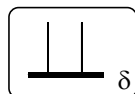


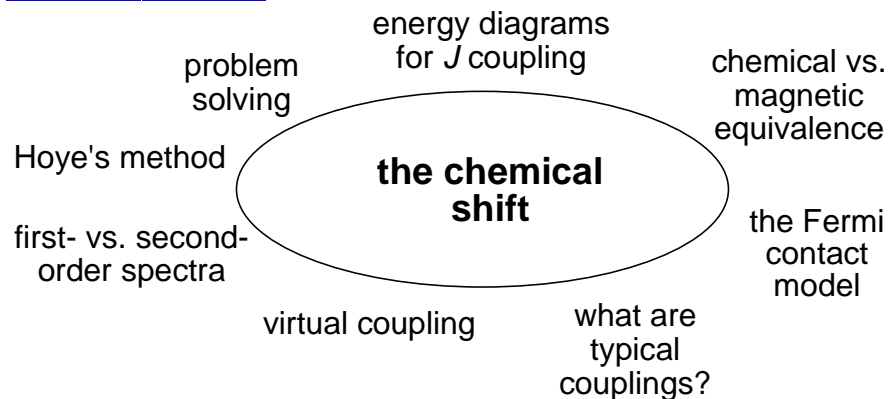
Coupling Constants

Eugene E. Kwan

January 31, 2012.



Scope of Lecture

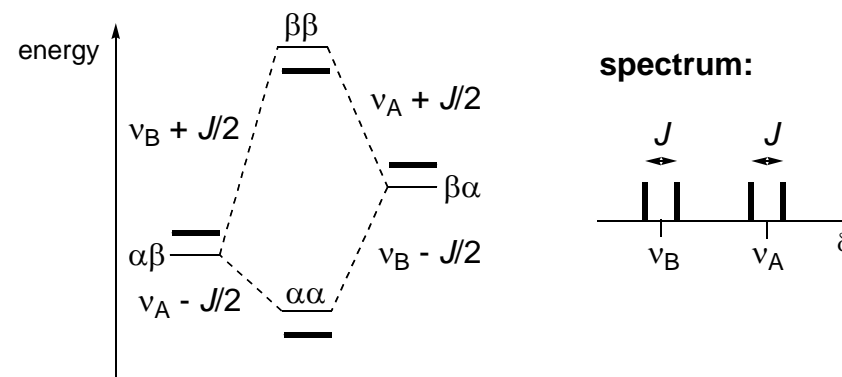


Helpful References

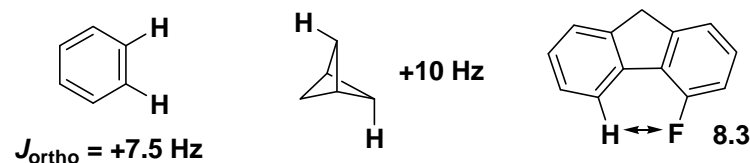
1. Nuclear Magnetic Resonance Spectroscopy... Lambert, J.B.; Mazzola, E.P. Prentice-Hall, **2004**. (Chapter 3)
2. The ABCs of FT-NMR Roberts, J.D. University Science Books, **2000**. (Chapter 10)
3. Spectrometric Identification of Organic Compounds (7th ed.) Silverstein, R.M.; Webster, F.X.; Kiemle, D.J. Wiley, **2005**. (useful charts in the appendices of chapters 2-4)
4. Organic Structural Spectroscopy Lambert, J.B.; Shurvell, H.F.; Lightner, D.A.; Cooks, R.G. Prentice-Hall, **1998**.
5. Organic Structure Analysis Crews, P. Rodriguez, J.; Jaspars, M. Oxford University Press, **1998**.

Key Questions

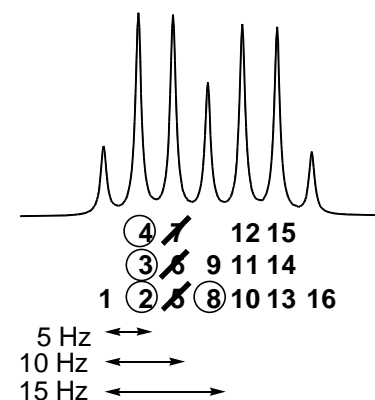
(1) What are coupling constants?



(2) How big are they?



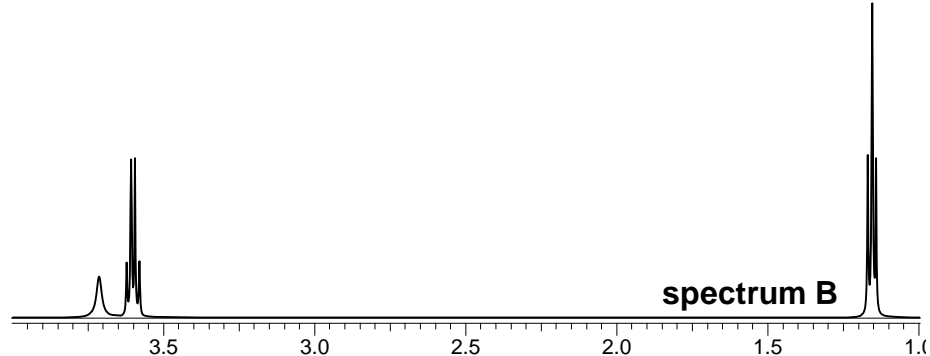
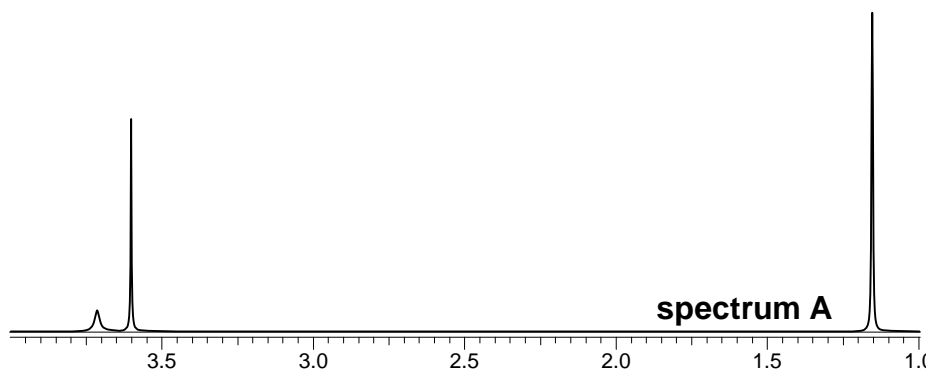
(3) How can they be extracted from first-order multiplets?



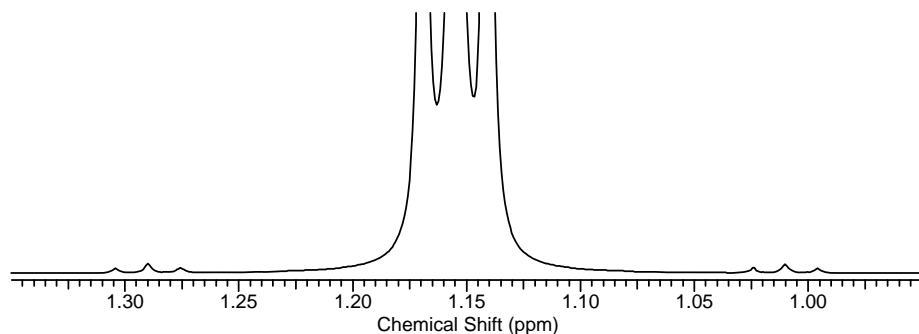
I thank Professor Mazzola (Maryland/FDA) and Professor Reich (Wisconsin-Madison) for providing useful material. I thank Professor Reynolds (Toronto) for useful advice.

Review: What's a Coupling Constant?

Q: Which one of these spectra corresponds to that of ethanol?



Of course, the answer is **spectrum B**, because spectrum A doesn't have any proton-proton couplings in it. Now, take a close look at the bottom of the methyl peak:



Q: What are these tiny peaks off to either side?

These are the carbon-13 satellites. Recall that:

- carbon-13: $I=1/2$ (natural abundance, 1.11%)
- carbon-12: $I=0$ (natural abundance, 98.89%)

So what we're seeing is a *mixture* of two isotopomers (for the sake of simplicity, let's assume that protium is 100% abundant, and we can ignore deuterium, tritium, etc.):

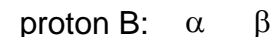
- ~99% $^1\text{H} - ^{12}\text{C}$ and
- ~1% $^1\text{H} - ^{13}\text{C}$.

I have bolded the protons, since those are the nuclei whose magnetic resonance frequency we are observing. Carbon-12 has no magnetic moment, so there is no coupling to it. Carbon-13 has $I=1/2$, so there is a doublet which is centered at the frequency of the $^1\text{H} - ^{12}\text{C}$ peak, but is separated by $^1J_{\text{CH}}$. (Isotopic substitutions usually only have very small effects on chemical shifts.)

Q: That's all great, but what exactly do coupling constants actually correspond to in terms of energy levels and spin states?

A: It's very complicated, and I defer a more rigorous discussion till later in the course. For now, take note of this hand-waving treatment of why line intensities obey Pascal's triangle for $I=1/2$ nuclei:

Scenario 1: proton A is adjacent (vicinal) to a proton B.
Only consider the spin states of proton B. It's trivial here:



There are only two states and only one way to arrange each one, so proton A looks like a doublet.

Scenario 2: proton A is adjacent (vicinal) to two protons, B and C, but B and C have the same chemical shift.

Now, we get a triplet:

βα
αα αβ ββ

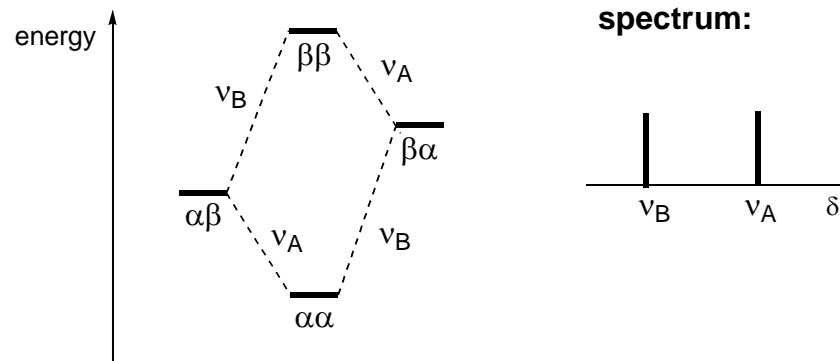
The double intensity for the middle line comes from the fact that there are two permutations. For a quartet:

ααβ ββα
αβα βαβ
ααα βαα αββ βββ

To me, this is not a very satisfactory description. For one thing, why don't protons which have the same chemical shift split each other? Why does the chemical shift difference between proton A and its neighbors matter at all?

I won't answer these questions now, but here is how to start thinking about it. Consider the energy diagram for the first scenario, where we have protons A and B. But let's set the coupling J to 0, so that A and B don't interact. What's the energy level diagram for this system?

Remember, α and β are short-hand notations for nuclei which are in the $+1/2$ and $-1/2$ states, respectively. By convention, the α state is more stable than the β state. If I write $\alpha\beta$, then it's understood that I mean that proton A is in the α state, and proton B is in the β state:

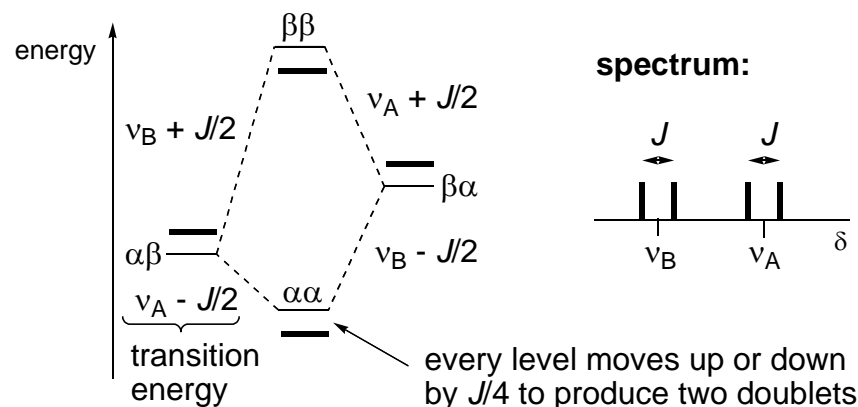


Although this is the simplest case, there's a lot going on here:

- (1) **Only single-quantum transitions are observable.** That means that the only transitions which flip one of the spins are allowed. A "double-quantum transition" from $\alpha\alpha$ to $\beta\beta$ does not result in an observable signal. (This is the weirdness of quantum-mechanical selection rules.)
- (2) Protons A and B are not interacting, so flipping A gives a transition of frequency ν_A and flipping B gives a transition of frequency of ν_B . From the diagram, ν_A is smaller than ν_B , so proton A has a smaller chemical shift than proton B.
- (3) Although there are four single-quantum transitions, each is doubly-degenerate and there will be two singlets of equal intensity (assuming we don't have to worry about other spins in the molecule).

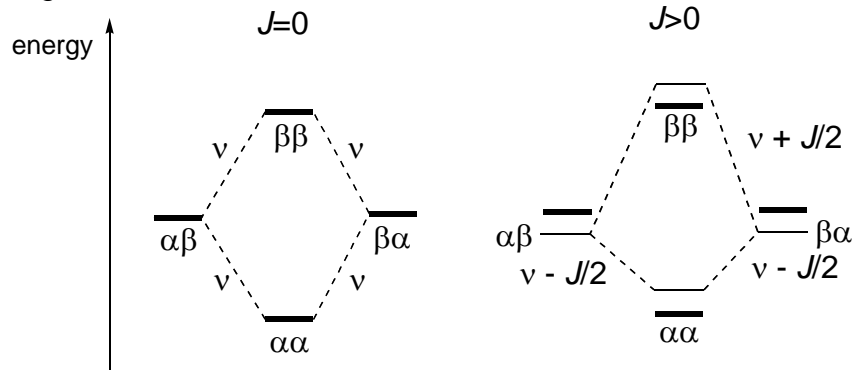
Q: What is the diagram if there is a coupling J ?

Here, we must consider the *weakly-coupled* or *first-order* case, where $J \ll |\nu_A - \nu_B|$. Additionally, A and B must be chemically and magnetically non-equivalent (but I'll tell you more about it in a moment). The new diagram is (thin solid lines are the new energy levels, bold lines are the old energy levels):

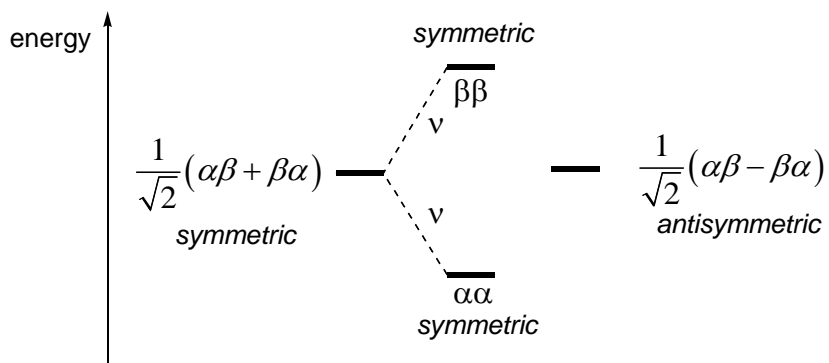


Every *level* is shifted by $J/4$; every *transition* is shifted by $J/2$.

Strange stuff happens if we try to construct the same two diagrams for the case where $\nu_A = \nu_B$. You might think the diagrams should be:

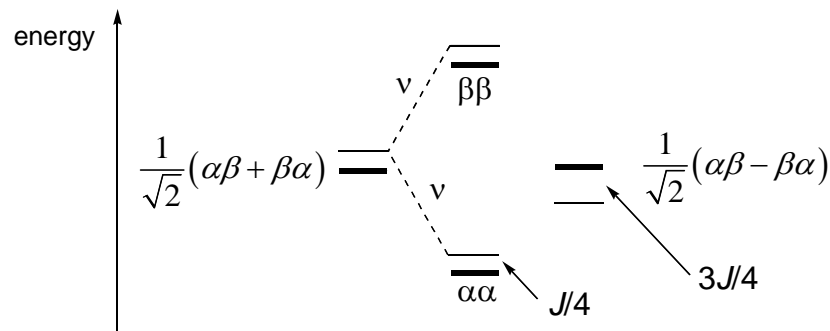


However, this would lead to a rather strange spectrum where the two protons couple to each other, even when they have the same chemical shift. But *why* are these diagrams incorrect? The spins are indistinguishable, but this description allows me to point to a particular nucleus and tell you what spin it is. Instead:



If we exchange the nuclei in the symmetric combination, the wavefunction does not change sign. Conversely, if we exchange the nuclei in the antisymmetric combination, the wavefunction gets multiplied by -1. Transitions between symmetric and antisymmetric states are not allowed, so there are no dashed lines between them.

What's the diagram look like for $J > 0$? It turns out that it's:



(If this seems a bit mysterious, don't panic--I'll derive it later on in the course. But not today.) In principle, there might be three possible lines: one at ν , one at $\nu - J/2$, and one at $\nu + J/2$, but the latter two are not allowed, as they involve transitions between symmetric and antisymmetric states.

Anyways, there are a few really important messages here:

- (1) "Normal behavior" is expected when $J \ll \Delta\nu$. This means that a nucleus coupled to n equivalent nuclei will give $n+1$ lines, with intensities corresponding to Pascal's Triangle.
- (2) Equivalent* nuclei don't split each other. Equivalent means they have to have the same chemical shift (chemical equivalence) and be completely indistinguishable (magnetic equivalence). More on this in a moment.
- (3) Lines in a spectrum correspond to transitions between energy levels. The only allowed transitions change the total spin number by 1. Transitions between symmetric and antisymmetric states are not allowed.

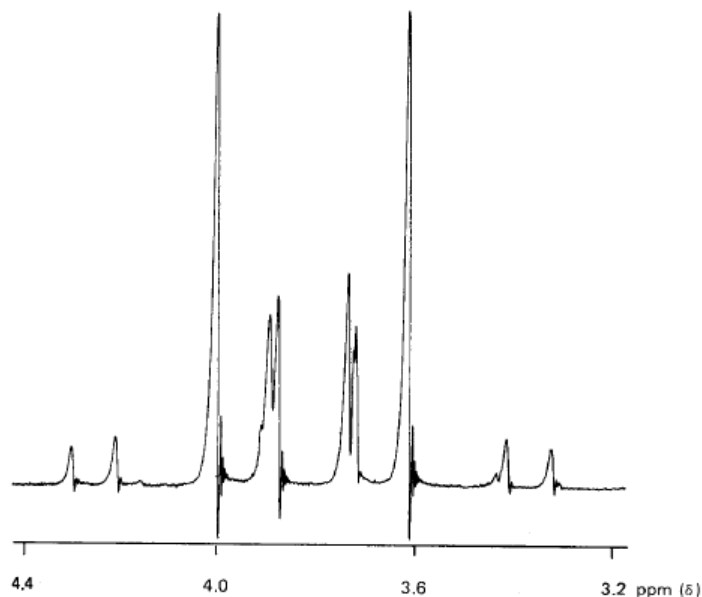
Chemical vs. Magnetic Equivalence

From this discussion, it's apparent that it's important to know whether two nuclei are "the same" or not. For example, what proton spectrum do you expect for 1,1-difluoroethene?

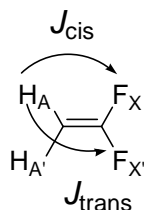


- (a) one line (b) two lines
(c) three lines
(d) more than three lines

Here is the observed spectrum at 90 MHz in CDCl_3 (Lambert and Mazzola, pg 101):



Uh oh: there are some **10 lines** visible! Note that this odd appearance will *not* be improved by going to a higher magnetic field strength. Here's why. This is called an $\text{AA}'\text{XX}'$ system:



Although symmetry makes the chemical shifts of protons A and A' the exact same, proton A has *different* couplings to F_X and $\text{F}_{X'}$ than does A'. So A and A' are *not* the same, and A and A' *can* split each other. There are essentially two *different* protons with the same chemical shift coupled to two fluorines. Since J is not less than the chemical shift difference (0), one gets a strange spectrum. (Later, we'll see where all these extra lines come from.) This leads to these definitions:

chemically equivalent: same chemical shift; nuclei can be interchanged by a symmetry operation on the molecule
magnetically equivalent: chemically equivalent *and* have the same coupling constant to any other NMR-active nucleus in the molecule

(This last caveat means that the protons in 1,1-dichloroethene are chemically and magnetically equivalent. Chlorine-35 and chlorine-37 are quadrupolar nuclei and the fast relaxation averages out the various spin states so they are not considered by this criterion.)

