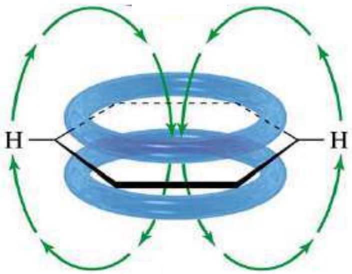
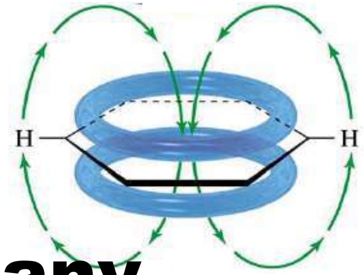


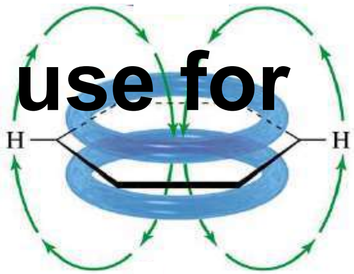
Video 1
Page(1-19)

Introduction



How to identify unknown drug or any chemical compound?

What sort of spectroscopy you might use for analysis and for what?



1] Mass Spectroscopy (M.S) to determine formula.

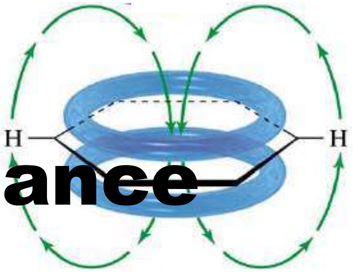
2] Infrared Spectroscopy (I.R) to determine functional groups.

3] **Ultra Violet Spectroscopy (U.V)** to determine availability of conjugated system.

4] Nuclear Magnetic Resonance Spectroscopy (NMR) to determine Hydrogen and carbons types and numbers.

NO ONE CAN DO THE JOB ALONE; EXCEPT IN THE CASE OF SIMPLE COMPOUNDS

How to identify an unknown substance ?



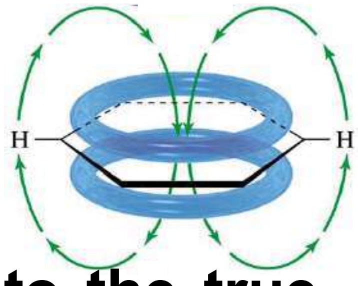
1- <u>Classic methods:-</u>

It is related to an old fashion procedures; such as using chemicals and physical properties (these methods are very limited)

2- Modern methods

Mainly depends on instrumentation; it is very advanced equipment. These methods are very fruitful, accurate, précised and have the ability to solve huge number of problems through providing all data about any compound

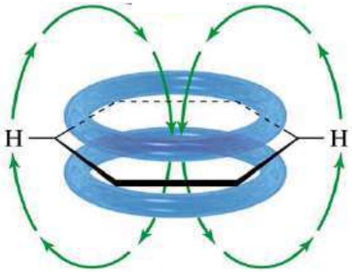
Accuracy *Vs* Precision

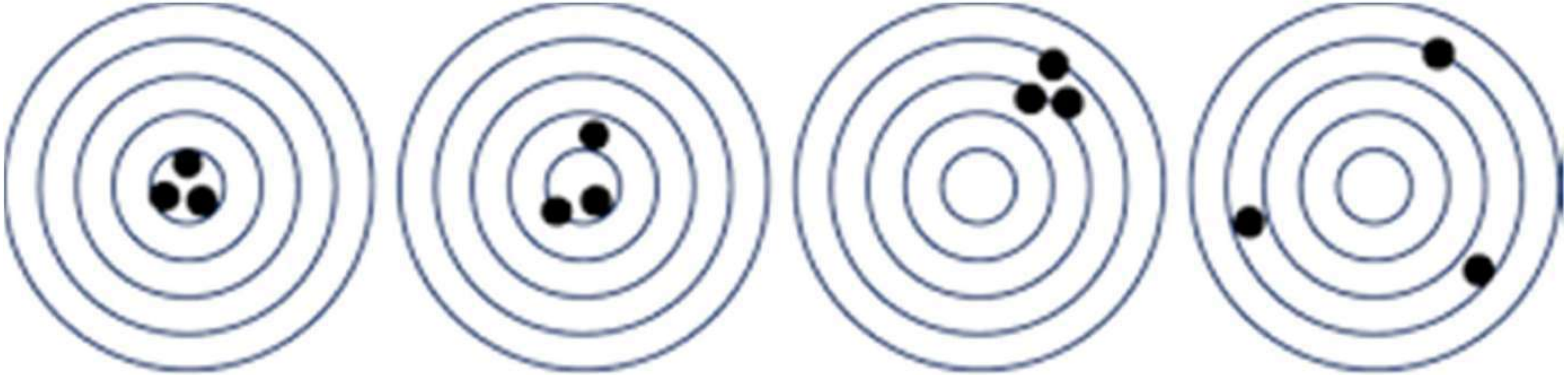


Accuracy refers to how close a measurement is to the true value. An example would be how close an arrow gets to the bulls eye center.

Precision is how repeatable a measurement is. An example would be how close a second arrow is to the first one (regardless of whether either is near the mark).

The left image shows a target hit with a high degree of *accuracy*, but low *precision*. The right image shows the target hit with high *precision*, but low *accuracy*





↑ Accuracy
↑ Precision

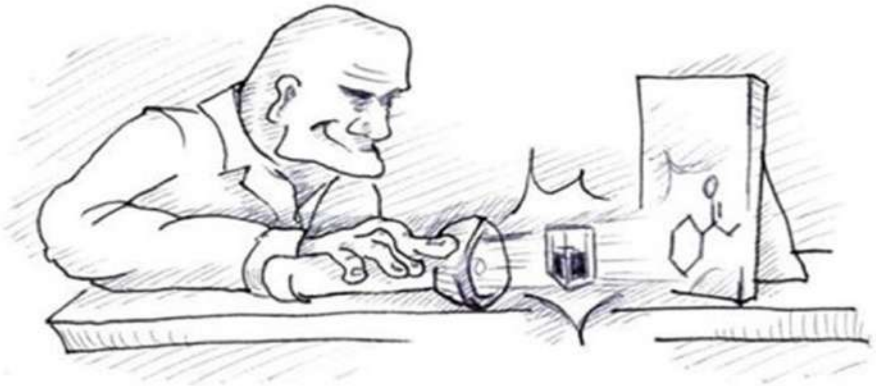
↑ Accuracy
↓ Precision

↓ Accuracy
↑ Precision

↓ Accuracy
↓ Precision

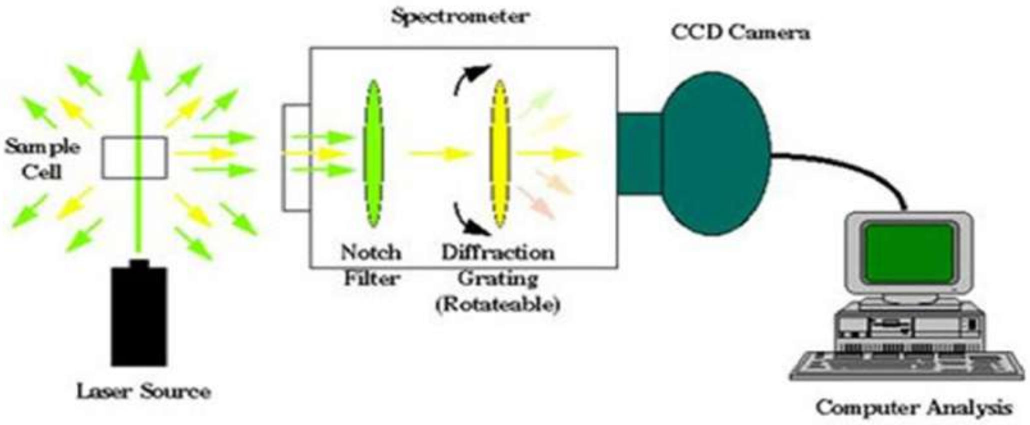
What is Spectroscopy?

- Spectroscopy: The study of the interaction of electromagnetic radiation(energy) with matter and can be used to obtain information about it.

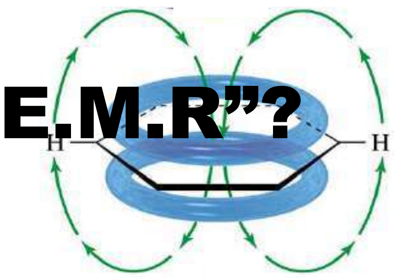


simple

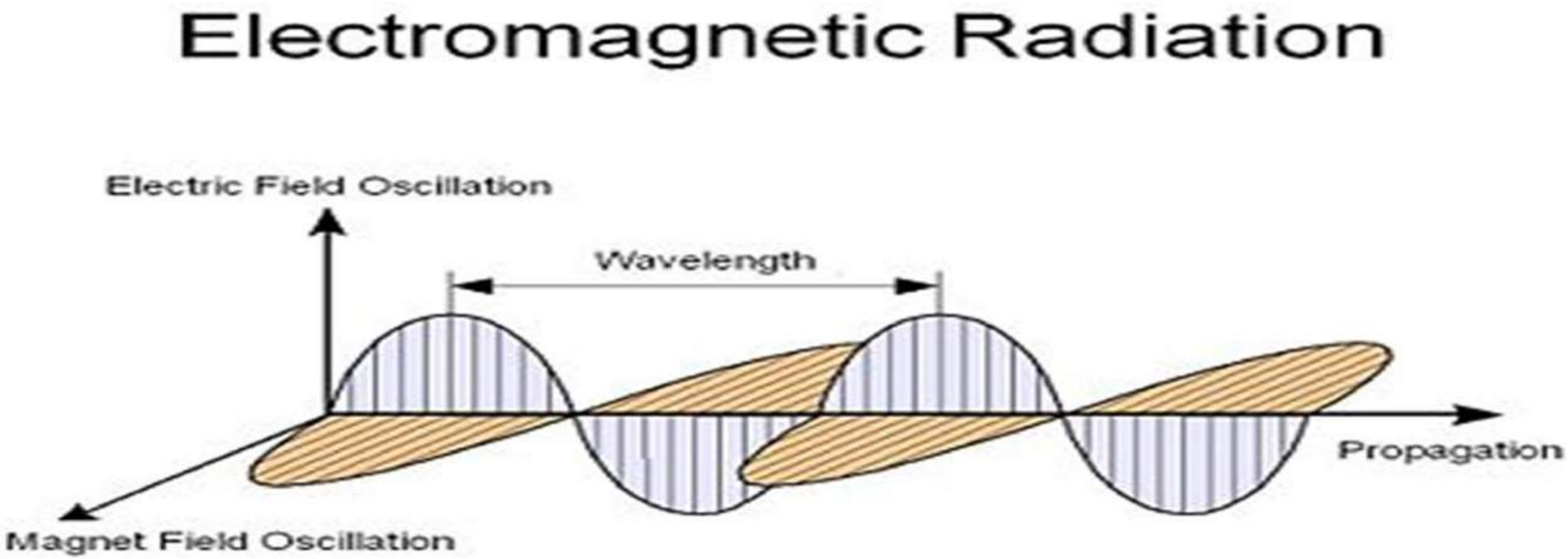
complicated



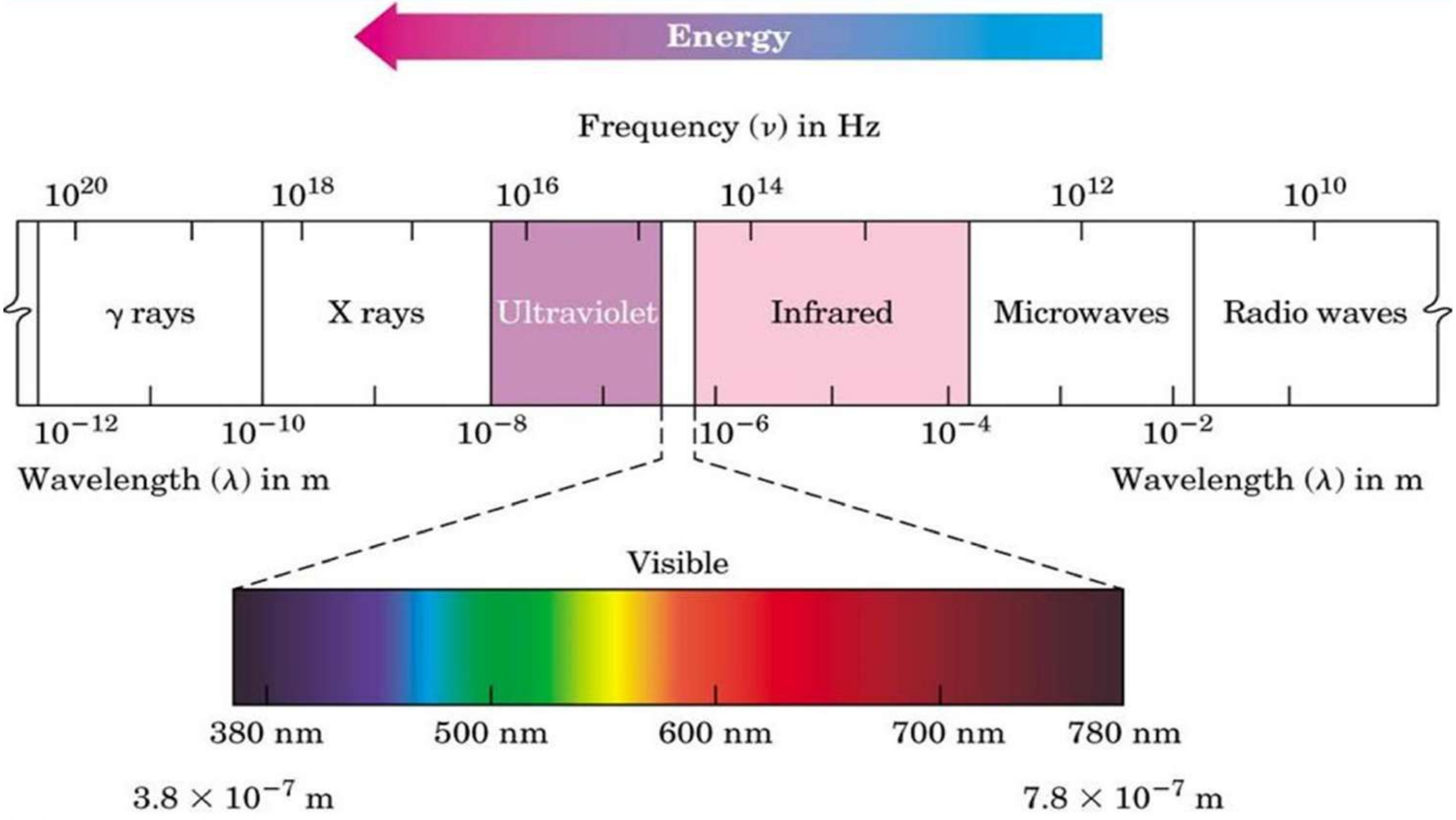
What is Electromagnetic radiation “E.M.R”?



E.M.R arises from the perpendicular overlapping of both magnetic and electric field



Spectroscopy and the Electromagnetic Spectrum



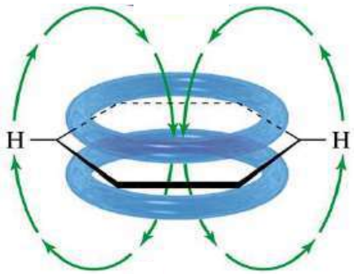
© Thomson - Brooks Cole

What is Spectroscopy?

Spectroscopy: The study or measurement of lights colour or ‘wavelength’

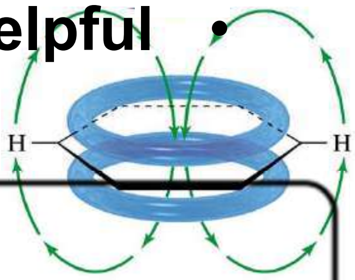
Spectrometer: An instrument to measure the wavelength of light

Spectrum: A plot of the colour profile (wavelengths present)



Degrees of Unsaturation
(DoU)
(Index of Hydrogen Deficiency)
“IHD”

The molecular formula of a compound can give helpful hints about its structure.



"Degrees of Unsaturation" (or "Index of Hydrogen Deficiency")

- In a hydrocarbon with no double bonds or rings, the number of hydrogens and carbons is related as follows:

#Hydrogens = (2 × #Carbons) + 2

- Each multiple bond *or* ring reduces the hydrogen count by 2, which we refer to as a "degree of unsaturation"
- The degrees of unsaturation in a molecule can be calculated from its molecular formula using the following calculation:

$$\text{Degrees of Unsaturation} = \frac{2C + 2 + N - H - X}{2}$$

C = #carbons

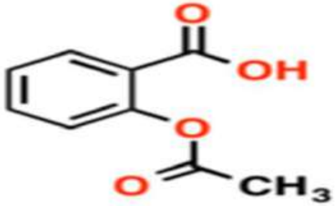
H = #hydrogens

N = #nitrogens

X = #halogens

- Note that this tells you the *sum* of [multiple bonds + rings], but does not specify exactly how many multiple bonds or rings are present.
- This simple and fast calcluation is a useful first step to take when confronted with determining the structure of an unknown molecule.

Aspirin



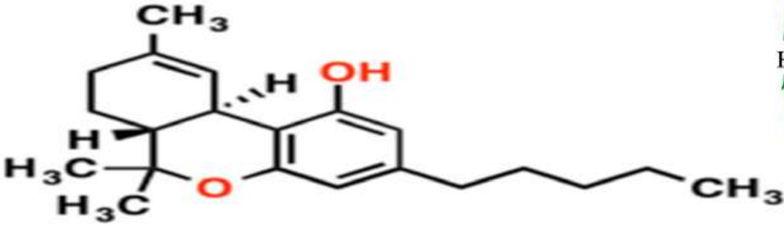
$C_9H_8O_4$

5 double bonds
1 ring

6 degrees of unsaturation

$$\frac{(2*9) + 2 - 8}{2} = 6$$

THC

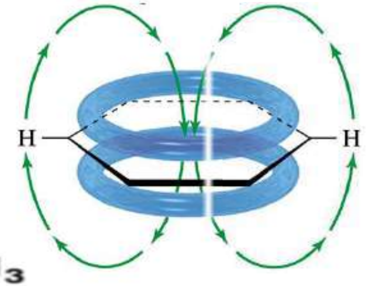


$C_{21}H_{30}O_2$

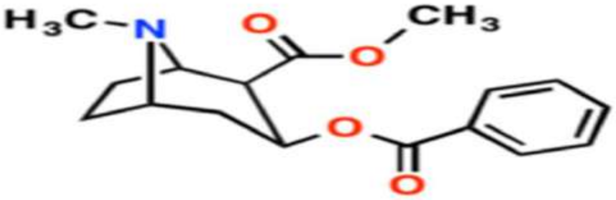
4 double bonds
3 rings

7 degrees of unsaturation

$$\frac{(2*21) + 2 - 30}{2} = 7$$



Cocaine



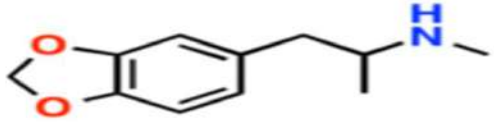
$C_{17}H_{21}NO_4$

5 double bonds
3 rings

8 degrees of unsaturation

$$\frac{(2*17) + 2 + 1 - 21}{2} = 8$$

MDMA



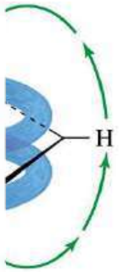
$C_{11}H_{15}NO_2$

3 double bonds
2 rings

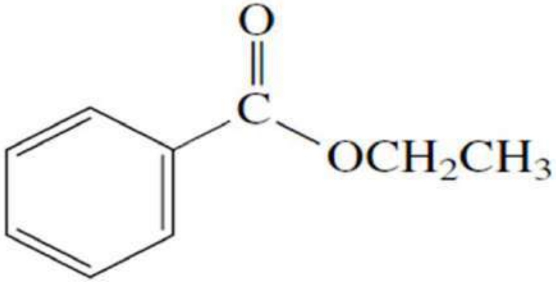
5 degrees of unsaturation

$$\frac{(2*11) + 2 + 1 - 15}{2} = 5$$

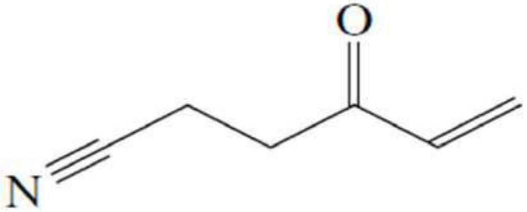
Determine the DU for each of these structures:



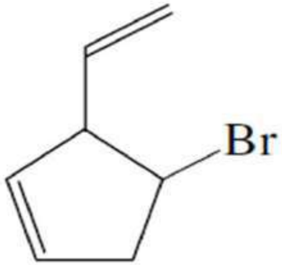
a)



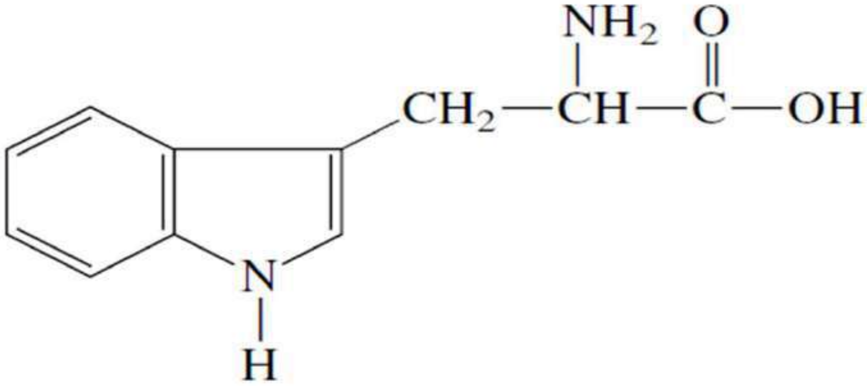
b)



c)

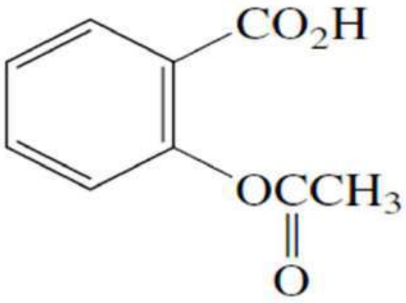


d)

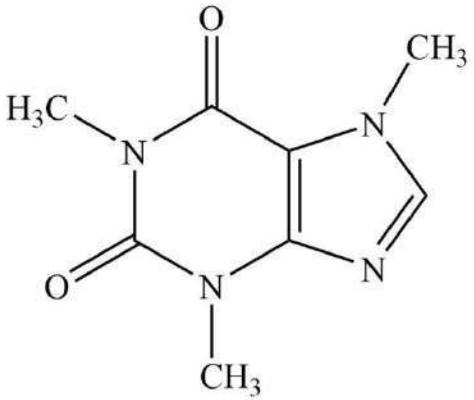


Tryptophan (an amino acid)

e)

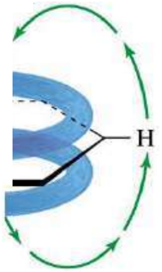


Acetylsalicylic acid
(aspirin)



a. C_7H_8 b. $C_5H_{10}O$ c. $C_4H_8O_2$ d. $C_6H_{11}N$ e. $C_7H_{17}NO$

f. $C_{10}H_9ClN_2O$ g. $C_9H_9NO_2$ h. $C_{12}H_8Cl_2$ i. C_7H_5N j. $C_6H_{10}SO_4$



a. C_7H_8

$$\begin{array}{r} \text{maximum } \# = 2(7) + 2 = 16 \\ - \text{ actual } \# = \ \ 8 \\ \hline = 8 \end{array}$$

degrees unsaturation = 8 / 2 = 4°
(pi bonds and/or rings)

b. $C_5H_{10}O$

$$\begin{array}{r} \text{maximum } \# = 2(5) + 2 = 12 \\ - \text{ actual } \# = 10 \\ \hline = 2 \end{array}$$

degrees unsaturation = 2 / 2 = 1°
(pi bond or ring)

c. $C_4H_8O_2$

$$\begin{array}{r} \text{maximum } \# = 2(4) + 2 = 10 \\ - \text{ actual } \# = \ \ 8 \\ \hline = 2 \end{array}$$

degrees unsaturation = 2 / 2 = 1°
(pi bond or ring)

d. $C_6H_{11}N$

$$\begin{array}{r} \text{maximum } \# = 2(6) + 2 + 1 = 15 \\ - \text{ actual } \# = \ \ 11 \\ \hline = 4 \end{array}$$

degrees unsaturation = 4 / 2 = 2°
(pi bonds and/or rings)

e. $C_7H_{17}NO$

$$\begin{array}{r} \text{maximum } \# = 2(7) + 2 + 1 = 17 \\ - \text{ actual } \# = \ \ 17 \\ \hline = 0 \end{array}$$

degrees unsaturation = 0 / 2 = 0°
(pi bond or ring)

f. $C_{10}H_9ClN_2O$

$$\begin{array}{r} \text{maximum } \# = 2(10) + 2 + 2 = 24 \\ - \text{ actual } \# = \ \ 10 \\ \hline = 14 \end{array}$$

degrees unsaturation = 14 / 2 = 7°
(pi bonds and/or rings)

g. $C_9H_9NO_2$

$$\begin{array}{r} \text{maximum } \# = 2(9) + 2 + 1 = 21 \\ - \text{ actual } \# = 9 \\ \hline = 12 \end{array}$$

degrees unsaturation = 12 / 2 = 6°
(pi bonds and/or rings)

h. $C_{12}H_8Cl_2$

$$\begin{array}{r} \text{maximum } \# = 2(12) + 2 = 26 \\ - \text{ actual } \# = \ \ 10 \\ \hline = 16 \end{array}$$

degrees unsaturation = 16 / 2 = 8°
(pi bonds and/or rings)

i. C_7H_5N

$$\begin{array}{r} \text{maximum } \# = 2(7) + 2 + 1 = 17 \\ - \text{ actual } \# = \ \ 5 \\ \hline = 12 \end{array}$$

degrees unsaturation = 12 / 2 = 6°
(pi bonds and/or rings)

j. $C_6H_{10}SO_4$

$$\begin{array}{r} \text{maximum } \# = 2(6) + 2 = 14 \\ - \text{ actual } \# = \ 10 \\ \hline = 4 \end{array}$$

degrees unsaturation = 4 / 2 = 2°
(pi bonds and/or rings)

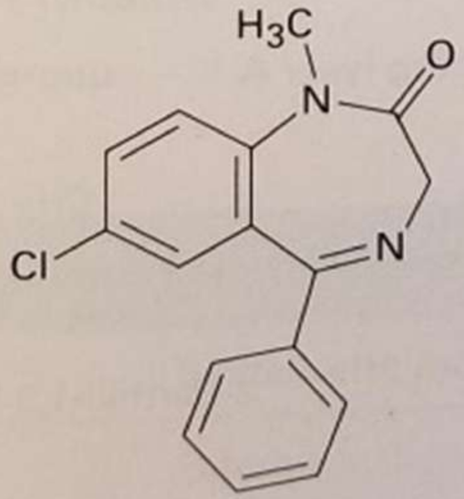
Calculate the degree of unsaturation in each of the following formulas, and then draw as many structures as you can for each:
(a) C_4H_8 (b) C_4H_6 (c) C_3H_4

PROBLEM 7-2

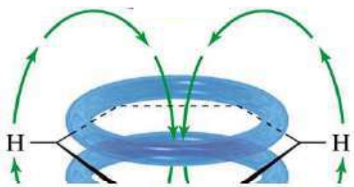
Calculate the degree of unsaturation in each of the following formulas:
(a) C_6H_5N (b) $C_6H_5NO_2$ (c) $C_8H_9Cl_3$
(d) $C_9H_{16}Br_2$ (e) $C_{10}H_{12}N_2O_3$ (f) $C_{20}H_{32}ClN$

PROBLEM 7-3

Diazepam, marketed as an antianxiety medication under the name Valium, has three rings, eight double bonds, and the formula $C_{16}H_?ClN_2O$. How many hydrogens does diazepam have? (Calculate the answer; don't count hydrogens in the structure.)



Diazepam

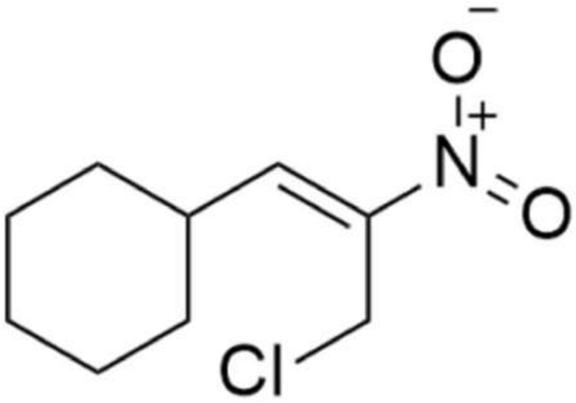


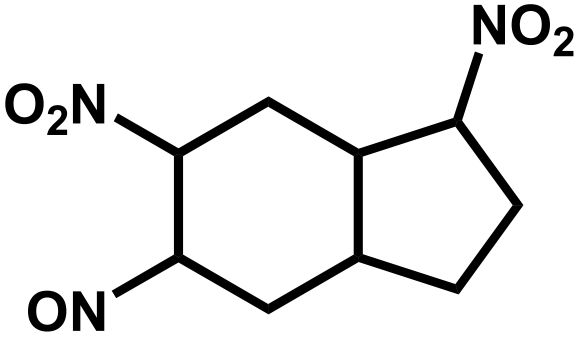
Calculate the DU for these formulas and draw two constitutional isomers for each:

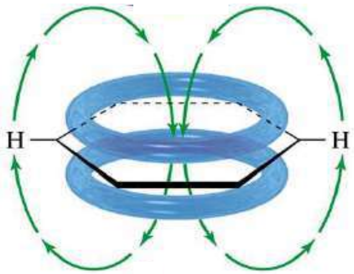
a) $C_{10}H_{20}O$ b) C_6H_9N c) $C_7H_{14}F_2$

d) C_6H_8ClN e) $C_9H_{15}NO$

Calculate the DU for the following compound





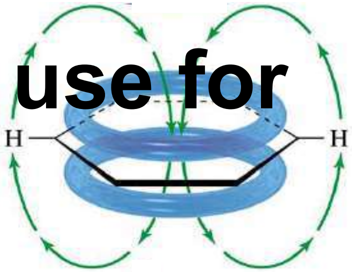


What is coming?

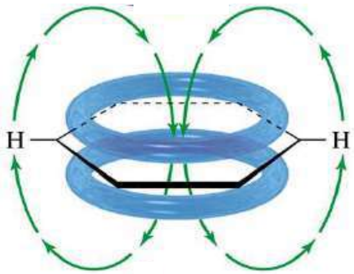
Different Spectroscopic radiation (Wave length or energy) will affect the substance in different way !!!!!

- **Electrons might be affected**
- **Bonds**
- **nuclei**
- **or the substance is broken (fragmentation)…….etc**

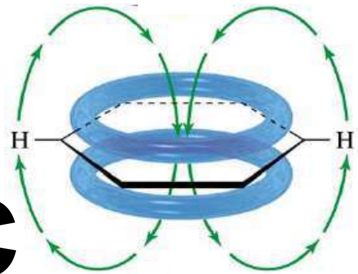
What sort of spectroscopy you might use for analysis and for what?



- To determine formula use {**Mass Spectroscopy (M.S)**}
- To determine functional groups use {**Infrared Spectroscopy (I.R)**}
- To determine availability of conjugated system use {**Ultra Violet Spectroscopy (U.V)**}
- To determine Hydrogen types and numbers use {**nuclear magnetic resonance Spectroscopy (NMR)**}



Video 2
Page(19-34)

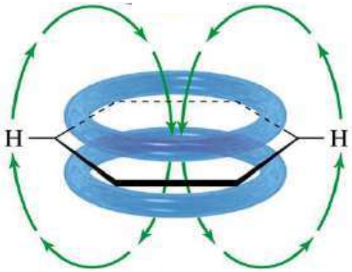


Nuclear Magnetic Resonance

NMR

- Why Nuclear?
- Why magnetic?
- Why Resonance?

History of NMR



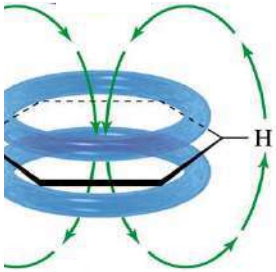
- 1937 Rabi's prediction and observation of nuclear magnetic resonance
- 1945 First NMR of solution (Bloch et al for H2O) and solids (Purcell et al for parafin)!
- 1953 **Overhauser** NOE (nuclear Overhauser effect)
- 1966 Ernst, Anderson Fourier transform NMR
- 1975 Jeener, Ernst 2D NMR
- 1980 NMR protein structure by Wuthrich
- 1990 3D and 1H/15N/13C Triple resonance
- 1997 Ultra high field (~800 MHz) & TROSY(MW 100K)

What are features of atoms to be analyzed using NMR? Or Can all atoms or compounds be analyzed using NMR ? No

The most important requirement is the magnetic feature.
Only atomic nuclei that have an <u>odd number of protons or neutrons</u> since they have magnetic moment.
The most familiar nuclei to be under focus are <u>hydrogen 1H and carbon 13C.</u> Nuclei such as 19F, 15N, 31P, 11B, 79Br and 127I have also the ability to be within the criteria but in less cases.

<u>In brief only nuclei with non-zero spins ($I \neq 0$) can absorb and emit electromagnetic radiation and undergo "resonance" when placed in a magnetic field.</u>

Nuclear Magnetic Resonance Spectroscopy



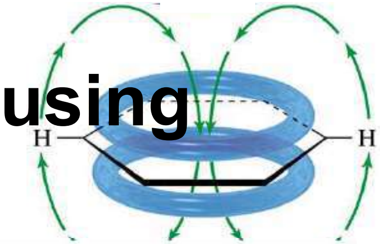
Many kinds of nuclei behave as if spinning around an axis

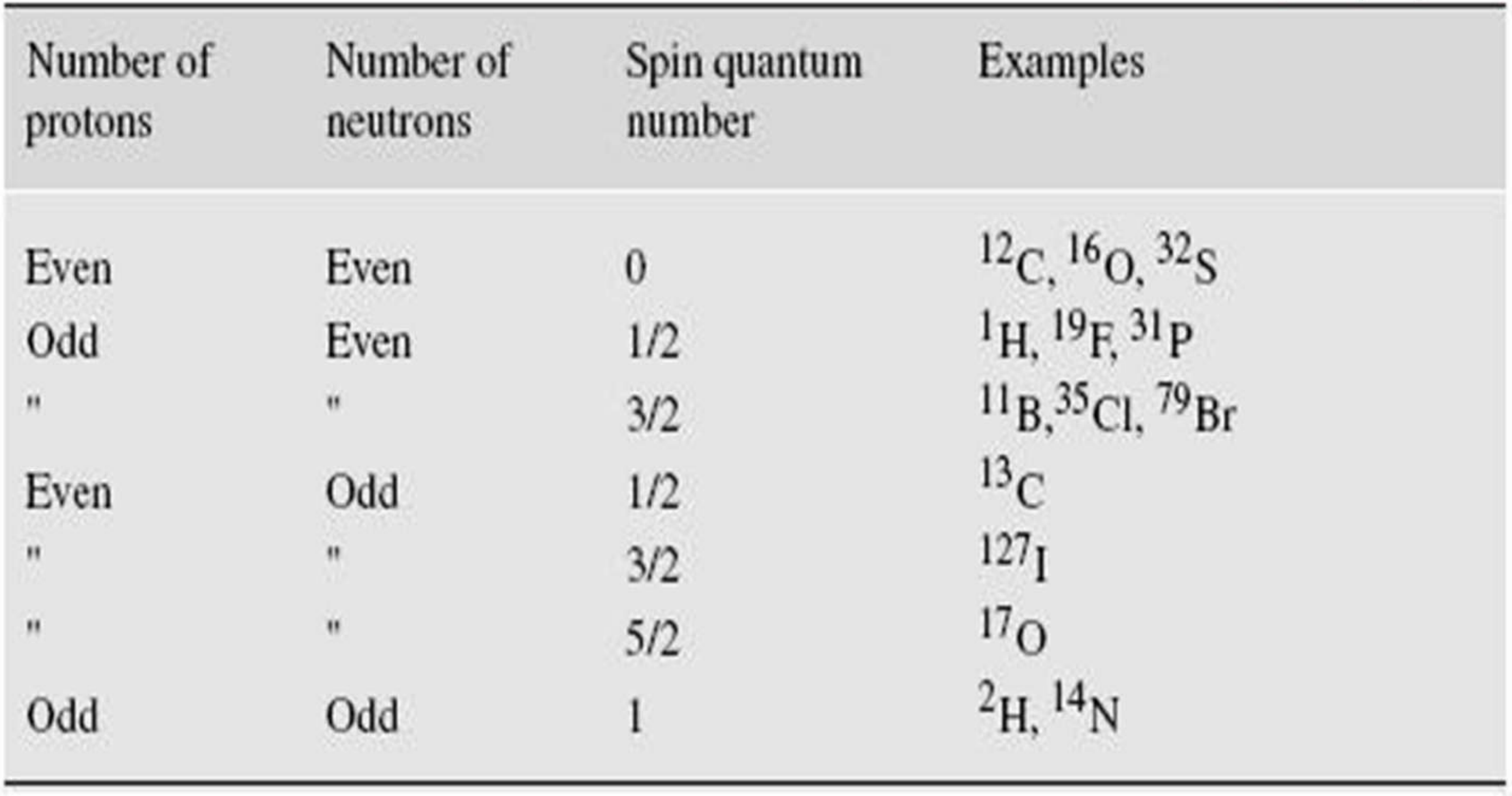
- All nuclei with odd number of protons has a spin
- All nuclei with an odd number of neutrons has a spin
- Nuclei with even number of both protons and neutrons do not have spin

Table 13.1 The NMR Behavior of Some Common Nuclei

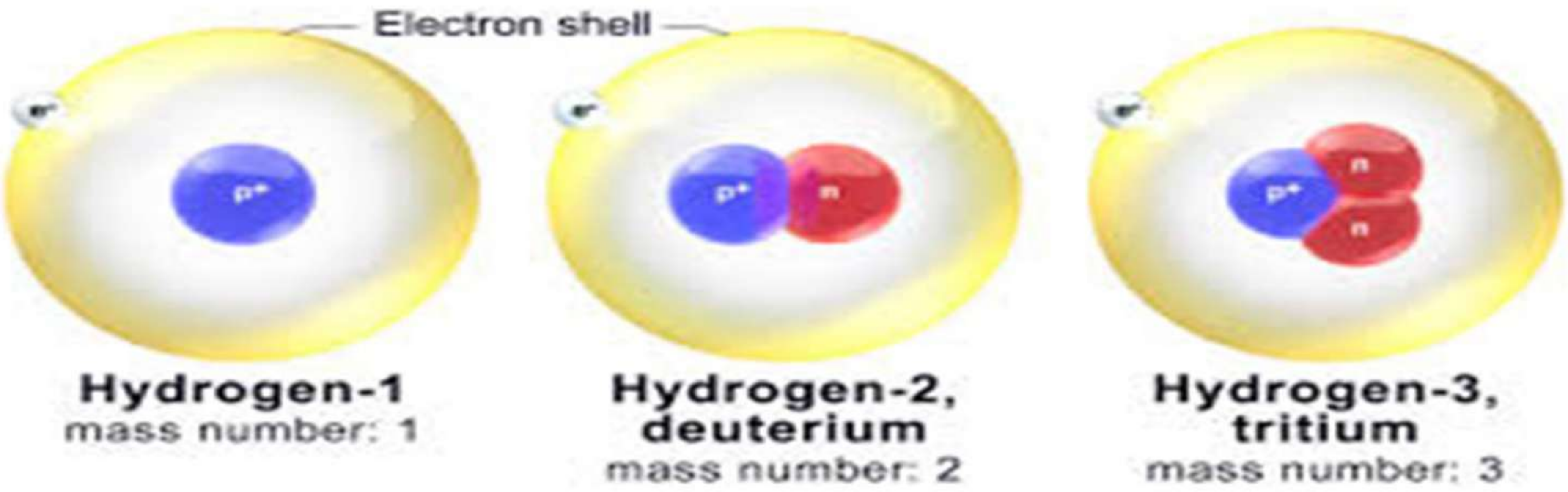
Magnetic nuclei	Nonmagnetic nuclei
^{1}H	^{12}C
^{13}C	^{16}O
^{2}H	^{32}S
^{14}N	
^{19}F	
^{31}P	

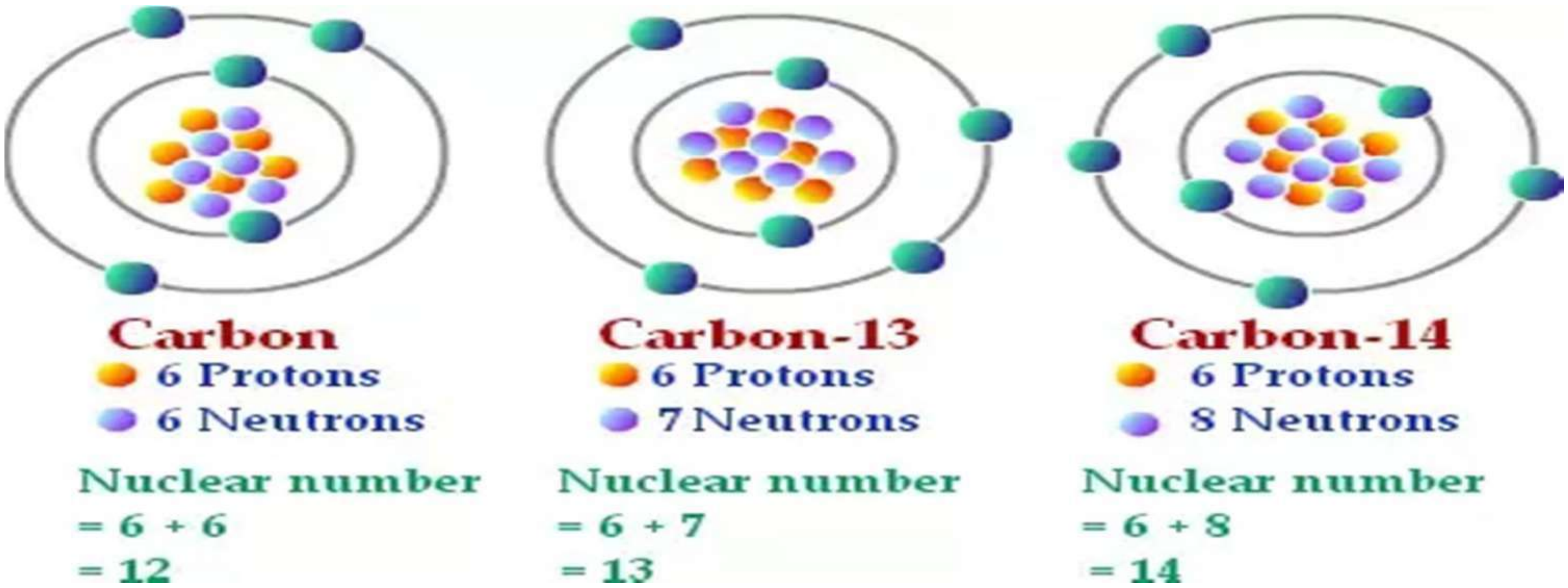
Examples of atoms that might be analyzed using NMR?



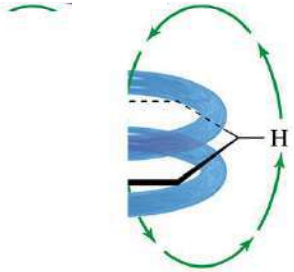


Number of protons	Number of neutrons	Spin quantum number	Examples
Even	Even	0	^{12}C, ^{16}O, ^{32}S
Odd	Even	1/2	^{1}H, ^{19}F, ^{31}P
"	"	3/2	^{11}B, ^{35}Cl, ^{79}Br
Even	Odd	1/2	^{13}C
"	"	3/2	^{127}I
"	"	5/2	^{17}O
Odd	Odd	1	^{2}H, ^{14}N

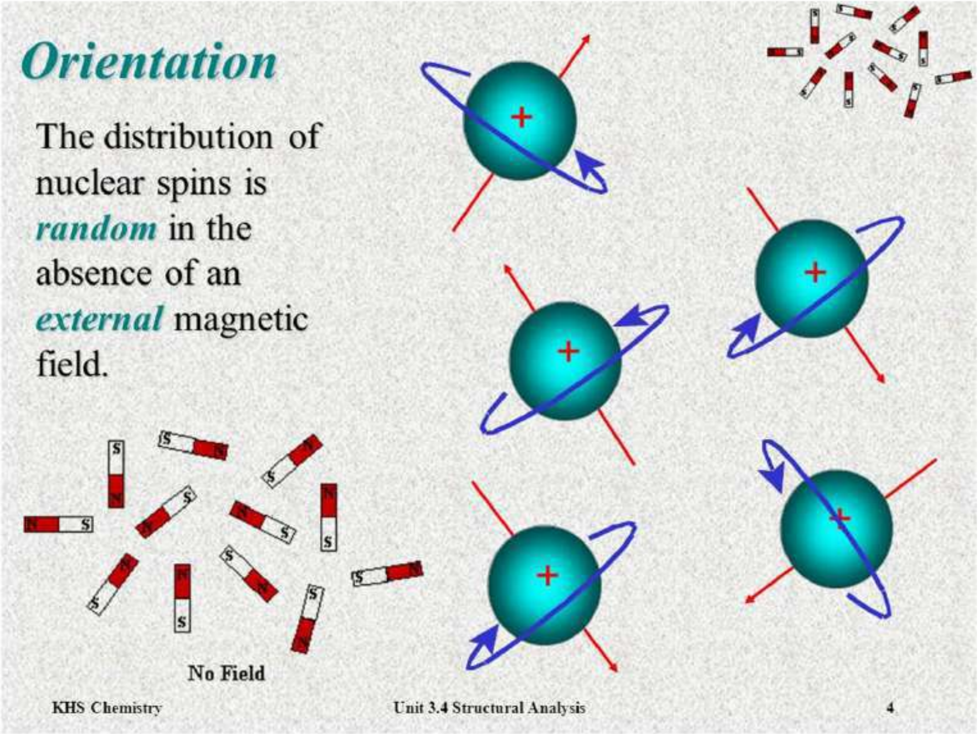

Electron shell
e⁻
p⁺
n
Hydrogen-1
mass number: 1
Hydrogen-2, deuterium
mass number: 2
Hydrogen-3, tritium
mass number: 3


Carbon
6 Protons
6 Neutrons
Nuclear number
= 6 + 6
= 12
Carbon-13
6 Protons
7 Neutrons
Nuclear number
= 6 + 7
= 13
Carbon-14
6 Protons
8 Neutrons
Nuclear number
= 6 + 8
= 14

Nuclear Magnetic Resonance Spectroscopy



- Many kinds of nuclei behave as if spinning around an axis
  - Nucleus is positively charged
    - Act as mini magnets
  - Spins of magnetic nuclei are randomly orientated
  - Nuclei become oriented if place in a magnetic field



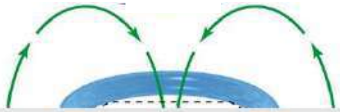
Orientation

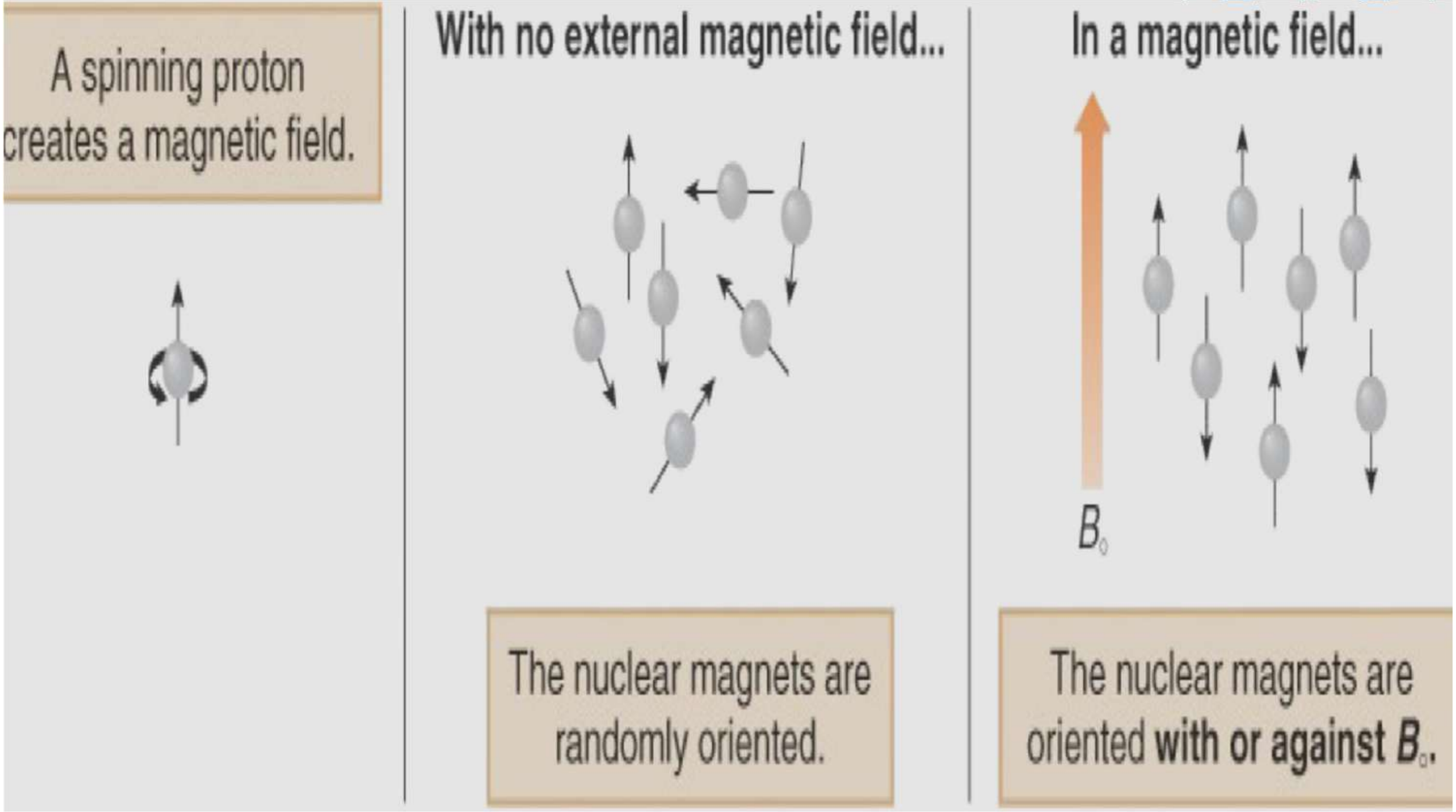
The distribution of nuclear spins is ***random*** in the absence of an ***external*** magnetic field.

No Field

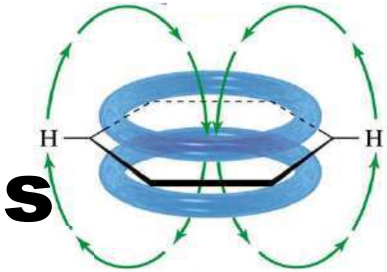
KHS Chemistry Unit 3.4 Structural Analysis 4

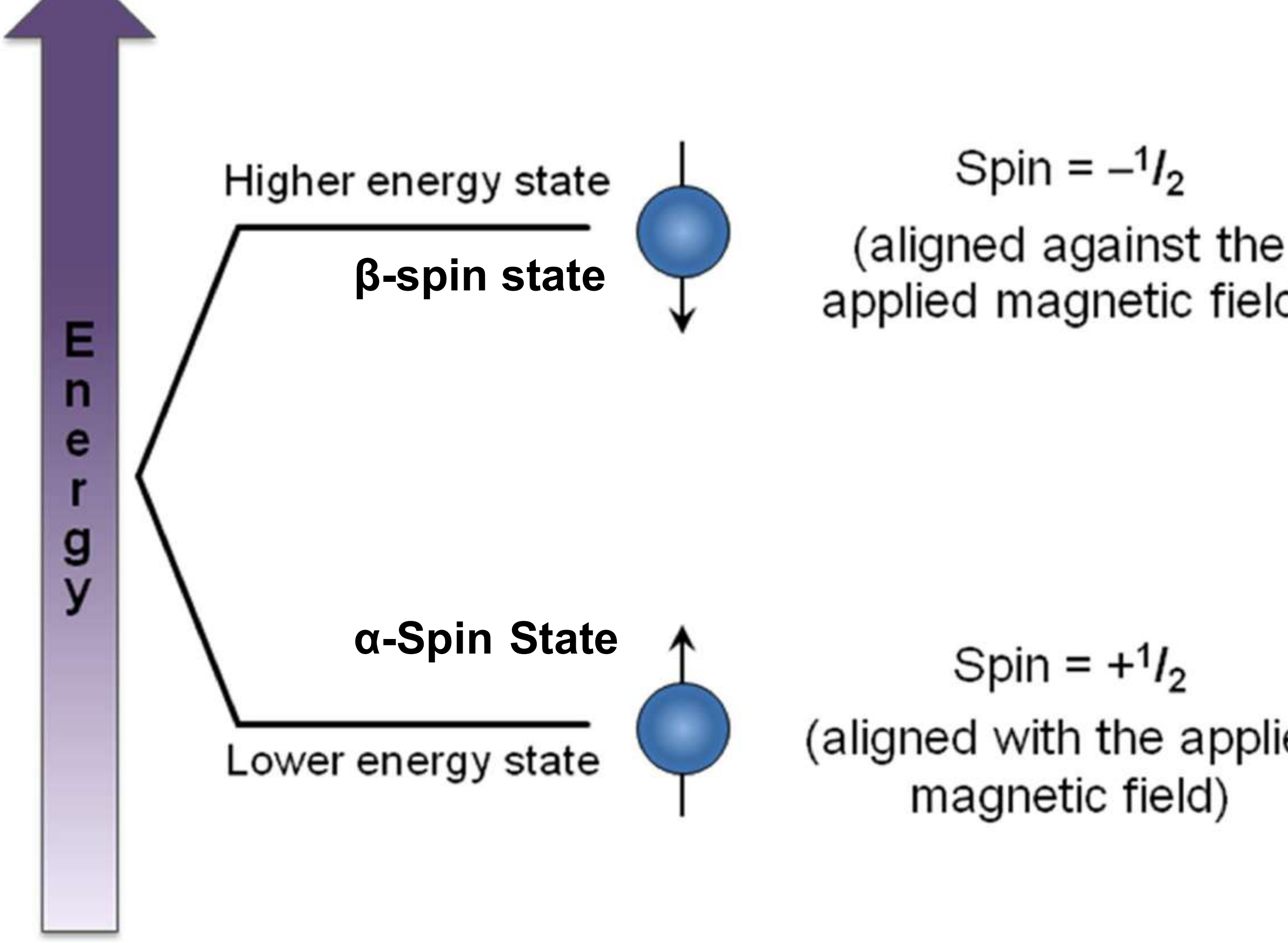
Random direction of spins




A spinning proton creates a magnetic field.
With no external magnetic field...
In a magnetic field...
B₀
The nuclear magnets are randomly oriented.
The nuclear magnets are oriented **with or against B₀**.

Proton Energy Spin States





Higher energy state

β-spin state

Spin = $-^1/_2$

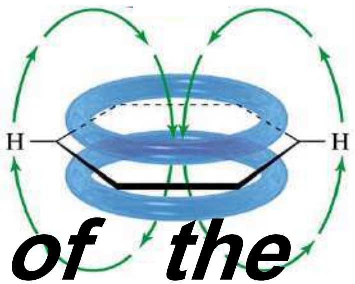
(aligned against the applied magnetic field)

α-Spin State

Lower energy state

Spin = $+^1/_2$

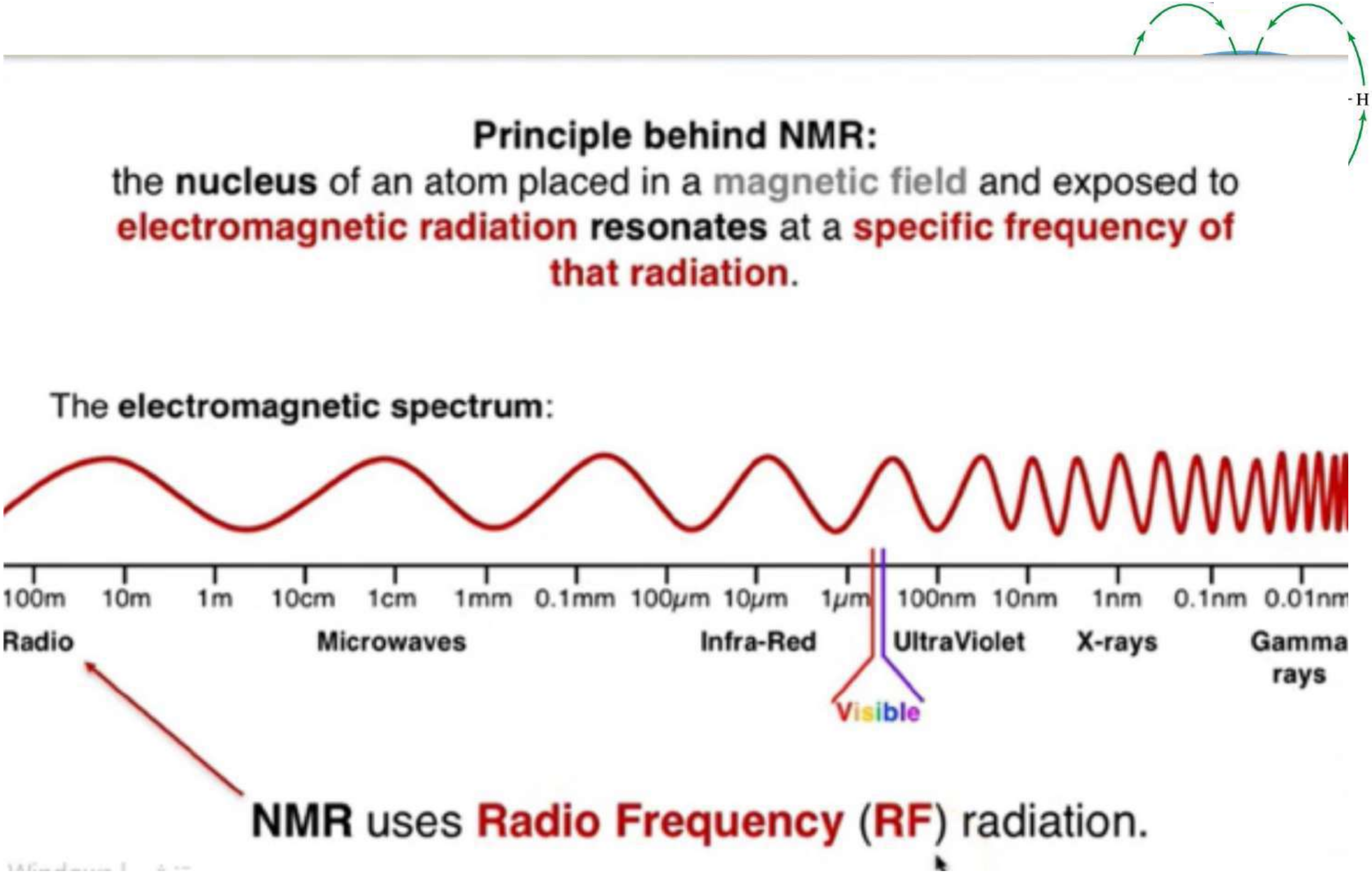
(aligned with the applied magnetic field)



Note:- Based on the direction of the angular moment that arises from spin motion; the two levels are formed

α-Spin State:- is known as the low energy level and its magnetic moment is in the direction of the external magnetic field.

β-spin state:- is known as the high energy level and its magnetic moment is in opposite direction of the external magnetic field.

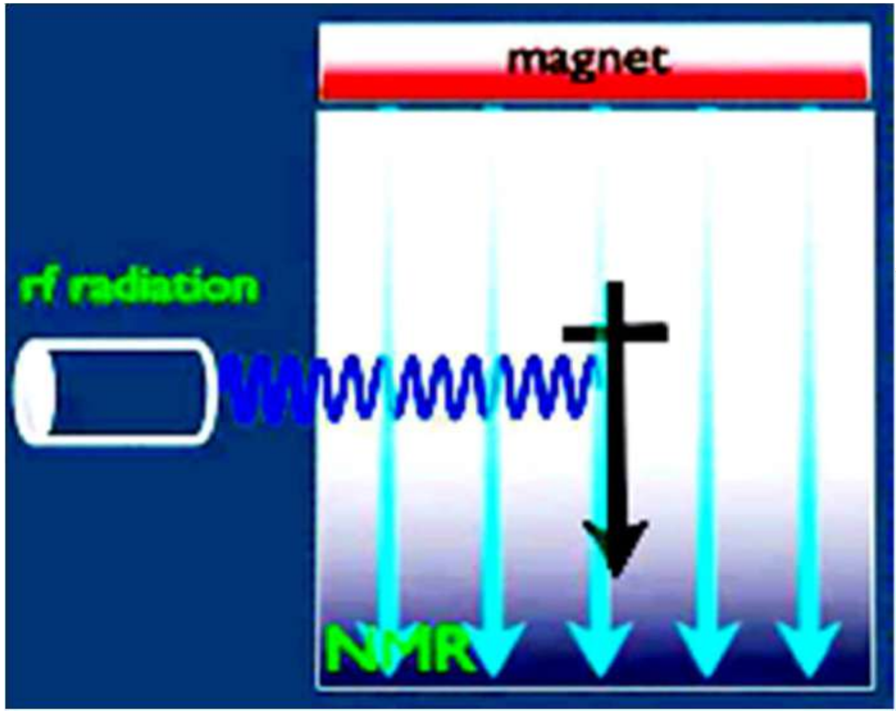


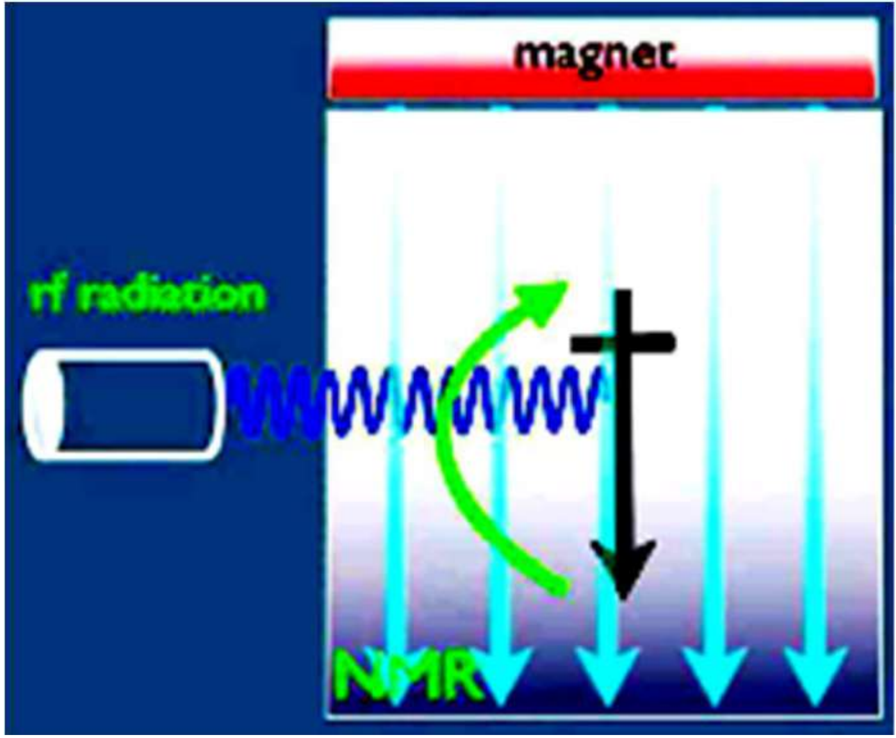
Principle behind NMR:

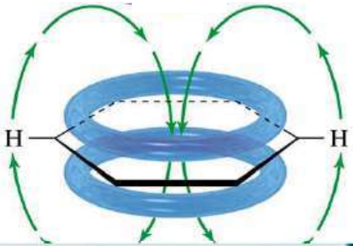
the **nucleus** of an atom placed in a magnetic field and exposed to **electromagnetic radiation resonates** at a **specific frequency of that radiation**.

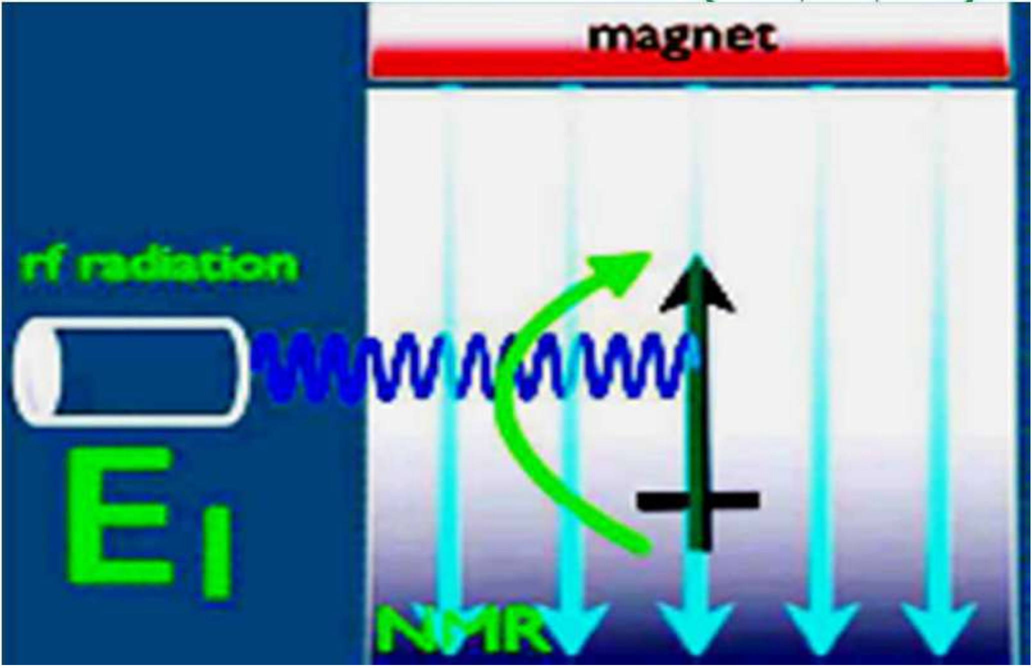
The **electromagnetic spectrum**:

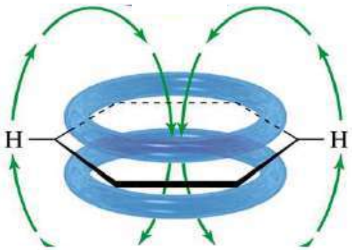
NMR uses **Radio Frequency** (**RF**) radiation.

