Electronic Supplementary Information for

SAP/TSAP Isomerisation in Cyclen-Based Lanthanide(III) Chelates May be Substantially Affected by Local Environmental Factors such as Solvent.

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Experimental

General Remarks: All reagents and solvent were purchased from commercial sources and used as received unless otherwise stated. 'Water' refers to deionized water with a resistivity of 18.2 MΩcm-1 or greater. NMR spectra were recorded on a Bruker Avance III spectrometer operating at 400.13 MHz (^{1}H) and 100.61 MHz (^{13}C). Emission spectra and luminescence lifetimes were determined on an Edinburgh Instruments FL/FS900CDT. Preparative HPLC purifications were performed on a Waters δ-prep HPLC using a 30 × 250 mm Phenomenex C18(2) Luna column. Melting points were recorded on a Fisher Johns melting point apparatus and are uncorrected. Mass spec data were collected by Andrew Ott and Jennifer Seymour of the Integrated Molecular Structure Education and Research Center, Northwestern University, whose contribution is gratefully acknowledged.

DOTAM, DTMA, DOTTA and **3** were all prepared using previously published methods {*J. Chem. Soc., Perkin Trans. 2* **1990**, 1425; *Angew. Chem., Int. Ed. Engl*. **1994**, **33**, 773; *J. Am. Chem. Soc.* **1999**, 5762; *Chem. Commun*. **2008**, 1671}.

General procedure for the preparation of tertiary haloacetamides

To a cooled solution of bromoacetyl bromide or chloroacetyl chloride (22 mmol) in dichloromethane (150 mL) (0 ºC, ice bath) was added potassium carbonate (44 mmol) and then a solution the appropriate secondary amine (17.6 mmol) in dichloromethane (50 mL), drop-wise. The resulting suspension was stirred at 0 ºC for 3 hours before warming to room temperature and stirring for a further 18 hours. The reaction was quenched by the cautious addition of water (30 mL) and the two phases separated. The aqueous phase was then further extracted with dichloromethane (2 × 50 mL). All organic phases were combined, dried (Na_2SO_4) and the solvents removed *in vacuo*.

2-Chloro-1-(pyrrolidin-1-yl)ethanone

The title compound was obtained as a colourless gum (2.27 g, 63 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.99 (2H, s, $ClC\underline{H}_2$), 3.46 (2H, m, $NC\underline{H}_2$), 3.40 (2H, m, $NC\underline{H}_2$), 1.94 (2H, m, $NCH_2C\underline{H}_2$), 1.82 (2H, m, $NCH_2C\underline{H}_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.0 ($NCH_2\underline{C}H_2$), 26.0 ($NCH_2\underline{C}H_2$), 42.1 ($N\underline{C}H_2CH_2$), 46.1 ($N\underline{C}H_2CH_2$), 46.4 ($Cl\underline{C}H_2$), 164.5 (C=O); m/z (ESMS, ESI+) 148 (100, [M+H$^+$]), 170 (46, [M+Na$^+$]) an appropriate isotope pattern was observed; ν_{max} / cm^{-1}; 2977, 2881, 1645 (C=O), 1449, 1280, 1231, 1166.1036, 930, 786; Anal. Found C = 48.9 %, H = 6.8 %, N = 9.5 % $C_6H_{10}ClNO$ requires C = 48.8 %, H = 6.8 %, N = 9.5 %.