From before, we also have these definitions:

homotopic: two nuclei can be interchanged by rotation; chemically equivalent in all media

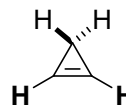
enantiotopic: molecule has no rotational axis of symmetry, and two nuclei can be interchanged by a plane of reflection; chemically equivalent in achiral media

diastereotopic: neither homotopic nor enantiotopic; chemically nonequivalent

If this seems a bit abstract, try these examples. Are the **bold** protons:

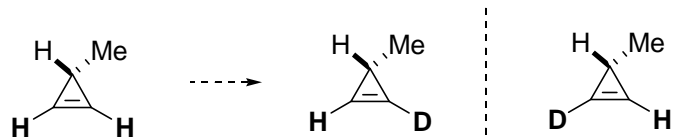
- chemically equivalent / magnetically equivalent?
- homotopic / enantiotopic / diastereotopic?

(We care because we want to know if they will split each other/act as two equivalent nuclei for the $n+1$ rule.)



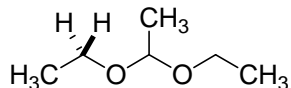
These protons are homotopic, chemically equivalent, and magnetically equivalent.

What about 3-methylcyclopropene?

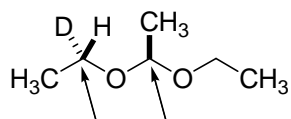


These protons are related by reflection and are enantiotopic. They are chemically and magnetically equivalent. This is an AX₂ system.

How about these acetal protons?



These are *diastereotopic* and chemically and magnetically non-equivalent, despite the lack of any stereocenters! Suppose the methyl group is "up" and we label one of the hydrogens:



Two chiral centers are simultaneously created!

If the other proton gets labeled, a diastereomer is formed.

To conclude, here are some nomenclature points for describing spin systems that you will come across:

AB: two protons are not chemically equivalent, but have similar chemical shifts

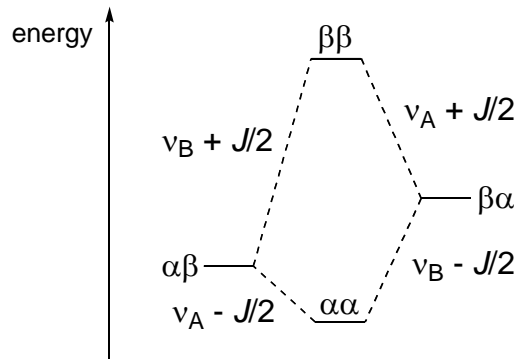
AX: two protons have completely different chemical shifts

AA': two protons are chemically equivalent, but magnetically non-equivalent

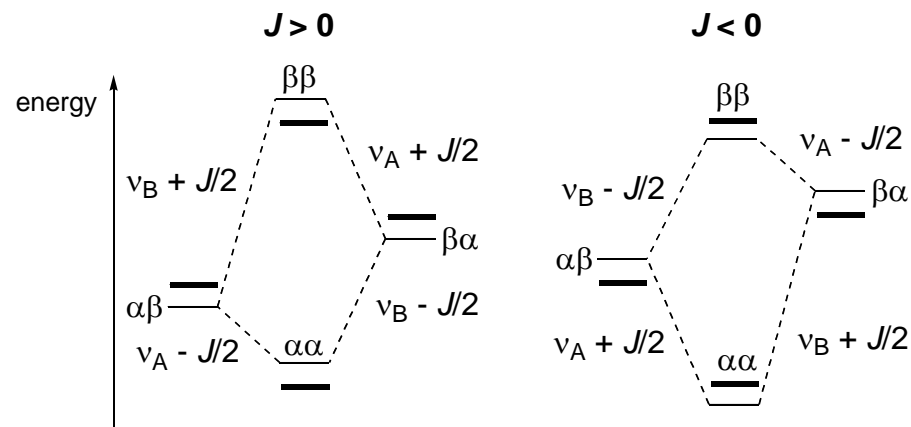
Common sense will tell you what happens when you mix and match these. For example, 1,2-dichlorobenzene is a AA'XX' system (why is that?).

The Fermi Contact Mechanism

Let's go back to the energy diagram for an AX system with an AX coupling constant J :



This diagram says that the $\alpha\beta$ state is more stable than the $\beta\alpha$ state. But what if $J < 0$? That seems like an odd thing to say if one interprets J as the spacing between lines, but with the energy diagram, it can be understood as:



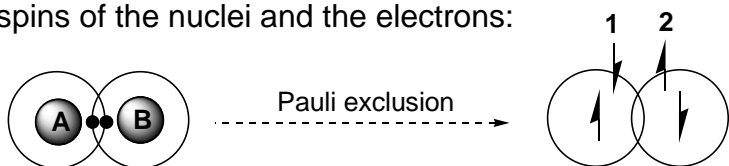
- (1) Positive J values mean that antiparallel states are stabilized relative to parallel ones. Negative J = opposite.
- (2) Spacings in first-order spectra = magnitude of J only.
- (3) Second order spectra look different depending on the sign of J . (Actually, only the relative signs of J matter.)

The Fermi Contact Mechanism

Couplings can be transferred by a number of different mechanisms, but the most important is the **Fermi contact mechanism**. For a more detailed discussion, please see:

"Analyzing and Interpreting NMR Spin-Spin Coupling Constants Using Molecular Orbital Calculations." Autschbach, J.; Guennic, B. Le *J. Chem. Ed.* **2007**, *84*, 156-170.

Consider a bond A-B. Here, the up and down arrows indicate the spins of the nuclei and the electrons:



- (1) Electron 1 will spend some time in the same space as nucleus A. Because of the Pauli exclusion principle, the spins will be opposed. This means that the spins of A and 1 are more likely to be antiparallel than parallel. This is called "spin polarization."
- (2) Similarly, (1 and 2) and (2 and B) should also be antiparallel-polarized. Overall, this means A and B should be antiparallel-polarized.
- (3) Antiparallel-polarization means a positive J value. Thus, one-bond coupling constants are almost always positive.
- (4) Geminal (two bond) couplings are usually negative, but numerous exceptions exist.
- (5) Vicinal (three bond) couplings are generally positive.
- (6) The sign of J can affect 2D NMR spectra.
- (7) J coupling is also known as "indirect coupling." If molecular tumbling is slow, dipolar or "direct" couplings D can also be observed.

One Bond Coupling Constants

Because the Fermi contact mechanism depends on overlap between electrons and the nucleus, the size of one bond couplings reflects the average degree of s character in a bond's hybrids.

For nonpolar C-H bonds, the approximate relationship is:

$$\% s = 0.2 \times {}^1J_{\text{CH}}$$

In general, these couplings are quite large--the closer two nuclei are, the larger their coupling. There are two places these are usually observed:

- (1) Carbon-13 satellites in proton spectra. However, these can often get covered by other signals.
- (2) HMBC spectra. This is a common type of 2D NMR experiment we will look at later. A lot of NMR experiments seek to sort one-bond from multiple-bond couplings (since they're much bigger). Errors appear because molecules have a spread of, rather than particular, ${}^1J_{\text{CH}}$ values.

Occasionally, an anomalous value of ${}^1J_{\text{CH}}$ can be a clue that a bond has an unusual degree of s-character (e.g., cyclopropane or epoxide). **An average value for organic molecules is 140 Hz.** Here are some values to calibrate you:

	CH ₃ CH ₃ 125 Hz	CH ₃ Cl 150 Hz			157 Hz (olefin)
118 Hz		CH ₂ Cl ₂ 177 Hz			159 Hz
H ₃ C-Li 98 Hz	125 Hz				248 Hz
	CH ₃ OH 142 Hz	137, 150 Hz	180 Hz	136 Hz	

(For my Chem 106 students, why does MeLi have a very small one bond C-H coupling constant?)

Geminal (Two Bond) Coupling Constants

These appear as parts of more complex multiplets and depend a lot on the angle between the three atoms. Here, we will just consider H-C-H coupling constants $^2J_{\text{HH}}$. Most values are negative, although sp^2 carbons can have positive values. Substituents have important effects. In general:

EWG by induction: J is more positive (e.g. fluorine substituent)

EWG by resonance: J is more negative (e.g. carbonyl group)

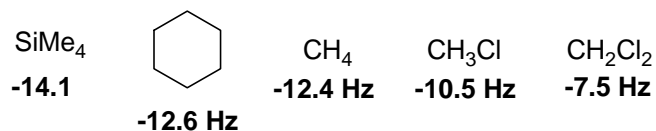
An explanation involving the ligand group orbitals of the CH_2 fragment has been given by Pople and Bothner-By and is explained by Professor Reich here: <http://www.chem.wisc.edu/areas/reich/nmr/notes-5-hmr-4-gem-coupling.pdf>.

Note that coupling in a H-C-D fragment is smaller than the coupling in an H-C-H fragment (by about 1/6.5) due to the smaller gyromagnetic ratio of deuterium.

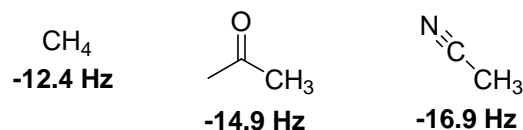
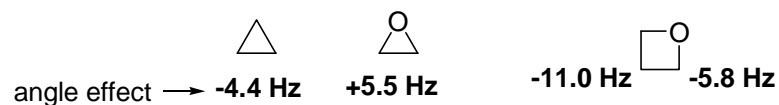
Alkanes: -5 to -20 Hz

Olefins: -3 to +3 Hz

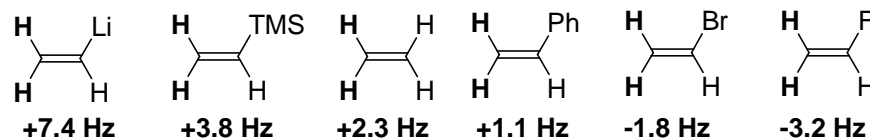
Halogens are both electron-withdrawing by induction and electron-donating by resonance (J more positive for both):



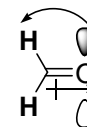
These are π -conjugation effects:



Olefin couplings are much smaller (it has been argued that there are two competing mechanisms which cancel each other out):

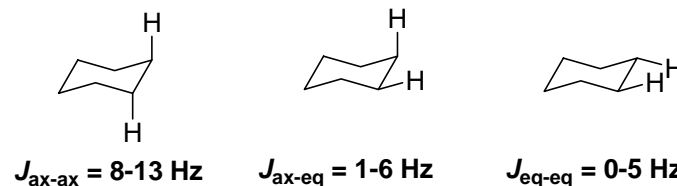


A particular anomaly is formaldehyde, which has a $^2J_{\text{HH}}$ of +40 Hz. This is a reinforcing effect from σ -withdrawal and π -donation:

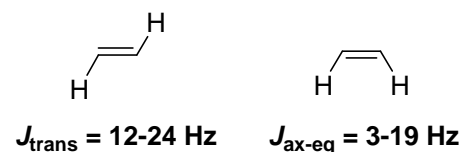
**Vicinal (Three Bond) Coupling Constants**

(Some material taken here from Professor Reich, lecture 5-HNMR-5; available at <http://www.chem.wisc.edu/areas/reich/chem605/index.htm>.)

These are by far the most interesting coupling constants, as they give stereochemical information. In general, the size of the coupling constant $^3J_{\text{HH}}$ depends on the H-C-C-H dihedral angle. **When the dihedral angle is 90° , the coupling is small. When the dihedral angle is 0° or 180° , the coupling is large.** In general 180° gives a larger coupling than 0° . Here the prototypical cases:



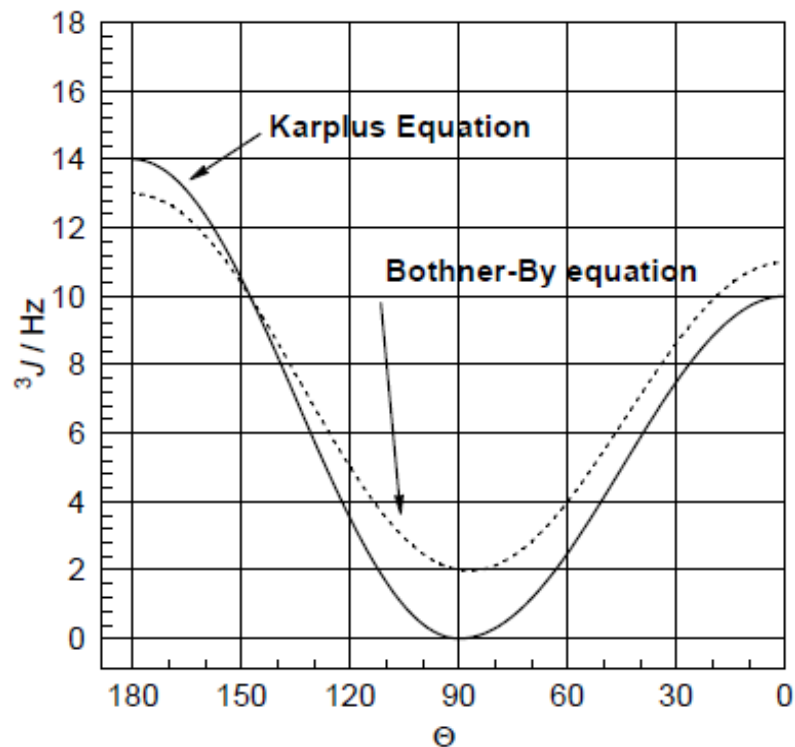
(Unfortunately, this means ax/eq and eq/eq are not distinct.)



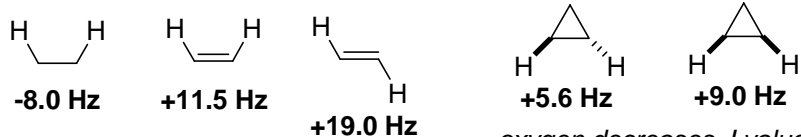
The trans coupling is virtually always bigger, even though the ranges overlap.

Vicinal (Three Bond) Coupling Constants

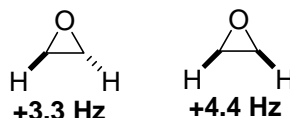
The **Karplus equation** relates $^3J_{\text{HH}}$ to the H-C-C-H angle (the Bothner-By equation is similar):



These curves are qualitatively correct, but are not quantitatively exact. Electronegative substituents will decrease the coupling constants. Here are some more numbers:



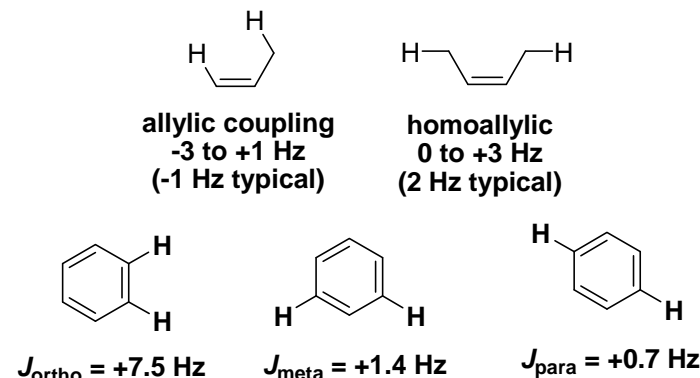
oxygen decreases J values:



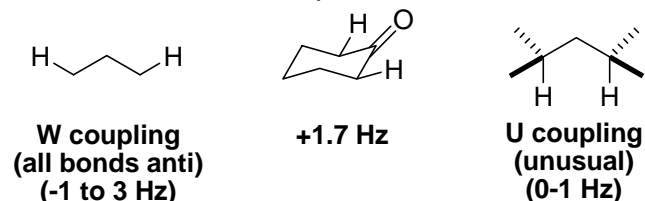
(The behavior right is because a dihedral angle of 0° gives a larger coupling than a dihedral angle of 120°)

Long-Range Couplings

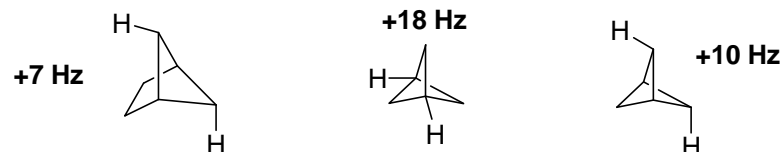
Couplings over four or more bonds are usually small and do not appear in spectra due to the limitations of linewidth. They can appear when the coupling is transmitted through π -systems:



"W couplings" are frequently encountered in polycyclic frameworks where orbital overlaps are favorable:



Ring strain can increase the size of these couplings:

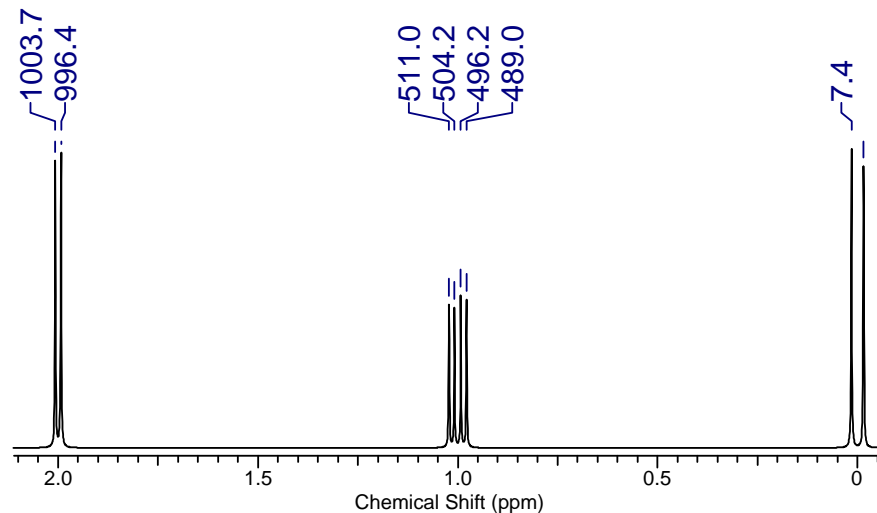


In rare cases, "through space" couplings are possible if one atom has lone pair electrons and the two nuclei are in van der Waals contact:

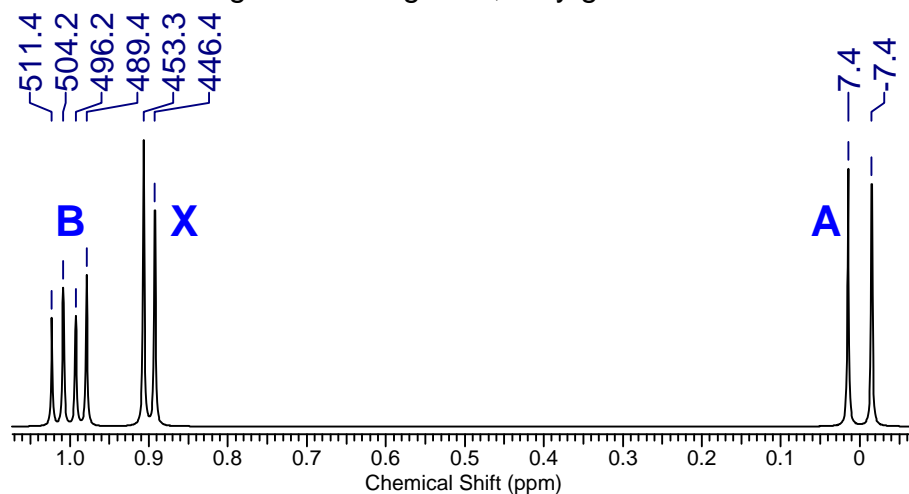


First- vs. Second-Order Spectra

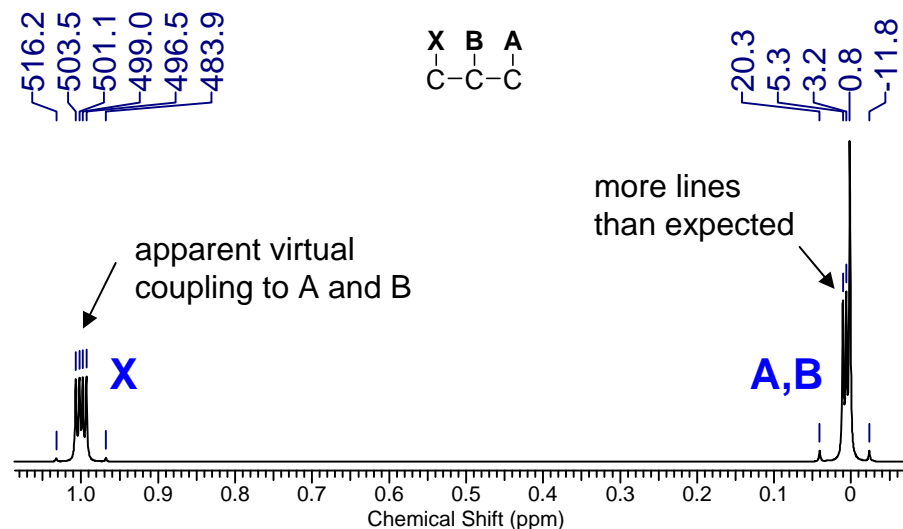
It's important to be able to determine coupling constants from multiplet patterns. If there is no problem due to chemical shift equivalence/magnetic non-equivalence, then a spectrum will be first-order if the separation between the peaks is much greater than the coupling: $\Delta\nu > 10 J$. Here is the transition from first-order behavior to second-order behavior in an ABX/AMX system where $J_{AB} = 15$, $J_{BX} = 7$, $J_{AX} = 0$ (simulated at 500 MHz):



