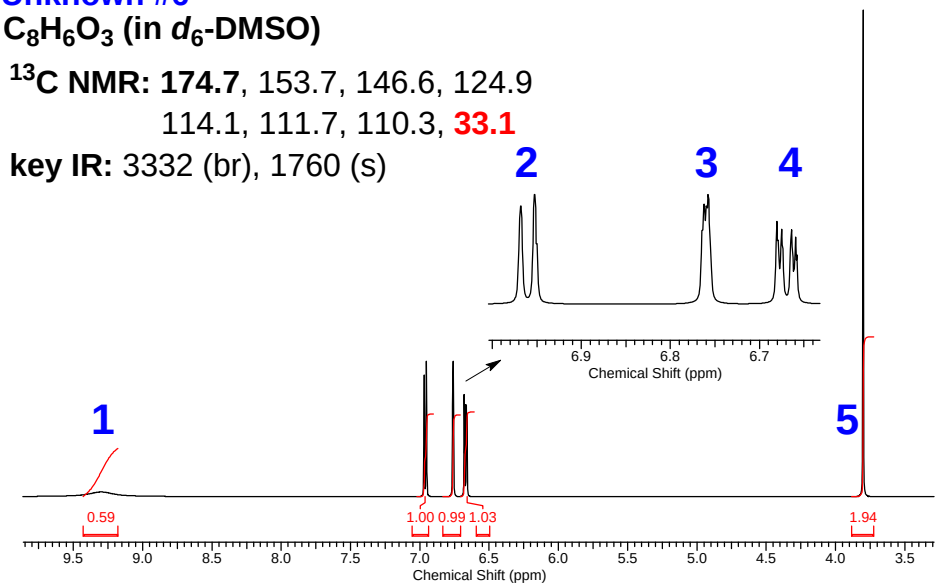
Q: Which of these is correct?

Unknown #6

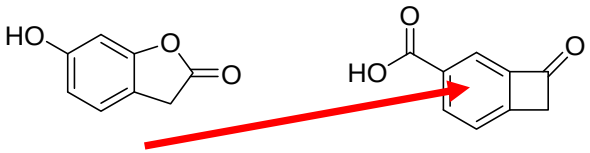
$C_8H_6O_3$ (in d_6-DMSO)

^{13}C NMR: 174.7, 153.7, 146.6, 124.9
114.1, 111.7, 110.3, **33.1**

key IR: 3332 (br), 1760 (s)



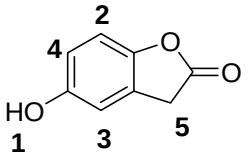
(1) Note that while the proton shift of **5** makes it look like it's next to oxygen, its corresponding carbon chemical shift is definitely ***not*** consistent with this. Thus, we must discard any structures bearing a methyleneoxy group. This leaves:



(2) The right-hand structure is inherently less likely, but still possible because of its four-membered ring. IR shifts: ethyl acetate, 1743; cyclobutanone, 1783; benzoic acid: 1696. The lack of a signal for the carboxylic acid suggests the left.

(3) Now we have to decide between these two structures:

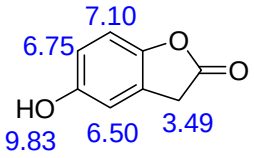
This is pretty hard, so I would normally turn to NMR prediction software. If you do this, you will find the right hand structure to be more reasonable. This gives assignments of:



How do these programs work?

(1) Empirical Shift Predictions

This looks at what functional groups are near every proton and makes additive adjustments. This is what happens when you ask ChemDraw to predict some shifts. In this course, I'll use ACD/NMR Predictor, which is more sophisticated.



advantages: fast, reasonable accuracy
disadvantages: can't handle unusual situations or stereochemistry

Protocol of the H-1 NMR Prediction:

Node	Shift	Base + Inc.	Comment (ppm rel. to TMS)
OH	9.83	5.00	aromatic C-OH
		4.83	general corrections
CH2	3.49	1.37	methylene
		1.22	1 alpha -1:C*C*C*C*C*C*1
		0.90	1 alpha -C(=O)O
CH	7.10	7.26	1-benzene
		-0.19	1 -OC(=O)C
		-0.12	1 -C
		-0.17	1 -O
		0.32	general corrections
CH	6.50	7.26	1-benzene
		-0.03	1 -OC(=O)C
		-0.20	1 -C
		-0.53	1 -O
CH	6.75	7.26	1-benzene
		-0.03	1 -OC(=O)C
		-0.19	1 -C
		-0.53	1 -O
		0.24	general corrections

(In this course, and in real life as you work in the lab, all the evaluations will be open-book. So I encourage you to use such programs to help you figure out your spectra. There's no point in memorizing additivity constants.)

