Solid-State and Solution Properties of the Lanthanide Complexes of a New Heptadentate Tripodal Ligand: A Route to Gadolinium Complexes with an Improved Relaxation Efficiency

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The tripodal ligand (α,α′,α″nitrilotri(6-methyl-2-pyridinecarboxylic acid)) (H_3tpaa) forms a Gd(III) complex which has a relaxivity (r_{1p} = 13.3 mM^{-1} s^{-1} at 25 °C and at 60 MHz) remarkably higher than those of the currently clinically used contrast agents based on octacoordinate polyaminocarboxylate complexes (3.5−4.7 mM^{-1} s^{-1}) and a reasonably good thermodynamic stability. The crystal structure of the ligand and of its La, Nd, Eu, Gd, Tb, Ho, Tm, Yb, and Lu complexes have been determined by X-ray crystallography. The neutral H_3tpaa molecule adopts, in the solid state, a preorganized tripodal conformation in which the three H_3tpaa arms are located on the same side of the molecule, ready to bind a metal ion in a heptadentate coordination mode. The structures of the Ln(III) complexes vary along the series for their nuclearity and number of water molecules coordinated to the metal, and a tetrameric structure is observed for the La^{3+} ion (9- and 10-coordinate metal centers), dimeric structures are formed from the Nd^{3+} ion through the Yb^{3+} ion (9-coordinate), and a monomeric structure results for Lu^{3+} (8-coordinate). The relaxivity studies presented here suggest that the high relaxivity of the Gd(tpaa) complex is mainly the consequence of a shorter bound water proton−Gd(III) distance associated with a probable water coordination equilibrium between tris(aqua) and bis(aqua) complexes, giving raise to a mean number of coordinated water molecules $q > 2$. Both effects are strongly related to the ligand flexibility, which allows for a large volume available for water binding. The observed rapid water exchange rate is probably due to the presence of a low-energy barrier between 10-, 9-, and 8- coordinate geometries. Although the low solubility of the Gd complex of tpaa prevents its practical application as an MRI contrast agent, the straightforward introduction of substituents on the pyridine rings allows us to envisage ligands with a higher water solubility, containing functional groups leading to macromolecular systems with very high relaxivity.

Introduction

In the last two decades there has been rapid growth in the field of coordination chemistry of lanthanides with multidentate ligands[1,2] due to the wide variety of potential applications in biology, medicine, and material science. In particular, a large number of studies have been spurred by the application of gadolinium complexes as magnetic resonance imaging (MRI) contrast agents[3−7] and of europium or terbium complexes as luminescent probes in time-resolved fluoroimmunoassays.[8,9] To be considered for application as MRI contrast agents, the Gd complexes need to fulfill a large number of requirements, such as good solubility in water, high thermodynamic stability, possibly kinetic inertness in vivo, to avoid release of the toxic Gd ions, and high relaxivity (which is the ability to enhance the relaxation rate of solvent water protons). Much of the work on MRI agents has focused on the macrocyclic octadentate poly(aminocarboxylate) ligand 1,4,7,10-tetrakis(carboxymethyl)-1,4,7,10-tetraazacyclododecane (dota) and the acyclic octadentate diethylenetriaminepentaacetic acid (dtpa), which form very stable, water soluble anionic complexes while leaving an open coordination site for water binding, Chart 1. Octadentate dtpa−bis(amide) derivatives such as dtpa−bma and dtpa-bea[10,11] have also been described; these lead to neutral complexes having a

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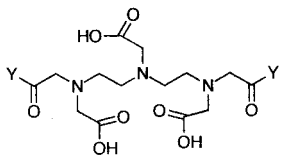
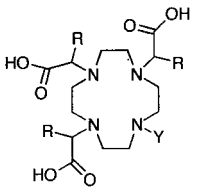
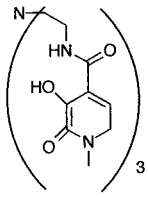
Chart 1



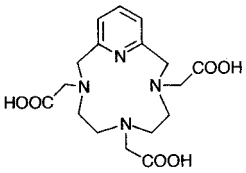
Y=OH H_3dtpa
Y=NHEt H_3dtpa-bea
Y=NHMe H_3dtpa-bma



R=H, Y=CH_2COOH H_4dota
R=H, Y=H H_3do3a
R= CH_3, Y=H H_3do3ma



H_3tren-Me-3,2-hopo



H_3pcta[12]

reduced possibility of osmotic cell damage. In addition, dtpa−bis(amide) derivatives show a strong selectivity for Gd(III) with respect to endogenous Ca(II), which results in a low toxicity despite the lower thermodynamic stability of its Gd(III) complexes with respect to dtpa complexes.[11,12]

The key property of an efficient contrast agent is the high ability to enhance the relaxation rate of solvent water protons. This can be obtained in the presence of a high number of inner sphere water molecules allied with fast water exchange, a long rotational correlation time, and a long electronic relaxation time. The current approach to achieve higher relaxivity consists of increasing the rotational correlation time (τ_R) by increasing the molecular weight of the contrast agent through the formation of macromolecular complexes by covalent or noncovalent linkage of Gd(III) chelates to large biomolecules. However, the attainable enhancement of the relaxivity in molecules with long rotational correlation time can be limited by the water exchange rate between the coordination site and the bulk solvent. The relatively long water exchange rate of Gd complexes of octadentate ligands, such as $[Gd(dota)(H_2O)]^-$, which appears to be related to the dissociative exchange mechanism of the water molecule, prevents dendrimeric Gd derivatives[13] and noncovalent adducts of Gd−chelates with large biomolecules[14] from attaining their potential relaxation enhancement.

The use of macrocyclic heptadentate ligands, such as do3a[15,16] and pcta[12],[17] allows the coordination of two water molecules in the inner sphere of the metal and consequently a higher relaxivity with respect to the Gd complexes of octadentate ligands. In addition, Gd(III) complexes containing heptadentate ligands[18,19] or hexadentate ligands[20,21] show a faster water exchange rate with respect to complexes with octacoordinating ligands. Despite this, heptadentate ligands have only seldom been considered for the design of contrast agents. This is not only because of the lower than acceptable stability (kinetic and thermodynamic) of their complexes, but also because the inner-sphere water molecules tend, in some cases, to be displaced either by endogenous anions[22] or by coordinating groups of the proteins.[23] Moreover, only a limited number of lanthanide complexes of heptadentate ligands have been structurally characterized. [24−26]

We have recently reported in a preliminary communication[27] the gadolinium complex of the new heptadentate tripodal ligand tpaa (H_3tpaa = α,α′,α″nitrilotri(6-methyl-2-pyridinecarboxylic acid)) containing three pyridinecarboxylato arms connected to a nitrogen atom. Although a decrease in the thermodynamic stability was observed for the tpaa complex with respect to the complexes of macrocyclic heptadentate ligands, the value of relaxivity (r_{1p} = 13.3 mM^{-1} s^{-1} at 25 °C and 60 MHz) found for the Gd(III) complex of tpaa is remarkably higher than those of the currently clinically used contrast agents based on complexes of octacoordinate ligands, such as $[Gd(dtpa)(H_2O)]^{2-}$ and $[Gd(dota)(H_2O)]^-$ (4.7 mM^{-1} s^{-1}).

Here we describe the structure and solution properties of several lanthanide complexes of tpaa and the relaxivity properties of the Gd(tpaa) complex.

Experimental Section

General Information. ^{1}H NMR spectra were recorded on a Varian U-400 spectrometer using deuterated DMSO and D_2O solutions, with DMSO and 2,2-dimethyl-2-silapentane-5-sulfonate, sodium salt as internal standards. Mass spectra were measured with a Finnigan LC-Q instrument. Elemental analyses were performed by SCA/CNRS, Vernaison, France.

