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RESTRICTED SELF-DIFFUSION MEASUREMENT BY MAGNETIC RESONANCE WITH GRADIENT MODULATION

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Principles and theory of the new continuous wave magnetic resonance method for self-diffusional motion measurements are described. When the magnetic field gradient modulation is superimposed on the usual homogeneous magnetic field modulation of the continuous wave (cw) spectrometer, self-diffusion along the gradient modifies the NMR signal in a simple and predictable way. Using the Bloch–Torrey equations, a derivation of the effect is given for various time-dependent gradient modulations. The pulse magnetic field gradient modulation makes it possible to study the restricted self-diffusions.

The method is easily adaptable to any cw spectrometer, and it allows the measurement of the self-diffusion coefficient of each component in a complex system using high-resolution NMR without Fourier transformations. Combined with the pulse NMR apparatus the periodic magnetic field gradient modulation can replace the role of π pulses at the spin-echo experiment.

1. Introduction

A number of recent publications [1–4] on nuclear magnetic resonance measurements of self-diffusional coefficients show progressive interest in this method. The original method with the spin-echo in a gradient field [1] for self-diffusion constant determination has been improved by using pulse gradients rather than a steady magnetic field gradient [2]. Other improvements include radiofrequency (rf) pulse sequences to destroy mutual spin interaction [3], Fourier transform spectroscopy to resolve the diffusion coefficient of different components [4], the measurements of restricted diffusions [5], *etc.* These techniques have been successfully applied to the studies of random non-localized molecular motions in liquids and gases.

Here a new technique is proposed that uses continuous wave (cw) magnetic resonance spectroscopy for measurement of molecular spatial motions determined by the self-diffusion constant. The main advantage is its simplicity and adaptability to any NMR spectrometer without significant modifications. Merely the magnetic field gradient modulation has to be superimposed to the usual uniform magnetic field modulation. In addition, the method exhibits very interesting features such as the possibility of simultaneous determination of the self-diffusion coefficient for various compounds distinguished by different chemical shifts from NMR spectra. The restricted self-diffusion can be measured by using the pulse magnetic field gradient modulation.

2. Bloch equations and gradient modulation

The measurement of self-diffusion coefficients requires labelling of diffusing species. In magnetic resonance this labelling is accomplished by the spin Larmor frequency. If an inhomogeneous external magnetic field is applied, the spin precession frequency changes along the sample, and any spin position shift along the gradient brings about a modification of its Larmor frequency. Since all spins inside the rf coils contribute to the NMR

signal, only an average response can be seen and individual spin properties are hidden in the bulk sample signal. In order to avoid this, the unique property of the spin-echo effect has been used.

Here we shall discuss a simple, but equally effective, equivalent of the spin-echo method. It involves the usual cw magnetic resonance experiment in which an additional magnetic field modulation is employed. This new modulation is not uniform but has a constant magnetic field gradient in a chosen direction. In the corresponding coordinate system it may be written as

$$G \cdot r \cdot g(t). \tag{1}$$

Here G is the magnetic field gradient $\partial B_z/\delta r$, r is the spin location vector and $g(t)$ is a periodic time-dependent function.

In order to describe essential features, and to establish a necessary condition for measurements, we solve the so-called Bloch–Torrey equations. These are the phenomenological Bloch equations after inclusion of terms due to the transfer of magnetization by spin motion [1, 2]. This approach does not include some minor details, but explains the idea in a simple way. In a following article the density matrix formalism will be employed to demonstrate these details.

The z-axis is defined by a static field B_0, whereas the weak rf field of amplitude $2B_1$, and frequency ω is along the x-axis. The modulation field, also along z, may include a usual homogeneous field and a magnetic gradient field:

$$B_m(r,t) = B_h(t) + G \cdot r \cdot g(t). \tag{2}$$

The Bloch–Torrey equations in a coordinate frame rotating with frequency ω about the z-direction are

$$\begin{aligned} dM_z/dt &= \omega_1 M_y - [(M_z - M_0)/T_1] + \nabla(\mathbf{D}\nabla)M_z, \\ dM_x/dt &= \Delta M_y - (M_x/T_2) + \nabla(\mathbf{D}\nabla)M_x + \gamma B_m M_y, \\ dM_y/dt &= -\Delta M_x - (M_y/T_2) - \omega_1 M_z + \nabla(\mathbf{D}\nabla)M_y - \gamma B_m M_x. \end{aligned} \tag{3}$$

The magnetization vector $M = (M_x, M_y, M_z)$ of a volume element depends upon the local coordinate and time. The transversal spin relaxation time T_2, and the spin–lattice relaxation time T_1, cause the magnetization attenuation and $\Delta = \omega - \omega_0$ defines the spin precession frequency in the rotating frame. The rf term, with $\omega_1 = -\gamma B_1$, is assumed sufficiently weak to avoid saturation of spin transitions. The term due to transfer of magnetization by spatial self-diffusion includes a self-diffusion tensor $\mathbf{D}$.