(2) *Ab Initio* Methods

These programs use quantum-mechanical methods to predict NMR spectra. They can calculate both chemical shifts and couplings *specific to particular geometries* with reasonable accuracy.

For common compounds, the accuracy of the empirical and *ab initio* methods is comparable. However, for unusual cases like fused rings systems where the shifts and couplings will depend on conformation, the *ab initio* methods will perform better.

The disadvantage is that the *ab initio* methods are costly (in terms of time). There's a significant dependence of the quality of the calculations and the size of the basis set. And there's an inherent cost to learning how to do the calculations. Later, I'll discuss these methods in more detail, but you will see that both the empirical and *ab initio* methods have their respective places. For now, I'll just point out that GIAO-B3LYP/6-31g(d,p) is a common method using a relatively small basis set that works.

Origin of the NMR Signal

(source: Prof. William Reynolds, lecture notes)

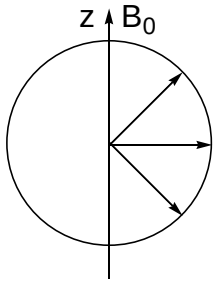
Intrinsic to every nucleus is a spin quantum number, *I*. Nuclei have a spin angular momentum vector *P*:

$$P_z = \hbar m_I;\ \ m_I = -I, -I+1, ..., I-1, I$$

$$|P| = \hbar\left[I(I+1)\right]^{1/2}$$

(The operators for the x- and y-components do not commute with the z-component or P^2.) *I* can be zero, a positive integer, or a positive half-integer.

For example, deuterium has *I*=1:



$P_z = +\hbar$

$P_z = 0$

$P_z = -\hbar$

- by convention, the external field B_0 is put along the z-axis
- since the magnitude of P only depends on *I*, the components P_z lie along a circle
- proton has *I*=1/2, so the diagram is the same, except P_z is removed

Associated with P is magnetic moment μ:

$$\mu = \gamma P$$

where γ is the gyromagnetic ratio. Thus, μ_z is also quantized:

$$\mu_z = \gamma \hbar m_I$$

Q: What are the energies of these spin states?

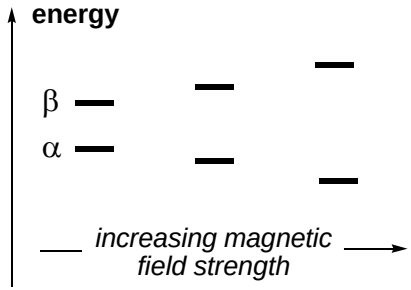
Let us consider the proton, which is a I=1/2 nucleus. As such, it has two possible spin states: α (m_I = +1/2) and β (m_I = -1/2). Semi-classically, one pictures these as spinning nuclei which create a magnetic field which can be aligned with or against the external magnetic field. However, this is a quantum-mechanical phenomenon which doesn't involve any actual rotation. More precisely:

$$E = -\mu \cdot B_0$$

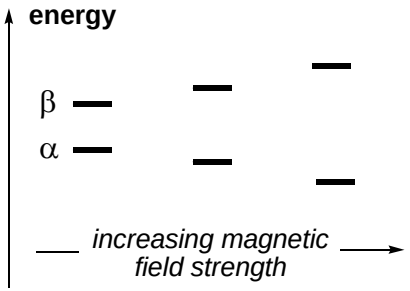
$$= -\mu_z B_0$$

$$= -\gamma \hbar m_I B_0$$

- in the absence of a magnetic field, the spin states are equal in energy
- the larger the field, the larger the energy gap



Origin of the NMR Signal



Note that if the nucleus has a negative γ, then β is more stable than α. Nitrogen is an example of such a nucleus. This will be important later for understanding the nOe and polarization transfer.

