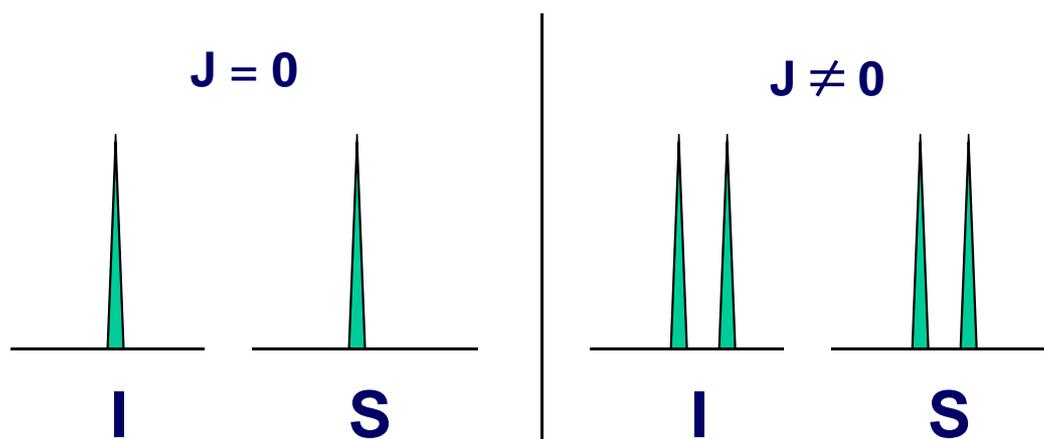


Spin-spin coupling analysis

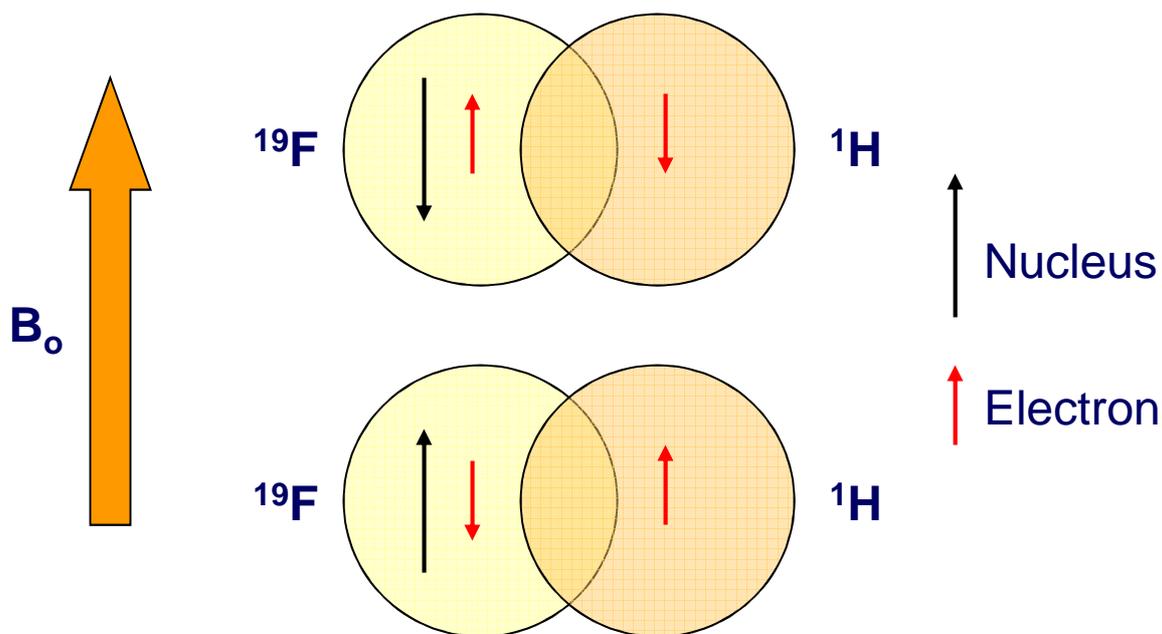
- The last parameter that we will discuss concerning the interpretation of NMR spectra is the ^1H spin-spin coupling. Couplings are perhaps the most important parameter in NMR, as they allow us to elucidate chemical structure.
- Scalar spin-spin coupling shows up as a splitting, or fine structure, in our spectrum. It will occur between two magnetically active nuclei that are connected through chemical bonds. We can see it for two atoms directly bonded, or for atoms that 'see' one another across several bonds.



- A splitting of a signal means that we have more energies involved in the transition of a certain nuclei. So why do we have more energies?
- The reason is the bonding electrons and their magnetic moments. The magnetic moment of the nuclei produces a small **polarization** (orientation...) of the bonding electron, and this is transmitted by overlapping orbitals to the other nuclei.

Spin-spin coupling (continued)

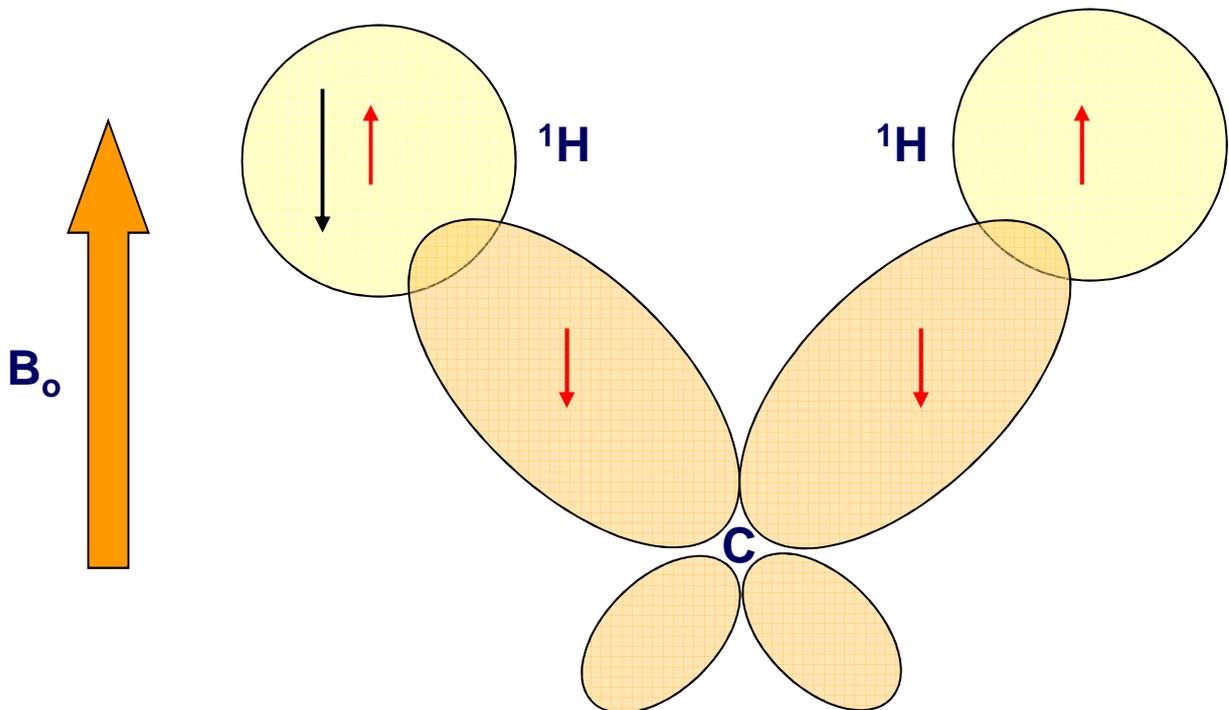
- We can explain this better by looking at HF:



- The nuclear magnetic moment of ^{19}F polarizes the F bonding electron (up), which, since we are following quantum mechanics rules, makes the other electron point down (the electron spins have to be antiparallel).
- Now, since we have different states for the ^1H electrons depending on the state of the ^{19}F nucleus, we will have slightly different energies for the ^1H nuclear magnetic moment (remember that the **1s** electron of the ^1H generates an induced field...).
- This difference in energies for the ^1H results in a splitting of the ^1H resonance line.

Spin-spin coupling (...)

- We can do a similar analysis for a CH₂ group:

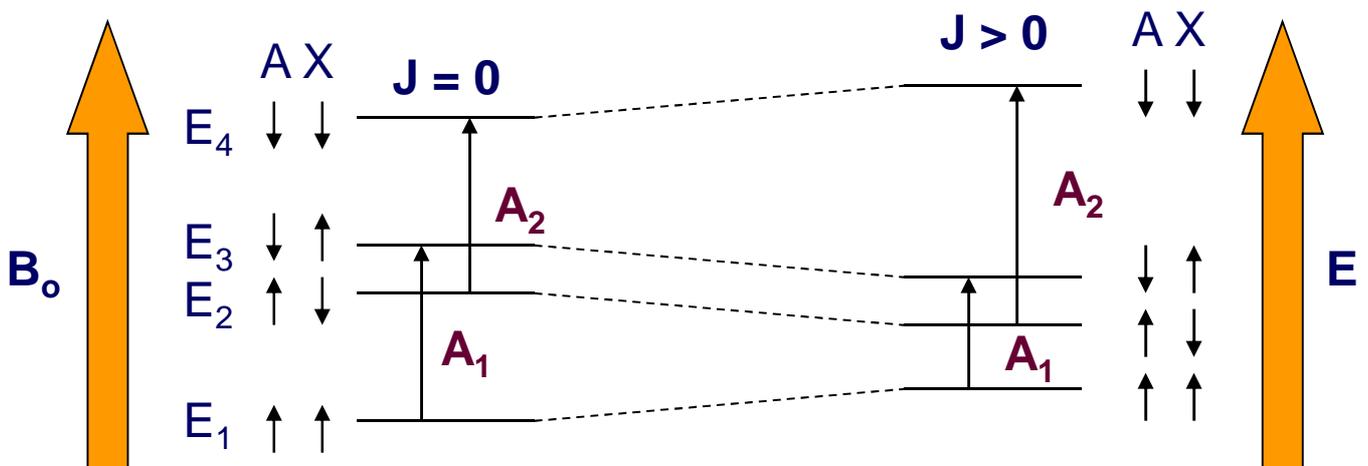


- The only difference here is that the C bonds are hybrid bonds (*sp*³), and therefore the **Pauli principle** and **Hundi's rules** predict that the two electrons will be parallel.
- Irrespective of this, the state of one of the ¹H nuclei is transmitted along the bonds to the other ¹H, and we get a splitting (a doublet in this case...). The energy of the interactions between two spins **A** and **B** can be found by the relationship:

$$E = J_{AB} * I_A * I_B$$

Spin-spin coupling (...)