Elaborate calculations can be avoided by assuming the magnetization M_z to be constant, *i.e.* the longitudinal magnetization does not follow the modulation. This condition is fulfilled even under saturation conditions, but in the following only the weak rf field is used in order to retain M_z constant and equal to the equilibrium magnetization M_0. After defining

$$m(r,t) = M_x + iM_y$$

eq. (3) becomes

$$dm/dt = -i(\Delta + \gamma B_m) \cdot m - (m/T_2) - i\omega_1 M_0 + \nabla(\mathbf{D}\nabla) \cdot m. \tag{4}$$

By substituting

$$m = \psi(t) \cdot \exp\left[-i\gamma \int_0^t B_m(\tau)\,d\tau\right],$$

it might be transformed into an inhomogeneous differential equation of the first order. When the transient part of its solution is neglected, the remaining steady-state part is

$$m_s(r,t) = i\omega_1 M_0 \int_{-\infty}^{t} \left\{ \exp\left[i\Delta(\tau - t) + i\gamma \int_t^{\tau} B_m(t')\,dt' - \gamma^2 G\cdot\mathbf{D}\cdot G \int_{\tau}^{t} \left[\int_0^{t'} g(u)\,du \right]^2 dt' - \frac{t-\tau}{T_2} \right] \right\} d\tau. \tag{5}$$

The magnetic resonance response (5) is a Fourier transformation of the resonance transient signal with the relaxation time T_2, and in addition with the damping term due to the spin self-diffusional motion in the gradient field. Since the additional term relates very much to the MFG time dependence, the detailed insight into nuclear magnetic resonance response will be defined by specifying the form of $g(t)$.

In the following two types of magnetic field, gradient time dependence will be carefully considered. One is the usual sine wave MFG modulation applied to the specimen by itself. Its function will be to broaden the NMR lines according to (5) and, in addition, to bring enough audio response for the lock-in detection. The other is MFG pulse modulation. While the uniform magnetic field modulation will serve for the lock-in detection, only the pulse MFG modulation will provide information about the diffusion.

3. MFG sine-wave modulation

The gradient of the magnetic field strength can be created by the use of a Helmholtz coil with opposite current direction or by a quadrupole coil. An alternating sine-wave electric current will induce a sine-wave time-dependent MFG modulation:

$$B_m(r,t) = G\cdot r\cdot\cos\omega_m t. \tag{6}$$

In order to justify the form of (6), the coordinate origin must be at the point where the amplitude of modulation is zero, *i.e.* at the point on the axis halfway between the coils in the case of a reversed Helmholtz coil. Such an oscillating MFG will provide the data on the molecular migration as well as generating a resonance audio response used for detection. At first only the magnetic resonance line modification due to the self-diffusion motion into a gradient field will be considered.

By putting (6) into expression (5) the self-diffusional damping term is given the following form:

$$\gamma^2 \frac{G\cdot\mathbf{D}\cdot G}{2\omega_m^2}\left(t - \frac{\sin 2\omega_m t}{2\omega_m}\right). \tag{7}$$

The expression (7) includes the term linearly dependent upon the time and the term having a sinusoidal form. Closer inspection reveals that the last one can be neglected if the time of spin migration across the distance of sample dimension is much longer than $2\pi/\omega_m$. Therefore, the apparent spin transversal relaxation time is

$$1/T_2^* = 1/T_2 + \gamma^2 \frac{G\cdot\mathbf{D}\cdot G}{2\omega_m^2}. \tag{8}$$

The resonance curve is not a simple line with the linewidth characterized by the new relaxation time T_2, since it is additionally modified due to the magnetic field modulation. In order to get the shape of the resonance curve, let

us expand the phasing term of (5) into

$$\exp\left(\mathrm{i}\gamma\int_0^t B_{\mathrm{m}}(\tau)\,\mathrm{d}\tau\right)=\sum_{k=-\infty}^{k=\infty}J_k(\zeta)\exp\left(\mathrm{i}k\omega_{\mathrm{m}}t\right). \tag{9}$$