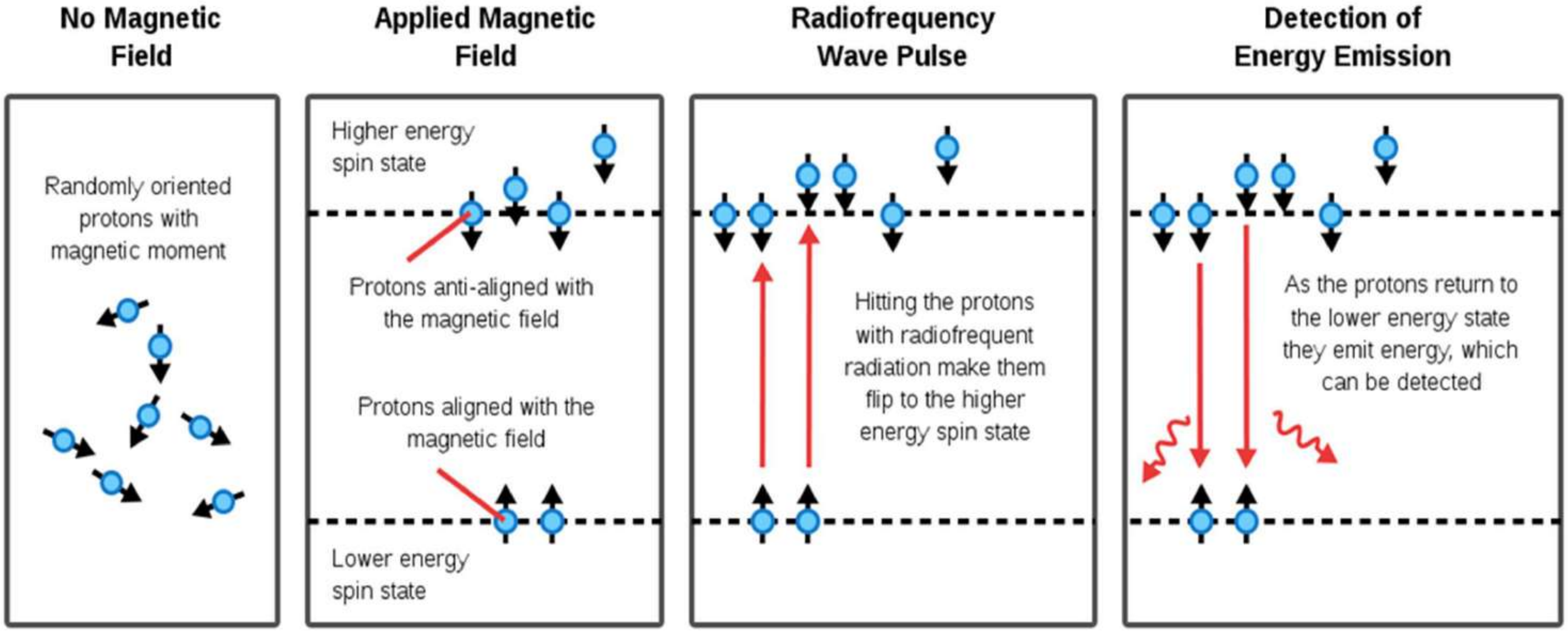

magnet
rf radiation
NMR


magnet
rf radiation
NMR


H
H


magnet
rf radiation
E1
NMR





No Magnetic Field

Randomly oriented protons with magnetic moment

Applied Magnetic Field

Higher energy spin state

Protons anti-aligned with the magnetic field

Protons aligned with the magnetic field

Lower energy spin state

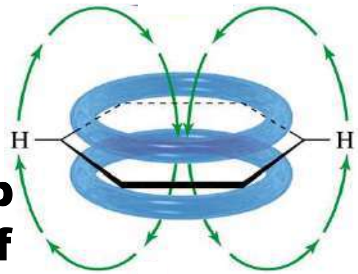
Radiofrequency Wave Pulse

Hitting the protons with radiofrequent radiation make them flip to the higher energy spin state

Detection of Energy Emission

As the protons return to the lower energy state they emit energy, which can be detected

Principles of NMR:-



- NMR is one of the physical phenomena that depends up on the magnetic quantum mechanics feature of nucleus.

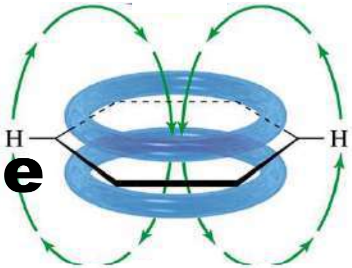
- All subatomic particles (neutrons, protons, electrons) have the fundamental property of spin. This spin corresponds to a small magnetic moment.

- In the absence of a magnetic field nucleus moment is randomly aligned. When a static magnetic field, Bo is applied this field, it acts as a turning force that aligns the nuclear spin axis of magnetic nuclei with the direction of the applied field. (the lower energy level α-state and the higher energy level (β-state) .

- This equilibrium alignment can be changed to an excited state by applying radio frequency (RF) pulses.

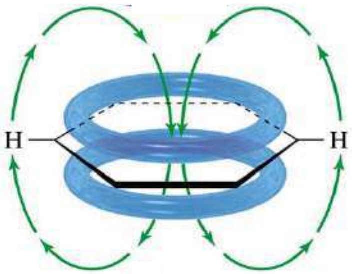
- When the nuclei revert to the equilibrium they emit RF radiation "Radiofrequency" that can be detected amplified as a linear spectral and the translated into signal known as resonance signal.

Types of NMR to be studied in this course



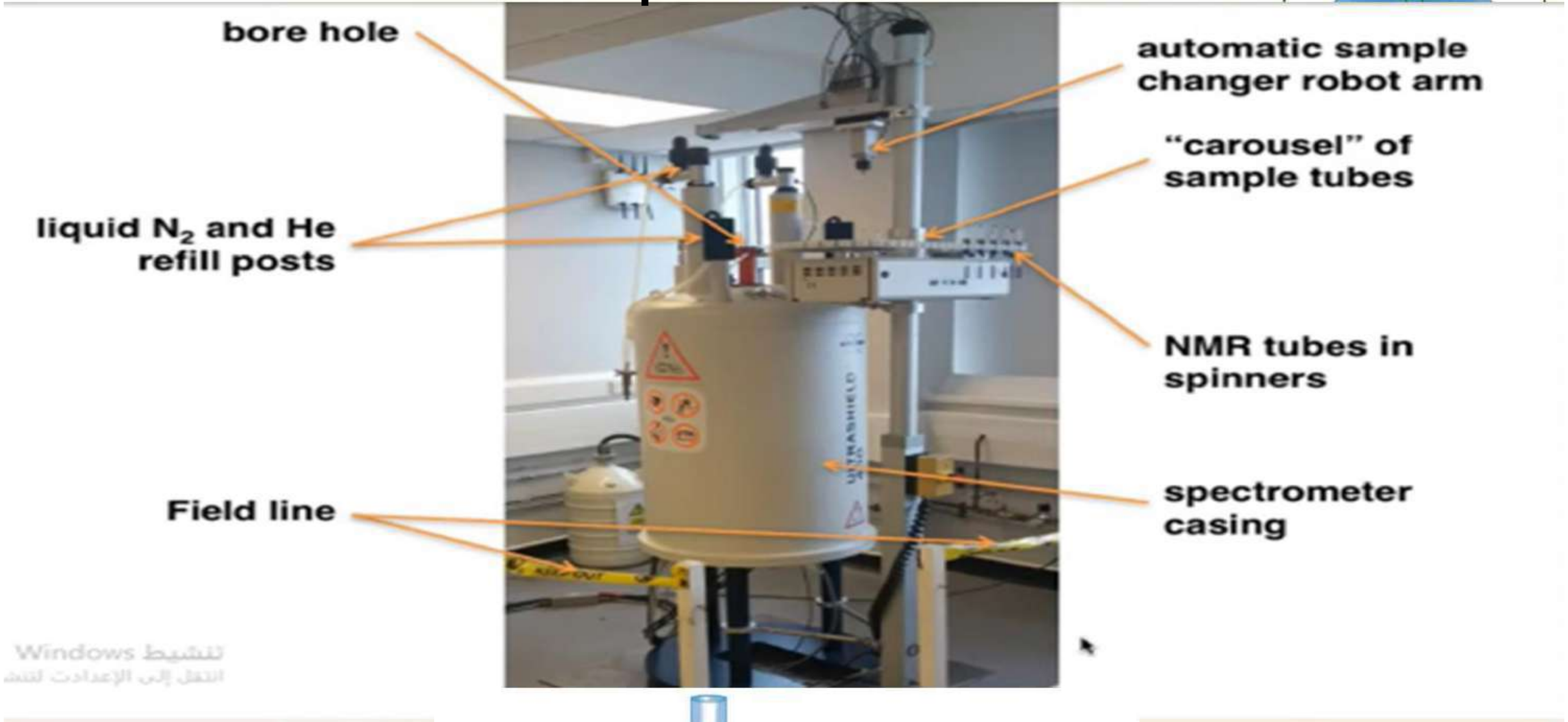
Two common types of NMR spectroscopy are used to characterize organic structure:

- ^{1}H NMR:- Used to determine the type and number of H atoms in a molecule
- ^{13}C NMR:- Used to determine the type of carbon atoms in the molecule



Video 3
Page(35-61)

NMR Spectrometer



bore hole

liquid N_2 and He refill posts

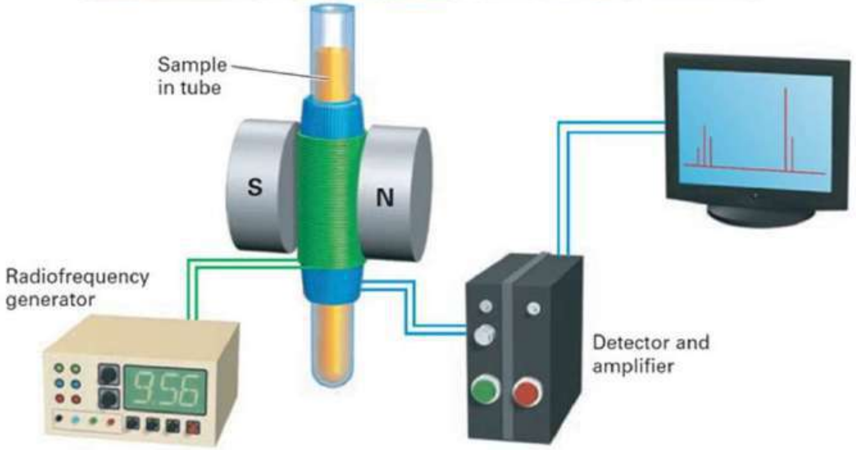
Field line

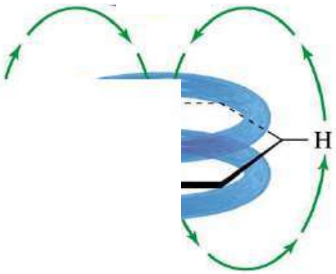
automatic sample changer robot arm

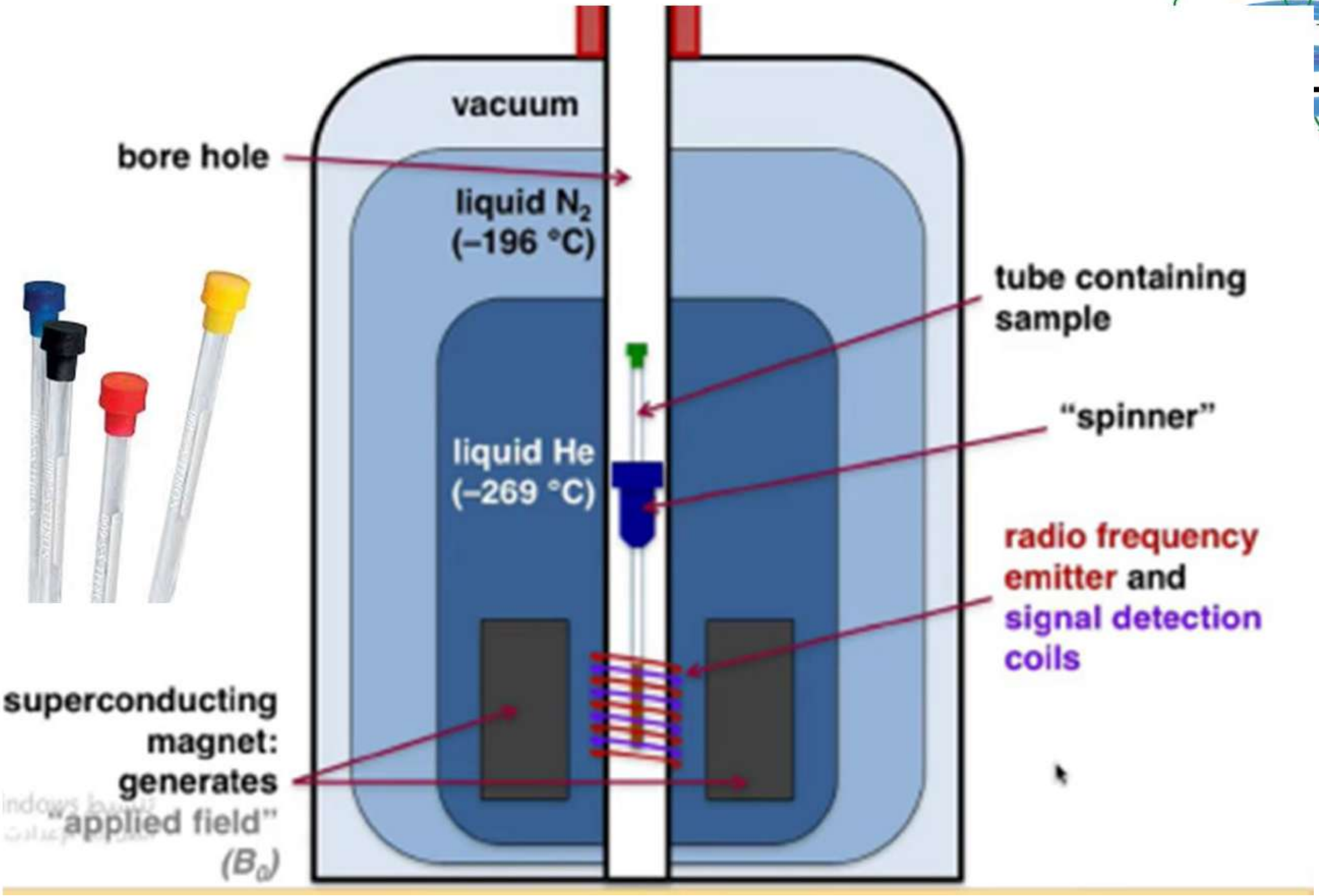
"carousel" of sample tubes

NMR tubes in spinners

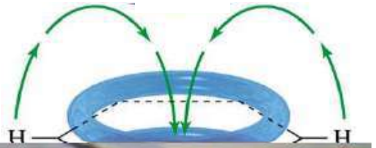
spectrometer casing



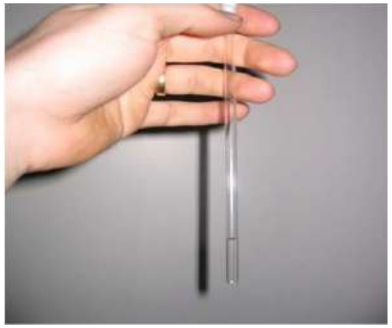

H


vacuum
bore hole
liquid N_2 (–196 °C)
tube containing sample
"spinner"
liquid He (–269 °C)
radio frequency emitter and signal detection coils
superconducting magnet: generates "applied field" (B_0)

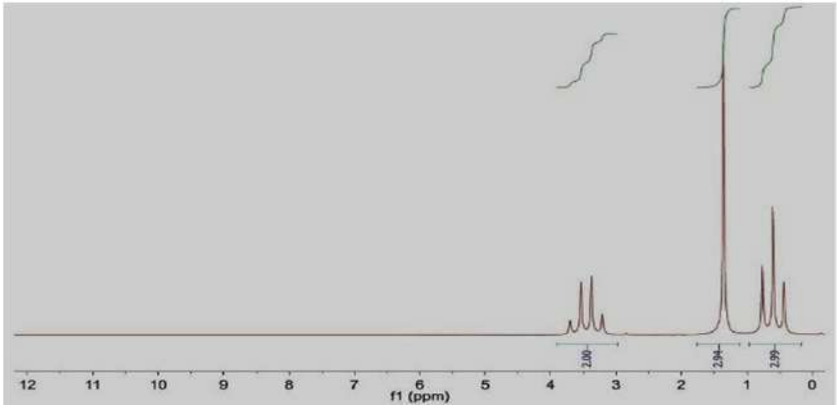
NMR Spectrometer

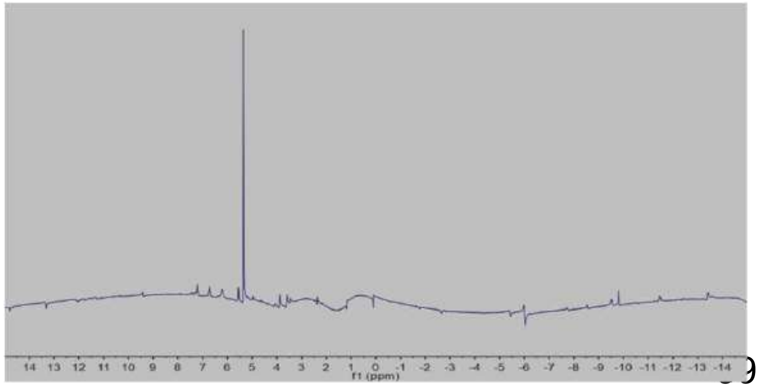


Solvents in NMR

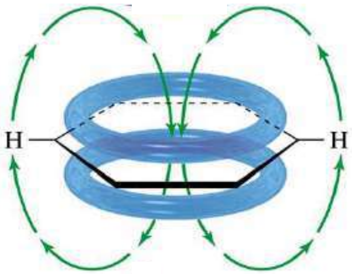


- The principle is as known " Like dissolves like“
- 20-30 mg of solid sample dissolved in 0.5 ml of appropriate solvent and 50µL of liquid sample dissolved in 0.5 ml of appropriate solvent.
- Turbidity causes mismatching of the spectrum and bad result (bad spectrum) is expected.
- If there was difficulty in solubility such as heterocyclic drugs; then try to use The DMSO otherwise add with one drop of deuterated acid to the $CDCl_3$





The most well-known solvents

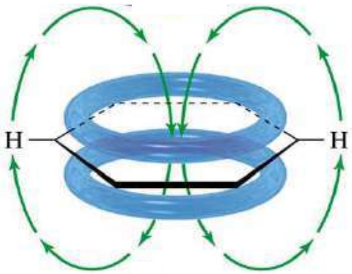


- **Deuterated Chloroform "$CDCl_3$"**
- **Deuterated Ethanol "C_2D_5OD"**
- **Deuterated Water "D_2O"**
- **Deuterated Dimethyl Sulfoxide DMSO "“$(CD_3)_2SO$"**

Why Deuterated solvent?

1. **If you use non deuterated solvent you will see only a giant signal in hydrogen NMR spectra from solvent. (To avoid swamping by the solvent signal).**
2. **Besides, NMR spectrometers use deuterium signal to keep magnetic field constant.**

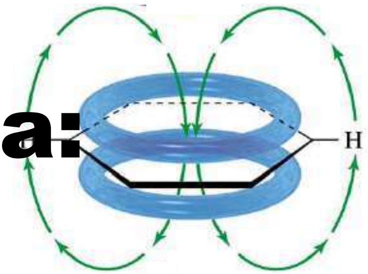
Why Deuterium cant be detected in H-NMR



Deuterium-deuterium couplings are about 40 times smaller than proton-proton couplings and are therefore not observed

Deuterium NMR is NMR spectroscopy of deuterium (2H or D), an isotope of hydrogen Deuterium is an isotope with spin = 1, unlike hydrogen which is spin = 1/2. Deuterium NMR has a range of chemical shift similar to proton NMR but with poor resolution. It may be used to verify the effectiveness of Deuteration: a deuterated compound will show a peak in deuterium NMR but not proton NMR.

Information from 1H-NMR spectra:

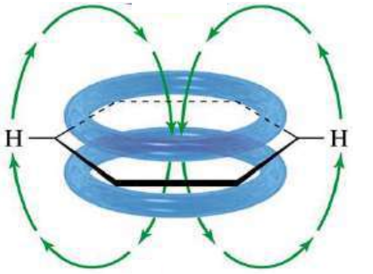


1. **Number of signals**:
How many different types of hydrogens in the molecule.

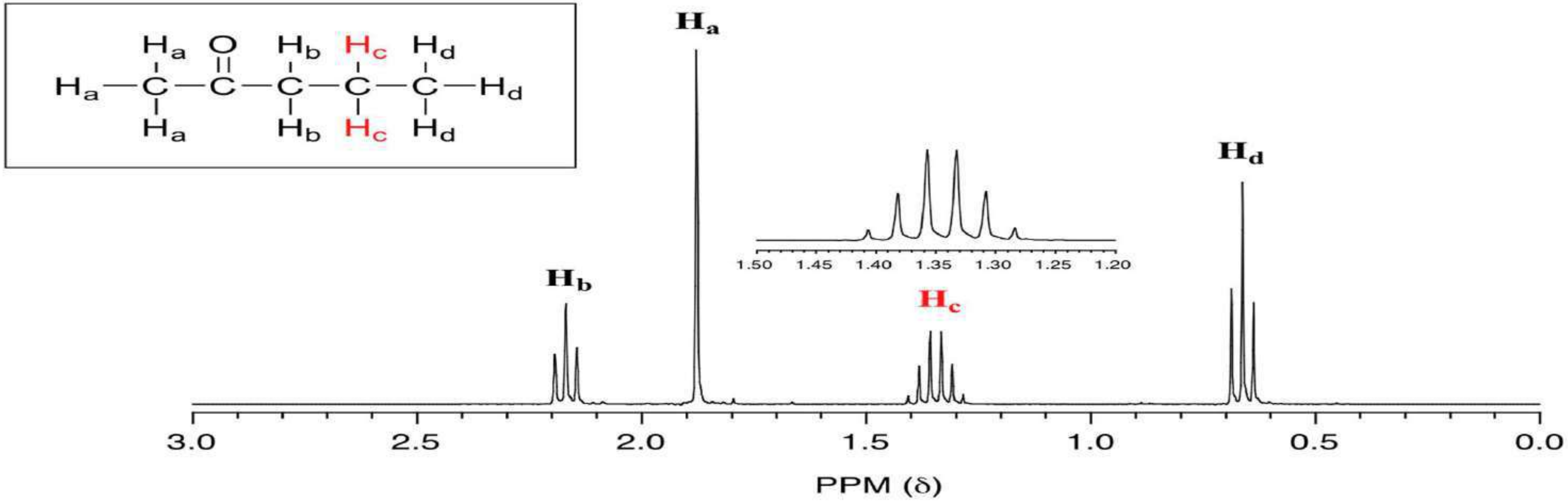
2. **Position of signals** (chemical shift):
What types of hydrogens.

3. **Relative areas under signals** (integration):
How many hydrogens of each type.

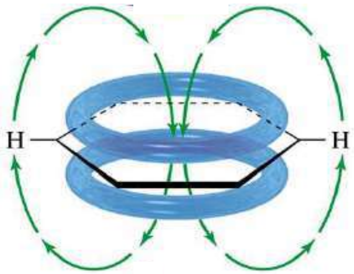
4. **Splitting pattern:** How many neighboring hydrogens.



(1)
Number of signals



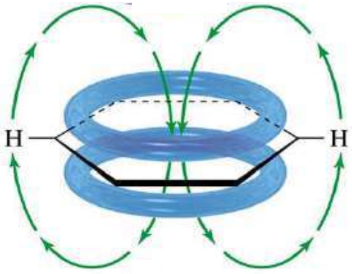
Number of signals:



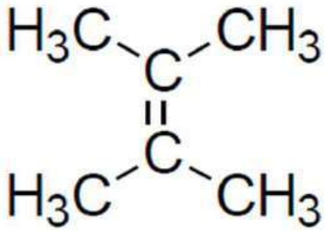
What is NMR signal?
{Peaks in the NMR spectrum or chart}

How many different types of hydrogen does the compound have??

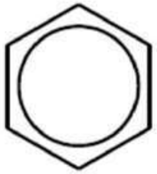
- **Magnetically equivalent hydrogen atoms resonate at the same applied field.**
- **Magnetically equivalent hydrogen atoms are also chemically equivalent.**



one

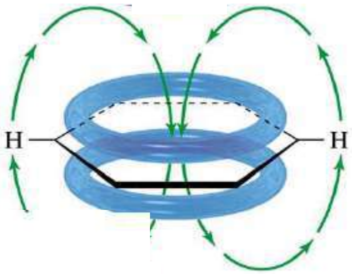


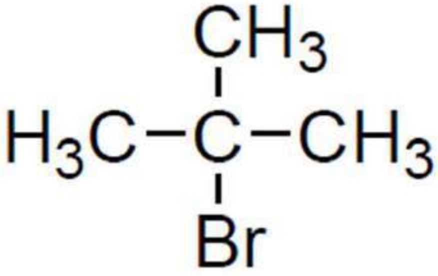
one



one

two





$$\begin{array}{c} \mathrm{CH_3} \\ | \\ \mathrm{H_3C-C-CH_3} \\ | \\ \mathrm{Br} \end{array}$$

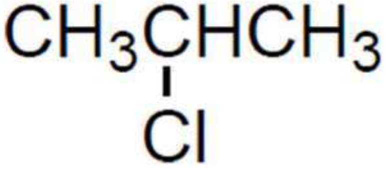
one

$CH_3CH_2\text{-}Br$

two

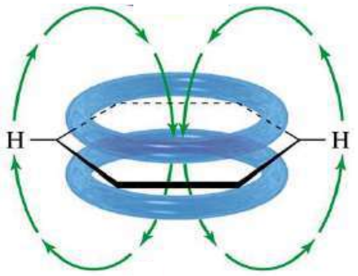
$CH_3CH_2CH_2\text{-}Br$

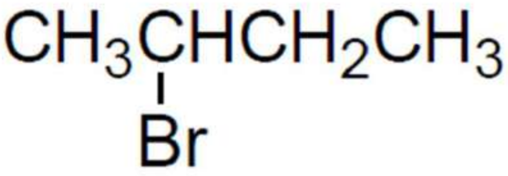
three



$$\begin{array}{c} \mathrm{CH_3CHCH_3} \\ | \\ \mathrm{Cl} \end{array}$$

two

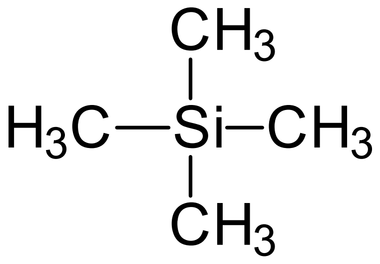



$CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_3$

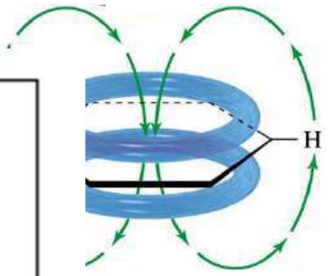
$Cl\text{-}CH_2CH_2CH_2\text{-}Cl$

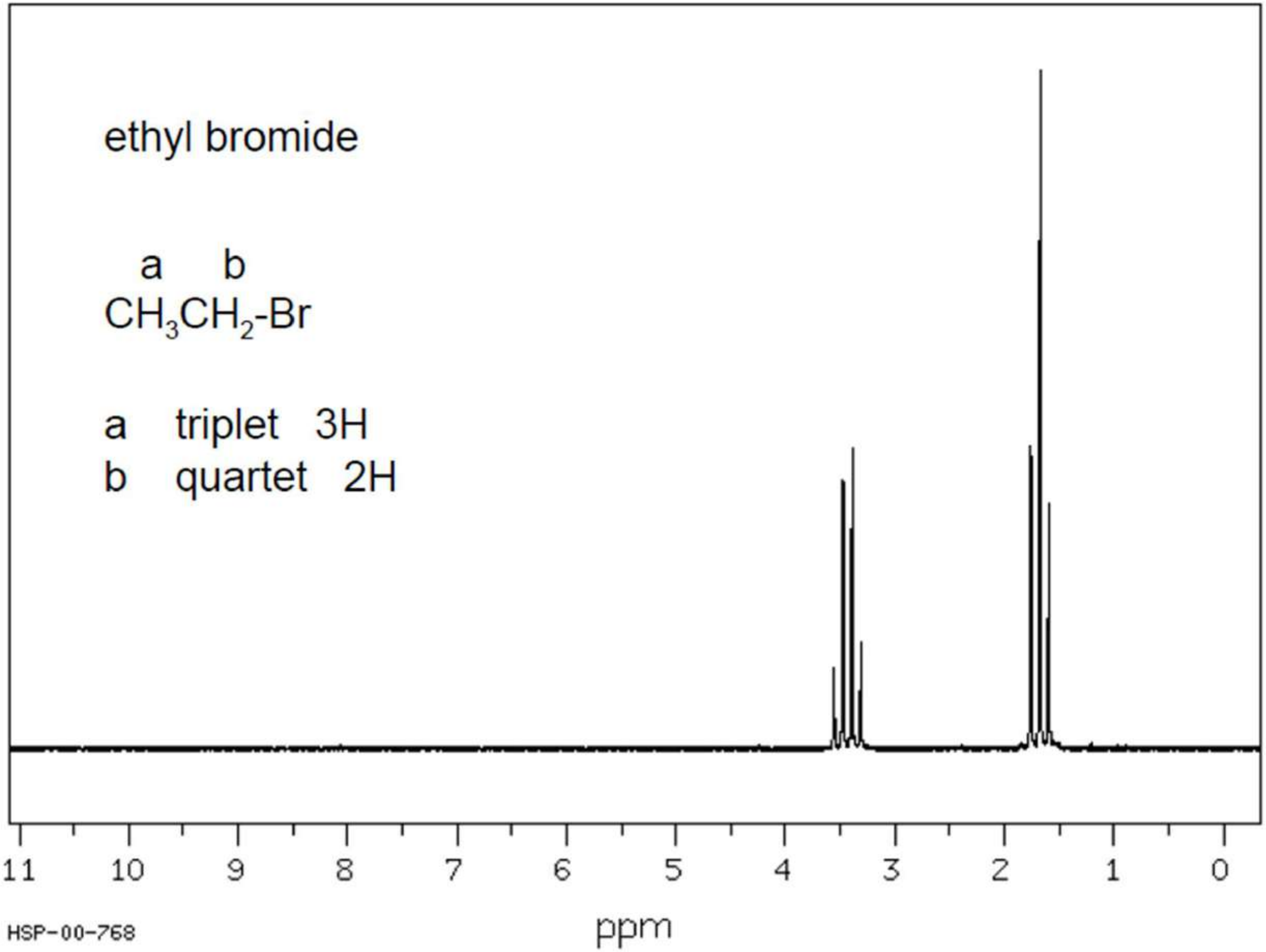
four

two


$H_3C{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{\overset{|}{\underset{|}{Si}}}}{-}CH_3$

one

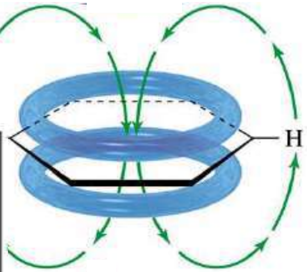


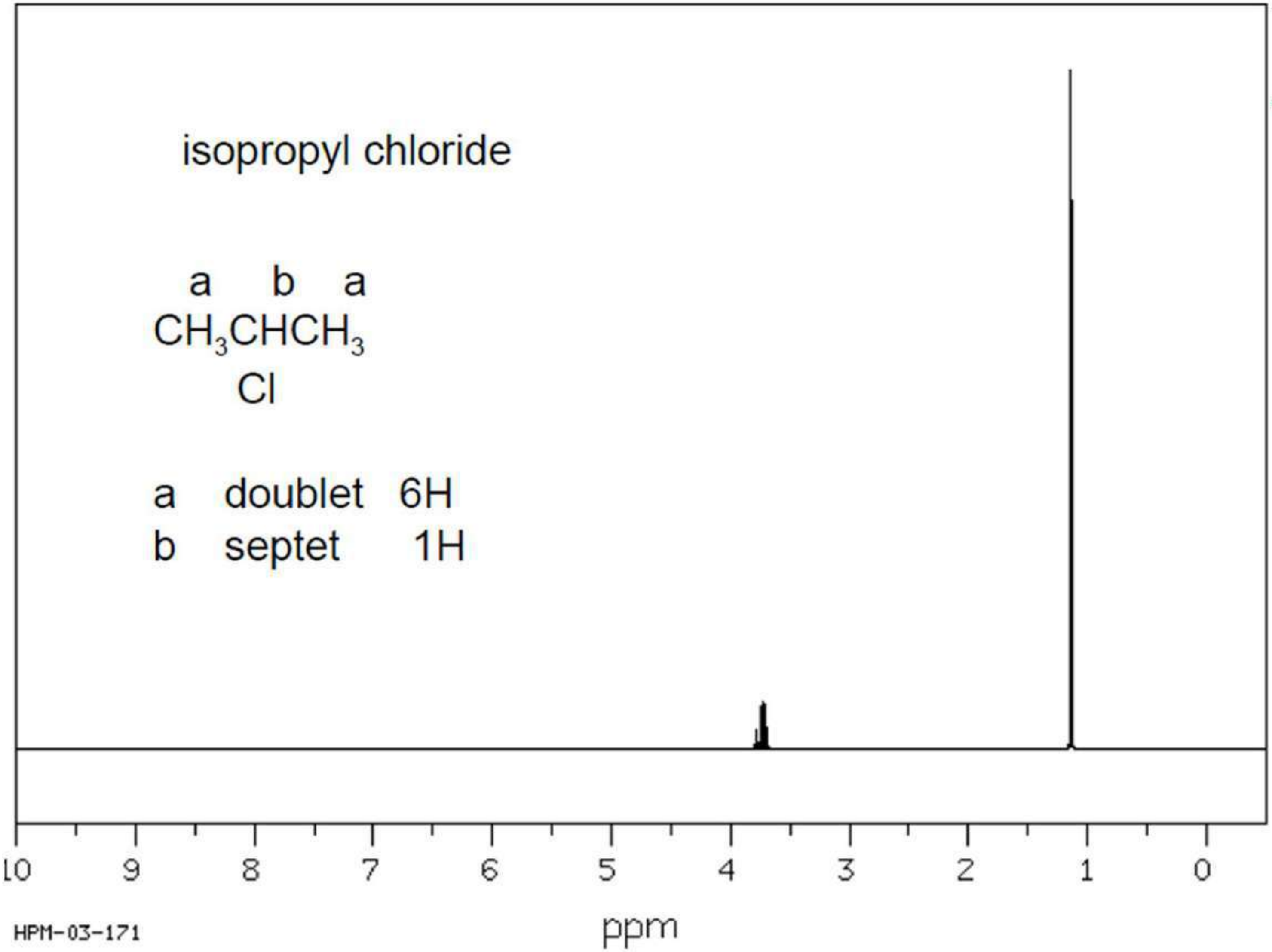


ethyl bromide

  a   b
CH_3CH_2-Br

a triplet 3H
b quartet 2H

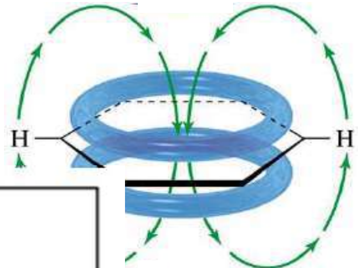


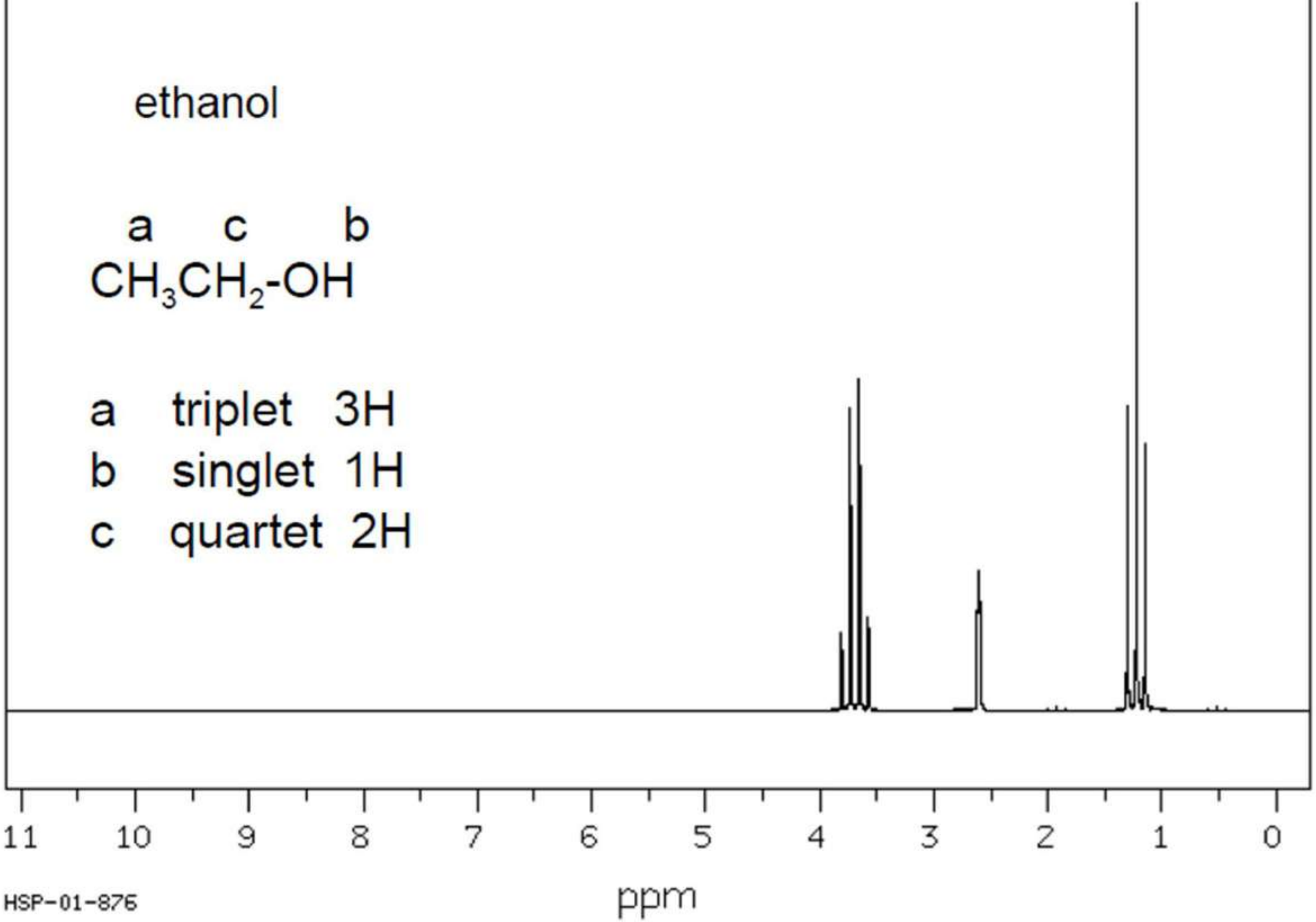


isopropyl chloride

$$\overset{a}{CH_3}\overset{b}{CH}\overset{a}{CH_3}$$
$$\quad Cl$$

a doublet 6H
b septet 1H

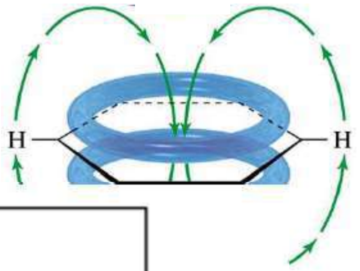


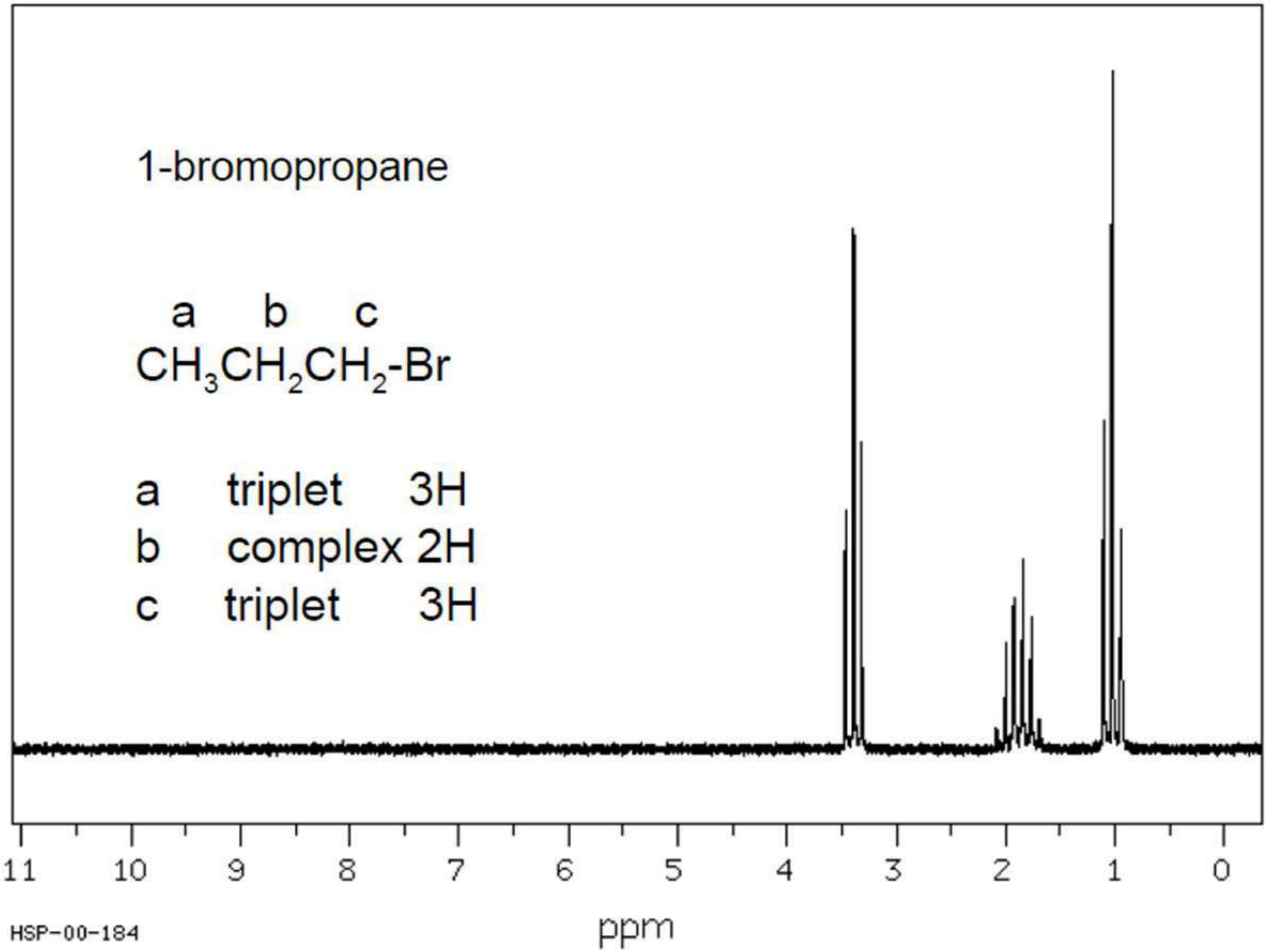


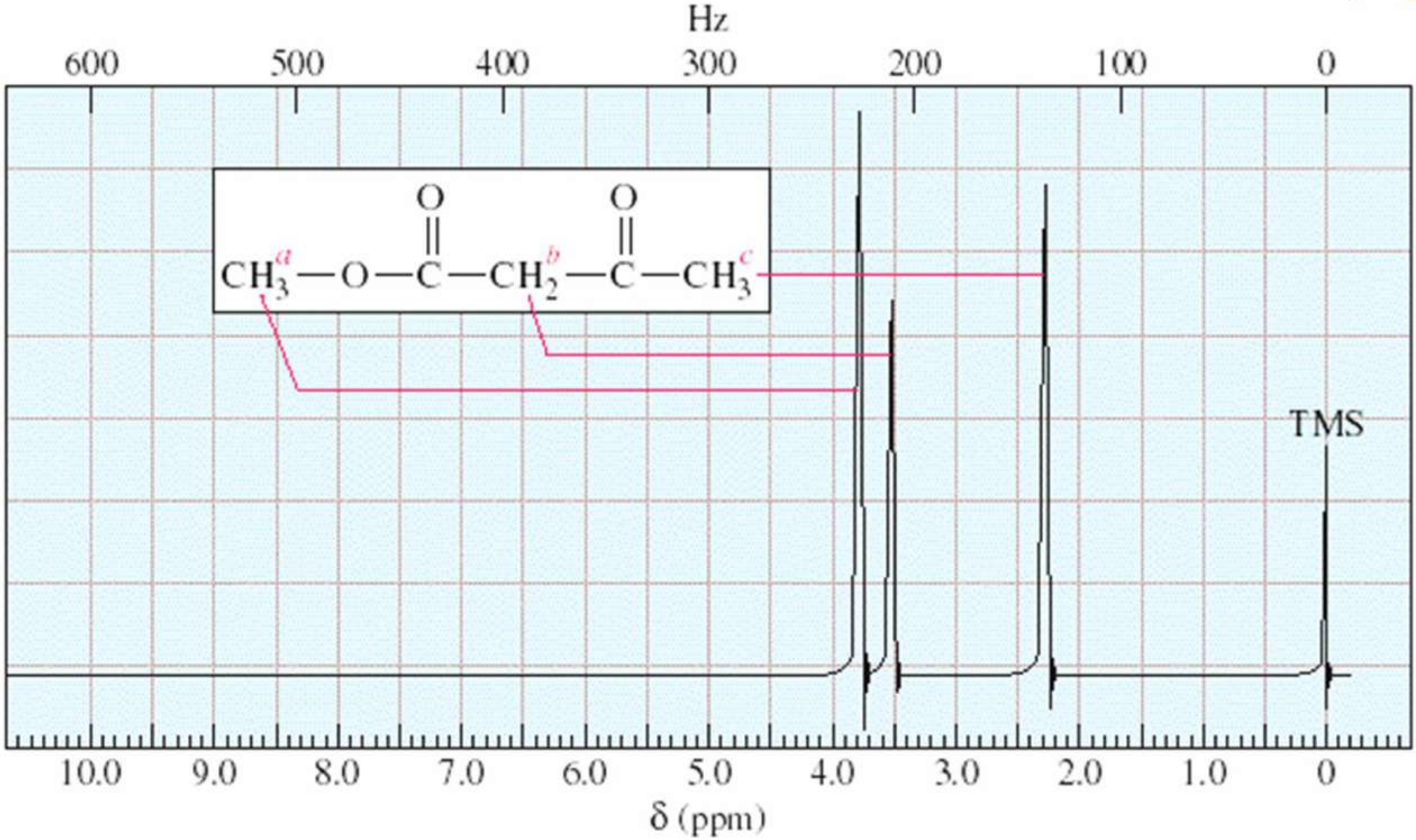
ethanol

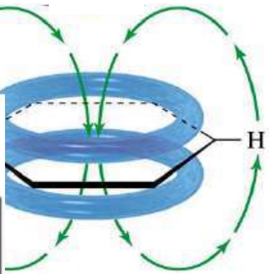
a c b
$CH_3CH_2\text{-}OH$

a triplet 3H
b singlet 1H
c quartet 2H

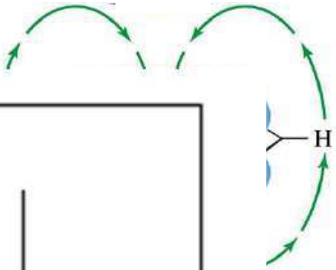

H
H

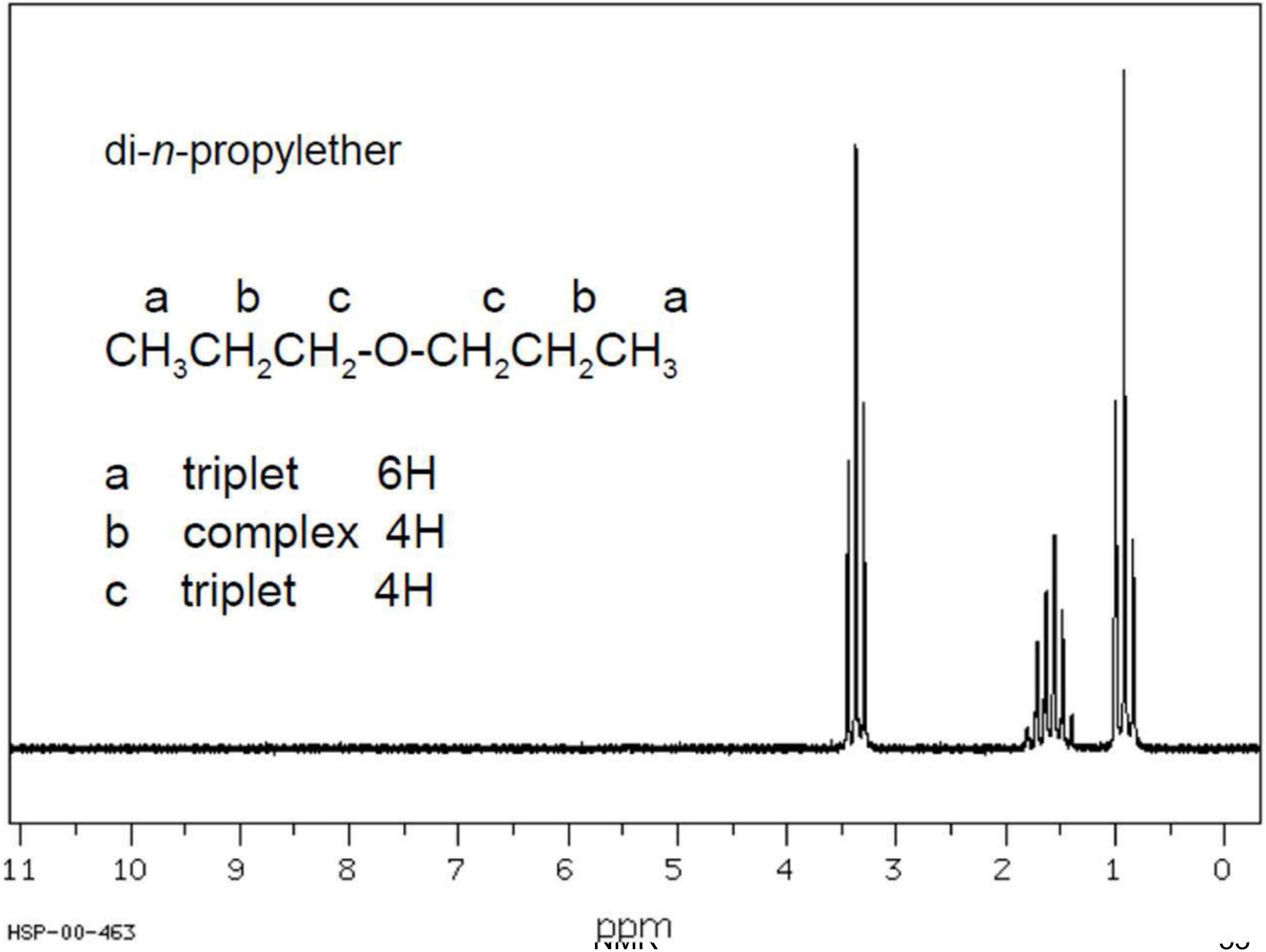

1-bromopropane
a b c
$CH_3CH_2CH_2$-Br
a triplet 3H
b complex 2H
c triplet 3H
11
10
9
8
7
6
5
4
3
2
1
0
ppm
HSP-00-184


Hz
600
500
400
300
200
100
0
O
O
$CH_3^a—O—C—CH_2^b—C—CH_3^c$
TMS
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
δ (ppm)


H

=>

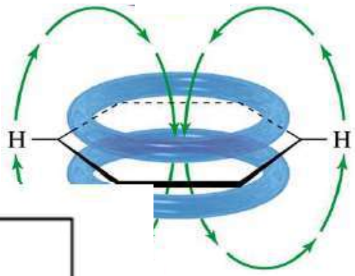


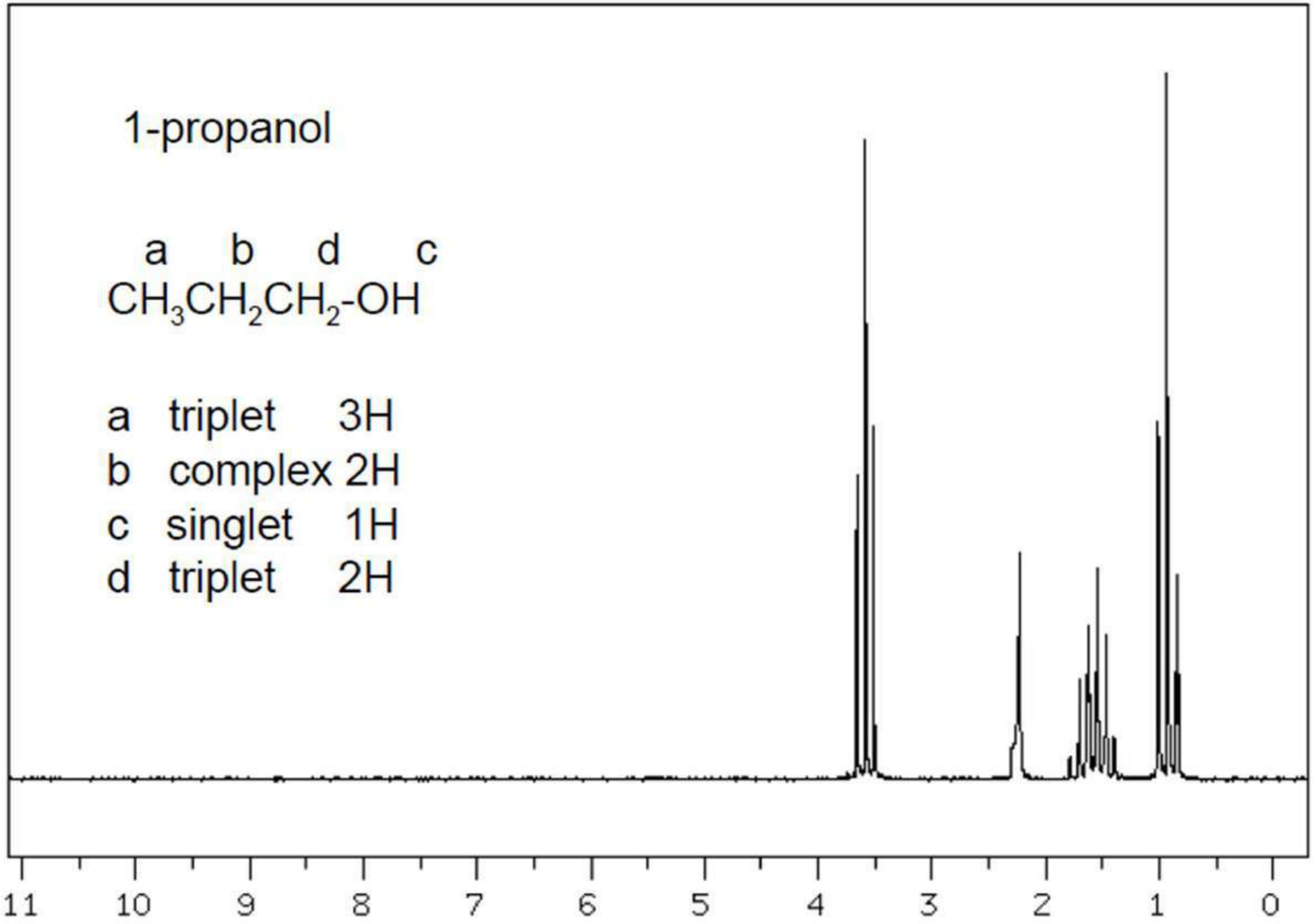


di-*n*-propylether

$$\overset{a}{CH_3}\overset{b}{CH_2}\overset{c}{CH_2}\text{-O-}\overset{c}{CH_2}\overset{b}{CH_2}\overset{a}{CH_3}$$

a	triplet	6H
b	complex	4H
c	triplet	4H

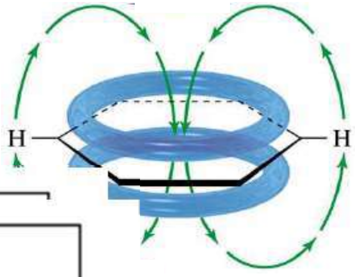


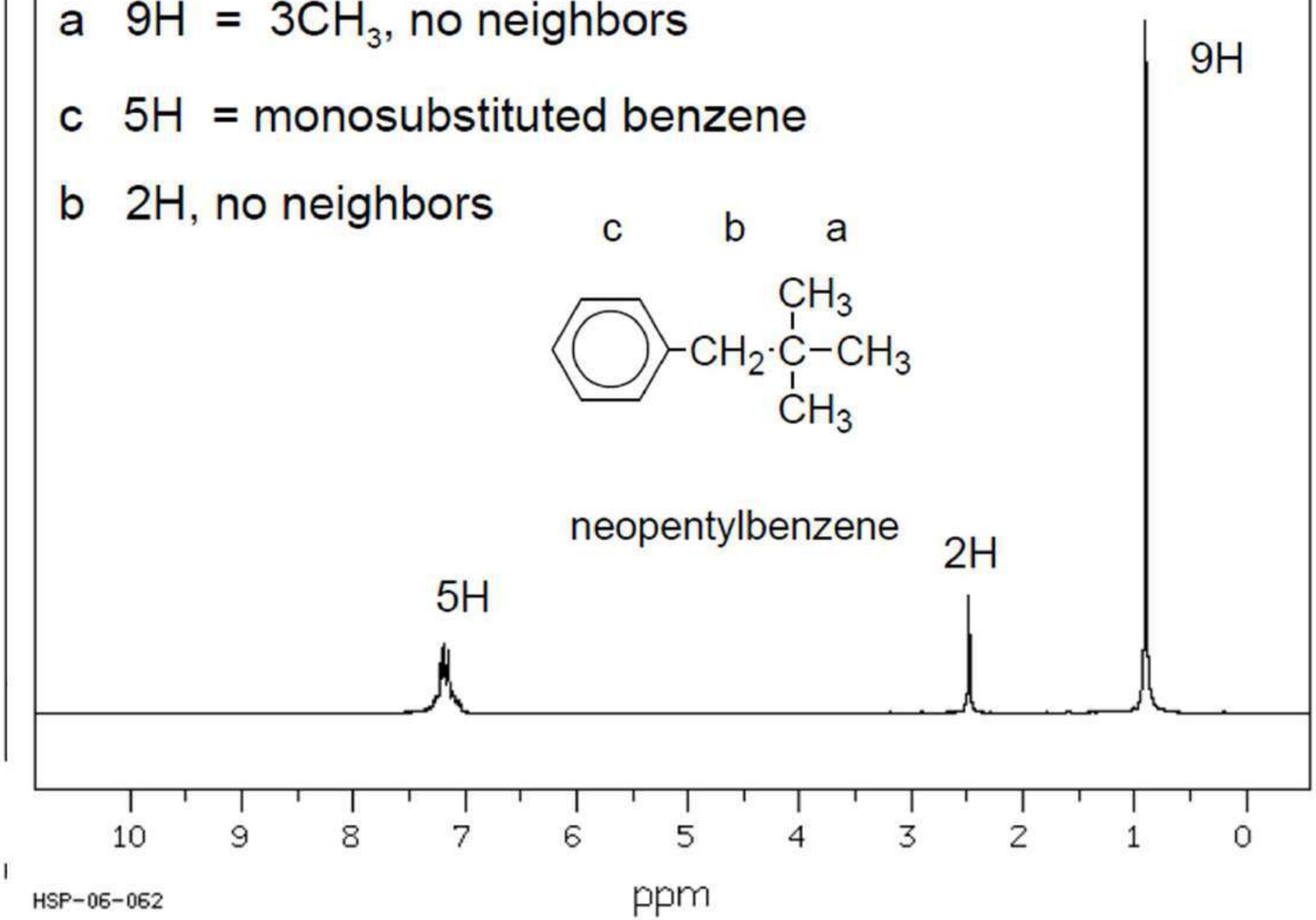


1-propanol

$\overset{a}{CH_3}\overset{b}{CH_2}\overset{d}{CH_2}\text{-}\overset{c}{OH}$

a	triplet	3H
b	complex	2H
c	singlet	1H
d	triplet	2H



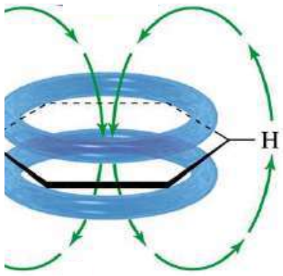


a 9H = $3CH_3$, no neighbors

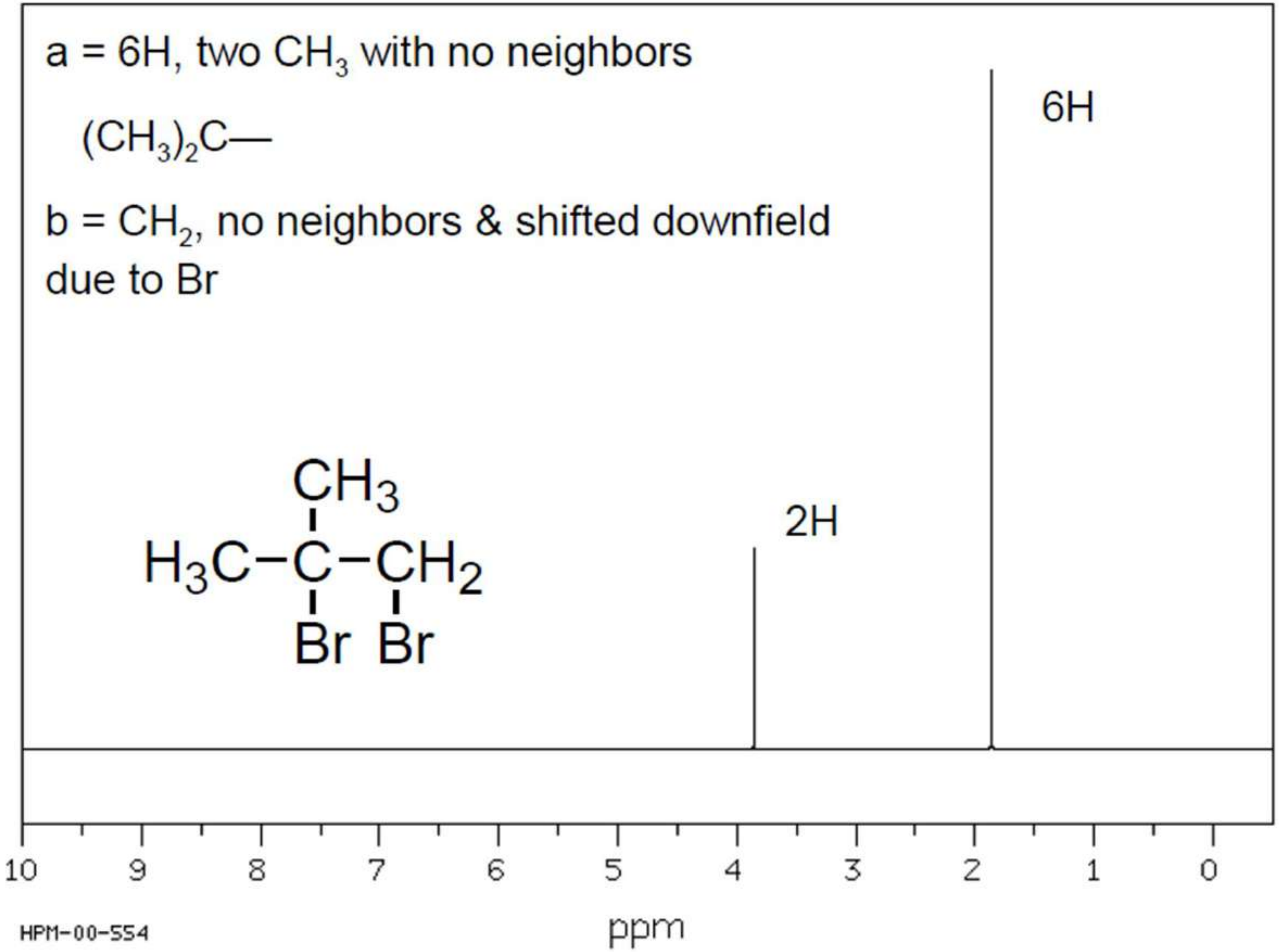
c 5H = monosubstituted benzene

b 2H, no neighbors

neopentylbenzene



$C_4H_8Br_2$

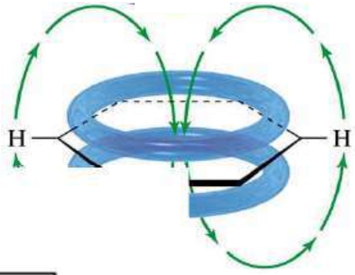


a = 6H, two CH_3 with no neighbors

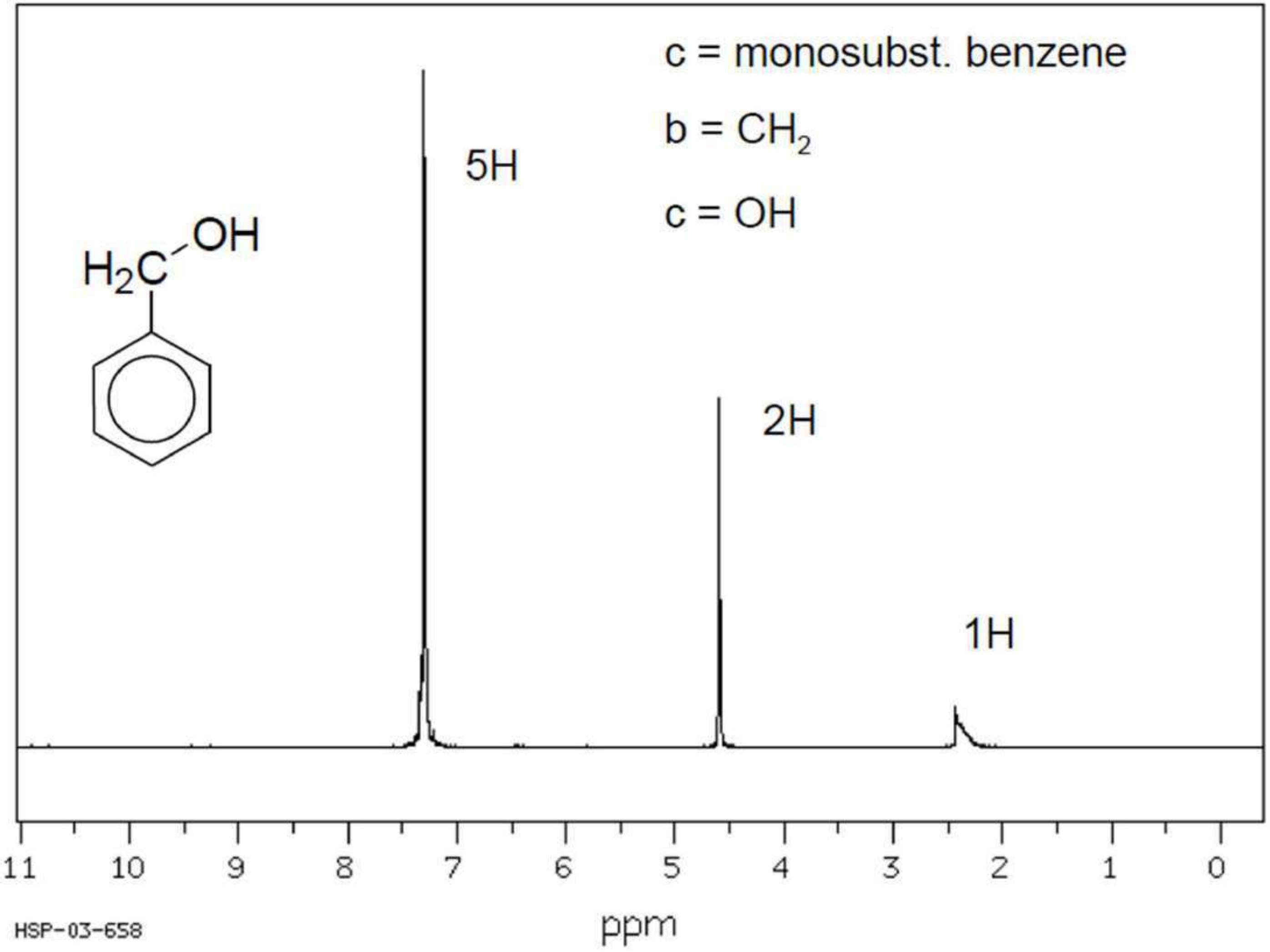
$(CH_3)_2C—$

b = CH_2, no neighbors & shifted downfield due to Br

$$\begin{array}{c} \quad CH_3 \\ \quad | \\ H_3C-C-CH_2 \\ \quad\;\; | \quad\;\; | \\ \quad\;\; Br \;\; Br \end{array}$$

