

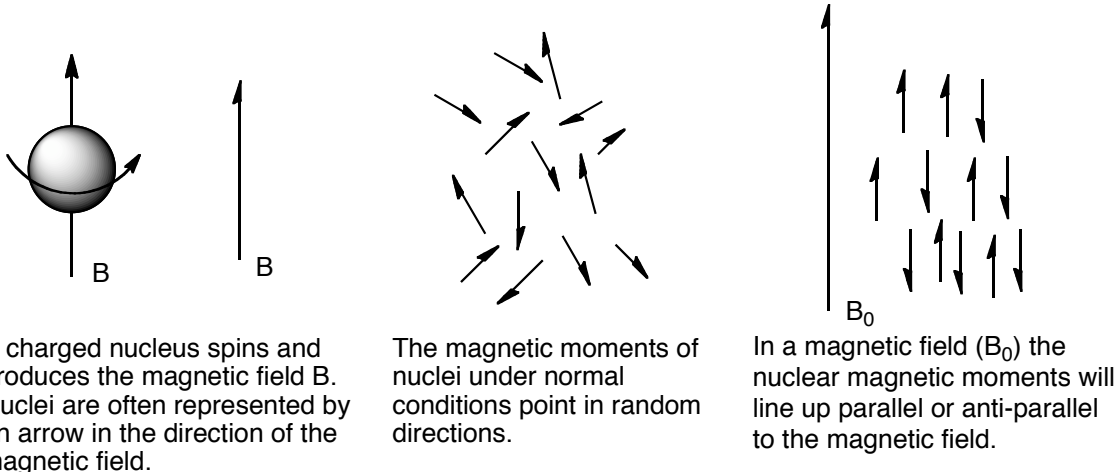
Introduction to Spectroscopy II: Basic Principles of NMR

Basic Theory:

NMR or Nuclear Magnetic Resonance allows a chemist to use radio waves to look at the chemical environment around active nuclei when the nucleus is placed in a magnetic field. It is one of the most useful techniques in modern chemistry to find the structure of novel compounds as small variations in bonding, neighboring nuclei, and functional group produced distinct predictable signals.

What the Magnet does:

The nuclei of atoms contain protons and sometimes neutrons and are overall positively charged. Because they are rotating charges they have a magnetic moment, which is randomly oriented under normal conditions, but will align either parallel (α) or anti-parallel (β) to a magnetic field. Only nuclei that produce a magnetic moment will be NMR active, so not every isotope of every atom is detectable.



The parallel spins are very slightly lower energy than the anti-parallel spins, so there are slightly more parallel spins than anti-parallel spins in a sample. The difference in energy (and the difference in number of spins) depends on the strength of the magnet, the larger the magnetic field, the larger the energy difference and the fewer anti-parallel spins. Even with very large magnets the difference in energy (and spin population) is very small. A 11.7 Tesla magnet will produce an energy difference in a ^1H nucleus of about 500 MHz (3.31×10^{-25} J) and the largest magnet used in a commercial NMR to date (June 2009) is the Bruker AVANCE 1000, which has a 23.5 Tesla magnet and produces an energy difference of 1000 MHz (6.63×10^{-25} J) in ^1H nuclei.

NMR Active Nuclei:

To be visible using NMR a nucleus must have a quality called spin (I).

- Nuclei with an EVEN mass number and an EVEN number of neutrons have $I = 0$ so cannot be observed with NMR.
- Nuclei with an EVEN mass number and ODD number of neutrons have $I = 1, 2, 3$ etc and can be observed with NMR.
- Nuclei with an ODD mass number will have $I = 1/2, 3/2, 5/2$ etc and can be observed with NMR.

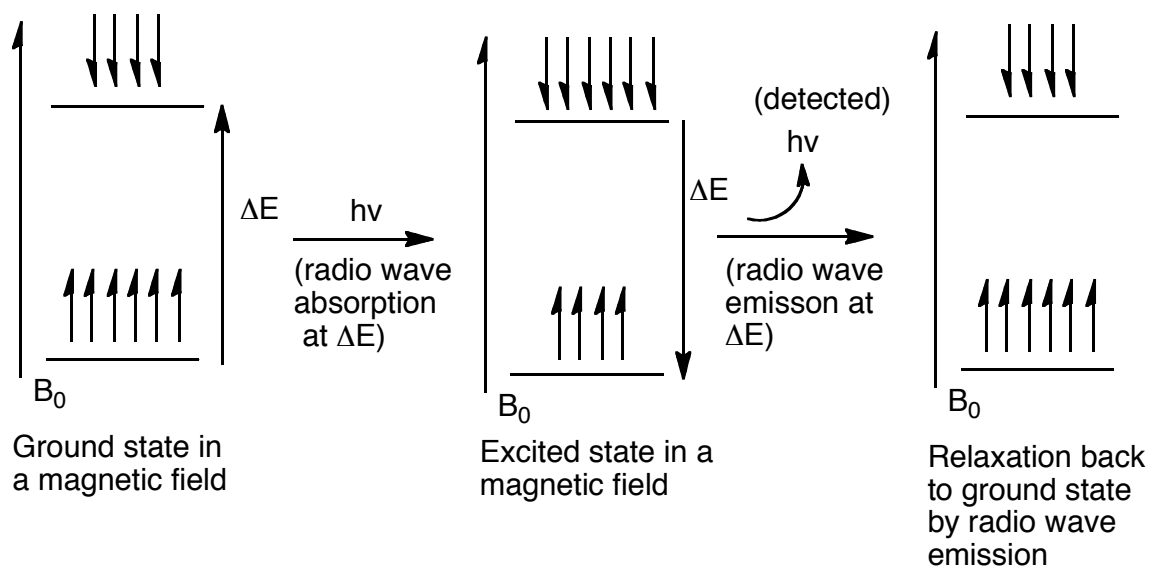
Common NMR active nuclei in organic chemistry are ^1H and ^{13}C .