The energy splitting is:

$$\Delta E = \frac{\gamma h}{2\pi} B_0 \quad \longleftrightarrow \quad \nu = \frac{\gamma B_0}{2\pi} \quad \longleftrightarrow \quad \omega_0 = \gamma B_0$$

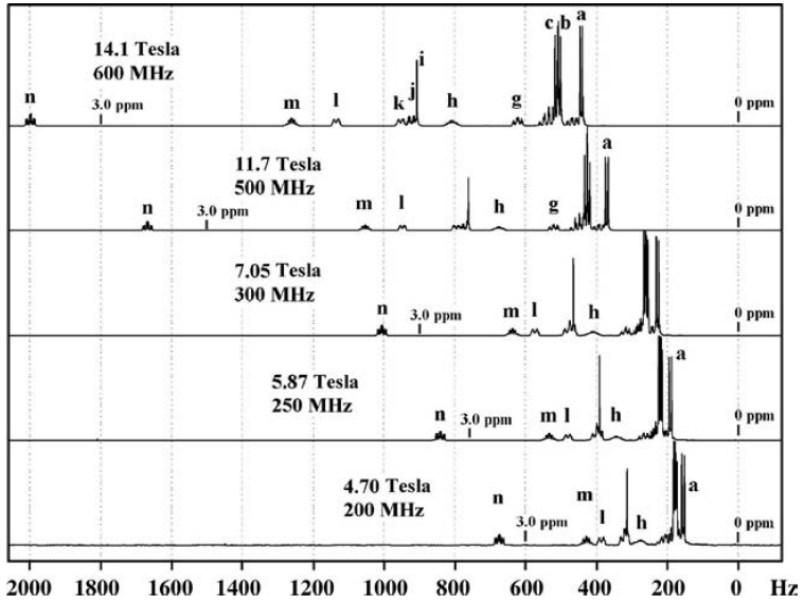
These expressions give the splitting in different units: energy (J), frequency (Hz), and angular frequency (rad/s). The **chemical shift** δ is related to the **Larmor frequency** (ν) by:

$$\delta = \frac{\nu - \nu_{ref}}{\nu_{ref}} \times 10^6 \quad \text{(ppm)}$$

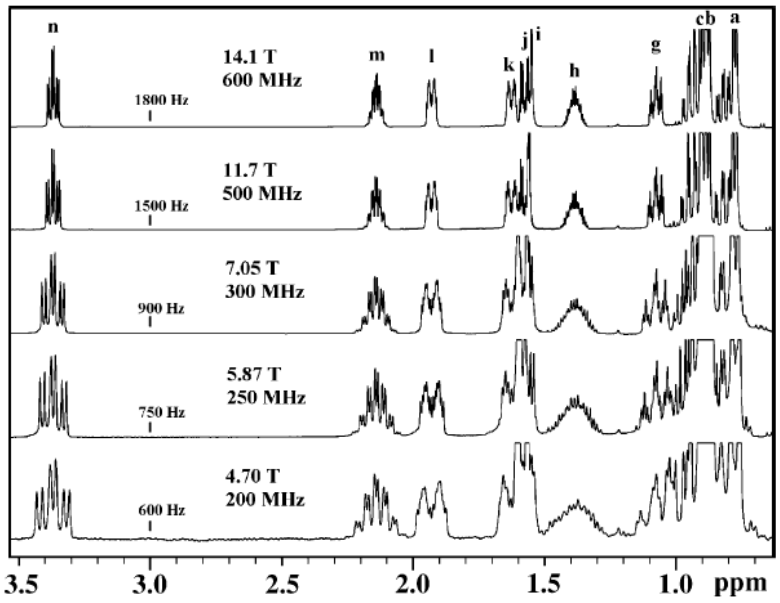
where ν is the frequency of the sample and ν_{ref} is a reference frequency (for protons, that of tetramethylsilane).

Chemical shifts are independent of field strength since both ν and ν_{ref} will increase equally in stronger fields. However, **coupling constants** represent energy splittings that don't depend on the external field strength. This means that at higher field strengths, the frequencies get spread out over a wider range. Because the coupling constants remain fixed, the multiplets look narrower in terms of chemical shift. Later, we'll see that if the frequency separation between two coupled protons approaches the size of their mutual coupling constant, the spectra get very complicatd. At higher field strengths, this is avoided.