Solvents and starting materials were purchased from Aldrich, Fluka, Acros, and Alfa and used without further purification, unless otherwise stated. Tris[6-(2-*N*,*N*-diethyl-carbamoyl)pyridyl)methyl]amine (tpaam) was prepared from *N*,*N*-diethyl(6-aminomethyl)pyridine-2-carboxamide and *N*,*N*-diethyl(6-chloromethyl)pyridine-2-carboxamide in acetonitrile in the presence of K_2CO_3.[28]

α,α′,α″Nitrilotri(6-methyl-2-pyridinecarboxylic acid) (H_3tpaa). Tris[6-(2-*N*,*N*-diethylcarbamoyl)pyridyl)methyl]amine (2.0 g, 3.4 mmol) was dissolved in ethanol (100 mL). A solution of potassium hydroxide (4.0 g, 20 equiv) in water (25 mL) was added, and the mixture was refluxed for 3 days. The reaction was monitored by ^{1}H NMR, and aliquots of potassium hydroxide (4.0 g, 20 equiv) were added each 24 h until the hydrolysis of the amide groups was complete. The solvent was then evaporated under reduced pressure, and the resulting solid was dissolved in water (100 mL). The solution was acidified with concentrated HCl to pH 8, and a white precipitate was

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Table 1. ^{1}H NMR Chemical Shifts of Ln(tpaa) Complexes in DMSO-d_6/D_2O (50/50) at pH = 6 (not Corrected for Deuterium Isotope Effect)

	$-CH_2-$	H_5	H_4	H_3
La	4.04	7.50	7.89	7.83
Lu	4.24	7.53	7.96	7.80
	$-CH_2-$	H_5 H_3[a]	H_3H_5[a]	H_4
Nd	1.85	10.39	7.22	8.79
Eu	5.59	4.21	7.11	6.76

[a] Too broad to be unambiguously assigned by NOESY experiment.

filtered off. The solution was further acidified (to pH 3) and concentrated (50 mL), causing the precipitation of a white powder which was crystallized from acetone (0.9 g, 63%). Anal. Calcd for H_3tpaa·1.6 H_2O ($C_{21}H_{15.2}N_4O_{7.6}$): C, 55.9; H, 4.7; N, 12.4; O, 26.9. Found: C, 55.9; H,4.8; N, 12.25; O, 27.0. ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ (ppm): 7.92 (H4, t, 3H), 7.89 (H3, dd, 3H, J = 7.2 Hz, J = 1.8 Hz); 7.82 (H5, dd, 3H, J = 7.2 Hz, J = 1.8 Hz); 3.93 (s, 6H, $-$C**H**$_2$-).^{13}C NMR (400 MHz, DMSO-d_6, 298 K), δ(ppm): 165.9 (**C**OO); 158.9; 147.6; 137.6; 125.9; 122.8; 59.2 (-**C**H_2-). ES$^+-$MS m/z: 423 $[MH_3 + H]^+$; 445 $[MH_3 + Na]^+$; 461 $[MH_3 + K]^+$; 401 $[MH_3 + Na-COO]^+$; 417 $[MH_3 + K-COO]^+$. ES$^-$, m/z: 459 $[MH_3 + K - 2H]^-$; 421 $[MH_3 - H]^-$; 415 $[MH_3 + K - 2H - COO]^-$; 322 $[MH_3 + K - C_7H_7NO_2]^-$.

Synthesis of [Ln(tpaa)(H_2O)]$_2$.7H_2O (Ln = Eu, Gd, Tb). H_3tpaa (30 mg, 0.07 mmol) was added to a solution of $LnCl_3$·6H_2O (0.07 mmol) in water (10 mL). The resulting suspension was heated at 100° for few minutes to give a clear solution. Slow cooling of this solution followed by slow evaporation yielded, after 48 h, the complexes [Ln(tpaa)(H_2O)]$_2$·7H_2O (Ln = Eu, **4**; Gd, **5**; Tb, **6**) as colorless crystals suitable for X-ray structure analysis (Yield: 60−80%).

Colorless X-ray quality crystals of [Lu(tpaa)(H_2O)]·4H_2O, **10**, [La_2(tpaa)$_2$(H_2O)$_3$]$_2$·20H_2O, **2**, [Ln(tpaa)(H_2O)]$_2$·7H_2O (Ln = Ho, **7**, Tm, **8**, Yb, **9**), and slightly violet crystals of [Nd(tpaa)(H_2O)$_2$]$_2$·5H_2O, **3**, were obtained by slow evaporation of 1:1 solutions of H_3tpaa (2 mg) and $LnCl_3$ in water. ES−MS molecular peaks and adduct ions observed for Ln(tpaa) (Ln = La, Pr, Gd, Tb, Ho, Yb, Lu) complexes are presented in the Supporting Information (Table S3).

Due to the low solubility ($<10^{-3}$ M) of these complexes in water, ^{1}H NMR spectra of Ln(tpaa) complexes for La, Nd, Eu, and Lu were recorded in a 50:50 mixture DMSO-d_6/D_2O (Table 1).

X-ray Crystallography. All the crystals were analyzed using a Bruker SMART CCD area detector three-circle diffractometer (Mo Kα radiation, graphite monochromator, λ = 0.71073 Å). The cell parameters were obtained with intensities detected on three batches of 15 frames with a 10 s exposure time for complexes **2**, **4**, **6**, **10**, and a 5 s exposure for compounds **1**, **3**, **5**, **7**−**9**. The crystal−detector distance was 5 cm. For three settings of Φ and 2Θ, 1200 narrow data frames were collected for 0.3° increments in ω. A full hemisphere of data was collected for compounds **1**−**5**, **8**, **10** (a quadrant was collected for complexes **6**, **7**, **9**). At the end of data collection, the first 50 frames were recollected to establish that crystal decay had not taken place during the collection. Unique intensities with $I > 10\sigma(I)$ detected on all frames using the Bruker program[29] were used to refine the values of the cell parameters. The substantial redundancy in data allows empirical absorption corrections to be applied using multiple measurements of equivalent reflection with the SADABS Siemens program.[29] Space groups were determined from systematic absences, and they were confirmed by the successful solution of the structure (see Table 2). Complete information on crystal data and data collection parameters is given in the Supporting Information.

The structures were solved by direct methods using the SHELXTL 5.03 package,[30] and for all structures, except for complex **2**, all atoms, including hydrogen atoms, were found by difference Fourier syntheses. All non-hydrogen atoms were anisotropically refined on F^2. Hydrogen atoms were refined isotropically. For complex **2**, hydrogen atoms were included in calculated positions and refined isotropically.

Potentiometric Titrations. Ligand protonation constants and metal ion stability constants with H_3tpaa were determined by potentiometric titrations. Gd(III) solutions were prepared by dissolving the appropriate amounts of $GdCl_3$·6H_2O (Aldrich, Alfa) in water. The exact metal ion concentration was determined by colorimetric titration in acetate buffer (pH = 4.5) using standardized EDTA solution (Aldrich) and xylenol orange as the indicators. The 1 M standardized $CaCl_2$ solution (Fluka) was used as received. 20 mL solutions of H_3tpaa (5×10^{-4} M) alone or of 1:1 metal:ligand mixtures ([L] = [M] $\approx 5 \times 10^{-4}$ M) were titrated in a thermostated cell (25.0 °C ± 0.1 °C) under a stream of argon with a 0.01 M KOH solution added by means of a 10 mL piston buret (Metrohm 665). The ionic strength was fixed with KCl (μ = 0.1 M). Titrations were carried out with a Metrohm 751 GPD Titrino potentiometer equipped with a combined pH glass electrode (Metrohm). Calibration of the electrode system was performed prior to each measurement. The electromotrive force is given by $E = E° + sp[H^+]$ and both $E°$ and s were determined by titrating a known amount of HCl by 0.01 M KOH at μ = 0.1 M (KCl), using the acid range of the titration. The value used for the ion product of water is log Kw = 13.78.[31] More than 200 data points were collected for each experiment.

