

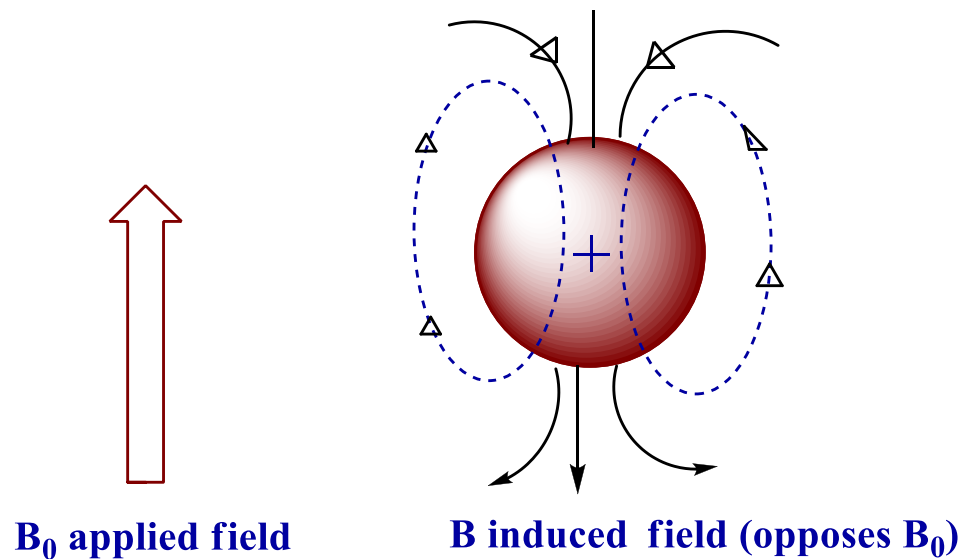
Lec 4

5th stage

**Advanced Pharmaceutical Chemistry
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When a molecule is placed in a magnetic field, its electrons are caused to circulate and thus, they produce secondary magnetic fields i.e., induced magnetic field. Rotation of electrons about the proton itself generates a field in such a way that at the proton, it opposes the applied field. Thus the field felt by proton, is diminished and the proton is said to be shielded. Rotation of electron (especially π electrons) about the nearby nuclei generates a field that can either oppose or reinforce the applied field at the proton. If the induced field opposes the applied field, then the proton is said to be shielded. But if the induced field reinforces the applied field the proton feels a higher field strength and thus, such a proton is said to be deshielded. Shielding shifts the absorption upfield and deshielding shifts the absorption downfield to get an effective field strength necessary for absorption.



Diamagnetic anisotropy—the diamagnetic shielding of a nucleus caused by the circulation of valence electrons

Chemical shifts: - are the positions of NMR absorptions, which arise due to the shielding or deshielding of protons by the electrons.

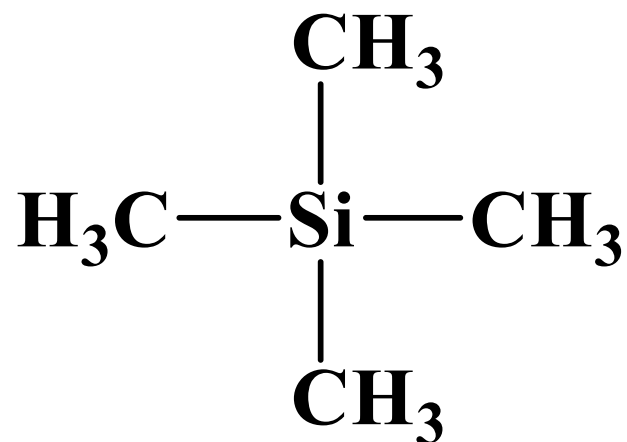
Note:- Protons with the same chemical shift are called equivalent protons. Non equivalent protons have different chemical shifts.

Positions of NMR absorptions  **Chemical shift (compared with a standard reference)**

Reference

It is very difficult to measure exact frequencies to that precision → No attempt is made to measure the exact resonance of any proton. So the frequency of a reference is measured and the resonance frequency of each nucleus is measured relative to resonance frequency of the reference (generally TMS)

For measuring chemical shifts of various protons in a molecule, the signal for tetramethyl silane (TMS) is taken as a reference.



