Nuclear Magnetic Resonance Spectroscopy:

Purpose: Connectivity, Map of C-H framework

Process:

In nuclear magnetic resonance spectroscopy, we are studying nuclei. Consider this circle to represent a nucleus of an atom: (i.e. hydrogen, carbon, phosphorus, boron, etc)

When it spins (like a top), it generates a magnetic field. Like a magnet, with a North and South pole, the nucleus also has a magnetic field, with a direction. The spinning nucleus generates a magnetic field, whose direction is represented by an arrow.

In a solution, there are thousands of atoms generating magnetic fields, all in random directions.

When an external magnetic field from an instrument is applied to the solution with the randomly spinning, atoms, the magnetic fields of the atoms are forced to align themselves parallel to the instrument’s field, either with or against the direction of the instrument’s magnetic field. The instrument’s external magnetic field is symbolized as $H_{app}$ (the “applied” magnetic field).

When aligned WITH the external magnet’s field:

$$H_{app}$$

$H_0$

When aligned AGAINST the external magnet’s field:

$$H_{app}$$

$H_0$
Overall, you see a mixture, but most of the atoms will align themselves parallel and with the external magnetic field's direction. Just a few will be parallel and against:

Based on this information, which is a lower energy state – aligned with or against – the external field?

Since most of the nuclei align themselves with that of the magnetic field of the instrument, it must be a naturally lower energy state:

The difference in energy of these two energy states, $\Delta E$, is very small and corresponds to low energy radiowaves. If energy of the correct radiofrequency is applied to the system, the energy is absorbed and the nucleus in the system can jump to the higher energy state.

When this jump occurs, the nucleus inverts its magnetic field by inverting its spin in the process. This is called "spin flipping".

**Nuclear Magnetic Resonance:**
The nucleus and the external magnetic field are said to be "in Resonance", at the frequency when spin flipping occurs.

The energy at which the "spin flipping" occurs determines where on the X-axis of an NMR the signal will appear. While all protons may look the same when we draw them ("H"), not all protons have the same radiofrequency for "spin flipping". The presence of electrons surrounding a proton also have an effect.
Electrons themselves generate their own tiny local magnetic fields, and these are always OPPOSITE to that of the external magnetic thus electron magnetic fields reduces the effect of the magnetic field of an instrument, making it feel less strong. Because of the presence of electrons, we say that the nuclei are “shielded” from the full effect of the instrument's magnetic field.

An electron-rich proton: “Shielding”

The nucleus never feels the full effect of the magnetic field ($H_{\text{app}}$) of an instrument. They feel a reduced magnetic field ($H_{\text{app}} - H_{\text{local}}$, where $H_{\text{local}}$ is the magnetic field of the electrons).

More electrons (more “shielded”, larger $H_{\text{local}}$) results in a greater reduced magnetic field and therefore a position further to the right on the X-axis of the NMR spectrum.

An electron-poor proton: the nucleus feels most of the full force of the instrument’s magnetic field

Less electrons (less “shielded” or “deshielded”, smaller $H_{\text{local}}$) results in a larger overall magnetic field and therefore a position further to the left on the X-axis of the NMR spectrum.

The electrons create tiny differences in the overall magnetic fields experienced by different proton nuclei but they are still detectable and as a result we see a different signal on different positions of the X-axis on the NMR spectrum for each chemically (or perhaps better called electronically) different proton nuclei.

Technical Info: NMR instruments contain a magnet, into which the sample to be analyzed is placed. The magnetic field of the instrument is generated using a superconducting magnet, of niobium/titanium alloy, which is cooled in liquid helium (to 4 Kelvin) whose container is cooled by a liquid nitrogen container to maintain low temperatures.
NMR instruments are identified by the operating frequency at which they operate. Instrument frequencies range from 60–600 MHz and the higher the frequency, the more detailed the spectra. Hydrogen nuclei require one frequency range. Carbon-13 nuclei require a different frequency range. The instrument’s external magnetic field and that of the individual nucleus or nuclei being studied determine the exact radiofrequency.

