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NMR Evidence of a Long Exchange Lifetime for the Coordinated Water in Ln(III)−Bis(methyl amide)-DTPA Complexes (Ln = Gd, Dy)[1]

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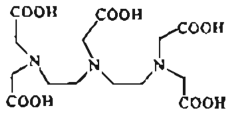
The magnetic field dependence of the water proton longitudinal relaxation rate for the paramagnetic complex Gd−BMA-DTPA has been measured and analyzed at different temperatures. Interestingly we have found that the solvent relaxivity is largely affected by the residence lifetime (τ_M) of the water molecule in the coordination site on the metal chelate. The calculated values for τ_M at 298 K is 0.81 μs, i.e. 4-fold longer than the values recently reported for Gd−DTPA and much longer than the values commonly assumed in the analysis of NMRD profiles of poly(amino carboxylate) complexes. This result has been also confirmed by an alternative approach for the structurally analogous Dy(III) complex. In this latter case, from the measurement of the paramagnetic contribution to ^{1}H NMR chemical shift and transverse relaxation rate of the solvent water protons, we evaluated the residence lifetime τ_M by solving iteratively the Swift−Connick equations.

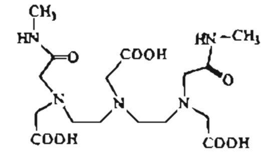
Introduction

The Gd(III)−bis(methyl amide)-DTPA complex (Gd−BMA-DTPA) is under intense scrutiny as a nonionic alternative to GdDTPA as contrast agent (CA) in magnetic resonance imaging (MRI) techniques[2] (Chart 1). It is expected to show a similar biodistribution and excretion pathway, but its lower osmolarity predicts a better physiological acceptance. This feature is particularly important in view of novel applications which require higher concentrations of the contrast agent.[3]

Chart 1

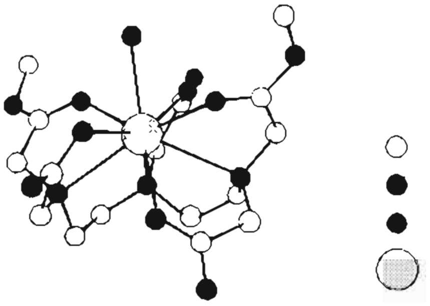


DTPA



BMA-DTPA

The X-ray structure[4] of the Dy(III) complex of this ligand shows a trigonal bicapped prismatic geometry analogous to that found for NdDTPA[5] and GdDTPA[6] complexes. The lanthanide (III) ion displays a nine-coordination ligand environment that includes the three amino nitrogens, the two carboxylic oxygens, the two amide oxygens and one water molecule (structure **1**).



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In solution the title complexes are expected to be present as a mixture of interconverting conformers, as recently suggested on the basis of a variable temperature ^{1}H-NMR study for the diamagnetic La(III) and Lu(III) derivatives.[7] This is consistent with the observations made by Geraldes and Peters on a series of Ln(III) complexes for the analogous bis(propyl amide)-DTPA ligand.[8,9] The dynamic behavior shown by these bisamide derivatives in aqueous solution appears to be of the same type of that previously found for the parent LnDTPA complexes.[10−12]

A major limitation in the use of Gd−BMA-DTPA as CA for MRI could be represented by its relatively low stability constant[13] (log $K_f = 16.86 \pm 0.05$), about 6 orders of magnitude smaller than the corresponding value for the DTPA complex.[14] This shortcoming may justify some concerns about the potential release in body fluids of the highly toxic Gd^{3+} ions and free

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ligand. However, since the release of the metal ion presumably occurs through an exchange mechanism involving Zn^{2+}, Cu^{2+}, and/or Ca^{2+} ions, it was suggested[13] that the chemotoxicity of the Gd^{3+} complexes is better related to the selectivity constant of the ligand (a function of its stability constant with Gd^{3+} and other metal ions) rather than to the Gd pK_f values only. In fact it has recently been reported that this complex has a very high *in vivo* stability, as it is excreted in urine without any metabolic alteration.[15] Besides safety another important requirement for an MRI-CA is a good value for the relaxivity ϱ_1, defined as the increment of water proton relaxation rate per unit concentration of the metal complex. In this work we present the results of a detailed study on the relaxation properties of Gd–BMA-DTPA as a function of magnetic field strength (by recording and analyzing the NMRD profiles) and temperature. We compare our results with published data for GdDTPA, in an attempt to gain a better understanding of the influence of the chemical and structural properties of the ligand on relaxivity.[16]

Experimental Procedure

The ligand BMA-DTPA was synthesized from DTPA-bis(anhydride) according to the procedure reported by Konings et al.[17] for DTPA-bis(ethyl amide). The Gd(III) and Dy(III) complexes were prepared from their chlorides and the ligand in water at pH = 6.5. The aqueous solutions of the complexes were then desalted by electrodialysis.

