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Aromatic Oligureas as Hosts for Anions and Cations

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Supplementary Information

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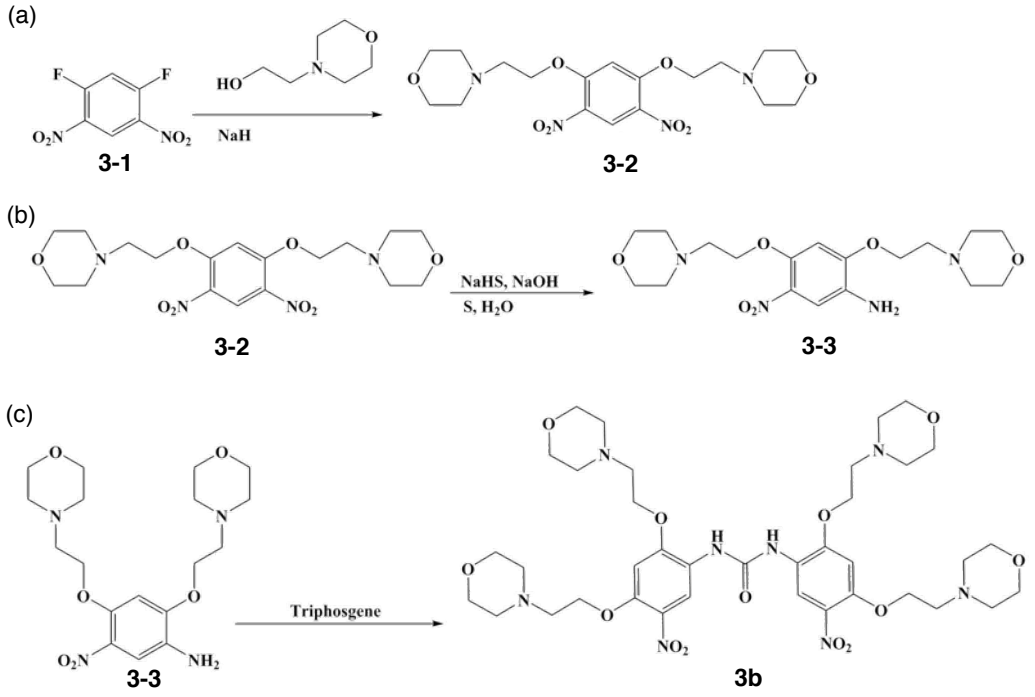
1. Synthesis

Compound 3a: This is a known compound that was reported in the literature.[1] It was prepared by mixing *o*-anisidine with one equivalent of *o*-methoxyphenyl isocyanate in CH_2Cl_2. The product was precipitated by adding ethanol to the reaction mixture and recrystallized from ethanol. ^{1}H NMR (500 MHz, $CDCl_3$) δ8.13 (d, J = 7.2 Hz, 2H), 7.21 (s, 2H), 6.99 (dd, J = 11.7, 8.1 Hz, 4H), 6.88 (d, J = 7.4 Hz, 2H), 3.86 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ152.33, 148.14, 128.12, 122.84, 121.20, 119.64, 110.10, 55.67. MS (ESI) m/z Calcd. for $C_{15}H_{16}N_2O_3$: 272.1 (M^+), found 273.0 ($M+H^+$), 295.1 ($M+Na^+$), 566.9 ($2M+Na^+$).

Scheme S1.Synthesis of Compound **3b**.



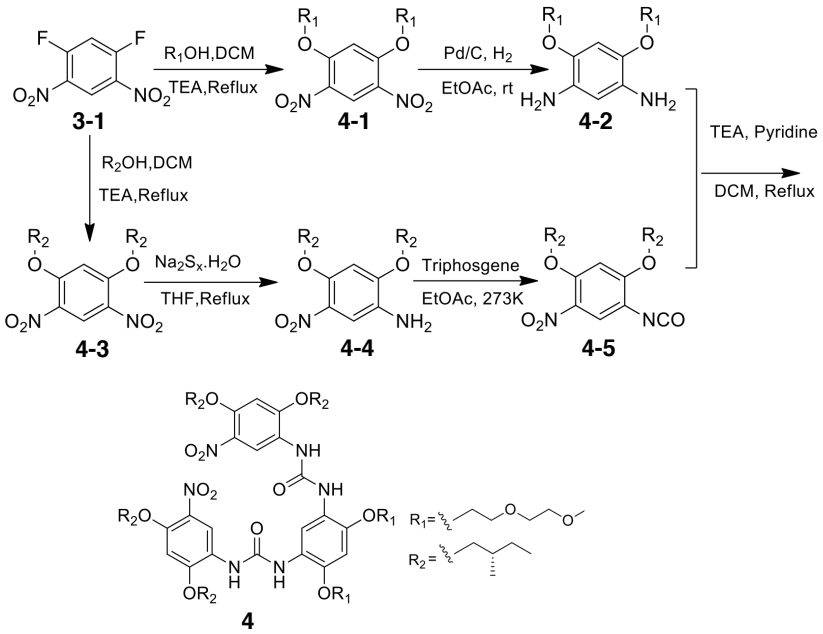
Compound 3-2: 4-(2-Hydroxyethyl)-morpholine (13. 29g, 103 mmol) was added to 100 mL tetrahydrofuran and cooled to 0 °C to which was added portion-wise 3 g of sodium hydride. After 5 mins, 1,3-Difluoro-4, 6-dinitrobenzene (**3-1**) (10g, 48.9 mmol) was dissolved in 22 mL tetrahydrofuran and added dropwise to the mixture. The cooling was removed after 30 minutes and the reaction was stirred at room temperature overnight. Tetrahydrofuran was removed under reduced pressure and the mixture was dissolved in methylene chloride and washed once with saturated sodium bicarbonate and dried over sodium sulfate. Removal of solvent and recrystallization in methanol afforded the tittle compound **3-2** as a red solid (10.84 g, 52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ8.85 – 8.71 (s, 1H), 6.66 (s, 1H), 4.30 (t, J = 5.5 Hz, 4H), 3.77 – 3.66 (m, 8H), 2.92 (t, J = 5.5 Hz, 4H), 2.68 – 2.56 (m, 8H). MS (ESI) m/z, Calcd for $C_{18}H_{26}N_4O_8$ (M^+) 428.18, Found 429.20 ($M + H^+$).

Compound 3-3: A polysulfide solution was prepared by heating a mixture of sodium hydrosulfide hydrate (11.1 g, NaSH.xH2O), sulfur (1.80 g, 56.2 mmol) and sodium hydroxide (3.3 g, 83.3 mmol) in 140 mL of water first at 90 °C for 1 hour and then being allowed to cool down to room temperature. The resulting clear, faint-orange solution was added to compound **3-2** (10 g, 23.5 mmol) and reflux at 90 °C for 3 hours. The reaction mixture was allowed to cool to room

temperature and all precipitate was removed by vacuum filtration. The filtrate was extracted with methylene chloride (100 mL x 3) and dried on sodium sulfate. Methylene chloride was concentrated under reduced pressure to a dark oil which was purified by flash column chromatography silica gel (1% TEA, 2% methanol in Chloroform) to afford the title product **3-3** as a red oil (8.9g, 95.8%).^{1}H NMR (300 MHz, $CDCl_3$) δ7.36 (s, 1H), 6.54 (s, 1H), 4.17 (q, J = 5.7 Hz, 4H), 3.75 (dd, J = 15.1, 10.6 Hz, 8H), 2.97 – 2.78 (m, 8H), 2.60 (ddd, J = 9.4, 8.2, 5.8 Hz, 8H. MS (ESI) m/z, Calcd for $C_{18}H_{28}N_4O_6$ (M+) 396.20, Found 397.2 (M+H+).