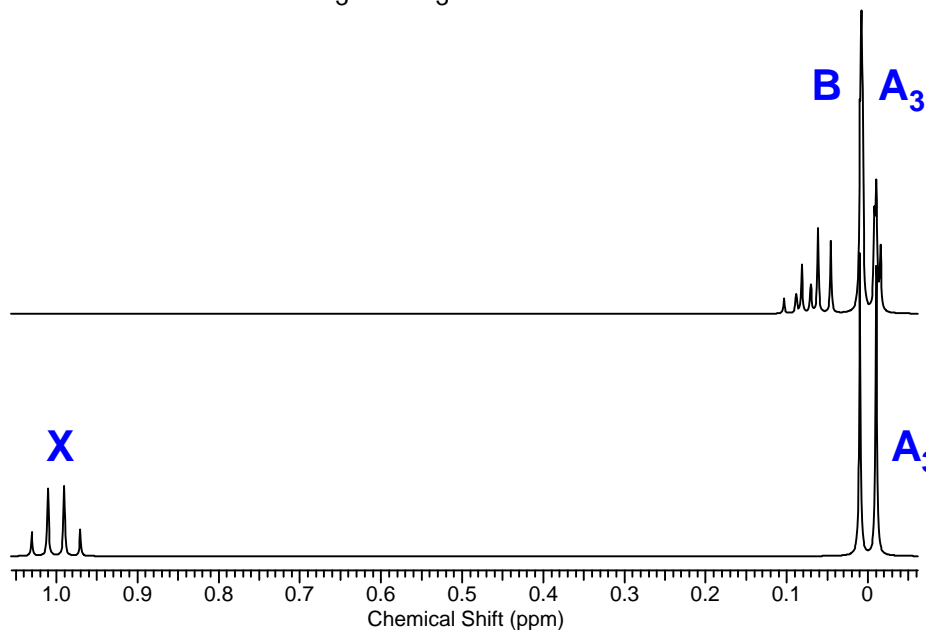
When the lines get closer together, they get a "roofed" look:



When A and B get too close, A and X *look* like they're coupled, but aren't actually coupled. This is called **virtual coupling**:



Other multiplet patterns can be much more complicated. Here is the transition from A_3X to A_3B :



Hoye's Method

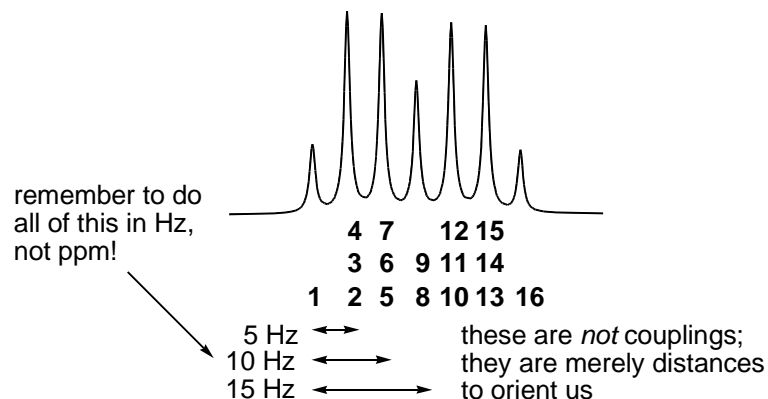
Here is the procedure of Hoye and co-workers:

- (0) Verify this is a first-order multiplet.
- (1) Determine the order of the multiplet (i.e., determine n in 2^n) and assign components above.
- (2) J_1 is the distance from component 1 to component 2; J_2 is the distance from component 1 to component 3.

However, further distances, like 1-4 are not *necessarily* couplings.

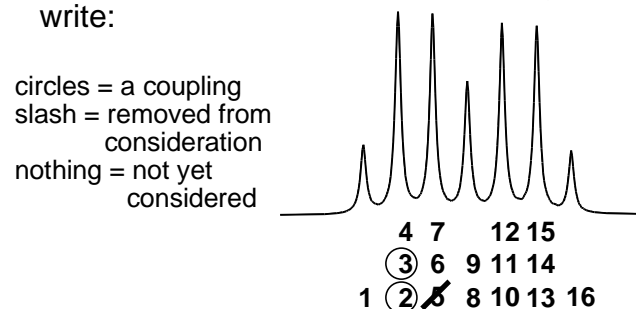
- (3) If there is a component $J_1 + J_2$ Hz from component 1, then remove it from consideration.
- (4) The distance from 1 to the next highest remaining component is J_3 .
- (5) Remove from consideration any components J_1+J_3 , J_2+J_3 , $J_1+J_2+J_3$. The distance from 1 to the next highest remaining component is J_4 . Etc.

If this seems too abstract, let's try it on the multiplet from the last page:

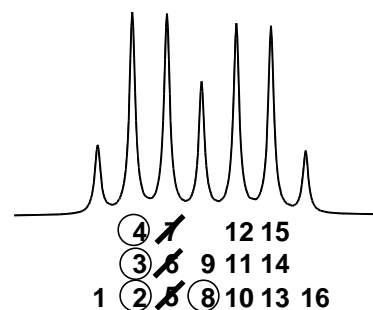


Let's go through the checklist:

- (0) This is a centrosymmetric multiplet: a dddd, which could have degenerate couplings.
- (1) Components assigned.
- (2) $J_1 = 1-2$, which is 5 Hz. $J_2 = 1-3$, which is also 5 Hz. (The fact that these are the same should not bother you.)
- (3) $J_1+J_2 = 10$ Hz. This corresponds to components 5, 6, and 7. However, we only remove one component (5) from further consideration. If I were doing it on paper, I would write:



- (4) The next highest component is 4. Thus, J_3 is 1-4, which is 5 Hz. (Once again, it doesn't matter this is the same as the values already extracted.)
- (5) $J_2+J_3=J_1+J_3=10$ Hz. Thus, I removed components 6 and 7 from further consideration (once for every duplication):



- (6) The final coupling is J_4 (since this is a fourth-order doublet. $J_4 = 1-8 = 15$ Hz. Thus:

$$J_1 = J_2 = J_3 = 5 \text{ Hz}$$

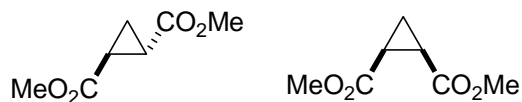
$$J_4 = 15 \text{ Hz}$$

This completes the analysis. (It can be checked by drawing a coupling tree diagram.)

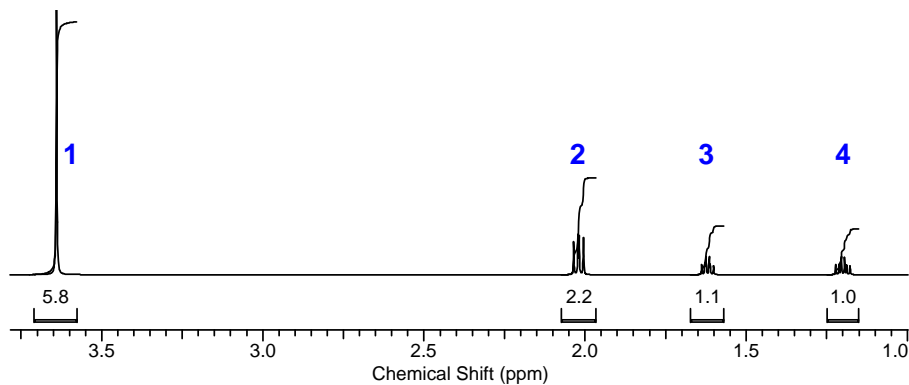
Practice Problem: Cyclopropane Stereoisomers

Think you know what's going on? Here is a question which is much trickier than it first appears. This question is adapted from Lambert and Mazzola, page 127.

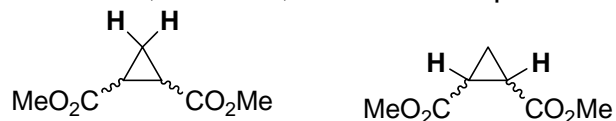
Please consider *cis*- and *trans*-dimethyl 1,2-cyclopropane dicarboxylate:



The 1D proton NMR spectrum of one of these isomers is shown below:

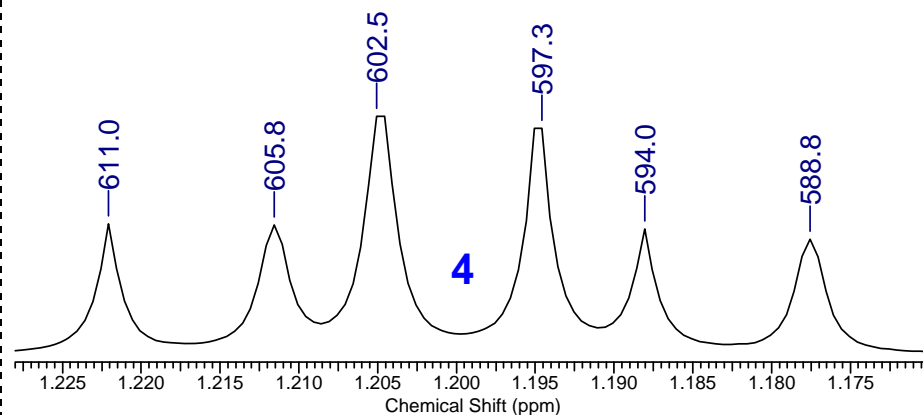
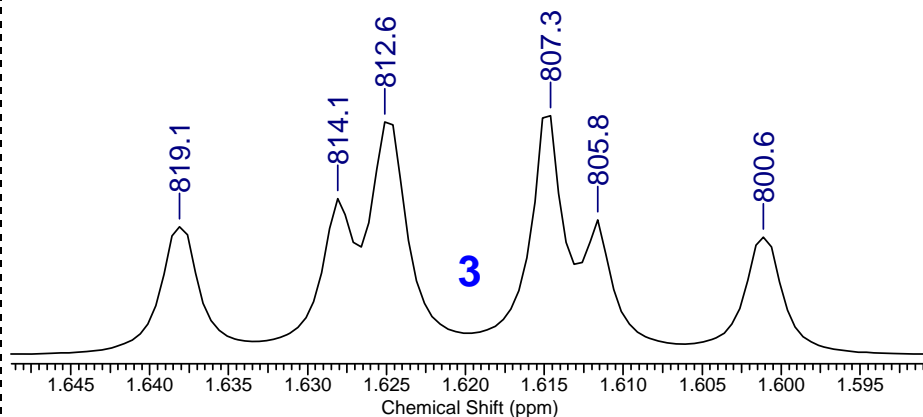
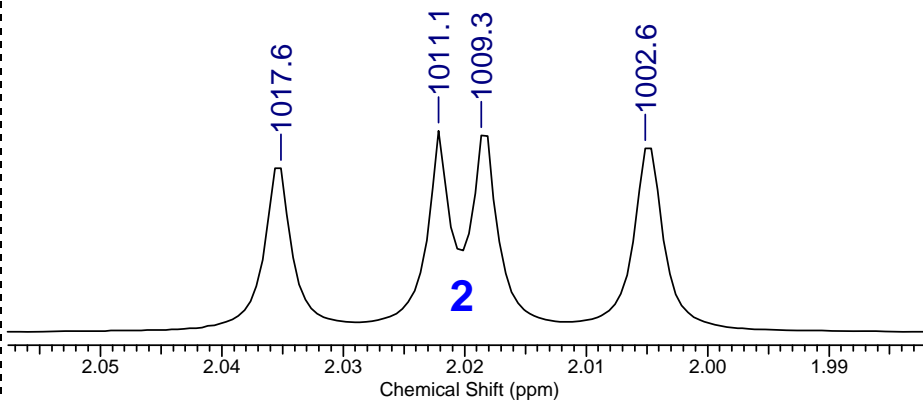


- (1) Consider these pairs of protons in each isomer and determine if they have homo-, enantio-, or diastereotopic relationships:



- (2) How many distinct signals should the *cis* isomer have? What about the *trans* isomer?
- (3) Determine the coupling constants in the spectra above.
- (4) Analyze the couplings to determine if this is the *cis* or *trans* isomer. For reference, these are the couplings in cyclopropane itself: geminal, -4.3; *trans* vicinal, 5.6; *cis* vicinal, 9.

Here are expansions of every peak (labels in Hz):

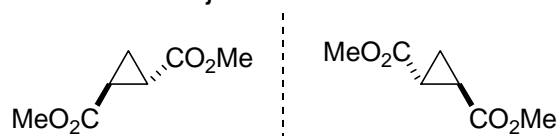


Practice Problem: Cyclopropane Stereoisomers

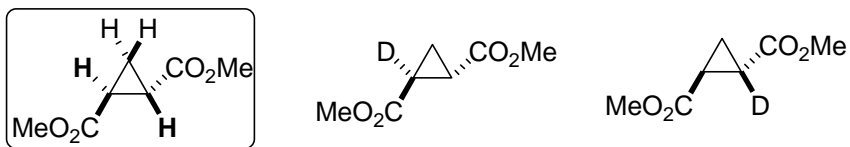
(1) Consider these pairs of protons in each isomer and determine if they have homo-, enantio-, or diastereotopic relationships.

Trans Isomer

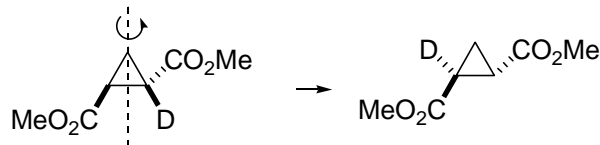
Note that this is a C_2 -symmetric, chiral molecule with two enantiomers, of which we'll just consider one:



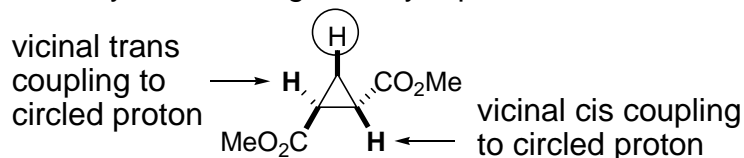
Rotation about the C_2 -axis simply turns one enantiomer into itself and does *not* interconvert them. Now, labelling one or the other proton in the pair gives these stereoisomers:



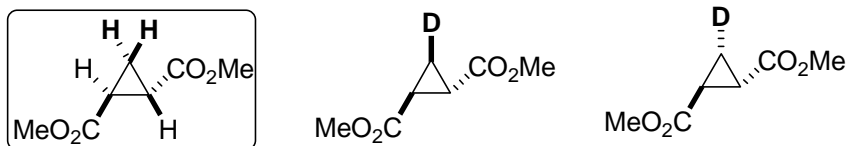
The compound on the right can be rotated about its C_2 axis:



This is exactly the same as the other compound. Therefore, these protons are homotopic and chemically equivalent. However, they are *not* magnetically equivalent:



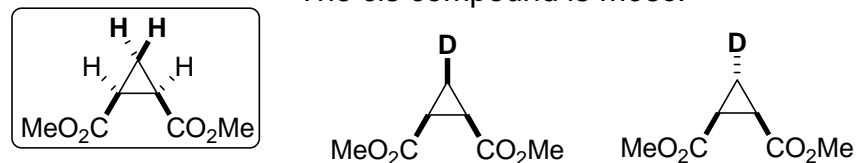
For the other pair:



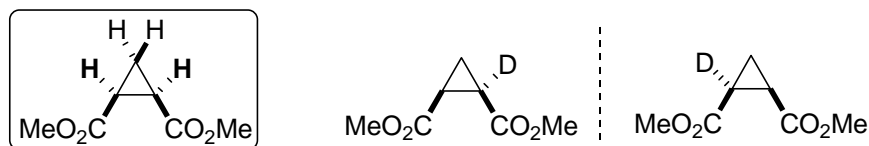
The same reasoning applies: these are **homotopic** and chemically equivalent, but not magnetically equivalent.

Cis Isomer

The cis compound is *meso*.



These are diastereomers: two different *meso* compounds. Thus, these protons are **diastereotopic**.



These compounds are enantiomers so these protons are **enantiotopic**.

(2) How many distinct signals should the cis isomer have? What about the trans isomer?

Cis Isomer: There are four protons, but one pair is enantiotopic, so there should be three signals overall in an "AMX₂" or "ABX₂" system, depending on the chemical shift.

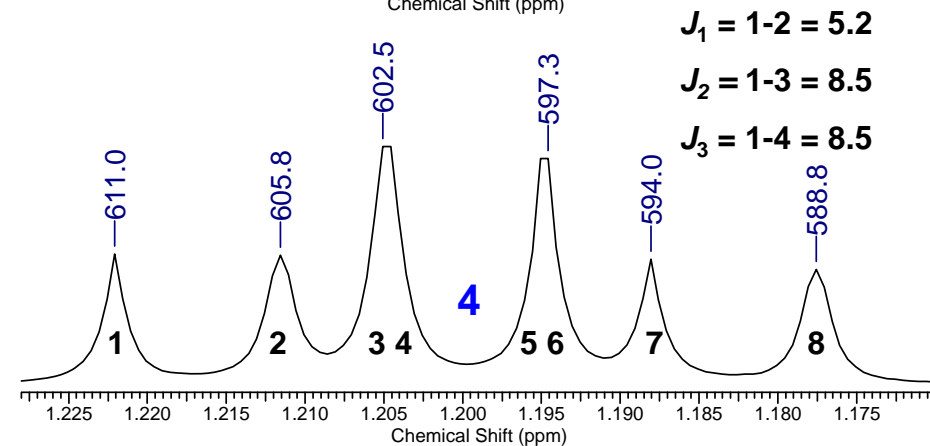
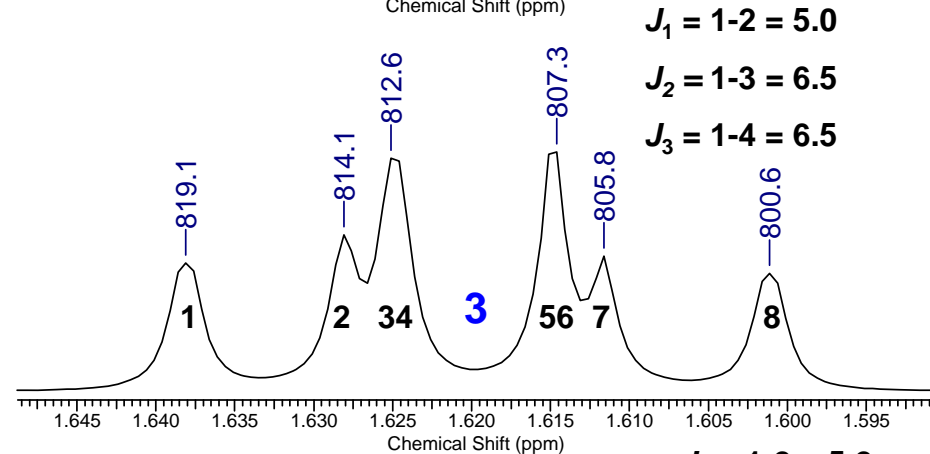
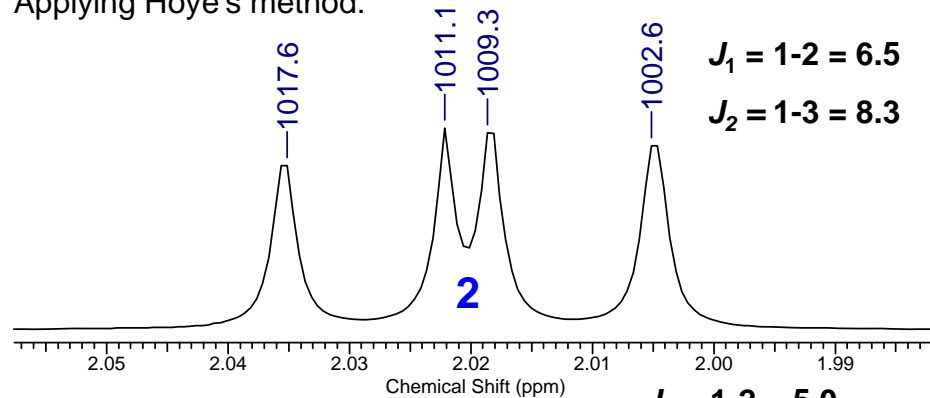
Trans Isomer: There are two sets of homotopic, but magnetically non-equivalent protons. This means an AA'XX' or AA'BB' system--two signals, but there will definitely be some second-order behavior in the coupling patterns.

(3) Determine the coupling constants in the spectra above.

The spectra are clearly first-order and therefore Hoyer's method is applicable. This also suggests the cis isomer!

