^{19}F NMR based pH probes: lanthanide(III) complexes with pH-sensitive chemical shifts

Alan M. Kenwright, Ilya Kuprov, Elena De Luca, David Parker[1], Shashi U. Pandya, P. Kanthi Senanayake and David G. Smith

ESI

1. Details of DFT calculations and selected Figures of the complexes derived from the calculated structures.
2. Relaxation Analysis.
3. Ligand and Complex Synthesis and characterisation.
4. Selected 19-F NMR spectra.
5. Selected HPLC chromatograms.

1. DFT Calculations

The DFT calculations were performed using the Gaussian03 package for La^{3+} and Y^{3+} complexes – the structures of complexes with other lanthanides as well as those with Y^{3+} are known to be nearly identical. Importantly, however, the use of diamagnetic La^{3+} and Y^{3+} for DFT calculations avoids a host of largely unresolved theoretical issues with spin-orbit coupling and zero-field splitting in open-shell lanthanides. Y^{3+} results are nearly identical to the La^{3+} results, therefore only the latter are tabulated below. Gaussian03 logs and checkpoints are available from IK upon request.

Molecular geometries were optimized *in vacuo* using spin-restricted B3LYP exchange-correlation functional with a compound basis set (cc-pVDZ for CHNOFS, Stuttgart ECP28MWB for Ln and WGBS for Y). Saddle points were located using QST2 and QST3 methods. Hessians were computed and intrinsic reaction coordinates traced in both directions to ensure that the saddle points located are first-order saddles corresponding to the process under consideration.

[1] *Email: david.parker@durham.ac.uk*

Figure 1.1 Stereoview of the calculated structure of the complex [Y.HL[1]]

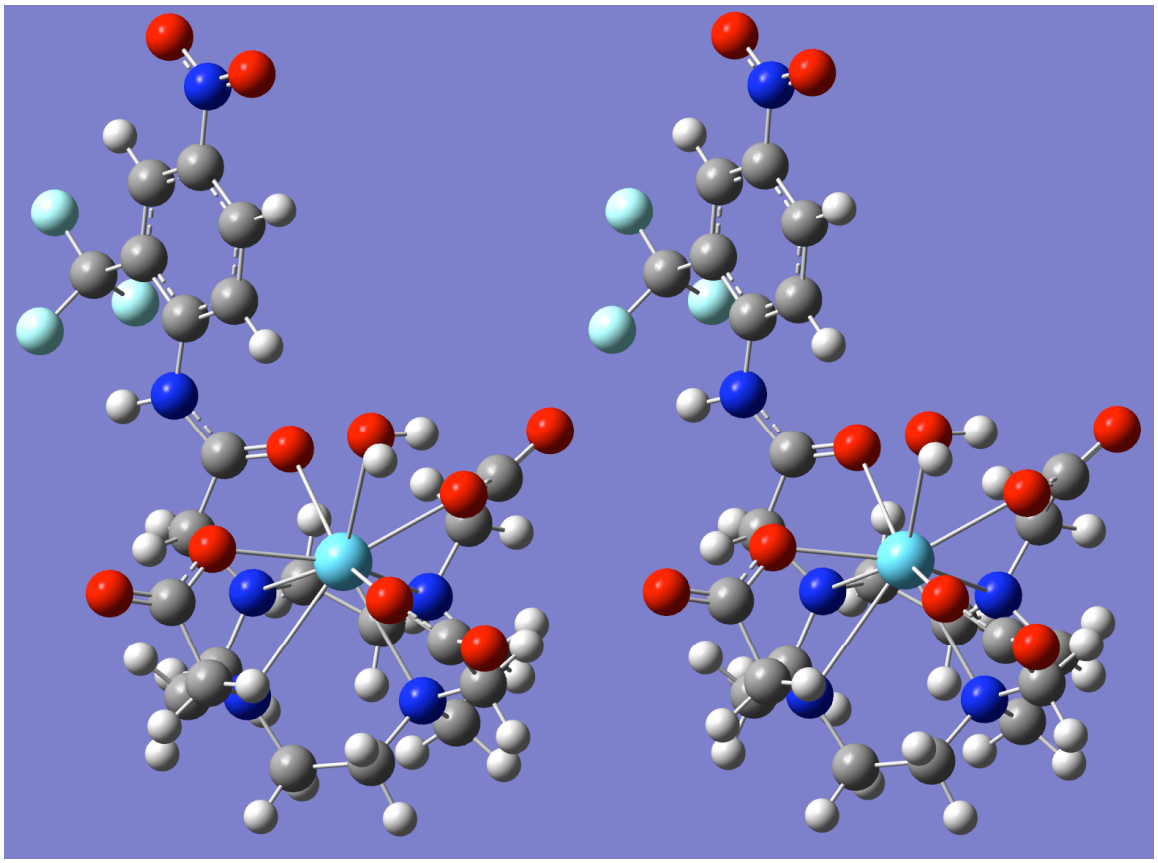


Figure 1.2 Stereoview of the calculated structures of the two isomers of the deprotonated complex, [Y.L^1]

