3B Analysis:

**What is Nuclear Magnetic Resonance - NMR**
- A very powerful analytical technique allowing chemists to identify even the most complex of structures.
- Developed by chemists and physicists together it works by the interaction of magnetic properties of certain nuclei and their chemical environment.
- This technique only works with atoms with an odd number of nucleons (protons and neutrons).
- At A2 this will be applied to $^1_1$H and $^{13}_6$C NMR.

**Nuclear spin**
- All nucleons spin, and pair up just as electrons do.
- Those with an odd number of nucleons will have a nucleon that has not been able to pair up.
- A spinning nucleus such as hydrogen behaves as a spinning charge and generates a magnetic field.
- For example - $^1_1$H and $^{13}_6$C possess spin whereas $^{12}_6$C does not.
- It can be likened to a bar magnet:

![Diagram of nuclear spin](image)

- When this is placed in an external magnetic field it will align with or against the field.
- The nuclei which align parallel are at a lower energy than those aligned anti-parallel.
Resonance:

- When they are subjected to a pulse of radiofrequency radiation, some nuclei flip from parallel to anti parallel:

- This promotes the nuclei from low energy spin (parallel) to high energy spin (antiparallel) thus absorbing energy - excitation.
- The frequency required to make this happen is specific to the difference in energy between the 'parallel' and 'antiparallel'
- The excited nuclei will at some point drop back to its low energy state (parallel) emitting the same amount of energy (that is specific for those nuclei)
- As electrons surround the nuclei, the energy needed to flip the nuclei depend on the environment they find themselves.
- This pulse oscillates so the nuclei continually flip or resonate back an forth, absorbing and emitting energy.
- The resonance is recorded as a trace.
- By looking at the field strength at which the nuclei absorb energy while resonating, we can work out the structure of a molecule

Nuclear shielding and chemical shift:

- The magnetic field felt by a nucleus depends on:

1) Applied magnetic field

2) The weak magnetic fields generated from electrons surrounding the nuclei and nearby atoms (the environment)

- The electrons in an atom also produce tiny magnetic fields which 'shield' the nucleus from the applied magnetic field.
- This is called nuclear shielding and the extent depends upon nearby atoms or groups of atoms.
- It alters the environment of a nucleus changing the energy gap.
- Nuclei in different environments will have different chemical resonance frequencies:
Chemical shift, δ:

- This is a place in the NMR spectrum where a nuclei absorbs and emits energy - resonates.
- The scale is in ppm or δ scale.
- The scale is measured against a reference signal, TMS = 0 chemical shift is measured from this.
- TMS is Tetramethylsilane:

![TMS molecule](image)

- This molecule has 12 equivalent protons giving rise to a single peak.
- This peak is assigned the value = 0
- All peaks of a sample under study are related to it and reported in parts per million.

Solvents for NMR spectroscopy:

- NMR is carried out in solution.
- The best solvent are usually hydrocarbons which will also produce a signal.
- Deuterated solvent are used as these have an even number of nucleons. These do not give a signal.
- CDCl₃ is usually used.
- This is volatile so can be recovered by evaporation.

Qu 1 - 2 P85

Carbon - 13 NMR spectroscopy

- 99% of any sample of carbon - ^12C
- 1% of any sample of carbon - ^13C
- This 1% has an uneven number of nucleons, this means it will have a magnetic spin and be detected using NMR

Typical carbon - 13 chemical shifts:

- The chemical shift indicates the environments the 'carbons' are in.
- An electronegative element causes a significant shift as carbon - 13 is sensitive to nuclear shielding.
The scale ranges 0 - 230, this means that each carbon is likely to have its own separate signal. Values will vary with different solvents.

Interpreting carbon - 13 NMR spectra
- 3 things obtained from a carbon - 13 NMR is:

1) The number of different carbons
2) The carbon environment
3) The relative ratio of each of the types of carbons

Propan - 1 - ol:
- 3 equally peaks indicating 3 different carbon environments
- A peak at ~ 64ppm: C - O
- A peak at ~ 27ppm: C - C (nearest the electronegative element O)
- A peak at ~ 10ppm: C - C (furthest from the electronegative O)

Propan - 2 - ol:
- 2 different sized peaks indicating 2 different carbon environments with different amounts of carbons
- A peak at ~ 64ppm: C - O
- A peak at ~ 27ppm: C - C
- The peak at ~ 27ppm is 2x the size of the peak of the one at ~64ppm as there are 2 equivalent carbons responsible for this peak