Compound 3b: A mixture of **3-3** (0.5g, 12.6 mmol) in 6 mL methylene chloride was added drop-wisely at room temperature with stirring to a solution of triphosgene (0.374 g, 1.26 mmol) in 20 mL methylene chloride. The reaction was stirred for 3 hours and methylene chloride was removed under reduced pressure. The crude solid was washed with diethyl ether and filtered to afford the title compound **3b** as a shining yellow solid (0.55 g, 53%). ^{1}H NMR (300 MHz, DMSO-d_6) δ8.76 (s, 2H), 8.64 (s, 2H), 6.99 (s, 2H), 4.32 (dt, J = 22.4, 5.8 Hz, 8H), 3.63 – 3.46 (m, 16H), 2.95 – 2.68 (m, 8H), 2.48 (Hidden, 16H). MS (ESI) m/z, Calcd for $C_{37}H_{54}N_8O_{13}$ (M^+) 818.3810, Found 819.2925 ($M + H^+$).

Scheme S2. Synthesis of Compound **4**.



Compound 4-1: Compound **3-1** (12 g, 58.5 mmol), diethylene glycol monomethyl ether(22 g, 176 mmol), and triethylamine (18 g, 176 mmol) were mixed and dissolved in CH_2Cl_2 (80 mL) at room temperature. The reaction mixture was heated at reflux for 12 h. The progress of the reaction was monitored with TLC (silica gel plate, petroleum ether/acetone（v/v）= 10:4，R_f = 0.3). After removing solving by evaporation，the remaining residue was purified with flash column chromatography (petroleum ether/acetone（v/v）= 4:1). The purified **4-1** was obtained as a yellow oil (19 g，82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 6.89 (s, 1H), 4.49 – 4.32 (m, 4H), 4.03 – 3.92 (m, 4H), 3.78 – 3.73 (m, 4H), 3.59 – 3.54 (m, 4H), 3.38 (d, *J* = 4.7 Hz, 6H); ^{13}C NMR (101MHz, $CDCl_3$) δ 157.79, 131.35, 125.53, 100.66, 71.89, 71.10, 70.62, 69.26, 58.99; MS (ESI) m/z, 404.1(M^+), found 405.0 ($M + H$)$^+$.

Compound 4-2: Compound **4-1** (3 g，7.4 mmol) was mixed with Pd/C (10%) (300 mg) in ethyl acetate (70 mL) at room temperature. The reaction flask was evacuated and flashed with hydrogen a few times. The reaction mixture was stirred at room temperature for 12 h with its progress being monitored with TLC (silica gel plate, petroleum ether/acetone (v/v) = 10:6，R_f = 0.2). The reaction mixture was then acidified by adding HCl dissolved in methanol. After removing Pd/C by filtration, removal of solvent gave greyish white solid (3.2 g, 91%). ^{1}H NMR (400 MHz, DMSO) δ9.65 (s, 4H), 7.39 (s, 1H), 7.08 (s, 1H), 4.40 – 4.14 (m, 4H), 3.92 – 3.70 (m, 4H), 3.70 – 3.54 (m, 4H), 3.54 – 3.37 (m, 4H), 3.25 (s, 6H).^{13}C NMR (101 MHz, MeOD) δ 157.41, 123.16, 116.40, 104.31, 75.37, 73.87, 73.19, 72.84, 61.69.

Compound 4-3: This compound was prepared based on the same procedures for preparing compound **4-2** by treating **3-1** with (*S*)-2-methylbutanol. ^{1}H NMR (400 MHz, $CDCl_3$): δ8.81 (s, 1H), 6.56 (s, 1H), 3.93 (d, *J* = 6.1 Hz, 6H), 2.09 – 1.90 (m, 2H), 1.60 – 1.46 (m, 4H), 1.15 (d, *J* = 6.5 Hz, 6H), 0.97 (t, *J* = 6.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 156.21, 134.80, 125.48, 98.85, 73.17, 34.73, 25.81, 16.26, 11.50. MS (ESI) m/z, calcd. for $C_{16}H_{24}N_2O_6$ 340.1 (M^+), found 341.1 ($[M + H]^+$).

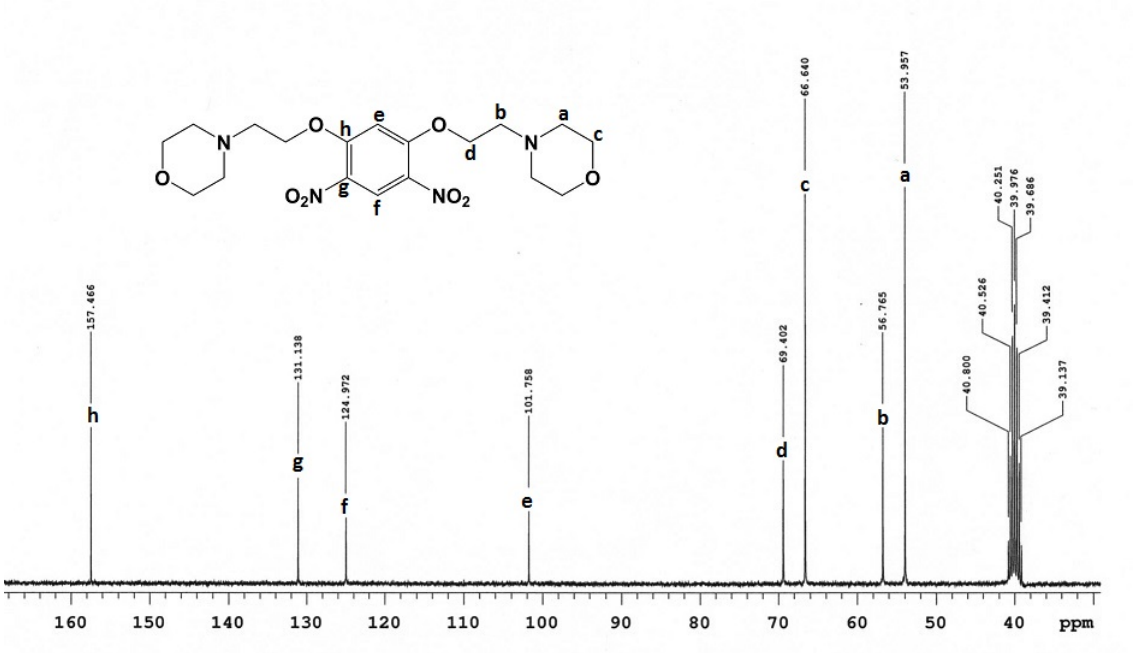
Compound 4-4: The mixture of sodium hydrosulfide hydrate ($NaS{\cdot}9H_2O$, 10.5 g, 44 mmol) and sulfur (1.44 g, 44 mmol) dissolved in water (50 mL), was heated under reflux for 30 min and then poured into a solution of **4-3** (9.67g, 30 mmol) dissolved in diethylene glycol dimethyl ether (120 mL). The reaction mixture was heated under reflux for 12h with its progress being monitored with TLC (silica gel plate, petroleum ether/acetone (v/v) = =10:1，R_f = 0.3). Upon completion of reaction, the solvent was removed by evaporation. The remaining residue was purified with column chromatography (silica, silica gel plate, petroleum ether/acetone (v/v) =10:1). The product 4-4 was obtained as a yellow oil (55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ7.42 (s, 1H), 6.46 (s, 1H), 3.94-3.81 (m, 4H), 2.00-1.88 (m, 2H), 1.65-1.53(m, 2H), 1.37-1.26(m, 2H), 1.08-1.05(m, 6H),1.00-0.94(m, 6H) ^{13}C NMR (101 MHz, $CDCl_3$): δ151.75, 148.02, 131.57, 128.48, 111.15, 98.41, 74.92, 73.16, 34.39, 34.13, 25.60, 25.44, 16.07. MS (ESI) m/z, calcd. for $C_{16}H_{26}N_2O_4$ 310.2(M^+), found 311.3 ($[M+H]^+$).