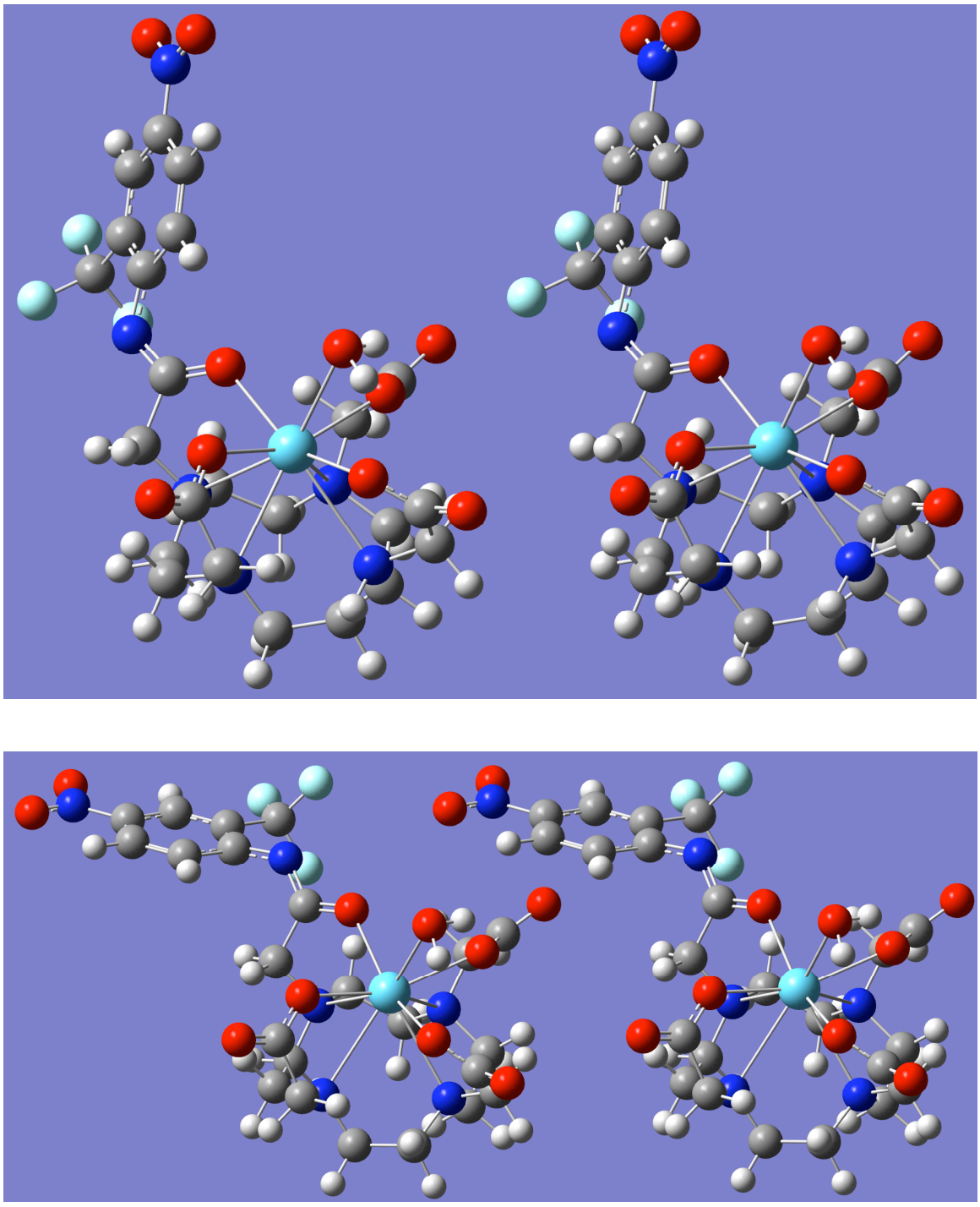


Figure 1.3 Stereoviews of the major isomer of the coordinated sulfonamide complex, $[Y.L^4]^-$

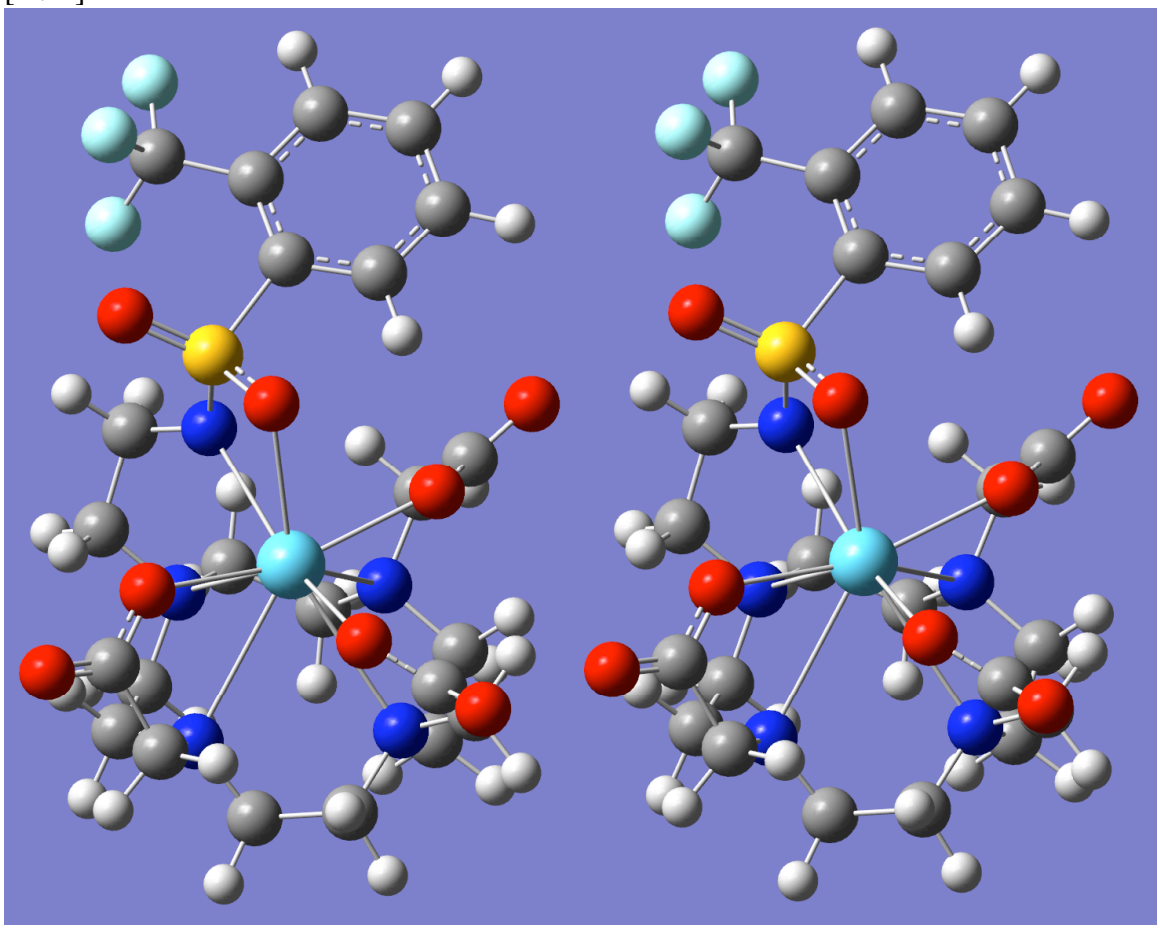


Table 1. DFT B3LYP energies and their complete basis set (CBS) extrapolation for the two coordination isomers of $[La.L^1]^-$.

