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Water Exchange and Rotational Dynamics of the Dimeric Gadolinium(III) Complex $[BO\{Gd(DO3A)(H_2O)\}_2]$: A Variable-Temperature and -Pressure ^{17}O NMR Study[1]

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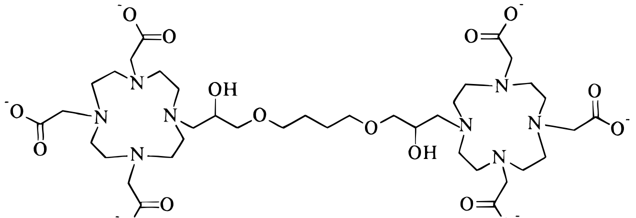
Rapid water exchange and slow rotation are essential for high relaxivity MRI contrast agents. A variable-temperature and -pressure ^{17}O NMR study at 14.1, 9.4, and 1.4 T has been performed on the dimeric $BO(DO3A)_2$, 2,11-dihydroxy-4,9-dioxa-1,12-bis[1,4,7,10-tetraaza-4,7,10-tris(carboxymethyl)cyclododecyl]dodecane, complex of Gd(III). This complex is of relevance to MRI as an attempt to gain higher ^1H relaxivity by slowing down the rotation of the molecule compared to monomeric Gd(III) complexes used as contrast agents. From the ^{17}O NMR longitudinal and transverse relaxation rates and chemical shifts we determined the parameters characterizing water exchange kinetics and the rotational motion of the complex, both of which influence ^1H relaxivity. The rate constant and the activation enthalpy for the water exchange, k_{ex} and $\Delta H^{‡}$, are $(1.0 \pm 0.1) \times 10^6$ $s^{-1}$and (30.0 ± 0.2) kJ mol^{-1}, respectively, and the activation volume, $\Delta V^{‡}$, of the process is $(+0.5 \pm 0.2)$ cm^3 mol^{-1}, indicating an interchange mechanism. The rotational correlation time becomes about three times longer compared to monomeric Gd(III) polyamino−polyacetate complexes studied so far: $\tau_R = (250 \pm 5)$ ps, which results in an enhanced proton relaxivity by raising the correlation time for the paramagnetic interaction.

Introduction

Recently there is a growing interest in the design, synthesis and characterization of new Gd(III) chelates of polyamino−polycarboxylates as potential contrast agents in magnetic resonance imaging (MRI).[3] The image contrast is a consequence of different relaxation rates of water protons in different tissues, which can be enhanced by paramagnetic ions like Gd^{3+} used in the form of stable and inert complexes for safety reasons. The relaxivity of such an agent—its ability to accelerate proton relaxation—is either due to short range dipolar interactions between the unpaired electron spins and the proton nuclei of water molecules bound in the first coordination sphere of the paramagnetic metal, mediated to the bulk by chemical exchange ("inner-sphere relaxation"), or to long range, through space dipolar interactions between the paramagnetic metal ion and the bulk water ("outer-sphere relaxation"). In the Gd complexes currently used as contrast agents, which contain one inner-sphere water molecule, the contribution of these two effects is of similar magnitude.[3,4] The inner-sphere relaxivity is governed by four correlation times: the correlation time for the rotation of the complex, τ_R, the residence time of a water proton in the inner coordination sphere, τ_m (or its inverse, the exchange rate $k_{ex} = 1/\tau_m$), and the longitudinal and transverse electronic relaxation rates ($T_{1,2e}$). The proton residence time, at least at neutral pH, equals the residence time of the oxygen nucleus, as the proton exchange at neutral pH takes place via the exchange of whole water molecules. This was confirmed recently e.g. for $Gd(DTPA\text{-}BMA)(H_2O)$[5,6] (DTPA-BMA = 1,7-bis[(*N*-methylcarbamoyl)methyl]-1,4,7-triazaheptane-1,4,7-triacetate or diethylenetriaminepentaacetatebis(methylamide)). The MRI contrast agents can be characterized by the magnetic field dependence of their proton relaxivity (nuclear magnetic relaxation dispersion (NMRD) profiles). However, this method falls short in determining the exchange rate of the bound water and can at best give an under limit. In order to better understand the function and efficacy of contrast agents it is desirable to determine their significant parameters (τ_m, τ_R, $T_{1,2e}$) from independent measurements, too. For that purpose ^{17}O NMR is a perfect tool as the oxygen atom of the coordinated water molecule is directly bound to the paramagnetic ion and thus experiences a far more efficient relaxation enhancement than the protons and permits us to observe for example the water exchange rate directly, a parameter that will be limiting once one tries to boost relaxivity by optimizing the other parameters.

