NMR (A2)

Nuclear magnetic resonance (NMR) spectroscopy is a widely used analytical technique for organic compounds.

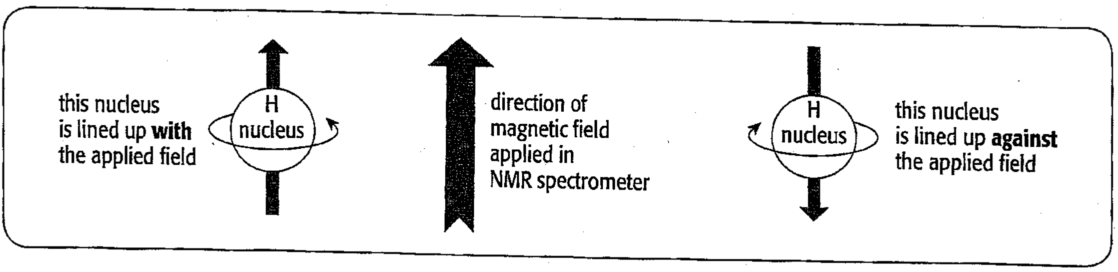
NMR is based on the fact that the nucleus of each hydrogen atom in an organic molecule behaves like a tiny magnet.

The nucleus of a hydrogen atom consists of a single proton. This proton can spin.

This movement of the positively charged proton causes a very small magnetic field to be set up.

In NMR, the sample to be analysed is put in a magnetic field.

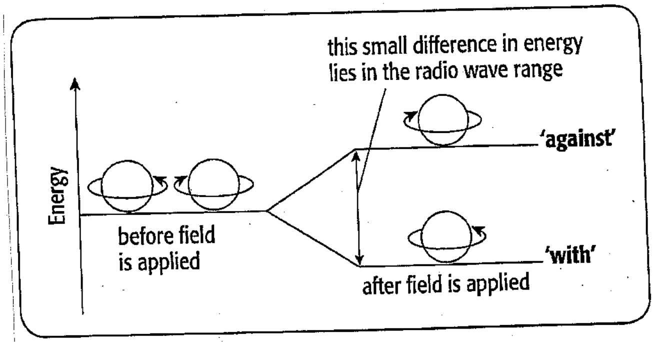
The hydrogen nuclei (protons) either line up with the field or, by spinning in the opposite direction, line up against it.



Hydrogen (^1H) nuclei will line up with or againt an applied magnetic field.

There is a tiny difference in energy between the oppositely spinning ^1H nuclei. This difference corresponds to the energy carried by waves in the radiowave range of the electromagnetic radiation spectrum.

In NMR spectroscopy the nuclei 'flip' between the two energy levels.



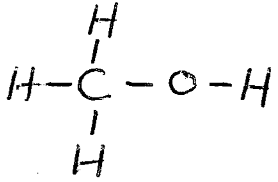
Hydrogen (^1H) nuclei will absorb energy in the radiowave range when they 'flip' from the lower energy level, lining up with the applied magnetic field, to higher energy level, lining ~~up~~ against it.

Only atoms whose mass number is an odd number, e.g. ^1H or ^{13}C, absorb energy in the range of frequencies that are analysed.

The size of the gap between the nuclear energy levels varies slightly, depending on the other atoms in the molecule – the molecular environment.

Therefore, NMR can be used to identify <u>^1H atoms</u> in <u>different parts</u> of a molecule.

Example: a molecule of methanol.



$$\begin{array}{ccccccc} & & H & & & & \\ & & | & & & & \\ H & - & C & - & O & - & H \\ & & | & & & & \\ & & H & & & & \end{array}$$

There are ^1H atoms in two different molecular environments:- <u>molecular environment</u>

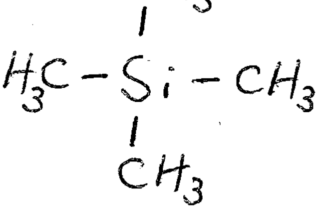
- 1) the ^1H atoms in the <u>$-CH_3$ group</u>
- 2) the ^1H atoms in the <u>$-OH$ group</u>.

- The energy absorbed by the ^1H atoms in $-CH_3$ group is different from the energy absorbed by the ^1H atoms in $-OH$.