Basis set[a]	N-coordinated isomer energy[c], Hartree	O-coordinated isomer energy[c], Hartree
cc-pVDZ	–2710.29498	–2710.31791
cc-pVTZ	–2710.98166	–2711.00458
cc-pVQZ	–2711.16717	–2711.19051
CBS limit[b]	–2711.23584	–2711.25955

[a]The basis set quoted is for HCNOFS, the basis set for La is Stuttgart RSC ECP28MWB basis set in all cases. [b]Dunning-Feller extrapolation. [c]Geometries optimized with cc-pVDZ (HCNOFS) and Stuttgart RSC ECP28MWB (La) basis set.

Table 2. DFT B3LYP energies and their complete basis set (CBS) extrapolation for the two constitutional isomers of $[La.\mathbf{L^1}]^-$ complex.

Basis set[a]	"Ring-down" isomer energy[c], Hartree	"Ring-up" isomer energy[c], Hartree	Saddle point energy[c], Hartree
cc-pVDZ	–2710.31084	–2710.31791	–2710.30056
cc-pVTZ	–2710.99738	–2711.00458	–2710.98864
cc-pVQZ	–2711.18342	–2711.19051	–2711.17477
CBS limit[b]	–2711.25257	–2711.25955	–2711.24379

[a]The basis set quoted is for HCNOFS, the basis set for La is Stuttgart RSC ECP28MWB basis set in all cases. [b]Dunning-Feller extrapolation. [c]Geometries optimized with cc-pVDZ (HCNOFS) and Stuttgart RSC ECP28MWB (La) basis set, saddle point located with QST2 method, Hessians and IRCs checked.

Table 3. DFT B3LYP energies and their complete basis set (CBS) extrapolation for the two coordination isomers of $[La.\mathbf{L^4}]^-$ ("sulphonamide") complex.

Basis set[a]	Isomer A energy[c], Hartree	Isomer B energy[c], Hartree	Saddle point energy[c], Hartree
cc-pVDZ	–2903.85656	–2903.86062	–2903.82499
cc-pVTZ	–2904.53840	–2904.54175	–2904.50889
cc-pVQZ	–2904.72079	–2904.72411	–2904.69169
CBS limit[b]	–2904.78740	–2904.79078	–2904.75837

[a]The basis set quoted is for HCNOFS, the basis set for La is Stuttgart RSC ECP28MWB basis set in all cases. [b]Dunning-Feller extrapolation. [c]Geometries optimized with cc-pVDZ (HCNOFS) and Stuttgart RSC ECP28MWB (La) basis set, saddle point located with QST2 method, Hessians and IRCs checked.

2. Relaxation Analysis

^{19}F T_1 times were measured in dilute D_2O solutions at 295 K using the inversion-recovery technique, without proton decoupling, on Varian spectrometers operating at magnetic inductions corresponding to proton frequencies of 200, 400, 500 and 700 MHz (Mercury-200, Mercury-400, Inova-500, VNMRS-700). The resulting free induction decays were subjected to backward linear prediction, optimal exponential weighting, zero filling, Fourier transform, phasing and baseline correction (by polynomial fitting to signal-free spectrum areas). The signals were integrated by Lorentzian line fitting. Inversion-recovery type function was fitted to the resulting data using Levenberg-Marquardt minimization of the non-linear least squares error functional.

Table 4. Longitudinal relaxation rates for four [Ln.**L**^{3}] complexes.

^{19}F NMR frequency, MHz	Longitudinal relaxation rate, s^{-1}			
	[Ho.L^3**]**	**[Tb.**L^3**]**	**[Tm.**L^3**]**	**[Dy.**L^3**]**
188.16	45.5 ± 2.5	74.4 ± 0.4	22.9 ± 0.5	88.9 ± 8.4
376.31	124.4 ± 9.5	132.5 ± 7.0	46.7 ± 7.0	162.4 ± 11.3
470.25	169.0 ± 1.9	161.7 ± 0.5	57.5 ± 0.7	201.3 ± 13.5
658.41	238.7 ± 1.6	211.1 ± 0.5	74.4 ± 0.5	286.3 ± 12.7

Table 5. Transverse relaxation rates, estimated as 2 ·(half-width@half-height), of a Lorentzian line fit) for four [Ln.**L**^{3}] complexes.

^{19}F NMR frequency, MHz	Transverse relaxation rate, s^{-1}			
	[Ho.L^3**]**	**[Tb.**L^3**]**	**[Tm.**L^3**]**	**[Dy.**L^3**]**
188.16	87	124	53	156
376.31	192	206	89	355
470.25	267	271	112	543
658.41	441	407	168	740

3. Ligand and Complex Synthesis

1. 2-Chloro-N-(4-nitro-2-trifluoromethyl)-ethanamide

Chloroacetylchloride (1.95 ml, 24.5 mmol) was added dropwise to a stirred solution of 4-nitro-2-trifluoromethyl aniline (2.01 g, 9.8 mmol), 4-dimethylaminoipyridine (10 mg) and triethylamine (1.70 ml, 12.1 mmol) in dry THF (35 ml) at 0˚C. The reaction mixture was allowed to warm to room temperature and stirred for 48 h. CH_2Cl_2 (30 ml) was added and the resulting white precipitate dissolved in H_2O (30 ml). The organic layer was washed with $HCl_{(aq)}$ (0.1 M, 30 ml) followed by H_2O (3 x 20 ml) then dried over K_2CO_3. After filtration the solvent was removed to yield a brown oil that was purified by column chromatography over silica gel eluting with CH_2Cl_2:hexane (50:50 then 80:20 and finally 100% CH_2Cl_2) giving a light yellow crystalline solid (1.35 g, 49%), m.p. 62-64 ˚C. δ_H (200 MHz, $CDCl_3$): 4.28 (2H, s, CH_2Cl), 8.44 (1H, d, J = 9.0 , H^6), 8.54 (1H, s, H^3), 8.69 (1H, d, J = 9.0, H^5), 9.08 (1H, br, s, NH); δ_C (50 MHz, $CDCl_3$) 43.09 (CH_2Cl), 122.59, 122.70, 123.05, 128.57, 140.15, 143.75 (Ar), 164.68 (C=O); δ_F (188 MHz, $CDCl_3$) -61.71 (CF_3); m/z (ESMS$^-$) 281.3 $[M-H]^-$; Found C, 38.3; H, 2.12; N, 9.80%; $C_9H_6N_2O_3F_3Cl$ requires C, 38.2; H, 2.14; N, 9.91%.