The sample is run in a dilute solution made from 1-200 mg of material, diluted by a deuterated solvent. Deuterated solvents have deuterium (²H isotope, with extra neutron), not the usual protons (¹H) in their structures. If you use a solvent with regular protons, the signals of protons of the solvent would appear on your spectrum, potentially obscuring signals you need to see. The most common deuterated solvent is deuterated chloroform, CDCl₃, which is 99.8% deuterated. 0.2% is still CHCl₃, which may appear on your spectrum at 7.2600 ppm. Another solvent commonly used is C₆D₆, or deuterated benzene.

General Notes:
1. We usually study one type of nucleus at a time. Each nucleus requires a different amount of energy (radiofrequency) to cause the spin flipping to occur.

   Not every nucleus generates a magnetic spin. All nuclei with an odd number of protons (¹H, ¹⁴N, ¹⁹F) or neutrons (¹³C isotope) show magnetic properties. In Organic Chemistry, we focus on the Hydrogen-1 isotope (¹H) and the Carbon-13 (¹³C) isotope as they are the most widely used nuclei in the spectroscopy of organic compounds.

2. Those protons surrounded by a lot of electron density are electron-rich and are called “shielded”. These are found on the right side of the NMR spectrum. Those protons that are electron-poor are called “deshielded” and are found on the left side of the NMR spectrum.

3. The position on the chart at which a nucleus absorbs is called its "chemical shift". The X-axis of a proton NMR spectrum ranges from 0-10 (as high as 14) ppm. The unit “ppm” stands for “parts per million” and is a standardized unit for the signal.

4. On most spectra, a calibration peak will be visible. There are two possibilities:
   a. Tetramethylsilane (TMS) may be added to the solution. The 12 hydrogen atoms in this solvent are all exactly the same and are assigned a value of 0.0000 ppm.
   b. The use of deuterated solvents provides us with an internal standard. Deuterated chloroform, CDCl₃ has a trace amount of CHCl₃ – 0.2% of a CDCl₃.
solution is CHCl₃ – causing a peak with a chemical shift value (X-axis) of 7.2600 ppm, which could be used for calibration.

While both proton NMR and carbon-13 NMR are widely used in the determination of organic structures, proton NMR provides a larger amount of information that carbon NMR. Due to the large abundance of protons in most organic molecules, a relatively small sample of material is required and a good spectrum can usually be obtained in a short period of time. We will study carbon NMR in Chem 332. Both may be found in McMurry, in Chapter 13.

Four Factors of Proton NMR (PMR OR ¹H NMR):
1. **Number of signals on spectrum**: Number of chemically different protons (symmetry)
2. **Chemical Shift**: value on the X-axis; this provides information regarding what kind of chemical environment the proton is in (electron-rich or electron-poor).
3. **Integration**: Electronic measurement of peak areas; this provides you with the number of chemically equivalent protons producing each signal on the spectrum.
4. **Splitting Patterns**: Complexity of peak patterns; information is gained regarding the connectivity of neighboring protons.

1. **SYMMETRY**:
When determining symmetry, remember that symmetrical hydrogen atoms are called “equivalent” and are interchangeable (so you cannot tell them apart). For instance, the three hydrogen atoms of a methyl group are all exactly the same. You can see when I rotate the three labeled hydrogen atoms, that they have changed positions:

But when the labels are removed, you cannot tell them apart. If you cannot tell them apart, they are the same.

This will be the case any time you have the same atoms or groups of atoms attached to the same carbon(s).

**Find the symmetry**:
Also watch for planes of symmetry:

How many different kinds of protons are in each of the following molecules? (i.e. how symmetrical are these?)

**Methane (CH\textsubscript{4}):**

Ethane (CH\textsubscript{3}CH\textsubscript{3}):

**tert-Butyl Methyl Ether ( (CH\textsubscript{3})\textsubscript{3}COCH\textsubscript{3}):**
Ethyl Ether ($\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3$):

Isobutane, $((\text{CH}_3)_3\text{CH})$:

And what about these?

$\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-Cl}$
(CH₃)₂-CH-CH₂-Cl

HO-CH₂-CH₂-C(CH₃)₃
What about these? How many types of protons in each?