As the magnetic field is varied, the ^1H nuclei in different molecular environments flip at different field strengths.

The different field strengths are measured relative to <u>a reference compound</u> which is given a value of <u>zero</u>.

The standard compound chosen is <u>tetramethylsilane</u>.



$$\begin{array}{ccccc} & & CH_3 & & \\ & & | & & \\ H_3C & - & Si & - & CH_3 \\ & & | & & \\ & & CH_3 & & \end{array}$$

TMS (tetramethylsilane)

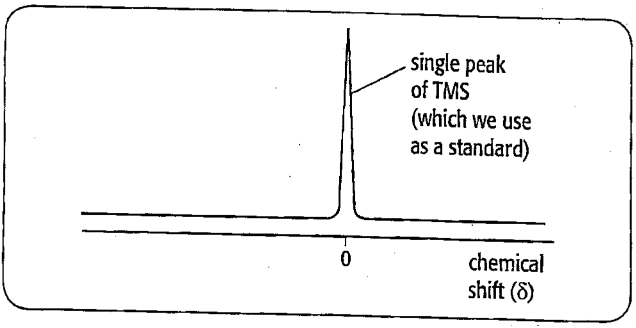
TMS is an inert, volatile liquid which mixes well with most organic compounds.

All its H atoms are equivalent – i.e. they are all in the same molecular environment.

TMS only gives one, sharp absorption, called a peak, and this peak is at a higher than most other protons.

All other absorptions are measured by their shift away from the TMS line on the NMR spectrum.

This is called the chemical shift (δ), and is measured in units of parts per million (ppm)



The standard TMS peak used as a reference on NMR spectra.

Example

a) Explain why tetramethylsilane (TMS) is used as a standard in NMR spectroscopy.

b) In NMR we use solvent such as tetrachloromethane to prepare samples for the machine.

i) What is the molecular formula of tetrachloromethane

ii) Why do you think tetrachloromethane is used as a solvent?

iii) Solvents which contain deuterium, D are also used as solvents in NMR. Deuterium is the isotope ^2H. A substance in which ^1H is replaced by ^2H is said to be deuterated. Why would the deuterated solvent $CDCl_3$ be used instead of $CHCl_3$?

Answers

a) Its formula is $Si(CH_3)_4$ so all its H atoms are equivalent that is they are all in the same molecular environment. So it only gives one, sharp absorption. It is also inert (it does not react with samples being tested), volatile (easily removed from the sample after NMR analysis) and mixed well with most organic compounds.

b) (i) CCl_4

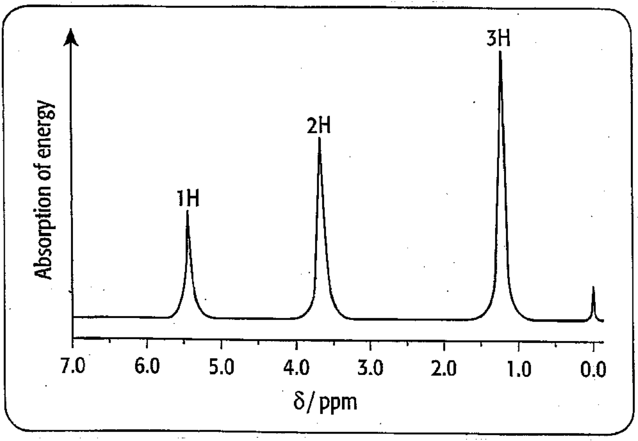
(ii) It has no hydrogen atoms so it wont produce a peak in the NMR spectrum.

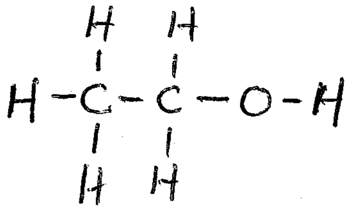
(iii) Only atoms whose mass number is an odd number, absorb energy in the range of frequencies that are analysed. Deuterium has even number of mass number. Hence Deuterium nuclei do not absorb radiowaves in the range used for NMR. So there will be no peaks to interfere with sample's NMR spectrum.

Low-resolution NMR

A low-resolution NMR spectrum shows a single peak for each non-equivalent hydrogen atom.

