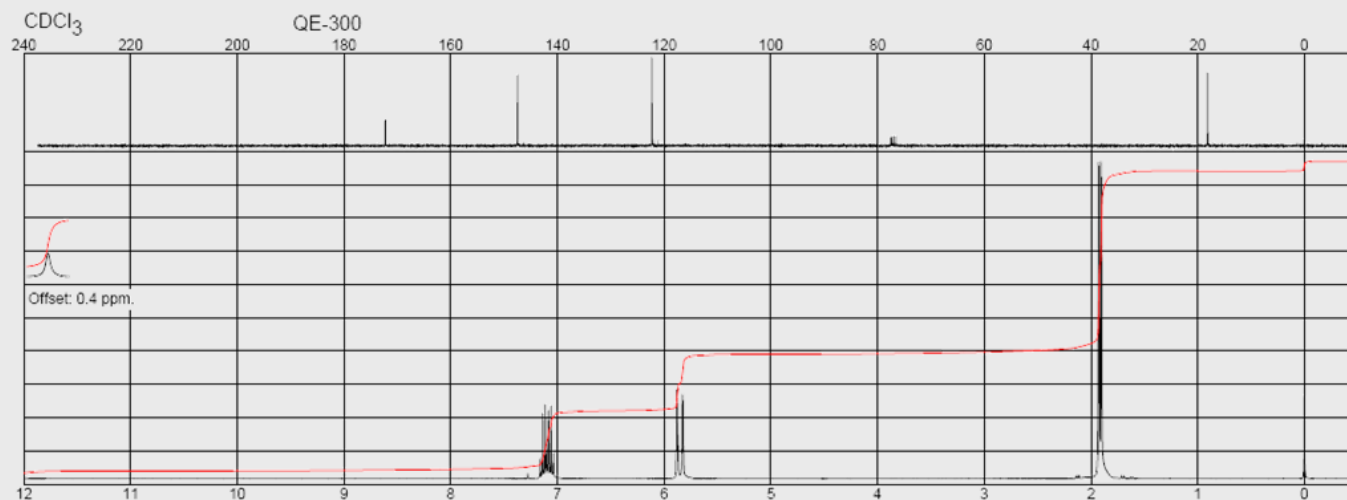
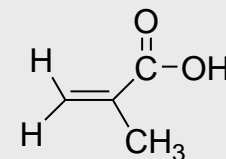
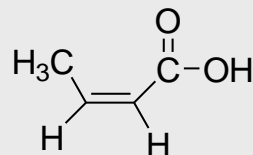
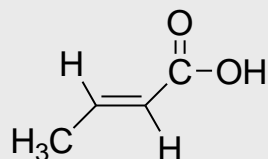


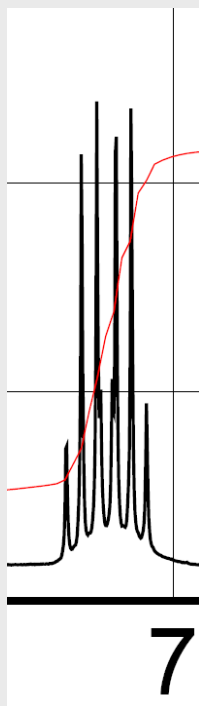
Without much effort, and any more detailed analysis of chemical shifts, several possibilities arise:



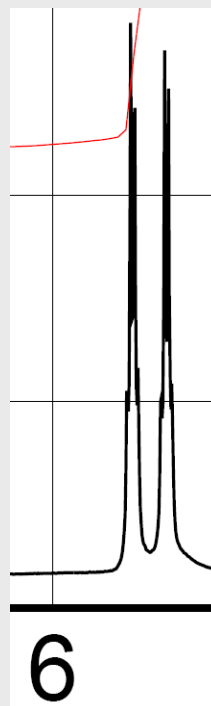
From analysis of J-values and knowledge of which protons are coupled by the various J-values can finish the analysis:

On most NMR spectrometers, ppm values can be converted to Hz; when this is not available, remember 1 ppm = n Hz where n is the operating frequency of the instrument in MHz

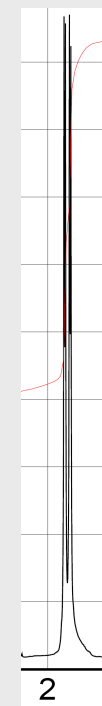
Inspection of the three multiplets shows the following Hz values:



H<sub>a</sub>  
 2150.34  
 2143.45  
 2136.39  
 2134.75  
 2129.50  
 2127.86  
 2120.97  
 2114.08



H<sub>b</sub>  
 1767.89  
 1766.25  
 1764.61  
 1762.96  
 1752.46  
 1750.82  
 1749.02  
 1747.38



H<sub>c</sub>  
 580.98  
 579.18  
 573.93  
 572.29

Start with the simplest multiplet:

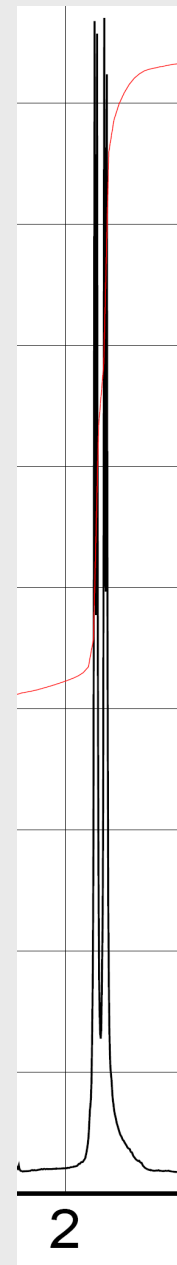
$H_c$  is an apparent doublet of doublets (dd)

Step 1:

- The distance between the first two lines always represents the smallest  $J$  value
- If the ratio of these two lines (integral) is 1:1, this  $J$  is unique; if it is 1:2, 1:3, etc. there are two or more identical smallest  $J$ s
- Label this  $J_{\text{small}}$

$$580.98 - 579.18 = 1.80 \text{ Hz}$$

$H_c$   
580.98  
579.18  
573.93  
572.29



Step 2: (most difficult step for complex multiplets)

- Find the full set of pairs within the multiplet that are separated by  $J_{\text{small}}$
- Each pair will have a reflected partner through the center of the multiplet
- For pairs where one of the lines has a relative intensity  $>1$ , that line will be part of more than one pair

