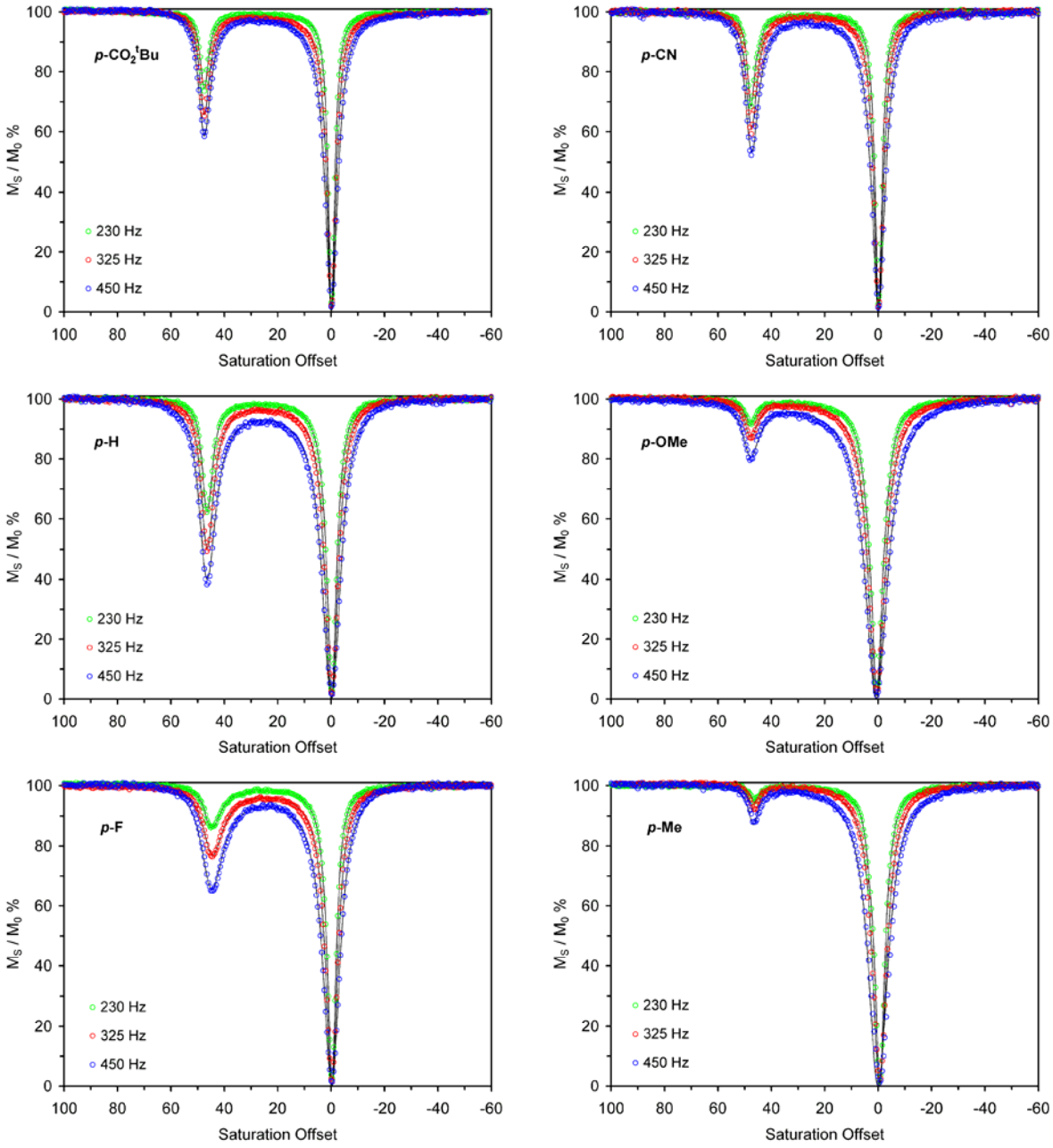
Modulation of Water Exchange in Europium(III) DOTA-tetraamide Complexes *via* Electronic Substituent Effects

S. James Ratnakar,[‡] Mark Woods,[†,§] Angelo J.M. Lubag,[‡] Zoltán Kovács, [§‡] and A. Dean Sherry.*[‡,§]

[‡] *Advanced Imaging Research Center, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, Texas, 75390,* [†] *Macrocyclics, 2110 Research Row, Ste 425, Dallas, Texas, 75235 and* [§] *Department of Chemistry, University of Texas at Dallas, 800 W. Campbell Rd, Richardson, Texas, 75080*

CEST Spectroscopy

CEST spectra of 20 mM solutions of the complexes in 50% water in acetonitrile were recorded on a Varian Mercury spectrometer operating at 300 MHz. Pre-saturation pulses of 2 s duration were applied at 450 Hz (blue), 325 Hz (red) and 230 Hz (green). The black lines through each point are fits to the experimental data using the Bloch equation modified for exchange.



