NMR SPECTROSCOPY

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Keywords: chemical shift, correlation spectroscopy, diffusion coefficient, Fourier transform spectroscopy, imaging, liquid crystals, magic angle spinning, magnetic properties, medical diagnosis, molecular dynamics, molecular structure, MRI, multidimensional NMR, NMR, nuclear Overhauser effect, nuclear spin, quality control, spectroscopy, structure determination.

Contents

Summary

Nuclear magnetic resonance (NMR) is a powerful and versatile spectroscopic technique for investigating molecular structure and dynamics. It involves reorientations of nuclear spins with respect to an applied static magnetic field. The overall process can be understood by using classical arguments, but a quantum treatment is needed in order to comprehend the details of the technique, especially those related to spin–spin interactions. While the proton is the most frequently studied nucleus, almost every element has an isotope active in NMR.

Multipulse and multidimensional Fourier transform NMR techniques provide an unlimited diversity of possibilities for simplifying and interpreting complicated spectra, thus allowing resolution of the three-dimensional structure of macromolecules, such as proteins and nucleic acids. As a non-destructive analytical technique, it finds many applications not only in chemistry but also in agriculture, food science, and the characterization of materials. Dynamical aspects ranging from the nanosecond to the reciprocal second can be characterized. Transient magnetic-field gradients applied across a sample allow the acquisition of images of great value for medical diagnosis.

1. Introduction

Nuclear magnetic resonance (NMR) is a spectroscopic technique that provides information about the structure and some dynamic properties of a sample subjected to a static magnetic field, from the analysis of the interaction between the magnetic moments of sample nuclei and an applied electromagnetic wave.

Nuclear magnetic moments will be introduced before proceeding to analyze their interaction with electromagnetic radiation.

A nucleus is built up of protons and neutrons moving in a very small volume (nucleus radii range from 10^{-15} to 10^{-14} m). Each of these particles can have orbital angular momentum associated with its motion and spin angular momentum intrinsic to the particle. The modulus of the spin angular momentum takes a fixed value for each kind of particle (like the mass or the charge) and is usually expressed in the form $\hbar\sqrt{s(s+1)}$, where $\hbar$ is the Plank constant divided by 2π and s is a spin quantum number. This number, usually referred to as the "particle spin," takes the value 1/2 for both protons and neutrons. The sum of the orbital and spin angular momenta of the particles within a nucleus is called "nuclear spin vector" (***I***) and its modulus is $\hbar\sqrt{I(I+1)}$ where I takes one of the values 0, 1/2, 1, 3/2, and so on. (I values greater than 4 are rare). Although I depends on the nuclear state, nuclei are normally in their ground state and the value of I for this state will be considered an intrinsic nuclear property. Nuclei with even numbers of protons and neutrons (like ^{12}C and ^{16}O) have a null spin, but most nuclei with odd numbers of protons and/or neutrons have $I \neq 0$. These nuclei have a magnetic (dipole) moment proportional to the spin vector:

$$\boldsymbol{\mu} = \gamma \boldsymbol{I} \qquad (1)$$

where the "gyromagnetic ratio" γ is a constant characteristic of each nuclide. γ can be positive or negative, and takes its largest values for ^{3}H (28.53×10^{7} $T^{-1}s^{-1}$) and ^{1}H (26.75×10^{7} $T^{-1}s^{-1}$). Nuclear magnetic moments interact with an applied magnetic field as a magnet does: its energy depends on the moduli and the relative orientation of the magnetic moment and magnetic field vectors. Some effects of this interaction can be understood by means of simple classical arguments, but many important aspects must be accounted for in a quantum framework. The classical description (usually referred to as the "vector model") will be presented first, so that readers not acquainted with quantum mechanics can grasp the physical basis of the technique. This picture is useful even in the context of the quantum treatment, which will be considered afterwards.

2. Classical Description

In a sample with no external fields, the nuclear magnetic moments are oriented at random giving a null resultant. If a static magnetic field $\boldsymbol{B}_0$ is applied to the sample, the energy of interaction between the magnetic moment $\boldsymbol{\mu}$ of each nucleus and $\boldsymbol{B}_0$ is

$$E = -\boldsymbol{\mu} \bullet \boldsymbol{B}_0 \qquad (2)$$

Since this energy is minimum when both vectors are parallel, the nuclei will tend to lose energy by orienting their magnetic moments in the direction of the field. Thermal agitation opposes this tendency so that, at room temperature, only a very small net orientation is achieved. Nevertheless, a non-null resultant parallel to $\boldsymbol{B}_0$ will now remain, and one says that the sample has acquired some "spin-polarization." The polarized sample acts as a magnet, and its magnetization ($\boldsymbol{M}$) is defined as the total magnetic moment per unit volume.

