Macrotricycles Featuring a π-Basic Tetrahedral Cavity : Preference for NH_4^+ Detected by ESI-MS

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Supporting Information

Synthesis

NMR spectra were recorded using Bruker Avance spectrometers, operating at 300 and 500 MHz. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. Melting points are uncorrected. Flash column chromatography was performed using 35-70 mesh silica gel. Elemental analyses were performed using an EA1108 CHNS Fisons Instrument apparatus. ESI-MS analyses were performed using Bruker Daltonics mass spectrometer. THF and CH_2Cl_2 were distilled over Na/benzophenone and CaH_2 respectively, and stored under dinitrogen before use. All commercially available products were reagent grade and used without further purification. All reactions were run under an inert atmosphere (N_2) unless otherwise stated.

3,5-Bis(methoxymethyloxy)benzyl thiolacetate (4)

A mixture of thiolacetic acid (1.5 mL, 20.7 mmol) and 3,5-bis(methoxymethyloxy)benzyl alcohol (**3**)[1, 2] (2.36 g, 10 mmol) in THF (20 mL) was added slowly at 0°C to a mixture of DIAD (2.72 g, 3.05 mmol) and triphenylphosphine (3.42 g, 12.9 mmol) in THF (20 mL). After 30 min at 0°C, the orange reaction mixture was stirred for 3 h at room temperature. The solvent was evaporated, leaving a crude yellow oil from which most of the used reagents could be removed by precipitation in Et_2O. The residue was purified by flash column chromatography (SiO_2, *n*-heptane/ethyl acetate 90:10 to 85:15) to afford **4** as a colorless oil (11.99 g, 77% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.35 (s, 3H, $COCH_3$), 3.46 (s, 6H, OCH_3), 4.05 (s, 2H, CH_2S), 5.13 (s, 4H, OCH_2O), 6.62 (s, 3H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 30.43, 33.62, 56.23, 94.59, 103.86, 110.29, 139.91, 158.49, 195.08; Anal.Calcd for $C_{13}H_{18}O_5S$•1/4H_2O: C, 53.68; H, 6.41. Found: C, 53.39; H, 6.18.

3,5-Bis(methoxymethyloxy)benzyl thiol (5)

A solution of **4** (11.99 g, 41.92 mmol) in THF (50 mL) was added dropwise to a suspension of LAH (3.35 g, 83.83 mmol) in THF (200 mL) at 0°C. The reaction mixture was stirred for 4 h at reflux. 5% aqueous HCl (62 mL) was carefully added to the reaction mixture at 0°C. After stirring overnight at room temperature, the white suspension was clarified by filtration, washed successively with water (twice) and brine (twice), dried over $MgSO_4$ and concentrated. **5** was obtained without further purification as a colorless oil (10.24 g, 100% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.78 (t, ^{3}J=7.7 Hz, 1H, SH), 3.48 (s, 6H, CH_3), 3.67 (d, ^{3}J=7.7 Hz, 2H, SCH_2), 5.15 (s, 4H, CH_2), 6.62 (t, ^{4}J=2.2 Hz, 1H, H_{Ar}), 6.62 (d, ^{4}J=2.2 Hz, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.17, 56.22, 94.57, 103.63, 109.48, 143.66, 158.54; Anal. Calcd for $C_{11}H_{16}O_4S$: C, 54.08; H, 6.60; S, 13.13. Found: C, 54.32; H, 6.95; S, 12.52.

1,3,5-Tris((3,5-bis(methoxymethyloxy)benzylthio)methyl)benzene (8)

A mixture of NaH (0.47 g, 60% in oil, 11.65 mmol) and **5** (2.84 g, 11.65 mmol) in THF (30 mL) at 0°C was added portionwise to a solution of **6**[3] (1.35 g, 3.76 mmol) in THF (170 mL) at 0°C . The reaction mixture was stirred for 2 h at room temperature. A saturated aqueous solution of NH_4Cl was added until pH = 6. The aqueous layer was extracted with ethyl acetate. The organic layer was successively washed with water (twice) and brine (twice), dried over $MgSO_4$ and concentrated. The crude product was purified by crystallisation in CH_2Cl_2/Et_2O 6:4 to afford pure **8** as colorless needles (3.5 g, 95%). mp: 73.2°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.46 (s, 18H, CH_3), 3.53 (s, 6H, SCH_2), 3.61 (s, 6H, SCH_2), 5.14 (s, 12H, OCH_2), 6.62 (t, ^{4}J=2.2 Hz, 3H, H_{Ph}), 6.65 (d, ^{4}J=2.2 Hz, 6H, H_{Ph}), 7.13 (s, 3H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 35.69, 35.87, 56.22, 94.56, 103.73, 110.33, 128.55, 138.79, 140.73, 158.48; Anal. Calcd for $C_{42}H_{54}O_{12}S_3$: C, 59.55; H, 6.43; S, 11.36. Found: C, 59.84; H, 6.85; S, 10.63.

1,3,5-Tris((3,5-dihydroxybenzylthio)methyl)benzene (10)

p-Toluenesulfonic acid (14.84 g, 73.76 mmol) was added to a solution of **8** (2.6 g, 3.07 mmol) in CH_2Cl_2/methanol (1:1, 100 mL). The reaction mixture was stirred overnight at room temperature. Subsequently, solid $NaHCO_3$ and water were added until pH = 6. The aqueous layer was extracted with ethyl acetate (twice). The organic layer was washed with water (twice) and brine (twice), dried over $MgSO_4$ and concentrated to give **10** as a vitrous solid (1.64 g, 97% yield) which did not require further purification. ^{1}H NMR (d_6-acetone, 300 MHz): δ 3.49 (s, 6H, SCH_2), 3.63 (s, 6H, SCH_2), 6.21 (t, ^{4}J=2.1 Hz, 3H, H_{Ph}), 6.31 (d, ^{4}J=2.1 Hz, 6H, H_{Ph}), 8.15 (s, 3H, H_{Ar}); ^{13}C NMR (d_6-acetone, 75 MHz): δ 36.17, 36.49, 102.10, 108.37, 129.03, 139.86, 141.52, 159.40; Anal.Calcd for $C_{30}H_{30}O_6S_3$•1.5$C_4H_8O_2$: C, 60.48; H, 5.92; S, 13.46. Found: C, 60.61; H, 5.93; S, 13.59.

Cage 1

A mixture of **10** (0.20 g, 0.354 mmol) and dibromomethane (0.21 g, 1.17 mmol) in DMF (50 mL) was slowly added (8 h) to a suspension of Cs_2CO_3 (0.76 g, 2.34 mmol) in DMF (350 mL) at 60°C. After being stirred overnight at 60°C, the reaction mixture was concentrated by removing the solvent under reduced pressure. The residue was extracted into CH_2Cl_2. The organic layer was washed with water (three times) and brine (twice), dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (*i.* SiO_2, CH_2Cl_2/heptane 8:2 to 10:0, then CH_2Cl_2/ethyl acetate 78:22; *ii.* SiO_2, CH_2Cl_2) to afford **1** as a colorless powder (20 mg, 18% yield). mp: 277 °C (dec.); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.24 (s, 6H, SCH_2), 3.69 (s, 6H, SCH_2), 5.60 (d, ^{2}J=7.0 Hz, 3H, OCH), 5.72 (d, ^{2}J=6.5 Hz, 3H, OCH), 6.47 (s, 3H, H_{Ar}), 6.50 (d, ^{4}J=2.0 Hz, 6H, H_{Ph}), 6.80 (t, ^{4}J=2.0 Hz, 3H, H_{Ph}); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 36.68, 38.11, 91.12, 105.62, 111.40, 126.13, 137.91, 141.01, 156.69; Anal.Calcd for $C_{33}H_{30}O_6S_3$•H_2O: C, 62.24; H, 5.07. Found: C, 62.57; H, 5.28.

1,3,5-Triethyl-2,4,6-tris((3,5-bis(methoxymethyloxy)benzylthio)methyl)benzene (9)

Synthesized as described for **8**, from **7**[4] (1.75 g, 3.96 mmol) and **5** (3 g, 12.29 mmol), with NaH (0.49, 60% in mineral oil, 12.29 mmol). Obtained in 75% yield (2.78 g) as a colorless solid after crystallization from Et_2O. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.98 (t, ^{3}J=7.2 Hz, 9H, CH_3), 2.58 (q, ^{3}J=7.8 Hz, 6H, CH_2), 3.47 (s, 18H, CH_3), 3.52 (s, 6H, SCH_2), 3.64 (s, 6H, SCH_2), 5.16 (s, 12H, OCH_2), 6.63 (t, ^{4}J=2.1 Hz, 3H, H_{Ph}), 6.71 (d, ^{4}J=2.4 Hz, 6H, H_{Ph}); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.14, 23.16, 30.96, 38.27, 56.12, 95.12, 104.07, 111.03, 132.10, 142.10, 143.41, 159.33; Anal.Calcd for $C_{48}H_{66}O_{12}S_3$: C, 61.91; H, 7.14; S, 10.33. Found: C, 62.54; H, 7.46; S, 10.17.