- Cl-CH₂-CH₂-Cl
- Cl-CH₂-CH₂-CH₂-Cl
- Cl-CH₂-CH₂-Br

**Symmetry in Aromatic rings:**

Aromatic compounds: Remember that the alternating double bonds of aromatic benzene rings are just a resonance form:

\[
\begin{array}{c}
\text{Benzenoid} \\
\equiv \\
\text{Conjugated double bonds}
\end{array}
\]

Monosubstituted:

Disubstituted - Para
Disubstituted - Meta

Disubstituted - Ortho

2. CHEMICAL SHIFT - Electronic Environments

Protons on sp$^3$C (no EWG near by) 0-2 ppm

Protons on sp$^3$C next to unsaturations 1.8-3 ppm

Protons on sp$^3$C with O, N or X attached 3-5 ppm

Protons on sp$^2$C (C=C) Aromatic protons 6.5-8.5 ppm

Proton on C=O (aldehyde) 8.5-10 ppm

Proton of CO$_2$H 10-14 ppm
Protons of Hydroxyl groups:
Aliphatic (alcohols)  2-5 ppm

Aromatic (phenols)  6-10 ppm

~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

A little extra commentary about hydroxyl groups (as well as amine/amide and carboxylic acid protons):

These protons are called “exchangeable” protons. Under acidic conditions, these protons swap on a regular basis:

\[
R-\text{O-H} \overset{H^+}{\underset{H^+}{\leftrightarrow}} R+\text{H} \quad R+\text{H} \underset{H^+}{\rightarrow} R-\text{O}
\]

This distorts the peak of the proton, making it appear broader and not as sharp in appearance as the other protons.

Find the alcohol proton (OH):

An easy way to identify which peak is an alcohol proton is to pick out which peak looks shorter and less sharp.
In the lab, an easy NMR trick to distinguish an alcohol proton from others on a spectrum is to add deuterated water (D$_2$O) to the sample. Deuterium does not have a nucleus that can generate a magnetic field so it cannot show up on the NMR spectrum. If deuterium substitutes for a proton, the signal will disappear!

\[
\begin{align*}
R-O-H & \xrightarrow{D^+} R-D-H + \xrightarrow{-H^+} R-O-D \\
\text{signal} & \quad \text{no signal}
\end{align*}
\]

Consider the proton NMR of isobutyl alcohol:

The alcohol signal is visible at 2.0 ppm (broad singlet).

So you run the original compound itself, as it is normally, then you open the sample, add D$_2$O, recap the tube and rerun the sample again.

Now view deuterated isobutyl alcohol:

The OH peak at 2.0 ppm is missing after using D$_2$O. Easy method to identify an exchangeable protons.
3. INTEGRATION - Ratio of Protons in each signal

- Peak areas are electronically measured by instrument:
- To determine the **ratio of protons** producing signals, divide each peak area by smallest area to determine whole number ratio of peaks

Remember: the total of protons calculated in the integration should equal number of protons in molecular formula

4. SPLITTING PATTERNS - “Spin-Spin Coupling”

What is “splitting”? Notice how many signals are not single peak signals but are multiple peaks together.

Splitting occurs due to the interaction of the magnetic fields of neighboring nuclei.
In proton NMR, only the magnetic fields of protons can interact with each other. Other nuclei, like carbon-13, show magnetic qualities and can do nuclear magnetic resonance, but these other nuclei have no effect on the magnetic fields of protons (no interactions).

**Splitting only occurs between non-equivalent (non-symmetrical) protons.** This is why recognizing symmetry can be important. Consider butane: \( \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_3 \) has two \( \text{CH}_2 \)-s that are next door to each other, but they are equivalent and therefore cannot split each other. Same for Cl- \( \text{CH}_2-\text{CH}_2-\text{Cl} \).

Splitting helps determine the number of protons on adjacent, neighboring carbon atoms

How does this possible?

You've already seen how the magnetic fields interact - those from the instrument and surrounding electrons. These magnetic fields impact where on the X-axis the signal appears (the chemical shift value).

Splitting occurs when the magnetic fields of neighboring protons also act to either increase or decrease the overall magnetic field that a nucleus might normally feel.