CEST Fitting

The CEST spectra were fitted by previously published methods {Woessner, D. E.; Zhang, S.; Merritt, M. E.; Sherry, A. D. *Magn. Reson. Med.* **2005**, *53*, 790-799, Woods, M.; Woessner, D. E.; Zhao, P.; Pasha, A.; Yang, M.-Y.; Huang, C.-H.; Vasalitiy, O.; Morrow, J. R.; Sherry, A. D. *J. Am. Chem. Soc.* **2006**, *128*, 10155-10162.} affording the following parameters:

	Metal Bound water				Solvent Water	
	τ_M (ms)	δ (ppm)	T_1 (s)	T_2 (s)	T_1 (s)	T_2 (s)
$CO_2{}^tBu$	0.352	47.69	0.176	0.011	0.795	0.487
CN	0.324	47.61	0.029	0.011	1.146	0.910
F	0.144	44.98	0.010	0.011	0.852	0.386
H	0.269	46.72	0.656	0.011	2.121	0.749
OMe	0.198	47.25	0.036	0.011	0.290	0.025
Me	0.310	46.89	0.010	0.011	0.171	0.020

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Imaging Protocol

CEST imaging was performed on a phantom of six different 5 mm NMR tubes containing 10 mM solutions of the complexes dissolved in water and acetonitrile (1:1 *v/v*). Images were acquired on a Varian Unity INOVA 400 MHz vertical wide - bore spectrometer (89 mm), with gradients capable of 120 gauss/cm. A 20 mm imaging probe (volume coil) and the standard spin-echo pulse sequence with saturation (SEMSCONSAT) were used. A 3 s presaturation pulse (B_1 = 24 μT) was employed with TR = 10 s, TE = 8.2 ms and a matrix =128 × 128, FOV = 25 mm × 25 mm, thickness = 5 mm transverse slice. Images were collected with saturation at two different frequencies: -47.5 ppm and at + 47.5 ppm from the bulk water signal.

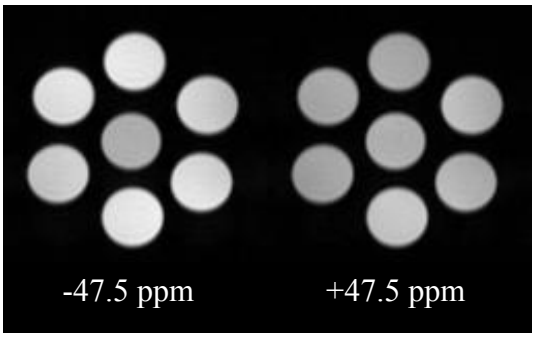

Figure S3. CEST images at two different frequencies: -47.5 ppm and + 47.5 ppm from the bulk water signal.

Image Processing

The CEST images were obtained by subtracting the corresponding -47.5 ppm (off-resonance) image from the +47.5 ppm image (on bound water resonance) using the ImageJ (NIH) program. A 2 × 2 median filter (replacing each pixel value with the median of the neighbouring pixel values) was applied to improve signal-to-noise in the images.

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Experimental

General Remarks. All solvents and reagents were purchased from commercial sources and used as received unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded on a Varian INOVA 400 spectrometer operating at 400 and 100 MHz, respectively. CEST spectra were recorded on a Varian Mercury spectrometer operating at 300 MHz. MALDI mass spectra were acquired on an Applied Biosystems Voyager-6115 mass spectrometer. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. "Water" refers to high purity water with a resistance of >18 MΩ.

Synthesis

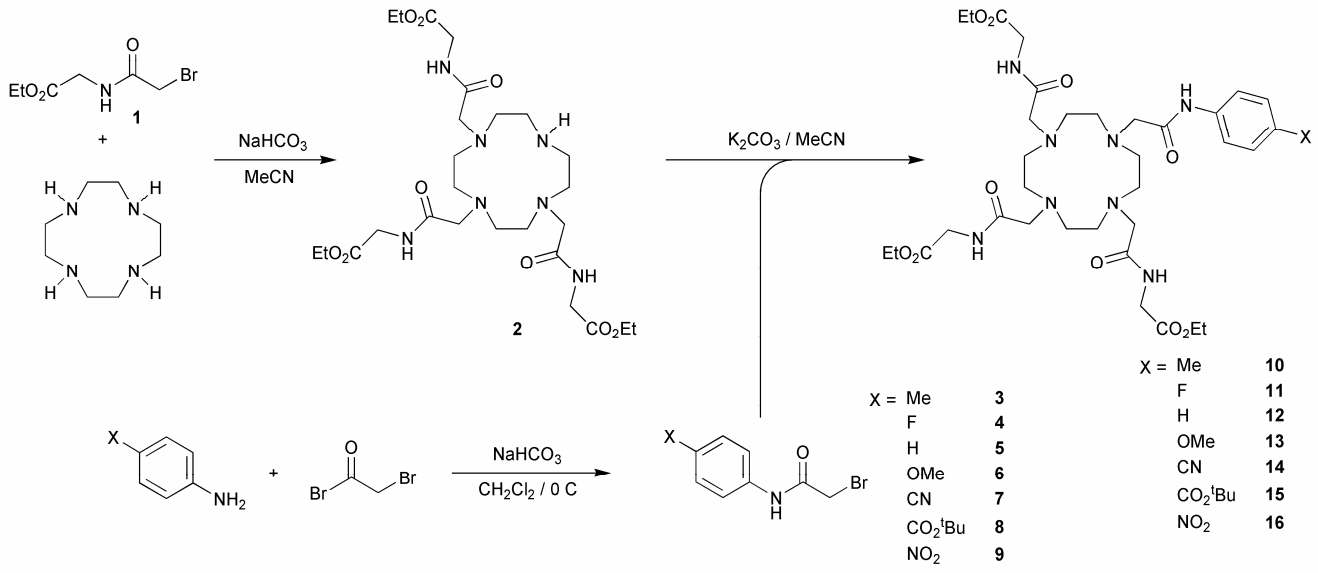
The ligands were synthesized according to the general scheme shown (Scheme 1). Ethyl bromoacetamidoacetate **1** was synthesized according to literature procedures (S. Zhang, K. Wu, M.C. Biewer, & A.D. Sherry, *Inorg. Chem.* **2007**, *40* (17), 4284-4290).

