

Supplementary data for the article:

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Electronic Supplementary Information

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

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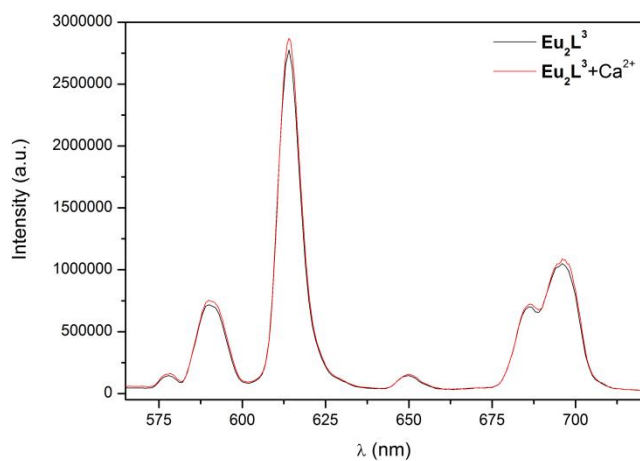
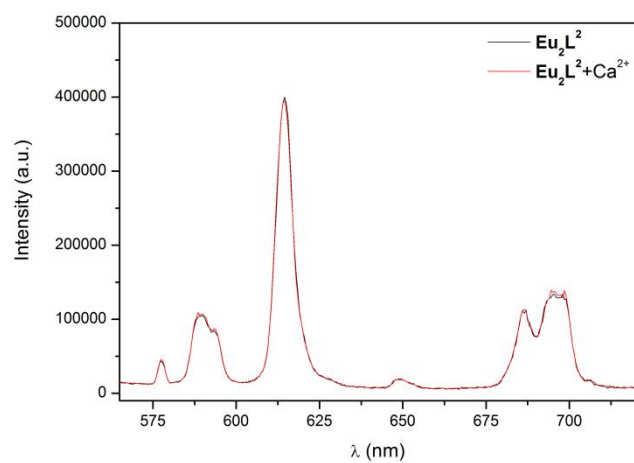
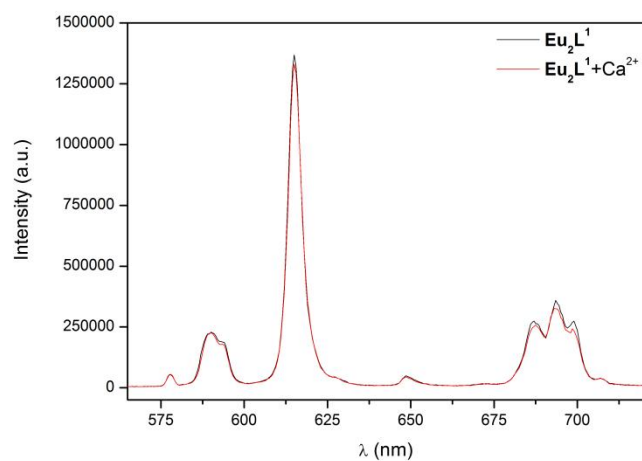


Figure S1. The luminescence emission spectra of $\text{Eu}_2\text{L}^{1-3}$ (5 mM Eu^{3+}) in absence and presence of Ca^{2+} (1 equiv.) at pH 7.4 (HEPES).

