Kinetically Stable Lanthanide Cryptates

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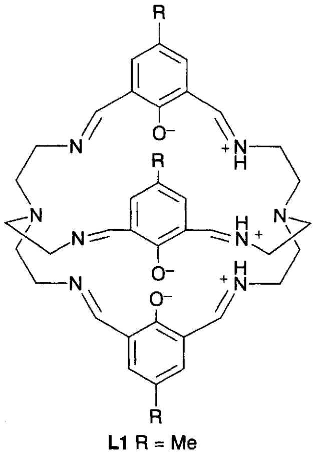
Two sets of lanthanide cryptates, kinetically stabilised against decomplexation, are reported; structures in one isomorphous series show eight-coordination including one coordinated water, while in the gadolinium cryptate of the second ligand, the coordinated water is replaced by acetate.

The unusual and, in many cases, potentially exploitable physical properties of lanthanides[1] have stimulated interest in the development of effective transport agents for these and related +3 oxidation state cations. Possible uses for such systems include transport of radionuclides for diagnostic or therapeutic purposes,[2] detoxification *via* chelatotherapy,[3] MRI[4] or fluorescent labelling.[5] For most of these applications it is essential that the necessary thermodynamic stability is accompanied by the high kinetic stability toward decomplexation, something that can be hard to achieve with normally labile cations such as lanthanides. We can expect to arrange a satisfactory combination of thermodynamic and kinetic stability by use of macrobicyclic cryptand ligands.[6] Ligands L^1 and L^2, which are easily made by a sodium template procedure[7] furnish an appropriate mixture of imino N- and anionic O-donors; transmetallation with M^{3+} then yields the mononuclear cryptates, ML^{3+} (Table 1), as confirmed by FAB-MS.

These ligands have already been shown[8,9] to coordinate Pb^{2+}, Cd^{2+}, Zn^{2+} and Fe^{3+} in mononuclear fashion, using a coordination mode which involves proton transfer to the uncoordinated imino nitrogen, the deprotonated phenol substituent providing a locally anionic coordination site. This local anionicity of O-donors diminishes the Lewis acidity of the coordinated cation, protecting the imino C=N bond from metal-assisted hydrolytic attack. The diamagnetic cryptates $[YL^2]^{3+}$ **3** and $[ScL^2]^{3+}$ **1** have ^1H NMR spectra similar to those already analysed[8] for the structurally characterised monozinc and monocadmium cryptates of L^1, suggesting a similar configuration. In particular, proton transfer from the coordinated phenoxy oxygen to the uncoordinated imino nitrogen is confirmed. Also the high degree of resolution of the spectra testifies to the absence of rapid exchange of cations between the solvent and the cryptand host, in other words to kinetic stabilisation of the cryptate. The ^1H NMR spectra of the europium and terbium cryptates **6**, **7** and **9** are equally sharp, although complex and paramagnetically shifted, covering a range between δ −25 and +45. In addition, ^{45}Sc NMR of **1** confirms the absence of scandium exchange between cryptand host and $[^2H_6]Me_2SO$ solvent; a strong, broad, δ 85 resonance is observed which shows no sign of broadening in the presence of 'free' (*i.e.* Me_2SO-solvated) Sc^{3+} with an increase of temperature over the range 296–353 K.

There is chemical evidence for kinetic stabilisation of the cryptates, in that no precipitation is observed over a period of several days when solutions are treated with aqueous hydroxide or phosphate solutions. Solutions in MeCN–EtOH are stable indefinitely, and crystals for X-ray diffraction studies are obtained by slow evaporation in air over weeks or months. This contrasts with the chemical behaviour of lanthanide complexes of iminophenolate podand ligands[10] having the same $N_4(O^-)_3$ donor set, which require synthesis under strictly anhydrous



