Unexpectedly Large Change of Water Exchange Rate and Mechanism on [Ln(DTPA-BMA)(H_2O)] Complexes along the Lanthanide(III) Series[1]

Dirk Pubanz, Gabriel González, D. Hugh Powell, and André E. Merbach*

Institute of Inorganic and Analytical Chemistry, University of Lausanne-BCH,
CH-1015 Lausanne, Switzerland

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We present here a ^{17}O NMR study at 1.41, 4.7, 9.4, and 14.1 T, at variable temperature and pressure of water exchange on [Ln(DTPA-BMA)(H_2O)], where Ln = Nd, Eu, Tb, Dy, and Ho and DTPA-BMA = 1,7-bis[(*N*-methylcarbamoyl)methyl]-1,4,7-triazaheptane-1,4,7-triacetate or diethylenetriaminepentaacetate−bis(methylamide). The number of inner sphere water molecules was found from chemical shift data to be one for all complexes studied. The water exchange rate is nearly constant—(4−7) × 10^5 s^{-1}—for the complexes of Nd^{3+}, Eu^{3+}, and Gd^{3+} and then takes a steep rise to reach the value of (6.0 ± 0.3) × 10^6 s^{-1} for the Ho^{3+} complex. This unexpectedly large change is rationalized in terms of a change of mechanism, which was determined from variable pressure studies. These show a changeover from an interchange activation mode for [Nd(DTPA-BMA)(H_2O)] to a limiting dissociative mechanism for the rest of the investigated complexes: the activation volume for water exchange on [Nd(DTPA-BMA)(H_2O)] is (−0.8 ± 1.6) cm^3 mol^{-1}, and for the other complexes it is between +7 and +10 cm^3 mol^{-1}. Implications for future MRI contrast agent design are discussed: we suggest that the steric crowding at the water binding site determines the mechanism and the rate of water exchange on lanthanide(III) poly(amino carboxylate) complexes.

Introduction

With the introduction of magnetic resonance imaging (MRI) to medical diagnostics, the need arose for contrast agents applicable to this technique.[5] Current MRI contrast agents for clinical use are poly(amino carboxylate) complexes of gadolinium. The fluctuating dipole−dipole interaction between the electron spin of the paramagnetic ion (Gd^{3+}) and the spins of the observed nuclei (normally water protons) accelerates T_1 and T_2 relaxation in the vicinity of the contrast agent to increase ("positive" contrast) or diminish ("negative" contrast) the intensity of the MRI signal in their vicinity. The ability of a reagent to enhance proton relaxation in aqueous solution per unit concentration is called *proton relaxivity*.

This relaxivity can be divided into two parts: (1) "outer sphere" relaxivity due to long range interactions with bulk water and (2) "inner sphere" relaxivity due to short range interactions with inner sphere water molecules, mediated by chemical exchange of water molecules from the inner sphere into the bulk. Inner sphere relaxivity depends on the rate of exchange of water protons between the inner sphere and the bulk, on the electronic relaxation rates of the metal center, and on the rotational correlation time of the complex. Current commercial MRI contrast agents bind a single water molecule in their inner coordination sphere. The "inner sphere" and "outer sphere" contributions to the proton relaxivity in these complexes are of similar magnitude.[5,6]

In early publications[5] the rate of chemical exchange of the inner sphere water molecule with the bulk was assumed to be about the same on complexes used as contrast agents as on the Gd^{3+} aqua ion[7] —(8.3 ± 1.0) × 10^8 s^{-1}—but recent NMR measurements[8,9] showed that the exchange can be between 200 and 2000 times slower for poly(amino carboxylate) complexes. These are rates of exchange for entire water molecules as determined by ^{17}O NMR and are thus lower limits for proton exchange, which is the real parameter to consider for proton relaxivity. At least around neutral pH, proton exchange occurs mainly via exchange of entire water molecules. This has been confirmed in a recent proton relaxivity study of [Gd(DTPA-BMA)(H_2O)][10] (see Figure 1 for chemical structure). The reason for this was found in the mechanism of the exchange reaction:[7−9] water exchange on the Gd $^{3+}$ aqua ion occurs via an *associative* activation mode,[7] whereas water exchange on the MRI contrast agents MAGNEVIST (Gd-DTPA, Schering), OMNISCAN, Gadodiamide (Gd-DTPA-BMA, Nycomed/Sterling Winthrop), and DOTAREM (Gd-DOTA, Guerbet) occurs via a *dissociative* pathway.[8,9] Without the assistance of the incoming water molecule in bond breaking the exchange requires a higher activation enthalpy and so is slowed down. This change in mechanism can be understood in terms of the change of the coordination number from eight for the Gd^{3+} aqua ion[11,12] to nine for the poly(amino carboxylate) complexes used as contrast agents (the multidentate ligand occupies eight sites and the inner sphere water the ninth).[13−17] For the existing commercial contrast agents, the limiting effect of the slow water

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(2) Powell, D. H.; Merbach, A. E.; Fábián, I.; Schindler, S.; van Eldik, R. *Inorg. Chem.* **1994**, *33*, 4468.
(3) Jestin, J. L.; Chottard, J. C.; Frey, U.; Laurenczy, G.; Merbach, A. E. *Inorg. Chem.* **1994**, *33*, 4277.
(4) Dadci, L.; Elias, H.; Frey, U.; Hörnig, A.; Koelle, U.; Merbach, A. E.; Paulus, H.; Schneider, J. S. *Inorg. Chem.* **1995**, *34*, 306.
(5) Lauffer, R. B. *Chem. Rev.* **1987**, *87*, 901.
(6) Koenig, S. H., Brown, R. D., III. *Prog. Nucl. Magn. Reson. Spectrosc.* **1990**, *22*, 487 and references therein.
(7) Micskei, K.; Powell, D. H.; Helm, L.; Brücher, E.; Merbach, A. E. *Magn. Reson. Chem.* **1993**, *31*, 1011.
(8) Micskei, K.; Helm, L.; Brücher, E.; Merbach, A. E. *Inorg. Chem.* **1993**, *32*, 3844.
(9) González, G.; Powell, D. H.; Tissières, V.; Merbach, A. E. *J. Phys. Chem.* **1994**, *98*, 53.
(10) Aime, S.; Botta, M.; Fasano, M.; Paoletti, S.; Anelli, P. M.; Uggeri, F.; Virtuani, M. *Inorg. Chem.* **1994**, *33*, 4707.
(11) Cossy, C.; Barnes, A. C.; Enderby, J. E.; Merbach, A. E. *J. Chem. Phys.* **1989**, *90*, 3254.
(12) Cossy, C.; Helm, L.; Powell, D. H.; Merbach, A. E. *New J. Chem.* **1995**, *19*, 27.
(13) Bryden, C. C.; Reilley, C. N.; Desreux, J. F. *Anal. Chem.* **1981**, *53*, 1418.

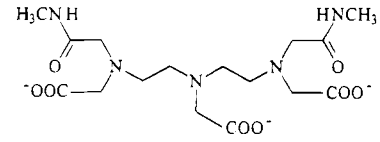

Figure 1. Structural formula of the ligand DTPA-BMA^{3-}.

exchange rates on their proton relaxivity at physiological temperature (310 K), and hence their efficacy as contrast agents, is marginal (nevertheless, this limiting effect is observable at 278 K[10]). This limiting effect will, however, be of crucial importance in the new generation of contrast agents, where the rotational correlation time τ_R is increased by increasing molecular volume or by binding to macromolecules with the aim of increasing the inner sphere relaxation.[5] Faster water exchange rates than those observed on current contrast agents will be necessary if this increase in inner sphere proton relaxation is to be translated into relaxivity. It is therefore important to understand the factors that influence the water exchange rates on lanthanide poly(amino carboxylates).

We present here a variable field, variable temperature, and variable pressure ^{17}O NMR study of water exchange on [Ln(DTPA-BMA)(H_2O)] with Ln = Nd, Eu, Tb, Dy, Ho. We started by varying the metal center, because it allows fine tuning of the ionic radius across the lanthanide series with isostructural ligation.[14,15,17] Thus a single and well-controlled feature of the complex is varied, and unambiguous conclusions can be drawn. As the ligand we choose DTPA-BMA because, of the ligands used for current contrast agents, it has the slowest water exchange on its gadolinium complex.[9]

Experimental Section

Sample Preparation. The poly(amino carboxylate) ligand H_3-DTPA-BMA·$2H_2O$ was provided by Nycomed, Salutar Inc. and was used without further purification. The lanthanide oxides (99.99%) were obtained from NUCOR Corporation, Phoenix; perchloric acid (72%, p.a.) and sodium hydroxide (p.a.) from Merck, Darmstadt, and ^{17}O-enriched water (10% $H_2{}^{17}O$) from Yeda R&D Co., Rehovot, Israel. The samples were prepared by weight. About 10 mmol of Ln_2O_3 was dissolved in 10 g of bidistilled water by adding a slight excess of perchloric acid (with stirring and refluxing where necessary). The solutions were filtered to remove undissolved oxide, and the concentrations of the resulting lanthanide perchlorate stock solutions were determined by titration with EDTA using xylenol orange indicator and the procedure described by Brunisholz *et al.*[18] A 2 mmol sample of H_3DTPA-BMA was partly deprotonated by adding 3 mmol of NaOH in the form of a 1 M solution. To this was added a stoichiometric amount (allowing for 1–2% excess ligand to avoid free metal) of lanthanide perchlorate stock solution. The absence of free lanthanide in the solution was verified using xylenol orange indicator. The pH—measured with a combined glass electrode, calibrated with Metrohm buffer solutions—was then adjusted to about 6.2 by adding 1 m sodium hyroxide. To improve sensitivity, ^{17}O-enriched water was added, to produce solutions with about 1% ^{17}O enrichment. The molalities of [Ln(DTPA-BMA)(H_2O)] and the mole fraction of the bound water are given in Table 1.

^{17}O NMR Measurements. For the variable field, variable temperature studies, the samples were sealed in glass spheres fitting into 10 mm NMR tubes to avoid the necessity of susceptibility corrections to the chemical shift.[19] The measurements were performed at at least three different fields per lanthanide using Bruker AC-200 (4.7 T, 27.1 MHz), AM-400 (9.4 T, 54.2 MHz), and AMX2-600 (14.1 T, 81.4 MHz) spectrometers, the data at 1.41 T (8.14 MHz) being obtained with an electromagnet connected to the Bruker AC-200 console. Bruker VT-1000 and VT-2000 temperature control units were used to stabilize the temperature, which was measured using a substitution technique.[20] Variable pressure measurements up to 200 MPa were performed on a Bruker AM-400 spectrometer equipped with a home-built probe head.[21] Temperature was controlled by circulating fluid from a temperature bath, and was measured with a built-in Pt resistor. Transverse relaxation rates were measured by the Carr–Purcell–Meiboom–Gill spin echo technique.[22] The relaxation rates and, for the variable temperature measurements, the chemical shifts were measured for the solutions containing the different complexes and for a reference solution (1% ^{17}O enriched water containing 0.9 *m* perchloric acid): thus, the diamagnetic shift was neglected.

Table 1. Molalities, Mole Fractions of Inner Sphere Water, and pH of [Ln(DTPA-BMA)(H_2O)] Solutions Used for ^{17}O-NMR Study of Water Exchange Parameters

solution	*m*(Ln) (mol kg^{-1})	$P_m \times 10^3$	pH
[Nd(DTPA-BMA)(H_2O)]	$0.400^a/0.329^b$	$7.38^a/5.94^b$	$6.01^a/6.20^b$
[Eu(DTPA-BMA)(H_2O)]	$0.190^{a,b}$	$3.42^{a,b}$	$6.15^{a,b}$
[Tb(DTPA-BMA)(H_2O)]	$0.509^a/0.279^b$	$9.12^a/3.95^b$	$6.12^a/6.00^b$
[Dy(DTPA-BMA)(H_2O)]	$0.144^a/0.186^b$	$2.59^a/3.35^b$	$6.16^a/6.28^b$
[Ho(DTPA-BMA)(H_2O)]	$0.200^a/0.163^b$	$3.61^a/2.93^b$	$6.29^a/6.23^b$

[a] Solutions used for the variable temperature ^{17}O NMR studies. [b] Solutions used for the variable pressure ^{17}O NMR studies.

Results

Variable Temperature and Field. From the measured transverse relaxation rates and angular frequencies for the solutions of the complexes, $1/T_2$ and ω, and for the acidified water reference reference $1/T_{2A}$ and ω_A, one can calculate reduced transverse relaxation rates and chemical shifts, $1/T_{2r}$ and $\Delta\omega_r$, which may be written as in eqs 1 and 2,[23] where $1/T_{2m}$

$$\frac{1}{T_{2r}} = \frac{1}{P_m}\left[\frac{1}{T_2} - \frac{1}{T_{2A}}\right] = \left(\frac{1}{\tau_m}\right)\frac{T_{2m}{}^{-2} + \tau_m{}^{-1}T_{2m}{}^{-1} + (\Delta\omega_m)^2}{(\tau_m{}^{-1} + T_{2m}{}^{-1})^2 + (\Delta\omega_m)^2} + \frac{1}{T_{2os}} \quad (1)$$

$$\Delta\omega_r = \frac{1}{P_m}(\omega - \omega_A) = \frac{\Delta\omega_m}{(1 + \tau_m T_{2m}{}^{-1})^2 + \tau_m^2(\Delta\omega_m)^2} + \Delta\omega_{os} \quad (2)$$

is the transverse relaxation rate in the inner sphere water, $\Delta\omega_m$ is the chemical shift difference between inner sphere water and bulk water (in the absence of paramagnetic interaction with the bulk water) and P_m is the mole fraction of inner sphere water. The exchange rate, k_{ex}, of water molecules between the inner sphere and the bulk is the inverse of the residence time, $1/\tau_m$, of water molecules in the inner sphere. The total outer sphere contributions to the reduced relaxation rate and chemical shift are represented by $1/T_{2os}$ and $\Delta\omega_{os}$.

In a first instance, the chemical shift of inner sphere water molecules, $\Delta\omega_m$, was represented by adjustment to the empirical power series in eq 3, where A_1 and A_2 are empirical constants and B is the magnetic field in T.[24] For all except the Eu^{3+} complex, the first term was sufficient to describe the observed

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(14) Peters, J. A. *Inorg. Chem.* **1988**, *27*, 4686.

(15) Geraldes, C. F. G. C.; Urbano, A. M.; Hoefnagel, M. A.; Peters, J. A. *J. Chem. Soc., Chem. Commun.* **1991**, *9*, 656.

(16) Ehnebom, L.; Pedersen, B. F. *Acta Chem. Scand.* **1992** , *46*, 126.

(17) Geraldes, C. F. G. C.; Urbano, A. M.; Hoefnagel, M. A.; Peters, J. A. *Inorg. Chem.* **1993**, *32*, 2426.

(18) Brunisholz, G.; Randin, M. *Helv. Chim. Acta* **1959**, *42*, 1927.

(19) Hugi, A. D.; Helm, L.; Merbach, A. E. *Helv. Chim. Acta* **1985**, *68*, 508.

(20) Amman, C.; Meyer, P.; Merbach, A. E. *J. Magn. Reson.* **1982**, *46*, 319.

(21) Frey, U.; Helm, L.; Merbach, A. E. *High Pressure Res.* **1990**, *2*, 297.

(22) Meiboom, S.; Gill, D. *Rev. Sci. Instrum.* **1958**, *29*, 688.

(23) Swift, T. J.; Connick, R. E. *J. Chem. Phys.* **1962**, *37*, 307.

(24) Cossy, C.; Helm, L.; Merbach, A. E. *Inorg. Chem.* **1989**, *28*, 2699.

$$\Delta\omega_m = \left[\frac{A_1}{T} + \frac{A_2}{T^2}\right]B \qquad (3)$$

temperature dependence of the shifts. A detailed analysis of the shifts will be provided below. We assume that the outer sphere contribution to $\Delta\omega_r$ has a temperature dependence similar to $\Delta\omega_m$ and is given by eq 4, where C_{os} is an empirical constant.

$$\Delta\omega_{os} = C_{os}\Delta\omega_m \qquad (4)$$

The transverse relaxation rate of the bound water $1/T_{2m}$ was fitted to a single exponential as in eq 5, where E_m is the activation energy of the relaxation of the bound water, R is the universal gas constant, and $1/T_{2m}{}^{298}$ is the relaxation rate of the bound water at 298.15 K.

$$\frac{1}{T_{2m}} = \frac{1}{T_{2m}{}^{298}}\exp\left[\frac{E_m}{R}\left(\frac{1}{298.15} - \frac{1}{T}\right)\right] \qquad (5)$$

The exchange rate k_{ex} (or inverse binding time $1/\tau_m$) of water molecules in the inner sphere should obey the Eyring equation (6).

$$\frac{1}{\tau_m} = k_{ex} = \frac{k_B T}{h}\exp\left[\frac{\Delta S^{\ddagger}}{R} - \frac{\Delta H^{\ddagger}}{RT}\right] = \frac{k_{ex}^{298}T}{298.15}\exp\left[\frac{\Delta H^{\ddagger}}{R}\left(\frac{1}{298.15} - \frac{1}{T}\right)\right] \qquad (6)$$

Figures 2–6 show the values of $1/T_{2r}$ and $\Delta\omega_r$, calculated from the measurements for the complexes mentioned above, as a function of temperature. The slope of $\ln(1/T_{2r})$ versus $1/T$ is negative at low temperature. This is characteristic of the "slow exchange" limit ($k_{ex} \ll 1/T_{2m}$ or $(\Delta\omega_m)^2/k_{ex}$), of eqs 1 and 2, where eq 7 is valid. Within this region, the exchange rate can

$$\frac{1}{T_{2r}} = k_{ex} + \frac{1}{T_{2os}};\ \Delta\omega_r = \Delta\omega_{os} \qquad (7)$$

be determined directly from the relaxation rates, provided that the outer sphere contribution can be neglected. At high temperatures the slope of $\ln(1/T_{2r})$ versus $1/T$ is positive. This is characteristic of the "fast exchange" limit ($k_{ex} \gg 1/T_{2m}$ and $(\Delta\omega_m)^2/k_{ex}$), where eqs 1 and 2 become eq 8. In this region,

$$\frac{1}{T_{2r}} = \frac{1}{T_{2m}} + \frac{(\Delta\omega_m)^2}{k_{ex}} + \frac{1}{T_{2os}} \qquad \Delta\omega_r = \Delta\omega_m + \Delta\omega_{os} \quad (8)$$

the exchange rate can be determined from the field dependent part of $\ln(1/T_{2r})$, *via* the $(\Delta\omega_m)^2/k_{ex}$ term, provided that $\Delta\omega_m$ can be obtained from $\Delta\omega_r$. The maxima in $\ln(1/T_{2r})$ correspond to points of inflection in $\Delta\omega_r$: this is characteristic of the changeover between these two limiting regions and confirms the presence of an exchange phenomenon.

In an earlier publication,[8] we made a comparison between the ^{17}O relaxivities of [Gd(DTPA)(H$_2$O)]$^{2-}$ and [Gd(DOTA)(H$_2$O)]$^-$ on one hand, and [Gd(TETA)]$^-$ on the other, which does not contain water in its inner coordination sphere and thus can act only by an outer sphere mechanism: the latter complex had negligible ^{17}O relaxivity in comparison to the first two complexes, allowing us therefore to neglect $1/T_{2os}$ in eqs 1, 7, and 8.

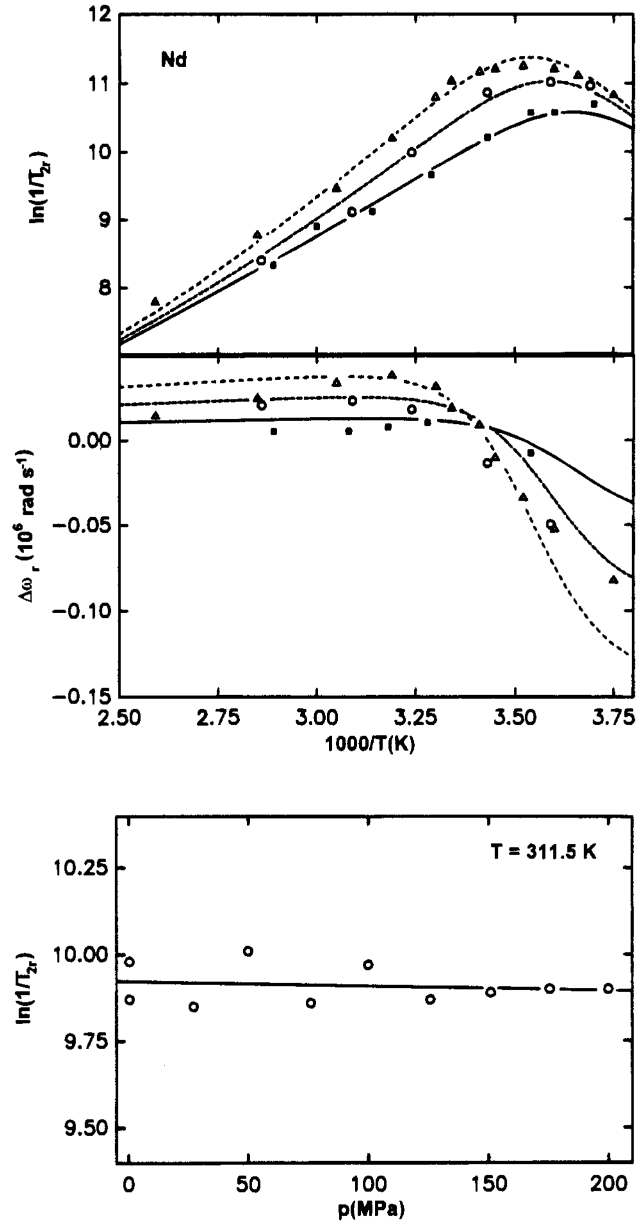

Figure 2. Temperature dependence of reduced ^{17}O transverse relaxation rates $\ln(1/T_{2r})$, chemical shifts $\Delta\omega_r$, and pressure dependence of reduced ^{17}O transverse relaxation rates for [Ln(DTPA-BMA)(H$_2$O)] complexes with Ln = Nd at 1.41 (▼), 4.7 (■), 9.4 (○), and 14.1 T (△). The lines represent simultaneous least squares fits to eqs 1–6 for the variable temperature ^{17}O NMR data and to eqs 1, 3, 5, 11, and 12 for the variable pressure ^{17}O NMR data.

A simultaneous least squares fit of eqs 1–6 yielded values for the water exchange rates, enthalpies and entropies of activation as well as the empirical parameters A_1, A_2 and C_{os}, describing the chemical shift, the activation energy of bound water relaxation E_m, and the relaxation rate of the bound water at 298.15 K, $1/T_{2m}{}^{298}$, which are given in Table 2. The errors shown are statistical errors: the associated systematic errors might be greater, especially for the entropies of activation. Entropies and enthalpies of activation as determined from NMR in paramagnetic systems are acquired from variable temperature studies, and thus stem from data that are dependent on several parameters (T_{2m}, $\Delta\omega_m$, τ_m, T_{2os}) with dominance that varies over the covered temperature region.[25,26] Together with the strong correlation of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ this leads to a systematic uncertainty

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(25) Newman, K. E.; Meyer, F. K.; Merbach, A. E. *J. Am. Chem. Soc.* **1979**, *101*, 1470.

(26) Merbach, A. E. Kinetics of Solvent Exchange at High Pressure. In *High Pressure Chemistry and Biochemistry*; van Eldik, R., Jonas, J., Eds.; D. Reidel Publishing Company: Dordrecht, The Netherlands, 1987; pp 311–331.

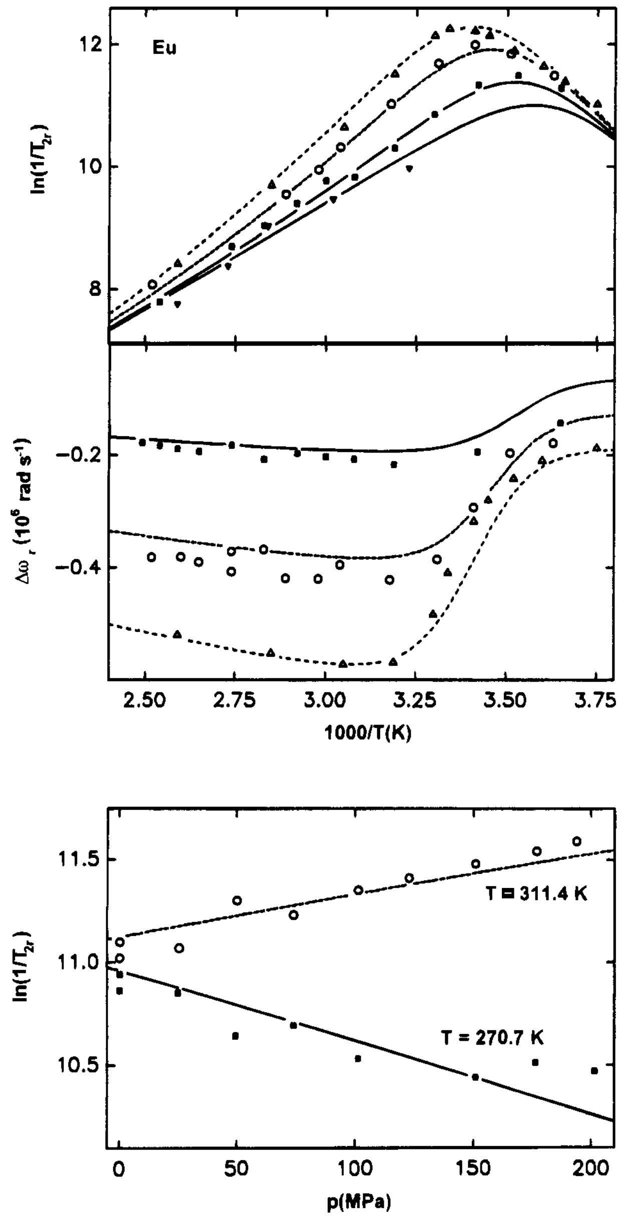

Figure 3. Same as Figure 2, but for Ln = Eu.

to the determination of the entropy that restricts confidence in its use to draw mechanistic conclusions, although activation entropies usually mimic the trends in activation volumes (*vide infra*). The activation volumes are determined at a fixed temperature, chosen deliberately for the well-defined dominance of τ_m, and therefore give a much more significant indication of the mechanism than do the entropies.

Each of the plots of the variable temperature measurements in Figures 2–6 shows a kinetic region and a fairly large field effect in the fast exchange region, so the values for $k_{ex}{}^{298}$ of the Nd^{3+}, Eu^{3+}, Tb^{3+}, Dy^{3+}, and Ho $^{3+}$ complexes are well determined. We were not able to fit the variable temperature data obtained for the Pr^{3+}, Sm^{3+}, and Tm^{3+} complexes to the full set of eqs 1–6 due to the absence of both the kinetic region and the field effect in these cases. But the absence of these effects alows us to estimate *lower limits* of $k_{ex}{}^{298}$ of 1×10^6 s^{-1} for [Pr(DTPA-BMA)(H_2O)], $0.5 \times 10^6 s^{-1}$ for [Sm(DTPA-BMA)(H_2O)], and 15×10^6 s^{-1} for [Tm(DTPA-BMA)(H_2O)].

Good fits to the chemical shift data were obtained with only the linear term A_1/T for all the complexes except [Eu(DTPA-BMA)(H_2O)], which needed the quadratic term A_2/T^2. The standard deviation of the parameter A_2 is of the same order of

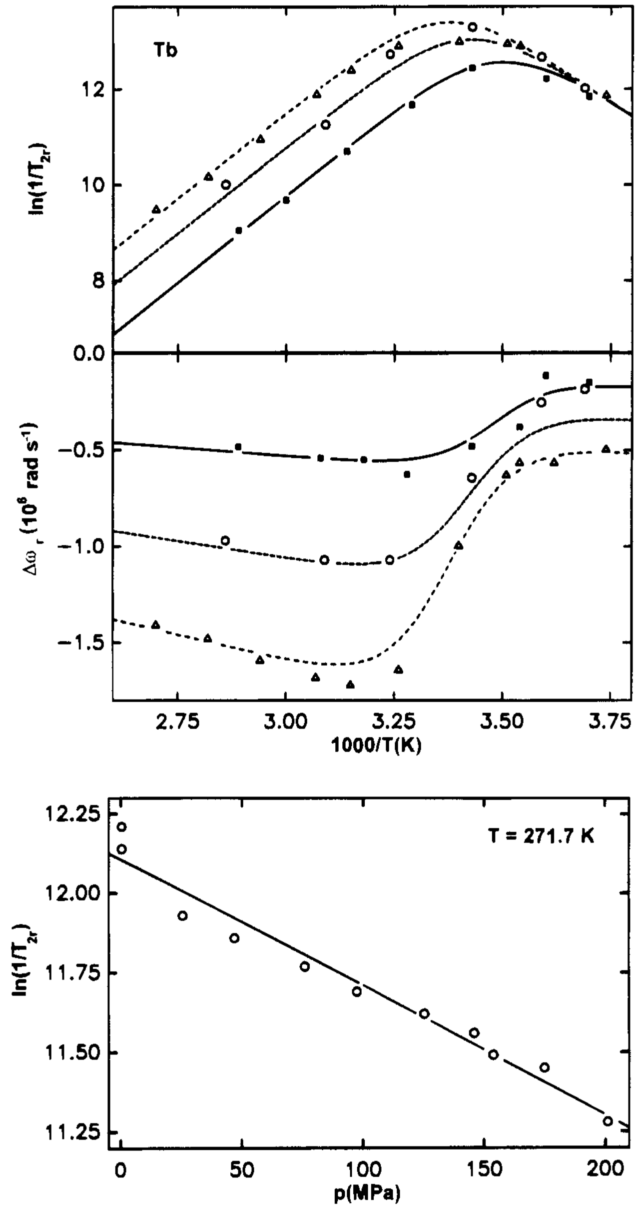

Figure 4. Same as Figure 2, but for Ln = Tb.

magnitude as the parameter itself, but without this term no satisfactory fit to the chemical shift data could be obtained. This is most probably due to the change in population of the electronic states with temperature. The Eu^{3+} ion is paramagnetic in virtually all excited states that are assessable at convenient temperatures and some of those excited states do contribute to its paramagnetic behavior at room temperature, which accounts for its peculiar chemical shift behavior.

We now consider the chemical shift in more detail. At high temperatures, the inner sphere contribution to $\Delta\omega_r$ is dominated by the chemical shift of the bound water, which is determined by the hyperfine coupling between the electron spin of the paramagnetic centre and the ^{17}O nucleus *via* the sum of a contact and a pseudo contact contribution[27,28] as in eq 9, where $A/\hbar$ is

$$\Delta\omega_m = \frac{\mu_B B}{3k_B T}\left(\frac{A}{\hbar}\right)\langle S_z\rangle + C_m{}^D G_i \qquad (9)$$

a hyperfine coupling constant, assumed independent of lan-

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(27) Granot, J.; Fiat, D. *J. Magn. Res.* **1975**, *19*, 372.

(28) Lewis, W. B.; Jackson, J. A.; Lemons, J. F.; Taube, H. *J. Chem. Phys.* **1962**, *36*, 694.

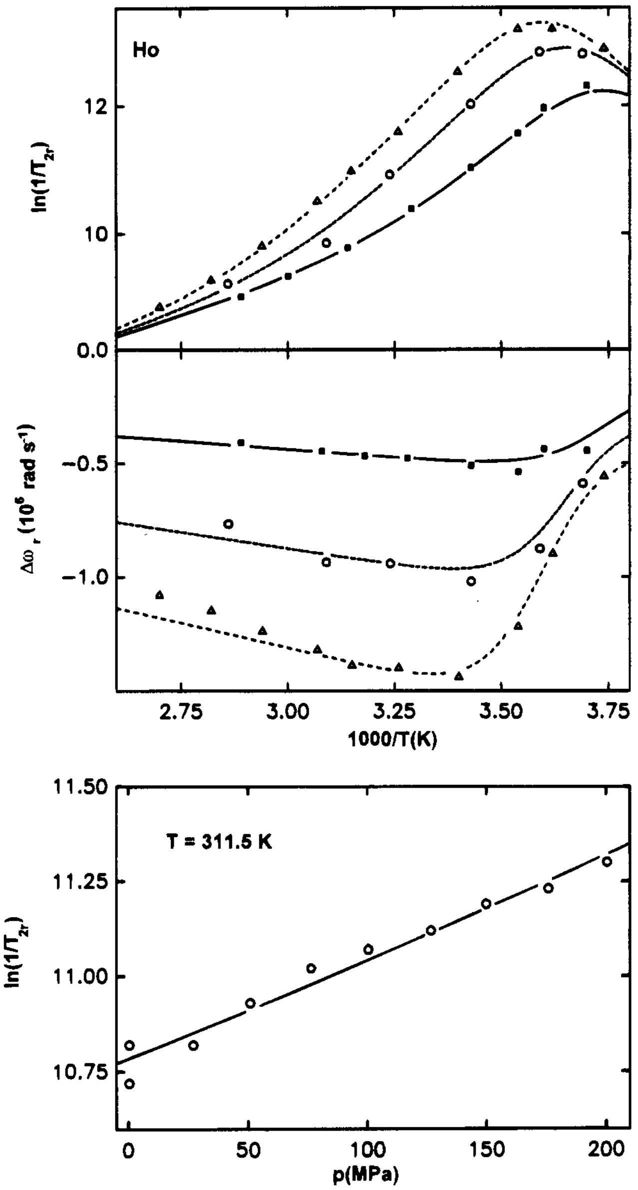

Figure 5. Same as Figure 2, but for Ln = Dy.

thanide, temperature and field strength. G_i is a structural constant, assumed independent of lanthanide, temperature, and field strength, and C_m^D describes the lanthanide dependent part of the pseudocontact shift. $\langle S_z\rangle$[29] has been taken from Golding and Halton,[32] and C_m^D from *Golding* and Pyykkö.[33] Equation 9 can be rearranged to eq 10. A plot of $\Delta\omega_m/C_m^D$ versus $\langle S_z\rangle/$

$$\frac{\Delta\omega_m}{C_m^D} = \frac{\mu_B B}{3k_B T}\left(\frac{A}{\hbar}\right)\frac{\langle S_z\rangle}{C_m^D} + G_i \qquad (10)$$

C_m^D should be a straight line with slope $A/\hbar$ and intercept G_i provided the structural constants $A/\hbar$ and G_i do not change across the series of lanthanides studied. Figure 7 shows such a plot using the values of $\Delta\omega_m$ at 300 K derived from our data using

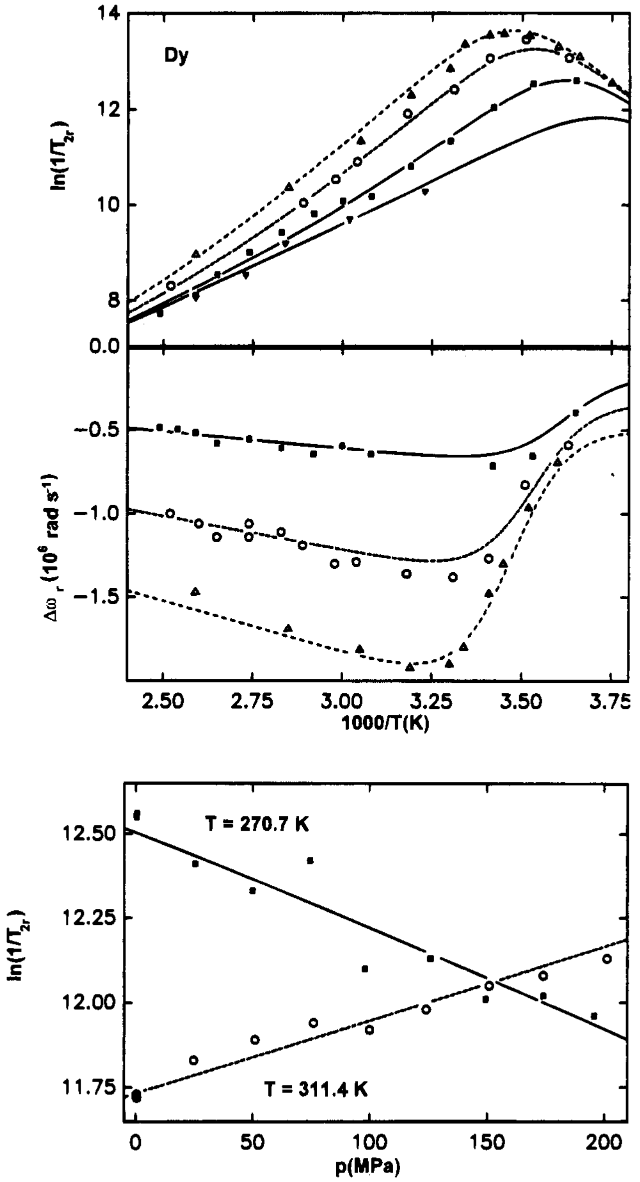

Figure 6. Same as Figure 2, but for Ln = Ho.

eq 3 and the values of A_1 and A_2 in Table 2. The fact that a straight line is obtained is an indication that these lanthanide complexes can be considered isostructural. The fitted value of $A/\hbar$ is $(-3.86 \pm 0.07) \times 10^6$rad/s, which can be compared with values obtained for Gd^{3+} poly(amino carboxylate) complexes such as $[Gd(DTPA)(H_2O)]^{2-}$ $((-3.8 \pm 0.2) \times 10^6\text{rad/s})^8$, $[Gd(DOTA)(H_2O)]^-$ $((-3.4 \pm 0.3) \times 10^6\text{rad/s})^8$, and [Gd(DTPA-BMA)($H_2O$)] $((-3.6 \pm 0.3) \times 10^6\text{rad/s})^9$ and suggests that our assumption of one inner sphere water molecule is correct.

Variable Pressure. The pressure dependence of the exchange rate can be described by eq 11,[34] where P is the pressure,

$$\frac{1}{\tau_m} = k_{ex} = k_0^T \exp\left[-\frac{\Delta V_0^\ddagger}{RT}P + \frac{\Delta\beta^\ddagger}{2RT}P^2\right] \qquad (11)$$

k_0^T the exchange rate at temperature T and zero (effectively ambient) pressure, $\Delta V_0^\ddagger$ the activation volume at temperature T and zero pressure, and $\Delta\beta^\ddagger$ the compressibility coefficient of activation. Here $\Delta\beta^\ddagger$ is taken as zero, since the pressure dependence of $\ln(k_{ex})$ was found to be linear within statistical

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(29) In previous publications[30,31] we have used the approximation $\langle S_z\rangle = g_l(g_l - 1)J(J + 1)$. At 300 K, this approximation is good to within 2% for Gd^{3+} and the heavier trivalent lanthanide cations.

(30) Powell, D. H.; Favre, M.; Graeppi, N.; Pubanz, D.; Merbach, A. E. *J. Alloys Comd.*, in press.

(31) Graeppi, N.; Powell, D. H.; Laurenczy, G.; Zékány, L.; Merbach, A. E. *Inorg. Chim. Acta*, in press.

(32) Golding, R. M.; Halton, M. P. *Aust. J. Chem.* **1972**, *25*, 2577.

(33) Golding, R. M.; Pyykkö, P. *Mol. Phys.* **1973**, *26*, 1389.

(34) van Eldik, R.; Merbach, A. E. *Contents Inorg. Chem.* **1992**, *12*, 341.

Table 2. Kinetic Parameters[a] of Water Exchange on [Ln(DTPA-BMA)(H_2O)] Complexes Determined from ^{17}O NMR Studies at Variable Temperature and Pressure

parameter	Nd	Eu	Gd[b]	Tb	Dy	Ho
k_{ex}^{298} (10^6 s^{-1})	0.53 ± 0.04	0.66 ± 0.04	0.43 ± 0.02	1.61 ± 0.10	3.53 ± 0.18	5.98 ± 0.30
$\Delta H^‡$ (kJ mol^{-1})	43.4 ± 2.2	49.2 ± 1.6	46.6 ± 1.3	50.3 ± 1.5	48.9 ± 0.9	54.2 ± 1.0
$\Delta S^‡$ (J K^{-1} mol^{-1})	10.2 ± 7.4	31.5 ± 5.4	18.9 ± 4.0	42.6 ± 5.1	44.4 ± 3.1	66.6 ± 3.4
A_1 (10^6rad s^{-1}K T^{-1})	3.41 ± 0.13	−14.1 ± 3.7		−28.0 ± 1.3	−34.0 ± 0.9	−22.8 ± 0.5
A_2 (10^9rad s^{-1} K^2 T^{-1})	0	1.52 ± 1.09		0	0	0
C_{os}	−0.74 ± 0.14	0.42 ± 0.07	0.13 ± 0.06	0.35 ± 0.05	0.27 ± 0.03	0.36 ± 0.03
E_m (kJ mol^{-1})	−24.9 ± 1.3	−28.6 ± 0.9		−61.6 ± 6.6	−28.2 ± 1.1	−17.0 ± 1.3
$1/T_{2m}^{298}$ (10^4 s^{-1})	1.65 ± 0.10	4.04 ± 0.25		10.1 ± 2.2	4.71 ± 0.38	2.06 ± 0.15
$\Delta V^‡$ (cm^3 mol^{-1})	−0.8 ± 1.6	8.5 ± 0.7	7.3 ± 0.2	9.8 ± 0.6	7.3 ± 0.5	9.4 ± 0.6

[a] Errors quoted correspond to 1 standard deviation in the calculations. [b] See ref 8.

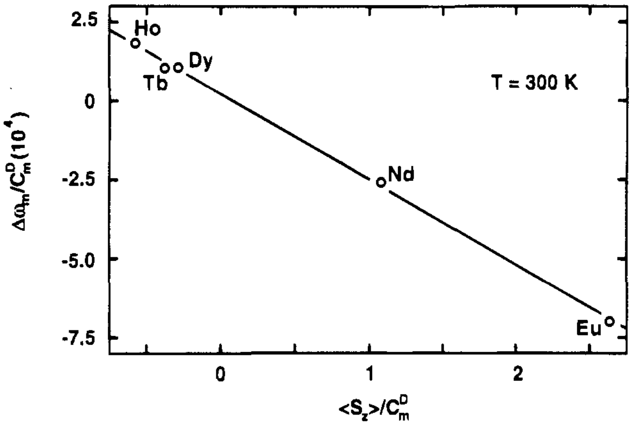

Figure 7. Plot of $\Delta\omega_m/C_m^D$ versus $\langle S_z\rangle/C_m^D$ as obtained from variable temperature ^{17}O NMR measurements of [Ln(DTPA-BMA)(H_2O)] solutions at 9.4 T. The slope delivers a hyperfine coupling constant of (−3.86 ± 0.07) × 10^6 rad s^{-1}.

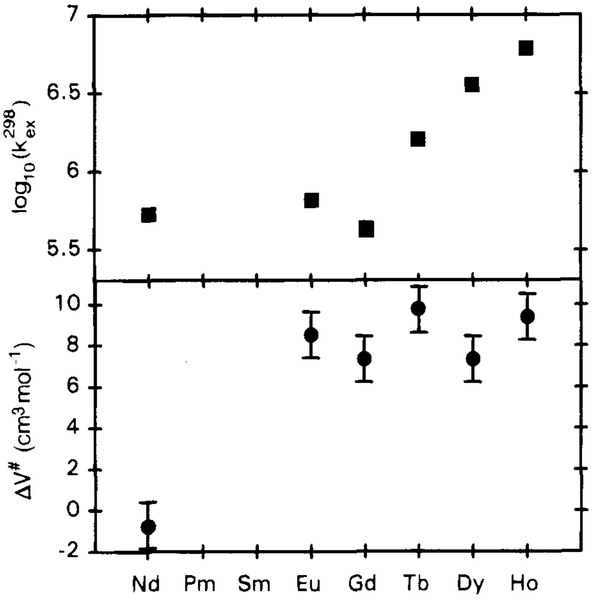

Figure 8. Synopsis of water exchange rates k_{ex}^{298} and activation volumes $\Delta V^‡$ of water exchange on the DTPA-BMA complexes of the trivalent cations of Nd, Eu, Gd, Tb, Dy, and Ho. It is generally accepted that the determination of $\Delta V^‡$ is subject to an experimental uncertainty of 10% or ±1 cm^3 mol^{-1}, whichever is the greatest.[36] The error bars of the activation volumes correspond to this systematic error and not to 1 standard deviation in the calculation.

error in previous studies[8,9,34,24] (see Figures 2−6 for the plots). Similarly, the scalar coupling constant $A/\hbar$ was previously found to be independent of pressure,[24] so we assumed that the chemical shift $\Delta\omega_m$ was independent of pressure.

In the fitting we included a possible pressure dependence of the bound water relaxation rate $1/T_{2m}$ as shown in eq 12. Fixing

$$\frac{1}{T_{2m}} = \frac{1}{T_{2m}^{\ 0}}\exp\left[-\frac{\Delta V_m^{\ ‡}}{RT}P\right] \tag{12}$$

$\Delta V_m^‡$ at values of ±5 cm^3 mol^{-1} did not alter the values in Table 2 (within statistical error). The simultaneous least squares fit of eqs 1, 3, 5, 11, and 12 yielded values for the activation volume of water exchange $\Delta V^‡$, and the water exchange rate at the chosen temperature and zero pressure k_0^T.

Discussion

The water exchange kinetic data for the [Ln(DTPA-BMA)-(H_2O)] complexes studied here, and for [Gd(DTPA-BMA)-(H_2O)][9] are summarized in Figure 8. The most striking feature is the large increase of k_{ex} by 1 order of magnitude along the series from Gd^{3+} to Ho^{3+}. The activation volumes between +7 and +10 cm^3 mol^{-1} for the DTPA-BMA complexes of Gd^{3+} to Ho^{3+} can be compared to the value of +7.2 cm^3 mol^{-1} for the Ni^{2+} aqua ion (I_d mechanism),[35] and show that the water exchange reaction takes place via a limiting dissociative D or a strongly dissociatively activated interchange I_d mechanism. The coordination number of the complexes studied in solution is nine.[13−17] In a limiting dissociative D mechanism, therefore, the reaction passes via an intermediate of coordination number 8. Looking at the lanthanide(III) aqua ions, one observes a change in coordination number from 9 to 8 along the series, caused by steric crowding of the first coordination sphere due to the decreasing ionic radius. In analogy, one might expect that for the DTPA-BMA complexes the decrease in ionic radius would reduce the free energy required to reach the eight-coordinate intermediate (stabilization of the eight coordinate species and/or destabilization of the nine-coordinate one) and hence increase the rate of water exchange. Extrapolated beyond the end of the lanthanide series, this trend would lead to an equilibrium between coordination numbers 9 (ligand plus one bound water molecule) and 8 (ligand without water in the inner coordination sphere). The dramatic increase of k_{ex}^{298} from Gd^{3+} to Ho^{3+}, together with the large positive activation volumes, is therefore strong evidence for a limiting dissociative D mechanism. The relative stabilization of the eight-coordinate intermediate with decreasing ionic radius dominates over the increased difficulty of dissociation with increased charge density. For the Nd^{3+}, Eu^{3+}, and Gd^{3+} complexes the exchange rate is nearly constant (unfortunately, it was not possible to measure exchange rates for the Pr^{3+}, Sm^{3+}, or Tm^{3+} complexes, as the chemical shifts produced by these lanthanides were too small).

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(35) Ducommun, Y.; Newman, K. E.; Merbach, A. E. *Inorg. Chem.* **1980**, *19*, 3696.

(36) Hugi, A. D.; Helm, L.; Merbach, A. E. *Helv. Chim. Acta* **1985**, *68*, 508.

The near-zero activation volume for the Nd^{3+} complex indicates an interchange I mechanism, where the incoming water molecule enters the inner-sphere simultaneously with the outgoing water molecule leaving in a synchronous process. For such a mechanism, there is no reason to expect a large variation for the exchange rate as the ionic radius decreases along the the series. One does expect, however, that decreasing ionic radius will favor a dissociatively activated interchange I_d mechanism, where both incoming and outgoing water molecules are relatively distant at the transition state, which therefore resembles the eight coordinate intermediate in a D mechanism. It seems likely that a strongly dissociatively activated I_d mechanism operates for the Eu^{3+} complex. The exchange rate is not decreased compared to Gd^{3+}, since the disfavoring of the dissociative activation process with increased ionic radius is compensated by the participation of the incoming water molecule at the transition state.

The exchange rate and activation volume results indicate a progressive change from I to I_d to D mechanisms along the lanthanide series, with a dramatic variation of exchange rate along the series for the D mechanism. This conclusion is supported by the activation entropies, which increase along the series due to the increasingly dissociative nature of the exchange mechanism.

These results are helpful in the interpretation of the variation of water exchange rates observed on Gd^{3+}–poly(amino carboxylates). In particular, water exchange rates and activation volumes have been measured for the three commercial contrast agents $[Gd(DTPA)(H_2O)]^{2-}$, $k_{ex}^{298} = (4.1 \pm 0.3) \times 10^6\ s^{-1}$, $\Delta V^{\ddagger} = (12.5 \pm 0.2)\ cm^3\ mol^{-1}$,[8] $[Gd(DOTA)(H_2O)]^{-}$, $k_{ex}^{298} = (4.8 \pm 0.4) \times 10^6\ s^{-1}$, $\Delta V^{\ddagger} = (10.5 \pm 0.2)\ cm^3\ mol^{-1}$,[8] and [Gd(DTPA-BMA)($H_2O$)], $k_{ex}^{298} = (4.3 \pm 0.2) \times 10^5\ s^{-1}$, $\Delta V^{\ddagger} = (7.3 \pm 0.2)\ cm^3\ mol^{-1}$.[9] The activation volumes indicate dissociatively activated D or I_d mechanisms on these three nine-coordinate complexes. It was, therefore, unclear why the exchange rate for [Gd(DTPA-BMA)(H_2O)] is an order of magnitude slower than that for the other complexes. We suggest the same reason to account for the differences in exchange rate between the various Gd^{3+} complexes that accounts for the rise in k_{ex} along the series of [Ln(DTPA-BMA)(H_2O)] complexes: increased steric crowding of the first coordination sphere (i.e. the water binding site) decreases the free energy gap between the nine-coordinate ground state and the eight-coordinate transition state. Again, an analogy can be drawn to the lanthanide aqua ions, in that water exchange is fastest where eight- and nine-coordinate species are in equilibrium.

This has important implications for the design of new Gd^{3+}-based contrast agents, where slow water exchange rates may limit the transfer of improved inner sphere relaxation into relaxivity. If the water exchange rate is too slow, and the activation volume indicates a dissociatively activated exchange mechanism, the exchange rate could be increased by modifying the ligand in such a way as to increase the crowding at the water binding site. We therefore have the first indications of how to "fine-tune" water exchange rates to optimize contrast agent performance.

Conclusion

The water exchange rate and thus the relaxivity of lanthanide DTPA-BMA complexes strongly depend on the size of the lanthanide. The trend observed, together with the activation volumes, indicates that the steric crowding of the water binding site determines both mechanism and rate of water exchange. In order to receive the full relaxivity benefit from raising the rotational correlation time τ_R of complexes for use as MRI contrast agents, one needs an increased water exchange rate. Raising the water exchange rate by controlled steric crowding of the water binding site could be a pathway to more efficient contrast agents.

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Supporting Information Available: Variable temperature ^{17}O transverse relaxation rates and chemical shifts of [Ln(DTPA-BMA)(H_2O)] solutions and of acidified water at 14.1, 9.4, and 4.7 T (Table S1), variable pressure ^{17}O transverse relaxation rates of acidified water at 9.4 T (Table S2), variable pressure ^{17}O transverse relaxation rates of [Ln(DTPA-BMA)(H_2O)] solutions at 9.4 T (Table S3), and activation volumes of water exchange, $\Delta V^{\ddagger}$, and water exchange rates at temperature T and zero pressure, k_0^T(VP), as obtained from simultaneous least squares fits of the variable pressure data to eqs 1, 3, 5, 11, and 12, compared to water exchange rates at zero pressure and temperature T, k_{ex}(VT), as calculated from eq 6 with the parameters obtained from the variable temperature data (Table S4) (23 pages). Ordering information is given on any current masthead page.

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