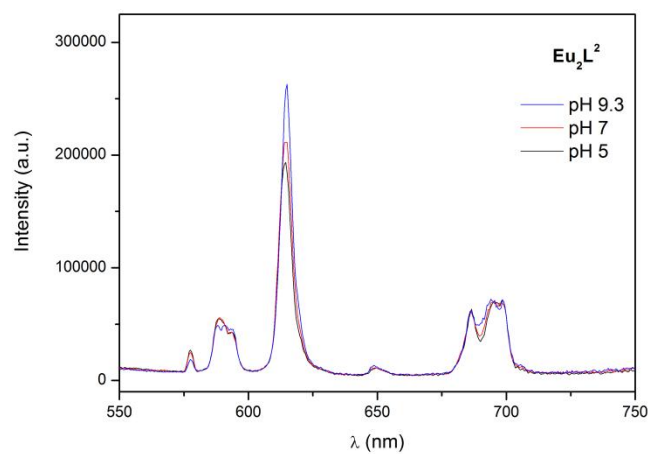
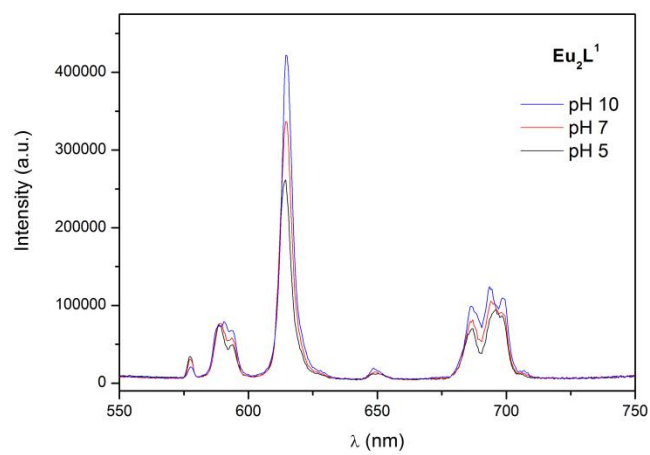


Figure S2. The luminescence emission spectra of $\text{Eu}_2\text{L}^{1-2}$ (5 mM Eu^{3+}) in H_2O at different pH values.

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 ($\mathbf{L} = \mathbf{L}^1$ and \mathbf{L}^2) complexes (charges in reactions are omitted for simplicity); $I=0.1$ M (NaCl), $t=25\pm 1$ °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 ₂ L)] (2, 2, 1)	36.14(7)	32.73(4)
[Eu ₂ (H ₃ L)] (2, 3, 1)	42.96(8)	37.16(7)
[Eu ₂ (OH) ₂ L] (2, -2, 1)	1.15(4)	1.74(5)
Reaction	$\log K^H$	
[Eu ₂ L] + H \rightleftharpoons [Eu ₂ (HL)]	8.72	7.34
[Eu ₂ (HL)] + H \rightleftharpoons [Eu ₂ (H ₂ L)]	8.29	5.20
[Eu ₂ (H ₂ L)] + H \rightleftharpoons [Eu ₂ (H ₃ L)]	6.82	4.43
[Eu ₂ (OH) ₂ L] + 2H \rightleftharpoons [Eu ₂ L(H ₂ O) ₂]	9.56	9.09
Statistics	χ^2	
	12.88	13.15
Statistics	s	
	0.70	1.08