1,3,5-Triethyl-2,4,6-tris((3,5-dihydroxybenzylthio)methyl)benzene (11)

Synthesized as described for **10**, from **9** (1.28 g, 1.37 mmol), with *p*-toluenesulfonic acid (7.38 g, 38.4 mmol). Obtained after trituration with diethyl ether in quantitative yield (0.90 g) as a vitrous solid. ^{1}H NMR (d_6-acetone, 300 MHz): δ 1.00 (t, ^{3}J=7.5 Hz, 9H, CH_3), 2.67 (q, ^{3}J=7.5 Hz, 6H, CH_2), 3.62 (s, 6H, SCH_2), 3.67 (s, 6H, SCH_2), 6.27 (t, ^{4}J=2.4 Hz, 3H, H_{Ph}), 6.41 (d, ^{4}J=2.4 Hz, 6H, H_{Ph}), 8.24 (brs, 6H, OH); ^{13}C NMR (d_6-acetone, 75 MHz): δ 16.48, 23.16, 31.11, 38.35, 102.05, 108.33, 132.18, 141.76, 143.36, 159.44.

Cage 2

Synthesized as described for **1**, from **11** (0.21 g, 0.32 mmol) with dibromomethane (0.12 g, 0.66 mmol) and Cs_2CO_3 (0.43 g, 1.32 mmol). Purification by flash column chromatography of the crude product (SiO_2, CH_2Cl_2) afforded **2** as a colorless powder (3 mg, 1.4% yield). mp: 219 °C (dec.); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.18 (t, ^{3}J=7.51 Hz, 9H, CH_3), 2.92 (q, ^{3}J=7.61 Hz, 6H, CH_2), 3.25 (s, 6H, SCH_2), 3.86 (s, 6H, SCH_2), 5.50 (d, ^{2}J=7.2 Hz, 3H, OCH), 5.65 (d, ^{2}J=7.2 Hz, 3H, OCH), 6.33 (t, ^{4}J=2.2 Hz, 3H, H), 6.40 (d, ^{4}J=2.2 Hz, 6H,H_{Ph}); ^{13}C NMR (d_6-acetone, 75 MHz): δ 16.12, 23.64, 30.07, 34.14, 92.63, 107.10, 112.95, 131.47, 140.14, 143.18, 157.54.

ESI-MS Binding studies

The samples were prepared according to the following procedure: 10 μl of solutions of cations of interest (10^{-2}M in MeOH) were added to a 10 μl solution of the cage (10^{-2}M in CH_2Cl_2) and the mixture was diluted to 10^{-4}M with MeOH (1 ml solutions). ESI mass spectrometry analysis was performed on an ESI-TOF mass spectrometer (micro TOF, Bruker, Germany) using the following parameters: running solvent, MeOH (4ml/min); inlet temperature, 100°C; mass range (m/z), 0 to 3000; capillary exit voltage, 70V.

References

1. Boehlow, T. R.; Harburn, J. J.; Spilling, C. D. *J. Org. Chem.* **2001,** 66, 3111-3118.
2. Hollinshead, S. P.; Nichols, J. B.; Wilson, J. W. *J. Org. Chem.* **1994,** 59, 6703-9.
3. Díez-Barra, E.; García-Martínez, J. C.; Merino, S.; del Rey, R.; Rodríguez-López, J.; Sánchez-Verdú, P.; Tejeda, J. *J. Org. Chem.* **2001,** 66, 5664-5670.
4. Walsdorff, C.; Saak, W.; Pohl, S. *J. Chem. Res.* **1996**, 1601-1618.

NMR Spectra of the new compounds

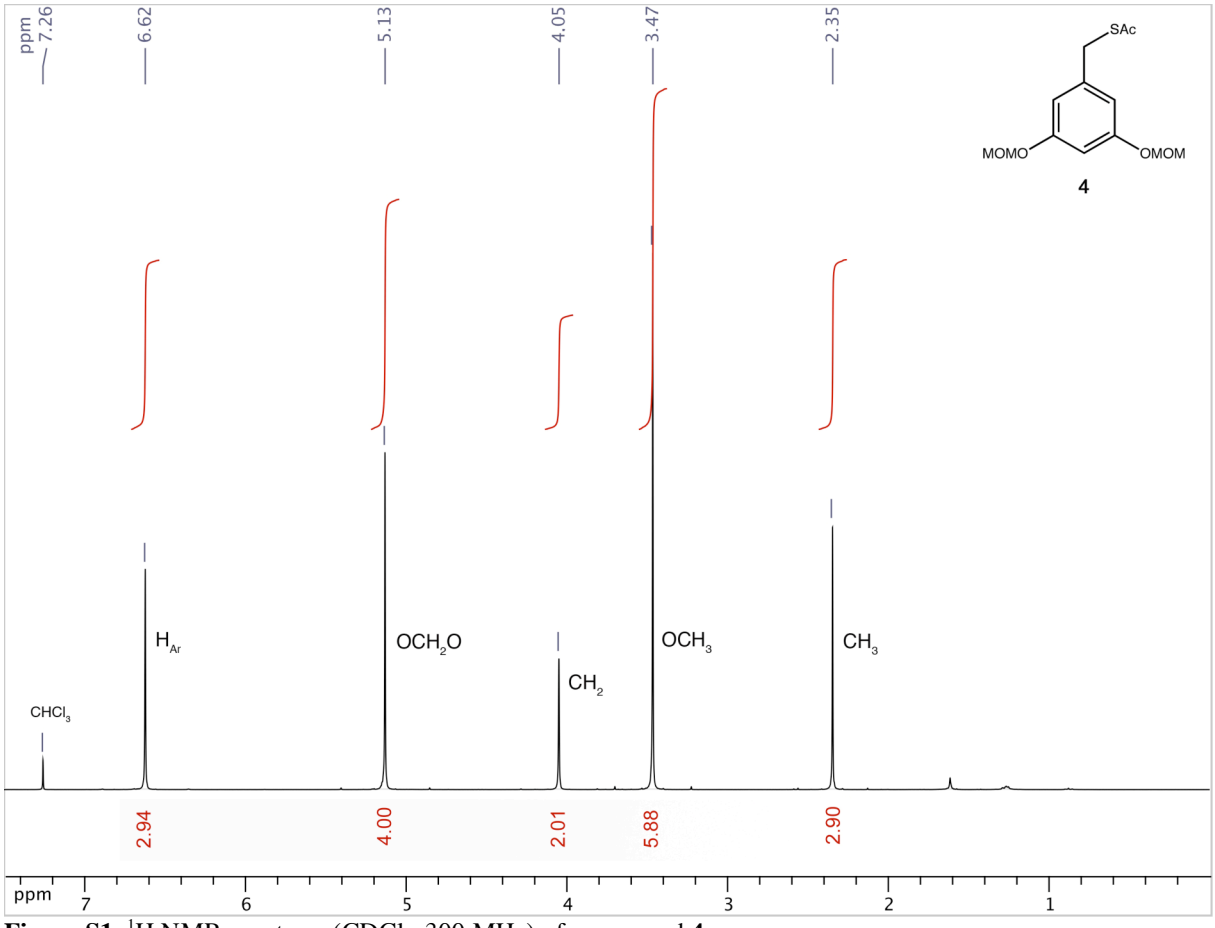

Figure S1. ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of compound **4**

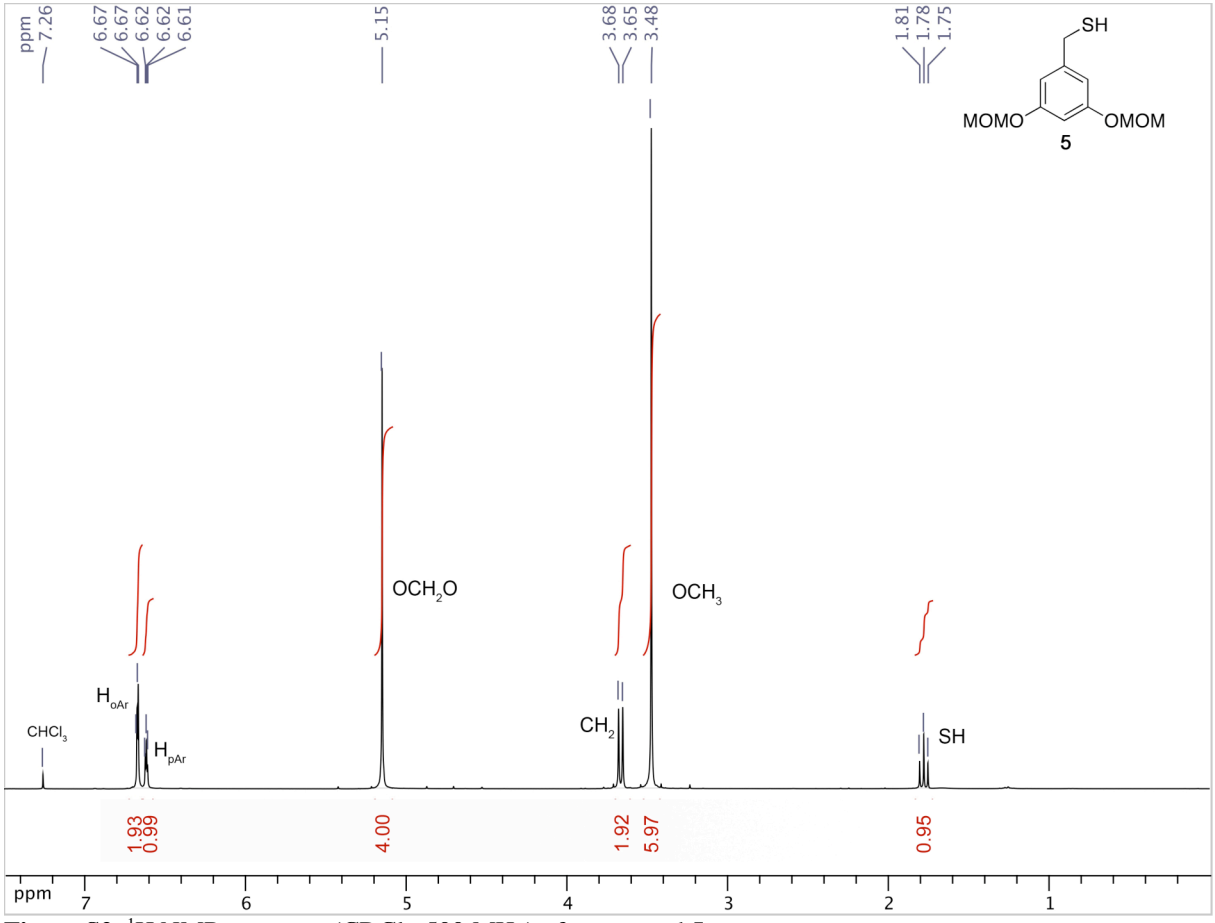

Figure S2. ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound **5**

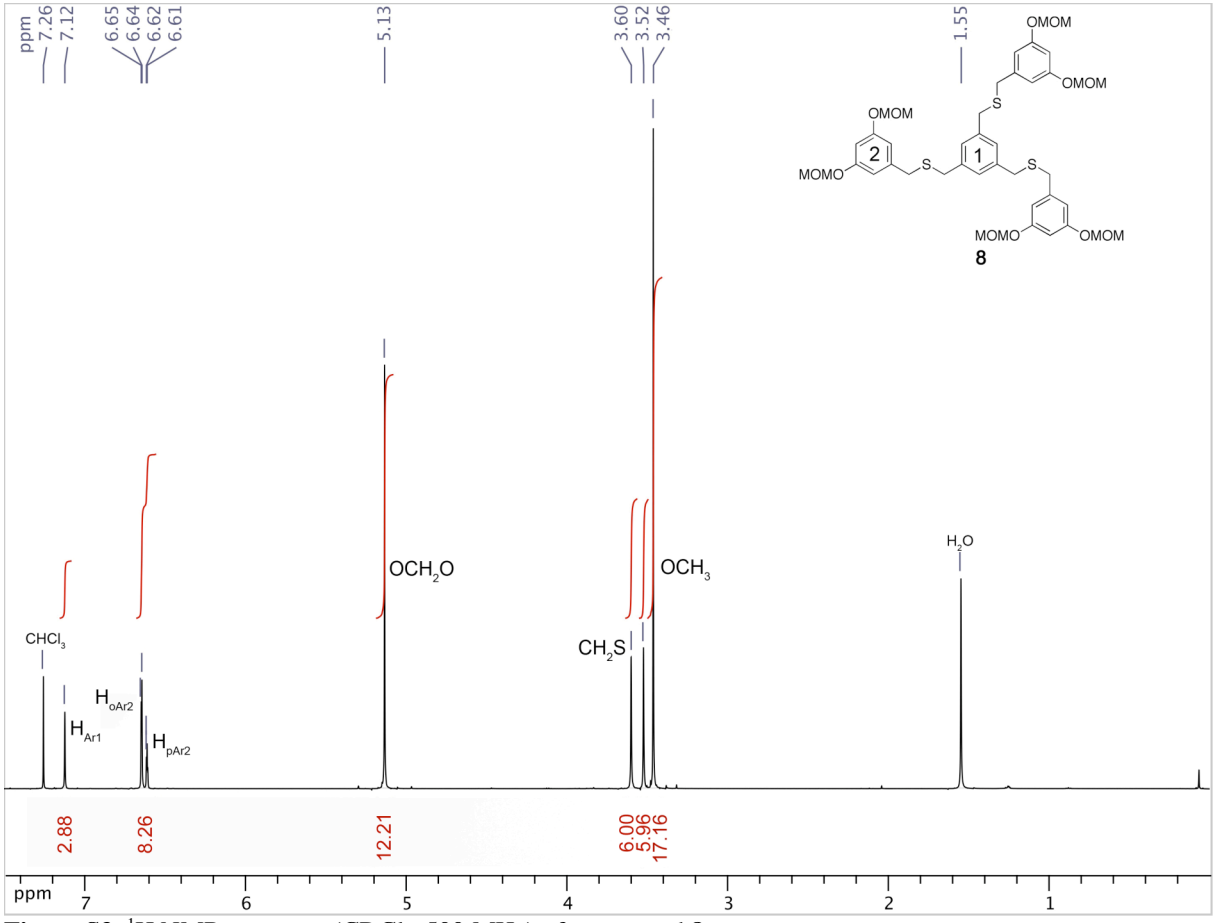

Figure S3. ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound **8**

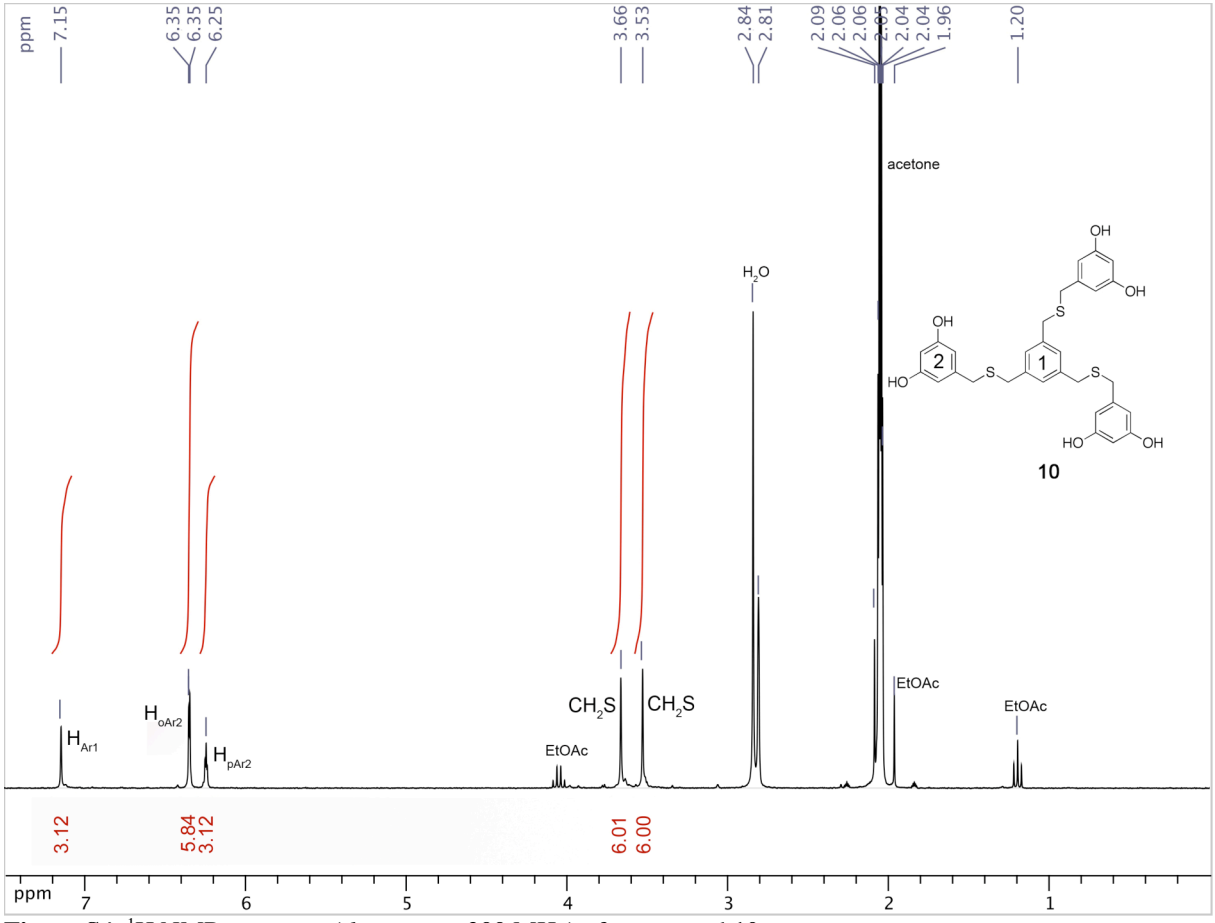

