Inorganic Chemistry

Complexation of Ln³⁺ lons with Cyclam Dipicolinates: A Small Bridge that Makes Huge Differences in Structure, Equilibrium, and Kinetic **Properties**

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Supporting Information

ABSTRACT: The coordination properties toward the lanthanide ions of two macrocyclic ligands based on a cyclam platform containing picolinate pendant arms have been investigated. The synthesis of the ligands was achieved by using the well-known bis-aminal chemistry. One of the cyclam derivatives (cb-tedpa²⁻) is reinforced with a cross-bridge unit, which results in exceptionally inert $[Ln(cb-tedpa)]^{+}$ complexes. The X-ray structures of the [La(cb-tedpa)Cl], [Gd(cbtedpa)]⁺, and $[Lu(Me_2tedpa)]^+$ complexes indicate octadentate binding of the ligands to the metal ions. The analysis of the Yb³⁺-induced shifts in [Yb(Me₂tedpa)]⁺ indicates that this complex presents a solution structure very similar to that



observed in the solid state for the Lu^{3+} analogue. The X-ray structures of $[La(H_2Me_2tedpa)_2]^{3+}$ and $[Yb(H_2Me_2tedpa)_2]^{3+}$ complexes confirm the exocyclic coordination of the metal ions, which gives rise to coordination polymers with the metal coordination environment being fulfilled by oxygen atoms of the picolinate groups and water molecules. The X-ray structure of $[Gd(Hcb-tedpa)_2]^+$ also indicates exocyclic coordination that in this case results in a discrete structure with an eight-coordinated metal ion. The nonreinforced complexes [Ln(Me₂tedpa)]⁺ were prepared and isolated as chloride salts in nonaqueous media. However, these complexes were found to undergo dissociation in aqueous solution, except in the case of the complexes with the smallest Ln^{3+} ions $(Ln^{3+} = Yb^{3+} \text{ and } Lu^{3+})$. A DFT investigation shows that the increased stability of the $[Ln(Me_2tedpa)]^+$ complexes in solution across the lanthanide series is the result of an increased binding energy of the ligand due to the increased charge density of the Ln³⁺ ion.

INTRODUCTION

Complexes of the trivalent lanthanide ions (Ln³⁺) with polyaminopolycarboxylate ligands are receiving increasing attention due to their important medical and bioanalytical applications. For instance, Gd³⁺ chelates are nowadays commonly used by radiologists as contrast agents in magnetic resonance imaging,^{1,2} while luminescent Ln³⁺ complexes are used in bioanalytical applications and are being intensively investigated as potential probes for optical imaging in vivo. These applications require a careful design of the ligand structure to achieve a high thermodynamic stability and, more importantly, a high kinetic inertness to ensure that the toxic Ln³⁺ ion is not released in vivo.⁴ Among the different polyaminopolycarboxylate ligands commonly used for Ln³⁺ complexation non-macrocyclic derivatives often form rather labile complexes, while some macrocyclic ligands form complexes with exceptionally high kinetic inertness.⁵

Cross-bridged tetraaza macrocyclic ligands based on 1,4,7,10tetraazacyclododecane (cyclen) or 1,4,8,11-tetraazacyclotetradecane (cyclam) platforms typically contain a linker connecting two trans nitrogen atoms of the macrocycle (i.e., ethylene or

Received: November 13, 2015

propylene groups or linkers integrating additional donor groups), which results in constrained positions of the four nitrogen lone pairs of the macrocyclic cavity.⁶ The presence of this linker increases the rigidity of the corresponding metal complexes, which as a result are often very inert with respect to complex dissociation.^{7,8} The first crossed-bridged cyclam derivative was prepared by Weisman, who also reported its unusual behavior as a proton sponge.⁹ Subsequently, Weisman and Busch reported different transition metal complexes of cross-bridged cyclam derivatives.^{10,11} Following these pioneering works, a wide range of cross-bridged metal complexes functionalized with different pendant arms were reported (i.e., acetate,¹² acetamide,¹³ picolinate,⁸ 2-pyridylmethyl,¹⁴ methylenephosphonate¹⁵). Many of the transition metal complexes formed with cyclam cross-bridge derivatives were found to be very inert, a property that in some cases was accompanied by relatively fast complexation kinetics.^{8,16} These two properties were important requisites for developing Cu2+-containing radiopharmaceuticals for PET imaging.

In a recent communication we reported the cross-bridged cyclam derivative containing picolinate pendant arms H_2 cb-tedpa (Chart 1),¹⁸ which was rationally designed to provide

Chart 1. Chemical Structure of the Ligands Discussed in This Work



stable Ln³⁺ complexation in aqueous solution. Owing the high coordination numbers often adopted by the Ln³⁺ ions in solution (generally 8-9) the cross-bridged cyclam platform was functionalized with two picolinate pendant arms to give a potentially octadentate ligand. The corresponding Ln³⁺ complexes were found to form very slowly even in harsh conditions, but once they were formed they were extremely inert (i.e., they did not dissociate in 2 M HCl over a period of several months). It has been reported that the Ln³⁺ complexes of the octadentate cyclam-based ligand teta⁴⁻ are considerably less stable from both the thermodynamic and kinetic point of view than the corresponding complexes of the cyclen-based dota^{4–} ligand,¹⁹ which suggests that the lack of dissociation of the [Ln(cb-tedpa)]⁺ complexes in strongly acidic media is a consequence of an extremely high kinetic inertness rather than a high thermodynamic stability. However, the extremely slow

formation and dissociation kinetics of $[Ln(cb-tedpa)]^+$ complexes precludes the determination of thermodynamic stability constants. Thus, herein we report the nonreinforced analogue H₂Me₂tedpa (Chart 1) and provide a detailed comparison of the acid–base properties of the cb-tedpa^{2–} and Me₂tedpa^{2–} ligands. An analysis of the structure of the [Ln(cb $tedpa)]^+$ and $[Ln(Me_2tedpa)]^+$ complexes in the solid state and in aqueous solutions is also accomplished. Finally, the relative stabilities of the two series of complexes and the stability trends observed along the lanthanide series have been investigated by using computational methods.

RESULTS AND DISCUSSION

Synthesis and Characterization of the Ligands. The synthesis of H_2 cb-tedpa was described in a previous communication.¹⁸ Single crystals of formula (H_4 cb-tedpa) (CIO_4)₂ were obtained from an aqueous solution containing equimolar amounts of the ligand and Lu(CIO_4)₃, which was prepared in an attempt to form the Lu³⁺ complex. A view of the structure of the H_4 cb-tedpa²⁺ unit is presented in Figure 1. The



Figure 1. View of the H_4cb -tedpa²⁺ cation present in crystals of $(H_4cb$ -tedpa) (ClO₄)₂. Hydrogen atoms bonded to carbon atoms and anions are omitted for simplicity. The ORTEP plot is at the 30% probability level.

X-ray structure indicates that protonation of the cyclam moiety occurs on the two *trans* N atoms containing the picolinic acid substituents. This reduces the electrostatic repulsion between the two protonated sites, as the distance between these nitrogen atoms (N3…N5 = 4.07 Å) is considerably longer than that between the two nitrogen atoms linked by the ethylenic bridge (N4…N2 = 2.83 Å). Each of the two protonated nitrogen atoms are involved in hydrogen-bonding interaction with a second nitrogen atom of the macrocycle: N2…N5 2.748(6) Å, N2–H2…N5 1.97 Å, N2–H2…N5 134.3°; N4… N3 2.686(6) Å, N4–H4…N3 1.86 Å, N4–H4…N3 139.6°. The structure of H₄cb-tedpa²⁺ also shows that protonation of the picolinate groups occurs at the oxygen atoms of the carboxylate groups, as observed previously for $(H_4Me_2dodpa)^{2+}$ (Chart 1).²⁰

The synthesis of H_2Me_2 tedpa was achieved by using the bisaminal chemistry,²¹ which provided a convenient access to *trans*-substituted cyclam derivatives (Scheme 1). Thus, cyclam was reacted with formaldehyde to give compound 2, which was alkylated with MeI to yield the *trans*-disubstituted diammonium salt 3 with a nearly quantitative yield. Hydrolysis of 3 in the presence of a base afforded the unprotected cyclam derivative 4, which was then alkylated with the 6-chloromethylpyridine Scheme 1. Synthesis of H₂Me₂tedpa and Numbering Scheme Used for NMR Spectral Assignment^{*a*}



"Reagents and conditions: (i) H_2CO , H_2O , 0 °C, 96%; (ii) MeI, CH₃CN, 98%; (iii) 3 M aqueous NaOH, 100%; (iv) K_2CO_3 , CH₃CN, 73%; (v) 6 M aqueous HCl, 98%.

derivative 5^{22} to give precursor 6 in 73% yield. Finally, deprotection of the methyl ester groups with 6 M HCl gave the H₂Me₂tedpa ligand with an overall yield of 67% over the five steps.

