

FYS-KJM4740

MR Spectroscopy and Tomography – Part I

Eddy W. Hansen (and Bjørn Pedersen)



The new (2010) solid-state NMR spectrometer located at SINTEF Oslo, which is available for researchers at KI/UiO/Sintef.

Department of Chemistry
University of Oslo
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Table 1.2 Acronyms and abbreviations

BEST	Blipped echo-planar single-pulse technique
BOLD	Blood oxygen level dependent contrast
BURP	Band-selective, uniform response, pure-phase pulse
COSY	Correlation spectroscopy
CP-MAS	Cross-polarization with magic angle spinning
CPMG	Carr–Purcell–Meiboom–Gill
CSF	Cerebrospinal fluid
DOSY	Diffusion-ordered spectroscopy
EXSY	Exchange spectroscopy
fMRI	Functional magnetic resonance imaging of the brain
HMQC	Heteronuclear multiple-quantum correlation
HOHAHA	Homonuclear Hartmann–Hahn technique
HPLC	High-performance liquid chromatography
HSQC	Heteronuclear single-quantum correlation
INADEQUATE	Incredible natural abundance double-quantum transfer experiment
INEPT	Insensitive nuclei enhanced by polarization transfer
ISIS	Image-selected <i>in vivo</i> spectroscopy
MLEV	Malcolm Levitt's phase cycle
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NOESY	Nuclear Overhauser enhancement spectroscopy
NMR	Nuclear magnetic resonance
PRESS	Point-resolved spectroscopy
ROESY	Rotating-frame Overhauser enhancement spectroscopy
STEAM	Stimulated echo acquisition mode
TOCSY	Total correlation spectroscopy
WAHUHA	Magic pulse cycle of Waugh, Huber and Haeberlen
WALTZ	Wideband alternating-phase technique for zero splitting
WURST	Adiabatic soft radiofrequency pulse shaped like a sausage

Some of the many acronyms and abbreviations used in MR (Freeman, 2003)

Preface

NMR is an exciting and challenging experimental technique which is also intellectually demanding. The present booklet is intended for students taking FYS-KJM 4740 *MR-theory and medical diagnostics* in spring 2016 and covers the initial part of the course. It gives a comprehensive introduction to the basic theory and concept of Magnetic Resonance (MR).

The first NMR lecture note was prepared in 1977 (in Norwegian) while the present document represents a strongly modified version. The content has been adjusted according to the available MR equipment at the Department of Chemistry and also on the changing research activities in the Laboratory for Physical NMR.

Since the application of gradient pulses has become a “must” in both MR-spectroscopy (MRS) and MR-imaging (MRI), we find the theory of diffusion to represent a soft conceptual transition from the field of MRS to MRI.

We will appreciate any response from the student concerning typographical errors or obscurities in the text. So please, send your remarks to: eddywh@kjemi.uio.no .

Oslo, January 2016

Eddy W. Hansn

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1. NMR – Concepts

1.1 Applications of magnetic resonance (MR)

Since 1938 Nuclear Magnetic Resonance (NMR or MR¹) has found an increasing number of applications, as illustrated on Figure 1.1. Chemical applications are found on the left and medical applications on the right. The two areas are not distinct, but are largely overlapping. However, the applications are becoming increasingly more specialized and are frequently divided into separate subjects and professions. In this course, however, we will concentrate on the more

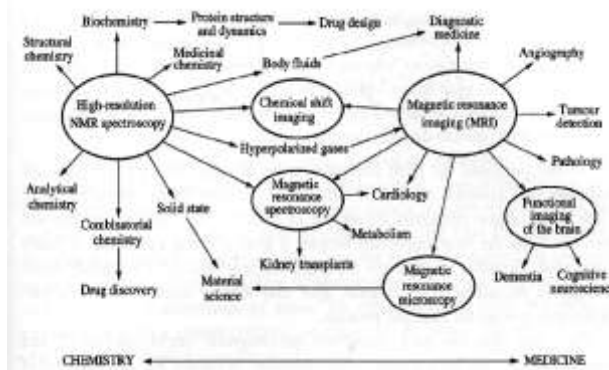


Figure 1.1 Applications of MR/MRI

fundamental aspects of NMR and will present some examples from the research activities

of the authors. NMR spectroscopy of substances in solution, often called high-resolution NMR, is the most frequently applied technique to probe the *type* of molecules, the *number* of molecules and the *structure* of molecules. Also, the *motional and dynamic characteristics* (translational, rotational) of the molecules can be probed by NMR. Because the molecular motion in solution averages out certain interactions, as will be explained later, the spectral peaks are very narrow. (The peaks are also called lines as in optical spectroscopy). Thus, the technique is called *high resolution* NMR

In contrast, the NMR peaks observed in solids are usually broad and featureless leading to the term: wide line NMR or solid-state NMR. By introducing some rather ingenious experimental modifications it is, however, possible to narrow the peaks from solids so the underlying fine structure can be made observable. NMR spectra of solids may also give information on the structure and motion (hindered rotation and diffusion) of the molecules, ions or atoms confined in the solid state.

MR is also capable of producing images of three-dimensional objects with a spatial resolution of 0.1 mm of large objects, like the human body (MRI) and down to 10 μm of smaller objects of dimension 1 cm (MR-microscopy). To extract this information one needs a radio transmitter, a radio receiver and a magnetic field as illustrated on Figure 1.2. The magnet is the largest and most expensive part of the equipment, making MR rather expensive as compared to other analytical equipment. Thanks to the development of micro-electronics that has given better and more sensitive radio-transmitters and receivers, combined with the development of new materials that has given stronger and more stable magnets, and the development

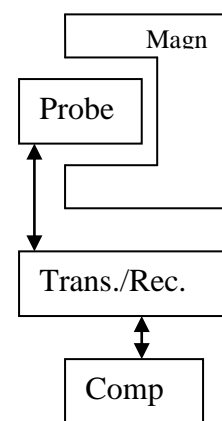


Figure 1.2. Set up

of cheaper computers that can collect and handle larger amounts

of data, MR has improved immensely since the first NMR-signal was detected in 1938.

During the last 35 years the sensitivity has increased by more than a million! At the end of this booklet we have briefly summarized the history of MR from the beginning of 1920-to the present day. Many scientists have contributed, and numerous surprising and

¹ Nuclear Magnetic Resonance. In medicine nuclear is usually associated with radioactivity. Therefore the N is dropped. (The use of radioactive compounds for medical purposes is called nuclear medicine.)

unexpected breakthroughs have appeared during the years. Most importantly, however, this development has not yet reached the end. Very likely, there are still new methods to be developed and new applications to be found that may surprise both the scientific community, as well as people in general!

Imaging (MRI) is mostly used in medicine as a forceful diagnostic tool, without the health risk connected to the use of ionizing radiation (X-rays) used in a CT (computer tomography). Moreover, MRI (also called magnetic tomography) does not only acquire images. For instance, equipment is available for recording ^1H - and/or ^{31}P -spectra of the object, or part of the object. The goal is to combine the two methods in order to first acquire a 3D-image which reveals the morphology of the object. Then to zoom in on the most interesting parts (f. ex. a small tumour) of this object in order to acquire a spectrum which may give further information on the chemistry taking place in this part.

Due to the broad range of applications of MR, a large number of textbooks are available. In the university library (BIBSYS) 347 reference books containing the phrase *magnetic resonance* were found of which 63 of were published between 2000 and 2005. Some references are summarized at the end of this booklet. You can also find review articles in different journals and yearbooks. Your choice of book(s) will depend on your background and the goal(s) of your study. The lecturer may give you further information.

1.2 A modern (MR) spectrometer

Figure 1.3 shows the relevant parts of a modern solution-NMR-spectrometer with a super-conductive magnet (right) to a computer (left). The sample is introduced from the top of the magnet and may be located within the magnet by an automatic sample changer. The basic rf-frequency is locked to the magnetic field by a ^2H -lock and makes the system more stable to any drift in the magnetic field, or the rf-frequency. ADC is the analogue to digital converter. Usually the spectrometer is equipped with several probes tailored for different purposes. To study solids one needs to generate rf-pulses of large amplitude to reduce the 90° -pulse down to $1\ \mu\text{s}$. This is because T_2 may be of the order of microseconds and not seconds as for liquids.

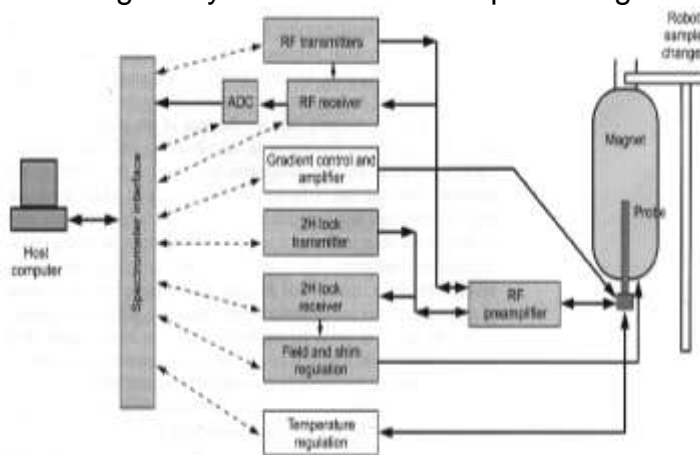


Figure 1.3. Relevant parts of a solution-NMR-spectrometer

Hence, solid state NMR spectrometer necessitates more powerful radio-transmitters.

1.3 MR - basic concepts

1.3.1 The Spin

MR is based on the fact that the atomic nuclei possess an *angular momentum* and hence a *magnetic dipole moment* (Figure 1.4). The angular momentum \mathbf{L}

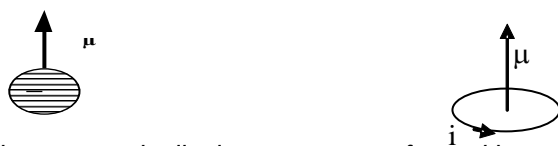


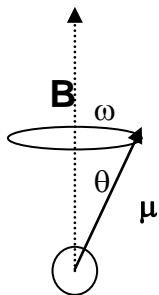
Figure 1. 4. A nuclear magnetic dipolemoment μ , as formed by a combination of the internal spin and the the charge of the nucleus which results in a current i .

is a characteristic property of the nucleus just like its mass and charge. Moreover, an atomic nucleus with angular momentum also possesses a magnetic dipole moment μ ². The magnetic dipole moment μ (a vector) is parallel to its angular momentum L (see Exercise 1):

$$\mu = \gamma L \quad (1.1)$$

γ is the ratio between the magnetic moment of the nucleus and its angular momentum. γ is termed the *gyromagnetic ratio*. It has been determined experimentally for all isotopes and can be found in tables. In the literature it is common practice to call a particle possessing an angular momentum and a magnetic dipole moment, a *spin*. An example of a macroscopic object having a magnetic dipole moment is a small rod magnet and/or a loop of wire (with current). A loop of wire enclosing an area of 1 m² and carrying a current of 1 A (ampere) will have a dipole moment equal to 1 Am². Therefore the SI-unit for magnetic dipole moment is Am².

1.3.2 The MR phenomenon – classical mechanics



In a magnetic field \mathbf{B} a spin will attain a potential energy which depends on the orientation of the magnetic dipole moment μ relative to \mathbf{B} .³ The potential energy is⁴:

$$E = -\mu \cdot \mathbf{B} = -\mu B \cos\theta \quad (1.2)$$

θ is the angle between μ and \mathbf{B} as shown in Figure 1.5. The equation that describes the motion of the dipole μ in a magnetic field \mathbf{B} (see Exercise 2) reads:

Figure 1.5

$$d\mu/dt = \gamma\mu \times \mathbf{B} \quad (1.3)$$

This is a differential equation that can be solved when given the initial conditions. If $\mathbf{B} = \mathbf{B}_0$ (constant, i.e. independent of time), and μ makes an angle θ with the magnetic field, the solution is that μ rotates (precesses) about \mathbf{B}_0 with an angular velocity ω_0 (see Exercise 1.2) given by:

$$\omega_0 = -\gamma\mathbf{B}_0 \quad (1.4)$$

and represents a particularly important equation in MR. The equation shows that the angular velocity ω_0 is proportional to the magnetic field strength B_0 with a proportionality constant γ , the gyromagnetic ratio. This angular frequency is called the Larmor frequency.⁵

²We use a bold letter for a vector as μ in this booklet.