Tetramethylsilane(TMS)

Due to the low electronegativity of silicon, the shielding of equivalent protons in tetramethyl silane is greater than most of the organic compounds. Therefore, NMR signal for tetramethyl silane is taken as a reference and chemical shifts for different kinds of protons are measure relative to it. **(i.e., Methyl protons of TMS are strongly shielded and therefore absorbs at higher field than almost all organic protons).**

Chemical shift:-

But the shift from reference depends on B_0

In $B_0 = 1.41$ Tesla, the $\nu_H \sim 60\text{MHz}$

In $B_0 = 2.35$ Tesla, the $\nu_H \sim 100\text{MHz}$

$$\frac{100\text{MHz}}{60\text{MHz}} = \frac{1.41 \text{ Tesla}}{2.53 \text{ Tesla}} = \frac{5}{3}$$

So for a given proton the shift in Hz from TMS in 100 MHz is larger by $5/3$ than that in 60 MHz

So the solution is to measure the chemical shift in ppm (which is **field independent**).

Chemical shift can be expressed as the difference between the resonance frequency of the protons in the sample (ν_{sample}) and the resonance frequency of the protons in the standard TMS (ν_{standard}). This quantity is measured in ppm and given the symbol delta δ . Its measure in equivalent frequency units which is then divided by the frequency of the spectrometer used.

δ (Delta) or τ (Tau) scales are commonly used. In majority of organic compounds, protons resonate at a lower field than the proton of TMS. Thus Delta (δ) value for TMS equal to zero.

Since the operating frequency of the instrument is directly proportional to the strength of magnetic field, we can define δ as

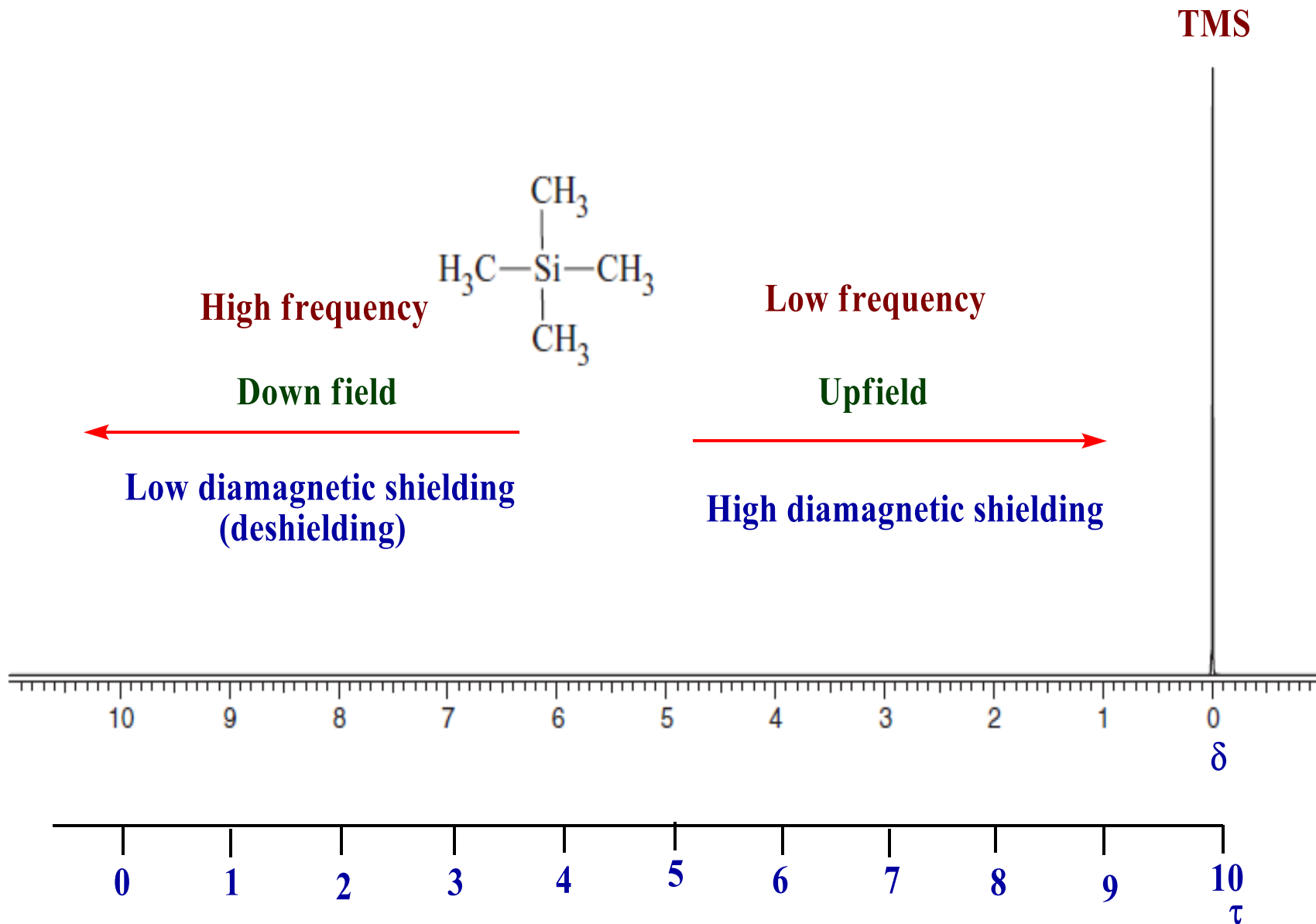
$$\delta_s = \frac{10^6(v_s - v_{\text{TMS}})}{\nu} = 10^6 \frac{\Delta\nu_s}{\nu} = \frac{\Delta\nu_s}{\nu'}$$

