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The highest water exchange rate ever measured for a Gd(III) chelate†

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The complex $[Gd(L)(H_2O)]^{3-}$ (H_6L = *N*,*N'*-bis(6-carboxy-2-pyridylmethyl)ethylenediamine-*N*,*N'*-methylenephosphonic acid) displays the highest water exchange rate ever measured for a Gd(III) chelate (k_{ex}^{298}= 8.8 × 10^8 s^{-1}), which is attributed to the flexibility of the metal coordination environment.

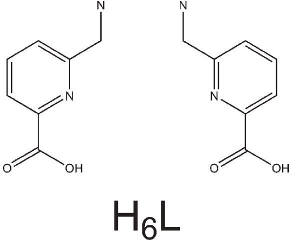
Stable chelates of trivalent lanthanide ions are of interest due to their application as contrast agents in magnetic resonance imaging (MRI).[1] Currently, about one third of all MRI scans are made after the administration of a Gd(III)-based contrast agent. Contrast agents enhance the image contrast by preferentially influencing the relaxation efficiency of the water proton nuclei in the target tissue. The efficiency of a contrast agent is evaluated in terms of its relaxivity, which is defined as the relaxation-rate enhancement of water proton nuclei per mM concentration of metal ion. These complexes contain at least one Gd(III)-bound water molecule that rapidly exchanges with the bulk water of the body, which provides an efficient mechanism for the longitudinal and transverse relaxation rate ($1/T_1$ and $1/T_2$) enhancement of water protons. The Solomon–Bloembergen–Morgan theory, which relates the observed paramagnetic relaxation rate enhancement to microscopic properties, predicts that high relaxivities at the imaging fields (0.5–1.5 T) may be observed for systems with optimal values for the three most important influencing factors: rotation, water exchange rate and electron paramagnetic relaxation.[2]

The current commercial Gd(III) chelates show water exchange rates that are an order of magnitude lower than the optimal value. Recently, it was shown that nine-coordinate Gd(III) complexes with fast water exchange can be obtained by inducing steric compression around the water binding site, for instance by replacing an ethylene bridge of $DOTA^{4-}$ or $DTPA^{5-}$‡ by a propylene bridge.[3,4] These Gd(III) poly(amino carboxylates) undergo dissociative, D, or dissociative interchange, I_d, water exchange. Thus, steric crowding around the bound water site facilitates its leaving, which, in a dissociative process, constitutes the rate determining step. The presence of a bulky phosphonate group replacing a carboxylate one in the frameworks of $DOTA^{4-}$ or $DTPA^{5-}$ also causes a similar effect in the water exchange rate of the corresponding Gd(III) complex.[5,6] However, these systems still show water exchange rates one order of magnitude below that of $[Gd(H_2O)_8]^{3+}$. The faster water exchange rate observed for $[Gd(H_2O)_8]^{3+}$ compared to those usually observed for Gd(III) poly(amino carboxylates) is explained, at least in part, by the easy rearrangement of the flexible coordination sphere, while chelates have a much more rigid inner-sphere structure whose rearrangement requires higher energy. Thus, an alternative approach to obtain fast water exchange rates is to prepare Gd(III) complexes with ligands forming octa- or nona-coordinate complexes in solution, and with little preference for one to another. Herein we illustrate this strategy with the Gd(III) complex of L (Scheme 1). Compound H_6L was prepared in moderate yield (40%) by the Mannich-type reaction of the corresponding diamine precursor[7] with paraformaldehyde and phosphorous acid in 6 M HCl.†

The emission lifetimes of the Eu($^5D_0$) excited level have been measured in D_2O and H_2O 10^{-3} M solutions of the Eu(III) complex (298 K, pH = 8.6), and were used to calculate the number of coordinated water molecules, *q*. The measured emission lifetime in H_2O solution ($\tau_{obs}(H_2O)$) was 0.80 ± 0.01 ms, while the $\tau_{obs}(D_2O)$ value amounts to 2.01 ± 0.01 ms. By using the expression proposed by Supkowski and Horrocks[8] we obtain $q = 0.5 \pm 0.1$. This result suggests the presence of a hydration equilibrium in aqueous solution according to:

$$[Eu(L)]^{3-} + H_2O \leftrightarrows [Eu(L)(H_2O)]^{3-} \quad K_{Eu}$$

UV-vis spectroscopy confirms that a hydration equilibrium exists between two species with $q = 0$ and $q = 1$ in aqueous solution. In the region were the $^5D_0 \leftarrow {}^7F_0$ transition occurs the spectrum of the Eu(III) complex (pH = 6.4) shows two absorption bands whose intensity ratio changes with temperature. The band at 578.9 nm is decreasing, while that at 579.4 nm is increasing with



H_6L

Scheme 1

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† Electronic supplementary information (ESI) available: Synthesis of H_6L and Cartesian coordinates (Å) of the HF/3-21G* calculated structures of $[Lu(L)(H_2O)]^{3-}\cdot 19H_2O$ and $[Lu(L)]^{3-}\cdot 20H_2O$. See http://dx.doi.org/10.1039/b508180g

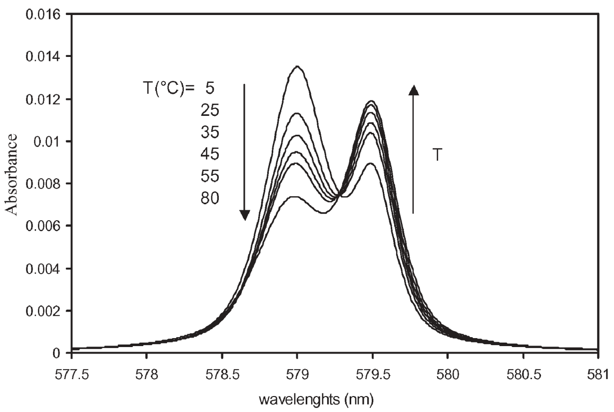

Fig. 1 UV-vis spectra of the Eu(III) $^5D_0 \leftarrow {}^7F_0$ transition in $[Eu(L)(H_2O)_x]^{3-}$ ($x = 0, 1$) recorded at different temperatures (pH = 6.4).

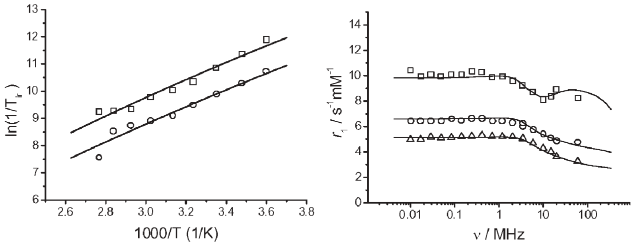

Fig. 2 Temperature dependence of longitudinal and transverse ^{17}O relaxation rates and ^1H NMRD profiles at 5 °C, 25 °C and 37 °C from top to bottom. ^{17}O NMR data for $[Gd(L)(H_2O)]^{3-}$ were obtained from a 95 mM solution of the complex at pH 7.09. NMRD profiles were obtained from a 4.87 mM solution at pH 6.94.

Table 1 Parameters obtained from ^{17}O NMR and NMRD data[a]

	$[Gd(H_2O)_8]^{3+}$	$[Gd(DTPA)(H_2O)]^{2-}$	$[Gd(L)(H_2O)]^{3-}$
$k_{ex}^{298}/10^8\ s^{-1}$	8.04	0.033	8.8 ± 0.5
$\Delta H^{\ddagger}/kJ\ mol^{-1}$	15.3	51.6	19.5 ± 1.3
$A/\hbar/10^6\ rad\ s^{-1}$	−5.3	−3.8	−3.8[b]
τ_R^{298}/ps	41	58	207 ± 6
$E_R/kJ\ mol^{-1}$	15.0	17.3	21.3 ± 0.9
τ_v^{298}/ps	7.3	25	28.2 ± 0.5
$\Delta^2/10^{20}\ s^{-2}$	1.19	0.46	0.41 ± 0.01
$D_{GdH}^{298}/10^{-10}\ m^2s^{-1}$	23	20	26 ± 2
$E_{DGdH}/kJ\ mol^{-1}$	22	19.4	26 ± 1
$\chi(1 + \eta^2/3)^{1/2}/MHz$	7.58	7.58	8.1 ± 0.5
$r_{GdO}/Å$	2.76	2.20	2.54[b]

[a] Data for $[Gd(H_2O)_8]^{3+}$ and $[Gd(DTPA)(H_2O)]^{2-}$ were taken from ref. 11. [b] Parameter was fixed during the fitting procedure.

temperature (Fig. 1). Thus, the band at lower energy is assigned to $[Eu(L)]^{3-}$, while that at 578.9 nm is attributed to $[Eu(L)(H_2O)]^{3-}$. The ratio of the integrals of the two bands is related to the equilibrium constant K_{Eu}, and its temperature dependence yields the reaction enthalpy and entropy. The fit of the experimental data[9,10] resulted in $\Delta H^\circ = -(11.6 \pm 2)$ kJ mol^{-1}, $\Delta S^\circ = -(34.2 \pm 5)$ J mol^{-1} K^{-1} and $K_{Eu}^{298} = (1.8 \pm 0.3)$.

Variable temperature ^{17}O transverse and longitudinal relaxation rates were measured at 7.05 T for the Gd(III) complex of L and on a diamagnetic reference solution. Proton relaxivities as a function of the magnetic field at different temperatures were also obtained (NMRD). The experimental ^{17}O NMR and NMRD data were simultaneously fitted with sets of equations usually used to predict variable-temperature ^{17}O NMR data, with the Solomon–Bloembergen–Morgan equations (which describe the field dependency of the inner sphere relaxivity) and with the Freed equation for the outer-sphere contribution to the relaxivity.[1] This allowed us to obtain the parameters describing water exchange, rotation and electron spin relaxation. The number of coordinated water molecules, q, was fixed to the values determined from the UV-vis spectra of the Eu(III) complex described above. The temperature dependence of q obtained from UV-vis experiments was also taken into account for the fitting of the experimental data. Following previous studies, the distance of closest approach for the outer-sphere contribution a_{GdH} was fixed to 3.5 Å. The distance between the protons of the coordinated water molecules and the Gd(III) ion was fixed at 3.084 Å, which corresponds to the averaged r_{GdH} distance obtained from our *ab initio* calculations for the $[Gd(L)(H_2O)]^{3-}\cdot 19H_2O$ system (*vide infra*). On the basis of our *ab initio* calculations the r_{GdO} distance was fixed at 2.54 Å. The fitted data are shown in Fig. 2, while the fitted parameters are given in Table 1. Most of the obtained parameters are within the normal range usually observed for small Gd(III) chelates. The long rotational correlation time obtained compared to that calculated for the $[Gd(DTPA)(H_2O)]^{2-}$ system may be explained, at least in part, due to the higher negative charge of the complex. However, the water exchange rate, k_{ex}, is the fastest of all Gd(III) complexes studied so far, being very similar to that determined for the aqua-ion. The water exchange proceeds *via* a dissociative mechanism ($\Delta V^{\ddagger} = +8.3 \pm 1.0$ cm^3 mol^{-1}, determined by variable pressure ^{17}O NMR).

In order to obtain direct information on the $[Ln(L)]^{3-}$ and $[Ln(L)(H_2O)]^{3-}$ systems, we carried out *ab initio* calculations at the HF level by using the 3-21G* basis set for the ligand atoms and the effective core potential (ECP) of Dolg *et al.*[12] and the related [5s4p3d]-GTO valence basis set for the lanthanide.[13] The calculations were performed on the molecular clusters $[Ln(L)(H_2O)]^{3-}\cdot 19H_2O$ and $[Ln(L)]^{3-}\cdot 20H_2O$ (Ln = Gd, Lu), which explicitly include a second hydration shell.[14,15] Attempts to model the $[Gd(L)]^{3-}$ complex were unsuccessful, a water molecule systematically entering the metal coordination sphere during the optimisation process. However, the smaller ionic radius of Lu(III) allowed us to model both the $[Lu(L)]^{3-}$ and $[Lu(L)(H_2O)]^{3-}$ complexes. The calculated structures of the $[Lu(L)(H_2O)]^{3-}\cdot 19H_2O$ and $[Lu(L)]^{3-}\cdot 20H_2O$ molecular clusters are shown in Fig. 3. Most of the second sphere water molecules are hydrogen bonded to the highly charged phosphonate groups. A comparison of the bond distances of the Lu(III) coordination sphere in the $[Lu(L)(H_2O)]^{3-}\cdot 19H_2O$ and $[Lu(L)]^{3-}\cdot 20H_2O$ molecular cluster reveals that the depletion of the coordinated water molecule results in a considerable shortening of the Lu(III)–L bond distances (Table 2). Thus, our quantum mechanical calculations point that the complexes of L possess a rather flexible coordination environment, in the sense that L can easily wrap around the metal ion to form both octa- or nona-coordinated species. These results are in agreement with variable pressure UV-vis measurements that were performed at 298 K to determine the reaction volume for the equilibrium described by K_{Eu} (*vide supra*). The spectra have been analysed as described previously,[9] and the resulting reaction volume was found to be $\Delta V^0 = -4.1 \pm 0.8$ cm^3 mol^{-1}. This value is considerably smaller than the one calculated for other Eu(III) poly(amino

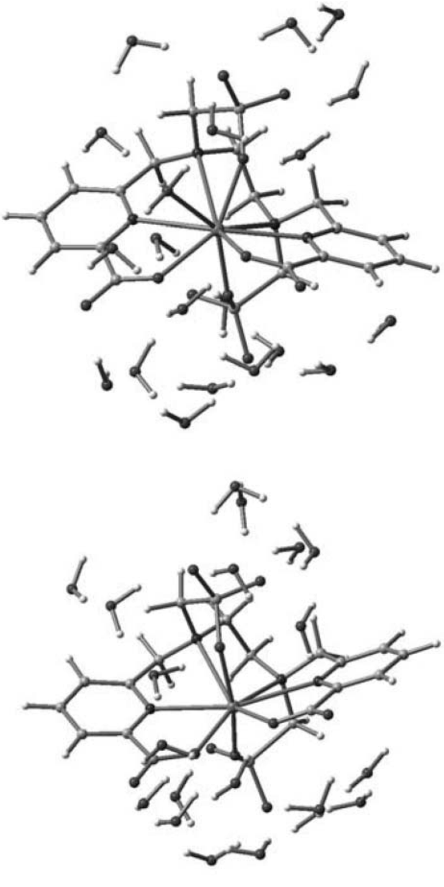

Fig. 3 The structure of the $[Lu(L)(H_2O)]^{3-}\cdot 19H_2O$ (top) and $[Lu(L)]^{3-}\cdot 20H_2O$ (bottom) molecular clusters optimised at the HF/3-21G* level.

Table 2 Values of the bond distances (Å) of the Lu(III) coordination environment obtained from *ab initio* calculations at the HF/3-21G* level[a]

	$[Lu(L)(H_2O)]^{3-}\cdot 19H_2O$	$[Lu(L)]^{3-}\cdot 20H_2O$
Lu–N_{PY}	2.785	2.710
	2.610	2.571
Lu–N_{AM}	3.283	3.121
	3.098	2.895
Lu–O_{PO3}	2.212	2.190
	2.188	2.143
Lu–O_{COO}	2.308	2.274
	2.253	2.226
Lu–O_W	2.454	—

[a] N_{PY}: pyridine nitrogen atoms; N_{AM}: amine nitrogen atoms; O_{PO3}: phosphonate oxygen atoms; O_{COO}: carboxylate oxygen atoms; O_W: water oxygen atom.

carboxylates),[1] which confirms that an important rearrangement of the Eu(III) coordination sphere occurs on going from species $q = 0$ to species $q = 1$.

In conclusion, we have demonstrated that complex $[Gd(L)(H_2O)]^{3-}$ presents a very fast water exchange rate, which is very similar to that reported for $[Gd(H_2O)_8]^{+3}$. The exchange process occurs *via* a dissociative mechanism, as demonstrated by variable presure ^{17}O NMR measurements. UV-vis measurements demonstrate that both $[Eu(L)(H_2O)]^{3-}$ and $[Eu(L)]^{3-}$ species are present in the solution in dynamic equilibrium. The concentrations of both species in equilibrium are very similar, which is attributed to a rather flexible metal-ion coordination sphere. Thus, one can expect the energy gap between the nine coordinate ground state and the eight coordinate transition state to be small, and thus the exchange to be very fast.

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Notes and references

‡ $DOTA^{4-}$ = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetate; $DTPA^{5-}$ = diethylenetriaminepentaacetate.

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