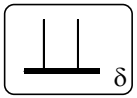
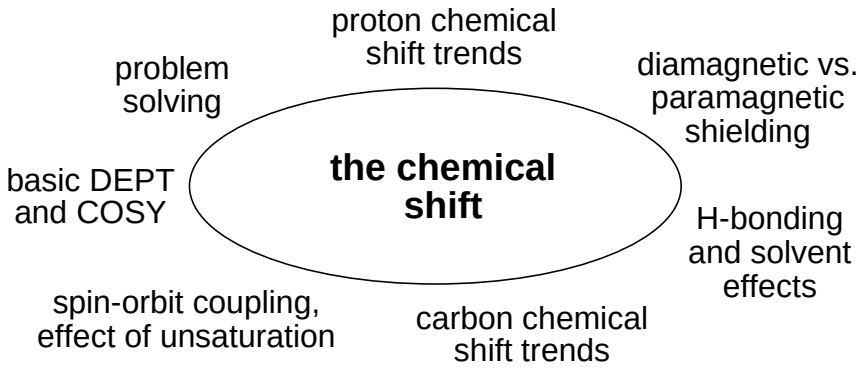
The Chemical Shift

Eugene E. Kwan

January 26, 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)

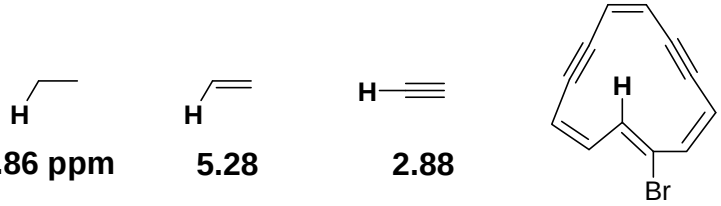
3. Spectrometric Identification of Organic Compounds (7th ed.) Silverstein, R.M.; Webster, F.X.; Kiemle, D.J. Wiley, **2005**. (useful charts in the appendices of chapters 2-4)

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**.

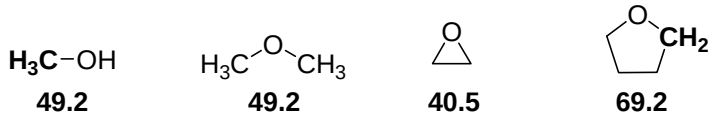
Key Questions

(1) What controls proton chemical shifts?



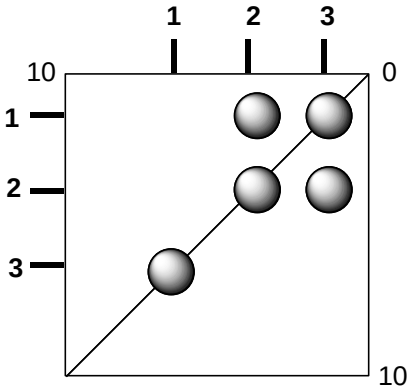
0.86 ppm **5.28** **2.88** **16.4**

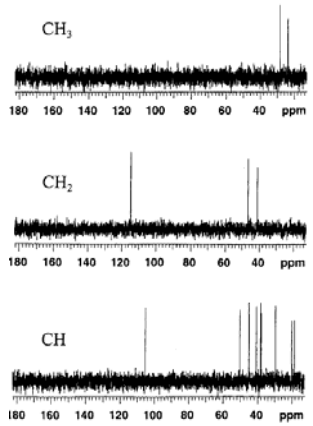
(2) What controls carbon chemical shifts?



49.2 **49.2** **40.5** **69.2**

(3) What are COSY and DEPT? What useful information can they give about a structure?





I thank Professors William F. Reynolds (Toronto) and Gene Mazzola (Maryland/FDA) for providing some useful material for this lecture. The section on chemical shifts is based on the discussion in Chapter 3 of reference 1.

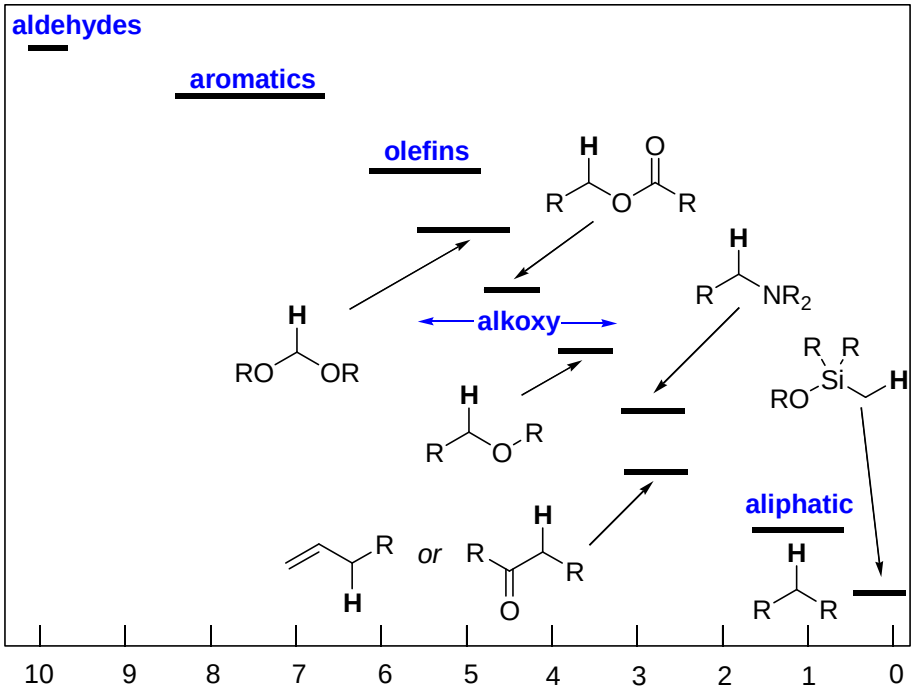
Proton Chemical Shifts

reference: Lambert and Mazzola, Chapter 3.

As mentioned last lecture, these are controlled primarily by electron density. The more electron-poor a proton is, as judged by classical induction or resonance arguments, the larger its chemical shift. For example:

CH_4	CH_3Cl	CH_2Cl_2	$CHCl_3$
0.23 ppm	**3.05**	**5.30**	**7.26**

Certainly, a lot of practice is the major factor in being good at spectral interpretation. Conversely, memorizing a lot of chemical shifts is not going to be very helpful. Instead, I suggest you think of proton NMR spectra as being broken down into different regions:



Silverstein has a good table for this (see handout). These sorts of trends *are* worth memorizing.

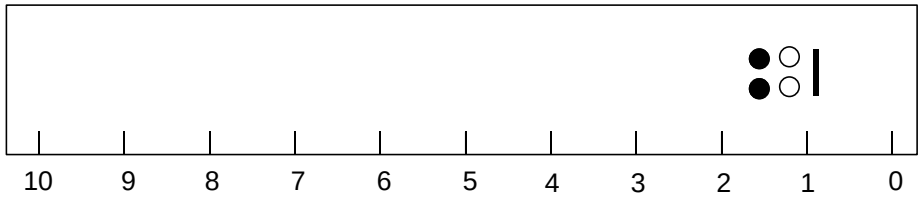
Clearly, the regions overlap:

(1) protons adjacent to ethers are upfield of those adjacent to esters (on the oxygen side); ethers are downfield of amines

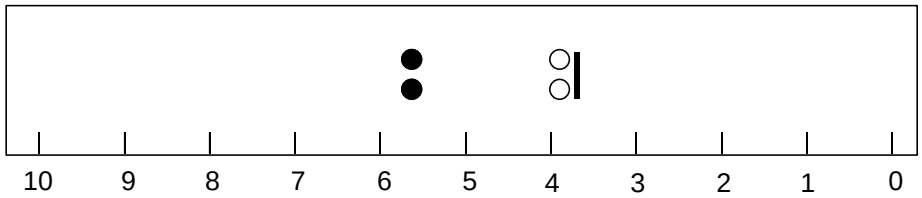
(2) *a priori*, it's hard to tell between allylic, α-keto, and α-amino groups

(3) The olefinic, aromatic, and aldehyde regions are relatively contained.

In general, methines are most deshielded, followed by methylene and methyl protons. For example, for alkyl protons of the form M-CH_2R:

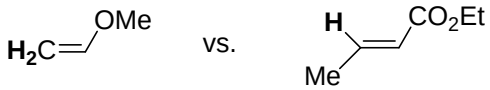


This follows the notation in Silverstein, where a solid bar means M=CH_3, two open circles means M=CH_2, and two shaded circles means M=CH. For other groups, this distinction is much pronounced. For tosylates of the form M-SO_2Ar:



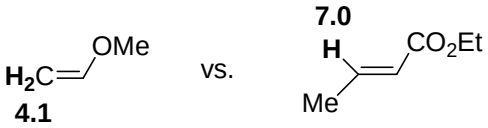
For the next few slides, I'll show you some interesting chemical shifts that will help calibrate your intuition.

Q: Which proton is more downfield?

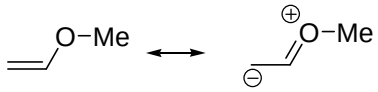


Proton Chemical Shifts

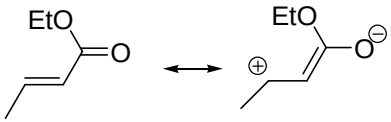
Based on what I just told you, the methine should certainly be downfield of the methylene:



However, in this case, resonance undoubtedly plays a larger role. These olefins show the unmistakable signs of π-polarization:

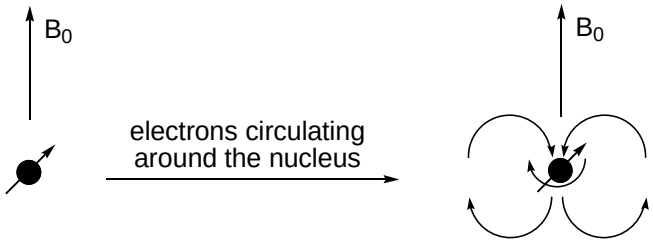


more electron density: smaller chemical shift



less electron density: larger chemical shift

This general trend (methyl < methylene < methine) could be attributed to the greater electronegativity of carbon over hydrogen. However, this behavior can be understood in the context of a classical "electron circulation" model:



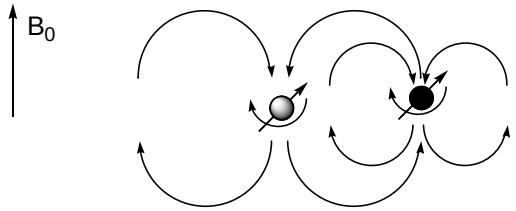
local currents

$B_{eff} = B_0 (1-\sigma)$

First, we consider the bare nucleus, which has a nuclear spin. In a magnetic field, it precesses at the Larmor frequency, which is proportional to the field strength. However, it has some electrons around it in various bonds and lone pairs. These electrons are thought of as spinning around the nucleus. In the presence of the external field, a magnetic field is induced. Through conservation of energy/Lenz's Law arguments, this induced field counters the external. Thus, the nuclues experiences a reduced field, B_{eff}.

This effect is called **diamagnetic shielding** (σ_d).

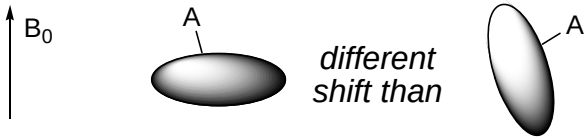
Additionally, neighboring groups have their own electrons that circulate and create other induced fields. If the nucleus is close enough to these fields, its chemical shift can be affected:



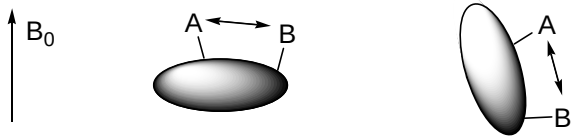
nonlocal currents

Because these non-local effects depend on the relative orientation of the the nucleus and its neighboring group, these are called **anisotropic effects**.

Note that the relative orientation of the nucleus with respect to the external field changes its chemical shift:



This is **chemical shift anisotropy**. In solution, tumbling averages these effects to give an overall isotropic shift. However, the anisotropic effects of neighboring groups are *not* cancelled by tumbling because the relative orientation of the nucleus and its neighboring group stay the same when the molecule tumbles (assuming the conformation doesn't change):



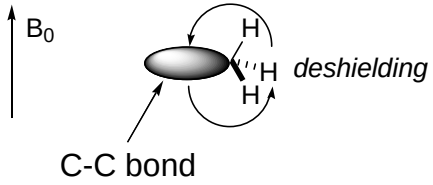
Proton Chemical Shifts

Thus, neighboring groups can affect chemical shifts:

(a) directly, by producing induced fields which are close enough to affect the magnetic field experienced by the adjacent nucleus; or

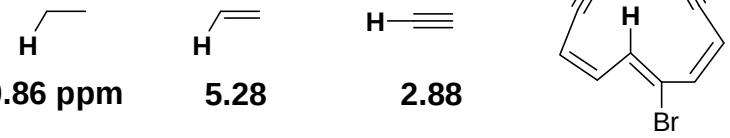
(b) indirectly, by changing electron density around a nucleus, thus changing the amount of circulation.

Methylene groups have larger chemical shifts than methyl groups. In indirect, diamagnetic shielding terms, this is due to the inductive effect of carbon (it's more electronegative than hydrogen). In direct, anisotropic shielding terms, one views the adjacent C-C bonds having electrons circulating in them:



The methylene has two C-C bonds, while the methyl only has one, so the methylene protons are more deshielded.

Q: Can you explain these chemical shifts?

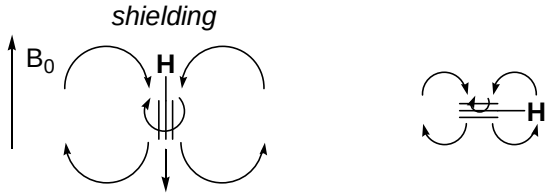


0.86 ppm **5.28** **2.88** **16.4**

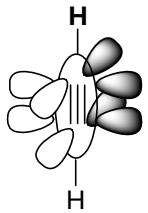
Clearly, hybridization arguments, where one considers carbons with more s-character to be more electronegative, don't work here. A more sophisticated version is to say that the C-H bond hybrid in ethene has more p-character due to Bent's Rule.

p-orbitals don't circulate as well as s-orbitals and are farther away from the nucleus, so they don't shield the nucleus from the external field as well. However, this doesn't explain why the ostensibly sp-hybridized alkyne has a *smaller* shift than the sp2-hybridized alkene!

The classical explanation for this is to treat acetylene as a "prolate ellipsoid" which has particularly effective π-electron circulation when the bond is parallel to the external field:



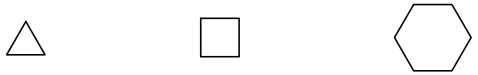
(A prolate ellipsoid is formed by spinning an ellipse about its major axis. If you spin it around its minor axis, it's called an oblate ellipsoid.) Thus, although tumbling will sample these two orientations equally, the circulation is much better on the left, so overall, acetylenic protons will be shielded. This effect runs counter to the hybridization effect, which is why it still has a higher shift than ethane. Why is circulation around the axis of the cylinder better? And why is the circulation in acetylene better than ethene?