Practice Problem: Cyclopropane Stereoisomers

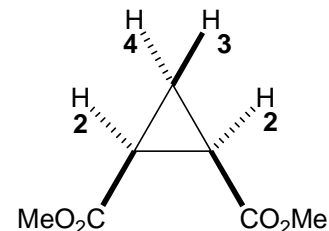
Applying Hoyer's method:



- (1) If A is coupled to B with coupling constant J , B must be coupled to A with the same coupling constant J .
- (2) However, spectra are rarely completely first-order or noise-free. So it's common to see couplings be "out of alignment" by a little bit.
- (3) Here, we have this spin system with these averaged couplings:

2	3	4
6.5	5.1	5.1
8.4	6.5	8.4
	6.5	8.4

Let's assume this is the cis isomer. **2** integrates to two protons, and must be next to the ester because those protons are enantiotopic. This also makes sense based on chemical shift. Because they are both chemically and magnetically equivalent, they do *not* couple to each other. This gives this assignment:



Why did I assign it this way? The couplings in cyclopropane are: geminal, -4.3; trans vicinal, 5.6; cis vicinal, 9. Therefore, the smallest coupling on **3** and **4** is the geminal coupling. That doesn't tell us anything about stereochemistry, so we can ignore it:

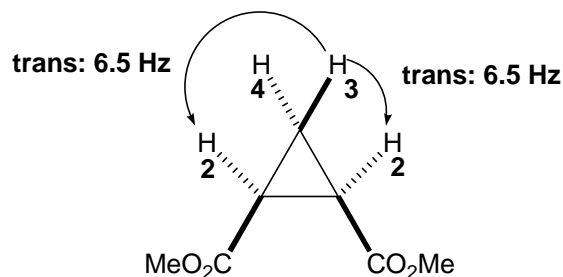
2	3	4
6.5	5.1	5.1
8.4	6.5	8.4
	6.5	8.4

Practice Problem: Cyclopropane Stereoisomers

Cyclopropane: geminal, -4.3; trans vicinal, 5.6; cis vicinal, 9.

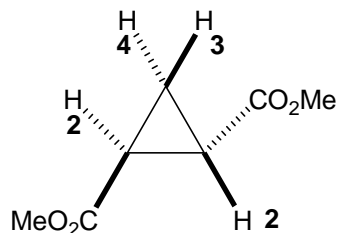
2	3	4
6.5	5.1	5.1
8.4	6.5	8.4
	6.5	8.4

Now, consider the proton marked tentatively as **3**. It has two protons in a vicinal relationship to it: **2** and the other **2** (which is the same). Therefore, it has a doubly-degenerate coupling. The coupling is 6.5 Hz, which makes sense for a trans vicinal coupling:



Similarly, **4** has two 6.5 Hz couplings to protons **2**. This makes sense for a trans coupling in a cyclopropane. Note that **2** does not couple to itself, which is why it's only a second-order "dd."

Now, a good spectroscopist always considers the other possibilities, which, here, is only one possibility: the trans isomer:

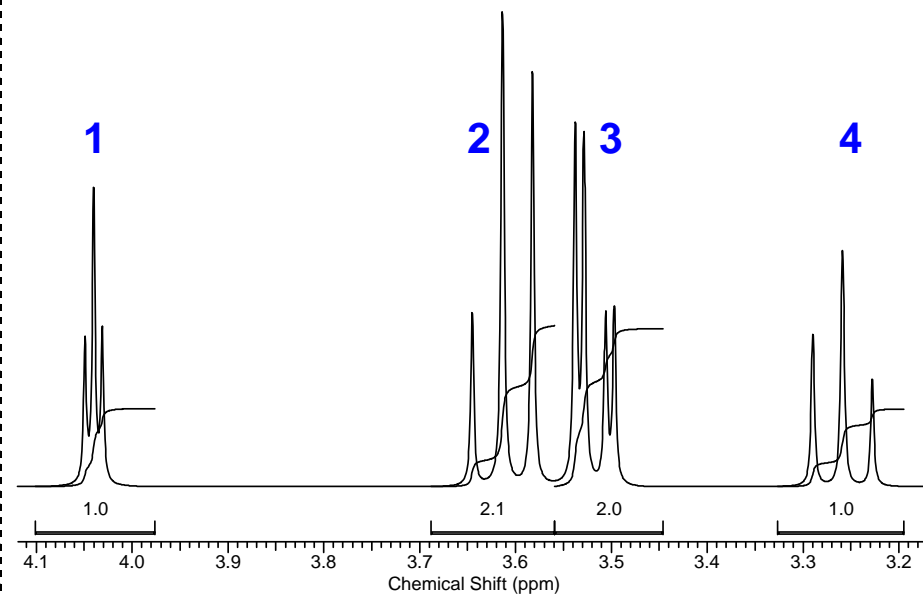


Now, you can see we have a number of problems. First, **3** and **4** ought to be pseudo-equivalent, but are actually widely separated. Second, **3** should have a cis coupling to one of the **2**'s and a trans coupling to the other. But clearly, **3** only has two different kinds of couplings. And third, why do **3** and **4** couple?

An Unknown Structure

Here's another practice question which doesn't involve a lot of measuring, but does involve a lot of thinking! (This and the final problem can be found on page 128 of Lambert and Mazzola).

An unknown compound has the molecular formula $C_6H_{12}O_6$ and has the following 1D proton NMR spectrum in D_2O (solvent and exchangeable protons are not shown, 300 MHz):



Couplings (Hz): **1** (2.8x2), **2** (9.6x2), **3** (2.8, 9.6), **4** (9.6x2).

The carbon-13 spectrum has exactly four resonances, all of which lie between 71 and 75 ppm. What is its structure?

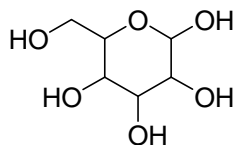
Hint 1: This compound is commercially available. What type of compound does the molecular formula suggest to you?

Hint 2: Protons next to two oxygens typically appear around 5 ppm.

Hint 3: Ignore the size of the couplings for now and begin by considering the connectivity of this unknown.

An Unknown Structure

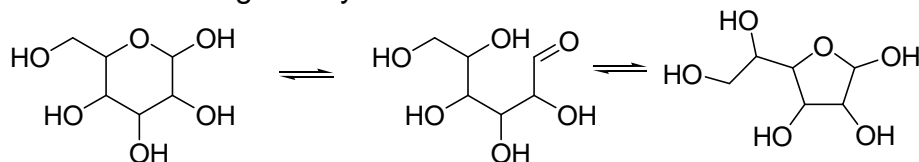
Ask any high school student worth his or her salt what molecule has the formula $C_6H_{12}O_6$, and they'll tell you glucose. So let's start there:



Now, notice I haven't drawn the stereochemistry. In all of these problems, I advise you to **determine connectivity first and work out the stereochemistry later**. Of course, sometimes couplings and other stereochemical information can also give clues to a connectivity pattern, but I find this is a good way to narrow down a lot of confusing information into what's essential.

Why can't it be glucose? For one thing, it has an anomeric proton, and our structure has nothing around 5 ppm. Further, it only has four kinds of carbons, while glucose has relatively low symmetry.

OK, what else could it be? I know glucose can exist in a bunch of forms involving aldehyde intermediates:



However, all of these structures have aldehydes (there's no carbonyl resonance) or anomeric protons. Another crucial clue comes from the fact that these sugars have **seven**, not six, non-exchangeable protons, and we need six.

So, clearly, we need to think a little harder. If you're feeling a bit lost, let me distract you with an excerpt from one of my favorite books, Surely You're Joking, Mr. Feynman! Adventures of a Curious Character:

(Here, Feynman is talking about trying to understand the complicated theorems mathematicians come up with.)

"I had a scheme, which I still use today when somebody is explaining something that I'm trying to understand: I keep making up examples. For instance, the mathematicians would come in with a terrific theorem, and they're all excited. As they're telling me the conditions of the theorem, I construct something that fits all the conditions. You know, you have a set (one ball)--disjoint (two balls). Then the ball turn colors, grow hairs, or whatever, in my head as they put more conditions on. Finally they state the theorem, which is a some dumb thing about the ball which isn't true for my hairy green ball thing, so I say, 'False!'"

(This is more or less what we're trying to do here.)

"If it's true, they get all excited, and I let them go on for a while. Then I point out my counterexample.

'Oh. We forgot to tell you it's Class 2 Hausdorff homomorphic.' 'Well, then,' I say, 'It's trivial! It's trivial!' By that time I know which way it goes, even though I don't know what Hausdorff homomorphic means."

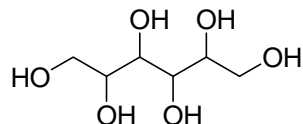
(Evidently, some degree of fakery is necessary, even for the best of us.) Now, back to the problem...

If you look at the topology of these structures, you can see the structure **cannot be an ether of any size**. The reason is that if two oxygens get connected, then you lose an exchangeable proton that has to be made up by a non-exchangeable one, and then you end up with more than six. (You might be able to get around this if you relax some of the other conditions, like not having an oxygen on every carbon, but you can't do it with the given functional group pattern.)

But there's clearly one degree of unsaturation!

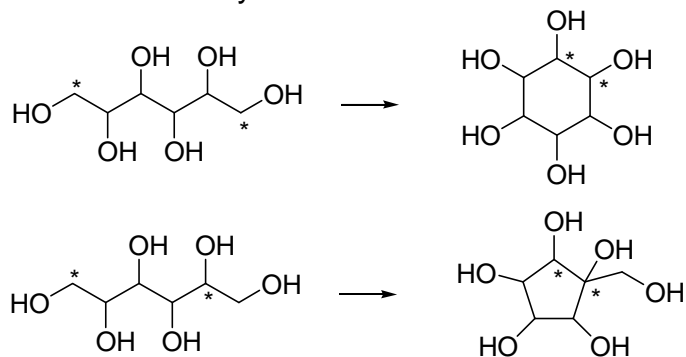
An Unknown Structure

The open chain that we have to add a degree of unsaturation to is this:



If connecting oxygens to form an ether are no good, then the logical alternative is to connect carbons. (You might also think about making peroxide-type structures. However, this will not solve the problem of having only six non-exchangeable protons. Also, remember what I said about horses vs. zebras!)

Here are two possibilities (there are more). We are connecting the carbons marked by asterisks:



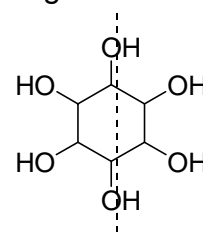
However, the carbon-13 says that we don't have any quaternary centers with oxygens on them. (My Ph.D. advisor, Professor Evans, says one cannot refer to tertiary carbinols as "quaternary." True enough, but in NMR, using the term quaternary to designate any non-protonated carbon is very useful.) Thus, the six-membered ring is the only possible ring size.

We have arrived at **inositol**, which looks sort of like a sugar, but isn't really very sweet. It's thought to be an important messaging compound in biology. It has 9 stereoisomers. Now, let's look at the couplings and overall symmetry to determine

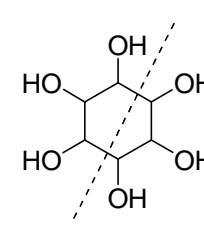
which one it is. Recall there are **four kinds of carbons**.

This implies some sort of symmetry. The simplest kind of symmetry is a plane of symmetry. Such a plane can either pass through two vertices or between two vertices:

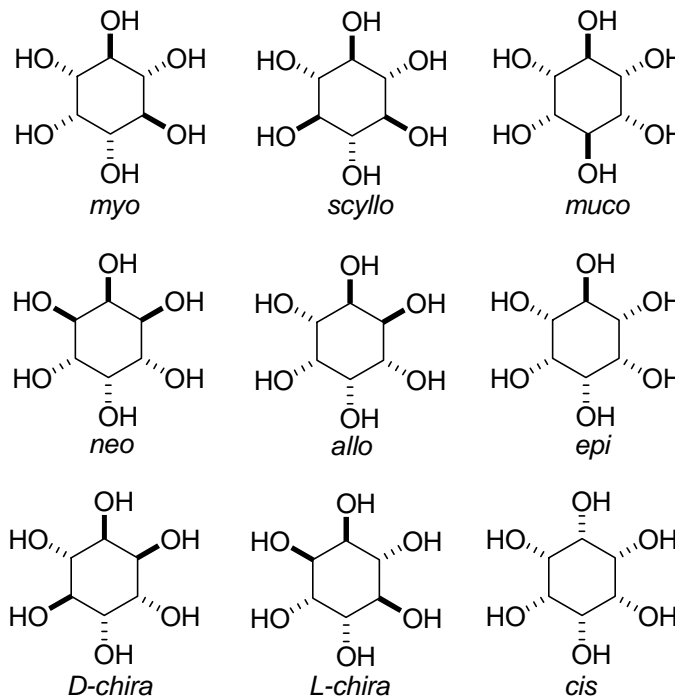
through two vertices:



between two vertices:



The latter is bad news, because that would mean only three kinds of carbons. Here are all the possibilities. Which of these is viable?

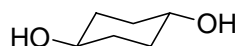


An Unknown Structure

We could sort through the stereoisomers on symmetry grounds, but it's easier to just guess a structure that has a plane of symmetry that passes through two vertices. I'll need to consider the couplings, too:

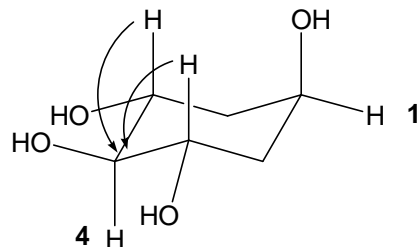
Couplings (Hz): **1** (2.8x2), **2** (9.6x2), **3** (2.8, 9.6), **4** (9.6x2).

As a reminder, **1** and **4** are worth 1H, while **2** and **3** are worth 2H. This means **1** and **4** lie along the symmetry plane:

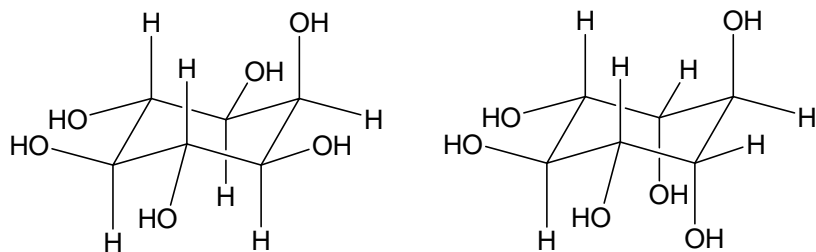


I've just arbitrarily drawn them in the equatorial positions, which is always a good place to start. However, in this case, it's wrong, because the coupling suggest that **1** is equatorial, while **4** is axial (if they were both equatorial, then neither of them would have trans-diaxial couplings of 10 Hz):

trans couplings are large: about 10 Hz

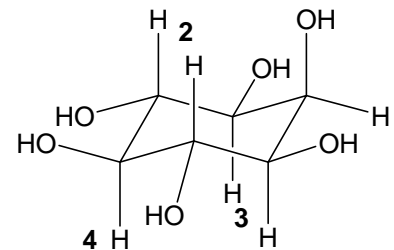


Because **4** has to have two diaxial couplings, its adjacent hydroxyls must be equatorial. But what about the hydroxyls adjacent to **1**? Here are the two possibilities, given that axial-equatorial and equatorial-equatorial couplings are relatively similar in size:



(The two other ax/eq possibilities don't obey the symmetry requirements.)

The key clue here is that **2** and **3** *both* have large couplings, meaning that the hydrogens **must be axial**:

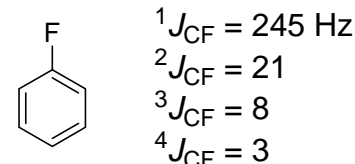


How did I make these assignments, despite the very similar chemical shifts? **2** has two axial couplings, while **3** has only one. This completes the problem: this is *myo*-inositol.

Note that in more complicated systems involving complex multiplet patterns in stereochemically rich and conformationally rigid environments (e.g., steroids), a wide range of short- and long-range couplings can be seen. The key there is to focus on the large vicinal ones. We'll see more of this later.

Practice Problem: Carbon-Fluorine Couplings

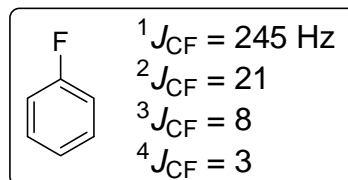
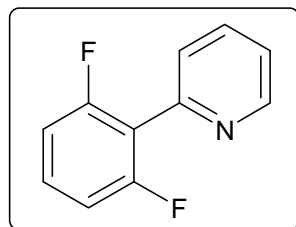
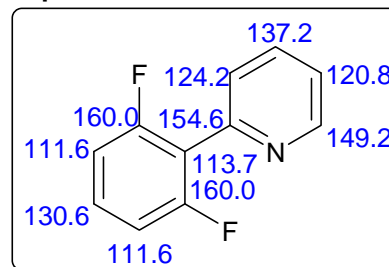
Fluorine-19 is 100% abundant, has a spin of 1/2, and has a gyromagnetic ratio which is almost as high as proton's (94%), so it's almost as sensitive as proton (about 83%). Because carbon-13 spectra are *not* fluorine-19 decoupled, fluorine couplings can and do appear in 1D carbon-13 spectra. The couplings range in size. Here it is for fluorobenzene:



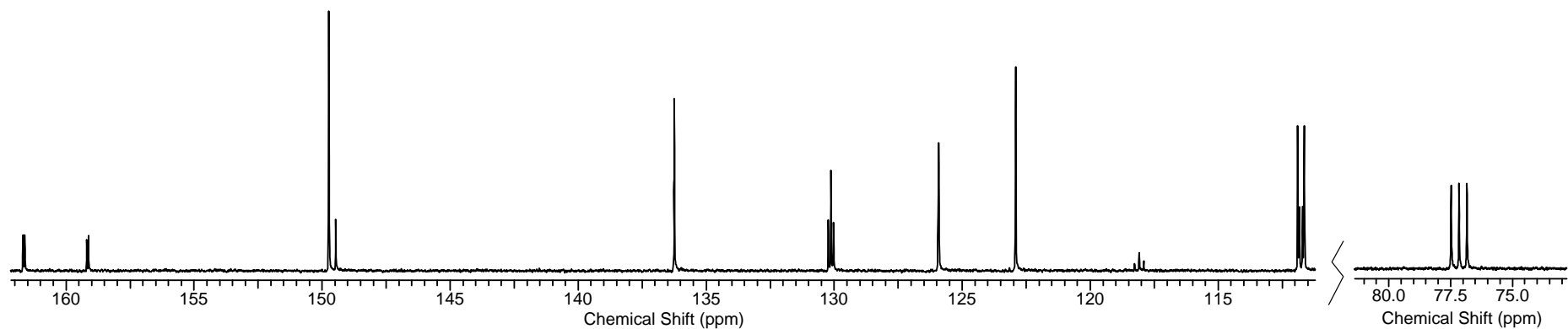
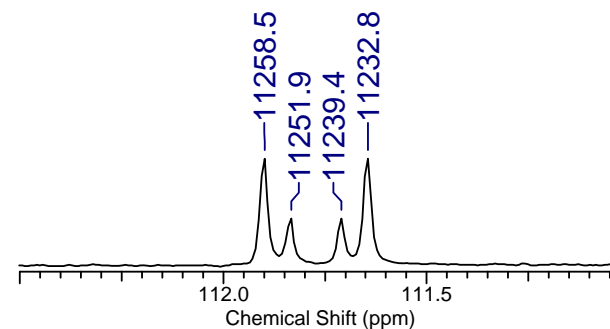
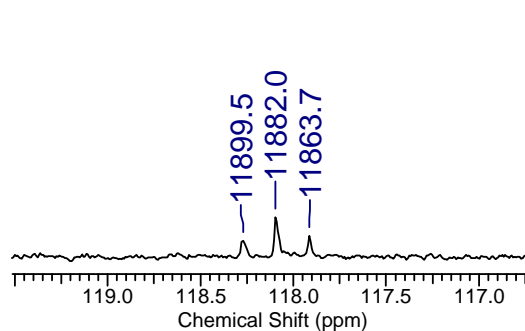
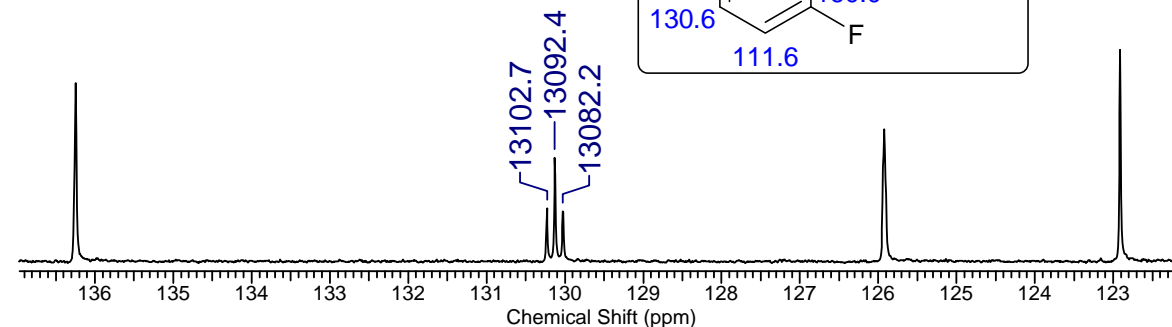
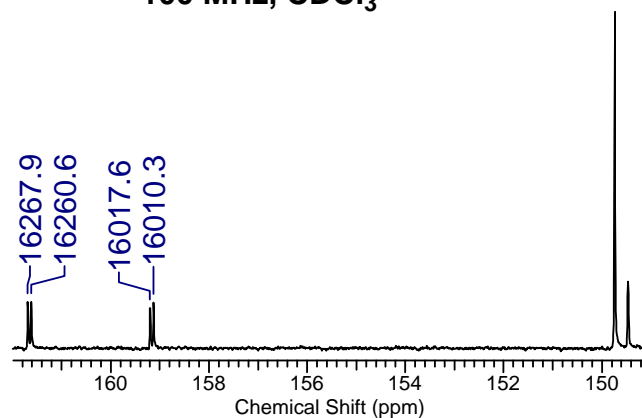
The size of a heteronuclear coupling is proportional to the product of their gyromagnetic ratios, so fluorine behaves very similarly to proton (e.g., carbon-fluorine and carbon-proton couplings are similar in size).