10-[(4-Nitro-2-trifluoromethyl(phenyl))carbamoylmethyl]-1,4,7-tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane

To a solution of 1,4,7-tris(tert-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (330 mg, 0.64 mmol) and 2-chloro-N-(4-nitro-2-trifluoromethyl)-ethanamide (200 mg, 0.71 mmol) in dry CH_3CN (20 ml) under argon, was added K_2CO_3 (106 mg, 0.77 mmol) and KI (5 mg, cat.). The mixture was boiled under reflux for 24 h. After filtration, the residue was washed with CH_2Cl_2 (2 x 30 ml) and solvent removed under reduced pressure to give a brown oil which was filtered through a layer of silica gel, washed first with diethyl ether and then with 20%MeOH/CH_2Cl_2 . Removal of solvent under reduced pressure afforded a pale brown oil (402 mg, 83%). δ_H (200 MHz, $CDCl_3$) 1.37 (27H, br, s, CH_3), 2.15-3.80 (24H, br, CH_2 ring and CH_2CO), 8.11 (1H, d, J = 8.5, aromatic H^6), 8.25 (1H, dd, J = 8.5, 2.4, aromatic H^5), 8.48 (1H, d, J = 2.5 Hz, aromatic H^3); δ_F (188 MHz, $CDCl_3$) -61.10 (CF_3); m/z (ESMS$^+$) 783.3 $[M + Na]^+$.

10-[(4-Amino-2-trifluoromethyl(phenyl))carbamoylmethyl]-1,4,7-tris(tert-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane

10-[(4-Nitro-2-trifluoromethyl(phenyl))carbomoylmethyl]-1,4,7-*tris*(tertbutoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (131 mg, 0.17 mmol) in MeOH (3ml) was placed in a hydrogenation vessel. A small amount (ca. 15 mg) of Pd/C catalyst was added and the mixture was hydrogenated at 40 psi for 20 h. The Pd/C was removed by syringe filtration and the solvent removed under reduced pressure to yield the product as a brown-red solid (122 mg, 97%). δ_F (188 MHz, $CDCl_3$) -62.3 (CF_3); m/z (ESMS$^+$) 769.3 $[M + K]^+$.

10-[(4-Nitro-2-trifluoromethyl(phenyl)carbamoylmethyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane, $H_6L^1Cl_2.xH_2O$

10-[(4-Nitro-2-trifluoromethyl(phenyl))carbamoylmethyl]-1,4,7-tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (310 mg, 0.41 mmol) was dissolved in CH_2Cl_2 (1 ml) and CF_3CO_2H (6 ml) was added. The solution was stirred at room temperature for 24h. The solvent was removed under reduced pressure and the resulting solid washed with DCM (5 x 5ml) removing the solvent each time under reduced pressure (KOH in trap) to give the product as a trifluoroacetate salt (δ_F -76.1 TFA). The residue was dissolved in water (5mL) and stirred overnight with anion exchange resin (DOWEX 1X8 200-400 MESH Cl, pre-treated with 1M HCl) in Purite H_2O to give the chloride salt. After filtration, the water was lyophilised to yield the product as a light yellow powder (113 mg, 47%). δ_H (200 MHz, D_2O) 2.60-4.20 (24H, br, CH_2 ring and CH_2CO), 7.84 (1H, d, J = 8.5, aromatic H^6), 8.36 (1H, d, J = 8.5, aromatic H^5), 8.51 (1H, br s, aromatic H^3); δ_C (126 MHz, D_2O) 46.83, 48.55, 51.13, 54.73, 79.91, 122.99, 128.04, 129.379; δ_F (188 MHz, D_2O) -61.75 (CF_3); m/z (ESMS$^+$) 593.3 $[M + H]^+$, 615.3 $[M + Na]^+$, 631.2 $[M + K]^+$; (ESMS$^-$) 629.1 $[M + Cl]^-$; Found 631.1739; $C_{23}H_{31}O_9N_6F_3K$ requires 631.1736; found 655.1403; $C_{23}H_{31}O_9N_6F_3Cu$ requires 655.1395

[HoL^1]

The ligand $H_6L^1\ Cl_2$ (assumed dihydrate;30.5 mg, 0.043 mmol) and Ho(III)Cl_3 (15.9 mg, 0.059 mmol) were dissolved in water (3ml) and the pH adjusted to 5.5 using $KOH_{(aq)}$. The reaction was left stirring overnight under reflux. After cooling to room temperature, the solution pH was adjusted to pH 10 and the mixture centrifuged to remove the precipitated metal hydroxide. The supernatant was adjusted back to pH 6 with $HCl_{(aq)}$ and the solution lyophilised to give a pale yellow solid that was extracted into 20%MeOH in

dichloromethane to give a colourless solid. δ_H (200 MHz, D_2O) -250 (1H, br), -248 (1H), -66 (1H), -58 (3H), -49 (1H), 55 (1H), 89 (1H), 161 (4H, br), 166 (1H); δ_F (188 MHz, D_2O) (exists as mixture of isomers) pD 5.5.: -55.1 (br, CF_3 major isomer, 88%); m/z (ESMS$^+$) 777.0 $[M + Na]^+$, 793.0 $[M + K]^+$; Found 777.1067; $C_{23}H_{28}O_9N_6F_3HoNa$ requires 777.1065; found 793.0816; $C_{23}H_{28}O_9N_6F_3HoK$ requires 793.0805.