Tris-(*N*-ethylacetate)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetamide (2). Cyclen (0.86 g, 5 mmol) and $NaHCO_3$ (2.07 g, 15 mmol) were added to acetonitrile (100 mL) and heated, with stirring, at 65 °C for 1 h. Ethyl-2-bromoacetamido acetate 1 (3.36 g, 15 mmol) in acetonitrile (20 mL) was then added and the reaction mixture stirred at 65 °C for 72 h. The reaction was cooled to room temperature and filtered. The solvents were removed from the filtrate under reduced pressure and the residue purified by column chromatography over silica gel, eluting with CH_2Cl_2/CH_3OH (80:20 *v/v*). The title compound was afforded as a pale yellow hygroscopic solid (1.22 g, 29%). R_f = 0.36 (SiO_2, 20% MeOH in CH_2Cl_2); ^{1}H NMR (400 MHz, D_2O), δ = 4.09 (4H, q, $^{3}J_{H-H}$ = 8 Hz, OCH_2), 4.09 (2H, q, $^{3}J_{H-H}$ = 8 Hz, OCH_2), 3.87 (6H, s, $NHC\underline{H}_2CO_2$), 3.23 (2H, s, NCH_2C=O), 3.22 (4H, s, NCH_2C=O), 2.92-2.62 (16H, m br, ring CH_2N), 1.15 (3H, t, $^{3}J_{H-H}$ = 8 Hz, CH_3), 1.14 (6H, t, $^{3}J_{H-H}$ = 8 Hz, CH_3); ^{13}C NMR (100 MHz, D_2O) δ = 174.9 (2 × CO_2Et), 171.7 (2 × NHC=O), 62.8 (OCH_2), 62.7 (OCH_2), 57.2 ($NH\underline{C}H_2CO_2Et$), 57.1 ($NH\underline{C}H_2CO_2Et$), 52.0 (ring CH_2N), 51.6 (ring CH_2N), 44.4 (ring CH_2N), 44.3 (ring CH_2N), 43.4 ($N\underline{C}H_2CO$), 41.3 ($N\underline{C}H_2CO$), 13.5 (2 × CH_3); *m/z* (MALDI+) 602 (100%), $[M+H]^+$, 624 (8%, $[M+Na]^+$). Accurate melting points and combustion analyses could not be determined for this compound owing to its hygroscopic nature.

General procedure for the synthesis of *N*-aryl-bromoacetamides. To a solution of *p*-substituted analine (32.2 mmol) in dichloromethane (50 mL) was added potassium carbonate (35.1 mmol). The reaction mixture was stirred vigorously and cooled to 0 °C in an ice bath. Bromoacetyl bromide (35.1 mmol) in dichloromethane (50 mL) was then added drop-wise over a period of 1 hr. The reaction mixture was then allowed to warm to room temperature and stirred for a further 6 h. The reaction was then quenched by cautious addition of water (30 mL). Methanol (60 mL) was added to afford a homogeneous solution and the *N*-aryl bromoacetamide isolated by slow evaporation of the solvents at room temperature.

4-Methylphenyl bromoacetamide (3). The title compound was obtained as colorless crystals (4.2 g, 72 %). Mp = 152 - 154 °C; ^{1}H NMR (400 MHz, CD_3CN) δ = 10.00 (1H, s br, NH), 7.16 (2H, d, $^{3}J_{H-H}$ = 8 Hz, Ar), 6.82 (2H, d, $^{3}J_{H-H}$ = 8 Hz, Ar), 3.72 (2H, s, $BrCH_2$), 1.94 (3H, s, CH_3); ^{13}C NMR (100 MHz, CD_3CN) δ = 165.2 (C=O), 136.7 (1-Ar), 133.5 (4-Ar), 129.9 (2-Ar, 3-Ar), 31.1 ($BrCH_2$), 21.1 (CH_3). *m/z* (MALDI+) 228 (100 %, $[M+H]^+$).

4-Fluorophenyl bromoacetamide (4). The title compound was obtained as colorless crystals (4.5 g, 84 %). Mp = 137 - 138 °C; ^{1}H NMR (400 MHz, CD_3CN) δ = 8.76 (1H, s br, NH), 7.57 (2H, dd, $^{3}J_{H-H}$ = 9 Hz, $^{4}J_{F-H}$ = 5 Hz, 2-Ar), 7.09 (2H, dd,



Scheme 1.

$^3J_{H\text{-}H}$ = 9 Hz, $^4J_{F\text{-}H}$ = 18 Hz, 3-Ar), 3.91 (2H, s, BrC*H*$_2$); ^{13}C NMR (CD_3CN) δ = 165.1 (C=O), 158.7 (s, 1-Ph), 147.7 (d, $^1J_{F\text{-}C}$ = 2600 Hz, 4-Ph), 122.0 (d, $^3J_{F\text{-}C}$ = 8 Hz, 2-Ph), 115.5 (d, $^2J_{F\text{-}C}$ = 20 Hz, 3-Ph), 29.8 ($BrCH_2$); *m/z* (MALDI+) 234 (100 %, $[M+H]^+$), 256 (45 %, $[M+Na]^+$), an appropriate isotope pattern was observed.

