Determination of the rate of a fast exchanging coordinated molecule in a lanthanide(III) complex by proton NMR

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I. Theoretical details

Appendix A. Anisotropic susceptibility and dipolar shift of a paramagnetic Ln^{3+} complex

Consider a complexed paramagnetic Ln^{3+} ion with a ground state multiplet *J* of Landé factor g_J. The susceptibility tensor $\boldsymbol{\chi}$ of a single Ln^{3+} ion is anisotropic because of the presence of a ligand field. In the molecular (M) frame of its principal axes $OXYZ$, it can be diagonalized as $\chi_{\alpha\beta} = \chi_{\alpha\alpha}\delta_{\alpha\beta}$ (α, β = X, Y, Z), so that in this frame the components μ_α of the Ln^{3+} magnetic moment $\boldsymbol{\mu}$ induced by an applied magnetic field $\mathbf{B}_0 = B_0\mathbf{n}$ of direction cosines n_α are

$$\mu_\alpha = \chi_{\alpha\alpha} n_\alpha B_0 \tag{A1}$$

Following Bleaney,[9] each component μ_α gives rise to a local dipolar magnetic field $\Delta\mathbf{B}_\alpha$ of components $\Delta B_{\alpha\beta}$ at the position of the studied nuclear spin *I*. The sum $\sum_{\alpha=X,Y,Z} \Delta\mathbf{B}_\alpha.\mathbf{n}$ of the projections of $\Delta\mathbf{B}_\alpha$ along the direction $\mathbf{n}$ of $\mathbf{B}_0$ in the (M) frame depends on the instantaneous orientation of the complex in the laboratory (L) frame. In the (M) frame, $\mathbf{n}$ has an isotropic distribution reflecting the orientation isotropy of the complexes in the liquid. Let (r_I, θ_I, ϕ_I) be the spherical coordinates in the (M) frame of the Ln^{3+}- *I* interspin vector $\mathbf{r}_I$. The average of $\sum_{\alpha=X,Y,Z} \Delta\mathbf{B}_\alpha.\mathbf{n}$ over all values of n_α is a local field ΔB along $\mathbf{B}_0$, which acts on the nuclear spin *I* during the lifetime of the complex and is given by

$$\frac{\Delta B}{B_0} = \frac{1}{2r_I^3} F\left(\theta_I, \phi_I\right) \tag{A2}$$

with

$$F\left(\theta_I, \phi_I\right) \equiv \left(\chi_{ZZ} - \bar{\chi}\right)\left(3\cos^2\theta_I - 1\right) + \left(\chi_{XX} - \chi_{YY}\right)\sin^2\theta_I \cos 2\phi_I \tag{A3}$$

and $\bar{\chi} \equiv \left(\chi_{XX} + \chi_{YY} + \chi_{ZZ}\right)/3$.

For a paramagnetic Ln^{3+} ion, but Gd^{3+}, the total Hamiltonian of the ground multiplet, including the Zeeman (Z) energy and the crystal field (cf) effects, is[13]

$$H = H_\mathrm{Z} + H_\mathrm{cf} = g_J \mu_\mathrm{B} \mathbf{B}.\mathbf{J} + \sum_{k=2,4,6} \sum_{-k\le q\le k} B_q^{(k)} T_q^{(k)} \tag{A4}$$

where $B_q^{(k)}$ are crystal field parameters and $T_q^{(k)} = T_q^{(k)}(J)$ ($-k \le q \le k$) are the standard components of an irreducible tensor operator[S1,8] of order *k*. Assuming that the crystal field energy splitting is much smaller than the energy separation of the ground and first excited multiplets, it can be shown[S2] that the high-temperature expansion of the susceptibility coefficient $\chi_{\alpha\alpha}$ limited to its two main terms is

$$\chi_{\alpha\alpha} = \chi^{\text{Curie}} + \chi_{\alpha\alpha}^{\text{anisotropy}} = \mu_0 g_J^2 \mu_{\text{B}}^2 \frac{J(J+1)}{3k_{\text{B}}T} - \mu_0 g_J^2 \mu_{\text{B}}^2 \frac{1}{(2J+1)\left(k_{\text{B}}T\right)^2} \operatorname{tr}\left(H_{\text{cf}} J_\alpha^2\right) \qquad \text{(A5)}$$

where the matrix trace is over the $(2J+1)$ states of the ground multiplet *J*. In eqn. (A5), the first term, χ^{Curie}, is the isotropic Curie contribution, whereas the second one, $\chi_{\alpha\alpha}^{\text{anisotropy}}$, is the source of the susceptibility anisotropy that induces the paramagnetic shift.

The fact that the susceptibility anisotropy is determined by the sole crystal field Hamiltonian of second order is a direct consequence of eqn. (A5). Indeed, J_α^2 is a linear combination of the components $T_q^{(2)}$, so that all the terms of H_{cf} of order k = 4, 6 do not contribute to $\operatorname{tr}\left(H_{\text{cf}} J_\alpha^2\right)$ since[8] $\operatorname{tr}\left(T_{q'}^{(k)} T_q^{(2)}\right) = 0$ if $k \neq 2$. Therefore, the effective part of H_{cf} is its second order term that can be written in the form[13]

$$H = D_X J_X^2 + D_Y J_Y^2 + D_Z J_Z^2 \qquad \text{(A6)}$$

with $D_X + D_Y + D_Z = 0$. The anisotropic terms $\chi_{\alpha\alpha}^{\text{anisotropy}}$ are calculated as follows. The trace of $\exp\left(\lambda J_{\text{Z}}\right)$ is $\operatorname{tr}\left[\exp\left(\lambda J_{\text{Z}}\right)\right] = \sum_{p=0}^{\infty} \frac{\lambda^{2p}}{(2p)!} \operatorname{tr}\left(J_Z^{2p}\right)$. It also takes the form $\operatorname{tr}\left[\exp\left(\lambda J_{\text{Z}}\right)\right] = \sum_{-J \le M \le J} e^{\lambda M} = \sinh\left[\lambda\left(J+1/2\right)\right] / \sinh\left[\lambda/2\right]$ that can be expanded in a power series of λ. The expression of $\operatorname{tr}\left(J_Z^{2p}\right)$ is obtained by equating the λ^{2p} coefficients in these two series. In particular, we have $\operatorname{tr}\left(J_Z^2\right) = (1/3)(2J+1)J(J+1)$ and $\operatorname{tr}\left(J_Z^4\right) = (2/30)(2J+1)J(J+1)(3J^2+3J-1)$. Because the components J_X, J_Y, J_Z of the angular momentum **J** play equivalent roles, the equalities $\operatorname{tr}\left(J_\alpha^4\right) = \operatorname{tr}\left(J_\beta^4\right)$ and $\operatorname{tr}\left(J_\alpha^2 J_\beta^2\right) = \operatorname{tr}\left(J_{\alpha'}^2 J_{\beta'}^2\right)$ hold if $\alpha \neq \beta$ or $\alpha' \neq \beta'$, so that $\operatorname{tr}\left(\mathbf{J}^2\mathbf{J}^2\right) = 3\operatorname{tr}\left(J_Z^4\right) + 6\operatorname{tr}\left(J_X^2 J_Z^2\right)$ and $\operatorname{tr}\left(J_X^2 J_Z^2\right) = (1/30)(2J+1)J(J+1)(2J^2+2J+1)$. Since $D_X + D_Y = -D_Z$, the anisotropic term $\chi_{ZZ}^{\text{anisotropy}}$ of the susceptibility tensor in eqn. (A5) is readily given by eqn. (A7) with $\alpha = Z$ and similar expressions of $\chi_{\alpha\alpha}^{\text{anisotropy}}$ hold for $\alpha = X, Y$.