The protonation constants of Me₂tedpa²⁻ and cb-tedpa²⁻ were measured by using the standard pH-potentiometric technique in 0.15 M NaCl. The ligand protonation constants (Table 1) are defined as in eq 1 (where i = 1, 2, ..., 5):

$$K_i^{\mathrm{H}} = \frac{\lfloor \mathrm{H}_i \mathrm{L} \rfloor}{[\mathrm{H}_{i-1} \mathrm{L}][\mathrm{H}^+]} \tag{1}$$

The data shown in Table 1 indicate that the first protonation constant of cb-tedpa²⁻ is ca. 2.7 log units higher than that of Me₂tedpa²⁻, while the second protonation constant $K_2^{\rm H}$ is ca. 0.7 log units higher in Me₂tedpa^{2–}. We want to highlight that even when the first protonation constant of cb-tedpa²⁻ is rather high (log $K_1^{\rm H} = 13.01(2)$) under our experimental conditions at pH 12.5 up to 25% of the ligand is in its deprotonated form, and therefore this protonation constant could be determined to a good accuracy. A similar trend, though less pronounced, is observed upon comparison of the protonation constants determined for cyclam and cb-cyclam (Table 1).^{23,24} The first protonation constant of cb-te1pa⁻ was also reported to be considerably higher than that of te1pa⁻, although its value is too high to be determined using potentiometric titrations.^{8,25} These results indicate that the monoprotonated forms of the crossbridged derivatives are particularly stabilized by intramolecular hydrogen-bonding interactions. A similar behavior has been observed for other cross-bridged derivatives, and attributed to a convergent disposition of the four nitrogen lone pairs, which

are particularly well-suited for the coordination of small hard metal ions as well as protons.^{11d,26} As stated earlier,²⁷ the third and fourth protonation constants can be assigned to the carboxylate groups of the picolinate moieties, while the fifth protonation process observed for Me₂tedpa²⁻ most likely occurs on a third nitrogen atom of the macrocycle.

Synthesis of Metal Complexes. Reaction of ligand H_2Me_2 tedpa with hydrated lanthanide chlorides in the presence of an excess of trimethylamine in 2-propanol resulted in the formation of compounds of formula $[Ln(Me_2tedpa)]Cl$ (Ln = La, Eu, Gd, Tb, Yb, or Lu), which were isolated in 51–90% yields (see the Experimental Section for full details). The high resolution mass spectra (ESI⁺-MS) of the complexes showed peaks due to the $[Ln(Me_2tedpa)]^+$ entities, thereby confirming the formation of the desired compounds (Figures S3–S8, Supporting Information).

The synthesis of compounds [Ln(cb-tedpa)]Cl (Ln = La, Eu, Gd, Tb, or Yb) was reported in a preliminary communication.¹⁸ The formation of the complexes required rather harsh conditions involving the use of a solvent with high boiling point (n-butanol) and long reaction times (4 days). Alternatively, the reaction times could be significantly shortened with the use of microwave radiation. In detail, reaction of H₂cb-tedpa and EuCl₃·6H₂O in *n*-butanol in the presence of diisopropylethylamine (DIPEA) under microwave radiation (150 °C, 250 psi, maximum power 300 W) during one hour provided a mixture composed of the [Eu(cb-tedpa)]⁺ complex (7%) and unreacted ligand (93%), as established by ¹H NMR spectroscopy. Using identical conditions but longer reaction times (4 h) gave a mixture whose ¹H NMR spectrum revealed the absence of unreacted ligand and the presence of two complex species with a 95:5 ratio (Figure 2). The major species presented paramagnetically shifted ¹H NMR signals in the range +11 to -11 ppm, while the minor species gave larger shifts, with signals spreading over the range 39 to -17 ppm. The HR-ESI⁺ spectrum of the mixture presented an intense peak at m/z = 647.1835 that corresponded to the [Eu(cbtedpa)]⁺ complex (calculated value m/z = 647.1848), and a weaker signal at m/z = 1143.4668 attributable to the [Eu(Hcbtedpa)₂]⁺ entity (calculated value m/z = 1143.4652). Structural evidence for the formation of this species was obtained from Xray crystallography (see below). The use of identical conditions but employing a 100% excess of EuCl₃·6H₂O resulted in the quantitative formation of the 1:1 species, which corresponded to the $[Eu(cb-tedpa)]^+$ complex. A close inspection of the reaction mixtures obtained under conventional conditions (nbutanol, reflux 4 days, 1:1 Eu³⁺:ligand ratio) revealed the formation of both the 1:1 and 1:2 species in ~95:5 ratio. These results suggested that the 1:1 and 1:2 complex species were both present once the thermodynamic equilibrium was attained, while the use of an excess of Eu³⁺ shifted the

Table 1. Protonation Constants of Me_2tedpa^{2-} and cb-tedpa²⁻ (25 °C, 0.15 M NaCl) and Values Reported in the Literature for Related Systems

	Me ₂ tedpa ²⁻	cb-tedpa ²⁻	cyclam ^a	cb-cyclam ^b	te1pa ^{-c}	cb-te1pa ^{-d}
$\log K_1^{H}$	10.29(1)	13.01(2)	11.29	12.42	11.55	е
$\log K_2^{H}$	10.28(2)	9.55(4)	10.19	10.20	10.11	10.13
$\log K_3^{H}$	3.79(3)	3.27(4)	1.61	1.39	2.71	2.42
$\log K_4^{H}$	2.85(3)	2.24(4)	1.91		1.7	<2
$\log K_{c}^{H}$	1.93(3)					

"Reference 23. "Reference 24. "Reference 25. "Reference 8. "Too high to be determined experimentally.



Figure 2. ¹H NMR and HR-ESI⁺ spectra of the crude mixture obtained upon reaction of equimolar EuCl₃ and H₂cb-tedpa in *n*-butanol in the presence of diisopropylethylamine (DIPEA) under microwave radiation (150 °C, 250 psi, maximum power 300 W, reaction time 4 h).

equilibrium to the exclusive formation of the 1:1 species. The counterion employed for the synthesis of the complex was also found to play an important role, as replacing $EuCl_3$ by $Eu(OTf)_3$ lead to the nearly exclusive formation of the $[Eu(Hcb-tedpa)_2]^+$ species (>95%).

X-ray Structures of [La(cb-tedpa)Cl]·5H₂O, [Gd(cb-tedpa)](PF₆)·2.5H₂O, and [Lu(Me₂tedpa)]Cl·6H₂O. Single crystals with formula [La(cb-tedpa)Cl]·5H₂O and [Lu-(Me₂tedpa)]Cl·6H₂O were obtained by slow evaporation of aqueous solutions of the complexes at neutral pH, while those of [Gd(cb-tedpa)](PF₆)·2.5H₂O were grown by addition of an excess of KPF₆ to a solution of the complex in water. The latter compound crystallized in the orthorhombic *Pbca* space group and it was isomorphous with respect to the Eu³⁺ complex reported in our previous communication.¹⁸ Bond distances of the metal coordination environments are given in Table 2, while views of the structures of the complexes are presented in Figures 3–5.

Table 2. Bond Distances (Å) of the Metal Coordination Environments in [La(cb-tedpa)Cl], $[Gd(cb-tedpa)]^+$, and $[Lu(Me_2tedpa)]^+$ Complexes

[La(cb-tedpa)Cl]		[Gd(cb-tedpa)] ⁺		$[Lu(Me_2tedpa)]^+$	
La1-N1	2.601(2)	Gd1-N1	2.497(6)	Lu1-N1	2.3657(12)
La1-N2	2.705(2)	Gd1-N2	2.614(6)	Lu1-N2	2.4767(12)
La1-N3	2.771(2)	Gd1-N3	2.573(6)	Lu1-N3	2.5907(12)
La1-O1	2.4695(17)	Gd1-N4	2.616(6)	Lu1-O1	2.2359(10)
La1-Cl1	3.0004(9)	Gd1-N5	2.554(6)		
		Gd1-N6	2.486(5)		
		Gd1-01	2.309(5)		
		Gd1-O3	2.318(5)		

The [La(cb-tedpa)Cl] and $[Lu(Me_2tedpa)]^+$ complexes possess a crystallographically imposed C_2 symmetry. On the other hand, crystals of the Gd³⁺ complex contain two [Gd(cbtedpa)]⁺ complex entities in the asymmetric unit with only slightly different bond distances and angles of the metal coordination environment. Thus, in the following we will focus



Figure 3. View of the [La(cb-tedpa)Cl] entity present in crystals of [La(cb-tedpa)Cl]·SH₂O. Hydrogen atoms are omitted for simplicity. The ORTEP plot is at the 30% probability level.



Figure 4. View of the $[Gd(cb\text{-tedpa})]^+$ cation present in crystals of $[Gd(cb\text{-tedpa})](PF_6)\cdot 2.5H_2O$. Hydrogen atoms and anions are omitted for simplicity. The ORTEP plot is at the 30% probability level.