Practice Problem: Carbon-Fluorine Couplings

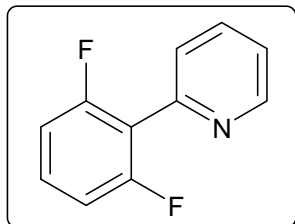
In the next two problems, we'll look at the carbon-13 spectra of some biaryls (courtesy Dr. Jaclyn Henderson). Please assign the spectrum of this compound. There is no reason to "fly blind" here, so the predicted spectra (ChemDraw 9) are provided right.

**predicted carbon-13 shifts**

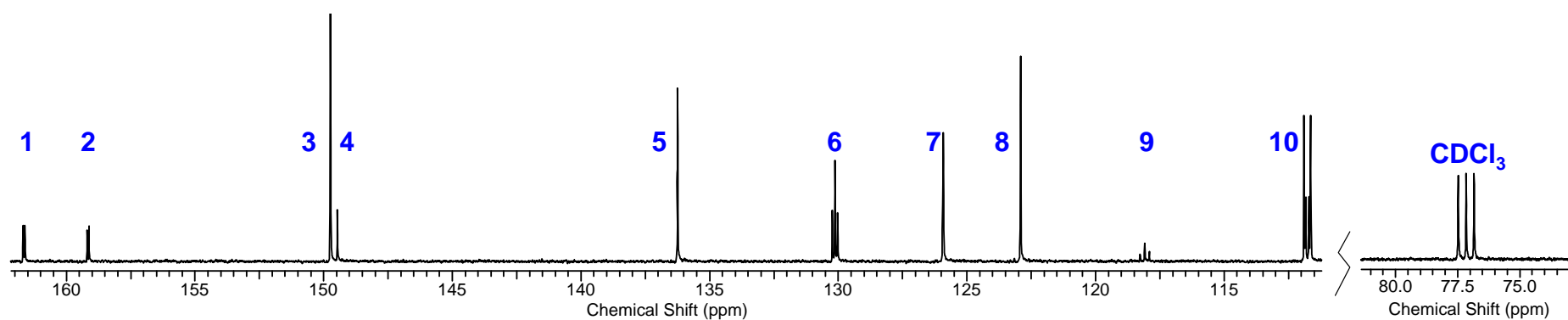
100 MHz, CDCl_3



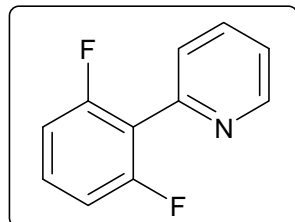
Practice Problem: Carbon-Fluorine Couplings

100 MHz, CDCl₃

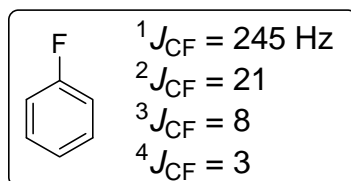
- (1) **How many distinct carbon signals are there?** There are **9**, due to the symmetry plane in the difluoroaryl ring.
- (2) **Does the spectrum have 9 signals in it?** Clearly, there are more than 9 signals here due to carbon-fluorine couplings. First, recognize that the peak near 77 ppm is deuteriochloroform, which is showing a 1:1:1 triplet due to coupling to an $I=1$ nucleus, deuterium. Next, label the carbons (blue numbers at the bottom).
- (3) **Why are there ten signals, not nine?**



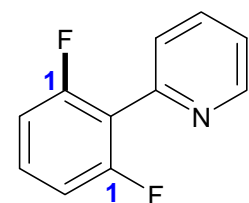
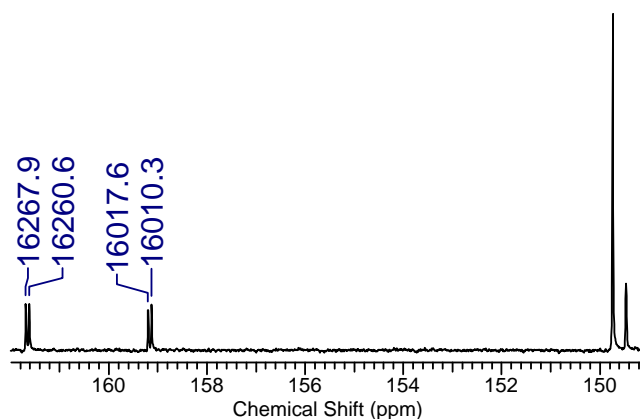
Practice Problem: Carbon-Fluorine Couplings

100 MHz, CDCl₃

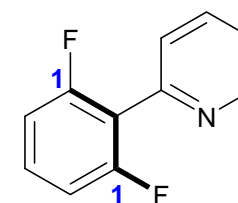
- (3) Why are there ten signals, not nine? The numbering isn't right. Recall the couplings in fluorobenzene:



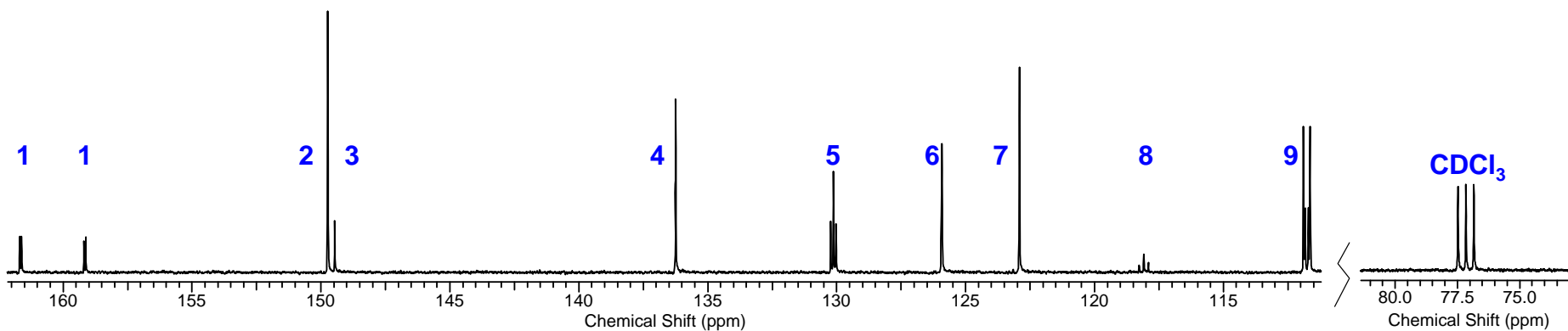
At 100 MHz, a 245 Hz coupling is 2.45 ppm. There are four or five notches between the peaks, which is about right (0.5 ppm/notch). More accurately, this is a doublet of doublets with a coupling of $16267.9 - 16017.6 = 250.3 \text{ Hz}$. Thus, this is a **one-bond coupling**. The smaller coupling is 7.3 Hz, which is a three-bond/vicinal coupling:



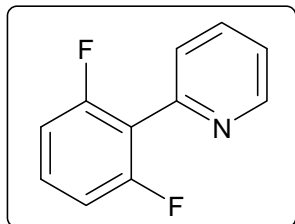
one-bond coupling



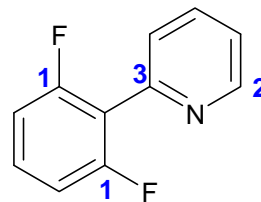
vicinal coupling



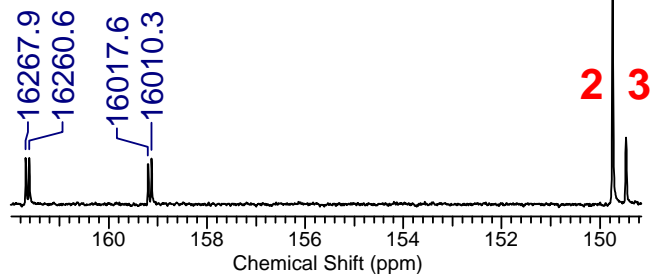
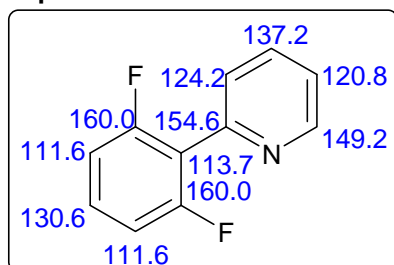
Practice Problem: Carbon-Fluorine Couplings



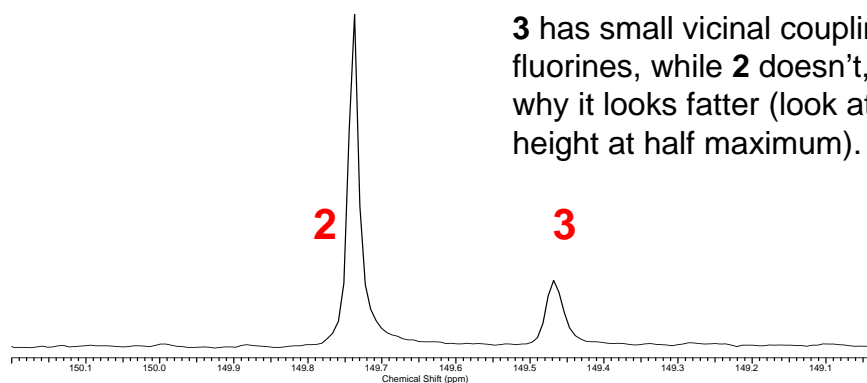
- (4) **Height of Peaks.** Recall that quaternary carbons are often shorter than protonated ones (this is due to differential relaxation and a lack of nOe enhancement; to be discussed in detail later). According to the ChemDraw predictions, the only carbons which should be really downfield are the ones next to nitrogen. One of them is quaternary, and one of them is protonated, which makes sense if this assignment is made:



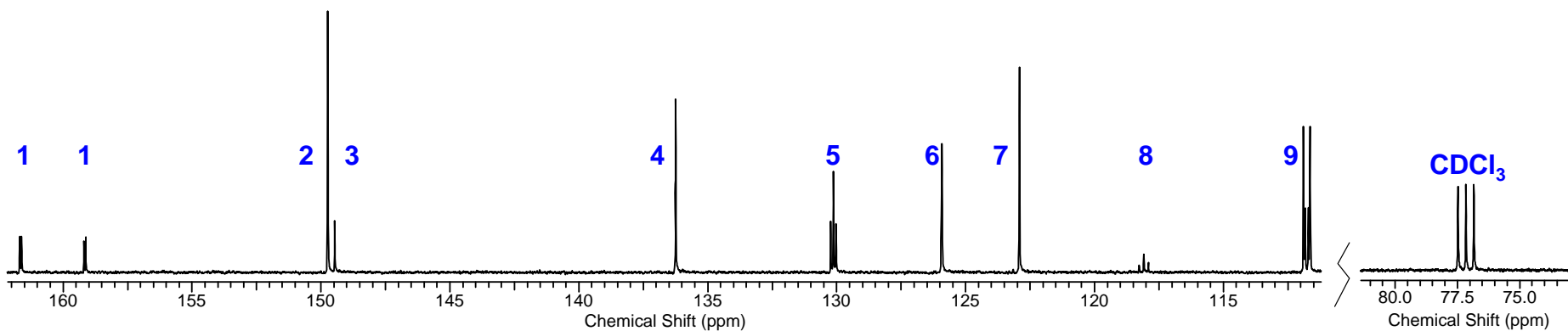
100 MHz, CDCl₃
predicted carbon-13 shifts



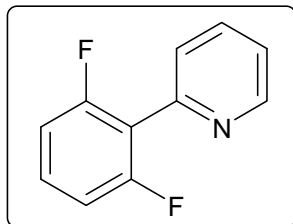
(4) Fluorine couplings.



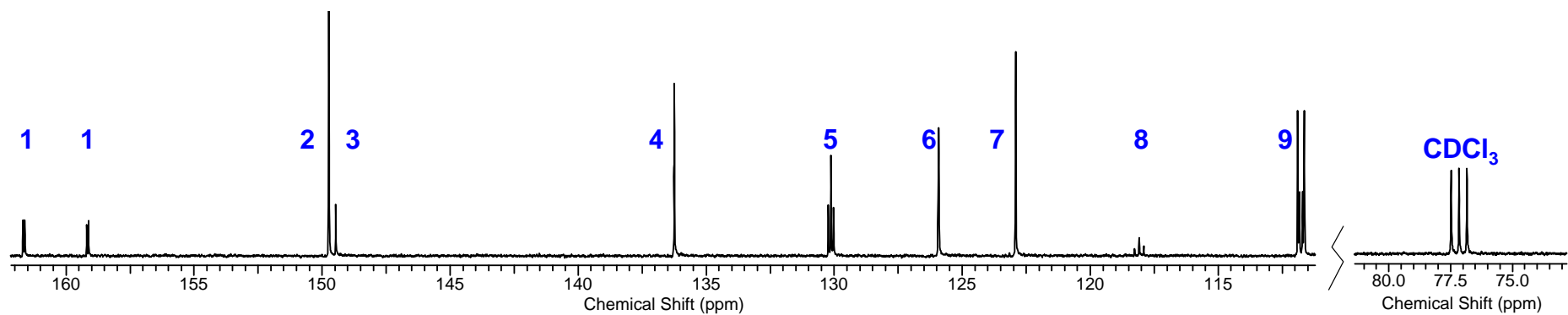
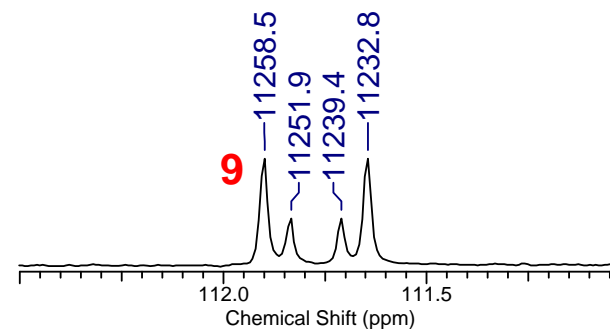
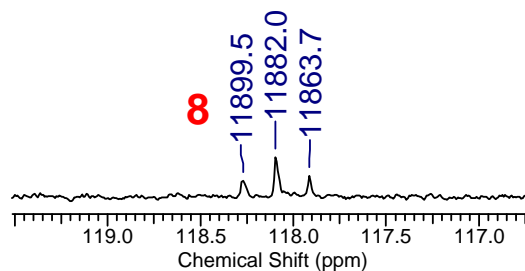
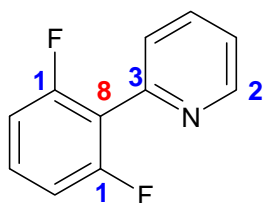
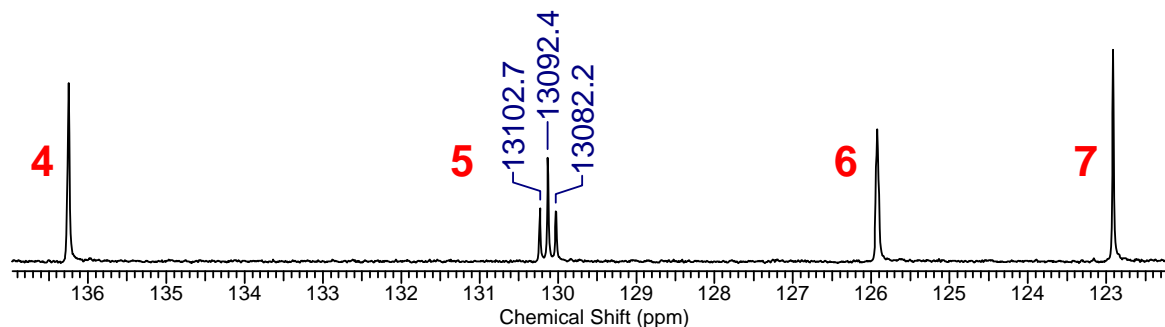
3 has small vicinal couplings to two fluorines, while **2** doesn't, which is why it looks fatter (look at the peak height at half maximum).



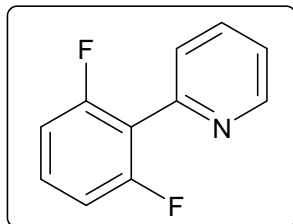
Practice Problem: Carbon-Fluorine Couplings

100 MHz, CDCl_3

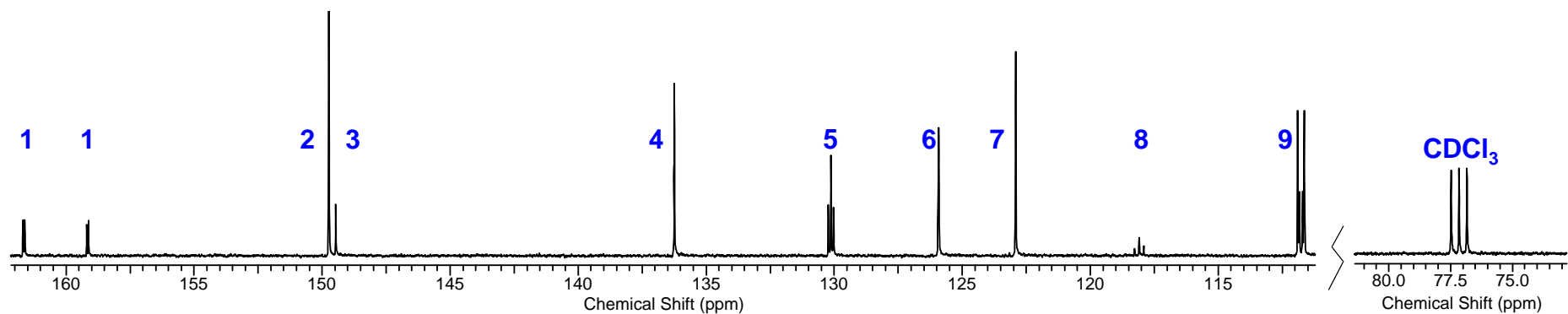
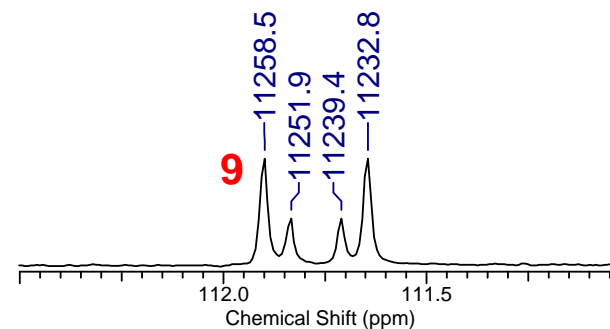
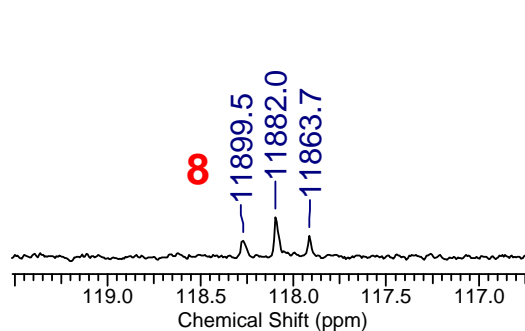
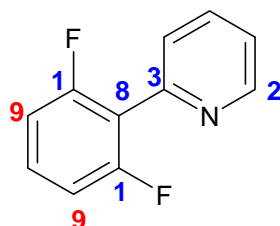
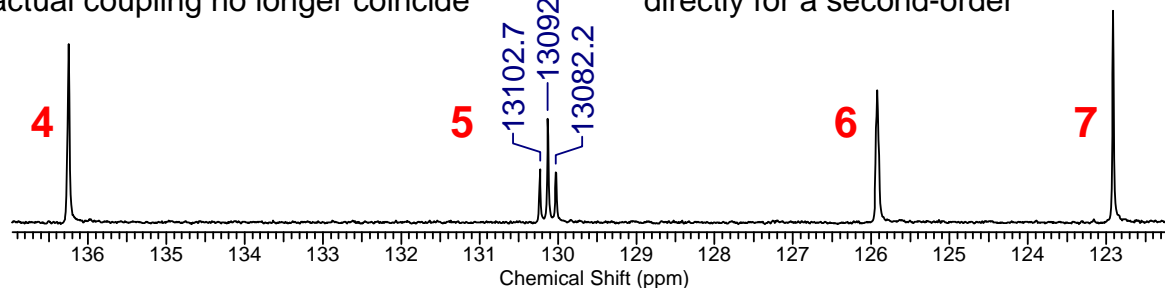
- (5) **Other Fluorine-Coupled Peaks.** What are the other peaks? Carbon **8** is a true 1:2:1 triplet with $J = 17.5 \times 2$ Hz, which can only happen if it has two geminal (two-bond) couplings to two equal fluorines. Therefore, it must be the *ipso* carbon on the fluorinated ring. It also has a very small height, which makes sense for a quaternary carbon.