$$\chi_{\alpha\alpha}^{\text{anisotropy}} = -\mu_0 g_J^2 \mu_{\text{B}}^2 \frac{D_\alpha J(J+1)(2J-1)(2J+3)}{30\left(k_{\text{B}}T\right)^2} \qquad \text{(A7)}$$

Setting $\hat{D} \equiv 3D_Z/2$, $\hat{E} \equiv \left(D_X - D_Y\right)/2$, the expression of H given by eqn. (A6) takes the standard form

$$H = \hat{D}\left[J_Z^2 - J(J+1)/3\right] + \hat{E}\left(J_X^2 - J_Y^2\right) \qquad \text{(A8)}$$

The linear combinations of the susceptibility coefficients $\chi_{\alpha\alpha}$ entering eqn. (A3) and given by eqn. (A5) can be expressed in terms of the anisotropic parts $\chi_{\alpha\alpha}^{\text{anisotropy}}$ as $\chi_{ZZ} - \overline{\chi} = \chi_{ZZ}^{\text{anisotropy}}$

since $\sum_{\alpha=X,Y,Z} \mathrm{tr}\left(H_{\mathrm{cf}} J_{\alpha}^{2}\right) = J(J+1)\mathrm{tr}\left(H_{\mathrm{cf}}\right) = 0$ and $\chi_{XX} - \chi_{YY} = \chi_{XX}^{\mathrm{anisotropy}} - \chi_{YY}^{\mathrm{anisotropy}}$. Replacing $\chi_{\alpha\alpha}^{\mathrm{anisotropy}}$ by their expressions in eqn. (A7), the local field ΔB given by eqns. (A2) and (A3) simplifies to

$$\frac{\Delta B}{B_0} = -\mu_0 g_J^2 \mu_{\mathrm{B}}^2 \frac{J(J+1)(2J-1)(2J+3)}{60\left(k_{\mathrm{B}}T\right)^2} r_I^{-3} F''\left(\theta_I, \phi_I\right) \tag{A9}$$

with

$$F''\left(\theta_I, \phi_I\right) \equiv \frac{2}{3}\hat{D}\left(3\cos^2\theta_I - 1\right) + 2\hat{E}\sin^2\theta_I \cos 2\phi_I \tag{A10}$$

The paramagnetic shift $\Delta\omega_{\mathrm{M}}$ in eqn. (1) readily follows from eqns. (A9) and (A10).

Appendix B. The standard equations for inner and outer-sphere paramagnetic relaxation enhancements

Let $A^{\mathrm{Curie}} \equiv (8\pi/5)\left[\omega_I \mu_{\mathrm{eff}}^2 / (k_{\mathrm{B}}T)\right]^2$ and $A^{\mathrm{SBM}} \equiv (8\pi/5)\gamma_I^2 \times g_J^2 \mu_{\mathrm{B}}^2 J(J+1)$ be the Curie and Solomon, Bloembergen and Morgan (SBM) dipolar relaxation factors, respectively.

Curie and SBM contributions to the intramolecular nuclear relaxation rates[15]

Let r_I be the Ln^{3+} - water proton distance in the complex. Introducing the spectral density of the isotropic rotational Brownian diffusion of the complex

$$j_{2\mathrm{R}}(\omega) \equiv \frac{1}{4\pi r_I^6} \frac{\tau_{\mathrm{R}}}{1+\omega^2\tau_{\mathrm{R}}^2} \tag{B1}$$

the Curie intramolecular relaxation rates $R_{\alpha\mathrm{M}}^{\mathrm{Curie}}$ read

$$R_{1\mathrm{M}}^{\mathrm{Curie}} = \frac{A^{\mathrm{Curie}}}{3} j_{2\mathrm{R}}(\omega_I),\ R_{2\mathrm{M}}^{\mathrm{Curie}} = \frac{A^{\mathrm{Curie}}}{3}\left[\frac{2}{3} j_{2\mathrm{R}}(0) + \frac{1}{2} j_{2\mathrm{R}}(\omega_I)\right] \tag{B2}$$

Besides, the SBM intramolecular relaxation rates $R_{\alpha\mathrm{M}}^{\mathrm{SBM}}$ are

$$R_{1\mathrm{M}}^{\mathrm{SBM}} = R_{2\mathrm{M}}^{\mathrm{SBM}} = \frac{10}{3} A^{\mathrm{SBM}} \frac{1}{4\pi r_I^6} \tau_{S0} \tag{B3}$$

Curie and SBM contributions to the outer-sphere paramagnetic relaxation enhancements

Consider the relative translational diffusion of the centres of two hard spheres in a continuous solvent.[17,18] The intermolecular dipolar spectral density $j_2(\omega)$ of this model of motion is

$$j_2(\omega) = \frac{10^{-6} N_{\mathrm{Avogadro}}}{3Da_{\mathrm{LnH}}} \mathrm{Re}\left(\frac{4+k}{9+9k+4k^2+k^3}\right) \text{ with } k = \sqrt{i\omega\tau} \tag{B4}$$

The Curie OS-PREs $R_{\alpha\mathrm{p}}^{\mathrm{OS\ Curie}}$ read

$$R_{1\mathrm{p}}^{\mathrm{OS\ Curie}} = \frac{1}{3} A^{\mathrm{Curie}} c\, j_2(\omega_I),\ R_{2\mathrm{p}}^{\mathrm{OS\ Curie}} = \frac{1}{3} A^{\mathrm{Curie}} c\left[\frac{2}{3} j_2(0) + \frac{1}{2} j_2(\omega_I)\right] \tag{B5}$$

Besides, the SBM OS-PREs $R_{\alpha\mathrm{p}}^{\mathrm{OS\ SBM}}$ are

$$R_{1\mathrm{p}}^{\mathrm{OS\ SBM}} = R_{2\mathrm{p}}^{\mathrm{OS\ SBM}} = \frac{10}{3} A^{\mathrm{SBM}} c 10^{-6} N_{\mathrm{Avogadro}} \frac{1}{3a_{\mathrm{LnH}}^3} \tau_{S0} \tag{B6}$$

Appendix C. Relation between transverse and longitudinal paramagnetic relaxation enhancements

The Curie transverse relaxation rate $R_{2\mathrm{M}}^{\mathrm{Curie}}$, which is proportional to $A^{\mathrm{Curie}} \propto \omega_I^2$, increases with field as B_0^2. Then, since τ_{S0} is very short,[11,15,16] the large magnetic fields used in high resolution NMR ensure that $R_{2\mathrm{M}}^{\mathrm{Curie}} >> R_{2\mathrm{M}}^{\mathrm{SBM}}$, so that the approximation $R_{2\mathrm{M}} \cong R_{2\mathrm{M}}^{\mathrm{Curie}}$ holds. Besides, according to eqns. (B1) and (B2), $R_{2\mathrm{M}}^{\mathrm{Curie}}$ is simply proportional to $R_{1\mathrm{M}}^{\mathrm{Curie}}$ as

$$R_{2\mathrm{M}}^{\mathrm{Curie}} = \left(\frac{7}{6} + \frac{2}{3}\omega_I^2 \tau_{\mathrm{R}}^2\right) R_{1\mathrm{M}}^{\mathrm{Curie}} \tag{C1}$$