Figure 5. View of the $[Lu(Me_2tedpa)]^+$ cation present in crystals of $[Lu(Me_2tedpa)]Cl \cdot 6H_2O$. Hydrogen atoms and anions are omitted for simplicity. The ORTEP plot is at the 30% probability level.

our discussion on the complex unit containing Gd1. The metal ions in $[Gd(cb-tedpa)]^+$ and $[Lu(Me_2tedpa)]^+$ are eightcoordinated, being directly bound to two oxygen atoms of the carboxylate groups, the nitrogen atoms of the pyridyl units, and the four nitrogen atoms of the macrocyclic entities. The metal ion in [La(cb-tedpa)Cl] is also directly coordinated to the eight donor atoms of the ligand, nine coordination being completed by the presence of a coordinated chloride anion. However, the La1–Cl1 distance (3.0004(9) Å) is considerably longer than those observed for different nine-coordinate La³⁺ complexes,²⁸ which points to a weak coordination of the chloride anion in the [La(cb-tedpa)Cl] complex. The bond distances of the metal coordination environment in [Lu- (Me_2tedpa)]⁺ are very similar to those reported for the eight-coordinate macrocyclic complexes [Lu(Me_2dodpa)]⁺ and [Lu(bp12c4)]^{+22,29} and slightly shorter than the ones observed for eight-coordinate Lu³⁺ complexes containing picolinate pendant arms.³⁰ The bond distances of the Gd³⁺ coordination sphere in [Gd(cb-tedpa)]⁺ are similar or even slightly shorter than those observed for the eight-coordinate [Ln(teta)]⁻ complexes (Ln = Eu, Tb).³¹

The distances between the Lu³⁺ ion and the amine nitrogen atoms of the macrocyclic unit functionalized with the picolinate pendants in [Lu(Me2tedpa)]+ (N2) are ~0.11 Å shorter than those involving the nitrogen atoms containing methyl substituents. In the case of [La(cb-tedpa)Cl] the distances to the nitrogen donor atoms linked by the ethylenic bridge are also longer than the La1-N2 distances. However, this situation is reversed in the [Gd(cb-tedpa)]⁺ complex, as the Gd1-N3 and Gd1-N5 distances are ca. 0.04-0.06 Å shorter than the Gd1-N2 and Gd1-N4 bonds. The different pattern observed for the bond distances involving the nitrogen atoms of the macrocycle in [La(cb-tedpa)Cl] and [Gd(cb-tedpa)]⁺ is likely related to the presence of the chloride anion in the former, which results in a considerably more open angles defined by the donor atoms of the pyridine units and the metal ion (N1- $La1-N1^{i} = 138.24(8)^{\circ}, N1-Gd1-N6 = 116.06(18)^{\circ}).$

The coordination of the macrocyclic unit to the Ln³⁺ ions introduces two sources of chirality in the complexes, one related to the layout of the picolinate pendant arms (absolute configurations Δ or Λ), and the second associated to the conformations of the two ([Lu(Me₂tedpa)]⁺) or three ([La(cbtedpa)Cl] and [Gd(cb-tedpa)]⁺) five-membered chelate rings formed upon coordination of the macrocyclic ethylenediamine moieties (absolute configuration δ or λ). Inspection of the crystal data shows that the three complexes are present in the solid state as racemic mixtures containing the $\Delta(\lambda\lambda)/\Lambda(\delta\delta)$ or $\Delta(\lambda\lambda\lambda)/\Lambda(\delta\delta\delta)$ enantiomeric pairs. The cyclam unit in $[Lu(Me_2tedpa)]^+$ adopts a *trans*-I configuration, while the presence of the bridging unit in [La(cb-tedpa)Cl] and [Gd(cbtedpa)]⁺ dictates a *cis*-V-folded configuration that provides four convergent nitrogen atoms for metal ion coordination. The sixmembered chelate rings in [La(cb-tedpa)Cl] and [Gd(cbtedpa)]⁺ adopt chair conformations. The bicyclo[6.6.2] ligand backbones of the cross-bridge derivatives present [2233]/ [2233] conformations, while complexes of smaller metal ions with cross-bridge derivatives often present [2323]/[2323] conformations.³² However, the six-membered chelate rings of $[Lu(Me_2tedpa)]^+$ present twist-boat conformations, which is in contrast with the chair conformations observed for [Ln(teta)]⁻ complexes (Ln = Eu, Tb).³

X-ray Structures of $[La(H_2Me_2tedpa)_2](PF_6)_3\cdot 8H_2O$, $[Yb(H_2Me_2tedpa)_2](PF_6)_3\cdot 4H_2O$, and $[Gd(Hcb-tedpa)_2]Cl 5H_2O$. Addition of an excess of KPF₆ to aqueous solutions of the $[Ln(Me_2tedpa)_2]^+$ complexes gives crystals of formula $[Ln(H_2Me_2tedpa)_2](PF_6)_3\cdot xH_2O$ (Ln = La, x = 8; Ln = Yb, x =4). In both compounds the Ln³⁺ ion presents an exocyclic coordination involving oxygen atoms of the carboxylate groups of the ligand. In the case of the La³⁺ derivative (Figure 6), two carboxylate groups of different H₂Me₂tedpa entities provide a slightly asymmetrical bidentate coordination to the metal ion, while a third H₂Me₂tedpa unit gives monodentate coordination through O4. Nine coordination around the metal ion is completed by the presence of four coordinated water molecules



Figure 6. View of the $[La(H_2Me_2tedpa)_3(H_2O)_4]^{3+}$ entity present in crystals of $[La(H_2Me_2tedpa)_2](PF_6)_3\cdot 8H_2O$. Hydrogen atoms bonded to carbon atoms and anions are omitted for simplicity. The ORTEP plot is at the 30% probability level.

with La–O distances of ca. 2.49–2.56 Å (Table 3). In the Yb³⁺ complex the metal ion is coordinated to four different

Table 3. Bond Distances (Å) of the Metal Coordination Environments in $[La(H_2Me_2tedpa)_3(H_2O)_4]^{3+}$, $[Yb(H_2Me_2tedpa)_4(H_2O)_2]^{3+}$, and $[Gd(Hcb-tedpa)_2]^+$ Entities

$[La(H_2Me_2tedpa)_3(H_2-O)_4]^{3+}$		[Yb(H ₂ Me H ₂ O	e2tedpa)4(-)2] ³⁺	[Gd(Hcb-tedpa) ₂] ⁺	
La1-O1	2.647(4)	Yb1-O1	2.323(3)	Gd1-01	2.305(2)
La1-O2	2.574(4)	Yb1-O2	2.282(3)	Gd1-03	2.287(2)
La1-O4	2.418(4)	Yb1-O3	2.395(3)	Gd1-05	2.280(2)
La1-O5	2.509(3)	Yb1-O4	2.358(3)	Gd1-07	2.292(2)
La1-06	2.606(4)	Yb1-O5	2.134(3)	Gd1-N1	2.664(3)
La1-09	2.564(4)	Yb1-O7	2.236(3)	Gd1-N6	2.674(2)
La1-010	2.498(4)	Yb1-O9	2.142(3)	Gd1-N7	2.643(2)
La1-011	2.556(4)			Gd1-N12	2.681(2)
La1-012	2.564(4)				

carboxylate groups, one providing a bidentate coordination and three of them being monodentated (Figure 7). Coordination number seven is completed by the presence of two inner-sphere water molecules. In both [La- $(H_2Me_2tedpa)_3(H_2O)_4$]³⁺ and [Yb(H_2Me_2tedpa)_4(H_2O)_2]³⁺ entities the carboxylate groups of the ligands are deprotonated, while two of the nitrogen atoms of the macrocyclic fragment are protonated. The protonated amine nitrogen atoms are involved in hydrogen bonding interaction with the nitrogen atoms of the pyridine units (Table S1, Supporting Information). The Ln³⁺–O distances involving oxygen atoms of bidentate carboxylates are longer than those comprising monodentate groups.

Crystals of formula $[Gd(Hcb-tedpa)_2]Cl-SH_2O$ have been obtained from a solution of $GdCl_3$ and H_2cb -tedpa prepared in an attempt to synthesize the $[Gd(cb-tedpa)]^+$ complex (Figure 8). The metal ion is directly bound to the nitrogen and oxygen donor atoms of the picolinate pendant arms of two Hcb-tedpa entities, which results in an eight-coordinate complex. One of the nitrogen atoms of each ligand is protonated, while the carboxylate groups of the ligand are deprotonated. The coordination polyhedron around the metal ion can be described as a twisted square antiprism with square faces defined by O3,



Figure 7. View of the $[Yb(H_2Me_2tedpa)_4(H_2O)_2]^{3+}$ entity present in crystals of $[Yb(H_2Me_2tedpa)_2](PF_6)\cdot 4H_2O$. Hydrogen atoms bonded to carbon atoms and anions are omitted for simplicity. The ORTEP plot is at the 30% probability level.



