Electronic Supplementary Information

Synthesis and characterisation of bismacrocyclic DO3A-amide derivatives – an approach towards metal-responsive PARACEST agents

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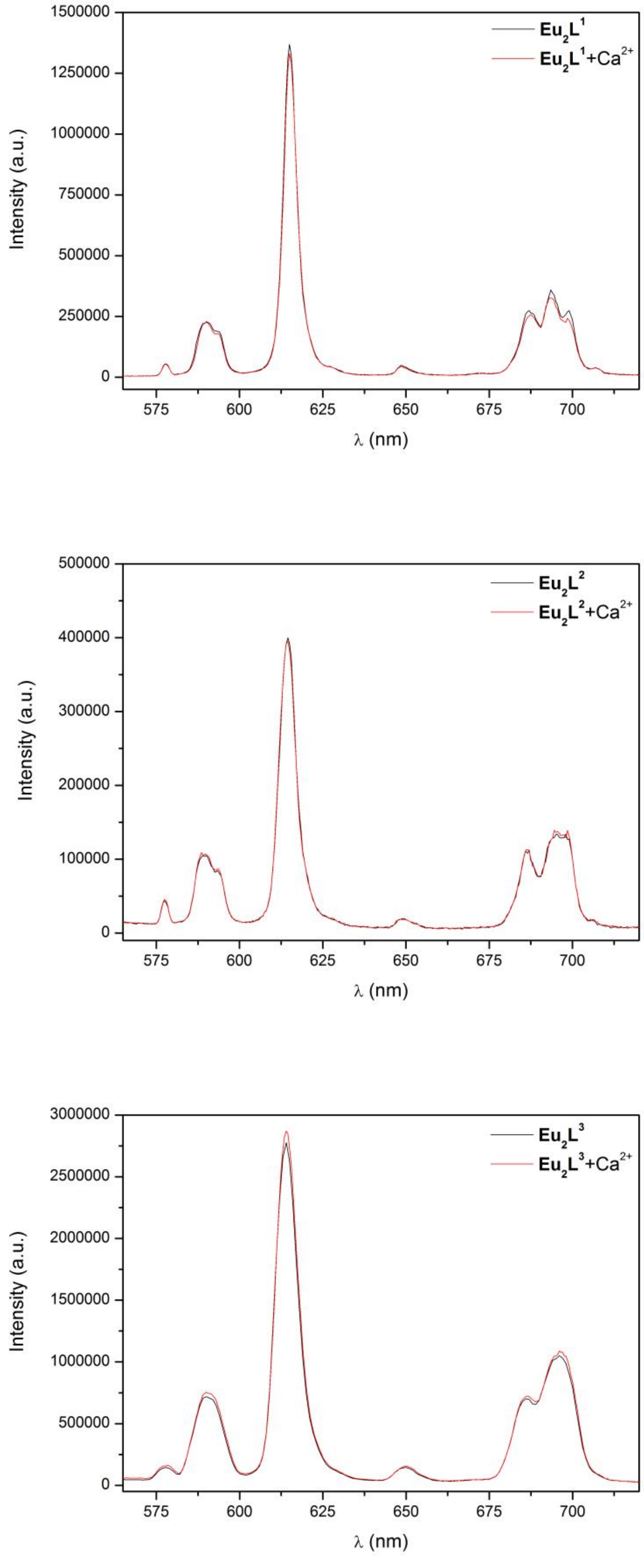

Figure S1. The luminescence emission spectra of **Eu_2L^{1-3}** (5 mM Eu^{3+}) in absence and presence of Ca^{2+} (1 equiv.) at pH 7.4 (HEPES).