³The correct name for \mathbf{B} is the magnetic flux density and the unit for \mathbf{B} is tesla (T). Also the older unit gauss (G) some times is used: 1 T = 10⁴ G. Using the basic SI-units 1 T = 1 kg/(As²). The unit for μ is Am². The product $\mu\mathbf{B}$ is then joule (J = kg (m/s)²). (Remember that $\mu\mathbf{B}$ is the potential energy of μ in \mathbf{B} .)

⁴ $\mu \times \mathbf{B}$ is called the vector product between μ and \mathbf{B} and is directed along a unit vector orthogonal to the plane determined by the two vectors μ and \mathbf{B} , respectively. Its norm or length is defined by $|\mu \times \mathbf{B}| = \mu B \sin \theta$. The scalar- or dot product between μ and \mathbf{B} is defined by $\mu \cdot \mathbf{B}$.

⁵Named after Sir Joseph Larmor (1857-1942) who first performed the classical calculation in 1895.

Isotope	I	Abundance in %	γ in 100·radMHz/T
^1H	1/2	99.985	2.67510
^2H	1	0.015	0.41064
^{13}C	1/2	1.108	0.67263
^{14}N	1	99.63	0.19324
^{15}N	1/2	0.37	-0.27107
^{19}F	1/2	100.0	2.51665
^{23}Na	3/2	100.0	0.70760
^{31}P	1/2	100.0	1.08290
^{39}K	3/2	93.10	0.12484

MR-data for some of the most popular nuclei are given in Table 1. Using Eq 1.3 we notice that $d\boldsymbol{\mu}/dt \cdot \mathbf{B}_0 = d(\boldsymbol{\mu} \cdot \mathbf{B}_0)/dt = (\boldsymbol{\mu} \times \mathbf{B}_0) \cdot \mathbf{B}_0 = 0$. i.e., θ in Eq 1.2 is constant.

Classical physics tells us that the spin in a magnetic field will behave in the same way as a spinning top in the gravitational field (Figure 1.6).

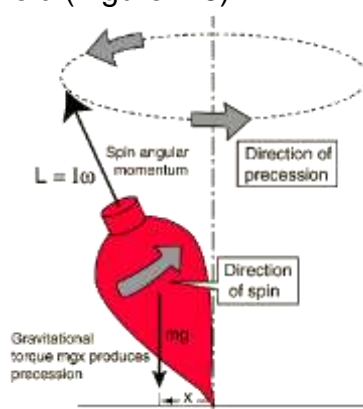


Figure 1.6. Spinning in a gravitational field

1.3.3 The NMR phenomenon – quantum mechanics

Nature has shown us that a nuclear spin, defined by a spin quantum number I , can only take $2I+1$ different directions in space.⁶ The quantum number I is known for all stable isotopes. In particular, isotopes with a spin quantum number I equal to 0 have no magnetic dipole moment and do not precess, and is therefore invisible to MR. ^{12}C and ^{16}O are two such nuclei.⁷ An isotope with $I = 1/2$ can take two directions. ^1H , ^{13}C , ^{15}N , ^{19}F and ^{31}P are examples of such spin-1/2 nuclei⁸ and are the simplest and also the most studied nuclei in MR.

⁶What nature has taught us is summed up in the quantum theory.

⁷An isotope where the number of protons and neutrons is an equal number has $I = 0$. The explanation is that both protons and neutrons have angular momentum, but because they are paired antiparallel in the nucleus the result is 0.

From a quantum mechanical point of view we may define an energy operator or Hamiltonian operator \hat{H} according to the Schrödinger equation:

$$\hat{H}|\Psi\rangle = E|\Psi\rangle \quad (1.5)$$

where E is the energy and $|\Psi\rangle$ is the spin wave function. For a single spin interacting with a magnetic field B_0 (directed along the z-axis) the Hamiltonian is denoted \hat{H}_Z , where Z stands for Zeeman⁹. From classical mechanics the energy E takes the form

$E = -\boldsymbol{\mu} \cdot \mathbf{B}_0$ and $\boldsymbol{\mu} = \gamma\mathbf{L}$. By replacing \mathbf{L} by its quantum mechanical analogous $\hbar\bar{I}$, where \hbar is Planck's constant and I is the spin operator¹⁰, we may write Eq 1.5 in the form:

$$\hat{H}_Z = -\boldsymbol{\mu} \cdot \mathbf{B}_0 = -\gamma\mathbf{L} \cdot \mathbf{B}_0 = -\gamma B_0 \hbar \bar{I}_z \quad (1.6)$$

For $I = 1/2$ particles there are two eigenstates, defined by the spin wave functions $|\alpha\rangle$ and $|\beta\rangle$, respectively:

$$\bar{I}_z|\alpha\rangle = \frac{1}{2}|\alpha\rangle \quad (1.7a)$$

$$\bar{I}_z|\beta\rangle = -\frac{1}{2}|\beta\rangle \quad (1.7b)$$

Hence, we may calculate the corresponding two energies, according to:

$$\hat{H}_Z|\alpha\rangle = -\gamma B_0 \hbar \bar{I}_z|\alpha\rangle = -\gamma B_0 \hbar / 2 |\alpha\rangle = E_+|\alpha\rangle \quad (1.7c)$$

$$\hat{H}_Z|\beta\rangle = -\gamma B_0 \hbar \bar{I}_z|\beta\rangle = \gamma B_0 \hbar / 2 |\beta\rangle = E_-|\beta\rangle \quad (1.7d)$$

Hence,

$$E_+ = -\frac{1}{2} \gamma B_0 \hbar \text{ and } E_- = \frac{1}{2} \gamma B_0 \hbar$$

where E_+ is the energy for the state where the magnetic dipole moment is parallel to the magnetic field and E_- is the energy for the magnetic dipole oriented anti-parallel to the external field, as illustrated in Figure 1.7. To produce the actual resonance

phenomenon, an alternating magnetic field B_1 is applied perpendicular to the static field B_0 , which introduces a perturbing term in the Hamiltonian:

$$\hat{H}_{\text{pert}} = -\gamma B_1 \hbar \bar{I}_z \quad (1.7e)$$

⁸An electron is also a spin 1/2 particle. So atoms with an unpaired electron can be studied with MR. Because the magnetic moment of an electron is about 2000 times larger than the proton magnetic moment the equipment used to study unpaired electrons are different from the equipment used for NMR (radio frequencies in NMR and microwave frequencies in ESR). Electron-MR is called ESR (Electron Spin Resonance) or EPR (Electron Paramagnetic Resonance). At UiO there are two EPR-spectrometers in the biophysics group in the Department of Physics (see <http://www.fys.uio.no/biofysikk/eee/esr.htm>). They are located two stories above the Physical NMR Laboratory.

⁹ The Dutch physicist Pieter Zeeman (1865-1943) discovered in 1896 that certain spectral lines split when the sample was placed in a magnetic field. That is called the Zeeman Effect.

¹⁰ $\hbar = 662.6176(36) \cdot 10^{-36}$ Js. $\hbar = h/(2\pi)$

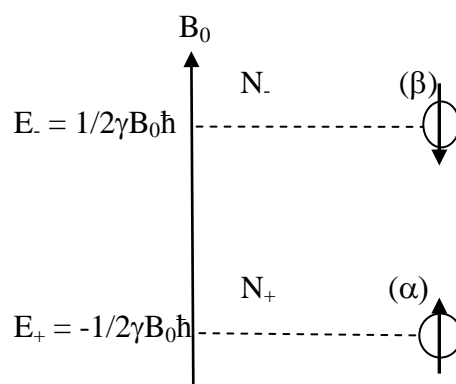


Figure 1.7. Energy levels (E_+ , E_-) and spin-populations (N_+ , N_-) of spin-states α and β .

Hence, using electromagnetic radiation with the correct frequency the spins will change orientation in space. The energy in electromagnetic radiation comes in packets called photons having energy $h\nu$, where ν is the radiation frequency and h is Planck's constant. Hence, the energy difference between the two eigenstates reads:

$$\Delta E = (E_- - E_+) = \hbar\omega = h\nu = \gamma B_0 \hbar \text{ or } \omega = \omega_0 = \gamma B_0 \text{ (note: } \omega = 2\pi\nu) \quad (1.7f)$$

and defines the basic equation in MR, the Larmor equation. The radio stations, i.e., the Larmor frequencies in a "MR-radio" are wider spaced than in an ordinary radio,¹¹ and can only be tuned to one type of nuclei at a time, for instance either protons or carbons. We notice that the basic equation describing the resonance phenomenon is the same whether derived from classical physics or quantum physics. One model is not better than the other. Actually, both models are used in tandem to explain different MR observations, making the MR-language somewhat special.

The basic equation shows that when a nuclear spin in a magnetic field is exposed to electromagnetic radiation with the right frequency (Larmor frequency), an exchange of energy between the spins and the radiation takes place. This exchange of energy is called resonance and the frequency is denoted the resonance frequency.¹²

In a 1.5 T field the resonance frequency for the protons is 64 MHz¹³. All other isotopes have a resonance frequency that is smaller, as shown in Table 1.2. However, all frequencies are in the radio frequency range (MHz).

¹¹The FM-band stretches from 88 to 108 MHz

¹²We are mostly acquainted with resonance in a mechanical system. When a glass scatters of a note it is because the note corresponds to one of the resonance frequencies of the glass.

¹³1 MHz = 10^6 Hz. 1 Hz = 1 s^{-1} . Hz = hertz.

Table 1.2. Resonance frequency of ^1H and some other isotopes in a 1.5 T magnetic field¹⁴.

<i>Table 1.2. The resonance frequency at 1.5 T</i>	
Isotope	Resonance frequency/MHz
^1H	63.9
^2H	9.8
^{13}C	16.1
^{14}N	4.6
^{15}N	6.5
^{19}F	60.1
^{23}Na	16.9
^{31}P	25.9
^{39}K	3.0

1.3.4 The spin system

A sample will contain many spins (Avogadro's number). Since each spin, or magnetic dipole, generates its own magnetic field, each spin in the system will experience the external magnetic field as well as the magnetic field set up by all its neighbouring spins. This local field will in general be smaller than the external field.¹⁵ However, we can continue to describe the collection of spins in the sample on the basis of the energy levels given for a single, isolated spin. If denoting the collection of spins of the same type in the sample a "spin-system" it may be uniquely described if knowing the number of spins (N_+) in the lowest energy level since the number (N_-) of spins in the highest energy level will then be equal $N_0 - N_+$ where N_0 is the total number of spins in the system. Such a spin system can be described in a thermodynamic sense by the Boltzmann equation:

$$\frac{N_-}{N_+} = \exp\left[-\frac{\Delta E}{kT}\right] = \exp\left[-\frac{\hbar\gamma B_0}{kT}\right] \quad (1.8a)$$

Since $\Delta E = \hbar\gamma B_0 \ll kT$, we may write:

$$N_+ = \frac{N_0}{2} \left[1 + \frac{\hbar\gamma B_0}{2kT} \right] \quad (1.8b)$$

$$N_- = \frac{N_0}{2} \left[1 - \frac{\hbar\gamma B_0}{2kT} \right] \quad (1.8c)$$

Moreover, because $N_+ + N_- = N_0$ then:

$$\Delta N = N_+ - N_- = \frac{\gamma\hbar B_0 N_0}{2kT} \quad (1.8d)$$

where ΔN is the difference in population between the two energy levels, i.e., the surplus of spins in the lowest energy level.

¹⁴1 MHz = 10^6 Hz. 1 Hz = 1 s^{-1} . Hz = hertz.

¹⁵This is one example of a local magnetic field. In the next chapter we will present other local fields.

