Improved complexation between dibenzo-24-crown-8 derivatives and dibenzylammonium salts by ion-pair recognition

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Electronic Supplementary Information (27 pages)

1. Materials and methods

All reagents were purchased from commercial suppliers and used as received. Dibenzo-24-crown-8 (**1**) was purchased from Acros. Compound **4**[S1] and secondary ammonium salts **2**[S2, S3] were synthesized according to literature procedures. The intermediates **5** and **6** were synthesized according to a similar method reported by Gibson et al.[S4] Solvents were either employed as purchased or dried according to procedures described in the literature. NMR spectra were recorded on a Bruker Advance DMX 500 spectrophotometer or a Bruker Advance DMX 400 spectrophotometer. Low-resolution electrospray ionization mass spectra were recorded on a Bruker Esruire 3000 Plus spectrometer. High-resolution mass spectrometry experiments were performed on a Bruker Daltonics Apex III spectrometer. C, H, and N were analyzed on a Carlo Erba 1110 elemental analyzer. The K_a values of **1**·**3** and **2**·**3** complexes, slow-exchange complexation systems, were calculated from integrations of complexed and uncomplexed peaks in 2.00 mM host and guest solutions.

*2. Synthesis of 5-(phthalimidomethyl)-1,2-phenylene-o-phenylene-24-crown-8 (**5**)*

A solution of **4**[S1] (1.12 g, 2.25 mmol), potassium phthalimide (2.00 g, 10.8 mmol) and DMF (50.0 ml) was held at 90 °C for 24 hr and then cooled to room temperature. The solvent was evaporated under reduced pressure. The residue was dissolved in 200 mL of CH_2Cl_2 and washed with 100 mL of water twice. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo to afford the crude product which was isolated by flash column chromatography using the EtOAc as the eluent to afford 900 mg (66%) of **5**. ^{1}H NMR (400 MHz, $CDCl_3$, 22 °C): δ 7.83 (2 H, m), 7.69 (2 H, m), 6.98 (2 H, m), 6.84–6.89 (4 H, m), 6.78 (1 H, m), 4.74 (2 H, s), 4.09–4.14 (8 H, m), 3.87–3.89 (8 H, m), 3.80 (8 H, s). ^{13}C NMR (100 MHz, $CDCl_3$, 22 °C): δ 168.0, 148.9, 148.9, 148.5, 133.9, 132.1, 129.6, 123.3, 121.8, 121.4, 114.6, 114.1, 114.1, 113.8, 69.9, 69.8, 69.5, 69.4, 41.3. Low-resolution ESI-MS: *m*/*z* 625.6 (84%) $[\mathbf{5} + NH_4]^+$, 630.6 (100%) $[\mathbf{5} + Na]^+$ and 646.6 (17%) $[\mathbf{5} + K]^+$. Anal. Calcd. for $C_{33}H_{37}NO_{10}$: C, 65.23; H, 6.14; N, 2.31. Found: C, 65.24; H, 6.12; N, 2.30.

*3. Synthesis of 5-aminomethyl-1,2-phenylene-o-phenylene-24-crown-8 (**6**)*

A solution of **5** (607 mg, 1.00 mmol)**,** hydrazine monohydrate (0.500 mL, 8.50 mmol) and methanol (10.0 mL) was refluxed for 17 hours, cooled, concentrated by rotary evaporation and a white solid was obtained. The mixture was filtered and the solid was washed with 2.00 mL of methanol twice. The combined filtrate was neutralized by 2.00 M NaOH and extracted with $CHCl_3$. The combined extracts

were dried over anhydrous Na_2SO_4 and evaporated in vacuo to afford **6** (400 mg, 84%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 22 °C) δ 6.85–6.89 (5 H, m),6.80 (2 H, s), 4.12–4.16 (8 H, m), 3.90–3.93 (8 H, m), 3.80–3.83 (10 H, m). ^{13}C NMR (100 MHz, $CDCl_3$, 22 °C) δ 148.6, 147.4, 121.2, 119.6, 113.8, 113.0, 70.9, 69.6, 69.2, 69.0. Low-resolution ESI-MS: *m*/*z* 478.3 (24%) [**6** + H]$^+$, 500.3 (100%) [**5** + Na]$^+$ and 516.2 (17%) [**5** + K]$^+$. High-resolution ESI-MS: *m*/*z* calcd for [**6** + H]$^+$ $C_{25}H_{36}NO_8$, 478.2441, found 478.2437, error –0.8 ppm and calcd for [**6** + Na]$^+$ $C_{25}H_{35}NO_8Na$ 500.2260, found 500.2257, error –0.6 ppm.

*4. Synthesis of 5-methylene-(N'-phenylureylene)-1,2-phenylene-o-phenylene- 24-crown-8 (**2a**)*

A solution of **6** (200 mg, 0.420 mmol) and phenylisocyanate (120 mg, 1.00 mmol) of in 20.0 ml of $CHCl_3$ was stirred at room temperature for 12 hours under N_2 protection. The reaction mixture was added with 10.0 ml of 1 M HCl and the organic layer was washed with 10.0 ml of brine twice and followed by 10.0 ml of deionized water twice. After dried over Na_2SO_4, the solvent was evaporated to afford the crude product which was purified by recrystallization from acetone to give **2a** as a white solide (227 mg, 91.0 %). ^{1}H NMR (500 MHz, CD_3CN, room temperature) δ 7.54 (1 H, s), 7.40 (2 H, d, *J* = 7.5 Hz), 7.23 (2 H, t, *J* = 7.5 Hz), 6.85–6.96 (8 H, m), 5.82 (1 H, s), 4.27 (2 H, d, *J* = 6.0 Hz), 4.09–4.13 (8 H, m), 3.75–3.78 (8 H, m), 3.65 (8 H, m). ^{13}C NMR (100 MHz, $CDCl_3$, 22 °C) δ 155.9, 148.9, 148.8, 148.7, 147.8, 139.2, 132.6, 128.9, 122.7, 121.5, 121.5, 120.4, 119.6, 114.1, 114.1, 114.0, 113.3, 71.2, 71.1, 71.1, 69.9, 69.9, 69.8, 69.5, 69.2, 69.2, 69.1, 43.7. Low-resolution ESI-MS: *m*/*z* 597.2 (19%) [**2a** + H]$^+$, 614.3 (19%) [**2a** + NH_4]$^+$, 619.3 (100%) [**2a** + Na]$^+$ and 635.2 (28%) [**2a** + K]$^+$. Anal. Calcd. for $C_{32}H_{40}N_2O_9$: C, 64.41; H, 6.76; N, 4.69; Found: C, 64.43; H, 6.77; N, 4.69.

*5. Synthesis of compound **2b***

Compound **2b** was prepared according to the procedure for **2a** in 92% yield as a white solid. ^{1}H NMR (400 MHz, CD_3CN, room temperature) δ 8.36 (1 H, s), 8.10 (2 H, d, *J* = 8.8 Hz), 7.62 (2 H, d, *J* = 8.8 Hz), 6.85–6.96 (7 H, m), 6.12 (1 H, s), 4.29 (2 H, d, *J* = 6.0 Hz), 4.10 (8 H, m), 3.77 (8 H, m), 3.66 (8 H, m). ^{13}C NMR (100 MHz, $CDCl_3$, 22 °C) δ 155.0, 148.4, 148.4, 148.2, 146.0, 141.2, 124.8, 117.0, 69.1, 68.8, 68.7, 68.6, 43.4. Low-resolution ESI-MS: *m*/*z* 659.3 (28%) [**2b** + NH_4]$^+$, 664.3 (100%) [**2b** + Na]$^+$ and 680.2 (27%) [**2b** + K]$^+$. Anal. Calcd. for $C_{32}H_{39}N_3O_{11}$: C, 59.90; H, 6.13; N, 6.55; Found: C, 59.89; H, 6.10; N, 6.56.

*6. Synthesis of compound **2c***

Compound **2c** was prepared according to the procedure for **2a** in 90% yield as a white solid. ^{1}H NMR (400 MHz, CD_3CN, room temperature) 7.53–7.60 (5 H, m), 6.83–5.93 (7 H, m), 5.67 (1 H, s), 4.28 (2H, d, J = 6.0 Hz), 4.08 (8 H, m), 3.79 (8 H, m), 3.64–3.67 (8 H, m). ^{13}C NMR (100 MHz, $CDCl_3$, 22 °C): δ 155.4, 148.7, 148.6, 148.5, 147.7, 142.7, 132.1, 125.9, 121.5, 121.4, 120.4, 117.7, 113.8, 113.7, 112.9, 71.2, 71.0, 69.9, 69.4, 69.0, 68.9, 68.7, 43.7. High-resolution ESI-MS: *m*/*z* calcd for [**2c** + Na]$^+$ $C_{33}H_{39}N_2O_9F_3Na$, 687.2505, found 687.2455, error –7.3 ppm and calcd for [**2c** + K]$^+$ $C_{33}H_{39}N_2O_9F_3K$ 703.2245, found 703.2213, error –4.6 ppm.

*7. ^{1}H and ^{13}C NMR spectra of **5**, **6**, **2a**, **2b** and **2c***

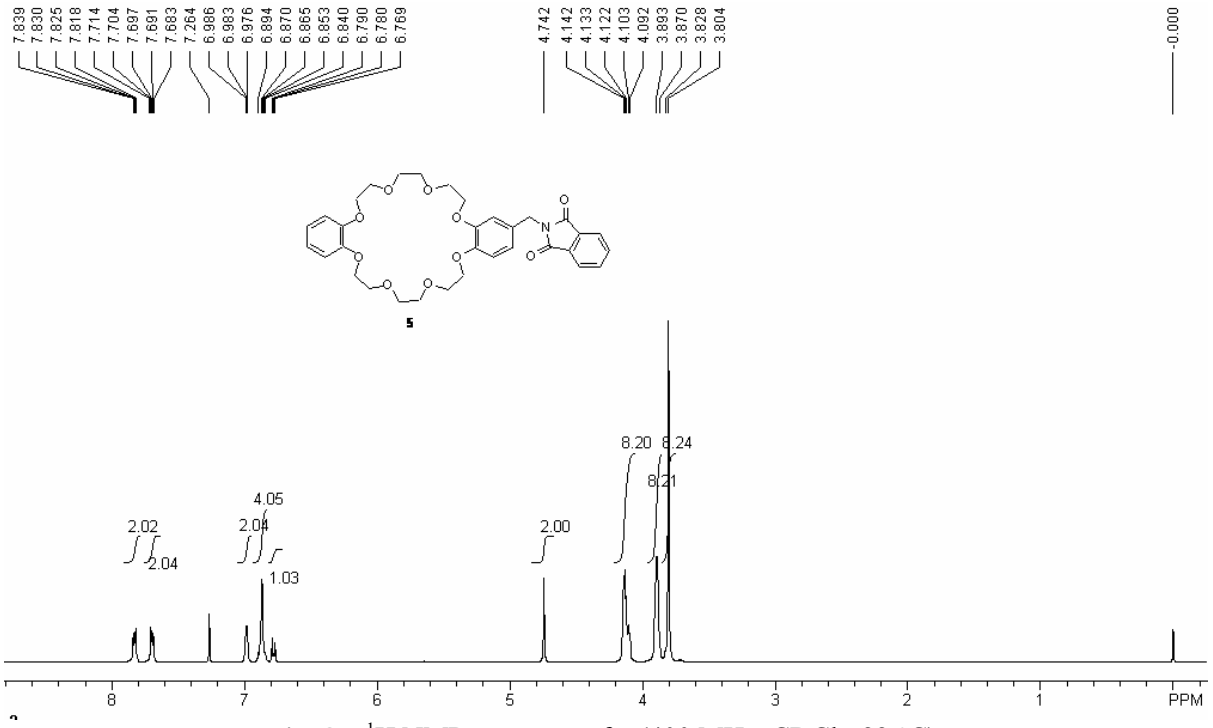

Fig. S1. ^{1}H NMR spectrum of **5** (400 MHz, $CDCl_3$, 22 °C).

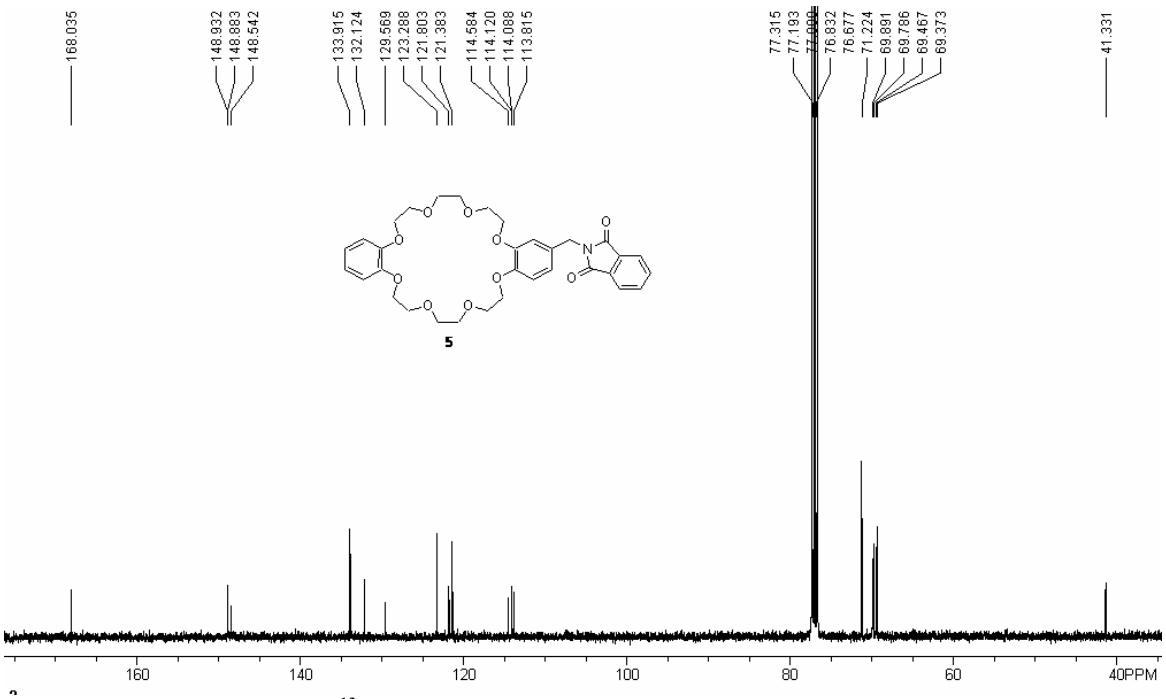

Fig. S2. ^{13}C NMR spectrum of **5** (100 MHz, $CDCl_3$, 22 °C).