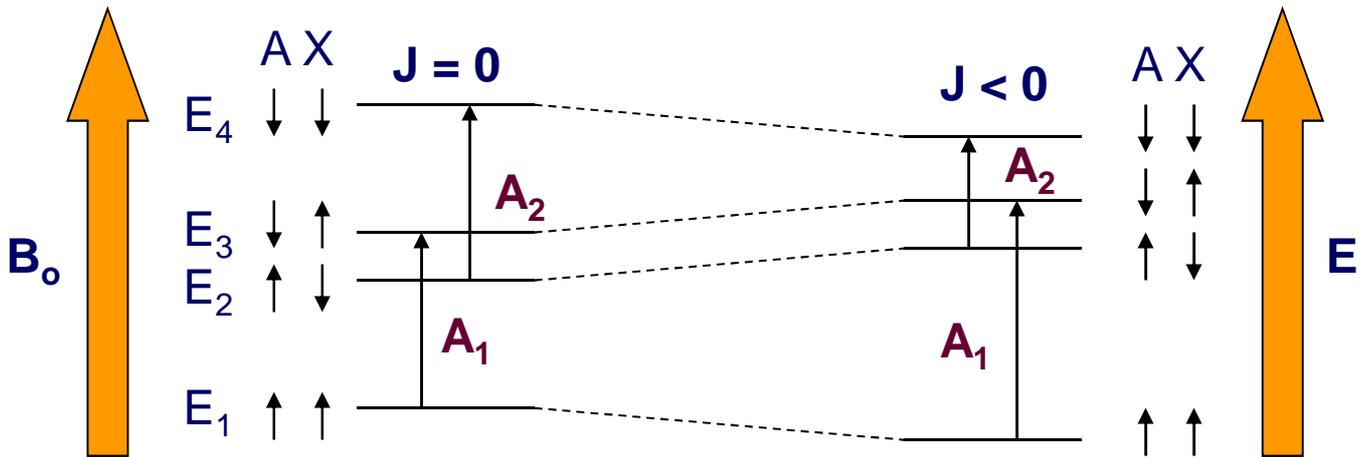
- I_A and I_B are the nuclear spin vectors, and are proportional to μ_A and μ_B , the magnetic moments of the two nuclei. J_{AB} is the **scalar coupling constant**. So we see a very important feature of couplings. It does not matter if we have a 60, a 400, or an 800 MHz magnet, **the coupling constants are always the same!!!**
- Lets do a more detailed analysis in term of the energies. Lets think a two energy level system, and the transitions for nuclei **A**. When we have no coupling ($J = 0$), the energy involved in either transition (A_1 or A_2) is equal (no spin-spin interaction).



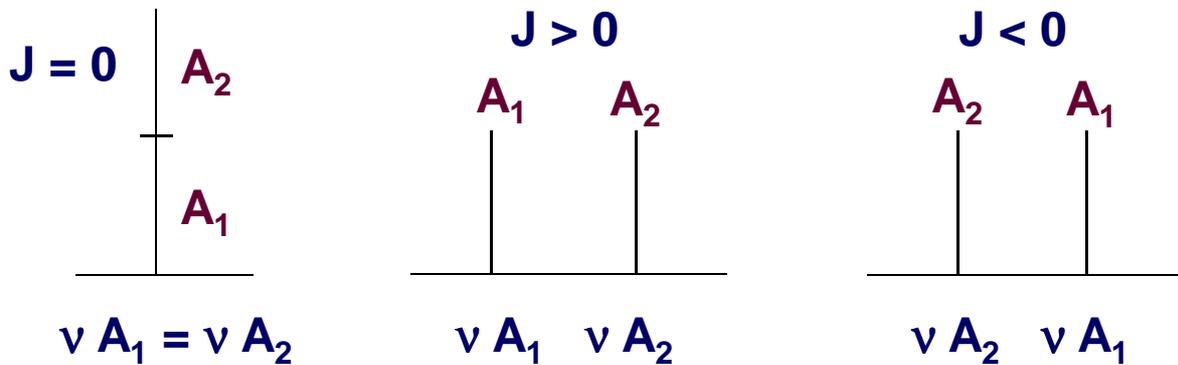
- The relative orientations of the nuclear moments does not matter. We see a single line (two with equal frequency).
- When $J > 0$, the energy levels of the spin system will be either stabilized or destabilized. Depending on the relative orientations of the nuclear moments, the energies for the A_1 and A_2 transition will change giving two different frequencies (two peaks for **A**).

Spin-spin coupling (...)

- We choose $J > 0$ as that related to antiparallel nuclear moments (lower energy). The energy diagram for $J < 0$ would then be:



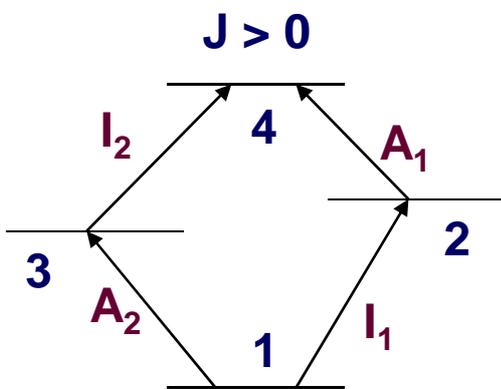
- If we look at it as a stick spectrum for either case we get:



- As mentioned before, the choice of positive or negative J is a definition. However, we see that we won't be able to tell if we have a positive or negative J , because the lines in the spectrum corresponding to the different transitions basically change places. Unless we are interested in studying the energies, this is not important for structure elucidation...

Spin-spin coupling (...)

- We can do a quantitative analysis of the energy values from to gain some more insight on the phenomenon. The base energies of the system are related to the **Larmor** frequencies, and the spin-spin interaction is J_{AX} :



$$\begin{aligned}
 E_4 &= \frac{1}{2} \nu_A + \frac{1}{2} \nu_B + \frac{1}{4} J_{AX} \\
 E_3 &= \frac{1}{2} \nu_A - \frac{1}{2} \nu_B - \frac{1}{4} J_{AX} \\
 E_2 &= -\frac{1}{2} \nu_A + \frac{1}{2} \nu_B - \frac{1}{4} J_{AX} \\
 E_1 &= -\frac{1}{2} \nu_A - \frac{1}{2} \nu_B + \frac{1}{4} J_{AX}
 \end{aligned}$$

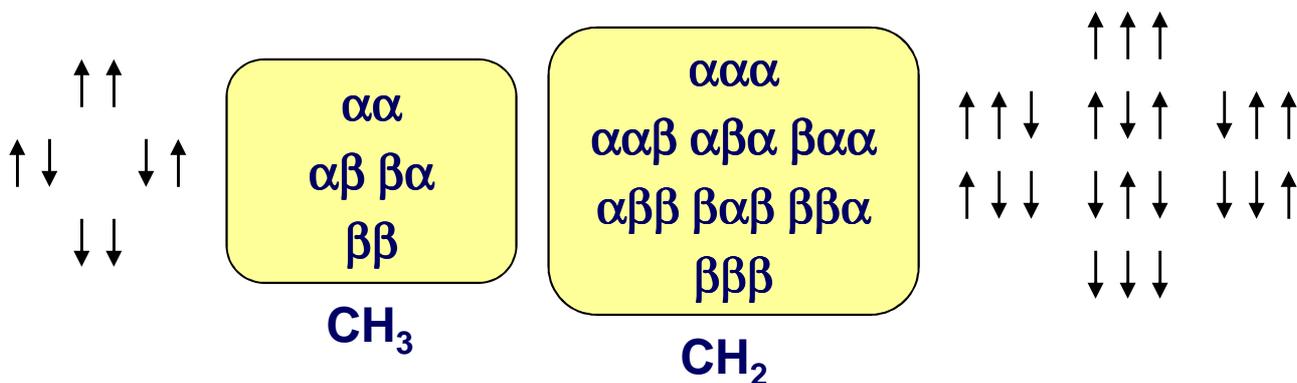
- So if we now consider the transitions that we see in the spectrum, we get:

$$\begin{aligned}
 A_1 &= E_4 - E_2 = \nu_A - \frac{1}{2} J_{AX} \\
 A_2 &= E_3 - E_1 = \nu_A + \frac{1}{2} J_{AX} \\
 I_1 &= E_2 - E_1 = \nu_B - \frac{1}{2} J_{AX} \\
 I_2 &= E_4 - E_3 = \nu_B + \frac{1}{2} J_{AX}
 \end{aligned}$$

- This explains the lines in our spectrum quantitatively...

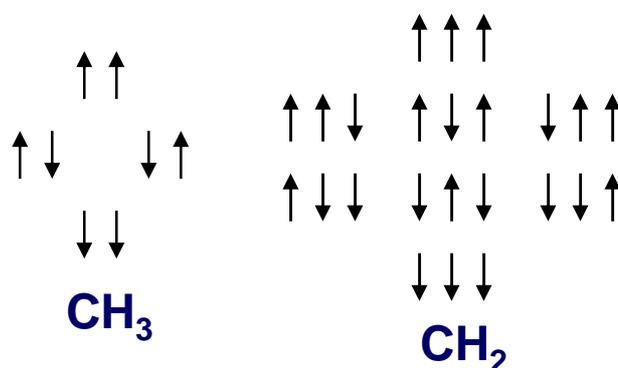
Analysis of 1st order systems

- Now we will focus on the simplest type of coupling we can have, which is one of the limits of a more complex quantum mechanical description.
- Lets say that we have ethylacetate. In this molecule, the resonance of the CH₃ from the ethyl will be ~ 1.5, while that for the CH₂ will be ~ 4.5 ppm. In most spectrometers this means that the difference in chemicals shifts, $\Delta\nu$, will be a lot bigger than the coupling constant **J**, which for this system is ~ 7 Hz. In this case, we say that we have a **first order spin system**.
- If we analyze the system in the same way we did the simple AX system, we will see that each ¹H on the CH₂ will see 4 possible states of the CH₃ ¹Hs, while each ¹H on the CH₃ will see 3 possible states of the CH₂ protons. We have to keep in mind that the two ¹Hs of the CH₂ and the three ¹Hs of the CH₃ are equivalent.
- In order to see this better, we can build a diagram that has the possible states of each ¹H type in EtOAC:

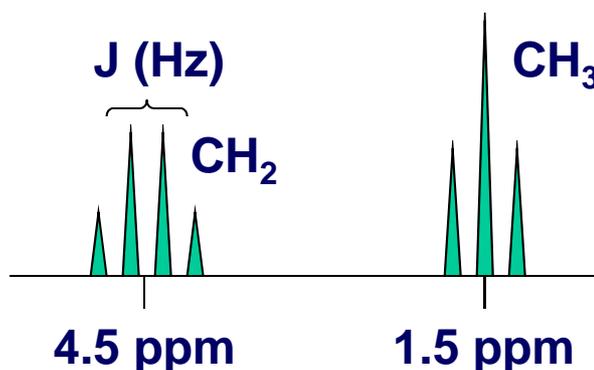


1st order systems (continued)