L1 R = Me
L2 R = Bu^t

Table 1 Spectroscopic and magnetic properties of lanthanide cryptates

Cryptate		Magnetic moment/μ_B		Selected ^1H NMR resonances[b]				
		90 K	293 K	ν/Hz	Solvent	(N)H^{+}[a]	Imino (C)H[a]	Aromatic (C)H[a]
$[ScL^2(H_2O)](ClO_4)_3·2H_2O$	**1**	—	—	500	CD_3CN	12.28, br	8.70, d;[f] 8.50, s	8.13;[c] 7.91[c]
				400	$[^2H_6]Me_2SO$	12.01, br	8.97, br; 8.69, s	8.13, br; 7.97
$[YL^1](ClO_4)_3·12H_2O$	**2**	—	—	400	CD_3CN	12.50, br	8.51, d;[f] br; 8.34, s	7.68; 7.52
$[YL^2(H_2O)](ClO_4)_3·8H_2O·2MeOH$[g]	**3**	—	—	400	CD_3CN	12.59, br	8.57, d;[f] 8.42, s	7.98;[c] 7.73[c]
$[GdL^1(MeCO_2)](ClO_4)_2$[g]	**4**	8.17	8.22	300	CD_3CN	[d]	[d]	[d]
$[GdL^2(H_2O)](ClO_4)_3·2EtOH·0.5MeOH$	**5**	8.00	8.11	300	CD_3CN	[d]	[d]	[d]
$[EuL^1](ClO_4)_3·2MeOH·3H_2O$	**6**	2.68	4.05	500	CD_3CN	[e]	[e]	[e]
$[EuL^2(H_2O)](ClO_4)_3·8H_2O$	**7**	1.94	3.48	400	$[^2H_6]Me_2SO$	[e]	[e]	[e]
$[TbL^1](ClO_4)_3·4MeOH·H_2O$	**8**	10.59	10.94	500	CD_3CN	[d]	[d]	[d]
$[TbL^2(H_2O)](ClO_4)_3·8H_2O$[g]	**9**	8.97	9.30	500	CD_3CN	[e]	[e]	[e]
$[DyL^2(H_2O)](ClO_4)_3·5MeOH·3H_2O$	**10**	10.30	10.53	300	CD_3CN	[d]	[d]	[d]

[a] δ From Me_4Si. [b] Methylene resonances comprise a complex pattern δ 2–4. [c] *ca.* 2 Hz doublet. [d] Severely broadened. [e] Paramagnetic shifting prohibits assignment. [f] $^3J[(C)H,N(H)]$ 25–35 Hz. [g] Solvation differs from that in industrial alcohol-recrystallised sample used for X-ray studies.

conditions because of reaction with any available competing O-donor ligand.

Three isomorphous structures of $[ML^2(H_2O)]^{3+}3ClO_4^-\cdot 2EtOH\cdot 0.5MeOH$, (M = Y **3**, Gd **5**, Tb **9**) have been determined by single crystal X-ray diffraction.† The dimensions of the metal coordination spheres (Table 2) are consistent with atomic radii Tb ≈ Gd > Y. Fig. 1 shows that the metal ion is eight-coordinate, being bonded to three imino-nitrogens and three O-donors from one end of the cryptand, as well as to the bridgehead nitrogen and one water molecule. The geometry of the coordination sphere can be considered as a distorted dodecahedron with two perpendicular trapezoids made up of (i) N(200), N(13B) in A sites and N(13A), O(11B) in B sites, and (ii) O(11A), O(11C) in A sites and OW(1) and N(13C) in B sites.

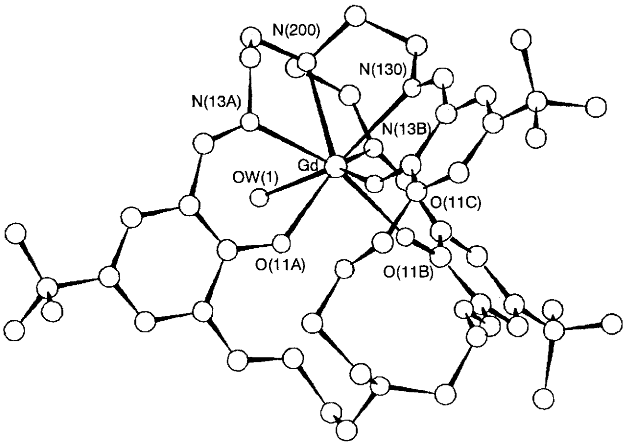


Fig. 1 The structure of $[GdL^2(H_2O)]^{3+}$;† the structures of the Tb and Y complexes are isomorphous