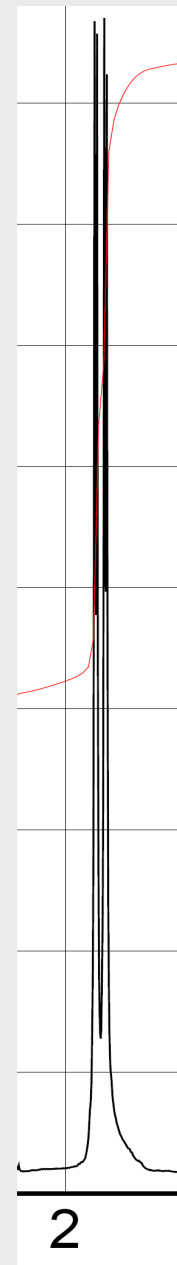
$$580.98 - 579.18 = 1.80 \text{ Hz}$$

$$579.18 - 573.93 = 5.25 \text{ Hz}$$

$$573.93 - 572.29 = 1.64 \text{ Hz}$$

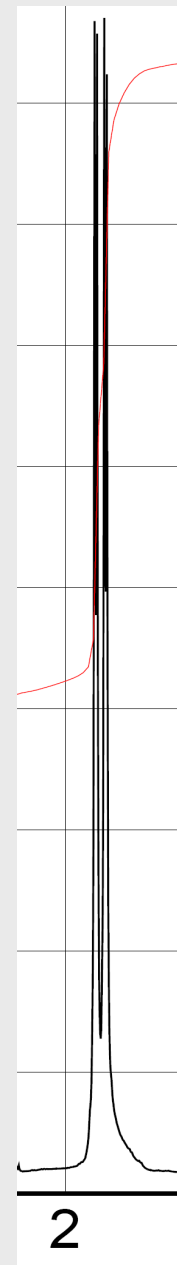
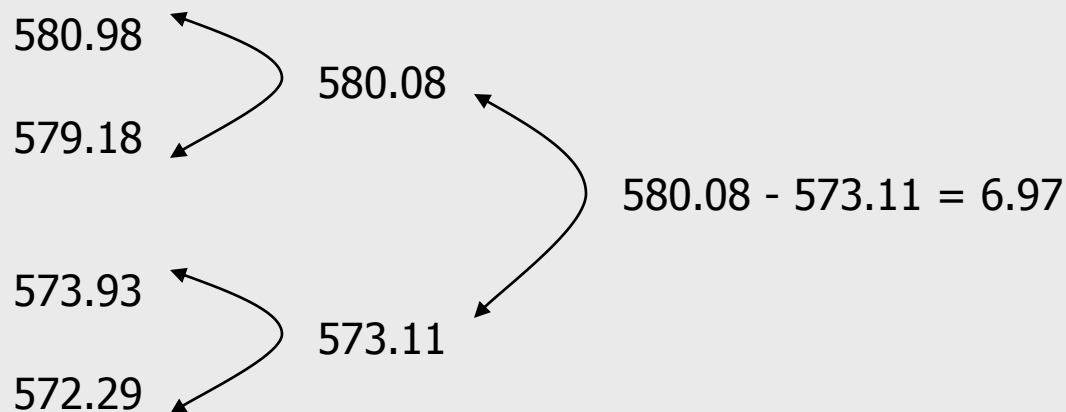
While these two may not seem equal, they must be matched if 1<sup>st</sup> order

H<sub>c</sub>  
580.98  
579.18  
573.93  
572.29



## Step 3:

- Find the centers of each of the pairs generated in step 2
- These will collectively represent a new pattern (as if the  $J_{\text{small}}$  was selectively decoupled)
- As with step 1, the spacing between the first two lines of this multiplet represent the next smallest  $J$
- Label this  $J$  as med-small, etc. as necessary



Step 4:

- Find the midpoint(s) of this new pair(s), and repeat step 3

Step 5:

- Repeat as necessary until all  $J$ -values have been found
- Remember, it must be internally consistent and all the  $J$  values must add up to the difference between the outer peaks of the multiplet.

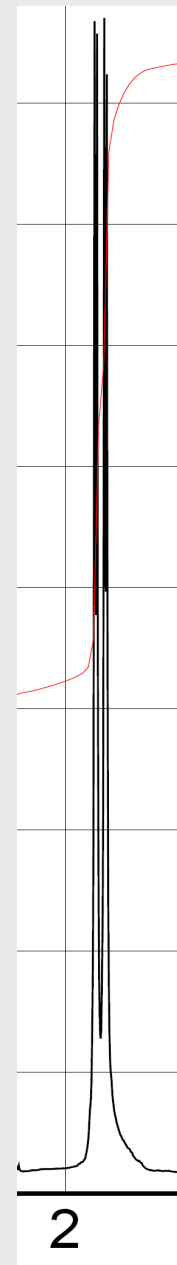
We check:

The two  $J$ s we determined are 1.80 (1.64) and 6.97

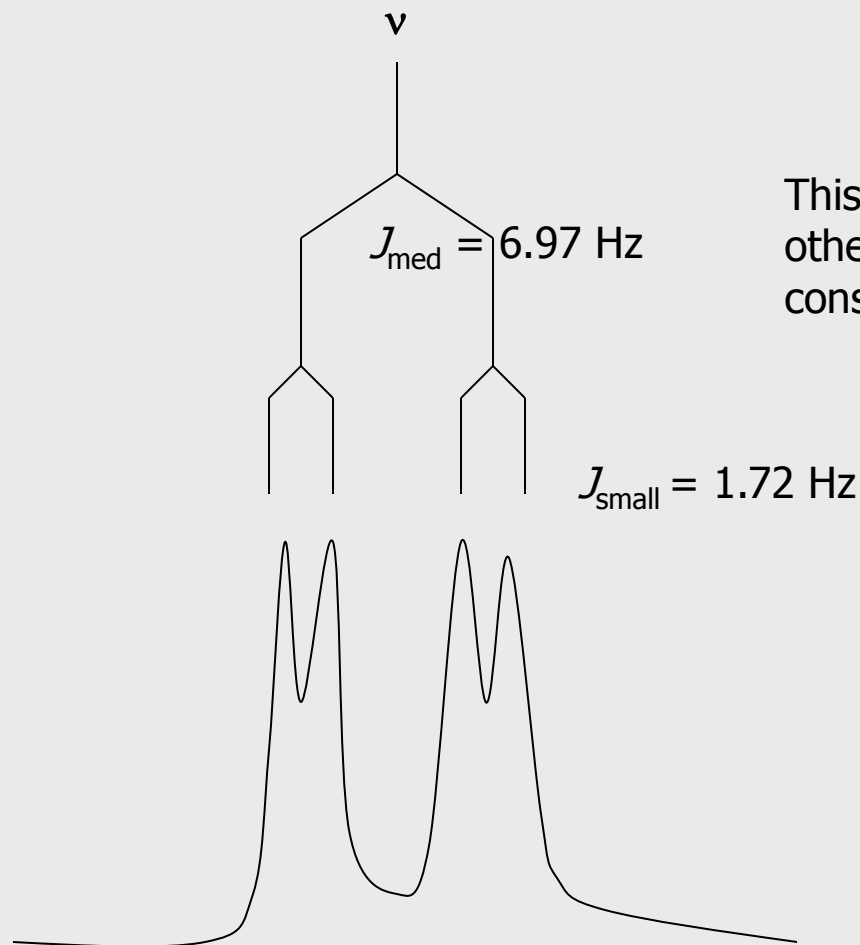
$$(1.80+1.64)/2 + 6.97 = 8.69$$

The difference between the outermost peaks of the multiplet:

$$580.98 - 572.29 = 8.69$$



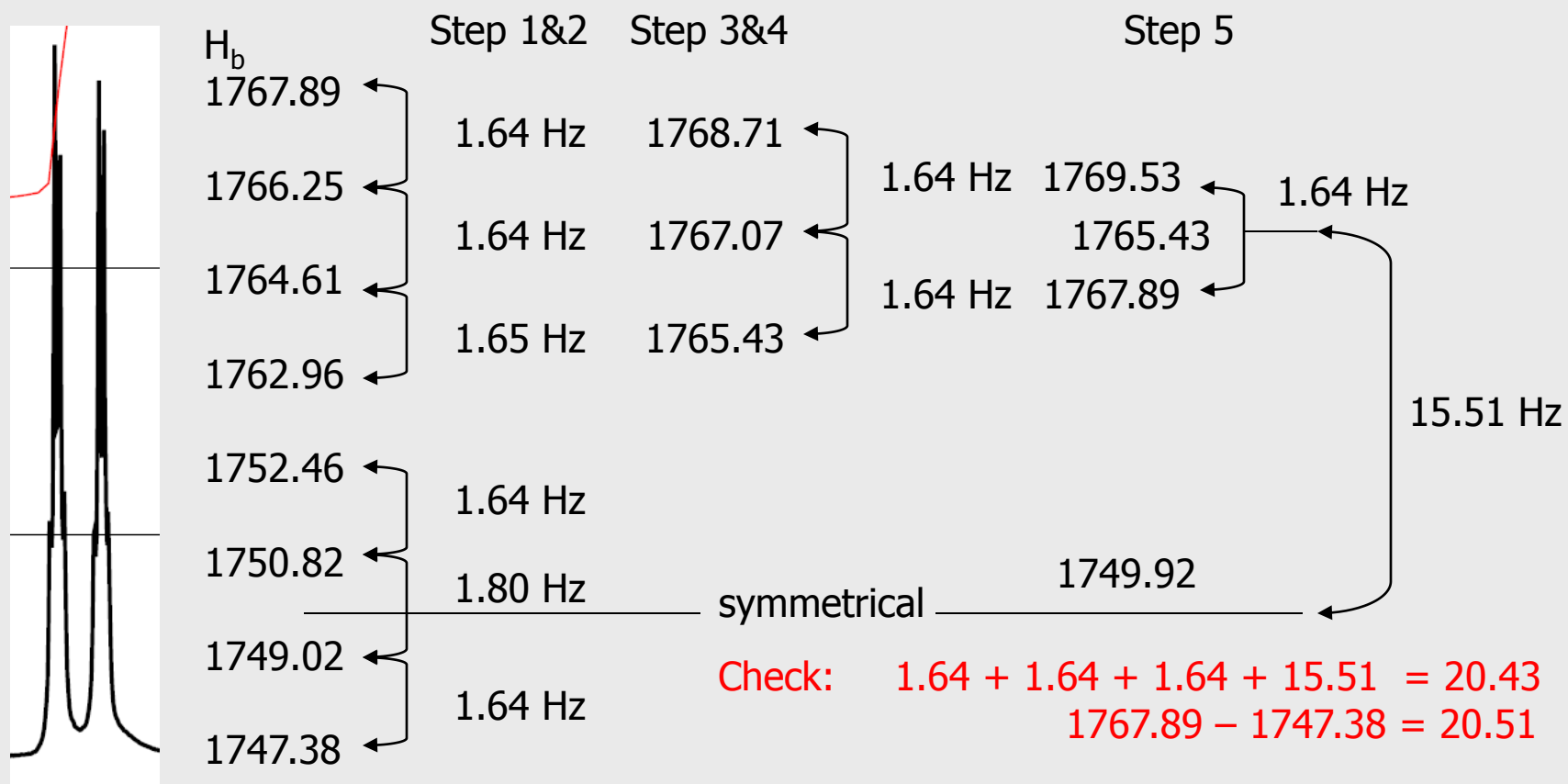
This effectively generates the tree-diagram discussed in the text:



This proton is coupled to two other protons, with coupling constants of 1.72 and 6.97

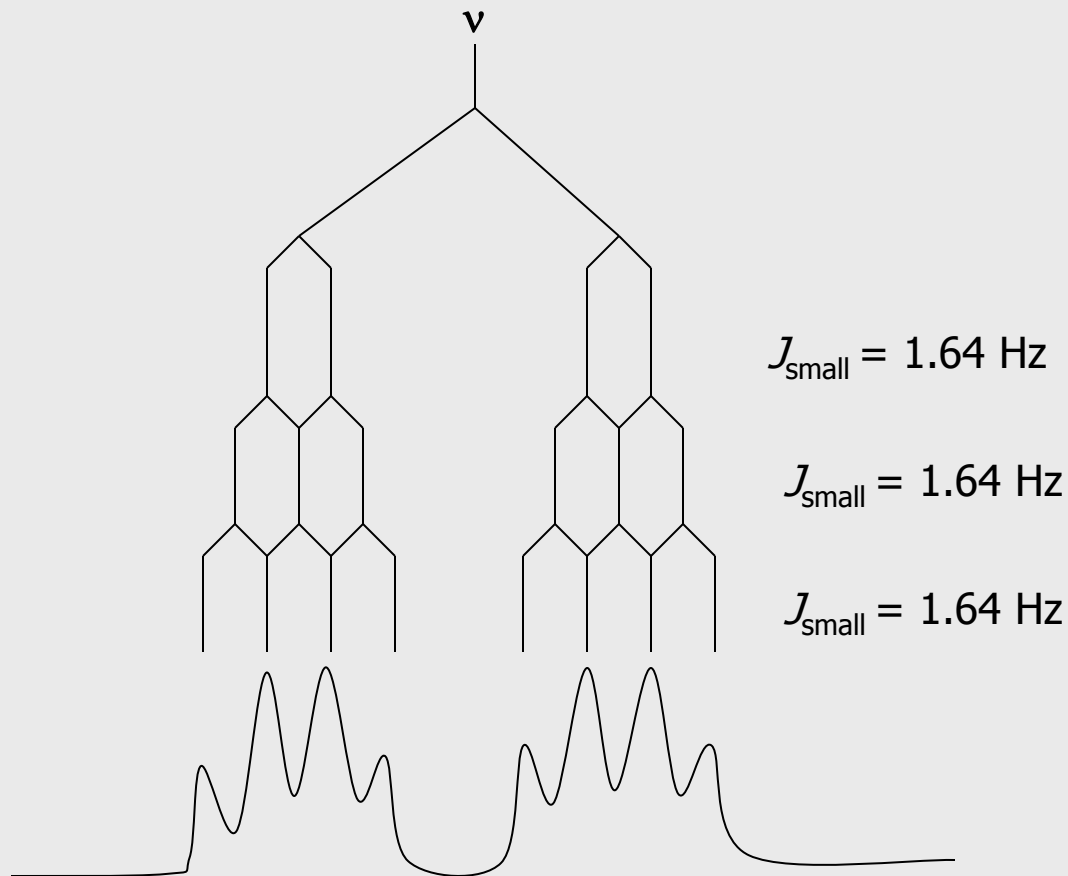
If we repeat the analysis with the next most complex multiplet, we now know to look for  $J$ -values of 1.72 and 6.97

Analyzing the  $H_b$  proton; apparent doublet of quartets (dq):





The tree diagram for  $H_b$ :