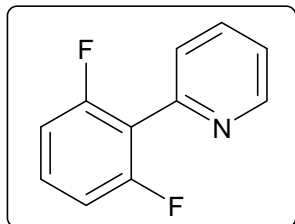
Practice Problem: Carbon-Fluorine Couplings

100 MHz, CDCl₃

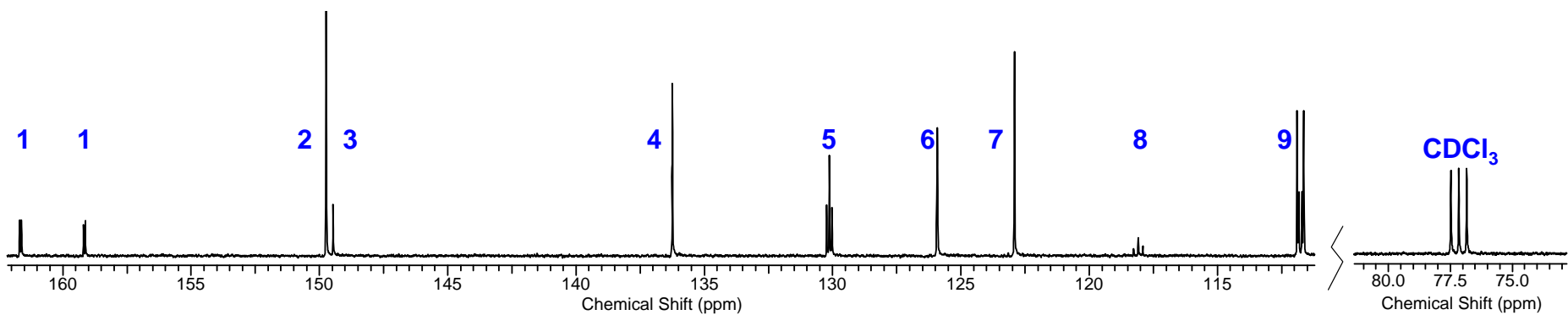
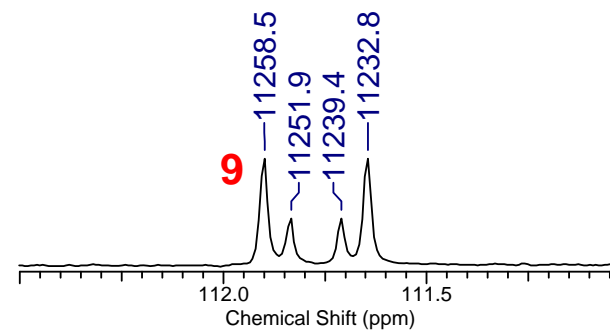
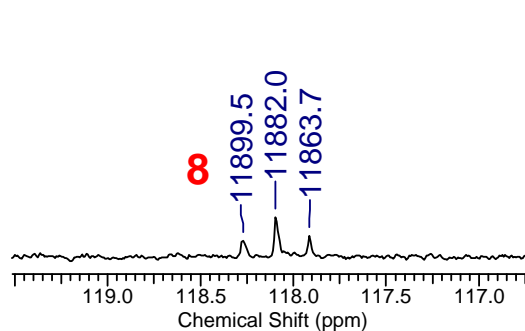
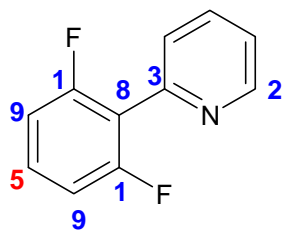
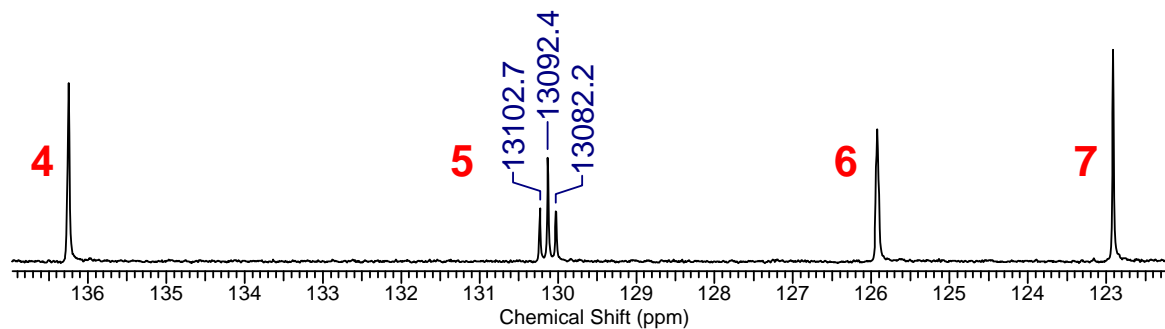
- (6) **Other Fluorine-Coupled Peaks.** Carbon 9 is quite intense, especially for a peak that has a splitting in it. It must be *ortho* to the fluorines. This is an **AA'XX'** system, where A and A' are these *ortho* carbons and X and X' are the fluorines—the carbons and fluorines are chemically equivalent but magnetically inequivalent and therefore this is a second-order multiplet pattern. It is reminiscent of an “AB quartet.” The coupling is *approximately* 6 Hz, but note that the line spacing and the actual coupling no longer coincide directly for a second-order spectrum.



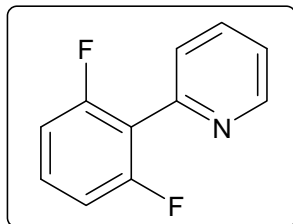
Practice Problem: Carbon-Fluorine Couplings

100 MHz, CDCl₃

- (7) **Other Fluorine-Coupled Peaks.** The only other peak with coupling is 5, which must be the carbon *meta* to the fluorines. The couplings are 2×10.3 Hz, which are right for an *anti* vicinal coupling.

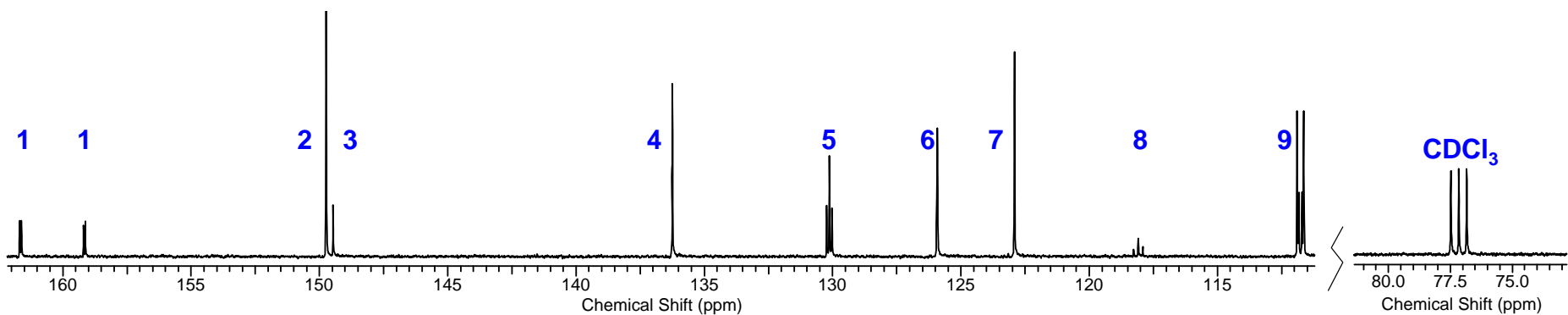
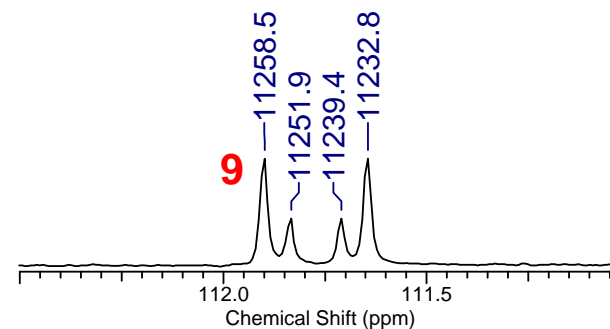
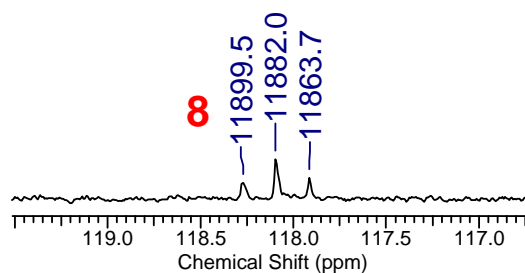
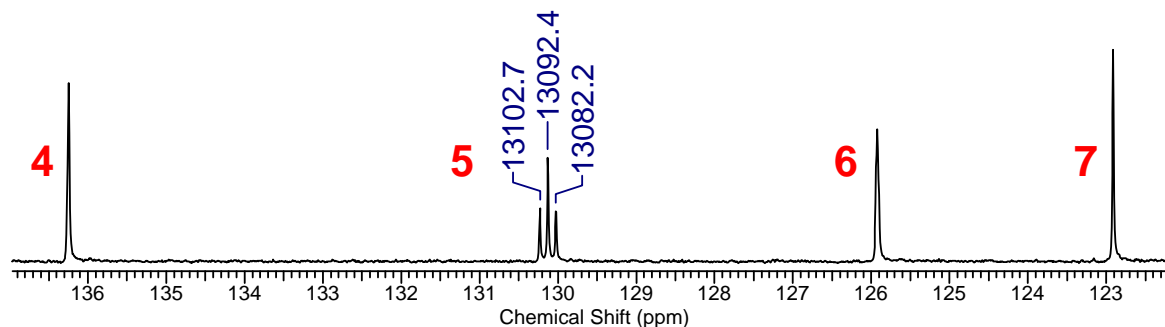
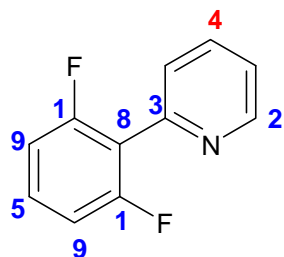
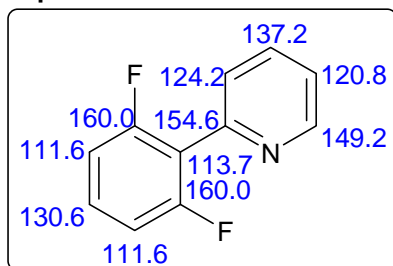


Practice Problem: Carbon-Fluorine Couplings

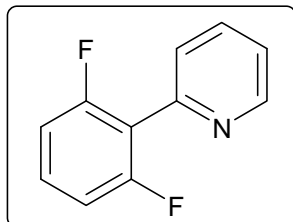
100 MHz, CDCl₃

- (8) **Pyridine Ring.** What remains is to assign carbons **4**, **6**, and **7**. Here is where chemical shift predictions come in handy again: they show that the carbon *para* to the pyridine nitrogen should be the most downfield. But how can **6** and **7** be distinguished?

predicted carbon-13 shifts

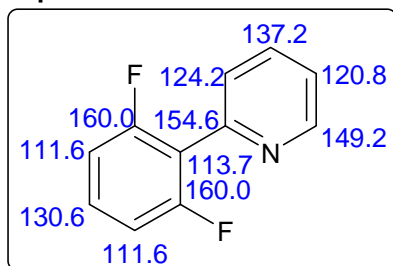


Practice Problem: Carbon-Fluorine Couplings

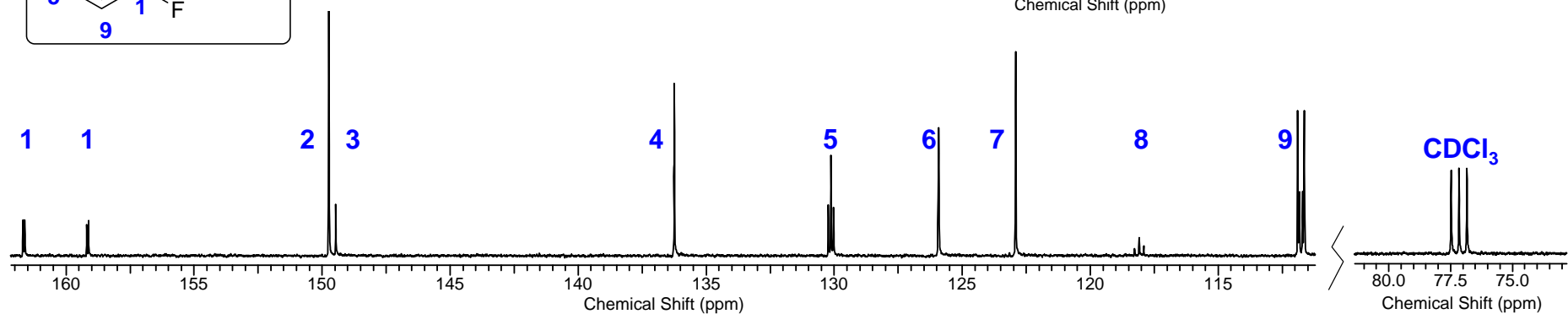
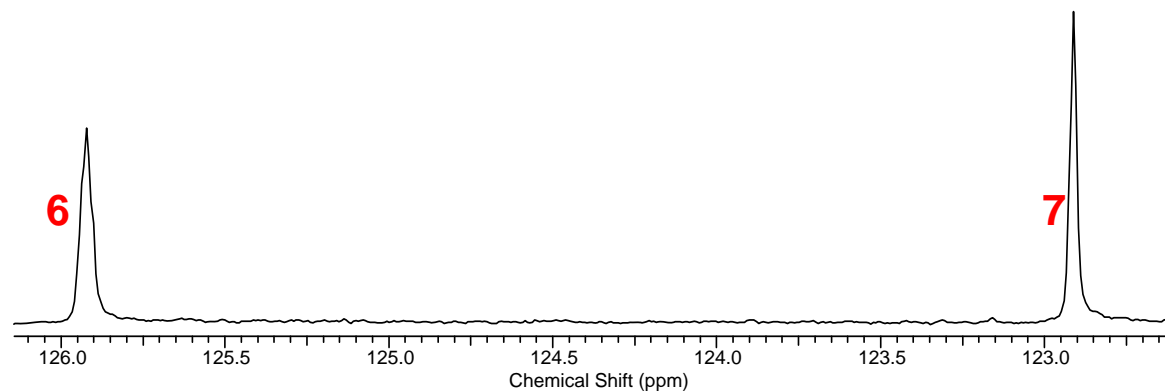
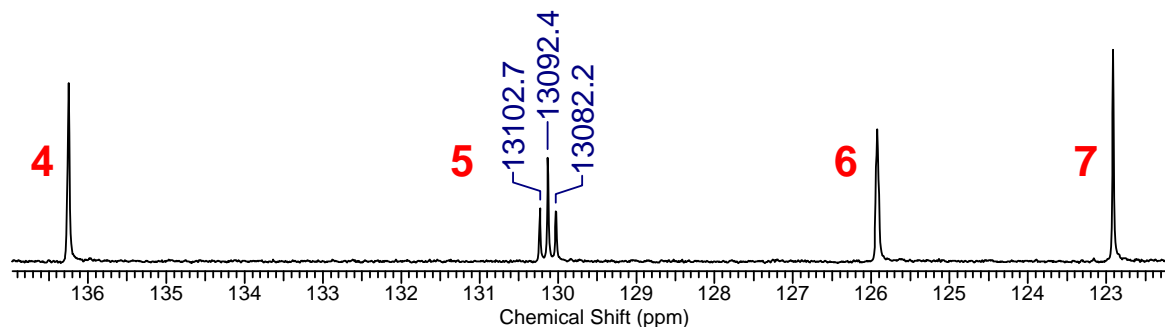
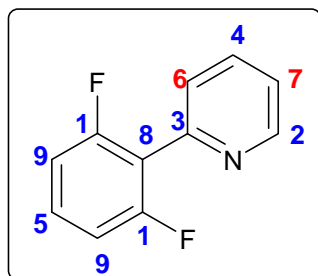
100 MHz, CDCl₃

- (9) **Pyridine Ring.** Chemical shifts predict that **6** should be on the left and **7** should be on the right. Examining an expansion reveals that **6** is much wider than **7**, consistent with two unresolved, small four-bond couplings to fluorine, confirming the predictions. This completes the assignment.

