A Coordination Chemistry Approach to Fine-Tune the Physicochemical Parameters of Lanthanide Complexes Relevant to Medical Applications

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Dedicated to Professors Carlos F. G. C. Geraldes and Lothar Helm on the occasion of their retirement

Abstract: *The geometric features of two pyclen-based ligands possessing identical donor atoms but different site organization have a profound impact in their complexation properties toward lanthanide ions. The ligand containing two acetate groups and a picolinate arm arranged in a symmetrical fashion (L1) forms a Gd³⁺ complex being two orders of magnitude less stable than its dissymmetric analogue GdL2. Besides, GdL1 experiences a much faster dissociation following the acid-catalyzed mechanism than GdL2. On the contrary, GdL1 exhibits a lower exchange rate of the coordinated water molecule compared to GdL2. These very different properties are related to different strengths of the Gd-ligand bonds associated to steric effects, which hinder the coordination of a water molecule in GdL2 and the binding of acetate groups in GdL1.*

The lanthanides are a group of elements with very important technological applications often associated to their peculiar optical and magnetic properties. Several of these applications require the input of coordination chemistry to obtain lanthanide complexes with the desired properties, particularly regarding the design of optical[1] and magnetic[2,3] probes for medical diagnosis and bioanalytical assays. The lanthanide(III) (Ln^{3+}) ions represent a series of hard Lewis acids that have a strong preference to form stable complexes with polydentate ligands containing hard oxygen donor atoms (i. e. polyaminopolycarboxylate ligands), generally adopting high coordination numbers (typically 8-9). The Ln^{3+}-ligand interaction is considered to be largely electrostatic in origin, so that the metal coordination environment is dictated by a subtle interplay between electrostatic interactions and steric constraints.[4] As a result, there has been a limited success in establishing relationships between the structures and properties of Ln^{3+} complexes in solution or designing complexes with pre-determined properties, though some major advances were reported for some specific systems[5] or with respect to some specific properties (i. e. relaxivity).[6] For instance, the water exchange kinetics in Ln^{3+} (often Gd^{3+}) complexes were accelerated by increasing the steric compression around the water binding site, which can be achieved by replacing carboxylate groups by bulkier phosphonate units,[7] or by increasing the size of one of the chelate rings from 5 to 6-membered.[8] On the contrary, water exchange was decelerated by replacing carboxylate groups by amide donors,[9] as this increses the positive charge of the complex resulting in a stronger Ln^{3+}-O_{water} bond. Increasing the size of the chelate and replacing carboxylate groups by amides is detrimental for complex stability, although DOTA-tetraamide Ln^{3+} complexes were found to possess higher kinetic inertness than the parent DOTA complexes.[10,11] Some structural modification on macrocyclic cyclen-based ligands were also found to accelerate the dissociation of the Gd^{3+} complexes, demonstrating that the kinetic inertness of some macrocyclic complexes cannot be generalized to all macrocyclic chelates.[12]
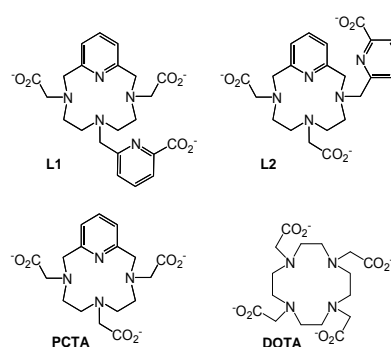
Scheme 1. Ligands discussed in the present work.

Herein we show that subtle changes in the arrangement of the ligand donor atoms have a deep impact in important features of the complexes, such as their thermodynamic stabilities and dissociation and solvent exchange kinetics. For this purpose, we have chosen the Gd^{3+} complexes of the recently reported macrocyclic ligands **L1** and **L2**,[13] which differ in the relative positions of the pendant arms attached to the pyclen (12-py-N4)