We will later show that we can change the population in each level by irradiating the spins. By turning all spins 180° the population difference will change sign. Thermodynamically the system can still be described by the Boltzmann distribution if accepting a negative absolute temperature (It requires energy to turn all spins). Consequently, a negative temperature is hotter than a positive temperature when the system is in thermal equilibrium!¹⁶

We define a macroscopic magnetic dipole moment \mathbf{M} as a (vector)-sum of all the dipole moments (or spins) in the spin system. At equilibrium \mathbf{M} will be parallel to \mathbf{B}_0 and reads: $\mathbf{M} = (\Delta N \mu_B) \mathbf{k}$ where \mathbf{k} is a unit vector along \mathbf{B}_0 (defined as the z-axis). \mathbf{M} is an important quantity in MR and forms the basis for the observable MR-signal.

Einstein showed that when a photon passes through a spin system the probability for absorption of the photon will be equal to the probability that a similar photon is emitted. Hence, a signal is detectable only when a population difference exists (absorption when $\Delta N > 0$ and emission when $\Delta N < 0$).

1.3.5 The Free Induction Decay (FID)

The motion of the macroscopic magnetization \mathbf{M} is governed by the same physical laws as for an individual magnetic dipole (Eq 1.3). Hence,

$$d\mathbf{M}/dt = \gamma \mathbf{M} \times \mathbf{B}_0 \quad (1.9)$$

However, it can be shown (lecture) that the macroscopic magnetization component \mathbf{M}_\perp , normal to the static magnetic field \mathbf{B}_0 , is zero. Since the receiver coils is placed normal to \mathbf{B}_0 , there is no sample magnetization to be detected. So, how can we actually probe the NMR signal?

The answer is that the macroscopic magnetization aligned along \mathbf{B}_0 (z-axis) must – somehow - be tilted, or flipped, or rotated into the xy-plane where the receiver coil is located. One way of performing this “tilt” is to apply a magnetic field B_1 in the xy-plane, for instance, along the x-axis. Importantly, this magnetic field must oscillate with a frequency ω (around the z-axis) which is close to the Larmor frequency ω_0 . This can be accomplished by sending an alternating current of frequency ω and amplitude B_1 into the coil, as illustrated on Figure 1.8. The oscillating magnetic field generated in this way may be regarded as composed of two rotating magnetic fields with opposite directions, as illustrated in Figure 1.8 (right). Only the B_1 -field component rotating in the same direction as \mathbf{M} will influence \mathbf{M} and suggests that the macroscopic magnetization \mathbf{M} will experience two magnetic fields, one static magnetic field (\mathbf{B}_0) and one rotating magnetic field \mathbf{B}_1 .

¹⁶ If you choose $-1/T$ as a horizontal temperature scale you will get a better scale to understand this. The low temperatures will be to the left and the high temperatures to the right. Then it is also easier to understand that you will never get to 0 K as this will be at minus infinity.

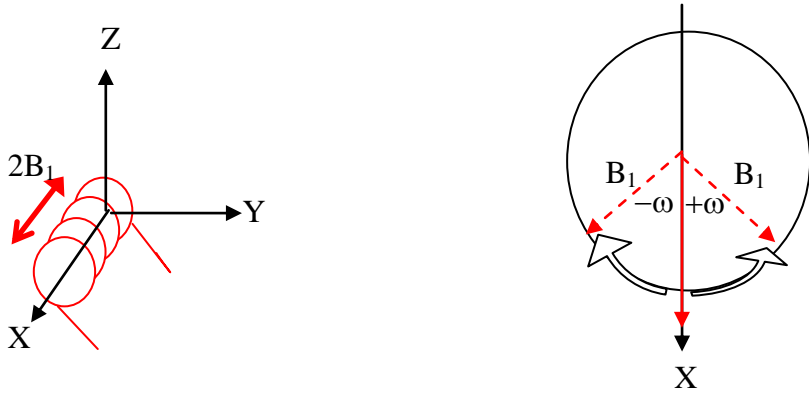


Figure 1.8. left: Coil arrangement with a linearly polarized (alternating) current along the x-axis. right: Decomposition of the alternating current into two oscillating magnetic fields with frequency ω and $-\omega$ (rotating in opposite directions).

To visualize the motion of the magnetization \mathbf{M} in a system of two orthogonal magnetic fields \mathbf{B}_0 and \mathbf{B}_1 is not too complex. It is simply composed of two independent rotations of circular frequencies $\omega_0 (= -\gamma B_0 \mathbf{k})$ and $\omega_1 (= -\gamma B_1 \mathbf{i})$ around the z-axis and the x-axis, respectively. However, this motion can be significantly simplified if viewing the motion in a coordinate system (uvz) rotating around the z-axis with frequency $\omega (= -\omega \mathbf{k})$, i.e., the same frequency as the oscillating B_1 field. In this rotating frame of reference \mathbf{B}_1 is directed along the u-axis and \mathbf{B}_0 is directed along the z axis. It can be shown that in this rotating frame of reference the magnetization can be considered to experience or sense an apparent or effective magnetic field \mathbf{B}_{eff} which can be written:

$$\mathbf{B}_{\text{eff}} = B_1 \mathbf{u} + (B_0 - \omega/\gamma) \mathbf{k} \quad (1.10)$$

where $\omega_0 = \gamma B_0$ (Figure 1.9; left). We notice that in the rotating coordinate system all magnetic fields can be considered constant and independent of time. Of particular interest is the situation when on resonance ($\omega = \omega_0 = -\gamma B_0$) because then only the B_1 field along the u-axis is non-zero. As long as B_1 is turned on, this causes a precession (rotation) of the magnetization around the negative u- axis with a resonance frequency $\omega_1 (= -\gamma B_1 \mathbf{u})$ as illustrated on Figure 1.9 (right). It follows that the angle (α) of rotation (phase angle) of \mathbf{M} around the negative u-axis after time t is:

$$\alpha = \omega_1 t = \gamma B_1 t \quad (1.11)$$

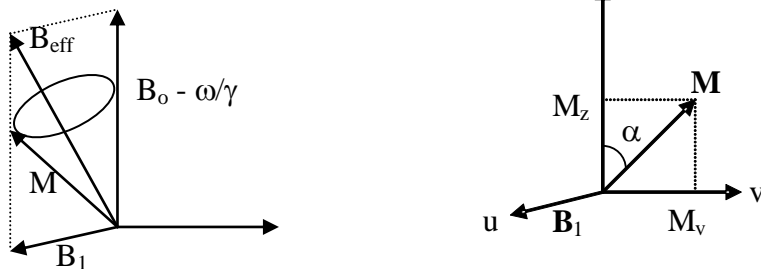


Figure 1.9. Rotation of a macroscopic magnetic moment \mathbf{M} around the effective magnetic field \mathbf{B}_{eff} (left) and the corresponding rotation of \mathbf{M} around \mathbf{B}_1 when on resonance ($B_0 - \omega/\gamma = 0$; right).

If the radio pulse is on for a time t_{90} , which corresponds to the magnetization being rotated an angle $\alpha = \pi/2$ (a so called “90° rf-pulse), the magnetization \mathbf{M} will be directed along the y -axis in the rotating frame. This signal can then be detected by a receiver coil placed along the x - or y - axis in the laboratory frame.

As $M_z = \Delta N \cdot \mu_z$, the signal intensity will be proportional to $\frac{\gamma^2 \hbar^2 B_0 N_0}{4kT}$ (Exercise 1.3). As a consequence, the signal intensity increases with the strength of the external magnetic field B_0 and it will become stronger for those nuclei that have the larger γ . This latter implies that ^1H and ^{19}F will give a stronger signal than ^{13}C and ^{15}N (see Table 1.1). Furthermore the signal is proportional to N_0 , the number of spins confined in the receiver coil. N_0 will be proportional to the density of spins, which in turn depends on the isotopic abundance of these spins (see Table 1.1). The abundance can be increased by isotope enrichment. We will return to this point in a later chapter when discussing the signal-to-noise ratio.

Also, a 90°- pulse that last a few microseconds (μs) is called a hard or non-selective pulse, while a 90°- pulse that last a few milliseconds (ms) is called a selective or soft pulse.¹⁷ A hard pulse covers a larger frequency range and will be commented on in a later section.

1.4 MR detection

How then can we detect the x - and y -components of the oscillating (magnetization) signal: $I_s = I_0 \cdot \exp[-i\omega t]$ ($= I_0 \cdot \cos \omega t \vec{i} + I_0 \sin \omega t \vec{j}$) when only one receiver coil (along the x -axis) is applied? That is, only the signal $I_s^R = I_0 \cos \omega t$ along the x -axis is sampled. One option is to have two coils, one along the x -axis and the other along the y -axis. However, such an arrangement is practically difficult to realize. There exists, however, an internally generated oscillating signal I_{REF} of frequency ω_0 , i.e., $I_{REF} = \exp[-i\omega_0 t]$ ($= \cos \omega_0 t \vec{i} + \sin \omega_0 t \vec{j}$) By mixing (multiplying) the two signal (see Figure 1.10) and filtering out the high frequency component ($\omega + \omega_0$), we obtain the two rotating frame signals $S_U = I_0 \cdot \cos((\omega - \omega_0)t)$ and $S_V = -I_0 \cdot \sin((\omega - \omega_0)t)$ which are stored in two separate channels, denoted U and V , respectively (see Problem 1.6). As can be noted, the two signals S_U and S_V are phase shifted by 90°.

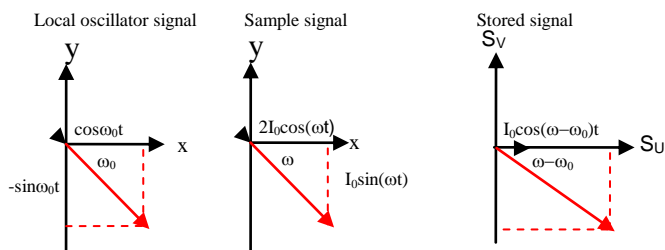


Figure 1.10. Illustration of the local oscillator signal, the sample signal and the resulting two signals U and V stored in the computer.

¹⁷1 $\mu\text{s} = 10^{-6}$ s

1.5 Exercises

- 1.1)** Try to argue why $\boldsymbol{\mu} = \gamma \mathbf{L}$ by applying the well known result that the magnetic dipole moment (μ) formed by a closed current loop (i) is proportional to the current times the area (A) defined by the current loop, i.e., $\mu = iA$ (assume a circular current loop).
- 1.2)** Discuss the motion of a magnetic dipole $\boldsymbol{\mu}$ in a magnetic field \mathbf{B}_0 , i.e., derive the equation; $d\boldsymbol{\mu}/dt = \gamma \boldsymbol{\mu} \times \mathbf{B}_0$ by combining the angular momentum $\mathbf{L} (= \mathbf{r} \times m\mathbf{v})$ and the torque $\boldsymbol{\tau} = (\mathbf{r} \times \mathbf{F} = \boldsymbol{\mu} \times \mathbf{B}_0)$.

- 1.3)** Show that the macroscopic magnetization M can be approximated by the formula:

$$M \propto \frac{1}{4kT} (\gamma \hbar)^2 B_0 N_0$$

- 1.4)** Describe the motion of the magnetic dipole moment $\boldsymbol{\mu}$ in the rotating frame of reference by solving the Equation:

$$\frac{d\boldsymbol{\mu}}{dt} = \gamma \boldsymbol{\mu} \times \mathbf{B}_{eff} \quad \text{when} \quad \mathbf{B}_{eff} = (B_0 - \omega/\gamma) \mathbf{k}$$

where $-\omega \mathbf{k}$ defines the frequency of the rotating frame of reference.

- 1.5)** What is the effect of a linearly polarized magnetic field $\mathbf{B}_1 = B_1 \cos \omega t \mathbf{i}$ (in the laboratory frame (xyz)) on the magnetic dipole moment $\boldsymbol{\mu}$, when “on resonance”, i.e., $\omega = \omega_0$. (Hint. Use the rotating frame concept)

- 1.6)** An internally generated oscillating signal $I_{RX} (= \exp(-i\omega_0 t))$ of frequency ω_0 is multiplied by the detected sample signal $I_S = 2I_0 \cos(\omega t) = I_0 \exp(i\omega t) + I_0 \exp(-i\omega t)$. Show that the resulting mixed signal S takes the form:

$$S = I_0 \cos[(\omega_0 - \omega)t] \vec{i} - I_0 \sin[(\omega_0 - \omega)t].$$

(Hint: The high-frequency component $|\omega_0 + \omega|$ is filtered out by using a low-pass filter.

See also notes from the lecture!)

