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Solid-state and solution properties of the lanthanide complexes of a new nonadentate tripodal ligand derived from 1,4,7-triazacyclononane

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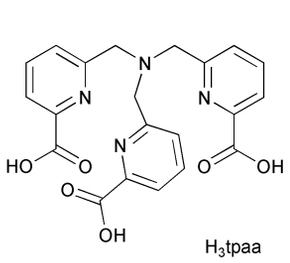
The synthesis of the potentially nonadentate ligand 1,4,7-tris[(6-carboxypyridin-2-yl)methyl]-1,4,7-triazacyclononane (H_3tpatcn), a new derivative of 1,4,7-triazacyclononane N-functionalised with three pyridinecarboxylate arms, is described. The complexes of four lanthanide ions (Nd, Eu, Gd, Lu) of this ligand have been prepared and structurally characterised. These complexes, which have high water solubility, show highly rigid C_3 symmetric solution structures. All the complexes present mononuclear nine-coordinated solid-state structures. The coordination polyhedron is a slightly distorted tricapped trigonal prism. The NMRD (Nuclear Magnetic Relaxation Dispersion) profiles measured for the [Gd(tpatcn)] complex indicate that the second-sphere contribution arising from the presence of water molecules tightly hydrogen-bonded to the carboxylate moieties on the surface of the complex are not large enough to explain the very high relaxivity of the previously reported [Gd(tpaa)(H_2O)$_2$] complex (H_3tpaa = α,α′,α″-nitrilotri(6-methyl-2-pyridinecarboxylic acid)). In fact the low-field relaxivity of [Gd(tpatcn)] more likely points to a favorable electronic relaxation rate.

Introduction

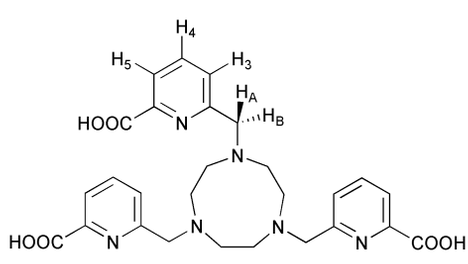
In the last two decades there has been rapid growth in the field of the coordination chemistry of lanthanides with multidentate ligands[1,2] due to the wide variety of potential applications in biology, medicine and materials science. In particular a large number of studies have been spurred by the application of gadolinium complexes as magnetic resonance imaging (MRI) contrast agents.[3–7] The key property of an efficient contrast agent is a 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.

We have recently reported the gadolinium complex of the new heptadentate tripodal ligand tpaa (H_3tpaa = α,α′,α″-nitrilotri(6-methyl-2-pyridinecarboxylic acid), Scheme 1) containing three pyridinecarboxylate arms connected to a nitrogen atom.[8,9] This rather insoluble complex shows a remarkably higher value of relaxivity (r_{1p} = 13.3 mM^{-1} s^{-1} at 298 K and at 60 MHz) than those found in the currently clinically used contrast agents based on mono-aqua complexes of octacoordinate ligands such as [Gd(dtpa)(H_2O)]$^{2-}$ or [Gd(dota)(H_2O)]$^-$, (4.3–4.7 mM^{-1} s^{-1}, 298 K, 20 MHz) or in the bis-aqua complexes containing heptadentate ligands such as [Gd(do3a)(H_2O)$_2$] (6.1 mM^{-1} s^{-1}, 298 K, 20 MHz) and [Gd(pcta[12])(H_2O)$_2$] (6.9 mM^{-1} s^{-1}, 298 K, 20 MHz),[10] † hence it can not only be explained by the presence of two water molecules coordinated to the Gd(III) ion. The observed high relaxivity was attributed to the shorter Gd–O_{water} distance and to a possible coordination equilibrium between species with two and three bound water molecules. However a large second-sphere contribution arising from

† H_4dota = 1,4,7,10-Tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid, H_5dtpa = diethylenetriaminepentaacetic acid, H_3pcta = 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-triacetic acid, H_3do3a = 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, H_4teta = 1,4,8,11-tetraazacyclotetradecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid, H_4ttha= trisethylenetetraaminehexaacetic acid, H_3ado3a = 1,4,7-tris[(3′-carboxyl)-1′-carboxybutyl]-1,4,7,10-tetraazacyclododecane.