Figure S4. ^{1}H NMR spectrum (d_6-acetone, 300 MHz) of compound **10**

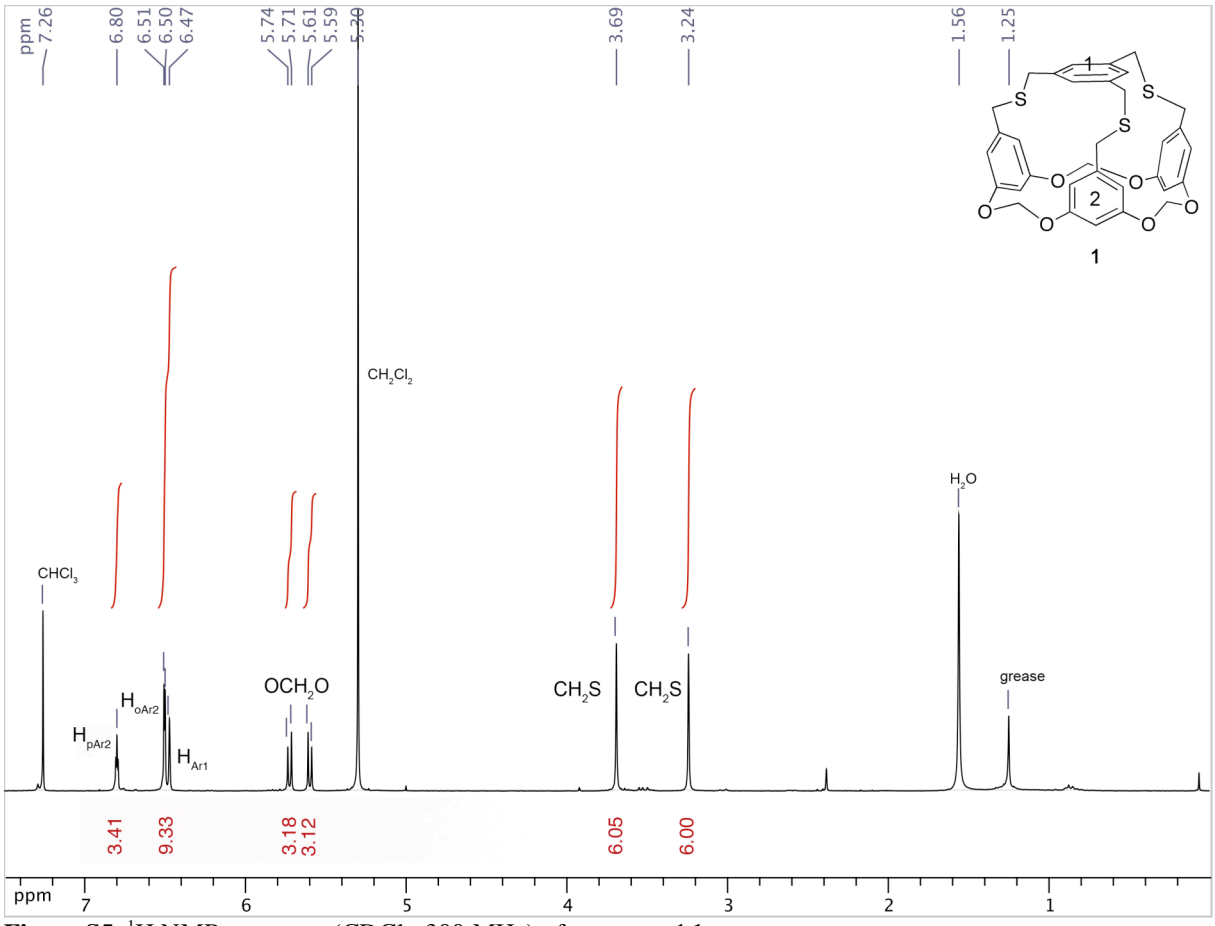

Figure S5. ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of compound **1**

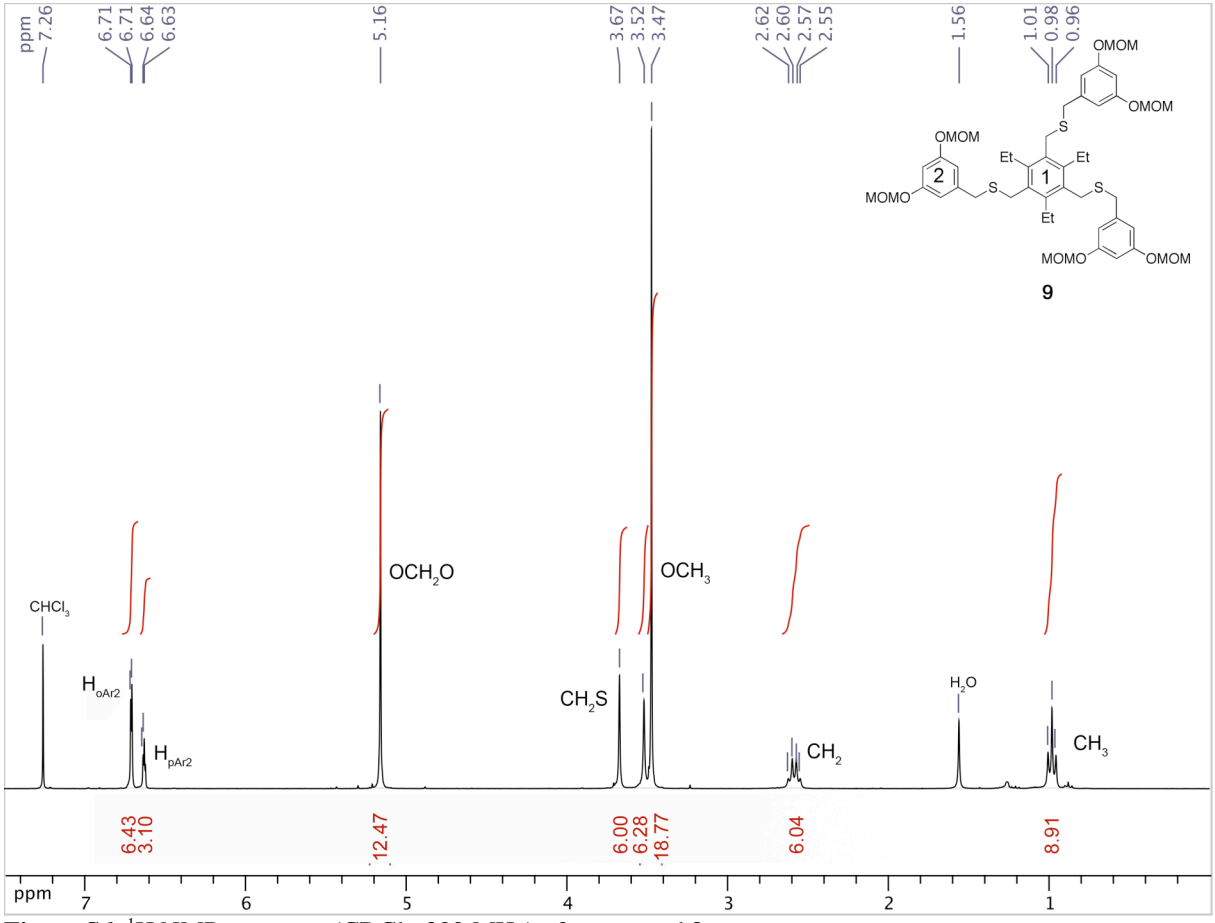

Figure S6. ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of compound **9**

