Measuring diffusion of xenon in solution with hyperpolarized $^{129}$Xe NMR

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Abstract

A hyperpolarized $^{129}$Xe Nuclear Magnetic Resonance (NMR) technique for measuring diffusion of xenon in solution is presented. The dramatically enhanced NMR signal of hyperpolarized $^{129}$Xe makes it possible to measure the xenon self-diffusion coefficient with a single-shot NMR experiment. Diffusion constants of xenon in various solvents are reported. A value of $(2.2 \pm 0.4) \times 10^{-5}$ cm$^2$ s$^{-1}$ was measured for xenon in water at room temperature. The potential applications of this technique to in vivo experiments are discussed. © 1998 Elsevier Science B.V. All rights reserved.

1. Introduction

Dissolved xenon is the prototypical hydrophobic solute and its physico-chemical properties have been intensely studied [1–3]. Xenon dissolved in water is believed to induce ordering of water molecules in its hydration shell, and serves as a simple model for the study of hydrophobic hydration and interactions of nonpolar groups in proteins at a molecular level [3].

The increased water structure in the vicinity of dissolved xenon atoms results in slower reorientational and translational motions of water molecules in the first coordination sphere. This retardation effect has recently been demonstrated by $^1$H and $^2$H NMR experiments [2]. Xenon hydration should be also reflected in the self-diffusion coefficient of the solute. The relatively low Ostwald solubility of xenon in water and the long spin-lattice relaxation times of dissolved $^{129}$Xe make self-diffusion measurements with $^{129}$Xe NMR very difficult. A $^{129}$Xe pulsed-field-gradient (PFG) NMR measurement of xenon in water has been recently reported [1]. In this experiments, high pressures of xenon gas were used to increase the amount of xenon in solution, and the $^{129}$Xe spin-lattice relaxation time was reduced by adding paramagnetic salt to the solution. However, the salt affects xenon diffusion, and the xenon self-diffusion coefficient was extrapolated from a set of experiments with different concentrations of dissolved salt. The authors [1] report a diffusion coefficient of $1.9 \times 10^{-5}$ cm$^2$ s$^{-1}$ at 25 °C, in sharp contrast with previous values reported in the literature [4–6], which range from $0.8 \times 10^{-3}$ cm$^2$ s$^{-1}$ to $1.4 \times 10^{-5}$ cm$^2$ s$^{-1}$.

The polarization of $^{129}$Xe nuclei can be enhanced by up to five orders of magnitude using optical pumping methods [7]. The resulting dramatically enhanced sensitivity in NMR detection makes hyper-
polarized $^{129}$Xe an excellent NMR probe to study the physico-chemical properties of xenon in solution. In this paper we use a Burst NMR sequence to make single-shot measurements of the diffusion coefficients of hyperpolarized xenon in a variety of solvents, using the method first introduced by Doran and Décorps [8] for bulk liquids. Burst was originally introduced as an ultra-rapid imaging sequence [9–12] with human brain perfusion studies [13] among its successful applications. Under these circumstances [14], its intrinsic sensitivity to diffusion can be both a limitation and a valuable source of contrast. Application of Burst to hyperpolarized xenon in solution provides a fast and accurate NMR technique to measure diffusion of xenon in solution. The potential applications of this technique to in vivo experiments are discussed.

2. Materials and methods

2.1. Optical pumping

Cylindrical glass cells of 60 cm$^3$ containing a small amount of rubidium metal were filled with a mixture of natural abundance Xe (BOC Ltd., Redhill, UK) and N$_2$ and pressurized with approximately 10 bar of helium. The cell was placed in the 130 gauss field of a Helmholtz coil and heated to 100°C. Hyperpolarization was achieved by optically pumping the D1 electron transition of the Rb vapour with circularly polarized light from a 90 W diode laser array (Opto Power Corporation, Tucson, AZ, USA) and spin exchange to the $^{129}$Xe nuclei [7]. Resulting $^{129}$Xe polarization was estimated to range between 2% and 5%. After approximately 15 minutes of optical pumping, the cell was cooled, and the xenon was collected in a distillator immersed in liquid nitrogen. During transport to the MR magnet the frozen xenon was located close to one pole of a small horseshoe magnet in order to prevent rapid relaxation in zero magnetic field. The xenon was warmed up in the bore of the MR magnet and admitted to the degassed liquid. Vigorous shaking was applied to dissolve the gas. Before starting the NMR sequence, the sample was left to equilibrate for 30 seconds to avoid errors in the diffusion measurement due to coherent flow in the sample tube.