Generally, the splitting effect is very local - typically only protons on adjacent carbon atoms can have an effect and cause splitting to occur:

\[
\text{H}_a \quad \text{H}_b
\]

Consider proton \( \text{H}_a \) having just one adjacent proton, \( \text{H}_b \). Remember that magnetic fields interact and can either increase or decrease the overall effective magnetic field felt by a proton. This adjacent proton, \( \text{H}_b \), creates a magnetic field when it spins and this can either add to or subtract from the overall magnetic field of \( \text{H}_a \):
In the first case, the new magnetic field of $H_b$ would ADD to that of the instrument’s applied magnetic field, $H_{app}$, and increase the overall magnetic field. The larger the overall magnetic field, the further to the left a signal appears increasing the chemical shift.

In the second case, the new magnetic field of $H_b$ would SUBTRACT from and decrease the overall magnetic field. The smaller the overall magnetic field, the further to the right a signal appears decreasing the chemical shift.

The term “splitting” refers to the fact that the signal no longer looks like just a single peak, but instead multiple peaks. The number of peaks is determined by (a) how many adjacent protons there are, and (b) whether their spin is adding or subtracting to the overall magnetic field. Probability and statistics plays a role in this.

Consider again that proton $H_a$ has one adjacent proton, $H_b$. There is a 50:50 chance that adding or subtracting of $H_b$’s magnetic field could happen. Half of the time a shift to the left occurs (add) and half the time a shift to the right occurs (subtract). The overall picture winds up being a combo of the two, as half of the time the signal shifted to the left and half the time the signal shifted to the right (and is no longer in the middle where it was originally expected to be).

1. Signal on proton NMR at freq of spin-flipping before incorporating mag field of neighboring proton

2. Magnetic field of neighboring proton can either align with (add to, shift left) or against (subtract from, shift right) the instrument’s magnet, changing the strength of the overall magnetic field felt by the proton

3. This results in TWO signal peaks appearing, in a 1:1 ratio, equal distances from the position of the original signal
Consider having two neighboring protons next door. What is the probability for what the magnetic fields may do?

The two H_b magnetic fields could both ADD or both SUBTRACT which causes shifting, left and right, as seen in the previous example. Alternatively, they could also take turns one adding and one subtracting (H_{b1} add, H_{b2} subtract or H_{b1} subtract, H_{b2} add) which cancels out the overall effect on the magnetic field and no shifting occurs. This happens twice as often than the double add or double subtract. The splitting pattern that results?

Three peaks form.

1. signal on proton NMR at freq of spin-flipping before incorporating mag field of neighboring proton

2. Magnetic field of neighboring protons can either both align with (add to, shift left) or both against (subtract from, shift right) the instrument’s magnet, or do both, (one with, one against, two options) changing the strength of the overall magnetic field felt by the proton

3. This results in THREE signal peaks appearing, in a 1:2:1 ratio, center peak where the original signal would have been and two other peaks, equally shifted left and right from the position of the original signal

Consider having three protons next door. What options should we consider?

The three H_b neighboring protons could ALL ADD, could ALL SUBTRACT, causing shifting to the left and right. Alternatively, they could also vary the ADD/SUBTRACT with two doing ADDs while one SUBTRACTs (slight shift left) or two doing SUBTRACTS while one does an ADD (slight shift right). Four peaks form.

Three neighboring protons:
So having 1 proton next door produces a signal with two peaks...
And having 2 protons next door produces a signal with three peaks...
And having 3 protons next door produces a signal with four peaks...

**N+1 Rule** - The (original) signal of a proton (or set of equivalent protons, as determined by integration), with N number of protons on an adjacent carbon atom, will be split into N+1 peaks in the final signal on the spectrum.

**More Examples: Splitting back and forth**

1. 
   \[ \text{signal on proton NMR at freq of spin-flipping before incorporating the magnetic field of the neighboring proton} \]

2. Magnetic field of neighboring protons can either all increase the overall magnetic field, all decrease the overall magnetic field or do both unevenly (2 Add, 1 Subtract or 2 Subtract, 1 Add) resulting in slight shifts left or right.

3. This results in FOUR signal peaks appearing, in a 1:3:3:1 ratio, 2 shifted left and 2 shifted right, equal distances from the position of the original signal.
Now that you are becoming familiar with what splitting patterns equate to, your goal will be to use the splitting patterns to determine the molecular fragments of a molecule (you need to build the puzzle pieces to put together the puzzle!). The splitting pattern tells you what is “next door”... When analyzing a spectrum, count your number of peaks in the signal and subtract 1!