- If we generalize, we see that if a certain nuclei **A** is coupled to n identical nuclei **X** (of spin $1/2$), **A** will show up as $n + 1$ lines in the spectrum. Therefore, the CH₂ in EtOAc will show up as four lines, or a **quartet**. Analogously, the CH₃ in EtOAc will show up as three lines, or a **triplet**.
- The separation of the lines will be equal to the coupling constant between the two types of nuclei (CH₂'s and CH₃'s in EtOAc, approximately 7 Hz).
- If we consider the diagram of the possible states of each nuclei, we can also see what will be the intensities of the lines:

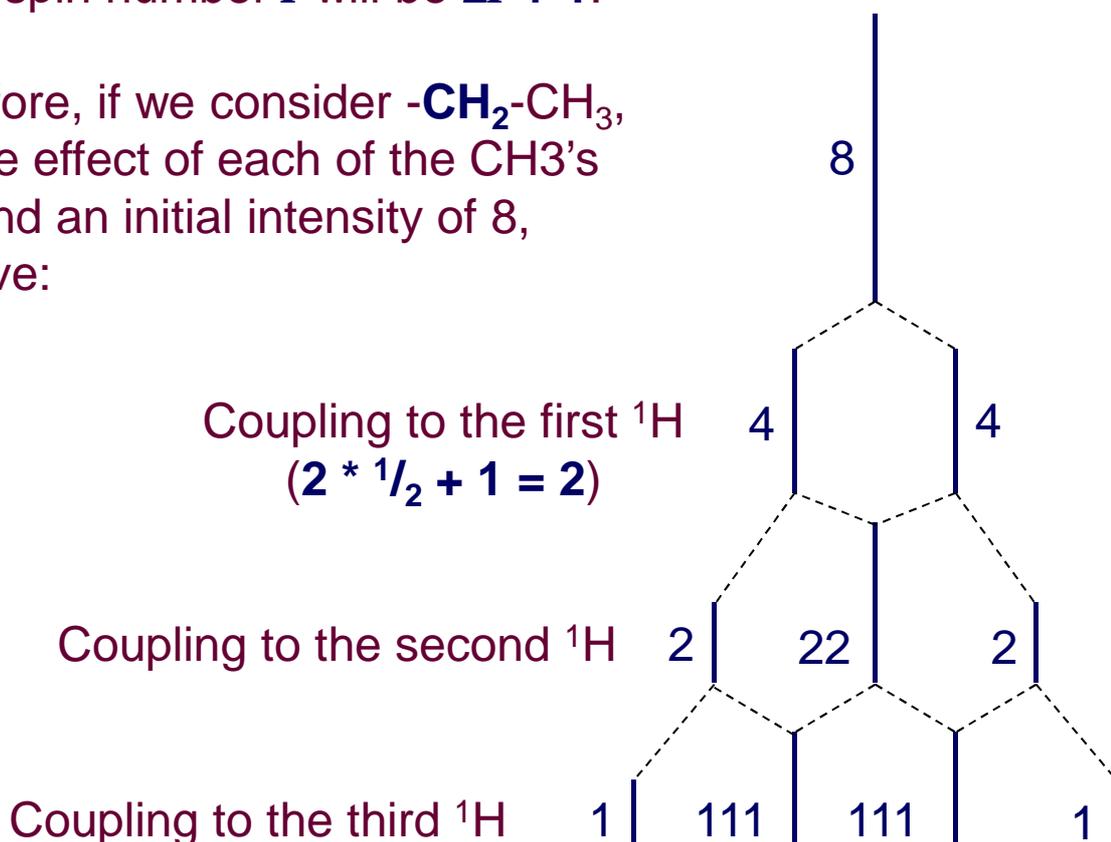


- Since we have the same probability of finding the system in any of the states, and states in the same rows have equal energy, the intensity will have a ratio **1:2:1** for the CH₃, and a ratio of **1:3:3:1** for the CH₂:



1st order systems (...)

- These rules are actually a generalization of a more general rule. The splitting of the resonance of a nuclei **A** by a nuclei **X** with spin number **I** will be **2I + 1**.
- Therefore, if we consider **-CH₂-CH₃**, and the effect of each of the CH₃'s ¹Hs, and an initial intensity of 8, we have:

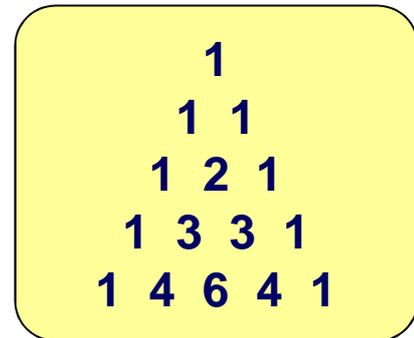


- Since the coupling to each ¹H of the CH₃ is the same, the lines will fall on top of one another.
- In general, the number of lines in these cases will be a binomial expansion, known as the **Pascal Triangle**:

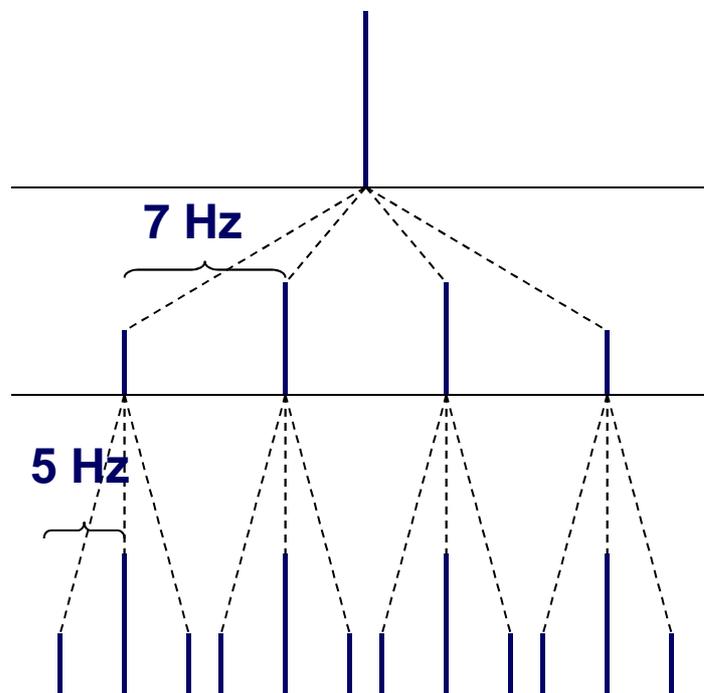
$$1 : n/1 : n(n-1)/2 : n(n-1)(n-2)/6 : \dots$$

1st order systems (...)

- Here **n** is the number of equivalent spins $1/2$ we are coupled to: The results for several **n**'s:



- In a spin system in which we have a certain nuclei coupled to more than one nuclei, all first order, the splitting will be basically an extension of what we saw before.
- Say that we have a CH (**A**) coupled to a CH₃ (**M**) with a J_{AM} of 7 Hz, and to a CH₂ (**X**) with a J_{AX} of 5 Hz. We basically go in steps. First the big coupling, which will give a quartet:



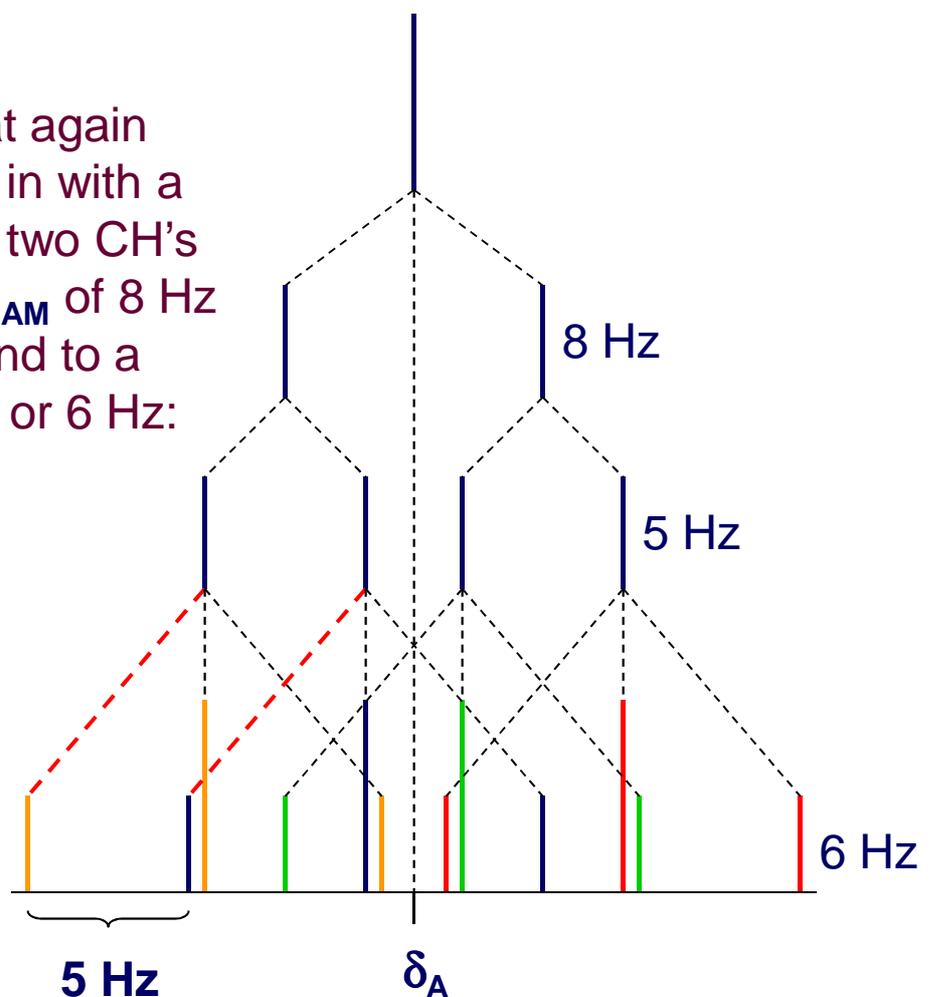
- Then the small coupling, which will split each line in the quartet into a triplet:

- This is called a **triplet of quartets** (big effect is the last...).

1st order systems (...)

- Lets finish our analysis of 1st order system with some pretty simple rules that we can use when we are actually looking at 1D ¹H spectra.