Operating frequency
in megahertz

ppm(parts per million)

Operating frequency in hertz

$$\Delta\nu_s = \nu_s - \nu_{\text{TMS}}$$



Proton NMR chemical shift spectrum of TMS

Most chemical shifts have values between 0-10. In the τ scale, signal for standard reference, TMS is taken as 10 ppm. The two scales are related by the expression,

$$\tau_s = 10 - \delta_s$$

The scale shown here is the now accepted one and is called delta (δ). The older scale is called tau (τ) and it references TMS at 10. NMR signal is usually plotted with magnetic field strength increasing to the right. Thus signal for TMS (highly shielded) appears at the extreme right of spectrum with $\delta = 0$ ppm. Greater the deshielding of protons, larger will be the value of δ .

The scale itself is quoted in parts per million (ppm). It is actually a frequency scale, but if we quoted the frequency, the chemical shift would be dependent on the magnetic field

(a 400MHz spectrometer would give different chemical shifts to a 300MHz spectrometer). To get around this, the chemical shift is quoted as a ratio compared with the main magnet field and is quoted in ppm

Note:- The chemical shift values expressed in hertz vary with the field strength, so it's more convenient and uniform to express them in parts per million from the reference frequency, which is field independent



For instance, at **60 MHz** the shift of the protons in CH₃Br is **162 Hz** from TMS, while at **100 MHz** the shift is **270 Hz**. However, both of these correspond to the same value of δ (**2.70 ppm**):

$$\delta = \frac{162\text{Hz}}{60\text{MHz}} = \frac{270\text{ Hz}}{100\text{ MHz}} = 2.7\text{ ppm}$$