H_3tpaa



H_3tpatcn

Scheme 1

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the presence of water molecules tightly hydrogen-bonded to the carboxylate moieties on the surface of the complex may also explain this value.[11] Indeed, the high relaxivity (12.3 mM^{-1} s^{-1}, 298 K, 20 MHz) of the bis-aqua complex $[Gd(ado3a)]^{3-}$ recently reported by Parker and coworkers[12] has been interpreted in terms of a substantial second-sphere contribution associated with the solvation of the ionized carboxylates.

In order to gain a better understanding of the mechanism for paramagnetic relaxation and of the structure–relaxivity relationship leading to the enhanced relaxivity in the Gd(tpaa) complex we have studied the gadolinium complex of a tripodal nonadentate analog of tpaa. Here we report the synthesis, the structure and the relaxometry study of lanthanide complexes of the new nonadentate ligand 1,4,7-tris[(6-carboxypyridin-2-yl)methyl]-1,4,7-triazacyclononane (H_3tpatcn) formed by addition of three pyridinecarboxylate arms to the macrocyclic core 1,4,7-triazacyclononane. While N-functionalised derivatives of 1,4,7-triazacyclononane with different arms such as pyridinylmethyl, carboxylate or phenolate groups have been widely used in transition metal coordination chemistry to form stable complexes,[13–15] the complexes reported here are a rare example of the use of ligands containing the 1,4,7-triazacyclononane core in f element coordination chemistry.[16–20] The coordination mode of tpatcn is comparable to that of the tpaa ligand with the three pyridinecarboxylate arms in a tripodal disposition and the triazacyclononane moiety acting as the capping group. The relaxometry study on the gadolinium complex of tpatcn therefore allows a good evaluation of the second-sphere contribution to the relaxivity in these complexes.

Experimental

General information

^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 spectrometer. Chemical shifts are reported in ppm with solvent or 3-(trimethylsilyl)-1-propanesulfonic acid, sodium salt as internal reference. Mass spectra were obtained with a Finnigan LCQ-ion trap equipped with an electrospray source. Elemental analyses were performed by the Service Central d'Analyses (Vernaison, France).

Solvents and starting materials were obtained from Aldrich, Fluka, Acros and Alfa and used without further purification. 6-Chloromethylpyridine-2-carboxylic acid ethyl ester was obtained from the commercially available 2,6-dipicolinic acid according to a published procedure.[21]

Synthesis of the ligand H_3tpatcn

1,4,7-Tris[(6-carbethoxypyridin-2-yl)methyl]-1,4,7-triazacyclononane. To a suspension of 1,4,7-triazacyclononane trihydrochloride (2.06 g, 8.63 mmol) in anhydrous acetonitrile (200 mL), K_2CO_3 (7.39 g, 53.47 mmol) and a solution of 6-chloromethylpyridine-2-carboxylic acid ethyl ester (5.34 g, 26.75 mmol) in anhydrous acetonitrile (50 mL) were successively added under argon atmosphere. The reaction mixture was refluxed for 16 h. After filtration and evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (150 mL). The organic layer was washed with 1 M aqueous $NaHCO_3$ solution (2 × 50 mL), dried with Na_2SO_4, and concentrated. The resulting crude product (6.15 g) was used without further purification. ^1H NMR (CD_3CN, 400 MHz): δ 1.38 (t, J = 7.0 Hz, 9H, $COOCH_2CH_3$), 2.88 (s, 12H, $N(CH_2)_2N$), 3.85 (s, 6H, NCH_2py), 4.38 (q, J = 7.0 Hz, 6H, $COOCH_2CH_3$), 7.75 (d, J = 7.6 Hz, 3H, CH), 7.86 (t, J = 7.6 Hz, 3H, CH), 7.94 (d, J = 7.6 Hz, 3H, CH). ES-MS: m/z 619 $[M + H]^+$, 641 $[M + Na]^+$.

1,4,7-Tris[(6-carboxypyridin-2-yl)methyl]-1,4,7-triazacyclononane (H_3tpatcn). A 1 M aqueous solution of KOH (53.5 mL) was added to a solution of the crude 1,4,7-tris[(6-carbethoxypyridin-2-yl)methyl]-1,4,7-triazacyclononane (6.15 g) in ethanol (80 mL) and the resulting mixture was refluxed for 18 h. After evaporation to dryness, the resulting oil was dissolved in water. Concentrated HCl was slowly added to the resulting solution until pH = 3. A white solid was obtained (2.733 g, 51%). A purity of 87% was estimated by potentiometric titration, in accordance with elemental analyses. ^1H NMR (D_2O, 400 MHz): δ 3.72 (s br, 12H, $N(CH_2)_2N$), 4.47 (s, 6H, NCH_2py), 7.30 (d, J = 7.8 Hz, 3H, CH), 7.52 (d, J = 7.8 Hz, 3H, CH), 7.68 (t, J = 7.8 Hz, 3H, CH). ^{13}C NMR (D_2O, 100 MHz): δ 51.77 (CH_2), 59.81 (CH_2), 124.75 ($C_{py}H$), 126.71 ($C_{py}H$), 139.77 ($C_{py}H$), 147.80 ($C_{py}CH_2$), 153.06 ($C_{py}COOH$), 167.99 (COOH). ES-MS: m/z 535 $[M + H]^+$. Anal. Calc. for H_3tpatcn·0.8NaCl·1.8H_2O, $C_{27}H_{33.6}N_6O_{7.8}Na_{0.8}Cl_{0.8}$: C 52.84, H 5.52, N 13.69. Found: C 52.71, H 5.72, N 13.59%.