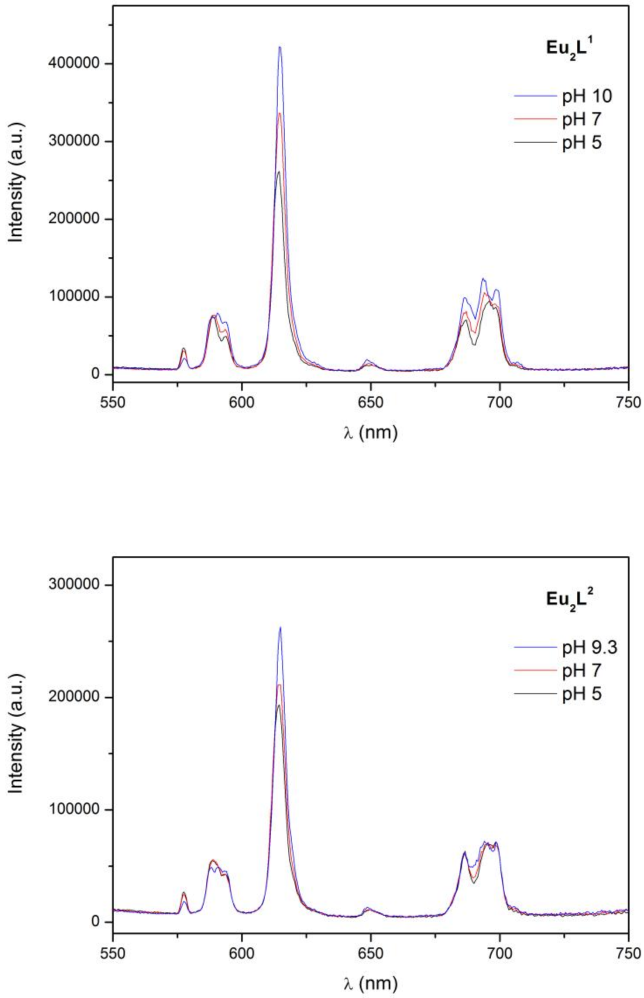

Figure S2. The luminescence emission spectra of $\mathbf{Eu_2L^{1\text{-}2}}$ (5 mM Eu^{3+}) in H_2O at different pH values.

Table S1. Stepwise protonation constants for ligands $\mathbf{L^1}$ and $\mathbf{L^2}$ calculated using the ADMET Predictor software.[1]

$\log K_a$	$\mathbf{L^1}$	$\mathbf{L^2}$
$\log K_{a1}$	8.68	8.45
$\log K_{a2}$	8.11	7.86
$\log K_{a3}$	7.49	7.13
$\log K_{a4}$	7.01	6.50
$\log K_{a5}$	6.57	6.11
$\log K_{a6}$	6.05	5.50
$\log K_{a7}$	4.66	3.68
$\log K_{a8}$	4.24	3.25
$\log K_{a9}$	3.94	2.92
$\log K_{a10}$	3.69	2.62
$\log K_{a11}$	3.47	2.30
$\log K_{a12}$	3.28	1.89
$\log K_{a13}$	3.09	
$\log K_{a14}$	2.90	
$\log K_{a15}$	2.71	
$\log K_{a16}$	2.50	
$\log K_{a17}$	2.24	
$\log K_{a18}$	1.86	

Table S2. Protonation constants of Eu(III)–L (L = $\mathbf{L^1}$ and $\mathbf{L^2}$) complexes (charges in reactions are omitted for simplicity); I=0.1 M (NaCl), t=25±1 °C.

Species (p,q,r)*	$\log\beta_{p,q,r}$ ($\pm\sigma$)*	
	$\mathbf{L^1}$	$\mathbf{L^2}$
$[Eu_2(L)]$ (2, 0, 1)	19.13(5)	20.19(4)
$[Eu_2(HL)]$ (2, 1, 1)	27.85(9)	27.53(5)
$[Eu_2(H_2L)]$ (2, 2, 1)	36.14(7)	32.73(4)
$[Eu_2(H_3L)]$ (2, 3, 1)	42.96(8)	37.16(7)
$[Eu_2(OH)_2L]$ (2, -2, 1)	1.15(4)	1.74(5)
Reaction	$\log K^H$	
$[Eu_2L] + H \rightleftarrows [Eu_2(HL)]$	8.72	7.34
$[Eu_2(HL)] + H \rightleftarrows [Eu_2(H_2L)]$	8.29	5.20
$[Eu_2(H_2L)] + H \rightleftarrows [Eu_2(H_3L)]$	6.82	4.43
$[Eu_2(OH)_2L] + 2H \rightleftarrows [Eu_2L(H_2O)_2]$	9.56	9.09
Statistics	χ^2	
	12.88	13.15
	s	
	0.70	1.08

*p, q, r and $\log\beta_{p,q,r}$ as defined in Eq. (1) and (2).