Figure 8. View of the $[Gd(Hcb-tedpa)_2]^+$ entity present in crystals of $[Gd(Hcb-tedpa)_2]Cl\cdot 5H_2O$. Water molecules and hydrogen atoms bonded to carbon atoms and anions are omitted for simplicity. The ORTEP plot is at the 30% probability level.

O5, N6, and N7 (mean deviation from planarity 0.091 Å) and O1, O7, N1, and N12 (mean deviation from planarity 0.072 Å). These square faces are nearly parallel (1.5°) and display a mean twist angle of 28.4°, which is relatively close to the ideal value for a twisted square antiprism (22.5°) .

Diprotonated species in which oxygen atoms of carboxylate groups are involved in coordination to the Ln^{3+} ion have been proposed as intermediates in the formation and dissociation of complexes with dota-like ligands.³³ Structural evidence for the formation of such diprotonated intermediates was provided in some cases using X-ray diffraction measurements.³⁴ The X-ray structures reported in this section suggest that the reaction intermediates responsible for the formation and dissociation of the [Yb(Me₂tedpa)]⁺ complexes are diprotonated. Furthermore, the higher rigidity and degree of preorganization of the cross-bridge derivative results in the formation of a rather stable [Ln(Hcb-tedpa)₂]⁺ intermediates that in the case of Eu^{3+} could be detected by ¹H NMR spectroscopy and mass spectrometry.

NMR Studies. The ^IH NMR spectra recorded upon dissolution of the $[Ln(Me_2tedpa)]Cl$ complexes (Ln = La or Eu) in D_2O at pH 7.0 show the signals corresponding to the free ligand, which in the case of the Eu^{3+} complex are somewhat broader due to the paramagnetism of the metal ion. This indicates that these complexes are not thermodynamically

stable in aqueous solution and thus experience dissociation. The ¹H NMR spectrum of the $[Ln(Me_2tedpa)]^+$ complex shows paramagnetically shifted resonances spreading over the range ~ 170 to -80 ppm at 25 °C, which testifies the existence of the complex in solution. However, the signals of the free ligand are also clearly visible, indicating partial dissociation of the complex (\sim 45% of the overall ligand is in the uncomplexed form). A similar situation holds for the Lu³⁺ complex, which also shows ¹H NMR signals corresponding to both the complex and the free ligand. These results indicate that the Ln- (Me_2tedpa) ⁺ complexes with the large Ln^{3+} ions display a very low stability in aqueous solution, while for the heaviest Ln³⁺ ions the low stability of the complexes still leads to partial dissociation. The relaxometric method²⁰ confirmed that the Gd³⁺ complex presents a very low thermodynamic stability, as at pH 7.0 only ca. 15% of the metal ion is in the complexed form. Different experiments were carried out to obtain accurate stability constants of this complex, including the use of different competitor ligands to prevent the formation of hydroxide species at the relatively high pH values required for Gd3+ complexation. In spite of our efforts, an accurate stability constant could not be obtained, but nevertheless these studies allowed us to obtain a rough estimate of the stability constant of the $[Gd(Me_2tedpa)]^+$ complex, which falls in the range log K = 8.0 - 8.5.

The Yb³⁺-induced paramagnetic ¹H NMR shifts are generally dominated by the pseudocontact contribution, which is the result of the dipolar coupling between the magnetic moments of the unpaired electrons and the observed nucleus.³⁵ The pseudocontact shift can be approximated by using eq 2:³⁶

$$\delta_{ij}^{\text{dip}} = \left(\chi_{zz} - \frac{1}{3}\text{Tr}\chi\right) \left(\frac{3z^2 - r^2}{r^5}\right) + (\chi_{xx} - \chi_{yy}) \left(\frac{x^2 - y^2}{r^5}\right)$$
(2)

with

$$r = \sqrt{x^2 + y^2 + z^2}$$
(3)

where $[\chi_{zz} - 1/3(\chi_{xx} + \chi_{yy} + \chi_{zz})]$ and $(\chi_{xx} - \chi_{yy})$ are respectively the axial and rhombic anisotropies of the magnetic susceptibility tensor (χ) , and x, y, and z are the Cartesian coordinates of the nucleus under study with the lanthanide at the origin. Following our previous studies on related systems,³ we used the molecular structure of the [Yb(Me₂tedpa)]⁺ complex obtained with density functional theory calculations (DFT) at the TPSSh/LCRECP/6-31G(d) level to assess the agreement between the observed paramagnetic shifts and those calculated with eq 2. The assignment of the ¹H NMR signals was achieved using line-width analysis and the ¹H-¹H COSY spectrum, which presented cross-peaks relating H11ax-H11eq, H8ax-H8eq, H8ax-H9ax, and H9ax-H9eq. The ¹H NMR spectrum recorded at 298 K revealed the position of 15 of the 16 signals expected for an effective C_2 symmetry of the complex in solution, while all 16 signals could be located at 278 K (Figure 9, see also Table S2, Supporting Information). The agreement between the experimental and calculated shifts of $[Yb(Me_2tedpa)]^+$ is excellent (Figure 9, see also Table S2, Supporting Information), with deviations between the experimental and calculated data in the range 0.6-6.1 ppm. Furthermore, the agreement factor $AFj = 0.057^{38}$ is similar to those reported for other Yb3+ complexes analyzed using this methodology.^{39,40} This confirms that our DFT calculations provide an adequate description of the solution structure of the



Figure 9. ¹H NMR (300 MHz, 278 K) spectrum of $[Yb(Me_2tedpa)]^+$ recorded in D₂O solution (~30 mM, pH = 7.0) and plot of the experimental shifts versus those calculated with the DFT optimized geometry and pseudocontact contributions. The solid line represents a perfect fit between experimental and calculated values.

 $[Yb(Me_2tedpa)]^+$ complex, which is very similar to that observed in the solid state for the Lu^{3+} analogue.

The components of the susceptibility tensor obtained from the analysis of the Yb³⁺-induced paramagnetic ¹H NMR shifts of [Yb(Me₂tedpa)]⁺ at 278 K ([$\chi_{zz} - 1/3(\chi_{xx} + \chi_{yy} + \chi_{zz})$] = 3974 ± 43 ppm Å³ and ($\chi_{xx} - \chi_{yy}$) = -2178 ± 79 ppm Å³) define a rhombic susceptibility tensor, as observed previously for [Yb(teta)]⁻ ([$\chi_{zz} - 1/3(\chi_{xx} + \chi_{yy} + \chi_{zz})$] = 3237 ppm Å³ and ($\chi_{xx} - \chi_{yy}$) = -2526 ppm Å³).⁴¹ Thus, the Yb³⁺-induced paramagnetic ¹H NMR shifts of these complexes show sizable contributions from both the axial and rhombic components, although the axial contribution dominates the observed paramagnetic shifts as a consequence of the prolate magnetic susceptibility tensor. On the contrary, [Yb(cb-tedpa)]⁺ presents an oblate magnetic susceptibility tensor dominated by the rhombic contribution ([$\chi_{zz} - 1/3(\chi_{xx} + \chi_{yy} + \chi_{zz})$] = 90 ppm Å³ and ($\chi_{xx} - \chi_{yy}$) = 3018 ppm Å^{3.18}

Assessment of the Thermodynamic Stabilities. The bond distances of the metal coordination environments calculated for $[Ln(Me_2tedpa)]^+$ and $[Ln(cb-tedpa)]^+$ complexes at the TPSSh/LCRECP/6-31G(d) level decrease quadratically along the lanthanide series (Figures S11–S14, Tables S3–S5 Supporting Information), in line with previous experimental and computational studies.^{42,43} This is typical of complexes presenting an increased stability across the series, as attenuated⁴⁴ or even reversed⁴⁵ stability trends have been related to the weakening of some of the Ln³⁺-donor bonds.