Preparation of the complexes

[Ln(tpatcn)] (Ln = Nd, Eu, Gd, Lu). A solution of $LnCl_3$·6H_2O (Ln = Nd, Eu, Gd, Lu) (0.445 mmol) in water (5 mL) was added to a solution of H_3tpatcn (287 mg, 0.467 mmol) in water (10 mL). The resulting solution was stirred at room temperature for 2 h and then the pH was adjusted to 5 by adding aqueous NaOH solution (0.445 M). After concentration to *ca.* half volume, slow evaporation of the resulting solution yielded after 1–2 days the complexes Ln(tpatcn)·$x$$H_2O$ (68–74%) as white (Eu, Gd, Lu) or light violet (Nd) crystals suitable for X-ray diffraction.

[Nd(tpatcn)]. ^1H NMR (D_2O, 400 MHz, 298 K): δ 0.29 (s br, 3H, $N(CH_2)_2N$), 2.39 (s br, 3H, HA/HB), 3.62 (s br, 3H, $N(CH_2)_2N$), 4.95 (s br, 3H, $N(CH_2)_2N$), 5.91 (s br, 3H, HA/HB), 6.95 (s br, 3H, $N(CH_2)_2N$), 8.98 (s br, 9H, H3/H4/H5) –^1H NMR (D_2O, 400 MHz, 343 K): δ 0.51 (s br, 3H, $N(CH_2)_2N$), 2.84 (s br, 3H, HA/HB), 3.24 (s br, 3H, $N(CH_2)_2N$), 4.45 (s br, 3H, $N(CH_2)_2N$), 5.58 (s br, 3H, H_A/H_B), 6.17 (d br, J = 14.2Hz, 3H, $N(CH_2)_2N$), 8.84 (d, J = 7.1 Hz, 3H, H_3/H_5), 8.89 (d, J = 7.5 Hz, 3H, H_3/H_5), 8.93 (t, J = 7.4 Hz, 3H, H_4). ES-MS: m/z 676 $[M + H]^+$. Anal. Calc. for [Nd(tpatcn)]·3.75H_2O, $C_{27}H_{34.5}NdN_6O_{9.75}$ (M = 743.345): C 43.63, H 4.68, N 11.30. Found C 43.77, H 4.56, N 11.39%

[Eu(tpatcn)]. ^1H NMR (D_2O, 400 MHz, 298 K): δ −4.65 (d br, J = 14.7 Hz, 3H, $N(CH_2)_2N$), −0.23 (s br, 3H, $N(CH_2)_2N$), 0.19 (s br, 3H, H_A/H_B), 1.69 (s br, 3H, $N(CH_2)_2N$), 4.13 (s br, 3H, $N(CH_2)_2N$), 5.09 (d, J = 7.5 Hz, 3H, H_3/H_5), 5.37 (s br, 3H, H_A/H_B), 6.15 (d, J = 7.2 Hz, 3H, H_3/H_5), 6.89 (t, J = 7.5 Hz, 3H, H_4). ^1H NMR (D_2O, 400 MHz, 343 K): δ −3.92 (d br, J = 14.0 Hz, 3H, $N(CH_2)_2N$), 0.08 (s br, 3H, $N(CH_2)_2N$), 0.54 (d br, J = 12.2 Hz, 3H, HA/HB), 1.79 (s br, 3H, $N(CH_2)_2N$), 3.88 (s br, 3H, $N(CH_2)_2N$), 5.20 (d br, J = 12.8 Hz, 3H, H_A/H_B), 5.31 (d, J = 7.6 Hz, 3H, H_3/H_5), 6.35 (d, J = 7.2 Hz, 3H, H_3/H_5), 7.02 (t, J = 7.5 Hz, 3H, H_4). ES-MS: m/z 685 $[M + H]^+$ Anal. Calc. for [Eu(tpatcn)]·3H_2O, $C_{27}H_{33}EuN_6O_9$ (M = 737.554): C 43.97, H 4.51, N 11.39. Found C 43.82, H 4.53, N 11.54%.