2. Bloch equation, relaxation and molecular motion

2.1 Spin-spin relaxation time - T_2

From the discussion above, we found that after a 90° -pulse \mathbf{M} will precess around \mathbf{B}_0 , and will induce a current in the coil. This current will be an alternating current which varies with the resonance frequency. It also follows that the amplitude of the current will stay constant. This is, however, unreasonable since “nothing can last for ever”. What will then make the signal decay? We know that \mathbf{M} will be directed along \mathbf{B}_0 when the system is at equilibrium. Since the 90° -pulse has brought the system out of equilibrium, how will the spins find their way back to equilibrium? We will now try to give the answers to these two questions.

\mathbf{M} represents the vector sum of all spins in the sample. The magnetic field experienced by each spin is the sum of the external field (B_0) and a local field from the neighbouring spins (B_{lok}). The external field is the same for each spin, but the local field may vary from one spin to another because it depends on the relative orientation of the neighbouring spins. (We will describe the local field in more detail in the next chapter). Because the resonance frequency is proportional to the magnetic field experienced by the actual spin ($B_0 + B_{lok}$), the spins sensing a large local field will necessarily precess faster than spins experiencing a smaller local field. This means that the components of \mathbf{M} in the rotating coordinate system will spread out in the xy -plane with time, due to loss of phase coherence, causing the resultant M to decay. A simple assumption is that M will decay exponentially with time (Figure 2.1)

$$M = M_0 e^{-t/T_2} \quad (2.1)$$

T_2 is called the spin-spin relaxation time and is an important time parameter in NMR.

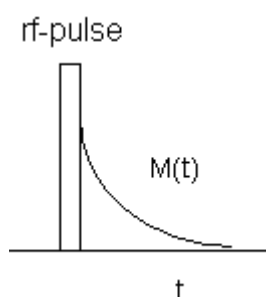


Figure 2.1 Signal decay after application of an rf-pulse

We note that when $t = T_2$ the signal intensity will be reduced by a factor e^{-1} ($e = 2.7183$) relative to its initial value.

2.2 Spin-lattice relaxation - T_1

The other question we asked was how long time it takes for a spin-system to relax to equilibrium after being perturbed. The answer is related to molecular motion through the time variation of the local magnetic field B_{lok} . For instance, the local magnetic field set up by the combined effect of electron currents within the molecule and the molecular motion will fluctuate with time. Of particular importance, the fluctuation frequency of these local magnetic fields which accurately matches the Larmor frequency of the spins will be the most effective source of relaxation. For simplicity,

we will assume the macroscopic magnetization to return to equilibrium exponentially with respect to time, after being perturbed by for instance an rf-pulse (Exercise 2.7) □ Actually, it can be shown that after the magnetization is first perturbed by an rf-pulse which tip the magnetization an angle θ relative to the external field, the magnetization M_z along the static magnetic field will increase with time according to:

$$M_z = M_0(1 - (1 - \cos\theta) e^{-t/T_1}) \quad (2.2)$$

where T_1 is called the spin-lattice relaxation time and is an important MR-parameter.

Within the rotating frame of reference, we may summarize: Before a 90° -pulse $M_z = M_0$ and $M_x = M_y = 0$. Immediately after applying a 90° -pulse $M_z = 0$, $M_x = 0$, and $M_y = M_0$. After a time $t \gg T_1$ it follows that $M_x = M_y = 0$ and $M_z = M_0$ and the system has returned back to equilibrium.

The signal detected in the radio receiver will be at a maximum immediately after the rf-pulse and later decay as shown in figure 2.2. Because the signal is detected after the transmitter has been turned off the signal is called a *free induction decay* (fid). Interestingly, we can determine T_2 by analyzing the decay of this fid.

One frequently approach to measure T_1 is to expose the spin system to a 90° -rf-puls, a time τ after applying a 180° pulse, and then monitor the time behaviour of M_z as a function of τ (Figure 2.3). This is denoted an Inversion Recovery pulse sequence and is illustrated in Figure 2.2).

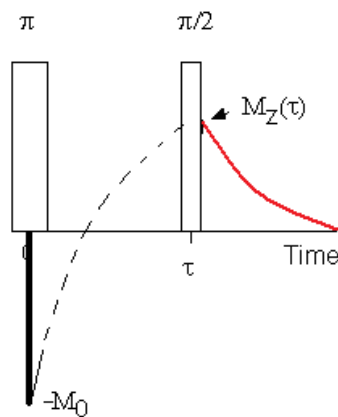
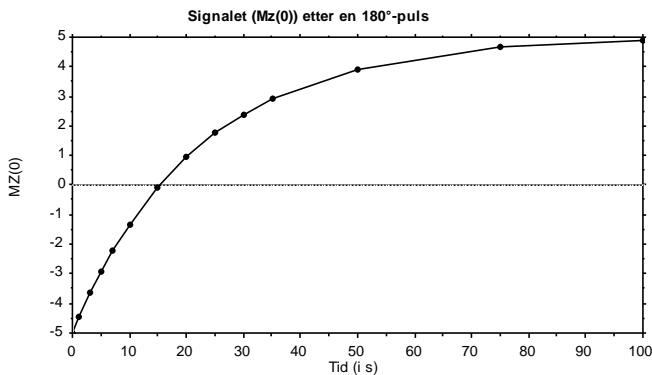


Figure 2.2. Inversion recovery pulse sequence. The initial magnetization M_0 directed along the positive z-axis (static magnetic field direction) is inverted by a π -rf-pulse. During time τ the magnetization is growing steadily until a second rf-pulse ($\pi/2$ -pulse) is applied for detection.

For instance, the first rf-pulse will be a 180°-pulse. Immediately after such a pulse M_z will be equal to $-M_0$ and no signal will be detected in the xy-plane ($M_x = M_y = 0$). However, if applying a 90°-puls a time τ after the 180°-pulse the magnetization in the xy-plane will be different from zero and equal to $M_z(\tau)$.

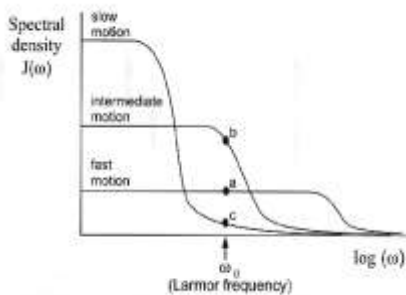


An example showing how $M_z(\tau)$ varies with τ is depicted on Figure 2.3. The points represent ^{13}C -signal intensities from a sample of benzene at room temperature. The solid curve represents a non linear least-squares model fit to the observed data with T_1 equal to 22.5 s.

Figure 2.3. Model fitted curve ($M_z = M_0(1 - 2e^{-\tau/T_1})$) to the observed spin-lattice relaxation data of benzene as obtained by an inversion recovery pulse sequence (Figure 2.2).

2.3 Molecular dynamics

Generally, a molecular motion can be characterized by some correlation time denoted τ_c .



For instance, the motion of a water molecule may be characterized by a rotational correlation time τ_R (the time needed to rotate one radian) and a translational correlation time τ_T (the time needed to diffuse one radian). We may then define a “memory” function:

$$f_c(\tau) = e^{-\tau/\tau_c} \quad (2.3)$$

Figure 2.4

which simply tells us that after a time of the order of $t \approx 5\tau_c$ memory about the motion is lost. By fourier transforming Eq 2.3 we obtain the characteristic frequency spectrum $J(\omega)$ of the molecular motion (fluctuations of the internally generated magnetic fields caused by molecular tumbling) which reads:

$$J(\omega) = \int_{-\infty}^{\infty} f_c(\tau) e^{i\omega\tau} d\tau = \frac{2\tau_c}{1 + \omega^2\tau_c^2} \quad (2.4)$$

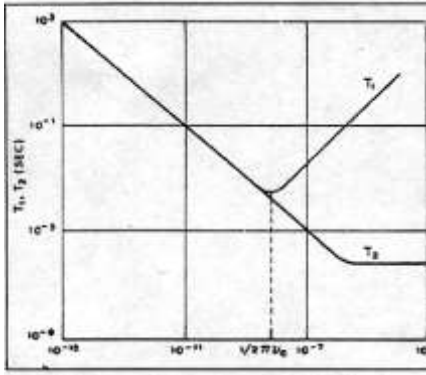


Figure 2.5

The frequency function $J(\omega)$ is denoted a spectral function in which $dN = J(\omega)d\omega$ simply represents the probability of finding dN molecules with motion frequencies between ω and $\omega+d\omega$. This function is illustrated in Figure 2.4 for three different values of τ_c (from Claridge 1999) where the inverse of the correlation time $1/\tau_c$ is the jump frequency. The molecular motion results in a fluctuating magnetic field in the position of the spins and will induce transitions between energy levels and thus affect both T_1 and T_2 . Figure 2.5 illustrates how T_1 and T_2 depend on the correlation time τ_c ; For instance:

$$\frac{1}{T_1} \propto J(\omega) = \frac{2\tau_c}{1 + \omega^2\tau_c^2} \quad (2.5)$$

It is, however, outside the scope of this work to derive Eq 2.5. The graph shows that T_1 goes through a minimum (Exercise 2.4). At the T_1 -minimum (Figure 2.5) the jump frequency $1/\tau_c$ can be assigned and is identified with the Larmor frequency, as illustrated by curve b in Figure 2.4. For slower motion (longer τ_c ; curve c in Figure 2.4) T_1 will increase while T_2 will decrease and subsequently reach a constant value, the rigid-lattice T_2 . (Figure 2.5). For faster motions, T_2 will be equal to T_1 (Figure 2.5) and both relaxation times will increase with decreasing correlation time (faster motion). Since there is an intimate relation between correlation time and temperature (ref. Arrhenius equation), short correlation times are often associated with motions at high temperature. Hence, from Eq 2.5 we notice that at high temperature ($\omega^2\tau_c^2 \ll 1$), T_1 (and T_2) will be independent on the resonance frequency and proportional to τ_c .

2.4 Exercises

2.1) Set up the general Bloch equation in the rotating frame of reference. Write down the Bloch equation when on resonance ($\omega = \omega_0$)

2.2) Assume that you have applied a B_1 field such that $M_y(0) = M_0$, $M_x(0) = 0$ and $M_z(0) = 0$ in the laboratory frame. Set up the Bloch equation (in the rotating frame) and find the solution for $M_y(t)$ and $M_z(t)$ when $\omega_1 = 0$ (B_1 field is turned off) and you are “on resonance”. Explain this experiment.

2.3) You want to perform an Inversion Recovery experiment. Set up the Bloch equation (in the rotating frame of reference) and show that the final result is equivalent to Eq 2.2 with $\cos\alpha = -1$. Consider only the z-component (M_z)

2.4) Show that T_1 goes through a minimum when increasing the correlation time (decreasing the temperature). (Hint: use Eq 2.5)

2.5) What is the frequency spectrum $F(\omega)$ of the transversal magnetization $M_y(t)$ in Exercise 2.2

2.6) Set up the Bloch equation in the rotating frame of reference ($\omega = \omega_0$) when a static gradient field $\mathbf{G} = g_0 z \mathbf{k}$ is present along the external magnetic field B_0 (z-axis). Assume $B_1 = 0$

2.7) If denoting the number of spins in the two possible energy levels of a spin- $\frac{1}{2}$ system by N^+ and N^- , and we introduce the so called transition probabilities W^+ and W^- . (W^+ defines the probability for a spin going from the lower to the higher energy level and W^- represents the probability for a spin going from the higher to the lower energy level) we can set up an equation for how the population difference ($\Delta N = N^+ - N^-$) varies with time: Show that:
$$\frac{d(\Delta N)}{dt} = -(W^+ + W^-) \cdot (\Delta N - \Delta N_0)$$

What is the meaning of ΔN_0 ?

Actually, the spin-lattice relaxation rate $1/T_1$ is defined by $1/T_1 = W^+ + W^-$.

Show that this leads to the famous result:
$$\frac{dM_z}{dt} = -\frac{M_z - M_0}{T_1}$$

3. Spin echo - Relaxation - Diffusion

3.1 Local magnetic fields

The magnetic field in the position of a spin is determined by the sum of the external magnetic field B_0 and the local magnetic field B_{lok} . There will be different types of local fields, some intrinsic to the sample, and some which may be more or less controlled. Some local fields shift the peaks in the spectrum while others are responsible for additional fine structures. As a consequence, the information obtainable from a MR-signal depends on how successful these shifts and fine structures can be detected and analyzed.