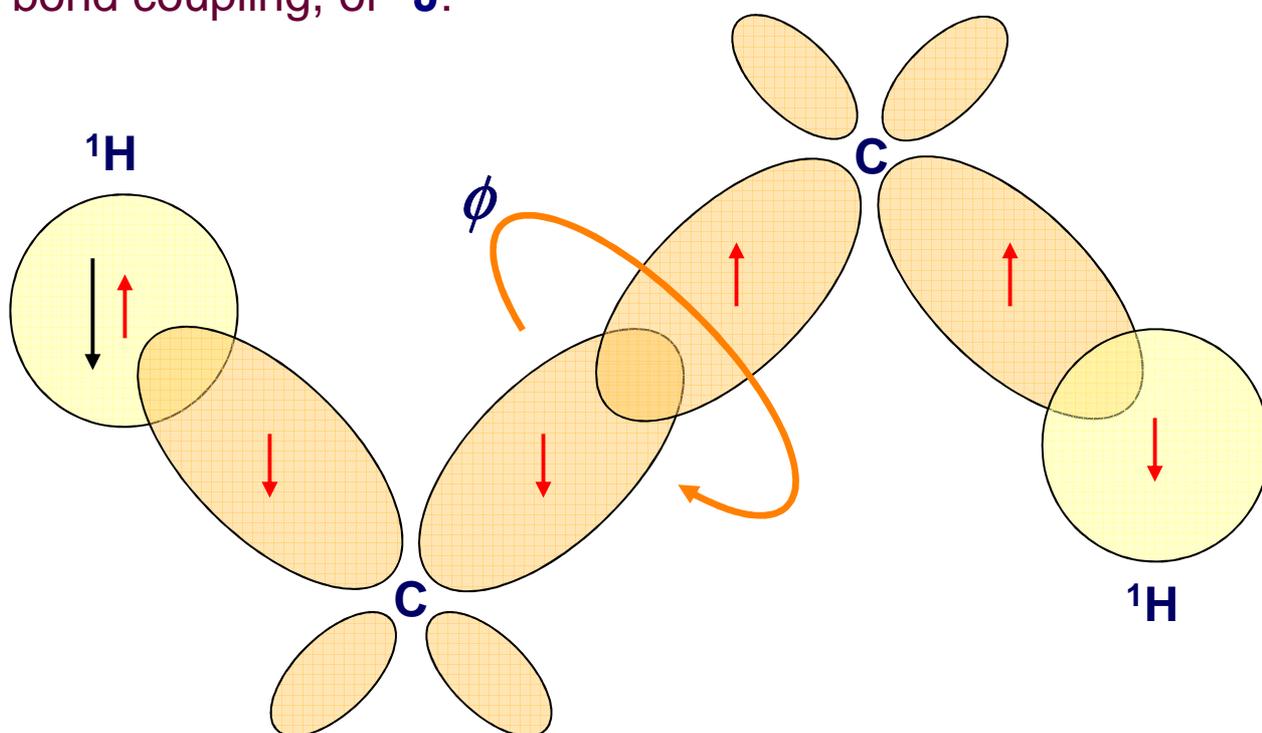
- To do that, say that again we have a system in with a CH (**A**) coupled to two CH's (**M** and **R**) with a J_{AM} of 8 Hz and J_{AR} of 5 Hz, and to a CH₂ (**X**) with a J_{AX} or 6 Hz:



- The first rule is that if we have a clear-cut first order system, the chemical shift of nuclei **A**, δ_A , is always at the center of mass of the multiplet.
- The second one is that no matter how complicated the pattern may end up being, the outermost splitting is always the smallest coupling for nuclei **A**. We can measure it without worrying about picking the wrong peaks from the pattern.

The Karplus equation

- The most common coupling constant we'll see is the three-bond coupling, or 3J :



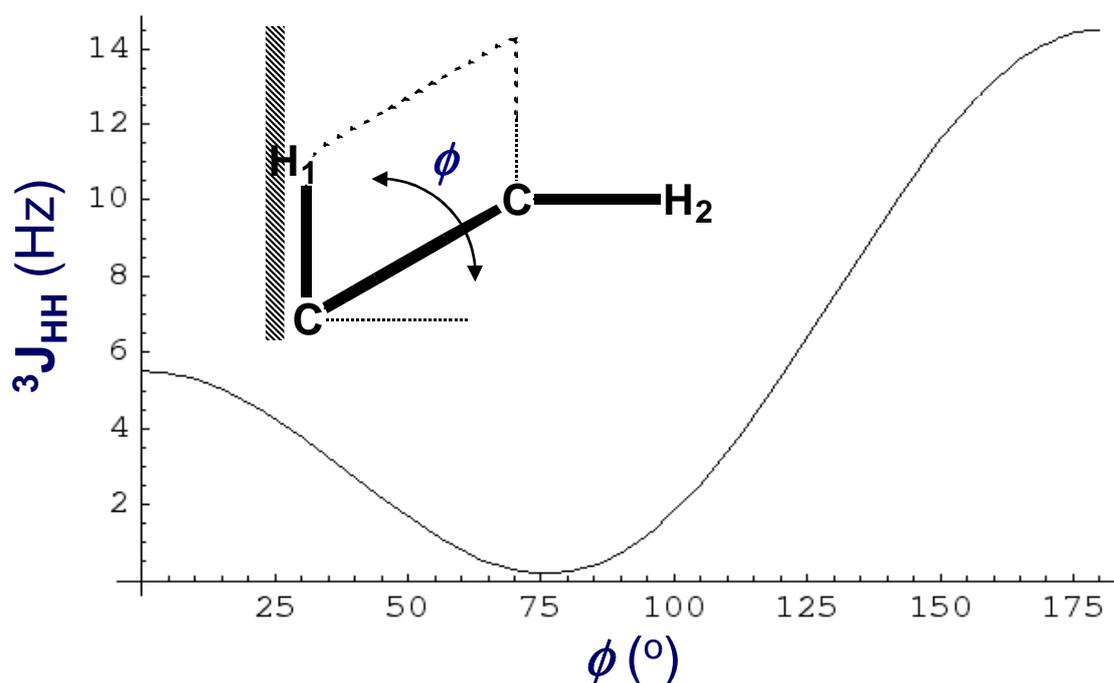
- As with the 1J or 2J , the coupling arises from the interactions between nuclei and electron spins. 1J and 3J will hold the same sign, while 2J will have opposite sign.
- However, the overlap of electron and nuclear wavefunctions in the case of 3J couplings will depend on the dihedral angle $\langle\phi\rangle$ formed between the CH vectors in the system.
- The magnitude of the 3J couplings will have a periodic variation with the torsion angle, something that was first observed by Martin Karplus in the 1950's.

The Karplus equation (...)

- The relationship can be expressed as a cosine series:

$${}^3J_{\text{HH}} = A \cdot \cos^2(\phi) + B \cdot \cos(\phi) + C$$

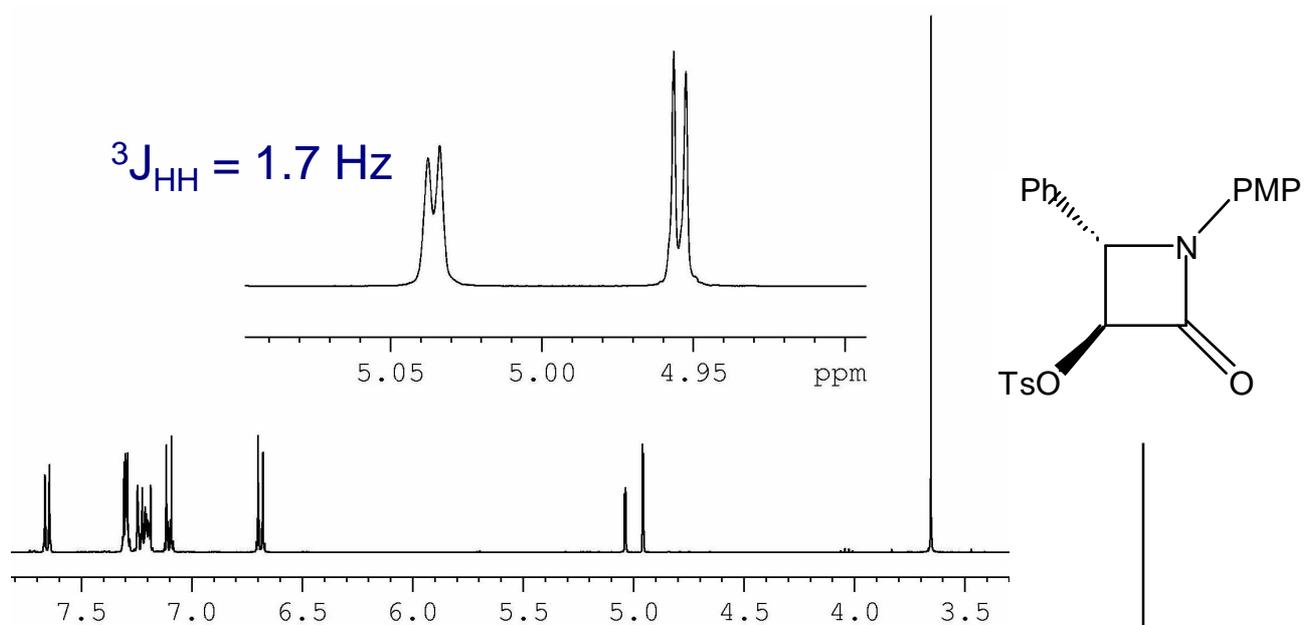
- Here **A**, **B**, and **C** are constants that depend on the topology of the bond (i.e., on the electronegativity of the substituents). Graphically, the Karplus equation looks like this:



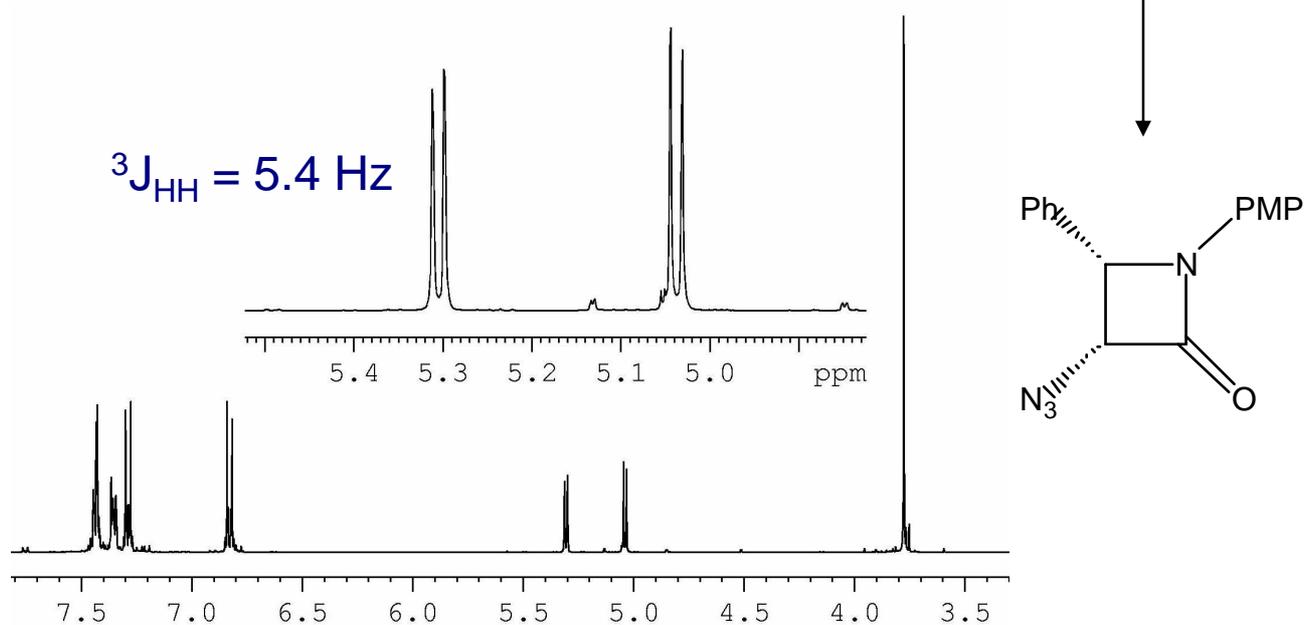
- A nice 'feature' of the Karplus equation is that we can estimate dihedral angles from 3J coupling constants. Thus, a variety of **A**, **B**, and **C** parameters have been determined for peptides, sugars, etc., etc.