Chart 1. Structural Formula of the Ligand $BO(DO3A)_2{}^{6-}$



One of the approaches to gain higher proton relaxivity is increasing the rotational correlation time,[3,4] which results in a longer correlation time for the dipole−dipole interaction between the electron spin and the proton spin. This effect can be achieved by increasing the size and the molecular weight of the complex. The first step in this approach is represented by the dimeric polyamino−polycarboxylate complexes.

Here we report a variable-temperature and -pressure ^{17}O NMR study on the dimeric macrocyclic complex of Gd(III), $[BO\{Gd(DO3A)(H_2O)\}_2]$ (see Chart 1 for the structural formula of $BO(DO3A)_2$). This complex incorporates several desirable features: as the ligand is a DOTA (DOTA = 1,4,7,10-tetraaza-

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Table 1. Composition of the [BO{Gd(DO3A)(H_2O)}$_2$] Solutions Used in Variable-Temperature (Samples 1 and 2) and Variable Pressure (Sample 3) ^{17}O NMR Measurements

sample	[Gd^{3+}]/mol kg^{-1}	10^3P_m	pH
acidified water			3.40
1	0.0982	1.77	6.51
2	0.2540	4.57	6.08
3	0.6900	12.44	6.02

1,4,7,10-tetrakis(carboxymethyl)cyclododecane) derivative, we can expect high kinetic inertness and thermodynamic stability, and as a neutral complex, it is favorable from the point of view of application (less painful injection because of lower osmolality). The fact that two Gd^{3+} ions are bound to one molecule allows for smaller injection volumes for the same total amount of mmol of Gd/kg of bodyweight. Finally, the increased molecular weight and volume may result in a longer rotational correlation time and thus in a higher proton relaxivity. The kinetic and rotational parameters obtained are compared to those of the aqua ion as well as to those of some Gd(III) complexes already used as MRI contrast agents, first of all to [Gd(DOTA)(H_2O)]$^-$, which has the most similar structure among the complexes studied so far by ^{17}O NMR.[7]

Experimental Section

Sample Preparation. The complex [BO{Gd(DO3A)(H_2O)}$_2$] was kindly supplied by Dr J. Platzek, Schering AG, Berlin, Germany, and used without further purification. The paramagnetic solutions for the ^{17}O NMR study were prepared by weight using the solid complex and 10% ^{17}O-enriched water. The pH was adjusted using weighed amounts of 0.1 m perchloric acid and sodium hydroxide solutions and was measured with a combined glass electrode, calibrated with Metrohm buffers. The absence of free Gd^{3+} in the solutions was verified using xylenol orange indicator.[8] The compositions of the solutions are shown in Table 1: most of the measurements were conducted on samples of two different concentrations to exclude artifacts due to concentration effects.

^{17}O NMR Measurements. Variable-temperature ^{17}O NMR measurements were performed using Bruker spectrometers (AMX2-600, 14.1 T, 81.4 MHz; AM-400, 9.4 T, 54.2 MHz; 1.41 T electromagnet connected to a AC-200 console, 8.1 MHz). Bruker VT-1000 and VT-2000 temperature control units were used to stabilize the temperature, which was measured by a substitution technique.[9] The samples were sealed in glass spheres, fitting into 10 mm NMR tubes, in order to eliminate susceptibility corrections to the chemical shift.[10] Longitudinal relaxation rates, $1/T_1$, were obtained by the inversion−recovery method, and transverse relaxation rates, $1/T_2$, were measured by the Carr−Purcell−Meiboom−Gill spin echo technique[11] or, for line widths greater than 500 Hz, directly from the line widths. Variable-pressure NMR measurements were made up to 200 MPa on a Bruker AM-400 spectrometer equipped with a home-built probe head.[12] The temperature was controlled by circulating fluid from a temperature bath and was measured using a built-in Pt resistor. The transverse relaxation rates were measured as for the variable-temperature work. The relaxation rates and, for the variable-temperature measurement, the chemical shifts were measured for the paramagnetic solutions and for a reference solution (a perchloric acid solution of pH = 3.4, containing 1% $H_2{}^{17}O$); thus, the diamagnetic shift was neglected.

The simultaneous least-squares fitting was performed by the program Scientist for Windows by Micromath, version 2.0.

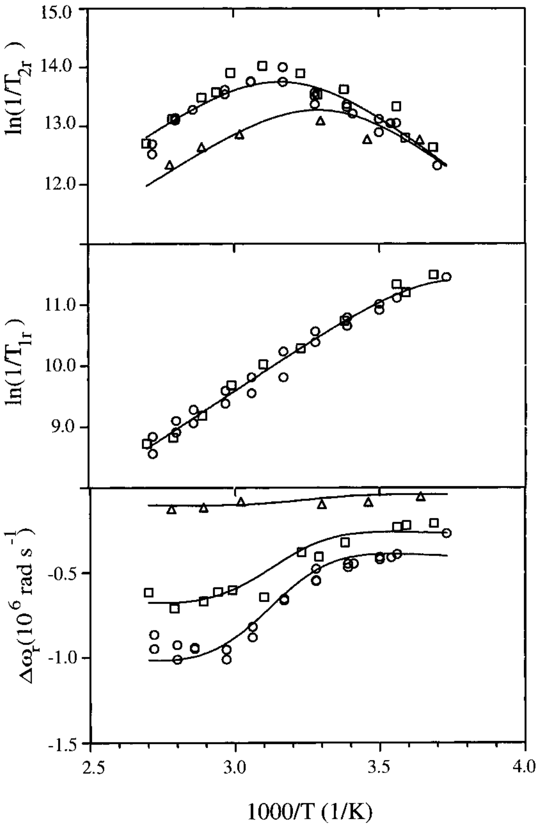

Figure 1. Temperature dependence of the reduced ^{17}O transverse and longitudinal relaxation rates (s^{-1}) and chemical shifts for [BO{Gd(DO3A)(H_2O)}$_2$] aqueous solutions at 14.1 T (○), 9.4 T (□) and 1.41T (△). The lines are functions calculated from a simultaneous nine-parameter least-squares fit (see text).

Results

From the measured ^{17}O NMR relaxation rates and angular frequencies of the paramagnetic solutions, $1/T_1$, $1/T_2$, and ω, and of the acidified water reference, $1/T_{1A}$, $1/T_{2A}$, and ω_A, one can calculate the reduced relaxation rates and chemical shift, $1/T_{1r}$, $1/T_{2r}$, and $\Delta\omega_r$, which may be written[13] as in eqs 1−3,

$$\frac{1}{T_{1r}} = \frac{1}{P_m}\left[\frac{1}{T_1} - \frac{1}{T_{1A}}\right] = \frac{1}{T_{1m} + \tau_m} + \frac{1}{T_{1os}} \qquad (1)$$

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

$$\Delta\omega_r = \frac{1}{P_m}(\omega - \omega_A) = \frac{\Delta\omega_m}{(1 + \tau_m T_{2m}{}^{-1})^2 + \tau_m{}^2\Delta\omega_m{}^2} + \Delta\omega_{os} \qquad (3)$$

where $1/T_{1m}$ and $1/T_{2m}$ are the relaxation rates of the bound water, $\Delta\omega_m$ is the chemical shift difference between bound water and bulk water (in the absence of a paramagnetic interaction with the bulk water), P_m is the mole fraction of bound water, and τ_m is the residence time of water molecules in the inner coordination sphere. The total outer-sphere contributions to the

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Table 2. Kinetic and NMR Parameters Derived from the ^{17}O Relaxation and Chemical Shift Data as a Function of Temperature and Pressure

	$[Gd(H_2O)_8]^{3+}$ [a]	$[Gd(DTPA)(H_2O)]^{2-}$ [b] Magnevist[e]	$[Gd(DTPA\text{-}BMA)(H_2O)]$[c] Omniscan[f]	$[Gd(DOTA)(H_2O)]^{-}$ [b] Dotarem[g]	$[BO\{Gd(DO3A)(H_2O)\}_2]$[d]
$k_{ex}^{298}/10^{-6}$ s^{-1}	830 ± 95	4.1 ± 0.3	0.43 ± 0.2	4.8 ± 0.4	1.0 ± 0.1
$\Delta H^{\ddagger}$/kJ mol^{-1}	14.9 ± 1.3	52.0 ± 1.4	46.6 ± 1.3	48.8 ± 1.6	30.0 ± 2
$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}	−24.1 ± 4.1	+56.2 ± 5.0	+18.8 ± 4.0	+46.6 ± 6	−29 ± 8
$\Delta V^{\ddagger}$/cm^3 mol^{-1}	−3.3 ± 0.2	+12.5 ± 0.2	+7.3 ± 0.2	+10.5 ± 0.2	+0.5 ± 0.2
$A/\hbar/10^{-6}$ rad s^{-1}	−5.33 ± 0.22	−3.8 ± 0.2	−3.6 ± 0.3	−3.4 ± 0.3	−2.8 ± 0.2
$\tau_R^{298}/10^{12}$ s	29 ± 2	103 ± 10	167 ± 5	90 ± 15	250 ± 5
E_R/kJ mol^{-1}	15 ± 2	18 ± 2	21.6 ± 0.1	17 ± 3	26.1 ± 0.7

[a] Reference 19. [b] Reference 7. [c] Reference 5. [d] This study. [e] Schering. [f] Nycomed. [g] Guerbet.

reduced relaxation rates and chemical shift are represented by $1/T_{1os}$, $1/T_{2os}$, and $\Delta\omega_{os}$.[7]

It has been proven that the outer-sphere contributions in eqs 1 and 2 can be neglected.[7] The maxima observed in the temperature dependence of $\ln(1/T_{2r})$ as depicted in Figure 1 are characteristic of a changeover from the "fast-exchange" limit at high temperatures, where T_{2m} is the dominant term in the denominator of eq 2, to the "slow-exchange" limit at low temperatures, where τ_m is the dominant term. Since $T_{1m} > T_{2m}$, the maximum in $1/T_{1r}$ is shifted to lower temperatures and can hardly be seen in the results in Figure 1.

The changeover between fast- and slow-exchange limits is also manifested in $\Delta\omega_r$, the maximum in the plot of $1/T_{2r}$ corresponding to the points of inflection in the plots of $\Delta\omega_r$. At high temperatures, the inner-sphere contribution to $\Delta\omega_r$ is given by the chemical shift of the bound water molecules $\Delta\omega_m$, which is determined by the hyperfine interaction between the Gd^{3+} electron spin and the ^{17}O nucleus *via* eq 4, where g_L is

$$\Delta\omega_m = \frac{g_L\mu_B S(S+1)B}{3k_BT}\frac{A}{\hbar} \qquad (4)$$

the isotropic Landé *g*-factor ($g_L = 2.0$ for Gd^{3+}), S is the electron spin ($S = {}^7/_2$ for Gd^{3+}), $A/\hbar$ is the hyperfine or scalar coupling constant, and B is the magnetic field.[14] We assume that the outer-sphere contribution to $\Delta\omega_r$ has a similar temperature dependence to $\Delta\omega_m$ and is given by eq 5, where C_{os} is an empirical constant.

$$\Delta\omega_{os} = C_{os}\Delta\omega_m \qquad (5)$$

The ^{17}O longitudinal relaxation rates in Gd^{3+} solutions are dominated by the dipole−dipole and quadrupolar mechanisms[14] and are given, to a good approximation, by eq 6, where $\gamma_S =$

$$\frac{1}{T_{1m}} = \left[{}^2/_5\left(\frac{\mu_0}{4\pi}\right)^2\frac{\hbar^2\gamma_I^{\,2}\gamma_s^{\,2}}{r^6}S(S+1) + \frac{3\pi^2}{10}\frac{2I+3}{I^2(2I-1)}\chi^2(1+\eta^2/3)\right]\tau_R \qquad (6)$$

$g_L\mu_B/\hbar$ is the electron gyromagnetic ratio ($\gamma_S = 1.76 \times 10^{11}$ rad s^{-1} T^{-1} for $g_L = 2.0$), γ_I is the nuclear gyromagnetic ratio ($\gamma_I = -3.626 \times 10^7$ rad s^{-1} T^{-1} for ^{17}O), r is the effective distance between the electron charge and the ^{17}O nucleus (the metal−oxygen distance in the point−dipole approximation), τ_R is the rotational correlation time of the complex, I is the nuclear spin ($I = {}^5/_2$ for ^{17}O), χ is the quadrupolar coupling constant, and η is an asymmetry parameter (we use here the value for acidified water, $\chi(1 + \eta^2/3)^{1/2} = 7.58$ MHz).[7] We estimate from neutron diffraction measurements of lanthanide aqua ions in solution that $r = 0.25$ nm.[15] With this r value, the dipole−dipole mechanism (the first term in eq 6) contributes to 68% of $1/T_{1m}$.

We assume that the rotational correlation time, τ_R, has a simple exponential temperature dependence as in eq 7, where

$$\tau_R = \tau_R^{298}\exp\{E_R/R(1/T - 1/298.15)\} \qquad (7)$$

τ_R^{298} is the rotational correlation time at 298.15 K and E_R is the activation energy of rotation. The binding time (or exchange rate, k_{ex}) of water molecules in the inner sphere is assumed to obey the Eyring equation as depicted in eq 8, where $\Delta S^{\ddagger}$ and

$$\frac{1}{\tau_m} = k_{ex} = \frac{k_BT}{h}\exp\left\{\frac{\Delta S^{\ddagger}}{R} - \frac{\Delta H^{\ddagger}}{RT}\right\} = \frac{k_{ex}^{298}T}{298.15}\exp\left\{\frac{\Delta H^{\ddagger}}{R}\left(\frac{1}{298.15} - \frac{1}{T}\right)\right\} \qquad (8)$$

$\Delta H^{\ddagger}$ are the entropy and enthalpy of activation for the exchange process and k_{ex}^{298} is the exchange rate at 298.15 K. The transverse relaxation rate of the bound water, $1/T_{2m}$, was assumed to have an exponential temperature dependence as can be seen in eq 9, where E_m is the activation energy of the relaxation of the bound water and $1/T_{2m}^{298}$ is the relaxation rate of the bound water at the given field at 298.15 K.

$$\frac{1}{T_{2m}} = \frac{1}{T_{2m}^{298}}\exp\left\{\frac{E_m}{R}\left(\frac{1}{298.15} - \frac{1}{T}\right)\right\} \qquad (9)$$

A more detailed approach to the ^{17}O transverse relaxation rate of the bound water in Gd^{3+} solutions can be given by including the electronic relaxation parameters.[5,16] This full treatment, however, requires reliable values for the parameters characterizing the electron spin relaxation, which can only be obtained from EPR measurements.[16] To check the validity of eq 9 we have refitted the previously published data for $[Gd(DTPA\text{-}BMA)(H_2O)]$[5] using this equation, and the resulting kinetic parameters were not affected by this simplified procedure.

We performed a simultaneous least squares fit of the data in Figure 1 using eqs 1−9 with the following fitted parameters: k_{ex}^{298} (or $\Delta S^{\ddagger}$), $\Delta H^{\ddagger}$, $A/\hbar$, C_{os}, τ_R^{298}, E_R, $1/T_{2m}^{298,HF}$, $1/T_{2m}^{298,LF}$, and E_m. The resulting curves are shown in Figure 1, and the fitted parameters are given in Table 2. Since there was no field dependence of the reduced transverse relaxation rates between 9.4 and 14.1 T, these data were fitted with a single value for the bound water relaxation at 298 K: $1/T_{2m}^{298,HF}$ ("HF" for "high

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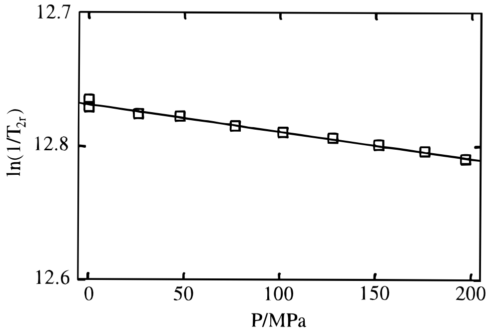

Figure 2. Pressure dependence of reduced ^{17}O transverse relaxation rates (s^{-1}) for aqueous solutions of [BO{Gd(DO3A)(H$_2$O)}$_2$] at 9.4 T and 277.3 K.

field" $B = 14.1$ and 9.4 T), while for "low field" ($B = 1.4$ T) the corresponding parameter $1/T_{2m}^{298,LF}$ was used. The values found are $1/T_{2m}^{298,HF} = (2.7 \pm 0.4) \times 10^6$ s^{-1} and $1/T_{2m}^{298,LF} = (1.3 \pm 0.2) \times 10^6$ s^{-1}. E_m was fitted for all three fields simultaneously to a single value: $E_m = (26.5 \pm 0.3)$ kJ mol^{-1}. The value of the empirical constant, C$_{os}$, for the outer-sphere contribution to $\Delta\omega_R$ has been adjusted to 0.38 ± 0.06.

The pressure dependence of the reduced transverse relaxation rates, $1/T_{2r}$, for [BO{Gd(DO3A)(H$_2$O)}$_2$] at 277.3 K and at 9.4 T is shown in Figure 2. At this magnetic field and the temperature chosen, the system is in the slow-exchange limit and $1/T_{2r}$ equals $1/\tau_m$. The small decrease of $1/T_{2r}$ with pressure in Figure 2 is, therefore, due to a slight decrease of the water exchange rate. The pressure dependence of the water exchange rate may be written as in eq 10, where $\Delta V_0^{\ddagger}$ is the activation

$$\frac{1}{\tau_m} = k_{ex} = (k_{ex})_0^T \exp\left\{-\frac{\Delta V_0^{\ddagger}}{RT}P + \frac{\Delta\beta^{\ddagger}}{2RT}P^2\right\} \qquad (10)$$

volume at zero pressure and temperature T, $(k_{ex})_0^T$ is the exchange rate at zero pressure and temperature T, and $\Delta\beta^{\ddagger}$ is the compressibility coefficient of activation. In the fitting procedure we included a possible pressure dependence of the bound water relaxation rate $1/T_{2m}$ as given in eq 11. We

$$\frac{1}{T_{2m}} = \frac{1}{T_{2m}^0} \exp\left(\frac{-\Delta V_m^{\ddagger}}{RT}P\right) \qquad (11)$$

performed a least-squares fit of the data in Figure 2 using eqs 2, 4, and 9−11 with $(k_{ex})_0^T$ and $\Delta V_0^{\ddagger}$ as adjustable parameters. In previous studies, the pressure dependence of ln(k_{ex}) has been found to be nearly linear,[7] so we assume that $\Delta\beta^{\ddagger} = 0$, and we have an activation volume independent of pressure ($\Delta V^{\ddagger}$ instead of $\Delta V_0^{\ddagger}$). The scalar coupling constant was found previously to be independent of pressure,[17] so we assume that it is constant and equal to the value in Table 2. Fixing $\Delta V_m^{\ddagger}$ at values from −5 to +5 cm^3 mol^{-1} did not alter the values in Table 2 within the statistical error. The fitted curve is shown in Figure 2, with the following adjusted parameters: $(k_{ex})_0^{277} = (3.6 \pm 0.2) \times 10^5$ s^{-1}, $\Delta V^{\ddagger} = (0.5 \pm 0.2)$ cm^3 mol^{-1}.

Discussion

The parameters obtained for the [BO{Gd(DO3A)(H$_2$O)}$_2$] dimer will be compared with those of the Gd^{3+}aqua ion and of three Gd(III)−poly(amino carboxylate) complexes used as commercial contrast agents in terms of structure, rate and mechanism of water exchange as well as rotational dynamics. The values which will be discussed are given in Table 2.

Structure. The Gd^{3+} aqua ion has a coordination number (from here "CN") of 8,[18] and the current contrast agents have a CN of 9: eight sites occupied by the poly(amino carboxylate) ligand, and the ninth by the inner-sphere water. The variation in the gadolinium−oxygen bond length from the [Gd(H$_2$O)$_8$]$^{3+}$ to the poly(amino carboxylate) complexes is manifested in the scalar coupling constants. One observes a smaller coupling constant for the latter, a sign of the larger Gd−O distance, which is a consequence of the higher CN. For the dimer, the four imino, the three carboxylate groups, and the hydroxo group plus one inner-sphere water molecule are expected to coordinate to the Gd^{3+} ion. The hydroxo group is a weaker and more labile donor than the carboxylate groups. Therefore, one could suspect that for the dimer a coordination equilibrium exists between an isomer where the hydroxo group and one water molecule are bound to the gadolinium and another where the hydroxo group is replaced by a second inner-sphere water molecule. The small value of the scalar coupling constant in comparison to that of the other poly(amino carboxylate) complexes permits us to exclude the presence of such an equilibrium: there is only one water molecule in the first coordination sphere.

Rate and Mechanism of Exchange. The vast majority of Ln^{3+}complexes are either eight or nine coordinated; ten- and seven-coordinated complexes are rare. For this reason, Ln^{3+} complexes of CN = 9 tend to exchange over an activated state of CN = 8, *i.e. via* a dissociatively activated mechanism. To the contrary, Ln^{3+} complexes of CN = 8 will exchange over an activated state of CN = 9, *i.e. via* an associatively activated mechanism. The most labile complexes are those that are close to a coordination equilibrium between these "magic numbers" 8 and 9. This is well exemplified by the aqua ions:[19] the fastest water exchange rate has been measured on the Gd^{3+} ion, which is eight coordinate, but whose ionic radius is close to that of Sm^{3+}, for which an equilibrium between CN = 8 and CN = 9 was indeed found.[18] The corresponding trend was observed for a series of nine-coordinate [Ln(DTPA-BMA)(H$_2$O)] complexes: the smaller the complexed cation (Nd^{3+} to Ho^{3+}), the higher the exchange rate, because with the increased steric crowding of the inner coordination sphere the nine-coordinate ground state becomes less stable and the eight-coordinate activated state more stable, increasing the lability of the inner-sphere water molecule and favoring a limiting dissociative exchange mechanism.[20]

In a comparison of [BO{Gd(DO3A)(H$_2$O)}$_2$] with the aqua ion, the change in coordination number from 8 to 9 is accompanied by a change in mechanism from associatively activated for the aqua ion to dissociatively activated (I$_d$) or pure interchange (I), as can be seen from the corresponding activation volumes, as well as by a decrease in exchange rate by 3 orders of magnitude. From [Gd(DOTA)(H$_2$O)]$^-$ to the dimeric complex, there is a decrease in exchange rate by a factor of 5, the mechanism being limiting dissociative (D) for the DOTA complex, as shown by the strongly positive activation volume. Whereas the exchange passes an activated state of CN = 8 for the DOTA complex, the dimeric complex does not change its CN during the exchange event as it is indicated by the activation volume being almost zero. Bearing the weakly donating hydroxo group which leaves more space for the inner-sphere

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water molecule, the free energy gap between nine- (with inner-sphere water) and eight- (without inner-sphere water) coordinate species is too great. On the other hand, there is too much crowding in the first coordination sphere to allow for a tenth donor atom, and the incoming water molecule cannot really participate in the activation of the exchange event.

Rotation. The rotational correlation time, τ_R, as computed from the reduced ^{17}O longitudinal relaxation rates, is considerably longer for $[BO\{Gd(DO3A)(H_2O)\}_2]$ than for any of the monometallic Gd complexes previously studied, as it is expected for a larger molecule. In comparison to $[Gd(DOTA)(H_2O)]^-$ there is an almost 3-fold increase. This τ_R value is a correlation time for both the dipolar and quadrupolar interactions between the gadolinium electron spin and the oxygen nuclear spin, the two contributions being 68% and 32%, respectively. We interpret this correlation time as the inverse tumbling rate of the molecule. The τ_R value is correlated with the values used for the effective distance between the Gd electron spin and the oxygen nucleus, as well as for the quadrupolar coupling constant and its asymmetry parameter. The choice of the distance is especially crucial as it enters into the 6th power in eq 6: an error of ±0.02 nm leads to an uncertainty of ±30% on τ_R. However, since we use the same values for r, χ, and η in this and previous papers,[5,7,19] the comparison of the tumbling rates of $[BO\{Gd(DO3A)(H_2O)\}_2]$ and the different monomeric complexes is justified.

The Debye formula[21] (eq 12) can be used to estimate r_{eff}, the effective radius of the complex, from the viscosity η of the

$$\tau_R = \frac{4\pi\eta {r_{eff}}^3}{3k_BT} \qquad (12)$$

solution and the τ_R value determined by NMR. This leads to an r_{eff} ratio of the order of 2 for the $[BO\{Gd(DO3A)(H_2O)\}_2]$ and $Gd(H_2O)_8{}^{3+}$ species. The radius of $[Gd(H_2O)_8]^{3+}$ is ca. 0.35 nm, which was obtained from neutron diffraction measurements. On the basis of this, r_{eff} for the dimer should be around 0.72 nm. This does not correspond to the increase in diameter across the largest dimension of the dimer, as could be expected, because τ_R is a correlation time of global rotation, including rotations around all axes and intramolecular rotation, which is important for the dimer with its flexible bridge. Nevertheless, there is a significant increase in τ_R which gives rise to some gain in proton relaxivity compared to e.g. $[Gd(DOTA)(H_2O)]^-$: $R_1 = 4.61$ s^{-1} mM^{-1} for $[BO\{Gd(DO3A)(H_2O)\}_2]$[22] and $R_1 = 3.4$ s^{-1} mM^{-1} for $[Gd(DOTA)(H_2O)]^-$ [23] ($T = 310$ K, at 20 MHz in water).[24] Of course the loss in water exchange rate will prevent much higher increase in proton relaxivity. However, at the present state, *i.e.* with rotation still far from being frozen out and with nonoptimal electronic relaxation times, the water exchange does not limit proton relaxivity at physiological temperature (37 °C), but it nevertheless presents a barrier if one wants relaxivities much higher than 20 mM^{-1} s^{-1}.

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Supporting Information Available: Variable-temperature ^{17}O transverse and longitudinal relaxation rates and chemical shifts of $[BO\{Gd(DO3A)(H_2O)\}_2]$ solutions and of acidified water at 1.4, 9.4, and 14.1 T (Table S1−S3, respectively) and variable-pressure ^{17}O transverse relaxation rates of $[BO\{Gd(DO3A)(H_2O)\}_2]$ solutions at 9.4 T (Table S4) (3 pages). Ordering information is given on any current masthead page.

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(21) Hertz, H. G. In *Water, A Comprehensive Treatise*; Franks, F., Ed.; Plenum: New York, 1973; Vol. 77, p 685.

(22) Private communication from J. Platzek.

(23) Meyer, D.; Schaeffer, M.; Doucet, D. In *Contrast and Contrast Agents in Magnetic Resonance Imaging, Proceedings of A Special Topic Seminar*; Trondheim, Norway,Sept 12−13, 1988; p 33.

(24) A reviewer has suggested that an even higher relaxivity value (6−7 mM^{-1} s^{-1}) would be reasonable for a complex of such a molecular weight. This discrepancy may arise from the uncertainty on τ_R.