**Organic Chemistry: CHEM2322**

**Structure Determination**

**NMR**

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**NMR**

- **NMR** or **Nuclear Magnetic Resonance** spectroscopy is the most powerful technique for the determination of molecular structure known today.
- It works because many types of nuclei (not all) behave as if they were spinning about an axis; they are said to have **spin**.
- In order to have spin a nucleus must have an odd number of protons or neutrons.
- The most useful nuclei have spin values of 1/2 and are \(^1H, ^{13}C, ^{15}N, ^{19}F, ^{31}P\), other are possible for example \(^{105}Pd\) is 5/2.
- However, we will only be concerned with \(^1H\) sometimes called proton NMR and \(^{13}C\) called carbon NMR.
- Since the nucleus is positively charged nuclei with spin behave as very tiny bar magnets.
- Due to these magnetic properties they therefore interact with an external magnetic field.
- This external field as you may recall from Gen. Chem. is denoted as \(B_0\).
- So what happens when we apply a magnetic field to nuclei with spin?

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**NMR**

- As you might expect before the field is applied the spins of the nuclei are arranged randomly.
- However, when the external field is applied the nuclei orientate so their magnetic field is either aligned with the external field or against it.
- As you might guess the lowest energy is when both fields are aligned hence most of the nuclei align this way.

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If we now irradiate these nuclei with electromagnetic radiation of the proper frequency, energy absorption occurs and the lower energy state spin-flips to the higher energy state.

- When this happens the nuclei are said to be in resonance with the applied EM radiation hence NMR.
- The exact frequency necessary for resonance depends both on the nuclei and the applied field. As the external field increases in strength so does the energy differences between both states.
NMR

- In practice, superconductive magnets that produce very strong magnetic fields are used typically 4.7-70 T (tesla)
- You may also hear chemists refer to a spectrometer as a 200 MHz machine or 400 MHz etc… This is the frequency $^1\text{H}$ nuclei resonates
- $^{13}\text{C}$ resonates roughly $1/4$ of the frequency of the $^1\text{H}$ nuclei, so on a 400 MHz machine the carbon resonates at 100 MHz, and on a 200 MHz machine it's 50 MHz and so on...
- Again energies involved here are small a 200 MHz machine use just $8 \times 10^{-6}$ kJ/mol in energy
- Quick test:

\begin{align*}
\text{Magnetic nuclei} & \quad \text{Nonmagnetic nuclei} \\
^1\text{H} & \quad ^{12}\text{C} \\
^1\text{H} & \quad ^{13}\text{C} \\
^{14}\text{N} & \quad ^{18}\text{O} \\
^{31}\text{P} & \quad \{ \text{No NMR observed} \}
\end{align*}

NMR Absorptions

- So you might expect all nuclei of the same type in a molecule to absorb energy at the same frequency.
- If this was true we would just see a single NMR absorption band in $^1\text{H}$ and $^{13}\text{C}$, for example. This would be of little use in structure determination
- In fact the absorption frequency for a nuclei can vary. This is due to electrons which surround the nucleus
- As they move around they set up tiny magnetic fields of their own. This helps shield the nucleus from the full applied field strength as a result the field felt by the nucleus is weaker. We say the nucleus is shielded
- This is summarized by:

\[ B_{\text{effective}} = B_{\text{applied}} - B_{\text{local}} \]

- Since each specific nucleus in a molecule has a slightly different electronic environment each is shielded differently and therefore absorbs differently
- Let's have a look

\begin{align*}
\text{(a)} & \quad \text{Intensity} \\
\text{Chemical shift (ppm)} & \quad \text{TMS} \\
\text{(b)} & \quad \text{Intensity} \\
\text{Chemical shift (ppm)} & \quad \text{TMS}
\end{align*}
NMR Absorptions

- So what does an NMR spectrometer look like?