The data were mathematically treated by the program HYPERQUAD2000.[32,33] All values and errors represent the average of at least three independent experiments.

Luminescence Measurements. Low-resolution luminescence measurements were recorded on a Perkin-Elmer LS-50B spectrofluorimeter at room temperature (20 °C) without external temperature control. Phosphorescence lifetimes (τ) were measured by monitoring the decay at the maximum of the emission spectra. Signals were analyzed as single-exponential decays. Phosphorescent instrument settings were used with a 1.00 ms gate time, 1 s integration time, excitation and emission slit widths of 2.5 (Tb) or 5 nm (Eu), and varying delay time. Lifetimes are the average of three independent measurements.

NMR Titrations. 2.5×10^{-3} M solutions of H_3tpaa were prepared in D_2O with 2,2-dimethyl-2-silapentane-5-sulfonate, sodium salt (10^{-3} M) as reference. Sample solutions with different pH values were prepared by adding dilute NaOD/D_2O or dilute DCl/D_2O (Aldrich). The pH values of the solutions were determined with a MeterLab, PHM 220 pH Meter. The ionic strength was not adjusted.

NMRD. The samples were prepared by dissolving a measured amount of the crystalline dimeric complex [Gd(tpaa)(H_2O)]$_2$·7H_2O in water (pH∼7, c_{Gd} = 0.169 or 0.183 mM). The absence of free gadolinium was checked by the xylenol orange test.[34] The $1/T_1$ NMRD profiles of the solvent protons at various temperatures (5−25 °C) were obtained: a) from 0.02 to 10 MHz using a Spinmaster FFC (Fast Field Cycling) NMR Relaxometer (Stelar, Italy), covering a range of magnetic fields from 5×10^{-4} to 0.47 T; b) at 60 MHz using an electromagnet (1.41 T) with a home-built tunable probehead (28−66 MHz) connected to a Bruker Avance-200 console. The temperature was stabilized by a gas flow and measured by a substitution technique described elsewhere.[35]

Results and Discussion

Synthesis and Structure of the Ligand H_3tpaa. α,α′,α″-nitrilotri(6-methyl-2-pyridinecarboxylic acid) (H_3tpaa) was obtained by hydrolysis of tris[6-(2-*N*,*N*-diethyl-carbamoyl)pyridyl)-methyl]amine (tpaam), which is prepared in nine steps from 2,6-lutidine with a total yield of 6%, (Scheme 1).[28] The coordination properties of the ligand tpaam will be described in detail in a separate paper. The ligand H_3tpaa can be prepared in gram

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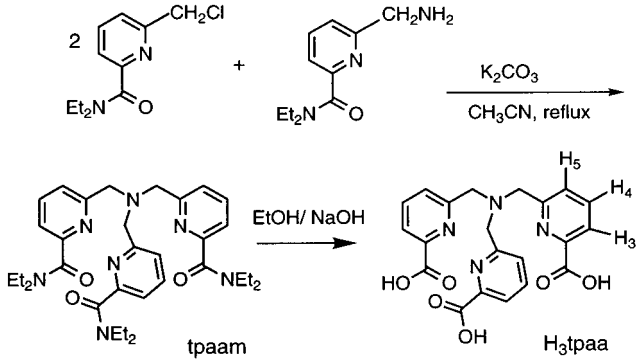
Table 2. Crystallographic Data for the Ten Structures

	H_3tpaa, **1**	La(tpaa), **2**	Nd(tpaa), **3**	Eu(tpaa), **4**	Gd(tpaa), **5**	Tb(tpaa), **6**	Ho(tpaa), **7**	Tm(tpaa), **8**	Yb(tpaa), **9**	Lu(tpaa), **10**
formula	$C_{21}H_{20}N_4O_7$	$C_{84}H_{112}N_{16}O_{50}La_4$	$C_{42}H_{44}N_8O_{19}Nd_2$	$C_{42}H_{48}N_8O_{21}Eu_2$	$C_{42}H_{48}N_8O_{21}Gd_2$	$C_{42}H_{48}N_8O_{21}Tb_2$	$C_{42}H_{48}N_8O_{21}Ho_2$	$C_{42}H_{48}N_8O_{21}Tm_2$	$C_{42}H_{48}N_8O_{21}Yb_2$	$C_{21}H_{25}N_4O_{11}Lu$
fw	440.41	2701.54	1253.33	1304.8	1315.38	1318.72	1330.74	1338.74	1346.96	684.42
cryst syst	triclinic	monoclinic	monoclinic	orthorombic	orthorombic	orthorombic	orthorombic	orthorombic	orthorombic	monoclinic
space group	*P*-1	*P*2(1)/*c*	*P*2(1)/*c*	*Pbcn*	*Pbcn*	*Pbcn*	*Pbcn*	*Pbcn*	*Pbcn*	*P*2(1)/*n*
a, Å	8.1463(6)	14.4473(16)	22.9762(10)	13.0050(9)	13.0347(15)	12.9206(5)	12.9007(16)	12.8585(7)	12.8499(7)	10.3001(4)
b, Å	8.8814(7)	15.020(3)	13.0157(5)	15.5912(11)	15.6221(17)	15.5322(7)	15.5190(19)	15.4897(8)	15.4787(9)	16.2687(7)
c, Å	14.8000(12)	23.954(2)	15.4341(6)	23.5684(17)	23.506(4)	23.3491(10)	23.378(3)	23.3167(12)	23.3070(13)	14.6820(6)
α,°	85.774(2)									
β,°	82.2720(10)	101.010(9)	101.7240(10)							102.2990(10)
γ, °	71.7840(10)									
V, Å^3	1007.32(14)	5102.3(11)	4519.3(3)	4778.8(6)	4786.5(12)	4685.8(3)	4680.4(10)	4644.1(4)	4635.8(5)	2403.79(17)
Z	2	2	4	4	4	4	4	4	4	4
D_{calc}, g cm^{-3}	1.452	1.758	1.842	1.814	1.825	1.869	1.889	1.915	1.930	1.891
μ (Mo Kα), mm^{-1}	0.111	1.747	2.362	2.691	2.837	3.086	3.449	3.889	4.103	4.176
temp, K	298(2)	193(2)	193(2)	298(2)	298(2)	193(2)	193(2)	193(2)	298(2)	193(2)
no. param. refined	369	703	760	426	426	426	426	418	414	434
R_1, wR_2[a]	0.0466, 0.1212	0.0497, 0.1228	0.0318, 0.0708	0.0240, 0.0613	0.0234, 0.0496	0.0267, 0.0605	0.0268, 0.0595	0.0256, 0.0562	0.0292, 0.0556	0.0252, 0.0531

[a] Structure was refined on F_0^2 using all data: $wR_2 = [\sum[w(F_0^2 - F_c^2)^2]/\sum w(F_0^2)^2]^{1/2}$, where $w^{-1} = [\sum(F_0^2) + (aP)^2 + bP]$ and $P = [\max(F_0^2, 0) + 2F_c^2]/3$.

quantities, and simple modifications of the synthetic procedure allow for facile derivatization of the pyridines.