N,N-Dibenzyl-2-bromoacetamide

The title compound was obtained as a colourless oil (4.97 g, 78 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43-7.307 (6H, m br, 3-Ar and 4-Ar), 7.24 (2H, d, $^3J_{H\text{-}H}$ 7 Hz, 2-Ar), 7.19 (2H, d, $^3J_{H\text{-}H}$ 7 Hz, 2-Ar), 4.64 (2H, s, $C\underline{H}_2Ar$), 4.54 (2H, s, $C\underline{H}_2Ar$), 3.93 (2H, s, $BrC\underline{H}_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 26.6 ($Br\underline{C}H_2CO$), 49.0 ($\underline{C}H_2Ar$), 50.9 ($\underline{C}H_2Ar$), 126.5 (Ar), 127.7 (Ar), 128.0 (Ar), 128.2 (Ar), 128.6 (Ar), 130.2 (Ar), 135.7 (Ar), 136.5 (Ar), 167.5 (C=O); m/z (ESMS, ESI+) 317 (58, [M+H$^+$]), 340 (100, [M+Na$^+$]) an appropriate isotope pattern was observed; ν_{max} / cm^{-1}; 3087, 3062 3030, 2926, 1657 (C=O), 1495, 1450, 1362, 1206, 1077, 1029, 950, 731.

General procedure for the preparation of DOTA-tetra tertiary amide ligands

To a solution of cyclen (2.4 mmol) in acetonitrile (100 mL) was added potassium carbonate (10 mmol) and the appropriate bromoacetamide (10 mmol) and the resulting suspension heated to 60 ºC with stirring for 48 hours. After cooling to room temperature the solvents were removed *in vacuo*. The residue was then divided between dichloromethane (200 mL) and water (30 mL). The aqueous phase was further extracted with dichloromethane (2 × 50 mL) and the combined organic phase dried (Na_2SO_4) and the solvents removed under reduced pressure.

2,2',2'',2'''-(1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetrayl)tetrakis(1-(pyrrolidin-1-yl)ethanone) (1)

The title compound was obtained as its dihydrochloride salt after purification by preparative RP-HPLC eluting isocratically with 99% water (0.037% HCl) and 1 % MeCN for 5 minutes followed by a linear gradient to 65 % water (0.037% HCl) and 35 %MeCN at 40 minutes. A colourless solid was thus obtained (0.55 g, 37 %).

Mp = 148 - 150 ºC; ^{1}H NMR (400 MHz, D_2O) δ = 3.87 (8H, s br, $NC\underline{H}_2CO$), 3.34 (16H, m, $NC\underline{H}_2CH_2$), 3.28 (16H, s br, NCH_2 ring), 1.90 (8H, m, $NCH_2C\underline{H}_2$), 1.80 (8H, m, $NCH_2C\underline{H}_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 22.1 ($NCH_2\underline{C}H_2$), 24.1 ($N\underline{C}H_2CH_2$), 43.7 ($N\underline{C}H_2CO$), 48.9 (ring NCH_2), 52.5 (ring NCH_2), 163.1 (C=O); m/z (ESMS, ESI+) 309 (82, [M+2H$^+$]), 617 (100, [M+H$^+$]); ν_{max} / cm^{-1}; 3433 (br, NH), 2973, 2877, 1646 (C=O), 1477, 1454, 1374, 1165, 1088, 979, 954, 858, 806. 707; Anal. Found C = 51.8 %, H = 8.4 %, N = 15.1 % $C_{32}H_{56}N_8O_4.2HCl.3H_2O$ requires C = 51.7 %, H = 8.7 %, N = 15.1 %.

1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetra-*N*,*N*-dibenzyl acetamide(2)

The title compound was obtained after purification by column chromatography over silica gel, eluting with 5% MeOH in CH_2Cl_2, as a colourless solid (1.5 g, 57 %).

R_f = 0.2 (SiO_2, 5% MeOH in CH_2Cl_2); Mp = 99 – 101 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28-6.83 (40H, m, Ar), 5.03 (4H, d, $^2J_{HH}$ = 15 Hz, NCH_2 ring), 4.27 (4H, d, $^2J_{HH}$ = 17 Hz aa′ system, $C\underline{H}_2Ar$), 4.27 (4H, d aa′ system, $^2J_{HH}$ = 15 Hz, $C\underline{H}_2Ar$), 4.17 (4H, d aa′ system, $^2J_{HH}$ = 15 Hz, $C\underline{H}_2Ar$), 3.91 (4H, d, $^2J_{HH}$ = 15 Hz, $C\underline{H}_2Ar$), 3.80 (4H, d, $^2J_{HH}$ = 15 Hz, $C\underline{H}_2Ar$), 3.08 (8H, m, $NC\underline{H}_2CO$), 2.71 (4H, m, $NC\underline{H}_2$ ring), 2.14 (8H, m, $NC\underline{H}_2$ ring); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 46.4 (ring NCH_2), 46.8 (NCH_2CO), 53.3 ($\underline{C}H_2Ar$), 124.4 (Ar), 125.5 (Ar), 125.8 (Ar), 126.3 (Ar), 126.6 (Ar), 127.1 (Ar) 134.0 (Ar), 135.0 (Ar), 169.9