The magnetic field exerts a torque on each nucleus given by the vector product

$$\boldsymbol{\tau} = \boldsymbol{\mu} \times \boldsymbol{B}_0 \tag{3}$$

If the vector $\boldsymbol{I}$ is treated as a classical (orbital) angular momentum, one can use Newton's law to relate its time derivative with the applied torque:

$$\boldsymbol{\tau} = \boldsymbol{\tau} = \frac{d\boldsymbol{I}}{dt} \tag{4}$$

From Eqs. (1), (3), and (4) one obtains

$$\frac{d\boldsymbol{\mu}}{dt} = \boldsymbol{\mu} \times \boldsymbol{B}_0 \tag{5}$$

Thus, the torque exerted by the magnetic field on the nucleus produces a change in its magnetic moment perpendicular to the plane formed by the vectors $\boldsymbol{\mu}$ and $\boldsymbol{B}_0$, that is, a rotation or "precession" of $\boldsymbol{\mu}$ round $\boldsymbol{B}_0$ (Figure 1).

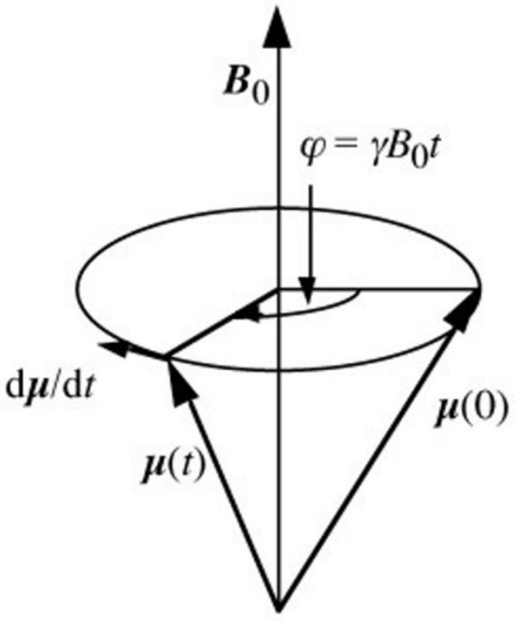

Figure 1. Precession of $\boldsymbol{\mu}$ in the laboratory system under a static magnetic field $\boldsymbol{B}_0$ for a nucleus with positive γ.

As frequently happens in NMR, this problem is conveniently viewed from a rotating reference system. Let us consider one that rotates with angular velocity $\boldsymbol{\omega}$. The relationship between the time derivative of $\boldsymbol{\mu}$ in the rotating system ($\delta\boldsymbol{\mu}/\delta t$) and that in the laboratory frame ($d\boldsymbol{\mu}/dt$) is the same as that relating the position derivatives (that is, the linear velocities):

$$\frac{\delta \boldsymbol{\mu}}{\delta t} = \frac{d\boldsymbol{\mu}}{dt} + \boldsymbol{\mu} \times \boldsymbol{\omega} \tag{6}$$

Using Eq. (5) one obtains

$$\frac{\delta \boldsymbol{\mu}}{\delta t} = \boldsymbol{\mu} \times \gamma \left(\boldsymbol{B}_0 + \frac{\boldsymbol{\omega}}{\gamma} \right) \tag{7}$$

As a consequence, in the rotating system everything happens as in an inertial system (Eq. (5)) except for a substitution of the actual magnetic field $\boldsymbol{B}_0$ by an effective one:

$$\boldsymbol{B}_{\text{eff}} = \boldsymbol{B}_0 + \frac{\boldsymbol{\omega}}{\gamma} \tag{8}$$

By choosing the angular velocity

$$\boldsymbol{\omega} = -\gamma \boldsymbol{B}_0 \tag{9}$$

one gets

$$\frac{\delta \boldsymbol{\mu}}{\delta t} = 0 \tag{10}$$

That is, the magnetic moment remains static in a frame rotating at the angular velocity $-\gamma\boldsymbol{B}_0$; thus it will precess in the laboratory frame with that speed. The precession phases (φ) of the sample nuclei are distributed at random ("incoherently"), so that the transversal (that is, perpendicular to $\boldsymbol{B}_0$) components of their magnetic moments give a null resultant and the magnetization is parallel to the rotation axis.