Phenyl bromoacetamide (5). The title compound was obtained as colorless crystals (4.0 g, 76 %). Mp = 125 – 128.5 °C; ^{1}H NMR (400 MHz, CD_3CN) δ = 10.25 (1H, s br, NH), 7.41 (2H, d, $^3J_{H\text{-}H}$ = 8 Hz, Ar), 7.07 (2H, d, $^3J_{H\text{-}H}$ = 8 Hz, Ar), 3.97 (2H, s, $BrCH_2$); ^{13}C NMR (CD_3CN) δ = 164.3 (C=O), 135.9 (1-Ar), 132.6 (4-Ar), 129.0 (2-Ar, 3-Ar), 30.3 ($BrCH_2$); *m/z* (MALDI+) 216 (100 %, $[M+H]^+$), an appropriate isotope pattern was observed; Anal. Found C 44.4 %, H 3.8 %, N 6.3 %, C_8H_9BrNO requires C 44.6 %, H 4.1 %, N 6.5 %.

4-Methyoxyphenyl bromoacetamide (6). The title compound was obtained as colorless solid (4.8 g, 81 %). Mp = 128 – 129.5 °C; ^{1}H NMR (400 MHz, CD_3CN) δ = 8.64 (1H, s br, NH), 7.46 (2H, d, $^3J_{H\text{-}H}$ = 9 Hz, Ar), 6.91 (2H, d, $^3J_{H\text{-}H}$ = 9 Hz, Ar), 3.94 (2H, s, $BrCH_2$), 3.77 (3H, s, OCH_3); ^{13}C NMR (CD_3CN) δ = 164.8 (C=O), 156.8 (4-Ar), 131.5 (1-Ar), 121.9 (3-Ar), 114.2 (2-Ar), 55.3 (OCH_3), 29.9 ($BrCH_2$); *m/z* (MALDI+) 246 (100 %, $[M+H]^+$), 267 (85 %, $[M+Na]^+$), an appropriate isotope pattern was observed; Anal. Found C 44.0 %, H 4.1 %, N 5.4 %, $C_9H_{11}BrNO_2$ requires C 44.1 %, H 4.5 %, N 5.7 %.

4-Cyanophenyl bromoacetamide (7). The title compound was obtained as white solid (0.90 g, 81%). Mp, sublimes above ~ 155 °C; ^{1}H NMR (400 MHz, CD_3CN) δ = 9.84 (1H, s br, NH), 7.78 (2H, d, $^3J_{H\text{-}H}$ = 8 Hz, Ar), 7.65 (2H, d, $^3J_{H\text{-}H}$ = 8 Hz, Ar), 4.00 (2H, s, $BrCH_2$); ^{13}C NMR (100 MHz, CD_3CN) δ = 165.5 (C=O), 142.9 (Ar), 133.3 (2-Ar, 3-Ar) 117.4 (CN), 107.0 (Ar), 29.5 ($BrCH_2$); *m/z* (MALDI+) 241 (100 %, $[M+H]^+$), an appropriate isotope pattern was observed; Anal. Found C 44.9 %, H 2.8 %, N 11.4 %, $C_9H_7BrN_2O$ requires C 45.2 %, H 2.9 %, N 11.7 %.

4-*tert*-Butyl (2-bromoacetamido)benzoate (8). The title compound was obtained as off white solid (1.5 g, 60 %). Mp = 111 - 113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.54 (1H, s br, NH), 7.90 (2H, d, $^3J_{H\text{-}H}$ = 8 Hz, Ar), 7.56 (2H, d, $^3J_{H\text{-}H}$ = 8 Hz, Ar), 4.13 (2H, s, $BrCH_2$), 1.52 (9H, s, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 165.3 (C=O), 164.3 (C=O), 140.6 (Ar), 130.7 (Ar), 128.4 (Ar), 119.2 (Ar), 81.2 ($\underline{C}(CH_3)_3$) 43.0 ($BrCH_2$), 28.3 ($C(\underline{C}H_3)_3$); *m/z* (MALDI+) 316 (100 %, $[M+H]^+$), an appropriate isotope pattern was observed; Anal. Found C 57.4 %, H 6.0 %, N 5.0 %, $C_{13}H_{17}ClNO_3$ requires C 57.9 %, H 6.3 %, N 5.2 %.

4-Nitrophenyl bromoacetamide (9). The title compound was obtained as yellow crystals (3.3 g, 64 %). Mp = 174 - 179 °C; ^{1}H NMR (400 MHz, CD_3CN) δ = 9.20 (1H, s br, NH), 8.27, (2H, d, $^3J_{H\text{-}H}$ = 8 Hz, Ar), 7.80 (2H, d, $^3J_{H\text{-}H}$ = 8 Hz, Ar), 4.03 (2H, s, $BrCH_2$); ^{13}C NMR (CD_3CN) δ = 165.8 (C=O), 144.5 (Ar), 143.8 (Ar), 125.1 (Ar), 119.4 (Ar), 29.6 ($BrCH_2$); *m/z* (MALDI+) 261 (100 %, $[M+H]^+$), an appropriate isotope pattern was observed; Anal. Found C 37.0 %, H 2.6 %, N 10.6 %, $C_8H_7BrN_2O_3$ requires C 37.1 %, H 2.7 %, N 10.8 %.