Here are spectra of menthol taken at different field strengths (Neil Jacobsen, NMR Spectroscopy Explained):



Notice the shrinking width of the multiplets at higher fields:



Origin of the NMR Signal

While the *frequency* of the NMR signal depends on the level splitting, the *size* of the signal depends on the population differences between the levels. This is given by the Boltzmann distribution:

$$\frac{N_\alpha}{N_\beta} = \exp\left(\frac{-\Delta E}{kT}\right)$$

$$= \exp\left(\frac{-\gamma\hbar B_0}{kT}\right)$$

$$\approx 1 - \frac{\gamma\hbar B_0}{kT}$$

To first-order, the population difference is linear in B_0. This is justified, since $\Delta E << kT$.

In 2.35 T field (100 MHz), the population difference N_α-N_β is only **16 in a million nuclei**, which is very tiny! In general, the relationship between signal to noise (S/N) and the gyromagnetic ratio is more complicated:

$$\frac{S}{N} \;\alpha\; \gamma_{exc}\gamma_{obs}^{3/2}B_0^{3/2}$$

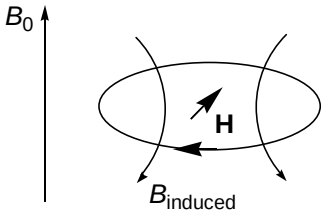
where exc refers to the nucleus being excited and obs refers to the nucleus being observed. This means that there is often an advantage in going to higher field strengths. (However, due to chemical shift anisotropy relaxation, which increases as the square of the magnetic field strength, this isn't always true.)

Origin of the Chemical Shift

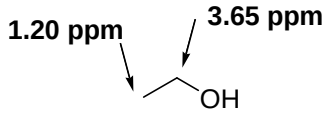
If all protons had the same Larmor frequency/chemical shift, then NMR would not give any useful structural information. In a semi-classical picture, one imagines that the electrons near the proton are "circulating" and therefore create magnetic fields $B_{induced}$ which tend to *oppose* the external field B_0. One writes:

$$B_{local} = B_0 + B_{induced} = B_0\,(1-\sigma)$$

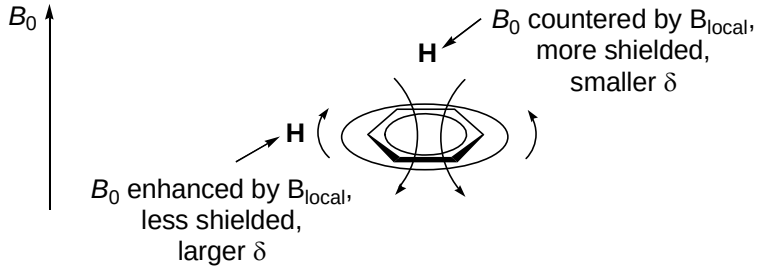
where σ is the screening or shielding constant. Here is a picture:



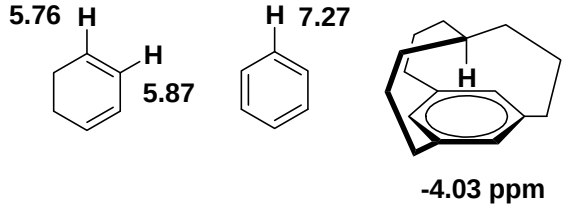
This reduction in the applied field is in accordance with Lenz's Law and is called **diamagnetic shielding**. The idea is that Just how much the field is opposed depends on how much electron density there is. Thus, for ethanol in chloroform:



This is very satisfying, since the protons on the carbinol carbon are expected to be more electron poor. Sometimes, **magnetic anisotropy** leads to particularly strong (de)shielding effects. The classic example is benzene. From this diagram, we expect that protons along the periphery of the ring to be deshielded, but protons above and below it to be shielded:

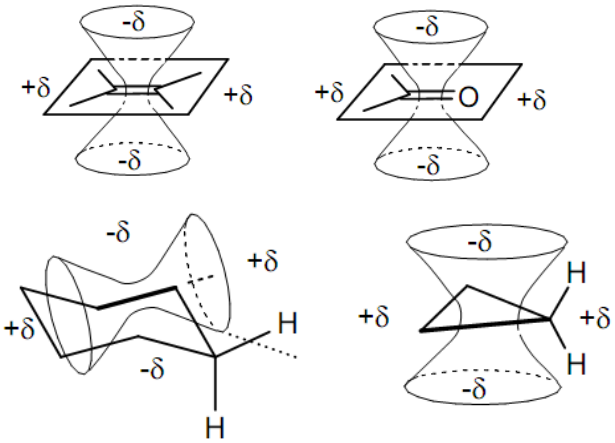


Indeed, this is precisely what is found:



Origin of the Chemical Shift

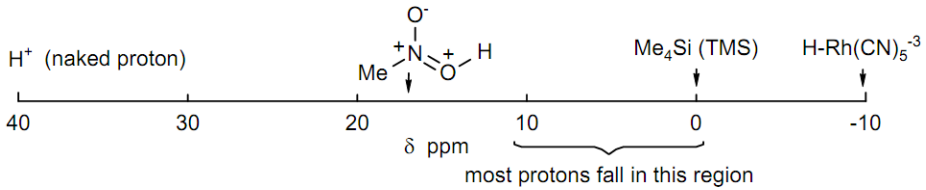
A variety of "shielding/deshielding cones" have been proposed: (Hans Reich Chem 605 notes):



Q: Why do protons have a relatively small range of chemical shifts, while carbons and other heteronuclei have a relatively large range?

Roberts. J.D. ABCs of FT-NMR Chapter 10

Most protons fall within the range 0-10 ppm, but a few don't (Hans Reich Chem 605 notes):



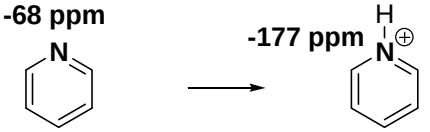
However, carbon has a routine range of 0-200 ppm, while other heteronuclei have an even wider range: 600 ppm (fluorine), 500 ppm (phosphorus), 900 ppm (nitrogen).

This is puzzling. Also odd is the shift of the hydroxylic proton in ethanol, which at small concentrations in carbon tetrachloride, is actually *more* shielded than the methyl group!

Similarly, consider protonation in pyridine:

"Understanding Chemical Shifts..." Dahn, H. *J. Chem. Ed.* **2000** *77* 905-909.

^{15}N shifts:

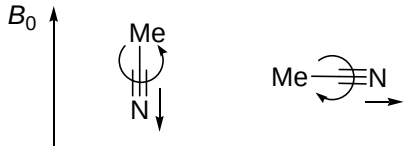


Protonation, which is expected to decrease the electron density at nitrogen, and therefore increase the chemical shift, actually decreases the chemical shift a lot! (These numbers are relative to nitromethane and are predicted, but are close enough to reality for our purposes.)

Additionally, there seems ot be a correlation between the ^{15}N shift and the *color* of the compound. What do visible light absorptions have to do with the magnetic resonances?

The answer is that in addition to diamagnetic shielding effects, there are also **paramagnetic effects** which are much larger in magnitude, but are only transfered through p-orbitals. (Protons, of course, only use s-orbitals.)

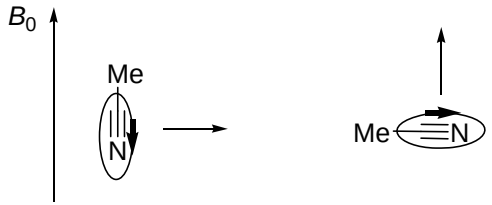
Consider acetonitrile. The diamagnetic contributions depend on the relative orientation of the acetonitrile to the magnetic field. The dependence of chemical shift on the orientation of the molecule is called **anisotropy**. The observed chemical shifts in solution are **isotropic**, since they arise from averaged values of the chemical shift *tensor*.



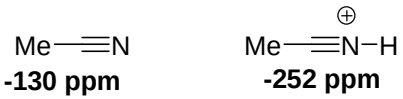
The idea is to mix the ground state wavefunction with some contribution from the excited state wavefunction. The nitrile has some low-lying π* orbitals which are of the right symmetry for this interaction to occur.