Following our recently developed methodology, the evolution of the stability of $[Ln(Me_2tedpa)]^+$ and $[Ln(cb-tedpa)]^+$ complexes in aqueous solution has been evaluated by using DFT calculations with the aid of the thermodynamic cycle presented in Scheme 2.⁴³

As expected, the $\Delta G_{\rm g}(1)$ values become more negative on proceeding to the right across the lanthanide series for the two series of complexes (Tables S6 and S7, Supporting Information) as a consequence of the increased charge density of the metal ion. In aqueous solution the $\Delta G_{\rm aq}(1)$ values also get more negative, which is the most common situation observed for Ln³⁺ complexes with polyaminocarboxylate Scheme 2. Thermodynamic Cycle Used for the Analysis of Complex Stabilities along the Lanthanide Series

$$\begin{array}{c|c} [\mathsf{La}(\mathsf{L})]^{*}_{(\mathrm{g})} + \mathsf{Ln}^{3*}_{(\mathrm{g})} & & & & & \\ \hline & & & & \\ \Delta G_{\mathrm{sol}}([\mathsf{La}(\mathsf{L})]^{*}) & & & & \\ & & & & & \\ \Delta G_{\mathrm{sol}}([\mathsf{Ln}(\mathsf{L})]^{*}) & & & & \\ & & & & \\ & & & \\ & & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ &$$

ligands. Thus, the unfavorable term corresponding to the hydration free energies of the Ln³⁺ ions ($\Delta G_{sol}(La^{3+})$ – $\Delta G_{sol}(Ln^{3+}) > 0)$ is compensated by the increasingly negative $\Delta G_{\sigma}(1)$ values. According to our calculations this trend is more pronounced for [Ln(Me₂tedpa)]⁺ complexes, which probably reflects the ability of the flexible Me₂tedpa²⁻ ligand to accommodate Ln³⁺ ions with different size. These results are in qualitative agreement with the NMR studies performed for $[Ln(Me_2tedpa)]^+$ complexes, which demonstrated that only the complexes with the heaviest Ln³⁺ ions are thermodynamically stable in aqueous solution. It is also worth noting that the solvation free energies of the complexes become significantly less negative on proceeding to the right across the series, which is related to a significant decrease of the dipole moment across the 4f period (Table 4 and Tables S6 and S7, Supporting Information).

Table 4. Thermodynamic Data (kcal mol⁻¹, Scheme 3) Obtained with DFT Calculations at the TPSSh/LCRECP/6-31G(d) Level for $[Ln(Me_2tedpa)]^+$ and $[Ln(cb-tedpa)]^+$ Complexes

Ln	$\Delta G_{\rm g}(2)^a$	$\Delta G_{ m sol}([{ m Ln}({ m cb-tedpa})]^+)^b$	$\Delta G_{\rm sol}([{\rm Ln}({\rm Me_2tedpa})]^+)^b$	$\Delta G_{ m aq}(2)^{ m cald}$
La	-12.29	-77.14	-70.66	-16.51
Nd	-11.84	-74.13	-68.15	-15.55
Gd	-10.98	-70.63	-65.46	-13.88
Dy	-10.49	-69.18	-64.12	-13.29
Yb	-9.75	-67.68	-62.48	-12.68
Lu	-9.64	-67.33	-62.09	-12.61

"Basis set superposition error (BSSE) corrections taken into account with the counterpoise method. ${}^{b}\Delta G_{sol}(LnL)$ were calculated in aqueous solution using the structures optimized in vacuo at the TPSSh/LCRECP/6-31G(d) level.

The relative thermodynamic stabilities of the [Ln- (Me_2tedpa)]⁺ and [Ln(cb-tedpa)]⁺ complexes were investigated by using the thermodynamic cycle presented in Scheme 3.

The calculated $\Delta G_g(2)$ and $\Delta G_{aq}(2)$ values (Figure 10, see also Table 4) are negative, which indicates that the [Ln(cbtedpa)]⁺ complexes are more stable than the [Ln(Me₂tedpa)]⁺ counterparts both in the gas-phase and in solution. The calculated $\Delta G_g(2)$ values range between -12.3 and -9.6 kcal mol⁻¹ and become steadily less negative across the series. This can be explained by the values of $\Delta G_g(1)$ calculated for [Ln(cbtedpa)]⁺ and [Ln(Me₂tedpa)]⁺ complexes, as they become more negative for the latter as the ionic radius of the metal ion decreases (Tables S6 and S7, Supporting Information). In solution the [Ln(cb-tedpa)]⁺ complexes are stabilized with respect to the [Ln(Me₂tedpa)]⁺ analogues, which is a consequence of the more negative hydration free energies of the cross-bridge derivatives (Table 4), as the hydration free energies of the ligands are very similar (-168.0 and -170.2 kcal

mol⁻¹ for Me₂tedpa²⁻ and cb-tedpa²⁻). The calculated $\Delta G_{aq}(2)$

values can be used to estimate equilibrium constants using the

relationship $\Delta G_{aq}(2) = -RT \ln K$, which in turn provide the

difference between the stability constants of [Ln(cb-tedpa)]⁺

and [Ln(Me2tedpa)]⁺ complexes. According to the results of

our calculations the $\Delta \log K = \log K_{[Ln(cb-tedpa)]} - \log$

 $K_{[Ln(Me2tedpa)]}$ values range between 11.4 (Ln = La) and 9.2

(Ln = Lu). This results suggest that the $[Ln(cb-tedpa)]^+$

complexes are several orders of magnitude more stable than

the $[Ln(Me_2tedpa)]^+$ ones, which is likely related to the higher

basicity of the cross-bridge derivative evidenced by the

potentiometric measurements described above. Although our

computational results should be taken with some caution, a stability constant of log $K \sim 8.0$ for $[Gd(Me_2tedpa)]^+$ (see

above) yields according to our DFT studies log $K \sim 18.0$ for

[Gd(cb-tedpa)]⁺. The latter value is very similar to that determined for $[Gd(Me_2dodpa)]^+$ complex (log K = 17.6).²⁰

Scheme 3. Thermodynamic Cycle Used for the Analysis of the Relative Stabilities of $[Ln(Me_1tedpa)]^+$ and $[Ln(cb-tedpa)]^+$ Complexes





Figure 10. Gibbs free energies calculated in the gas phase $(\Delta G_{\alpha}(2),$ blue squares) and in aqueous solution phase ($\Delta G_{aq}(2)$, green circles) according to Scheme 3. The solid lines are only a guide for the eye.

ble 5. Crystal Data and Refinement Details					
	(H ₄ cb-tedpa) (ClO ₄) ₂	[La(cb-tedpa)Cl] ^a	$[Gd(cb-tedpa)](PF_6)^b$	[Gd(Hcb-tedpa) ₂]Cl ^c	
formula CCDC number	$C_{26}H_{38}Cl_2N_6O_{12}$ 1436890	C ₂₆ H ₄₄ ClLaN ₆ O ₉ 1434304	$\begin{array}{c} C_{52}H_{78}F_{12}Gd_2N_{12}O_{13}P_2\\ 1434305 \end{array}$	C ₅₂ H ₈₀ ClGdN ₁₂ O ₁₃ 1434308	
MW	697.52	759.03	1683.70	1273.98	
crystal system	monoclinic	monoclinic	orthorhombic	monoclinic	
space group	$P2_1/n$	C2/c	Pbca	$P2_1/n$	
T/K	100(2)	100(2)	100(2)	100(2)	
a/Å	8.838(3)	13.5447(6)	13.9271(8)	16.0360(4)	
b/Å	18.252(7)	16.3852(6)	21.5806(12)	16.4812(4)	
c/Å	18.672(7)	14.1598(6)	41.373(2)	22.7258(6)	
α/deg	90	90	90	90	
β/\deg	99.33(2)	102.195(2)	90	107.432(2)	
γ/deg	90	90	90	90	
$V/Å^3$	2972.1(19)	3071.6(2)	12435.0(12)	5730.4(3)	
F(000)	1464	1552	6752	2644	
Z	4	4	8	4	
$\lambda/\text{Å}$ (Mo K α)	0.71073	0.71073	0.71073	0.71073	
$D_{\rm calc}/{\rm g}~{\rm cm}^{-3}$	1.559	1.641	1.799	1.477	
μ/mm^{-1}	0.294	1.539	2.274	1.276	
heta range/deg	2.211 to 26.372	2.49 to 25.10	8.631 to 24.411	1.816 to 30.033	
R _{int}	0.1204	0.0407	0.2041	0.0731	
reflns measd	16855	14091	116346	128809	
unique reflns	5775	2743	9752	16768	
reflns obsd	2926	2548	6520	11698	
GOF on F^2	1.003	1.056	1.026	1.037	
R1 ^d	0.0797	0.0230	0.0468	0.0382	
wR2 (all data) ^e	0.2086	0.0528	0.1035	0.0933	
largest differences peak and hole/e $Å^{-3}$	0.496/-0.641	0.720/-1.061	0.907/-0.826	1.614/-0.979	

Ta

^{*a*}Full formula [La(cb-tedpa)Cl]·5H₂O. ^{*b*}Full formula [Gd(cb-tedpa)](PF₆)·2.5H₂O. ^{*c*}Full formula [Gd(Hcb-tedpa)₂]Cl·5H₂O. ^{*d*}R1 = $\sum ||F_0| - |F_c||/|P_0|$ $\sum |F_{o}| \cdot {}^{e} wR2 = \{ \sum [w(||F_{o}|^{2} - |F_{c}|^{2})^{2}] / \sum [w(F_{o}^{4})] \}^{1/2} \cdot$