Other NMR active nuclei include: ^{15}N , ^{19}F , ^{29}Si , and ^{31}P .

Most high-resolution NMR works with nuclei that are spin $1/2$, as larger spins have additional complexities that will not be discussed here. Both ^1H and ^{13}C are spin $1/2$ nuclei.

What the Radio Waves do:

The magnet produces two different positions for the nuclear magnetic spin (parallel and anti-parallel). Because the difference in energy is on the order of the energy in radio waves, the nuclei can be put into an excited state by irradiating them with radio waves, just as an electron can be excited into a different orbital using ultraviolet light (absorption spectra). We can then observe the radio waves that are given off as the excited state relaxes back to the ground state (just as in atomic emission spectra). When the sample is irradiated at the ΔE for a particular nucleus we see continuous absorption/emission, this is called the resonance frequency.



The identity of the active nucleus and the magnet strength are the major factors in the ΔE between the parallel and anti-parallel spins. The operating frequency is the frequency in MHz that correlates to the ΔE for that particular nucleus and magnet combination. Most NMR spectrophotometers are referred to by their ^1H operating frequency i.e. 300 MHz, 400 MHz or 500 MHz spectrophotometers. ^{13}C NMR operating frequencies are about $\frac{1}{4}$ of ^1H operating frequencies for the same magnet. However, the exact environment of the nucleus also affects ΔE to give a particular resonance frequency for that particular nucleus and those differences are what allow us to use NMR as a diagnostic tool in organic molecules. High-resolution NMR can differentiate between the ^1H or ^{13}C nuclei in different chemical environments, which allows us to make conclusions about structure.

NOTE: A consequence of increasing the magnet strength is with ΔE , small changes become more significant, a .0001% difference is a larger ΔE with a larger magnet so subtle differences become more distinct. What is a blur of signals a 60 MHz, may resolve into a half dozen peaks at 300 MHz, and clearly distinct peaks at 600 MHz.

Chemical Shift and TMS:

Since the magnet strength affects the ΔE of a nucleus each individual NMR spectrophotometer has a very slightly different operating frequency for ^1H nuclei, as each individual magnet is slightly different. This means that if the resonance frequency of a particular ^1H nucleus is .001% off the operating frequency it will resonate at 300.003 MHz in a 300 MHz NMR and at 500.005 MHz in a 500 MHz NMR. This causes different signals for different people using different physical NMR spectrophotometers for the same nucleus.

To avoid confusion chemists use a ratio unit instead of individual resonance frequencies: chemical shift. Chemical shift (δ) is measured in parts per million (ppm). This is the ratio of the resonance frequency of the particular nucleus to the operating frequency of the spectrophotometer times 10^6 .

$$\delta \text{ (ppm)} = \frac{\text{resonance frequency of nucleus (Hz)}}{\text{operating frequency of NMR (MHz)}}$$

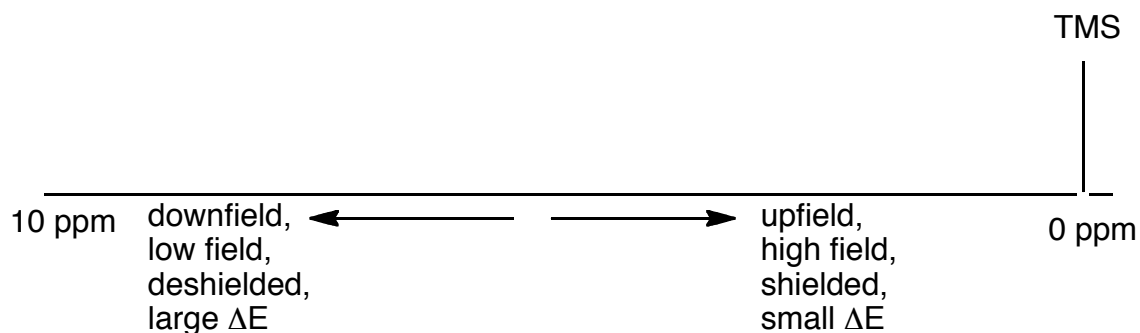
Chemical shift is the same for all spectrophotometers so chemists can easily compare data from lab to lab and spectrophotometer to spectrophotometer. To further standardize chemical shift, tetramethylsilane (TMS, $(\text{CH}_3)_4\text{Si}$) is defined as a standard 0.00 ppm in both ^1H and ^{13}C NMR. The typical chemical shift ranges compared to TMS are 0-10 ppm for ^1H NMR and 0-200 ppm for ^{13}C NMR.

NOTE: As the range of ΔE (resonance frequencies) increases with larger magnets the ppm do not change, but the appearance of the signals becomes

sharper and narrower allowing much clearer differentiation of different signals. This makes interpretation of spectra where many signals are similar or highly coupled much easier.

Shielded vs. Deshielded:

In organic chemistry different chemical environments in a molecule will result in different resonance frequencies. The general pattern is signals near TMS (low ppm) are *downfield*. Downfield signals are *shielded* and have relatively high electron densities around the observed atom's nucleus. The large electron densities buffer the nucleus from effects of the magnetic field (shield the nucleus). The movement of electrons (also charges in a magnetic field) around the nucleus produces local magnetic field (B_{local}) anti-parallel to the applied field B_0 . The B_{local} reduces the effective strength of B_0 , thus the nucleus feels less B_0 , and the resonance frequency has a smaller ΔE . Signals further from TMS (high ppm) are *upfield*. Upfield signals are *deshielded* and have relatively low electron densities around the observed atom's nucleus. The small electron densities allow the nucleus to feel the magnetic field (B_0) more effectively (less B_{local}) so it has a larger ΔE .



Typically nuclei are deshielded by induction due to nearby electronegative atoms or by movement of pi electrons (electrons are charges too) to produce a parallel B_{local} increasing the applied magnetic field (B_0).

Chemical Equivalence:

Differences in chemical environment due to bonds and functional groups will cause different atoms in a molecule to have different chemical shifts (resonance frequencies). NMR is capable of differentiating very small differences in chemical environment. The following discussion will refer directly to ^1H NMR, but the principles apply to all nuclei.

