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PAPER

Lanthanide complexes of DOTA monoamide derivatives bearing an isophthalate pendent arm†

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An isophthalate-bearing DOTA monoamide derivative has been synthesised and used to prepare a family of lanthanide complexes. Luminescence and NMR studies in solution show that the predominant form of the complexes in solution is a mono-capped square antiprism about the lanthanide centre, in which a solvent molecule occupies the ninth coordination site. The crystal structure of the terbium complex is presented and is in close agreement with the solution state data.

Introduction

Kinetically stable lanthanide complexes are already being widely used as imaging agents in both whole body MRI and luminescence microscopy.[1,2] In recent years, the use of gadolinium complexes as MRI contrast agents has become almost ubiquitous in MRI blood pool imaging,[3] and the strategy has been extended using complexes that respond to changes in their environment,[4] and to bioconjugates with peptides that are internalised by specific cell types.[5] Luminescent lanthanide complexes have become a keystone of bioassay,[6] and are beginning to be exploited as tags[7] and responsive probes[8] for time-gated luminescence microscopy, where the long luminescence lifetimes associated with lanthanide centred transitions lend themselves to such applications.

Over the last few years, we and others have devoted considerable effort to developing strategies that can be used to link lanthanide complexes together through carrying out chemical modifications to stable complexes, using Ugi[9] and click[10] reactions, and developing orthogonal protection strategies that can be used to control the position of lanthanide complexation.[11] Related strategies have also been used to incorporate aromatic and transition metal complexes into lanthanide containing systems.[12,13]

We now report the synthesis of a family of DOTA-monoamide complexes bearing an isophthalate group which is suitable for further functionalisation with a pair of targeting vectors.

Results and discussion

Our synthetic strategy is shown in Scheme 1. Reaction of dimethyl 3-aminoisophthalate (**1**) with chloroacetyl chloride in the presence of sodium hydrogencarbonate yielded 2-chloro-*N*-(3,5-di(methoxycarbonyl)phenyl)acetamide (**2**). Reaction of the well-known triester[14] (**3**) with compound **2** yielded the orthogonally protected DOTA-monoamide derivative (**4**). Cleavage of the *tert*-butyl ester groups using trifluoroacetic acid yielded H_3·**5**, which was used to form the Ln·**5** complexes. Base hydrolysis of H_3·**5** and subsequent work up and complexation with the appropriate lanthanide triflate yielded H_5·**6** and Ln·**6** respectively. We elected to use this approach in the light of previous experience of lability of lanthanide coordinated amide bonds:[11] indeed, attempts at base hydrolysis of Ln·**5** proved capricious, with evidence of Ln·DOTA contaminants being observed in NMR spectra of the crude mixtures that were obtained. This lends further weight to the supposition that treatment of aqueous solutions of such complexes with strong base should be avoided wherever possible.

Structures of the complexes in solution

Initially, NMR spectroscopy was used to probe the structures of the complexes in solution. The NMR spectra of the complexes are shown in Fig. 1 and 2. All bear a clear resemblance to the NMR spectra of other DOTA-monoamide complexes,[9,11] and the chemical shifts observed are similar to the analogous complexes of DOTA itself,[15] with the obvious difference that the broken symmetry in these structures gives rise to a much greater number of peaks in the spectra of the monoamide complexes (since all the protons in the structure are now inequivalent). For the neodymium complexes, this inequivalence is much less obvious than it is in the other complexes, since exchange broadening gives rise to broad and relatively featureless spectra. The other complexes all give rise to clearly defined spectra, and in all cases comparison of the chemical shifts observed for the most shifted protons with those corresponding to the same protons in literature

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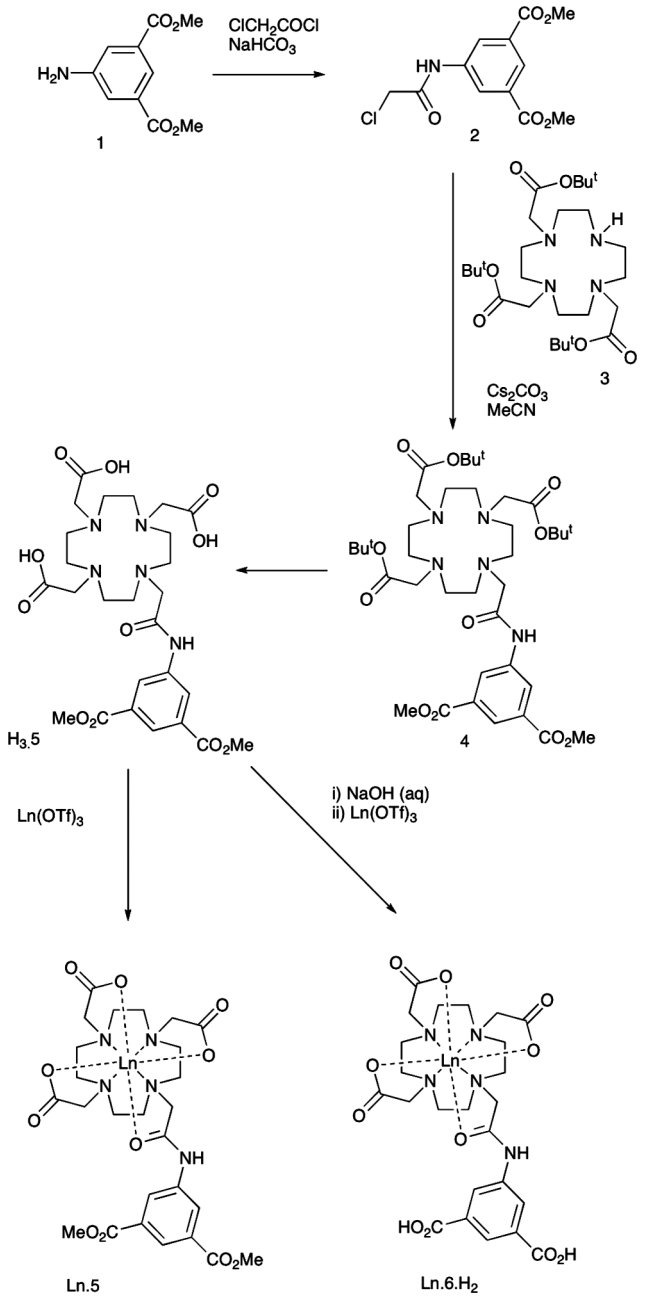
† Electronic supplementary information (ESI) available: Crystallographic Information File (CIF) of Tb·**5**. CCDC reference number 828726. See DOI: 10.1039/c1dt11029b