	[Lu(Me ₂ tedpa)]Cl ^a	$[La(H_2Me_2tedpa)_2](PF_6)_3^b$	$[Yb(H_2Me_2tedpa)_2](PF_6)_3^c$
formula	C26H48ClLuN6O10	$C_{52}H_{92}F_{18}LaN_{12}O_{16}P_3$	$C_{52}H_{84}F_{18}N_{12}O_{12}P_3Yb$
CCDC number	1434303	1434306	1434307
MW	815.12	1715.19	1677.26
crystal system	monoclinic	monoclinic	triclinic
space group	C2/c	$P2_1/n$	$\overline{P}1$
T/K	100(2)	100(2)	100(2)
a/Å	17.7491(5)	15.2720(8)	10.7944(4)
b/Å	15.1219(4)	25.6660(13)	11.6488(4)
c/Å	12.1887(3)	19.5730(10)	28.2797(12)
lpha/deg	90	90	85.196(2)
β /deg	103.7850(10)	111.425(3)	87.336(3)
γ/deg	90	90	74.556(2)
$V/Å^3$	3177.22(15)	7141.9(7)	3414.4(2)
F(000)	1656	3520	1706
Z	4	4	2
λ , Å (Mo K α)	0.71073	0.71073	0.71073
$D_{\rm calc}/{ m g}~{ m cm}^{-3}$	1.704	1.595	1.631
μ/mm^{-1}	3.254	0.782	1.554
heta range/deg	3.20 to 28.36	2.259 to 24.412	2.01 to 24.71
$R_{\rm int}$	0.0274	0.1842	0.0959
reflns measd	20762	163636	82045
unique reflns	3973	11737	11598
reflns obsd	3829	7856	9710
GOF on F^2	1.055	1.032	1.038
$R1^d$	0.0141	0.0531	0.0366
wR2 (all data) ^e	0.0374	0.1309	0.0809
largest differences peak and hole/e ${\rm \AA}^{-3}$	0.521/-0.702	0.926/-0.633	1.288/-0.882
angest unterences peak and hole/e h	0.021/ 0.702	0.7207 0.000	1.2007 0.002

^{*a*}Full formula [Lu(Me₂tedpa)]Cl·6H₂O. ^{*b*}Full formula [La(H₂Me₂tedpa)₂](PF₆)₃·8H₂O. ^{*c*}Full formula [Yb(H₂Me₂tedpa)₂](PF₆)₃·4H₂O. ^{*d*}R1 = $\sum ||F_0| - |F_c|| / \sum |F_0|$. ^{*e*}wR2 = { $\sum [w(||F_0|^2 - |F_c|^2)^2] / \sum [w(F_0^{+4})]^{1/2}$.

Due to the slow formation kinetics of metal complexes with cross-bridge derivatives, there are only a few examples of metal complexes whose thermodynamic stabilities are known for the cross-bridge ligand and the nonreinforced analogue.^{6e,26} In the latter cases it was found that the stability of the Cu^{2+} and Zn^{2+} complexes with the cross-bridge ligands was smaller than that of the nonreinforced derivatives. Our results suggest however that this situation might be reversed for the Ln^{3+} ions.

CONCLUSIONS

The comparison of the coordination properties of the crossbridge cb-tedpa²⁻ ligand and the nonreinforced analogue Me₂tedpa²⁻ allows rationalizing the origin of the exceptional stability of the [Ln(cb-tedpa)]⁺ complexes. Both ligands provide octadentate binding to the Ln³⁺ ions both in the solid state and in solution, the $[Ln(cb-tedpa)]^+$ and $[Ln-tedpa]^+$ (Me_2tedpa) ⁺ complexes presenting similar structures. The formation of the [Ln(cb-tedpa)]⁺ complexes is very slow and requires a slight excess of Ln³⁺ ion to avoid the formation of exocyclic [Ln(Hcb-tedpa)₂]⁺ intermediates. In aqueous solutions the $[Ln(Me_2tedpa)]^+$ complexes are not stable from the thermodynamic point of view, except in the case of the smallest Ln³⁺ ions, which were found to dissociate partially. Crystals of the exocyclic $[Ln(H_2Me_2tedpa)_2]^{3+}$ (Ln = La or Yb) complexes were obtained from aqueous solutions prepared upon dissolution of the corresponding $[Ln(Me_2tedpa)]Cl$ salts. Furthermore, the $[Eu(Hcb-tedpa)_2]^+$ species was characterized using ¹H NMR and mass spectrometry during the formation of the [Eu(cb-tedpa)]⁺ complex. Thus, these exocyclic derivatives can be regarded as key intermediates in the formation and dissociation of this family of complexes. The computational study presented in this work suggests that the $[Ln(cb-tedpa)]^+$ complexes are considerably more stable thermodinamically than the $[Ln(Me_2tedpa)]^+$ analogues.

EXPERIMENTAL SECTION

Chemicals, Starting Materials, and General Procedures. Chemicals were purchased from commercial sources and used without further purification. Compounds 1,4,8,11-tetraazatricyclo[9.3.1.14, hexadecane (2), 1,8-dimethyl-1,4,8,11-tetraazatricyclo[[9.3.1.1^{4,8}]hexadecane-1,8-diium iodide (3), and 1,8-dimethyl-1,4,8,11-tetraazacyclotetradecane (4) were prepared following the published procedures.²¹ Preparative medium pressure liquid chromatography was carried out using a CombiFlash Rf system using neutral Al₂O₃ RediSepRf columns (column size 48 g, particle size 40–63 μ m, pore size 60 Å). ¹H and ¹³C NMR spectra were recorded at 25 °C on Bruker Avance 300 or Bruker Avance 500 spectrometers. ESI-TOF mass spectra were recorded using a LC-Q-q-TOF Applied Biosystems QSTAR Elite spectrometer in the positive mode. Elemental analyses were carried out on a ThermoQuest Flash EA 1112 elemental analyzer. IR spectra were recorded using a Bruker Vector 22 spectrophotometer equipped with a Golden Gate Attenuated Total Reflectance (ATR) accessory (Specac). The longitudinal relaxation times (T_1) of water protons were measured at 20 MHz with a Bruker Minispec MQ-20 NMR Analyzer at 25.0 \pm 0.2 °C.

Dimethyl 6,6'-((4,11-Dimethyl-1,4,8,11-tetraazatricyclotetradecane-1,8-diyl)bis(methylene))dipicolinate (6). A mixture of compound 4 (0.438 g, 1.92 mmol) and Na_2CO_3 (1.330 g, 9.62 mmol) in dry acetonitrile (40 mL) was stirred for 30 min, and then a solution of compound 5 (0.750 g, 4.04 mmol) in acetonitrile (15 mL) was added dropwise. The mixture was stirred at 45 °C for a period of 3 days, and then the excess Na_2CO_3 was filtered off. The filtrate was concentrated to dryness and the yellow oil was partitioned between a 2:5 H₂O:CH₂Cl₂ mixture (70 mL). The aqueous phase was further extracted with CH_2Cl_2 (2 × 50 mL). The organic phase was dried over MgSO₄, filtered, and evaporated to dryness to give an oily residue that was purified by preparative medium pressure liquid chromatography (neutral Al₂O₃ with a CH₂Cl₂/MeOH mixture as the eluent; gradient 0–10%) to give 6 (0.740 g) as a yellow oil. Yield: 73%. MS (ESI^+ , % BPI): m/z 527,33 (100) ([$C_{28}H_{43}N_6O_4$]⁺). IR (ATR): 2977, 2955, 2931, 2781 (C-H), 1733 (C=O), 1588 cm⁻¹ (C=N)py. ¹H NMR $(CDCl_3, 300 \text{ MHz}, 25 \text{ °C}, TMS): \delta 7.98 (dd, {}^{3}J = 7.4 \text{ Hz}, {}^{4}J = 1.3 \text{ Hz},$ 2H, py), 7.89–7.83 (m, 2H, py), 7.78 (t, ³J = 7,7 Hz, 2H, py), 3.98 (s, 6H, OCH₃), 3.82 (s, 4H, CH₂ arm), 2.71–2.58 (m, 8H, α-CH₂ cyclam), 2.55–2.35 (m, 8H, α-CH₂ cyclam), 2.08 (s, 6H, Me), 1.72– 1.58 ppm (m, 4H, β-CH₂ cyclam). ¹³C NMR (CDCl₃, 75.5 MHz, 25 °C): δ 166.1 (CO), 161.8, 147.2, 137.2, 126.5, 123.6 (py), 61.1 (CH₂ arm), 54.9 (OCH₃), 54.7, 53.0, 52.0 (α-CH₂ cyclam), 51.7 (Me), 43.2 (α -CH₂ cyclam), 24.5 ppm (β -CH₂ cyclam).

6,6'-((4,11-Dimethyl-1,4,8,11-tetraazacyclotetradecane-1,8diyl)bis(methylene))dipicolinic acid (H2Me2tedpa). The dimethyl ester 6 (1.121 g, 2.13 mmol) was dissolved in a 6 M HCl aqueous solution (20 mL). The mixture was heated to reflux with stirring for 24 h, and then the solvents were removed in a rotary evaporator to give a dark oil. This was dissolved in H₂O (10 mL) and the solvent was evaporated. This process was repeated twice, and then the residue was dried under vacuum to give 1.538 g of the expected compound as a white solid. Yield: 98%. Anal. Calcd. for C26H38N6O4·5HCl·3H2O: C 42.49, H 6.72, N 11.43%. Found: C 42.42, H 6.61, N 10.88%. MS (ESI⁺, %BPI): m/z 250.16 (100) ([$C_{26}H_{40}N_6O_4$]²⁺), 499.31 (30) $([C_{26}H_{39}N_6O_4]^+)$. IR (ATR): 2582, 2487 (C-H), 1750 (C=O), 1649 (C=N)py. ¹H NMR (D₂O, pD = 0.73, 500 MHz, 25 °C): δ cm⁻ 8.20-8.12 (m, 4H, py), 7.76 (d, ${}^{3}J = 7.7$ Hz, 2H, py), 4.25-3.95 (m, 4H, CH₂ arm), 3.75–2.78 (m, 16H, α-CH₂ cyclam), 2.80 (s, 6H, Me), 2.10–1.90 (m, 4H, β -CH₂ cyclam). ¹³C NMR (D₂O, pD = 0.73, 125.8 MHz, 25 °C): 165.93 (CO), 154.94, 146.26, 142.50, 128.20, 125.29 (py), 57.03 (CH₂ arm), 52.21, 51.70, 51.07, 47.33 (α-CH₂ cyclam), 41.88 (Me), 21.20 (β-CH₂ cyclam).

Synthesis of [La(Me2tedpa)]Cl Complex Salt. A mixture of H₂Me₂tedpa·5HCl·3H₂O (0.053 g, 0.072 mmol) and triethylamine (0.062 g, 0.615 mmol) in 2-propanol (7 mL) was heated to reflux for 30 min, and then a solution of LaCl₃·6H₂O (0.026, 0.072 mmol) in 2propanol (3 mL) was added dropwise. The mixture was heated to reflux for a period of 2 days. After this, the reaction was allowed to cool to room temperature and then concentrated to dryness. The addition of chloroform (4 mL) resulted in the formation of a white precipitate, which was isolated by filtration. The solid was washed with chloroform $(3 \times 7 \text{ mL})$, diethyl ether $(1 \times 7 \text{ mL})$ and dried under vacuum. Yield 0.044 g, 90%. Anal. Calcd. for C26H36ClLaN6O4: C, 46.54; H, 5.41; N, 12.53%. Found: C, 46.80; H, 5.69; N, 12.66%. MS (ESI⁺, %BPI): m/z 499.30 (100) ([C₂₆H₃₉N₆O₄]⁺), 559.23 (62) $([C_{26}H_{37}KN_6NaO_4]^+), 537.25 (28) ([C_{26}H_{38}KN_6O_4]^+), 521.28 (18)$ $([C_{26}H_{38}N_6NaO_4]^+)$, 635.18 (7) $([C_{26}H_{36}LaN_6O_4]^+)$. HS-MS (ESI⁺): m/z 635.1843; calcd. for $[C_{26}H_{36}LaN_6O_4]^+$ 635.1856. IR (ATR): 1612 (C=O), 1568 cm⁻¹ (C=N)py.

[Eu(Me₂tedpa)]Cl. The preparation of the white solid followed the same procedure as that described for [La(Me₂tedpa)]Cl by using H_2Me_2 tedpa·5HCl·3H₂O (0.067 g, 0.091 mmol), triethylamine (0.078 g, 0.775 mmol) and EuCl₃·6H₂O (0.033, 0.091 mmol). Yield 0.050 g, 80%. Anal. calcd. for C₂₆H₃₆ClEuN₆O₄: C, 45.65; H, 5.31; N, 12.29%. Found: C, 45.54; H, 5.66; N, 12.31%. MS (ESI⁺, %BPI): *m/z* 649.19 (100) ([C₂₆H₃₆EuN₆O₄]⁺). HS-MS (ESI⁺): *m/z* 649.1984; calcd. for [C₂₆H₃₆EuN₆O₄]⁺ 649.2005. IR (ATR): 1613 (C=O), 1568 cm⁻¹ (C=N)py.

[Gd(Me₂tedpa)]Cl. The preparation of the white solid followed the same procedure as that described for [La(Me₂tedpa)]Cl by using H₂Me₂tedpa·5HCl·3H₂O (0.070 g, 0.095 mmol), triethylamine (0.081 g, 0.805 mmol) and GdCl₃·6H₂O (0.035, 0.095 mmol). Yield 0.047 g, 72%. Anal. calcd. for C₂₆H₃₆ClGdN₆O₄: C, 45.30; H, 5.26; N, 12.19%. Found: C, 44.91; H, 5.06; N, 12.18%. MS (ESI⁺, %BPI): *m/z* 654.20 (100) ([C₂₆H₃₆GdN₆O₄]⁺). HS-MS (ESI⁻): *m/z* 654.2045; calcd. for [C₂₆H₃₆GdN₆O₄]⁺ 654.2034. IR (ATR): 1614 (C=O), 1568 cm⁻¹ (C=N)py.

[Tb(Me₂tedpa)]Cl. The preparation of the white solid followed the same procedure as that described for [La(Me₂tedpa)]Cl by using $H_2Me_2tedpa\cdot SHCl\cdot 3H_2O$ (0.066 g, 0.090 mmol), triethylamine (0.077 g, 0.763 mmol) and TbCl₃·6H₂O (0.034, 0.090 mmol). Yield 0.043 g, 70%. Anal. calcd. for $C_{26}H_{36}ClN_6O_4Tb$: C, 45.19; H, 5.25; N, 12.16%. Found: C, 44.99; H, 5.43; N, 12.22%. MS (ESI⁺, %BPI): *m/z* 655.21 (100) ([$C_{26}H_{36}N_6O_4Tb$]⁺). HS-MS (ESI⁺): *m/z* 655.2044; calcd. for [$C_{26}H_{36}N_6O_4Tb$]⁺) 655.2046. IR (ATR): 1568 cm⁻¹ (C=N)py.

[Yb(Me₂tedpa)]Cl. The preparation of the white solid followed the same procedure as that described for [La(Me₂tedpa)]Cl by using H_2Me_2tedpa ·SHCl·3H₂O (0.053 g, 0.072 mmol), triethylamine (0.062 g, 0.613 mmol), and YbCl₃·6H₂O (0.028, 0.072 mmol). Yield 0.030 g, 59%. Anal. calcd. for C₂₆H₃₆ClN₆O₄Yb: C, 44.29; H, 5.15; N, 11.92%. Found: C, 44.08; H, 5.31; N, 11.75%. MS (ESI⁺, %BPI): *m/z* 670.22 (100) ([C₂₆H₃₆N₆O₄Yb]⁺). HS-MS (ESI⁺): *m/z* 670.2176; calcd. for [C₂₆H₃₆N₆O₄Yb]⁺ 670.2181. IR (ATR): 1632 cm⁻¹ (C=O).

[Lu(Me₂tedpa)]Cl. The preparation of the white solid followed the same procedure as that described for [La(Me₂tedpa)]Cl by using H₂Me₂tedpa·SHCl·3H₂O (0.052 g, 0.071 mmol), triethylamine (0.061 g, 0.601 mmol) and LuCl₃·6H₂O (0.028, 0.071 mmol). Yield 0.026 g, 51%. Anal. calcd. for C₂₆H₃₆ClLuN₆O₄: C, 44.17; H, 5.13; N, 11.89%. Found: C, 43.88; H, 5.41; N, 11.66%. MS (ESI⁺, %BPI): *m/z* 671.22 (100) ([C₂₆H₃₆LuN₆O₄]⁺). HS-MS (ESI⁺): *m/z* 671.2204; calcd. for [C₂₆H₃₆LuN₆O₄]⁺ 671.2200. IR (ATR): 1633 (C=O), 1575 cm⁻¹ (C=N)py.

