

ESI

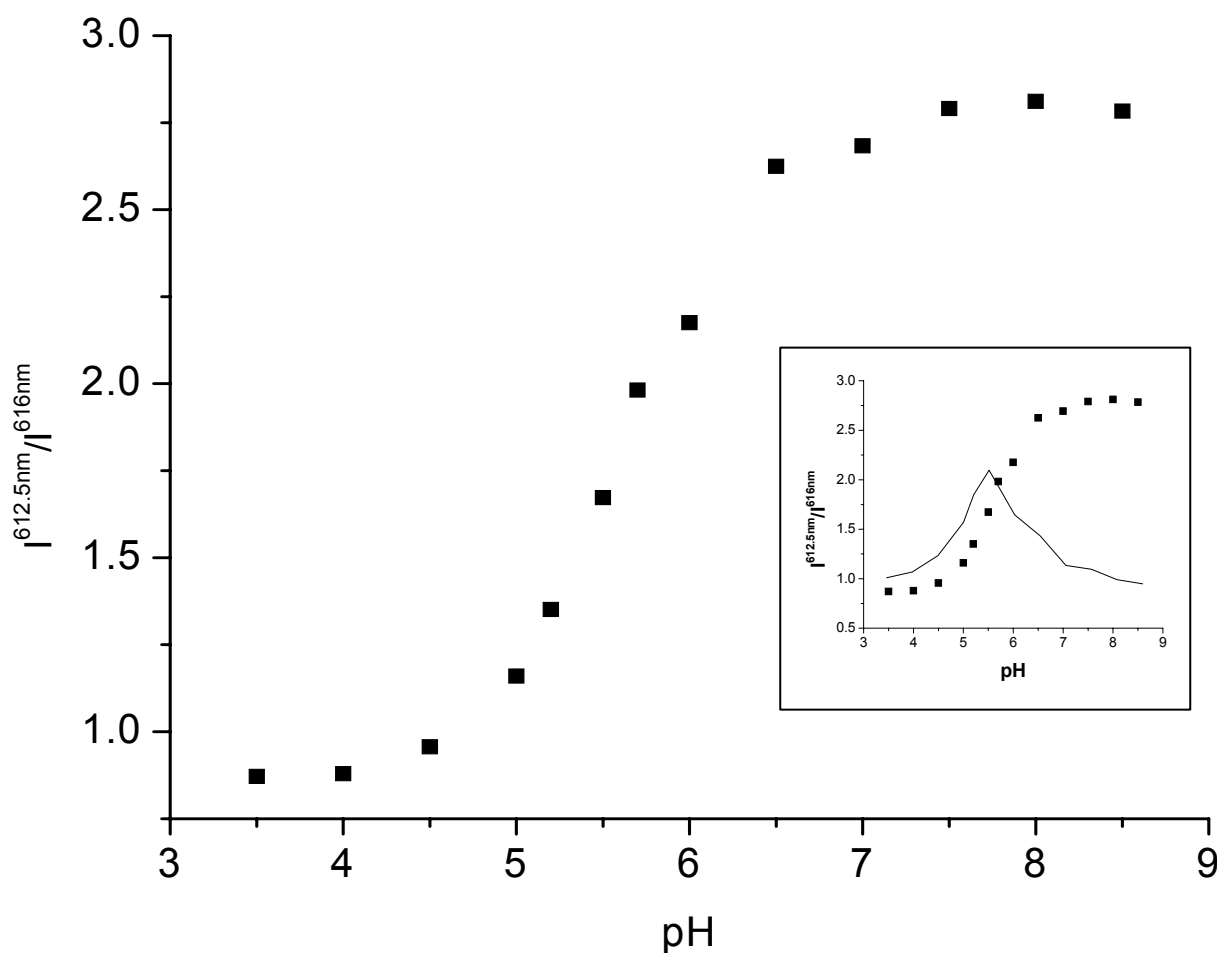
Responsive Fluorinated Lanthanide Probes for ^{19}F Magnetic Resonance Spectroscopy

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1. Plot of the variation of ratio of Eu emission band intensities vs pH for $[\text{EuL}^2]/[\text{EuL}^2\text{H}]$.
2. Ligand and Complex Synthesis.
3. Equations defining the temperature and field dependence of R_1 and R_2 for lanthanide systems.

