Supporting Information for

5-(2-Pyrrolo)tetrazoles are simple, highly potent anion recognition elements

Rebecca J.M. Courtemanche, Thomas Pinter, and Fraser Hof*

University of Victoria, Department of Chemistry, Victoria, BC, V8W 3V6, Canada

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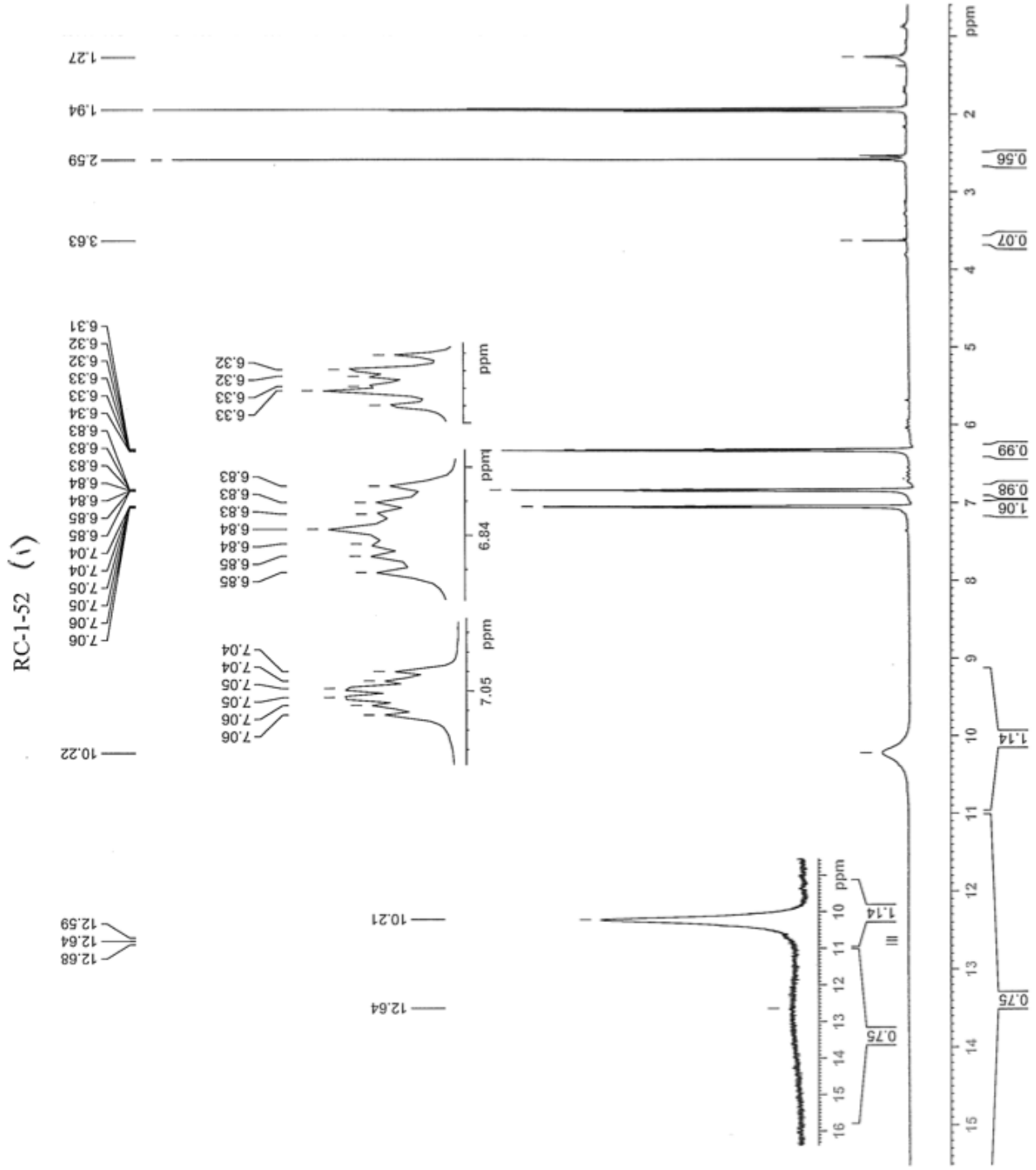
Experimental procedure — synthesis