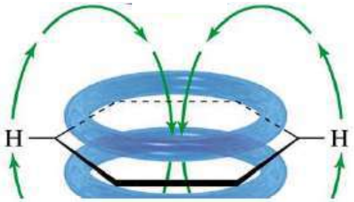


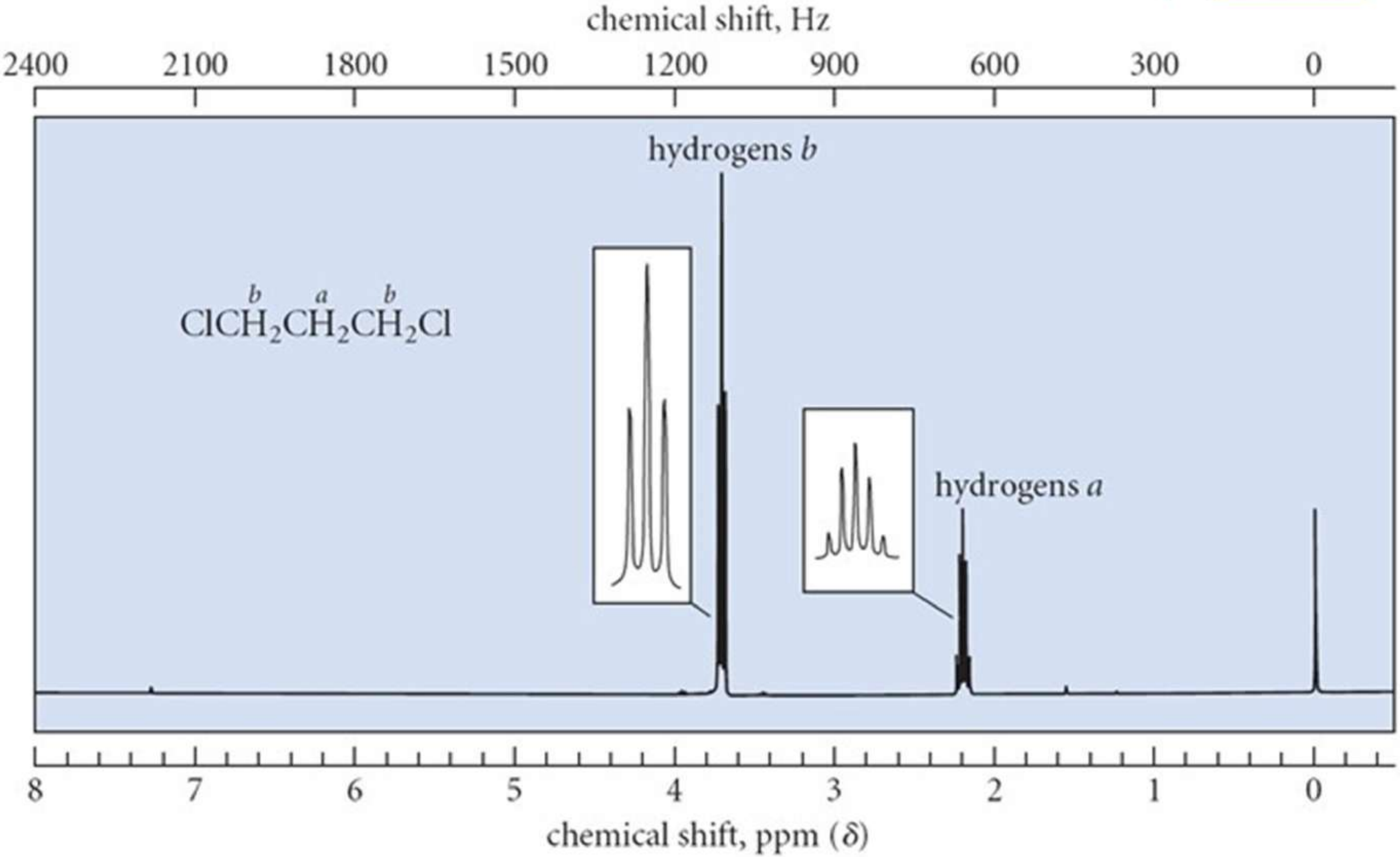
C_7H_8O

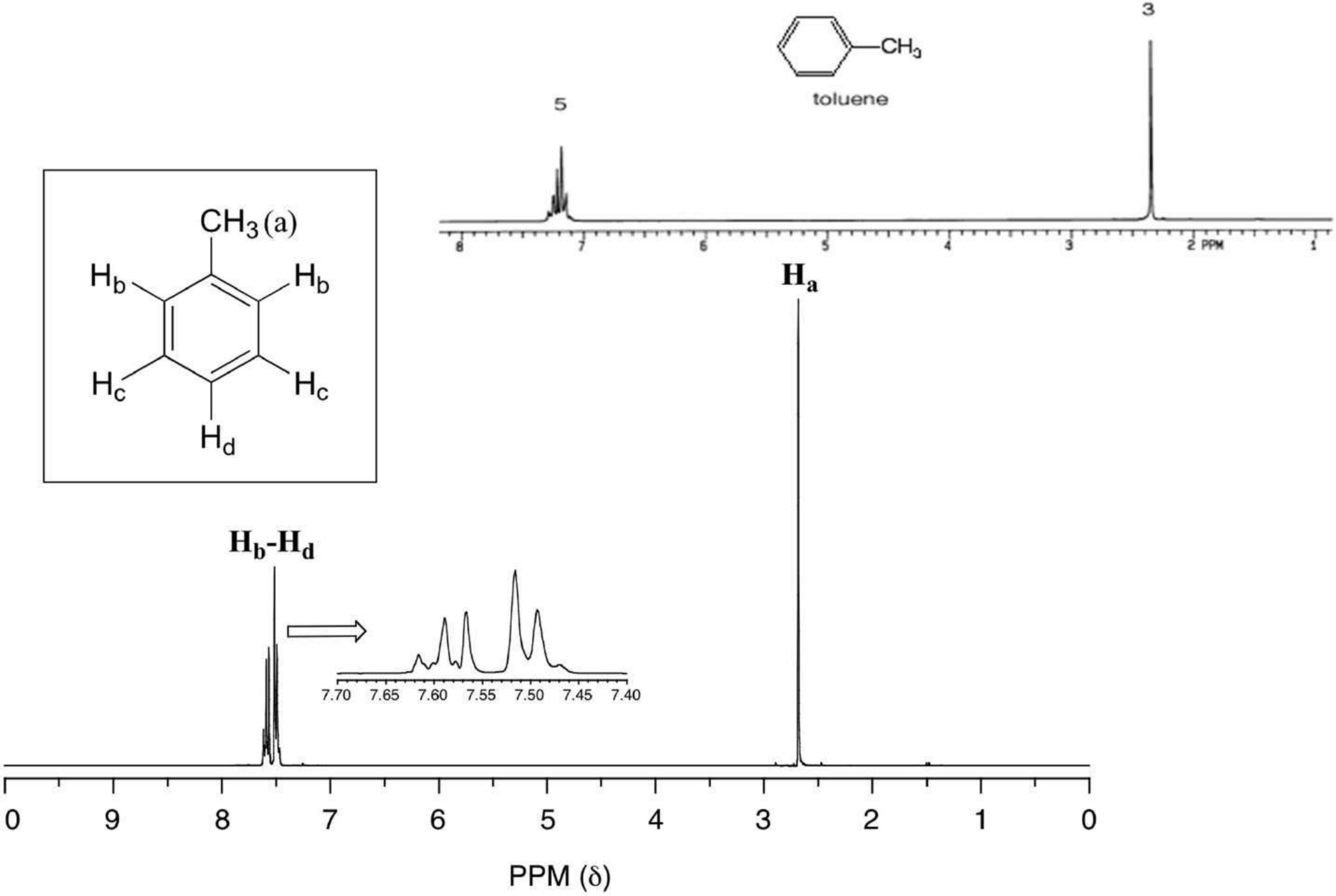

c = monosubst. benzene

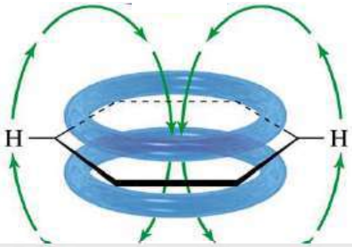
b = CH_2

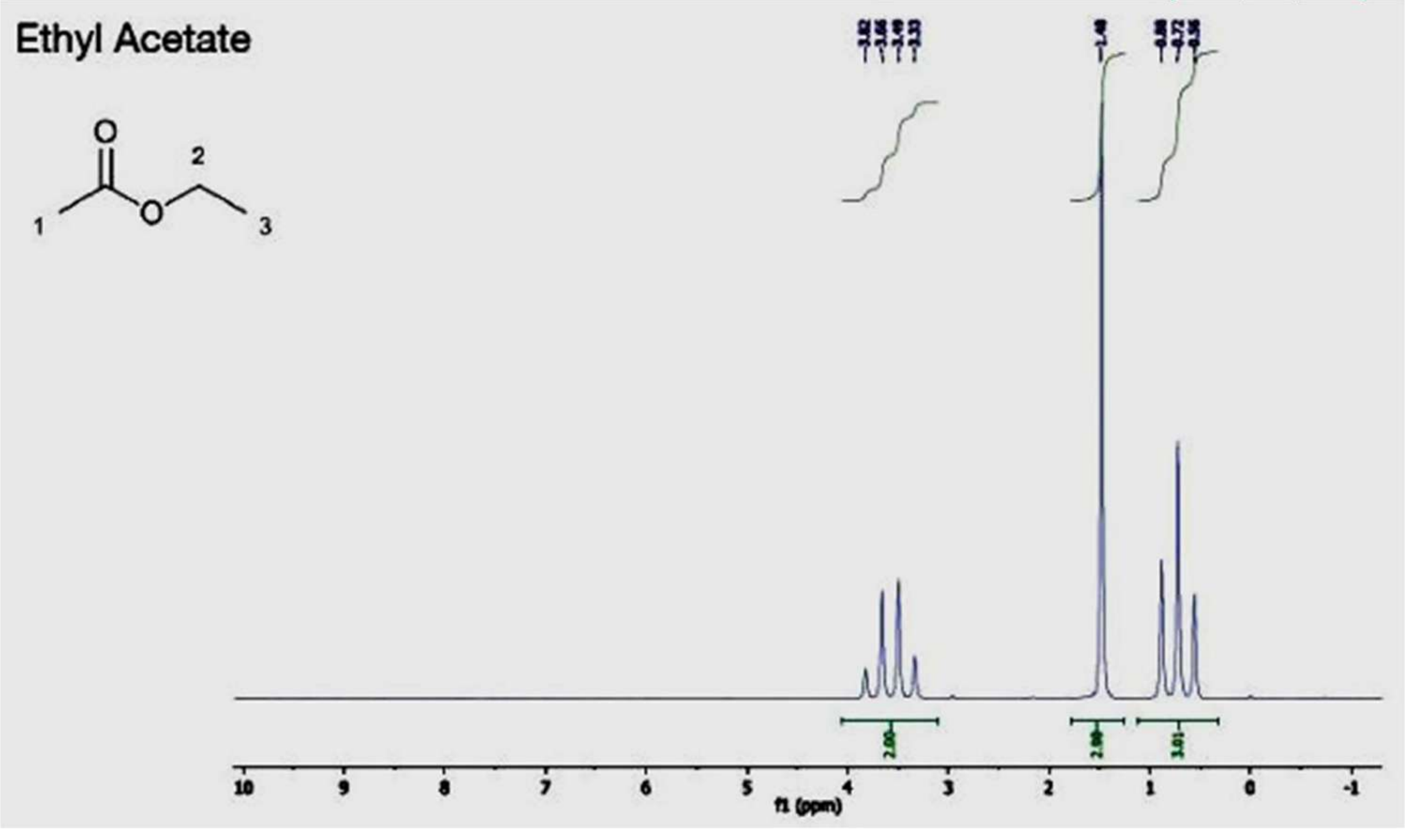
c = OH

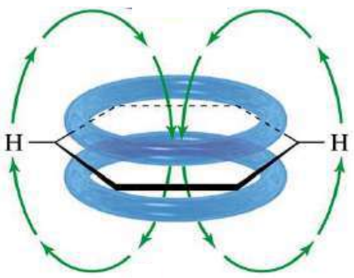

H
H

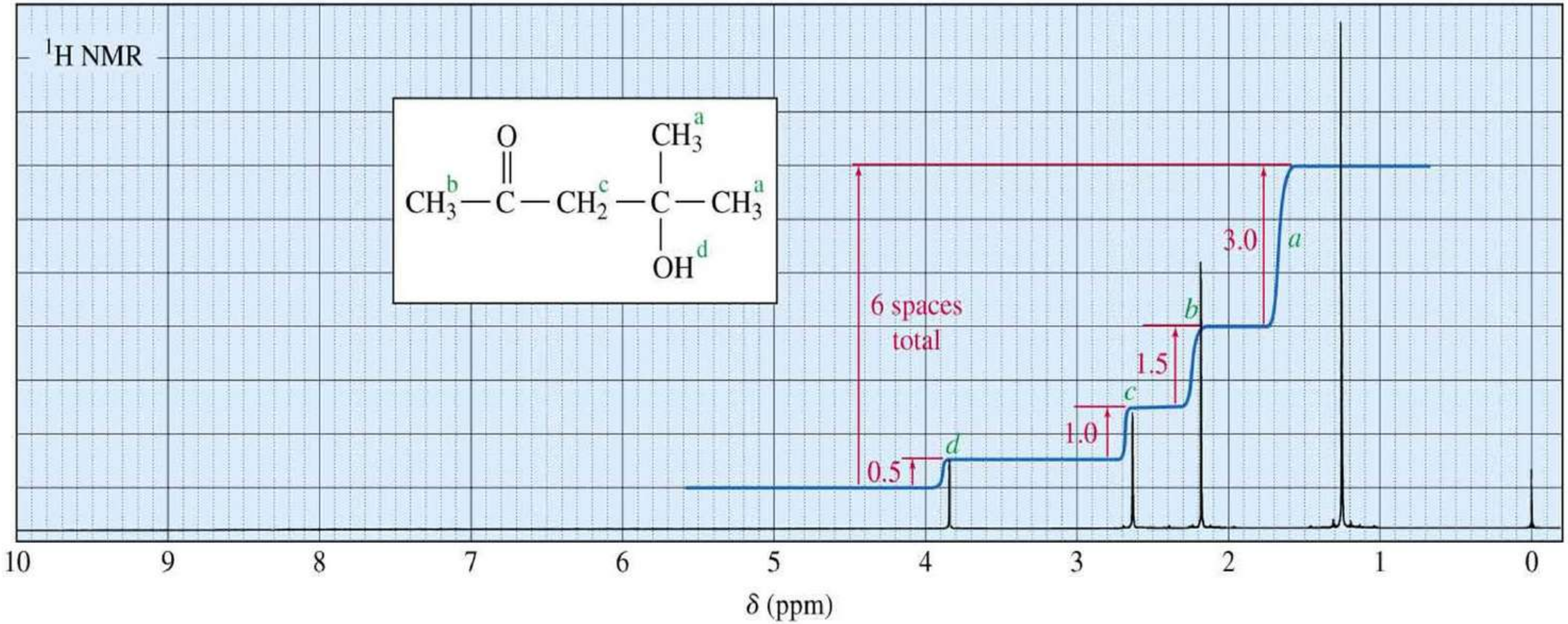

chemical shift, Hz
2400
2100
1800
1500
1200
900
600
300
0
hydrogens b
b a b
ClCH$_2$CH$_2$CH$_2$Cl
hydrogens a
8
7
6
5
4
3
2
1
0
chemical shift, ppm (δ)


3
5
toluene
CH3
8
7
6
5
4
3
2 PPM
1
CH3 (a)
Hb
Hb
Hc
Hc
Hd
Ha
Hb-Hd
7.70
7.65
7.60
7.55
7.50
7.45
7.40
10
9
8
7
6
5
4
3
2
1
0
PPM (δ)

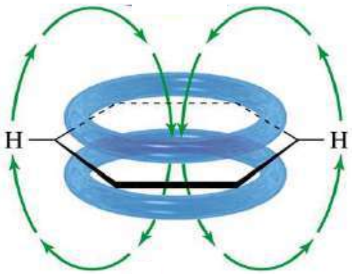

H
H


Ethyl Acetate
O
O
1
2
3
2.00
2.98
3.01
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


H
H


^{1}H NMR
O
CH_3^a
CH_3^b—C—CH_2^c—C—CH_3^a
OH^d
6 spaces
total
3.0
a
b
1.5
c
1.0
d
0.5
10
9
8
7
6
5
4
3
2
1
0
δ (ppm)

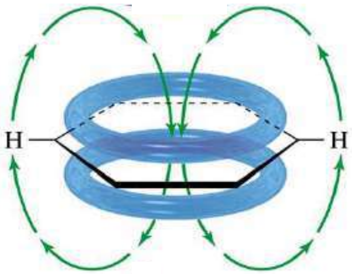
=>



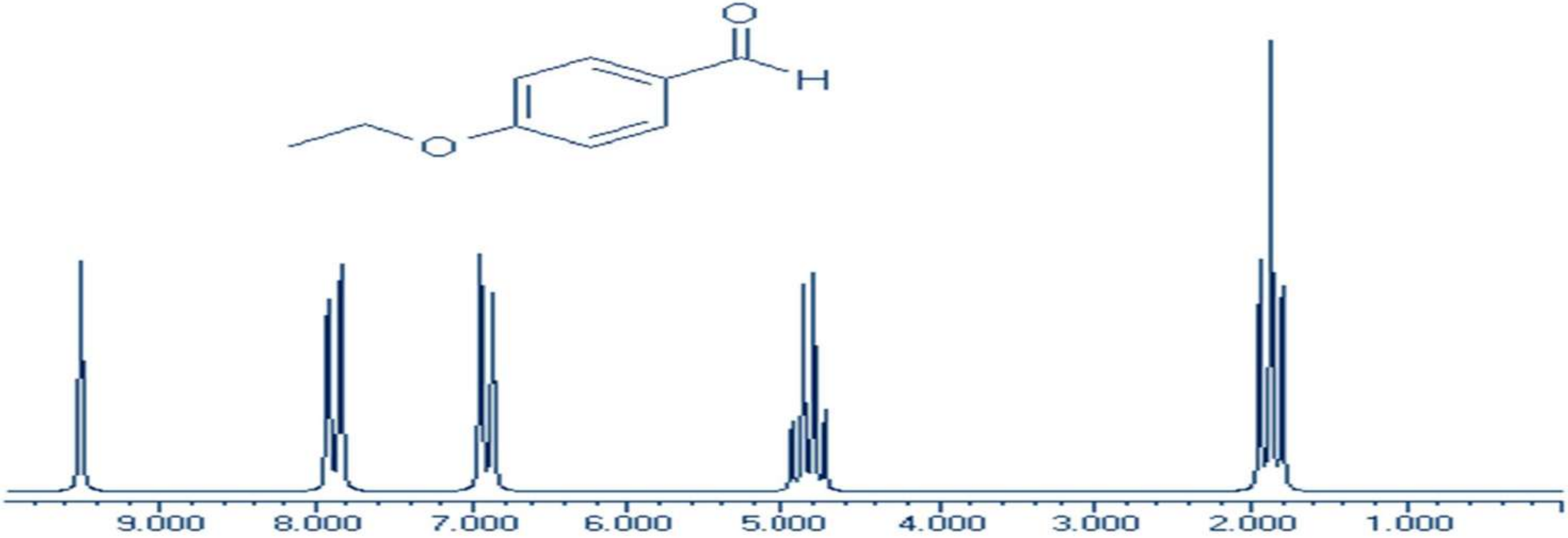
Video 4
Page(62-79)

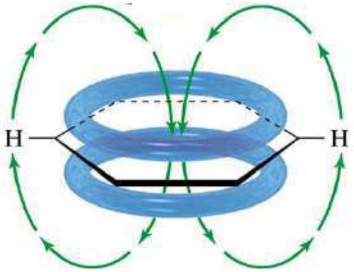
2] Chemical Shift

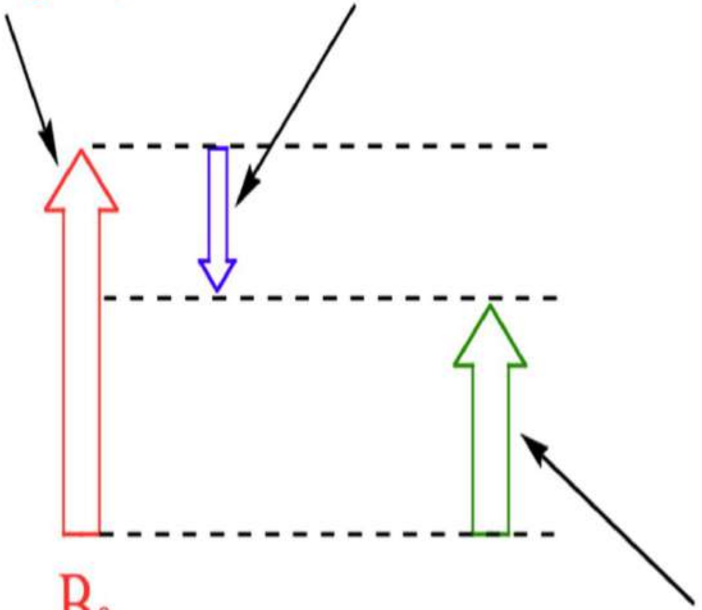
"Location of Signals"



The position of a signal in an NMR spectrum or It is the position on the chart at which a nucleus absorbs electromagnetic radiation.







shielding magnetic field from electrons
(induced field) local

applied field (from magnet)

B_0

effective field experienced by protons

$$B_{\text{effective}} = B_{\text{applied}} - B_{\text{local}}$$

- The absorption frequency is not the same for all ^{1}H or ^{13}C nuclei in a molecule.
- All nuclei in molecules are surrounded by electrons with their own magnetic fields B_{local}
- When an external field is applied to a molecule, the effective field ($B_{effective}$) felt by the nucleus is a bit smaller than the applied field ($B_{applied}$) :

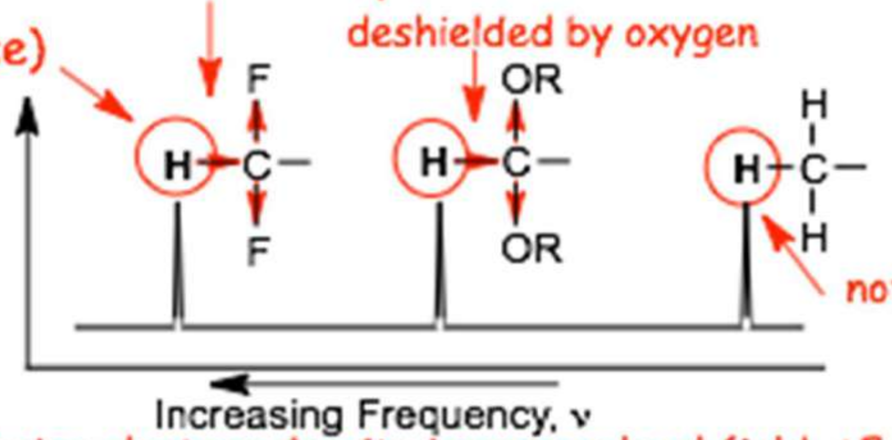
$$\boxed{B_{effective} = B_{applied} - B_{local}}$$

Shielding:-

Opposing magnetic field produced electrons surrounding nuclei to counteract the effects of an external magnetic field.

As a result effect of nucleus is less than the applied magnetic field .

larger ΔE
larger ν (resonance)

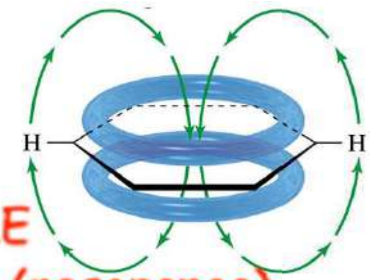


more deshielded by fluorine

deshielded by oxygen

not deshielded

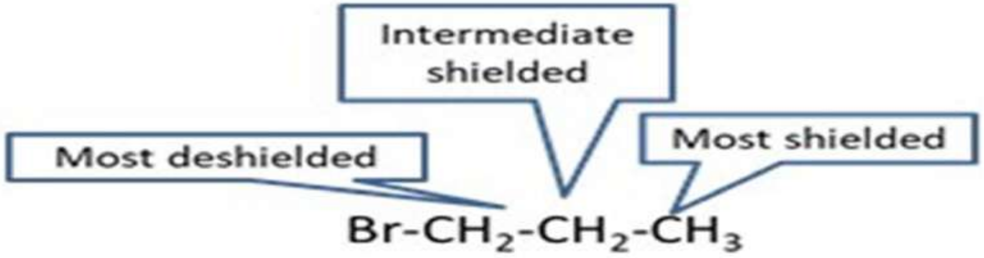
smaller ΔE
smaller ν (resonance)



Increasing Frequency, ν

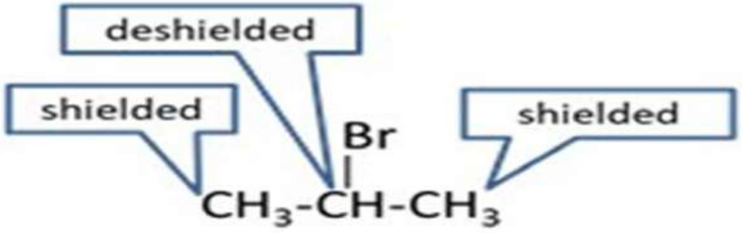
reducing electron density increases local field, ΔE and ν

← deshielding in this direction ←



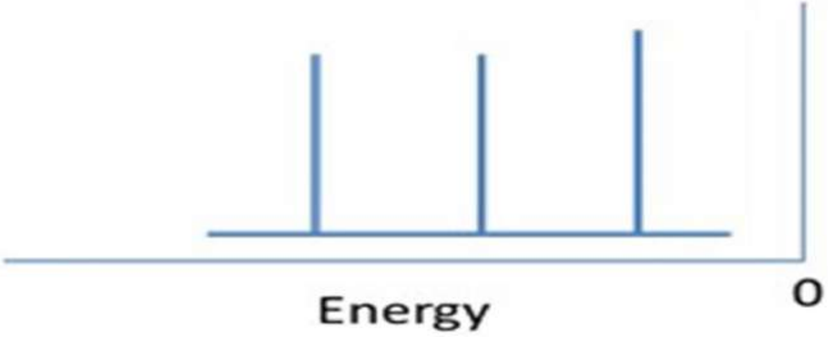
Br-CH$_2$-CH$_2$-CH$_3$

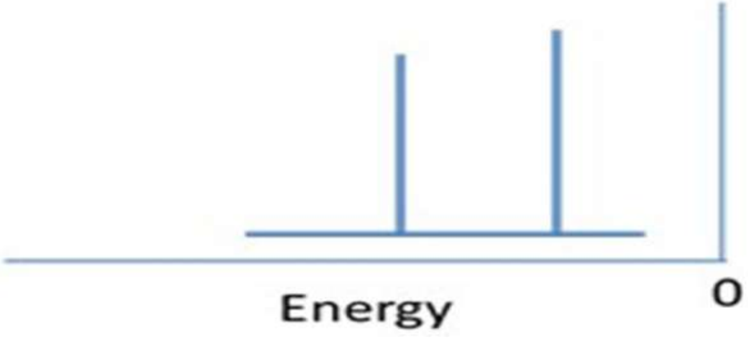
1-bromopropane



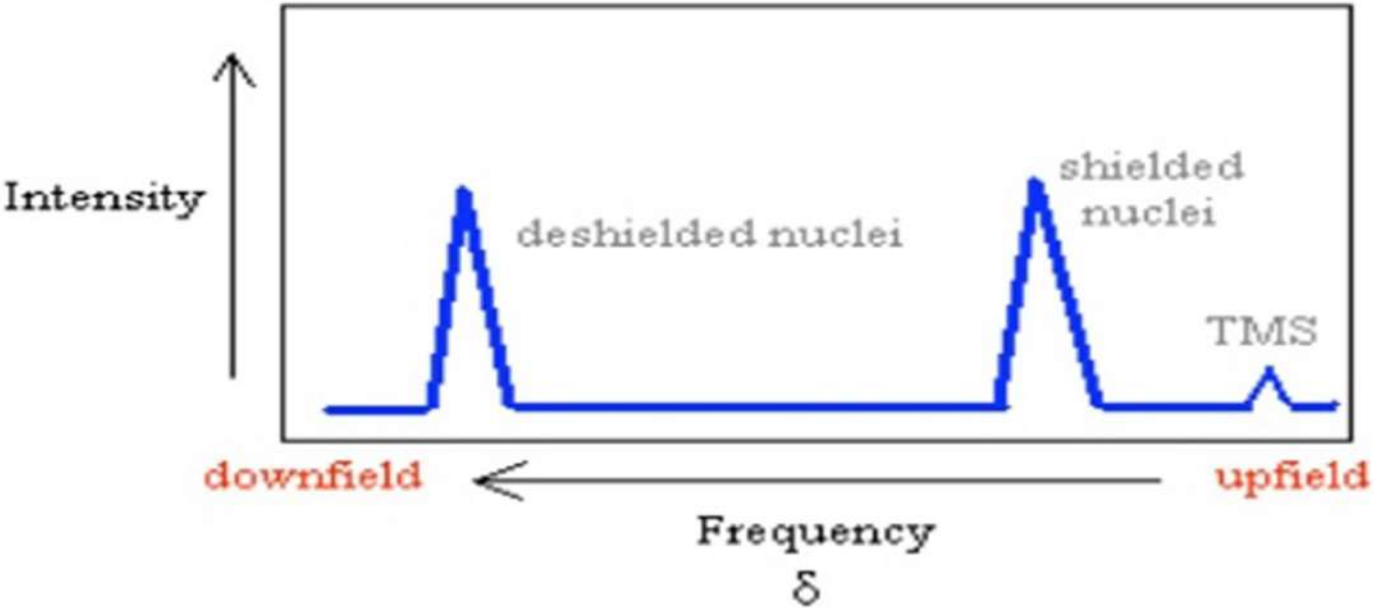
$$\mathrm{CH_3\text{-}\overset{\displaystyle Br}{CH}\text{-}CH_3}$$

2-bromopropane





NMR spectrum



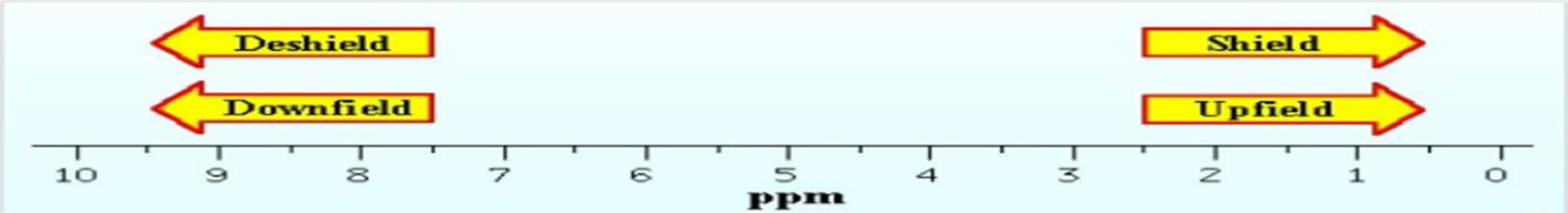
The NMR spectrum is a plot of intensity of NMR signals VS magnetic field (frequency) in reference to TMS

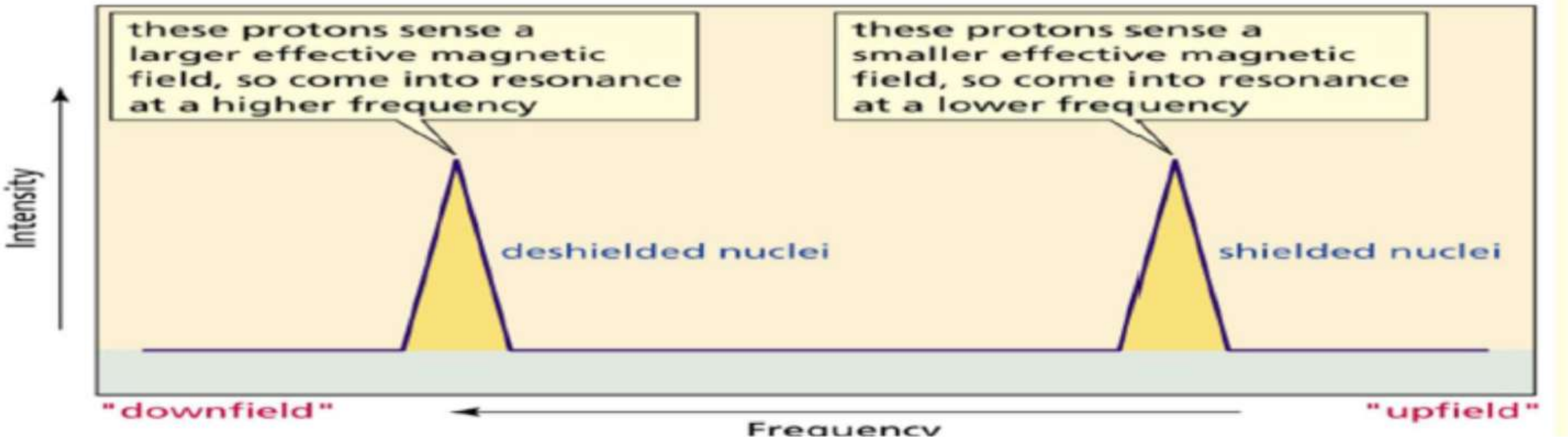
Shielding of protons:-

High electron density around a nucleus **shields** the nucleus from the external magnetic field and the signals are **upfield** in the NMR spectrum

Deshielding of protons:-

Lower electron density around a nucleus **deshields** the nucleus from the external magnetic field and the signals are **downfield** in the NMR spectrum





Typical Values of chemical shift

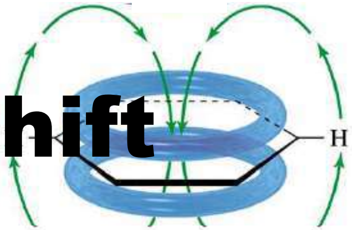
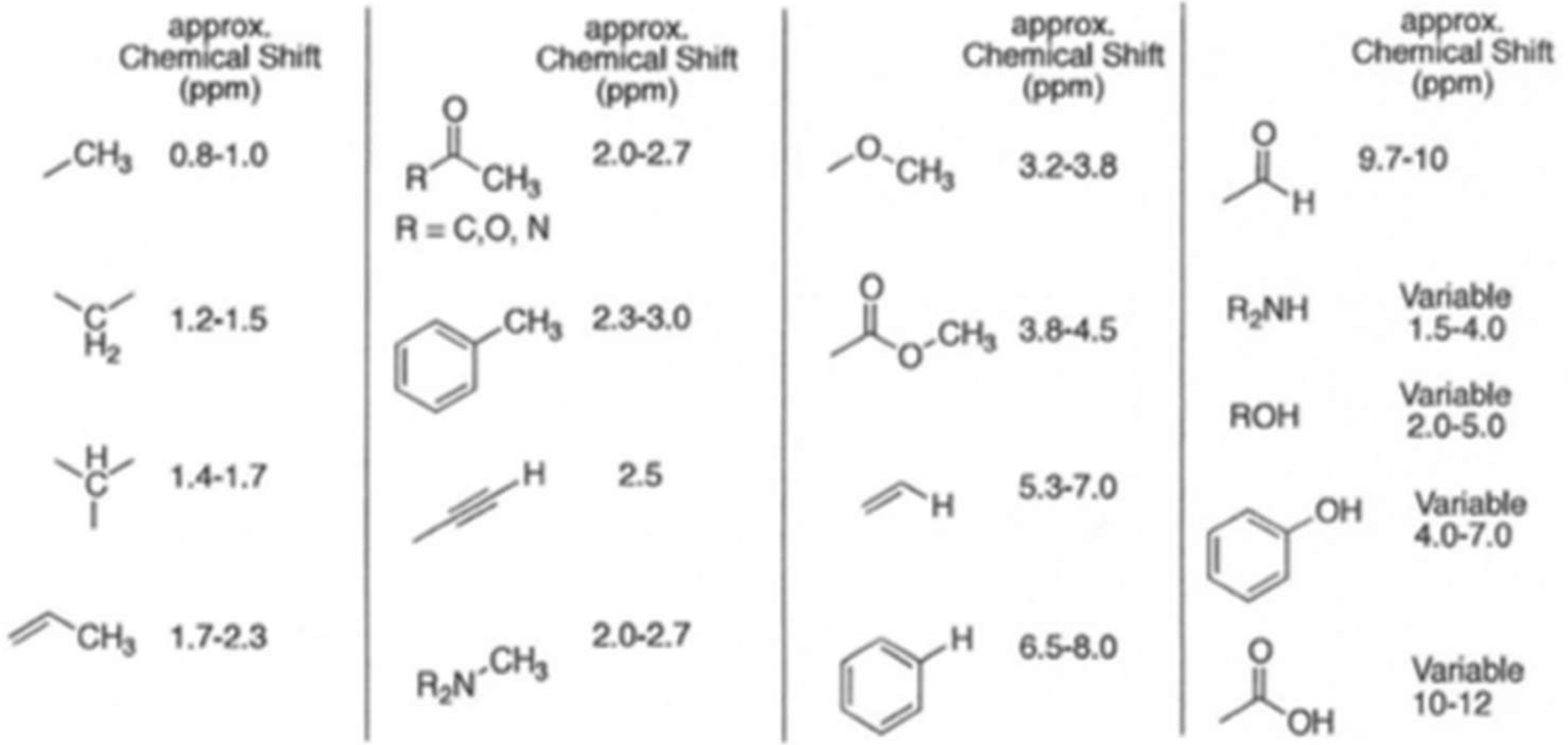


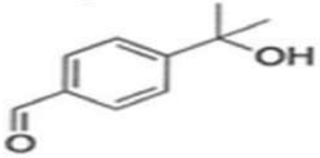
Table 1 Chemical Shifts of Common Protons

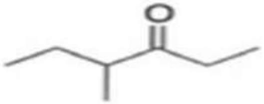


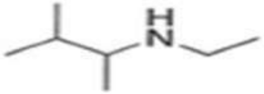
	approx. Chemical Shift (ppm)		approx. Chemical Shift (ppm)		approx. Chemical Shift (ppm)		approx. Chemical Shift (ppm)
CH$_3$	0.8-1.0	O R CH$_3$ R = C,O, N	2.0-2.7	O CH$_3$	3.2-3.8	O H	9.7-10
C H$_2$	1.2-1.5	CH$_3$	2.3-3.0	O O CH$_3$	3.8-4.5	R$_2$NH	Variable 1.5-4.0
H C	1.4-1.7	H	2.5	H	5.3-7.0	ROH	Variable 2.0-5.0
CH$_3$	1.7-2.3	R$_2$N CH$_3$	2.0-2.7	H	6.5-8.0	OH	Variable 4.0-7.0
						O OH	Variable 10-12

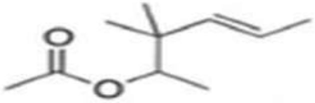
=>

– Using the table above predict the approximate chemical shifts for the hydrogens on the following molecules.

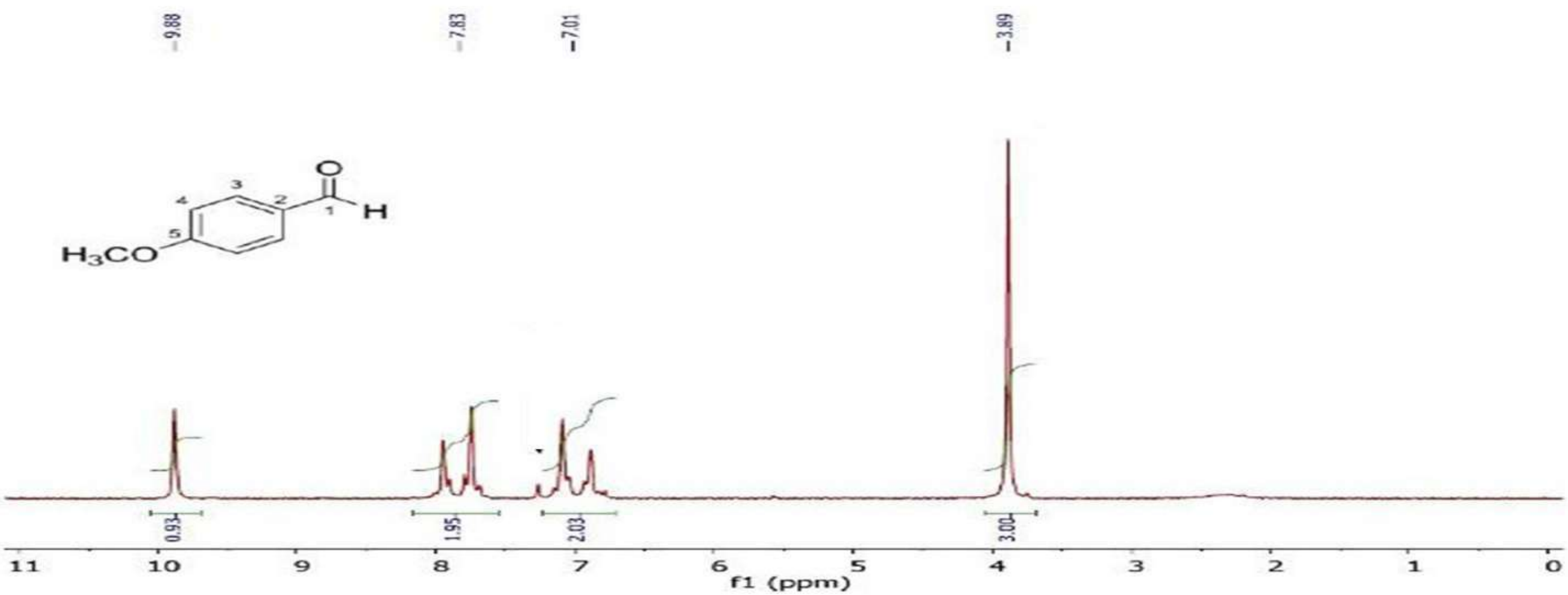




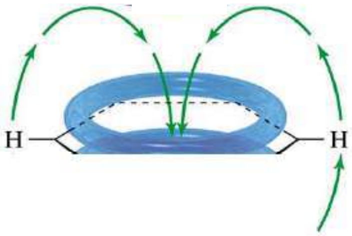


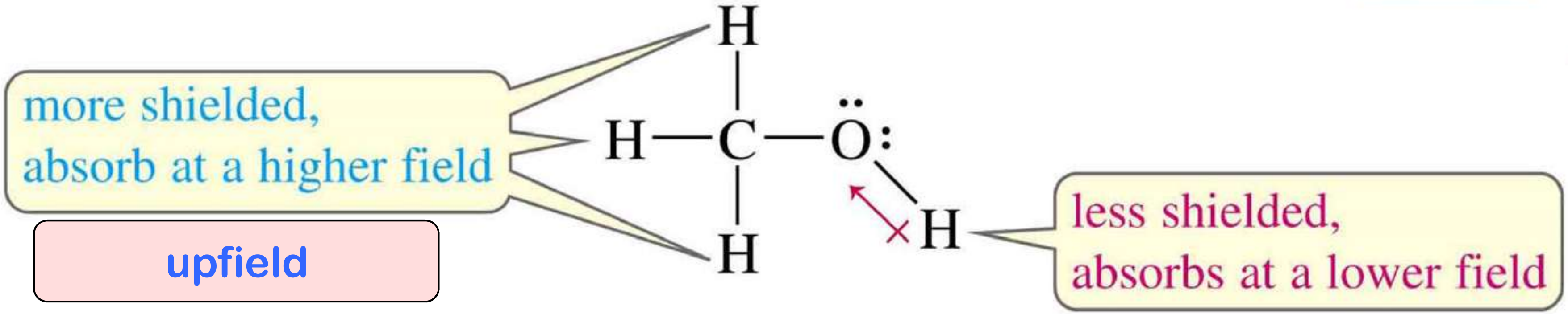


– Based on the following spectra, predict what type of protons are present in the molecule.



Protons in a molecule



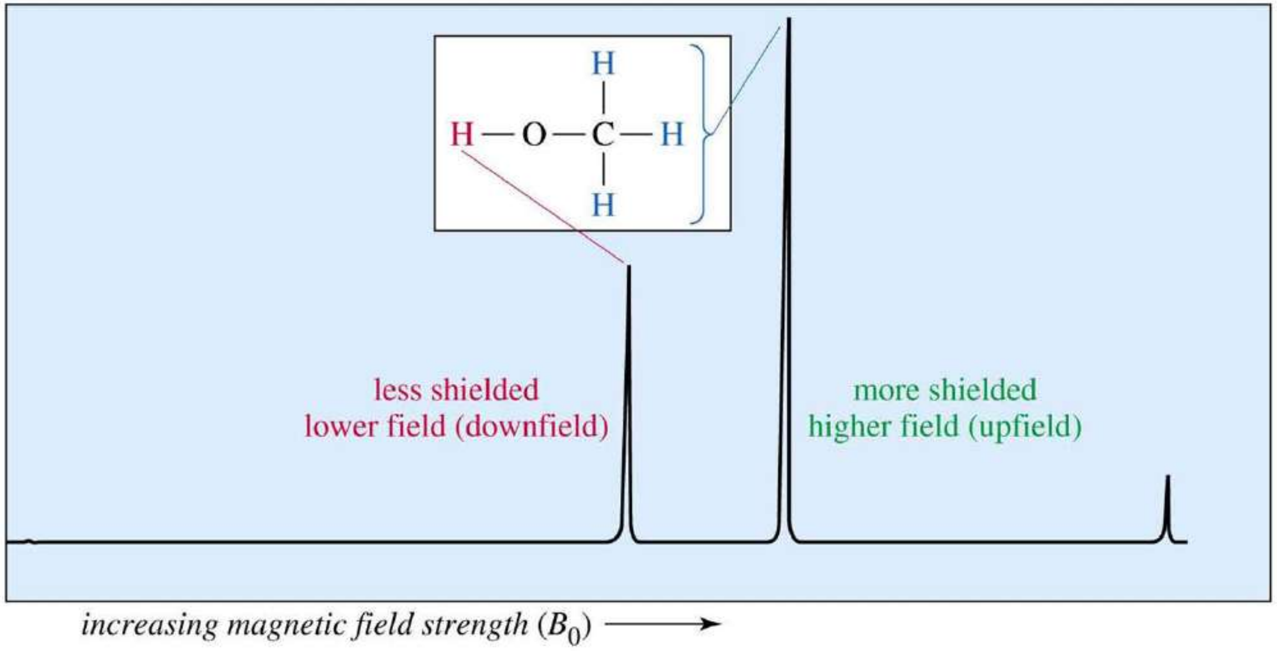


upfield

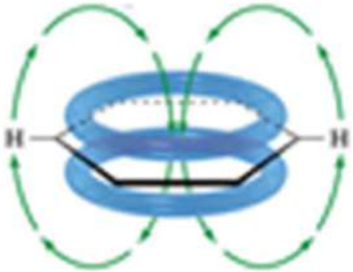
Lower frequency

downfield

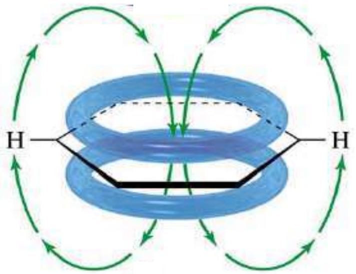
higher frequency



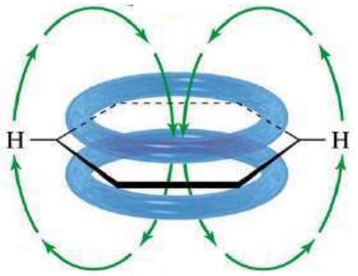
Magnetic Shielding



- All protons absorbed the same amount of energy in a given magnetic field, if and only if they have the same circumstances. (chemical environment).
- NMR would not be very valuable if all protons absorbed at the same frequency.
- Different protons usually absorb different radiofrequencies (ν).
- The electrons in a bond shield the nuclei from the magnetic field. A moving charge (electron) creates a magnetic field, and the field created by the moving electrons opposes the applied magnetic field B_0.
- **NOTE:- Circulating electrons create an induced magnetic field that opposes the external magnetic field.**

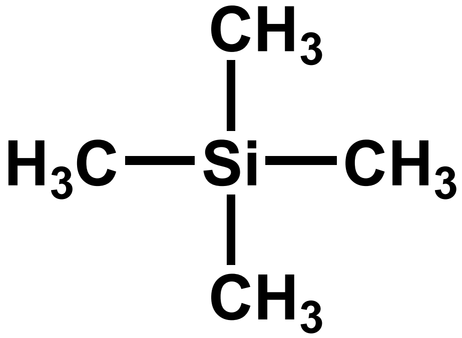


The **more electron density** around a proton, the **more** the shield, the **lower** magnetic field affecting the proton , The **less electron density , the less the shield , the higher** magnetic field.



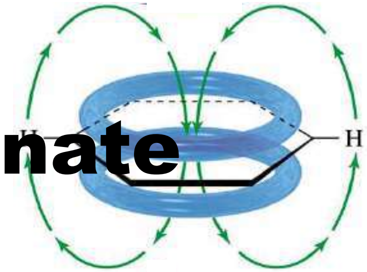
Chemical Shift Reference

a] Tetramethylsilane (TMS)

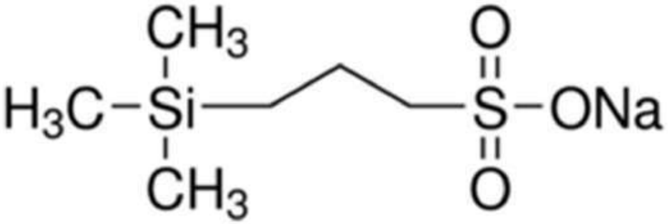


$Si(CH_3)_4$

1. TMS is added to the sample as internal standard.
2. TMS protons are all identical, highly shielded providing a single sharp peak always isolated from peaks of interest. The TMS was assigned d = 0.00 ppm
3. Organic protons absorb downfield (to the left) of the TMS signal.
4. TMS is inert , highly soluble in organic liquids and easily removed from samples by distillation.



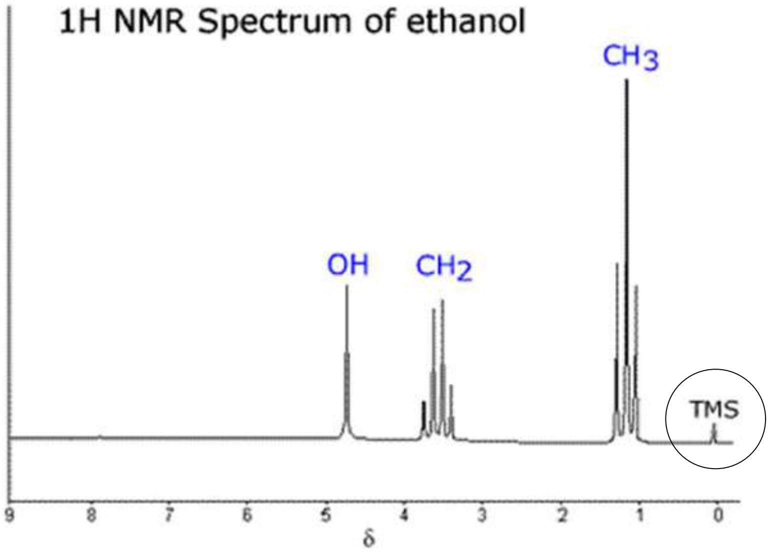
b] 3-(trimethyl silyl) propane sulphonate (sodium salts)

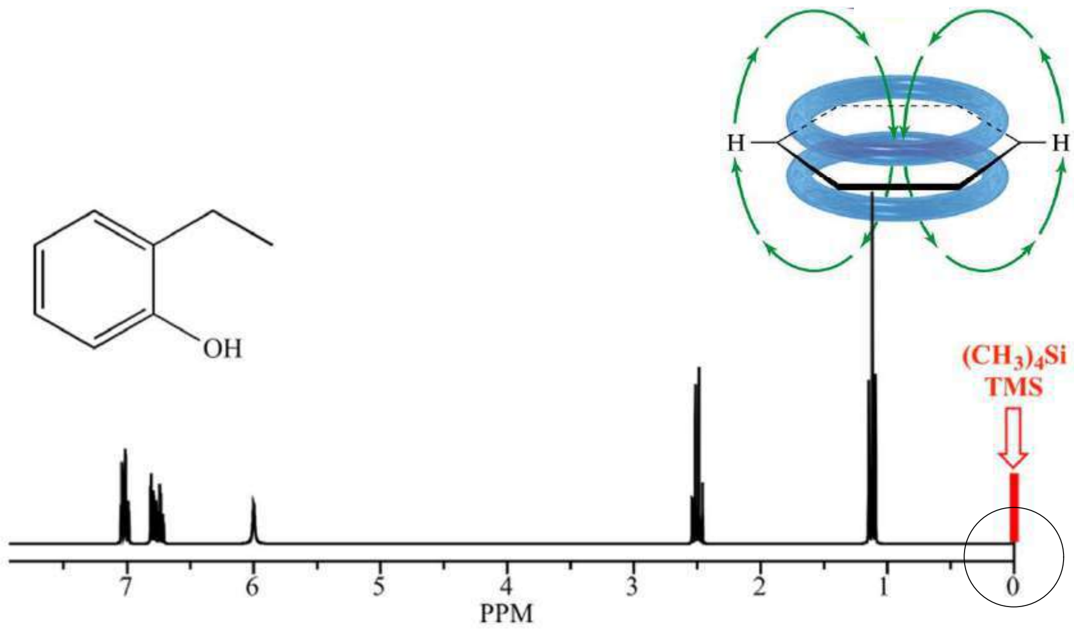


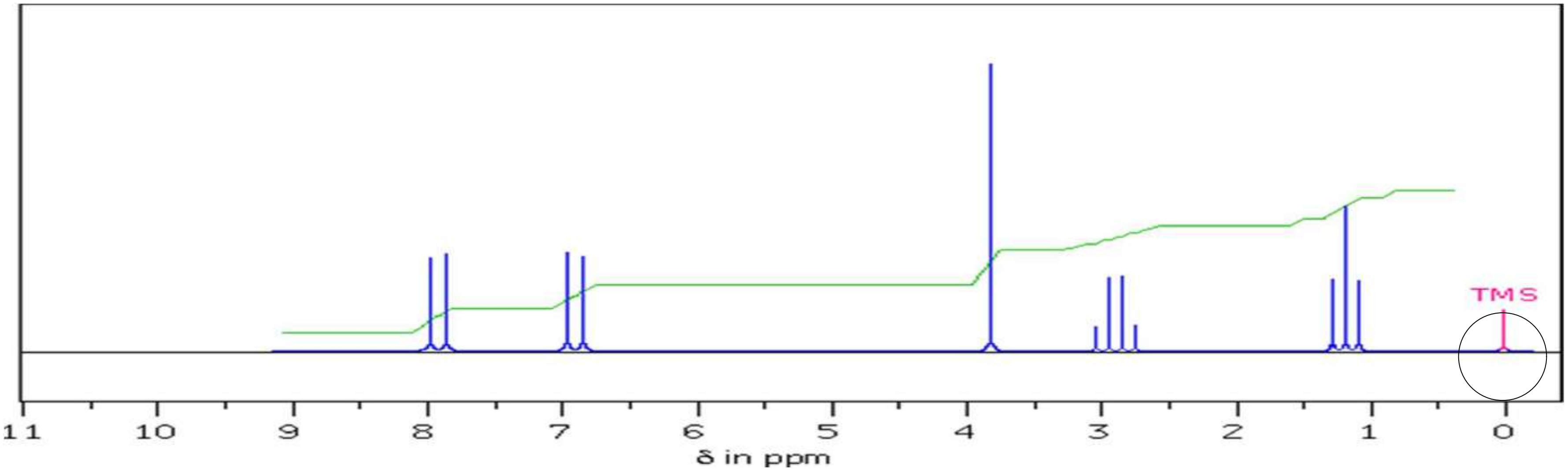
It is used as internal standard for scanning NMR spectra of water soluble substances in deuterium oxide solvent.

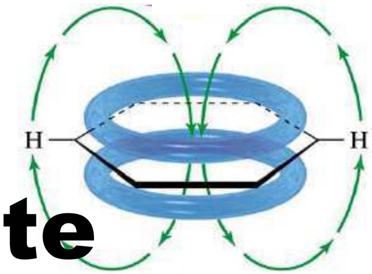
- **It has more water solubility than TMS and is commonly used for protein experiments in water.**

- **The low electro negativity of the silicon shields the nine identical methyl protons and show almost lower chemical shift than naturally occurring organic molecule.**


1H NMR Spectrum of ethanol
CH$_3$
OH
CH$_2$
TMS
9
8
7
6
5
4
3
2
1
0
δ


H
H
OH
(CH$_3$)$_4$Si
TMS
7
6
5
4
3
2
1
0
PPM


TMS
11
10
9
8
7
6
5
4
3
2
1
0
δ in ppm

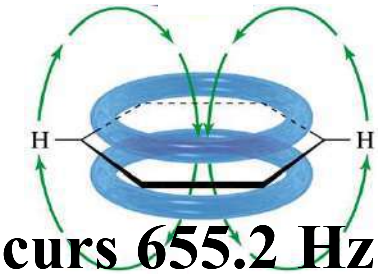


How to measure and calculate chemical shift

$$\delta(ppm) = \frac{\upsilon\ (Hz)}{spectrometer\ frequency\ (MHz)}$$

$$\text{Chemical Shift} = \frac{\text{Position of signal(Hz)-Position of TMS peak (Hz)}}{\text{Spectrometer Frequency (MHz)}}$$

Calculation of chemical shift



Q1] What would be the chemical shift of a peak that occurs 655.2 Hz downfield of TMS on a spectrum recorded using a 90 MHz spectrometer?

655.2 Hz / 90 MHz = 7.28 ppm (the chemical shift of chloroform).

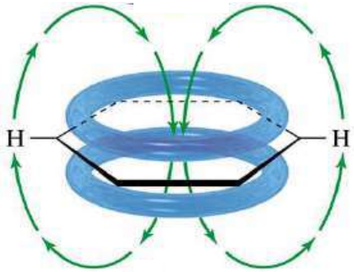
Q2] At what Frequency would the chemical shift of chloroform ($CHCl_3$, δ = 7.28 ppm) occur relative to TMS on a spectrum recorded on a 300 MHz spectrometer?

7.28 ppm x 300 MHz = 2184 Hz

Q3] A 1 GHz (1000 MHz) NMR spectrometer is being developed, at what Frequency and chemical shift would chloroform?

Chemical shift = 7.28 ppm Frequency = 7280 Hz

Factors affecting on chemical shift



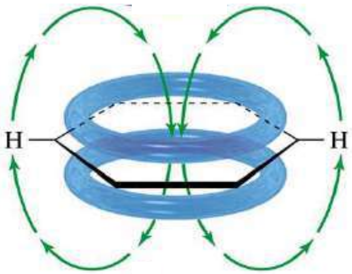
Four major factors account for the resonance positions (on the ppm scale) of most protons

1] Inductive effect by electronegative groups “Deshielding by electronegative elements”

2] Magnetic Anisotropic effect (magnetic fields usually due to π-bonded electrons in the molecule)

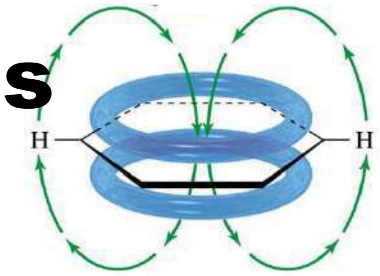
3] Hydrogen bonding.

4] Van der Waals forces ??



Video 5
Page (80-107)

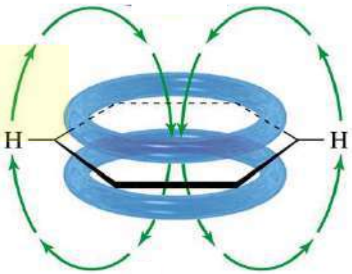
Factors affecting chemical shifts



1- Electronegativity and inductive effect.

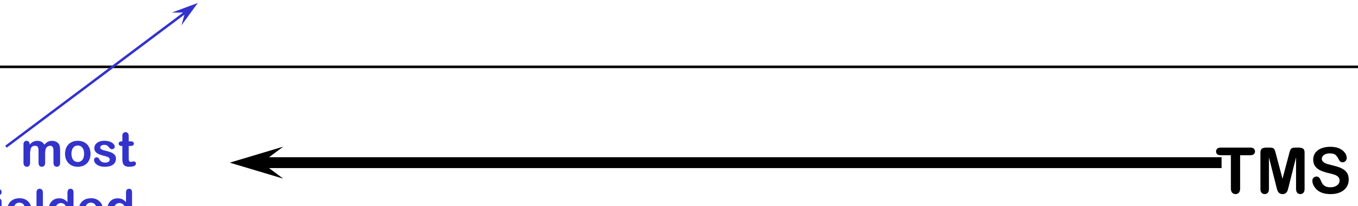
In proton NMR spectroscopy; the chemical shift of a particular C-H system depends on the electronic environment around the proton. Electrons in the neighboring atoms could reduce the field experienced by the proton, shielding it from the external magnetic field and moving the signal to lower ppm (or upfield). On the contrary, electronegative groups close to the C-H system reduce the surrounding electron density, deshielding the proton from the external magnetic field and moving the signal to higher ppm (downfield).

ELECTRONEGATIVITY DEPENDENCE OF CHEMICAL SHIFT



Dependence of the Chemical Shift of CH_3X on the Element X

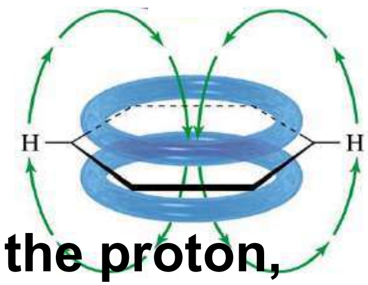
Compound CH_3X	CH_3F	CH_3OH	CH_3Cl	CH_3Br	CH_3I	CH_4	$(CH_3)_4Si$
Element X	F	O	Cl	Br	I	H	Si
Electronegativity of X	4.0	3.5	3.1	2.8	2.5	2.1	1.8
Chemical shift δ	4.26	3.40	3.05	2.68	2.16	0.23	0

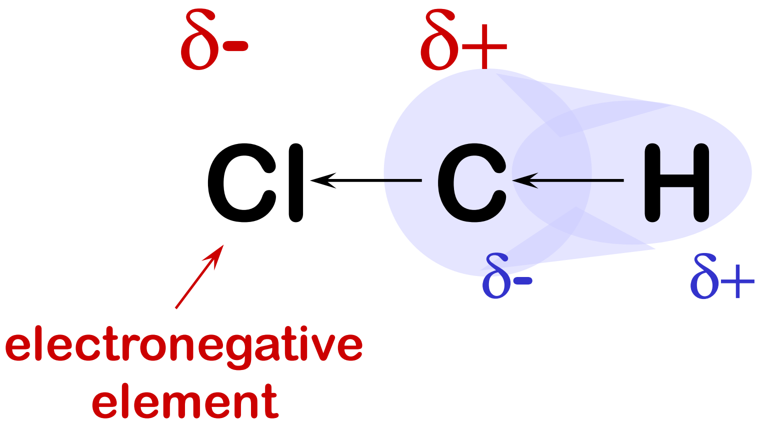


most deshielded

TMS

deshielding increases with the electronegativity of atom X





Chlorine "deshields" the proton, that is, it takes valence electron density away from carbon, which in turn takes more density from hydrogen <u>deshielding</u> the proton.

