

Can the Theoretical Fitting of the Proton-Nuclear-Magnetic-Relaxation-Dispersion (Proton NMRD) Curves of Paramagnetic Complexes Be Improved by Independent Measurement of Their Self-Diffusion Coefficients?

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Dedicated to Professor *André E. Merbach* on the occasion of his 65th birthday

The self-diffusion (D_c) coefficients of various lanthanum(III) diamagnetic analogues of open-chain and macrocyclic complexes of gadolinium used as MRI contrast agents were determined in dilute aqueous solutions (3–31 mM) by pulsed-field-gradient (PFG) high-resolution $^1\text{H-NMR}$ spectroscopy. The self-diffusion coefficient of H_2O (D_w) was obtained for the same samples to derive the relative diffusion constant, a parameter involved in the outersphere paramagnetic-relaxation mechanism. The results agree with an averaged relative diffusion constant of $2.5 (\pm 0.1) \times 10^{-9}$ and of $3.3 (\pm 0.1) \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$ at 25 and 37°, respectively, for 'small' contrast agents (M_r 500–750 g/mol), and with the value of bulk H_2O (2.2×10^{-9} and $2.9 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$ at 25° and at 37°, respectively) for larger complexes. The use of the measured values of D_c for the theoretical fitting of proton NMRD curves of gadolinium complexes shows that the rotational correlation times (τ_R) are very close to those already reported. However, differences in the electronic relaxation time (τ_{s0}) at very low field and in the correlation time (τ_v) related to electronic relaxation were found.

Introduction. – Paramagnetic contrast agents for Magnetic Resonance Imaging (MRI) increase the nuclear relaxation rates of the H_2O H-atoms through magnetic dipolar interactions, which are usually classified as short-distance interactions ('inner-sphere relaxation') and long-distance interactions ('second-sphere and outer-sphere relaxations'). The inner-sphere contribution described by *Solomon* [1] and *Bloembergen* [2] depends on the rotational correlation time (τ_R) of the supramolecular complex, the number of H_2O molecules (q) coordinated to the paramagnetic ion, their residence time (τ_M) in the bound state, the electronic relaxation times (τ_{s1} , τ_{s2}) of the paramagnetic center, and the distance (r) between the H-atoms of the coordinated H_2O and the ion. The second-sphere relaxation is due to the fast exchange of H_2O molecules in a second hydration shell; it is also described by the equations of *Solomon* and *Bloembergen*, but with a larger distance r and a shorter H_2O residence time [3]. The outer-sphere contribution, as reported by *Freed* [4], is related to the electronic relaxation times (τ_{s1} , τ_{s2}), the distance d of closest approach of the H_2O molecules in the vicinity of the paramagnetic center, and the relative diffusion constant (D), defined as the sum of the self-diffusion coefficients of the supramolecular complex (D_c) and of bulk H_2O (D_w).

Very often, due to different size, the self-diffusion constant of a paramagnetic complex is neglected, and the relative diffusion constant is set to that of H_2O or very

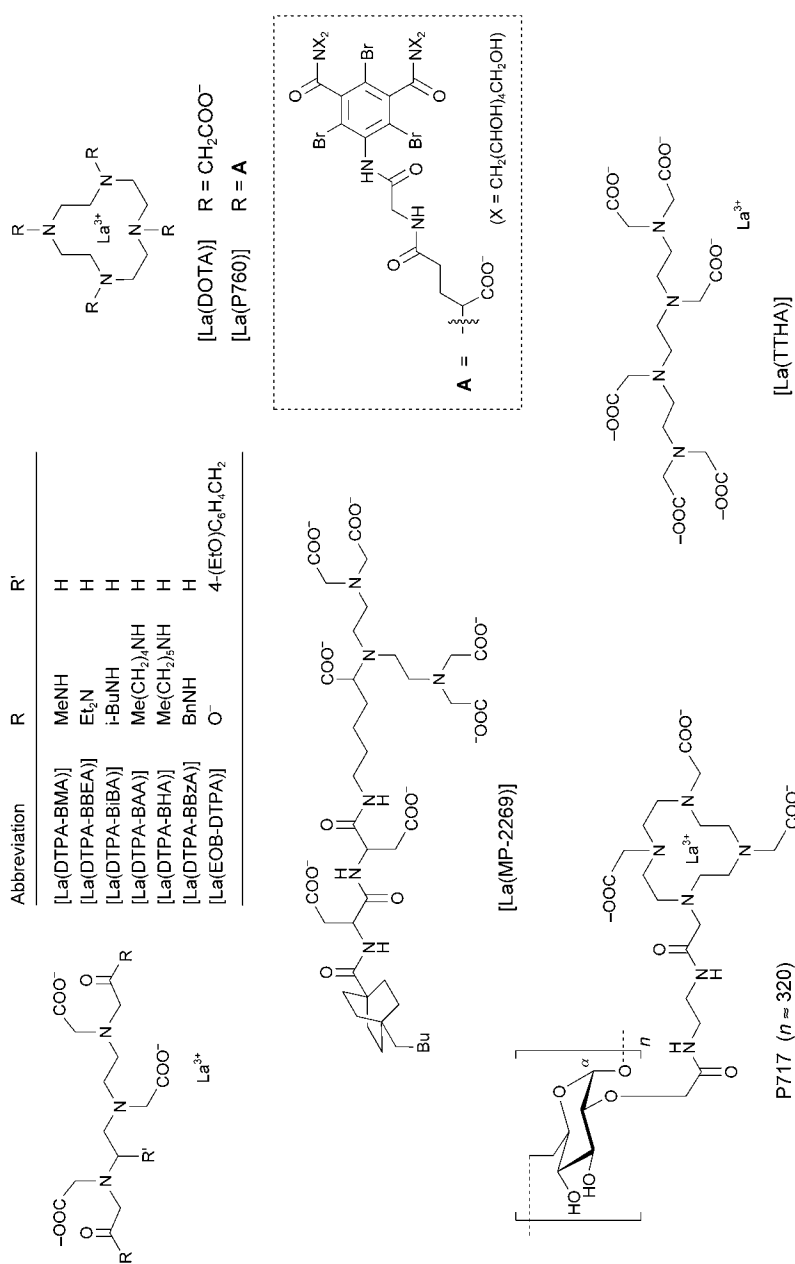


Fig. 1. Chemical structures of selected lanthanum complexes and of the ligand of P717