(C=O); m/z (ESMS, ESI+) 1144 (100, [M+Na$^+$]); ν_{max} / cm^{-1}; 2061, 3028, 2923, 2817, 1650 (C=O), 1468, 1452, 1358, 1220, 1120, 1107, 1081, 1029, 995, 971, 734; Anal. Found C = 69.6 %, H = 6.8 %, N = 8.7 % $C_{72}H_{80}N_8O_4.1.8CH_2Cl_2$ requires C = 69.6 %, H = 6.6 %, N = 8.8 %.

Additional Figures

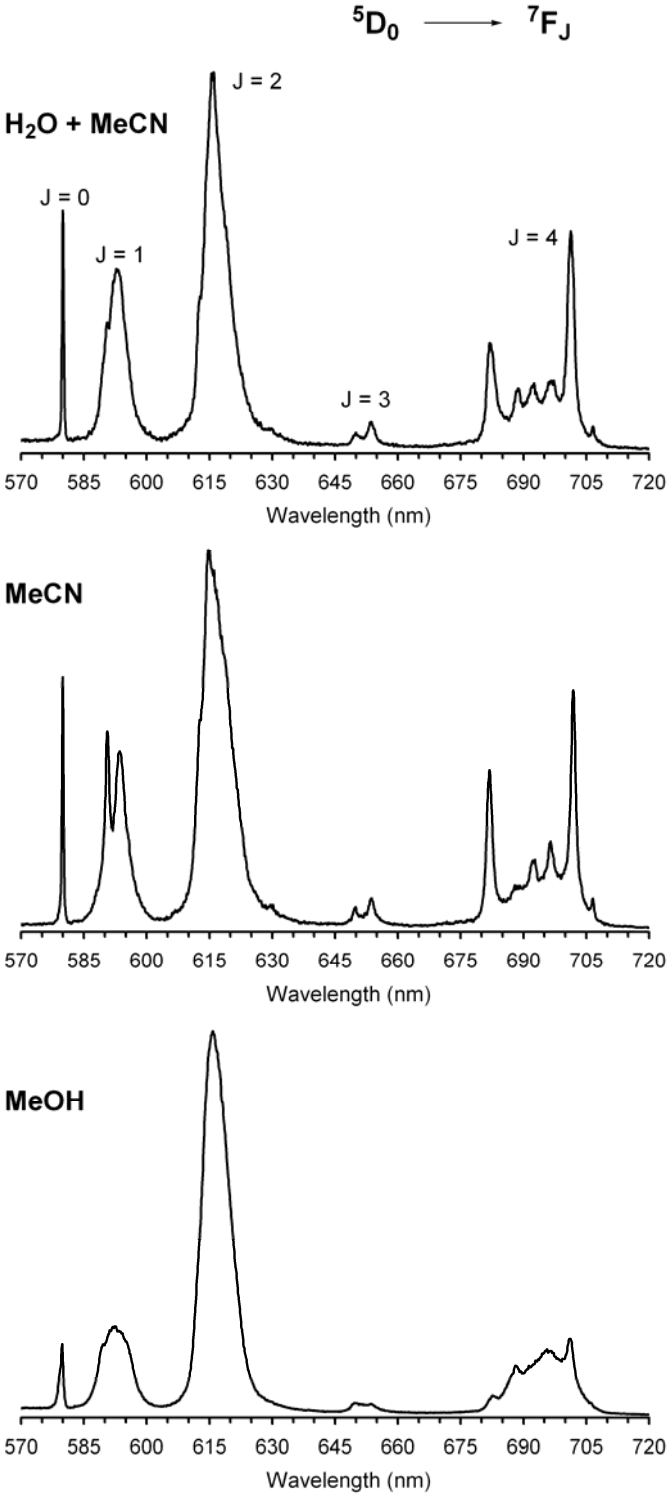

Figure S1. Emission spectra of Eu**2** recorded at 0.1 nm spectral resolution in the solvents specified. No change in the energy of the non-degenerate $^5D_0 \rightarrow {}^7F_0$ transition was observed upon changing the solvent.