3.2 Spin echo

The MR-signal originates from that part of the sample which is located within the receiver coil. Ideally, the external magnetic field does not vary over the sample volume. However, this is not the case in practise. In the real world the magnetic field will vary from one place in the sample to another.

This variation in magnetic field over the sample volume is called inhomogeneity and may be reduced by shimming. All MR-magnets are equipped with (correction) coils. When a current is introduced in these coils they set up magnetic fields which may partly counteract and hence reduce the inhomogeneities within the sample volume. How constant the resulting magnetic field will be depends on the size

of the sample and the skills of the operator.

In all modern MR spectrometers, this shimming may be performed automatically within a reasonable time. For a liquid sample the width of the resonance peaks are generally determined by the residual magnetic field inhomogeneities and implies that the experimentally determined T_2 (from the fid) is shorter than the real and inherent T_2 . The former is therefore usually denoted T_2^* .

The true T_2 can be determined in an ingenious way by applying a series of rf-pulses in series. If we first apply a 90° -pulse and then, after a time τ , irradiate the sample with a 180° -pulse, a signal will appear after a further time τ , as illustrated in Figures 3.1 and 3.2. (The first rf-pulse is applied along the x axis and the second rf-pulse is applied along the y axis).

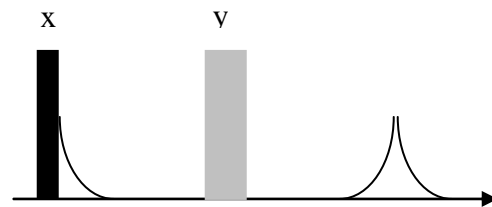


Figure 3.1

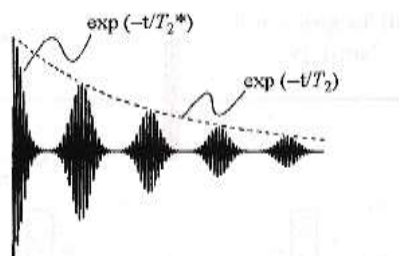


Figure 3.2

The signal, which consists of two fids, is called an echo. We can apply a series of 180° -pulses with a time separation 2τ . Between each 180° -pulses an echo is formed. The envelope of these echoes will be an exponential function with time constant T_2 , as shown in Figure 3.2 (from Freeman, 2003). The actual pulse sequence is called a CPMG pulse sequence after the people who developed it, Carr, Purcell, Meibom and Gill.

Actually, the appearance of an echo was first observed and reported by Erwin Hahn around 1950. An important property of the echo, utilized in MRI, is that it appears far from the transmitter pulse in the time domain. The echo is much stronger than the fid, because the latter is not observable during the time when the receiver is turned off. The receiver is blanked for a few micro seconds to avoid break through of the transmitter pulse.

We will now explain why an echo appears. To make it simple we will assume that the local magnetic field only has two values $\pm b$. M is then the sum of two components. After a 90° -pulse about the y -axis M is located along the x -axis.

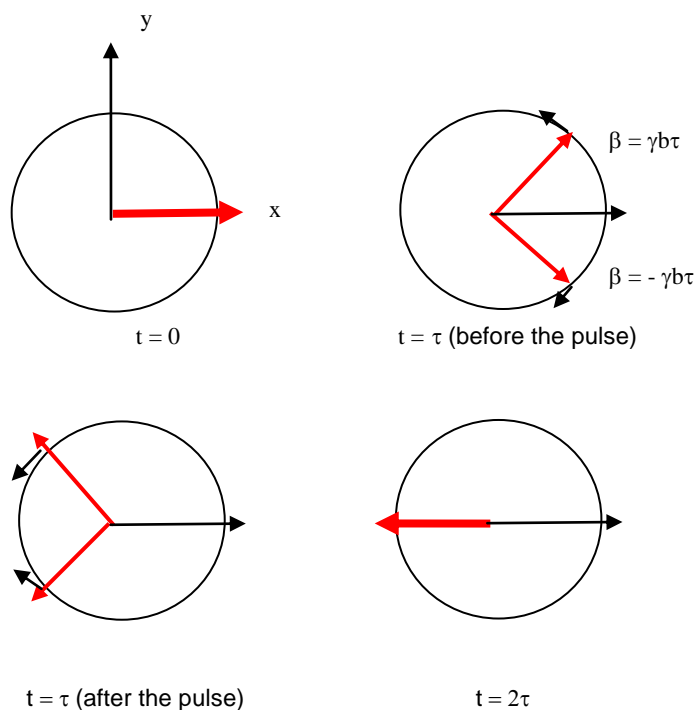


Figure. 3.3. Illustration of the spin-echo experiment. After the magnetization is rotated into the xy -plane by a 90° -pulse (around the y -axis), it loses phase coherence (due to inherent T_2 -effects and/or magnetic field inhomogeneities) and is exemplified by the formation of different local magnetic fields ($\pm b$), which in turn causes the spins to precess with slightly different frequencies.

After a time τ the faster rotating component will have dephased an angle $+\beta$ ($=\gamma b\tau$) while the other component will have moved an angle $-\beta$. If we now apply a 180° -pulse to the spin system about the y -axis, the component that rotates faster will make an angle $-\beta$ with the y -axis after the pulse, while the one that rotates slower will make an angle $+\beta$ with the y -axis. However, since they both have the same angular velocity they will both be located along the y -axis after a further time τ and will thus generate an echo.

If we assume a normal distribution of local magnetic fields, M will consist of a continuum of components. After the 90° -pulse the components will be spread out in the xy -plane. As the fid is a measure of this spread, the fid will die out with a time constant of T_2^* . If we after a time τ ($>T_2^*$ but $<T_2$) apply an 180° -pulse we will get a situation where the fastest components suddenly are lagging behind and the slower components are ahead. Since they still rotate with the same speed as before the pulse, they will again meet at the y -axis after time τ (echo). The actual reduction in signal intensity of the echo is due to the inherent and true T_2 -processes.

This pulse experiment may be compared to a track-race, i.e., before start the runners are all positioned on the same line. After start they will spread out because they run at different speeds. If the starter fires again, and everybody has to turn and run in the opposite direction, at their earlier speeds, they will cross the start line simultaneously.

If some of the runners change speed or give up, the number of runners coming back to the start line at the same time will be reduced.

It follows from this explanation that the echo will consist of two fids (as shown in Figure 3.2); one fid building up to an echo maximum, and the other fid decaying from the time of the echo maximum.

An advantage with the echo technique is that the complete fid is observed. The fid observed immediately after an rf-pulse is truncated because the receiver is turned off during the rf-pulse and for a short time afterwards (to circumvent breakthrough of the rf-pulse). The time between the end of the transmitter pulse and the opening of the receiver is called the dead time. The echo on the other hand, is recorded in a situation where the transmitter has been turned off for a long time. It is therefore an advantage to use the echo and not the initial fid in situations where T_2 is short. This is used in whole body MRI where the magnetic field is fairly inhomogeneous.

3.3 Diffusion.

The equation describing the time (t) and spatial (z) dependence of the transversal magnetization $\hat{M} (= M_x + iM_y)$ during diffusion, normal to this plane reads (see Excercise 3.1):

$$\frac{\partial \hat{M}}{\partial t} = -i\gamma z g \hat{M} - \frac{\hat{M}}{T_2} + D \nabla^2 \hat{M} \quad (3.1)$$

with; $\hat{M} = M_x + iM_y$

where D is the diffusion coefficient and $1/T_2$ is the spin-spin relaxation rate. After some complex and elaborate calculations using inverse Laplace transformation R.F. Karlicek and I.J. Lowe presented a solution to this equation:

$$\hat{M}(2\tau) = \hat{M}_0 \exp \left[-t/T_2 - \gamma^2 D \int_0^{2\tau} \left(\int_0^{t'} g(t'') dt'' \right)^2 dt' \right] \quad (3.2)$$

In Excercises 3.2 and 3.3 we justify that Eq 3.2 actually represents a solution to Eq 3.1 where $\hat{M}(2\tau)$ is the signal amplitude at the echo maximum. In particular, we note that the z-parameter is eliminated in Eq 3.2 (see Exercise 3.2). We will in the next section illustrate the applicability of Eq 3.2.

3.4 Spin-echo in a constant magnetic field gradient

The pulse sequence applied is illustrated on Figure 3.4 with $g = G_0$ representing a constant gradient field across the sample.

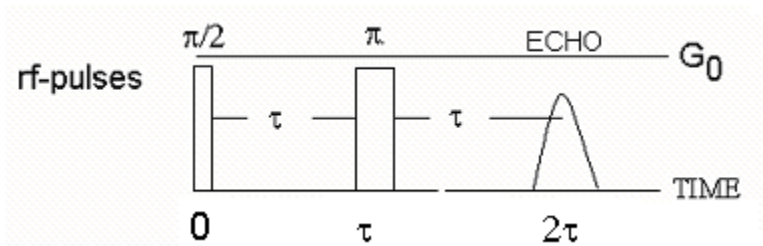


Figure 3.4 Spin-echo pulse sequence performed in a static magnetic field gradient $g = G_0$ where τ is the time at which a $\pi/2$ -pulse is applied with a subsequent occurrence of an echo at time 2τ .

Before applying Eq. 3.2, we note that in a rotating frame of reference (on resonance), the integral term $z_0 \gamma \int_0^{t'} g(t'') dt''$ represents the phase of the magnetization at time t' , at position z_0 . Without loss of generality we may set $z_0 = 1$, which implies that the integral $g(t') = \gamma \int_0^{t'} g(t'') dt''$ in Eq 3.2 is identical to (or proportional to) the phase angle. Figure 3.5 illustrates how this phase angle changes during time when applying the pulse sequence in Figure 3.4. Again,

assuming on resonance conditions and describing the phase angle in the rotating frame of reference we can easily determine the phase angle as a function of time (Figure 3.6) by referring to Figure 3.5.

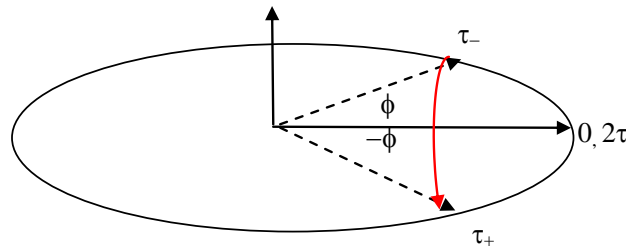


Figure 3.5. Phase angle as a function time when applying the pulse sequence shown in Figure 3.4.

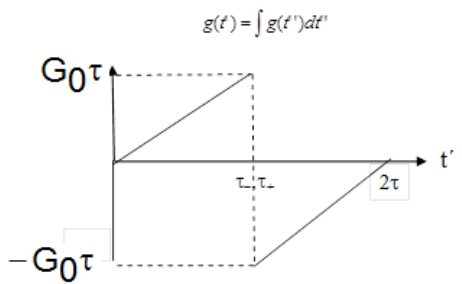


Figure 3.6. Schematic view of the phase angle $g(t')$ as a function of time (t') when applying the pulse sequence shown in Figure 3.4.

A more detailed numerical analysis is shown in the Table 3.1.

Table 3.1. Derivation of the phase term $g(t') = \int g(t'') dt''$ as a function of time t' by referring to Figures 3.5 and 3.6.