Scheme 1

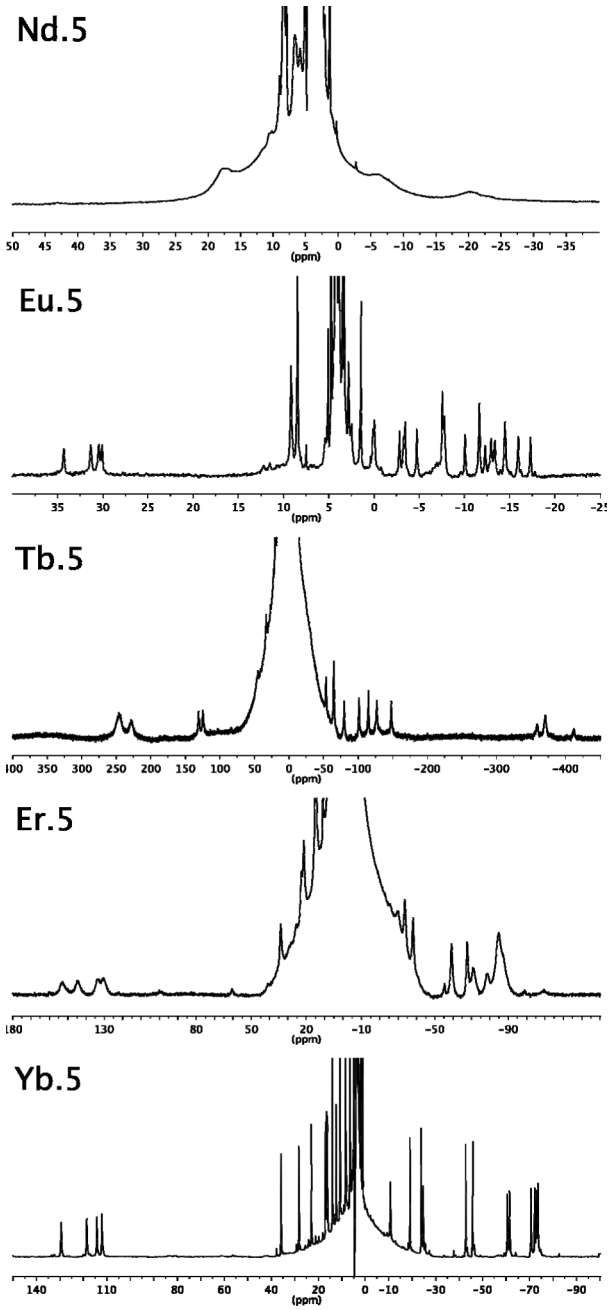


Fig. 1 ^{1}H NMR spectra (500 MHz, D_2O, 295 K) of the lanthanide complexes of **5**.

reports[9,11,15,16] suggest that the dominant isomer in solution is a hydrated square antiprismatic structure. Tb·**5**, Tb·**6**, Yb·**5** and Yb·**6** are all dominated by a single set of resonances, with only traces of the diastereomeric twisted square antiprismatic form being observed in solution at 295 K (*e.g.* around 80 ppm in the case of Yb·**6**). In the case of the europium complexes, there is much clearer evidence for a minor isomer in which the metal adopts a twisted square antiprismatic geometry.

Furthermore, it is clear that the spectra of the complexes of **5** and **6** with the same lanthanide are very similar to one another, implying that remote substituents have little effect on the local environment close to the lanthanide.

Luminescence spectroscopy was used to probe the structures further. All the complexes were found to be luminescent, though facile quenching by O–H oscillators ensured that only weak emission was observed from the erbium complexes. Key aspects of their properties are shown in Table 1.

Time-resolved data was used to assess the inner sphere hydration of the complexes. The lifetimes of lanthanide-centred emission in water and deuterium oxide can be used to calculate q_{Ln}, the number of inner-sphere water molecules bound to the lanthanide ion, using the equation