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unit (Scheme 1). We have selected Gd^{3+} because of the relevance of complexes of this metal ion as contrast agents in MRI.[2] Besides, the paramagnetic properties of Gd^{3+} allow a detailed characterization of complexes of this metal ion using NMR relaxometry.[14] The Gd**L1** and Gd**L2** complexes, as well as the corresponding Eu^{3+} and Yb^{3+} analogues, were obtained in excellent yields (89-98%) by reaction of the ligand with the corresponding lanthanide chloride salt in water at pH 5 (see Supporting Information).
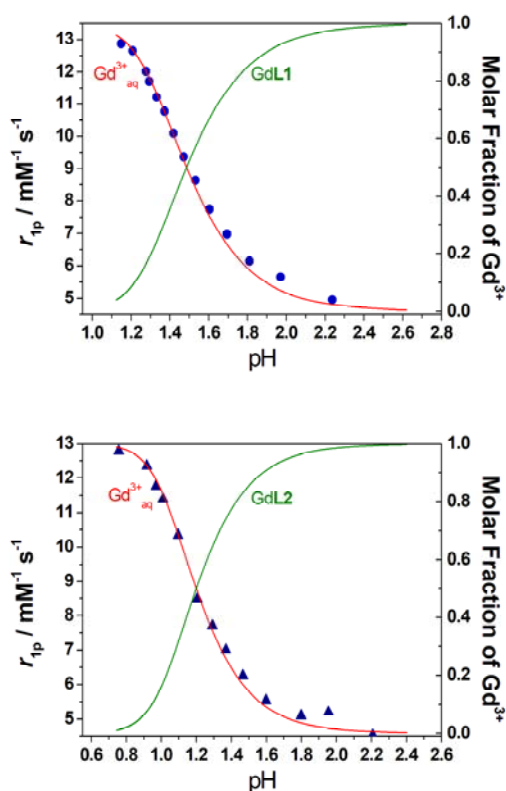

Figure 1. Proton relaxivities (r_{1p}) of Gd**L1** (top) and Gd**L2** (bottom) as a function of proton concentration. The solid lines show the species distributions calculated with the stability constants given in Table 1 (25 ºC, 0.15 M NaCl).

Our investigation was initiated by determining the thermodynamic stability constants of the Gd**L1** and Gd**L2** complexes using the relaxometric technique.[14] The relaxivity (r_{1p}) of the complexes recorded at 20 MHz and 25 ºC is typical of small Gd^{3+} complexes containing a coordinated water molecule (Table 1). Below pH~2 the relaxivity of aqueous solutions of the complexes increases as a result of complex dissociation and formation of $[Gd(H_2O)_8]^{3+}$, which shows a relaxivity of 13.5 $mM^{-1}s^{-1}$ at 20 MHz and 25 ºC (Figure 1).[15] One can notice that in the case of Gd**L2** a lower pH is required to provoke the full dissociation of the complex. Given that the two ligands present very similar basicities,[6] this is an indication that the complex of **L2** presents a higher thermodynamic stability than that of **L1**. The analysis of the relaxivity data provide the stability constants reported in Table 1. The results of this studies show that the stability constant of Gd**L1** is two orders of magnitude higher than

that of GdPCTA (also reported here),[16] but two orders of magnitude lower than that of Gd**L2**.

Table 1. Relaxivities, stability constants, dissociation rate constants (k_1) and water exchange rates (k_{ex}^{298}) determined for Gd**L1** and Gd**L2**.

Parameter	Gd**L1**[a]	Gd**L2**[a]	GdPCTA
r_{1p} / mM^{-1} s^{-1} [b]	4.74	4.95	7.09[a]
$\log K_{GdL}$	20.49 ± 0.02	22.37 ± 0.03	18.28±0.03[a]
pGd[c]	17.74	20.25	16.62[a]
k_1 / M^{-1} s^{-1} [d]	(6.9 ± 0.1) ×10^{-4}	(2.13 ± 0.08) ×10^{-4}	5.08×10^{-4}
$t_{1/2}$ / min [e]	167	542	231
k_{ex}^{298} / 10^6 s^{-1}	1.08 ± 0.02	22.5 ± 2.3	14.3
τ_m^{298} / µs	926 ± 17	44 ± 5	70
$\Delta H^{\ddagger}$ / kJ mol^{-1}	28.6 ± 0.6	37.5 ± 0.2	45

[a] This work. [b] At 20 MHz, 25 ºC. [c] Calculated at pH = 7.4 using c_{ligand} = 10^{-5} M and c_{iGd} = 10^{-6} M. [d] Rate constants characterizing the proton-assisted dissociation of the complexes. Data for GdPCTA was taken from reference [17] and correspond to the Eu complex. [e] Half-lives calculated from the rate constants 0.1 M proton concentration.
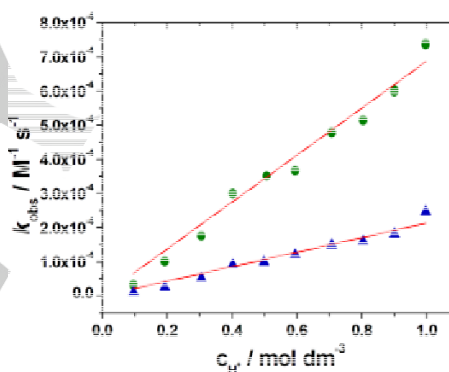