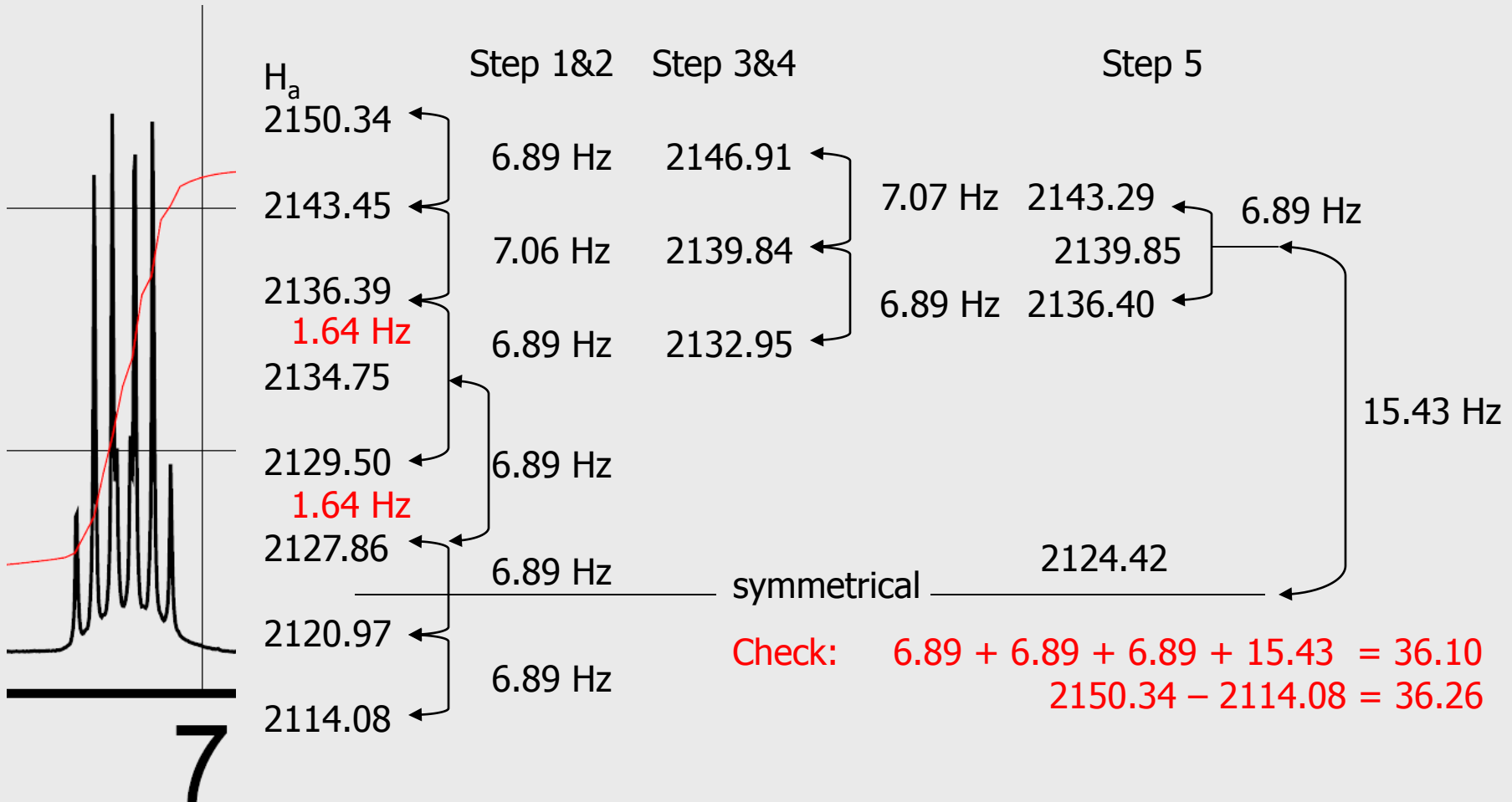


We see three generational iterations of the 1.64 similar to  $\sim 1.7$  as found for  $H_c$

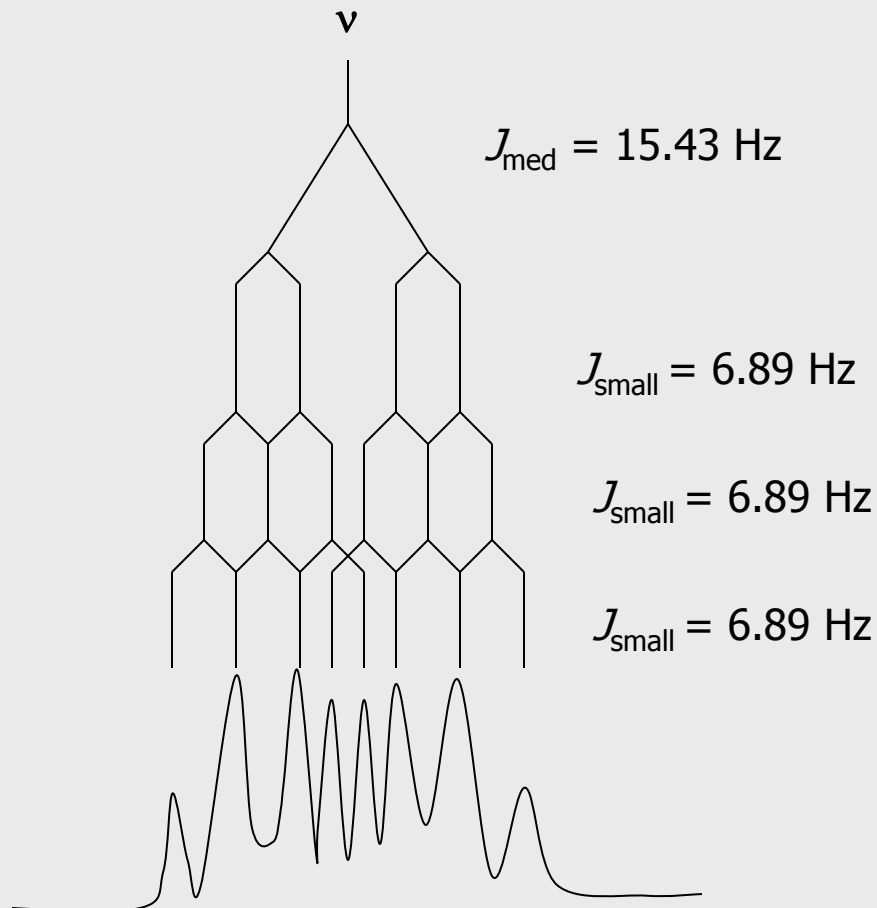
We also see a new constant of 15.51

Lastly, repeat the process for H<sub>a</sub>; looking for 1.64, 15.51 or 6.97:

Analyzing the H<sub>a</sub> proton; apparent doublet of quartets (dq):



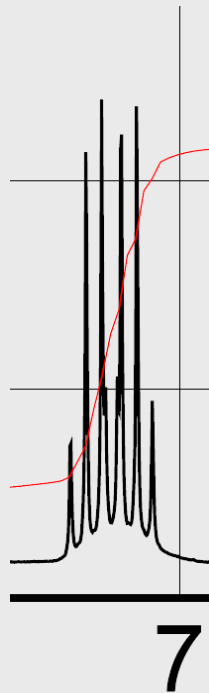
The tree diagram for  $H_a$ :



We see three generational iterations of the 6.89 similar to  $H_c$

We also see a new constant of a similar constant to 15.51, at 15.43

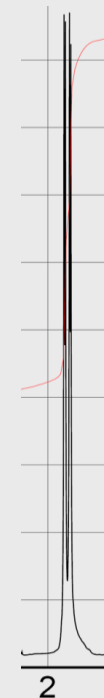
From analysis of  $J$ -values we can finish the analysis:



$H_a$  has coupling constants of 15.51 and 6.89



$H_b$  has coupling constants of 1.64 and 15.51



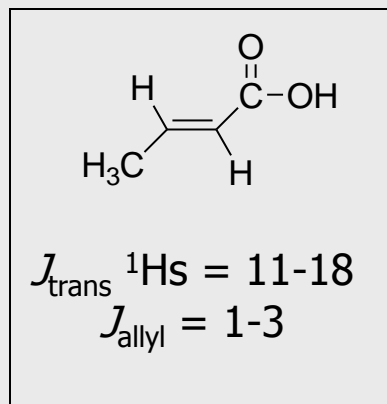
$H_c$  has coupling constants of 1.72 and 6.97

Conclusion:  $H_a$  is coupled to  $H_b$  and  $H_c$   
 $H_b$  is coupled to  $H_a$  and  $H_c$   
 $H_c$  is coupled to  $H_b$  and  $H_a$   
 Wow.

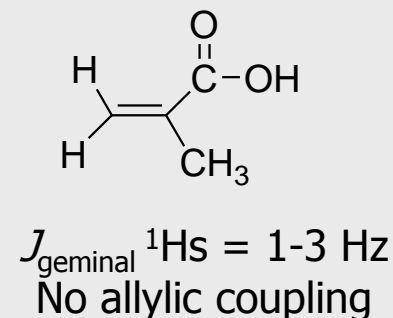
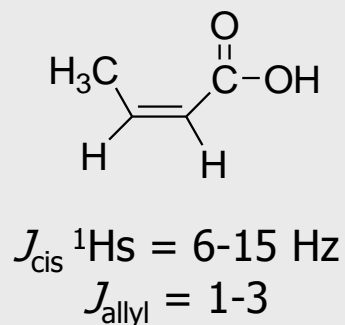
## Conclusion:

- On such a small system, the conclusion that all three of these proton families are coupled to one another is trivial; on more complex systems, this is a powerful tool to determine the position and relationship of protons on chains or rings
- In this system, it helps us deduce which isomer we are observing by analysis of the magnitude of the coupling constants that were generated

For each isomer, hypothesize as to what  $J$ s would be observed:



$$J_{\text{trans}} = 15.5$$



Analysis of coupling constants in first-order spectra

Another Method:

1. From our adapted method:

Hoye, T. R.; Hanson, P. R. Vyvyan, J. R. *J. Org. Chem.* **1994**, *59*, 4096-4103