Time interval nr. (i)	Time interval	Gradient $g(t'')$	$g_i(t') = \int_0^{t'} g(t'') dt''$	$(\int_0^{t'} g(t'') dt'')^2$
1	$t_1=0, t_2=\tau (= \tau_-)$	G_0	$G_0 t'$	$G_0^2 t'^2$
2	$t_2=\tau (= \tau_+) t_3=2\tau$	G_0	$= G_0 (t' - 2\tau)$	$G_0^2 (t' - 2\tau)^2$

We can now easily calculate the last exponential term in Eq. 3.2 by insertion, i.e.:

$$\begin{aligned}
 - \int_0^{2\tau} \left(\int_0^{t'} g(t'') dt'' \right)^2 dt' &= - \int_0^{\tau} \left(\int_0^{t'} g(t'') dt'' \right)^2 dt' - \int_{\tau}^{2\tau} \left(\int_0^{t'} g(t'') dt'' \right)^2 dt' \\
 &= -G_0^2 \cdot \left[t^3 / 3 \Big|_0^{\tau} + (t' - 2\tau)^3 / 3 \Big|_{\tau}^{2\tau} \right] = -2G_0^2 \tau^3 / 3
 \end{aligned} \tag{3.1}$$

The first echo intensity will thus have the intensity;

$$\frac{I(2\tau)}{I(0)} = \exp(-2\tau/T_2 - 2DG_0^2\gamma^2\tau^3/3) \quad (3.3)$$

Likewise, the n'th echo intensity reads:

$$\frac{I((n+1) \cdot 2\tau)}{I(n \cdot 2\tau)} = \exp(-2\tau/T_2 - 2DG_0^2\gamma^2\tau^3/3) \quad (3.4)$$

It follows from Eq 3.3 that:

$$\begin{aligned} \frac{I(n \cdot 2\tau)}{I(0)} &= \frac{I(t)}{I(0)} = \prod_n \exp(-2\tau/T_2 - 2DG_0^2\gamma^2\tau^3/3) \\ &= \exp(-n \cdot 2\tau/T_2 - 2DG_0^2\gamma^2n \cdot \tau^3/3) = \exp\left[-t(1/T_2 + DG_0^2\gamma^2\tau^2/3)\right] \end{aligned} \quad (3.5)$$

3.5 Exercises

3.1) You apply a gradient field ($\vec{g} = g_0 \cdot \vec{z}$) along the z-axis which is parallel to the external magnetic field $\vec{B}(= B_0 \vec{k})$. If applying the Bloch equation, show that the transversal magnetization, i.e., the complex magnetization \hat{M} ($\hat{M} = M_x + iM_y$), satisfies the following

$$\text{relation; } \frac{\partial \hat{M}}{\partial t} = -i\gamma g_0 z \hat{M} - \frac{\hat{M}}{T_2} + D \frac{\partial^2 \hat{M}}{\partial z^2}$$

3.2) Show that a general solution to the above equation can be written:

$$\hat{M}(z, t) = e^{-t/T_2} \hat{m}(z, t) \quad \text{with} \quad \frac{\partial \hat{m}}{\partial t} = -i\gamma g_0 z \hat{m} + D \frac{\partial^2 \hat{m}}{\partial z^2}$$

4. Spectral Characteristics - Shift and Coupling

4.1 Chemical shift

All atoms in a molecule are surrounded by electrons which bind the atoms together. The electron distribution can be regarded as a charged cloud. When such an electron cloud is placed in a magnetic field B_0 a current will be induced which in turn generates a local magnetic field B_{loc} (according to Lenz' law this magnetic field will oppose the static magnetic field B_0). We say that the electron cloud *shields* the spins. When the cloud has spherical symmetry this induced field will be directly proportional to the external field ($B_{loc} = -\sigma B_0$). The proportionality factor σ is called the shielding constant and the actual magnetic field sensed by any nucleus may be expressed by:

$$B = B_0 + B_{loc} = (1-\sigma)B_0 \quad (4.1)$$

which can be rewritten in the form form:

$$\omega = \gamma(1-\sigma)B_0 \quad (4.2)$$

In a molecule or ion the shielding constant will vary from one spin to another if they are chemically different.

For example in ethanol (CH_3CH_2OH) - the cloud around the methyl carbon (CH_3 -) is different from the electric cloud around methylene carbon ($-CH_2$ -).

The ^{13}C -MR spectrum of ethanol therefore

is expected to consist of two peaks with resonance frequency ν_1 and ν_2 (plus three small peaks from the solvent (deuterated chloroform ($DCCl_3$))) as shown in Figure 4.1. Using Eq 4.2, the frequency difference between the two peaks can be written:

$$\nu_1 - \nu_2 = (\sigma_2 - \sigma_1) \nu_0 \quad \text{where } \nu_0 = \gamma B_0 / 2\pi \quad (4.3)$$

We see that the frequency difference is proportional to the frequency ν_0 of the spectrometer. To be able to compare data recorded in spectrometers with different magnetic fields a dimensionless parameter denoted the chemical shift δ was introduced:

$$\delta = \frac{\nu_1 - \nu_2}{\nu_0} (\nu_0 \text{ in MHz}) \quad (4.4)$$

It is common practise to measure the chemical shift relative to a peak in a reference compound. For 1H - and ^{13}C , this reference compound is tetramethyl silane (TMS; $(CH_3)_4Si$) as indicated on the spectrum in Figure 4.1. In TMS the spins are well shielded so the peak does not generally interfere with the peaks from common organic molecules.

Conventionally the TMS-peak is to the right in the spectrum and the δ axis increases to the left. In our example, δ for the methyl carbon is 18.0 ppm and for the methylene carbon 57.3 ppm. The shift difference in frequency units in the magnetic field applied is (4.7 T; 200 MHz for 1H) is ca 2 kHz $((57.3-18.0) \times 50)$.

For a solid, the chemical shift is described by a tensor. However, for a liquid the tensor is

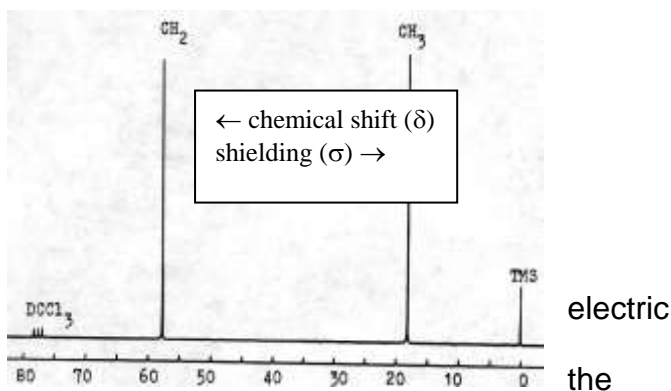


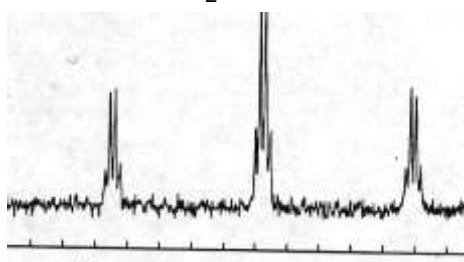
Figure 4.1

averaged to a scalar. The shielding tensor is analogous to the moment of inertia of a body. It is possible to find a coordinate system where all off diagonal elements are zero and the sum of the diagonal elements is zero. The shielding tensor may therefore be uniquely characterized by two parameters: σ_z and the asymmetry factor η (the largest of the diagonal elements is chosen to be σ_z) and η is a number between 0 and 1:

$$\eta = (\sigma_x - \sigma_y) / \sigma_z \quad (4.5)$$

4.2 Indirect spin-spin coupling (J coupling) – 1. order spectral analysis

In the ^{13}C -MR spectrum of ethanol (Figure 4.1) all interactions between the protons and the carbon are removed by what is called ^1H -decoupling. However, if these interactions are not removed, the ^{13}C -MR spectrum looks quite different. For instance, Figure 4.2 shows the ^{13}C spectrum of the $-\text{CH}_2-$ group in ethanol (the scale is 30 Hz/division).

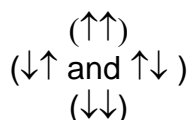


methylene group

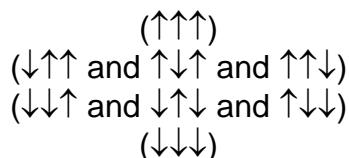
Figure 4.2

and demonstrates that the single peak from the $-\text{CH}_2-$ carbon (Figure 4.1) is split up in triplets of quartets. It can be shown theoretically (see next section) that this appearance of fine structure in the spectrum originates from an interaction between the proton spins and the carbon spins. This fine structure of the carbon resonance in methylene can be simply explained by the following arguments: In the

($-\text{CH}_2-$) there are two ^1H -spins directly bonded to the ^{13}C nucleus. Each of these proton spins can take two orientations with respect to the external field, up (\uparrow) or down (\downarrow). For two ^1H -spins there are four combinations of spin orientations:



These different proton spin orientations generate different local magnetic fields at the ^{13}C nucleus and give rise to a triplet peak with an intensity distribution 1:2:1. In addition, the methylene carbon is also coupled to three ^1H -spins located on the methyl group ($-\text{CH}_3$). By a similar reasoning, as for the coupling to two ^1H -spins, we obtain the following four different spin-orientations of a three-proton-spin system:



Since these four different proton spin-orientations generate different local magnetic fields at the methylene carbon, the latter is further split into four peaks (quartet). The conclusion is that when the protons are not decoupled they split the methylene carbon peak into a triplet, which in turn is split into a quartet.

We can generalise these findings to what is called the “(n+1)”-rule. When a spin-1/2 nucleus is coupled to n equivalent spin-1/2 nuclei, the resonance peak of the former is

split up in $(n+1)$ -peaks with an binominal intensity distribution (1:1, 1:2:1, 1:3:3:1, 1:4:6:4:1 for $n = 1, 2, 3, 4, \dots$ etc). The distance (Hz) between the resolved peaks define the coupling constant J and it is found to be independent on the external magnetic field strength B_0 .

The above simplified spectral analysis is correct as long as the chemical shift difference (δ ; in Hz) between the coupled nuclei is larger than the coupling constant J between them. We call such spectra "1. order spectra".

As already pointed out in a previous section, the "n+1"-rule is valid as long as the chemical shift difference δ (Hz) between the nuclei is large compared to the coupling constant J between them, i.e., $\Delta\delta$ (in Hz) $\gg J$. When $\Delta\delta$ (in Hz) $\approx J$, the intensity distribution of the peaks will not be as predicted by the "n+1"-rule. The positions of the peaks are changed and the multiplet may contain additional peaks. The general analysis of MR spectra necessitates a rigorous quantum mechanical approach and is shown in Appendix B for a two-spin system (two interacting nuclei).

Generally, the coupling constant J is ordered after how many chemical bonds there are between the coupled spins. In the above example, the coupling between the methylene carbon and protons is a one bond coupling of size 120 Hz. The two-bond coupling between the methylene carbon and the methyl proton is smaller, approximately 4 Hz.

One may ask why we do not see a coupling between the carbon nuclei in the molecule. The answer is that only 1.1% of the carbon atoms (^{13}C) possess a spin while the rest (^{12}C) have no spin ($I = 0$). The observed carbon peaks are from the 98.9% of the ethanol molecules in which the neighbouring carbon nucleus is ^{12}C ¹⁸.

Moreover, why does no coupling show up between the methylene carbon and the -OH proton in ethanol, since the latter nucleus is also located two bonds away from the methylene carbon. This is due to molecular motion, i.e., the proton nucleus on the -OH group is hydrogen bonded to other ethanol molecule and hence may jump (or exchange) quickly between different sites which averages out any chemical shift difference due to coupling¹⁹.

4.3 Molecular structure

A typical MR-spectrum (of a liquid) consists of various peaks grouped in multiplets. The number of multiplets tells us how many functional groups are involved in the molecule. For instance, a ^1H -decoupled ^{13}C -spectrum will tell how many different carbon atoms there are in a molecule. If the molecule is symmetric, the spectrum will reveal an analogous symmetry.

For instance, a benzene molecule consists of six carbon atoms, but because the molecule has six-fold symmetry the carbon atoms have the same chemical shift and consequently the spectrum will contain only one peak. If one of the protons is replaced by a Cl-atom the molecule will have mirror symmetry and the spectrum will consist of four peaks, two peaks of intensity "1" and two peaks of intensity "2".

As pointed out previously, the molecular motion may average out chemical shift differences. The molecular symmetry found by MR can therefore be higher than the real symmetry of the molecule.

¹⁸This is true at first sight. If the signal/noise is good small multiplets may be observed symmetrically about the main peaks.

¹⁹ The jump rate depends on traces of acid present and the temperature. In pure 100 % ethanol the coupling to the H atom in the -OH group can be seen at room temperature.