The Curie longitudinal relaxation rate $R_{1\mathrm{M}}^{\mathrm{Curie}}$ = $\left(A^{\mathrm{Curie}}/3\right) j_{2\mathrm{R}}(\omega_I)$ is proportional to $\omega_I^2 \tau_{\mathrm{R}} \Big/ \left(1+\omega_I^2 \tau_{\mathrm{R}}^2\right)$. It also increases all the more rapidly with field since $\omega_I \tau_{\mathrm{R}} \leq 1$, i.e., for complexes of low and moderate molecular weights. Then, $R_{1\mathrm{M}}^{\mathrm{Curie}}$ is significantly larger than $R_{1\mathrm{M}}^{\mathrm{SBM}}$ and the approximation $R_{1\mathrm{M}} \cong R_{1\mathrm{M}}^{\mathrm{Curie}}$ is also reasonable. Replacing $R_{2\mathrm{M}}^{\mathrm{Curie}}$ and $R_{1\mathrm{M}}^{\mathrm{Curie}}$ by their approximate values $R_{2\mathrm{M}}$ and $R_{1\mathrm{M}}$, respectively, rigorous eqn. (C1) transforms into the approximate relation

$$R_{2\mathrm{M}} \cong \left(\frac{7}{6} + \frac{2}{3}\omega_I^2 \tau_{\mathrm{R}}^2\right) R_{1\mathrm{M}} \tag{C2}$$

which is close to eqn. (C3)

$$R_{2\mathrm{M}} \cong \frac{7}{6} R_{1\mathrm{M}} \tag{C3}$$

for complexes with fast enough Brownian rotation. Substituting the approximation (C2) for $R_{2\mathrm{M}}$ in the expression (8) of $R_{2\mathrm{p}}$ and then $R_{1\mathrm{p}} - R_{1\mathrm{p}}^{\mathrm{OS}}$ for $q\,f\,R_{1\mathrm{M}}$, $R_{2\mathrm{p}}$ can be rewritten as

$$R_{2\mathrm{p}} = q\,f\,\frac{x\Delta\omega_{\mathrm{M}}}{1+x^2} + \frac{7/6 + (2/3)\,\omega_I^2 \tau_{\mathrm{R}}^2}{1+x^2} R_{1\mathrm{p}} + \varepsilon \tag{C4}$$

with a residual

$$\varepsilon \equiv R_{2\mathrm{p}}^{\mathrm{OS}} - \frac{7/6 + (2/3)\,\omega_I^2 \tau_{\mathrm{R}}^2}{1+x^2} R_{1\mathrm{p}}^{\mathrm{OS}} \tag{C5}$$

Consider the situations where the residual ε is small with respect to $q\,f\,x\Delta\omega_{\mathrm{M}} \Big/ \left(1+x^2\right)$ and can be neglected in eqn. (C4). The first situation occurs when the exchange rate is intermediate, $x = \Delta\omega_M \tau_M$ $\cong$ 1, so that $q\,f\,x\Delta\omega_{\mathrm{M}} \Big/ \left(1+x^2\right)$ is the dominant term of $R_{2\mathrm{p}}$ in eqn. (8) and (C4) at high field and ε is negligible. In the second situation, the exchange is fast, $x = \Delta\omega_M \tau_M$ < 1, and the rotational diffusion of the complex is fast, $\omega_I \tau_{\mathrm{R}}$ < 1, as for complexes of low and moderate molecular weights in a solution of normal viscosity. In such a solution, any reasonably small molecule $\mathfrak{M}_I$ has a fast self-diffusion and a short translational correlation time τ, so that $\omega_I \tau < 1$ and $j_2(\omega_I) \cong j_2(0)$. According to eqn. (B5), the approximation

$$R_{2\mathrm{p}}^{\mathrm{OS\ Curie}} \cong \frac{7}{6} R_{1\mathrm{p}}^{\mathrm{OS\ Curie}} \tag{C6}$$

holds. Then, since $R_{\alpha\mathrm{p}}^{\mathrm{OS}} \cong R_{\alpha\mathrm{p}}^{\mathrm{OS\ Curie}}$ at high field, the residual ε given by eqn. (C5) is small and the approximation $\varepsilon \cong 0$ is reasonable. In brief, in a usual liquid solution, except in the case of a fast exchanging molecule $\mathfrak{M}_I$ that coordinates Ln^{3+} in a slowly rotating complex, eqn. (C4) can be approximated by the searched expression (9) of $R_{2\mathrm{p}}$ in terms of $\Delta\omega_I$ and $R_{1\mathrm{p}}$

$$R_{2\mathrm{p}} = x\Delta\omega_I + \frac{7/6 + (2/3)\omega_I^2 \tau_{\mathrm{R}}^2}{1+x^2} R_{1\mathrm{p}} \tag{9}$$

It should be emphasized that eqns. (C3) and (C6), which are at the basis of the approximation eqn. (9), were proven in the case of the representative standard relaxation model of Appendix B. However, they rest only on eqns. (B2) and (B5), which hold for the spectral densities $j_{2\mathrm{R}}$ and j_2 of any models of IS and OS dynamics. This is the fundamental reason of the general applicability of eqn. (9). The value of $x = \Delta\omega_M \tau_M$ at a given temperature is the solution of eqn. (9) obtained by replacing $R_{1\mathrm{p}}$, $R_{2\mathrm{p}}$, and $\Delta\omega_I$ by their values measured on any high-resolution spectrometer and τ_{R} by a reasonable estimate from the molecular weight of the complex.[5] Finally, the well-known expression[3] of the observed paramagnetic frequency shift

$$\Delta\omega_I = q\,f \frac{\Delta\omega_{\mathrm{M}}}{[1+(\tau_{\mathrm{M}}/T_{2\mathrm{M}})^2]+x^2} \tag{C7}$$

here simplifies to

$$\Delta\omega_I = q\,f \frac{\Delta\omega_{\mathrm{M}}}{1+x^2} \tag{C8}$$

Multiplication of the two members of this equation by τ_{M} yields the searched expression (10) for the residence time

$$\tau_{\mathrm{M}} = \frac{q\,f}{\Delta\omega_I} \frac{x}{1+x^2} \tag{10}$$

Note that the correction factor $7/6 + (2/3)\omega_I^2 \tau_{\mathrm{R}}^2$ in eqn. (9) stems from the approximate expression of $R_{2\mathrm{M}}$ in eqn. (C2), which is based on the fact that $R_{\alpha\mathrm{M}}^{\mathrm{Curie}} >> R_{\alpha\mathrm{M}}^{\mathrm{SBM}}$ at sufficiently high magnetic field. For the paramagnetic Ln^{3+} ions of the first series (Ce^{3+} to Nd^{3+}), even at rather high magnetic field, the SBM intramolecular and OS relaxation rates can dominate their Curie counterparts as seen in ESI, section V. Then, substituting $R_{1\mathrm{M}} \cong R_{1\mathrm{M}}^{\mathrm{SBM}}$

for $R_{2\mathrm{M}} \cong R_{2\mathrm{M}}^{\mathrm{SBM}}$ in the expression (8) of $R_{2\mathrm{p}}$, and then $R_{1\mathrm{p}} - R_{1\mathrm{p}}^{\mathrm{OS}}$ for $q\,f\,R_{1\mathrm{M}}$, $R_{2\mathrm{p}}$ can be rewritten as

$$R_{2\mathrm{p}} = x\Delta\omega_I + \frac{1}{1+x^2}R_{1\mathrm{p}} + \varepsilon' \text{ with } \varepsilon' \equiv R_{2\mathrm{p}}^{\mathrm{OS}} - \frac{1}{1+x^2}R_{1\mathrm{p}}^{\mathrm{OS}} \qquad \text{(C9)}$$

The shifts $\Delta\omega_{\mathrm{M}}$ of the paramagnetic Ln^{3+} ions of the first series are significantly smaller than those of the heavy paramagnetic Ln^{3+} ions, so that $x << 1$ except for a particularly long lifetime τ_{M}. The approximation $\varepsilon' \cong 0$ is reasonable and eqn. (C9) reduces to

$$R_{2\mathrm{p}} = x\Delta\omega_I + \frac{1}{1+x^2}R_{1\mathrm{p}} \qquad \text{(C10)}$$

The correction factor $7/6 + (2/3)\omega_I^2\tau_{\mathrm{R}}^2$ in eqn. (9) is simply replaced by 1 in eqn. (C10). The value of $7/6 + (2/3)\omega_I^2\tau_{\mathrm{R}}^2$ differs from 1 by less than 20 % for the many fast rotating complexes with $\omega_I\tau_{\mathrm{R}} \le 0.2$. Moreover, in a real situation, the Curie relaxation mechanisms are not fully negligible with respect to their SBM counterparts, so that the true correction factor replacing $7/6 + (2/3)\omega_I^2\tau_{\mathrm{R}}^2$ in eqn. (9) should have an intermediate value between 1 and $7/6 + (2/3)\omega_I^2\tau_{\mathrm{R}}^2$. To sum up, eqn. (9) is still expected to be a reasonable approximation for the paramagnetic Ln^{3+} ions of the first series. This is checked in ESI, section V.

