

Magnetic Relaxation Dispersion of ^7Li

II. Complex Formation with Nitroxides in the Aqueous Phase

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Measurements of ^7Li nuclear spin–lattice relaxation times are made at applied magnetic field strengths from 0.25 mT to 7.05 T, in order to determine directly the form of the frequency-dependent spectral densities that modulate relaxation. This magnetic resonance dispersion (MRD) technique provides detailed information regarding molecular dynamics down to the picosecond time scale. ^7Li MRD measurements made on aqueous lithium ion in the presence of small concentrations of nitroxide free radicals give direct evidence supporting the formation of a coordination complex. The dipole–dipole electron–nuclear coupling is modulated by both translational and rotational diffusive motions, and both of these contributions are resolved. However, scalar coupling arising from the presence of paramagnetic electron spin density at the nucleus dominates the nuclear relaxation. Changes in the pH and free radical moiety are compared with dynamical variables, geometric constraints, and formation constants obtained from a model of nuclear relaxation. The calculated bimolecular formation constants are on the order of $2 \times 10^{-3} \text{ M}^{-1}$, and the relative accuracy of this parameter is tested. © 1998 Academic Press

Key Words: magnetic relaxation dispersion; lithium relaxation; spin–lattice relaxation; lithium coordination complex; nitroxide spin label.

1. INTRODUCTION

The magnetic field dependence of the spin–lattice relaxation rate, or the magnetic relaxation dispersion (MRD), provides a direct means for investigating *inter-* and *intramo-*lecular dynamics over a wide range of time scales, and also provides a test of the relaxation equations used to interpret the data. The magnetic field strength may be varied from the order of the earth's field up to 14 T or so, corresponding to proton Larmor frequencies of 1.26×10^4 to $3.77 \times 10^9 \text{ rad s}^{-1}$, respectively. The time scale probed by the experiment is on the order of the reciprocal Larmor frequency; thus the time range probed extends from about 0.1 ms to the order of 300 ps for diamagnetic systems. In the case where the nuclear spin relaxation is dominated by interactions with an electron spin, the relaxation equations contain terms in the electron Larmor frequency which is 658 times larger than

the proton Larmor frequency for a $g = 2.00232$ system, extending the time scale accessible for direct characterization to the order of 0.5 ps. Because the electron Larmor frequency does not depend upon which nucleus is relaxed, any nuclear spin may be used to investigate the high-frequency dynamics provided by the electron resonance frequency.

The MRD experiment has been common for almost 30 years, but has been dominated by instruments that switch the current very rapidly in solenoidal electromagnets (I). This technique has the advantage of rapid field switching, which permits exploration of a wide range of relaxation rates; the primary limitations of this technique are low resolution and low sensitivity associated with relatively low resonance frequencies. We have constructed an instrument that utilizes two magnets and overcomes the resolution and sensitivity problems. A superconducting magnet at 7 T provides a high polarization and detection field that in turn provides high resolution and sensitivity. A satellite magnet, separated from the 7-T magnet by an iron shield, provides a continuously variable relaxation field that may be varied from 0 to 1.6 T. The sample is polarized in the high field, pneumatically moved to the relaxation field, and then pneumatically returned to the 7-T field where the magnetization is sampled. The great improvement in sensitivity afforded by this system permits detection of the MRD profiles of solute species which now provide a number of opportunities for dynamical studies.

The motivation of the present work was to characterize the local translational motion of the lithium at macromolecular and membrane surfaces by exploiting the relaxation induced by nitroxide species localized at these surfaces. This approach has been successful for characterization of solvent diffusion constants at protein, phospholipid, and silica surfaces (2–5). ^7Li is convenient for the study of alkali metal ion dynamics because the spin–lattice relaxation time in aqueous solutions is 10 s or longer, the sensitivity is high, and the aqueous solutions are well studied. When the spin–lattice relaxation is dominated by the relative translational

motion of the interacting spins, the MRD profile is not Lorentzian, but is much broader and is characterized by the translational correlation time and distance of closest approach between the nuclear and electron spin (6). For the case in which a complex is formed with a lifetime sufficiently long that it has a chance to rotate as a unit, then the MRD profile is Lorentzian and is usually characterized by the intermoment distance and the reorientational correlation times (7). The experiments reported here show that the strategy of measuring the translational diffusion constant of the lithium ion is defeated by the formation of a complex between the lithium ion and the nitroxide radicals in water. Nevertheless, the results demonstrate that the high-frequency dynamics of solute interactions may be easily studied in the picosecond range.