The magnitude of the chemical shift depends on the molecular structure and what functional groups exist and where they are located in the molecule. Through the years a large empirical material has been collected and systematized in different ways, originally in form of tables and collections of typical spectra, recently in the form of computer databanks and data programs. This material can be used in the interpretation of MR-spectra of molecules with unknown structure.

Also, the coupling constants give structural information, mainly how the different atoms or functional groups are connected together to form the molecule. Especially the so called vicinal coupling, that is a three bond coupling. The vicinal coupling in an ethane fragment (-H₂C-CH₂-) depends on the dihedral angle as shown in the graph. The gauche coupling ($\varphi = 60^\circ$) is small ca 2 Hz, but the trans-coupling ($\varphi = 180^\circ$) is much larger 9 Hz. This variation has been used to determine the conformation of molecular rings.

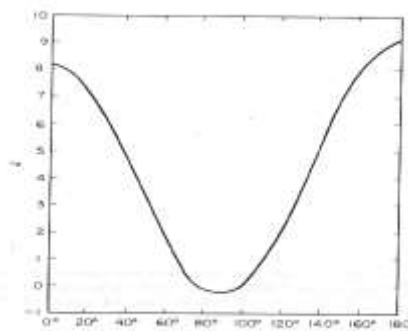


Figure 4.5

The vicinal coupling does not only depend on the dihedral angle, but also on the electronegativity of the substituents. Electronegative substituents will reduce the vicinal coupling constant so the derived coupling constant must be used with caution. The coupling constants have also been systematized and the material is accessible in various data bases.

In many cases it is rather trivial to interpret MR-spectra to obtain chemical shifts and coupling constants, in particular regarding 1. order spectra. However, when chemical shift differences and coupling constants are of the same order of magnitude, the analysis becomes much more complex and difficult to analyze without sorting to some kind of simulation. Also, use of two dimensional MR may be advantageous, however, this is outside the scope of this course (see Claridge 1999).

4.4 Fourier Transformation (FT)

In practical NMR spectroscopy it is easier to analyze a frequency spectrum $F(\omega)$ rather than the time signal $f(t)$, or the fid. The spectrum and the fid contain the same information, but is presented in different ways. It is possible to calculate the one from the other by a mathematical operation called Fourier Transformation.

If we denote the fid by:

$$f(t) = M_0 e^{-t/T_2} e^{-i\omega_0 t} \quad (4.6)$$

its fourier transform $F(\omega)$ can be derived (see Exercice 2.5) and reads:

$$F(\omega) = \int_{-\infty}^{\infty} f(t) e^{i\omega t} dt = R(\omega) + iI(\omega) \quad '$$

$$F(\omega) = \frac{T_2}{1 + ((\omega - \omega_0)T_2)^2} M_0 + i \frac{(\omega - \omega_0)T_2^2}{1 + ((\omega - \omega_0)T_2)^2} M_0 \quad (4.7)$$

where the real component $R(\omega)$ represents the absorption mode (Lorentzian function) and the imaginary component $I(\omega)$ represents the dispersion mode, respectively.

The opposite is also true, i.e., the fid is the Fourier transform of the (frequency) spectrum:

$$f(t) = \int_{-\infty}^{\infty} F(\omega) e^{-i\omega \cdot t} d\omega = M_0 e^{-t/T_2} \quad (4.8)$$

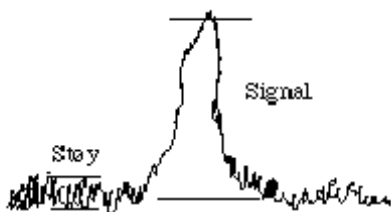
We notice from the real part $R(\omega)$ of the spectrum (Eq 4.7) that the width (Δ) at half height is related to the decay rate $1/T_2$ of the fid, i.e., $\Delta = 1/\pi T_2$. When T_2 is short, the fid will decay fast and the frequency peak will become broad.

The FT is quickly performed using a dedicated computer. In principle the relation between the fid and the frequency spectrum has been known from the early days of NMR. However, it was first when computers got cheap enough that it became advantageous to transform the fid by FT.

It is important to know that actually two time-signals, differing in phase by 90° , are sampled and that the two spectra are mixed in an operation called phasing in order to obtain a pure absorption spectrum.

Because a computer is a digital sampling device, it is necessary to chop the fid. This is done in an analogue-to-digital converter. After the fid has been digitized, the fid consists of a series of points. It is necessary to select a sufficiently large number of points to get the shape sufficiently accurate. A least 4 points are needed to define a peak. On the other hand: the calculating time increases with the number of points. To make the calculation faster the number of points is always 2^n (with n being an integer). In MRI one frequently apply 512 ($n = 9$) data points. In MR-spectroscopy the number of points is often set to 16384 ($n = 14$). It is also possible to use other tricks to improve the quality of the spectrum, for instance by filtering or selective weighting of parts of the fid before FT.

4.5 Signal-to-noise



MR is not very sensitive compared to other spectroscopic techniques. This is due to the fact that the energy of a photon is small compared to kT , making the difference between the number of spins in the two energy levels small, which in turn results in a weak signal (see Eq 1.8). However, in one respect this is an advantage. The amount of energy absorbed by the sample will be so small that it will not significantly affect the sample

Figure 2.6

affect the temperature. This is in contrast to other spectroscopic methods where the irradiation may substantially heat the sample. A number of methods have been introduced

to increase the signal-to-noise ratio in the MR-spectrum (see the figure where *støy* stands for *noise*). A closer analysis shows that the S/N-ratio is given by the following expression (Claridge 1999):

$$\text{S/N-ratio} = (\text{number of spins}) \times (\text{Abundance}) \times (\text{number of fids})^{1/2} \frac{\gamma^{5/2} B_o^{3/2} T_2^*}{T} \quad (2.9)$$

A simple method to increase S/N is thus to sum the fids after acquiring a larger number of individual fids. After each fid the digitized fid is stored in the computer. The stored signal will increase proportional to the number of fids, while the (random) noise will only increase as the square root of the number of fids. The S/N-ratio therefore increases with the square root of the number of fids. For instance, the S/N-ratio after 100 pulses will be enhanced by a factor of 10.

This increase in the S/N-ratio implicitly assumes that the spin system returns to equilibrium between each rf-pulse and implies that the time between each pulse must be set to approximately 5 times the T_1 . If this condition is satisfied the spectrum can be used for quantitative analysis as each peak in the spectrum will be proportional to the number of spins contributing to that peak. If the spectrum is needed to be recorded faster, a closer analysis shows that the best S/N-ratio is obtained by pulsing as fast as possible with a pulse angle shorter than 90° . However, this approach will introduce systematic errors. Since T_1 may be different for different peaks in the spectrum, peaks with the longest T_1 will be systematically smaller.

4.4 Exercises

4.1) Make a sketch of the proton spectra of the following structural fragments and explain your results (use a 1.order approximation).

a) $-\text{CHC}-$ **b)** $-\text{CH}_2\text{CH}-$ **c)** CH_3CH_2- **d)** $\text{CH}_3\text{CH}-$ **f)** $-\text{CH}_3$.

4.2) How will the ^{13}C -NMR spectrum of **b)** and **f)** look like?

4.3) See Appendix for a more general spectral treatment of a "2-spin" system.

5 NMR history

5.1 How did it all start?

In 1925 two Dutch Ph.D.-students, Uhlenbeck (1900-88) and Goudsmit (1902-78), noticed some fine structure in their optical spectra and suggested that the reason for the observed fine-structure originated from some specific property of the electron, namely its angular momentum. Interestingly, a year earlier Wolfgang Pauli (1900-54) had claimed that the atomic nuclei also possessed an angular momentum which is a fundamental property of the NMR phenomenon. A particularly important event occurred, however, in 1938 when Isidor Isaac Rabi (1898-1988) used magnetic resonance to improve the accuracy of his measurements and then discovered ^7Li - and ^{35}Cl -NMR in LiCl-molecules in the gas phase. Although the experiment was proposed by the Dutch C. J. Gorter (1907-80) during his visit to Rabi's laboratory, Rabi was the one that received the Nobel Prize in physics in 1944. Gorter was only acknowledged in Rabi's publication.²⁰ This is the first case of many in the history of magnetic resonance. Many contribute, but not more than 3 get a Nobel Prize. Furthermore it is always the "boss" who gets the prize, not the ones that build the equipment and do the experiments.



Isidor Isaac Rabi



C. J. Gorter

However, it really started in 1945 when the physicists returned to Basic research again after the Second World War. Felix Bloch (1905-83) at Stanford and Henry M. Purcell (1912-97) at Harvard discovered - independent of each other - magnetic resonance in a condensed phase: Bloch in liquid water and Purcell in paraffin wax. They knew that Gorter had tried both before and during the war, but in vain. In retrospect, it was realized that the T_1 of Gorte's samples was too long because they were too pure and the temperature was too low.



Felix Bloch

Actually, Bloch was not interested in magnetic resonance per se, but was basically looking for a method to measure the magnetic field strength. He used two orthogonal coils and called his method nuclear induction. Due to the brothers Varian, who had earned money on making klystrons during the war, he patented the method and founded a company that marketed the first commercial NMR spectrometers in the early 1950's.²¹ Bloch published his famous work in 1946²².



H.M. Purcell

In some contrast, Purcell used micro waves in his first measurements and soon after, his colleagues/students built spectrometers using radio equipment.

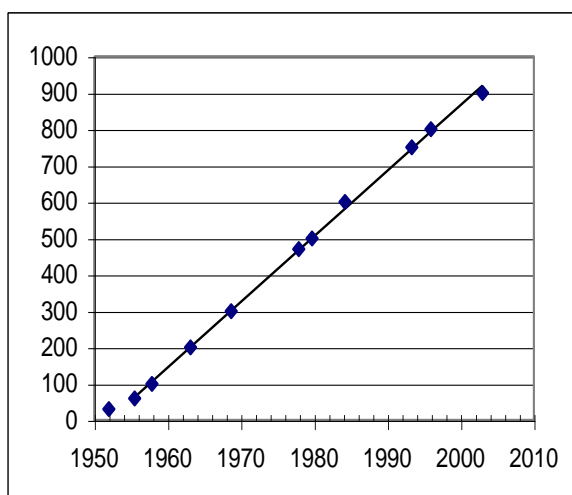
²⁰ Rabi et al Phys. Rev. 53(1938)677.

²¹ [http://www.varianinc.com/cgi-bin/nav/?/](http://www.varianinc.com/cgi-bin/nav?/) The most serious competitor is Bruker-biospin <http://www.bruker-biospin.de>. Another is Jeol – a Japanese company. Most of the spectrometers presently at the institute are from Bruker, only one older from Varian.

²² F. Bloch Phys Rev 70(1946)460

Together with Pound and the Dutch Ph.D. student Niels Bloembergen²³, they developed a simple theory for magnetic relaxation known as the BPP (Bloembergen-Purcell-Pound) model (see Figure 2.5).²⁴

The practical limitation during the first years after the discovery of NMR was not the electronics, but rather the poor homogeneity and stability of the magnets (they used iron magnets; large heavy beasts). In this respect, Erwin Hahn (Bloch's PhD-student) built the first pulse NMR spectrometer before 1950 and discovered the "spin echo" technique which circumvented the magnet homogeneity problem by applying radio-frequency (rf) pulses rather than continuous wave (CW) NMR. As the spectral fine structure (dipole coupling, chemical shift, J-coupling and quadrupole coupling) was discovered during 1948 – 1950, an enormous effort was initiated to improve the magnet properties.



The graph on the left shows the development of the magnetic field strength since the first commercial magnets appeared on the market in 1952. The graph is valid for magnets with a gap of 5 cm (liquid-state NMR). The maximum field for a commercial magnet to day is 23.5 Tesla (1000 MHz for ¹H). If we extrapolate the straight line in the graph we can predict (and expect) that a 1200 MHz instrument will be available by 2015-2020. The technology needed to produce such an apparatus is in progress and requires a strong collaboration between the researchers. Starting from the 200 MHz-

magnet, all later magnets are superconducting (the coil is cooled to 4 K or lower). The same magnet technology gives a smaller field for a larger gap. In solid state NMR a 9 cm gap is used with a maximum field of 700 MHz. In MRI, the magnet gap is much larger. Commonly a magnetic field of 1.5 T is used, but 3 T magnets are now increasing in number (3 T corresponds to 128 MHz frequency for ¹H).

A 900 MHz NMR-spectrometer (right) costs ca 50 MNOK. There is no such instrument in Norway (but in all the other countries in Scandinavia). One problem with high field magnets is their significant stray fields, which implies that they occupy a lot of space. However, shielded magnets have come available which reduces the required space (but increases the cost). With better magnets the electronics became the limiting factor.



900 MHz magnet

²³ He was born in 1920 and got the Nobel Prize in physics in 1981 for his contribution to the development of laser spectroscopy.

²⁴ N. Bloembergen, E.M. Purcell and R.V. Pound Phys Rev 73(1948)986

As transistors replaced radio tubes, and Integrated circuits were developed, the first Digital computers were build into a spectrometer in the 1960's and the cw-method was replaced by the rf-pulse method in the 1970's. The man who got the honour for this was the Swiss scientist, Prof. Richard Ernst (1933-) at ETH in Zürich. Before this time it was mainly the proton nucleus that was studied (at least by chemists). Due to the invention of the rf-pulse technique, natural abundance spectra of both ^{13}C as well as ^{15}N could be acquired. Ernst also developed 2D-methods in the 1970's. Although the idea came from the Belgian thermodynamics Jean Jeener, it was Ernst that did the development work.



R. R. Ernst

These methods made it possible to interpret increasingly more complex spectra of larg molecules. The Swiss scientist Prof. Kurt Wütrich (1938-), at ETH in Zürich, received one half of the Nobel Prize in 2002 for his development of nuclear magnetic resonance spectroscopy for dermining the three-dimensional structure of biological macromolecules in solution.



Kurt Wütrich



P. Lauterbur

Magnetic field gradients were introduced in the 1960's to study diffusion and makes the NMR-signal dependent on position. Paul Lauterbur (1929-) got the idea in 1973, i.e., that a field gradient can applied to image an object, as pointed out in section 3.5. Also, Peter Mansfield (1933-) had the same idea (at the same time) but he used pulse methods. In 2003 they both sheared the Nobel Prize in medicine for their discoveries on magnetic resonance imaging. A more updated and complete information on the NMR history and on the Nobel laureates can be found at <http://www.nobel.se/>



Sir. P. Mansfield

5.2 NMR in Norway



The first NMR spectrometer came to Norway in 1960 (left). It was a 60 MHz spectrometer from Varian (picture) placed at SI (now Sintef Oslo) and included all additional equipment that one could buy at that time. The instrument could be used to study both liquids and solids. A pulse spectrometer was also built at SI in the 1960's. The



NMR laboratory was closed in 1980, and the activity transferred to the Department of Chemistry at the University of Oslo (right).

The organic chemists at the Department of Chemistry got their first NMR-spectrometer in 1965 (Varian A-60; top right). The "A-60" has now the same status among NMR users as a T-Ford for a car enthusiast. The "A-60" was replaced by a 100 MHz spectrometer, also from Varian, in 1970 and was a more



advanced and complex spectrometer. The first pulse spectrometer with a computer (24K memory!) came in 1975 (Jeol FT-60), and the first multi-purpose, superconducting instrument was installed in 1981 (CPX-200 in 1981; see previous picture). In 1989 the organic chemist installed a 300 MHz-spectrometer (Varian) for liquid-state NMR.

The great year of NMR in Norway was 1995 when 12 new NMR spectrometers were bought from the German company Bruker and placed in Bergen, Oslo and Trondheim, respectively. The Chemistry Department at UiO got four spectrometers, 3 for liquid-state application (200, 300 and 500 MHz) and one (200 MHz) for solid-state application.

The Laboratory for liquid-state NMR is located in the east wing of the Chemistry Department and is lead by Prof. Frode Rise and Ing. Dirk Petersen who also installed 600 MHz-spectrometer which is coupled to a liquid chromatograph (LC), denoted "LC-NMR". All research activities are devoted to structural analysis of organic molecules in solution.

In the west wing, a Laboratory for physical NMR (solid-state NMR) is located and lead by Prof. Eddy W. Hansen. Hansen is studying morphological properties, structure and molecular dynamics of solid polymers and also characterizing molecular dynamics (diffusion) of liquids in porous solids. They have one low field NMR instrument operating at 22 MHz (Maran Ultra from the British company Resonance). In addition, they also have access to a 500 MHz, solid state NMR spectrometer located at Sintef. The two institutions initiated a major collaboration within solid state NMR in 2010 (Gemini-senter).

Appendix

A general approach to spectral analysis (two-spin system)

As pointed out in the previous section, the “n+1”-rule is valid as long as the chemical shift difference δ (Hz) between the nuclei is large compared to the coupling constant J between them, i.e., $\Delta\delta$ (in Hz) $\gg J$. When $\Delta\delta$ (in Hz) $\approx J$, the intensity distribution of the peaks will not be as predicted by the “n+1”-rule. The positions of the peaks are changed and the multiplet may contain additional peaks. Before considering some simple cases, we need to discuss the nomenclature.

Spins with the same chemical shift have the same letter in the alphabet. Spins that are separated by small chemical shift differences have letters that are close in the alphabet. Some examples: A_2 , AB and AX. A_2 and AX will give first order spectra: A_2 - singlet, AX - two doublets. AB will give a more complex spectrum, which we will now calculate. We start with two spins, 1 and 2, which generate four spin-functions according to:

$$f_1 = |\alpha\alpha\rangle \quad f_2 = |\alpha\beta\rangle \quad f_3 = |\beta\alpha\rangle \quad f_4 = |\beta\beta\rangle \quad (\text{A1})$$

Actually, we should have written $\alpha(1)\beta(2)$ to identify the two nuclei 1 and 2, however, to simplify, the first wave function in each pair is assigned to spin 1 and the second one to spin 2). The Hamiltonian takes the form:

$$\hat{H} = \hat{H}_Z + \hat{H}_J \quad (\text{A2})$$

By writing the operator in frequency units (Hz):

$$\hat{H}_Z = \nu_1 \bar{I}_1^z + \nu_2 \bar{I}_2^z \quad (\text{A3})$$

ν_1 and ν_2 define the chemical shift (Hz) of the two spins. The term \hat{H}_J in Eq A2 which defines the coupling Hamiltonian can be written:

$$\hat{H}_J = J \bar{I}_1^z \bar{I}_2^z + (J/2)(\bar{I}_1^+ \bar{I}_2^- + \bar{I}_1^- \bar{I}_2^+) \quad (\text{A4})$$

By introducing the raising and lowering operators ($i = \sqrt{-1}$):

$$\bar{I}^+ = \bar{I}^x + i\bar{I}^y \quad \text{and} \quad \bar{I}^- = \bar{I}^x - i\bar{I}^y \quad (\text{A5a})$$

$$\bar{I}^+|\alpha\rangle = 0, \bar{I}^+|\beta\rangle = |\alpha\rangle, \bar{I}^-|\alpha\rangle = |\beta\rangle, \bar{I}^-|\beta\rangle = 0 \quad (\text{A5b})$$

we will look for solutions of the Schrödinger equation ($\hat{H}|\Psi_i\rangle = E_i|\Psi_i\rangle$) of the form:

$$|\Psi_j\rangle = \sum_{i=1}^4 c_{ji} |f_i\rangle \quad \text{for } j=1,2,3,4 \quad (\text{A6a})$$

From the theory of linear algebra, we can find the energies (E_i) by solving the following “secular” determinant:

$$\begin{pmatrix} H_{11}-E & H_{12} & H_{13} & H_{14} \\ H_{21} & H_{22}-E & H_{23} & H_{24} \\ H_{31} & H_{32} & H_{33}-E & H_{34} \\ H_{41} & H_{42} & H_{43} & H_{44}-E \end{pmatrix} = 0 \quad (\text{A6b})$$

with $H_{ij} = \langle f_i | H | f_j \rangle$

The solution to Eq 4.9b (see Exercises 4.1 – 4.4):

$$\begin{aligned} E_1 &= -V/2 + J/4 & |\Psi_1\rangle &= |\alpha\alpha\rangle \\ E_2 &= -C/2 - J/4 & |\Psi_2\rangle &= \cos\theta|\alpha\beta\rangle + \sin\theta|\beta\alpha\rangle \\ E_3 &= C/2 - J/4 & |\Psi_3\rangle &= -\sin\theta|\alpha\beta\rangle + \cos\theta|\beta\alpha\rangle \\ E_4 &= V/2 + J/4 & |\Psi_4\rangle &= |\beta\beta\rangle \end{aligned} \quad (\text{A6c})$$

We have introduced the parameters C, V and θ to simplify the equations:

$$V = \nu_1 + \nu_2 \quad (\text{A6d})$$

$$C = \sqrt{(\nu_1 - \nu_2)^2 + J^2} \quad (\text{A6e})$$

$$\sin 2\theta = J/C \quad (\Leftrightarrow \cos 2\theta = (\nu_1 - \nu_2)/C) \quad (\text{A6f})$$

The calculated spectrum will consist of 4 lines, symmetrically distributed about its mean value $1/2(\nu_1 + \nu_2)$. The frequencies and intensities are given in the Table 1.

Table 1. Frequency and relative intensity of the resonances within an AB-spin system.

Transition (n m)	Frequency ($E_n - E_m$)	Relative intensity
2 1	$(V - C - J)/2$	$(1 - \sin 2\theta)/4$
4 3	$(V - C + J)/2$	$(1 + \sin 2\theta)/4$
3 1	$(V + C - J)/2$	$(1 + \sin 2\theta)/4$
4 2	$(V + C + J)/2$	$(1 - \sin 2\theta)/4$

We will discuss two limiting cases.

Case 1: $(\nu_1 - \nu_2) \gg J$

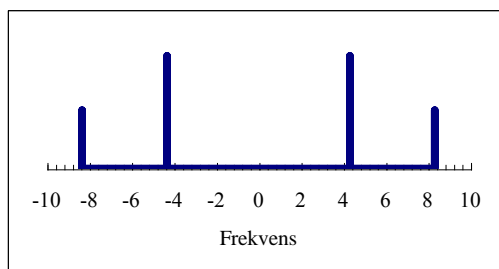


Figure 4.3

Then $C = (\nu_1 - \nu_2)/2$ and $\theta = 0$. The spectrum consists of two doublets. One doublet is centred at ν_1 with a distance between the two lines equal to J. The other doublet is centred at ν_2 with the same distance J between the two lines. All lines have the same intensity when $(\nu_1 - \nu_2) \gg J$ (Figure 4.3 shows the calculated spectrum for $J = 4$ and $(\nu_1 - \nu_2) = 3J$. The intensity of the outer lines is reduced).

Case 2: $\nu_1 = \nu_2$

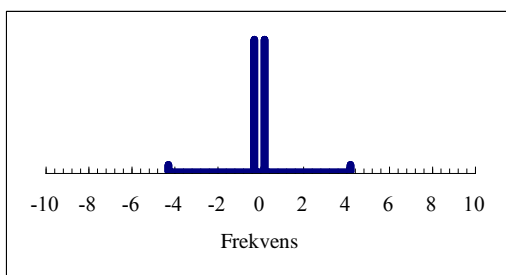


Figure 4.4

Then $C = J$ and $\theta = \pi/4$. The spectrum is then a single line. Figure 4.4 shows the calculated spectrum for $J = 4$ and $(\nu_1 - \nu_2) = J/2$. Compared to case 1 we see that the outer lines disappear when the chemical shift $(\nu_1 - \nu_2)$ gets small compared to the coupling constant J . The distance between the two outer lines is J and can be found directly from the spectrum and reads:

$$J = (\nu_1 - \nu_2) = (\nu_3 - \nu_4) \quad (\text{A7a})$$

The value of the chemical shift can be calculated from this equation:

$$\delta(\text{in Hz}) = \sqrt{(\nu_1 - \nu_4)(\nu_2 - \nu_3)} \quad (\text{A7b})$$

To check that the four lines really belong to an AB-quartet we can test the assumption by calculating the intensity distribution. In an AB quartet the intensity ratio of the inner lines and the outer lines is $(\nu_1 - \nu_4) / (\nu_2 - \nu_3)$.

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