ESI Figure 1

Variation of the ratio of Eu emission band intensities (λ_{exc} 255 nm, 298K, H_2O , 0.1 M NaCl) versus pH ; the inset shows the first derivative plot consistent with an apparent protonation constant of 5.5.



2. Ligand and Complex Synthesis

N-2-Chloroethyl-2',5'-bis(trifluoromethyl)benzenesulfonamide, 4.

2,5-Bis(trifluoromethyl) benzenesulfonyl chloride (2g, 6.39 mmol) was added to a solution of ethanolamine (0.20g, 3.19 mmol) and pyridine (0.62g, 7.67 mmol) in dichloromethane (15 cm³) while maintaining the temperature below -10°C. The reaction mixture was kept at 4°C overnight and then poured onto ice. The product was extracted using dichloromethane (15 cm³), washed with water (3x20cm³), dried (K₂CO₃), filtered and solvent removed under reduced pressure to yield a white solid that was purified using column chromatography on silica, (DCM, R_f= 0.5) to give a colourless solid (0.5g, 44%), m.p. 65-67°C, m/z (ES⁺): 355, δ_H (CDCl₃, 200MHz) : 3.41 (m, 2H, CH₂NH), 3.59 (t, J= 6Hz, 2H, CH₂Cl), 5.29(t, J=6Hz, 1H, NH), 8.00 (m, 2H, Ar, C3 and C4), 8.47 (s, 1H, Ar C6), δ_C(CDCl₃ , 50.3 MHz): 43.52 (CH₂NH), 45.23 (CH₂Cl), 119.82 [q, ¹J_{CF} 18, C-2(CF₃)], 125.29 [q, ²J_{CF} 18, (C-5(CF₃)], 128.50(Ar CH), 128.61(Ar CH), 129.92(Ar CH), 133.07(q, ¹J_{CF} 162 Hz, CF₃), 140.64 (Ar C). δ_F (CDCl₃ , 188MHz): -58.2 (o-F), -63.7 (m-F). Found: C, 33.66%; H, 2.22%; N, 3.45%. C₁₀H₈NSO₂F₆Cl requires: C, 33.76%; H, 2.25%; N, 3.39%.

1-(2',5'-Bis(trifluoromethyl)benzenesulfonamidoethyl)-4,7,10, tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane

To the 2,5-bis(trifluoromethyl) benzenesulfonamide, 4, (0.15g, 0.42 mmol) was added to a solution of 1,4,7-tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane, 1, (0.22g, 0.42mmol) and K₂CO₃ (0.09g, 0.63g) in acetonitrile (10 cm³) heated at reflux overnight. Inorganic solids were filtered off, solvent was removed under reduced pressure and the tris-ester N-alkylated product was purified using column chromatography on silica, (5% MeOH / DCM R_f= 0.3) to give an oily material, (0.25g, 79%). m/z (ES⁺): 834 (M⁺), 856 [(M+Na)⁺], 872 [(M+K)⁺]. δ_H (CDCl₃, 200MHz) : 1.46 (s, 27H, t-Bu), 2.43 (br, 16H, ring CH₂N), 2.55 (m, 6H, NCH₂CO), 3.09 (br, 4H, NCH₂), 3.31(s, br, 1H, NH), 7.57 (d, 1H, J=8Hz, Ar ring C4), 7.77 (d, 1H, J=8Hz, Ar ring C3), 8.49 (s, 1H, Ar ring C6). δ_C(CDCl₃, 50.3MHz) : 28.27, 28.43 [C(CH₃)], 43.06(CH₂NH), 52.22, 53.60, 55.61, 56.93, 58.52 (CH₂N), 56.41, 57.22, 57.52 (CH₂CO), 81.93[C(CH₃)], 119.80 [q, ²J_{CF} 18, C-2(CF₃)], 125.27[q, ²J_{CF} 18, (C-5(CF₃)], 128.51 (Ar CH), 128.63 (Ar CH), 129.92(Ar CH), 133.07 (q, ¹J_{CF} 163 Hz, CF₃), 140.64 (Ar C) 171.4, 171.6(C=O). δ_F(CDCl₃, 188 MHz): -58.4 (o-F), -63.5 (m-F) .