$$q_{Ln} = A(1/\tau_{H_2O} - 1/\tau_{D_2O} - B) \quad (1)$$

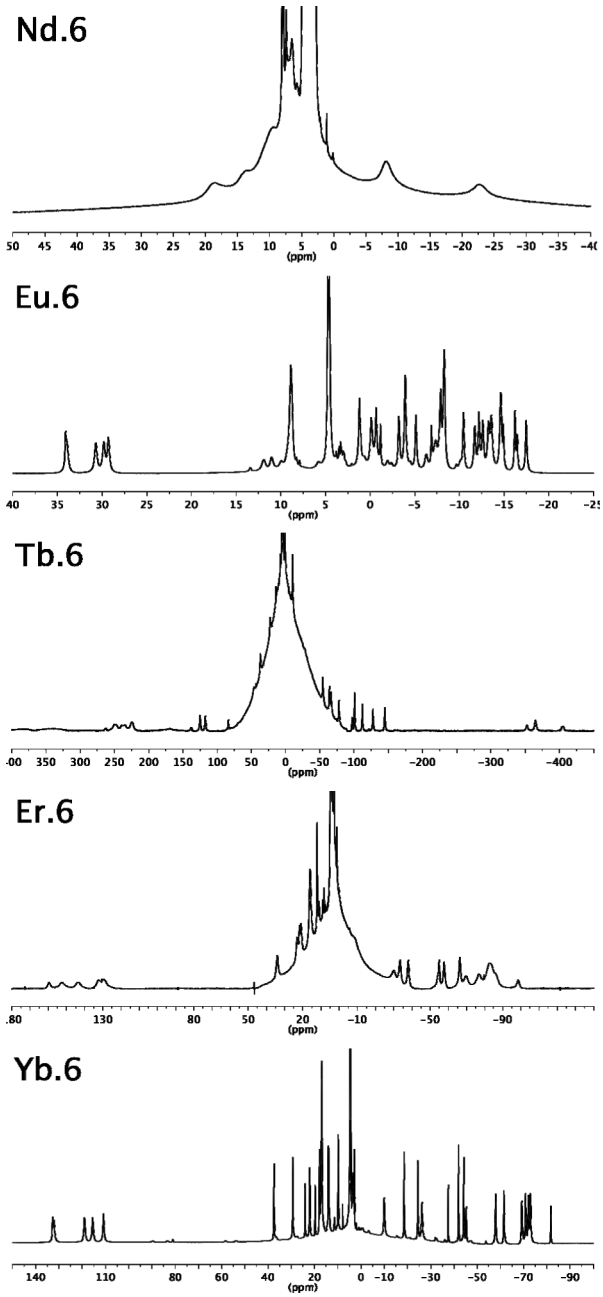


Fig. 2 ^{1}H NMR spectra (500 MHz, D_2O, 295 K) of the lanthanide complexes of **6**.

where A and B are constants for a given lanthanide ion. For europium A_{Eu} = 1.2 ms and B_{Eu} = (0.25 − 0.075x) ms^{-1}, where x is the number of exchangeable N–H oscillators (*i.e.* x = 1, in this case). Effective calculations of q are also possible for terbium and ytterbium complexes (A_{Tb} = 5 ms, B_{Tb} = 0.06 ms^{-1}, A_{Yb} = 1 μs and B_{Yb} = 0.1 μs^{-1}), but the facility of C–H quenching in neodymium and erbium complexes means that this approach cannot be applied to calculate q_{Nd} and q_{Er}.[18] In the cases for which q can be calculated effectively, it is clear that the data from luminescence spectroscopy bears out the NMR study. In all cases, calculated values of q are close to 1, implying that a hydrated square antiprismatic structure dominates in solution.

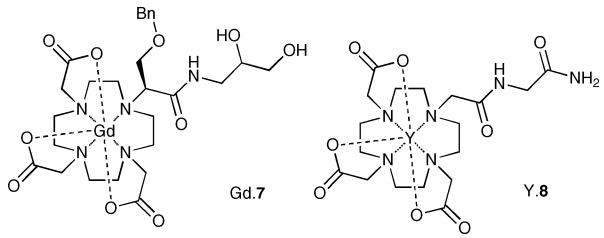
Table 1 Photophysical properties of the complexes[a]

Complex	λ_{ex}/nm	λ_{em}/nm	τ_{H_2O}/μs	τ_{D_2O}/μs	q_{calc}
Nd·**5**	337	1055	0.14	0.38	
Eu·**5**	260	617	550	1850	1.1
Tb·**5**	260	545	1630	2730	0.9
Er·**5**	337	1530	—	0.81	
Yb·**5**	337	980	0.78	5.21	0.9
[Eu·**6**]$^{2-}$	260	617	570	2180	1.0
[Tb·**6**]$^{2-}$	260	545	1690	3030	1.0
[Er·**6**]$^{2-}$	337	1530	—	0.94	
[Yb·**6**]$^{2-}$	337	980	0.79	7.74	1.0
[Nd·**6**]$^{2-}$	337	1055	0.11	0.34	

[a] q_{Ln} was calculated using eqn (1), and the A and B parameters in ref. 17.

Crystal structure of Tb·5

Suitable colourless needles of Tb·**5** for structural analysis were obtained by slow evaporation of a saturated aqueous solution at room temperature. To the best of our knowledge, there is only one previous structural report of a DOTA monoamide complex and one group 3 derivative; these are Gd·**7**[19] and Y·**8**.[20]



The complex crystallises as a racemate and both $\Lambda(\delta\delta\delta\delta)$ and $\Delta(\lambda\lambda\lambda\lambda)$ configurations are observed in the asymmetric unit cell. Average cyclen N–C–C–N and N–C–C–O torsion angles are respectively measured as +58.7° and −28.6° for the $\Lambda(\delta\delta\delta\delta)$ diastereomer and −58.9° and +28.2° for the $\Delta(\lambda\lambda\lambda\lambda)$ configuration.