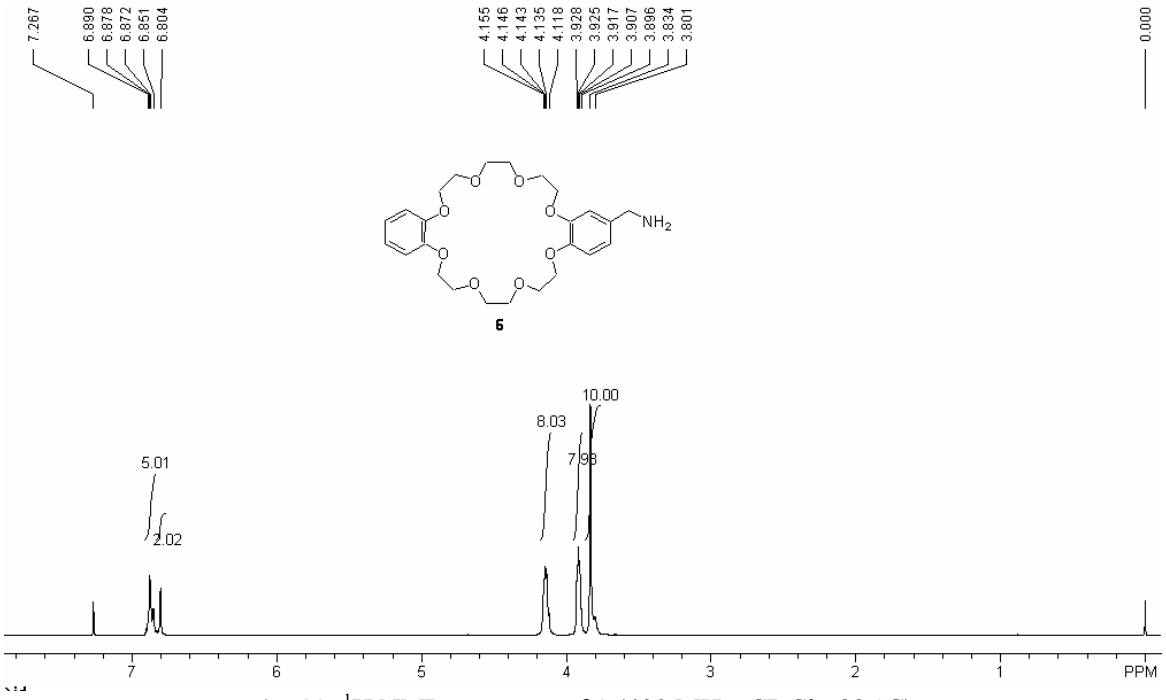

Fig. S3. ^{1}H NMR spectrum of **6** (400 MHz, $CDCl_3$, 22 °C).

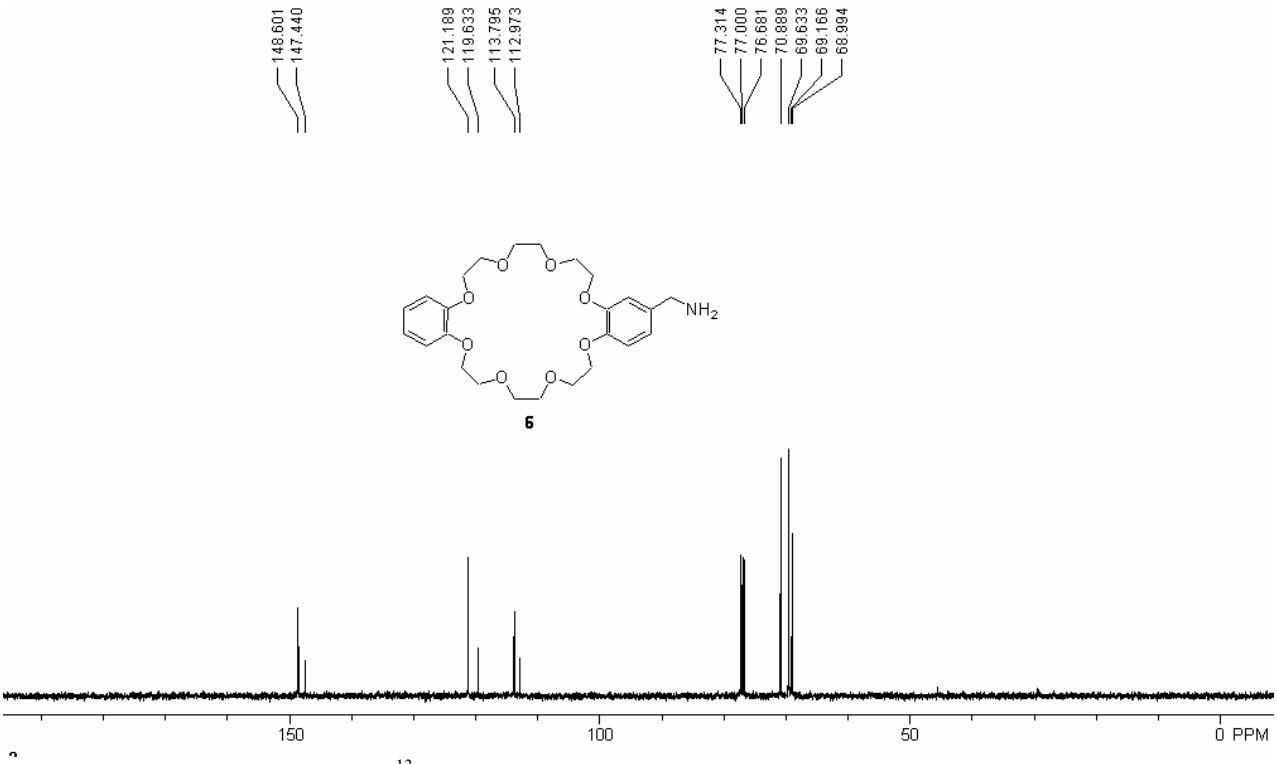

Fig. S4. ^{13}C NMR spectrum of **6** (100 MHz, $CDCl_3$, 22 °C).

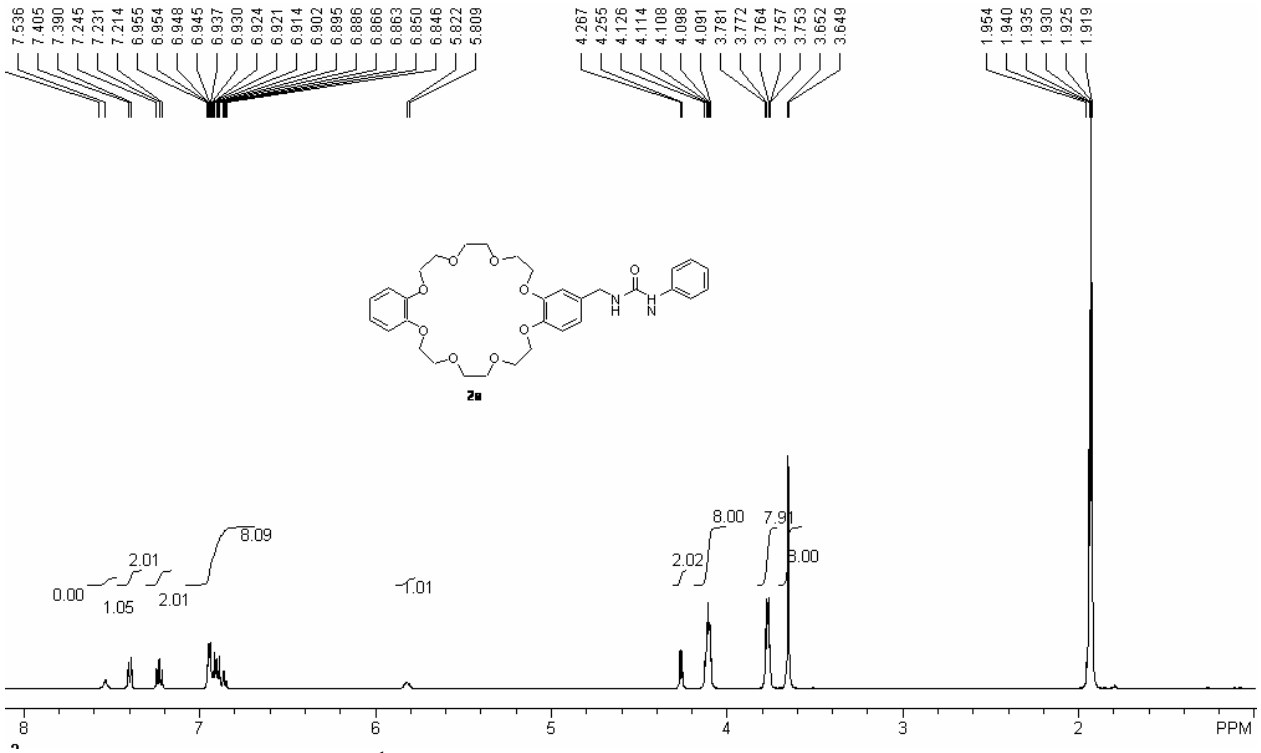

Fig. S5. ^{1}H NMR spectrum of **2a** (400 MHz, CD_3CN, 22 °C).

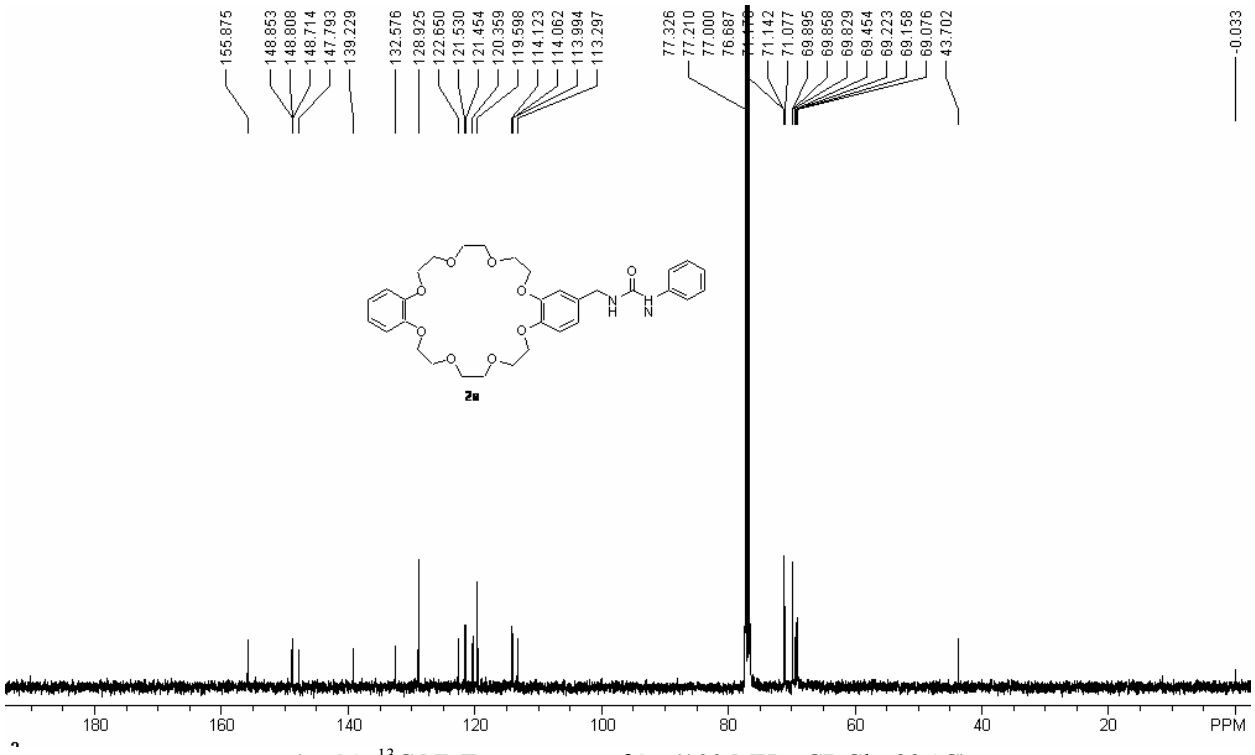

Fig. S6. ^{13}C NMR spectrum of **2a** (100 MHz, $CDCl_3$, 22 °C).

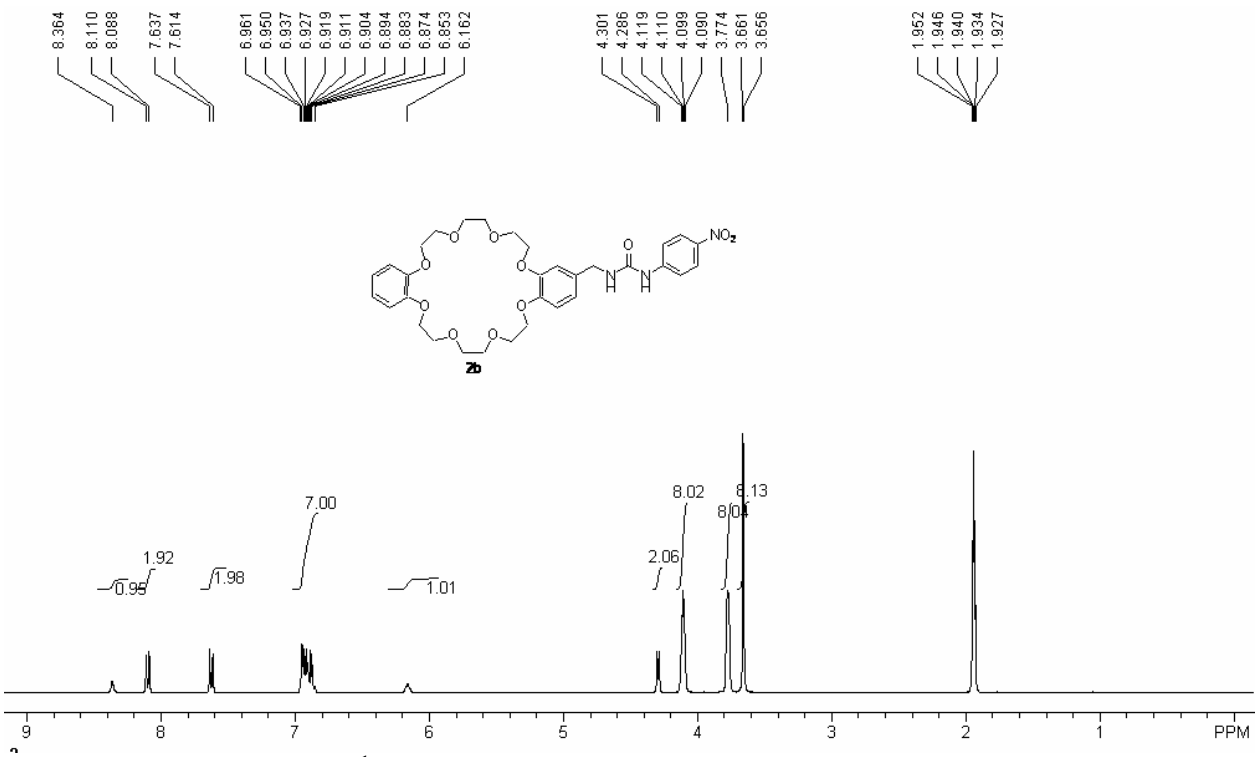

Fig. S7. ^{1}H NMR spectrum of **2b** (400 MHz, CD_3CN, 22 °C).