General procedure for the preparation of ligands. Potassium carbonate (46 mg, 0.33 mmol) was added to a solution of the triacetamide **2** (0.20 g, 0.33 mmol) in acetonitrile (50 mL) and mixture stirred. The *p*-bromoacetamide **6** (81 mg, 033 mmol) was added and the reaction heated to 60 °C for 24 hours with stirring. The reaction was cooled to room temperature and filtered to remove the inorganic salts. The title compound was purified by column chromatography over silica gel eluting with 15% methanol in dichloromethane.

1-*N*-(4-Methylphenyl)-4,7,10-tris-(*N*-ethylacetate)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetamide (10). The title compound was obtained as a pale yellow solid (0.14 g, 51 %). R_f = 0.40 (SiO_2, 15% MeOH in CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3CN) δ = 7.59 (2H, d, $^3J_{H\text{-}H}$ = 10 Hz, Ar), 7.15 (2H, d, $^3J_{H\text{-}H}$ = 10 Hz, Ar), 4.14 (6H, m, 2 × OCH_2), 3.4 - 3.8 (14H, m br, $N\underline{C}H_2CO$, $NH\underline{C}H_2CO_2Et$), 2.7- 2.9 (16H, m br, ring CH_2N), 2.3 (3H, s, CH_3), 1.26 (6H, t, $^3J_{H\text{-}H}$ = 8 Hz, CH_3), 1.23 (3H, t, $^3J_{H\text{-}H}$ = 8 Hz, CH_3); ^{13}C NMR (100 MHz, CD_3CN) δ = 172.6 (C=O), 171.7 (2 × C=O), 170.6 (C=O), 170.0 (C=O), 136.3 (1-Ar), 129.5 (3-Ar), 129.3 (4-Ar), 120.3 (3-Ar), 61.2 (2 × OCH_2), 57.5 (br, ring CH_2N), 52.2 (br, $N\underline{C}H_2CO$), 50.2 (ring CH_2N), 41.3 ($NH\underline{C}H_2CO_2Et$), 41.0 ($NH\underline{C}H_2CO_2Et$), 20.1 (CH_3), 13.7 (2 × CH_3); *m/z* (MALDI+) 749 (100%) $[M+H]^+$, 787 (85% $[M+K]^+$); Anal. found C 46.9 %, H 6.6 %, N 11.6 %, $C_{35}H_{56}N_8O_{10}\cdot KHCO_3\cdot 4.4H_2O$ requires C 46.6 %, H 7.1 %, N 12.1 %.

1-*N*-(4-Fluorophenyl)-4,7,10-tris-(*N*-ethylacetate)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetamide (11). The title compound was obtained as a colourless solid. (0.19 g, 66 %). R_f = 0.45 (SiO_2, 15% MeOH in CH_2Cl_2); Mp = 116 - 119 °C; ^{1}H NMR (400 MHz, CD_3CN) δ = 7.73 (2H, br, Ar), 7.06 (2H, br, Ar), 4.14 (6H, m, 2 × OCH_2), 3.3-3.8 (14H, m br, $N\underline{C}H_2CO$, $NH\underline{C}H_2CO_2Et$), 2.4-2.6 (16H, m br, ring CH_2N), 1.25 (6H, t, $^3J_{H\text{-}H}$ = 8 Hz, CH_3), 1.23 (3H, t, $^3J_{H\text{-}H}$ = 8 Hz, CH_3); ^{13}C NMR (100 MHz, CD_3CN) δ = 173.2 (C=O), 172.8 (2 × C=O), 170.0 (C=O), 169.9 (C=O), 157.4 (s, 1-Ar), 147.9 (d, $^1J_{C\text{-}F}$ = 2490 Hz, 4-Ar), 121.9 (d, $^2J_{C\text{-}F}$ = 41 Hz, 3-Ar), 115.3 (d, $^3J_{C\text{-}F}$ = 22 Hz, 2-Ar), 61.2 (2 × OCH_2), 57.4 (br, $N\underline{C}H_2CO$), 56.9 (br, $N\underline{C}H_2CO$), 53.6 ($N\underline{C}H_2CO$), 50.7 (ring CH_2N), 41.3 ($NH\underline{C}H_2CO_2Et$), 41.1 ($NH\underline{C}H_2CO_2Et$), 13.6 (2 × CH_3); *m/z* (MALDI+) 753 (100%, $[M+H]^+$); Anal. found C 45.3 %, H 6.3 %, N 11.6 %, $C_{34}H_{53}FN_8O_{10}\cdot KHCO_3\cdot 4.4H_2O$ requires C 45.1 %, H 6.8 %, N 12.0 %.

1-*N*-Phenyl-4,7,10-tris-(*N*-ethylacetate)-1,4,7,10-tetraaza-cyclododecane-1,4,7,10-tetraacetamide (12). The title compound was obtained as a colourless amorphous solid (0.15 mg, 52 %). R_f = 0.35 (SiO_2, 20% MeOH in CH_2Cl_2); Mp = 32 - 34 °C; ^{1}H NMR (400 MHz, CD_3CN) δ = 7.47 (2H, m, Ar), 7.17 (2H, m, Ar), 6.93 (1H, m, 4-Ar), 3.94 (6H, m, OCH_2), 3.70 (6H, m, $NHC\underline{H}_2CO_2Et$), 3.16 (8H, m, $NC\underline{H}_2CO$), 2.2 - 2.7 (16H, m br, ring CH_2N), 1.06 (9H, m, CH_3); ^{13}C NMR (100 MHz, CD_3CN) δ = 172.5 (2 × C=O), 170.5 (C=O), 170.1 (C=O), 170.0 (C=O), 142.6 (Ar), 129.2 (Ar), 124.0 (Ar), 117.6 (Ar), 61.2 (2 × OCH_2), 58.3 (br ring CH_2N), 53.1 (br ring CH_2N), 46.8 ($N\underline{C}H_2CO$), 46.4 ($N\underline{C}H_2CO$), 44.8 ($N\underline{C}H_2CO$), 41.0 ($NH\underline{C}H_2CO_2$), 13.7 (2 × CH_3). *m/z* (MALDI+) 735 (100%, $[M+H]^+$).