[DyL^1]

Prepared similarly, as for the Ho complex: δ_F (188 MHz, D_2O) -58.3 (br, CF_3 major isomer), -66.5 (minor); m/z (ESMS$^+$) 776.0 $[M + Na]^+$; Found 776.1064; $C_{23}H_{28}O_9N_6F_3DyNa$ requires 776.1054.

10-[(4-Amino-2-trifluoromethyl(phenyl)carbamoylmethyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane, $H_5L^2(CF_3CO_2)_2$

This was prepared from the *tris*-t-butyl ester using TFA, as described for L^1 above.

δ_H (200 MHz, D_2O) 2.70-4.30 (16H, br, cyclen ring), 4.60-4.90 (8H, m, br, acetate CH_2's), 7.64 (1H, d, J = 4, aromatic H^6), 7.71 (1H, d, J = 4.2, aromatic H^5), 7.75 (1H, s, aromatic H^3); δ_C (126 MHz, D_2O) 27.31, 29.68, 49.95, 54.03, 121.65, 127.60, 131.57, 171.15; δ_F (188 MHz, D_2O, pD 5.4) -62.00 (CF_3); m/z (ESMS$^-$) 599.4 $[M + Cl]^-$.

The following complexes were prepared as described for the complexes of L^1.

[TbL^2]

δ_H (200 MHz, D_2O) -400 (2H), -370 (2H), -348 (1H), -140 (1H), -126 (1H), -110 (1H), -98 (2H), -94 (1H), -73 (1H), -68 (1H), -64 (1H), -51 (1H), -18 (1H), -15 (1H), -2 (1H), 28 (1H), 41 (1H), 50 (1H), 86 (1H), 117 (1H), 128 (1H), 140 (1H), 224 (1H, br), 230 (1H, br), 238 (1H), 252 (1H, br), 263 (1H); δ_F (188 MHz, D_2O) -53.0 (CF_3 major isomer), -51.9, -39.1 (minor isomers); m/z (ESMS$^+$) 741.1 $[M + Na]^+$; (ESMS$^-$) 717.3 $[M - H]^-$; Found 741.1283; $C_{23}H_{30}O_7N_6F_3TbNa$ requires 741.1274.

[DyL^2]

δ_H (200 MHz, D_2O) -508 (1H), -472 (1H), -439 (1H), -426 (1H), -398 (1H), -200 (1H), -155 (1H), -143 (1H), -107 (1H), -100 (1H), -99 (1H), -72 (1H), -58 (1H), -52 (1H), -45 (1H), -32 (1H), -18 (1H), -10 (1H), 10 (1H), 111 (1H), 163 (1H), 194 (1H), 215 (1H), 272 (1H, br), 316 (2H, br), 324 (1H, br); δ_F (188 MHz, D_2O) –66.0 (CF_3 major isomer), -

46.5 (minor); m/z (ESMS$^+$) 743.1 [M + Na]$^+$; Found :743.1354; $C_{23}H_{31}O_7N_6F_3{}^{161}DyNa$ requires 743.1364.

Synthesis of ligand L^3 and its lanthanide (III) complexes

The ligand was prepared as its trifluoroacetate salt, as described in reference 13.

m.p. 122-124 °C. m/z (ES$^-$): 563 (M$^-$). δ_H (CD_3OD, 400MHz): 2.9-3.8(br m, 25H, NCH_2 and NCH_2 ring),4.11(br s, 2H, CH_2NH), 7.75 (d, $J_{H\text{-}H(o)}$ = 8Hz, 1H, Ar H ortho), 7.95(s, 1H, Ar H ortho). 8.31 (d, $J_{H\text{-}H(o)}$ = 8Hz, 1H, Ar H meta). δ_C(CD_3OD, 50.3MHz): 41.11($\underline{C}H_2NH$) 42.41, 47.83, 49.21 , 52.1 1($\underline{C}H_2N$), 59.422, 60.13, 60.52 ($\underline{C}H_2CO$), 119.80 (q, $^2J_{CF}$ = 18 Hz, $\underline{C}$ (CF3), 121.32(Ar $\underline{C}$H), 124.97 (q, $^1J_{CF}$ = 162 Hz, $\underline{C}F_3$),127.89 (Ar $\underline{C}$H), 129.96(Ar $\underline{C}$),130.82 (Ar $\underline{C}$), 168.63 (Ar $\underline{C}$H), 178 .54 (C=O). δ_F($CDCl_3$, 376.3MHz): -61.54(s). δ_F(CD_3OD, 376.3MHz): -62.8 (s).

The ligand $H_5L^3(CF_3CO_2)_2$ and an equimolar quantity of $LnCl_3(H_2O)_6$ (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 ^{0}C for 24 h. 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 complex was extracted from the residue using 10% MeOH/ DCM to yield a colourless or pale cream solid, typically in 80-90% yield. For the Eu, (151 and 153 at 47.8 and 52.2%) Gd and Dy complexes (n.b. Tb-159, Ho-165 and Tm-169 are 100% at natural abundance), excellent agreement was observed between found and calculated isotope patterns for their positive ion electrospray mass spectra, using solutions presented in methanol.

Fluorine-19 NMR shifts (±0.3 ppm) and linewidths (±4Hz) for the complexes listed were invariant over the pH range 4 to 9.

[Tm.$\mathbf{L^3}$]: m/z (MeOH, ES$^+$): 752: Found: 752.1200; $C_{23}H_{29}O_8N_5F_3NaTm$ requires: 752.1202; δ_F(D_2O, 188MHz) pH 7.5: -78.1 ($\nu_{1/2}$ = 36 Hz), -89.2 (minor isomer 9%).

[Tb.$\mathbf{L^3}$]: m/z (MeOH, ES$^+$): 720, 742; Found 742.1115; $C_{23}H_{29}O_8N_5F_3NaTb$ requires: 742.1114; δ_F(D_2O, 188MHz): pH 7.4: br -52.5 ($\nu_{1/2}$ = 52 Hz),), br -40.6 (minor isomer 12%)

[Ho.$\mathbf{L^3}$]: m/z (ES$^+$): 748; Found: 748.1169; $C_{23}H_{29}O_8N_5F_3NaHo$ requires: 748.1164 ; δ_F(D_2O, 188MHz): pH 7.8: br -57.9 ($\nu_{1/2}$ = 31 Hz), br –49.0 (minor isomer 12%).