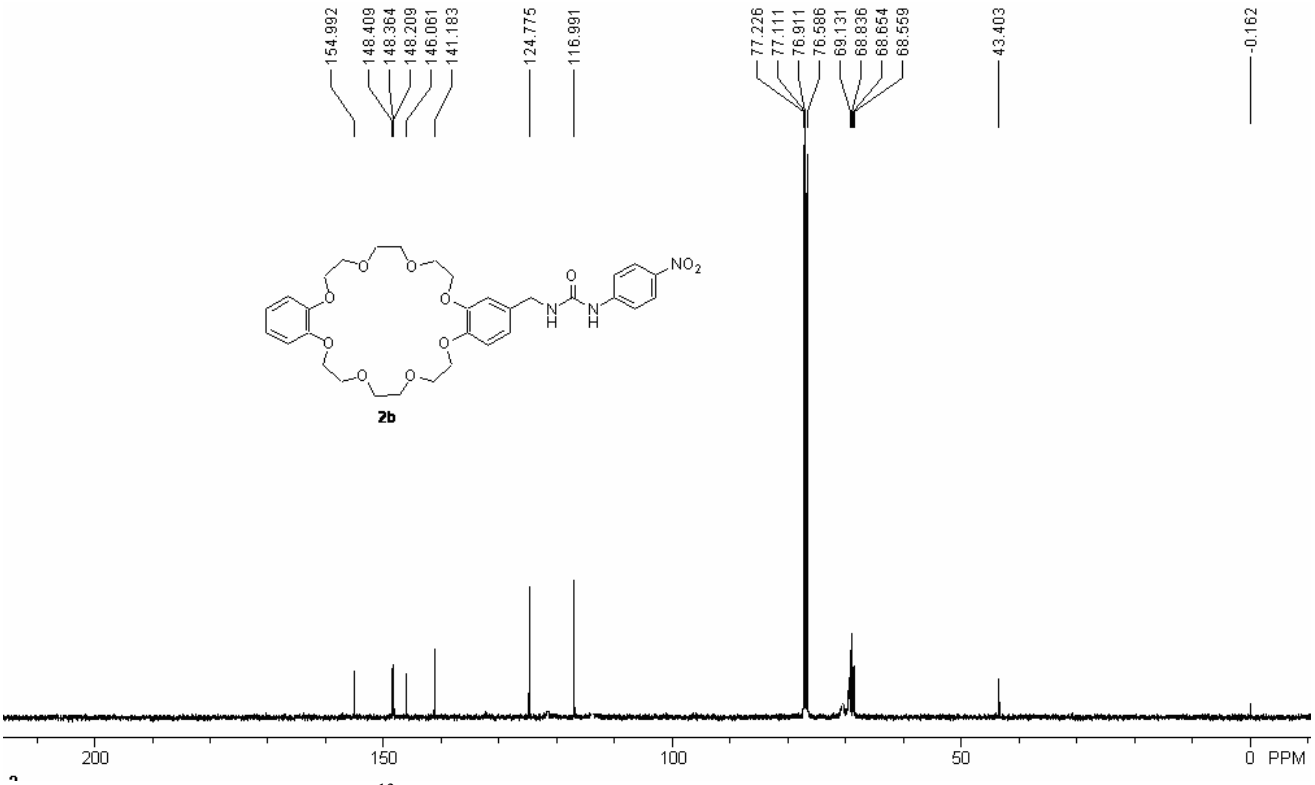

Fig. S8. ^{13}C NMR spectrum of **2b** (100 MHz, $CDCl_3$, 22 °C).

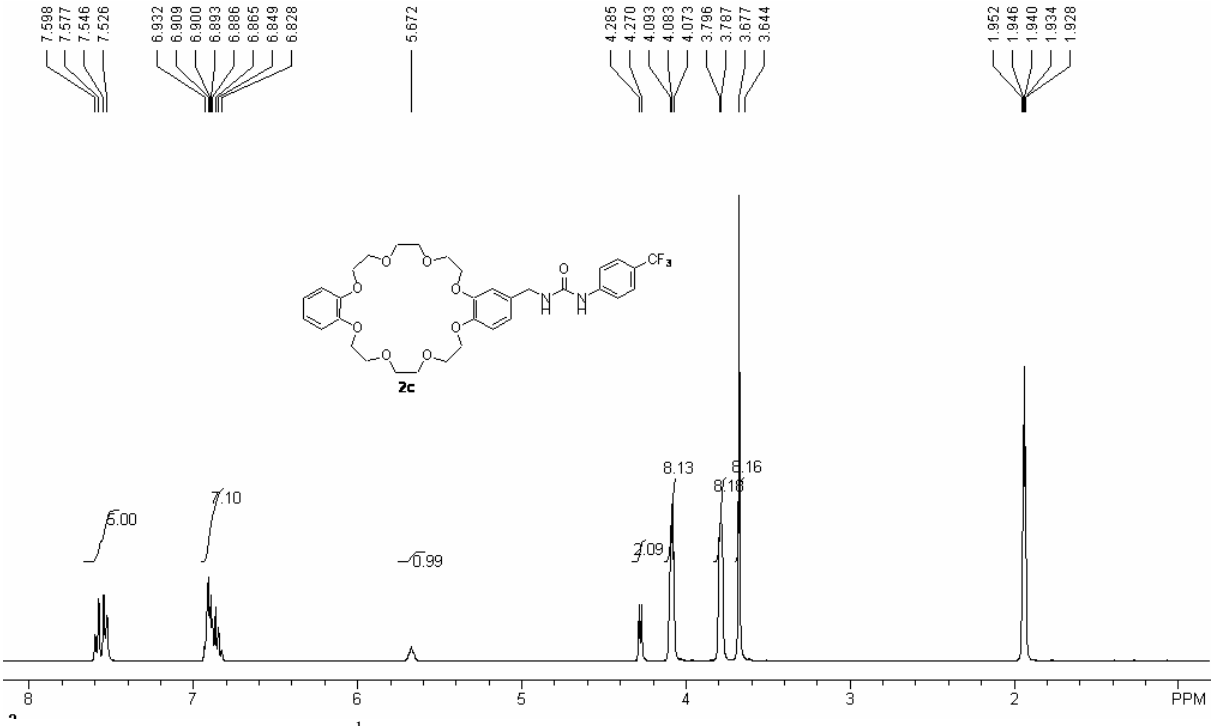

Fig. S9. ^{1}H NMR spectrum of **2c** (400 MHz, CD_3CN, 22 °C).

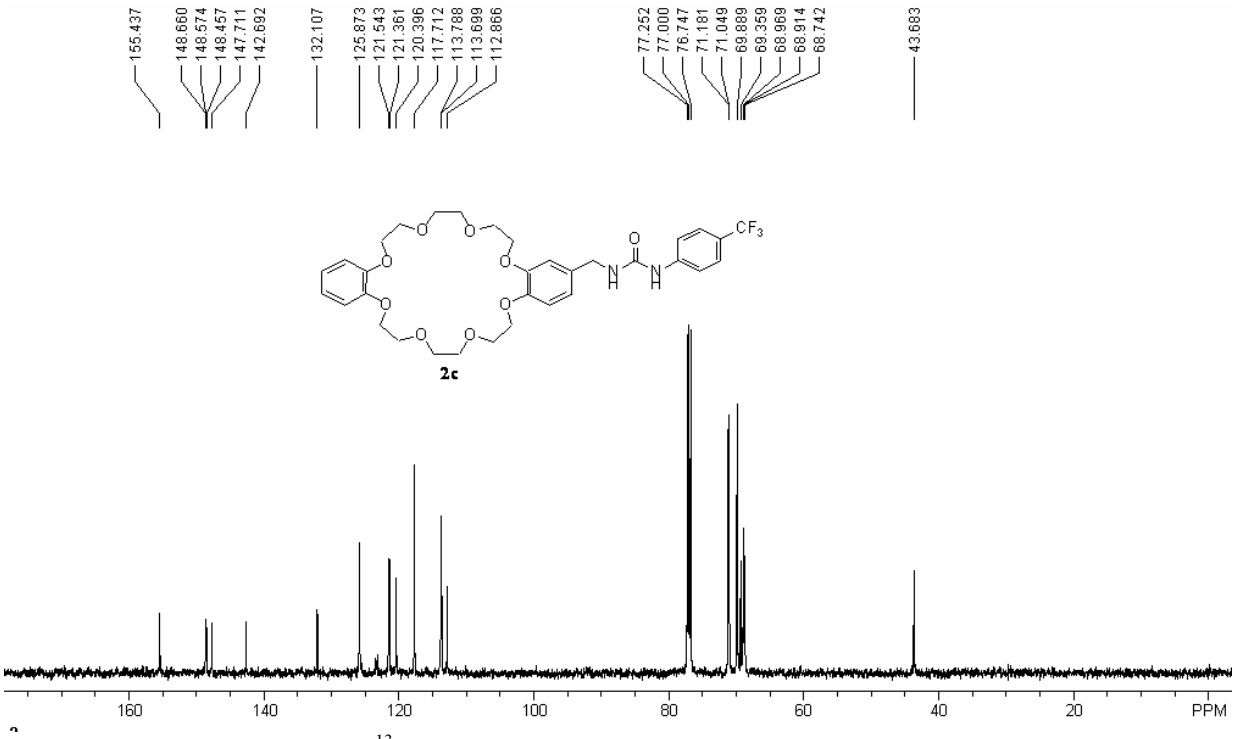

Fig. S10. ^{13}C NMR spectrum of **2c** (100 MHz, $CDCl_3$, 22 °C).

*8. Determination of association constants of **1•3a**, **1•3b**, **1•3c, 2a•3a, 2a•3b, 2a•3c, 2b•3a, 2b•3b, 2b•3c, 2c•3a, 2c•3b and 2c•3c** from integrations of complexed and uncomplexed peaks in 1:1 host and guest solutions*

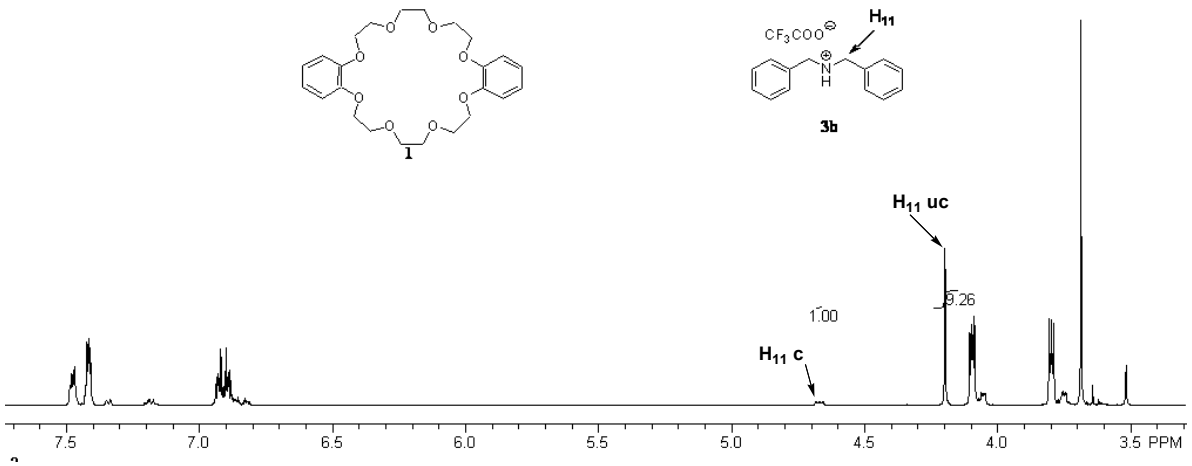

Fig. S11. ^{1}H NMR spectrum (500 MHz, CD_3CN, 22 °C) of 2.00 mM **1** and **3b**. The association constant $K_{a,\mathbf{1\bullet 3b}}$ value calculated from integrations of complexed and uncomplexed peaks of H_{11} of **3b** is $[(1.00/10.26) \times 1.00 \times 10^{-3}]/[(1 - 1.00/10.26) \times 1.00 \times 10^{-3}]^2 = 59\ M^{-1}$.

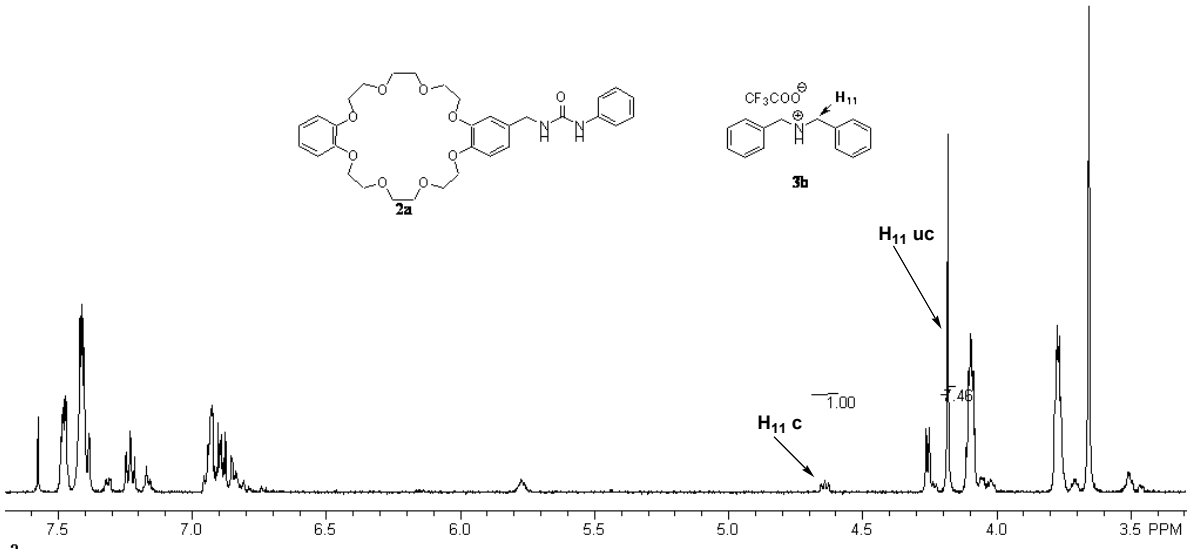

Fig. S12. ^{1}H NMR spectrum (500 MHz, CD_3CN, 22 °C) of 2.00 mM **2a** and **3b**. The association constant $K_{a,\mathbf{2a\bullet 3b}}$ value calculated from integrations of complexed and uncomplexed peaks of H_{11} of **3b** is $[(1.00/8.46) \times 1.00 \times 10^{-3}]/[(1 - 1.00/8.46) \times 1.00 \times 10^{-3}]^2 = 78\ M^{-1}$.