close to it [5–9]. Some authors have evaluated this parameter and the activation energy of the diffusion process from the proton-NMRD profiles of paramagnetic complexes recorded at various temperatures [10][11]. While the D values used until now for the theoretical fitting of such profiles lie in the same range, experimental data are still lacking. Therefore, this work aimed at obtaining accurate values for the molecular self-diffusion constant of a series of paramagnetic gadolinium (Gd) complexes that are potential MRI contrast agents in aqueous solution. The self-diffusion constants were measured for the diamagnetic lanthanum (La) analogues at various temperatures using the pulsed-field-gradient (PFG) spin-echo technique. Eleven (open-chain or macrocyclic) La^{III} complexes of increasing molecular weight (M_r 500–5000 g/mol), as well as a macromolecular macrocyclic ligand (P717; M_r 52000 g/mol), were investigated (see *Fig. 1* and *Exper. Part*).

Results. – Self-Diffusion Coefficients. For the measurements of self-diffusion coefficients, all ligands (except for P717) were complexed to diamagnetic La³⁺ instead of paramagnetic Gd³⁺ ions to avoid excessive reduction of T_2 and broadening of the ¹H-NMR resonances. The slightly lower molecular weight of the La^{III} complexes with respect to the Gd analogues (< 3.5%) should not significantly affect the self-diffusion coefficient. The concentration range was a compromise allowing, on the one hand, to match as closely as possible the concentrations commonly used for proton-NMRD measurements and, thus, to avoid viscosity differences and, on the other hand, to obtain acceptable signal-to-noise ratios over reasonable measurement periods. For each sample, the longitudinal relaxation rate of the H₂O H-atoms as well as the self-diffusion coefficients of H₂O (D_w) and of the complex (D_c) were determined at four temperatures (*Table 1*).

Table 1. *Temperature Dependence of the Longitudinal Relaxation of H₂O in the Absence and Presence of Different Lanthanum Complexes or a Macrocyclic Ligand (P717)*

Compound	M_r [g/mol]	Conc. [mM]	T_1 [s]			
			20°	25°	30°	37°
H ₂ O	–	–	2.73	3.04	3.54	3.86
[La(DTPA-BMA)(H ₂ O)]	527	31.25	2.36	2.57	2.87	3.30
[La(DOTA)(H ₂ O)] [–]	539	28.02	2.50	2.76	3.18	3.62
[La(TTHA)] ^{3–}	627	22.14	2.63	3.00	3.28	3.90
[La(DTPA-BBEA)(H ₂ O)]	639	18.20	2.27	2.51	2.79	3.10
[La(DTPA-BiBA)(H ₂ O)]	639	22.36	2.17	2.48	2.68	3.04
[La(EOB-DTPA)(H ₂ O)] ^{2–}	661	17.73	2.36	2.68	3.10	3.52
[La(DTPA-BAA)(H ₂ O)]	667	25.11	2.46	2.71	2.95	3.49
[La(DTPA-BHA)(H ₂ O)]	695	20	2.27	2.60	2.78	3.26
[La(DTPA-BBzA)(H ₂ O)]	707	13.05	2.23	2.42	2.59	3.00
[La(MP-2269)(H ₂ O)] ^{4–}	1031	25.04	2.34	2.67	3.08	3.24
[La(P760)(H ₂ O)] [–]	5000	2.95	2.38	2.78	3.07	3.27
P717	52000	0.33	2.23	2.45	2.63	3.03

In all solutions, except for [La(TTHA)], T_1 was lower than that of bulk H₂O. All investigated La complexes, except [La(TTHA)], have one exchanging H₂O molecule coordinated to the metal ion. In the bound state, the rotational motion of this H₂O

molecule is reduced resulting in a decreased averaged relaxation rate. For the ligand of P717, the sugar OH groups can additionally bind H₂O molecules and, thus, induce a similar effect.

The values of the self-diffusion coefficient of H₂O agree very well with those reported by Holz *et al.* [12]. The self-diffusion coefficients of the La^{III} complexes and of the ligand of P717 were determined by means of the peaks labeled in Fig. 2. In the La complex solutions, D_w values are only slightly decreased (on average by 3.9% at 37°) as compared to bulk H₂O at the same temperature. This indicates that the concentrations used do not affect significantly the viscosity (Table 2), even if the small differences in D_w could be related to a slight viscosity increase. The values of D_c are, as expected, smaller than for D_w , and decrease with increasing molecular size.

Table 2. Temperature Dependence of Diffusion Coefficients of Different Complexes (D_c) Relative to Those of Bulk H₂O (D_w). Units: 10⁻¹⁰ m² s⁻¹.

Compound	20°		25°		30°		37°	
	D_w	D_c	D_w	D_c	D_w	D_c	D_w	D_c
H ₂ O (bulk)	19.6		22.0		25.4		28.4	
[La(DTPA-BMA)(H ₂ O)]	18.6	3.96	21.3	4.49	24.3	5.24	27.8	6.12
[La(DOTA)(H ₂ O)] ⁻	17.9	4.81	20.7	5.44	24.0	6.52	27.3	6.86
[La(TTHA)] ³⁻	18.6	3.87	20.9	4.36	23.1	4.97	27.7	5.74
[La(DTPA-BBEA)(H ₂ O)]	18.4	3.78	21.1	4.28	23.5	4.77	27.9	5.81
[La(DTPA-BiBA)(H ₂ O)]	17.5	3.98	20.4	4.42	22.2	4.75	26.9	5.56
[La(EOB-DTPA)(H ₂ O)] ²⁻	18.3	3.72	20.8	3.96	24.0	4.75	27.6	5.37
[La(DTPA-BAA)(H ₂ O)]	18.1	3.57	20.3	4.05	22.9	4.59	28.2	5.42
[La(DTPA-BHA)(H ₂ O)]	17.7	3.14	20.1	3.63	22.4	4.03	26.4	4.75
[La(DTPA-BBzA)(H ₂ O)]	17.9	3.31	20.1	3.91	22.3	4.20	26.6	5.12
[La(MP-2269)(H ₂ O)] ⁴⁻	17.8	2.49	20.0	2.90	23.7	3.26	27.0	3.70
[La(P760)(H ₂ O)] ⁻	18.5	1.40	21.0	1.62	23.9	1.81	27.3	1.98
P717	18.0	0.28	20.8	0.32	22.6	0.35	27.6	0.39

Proton-NMRD Profiles. The complex [Gd(TTHA)] has the lowest relaxivity due to the absence of H₂O in the first coordination sphere, whereas the ‘small’ bisamide derivatives of [Gd(DTPA)] have a low-field relaxivity of 6.5–7.5 s⁻¹ mm⁻¹, and a high-field relaxivity of 3–4 s⁻¹ mm⁻¹ (Fig. 3). As already reported, the macrocyclic complex [Gd(DOTA)] has a high-field relaxivity in the same range, but a much larger low-field relaxivity attributed to a higher symmetry and/or rigidity. The relaxivity of the C-substituted [Gd(EOB-DTPA)] is larger over the whole magnetic-field range. Similarly, the larger complex [Gd(MP-2269)] is characterized by a significantly higher relaxivity both at low and high magnetic fields (9 and 6 s⁻¹ mm⁻¹, resp.), whereas the proton NMRD profile of the bulky P760 complex is typical of slowly rotating systems with a large low-field relaxivity (32 s⁻¹ mm⁻¹) and a hump at medium fields, with relaxivities ranging from 20 to 25 s⁻¹ mm⁻¹ between 10 and 100 MHz.

Discussion. – As expected, all the La complexes and the ligand of P717 diffuse more slowly than H₂O. For the ‘small’ complexes ($M_r < 750$ g/mol), the ratio between the self-diffusion coefficients of H₂O and of the solute ranges between 3.7 for [La(DOTA)] and 5.6 for [La(DTPA-BHA)] (Table 2). By comparison, the ratio is

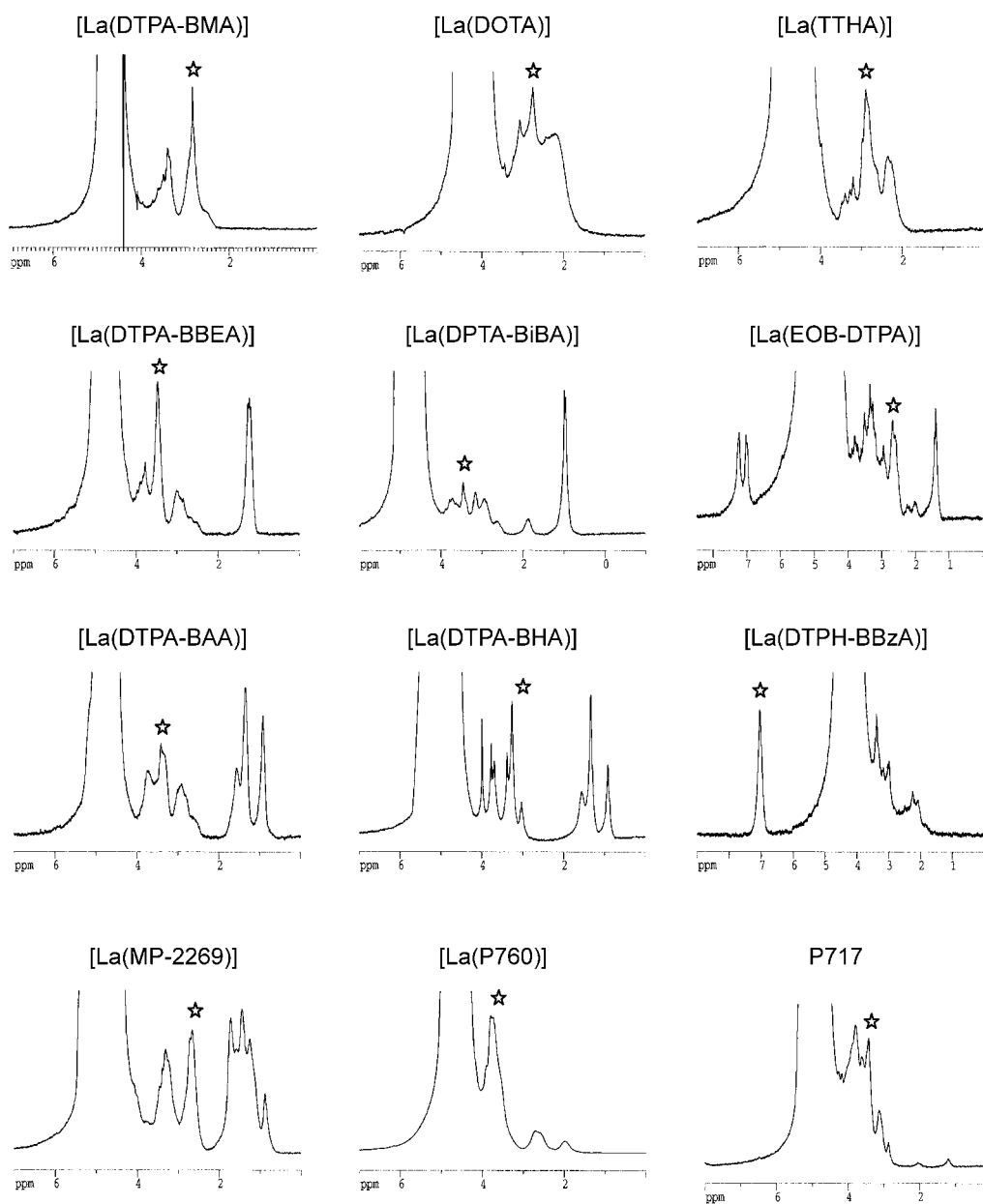


Fig. 2. $^1\text{H-NMR}$ Resonances used for the determination of self-diffusion coefficients (D_c)

equal to *ca.* 7.2, 13.3, and 66 for [La(MP-2269)], [La(P760)], and the ligand of P717, respectively. The complex [La(DOTA)], which has a molecular weight similar to that of [La(DTPA-BMA)], diffuses faster, probably because of the more-compact structure

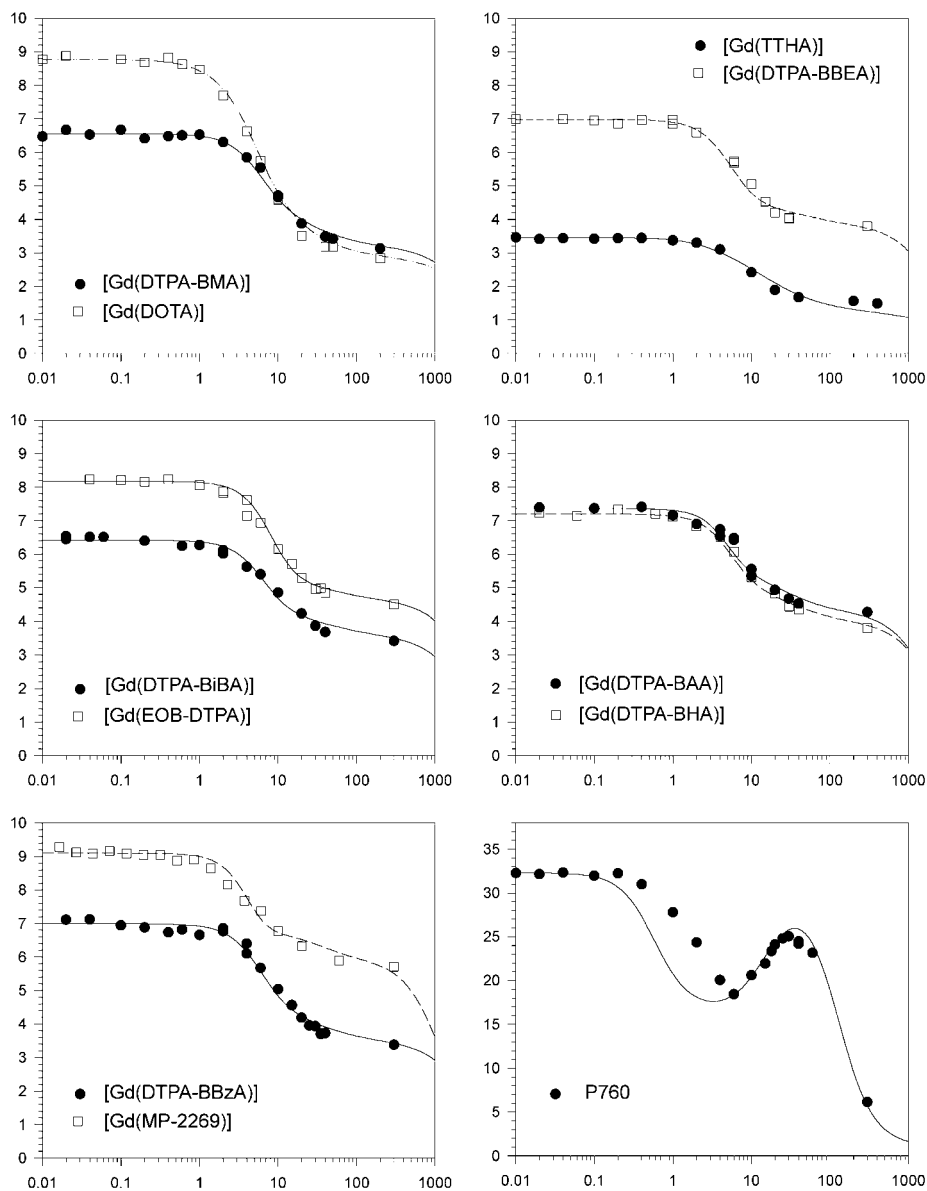


Fig. 3. Fitted proton NMRD data of various gadolinium complexes (see text). Vertical axes: r_1 [$\text{s}^{-1} \text{mm}^{-1}$]; horizontal (logarithmic) axes: proton Larmor frequency [MHz].

of the macrocyclic ligand. Fig. 4 illustrates the decrease of the self-diffusion coefficient with molecular weight of the compounds at 25° .

The data shown in Fig. 4 could be fitted with an empirical equation (Eqn. 1), which, in turn, can be used to predict the value of D_c of any complex.

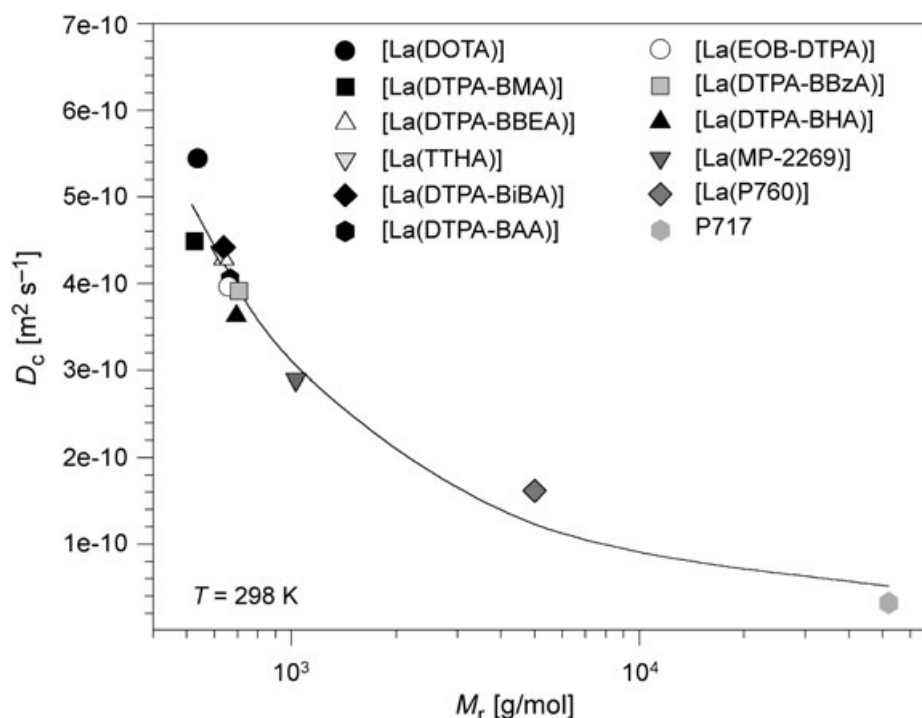


Fig. 4. Relationship between the self-diffusion coefficient (D_c) of different compounds at 25° in H_2O and their molecular weight (M_r). For structures, see Fig. 1.

$$D_c = 2.765 \times 10^{-11} + \frac{4.93 \times 10^{-9}}{\sqrt{M_r}} + \frac{1.28 \times 10^{-7}}{M_r} \quad (1)$$

Calculation of the Molecular Radius and of the Rotational Correlation Time. The relationship between the self-diffusion coefficient (D_c) and the radius (r_0) of a solute is given by the *Stokes–Einstein* equation (Eqn. 2), where k is the *Boltzmann* constant and T the temperature.

$$D_c = \frac{kT}{\beta_t} \quad (2)$$

For a spherical particle with an effective hydrodynamic radius r_0 in a medium of viscosity η , the parameter β_t is given by Eqn. 3:

$$\beta_t = 6\pi\eta r_0 \quad (3)$$

If the particle is not diffusing in a continuous medium, a translational microviscosity coefficient, f_t , as described by *Gierer* and *Wirtz* [13], can be introduced (Eqn. 4). Here, f_t depends on the relative size of the solvent and solute molecules according to Eqn. 5, r_s being the solvent radius:

$$\beta_t = 6\pi\eta r_0 f_t \quad (4)$$

$$f_t = \left[\frac{3}{2} \frac{r_s}{r_0} + \frac{1}{1 + \frac{r_s}{r_0}} \right]^{-1} \quad (5)$$

For large molecules, f_t tends to approach unity, but for a molecule similar in size to the solvent, f_t is equal to 0.5. A parameter $f_t \times r_0$, which we will call r_{app} , can, thus, be calculated from the experimental value of D_c . From *Eqn. 5*, we derived the relationship between $f_t \times r_0/r_s$ ($= r_{\text{app}}/r_s$) and r_0/r_s (*Eqn. 6*), which gives r_0 , the actual radius of the solute.

$$r_0 = \left(\frac{r_{\text{app}}}{r_s} + 0.50873 \right) \frac{r_s}{0.999125} \quad (6)$$

The data are summarized in *Table 3*. [La(DOTA)] is characterized, as expected, by the smallest radius. The low-molecular-weight ($M_r < 750$ g/mol) DTPA complexes have radii, ranging from 0.636 nm for [La(DTPA-BMA)] to 0.783 nm for [La(DTPA-BHA)]. Compounds [La(DTPA-BBzA)] and [La(DTPA-BHA)] have different radii, although they have similar molecular weights. This is due to structurally different substituents (*N*-benzyl- vs. *N*-hexyl amides, resp.). As expected, the higher-molecular-weight compounds [La(MP-2269)], [La(P760)], and the ligand of P717 have significantly larger radii.

Eqn. 7 relates τ_R to the radius of the molecule (r_0) and to the rotational microviscosity coefficient f_R [13] (defined by *Eqn. 8*). These equations were used to estimate the rotational correlation time (τ_R^{calc} ; see below).

$$\tau_R = \frac{4\pi\eta r_0^3 f_R}{kT} \quad (7)$$

Table 3. Mean Values of r_{app} and of r_0 Calculated from the Temperature-Dependent Measurement of D_c . The viscosity (η) was set to that of bulk H₂O.

Compound	M_r [g/mol]	r_{app} [10^{-10} m]	r_0 [10^{-10} m] ^{a)}
[La(DTPA-BMA)(H ₂ O)]	527	5.39	6.36
[La(DOTA)(H ₂ O)] ⁻	539	4.50	5.48
[LaTTHA] ³⁻	627	5.62	6.60
[La(DTPA-BBEA)(H ₂ O)]	639	5.72	6.70
[La(DTPA-BiBA)(H ₂ O)]	639	5.67	6.66
[La(EOB-DTPA)(H ₂ O)] ²⁻	661	5.98	6.96
[La(DTPA-BAA)(H ₂ O)]	667	6.04	7.03
[La(DTPA-BHA)(H ₂ O)]	695	6.85	7.83
[La(DTPA-BBzA)(H ₂ O)]	707	6.44	7.43
[La(MP-2269)(H ₂ O)] ⁴⁻	1031	8.62	9.60
[La(P760)(H ₂ O)] ⁻	5000	15.60	16.59
P717	52000	79.19	80.24

^{a)} The value r_s (see *Eqn. 6*) was set to 0.192 nm.

$$f_R = \left[6 \frac{r_s}{r_0} + \frac{1}{\left(1 + \frac{r_s}{r_0}\right)^3} \right]^{-1} \quad (8)$$

Relative Diffusion Constant. The value of D used in the theoretical model of the paramagnetic translational relaxation rate is the sum of D_w and D_c . As can be seen in *Table 4*, for the ‘small’ complexes, this value is close to $3.5 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$, a value currently used in the fittings of the proton-NMRD curves at 37° . For compounds of molecular weights above 1000 g/mol, the deviation becomes significant, reaching 20% for P717. The evolution of D vs. M_r of the complex at 25° and 37° is shown in *Fig. 5*. The data were fitted with an empirical equation (*Eqn. 9*).

$$D = a + \frac{b}{M_r} + \frac{c}{(M_r)^2} \quad (9)$$

Table 4. *Relative Diffusion Constants of Aqueous Solutions of the Different Compounds at Body Temperature (310 K) and Corresponding Activation Energies of Diffusion (E_D)*

Compound	D_c [$10^{-10} \text{ m}^2 \text{ s}^{-1}$]	E_D (kJ/mol)
[La(DTPA-BMA)(H ₂ O)]	33.8	18.2
[La(DOTA)(H ₂ O)] ⁻	34.1	18.4
[La(TTHA)] ³⁻	33.4	17.5
[La(DTPA-BBEA)(H ₂ O)]	33.7	18.4
[La(DTPA-BiBA)(H ₂ O)]	32.4	17.9
[La(EOB-DTPA)(H ₂ O)] ²⁻	33.0	18.9
[La(DTPA-BAA)(H ₂ O)]	33.6	19.5
[La(DTPA-BHA)(H ₂ O)]	31.1	17.7
[La(DTPA-BBzA)(H ₂ O)]	31.8	17.7
[La(MP-2269)(H ₂ O)] ⁴⁻	30.7	18.8
[La(P760)(H ₂ O)] ⁻	29.3	17.2
P717	28.0	18.4

The values of the empirical parameters a , b , and c of *Eqn. 9* are equal to 2.17×10^{-9} , 3.97×10^{-8} , and 1.01×10^{-4} , respectively, at 25° , and to 2.83×10^{-9} , 2.04×10^{-7} , and 5.80×10^{-5} , respectively, at 37° . It is worth mentioning that, as expected, the a -values are similar to those for bulk H₂O. *Eqn. 9* could, thus, be used to predict the relative diffusion constant of any complex.

The analysis of the temperature dependence of D using *Eqn. 10* gives an activation energy for diffusion (E_D) almost identical for all the complexes (*Fig. 6* and *Table 4*). Here, D^0 is the diffusion constant at infinite temperature, and R is the gas constant. An average value of $E_D = 18.2 \pm 0.6 \text{ kJ/mol}$ was calculated.

$$D = D^0 \exp\left(\frac{-E_D}{RT}\right) \quad (10)$$

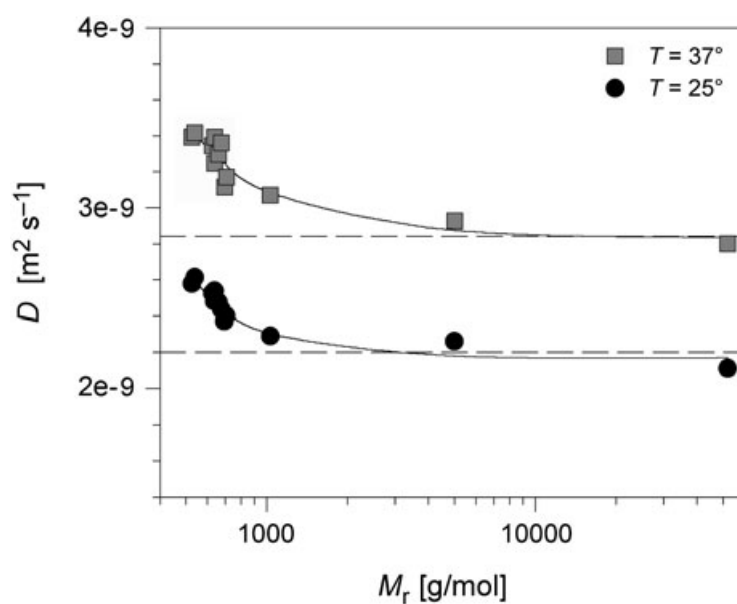


Fig. 5. Evolution of the diffusion constant with molecular weight at 25° and 37° . The dashed lines correspond to the diffusion coefficient of bulk H_2O .

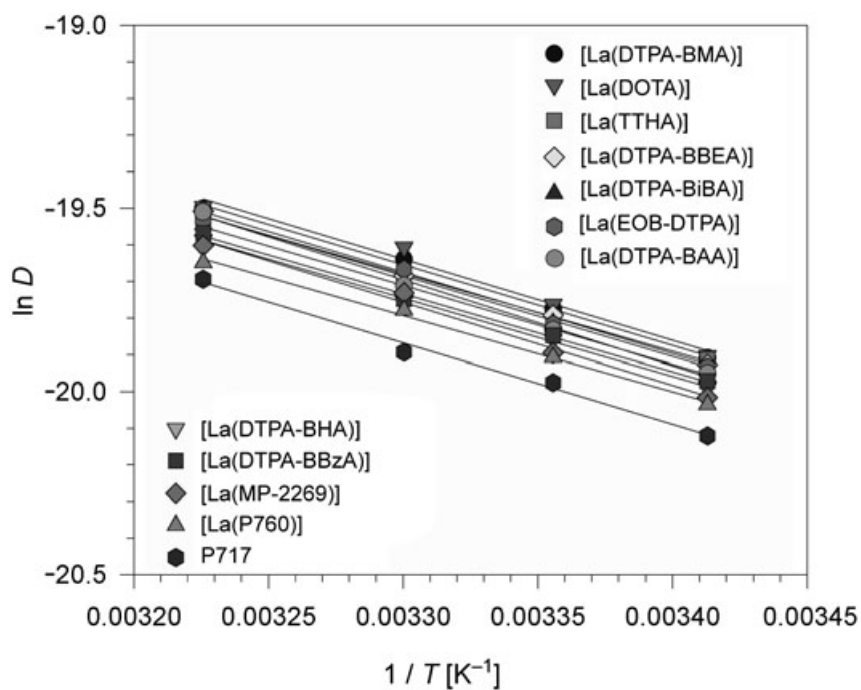


Fig. 6. Semilogarithmic plot of relative-diffusion constant vs. reciprocal temperature

Fitting of the Proton-NMRD Curves. A value for D^{310} of $3.5 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$ has been used previously in the theoretical fitting of the proton-NMRD data of the Gd^{III} complexes at 310 K. As the difference between this value and those measured for the ‘small’ complexes remains small ($\leq 18\%$), the fitted parameters should be quite similar. The fittings were performed with a distance d equal to 0.36 nm, a value of r set to 0.31 nm, and τ_{M} set to the value obtained by ^{17}O -NMR relaxometry [8][9][14][15]. The other parameters describing the inner-sphere and outer-sphere relaxivities were adjusted simultaneously (τ_{R} , τ_{SO} , τ_{V}). Since no H_2O molecule is coordinating the Gd^{3+} ion in the first coordination sphere of $[\text{Gd}(\text{TTHA})]$, only the outer-sphere relaxation was taken into account for this complex. For the other complexes, both inner-sphere and outer-sphere relaxations were included in the fitting. The τ_{R} values obtained from both fittings were very close (*Fig. 3* and *Table 5*), whereas larger differences were observed for τ_{SO} and τ_{V} . For $[\text{Gd}(\text{EOB-DTPA})]$, the previous fittings had been performed with $r = 0.281 \text{ nm}$ [8]. The new fittings were, thus, carried out with this value. The τ_{R} obtained from the fittings of the proton-NMRD curves were compared with the theoretical values obtained from *Eqns. 7* and *8*.

Table 5. Values of τ_{R} , τ_{SO} , and τ_{V} (all in ps) for Different Gadolinium Complexes. The values were derived by Proton-NMRD curve fitting at 37° (310 K) for different relative diffusion constants (D_{c}). τ_{M} is given in ns.

Complex	τ_{M}	$D_{\text{c}} (1)^{\text{a}}$			$D_{\text{c}} (2)^{\text{b}}$		
		τ_{R}	τ_{SO}	τ_{V}	τ_{R}	τ_{SO}	τ_{V}
$[\text{Gd}(\text{TTHA})]^{3-}$	–	–	250	21	–	192	14
$[\text{Gd}(\text{DTPA-BMA})(\text{H}_2\text{O})]$	970	68	113	20	68	104	18
$[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^{-}$	122	55	440	9.5	52	590	9
$[\text{Gd}(\text{DTPA-BBEA})(\text{H}_2\text{O})]$	650	86	92	19	89	90	15
$[\text{Gd}(\text{DTPA-BiBA})(\text{H}_2\text{O})]$	660	80	80	19	78	75	16
$[\text{Gd}(\text{DTPA-BAA})(\text{H}_2\text{O})]$	669	107	96	29	106	94	28
$[\text{Gd}(\text{DTPA-BHA})(\text{H}_2\text{O})]$	680	94	99	31	92	90	23
$[\text{Gd}(\text{DTPA-BBzA})(\text{H}_2\text{O})]$	454	70	108	25	72	94	17
$[\text{Gd}(\text{EOB-DTPA})(\text{H}_2\text{O})]^{2-}$	80	60	62	16	60	59	16
$[\text{Gd}(\text{MP-2269})(\text{H}_2\text{O})]^{4-}$	100	150	101	33	145	96	32
$[\text{Gd}(\text{P760})(\text{H}_2\text{O})]^{-}$	320	1700	820	13	1760	740	14

^{a)} Set to $3.5 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$. ^{b)} Experimental values from *Table 4*.

As shown in *Fig. 7a*, quite good agreement was found between fitted values and those calculated with r_0 estimated from the measured self-diffusion coefficient D_{c} . However, it should be noted that the values of τ_{R} obtained from the diffusion measurement are overestimated. Two possible explanations can be invoked. First, the coordinated H_2O molecule could have some additional mobility with respect to the whole complex. Second, the approximations regarding the translational and rotational microviscosity coefficients made in the calculation of τ_{R} from the diffusion coefficient can affect the results. For complexes of molecular weight $\leq 1000 \text{ g/mol}$, the evaluation of τ_{R} from ^2H -NMR relaxometric data [8][9] seems to agree better (*Fig. 7b*).

Conclusions. – The measurements of the diffusion coefficients of H_2O water and of diamagnetic analogues of Gd complexes by means of PFG ^1H -NMR allowed accurate

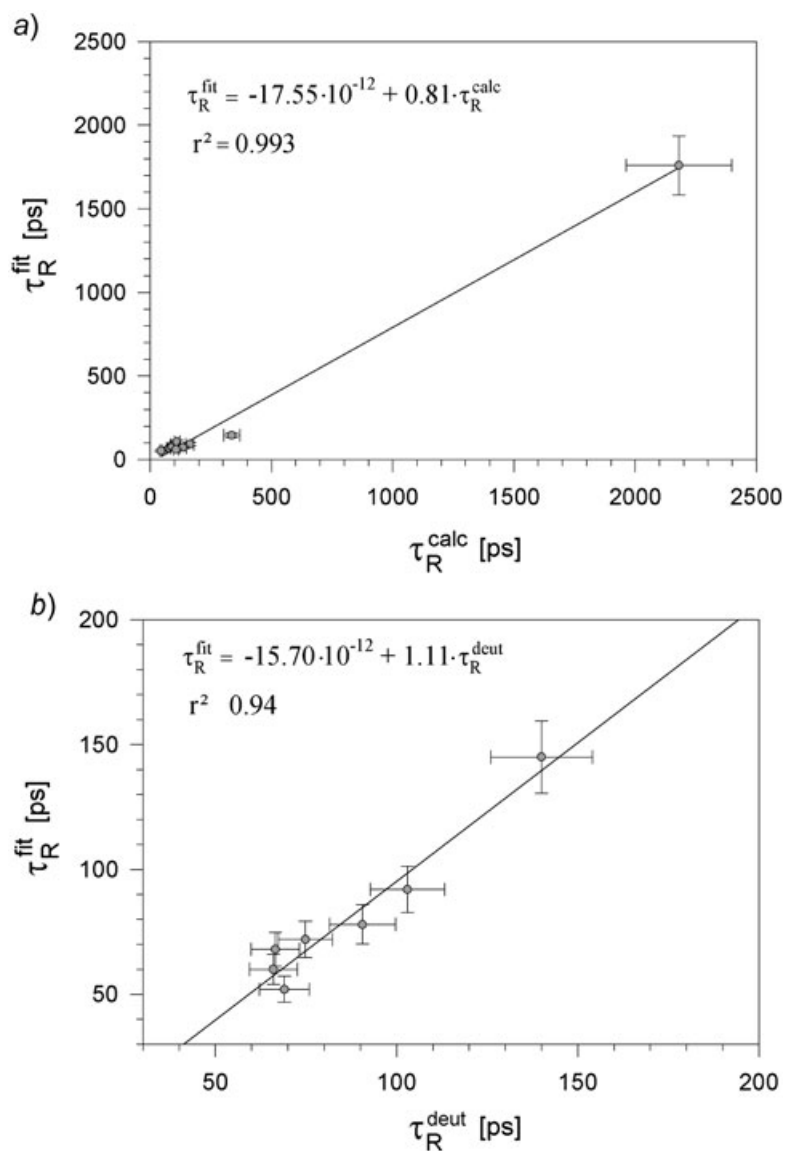


Fig. 7. Determination of τ_R values. a) Fitting of the proton-NMRD profiles vs. τ_R calculated from the molecular radius derived from D_c . b) Fitting of the proton-NMRD profiles vs. τ_R obtained from ^2H -NMR relaxation.

evaluation of the relative diffusion constant, one of the parameters involved in outer-sphere relaxation. The diffusion coefficients obtained for twelve compounds are correlated with solute size and structure, and the analysis based on the microviscosity theory of *Gierer* and *Wirtz* [13] gave an estimation of their molecular radii. For ‘small’ complexes (M_r 500–750 g/mol), the relative diffusion coefficient D_c is increased by 6 to 18% compared to the measured value for bulk H_2O . Values of $3.3 (\pm 0.1) \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$

at 37° and $2.5 (\pm 0.1) \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$ at 25° seem to be good approximations. For larger complexes, as expected, the value is close to that of pure H₂O ($D_w \approx 2.9 \times 10^{-9}$ and $2.2 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$ at 37° and 25°, resp.). These values are close to those used until now in the theoretical fittings of proton-NMRD curves, but more-accurate parameters can be obtained with the values reported in this work.

Experimental Part

The ligand of P717, DOTA, and the [La(P760)] complex were provided by *Guerbet Laboratories* (Aulnay-sous-Bois, France). The ligands MP-2269 and EOB-DTPA were gifts from Dr. *K. Adzamlı* (*Mallinckrodt*, St Louis, USA) and *Schering AG* (Berlin, Germany), resp. DTPA Bismethylamide (DTPA-BMA), DTPA bisbenzylamide (DTPA-BBzA), DTPA bisamylamide (DTPA-BAA), DTPA bisbisethylamide (DTPA-BBEA), DTPA bisisobutylamide (DTPA-BiBA), and DTPA bishexylamide (DTPA-BHA) were synthesized as previously described [9][16][17], and their La^{III} or Gd^{III} complexes were obtained by reaction with the corresponding lanthanide(III) chloride. The structure of the complexes was confirmed by mass spectrometry on a *Micromass Q-tof 2* mass spectrometer. Samples were dissolved in MeOH/H₂O 1:1 and injected at a rate of 5 $\mu\text{l}/\text{min}$. The reported mass corresponds to the most-abundant isotopic peak.

Self-diffusion coefficients were measured on a 4.7-T *Bruker Avance-200* NMR spectrometer equipped with a variable-temperature, high-resolution diffusion probe. All samples were dissolved in demineralized H₂O. Samples of 260 μl in 5-mm NMR tubes were used. The diffusion coefficients of H₂O and of the complexes were measured for the same sample. A PFG pulse sequence with H₂O presaturation was used for the determination of the diffusion coefficient (D_c) of the complex. The parameters used were $\delta = 1 \text{ ms}$ and $\Delta = 6.045 \text{ ms}$. The longitudinal relaxation time (T_1) of H₂O H-atoms was measured for each sample, and the repetition time for PFG measurements was larger or equal to three times the relaxation time of H₂O. The temperature of the sample was maintained by water circulation in the gradient coil. A total of 25 to 30 gradient strengths were used for each measurement. The calibration of the magnetic-field gradients was performed on pure H₂O.

Proton-NMRD profiles were obtained on fast-field-cycling relaxometers (*Field Cycling Systems*, Oradell, New Jersey, USA; and *Stelar*, Mede, Italy) working between 0.24 mT and 1.2 T on 0.6-ml solns. contained in 10-mm (o.d.) tubes. ¹H-NMR relaxation rates were also measured at 0.47, 0.94, and 1.4 T on *Minispec PC-120*, *PC-140*, and *mq-60* (*Bruker*, Karlsruhe, Germany). The additional relaxation rates at 4.7 or 7.05 T were obtained on *Bruker MSL-200* or *AMX-300* spectrometers. Proton-NMRD data were fitted according to the theoretical inner-sphere model described in [1] and [2], and to the outersphere contribution described in [4]. Calculations were performed with a software described in [18][19].

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