Scheme 1



Crystals of H_3tpaa·H_2O, **1**, were obtained by slow evaporation of a water solution of the ligand. The structure is shown in Figure 1. In the triclinic unit cell, two molecules of H_3tpaa are linked by two strong hydrogen bonds between a carboxylate oxygen from each molecule and a carboxylic hydrogen from the other molecule (O(11)−O(32A), 2.5119(16) Å; (O(11)−H(1O−O(32A), 174(2)°), leading to the formation of a centrosymmetric dimer. The bond distances and angles are typical for this type of organic molecules. The ligand adopts a zwitterionic form with two protonated carboxylate groups (carboxylic acids), a deprotonated carboxylate group, and a protonated tertiary amine nitrogen. A water molecule is strongly bound to the ligand through the formation of four hydrogen bonds with the two carboxylic groups, the carboxylate group, and the protonated amine. This leads to a preorganized tripodal conformation of the neutral H_3tpaa molecule, presenting a pseudo C_3 symmetry axis. The three H_3tpaa arms are located on the same side of the molecule ready to bind a metal ion in a heptadentate coordination mode.

Protonation Constants and Metal Ion Stability Constants. H_3tpaa displays a low solubility in water at low pH (10^{-3}M); however, at pH > 7, deprotonation occurs and the solubility increases. The potentiometric titration of H_3tpaa is indicative of three fairly strongly acidic sites and one weakly acidic site.

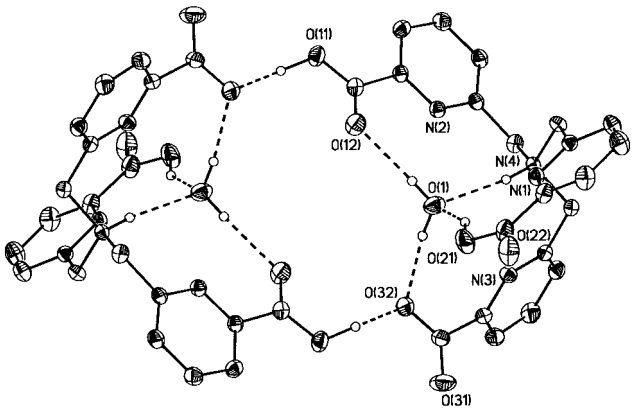


Figure 1. Side view of the crystal structure of the ligand H_3tpaa with thermal ellipsoids at 30% probability.

The deprotonation constants of H_3tpaa, defined as $K_{ai} = [H_{5-i}L]^{2-i}/[H_{4-i}L]^{1-i}[H]^+$, were determined to be to pK_{a1} = 2.5(2), pK_{a2} = 3.3(1), pK_{a3} = 4.11(6), and pK_{a4} = 6.78(4) (0.1 M KCl, 298 K). The titration curves of H_3tpaa and its Gd(III) and Ca(II) complexes are shown in Figure 2. Variable pH proton NMR spectroscopy of the ligand allows the assignment of the protonation scheme (Figure 3). Significant variations in the chemical shift of the three pyridyl protons (H4 and H5, 0.37 ppm; H3, 0.24 ppm) are detected upon the first, second, and third protonation processes (pH = 2−5.8), while no variation is observed in the chemical shift of the methylene protons. Therefore, the three first proton associations occur at the carboxylate functions, and the corresponding pK_{a3} value can be compared with those obtained for picolinic acid (pK_{a2} = 5.4), dipicolinic acid (pK_{a1} = 1.4, pK_{a2} = 5.3), and benzoic acid (pK_a = 4.2). A large variation (0.7 ppm) occurs in the chemical shift of the methylene for the fourth proton association, which indicates that the fourth protonation takes place at the apical tertiary amine nitrogen. The low value of pK_{a4} = 6.78(4) found for the tertiary amine nitrogen is due to the presence of three 6-methyl-2-pyridinecarboxylic acid groups and is consistent with the value of pK_a = 7.30 reported for the secondary amine nitrogen of dpa (bis(2-pyridylmethyl)-amine).[36]

(36) Anderegg, G.; Wenk, F. *Helv. Chim. Acta* **1967**, *50*, 2330.

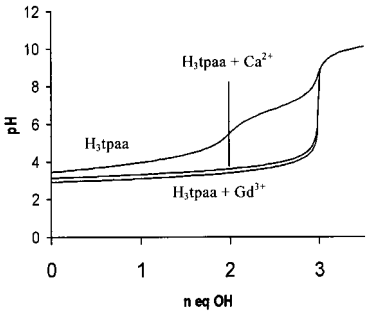


Figure 2. Titration curves (pH versus mol of OH^-/mol H_3tpaa) for: a) H_3tpaa (5×10^{-4} M), b) Gd (5×10^{-4} M)/H_3tpaa (5×10^{-4} M), and c) Ca (5×10^{-4} M) /H_3tpaa (5×10^{-4} M).

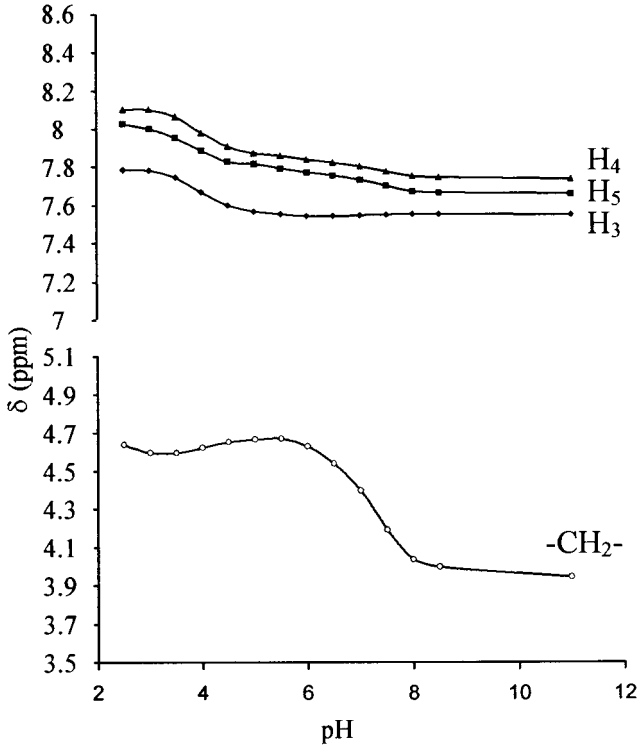


Figure 3. Variation of the chemical shift (δ) of H_3tpaa versus pH at 25°.

The stability constants of the complexes formed between Gd(III) and Ca(II) ions and H_3tpaa have been determined by potentiometric titration of 1:1 metal:H_3tpaa mixtures in the pH range 2.5−8. Titration data could be fitted to eqs 1 and 2

$$Gd^{3+} + tpaa^{3-} \rightleftarrows [Gd(tpaa)] \quad \log\beta_{GdL} = 10.2(2) \quad (1)$$

$$Ca^{2+} + tpaa^{3-} \rightleftarrows [Ca(tpaa)]^- \quad \log\beta_{CaL} = 8.5(2) \quad (2)$$

The pGd value of 11.2 for Gd(III) ($-\log[M]_{free}$ at pH 7.4, $[M]_{total}$ = 1 μM, and $[tpaa]_{total}$ = 10 μM) indicates a reasonable physiological stability of the Gd(tpaa) complex as compared to the pGd value of Gd(dtpa−bma) (15.8), which has the lowest pGd of all commercially used MRI agents. Yet tpaa is less ion discriminating than dtpa−bma, which forms a Gd(III) complex ($\log\beta_{GdL}$ = 16.85) more stable toward transmetalation with Ca(II) ($\log\beta_{CaL}$ = 7.17).

A decrease of the physiological stability is observed for the Gd complex of the less rigid podate tpaa with respect to Gd complexes containing macrocyclic heptadentate ligands, such as do3a (pGd = 15.8). However, we expect that the stability of the gadolinium complex could be improved by a suitable substitution of the pyridine rings that would increase the electron density on the pyridine nitrogens.

Crystal and Molecular Structure of Complexes of tpaa. X-ray quality crystals of the lanthanide complexes of the triply deprotonated heptadentate ligand tpaa were obtained for Ln = La, Nd, Eu, Gd, Tb, Ho, Tm, Yb, and Lu, by slow evaporation of 1:1 solutions of $LnCl_3$ and H_3tpaa in water. The solid-state structures of the complexes vary along the series for their nuclearity, with a tetrameric structure being observed for La^{3+}, dimeric structures being formed from the Nd^{3+} ion through the Yb^{3+} ion, and a monomeric structure for Lu^{3+}, Tables 3−5.

While linear amide carboxylate complexes crystallize only as mononuclear complexes,[10] this trend to oligomerize in the solid state has already been observed for macrocyclic amide carboxylate complexes and has been attributed to the presence of an exposed metal face favoring the access to the metal for a carboxylate from an adjacent complexed ligand.[37] Lanthanide complexes of tripodal poly(imino carboxylate) have also been reported to crystallize out of methanol solutions as oligomeric complexes. However, recrystallization of these oligomeric complexes in water leads to monomeric structures.[25]

The complex $\{[La(tpaa)(H_2O)][La(tpaa)(H_2O)_2]\}_2 \cdot 20\ H_2O$, **2**, crystallizes as a M_4L_4 tetramer about a point of inversion (Figure 4a). Two symmetry related lanthanum ions are joined into a dimer by two monodentate bridging carboxylates with the closest La(1)−La(1)A distance being 4.277 Å. Each lanthanum La(1) is nine coordinate by the four nitrogen and three carboxylate oxygens of the heptadentate tpaa ligand, one water molecule, and one carboxylate oxygen from the monodentate carboxylate moiety of an adjacent complexed ligand. La(1)−O distances vary from 2.455(5) to 2.552(4) Å, with the shortest distance being for the non bridging carboxylate oxygen. La(1)−N distances vary from 2.624(5) to 2.878(5) Å, with the longer distance found for the capping tertiary amine nitrogen. La(1)−O and La(1)−N distances are in the range of values found in the literature.[26,37] Two symmetry related carboxylates not involved in the dimer formation (one from each symmetry related La(1) complex moiety) act as bidentate ligands bridging through the carbonyl oxygen to the adjacent lanthanum ion (La(2)) to form a tetramer (the closest La(1)−La(2) distance being 6.910 Å). Each symmetry related lanthanum ion La(2) is ten-coordinate by one tpaa acting as an heptadentate ligand and by two water molecules and one carbonyl oxygen from the carboxylate ligand of the adjacent complexed ligand. The La(2) ion is situated 1.04 Å above the plane defined by the carboxylate oxygens of the tpaa ligand (O(31), O(41), and O(51)), while the water oxygens are situated 1.48 Å (O(3)) and 0.07 Å (O(4)) below this plane. La(2)−O distances vary from 2.462(5) to 2.634(4) Å, with the shortest distance found for the bridging carbonyl oxygen. La(2)−N distances vary from 2.752-(5) to 2.944(5) Å, with the longer distance found for the apical amine nitrogen. The value of the La(2)−N apical distance is larger than other Ln−N values found in the literature (2.649-(12)[38]−2.889(6) Å.[37])

Ln(tpaa) complexes crystallize as M_2L_2 dimers of formula $[Ln(tpaa)(H_2O)]_2 \cdot xH_2O$, with x = 5 for Ln = Nd, **3**, and x = 7 for Eu, **4**, Gd, **5**, Tb, **6**, Ho, **7**, Tm, **8** and Yb, **9**, and accordingly, only the structure of the Gd dimer is shown in Figure 5. The formation of a dimer rather than a tetramer for these metal ions can probably be explained by the presence of an increased sterical hindrance to the approach of another metal complex to the dimer, which is due to the shorter M−ligand distances of

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(38) Fréchette, M.; Bensimon, C. *Inorg. Chem.* **1995**, *34*, 3520.

Table 3. Selected Bond Distances (Å) in Complexes **3**−**9**

	Nd1(tpaa), **3**	Eu(tpaa), **4**	Gd(tpaa), **5**	Tb(tpaa), **6**	Ho(tpaa), **7**	Tm(tpaa), **8**	Yb(tpaa), **9**
M−O(11)	2.491(2)	2.4782(19)	2.4726(17)	2.462(2)	2.464(2)	2.448(3)	2.455(3)
M−O(11)A	2.4353(18)	2.4080(17)	2.4010(15)	2.383(2)	2.360(2)	2.337(3)	2.326(3)
M−O(1)	2.4657(19)	2.448(2)	2.4414(17)	2.428(2)	2.413(2)	2.390(3)	2.389(3)
M−O(21)	2.446(2	2.3807(19)	2.3783(17)	2.355(2)	2.341(2)	2.313(3)	2.306(3)
M−O(3)	2.514(2)	2.413(2)	2.399(2)	2.374(3)	2.347(2)	2.314(3)	2.302(3)
M−N(1)	2.594(2)	2.555(2)	2.546(2)	2.528(3)	2.519(3)	2.501(4)	2.487(3)
M−N(3)	2.582(2)	2.544(2)	2.531(2)	2.517(3)	2.496(3)	2.475(4)	2.455(3)
M−N(2)	2.636(2)	2.607(2)	2.6051(19)	2.583(3)	2.561(3)	2.543(3)	2.534(3)
M−N(4)	2.793(2)	2.787(2)	2.7886(19)	2.777(3)	2.766(3)	2.754(3)	2.757(3)
M−M#	4.191	4.1387	4.125	4.109	4.098	4.071	4.0627

Table 4. Selected Bond Distances (Å) in $[La(tpaa)]_4$

La1−O1	2.455(5)	La2−O41	2.528(5)
La1−O11	2.497(4)	La2−O31	2.532(5)
La1−O5	2.528(4)	La2−O51	2.549(5)
La1−O21A	2.539(4)	La2−O3	2.576(6)
La1−O21	2.552(4)	La2−O4	2.634(6)
La1−N2	2.624(5)	La2−N5	2.752(6)
La1−N1	2.651(5)	La2−N6	2.756(5)
La1−N3	2.716(5)	La2−N7	2.763(6)
La1−N4	2.878(5)	La2−N8	2.944(5)
La2−O12	2.462(4)		

Table 5. Selected Bond Distances (Å) in [Lu(tpaa)]

Lu−O(1)	2.2438(15)
Lu−O(21)	2.2599(15)
Lu−O(11)	2.3035(15)
Lu−O(31)	2.3391(17)
Lu−N(3)	2.4152(16)
Lu−N(1)	2.4361(17)
Lu−N(2)	2.474(2)
Lu−N(4)	2.6071(18)

the smaller ions. Two metal ions are joined by two bridging oxygens from the monodentate carboxylate groups of two different tpaa ligands to form a dimeric complex. The metal ion is nine-coordinate by four nitrogens and three carboxylate oxygens of tpaa, one water molecule, and a carboxylate oxygen of the neighboring complexed ligand. The coordination geometry of the metal ion can be described as a highly distorted tricapped trigonal prism in which O(1), N(2), and N(3) occupy the capping positions in the rectangular faces. The average M−N pyridyl distances are shorter than the average M−N tert distances found in other lanthanide polyaminopolycarboxylate complexes,[10,37] and their value shows a decrease of 0.11 Å from Nd (2.604 Å) to Yb (2.493 Å), which is clearly correlated to the decrease in ionic radius (a decrease of 0.12 Å is expected). Conversely, the M−N apical distances are longer than the average M−N tert distances found in other lanthanide polyaminopolycarboxylate complexes and are also significantly longer than the sum of their ionic radii. However, the value of the Gd−N apical distance (2.7886(19) Å) in **5** is smaller than the value observed for the octacoordinate dimeric Gd complex of the trianionic heptadentate amine phenolate ligand tris(((2-hydroxybenzyl)-amino)ethyl)amine (2.813(3) Å).[39] Only a small variation of these distances is observed along the series, with a decrease in the value of 0.04 Å, which is largely inferior to the expected decrease of ionic radii (0.12 Å). This can be attributed to the dimer formation which results in a lengthening of the M−N apical distance with decreasing ion size. The Gd−O water distance (2.399(2) Å) is shorter than the ones found in the dimeric nine-coordinate complex $[Gd(do3ma)(H_2O)]_2$ [40] (2.451-

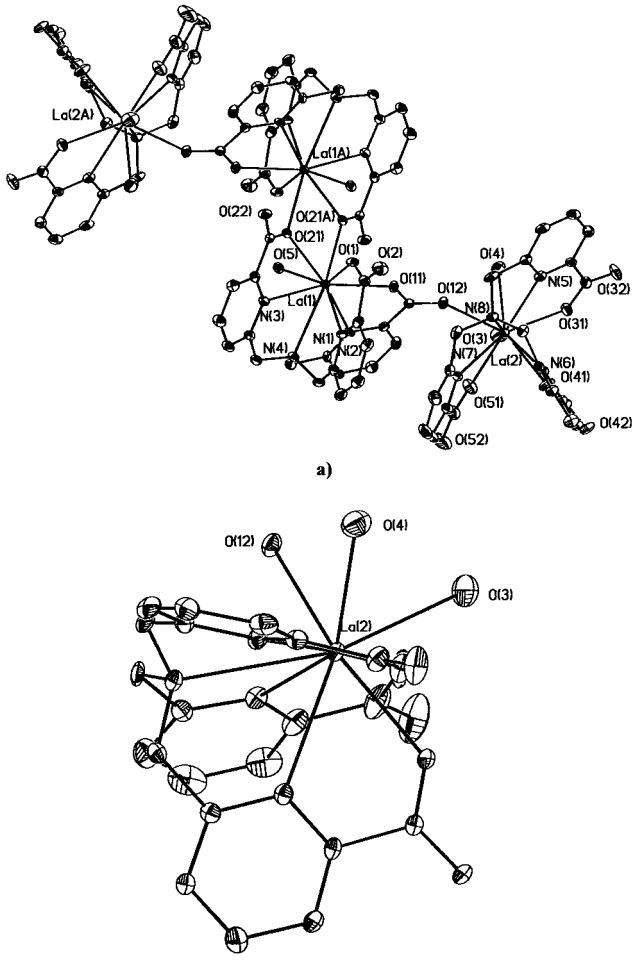

Figure 4. a) Side view of the crystal structure of the complex $\{[La(1)(tpaa)(H_2O)][La(2)(tpaa)(H_2O)_2]\}_2$ with thermal ellipsoids at 30% probability; b) view of the coordination environment of La(2) emphasizing the exposed metal face.

(5) and 2.56(4) Å), in the eight-coordinate complex $[Gd(tren-Me-3,2-hopo)(H_2O)_2]$[21] (2.446(5) and 2.436(4) Å), and in the monomeric nine-coordinate complex $[Gd(dtpa-bea)(H_2O)]$ (2.423-(3) Å).[10] The Lu complex crystallizes as a monomer of formula $[Lu(tpaa)(H_2O)]\cdot 4H_2O$, **10**, and its structure is shown in Figure 6. The absence of dimerization is probably due to the small ionic radius of Lu which would require too much of an increase in the metal−N apical distances in each complexed moiety to avoid the steric crowding arising from the dimer formation. The value of the distance Lu−N apical (2.6071(18) Å) in **10**, which is only slightly longer than that found for the Lu−N apical distance (2.555(1) Å) in the heptacoordinate complex $[Lu(tpa)Cl_3]$ (tpa = (tris[(2-pyridyl)methyl]amine)),[41] is indeed much shorter than that found for the complex $[Yb(tpaa)(H_2O)]_2$ (2.757-

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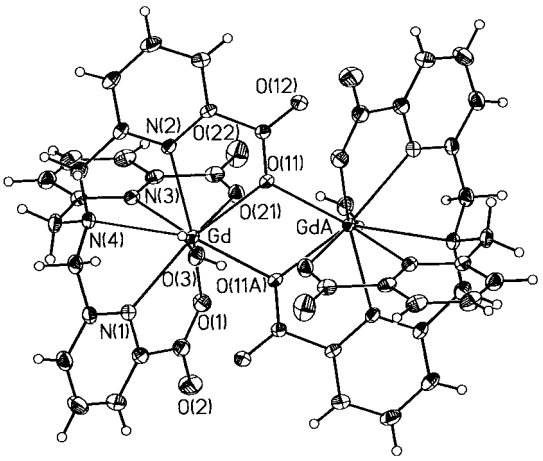

Figure 5. Side view of the crystal structure of the complex [Gd(tpaa)-$(H_2O)]_2$ with thermal ellipsoids at 30% probability.

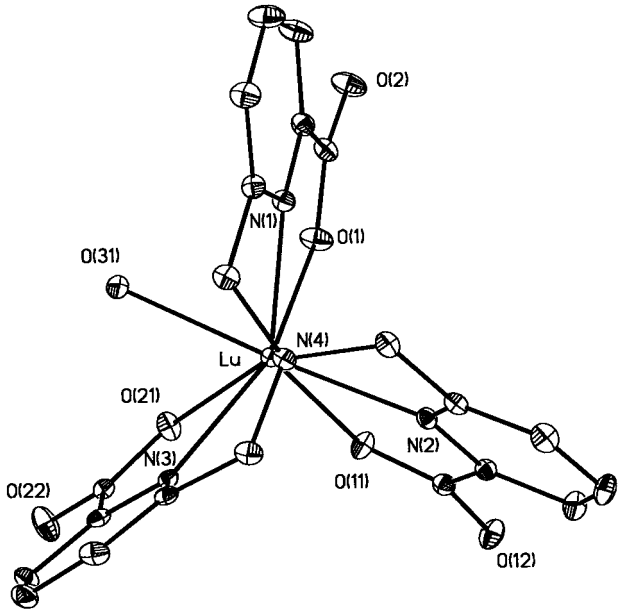

Figure 6. Top view of the crystal structure of the complex [Lu(tpaa)-(H_2O)] with thermal ellipsoids at 30% probability, emphasizing the pseudo C_3 symmetry of the ligand.

(3) Å). The Lu ion is octacoordinate by the heptadentate ligand tpaa and a water molecule. The geometry can be described as a highly distorted dodecahedron. The pseudo C_3 symmetry of tpaa is retained in the monomeric lutetium complex. Conversely, the pseudo C_3 symmetry of the ligand tpaa is disrupted in the oligomeric complexes **2**−**9** by inversion of the orientation of one pyridinecarboxylate.

The tendency of the Ln(tpaa) complexes to oligomerize in the solid state arises from the presence of a relatively exposed metal face due to the flexibility of the tpaa ligand, as evidenced by the view of the lanthanum structure shown in Figure 4b.