2. THEORY

In aqueous solution, the Li^+ ion is symmetrically coordinated by solvent molecules that are reported to be very labile, with exchange lifetimes on the order of 20 ps (8, 9). Since the electric quadrupole moment (eQ) of the ${}^7\text{Li}$ nucleus ($I = 3/2$) is also small (10), dipole-dipole coupling with surrounding water protons is a significant relaxation mechanism. Designated $R_{1D} = T_{1D}^{-1}$, the diamagnetic contribution to the total relaxation of ${}^7\text{Li}^+$ in solution is thus due to interactions with field gradients at the nucleus, and dipolar coupling with both ligated water protons (“is”) and those inhabiting the outer sphere (“os”):

$$T_{1D}^{-1} = T_{1H, \text{is}}^{-1} + T_{1H, \text{os}}^{-1} + T_{1Q}^{-1}. \quad [1]$$

This relaxation is concentration dependent (11), and amounts to a baseline shift of the dispersion data, and all data presented are corrected for this diamagnetic contribution.

Addition of even a small amount of a paramagnetic species changes the situation dramatically, because the nucleus interacts with the much larger magnetic induction fields generated by the magnetic moments of unpaired electrons. Since $\gamma_e = 658\gamma_{1H} = 1693\gamma_{7Li}$, the dipolar fields produced by the presence of unpaired electron spin density provide much more efficient relaxation mechanisms, particularly for those nuclei in close proximity to the paramagnetic center. For nuclei that participate in some binding process with the paramagnetic electron spin-bearing molecule, the total observed relaxation rate is (12, 13)

$$T_{1\text{obs}}^{-1} = P_{\text{free}}(T_{1D}^{-1} + T_{1\text{trans}}^{-1}) + P_{\text{bound}}(\tau_{\text{ex}} + T_{1M})^{-1}, \quad [2]$$

where $T_{1M}^{-1} = T_{1P}^{-1} + T_{1Q}^{-1}$, and where the mole fraction of bound ${}^7\text{Li}$ is denoted $P_{\text{bound}} = 1 - P_{\text{free}}$. Here, the definition of a bound complex is taken to mean one in which the intermoment vector is rotationally correlated, as opposed to a

translational pair. Because the total lithium ion concentration $[\text{Li}(\text{I})]_{\text{TOT}}$ is very large compared with that of the nitroxide radical $[\text{RN} \cdot \text{O}]_{\text{TOT}}$, we may write

$$P_{\text{bound}} = \frac{[\text{RN} \cdot \text{O}]_{\text{TOT}}}{[\text{Li}(\text{I})]_{\text{TOT}} + K^{-1}}, \quad [3]$$

where K is the bimolecular association constant. We denote the mean lifetime of the complex as τ_{ex} , and the relaxation attributable to the intramolecular mechanisms associated with the presence of the paramagnetic spin density in the first coordination sphere by T_{1P} . The intramolecular electron-nuclear dipolar and Fermi contact contributions to the relaxation have been described in a series of papers by Solomon (14), Bloembergen (15, 16), and Morgan (16), and have been reviewed extensively elsewhere (7, 17). For relaxation in the weak coupling approximation, the result for isotropic rotational diffusion is

$$\begin{aligned} \frac{1}{T_{1P}} = & \frac{2}{15} \left(\frac{\mu_0}{4\pi} \right)^2 \gamma_I^2 \gamma_S^2 \hbar^2 \frac{S(S+1)}{r_{\text{IS}}^6} \\ & \times \left[3 \frac{\tau_c}{1 + (\omega_I \tau_c)^2} + 7 \frac{\tau_c}{1 + (\omega_S \tau_c)^2} \right] \\ & + \frac{2}{3} S(S+1) \left(\frac{a}{\hbar} \right)^2 \left(\frac{\tau_e}{1 + (\omega_S \tau_e)^2} \right) \end{aligned} \quad [4]$$

given that $\gamma_S \gg \gamma_I$. The γ_i are the magnetogyric ratios with corresponding angular frequencies

$$\omega_i = \gamma_i B_L, \quad [5]$$

$\mu_0 = 4\pi \times 10^{-7} \text{ T m A}^{-1}$ is the free space permeability, r_{IS} is the radial separation between the nucleus and the center of paramagnetic spin density, a is the hyperfine coupling constant, and S is the electron spin quantum number of the paramagnetic species ($S = 1/2$ for nitroxide free radicals). The relevant correlation times are given by

$$\tau_c^{-1} = \tau_{\text{rot}}^{-1} + \tau_{\text{ex}}^{-1} + T_{1e}^{-1} \quad [6]$$

$$\tau_e^{-1} = \tau_{\text{ex}}^{-1} + T_{1e}^{-1}. \quad [7]$$

The electron relaxation times $T_{2e} \approx T_{1e}$ are expected to be on the order of several microseconds and so should not be significant relative to the fast rotational correlation time τ_{rot} . Furthermore, the long electron relaxation times permit decoupling of the electron spin and spatial variables (a required condition for the validity of Eq. [4]) (18, 19), and imply that the scalar coupling correlation times are well approximated by the mean lifetime of the complex. No attempt is made to seek resolution on the time scale of internal motion; hence, lattice dynamics determining the explicit time

evolution of the geometric coupling terms r_{IS} and a are neglected. Disregarding the high-frequency internal motions yields a rigid molecule model, and at this level of approximation, $\tau'_c = \tau_{rot}$.

Regardless of whether or not a rotationally correlated complex is formed, the ubiquitous intermolecular relaxation mechanisms must be considered. Liquid phase intermolecular correlation functions are appropriately treated in the classical limit, and for the dipolar interaction between spins I and S are written (20)

$$G_m^{IS}(t) = \int d^3\mathbf{r} \int d^3\mathbf{r}_0 D_{0m}^{(2)\dagger}(\Omega_{\mathbf{r}}) \times D_{0m}^{(2)}(\Omega_{\mathbf{r}_0}) P(\mathbf{r}_0, t|\mathbf{r}) \frac{g(r_0)}{r^3 r_0^3}. \quad [8]$$

The pair correlation functions $g(r_0)$ describe the initial equilibrium pair distribution, and are related to the intermolecular potential $U(r)$ of averaged forces between the spin-bearing molecules (6), and to the number density of S spins \aleph in an infinitesimal volume contained by \mathbf{r} centered about the spin I :

$$g(r_0) = \frac{5}{4\pi} \aleph f_0(r). \quad [9]$$

In the absence of electrostatic potentials, $f_0(r) = 1$. Radial probability distributions $P(\mathbf{r}_0, t|\mathbf{r})$ determine the likelihood that an initial intermoment vector \mathbf{r}_0 will evolve into \mathbf{r} after some time t , and as solutions to a stochastic differential equation, determine the time evolution of Brownian motion. The work of Torrey (21), describing the molecular motion as a sequence of random jumps between nodes of a discrete lattice, was later modified by Hwang and Freed (6, 22) to exclude mutual penetration of hard spheres. Taking the limits of continuous diffusion and $T_{k_c}\omega \gg 1$ one obtains for the force free model (22)

$$J(\omega) = \left(\frac{1 + \frac{5z}{8} + \frac{z^2}{8}}{1 + z + \frac{z^2}{2} + \frac{z^3}{6} + \frac{4z^4}{81} + \frac{z^5}{81} + \frac{z^6}{648}} \right) \quad [10]$$

with

$$z = \left(2\omega \frac{d^2}{6D} \right)^{1/2}, \quad [11]$$

where $D = D_1 + D_S$ is the relative diffusion constant between the two spin-bearing molecules, and d is the distance of

closest translational approach. The resulting contribution to spin–lattice relaxation resembles the dipolar part of Eq. [4]:

$$\frac{1}{T_{1trans}} = \frac{32\pi}{405} \left(\frac{\mu_0}{4\pi} \right)^2 \gamma_I^2 \gamma_S^2 \hbar^2 S(S+1) \frac{\aleph}{dD} \times [J(\omega_S - \omega_I) + 3J(\omega_I) + 6J(\omega_S + \omega_I)]. \quad [12]$$

The translational correlation time, τ_{trans} , of random Brownian motion is

$$\tau_{trans} = \frac{\overline{\lambda^2}}{6D} = \frac{d^2}{6D} \quad [13]$$

in terms of the mean-squared displacement λ , which we approximate by d .

3. EXPERIMENTAL

Relaxation time measurements were made as a function of magnetic field strength on an instrument to be described elsewhere that was assembled in this laboratory and utilizes a 7.05-T superconducting Magnex solenoid in close proximity to a GMW 4-inch electromagnet which is isolated magnetically from the higher field by an iron shield. The sample is stored in the high field, moved pneumatically to the variable lower field for various relaxation delay periods, and then returned pneumatically to the high field where the remaining magnetization is measured with a 90° pulse or other sequence. The liquid sample is degassed with an Ar stream and sealed in a threaded Delrin cylinder. The sample movement is controlled by a Tecmag Libra system controlled by a MacIntosh Quadra 800 computer, which activates dual dc solenoid valves to control the air/vacuum pressure that drives the sample through the field cycle. The magnetic resonance probes were constructed in this laboratory employing commonly used LRC single-resonance circuits.

The nitroxide free radicals 4-hydroxy-TEMPO, 4-amino-TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl), and 3-carboxy-PROXYL (2,2,5,5-tetramethylpyrrolidine-*N*-oxyl) were used as received from Sigma. LiCl (99.99%) was used as received from Aldrich.

4. RESULTS AND DISCUSSION

Figure 1 shows the representative MRD data for the interaction between ⁷Li_(aq) and substituted nitroxides, collected from a 2.0 M LiCl solution containing 10.0 mM 4-hydroxy-TEMPO at pH 7.0. Several nitroxides were studied at various pH values, and all displayed the same qualitative features. The experimental results show a strong, nearly Lorentzian dispersion with an inflection point around 300 ps. The presence of a Lorentzian-shaped spectral density function in and

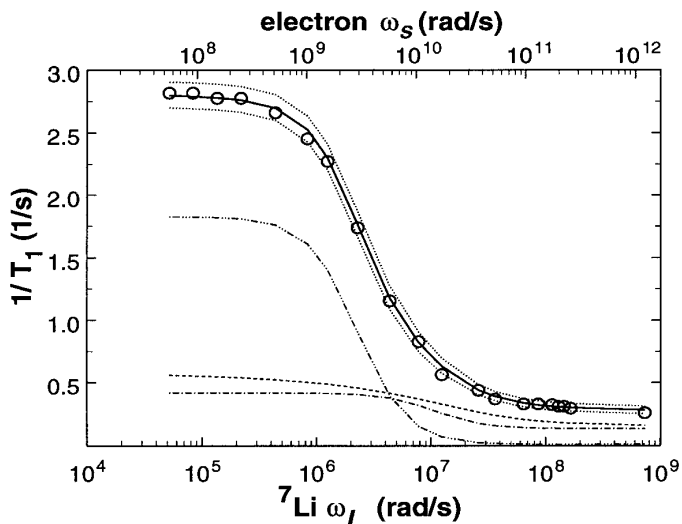


FIG. 1. MRD data (circles) for ${}^7\text{Li}$ coupled to the paramagnetic electron spin on 4-OH-TEMPO at pH 7.0. The solid line represents the total contribution from intermolecular (dash) and intramolecular (dash-dot) dipolar coupling as well as the hyperfine interaction (dash-dot-dot). The two dotted lines show the range over which the total calculated relaxation deviates upon changing the value of K by $\pm 25\%$ while maintaining a constant contribution from scalar relaxation. Molecular parameters are discussed in the text and are summarized in Table 1 for a number of different systems.

of itself implies the existence of a rotationally correlated intermoment vector (in this case, the ${}^7\text{Li}_{(\text{aq})}$ ion and the center of paramagnetic electron spin density), or a scalar coupling modulated by electron relaxation and chemical exchange. Nuclear spin relaxation modulated by translational diffusion is dispersed over a much wider range of Larmor frequencies via Eq. [10] (2–5). The ${}^7\text{Li}$ relaxation is, therefore, not dominated by translational motions, but by processes that produce Lorentzian relaxation dispersion profiles. There are two obvious mechanisms: (1) electron-nuclear dipole–dipole coupling characterized by an effective correlation time that is a function of the (isotropic) rotational and exchange contributions, and a scalar or hyperfine coupling characterized by a correlation time that is a function of the chemical exchange rate constant and electron relaxation times (Eqs. [6] and [7]). The correlation time deduced from the data is 300 ps, which is significantly larger than that expected for rotational reorientation of solutes this size in water. For example, the $[\text{Gd DTPA}]^{2-}$ ion has a rotational correlation time of approximately 50 ps (23), far less than the present value. Thus, the dipole–dipole mechanism does not appear to be dominant. However, the data are consistent with the rotationally invariant scalar mechanism that is expected if the complex formed is a first coordination sphere association between the lithium ion and the nitroxide oxygen atom. In this case, the coupling is modulated either by the electron spin relaxation or by the dissociation of the complex. Nitroxide electron spin relaxation times are generally

orders of magnitude longer than 300 ps; thus, the correlation time of 300 ps is identified with the mean lifetime of the lithium–nitroxide complex.