H₆L² (CF₃CO₂)₂

Ligand L² (0.25g, 3.0 mmol) was dissolved in dichloromethane (2mL) and treated with TFA (3mL) and the solution stirred at room temperature overnight. Solvent was removed under reduced pressure and residual TFA was removed by the stepwise addition of DCM (3x10 cm³), removing solvent under reduced pressure each time to give the ligand as its trifluoroacetate salt, as a glassy solid in quantitative yield. M.p. 142-146°C. m/z (ES⁻): 666 (M⁻). δ_H (CD₃OD, 200MHz) : 2.9-3.8(br m, 25H, NCH₂ and NCH₂ ring), 4.11(br s, 2H, CH₂NH), 8.18 (br s, 2H, Ar H), 8.45 (br s, 1H, Ar H). δ_C(CD₃OD, 50.3 MHz) : 41.11(CH₂NH) 42.41, 47.83, 49.21, 52.11 (CH₂N), 59.42, 60.13, 60.52 (CH₂CO), 119.81(q, ²J_{CF} 18, C-2(CF₃)], 125.29(q, ²J_{CF} 18, (C-5(CF₃)]

128.52 (Ar CH), 128.61(Ar CH), 129.91(Ar CH), 133.06(q, $^1J_{CF}$ 162, CF₃), 140.64 (Ar C1) 173.41, 174.62(C=O). δ_F (D₂O, 188 MHz): -58.7 (*o*-F), 63.7 (*m*-F) .

Synthesis of Complexes:

The ligand H₆L²(CF₃CO₂)₂ and an equimolar quantity of LnCl₃(H₂O)₆ (1:1) (Ln = Eu, Tb, Dy or Yb) were taken into the minimum volume of Purite water (<1mL) and the pH was adjusted to 5.5. The solution was heated at 90 °C for 24 hrs. The reaction mixture was cooled to room temperature and pH was adjusted to 10. The resulting white precipitate was filtered off, and the solution pH was adjusted to 5.5. The solvent was removed by lyophilisation and the residue was extracted from the residue using 10% MeOH/ DCM to yield a colourless or pale cream solid. For each complex, excellent agreement was observed between found and calculated isotope patterns for their negative ion electrospray mass spectra, using solutions presented in methanol.

[Eu.L²]: m/z (MeOH, ES⁻): 812, 814; Found: 812.0842; C₂₄H₂₉O₈N₅F₆SEu requires: 812.0845; δ_F (D₂O, 188MHz) pH 5.5: -65.19, -63.90, -58.97, -53.4 (1:1;1;1); pH 10.2: -65.15, -53.36, pH 4.2: -63.87, -58.93.

[Tb.L²]: m/z (MeOH, ES⁻): 820, 821; Found 820.0887; C₂₄H₂₉O₈N₅F₆STb requires: 820.0890; δ_F (D₂O, 188MHz): pH 5.5: br -45.5, br -61.5, -157.5.
pH 10 : -44.87, -159.59; pH 3.5 : -63.9, -58.89

[Dy.L²]: m/z (ES⁻): 822, 823, 824, 825, 826; Found: 822.0913; C₂₄H₂₉O₈N₅F₆SDy requires: 822.0916 ; δ_F (D₂O, 188MHz): pH 6.0: -38.95, br 59.1, 159.18; pH 10: -39.39, -158.41; pH 3.5: -59.13, -64.22.