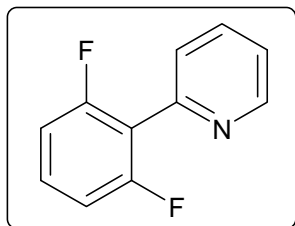
predicted carbon-13 shifts



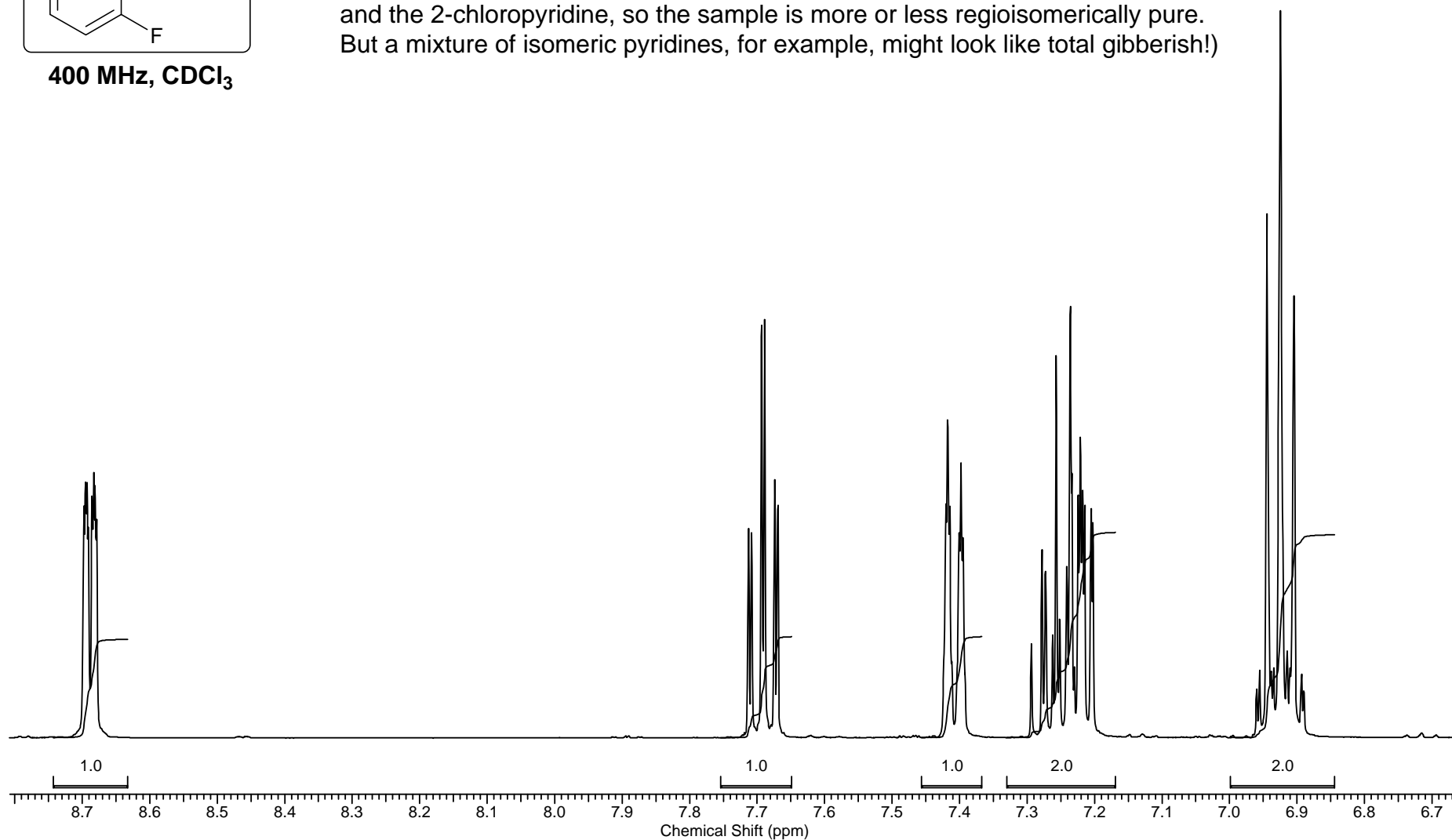
final answer



Practice Problem: Carbon-Fluorine Couplings

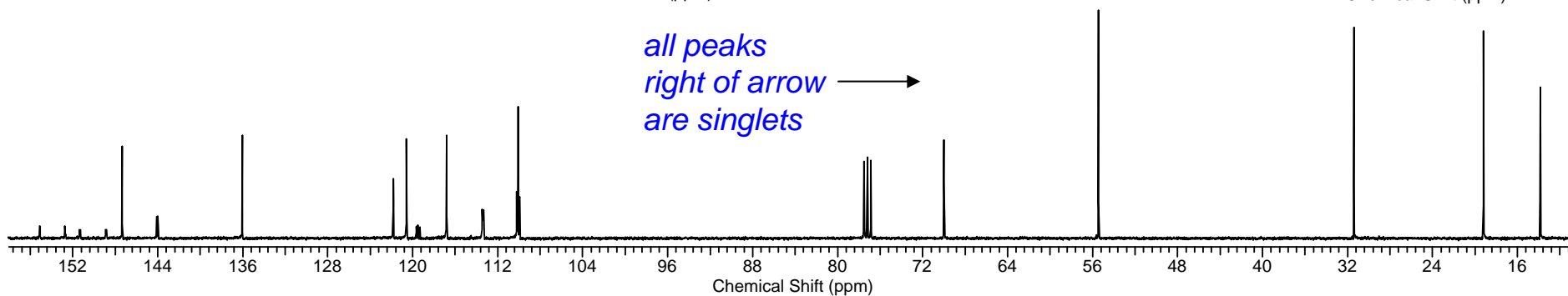
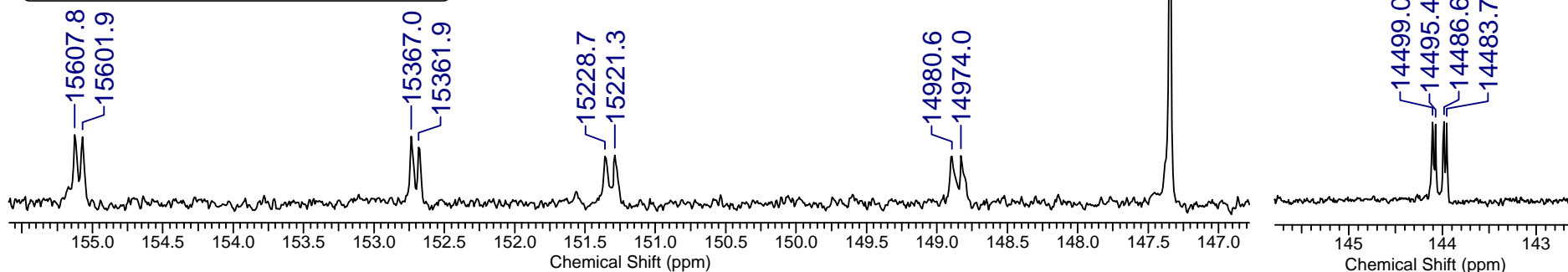
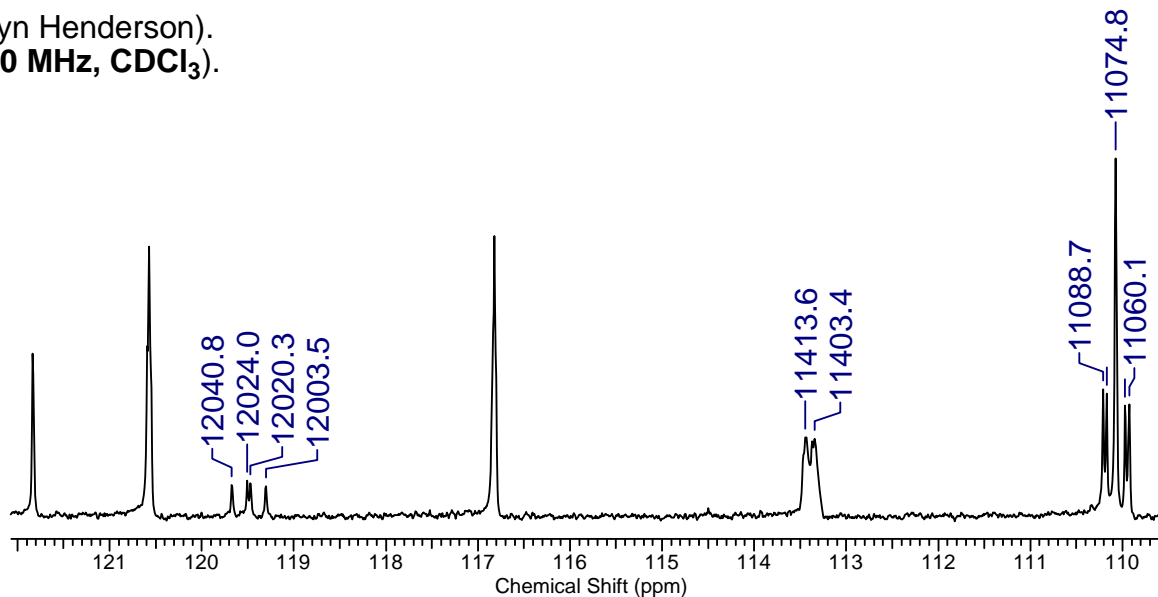
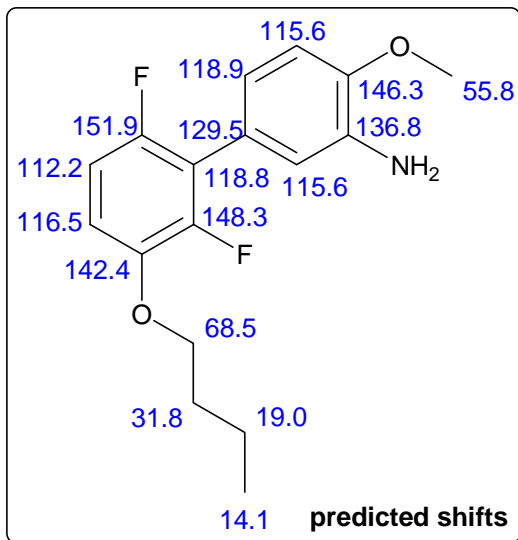
400 MHz, CDCl₃

(10) Proton Spectrum. We won't bother interpreting this, but I just wanted to point out that although the proton spectrum is very well resolved, it is a very complex series of partially overlapping second-order multiplets due to the symmetry, and therefore magnetic inequivalence, of the fluorines. (This compound came from a Pd-catalyzed cross-coupling of the difluorarylboronic acid and the 2-chloropyridine, so the sample is more or less regioisomerically pure. But a mixture of isomeric pyridines, for example, might look like total gibberish!)

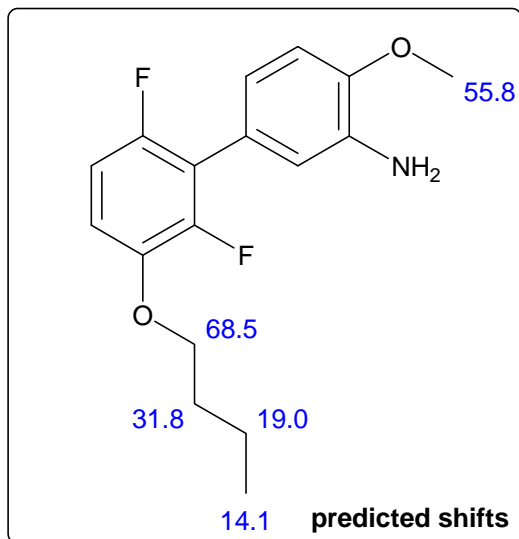


Practice Problem: Carbon-Fluorine Couplings

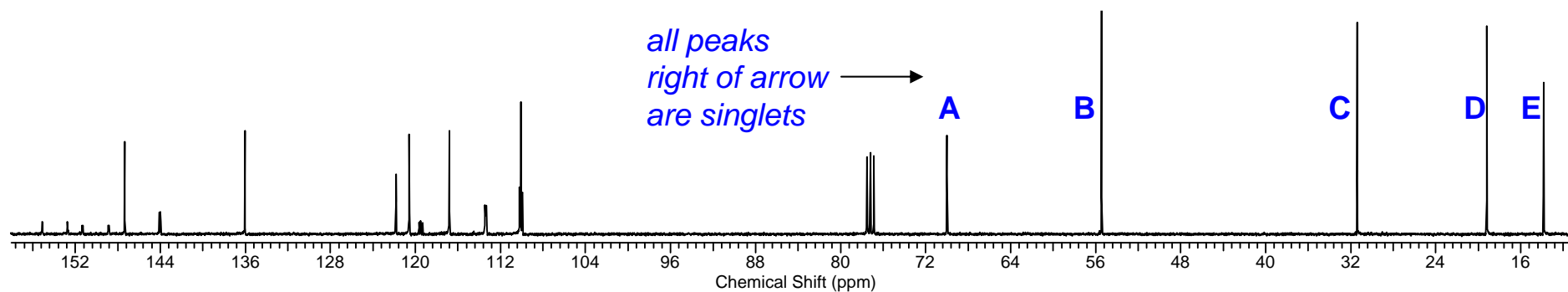
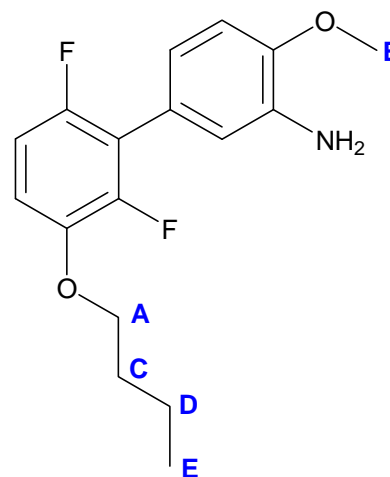
Here is a harder example (also courtesy Dr. Jaclyn Henderson).
Please assign this carbon-13 NMR spectrum (**100 MHz, CDCl₃**).



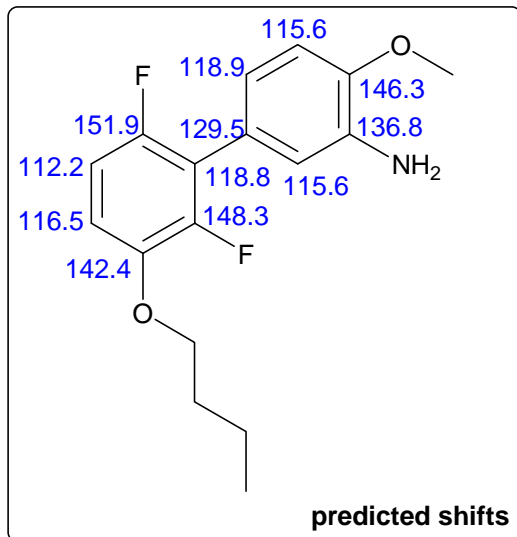
Practice Problem: Carbon-Fluorine Couplings



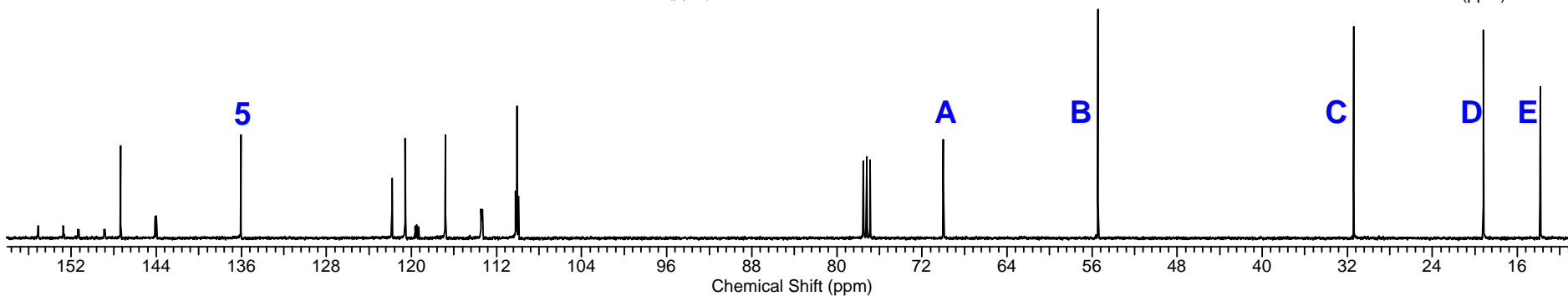
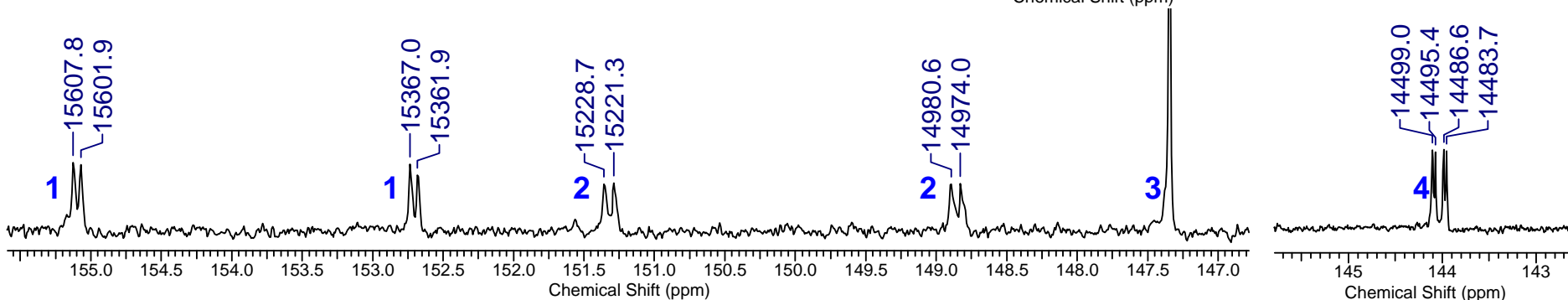
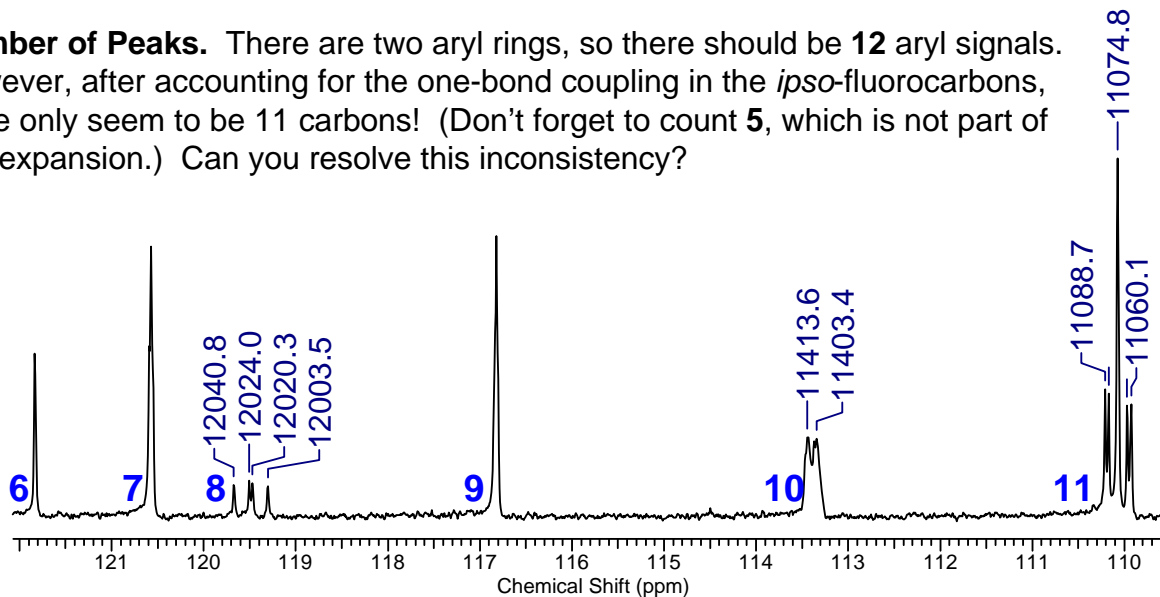
- (1) **Number of Peaks.** There is no symmetry in this molecule, so there should be **17 signals total**. There are a lot of peaks in this molecule, so I'll label the carbons below the chloroform peaks A-E. These are trivial to assign, particularly if you have ChemDraw handy:



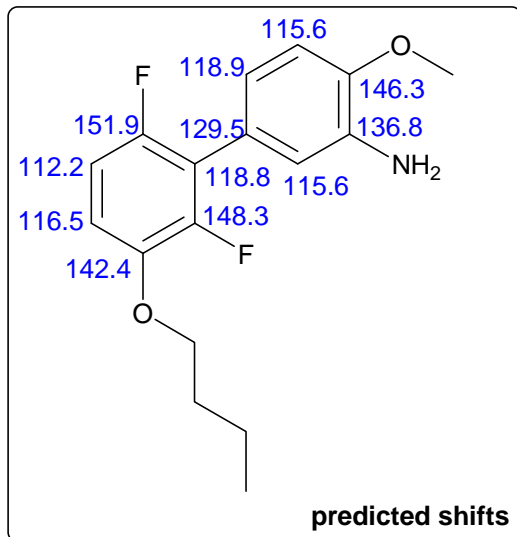
Practice Problem: Carbon-Fluorine Couplings



- (2) **Number of Peaks.** There are two aryl rings, so there should be 12 aryl signals. However, after accounting for the one-bond coupling in the *ipso*-fluorocarbons, there only seem to be 11 carbons! (Don't forget to count 5, which is not part of any expansion.) Can you resolve this inconsistency?

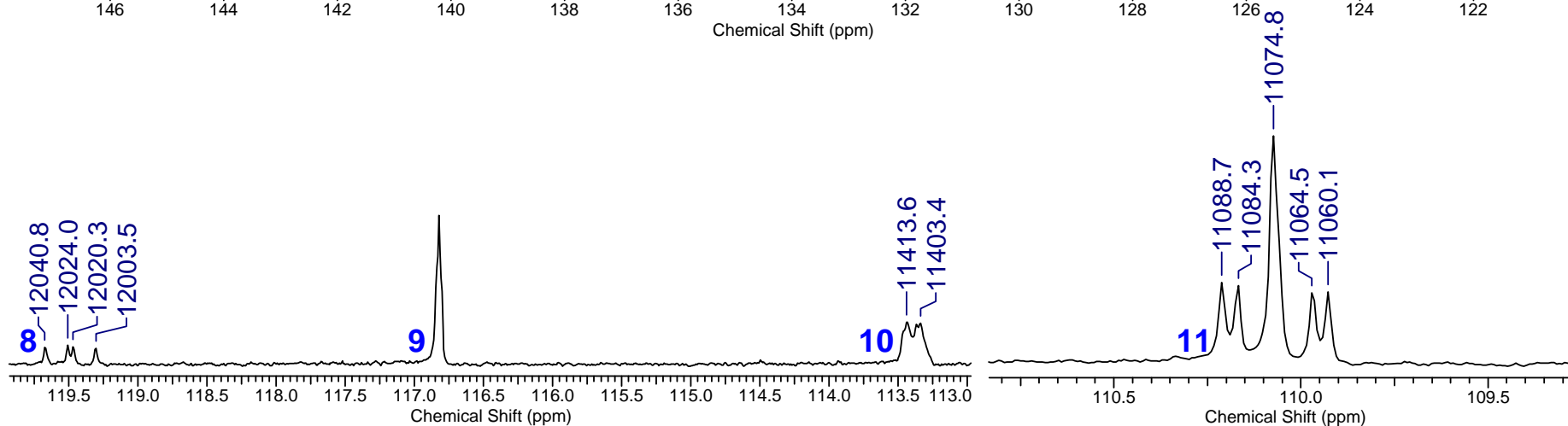
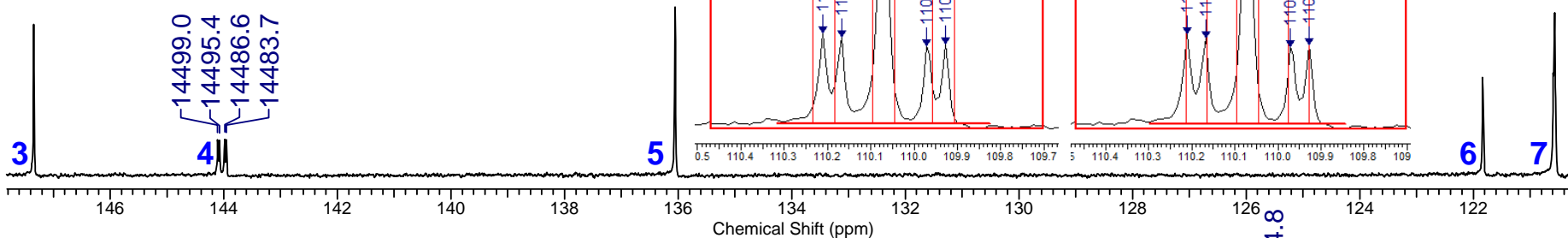


Practice Problem: Carbon-Fluorine Couplings

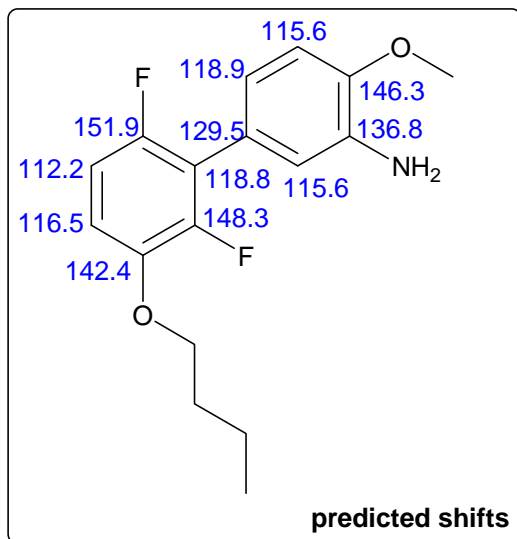


(2) *Ips*o-Fluorocarbons. Obviously, these are 1 and 2. We can guess that 1 is on top.