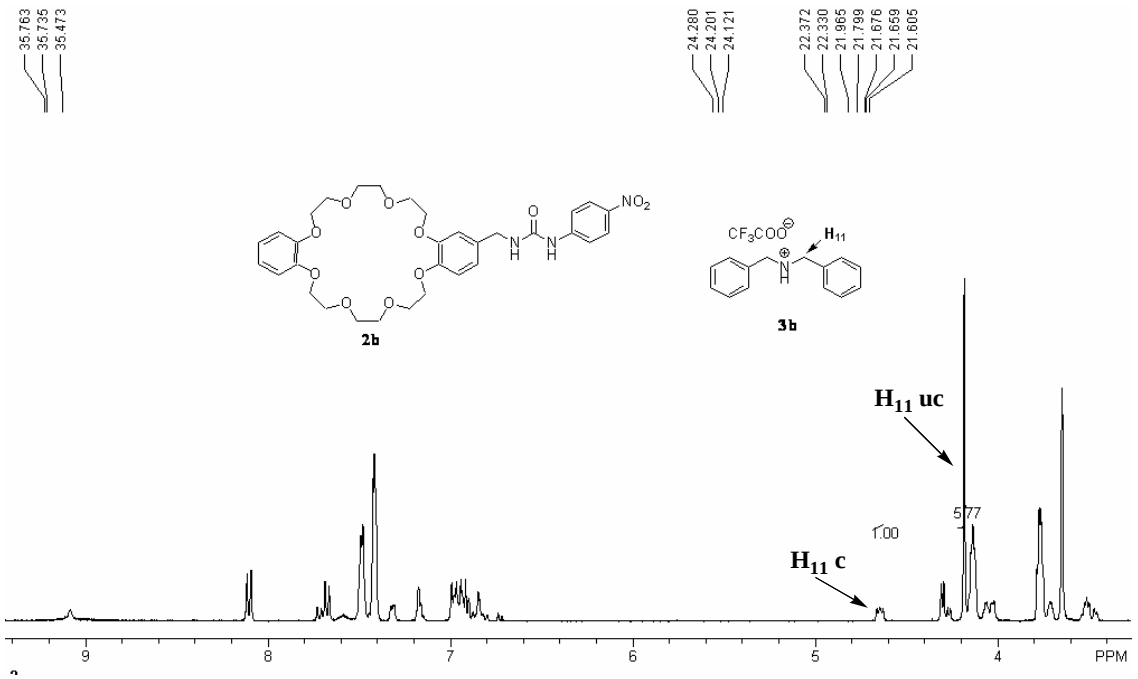

Fig. S13. ^{1}H NMR spectrum (500 MHz, CD_3CN, 22 °C) of 2.00 mM **2b** and **3b**. The association constant $K_{a,\mathbf{2b•3b}}$ value calculated from integrations of complexed and uncomplexed peaks of H_{11} of **3b** is $[(1.00/6.77) \times 2.00 \times 10^{-3}]/[(1 - 1.00/6.77) \times 2.00 \times 10^{-3}]^2 = 102\ M^{-1}$.

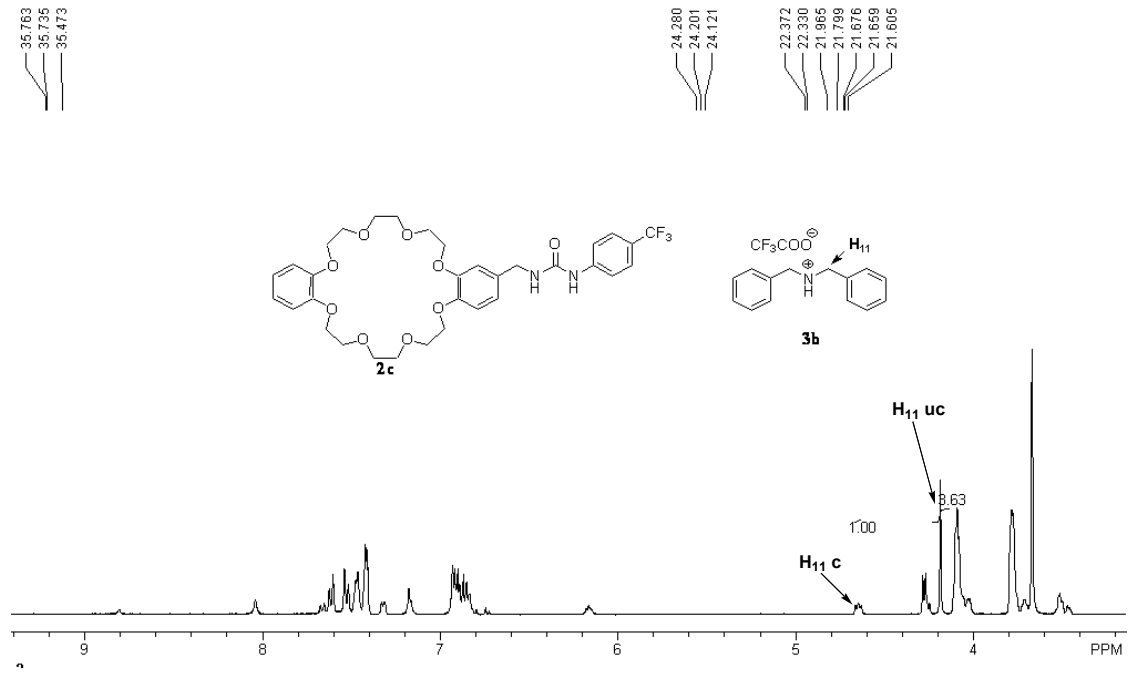

Fig. S14. ^{1}H NMR spectrum (500 MHz, CD_3CN, 22 °C) of 2.00 mM **2c** and **3b**. The association constant $K_{a,\mathbf{2c•3b}}$ value calculated from integrations of complexed and uncomplexed peaks of H_{11} of **3b** is $[(1.00/4.63) \times 2.00 \times 10^{-3}]/[(1 - 1.00/4.63) \times 2.00 \times 10^{-3}]^2 = 176\ M^{-1}$.

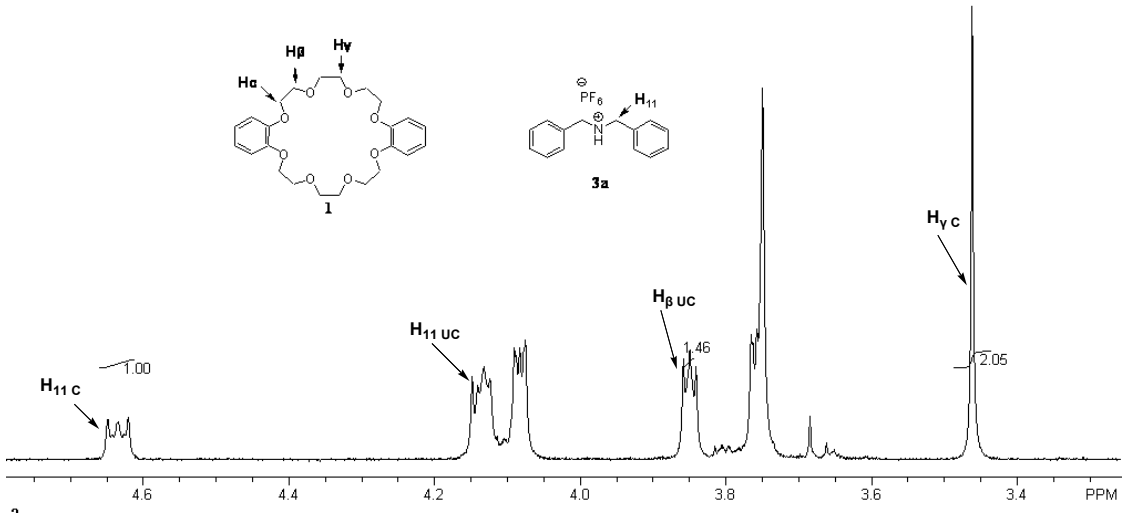

Fig. S15. ^{1}H NMR spectrum (500 MHz, 3:2 $CDCl_3$:CD_3CN, 22 °C) of 2.00 mM **1** and **3a**. The association constant $K_{a,\mathbf{1}\bullet\mathbf{3a}}$ value calculated from integrations of complexed peaks of H_γ of **1** and uncomplexed peaks of H_β of **1** is $[(2.05/3.51) \times 2.00 \times 10^{-3}]/[(1 - 2.05/3.51) \times 2.00 \times 10^{-3}]^2 = 1687\ M^{-1}$.

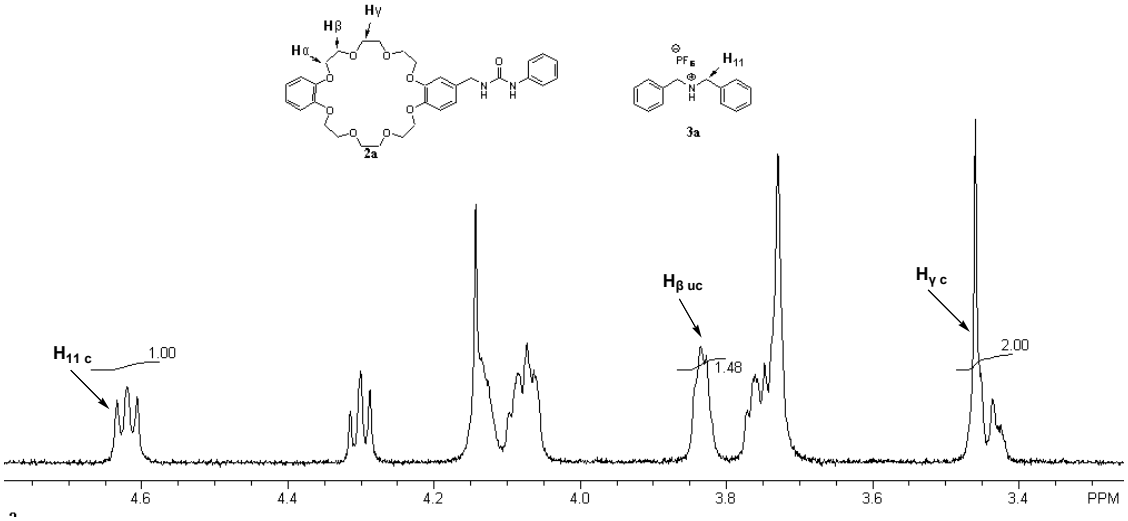

Fig. S16. ^{1}H NMR spectrum (500 MHz, 3:2 $CDCl_3$:CD_3CN, 22 °C) of 2.00 mM **2a** and **3a**. The association constant $K_{a,\mathbf{2a}\bullet\mathbf{3a}}$ value calculated from integrations of complexed peaks of H_γ of **2a** and uncomplexed peaks of H_β of **2a** is $[(2.00/3.48) \times 2.00 \times 10^{-3}]/[(1 - 2.00/3.48) \times 2.00 \times 10^{-3}]^2 = 1589\ M^{-1}$.

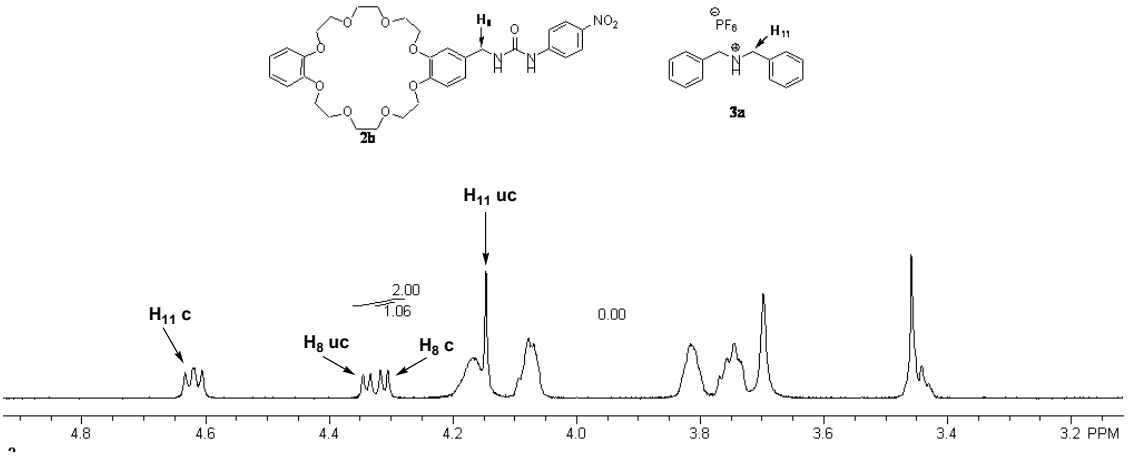

Fig. S17. ^{1}H NMR spectrum (500 MHz, 3:2 $CDCl_3$:CD_3CN, 22 °C) of of 2.00 mM **2b** and **3a**. The association constant $K_{a,\mathbf{2b•3a}}$ value calculated from integrations of complexed and uncomplexed peaks of H_8 of **2b** is $[(1.060/2.00) \times 2.00 \times 10^{-3}]/[(1 - 1.060/2.00) \times 2.00 \times 10^{-3}]^2 = 1200\ M^{-1}$.

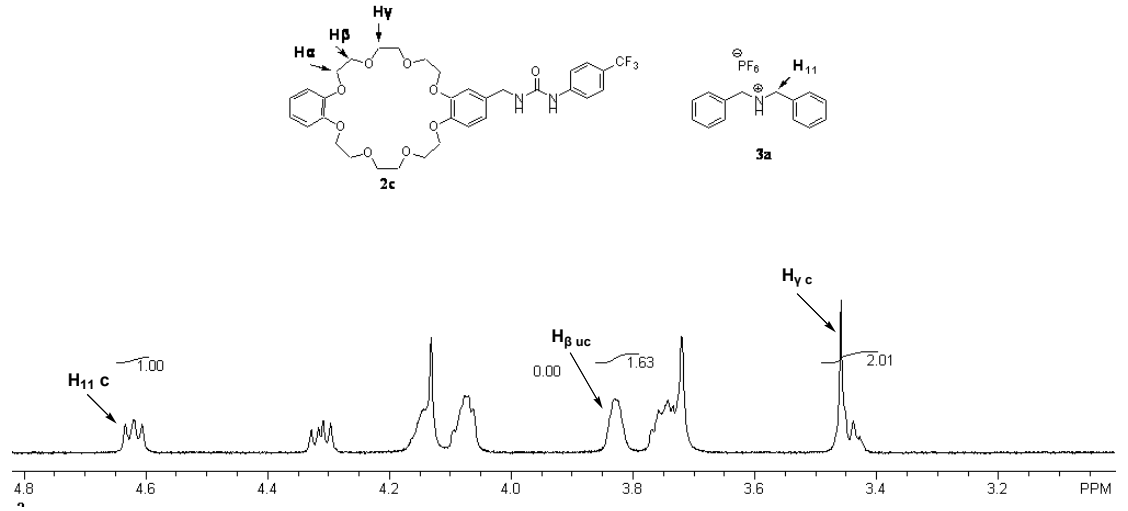

Fig. S18. ^{1}H NMR spectrum (500 MHz, 3:2 $CDCl_3$:CD_3CN, 22 °C) of 2.00 mM **2c** and **3a**. The association constant $K_{a,\mathbf{2c•3a}}$ value calculated from integrations of complexed peaks of H_γ of **2c** and uncomplexed peaks of H_β of **2c** is $[(2.01/3.64) \times 2.00 \times 10^{-3}]/[(1 - 2.01/3.64) \times 2.00 \times 10^{-3}]^2 = 1377\ M^{-1}$.