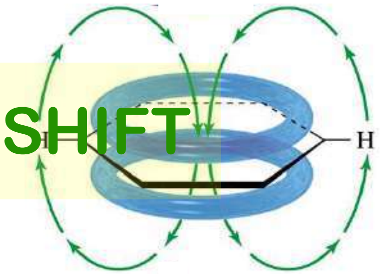
NMR CHART

"deshielded" protons appear at downfield (higher δ)

"highly shielded" protons appear at upfield (lower δ)

deshielding moves proton resonance to lower field and higher δ

SUBSTITUTION EFFECTS ON CHEMICAL SHIFT



Cumulative Effect

most deshielded

$CHCl_3$	CH_2Cl_2	CH_3Cl	
7.27	5.30	3.05	ppm

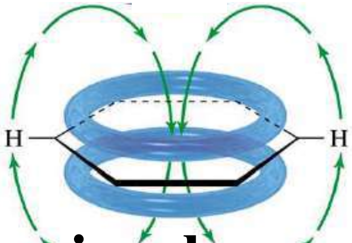
The effect increases with greater numbers of electronegative atoms.

most deshielded

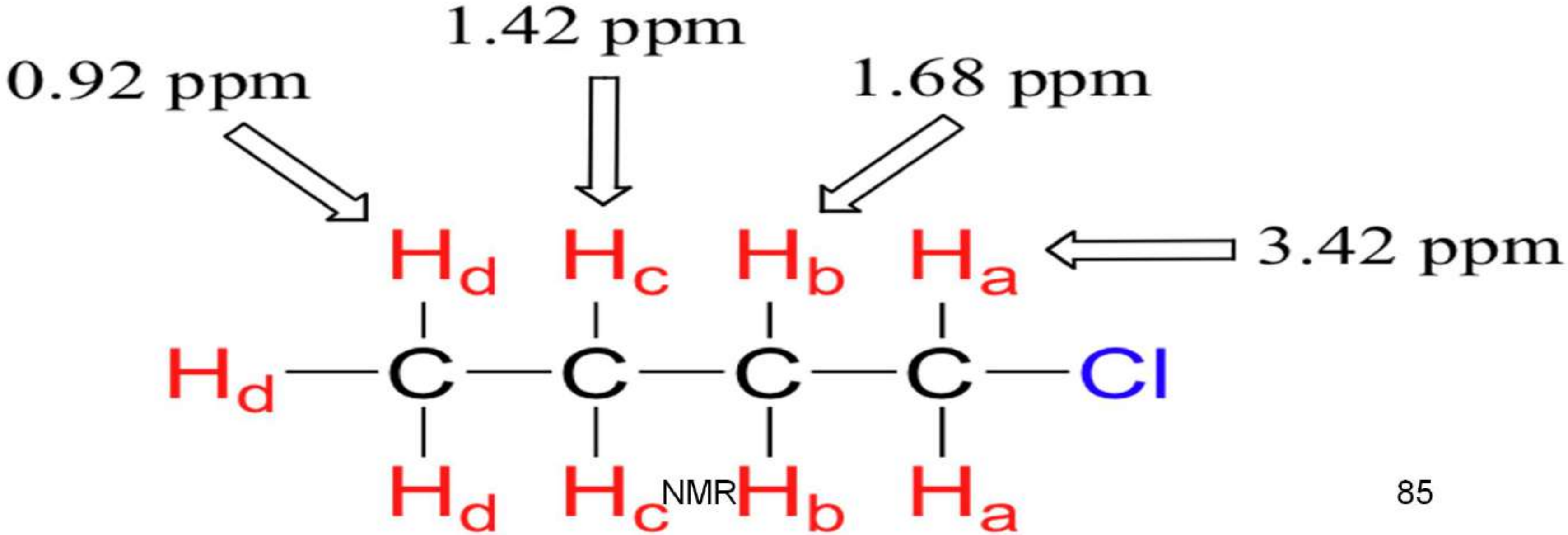
$-CH_2-Br$	$-CH_2-CH_2-Br$	$\xcancel{-}CH_2-CH_2-CH_2-Br$	
3.30	1.69	1.25	ppm

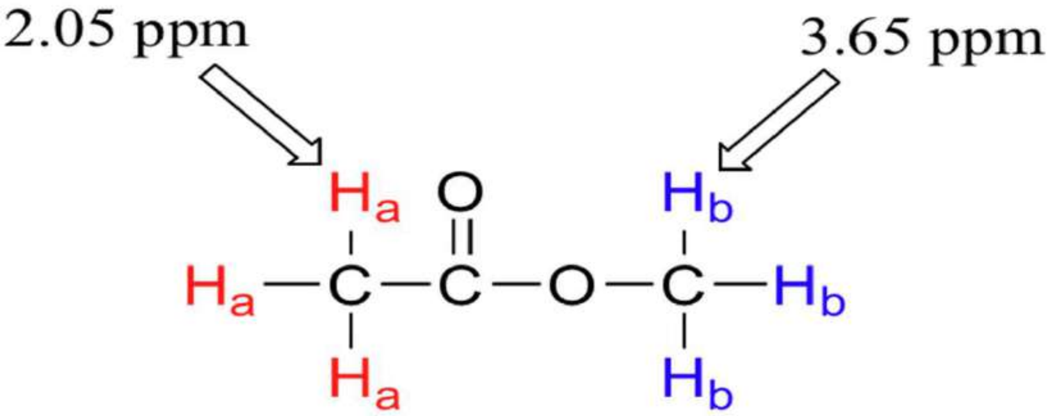
The effect decreases with increasing distance from the electronegative atom. The effect completely vanished at the fourth bond from the electronegative atom.

Location of Signals



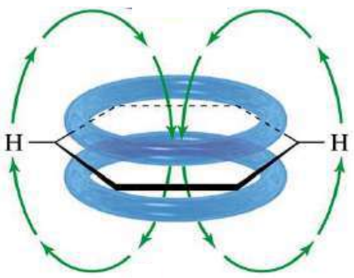
- More electronegative atoms deshield more and give larger shift values.
- Effect decreases with distance.
- Additional electronegative atoms cause increase in chemical shift.

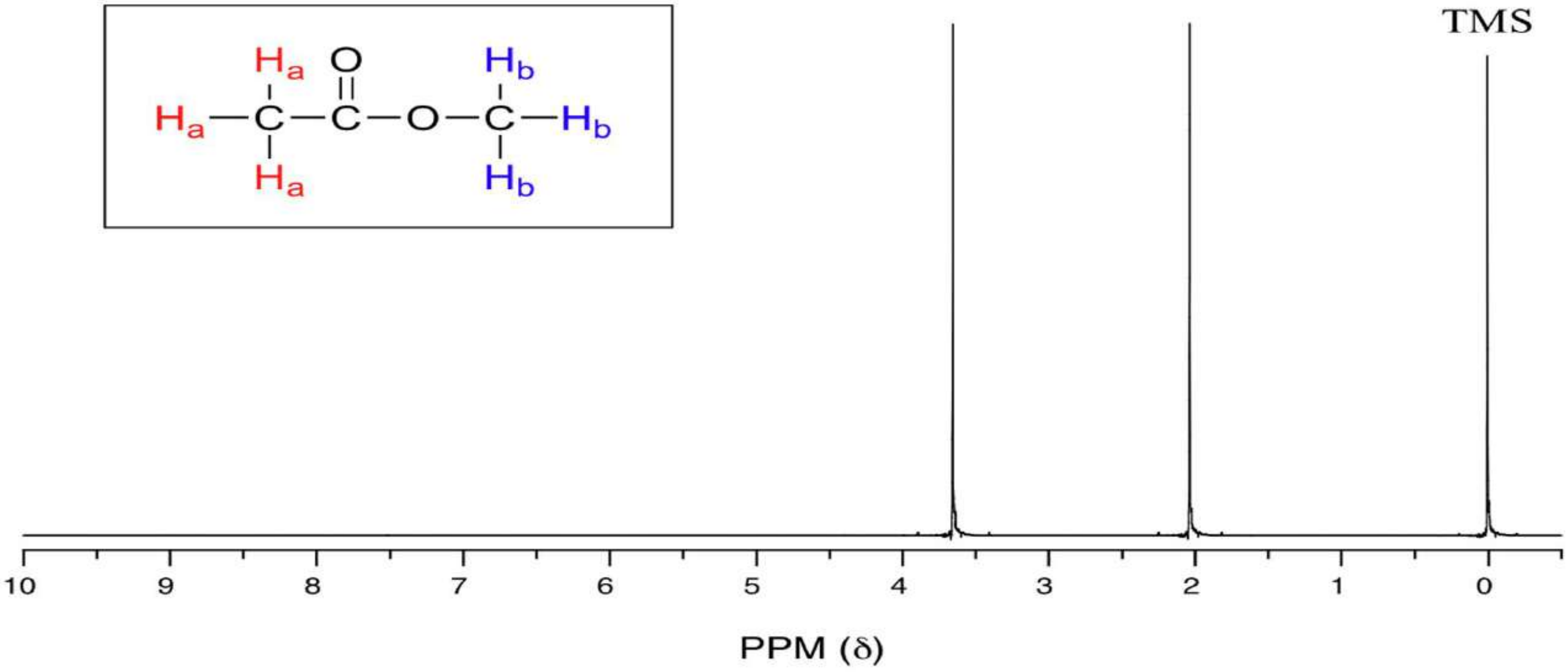



2.05 ppm

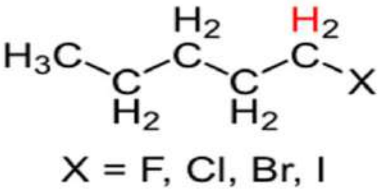
3.65 ppm

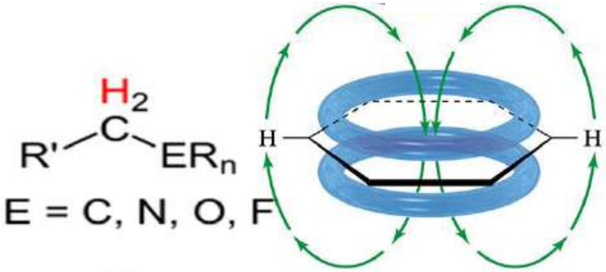
$CH_3-C(=O)-O-CH_3$

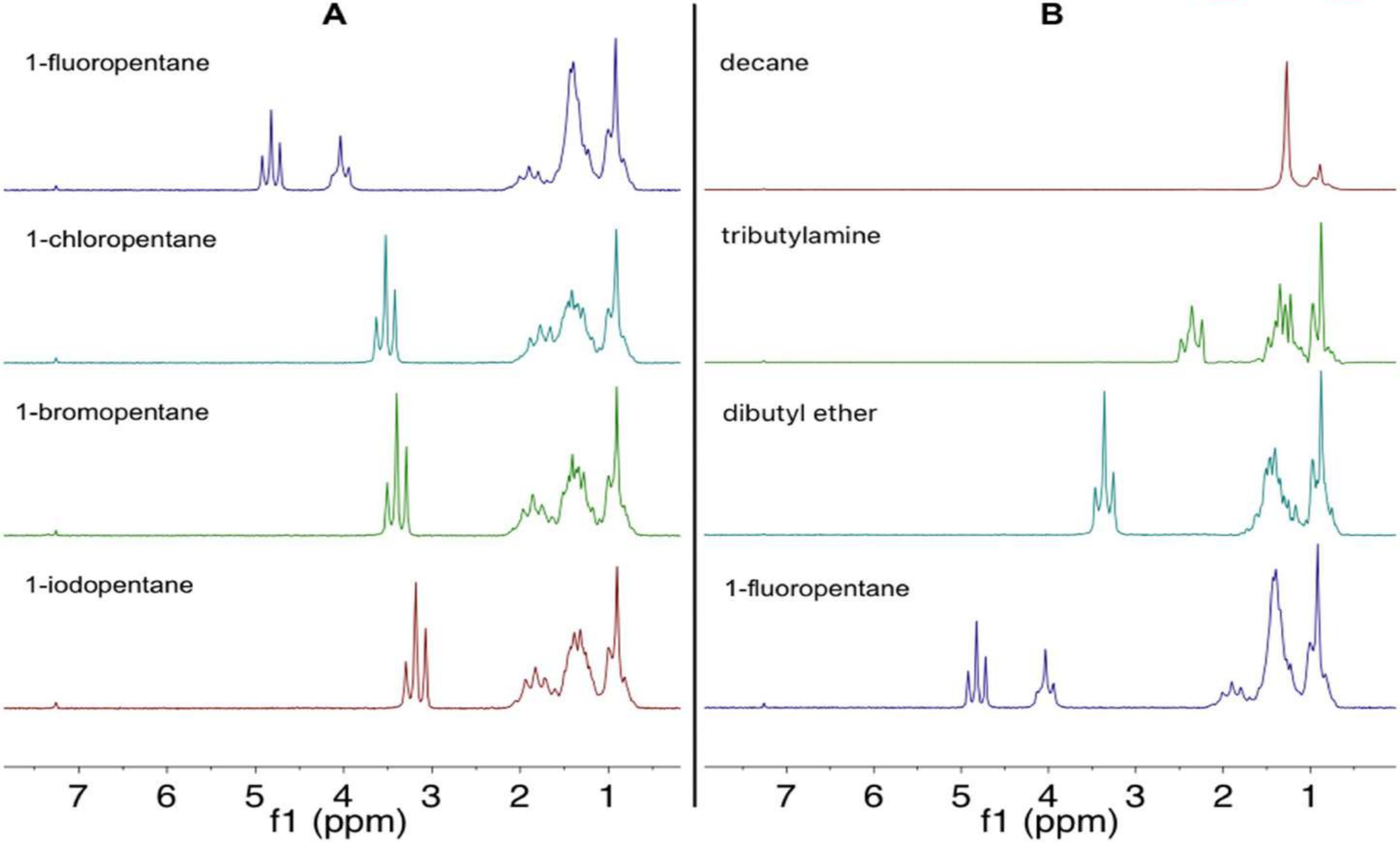




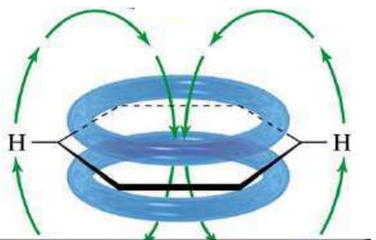
The more EN atoms leads to more deshielding and thus greater ppm

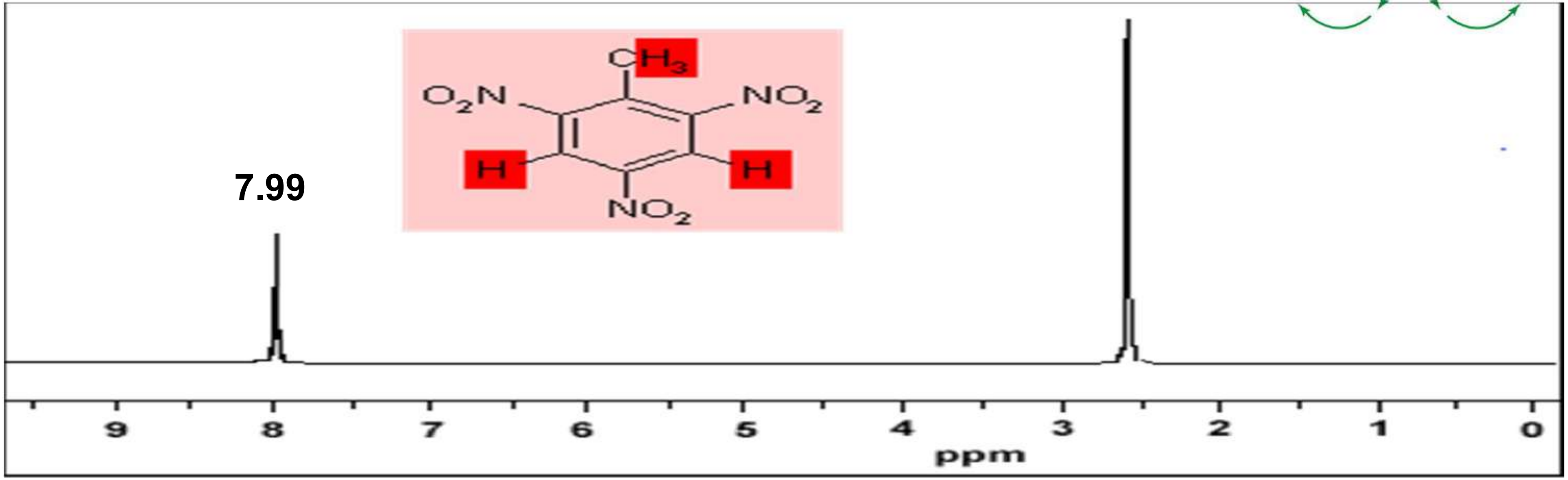


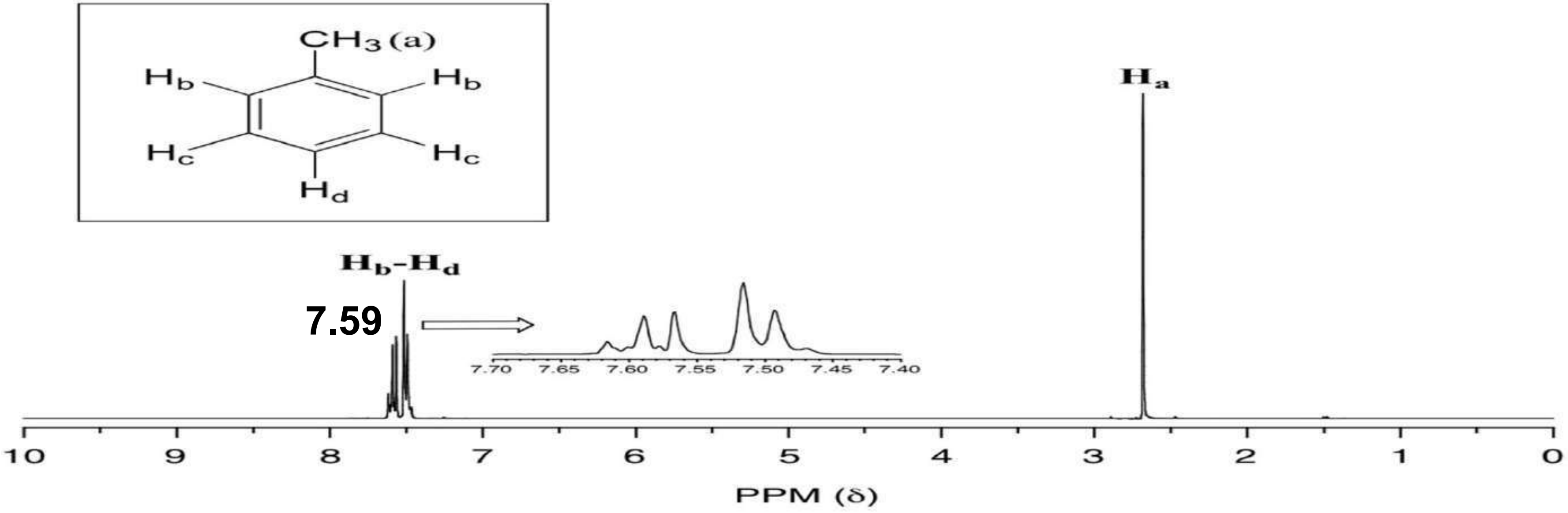




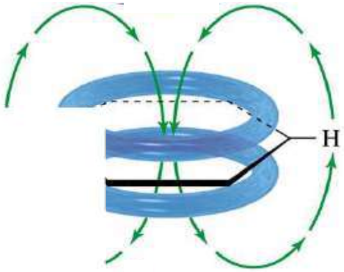
The presence of Nitro group leads to make the protons more deshielded and then greater ppm



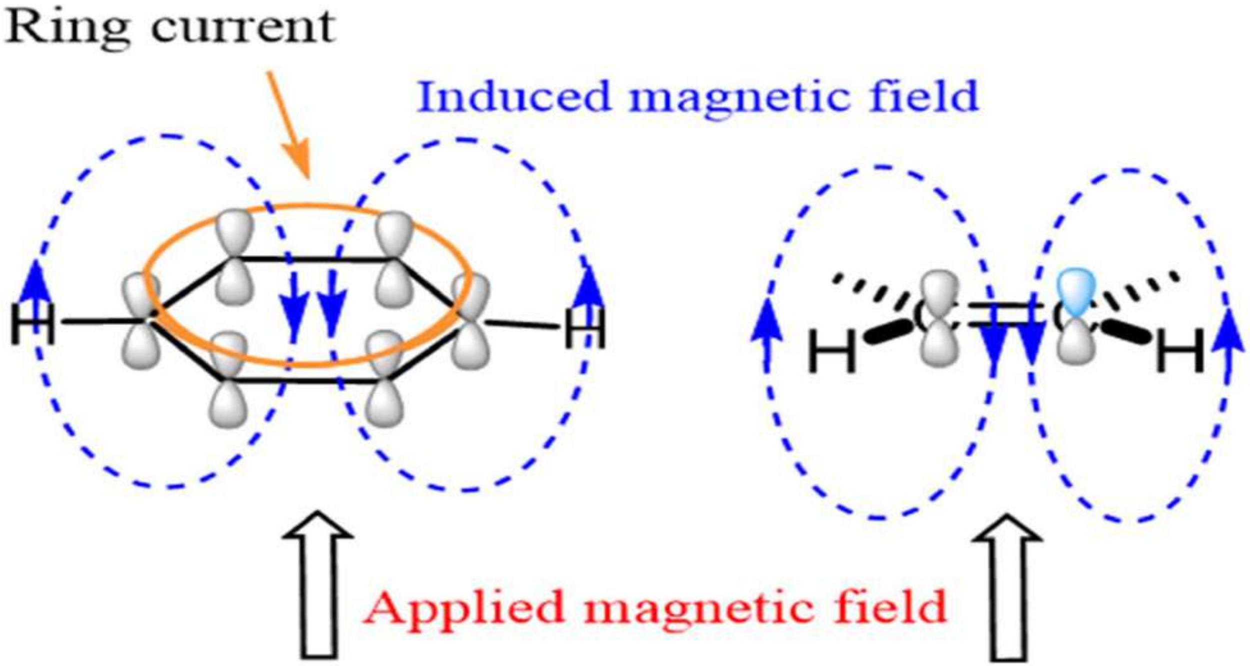




2- Anisotropic effect

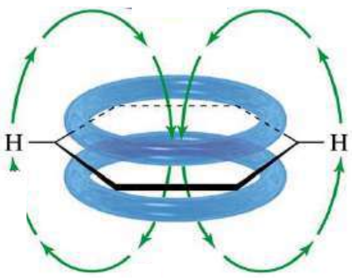


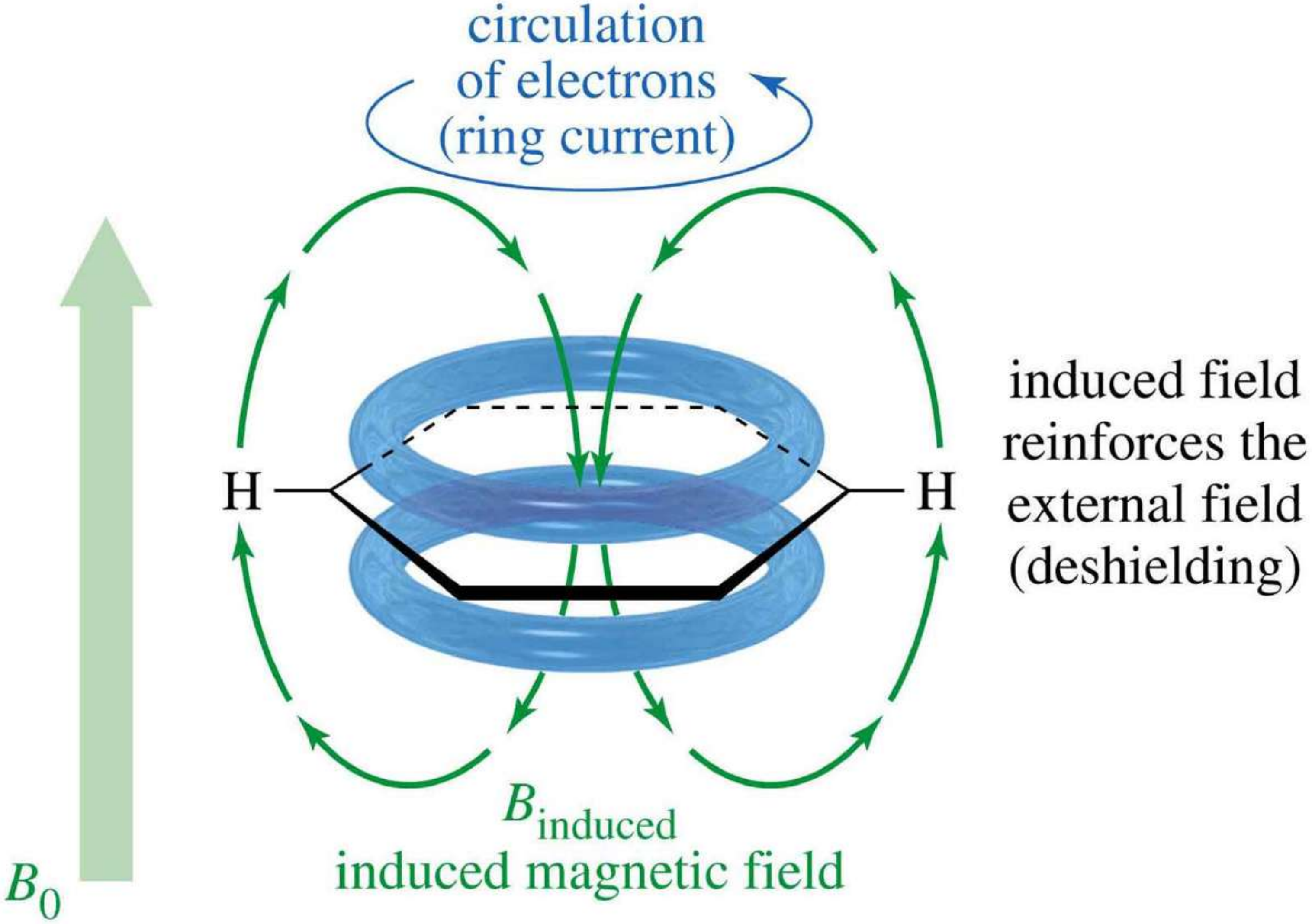
Magnetic Anisotropy Effect in sp^2 Carbons



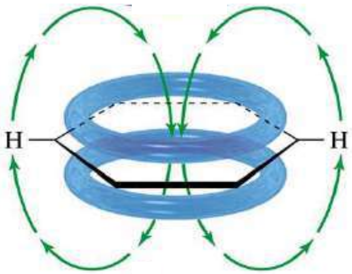
The circulating π electrons induce a magnetic field that adds to the applied field which causes them to experience a ***stronger net field*** *and therefore resonate at* ***higher frequency****.*

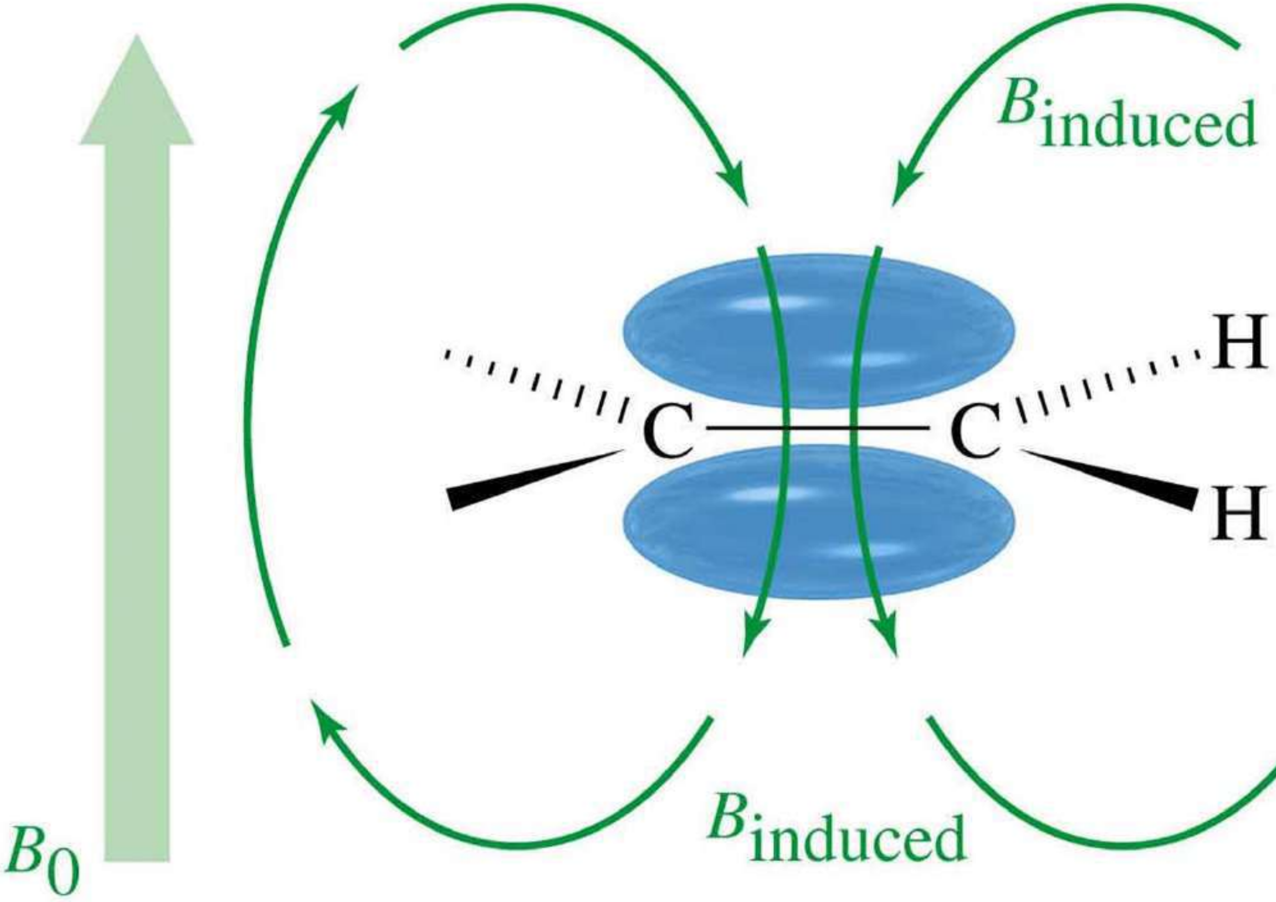
Aromatic Protons, δ7-δ8





Vinyl Protons, δ5-δ6

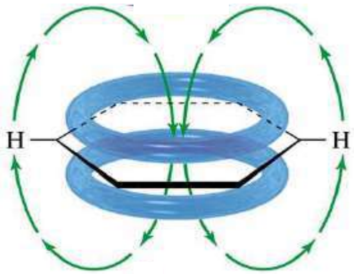


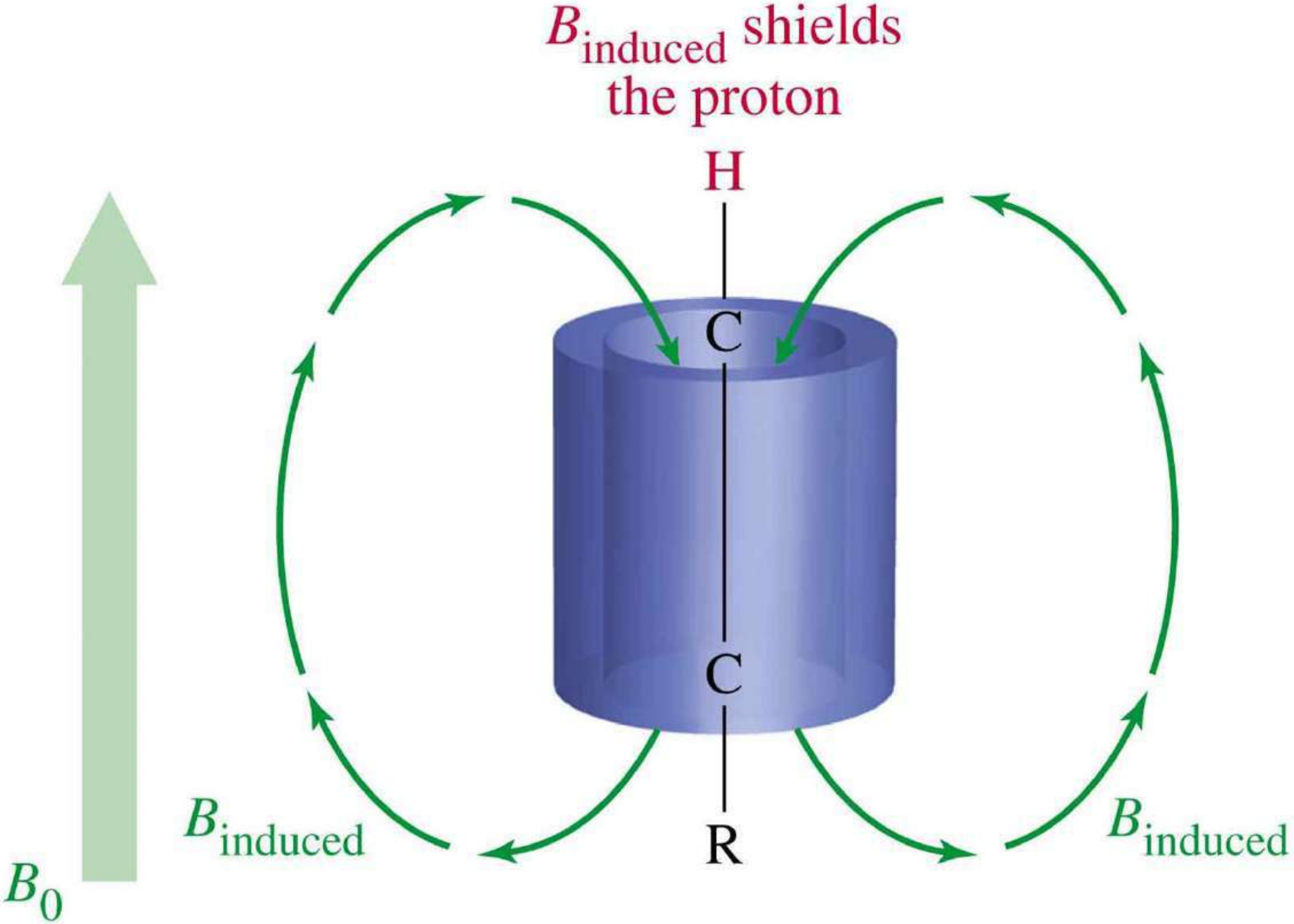


induced field reinforces the external field (deshielding)

=>

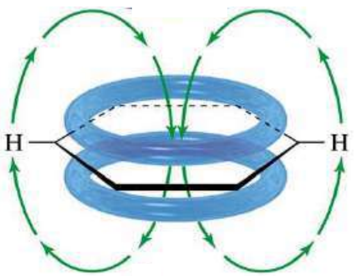
Acetylenic Protons, δ2.5

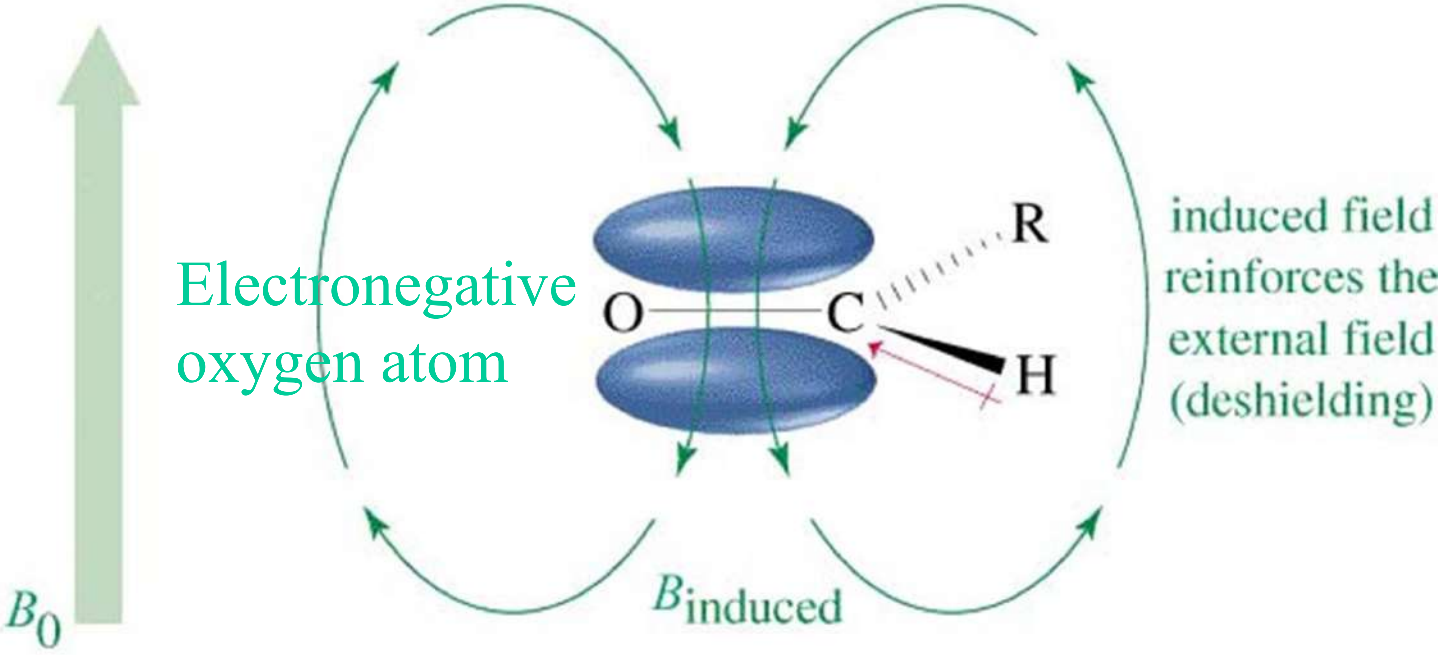




NMR

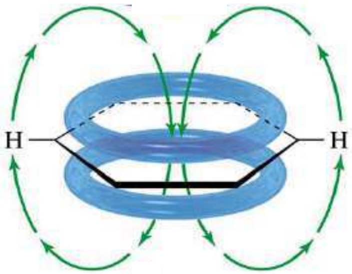
Aldehyde Proton, δ9-δ10




Electronegative
oxygen atom

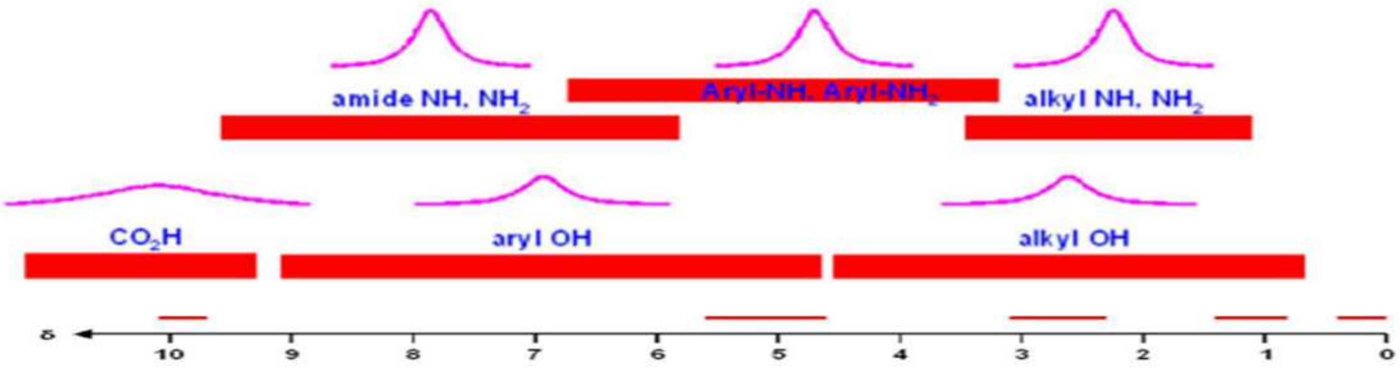
=>

O-H and N-H Signals



- **OH and NH protons cause problems because:-**

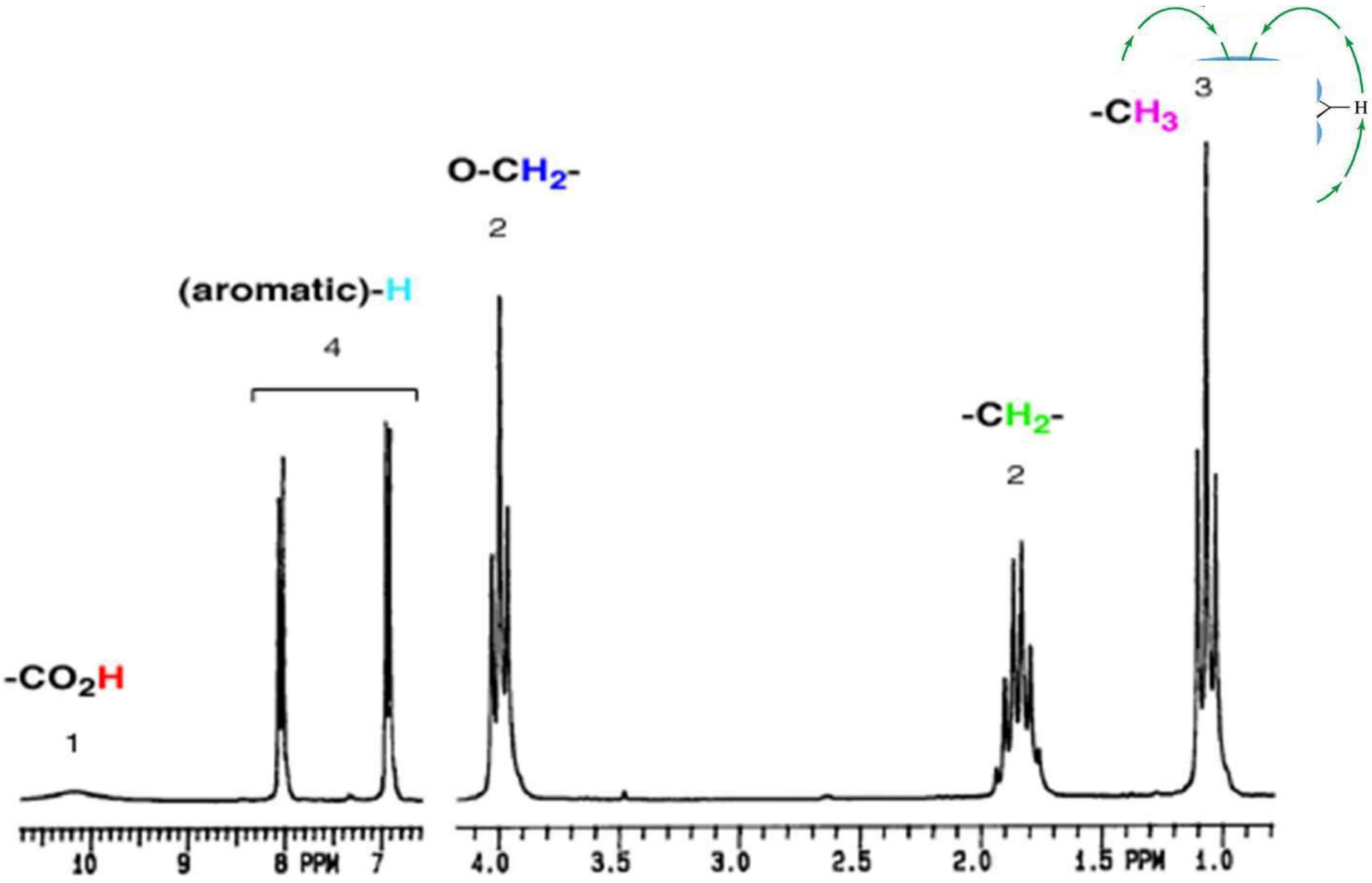
1. **Appear over wide ranges of shift values due to concentration.**

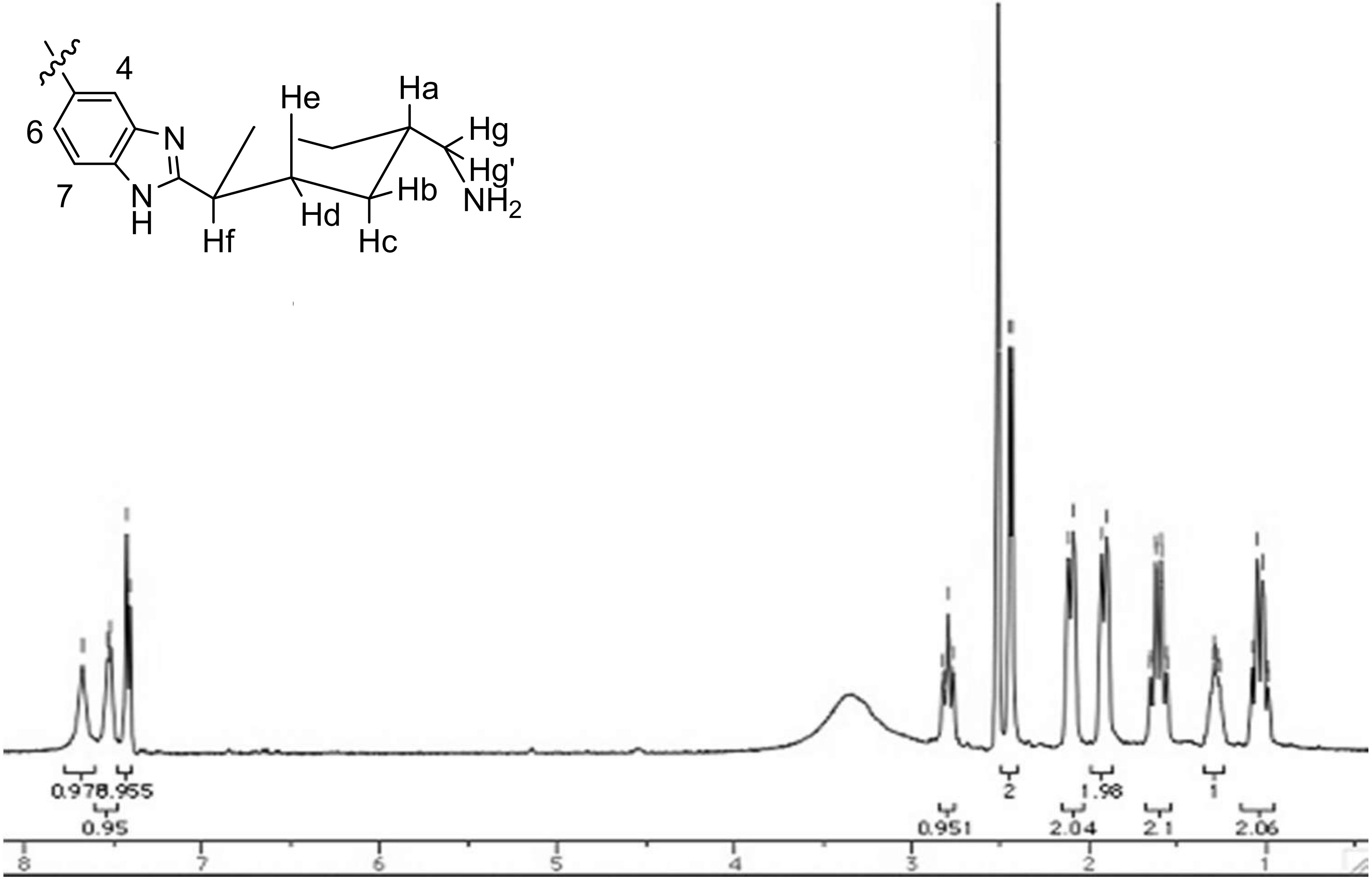


2. **Broad signals are expected and may be extremely broad and may be applied on base line or not seen.**

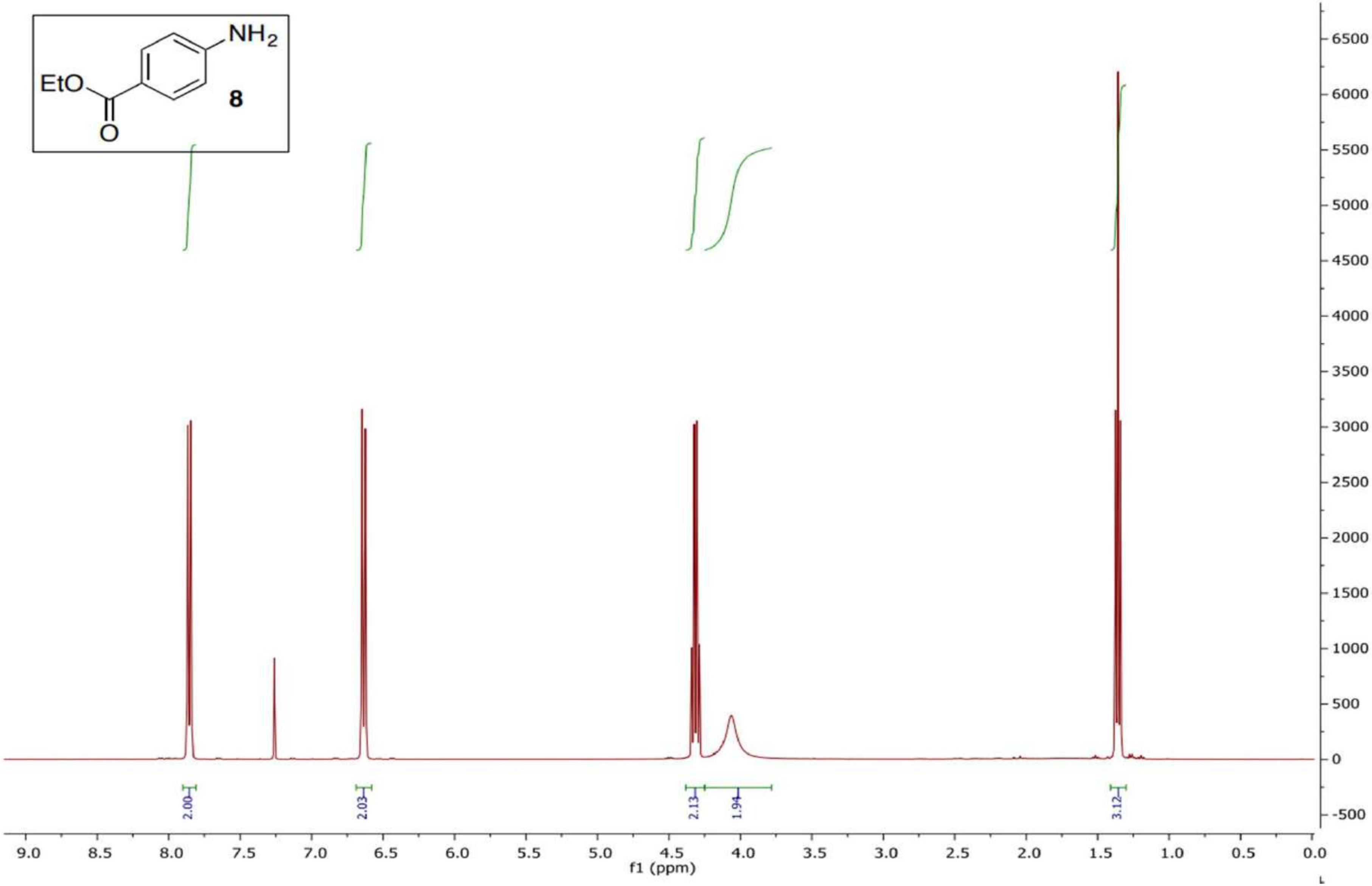
Chemical shift depends on concentration; hydrogen bonding in concentrated solutions deshields the protons, so signal is around δ3.5 for N-H and δ4.5 for O-H.

3. **No splitting is observed for protons on N or O if the sample is run with acid or base. This is due to proton exchange.**

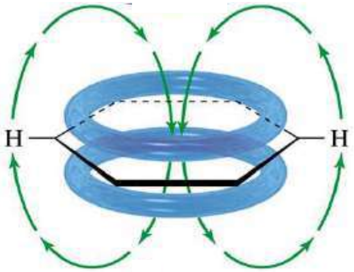

-CO$_2$H
1
(aromatic)-H
4
O-CH$_2$-
2
-CH$_2$-
2
-CH$_3$
3
H
10
9
8 PPM
7
4.0
3.5
3.0
2.5
2.0
1.5 PPM
1.0


4
6
7
N
N
H
He
Ha
Hg
Hg'
Hb
Hd
Hc
Hf
NH2
0.978
0.955
0.95
0.951
2
2.04
1.98
2.1
1
2.06
8
7
6
5
4
3
2
1

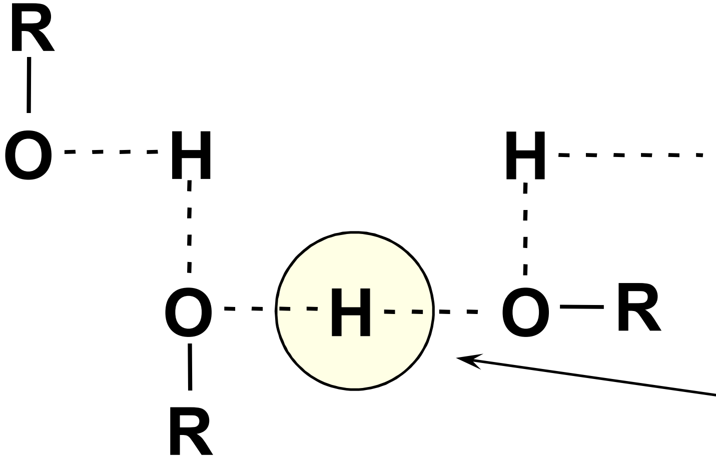
NMR


NH2
EtO
O
8
2.00
2.03
2.13
1.94
3.12
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
6500 6000 5500 5000 4500 4000 3500 3000 2500 2000 1500 1000 500 0 -500

3. Hydrogen Bonding and (O-H and N-H Signals)



Hydrogen bonding deshields protons



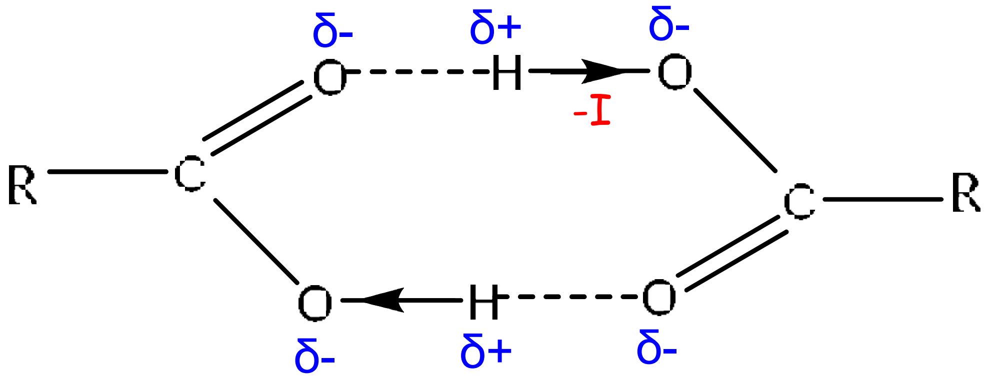
The chemical shift depends on how much hydrogen bonding is taking place (observed in high concentrated solutions).

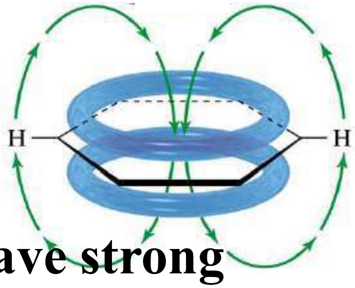
1] Hydrogen bonding lengthens the O-H bond and reduces the valence electron density around the proton

2] It is deshielded and shifted downfield in the NMR spectrum.

D_2O-exchangeable (peak for OH proton in <u>alcohol</u> and NH <u>in amines</u> disappears upon shaking with D_2O)

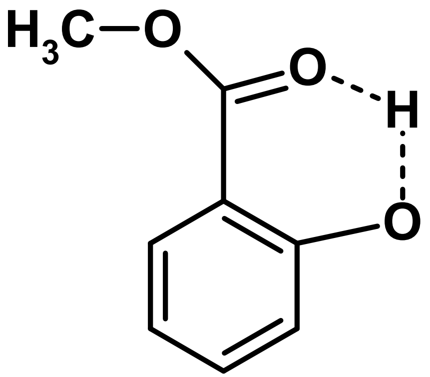
SOME MORE EXTREME EXAMPLES





Carboxylic acids have strong hydrogen bonding - they form dimers.

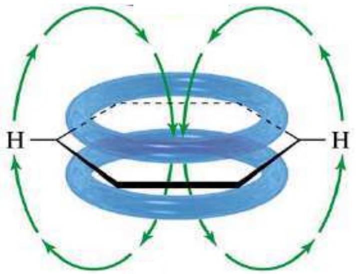
- **Resonance, electronegativity of oxygen and the formation of hydrogen bonding withdraw electron cloud from the acid protons.**
- **Thus, protons attached to carboxylic acids are the least shielded protons and have a chemical shift of 10-12 ppm and may be more it depends on total chemical environmental**



In methyl salicylate, which has strong internal hydrogen bonding, the NMR absorption for O-H is at about 14 ppm, (highly downfield)

Notice that a stable 6-membered ring is formed

Identifying the O-H or N-H Peak



- Chemical shift will depend on concentration and solvent. (different chemical shift value might be noticed)
- The signal of both N-Hand O-H in most cases are broad.
- To verify that a particular peak is due to O-H or N-H, shake the sample with D2O
- Deuterium will exchange with the O-H or N-H protons.
- On a second NMR spectrum the peak will be absent, or much less intense.

Deuterium Exchange :

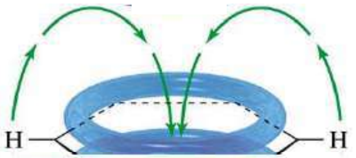
If deuterium oxide, D_2O, is used as solvent for NMR work, the D_2O exchanges with labile protons such as OH, NH and SH. In effect, because of the rapidity of the exchange, R-OH becomes ROD, RCOOH becomes RCOOD, $RCONH_2$ becomes $RCOND_2$ Etc.

$$\mathbf{ROH + D\text{--}O\text{--}D \rightleftharpoons ROD + H\text{--}O\text{--}D}$$

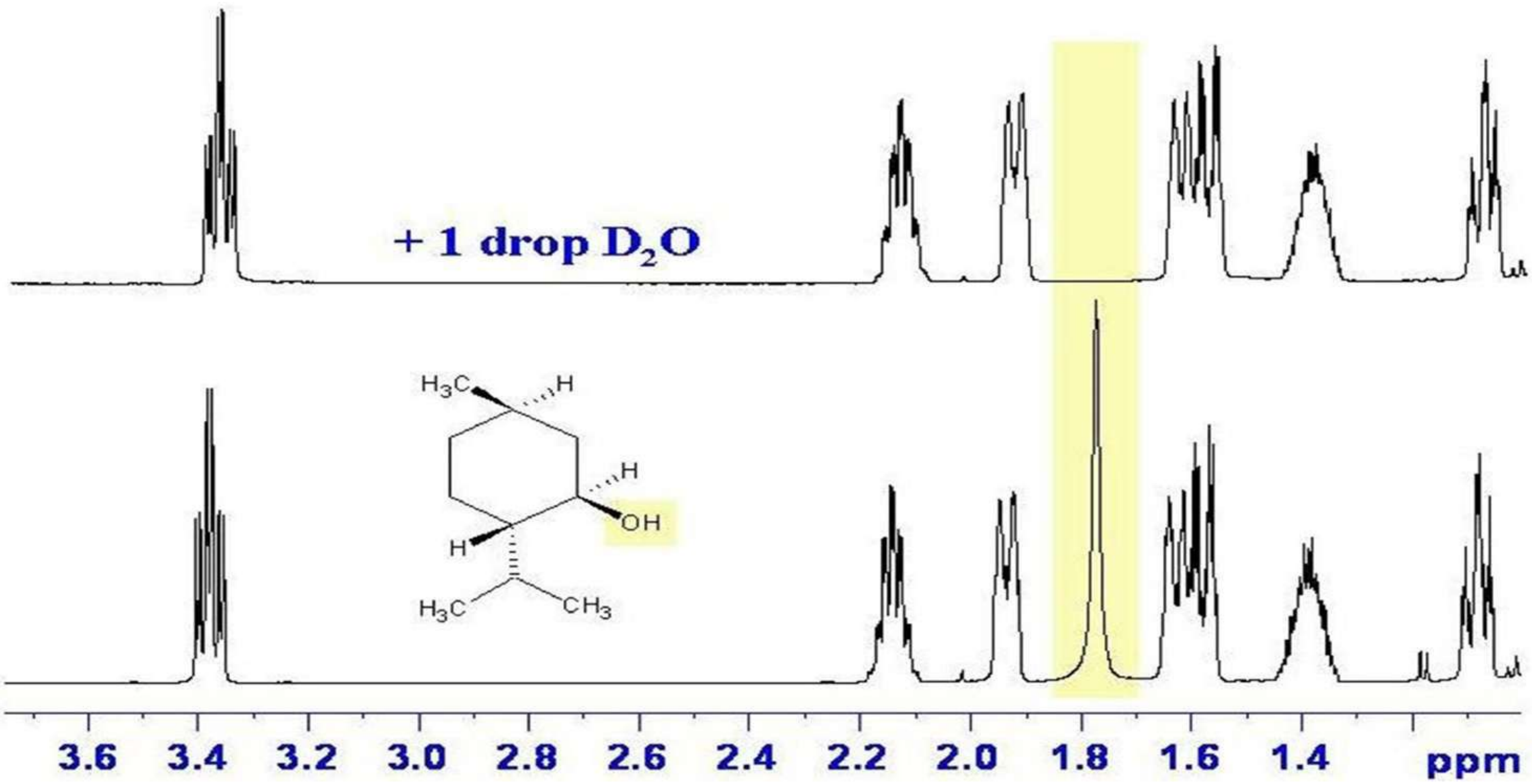
This technique of detraction is widely used to detect the presence of –OH, -NH & SH groups and is easily carried out,. The NMR spectrum can be carried out.

The method can be extended to detect reactive methylene groups, such as those flanked by carbonyl.