[Dy.$\mathbf{L^3}$]: m/z (ES^+): 744, 745, 746, 747(isotope pattern); Found: 747.1165; $C_{23}H_{29}O_8N_5F_3Na^{164}Dy$ requires 747.1158; δ_F(D_2O,188MHz): pD 7.5: br -66.7 ($\nu_{1/2}$ = 64 Hz), br -43.8 (minor 20%).
[Gd.$\mathbf{L^3}$]: m/z (ES^+): 742; Found: 738.1101; $C_{23}H_{29}O_8N_5F_3Na^{155}Gd$ requires: 738.1087; δ_F (D_2O, 376 MHz): -61 ppm ($\nu_{1/2}$ = 3,500 Hz).

Synthesis of ligand L^4 and its lanthanide(III) complexes

2-Trifluoromethylphenylsulfonylaminoethyl-2-trifluoromethylphenylsulfonate.
2- Trifluoromethylbenzenesulfonyl chloride (3g,12.3 mmol) was added to a solution of ethanolamine (0.37g, 6.2 mmol) and pyridine (1.16g, 14.3mmol) in dichloromethane (15 cm^3) while maintaining the temperature below -10ºC. The reaction mixture was kept at 4°C overnight and then poured onto ice. The product was extracted using dichloromethane (15 cm^3), washed with water (3x20cm^3), dried (K_2CO_3), filtered and solvent removed under reduced pressure to yield a white solid which was purified using column chromatography on silica, (DCM, R_f= 0.3) to give a colourless solid. Yield:(1.5g, 52%), m.p.132-133°C, m/z (ES+): 500 $(M+Na)^+$, δ_H (CD_3OD, 500MHz): 3.29 (t, J = 6Hz, 2H, CH_2NH),3.30 (s, OH), 4.11 (t, J= 6Hz, 2H, CH_2O), 4.87 (s, broad, NH), 7.75 (dd, J=7.5 Hz, Ar-C5), 7.86 (dd, J=7.5 Hz, Ar-C5'), 7.88 (dd, J=7.5 Hz, Ar-C4'), 7.89(dd, J=7.5Hz, Ar-C6), 7.90 (dd, J=7.5Hz, Ar-C3), 8.00 (d, J=7.5Hz, Ar-C3'), 8.11(dd, J=7.5Hz,Ar-C4), 8.20(d, J=7.5Hz, Ar-C6'), δ_C(CD_3OD, 125.6 MHz): 41.72 ($\underline{C}H_2NH$), 59.72 ($\underline{C}H_2O$), 122.9 [q,$^1J_{CF}$=275Hz,Ar$\underline{C}$F3)], 127.7 [q,$^1J_{CF}$=114Hz, Ar'$\underline{C}$F)], 128.4 [q,$^2J_{CF}$=6Hz, $\underline{C}$2CF3)], 128.7 [q, $^2J_{CF}$ 6Hz, $\underline{C}$2'CF3)], 130.7 (Ar$\underline{C}$H), 132.18(Ar$\underline{C}$H), 132.70(Ar$\underline{C}$H), 132.8 (Ar$\underline{C}$H,132.98(Ar$\underline{C}$H), 134.11(Ar$\underline{C}$),134.47(Ar$\underline{C}$H), 139.53(Ar$\underline{C}$H), δ_F(CD_3OD,188MHz):-58.6, 58.9. Found: C, 40.24%; H, 2.75%; N, 2.92%. $C_{16}H_{13}NSO_5F_6$ requires: C, 40.25%; H, 2.73%; N, 2.93%.

1-(2-Trifluoromethylbenzenesulfonamidoethyl)-4,7,10,tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane
2-(Trifluoromethylphenylsulfonylamino)ethyl(2-trifluoromethylphenylsulfonate) (0.46g, 0.96 mmol) was added to a suspension of 1,4.7-tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane,**1**, (0.50g, 0.96mmol) and K_2CO_3(0.26g, 1.92mmol) in acetonitrile (20cm^3) heated under reflux overnight. Inorganic salts were removed by filtration, solvent

was removed under reduced pressure and the product was purified using column chromatography on silica, (5% MeOH / DCM R_f = 0.3) to give an oily material, Yield: (0.45g, 60%), m/z (ES+): 766 (M^+), 789 [$(M+Na)^+$], δ_H ($CDCl_3$, 200MHz): 1.46 (s, 27H, ^tBu)), 2.43(br, 16H, ring CH_2N), 2.65 (m, 6H, NCH_2CO), 3.00 (br, 4H, NCH_2),3.41 (br s, 1H, NH), 6.62 (dd, 1H,J=8Hz, Ar-C4), 7.69 (dd, 1H, J=8Hz, Ar-C2), 8.49 (dd, 1H, J=8Hz Ar-C3), 8.28 (d, 1H,J=8Hz, ArC6), δ_C($CDCl_3$,50.3MHz): 28.27, 28.43 [C($\underline{C}H_3$)], 43.06($\underline{C}H_2NH$), 52.22, 53.60, 55.61, 56.93, 58.52 (CH_2N),56.41, 57.22, 57.52 (CH_2CO), 81.93 [$C(CH_3)$], 119.80 [q,$^2J_{CF}$=18Hz,$\underline{C}$ (CF_3)], 125.27, 128.5, 128.63 (Ar $\underline{C}H$), 129.92(Ar $\underline{C}H$), 133.07 (q, $^1J_{CF}$= 163 Hz, CF_3), 140.64 (Ar $\underline{C}$)171.4, 171.6(C=O). δ_F($CDCl_3$, 188 MHz): -57.9.