Proton solvent longitudinal relaxation times were measured at 20 MHz and variable temperature on a Stelar SpinMaster spectrometer (Stelar, Mede (PV), Italy) by means of the inversion–recovery technique (16 experiments, four scans). The reproducibility in T_1 measurements was ±0.4%. The temperature was controlled by a JEOL air flow heater, equipped with a copper–constantan thermocouple; the actual temperature in the probehead was measured with a Fluke 52 k/j digital thermometer, with an uncertainty of 0.5 K.

The $1/T_1$ NMRD profiles of water protons were measured over a continuum of magnetic fields from 0.00024 to 1.2 T (corresponding to 0.01–50 MHz proton Larmor frequency) on the Koenig–Brown field-cycling relaxometer installed at the Department of Chemistry, University of Florence, Italy. The relaxometer works under complete computer control with an absolute uncertainty in $1/T_1$ of ±1%. The temperature inside the probe was controlled with a circulating bath of perfluoroalkanes.

The paramagnetic shift $\Delta\omega_p$ of the water proton signal in the presence of Dy–BMA-DTPA has been measured at the proton Larmor frequency of 400 MHz at 298 K on a Jeol EX-400 spectrometer. The contribution to the observed ^1H shift from change in magnetic susceptibility has been ruled out by using *tert*-butyl alcohol as an internal reference. The difference in the frequency separation between water and reference signal measured in the presence and in the absence of Dy–BMA-DTPA provided the actual $\Delta\omega_p$ value, because the ^1H shift of *tert*-butyl alcohol is only affected by the change in the magnetic susceptibility of the solution containing the paramagnetic complex.

The nonlinear set of Swift–Connick equations has been solved iteratively, by approximating the equations to their Taylor series truncated to the first term. The roots of this linear set has been used as initial guess for the next Taylor series, until convergence has been achieved. The Fortran code has been compiled and run on a DECstation 2100.

Results and Discussion

The ability to enhance the water proton longitudinal relaxation rate R_1^{obs} shown by Gd^{3+} complexes is well understood on the basis of the Solomon–Bloembergen equations:[18–20]

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

$$R_{1,p}^{is} = \frac{Mq}{55.6}\frac{1}{T_{1M} + \tau_M} \tag{2}$$

$$\frac{1}{T_{1M}} = \frac{2}{15}\gamma_H^2 g^2 \mu_B^2 S(S+1) r^{-6}\left(\frac{7\tau_c}{1 + \omega_S^2\tau_c^2} + \frac{3\tau_c}{1 + \omega_I^2\tau_c^2}\right) \tag{3}$$

$$\frac{1}{\tau_c} = \frac{1}{\tau_R} + \frac{1}{\tau_S} + \frac{1}{\tau_M} \tag{4}$$

$$\tau_S^{-1} = \frac{1}{5\tau_{S0}} + \frac{1}{1 + \omega_S^2\tau_v^2} + \frac{4}{1 + 4\omega_S^2\tau_v^2} \tag{5}$$

In eqs 1–5 $R_{1,p}$ is the contribution from the exchange of water molecules in the inner coordination sphere of the paramagnetic metal ion to the bulk water, $R_{1,p}^{os}$ is the contribution from water molecules in the outer coordination sphere of the metal ion, $R_{1,w}$ represents the solvent relaxation rate in the absence of the paramagnetic compound, M is the molar concentration of the metal complex, q is the number of water molecules directly coordinated to the Gd^{3+} ion, τ_M is their mean residence lifetime; T_{1M} is their longitudinal relaxation time, γ_H is the magnetogyric ratio of proton nuclei, g is the electronic Landè factor, μ_B is the Bohr magneton, S is the electronic spin quantum number, r is the distance of the coordinated water proton nuclei from the paramagnetic metal ion, τ_R is the molecular reorientational correlation time, and τ_S is the electronic relaxation time. The latter parameter is frequency-dependent through eq 5, and it is determined by the electronic relaxation time at zero magnetic field τ_{S0} and by the field-independent correlation time τ_v.

The outer sphere term $R_{1,p}^{os}$ may represent a sizable contribution to the observed relaxation rate of low molecular weight Gd^{3+} complexes. It has been shown[21] that its contribution may be safely evaluated through Freed's equation,[22,23] originally suggested for the study of the interaction between stable free radicals and organic solvent molecules:

$$R_{1,p}^{os} = (32\pi/405)\,\gamma_H^2 g^2 \mu_B^2 S(S+1)(N_A/1000)\,(M/aD) \times [7J(\omega_S) + 3J(\omega_I)] \tag{6}$$

where N_A is Avogadro's number, a is the distance of closest approach between the paramagnetic center and the water molecules, and D is the sum of the diffusion coefficients for water and paramagnetic complex. The spectral density function $J(\omega)$ is given by the equations below:

$$J(\omega) = \frac{1 + 5z/8 + z^2/8}{1 + z + z^2/2 + z^3/6 + 4z^4/81 + z^5/81 + z^6/648} \tag{7}$$

$$z = 2\,(\omega\tau_D + \tau_D/\tau_S)^{1/2} \tag{8}$$

$$\tau_D = a^2/D \tag{9}$$

The differential ability of small Gd^{3+} complexes to relax water protons at the imaging magnetic fields (0.5–1.5 T) is mainly

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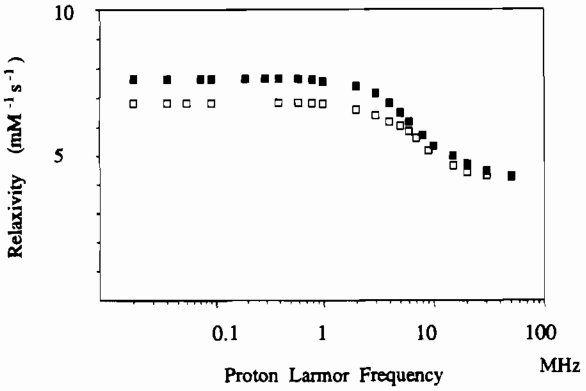

Figure 1. Magnetic field dependence of the relaxivity for GdDTPA (■) and Gd–BMA-DTPA (□) at 25 °C and pH = 7.3.

related to the different value of the parameter τ_R.[24] In fact, as defined in eq 4, τ_c is determined by the shortest of the three correlation times, τ_R, τ_S and τ_M. Usually, for a small Gd^{3+} complex, τ_R is about 10^{-10} s, whereas τ_S and τ_M are significantly longer.[14,16,25,26] However, if τ_M becomes so long to approach the value of T_{1M} (~10^{-6} s) it may largely influence the solvent proton relaxation rate, through eq 2, determining a lower value of $R_{1,p}$.

Very recently Merbach et al.[27,28] reported that the water lifetime in GdDTPA and GdDOTA are unexpectedly, and comparably, long, about 0.2 μs at ambient temperature. However as they concluded, the effectiveness of these complexes as contrast agents for MRI is not limited by the relatively low water exchange rates but by T_{1M}, the longitudinal relaxation time of water protons in the first coordination sphere.

On comparing the $1/T_1$ NMRD profiles[29] (Figure 1) of Gd^{3+} complexes of DTPA and BMA-DTPA at 25 °C, we note that the observed relaxivities are smaller for the latter complex at low frequencies. Furthermore the dispersion in the Gd–BMA-DTPA curve is rather smooth. Both features are not expected on the basis of the close similarity in the coordination ligand environments shown by the two complexes and of their similar molecular weights. A good fitting of the relaxivity data of the Gd–BMA-DTPA profile was possible only by introducing a τ_M value of 0.81 μs, (Figure 2), about 4-fold longer than that just reported for GdDTPA and exceedingly longer than those assumed for similar Gd(III) complexes.[14,16] All the other parameters compare very well with those obtained from the fitting procedure of GdDTPA curve.[16] Although qualitatively, an indication of the relevant role of τ_M in controlling the relaxivity of Gd–BMA-DTPA complex was also gained from $R_{1,p}$ measurements as a function of the temperature at the fixed frequency of 20 MHz. As shown in Figure 3, $R_{1,p}$ of GdDTPA steadily decreases as the temperature increases whereas Gd–BMA-DTPA shows an almost flat profile in the 5–30 °C temperature range. Since both τ_R and τ_M increase with decreasing temperature, thus resulting in an opposite temperature dependence of τ_M and T_{1M}, this behavior can be well accounted for by assuming that in eq 2 the fast exchange condition ($T_{1M} \gg \tau_M$), valid for GdDTPA in the temperature range investigated, does not hold for the BMA-DTPA complex for which T_{1M}~τ_M.

τ_{S0}= 65 ps
τ_v = 17 ps
τ_M= 0.81 μ s
τ_R = 72 ps

q = 1
r = 3.1 A
a = 3.6 A
D = $2.2 \cdot 10^{-5}$

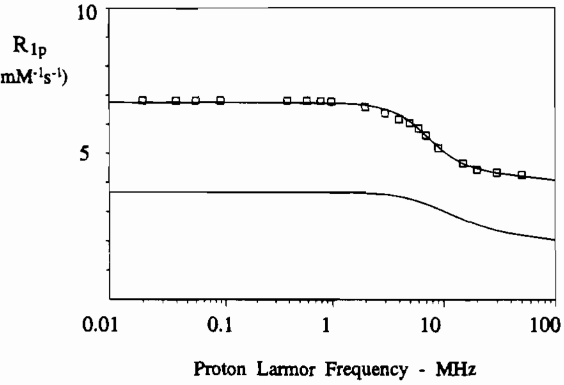

Figure 2. $1/T_1$ NMRD profile for 1 mM aqueous solution of Gd–BMA-DTPA at 25 °C and pH = 7.3. The solid curve through the experimental data has been calculated with the best fitting parameters reported above. The lower curve represents the outer sphere contribution to the relaxivity.

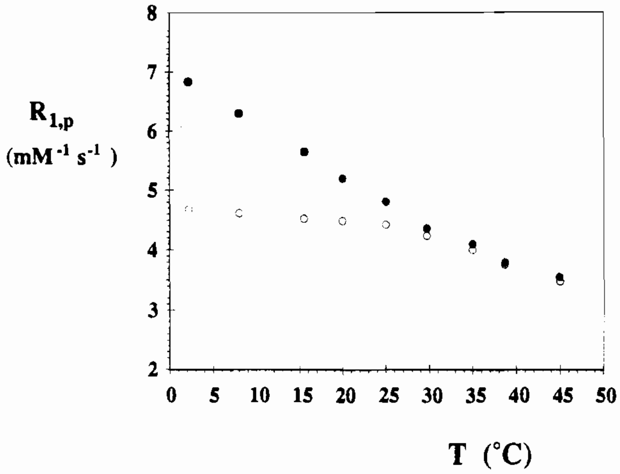

Figure 3. Temperature dependence of the relaxivity for 1 mM aqueous solutions of GdDTPA (●) and Gd–BMA-DTPA (○), measured at 20 MHz and pH = 7.3.

Quantitatively, the temperature dependences of the various parameters affecting the proton relaxation rate enhancement of the aqueous solutions of Gd–BMA-DTPA have been evaluated through the fitting of the $1/T_1$ NMRD profiles measured at three temperatures, 5, 25, and 35 °C (Figures 2, 4, and 5). First of all, it is worth noting that the three profiles look very similar in shape and magnitude and overlap to some extent in several regions. The separation of inner and outer sphere contributions to the overall relaxivity by the fitting procedure to eqs 1–9 allows us to gain more insight into the observed behavior. Whereas for short values of τ_M the relaxivity increases at any frequency as the temperature decreases, mainly as a consequence of the increase of τ_R (and then of the inner sphere contribution), in Gd–BMA-DTPA solutions we observe a steady decrease of the inner sphere contribution with decreasing temperature (Figure 6). The profile of the inner sphere contribution at 5 °C is almost flat and accounts for only about 16% (at low field) to 22% (at high field) of the overall relaxivity whereas for solutions of GdDTPA at the same temperature is the inner sphere contribution which largely dominates the profiles. Thus, although the τ_R value (and its temperature dependence) is strictly

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τ_{SO} = 89 ps q = 1

τ_v = 21 ps r = 3.1 A

τ_M = 1.3 µs a = 3.6 A

τ_R = 107 ps D = 1.4·10^{-5}

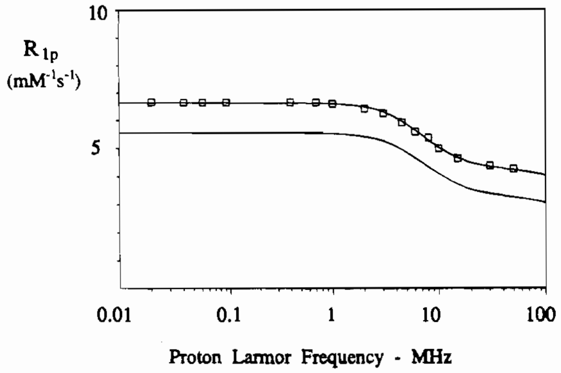

Figure 4. $1/T_1$ NMRD profile for 1 mM aqueous solution of Gd−BMA-DTPA at 5 °C and pH = 7.3. The solid curve through the experimental data has been calculated with the best fitting parameters reported above. The lower curve represents the outer sphere contribution to the relaxivity.

τ_{SO} = 72 ps q = 1

τ_v = 15 ps r = 3.1 A

τ_M = 0.28 µs a = 3.6 A

τ_R = 58 ps D = 2.7·10^{-5}

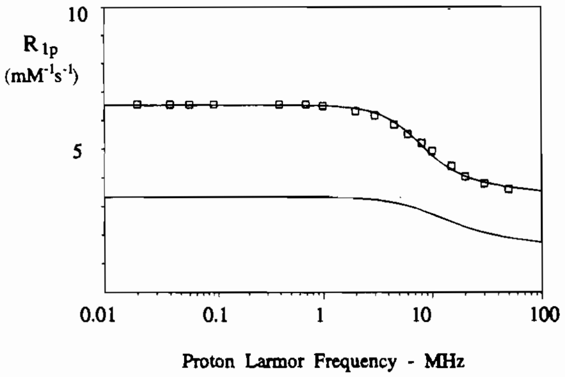

Figure 5. $1/T_1$ NMRD profile for a 1 mM aqueous solution of Gd−BMA-DTPA at 35 °C and pH = 7.3. The solid curve through the experimental data has been calculated with the best fitting parameters reported above. The lower curve represents the outer sphere contribution to the relaxivity.

analogous to those of other Gd complexes of similar size and then affects T_{1M} to a similar extent, its effect on $R_{1,p}{}^{is}$ is quenched by the long value of τ_M (see eq 2). The increase of the outer sphere contribution as the temperature decreases is mainly due to a shortening of the diffusion coefficient D following the increased viscosity of the solution.

The value of τ_{SO} at 25 °C is only slightly lower than that reported for GdDTPA,[16] suggesting that the substitution of two carboxylate groups by two amide functionalities in the coordination cage does not cause any dramatic change in the electronic relaxation pathway.[30,31] The changes in τ_R and τ_v values with the temperature are consistent with the behavior predicted by the established theory.[16,33] As expected τ_M varies extensively as the temperature changes, and from the best fitting data calculated at the three temperatures, a free energy value ΔG^{298} = 38.3 KJ/mol is obtained for the exchange process.

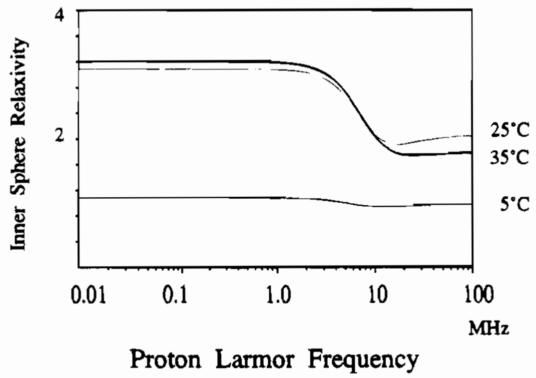

Figure 6. Calculated NMRD profiles of the inner sphere contribution to the relaxivity of Gd−BMA-DTPA at three temperatures. This representation of the data clearly evidences the dramatic changes of the profiles, both in magnitude and shape, occurring by small variations of the exchange lifetime value for the coordinated water molecule.

Actually only few τ_M values were previously determined for lanthanide(III) complexes. Merbach and co-workers[33−35] developed a ^{17}O NMR approach based on the measurement of T_1, T_2, and the isotropic shift of ^{17}O nuclei of bulk water. Through this procedure they were able to determine the water exchange rate in several Ln(III) aquo ions[35] (Ln = Gd−Yb) and observed that the exchange lifetime of the coordinated water molecules increases along the considered row. They also reported a water exchange time of 7−10 ns for GdPDTA,[33] which results is sizably longer than the value found for the parent aquo ion.[33,35] As mentioned above, very recently Merbach's group showed that τ_M is almost 2 orders of magnitude longer in both GdDTPA and GdDOTA.[27,28]

It is worth noting that among the large number of Gd(III) complexes investigated through the NMRD technique Gd−BMA-DTPA is the first compound that shows a profile markedly affected by τ_M. As it was pointed out,[16] in the former cases the fitting results are insensitive to the exact value of τ_M, since the conditions $T_{1M} \gg \tau_M$ (eq 2) and $\tau_R \ll \tau_M$ (eq 4) hold. The $1/T_1$ NMRD profile of Gd−BMA-DTPA in citrate human plasma at 37 °C was already reported by Tweedle.[36] It shows relaxation rates higher than those measured by us (at 35 °C) at any frequency and, at the imaging fields, coincident with those of GdDTPA. We think that the origin of this discrepancy lies chiefly in the effect on solvent relaxation of citrate ions, added to the blood sample to avoid coagulation. In fact we proved that the addition of potassium citrate to an aqueous solution of Gd−BMA-DTPA causes a steady increase of the observed water proton relaxation rate (Figure 7). Since no effect is observed in the case of GdDTPA, the increase of proton relaxation rates of Gd−BMA-DTPA solutions likely arises from competition of the citrate with BMA-DTPA for Gd(III), because of the lower thermodynamic stability of the bis(amide) complex in respect to the parent GdDTPA. On the other hand no detectable effect on the relaxation rates has been observed upon the addition of bovine serum albumin to an aqueous solution of Gd−BMA-

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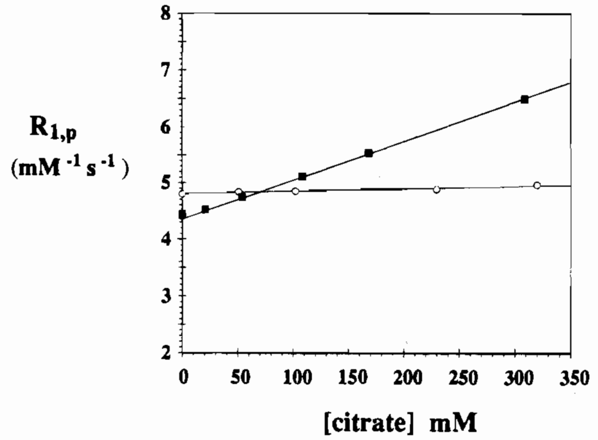

Figure 7. Relaxivities of GdDTPA (○) and Gd−BMA-DTPA (●), measured at 20 MHz and 25 °C, as a function of the concentration of citrate ions added to their 1 mM aqueous solutions.

DTPA. As expected the absence of residual electric charge and/or of an hydrophobic substituent on the complex makes the interaction with albumin unfavorable.[37]

An alternative approach for evaluating the water exchange lifetime τ_M is provided by the observation of the high resolution ^{1}H-NMR spectrum of complexes in which the Gd(III) ion has been substituted by a lanthanide(III) ion with a shorter electronic relaxation time. To this purpose we prepared the corresponding Dy−BMA-DTPA complex. The ^{1}H-NMR resonances of the ligand protons are too broad to allow any meaningful assignment. The ^{1}H-NMR water signal is strongly affected in both chemical shift value and half-height line width by the presence of the paramagnetic complex whose inner sphere coordinated water is exchanging with the bulk water. According to the Swift−Connick theory,[38] the transverse relaxation rate ($R_{2,p}$) of the solvent water protons and the shift of the water ^{1}H signal from the diamagnetic position ($\Delta\omega_p$), in the presence of a concentration M of paramagnetic complex, are given by eqs 10 and 11, where $\Delta\omega_M$ is the chemical shift difference (in rad/s) between the free and coordinated water resonance.

$$R_{2,p} = \frac{qM}{55.56\tau_M}\,\frac{T_{2M}^{-2} + T_{2M}^{-1}\tau_M^{-1} + \Delta\omega_M^{\ 2}}{(T_{2M}^{-1} + \tau_M^{-1})^2 + (\Delta\omega_M)^2} \qquad (10)$$

$$\Delta\omega_p = \omega_p - \omega_f = \frac{(qM/55.56)\Delta\omega_M}{\tau_M^{\ 2}[(T_{2M}^{-1} + \tau_M^{-1})^2 + (\Delta\omega_M)^2]} \qquad (11)$$

At 400 MHz and 25 °C, a 4.9 mM solution of Dy−BMA-DTPA afforded a $R_{2,p}$ value of 56.2 s^{-1} and a $\Delta\omega_p$ of 56.6 rad/s. In order to obtain τ_M from these data we needed an independent evaluation of T_{2M}^{-1}. This parameter is the sum of two contributions, namely the dipolar term R_2^{DD} and the Curie term $R_2\chi$.[32]

$$R_2^{DD} = \frac{1}{15}\,\frac{\gamma_H^{\ 2}g^2\mu_B^{\ 2}S(S+1)}{r^6} \times \left[4\tau_S + \frac{3\tau_s}{1+\omega_I^{\ 2}\tau_S^{\ 2}} + \frac{13\tau_s}{1+\omega_S^{\ 2}\tau_S^{\ 2}}\right] \qquad (12)$$

$$R_2\chi = \frac{1}{5}\,\frac{\omega_H^{\ 2}g^4\mu_B^{\ 4}S^2(S+1)^2}{r^6(3kT)}\left[4\tau_R + \frac{3\tau_R}{1+\omega_I^{\ 2}\tau_R^{\ 2}}\right] \qquad (13)$$

By using the values of 3.14 Å for the water proton−dysprosium distance as found in its X-ray structure,[4] of 3 × 10^{-12} s for the electronic relaxation time τ_S as found in related Dy(III) complexes[39,40] and of 7 × 10^{-11} s for the reorientational correlation time τ_R as determined from the NMRD profile of Gd−BMA-DTPA, we obtained an evaluation of the dipolar term ($R_2^{DD} = 2.91 \times 10^3$ s^{-1}) and of the Curie term ($R_2\chi = 2.45 \times 10^3$ s^{-1}) that allow a calculation of $T_{2M} = 2.0 \times 10^{-4}$ s.

Finally, the numerical solution of eqs 10 and 11 provides a value of 7.8 × 10^{-7} s for τ_M together with a ω_M value of −502 ppm for the protons of the water molecule coordinated to the Dy(III) ion. This τ_M value for the Dy(III) complex is then of the same order of magnitude as that obtained from the NMRD profile of the Gd(III) complex, thus supporting the hypothesis of comparable lifetimes for Gd(III) and Dy(III) chelates. Furthermore we anticipate that such a behavior is found in several other Ln(III)−bis(amide)-DTPA complexes.

Tentatively we may speculate that the remarkable elongation of τ_M may find its explanation in the extended hydrogen-bonding three-dimensional network involving a number of water molecules and ligand carboxylate and amide functionalities as shown in the X-ray structure of Dy−BMA-DTPA.[4] In addition to H-bonding, the restricted coordination geometry of these bis(amide) complexes may cause a further constrain in the dissociative pathway of the exchanging water molecule.

Another explanation may be based on the decrease of the residual charge on the metal ion upon the transformation of carboxylate to amide functionalities. This may be responsible for a stronger Ln−OH$_2$ bond, which then results in a decrease of the water exchange rate.[41]

In conclusion, we think that this generalized observation of long τ_M values in Ln(III)−bis(amide)-DTPA complexes could imply the existence of a drastic limit in the search for higher relaxivity through the formation of conjugates with protein via the amide group.[42] Actually the lack of the very strong relaxivity peak expected in the NMRD profile of the ternary albumin−DTPA−Gd complex could also be a consequence of the quenching effect of a long τ_M value.

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