$J_k(\zeta)$ are the Bessel functions of the first kind, with $\zeta=(\gamma G\cdot r)/\omega_{\mathrm{m}}$. Substituting (8) and (9) into eq. (5) the steady-state complex magnetization becomes

$$m_{\mathrm{s}}(r,t)=-\mathrm{i}\omega_1 M_0\sum_{k,L}J_k(\zeta)J_L(\zeta)\,\frac{T_2^*\exp\left(\mathrm{i}(k-L)\omega_{\mathrm{m}}t\right)}{1+\mathrm{i}T_2^*(\Delta+k\omega_{\mathrm{m}})}. \tag{10}$$

By resolving the expression (10) into the real and imaginary parts and then ordering them into audio-harmonics the components of the transversal magnetization density are obtained. Therefore, the induced voltage in the rf coil, either u-mode or v-mode, is proportional to

$$u=-\omega_1 M_0\sum_{n=0,k=-\infty}^{n=\infty,k=\infty}\left[A_{k,n}\,g(\Delta+k\omega_{\mathrm{m}})\cos\left(n\omega_{\mathrm{m}}t\right)+B_{k,n}\,h(\Delta+k\omega_{\mathrm{m}})\sin\left(n\omega_{\mathrm{m}}t\right)\right], \tag{11}$$

$$v=\omega_1 M_0\sum_{n=0,k=-\infty}^{n=\infty,k=\infty}\left[B_{k,n}\,g(\Delta+k\omega_{\mathrm{m}})\sin\left(n\omega_{\mathrm{m}}t\right)+A_{k,n}\,h(\Delta+k\omega_{\mathrm{m}})\cos\left(n\omega_{\mathrm{m}}t\right)\right],$$

with

$$A_{k,n}=\tfrac{1}{2}\,\epsilon_n\int J_k(\zeta)\left[J_{k+n}(\zeta)+J_{k-n}(\zeta)\right]\mathrm{d}V,\quad \epsilon_0=1\quad\text{and}\quad \epsilon_{n\neq 0}=2, \tag{12}$$

and

$$B_{k,n}=\int J_k(\zeta)\left[J_{k-n}(\zeta)-J_{k+n}(\zeta)\right]\mathrm{d}V.$$

The magnetic resonance response (11) contains a number of modulation frequency harmonics. Any of the harmonics can be extracted out of the total response by employing the selective lock-in detection. After that, the resonance curve consists of a series of lines which are equally spaced from ω_0 by a multiple of the modulation frequency ω_{m} [6]. By proper phase setting of the audio frequency, either the lines of shape

$$g(\Delta)=T_2^*/[1+(\Delta T_2^*)^2]\quad\text{or}\quad h(\Delta)=\Delta T_2^{*2}/[1+(\Delta T_2^*)^2] \tag{13}$$

are the constituents of the observed spectra. Whenever the frequency ω_{m} is larger than the linewidth T_2^*, the response signal consists of several distinct lines. Following the change of width of a particular line as a function of applied gradient amplitude, the data of the molecular self-diffusion motion can be obtained. The plot of the linewidth $1/T_2^*$ *versus* $\gamma^2G^2/2\omega_{\mathrm{m}}^2$ is a straight line with intercept $1/T_2$ and a slope proportional to the self-diffusion constant D.

Instead of following the linewidth modification the same information can be taken by measuring the reciprocal of the line intensity *versus* $\gamma^2G^2/2\omega_{\mathrm{m}}A_{k,n}$. When dealing with narrow lines this method may be more convenient, but care must be exercised with regard to eventual line saturation if the rf field is not weak enough.

The MFG sine-wave modulation technique has demonstrated its applicability when used for the measurement of the self-diffusion constant in water. But there was a drastic reduction of the signal magnitude at large values of the MFG amplitude. Since the signal intensity (12) depends upon the modulus $G\cdot l/\omega_{\mathrm{m}}$, the signal-to-noise ratio could be improved if the sample dimension along the gradient, l, is small enough. However, the method is expected to be useful mostly for a measurement of large self-diffusion constants, *e.g.* in gases.

4. MFG pulse modulation

In an attempt to eliminate the restriction established when the sine-wave modulation technique is employed we have tried to find a kind of modulation which will provide the information about spin migration but will not reduce the signal significantly. Since the modulation function $g(t)$ is only required to be a periodic antisymmetric function of time, the repetition sequence of two gradient pulses may be suitable for such a purpose. The gradient direction of the first applied pulse is taken to be reversed with regard to the gradient direction of the second pulse in order to meet the antisymmetric condition for $g(t)$, whereas the strong spin dephasing (which means signal reduction) will be prevented by using a pulse width δ which is short compared to the pulse interspace τ and repetition time T, fig. 1. Using Fourier transform expansion, this MFG pulse modulation can be written as follows:

$$g(t) = -(2i\delta/T) \sum_{\substack{n=-\infty \\ n\neq 0}}^{n=\infty} (-1)^n \sin(n\pi\tau/T) \exp(2in\pi t/T). \tag{14}$$

Inherent damping due to the diffusional molecular migration can be found by putting (14) into the corresponding term of (5):

$$\gamma^2 \frac{\delta^2 \boldsymbol{G}\cdot\mathbf{D}\cdot\boldsymbol{G}}{\pi^2} \int_0^t \sum_{n,n'} \frac{\sin(n\pi\tau/T)\sin(n'\pi\tau/T)}{n\cdot n'} \{\exp[-i(n+n')2\pi t'/T]$$

$$- \exp(-2in\pi t'/T) - \exp(-2in'\pi t'/T) + 1\}\,dt'. \tag{15}$$

The expression (15) includes the terms linearly dependent upon the time as well as the harmonics of the modulation frequency $2\pi/T$. By arguments similar to those for eq. (7) the oscillating terms in (15) may be neglected, presuming that the time of particle migration across the distance of specimen dimension is longer than the time T. Then, the remaining part of (15) is

$$\gamma^2 \frac{\delta^2 \boldsymbol{G}\cdot\mathbf{D}\cdot\boldsymbol{G}}{\pi^2} \left\{ \left[\sum_n (-1)^n \frac{\sin(n\pi\tau/T)}{n} \right]^2 + \sum_n \frac{\sin^2(n\pi\tau/T)}{n^2} \right\} t, \tag{16}$$

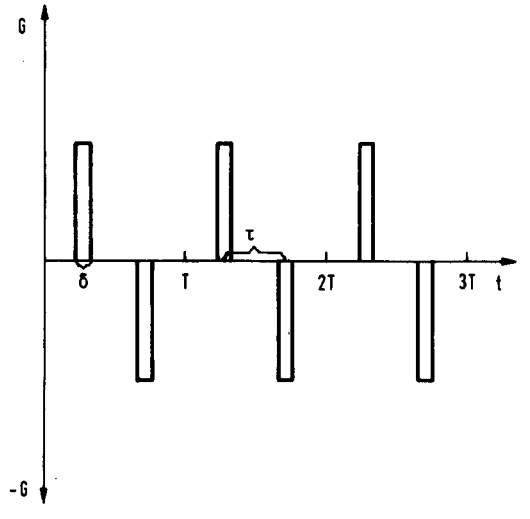

Fig. 1. The pulse sequences used for a magnetic field gradient modulation.

which is nothing more than

$$\gamma^2\delta^2 \boldsymbol{G}\cdot\mathbf{D}\cdot\boldsymbol{G}\,\tau t/T. \tag{17}$$

From the above expression, one can see that by changing the pulse interspace τ and keeping unchanged the MFG amplitude and pulse width δ, the self-diffusion constant can be determined directly from the linewidth modification. A plot of the linewidth *versus* τ will give a straight line with an intercept $1/T_2$ and a slope proportional to the self-diffusion constant

$$1/T_2^* = 1/T_2 + \gamma^2\delta^2 \boldsymbol{G}\cdot\mathbf{D}\cdot\boldsymbol{G}\cdot\tau/T. \tag{18}$$

Let us consider the physical meaning of this additional line broadening. If the gradient is applied along the x-axis then the averaged squared molecular shift along the x-axis per time τ is equal to

$$\langle [x(0) - x(\tau)]^2 \rangle = 2D_{xx}\tau. \tag{19}$$

Therefore, the extra line-broadening is directly related to the distance of spin migration in the pulse interspace time τ. The value τ may be varied independently of the sequence period T so that various diffusion times may be measured. The upper limit is set by the spin relaxation time T_2 because the sequence repetition time must be shorter than the spin evolution decay. The lower limit is set by the magnitude of the gradient which can be applied. But when the molecules are migrating in small compartments, *e.g.* in tissues restricted by membranes, some precaution must be exercised regarding the time τ. For a sufficiently long pulse interspace the compartment diameter might be smaller than $(D_{xx}\tau)^{\frac{1}{2}}$. Since the molecular motion is bounded inside a volume of diameter R, then the $D_{xx}\tau$ in (18) must be replaced by R^2 for large τ. By plotting again the linewidth *versus* τ, the previous straight line undergoes a kink at the point $\tau = R^2/D_{xx}$ (fig. 2). It is evident that the MFG pulse modulation method can also provide the information on the restricted diffusion motion.