The solid state structure of Tb·**5** (Fig. 3) shows that the terbium(III) ion is 9 coordinate and the resultant coordination geometry is best described as a distorted mono capped square antiprism (SAP). The basal plane is described by the four cyclen N atoms (N(1)–N(4)) and the orthogonal plane occupied by the three acetate O atoms (O(2), O(4), O(6)) and the amide O atom (O(8)). The displacements of these atoms from their respective mean planes are 0.006 and 0.019 Å respectively. The two planes lie almost parallel to one another; the angle between them being 1.8° and the Tb^{3+} ion lies 1.611 Å from the centre of the N_4 plane and 0.709 Å from the O_4 plane. The dihedral or twist angle between the cyclen N_4 donor set and that of the acetate/amide donor set is 39° (±1°) and is characteristic of distorted SAP coordination polyhedra observed in mono, bis, tri and tetraamide DOTA derivatives.[21]

The average N_{cyclen}–Tb distance is 2.641(4) Å, the mean $O_{acetate}$–Tb distance is 2.341(3) Å and the O_{amide}–Tb distance is longer at 2.409(3) Å. These values are again consistent with those reported for mid-lanthanide DOTA and amide derivatives.[21] The axial position is occupied by a water molecule; the interatomic distance between the oxygen atom and the terbium ion is 2.415(4) Å. This value is comparable to that measured for the Gd·**7** (2.429(5) Å), and to [Gd·DOTA(OH_2)]$^-$ (2.463 Å), [Gd·DOTAM(OH_2)]$^{3+}$ (2.395 Å) and related terbium triamide complexes.[22]

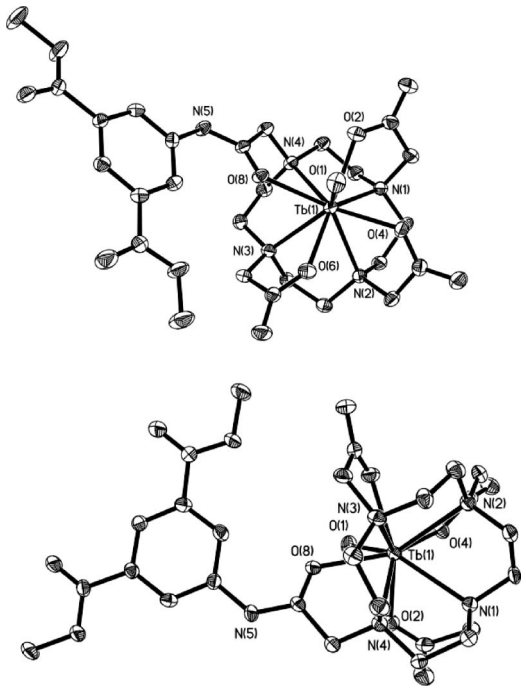


Fig. 3 Thermal ellipsoid drawings of Tb·**5** at the 50% probability level, H atoms and lattice water molecules removed for clarity. Top: perspective above the plane of the aza macrocycle. Bottom: perspective in the mean plane of the isophthalate ring. Selected distances (Å) and angles (°): Tb(1)–O(1) 2.415(4), Tb(1)–O(2) 2.364(3), Tb(1)–O(4) 2.295(3), Tb(1)–O(6) 2.365(3), Tb(1)–O(8) 2.409(3), Tb(1)–N(1) 2.612(4), Tb(1)–N(2) 2.659(4), Tb(1)–N(4) 2.654(4); O(4)–Tb(1)–O(2) 87.57(12), O(2)–Tb(1)–O(6) 146.11(13), O(6)–Tb(1)–O(8) 83.67(11), O(8)–Tb(1)–O(1) 69.56(12), O(6)–Tb(1)–N(1) 140.41(12), N(1)–Tb(1)–N(3) 104.00(13), N(1)–Tb(1)–N(4) 69.08(13), N(4)–Tb(1)–N(2) 105.65(12), N(1)–Tb(1)–N(2) 67.81(12).

The solid state structure clearly correlates closely with the structure in solution in this case. Though attempts to crystallise Ln·**6** complexes proved unsuccessful, the similarities between solution state data for Ln·**5** and Ln·**6** suggest that this structural motif persists in the fully deprotected form.

Conclusions

Isophthalate appended DOTA-monoamide derivatives form stable and well-defined complexes in solution and in the solid phase. The dominant form is a nine-coordinate square antiprismatic diastereoisomer with a single water molecule bound to the metal ion. This structural motif is well suited to applications in luminescence spectroscopy and contrast imaging. Furthermore, the two carboxylic acid groups lend themselves to further functionalisation with chromophores or targeting vectors. In the latter case, this complex offers the potential for functionalisation with more than one vector, raising the possibility of chelating interactions that can enhance specificity. We are currently investigating these possibilities.

Experimental

General methods

Cyclen was purchased from Strem Chemicals, and other reagents, solvents and starting materials were obtained from the Aldrich Chemical Company. All chemicals were used as supplied.

Mass spectra were obtained using positive electrospray in acetonitrile or methanol solutions on a Micromass Platform II spectrometer, or by MALDI using methanol solutions with an ALPHA matrix on a Micromass TOF Spec 2E spectrometer.

Elemental analyses were performed using a Carlo ERBA Instruments CHNS-O EA1108 elemental analyzer (C, H, N and S analysis) and a Fisons Horizon Elemental Analysis ICP-OED spectrometer for metals and halogens.

Absorption spectra were recorded in H_2O on a T60U spectrometer (PG Instruments Ltd.) using fused silica cells with a path length of 1 cm.

NMR spectra of the complexes were recorded at 500 MHz and 295 K unless otherwise stated, using millimolar solutions of the complex and referencing spectra to the water peak at 4.7 ppm. Spectra were acquired over 5000 repetitions using an acquisition time of 0.1 s, relaxation delay of 0.1 s, and appropriate spectral widths of up to 500 kHz.

Preparation of ligands and complexes

1,3-Dimethyl-5-aminoisophthalate acetylchloride, (2). Dimethyl-5-aminoisophthalate (1.02 g, 4.79 mmol) was dissolved in dichloromethane (50 cm^3), and then $NaHCO_3$ (5.08 g, 47.9 mmol) was added to the stirring mixture. Chloroacetyl chloride (0.53 g, 0.37 cm^3, 4.79 mmol) was added drop-wise to the solution, and then the mixture was stirred at room temperature for 24 h. Dichloromethane (200 cm^3) was added to the mixture, which was then filtered. The filtrate was evaporated under reduced pressure, to produce a creamy beige/white solid. The crude product was then recrystallised using minimum hot DCM (~75 cm^3) to leave the product as a white solid, (1.29 g, 93%). ES^- MS (MeCN): m/z 284 $\{M - H\}^+$; ES^+ MS (MeCN): m/z 308 $\{M + Na\}^+$; ^1H NMR (400 MHz, $CDCl_3$, 300 K) δ_H (ppm) 3.8 (6H, s, 2C$\underline{H}_3$), 4.2 (2H, s, C$\underline{H}_2$-Cl), 8.4 (3H, s, Ar-$\underline{H}$), 8.5 (1H, s, N$\underline{H}$); $^{13}C\{^1H\}$ NMR (400 MHz, MeOD, 300 K) δ_C (ppm) 42.8 ($CO_2\underline{C}H_3$), 52.6 ($CO\underline{C}H_2Cl$), 125.1, 127.3, 131.7, 137.2 (Ar-$\underline{C}$), 164.1 ($\underline{C}ONH$), 165.7 (Ar-$\underline{C}O_2CH_3$); IR(ATR): ν (C═O) 1716 cm^{-1}, (C═O) 1683 cm^{-1}, (N–H) 1547 cm^{-1}; CHN expected for $C_{12}H_{12}NO_5Cl$: C, 50.45; H, 4.23; N, 4.90; found: C, 50.21; H, 4.15; N, 4.86.

Tris-*tert*-butyl 1,4,7,10-tetraazacyclododecane-1,4,7-triacetate hydrobromide salt (3). Prepared as described in ref. 14.

1,4,7-Tris-(*tert*-butoxycarbonylmethyl)-10-acetyldimethyl-5-aminoisophthalate-1,4,7,10-tetraazacyclododecane, (4). Triester **3** (1.02 g, 1.98 mmol) was dissolved in acetonitrile (30 cm^3), then caesium carbonate (3.18 g, 9.78 mmol) was added to the stirring solution. Dimethyl-5-aminoisophthalate acetylchloride **2** (0.55 g, 1.98 mmol) was dissolved in acetonitrile (10 cm^3), and added drop-wise to the triester mixture. The mixture was stirred at room temperature for 5 d, and was monitored by TLC. The solution was filtered and the filtrate was evaporated under reduced pressure to yield a yellow solid. The yellow solid was dissolved in minimum hot methanol (~10 cm^3), from which the product crystallised out as a white powder overnight in the fridge (0.51 g, 34%). λ_{max} ($\pi \rightarrow \pi^*$) = 263 nm (ε 11 588 M^{-1} cm^{-1}); ES^+ MS (MeCN): m/z 764 $\{M + H\}^+$, 785 $\{M + Na\}^+$; ^1H NMR (400 MHz, $CDCl_3$, 300 K) δ_H 1.3 (81H, m, CC$\underline{H}_3$), 2.6, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4 (24H, m,

N-CH$_2$ and NCH$_2$CO), 8.3 (1H, s, ArH), 8.5 (2H, s, ArH); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$, 300 K) δ_C 28.2 (CCH$_3$), 50.8, 51.9, 52.3, 52.9, 55.2, 56.0, 56.9, 59.0 (CO_2CH_3, N-CH$_2$CONH, N-CH$_2$ and N-CH$_2$COO), 80.8, 81.1 (CCH$_3$), 124.7, 125.8, 131.1, 139.2 (Ar-C), 166.2 (CONH), 170.5, 170.7, 171.2 (CO_2CH_3 and CO_2CCH_3); IR(ATR): ν (C=O) 1720 cm^{-1}, (C=O) 1682 cm^{-1}; CHN expected for $C_{38}H_{61}N_5O_{11}$: C, 59.75; H, 8.05; N, 9.17. Found: C, 59.46; H, 8.21; N, 8.99.

10-Acetyldimethyl-5-aminoisophthalate-1,4,7,10-tetraazacyclododecane-1,4,7-triacetate (H_3·5). 1,4,7-Tris-(*tert*-butoxycarbonylmethyl)-10-acetyldimethyl-5-aminoisophthalate-1,4,7,10-tetraazacyclododecane **4** (0.6 g, 7.9 × 10^{-4} mol) was dissolved in dichloromethane (10 cm^3) and trifluoroacetic acid (10 cm^3) was added drop-wise to the stirring solution. The reaction mixture was stirred at room temperature for 24 h. The solvents were then removed *in vacuo* and the residue was washed repeatedly with dichloromethane (3 × 10 cm^3) and methanol (5 × 10 cm^3). This yielded a hygroscopic yellow solid (0.43 g, 91%). λ_{max} ($\pi\rightarrow\pi^*$) = 261 nm (ε 79 250 M^{-1} cm^{-1}); Maldi MS (α-MeOH): *m*/*z* 596 {M+H}$^+$; ^{1}H NMR (400 MHz, D_2O, 300 K) δ_H 3.0–3.6 (24H, broad signal, N-CH$_2$ and NCH$_2$CO), 3.9 (6H, s, CO_2CH_3), 8.15 (2H, s, arH), 8.25 (1H, s, ArH); ^{13}C{^{1}H} NMR (400 MHz, D_2O, 300 K) δ_C 50.9, 54.9 (broad signal, CO_2CH_3, N-CH$_2$CONH, N-CH$_2$ and N-CH$_2$COO), 114.9, 117.6, 125.2, 126.2, 130.9 (Ar-C), 162.3, 163.4, 167.5 (CONH, CO_2CH_3 and COOH); IR(ATR): ν (C=O) 1718 cm^{-1}, (C=O) 1664 cm^{-1}, (N–H) 1574 cm^{-1}; CHN expected for $C_{26}H_{37}N_5O_{11}(CF_3COOH)(H_2O)_2$: C, 45.10; H, 5.68; N, 9.39. Found: C, 45.69; H, 5.95; N, 9.19.

