Synthesis and characterisation of bis-cyclen based dinuclear lanthanide complexes

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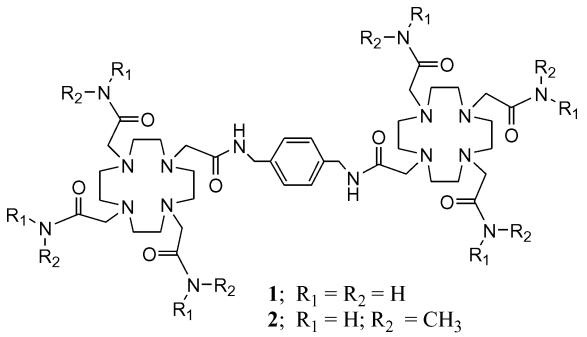
The design and synthesis of several bis-macrocyclic cyclen (1,4,7,10-tetraazacyclododecane) ligands and their corresponding lanthanum or europium complexes is described; these dinuclear lanthanide systems were made by connecting two macrocyclic cyclen moieties through a rigid, covalent, *p*-xylylenediamide bridge or a flexible aliphatic hexane bridge. These ligands were subsequently functionalised with six acetamide pendant arms ($CONR_1R_2$: $R_1 = R_2 = H$ or CH_3, or $R_1 = H$, $R_2 = CH_3$). The corresponding lanthanide bis-complexes were then formed by reaction with La(III) and Eu(III) triflates, yielding overall cationic (+VI charged) complexes.

Introduction

Currently, there is significant interest in the development of synthetic enzyme mimics, based on functionalised macrocyclic ligands, which can catalyse or accelerate the hydrolysis or cleavage of phosphate esters.[1,2,3] Such macrocycle design gives rise to a reorganised platform where cofactors commonly employed by natural substrates can be included with the aim of achieving fast and affective hydrolysis. We have, over the past few years, synthesised many such mimics based on the use of divalent transition and trivalent lanthanide ion coordination complexes.[4] For the latter, we have focused our efforts on the use of the macrocycle 1,4,7,10-tetraazacyclododecane, or cyclen, as such a structural platform for the synthesis of mononuclear lanthanide complexes. In these, the four ring nitrogen moieties of cyclen have been functionalised using acetamides, small peptides, simple amines and heterocyclic units as cofactors. These structures have given rise to kinetically and thermodynamic stable complexes with lanthanide ions such as Eu(III) and La(III). These aforementioned synthetic modifications have also given rise to significant enhancements in the rate of hydrolysis of the RNA model compound HPNP (2-hydroxypropyl-*p*-nitrophenylphosphate), commonly used for such studies, and in the cleavage of mRNA strands.

Many enzymes that promote phosphodiester hydrolysis utilise more than one metal centre.[1,2,5,6,7] Because of this, ribonuclease mimics have recently been reported where two or more transition metal ions have been employed within a single molecule.[2,8,9–19,20–24] However, the development of such lanthanide-based macrocycles is less common. Herein, we present the design and synthesis of several bis-macrocyclic, dinuclear lanthanide systems **1**–**3** and **16**, and their Eu(III) and La(III) complexes with the aim of achieving cooperative effects between two metal centres, and hence faster hydrolysis of phsophodiesters. Our strategy was to connect the two macrocyclic complexes together with a covalent spacer that would be either rigid (as in the case of **1**–**3**) or flexible, *e.g.* **16**. The cyclen macrocycle was chosen as the basic template for the ligand in order to allow comparison with mononuclear lanthanide systems previously reported by us[4] and by Morrow *et al.*[20] To the best our knowledge, **1**–**3** and **16** are the first examples of such dinuclear cyclen lanthanide complexes.



1; $R_1 = R_2 = H$
2; $R_1 = H$; $R_2 = CH_3$
3; $R_1 = R_2 = CH_3$

Results and discussion

Design and synthesis

Our design consisted of a simple spacer (aliphatic or aromatic) separating the cyclen lanthanide complexes. Each cyclen structure has eight coordinating sites, with four of these coordination sites provided by the nitrogens of the ring and the remaining four provided by amide functionalities, three of which consist of simple acetamide pendant arms, while the fourth amide is part of the spacer structure itself. As the lanthanide ions have high coordination requirements, the remaining coordination sites are expected to be occupied by solvent molecules such as water, one for Eu(III) and two for La(III).†

Our first target in the current study was the incorporation of a xylylene bridge into the cyclen structure, yielding the ligands **1**, **2** and **3**, Scheme 1. The synthesis of 1,4-bis-(2-chloro-acetylamino)-xylylene, **7** was attempted in several organic solvents, by acylation

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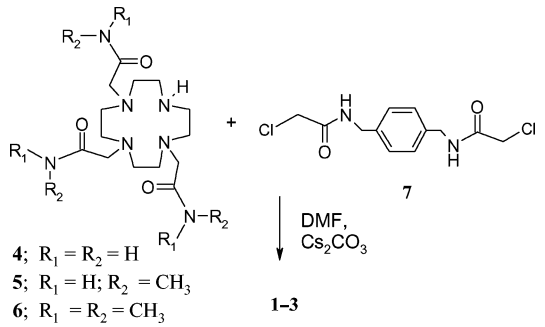
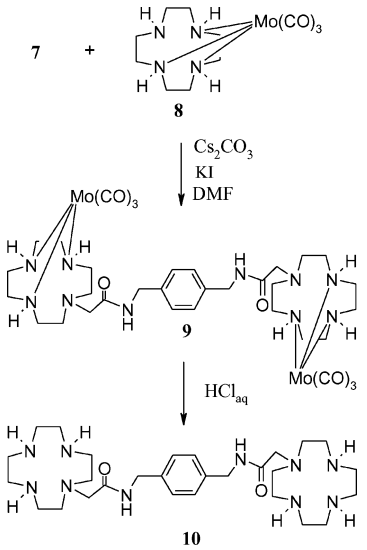
† Even though this design was aimed towards achieving enhanced activity in phosphodiester hydrolysis, it is also applicable for use in other fields such as the development of novel contrast agents for magnetic resonance imaging. We are currently investigating this.