H_6L^4 ($CF_3CO_2^-$)$_2$

The tris-*t*-butyl ester (0.45g, 0.6 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 cm^3), 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-): 598 (M^-). δ_H (D_2O, 200MHz): 2.98 (br m,8H, NCH_2 and NCH_2 ring), 3.26 (br m, 12H, NCH_2ring), 3.48 (br s, 4H, NCH_2CO), 3.96(br s, 2H, NCH_2CO), 7.71 (br s, 2H, Ar H), 7.85 (br s, 1H. Ar H,) 7.97(br s, 1H. Ar H,). δ_C(CD_3OD, 50.3 MHz) : 41.11($\underline{C}H_2NH$) 42.41, 47.83, 49.21, 52.11 ($\underline{C}H_2N$), 59.42, 60.13, 60.52 ($\underline{C}H_2CO$), 119.81(q, $^2J_{CF}$ 18, $\underline{C}(CF_3)$], 125.29, 128.52, 128.61, 129.91(Ar $\underline{C}H$), 133.06 (q, $^1J_{CF}$ 162, CF_3),140.64 (Ar $\underline{C}$1)173.41, 174.62(C=O). δ_F(D_2O, 188 MHz): -58.3.

Synthesis of lanthanide (III) complexes

The ligand $H_6L^4(CF_3CO_2)_2$ was dissolved in water (1 ml) and treated with excess anion exchange resin (Dowex 1X8 Cl, 200-400mesh), and filtered. An equimolar quantity of $LnCl_3(H_2O)_6$ (1:1) (Ln = Ho, Tm, Eu) was added dissolved in the minimum volume of Purite water (total volume <1.5 mL) and the pH adjusted to 5.5. The solution was heated at 90 *C for 24 h. The reaction mixture was cooled to room temperature and pH was adjusted to 10. The resulting fine white precipitate was filtered off, and the solution pH was re-adjusted to 5.5. The solvent was removed by lyophilisation and the complex was extracted from the residue using 10% MeOH/ DCM to yield a colourless or pale cream solid. For

the Eu complex, excellent agreement was observed between the found and calculated isotope pattern in negative ion electrospray mass spectra, using a solution presented in methanol.

[Eu.**L**^{4}]: m/z (MeOH, ES^{-}): 744, 746 (M^{-}): Found: 746.0984; $C_{23}H_{30}O_8N_5F_3S^{153}Eu$ requires: 746.0973; δ_F(D_2O, 188MHz) pH 5.8: -53.2, -58.3 (1:1); pH 10.2: -53.2; pH 4.2: -58.3.

[Ho.**L**^{4}]: m/z (MeOH, ES^{+}):782.1(M+Na^{+}); Found 782.1041; $C_{23}H_{31}O_8N_5F_3S^{165}HoNa$ requires: 782.1041; δ_F(D_2O, 188MHz): pH 5.8: -57.1, -96.4; pH 10 : -96.4; pH 4.0 : -57.1.

4. Selected 19-F NMR spectra.

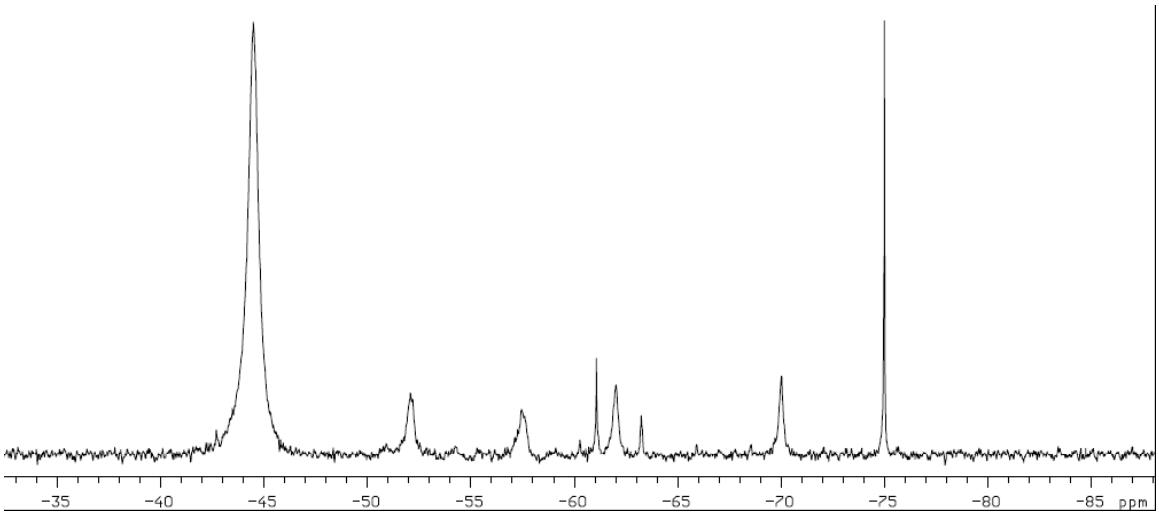


Figure 1: 19-F NMR spectrum of [Ho.L^{1}] (376MHz, D_2O, 328K, pD 8.6, 1 mM complex); the sharp resonance at –75 ppm is sodium trifluoroacetate, added as a reference, and the other resonances correspond to minor isomers of the major species.

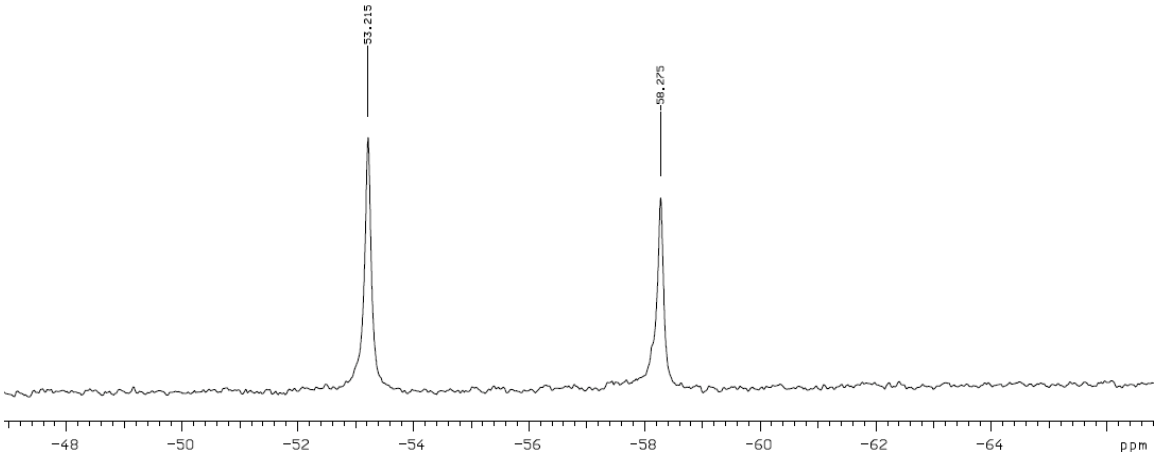


Figure 2 19-F NMR spectrum of [Eu.L^4] (pH 5.5, 188MHz, 295K, H_2O 1mM complex, D_2O capillary as lock) showing the sulfonamide –bound complex at –53.2 ppm and the protonated complex at -58.3 ppm