Let us now apply to the sample an electromagnetic wave whose magnetic field $\boldsymbol{B}_1$ rotates clockwise with angular velocity ω_{rad} (for "radiation") in a plane perpendicular to the vector $\boldsymbol{B}_0$, which will be taken to define the *z* axis (Figure 2):

$$\boldsymbol{B}_1 = B_1 \left(\boldsymbol{i} \cos \omega_{\text{rad}} t - \boldsymbol{j} \sin \omega_{\text{rad}} t \right) \tag{11}$$

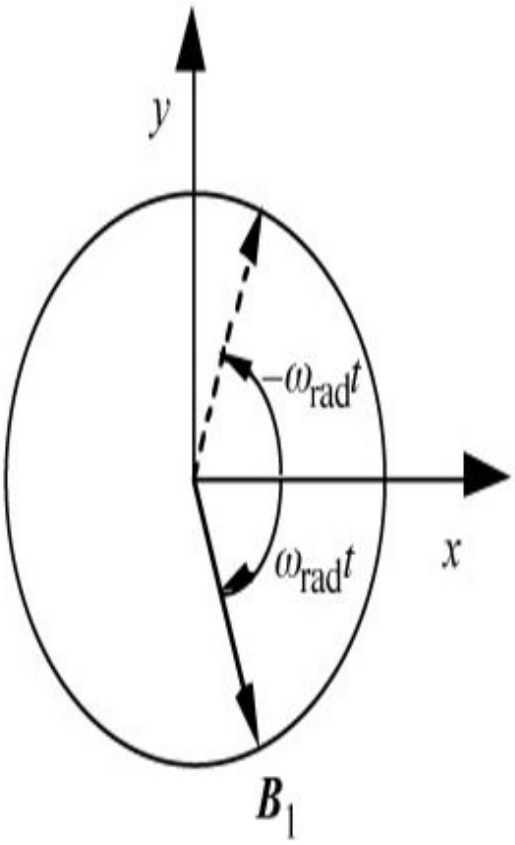

Figure 2. Magnetic field of a circularly polarized electromagnetic wave of angular frequency ω_{rad}. In practice, a linearly-polarized wave is used, the magnetic field of which has a constant direction, but this kind of wave is equivalent to a superposition of two circularly-polarized waves whose magnetic fields rotate in opposite directions, and only one of these (represented with a solid line in the figure) has the right angular momentum to affect nuclear magnetic moments; that is, angular momentum conservation rules out its interaction with the other (the dashed arrow).

It will be assumed that γ is positive (for negative γ values the sign of ω_{rad} should be reversed in every equation). The effective field in a frame that rotates with angular velocity $\boldsymbol{\omega}$ is now obtained by substituting the total field $\boldsymbol{B}_0+\boldsymbol{B}_1$ for $\boldsymbol{B}_0$ in Eq. (8). (See Figure 3.)

$$\boldsymbol{B}_{\text{eff}} = \boldsymbol{B}_0 + \boldsymbol{B}_1 + \frac{\boldsymbol{\omega}}{\gamma} \tag{12}$$

By choosing the modulus of $\boldsymbol{\omega}$ equal to the angular velocity of the radiation field ($|\boldsymbol{\omega}| = \omega_{rad}$) this field will remain static in the rotating frame, so the argument following Eq. (10) can be applied to conclude that the magnetic moment $\boldsymbol{\mu}$ of each nucleus will precess around $\boldsymbol{B}_{\text{eff}}$ in that frame with angular velocity $-\gamma\boldsymbol{B}_{\text{eff}}$. If all the nuclei with spin are of the same type (same "nuclide"), they will have the same γ value and they will precess at the same angular velocity; hence, their sum $\boldsymbol{M}$ will also precess at the angular velocity $-\gamma\boldsymbol{B}_{\text{eff}}$ in the rotating frame.