[Gd(tpatcn)]. ES-MS: m/z 690 $[M + H]^+$ Anal. Calc. for [Gd(tpatcn)]·3H_2O, $C_{27}H_{33}GdN_6O_9$ (M = 742.844): C 43.66, H 4.48, N 11.31. Found C 43.81, H 4.50, N 11.30%.

[Lu(tpatcn)]. ^1H NMR (D_2O, 400 MHz, 298 K): δ 2.21 (td, J = 13.1, 5.5 Hz, 3H, $N(CH_2)_2N$), 2.62 (dd, J = 13.0, 4.5 Hz, 3H, $N(CH_2)_2N$), 2.91 (dd, J = 16.2, 5.4 Hz, 3H, $N(CH_2)_2N$), 3.50–3.60 (m, 3H, $N(CH_2)_2N$), δ_A = 4.02, δ_B = 4.15 (AB system, J_{AB}= 14.6 Hz, 6H, H_A/H_B), 7.76 (d, J = 7.9 Hz, 3H, H_3/H_5), 8.06 (d, J = 7.6 Hz, 3H, H_3/H_5), 8.20 (t, J = 7.8 Hz, 3H, H_4). ^1H NMR (D_2O, 400 MHz, 343 K): δ 2.17 (td, J = 13.2, 5.7 Hz, 3H, $N(CH_2)_2N$), 2.62 (dd, J = 12.9, 5.3 Hz, 3H, $N(CH_2)_2N$), 2.88 (dd, J = 16.3, 5.6 Hz, 3H, $N(CH_2)_2N$), 3.45–3.60 (m, 3H, $N(CH_2)_2N$), δ_A = 4.00, δ_B = 4.13 (AB system, J_{AB}= 14.6 Hz, 6H,

Table 1 Crystallographic data for the four structures

	[Nd(tpatcn)]·3H_2O, **1**	[Eu(tpatcn)]·3H_2O, **2**	[Gd(tpatcn)]·3H_2O, **3**	[Lu(tpatcn)]·3H_2O, **4**
Formula	$C_{27}H_{33}NdN_6O_9$	$C_{27}H_{33}EuN_6O_9$	$C_{27}H_{33}GdN_6O_9$	$C_{27}H_{33}LuN_6O_9$
M_w	729.83	737.55	742.84	760.56
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	*Pn*	*Pn*	*Pn*	*Pn*
a/Å	8.042(4)	7.9946(18)	8.0251(7)	8.0084(6)
b/Å	11.948(7)	11.947(3)	11.9508(11)	11.8544(9)
c/Å	14.985(6)	14.884(3)	14.9011(13)	14.8334(12)
β/°	100.40(1)	99.953(15)	99.992(2)	99.694(1)
V/Å^3, *Z*	1416.2(12), 2	1400.1(5), 2	1407.4(2), 2	1388.1(2), 2
λ/Å	0.71073	0.71073	0.71073	0.71073
D_c/g cm^{-3}	1.712	1.749	1.753	1.820
μ(Mo-Kα)/mm^{-1}	1.898	2.306	2.422	3.622
T/K	298(2)	223(2)	298(2)	298(2)
R_1, wR_2 [a]	0.0414, 0.0854	0.0225, 0.0439	0.0349, 0.0786	0.0316, 0.0644

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

H_A/H_B), 7.75 (d, J = 7.8 Hz, 3H, H_3/H_5), 8.06 (d, J = 7.8 Hz, 3H, H_3/H_5), 8.20 (t, J = 7.7 Hz, 3H, H_4). ES-MS: *m*/*z* 707 $[M + H]^+$ Anal. Calc. for [Lu(tpatcn)]·3H_2O, $C_{27}H_{33}LuN_6O_9$ (M = 760.564): C 42.64, H 4.37, N 11.05, Found C 42.66, H 4.30, N 10.83%.