The total observed relaxation rate consists of distinct contributions: the diamagnetic relaxation of unbound lithium ion (T_{LD}^{-1}), the intermolecular electron-nuclear dipolar interaction (T_{trans}^{-1}), and the intramolecular mechanisms (T_{IP}^{-1}). T_{LD}^{-1} is concentration dependent and frequency independent (24), so measurement of ${}^7\text{Li}$ T_{obs} in the absence of any paramagnetic agent gives the baseline correction applied to both individual samples and Eq. [2], i.e., ${}^7\text{Li}$ $T_{\text{LD}} = T_{\text{obs}}$. ${}^1\text{H}_2\text{O}$ relaxation has been studied in detail for several nitroxide systems (3), in which the proton relaxation is demonstrably modulated by translational diffusion. We are, however, interested only in that fraction of nitroxide radicals that are also bonded to lithium ion. From the reported bimolecular formation constants (approximately $3 \times 10^{-3} \text{ M}^{-1}$) this fraction would be exceedingly small, and the proton MRD profile of the Li–nitroxide system would be identical to that in the absence of lithium, given the resolution of the experiment.

The dashed line in Fig. 1 represents the translational term of the total relaxation and is computed from Eq. [12]. The values that minimize the sum of the squares of the deviation are $d = 4.0 \text{ \AA}$ and $D = 2.0 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$, which imply that through Eq. [13] $\tau_{\text{trans}} = 13 \text{ ps}$. The distance of closest approach is consistent with the nitroxide diffusing in the outer coordination sphere of the hydrated ion, indicating that while the hydration shell water molecules may be labile, on the level of resolution afforded by macroscopic relaxation, the integrity of the first hydration shell of the $\text{Li}(\text{H}_2\text{O})_n^+$ complex is intact during a translational encounter with the nitroxide. Clearly translational contributions do not dominate the relaxation.

The intramolecular electron-nuclear dipole coupling part of Eq. [4] is shown by the dash-dot line for a displacement between the molecular centers of $r_{\text{IS}} = 2.15 \text{ \AA}$, and an intramolecular dipolar correlation time of $\tau_c = 70 \text{ ps}$. This intermoment separation is deduced with the point dipole approximation implicit in Eq. [4] and may be questioned. Nevertheless, this distance is short and implies the formation of a first coordination sphere complex with the lithium ion. This intimate association is also consistent with a significant, and, in fact, dominant scalar or hyperfine interaction shown by the dash-dot-dot line in Fig. 1. The hyperfine coupling required is 3.2 MHz, and application of Eq. [7] gives an exchange lifetime of $\tau_{\text{ex}} = 270 \text{ ps}$. As mentioned, we expect the electron T_{IC} to be several orders of magnitude larger than the correlation times deduced from the lithium spin–lattice relaxation, and we do not anticipate significant changes in T_{IC} caused by transient interaction with the lithium nucleus.

Theoretical results for all sets of experiments are presented in Table 1, and some general trends can be seen. The molecular parameters that define the geometry of the

TABLE 1
Molecular Parameters Determined from Theoretical Analysis of ${}^7\text{Li}$ /Nitroxide MRD Data

	4-NH ₂ -TEMPO (pH 4.0)	4-NH ₂ -TEMPO (pH 7.0)	4-OH-TEMPO (pH 7.0)	3-CO ₂ H-PROXYL (pH 10.0)
d (m)	4.0×10^{-10}	4.0×10^{-10}	4.0×10^{-10}	4.0×10^{-10}
D (m ² s ⁻¹)	2.0×10^{-9}	2.0×10^{-9}	1.9×10^{-9}	2.0×10^{-9}
a/h (MHz)	3.2	3.2	4.2	4.0
τ_{ex} (s)	2.0×10^{-10}	2.7×10^{-10}	2.6×10^{-10}	2.6×10^{-10}
r_{IS} (m)	2.15×10^{-10}	2.15×10^{-10}	2.15×10^{-10}	2.15×10^{-10}
τ_{rot} (s)	0.70×10^{-10}	0.70×10^{-10}	0.70×10^{-10}	0.70×10^{-10}
K (M ⁻¹)	2.9×10^{-3}	2.8×10^{-3}	2.7×10^{-3}	2.5×10^{-3}