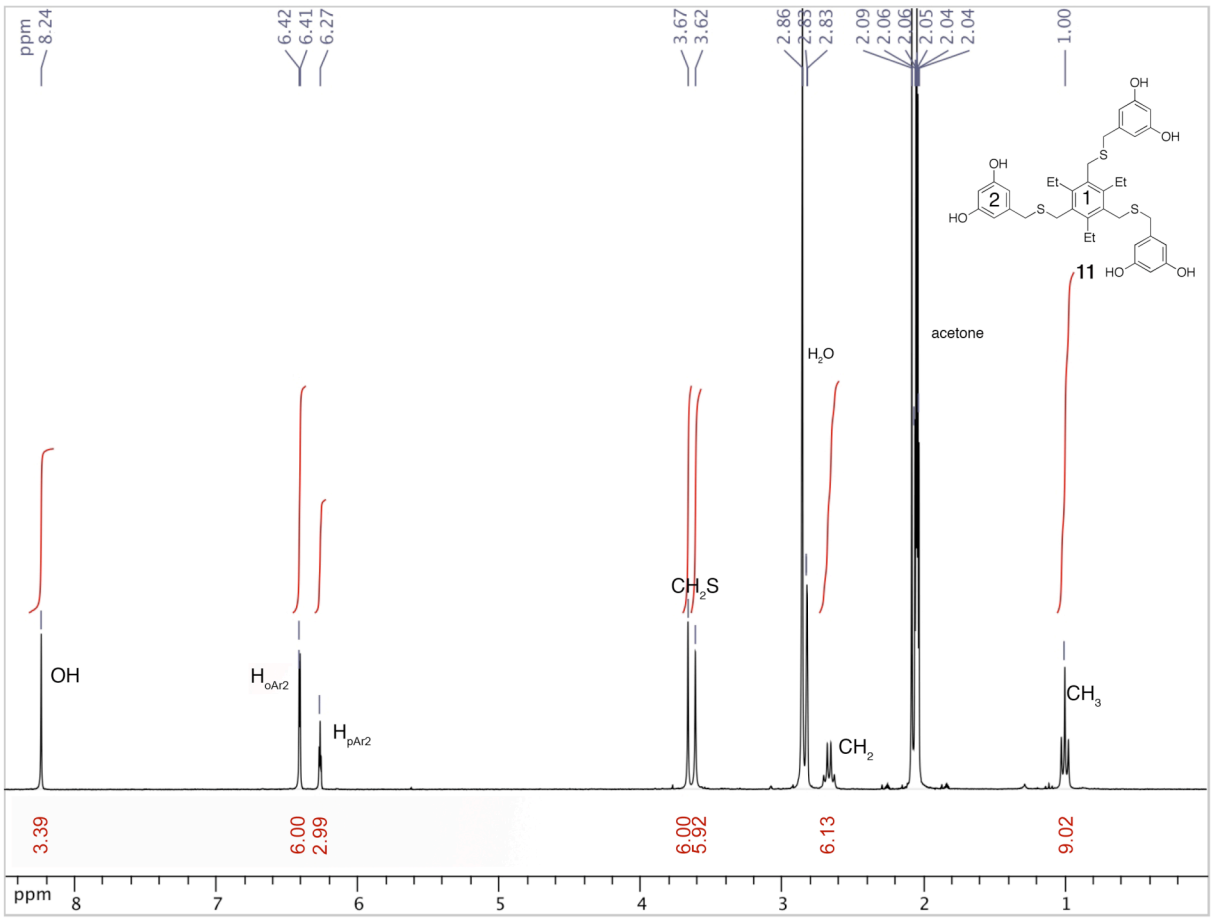

Figure S7. ^{1}H NMR spectrum (d_6-acetone, 300 MHz) of compound **11**

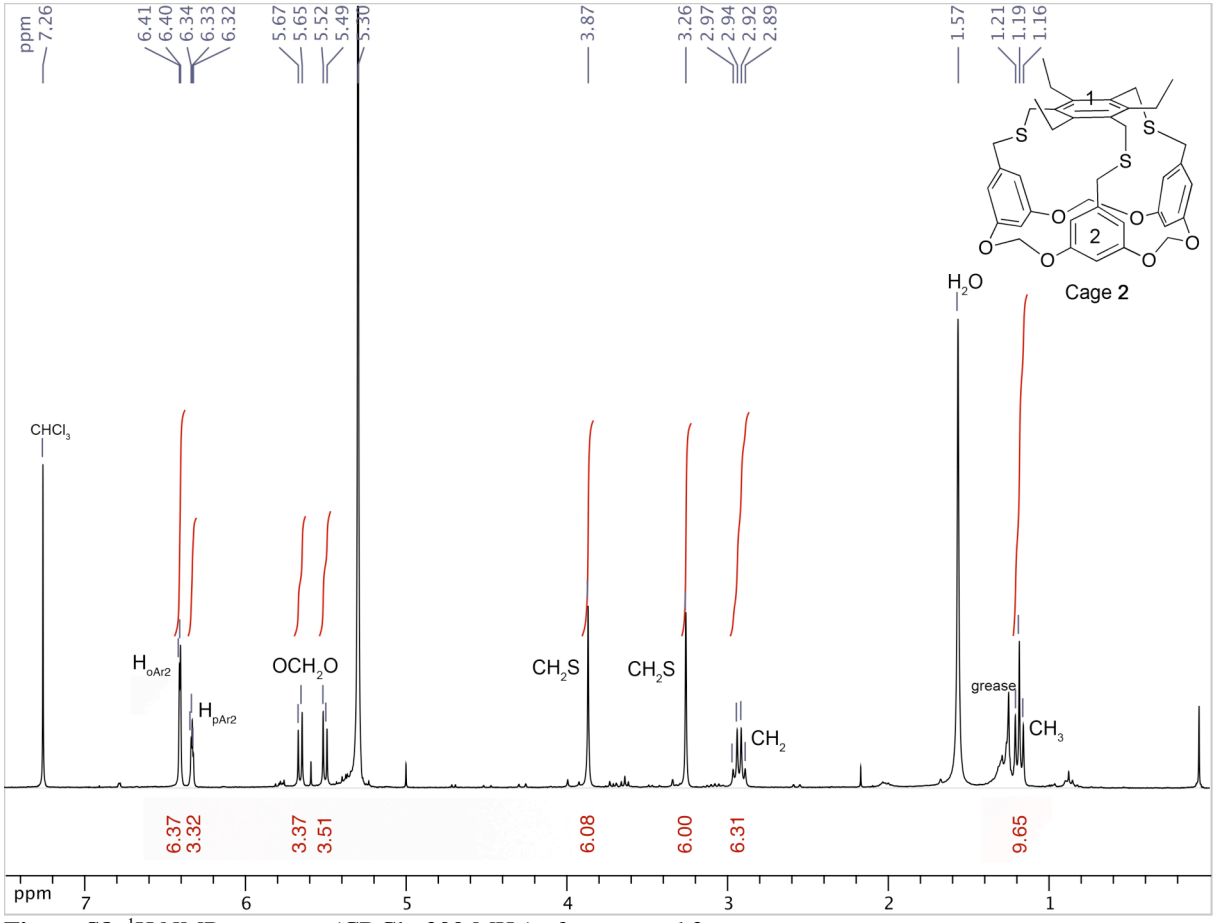

Figure S8. ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of compound **2**