Example: ethanol molecule.





The low-resolution NMR spectrum of ethanol, CH_3CH_2OH

Take note the zero point on the x-axis, chemical shift (δ), is on the right of the spectrum and the shift increases in value going left.

There are three peaks on ethanol's low-resolution NMR spectrum. These correspond to the ^1H atoms in

- $-OH$
- $-CH_2-$
- $-CH_3$

The peaks have different heights. The area under each peak tells us the relative number of equivalent ^1H atoms responsible for that particular chemical shift.

The largest peak will be from the hydrogen atoms of $-CH_3$ group.

The middle peak from the hydrogen atoms of $-CH_2-$ group.

The smallest peak from the hydrogen atoms of $-OH$ group.

The relative areas under the peak are shown on the NMR spectrum by the labels 1H, 2H and 3H.

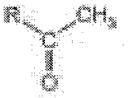
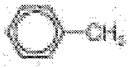
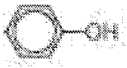
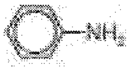
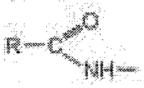
The type of H atom present can be checked against tables of data (data booklet). NMR spectrum is then used to identify unknown organic compounds.

By refering to table,

peak at δ/ppm	Type of proton
1.2	$-CH_3$ (0.9)
3.7	$-CH_2-$ (3.3–4.0)
5.4	$-OH$ (0.5–6.0)

6. Appendix

Typical proton chemical shift value (δ) relative to T.M.S.=0

Type of proton	*Chemical shift (ppm)*
$R—CH_3$	0.9
$R—CH_2—R$	1.3
R_3CH	1.4–1.7
	2.0
	2.1
	2.3
$R—C≡C—H$	1.8–3.1
$R—CH_2—Hal$	3.2–3.7
$R—O—CH_3$	3.3–4.0
$R—O—H$	0.5–6.0*
$R_2C=CH—$	4.5–6.0
	4.5–7.0*
	6.0–9.0
	9.0–10.0
	9.0–13.0*
$R—NH_2$	1.0–5.0*
	3.0–6.0*
	5.0–12.0*

*Sensitive to solvent, concentration

Example:

Predict the number of peaks and the relative areas under each peak, where appropriate, on the low-resolution proton NMR spectrum of:

a) methanol, CH_3OH

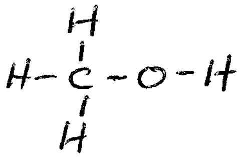
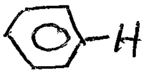
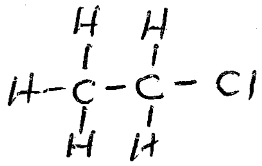
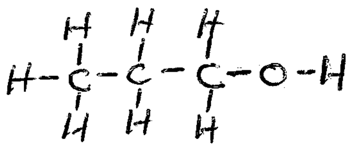
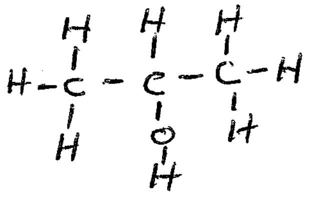
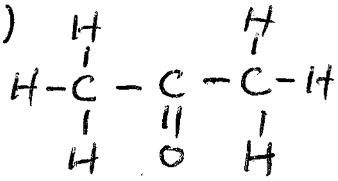
b) benzene, C_6H_6

c) chloroethane, C_2H_5Cl

d) propan-1-ol

e) propan-2-ol

f) propanone.

Answers		type of proton	ratio	no peak
a)		$-CH_3$; $-OH$	3 : 1	2
b)			(all the H atoms are equivalent)	1
c)		$-CH_3$; $R-CH_2-Cl$	3 : 2	2
d)		$-CH_3$; $R-CH_2-R$; $R-CH_2-O-$; $-OH$	3 : 2 : 2 : 1	4
e)		$-CH_3$; $R-\underset{\underset{\vert}{O}}{CH}-R$; $-OH$	6 : 1 : 1	3
f)		$-CH_3$	(all the H atoms are equivalent)	1

High-resolution NMR

From the table, the chemical shifts are given over ranges, and the ranges for different types of hydrogen atoms do overlaps.