X-Ray crystallography

All diffraction data were taken using a Bruker SMART CCD area detector three-circle diffractometer (Mo-Kα radiation, graphite monochromator, λ = 0.71073 Å). To prevent evaporation of cocrystallised water molecules the crystals were coated with a light hydrocarbon oil. The cell parameters were obtained with intensities detected on three batches of 15 frames with a 30 s exposure time for Eu and with all data collection for Nd, Gd, Lu. The crystal-detector distance was 5 cm. For three settings of Φ, 1271 narrow data frames for Nd and Gd, 1041 for Eu, and 1077 for Lu, were collected for 0.3° increments in ω with a 300 s exposure time for Nd and Lu, 180 s for Gd and 60 s for Eu. At the end of data collection, the first 50 frames were recollected to establish that crystal decay had not taken place during the collection for Nd and Lu. Unique intensities with $I > 10\sigma(I)$ detected on all frames using the Bruker Smart program[22] 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 reflections with the SADABS Bruker program.[22] Space groups were determined from systematic absences, and they were confirmed by the successful solution of the structure (Table 1).

The structures were solved by direct methods using the SHELXTL 5.03 package[23] and for all structures all atoms, including hydrogen atoms for complex **2**, were found by difference Fourier syntheses. All non-hydrogen atoms were anisotropically refined on F^2. Hydrogen atoms were refined isotropically. For complexes **1**, **3** and **4** hydrogen atoms were included in calculated positions.

CCDC reference numbers 206375–206378.

See http://www.rsc.org/suppdata/dt/b3/b303079b/ for crystallographic data in CIF or other electronic format.

NMRD

The samples were prepared by dissolving a measured amount of the solid tpatcn ligand in a $Gd(ClO_4)_3$ solution (pH ~7, c_{Gd} = 13.46 mM). The absence of free gadolinium was checked by the xylenol orange test.[24] The $1/T_1$ NMRD profiles of the solvent protons at various temperatures (298, 310 K) were obtained: (a) from 0.02 to 18 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 30–50 MHz using an electromagnet (1.41 T) with a homebuilt 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 as described elsewhere.[25]

Results and discussion

Synthesis and characterisation of the ligand H_3tpatcn

1,4,7-tris[(6-carboxypyridin-2-yl)methyl]-1,4,7-triazacyclononane (H_3tpatcn) was obtained with a total yield of 51% by saponification of 1,4,7-tris[(6-carbethoxypyridin-2-yl)-methyl]-1,4,7-triazacyclononane which was prepared by reacting 1,4,7-triazacyclononane trihydrochloride with 6-chloromethylpyridine-2-carboxylic acid ethyl ester in the presence of K_2CO_3. The proton NMR spectrum of an aqueous solution of H_3tpatcn at pH = 5 shows one signal for the 12 protons of the 6 methylene groups of the 1,4,7-triazacyclononane core, one signal for the three methylene of the pendant arms and three signals for the 9 pyridyl protons of the pyridinecarboxylate arms in agreement with a C_{3v} symmetry of the ligand in solution.

Synthesis and structural characterisation of the complexes of tpatcn

The lanthanide complexes [Ln(tpatcn)] (Ln = Nd (**1**), Eu (**2**), Gd (**3**), Lu (**4**)) of the triply deprotonated nonadentate ligand tpatcn were obtained by reaction of the Ln(III) chloride salt and H_3tpatcn in water followed by adjustement of the pH at 5 with an aqueous solution of NaOH. Elemental analysis and electrospray mass spectra of all complexes were consistent with the formulation [Ln(tpatcn)]. The complexes show a high solubility in water differently from the [Ln(tpaa)] complexes which are rather insoluble in water. The ^{1}H NMR spectra of Ln(tpatcn) (Ln = Nd, Eu, Lu) complexes in a D_2O solution at room temperature and at pH = 6 show the presence of only one set of signals with three resonances for the 9 pyridine protons, four resonances for the 12 diasterotopic methylene protons of the macrocyclic moiety (six equatorial and six axial) and two resonances for the 6 methylene protons of the pendant arms in agreement with a C_3 symmetry of the solution species in which all chelating arms of tpatcn are equivalent. For the Nd complex the three resonances of the 9 pyridine proton are partially overlapped at room temperature, while three distinct signals can be observed at 343 K. These features are consistent with the presence of a highly rigid solution structure in which the macrocyclic framework remains bound and rigid on the NMR time scale. The proton NMR spectra of the three complexes at 343 K show the same number of signals indicating the absence of dynamic processes even at high temperature with the metal remaining encapsulated in a rigid structure by the three arms of the ligands. The replacement of the apical nitrogen with the

