

Click Chemistry with Lanthanide Complexes: a Word of Caution

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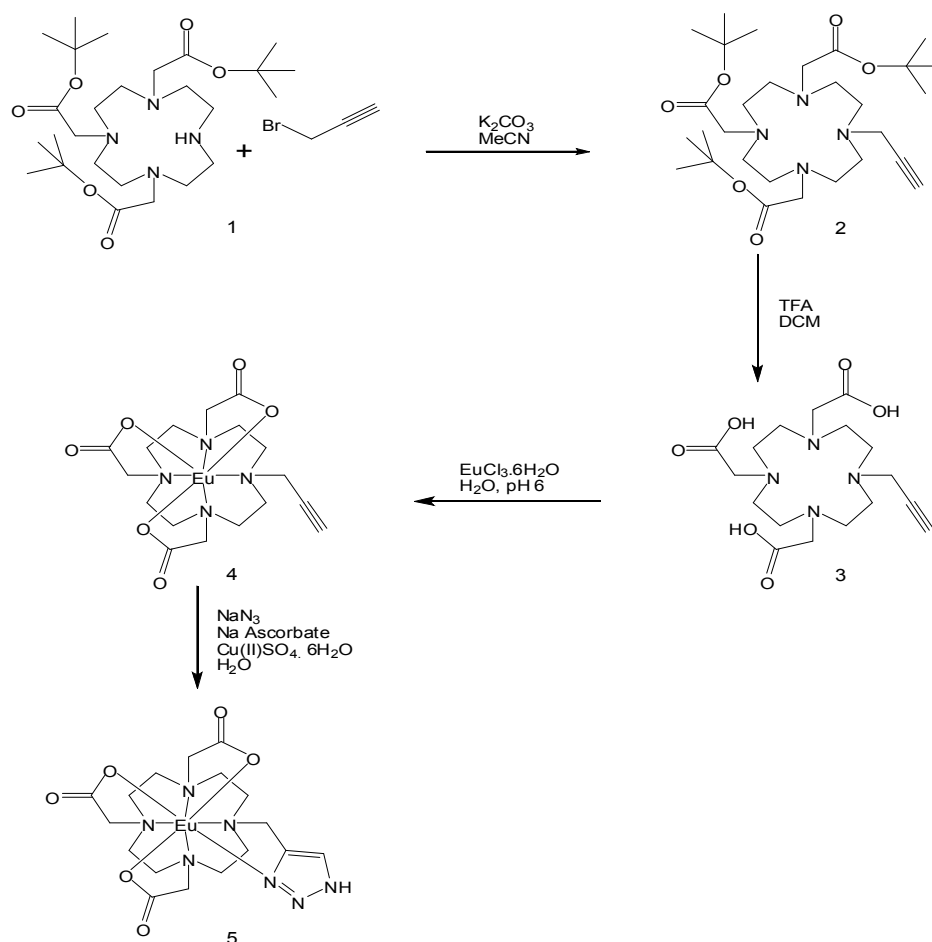
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Supporting Information

Experimental

General procedures. NMR spectra were recorded on Brüker DRX400 and AV500 instruments using standard Brüker software. Low resolution ESMS were recorded on an open access Micromass Quatro (LC) spectrometer. Accurate mass ESMS for the Eu(III) complexes were recorded on a Finnigan MAT 900 XLT high resolution double focussing mass spectrometer with tandem ion trap (polyethylenimine reference compound).

Materials. Reagents are commercially available and were used without further purification. 1,4,7-tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane¹ was prepared according to literature procedure.



Scheme S1. Synthesis of Europium(III)1,4,7-tris(carboxymethyl)-10-((1H-1,2,3-triazol-4-yl)methyl)-1,4,7,10-tetraazacyclododecane.

1,4,7-tris(*tert*-butoxycarbonylmethyl)-10-(prop-2-ynyl)-1,4,7,10-tetraazacyclododecane, **2**.

A solution of **1** (0.100 g, 0.194 mmol), propargyl bromide (0.022 g, 0.0164 mL, 0.194 mmol) and K_2CO_3 (0.026 g, 0.194 mmol) in MeCN (2 mL) was stirred under nitrogen for 2 h at room temperature. The inorganic salts were filtered off and the solvent was concentrated under vacuo, giving a pale yellow oil (0.100 g, 86%) δ_H (400 MHz, $CDCl_3$) 1.38 (27H, s, $\sim C(CH_3)_3$), 2.07 (1H, t, $^4J_{HH}$ 2.3 Hz, $\sim C\equiv CH$), 2.61-2.63 (4H, bm, $\sim CH_2NCH_2$), 2.72-2.75 (12H, bm, $\sim NCH_2CH_2N$), 3.21 (6H, bm, $\sim NCH_2CO_2$), 3.36 (2H, bm, $\sim NCH_2C\equiv CH$). δ_C (75.4 MHz, $CDCl_3$): 173.4, 172.7, 169.4 ($\sim CO$), 82.8, 82.6 ($\sim C(CH_3)_3$), 78.9 ($\sim C\equiv CH$), 72.6 ($\sim C\equiv CH$), 56.7 ($\sim NCH_2C\equiv CH$), 56.4 ($\sim NCH_2CO_2$), 55.7 ($\sim NCH_2CO_2$), 51.0, 50.5, 49.8, 49.7 ($\sim NCH_2$), 27.8 ($\sim C(CH_3)_3$). m/z (ESMS+) 553 $[M + H]^+$

1,4,7-tris(carboxymethyl)-10-(prop-2-ynyl)-1,4,7,10-tetraazacyclododecane **3**.

2 (0.100 g, 0.18 mmol), was dissolved in DCM (2.5 mL), to this trifluoroacetic acid (2.5 mL) was added and the solution was stirred at room temperature for 24 h. The solvent was removed in vacuo.

Then DCM (2 x 5 mL) was added and removed in vacuo, followed by diethylether (2 x 5 mL) and removed in vacuo, yielding a hygroscopic white solid as the bis-trifluoroacetate salt (0.06 g, 89%). δ_{H} (400 MHz, D₂O) 2.95 (1H, bm, $\sim\text{C}\equiv\text{CH}$), 3.16 (8H, bm, $\sim\text{NCH}_2\text{CH}_2\text{N}\sim$) 3.34 (8H, bm, $\sim\text{NCH}_2\text{CH}_2\text{N}\sim$), 3.73 (2H, bs, $\sim\text{NCH}_2\text{C}\equiv\text{CH}\sim$), 3.95 (6H, bm, $\sim\text{NCH}_2\text{CO}_2\sim$). δ_{C} (125.7 MHz, D₂O): 163.3, 163.1, 162.7 ($\sim\text{CO}\sim$), 78.5 ($\sim\text{C}\equiv\text{CH}\sim$), 72.4 ($\sim\text{C}\equiv\text{CH}$), 52.9 ($\sim\text{NCH}_2\text{C}\equiv\text{CH}$), 51.7 ($\sim\text{NCH}_2\text{CO}_2\sim$), 50.1 ($\sim\text{NCH}_2\text{CO}_2\sim$), 49.1, 48.2, 47.8, 46.9 ($\sim\text{NCH}_2\sim$). m/z (ESMS+) 385 [M + H]⁺.

Europium(III) 1,4,7-tris(carboxymethyl)-10-(prop-2-ynyl)-1,4,7,10-tetraazacyclododecane, 4.

A solution of **3** (0.173 g, 0.452 mmol) and EuCl₃·6H₂O (0.198 g, 0.544 mmol) were prepared in water (5 mL) and adjusted to pH 7 by addition of NaOH. On mixing the pH fell to \sim 5, due to the release of protons on complexation. The solution was adjusted to pH 6 using NaOH and was stirred at room temperature for 72 h. The solution was then added to Dowex Mac-3 cation exchange resin at pH 5. Xylenol orange was used to test for free europium, once the absence free metal ion was demonstrated, the solution was filtered and lyophilised giving a white hygroscopic solid (0.275 g, 86%). m/z (ESMS+) 533 [M + H]⁺ (¹⁵¹Eu), (HR-ESMS+) [M+H]⁺ calcd for C₁₇H₂₆N₄O₆Eu; 533.1045, found; 533.1039 (¹⁵¹Eu).

Europium(III) 1,4,7-tris(carboxymethyl)-10-((1H-1,2,3-triazol-4-yl)methyl)-1,4,7,10-tetraazacyclododecane, 5.

4 (30 mg, 56 μmol) and sodium azide (40 mg, 62 μmol) were dissolved in H₂O (5 mL). To this sodium ascorbate (1 mg, 5.6 μmol) and CuSO₄·5H₂O (0.7 mg, 2.3 μmol) were added sequentially. The solution was stirred at room temperature for 24 h. After passing down an Amberlite XAD-16 resin column, the fractions containing the complex were lyophilised to give a hygroscopic white solid (0.022 g, 68%). ¹H NMR (D₂O, 400 MHz, 278K) multiple resonances from δ -20 to +40 ppm characteristic of DOTA-like complexes of Eu(III). The four resonances shifted to highest frequency correspond to four axial ring hydrogens of the square antiprismatic geometry (the enantiomers; $\Delta(\lambda\lambda\lambda\lambda)$ and $\Lambda(\delta\delta\delta\delta)$), δ 33.38, 33.14, 32.58, 31.29 ppm. The resonances corresponding to four axial ring hydrogens of the twisted square antiprismatic geometry ($\Delta(\lambda\lambda\lambda\lambda)$ and $\Lambda(\delta\delta\delta\delta)$), δ 13.55, 13.31, 11.29, 9.87 ppm. m/z (ESMS-) 574 [M-H]⁻ (¹⁵¹Eu), (HR-ESMS-) [M-H]⁻ calcd for C₁₇H₂₅N₇O₆Eu; 574.1070, found; 574.1060 (¹⁵¹Eu).

Luminescence Spectroscopy

Luminescence data was recorded using a Jobin Yvon Horiba FluoroMax-P spectrometer (using DataMax for Windows v2.2). Samples were held in a 10x10 nm or 10x2 nm quartz Hellma cuvette and cut-off filter (450 nm) was used to avoid second-order diffraction effects.

Europium Lifetime Measurements

Excited state lifetime measurements were made on a Jobin Yvon Horiba Fluoromax-P (using DataMax for Windows v2.2). Lifetimes were measured by excitation (395 nm direct) of the sample with a short 40 ms pulse of light (500 pulses per point) followed by monitoring the integrated intensity of light (617 nm) emitted during a fixed gate time of 0.1 ms, at a delay time later. Delay times were set at 0.1 ms intervals, covering 4 or more lifetimes. Excitation and emission slits were set to 5:5 nm bandpass respectively. The obtained decay curves were fitted to a simple mono-exponential first-order decay curve using Microsoft Excel.

q -values were calculated using the following equation:²

$$q = 1.2[k_{\text{H}_2\text{O}} - k_{\text{D}_2\text{O}} - 0.25]$$

pH Titrations

pH measurements were recorded using a Jenway 3510 pH meter with a BDH probe, model 309-1025-02 calibrated at pH 4, 7 and 10. The pH titration was carried out in a background of constant ionic strength ($I = 0.1$ NaCl, 298 K). For luminescence Studies, aqueous solutions of 1 mM Eu complexes were raised to pH 10 by addition of 1 M NaOH and titrated to acid pH by addition of small aliquots of 1 M or 0.1 M HCl. For NMR studies, solutions of 2 mM Eu complex in D₂O were raised to pD 10 by addition of 1 M NaOD and titrated to acid pH by addition of small aliquots of 1 M or 0.1 M DCl. For each titration 15-20 points were recorded. Data analysis was performed using an iterative least-square fitting procedure, operating in Microsoft Excel

References

- (1) A. Beeby, L. M. Bushby, D. Maffeo and J. A. G. Williams, *J. Chem. Soc., Dalton Trans.*, 2002, 48-54; L. M. Shultze and A. R. Bulls, U. S. patent 5,631,368, 1997; *Chem. Abstr.*, 1996, **125**, 315328.
- (2) A. Beeby, I. M. Clarkson, R. S. Dickins, S. Faulkner, D. Parker, L. Royle, A. S. de Sousa, J. A. G. Williams and M. Woods, *J. Chem. Soc., Perkin Trans. 2*, 1999, 493-503.