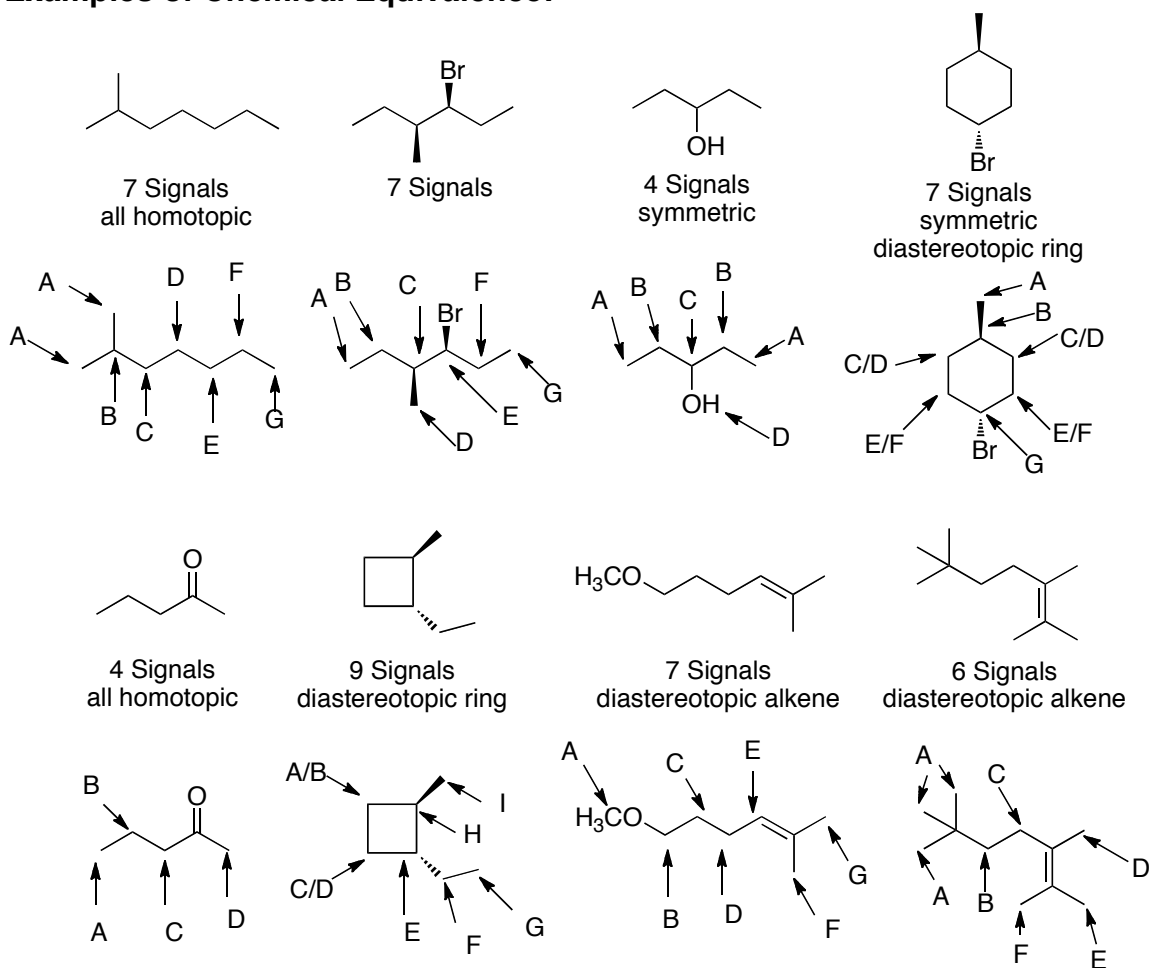
- Homotopic protons are exactly identical. If replaced with a bromine atom, they would give exactly the same molecule. Homotopic protons are always the same chemical shift. The 3H in any CH_3 are homotopic. The 2H on carbon-2 of propane are homotopic.

- Enantiotopic protons are the same carbon, but if replaced with a bromine atom, they would give a pair of enantiomers. Enantiotopic protons usually give the same signal, but may be different if a chiral solvent is used. (Remember the physical properties of enantiomers are the same except in a chiral environment). The 2H on carbon-2 of butane are enantiotopic.
- Diastereotopic protons are attached to the same carbon, but if replaced with a bromine atom, they would give a pair of diastereomers. Diastereotopic protons usually give different signals, but may be the same if the two diastereotopic environments are similar enough. The 2H on carbon-3 of 2-chlorobutane are diastereotopic.

NOTE: Generally linear and branched alkane systems have free rotation around the C-C bonds so even diastereotopic protons will tend to average out and have the same signal. However, systems without free rotation (rings and alkenes) will have distinctly different signals for diastereotopic protons.

NOTE: For purposes of 118 A/B/C consider diastereotopic protons on linear and branched alkanes as the same and diastereotopic protons on rings as different, this is an over-generalization, but makes things simpler to start.

Examples of Chemical Equivalence:



Introduction to Spectroscopy III: Interpreting ^1H NMR

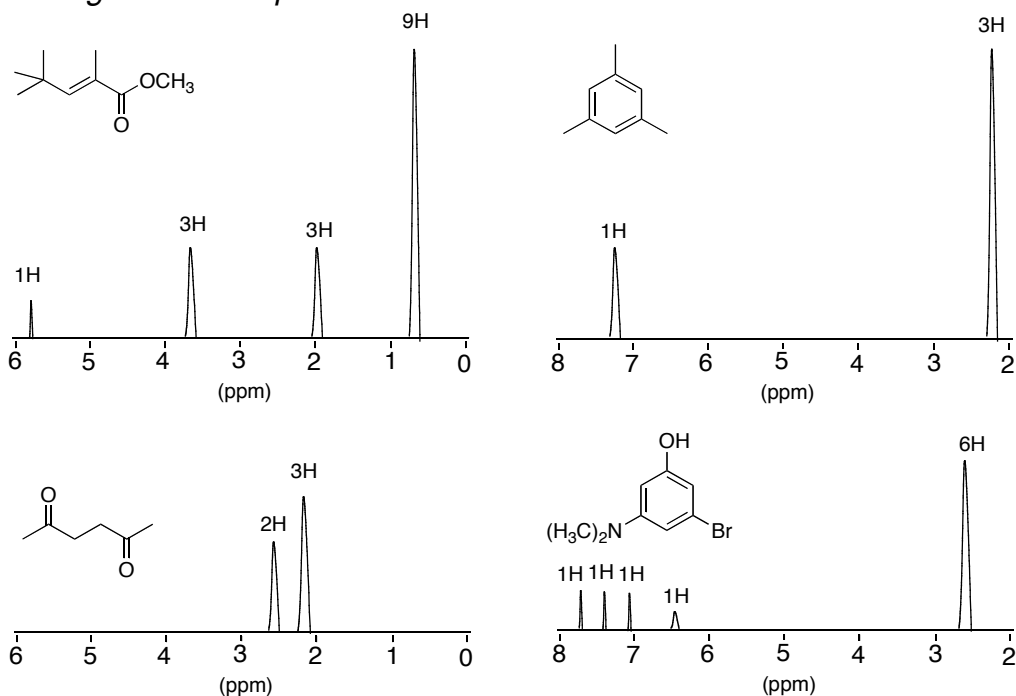
Integration:

Since the signals in NMR are related to the relaxation emission they are also directly related to the population of active nuclei. Since a molecule has a fixed whole number of atoms in fixed positions, the ratio of active nuclei at each resonance frequency (chemically equivalent nuclei) depends on the formula. Thus the intensity of the signal is related back to the number of atoms with the same chemical equivalence within the molecule. And the signal intensity can be calculated by integration of the area under the curve of the peak for each resonance frequency.

Classically the integral is charted and the heights of the integrals are measured by a ruler, and then compared to give whole number ratios. Or if no integral was measured, the peaks can be cut out of the chart paper and weighed to find the mass ratio! More modern spectrophotometers can automatically calculate peak area ratios. However, the integral only shows the ratios of signal intensity, so some care is needed in determining the exact number of H per peak.

Generally the smallest peak in the spectra integrates to 1H, however, in highly symmetrical molecules it may integrate to 2H. When interpreting integrations if the number of protons in the spectrum sum to the correct number then the integrations are correct, if they only sum to half the number of protons then all the ratios need to be multiplied by a factor of 2 and the molecule is symmetrical.

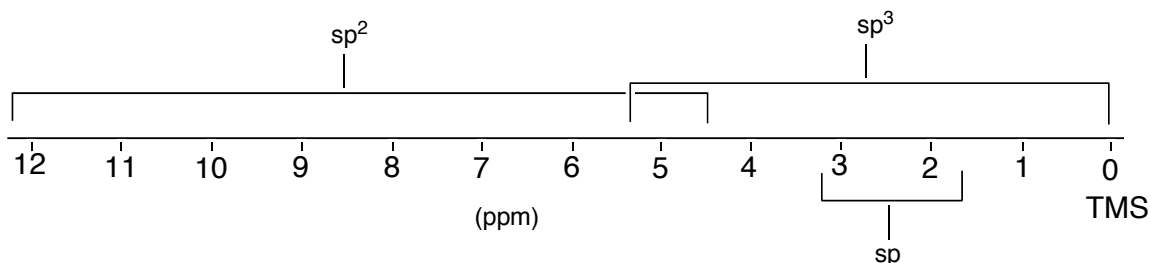
Integration Examples:



Chemical Shift:

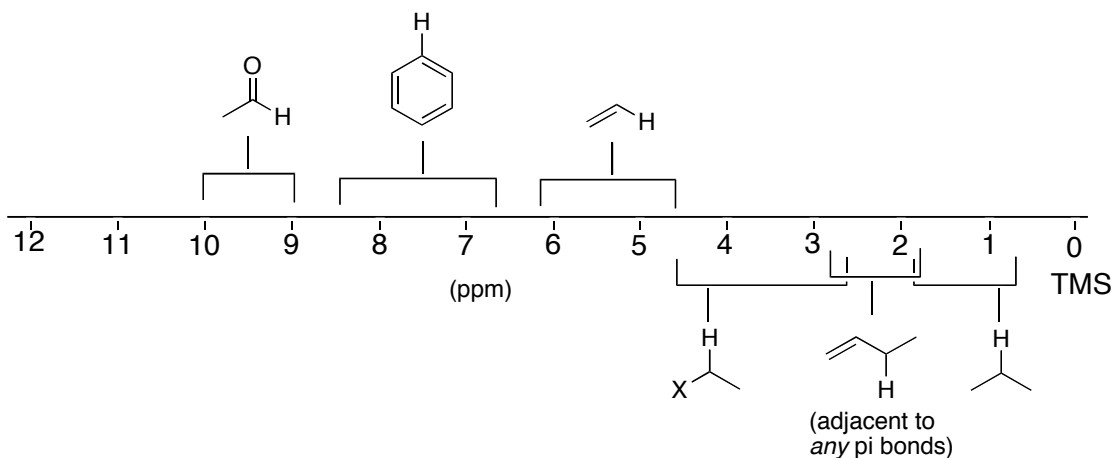
The chemical shift of ^1H NMR signals ranges from 0 ppm to 10 ppm for most functional groups. The acidic $-\text{OH}$ of carboxylic acids can be found as far downfield as 13 ppm, but this is the only common exception. Tables of typical chemical shift ranges can be found in many sources (Table 10.4 Vollhardt + Schore) and these numbers should be memorized in order to facilitate interpretation of spectra. While these numbers may seem random there are patterns based on chemical principles of organic chemistry.