Acetylene is ringed by two sets of p-orbitals, whereas ethene only has one. What about the macrocycle? The bromine is there to prevent conformational inversion. The proton is in the "deshielding cones" of a number of π-bonds, and hence is quite deshielded. This is a remarkable through-space effect. (The σ–σ^* effect is probably minor compared to this.)

Proton Chemical Shifts

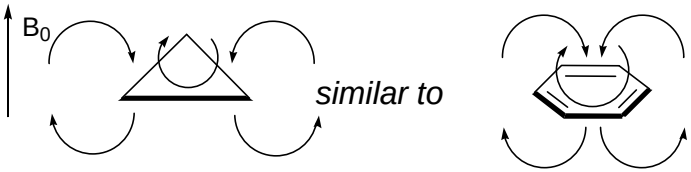
Q: Can you explain these chemical shifts?



0.22 ppm **1.96** **1.43**

(1) σ-Aromaticity

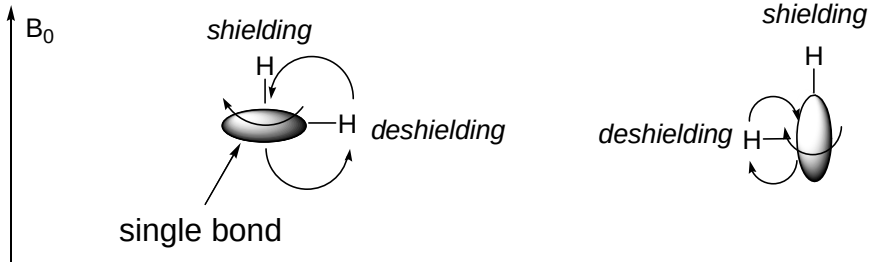
But what about cyclopropane? This could be attributed to a benzene-like circulation where one treats thes the cyclopropane like an oblate ellipsoid of circulating electrons:



In benzene, the protons are in the plane, so they are deshielded by anisotropy. However, in cyclopropane, they are above and below it, so they are shielded.

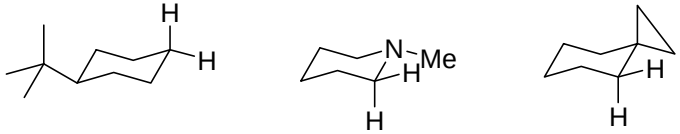
(2) Shielding Effects of Ring Bonds

The alternative approach is to consider the bolded bond in the front of cyclopropane as a prolate ellipsoid. In general, protons at the end of a single bond are deshielded, while protons at the sides are shielded:



This is true regardless of the orientation of the bond relative to the external field. Circulation is more effective in the left hand case for a single bond. Since the protons are to the side of the prolate ellipsoid, they are shielded.

Q: Can you explain these chemical shifts?

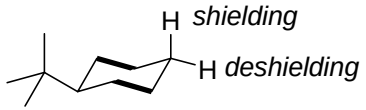


H_{eq} = 1.64
H_{ax} = 1.08

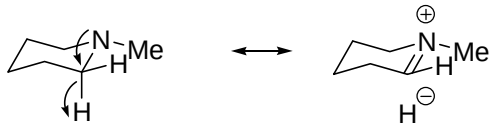
H_{eq} = 2.73
H_{ax} = 1.96
(predicted)

H_{eq} is 1.2 ppm *upfield* of H_{ax}

For 4-*tert*-butylcyclohexane, we must consider the vicinal C-C bonds, as the axial and equatorial protons are equivalently diposed relatively to the geminal bonds. The axial proton is in the shielding cones of its two vicinal C-C bonds, while the equatorial proton is in the corresponding deshielding cones:



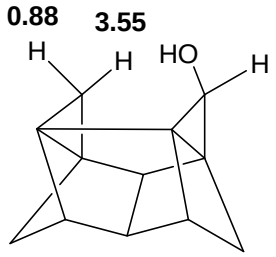
This is why axial protons are upfield of equatorial ones in most cases. However, this effect is overcome by the anisotropy of the cyclopropane as just discussed. In 1-methylpiperidine, the axial proton is deshielded by an *n* to σ* hyperconjugation:



The increased negative charge on the hydrogen makes it go upfield by quite a bit, relative to the equatorial hydrogen, which is poorly aligned for this interaction.

Van der Waals Effects

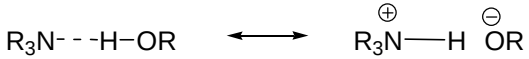
Sometimes, chemical shifts are affected by van der Waals repulsion. This is a spectacular example in a very congested partial cage compound:



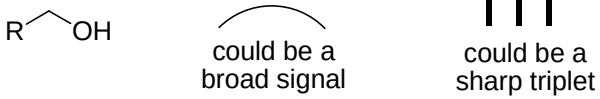
The idea is that the forced H)(HO repulsive contact removes some of the electron density from the neighborhood of the internal proton. The proton becomes less shielded, and therefore has a much higher chemical shift than usual.

Hydrogen Bonding Effects

As mentioned before, hydrogen-bonding will increase chemical shifts. One way to think about it is that hydrogen-bonding involves a transfer of electron density from the H-bond acceptor to the H-bond donor:



In the limit, hydrogen-bonding becomes a complete proton transfer. Here, the transfered proton gets attached to a cationic nitrogen, which is relatively electron withdrawing. When the rate of the exchange process is on the NMR timescale, the peaks will naturally become very broad. This is why exchangeable protons sometimes don't appear. Others, they are very sharp, and even coupling through the heteroatom can occur.

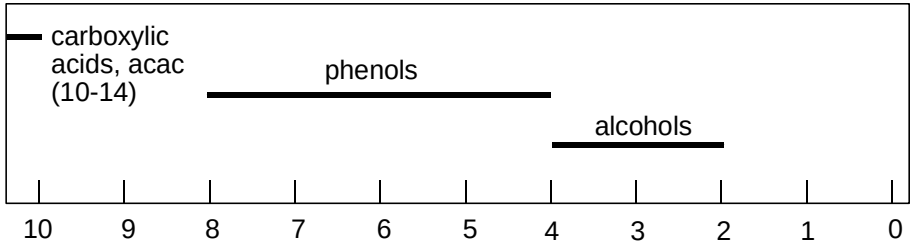


In general, the shifts of hydrogen-bonded protons will change a lot from solvent to solvent and be affected by how much water, acid, or base is present. In contrast, non-H-bonded protons will generally remain more or less constant on going from one solvent to another (but not quite, see below).

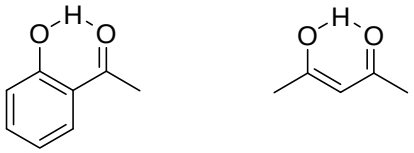
Acidic protons bound to heteroatoms are called **exchangeable**, since they can readily exchange with acidic solvent protons. The classic way to tell if a spectrum contains such protons is to add D_2O and shake the sample. Why does this work?

This is simply Le Chatelier's Principle in action. In the total pool of exchangeable hydrons (solvent + substrate), most of the nuclides are now deuterium, rather than hydrogen. As the sample is shaken, the protons on the substrate, on average, get replaced by deuteriums and the signals disappear. D_2O is not miscible with many NMR solvents. In deuterochloroform, the phases separate and the protons essentially float to the top of the tube, where no signal is collected.

These are some characteristic shifts to know, assuming a 5-20% solution in a nonpolar solvent like deuterochloroform:

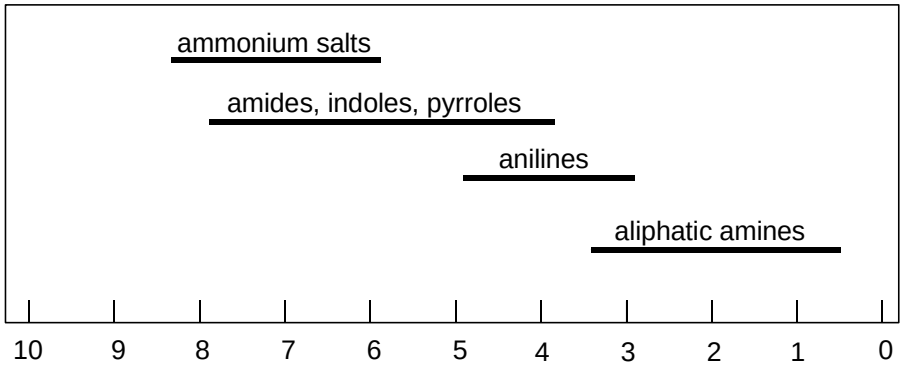


Carboxylic acids have high chemical shifts because they exist as oligomeric or dimeric species, even in dilute solution, such that virtually every proton is hydrogen-bound. Internal hydrogen bonding can also result in high chemical shifts:



Exchangeable Protons

Protons on nitrogen are also acidic, but because nitrogen is not as electronegative as oxygen, the shifts are not quite as high:



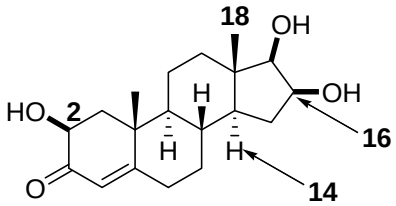
Coupling to nitrogen-14 (I=1) is generally not an issue, due to quadrupolar relaxation, but this does cause some broadening.

These values should only be considered a guide, since the actual shifts will depend on the exact experimental conditions.

Solvent Effects

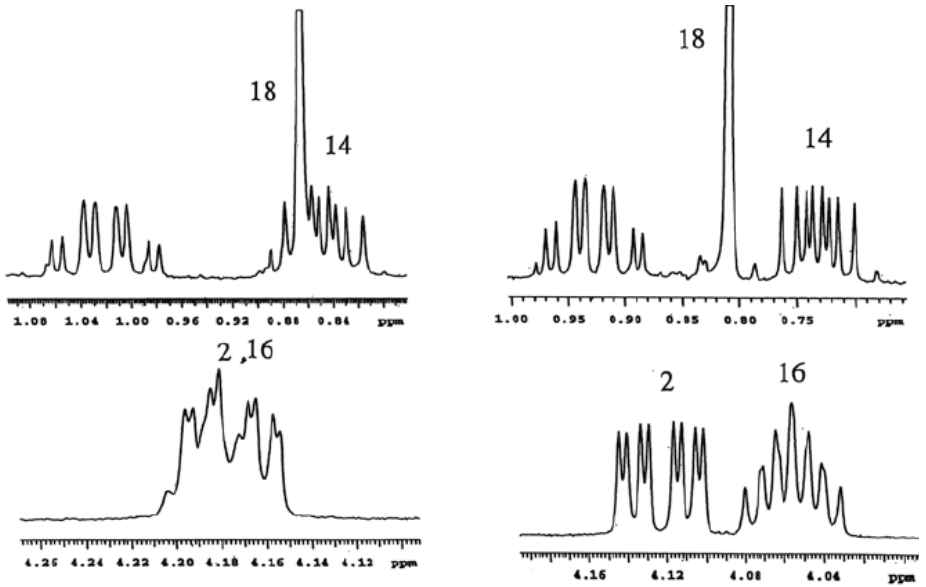
Q: How can changing the solvent affect the chemical shift?

Certainly, there can be specific interactions, like hydrogen bonding involved. These cause big changes. But spectra can shift in subtle ways that are very useful. For example, H-2/H-16 and H-14/H-18 of this steroid derivative overlap in deuterochloroform:



Overlapping signals are a big reason why the spectra of complex molecules are hard to interpret. Later, we will discuss some strategies for dealing with this problem. In this case, "benzene titration" solved the problem:

The left-hand spectra are in deuterochloroform; the right-hand spectra are in 10% d_6-benzene/90% deuterochloroform:



Sometimes, no one solvent will be able to resolve all of the resonances. This means that one must either find a solvent in which the degree of overlap is acceptable, or work with a composite data collected from a variety of solvents.

In the spectra above, it seems the protons moved upfield. In general, aromatic, dish-like solvents like benzene move shifts upfield, while polar, rod-like solvents move shifts downfield.

Evidently, this means that despite the averaging of molecular tumbling, the orientation of the solvent with respect to solute is not quite random. In the absence of any specific interaction, the internal standard and the solute would shift the same amount, and there would be no effect. In this case, one can imagine that the benzene stacks on top of the steroid, exposing its shielding cone to the protons. Since these are specific intermolecular interactions, different protons will shift different amounts (by up to 0.5 ppm).

Solvent Effects

What about a generalized medium effect? Different solvents have different polarities. Polar solutes, or nonpolar solutes with polar groups in them, induce electric fields in the surrounding solvent. This "reaction field" is proportional to the dielectric of the solvent:

$$\text{reaction field } \alpha \quad \frac{\varepsilon - 1}{\varepsilon + 1}$$

This effect is *not* compensated for by the internal standard and can be large for polar molecules in polar solvents (up to 1 ppm).

Interestingly, isotopic substitution, either in the solvent or the substrate usually have very small and unimportant effects on chemical shift. Later, I will show you some spectra of reactive intermediates *taken in regular THF*. Their chemical shift patterns follow the same trends and regimes as shown above.

Carbon Chemical Shifts

From lecture 1, recall that:

(1) Carbon-12 has no NMR signal (I=0) but carbon-13 does (I= 1/2).

(2) The natural abundance of carbon-13 is 1.11%. Therefore, it is unlikely for two carbon-13 nuclides to be next to each other in the same molecule and carbon-carbon coupling is generally not important.

(3) Carbon-*proton* coupling, however, is not negligible, and must be removed by broadband decoupling.

Q: What affects carbon-13 chemical shifts?

This is more complicated than proton chemical shifts, which are primarily determined by diamagnetic and anisotropic shielding effects. Recall that **paramagnetic shielding** is important for nuclides whose bonding involve p orbitals and can be the dominant term.

The Ramsay-Karplus-Pople equation describes the size of the paramagnetic term, σ_p (recall that *positive* shielding values mean the nucleus experiences *less* of the external magnetic field, and has a *smaller* chemical shift):

$$\sigma_p \; \alpha \; -\frac{1}{\Delta E} \cdot \left\langle r^{-3} \right\rangle \cdot \sum Q_{ij}$$

For a more detailed discussion of exactly how the paramagnetic term works, see The ABCs of FT-NMR by John D. Roberts, pp. 249-251. For our purposes, it involves mixing of a closed-shell ground state electronic wavefunction and small amount of an open-shell excited state wavefunction. This mixing produces a new wavefunction which a lower variational energy than the purely closed-shell one. It has the effect of introducing states which have a circulation of electrons in p-orbitals. Although the mixing is small, the paramagnetic effect is large, and this is often the dominant factor in determining chemical shift.

(1) The first term involving ΔE says that the smaller the HOMO-LUMO gap, the bigger the paramagnetic effect is. This means that molecules with small HOMO-LUMO gaps have carbons with big chemical shifts. This explains why alkanes, which have no low-lying acceptor orbitals, have small carbon shifts, while carbonyls, which have a low-energy π^*, have very high shifts.

(2) The second term involves the average distance *r* between the nucelus and its p-electrons. This means that an electron-withdrawing substituent on a carbon will make the carbon more electropositive. In turn, the distance from the nucleus to its p-electrons will decrease, increasing the paramagnetic deshielding. This means the carbon will have a larger chemical shift. This also explains why many carbon chemical shift trends parallel the diamagnetic arguments used for proton.

