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Brian McMahon and David Parker*

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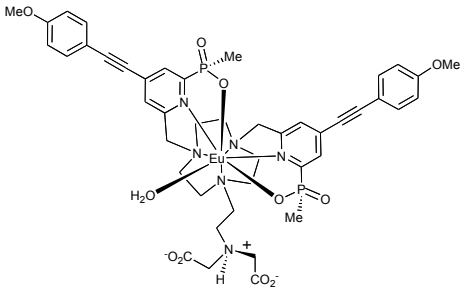

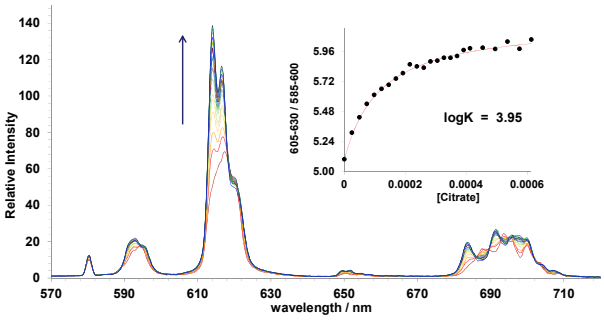

Selective ion pair recognition of citrate AND zinc ions in water by ratiometric luminescence signaling

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Emission from a bright europium(III) complex, based on a 1,4,7-triazacyclononane ring bearing an alkyliminodiacetate group, is modulated only when in the presence of zinc(II) ions and a carboxylate anion and was characterised by ratiometric luminescence analysis at pH 7.4. No change in emission spectral form was observed when either the metal ion or oxy-anion was added separately. Amongst the diamagnetic systems examined, the strongest binding was observed for zinc and citrate (log K = 3.9, pH 7.4) and anion selectivity was observed in the order citrate>lactate/acetate/bicarbonate. No changes in the Eu spectral characteristics were found in the presence of added Ca^{2+} or Mg^{2+} ions, consistent with the much lower affinity of these cations for the iminodiacetate binding site.

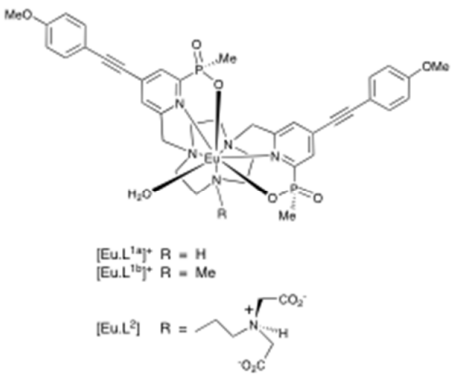
Introduction

The cooperative recognition of a cation and an anion has attracted interest in supramolecular science, [1,2] as such ditopic systems may have utility in membrane co-transport, [3-6] in metal ion extraction into lipophilic solvents at low pH [7-10] and in salt solubilisation. The majority of published studies on ion-pair binding operate in non-aqueous media, often via relatively weak, directed hydrogen bond interactions. Typically, the solvents are aprotic, e.g. chlorinated solvents, MeCN or DMSO, and solvate the anion weakly. [11-13] Given that the free energies of hydration of the common oxy-anions range from 300 to 400 $kJmol^{-1}$ for singly charged species to well over 1000 $kJmol^{-1}$ for di-anions, [14] the vast majority of reported systems do not have sufficient binding affinity to operate in aqueous media. Their scope for any application is restricted to interfacial transport or solvent extraction processes.

The ion-pair recognition event is commonly monitored by spectral titration methods, ranging from insensitive NMR analyses in solution[15] to absorbance and

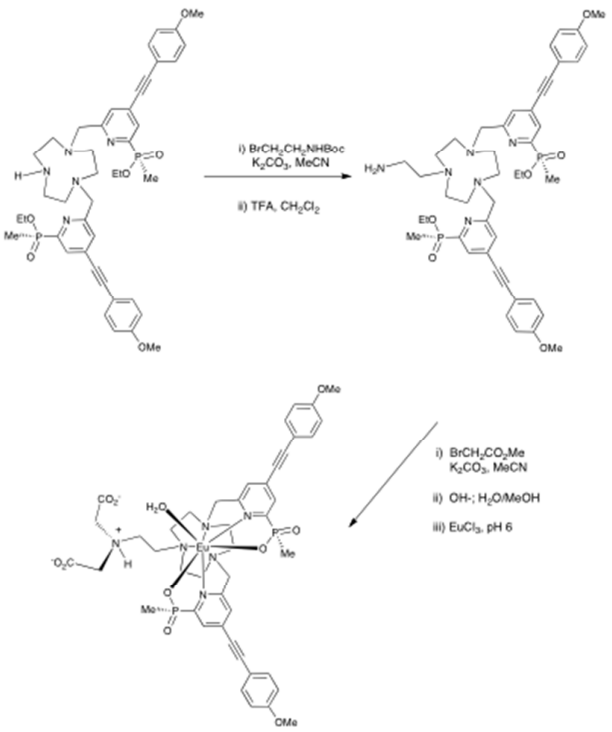
fluorescence signaling that allow much lower concentrations of the receptor to be addressed. [16,17,18] Here, we extend our studies on anion binding in water at coordinatively unsaturated lanthanide centres, e.g. [Eu.L^{1a}] [14,19] to examine a zwitterionic system with a pendant iminodiacetate moiety, [Eu.L^2], using fluorimetric methods of analysis. The parent chelating agent, N-methyl-iminodiacetate (MIDA) , possesses a well defined affinity and selectivity towards divalent metal ions. The order of stability follows the traditional Irving-Williams series. [20] Thus, the log K_{ML} stability sequence is in the order: Cu^{2+} > Ni^{2+} > Zn^{2+}/Co^{2+} >Fe^{2+} > Cd^{2+} > Mn^{2+} > Ca^{2+} > Mg^{2+}. Given that the paramagnetic complexes of copper, nickel, iron and cobalt are likely to lead to quenching of the excited state of the proximate luminescent signaling moiety by electron transfer, then the zinc affinity is the most notable amongst the common diamagnetic cations. The behaviour of the N-methyl derivative, [Eu.L^{1b}]$^+$ was examined in parallel, and serves as a negative control.

These complexes of Eu(III) are particularly bright, [21-23] combining a high extinction coefficient (ca. 40 $mM^{-1}cm^{-1}$) in the range 330 to 355 nm, with an emission quantum yield of the order of 15 to 20%, notwithstanding the presence of the quenching water molecule. [24]



Results and Discussion

The ligands L^{1b} and L^2 were made by the dialkyation of 1-N-methyl triazacyclononane or 1,4,7-triazacyclononane using two equivalents of a pyrdinyl mesylate chromophore sub-unit, (Scheme 1), using methods reported in recent work [19,21,23]. Following base hydrolysis of the phosphinate ester groups complexation with $EuCl_3$ was undertaken at pH 6 and each europium complex was purified by preparative reverse phase HPLC.



Scheme 1 Synthesis of the ditopic complex [Eu.L^2]

The emission and excitation spectral form and lifetime of [Eu.L^2] did not vary with pH over the range 4.5 to 7.5 and did not change in the presence of added anions, even when added in 1000-fold excess (e.g. bicarbonate, citrate, lactate, acetate, phosphate) in water at pH 7.4 (295K). In a separate experiment, the addition of $ZnCl_2$ (10 μM to 10 mM) to [Eu.L^2] also did not lead to any significant change in emission or excitation intensity nor in spectral form. Such behaviour indicates that the europium coordination environment is not perturbed under either of these sets of conditions, and contrasts with the properties of the mono-N-methyl complex, [Eu.L^{1b}]$^+$, for which anion addition was found earlier to lead to major changes in emission lifetime and relative emission band intensities, as observed with the parent complex, [Eu.L^{1a}]$^+$. [19]

The addition of $Zn(OAc)_2$ to [Eu.L^2] (5 μM, pH 7.4 295K, λ_{exc} 332 nm), however, led to significant changes in Eu emission intensity and spectral form (Figure 1), characterized by an isoemissive point at 686 nm. The titrimetric data were fitted to a 1:1 binding isotherm and an association constant for log K of 2.69 (±0.04) was estimated by iterative, non-linear least squares methods, by assuming 1:1

stoichiometry. When the same experiment was repeated in the presence of a fixed concentration of $ZnCl_2$ (10 mM), followed by incremental addition of sodium acetate, identical changes in spectral form were observed (ESI), with a log K value of 2.71(±0.04). In each case, no significant change occurred in the corresponding absorption spectra (nor in the excitation spectra), as the strong internal charge transfer band (ICT) of the chromophore is not perturbed by the remote changes in Eu coordination environment.

Table 1 Binding constants for 1: 1 association determined by spectral titration (pH 7.4, 295 K; λ_{exc} = 332 nm; experimental errors are shown in parenthesis, referring to standard deviations from the mean value for 3 replicates) for the interaction of Eu(III) complexes with selected oxy-anions

anionic guest species	$[Eu.L^{1b}]^{+c}$	$[Eu.L^2]^a$
citrate	4.88(0.05)	3.95 [2.74][d] (0.04)
lactate	3.70(0.03)	2.33 (0.04)
acetate	3.65(0.04)	2.71 [2.69][b] (0.04)
bicarbonate	3.73 (0.04)	3.05(0.05)
phosphate	4.32(0.05)	n.d.

[a] In water in the presence of 10 mM $ZnCl_2$; in the absence of added Zn ions no change in Eu spectral form or intensity was observed; [b] value in parenthesis ([/]) refers to titration of $Zn(OAc)_2$, in the absence of added $ZnCl_2$; [c] in 50/50 MeOH/H_2O due to the limited water solubility of the cationic complex; anion affinities are systematically higher in this case due to lower anion solvation and preferential solvation of the complex by MeOH; [d] value in parenthesis refers to the 1:1 binding constant determined in a medium containing 0.1 M NaCl, 30 mM $NaHCO_3$, 2.3 mM sodium lactate and 0.9 mM Na_2HPO_4.

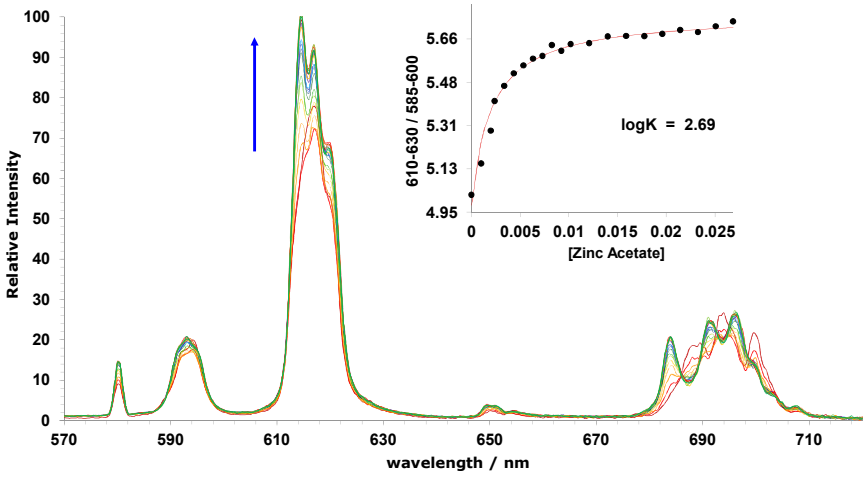


Figure 1 Variation of the europium (III) emission spectral profile for $[Eu.L^2]$ (5 μM) as a function of added zinc acetate (λ_{exc} = 332 nm, H_2O, pH 7.4). The inset shows the fit (line) to the data for 1:1 association, with log K_a = 2.69 (± 0.04).

The titration of [Eu.L[2]] with added oxy-anions in the presence of a fixed concentration of 10 mM $ZnCl_2$ was repeated for bicarbonate, lactate, citrate and phosphate and variations in emission spectral data were analysed in terms of formation a 1:1 (Eu/anion) species (Table 1 and Figure 2). The changes in the intensity ratio were examined as a function of added anion concentration for the electric-dipole allowed $\Delta J = 2$ manifold at 605-630 nm versus the magnetic-dipole allowed $\Delta J = 1$ transitions, centred around 595 nm. Changes in spectral form, notably in the hypersensitive $\Delta J = 2$ and $\Delta J = 4$ transitions around 615-625 nm and 680-700 nm, were nearly identical for added acetate, lactate and citrate, suggesting that the coordination environment at Eu in each anion-bound species was very similar. [14a, 25-27] The exquisite sensitivity of Eu emission spectral form to small perturbations in coordination has been documented many times. [14,24,25] The anion binding affinity sequence followed the order: citrate>lactate/acetate; a similar sequence to that observed for [Eu.L[1b]]$^+$ (Table 1), for which binding affinities were typically higher. Such behaviour is consistent with the mono-cationic character of the complex and the use of 50/50 aqueous methanol, in which preferential methanol solvation occurs.

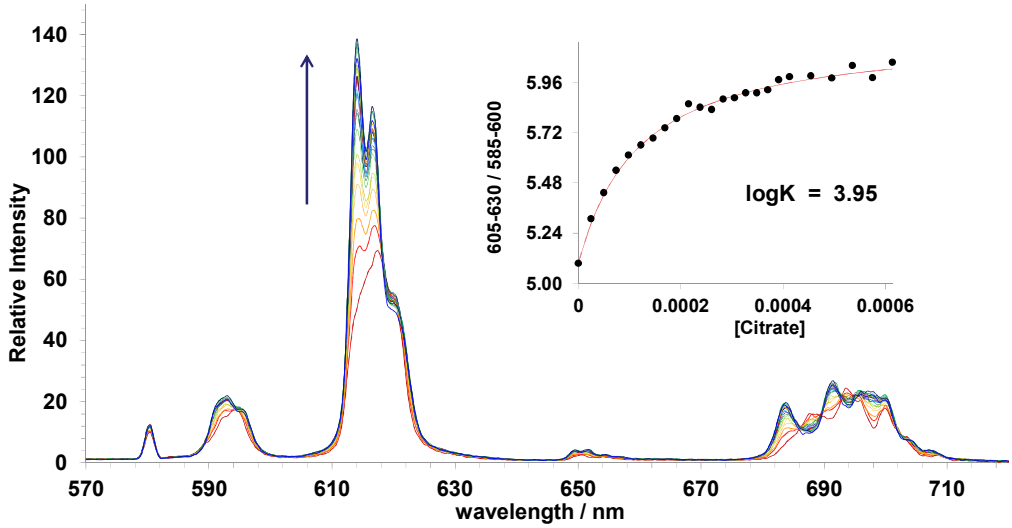


Figure 2 Variation of the europium (III) emission spectral profile for $[Eu.L_2]^+$ (5 μM) as a function of added citrate in the presence of 10 mM zinc chloride (λ_{exc} = 332 nm, H_2O, pH 7.4). The inset shows the fit (line) to the data points for log K_a = 3.95 (± 0.02).

The binding of citrate to [Eu.L[2]] in the presence of 10 mM $ZnCl_2$ was also studied in an aqueous solution containing 100 mM NaCl, 30 mM $NaHCO_3$, 2.3 mM sodium lactate and 0.9 mM NaH_2PO_4. The spectral form changes that were observed

were consistent with the competitive displacement of bicarbonate by citrate and an apparent binding constant of log K = 2.74 was obtained, i.e. the K_d value associated with citrate binding, under these competitive conditions, is 1.8 mM.

No changes in Eu band emission intensities (5 μM Eu complex) with added anion were observed in the presence of added $CaCl_2$ or $MgCl_2$ (up to 20 mM). The variation in Eu emission intensity observed with added $ZnCl_2$ required a certain threshold concentration to be reached that allowed formation of the 1:1 zinc complex with the alkyliminodiacetate metal binding site. This threshold value was about 0.3 mM in order to observe citrate modulation and was about an order of magnitude higher for lactate/acetate. Such behaviour can be interpreted by consideration of the 1:1 ML stability constants reported for N-methyliminodiacetate (MIDA). [20] Values of log K_{ML} for Zn^{2+}, Ca^{2+} and Mg^{2+} binding are reported to be 7.7, 3.8 and 3.4 respectively (298K, I = 0.1), so that the Ca and Mg complexes with $[Eu.L^2]$ will not be formed significantly under the experimental conditions used here.

The europium emission lifetimes for $[Eu.L^2]$ and $[Eu.L^{1b}]^+$ were measured in water and D_2O, in the presence and absence of excess metal ion, with and without added oxy-anion, to assess the Eu(III) hydration state in each case (Table 2). [24] The values obtained indicate that in the presence of 10 mM zinc ions and oxy-anion, any coordinated water is displaced and the Eu(III) centre has no bound water molecule. The displacement of the bound molecule of water removes the OH oscillators that efficiently quench the Eu excited state by intramolecular energy transfer, thereby leading to the observed emission intensity enhancements. In the absence of a coordinating anion, partial hydration exists for $[Eu.L^2]$, suggesting that a weak intramolecular interaction may occur between a carboxylate group of the NMDA moiety and the Eu(III) centre.

Table 2 **Radiative rate constants for Eu(III) complexes in water and D_2O (295 K)**

Complex	$k(H_2O)$ $(ms)^{-1}$	$k(D_2O)$ $(ms)^{-1}$	*q*
$[Eu.L^{1b}]^{+}$ [a]	1.79	0.70	1.0
$[Eu.L^2]$ [b]	1.43	0.70	0.5
$[Eu.L^2]^+$	1.25	0.76	0.3

10mM $ZnCl_2$			
$[Eu.L^2]$ [c]	1.01	0.77	0
+			
10mM $Zn(OAc)_2$			

[a] Unchanged in the presence of 10mM $ZnCl_2$; [b] addition of oxy-anions led to zero or near zero hydration states for added HCO_3^- and acetate; [c] similar values were measured for excess added acetate (or urate/lactate/bicarbonate) in the presence of 10mM $ZnCl_2$.

Summary and conclusions

The results of these luminescence experiments strongly indicate that modulation of europium emission lifetime and spectral form with added oxy-anions occurs only in the presence of zinc ions, beyond a threshold concentration. No changes were observed in absorption or excitation spectra, highlighting the utility of examining Eu emission changes, due to its exquisite sensitivity to small changes in the coordination environment, as the local ligand field is perturbed. [14,25] The spectral response change was most evident with added citrate, when the concentration of zinc was >0.5 mM. Under these conditions, citrate was most strongly bound by over an order of magnitude from lactate, acetate and bicarbonate. Such behaviour allowed its presence and concentration to be selective signalled in a mixed salt solution that simulates an extracellular ionic medium.

The europium complex forms a 1:1 complex with zinc, in which the divalent metal ion is bound to the iminodiacetate moiety. The absence of the negatively charged free carboxylate groups then permits anion binding to the Eu centre. The oxy-anions acetate, citrate and lactate give rise to near-identical limiting fingerprint Eu emission spectra, suggesting a common coordination mode, with cooperative carboxylate oxygen binding and not the five–ring chelate formation (involving the OH group and one carboxylate oxygen) that is often observed for lactate and citrate in less sterically demanding systems and has been characterised by NMR and crystallographic methods. [26,27]

The only situation in which zinc and citrate ion concentrations are to be found in the millimolar range is to be found in seminal or prostatic fluid samples, where the zinc concentration is typically of the order of 2 to 7 mM and citrate levels vary between 20

and 100 mM. [28] In diseased men with severe prostatitis or prostate cancer, these levels are reduced by a factor of three or more. This fall in citrate levels may reduce further in high or intermediate grade cancer cases as the disease progresses, suggesting a role for repeated citrate analysis of these fluids as a function of time, to monitor disease progression.

Experimental

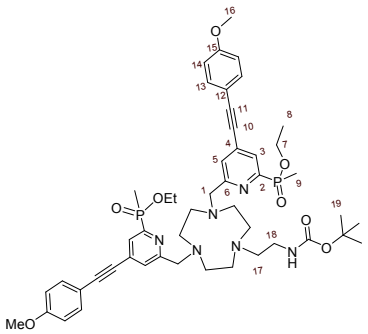
Details of purification methods, instrumentation, spectral analysis and data fitting methods have been reported elsewhere recently [19,21,23]. The ESI contains further examples of spectral titrations of different anions (12).

Emission spectra were recorded using an ISA Jobin-Yvon Spex Fluorolog-3 luminescence spectrometer. Lifetime measurements were carried out with a Perkin Elmer LS55 spectrometer using FL Winlab software. Quantum yield measurements were measured using an integrating sphere or were calculated by comparison with $Ru(bpy)_3^{2+}$ as standard ($\phi = 0.028$ in aerated water) [29] as a standard. For the standards and each of the unknowns, five solutions with absorbance values between 0.05 and 0.1 were used. The quantum yield was calculated according to the equation:

$$\Phi_x = \Phi_r \cdot \frac{A_r}{A_x} \cdot \frac{E_x}{E_r} \cdot \frac{I_r}{I_x} \cdot \frac{\eta_x^2}{\eta_r^2}$$

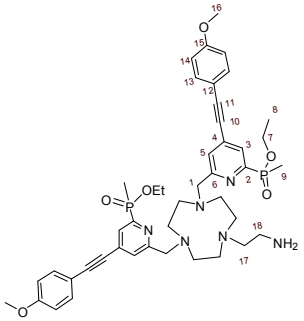
where *r* and *x* refer to reference and unknown respectively; *A* is the absorbance at λ_{ex}, which equals 332 nm here; *E* is the corrected integrated emission intensity; *I* is the corrected intensity of excitation light; η is the refractive index of solution.

1-t-Butoxycarbonyl-2-aminoethyl-4,7-bis((6-(ethoxy(methyl)phosphoryl)-4-((4-methoxyphenyl)ethynyl)pyridine-2-yl)methyl)-1,4,7-triazacyclononane



The di-ethyl methylphosphinate ester of **L**[1a] (0.12 g, 0.14 mmol) and N-butoxycarbonyl-2-bromoethylamine (0.03 g, 0.14 mmol) were dissolved in CH_3CN (10 mL) and K_2CO_3 (0.04 g, 0.28 mmol) was added. The mixture was stirred under argon at 65 °C and monitored by TLC (silica; CH_2Cl_2:10 % CH_3OH, R_f(product) = 0.42). After 16 h, the starting material had been consumed and the reaction was cooled and the solution decanted from excess potassium salts. The solvent was removed under reduced pressure to yield a yellow viscous oil that was used without further purification (0.1 g, 77 %); δ_H (700 MHz, $CDCl_3$) 7.94 (2H, m, H^3), 7.50 (2H, bs, H^5), 7.42 (4H, m, H^{13}), 6.88 (4H, m, H^{14}), 4.16 – 4.09 (2H, m, H^7), 3.99, (4H, s, H^1), 3.92 – 3.86 (2H, m, H^7), 3.79 (6H, s, H^{16}), 3.40 – 2.62 (16H, m, ring Hs + $H^{17,18,}$), 1.75 (6H, m, H^9), 1.46 – 1.40 (9H, m, H^{19}) 1.24 (6H, m, H^8); δ_C (176 Hz, $CDCl_3$) 160.9 (d, C^6), 158.5 (s, C^{15}), 154.8 (d, C^2), 133.6 (s, C^{13}), 133.2 (d, C^4), 127.5 (d, C^3), 126.5 (d, C^5), 113.9 (s, C^{14}), 113.7 (s, C^{12}), 95.7 (s, C^{11}), 85.4 (s, C^{10}), 63.2 (s, C^{19}), 61.3 (s, C^1), 61.1 (d, C^7), 55.3 (s, C^{16}), 51.6 – 36.9 (br m, ring Cs + $C^{17,18}$), 28.6 (C^{19}) 16.2 (d, C^8), 13.6 (m, C^9); δ_P (283 MHz, $CDCl_3$) +39.6; *m/z* (HRMS$^+$) 927.4345 $[M + H]^+$ ($C_{49}H_{65}O_8N_6P_2$ requires 927.4339).

1-2-Aminoethyl-4,7-bis((6-(ethoxy(methyl)phosphoryl)-4-((4-methoxyphenyl)ethynyl)pyridine-2-yl)methyl)-1,4,7-triazacyclononane



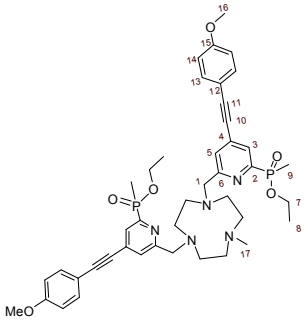
The carbamate (0.08 g. 0.09 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL) and trifluoroacetic acid (0.5 mL) was added. The solution was stirred under argon at 23 °C for 45 min. TLC analysis (silica; CH_2Cl_2 : 10 % CH_3OH, R_f(product) = 0.10, R_f(reactant) = 0.42) was used to confirm that the protecting group removal had gone to completion. The solvent was removed using a high vacuum line (without heating) and the residue re-dissolved in CH_2Cl_2 (1 mL), which was again removed using the same method. This process was repeated 5 times to ensure complete removal of trifluoroacetic acid to give a pale yellow oil (30 mg, 40 %); δ_H (700 MHz, $CDCl_3$) 7.92 (2H, m, H^3), 7.48 (2H, bs, H^5), 7.42 (4H, m, H^{13}), 6.86 (4H, m, H^{14}), 4.16 – 4.10 (2H, m, H^7), 4.10, (4H, s, H^1), 3.92 – 3.88 (2H, m, H^7), 3.76 (6H, s, H^{16}), 3.44 – 2.58 (16H, m, ring Hs + $H^{17,18,}$), 1.72 (6H, m, H^9), 1.24 (6H, m, H^8); δ_C (176 Hz, $CDCl_3$)

160.7 (d, C^6), 157.0 (s, C^{15}), 154.8 (d, C^2), 133.4 (s, C^{13}), 133.0 (d, C^4), 127.5 (d, C^3), 127.0 (d, C^5), 113.9 (s, C^{14}), 113.6 (s, C^{12}), 95.7 (s, C^{11}), 85.4 (s, C^{10}), 61.3 (s, C^1), 61.2 (d, C^7), 55.3 (s, C^{16}), 53.8 – 37.9 (br m, ring Cs + $C^{17,18}$), 28.4 (C^{19}) 16.0 (d, C^8), 13.7 (d, C^9); δ_P (283 MHz, $CDCl_3$) +39.8; *m/z* (HRMS$^+$) 827.3802 $[M + H]^+$ ($C_{44}H_{57}O_6N_6P_2$ requires 827.3809).

[EuL$_2$]

1-N-2'-Aminoethyl-4,7-bis((6-(ethoxy(methyl)phosphoryl)-4-((4-methoxyphenyl)ethynyl)pyridine-2-yl)methyl)-1,4,7-triazacyclononane (5 mg, 0.005 mmol) and K_2CO_3 (1.8 mg, 0.014 mmol) in anhydrous MeCN was stirred at room temperature for 30 min. Methyl bromoacetate (1.7 mg, 0.011 mmol) was added and the mixture was heated at 70°C for 16 hr. On reaction completion (monitored using ESI-MS), the reaction was cooled and the solution decanted from excess potassium salts. Without further purification, the crude product mixture was dissolved in CD_3OD (3 mL) and NaOH (0.1 M in D_2O, 1 mL) was added. The solution was stirred at 60 °C and monitored by ^{1}H-NMR (loss of C*H*$_3$C*H*$_2$ peaks) and ^{31}P-NMR (reactant 39.8 ppm, product 26.4 ppm) and stopped after 16 h. The pH of the solution was adjusted to 6 by addition of HCl (1 M). $EuCl_3$ (1.8 mg, 0.005 mmol) in a H_2O: CH_3OH solution (0.5 mL, 1:1 v/v) was added and the solution was stirred at 50 °C for 24 h The solvent was removed under reduced pressure and the crude material purified by preparative-HPLC to give a white solid (1.5 mg, 29 %); *m/z* (HRMS$^+$) 1037.230 $[M(^{151}Eu)]^+$ ($C_{44}H_{50}O_{10}N_6P_2{}^{151}Eu$ requires 1037.228); τ_{H2O} = 0.70 ms, τ_{D2O} = 1.31 ms; ε_{H2O} (332 nm) = 38,500 M^{-1} cm^{-1}.

1-N-Methyl-4,7-bis((6-(ethoxy(methyl)phosphoryl)-4-((4-methoxyphenyl)ethynyl)pyridine-2-yl)methyl)-1,4,7-triazacyclononane



N-Methyl-1,4,7-triazacyclononane (15 mg, 0.105 mmol) and ethyl(6-(ethyl methanesulfonate)-4-[2-(4-methoxyphenyl)ethynyl]pyridin-2-yl)(methyl)phosphinate (80 mg, 0.189 mmol) were dissolved in anhydrous CH_3CN (10 mL) and K_2CO_3 (44 mg, 0.315 mmol) was added. The mixture was stirred under argon at 78 °C. After 12 h the reaction was cooled and the solution decanted from excess potassium salts. The

solvent was removed under reduced pressure to give a viscous yellow oil (40 mg, 48 %): δ_H (700 MHz, $CDCl_3$) 7.94 (2H, m, H^3), 7.49 (2H, bs, H^5), 7.46 (4H, m, H^{13}), 6.87 (4H, m, H^{14}), 4.08 – 4.02 (2H, m, H^7), 3.89, (4H, s, H^1), 3.90 – 3.86 (2H, m, H^7), 3.82 (6H, s, H^{16}), 3.45 – 2.64 (15H, m, ring Hs + H^{17}), 1.76 (6H, m, H^9), 1.24 (6H, m, H^8); δ_C (151 Hz, $CDCl_3$) 161.4 (d, C^6), 160.5, (s, C^{15}), 153.6 (d, C^2), 133.6 (s, C^{13}), 133.5 (d, C^4), 127.6 (d, C^3), 126.4 (d, C^5), 114.2 (s, C^{14}), 113.9 (s, C^{12}), 95.6(s, C^{11}), 95.3 (s, C^{11}), 85.6 (s, C^{10}), 62.8 (s, C^{19}), 62.5 (s, C^1), 60.8 (d, C^7), 55.3 (s, C^{16}), 55.0 – 38.5 (br m, ring Cs), 16.4 (d, C^8), 13.2 (d, C^9); δ_P (283 MHz, $CDCl_3$) +39.4; ; *m/z* ($HRMS^+$) 798.3553 $[M + H]^+$ ($C_{43}H_{54}O_6N_5P_2$ requires 798.3549).

$[EuL^{1b}]^+ Cl^-$

The diester (4.0 mg, 0.005 mmol) was dissolved in CD_3OD (3 mL) and NaOH (0.1 M in D_2O, 1 mL) was added. The solution was stirred at 60 °C and monitored by ^{1}H-NMR (loss of CH_3CH_2 peaks) and ^{31}P-NMR (reactant 39.4 ppm, product 25.9 ppm) and stopped after 16 h. The pH of the solution was adjusted to 6 by addition of HCl (1 M). $EuCl_3$ (2.0 mg, 0.005 mmol) in a H_2O: CH_3OH solution (0.5 mL, 1:1 v/v) was added and the solution was stirred at 50 °C for 24 h The solvent was removed under reduced pressure and the crude material purified by preparative-HPLC to give a white solid (1.2 mg, 26 %); *m/z* ($HRMS^+$) 892.1917 $[M(^{151}Eu)]^+$ ($C_{39}H_{43}O_6N_5P_2{}^{151}Eu$ requires 892.1912); τ_{H2O} = 0.56 ms, τ_{D2O} = 1.42 ms; ε_{H2O} (332 nm) 38,550 M^{-1} cm^{-1}.

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Notes and References

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