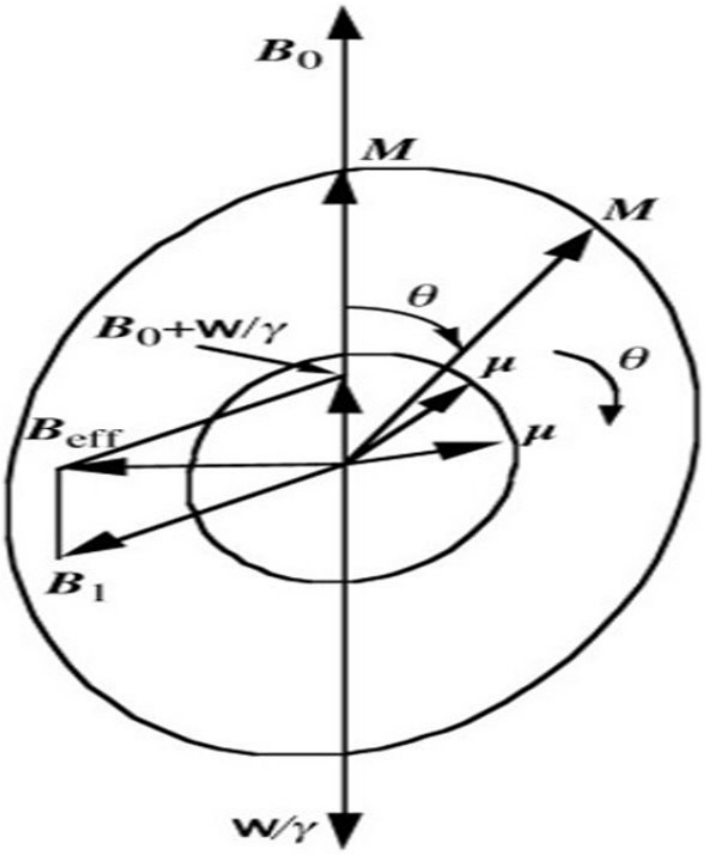

Figure 3. Precession of $\boldsymbol{\mu}$ and $\boldsymbol{M}$ in a frame rotating at the angular velocity (ω_{rad}) of the radiation field ($\boldsymbol{B}_1$) during a pulse of angle $\theta = \gamma B_{eff}\, t_p$, where t_p is the pulse duration (γ is assumed positive).

Since the magnetization is initially directed along $\boldsymbol{B}_0$, the radiation field causes a maximum effect on it when $\boldsymbol{B}_{eff}$ is perpendicular to $\boldsymbol{B}_0$ (and equal to $\boldsymbol{B}_1$). This implies (see Eq. (12)):

$$\frac{\boldsymbol{\omega}}{\gamma} = -\boldsymbol{B}_0 \tag{13}$$

and leads to the "resonance condition"

$$\omega_{rad} = \gamma B_0 \tag{14}$$

As ω_{rad} moves away from γB_0, $\boldsymbol{B}_{eff}$ acquires a component along $\boldsymbol{B}_0$ and the pulse effect on $\boldsymbol{M}$ tends to vanish. One normally uses the frequency rather than the angular velocity to characterize the radiation, so the resonance or "Larmor" frequency for the nuclide being considered will be (dropping the subscript "rad"):

$$\nu = \frac{\gamma B_0}{2\pi} \tag{15}$$

If the radiation acts during a time interval t_p the rotation angle of $\boldsymbol{M}$ in radians will be (see Figure 3)

$$\theta = \gamma B_{\text{eff}}\, t_p \tag{16}$$

and it is said that a "pulse" of angle θ has been applied to the sample. Most common pulses are those of 90° and 180°. As the direction of $\boldsymbol{M}$ separates from that of $\boldsymbol{B}_0$ the energy of interaction with the static field ($-\boldsymbol{M}\cdot\boldsymbol{B}_0$) becomes more positive, which means that the sample is absorbing energy from the radiation.

After the pulse, $\boldsymbol{B}_0$ is anew the only applied field but, in contrast with the initial equilibrium situation, $\boldsymbol{M}$ is no longer directed along the z axis. By adding up equations like Eq. (5) for every nucleus of a (unit volume) sample one obtains a similar equation for $\boldsymbol{M}$:

$$\frac{d\boldsymbol{M}}{dt} = \boldsymbol{M} \times \gamma \boldsymbol{B}_0 \tag{17}$$

so the conclusions above drawn for $\boldsymbol{\mu}$ (see the discussion following Eq. (10)) can now be extended to $\boldsymbol{M}$: the magnetization vector will precess about $\boldsymbol{B}_0$ with angular velocity $-\gamma\boldsymbol{B}_0$ in the laboratory frame (Figure 4).