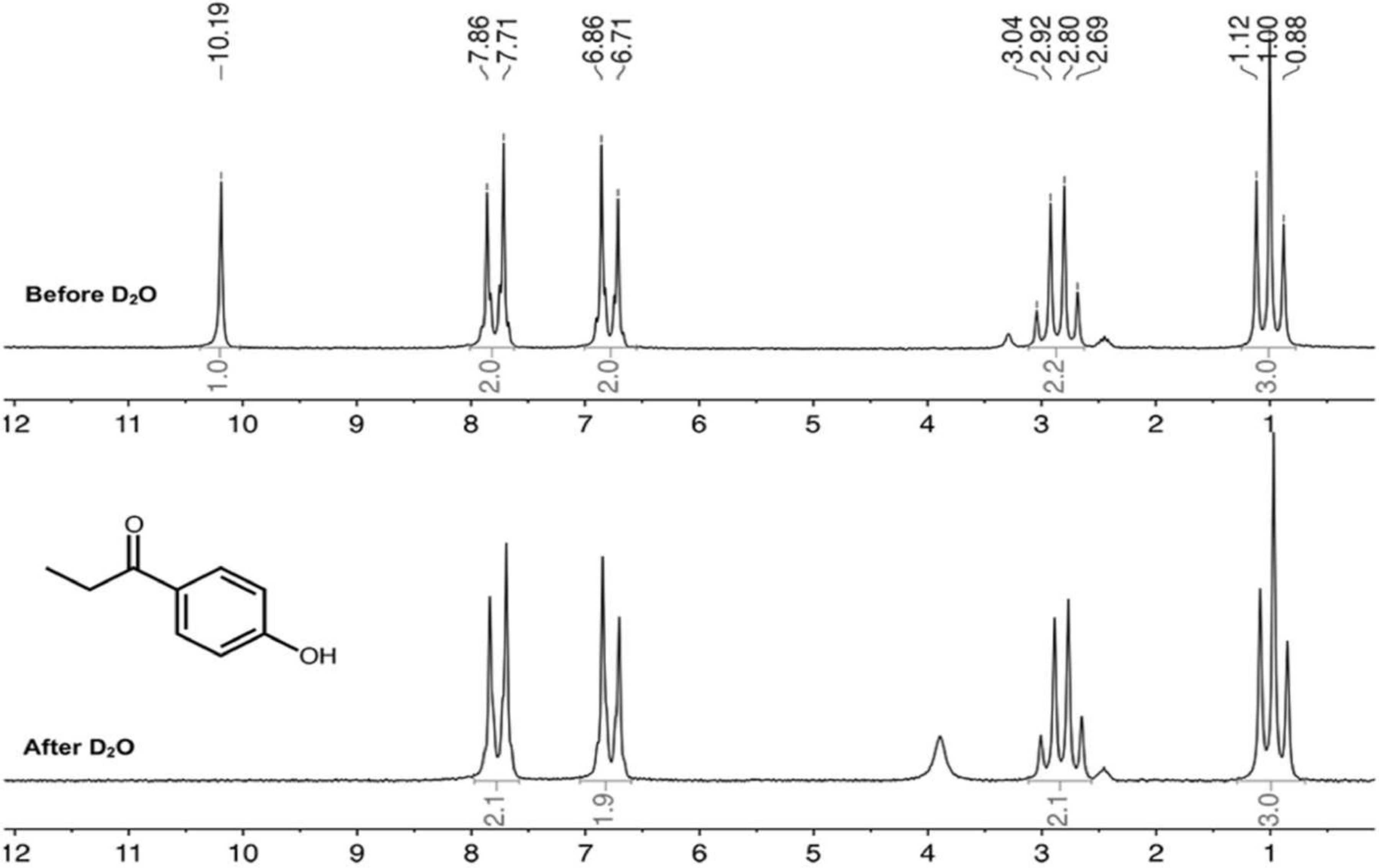
H_2O and D_2O Exchange

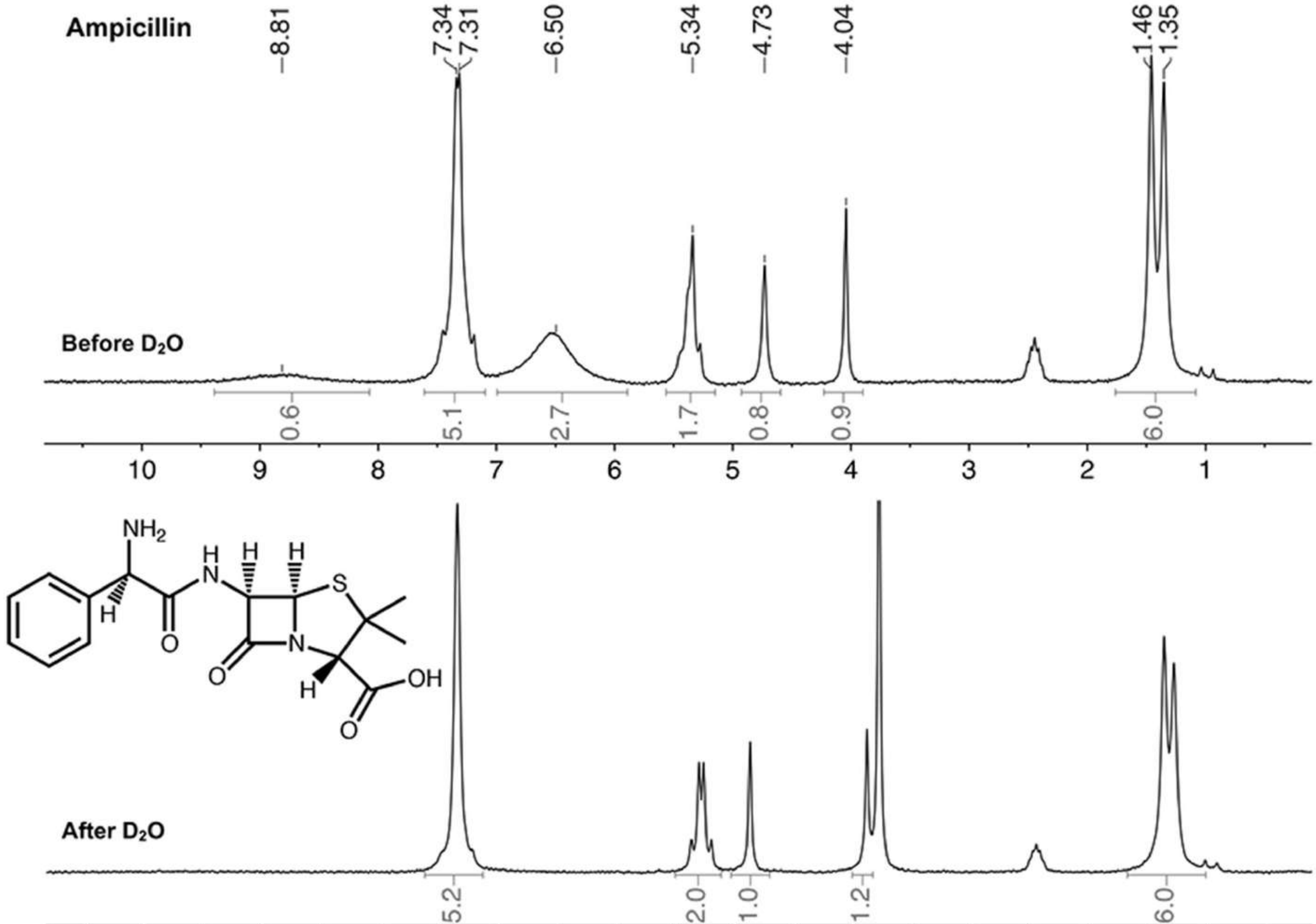


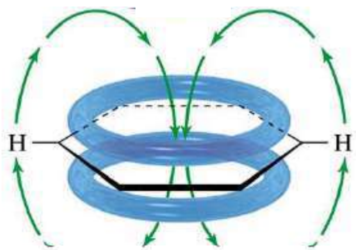
Partial ^{1}H NMR Spectrum of Menthol in $CDCl_3$

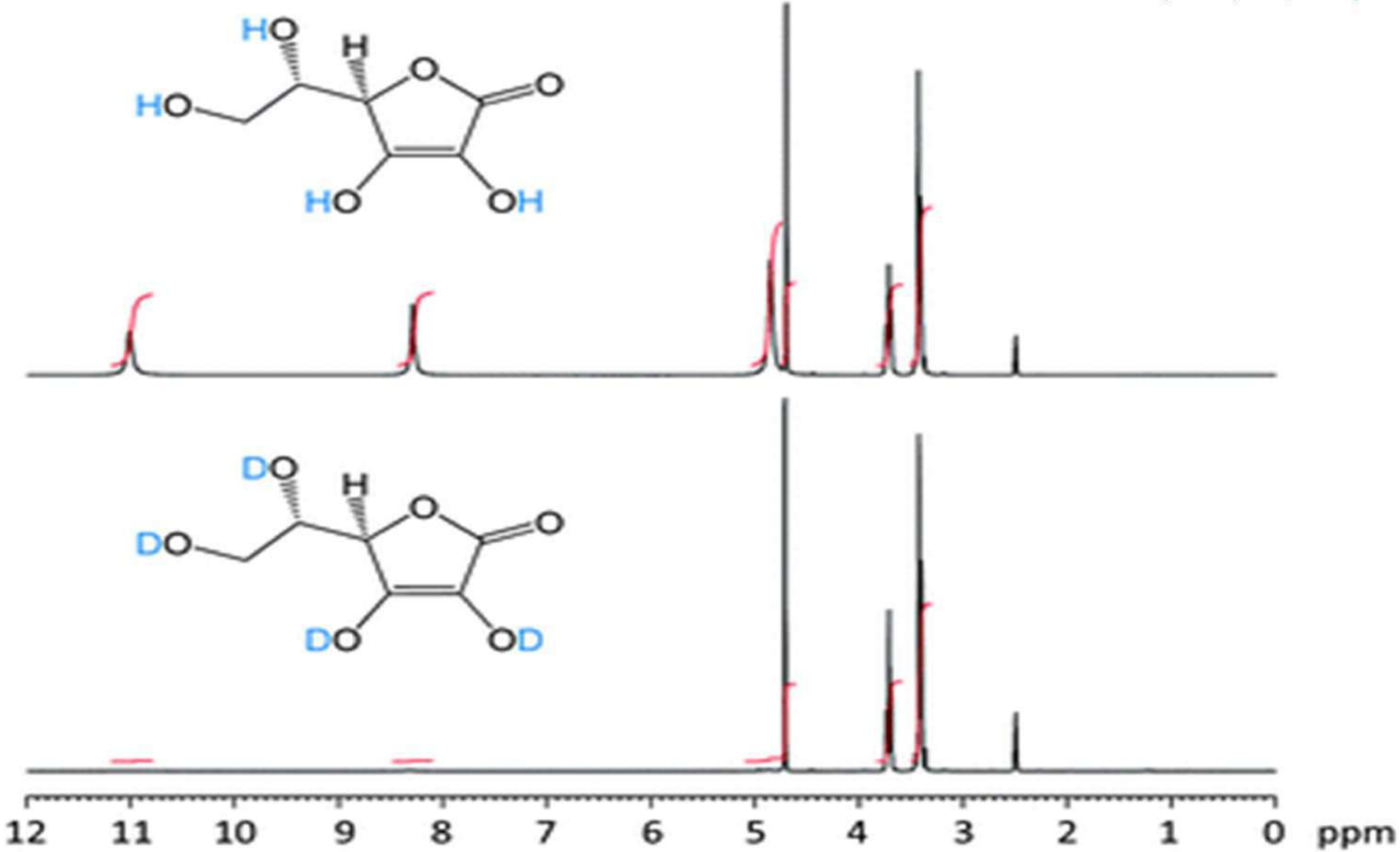


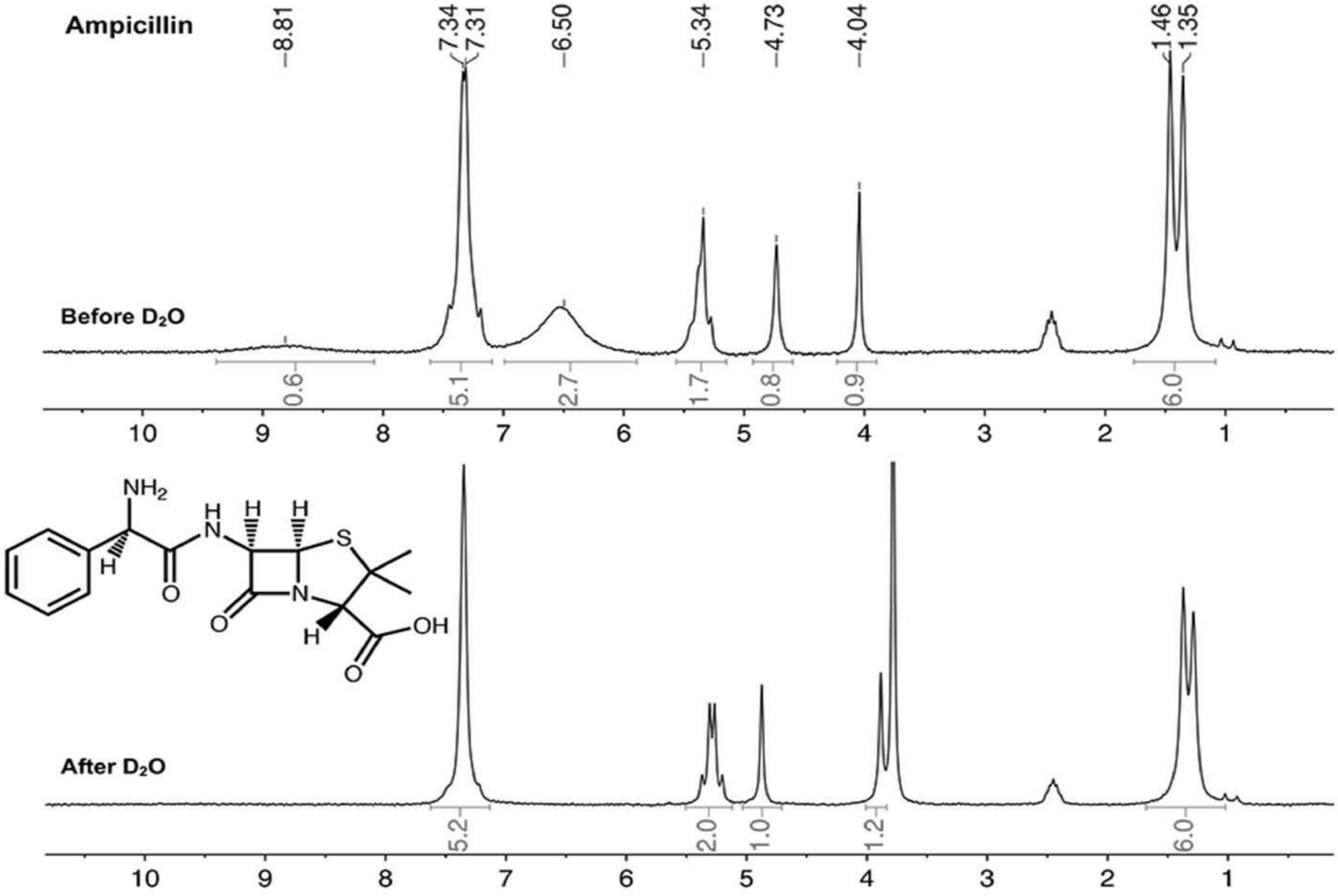
4-hydroxypropiophenone

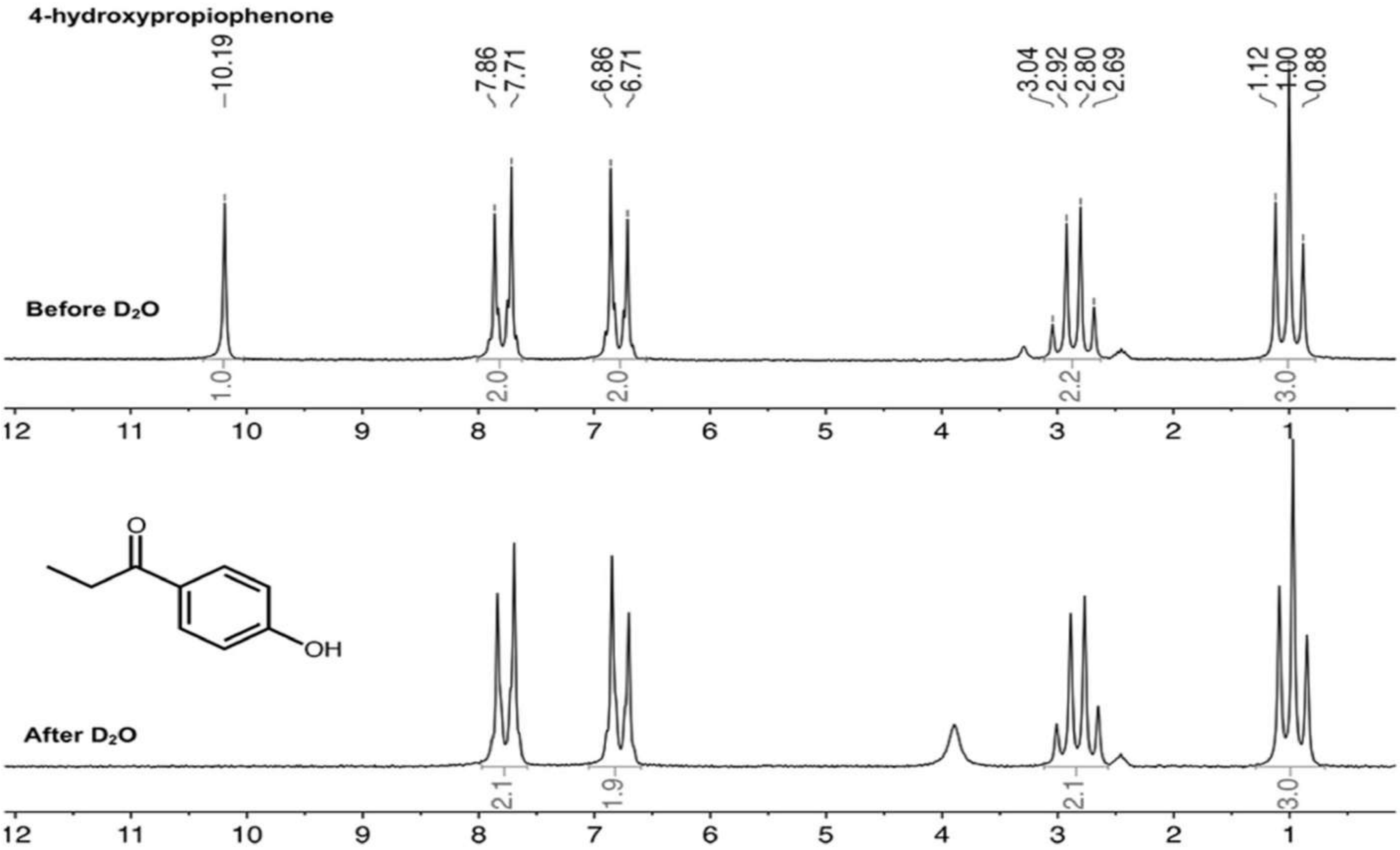


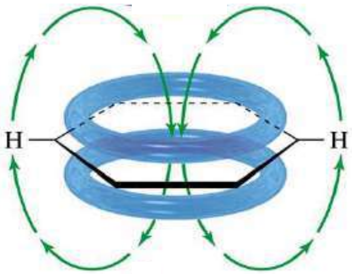

Ampicillin
8.81
7.34
7.31
6.50
5.34
4.73
4.04
1.46
1.35
Before D₂O
0.6
5.1
2.7
1.7
0.8
0.9
6.0
10
9
8
7
6
5
4
3
2
1
NH₂
H
N
H
H
S
H
O
N
O
H
OH
O
After D₂O
5.2
2.0
1.0
1.2
6.0
10
9
8
7
6
5
4
3
2
1


H
H

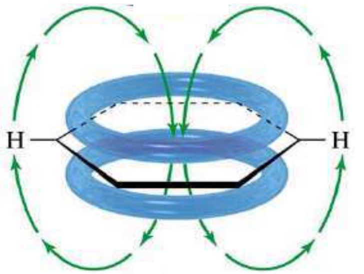

HO
H
O
O
HO
HO
OH
DO
H
O
O
DO
DO
OD
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


Ampicillin
8.81
7.34
7.31
6.50
5.34
4.73
4.04
1.46
1.35
Before D₂O
0.6
5.1
2.7
1.7
0.8
0.9
6.0
10
9
8
7
6
5
4
3
2
1
NH₂
H
N
H
H
S
H
O
O
N
H
OH
O
After D₂O
5.2
2.0
1.0
1.2
6.0
10
9
8
7
6
5
4
3
2
1


4-hydroxypropiophenone
10.19
7.86
7.71
6.86
6.71
3.04
2.92
2.80
2.69
1.12
1.00
0.88
Before D₂O
1.0
2.0
2.0
2.2
3.0
12
11
10
9
8
7
6
5
4
3
2
1
O
OH
After D₂O
2.1
1.9
2.1
3.0
12
11
10
9
8
7
6
5
4
3
2
1



Video 6
Page (108-121)



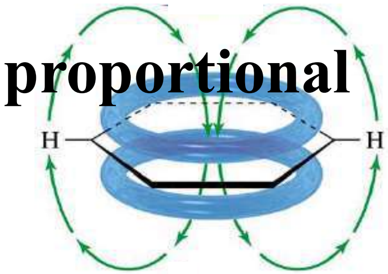
(3)
Area Under Signals
“Integration”

<u>Integration of Peaks</u>

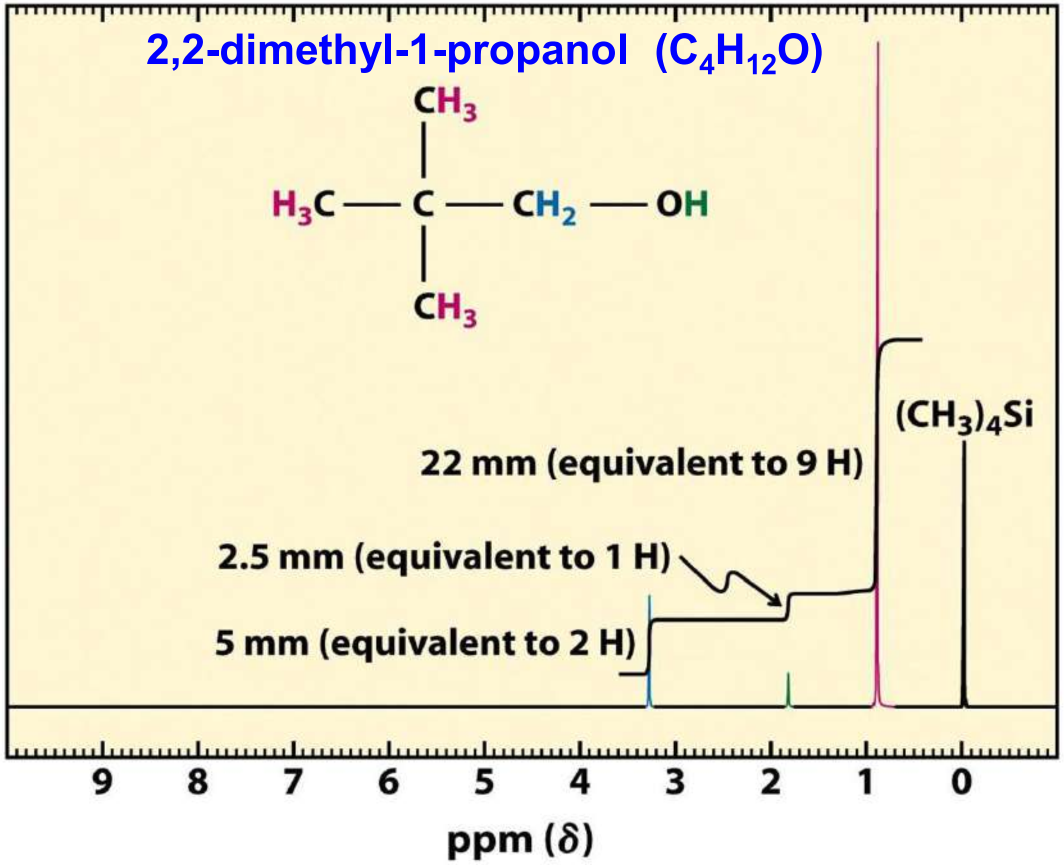
Not only does each different type of hydrogen give a distinct peak in the NMR spectrum, but we can also tell the <u>relative numbers</u> of each type of hydrogen by a process called integration.

Integration = determination of the area under a peak

- **In the NMR spectrum, the area under each peak is proportional to the number of hydrogens generating that peak.**



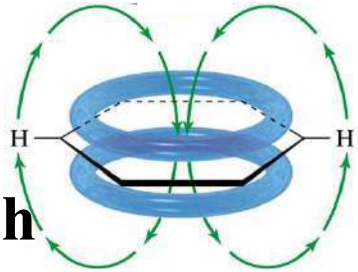
- **The NMR spectrometer has the capability to electronically integrate the area under each peak.**



☝ **The integrated area measured by a ruler are 5 : 2.5 : 22**

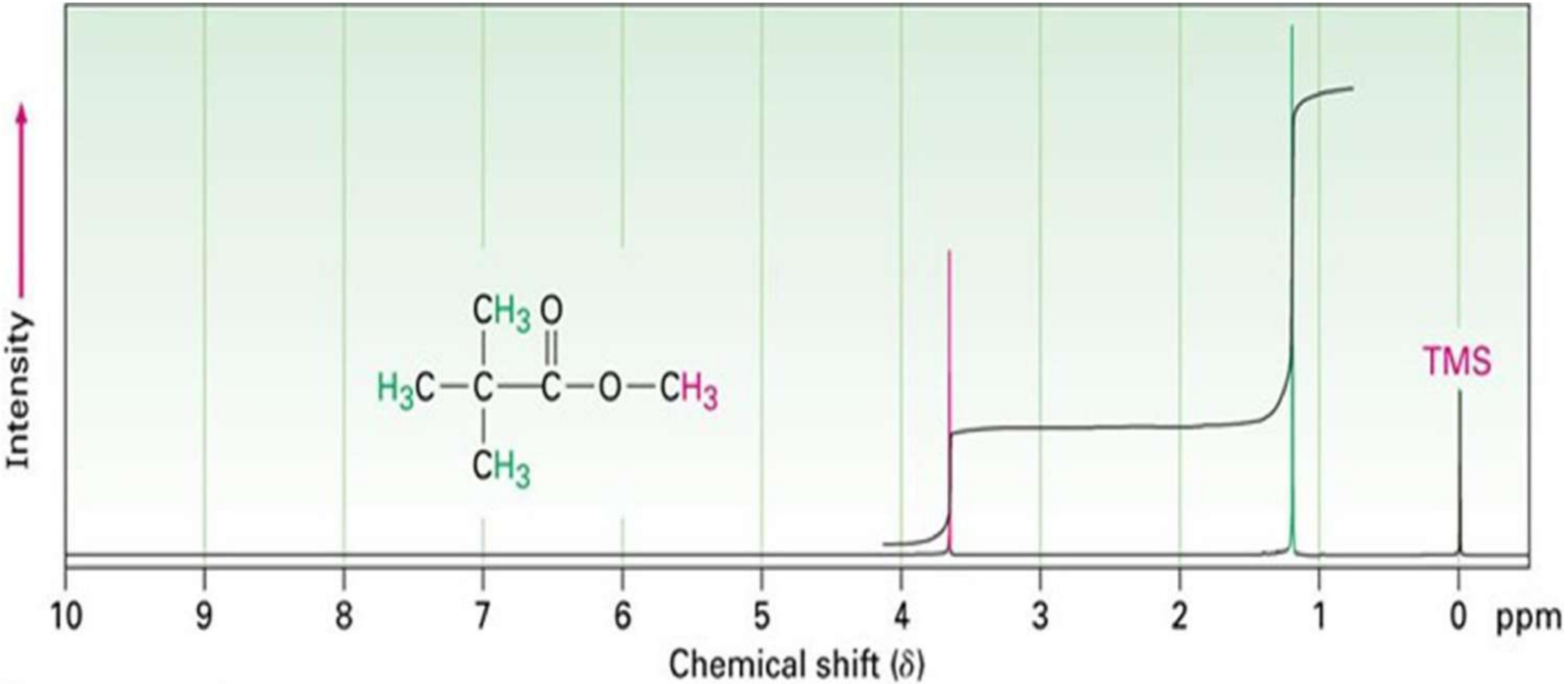
Divide by the smallest number give us the simplest ratio of 2 : 1 : 9

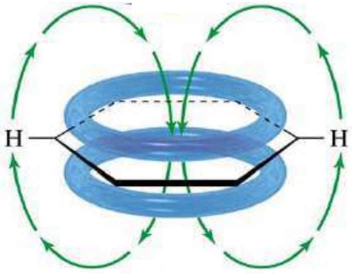
Note that the integration gives only ratios, not absolute values for the number of the hydrogen present in the sample

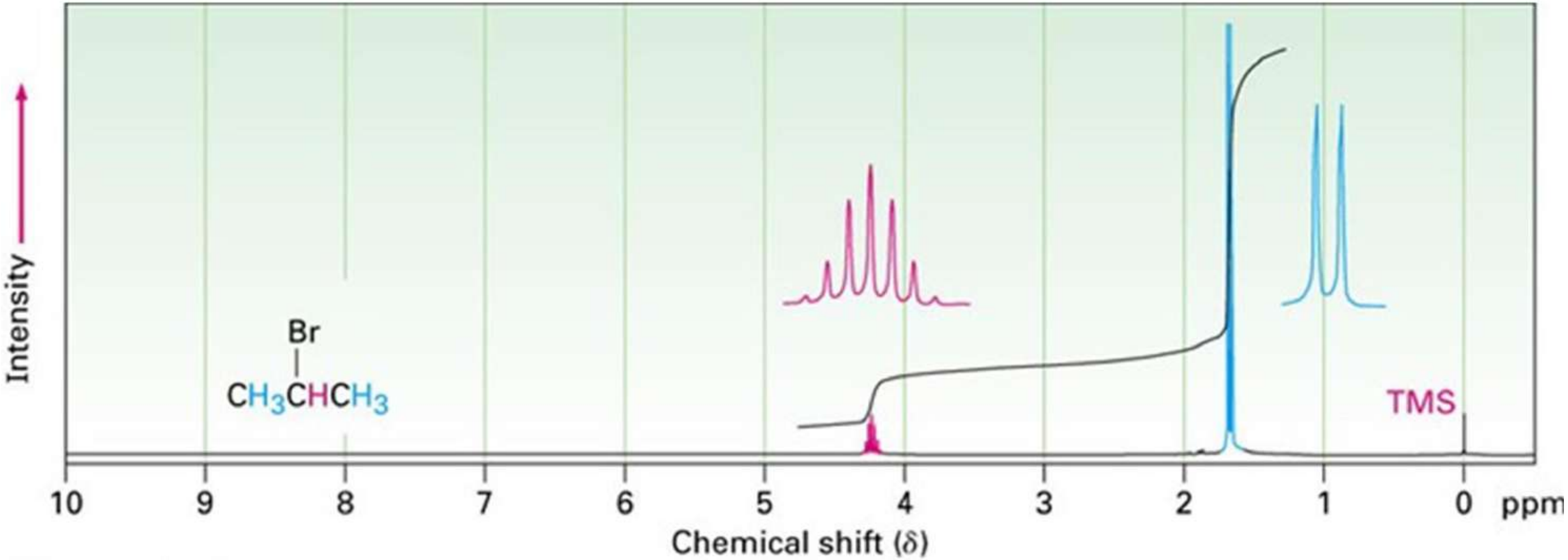


1- Measure the length of the integral with a ruler.

2- Establish a relative ratio of protons (divide each length by the lowest number)







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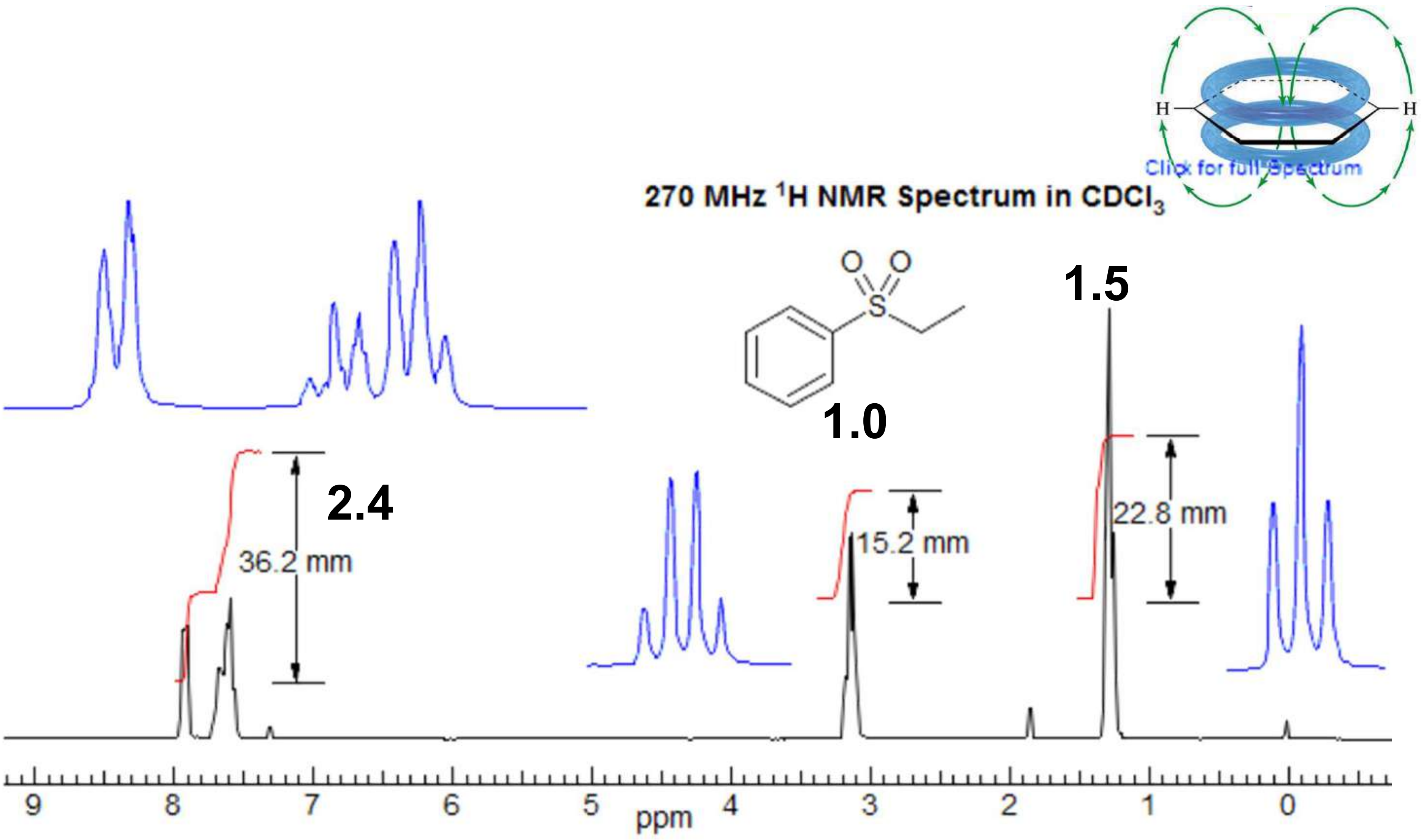
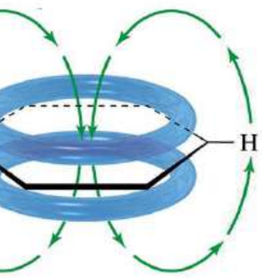
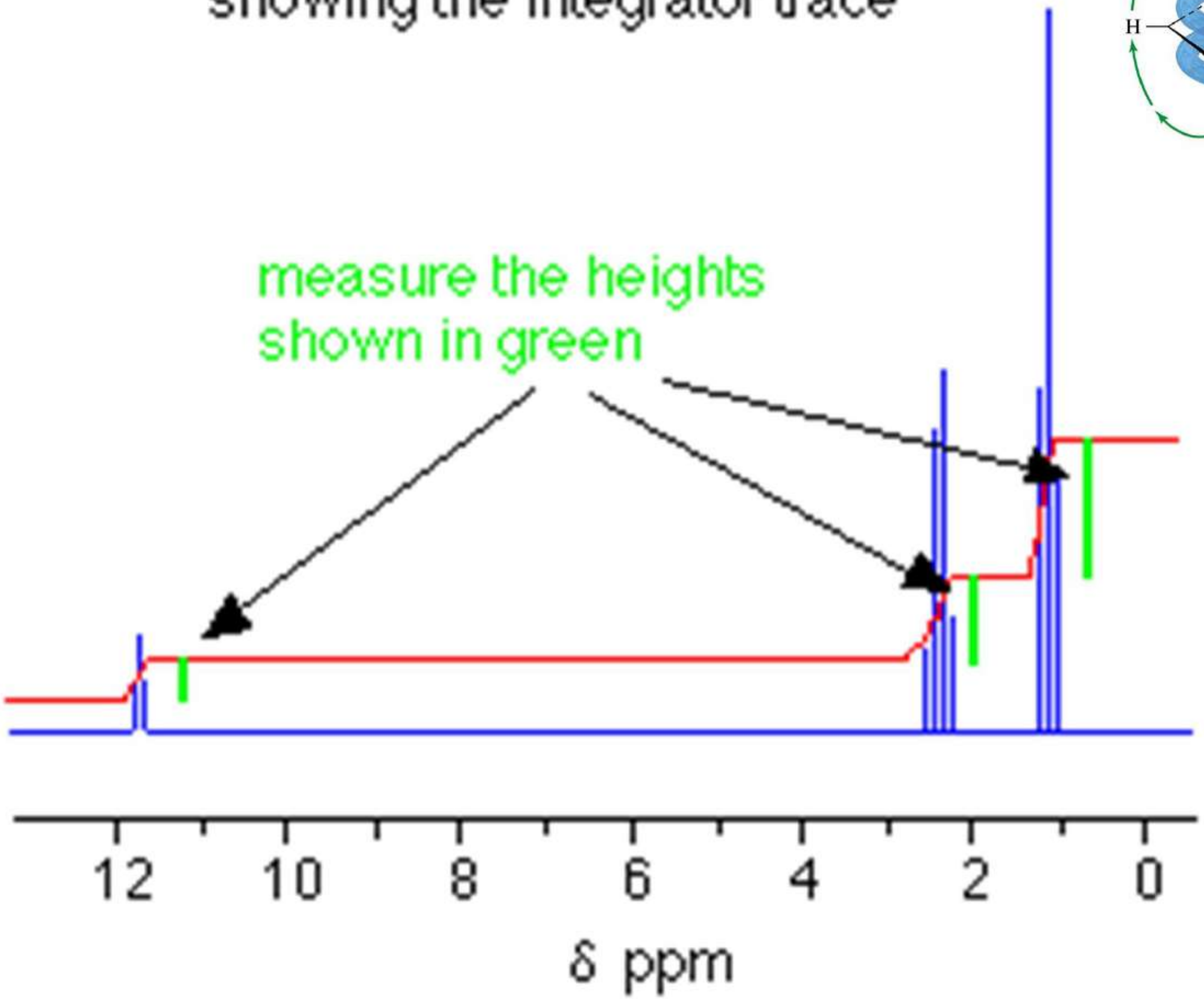
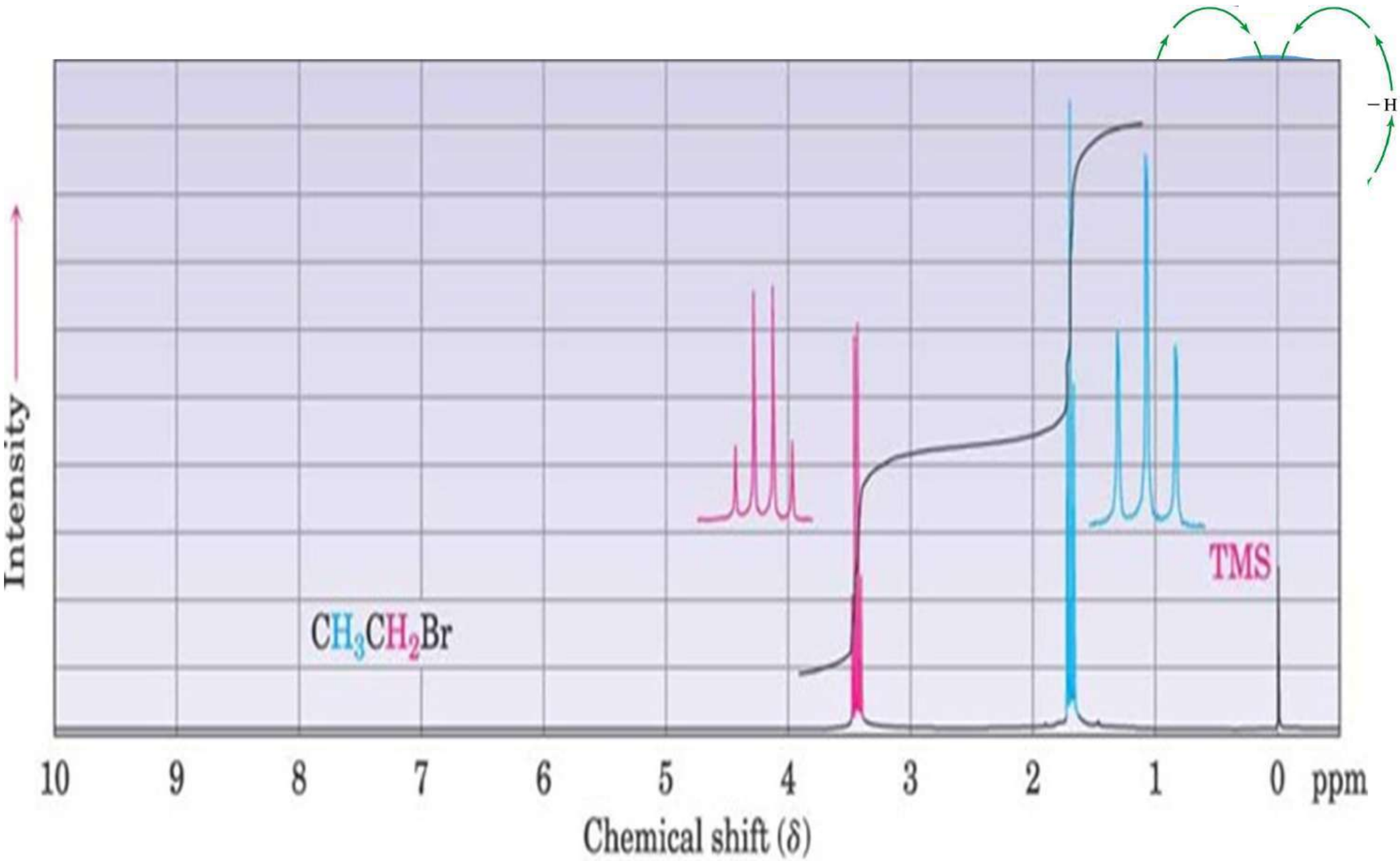
270 MHz ^{1}H NMR Spectrum in CDCl$_3$



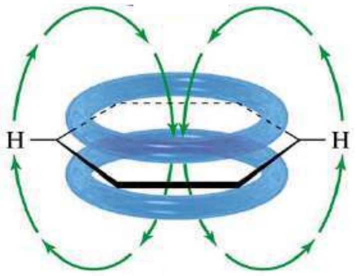
nmr spectrum for propanoic acid, CH_3CH_2COOH showing the integrator trace




measure the heights shown in green



Intensity
CH3CH2Br
TMS
− H
10
9
8
7
6
5
4
3
2
1
0
ppm
Chemical shift (δ)


H
H

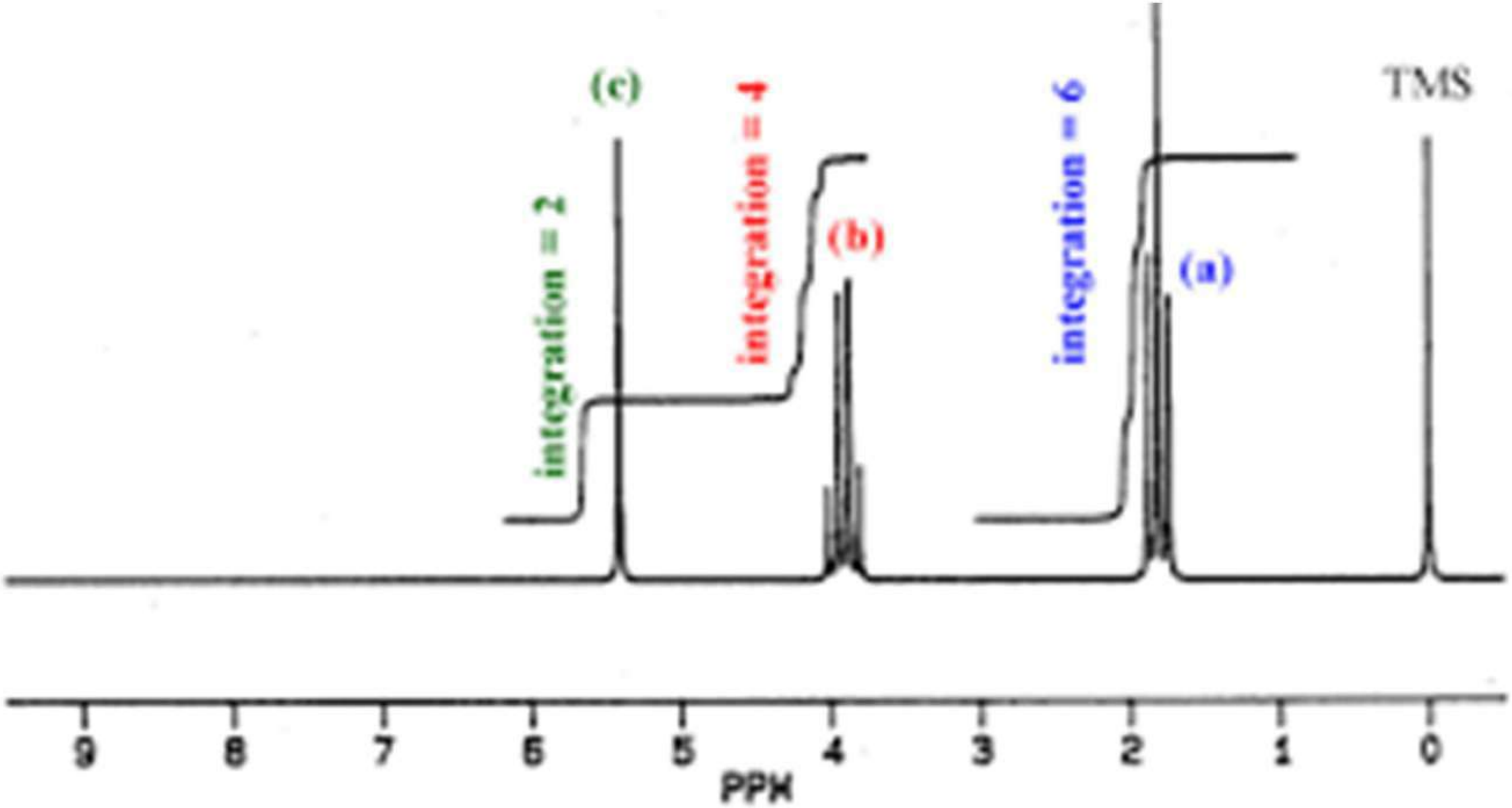
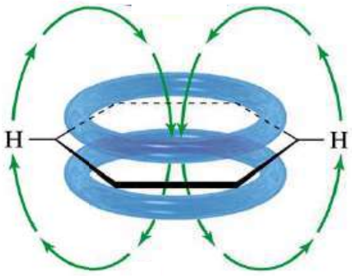

(c)
integration = 2
integration = 4
(b)
integration = 6
(a)
TMS
9
8
7
6
5
4
3
2
1
0
PPM

Figure 22. ^{1}H NMR spectrum of methyl propanoate.



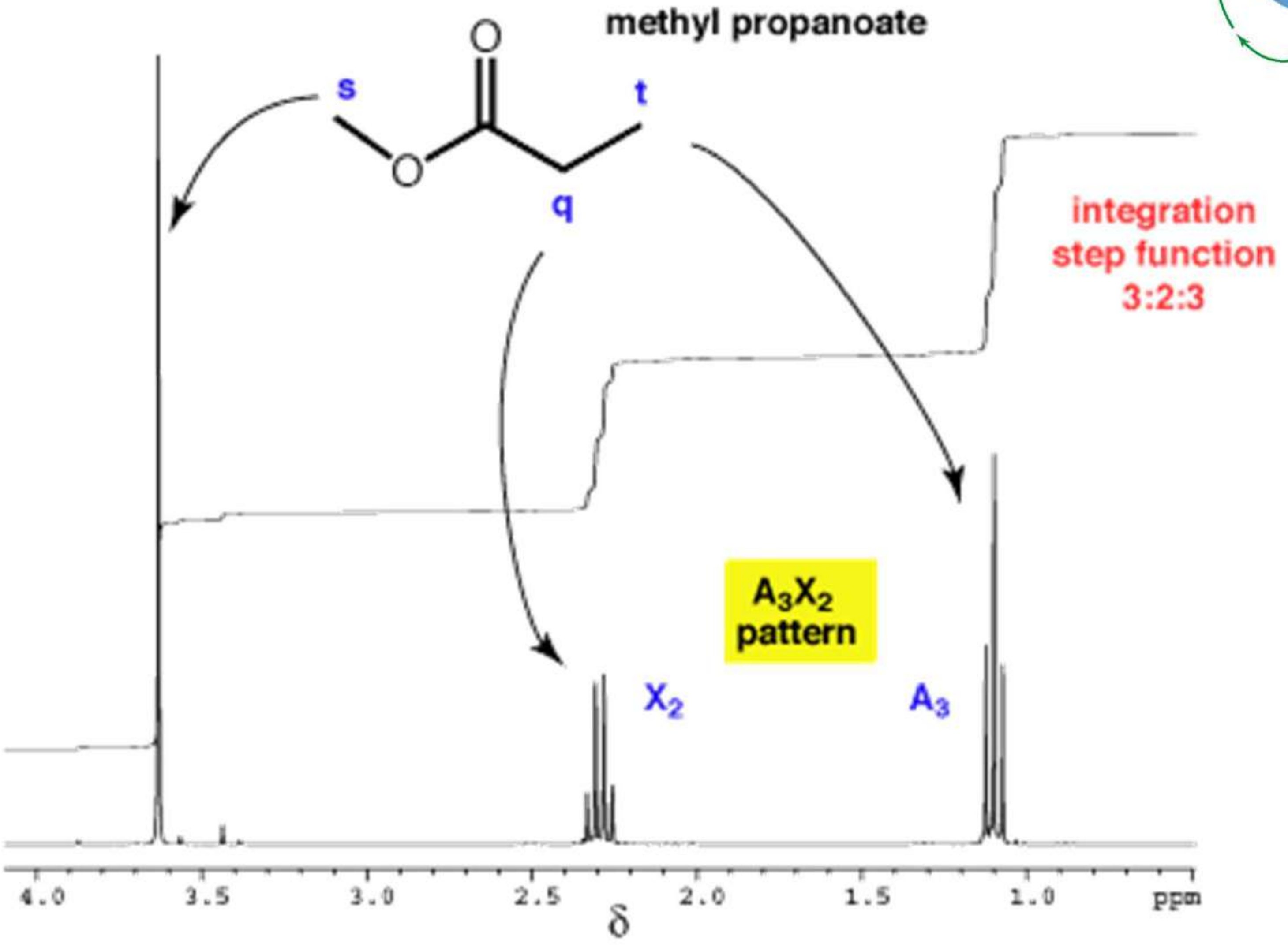
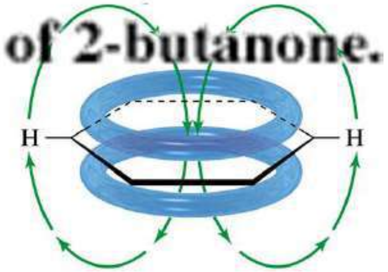
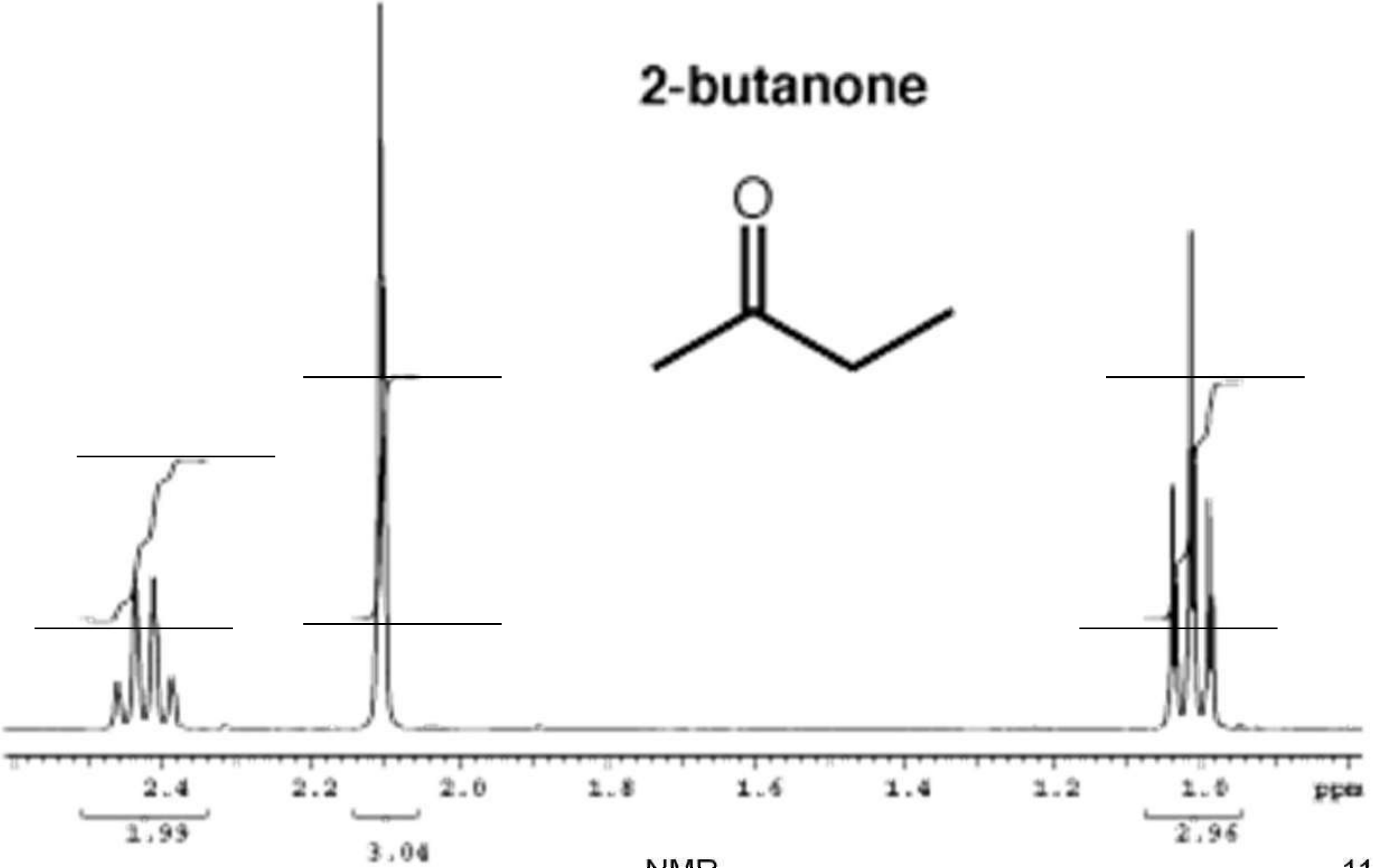
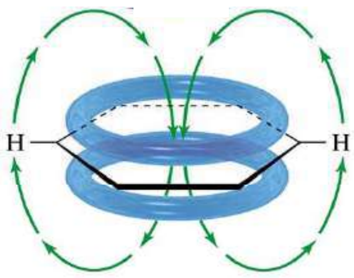
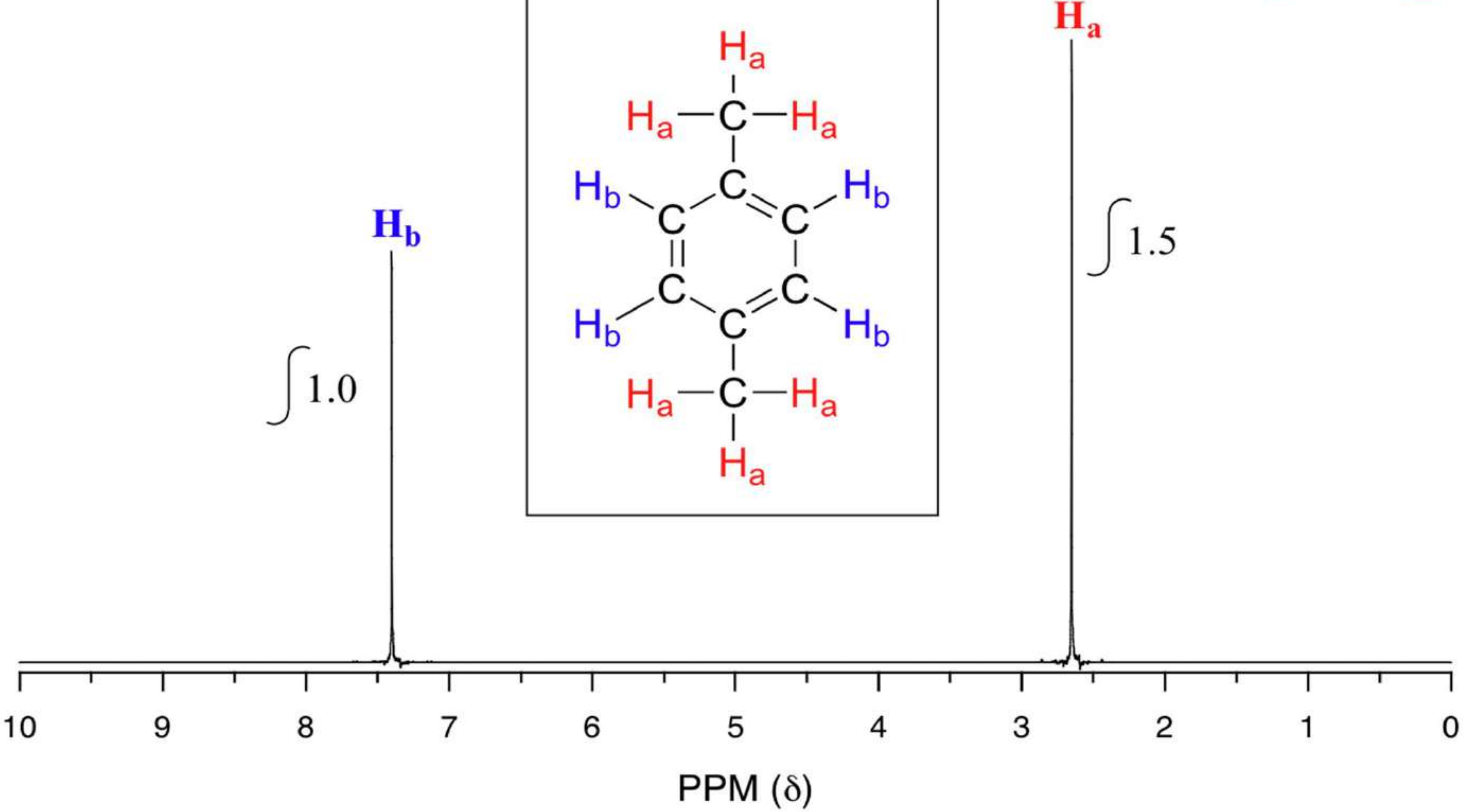


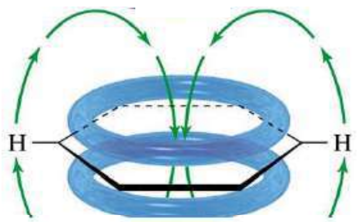
Figure 27. Integration values for the ^{1}H NMR spectrum of 2-butanone.

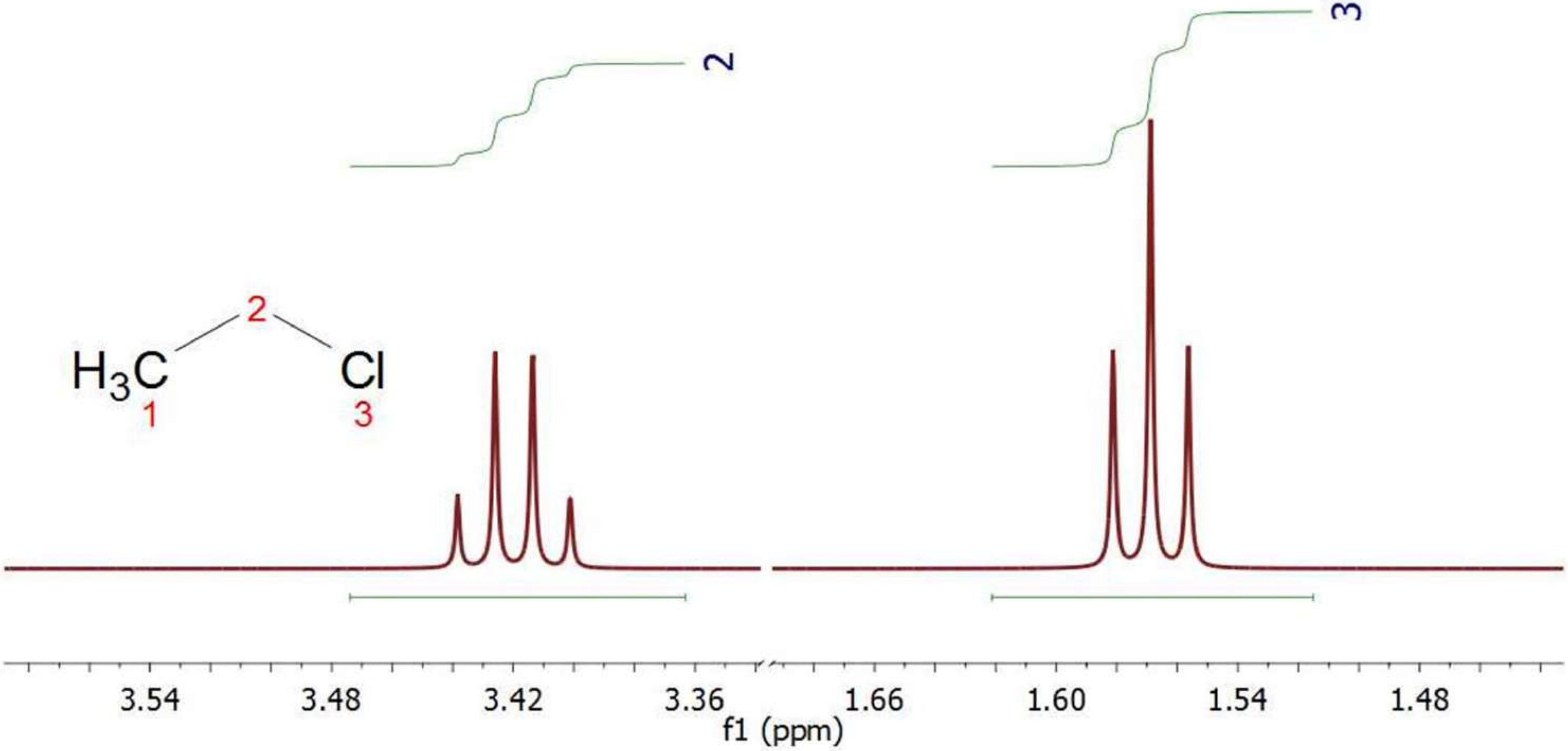




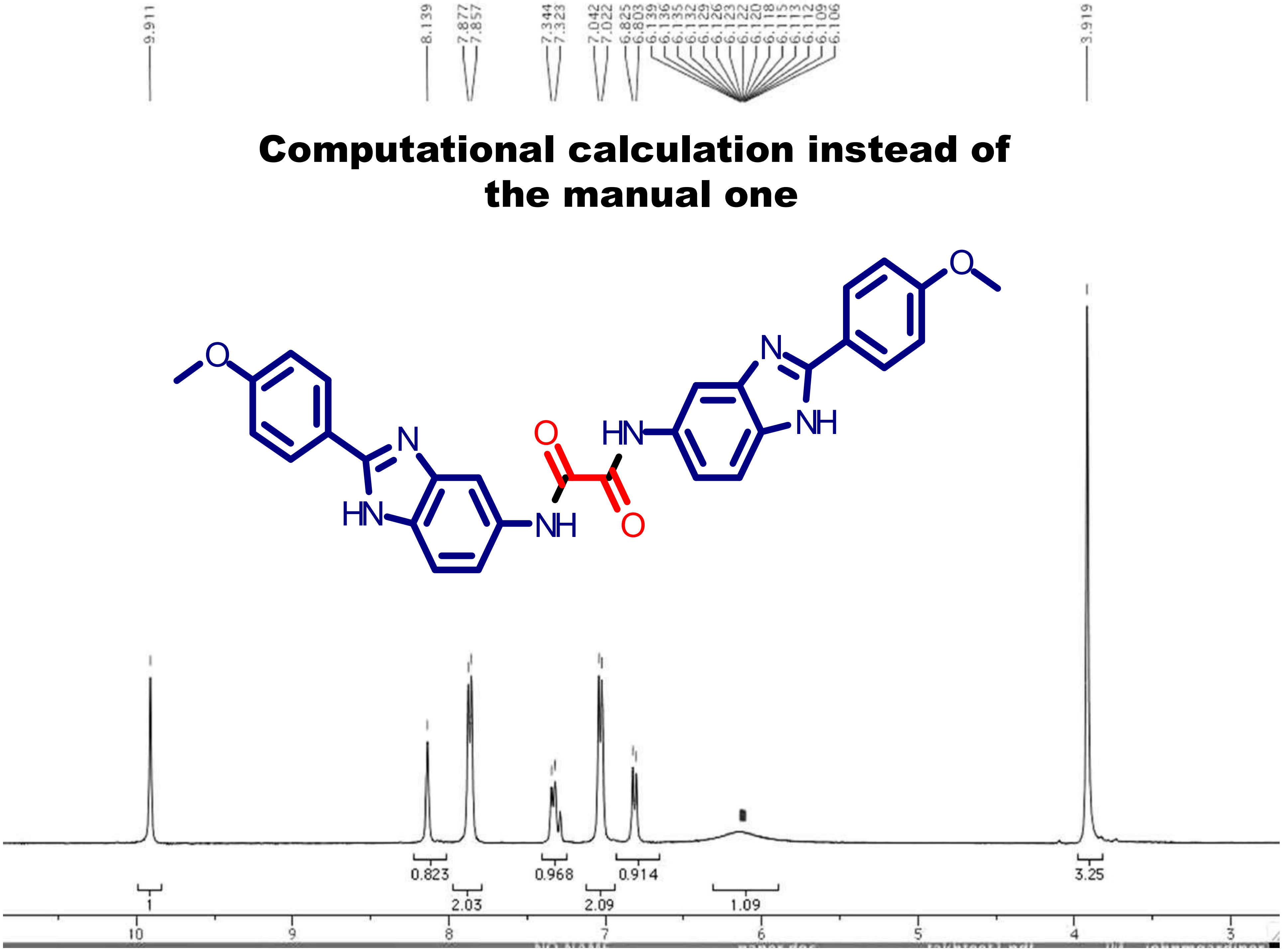

H
H

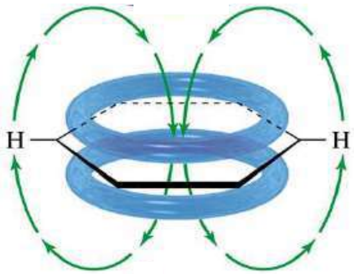

H_b
H_a
$\int 1.0$
$\int 1.5$
H_a
H_a — C — H_a
H_b C H_b
C C
C C
H_b C H_b
H_a — C — H_a
H_a
10
9
8
7
6
5
4
3
2
1
0
PPM (δ)


H
H

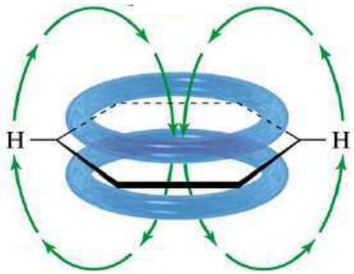

2
3
H_3C
2
Cl
1
3
3.54
3.48
3.42
3.36
1.66
1.60
1.54
1.48
f1 (ppm)

Computational calculation instead of the manual one





Video 7
Page (124-166)



(4)
Splitting
“Multiplicity”

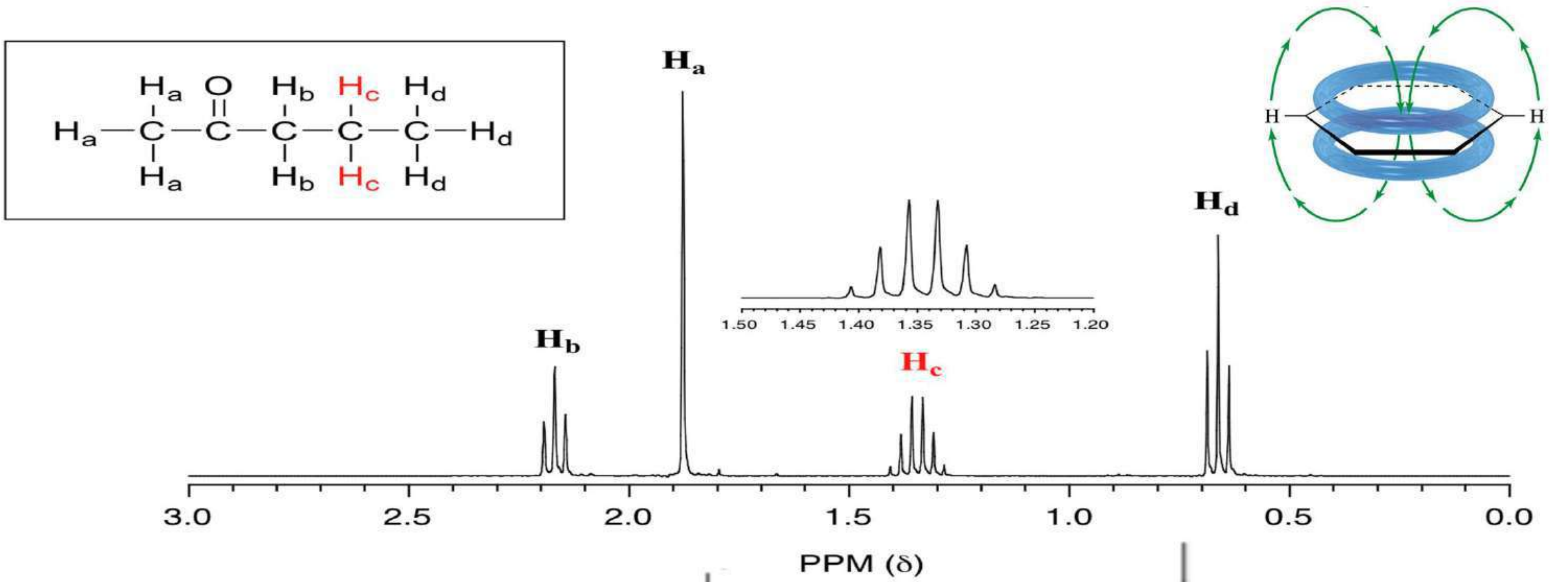
How does the signal appear?