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

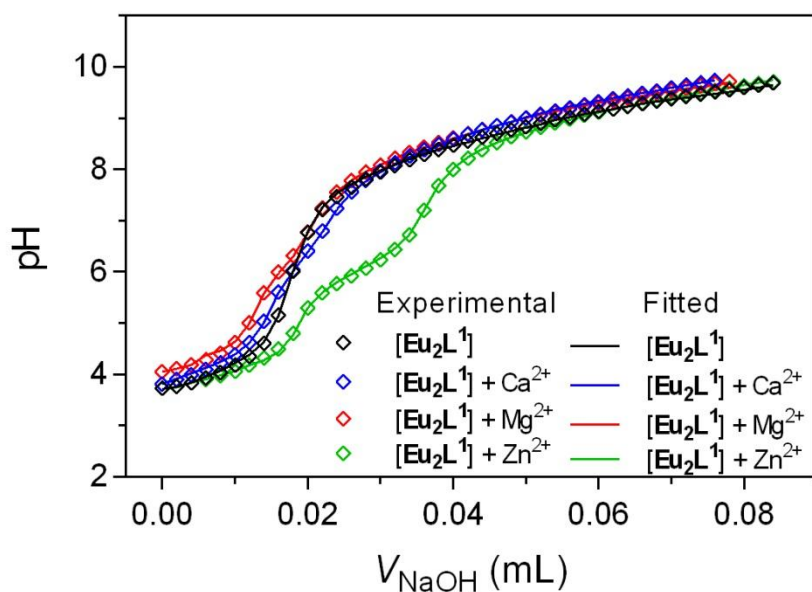


Figure S3. Titration curves of the Eu_2L^1 and $[\text{Eu}_2\text{L}^1]\text{-M}$ ($\text{M} = \text{Ca}^{2+}$, Mg^{2+} and Zn^{2+}) systems with standard NaOH, $I=0.1$ M (NaCl), $t=25\pm 1$ °C. $[\text{Eu}_2\text{L}^1]_{\text{total}} = 2.3185\times 10^{-4}$ M, $[\text{Ca}^{2+}]_{\text{total}} = 2.3530\times 10^{-4}$ M, $[\text{Mg}^{2+}]_{\text{total}} = 2.5260\times 10^{-4}$ M and $[\text{Zn}^{2+}]_{\text{total}} = 2.4057\times 10^{-4}$ M. Full lines denote calculated curves.

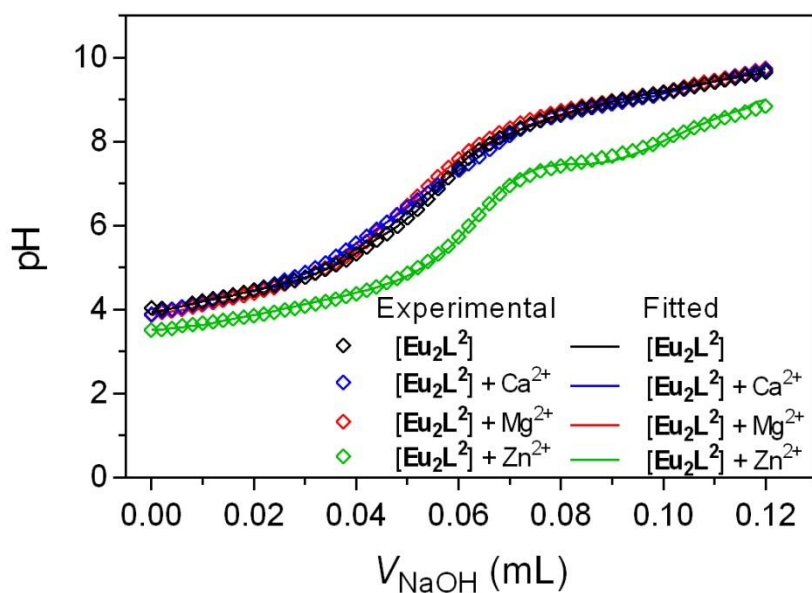


Figure S4. Titration curves of the Eu_2L^2 complex and $[\text{Eu}_2\text{L}^2]\text{-M}$ ($\text{M} = \text{Ca}^{2+}$, Mg^{2+} and Zn^{2+}) systems with standard NaOH, $I=0.1$ M (NaCl), $t=25\pm 1$ °C. $[\text{Eu}_2\text{L}^2]_{\text{total}} = 4.4817\times 10^{-4}$ M, $[\text{Ca}^{2+}]_{\text{total}} = 4.4817\times 10^{-4}$ M, $[\text{Mg}^{2+}]_{\text{total}} = 4.7970\times 10^{-4}$ M and $[\text{Zn}^{2+}]_{\text{total}} = 4.5686\times 10^{-4}$ M. Full lines denote calculated curves.