Compound 4-5: A solution of compound **4-4** (0.8g, 2.6 mmol) dissolved in ethyl acetate (60 mL) was cooled in an ice bath, to which triphosgene (0.4g, 0.13 mmol) dissolved in ethyl acetate was added dropwise. The reaction was monitored with TLC (silica gel plate, petroleum ether/acetone (v/v) = 10:1，R_f = 0.4). The reaction solution was then washed with saturated $NaHCO_3$ and then dried with anhydrous Na_2SO_4. Removing solvent led to **4-5** that was directly used for the next step.

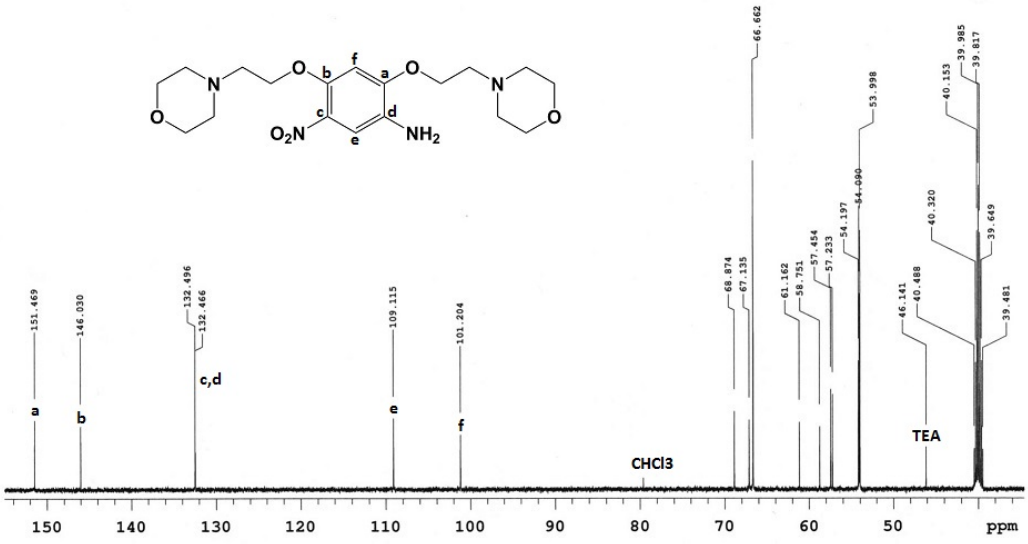
Compound 4：To the solution of compound **4-2** (750 mg, 2 mmol) dissolved in CH_2Cl_2 (50 mL)，triethylamine (606 mg, 6 mmol) and pyridine (475 mg, 6 mmol) were added under nitrogen，followed by the addition of **4-5** (2 g, 6 mmol). The reaction mixture was heated under reflux for 12 h. Removing solvent led to a residue that was subjected to column chromatography (silica gel, petroleum ether/acetone (v/v) = 2:1). Compound 4 was obtained as a yellow solid (1.4g，80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ8.76 (s, 2H), 8.33(s, 1H), 7.43(s, 2H), 7.40(s, 2H), 6.54(s, 1H), 6.43(s, 2H), 4.08 (t, *J*=4.2Hz, 4H), 3.94-3.87(m, 4H), 3.83-3.76(m, 8H), 3.72-3.70(m, 4H), 3.60-3.58(m, 4H), 3.36(s, 6H), 1.94-1.87(m, 4H), 1.63-1.47(m, 4H), 1.33-1.19(m, 4H), 1.05-0.90(m, 24H).^{13}C NMR (101 MHz, $CDCl_3$) δ153.30, 152.89, 149.83, 145.35, 131.60, 122.01, 116.71, 97.51, 74.72, 74.21, 71.66, 70.22, 69.31, 68.90, 58.76, 34.79, 34.28, 25.91, 16.41, 11.33, 11.14. ESI-MS (m/z) calcd. For $C_{50}H_{76}N_6O_{16}$ 1016.5318 (M^+), found 1017.3403 ($M + H^+$), 1039.5288 ($M + Na^+$)

2. NMR and MS Spectra

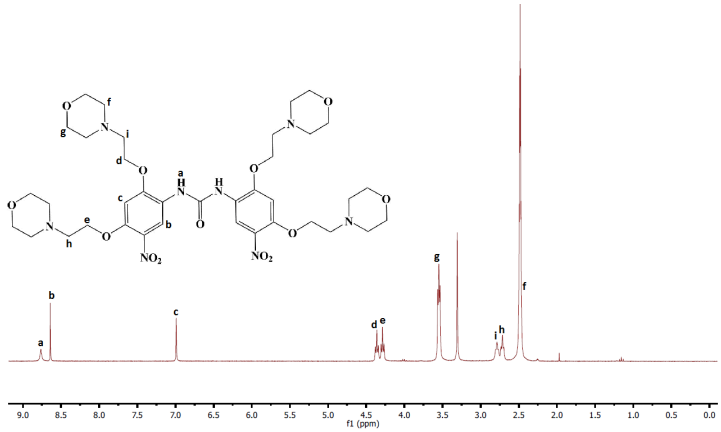
^{13}C NMR spectrum of **3-2** (75 MHz, DMSO-d_6, 298K)



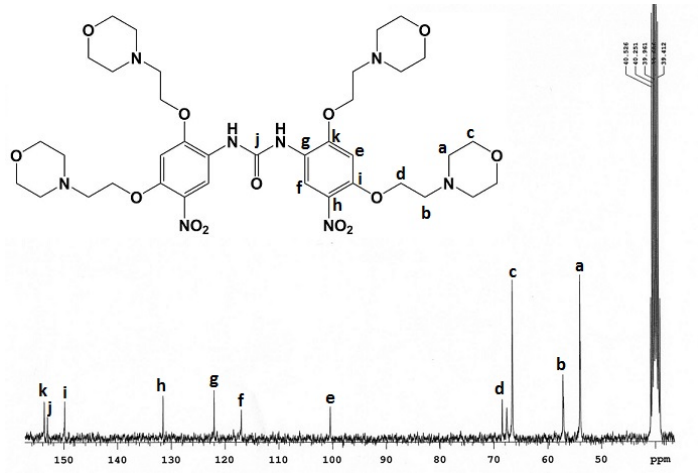
^{13}C NMR spectrum of **3-3** (75 MHz, DMSO-d_6, 298K)



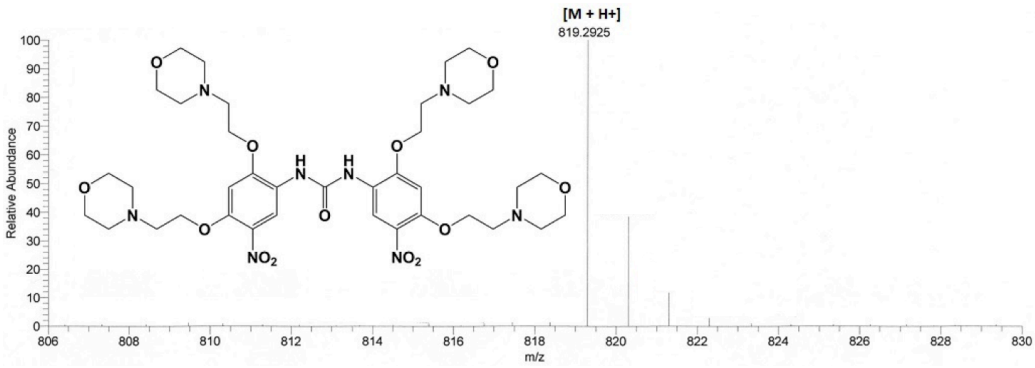
^{1}H NMR spectrum of **3b** (300 MHz, DMSO-d_6, 298K)