Finally, replacing the PREs $R_{\alpha\mathrm{p}}$ by their definitions $R_{\alpha\mathrm{p}} = R_\alpha - R_{\alpha 0}$ in eqn. (9), we obtain

$$R_2 = x\Delta\omega_I + \frac{7/6 + (2/3)\omega_I^2\tau_{\mathrm{R}}^2}{1+x^2}R_1 + \varepsilon_0 \text{ with } \varepsilon_0 \equiv R_{20} - \frac{7/6 + (2/3)\omega_I^2\tau_{\mathrm{R}}^2}{1+x^2}R_{10} \qquad \text{(C11)}$$

In many situations, ε_0 is much smaller than R_2 as it is the difference of two quantities which (i) are intrinsically small since R_{10} and R_{20} originate from relaxation mechanisms that are of purely nuclear origin and less efficient than those involving the paramagnetic Ln^{3+} ions and (ii) approximately cancel out each other since R_{20} is just slightly larger than R_{10} in the frequent case of extreme narrowing. Then, the approximation $\varepsilon_0 \cong 0$ is reasonable and the exchange rate can be obtained from the sole relaxation rates R_1 and R_2 measured in the paramagnetic solution.

Appendix D. Measurement of the relative frequency shift $\Delta\omega_I/\omega_I$

Consider a molecule $\mathfrak{M}_I$ (here, HOD and MeOD) carrying the nuclear spin *I* of a resonating isotope (here, ^{1}H) of screening constant σ. Diamagnetic (dia) and paramagnetic (para) solutions of the molecules $\mathfrak{M}_I$ are prepared in D_2O without and with paramagnetic LnL complexes. Denote the susceptibility values per volume unit of these solutions by χ_{dia} and $\chi_{\mathrm{dia}} + \chi_{\mathrm{para}}$, respectively. Standard NMR tubes of 5 mm diameter are filled with these solutions by $\cong 5$ cm to form cylindrical liquid samples of large height/diameter ratio. Let

$S_\mathrm{f} \cong -4.1/(4\pi)$ be the form factors of these NMR samples[16,21] in SI units. When the paramagnetic solution is in an applied magnetic field (induction) B_0, the average magnetic field acting on the spin *I* of a molecule $\mathfrak{M}_I$, coordinating a complexed Ln^{3+} ion, is[21]

$$B = B_0\left(1-\sigma\right) - B_0 S_\mathrm{f}\left(\chi_\mathrm{dia} + \chi_\mathrm{para}\right) + \Delta B_\mathrm{M} \tag{D1}$$

where ΔB_M is the average pseudo-contact dipolar field giving rise to the pseudo-contact dipolar shift $\Delta\omega_\mathrm{M}$ of eqn. (1). Because of the chemical exchange of $\mathfrak{M}_I$, $\Delta\omega_\mathrm{M}$ reduces to the observed shift $\Delta\omega_I$ given by eqn. (C7) or its simplified form eqn. (C8), so that the resonance frequency of *I* in the paramagnetic solution is

$$\omega = \omega_I\left(1-\sigma\right) - \omega_I S_\mathrm{f}\left(\chi_\mathrm{dia} + \chi_\mathrm{para}\right) + \Delta\omega_I \tag{D2}$$

Our goal is to measure $\Delta\omega_I$. In order to get rid of the shift effects of the demagnetizing field represented by $-\omega_I S_\mathrm{f}\left(\chi_\mathrm{dia} + \chi_\mathrm{para}\right)$, a non-coordinating reference solute[11] (here, *tert*-Butanol-OD C(CH$_3$)$_3$OD) carrying a nuclear spin I^ref of the same isotope, but with a different screening constant $\sigma^\mathrm{ref} \neq \sigma$, is added to the diamagnetic and paramagnetic solutions. The magnetic field acting on the spin I^ref is

$$B_\mathrm{ref} = B_0\left(1-\sigma^\mathrm{ref}\right) - B_0 S_\mathrm{f}\left(\chi_\mathrm{dia} + \chi_\mathrm{para}\right) \tag{D3}$$

so that the resonance frequency of this spin is

$$\omega^\mathrm{ref} = \omega_I\left(1-\sigma^\mathrm{ref}\right) - \omega_I S_\mathrm{f}\left(\chi_\mathrm{dia} + \chi_\mathrm{para}\right) \tag{D4}$$

Consequently, substracting eqn. (D4) from eqn. (D2) member by member and dividing the obtained equation by ω_I, the observed relative frequency difference between the spins *I* and I^ref in the paramagnetic solution is

$$\frac{\Delta\omega_\mathrm{para}}{\omega_I} \equiv \frac{\omega - \omega^\mathrm{ref}}{\omega_I} = \sigma^\mathrm{ref} - \sigma + \frac{\Delta\omega_I}{\omega_I} \tag{D5}$$

The quantity $\left(\omega - \omega^\mathrm{ref}\right)/\omega_I$ is just obtained from the high resolution NMR spectrum of the paramagnetic solution as the difference expressed in ppm of the resonance frequencies of the peaks of *I* and I^ref. Similarly, in the diamagnetic solution without Ln^{3+} complexes, the observed relative frequency difference between the spins *I* and I^ref is

$$\frac{\Delta\omega_\mathrm{dia}}{\omega_I} \equiv \frac{\omega_\mathrm{dia} - \omega_\mathrm{dia}^\mathrm{ref}}{\omega_I} = \sigma^\mathrm{ref} - \sigma \tag{D6}$$

where $\left(\omega_{\mathrm{dia}}-\omega_{\mathrm{dia}}^{\mathrm{ref}}\right)/\omega_I$ is the difference of the resonance frequencies of the peaks of I and I^{ref} measured on the high resolution NMR spectrum. From eqns. (D5) and (D6), the paramagnetic frequency shift $\Delta\omega_I/\omega_I$ used to determine k_{ex} is given by

$$\frac{\Delta\omega_I}{\omega_I}=\frac{\Delta\omega_{\mathrm{para}}}{\omega_I}-\frac{\Delta\omega_{\mathrm{dia}}}{\omega_I} \tag{D7}$$

The values of $\left(\omega_{\mathrm{dia}}-\omega_{\mathrm{dia}}^{\mathrm{ref}}\right)/\omega_I$ and $\left(\omega-\omega^{\mathrm{ref}}\right)/\omega_I$ measured for HOD and MeOD are reported in Tables 2, 3, and 4 together with the derived paramagnetic frequency shifts $\Delta\omega_I/\omega_I$.