The Karplus equation (...)

- As an example, consider an S_N2 inversion reaction we do in our lab. We go from a **trans** to a **cis** β -lactam.



- The $\langle \phi_{HH} \rangle$ in the **trans** is 137.3° , while in the **cis** product it is 1.9° . So, we know we have inversion...

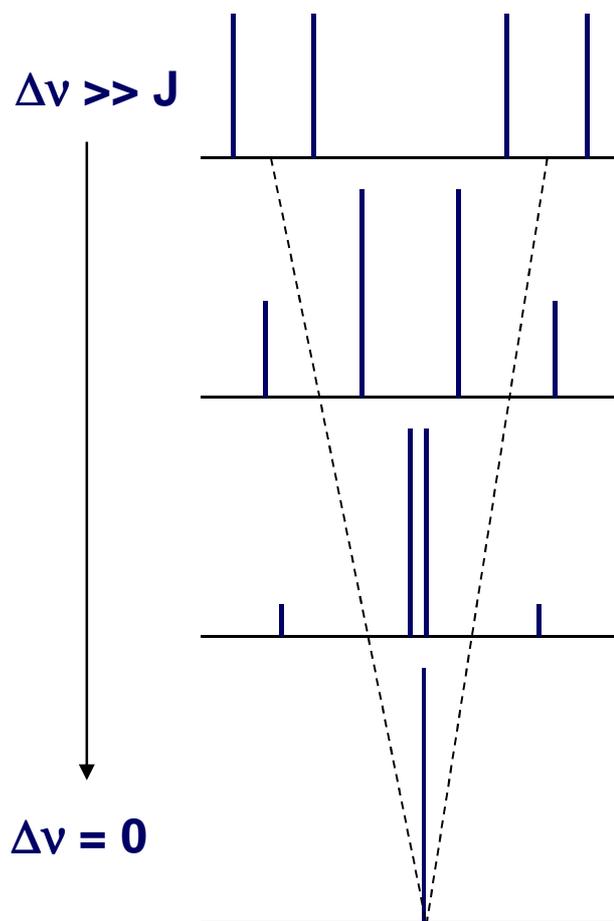


2nd order systems - The AB system

- What we have been describing so far is a spin system in which $\Delta\nu \gg J$, and as we said, we are analyzing one of the limiting cases that QM predict.
- As $\Delta\nu$ approaches J , there will be more transitions of similar energy and thus our spectrum will start showing more signals than our simple analysis predicted. Furthermore, the intensities and positions of the lines of the multiplets will be different from what we saw so far.

- Lets say that we have two coupled nuclei, **A** and **B**, and we start decreasing our B_0 . $\Delta\nu$ will get smaller with J staying the same. After a while, $\Delta\nu \sim J$. What we see is the following:

- What we did here is to start with an **AX** system (the chemical shifts of **A** and **X** are very different) and finish with an **AB** system, in which $\Delta\nu \sim J$.

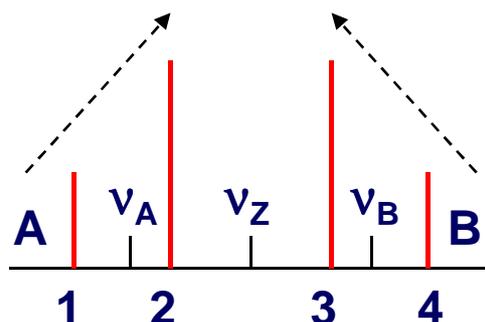


- Our system is now a second order system. We have effects that are not predicted by the simple multiplicity rules that we described earlier.

The AB system (continued)

- Thus, the analysis of an **AB** system is not as straightforward as the analysis of an **AX** system. A full analysis cannot be done without math and QM, but we can describe the results.

- A very simple way to determine if we have an **AB** system is by looking at the **roofing effect**: coupled pairs will lean towards each other, making a little roof:



- As with an **AX** system, J_{AB} is the separation between lines **1** and **2** or **3** and **4**:

$$|J_{AB}| = |f_1 - f_2| = |f_3 - f_4|$$

- Now, the chemical shifts of nuclei **A** and **B** are not at the center of the doublets. They will be at the center of mass of both lines. Being $\Delta\nu$ the $\nu_A - \nu_B$ chemical shift difference, ν_A and ν_B will be:

$$\Delta\nu^2 = |(f_1 - f_4)(f_2 - f_3)|$$

$$\nu_A = \nu_Z - \Delta\nu / 2$$

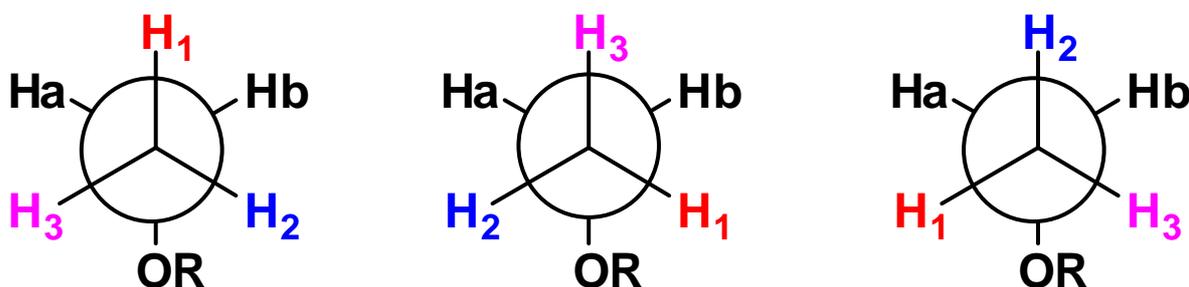
$$\nu_B = \nu_Z + \Delta\nu / 2$$

- Peak intensities can be computed similarly:

$$\frac{I_2}{I_1} = \frac{I_3}{I_4} = \frac{|f_1 - f_4|}{|f_2 - f_3|}$$

Magnetic and chemical equivalence

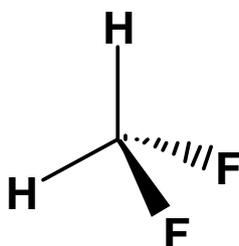
- Before we get deeper into analysis of coupling patterns, let's pay some more attention to naming conventions, as well as to some concepts regarding chemical and magnetic equivalence.
- Our first definition will be that of a **spin system**. We have a spin system when we have a group of n nuclei (with $I = 1/2$) that is characterized by no more than n frequencies (chemical shifts) ν_i and $n(n-1)/2$ couplings J_{ij} . The couplings have to be within nuclei in the spin system.
- We start by defining **magnetic equivalence** by analyzing some examples. Say that we have an ethoxy group (-O-CH₂-CH₃).
- As we saw last time, we can do a very simple first order analysis of this spin system, because we assumed that all CH₂ protons were 'equal,' and all CH₃ protons were 'equal.' Is this true?



- We can easily see that they are chemically equivalent. Additionally, we have free rotation around the bond, which makes their chemical shifts and couplings equal.

Magnetic equivalence (continued)

- Since the ^1H s can change places, they will alternate their chemical shifts (those bonded to the same carbon), and we will see an average.
- The same happens for the **J** couplings. We'll see an average of all the J_{HH} couplings, so in effect, the coupling of any proton in CH_2 to any proton in the CH_3 will be the same.
- If we introduce some notation, and remembering that $\delta(\text{CH}_2)$ is $\gg \delta(\text{CH}_3)$, this would be an **A₂X₃** system: We have 2 magnetically equivalent ^1H s on the CH_2 , and 3 on the CH_3 .
- The $^2\text{J}_{\text{HH}}$ coupling (that is, the coupling between two nuclei bound to the same carbon) is zero in this case, because the energies for any of the three (or two) protons is the same.
- Finally, we use **A** to refer to the CH_2 protons, and **X** to refer to the CH_3 protons because they have very different δ s. We usually start with the letter **A** for the most deshielded spin.
- Difluoromethane is another example of an '**AX**' type system:

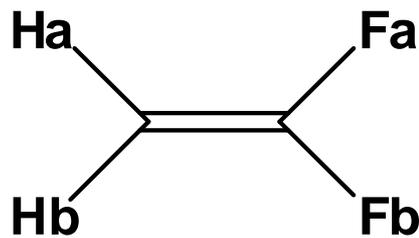


- In this case, ^1H s and ^{19}F s are equal not due to rotation, but to symmetry around the carbon. It's an **A₂X₂** system.

Magnetic equivalence (...)

- For CH_2F_2 , we can also compare the couplings to check that the ^1H s and ^{19}F s are equivalent: $J_{\text{H}_1\text{F}_1} = J_{\text{H}_1\text{F}_2} = J_{\text{H}_2\text{F}_1} = J_{\text{H}_2\text{F}_2}$. All due to their symmetry...