Table 2 Selected bond distances (Å) in complexes **1**–**4**

	[Nd(tpatcn)] **1**	[Eu(tpatcn)] **2**	[Gd(tpatcn)] **3**	[Lu(tpatcn)] **4**
M–O(11)	2.422(6)	2.400(3)	2.379(6)	2.322(6)
M–O(21)	2.401(6)	2.377(3)	2.367(6)	2.293(5)
M–O(31)	2.436(6)	2.391(3)	2.395(6)	2.311(5)
M–N(1)	2.731(7)	2.678(4)	2.670(6)	2.609(6)
M–N(2)	2.720(7)	2.688(4)	2.699(7)	2.628(6)
M–N(3)	2.692(7)	2.652(3)	2.651(7)	2.603(7)
M–N(11)	2.611(7)	2.553(3)	2.547(7)	2.490(6)
M–N(21)	2.580(9)	2.554(4)	2.542(7)	2.495(7)
M–N(31)	2.606(7)	2.560(3)	2.564(7)	2.498(6)

macrocyclic core leads to an increased rigidity of the Ln(tpatcn) solution species with respect to the Ln(tpaa) complexes for which the chemical shift equivalence of the methylene protons indicate a conformational mobility of the ligand branches in solution. Such conformational rigidity has been also observed for the lanthanide complexes of the nonadentate ligand obtained by Schiff-base condensation of 1,4,7-triazacyclononane with sodium pyruvate.[17] Conversely the lanthanide complexes of the trianionic hexadentate triaza ligand 1,4,7-triazacyclononane-*N*,*N*′,*N*″-triacetic acid (nota)[16] in water and those of the neutral hexadentate ligand 1,4,7-tris(carbamoylmethyl)-1,4,7-triazacyclononane[20] in acetonitrile solution show at room temperature proton NMR spectra characteristic of a flexible triaza core with a fast interconversion between the two staggered conformations of the five-membered chelate rings M–N–C–C–N.

X-Ray quality crystals of these complexes were obtained by slow evaporation of 1 : 1 solutions of $LnCl_3$ and H_3tpatcn in water after adjustment of the pH at 5.

The four complexes are isostructural and accordingly only the crystal structure of the gadolinium complex is shown in Fig. 1. Selected bond distances for the four complexes are presented in Table 2. While the lanthanide complexes of tpaa oligomerize in the solid state and their crystal structures show different nuclearity along the series, with a tetrameric structure being observed for the La^{3+} ion, dimeric structures being formed from the Nd^{3+} ion through the Yb^{3+} ion and a monomeric structure for Lu^{3+}, the four complexes of tpatcn crystallize only as mononuclear complexes as do the dota complexes.[26] This is due to the fact that in the tpatcn complexes the Ln(III) ion has a saturated coordination sphere while in the complexes of the heptadentate tpaa the Ln(III) ion presents two vacant coordination sites that can be filled by the carboxylate oxygens from an adjacent complexed ligand. This different behaviour towards aggregation could explain at least in part the dramatic difference in water solubility between the two complexed ligands.

The same difference in nuclearity was observed by Schröder and coworkers between the Ln(III) complexes of the nonadentate ligand obtained by Schiff-base condensation of 1,4,7-triazacyclononane with sodium pyruvate which were isolated from methanol only as mononuclear complexes and the Ln(III) complexes of the corresponding heptadentate tripode obtained by Schiff-base condensation of tris(2-aminoethyl)amine with sodium pyruvate which lead to the formation of tetrameric structures.[17,27]

Moreover in the four structures of the [Ln(tpatcn)] complexes the Ln(III) ions adopt the same coordination number while different coordination numbers have been found along the series for the Ln(tpaa) complexes with the coordination numbers nine and ten found for the large lanthanum ion, coordination number eight for the small Lu ion and coordination nine only for the intermediate lanthanides ions (Nd–Yb).

In each complex the Ln(III) ion is nine-coordinated by the nine donor atoms of the ligand, the three nitrogen atoms of the 1,4,7-triazacyclononane core, the three pyridine nitrogens and the three carboxylate oxygens. The wrapping of the pyridinecarboxylate arms around the Ln(III) ion leads to the formation of a triple helix. The complexes crystallize as a racemic mixture of the two Λ and Δ enantiomers.