pH-Potentiometric Titrations of the Ligands. The protonation constants of the ligands were determined by using pH-potentiometric titrations with Methrohm 888 Titrando and a 785 DMP titrator systems and Metrohm-6.0233.100 combined electrode. For the pHcalibration of the electrode KH-phthalate (pH = 4.005) and borax (pH = 9.180) buffers obtained from commercial sources (Merck certified standard reference materials for pH measurements) were used.⁴⁶ The titrated solutions (6.00 mL) were thermostatted at 25 °C and kept under inert gas atmosphere (N_2) to avoid the effect of CO₂. The concentrations of the ligands in the samples were set to 2.35 and 4.24 mM for Me_2 tedpa²⁻ and cb-tedpa²⁻, respectively. In the pHpotentiometric titrations 284 to 440 mL-pH data pairs were recorded in the pH range of 1.7-12.5. The calculation of [H⁺] from the measured pH values was performed with the use of the method proposed by Irving et al.⁴⁷ by titrating a 0.01 M HCl solution (I = 0.15M NaCl) with a standardized ($c_{NaOH} = 0.2190$ M) NaOH solution. The differences between the measured and calculated pH values were used to obtain the [H⁺] concentrations from the pH data obtained in the titrations. The ion product of water was determined from the same experiment in the pH range 11.4–12.0 and was found to be 13.81(1), which is acceptably close to the value referred in the literature (pKw = 13.78 in 0.15 M NaCl at 25 °C). The protonation and stability constants were calculated from the titration data with the PSEQUAD program.48

Single Crystal X-ray Diffraction Measurements. Single crystals of formula $(H_4cb-tedpa)(ClO_4)_2$ were obtained from an aqueous solution containing equimolar amounts of $Lu(ClO_4)_3$ and the ligand, prepared in an attempt to form the Lu^{3+} complex (pH ~ 6.0). Partial complex formation (i.e., out-of-cage complexes) likely lowered the pH of the mixture, as the ligand crystallized in its tetraprotonated form. Crystals of $[La(H_2Me_2tedpa)_2](PF_6)_3 \cdot 8H_2O$, $[Yb(H_2Me_2tedpa)_2]$ -(PF₆)₃·4H₂O, and [Gd(cb-tedpa)](PF₆)·2.5H₂O were obtained by dissolving small amounts of the isolated [Ln(Me2tedpa)]Cl (Ln = La, Yb) or [Gd(cb-tedpa)]Cl complexes in water and addition of an excess of KPF₆. Crystals of [La(cb-tedpa)Cl]·5H₂O and [Lu(Me₂tedpa)]Cl· 6H₂O were obtained by slow evaporation of aqueous solutions of the complexes at neutral pH. Crystals of [Gd(Hcb-tedpa)₂]Cl·5H₂O were obtained by reacting the ligand (~30 mg) and equimolar GdCl₃ in 5 mL of n-butanol in the presence of DIPEA as a base under microwave irradiation (8-10 W to set the temperature to 140-145 °C) for nearly 40 h. The crystals were obtained upon storing the resulting solution at room temperature for a few days.

Three dimensional X-ray data were collected on Bruker-Nonius X8 APEX Kappa CCD or Bruker Kappa APEXII CCD ($[Gd(Hcb-tedpa)_2]Cl\cdotSH_2O$) diffractometers. Data were corrected for Lorentz

and polarization effects and for absorption by semiempirical methods⁴⁹ based on symmetry-equivalent reflections. Complex scattering factors were taken from the programs SHELX97⁵⁰ running under the WinGX program system.⁵¹ The structures were solved by Patterson methods with DIRDIF2008⁵² ([Lu(Me₂tedpa)]Cl and [Yb(H₂Me₂tedpa)₂]- $(PF_6)_3$) and with SHELXS97⁵⁰ ([La(cb-tedpa)Cl] and [Gd(cbtedpa)](PF₆)). The other three structures were solved by direct methods with SIR 2004⁵³ ([La(H₂Me₂tedpa)₂](PF₆)₃) or SIR2011⁵⁴ $((H_4cb-tedpa) (ClO_4)_2$ and $[Gd(Hcb-tedpa)_2]Cl-SH_2O)$. All the structures were refined⁵⁰ by full-matrix least-squares on F^2 . The hydrogen atoms were included in calculated positions and refined in riding mode, with the following exceptions: Hydrogen atoms of water molecules were located in a difference electron-density map and the distances restrained (DFIX 0.84(1) DANG 1.34(2)). In the case of the $[Lu(Me_2tedpa)]Cl$ hydrogen atoms bonded to O1W were refined freely and those bonded to O2W and O3W were refined with all the positional parameters fixed. For [Gd(Hcb-tedpa)₂]Cl·5H₂O the N-H distances involving N3 and N9 were refined, H91 an H92 (bonded to O9) were refined freely and finally the position of H122, H141, and H142 had to be fixed to achieve convergence. Three of the crystals present positional disorder; Crystals of [Gd(cb-tedpa)](PF₆) contain two disordered water molecules with occupation factors for the main positions of O3W and O5W of 0.81(1). One noncoordinated PF₆anion also shows positional disorder with occupational factors of 0.810(9) for F8A, F9A, F10A, and F11A, so that 16 restraints had to be applied in order to reach convergence. Crystals of [Yb- $(H_2Me_2tedpa)_2](PF_6)_3$ contain one disordered perchlorate with occupation factors for O9, O11, and O12 of 0.679(5). The refinement converged with anisotropic displacement parameters for all nonhydrogen atoms in all the cases. Two water molecules present in the crystal of [Gd(Hcb-tedpa)₂]Cl·5H₂O show positional disorders into three positions that have been solved. The total occupancy factor was restrained initially with SUMP to 2 but finally the occupancy factors had to be fixed to 0.68 for O12, 0.62 for O13, and 0.50 for O14 in order to achieve convergence. Crystal data and details on data collection and refinement are summarized in Tables 5 and 6.

Computational Details. All calculations presented in this work were performed employing the Gaussian 09 package (Revision D.01).³⁵ Full geometry optimizations of the [Ln(cb-tedpa)]⁺ and $[Ln(Me_2tedpa)]^+$ systems (Ln = La, Pr, Nd, Eu, Gd, Dy, Ho, Yb, or Lu) were conducted employing DFT within the hybrid meta generalized gradient approximation (hybrid meta-GGA), with the TPSSh exchange-correlation functional.⁵⁶ Geometry optimizations were carried out by using the large-core quasirelativistic effective core potential (LCECP) of Dolg and co. and its associated [5s4p3d]-GTO valence basis set,⁵⁷ while the ligand atoms were described by using the standard 6-31G(d) basis set. Input geometries were taken from our previous computational studies in the case of [Ln(cb-tedpa)]+ complexes.¹⁸ No symmetry constraints have been imposed during the optimizations. The stationary points found on the potential energy surfaces as a result of geometry optimizations were tested to represent energy minima rather than saddle points via frequency analysis. Gibbs free energies were obtained at T = 298.15 K within the harmonic approximation. The ΔG_{σ} values reported in this work include basis-set superposition errors, which were estimated using the Counterpoise method of Boys and Bernardi (Table S8, Supporting Information).⁵⁸ The default values for the integration grid (75 radial shells and 302 angular points) and the SCF energy convergence criteria (10^{-8}) were used in all calculations.

Throughout this work solvent effects were included by using the polarizable continuum model (PCM), in which the solute cavity is built as an envelope of spheres centered on atoms or atomic groups with appropriate radii. In particular, the integral equation formalism (IEFPCM) variant as implemented in Gaussian 09 was used.⁵⁹ Hydration free energies were obtained using the radii and non-electrostatic terms obtained by Truhlar et al. (SMD solvation model).⁶⁰ The radii used for the Ln^{3+} ions were parametrized in a previous paper.⁴³

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorg-chem.5b02627.

¹H and ¹³C NMR spectra, HR-ESI⁺ mass spectra, calculated bond distances of the metal coordination environments, quadratic fits of the average bond distances of the metal coordination environments, hydrogen-bonding data, experimental and calculated ¹H NMR shifts of [Yb(Me₂tedpa)]⁺, thermodynamic data obtained using DFT calculations according to Scheme 2, basis set superposition errors, \setminus optimized Cartesian coordinates obtained with DFT calculations (PDF) Crystallographic data (CIF)

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The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors are indebted to Centro de Supercomputación de Galicia (CESGA) for providing the computer facilities. A.R.-R., M.R.-F., D.E.-G., A.deB., T.R.-B., and C.P.-I. thank Ministerio de Economía y Competitividad (CTQ2009-10721-PPQ) for generous financial support. G.T., F.K.K., and I.T. thank the Hungarian Scientific Research Fund (OTKA K-84291 and K-109029) for their financial support. This work was also supported by the János Bolyai Research Scholarship (G.T. and F.K.K.) of the Hungarian Academy of Sciences. A.R.-R., G.T., F.K.K., I.T., and C.P.-I. gratefully acknowledge support from the COST CM1006 "European F-Element Network (EuFen)" and COST TD1004 "Theragnostics Imaging and Therapy: An Action to Develop Novel Nanosized Systems for Imaging-Guided Drug Delivery" Actions. A.R.-R. thanks the Ministerio de Educación y Ciencia (FPU program) for a predoctoral fellowship. R.T. acknowledges the Ministère de l'Enseignement Supérieur et de la Recherche, the Centre National de la Recherche Scientifique, and the "Service Commun" of NMR facilities of the University of Brest. C.P.-I. acknowledges the University of Brest for his invited Professor position.

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