bound complexes and diffusive characteristics are nearly identical regardless of the free radical moiety or the pH at which the experiment was performed. However, the hyperfine interaction is affected by the substitution on the free radical (but is independent of pH), while the opposite is true for the exchange lifetimes and formation constants. These observations are consistent with expectation. From Coulomb's law, a simple calculation of the magnitude of the repulsive electrostatic force between a cation-cation pair in aqueous solution with a dielectric constant near 80 shows that the energy required to bring these two cations to within 6 Å of each other is less than 3 kJ/mol, which is small compared to most coordination bond enthalpies. Any center of charge density will be dispersed by the presence of solvating water molecules. We have established that the MRD curve is dominated by the Fermi interaction, which implies the existence of a chemical bond between the nitroxide moiety and the lithium inner sphere. We might expect the magnitude of this interaction to change with substitution at a remote site on the nitroxide, as is reported in Table 1. The lifetime of water in the lithium ion coordination sphere is reported to be extremely short (8, 9), so any translational encounter between the lithium ion and a nitroxide is a potential bonding event. However, the bond does not involve the remote charged group of the nitroxide molecule, but presumably the nitroxide oxygen itself. Lithium ion binding at the charged site would have no contact contribution and negligible electron-nuclear dipolar contribution to ${}^7\text{Li}$ relaxation because of the long intermoment distance.

To demonstrate the sensitivity of the fit to the parameters reported in Table 1, we discuss calculations of several choices of key parameters. Inspection of Eqs. [2]–[4] shows that the magnitude of the calculated hyperfine contribution is determined by the product of P_{bound} and the squared coupling constant, $(a/\hbar)^2$, whereas the shape of the Lorentzian curve is determined by the form of the spectral density, and is sensitive to the value of the correlation time. In spite of the fact that the *intramolecular* dipolar contribu-

tion is also dependent upon P_{bound} , it might be suspected that P_{bound} and a cannot be determined independently, given the fact that the relaxation is dominated by the hyperfine interaction. Changing the value of P_{bound} and simultaneously adjusting a to keep the hyperfine contribution to Eq. [2] constant will reveal the dependence of the total calculated relaxation on the formation constant. The dotted lines in Fig. 1 show the result of varying the value of the formation constant by $\pm 25\%$, while maintaining the absolute contribution from the scalar interaction. Only the *intramolecular* dipolar contribution is affected, and the change is most dramatic at low frequencies. While this is by no means a comprehensive statistical analysis of the data, it demonstrates that the tabulated formation constants are reliable to within a factor of 2. Furthermore, the parameters derived from the data are in agreement with the bond lengths and diffusional properties normally associated with the chemistry of nitroxides in polar solvents (25).

5. CONCLUSION

In concert with the theory of magnetic relaxation, these MRD data have provided experimental evidence for inner sphere coordination of nitroxide free radicals by $\text{Li}(\text{H}_2\text{O})_n^+$. Translational dynamics within the solvent cage are a significant source of nuclear relaxation, and the distance of closest translational approach is consistent with the nitroxide diffusing in the outer sphere of the solvated species. Formation of a rotationally correlated intermoment vector changes the form of the dipolar contribution to the relaxation, and the distance constraints and rotational diffusion time constants are in keeping with those expected for molecules of these dimensions. Relaxation is dominated by the direct scalar coupling between the ${}^7\text{Li}$ nucleus and the nitroxide paramagnetic electron spin, and the magnitude of the hyperfine coupling constant changes with the free radical moiety. Neither the geometrical characteristics of the chemical bond formed between the nitroxide center and the lithium ion nor the diffusion properties of the bound complex are affected by pH. Conversely, the small bimolecular formation constants

and exchange lifetimes are pH dependent, but are insensitive to changes in the nitroxide moiety. Furthermore, these experiments demonstrate the sensitivity of multinuclear MRD to high-frequency dynamics often thought to be well outside the NMR time scale.

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