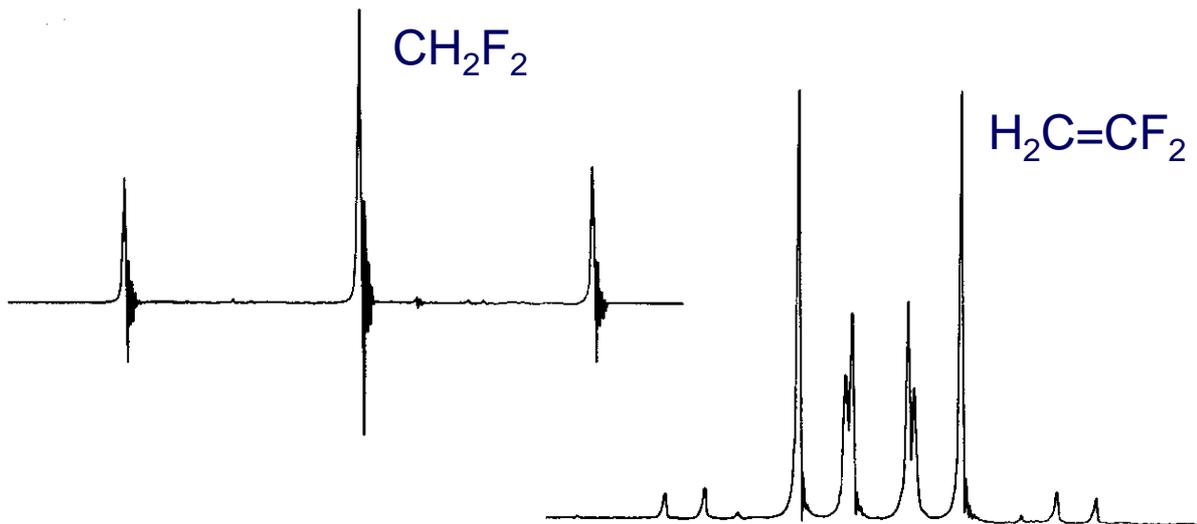
- Now, what about the the ^1H s and ^{19}F s in 1,1-difluoroethene?



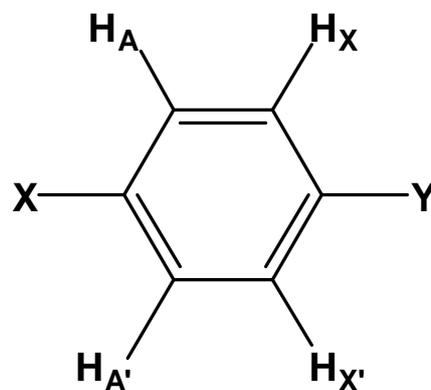
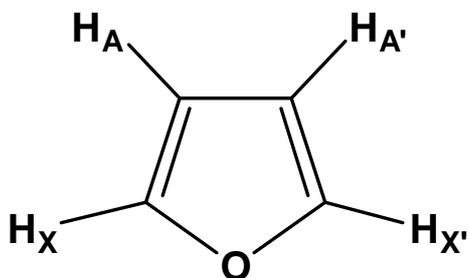
- Here we also have symmetry, but no rotation. The two ^1H s and the two ^{19}F s are chemically equivalent, and we can easily see that $\delta\text{H}_a = \delta\text{H}_b$ and $\delta\text{F}_a = \delta\text{F}_b$.
- However, due to the geometry of this compound, $J_{\text{H}_a\text{F}_a} \neq J_{\text{H}_a\text{F}_b}$. Analogously, $J_{\text{H}_b\text{F}_a} \neq J_{\text{H}_b\text{F}_b}$.
- Furthermore, since the couplings are different, the energy levels for H_a and H_b are different (not degenerate anymore as in CH_3), and we have $J_{\text{H}_a\text{H}_b} \neq 0$.
- If we consider all the possible couplings we have, we have three different couplings for each proton. For H_a , we have $J_{\text{H}_a\text{F}_a}$, $J_{\text{H}_a\text{F}_b}$, and $J_{\text{H}_a\text{H}_b}$. For H_b , we have $J_{\text{H}_b\text{F}_a}$, $J_{\text{H}_b\text{F}_b}$, and $J_{\text{H}_b\text{H}_a}$. This means *more* than the eight possible transitions ($2 \times 2 \times 2$) in the energy diagram, and an equal number of possible lines in the spectrum!

Magnetic equivalence (...)

- These are representative spectra (only the ^1H spectrum is shown) of CH_2F_2 and $\text{F}_2\text{C}=\text{CH}_2$:

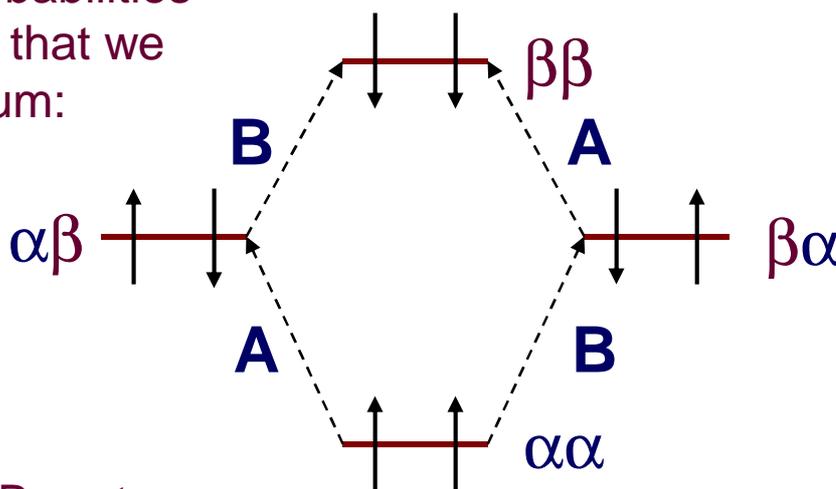


- A system like this is not an A_2X_2 , but an $\text{AA}'\text{XX}'$ system. We have two A nuclei with the same chemical shift but that are not magnetically equivalent. The same goes for the X nuclei.
- The following are other examples of $\text{AA}'\text{XX}'$ systems:

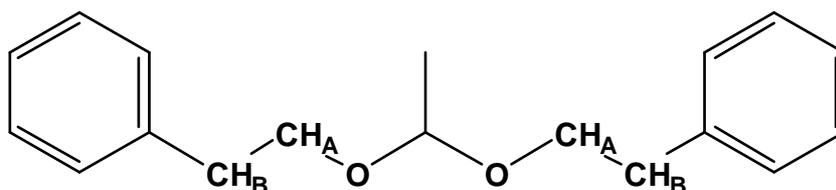
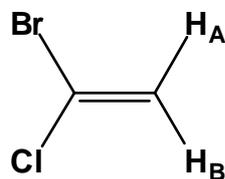
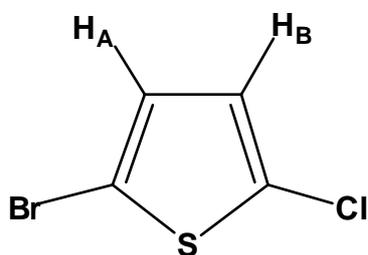


Energy diagrams for 2nd order systems

- From what we've seen, most cases of magnetic non-equivalence give rise to 2nd order systems, because we will have two nuclei with the same chemical environment and the same chemical shift, but with different couplings (**AA'** type...).
- We have analyzed qualitatively how a 2nd order **AB** looks like. In an **AB** system we have two spins in which $\Delta\delta \sim J_{AB}$. The energy diagram looks a lot like a 1st order **AX** system, but the energies involved (frequencies) and the transition probabilities (intensities) are such that we get a messier spectrum:

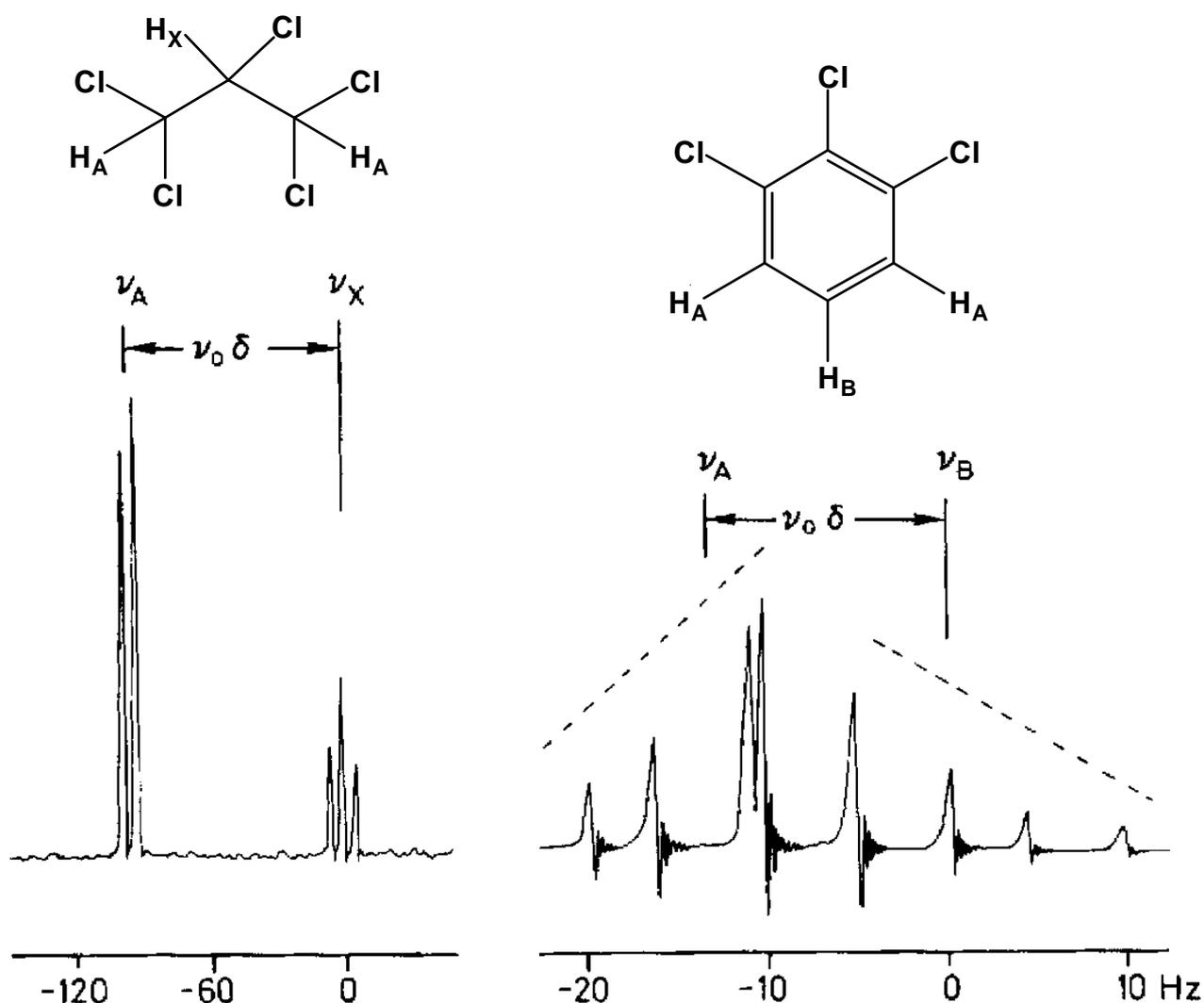


- Some examples of AB systems:



Transition from 1st order to 2nd order

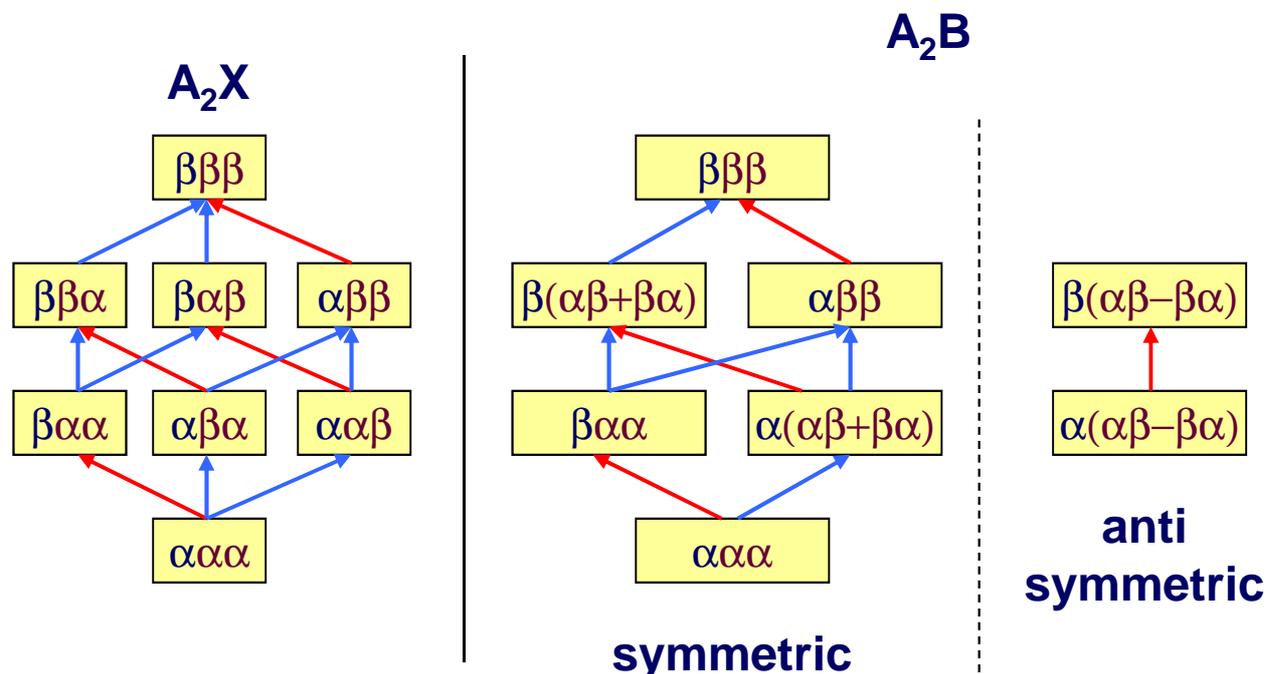
- The following is a neat experimental example of how we go from a 1st order system to a 2nd order system. The protons in the two compounds have the same 'arrangement', but as $\Delta\delta$ approaches J_{AB} , we go from, in this case, **A₂X** to **A₂B**:



- Most examples have 'ringing' and are obtained at relatively low fields (60 MHz) because at these fields 2nd order effects are more common...

2nd order systems with more than 2 spins.

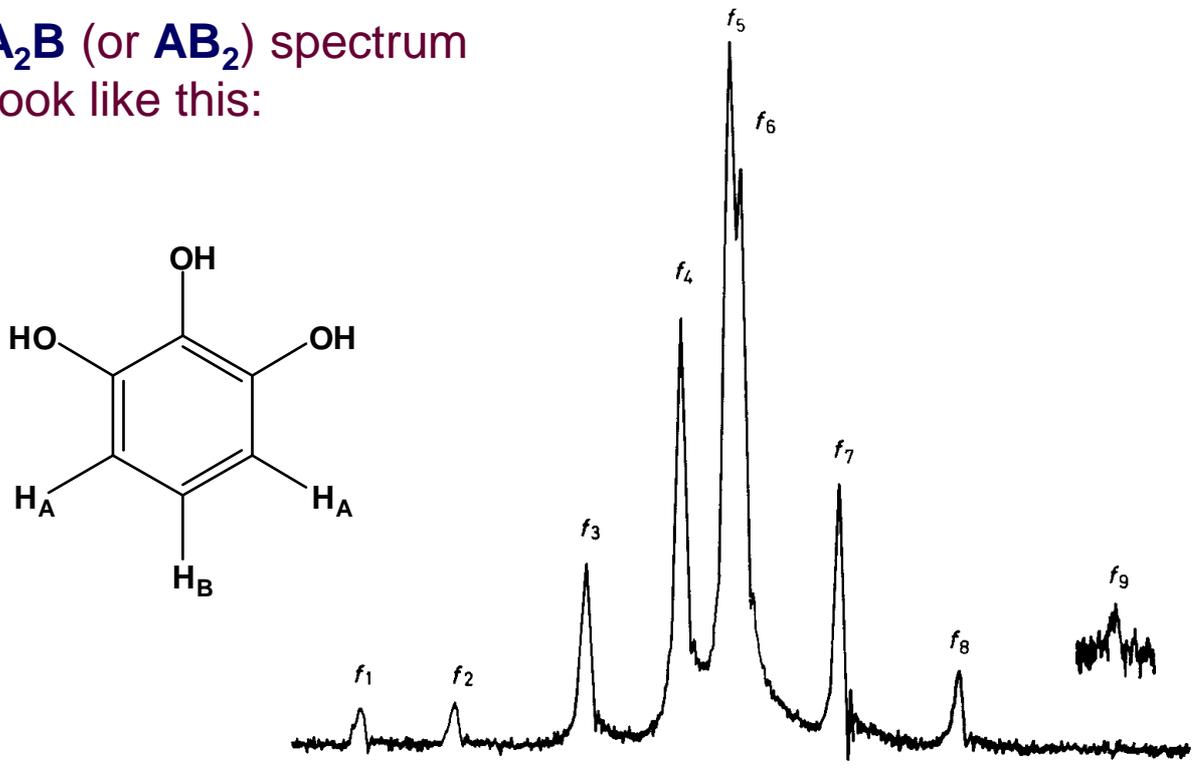
- Now, let's analyze 2nd order systems with more than 2 spins. We already saw an example, the A_2X system and the A_2B system. The A_2X system is 1st order, and is therefore easy to analyze.
- The A_2B is 2nd order, and energy levels includes transitions for what are known as **symmetric** and **antisymmetric wavefunctions**. They are related with the symmetry of the quantum mechanical wavefunctions describing the system.
- In any case, we have additional transitions from the ones we see in a A_2X system:



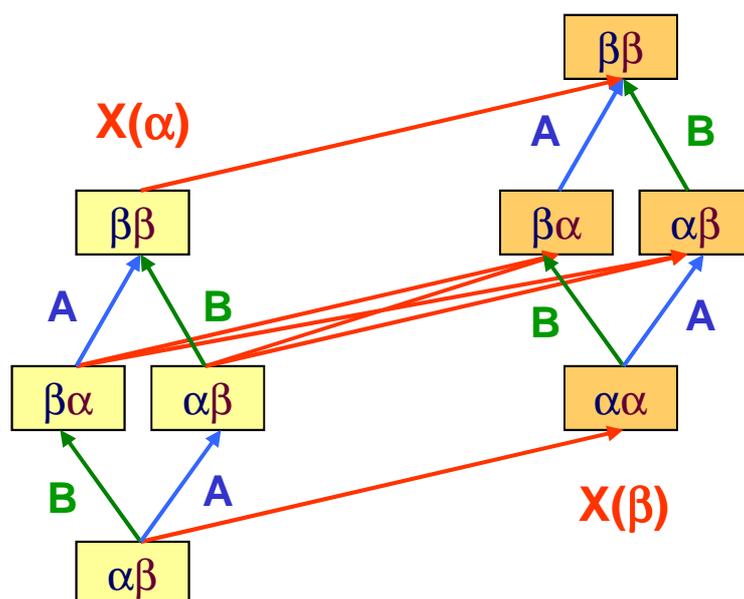
- We now have 9 lines in the A_2B system, instead of the 5 we have in the A_2X system (we have to remember that in the A_2X many of the transitions are of equivalent energy...).

More than 2 spins (continued)

- An A_2B (or AB_2) spectrum will look like this:

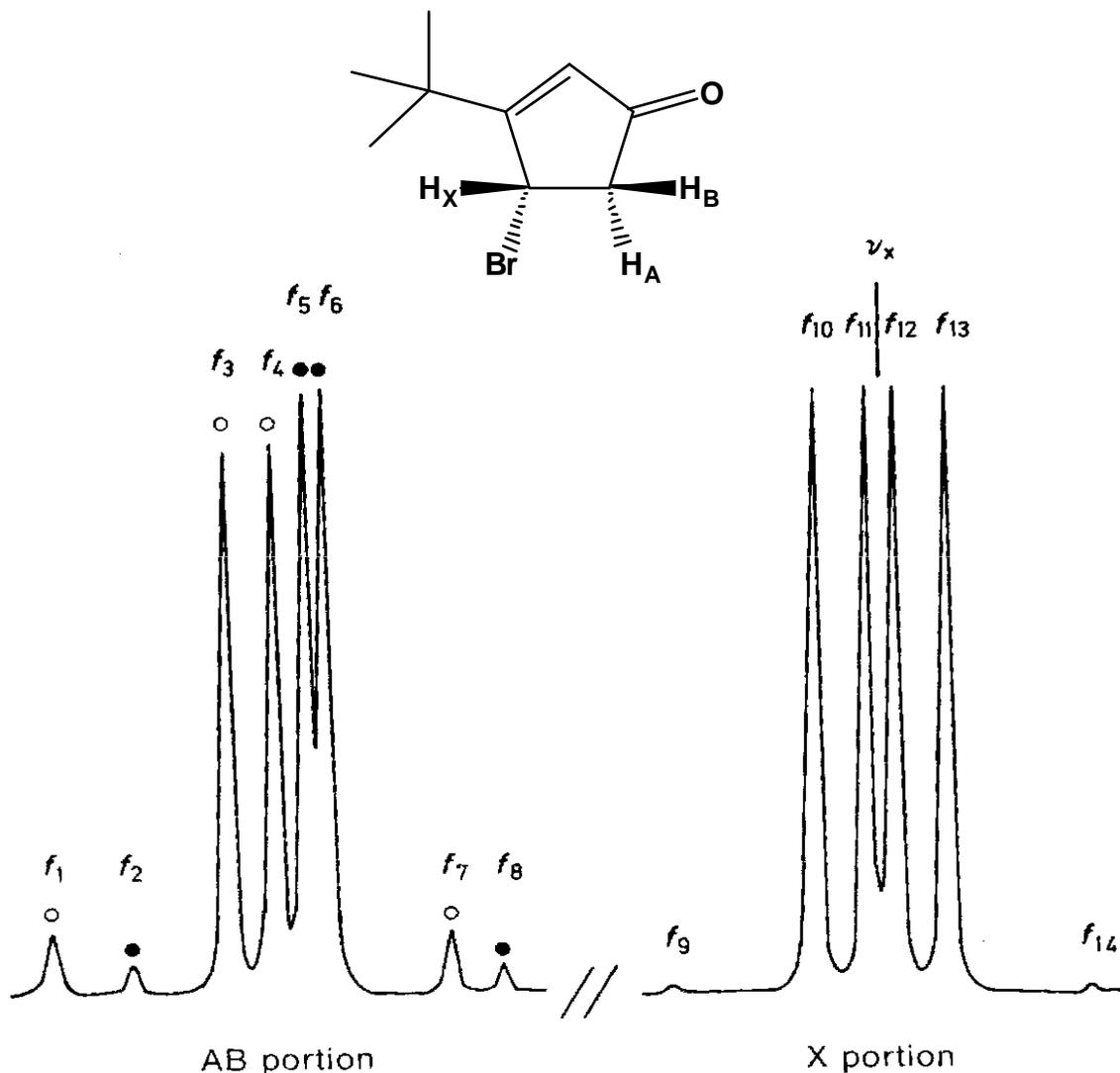


- Another system that we will encounter is the ABX system, in which two nuclei have comparable chemical shifts and a third is far from them. The energy levels look like this:



More than 2 spins (...)