Analysis of carbon - 13 NMR spectra
Making predictions:
Example 1: A carbonyl compound, C₃H₆O has the following C - 13 NMR:
- 3 peaks indicating 3 different carbon environments
- A peak at ~ 205ppm: C = O
- A peak at ~ 37ppm: C - C (nearest the electronegative element O)
- A peak at ~ 6ppm: C - C (furthest from the electronegative O)
- Must be Propanal
Example 2: An aromatic compound, $\text{C}_8\text{H}_8\text{O}$ has the following C-13 NMR:

Possible structures:

<table>
<thead>
<tr>
<th>Carbon environments</th>
<th>4</th>
<th>5</th>
<th>3</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aromatic environments</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

Qu 1 - 2 P87 / Qu 1 P89
Proton NMR spectroscopy

Proton NMR:
- Is based around the $^1\text{H}$ which is a single proton.
- $^1\text{H}$ is much more abundant than $^{13}\text{C}$. 99.9% $^1\text{H}$ to 1.1% $^{13}\text{C}$.
- This means less needs to be used.
- Proton NMR is done in the same way as $^{13}\text{C}$ NMR and gives all the same information as $^{13}\text{C}$ NMR but for protons.
- In addition - it gives you information about adjacent protons (later)

Typical chemical shifts:
- The scale is narrower which means some signals will overlap.
- Actual chemical shifts can vary depending on environments.
- The scale should be used as a rule of thumb.

Integration traces:
- The area under the peak is proportional to the number of protons.
- On the NMR spectrum, the spectrometer measures this and is recorded as an integration trace.
- This is usually an integration line above the peak and can be measured for relative abundances.

Example: This is the proton NMR for $\text{C}_3\text{H}_6\text{O}_2$

- 2 equally sized peaks indicating 2 different proton environments
- This means that there are 2 areas of 3 protons
- A) peak at $\sim 3.7$ppm: O - CH$_3$ (nearest the electronegative element O)
- B) peak at $\sim 2.2$ppm: OC - CH$_3$ (furthest from the electronegative O)
- Must be methyl propanoate - CH$_3$COOCH$_3$

Qu 1 - 2 P91
Spin - spin coupling in proton NMR spectra

Spin - Spin coupling:

- Splitting patterns are worked out by considering the effect that adjacent, chemically different hydrogen's have on another signal in a given environment.
- The spin of the proton producing the signal is affected by each of the two forms of the adjacent hydrogen’s (parallel and anti parallel).
- One orientation enhances its field and the other reduces it.
- We can work this out by calculating the various possible combinations of alignment of adjacent protons.

Theory:

- The proton gives a signal by its magnetic field from its spin.
- Its signal is influenced by adjacent protons (on neighbouring carbons).
- Each proton will either spin in the same direction or the opposing direction.
- This means that each adjacent proton either enhances the magnetic field or diminishes it.
- There are 2 possibilities of equal chance per adjacent proton - enhancing or diminishing the magnetic field.
- This splits the signal given by the proton
Analogy:

- Imagine you had an opinion on something. If nobody influenced you, your opinion would be the same.
- If another person had a view on the topic, they would either agree or disagree with you.
- Their ideas would either enhance what you thought or diminish it.
- There would be 2 possibilities of equal chance per person agreeing or disagreeing with you:

  1 adjacent proton

  - The adjacent proton spins in the same or opposing direction.
  - Agree
  - Disagree

  2 adjacent proton

  - Each of the 2 adjacent protons spins in the same or opposing direction.
  - Agree - Agree
  - Agree - Disagree / Disagree - Agree
  - Disagree - Disagree

  3 adjacent proton

  - Each of the 2 adjacent protons spins in the same or opposing direction.
  - Agree - Agree
  - Agree - Disagree / Disagree - Agree
  - Disagree - Disagree

  - The adjacent proton spins in the same or opposing direction.
  - Agree
  - Disagree

  2 fields of equal intensity

  3 fields with an intensity of 1:2:1

  4 fields with an intensity of 1:3:3:1

- There is always an extra field than the number of adjacent protons - known as the n+1 rule:
### n+1 rule:

<table>
<thead>
<tr>
<th>Neighbouring H</th>
<th>Peaks</th>
<th>Signal</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>DOUBLET</td>
<td>1:1</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>TRIPLET</td>
<td>1:2:1</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>QUARTET</td>
<td>1:3:3:1</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>QUINTET</td>
<td>1:4:6:4:1</td>
</tr>
</tbody>
</table>

Signals for H in an O-H bond are unaffected by hydrogen's on adjacent atoms = singlet only

### NOTE: Pascal's triangles

- Just a note of interest. The signal peaks show the patterns described by Pascal's triangles:

```
1
1 1
1 2 1
1 3 3 1
1 4 6 4 1
```
The proton NMR spectrum of methyl propanoate:

- There are 3 areas of protons - this will give 3 areas of signal:

There are 3 areas of protons:

- These protons are adjacent to = 0 protons
- $n+1 = 1$ field
- Singlet

- These protons are adjacent to = 3 protons
- $n+1 = 4$ field
- Quartet

- These protons are adjacent to = 2 protons
- $n+1 = 3$ field
- Triplet

Qu 1 - 2 P93
**NMR spectra of OH and NH protons**

- These are not only difficult to identify but can also confuse the rest of the spectra.
- The reason for this is:
  1. Peaks can appear over a wide range of chemical shifts
  2. Signals are often broad
  3. There is no splitting pattern (due to ease of proton exchange in OH / NH - not needed)

- These signals can be removed by using heavy water, deuterium oxide, D₂O
- It is the same as water but the hydrogen's are replaced with deuterium.
- **Deuterium does not give a signal in NMR**

**Use of D₂O**

**How D₂O is used:**
- 1) An NMR is run as normal
- 2) A small amount of D₂O is added to the mixture, shaken and a second NMR is run

  The OH or NH signal disappears

**How it works:**

The Deuterium atoms in heavy water can replace the protons on OH or NH:

\[
\text{CH₃CH₂OH} + \text{D₂O} \rightleftharpoons \text{CH₃CH₂OD} + \text{HOD}
\]

Remember only atoms with an odd number of nucleons gives an NMR peak.

This means that the -OH $\rightarrow$ -OD and -NH $\rightarrow$ -ND

Deuterium has an even number of nucleons which means the -OD and -ND will no longer give a signal.
Example: NMR spectra of ethanol, (a) CH₃CH₂OH in water and (b) in D₂O, CH₃CH₂OD

**THE OH SIGNAL HAS DISAPPEARED**

Splitting from -OH and -NH protons:
- -OH and -NH peaks **DO NOT** split and **DO NOT** contribute to splitting
- Hydrogen bonding between water (solvent) and -OH / -NH protons broaden the peak

Qu 1-2 P95

**Spin - spin coupling examples**

1) Using splitting patterns:

H - NMR of 2 isomers of C₃H₅ClO₂: 1) CH₃CHCICOOH and 2) ClCH₂CH₂COOH both run in D₂O

As it is run in D₂O, we do not need to worry about the COOH signal.
- Quartet: is made from **proton(s)** adjacent to 3H (CH-CH₂)
- Doublet: is made from **proton(s)** adjacent to 1H (CH₃-CH)
- This leads to isomer 1) CH₃CHCICOOH
- Triplet: is made from **proton(s)** adjacent to 2H (CH₂-CH₂)
- As there is 2 of them, there must be 2 lots of CH₂’s next to each other
- This leads to isomer 2) ClCH₂CH₂COOH
2) Using splitting, integration and chemical shift:

**H - NMR of 4 isomers of the ester, C₄H₈O₂:**

A) CH₃CH₂COOCH₃  B) CH₃COOCH₂CH₃  C) HCOOCH₂CH₂CH₃  D) HCOOCH(CH₃)₂

2 of these esters are shown below, match the ester to the spectra:

<table>
<thead>
<tr>
<th>Chemical shift:</th>
<th>1.1</th>
<th>2.1</th>
<th>3.6</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Chemical shift 1" /></td>
<td><img src="image2.png" alt="Chemical shift 2" /></td>
<td><img src="image3.png" alt="Chemical shift 3" /></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Integration</th>
<th>3</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splitting pattern</td>
<td>Triplet - signal adjacent to 2H's</td>
<td>Quartet - signal adjacent to 3H's</td>
<td>Singlet - signal adjacent to 0H's</td>
</tr>
<tr>
<td>Interpretation</td>
<td>3H's adjacent to 2H's</td>
<td>2H's adjacent to 3H's</td>
<td>3H's adjacent to 0H's</td>
</tr>
<tr>
<td>Assignment</td>
<td>CH₃CH₂</td>
<td>O=CCH₂CH₃</td>
<td>O-CH₃</td>
</tr>
</tbody>
</table>

Put the assignments together: CH₃CH₂COOCH₃
<table>
<thead>
<tr>
<th>Chemical shift:</th>
<th>1.1</th>
<th>2.1</th>
<th>4.1</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Chemical shift diagram" /></td>
<td><img src="image2.png" alt="Chemical shift diagram" /></td>
<td><img src="image3.png" alt="Chemical shift diagram" /></td>
<td></td>
</tr>
<tr>
<td>Integration</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Splitting pattern</td>
<td>Triplet - signal adjacent to 2H's</td>
<td>Singlet - signal adjacent to 0H's</td>
<td>Quartet - signal adjacent to 3H's</td>
</tr>
<tr>
<td>Interpretation</td>
<td>3H's adjacent to 2H's</td>
<td>3H's adjacent to 0H's</td>
<td>2H's adjacent to 3H's</td>
</tr>
<tr>
<td>Assignment</td>
<td>CH₃CH₂</td>
<td>O=CCH₃</td>
<td>O-CH₂CH₃</td>
</tr>
</tbody>
</table>