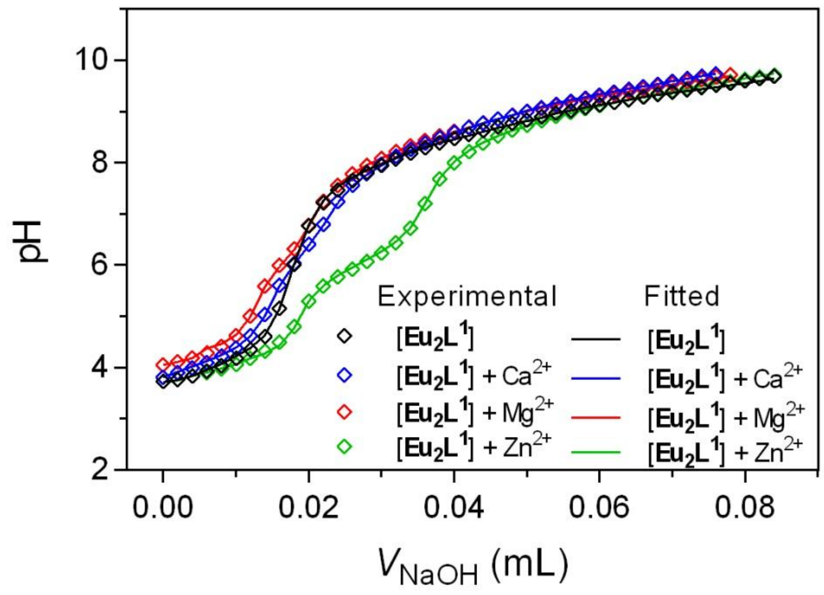

Figure S3. Titration curves of the $\mathbf{Eu_2L^1}$ and [$\mathbf{Eu_2L^1}$]-M (M = Ca^{2+}, Mg^{2+} and Zn^{2+}) systems with standard NaOH, *I*=0.1 M (NaCl) , *t*=25±1 °C. $[\mathbf{Eu_2L^1}]_{total}$ = 2.3185×10^{-4} M, $[Ca^{2+}]_{total}$ = 2.3530×10^{-4} M, $[Mg^{2+}]_{total}$ = 2.5260×10^{-4} M and $[Zn^{2+}]_{total}$ = 2.4057×10^{-4} M. Full lines denote calculated curves.

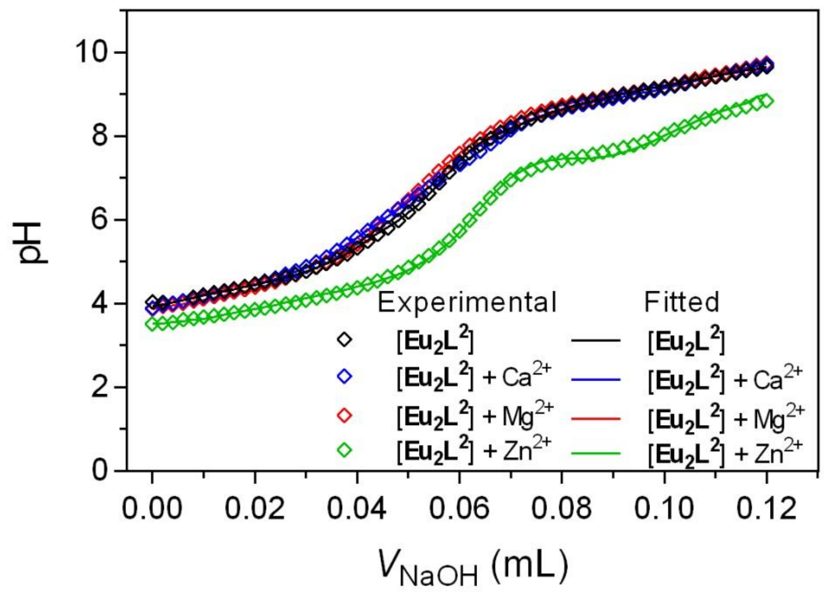

Figure S4. Titration curves of the $\mathbf{Eu_2L^2}$ complex and [$\mathbf{Eu_2L^2}$]-M (M = Ca^{2+}, Mg^{2+} and Zn^{2+}) systems with standard NaOH, *I*=0.1 M (NaCl) , *t*=25±1 °C. $[\mathbf{Eu_2L^2}]_{total}$ = 4.4817×10^{-4} M, $[Ca^{2+}]_{total}$ = 4.4817×10^{-4} M, $[Mg^{2+}]_{total}$ = 4.7970×10^{-4} M and $[Zn^{2+}]_{total}$ = 4.5686×10^{-4} M. Full lines denote calculated curves.

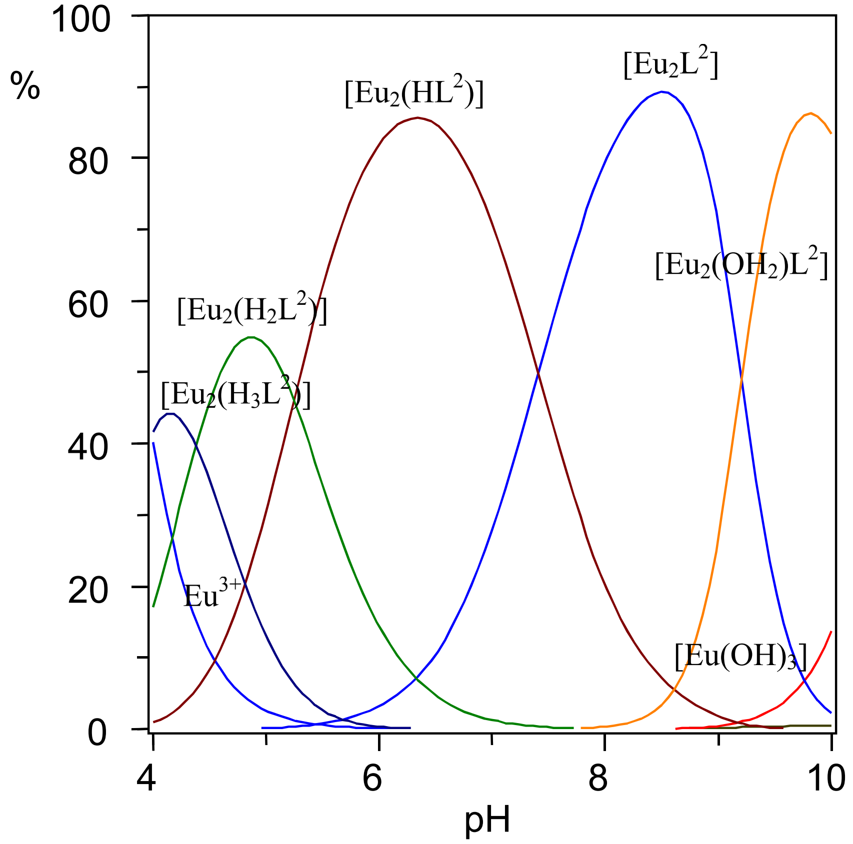

Figure S5. Distribution diagram of Eu – $\mathbf{L}^2$ species at [Eu]:[$\mathbf{L}^2$]=2:1 concentration ratio; total Eu^{3+} concentration 1.0 mM; I=0.1 M (NaCl), t=25±1 °C.

Total concentrations of Eu_2L (L= $\mathbf{L}^1$ or $\mathbf{L}^2$) and [Ca^{2+}], [Mg^{2+}] or [Zn^{2+}] used in the potentiometric titration experiments:

Ca^{2+} binding to Eu_2L^1:
1. [Eu_2L^1]=2.3185×10^{-4} M [Ca^{2+}]=2.3530×10^{-4} M;
2. [Eu_2L^1]=2.2968×10^{-4} M [Ca^{2+}]=2.7972×10^{-4} M;
3. [Eu_2L^1]=2.2650×10^{-4} M [Ca^{2+}]=3.4481×10^{-4} M.

Ca^{2+} binding to Eu_2L^2:
1. [Eu_2L^2]=4.4817×10^{-4} M [Ca^{2+}]=4.4686×10^{-4} M;
2. [Eu_2L^2]=4.4027×10^{-4} M [Ca^{2+}]=5.2678×10^{-4} M;
3. [Eu_2L^2]=4.2894×10^{-4} M [Ca^{2+}]=6.4152×10^{-4} M.

Mg^{2+} binding to Eu_2L^1:
1. [Eu_2L^1]=2.3185×10^{-4} M [Mg^{2+}]=2.5260×10^{-4} M;
2. [Eu_2L^1]=2.2968×10^{-4} M [Mg^{2+}]=3.0028×10^{-4} M;
3. [Eu_2L^1]=2.2650×10^{-4} M [Mg^{2+}]=3.7015×10^{-4} M.