10-Acetyldicarboxylic acid-5-aminoisophthalate-1,4,7,10-tetraazacyclododecane-1,4,7-triacetate sodium salt, (Na_5·6). H_3·5 (0.2 g, 3.36 × 10^{-4} mol) was dissolved in distilled water (2 cm^3), then 5 molar equivalents of NaOH (1.67 cm^3, 1 M) were added drop-wise to the stirring solution. The solution was stirred at room temperature for 5 h. Any precipitate was filtered off, before adding an excess of acetone to the filtrate, until the solution went cloudy. The solution was kept in the fridge overnight, where an orange oil formed at the bottom of the flask. The solution was carefully decanted off, to leave behind the orange oil product, which was dried overnight under vacuum, to yield the product (0.13 g, 68%). Maldi MS (α-MeOH): *m*/*z* 568 {M+H}$^+$, 590 {M+Na}$^+$, 612 {M-H+2Na}$^+$, 634 {M-2H+3Na}$^+$, 656 {M-3H+4Na}$^+$; ^{1}H NMR (400 MHz, D_2O, 300 K) δ_H 2.2, 2.4, 2.6, 2.9, 3.2, 3.3 (24H, br m, N-CH$_2$ and N-CH$_2$CO), 7.8 (2H, s, Ar-H), 7.9 (1H, s, Ar-H); ^{13}C {^{1}H} NMR (400 MHz, D_2O, 300 K) δ_C 56.9, 58.6, 58.7, 59.3 (broad signal, N-CH$_2$CONH, N-CH$_2$ and N-CH$_2$COO), 123.9, 124.1, 125.6, 136.9, 137.4 (Ar-C), 172.2, 173.5, 174.3, 180.2, 180.3, 180.4 (CONH, Ar-CO_2H and COOH); IR(ATR): ν (O–H) 3319 cm^{-1}, (C=O) 1695 cm^{-1}, (N–H) 1590 cm^{-1}; CHN expected for $C_{24}H_{27}N_5O_{11}Na_6(NaOH)_6\cdot 6H_2O$: C, 27.52; H, 4.33; N, 6.69; Na, 26.34. Found: C, 27.91; H, 4.24; N, 6.57; Na, 26.78.

General procedure for the preparation of Ln·5

5 (0.13 g, 1.4 × 10^{-4} mol) was dissolved in the minimum volume of methanol (3 cm^3), and mixed with a solution of the lanthanide triflate salt (1.0 eq, 1.4 × 10^{-4} mol) in methanol (3 cm^3). The solution was stirred at room temperature for 7 d. The solution was filtered, and the filtrate was evaporated under reduced pressure to yield a colourless oil. To the residue minimum ethanol (3 cm^3) was added, followed by the addition of diethyl ether until precipitate formed. The white precipitate was filtered, washed with diethyl ether and dried under vacuum to give the product.

Nd·5 (0.09 g, 88%). λ_{max} ($\pi\rightarrow\pi^*$) = 260 nm (ε 2102 M^{-1} cm^{-1}); Maldi MS (α-MeOH) *m*/*z*: 596 {M-Nd + H}$^+$, 737 {M + 3H}$^+$; NMR (500 MHz, D_2O, 295 K) δ_H –20.0, –7.7, –6.1, 10.2, 16.9, Only major resolved peaks outside the range +10 to –5 ppm reported; IR (ATR): ν (C=O) 1722 cm^{-1}, (C=O) 1581 cm^{-1}; Luminescence: λ_{em} = 1055 nm, λ_{ex} = 337 nm, $\tau_{(H_2O)}$ = 144 ns, $\tau_{(D_2O)}$ = 376 ns.

Eu·5 (0.10 g, 96%). λ_{max} ($\pi\rightarrow\pi^*$) = 260 nm (ε 1547 M^{-1} cm^{-1}); Maldi MS (α-MeOH) *m*/*z*: 598 {M-Eu + 3H}$^+$, 748 {M+3H}$^+$, 768 {M+Na+2H}$^+$, 1492 {Mx2+2H}$^+$; NMR (500 MHz, D_2O, 295 K) δ_H –17.3, –15.9, –14.5, –13.4, –10.1, –7.8, –7.6, –4.7, –3.4, –2.8, –0.01, 1.5, 7.5, 8.5, 9.1, 9.2, 30.1, 30.5, 31.4, 34.4 (only major resolved peaks outside the range +2 to +6 ppm reported); IR (ATR): ν (C=O) 1721 cm^{-1}, (C=O) 1582 cm^{-1}; Luminescence: λ_{em} = 617 nm, λ_{ex} = 260 nm, $\tau_{(H_2O)}$ = 0.55 ms, $\tau_{(D_2O)}$ = 1.83 ms, *q* = 1.1.

Gd·5 (0.05 g, 45%). λ_{max} ($\pi\rightarrow\pi^*$) = 260 nm (ε 33 100 M^{-1} cm^{-1}); Maldi MS (α-MeOH) *m*/*z*: 595 {M-Gd}$^+$, 751 {M+H}$^+$, 1500 {Mx2}$^+$; IR (ATR): ν (C=O) 1718 cm^{-1}, (C=O) 1583 cm^{-1}; CHN expected for $C_{26}H_{34}N_5O_{11}(H_2O)_4$: C, 38.00; H, 5.15; N, 8.52; Gd, 19.13. Found: C, 38.00; H, 4.69; N, 8.48; 19.37.

Tb·5 (0.10 g, 90%). λ_{max} ($\pi\rightarrow\pi^*$) = 260 nm (ε 2832 M^{-1} cm^{-1}); Maldi MS (α-MeOH) *m*/*z*: 596 {M-Tb + H}$^+$, 752 {M+H}$^+$; NMR (500 MHz, D_2O, 295 K) δ_H –411.6, –370.8, –359.1, –147.8, –142.4, –126.6, –114.4, –100.7, –95.9, –88.9, –79.4, –63.9, –52.9, 84.2, 125.8, 131,9, 181.0, 189.1, 230.8, 246.7 (only major peaks outside the range +60 to – 45 ppm reported); IR (ATR): ν (C=O) 1721 cm^{-1}, (C=O) 1582 cm^{-1}; CHN expected for $C_{26}H_{34}N_5O_{11}Tb\cdot(CF_3COOH)_3(H_2O)_3$: C,33.49; H, 3.78; N, 6.10; Tb, 13.84. Found: C, 29.39; H, 3.61; N, 6.02; Tb, 14.32. Luminescence: λ_{em} = 545 nm, λ_{ex} = 260 nm, $\tau_{(H_2O)}$ = 1.63 ms, $\tau_{(D_2O)}$ = 2.73 ms, *q* = 0.9.

Er·5 (0.07 g, 66%). λ_{max} ($\pi\rightarrow\pi^*$) = 260 nm (ε 1984 M^{-1} cm^{-1}); Maldi MS (α-MeOH) *m*/*z*: 597 {M-Er + H}$^+$, 760 {M}$^+$, 1520 {Mx2}$^+$; NMR (500 MHz, D_2O, 295 K) δ_H –84.4, –77.9, –70.7, –67.6, –59.0, –55.2, –37.9, –33.5, –30.0, 14.9, 21.4, 22.7, 25.5, 33.9, 130.2, 133.4, 144.6, 152.7 (only major peaks outside the range +10 to –20 ppm reported); IR (ATR): ν (C=O) 1722 cm^{-1}, (C=O) 1582 cm^{-1}; Luminescence: λ_{em} = 1530 nm, λ_{ex} = 337 nm, $\tau_{(D_2O)}$ = 805 ns.

Yb·5 (0.09 g, 84%). λ_{max} ($\pi\rightarrow\pi^*$) = 260 nm (ε 967 M^{-1} cm^{-1}); Maldi MS (α-MeOH) *m*/*z*: 596 {M-Yb + H}$^+$, 767 {M+H}$^+$, 1534 {Mx2 + 2H}$^+$; NMR (500 MHz, D_2O, 295 K) δ_H –73.5, –72.9, –72.1, –70.5, –61.4, –60.4, –45.6, –42.7, –24.6, –23.8, –18.9, –10.7, 10.8, 12.5, 14.1, 16.2, 16.5, 17.0, 23.1, 28.3, 35.9, 112.0, 114.2, 118.5, 129.5 (only major peaks outside the range +10 to –4 ppm reported); IR (ATR): ν (C=O) 1719 cm^{-1}, (C=O) 1584 cm^{-1}; Luminescence: λ_{em} = 980 nm, λ_{ex} = 337 nm, $\tau_{(H_2O)}$ = 0.78 μs, $\tau_{(D_2O)}$ = 5.21 μs, *q* = 0.9.

General procedure for the preparation of [Ln·6]$^{2-}$

Na_5·6 (0.05 g, 4.8 × 10^{-5} mol) was dissolved in distilled water (1 cm^3), and the pH was adjusted from pH 11 to pH 5 by

adding dilute HCl (~3 cm^3, 1 M) to the solution. A solution of the lanthanide triflate salt dissolved distilled water (1 cm^3) was then added drop-wise to the mixture. The solution was heated at 60 °C for 18 h. The solvent was then evaporated under reduced pressure to yield a white solid. Minimum ethanol (3 cm^3) was added to dissolve the white residue, followed by the addition of excess diethyl ether until the white product precipitated out. The solution was filtered using a filter stick under vacuum, and the hygroscopic white product was then washed with diethyl ether and dried under vacuum to give the product.

[Nd·6]$^{2-}$ (0.02 g, 67%). Maldi MS (α-MeOH) *m/z*: 710 {M+4H}$^+$, 1418 {Mx2 + 6H}; IR (KBr): *ν* (O–H) 3449 cm^{-1}, (C═O) 1702 cm^{-1}, (N–H) 1614 cm^{-1}. Luminescence: λ_{em} = 1055 nm, λ_{ex} = 337 nm, $\tau_{(H_2O)}$ = 110 ns, $\tau_{(D_2O)}$ = 340 ns.

[Eu·6]$^{2-}$ (0.03 g, 81%). λ_{max} ($\pi \rightarrow \pi^*$) = 260 nm (ε 4700 M^{-1} cm^{-1}); Maldi MS (no matrix) *m/z*: 718 {M+H}$^+$; ^{1}H NMR (500 MHz, D_2O, 300 K) δ_H (ppm) –17.5, –16.5, –16.2, –14.9, –14.6, –13.6, –13.2, –12.6, –12.2, –11.7, –10.5, –8.3, –7.9, –7.3, –6.9, –5.1, –3.9, –3.2, –1.2, –0.7, –0.1, +1.0, +1.2, +8.9, +11, +12, +13.5, +29.3, +29.8, +30.7, +34.1 (only major resolved peaks outside the range +3 to +5 ppm reported); IR (ATR): *ν* (O–H) 3427 cm^{-1}, (C═O) 1708 cm^{-1}, (N–H) 1582 cm^{-1}; Luminescence: λ_{em} = 617 nm, λ_{ex} = 260 nm, $\tau_{(H_2O)}$ = 0.57 ms, $\tau_{(D_2O)}$ = 2.18 ms, *q* = 1.2.

[Tb·6]$^{2-}$ (0.03 g, 87%). λ_{max} ($\pi \rightarrow \pi^*$) = 260 nm (ε 3840 M^{-1} cm^{-1}); Maldi MS (α-MeOH) *m/z*: 746 {M+Na}$^+$, 768 {M+2Na – H}$^+$, 790 {M+3Na – 2H}$^+$, 1447 {Mx2 + H}$^+$, 1470 {Mx2+Na + H}$^+$, 1491 {Mx2 + 2Na – H}$^+$, 1513 {Mx2 + 3Na – 2H}$^+$, 1535 {Mx2 + 4Na – 3H}$^+$, 1557 {Mx2 + 5Na – 4H}$^+$, 1578 {Mx2 + 6Na – 6H}$^+$; ^{1}H NMR (500 MHz, D_2O, 300 K) δ_H (ppm) –405.4, –364.6, –352.4, –144.7, –127.3, –121.3, –111.9, –100.6, –96.8, –77.9, –73.7, –66.3, –63.9, –54.2, +83.9, +117.4, +125.2, +138.0, +169.5, +224.2, +234.3, +238.7, +247.8, +262.7 (only major resolved peaks outside the range –40 to +100 ppm reported), IR (KBr): *ν* (O–H) 3446 cm^{-1}, (C═O) 1700 cm^{-1}, (N–H) 1617 cm^{-1}; Luminescence: λ_{em} = 545 nm, λ_{ex} = 260 nm, $\tau_{(H_2O)}$ = 1.69 ms, $\tau_{(D_2O)}$ = 3.03 ms, *q* = 1.0.

[Er·6]$^{2-}$ (0.03 g, 81%). λ_{max} ($\pi \rightarrow \pi^*$) = 260 nm (ε 4660 M^{-1} cm^{-1}); Maldi MS (α-MeOH) *m/z*: 755 {M+Na}$^+$, 778 {M+2Na}$^+$, 800 {M+3Na – 1H}$^+$, 1468 {Mx2 – 4H}$^+$, 1486 {Mx2+Na – 1H}$^+$, 1508 {Mx2 + 2Na – 2H}$^+$, 1530 {Mx2 + 3Na – 3H}$^+$, 1551 {Mx2 + 4Na – 5H}$^+$, 1572 {Mx2 + 5Na – 7H}$^+$; ^{1}H NMR (500 MHz, D_2O, 300 K) δ_H (ppm) –98.5, –82.9, –76.6, –69.5, –66.2, –57.6, –54.9, –37.9, –37.4, –33.4, –29.9, +21.0, +21.9, +34.0, +129.4, +132.2, +143.8, +152.5, +159.7 (only major resolved peaks outside the range –20 to +20 ppm reported); IR (KBr): *ν* (O–H) 3437 cm^{-1}, (C═O) 1697 cm^{-1}, (N–H) 1631, 1608 and 1586 cm^{-1}.

[Yb·6]$^{2-}$ (0.03 g, 89%). λ_{max} ($\pi \rightarrow \pi^*$) = 260 nm (ε 6120 M^{-1} cm^{-1}); Maldi MS (α-MeOH) *m/z*: 761 {M+Na}$^+$, 783 {(M+6H + K}$^+$, 1498 {Mx2 – H + Na}$^+$; ^{1}H NMR (500 MHz, D_2O, 300 K) δ_H (ppm) –81.6, –72.9, –72.0, –70.8, –69.2, –61.6, –57.9, –45.2, –44.1, –41.9, –37.5, –26.2, –24.4, –18.5, –9.9, +19.8, +22.1, +24.1, +29.4, +37.4, +110.9, +115.5, +119.0, +132.1, +132.8 (only major resolved peaks outside the range –5 to +19 ppm reported); IR (KBr): *ν* (O–H) 3488 cm^{-1}, (C═O) 1694 cm^{-1}, (N–H) 1633, 1614 and 1588 cm^{-1}.

Photophysical measurements

Steady state and time-resolved luminescence properties of the terbium and europium complexes were determined using a Perkin-Elmer LS55 fluorimeter operating in phosphorescence mode counting. In the case of the erbium, ytterbium and neodymium complexes, the sample was excited using a pulsed nitrogen laser (337 nm) operating at 10 Hz. Light emitted at right angles to the excitation beam was focused onto the slits of a monochromator, which was used to select the appropriate wavelength. The growth and decay of the luminescence at selected wavelengths was detected using a germanium photodiode (Edinburgh Instruments, EI-P) and recorded using a digital oscilloscope (Tektronix TDS220) before being transferred to a PC for analysis. Luminescence lifetimes were obtained by iterative reconvolution of the detector response (obtained by using a scatterer) with exponential components for growth and decay of the metal centred luminescence, using a spreadsheet running in Microsoft Excel. The details of this approach have been discussed elsewhere.[23] Unless otherwise stated, fitting to a double exponential decay yielded no improvement in fit as judged by minimisation of residual squared and reduced chi squared.

X-Ray crystallography

X-Ray diffraction data for Tb·**5** were collected at 150 K using a Bruker APEX II CCD diffractometer on station 9.8 of the Synchrotron Radiation Source at CCLRC Daresbury Laboratory, at 0.69040 Å, from a silicon 111 monochromator using ω scans. The structure was solved by direct methods using SHELXS-97.[24] The structure was completed by iterative cycles of Δ*F*-syntheses and a full matrix least squares refinement. All non-H atoms were refined anisotropically and difference Fourier syntheses were employed in positioning idealised hydrogen atoms and were allowed to ride on their parent C or N-atoms. All refinements were against F^2 and used SHEL-XL-97.[25]

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