General. 2-pyrrolo carbonitrile was used as purchased from Aldrich. 2,5-dicyanopyrrole was prepared from pyrrole by the methods reported in references 12 and 13. Melting points are uncorrected. Infrared spectra were recorded from thin films on KBr plates or KBr pellets. Proton (^{1}H) NMR spectra were recorded on 500 MHz or 300 MHz spectrometers, as indicated in each case. Carbon (^{13}C) NMR spectra were recorded 125 MHz or 75 MHz as indicated in each case. NMR spectra were referenced to signals for deuterated solvent bearing residual protons. High-resolution electrospray ionization mass spectra (HR-ESI-MS) were recorded on a Quadrupole-ToF mass spectrometer using 2,2'-bipyridine as a lockmass reference.

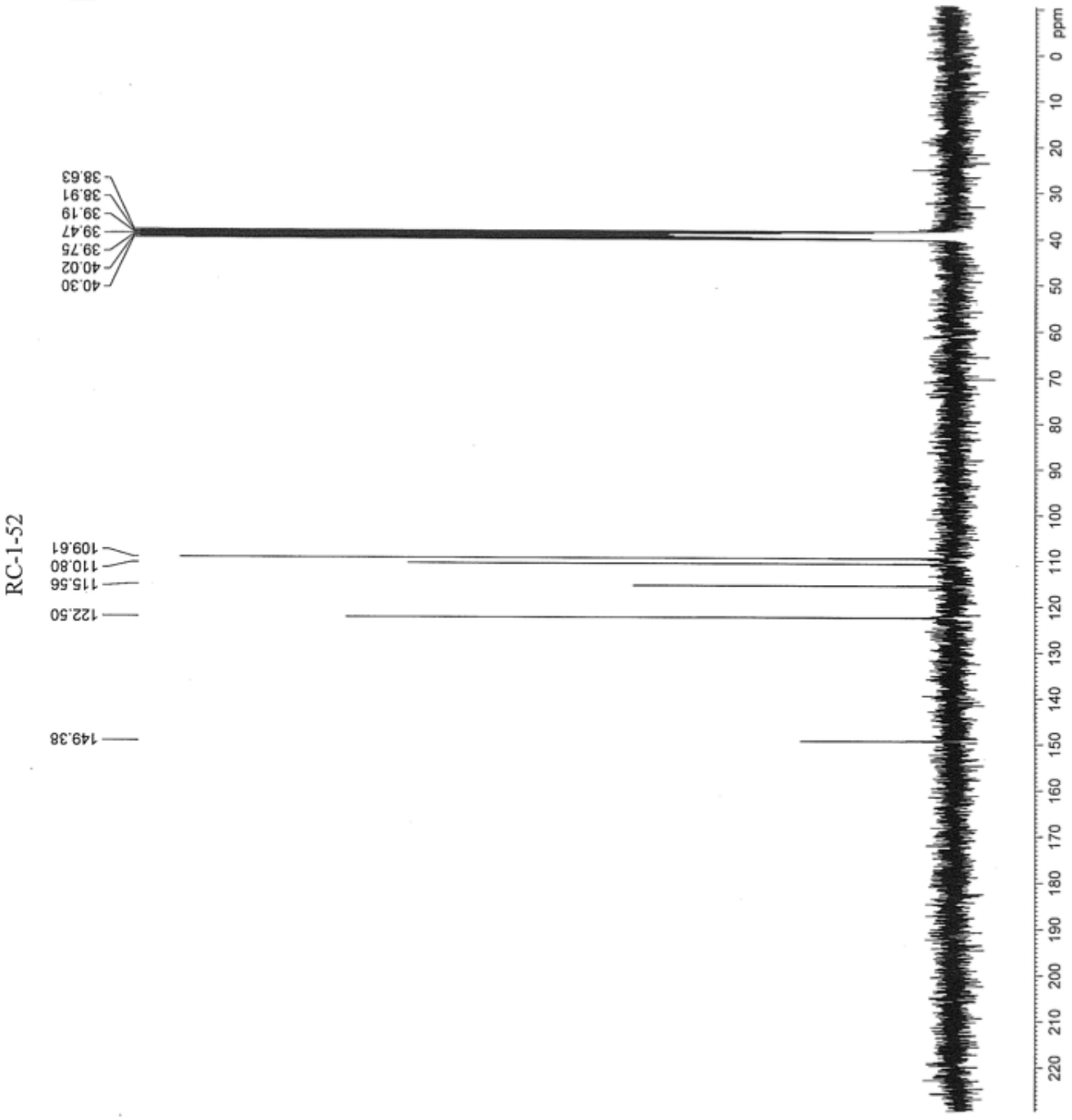
5-(2-Pyrrolo)tetrazole (1). Adapted from Ref. 11. 2-pyrrole carbonitrile (385 mg, 4.18 mmol), NaN_3 (541 mg, 8.32 mmol), and $Et_3N{\cdot}HCl$ (1.122 g, 8.15 mmol) were added to a 250 mL round bottom flask. Toluene (50 mL) was added and the reaction stirred and heated at reflux under N_2 overnight. The reaction was cooled to room temperature and the reaction mixture was extracted with H_2O (3 x 30 mL). Concentrated HCl was added dropwise to the aqueous layer until pH = 1 and a precipitate formed. The mixture was then extracted with ethyl acetate (3 x 30 mL), dried over $NaSO_4$ and concentrated to dryness on a rotary evaporator, which gave the product (357 mg, 63%) as a pale pink solid. Mp 223-225°C. IR: 3290*s*, 3157*w*, 3012*w*, 2909*w*, 2832*w*, 2752*w*, 2673*w*, 2578*w*, 2502*w*, 1790*w*, 1708*w*, 1636*s*, 1541*m*, 1469*s*, 1445*sh*, 1350*w*, 1268*w*, 1209*m*, 1129*s*, 1073*m*, 1054*s*, 1033*m*, 998*m*, 903*w*, 736*w*, 701*w*, 675*w*, 589*m*. ^{1}H NMR (CD_3CN, 300 MHz): δ 12.64 (*br s*, 1 H); 10.21 (*br s*, 1 H); 7.05 (*td*, *J* = 2.6, 1.5, 1 H); 6.84 (*ddd*, *J* = 3.8, 2.5, 1.4, 1 H); 6.33 (*dt*, *J* = 3.3, 2.5, 1 H). ^{13}C NMR (DMSO, 75 MHz): δ 149.4; 122.6; 115.6; 110.9; 109.7. HR-ESI-MS (*M*H$^+$, *m/z*): calc. for $C_5H_6N_5^+$ 136.0623, found 136.0623.