Figure 2. Pseudo-first-order rate constants (k_{obs}) measured for the acid-assisted dissociation of Gd**L1** (circles) and Gd**L2** (triangles) as a function of proton concentration. The solid lines correspond to the linear fit of the data.

Given the results obtained from the thermodynamic studies, we next analyzed whether these complexes present significantly different dissociation kinetics. The dissociation of Ln^{3+} complexes with macrocyclic ligands generally takes place following the acid-catalyzed mechanism.[17] Thus, the dissociation of the complexes was followed under pseudo-first order conditions (proton concentration range 0.1 – 1 M) by following the changes in the UV absorption band of the picolinate group at 279 nm. The observed rate constants (k_{obs}) show a linear dependence with proton concentration (Figure 2). The rate constants (k_{obs}) of Gd**L2** are clearly lower than those of Gd**L1** at a given proton concentration, indicating that the complex of **L2** presents a higher kinetic inertness. The kinetic data was analyzed by fitting the experimental data to k_{obs} = k_0 + $k_1[H^+]$, where k_0 and k_1 represent the rate constants characterizing the spontaneous and proton-assisted dissociation, respectively. The linear least-squares fits of the

data provided very small values for k_0 with large statistical errors, indicating that the spontaneous dissociation does not contribute to the overall dissociation reaction under the conditions applied. The k_1 values obtained (Table 1) reveal a considerably faster proton-assisted dissociation of Gd**L1** compared to Gd**L2**, the latter showing a half-life ~3 times longer at a proton concentration of 0.1 M. The Gd**L2** complex is considerably more inert than EuPCTA (Scheme 1), for which an acid-catalyzed rate constant of 5.08×10^{-4} M^{-1} s^{-1} was reported.[17] Besides being considerably more inert, Gd**L2** also presents much faster complexation kinetics than Gd**L1** (Supporting Information).

The absorption spectra of the Eu^{3+} complexes of **L1** and **L2** recorded in H$_2$O solution show an absorption band with a maximum at 274 nm characteristic of the pyridyl chromophores (Supporting Information).[18] The emission spectra were recorded in H$_2$O and D$_2$O solutions of the Eu^{3+} complexes (pH 7.45, tris buffer). The corresponding excitation spectra recorded upon analyzing at the maxima of the metal-centered emission are very similar to the corresponding absorption spectra. This indicates sensitization of the metal ion through energy transfer from the ligand to the metal ion.[19] The complexes present the red emission associated to the $^5D_0 \rightarrow {}^7F_J$ (J = 0-4) transitions of this metal ion. A detailed comparison of the emission spectra recorded for Eu**L1** and Eu**L2** evidences different splitting patterns of the ΔJ = 1 and the hypersensitive ΔJ = 2 transitions (Supporting Information), reflecting significantly different coordination environments in the two complexes. The emission lifetimes of the Eu^{3+} ($^5D_0$) excited states were measured in H$_2$O and D$_2$O solutions to determine the number of water molecules coordinated to the metal ion (Supporting Information). These studies provided hydration numbers close to 1 using the methodology proposed by Beeby,[20] which indicates the presence of a water molecule coordinated to the metal ion.
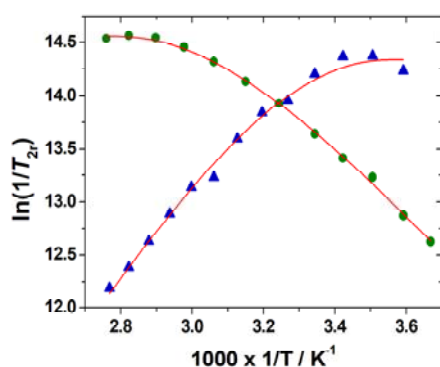

Figure 3. Reduced transverse ^{17}O relaxation rates measured at 9.4 T (pH = 7.2) for Gd**L1** (circles) and Gd**L2** (triangles). The solid lines correspond to the fits of the data as described in the text. The reduced relaxation rates are defined as $1/T_{2r}$ = $[1/c_{Gd}/55.5)][1/T_i-1/T_{iA}]$, where T_i and T_{2A} are the paramagnetic and diamagnetic relaxation times and c_{Gd} is the concentration of the complex.