2.2. Sample preparation

Our aim was to demonstrate the feasibility of the method by measuring the diffusion coefficient of hyperpolarized xenon in various liquids. De-ionized water was selected for the reasons outlined in the introduction. Benzene (BDH, Dorset, UK) was chosen due to its high xenon solubility [15]. Diffusion in the linear perfluorocarbon Perfluorooctyl bromide (PFOB; Aldrich, Dorset, UK) was also measured, as PFOB is a highly suitable solvent for hyperpolarized xenon, since PFOB is characterized by long $^{129}$Xe $T_1$ and high xenon solubility [16–18]. Concentrated PFOB-in-water emulsions have been investigated as potential intravenous xenon delivery media [17,18] for in vivo $^{129}$Xe MR studies. The $^{129}$Xe NMR spectrum of the gas dissolved in the emulsion is characterized by xenon exchange, and xenon diffusion in PFOB is an important parameter that determines the exchange rate [18].

Before admitting the hyperpolarized xenon, oxygen was removed from the samples. This was achieved by freezing the liquid and pumping away the air on top. On thawing the sample, the dissolved gas equilibrates with the vacuum, and gas is released from the liquid. This cycle was repeated several times for each sample.

2.3. NMR spectroscopy

All NMR experiments were performed at room temperature using a Siemens Magnetom Vision 1.5T clinical MR system. A home-built solenoid coil resonating at the Larmor frequency of $^{129}$Xe at 17.6 MHz was utilized.

The Burst pulse sequence used is shown in Fig. 1. A train of small flip angle excitation pulses is applied in the presence of a read gradient. After a 180° refocussing pulse the same gradient is applied while acquiring the echo train. Due to self-diffusion of xenon in the solution during the time for which the gradient is applied, a loss of spin-spin coherence in the transverse plane of the rotating frame is encountered. This dephasing is not refocussed, and the amplitudes of the later spin echoes are decreased.

The Burst pulse train used in our sequence consists of 16 rectangular pulses with a flip angle of 8°. A rectangular 180° pulse was chosen as refocussing
pulses. A major problem of the original Burst sequence is the fact that higher-order echoes are created by interactions between the multiple excitation pulses, and these interfere with the desired echo train giving highly non-uniform echo amplitudes. In this study these unwanted higher-order echoes were suppressed using an optimized two-phase modulation for the pulse train as suggested by Zha and Lowe [19]. By using this phase-modulation scheme, the signal-to-noise ratio of the primary echo train is greatly improved compared to the basic Burst sequence [12], and larger flip angles for the excitation pulses can be applied. Zha and Lowe demonstrate that in the absence of diffusion all the echoes in the train have uniform amplitude. Therefore the introduction of variable flip angles [20,21] is not necessary for the Burst excitation pulses. Sequences with Burst echo train durations of either 40.96 ms or 81.92 ms were used.

3. Results

A typical hyperpolarized $^{129}$Xe NMR Burst echo train obtained for xenon in benzene is shown in Fig. 2, with a readout gradient of 15 mT/m. The inverted phase of some of the echoes is due to the two-phase modulation scheme applied. The attenuation of the echo amplitudes is purely due to diffusion as the transverse relaxation time $T_2$ is very long (8.5 s) compared to the timescale of the diffusion experiment.

In processing the data, we follow the method introduced in Ref. [8], which utilizes the notation introduced in the original work by Stejskal and Tanner [22]. The attenuation due to diffusion of the $j$th echo (which is created by the $(n-j-1)$th excitation pulse) is

$$A_j = \exp \left[ -D (\gamma G)^2 \cdot \delta_j^2 \left( \Delta_j - \delta_j/3 \right) \right],$$

where $\delta_j$ and $\Delta_j$ are defined by

$$\delta_j = j \cdot \tau + d_1 \quad \text{and} \quad \Delta_j = j \cdot \tau + d_2.$$

$\tau$ is the time separation of two subsequent excitation pulses and $d_1$ and $d_2$ are the intervals shown in Fig. 1. We performed several experiments with gradient amplitudes ranging from 8 mT/m to 17 mT/m. In case of xenon in water and xenon in benzene. The applied gradient strength is 15 mT/m.
PFOB we used $\tau = 5.12$ ms throughout. In case of xenon in benzene the same parameters were used for gradient amplitudes up to 15 mT/m, whereas in the experiment with a gradient of 17 mT/m we applied a sequence with $\tau = 2.56$ ms due to the relatively fast signal decay. Values of $d_1 = 2.5$ ms and $d_2 = 5.6$ ms were used in all measurements.