Scheme 1 Attempted synthesis of **1**–**3** using the alkylation of **7** by the heptadentate cyclen ligands such as **6** in DMF.

of *p*-xylylenediamine using chloroacetyl chloride in the presence of a base, such as triethylamine. Unfortunately, these conditions only gave the desired product in low yield and often highly impure. Consequently, we attempted the synthesis of **7** using modified Schotten–Baumann conditions, by carrying out the reaction in water in the presence of NaOH, rather than in the usual two solvent phase mixture. This modified procedure involved reacting the diamine, along with four equivalents of NaOH in H_2O with four equivalents of chloroacetyl chloride. The resulting solution was left to stir overnight and the desired product **7**, precipitated out of solution and was isolated by filtration in 75% yield with no need for further purification. This method was further investigated in our laboratory and extended to the formation of a range of other aliphatic and aromatic based α-chloroamides and shown to be highly successful.

We have recently developed a method for the formation of heptadentate triamide ligands of cyclen in one-step synthesis from the corresponding α-chloroamides and cyclen.[25a] Consequently, the synthesis of **1**–**3** was attempted by reacting the corresponding ligands **4**–**6**, with **7**. The synthesis of **3** was first attempted by reacting **6** with **7** in DMF and in the presence Cs_2CO_3 at 80 °C, Scheme 1. Unfortunately, the desired product was only obtained in low yield of 16% after a tedious workup. Due to the insolubility of **7** in many organic solvents such as CH_3CN, THF and CH_3Cl (only partially soluble) this alkylation was not particularly successful and as a result this approach was abandoned. Instead, we attempted the synthesis of **1**–**3** using an alternative method developed by Parker *et al.*, which involved the use of a molybdenum carbonyl protected cyclen complex, formed by reacting cyclen with molybdenum hexacarbonyl under inert atmosphere in dry dibutyl ether.[25b] The product, 1,4,7-molybdenum tris carbonyl-(1,4,7,10-tetraazacyclododecane) **8**, which allows for the selective functionalisation of one of the amino moieties of the ring, was isolated by filtration in 88% yield. This was reacted with half an equivalent of **7**, in the presence of one equivalent of both Cs_2CO_3 and KI in DMF, Scheme 2. The resulting solution was then heated at 85 °C for 40 h. After filtration, the DMF was removed under reduced pressure and the resulting residue was left stirring overnight in an aqueous solution of HCl (15% *v*/*v*), in order to deprotect the cyclen moieties. Following this, the solution was washed with CH_2Cl_2 and the pH of the aqueous fraction was adjusted to *ca.* 13 using KOH (pellets). This solution was then extracted with CH_2Cl_2 and the resulting organic solution was dried over K_2CO_3 before the solvent was removed under reduced pressure. The desired product

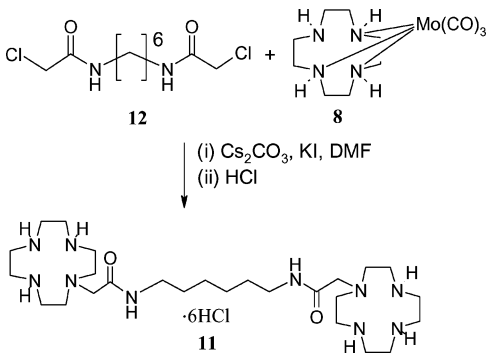


Scheme 2 Synthesis of the bis-cyclen macrocycle **10** from molybdenum tris carbonyl-(1,4,7,10-tetraaza-cyclododecane) (**8**).

10 was isolated as yellow oil in 41% yield. The inherent symmetry of **10** was evident in the ^{1}H NMR where the aromatic protons resonated as a singlet at 7.25 ppm (overlapping with the $CDCl_3$ signal). The four benzylic protons appeared at 4.38 ppm, while the acetamide protons resonanced at 3.19 ppm. The cyclen protons appeared as two singlets at 2.61 and 2.50 ppm, respectively. The ^{13}C NMR spectra of **10** showed the presence of one carbonyl group at 171.1 ppm, while the aromatic signals were observed at 137.2 and 127.7 ppm, respectively. The mass spectrum presented signals at *m*/*z* 561.4, 583.4, 599.4 and 281.2 corresponding to the [M + H], [M + Na], [M + K] and [M + 2H]/2 species, respectively.

The intermediate **10** allows for the incorporation of six further amide or carboxylate pendant arms, and as such is an ideal scaffold for the further development of new lanthanide ion complexes. We are currently in the process of constructing a large library of such molecules using amino acids, dipeptides, amines and heterocyclic moieties which can be incorporated into **10**, *via* the corresponding α-chloroamide.

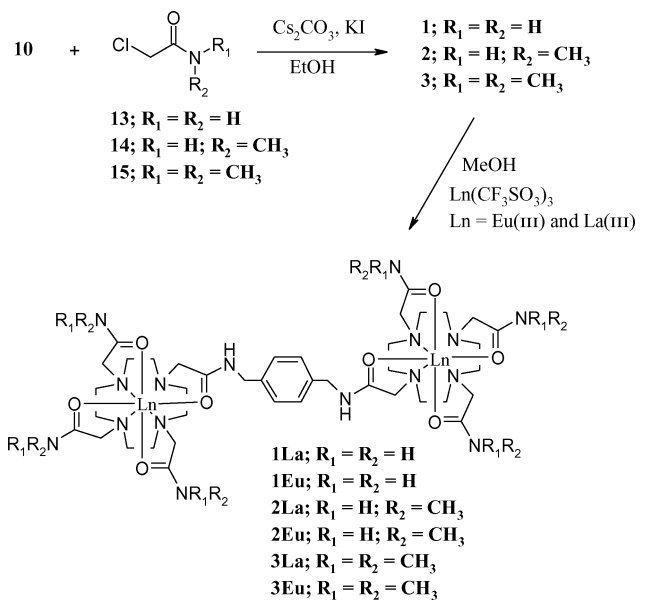
The hexane spacer analogue **11**, was also synthesised under similar conditions by stirring **8** with half an equivalent of **12** in DMF at 85 °C for 40 h, in the presence of two equivalents of Cs_2CO_3 and KI, Scheme 3. However, unlike **10**, **11** was isolated as its hydrochloride salt in 37% yield after precipitation from a



Scheme 3 Synthesis of the bis cyclen macrocycle unit **11**, from the aliphatic diamide spacer **12**.

EtOH–conc. HCl 5 : 1 solution. As in the case of **10**, the ^{1}H NMR of **11** in D_2O was relatively simple due to the high degree of symmetry in the molecule. The two acetamide protons were observed at 3.31 ppm, while the cyclen protons resonated as two broad signals at 3.06 and 2.88 ppm, respectively. The three sets of methylene protons from the alkyl spacer were observed at 2.88 ppm (overlapping with 8 cyclen protons), 1.39 and 1.20 ppm, respectively. The mass spectrum contained two signals at *m*/*z* 541.6 and 271.4 corresponding to the [M + H] and [M + 2H/2] species. Elemental analysis confirmed the presence of the six HCl molecules.