The water exchange rates of the coordinated water molecules in the Gd**L1** and Gd**L2** complexes were determined by measuring the ^{17}O NMR transverse relaxation rates of aqueous solutions of the complexes at different temperatures (see Supporting Information for details). A qualitative analysis of the reduced transverse relaxation rates ($1/T_{2r}$) can be performed using the following simplified equation (Eq [1]) that neglects the chemical shift difference between bound and bulk water:[21]

$$\frac{1}{T_{2r}} \cong \frac{1}{\tau_m + T_{2m}} \qquad [1]$$

In this equation, τ_m is the mean residence time of a water molecule in the inner coordination sphere of Gd^{3+} and T_{2m} is the transverse relaxation time of the bound water molecule. Generally τ_m and T_{2m} present an opposite temperature dependence, as water exchange is accelerated with increasing temperature ($\tau_m = 1/k_{ex}$ decreases) while T_{2m} increases with increasing temperature. The ^{17}O NMR data obtained for Gd**L1** and Gd**L2** show opposite temperature dependences, which evidences very different water exchange rates for these complexes. The $1/T_{2r}$ values increase with increasing temperature for Gd**L1**, which shows that τ_m dominates the denominator of Eq [1], pointing to a rather slow water exchange.

The ^{17}O NMR transverse relaxation rates were fitted using standard procedures.[22] In this analysis we fixed the ^{17}O hyperfine coupling constant to the standard value of -3.8×10^6 rad s^{-1}.[15,18] The longitudinal electron spin relaxation rate $1/T_{1e}$ was assumed to follow an Arrhenius-type temperature dependence with an activation energy of 1 kJ mol^{-1}.[15] The parameters obtained from the least-squares fit of the data are shown in Table 1, while the fitted curves are presented in Figure 3. The water exchange of the coordinated water molecule was found to be 20 times faster for Gd**L2** compared to Gd**L1**, highlighting that the different arrangement of the donor atoms of the ligand around the metal ion has a striking impact in the exchange rate of the coordinated water molecule. The water exchange rate obtained for Gd**L1** is about four times slower than that of GdDOTA$^-$ (k_{ex}^{298} = 4.1×10^6 s^{-1}),[15] while the exchange rate obtained for Gd**L2** is faster than the bis-aquated GdPCTA complex (k_{ex}^{298} = 14.3×10^6 s^{-1}).[23] The analysis of the ^{17}O NMR data also provided the relaxation times of the electron spin, which turned out to be similar for Gd**L1** and Gd**L2** (T_{1e}^{298} = 49.4 ± 1.4 and 35.9 ± 2.7 ns, respectively, at 298 K and 9.4 T).

The structure of the Yb**L2** complex in the solid state was established using single-crystal X-ray diffraction measurements. The crystal structure (Figure 4) shows eight coordination of the metal ion by the ligand, with coordination number nine being completed by the presence of an inner-sphere water molecule. The metal coordination environment can be best described as tricapped trigonal prismatic, where the capping tripod is defined by the coordinated water molecule O1 and the amine nitrogen atoms N3l and N1l. Atoms O3l, O5l and N4l define the upper tripod while O1l, N2l and N5l delineate the lower tripod (see labelling Figure 4).
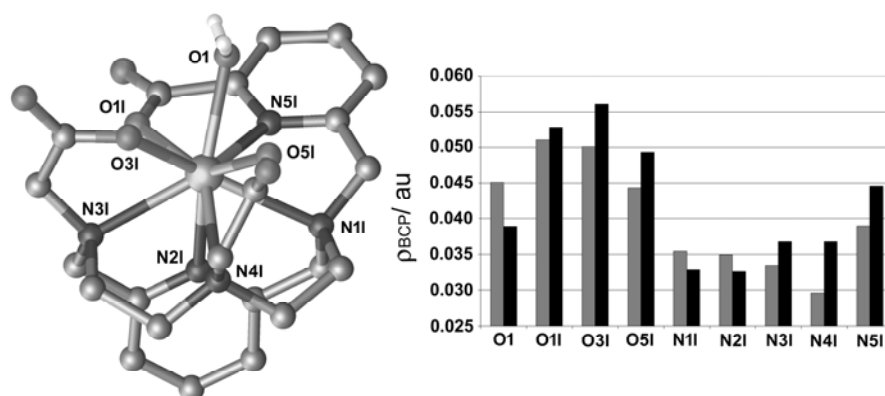
Figure 4. Left: X-ray structure of Yb**L2** with atom numbering. Right: Electron densities at the bond critical points obtained with DFT calculations for Gd**L1** (grey bars) and Gd**L2** (black bars).