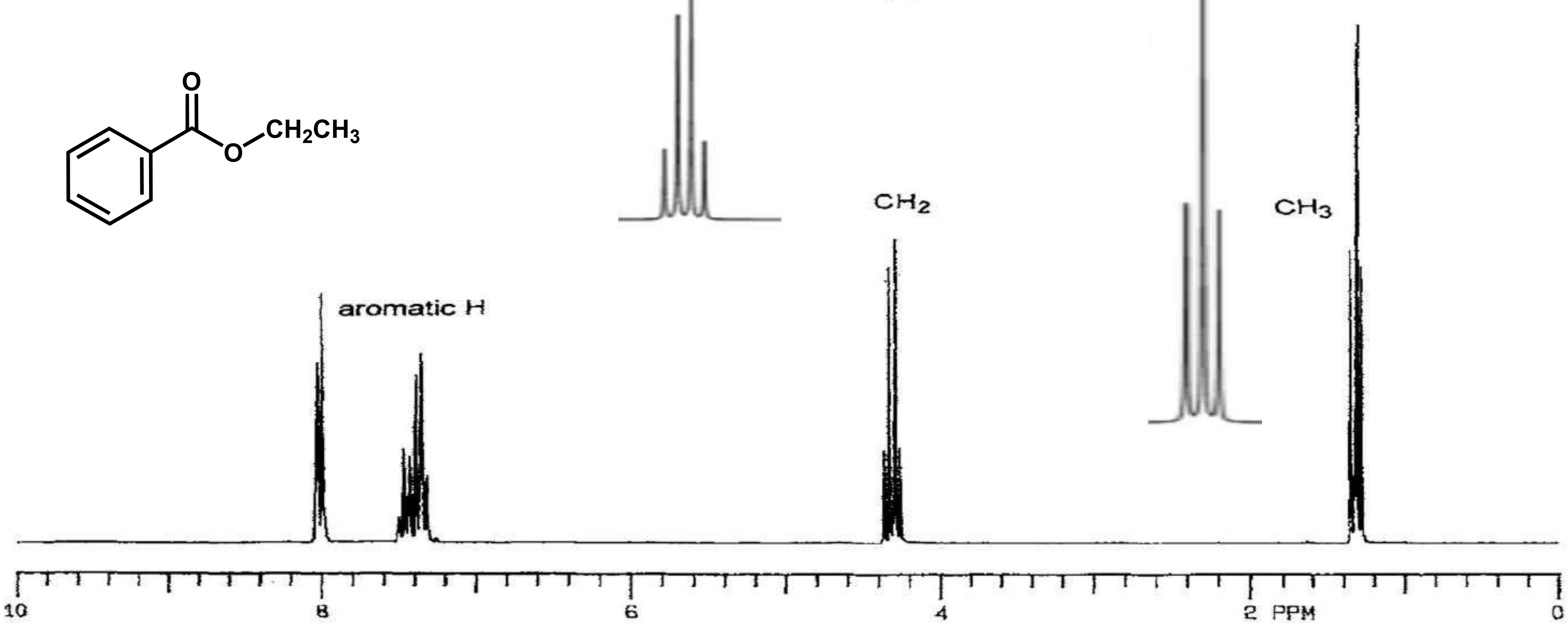
Spin-Spin Splitting

- Nonequivalent protons on adjacent carbons have magnetic fields that may align with or oppose the external field.
- This magnetic coupling causes the proton to absorb slightly downfield when the external field is reinforced and slightly upfield when the external field is opposed.
- All possibilities exist, so signal is split.

HOW IT HAPPENS ?

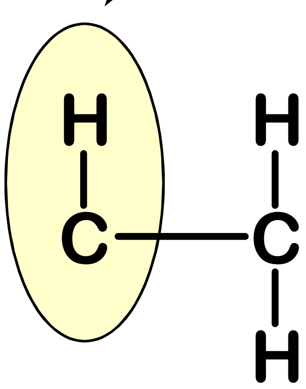
Spin-spin splitting arises because hydrogen on adjacent carbon atoms can “sense” one another


Ha O Hb Hc Hd
Ha—C—C—C—C—C—Hd
Ha Hb Hc Hd
Ha
Hb
Hc
Hd
H
H
1.50 1.45 1.40 1.35 1.30 1.25 1.20
3.0 2.5 2.0 1.5 1.0 0.5 0.0
PPM (δ)


O
O
CH2CH3
aromatic H
CH2
CH3
10 8 6 4 2 PPM 0

Simple splitting n + 1 RULE

this hydrogen's peak
is split by its two
neighbors

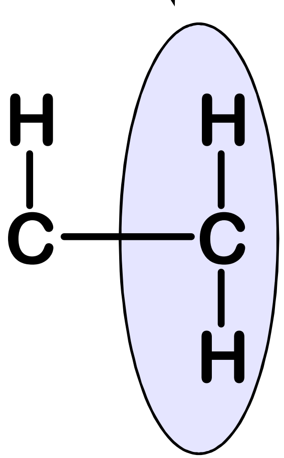


two neighbors

n+1 = 3

triplet

these hydrogens are
split by their single
neighbor

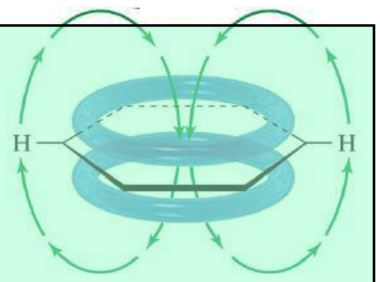


one neighbor

n+1 = 2

doublet

Where **n** is the number of **EQUIVALENT** protons on
Adjacent carbon atoms



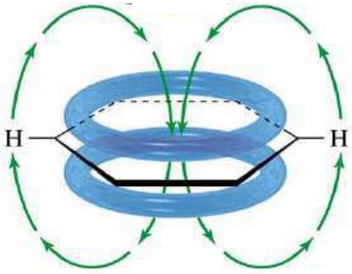
multiplicity

↓

singlet
doublet
triplet
quartet
quintet
sixtet
septet
multiplet

Simple Splitting Rule

The *N* + 1 Rule



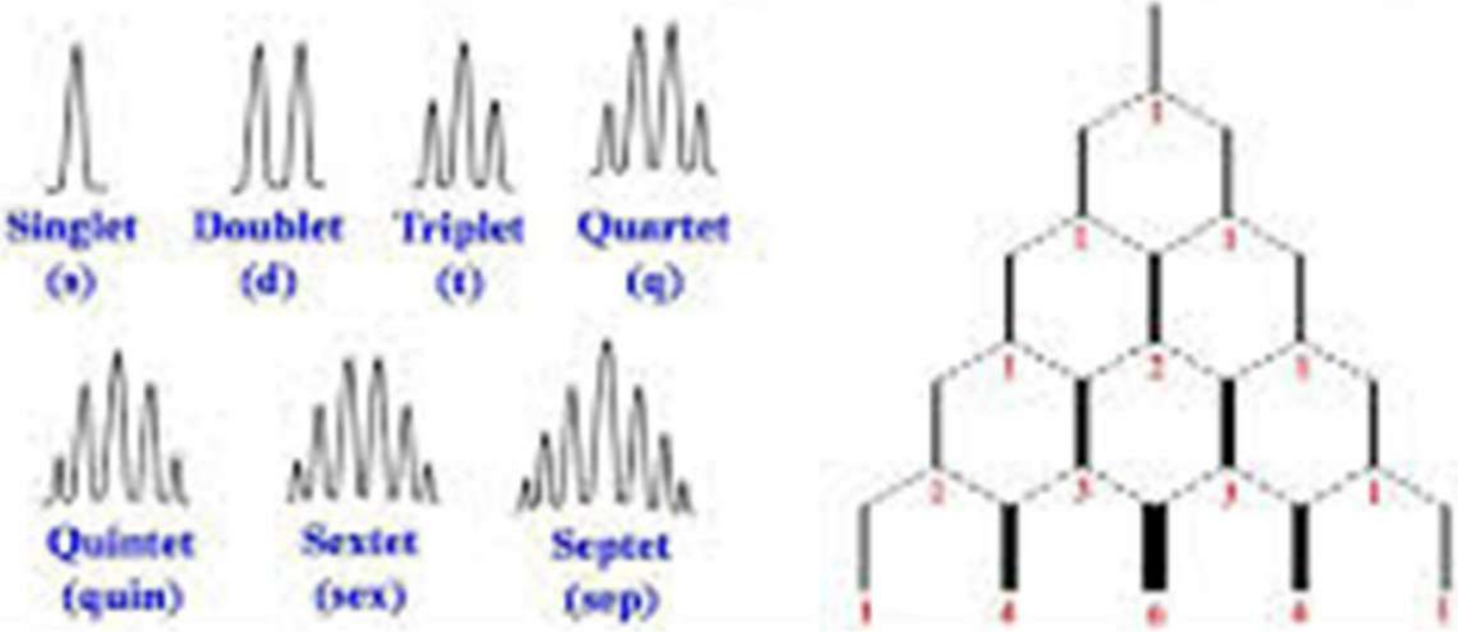
If a signal is split by *N* <u>EQUIVALENT</u> protons, it is split into *N* + 1 peaks.

Relative Peak Intensities of Symmetric Multiplets

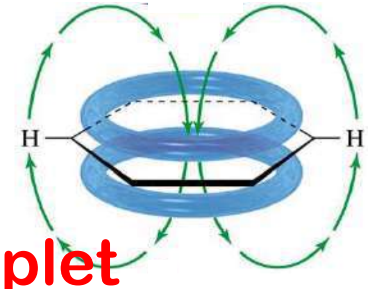
Number of Equivalent Protons Causing Splitting	*Number of Peaks (multiplicity)*	*Area Ratios (Pascal's triangle)*
0	1 (singlet)	1
1	2(doublet)	1 1
2	3 (triplet)	1 2 1
3	4 (quartet)	1 3 3 1
4	5 (quintet)	1 4 6 4 1
5	6 (sextet)	1 5 10 10 5 1
6	7 (septet)	1 6 15 20 15 6 1

=>

Multiplicity of ^{1}H NMR signals (spin-spin coupling)



SPIN-SPIN SPLITTING

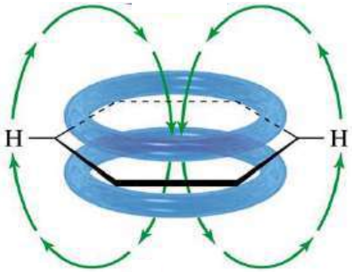


Often a group of hydrogens will appear as a multiplet rather than as a single peak.

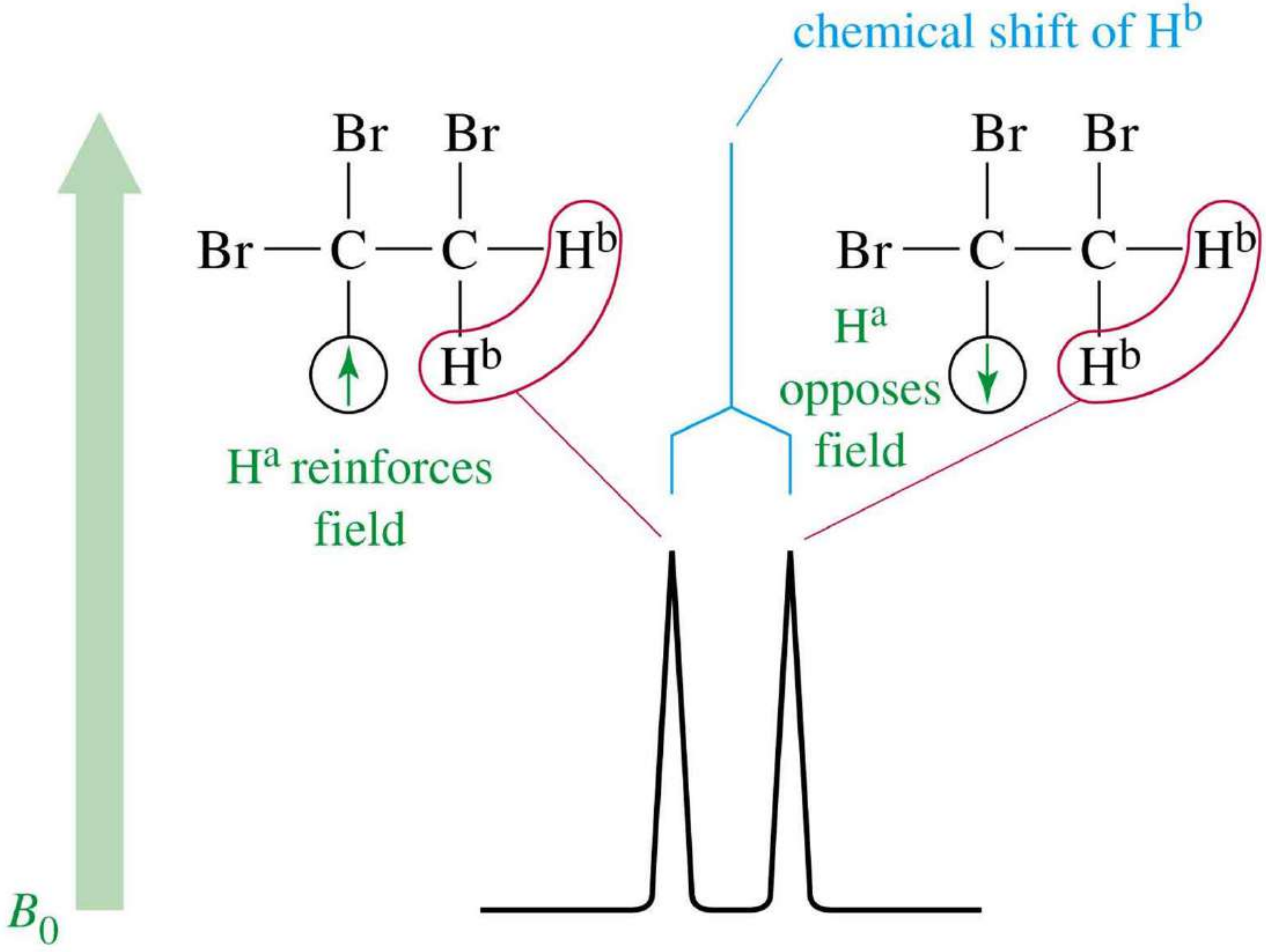
Multiplets are named as follows:

Quintet (quin)
Sixtet (six)
Septet (sept)
Multiplet (m)
Singlet (s)
Doublet (d)
Triplet (t)
Quartet (q)

This happens because of interaction with neighboring hydrogens and is called COUPLING.

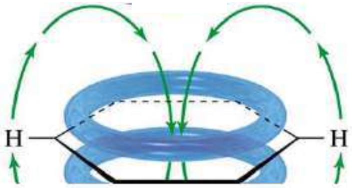


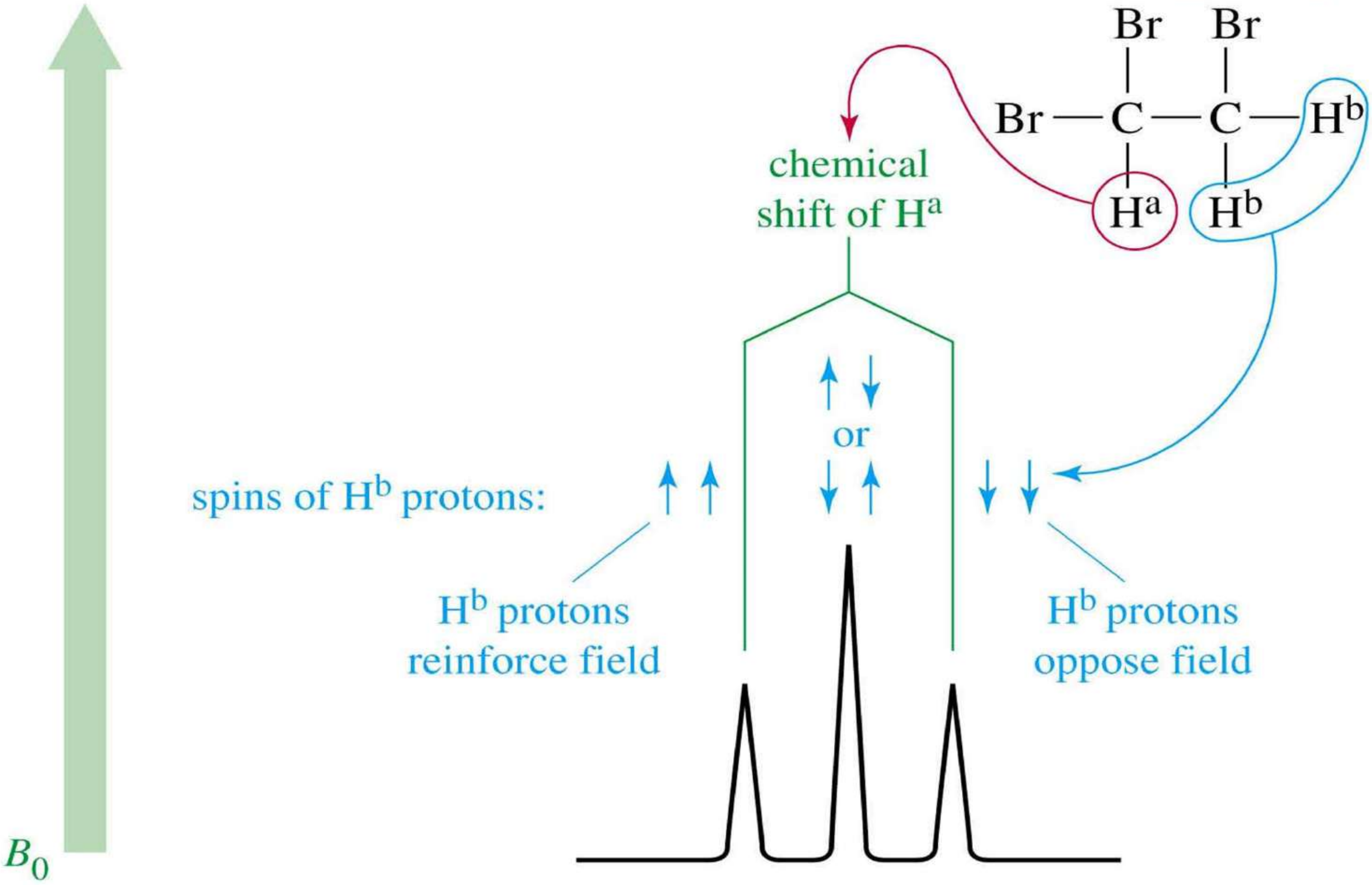
Doublet: 1 Adjacent Proton



=>

Triplet: 2 Adjacent Protons





chemical shift of H^a

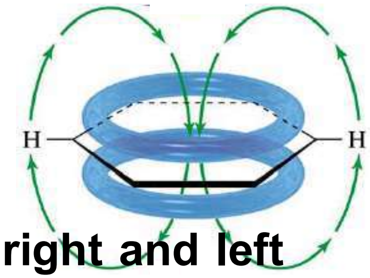
↑↓
or
↓↑

spins of H^b protons: ↑↑ ↓↓

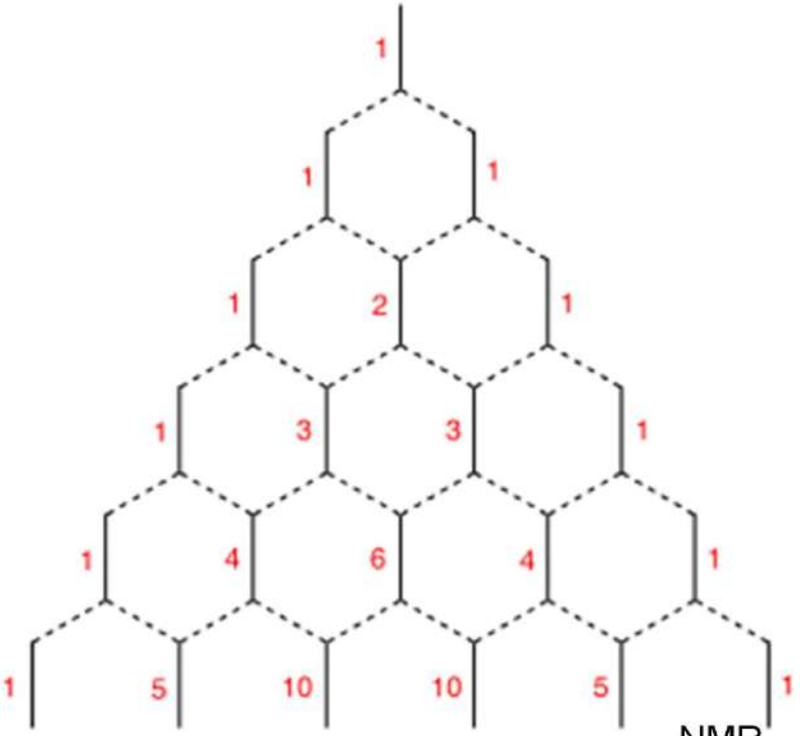
H^b protons reinforce field

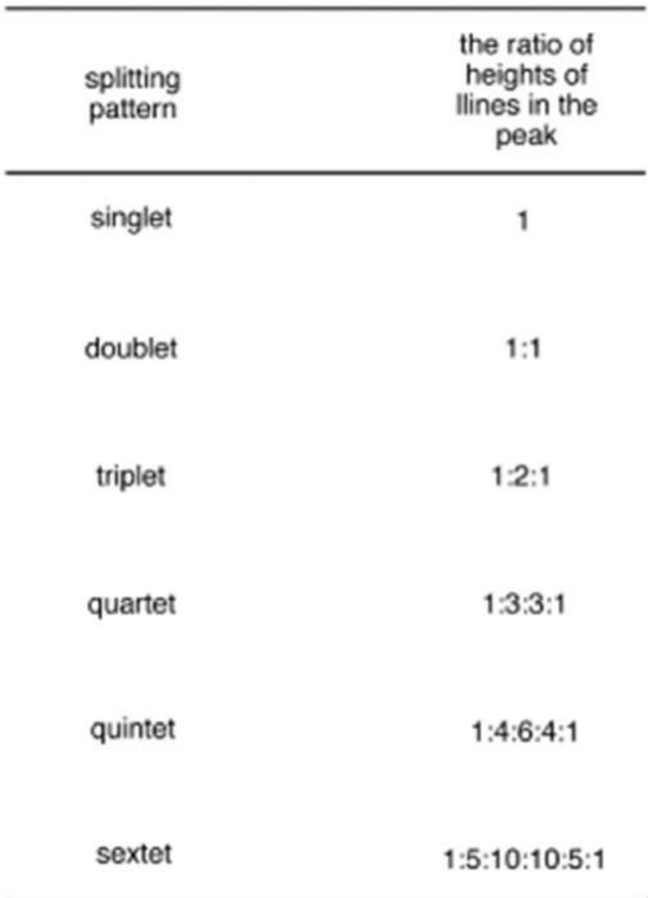
H^b protons oppose field

Splitting Pattern “Multiplicity” “Pascal Triangle”



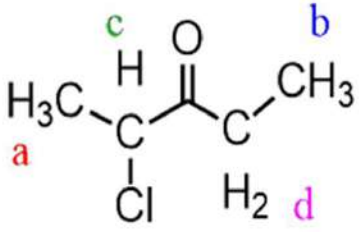
Pascal's triangle is a triangle of numbers bordered by ones on the right and left sides. Every number inside the triangle is the sum of the two numbers above it. You can use Pascal's triangle to predict the intensity ratios of proton NMR Multiplets.





splitting pattern	the ratio of heights of llines in the peak
singlet	1
doublet	1:1
triplet	1:2:1
quartet	1:3:3:1
quintet	1:4:6:4:1
sextet	1:5:10:10:5:1

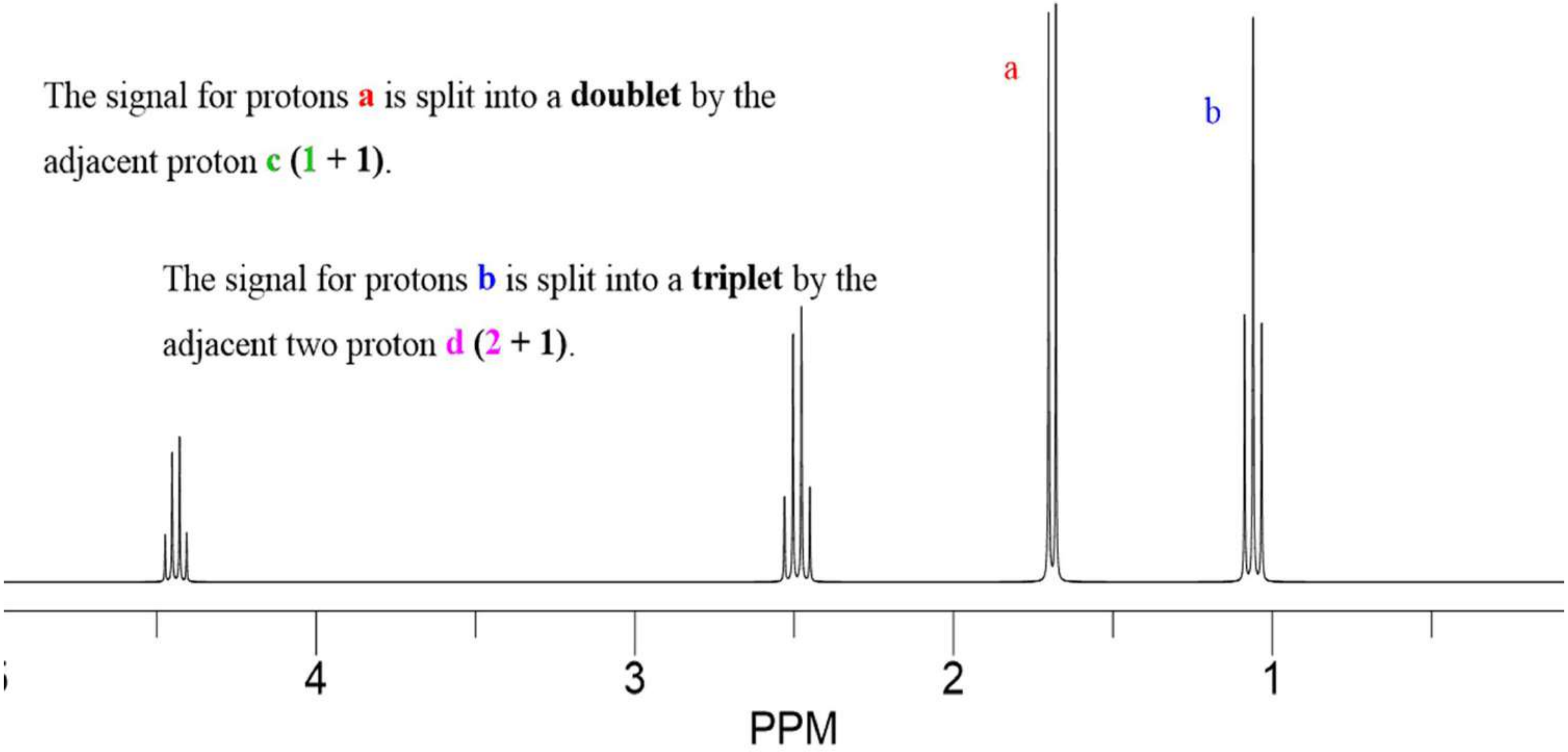
How do we distinguish between the two methyl groups in the following molecule?



They are both next to electron-withdrawing groups with comparable power and they will both have the same integration. This is where the spin splitting gets into play as, based on it, one of the methyls is expected to be a triplet and the other - a doublet (n+1 rule).

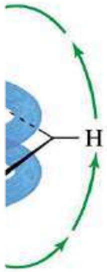
The signal for protons **a** is split into a **doublet** by the adjacent proton **c** **(1 + 1)**.

The signal for protons **b** is split into a **triplet** by the adjacent two proton **d** **(2 + 1)**.



$Cl\text{-}CH_2\text{-}CH_2\text{-}Cl$

a

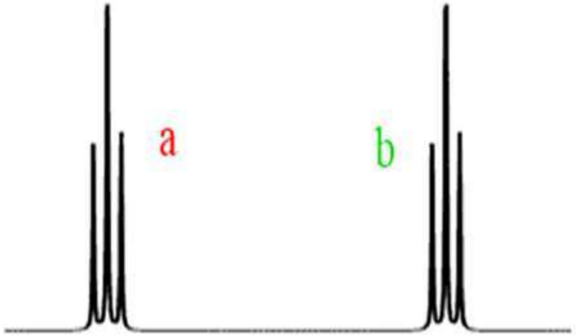


All the ***protons are equivalent*** *(H_a), so there is* ***no splitting*** *and the NMR signal is one* ***singlet****.*

$Cl\text{-}CH_2\text{-}CH_2\text{-}Br$

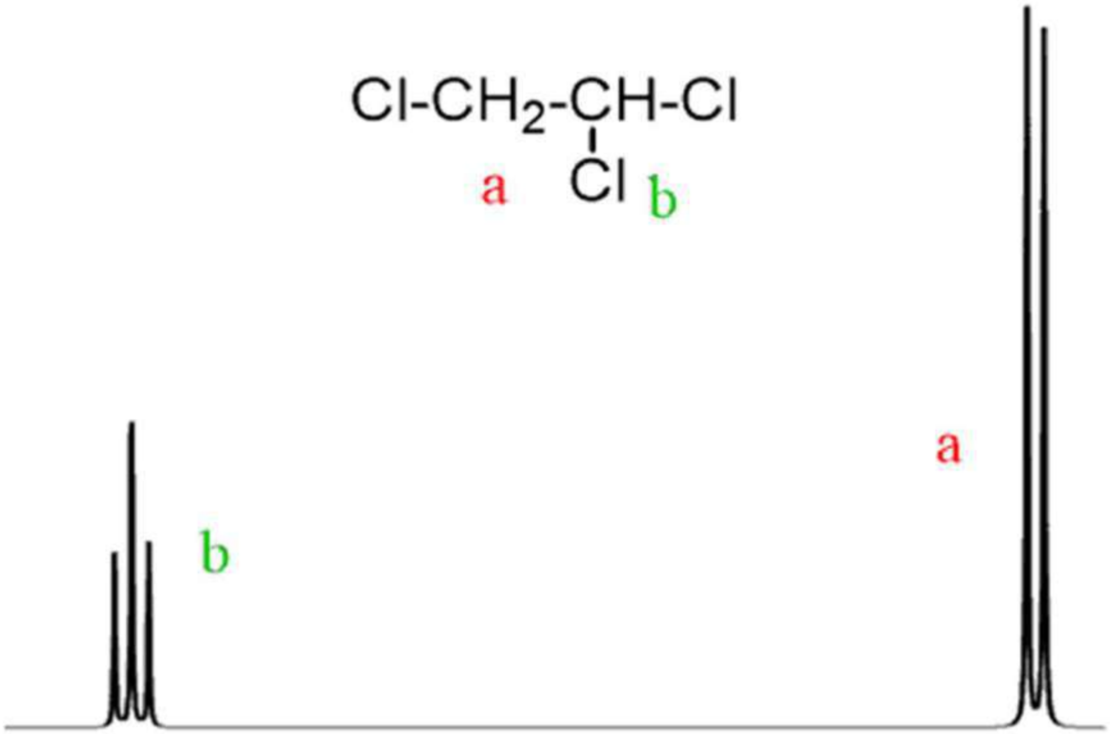
a b

Ha protons are nonequivalent to Hb but they are equivalent to themselves. . That's why the signal is split only by Hb.



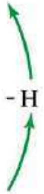
Hb protons are nonequivalent to Ha but they are equivalent to themselves. That's why the signal is split only by Ha.

There are **two NMR signals**. Bacause of different halogens, H_a and H_b are **nonequivalent** and split each other's NMR signals into **triplets** since **there are two Ha** and **two Hb protons (n+1).**

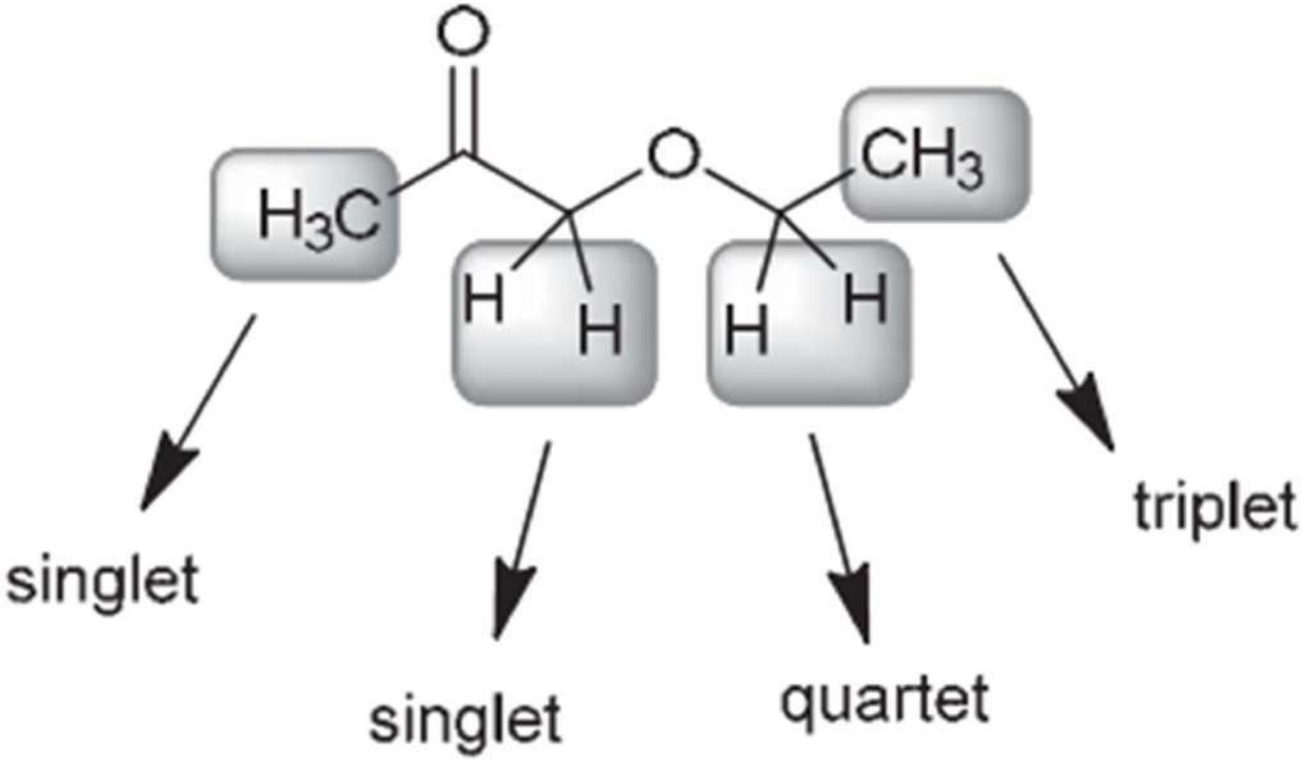

$Cl\text{-}CH_2\text{-}\underset{Cl}{CH}\text{-}Cl$

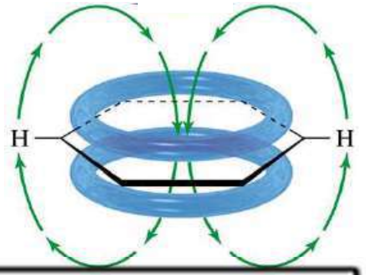
The two NMR signals originate from two sets of nonequivalent protons.

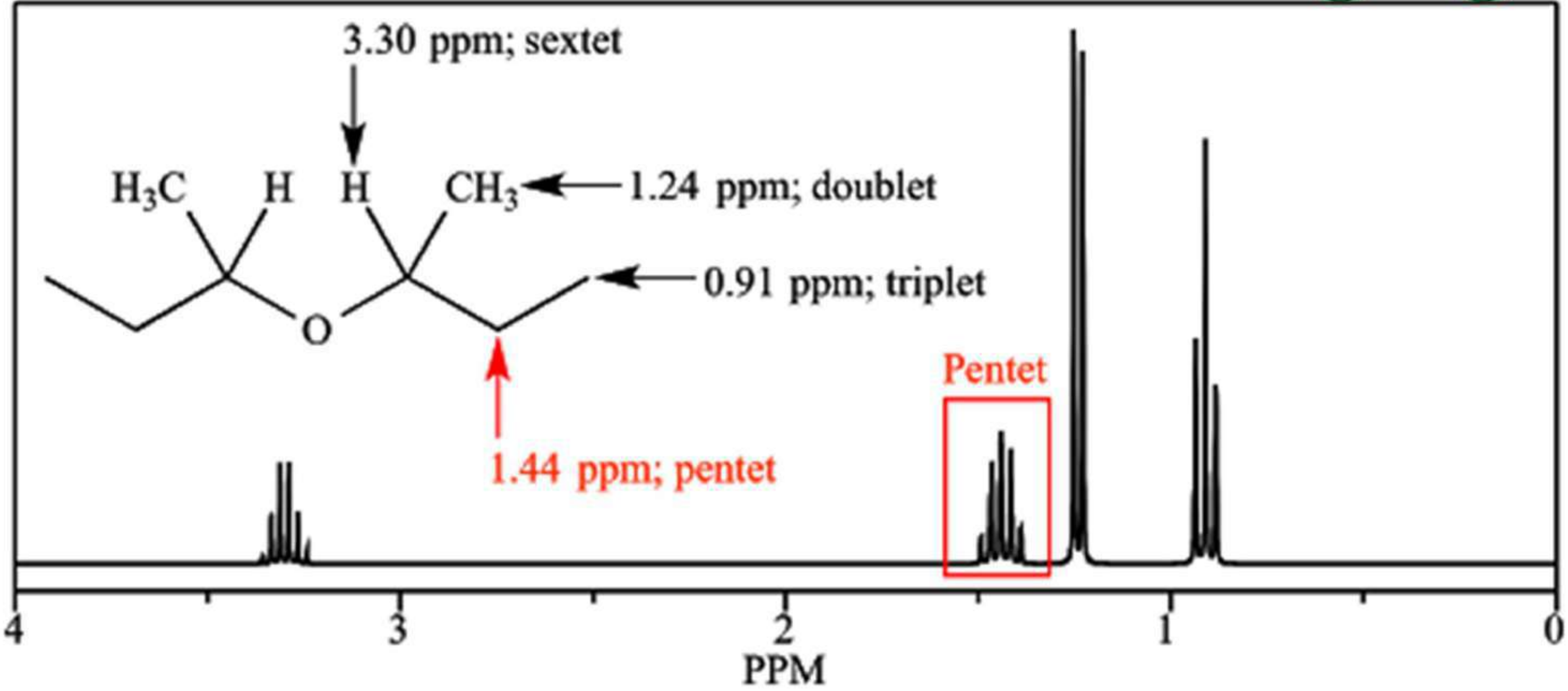
The two **H_a protons split the signal of Hb into a triplet**, while the **H_b proton splits the H_a** signal into a **doublet** according to the **n+1 rule**.



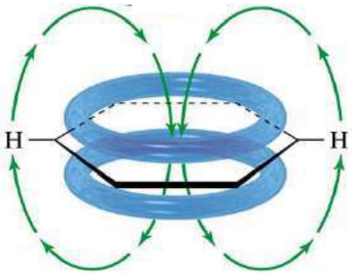
This compound has four different kinds of protons, highlighted here. In each case, we apply the n+1 rule, giving the multiplicities shown:



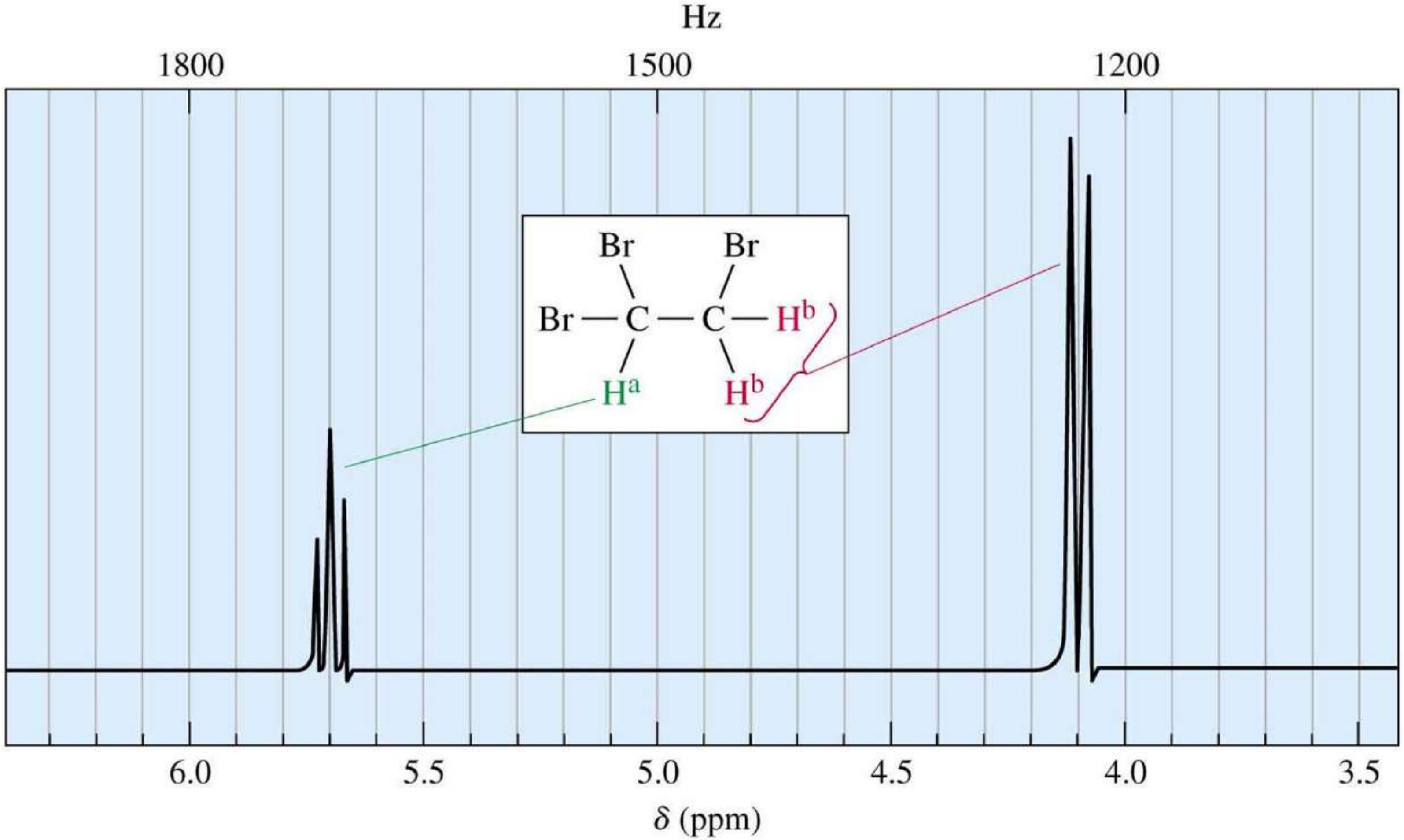

H
H

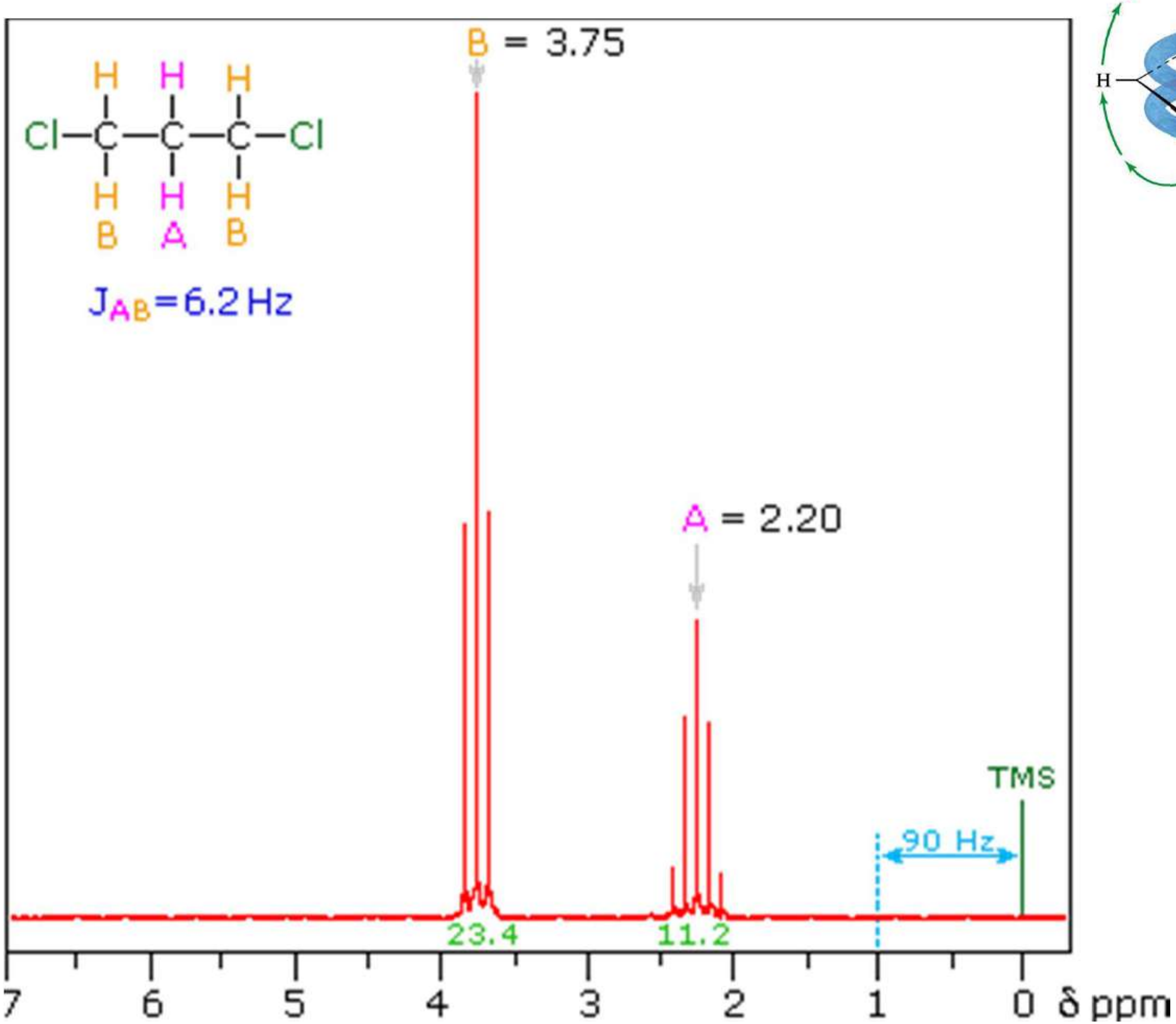

3.30 ppm; sextet
H₃C
H
H
CH₃
1.24 ppm; doublet
0.91 ppm; triplet
O
1.44 ppm; pentet
Pentet
4
3
2
1
0
PPM

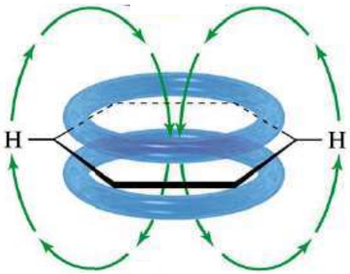
1,1,2-Tribromoethane



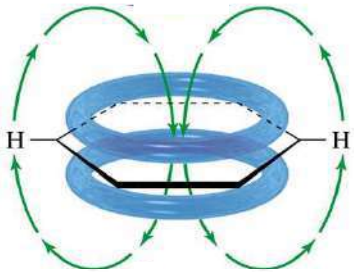
Nonequivalent protons on adjacent carbons.

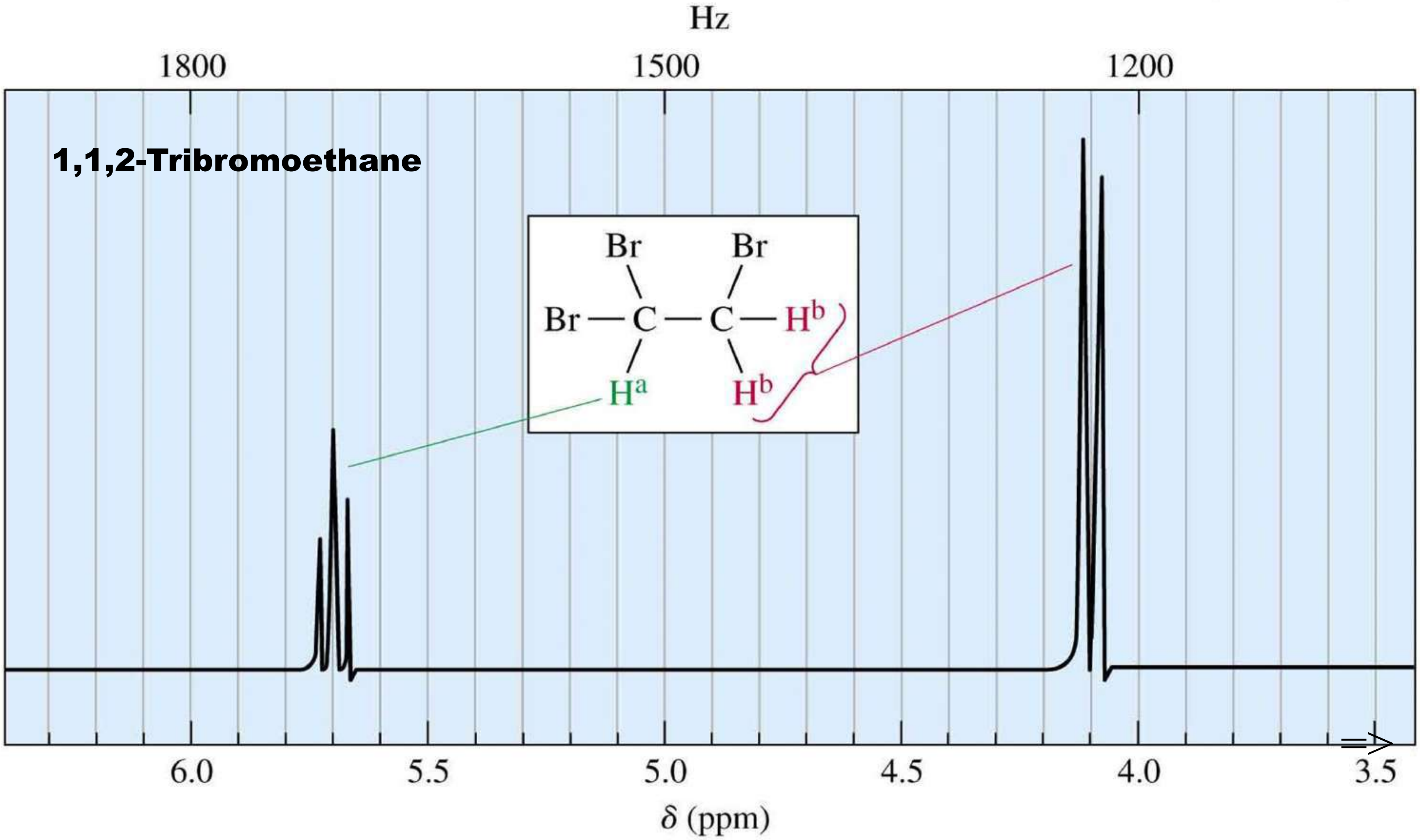



H H H
Cl–C–C–C–Cl
H H H
B A B
J_AB = 6.2 Hz
B = 3.75
A = 2.20
TMS
90 Hz
23.4
11.2
7
6
5
4
3
2
1
0
δ ppm


H
H

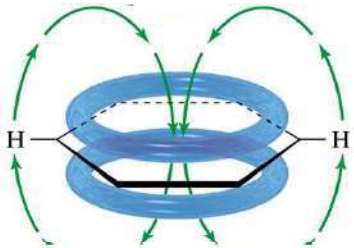
Nonequivalent protons on adjacent carbons.

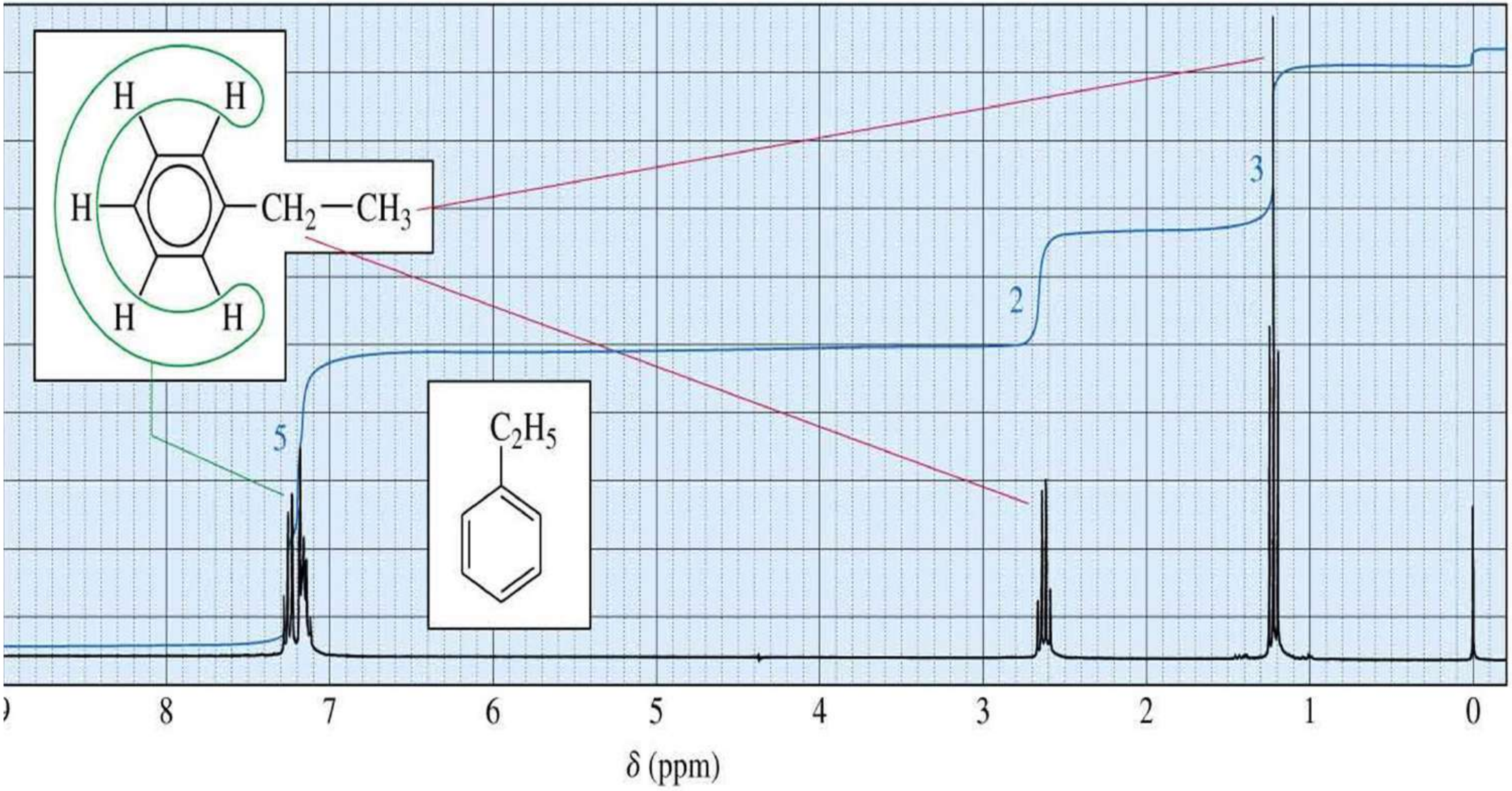




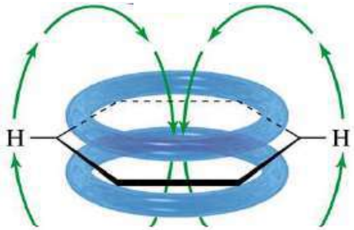
=>

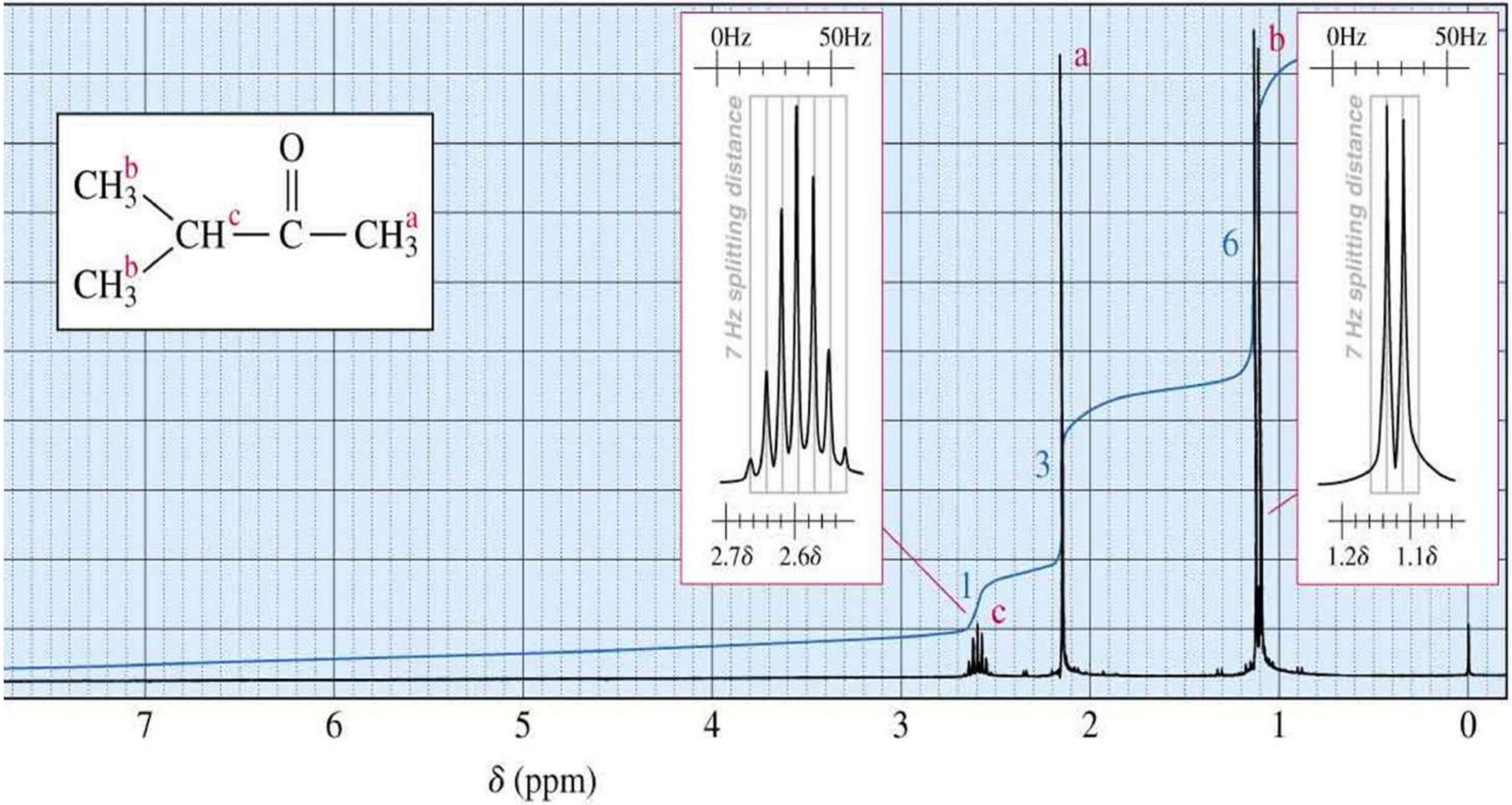
Splitting for Ethyl Groups



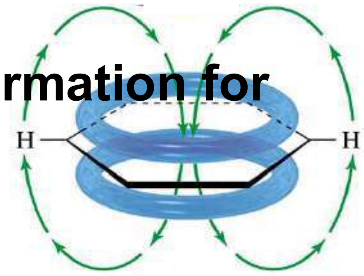


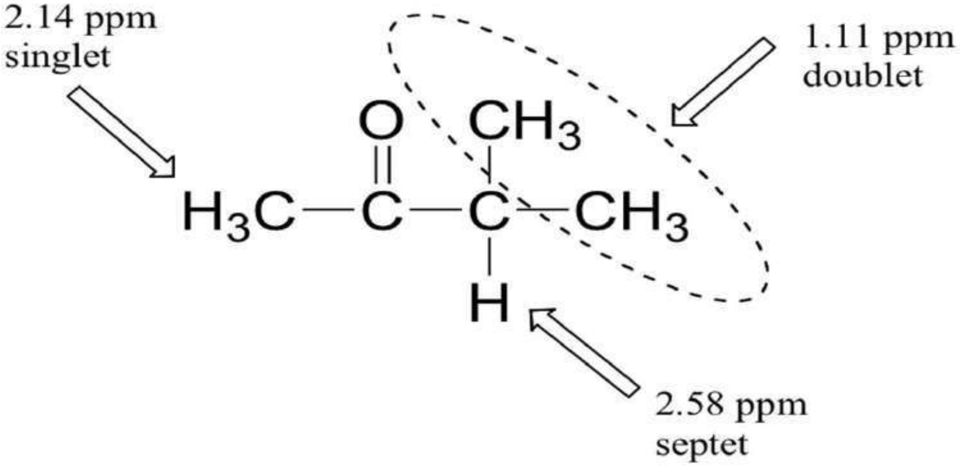
Splitting for Isopropyl Groups





Few more examples of chemical shift and splitting pattern information for some relatively simple organic molecules.