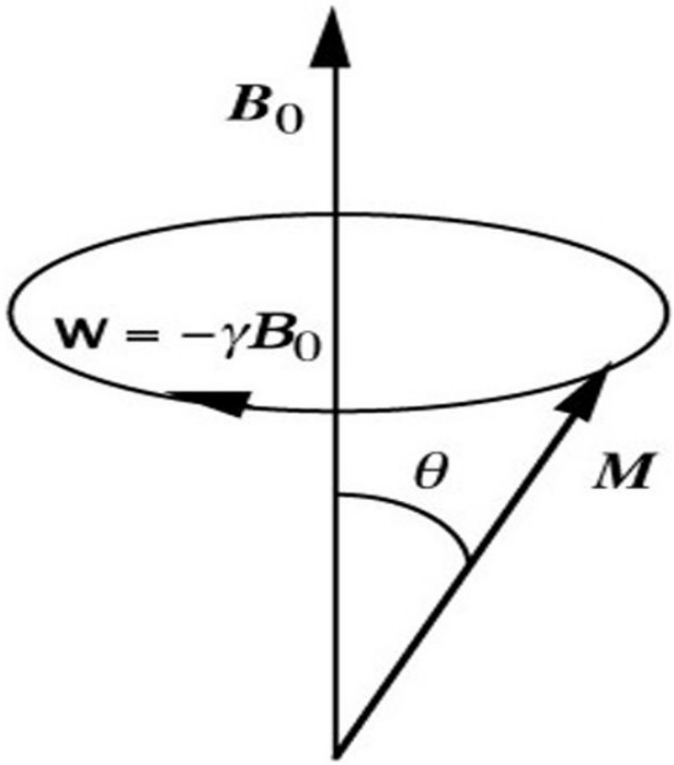

Figure 4. Precession of $\boldsymbol{M}$ in the laboratory frame after a pulse of angle θ for nuclei with positive γ.

After the pulse, the precession phases of the individual nuclear spin vectors are not distributed at random, as in the initial equilibrium state, but are grouped around the phase of ***M***. It is thus said that the nuclei precess "coherently," or that the pulse has generated some "phase-coherence" in the sample (there are other types of "coherences" relevant to NMR that cannot be visualized with the present classical model).

The precession of ***M*** can be detected by measuring the current induced by the transversal magnetization in a coil surrounding the sample. The resulting time-domain signal is digitalized and converted into a frequency-domain plot by carrying out a mathematical Fourier transformation on a digital computer (Figure 5).