In some molecules where there is heavy shielding of the hydrogen nuclei by lots of electrons in surrounding atoms, peaks are shifted beyond their usual range.

In such cases high-resolution NMR is useful in providing more information to interpret.

Peak that appear as one 'signal' on a low-resolution NMR spectrum are often revealed to be made up a series of closely group peaks

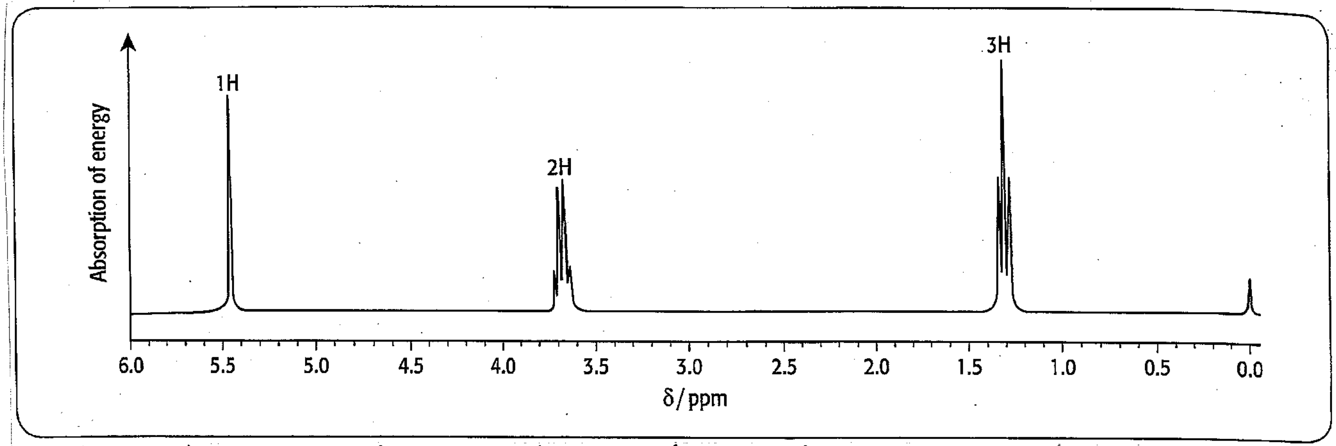
This is because the magnetic field generated by spinning nuclei interfere slightly with those of neighbouring nuclei. This is called spin-spin coupling.

The exact splitting pattern of a peak depends on the number of hydrogen atoms on the adjacent carbon atom or atoms.

The number of signals a peak splits into $= \boxed{n+1}$.

where n = the number of ^1H atoms on the adjacent carbon atom

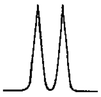
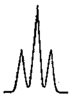
Example: high-resolution NMR of ethanol.



The high-resolution NMR spectrum of ethanol, showing the splitting pattern in two of the peak. The area under each series of peak still represents the number of equivalent ^1H atoms in the molecule, as in low-resolution NMR.

- The $-CH_3$ peak is split into 3 because there are 2 ^1H atoms on the adjacent $-CH_2-$ group, $n=2$.
  $2+1=3 \longrightarrow$ triplet.
- The $-CH_2-$ peak is split into 4 because there are 3 ^1H atoms on the adjacent $-CH_3$ group, $n=3$.
  $3+1=4 \longrightarrow$ quartet.
- The $-OH$ peak is not usually split as its ^1H atom is constantly being exchanged with the ^1H atoms of other ethanol molecules and any water present. This results in one average peak being produced.

The relative intensities and distribution of the splitting patterns in high-resolution NMR spectra:

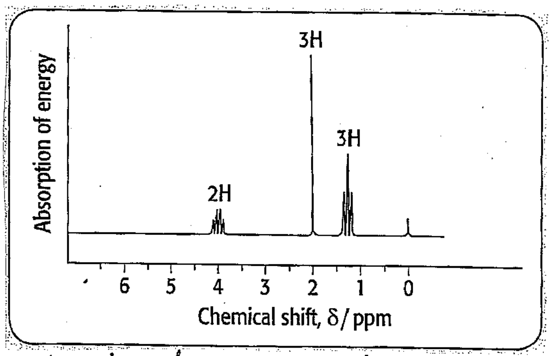
Number of adjacent ^{1}H atoms	Using the $n + 1$ rule, the peak will be split into …	Relative intensities in the splitting pattern	Observed on the NMR spectrum as …
0	1 peak, called a singlet	1	
1	2 peaks called a doublet	1:1	
2	3 peaks called a triplet	1:2:1	
3	4 peaks called a quartet	1:3:3:1	