- While there are exceptions H attached to sp^3 hybridized atoms tend to show up between 0-5 ppm.
- While there are exceptions H attached to sp^2 hybridized atoms tend to show up between 5-10 ppm.

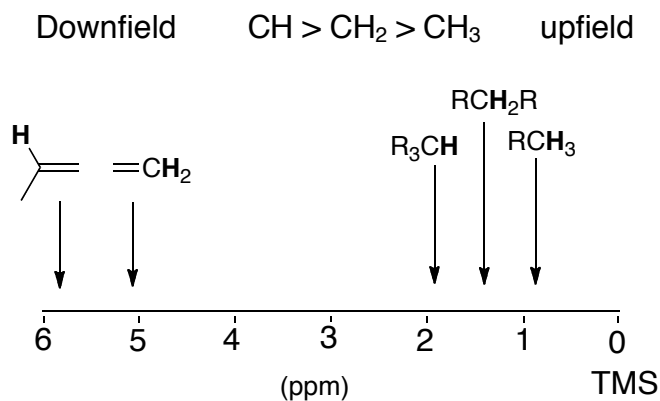


- Within those ranges hydrocarbons are most upfield, then C-H adjacent to pi-bonds, and C-H attached to electronegative atoms are furthest downfield, this pattern repeats in the sp^3 and sp^2 regions.
 - The downfield shift is caused by to increasing deshielding of the H due to increasing electron-withdrawing by the attached functional group. Alkyl groups are not electron-withdrawing, pi bonds are only slightly electron withdrawing, and electronegative atoms are more so.

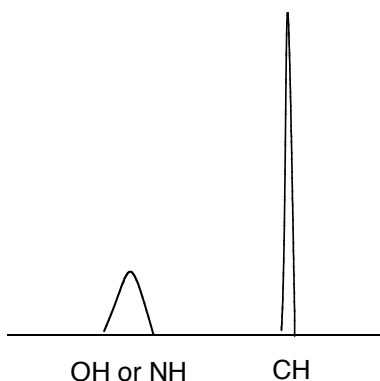
Downfield $\text{O}-\text{C}-\text{H} > \text{N}-\text{C}-\text{H} > =\text{C}-\text{C}-\text{H} > \text{C}-\text{C}-\text{H}$ upfield



- Within the range for a particular functional group a CH (methine proton) will be downfield/left of a CH₂ (methylene protons), which will be downfield/left of a CH₃ (methyl protons).



- H attached to OH and NH will have a broadened signal with a variable chemical shift due to varied degrees of hydrogen bonding from molecule to molecule. However, alcohols and amines (sp³) will tend to be between 0.5-5 ppm, amides and phenols (sp²) will tend to be between 6-8 ppm and carboxylic acids (sp²) will tend to be between 10-13 ppm.

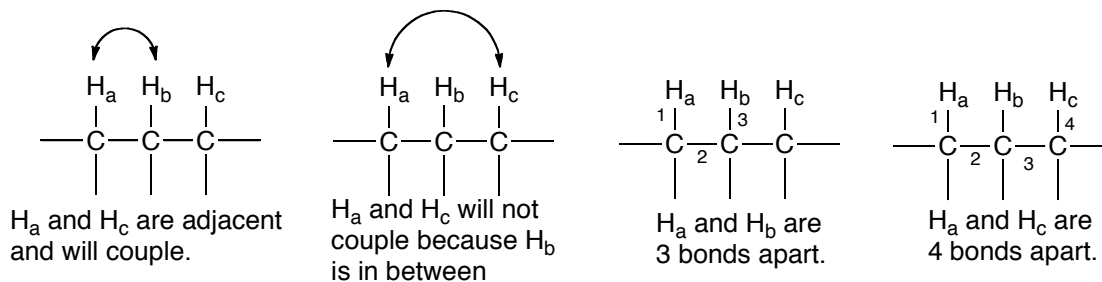


Basic Coupling:

Since nuclei are spinning charges that create magnetic fields and the measurement in NMR is the ΔE caused by the total magnetic field, nearby nuclei will effect each other's chemical environment. This effect is spin-spin splitting, also known as coupling.

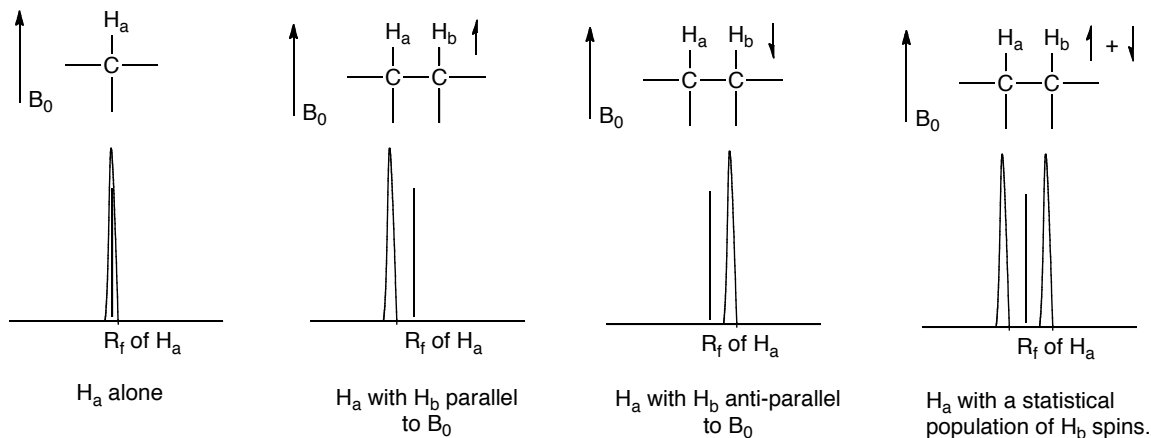
Picture each carbon in a carbon chain as a house along a street and the hydrogens attached to those carbons as the people living in the house. Neighboring hydrogen atoms can 'talk' to each easily over the fence, but atoms that are further away cannot 'talk' easily because there is too much distance in between them. The 'talking' between hydrogens on adjacent carbons is called 3-bond coupling and it's the most common type of coupling. Typically the H on the same carbon (2-bonds) are the same so do not 'talk' or couple with

each other, and while H further away (4-bonds) may couple it's typically too small an effect to be measured.