There is a second method for determining coupling constants – *graphical analysis*

2. For first-order spectra, there are a finite number of combinations of an observed  $^1\text{H}$  with a maximum number of interactions

3. Theoretically, the maximum  $^3J$  interactions would be nine:

4. In synthetically interesting systems (middle of chains, rings, etc.) it is typically 2-4 couplings

5. The authors of the article suggest the method of visual pattern recognition to save some of the tedium of the more analytical analysis we just covered
6. In the paper, they generated a series of tables that systematically cover the most commonly encountered spin systems
7. For each table, an example compound is used to show where such a spin pattern would be observed
8. It is suggested that you go through the paper, in conjunction with your text (as a reference for representative J-values) to see how each of the tables apply to the example the authors used

Table 1. dd's

entry	Multiplet Appearance	$J_z$ $J_{13}$	$J_y$ $J_{12}$	$\Sigma$ $J$ 's	Special Relationships
a		12	4	16	
<b>b</b>		8	4	12	
c		6	4	10	
d		5	4	9	
<b>e</b>		4	4	8	$J_{13} = J_{12}$
f		3	4	7	
g		2	4	6	
h		1	4	5	
i		0	4	4	

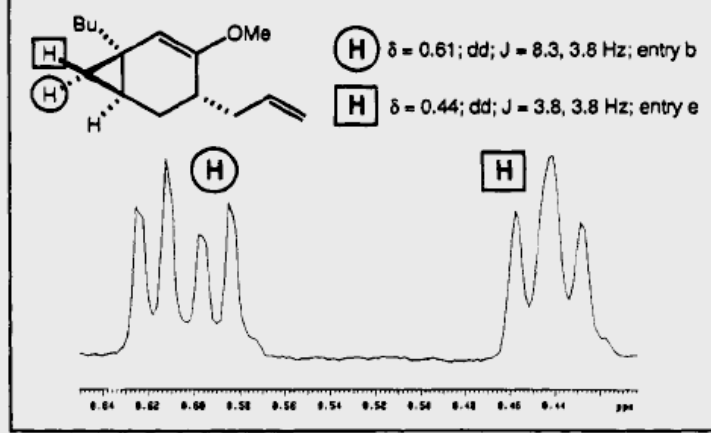
Example:

- In each table, one coupling constant is varied ( $J_z$ ) while all others are held constant

- As a consequence for any table you see a symmetrical distribution of the multiplet which converge as  $J_z$  approaches zero at the bottom of each table

- 1Hs that are exemplified are highlighted by a circle or square

- Note, as we have discussed the  $\Sigma J$ s is equal to the distance between the outermost peaks in a multiplet (Hz scale below each graphical analysis)

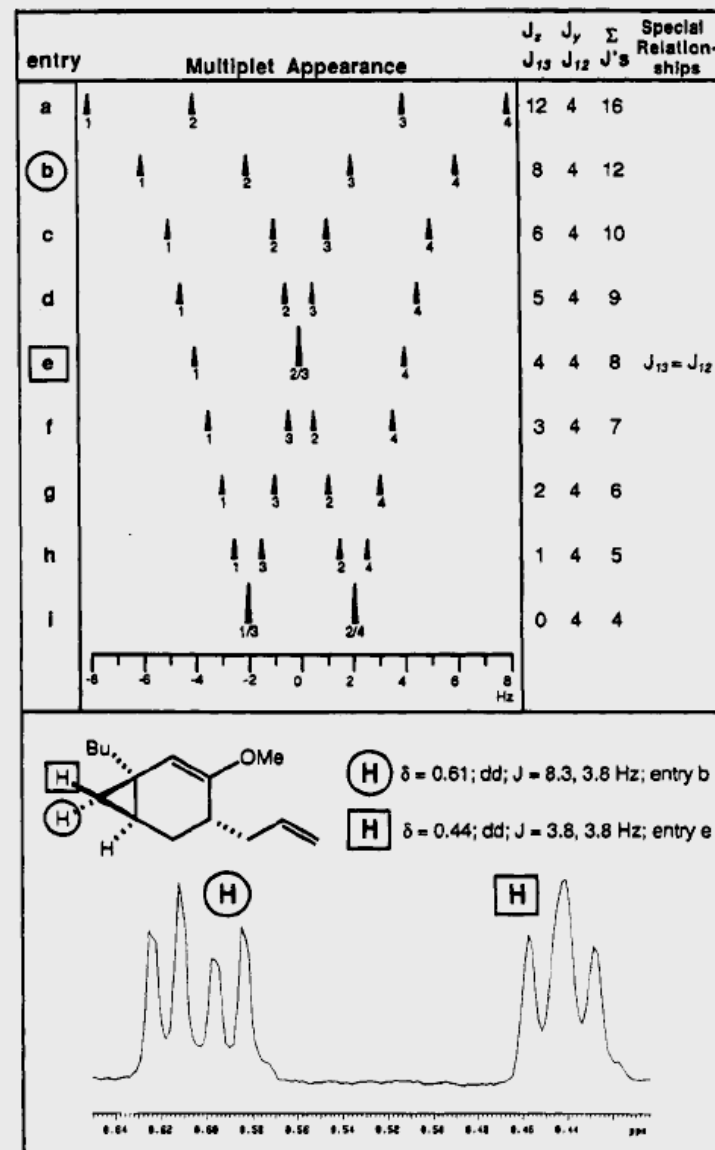




Example:

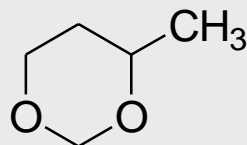
- It is important to note, that as additional coupling decreases, or certain couplings become equal, the patterns simplify to what we recognize from the  $n+1$  rule
- Therefore, it should start to be clear that the  $n+1$  rule is a highly coincidental case where all possible couplings ( $^3J$ s) become equal
- In other words, the  $n+1$  rule is the exception, and the first order relationships we have just discussed are the rule

Table 1. dd's



## Advanced NMR Homework I:

- Download and read the paper!
- Use the analytical analysis to determine the coupling constants and assignments for text problem 5, pg. 279 and problem 20, pg. 295.
- Use any method (analytical or graphical) you choose to determine the proper structures and make the proton assignments for text problems 18 and 19.
- Download and make the proton assignments for the following compound:



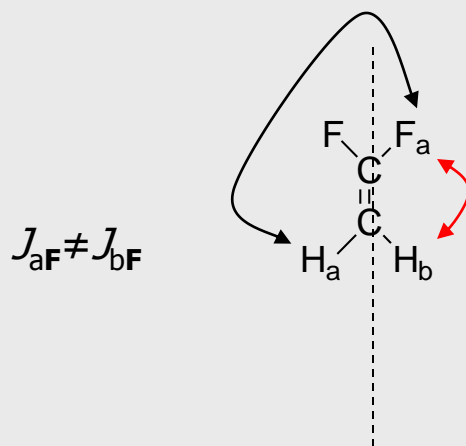
Deduce the conformation of the ring based on your analysis.