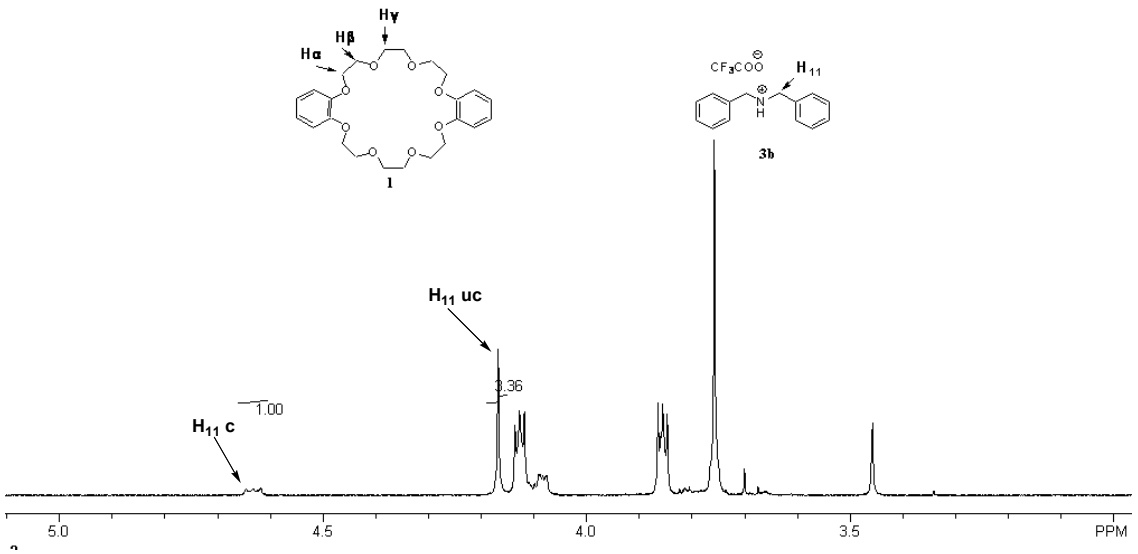

Fig. S19. ^{1}H NMR spectrum (500 MHz, 3:2 $CDCl_3$:CD_3CN, 22 °C) of 2.00 mM **1** and **3b**. The association constant $K_{a,\mathbf{2a•3b}}$ value calculated from integrations of complexed and uncomplexed peaks of H_{11} of **3b** is $[(1.00/4.36) \times 2.00 \times 10^{-3}]/[(1 - 1.00/4.36) \times 2.00 \times 10^{-3}]^2 = 193\ M^{-1}$.

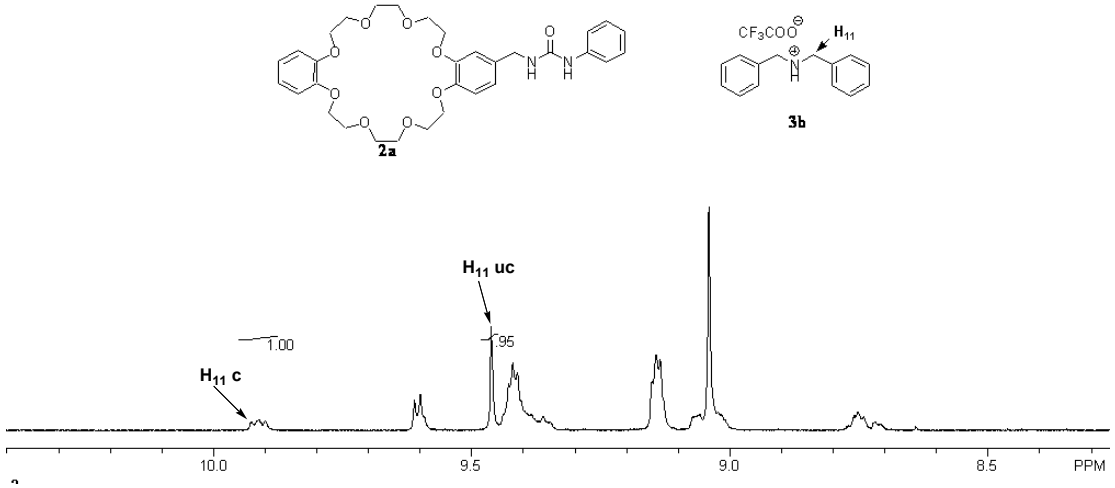

Fig. S20. ^{1}H NMR spectrum (500 MHz, 3:2 $CDCl_3$:CD_3CN, 22 °C) of 2.00 mM **2a** and **3b**. The association constant $K_{a,\mathbf{2a•3b}}$ value calculated from integrations of complexed and uncomplexed peaks of H_{11} of **3b** is $[(1.00/2.95) \times 2.00 \times 10^{-3}]/[(1 - 1.00/2.95) \times 2.00 \times 10^{-3}]^2 = 388\ M^{-1}$.

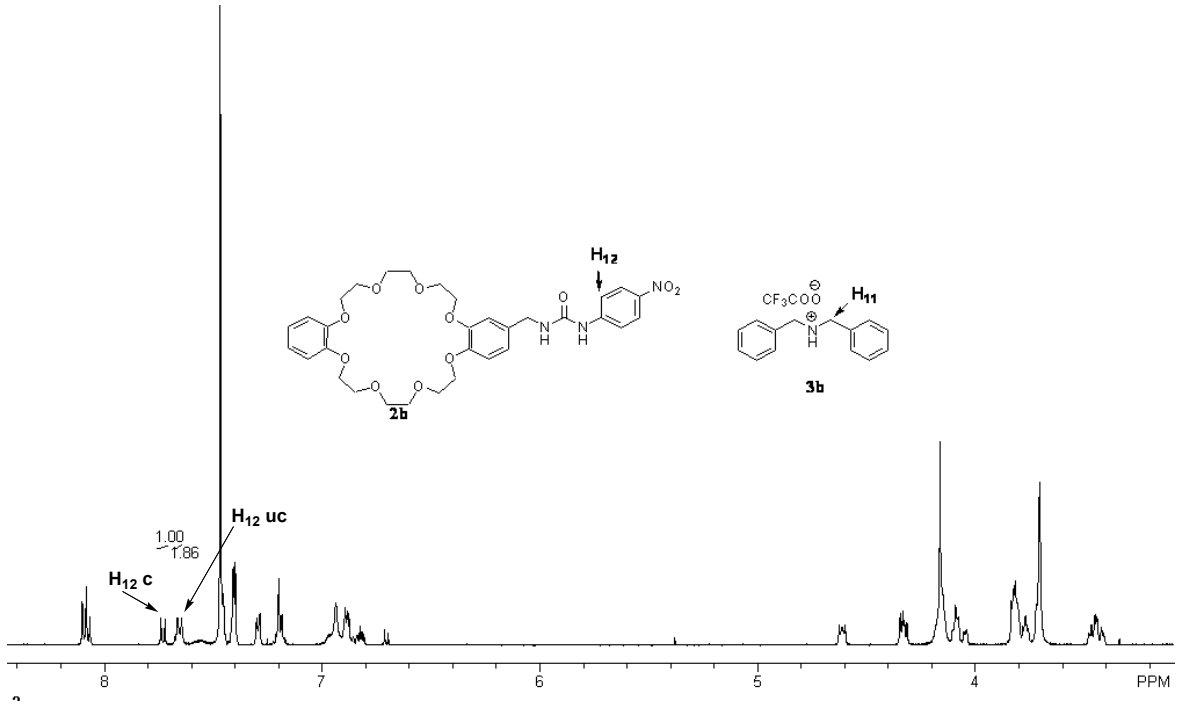

Fig. S21. ^{1}H NMR spectrum (500 MHz, 3:2 $CDCl_3$:CD_3CN, 22 °C) of 2.00 mM **2b** and **3b**. The association constant $K_{a,\mathbf{2b•3b}}$ value calculated from integrations of complexed and uncomplexed peaks of H_{12} of **2b** is $[(1.00/2.86) \times 2.00 \times 10^{-3}]/[(1 - 1.00/2.86) \times 2.00 \times 10^{-3}]^2 = 413\ M^{-1}$.

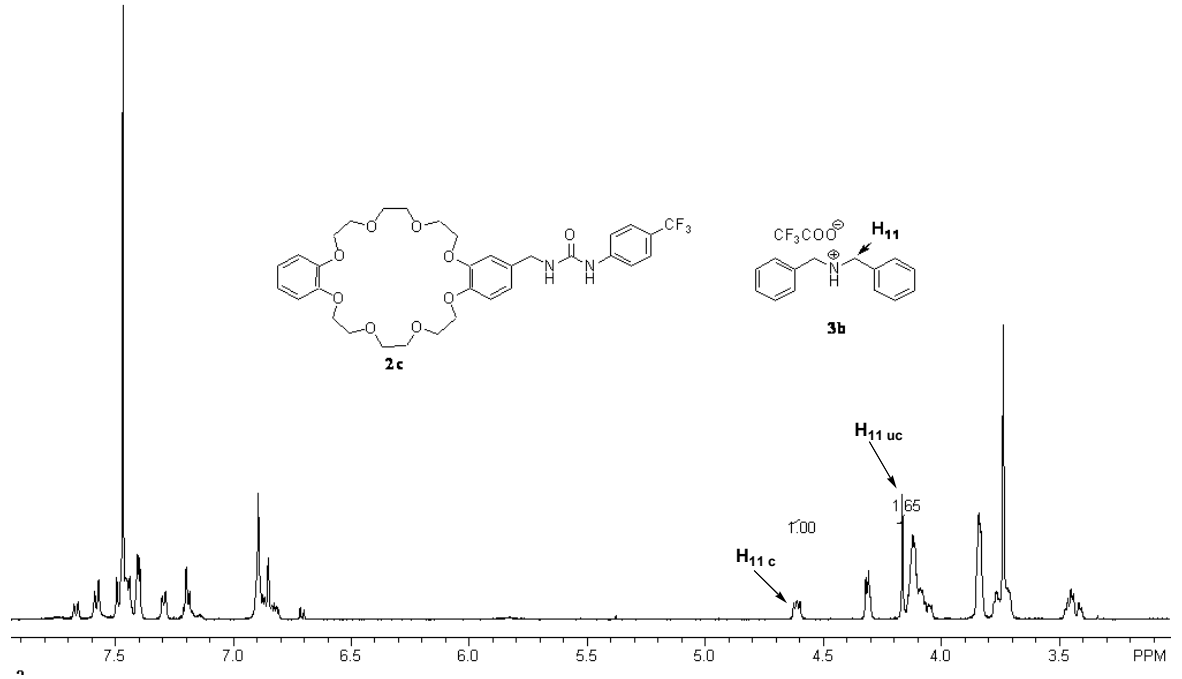

Fig. S22. ^{1}H NMR spectrum (500 MHz, 3:2 $CDCl_3$:CD_3CN, 22 °C) of 2.00 mM **2c** and **3b**. The association constant $K_{a,\mathbf{2c•3b}}$ value calculated from integrations of complexed and uncomplexed peaks of H_{11} of **3b** is $[(1.00/2.65) \times 2.00 \times 10^{-3}]/[(1 - 1.00/2.65) \times 2.00 \times 10^{-3}]^2 = 487\ M^{-1}$.

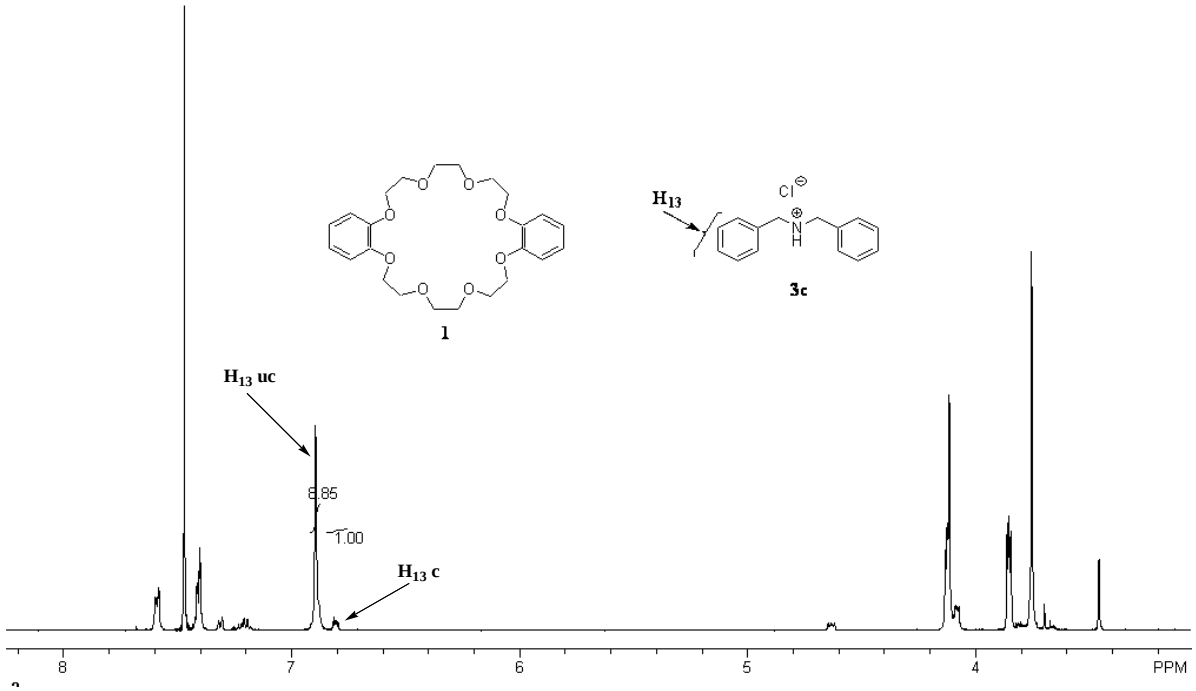

Fig. S23. ^{1}H NMR spectrum (500 MHz, 3:2 $CDCl_3$:CD_3CN, 22 °C)) of 2.00 mM **1** and **3c**. The association constant $K_{a,\mathbf{1}\bullet\mathbf{3c}}$ value calculated from integrations of complexed and uncomplexed peaks of H_{13} of **3c** is $[(1.00/9.85) \times 2.00 \times 10^{-3}]/[(1 - 1.00/9.85) \times 2.00 \times 10^{-3}]^2 = 63\ M^{-1}$.