1-*N*-(4-Methoxyphenyl)-4,7,10-tris-(*N*-ethylacetate)-1,4,7, 10-tetraazacyclododecane-1,4,7,10-tetraacetamide (13). The title compound was obtained as a colourless solid (0.18 g, 64 %). R_f = 0.40 (SiO_2, 20% MeOH in CH_2Cl_2); Mp = 137.5 - 139 °C; ^{1}H NMR (400 MHz, CD_3CN) δ = 7.62 (2H, d, $^3J_{H-H}$ = 10 Hz, Ar), 6.86 (2H, d, $^3J_{H-H}$ = 10 Hz, Ar), 4.11 (6H, m, 2 × OCH_2), 3.74 (3H, s, OCH_3), 3.2-3.9 (14H, m br, N<u>C</u>H_2CO, NH<u>C</u>H_2CO_2Et), 2.2-2.8 (16H, m br, ring CH_2N), 1.22 (6H, t, $^3J_{H-H}$ = 8 Hz, CH_3), 1.21 (3H, t, $^3J_{H-H}$ = 8 Hz, CH_3); ^{13}C NMR (100 MHz, CD_3CN) δ = 173.2 (C=O), 172.8 (2 × C=O), 170.0 (2 × C=O), 156.3 (4-Ar), 132.1 (1-Ar), 121.9 (3-Ar), 114.0 (2-Ar), 61.2 (2 × OCH_2), 57.5 (br, ring CH_2N) 55.4 (OCH_3), 53.2 (N<u>C</u>H_2CO), 52.8 (N<u>C</u>H_2CO), 52.2 (N<u>C</u>H_2CO), 50.7 (ring CH_2N), 41.2 (NH<u>C</u>H_2CO_2Et), 41.1 (NH<u>C</u>H_2CO_2Et), 13.3 (2 × CH_3); *m/z* (MALDI+) 765 (70%) $[M+H]^+$, 787 (70%, $[M+Na]^+$), 805 (100%, $[M+K]^+$), Anal. found C 46.5 %, H 6.1 %, N 13.0 %, $C_{35}H_{56}N_8O_{11}$·0.9KBr·H_2O requires C 47.0 %, H 6.5%, N 12.5 %.

1-*N*-(4-Cyanophenyl)-4,7,10-tris-(*N*-ethylacetate)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetamide (14). The title compound was obtained as an off-white solid (0.16 g, 55 %). R_f = 0.54 (SiO_2, 15% MeOH in CH_2Cl_2); Mp = 94.5 - 96 °C; ^{1}H NMR (400 Hz, CD_3CN) δ = 7.86 (2H, d, $^3J_{H-H}$ = 8 Hz, Ar), 7.69 (2H, d, $^3J_{H-H}$ = 8 Hz, Ar), 4.15 (4H, q, $^3J_{H-H}$ = 7 Hz, OCH_2), 4.14 (2H, q, $^3J_{H-H}$ = 7 Hz, OCH_2), 3.87 (8H, br, NCH_2CO), 2.92 (6H, m br, NHC<u>H</u>$_2CO_2$Et), 2.29 (16H, s br, ring CH_2N), 1.24 (9H, t, $^3J_{H-H}$ = 7 Hz, 2 × CH_3); ^{13}C NMR (100 MHz, CD_3CN) δ = 172.7 (C=O), 172.3 (2 × C=O), 170.1 (C=O), 166.3 (C=O), 143.3 (4-Ar), 142.6 (1-Ar), 133.4 (3-Ar), 119.8 (2-Ar), 118. 5 (CN), 62.3 (N<u>C</u>H_2CO), 61.3 (2 × OCH_2), 58.3 (N<u>C</u>H_2CO), 57.1 (N<u>C</u>H_2CO), 51.0 (ring CH_2N), 41.2 (NH<u>C</u>H_2CO_2Et), 41.1 (NH<u>C</u>H_2CO_2Et), 13.9 (2 × CH_3); *m/z* (MALDI+) 760 (80%, $[M+H]^+$), 782 (100%, $[M+Na]^+$), 798 (10%, $[M+K]^+$); Anal. found C 46.7 %, H 6.3 %, N 13.3 %, $C_{35}H_{53}N_9O_{10}$·0.9KBr·2.2H_2O requires C 46.2 %, H 6.4 %, N 13.8 %.