To rationalize the very different properties of the Gd**L1** and Gd**L2** complexes we performed DFT calculations using standard methods (See Supporting Information).[17] The theoretical structure of Gd**L2** is very similar to that observed in the solid state for the Yb^{3+} analogue. A comparison of the bond distances of the metal coordination environment calculated for Gd**L1** and Gd**L2** reveals significant differences. In particular, the distance involving the coordinated water molecule is clearly longer in Gd**L2** (Gd-O1 = 2.519 Å) than in Gd**L1** (2.450 Å). It is also worth noting that the average Gd···H distances involving the coordinated water molecules are virtually identical in the two complexes (3.010 Å), as a result of a different orientation of the HOH plane of the coordinated water molecule with respect to the Gd-O1 vector. Another important difference concerns the Gd-O3l distances (2.458 and 2.407 Å for Gd**L1** and Gd**L2**, respectively), which suggest a weaker coordination of an acetate arm in Gd**L1**. A more detailed analysis of the Gd^{3+} coordination environment was carried out by calculating the electron density (ρ) at the bond critical points (BCPs). Both ρ_{BCP} and ELF_{BPC} can be correlated to the strength of the Gd-donor bonds.[24] The results (Figure 4, see also Supporting Information) show that the Gd-O bonds are generally stronger than the Gd-N ones, as would be expected. The values of ρ_{BCP} calculated for the Gd-O bonds involving carboxylate oxygen atoms (O1l, O3l and O5l) evidence stronger bonds in the case of Gd**L2** compared to Gd**L1**, in line with the higher stability of the former. However, the inner-sphere water molecule is more tightly bound in Gd**L1**, resulting in a lower water exchange rate.

In conclusion, we have shown that subtle changes in the arrangement of the donor atoms around the central metal ion have profound consequences in important properties of lanthanide complexes, including: i) Their thermodynamic stability; ii) Complexation kinetics; iii) Kinetic inertness with respect to complex dissociation, and iv) The lability of coordinated water molecules. All these parameters must be optimized to develop efficient diagnostic and therapeutic agents relying on the use of Ln(III) ions. This effect is related to the high coordination numbers adopted by the Ln^{3+} ions and the fact that some donor atoms might be hindered by the environment. In Gd**L2** the coordinated water binding site is sterically compressed,

which results in a fast water exchange. However, in Gd**L1** the oxygen atoms of carboxylate groups provide weaker interactions with the metal ion, which results in a lower thermodynamic stability. The faster proton-assisted dissociation kinetics of Gd**L1** is likely caused by the protonation of the weakly coordinated carboxylate, which triggers complex dissociation. A similar effect is probably responsible for the different water exchange rates and stabilities observed for the bis-hydrated Gd(DTTA-Me)⁻ regioisomers (DTTA-Me = *N*-methyl diethylenetriamine tetraacetate), as the complex with the methyl group on the terminal nitrogen is two orders of magnitude more stable than the derivative with the methyl group at the central nitrogen,[25,26] while the terminal N-Me isomer has about 100-fold slower water exchange kinetics compared to the central N-Me isomer.[26,27] Thus, the results of this study provide the basis for the rational design and prediction of the geometric features of multidentate ligands for efficient lanthanide complexation, an issue with great potential impact in many areas where the coordination chemistry of the rare-earths is present.

Acknowledgements

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Entry for the Table of Contents

COMMUNICATION

An apparently innocent change in the arrangement of the ligand donor atoms around the central Ln^{3+} ion has profound consequences in the thermodynamic stability and dissociation and water exchange kinetics of the complexes

M. Le Fur, E. Molnár, M. Beyler, F. K. Kálmán, O. Fougère, D. Esteban-Gómez, O. Rousseaux, R. Tripier, Gy. Tircsó,* and C. Platas-Iglesias*

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