Put the assignments together: CH₃COOCH₂CH₃
3) Protons adjacent on both sides:

The spectra below is for CH$_3$CHClCH$_3$

<table>
<thead>
<tr>
<th>Chemical shift:</th>
<th>1.6</th>
<th>3.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integration</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Splitting pattern</td>
<td>Doublet - signal adjacent to 1H's</td>
<td>Heptet - signal adjacent to 6 equivalent H's</td>
</tr>
<tr>
<td>Interpretation</td>
<td>6 equivalent H's adjacent to 1H's</td>
<td>1H's adjacent to 6 equivalent H's</td>
</tr>
<tr>
<td>Assignment</td>
<td>CH$_3$CHClCH$_3$</td>
<td>CH$_3$CHClCH$_3$</td>
</tr>
</tbody>
</table>

Put the assignments together: CH$_3$CHClCH$_3$

4) Equivalent protons not split:

The spectra below is for ClCH$_2$CH$_2$Cl
<table>
<thead>
<tr>
<th>Chemical shift:</th>
<th>3.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integration</td>
<td>4</td>
</tr>
<tr>
<td>Splitting pattern</td>
<td>Singlet - signal adjacent to 2H's</td>
</tr>
<tr>
<td>Interpretation</td>
<td>2H's adjacent to 6H's</td>
</tr>
<tr>
<td>Assignment</td>
<td>ClCH₂CH₂Cl x 2</td>
</tr>
<tr>
<td>Put the assignments together: ClCH₂CH₂Cl</td>
<td></td>
</tr>
</tbody>
</table>

Qu 1 P97

**NMR in medicine**

- It is used to determine the structure of synthetic drugs.
- It is used in MRI scans - Magnetic Resonance Imaging.
- The word Nuclear was dropped as it was thought people would associate it with radiation.
- The patient is the sample and although their protons are resonating, it is painless and harmless.
- Only patients with ferromagnetic metal implants (Fe, Co, Ni) should not use MRI such as pacemakers.
- MRI takes a 3D image of the water in tissue as slices which a computer then puts together.
- Diseases affect the water in tissues and this can be identified - cancers / spinal injuries
- Used in sporting injuries to identify tendon / muscle / ligament tears as dense materials such as bones appear darker due to less protons.

Qu 1 - 4 P 99
Combined techniques:

- A single spectroscopic technique tells you 'bits' of information on the structure of a molecule or compound.
- Combining the techniques give you lots of 'bits' of information that can be used to determine the actual structure of the molecule or compound:

Mass Spectroscopy:

- Chemical analysis provides the empirical formula of the compound.
- Mass spectroscopy gives the Mr and hence the molecular formula.
- Fragmentation patterns give clues about the carbon skeleton.

IR spectroscopy:

- IR spectroscopy gives information about functional groups present in the molecule:
  - O - H
  - C = O
  - C - O
- However many functional groups can have these bonds present

NMR spectroscopy:

Carbon - 13 NMR:

- Gives information about the numbers and types of carbon environments.

Proton NMR:

- Gives information about the numbers and types of protons.
- It also tells you the environments the protons are in.
Worked example:

Chemical analysis has identified the empirical formula as \( \text{C}_2\text{H}_4\text{O} \) (\( \text{Mr} = 44 \))

**IR spectra:**
- O - H present
- C = O present

**Mass Spectra:**
- Molecule has a mass, \( \text{Mr} = 88 \)
- Molecular formula = \( \text{C}_4\text{H}_8\text{O}_2 \)

**NMR:**

<table>
<thead>
<tr>
<th>Chemical shift</th>
<th>2.1</th>
<th>2.7</th>
<th>3.8</th>
<th>3.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integration</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Splitting pattern</td>
<td>Singlet - signal adjacent to O'H's</td>
<td>Triplet - signal adjacent to 2H's</td>
<td>Triplet - signal adjacent to 2H's</td>
<td>Singlet</td>
</tr>
<tr>
<td>Interpretation</td>
<td>3H's adjacent to 0H's</td>
<td>2H's adjacent to 2H's</td>
<td>2H's adjacent to 2H's</td>
<td>O-H?</td>
</tr>
<tr>
<td>Assignment</td>
<td>O=CCH(_3)</td>
<td>O=CCH(_2)CH(_2)</td>
<td>O-CH(_2)CH(_2)</td>
<td>-O-H</td>
</tr>
</tbody>
</table>
Put the assignments together:

Qu 1-2 P103 Qu 3-8 P105 Qu 2 - 8 P108/109