Origin of the Chemical Shift

The mixing is only slight, but the effect is intrisically very large, so it's still significant. Here's a diagram:



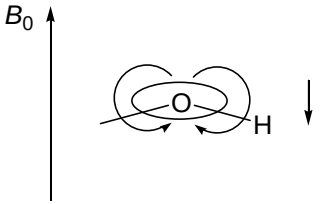
It is this **second-order paramagnetic effect** that is the dominant factor in determining the nitrogen's chemical shift. When the molecules is not protonated, there is effective ground-state/ excited-state mixing due to the *n* to π* transition. Upon protonation, we are now talking about a σ to π* transition, which is a higher energy process. Since the energy gap between the ground and excited states has gone up, the magnitude of the second-order paramagnetic effect has gone down. Thus, the predicted shifts are:



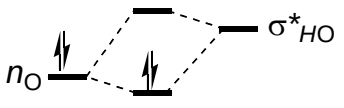
-130 ppm **-252 ppm**

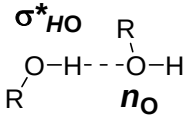
So the shift went *down* because the paramagnetic effect normally keeps the shift high. Protonation has turned off the effect. We can also understand why hydrogen-bonding affects the shifts of protons so much.

In the absence of hydrogen bonding, we have paramagnetic shielding:

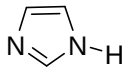


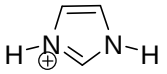
Thus, at low concentrations in nonpolar solvents, hydroxylic protons are therefore expected to have small chemical shifts even though they are attached to a very electronegative atom. At high concentrations, hydrogen bonding, which is a weak form of protonation gets more important. The paramagnetic effect, which arises from an *n* to σ* electronic transition, becomes less important as the energy of the σ* orbital increases:



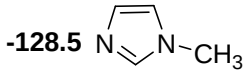


Here are some examples with ^{15}N chemical shifts relative to nitric acid. Which compound has the higher chemical shift?

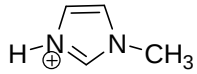




The shifts are -171 ppm (imidazole) and -202 ppm (imidazolium). Can you explain this?



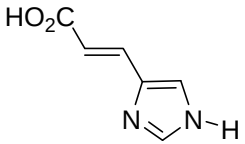
-211.5

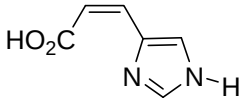


-203.6 -204.1

This is the same idea. The only difference is that when the proton is replaced with a methyl group, there is no fast tautomeric equilibrium, so the two nitrogens are distinguishable.

Here is a more complicated example. We will consider the ^{15}N shifts of *cis*-urocanic acid and *trans*-urocanic acid at various pH values:

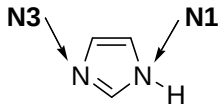




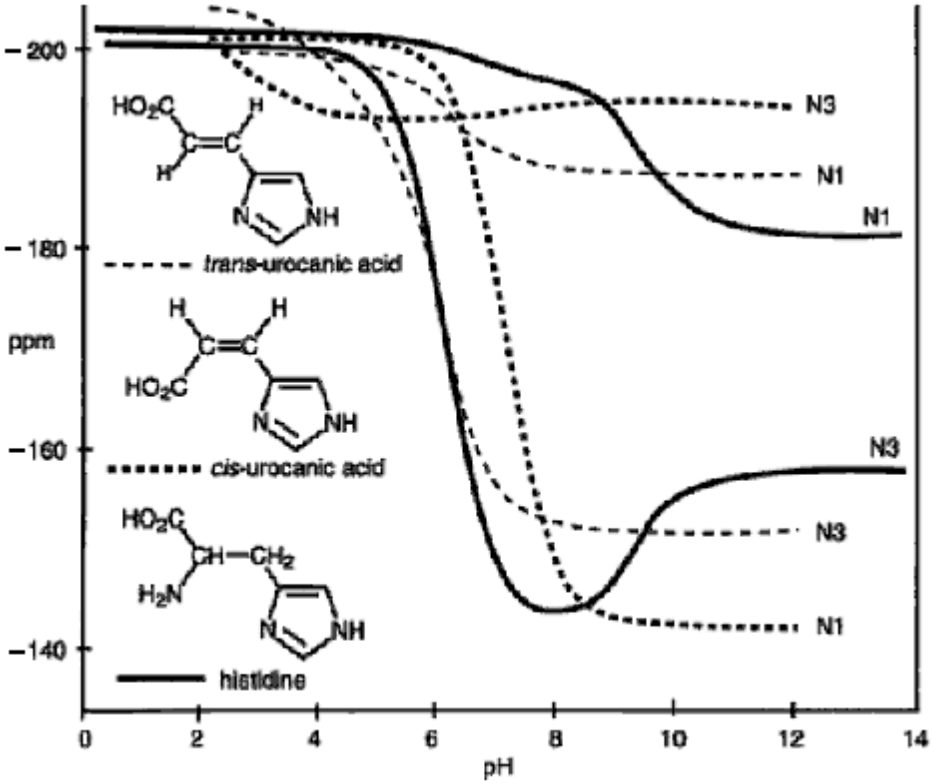
First things first, though: what are the relevant p*K*a values?
α,β-unsaturated carboxylic acid: 4
protonated imidazole: 7