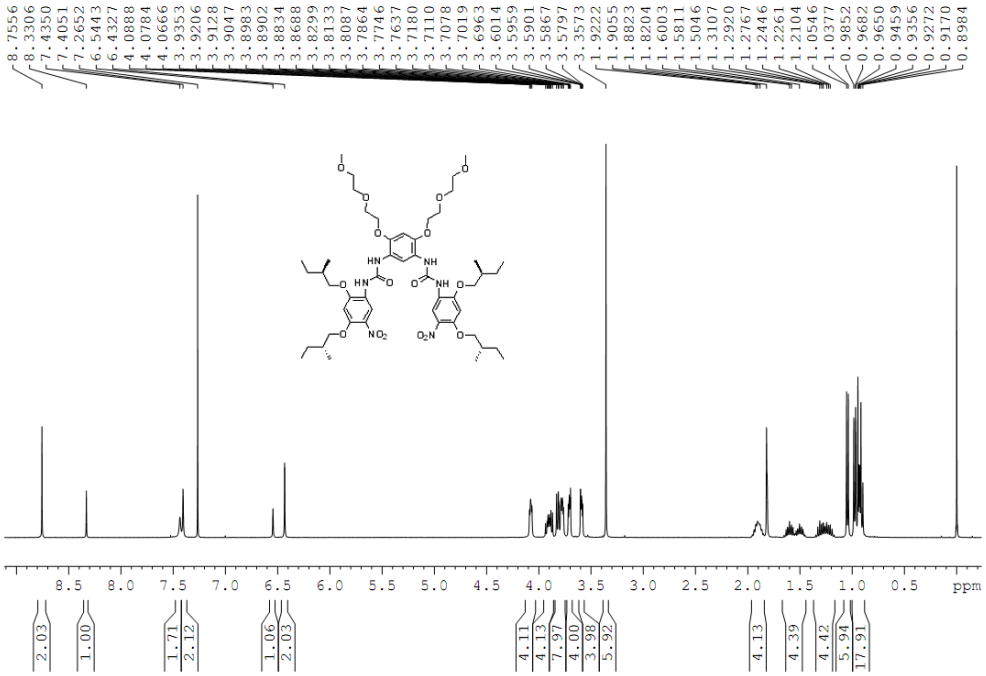
^{13}C NMR spectrum of **3b** (75 MHz, DMSO-d_6, 298K)



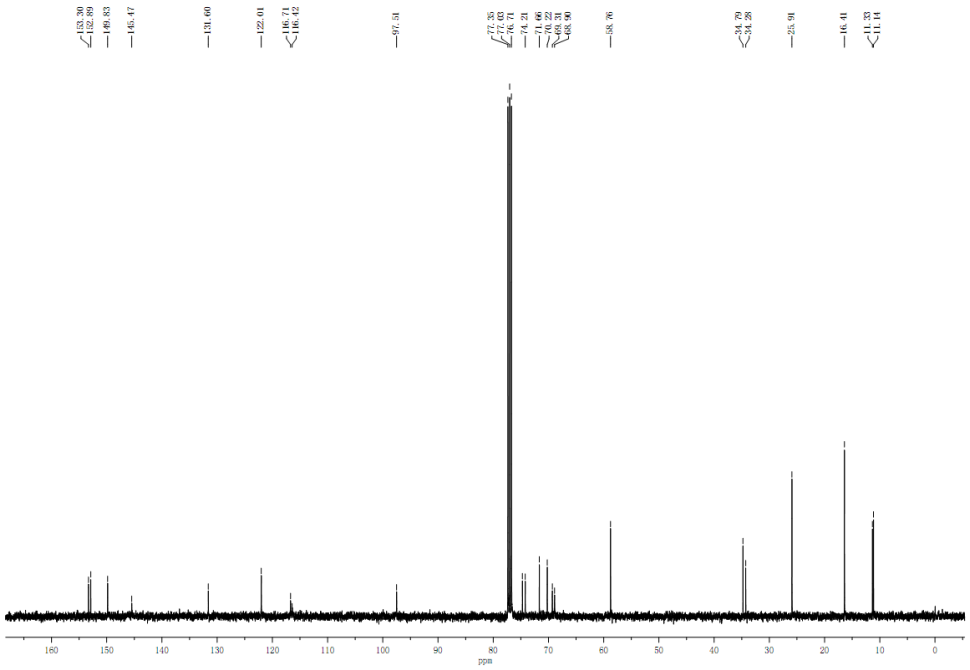
High-resolution ESI spectrum of **3b**.



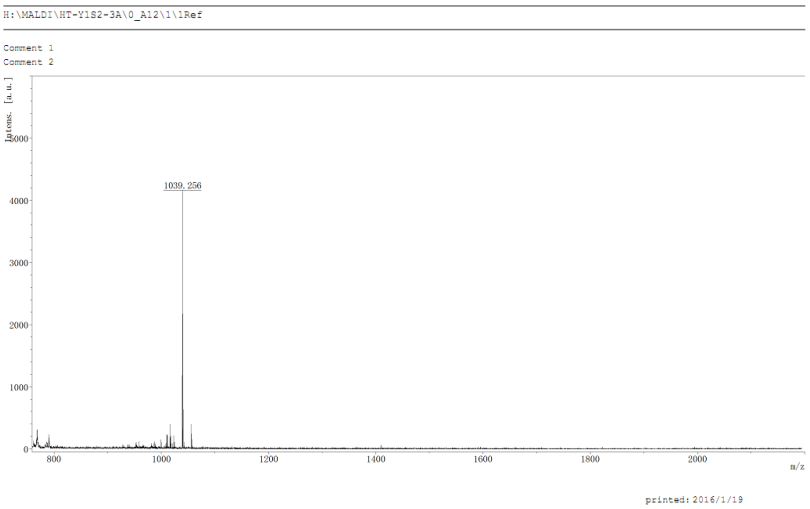
^{1}H NMR spectrum of **4** (400 MHz, $CDCl_3$, 298K)



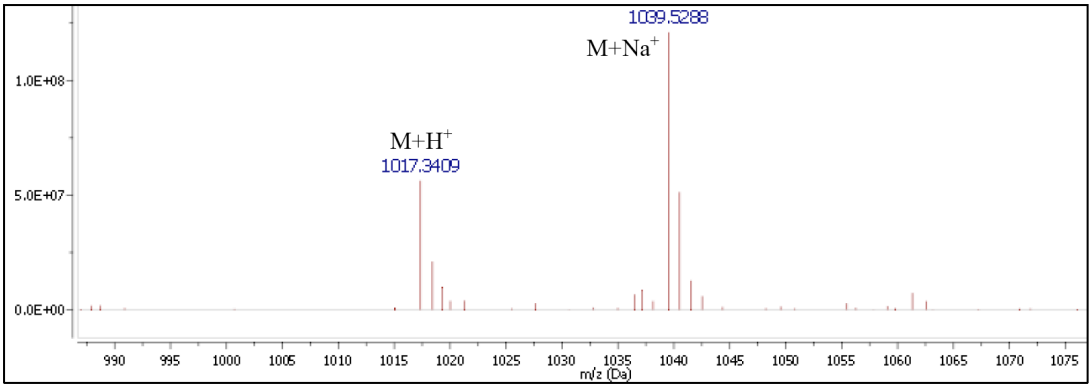
^{13}C NMR spectrum of **4** (101 MHz, $CDCl_3$, 298K)