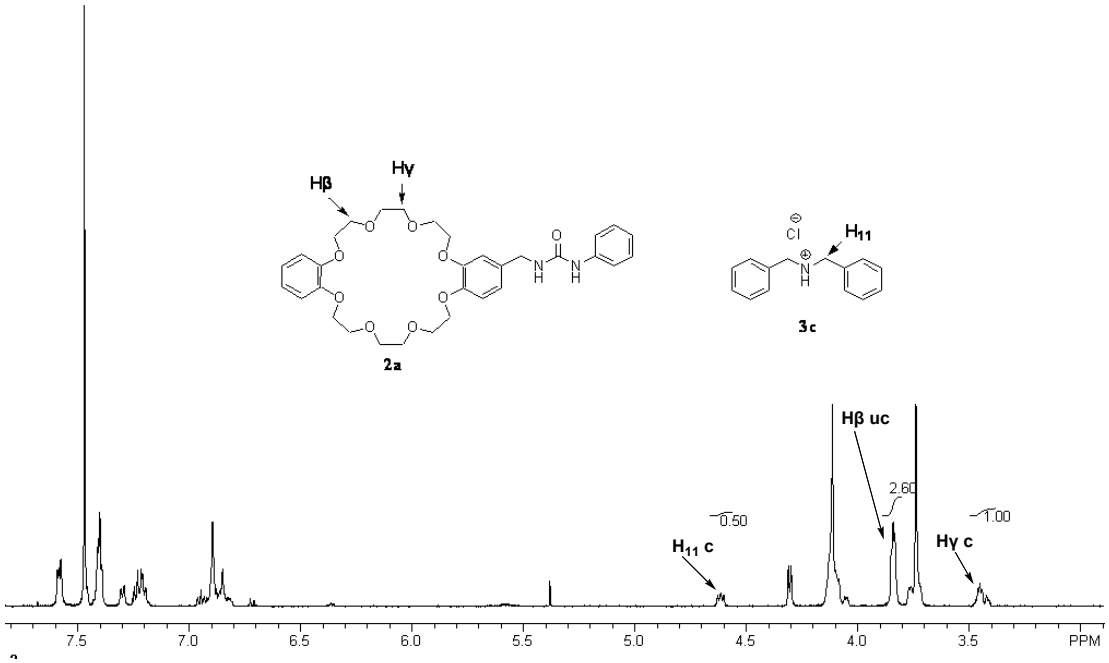

Fig. S24. ^{1}H NMR spectrum (500 MHz, 3:2 $CDCl_3$:CD_3CN, 22 °C)) of 2.00 mM **2a** and **3c**. The association constant $K_{a,\mathbf{2a}\bullet\mathbf{3c}}$ value calculated from integrations of complexed peaks of H_γ of **2a** and uncomplexed peaks of H_β of **2a** is $[(1.00/3.60) \times 2.00 \times 10^{-3}]/[(1 - 1.00/3.60) \times 2.00 \times 10^{-3}]^2 = 266\ M^{-1}$.

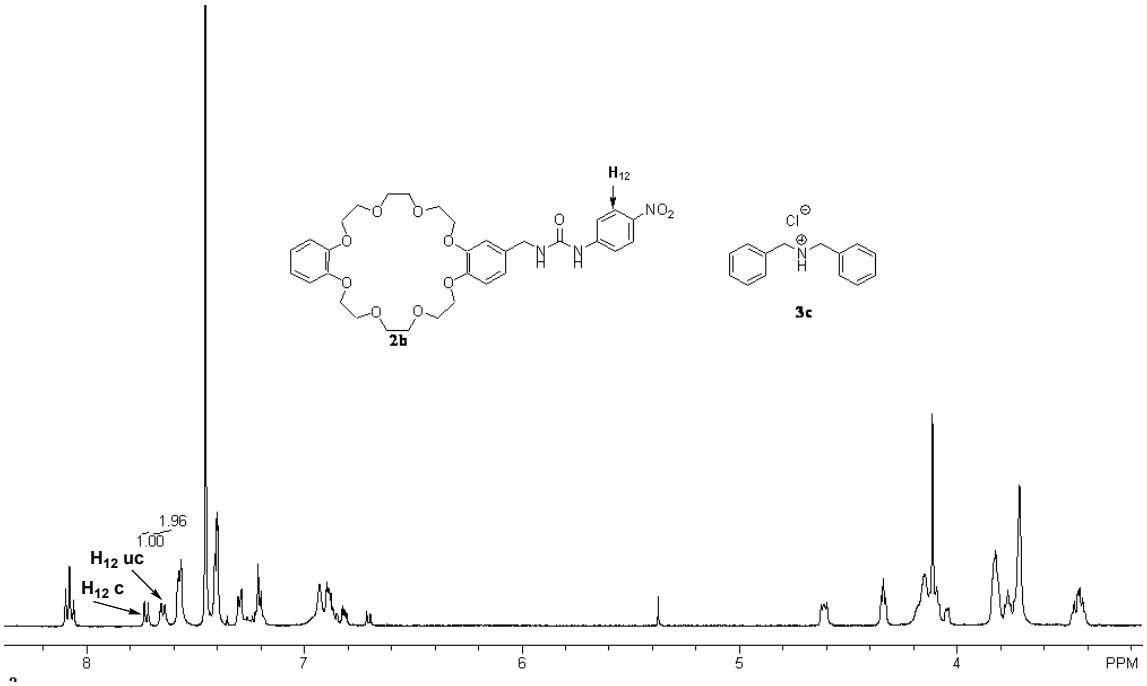

Fig. S25. ^{1}H NMR spectrum (500 MHz, 3:2 $CDCl_3$:CD_3CN, 22 °C)) of 2.00 mM **2b** and **3c**. The association constant $K_{a,\mathbf{2b•3c}}$ value calculated from integrations of complexed and uncomplexed peaks of H_{12} of **2b** is $[(1.00/2.96) \times 2.00 \times 10^{-3}]/[(1 - 1.00/2.96) \times 2.00 \times 10^{-3}]^2 = 385\ M^{-1}$.

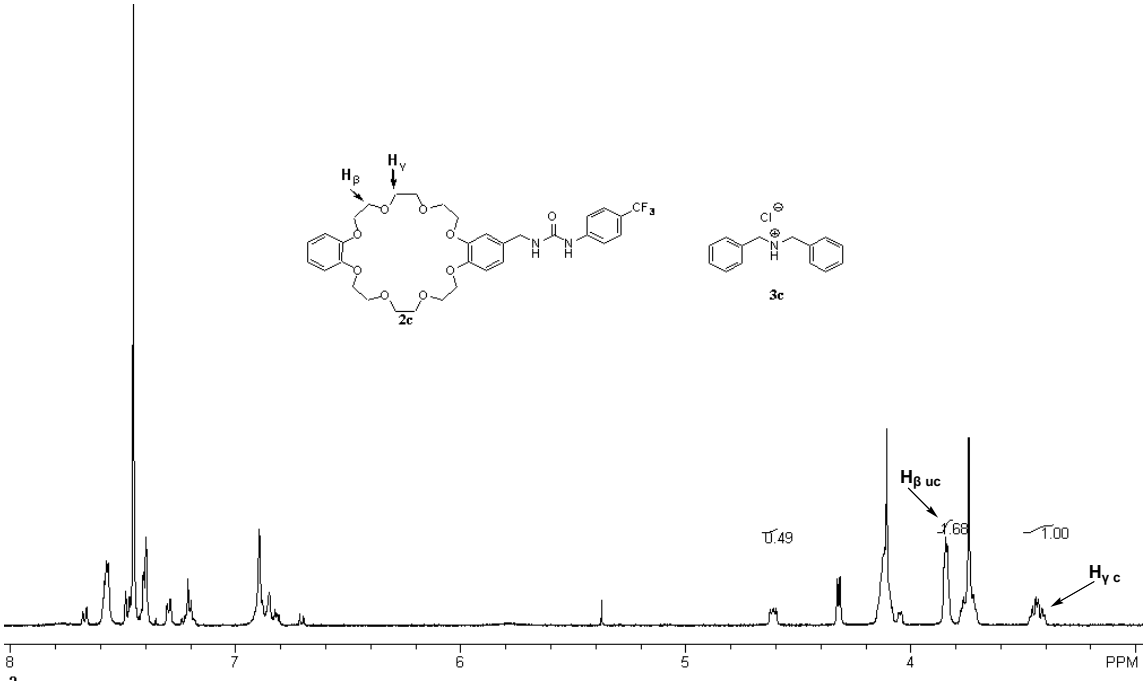

Fig. S26. ^{1}H NMR spectrum (500 MHz, 3:2 $CDCl_3$:CD_3CN, 22 °C)) of 2.00 mM **2c** and **3c**. The association constant $K_{a,\mathbf{2c•3c}}$ value calculated from integrations of complexed peaks of H_γ of **2c** and uncomplexed peaks of H_β of **2c** is $[(1.00/2.68) \times 2.00 \times 10^{-3}]/[(1 - 1.00/2.68) \times 2.00 \times 10^{-3}]^2 = 475\ M^{-1}$.

*9. ESI-MS spectra of **5**, **6**, **2a**, **2b** and **2c***

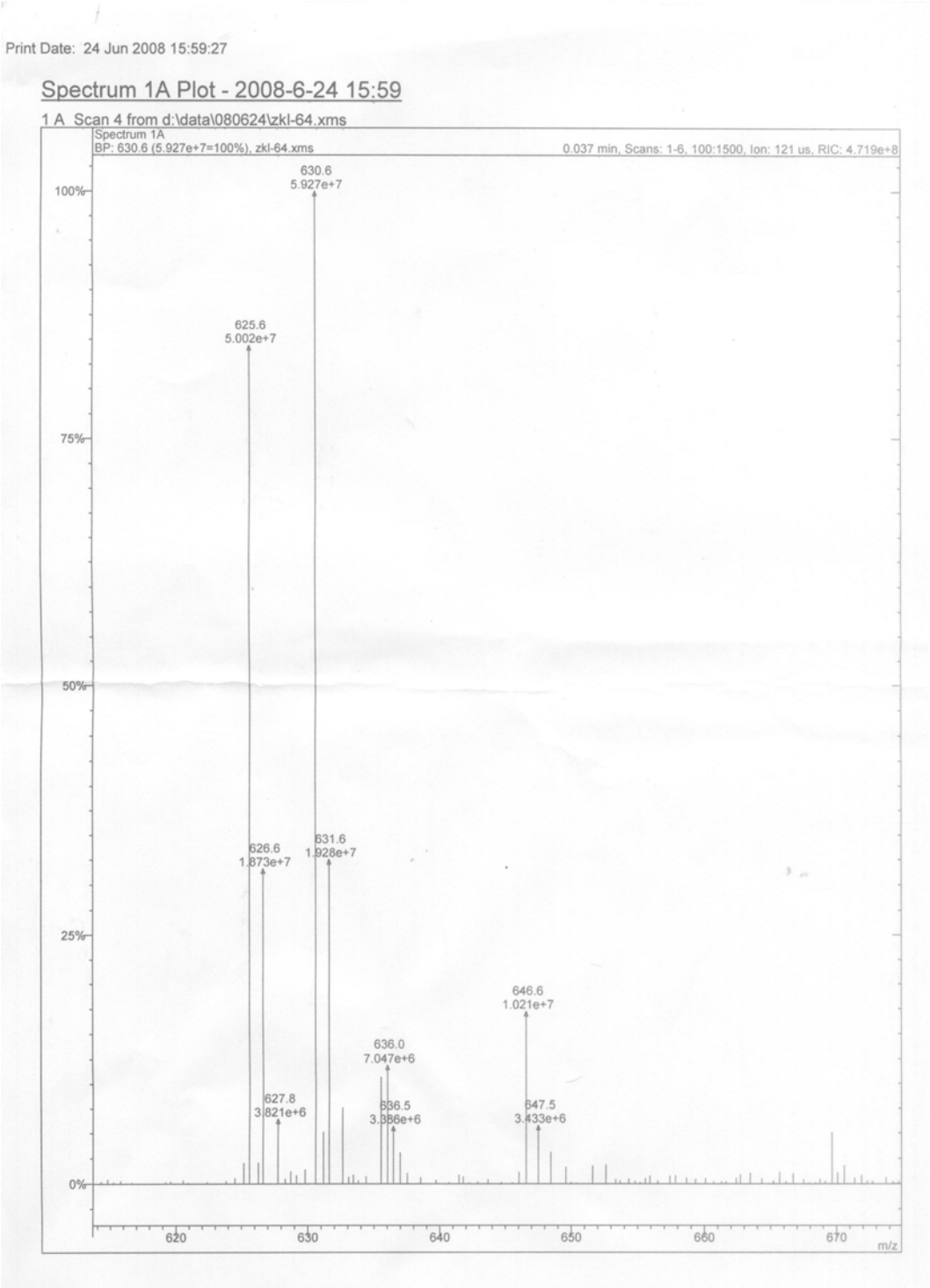

Fig. S27. ESI$^+$-MS of **5** in acetonitrile/methanol. Assignment of main peaks: *m/z* 625.6 (84%) [**5** + NH_4]$^+$, 630.6 (100%) [**5** + Na]$^+$ and 646.6 (17%) [**5** + K]$^+$.

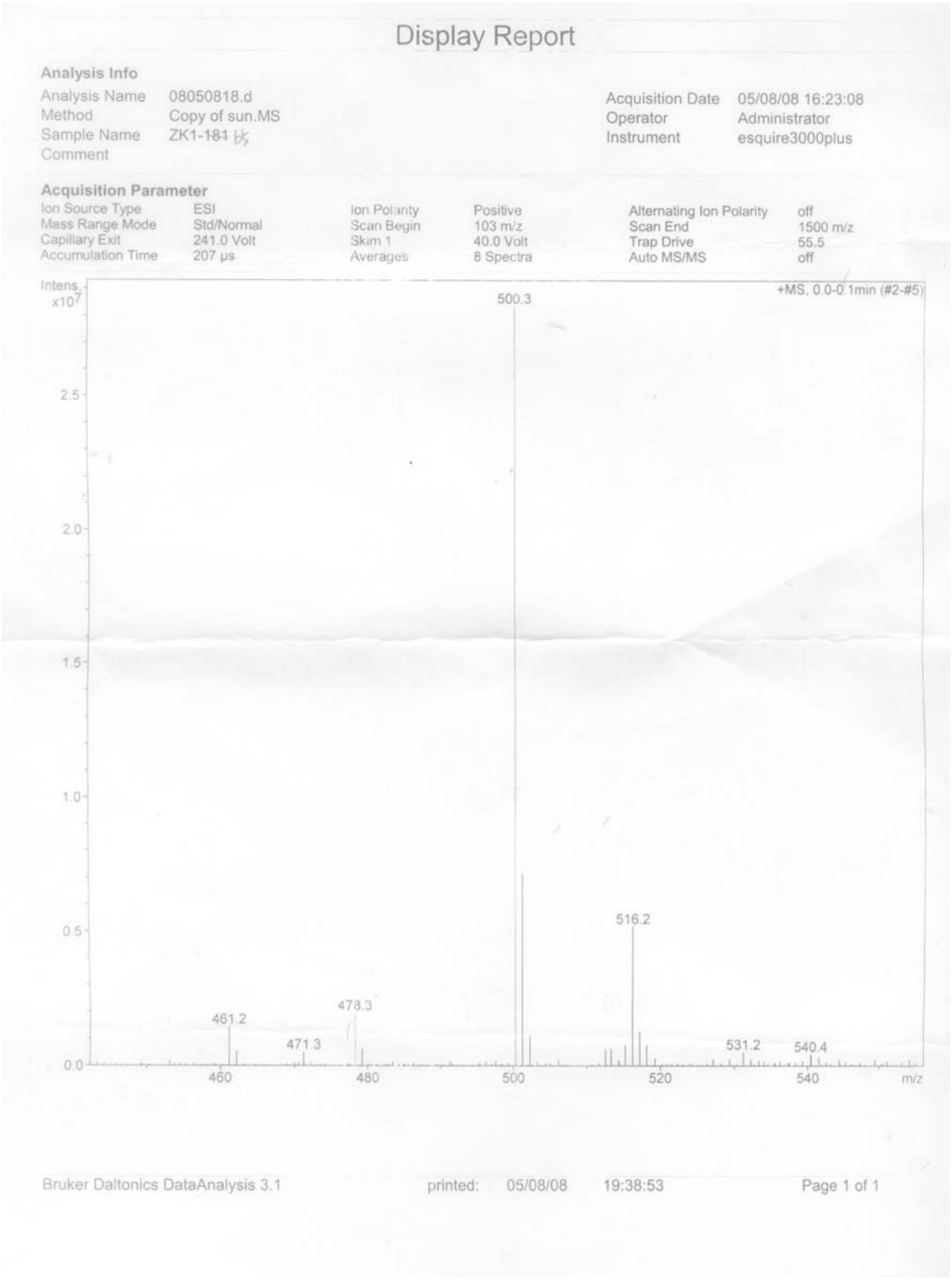

Fig. S28. ESI$^+$-MS of **6** in acetonitrile/methanol. Assignment of main peaks: *m/z* 478.3 (24%) [**6** + H]$^+$, 500.3 (100%) [**5** + Na]$^+$ and 516.2 (17%) [**5** + K]$^+$