[Yb.L²] (exists as mixture of two major isomers): m/z (ES⁻): 831, 832, 833, 834, 835, 836, 837, 838; Found: 833.1010 ; C₂₄H₂₉O₈N₅F₆SyYb requires: 822.1010; δ_F (D₂O, 188MHz): pH 6.0: br -22.88, br 39.66, -61.11, -65.07, br -70.3; pH10: br -22.73, br -39.82, br -70.63; pH 3.5 : br -59.05 (minor), br -61.77, br 64.29 (minor), br -65.77.

3-Trifluoromethyl-4-nitro- methoxyethoxymethylbenzene

3-Trifluoromethyl-4-nitro-phenol (1.0, g, 4.9 mmol) and sodium hydride (0.11, 4.9 mmol) were taken to anhydrous THF (30 ml). MEM chloride (0.6, 4.9 mmol) was added to the solution keeping the temperature below 0°C using iso-propanol and dry ice. The solution was warmed to room temperature and stirred for 1h. Inorganic residues were filtered off; solvent was removed under reduced pressure to leave a pale yellow residue. The product was isolated following purification using column chromatography on silica, (DCM/ 2% MeOH, R_f = 0.4, DCM) to give a pale yellow oil, (1.2g, 85%), m/z (ES⁺): 318 [(M+Na)⁺]. δ_H (CDCl₃, 200MHz): 3.35 (s, 3H, O-CH₃), 3.53 (t, J = 6Hz, 2H, O-CH₂), 3.82 (t, J = 6Hz, 2H, O-CH₂), 5.36 (s, 2H, O-CH₂-O), 7.32 (dd, J H-H(o) = 8Hz, J H-H(m) = 4Hz, 1H, Ar H ortho), 7.43 (d, J_{H-H(m)} = 4Hz, 1H, Ar H ortho), 7.96 (d, J_{H-H(o)} = 8Hz, 1H, Ar H meta). δ_C (CDCl₃, 50.3MHz): 58.85 (O-CH₃), 68.54 (O-CH₂), 71.47 (O-CH₂), 93.75 (O-CH₂-O), 116.44 (q, $^2J_{CF}$ = 18Hz, C (CF₃)), 118.91(Ar CH), 119.24(Ar C), 125.64(q, $^1J_{CF}$ = 162 Hz, CF₃), 127.95 (Ar CH), 141.61 (Ar C), 160.61 (Ar CH). δ_F (CDCl₃, 188MHz): 60.59 (s).

3-Trifluoromethyl- 4 – amino-methoxyethoxymethylbenzene.

3-Trifluoromethyl-4-nitro-methoxyethoxymethylbenzene. (1.2 g, 4.1 mmol) was dissolved in ethanol and a catalytic amount of Pd(OH)₂/C was added and the mixture stirred at room temperature under hydrogen (40 psi) for 24 hrs. Catalyst was filtered and solvent removed under reduced pressure to give a pale yellow oil in quantitative yield. m/z (ES⁺):288 [(M+Na)⁺], δ_{H} (CDCl₃, 200MHz): 3.30(s, 3H, O-CH₃), 3.50(t, J = 6Hz, 2H, O-CH₂), 3.75(t, J = 6Hz, 2H, O-CH₂), 5.15(s, 2H, O-CH₂-O), 6.77 (d, J_{H-H(o)} = 8Hz, 1H, Ar H ortho), 7.00 (d, J_{H-H(o)} = 8Hz, 1H, Ar H meta), 7.15(s, 1H, Ar H ortho). δ_{C} (CDCl₃, 50.3Hz): 59.18 (O-CH₃), 67.78(O-CH₂), 71.76 (O-CH₂), 94.66(O-CH₂-O), 115.18 (q, ²J_{CF} = 18Hz, CCF₃), 119.21(Ar CH), 125.64 (q, ¹J_{CF} = 162 Hz, CF₃), 122.22 (Ar CH), 123.29(Ar C), 138.72 (Ar C), 149.74 (Ar CH). δ_{F} (CDCl₃, 188MHz): 60.59 (s).