(3) Fluorine-Carbon Couplings. 4 and 8 are easy: 4 (3.7, 12.4 Hz); 8 (16.8, 20.5). 11 seems to have one 11088.7-11084.3 = 4.4 Hz and two 11088.7-11074.8 = 13.9 Hz couplings. However, you will see this doesn't really fit the multiplet very well (left). A better fit (for a first-order multiplet) is 4.4, 12.1x2 Hz, but in both cases, there should be two central peaks, not one, even accounting for line width. What's wrong?

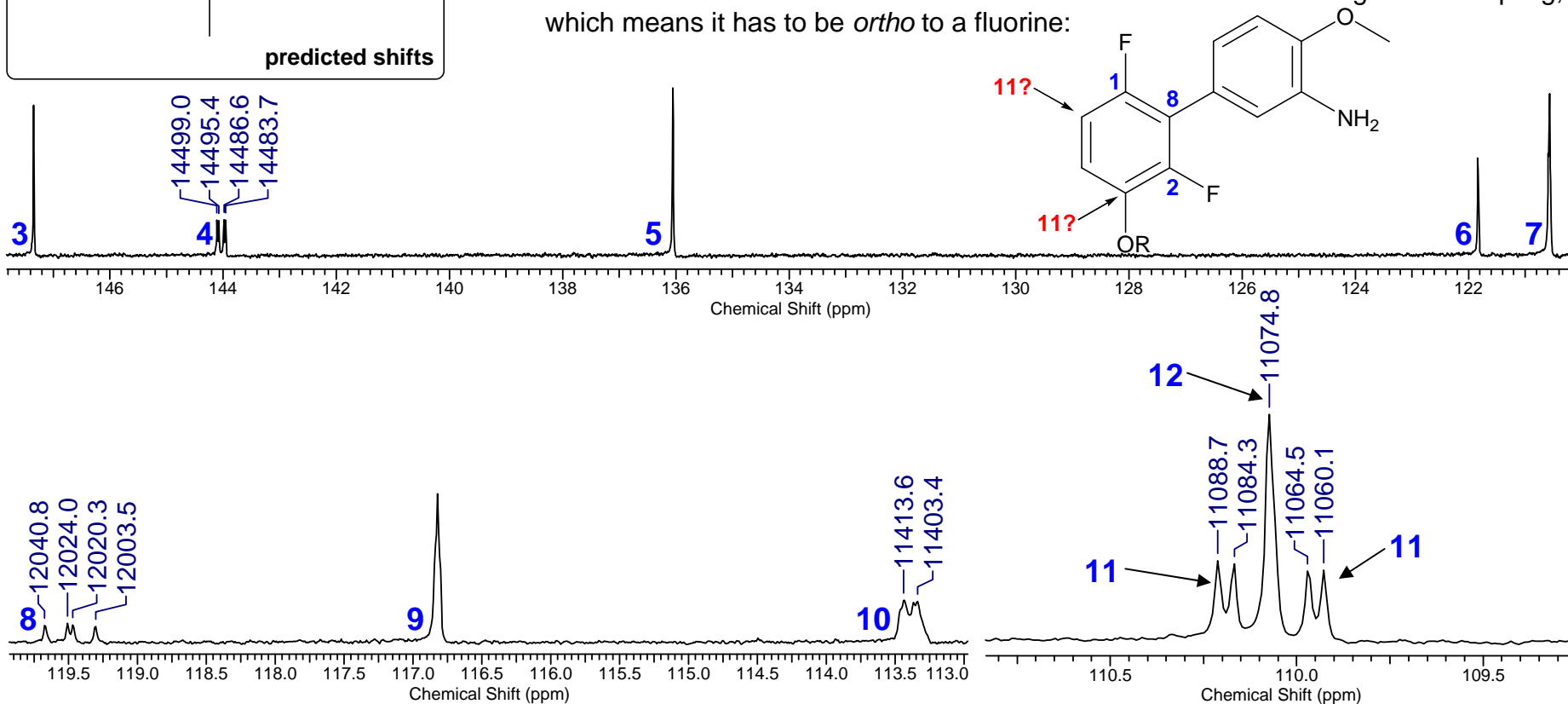


Practice Problem: Carbon-Fluorine Couplings

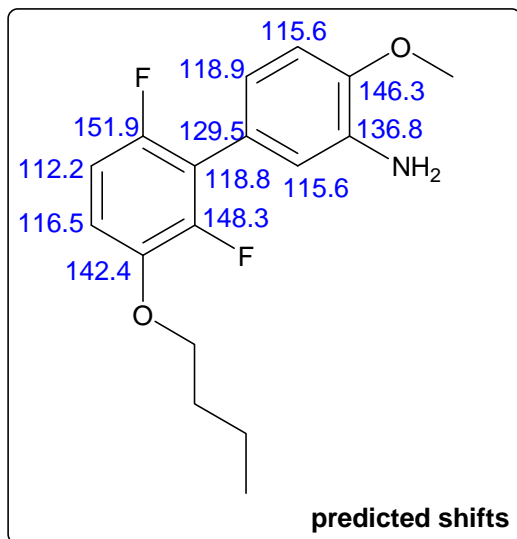


(4) **Accidental Overlap.** In this molecule, there are *only two fluorines*, so *no carbon can have more than two fluorine-carbon couplings!* The only explanation is that the relatively intense central peak is really a protonated carbon, and there's a doublet of doublets ($J = 4.4, 24.1$ Hz) sandwiching it. This is where the missing twelfth carbon is. (I usually get worried when I can't find the right number of carbons. You should be too—it's one of the first things to check. One exception is carbamate carbons, which are usually part of *N*-acyl protecting groups like BOC. Chemical exchange and quadrupolar broadening can make those resonances hard to detect.)

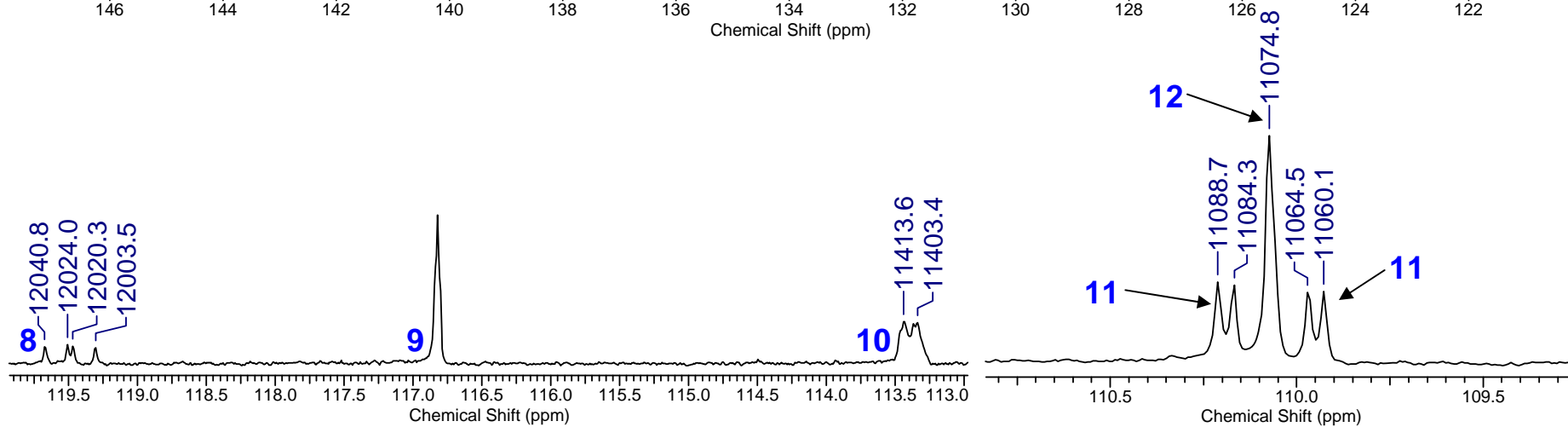
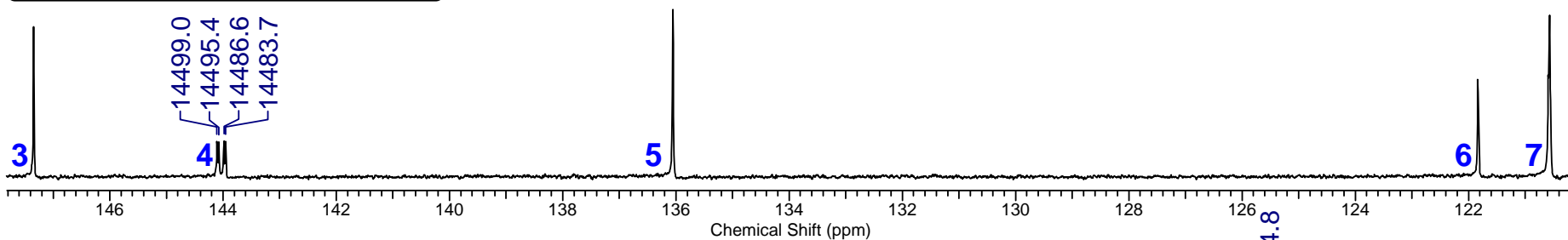
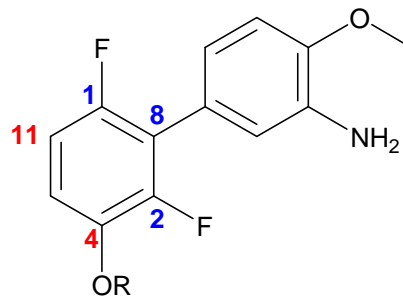
(5) **Difluoraryl Ring.** The full list of couplings is now: **4** (3.7, 12.4 Hz); **8** (16.8, 20.5); **10** (10.2); **11** (4.4, 24.1). **8** clearly has two geminal couplings and has the right chemical shift to be the carbon between the fluorines. **11** has one geminal coupling, which means it has to be *ortho* to a fluorine:



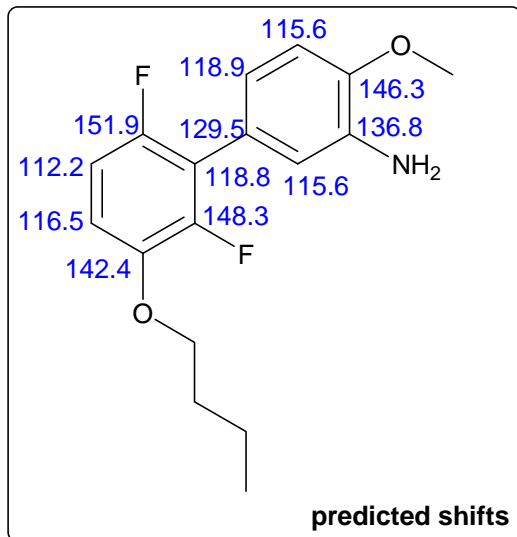
Practice Problem: Carbon-Fluorine Couplings



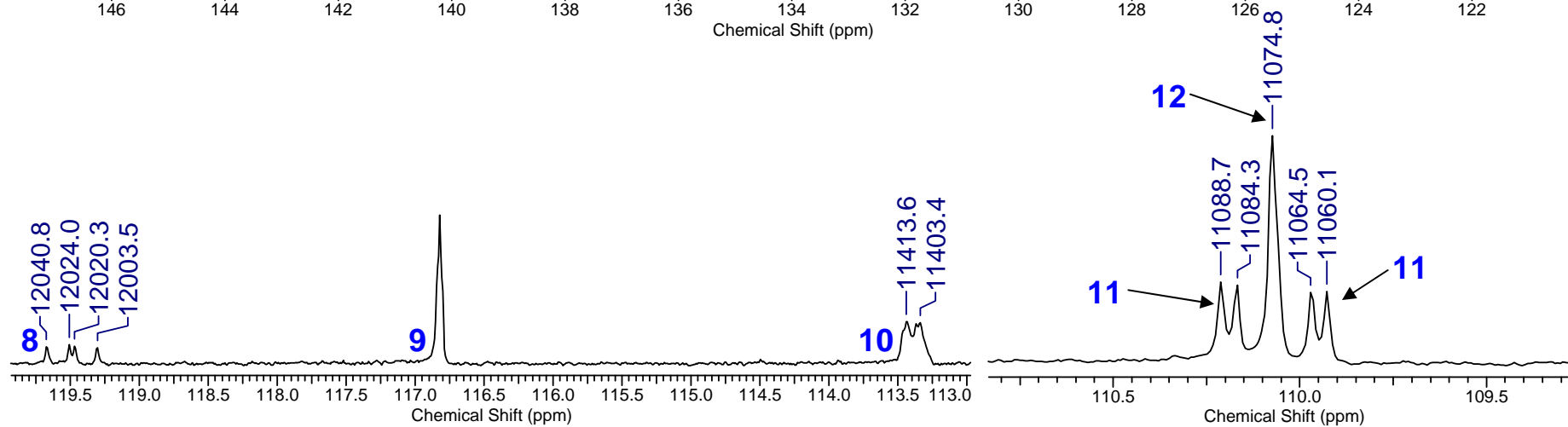
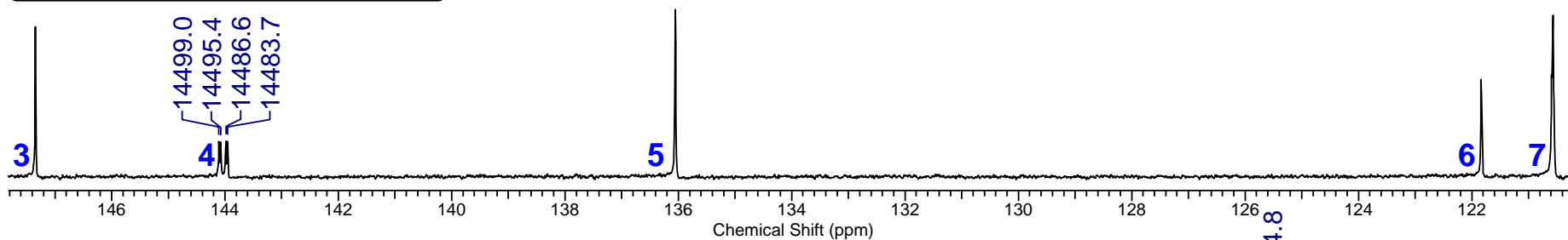
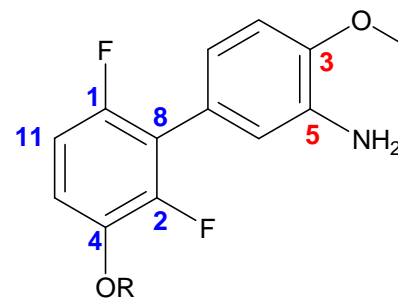
- (6) **Difluoraryl Ring.** Couplings: **4** (3.7, 12.4 Hz); **8** (16.8, 20.5); **10** (10.2); **11** (4.4, 24.1). By chemical shift, **11** must be the protonated carbon. **4** seems to have a smaller geminal coupling, but must be the carbon next to oxygen:



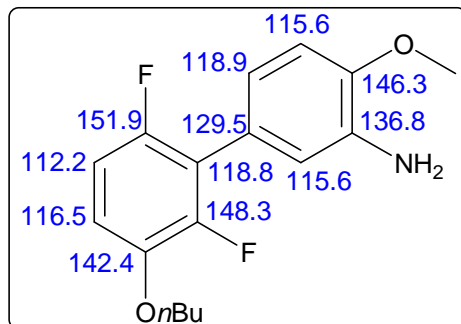
Practice Problem: Carbon-Fluorine Couplings



(7) **Ipsso Carbons.** 3 and 5 clearly do not have any couplings and by chemical shift, must be *ipso* to the methyl ether and the arylamine:

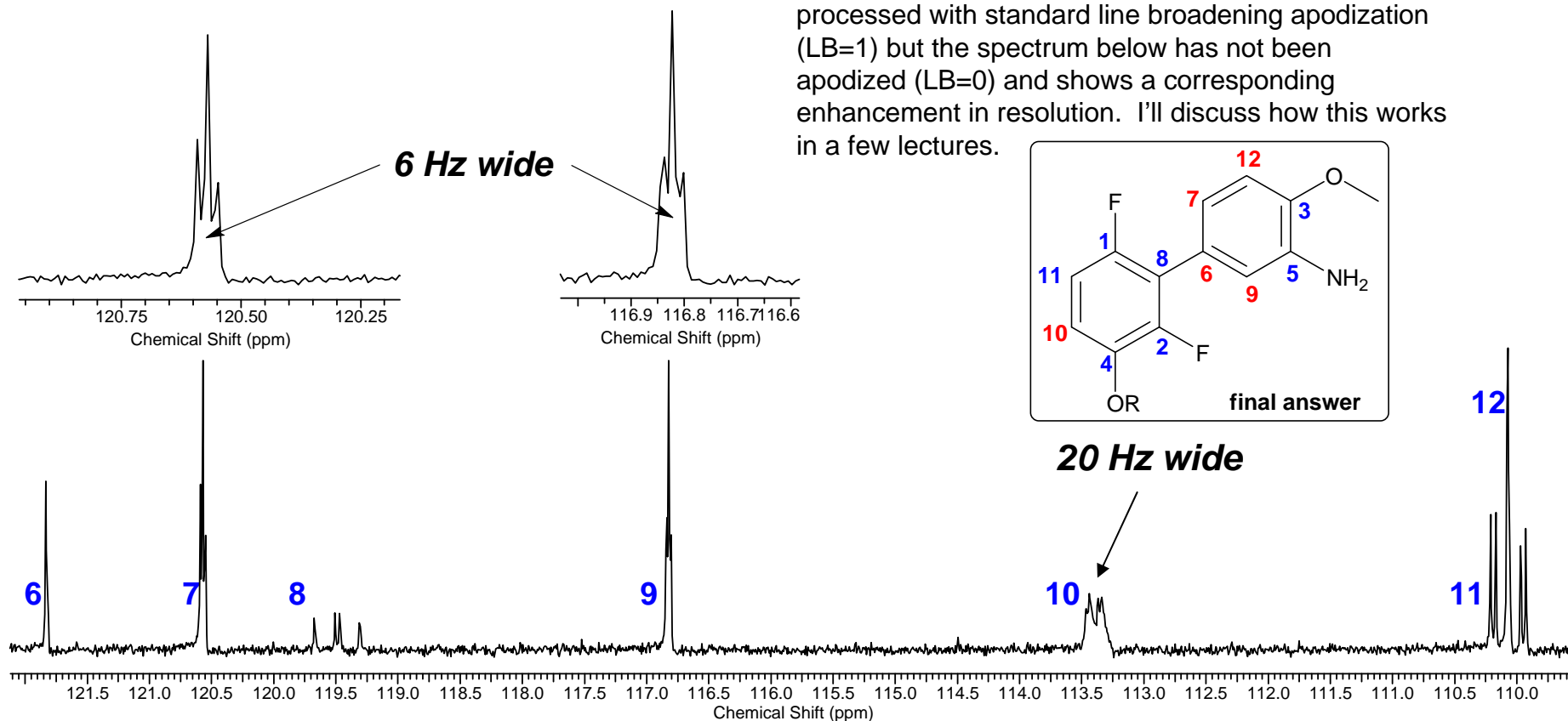


Practice Problem: Carbon-Fluorine Couplings

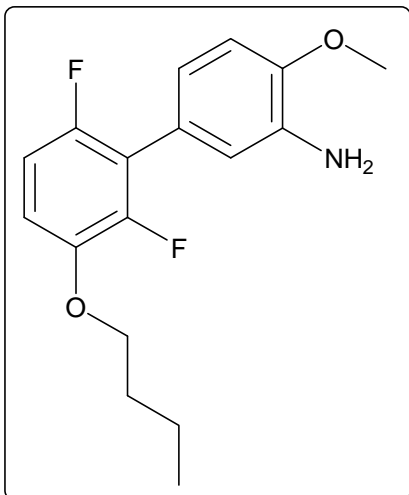


(7) **What's Left?** The carbons left are **6**, **7**, **9**, **10**, and **12**. This is tricky, but we can use the line widths and heights to help us make an educated guess. **12**, as a sharp singlet, must be *ortho* to the methyl ether. **10** has a lot of unresolved couplings and must be either *meta* to the fluorines or at the *ipso* ring junction. Based on chemical shift, it is likely on the difluoroaryl ring. **7** and **9** have some unresolved long-range couplings, and based on chemical shift **7** is *para* to the amine. This puts **6**, as the shortest peak, at the *ipso* ring junction. The only trouble is that **6** should have some vicinal couplings. (Professor Reynolds suggests this could be a cancellation of through-space and through-bond couplings.) Thus, further experiments would be needed to confirm this set of assignments (any inconsistency is always a concern).

(8) **Spectrum Processing.** The previous spectra were processed with standard line broadening apodization (LB=1) but the spectrum below has not been apodized (LB=0) and shows a corresponding enhancement in resolution. I'll discuss how this works in a few lectures.



Practice Problem: Carbon-Fluorine Couplings



- (9) **Proton Spectrum.** With the removal of the symmetry in the difluoroaryl group, the magnetic inequivalence problem disappears. Can you identify all the peaks?