Steps in interpreting high-resolution NMR spectrum

1. Use δ values to identify the environment of the equivalent protons (^{1}H atoms) present at each peak. The peak at zero is the TMS standard reference peak.
2. Look at the relative areas under each peak to determine the number of each type of non-equivalent protons (^{1}H atoms) are present. Note the numbers given above the peaks.
3. Apply the n+1 rule to the splitting pattern to see which proton (^{1}H atoms) are on adjacent carbon atoms in the unknown molecule.
4. Put all this information together to identify the structure of the molecule.

Example:

An ester is used as a solvent in a glue. A chemist was given a sample of the ester to analyse. The NMR Spectrum of the ester is shown as:



The high-resolution NMR spectrum of an unknown ester in a glue.

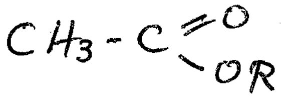
Step 1: Identify possibilities for the three major peaks that appear at chemical shifts of 1.3, 1.9 and 4.1ppm.

Chemical Shift, δ/ppm	Possible type of proton
1.3	$R-CH_3$, $R-CH_2-R$
1.9	CH_3-COOR, RCH_2-COOR, $R_2CH-COOR$.
4.1	$-O-CH_3$, $-O-CH_2R$, $-O-CHR$.

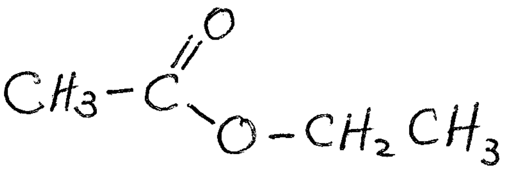
Step 2: Use the relative numbers of each type of proton (^1H atom) labelling each major peak to narrow down possibilities.

δ/ppm	Type of proton
1.3	labelled 3H → $R-CH_3$
1.9	labelled 3H → CH_3-COOR
4.1	labelled 2H → $-O-CH_2R$.

Step 3: By applying the n+1 rule to the splitting patterns we can see which proton (^1H atoms) are on adjacent carbon atoms.

δ/ppm	adjacent carbon atoms
1.3	labelled 3H and split into triplet, so R-CH_3 would be next to a C atom bonded to two ^1H atoms. $2+1=3$ triplet
1.9	labelled 3H and a singlet, so CH_3-COOR would be next to a C atom with no ^1H atoms attached. $0+1=1$ singlet. It could well be next to the C=O as in an ester  $CH_3-C(=O)-OR$. (carbonyl also has C atom bonded to an O atom as C=O)
4.1	labelled 2H and split into quartet, $-O-CH_2R$ would be next to a C atom bonded to three ^1H atoms. $3+1=4$ quartet.

Step 4: Putting this information together we get the ester ethyl ethanoate, $CH_3COOCH_2CH_3$

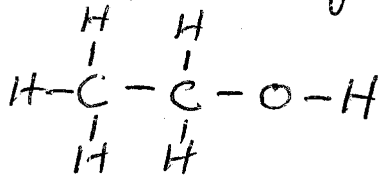


$$CH_3-C(=O)-O-CH_2CH_3$$

The $-OH$ or $-NH-$ signal in an NMR spectrum

The <u>$-OH$ signal</u> in the high-resolution NMR spectrum of ethanol appears as <u>a single peak</u>.

The peak is not split by the ^1H atoms (protons) on the neighbouring $-CH_2-$ group.



$$H-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-O-H$$

The reason for this is that the $-OH$ proton <u>exchanges</u> very rapidly with protons in any traces of water (or acid) present:

$$CH_3CH_2O\enclose{circle}{H} + \boxed{H}_2O \rightleftharpoons CH_3CH_2O\boxed{H} + \enclose{circle}{H}O\boxed{H}$$

The exchange takes place so <u>rapidly</u> that the signal for the $-OH$ protons becomes a single peak.