![Diagram of an NMR spectrometer]

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NMR Timescale

- NMR differs from IR in timescale, IR is a very fast process typically taking place in $10^{-13}$ s; NMR however take place on a timescale of $10^{-3}$ s
- We can think of this like different shutter speeds in a camera, with a slow shutter speed leading to blurring as time averaging occurs
- This happens in NMR if two species interconvert fast than $10^3$ times per second; NMR with show one averaged spectrum not two. Such a case is cyclohexane
- This is extremely useful if we wish to calculate activation energies; knowing the temperature at which signal burring occurs we can calculate the activation energy for ring flipping

![Diagram of cyclohexane molecule]

$^1$H NMR: 1 peak at 25°C
2 peaks at -90°C

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Chemical Shifts

- NMR spectra are displayed on charts that show the applied field strength increasing from left to right
- To define where a peak comes on the chart below it is calibrated either with tetramethylsilane (TMS) or on the residual solvent peak of the NMR solvent
- The position on the chart where a nucleus absorbs is called its chemical shift, with the chemical shift of TMS set to zero

![Chemical shift chart]

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Chemical Shifts

- As you may have noticed the charts are calibrated using the delta ($\delta$) scale where 1 $\delta$ is equal to 1 part per million (ppm) of the spectrometer operating frequency
- $\delta$ is derived using the following equation

$$\delta = \frac{\text{Observed chemical shift (number of Hz away from TMS)}}{\text{Spectrometer frequency in MHz}}$$

- The reason that the $\delta$ system was developed was to ensure that peak positions remain constant across spectrometers which may have different field strengths
- Most $^1$H signals come between 0-10 ppm and for $^{13}$C its 0-220 ppm
- One advantage of a higher field machine is that dispersion is far greater as there are more Hz per ppm this leads to the peaks begin more widely spread out avoiding overlap

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• Ok so let’s focus on carbon NMR
• Remember only $^{13}$C is NMR active problem is its natural abundants is only 1.1%
• This could mean we many have to noisy spectra as we have such a week signal, however we can use a trick call **Fourier-transform** (FT)-NMR and **signal averaging**
• FT increases the speed of acquisition and **signal averaging** increases the instruments sensitivity
• Signal averaging works by measuring the same spectrum many times then combining them into one.
• This greatly reduces the signal to noise of the spectrum
• However even with these techniques it still takes 15 mins with 100 mg of compound to obtain a good $^{13}$C-NMR spectrum

• In it simplest form carbon NMR allows us to count the number of different carbons
• However it tell us much more as certain types of carbon come in specific places
• For example C-C single bonded carbons are always found at the high field end with increasing unsaturation signals moving down field
• Let’s have a look as some spectra
But wait we can do more!

- A technique allows us to find out how many hydrogen atoms are bonded to our carbons.
- This is called distortionless, enhanced by polarization transfer or DEPT.
- This allows us to distinguish which signals are due to CH₃, CH₂, and CH.
- Normally when we run a DEPT analysis, we run a normal carbon spectrum first (called a broadband decoupled spectrum) to show all the carbons.
- Then we run a DEPT 90 which shows just the signals due to CHs.
- Finally, we run DEPT 135 with places the CH₃ and CH up and the CH₂ groups down.
- So let’s have a look at these then.
DEPT $^{13}$C-NMR

<table>
<thead>
<tr>
<th>Broadband decoupled</th>
<th>DEPT-90</th>
<th>DEPT-135</th>
</tr>
</thead>
<tbody>
<tr>
<td>C, CH, CH$_2$, CH$_3$</td>
<td>CH</td>
<td>CH$_2$, CH are positive</td>
</tr>
<tr>
<td>CH</td>
<td>DEPT-90</td>
<td></td>
</tr>
<tr>
<td>CH$_2$</td>
<td>Negative DEPT-135</td>
<td></td>
</tr>
<tr>
<td>CH$_3$</td>
<td>Subtract DEPT-90 from positive DEPT-135</td>
<td></td>
</tr>
</tbody>
</table>

What can we use $^{13}$C-NMR for?

- What can we use it for?
- Let's say you did this reaction below

$\text{H}_2\text{O}$ $\text{Cl}$ $\text{CH}_3$ or $\text{CH}_2$

\[ \text{1-Chloro-1-methylcyclohexane} \]

\[ \text{I-Methylecyclohexane} \]

\[ \text{Methylecyclohexane} \]

$^{1}$H-NMR

- Just like with $^{13}$C-NMR, $^{1}$H-NMR allows us to see how many different $^{1}$H nuclei we have in a compound.
- Sometimes it is easy to spot different $^{1}$H nuclei sometimes it is hard, let's have a look at how to spot different $^{1}$H nuclei.
- One way to think of this is to replace the hydrogens with an X and ask yourself is it the same or different.
- Here we can see that the CH$_2$s are different from the CH$_3$s.