Example

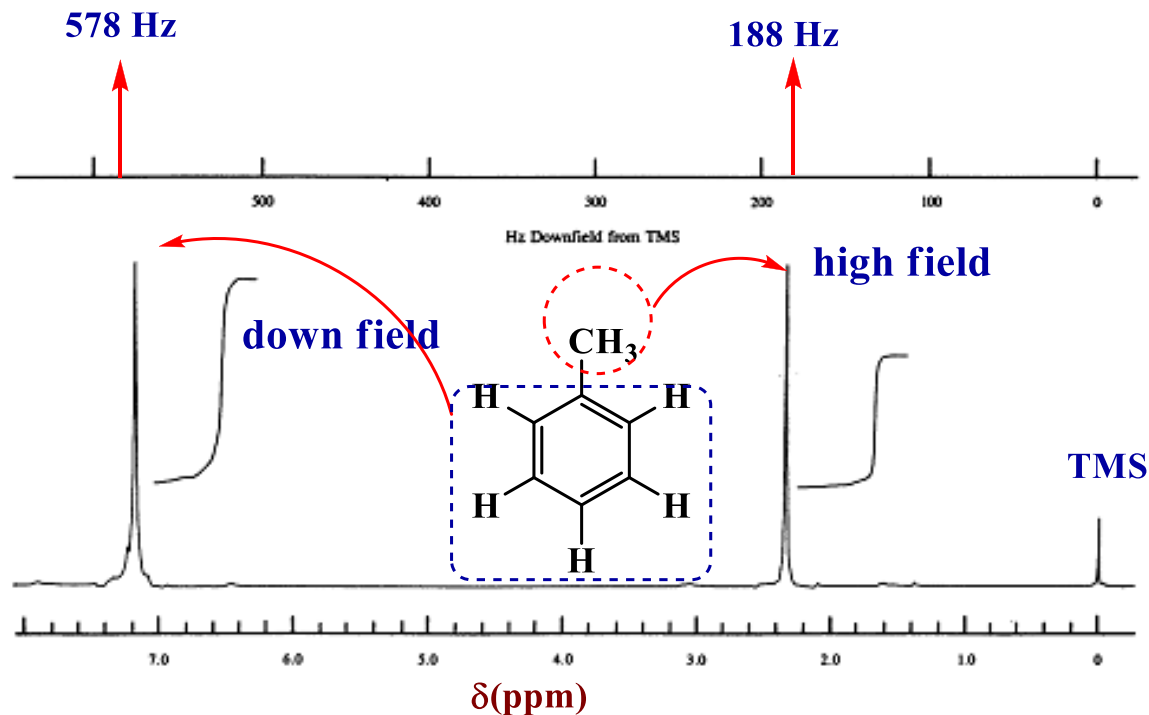
The chemical shift position for the proton resonance in benzene (all six protons being equivalent) is δ 7.27 ppm. How many hertz is this from the TMS resonance when instrument is working at (a) 100 MHz, (b) 60 MHz.

$$\delta_i = \frac{\nu_s \text{ (Hz)}}{\nu'}$$

$$7.27 \text{ ppm} = \frac{\nu_s \text{ (Hz)}}{100\text{MHz}} \implies \nu_s \text{ (Hz)} = 727 \text{ Hz}$$

$$7.27 \text{ ppm} = \frac{\nu_s \text{ (Hz)}}{60\text{MHz}} \implies \nu_s \text{ (Hz)} = 436.2 \text{ Hz}$$

Example:- Calculate the chemical shifts of the toluene signals using the 80-MHz data.



The 80 MHz ¹H spectrum of toluene

$$\delta_{\text{i upfield}} = \frac{\delta\nu_s}{\nu'} = \frac{188\text{Hz}}{80\text{MHz}} = 2.35 \text{ ppm}$$

$$\delta_{\text{i downfield}} = \frac{\delta\nu_s}{\nu'} = \frac{578\text{Hz}}{80\text{MHz}} = 7.23 \text{ ppm}$$

**Tetramethylsilane (TMS) is commonly used as an internal reference
TMS is a good standard because**

- 1- It can be used to reference both ^1H and ^{13}C in the same sample.**
- 2-TMS is un reactive (except with con. H_2SO_4 with which it should not be used) and it does not associate with the sample.**
- 3- TMS is symmetrical, and thus gives a sharp peak of 12 equivalent protons.**
- 4- It is extremely volatile, and thus allows recovery of the pure sample.**
- 5- It is soluble in most organic solvents.**
- 6- Methyl protons of TMS are strongly shielded and therefore absorbs at higher field than almost all organic protons.**
- 7- It does not take part in intermolecular association with the sample.**

Note:-

TMS cannot be used as an internal reference for substances dissolved in D_2O . For aqueous solutions, the standard used is often the sodium salt of 2,2-dimethyl-2-silapentane-5-sulfonic acid or DSS.



Internal and External References

1- Internal reference:- is a compound giving a sharp NMR line that is dissolved directly in the sample solution under study (such as TMS and DSS).