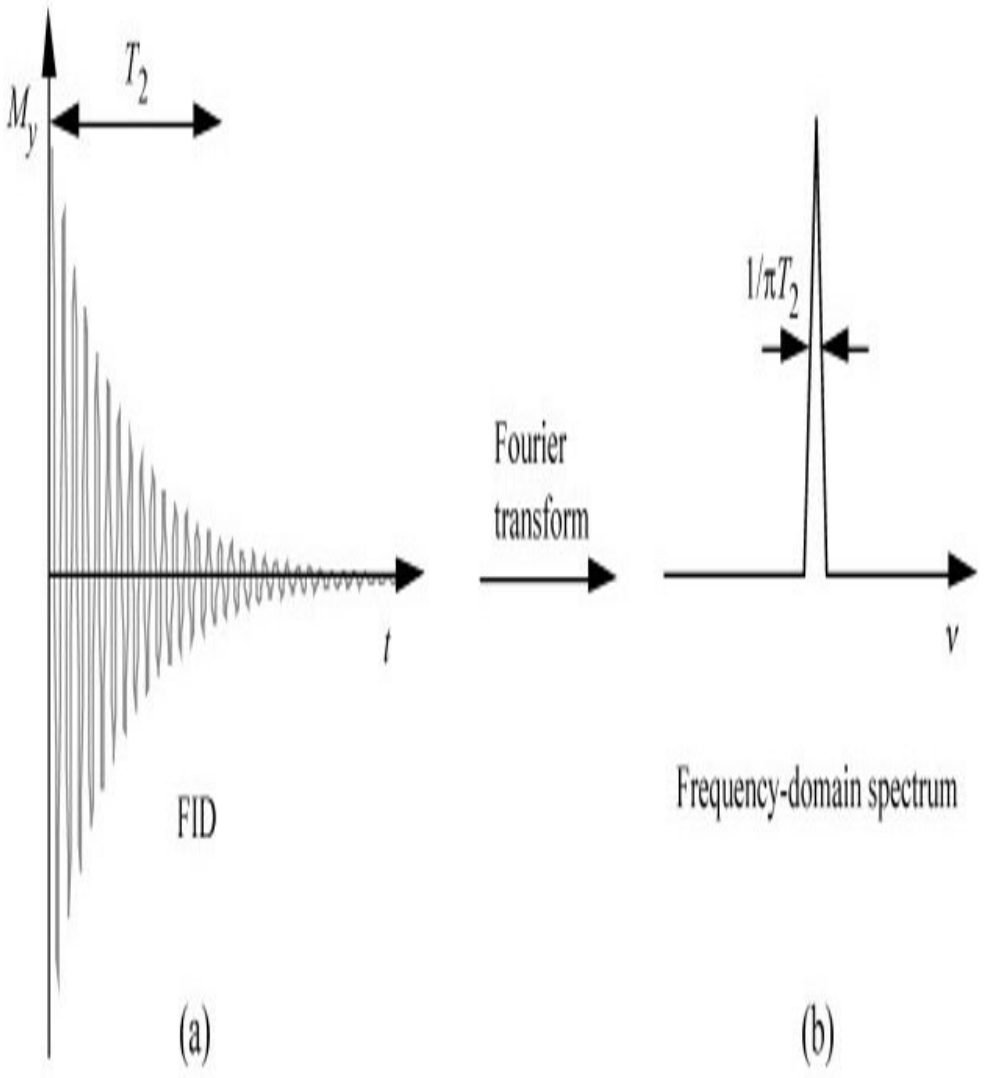

Figure 5. The magnetization component on an axis perpendicular to $\boldsymbol{B}_0$ is registered as a function of time (a) and Fourier transformed to give a frequency function (b). The faster the time-domain signal decays (shorter T_2), the wider the frequency-domain signal results.

Relaxation tends to restore thermodynamic equilibrium, so that the magnetization will tend to recover the direction of $\boldsymbol{B}_0$ and the time-domain signal will eventually disappear, blurred by the spectrometer noise (Figure 5a). The time-domain signal is thus referred to as the "free induction decay" (FID).

Two different relaxation mechanisms bring the longitudinal (that is, parallel to $\boldsymbol{B}_0$) and transversal components of $\boldsymbol{M}$ towards their equilibrium values. Both are approximately first-order processes with characteristic evolution times: the longitudinal or "spin-lattice" relaxation time (T_1) and the transversal or "spin–spin" relaxation time (T_2). By including the corresponding terms in the equation for the evolution of $\boldsymbol{M}$ in the rotating frame (which results from adding up equations like Eq. (7) for the nuclei), one obtains the so-called "Bloch equation":

$$\frac{\delta \boldsymbol{M}}{\delta t} = \boldsymbol{M} \times \gamma \boldsymbol{B}_{\text{eff}} + \frac{M_{\text{eq}} - M_z}{T_1}\boldsymbol{k} - \frac{M_x \boldsymbol{i} + M_y \boldsymbol{j}}{T_2} \tag{18}$$

Spin-lattice relaxation restores the equilibrium value (M_{eq}) of the z component of $\boldsymbol{M}$ by means of a non-radiative energy transfer between nuclear spins and the surroundings: the lattice vibrations in the case of solid samples, and molecular motions (mainly rotations) for liquids and gases. Typical T_1 values range from 10^{-2} to 10^{2} s.

Of course, the transversal magnetization must have disappeared by the time M_z has reached its equilibrium value, but the interactions between nuclear spins introduce random variations in their precession frequencies, which result in a coherence loss and speed up the transversal-magnetization decay. Transversal relaxation times (T_2) determine the line-width of the frequency-domain signals: the faster the FID decays the wider the signal results after Fourier transformation (Figure 5).

The magnetic field inhomogeneities over the sample also contribute to fade the transversal magnetization (and to increase line-width), since variations in B_0 from one region of the sample to another produce some spread of resonance frequencies (see Eq. (15)). This leads to an effective transversal relaxation time (T_2^*) shorter than T_2. Field inhomogeneities are partially averaged out by rapidly spinning the sample. Nuclei with $I > 1/2$ have an electric quadrupole moment whose interaction with the electric field gradient at the nuclear site further accelerates the transversal relaxation.