Origin of the Chemical Shift

Here are the data (Roberts, pg 259):

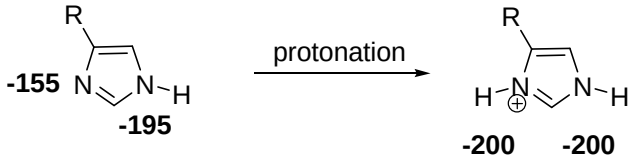


(For baffling reasons, the data were plotted on the σ, rather than δ chemical shift scale, but I have corrected it with minus signs. As usual, more positive numbers are more deshielded.)

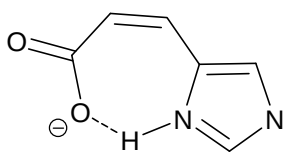


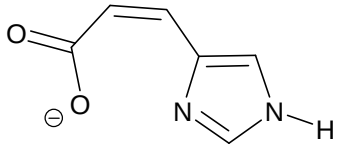
Note that we are only considering the shifts of the aromatic nitrogens. First, let's tackle *trans*-urocanic acid, which is the dashed line. Around pH 7, the imidazole ring gets protonated, which sends N3 upfield more than it sends N1 upfield.

Approximately speaking:

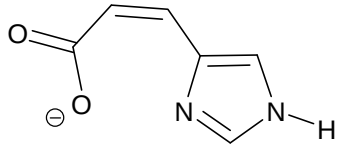


What about *cis*-urocanic acid (the dotted line)? At high pH, we must consider two tautomers:



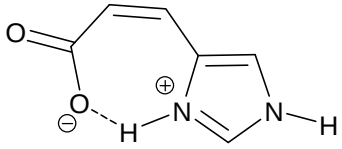


1,3-allylic strain means that the right-hand tautomer is favored, even though hydrogen bonding is possible on the left. So we have a series of tautomers at different pHs:



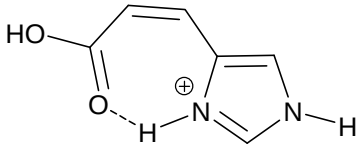
pH 14

So at high pH, we have one deshielded signal from the unprotonated nitrogen and one shielded signal from the protonated one.



pH 6

On crossing the p*K*a of the imidazole, we protonate the ring, making both nitrogens quite shielded.



pH 3

At some point, we protonate the carboxylic acid, changing the shifts slightly.

For a more detailed discussion, see Bachovin, *JACS* **1993** *115* 6813.

Summary

(1) Solving Problems

- two major types: assign a known structure or deduce the structure of a complete unknown
- unsaturation number U = C + 1 - (H + X - N)/2
- integrations in proton spectra imply empirical molecular formulas
- functional groups can be identified using IR

(2) Chemical Shift

- diamagnetic contribution: related to electron density
- in general, for protons, higher chemical shift for electron poor hydrogens
- paramagnetic contribution: relates to mixing of ground and excited states
- more important for heteronuclei which use p-orbitals for bonding
- through space/anisotropy effects can also be important

(3) Coupling Constants

- nuclei are chemically equivalent if they are related by a symmetry operation
- a proton coupled to *n* equivalent nuclei gives an *n*-fold degenerate multiplet with intensities corresponding to Pascal's triangle
- couplings to non-equivalent nuclei produce non-degenerate splitting patterns
- these splitting patterns can be used to identify molecules