Moreover, the crystal structures of the La(III), Gd(III), and Lu(III) complexes demonstrate that the tpaa ligand can easily accommodate three different coordination numbers for the lanthanides ions; both the coordination numbers nine and ten are observed for the large lanthanum ion, the coordination number eight is found for the small Lu ion, and the intermediate lanthanides ions (Nd−Yb) are nine coordinate.

Solution Structure of tpaa Complexes. The ^{1}H NMR spectra of Ln(tpaa) (Ln = La, Nd, Eu, Lu) complexes in a 1/1 D_2O/d_6-DMSO solution at room temperature and pH = 6 show the presence of only one set of signals, with three resonances for the nine pyridine protons and one resonance for the six methylene protons. These features are consistent with a C_{3v} symmetry of the solution species in which all chelating arms of tpaa are equivalent. This seems to indicate that the asymmetric oligomeric structures observed in the solid state are disrupted in solution for all complexes to give a C_{3v} symmetric monomeric species in which the bridging carboxylate oxygens are replaced by solvent molecules and all coordinated solvent molecules exchange rapidly with the bulk solvent. Moreover, the chemical shift equivalence of the methylene protons requires a conformational mobility of the ligand branches in solution.

The solvation state of the tpaa complexes of Eu and Tb was studied by comparison of their luminescence decays in H_2O and D_2O. Due to the different quenching efficiencies of the O−H and O−D oscillators, the measurement of Ln^{3+} phosphorescence lifetimes (τ) in H_2O and D_2O solutions allows an accurate estimation of the number of coordinated water molecules present in solution, q, using the equation of Parker and co-workers ($q = A_{Ln}(1/\tau H_2O - 1/\tau D_2O - \alpha_{Ln})$ with $A_{Tb} = 5$, $A_{Eu} = 1.2$ ms, $\alpha_{Tb} = -0.06$ and $\alpha_{Eu} = -0.25$ ms^{-1} [42] (a corrected version of the empirical equation of Horrocks and Sudnick[43,44] accounting for closely diffusing OH oscillators). The observed lifetimes of the Eu($^5D_0$) (λ exc (nm) = 290, λ em (nm) = 616, τ H_2O (ms) = 0.438(5), and τ D_2O (ms) = 2.32(2)) and Tb ($^5D_4$) levels (λ exc (nm) = 291, λ em (nm) = 545, τ H_2O (ms) = 1.08(8), and τ D_2O (ms) = 2.2(1)) for the Tb(tpaa) and Eu(tpaa) complexes in water solutions (0.13 mM in H_2O (D_2O)) at 295 K are in agreement with the presence of 1.93 ± 0.2 and 2.02 ± 0.2 coordinated water molecules in the Eu and Tb complexes, respectively. A similar number of coordinated molecules can be expected for the Gd ion, which has a ionic radius intermediate between those of Eu and of Tb. The presence of two coordinated water molecules would be in agreement with the presence in solution of a monomeric nine-coordinate bis(aqua) complex for the Eu, Gd, and Tb ions in which the bridging carboxylate occupying the ninth coordination position in the solid state has been replaced by a water molecule. However, in view of the incertitude (ca ±0.2) associated to the measure of q, we cannot rule out either the presence in solution of an equilibrium between an eight-coordinate mono(aqua) complex and a nine-coordinate bis(aqua) one, leading to a number of coordinate water molecules lower than two or the presence of an equilibrium between a ten-coordinate tris(aqua) complex and a nine-coordinate bis-(aqua) complex, resulting in a number of coordinated water molecules sligthly higher than two. Indeed, the free interchange between 10-, 9-, and 8-coordinate complexes in solution is conceivable since the solid state structures of La, Gd, and Lu show that the ligand tpaa can accommodate the coordination numbers 10, 9, and 8. While commercial contrast agents only display 9-coordinate geometries, even for the smaller lanthanides, the tripodal ligand tren-Me-3,2-hopo has also been shown to accommodate both 8- and 9-coordinate geometries. The rapid rate of water exchange observed for hopo complexes

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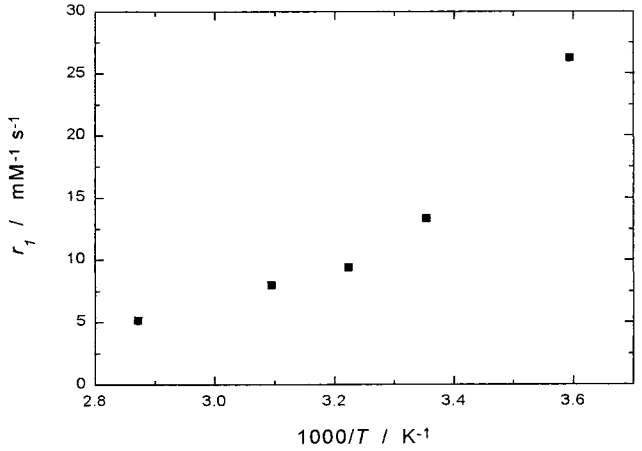

Figure 7. Temperature dependence of the relaxivity of the Gd(tpaa) complex at 60 MHz ($c_{Gd} = 0.169$ mM).

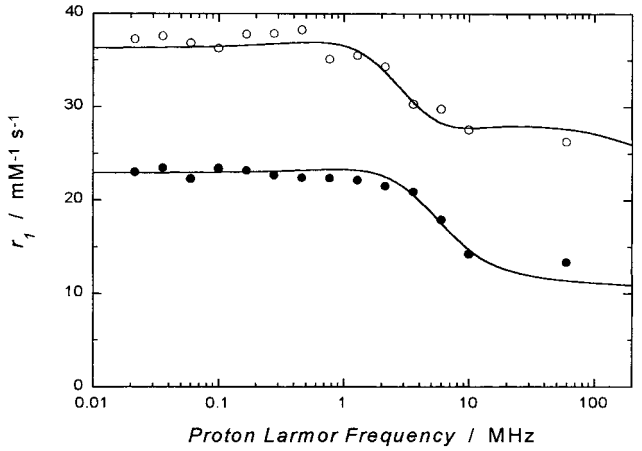

Figure 8. Water proton NMRD profiles of the Gd(tpaa) complex at 278 (○) and 298 K (●) ($c_{Gd} = 0.169$ mM). The lines represent the best fit of the experimental data to the equations described in the Supporting Information with the parameters: $q = 2.5$, $r_{GdH} = 2.88 \pm 0.05$ Å, $\tau_r^{298} = 76 \pm 10$ ps, $E_r = 33.8 \pm 2$ kJ mol^{-1}, $\tau_v^{298} = 48 \pm 11$ ps, $E_v = 1$ kJ mol^{-1}, $\Delta^2 = 0.14 \pm 0.05 \times 10^{20}$ s^{-2}, $D_{GdH}^{298} = 23 \times 10^{-10}$ m^2 s^{-1}, $E_{GdH} = 22$ kJ mol^{-1}, and $a_{GdH} = 3.5$ Å.

has been interpreted in terms of a low-energy barrier between the 8- and 9-coordinate complexes.[45]

Relaxometry. As we have already revealed in a previous communication,[27] the relaxivity (the critical property of a potential contrast agent which represents the increase in the water proton nuclear magnetic relaxation rate per millimolar concentration of paramagnetic compound) of the Gd(tpaa) complex is higher (13.3 mM^{-1} s^{-1}, 25 °C, 60 MHz) than those found in the monoaqua complexes ($q = 1$) $[Gd(dtpa)(H_2O)]^{2-}$ or $[Gd(dota)(H_2O)]^-$ (4.3−4.7 mM^{-1} s^{-1}, 25 °C, 20 MHz) or in bisaqua complexes ($q = 2$) containing heptadentate ligands, such as $[Gd(do3a)(H_2O)_2]$ (6.1 mM^{-1} s^{-1}, 25 °C, 20 MHz) and $[Gd(pcta[12])(H_2O)_2]$ (6.9 mM^{-1} s^{-1}, 25 °C, 20 MHz),[18] hence, it cannot only be explained by the presence of two water molecules coordinated to the Gd(III) ion. The water exchange rate could not be estimated by ^{17}O NMR as is usually done[46] because of the poor solubility of the complex, but the monoexponential increase of the relaxivity with decreasing temperature, as measured at 60 MHz (Figure 7), is a proof of a water exchange rate which is fast enough not to limit the relaxivity. This allows us to neglect the water exchange contribution in the analysis. Many parameters such as electronic parameters (τ_v, Δ^2) or the rotational correlation time (τ_R) can be extracted from the analysis of the NMRD (nuclear magnetic relaxation dispersion) data. The $1/T_1$ NMRD profiles of the water proton at 278 and 298 K (Figure 8) are analyzed according to the equations given in the Supporting Information. The outersphere contribution to the relaxivity is described by the Freed model, where the distance of closest approach for an outersphere water proton $a_{GdH} = 3.5$ Å, as well as the diffusion parameters $D_{GdH}^{298} = 23 \times 10^{-10}$ m^2 s^{-1} and $E_{GdH} = 22$ kJ mol^{-1}, were fixed to these standard values in the fitting procedure.

No suitable fitting of the experimental data could be attained while considering two innersphere water molecules and the usual distance of 3.1 Å for the bound water protons. If one assumes that the electronic parameters are not very much affected as compared to what is usually observed ($\tau_v^{298} = 10-60$ ps and $\Delta^2 = 0.1-1 \times 10^{20}$ s^{-2}),[7,46] two factors can be the cause of such a high relaxivity: a mean number of innersphere water molecules higher than two, or a shorter distance between the bound water protons and the gadolinium. In view of the number of the coordinated water molecules in solution measured by luminescence to be 1.93 ± 0.2 for Eu(III) and 2.02 ± 0.2 for Tb(III), the q value is clearly around two.

The analysis of the NMRD profiles with $q = 2$ gave the electronic parameters $\tau_v^{298} = 48 \pm 11$ ps and $\Delta^2 = 0.14 \pm 0.05 \times 10^{20}$ s^{-2}, these are in the usual order of magnitude for polyaminocarboxylate complexes of Gd(III).[7,46] The rotational correlation time $\tau_R^{298} = 76 \pm 10$ ps is in agreement with the molecular weight of $[Gd(tpaa)(H_2O)]$ as compared to $[Gd(dtpa-bma)(H_2O)]$ ($\tau_R^{298} = 66 \pm 11$ ps) or $[Gd(dota)(H_2O)]^-$ ($\tau_R^{298} = 77 \pm 4$ ps).[46] The fit gives a Gd(III)-bound water proton distance $r_{GdH} = 2.78 \pm 0.05$ Å; this value seems very short in light of neutron diffraction studies on lanthanide aqua ions,[47] although a value of the Gd−D distance of 2.7 Å has been determined by Clarkson et al.[48] using electron spin−echo modulation spectroscopy for Gd(III) complexes of dtpa and edta in D_2O solution. The analysis was performed again using a value of $q = 2.5$, on the basis that a water coordination equilibrium is possible for the gadolinium complex. Indeed, the existence for La(III) of an equilibrium in water solution between a ten-coordinate complex containing three coordinated water molecule and a nine-coordinate complex containing two coordinated water molecules is supported by the crystal structure of the La(tpaa), which shows both a ten- and nine-coordinate La. The electronic and rotational parameters remained unchanged as the distance increased to $r_{GdH} = 2.88 \pm 0.05$ Å. These short distances are in agreement: i) with the 2.95 Å Gd−H distance reported for a Gd-tripod complex by Cohen et al[45] or the 2.92 Å Gd−H distance reported for a Gd−dota−tetramide complexe by Woods et al.[49] and ii) with the extent of available room for close binding of the water molecules as highlighted by the oligomerization process.

The high relaxivity is, hence, mainly the consequence of a shorter bound water proton−Gd(III) distance associated with a probable water coordination equilibrium between tris(aqua) and

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bis(aqua) complexes, giving rise to a mean coordination number *q* sligthly higher than two. We cannot rule out a larger than usual second sphere or outersphere contribution due to H bonding to the apical nitrogen, but these contributions are very difficult to quantify. One should take notice that the dimer formation in solution would decrease the number of water molecules in the first coordination sphere and make the fitting of the NMRD data less reasonable. The fast water exchange rate observed for the Gd complex probably arises from the fact that a dissociative intermediate for the tris(aqua) complex and a dissociative or associative intermediate for the bis(aqua) complex can be readily accessible due to a low energy difference between ten-, nine-, and eight-coordinate geometries. This means that binding of such a chelating unit to a macromolecular system should lead to a very high relaxivity.

Concluding Remarks

The synthesis and the structural properties of the lanthanide (III) complexes of the new heptadentate ligand tpaa have been presented. This flexible heptadentate podate leads to a Gd complex with a relaxivity that is significantly higher than those of macrocyclic heptadentate ligands without a great loss in stability. Three types of crystal structures have been found for these complexes along the lanthanide series, which differ in their nuclearity and in the coordination number of the metal ion. The number of water molecules coordinated to the metal, estimated by luminescence studies and the relaxivity studies, indicate that the Gd(tpaa) complex is present in solution as a bis(aqua) species, probably in equilibrium with a tris(aqua) species (although the presence of small amounts of mono(aqua) cannot be excluded). The very short metal−water bond distance associated with a probable water coordination equilibrium is at the origin of the high relaxivity of the Gd(tpaa) complex, although larger than usual second sphere or outersphere contributions cannot be excluded. The rapid water exchange rate can be attributed to a low-energy barrier between 10-, 9- and 8-coordinate geometries, as indicated by the structural data.

Although the low solubility of the Gd complex of tpaa prevents its practical application as a MRI contrast agent, we expect that a suitable substitution of the pyridine rings could improve the stability and solubility of the Gd complex and, therefore, its potential application as an MRI contrast agent. Variable *T* and *P* ^{17}O NMR studies of more soluble complexes would also allow for a better understanding of the solution structure and dynamics (number of innersphere water molecules and their exchange rate and pathway). Moreover, the straightforward introduction of substituents on the pyridine rings allows us to envisage ligands containing functional groups capable of noncovalent or covalent interactions with slowly moving substrates, such as proteins or polysaccharides. Since the Gd complex of tpaa displays a fast exchange rate with the coordinated water, this could lead to contrast agents with longer rotational correlation times and, consequently, higher relaxivities or to increased specific tissue affinity. Finally, the use of carefully tailored podates could prove to be a very efficient way to achieve optimized relaxivity properties. A successful and quite unique example of this approach is given by the work of the Hajela et al. on gadolinium hydroxopyridonate complexes.[20]

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Supporting Information Available: Complete tables of crystal data and structure refinement, atomic coordinates, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates, intra- and intermolecular hydrogen bond distances and angles for compounds **1**−**10**; temperature dependence of the relaxivity of the Gd(tpaa) complex at 60 MHz (Table S1), NMRD data of the Gd(tpaa) complex at 278 and 298 K (Table S2); text and equations presenting the theory behind relaxation measurements; ES−MS molecular peaks and adduct ions observed for Ln(tpaa) (Ln = La, Pr, Gd, Tb, Ho, Yb, Lu) complexes (Table S3); and species distribution plot of H_3tpaa (Figure S4). This material is available free of charge via the Internet at http://pubs.acs.org.

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