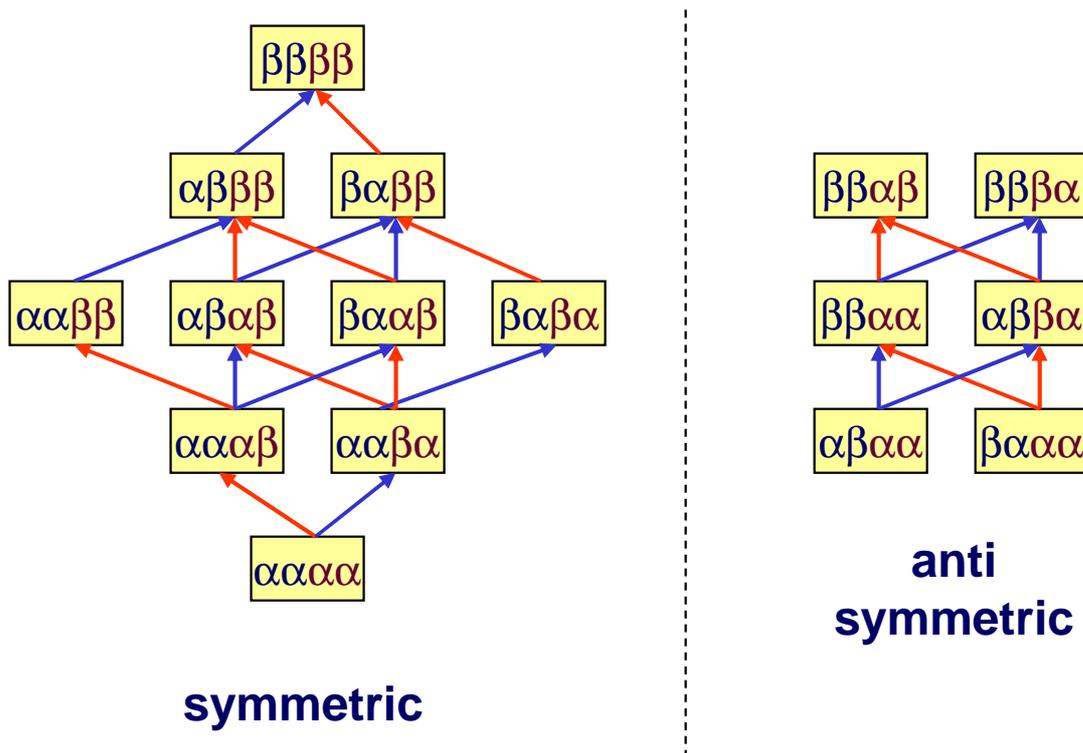
- In a **ABX** spectrum, we will have 4 lines for the **A** part, 4 lines for the **B** part, and 6 lines for the **X** part:



- ABX** spin systems are very common in trisubstituted aromatic systems.
- The last system we will discuss is the **AA'BB'** system, that we saw briefly at the beginning (actually, we saw **AA'XX'**...).

More than 2 spins (...)

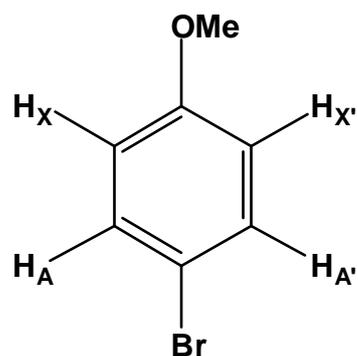
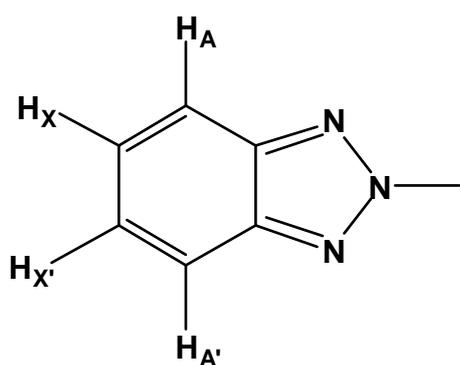
- In an **AA'BB'/AA'XX'** system we have 2 pairs of magnetically non-equivalent protons with the same chemical shift. The energy diagram for such a system is:



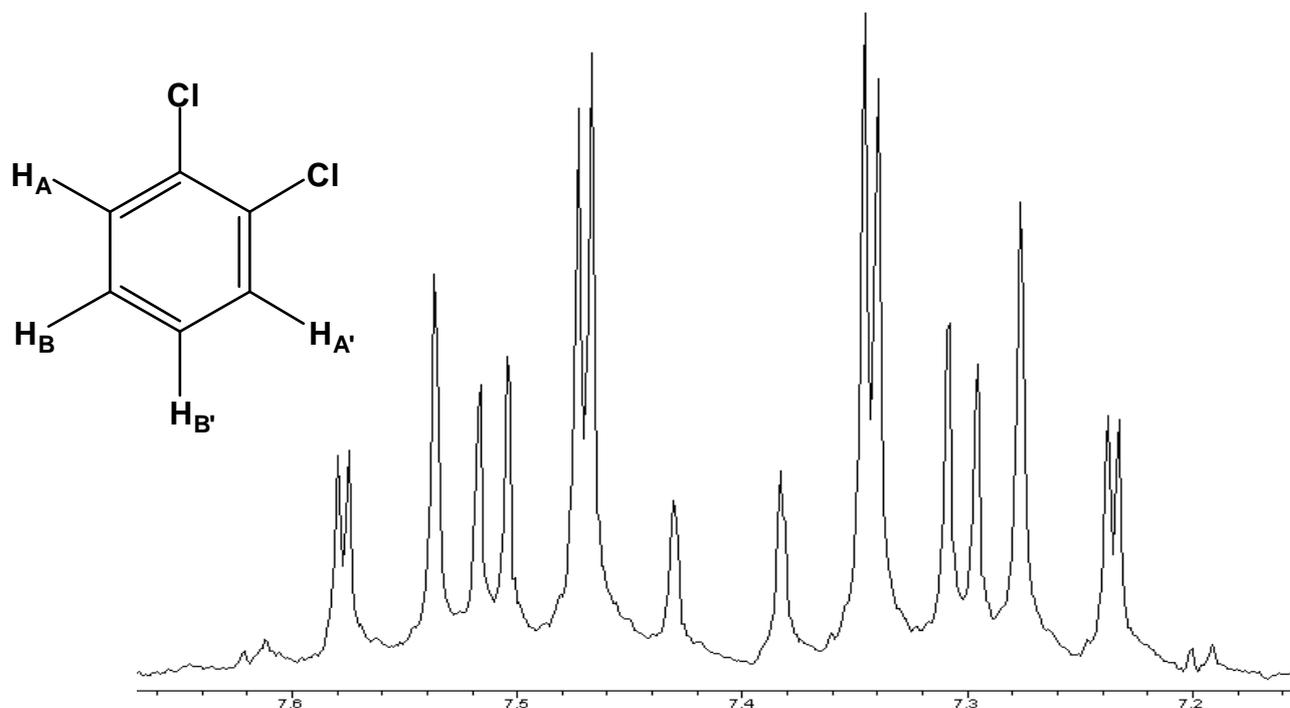
- We see that we can have a total of 12 transitions for each spin (the **AA'** part or the **BB'** part). However, some of the energies are the same (they are degenerate), so the total number of lines comes down to 10 for each, a total of 20!
- In an **AA'XX'** we see two sub-spectra, one for the **AA'** part and one for the **XX'** part. In a **AA'BB'** we see everything on the same region of the spectrum.

More than 2 spins (...)

- Some examples of spin systems giving rise to **AA'XX'** and **AA'BB'** patterns are given below.

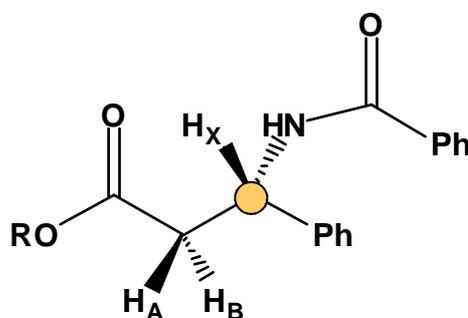
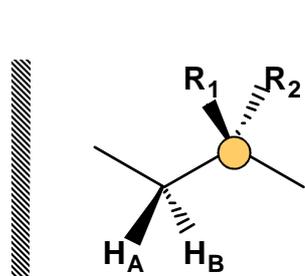


- A typical **AA'BB'** spectrum is that of **ODCB**, *orthodichloro benzene*. There are so many signals and they are so close to each other, that this compound is used to calibrate instrument resolution.



Common cases for 2nd order systems

- So what type of systems we will commonly encounter that will give rise to 2nd order patterns? Most of the times, aromatics will give 2nd order systems because the chemical shift differences of several of the aromatic protons will be very close (0.1 to 0.5 ppm), and J_{HH} in aromatics are relatively large (9 Hz for 3J , 3 Hz for 4J , and 0.5 Hz for 5J).
- For other compounds, the general rule is that if protons in similar environments are 'fixed' (that is, they have restricted rotation), we will most likely have 2nd order patterns.
- A typical example of this, generally of an **ABX** system, are *pro-R* and *pro-S* (i.e., diastereotopic) protons of methylenes next to a chiral center:



- In this case, we will have two protons that are coupled to one another (because they are different, **A** and **B**), they will have very similar chemical shifts, and can be coupled to other spins. For example, the oxetane protons in taxol:

