Self-diffusion measurements with chemical shift resolution in inhomogeneous magnetic fields

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Abstract

A methodology for chemical shift resolved molecular self-diffusion measurements in time-independent static and radiofrequency field gradients is demonstrated. Diffusion encoding is provided by a stimulated echo sequence with additional $z$-storage that allows for a change of diffusion time without affecting the relaxation weighting. The signal is acquired stroboscopically between the pulses of a train of adiabatic double passages that induces a $z$-rotation counteracting the phase spread resulting from precession in the inhomogeneous static field, as demonstrated in recent approaches to the goal of high-resolution “ex situ” NMR. Simulations of the pulse sequence show that the acquired signal results from the desired coherence pathway. Successful demonstrations of the experiment were performed on a mixture of water and isopropanol.

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Keywords: Inhomogeneous magnetic fields; Chemical shift; Self-diffusion; Adiabatic pulses; Stimulated echo

1. Introduction

Techniques and equipment for single-sided NMR have been developed in the last few years, most notably the NMR-MOUSE [1]. The benefits of not having to put the sample under investigation inside the bore of a magnet are numerous: the possibility of studying bulky objects, subjects in the doctor’s office, or demonstrating NMR-scanners for quality control in existing process lines in the industry being just a few. With such a setup both the static and radiofrequency magnetic fields are necessarily inhomogeneous. Alleviating the problems associated with the single-sided design has been the subject of extensive research. Methods for relaxation, diffusion, and imaging experiments in inhomogeneous fields have been devised [1–7].

The greatest loss of information when using inhomogeneous fields is the chemical shift. The shift range for the most common NMR-active nucleus, the proton, is about 10 ppm. Static magnetic field inhomogeneity on the ppm-scale will thus obscure the shift information. As shown recently [8–11], this information can be restored through stroboscopic signal acquisition while applying a train of $z$-rotation radiofrequency pulses with a field strength spatially matched to the static magnetic field.

Self-diffusion measurements using NMR is a powerful tool for the study of porous materials [12–14] and supermolecular organization [15,16]. Current NMR equipment dedicated to self-diffusion measurements allows for the determination of the self-diffusion coefficient of all the components in a complex liquid mixture within a couple of minutes [17]. The chemical shift is the most important factor to distinguish between different molecular species although differences in relaxation and diffusion provide additional means of discrimination.

Here we propose and demonstrate a method to measure molecular self-diffusion with chemical shift resolution in the presence of constant inhomogeneous static and radiofrequency magnetic fields.
2. Method

The pulse sequence for measuring self-diffusion with chemical shift resolution under the influence of time-constant gradients of the static $B_0$ and radiofrequency $B_1$ magnetic fields is shown in Fig. 1. It can be considered as consisting of two parts: a first part with five RF pulses providing diffusion sensitizing and a second part with stroboscopic signal acquisition between the pulses in a train of adiabatic double passages yielding resolved chemical shifts.

2.1. Diffusion encoding

The first three RF pulses produce a stimulated echo that is stored and recalled with the fourth and fifth pulses. The magnetization is in the transverse plane for a time $\delta$ between the first and second pulses and between the third and fourth pulses. The spins are labeled with respect to position due to precession in the spatially inhomogeneous $B_0$ field in the first of these periods. In the second period the spins are refocused. Molecular motion between the periods results in an incomplete refocusing and an attenuation of the stimulated echo.

The amplitude $M$ of the signal after the fifth RF pulse is given by [18],

$$M = \frac{M_0}{2} \exp \left(-\frac{T}{T_1} - \frac{2\delta}{T_2}\right) \exp \left[-\left(\gamma G_0 \delta\right)^2(\Delta - \delta/3)D\right],$$

(1)

where $M_0$ is the signal strength after a single 90° pulse and the delays $\delta$, $\Delta$, and $T$ are defined in Fig. 1. $\gamma$, $T_1$, and $T_2$ have their usual meanings. $D$ is the self-diffusion coefficient and $G_0$ is the strength of the gradient of the static magnetic field. The direction of the gradient defines the direction in which motion is monitored. Varying $\Delta$ while keeping $\delta$ and $T$ constant will separate the signal attenuation due to diffusion.

This version of motion encoding has some advantages over other methods proposed in the literature in that, when $\delta \ll \Delta$ displacements are monitored over a well-defined time interval [4,5,18,19]. The established propagator formalism [12,20,21] can be used in this case for the analysis, which is advantageous especially for more complicated types of motion such as diffusion of molecules confined to pores, or superimposed flow and diffusion.

Eq. (1) is valid for Gaussian diffusion. Norwood [18] demonstrated the application of the diffusion part of the pulse sequence to a system exhibiting restricted diffusion, which means that the measured $D$ depends on the observational time scale because of the presence of confinements on the same length scale as the typical molecular displacement. Performing the experiment in the Callaghan [12] $q$-space way, where the gradient strength is incremented while keeping all other variables constant, is somewhat harder to realize since the experiment by design is performed with a constant gradient. However, acquiring data as a function of $\Delta$ and $\delta$ with relaxation correction for the different values of $\delta$ resembles the $q$-space experiment acquired as a function of gradient strength and $\Delta$ with relaxation correction for the different values of $\Delta$. The information from the two methods about the geometry of the confinement is expected to be quite similar.

2.2. Chemical shift resolution

Spins precessing in an inhomogeneous field will lose coherence. The phase spread can be refocused with a z-rotation RF pulse where the angle of rotation depends on the $B_1$ strength. Refocusing is perfect if the $B_0$ and $B_1$ fields are matched in the sense that the z-rotation induced by the RF pulse is unwrapped by precession simultaneously for all points in space. Several pulses have been proposed for this purpose [8–10]. Two consecutive adiabatic full passages of unequal amplitude have been shown to be effective over a wide bandwidth [11]. When $B_1$ is higher than some critical value this pulse provides a rotation of the transverse magnetization around the $z$-axis with an amount roughly proportional to $B_1$. In contrast to the ordinary spin echo, the nutation echo formed after such a pulse is modulated by the chemical shift. A signal similar to the free induction decay that would be observed in a homogeneous field is obtained if the echo maxima formed during a train of adiabatic pulses are recorded.

The paramount importance of spatial matching between the $B_0$ and $B_1$ fields needs to be emphasized. Only the inhomogeneous broadening correlated (not necessarily in a linear way) with $B_1$ can be corrected. Currently existing single-sided designs [1] are not ideal for obtaining chemical shift resolution because of the magnitude of the gradients and the different shapes of the $B_0$ and $B_1$ fields. In a forthcoming paper by Sakellariou et al. [22] this problem is treated.

In addition to the quality of field matching, the chemical shift resolution is limited by diffusion during the z-rotation pulse. In order to eliminate the resolution degradation due to diffusion, it is necessary that the typical distance traveled by the molecules during the pulse is much smaller than the spatial wavelength of the phase imposed by the pulse. Recent Brownian dynamics simulations, that will be presented elsewhere, have shown that the signal starts to be affected when the traveled distance approaches 1% of the spatial wavelength of the phase. With the parameters used here diffusion can be neglected, but it is clear that with stronger gradients and longer pulses diffusion will be a limiting factor. Note that this diffusion effect is completely independent of the diffusion encoding. For the analysis to obtain diffusion coefficients this kind of signal loss can be factored out in much the same way as relaxation.
Fig. 1. Pulse sequence for measuring molecular self-diffusion with chemical shift resolution in spatially inhomogeneous static and radiofrequency fields. The phases of the receiver and the five RF pulses during the diffusion encoding part of the pulse sequence are cycled according to [18]. During acquisition the magnetization is periodically refocused with a pair of adiabatic pulses with unequal amplitude. A static magnetic field gradient is applied throughout the pulse sequence.

Fig. 2. Results of the simulations of the pulse sequence in Fig. 1 for an ensemble of spins with properties given in Table 1. Squares and circles are simulated peak maxima of the two components. Lines in (B–D) are calculated with Eq. (1) and the parameters in Table 1. (A) Simulated spectrum obtained at $\delta = 10$ ms, $\Delta = 0.1$ s, and $T = 1$ s. (B) Variable $T$ with $\delta = 50$ ms and $\Delta = 140$ ms. (C) Variable $\delta$ with $T = 0.2$ ms and $\Delta = 0.1$ ms + $\delta$. (D) Variable $\Delta$ with $\delta = 10$ ms and $T = 1$ s. The mid-spectrum artifact in (A) originates from regions with too low $B_1$ to be affected by the $z$-rotation pulses in the ideal way.

Fig. 3. Experimental results. Squares and circles indicate the peak maxima of water and isopropanol, respectively. (A) $^1$H spectrum obtained through direct detection of the FID following a single RF pulse. (B) Chemical shift resolved $^1$H spectrum obtained with the pulse sequence in Fig. 1. (C) Peak intensity vs. $(\gamma G_0 \delta^2 (\Delta - \delta/3)) / 10^9 \text{s/m}^2$. The lines indicate a fit of Eq. (1) to the data. The mid-spectrum artifact in (B) originates from regions with too low $B_1$ to be affected by the $z$-rotation pulses in the ideal way.
Table 1. Parameters for the simulation of the pulse sequence in Fig. 1

<table>
<thead>
<tr>
<th>Shift/ppm</th>
<th>$T_1$/s</th>
<th>$T_2$/s</th>
<th>$D$/m²/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1</td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0.8</td>
<td>0.8</td>
<td>0</td>
</tr>
</tbody>
</table>

3. Simulations

As with all but the very simplest pulse sequences, several coherence pathways are possible [23]. The strongly inhomogeneous $B_1$ field makes an efficient suppression of unwanted coherences especially important. The selection of coherences is handled with phase cycling and/or $B_0$ gradient pulses. Whereas, standard phase cycling is sufficient to isolate the desired coherence when direct detection of the FID is used, it is not evident that the same phase cycling should work also for the stroboscopic detection used here. Some mixing of transverse and longitudinal magnetization with the refocusing pulses is inevitable and it is unclear how this will affect the efficiency of the phase cycling.

In order to elucidate this point, simulations were performed. An ensemble of 1000 non-interacting spin 1/2 were prepared in an environment resembling the experimental setup with linearly correlated $B_0$ and $B_1$ fields. The $B_1$ field varied between 0 and 10 kHz and the $B_0$ field varied 10 kHz centered on 180 MHz. The adiabatic pulses were 1.7 ms hyperbolic secant pulses [24,25] with a bandwidth of 10 kHz and digitized in 250 steps. The amplitude of the second passage was a factor 0.5 lower than the first. Optimal spectral resolution was obtained for an evolution period of 225 μs between each adiabatic double passage. The five pulses during the diffusion encoding part of the pulse sequence were 40 μs square pulses. These pulses and the phase of the receiver were cycled according to the procedure suggested in [18].

The simulations took finite RF power and off-resonance effects into account. Relaxation was introduced through the phenomenological parameters $T_1$ and $T_2$. Relaxation was neglected during the RF pulses. Diffusion was assumed to be negligible. Gaussian noise was added to a level corresponding to a signal-to-noise ratio of 100 was assumed to be negligible. Gaussian noise was added.

For the diffusion measurements with the proposed pulse sequence a steady current was applied to the gradient coil producing a $B_0$ gradient of 8.5 mT/m parallel to the axis of the conical coil. Direct acquisition of the FID yields a 10 kHz (60 ppm) broad peak after Fourier transformation as is shown in Fig. 3A. z-rotation was induced by an adiabatic double passage employing 1.7 ms hyperbolic secant pulses [24,25] with a bandwidth of 10 kHz and a peak RF amplitude of 6 kHz in the region of space with strongest $B_1$. The amplitude of the second passage was 50% of the first. A free precession delay of 140 μs between each adiabatic double passage was found to give best spectral resolution. The five pulses during the diffusion sensitizing part of the sequence were 40 μs square pulses. The following parameters were used: $\delta = 10$ ms, $T = 1$ s, and $\Delta$ varying in 40 steps between 15 and 985 ms.

A simulated spectrum is shown in Fig. 2A. The chemical shift scale is referenced with respect to the input values used in the simulation. The rather intense glitch at zero frequency is not the common quadrature glitch, but can be traced to spins experiencing $B_1$ fields lower than about 4 kHz. The adiabatic pulses are less effective for such low values of $B_1$ [11].

The simulations were performed as three sets of two-dimensional experiments: variable $T$ with $\delta$ and $\Delta$ constant, variable $\delta$ with $T$ constant, and variable $\Delta$ with $\delta$ and $T$ constant. According to Eq. (1), the first simulation yields $T_1$ and the second yields $T_2$ (note that $D = 0$). The third simulation should be independent of $\Delta$. As is shown in Fig. 2 this is indeed the case. While not a rigorous proof that standard phase cycling in general is effective also for the stroboscopic acquisition method, it appears that for practical purposes the phase cycling is sufficient under the conditions used here.

4. Experiments

Experiments were performed at 295 K in a 4 T Nalorac super-widebore magnet using a Varian/Chemagnetics Infinity spectrometer. The samples were pure water and a mixture of water and isopropanol. Inhomogeneous magnetic fields were produced with an apparatus described in [10]. In short, $B_1$ gradients are produced by a conical RF coil and $B_0$ gradients are generated with a homebuilt imaging probehead with three perpendicular gradient coils. The $B_0$ gradient strength was calibrated with self-diffusion measurements on pure water [26] using the standard pulsed field gradient spin echo method [27].
with experiments performed on the same equipment using a more standard technique with pulsed field gradients. For this particular mixture the chemical shift resolution is necessary to estimate $D$ of both components since relaxation times and the values of $D$ are quite similar.

5. Conclusions

With the proposed technique the most powerful means to distinguish different chemical species—the chemical shift—is introduced as a contrast agent for the study of molecular motion under ex situ (outside-the-magnet) conditions. The diffusion encoding is similar to standard experiments using two pulsed field gradients and is thus appropriate for the study of flow and non-Gaussian diffusion.

The experiments were performed in a simulated ex situ setup inside the bore of a superconducting magnet with linearly correlated $B_0$ and $B_1$ gradients which simplifies both the diffusion sensitizing and refocusing. Methods to account for diffusion in non-linear $B_0$ fields have already been published [4] and tuning of the parameters of the adiabatic pulses has been proposed as a means of providing chemical shift resolved spectra even in the case of non-linearly correlated $B_0$ and $B_1$ fields [11]. A combination of these seems promising for the realization of chemical shift separated diffusion measurements under true ex situ conditions.

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References