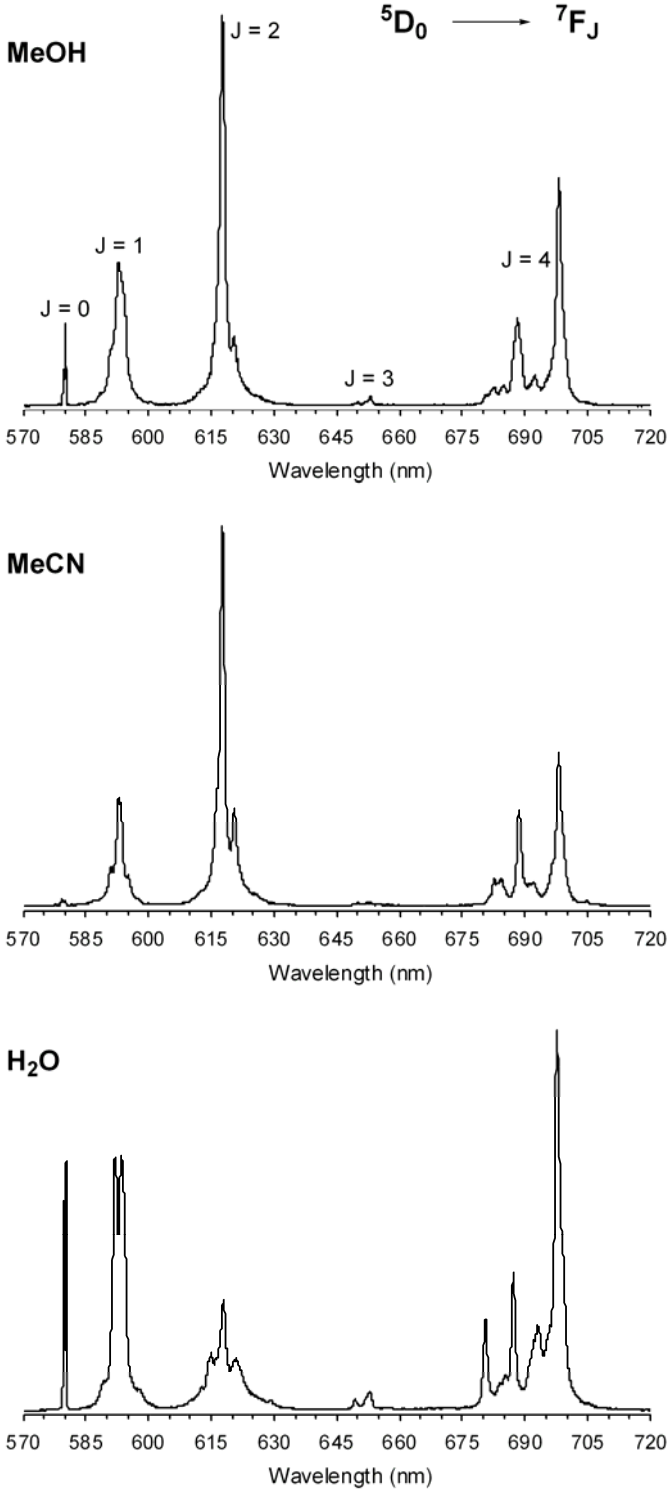

Figure S2. Emission spectra of Eu**3** recorded at 0.1 nm spectral resolution in the solvents specified. More than one energy gap for the non-degenerate $^5D_0 \rightarrow {}^7F_0$ transition is observed in each spectrum upon changing the solvent indicating the presence of multiple species in each sample. Notably this 'splitting' of the $\Delta J = 0$ transition mirrors the SAP/TSAP isomerism observed in the ^{1}H NMR spectra of this chelate. The ^{1}H NMR shift patterns, unusual for cyclen derived chelates, (*Inorg. Chem.* **2010**, 49 7700) may in turn help to explain the high ratio between the $^5D_0 \rightarrow {}^7F_1$ and $^5D_0 \rightarrow {}^7F_2$ transition peaks (except in the case of MeOH), that is usually indicative of Eu^{3+} present in a centrosymmetric environment (*e.g. Inorg. Chem*. **2008**, 47, 7802 and *J. Phys. Chem. A* **2002**, 106, 3681)

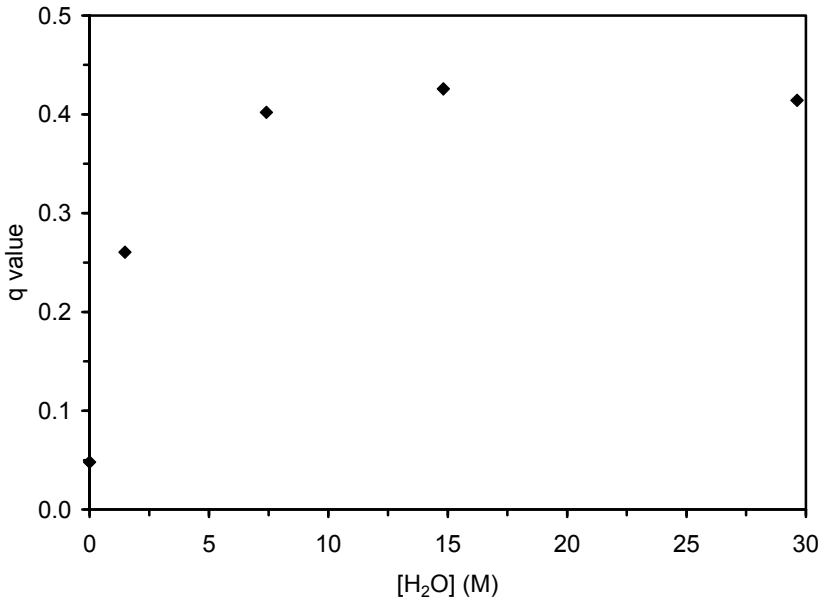

Figure S3. The variation in hydration state of Eu^{3+} as water (H_2O/D_2O) was titrated into a dry solution of Eu**2** in CH_3CN; λ_{ex} = 397 nm, λ_{em} = 613 nm.