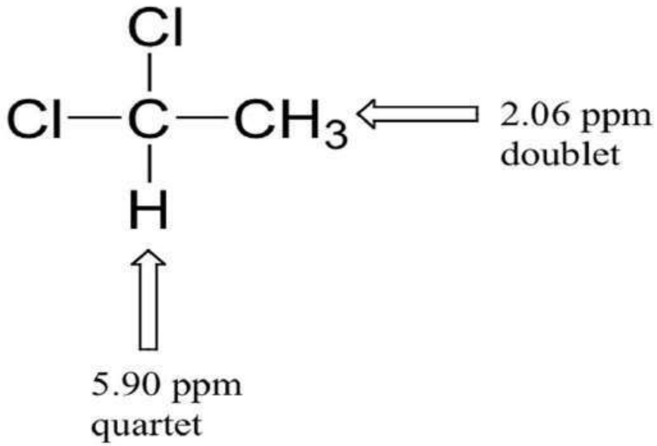


$H_3C-C(=O)-CH(CH_3)-CH_3$

2.14 ppm singlet

1.11 ppm doublet

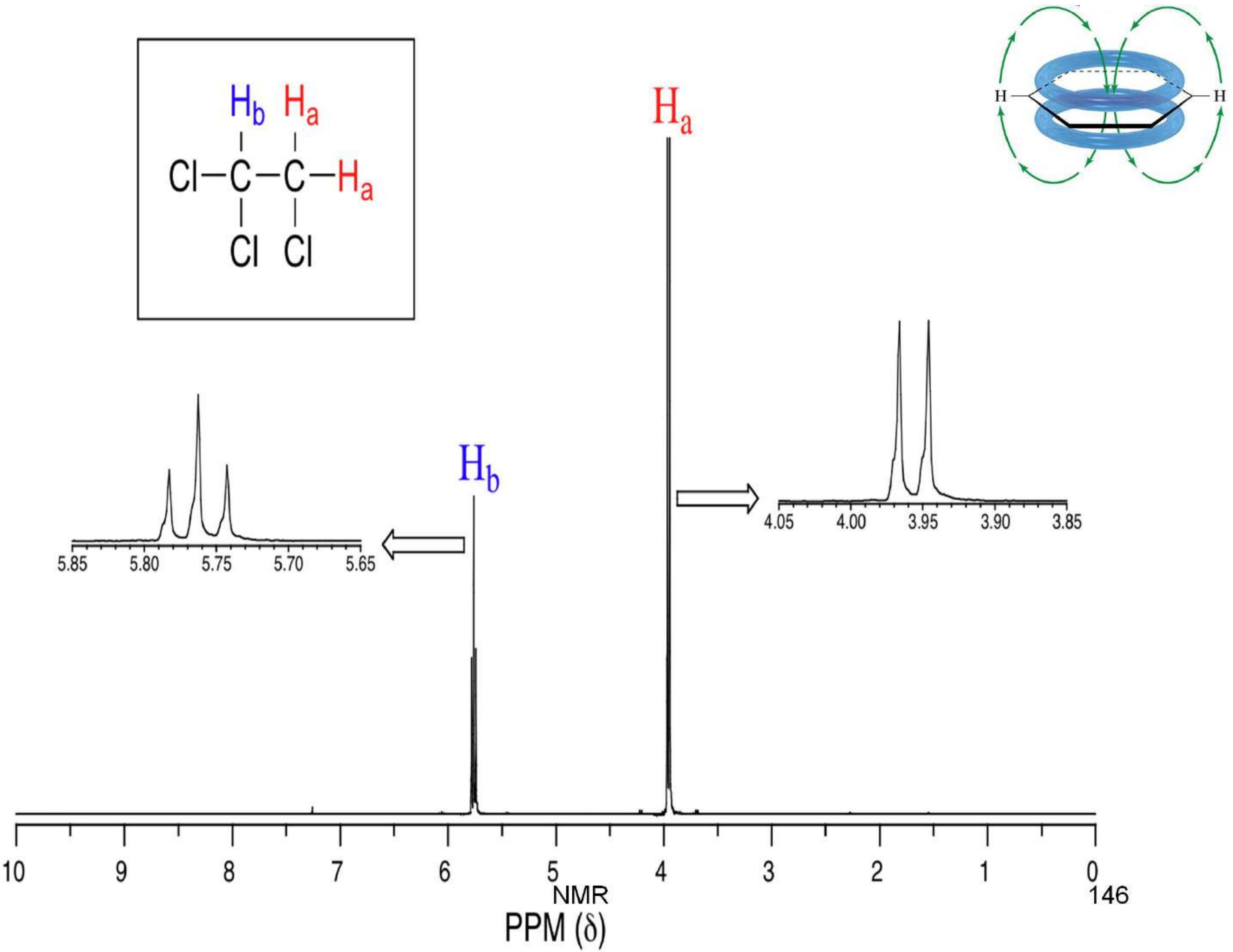
2.58 ppm septet

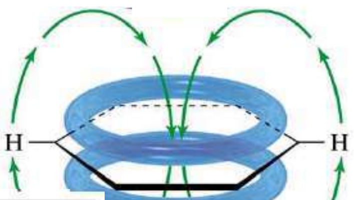


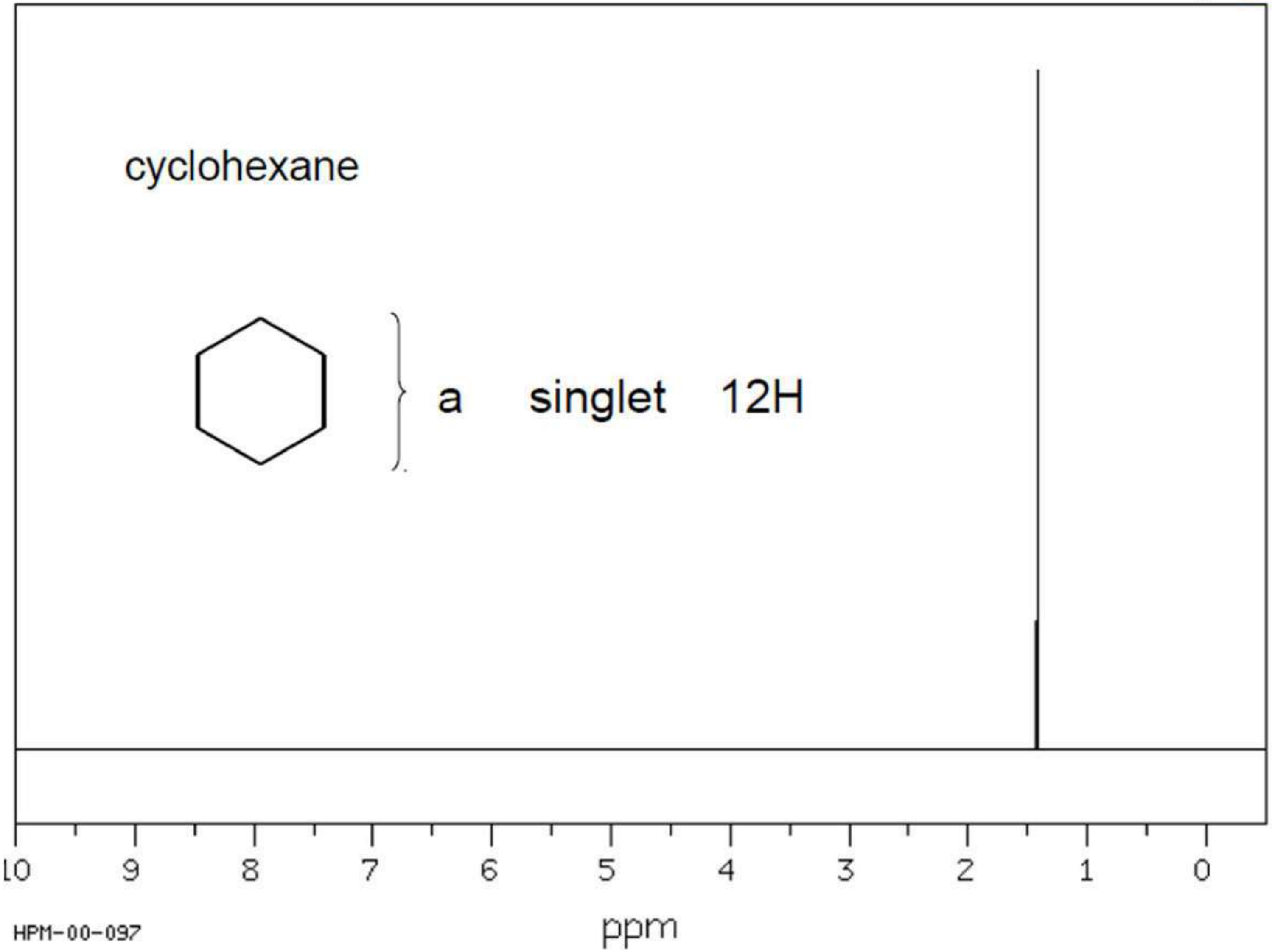
Cl_2CH-CH_3

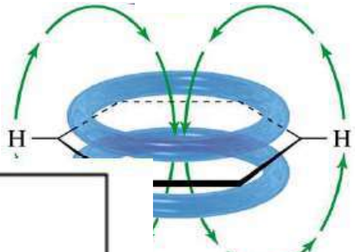
2.06 ppm doublet

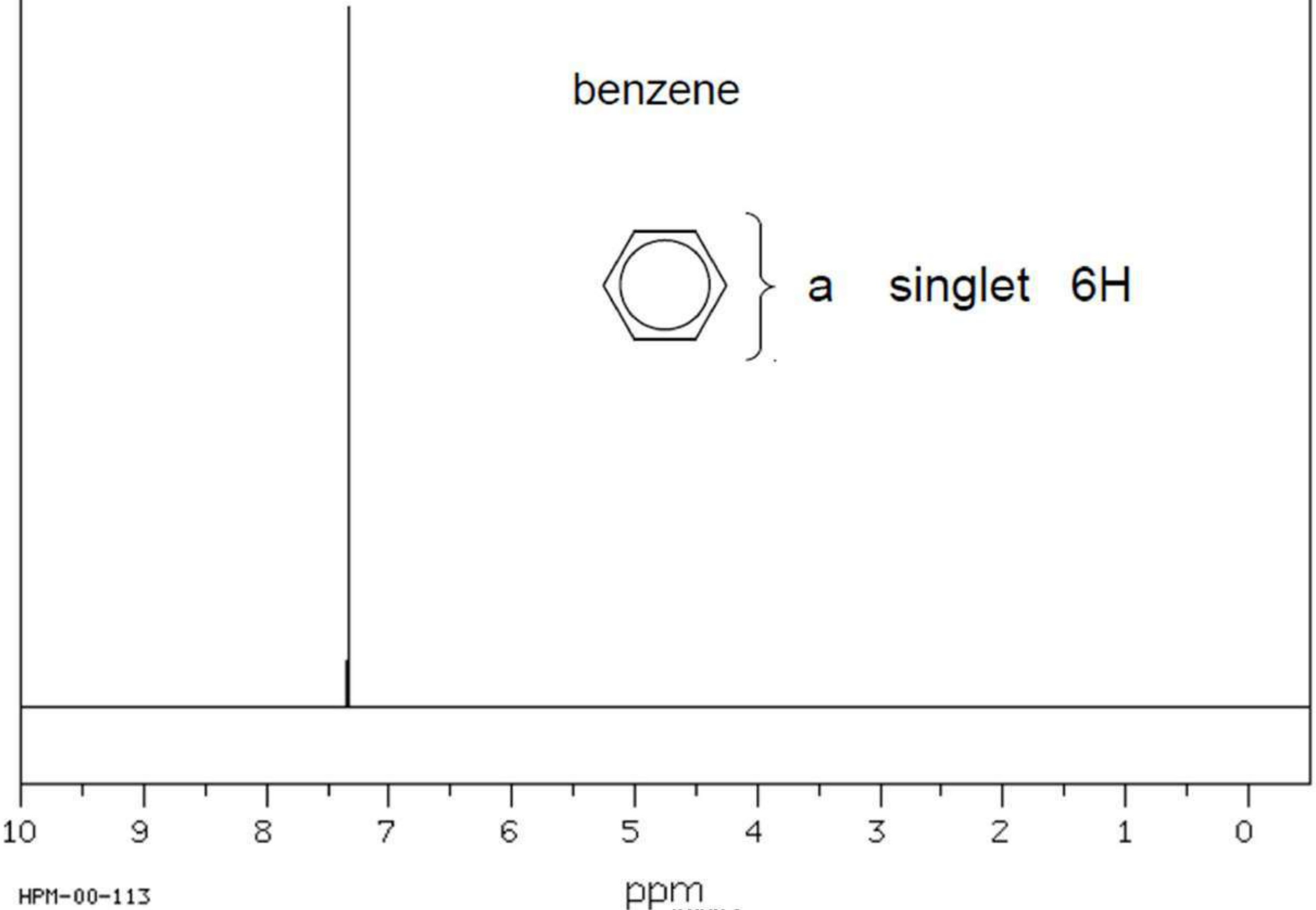
5.90 ppm quartet

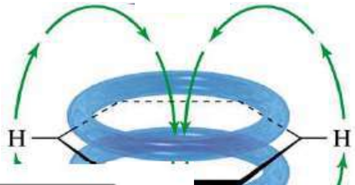

H
H
Hb
Ha
Cl
C
C
Ha
Cl
Cl
Ha
Hb
5.85
5.80
5.75
5.70
5.65
4.05
4.00
3.95
3.90
3.85
10
9
8
7
6
5
4
3
2
1
0
PPM (δ)

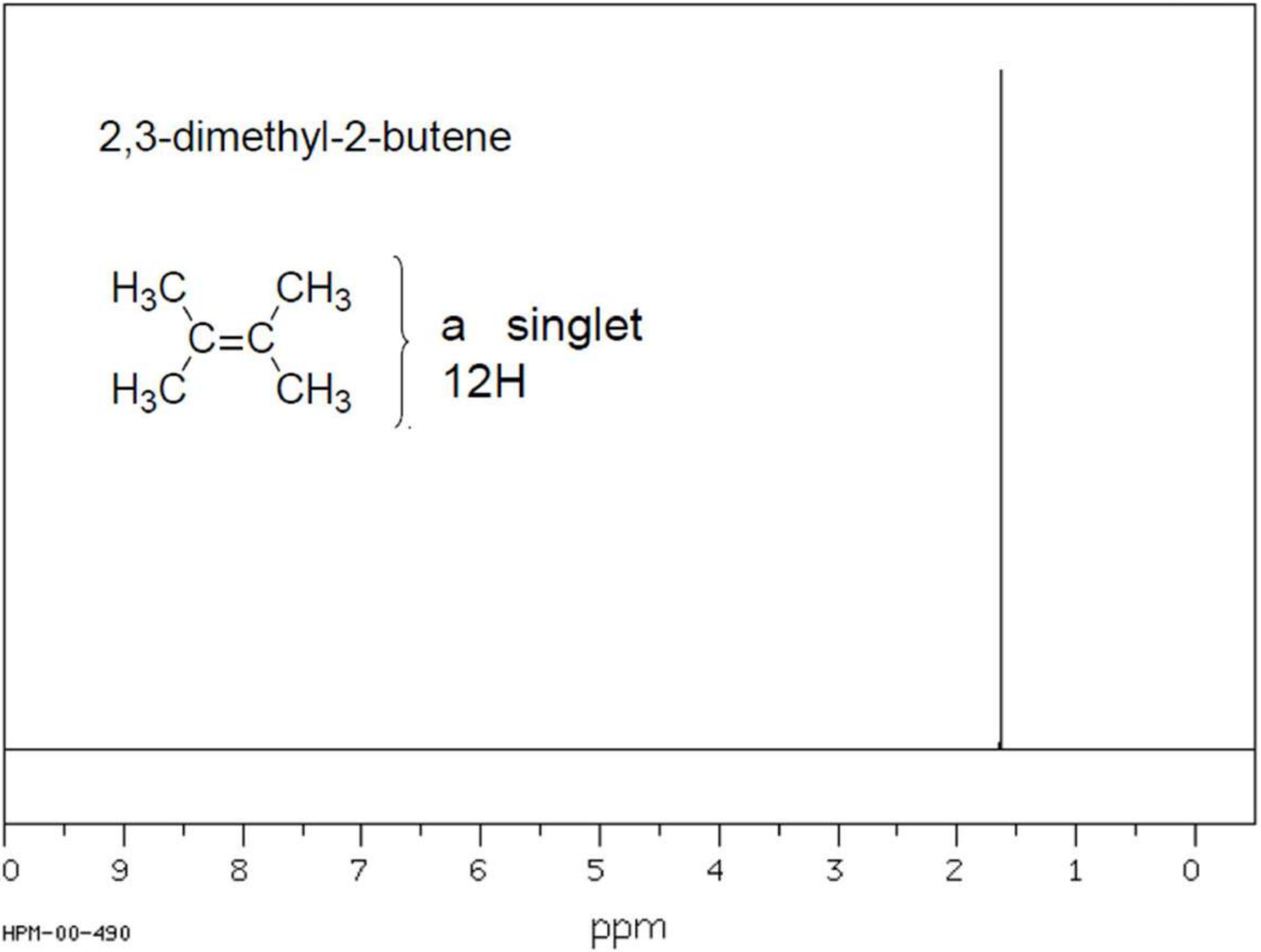

H
H


cyclohexane
a singlet 12H
10
9
8
7
6
5
4
3
2
1
0
ppm
HPM-00-097


H
H

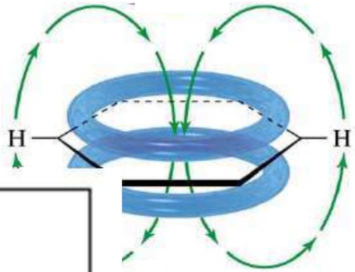

benzene
a singlet 6H
10
9
8
7
6
5
4
3
2
1
0
ppm
HPM-00-113

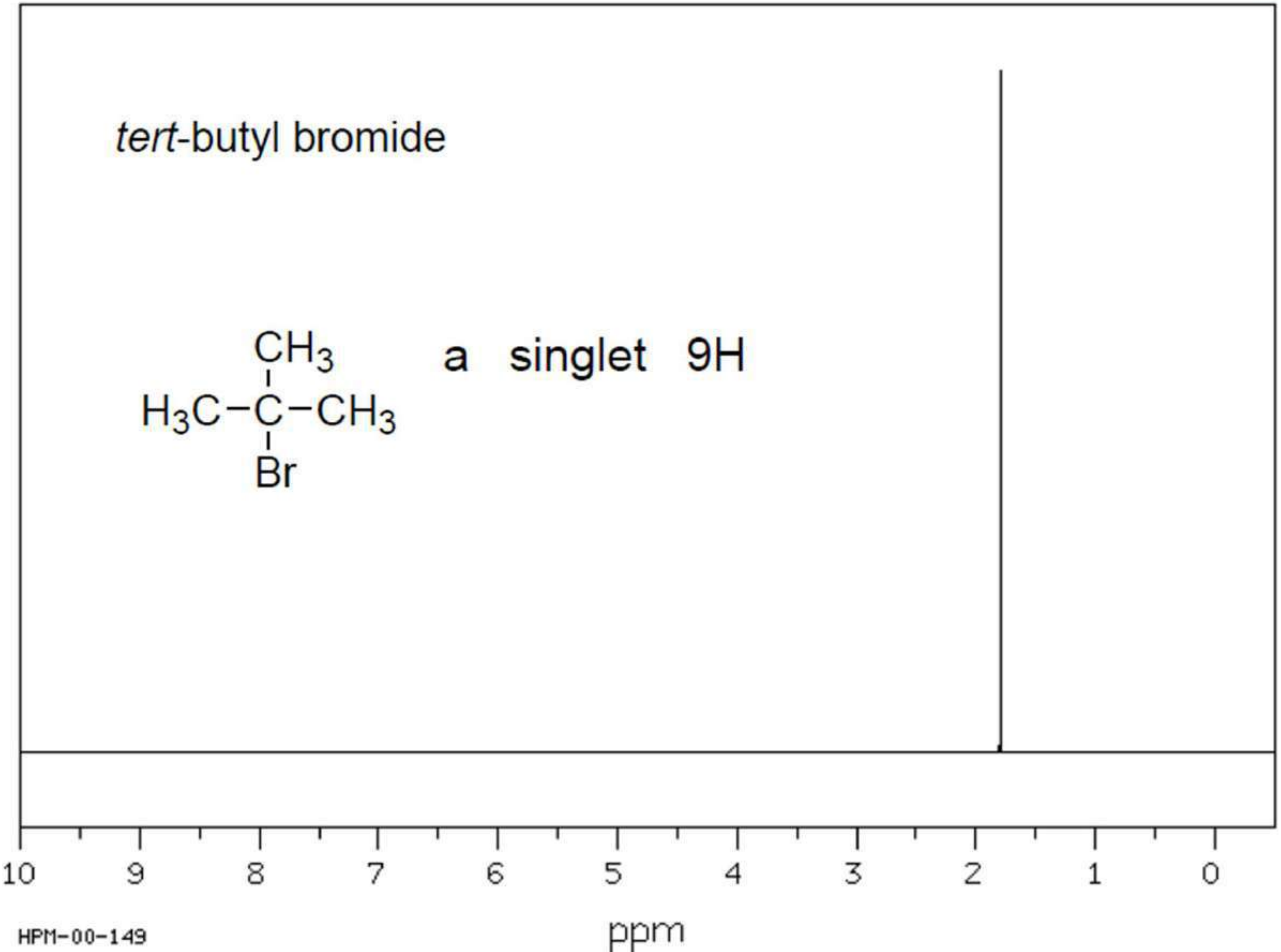


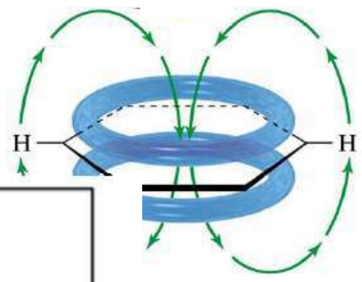


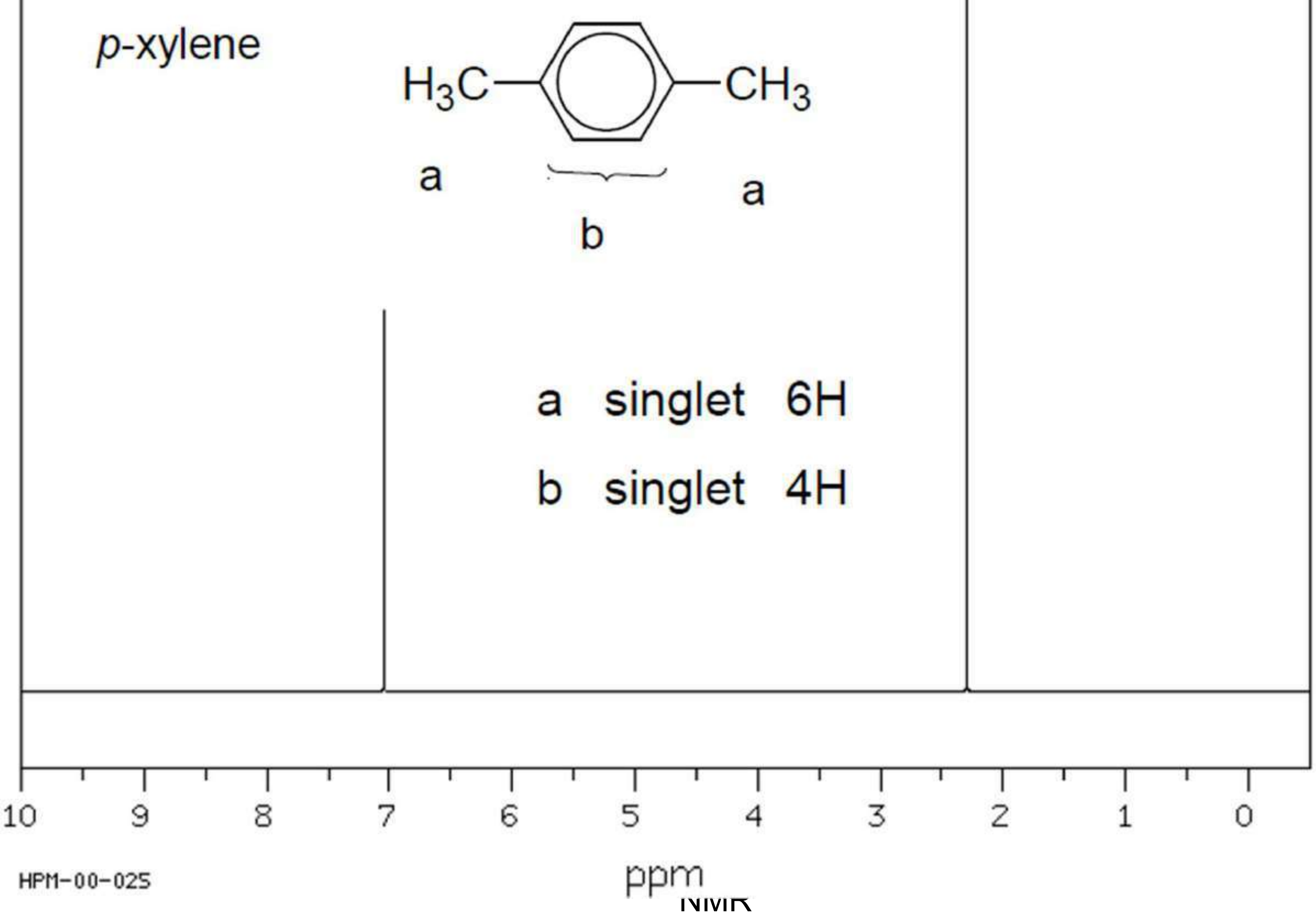
2,3-dimethyl-2-butene

a singlet
12H


H
H

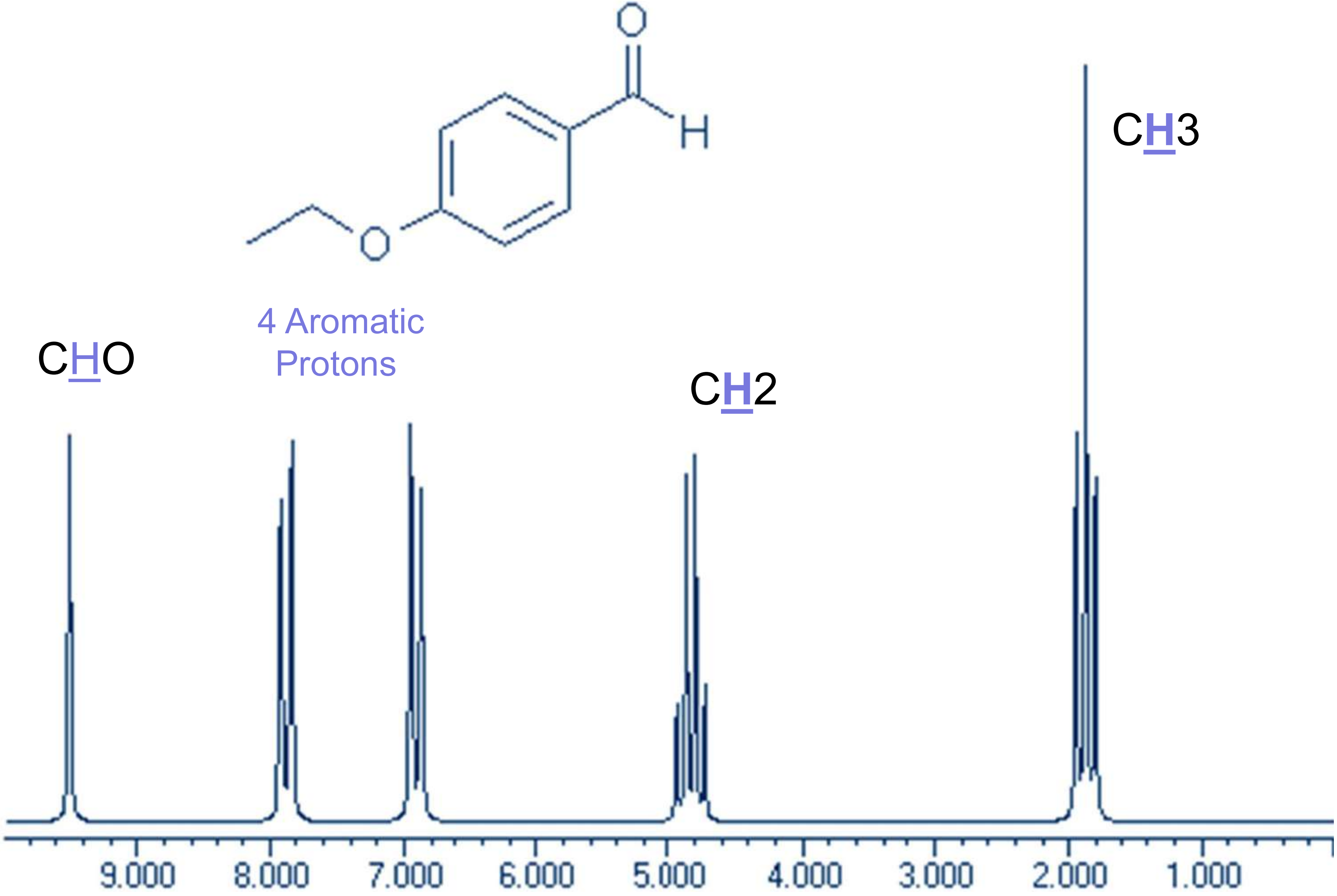

tert-butyl bromide
CH3
H3C−C−CH3
Br
a singlet 9H
10
9
8
7
6
5
4
3
2
1
0
ppm
HPM-00-149

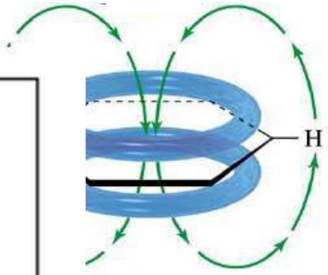


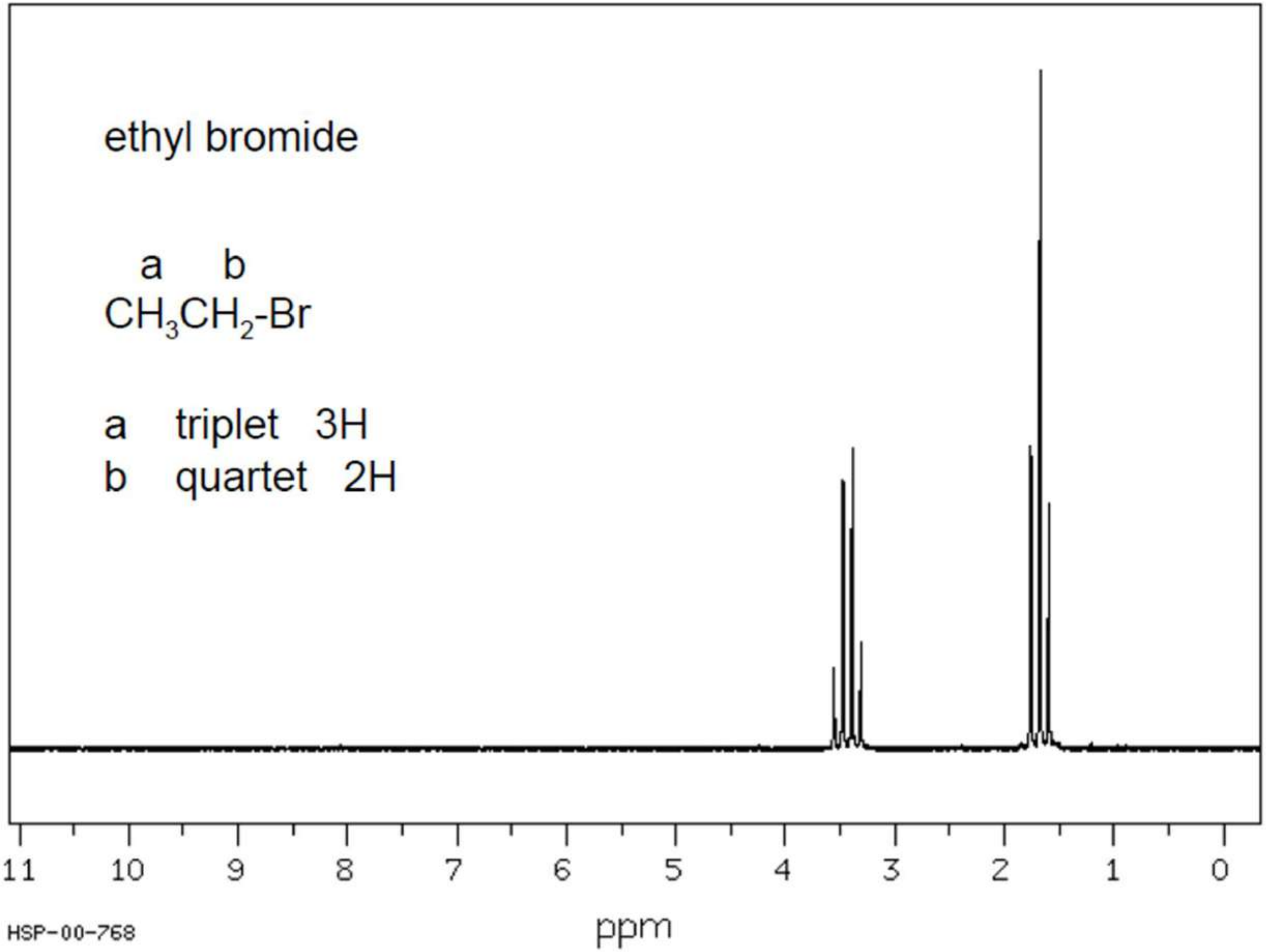


a singlet 6H

b singlet 4H


CHO
4 Aromatic Protons
CH2
CH3
O
H
O
9.000
8.000
7.000
6.000
5.000
4.000
3.000
2.000
1.000





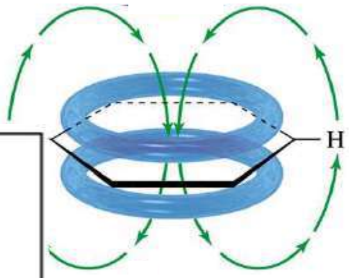
ethyl bromide

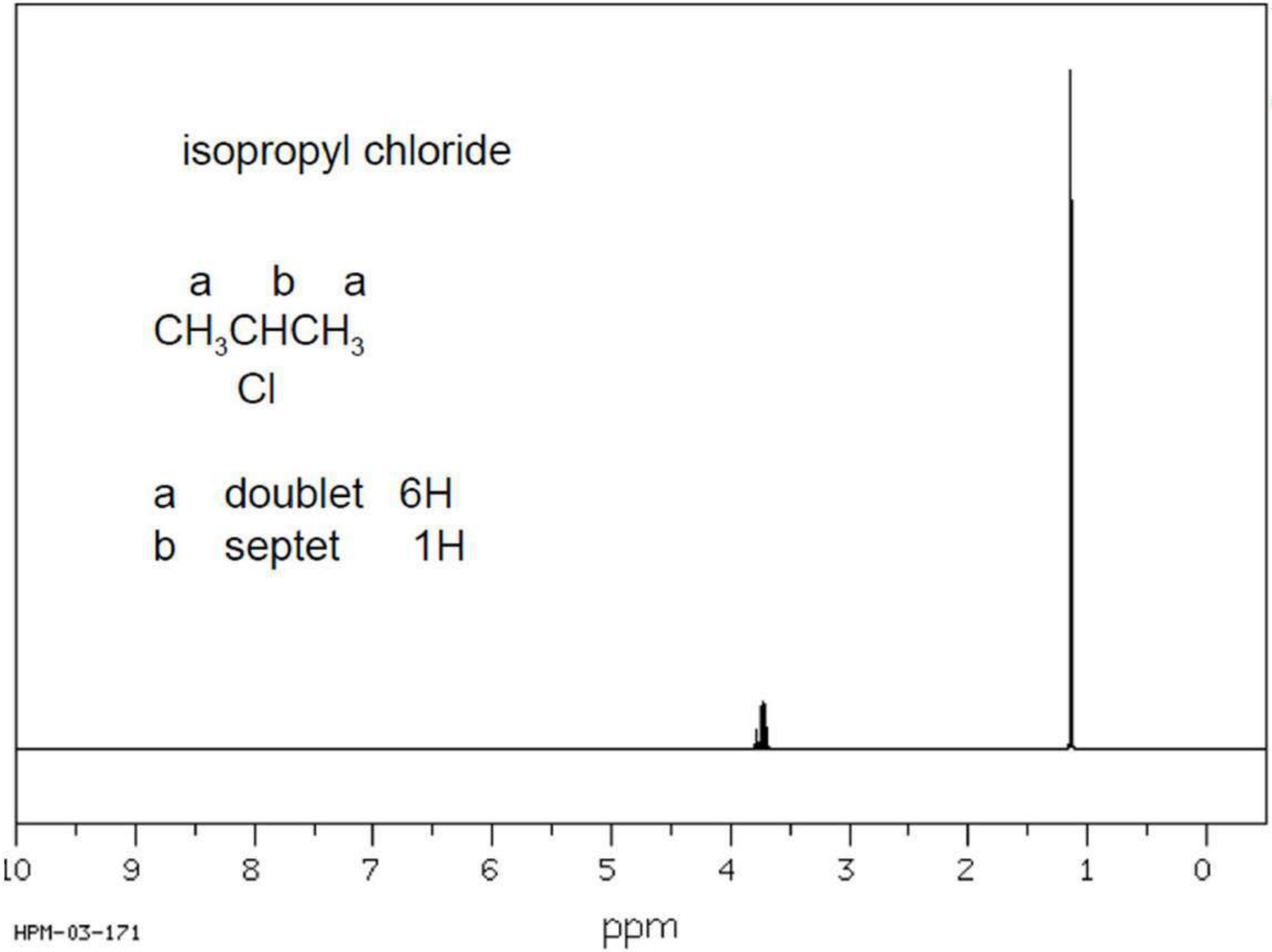
a b

CH_3CH_2-Br

a triplet 3H

b quartet 2H





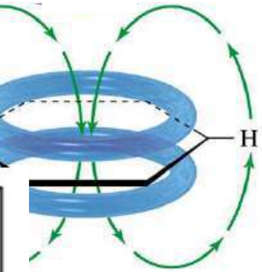
isopropyl chloride

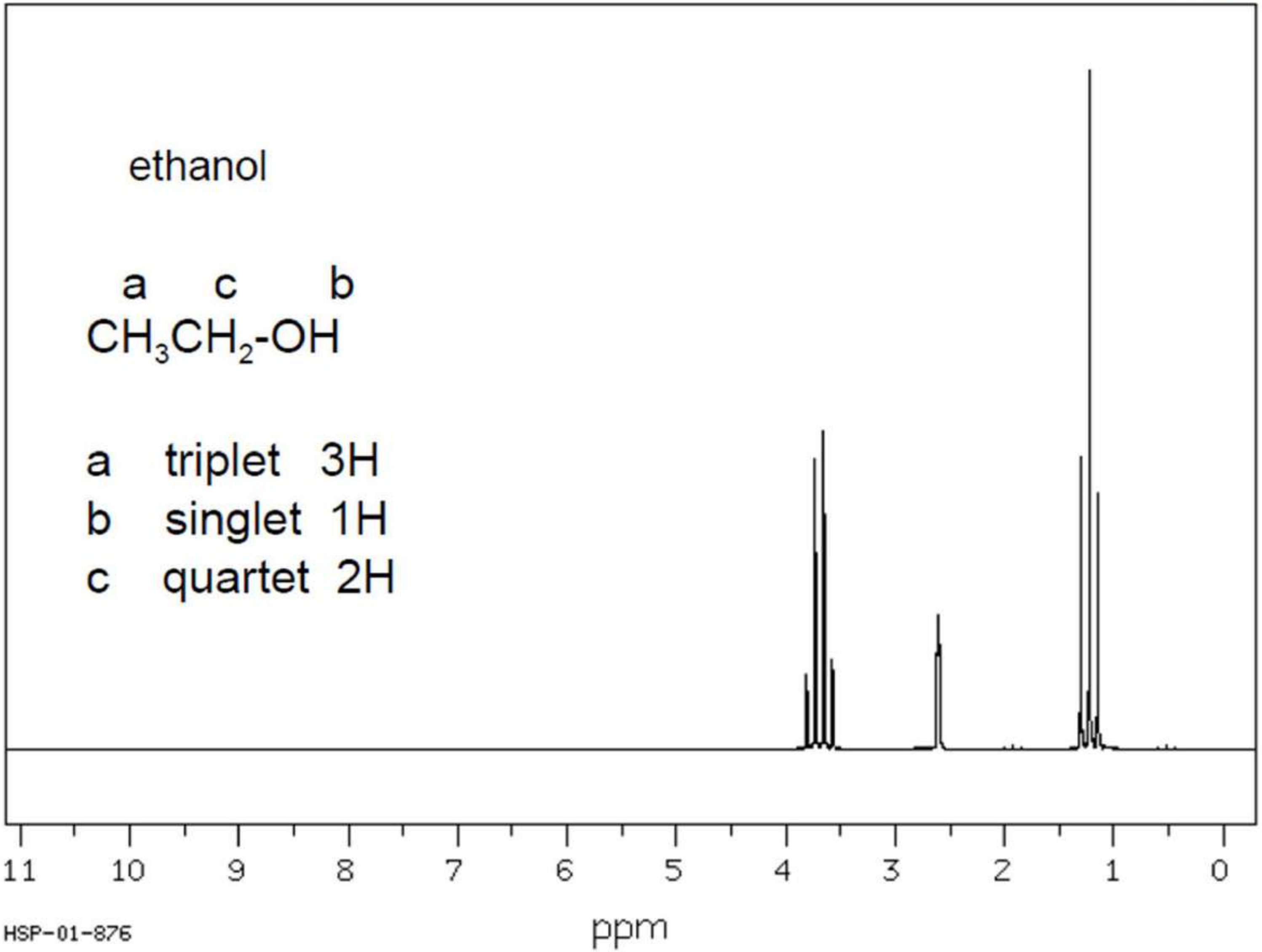
a b a

CH_3CHCH_3

Cl

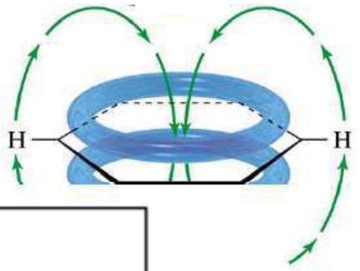
a	doublet	6H
b	septet	1H

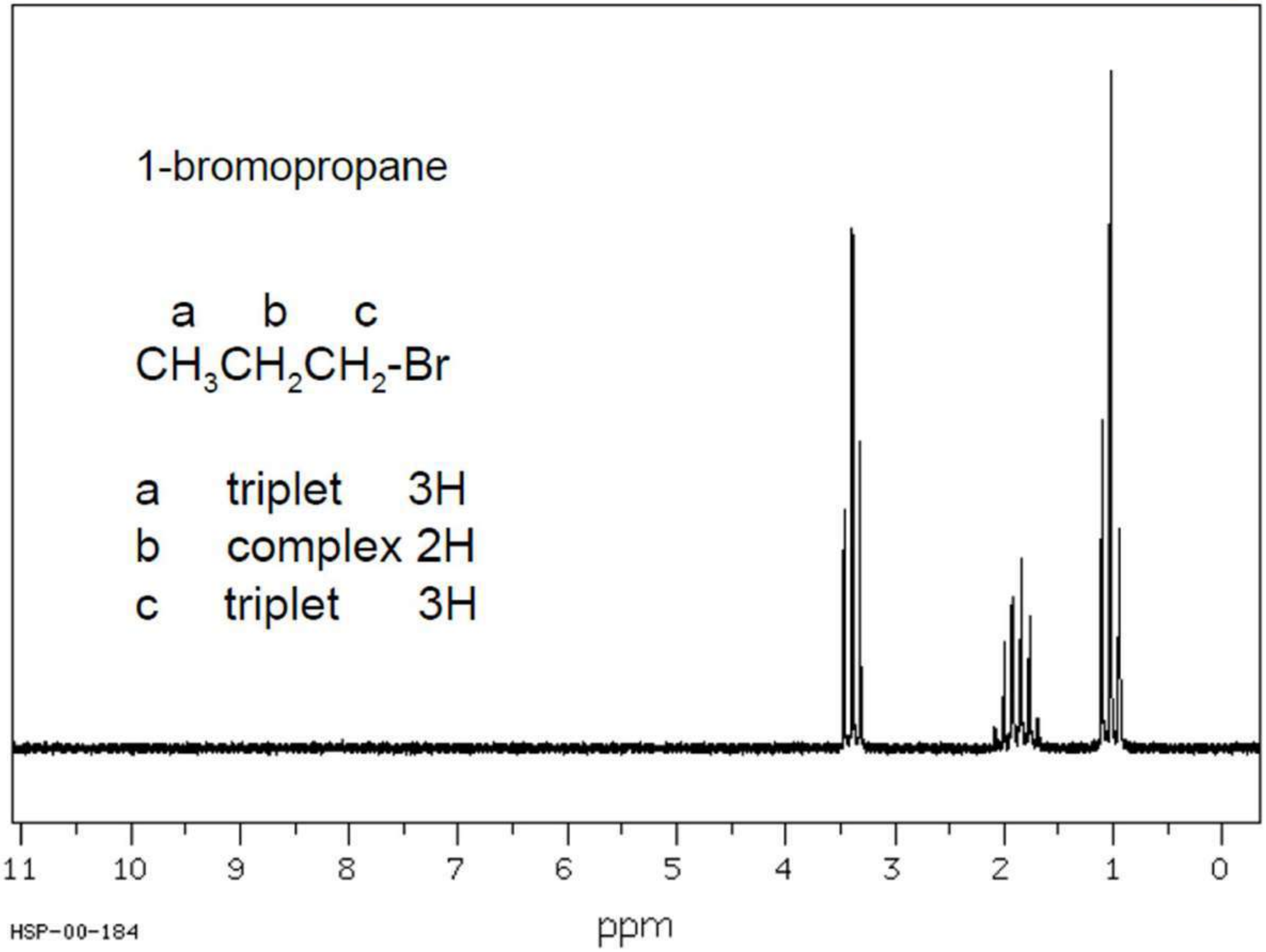



ethanol

a c b
CH_3CH_2-OH

a triplet 3H
b singlet 1H
c quartet 2H



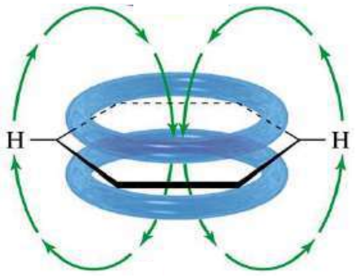


1-bromopropane

a b c

$CH_3CH_2CH_2$-Br

a triplet 3H
b complex 2H
c triplet 3H

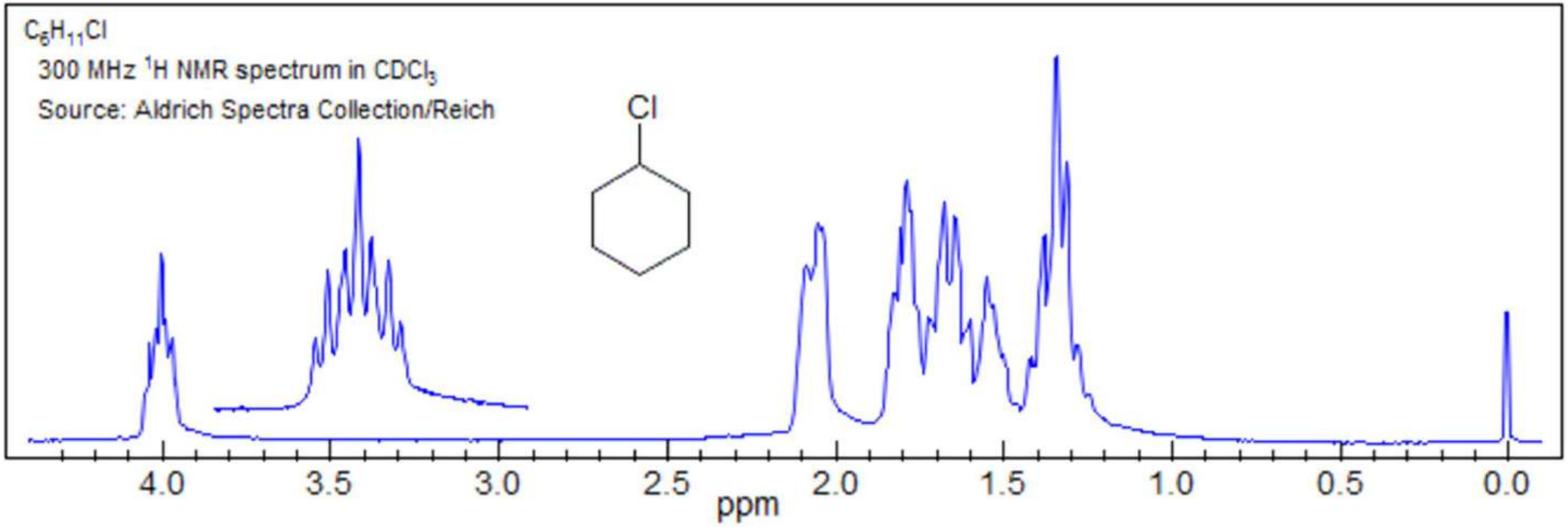


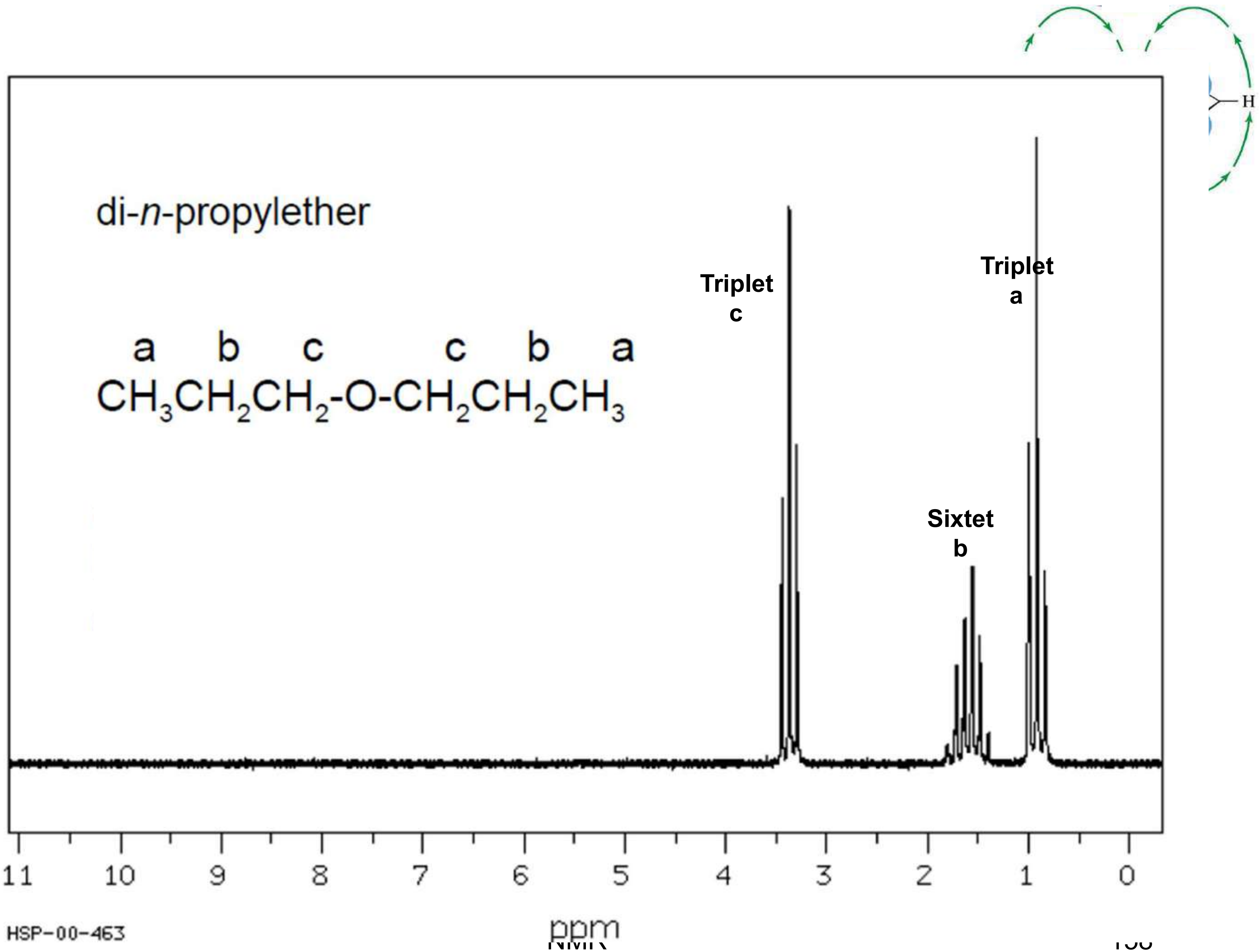
NOTE:-

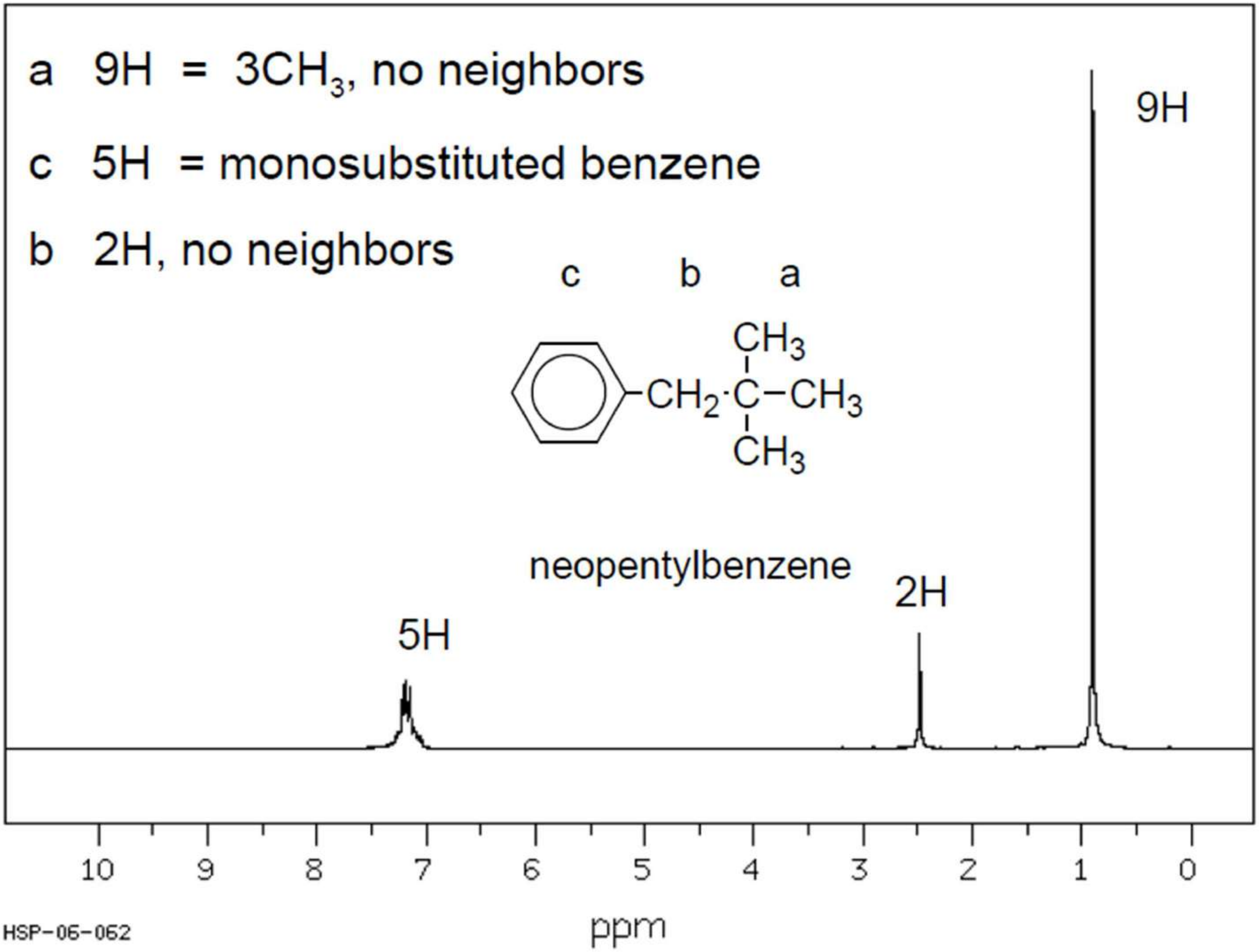
Many times; it is difficult to specify the peaks and which is which!!!!!!

so what we can do???

2D nmr, mass spec …etc




di-*n*-propylether
a b c c b a
$CH_3CH_2CH_2\text{-}O\text{-}CH_2CH_2CH_3$
Triplet
c
Sixtet
b
Triplet
a
H
11
10
9
8
7
6
5
4
3
2
1
0
ppm
HSP-00-463



a 9H = 3CH_3, no neighbors

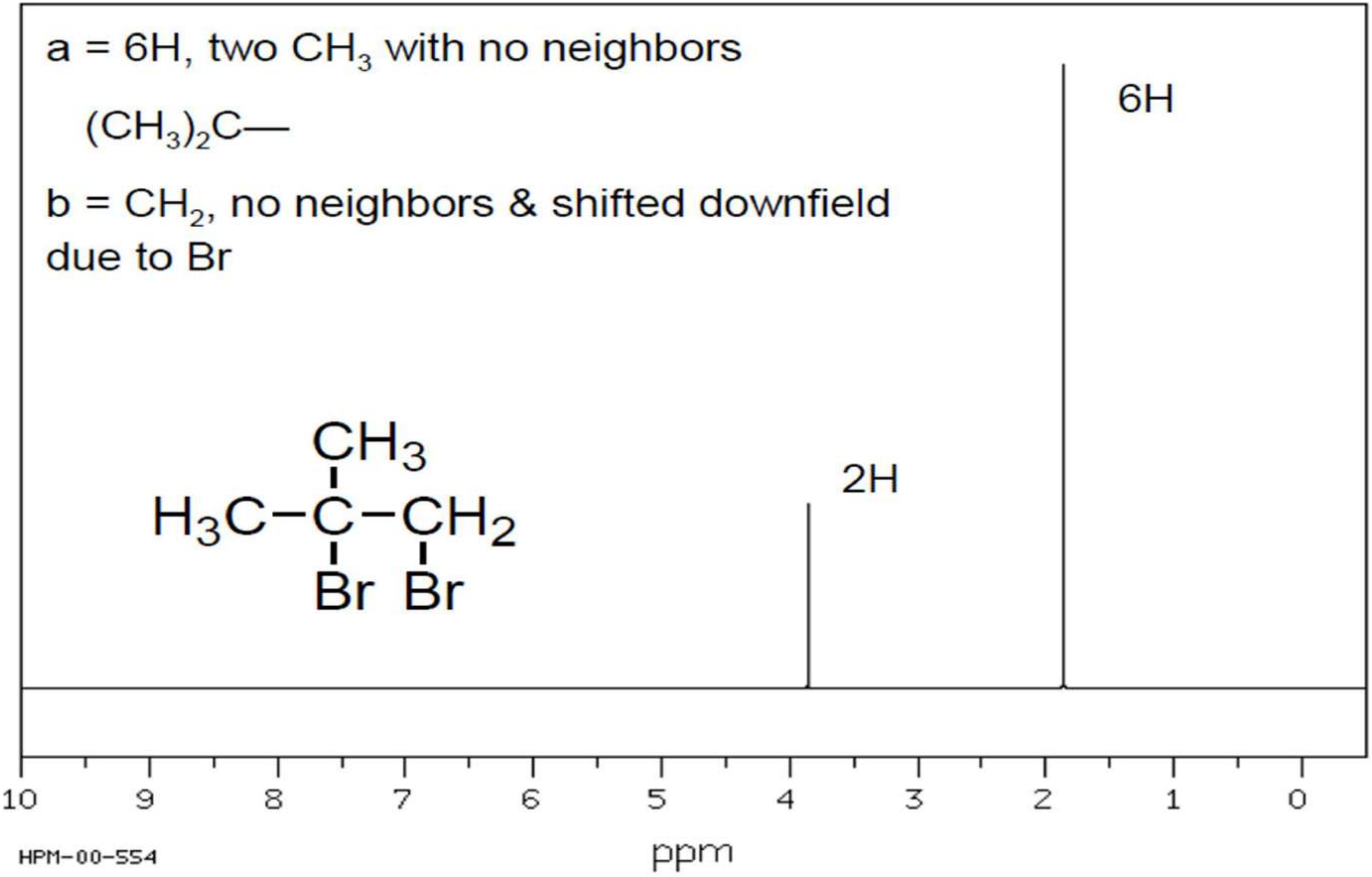
c 5H = monosubstituted benzene

b 2H, no neighbors

neopentylbenzene

HSP-06-062

$C_4H_8Br_2$



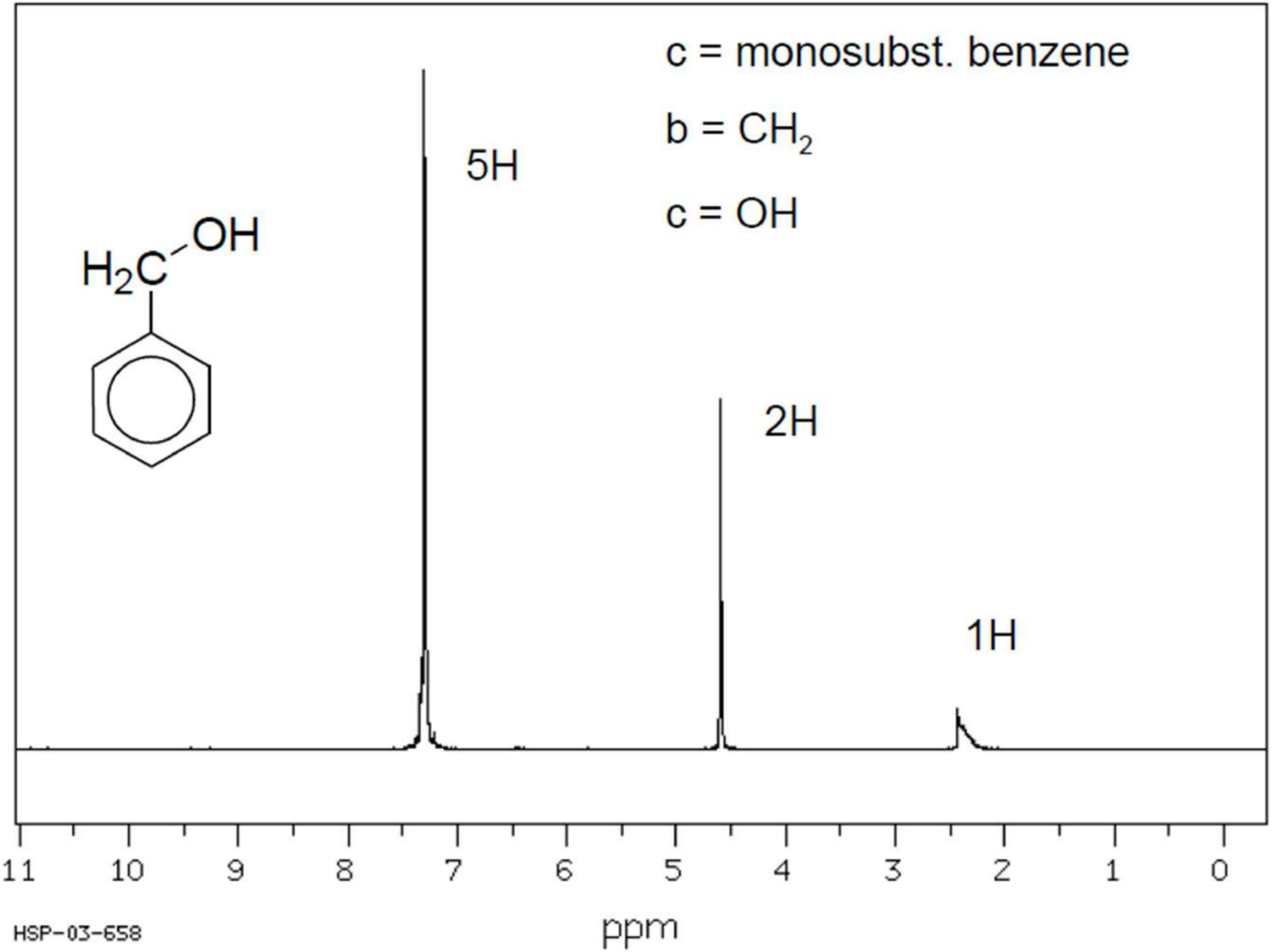
a = 6H, two CH_3 with no neighbors

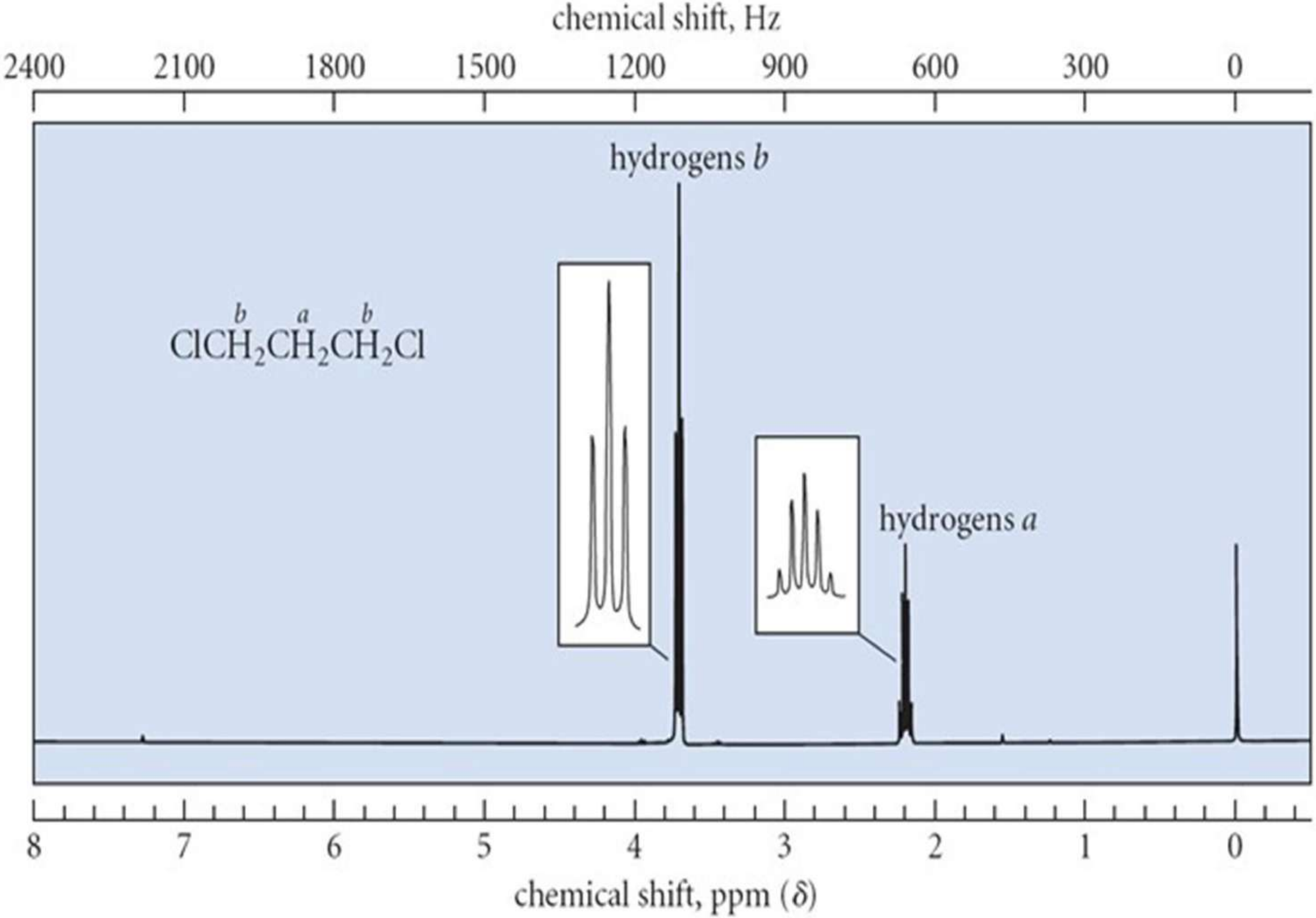
$(CH_3)_2C—$

b = CH_2, no neighbors & shifted downfield due to Br

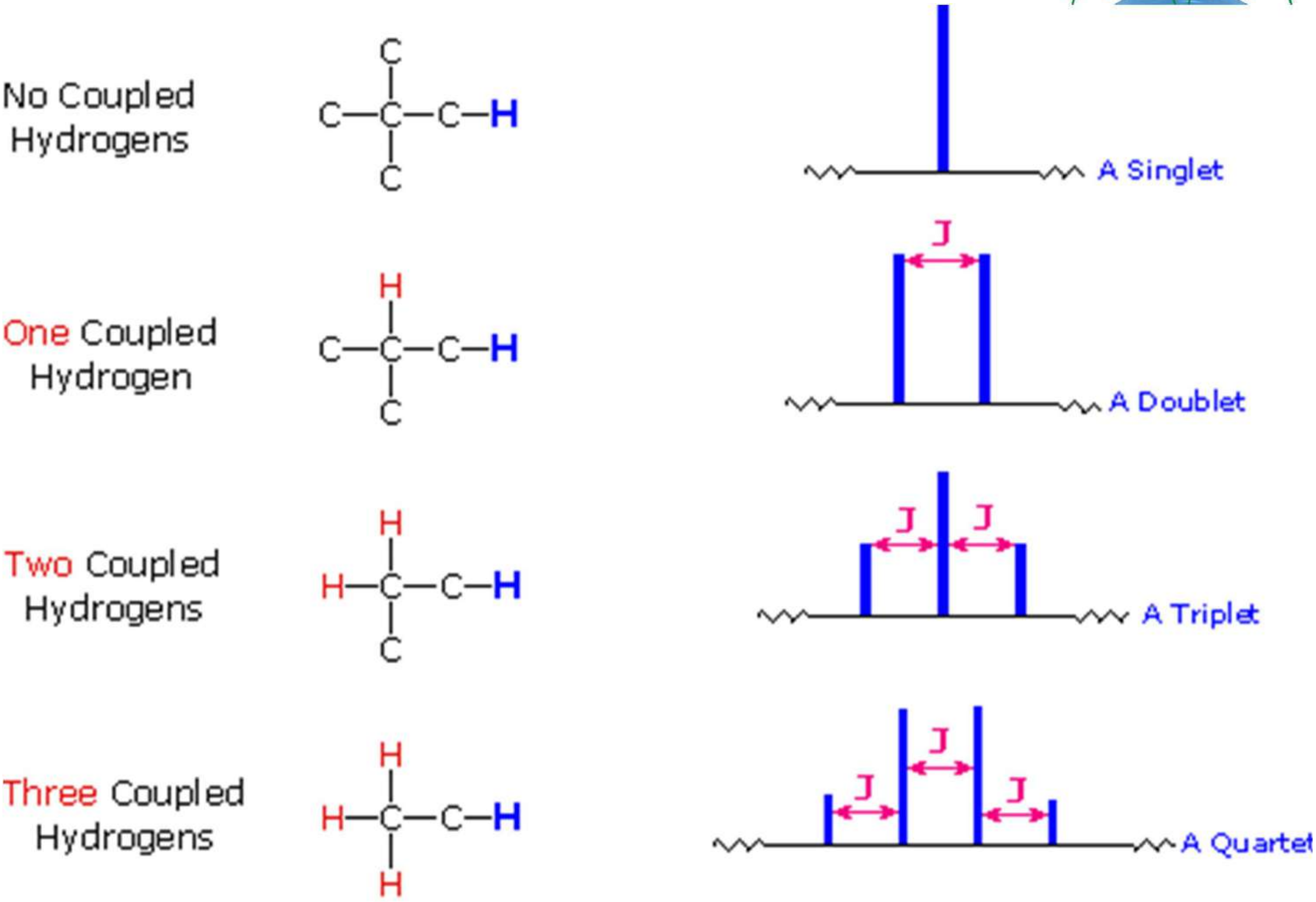
$$H_3C-\overset{\displaystyle CH_3}{\underset{\displaystyle Br}{C}}-\underset{\displaystyle Br}{CH_2}$$

C_7H_8O

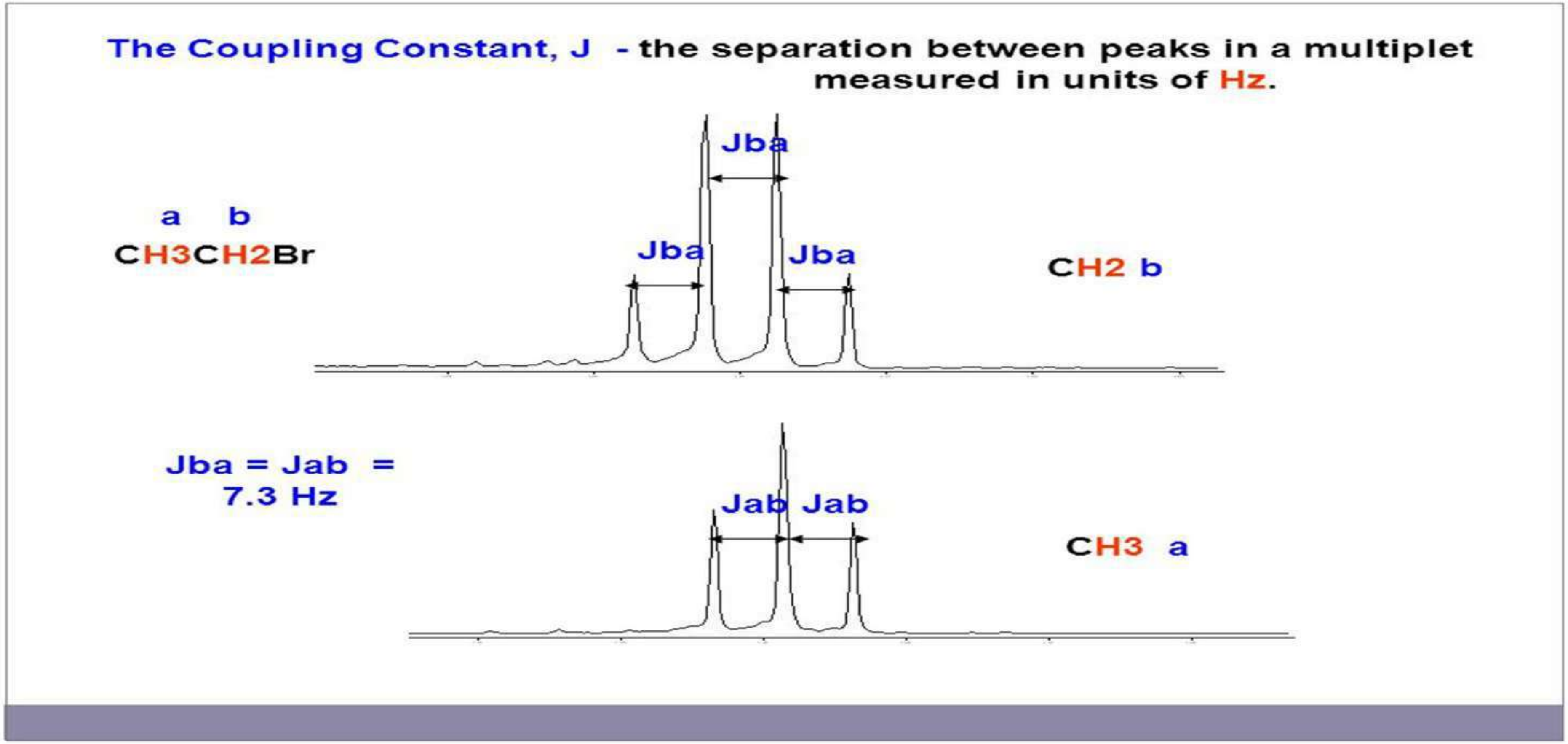

c = monosubst. benzene
b = CH_2
c = OH
H_2C
OH
5H
2H
1H
11
10
9
8
7
6
5
4
3
2
1
0
ppm
HSP-03-658


chemical shift, Hz
2400
2100
1800
1500
1200
900
600
300
0
hydrogens b
hydrogens a
$\overset{b}{ClCH_2}\overset{a}{CH_2}\overset{b}{CH_2}Cl$
8
7
6
5
4
3
2
1
0
chemical shift, ppm (δ)

Coupling Constant J-Coupling

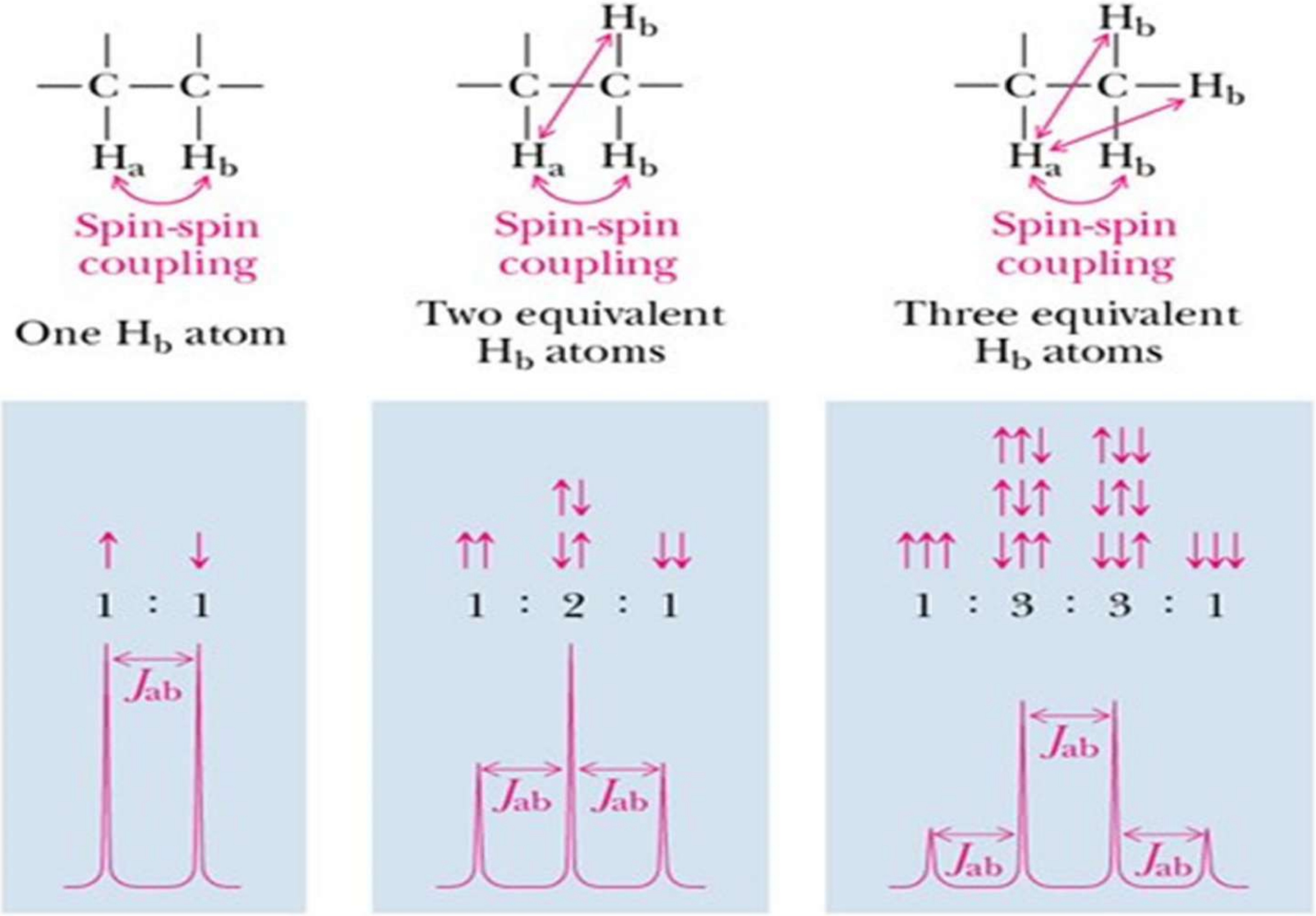


When two protons couple to each other, they cause splitting of each other's peaks. The spacing between the peaks is the same for both protons, and is referred to as the **coupling constant or J constant**.