This exchange also happens in amines and amides which contain the $-NH-$ group.

However, there are <u>chemical shifts ranges</u> for the different $-OH$ and $-NH-$ signals in <u>different molecular environments</u>:

Different -OH and -NH- protons	Range of chemical Shift (δ)/ppm
in alcohols, R-OH protons	0.5 – 6.0
in phenols, -OH protons	4.5 – 7.0
in carboxylic acids, R-COOH protons	9.0 – 13.0
in amines, $-NH_2$ / -NH-	1.0 – 5.0
in aryl amines, -NH_2	3.0 – 6.0
in amides, $-CONH_2$, -CONH-	5.0 – 12.0

These ranges overlap with the chemical shifts of other types of proton.

The signals can also appear outside the quoted ranges under certain conditions, e.g. choice of solvent or concentration. This makes NMR spectra difficult to interpret.

However, there is a technique for positively identifying -OH or -NH- groups in a molecule.

Their peaks 'disappear' from the spectra when a small amount of deuterium oxide, D_2O is added to the sample.

The deuterium atoms (^2H) in D_2O (heavy water), exchange reversibly with the protons in the -OH or -NH- groups.

$$-O\boxed{H} + \textcircled{D}_2O \rightleftharpoons -O\textcircled{D} + \boxed{H}O\textcircled{D}$$

$$-N\boxed{H}-CO- + \textcircled{D}_2O \rightleftharpoons -N\textcircled{D}-CO- + \boxed{H}O\textcircled{D}$$

The deuterium atoms do not absorb in the same region of the electromagnetic spectrum as protons (^1H atoms).

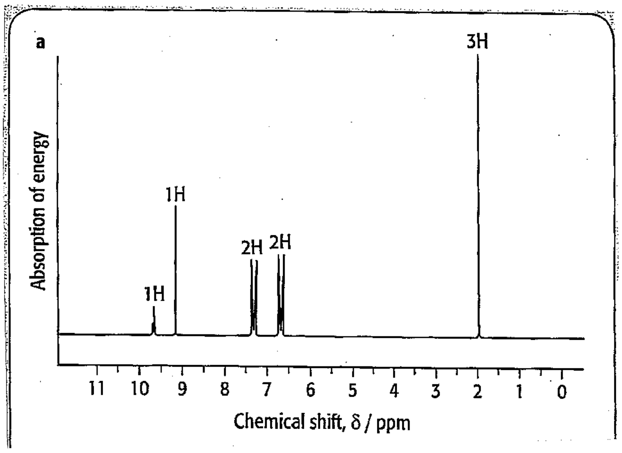
This makes the $-OH$ or $-NH-$ signal disappear from the NMR spectrum.

By checking against the peaks in the original NMR spectrum, without D_2O, the present of the $-OH$ or $-NH-$ can be determined.

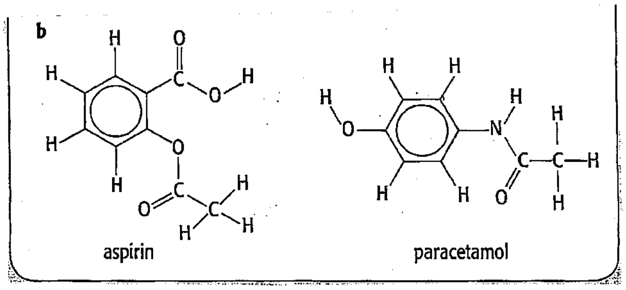
The ^1H atom in the $-OH$ or $-NH-$ group is referred to as a 'labile' proton

Example:

A pathologist was given a sample of white tablet found at the scene of a suicide. In order to complete her report, the pathologist received an NMR spectrum of the sample as below and information from the police that the tablets involved were either aspirin or paracetamol. The displayed formulae of both drugs are also shown.



NMR analysis of the unknown drug sample.



Structure of aspirin and paracetamol.

a. Using this information, which drug was in the white tablet? Explain your answer.

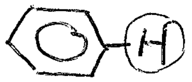
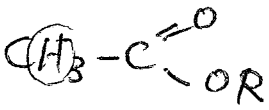
b. Sketch the NMR spectrum you would expect to see if the other drug undergone NMR analysis. Label each peak with its relative area and the type of proton that caused it.