## Magnetic Equivalence (Revisited)

Remember the following example:

## 1,1-difluoroethene

- The two protons are chemically equivalent
- The two protons are not magnetically equivalent as they each have a different coupling constant to F (and respectively  $F_a$ )

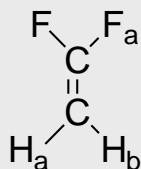


The confusion arises from the fact that although the two protons are not (by definition) magnetically equivalent, any difference in coupling constant to F and  $F_a$  respectively would be degenerate in energy

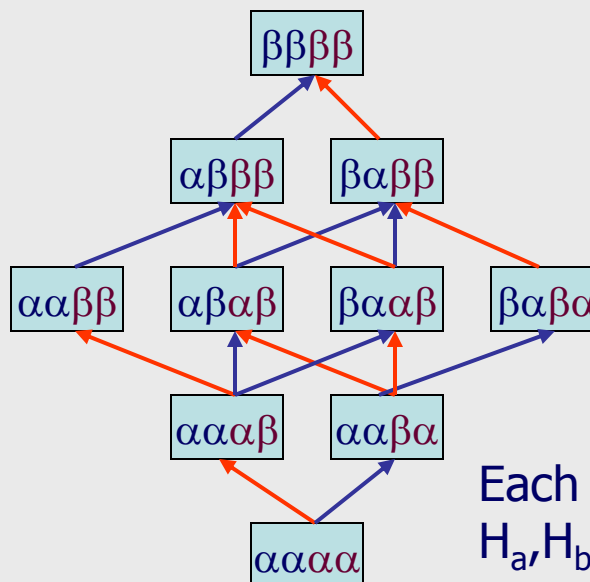
## Magnetic Equivalence (Revisited)

Looking at the various spin states, you can see why there are spectral consequences for magnetic non-equivalence:

Let's use  $\alpha$  to show spin  $+1/2$  and  $\beta$  to show spin  $-1/2$



$J_{\text{HF-trans}} = 45 \text{ Hz}$ ,  $J_{\text{HF-cis}} = 18 \text{ Hz}$   
 (and yes,  $J_{\text{H}_a\text{-F}} = J_{\text{H}_b\text{-F}}$  and  $J_{\text{H}_a\text{-F}_a} = J_{\text{H}_b\text{-F}_a}$  !)



Each box:  
 $H_a, H_b, F, F_a$  spin states

## Second-Order Spectra

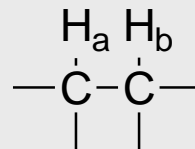
1. Spectra that can be analyzed and interpreted by the  $n+1$  rule or the analysis we just covered are first-order spectra
2. Second order spectra are those that require advanced analysis due to the effects of:
  - Magnetic non-equivalence
  - The difference in chemical shift ( $\nu$ , in Hz) between the two protons that are coupled is similar to the coupling constant ( $J$ )
3. We will consider  $\Delta\nu/J$ :
  - For  $\Delta\nu/J > 10$ , the pattern becomes first order and we say the two are weakly coupled
  - For  $\Delta\nu/J < 10$ , the pattern becomes second-order and we say the two protons are strongly coupled

## Second-Order Spectra – Some nomenclature

1. There are general patterns for the finite number of possibilities for groups of coupled  $^1\text{H}$ s
2. Nuclei that are engaged in mutual coupling constitute a *spin system*
3. Each chemically distinct proton is assigned a letter, A,B,C...
  - If these protons are chemically and magnetically equivalent, they are subscripted like a chemical formula:  $A_2$ ,  $B_2$ , etc.
  - If these protons are chemically equivalent, but not magnetically they are designated as  $AA'$ ,  $BB'$ , etc.
4. If a pair protons are very different in chemical shift, they are assigned letters far apart in the alphabet – X, Y, Z
5. If three sets of protons are involved, with widely spaced chemical shift, an intermediate letter is used, M, N, etc.

Second-Order Spectra:

A2, AB and AX spin systems



Starting with a very simple spin system – two vicinal protons,  $J = 7$  Hz

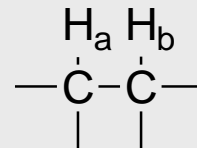
If  $\Delta\nu/J$  is large, a first order spectrum results – and we say the spin system is "AX" and weakly coupled (relative to chemical shift)

We see the expected first order spectrum – two doublets



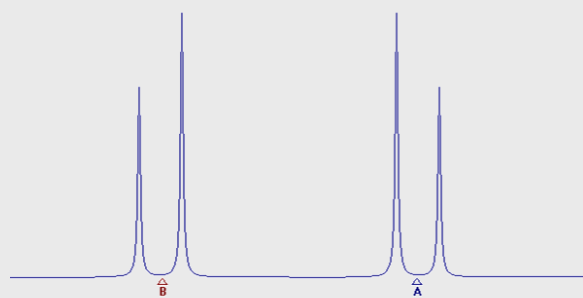
Second-Order Spectra:

$A_2$ , AB and AX spin systems

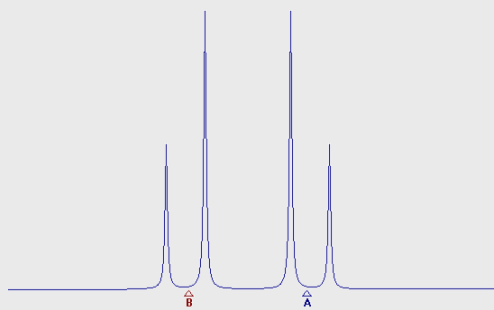


As  $\Delta\nu/J$  becomes smaller, second order effects come into play, the energy levels of coupling overlap with those of chemical shift – and we say the spin system is “AB” and becoming strongly coupled

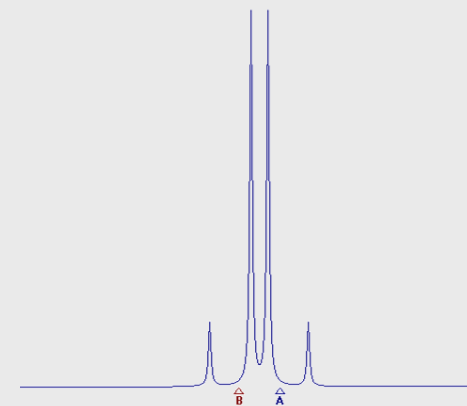
We see the progression, keeping  $J = 7$  Hz



$$\Delta\nu/J = 6$$



$$\Delta\nu/J = 3$$

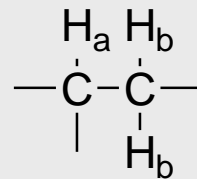


$$\Delta\nu/J = 1$$

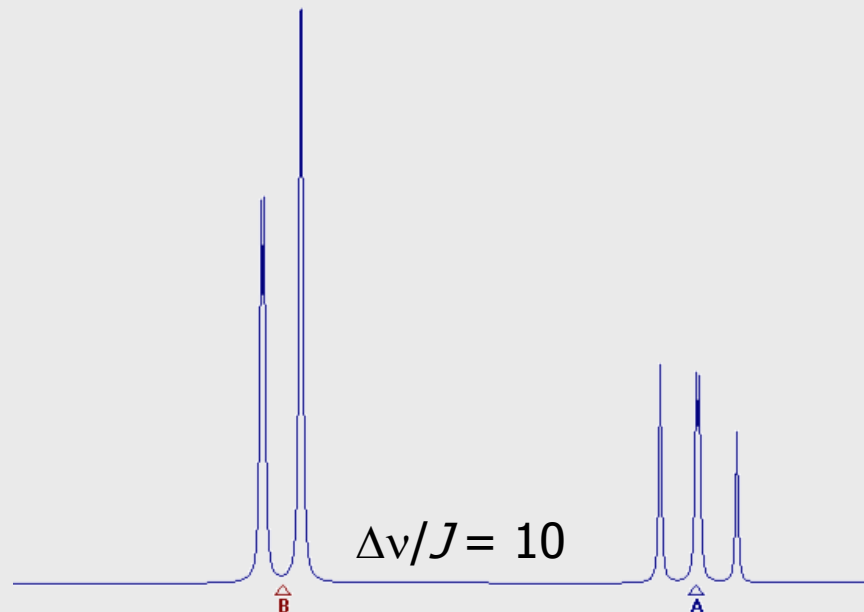


Second-Order Spectra:

$AX_2$ ,  $AB_2$  spin systems

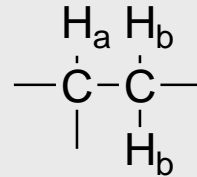


When  $\Delta\nu/J$  is large, we see the first-order spectrum that we would expect – a doublet and triplet:

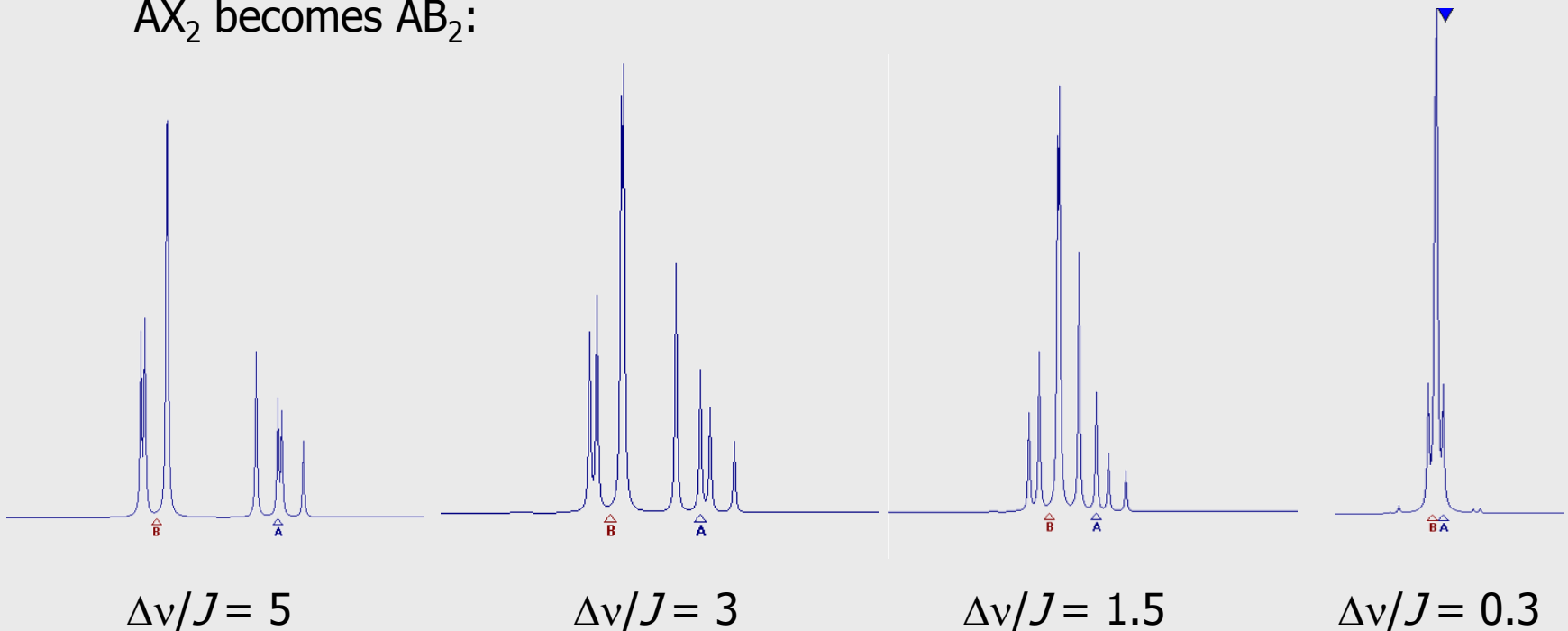


Second-Order Spectra:

$AX_2$ ,  $AB_2$  spin systems

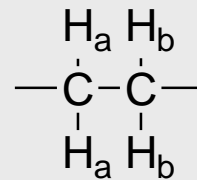


Again we see the progression into second-order behavior as  $\Delta\nu/J$  is decreased;  
 $AX_2$  becomes  $AB_2$ :

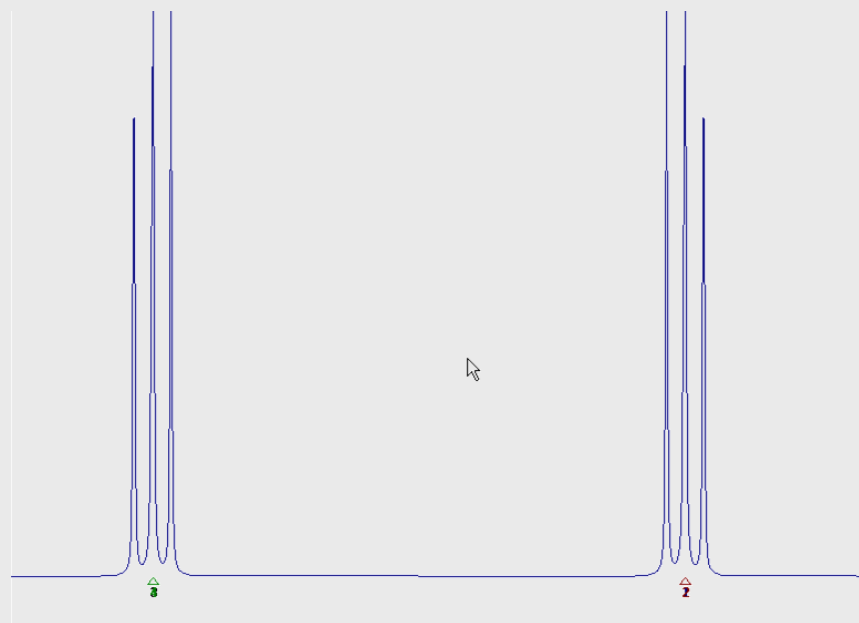


Second-Order Spectra:

$A_2X_2$ ,  $A_2B_2$  spin systems



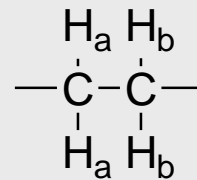
When  $\Delta\nu/J$  is large, we see the first-order spectrum that we would expect – a pair of triplets:



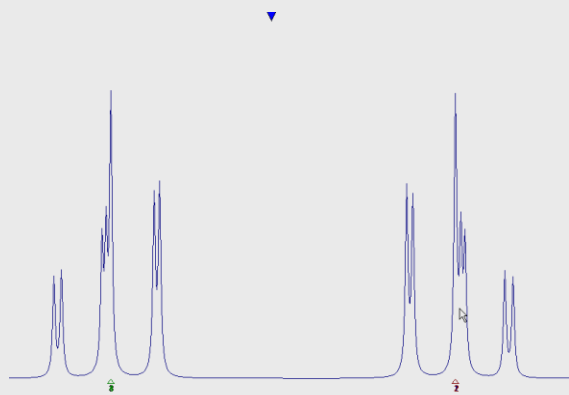
$$\Delta\nu/J = 10$$

Second-Order Spectra:

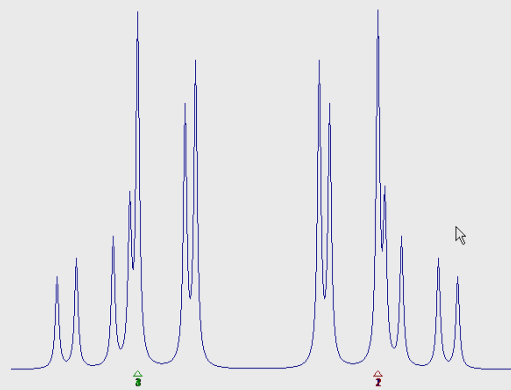
$A_2X_2$ ,  $A_2B_2$  spin systems



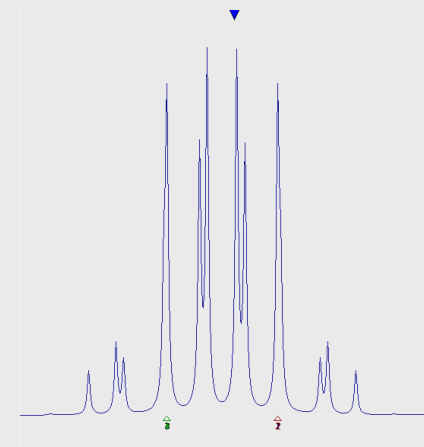
Now we will expect to see second order effects as  $\Delta\nu$  becomes smaller;  $A_2X_2$  becomes  $A_2B_2$ :