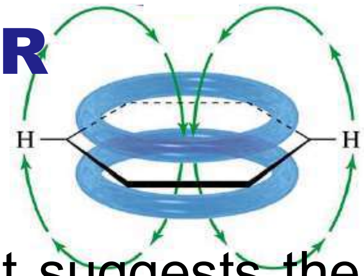
The Coupling Constant, J - the separation between peaks in a multiplet measured in units of Hz.

NOTE:- J-Coupling for simple splitting is equal



Observed splitting in signal of H_a

Some valuable observations from NMR spectrum and Interpretation



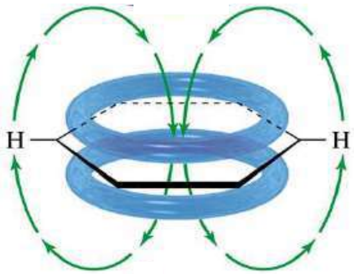
1] A peak with integration equal to 3 and appear as singlet suggests the presence of methyl group attached to carbonyl or methyl benzene or to Oxygen as ether (methoxy) or ester (methyl carboxylate).

2] Two peaks appear as (septet with integration equal to 1 and doublet with integration equal to 6) suggests the presence of isopropyl group.

3] Two peaks appear as (triplet with integration equal to 3 and quartet with integration equal to 2) suggests the presence of ethyl group.

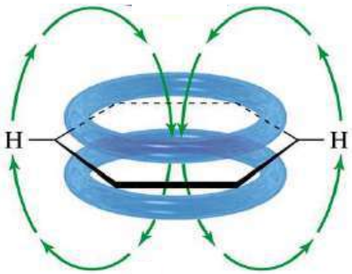
4] Two peaks in the aromatic region (6-8 ppm) appear as doublet of doublts (dd) suggests the presence of para disubstituted benzene

5] A peak with integration equal to 9 and appear as singlet suggests the presence of tert-butyl group



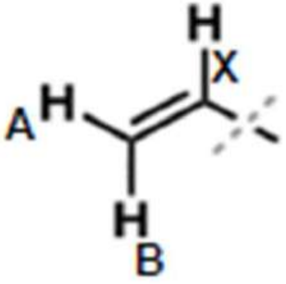
Video 8
Page (167-185)

Complex Splitting



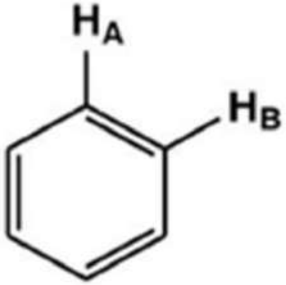
We will focus on two types of complex splitting

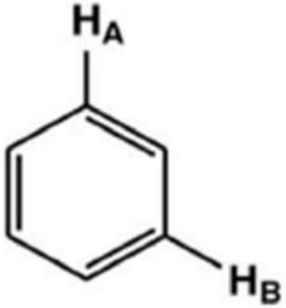
1- Vinylic system (cis, trans and geminal)



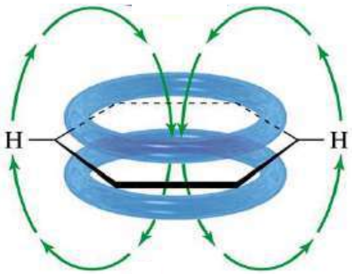
vinyl group

2- Aromatic system (ortho, meta and para)





Coupling Constants
J-coupling



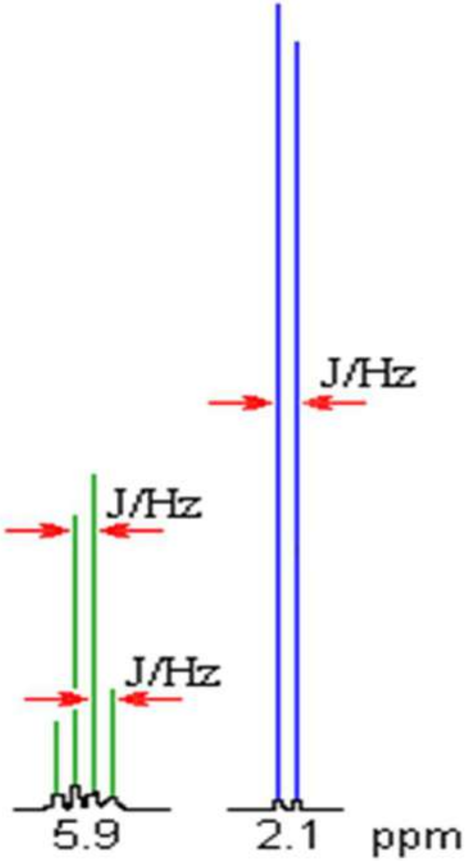
- Distance between the peaks of multiplet

- Measured in Hz

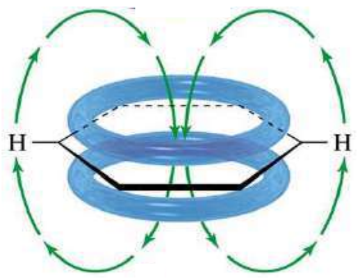
- Not dependent on strength of the external field

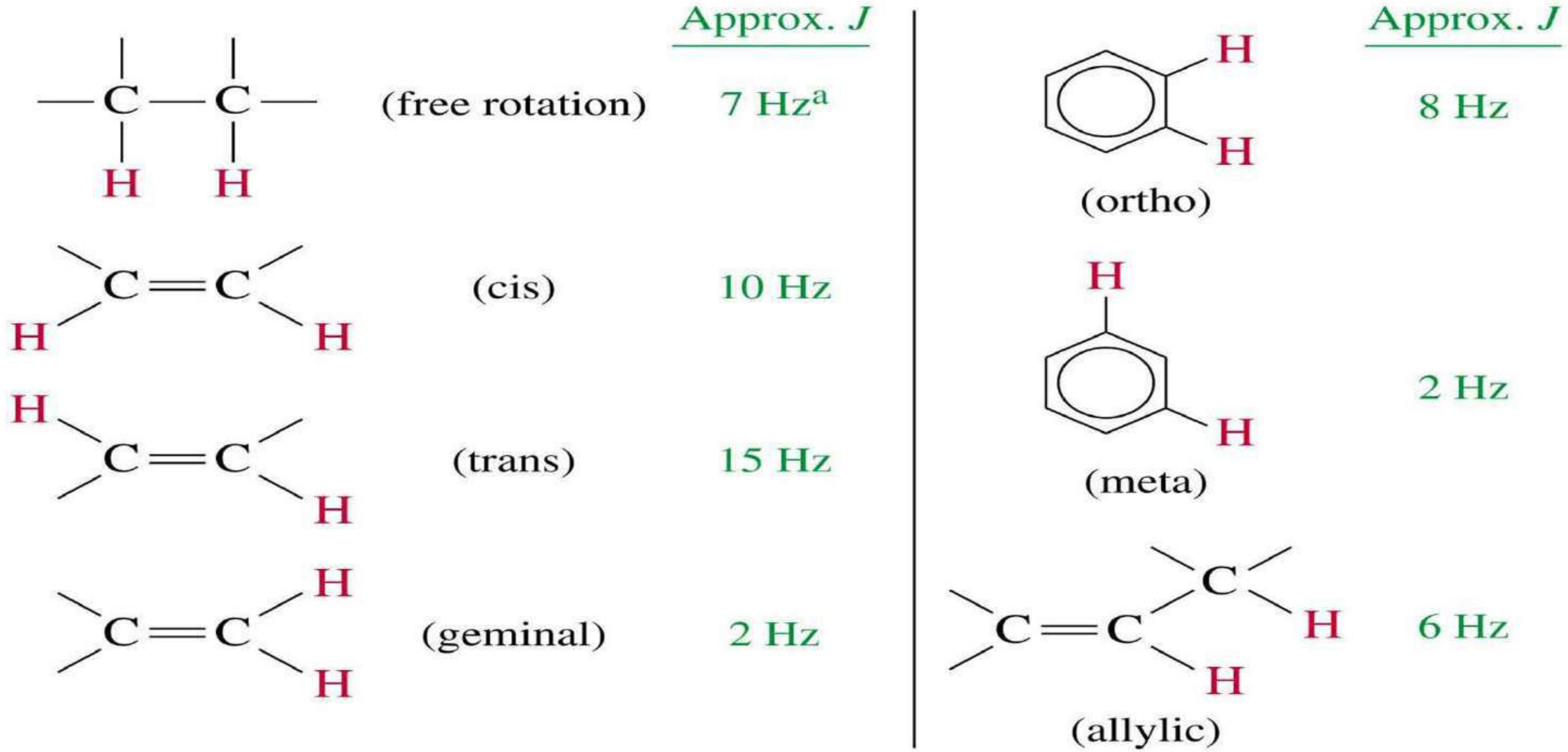
- Depends on EN and geometry

  dihedral angle(angle between planes Carplus equation)



Values for Coupling Constants

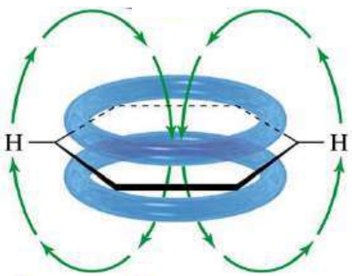


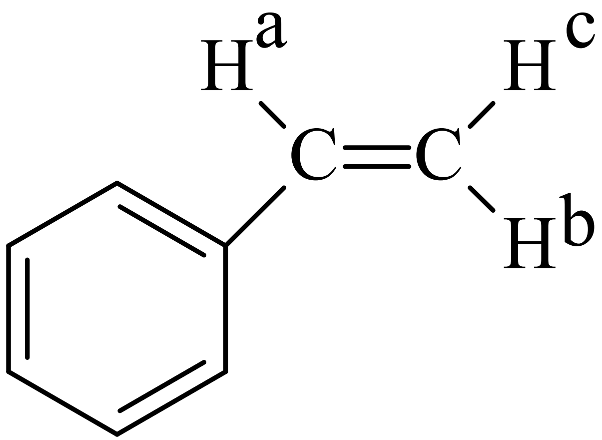


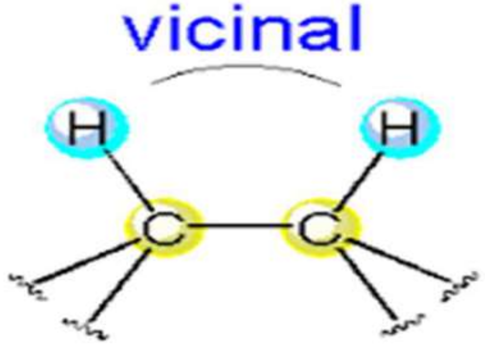
	Approx. *J*		Approx. *J*
(free rotation)	7 Hz[a]	(ortho)	8 Hz
(cis)	10 Hz	(meta)	2 Hz
(trans)	15 Hz	(allylic)	6 Hz
(geminal)	2 Hz		

[a] The value of 7 Hz in an alkyl group is averaged for rapid rotation about the carbon–carbon bond. If rotation is hindered by a ring or bulky groups, other splitting constants may be observed.

1- Vinylic complex system

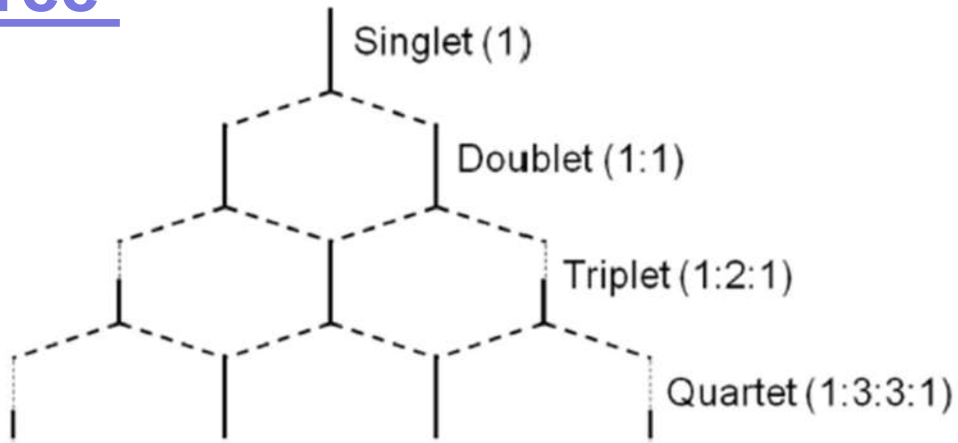




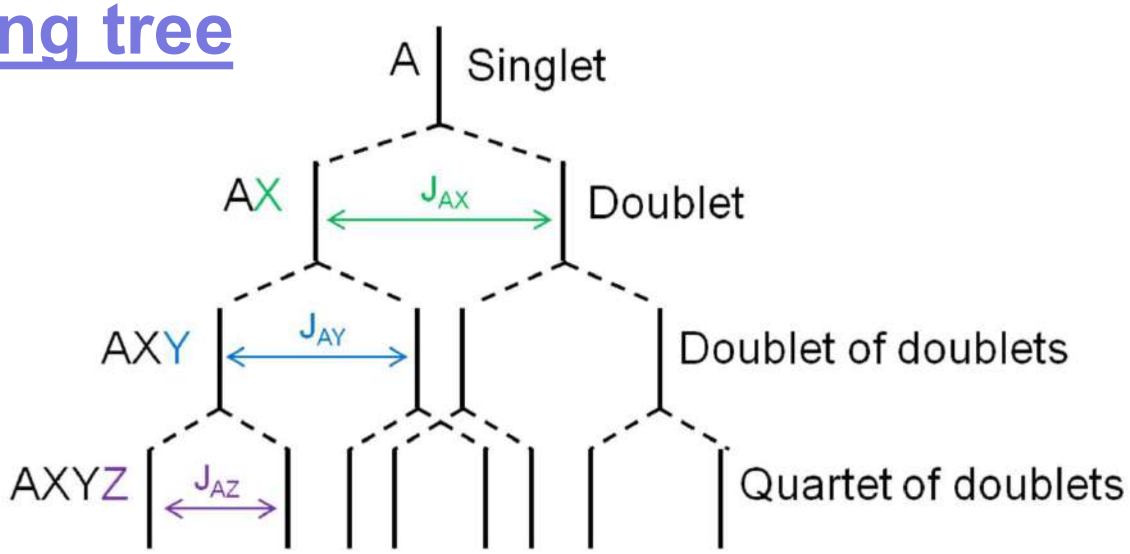


- **Signals may be split by adjacent protons, different from each other, with different coupling constants.**
- **Example: H^a of styrene which is split by an adjacent H *trans* to it (J = 17 Hz) and an adjacent H *cis* to it (J = 11 Hz).**

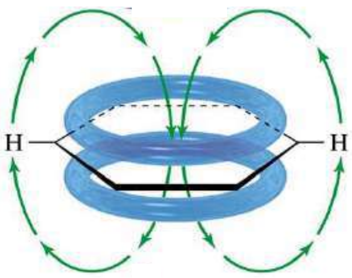
Simple splitting tree



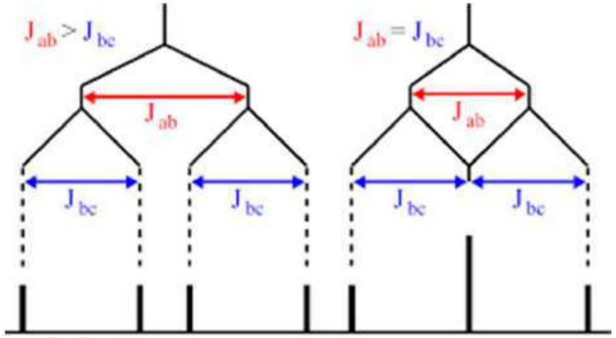
Complex splitting tree

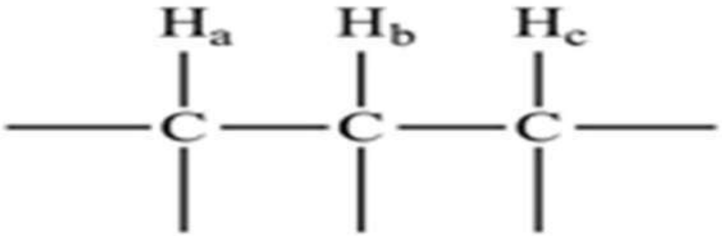


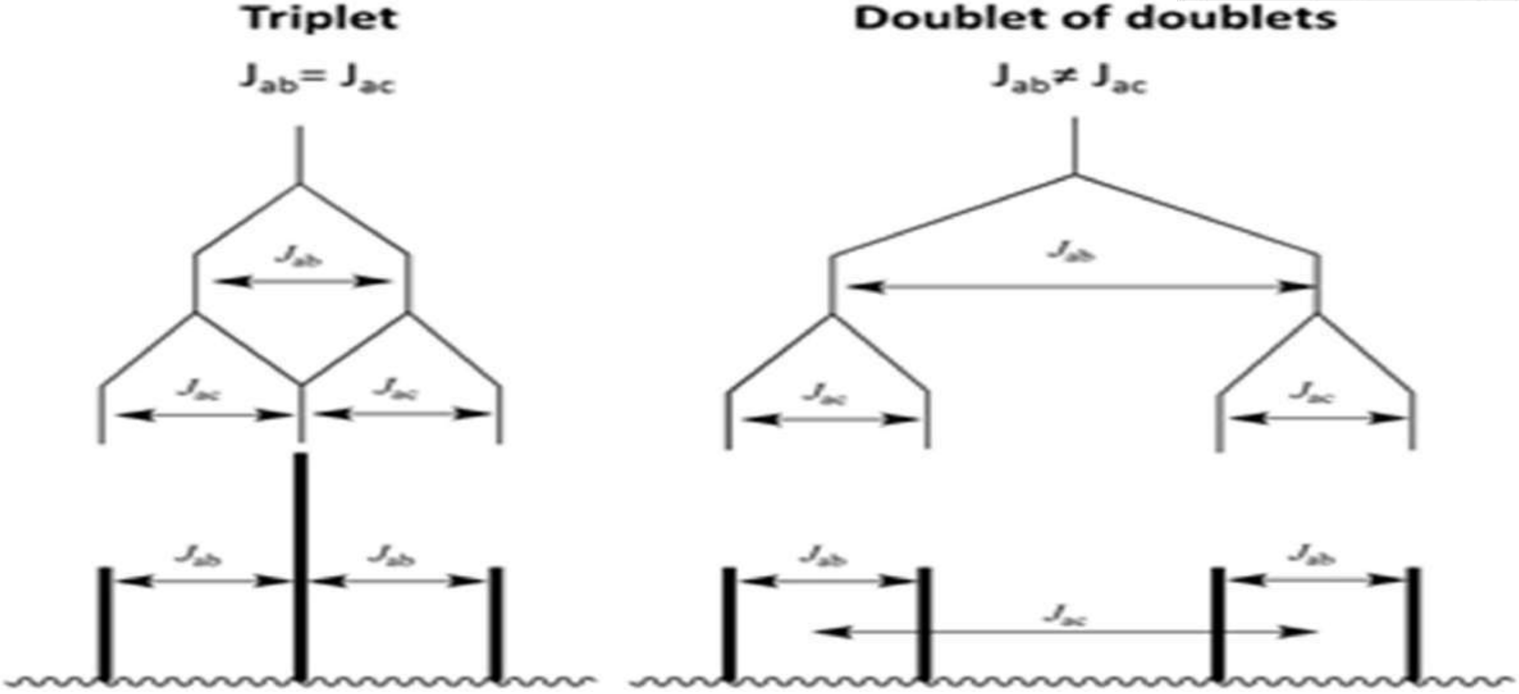
What is the difference between triplet and doublet of doublet?



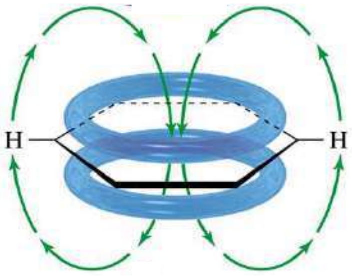
****** J coupling is equal in simple splitting while is unequal in the case of complex**

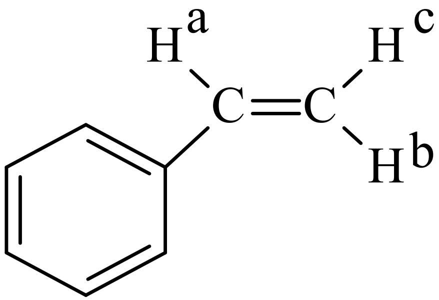


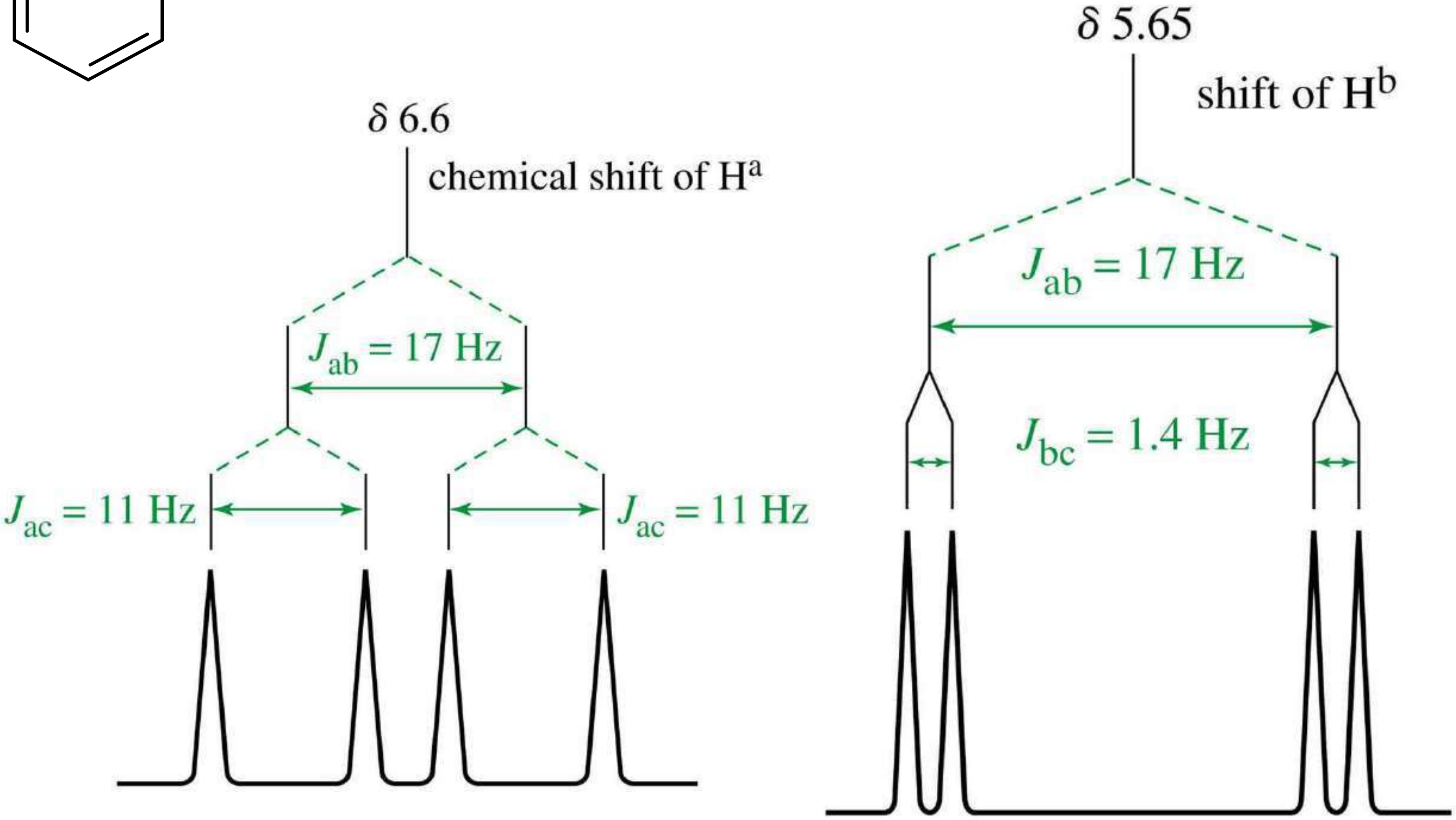




Splitting Tree

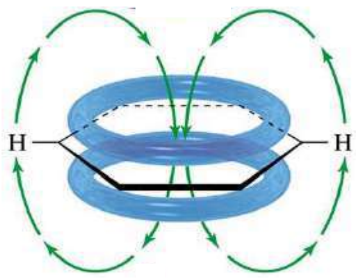






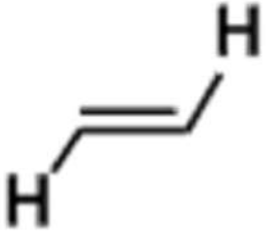
=>

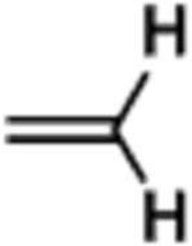
J Coupling values for some well-known cases

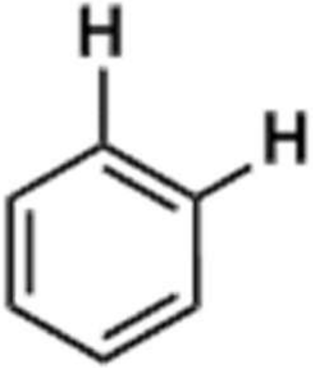


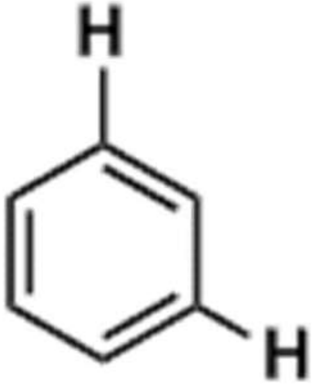

alkane
6-8 Hz


cis 6-15 Hz


trans 11-18 Hz

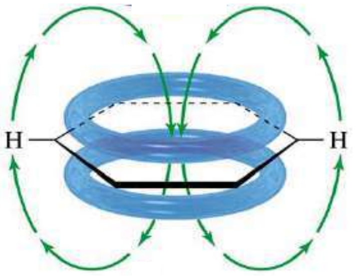

geminal 0-5 Hz


ortho 7-10 Hz

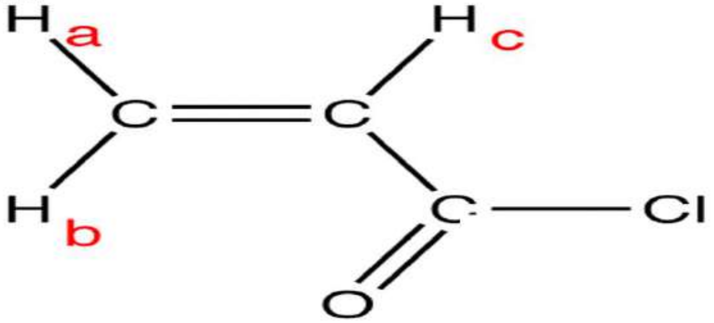

meta 2-3 Hz


para 0-1 Hz

Complex splitting (n+1) Rule for each hydrogen independently)

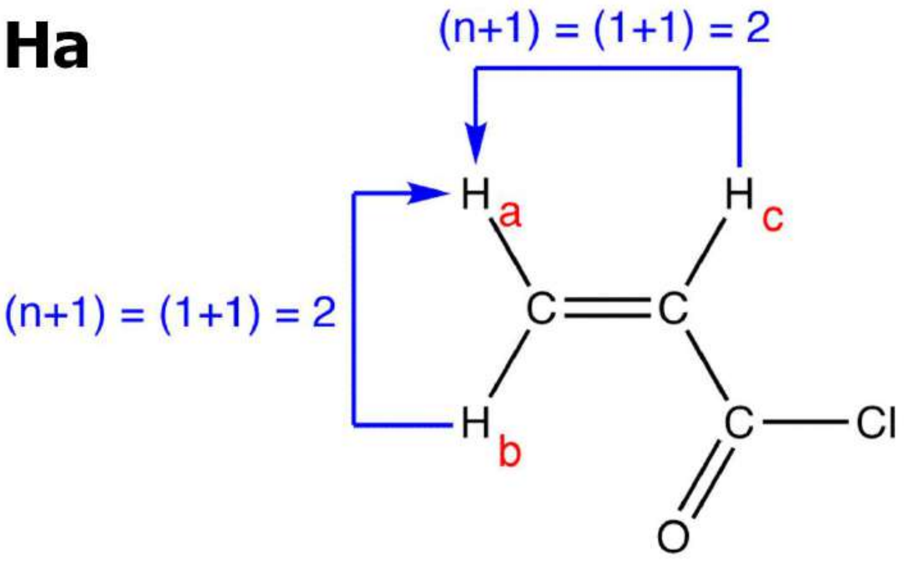


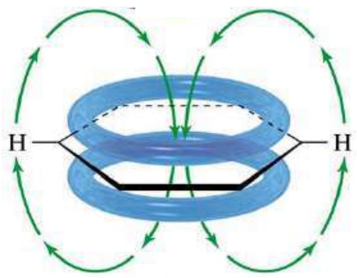
To determine the multiplicity of a peak of a nucleus coupled to more than one set of equivalent nuclei, apply the (n+1) Rule independently to each other.

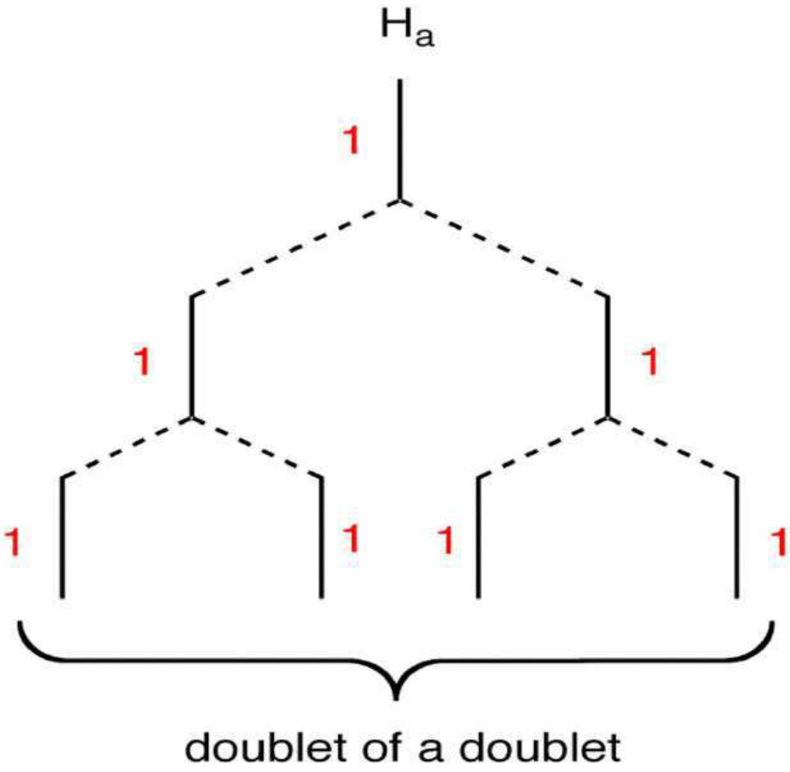


	H_a	H_b	H_c
H_a		geminal; coupling occurs	vicinal; coupling occurs
H_b	geminal; coupling occurs		vicinal; coupling occurs
H_c	vicinal; coupling occurs	vicinal; coupling occurs	

Peak of Ha





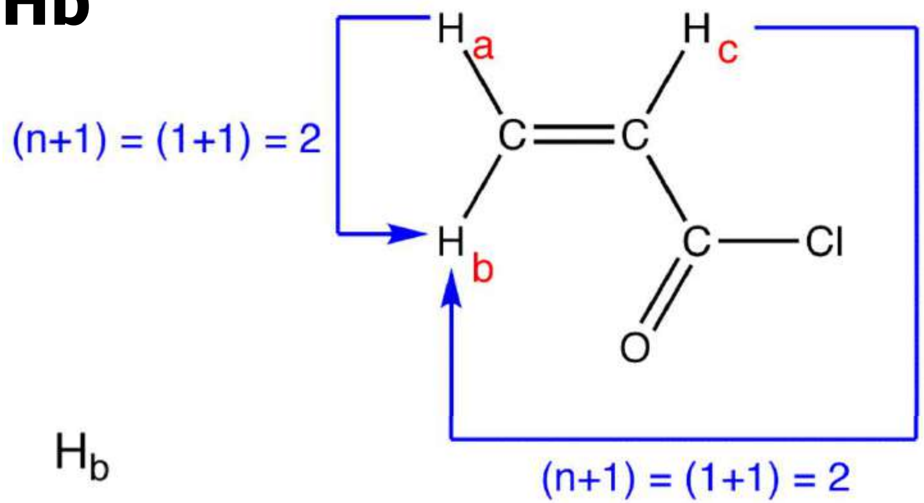


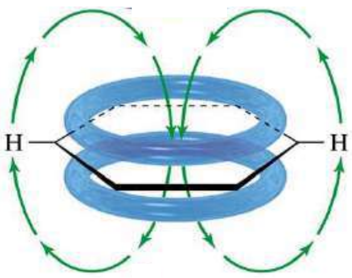
peak of H_a if coupled to no hydrogen nuclei

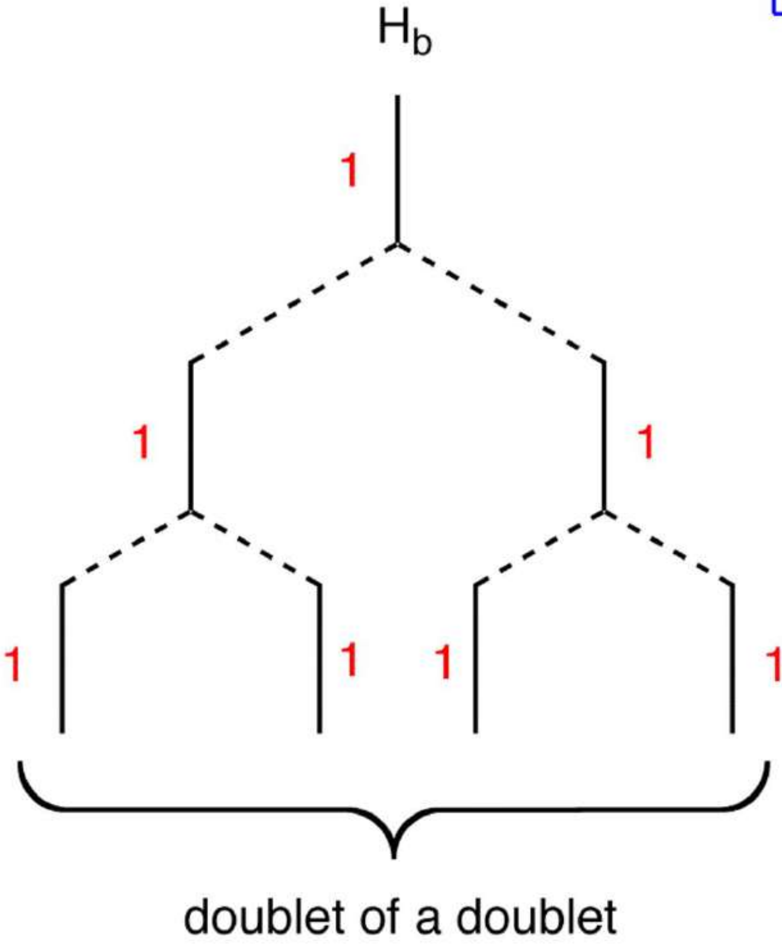
peak of H_a if coupled only to H_c

peak of H_a when coupled to both H_b and H_c

Peak of Hb





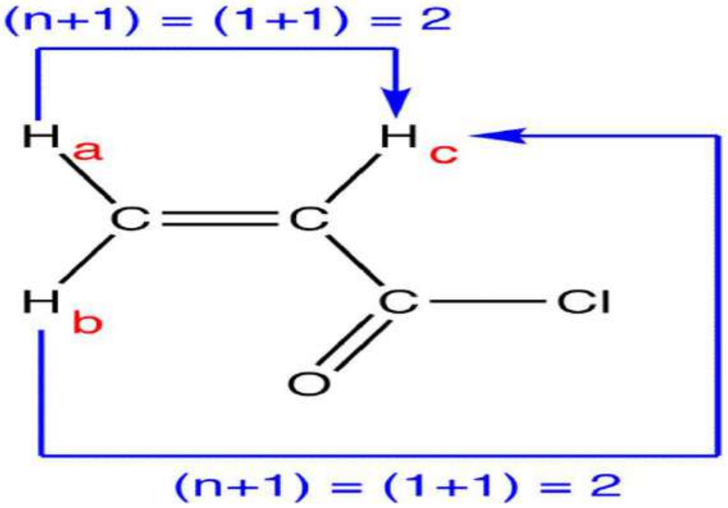


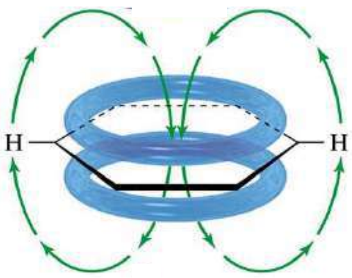
peak of H_b if coupled to no hydrogen nuclei

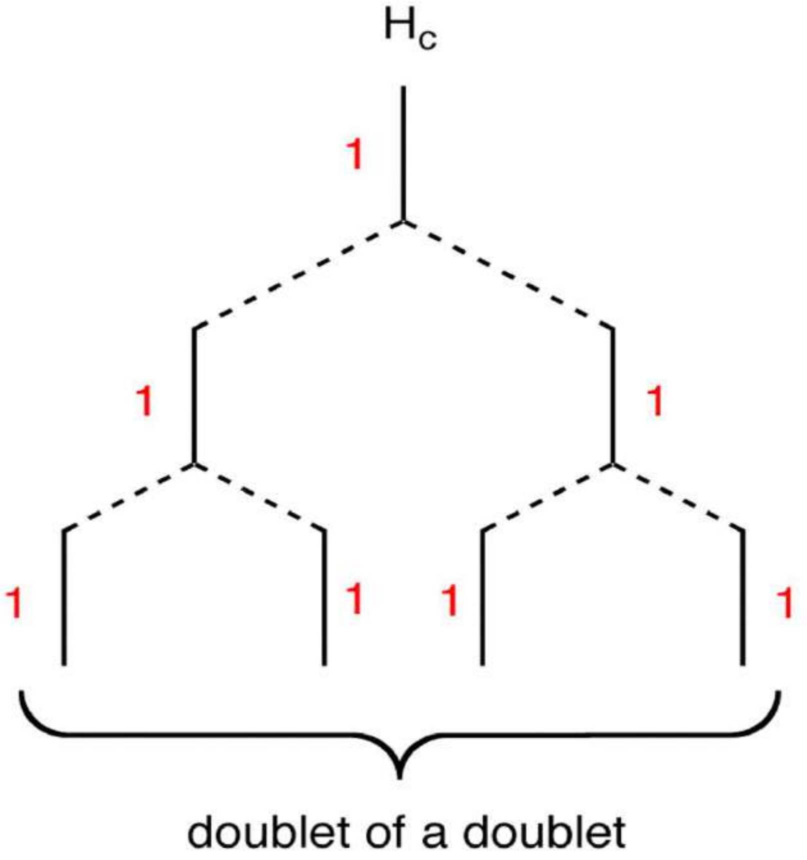
peak of H_b if coupled only to H_c

peak of H_b when coupled to both H_a and H_c

Peak of Hc



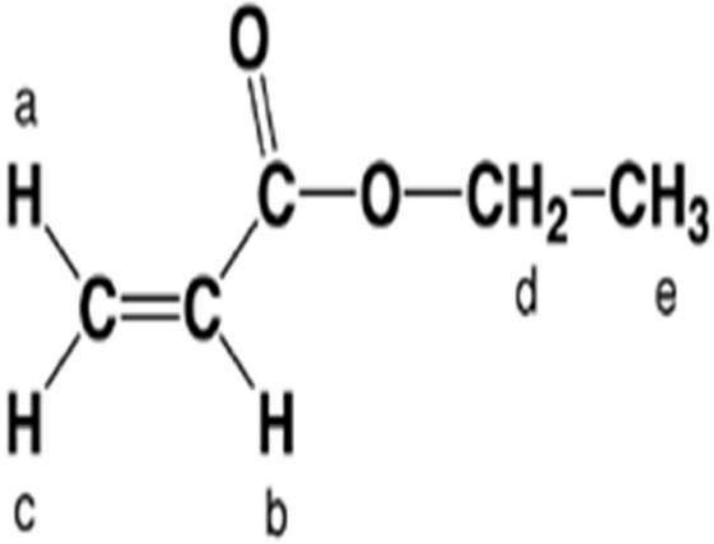


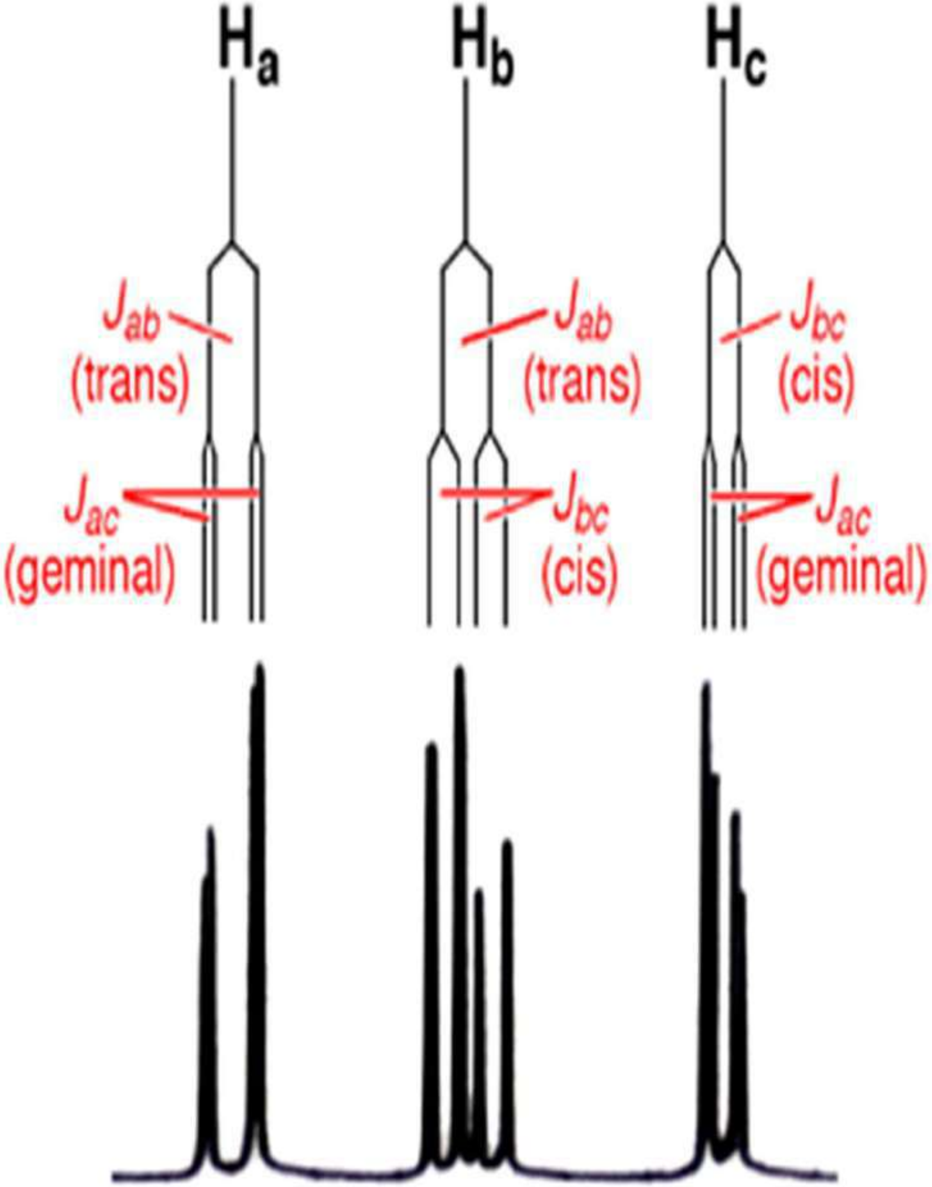


peak of H_c if coupled to no hydrogen nuclei

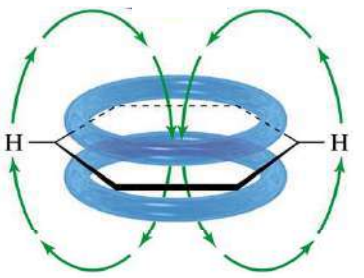
peak of H_c if coupled only to H_b

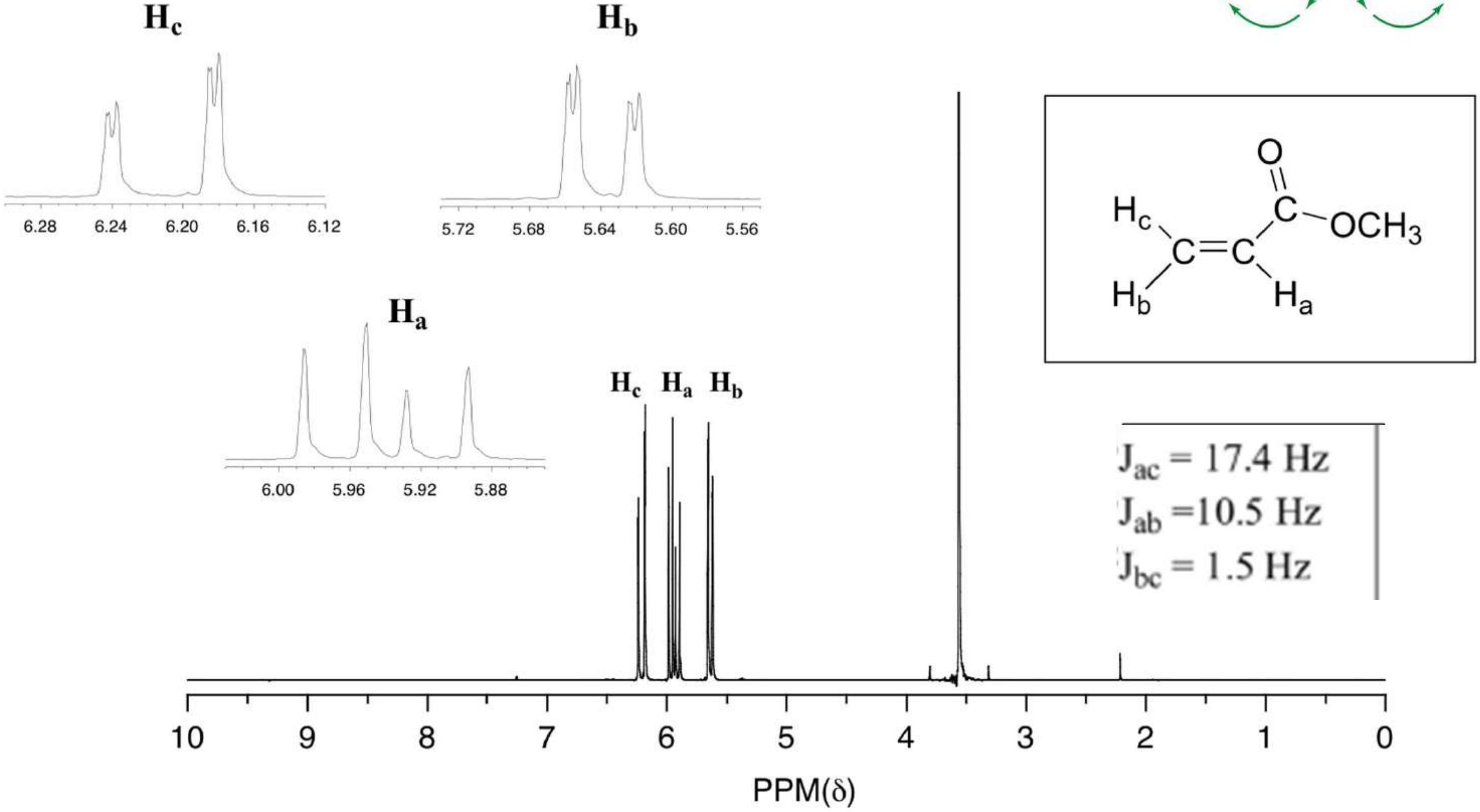
peak of H_c when coupled to both H_a and H_b


a
H
O
C
O
CH2
CH3
C
C
H
H
c
b
d
e


Ha
Hb
Hc
Jab (trans)
Jac (geminal)
Jab (trans)
Jbc (cis)
Jbc (cis)
Jac (geminal)

Example for vinylic coupling



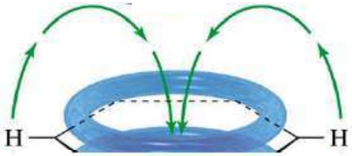


J_{ac} = 17.4 Hz

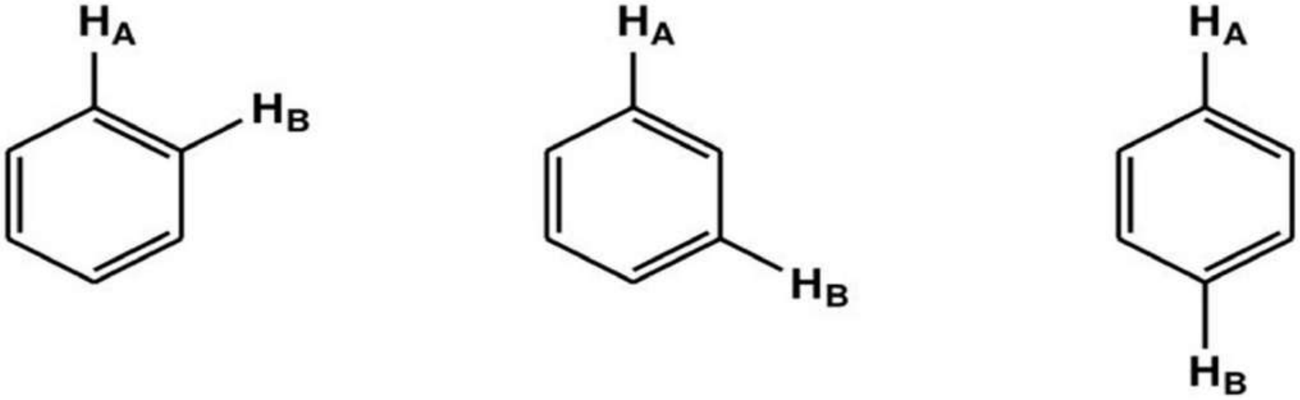
J_{ab} =10.5 Hz

J_{bc} = 1.5 Hz

2- Aromatic complex system



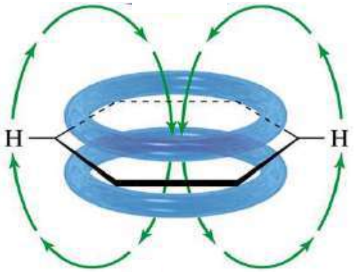
Magnitudes of coupling constants

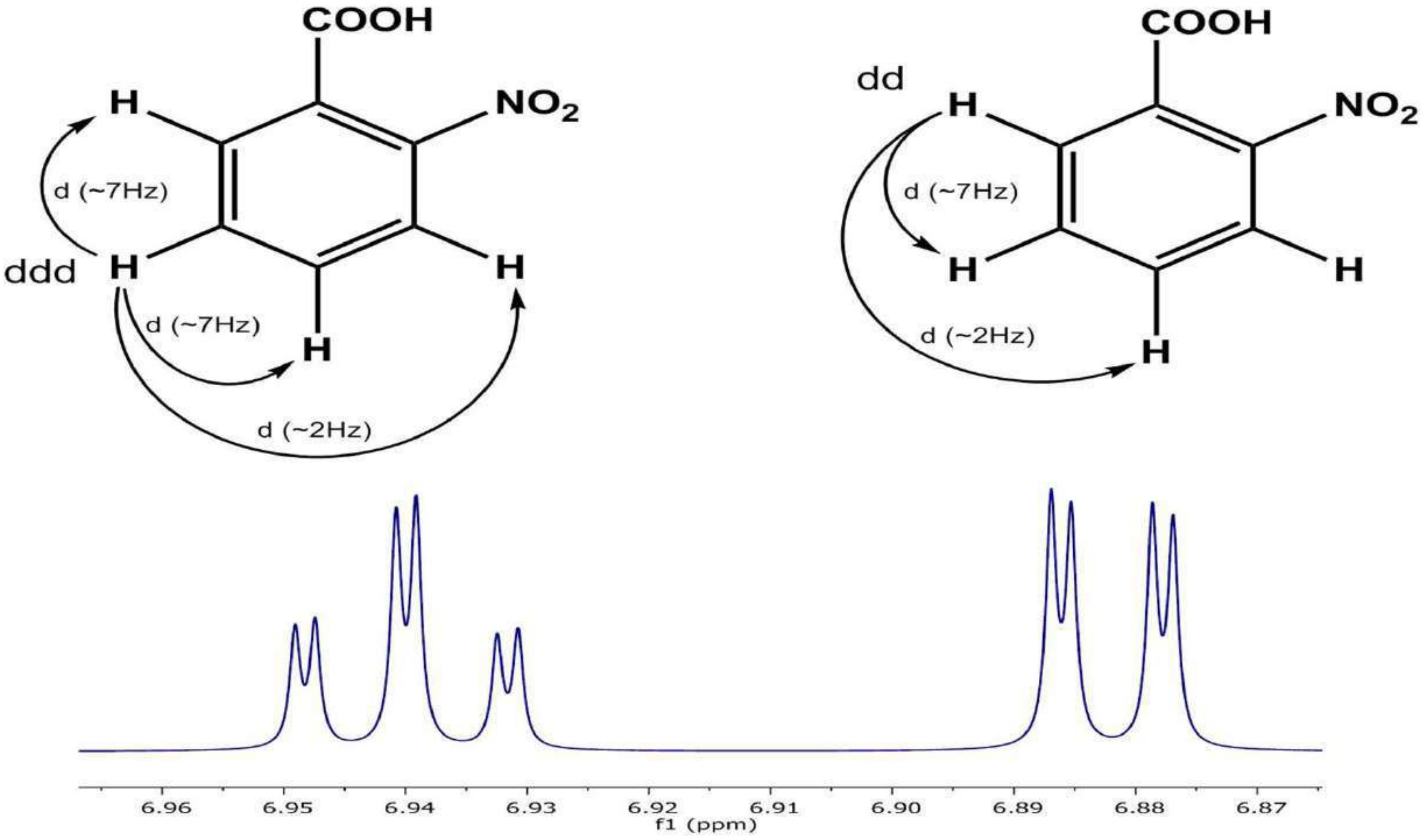


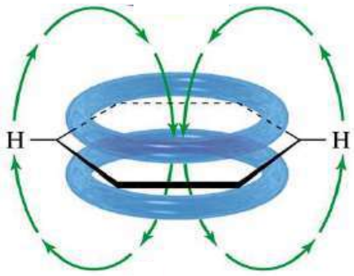
$^{3}J_{AB(ortho)} = 6 - 10$ Hz $^{4}J_{AB(meta)} = 1 - 3$ Hz $^{5}J_{AB(para)} = 0 - 1.5$ Hz

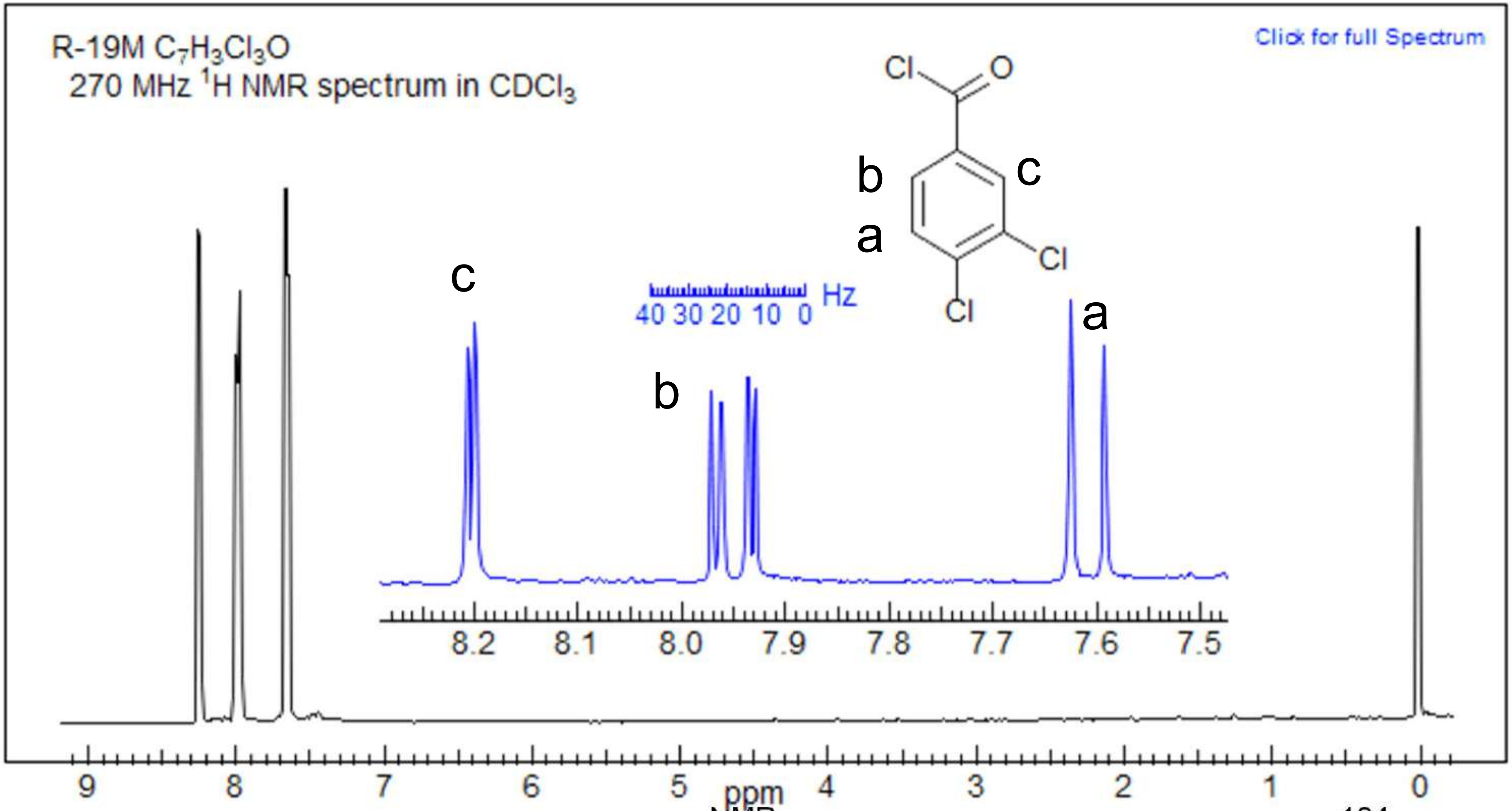
- in aromatic systems, protons *ortho* to one another show a large coupling (typically 8 Hz)
- *meta*-couplings are much smaller (1 – 3 Hz) and thus may or may not appear in the ^{1}H NMR spectrum (signals may simply be broadened)
- *para*-couplings are very small (0 – 1 Hz) and normally do not appear in the ^{1}H NMR spectrum

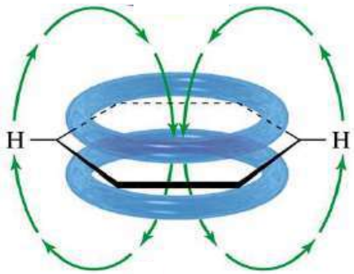
2- Aromatic complex system






H
H


R-19M $C_7H_3Cl_3O$
270 MHz ^1H NMR spectrum in $CDCl_3$
Click for full Spectrum
Cl
O
b
c
a
Cl
Cl
c
b
a
40 30 20 10 0 Hz
8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
9
8
7
6
5
ppm
4
3
2
1
0



The End