The coordination geometry of the metal ion can be described as a slightly distorted tricapped trigonal prism with a pseudo-C_3 axis passing through the center of the 1,4,7-triazacyclononane core and through the lanthanide ion (Fig. 2). The presence of the capping macrocyclic moiety forces the ion to

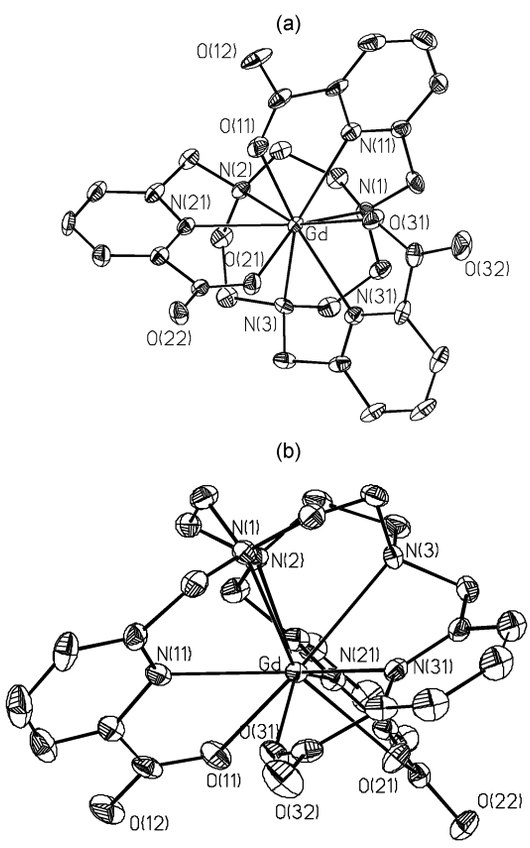

Fig. 1 Top (a) and side view (b) of the crystal structure of [Gd(tpatcn)] with thermal ellipsoids at 30%.

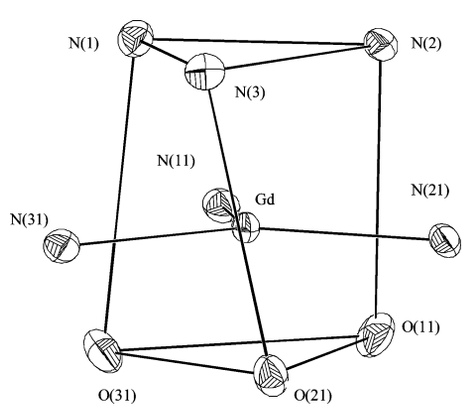

Fig. 2 Coordination geometry about the metal center in [Gd(tpatcn)].

assume the trigonal prismatic geometry by imposing the first triangular face. The second triangular face is formed by the carboxylate oxygens, while the pyridyl nitrogens occupy the capping positions in the rectangular faces. The upper and lower triangular faces are parallel with the angle between the planes defined by the faces varying from 1.7° for Nd to 1.3° for Lu. The oxygen faces are slightly twisted around the three-fold axis with respect to the nitrogen faces. The average values of the torsion angles formed by the atoms of the rectangular faces (24.2(8)° for Nd, 22.0(3)° for Eu, 21.8(7)° for Gd and 19.4(3)° for Lu) show an increased distorsion from a regular trigonal prismatic geometry for the larger ions. A very similar type of coordination was found in the lanthanide complexes of the nonadentate ligand obtained by Schiff-base condensation of 1,4,7-triazacyclononane with sodium pyruvate.

The average $M–N_{pyridinyl}$ distances are shorter than the average $M–N_{tert}$ distances found in other lanthanide polyaminopolycarboxylate complexes[28,29] but similar to those found in the [Ln(tpaa)] complexes. Their values show a decrease of 0.11 Å from Nd (2.60(1) Å) to Lu (2.49(0) Å) which is clearly correlated to the decrease in ionic radius (a decrease of 0.13 Å is expected). The values of the average bond distances between the Ln(III) and the macrocyclic N donors (2,67(2) Å for Gd) are shorter than the values found for the Ln–apical nitrogen distances in the [Ln(tpaa)] complexes (2,7886(19) Å for Gd) and also show a decrease along the series of 0.10 Å from Nd to Lu correlated to the decrease in ionic radius. The same behaviour is observed for the values of the average bond distances between the Ln(III) and the carboxylate oxygens with a decrease of 0.11 Å from Nd to Lu. This indicates that the ligand tpatcn is flexible enough to encapsulate lanthanide ions of different size. In all complexes three water molecules are found in the unit cell with two of them strongly hydrogen bound to the carboxylates of two different complexes moieties. This results in the formation of a bidimensional array.

Relaxometry

The NMRD (Nuclear Magnetic Relaxation Dispersion) profile of the free water protons in presence of [Gd(tpatcn)] has been measured at 298 and 310 K between 0.021 and 50 MHz (Fig. 3). The profile is typical for a complex without a water molecule in the first coordination sphere. At high field (>10 MHz) and 298 K the relaxivity of [Gd(tpatcn)] is comparable to that of $[Gd(ttha)]^{3-}$[30]or $[Gd(teta)]^{-}$[31] which have no bound water molecule.

The outer sphere relaxation, $1/T_{1os}$, can be fitted using Freed's force-free model (eqn. (1)).[32–34]

$$\frac{1}{T_{1os}} = \frac{32\pi}{405}\left(\frac{\mu_0}{4\pi}\right)^2 \frac{N_A[Gd]}{r_{os}D}\gamma_I^2\gamma_S^2\hbar^2 S(S+1)\left[3J_1(\omega_I)+7J_2(\omega_S)\right]$$

$$J_k(\omega) = \mathrm{Re}\left[\frac{1+z/4}{1+z+4z^2/9+z^3/9}\right]; z=\sqrt{i\omega\tau+\tau/T_{ke}}; \tau=\frac{r_{os}^2}{D}; k=1,2 \quad (1)$$

N_A is the Avogadro number, r_{os} is the closest distance of approach, D is the diffusion coefficient of relative diffusion, [Gd] is the molar concentration of gadolinium ions and $1/T_{ke}$ are the electron spin relaxation rates which can be calculated using Bloembergen–Morgan theory.[35] The experimental data can be fitted with a closest distance of approach of 4.2 ± 0.1 Å (Fig. 3). The diffusion constant was fixed to 2.3×10^{-9} m^2 s^{-1} (at 298 K) and its activation energy to 17.6 kJ mol^{-1}.[36] The parameters of electron spin relaxation rates are $\Delta^2 = 1 \times 10^{20}$ s^{-2} (fixed), $\tau_v^{298} = 4 \times 10^{-13}$ s (fitted, error = 1×10^{-13} s) and E_v = 6 kJ mol^{-1} (fixed). The estimated electron spin relaxation rates with these parameters are 4×10^8 s^{-1} ($1/T_{1e}$) and 5×10^8 s^{-1} ($1/T_{2e}$) at 298 K.[37]

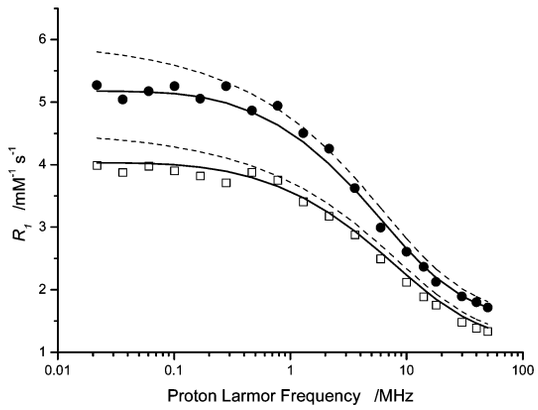

Fig. 3 Water proton NMRD profiles of the [Gd(tpatcn)] complex at 298 K (●) and 310 K (□) (c_{Gd} = 13.36 mM); (—) fitted profiles; (---) calculated profiles without electron spin relaxation.

The calculations presented in Fig. 3 show that the modulation of the local magnetic field sensed by the outer sphere water protons is governed by the translational motion of the water molecules and not by the electron spin relaxation which is predicted to be slower compared to the complexes of other cyclic poly(aminocarboxylates) like dota. The fitted closest distance of approach, r_{os}, is however longer (4.2 Å *vs.* 3.5 Å) than normally assumed.[37] This can be understood by considering the coordination geometry about the metal centre (Fig. 2). As previously shown by molecular dynamics simulations, the outer sphere water molecules approach the paramagnetic centre close to the hydrophilic carboxylate groups with their protons pointing towards the Gd(III).[31] The water molecules close to the hydrophobic part of the molecule are further away and not oriented. Therefore, on average, the r_{os} is longer in the case of the tpatcn ligand containing only three carboxylate groups compared for example to the case of ttha containing six carboxylate groups.

The very high relaxivity of the similar [Gd(tpaa)] complex was attributed to the short distance between the Gd(III) ion and the inner-sphere water oxygen and/or to the possibility of an equilibrium between two and three bound water molecules.[8,9] The results obtained for the [Gd(tpatcn)] complex show that the outer-sphere contribution is not responsible for the high relaxivity of [Gd(tpaa)]. However, a relatively slow electron spin relaxation such as estimated above in the case of the tpatcn-ligand will favour high proton relaxivities. A detailed EPR investigation on both complexes would allow to verify this assumption.

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