Mass spectrum (MALDI-TOF) of **4**



Mass spectrum (ESI) of **4**



3. Supplementary Figures S1-S6

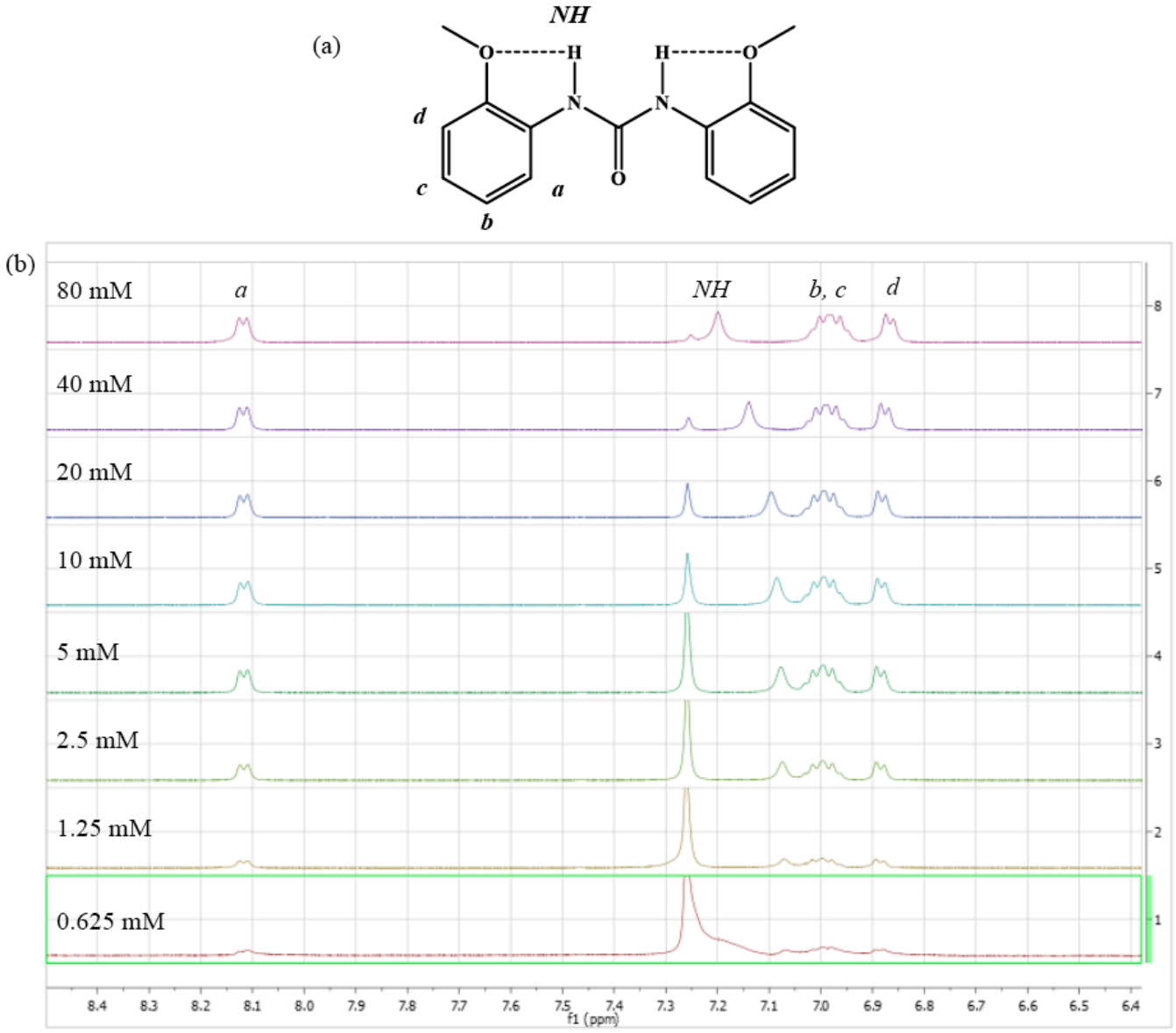


Figure S1. (a) Structure of **3a**. (b) 1D ^{1}H NMR dilution study of **3a** in $CDCl_3$ (500 MHz, 298 K).

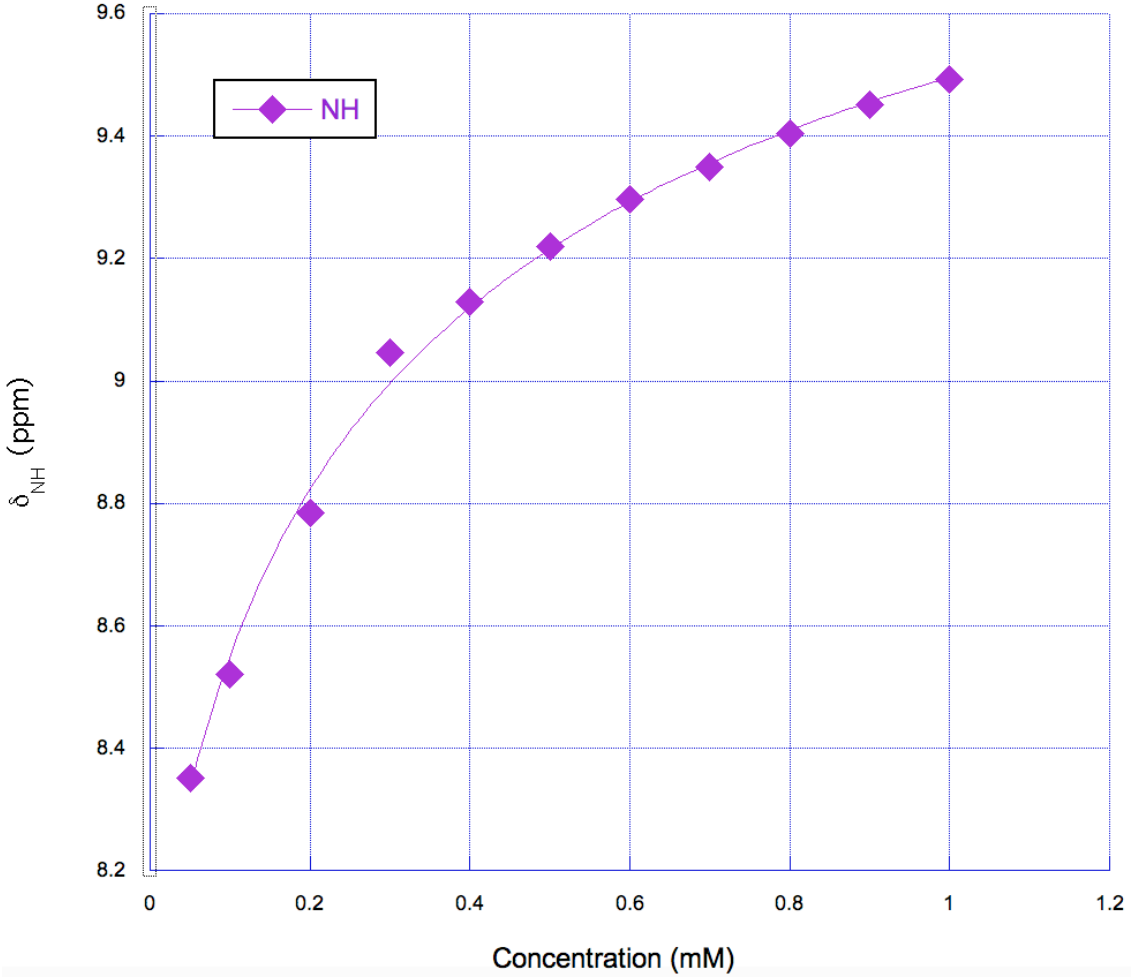


Figure S2. (a) Plots of the chemical shifts of the NH signals of **3b** vs concentrations in the presence one equivalent of $Et_4N^+Ac^-$.