$^{1}$H-NMR Proton Equivalence

- However the CH$_3$s are identical and are said to be homotopic.

\[ \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_3 \rightarrow \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-X \]

- But the CH$_2$s are not identical and are said to be enantiotopic. However enantiotopic hydrogens are magnetically equivalent and therefore have the same NMR absorption.

\[ \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-X \rightarrow \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-X \]

The two replacement products are enantiomers.
1H-NMR Proton Equivalence

- What happens if we add a chiral center?
- Again we have pro-R and pro-S hydrogens, this time we would be generating a diastereomer.
- Such protons are said to be diastereotopic. Diastereotopic hydrogens are neither chemically or magnetically equivalent therefore we would expect them to have different NMR absorptions.

Chemical Shifts in 1H-NMR

- Remember 13C-NMR we said chemical shifts come from differences in the local magnetic fields of the electrons surrounding the nuclei
- Electron rich or shielded nuclei moving to higher field and electron deficient nuclei moving to lower field
- Most 1H-NMR shifts come between 0 and 10 δ (See your hand out)
- By remembering the rough positions it’s possible to tell quickly what type of protons a molecule contains

Integration in 1H-NMR

- Look at the spectra below do you notice that one peak is bigger than the other?
- A special feature of 1H-NMR is that the area of the peak is directly proportional to the amount of protons causing a specific peak!
- As you can see there are two types of hydrogens 9 of one kind and 3 of another
- Therefore we should expect to see a peak area ratio of 1:3 (3:9)
Spin-Spin Splitting $^1$H-NMR

- This is probably the most important characteristic of $^1$H-NMR and allows us to get information on what the neighboring protons are.
- Consider the spectrum of CH$_3$CH$_2$Br below.
- Why does the CH$_3$ appear as a so called triplet and the CH$_2$ as a quartet?
- The answer is a spin-spin interaction called coupling.

Let’s first consider the splitting of the CH$_3$ signal, which is a triplet.
- There are two adjacent protons on the neighboring CH$_2$Br these can align with or against the magnetic field.
- This produces a tiny effect which is felt by the CH$_3$ protons.
- There are now three ways in which the spins of the two CH$_2$Br protons can align.
- Both with the applied field this results in the CH$_3$ proton experiencing a field slightly larger than would normally be the case and the proton’s resonance is slightly down field.
- One with and one against the applied field hence just the applied field felt by the CH$_3$, there are two arrangements for this.
- Both against the applied field this results in the CH$_3$ proton experiencing a field slightly lower than would normally be the case and the proton’s resonance is slightly up field.
- A given molecule can only adopt one of the three alignments but overall a triplet signal is formed with the ratio 1:2:1.
- In the same way the CH$_2$Br signal is split into a 1:3:3:1 quartet by the three spins of the neighboring CH$_3$ group.

$n + 1$ Rule

- As a general rule, there are $n + 1$ peaks where $n$ is the number of equivalent protons.
- Let’s consider the spectrum of 2-bromopropane.
- There are two types of protons first the CH$_3$, they have a neighboring CH so $n + 1 = 2$ so we expect to see a doublet and do!
- For the CH it is neighboring 2 equivalent CH$_3$ groups (6 protons) so we expect to see $6 + 1 = 7$ a septet.
**$n + 1$ Rule**

- The distance between the peaks/lines is called a **coupling constant** and is denoted by the letter $J$
- Coupling constants are measure in Hz and in a proton NMR are normal between 0-18 Hz
- However the exact value is dependent on the geometry of the molecule with open alkyl chains, $J = 6-8$ Hz
- Importantly the same coupling constant is shared between the protons that are coupling therefore in $\text{CH}_3\text{CH}_2\text{Br}$ both the triplet and quartet must have the same constant and do $J = 7$ Hz
- If two types of protons you think are coupled do not share within experimental error the same coupling constant they’re not couple together!

<table>
<thead>
<tr>
<th>Number of equivalent adjacent protons</th>
<th>Type of multiplet observed</th>
<th>Ratio of intensities</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Singlet</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>Doublet</td>
<td>1:1</td>
</tr>
<tr>
<td>2</td>
<td>Triplet</td>
<td>1:2:1</td>
</tr>
<tr>
<td>3</td>
<td>Quartet</td>
<td>1:3:3:1</td>
</tr>
<tr>
<td>4</td>
<td>Quintet</td>
<td>1:4:6:4:1</td>
</tr>
</tbody>
</table>

**To Sum Up**

- **Rule 1:** Chemically equivalent protons do not show spin-spin coupling.
- The equivalent protons must be on the same carbon or different carbons but the signals don’t split. **The protons must ALL be identical!**

- **Rule 2:** The signal of a proton that has $n$ equivalent neighboring protons is split into a signal of $n + 1$ peaks with a coupling constant $J$.
- Protons further than two carbons away don’t usually couple, however with $\pi$-bonds you can see small coupling at further distances.