If the molecules of the sample have different nuclides with $I \neq 0$ (e. g. ^{1}H and ^{13}C) the above reasoning can be applied to every nuclide, and a specific signal could be detected for each one by conveniently adjusting the radiation frequency:

$$\nu_{\text{H}} = \frac{\gamma_{\text{H}} B_0}{2\pi}, \quad \nu_{\text{C}} = \frac{\gamma_{\text{C}} B_0}{2\pi}, \text{ etc.} \tag{19}$$

Magnetic field intensities of present day commercial spectrometers range from 1.4 to 21.14 T, which leads to resonance frequencies of 60 to 900 MHz for ^{1}H and 15.1 to 226.3 MHz for ^{13}C (whose gyromagnetic ratio is almost four times smaller). These fall

in the radiofrequency region of the electromagnetic spectrum. Spectrometers are usually classified according to their proton resonance frequency.

Each nuclide would certainly give a unique signal in a low-resolution spectrum but, under the usual high-resolution conditions, nuclei of the same type in different chemical environments (an OH bond, a methyl group, and so on) can be distinguished thanks to small differences in their resonance frequencies. These are due to the small magnetic field produced on each nucleus by the rest of the particles of the molecule. Let us first consider the effect of the electrons. These have orbital and spin angular momenta, whose associated magnetic moments generate magnetic fields. However, many molecules have a closed shell electronic structure with no net angular momentum and, in the absence of external magnetic fields, no significant magnetic interaction with the nuclei. Nevertheless, the external static field distorts the electron distribution in such a way that a net electronic magnetic moment remains. The magnetic field produced by this moment depends on the nuclear position, which gives different total fields and resonance frequencies for identical nuclei in different environments. Thus, if the electrons produce a field $\boldsymbol{B}_{\mathrm{el},i}$ at the position of a nucleus *'i'* whose gyromagnetic ratio is γ_i, its resonance frequency will be:

$$\nu_i = \nu_i = \frac{\gamma_i \left| \boldsymbol{B}_0 + \boldsymbol{B}_{\mathrm{el},i} \right|}{2\pi} \tag{20}$$

The field produced by the electrons at the position of a nucleus is proportional to the external field. In general, it is not parallel to $\boldsymbol{B}_0$, so that the proportionality relationship must be expressed in terms of a tensorial magnitude, the "shielding" or "screening" tensor at nucleus *'i'* ($\boldsymbol{\sigma}_i$):

$$\boldsymbol{B}_{\mathrm{el},i} = -\boldsymbol{\sigma}_i \boldsymbol{B}_0 \tag{21}$$

For protons, $\boldsymbol{B}_{\mathrm{el},i}$ is mainly due to an induced electronic current that opposes the external field, whence the term "shielding" and the negative sign in Eq. (21). Molecular rotation in gas or (not very viscous) liquid samples produces an averaging of this tensor that leads to a scalar magnitude: the shielding constant σ_i:

$$\left\langle \boldsymbol{B}_{\mathrm{el},i} \right\rangle = -\sigma_i \boldsymbol{B}_0 \tag{22}$$

The resonance frequency of the nucleus *'i'* is then:

$$\nu_i = \frac{\gamma_i (1-\sigma_i) B_0}{2\pi} \tag{23}$$

The values of σ_i are much smaller than 1, so that the resonance frequencies of the same nuclide in different molecular environments are very close to each other compared with typical frequency differences of distinct nuclides. Consequently, NMR spectra of different nuclides rarely overlap.

The magnetization of a sample with identical nuclei in different environments is a sum of components that precess at slightly different frequencies. This leads to a complicated FID that, after Fourier transformation, shows up the component frequencies. Before 1970, NMR spectra were recorded either by sweeping the radiation frequency at a fixed B_0 or by varying this field intensity at a fixed radiofrequency. Nowadays, those continuous-wave operation modes have been superseded by pulse techniques, in which nuclei with different shielding constants are simultaneously irradiated. In fact, the radiation used is essentially monochromatic, but one can show that a short pulse is equivalent (by a Fourier transform) to a mixture of infinite monochromatic waves whose frequencies spread over an interval centered on the pulse frequency. This makes it possible to obtain the whole spectrum of a nuclide (or a substantial part of it) with a single pulse, and to obtain many spectra in a short time by repeating the sequence pulse-FID registration. These are then digitally added to improve the signal to noise ratio.