3-Trifluoromethyl-4-(chloroethanoyl)-methoxyethoxymethylbenzene 3.

3-Trifluoromethyl-4-amino-methoxyethoxymethylbenzene (0.5g, 0.2 mmol), and N-hydroxysuccinimidyl chloroacetate (0.36g, 0.2 mmol) were dissolved in dichloromethane (10 cm³), and stirred at room temperature overnight. Solvent was removed and the product purified using column chromatography on silica, (DCM/MeOH, R_f = 0.6, 5% MeOH/DCM), followed by recrystallisation from hexane/EtOAc to give a white solid, (0.25g, 52%), m.p. 72-74°C, Found C, 45.76%, H, 4.63%, N, 4.21%. C₁₃H₁₅NO₄F₃Cl requires C, 45.72%, H, 4.43%, N, 4.13%, m/z (ES⁺):341 (M⁺), 364 [(M+Na)⁺], δ_{H} (CDCl₃, 400MHz): 3.37(s, 3H, O-CH₃), 3.55(t, J = 4.8 Hz, 2H, O-CH₂), 3.81(t, J = 4.8Hz, 2H, O-CH₂), 4.22 (s, 2H, CH₂Cl), 5.28(s, 2H, O-CH₂-O), 7.27 (d, J_{H-H(o)} = 8Hz, 1H, Ar H ortho), , 7.34(s, 1H, Ar H ortho). 7.96 (d, J_{H-H(o)} = 8Hz, 1H, Ar H meta), 8.57 (br s, 1H, NH). δ_{C} (CDCl₃, 100.6Hz): 43.10 (CH₂Cl), 59.25 (O-CH₃), 68.09(O-CH₂), 71.68 (O-CH₂), 93.82(O-CH₂-O), 114.65 (q, ²J_{CF} = 18Hz, CCF₃), 120.37(Ar CH), 122.97(q, ¹J_{CF} = 162 Hz, CF₃),126.89 (Ar CH), 127.96(Ar C),154.82 (Ar C), 164.63 (Ar CH),178.54 (C=O)], δ_{F} (CDCl₃, 188MHz): 61.5 (s).

Ligand L^{3a}.

3-Trifluoromethyl-4-(chloroethanoyl)-methoxyethoxymethylbenzene,3, (0.10g,0.3mmol) was added to a solution of 1,4,7-tris(t-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane(1) (0.16g, 0.31mmol) and K₂CO₃ (0.04g, 0.63mmol) in acetonitrile (10 cm³) and the mixture was boiled under reflux overnight. Inorganic solids were filtered off, solvent was removed and the product was purified using column chromatography on silica, 5% MeOH / DCM R_f = 0.2) to give a clear oily product, (0.10g, 79%). m/z (ES⁺): 821 (M⁺), 844 [(M+Na)⁺], δ_{H} (CDCl₃, 400MHz):1.42 (S, 27H, t-Bu), 2.13-2.62 (br,16H, ring CH₂N), 2.72-3.10(m, 6H, NCH₂CO), 3.09 (br,4H,NCH₂), 3.31 (s,br,1H,NH), 3.55 (s, 3H, OCH₃), 3.54 (d, J = 4.8 Hz, 2H, OCH₂), 3.78 (d, J = 4.8 Hz, 2H, OCH₂), 5.22 (2H, s, OCH₂O), 7.15 (d, J_{H-H(o)} = 8Hz, 1H, Ar H ortho), 7.25(s, 1H, Ar H ortho). 7.45 (d, J_{H-H(o)} = 8Hz, 1H, Ar H meta). δ_{C} (CDCl₃, 100.6 MHz) : 28.06,28.38 (C(CH₃)), 43.06(CH₂NH), 52.21, 53.61, 55.62,56.90, 58.51 (CH₂N), 56.43, 57.21, 57.53 (CH₂CO), 59.25 (O-CH₃), 68.09(O-CH₂), 71.68 (O-CH₂), 81.94 (CCH₃), 93.82(O-CH₂-O), 114.65 (q, ²J_{CF} = 18Hz, C(CF₃)), 120.37(Ar CH), 122.97(q, ¹J_{CF} = 162 Hz, CF₃),126.89 (Ar CH),