1-*N*-(4-(*tert*-Butoxycarbonyl)phenyl)-4,7,10-tris-(*N*-ethylacetate)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetamide (15). The title compound was obtained as a colourless solid (0.17 g, 60 %). R_f = 0.43 (SiO_2, 15% MeOH in CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3CN) δ = 8.29 (2H, d, $^3J_{H-H}$ = 8 Hz, Ar), 8.14 (2H, d, $^3J_{H-H}$ = 8 Hz, Ar), 4.66 (6H, m, NHC<u>H</u>$_2CO_2$Et), 4.49 (6H, m, OCH_2) 4.25 (8H, m br, NCH_2CO), 3.45 (8H, br, ring CH_2N), 3.03 (8H, br, ring CH_2N), 1.94 (9H, s, C(CH_3)$_3$), 1.59 (9H, t, $^3J_{H-H}$ = 8 Hz, 2 × CH_3); ^{13}C NMR (100 MHz, CD_3CN) δ = 173.4 (2 × C=O), 173.0 (2 × C=O), 170.8 (C=O), 166.3 (C=O), 143.4 (4-Ar), 131.2 (3-Ar), 128.4 (2-Ar), 118.4 (1-Ar), 81.6 (<u>C</u>(CH_3)$_3$), 61.1 (2 × OCH_2), 59.2 (br, 2 × N<u>C</u>H_2CO), 57.8 (N<u>C</u>H_2CO), 53.63 (ring CH_2N), 51.28 (ring CH_2N), 44,5 (NH<u>C</u>H_2CO_2Et), 41.9 (NH<u>C</u>H_2CO_2Et), 28.4 (C(<u>C</u>H_3)$_3$), 14.6 (2 × CH_3); *m/z* (MALDI+) 835 (100%, $[M+H]^+$), 857 (20%, $[M+Na]^+$).

1-*N*-(4-Nitrophenyl)-4,7,10-tris-(*N*-ethylacetate)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetamide (16). The title compound was obtained as a yellow solid (0.18 g, 64 %). R_f = 0.48 (SiO_2, 10% MeOH in CH_2Cl_2); Mp = 92 - 94 °C; ^{1}H NMR (400 MHz, CD_3CN) δ = 8.18 (2H, d, $^3J_{H-H}$ = 8 Hz, Ar), 7.40 (2H, d, $^3J_{H-H}$ = 8 Hz, Ar), 4.14 (6H, q, $^3J_{H-H}$ = 8 Hz, OCH_2-overlapping), 3.87 (6H, s br, NH<u>C</u>H_2CO_2Et), 2.2-3.4 (24H, m br, ring CH_2N, N<u>C</u>H_2CO), 1.23 (6H, t, $^3J_{H-H}$ = 8 Hz, CH_3), 1.22 (3H, t, $^3J_{H-H}$ = 8 Hz, CH_3); ^{13}C NMR (100 MHz, CD_3CN) δ = 172.6 (C=O), 172.3 (C=O), 170.1 (C=O), 125.0 (Ar), 144.6 (Ar), 135.6 (Ar), 119.4 (Ar), 117.5 (Ar CH), 61.2 (2 × CH_2O), 58.2 (br, 3 × N<u>C</u>H_2CO), 57.0 (br, 2 × NH<u>C</u>H_2CO_2Et), 50.9 (br, ring CH_2N), 41.1 (CH_2N), 13.8 (2 × CH_3); *m/z* (MALDI+) 780 (100%, $[M+H]^+$), 802 (100%, $[M+Na]^+$), 818 (30%, $[M+K]^+$); Anal. found C 45.3 %, H 6.0 %, N 13.2 %, $C_{34}H_{53}N_9O_{12}$·KH CO_3·2.5H_2O requires C 45.5 %, H 6.4 %, N 13.6 %.

General procedure for the synthesis of Eu^{3+} complexes. To a solution of the ligand (0.15 mmol) in acetonitrile (20 mL) was added a solution of the europium triflate (0.1 mmol) in acetonitrile (5 mL). The reaction was stirred at room temperature for 18 hours and the solvents removed under reduced pressure. The residue was dried under high vacuum for 3 hours to afford the complex in quantitative yield.

Europium (III) 1-*N*-(4-methylphenyl)-4,7,10-tris-(*N*-ethyl-acetate)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacet-amide triflate salt (Eu10). The complex was obtained as a colourless solid. ^{1}H NMR (400 MHz, CD_3CN) δ = 24.8 (4H, br, ring ax^S), 7.6 (2H, Ar), 7.1 (2H, Ar), 3.4 (6H, m, OCH_2), 2.0 (3H, s, $ArCH_3$), 1.1 (9H, m, CH_3), -0.8 (4H, br, ring eq^S), -2.3 (4H, br, ring ax^C), -5.1 (4H, br, ring eq^C), -8.4 (4H, br, *ac*), -12.7 (4H, br, *ac*); *m/z* (MALDI+) 898 (100%, $[EuL-2H]^+$), an appropriate isotope pattern was observed.

Europium (III) 1-*N*-(4-fluorophenyl)-4,7,10-tris-(*N*-ethyl-acetate)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacet-amide triflate salt (Eu11). The complex was obtained as a colourless solid. ^{1}H NMR (400 MHz, CD_3CN) δ = 24.2 (4H, br, ring ax^S), 6.9 (2H, m, Ar), 6.4 (2H, m, Ar), 2.3 (6H, m, OCH_2), 0.1 (9H, m, CH_3), -1.8 (4H, br, ring eq^S), -4.5 (4H, br, ring ax^C), -7.4 (4H, br, ring eq^C), -10.6 (4H, br, *ac*), -12.1 (4H, br, *ac*); *m/z* (MALDI+) 902 (100%, $[EuL-2H]^+$) an appropriate isotope pattern was observed.

Europium (III) 1-*N*-phenyl-4,7,10-tris-(*N*-ethylacetate)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetamide triflate salt (Eu12). The complex was obtained as a colourless solid. ^{1}H NMR (400 MHz, CD_3CN) δ = 24.9 (4H, br, ring ax^S), 7.8 (2H, Ar), 7.3 (2H, Ar), 3.3 (6H, m, OCH_2), 0.9 (9H, m, CH_3), -0.6 (4H, br, ring eq^S), -2.2 (4H, br, ring ax^C), -5.3 (4H, br, ring eq^C), -8.2 (4H, br, *ac*), -12.5 (4H, br, *ac*); *m/z* (MALDI+) 884 (100%, $[EuL-H_2]^+$), an appropriate isotope pattern was observed.

Europium (III) 1-*N*-(4-methoxyphenyl)-4,7,10-tris-(*N*-ethyl-acetate)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacet-amide triflate salt (Eu13). The complex was obtained as a colourless solid. ^{1}H NMR (400 MHz, CD_3CN) δ = 24.6 (4H, br, ring ax^S), 7.5 (2H, Ar), 7.0 (2H, Ar), 4.2 (3H, s, $ArOCH_3$), 3.4 (6H, m, OCH_2), 1.2 (9H, m, CH_3), -0.6 (4H, br, ring eq^S), -2.5 (4H, br, ring ax^C), -4.9 (4H, br, ring eq^C), -8.3 (4H, br, *ac*), -12.7 (4H, br, *ac*); *m/z* (MALDI+) 916 (100%, $[EuL-H_2]^+$), an appropriate isotope pattern was observed.

Europium (III) 1-*N*-(4-cyanophenyl)-4,7,10-tris-(*N*-ethyl-acetate)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacet-amide triflate salt (Eu14). The complex was obtained as a colourless solid. ^{1}H NMR (400 MHz, CD_3CN) δ = 27.6 (4H, br, ring *ax*^{S}), 10.1 (4H, m, Ar), 5.4 (6H, m, OCH_2), 3.5 (9H, m, CH_3), 1.9 (4H, br, ring *eq*^{S}), 0.0 (4H, br, ring *ax*^{C}), -2.3 (4H, br, ring *eq*^{C}), -5.9 (4H, br, *ac*), -10.3 (4H, br, *ac*); *m/z* (MALDI+) 909 (100%, $[EuL\text{-}2H]^+$), an appropriate isotope pattern was observed.

Europium(III) 1-*N*-(4-(*tert*-butoxycarbonyl)phenyl)-4,7,10-tris-(*N*-ethylacetate)-1,4,7,10-tetraazacyclododecane-1,4,7, 10-tetraacetamide triflate salt (Eu15). The complex was obtained as a colourless solid. ^{1}H NMR (400 MHz, CD_3CN) δ = 27.7 (4H, br, ring *ax*^{S}), 10.7 (2H, Ar), 10.4 (2H, Ar), 6.0 (6H, m, OCH_2), 4.6 (9H, m, CH_3), 4.0 (9H, s, $C(CH_3)_3$) 1.8 (4H, br, ring *eq*^{S}), 0.3 (4H, br, ring *ax*^{C}), -2.3 (4H, br, ring *eq*^{C}), --5.8 (4H, br, *ac*), -10.2 (4H, br, *ac*); *m/z* (MALDI+) 985 (100%, $[EuL\text{-}2H]^+$), an appropriate isotope pattern was observed.

Europium(III) 1-*N*-(4-nitrophenyl)-4,7,10-tris-(*N*-ethyl-acetate)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacet-amide triflate salt (Eu16). The complex was obtained as a yellow solid. ^{1}H NMR (400 MHz, CD_3CN) δ = 27.4 (4H, br, ring *ax*^{S}), 10.1 (4H, m, Ar), 5.8 (6H, m, OCH_2), 3.2 (9H, m, CH_3), 1.8 (4H, br, ring *eq*^{S}), 0.2 (4H, br, ring *ax*^{C}), -2.4 (4H, br, ring *eq*^{C}), -6.0 (4H, br, *ac*), -10.4 (4H, br, *ac*); *m/z* (MALDI+) 929 (100%, $[EuL\text{-}2H]^+$) an appropriate isotope pattern was observed.

Europium(III) 1-*N*-(4-aminophenyl)-4,7,10-tris-(*N*-ethyl-acetate)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacet-amide triflate salt (Eu17). 10 % palladium on carbon (10 mg) was added to a solution of Eu**10** (42 mg, 45 μmol) in ethanol (10 mL) and the flask was flushed with N_2 for 30 min. The reaction mixture was then shaken on a Parr hydrogenator under a hydrogen pressure of 40 psi at room temperature for 3 hours. The solution was filtered and the solvents removed under vacuum to afford the title complex as a colorless solid in quantitative yield.
^{1}H NMR (400 MHz, CD_3CN) δ = 24.9 (4H, br, ring *ax*^{S}), 7.8 (2H, m, Ar), 7.5 (2H, m, Ar) , 5.92 (6H, m, OCH_2), 3.4 (9H, m, CH_3), 1.5 (4H, br, ring *eq*^{S}), 0.4 (4H, br, ring *ax*^{C}), -2.2 (4H, br, ring *eq*^{C}), -8.22 (4H, br, *ac*), -12.4 (4H, br, *ac*); *m/z* (MALDI+) 899 (100%, $[EuL\text{-}2H]^+$) an appropriate isotope pattern was observed.