$\Delta\nu/J = 6$



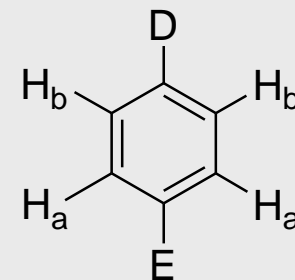
$\Delta\nu/J = 3$



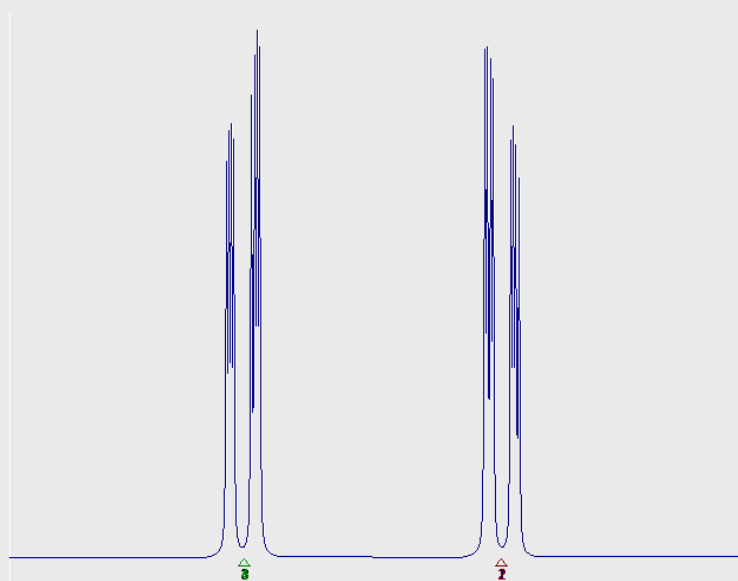
$\Delta\nu/J = 1$

Second-Order Spectra:

AA'XX', AA'BB' spin systems – here we see the consequence of magnetic non-equivalence



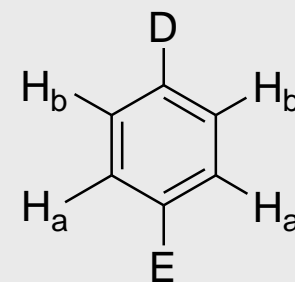
Starting out;  $J_{ortho} = 10$  Hz,  $J_{meta} = 3$  Hz,  $J_{para} = 0$  Hz: the spectrum looks deceptively like two doublets



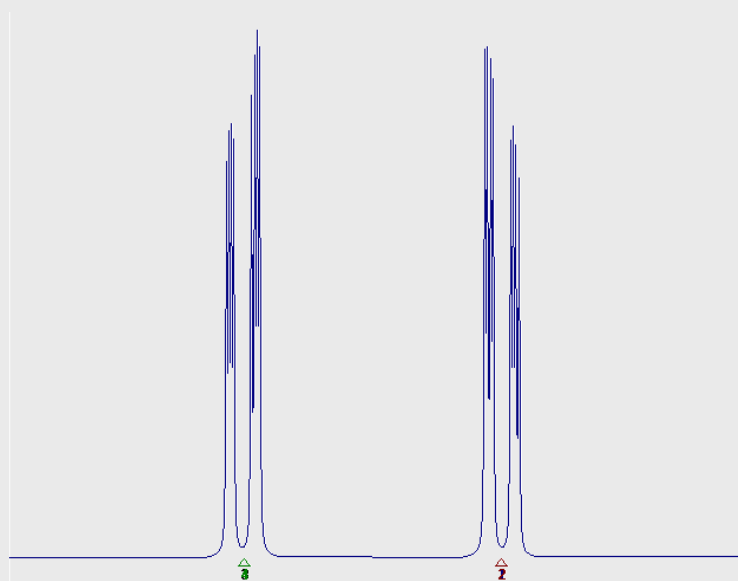
$\Delta\nu/J = 10$ , when D and E are very different electronegatively

Second-Order Spectra:

AA'XX', AA'BB' spin systems – here we see the consequence of magnetic non-equivalence



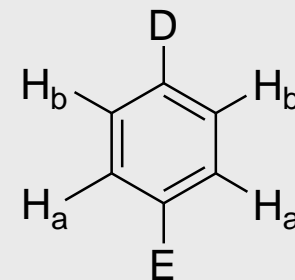
Starting out;  $J_{ortho} = 10$  Hz,  $J_{meta} = 3$  Hz,  $J_{para} = 0$  Hz: the spectrum looks deceptively like two doublets



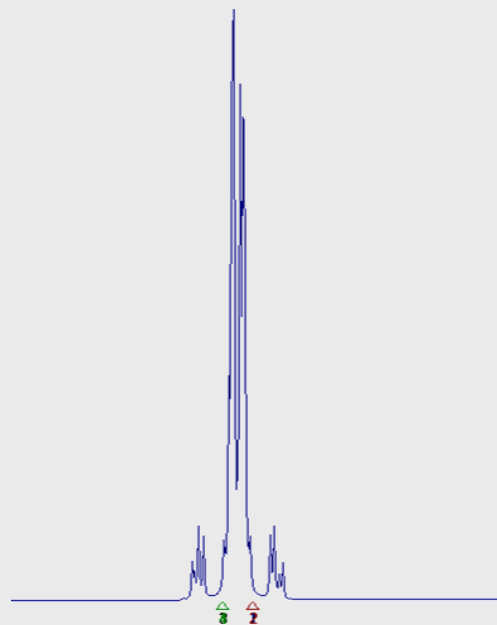
$\Delta\nu/J = 10$ , when D and E are very different electronegatively

Second-Order Spectra:

AA'XX', AA'BB' spin systems – here we see the consequence of magnetic non-equivalence



Starting out;  $J_{ortho} = 10$  Hz,  $J_{meta} = 3$  Hz,  $J_{para} = 0$  Hz: as D and E approach one another as far as electronegativity, we clearly see the 2<sup>nd</sup> order effect:



$\Delta\nu/J = 1$ , when D and E are similar electronegativity

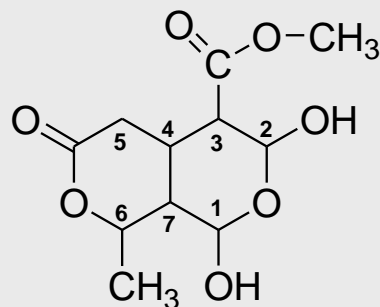
## Second-Order Spectra – How are they analyzed?

1. Second order spectra can not be analyzed by traditional methods of comparison of  $J$ -values
2. Some of the simple patterns are recognizable to an experienced NMR analyst and can be used to interpret a spectrum
3. More complex spin systems are typically analyzed by spectral simulation software – the various expected  $J$ -values and differences in chemical shift can be entered and a theoretical spectrum produced
4. This software – WINDNMR, developed by Hans Reich at the University of Wisconsin, Madison, was used to produce the spectral patterns in this lecture – it is freeware available for download
5. More sophisticated software is available, and is usually part of any NMR processing package



## Advanced Homework Assignment II:

- Based on your knowledge of first-order coupling patterns and the ability to use tables of  $J$ -values, make the stereochemical assignments for xylomollin, a secoiridoid-type monoterpene:



H	$\delta$	mult	$J$ s (Hz)
1	5.88	d	3
2	5.48	d	8
3	2.59	dd	10, 8
4	3.00	dddd	12, 10, 10, 5
5a	2.49	dd	17, 5
5b	2.54	dd	17, 12
6	4.52	dq	10, 7
7	1.75	ddd	10, 10, 3

## Advanced Homework Assignment II:

2. Text problems 16 and 17

3. In cycloheptatriene,  $J_{23}$  is 5.3 Hz; in the *bis*-trifluoromethyl derivative,  $J_{23}$  is 6.9. Explain.