- **Rule 3:** Two groups of protons coupled to each other have the same coupling constant $J$.

**Examples**

- **OK:** Let’s walk through this spectrum
  - Interestingly: no coupling between carbons is seen due to the low abundance of $^{13}$C.
  - Coupling between $^{13}$C and $^1$H is removed by a second irradiation during $^{13}$C-NMR and is beyond the scope of this course.
  - Just remember that most $^{13}$C are proton decoupled!
• Up until now we have dealt with straightforward patterns, however it is often seen that protons in a molecule may accidentally overlap due to chemical shift.

• Consider toluene below all the aromatic protons are not all equivalent their chemical shifts overlap so a complex spectrum results.

• Yet another complication to $^1$H-NMR arises when the signal is split by two or more nonequivalent protons.

• Here the $n + 1$ rule breaks down.

• So how do we understand the multiplicity below.

• General rule chemical shift gives position, coupling constants give multiplicity.

• First like toluene the aromatic signals overlap to yield a complex pattern.

• The aldehyde signal at C1 is split by the proton on C2 to yield a double at $9.69 \delta$, $J = 6$ Hz.

• The vinylic proton is on C3 is split by the proton on C2, $J = 12$ Hz, into a doublet at $7.49 \delta$.

• The C2 vinylic proton is split by C1, $J = 6$ Hz and by C2, $J = 12$ Hz, into a doublet of doublets at $6.73 \delta$. 
Complex Splitting Patterns

- One further point you may have noticed that some peaks are bigger than others in the doublet of C3 and the doublet of doublet of C2.
- In C2 the two left-hand peaks are bigger than the two right-hand peaks, this size difference happens only when two nuclei are close in chemical shift.
- C2 6.73 $\delta$ and C3 7.49 $\delta$
- The peaks closest to the coupling partner tend to bigger so in C2 it’s the left-hand peaks while in C3 it is the right-hand peak.
- This skewing or roofing is useful as it tells you where to look for the coupling partner, look towards the direction of the larger peaks.

Uses of $^1$H-NMR

- The understanding and routine employment of $^1$H-NMR is the bread and butter of a research chemist's life.
- For example the $^1$H-NMR would easily tell you which product was formed in the reaction below.

$$\begin{align*}
\text{Methylenecyclohexane} & \rightarrow \begin{array}{c}
\text{CH}_2 \\
\text{1. BH}_3 \text{THF} \\
\text{2. H}_3\text{O}^+ \text{OH}^-
\end{array} \rightarrow \begin{array}{c}
\text{CH}_3\text{OH} \\
\text{or}
\end{array} \\
\text{Cyclohexymethanol} & \rightarrow \begin{array}{c}
\text{CH}_3 \\
? \\
\text{1-Methylocyclohexanol}
\end{array}
\end{align*}$$
Summary

- When magnetic nuclei such as $^1$H and $^{13}$C are placed in a strong magnetic field, their spins orientate with or against the applied field.
- The nuclei are irradiated with radio waves and they spin flip from the lower energy (aligned) to the higher energy (against) spin state.
- **This absorption of rf energy is detected, amplified, and displayed as a Nuclear Magnetic Resonance (NMR) Spectrum**
- Each electronically distinct $^1$H and $^{13}$C nucleus in a molecule comes into resonance at a slightly different value, therefore producing a unique absorption.
- The exact position of a signal is called chemical shift caused by tiny local magnetic fields that shield the nucleus. The chemical shift is measured in $\delta$.
- The NMR is calibrated with TMS or the residual solvent peak.
- Nearly all NMRs today are **FT-NMRs** as this gives better signal to noise and shortens acquisition times.
- $^{13}$C-NMR DEPT experiments allow us to identify which carbons are CH$_3$, CH$_2$, CH, and C.
- In $^1$H-NMR the area under the peak is proportional to the number of protons.
- In addition, coupling of neighboring protons leads to splitting with equivalent protons following the $n + 1$ rule with a coupling constant $J$. 