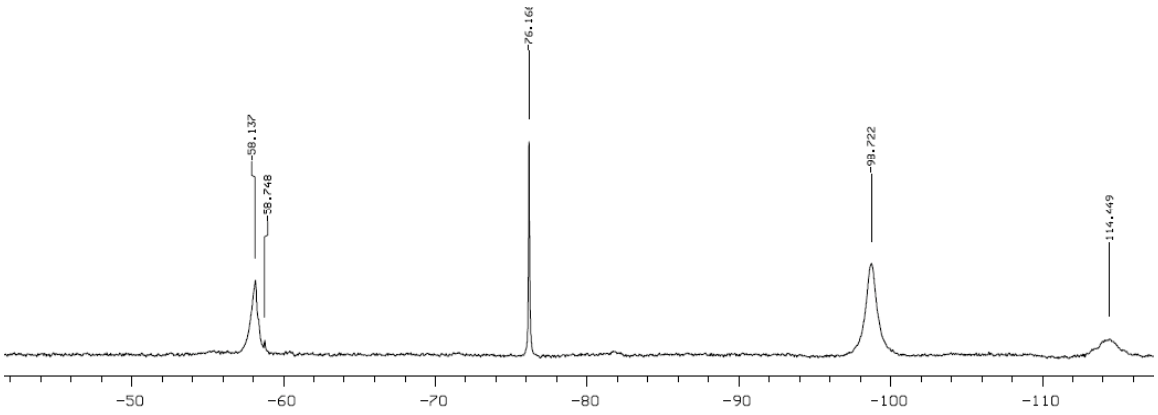
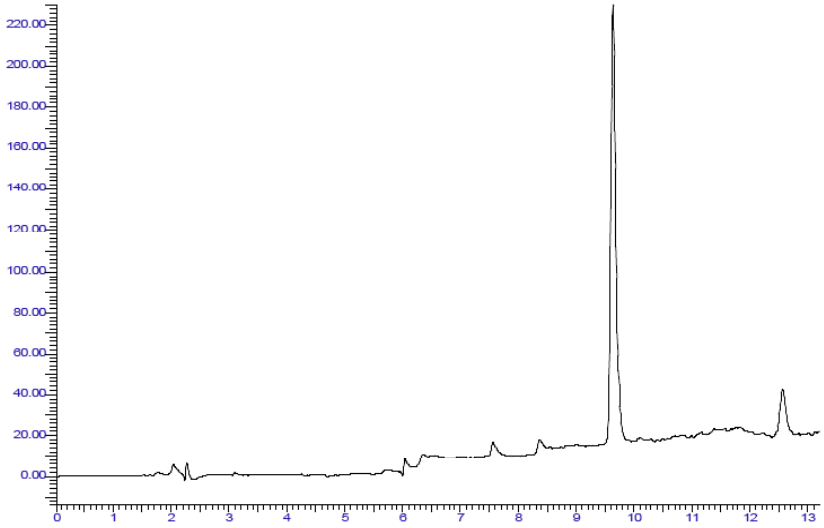
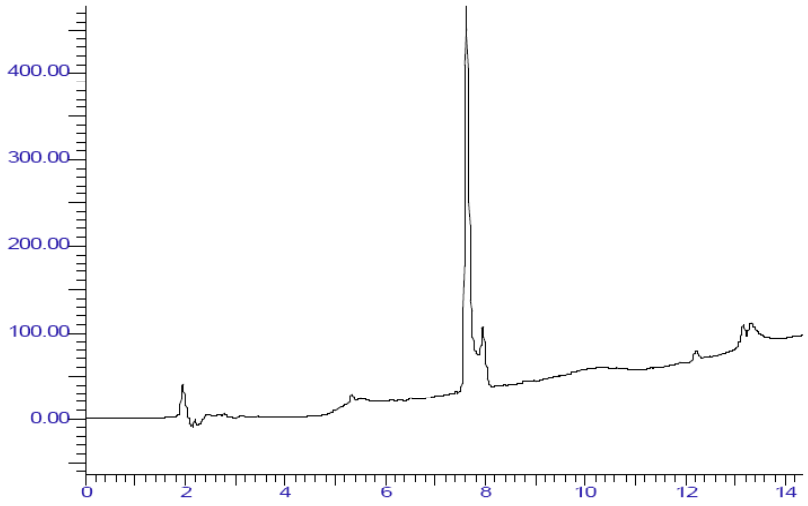


Figure 3: 19-F NMR spectrum of [Ho.L4] showing the two species at –98.7 and –114.4 for the major and minor sulphonamide-bound diastereoisomers, and the protonated complex at -58.1 ppm (resonances at –58.7 and –76.1 correspond to free ligand impurity and added sodium trifluroacetate added as a reference) : spectrum recorded in H_2O, 376MHz, 295K, 0.5mM complex, D_2O capillary lock, pH 6.0)

6. Selected HPLC chromatograms



HPLC trace of [HoL^1] (eluted with 100% H_2O/0.1 Formic acid→100% MeCN/0.1 Formic acid)



HPLC trace of [HoL^3] (eluted with 100% H_2O/0.1 Formic acid→100% MeCN/0.1 Formic acid)

The peak (UV detection at 245 nm) at 8 mins in the lower trace corresponds to the% of the minor diastereoisomeric species observed by 19-F NMR. In each trace, under the given conditions, a low % of complex dissociation may occur on the experimental timescale as a result of the formic acid used (ligand at ca. 12-13 mins).