Pyrrole-2,5-bis(5-tetrazole) (2). 2,5-dicyanopyrrole (100 mg, 0.85 mmol), NaN_3 (222 mg, 3.42 mmol), $Et_3N{\cdot}HCl$ (470 mg, 3.42 mmol), and toluene (15 mL) were added to a round bottom flask. The reaction mixture was stirred under N_2 and heated at reflux for 24 h. After cooling to room temperature, the reaction mixture was extracted with H_2O (3 x 10 mL) and acidified to pH 1 with 1 M HCl to cause a precipitation of the product. Filtration isolated the pure product as a pale pink solid (113 mg, 65%). Mp 153°C (decomp.). IR: 3266*s*, 3137*w*, 3103*w*, 3053*w*, 2929*w*, 2817*w*, 2705*w*, 2588*w*, 1625*s*, 1527*m*, 1412*m*, 1325*w*, 1272*w*, 1255*w*, 1163*w*, 1152*w*, 1102*w*, 1074*w*, 1037*m*, 995*w*, 931*sh*, 909*m*, 811*m*, 741*m*, 696*w*, 618*w*, 433*w*. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 16.53 (*s*, 1 H); 12.81 (*s*, 1 H); 6.98 (*d*, J = 2.25, 1 H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 149.1; 119.9; 112.5. HR-ESI-MS (MH^+, *m/z*): calc. for $C_6H_6N_9^+$ 204.0746, found 204.0746.