ESI-MS Experiments

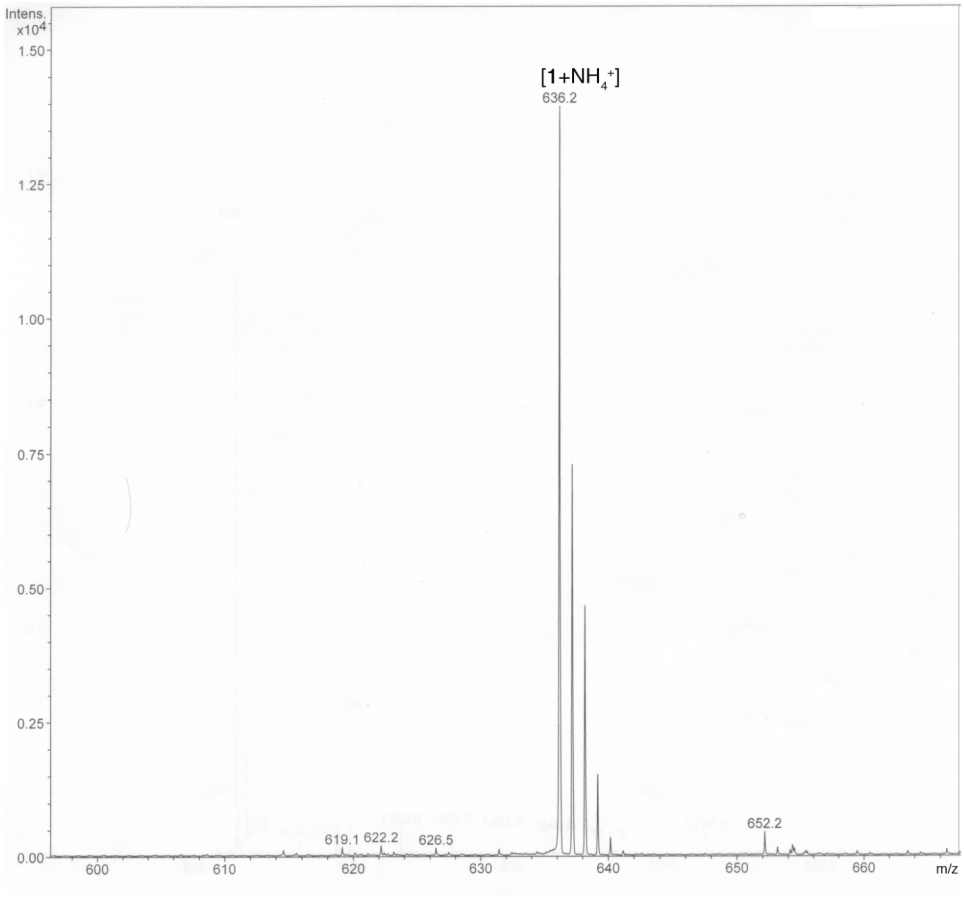

Figure S9. ESI mass spectrum of **1**+NH_4PF_6 (10^{-4}M) in MeOH

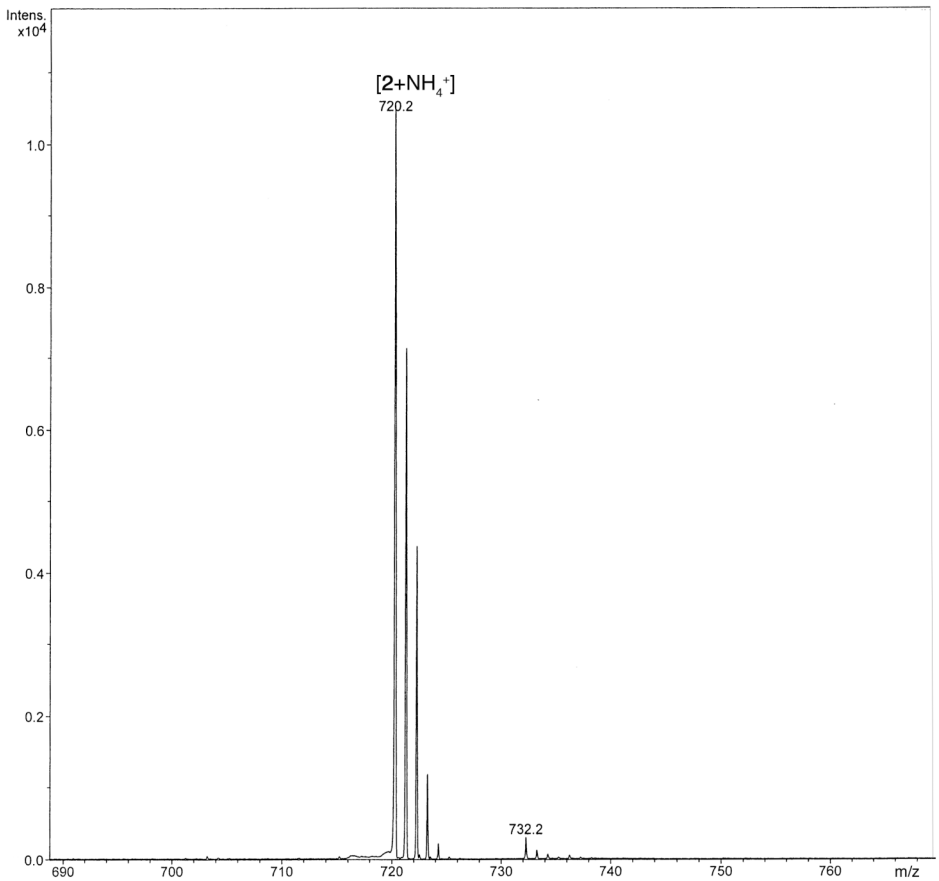

Figure S10. ESI mass spectrum of **2**+NH_4PF_6 (10^{-4}M) in MeOH

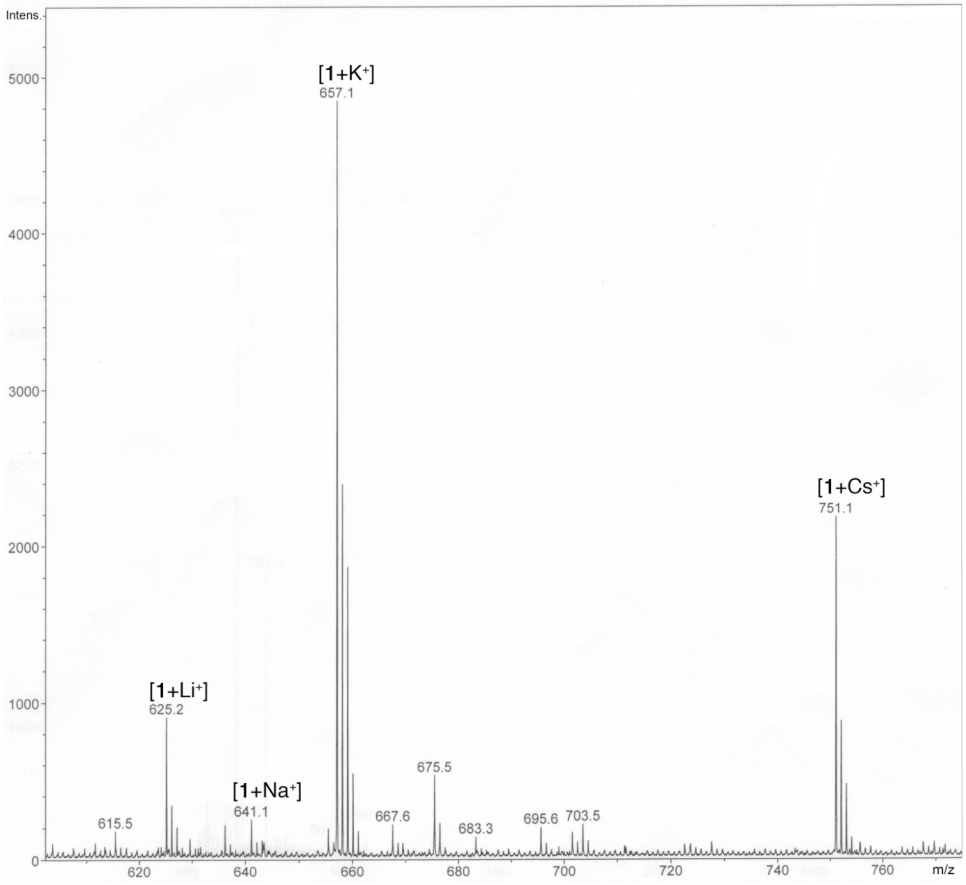

Figure S11. ESI mass spectrum of **1**+LiCl+NaCl+KCl+CsCl (10^{-4}M) in MeOH

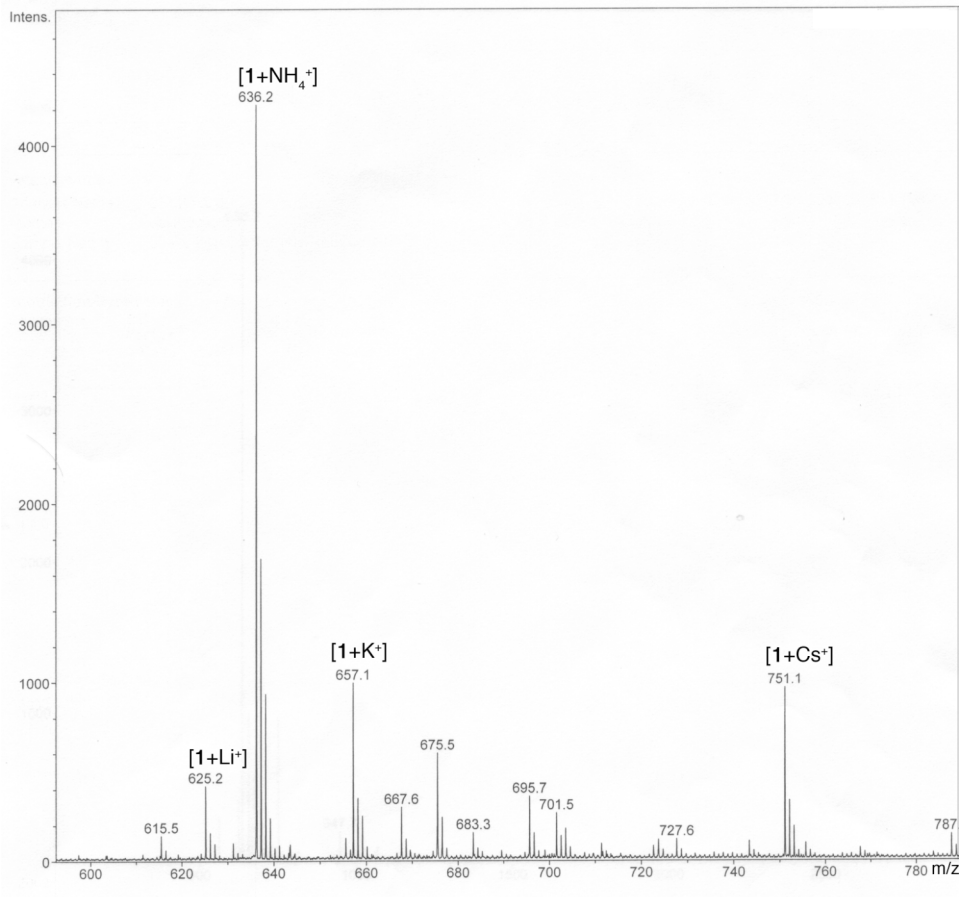

Figure S12. ESI mass spectrum of **1+**LiCl+NaCl+KCl+CsCl+NH_4PF_6 (10^{-4}M) in MeOH

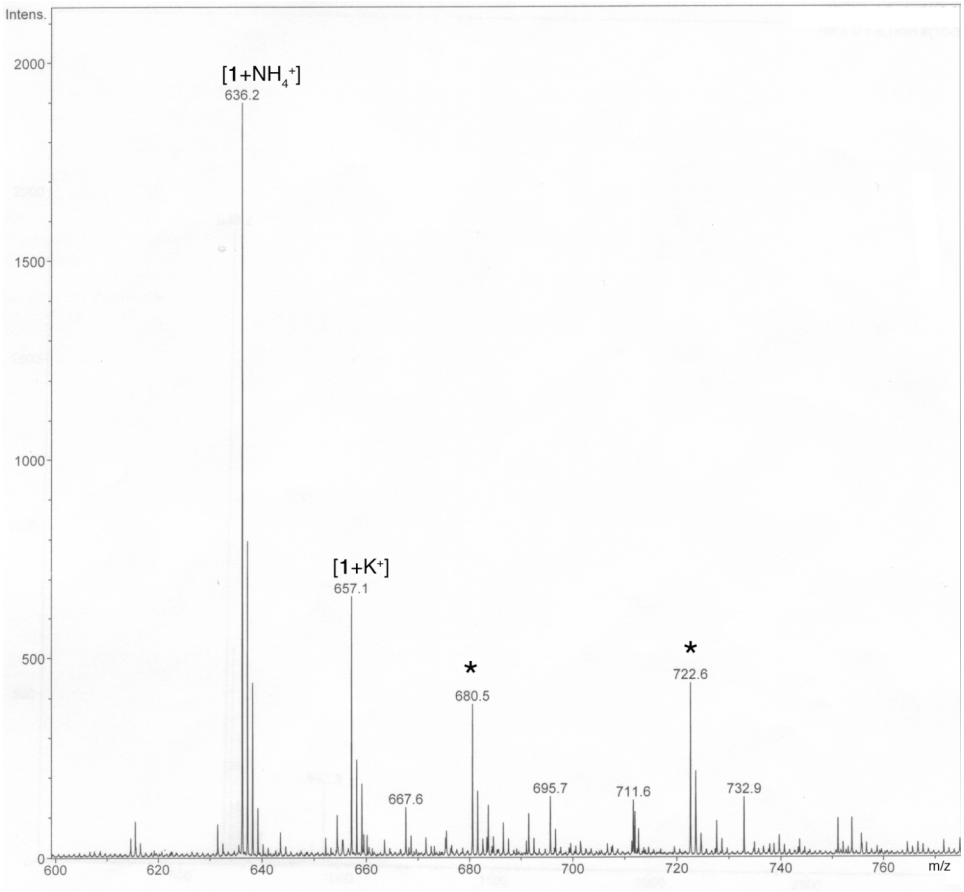

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Figure S13. ESI mass spectrum of **1**+KPF_6+NH_4PF_6 (10^{-4}M) in MeOH