Disadvantage

- **Intermolecular interactions or chemical reaction with the sample may occur.**
- **There are some problems with solubility of the reference in the sample solution.**

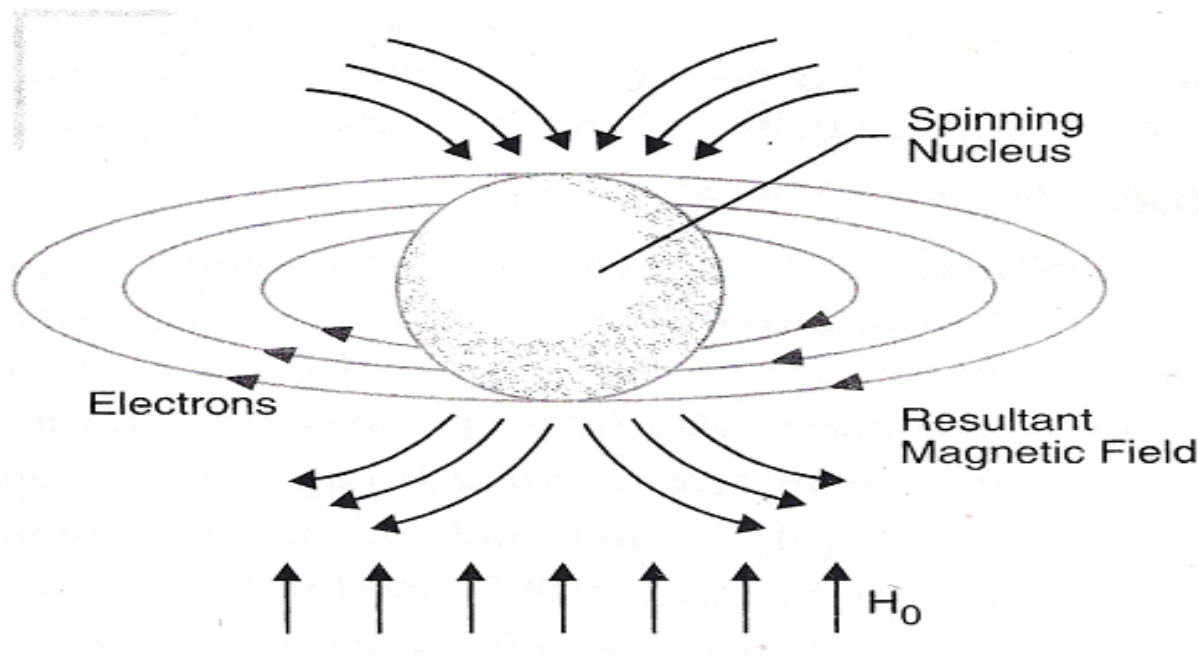
2- External reference. An external reference is a compound placed in a separate container from the sample. For liquid samples, an external reference compound is often placed as a neat (undiluted) liquid either in a small sealed capillary tube inside the sample tube or in the thin annulus formed by two precision coaxial tubes. The external reference compound is chosen in some cases, when it's not inert toward most samples. Like in ^{31}P NMR used 85% H_3PO_4 as external reference.

Advantage

- **Eliminating the possibility of intermolecular interactions or chemical reaction with the sample.**
 - **There are no problems with solubility of the reference in the sample solution.**
- There is, however, a serious difficulty raised by the difference in bulk magnetic susceptibility between sample and reference.**

Shielding and deshielding effects


Hydrogen nuclei in a molecule are surrounded by the electronic charge which shields the nucleus from the influence of the applied field. Thus, to overcome the shielding effect and to bring the proton to resonance, greater external field is required. The greater the electron density around the proton, greater will be the induced secondary magnetic field (local diamagnetic effect) which opposes the applied field and thus greater external field will cause proton absorption.



Diamagnetic shielding about the nucleus

The extent of shielding is represented in terms of the shielding parameter σ , when absorption occurs the field B felt by the proton is represented as

Field felt by the proton $\longrightarrow B = B_0 (1 - \sigma) \dots\dots 1$

Shielding parameter 

$$\nu = \frac{\gamma B}{2\pi} \dots\dots\dots 2$$

$$\nu = \frac{\gamma B_0 (1 - \sigma)}{2\pi} \dots\dots\dots 3$$

From this relation, it is clear that the protons with different electronic environments or with different shielding parameter can be brought into resonance in two ways:-

1- The strength of the external field is kept steady and the radiofrequency is constantly varied.