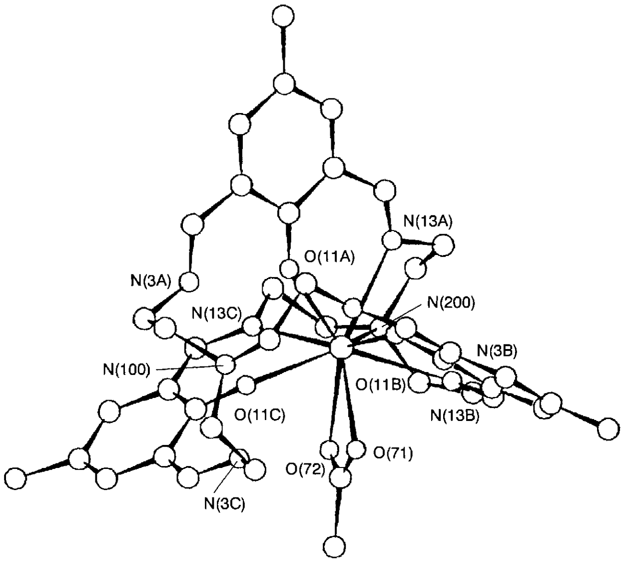


Fig. 2 The structure of $[GdL^1(OAc)]^{2+}$ †

In the L^1 series, the triperchlorate salts were unsuitable for X-ray crystallographic studies, but mixed acetate/perchlorate crystals (obtained in an attempt to deprotonate the second coordination site)[11] proved suitable in one case. The structure of $[GdL^1(MeCO_2)]^{2+}2ClO_4^-$ **4** is shown in Fig. 2. The metal ion is nine-coordinate, being bonded to three imino-nitrogen atoms and three O-donors as well as one bridgehead nitrogen atom and one acetate anion. Despite the difference in coordination number, the structure is remarkably similar to **5**, particularly if the acetate is considered to take up one coordination site. Fig. 2 clearly shows how the macrocycle is folded so that the acetate group is directed outside the macrobicycle. The bond lengths in the coordination sphere are somewhat larger than in the L^1 complex, reflecting the larger coordination number.

The M–N and M–O contacts in these cryptates are close to those in the unstable $N_4(O^-)_3$ podate, Ybtrac[10] {trac = $N[CH_2CH_2N{=}C(Me)CH_2CH(Me)O^-]_3$}, but significantly shorter (by 0.2–0.4 Å) than in other structurally characterised lanthanide cryptates.[12] In the isomorphous L^2 cryptates, obtained by recrystallisation from alcohol–acetonitrile, alcohol solvate molecules are located in disordered positions in the crystal; on standing in air, however, the crystals disintegrate as these solvate molecules are replaced by water.

The coordinated and solvated water molecules are likely to be of value in MRI experiments where rapid relaxation of inner- and outer-sphere water molecules is responsible for enhanced contrast of tissue in the neighbourhood of paramagnetic cations. Among the lanthanides, Gd^{3+} and Dy^{3+} have found application as contrast agents, on the basis of their short (longitudinal) T_1 or (transverse) T_2 relaxation times, respectively.[4] There is evidence for rapid relaxation in the ^1H NMR spectra of the Gd^{3+} and Dy^{3+} cryptates **4**, **5** and **10** in that ligand (C)H resonances are severely broadened and this broadening extends even to the adventitious HDO in solvent. ESR $g \approx 2$ signals are easily observed for the gadolinium cryptates at temperatures near ambient, demonstrating the required slow electronic relaxation. The short residence time likely for the coordinated water molecule, in consequence[13] of strong binding by the remaining cryptand donors and the increased correlation time arising from encryptation, may also favour relaxivity enhancement.[14]

In conclusion, the relaxivity properties of the cryptates currently under study are likely to be of interest in connection with MRI. While the solubility of the present series may be insufficient for *in vivo* use, further syntheses will be directed at enhancing aqueous solubility. It is possible that a superior resistance to dissociation may allow cryptates of this series to compete with existing pendant-armed macrocyclic ligand carriers, for at least some purposes.

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Table 2 Geometry of the metal coordination spheres in **3**, **5**, **9** and **4**

Interatomic distance/Å	M = Tb **9**	M = Gd **5**	M = Y **3**	$[GdL^1(MeCO_2)]^{2+}$ **4**
M(1)–O(11B)	2.251(7)	2.227(10)	2.180(10)	2.322(5)
M(1)–O(11C)	2.315(8)	2.307(11)	2.286(11)	2.347(6)
M(1)–O(11A)	2.362(7)	2.345(9)	2.304(11)	2.367(6)
M(1)–OW(1)	2.426(9)	2.402(13)	2.346(13)	—
M(1)–N(13A)	2.490(9)	2.486(13)	2.407(14)	2.565(7)
M(1)–N(13C)	2.532(9)	2.505(13)	2.45(2)	2.583(7)
M(1)–N(13B)	2.555(9)	2.549(14)	2.50(2)	2.552(7)
M(1)–N(200)	2.644(9)	2.639(12)	2.594(14)	2.715(7)
M(1)–O(acetate)				2.441(6); 2.466(6)

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Footnote

† *Note added in proof*: we have recently shown that EtOH-recrystallised **10** is isomorphous with **3**, **5** and **9**.