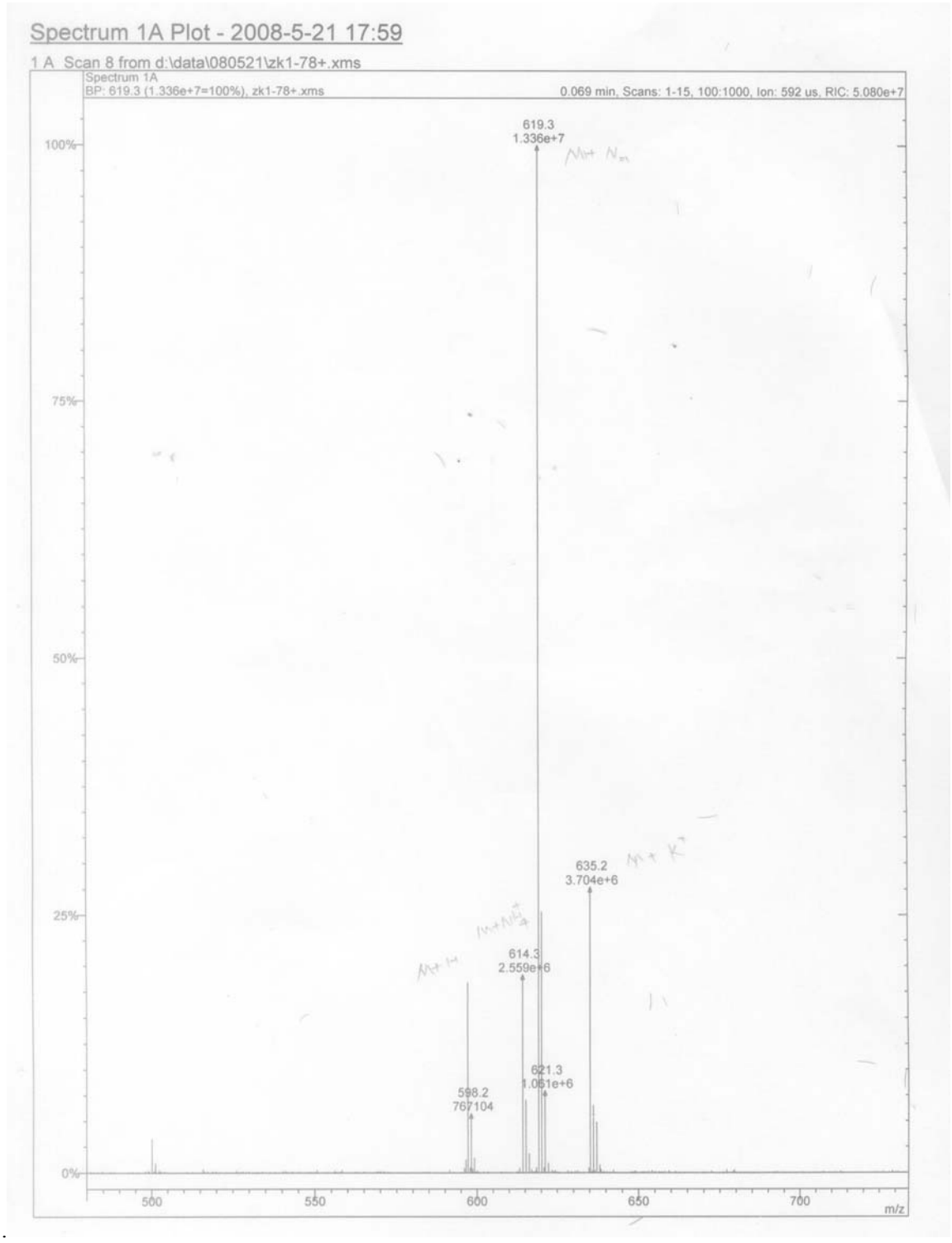

Fig. S29. ESI$^+$-MS of **2a** in acetonitrile/methanol. Assignment of main peaks: *m/z* 597.2 (19%) [**2a** + H]$^+$, 614.3 (19%) [**2a** + NH_4]$^+$, 619.3 (100%) [**2a** + Na]$^+$ and 635.2 (28%) [**2a** + K]$^+$.

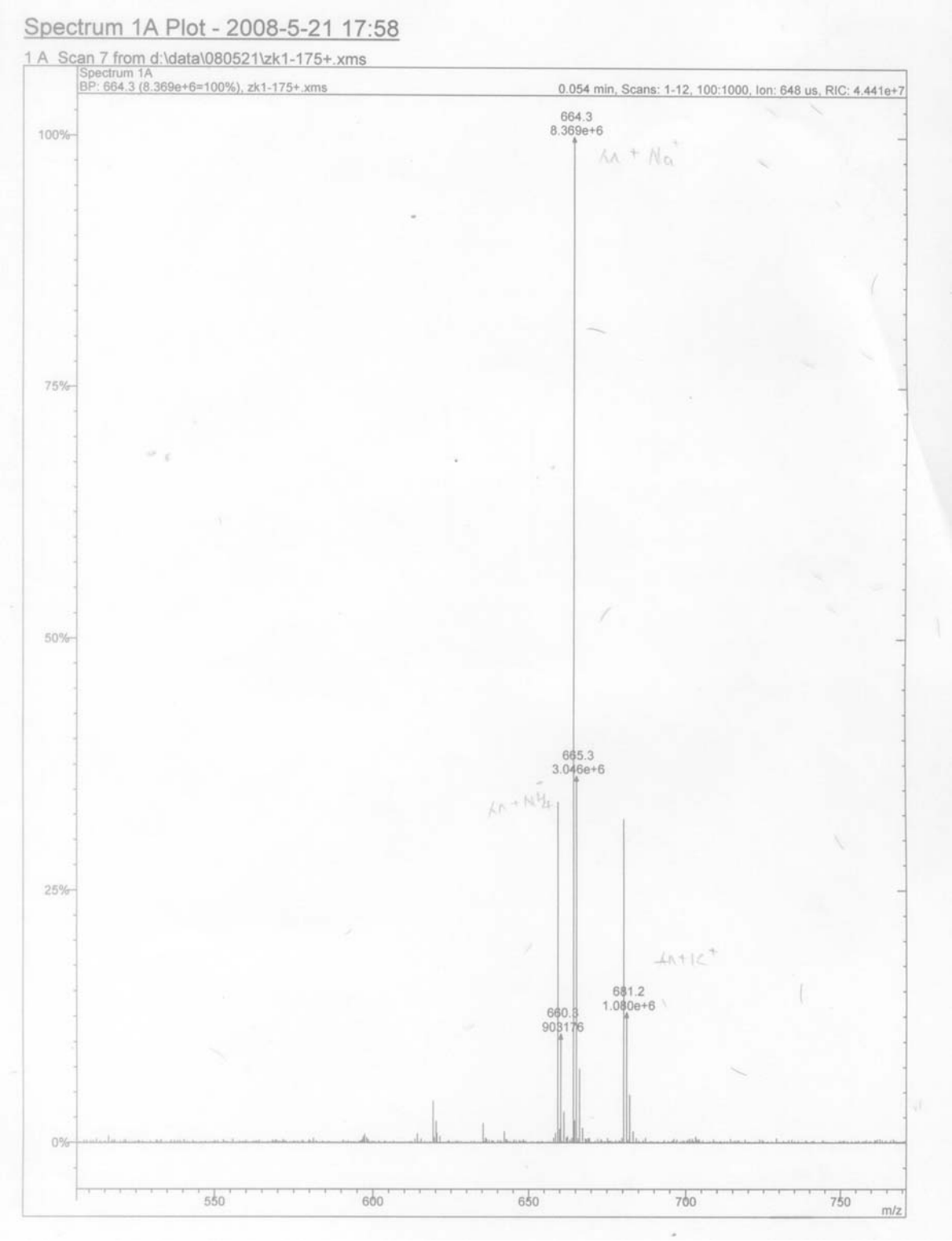

Fig. S30. ESI$^+$-MS of **2b** in acetonitrile/methanol. Assignment of main peaks: *m/z* 659.3 (28%) [**2b** + NH_4]$^+$, 664.3 (100%) [**2b** + Na]$^+$ and 680.2 (27%) [**2b** + K]$^+$.

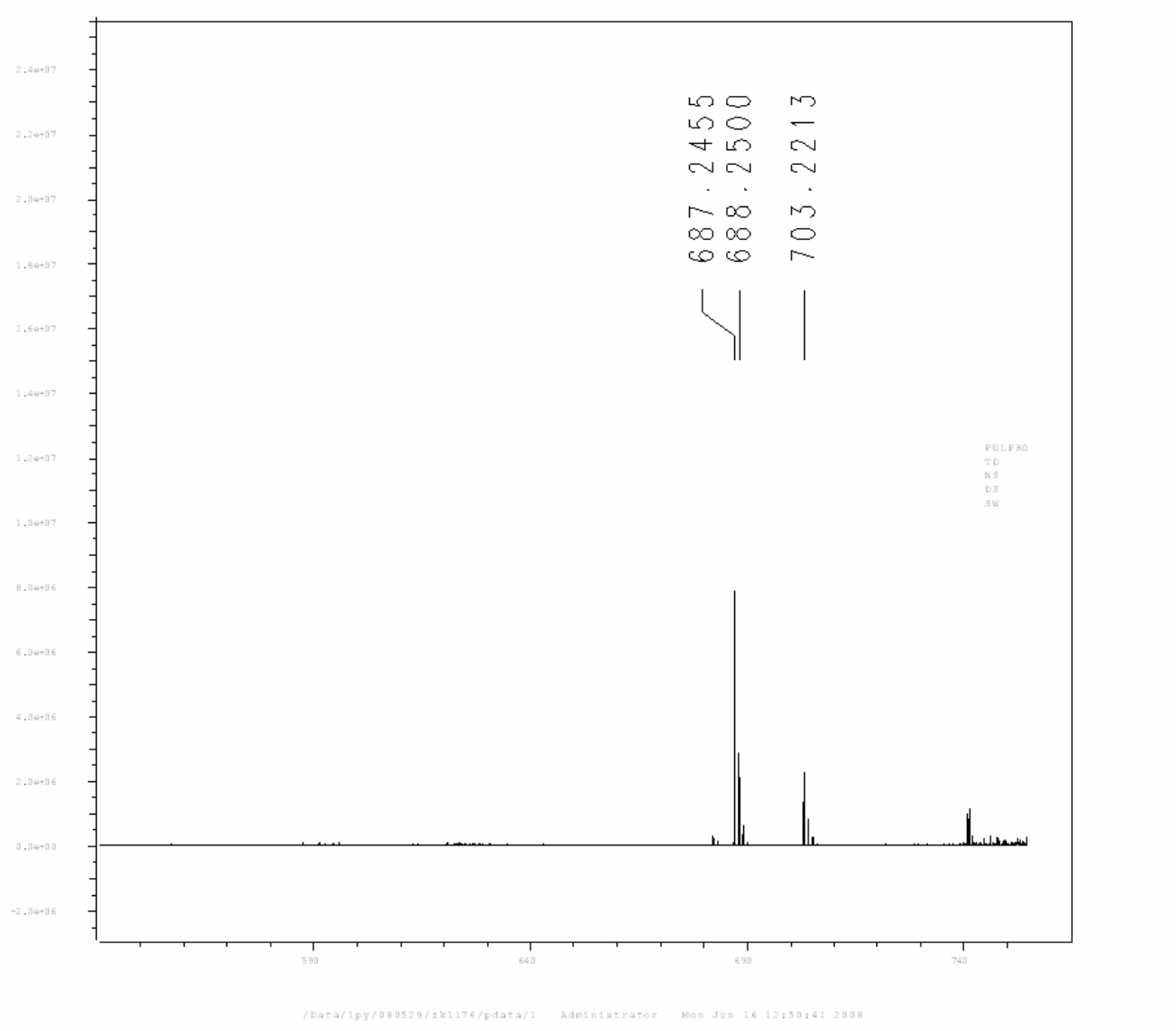

Fig. S31. HR-ESI$^+$-MS of **2c** in acetonitrile/methanol. Assignment of main peaks: *m*/*z* calcd for [**2c** + Na]$^+$ $C_{33}H_{39}N_2O_9F_3Na$, 687.2505, found 687.2455, error –7.3 ppm and calcd for [**2c** + K]$^+$ $C_{33}H_{39}N_2O_9F_3K$ 703.2245, found 703.2213, error –4.6 ppm.