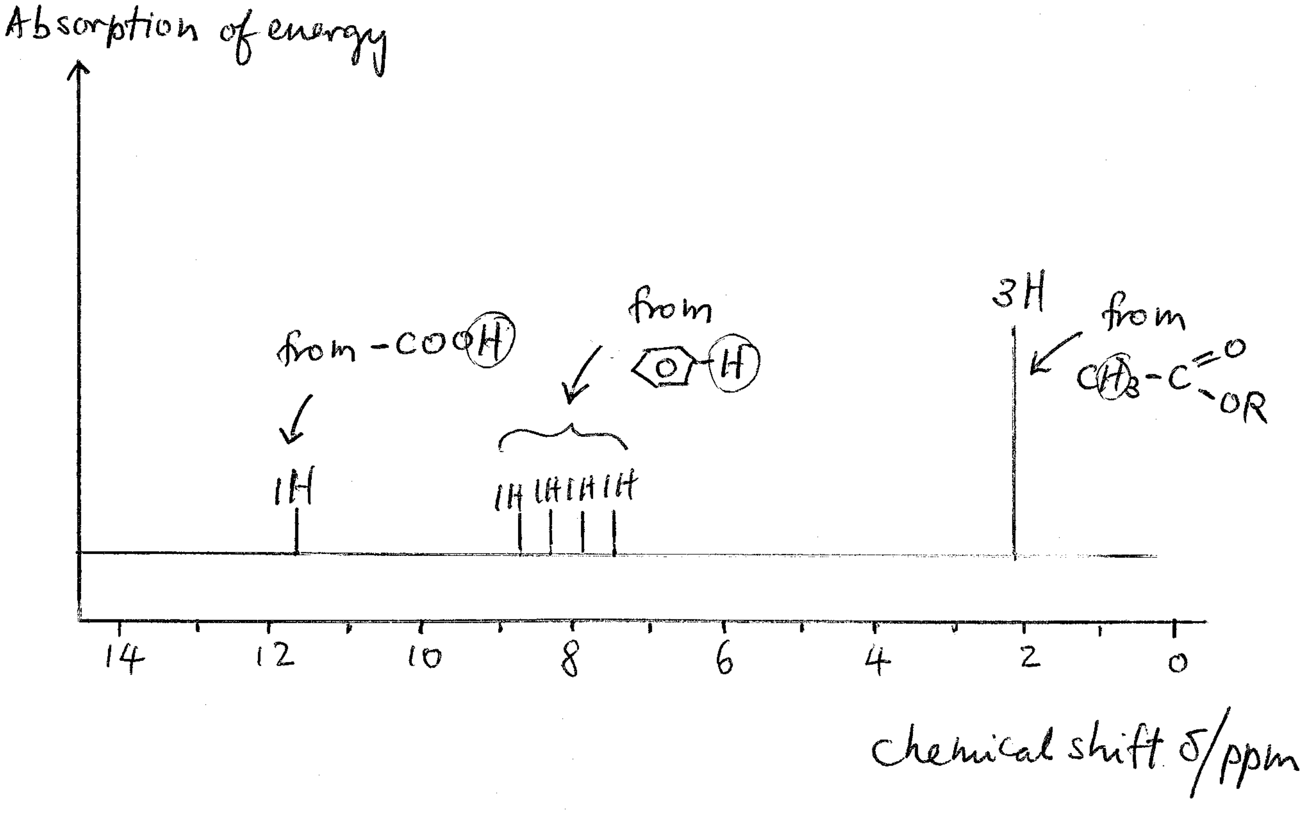
Answers.

a) Paracetamol. Because there are 2 peaks from single protons with relatively high chemical shifts, corresponding to the $-O\text{(H)}$ and $-N\text{(H)}-$ protons in paracetamol.

Whereas aspirin will have only one peak between 9 and 13 ppm at the high end of the spectrum from its $-COO\text{(H)}$ proton.