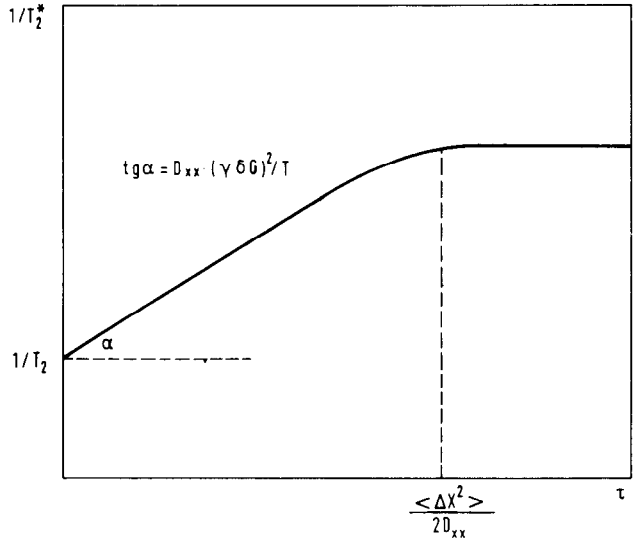

Fig. 2. The dependence of the magnetic resonance linewidth upon a pulse interspace time τ. The initial slope of the curve is proportional to the self-diffusion constant, whereas the intercept of the horizontal line and the rising curve is determined by the restricted volume dimension.

The short MFG pulses have been employed to avoid strong spin precession dephasing resulting in a reduction of the magnetic resonance signal. Such pulses, in general, do not generate enough audio response to be used for lock-in detection. Therefore, it requires the usual uniform magnetic field modulation to be imposed in conjunction with the MFG pulses. This can be considered as a multiple magnetic field modulation which has been studied in great detail elsewhere [6]. By assuming that the frequency of the homogeneous modulation ω_m as well as the pulse repetition frequency $\omega_g = 2\pi/T$ are larger than the linewidth $2\pi/T_2^*$ and that the ratio ω_g/ω_m is given by the ratio of large integers, then the central line intensity of the observed v-mode signal is equal to

$$v'(0) = v(0) \int a_0(r) \cdot a_0(r)^+ \mathrm{d}V. \tag{20}$$

Here $v(0)$ is the signal intensity without applied MFG modulation, whereas $a_0(r)$ is the zeroth order term of the expansion of the phasing factor in (5):

$$\exp\left(\mathrm{i}\gamma \boldsymbol{G}\cdot\boldsymbol{r} \int_0^t g(t')\mathrm{d}t'\right) = \sum_{n=-\infty}^{n=\infty} a_n(r) \exp\left(-\mathrm{i}2n\pi t/T\right). \tag{21}$$

In the case of short pulses ($\delta \ll T$) $a_0(r)$ is equal to

$$a_0(r) = 1 - (1 - \exp(-\mathrm{i}\gamma \boldsymbol{G}\cdot\boldsymbol{r})). \tag{22}$$

For a cylindrically shaped specimen with the axis along the applied magnetic field gradient, the volume integration of eq. (20) could be simplified, resulting in

$$v'(0) = v(0)\,[1 - 2\tau/T + 2(\tau/T)^2]. \tag{23}$$

The maximal intensity reduction is one-half of that which appears when the pulse interspace time is one-half of the sequence repetition time. It is advantageous compared to the sine-wave MFG modulation method, that the signal reduction does not depend upon the applied gradient amplitude.

5. Conclusion

It is evident that there is a close resemblance between the pulse magnetic field gradient spin-echo technique and the MFG pulse modulation method. The main difference is that the role of two MFG pulses, with an intermediate radio frequency π pulse in the spin-echo case is replaced by two pulses with reversed direction of the MFG. In this paper we have considered such a pulse sequence only in connection with the cw experiment. It may also be applied with the pulse magnetic resonance experiment. Absence of the intermediate rf π pulse enables still further reduction of the MFG pulse interspacing, thus making possible investigation of self-diffusion inside very small restricted compartments, *e.g.* in living cells.

Time-domain information from the spin-echo experiment, and frequency-domain information from the cw spectrometer method, are of course related by Fourier transformation. However, it seems to us that MFG-modulation cw spectroscopy has an advantage when determining the self-diffusion coefficients of different compounds in a liquid. Inasmuch as the various compounds can be identified by their characteristic spectra, by applying MFG modulation with a frequency larger than the width of the entire spectrum, the gradient dependence of individual resonance linewidths may be obtained. Thus, the self-diffusion constants of different compounds can be determined simultaneously.

The method can be also useful for determination of diffusion coefficients in samples with broad NMR lines if it is used in conjunction with the line narrowing by sample rotation. However, in that case, the gradient must be applied along the rotation axis.

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