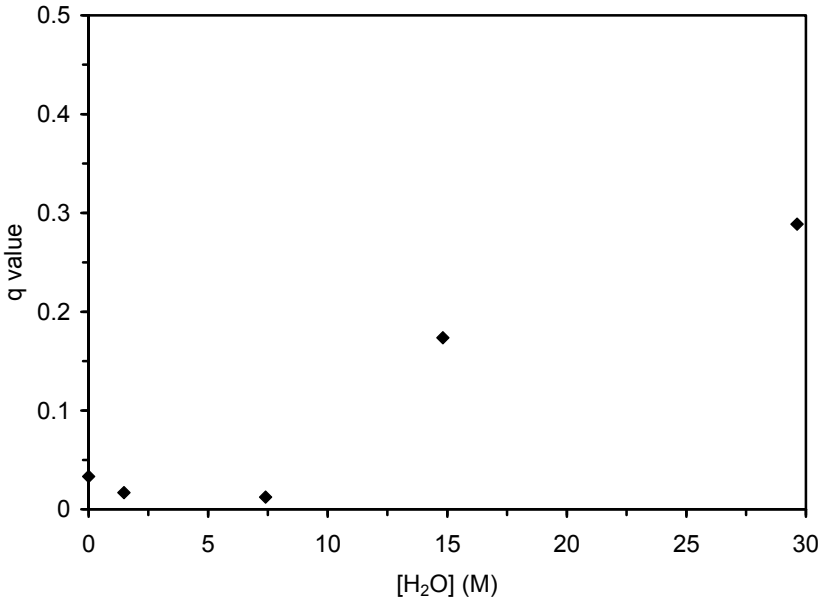

Figure S4. The variation in hydration state of Eu^{3+} as water (H_2O/D_2O) was titrated into a dry solution of Eu**3** in CH_3CN; λ_{ex} = 397 nm, λ_{em} = 613 nm.

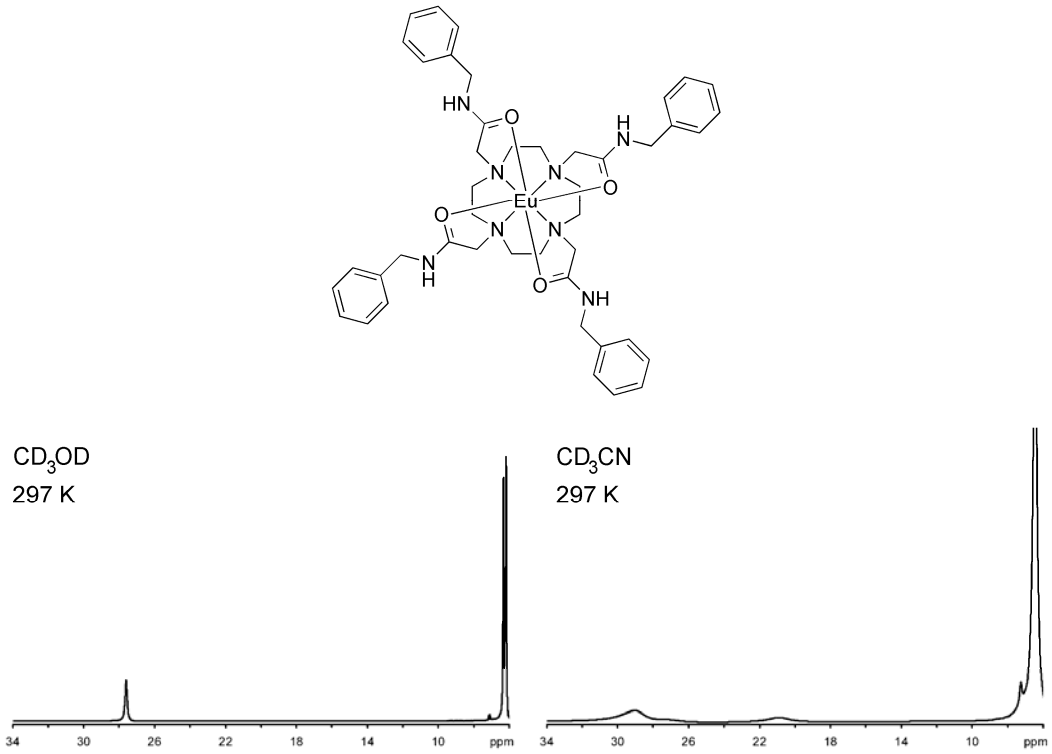

Figure S5. ^{1}H NMR spectra of the Eu^{3+} chelate of the monobenzyl DOTA-tetramide triflate salt (structure shown) focusing on the highly shifted *ax*^{S} resonance. Spectra were acquired at 400 MHz in CD_3OD at 297K (left) and CD_3CN at 297K (right). Resonances with hyperfine shifts of 27.6 ppm (CD_3OD) and 28.9 ppm (CD_3CN) correspond to the SAP isomer. Note that a peak arising from the TSAP isomer (20.8 ppm) can only be observed in the spectrum recorded in CD_3CN.