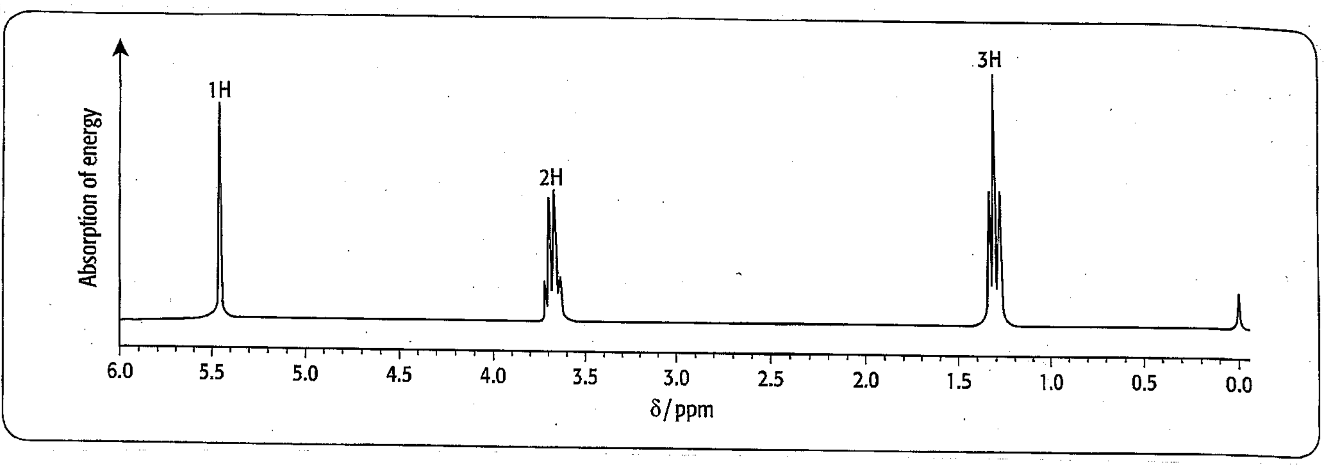
b)

Proton type	Chemical shift (δ)/ppm	relative area
	6.0 – 9.0	1×4
$-COO\text{(H)}$	9.0 – 13.0	1
	2.0.	3

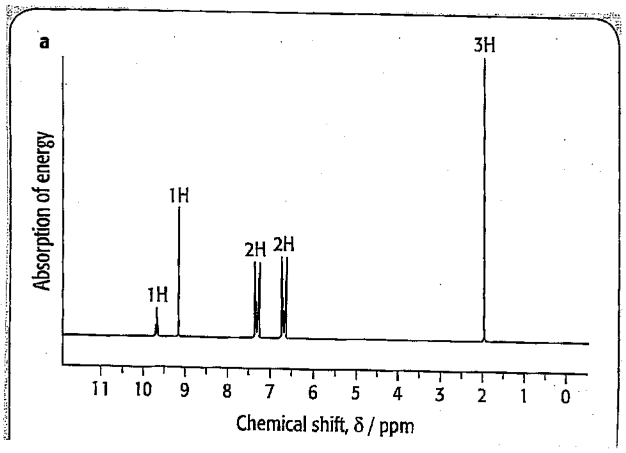


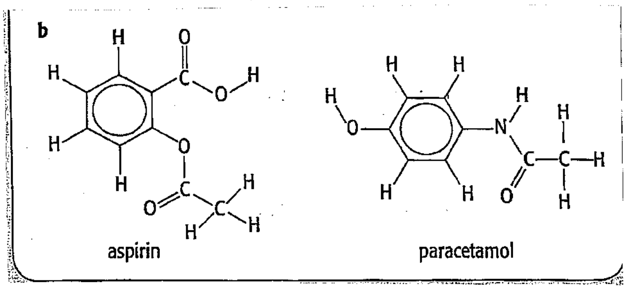
Example:

a) Look back to the high-resolution NMR-spectrum for a sample of ethanol. How would the NMR spectrum differ if D_2O had been



b) Look back to the question involving aspirin and paracetamol. How would repeating the NMR analysis using a solvent of D_2O be able to help the pathologist distinguish between aspirin and paracetamol?





Answers

a) The single $-OH$ peak would diappear from the NMR spectrum.

b) Two peaks (from the $-OH$ and $-NH-$ protons) would disappear from the NMR spectrum of paracetamol but only one peak would disappear from aspirin's spectrum (from the $-COOH$ peak)