Crystal Data: collected on a MARresearch image plate System with Mo-Kα radiation. The crystals were set up at 75 mm (for **9**, **4** and **3**) and 90 mm (for **5**) from the Image Plate and 95 images were taken at 2° intervals. Data analysis was carried out with the XDS program.[15] The structures **9**, **5** and **3** were isomorphous. **9** and **4** were solved using direct methods with the SHELX86 program[16] and **5** and **3** were refined using the coordinates of **9** as a starting set. There was much disorder in all structures. In **9**, **5** and **3** the disorder encompassed one *tert*-butyl group, all perchlorates and the solvent molecules. All ordered non-hydrogen atoms were refined with anisotropic thermal parameters. Disordered non-hydrogen atoms were refined with isotropic thermal parameters. By contrast, in **4** the disorder was restricted to the perchlorate anions. Two tetrahedra were refined for each anion, with occupancies that added up to 1.0. All non-hydrogen atoms apart from the perchlorate oxygen atoms were refined anisotropically. In all four structures the hydrogen atoms were included in geometric positions. The structures were refined by full-matrix least-squares methods using SHELXL.[17] Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

For **9**, $[TbL^2(OH_2)]3ClO_4{\cdot}2.0EtOH{\cdot}0.5MeOH$, $C_{52.5}N_8H_{82}Cl_3TbO_{18.5}$, M = 1386.6, Mo-Kα radiation, λ = 0.7107 Å, monoclinic, space group $C2/c$, a = 18.315(7), b = 22.092(8), c = 36.052(8) Å, β = 93.3(1)°, U = 14563.3 Å^3, Z = 8, D_c = 1.212 Mg m^{-3}, μ = 1.14 mm^{-1}. Reflections collected 24623, independent reflections 13109 [R(int) = 0.0486]. Final R indices [$I > 2\sigma(I)$] $R1$ = 0.0854, $wR2$ (on F^2; all reflections) = 0.2583.

For **5**, $[GdL^2(OH_2)]3ClO_4{\cdot}2.0EtOH{\cdot}0.5MeOH$, $C_{52.5}N_8H_{82}Cl_3GdO_{18.5}$, M = 1384.9, Mo-Kα radiation, λ = 0.7107 Å, monoclinic, space group $C2/c$, a = 18.348(7), b = 22.062(7), c = 36.001(11) Å, β = 93.26(1)°, U = 14549.3 Å^3, Z = 8, D_c = 1.212 Mg m^{-3}, μ = 1.085 mm^{-1}. Reflections collected 14660, independent reflections 8737 [R(int) = 0.0477]. Final R indices [$I > 2\sigma(I)$] $R1$ = 0.1046, $wR2$ (on F^2; all reflections) = 0.3244.

For **3**, $[YL^2(OH_2)]3ClO_4{\cdot}2.0EtOH{\cdot}0.5MeOH$, $C_{52.5}N_8H_{82}Cl_3YO_{18.5}$, M = 1317.6, Mo-Kα radiation, λ = 0.7107 Å, monoclinic, space group $C2/c$, a = 18.208(7), b = 21.842(8), c = 35.637(13) Å, β = 92.5(1)°, U = 14159.7 Å^3, Z = 8, D_c = 1.180 Mg m^{-3}, μ = 0.998 mm^{-1}. Reflections collected 21943, independent reflections 11812 [R(int) = 0.0817]. Final R indices [$I > 2\sigma(I)$] $R1$ = 0.1350, $wR2$ (on F^2; all reflections) = 0.2874.

For **4**, $[GdL^1(MeCO_2)]2ClO_4{\cdot}2MeCN$, $C_{45}N_{10}H_{57}Cl_2GdO_{13}$, M = 1171.2, Mo-Kα radiation, λ = 0.7107 Å, triclinic, space group $P\bar{1}$, a = 10.018(7), b = 13.024(7), c = 19.800(8) Å, α = 95.5(1), β = 92.0(1), γ = 99.2(1)°, U = 2535.2'Å^3, Z = 2, D_c = 1.521 Mg m^{-3}, μ = 1.484 mm^{-1}. Reflections collected 7893, final R indices [$I > 2\sigma(I)$] $R1$ = 0.0732, $wR2$ (on F^2; all reflections) = 0.1947.

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