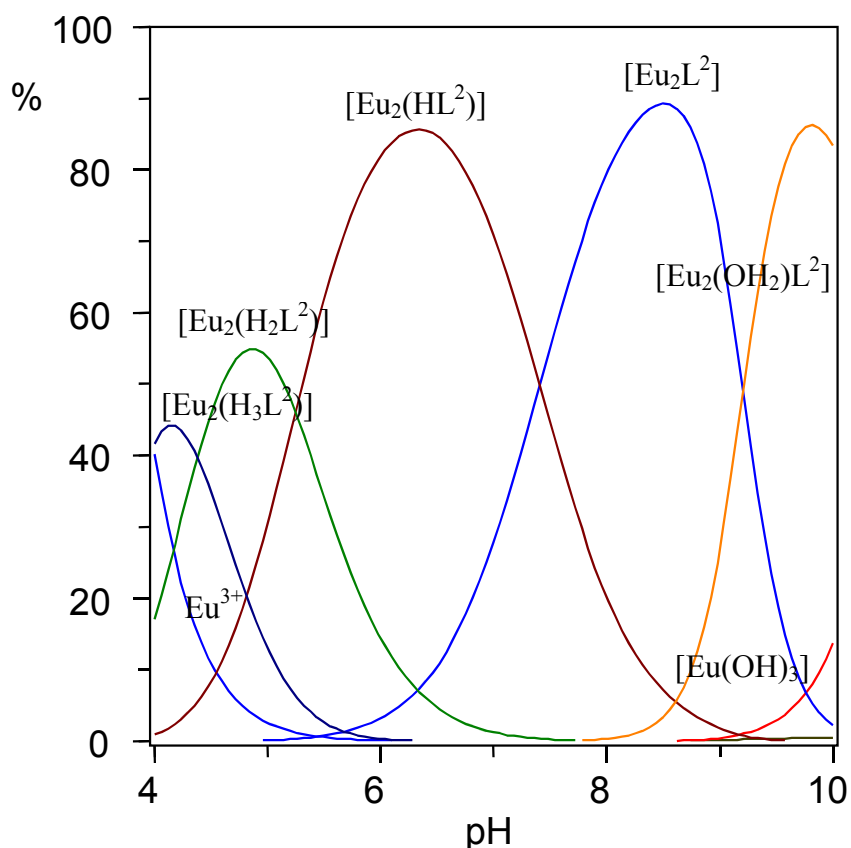


Figure S5. Distribution diagram of Eu – L² species at [Eu]:[L²]=2:1 concentration ratio; total Eu³⁺ concentration 1.0 mM; I=0.1 M (NaCl), t=25±1 °C.

Total concentrations of Eu₂L (L= L¹ or L²) and [Ca²⁺], [Mg²⁺] or [Zn²⁺] used in the potentiometric titration experiments:

Ca²⁺ binding to Eu₂L¹:

1. [Eu₂L¹]=2.3185×10⁻⁴ M [Ca²⁺]=2.3530×10⁻⁴ M;
2. [Eu₂L¹]=2.2968×10⁻⁴ M [Ca²⁺]=2.7972×10⁻⁴ M;
3. [Eu₂L¹]=2.2650×10⁻⁴ M [Ca²⁺]=3.4481×10⁻⁴ M.

Ca²⁺ binding to Eu₂L²:

1. [Eu₂L²]=4.4817×10⁻⁴ M [Ca²⁺]=4.4686×10⁻⁴ M;
2. [Eu₂L²]=4.4027×10⁻⁴ M [Ca²⁺]=5.2678×10⁻⁴ M;
3. [Eu₂L²]=4.2894×10⁻⁴ M [Ca²⁺]=6.4152×10⁻⁴ M.

Mg²⁺ binding to Eu₂L¹:

1. [Eu₂L¹]=2.3185×10⁻⁴ M [Mg²⁺]=2.5260×10⁻⁴ M;
2. [Eu₂L¹]=2.2968×10⁻⁴ M [Mg²⁺]=3.0028×10⁻⁴ M;
3. [Eu₂L¹]=2.2650×10⁻⁴ M [Mg²⁺]=3.7015×10⁻⁴ M.

Mg²⁺ binding to Eu₂L²:

1. [Eu₂L²]=4.4817×10⁻⁴ M [Mg²⁺]=4.7970×10⁻⁴ M;
2. [Eu₂L²]=4.4027×10⁻⁴ M [Mg²⁺]=5.6550×10⁻⁴ M;
3. [Eu₂L²]=4.2894×10⁻⁴ M [Mg²⁺]=6.8867×10⁻⁴ M.

Zn²⁺ binding to Eu₂L¹:

1. [Eu₂L¹]=2.3185×10⁻⁴ M [Zn²⁺]=2.4057×10⁻⁴ M;
2. [Eu₂L¹]=2.2968×10⁻⁴ M [Zn²⁺]=2.8598×10⁻⁴ M;
3. [Eu₂L¹]=2.2650×10⁻⁴ M [Zn²⁺]=3.5253×10⁻⁴ M.

Zn²⁺ binding to Eu₂L²:

1. [Eu₂L²]=4.4817×10⁻⁴ M [Zn²⁺]=4.5686×10⁻⁴ M;
2. [Eu₂L²]=4.4027×10⁻⁴ M [Zn²⁺]=5.3857×10⁻⁴ M;
3. [Eu₂L²]=4.2894×10⁻⁴ M [Zn²⁺]=6.5588×10⁻⁴ M.

Table S3. Stability constants of Eu(III)–L–M (L = L¹ or L²; M = Ca²⁺, Mg²⁺ or Zn²⁺) complexes (charges in reactions are omitted for simplicity); I=0.1 M (NaCl), t=25±1 °C.

Species (p,q,r,m) [*]	logβ _{p,q,r,m} (±σ) [*]					
	L ¹			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 ₂ L)M] (2, 2, 1, 1)	40.66(9)	39.76(7)	-	38.11(6)	37.21(8)	-
[Eu ₂ (H ₃ L)M] (2, 3, 1, 1)	-	-	-	42.64(8)	41.88(5)	-
Reaction	logK _s					
[Eu ₂ (L)] + M ⇌ [Eu ₂ (L)M]	4.60	4.08	6.93	4.24	3.38	5.59
[Eu ₂ (HL)] + M ⇌ [Eu ₂ (HL)M]	4.68	3.86	6.68	4.58	4.12	5.47
[Eu ₂ (H ₂ L)] + M ⇌ [Eu ₂ (H ₂ L)M]	4.52	3.62	-	5.38	4.48	-
[Eu ₂ (H ₃ L)] + M ⇌ [Eu ₂ (H ₃ L)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 logβ_{p,q,r,m} as defined in Eq. (3) and (4).

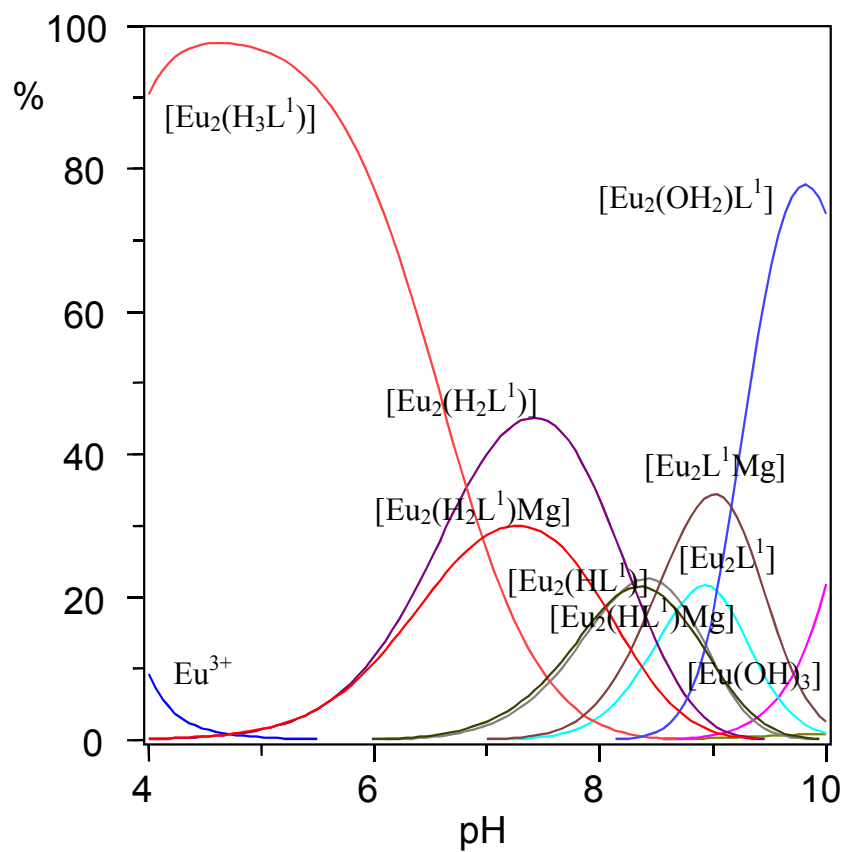


Figure S6. Distribution diagram of Eu–L¹–Mg species at [Eu]:[L¹]:[Mg]=2:1:1 concentration ratio; total Eu³⁺ concentration 0.5 mM; *I*=0.1 M (NaCl), *t*=25±1 °C.

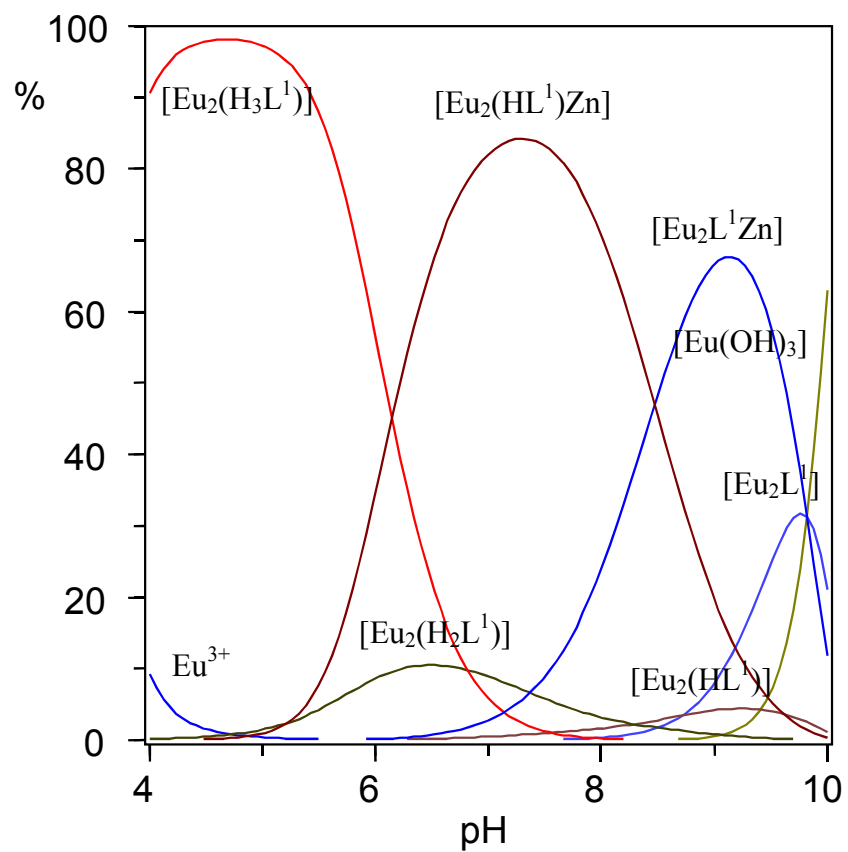


Figure S7. Distribution diagram of Eu–L¹–Zn species at [Eu]:[L¹]:[Zn]=2:1:1 concentration ratio; total Eu³⁺ concentration 0.5 mM; *I*=0.1 M (NaCl), *t*=25±1 °C.

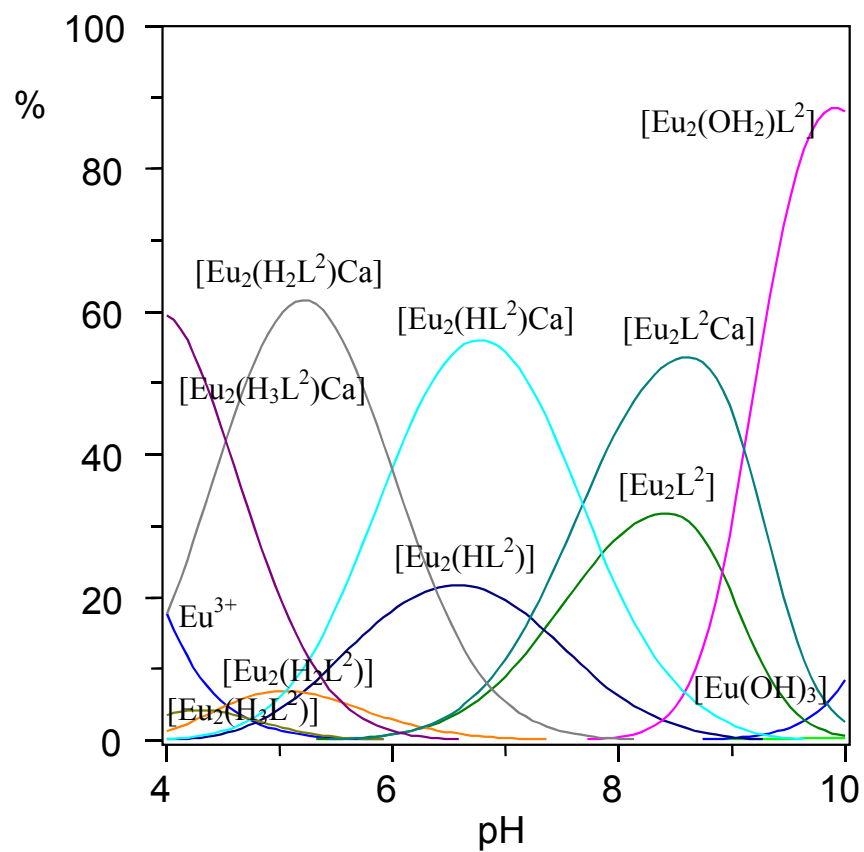


Figure S8. Distribution diagram of Eu–L²–Ca species at [Eu]:[L²]:[Zn]=2:1:1 concentration ratio; total Eu³⁺ concentration 1.0 mM; *I*=0.1 M (NaCl), *t*=25±1 °C.