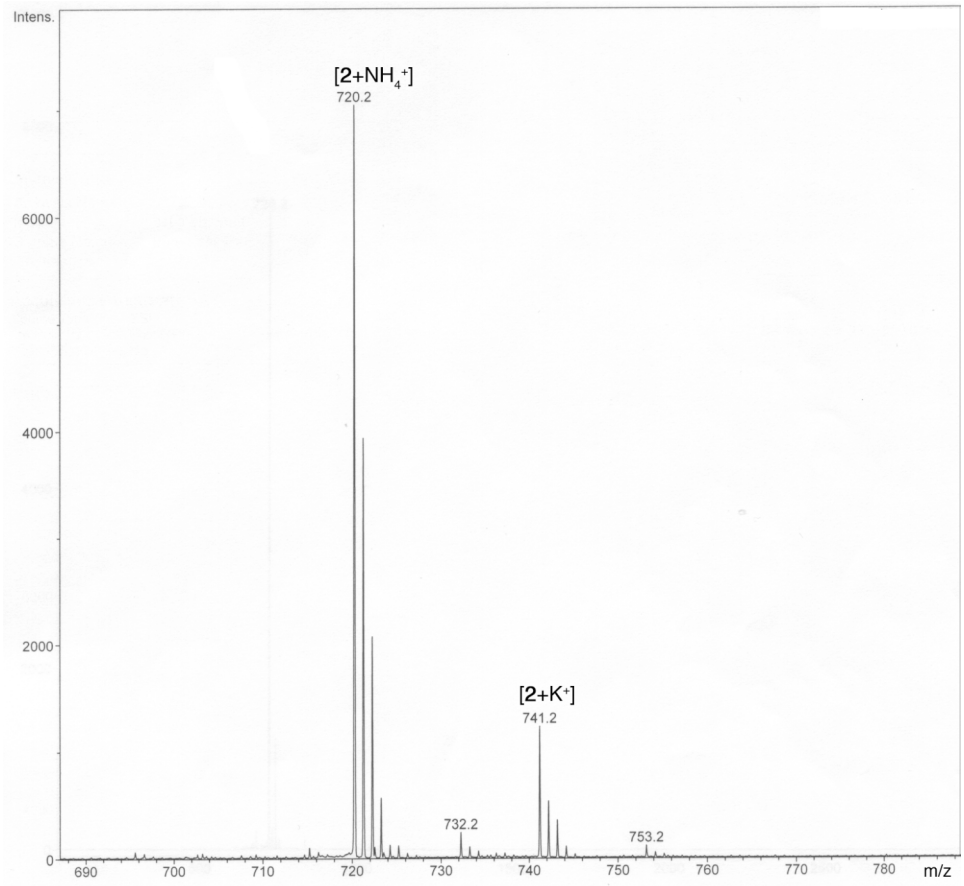

Figure S14. ESI mass spectrum of **2**+KPF_6+NH_4PF_6 (10^{-4}M) in MeOH

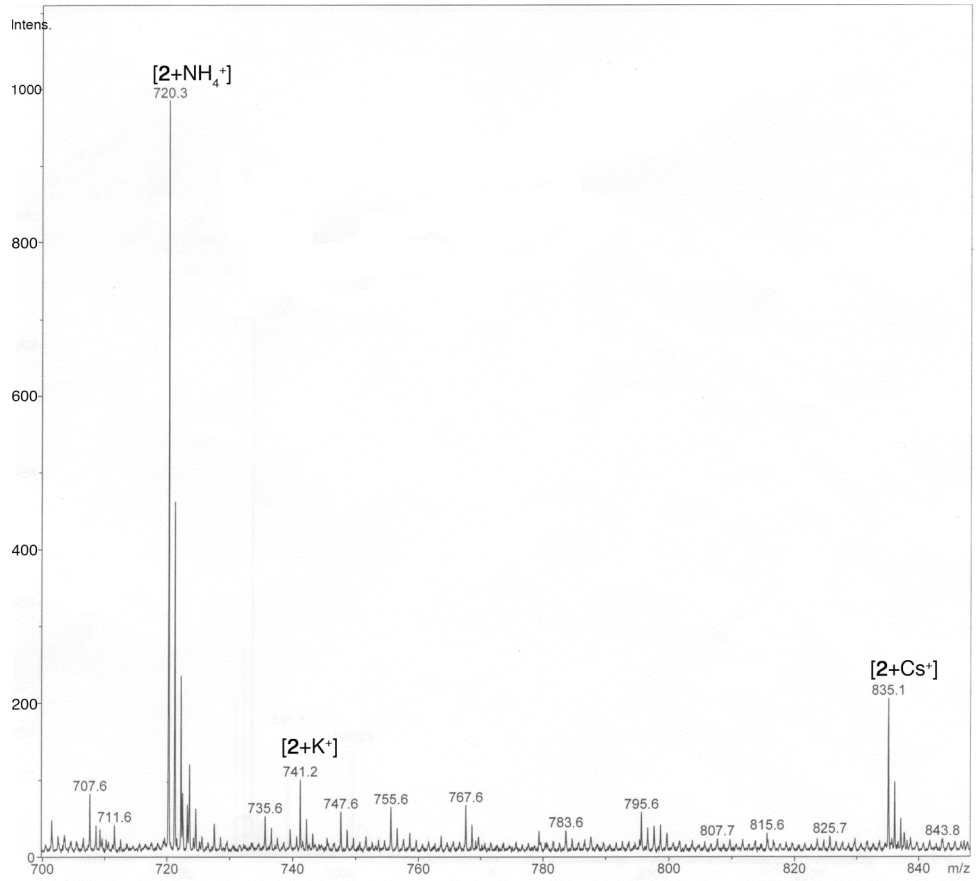

Figure S15. ESI mass spectrum of **2**+LiCl+NaCl+KCl+CsCl+NH_4PF_6 (10^{-4}M) in MeOH

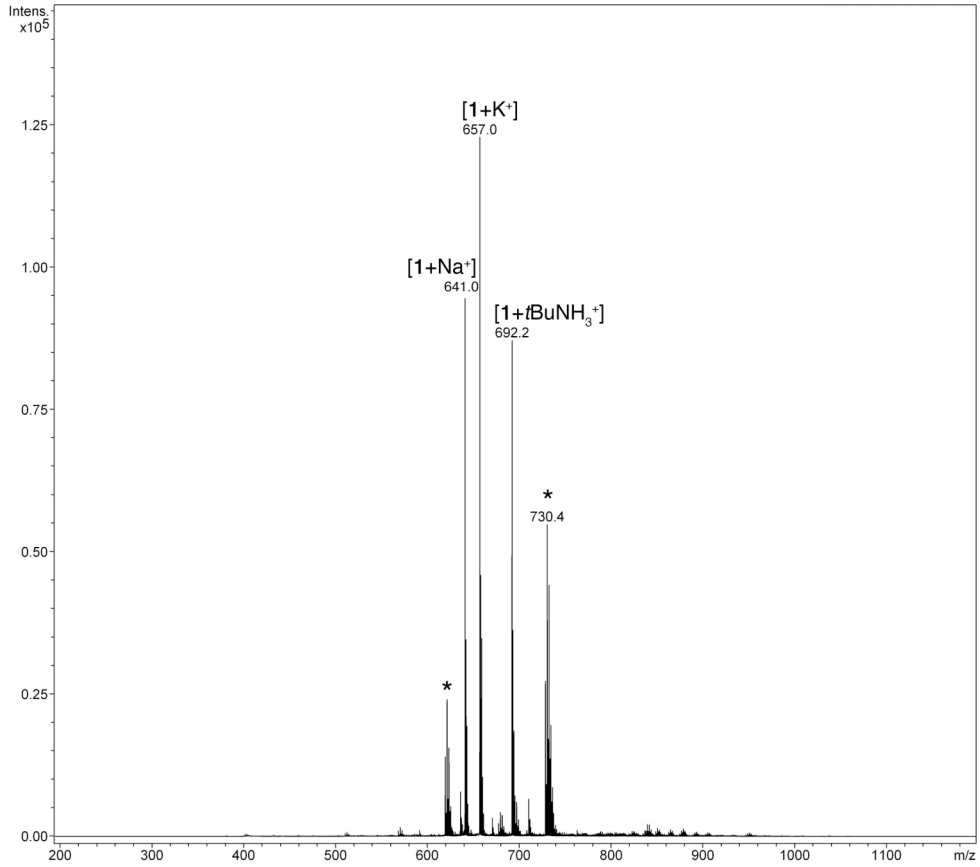

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Figure S16. ESI mass spectrum of **1**+ *t*$BuNH_3Cl$(10^{-4}M) in MeOH