So what is actually happening? Remember that each H nucleus is a spinning charge that produces a magnetic field (spin). When that nucleus is placed in a magnetic field the spin of the nucleus can align parallel (α) or anti-parallel (β) to the outside magnet (B_0). The alignment of each nucleus is independent so a multi atom molecule may have some nuclei parallel and some anti-parallel.

If we're looking at H_a 's resonance frequency we'll see a single frequency in the NMR (a singlet). If H_a is adjacent to H_b , then H_b 's spin will affect the magnetic field that H_a feels. If H_b is parallel to the magnetic field B_0 then H_a will feel a slightly stronger overall field, the ΔE will increase and the signal will shift slightly downfield (deshielded). If H_b is anti-parallel to the magnetic field B_0 then H_a will feel a slightly weaker overall field, the ΔE will decrease and the signal will shift an equal amount upfield (shielded). This results in two possible resonance frequencies for H_a (a doublet). In the analogy H_b is either 'home' or 'not home' so we have two possible states, H_a and H_b can talk (home/parallel) or cannot talk (not home/anti-parallel).



In a real sample there are billions of molecules and nearly equal populations of parallel/anti-parallel spins so we see two equally possible cases for the environment of H_a , due to its spin being split by the spin on H_b (coupling to H_b). We would also see a corresponding doubling of resonance frequencies in H_b

as its spin is split by the spin on H_a (coupling to H_a). The distance between the split peaks is the coupling constant and it is the same for both H_a and H_b .

Coupling Constants:

- The distance between the split peaks in a signal with spin-spin splitting can be measured in hertz (Hz) and the value called is the coupling constant also known as the J -value and abbreviated as J .
- The coupling constant for a particular pair of H is always the same regardless of spectrophotometer, it depends on the relationship between H_a and H_b not the original magnet.
- The coupling constant is the same number of Hz for both coupled H (they have the same value as they're having the same conversation!).
- The values of J range from 0-18 Hz and depend primarily on the angle between the two H (called the Karplus angle). But in cases of complex splitting J -values also depend on the distance (2, 3 or 4 bonds apart).
- In alkanes with free rotation (straight or branched chains) the bonds spin so the angles average out and the value of J is approx. 7 Hz, so all alkane C-H can be treated as having the same J value.
- The similarity of J in alkanes allows for the use of the $n+1$ rule.
- Chemically equivalent nuclei will not couple with each other (they don't need to talk as they're the same thing.)

Pascal's Triangle and the $n+1$ Rule (Alkane Coupling):

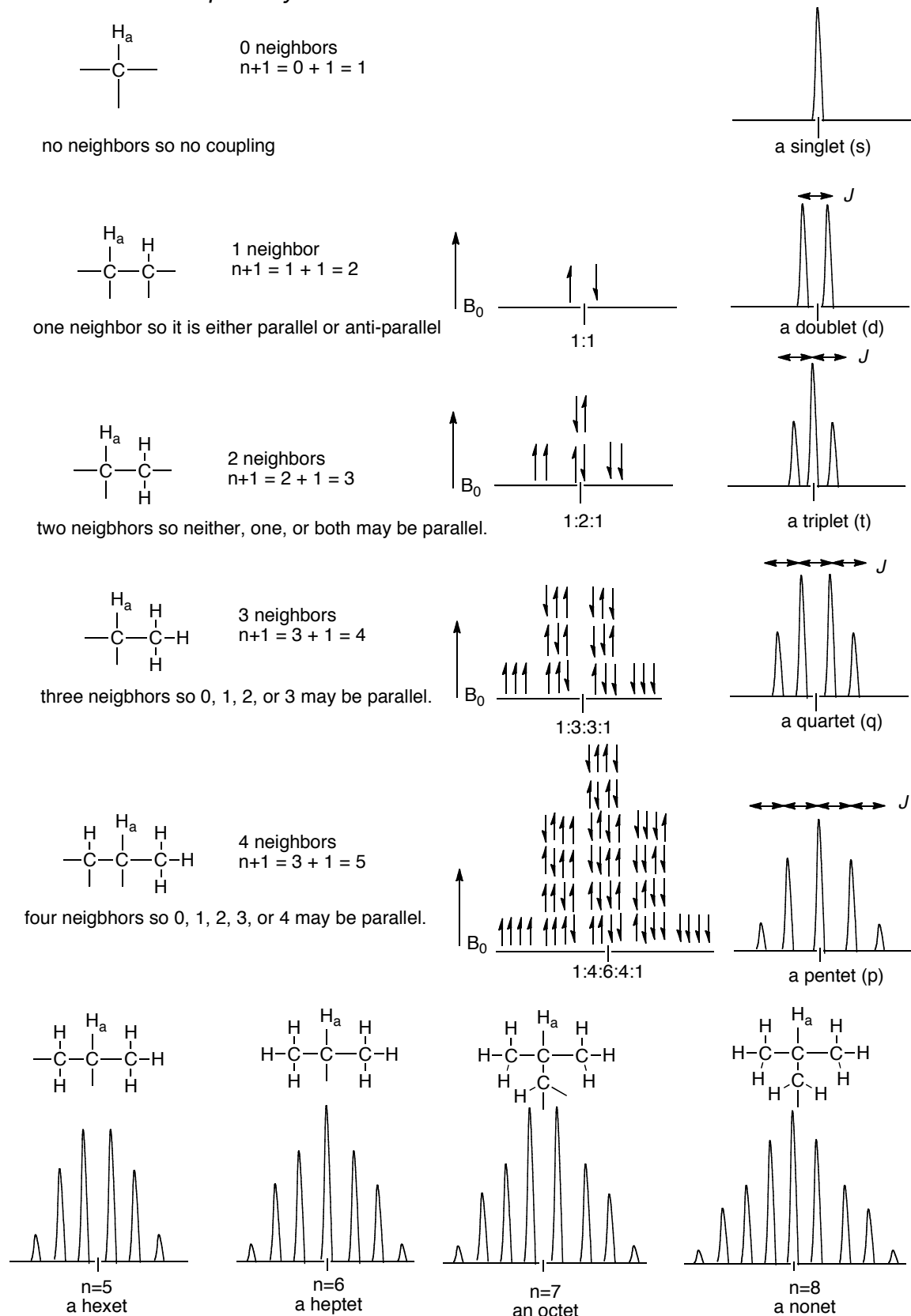
In coupling (spin-spin splitting) the final shape of the signal (also called a multiplet), depends on the number of neighboring nuclei and their particular coupling constants. In ^1H NMR, the signal for each ^1H nucleus contains the resonance of that H in all the molecules in the sample, so each signal shows the probability distribution of each possible spin state. For organic molecules with basic alkane skeletons we can treat all neighboring H as having the same coupling constant, so the shape of the coupled signal depends only on the number of neighbors. This is *the $n+1$ rule*.