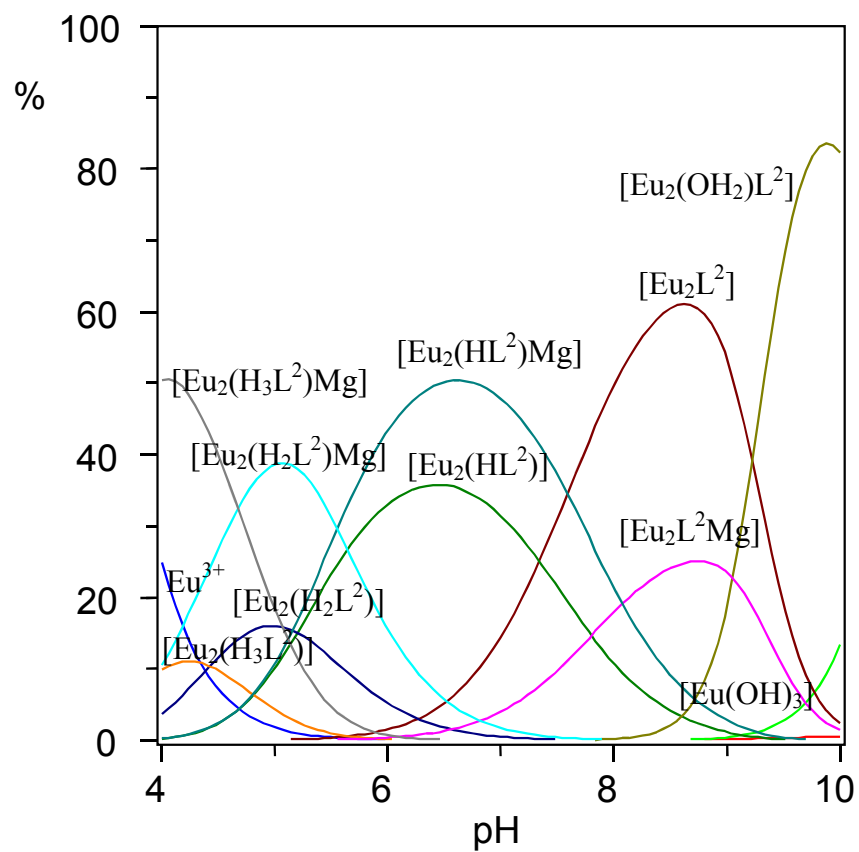


Figure S9. Distribution diagram of Eu–L²–Mg species at [Eu]:[L²]:[Mg]=2:1:1 concentration ratio; total Eu³⁺ concentration 1.0 mM; *I*=0.1 M (NaCl), *t*=25±1 °C.

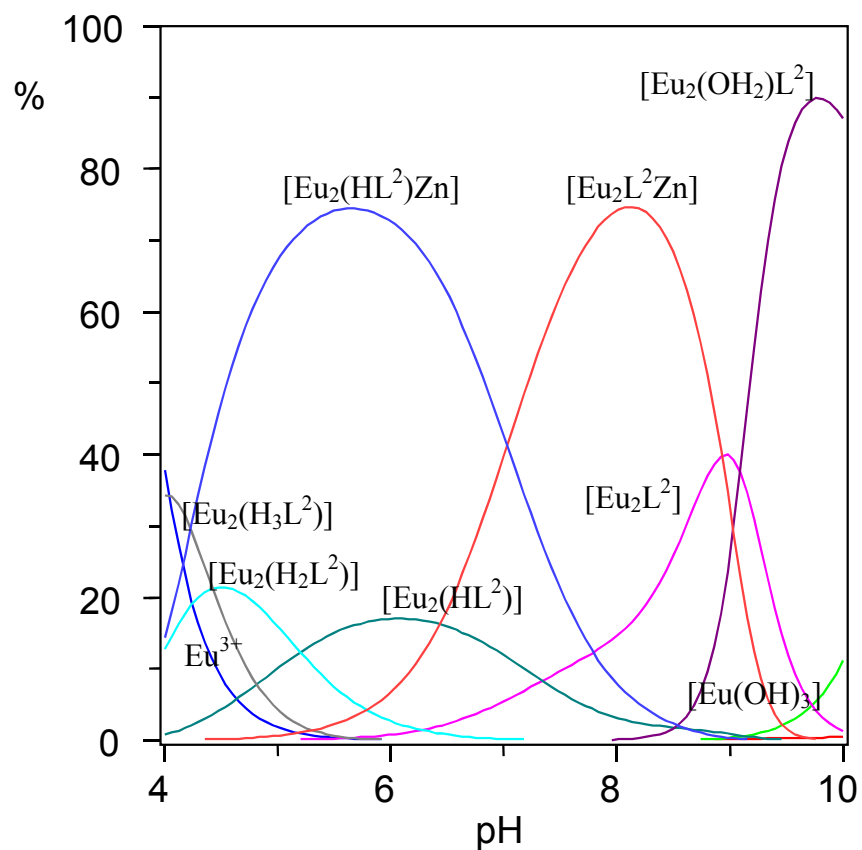


Figure S10. Distribution diagram of Eu–L²–Zn species at [Eu]:[L²]:[Zn]=2:1:1 concentration ratio; total Eu³⁺ concentration 1.0 mM; *I*=0.1 M (NaCl), *t*=25±1 °C.

References

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