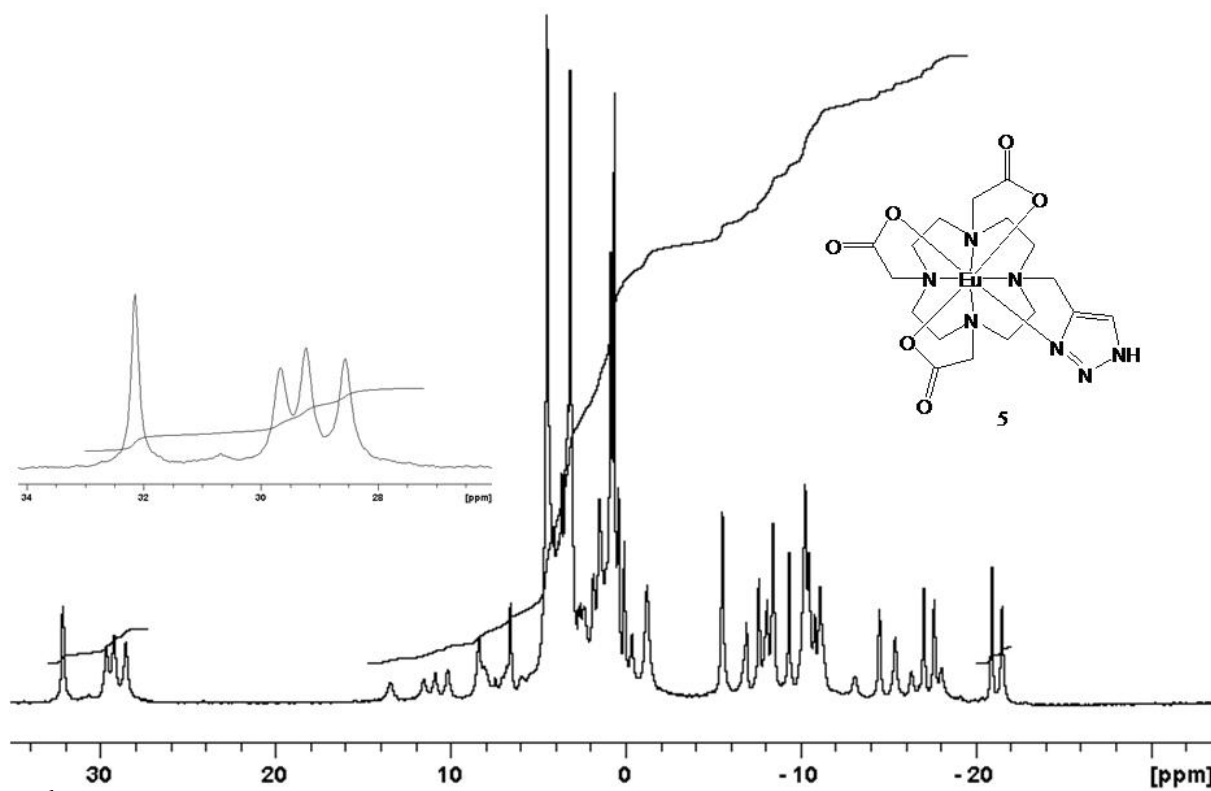


Figure S1. ¹H NMR spectrum of 5 (400 MHz, 278K, pD 4).

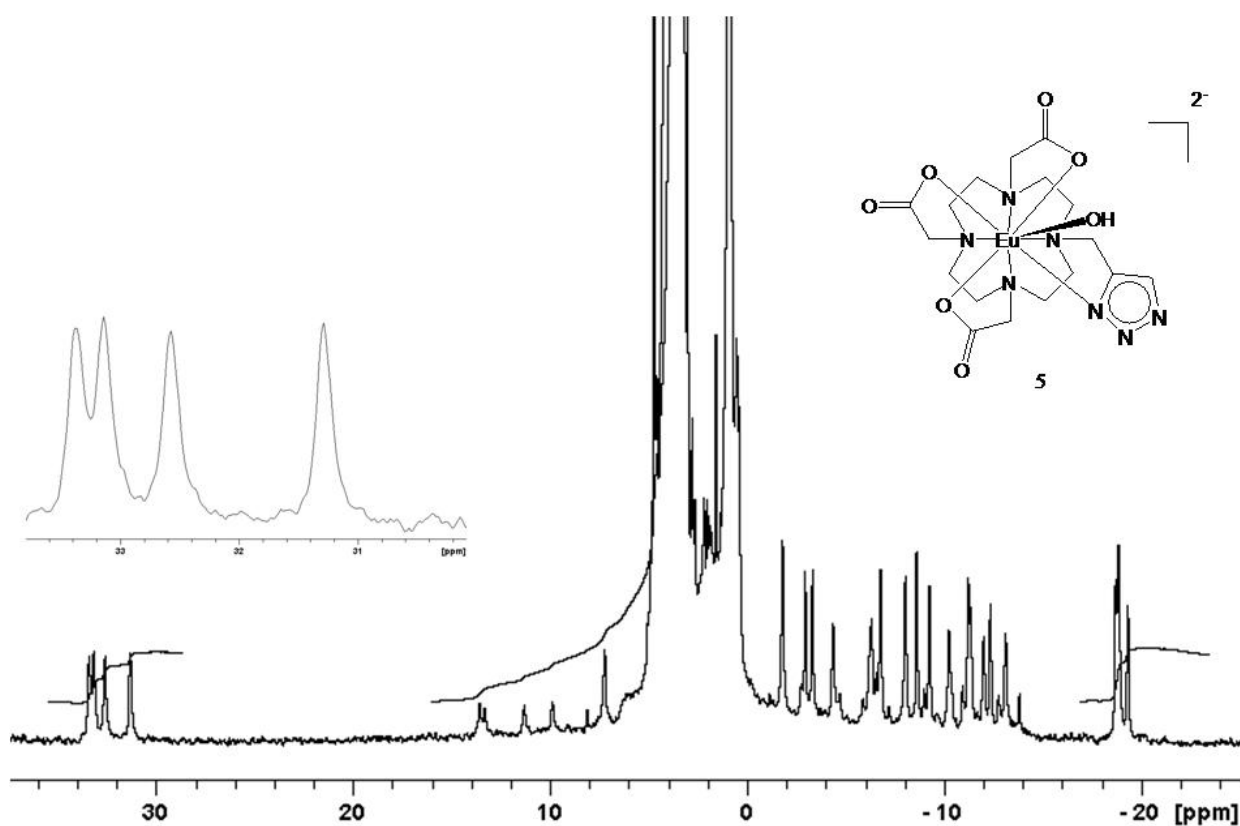


Figure S2. ¹H NMR spectrum of 5 (400 MHz, 278K, pD 10).

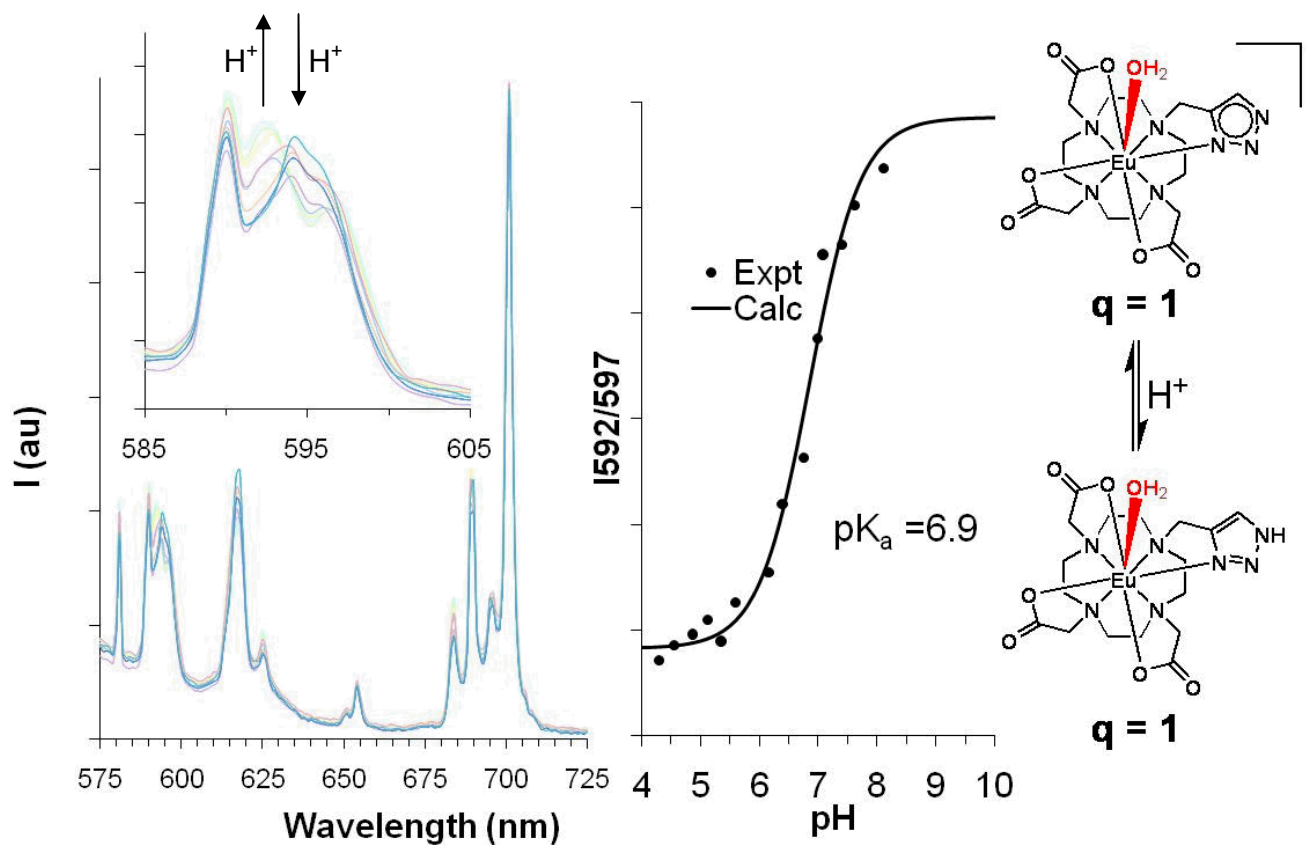


Figure S3. Luminescent emission vs. pH for **5** (At pH > 8.5 spectral changes due to deprotonation of bound water overlap this protonation event).