Carbon Chemical Shifts

$$\sigma_p \propto -\frac{1}{\Delta E}\cdot\left\langle r^{-3}\right\rangle\cdot\sum Q_{ij}$$

For example, the shifts in chlorinated methanes are:

CH_3Cl (24), CH_2Cl_2 (54), $CHCl_3$ (77), and CCl_4 (97).

The numbers follow the "expected" diamagnetic/inductive trends, but the magnitude of the changes is much larger due to a matched diamagnetic/paramagnetic effect.

(3) The third term relates to the bond orders and charge densities of the atoms involved and is a measure of multiple bonding. The more multiple-bonding, the more paramagnetic deshielding.

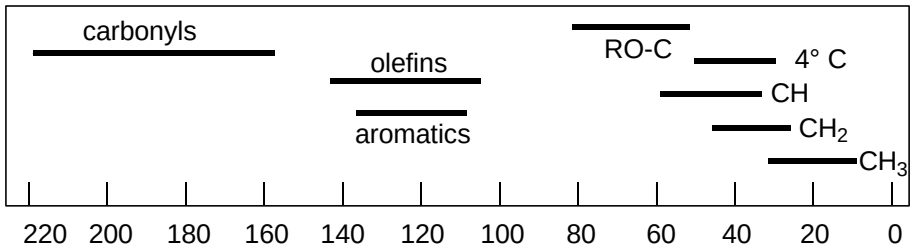
An exception occurs for atoms bonded to heavy atoms like bromine. Here, **spin-orbit coupling** must also be considered: it is thought that the heavy atoms introduce a new source of angular momentum that gives more shielding. For example:

CH_3Br (10), CH_2Br_2 (22), $CHBr_3$ (12), and CBr_4 (-29).

The shift of tetraiodomethane is even more dramatic: CI_4 (-290).

Range of Carbon Chemical Shifts

Carbon spectra are harder to interpret than proton spectra, despite the larger range of shifts (0-10 vs 0-220 ppm under normal conditions). This is because there are no couplings to distinguish groups of similar signals. Here are some ranges:



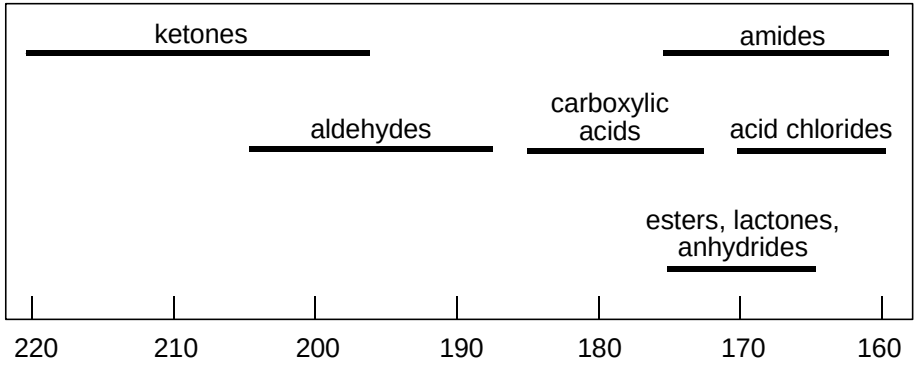
When I look at a carbon spectrum, I think about four different regions:

(1) **Alkanes**
- **methyl groups**: 5-25 ppm, strong intensity, number can be matched to information from the proton spectrum
- other peaks are not easy to tell apart without further information, but quaternary carbons are generally easier to see because they have low intensity

(2) **Ethers**
- These generally come between 50-85 ppm.

(3) **Double Bonds**
- These come between 105-140 ppm, but it's hard to tell the difference between a regular olefin and an aromatic olefin.
- However, the numbers of olefin signals in the proton and carbon spectra together might be useful.

(4) **Carbonyl Groups**
- The good news: these are well-removed from the shifts of other functional groups. The bad news: many different carbonyl groups look the same. These generally have low intensity as well.



Thus, carbon spectra give clues as to which **functional groups** are present, but don't necessarily give a lot information as to what the structure is (without other information).

Carbon Chemical Shifts

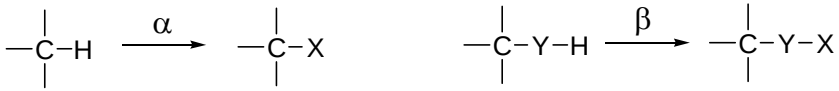
To further calibrate you, here is a brief listing of some common chemical shifts. That said, it will be a while before this makes any intuitive sense to you. For now, you should rely on NMR prediction software and tables of data heavily for solving problems. But keep in mind that analogies aren't perfect!

Alkanes

Like protons, more carbon substituents pushes the shift up:

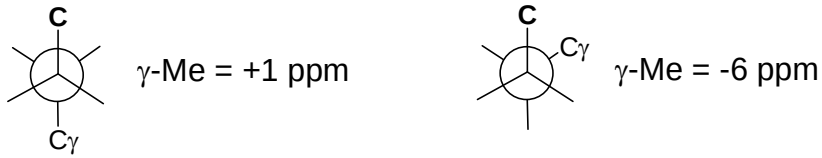
CH_4	CH_3CH_3	$CH_3\mathbf{C}H_2CH_3$	$(CH_3)_3\mathbf{C}H$
-2.5	**5.7**	**16.1**	**25.2**

The "α effect" is the increase in chemical shift caused by adding a group X to a carbon:



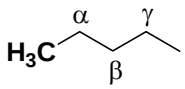
The β effect is defined the same way. For alkanes, where X is a methyl group, both the α and β effects are worth about +9 ppm. That is, adding a methyl group α or β to a carbon will increase its chemical shift by 9 ppm on average.

Interestingly, the γ methyl effect has a strong stereochemical component. On average, it is -2.5 ppm, but:



The origin of this effect might be steric or electronic in origin, but is not really clear. The α, β, and γ effects are what make the alkane region so large.

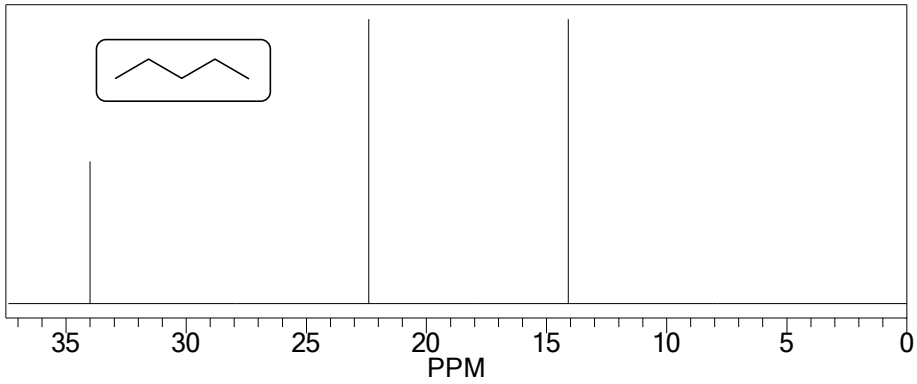
Q: Estimate the chemical shift of the terminal methyl groups in pentane.



Starting with the value for methane:

- 2.5 + 9 + 9 - 2.5 = 13 (observed, 14)

More sophisticated tables of values are available and are programmed into ChemDraw:

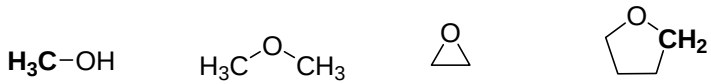



```
Protocol of the C-13 NMR Prediction:

Node      Shift     Base + Inc.    Comment (ppm rel. to TMS)

 CH3       14.1         -2.3       aliphatic
                          9.1          1 alpha -C
                          9.4          1 beta -C
                         -2.5          1 gamma -C
                          0.3          1 delta -C
```

Cyclic alkanes have some different parameters. Here are some basic shift values:

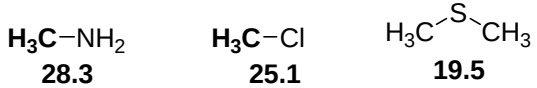
-2.6	23.3	26.5	27.7	29.4

Functionalized alkanes have characteristic shifts, too. Here are some numbers for various ethers/alcohols:



49.2	**49.2**	**40.5**	**69.2**

As usual, less electronegative versions aren't as far downfield:



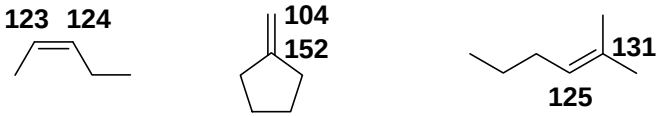
28.3	**25.1**	**19.5**

Carbon Chemical Shifts

Of course, the most useful shifts are those of sp^2 carbons, since there are often fewer of them, and they are better separated than the alkane resonances.

With no polarizing groups attached, olefins resonate at relatively low frequency. Note that methyl groups attached to olefins don't experience much of an increase:

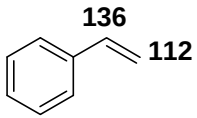
As usual, the more substituted the carbon, the higher its chemical shift:



Polar groups will increase the chemical shift, but in a complicated way:

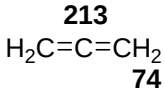
Conjugation to a carbonyl group shows the effects of π-polarization:

Conjugation to an aromatic group has a small effect:



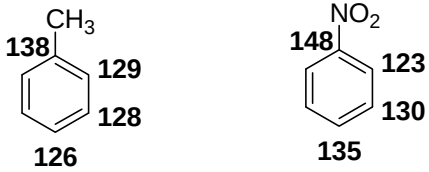
Note that electron donation/withdrawl has a matched effect on both diamagnetic shielding and the radial paramagnetic term.

One exception is the allene, which has a very high chemical shift:



The central carbon has p-orbitals going all the way around it, which leads to anisotropic deshielding and affects the third multiple bond part of the paramagnetic term.

Aromatic rings tend to have higher shifts for their *ipso* carbons:



In general, *ipso* carbons, being quaternary, also have a lower intensity than other protonated carbons. For nitrobenzene, the chemical shifts don't seem to parallel the expected electron densities based on π-resonance structures. When solving problems, I either use prediction software to understand these patterns, or else obtain information from 2D NMR spectra to assign the peak positions exactly.

Heterocycles have an even more complicated mixture of α, β, and γ effects, as well as π-resonance effects:

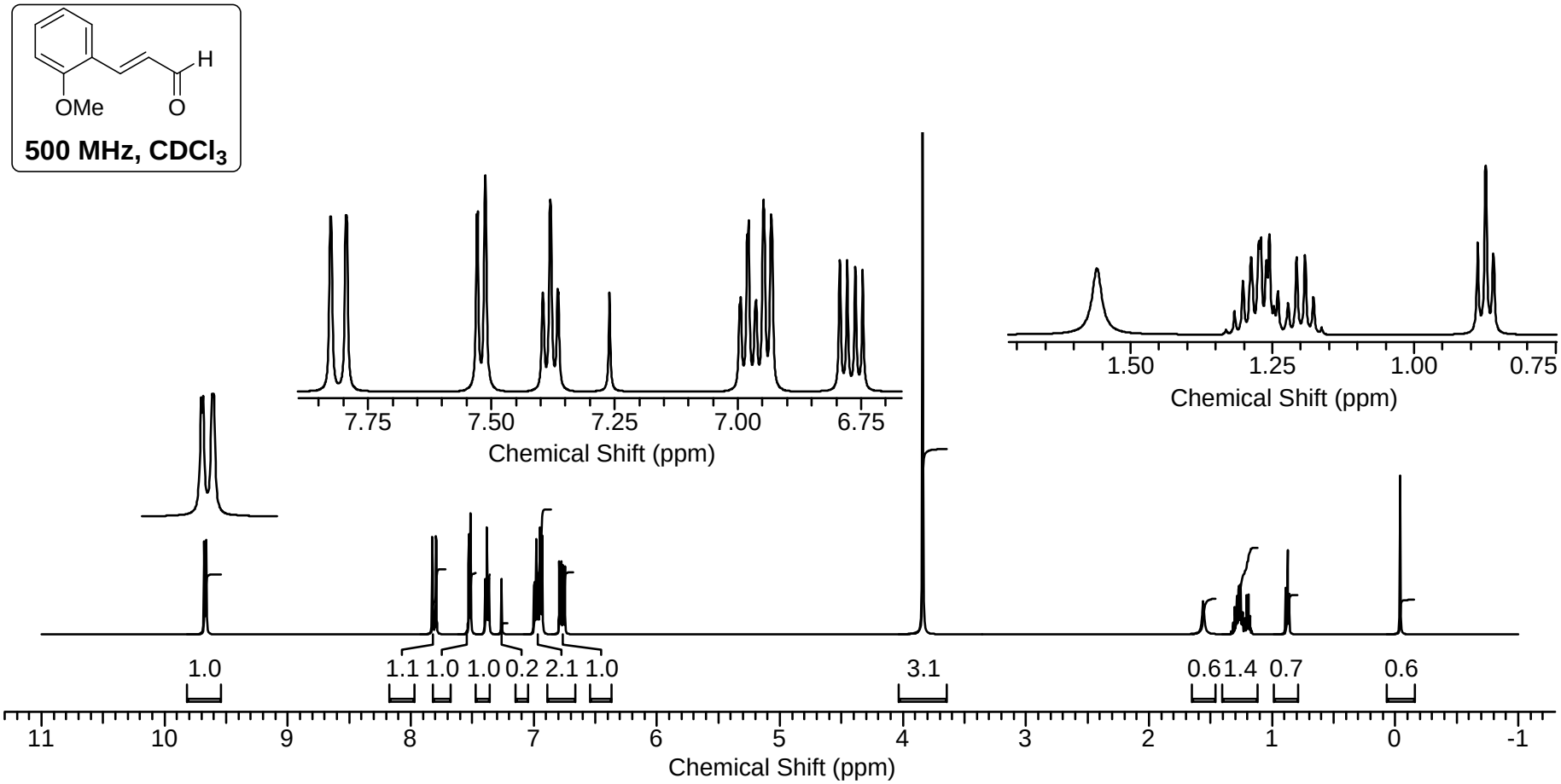
Conjugation generally shifts carbonyl resonances upfield:

Presumably, π to π* donation is enough to overcome the decrease in the HOMO-LUMO gap, which would be expected to increase the paramagnetic deshielding.

Conclusion: Know a few basic shifts, use software and tables for the rest, and do a lot of problems to get experience.

Solvent Residual Signals

Q: Please assign the signals in the following spectrum.



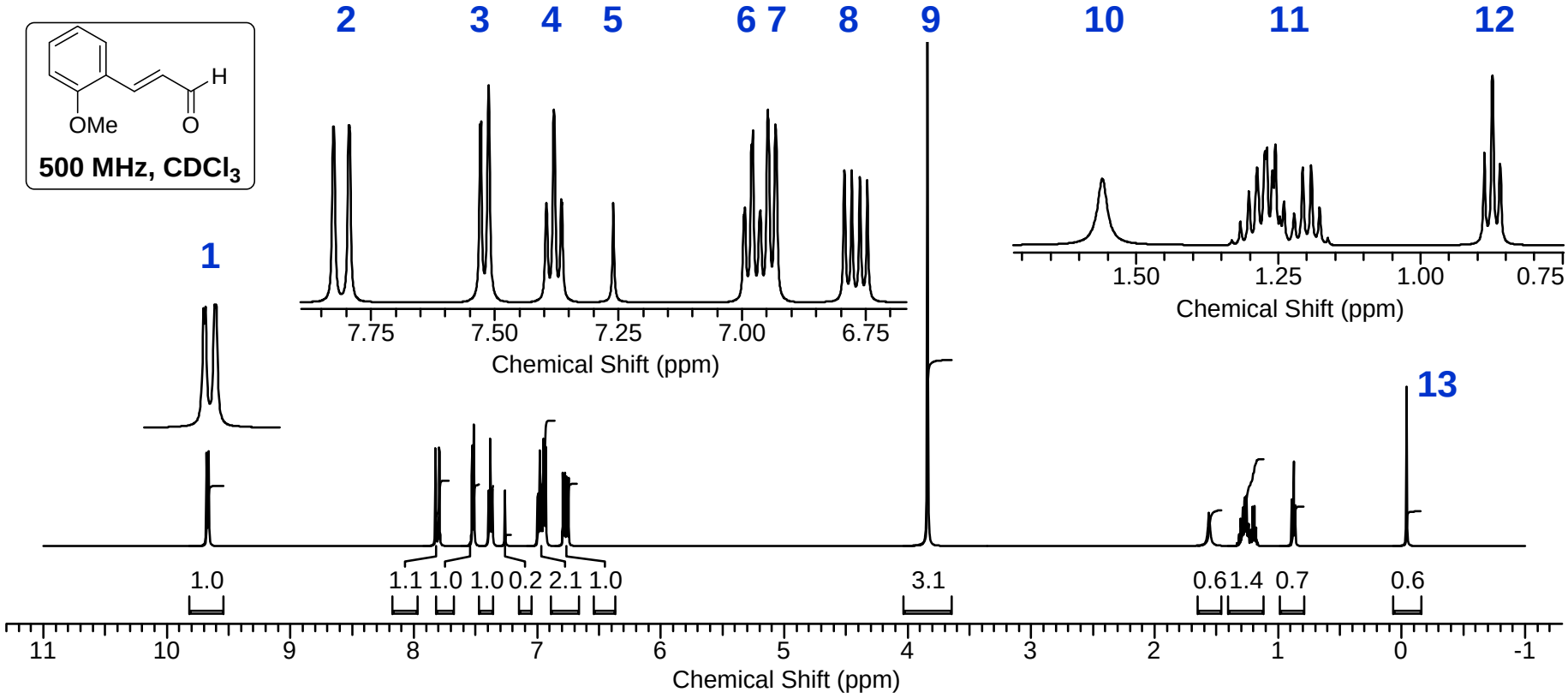
(Please note the small signals. You should be able to explain every signal.)

As I mentioned last lecture, almost nobody obtains NMR spectra with neat liquids. From experience, these are unpleasantly viscous, don't give good spectra, and certainly can't be done for solids. So NMR spectra are obtained on solutions of material in deuterated solvents (to prevent the solvent signals from overwhelming the analyte signals). However, deuteration is never perfect, and it is important to be able to recognize any solvent residual signals that may be present. An extensive list of data has been tabulated: "NMR Chemical Shifts of Common Laboratory Solvents as Trace Impurities." Gottlieb et al. *J. Org. Chem.* **1997**, *62*, 7512-7155.

Solvent Residual Signals

(1) The first task is to number the signals, as shown below.

(2) Examine the aromatic region first. Most NMR spectra are obtained in $CDCl_3$. Thus, it is not surprising to find a singlet at 7.26 ppm.



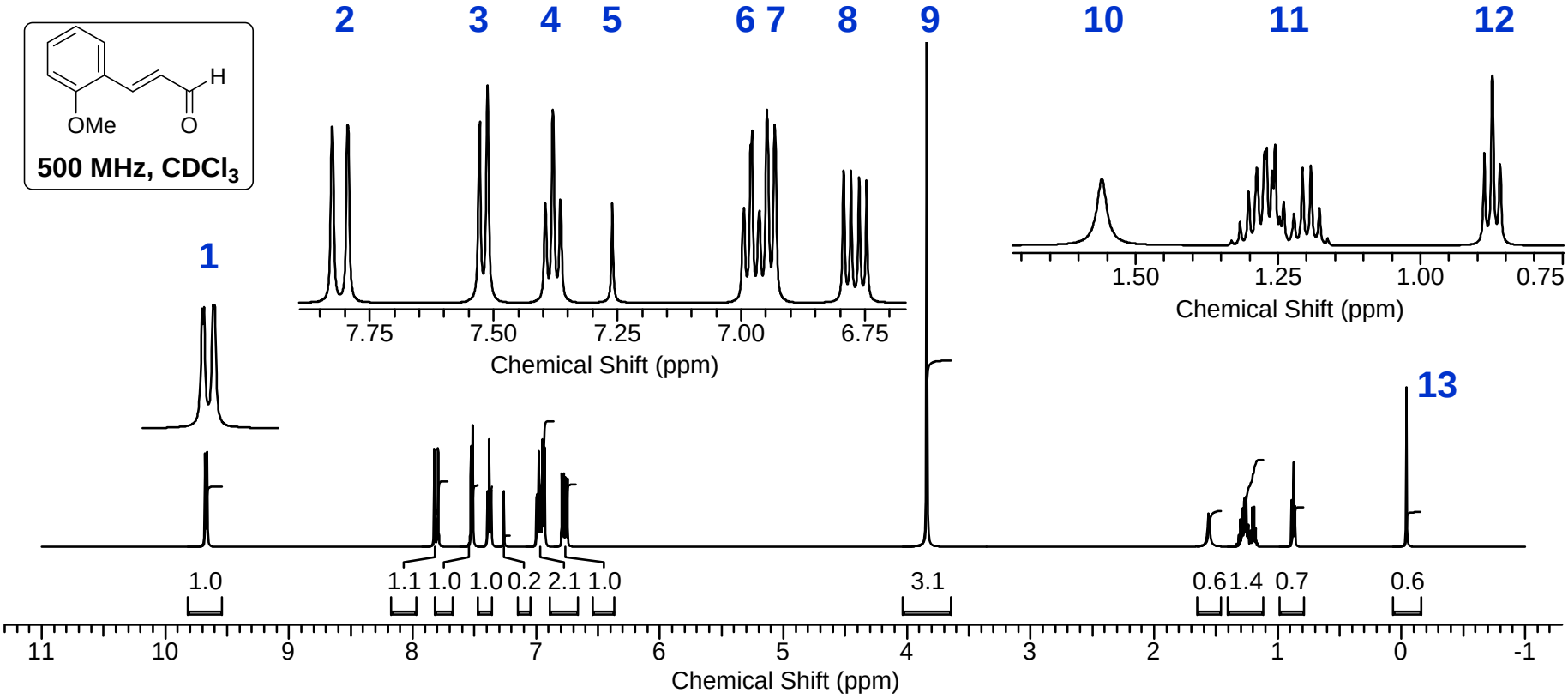
(4) **1** is the aldehyde. It's a doublet because it has a vicinal coupling to the olefinic proton.

(5) α,β–unsaturated carbonyls have a characteristic wide dispersion in the chemical shifts of their olefin protons. One will be a doublet and one will be a dd. (Why is that?)

(6) The aromatic ring has the doublet-triplet-triplet-doublet pattern expected for an unsymmetrically-substituted 1,2-disubstitued aromatic ring.

Solvent Residual Signals

(7) There are two triplets, **4** and **6**. The shifts of aromatic protons follow the trend you would expect based on inductive/ resonance arguments. Thus, **4** is para to the methoxy group, while **6** is meta to the methoxy group. (Fancier experiments would be able to confirm this more directly.



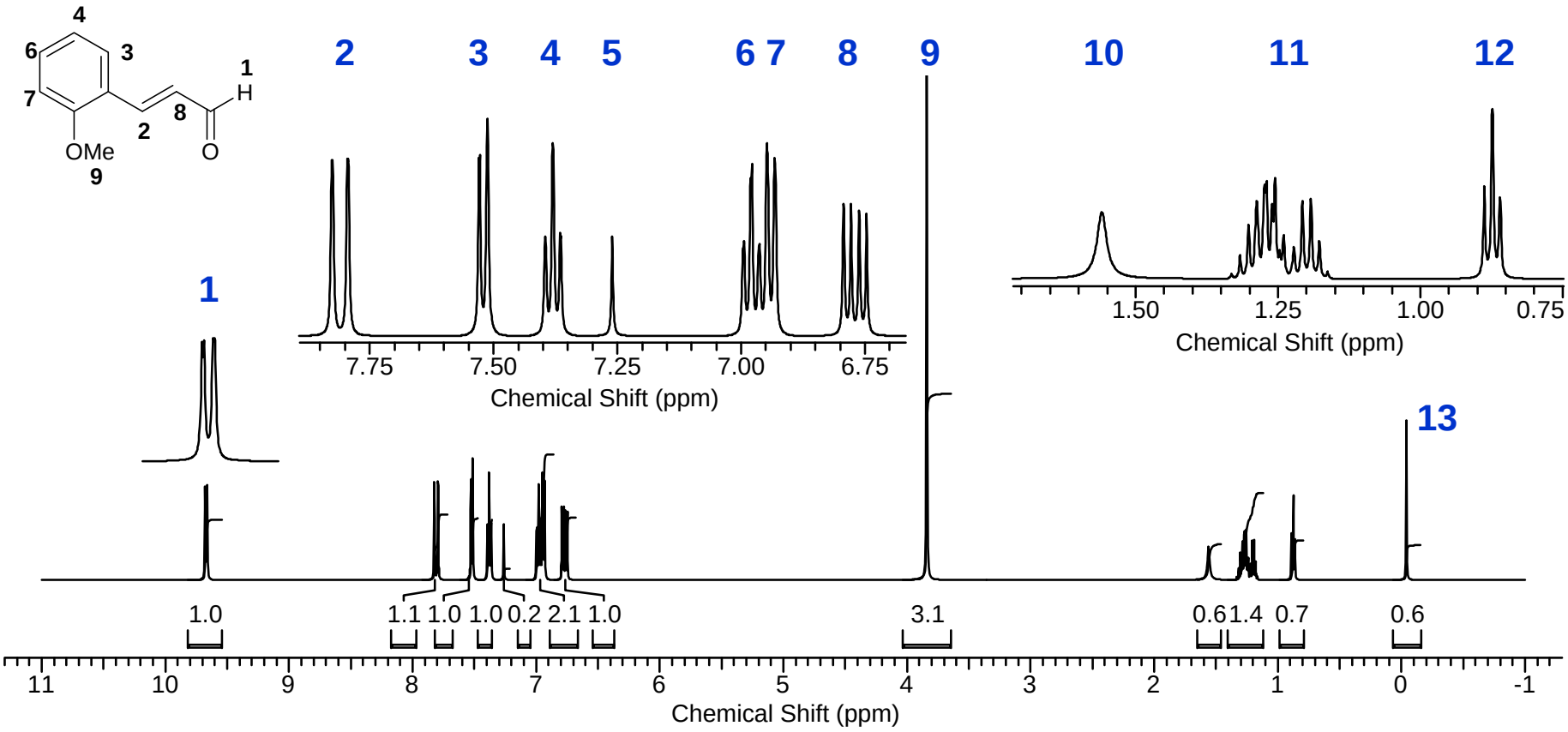
(8) **8** is certainly the α-proton on the olefin, since it is a dd.

(9) There are three doublets: **2**, **3**, and **7**. Of these, **2** has the right coupling constant to be attached to **8**. (If A is coupled to B with a coupling constant of *J*, B is coupled to A with the same constant.)

(10) Chemical shift predictions show that **7** is ortho to the methoxy group, while **3** is ortho to the olefin.

Solvent Residual Signals

(11) Clearly, the methoxy group is **9**. This gives the assignments below:



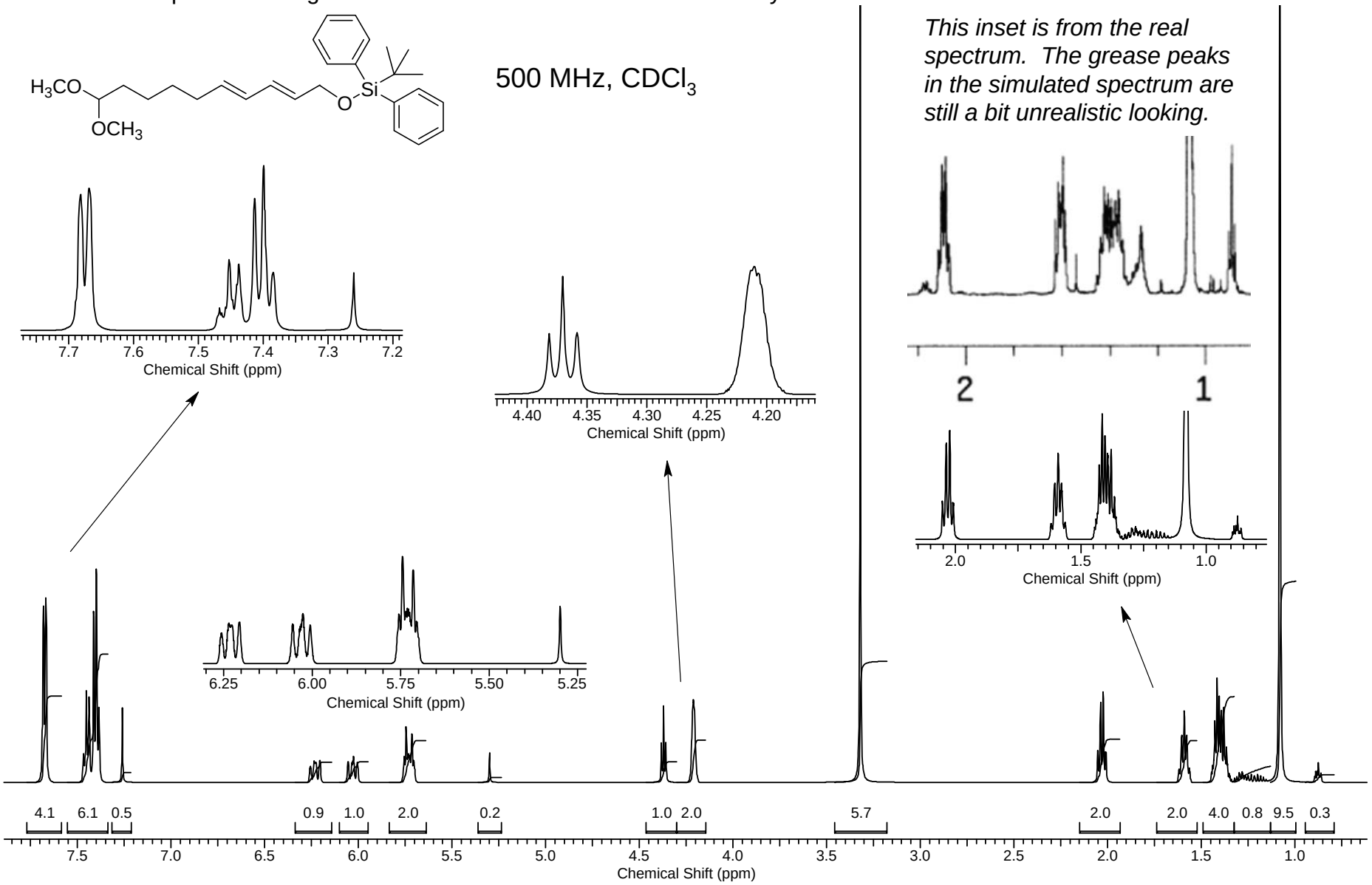
(12) Signals near 0 ppm (i.e. **13**) are invariably "silyl grease."

(13) Carbon grease (i.e., long aliphatic chains) appear at 0.86 (**12**) and 1.26 (**11**) ppm. Why is **12** a triplet? The fine structure in this spectrum is unusually resolved (this is just because it's a simulation).

(14) Water typically appears at ~1.6 ppm, while HDO appears around ~4.8 ppm. This spectrum only has water in it (**10**). These shifts can be affected by the presence of hydrogen bond donors like DMSO (which would send the signals downfield).

Example #2

Often, you'll perform a reaction and want to know if it worked or not. Here is the starting material for a reaction carried out by my colleague Dr. Drew Adams in his synthesis of the alkaloid GB-13 (*JACS* **2007** *129* 1048-1049). Please assign all the peaks. This is a simulated spectrum using the real chemical shifts. This is not as easy as it first seems!



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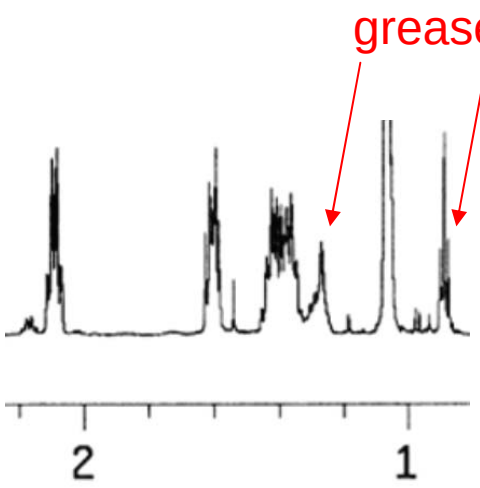
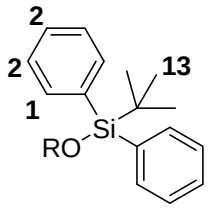
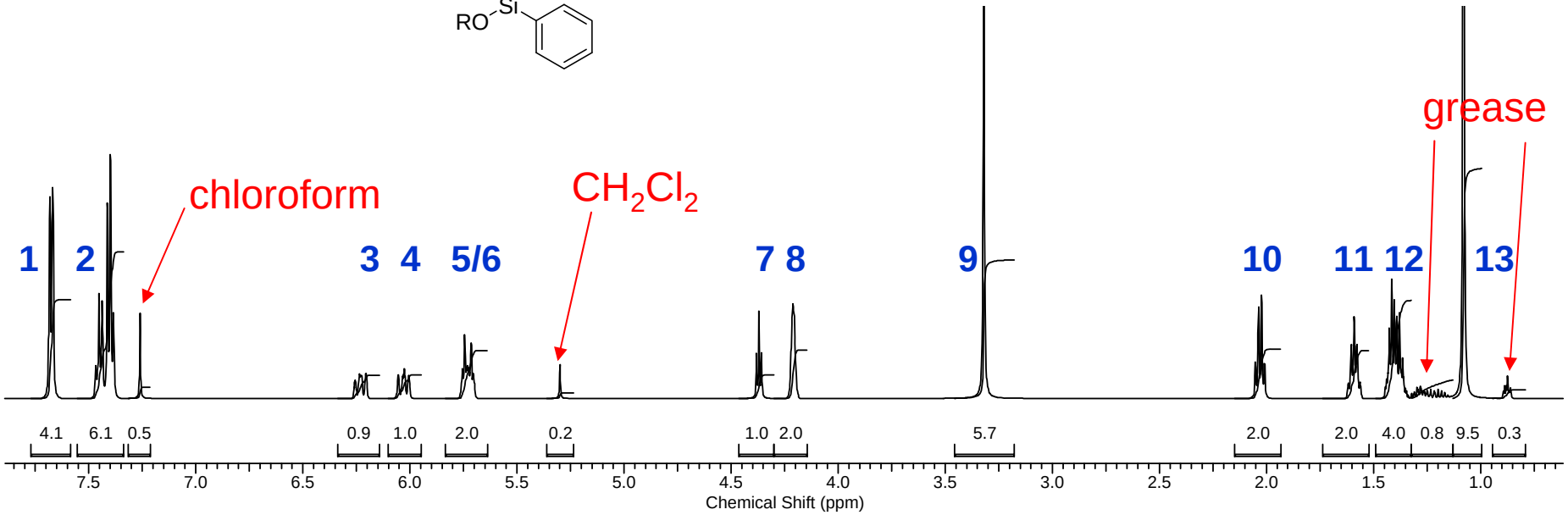
(1) **Solvent Residuals.** Always eliminate these first. This spectrum has chloroform, dichloromethane, and grease in it. Dichloromethane comes from aqueous extractions. Another common impurity is ethyl acetate. I have found that azeotropic drying with chloroform or heptane can be useful for removing these residual signals.

(2) This molecules has a **TBDPS group**. These always come in more or less the same place. It's a bit odd, but the ortho protons are always downfield of the meta and para protons, which invariably overlap. The tert-butyl signal is a highly recognizable 9H singlet near 1.1 ppm. (BOC groups come at 1.4 ppm). Here are the assignments so far:







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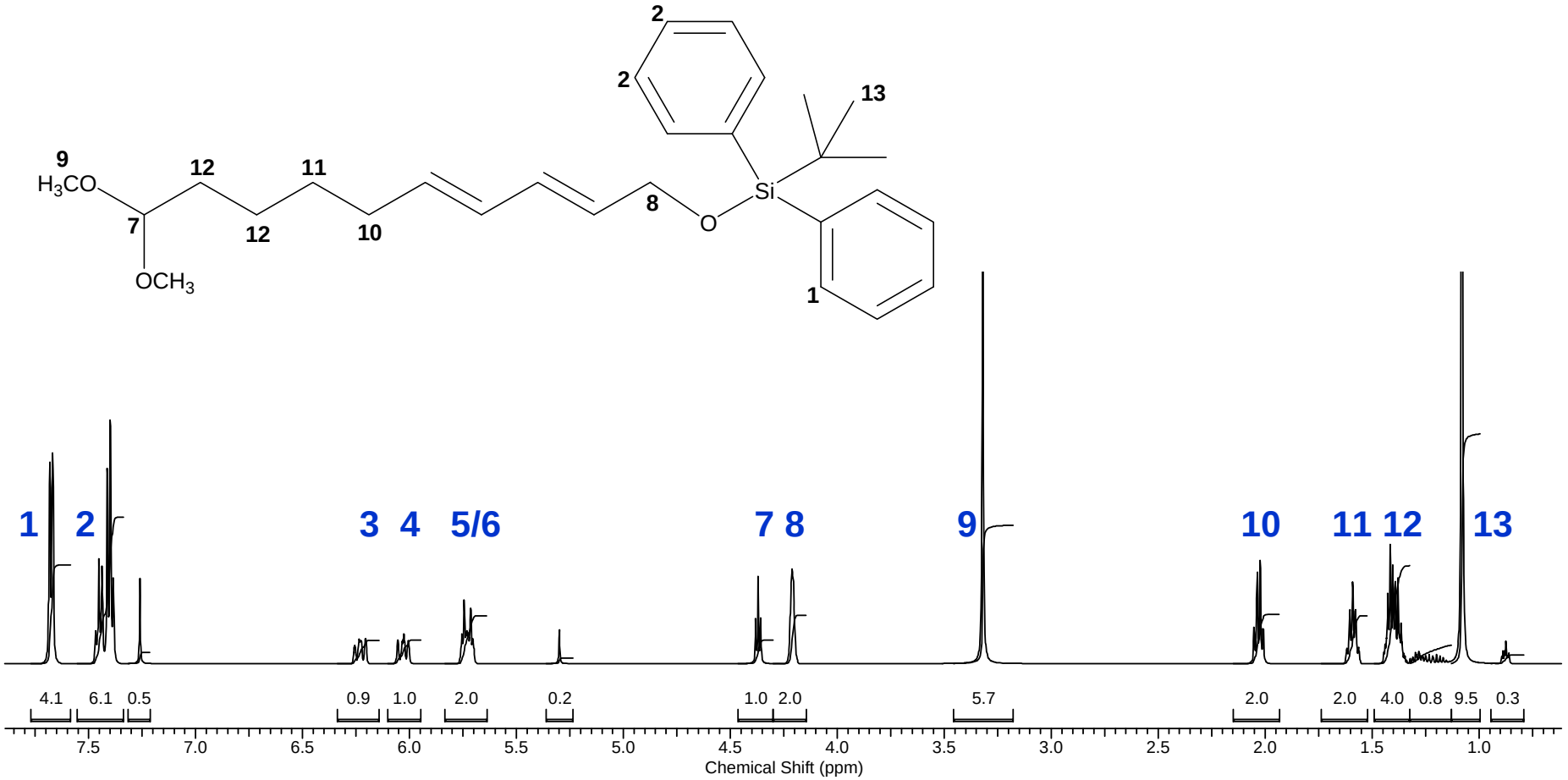
(3) **Dimethyl Acetal:** this is **9**, a 6H singlet.

(4) **Ether Region:** From the integrals, it is clear that **7** is the CH next to the acetal, while **8** is the CH_2 next to the silyl ether. Also, **7** is a triplet, which is to be expected, since **7** is a methine adjacent to a methylene.

(5) **Aliphatic Region:** Protons adjacent to olefins (i.e., allylic) are always deshielded and come at 2-2.5 ppm. Homoallylic protons are less deshielded. This gives us this assignment:



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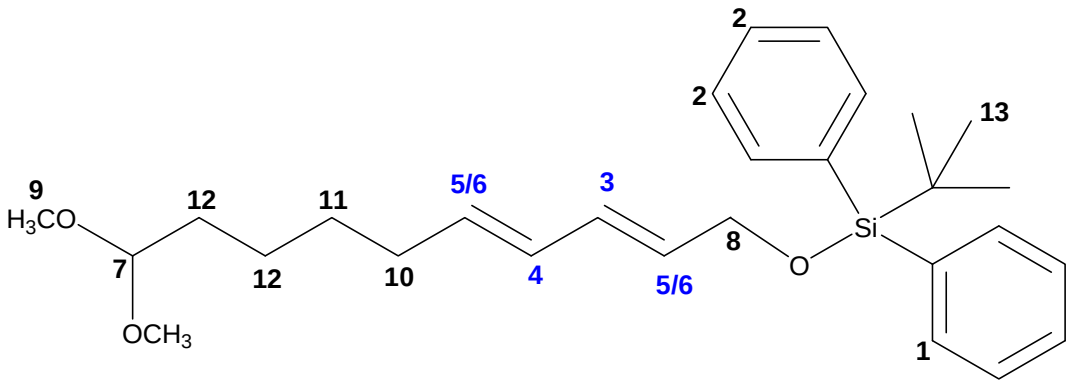
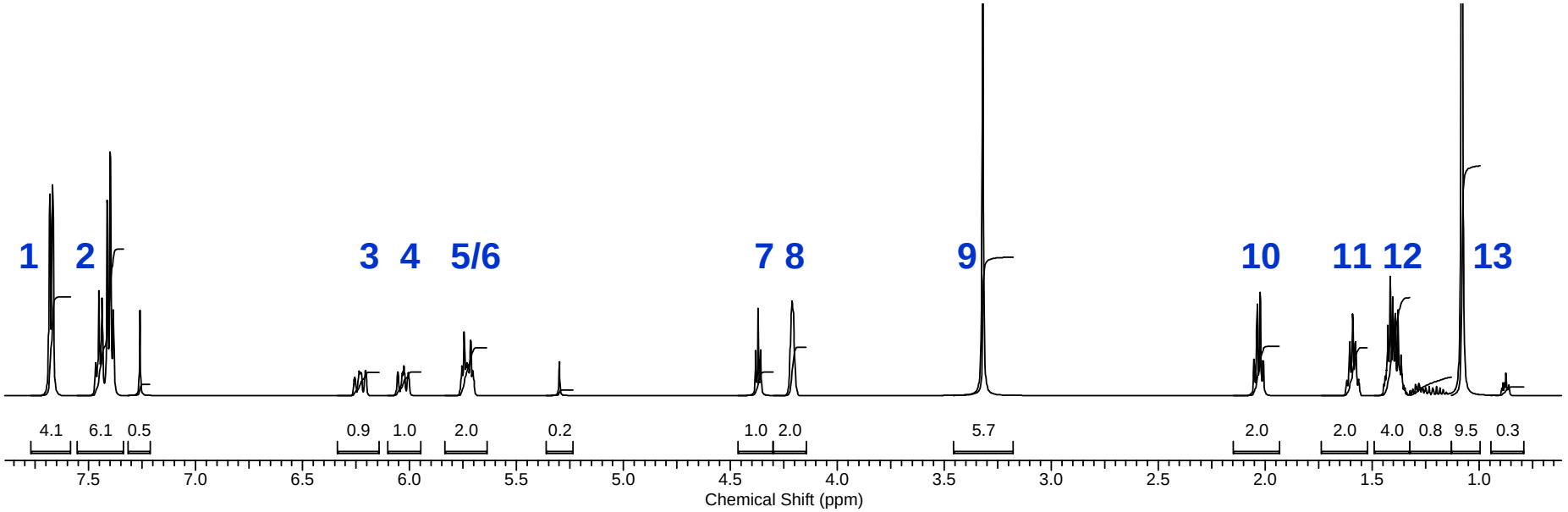
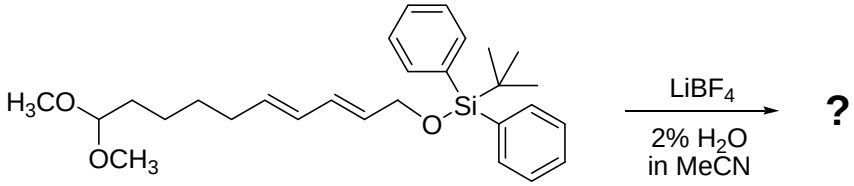
(6) **Olefinic Region:** This is the trickiest part. It's tempting to assign **5/6** to one olefin and **3/4** to another, but this is not correct. The best way to think about this is to treat the internal diene protons as doubly allylic. Thus, they are the most downfield: **3/4**. **3** must be the one closest to the ether, since it's more downfield. This completes the assignment:



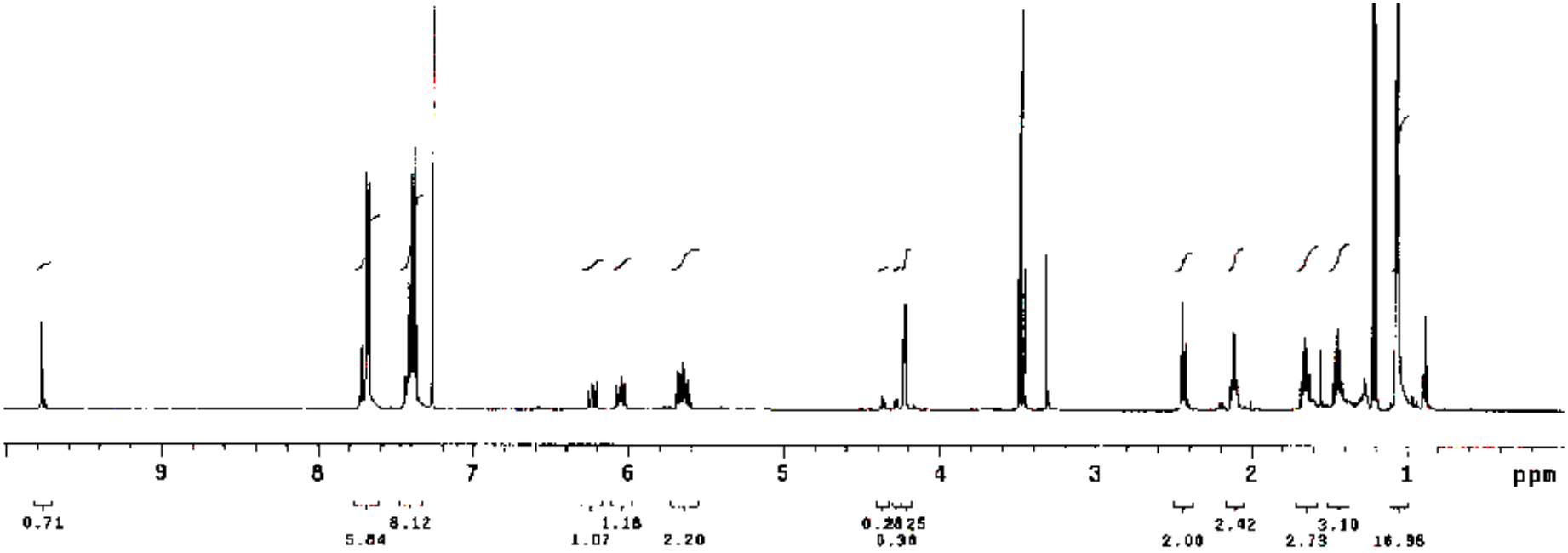


Example #3

Next, the compound was exposed to some reaction conditions. What happened?

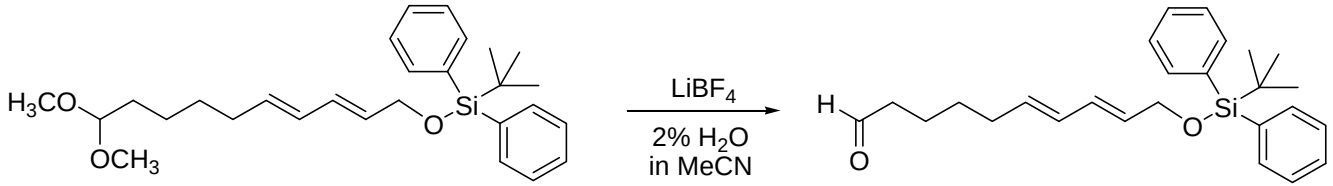


Here is the crude NMR spectrum (the product was not purified before the next step). Can you estimate the conversion?



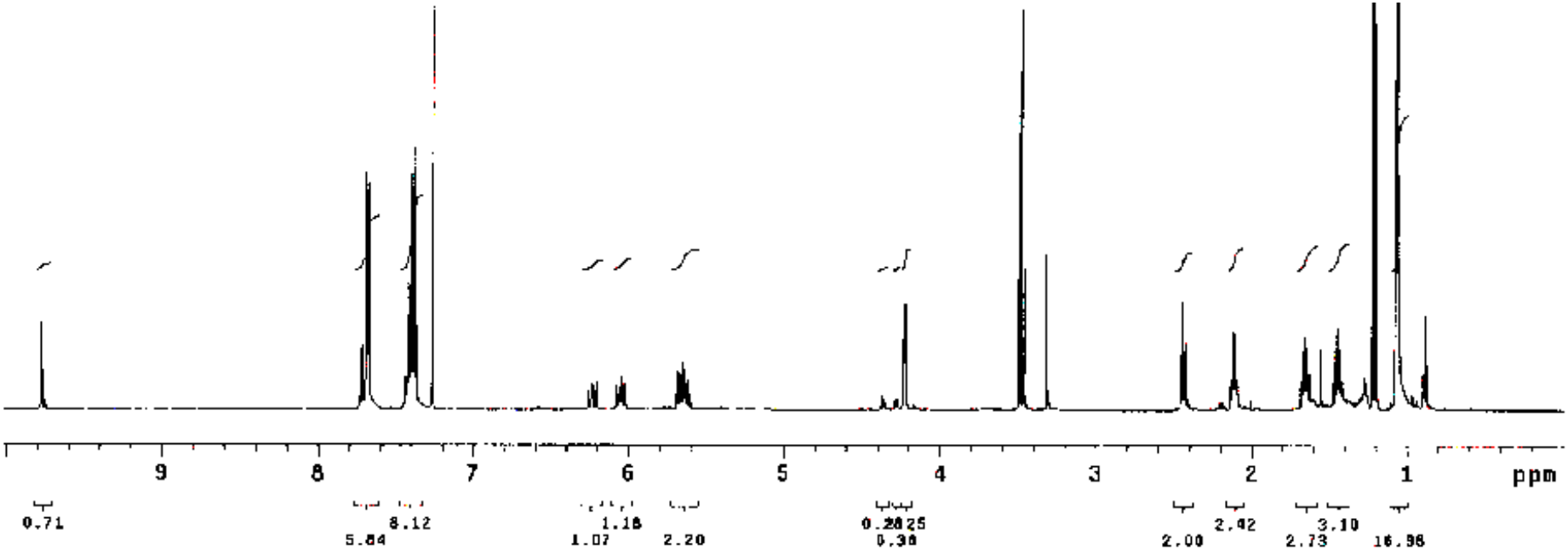
Example #3

This produced the aldehyde through acetal hydrolysis under relatively mild conditions which did not affect the TBDPS ether. ($LiBF_4$ may be a Lewis acid, or might form some small amount of HF with water present.)



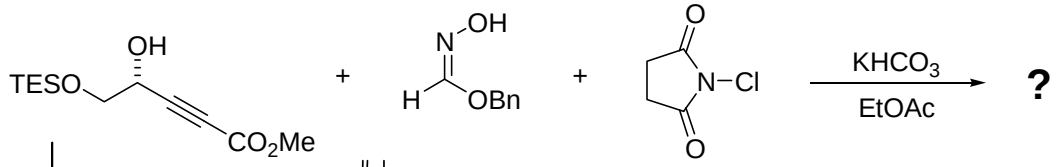
(1) There is clearly an aldehyde proton present at 9.8 ppm. The only common things that appear in this region are hydroxylic protons (typically hydrogen-bonded or phenolic) or aldehydes. For reasons I'll tell you about later, aldehyde protons are prone to under-integration (the integral is less than one). Aldehyde protons are *not* exchangeable.

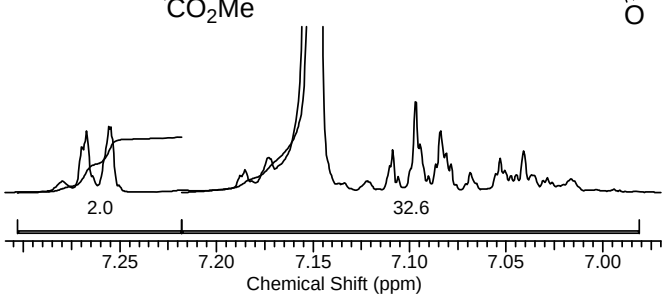
(2) The most diagnostic feature is the substantial disappearance of the methine peak at ~4.4 ppm, which used to be called **7** in the starting material. From the integrals, one might guess a conversion of around 90% (0.28 vs ~2). (Note that on Varian printouts, integral numbers get jumbled if there are too many integral "bins" next to each other.)

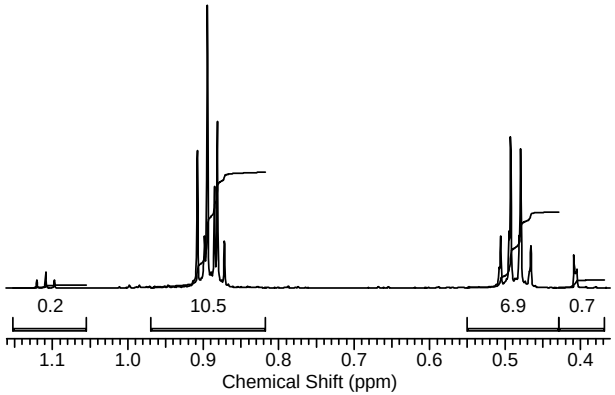


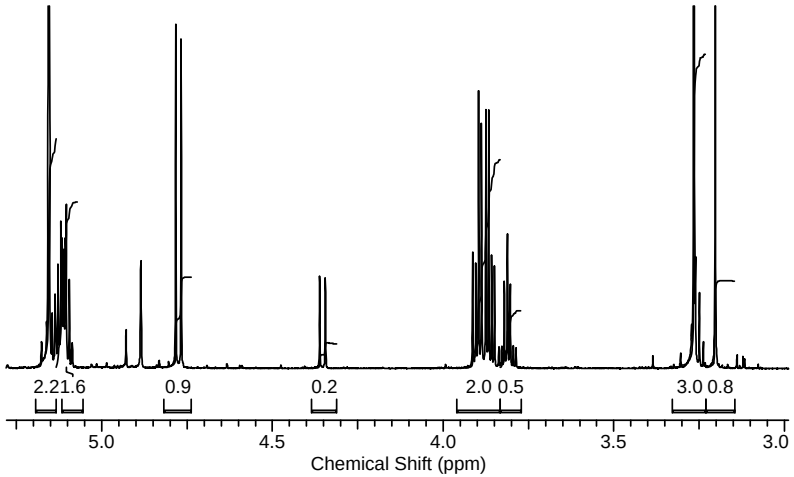
Example #4

Here is a trickier case (spectrum courtesy of Mr. Joe Wzorek). What kind of reaction is this? Did it work? Try to assign most of the peaks in the spectrum (500 MHz, ***d_6-benzene***). Benzene is probably the next best NMR solvent for small organic molecules after chloroform. It's also non-polar, but because of its anisotropic shielding properties, it tends to shift peaks in an orthogonal way to chloroform. (This material shown here has been purified by flash chromatography.)



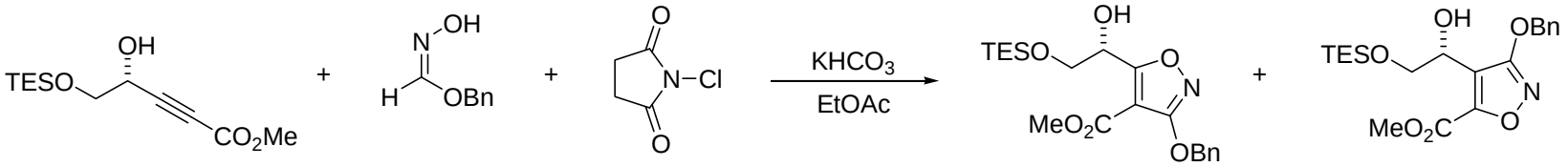






Example #4

These are conditions for [3+2] cycloaddition. The oxime gets *N*-chlorinated and then HCl is eliminated to form the nitrile oxide (this is what the potassium bicarbonate is for). This spectrum shows that a ca. 3:1 ratio of regioisomers was formed:

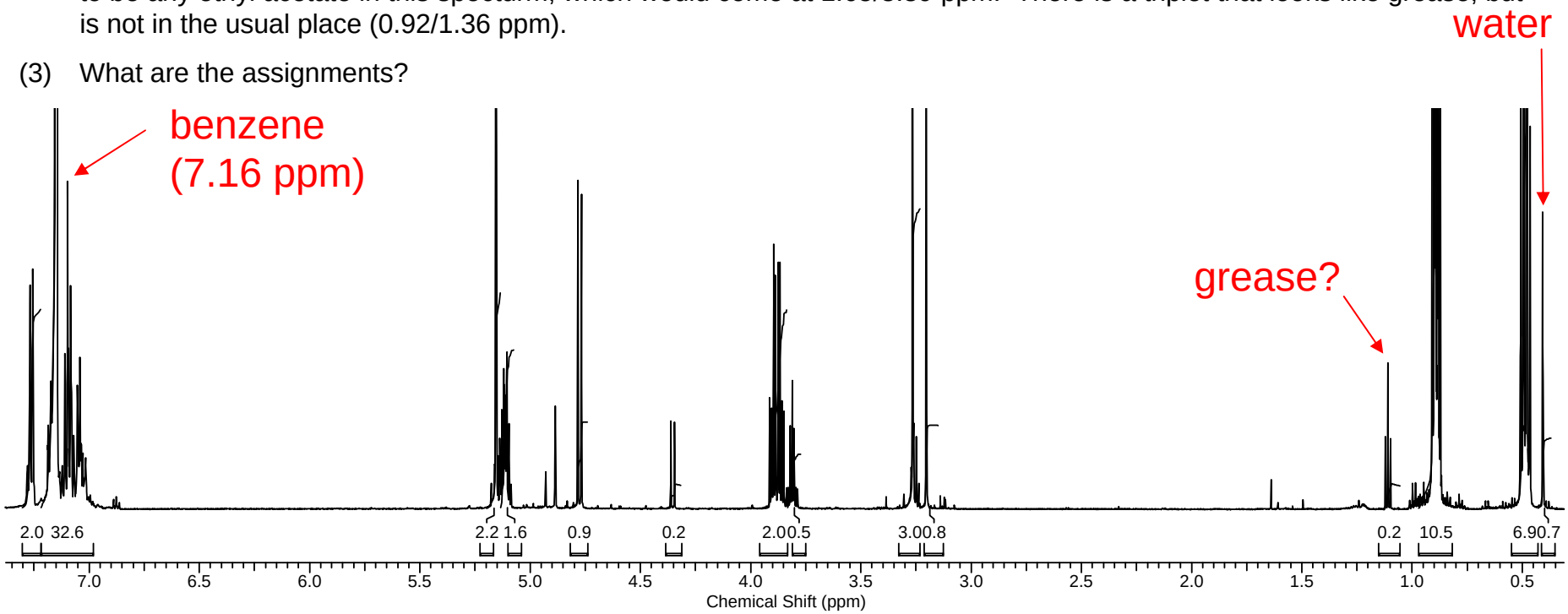


(No matter how good you are at interpreting NMR spectra, it's important to start by thinking about the *chemistry* behind what you're looking at.)

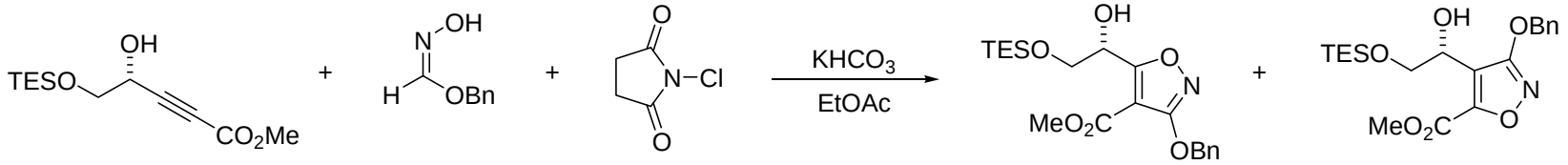
(1) Integrals don't always add up as expected. In this case, it's because there's a mixture of products. Mixtures of isomers are very challenging to understand by NMR, and you should make every effort to separate them before any sort of detailed analysis (which wasn't required here).

(2) This spectrum is in **benzene**, which has different residual signals than chloroform does (see below). There doesn't seem to be any ethyl acetate in this specturm, which would come at 1.65/3.89 ppm. There is a triplet that looks like grease, but is not in the usual place (0.92/1.36 ppm).

(3) What are the assignments?



Example #4



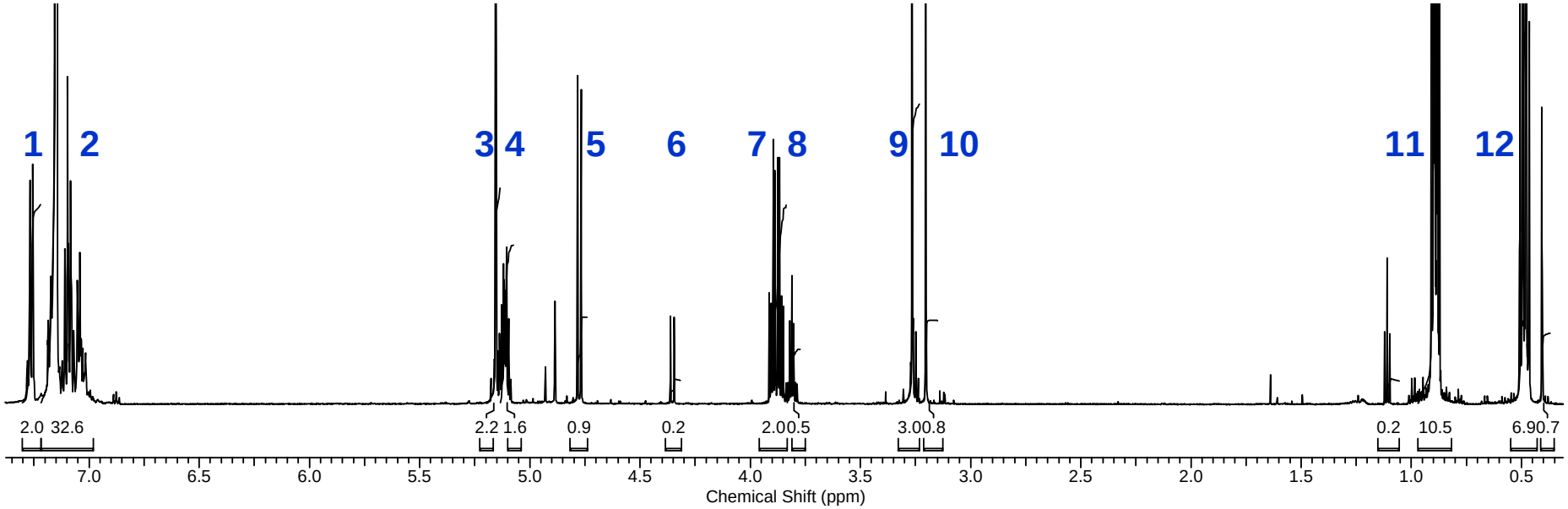
(1) In a series of more sophisticated experiments, we verified that the major isomer is the one on the left.

(2) This molecule has a TES group which is short for triethylsilyl. Like TBDPS ethers, these have very characteristic shifts that don't change much from compound to compound. Here, they are **11** and **12**.

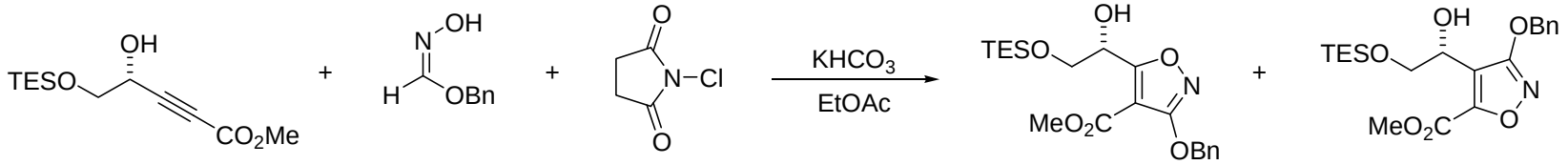
(3) The signals in the aromatic region are all overlapping, but come from the benzyl ether.

(4) The rest of the signals are noticeably doubled, which is characteristic of a mixture of isomers. The methyl esters are **9** and **10**. From the integration, this looks like a 3:1 mixture.

(5) The hydroxyl protons are visible here as **5** and **6**. Heteroatom-bound protons are not always broad!

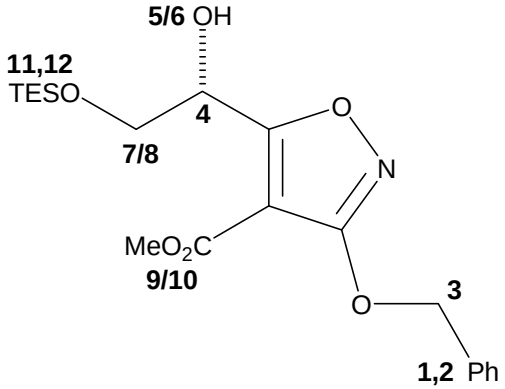


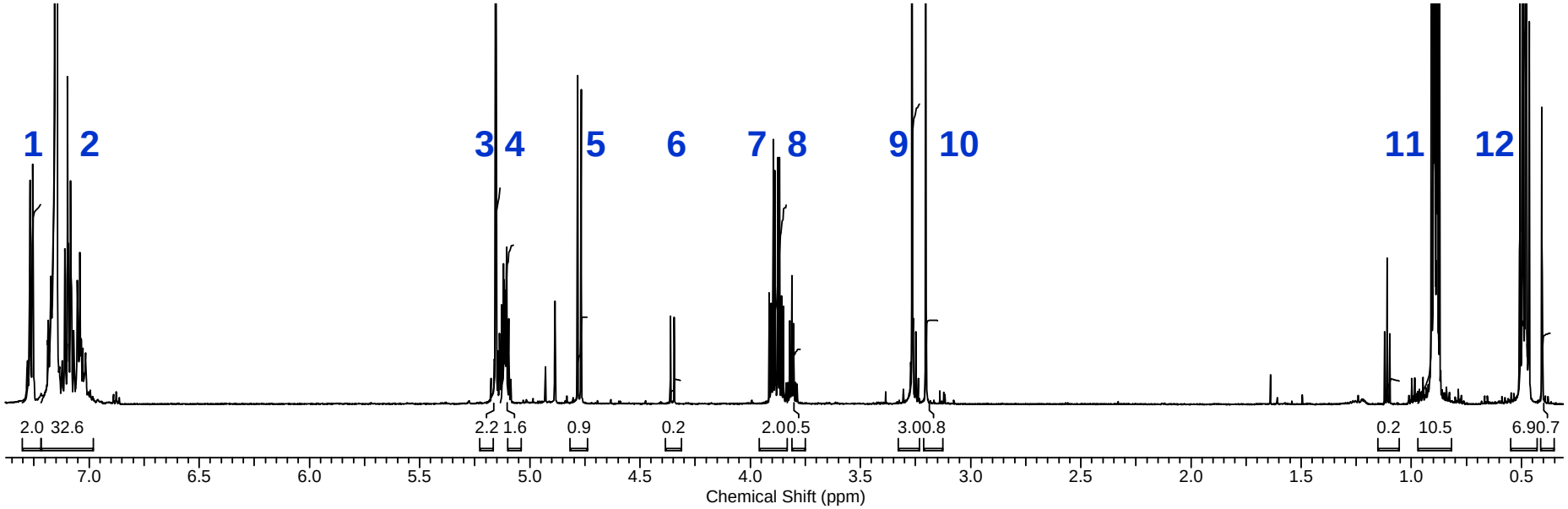
Example #4



(6) The methylene adjacent to the silyl ether is represented by **7**, while the methine adjacent to the alcohol is **4**. **3** is the benzyl methylene.

(7) The final assignments are:





More Advanced NMR Experiments

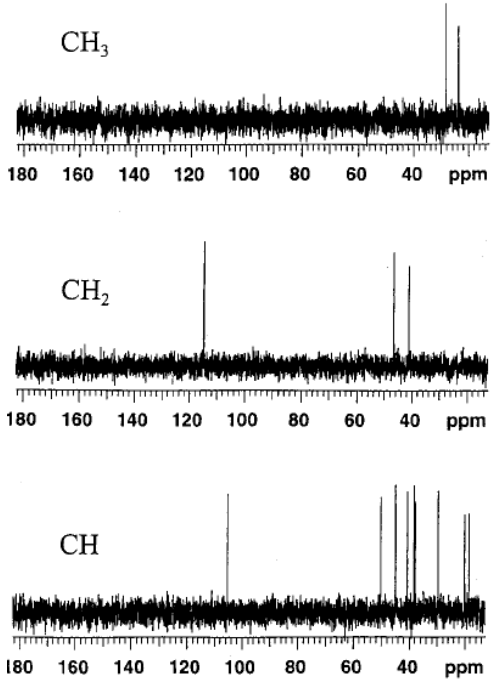
Clearly, 1D NMR spectra are powerful sources of information. However, despite this, often we will need more information. Two of the simplest tools for getting more information are DEPT and COSY.

DEPT: distortionless enhancement by polarization transfer

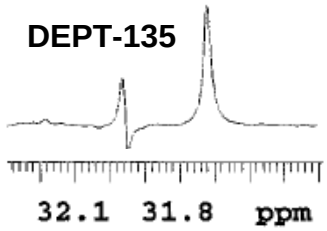
The details of how this works are very complicated, and we will look at it later in the course when we examine the product operator formalism. For now, think of DEPT as a way to distinguish between C, CH, CH_2, and CH_3 peaks in carbon spectra. Traditionally, there are three DEPT spectra:

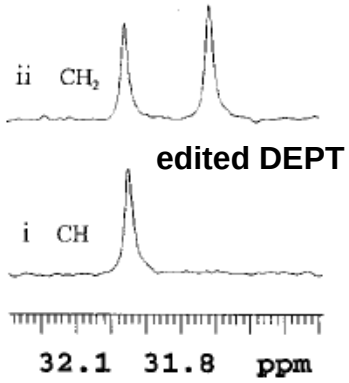
DEPT-45 = all protonated carbons
DEPT-90 = CH only
DEPT-135 = CH/CH_3 opposite in sign to CH_2

These can be combined mathematically to produce "edited" DEPT spectra:



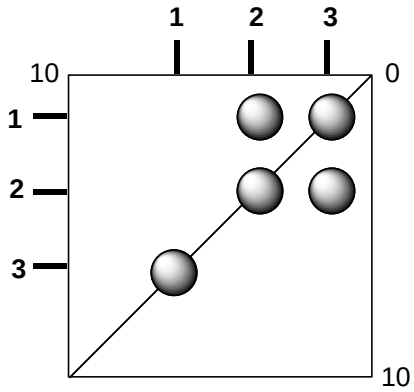
As we will see later, the DEPT experiment is not perfect and is sensitive to the size of $^1J_{CH}$ and some imperfections are to be expected. If a CH and CH_2 have the same chemical shift, then there can be some distortions. However, edited DEPT spectra can reveal this problem:





COSY: correlation spectroscopy

The DEPT experiment answers the question: "what kind of carbon are you?" while the COSY experiment answers the question "which protons are coupled to each other?" This is a *2D* spectrum where crosspeaks indicate couplings:

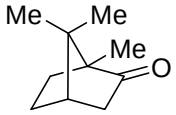


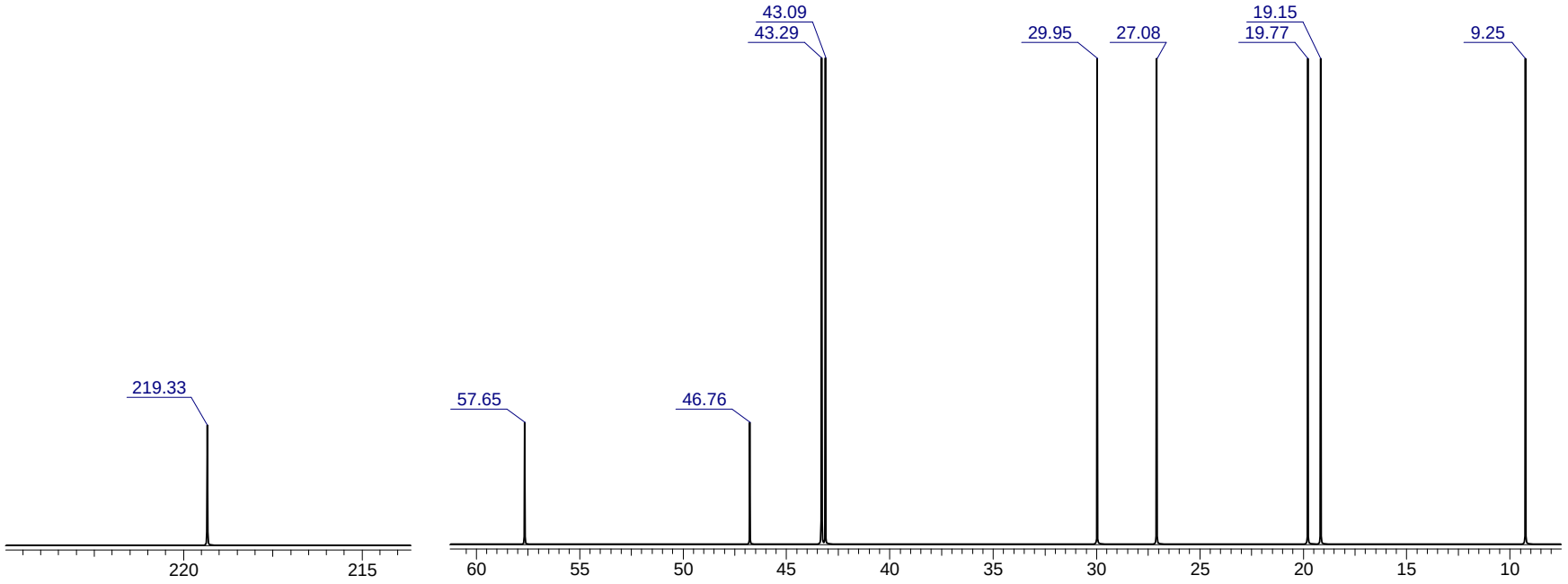
(fine multiplet structure has not been drawn)

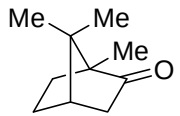
The peaks on the diagonal don't contain any useful information. But the off-diagonal crosspeaks tell us that protons **2** and **3** are coupled to each other. This information can be used to assign protons to *spin systems* in the molecule. (Spin systems are protons which are connected through a contiguous set of couplings.)

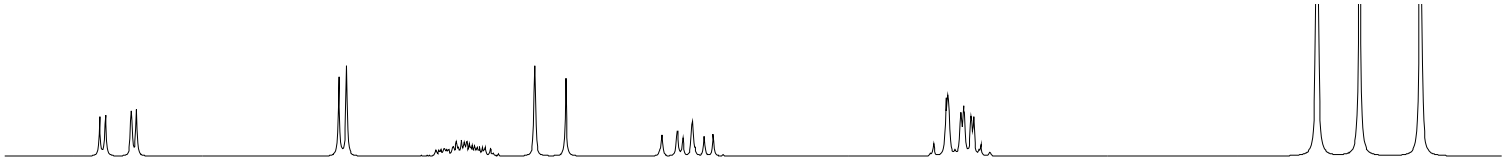
Assignment #1

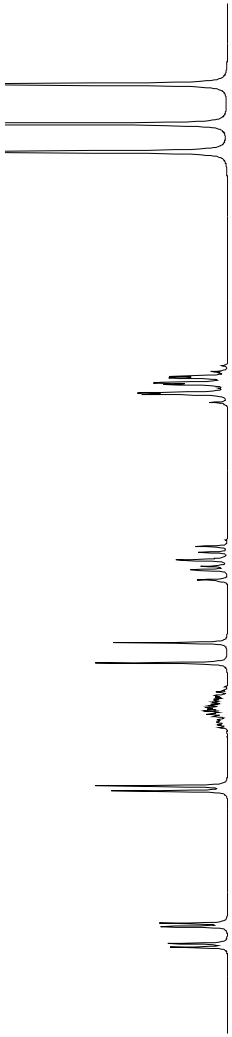
Please assign the peaks in the NMR spectra of camphor.





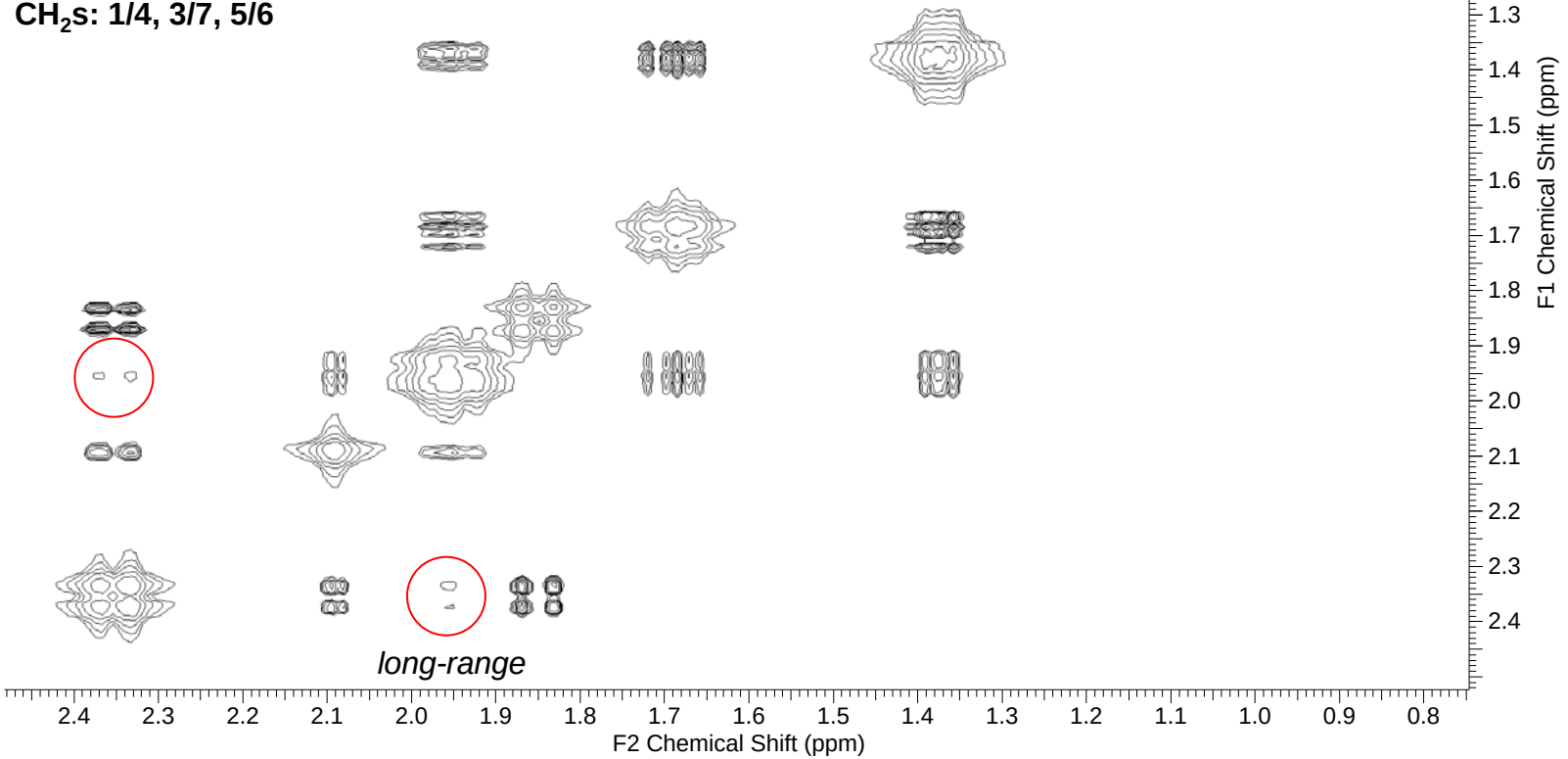


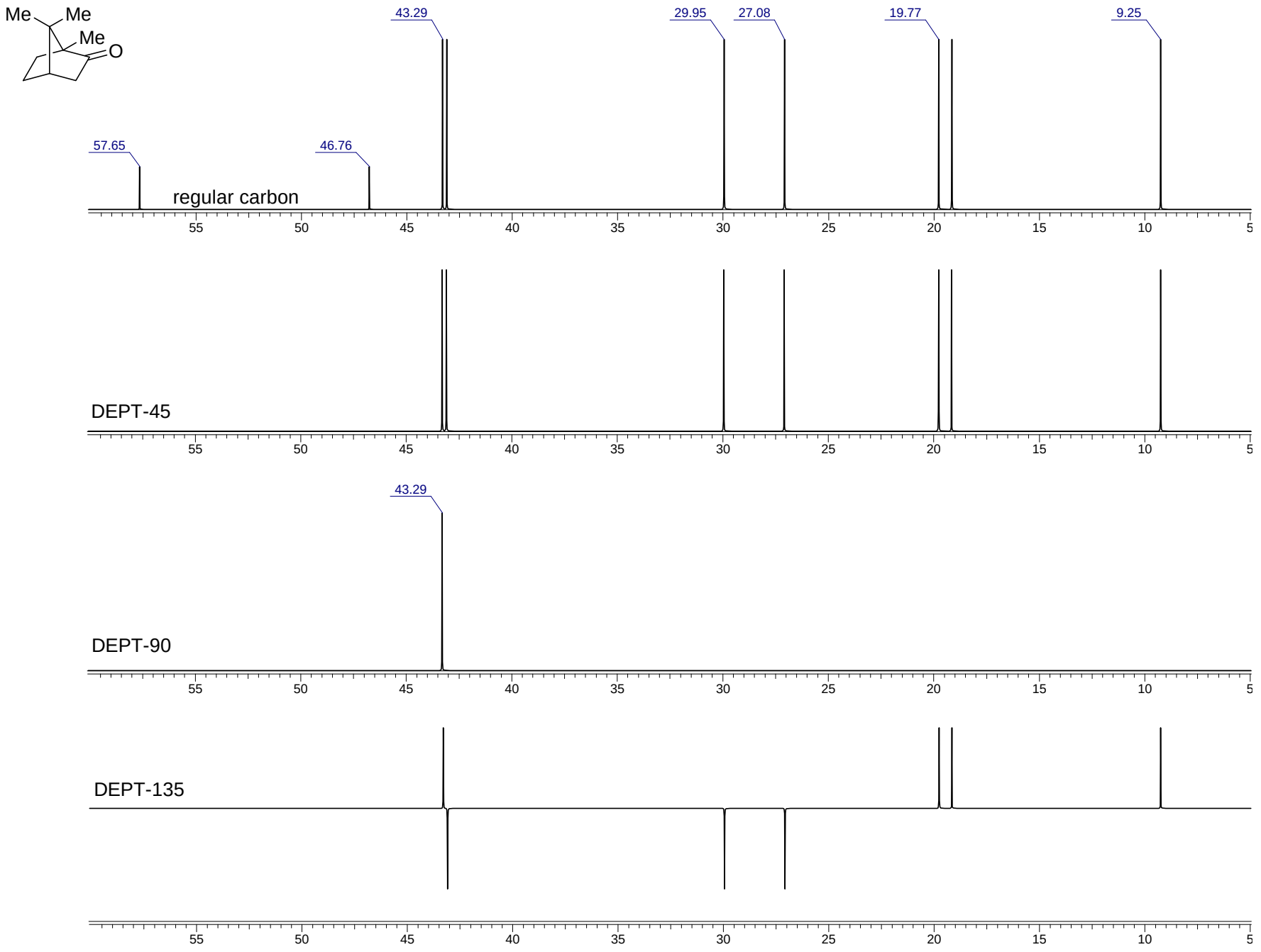




COSY spectra typically show vicinal (two-bond) and geminal (three-bond) couplings. However, long-range couplings can appear as fainter peaks. The inability to distinguish between geminal and vicinal couplings is a major drawback of this experiment. Fortunately, there are other convenient 2D methods that allow this to be done. For the purposes of this example, I will just tell you which protons are vicinal couplings. Note that if two protons have a vicinal coupling, they must be on the same carbon and are therefore a methylene.

CH_2s: 1/4, 3/7, 5/6




Me
Me
Me
O
43.29
29.95
27.08
19.77
9.25
57.65
46.76
regular carbon
DEPT-45
DEPT-90
DEPT-135
55
50
45
40
35
30
25
20
15
10
5

Assignment of Camphor

This is quite a hard problem, so don't panic. The first place to start is to assemble some tables of what data you have. At this stage, it doesn't have to be fancy:

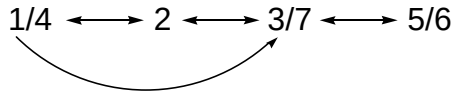
1	2.35	1H	dd
2	2.09	1H	d
3	1.95	1H	m
4	1.85	1H	d
5	1.69	1H	m
6	1.38	1H	m
7	1.37	1H	m
8	0.96	CH_3	s
9	0.91	CH_3	s
10	0.84	CH_3	s

(Let's deal with the carbon in a minute.) I always check that there are the correct number of protons here. This could save you confusion later.

At this point, it's clear that protons 8, 9, and 10 are methyl groups, but it's not clear what the others are. Fortunately, there is a rather simple experiment (HSQC-DEPT) that will tell you which protons are methylenes and which protons are methines. Thus, I'll just give that information to you. The methylene pairs are:

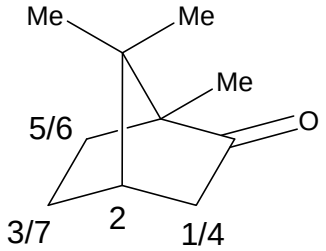
1/4, 3/7, 5/6.

From the COSY, you can assemble this connectivity map:



long-range coupling

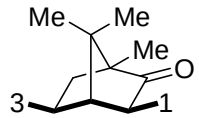
Given the topology of this molecule, there is only one possible interpretation. What is it?



(1) By process of elimination, 2 must be a methine. There is only one methine in the molecule.

(2) This makes sense based on the chemical shifts: the most downfield proton should be next to the carbonyl group.

(3) The long-range coupling arises from a "W-coupling."



These are commonly observed in caged, polycyclic molecules like this one. However, the *absence* of such signals should not be considered diagnostic. Mostly, they just serve to confuse you. In real COSY spectra, you can identify these because they are weaker than the geminal and vicinal couplings. Also, they are frequently more intense on one side of the diagonal than the other. But this subtlety is not reproduced in the simulated specturm.)

What are the carbons? Recall that, for a DEPT:

DEPT-45 = all protonated carbons
DEPT-90 = CH only
DEPT-135 = CH/CH3 opposite to CH2

In real DEPT spectra, there will sometimes be incomplete cancellation of signals, so small "bumps" may appear where they don't make sense; read the spectra carefully.

Assignment of Camphor

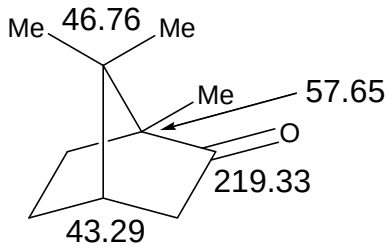
For the carbon/DEPT, I get:

219.33	4°
57.65	4°
46.76	4°
43.29	CH
43.09	CH_2
29.95	CH_2
27.08	CH_2
19.77	CH_3
19.15	CH_3
9.25	CH_3

(1) The convention I use is to label the protons by their ID#, which goes from left to right on the spectrum (so that low ID numbers mean bigger chemical shifts). But I label carbons by their chemical shift.

(2) If a carbon doesn't appear in any of the DEPT spectra, it must be quaternary. (Actually, it is easy to get software which will turn the native DEPT spectra in to CH, CH2, and CH3 "subspectra." The software will add and subtract the spectra in various ratios to do this. It turns out there are a few cases where this is an advantage beyond mere convenience (spectral overlap). But I show you this so you know how to interpret the spectra manually.)

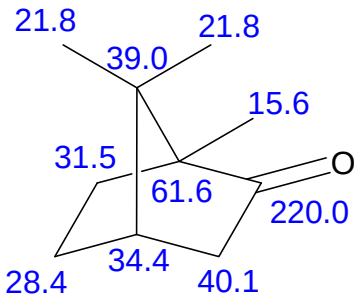
(3) Immediately, we can make these assignments:



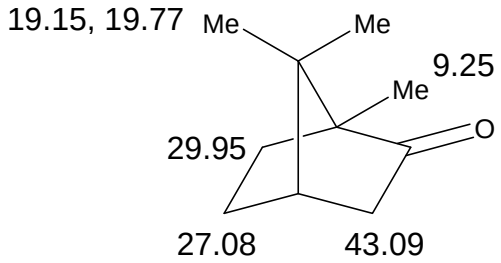
This is just because there is only one CH and one ketone in the molecule.

(4) There are two more quaternary carbons, one of which is far more downfield than the other. Logically, this the one next to the carbonyl.

(5) The rest of them are quite tricky. Here is where chemical shift predictions come in handy. ChemDraw 9 predicts:



From this, we can assign the rest:



(6) It's hard to tell which methyl groups are which. There may be a peculiar anisotropic shielding effect from the carbonyl group. However, the methylene orderings are quite clear and make sense based on electronegativity.

(7) Now, although these chemical shift predictions are quite good, they should not be taken as definitive. Further 2D NMR experiments would be needed to verify the assignments.