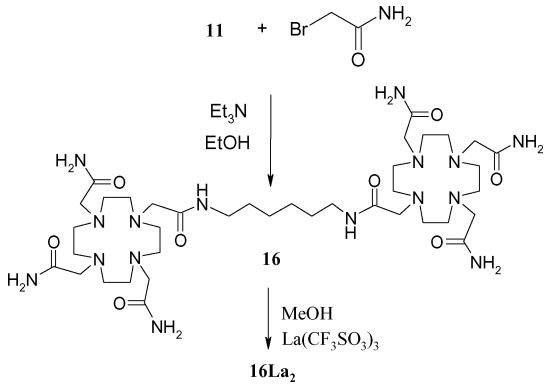
Having obtained **10** and **11**, the remaining amino moieties of the cyclen rings were functionalised with pendant amide arms, which would fulfil the high coordination requirements of the lanthanide ions. Initially, simple acetamide arms (Scheme 4) were investigated in order to probe the validity of the bis lanthanide systems as cleaving agents for phosphodiester hydrolysis as they would allow comparison with analogous mononuclear lanthanide systems previously reported by Morrow *et al.* The three pendant arms employed in this case were, 2-chloroacetamide, **13**, 2-chloro-*N*-methylacetamide **14** and 2-chloro-*N*,*N*-dimethylacetamide, **15**. As previously mentioned, the bis-cyclen ligand **10**, was only sparingly soluble in solvents such as MeCN, CH_2Cl_2 and $CHCl_3$ and using these solvents, the alkylation did not proceed, even under reflux. Consequently, the reactions were conducted in refluxing EtOH solution in the presence of KI and the relevant base. The primary amide **1**, was isolated in 57% yield, after precipitation from CH_2Cl_2, followed by recrystallisation from boiling EtOH. In a similar way, **2** was isolated in 30% yield, whereas, **3** was found to be soluble in CH_2Cl_2 and so was isolated in 38% yield after washing with H_2O and 0.1 M HCl solutions.



Scheme 4 Synthesis of the three ligands **1**–**3** and their corresponding La(III) and Eu(III) complexes.

The ^{1}H NMR in D_2O (400 MHz) of **1**, revealed the expected high degree of symmetry, where four aromatic protons resonated at 7.16 ppm while the benzyl protons were observed at 4.26 ppm. The ^{13}C NMR was more confirmative, revealing the presence of three signals at 173.8, 173.4 and 170.2 ppm for the amide carbonyls, respectively, while the aromatic carbon signals were observed at 136.6 and 127.1 ppm, respectively. Eight methylene signals were also observed between at 58.1 and 42.2 ppm. High-resolution mass spectrometry and elemental analysis both confirmed that the desired product had been formed. Characterisation of **2** and **3** yielded similar results (see the Experimental section).

In a similar manner the hexane linker analogue of **1** was synthesised by refluxing **11** in EtOH, with seven equivalents of bromoacetamide in the presence of fourteen equivalents of Et_3N. A large excess of Et_3N was needed, as **11** had been synthesised as the hexa-HCl salt. The desired product **16**, Scheme 5, was isolated in 83% yield, after precipitation from CH_2Cl_2, followed by further precipitation from *i*-propanol–EtOH 3 : 1 mixture. As anticipated, the ^{1}H NMR (400 MHz, D_2O) revealed the high degree of symmetry inherent in the molecule, as four of the methylene resonances of the alkyl chain appeared at 1.38 and 1.19 ppm, respectively. Moreover, the ^{13}C NMR revealed the three carbonyl peaks at 174.2, 173.5 and 169.7 ppm as well as eight methylene resonances between 56.1 and 25.3 ppm, respectively.



Scheme 5 Synthesis of the bis acetamide cyclen ligand **16** and the resulting La(III) complex **16La$_2$**.

The La(III) and the Eu(III) complexes of **1**–**3** (Scheme 4) and the La(III) complex of **16** (Scheme 5) were prepared by refluxing each ligand with two molar equivalents of the relevant lanthanide triflate salt in dry MeOH for 16 h. The resulting solution was filtered and reduced in volume to *ca.* 5 mL, and added dropwise to a swirling solution of ether. This produced white precipitates that were collected by filtration and washed with ether. The resulting complexes were subsequently further purified by precipitation from CH_2Cl_2, giving the desired complexes **1La$_2$**, **1Eu$_2$**, **2La$_2$**, **2Eu$_2$**, **3Eu$_2$**, and **16La$_2$** in 50–90% yields.

Analysis of the resulting Eu(III) complexes using ^{1}H NMR (400 MHZ) confirmed that the desired bis complexes were formed successfully. For instance, the ^{1}H NMR spectrum of **1Eu$_2$**, shown in Fig. 1, showed resonances appearing at 26.16, −2.66, −5.25, −9.09, −11.28, and −13.56 ppm. These are indicative of the presence of the Eu(III) ion, that acts as a paramagnetic shift reagent, which in the cyclen complexes results in shifted axial and equatorial protons of the cyclen and acetamide CH_2s, implying a square antiprismatic geometry for each of the lanthanide centres.[26,27] The electrospray mass spectrum (ESMS) also showed that complexation had occurred, as seen by the characteristic europium isotope distribution pattern for [**1Eu$_2$** + 4Trif]/2 in Fig. 2, which shows the calculated and the observed isotopic distribution patterns.

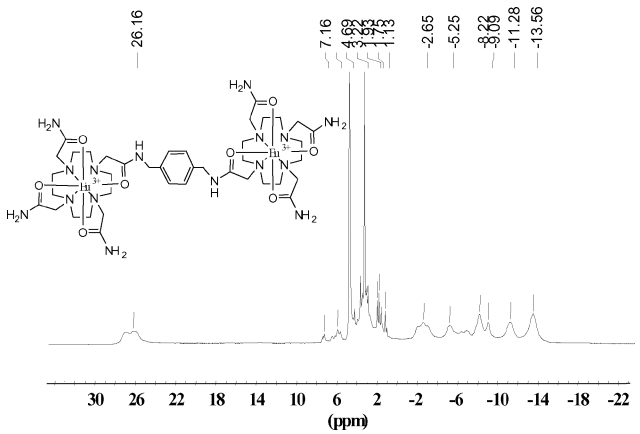


Fig. 1 The ^{1}H NMR (400 MHz, D_2O) of **1Eu$_2$** showing the shifted axial and equatorial protons of the ring and the α-protons.

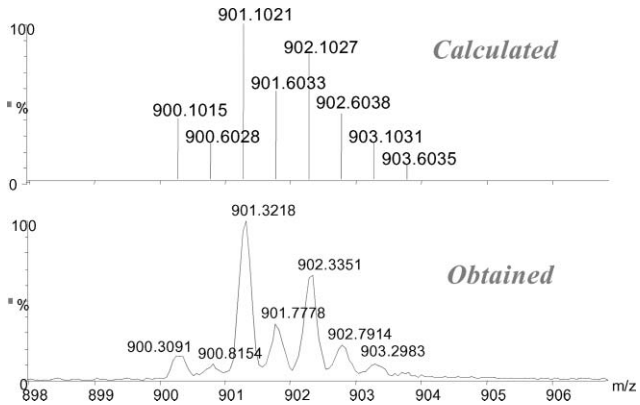


Fig. 2 Top: the calculated isotopic distribution pattern for [**1Eu$_2$** + 4Trif]/2. Bottom: the obtained ESMS (+ mode) isotopic distribution pattern for the same.

The europium complexes **2Eu$_2$** and **3Eu$_2$** gave similar results to that observed for **1Eu$_2$**, *e.g.* their ^{1}H NMR spectra (in D_2O) showed the expected shifted resonances for the α-methylene protons and the axial and the equatorial protons of the cyclen macrocycle between +30 and −16 ppm. Moreover, as in the case of **1Eu$_2$**, the correct europium isotope distribution pattern was observed in the ESMS for both of these complexes. The ^{1}H NMR and the ESMS of the corresponding La(III) complexes also revealed that the desired products were obtained. IR spectroscopy also confirmed the formation of the desired lanthanide complexes as the carbonyl vibration bands were shifted to lower frequency upon complexation of the metal ions, *e.g.* for **1**, **2**, **3** and **16** the carbonyl stretch occurred at 1678, 1657, 1647 and 1670 cm^{-1}, respectively, whereas for the corresponding Eu(III) complexes **1Eu$_2$**, **2Eu$_2$**, and **3Eu$_2$**, these were shifted to 1665, 1638 and 1621 cm^{-1}, respectively. For the La(III) complexes, this shift was even more pronounced being 1634, 1638 and 1635 cm^{-1} for **1La$_2$**, **2La$_2$** and **16La$_2$**, respectively.

Determination of the hydration state of the Eu(III) complexes

As previously discussed, the above bis-cyclen Eu(III) complexes **1Eu$_2$**, **2Eu$_2$**, and **3Eu$_2$**, were expected to have one free coordination site, and this vacant site was expected to be occupied by a metal -bound water molecule. In order to confirm this, the excited state lifetimes (τ) for these complexes were measured in D_2O and H_2O, respectively, after direct excitation of the Eu(III) ion at 395 nm. The lifetimes obtained from these two solvents were then used to determine the hydration state of the complexes, or the q value, using eqn (1):

$$q_{Eu(III)} = 1.2\,[(1/\tau_{H2O} - 1/\tau_{D_2O}) - 0.25\text{–}0.075x] \quad (1)$$

which was developed by Horrock *et al.*[28] and later modified by Parker *et al.*[29] to allow for the quenching of N–H oscillators. The results of these measurements and the resulting q-values are shown in Table 1. As expected, each of the Eu(III) complexes were found to have one metal bound water molecule per Eu(III) ion, giving an overall nine coordinate environment at each metal ion centre within the complexes.

Table 1 Results from the excited state lifetime measurements and the determination of the hydration state (q) of **1Eu$_2$**, **2Eu$_2$**, and **3Eu$_2$**[a]

Complex	τ_{H_2O}/ms	k_{H_2O}/ms^{-1}	τ_{D_2O}/ms	k_{D_2O}/ms^{-1}	q (±0.5)
1Eu$_2$	0.507	1.971	2.265	0.440	0.9
2Eu$_2$	0.553	1.808	2.451	0.408	1.0
3Eu$_2$	0.553	1.808	1.851	0.541	1.1

[a] All measured at neutral pH or pD at room temperature.

Conclusion

In this article we have presented the synthesis of several bis cyclen ligands that were bridged by either flexible hexyl diamide or rigid *p*-xylyl diamide spacers **1**, **2**, **3** and **16**. The lanthanide complexes of these ligands, **1La$_2$**, **1Eu$_2$**, **2La$_2$**, **2Eu$_2$**, **3Eu$_2$**, and **16La$_2$**, were characterised using conventional methods. We are currently carrying our a comprehensive study of the ability of these complexes to cleave HPNP and RNA molecules.‡

Experimental

Starting materials were obtained from Sigma Aldrich, Strem Chemicals and Fluka. Solvents used were HPLC grade unless otherwise stated. ^{1}H NMR spectra were recorded at 400 MHz using a Bruker Spectrospin DPX-400, with chemical shifts expressed in parts per million (ppm or δ) downfield from the standard. ^{13}C NMR were recorded at 100 MHz using a Bruker Spectrospin DPX-400 instrument. Infrared spectra were recorded on a Mattson Genesis II FTIR spectrophotometer equipped with a Gateway 2000 4DX2-66 workstation. Mass spectroscopy was carried out using HPLC grade solvents. Mass spectra were determined by detection using Electrospray on a Micromass LCT spectrometer, using a Water's 9360 to pump solvent. The system was controlled by MassLynx 3.5 on a Compaq Deskpro

‡ Preliminary evaluation of the ability of these compounds to cleave HPNP has been undertaken. All complexes promote the hydrolysis of HPNP, *e.g.* for **1La$_2$**, the rate enhancement (k_{rel}) was *ca.* 733 fold. In comparison **16La$_2$**, was significantly faster with *ca.* 2058 fold enhancement at pH 7.4, over the unanalysed reaction. This is a four fold enhancement over the mononuclear analogue, indicating a cooperative rate enhancement. Moreover, as a function of pH the rate profile for **16La$_2$** gave rise to a bell-shaped pH-dependent curve which peaked at physiological pH. We are currently evaluating these phenomena in greater detail; results will be published in due course.

workstation. Uv-Vis spectroscopy analysis was carried out on a Varian Cary 100 UV-Vis spectrophotometer. Luminescence measurements were carried out on Varian Carey Eclipse spectrophotometer.

1,4-Bis-(2-chloroacetylamino)xylyene (7)

p-Xylylenediamine (0.50 g, 3.67 mmol), was placed in a 100 mL RBF with NaOH (0.59 g, 14.70 mmol), and dissolved in H_20 (10 mL). The solution was placed in an acetone–ice bath and allowed to cool. Chloroacetyl chloride (1.66 g, 14.70 mmol) was then added dropwise over 1 h. The solution was left to stir overnight and the resulting precipitate was then filtered and washed with water and ether. The product was isolated as white solid, 0.79 g, 75% yield. Mp 206–207 °C. Calculated for $C_{12}H_{14}N_2O_2Cl_2$: C, 49.85; H, 4.88; N, 9.69. Found: C, 49.64; H, 4.75; N, 9.55. Calculated for $C_{12}H_{14}N_2O_2Cl_2Na$ [M + Na] $m/z = 311.0330$. Found $m/z = 311.0339$ (+ 2.8 ppm). δ_H (400 MHz, DMSO) 8.72 (b.s, 2H, N–H), 7.22 (s, 4H, Ar–H), 4.26 (d, 4H, $J = 6.0$ Hz, CH_2NH), 4.11 (s, 4H, CH_2Cl). δ_C (100 MHz, DMSO) 165.9, 137.5, 127.3, 42.6, 42.2. Mass spectrum: (MeOH, ES+): m/z. Expected: 288.0. Found: 311.0 [M + Na], 326.9 [M + K]. IR υ_{max} (cm^{-1}) 3280, 3072, 2952, 1656, 1549, 1415, 1267, 1235, 1066, 1001, 831, 769, 680, 547, 416.

2-Chloro-*N*-[3-(2-chloroacetylamino)propyl]acetamide (12)

Compound **12** was synthesised using 1,3 diamino propane (0.44 g, 6.00 mmol), was placed in a 100 mL RBF with NaOH (0.72 g, 18 mmol) and dissolved in H_2O (25 mL). The solution was placed in an ice bath at 0 °C and allowed to cool. Chloroacetyl chloride (1.65 g, 15.00 mmol) was then added dropwise over 1 h and the solution left to stir overnight. The solution was then filtered and the precipitate was washed with ether. The solution was then extracted with CH_2Cl_2 (4 × 20 mL) and the solvent was subsequently evaporated and the residue suspended in ether and filtered. The product was isolated as a white solid, 0.28 g, 20% yield. Mp 128–129 °C. Calculated for $C_7H_{12}N_2O_2Cl_2Na$ [M + Na] $m/z = 249.0174$. Found $m/z = 249.0168$ (−2.2 ppm). δ_H (400 MHz, $CDCl_3$) 7.17 (s, 2H, NH), 4.09 (s, 4H, CH_2Cl), 3.38 (dt, 4H, $J = 6$ Hz, $J = 6$ Hz, CH_2NH), 1.73 (quintet, 2H, $J = 6$ Hz, CH_2). δ_C (100 MHz, $CDCl_3$) 166.3, 42.2, 35.9, 28.9. Mass spectrum: (MeOH, ES+): m/z. Expected: 226.0. Found: 249.0 [M + Na]. IR υ_{max} (cm^{-1}) 3283, 3078, 3005, 2970, 2953, 2879, 2361, 1675, 1638, 1554, 1464, 1448, 1401, 1316, 1292, 1269, 1249, 1194, 1128, 923, 759, 626, 574, 469, 414.

2-(1,4,7,10-Tetraazacyclododec-1-yl)-*N*-{4-[(2-1,4,7,10-tetraazacyclododec-1-yl-acetylamino)methyl]benzyl}acetamide (10)

1,4,7,-Molybdenum tris carbonyl-(1,4,7,10-tetraazacyclododecane) **8**[25b] (1.08 g, 3.07 mmol), 1,4-bis-(2-chloroacetylamino)-xylyene (**7**) (0.44 g, 1.5 mmol), Cs_2CO_3 (1.00 g, 3.07 mmol) and KI (0.49 g, 3.07 mmol) were placed in a 100 mL RBF. To this was added DMF (50 mL) under vacuum and the solution was freeze–pump–thawed three times. The resulting solution was left to stir for 40 h at 85 °C, under argon. After cooling to room temperature, the resulting cream precipitate was filtered off and the DMF removed under reduced pressure. The residue was dissolved in HCl (15% *v*/*v*; 25 mL) and left stirring overnight. This aqueous solution was filtered and washed with CH_2Cl_2 (3 × 20 mL). The aqueous layer was then basified to pH >13 with KOH pellets and was subsequently filtered and extracted with CH_2Cl_2 (5 × 20 mL). The organic extracts were combined and dried over K_2CO_3. The solvent was removed under reduced pressure to yield **10** as a yellow oil (0.35 g), in 41% yield. Calculated for $C_{28}H_{53}N_{10}O_2$: [M + H] $m/z = 561.4353$. Found: $m/z = 561.4340$ (−2.4 ppm). δ_H (400 MHz, $CDCl_3$) 8.45 (s, 2H, NH), 7.25 (s, 4H, Ar–H), 4.39 (d, $J = 6.0$ Hz, 4H, CH_2NH), 3.18 (s, 4H, CH_2CO), 2.61 (s, 24H, cyclen CH_2), 2.50 (s, 8H, cyclen CH_2).δ_C (100 MHz, $CDCl_3$) 171.1, 137.2, 127.7, 58.6, 52.8, 46.6, 46.2, 45.1, 42.4. Mass spectrum (MeOH, ES+) m/z. Expected: 560.4. Found: 561.4 [M + H], 583.4 (M + Na), 599.4 (M + K), 281.2 [M + H]/2. IR υ_{max} (cm^{-1}) 3194, 2724, 2362, 1640, 1543, 1269, 1170, 1076, 1020, 972, 941, 722.

2-{4,10-Bis-carbamoylmethyl-7-[(4-{[2-(4,7,10-tris-carbamoylmethyl-1,4,7,10-tetraazacyclododec-1-yl)-acetylamino]methyl}benzylcarbamoyl)methyl]-1,4,7,10-tetraazacyclododec-1-yl}acetamide (1)

The bis-cyclen ligand **10** (0.11 g, 0.19 mmol), bromo acetamide (0.19 g, 1.36 mmol) and Et_3N (0.19 g, 1.95 mmol) were placed in a 50 mL RBF. EtOH (20 mL) was added and the solution was refluxed at 85 °C for 40 h. After cooling, the solution was filtered and then reduced in volume (5 mL) before it was added dropwise to a solution of CH_2Cl_2 (150 mL). The resulting precipitate was filtered, dissolved in hot EtOH (5 mL) and left to stand. The resulting precipitate was filtered, yielding a pale yellow solid (0.10 g), in 57% yield. Mp decomposes above 163 °C. Calculated for $C_{40}H_{70}N_{16}O_8\cdot(CH_2Cl_2)_2\cdot(H_2O)_2\cdot$MeOH: C, 45.26; H, 7.24; N, 19.64. Found: C, 45.19; H, 6.89; N, 19.51. Calculated for $C_{40}H_{72}N_{16}O_8$: [M + 2H] $m/z = 904.5719$. Found: $m/z = 904.5726$ (+ 0.8 ppm). δ_H (400 MHz, D_2O) 7.16 (s, 4H, Ar–H), 4.26 (s, 4H, CH_2NH), 3.46 (bs, 4H, CH_2CO), 3.27 (s, 4H, $CH_2C{=}O$), 3.19 (s, 6H, $CH_2C{=}O$), 3.12 (s, 2H, $CH_2C{=}O$), 2.75 (bs, 32H, cyclen CH_2). δ_C (100 MHz, D_2O) 173.8, 173.4, 170.2, 136.6, 127.1, 58.1, 56.9, 56.7, 56.1, 55.5, 55.3, 50.2, 42.2. Mass spectrum: (MeOH, ES+) m/z. Expected: 902.6. Found: 902.7 (M+), 924.7 (M + Na), 451.9 (M + 2H)/2, 301.7 (M + 3H)/3. IR υ_{max} (cm^{-1}) 3336, 2949, 2831, 2074, 1959, 1678, 1551, 1420, 1288, 1117, 971, 902, 806, 647, 469.

2-{4,7-Bis-methylcarbamoylmethyl-10-[(4-{[2-(4,7,10-tris-methylcarbamoylmethyl-1,4,7,10-tetraazacyclododec-1-yl)-acetylamino]methyl}benzylcarbamoyl)methyl]-1,4,7,10-tetraazacyclododec-1-yl}acetamide (2)

The bis-cyclen ligand **10** (0.28 g, 0.50 mmol), K_2CO_3 (0.25 g, 1.85 mmol) and 2-chloro-*N*-methylacetamide (0.35 g, 2.25 mmol) were placed in a 100 mL RBF. EtOH (30 mL) was added and the solution was refluxed at 85 °C for 40 h. After cooling, the solution was filtered to remove the cream precipitate and the EtOH was removed under reduced pressure. The residue was suspended in CH_2Cl_2 (30 mL) and filtered. The resulting solid was dissolved in EtOH (5 mL) and added to CH_2Cl_2–Et_2O 25 : 7. The resulting precipitate was filtered and then dissolved in a small volume of EtOH (<10 mL) and left to sit overnight. The resulting precipitate was filtered and was then dissolved in DMF and

filtered, before being precipitated from Et_2O to yield a yellow solid (0.15 g), in 30% yield. Mp decomposes above 139 °C. Calculated for $C_{46}H_{82}N_{16}O_8{\cdot}CH_2Cl_2{\cdot}H_2O{\cdot}EtOH$: C, 51.79; H, 8.16; N, 19.72. Found: C, 51.72; H, 7.48; N, 19.67. Calculated for $C_{46}H_{84}N_{16}O_8$ [M + 2H] m/z = 988.6658. Found m/z = 988.6623. (−3.6 ppm). δ_H (400 MHz, D_2O) 7.12 (s, 4H, Ar–H), 4.22 (s, 4H, CH_2NH), 3.21 (s, 4H, CH_2CO), 2.86 (bs, 12H, CH_2CO), 2.57 (s, 8H, cyclen CH_2), 2.52 (s, 18H, CH_3), 2.43 (s, 24H, cyclen CH_2). δ_C (100 MHz, D_2O) 173.6, 172.9, 136.7, 127.1, 62.8, 57.4, 51.3, 41.9, 25.0. Mass spectrum: (MeOH, ES+): m/z. Expected: 986.6. Found: 987.9 [M + H], 1024.9 [M + K], 531.9 [M+ 2 K]/2, 512.9 [M + K]/2, 494.0 [M + 2H]/2. IR υ_{max} (cm^{-1}) 3453, 3276, 3080, 2943, 2820, 2067, 1657, 1549, 1449, 1412, 1371, 1308, 1245, 1152, 1116, 972, 870, 707, 587.

2-{4,10-Bis-dimethylcarbamoylmethyl-7-[(4-{[2-(4,7,10-tris-dimethylcarbamoylmethyl-1,4,7,10-tetraazacyclododec-1-yl)acetylamino]methyl}benzylcarbamoyl)methyl]-1,4,7,10-tetraazacyclododec-1-yl}-*N*,*N*-dimethylacetamide (3)

The bis-cyclen ligand **10** (0.15 g, 0.26 mmol), Cs_2CO_3 (0.30 g, 0.92 mmol), 2-chloro-*N*,*N*-dimethylacetamide (0.21 g, 1.70 mmol) and KI (0.13 g, 0.92 mmol) were placed in a 100 mL RBF and dissolved in EtOH (20 mL). The solution was refluxed at 85 °C for 4 d. The solution was filtered to remove the cream precipitate and the solvent removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL) and filtered. The CH_2Cl_2 was extracted with 0.1 M HCl (4 × 20 mL), which was then washed with CH_2Cl_2 (4 × 15 mL). The pH was adjusted to 7 using K_2CO_3 (10%) and the solution extracted with CH_2Cl_2 (4 × 15 mL). The solvent was then removed to give a clear oil which solidified after drying under vacuum over P_2O_5 (0.11 g), in 38% yield. Mp decomposes above 124 °C. Calculated for $C_{52}H_{96}N_{16}O_8$ [M + 2H] m/z = 1072.7597. Found m/z = 1072.7567 (−2.8 ppm). δ_H (400 MHz, $CDCl_3$) 7.17 (s, 4H, Ar–H), 4.31 (s, 4H, CH_2NH), 3.49 (s, 4H, CH_2CO), 3.09 (bm, 12H, CH_2CO), 2.89 (bm, 68H, cyclen and CH_3). δ_C (100 MHz, $CDCl_3$) 170.8, 170.4, 169.4, 139.8, 126.7, 63.6, 59.8, 55.6, 50.3, 48.3, 42.1, 36.5, 35.7, 35.3, 34.9. Mass spectrum: (MeOH, ES+) m/z. Expected: 1070.7. Found: 1071.9 [M + H], 535.9 [M + 2H]/2, 357.9 [M + 3H]/3. IR υ_{max} (cm^{-1}) 3448, 3279, 3055, 2933, 2817, 1647, 1542, 1508, 1450, 1403, 1348, 1301, 1262, 1102, 1062, 1006, 950, 900, 822.

General procedure for synthesis of lanthanide complexes

Lanthanide complexes were prepared by refluxing each ligand with the relevant lanthanide triflate (2.1 equivalents) in MeOH (15 mL) for 16 h. The resulting solution was filtered and reduced in volume to *ca.* 5 mL. This solution was added dropwise to swirling Et_2O (100 mL) and the resulting precipitate was collected by filtration. The complexes were further purified by precipitation from CH_2Cl_2 (75 mL) and isolated by filtration. The complexes were dried under vacuum over P_2O_5.

1La$_2$. The complex **1La$_2$** was synthesised using **1** (41.0 mg, 45.40 μmol) and $La(CF_3SO_3)_3$ (53.2 mg, 90.80 μmol) giving an oil which became a yellow solid upon drying in a dessicator (83 mg), in 88% yield. Mp decomposes above 227 °C. Calculated for $C_{40}H_{70}N_{16}O_8{\cdot}La_2{\cdot}(CF_3SO_3)_6{\cdot}(H_2O)_4{\cdot}(MeOH)_4$: C, 26.39; H, 4.16; N, 9.85. Found: C, 26.26; H, 3.76; N, 9.51. Calculated for $C_{43}H_{70}N_{16}O_{17}F_9S_3{}^{139}La_2$ [M + 3 triflate]/3 m/z = 1627.2250. Found m/z = 1627.2285 (+ 2.1 ppm). δ_H (400 MHz, D_2O) 7.26, 4.36, 3.54, 3.52, 3.37, 3.22. Mass spectrum: (MeOH, ES+): m/z. Expected: 542.4. Found: 542.4 [M + 3Trif]/3, 885.11 [M + 4Trif]/2. IR υ_{max} (cm^{-1}) 3401, 2872, 1669, 1634, 1466, 1253, 1169, 1084, 1029, 913, 639, 575, 518.

1Eu$_2$. The complex **1Eu$_2$** was prepared using **1** (0.13 g, 0.15 mmol) and $Eu(CF_3SO_3)_3$ (0.20 g, 0.33 mmol) yielding a pale yellow solid upon drying (0.25 g), in 80% yield. Mp decomposes above 215 °C. Calculated for $C_{40}H_{70}N_{16}O_8{\cdot}Eu_2{\cdot}(CF_3SO_3)_6(H_2O)_2$: C, 25.85; H, 3.49; N, 10.48. Found: C, 26.31; H, 3.48; N, 10.03. Calculated for $C_{42}H_{70}N_{16}O_{14}F_6S_2{}^{151}Eu^{153}Eu$ [M + 2triflate] m/z = 1504.3014. Found m/z = 1504.3027 (+0.9 ppm). δ_H (400 MHz, D_2O) 27.10, 26.28, 7.33, 7.16, 5.87, 4.20, 3.61, 3.22, 2.87, 1.93, 1.75, 1.55, 1.14, 1.04, −2.65, −5.25, −8.22, −9.09, −11.28, −13.55. Mass spectrum: (MeOH, ES+): m/z. Expected: 1208.4. Found: 901.1 [M + 4Trif]/2, 376.5 [M + 2Trif]/4. IR υ_{max} (cm^{-1}) 3374, 1665, 1459, 1252, 1150, 1082, 1029, 989, 638.

2La$_2$. The complex **2La$_2$** was synthesised using **2** (35.20 mg, 35.66 μmol) and $La(CF_3SO_3)_3$ (42.00 mg, 71.67 μmol). The resulting yellow–brown precipitate was dried in a dessicator (53 mg), in 69% yield. Mp decomposes above 215 °C. Calculated for $C_{46}H_{82}La_2N_{16}O_8{\cdot}(CF_3SO_3)_6{\cdot}(H_2O)_4{\cdot}(CH_2Cl_2)_5$: C, 25.77; H, 3.79; N, 8.44. Found: C, 26.17; H, 3.39; N, 8.35. δ_H (400 MHz, D_2O) 7.26, 4.37, 3.23, 2.74. Mass spectrum: (MeOH, ES+): m/z. Expected: 1264.4 Found: 930.5 [M+ 4Trif]/2, 570.4 [M+ 3Trif]/3, 390.9 [M+ 2Trif]/4. IR υ_{max} (cm^{-1}) 3518, 3326, 3131, 2955, 1638, 1417, 1255, 1168, 1086, 1029, 761, 639, 575, 517.

2Eu$_2$. The complex **2Eu$_2$** was prepared by using **2** (36.40 mg, 36.88 μmol) and $Eu(CF_3SO_3)_3$ (46.40 mg, 77.45 μmol). This yielded a pale yellow solid (66.00 mg), in 81% yield. Mp decomposes above 215 °C. Calculated for $C_{45}H_{79}N_{16}O_8Eu_2{\cdot}(CF_3SO_3)_6{\cdot}(H_2O)_2{\cdot}(CH_2Cl_2)_5$: C, 25.87; H, 3.66; N, 8.47. Found: C, 25.75; H, 3.29; N, 8.31. δ_H (400 MHz, D_2O) 26.81, 8.41, 5.62, 3.51, 2.60, 2.04, 1.03, 0.78, −2.47, −6.26, −8.14, −11.88, −13.76. Mass spectrum: (MeOH, ES+): m/z. Expected: 1292.5. Found: 944.3 [M+ 4Trif]/2, 580.0 [M+ 3Trif]/3. IR υ_{max} (cm^{-1}) 3504, 3324, 3134, 2951, 1638, 1419, 1256, 1168, 1083, 1029, 978, 639, 575, 517.

3Eu$_2$. The complex **3Eu$_2$** was synthesised using **3** (58.00 mg, 54 μmol) and $Eu(CF_3SO_3)_3$ (90.00 mg, 120 μmol, 2.2 equivalents). The product was successfully isolated as a yellow solid (58.00 mg), in 47% yield. Mp decomposes above 235 °C. Calculated for $C_{52}H_{94}N_{16}O_8Eu_2{\cdot}(CF_3SO_3)_6{\cdot}(H_2O)_2{\cdot}(CH_2Cl_2)_6$: C, 27.30; H, 3.94; N, 7.96. Found: C, 27.02; H, 3.61; N, 8.33. δ_H (400 MHz, D_2O) 31.63, 9.90, 3.21, 2.81, 2.56, 1.51, 1.14, 1.00, 0.76, 0.24, −1.04, −5.89, −7.44, −7.94, −12.30, −13.22, −16.19. Mass spectrum: (MeOH, ES+) m/z. Expected: 1376.6. Found: 985.1 [M + 4trif]/2, 607.1 [M + 3trif]/3, 557.1 [M + 2trif]/3, 343.1. IR υ_{max} (cm^{-1}) 3465, 2872, 2350, 1621, 1463, 1253, 1163, 1081, 1029, 957, 911, 824, 758, 638, 574, 427.

2-(1,4,7,10-Tetraazacyclododec-1-yl)-*N*-[6-(2-1,4,7,10-tetraazacyclododec-1-yl-acetylamino)hexyl]acetamide (11)

1,6-Bis-(2-chloroacetylamino)hexane (**12**) (0.40 g, 1.49 mmol), molybdenum cyclen (**8**) (1.05 g, 2.97 mmol), Cs_2CO_3 (1.45 g,

4.46 mmol) and KI (0.20 g, 0.12 mmol) were placed in a 100 mL RBF. DMF (35 mL) was added under vacuum and the suspension was freeze–pump–thawed three times. The reaction was left to stir for 120 h at 85 °C under argon. After cooling, the solution was filtered and the DMF was removed under reduced pressure. The residue was suspended in HCl (15%; 25 mL) and left stirring overnight. The solution was filtered and then washed with CH_2Cl_2 (3 × 20 mL). The aqueous solution was basified with KOH and extracted with CH_2Cl_2 (4 × 20 mL). The CH_2Cl_2 was dried over K_2CO_3, filtered and the solvent removed. The residue was dissolved in EtOH (15 mL) and conc. HCl (3 mL) was added and the solution. The resulting precipitate was filtered and washed with EtOH to yield a brown solid (0.42 g), in 37% yield. Mp decomposes above 178 °C. Calculated for $C_{26}H_{62}N_{10}O_2Cl_6$·MeOH: C, 40.97; H, 8.40; N, 17.69. Found: C, 41.14; H, 7.97; N, 17.77. δ_H (400 MHz, D_2O) 3.31 (s, 4H, CH_2CO), 3.06, (s, 24H, cyclen CH_2), 2.88 (bs, 12H, cyclen CH_2 & CH_2NCO), 1.39 (bs, 4H CH_2), 1.20 (s, 4H, CH_2). δ_C (100 MHz, D_2O) 172.4, 54.9, 49.2, 43.9, 42.2, 41.8, 39.1, 27.6, 25.3. Mass spectrum: (MeOH, ES+) *m*/*z*. Expected: 540.5. Found: 541.6 [M + H], 271.4 [M + 2H/2]. IR υ_{max} (cm^{-1}) 3427, 2935, 2648, 1647, 1554, 1444, 1375, 1271, 1175, 1075, 1009, 947, 728, 574, 489.

2-[4,7-Bis-carbamoylmethyl-10-({6-[2-(4,7,10-tris-carbamoylmethyl-1,4,7,10-tetraazacyclododec-1-yl)-acetylamino]hexylcarbamoyl}methyl)-1,4,7,10-tetraazacyclododec-1-yl]acetamide (16)

The bis-cyclen ligand **11** (0.10 g, 0.14 mmol), bromo acetamide (0.13 g, 0.97 mmol) and Et_3N (0.21 g, 2.07 mmol) were placed in a 100 mL RBF and dissolved in EtOH (35 mL). The solution was heated at 70 °C for 96 h. The solvent was removed under reduced pressure and the residue was triturated with CH_2Cl_2. The residue was dissolved in EtOH (2 mL) and added dropwise to swirling CH_2Cl_2 (100 mL). The resulting precipitate was filtered. This was then dissolved in boiling *i*-propanol–EtOH 3 : 1 (5 mL) and left to stand. The resulting precipitate was filtered, isolating a pale yellow solid (0.10 g), in 83% yield. Mp decomposes above 147 °C. Calculated for $C_{38}H_{74}N_{16}O_8$·$(CH_2Cl_2)_3$·MeOH: C, 43.12; H, 7.24; N, 19.16. Found: C, 43.12; H, 7.61; N, 19.55. δ_H (400 MHz, D_2O) 3.35 (m, 12H, CH_{2acet}), 3.12 (bm, 4H, CH_2CO_{bridge}) 3.08 (bm, 12H, 4 × $CH_{2cyclen}$ + 2 × $CH_{2(1,6)}$), 2.87 (bs, 24H, $CH_{2cyclen}$), 1.38 (s, 4H, $CH_{2(2,5)}$), 1.19 (s, 4H, $CH_{2(3,4)}$). δ_C (100 MHz, D_2O) 174.2, 173.5, 169.7, 56.1, 55.6, 50.1, 49.8, 48.9, 38.9, 27.8, 25.3. Mass spectrum: (MeOH, ES+) *m*/*z*. Expected: 882.6. Found: 883.7 [M + H], 442.5 [M + 2H/2]. IR υ_{max} (cm^{-1}) 3388, 3187, 2935, 2851, 1670, 1551, 1457, 1407, 1288, 1161, 1118, 1088, 974, 888, 772, 592.

16La$_2$. The complex **16La$_2$** was prepared using **16** (65.00 mg, 74.06 μmol) $La(CF_3SO_3)_3$ (91.00 mg, 155.53 μmol). The residue was triturated with acetone and dried under vacuum, yielding a yellow solid (13.70 mg), in 87% yield. Mp decomposes above 127 °C. Calculated for $C_{38}H_{74}N_{16}O_8$ La_2·$(CF_3SO_3)_6(H_2O)_4$·$(CH_2Cl_2)_4$. $(MeOH)_4$: C, 24.07; H, 4.12; N, 8.64. Found: C, 24.05; H, 4.22; N, 8.38. δ_H (400 MHz, D_2O) 4.03, 3.76, 3.43, 3.27, 2.89, 2.59, 1.45, 1.25. Mass spectrum: (MeOH, ES+) *m*/*z*. Expected: 1160.4. Found: 535.7 [M + 3Trif]/3, 364.5 [M + 2Trif]/4. IR υ_{max} (cm^{-1}) 3377, 2975, 2868, 1669, 1635, 1466, 1270, 1169, 1085, 1030, 974, 913, 819, 762, 639, 576, 517, 434.

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