*10. ESI-MS spectra of equimolar acetonitrile solutions of **2a** with **3b** or **3c***

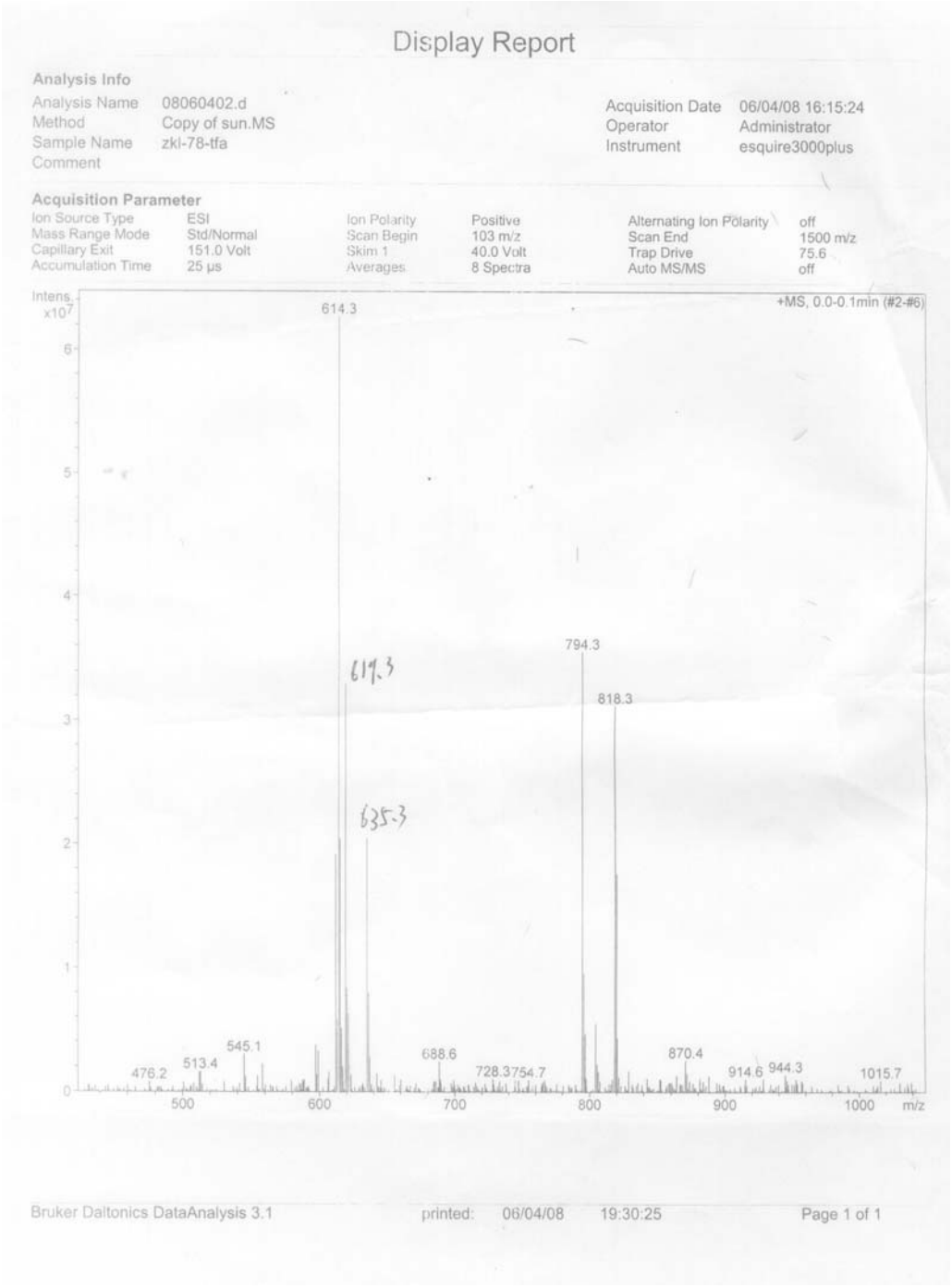

Fig. S32. ESI^+-MS of a equimolar acetonitile solution of **2a** and **3b**. Assignment of main peaks: *m*/*z* 794.3 (60%) $[\mathbf{2a}\bullet\mathbf{3b} - CF_3COO]^+$, 614.3 (100%) $[\mathbf{2a} + NH_4]^+$, 619.3 (52%) $[\mathbf{2a} + Na]^+$ and 635.2 (35%) $[\mathbf{2a} + K]^+$.

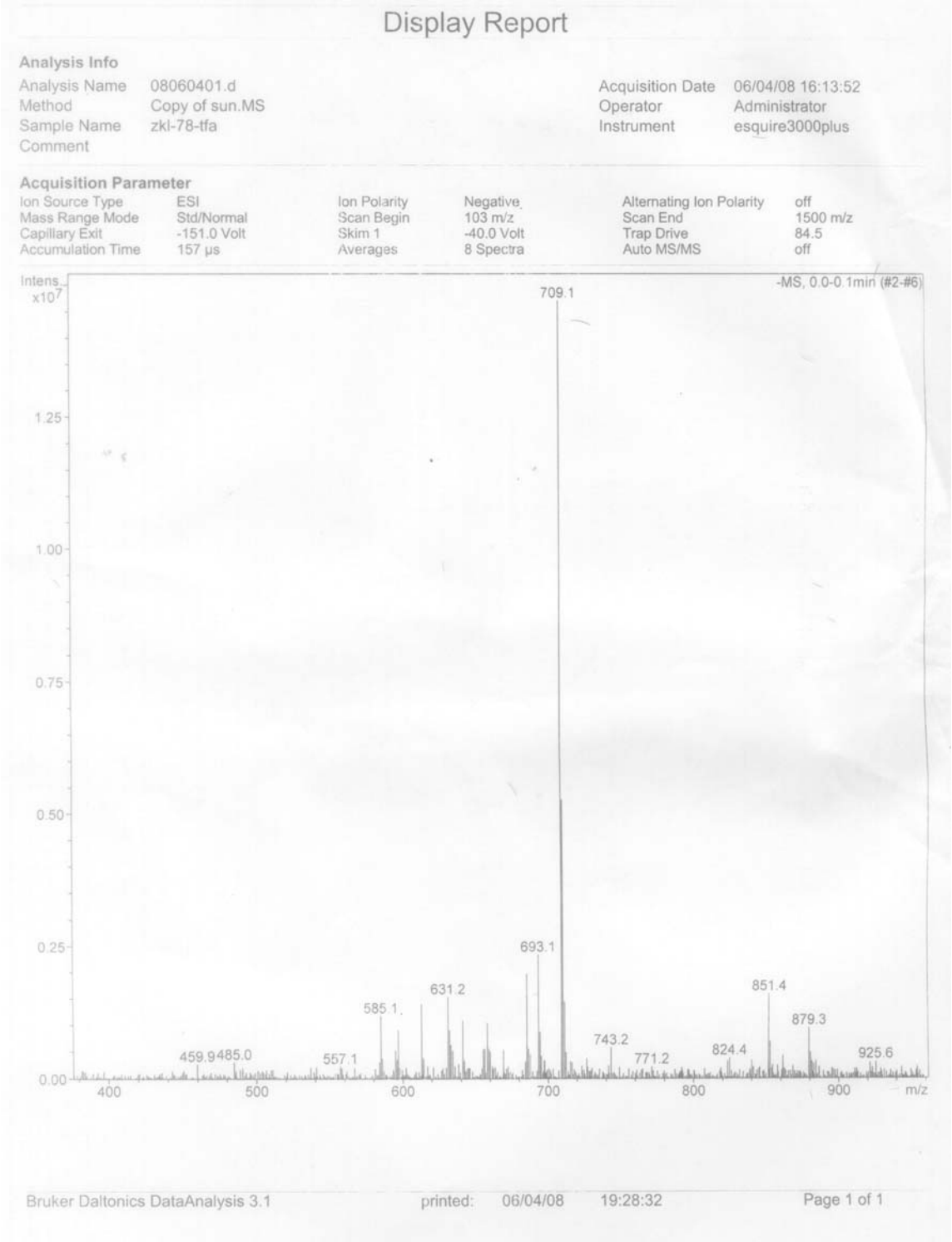

Fig. S33. ESI$^-$-MS of a equimolar acetonitile solution of **2a** and **3b**. Assignment of main peaks: 709.1 (100%) [**2a** + CF_3COO]$^-$.

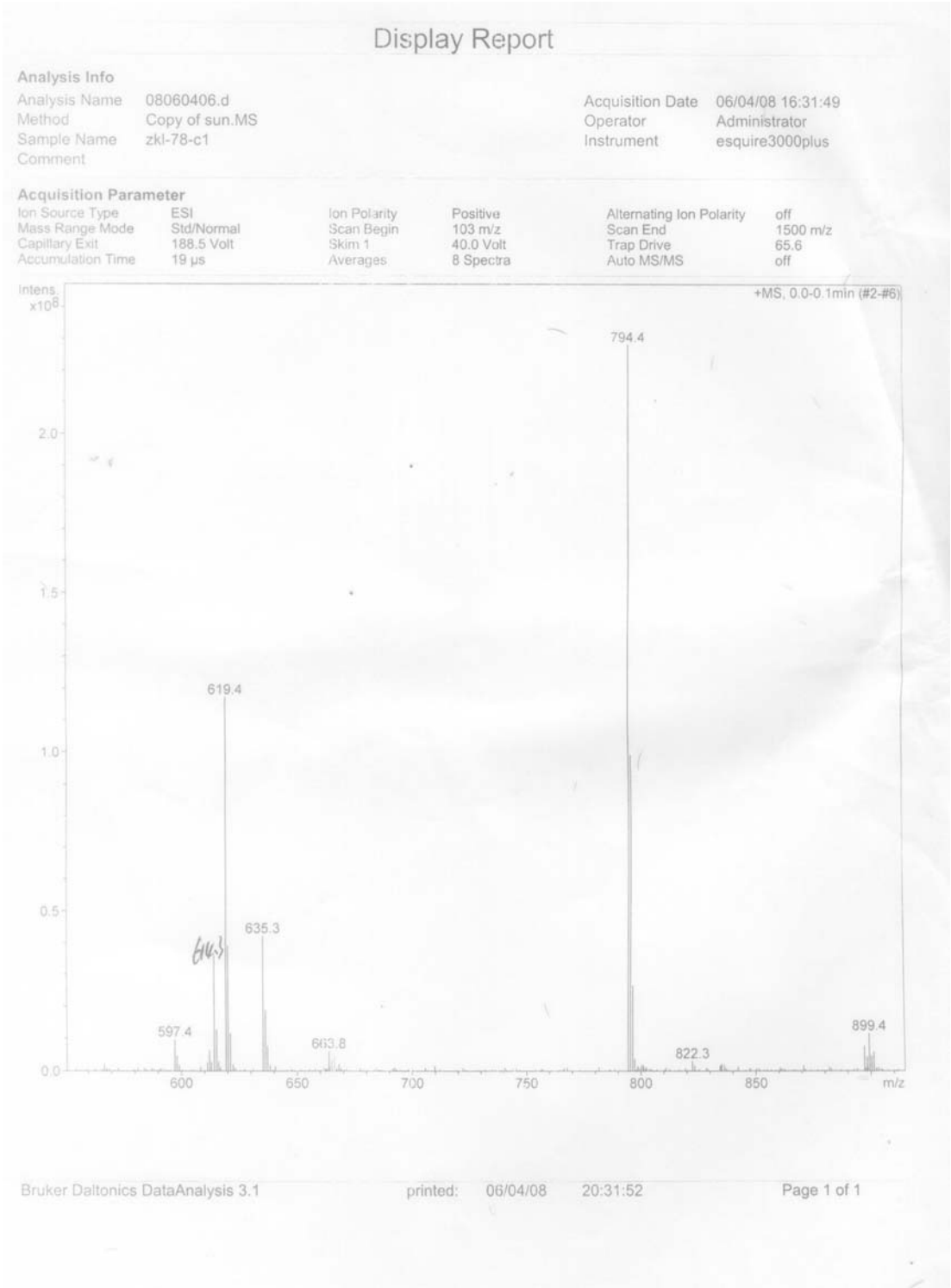

Fig. S34. ESI$^+$-MS of a equimolar acetonitile solution of **2a** and **3c**. Assignment of main peaks: *m*/*z* 794.3 (100%) [**2a•3b** – Cl]$^+$, 614.3 (17%) [**2a** + NH_4]$^+$, 619.3 (52%) [**2a** + Na]$^+$ and 635.2 (20%) [**2a** + K]$^+$.

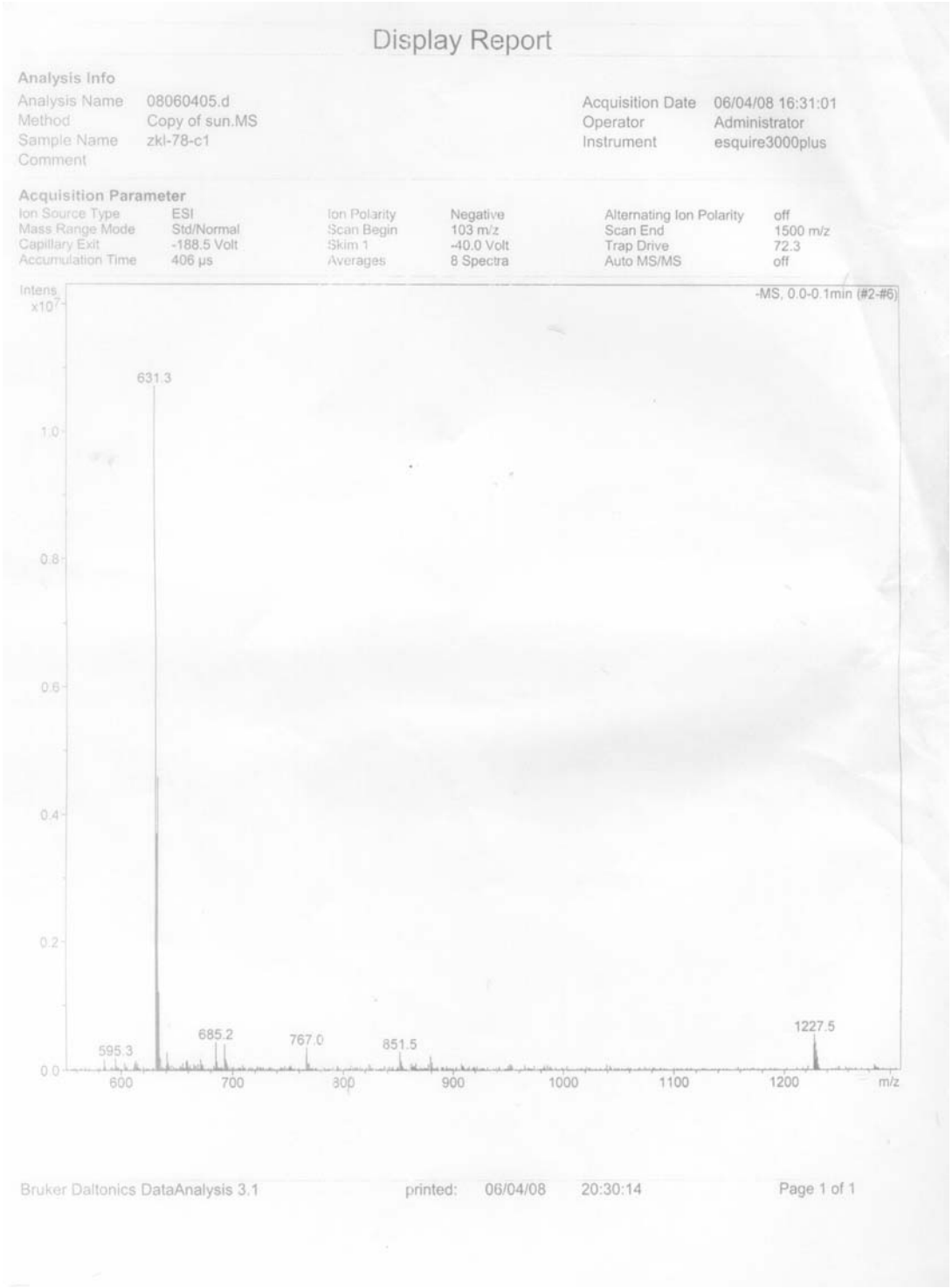

Fig. S35. ESI$^-$-MS of a equimolar acetonitile solution of **2a** and **3c**. Assignment of main peaks: 631.3 (100%) [**2a** + Cl]$^-$ and 1227.5 (10%) for [**2a** + **2a** + Cl]$^-$.

(S1) S. J. Loeb and A. D. Tramontozzi, *Org. Biomol. Chem*., 2005, **3**, 1393.

(S2) P. R. Ashton, E. J. T. Chrystal, P. Glink, T. S. Menzer, C. Schiavo, N. Spencer, J. F. Stoddart, P. A. Tasker, A. J. P. White and D. J. Williams, *Chem. Eur. J.*, 1996, **2**, 709.

(S3) J. W. Jones and H. W. Gibson, *J. Am. Chem. Soc.* , 2003, **125**, 7001.

(S4) H. W. Gibson, D. S. Nagvekar, N. Yamaguchi, F. Wang and S. W. Bryant, *J. Org. Chem.*, 1997, **62**, 4798.