Appendix E. Measurement of the concentration of LnL complexes in a paramagnetic solution

The paramagnetic (para) solution can be prepared from a diamagnetic (dia) solution by adding the complex LnL. As in Appendix D, a non-coordinating reference solute[11] (here, *tert*-Butanol-OD $C(CH_3)_3OD$) carrying a nuclear spin I^{ref} of screening constant σ^{ref} are dissolved in the diamagnetic and paramagnetic solutions. In a given external magnetic field, the resonance frequency shift of the spin I^{ref} between the paramagnetic and diamagnetic solutions is proportional to the concentration *c* (mM) of the complexes. Various methods based on this property can be used to measure this concentration as discussed by Corsi *et al.*.[22] Here, we use the simple method successfully employed to measure the frequency shifts due to all the paramagnetic Ln^{3+} ions.[16,21] In this method, the field serving to lock the deuterium ^2H frequency has to keep the same value for the diamagnetic and paramagnetic NMR samples. For that purpose, after recording the spectrum of the diamagnetic sample, the ^2H frequency tuning channel is shut down and immediately followed by the record of the spectrum of the paramagnetic sample in order to avoid the field variation with time. Then, the same total external field acts on the paramagnetic and diamagnetic samples, so that the resonance frequency of I^{ref} is given by eqn. (D4) in the paramagnetic sample and by the similar equation

$$\omega_{\mathrm{dia}}^{\mathrm{ref}}=\omega_I\left(1-\sigma^{\mathrm{ref}}\right)-\omega_I S_{\mathrm{f}}\,\chi_{\mathrm{dia}} \tag{E1}$$

in the diamagnetic sample. By subtracting eqn. (E1) from eqn. (D4) member by member and dividing by ω_I, the relative shift of the resonance frequency in the paramagnetic solution with respect to that in the diamagnetic solution is

$$\frac{\Delta\omega^{\mathrm{ref}}}{\omega_I}=\frac{\omega^{\mathrm{ref}}-\omega_{\mathrm{dia}}^{\mathrm{ref}}}{\omega_I}=-S_{\mathrm{f}}\,\chi_{\mathrm{para}} \tag{E2}$$

The paramagnetic susceptibility per volume unit χ_{para} for a concentration *c* (mM) of complex is

$$\chi_{\text{para}} = c\mu_0 N_{\text{Avogadro}} \frac{\mu_{\text{eff}}^2 \mu_{\text{B}}^2}{3k_{\text{B}}T} \tag{E3}$$

so that the relative frequency shift becomes

$$\frac{\Delta\omega^{\text{ref}}}{\omega_I} = -S_{\text{f}} c\mu_0 N_{\text{Avogadro}} \frac{\mu_{\text{eff}}^2 \mu_{\text{B}}^2}{3k_{\text{B}}T} \tag{E4}$$

Since the form factor[16,21] of a cylindrical NMR liquid sample with a large standard height/diameter ratio ≅ 10 is $S_{\text{f}} \cong -4.1/(4\pi)$, eqn. (E4) simplifies to

$$\frac{\Delta\omega^{\text{ref}}}{\omega_I} = 1.720\times10^{-9} \frac{298.15}{T} \mu_{\text{eff}}^2 c \tag{E5}$$

When the temperature *T* and the effective magnetic moment μ_{eff} of the complexed Ln^{3+} ion are known, the measured value of $\Delta\omega^{\text{ref}}/\omega_I$ directly yields the concentration *c* (mM) from eqn. (E5).

II. Experimental details

Materials and sample preparation

The NMR samples were prepared *in situ* by mixing appropriate volumes of two solutions **A** and **B**. Solution **A** contains the complex and was obtained by weighing the appropriate amounts of ligand H_5dtpa (Sigma) and lanthanide salt $TbCl_3.6H_2O$ (99.9 %, Aldrich), which were dissolved in ultra-pure D_2O (99.96 % enrichment, Eurisotop). Then, the pH value of the solution was adjusted to approximatively 5.5, so that the final concentration of $Tb(dtpa)^{2-}$ in this mother-solution is 30 mM. The amount of added ligand was set to 1.1 times that of Tb^{3+} to avoid the presence of free metal ion. Solution **B** contains the probes and was obtained by dissolving the appropriate amounts of methanol CH_3OD (99.5% enrichment, Aldrich), abbreviated as MeOD, and *tert*-butanol $(CH_3)_3COD$ (2-methyl-2-propan(ol-d), 99 atom % D, ISOTEC), abbreviated as *t*-BuOD in ultra-pure D_2O. The concentrations of these solutes were around 670 mM and 220 mM for MeOD and *t*-BuOD, respectively.

The two solutions **A** and **B** were mixed in appropriate proportions to prepare a first paramagnetic NMR sample (sample 1) containing $Tb(dtpa)^{2-}$, MeOD, and *t*-BuOD at concentrations of 24.2, 131.5, and 43 mM, respectively. A second paramagnetic sample

(sample 2) was made by dissolving the appropriate amount of pure MeOD and *t*-BuOD in a more concentrated mother-solution **A'** of Tb(dtpa)$^{2-}$ ($\left[\mathrm{Tb(dtpa)}^{2-}\right]$ = 58 mM, pH $\cong$ 7), so that the final concentrations of Tb(dtpa)$^{2-}$, MeOD, and *t*-BuOD in sample 2 were 57.9, 39, and 26 mM, respectively.

Paramagnetic dioxygen was removed from the NMR sample by gently bubbling argon through the solution for about 20 minutes with the help of a long needle plunged down to the bottom of the NMR tube.

The Tb(dtpa)$^{2-}$ concentration was controlled by measuring the shift $\Delta\omega^{\mathrm{ref}}/\omega_I$ of the resonance frequency of the *t*-BuOD methyl protons in each NMR sample with respect to their resonance frequency in the diamagnetic solution. The measured shifts at 298 K were 3.805 and 9.046 ppm in samples 1 and 2. Assuming that the effective magnetic moment of Tb^{3+} in Tb(dtpa)$^{2-}$ is μ_{eff}^2 = 92.3 and slightly smaller than the free ion value[16] 94.5, the concentrations of complex derived from eqn. (E5) were found to be 24.0 and 57.0 mM in samples 1 and 2, respectively, in excellent agreement with the values 24.2 and 57.9 obtained by weighing.

NMR experiments

Instruments. The values of T_1, T_2, $T_{1\rho}$, $\Delta\omega_{\mathrm{para}}/\omega_I$ and T_{10}, $\Delta\omega_{\mathrm{dia}}/\omega_I$ were measured at 200 MHz on a Brucker Avance DMX 200, at 400 MHz on a Varian Unity 400, at 500 MHz on a Bruker Avance 500, and at 800 MHz on a Varian Inova 800. Because chemical exchange is an activated process with a rate that varies rapidly with temperature, particular attention was paid to the temperature accuracy. Prior to the NMR study, the temperature at the position of the NMR sample was calibrated on each spectrometer by comparing the measured peak separations of the protons in pure methanol (temperature window -130°C, +50°C) and/or in ethylene glycol (temperature window 20°C, 200°C) to the values tabulated *vs* temperature in the Varian documentation. Then, the temperature was controlled during the experiment by a N_2 flow heating system, in order to have an accuracy of ±0.5 K.

Proton relaxation times. In the paramagnetic solutions, the longitudinal and transverse relaxation times T_1 and T_2 were measured with the standard inversion-recovery (IR) and Carr-Purcell Meiboom-Gill (CPMG) sequences,[20] respectively. The longitudinal relaxation time in the rotating frame $T_{1\rho}$ was measured as follows: First, the equilibrium magnetization was rotated towards the y axis of the rotating frame with the help of a standard $(90°)_x$ pulse. Second, the time evolution of the rotated magnetization locked along the y axis was measured for variable delays τ by application of a radio-frequency field B_1 along this axis.[20] In the diamagnetic solution, the relaxation times of the HOD and MeOD protons are long because the molecules are small rapidly rotating bodies in a deuterated solvent. The longitudinal relaxation time T_{10} was obtained by using a saturation recovery sequence that avoids the need of a very long repetition time between two measurements.[20]

III. Measured values

Diamagnetic reference solution

Table 1 Temperature dependence of the measured relaxation times T_{10} of the HOD and MeOD protons in the diamagnetic solution B.

$T-273.15$ (K)	0.5	25	75
T_{10} (s) HOD	19.7[a]	38.5[b]	66[b]
T_{10} (s) MeOD	7.8[a]	14.2[b]	16[b]

[a] Varian Unity 400
[b] Bruker Avance 500 equipped with

These long relaxation times have an accuracy of about 10 %. Because the processes giving rise to the relaxation are fast, the relaxation times T_{20} and $T_{1\rho 0}$ are assumed to be equal to T_{10} and independent of field (extreme narrowing situation). The PREs $R_{\alpha \mathrm{p}} = R_\alpha - R_{\alpha 0}$ are obtained as the differences of the large relaxation rates R_α measured in the paramagnetic solution minus the small diamagnetic corrections $R_{\alpha 0} = 1/T_{\alpha 0}$ that can be estimated roughly without introducing significant errors. Therefore, the values of T_{10} at the intermediate temperatures were simply interpolated from the measured values.

Table 2 Temperature dependence of the measured chemical shift differences $\Delta\omega_{\mathrm{dia}}/\omega_I$ of the HOD and MeOD protons in the diamagnetic solution B at 500 MHz. The reference nuclei are the *t*-BuOD methyl protons

$T-273.15$ (K)	0.5	12.2	25	36	50.8	75
$\Delta\omega_{\mathrm{dia}}/\omega_I$ (ppm) HOD	3.816	3.675	3.532	3.406	3.2605	3.0449
$\Delta\omega_{\mathrm{dia}}/\omega_I$ (ppm) MeOD	2.100	2.102	2.105	2.1063	2.1085	2.1122

Paramagnetic solutions of Tb(dtpa)

Table 3 Temperature dependence at 500 MHz of the measured relaxation times T_1, T_2, $T_{1\rho}$, chemical shift differences $\Delta\omega_{\text{para}}/\omega_I$, and paramagnetic shifts $\Delta\omega_I/\omega_I$ of the HOD protons in the paramagnetic sample 1 with $[\text{Tb(dtpa)}]$ = 24.2 mM. The reference nuclei are the *t*-BuOD methyl protons

$T - 273.15$ (K)	0.5	12.2	25	36	50.8	75
T_1 (ms)	112.5	142.8	187.4	230.8	288	375.2
T_2 (ms)	3.24	6.18	16.9	35.7	80.5	187
$T_{1\rho}$ (ms)	3.1	5.76	16.3	35.7	82.3	195.2
$\Delta\omega_{\text{para}}/\omega_I$ (ppm)	3.634	3.453	3.3226	3.221	3.094	2.9071
$-\Delta\omega_I/\omega_I$ (ppm)	0.182	0.222	0.2094	0.185	0.1665	0.1378

Table 4 Temperature dependence at 500 MHz of the measured relaxation times T_1, T_2, $T_{1\rho}$, chemical shift differences $\Delta\omega_{\text{para}}/\omega_I$, and paramagnetic shifts $\Delta\omega_I/\omega_I$ of the MeOD protons in the paramagnetic sample 1 with $[\text{Tb(dtpa)}]$ = 24.2 mM. The reference nuclei are the *t*-BuOD methyl protons

$T - 273.15$ (K)	0.5	12.2	25	36	50.8	75
T_1 (ms)	257.5	322	417.2	509.7	633.7	821.9
T_2 (ms)	16.6	38.2	102.1	192.2	350.3	584.4
$T_{1\rho}$ (ms)	17	38.9	98.3	192.1	349	625
$\Delta\omega_{\text{para}}/\omega_I$ (ppm)	2.074	2.072	2.0812	2.086	2.092	2.1004
$-\Delta\omega_I/\omega_I$ (ppm)	0.026	0.03	0.0238	0.0203	0.0165	0.0118

Table 5 Magnetic field dependence at 298 K of the measured relaxation times T_1, $T_{1\rho}$, chemical shift differences $\Delta\omega_{\text{para}}/\omega_I$, and paramagnetic shifts $\Delta\omega_I/\omega_I$ of the HOD protons in the paramagnetic sample 1 with $[\text{Tb(dtpa)}]$ = 24.2 mM. The reference nuclei are the *t*-BuOD methyl protons

$\nu_I = \omega_I/(2\pi)$ (MHz)	200	400	500	800
T_1 (ms)	377	230.3	187.4	105.8
$T_{1\rho}$ (ms)	79.1	23.4	16.3	6.30
$\Delta\omega_{\text{para}}/\omega_I$ (ppm)	3.323	3.328	3.3226	3.3351
$-\Delta\omega_I/\omega_I$ (ppm)	0.209	0.204	0.2094	0.1969

Table 6 Measured relaxation times T_1, $T_{1\rho}$, chemical shift differences $\Delta\omega_{\text{para}}/\omega_I$, and paramagnetic shifts $\Delta\omega_I/\omega_I$ of the HOD and MeOD protons in the paramagnetic sample 2 with $[\text{Tb(dtpa)}]$ = 57.9 mM at 298 K and 500 MHz. The reference nuclei are the *t*-BuOD methyl protons

$\mathfrak{M}_I$	HOD	MeOD
T_1 (ms)	78.7	183.5
$T_{1\rho}$ (ms)	6.56	45.5
$\Delta\omega_{\text{para}}/\omega_I$ (ppm)	3.047	2.066
$-\Delta\omega_I/\omega_I$ (ppm)	0.485	0.039

The values of $R_{1\text{p}}$, $R_{1\rho\text{p}}$, and $-\Delta\omega_I/\omega_I$ of the HOD protons in sample 2 are to within ± 3 % just those of sample 1 multiplied by the ratio $57.9/24.2$ = 2.39 of the Tb(dtpa) concentrations in these samples. In the case of MeOD, this expected scaling still holds for the PREs $R_{1\text{p}}$, $R_{1\rho\text{p}}$ of its methyl protons. However, the ratio of the value of $-\Delta\omega_I/\omega_I$ in sample 2 divided by that in sample 1 is just 1.64 instead of 2.39. A similar result was obtained at 400 MHz and might be attributed to some change of the weak coordination structure of MeOD induced by the significant concentration increase of Tb(dtpa)$^{2-}$ salt between sample 1 and sample 2. Clearly, understanding the effects of the molecular environment on the structure of labile adducts like TbMeOD(dtpa)$^{2-}$ needs further investigation in the future.

Temperature dependence of τ_R. The rotational correlation time τ_R of Tb(dtpa)$^{2-}$ in D_2O is assumed to vary with temperature according to the Arrhenius law

$$\tau_\text{R} = \tau_\text{R}^{298} \exp\left[\frac{E_\text{R}}{R}\left(\frac{1}{T} - \frac{1}{298}\right)\right]$$

where τ_R^{298} = 80 ps is a reasonable value[7,11,24] at 298 K and E_R = 18.8 kJ mol^{-1} is the activation energy of the diffusional process obtained under the following assumption. The rotational diffusion coefficient D_R is given by a Stokes – Einstein law so that it is proportional to the ratio T/η, where η is the viscosity of D_2O. The activation energy of $\tau_\text{R} \equiv 1/(6D_\text{R}) \propto \eta/T$ was simply obtained from the fit of the measured values[S3] of η. The value τ_R^{298} = 80 ps retained for τ_R in D_2O at 298 K was obtained simply by multiplying the rotational correlation time[24] $\tau_{\text{R, Gd}}^{298} \cong 65$ ps of Gd(dtpa)$^{2-}$ in H_2O at 298 K by the viscosity[S3] ratio $\eta(\text{D}_2O)/\eta(\text{H}_2O)$ = 1.23 at 298 K. The value $\tau_{\text{R, Gd}}^{298} \cong 65$ ps was obtained through the reinterpretation[23] of measured peak-to-peak EPR linewidths[S4] of Gd(dtpa)$^{2-}$ in H_2O. It corresponds to an overall[7] rotational correlation time of the complex. It is somewhat shorter than the values 80 ps and 85 ps of the Dy(dtpa)$^{2-}$ and La(dtpa)$^{2-}$ complexes, which were obtained by Vander Elst *et al.*[11]

and account for some internal motion of the bound water molecule. It is significantly shorter than the overall correlation time τ_{RO}^{298} = 110 ps of Gd(dtpa)$^{2-}$ derived by Dunand *et al.*[7] from a combined analysis of EPR and NMR data, but rather near the correlation time τ_{RH}^{298} = 0.52 τ_{RO}^{298} = 57 ps of the Gd^{3+} - water proton, which was obtained by these authors and capture overall and internal rotational dynamics similar to those involved in the proton relaxation considered in the present work. It should be emphasized that the accuracy of τ_{R}^{298} is not critical as long as the inequality $\omega_I^2\tau_{\mathrm{R}}^2 << 1$ holds, so that the residual ε defined by eqn. (C5) keeps a negligible value. For instance, in the case of Tb(dtpa)$^{2-}$, changing τ_{R}^{298} by 50 % implies variations of k_{ex}^{298} and $\Delta H^{\ddagger}$ less than 1 %!

IV. Analysis of typical paramagnetic relaxation and frequency shift data of the water protons due to Dy(dtpa) derivatives

Table 7 Longitudinal and transverse relaxivities $r_1 \equiv R_{1\mathrm{p}}/c$ and $r_2 \equiv R_{2\mathrm{p}}/c$ of the H_2O protons in light water due to Dy(dtpa) and its derivatives Dy(dtpa-BEA) (BEA = bisethylamide), Dy(dtpa-BnBA) (BnBA = bis-n-butylamide) measured by Vander Elst *et al.*[11] at 300 and 600 MHz.

300 MHz	r_1 (s^{-1} mM^{-1}) 298 K	r_2 (s^{-1} mM^{-1}) 298 K	r_1 (s^{-1} mM^{-1}) 310 K	r_2 (s^{-1} mM^{-1}) 310 K
Dy(dtpa-BEA)	0.175	4.907	0.157	1.975
Dy(dtpa-BnBA)	0.184	2.2361	0.161	1.333

600 MHz	r_1 (s^{-1} mM^{-1}) 298 K	r_2 (s^{-1} mM^{-1}) 298 K	r_1 (s^{-1} mM^{-1}) 310 K	r_2 (s^{-1} mM^{-1}) 310 K
Dy(dtpa)	0.300	3.047	0.261	1.12
Dy(dtpa-BEA)	0.351	15.846	0.272	7.835
Dy(dtpa-BnBA)	0.350	12.205	0.274	5.600

Table 8 Temperature dependence at 300 MHz of the reduced frequency shift $\Delta\omega_{\mathrm{r}} = \Delta\omega_I/(q\,f)$ of the water protons due to Dy^{3+} in Dy(dtpa), Dy(dtpa-BEA), Dy(dtpa-BnBA) and measured by Vander Elst *et al.*.[11]

T (K)	298	310
$\Delta\omega_{\mathrm{r}}$ (10^6 rad s^{-1}) Dy(dtpa)	-1.2517	-1.1294
$\Delta\omega_{\mathrm{r}}$ (10^6 rad s^{-1}) Dy(dtpa-BEA)	-1.1583	-1.0379
$\Delta\omega_{\mathrm{r}}$ (10^6 rad s^{-1}) Dy(dtpa-BnBA)	-1.1488	-1.0523

Table 9 The values of the residence time τ_{M} of H_2O bound to Dy(dtpa), Dy(dtpa-BEA), Dy(dtpa-BnBA) derived through the careful molecular analysis of Vander Elst *et al.*[11] are compared with those obtained from eqns. (9) and (10) summarizing the present method

Dy^{3+} complex	τ_{M} (ns) Vander Elst *et al.* 298 K	310 K	τ_{M} (ns) present method 298 K	310 K
Dy(dtpa)	29	12	24(35)	9(11)
Dy(dtpa-BEA)	225	110	185 (235)	91(97)
Dy(dtpa-BnBA)	115	51	84(150)	57(54)

The τ_{M} values given by the present method in Table 9 were obtained as follows. For Dy(dtpa), the relaxivity values measured at 600 Mhz were used since they are approximately located on the fitted relaxivity curves shown in Figs. 2 and 4 of Vander Elst *et al.*. The value of $\Delta\omega_{\mathrm{r}}$ at 600 MHz was simply approximated as the double of the measured value at 300 MHz reported in Table 8. The values of τ_{M} in parentheses were all obtained from the relaxivities measured at 600 MHz and from the shifts $\Delta\omega_{\mathrm{M}}^{298}$ and $\Delta\omega_{\mathrm{M}}^{310}$ of bound water reported in Table 3 of Vander Elst *et al*..

Table 10 Reduced (r) frequency shift $\Delta\omega_{\mathrm{r}} = \Delta\omega_I / (q f)$ *vs* temperature of the water protons due to Dy^{3+} and Tb^{3+} in dtpa complexes. The values in the H_2O solution of Dy(dtpa) measured by Vander Elst *et al.*[11] at 300 MHz are compared to their counterparts in the D_2O solution of Tb(dtpa), which are calculated by the expression $\Delta\omega_{\mathrm{r}} = \Delta\omega_{\mathrm{M}} / (1 + x^2)$, where the shift $\Delta\omega_{\mathrm{M}} = \Delta\omega_{\mathrm{M}}^{298} (298.15/T)^2$ with $\Delta\omega_{\mathrm{M}}^{298} / B_0 =$ 1.292×10^5 rad s^{-1} T^{-1} and the auxiliary variable $x = \Delta\omega_{\mathrm{M}} \tau_{\mathrm{M}}$ with $\tau_{\mathrm{M}} = 1/k_{\mathrm{ex}}$ are derived from our NMR data.

T (K)	290	298	310	320	335
$\Delta\omega_{\mathrm{r}}$ (10^6 rad s^{-1}) Dy(dtpa)	-1.3484	-1.2517	-1.1294	-1.0604	-0.9276
$\Delta\omega_{\mathrm{r}}$ (10^6 rad s^{-1}) Tb(dtpa)	-0.953	-0.909	-0.842	-0.790	-0.721

The reduced shift due to Tb(dtpa) is significantly smaller than that due to Dy(dtpa) as expected from the electronic properties of the Tb^{3+} and Dy^{3+} ions under the reasonable hypothesis that the two complexes are isostructural.[7] At 298 K, the ratio $\Delta\omega_{\mathrm{M}}^{298}[\mathrm{Tb(dtpa)}] / \Delta\omega_{\mathrm{M}}^{298}[\mathrm{Dy(dtpa)}]$ is 0.88. This value is deduced from the shifts $\Delta\omega_{\mathrm{M}}^{298}[\mathrm{Tb(dtpa)}] / B_0$ given in Table 10 and $\Delta\omega_{\mathrm{M}}^{298}[\mathrm{Dy(dtpa)}] / B_0 =$ 1.47×10^5 rad s^{-1} T^{-1} reported in Table 3 of Vander Elst *et al*. and adjusted to fit the experimental relaxivity r_2. It is in excellent agreement with the expected value 0.86 for isostructural complexes. However, at 298 K, the ratio $\Delta\omega_{\mathrm{r}}[\mathrm{Tb(dtpa)}] / \Delta\omega_{\mathrm{r}}[\mathrm{Dy(dtpa)}] =$ 0.73 calculated from the values of Table 10 is somewhat too small for these complexes with very fast exchanging water molecules.

V. Experimental limits of applicability of the method

These limits are determined by the accuracy of the measurements of $R_{1\mathrm{p}}$, $R_{2\mathrm{p}}$, and $\Delta\omega_I / \omega_I$. The accuracy is improved by increasing the field to get larger values of $R_{1\mathrm{p}}$, $R_{2\mathrm{p}}$ and $\Delta\omega_I$ and by using perdeuterated solvent like D_2O to get smaller diamagnetic corrections R_{10} and R_{20}. Moreover, the ratio $R_{2\mathrm{p}} / R_{1\mathrm{p}} \cong T_1 / T_{1\rho}$ increases with field as shown in Table 5. This increase is caused by the term $(\Delta\omega_{\mathrm{M}})^2 \tau_{\mathrm{M}} = x \Delta\omega_{\mathrm{M}}$ in the expression (8) of $R_{2\mathrm{p}}$. It is particularly favourable because it reduces the influence in eqn. (9) of the correction term that is proportional to $R_{1\mathrm{p}}$ and only approximate. Thus, especially at very high field, accurate PRE values can be obtained for the paramagnetic Ln^{3+} ions of the second series (Tb^{3+} to Yb^{3+}) because of their large values[9,16] of μ_{eff}^2 and $\Delta\omega_{\mathrm{M}}$, even if the concentration c of Ln^{3+} complexes is low, down to 0.2 mM for the exchange of water and 1 mM for the exchange of molecules like methanol with protons that are more distant to the paramagnetic ion. The measurement of accurate $\Delta\omega_I / \omega_I$ values typically requires $\Delta\omega_I / \omega_I \geq$ 0.01 ppm, i.e., $c \geq 1$

and 10 mM, respectively for the exchange of water and of a weakly coordinating molecule $\mathfrak{M}_I$ like methanol.

Turn to a Ln^{3+} ion of the first series (Ce^{3+} to Nd^{3+}), which is "truly" paramagnetic in the sense that it has a total angular momentum of its ground multiplet $J \neq 0$, so that eqn. (1) holds. This excludes Eu^{3+}. The $\Delta\omega_{\text{M}}$ values of these Ln^{3+} ions are about 10 times smaller[9] than that of Tb^{3+}, leading to induced shifts $\Delta\omega_I$ that are also ten times smaller than the Tb^{3+} induced shift, but can still be measured with accuracy as shown by the methanol study. Their rates $R_{1\text{M}}^{\text{Curie}}$, $R_{2\text{M}}^{\text{Curie}}$ given by eqn. (B2) and their $\left(\Delta\omega_{\text{M}}\right)^2$ values are 10^2 times smaller than their Tb^{3+} counterparts. According to eqns. (3), (5), (7), their IS-PREs are also 10^2 times smaller than those due to Tb^{3+} for the same concentration c of complexes. Thus, their PREs $R_{2\text{p}}$ are expected to be of the order of 1 s^{-1} for $c \cong$ 25 mM in the case of the water protons in D_2O at 298 K. They can still be measured with accuracy given the small values of the diamagnetic corrections $R_{20} \cong R_{10}$ reported in Table 1 ($R_{10} \cong$ 0.025 s^{-1} at 298 K). The applicability of the method can be further checked by considering the very unfavourable case of Nd(dtpa), since Nd^{3+} has the smallest $\Delta\omega_{\text{M}}$ value[9] in addition to a particularly long electronic relaxation time[23] τ_{S0} that invalidates the inequalities $R_{\alpha\text{M}}^{\text{SBM}} < R_{\alpha\text{M}}^{\text{Curie}}$ used to assess the fundamental eqn. (9). The general method sketched in section 5 to justify eqn. (9) is used now for the water protons. Assume the values[2,5-7] r_I = 0.31 nm, a_{LnH} = 0.4 nm and $\tau_{\text{R}} = 80\,\text{ps}$, D = 2.2×10^{-5} cm^2 s^{-1} at 298 K. Further assume that τ_{M} in Nd(dtpa) is about 3 times longer than in Tb(dtpa) as in the series of Ln(dtpa-bma) complexes,[2] so that τ_{M} = 180 ns at 298 K. For ν_I = 500 MHz, from eqn. (A2), we have $R_{1\text{M}}^{\text{Curie}}$ = 76 s^{-1}, $R_{2\text{M}}^{\text{Curie}}$ = 92 s^{-1}. From eqn. (A3), if the electronic spin relaxation time τ_{S0} of Nd^{3+} in Nd(dtpa) has the rather large, but still reasonable, unfavourable value[16,23] τ_{S0} = 0.2 ps, the SBM intramolecular relaxation rates are $R_{1\text{M}}^{\text{SBM}}$ = $R_{2\text{M}}^{\text{SBM}}$ = 250 s^{-1}. The fast exchange hypothesis $T_{1\text{M}} \geq T_{2\text{M}} >> \tau_{\text{M}}$ at the basis of our method is fully satisfied. For c = 25 mM, the exact value 0.65 s^{-1} of $R_{2\text{p}}$ given by eqn. (8) differs from its estimate derived from eqn. (9) by about 3 %. The term $x\Delta\omega_I$ in eqn. (9) is dominant, so that the exact value of τ_{M} differs by less than 5 % from its approximation obtained as the solution of eqns. (9) and (10) with $R_{1\text{p}}$, $R_{2\text{p}}$, $\Delta\omega_I$ calculated from eqns (2) to (6) with the relaxation model of Appendix B. Thus, the method should apply to the complexed Ln^{3+} ions of the first series at moderate Ln^{3+} concentrations. Furthermore, the Ln^{3+} complexes corresponding to the Gd^{3+} complexes serving as MRI contrast agents are soluble in water at concentrations higher than 500 mM. The proposed method can be used with Ln^{3+} concentrations more than 10 times larger than those considered in the present study, leading to similar increases of the PREs. Then, even the PREs of the Ln^{3+} ions of the first series should largely dominate the measured relaxation rates and be accurately measured. Of course, if large concentrations c of paramagnetic Ln^{3+} ions are employed, the diamagnetic corrections R_{10} and R_{20} have to be determined in the presence of the same concentrations of the diamagnetic La^{3+} or Lu^{3+} corresponding complexes.

Now, consider the role of the formation constant of the $\text{Ln}\left(\mathfrak{M}_I\right)_q \text{L}$ complex. When this formation constant increases, the ratio $f \equiv \left[\text{Ln}\left(\mathfrak{M}_I\right)_q \text{L}\right] \big/ \left[\mathfrak{M}_I\right]$ becomes larger than Pc, giving rise to favourable enhancements $R_{1\text{p}}$, $R_{2\text{p}}$, and $\Delta\omega_I / \omega_I$. In addition, if the fast exchange condition $\Delta\omega_{\mathrm{M}}\tau_{\mathrm{M}} \leq$ 1 still applies, the resulting enhancements of $R_{1\mathrm{p}}$, $R_{2\mathrm{p}}$, and $\left|\Delta\omega_I / \omega_I\right|$ per mM of added LnL complexes should be a few orders of magnitude larger than for methanol, so that the Ln^{3+} concentration required for their accurate measurements could be reduced in the same proportion. Finally, consider a weakly coordinating molecule $\mathfrak{M}_I$ at a 10 µM concentration that can be rather easily observed on a spectrometer operating at 800 MHz and equipped with a cold probe. Then, the concentration of $\mathrm{Ln}\left(\mathfrak{M}_I\right)_q\mathrm{L}$ adducts is about $10\,P \times 10$ µM = 2 nM and the number of $\mathrm{Ln}\left(\mathfrak{M}_I\right)_q\mathrm{L}$ complexes in a 500 µl NMR sample is 1 pico-mole. The possibility of evidencing such a tiny quantity of species by an NMR method is worth noting.

ESI References

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