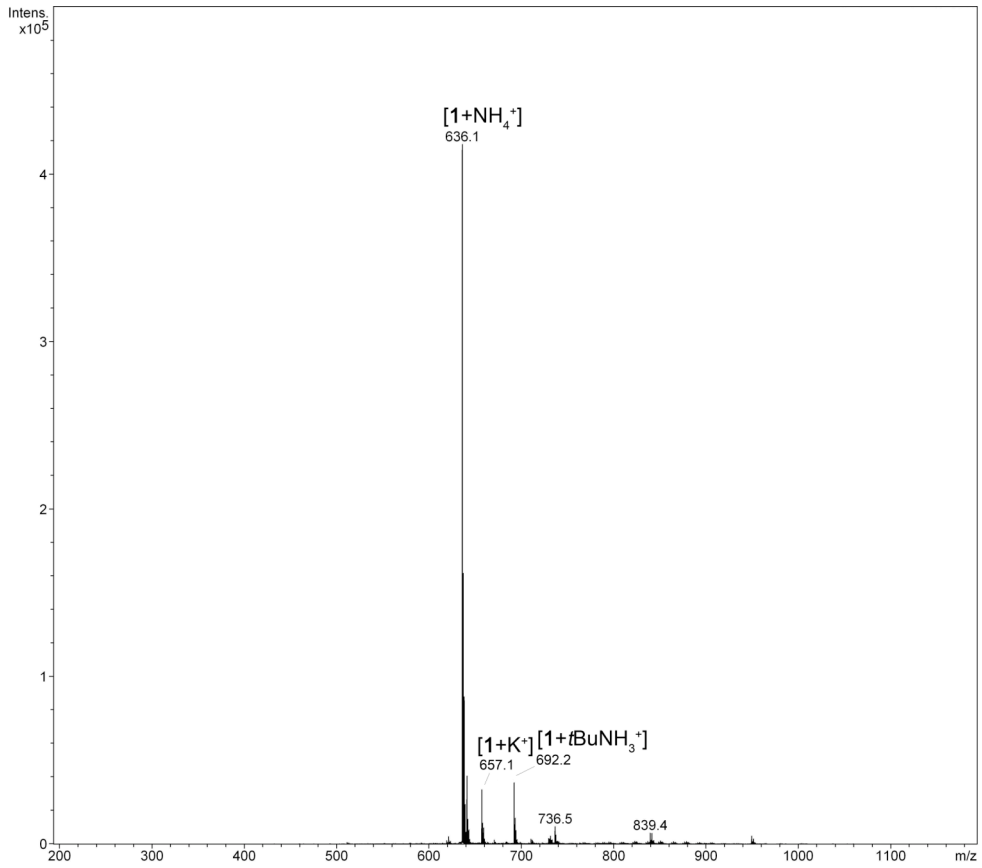

Figure S17. ESI mass spectrum of **1**+ *t*BuNH$_3$Cl+ NH$_4$PF$_6$ (10^{-4}M) in MeOH

NMR Experiments

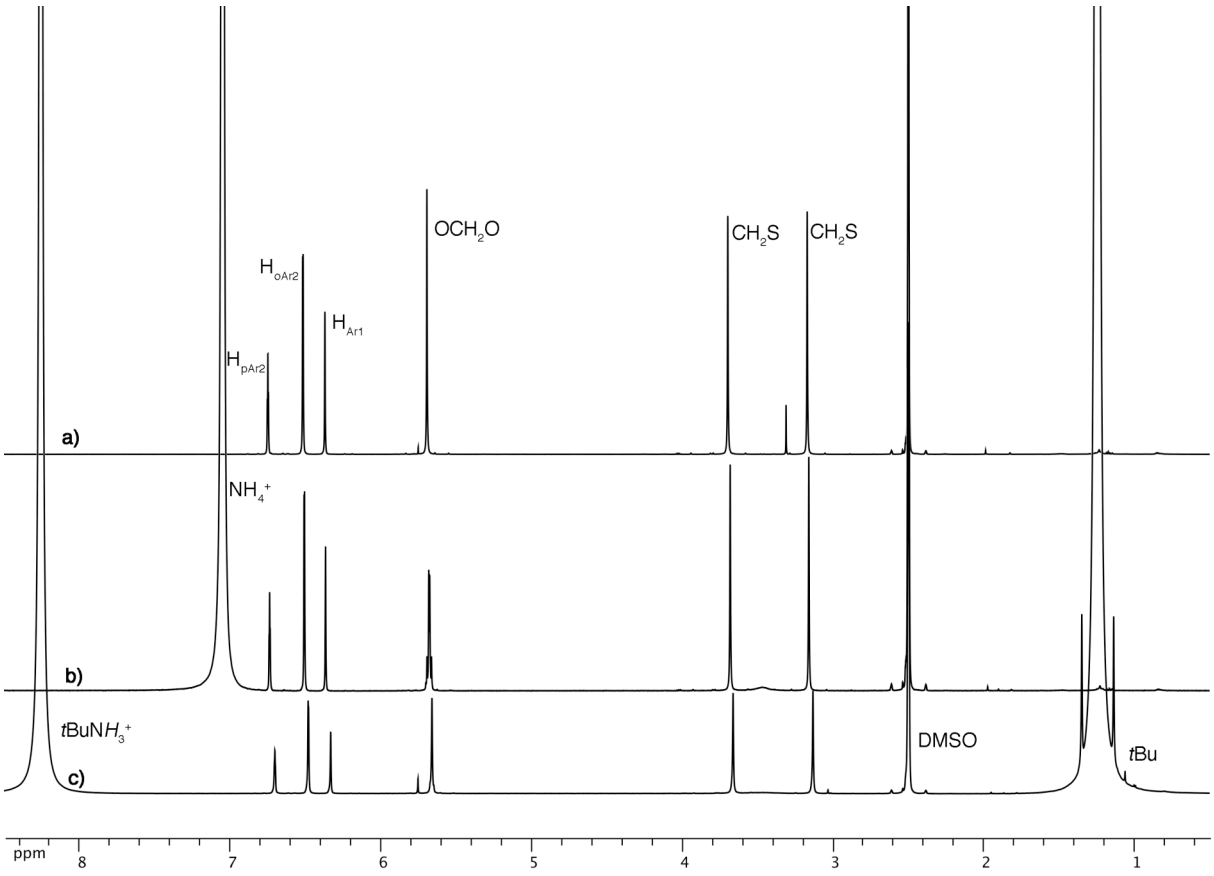

Figure S18.[1]H NMR spectra (d_6-dmso, 600 MHz) of a) **1**, b) **1**+ NH$_4$PF$_6$ (1:118), c) **1**+ *t*BuNH$_3$Cl (1:170)

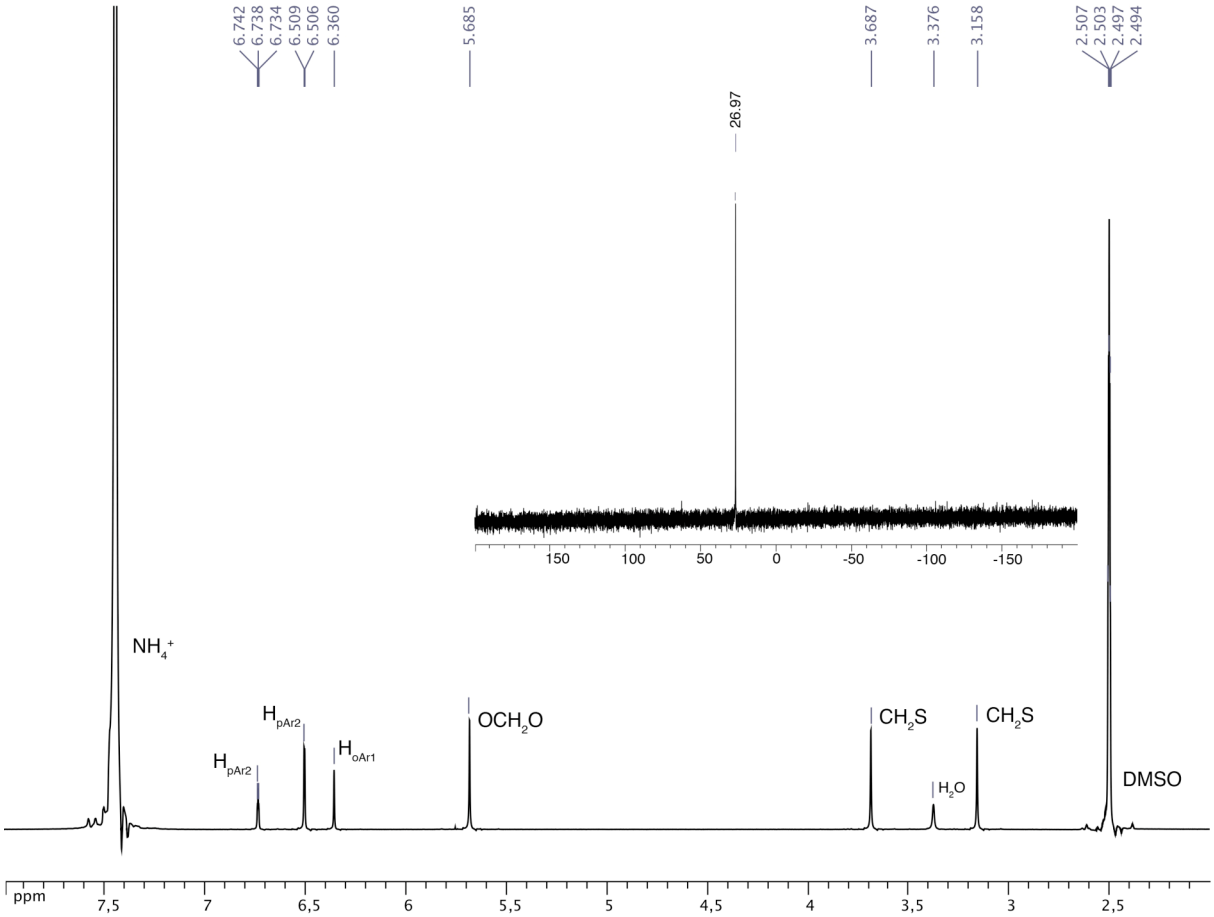

Figure S19.[1]H NMR spectrum (d_6-dmso, 600 MHz) of **1**+ $^{15}NH_4Cl$ (100 equiv). In the inset is shown the ^{15}N NMR spectrum (d_6-dmso, 61 MHz) of **1**+ $^{15}NH_4Cl$ (100 equiv)