127.96(Ar C), 154.82 (Ar C), 164.63 (Ar CH), 171.4, 171.6 (C=O), 178.54 (C=O),
 $\delta_F(\text{CDCl}_3, 376.3\text{MHz})$: 61.14(s)

$\text{H}_5\text{L}^3(\text{CF}_3\text{CO}_2)_2$

Ligand L^3 (0.10g, 0.12 mmol) was dissolved in dichloromethane (2cm^3) and TFA (3cm^3) was added and the mixture was stirred at room temperature overnight. Solvent was removed under reduced pressure. Traces of TFA were removed by the successive addition of DCM ($3 \times 10\text{cm}^3$) removing solvent each time under reduced pressure to give the trifluoroacetate salt, as a glassy solid, m.p. 122-124 °C. m/z (ES⁻): 563 (M).
 $\delta_H(\text{CD}_3\text{OD}, 400\text{MHz})$: 2.9-3.8(br m, 25H, NCH₂ and NCH₂ ring), 4.11(br s, 2H, CH₂NH), 7.75 (d, $J_{\text{H-H(o)}} = 8\text{Hz}$, 1H, Ar H ortho), 7.95(s, 1H, Ar H ortho). 8.31 (d, $J_{\text{H-H(o)}} = 8\text{Hz}$, 1H, Ar H meta). $\delta_C(\text{CD}_3\text{OD}, 50.3\text{MHz})$: 41.11(CH₂NH) 42.41, 47.83, 49.21, 52.11(CH₂N), 59.422, 60.13, 60.52(CH₂CO), 119.80 (q, $^2J_{\text{CF}} = 18\text{Hz}$, C(CF₃), 121.32(Ar CH), 124.97 (q, $^1J_{\text{CF}} = 162\text{Hz}$, CFC₃), 127.89 (Ar CH), 129.96 (Ar C), 130.82 (Ar C), 168.63 (Ar CH), 178.54 (C=O). $\delta_F(\text{CD}_3\text{OD}, 376.3\text{MHz})$: 61.54(s)

3. Equations defining magnetic field and T dependence of relaxation rates

The electron-nuclear interaction is modulated by electron spin relaxation, molecular tumbling and chemical exchange. The relaxation rates are determined by contributions from the hyperfine (negligible for all but Gd), dipolar and Curie mechanisms:

$$R_{iM} = R_{icon} + R_{idip} + R_{i\chi} \quad (1)$$

for Ln ions with short electronic relaxation times: $R_{1dip} = R_{2dip} = \frac{4}{3} \left(\frac{\mu_o}{4\pi} \right)^2 \frac{\gamma^2 \mu_{eff}^2 T_{1e}}{r^6}$ (2)

Curie spin contribution to $R_2 > R_1$: $R_{1\chi} = \frac{6}{5} \left(\frac{\mu_o}{4\pi} \right)^2 \frac{\gamma^2 \mu_{eff}^4 B_o^2}{(3kT)^2 r^6} \left(\frac{\tau_r}{1 + \omega^2 \tau_r^2} \right)$ (3)

$$R_{2\chi} = \frac{1}{5} \left(\frac{\mu_o}{4\pi} \right)^2 \frac{\gamma^2 \mu_{eff}^4 B_o^2}{(3kT)^2 r^6} \left(\frac{4\tau_r + \frac{3\tau_r}{1 + \omega^2 \tau_r^2}}{1 + \omega^2 \tau_r^2} \right) \quad (4)$$