The $n+1$ Rule: A single H resonance frequency will be split into a multiplet with $n+1$ number of peaks, where n is the number of neighboring H.

- Since each nucleus has two possible states (parallel or anti-parallel spin) the n+1 rule follows Pascal's triangle both for number of peaks in the multiplet and the relative area of each of these peaks.
- In integration all the peaks in a multiplet are added to give the total signal for that type of H. And the chemical shift is measured from the center of the multiplet where the resonance frequency of the uncoupled H would be.
- H that have an even number of neighboring H will give a multiplet with an ODD number of peaks, which gives a single tallest central peak. H that have an odd number of neighboring H will give a multiplet with an EVEN number of peaks, which gives a doubled tallest central peak.
- Sometimes it's helpful to think of the n+1 rule as a series of coin flips. The number of neighbors equals the number of flips. The total number of heads/tails gives the resonance frequency. The number of possibilities that would give that heads/tails total gives the intensity.

So what kind of shapes do we see? Following the analogy: a singlet H has no neighbors so has no conversations and only one possible resonance frequency. A doublet H has one neighbor who may or may not be home so has two possible states and two resonance frequencies. A triplet H has two neighbors who 1) are both home, 2) are both not home, 3) one is home and the second is not, or 4) one is away but the second is home, this gives four possible states at three resonance frequencies. States 3 and 4 have the same ΔE because they both have the same number of neighbors (one home, one not) so the central resonance frequency will have twice the intensity.

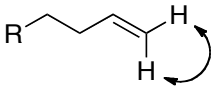
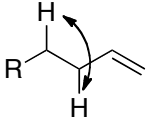
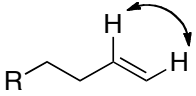
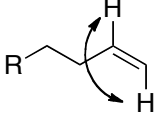
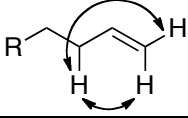
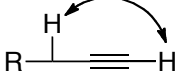
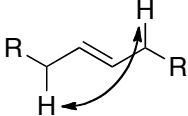
Formation of Multiplets by the $n+1$ Rule:



Advanced Coupling (118B and 118C):

In systems that do not freely rotate, angles between C-H bonds can be fixed. Fixed angles lead to observable variations in coupling constant (J), which can result in complex spin-spin splitting patterns that allow determination of relative position of H in a molecule. In the 118 series this effect is mostly observed in alkenes and alkynes and these values should be remembered to help interpret spectra. (See Table 11.2 in Vollhardt + Schore)

Typical Coupling Constants of Alkenes + Alkynes

Relationship	Name	Distance	Range of J	Typical J	Shape
	geminal	2-bond	0-3 Hz	2 Hz	d
	alkane / none	3-bond	4-10 Hz	7 Hz	d, t, q
	vicinal (cis)	3-bond	6-14 Hz	10 Hz	d
	vicinal (trans)	3-bond	11-18 Hz	16 Hz	d
	allylic	4-bond	0-3 Hz	2 Hz	d, t, q
	propargylic	4-bond	2-4 Hz	3 Hz	d, t, q
	long-range*	5-bond	0-1.5 Hz	1 Hz	d, t, q

*Long-range couplings are only seen in very rigid systems with very sensitive spectrophotometers.

Important considerations for complex splitting:

- The $n+1$ rule still applies to each individual J value.
- Variations in J mean that each separate value coupling constant will split the signal independently.
- All independent splittings/couplings of the signal act simultaneously to produce the multiplet.
- The shape of the multiplet is a probability distribution of all the possible neighboring spin states.

- Split peaks are generically referred to as multiplets, but may be specifically referred to as a listing of their coupling patterns if the patterns are known (e.g. ddt → doubled doubled triplet or dddd → doubled doubled doublet doublet)
- All possible couplings are not always observable. Most spectrophotometers cannot resolve a coupling constant less than 1 Hz, so geminal and allylic couplings may not be observed and long-range couplings are almost never observed.

Reporting complex multiplets:

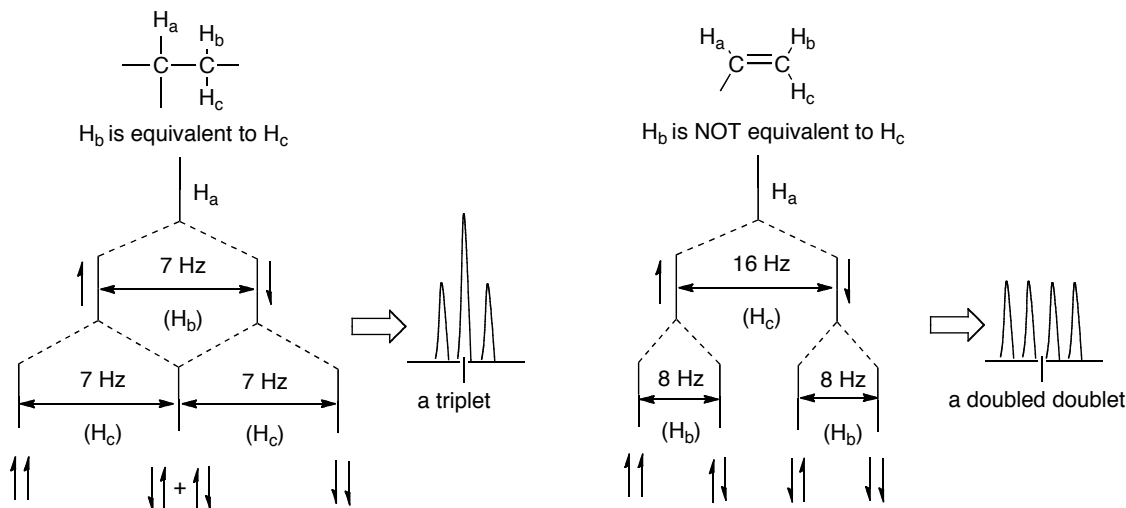
Typically the data from a complex multiplet is written in a formal short hand. A single signal might be written as follows (H_A : δ 5.89 ppm, 1H, $J = 16$ Hz (d), 10 Hz (d), 7 Hz (t)). This is interpreted as the signal for H_A is 5.89 ppm downfield from TMS, integrates to 1H and there is a coupling of 16 Hz that is a doublet (i.e. 1 neighbor of that type), a coupling of 10 Hz that is a doublet (1 neighbor of that type) and a coupling of 7 Hz that is a triplet (2 neighbors of that type). The couplings are typically listed largest to smallest. This signal may be referred to as a multiplet (m) or as a doubled doubled triplet (ddt).

Interpreting complex multiplets:

Complex multiplets are formed the same way as simple alkane multiplets so can be interpreted the same way. However due to the variation in J values the splitting patterns appear as complex combinations of doublets, triplets and quartets rather than $n+1$ peaks following Pascal's triangle. Often the easiest way to interpret complex multiplets is to use a splitting tree. Draw a splitting tree by starting the original signal as a single resonance frequency and apply each coupling in series. This works for both simple $n+1$ multiplets and complex splitting patterns.

Doing the reverse and finding coupling constants from the observed peak shape and Hz values is made difficult when peaks overlap due to similar coupling constants. In principle it is the reverse of drawing a splitting tree where each coupling is removed until a single peak at the resonance frequency is seen, but the practice can be quite challenging and is beyond the scope of this course.

Drawing Splitting Trees:



H_b and H_c have the same J value. H_a starts with a single resonance frequency which is then split into a doublet by H_b ($J = 7$ Hz (d)). The resulting doublet is also split into a doublet by H_c ($J = 7$ Hz (d)). Since the two J are the same the case of H_b parallel and H_c anti-parallel has the same resonance frequency as H_b anti-parallel and H_c parallel. So the multiplet appears as a triplet.

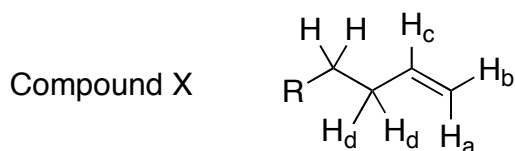
H_b and H_c have different J values. H_a starts with a single resonance frequency which is then split into a doublet by H_c ($J = 16$ Hz (d)). H_c is considered first as it is trans and will have a larger coupling constant than H_b which is cis. The result will be the same regardless of order, but the tree is easier to write largest to smallest. The resulting doublet is then doubled by H_b ($J = 8$ Hz (d)). The two cases with one parallel and one anti-parallel neighbor are not equivalent so do not overlap and the result is a doubled doublet.

NOTE: A doubled doublet is NOT a quartet. A doubled doublet has the peak area ratio of 1:1:1:1 while a quartet has a 1:3:3:1 ratio.

The Analogy:

Picture the given alkene with each C being a house on a street and each H living at its given house. If one of the H wants to throw a party, it needs to pay attention to whether its neighbors are home (parallel spin) or not home (anti-parallel spin) so they don't get annoyed and stop the party. The distance (number of bonds apart) and angle (cis, trans, free rotation) of the neighboring H will affect how much attention the observed H will have to pay (magnitude of J value). The observed H has to pay attention to *all* of the neighboring H simultaneously or it might miss something and get its party shut down (no fun). The resulting multiplet will show the different resonance frequencies for all possible variations on number of neighbors home (parallel spin) or not home (anti-parallel spin) and all possible levels of attention the host H could have.

Example:



Now consider compound X. H_a needs to pay a bit of attention to H_b (geminal coupling 0-3 Hz), H_b lives in the same house so will be at the party if it's home so it's not a lot of attention as H_b is having fun, but H_a doesn't get to completely ignore it (it's not polite to annoy the roommates!). Now H_c lives next door and is in a trans relationship with H_a (trans coupling 10-18 Hz), so not only can H_c hear the party it can see directly across into the windows! If H_c were in a cis relationship it couldn't see in the windows so H_a would not have to pay as much attention and the J value will be lower (cis coupling 6-14 Hz). H_a wants to be sure not to annoy H_c so pays a lot of attention to whether H_c is home (this results in a large coupling). There are two H_d down the street (allyl coupling 0-3 Hz), and both, either or neither of them may be home. So there are three possible levels of attention that H_a needs to pay, they are too far away to see in or not see in so both H_d can be considered as the same and result in a triplet. However at two doors down H_a only has a small amount of attention (small J value) it needs to pay to H_d as if H_d is annoyed then the closer neighbors probably are too.

So the total multiplet for H_a is (1H, $J = 16$ Hz (d), 3 Hz (d), 1 Hz (t))(see below for peak shapes). We know the 3 Hz is the geminal coupling and the 1 Hz is the allyl coupling as the 1 Hz is a triplet and geminal couplings can only be doublets.

Approximate Multiplets of Compound X:

