Experimental Evidence for a Second Coordination Sphere Water Molecule in the Hydration Structure of YbDTPA – Insights for a Re-Assessment of the Relaxivity Data of GdDTPA

Kenneth Irvin Hardcastle,*[a] Mauro Botta,*[b] Mauro Fasano,[c] and Giuseppe Digilio[d]

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The low temperature (–100 °C) X-ray structure of the complex $K_2[Yb(DTPA)(H_2O)]$ has been determined. The metal ion is at the center of a tricapped trigonal prism and is nine-coordinate, binding to the three nitrogens and five oxygens of the ligand and one water molecule. From the structure obtained, three well-defined hydration shells can be observed consisting of: i) one coordinated water molecule; ii) several water molecules in the outer coordination sphere of the Yb^{III} ion and iii) one water molecule surprisingly close to the metal center and hydrogen-bonded to proximate carboxylate groups. A variable-field and temperature NMRD study of the corresponding Gd complex has been performed and the data interpreted by taking into account the presence of second-sphere water molecule(s). The results of the analysis are in excellent agreement with the X-ray structural data.

Introduction

The use of paramagnetic metal complexes to alter the nuclear magnetic relaxation times of water protons in tissues is a well established procedure in clinical diagnosis for enhancing the contrast between healthy and diseased regions in MRI (**M**agnetic **R**esonance **I**maging) images.[1] Currently, about 35% of the MRI examinations are performed with the use of contrast enhancing agents (CA). The most common class of these compounds are neutral or negatively charged polyaminocarboxylate complexes of Gd^{III}, both linear and macrocyclic, which are extracellular, nonspecific CA which rapidly diffuse throughout the body after injection and are excreted via the renal route.[2–4] The first of these complexes to be considered as a CA and to be tested on humans was $[Gd(DTPA)(H_2O)]^{2-}$ ($DTPA^{5-}$ = diethylenetriamine-*N*,*N*′,*N*′′-pentaacetate).[5] Much is known about this compound; the ligand is octadentate and fully exploits its chelating ability towards lanthanide(III) ions to form thermodynamically stable tricapped trigonal structures where one of the capping positions is occupied by a water molecule. In solution the complexes are stereochemically non-rigid and the fluxional process involves conformational inversion of the ethylenediamine rings and rotation of the acetate arms which corresponds to the interconversion between two enantiomeric forms;[6,7] isostructurality across the lanthanide series has been suggested by the analysis of NMR data.[8] The coordination sphere of the Gd^{III} complex is completed by a water molecule that has a mean residence lifetime of about 300 ns at 298 K, as assessed by Merbach et al. by ^{17}O NMR.[9] It is common practice to evaluate the efficacy of a given Gd complex as a CA in terms of the relaxivity parameter, r_{1p} ($mM^{-1}\ s^{-1}$), the net increment in the water proton longitudinal relaxation rate per millimolar concentration of the paramagnetic compound.[1,2] The relaxivity reflects the efficiency of the nuclear-electron dipolar coupling between the nuclear magnetic moment of the water protons and the electronic magnetic moment of the metal ion and is traditionally described on the basis of a model that considers two distinct contributions: *inner sphere*, related to the exchange of the bound water molecule(s) from the coordination site to the bulk, and *outer sphere*, which involves the water molecules diffusing near the paramagnetic center during their translational diffusion.[10] The relaxivity has a strong dependence upon the applied magnetic field strength and from the analysis of this dependence (NMRD, **N**uclear **M**agnetic **R**elaxation **D**ispersion profiles) several important structural and dynamic parameters may be obtained.[11] However, the polar nature of these complexes, featuring negative charges localized on the carboxylate groups, has recently suggested the presence of structured, hydrogen-bonded water molecules in the second coordination sphere of Gd^{III} and thus a possible inadequacy in the physical model used for the interpretation of the relaxation data and the analysis of the NMRD profiles.[1,12–14] The contribution

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[a] Department of Chemistry, California State University Northridge,
18111 Nordhoff Street, Northridge, CA 91330–8262 (USA)
Fax: (internat.) +1–818–677–2912
E-mail: ken.hardcastle@csun.edu
[b] Dipartimento di Scienze e Tecnologie Avanzate, Universita‘ del Piemonte Orientale
“Amedeo Avogadro”, Corso Borsalino 54,
15400 Alessandria (Italy)
Fax: (internat.) +39–011–670–7524
E-mail: botta@ch.unito.it
[c] Dipartimento di Chimica I.F.M., Universita‘ di Torino,
Via P. Giuria 7, 10125 Torino (Italy)
[d] Bioindustry Park del Canavese,
Via Ribes 5, Colleretto Giacosa (TO)

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of second sphere water molecules to r_{1p} has been suggested in a few special cases over the last few years by some indirect evidence, but the possibility of its more general role and its influence on the correct evaluation of the relaxation parameters has not yet been discussed.[15] Here we report on a low temperature single crystal X-ray structural determination of $K_2[Yb(DTPA)(H_2O)]$ where the hydration structure of the complex is clearly detectable and provides firm evidence of a water molecule adjacent to the carboxylate oxygens at a distance sufficiently close to the metal ion to be able to influence significantly the relaxivity of the corresponding Gd^{III} complex. On the basis of these findings, the NMRD data are reinterpreted and the new set of relaxation parameters are found to be in a better agreement with the available structural data.

Results and Discussion

Solid State Structural Characterization

Table 1 lists some selected interatomic distances for $K_2[Yb(DTPA)(H_2O)]$; the molecular geometry of the anion, $[Yb(DTPA)(H_2O)]^{2-}$, along with associated water molecules is shown in Figure 1. The Yb^{III} ion is surrounded by nine coordinating atoms: three nitrogen atoms, N1, N2, N3, five carboxylato oxygen atoms, O1, O3, O5, O7 and O9 and a bound water molecule, O1 W, which form a tri-capped trigonal prism (TTP) geometry around the central ytterbium ion. The capping atoms are the bound water, O1 W, and N1 and N3 (crystallographic data see Table 2).

Table 1. Selected interatomic distances [Å] for $K_2[Yb(DTPA)(H_2O)]$

Yb(1)–N(1)	2.553(5)	Yb(1)–O(5)	2.291(4)
Yb(1)–N(2)	2.553(5)	Yb(1)–O(7)	2.320(4)
Yb(1)–N(3)	2.742(5)	Yb(1)–O(9)	2.303(4)
Yb(1)–O(1)	2.295(4)	Yb(1)–O(1 W)	2.423(4)
Yb(1)–O(3)	2.324(4)	Yb(1)–O(7 W)	4.178(4)
Yb(1)–H(7WA)	3.280(7)	Yb(1)–H(7WB)	4.539(7)

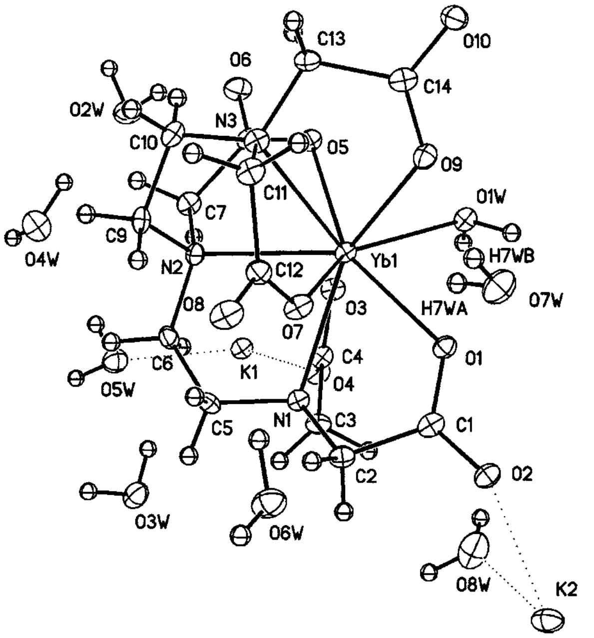

Figure 1. Solid state structure of $K_2[Yb(DTPA)(H_2O)]$

The geometry of the ligand can also be described as a monocapped square antiprism (CSAP); however, the distortions from a regular geometry are much greater in this configuration than in the trigonal prism geometry. For example, in the trigonal prismatic geometry, only the Yb–N2 distance is significantly longer, 2.553(5) Å, than the Yb–O1, O3, O6, O7, O10 distances, 2.307(4) Å (ave); whereas with the square antiprism geometry, the N1, N2, N3, O7 atom deviations from a regular plane are +0.24, –0.21, +0.25 and –0.28 Å, respectively. The geometry of the anion, $[Yb(DTPA)(H_2O)]^{2-}$ is very similar to that of other lanthanide DTPA complexes of gadolinium[16,17] and neodymium.[18] The bound water molecule to ytterbium ion distance, Yb–O1 W, is 2.423(4) Å, which is significantly shorter than the corresponding distance in the analogous Gd^{III} complex of 2.490 Å. Interestingly, unlike the few structures of lanthanide complexes with DTPA previously reported, in this low temperature X-ray diffraction study we were able to observe the hydration structure of the complex. The structure of $K_2[Yb(DTPA)(H_2O)]$ has eight associated water molecules, one bound water, O1 W, and six water molecules in the outer coordination sphere surrounding the anionic ytterbium complex, at an average distance of 5.8 Å from the Yb to the oxygen atoms of the water molecules. One additional water molecule, O7 W, was located 4.18 Å from the ytterbium atom and strongly hydrogen-bonded to the carboxylate oxygen atoms O1, O7 and O9 at distances of 2.38–2.54 Å, respectively, which are significantly shorter than the van der Waals distance and within the accepted range for hydrogen bonds .

Relaxometry

The water proton longitudinal relaxation rate is strongly enhanced in a solution containing a paramagnetic Gd^{III} complex and the measured value, R_1^{obs} (s^{-1}), is normally resolved into three contributions:

$$R_1^{obs} = R_{1p}^{is} + R_{1p}^{os} + R_1^{w} \tag{1}$$

where R_1^{w} is the background diamagnetic term, corresponding to the water relaxation rate in a solution of a related diamagnetic derivative, R_{1p}^{is} the represents the contribution arising from exchange ($k_{ex} = 1/\tau_M$) of the metal-bound water molecule(s) from the coordination site to the bulk solvent and R_{1p}^{os} is the contribution associated with the solvent molecules diffusing near the paramagnetic center in the outer coordination sphere. The inner sphere relaxation rate arises from the modulation of the dipolar electron-nucleus interaction by chemical exchange (τ_M), electron spin relaxation (τ_S) and reorientation of the Gd–O_w vector (τ_R) and is described in terms of the following set of Equations:[2,10]

Table 2. Crystal data and structure refinement for $K_2[Yb(DTPA)(H_2O)]$

Identification code	$K_2[YbDTPA(H_2O)]$	
Empirical formula	$C_{14}H_{34}K_2N_3O_{18}Yb$	
Formula weight	783.68	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	a = 9.558(3) Å	α = 76.92(5)°.
	b = 11.277(9) Å	β = 87.02(3)°.
	c = 13.412(7) Å	γ = 69.04(5)°.
Volume	1314.3(13) $Å^3$	
Z	2	
Density (calculated)	1.980 Mg/m^3	
Absorption coefficient	3.961 mm^{-1}	
$F(000)$	782	
Crystal size	0.40 × 0.32 × 0.25 mm^3	
Theta range for data collection	1.56 to 27.47°.	
Index ranges	$-12 \le h \le 12$, $-14 \le k \le 14$, $-17 \le l \le 17$	
Reflections collected	7824	
Independent reflections	6016 [R_{int} = 0.0288]	
Absorption correction	Psi scans	
Max. and min. transmission	0.4792 and 0.3211	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	6016/16/351	
Goodness-of-fit on F^2	1.404	
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0406, $wR2$ = 0.1142	
R indices (all data)	$R1$ = 0.0418, $wR2$ = 0.1150	
Largest diff. peak and hole	2.250 and –1.404 e.$Å^{-3}$	

$$R_{1p}^{is} = \frac{[M] \times q}{55.6} \times \frac{1}{T_{1M} + \tau_M} \tag{2}$$

$$\frac{1}{T_{1M}} = \frac{2}{15}\left(\frac{\mu_0}{4\pi}\right)^2 \frac{\hbar^2 \gamma_S^2 \gamma_I^2}{r_{GdH}^6} S(S+1)\left[\frac{3\tau_{c1}}{1+\omega_I^2\tau_{c1}^2} + \frac{7\tau_{c2}}{1+\omega_S^2\tau_{c2}^2}\right] \tag{3}$$

$$\frac{1}{\tau_{ci}} = \frac{1}{\tau_M} + \frac{1}{\tau_R} + \frac{1}{\tau_{Si}} \qquad i = 1, 2 \tag{4}$$

$$\left(\frac{1}{\tau_{S1}}\right)^{ZFS} = \Delta^2\tau_v\left(\frac{2.4}{1+\omega_S^2\tau_v^2} + \frac{9.6}{1+4\omega_S^2\tau_v^2}\right) \tag{5}$$

$$\left(\frac{1}{\tau_{S2}}\right)^{ZFS} = \Delta^2\tau_v\left[\frac{5.26}{1+0.372\omega_S^2\tau_v^2} + \frac{7.18}{1+1.24\omega_S\tau_v}\right] \tag{6}$$

In Equations 2–6 [M] is the molar concentration of the paramagnetic complex; q is the number of water molecules coordinated to the metal ion; τ_M is their mean residence lifetime; T_{1M} is their longitudinal relaxation time; S is the electron spin quantum number; γ_H is the proton nuclear magnetogyric ratio; g and β are the electronic g factor and Bohr magneton, respectively; $r_{Gd–H}$ is the distance between the metal ion and the protons of the coordinated water molecules; ω_H and ω_S are the proton and electron Larmor frequencies, respectively; τ_R is the reorientational correlation time; and τ_{S1} and τ_{S2} are the longitudinal and transverse electron spin relaxation times. These latter terms, in analogy with the nuclear magnetic relaxation times, have a frequency dependence which is normally represented by Equations 5 and 6 where τ_v is the correlation time associated with the modulation of the electron-lattice interaction and Δ is the square root of the average quadratic (transient) zero-field splitting tensor. This latter term is often expressed in terms of τ_{S0}, the limiting value of the electronic relaxation time at zero magnetic field, according to the expression:

$$\Delta^2 = \frac{1}{12\tau_{S0}\tau_v} \tag{7}$$

The outer-sphere relaxivity has a dependence on the electronic relaxation times, τ_{S1} and τ_{S2} of the metal ion, on the distance of closest approach of solute and solvent (d), on the sum of solvent and solute diffusion constants (D) and on the magnetic field strength. This term is well described by the Freed equation modified in a form suitable for small paramagnetic metal chelates:

$$R_{1p}^{os} = C^{os}\left(\frac{1}{aD}\right)\left[7J(\omega_S) + 3J(\omega_H)\right] \tag{8}$$

where C^{os} is a constant ($5.8 \cdot 10^{-13}$ $s^{-2}M^{-1}$) and the dependence on the electronic relaxation times is expressed in the non-Lorentzian spectral density functions $J(\omega_i)$.[19] Thus the paramagnetic contribution to the water protons' relaxation rate implicitly contains very useful information for a series of important structural and dynamic parameters which would allow for a complete characterization of the solute and its interaction with the solvent. In order to obtain reliable values for these parameters the magnetic field dependence of r_{1p} through Equations 3–6 is exploited by measuring the paramagnetic relaxation rate as a function of the applied magnetic field strength. This is best done by using specialized instrumentation, the field-cycling relaxometer, which switches magnetic field strength very rapidly over the desired range (typically corresponding to proton Larmor frequencies of 0.01 to 50 MHz), thus allowing a complete and accurate dataset to be recorded in about 0.5 h. The $1/T_1$ dataset, otherwise known as a NMRD profile, represents the sum of the spectral density functions of the active relaxation mechanisms and can be fitted to the inner- and outer-sphere equations to yield the values of the relaxation parameters.[11]

For small, rapidly tumbling Gd^{III} chelates the NMRD profile near room temperature is flat, ie. r_{1p} assumes a constant value for frequency values up to about 1–2 MHz, then it decreases because of the dispersion of the $\omega_S \tau_{c2}$ term in Equation 3 and tends to level off in the high field region. For polyaminocarboxylate complexes with $q = 1$, inner- and outer sphere terms at the imaging fields (10–60 MHz) make a similar contribution to the relaxivity, the contribution being determined primarily by the terms τ_R/r^6_{Gd-H} (r^{is}_{1p}) and d^2/D (r^{os}_{1p}).[2,11] For this reason, complexes of similar size and molecular weight are expected to have similar relaxivity at these magnetic fields. Normally, the NMRD profiles are not sensitive to the value of τ_M, which at 25 °C is of the order of a few hundred nanoseconds for enneacoordinate Gd^{III} chelates and thus makes a negligible contribution to τ_{ci} (Equation 4). In the low field region r_{1p} is affected by the value of the electronic relaxation time which varies from one complex to another as a result of their different symmetries, rigidities and donor atoms.[20,21] In Figure 2, the experimental NMRD data of $[Gd(DTPA)(H_2O)]^{2-}$ are reported as measured at 25 °C and pH = 7.2. Because of the particularly important role played by this complex in the field of MRI contrast agents, where it has been considered as a reference in the development of new compounds, its profile is well-known and has been analyzed and discussed in considerable detail, primarily by S. H. Koenig and R. D. Brown III.[11]

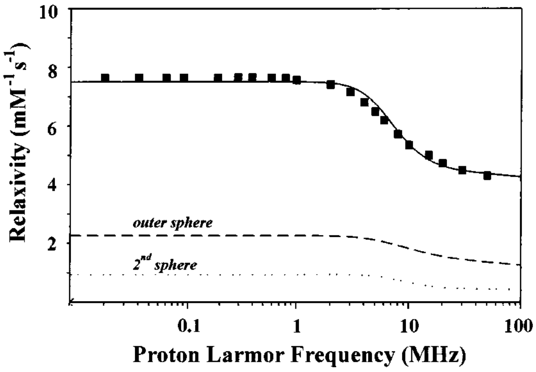

Figure 2. NMRD profile at 25 °C and pH = 7.2 of $Na_2[Gd(DTPA)(H_2O)]$. The curve through the data points has been calculated with the parameters of Table 3, obtained through a best-fitting procedure to equations for paramagnetic relaxation, as described in the text. The lower dashed and dotted curves represent the outer- and 2nd sphere contributions, respectively.

An excellent fit of the data to both inner and outer sphere theory was obtained by considering as adjustable parameters τ_{S0} (85 ps), τ_v (20 ps), τ_R (80 ps) and r_{Gd-H} (3.05 Å), whereas reasonable assumptions were made with regard to d (3.6 Å), D (the diffusion constant of the complex is assumed to be about 25% that of water), q (= 1) and τ_M (1 ns). This interpretation, based on resolution of the data into inner and outer sphere contributions, has proven to be very useful for comparing the data of different complexes, understanding the relaxometric behavior as a function of viscosity, temperature and pH and provides a good basis for rational design of new CA.

However, when one compares the parameters of the fitting procedure with the available structural data on a series of related Gd^{III} complexes several discrepancies are found. The solid state X-ray structures of numerous Gd^{III} chelates reveal that the Gd–O$_w$ distance does not show significant variation from a value of about 2.45 Å, which corresponds to a r_{Gd-H} value of about 2.9 Å.[16,17,22] When compared to the fitted value of 3.05 Å, this represents a significant difference, considering that the relaxivity has a dependence on the inverse of the 6th power of this parameter. On the other hand, the value of 3.6 Å for the closest distance of approach of the outer sphere water molecules to the paramagnetic center is far too short, even shorter than metal-ligand proton distances found in Ln^{III} complexes with DTPA. The X-ray structural determination presented here clearly indicates for this parameter an average value of 4.5 Å, which implies a contribution of the outer sphere relaxivity which is markedly lower than normally calculated. The reorientational correlation time, τ_R = 80 ps, is sensibly longer than the value, about 70 ps, calculated from ^{13}C NMR data on diamagnetic derivatives (La^{III}, Y^{III} or Lu^{III} complexes), probably a consequence of its strong correlation with the value of r_{Gd-H} . On the other hand, when we try to fit the NMRD profile by fixing the parameters r_{Gd-H}, d, D and τ_R to more realistic values (and by using q = 1 and τ_M = 360 ns, as calculated by Merbach et al.),[9] a very poor result is obtained. The much larger value of d reduces by almost 50% the contribution of r^{os}_{1p} and is not compensated by the shorter value of the distance r_{Gd-H} . We tried to account for the remaining contribution to the relaxivity by including into the fitting model a term which considers the dipolar interaction of second sphere water molecules with the paramagnetic Gd^{III} ion (r^{2s}_{1p}). Over the last 15 years this contribution has seldom been taken into account for the interpretation of relaxometric data and, in the case of MRI contrast agents, only in studies involving small Gd^{III} chelates with q = 0.[12,15] The X-ray crystal structure of $[Yb(DTPA)(H_2O)]^{2-}$ provides clear evidence of the presence of a water molecule hydrogen-bonded to oxygen atoms of adjacent carboxylate groups and at a distance significantly closer than that of the outer sphere solvent molecules. In fact, the orientation of this water molecule, directed towards the metal ion, is such that a hydrogen atom is located only 3.28 Å from Gd^{III}. A contribution to relaxivity is thus expected provided that the mean residence lifetime of the molecule is longer than the diffusional correlation time, i.e. the time necessary for the solvent and the metal complex to diffuse apart from each other (proportional to d^2/D, about 50 ps). Under this condition,

Table 3. Best fitting parameters derived from the variable temperature NMRD data of $Na_2[Gd(DTPA)(H_2O)]$

Parameter	4 °C	10 °C	18 °C	25 °C	32 °C	39 °C
τ_{SO} (ps)	85	82	74	72	73	65
τ_V (ps)	35	31	27	22	19	17
τ_M (ns)	1270	864	531	363	241	166
τ_R (ps)	126	106	86	65	61	52
D (10^5 cm^{2}s^{-1})	1.62	1.92	2.38	2.84	3.38	3.99
τ_{M1} (ps)	156	129	101	94	67	56

the second sphere water molecule experiences rotation of the complex and its effect to the measured solvent relaxation rate can be evaluated by using the inner sphere approach. We then fitted the experimental NMRD data at 25 °C with a model that includes the second sphere term and thus 3 more parameters: the number of the second sphere water molecules, q_{2S}, their distance from Gd^{III}, r_{2S} and their mean residence lifetime τ_{M2S}. The total number of relaxation parameters is 11, but several of them can be fixed by using structural data or can be estimated by using values obtained with other techniques. An accurate value of τ_M has been obtained by Merbach and co-workers by ^{17}O NMR ($\tau_M \cong 360$ ns at 25 °C); τ_R has been calculated by ^{13}C NMR relaxation data to be about 70 ps; r_{Gd-H} is allowed to vary slightly about the value of 2.93 Å estimated from X-ray data; the D value has been previously assessed by the analysis of NMRD profiles for complexes whose relaxivity is exclusively controlled by the outer sphere term ($q = 0$); to d we may assign the value of 4.50 Å as estimated before. The adjustable parameters are then the electronic relaxation time (τ_{S0} and τ_v), τ_{M2S} and q_{2S}/r_{2S}, whereas τ_R and τ_M were allowed to vary a little from the initial estimates in order to optimize the fitting. The results of the fitting procedure of the data measured at 4, 10, 18, 25, 32 and 39 °C to this model are reported in Table 3. In Figure 2 the experimental and calculated profiles at 25 °C, along with the calculated contributions of the outer- and second sphere components are shown. The experimental data for all temperatures are fit nicely with a set of structural parameters that match the crystallographic data, reproduce very well previous estimates on the electronic relaxation times and water exchange lifetime and account for a second sphere water contribution of about 13% of the observed relaxivity at low fields. The calculated (20 MHz; 25 °C) temperature dependence of the second sphere contribution is reported in Figure 3 and shows an exponential decrease with increasing temperature, in accord with the fitting results, indicating that the residence lifetime of the hydrogen-bonded water molecules represents the dominant correlation time of the dipolar interaction. This behavior is in agreement with the expectation that at high temperatures the lifetime of the hydrogen-bonding interaction becomes so short as to approach the diffusion limit, where this contribution vanishes.

The best fit value of q_{2S}/r_{2S} is $1.5 \cdot 10^7$ cm^{-1} which could be assigned to a water molecule with a proton at 3.28 Å from the Gd^{III} ion by analogy with the crystal structure of the Yb complex. Clearly, this is only an approximation, as the number of water molecules hydrogen-bonded to the carboxylate groups is surely higher than one. On the other hand, it must be stressed that the technique is only capable of detecting the effects associated with those solvent molecules whose mean residence lifetime is sufficiently long. Thus, it cannot be excluded that the second sphere contribution evidenced in this work is attributable to a single water molecule located in a well-defined position, as revealed by the X-ray crystal structure. The estimated residence lifetime of this water is 94 ps at 25 °C, in good agreement with previous estimates on related systems.

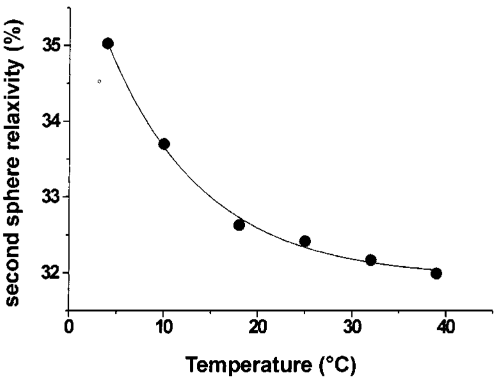

Figure 3. Temperature dependence of the second sphere contribution (%) to the overall relaxivity of $[Gd(DTPA)(H_2O)]^{2-}$ at 20 MHz and 25 °C.

It is generally assumed that the temperature dependence of the correlation time τ_v (and of Δ^2) follows

$$\frac{1}{\tau_v} = \frac{RT}{Nh} exp\left(\Delta S^{\#}/R - \Delta H^{\#}/RT\right) \tag{9}$$

an Eyring behavior (Equation 9) and the plot of data versus temperature, reported in a linear form in Figure 4, represents a good check of the reliability and accuracy of the fitting procedure. The two straight lines in Figure 4 have R factors > 0.99 indicating that the assumptions made for deriving the parameters listed in Table 3 are reasonable and provide correct estimates of the electronic relaxation times of Gd^{III}.

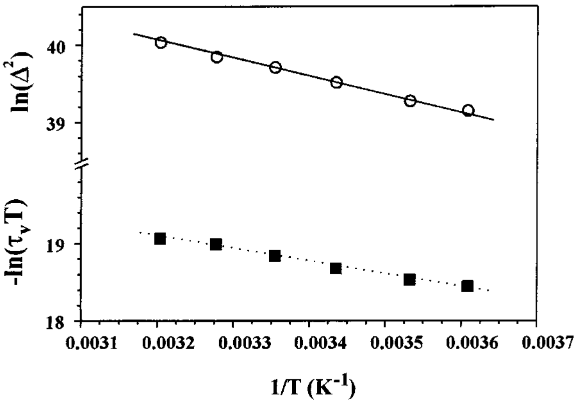

Figure 4. Temperature dependence of the relaxation parameters Δ^2 and $\tau_V T$, calculated from the best-fitting procedure of the NMRD profiles measured at 4, 10, 18, 25, 32 and 39 °C.

Conclusion

The X-ray crystal structure of $K_2[Yb(DTPA)(H_2O)]$ shows that the coordination polyhedron around the metal ion is very similar to that previously found for the Gd^{III} complex, with a nine-coordinate ligand environment composed of the three amine nitrogens, five carboxylate oxygens and one water molecule. The coordination geometry is best described as a tricapped trigonal prism. Additional water molecules have been localized and described as belonging to the outer- and second hydration spheres of the metal ion. In particular, the second sphere water molecule is involved in an hydrogen bond network with the bound water and the uncoordinated carboxylate oxygens and is located very close to the metal ion. From the X-ray results we have reconsidered the NMRD relaxivity profiles of the MRI contrast agent $[Gd(DTPA)(H_2O)]^{2-}$, based on a model comprising contributions from the water molecules in the three different environments: inner-, outer- and second sphere. An excellent fit of the experimental data to this model has been obtained with a set of the relaxation parameters which is in much better agreement with the available structural data. The contribution of the second sphere term is about 10% of the total relaxivity but is very important for a correct and more realistic interpretation of the experimental data. Furthermore, its contribution could be optimized and the relaxivity enhanced through suitable ligand design.[23]

Experimental Section

General Remarks: $GdCl_3{\cdot}6H_2O$, $YbCl_3{\cdot}6H_2O$ and H_5DTPA were purchased from Aldrich. The metal complexes were prepared by mixing stoichiometric amounts of the ligand and of the metal chloride and by adjusting the pH to 7 with KOH. The solutions were kept at room temperature under vigorous stirring for one hour until the pH stabilized. The compounds were then purified by precipitation by addition of acetone. In the case of $K_2[Gd(DTPA)(H_2O)]$, the absence of free metal ion was assessed by the constant value of the water proton relaxation rate, measured at 298 K and 20 MHz, after successive additions of a small excess of the free ligand. The paramagnetic solutions of the Gd^{III} complex for the ^1H low resolution NMR study were prepared by weight of the solid compound and their concentrations (1–2 mM) measured by relaxometry from the known value of the relaxivity at 312 K. A 0.15 M solution of the Yb^{III} complex was prepared in D_2O and the purity of the compound was ascertained by recording the ^1H NMR spectrum. Crystals suitable for the X-ray diffraction study were obtained after very slow evaporation at room temperature of a concentrated aqueous solution of the complex.

^{1}H NMR Measurements: Water proton relaxation measurements (20 MHz, 25 °C) were carried out with a Stelar Spinmaster Spectrometer (Mede, Pv, Italy) on 0.5–2 mM solutions of $K_2[Gd(DTPA)(H_2O)]$ at pH = 7.2, $I = 0.1$. Spin-lattice relaxation times T_1 were measured by the standard inversion recovery method with typical 90° pulse width of 3.5 ms, 16 experiments of 4 scans. The reproducibility of the data is ±1%. The $1/T_1$ nuclear magnetic relaxation dispersion profiles of water protons were measured at 4, 10, 18, 25 and 39 °C using 1.5 mM solutions of the complex on the field-cycling Koenig–Brown relaxometer of the University of Torino (Italy). The temperature was controlled by circulating a freon from an external bath and measured by a thermometer inserted into the freon close to the sample. The reproducibilities of the measured T_1 values were estimated to be ±2%.

X-ray Crystallographic Study

A suitable crystal of $K_2[Yb(DTPA)(H_2O)]$ was coated with Paratone oil, placed on the end of a silica fiber and mounted in a goniometer head on the Nonius CAD4 diffractometer in a stream of cold nitrogen gas. The crystal was centered optically and unit cell parameters and an orientation matrix for data collection were obtained at –100 °C by using the centering program in the CAD4 system. Details of the crystal data are given in Table 2 The actual scan range was calculated by scan width = scan range + 0.35 tanθ and backgrounds were measured by using the moving-crystal – moving-counter technique at the beginning and end of each scan. Two representative reflections were monitored every 2 h as a check on instrument and crystal stability. Lorentz, polarization, and decay corrections were applied to the data as well as an absorption correction based on a series of ψ scans. The weighting scheme used during refinement was $1/\sigma^2$, based on counting statistics.

The structure was solved by Direct Methods using SHELXTL/PC V5.03[24] which revealed the positions of most of the non-hydrogen atoms. All other non-hydrogen atoms were found by successive difference Fourier syntheses including the ytterbium-bound water, O(1 W), the second sphere water molecule, O(7 W) and the outer sphere water molecules, O(2,3,4,5,6,8 W). Hydrogen atoms were placed their expected chemical positions using the HFIX command for all ligand hydrogens, but hydrogens attached to oxygen-water molecules were identified from a difference Fourier; all hydrogens were included in the final cycles of least squares with isotropic U_{ij} 's related to the atoms on which they rode. All other non-hydrogen atoms were refined anisotropically.

Neutral atom scattering factors and values of $\Delta f'$ and $\Delta f''$ were taken from Volume C of the *International Tables for X-ray Crystallography.*[25] Structure refinement and preparation of figures and tables for publication were carried out on PCs by using SHELXTL/PC V5.03.[24] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC- 133337. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44–1223/336–033; E-mail: deposit@ccdc.cam.ac.uk].

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