It is not easy to measure accurate absolute values of shielding constants and one usually gives values relative to that of a reference substance added to the sample (for ^{1}H and ^{13}C tetramethylsilane, commonly referred to as TMS, is normally used). These are obtained from the adimensional "chemical shift," which is independent of the spectrometer static-field intensity B_0:

$$\delta_i = \delta_i = \frac{\nu_i - \nu_{i,\mathrm{ref}}}{\nu_{i,\mathrm{ref}}} \times 10^6 = \frac{\sigma_{i,\mathrm{ref}} - \sigma_i}{1 - \sigma_{i,\mathrm{ref}}} \times 10^6 \tag{24}$$

Here the subscript "ref" refers to the reference substance and the factor 10^6 is included to obtain convenient values (the unit "ppm" is usually added to δ_i values). By taking into account that $\sigma_{i,\mathrm{ref}} << 1$, chemical shifts can be identified with relative shielding constants:

$$\delta_i = \left(\sigma_{i,\mathrm{ref}} - \sigma_i\right) \times 10^6 \tag{25}$$

Chemical shifts of protons in typical organic compounds range from 0 to 16 ppm; for ^{13}C the range is about 300 ppm. Conventionally, NMR spectra are plotted with δ_i increasing from right to left.

Let us look at the evolution of nuclear spins after a pulse of, say, 90° from a frame that rotates at a reference frequency (which may be that of the radiation source). A nucleus with exactly that Larmor frequency will remain static, but one with chemical shift δ_i will precess at an offset angular frequency (see Eq. (23)):

$$\Omega_i = \omega_i - \omega_{i,\mathrm{ref}} = \gamma_i \left(1 - \sigma_i\right) B_0 - \gamma_i \left(1 - \sigma_{i,\mathrm{ref}}\right) B_0 = \gamma_i \delta_i B_0 \times 10^{-6} \tag{26}$$

Offset frequencies, which lie in the audio frequency region of the spectrum, are what NMR spectrometers actually measure.

Nuclei that can be interchanged by a molecular symmetry operation or a rapid conformational change have the same chemical shift, and are said to be “chemically equivalent” or “isochronous.”

Chemical shift values can be related to molecular structure, either by theoretical calculations or, most conveniently for routine applications, by using tabulated empirical correlations. Thus, chemical shift information is a valuable aid for structure determination.

Another important source of information, present in most NMR spectra, is related to the interaction between nuclear spins. While the electronic environment produces a shift in the resonance frequency with respect to that of the bare nucleus, the spins of other nuclei can split that frequency into two or more signals. Quantum arguments are needed to understand this effect. Actually, the reason why classical mechanics works well for predicting NMR spectra of independent nuclei is that the quantum evolution equation (the time-dependent Schrödinger equation) leads, in that case, to the classical result shown in Eq. (5); however, important divergences appear for coupled nuclei.

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Biographical Sketches

Juan Carlos Paniagua was born in 1955 in Bilbao (Spain). Graduated in Chemistry (1977) at the University of Barcelona. He obtained his Ph. D. degree by the same university in 1984 under the supervision of Prof. Luis Maria Tel for work on localised molecular orbitals. Presently he is Associate Professor in the Physical Chemistry Department at the University of Barcelona. He has worked on different aspects of quantum chemistry including its application to spectroscopy and, specially, to NMR.

Miquel Pons was born in 1956 in Manresa (Spain). Graduated in Chemistry (1979) and in Biology (1986) at the University of Barcelona. He obtained his Ph. D. degree by the University of London in 1983 under the supervision of Prof. Dennis Chapman for work on spectroscopic studies of diacetylenic phospholipids. Presently he is Professor of Organic Chemistry and group leader of Biomolecular NMR at the Institute for Research in Biomedicine located in the Barcelona Science Research Park. His work is focussed in the structural aspects of molecular recognition, de novo peptide design, and in the applications of NMR to the study of molecular structure and dynamics. In particular he is interested in the study of ordered or anisotropic systems, stereochemically and dynamically complex organic molecules and the dynamics of proteins and protein-ligand interactions. He has published more than 100 papers in the fields of NMR and structural chemistry and has received the 2nd Bruker-SBE award (2000) for his contributions to Structural Biophysics in Spain and is chairman of the Grupo Especializado de RMN (GERMN) of the Spanish Royal Society of Chemistry.