Mg^{2+} binding to Eu_2L^2:
1. $[Eu_2L^2]$=4.4817×10^{-4} M $[Mg^{2+}]$=4.7970×10^{-4} M;
2. $[Eu_2L^2]$=4.4027×10^{-4} M $[Mg^{2+}]$=5.6550×10^{-4} M;
3. $[Eu_2L^2]$=4.2894×10^{-4} M $[Mg^{2+}]$=6.8867×10^{-4} M.

Zn^{2+} binding to Eu_2L^1:
1. $[Eu_2L^1]$=2.3185×10^{-4} M $[Zn^{2+}]$=2.4057×10^{-4} M;
2. $[Eu_2L^1]$=2.2968×10^{-4} M $[Zn^{2+}]$=2.8598×10^{-4} M;
3. $[Eu_2L^1]$=2.2650×10^{-4} M $[Zn^{2+}]$=3.5253×10^{-4} M.

Zn^{2+} binding to Eu_2L^2:
1. $[Eu_2L^2]$=4.4817×10^{-4} M $[Zn^{2+}]$=4.5686×10^{-4} M;
2. $[Eu_2L^2]$=4.4027×10^{-4} M $[Zn^{2+}]$=5.3857×10^{-4} M;
3. $[Eu_2L^2]$=4.2894×10^{-4} M $[Zn^{2+}]$=6.5588×10^{-4} M.

Table S3. Stability constants of Eu(III)–L–M (L = $\mathbf{L^1}$ or $\mathbf{L^2}$; M = Ca^{2+}, Mg^{2+} or Zn^{2+}) complexes (charges in reactions are omitted for simplicity); I=0.1 M (NaCl), t=25±1 °C.

	$\log\beta_{p,q,r,m}$ (±σ)*					
Species (p,q,r,m)*	$\mathbf{L^1}$			$\mathbf{L^2}$		
	Ca^{2+}	Mg^{2+}	Zn^{2+}	Ca^{2+}	Mg^{2+}	Zn^{2+}
$[Eu_2(L)M]$ (2, 0, 1, 1)	23.73(6)	23.21(4)	26.06(6)	24.43(3)	23.57(4)	25.78(6)
$[Eu_2(HL)M]$ (2, 1, 1, 1)	32.53(8)	31.71(8)	34.53(3)	32.11(5)	31.65(6)	33.00(8)
$[Eu_2(H_2L)M]$ (2, 2, 1, 1)	40.66(9)	39.76(7)	-	38.11(6)	37.21(8)	-
$[Eu_2(H_3L)M]$ (2, 3, 1, 1)	-	-	-	42.64(8)	41.88(5)	-
Reaction	$\log K_s$					
$[Eu_2(L)] + M \rightleftarrows [Eu_2(L)M]$	4.60	4.08	6.93	4.24	3.38	5.59
$[Eu_2(HL)] + M \rightleftarrows [Eu_2(HL)M]$	4.68	3.86	6.68	4.58	4.12	5.47
$[Eu_2(H_2L)] + M \rightleftarrows [Eu_2(H_2L)M]$	4.52	3.62	-	5.38	4.48	-
$[Eu_2(H_3L)] + M \rightleftarrows [Eu_2(H_3L)M]$	-	-	-	5.48	4.72	-
Statistics	χ^2					
	12.95	12.86	12.17	13.31	12.23	11.39
	s					
	1.07	0.73	0.77	1.07	1.15	0.95

*p, q, r, m and $\log\beta_{p,q,r,m}$ as defined in Eq. (3) and (4).

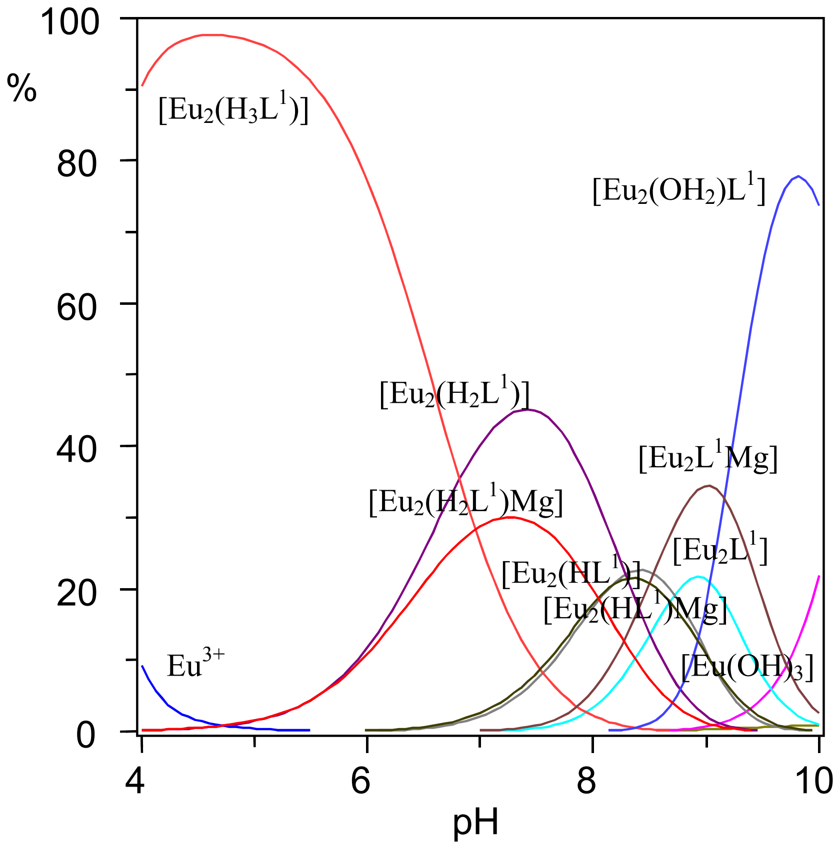

Figure S6. Distribution diagram of Eu–**L**[1]–Mg species at [Eu]:[**L**[1]]:[Mg]=2:1:1 concentration ratio; total Eu^{3+} concentration 0.5 mM; *I*=0.1 M (NaCl), *t*=25±1 °C.

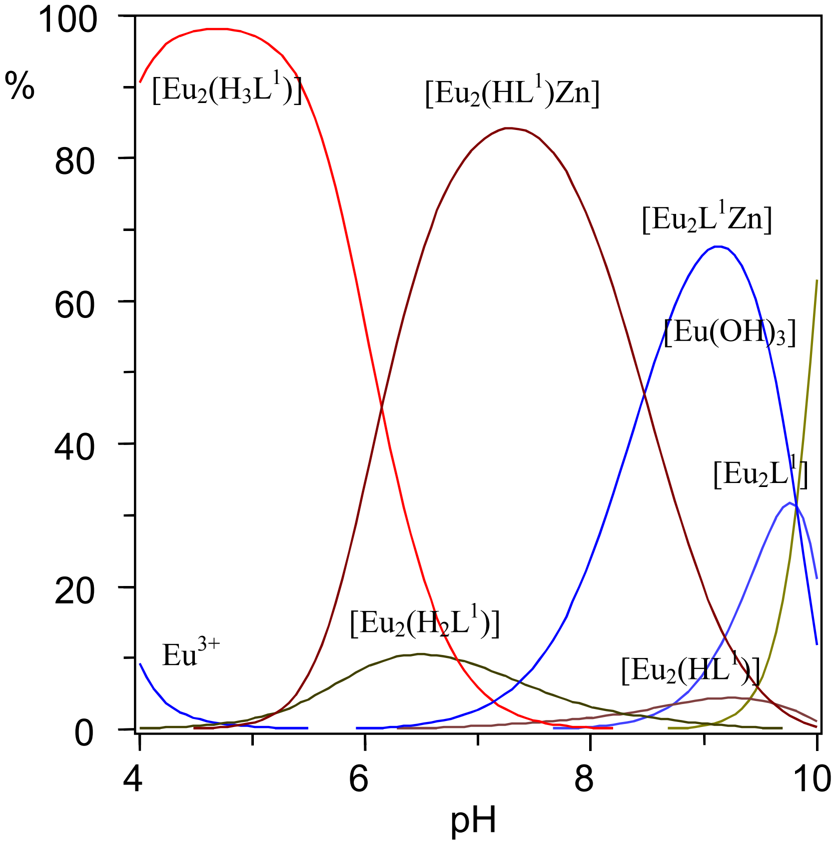

Figure S7. Distribution diagram of Eu–**L**[1]–Zn species at [Eu]:[**L**[1]]:[Zn]=2:1:1 concentration ratio; total Eu^{3+} concentration 0.5 mM; *I*=0.1 M (NaCl), *t*=25±1 °C.

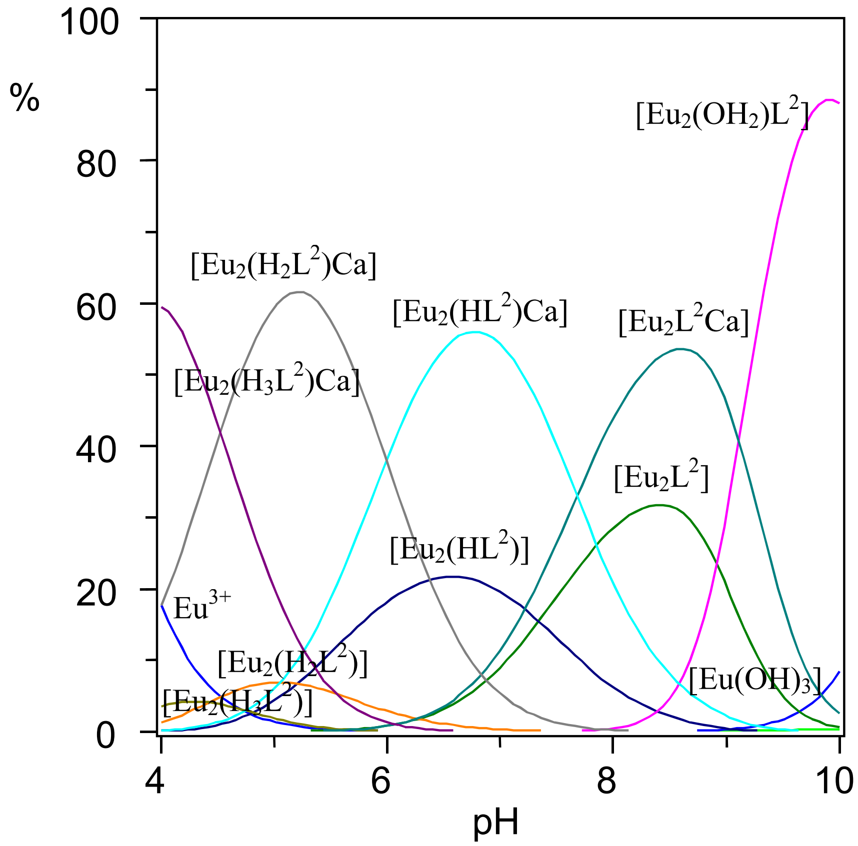

Figure S8. Distribution diagram of Eu–**L**^{2}–Ca species at [Eu]:[**L**^{2}]:[Zn]=2:1:1 concentration ratio; total Eu^{3+} concentration 1.0 mM; *I*=0.1 M (NaCl), *t*=25±1 °C.

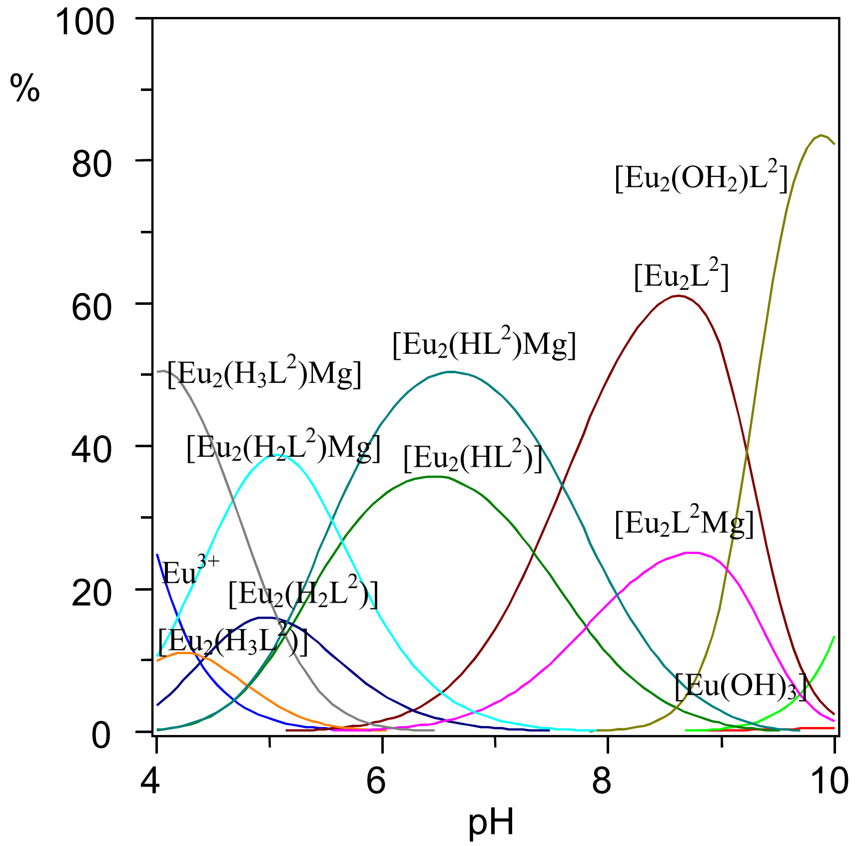

Figure S9. Distribution diagram of Eu–**L**^{2}–Mg species at [Eu]:[**L**^{2}]:[Mg]=2:1:1 concentration ratio; total Eu^{3+} concentration 1.0 mM; *I*=0.1 M (NaCl), *t*=25±1 °C.

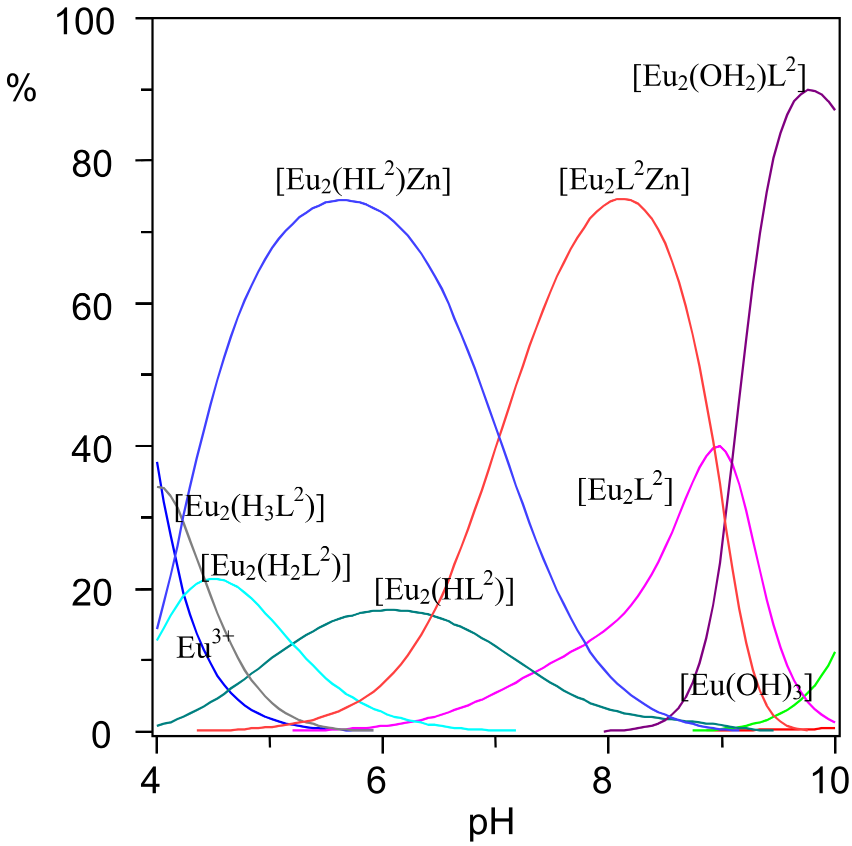

Figure S10. Distribution diagram of Eu–**L**^{2}–Zn species at [Eu]:[**L**^{2}]:[Zn]=2:1:1 concentration ratio; total Eu^{3+} concentration 1.0 mM; *I*=0.1 M (NaCl), *t*=25±1 °C.

References

1. ADMET Predictor, Simulations Plus, Inc., Lancaster, CA, USA, ver. 7.2, 2015.