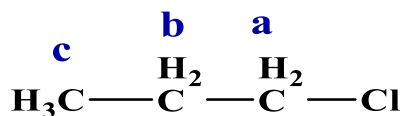
2- The radio-frequency is kept steady and the strength of the external field is constantly varied

At constant radiofrequency, shielding shifts the absorption up field ($\delta \downarrow$, $\tau \uparrow$), in the molecules where there is spherical distribution of electrons around the proton. While deshielding shifts the absorption down field ($\delta \uparrow$, $\tau \downarrow$).

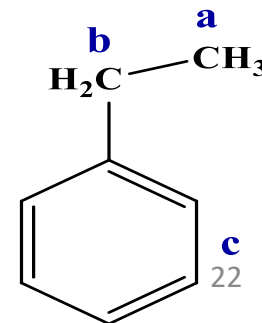
The deshielding effect due to particular group decreases as its distance from the absorption proton increases.

Due to the decreasing deshielding influence, the τ values of absorption decrease in the following order

$$c > b > a$$



$$a > b > c$$



Useful Solvents in NMR

A substance free of proton should be used as solvent (i.e., which does not give absorption of its own in NMR spectrum).

Some important characteristics of solvents for NMR spectroscopy are:

1. It should be chemically inert and magnetically isotropic.
2. It should be devoid of hydrogen atom.
3. It should dissolve the sample to a reasonable extent

The NMR spectrum of even completely deuterated solvent does show one or more peaks. It is due to the presence of minor impurities in the solvent (the deuterated solvents are available commercially in 98-99.9% isotopic purity).

Chemical shift and multiplicities of residual protons in commercially available deuterated solvents.

Solvent	Approximate δ for ^1H equivalent (as contaminant)	^{13}C δ value
Acetic acid d_4 (CD_3COOD)	13 and 2(5)	21(7) , 177
Acetone- d_6 (CD_3COCD_3)	2(5)	30(7), 205
Acetonitrile- d_3 (D_3CCN)	2(5)	1.3(7), 117
Benzene $-\text{d}_6$ (C_6D_6)	7.15	128(3)
Carbon tetrachloride (CCl_4)	-	97
Chloroform d (CDCl_3)	7.24	77(3)
Deuterium oxide $-\text{d}_2$ (D_2O)	4.82	-
Dimethylsulphoxide- d_6 ($\text{D}_3\text{CS}(=\text{O})\text{CD}_3$)	2.5(5)	39.4(7)
Methanol- d_4 (CD_3OD)	3.4 (5), 4.8	49(7)
Ethanol- d_6 ($\text{D}_3\text{CCD}_2\text{OD}$)	1.1(br), 3.55(br), 5.26	17.2(7), 56.8(5)
Pyridine- d_5 ($\text{C}_5\text{D}_5\text{N}$)	7.5	123.4(3), 135.4(3), 149.8(3)
Dioxane d_8 ($\text{C}_4\text{H}_8\text{O}_2$)	3.53(m)	66.5(5)

Notes about some solvent

1. D6-DMSO has affinity for water, which makes it almost impossible to keep dry, even if it's stored over molecular sieve. Which make D6-DMSO has a large water peak, which varies in shape and position, from sharp and small at around 3.46 ppm, to very large and broad at around 4.06 ppm in wetter samples.
2. Deutero Methanol (CD_3OD), like DMSO it has a very high affinity for water and is almost impossible to keep dry. Its water peak is sharper and occurs more predictably at around 4.8 ppm.
 - Its main disadvantage of deutero methanol (CD_3OD) is that it will exchange ionisable protons in your sample for deuterons, and hence they will be lost from the spectrum, e.g., -OH, -NH and even -CONH₂; though these can often be relatively slow to exchange.
 - D_2O , like deutero methanol, it exchanges all acidic protons readily and exhibits a strong HOD signal at about 4.9 ppm. Samples made up in D_2O often fail to dissolve cleanly and benefit from filtration through a tight cotton wool filter.

- a) What is the energy difference between the two spin states of ^1H in a magnetic field of 5.87T?**
- b) b) of ^{13}C**