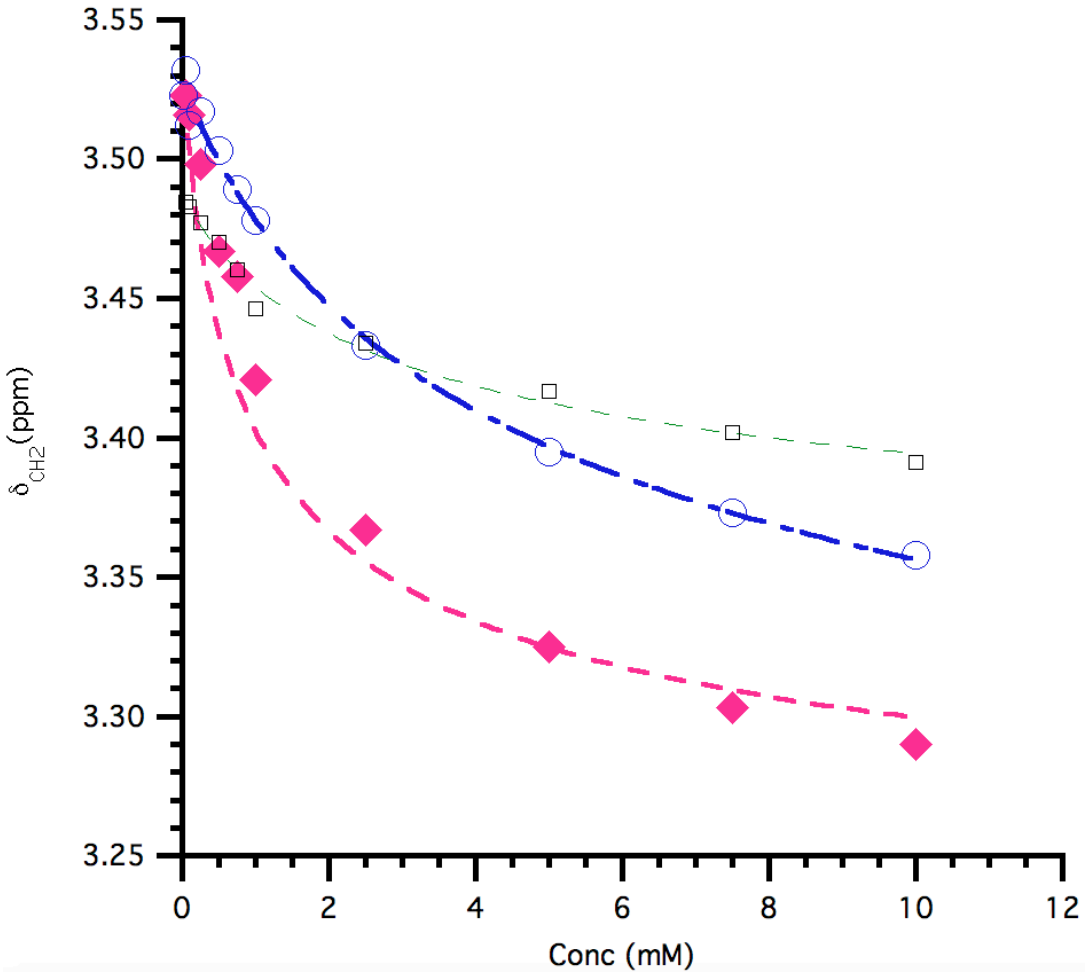
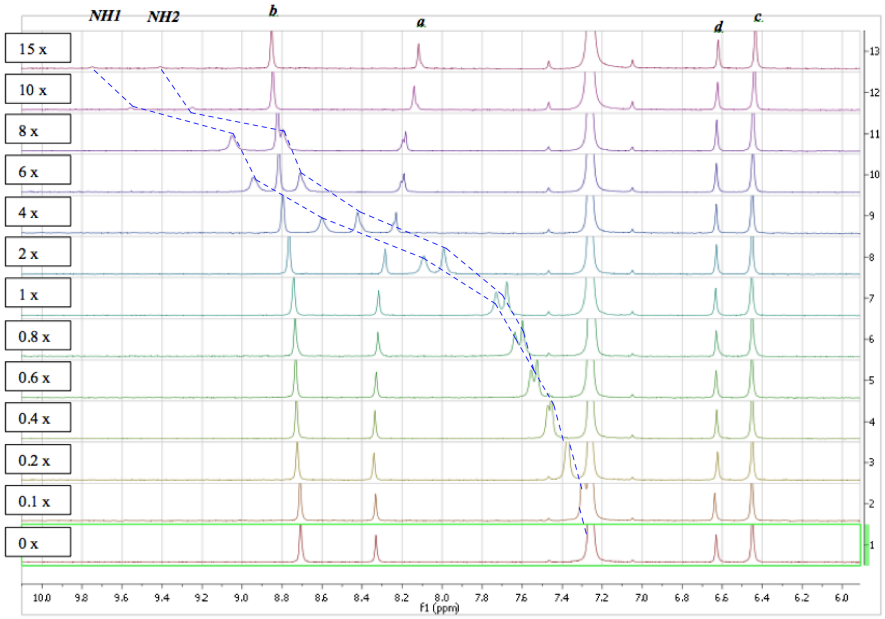


Figure S3. (a) Plots of the chemical shifts of the CH_2 signals of $Et_4N^+Ac^-$ (red), $Et_4N^+Cl^-$ (blue), or $Et_4N^+I^-$ (green) with one equivalent of **4** vs concentrations.

(a)



(b)

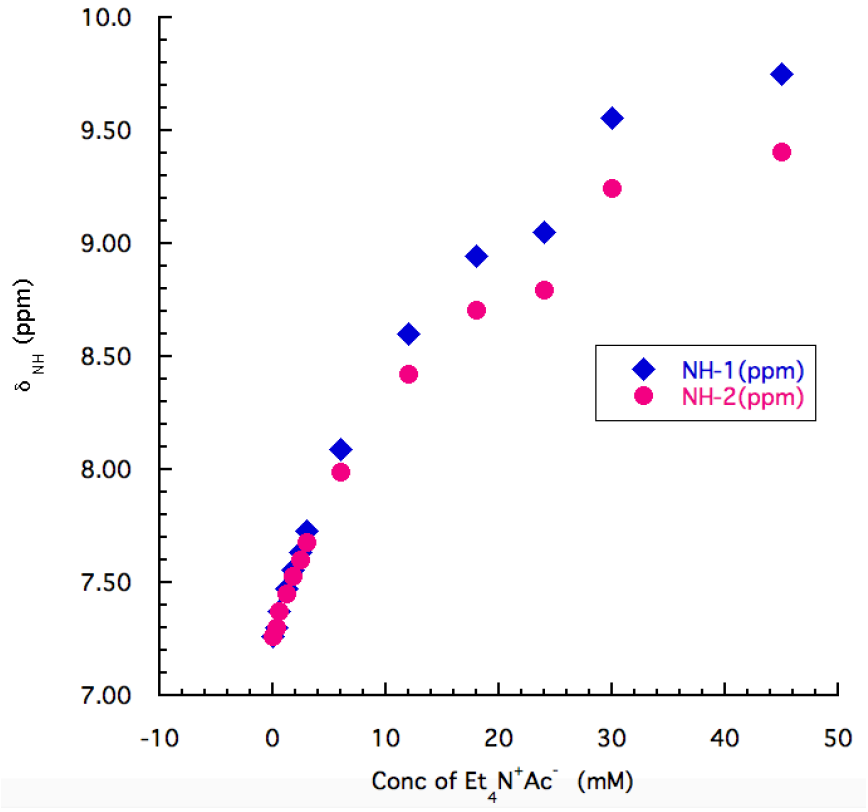


Figure S4. (a) Partial ^{1}H NMR spectra (aromatic and NH region) of 3 mM of **4** and 0-15 equivalents of $Et_4N^+Ac^-$ in $CDCl_3$ (500 MHz, 298 K). The two urea NH signals are traced with blue dashed lines. (b) Plots of the chemical shifts of the two urea signals vs the concentration of $Et_4N^+Ac^-$.