In Fig. 3 the logarithm of the normalized diffusion decay is displayed as a function of the Stejskal-Tanner parameter $\delta_1/(\Delta - \delta_1/3)$ for three liquids with different xenon diffusion coefficients. The excitation and readout gradient was 15 mT/m in each experiment shown. The signal amplitudes were normalized to the amplitude of the first echo. A linear least-square fit was applied to the datasets in order to quantify the diffusion coefficients. In all fits, attenuation due to transverse relaxation is not taken into account. Whereas this might lead to problems in case of short $T_1$ relaxation [8], the assumption is well justified in our measurements. We measured $T_2$ values using a Carr–Purcell sequence containing 16 rectangular 180° pulses preceded by a 90° pulse. We found $T_2 = 8.5$ s for xenon in benzene and $T_2 = 15$ s in case of xenon in PFOB. A $T_2$ value of 5 s for xenon in water was measured by Zhao et al. [23].

In Table 1 our results are summarized. Errors were estimated to be 12% in case of xenon in PFOB and xenon in benzene from the spread of $D$ for several experiments. The error is mainly due to the difficulty of controlling the sample temperature in a clinical scanner. In case of xenon in water, the lower solubility of xenon in water of 0.108 [15] results in poorer signal-to-noise ratio of the data, and the error is larger (approximately 20%).

### 4. Discussion

The diffusion coefficient of xenon in water compares well with the value reported in Ref. [1] and with molecular dynamics simulations [24], which predict similar diffusion rates for dissolved xenon and the solvent water. Other techniques based on xenon concentration gradients yield much smaller values [4–6], and seem inadequate for measuring xenon self-diffusion.

The hyperpolarized gas can be utilized for Magnetic Resonance (MR) lung imaging and in vivo spectroscopy [25,26]. The high solubility of xenon in blood and lipids suggests a variety of MR applications for hyperpolarized xenon, for instance functional imaging or perfusion and permeability studies. In this context intravenous injection of hyperpolarized xenon in solution has been proposed as an efficient delivery method [16–18,27,28]. In vivo studies of xenon self-diffusion might provide a useful means to characterize tissues. Diffusion weighted MR imaging of free water in tissues is a well established technique to study pathological conditions, for instance acute stroke. Xenon is highly lipophilic, and could be used to probe tissues that are not accessible to conventional $^1$H MRI. By introducing phase-encode gradients [9–12], the Burst sequence could be used to acquire diffusion weighted MR images. Due to its high speed, Burst is likely to be a suitable technique for time-resolved in vivo hyperpolarized $^{129}$Xe MR applications as for instance functional imaging or perfusion studies.

Various techniques have been proposed to measure the diffusion coefficient of hyperpolarized $^{129}$Xe
in the gas phase [20,23] in lungs. Burst is particularly suitable for diffusion studies with hyperpolarized $^{129}$Xe. Whereas the technique used by Zhao et al. [23] requires at least two shots and subsequent corrections for loss of polarization to determine the diffusion coefficient, Burst acquires the entire series of echoes in a single shot, and such corrections do not need to be applied. Furthermore, as Burst is a very fast technique, it is not limited by longitudinal relaxation ($T_1$ relaxation) during the measurement, as for instance the method used by Patyal et al. [20].

The non-equilibrium polarization cannot be renewed during the MR experiment. Therefore, special imaging sequences for efficient use of the magnetization have to be designed. Loss of polarization is determined by the $T_1$ relaxation time of the hyperpolarized gas in its environment. This suggests the use of fast imaging sequences like Echo-Planar Imaging (EPI) [29] where the entire image can be acquired in a single shot. Fast imaging sequences also provide improved time resolution which is important, for instance, in functional studies. Xenon diffusion is a potential factor limiting the use of fast MRI techniques. Although the actual diffusion length of one particular xenon atom may be much smaller than the resolution of the MR image, dephasing of spins due to diffusion during application of the imaging gradients may result in substantial loss of signal. The present study shows that the diffusion of xenon is comparable to the diffusion coefficient of the water solvent [30]. Therefore, the application of fast imaging sequences like EPI or Burst imaging to hyperpolarized dissolved xenon is not severely limited by diffusion, and multi-echo sequences that are being used for proton MRI should be applicable to dissolved-phase hyperpolarized xenon MRI as well.

5. Conclusion

In conclusion, we have presented a fast NMR technique to measure diffusion coefficients of hyperpolarized xenon in solution in a single shot. We have measured the diffusion coefficient for xenon dissolved in various solvents. The self-diffusion coefficient of xenon in water at room temperature is comparable to the diffusion coefficient of the solvent. This technique can be extended to in vivo studies to measure diffusion coefficients of xenon in tissues. Our results also suggest the potential for MR imaging of hyperpolarized xenon in solution by using the Burst sequence in an imaging context by introducing a phase-encode gradient into our sequence.

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