What about this one? What is THIS?

This is not an evenly split signal, so no splitting pattern can be counted for this mess! Call it a “multiplet” and move on... If you can't count N+1, you can't figure out N... But you still have a chemical shift and integration result to work with.

How many neighbors? Check each splitting pattern and determine the number of neighbors.
Aromatic Rings – Splitting Patterns

Monosubstituted: If a spectrum shows an integration of FIVE protons in the aromatic region (6.5-8.5 ppm), the ONLY option will be a monosubstituted aromatic ring – therefore splitting pattern analysis is not necessary.

For X = CH₃:
Since the aromatic region integrates to a total of 5, the only possible aromatic ring is one that is monosubstituted. Splitting pattern doesn't matter.

**Disubstituted:** Each of the following shows an integration of **FOUR** protons in the aromatic region (6.5-8.5 ppm).

![Chemical structures](image)

Example of Ortho ring splitting pattern in aromatic region:

![Diagram](image)

No plane of symmetry. All four protons are different. All four protons undergo splitting. Note the two signals that are overlapped... these make the analysis harder...

![NMR spectrum](image)

Note the extra fine splitting that makes the doublet look like more than a doublet. This extra fine splitting is called “W” coupling. It happens in aromatic rings, due to shorter bonds and occurs between protons that you could draw a “W” between.

![Chemical structure](image)

It would be easier for you if you were to just ignore the extra fine splitting. Please feel free to ask/clarify if you think you are seeing “W” coupling that is confusing you.
Example of Meta ring, aromatic region:

No plane of symmetry again but this is the only disubstituted ring that can have a singlet in the aromatic region of the NMR.

Example of Para ring, aromatic region:

Plane of symmetry and two types of protons on the ring.

Integration ratio: 2 and 2.

Splitting patterns? Doublets for each type of proton.

Break down of most typical splitting patterns:

<table>
<thead>
<tr>
<th>Peaks</th>
<th>N+1</th>
<th>N</th>
<th>Protons Next Door</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singlet</td>
<td>1</td>
<td>0</td>
<td>none</td>
</tr>
<tr>
<td>Doublet</td>
<td>2</td>
<td>1</td>
<td>one (CH or OH)</td>
</tr>
<tr>
<td>Triplet</td>
<td>3</td>
<td>2</td>
<td>two (CH₂ or two CH)</td>
</tr>
<tr>
<td>Doublet-Doublet</td>
<td>3</td>
<td>2</td>
<td>one and one (CH and OH or two different CH's)</td>
</tr>
<tr>
<td></td>
<td>(2/2)</td>
<td>(1/1)</td>
<td></td>
</tr>
</tbody>
</table>
Quartet  4  3  three (CH₃)
Doublet-Triplet  4  3  one and two  
                   (2/3)  (1/2)  (CH and CH₂)
Quintet  5  4  four (CH₂- -CH₂)
Doublet-Quartet  5  4  one and three  
                   2/4  1/3  (CH and CH₃)
Sextet  6  5  five (CH₂- -CH₃)
Septet  7  6  six (CH₃- -CH₃)
Nonet  9  8  2CH₃ and a CH₂
Multiplet  ??  ??  ??

End of Qual Lecture Two.
What should you do after today? Continue filling out your answer sheet.
1. Identify the number of signals on your NMR.
2. Identify the Chemical Shift for each signal.
3. Calculate the integration ratio for each signal. Sum total must equal total number of H's in the molecular formula.
4. Work out your splitting patterns (N+1) and your number of neighboring protons (N)

Set up a table to organize your information, listing the chemical shift, integration calculation for each signal and the splitting pattern (so you can figure out N):

Ex.

<table>
<thead>
<tr>
<th>Chemical Shift</th>
<th>Integration</th>
<th>Splitting Pattern</th>
<th>Fragments</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9 ppm</td>
<td>3H</td>
<td>t</td>
<td>CH₃-CH₂</td>
</tr>
</tbody>
</table>

Next week, we will talk about how to assemble the molecule's fragments from each signal.