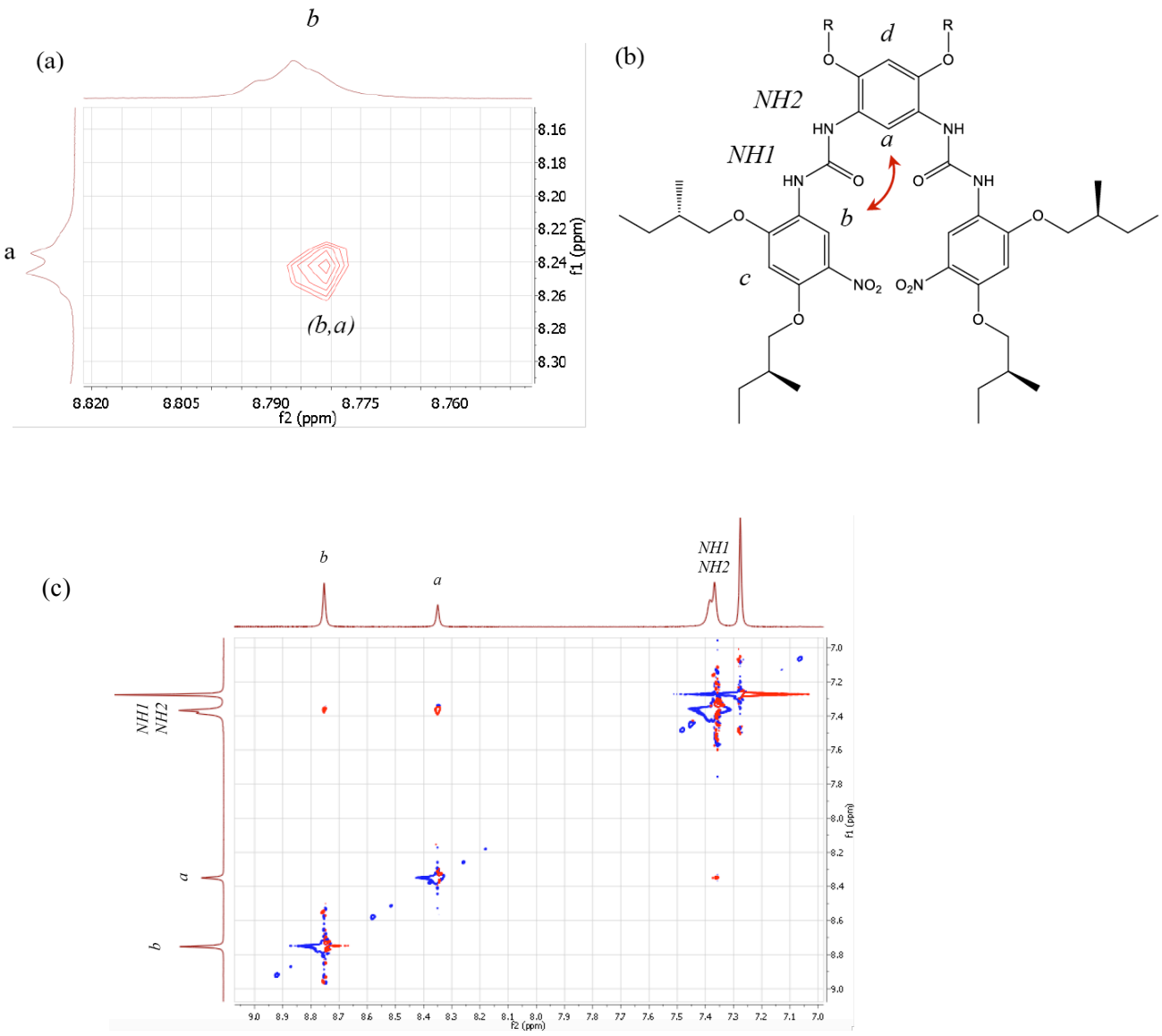


Figure S5. (a) Partial ROESY spectrum of the 1:1 mixture (5 mM) of **4** and $Et_4N^+Ac^-$ in $CDCl_3$ (500 MHz, 298 K, mixing time: 0.3s); (b) Structural assignment of **4** including detected ROE between protons a and b with the 1:1 mixture; (c) Partial ROESY spectrum of **4** alone in $CDCl_3$ under identical conditions (500 MHz, 298 K, mixing time: 0.3s).

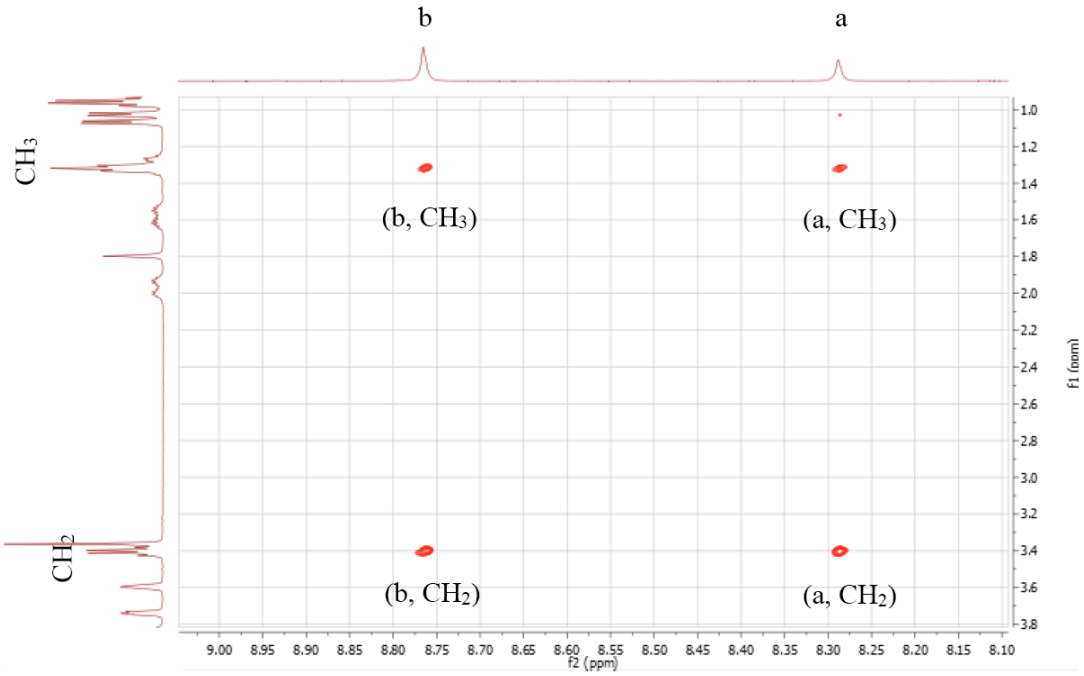
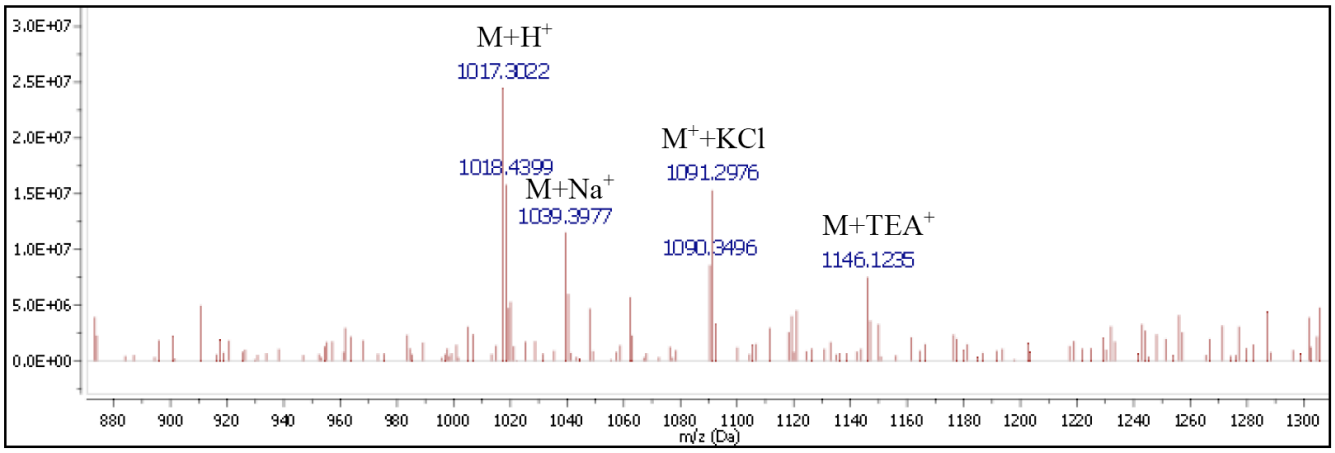


Figure S6. (a) Partial ROESY spectrum of the 1:1 mixture (5 mM) of **4** and $Et_4N^+Cl^-$ in $CDCl_3$ (500 MHz, 298 K, mixing time: 0.3s).

(a)



(b)

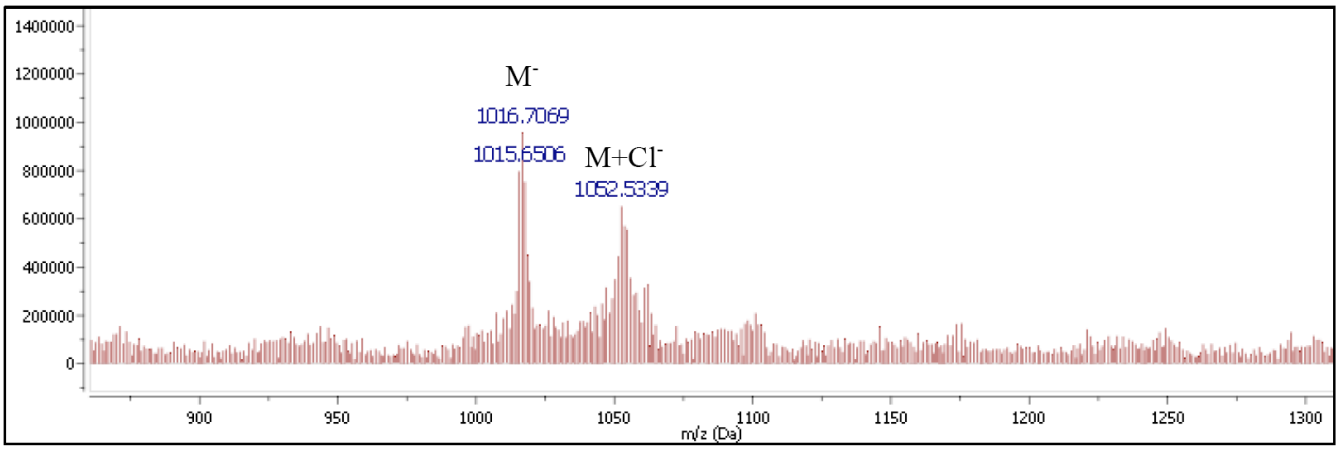


Figure S7. (a) Positive-ion and (b) Negative-ion ESI-MS spectra of **4** with 1 equivalent of $Et_4N^+Cl^-$ (or TEA^+Cl^-).

4. Equations used for Nonlinear Regression Analysis

4.1 Basic equations

• For a binding equilibrium involving a receptor (R, or host) and a substrate (S, or guest) and the corresponding complex R•S:

$$R + S \rightleftharpoons R{\bullet}S$$

• The observed chemical shift of protons on the host (R) or guest (S) can be expressed as a function of S_0, R_0, $\Delta\delta$, and δ_s with Equation 1:[2]

$$\delta_{obs} = \delta_s + \frac{\Delta\delta}{2S_0}\left[K_d + R_0 + S_0 - \sqrt{(K_d + R_0 + S_0)^2 - 4R_0S_0}\right] \quad (1)$$

S_0: Initial substrate (S) concentration
R_0: Initial receptor (R) concentration
K_d: dissociation constatnt
δ_{obs} : observed chemical shift of the monitored proton(s) of the receptor in the complex
δ_s: chemical shift of the montiored proton(s) of free (unbound) receptor
$\Delta\delta$: chemical shift of complex - chemical shift of free receptor

• Given that K_d is related to the associtation constant (K_a), Equation 1 can converted into Equation 2:

$$\delta_{obs} = \delta_s + \frac{\Delta\delta}{2S_0}\left[1/K_a + R_0 + S_0 - \sqrt{(1/K_a + R_0 + S_0)^2 - 4R_0S_0}\right] \quad (2)$$

4.2 Equations for fitting data from diluting a 1:1 mixture of a host and a guest

• For a 1:1 mixture of host (R) and guest (S), i.e., the 1:1 pair consisting of **3a** or **3b** with one of the salts, $[R_0] = [S_0] = [C_0]$, the expression for observed chemical shift of a proton of S as a function of R_0, S_0, (= C_0), $\Delta\delta$, and δ_s:

$$\delta_{obs} = \delta_s + \Delta\delta\left[1 + \frac{K_d}{2C_0} - \sqrt{\left(\frac{K_d}{2C_0}\right)^2 + \left(\frac{K_d}{C_0}\right)}\right] \quad (3)$$

or:

$$\delta_{obs} = \delta_s + \Delta\delta\left[1 + \frac{1}{2K_aC_0} - \sqrt{\left(\frac{1}{2K_aC_0}\right)^2 + \left(\frac{1}{2K_aC_0}\right)}\right] \quad (4)$$

• Equation 4 was used for fitting the concentration-dependent change of the urea ^{1}H NMR signals of compound **3** in the 1:1 mixture of **3a** or **3b** with one of the salts; or the CH_2 signal of Bu_4N^+ in the 1:1 mixture of **4** and one of the salts.

- For a 1:1 mixture of host (R) and guest (S) in which the "guest or substrate" has two binding sites, such as the two urea moieties of **4**, and the "host or receptor" has one binding sites such as one of the anions, $2[R_0] = [S_0] = 2[C_0]$, the expression for observed chemical shift of a proton of S as a function of R_0, S_0, $\Delta\delta$, and δ_S:

$$\delta_{obs} = \delta_s + \frac{\Delta\delta}{4C_0}\left[K_d + 3C_0 - \sqrt{(K_d + 3C_0)^2 - 8C_0^2} \right] \quad (5)$$

$$\delta_{obs} = \delta_s + \frac{\Delta\delta}{4C_0}\left[1/K_a + 3C_0 - \sqrt{(1/K_a + 3C_0)^2 - 8C_0^2} \right] \quad (6)$$

- Equation 6 was used for fitting the concentration-dependent change of the urea ^{1}H NMR signals of compound **4** in the 1:1 mixture of **4** with one of the salts.

- As detailed before,[2] diluting a 1:1mixture of a host and a guest is the favored method in systems that involve protons that undergo both binding interaction and potential deprotonation.

5. References

1. M. C. Etter, Z. Urbanczyk-Lipkowska, M. Zia-Ebrahimi and T. W. Panunto, *J. Am. Chem. Soc.* 1990, **112**, 8415.
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