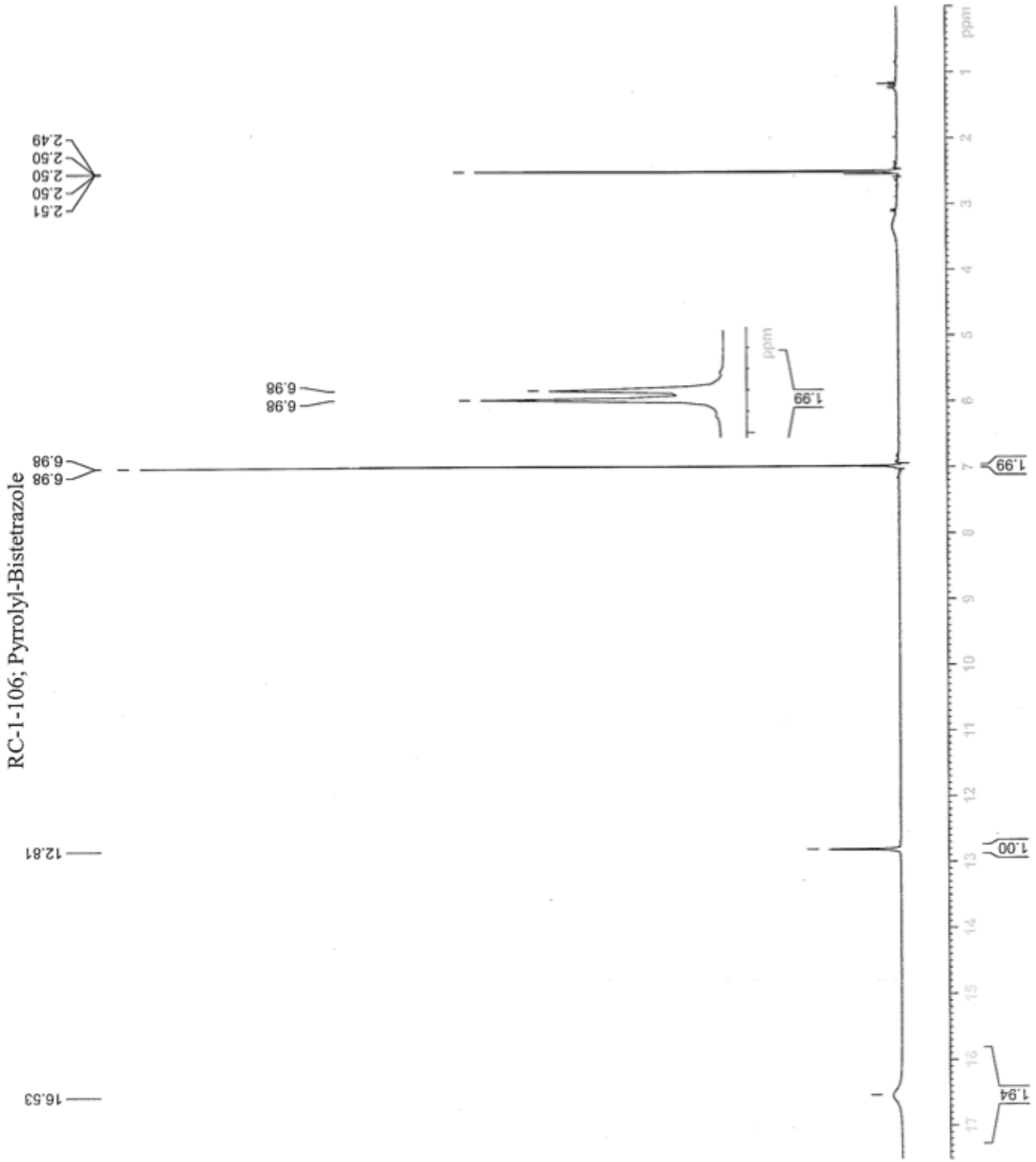
^{1}H and ^{13}C NMR spectra for hosts 1 and 2



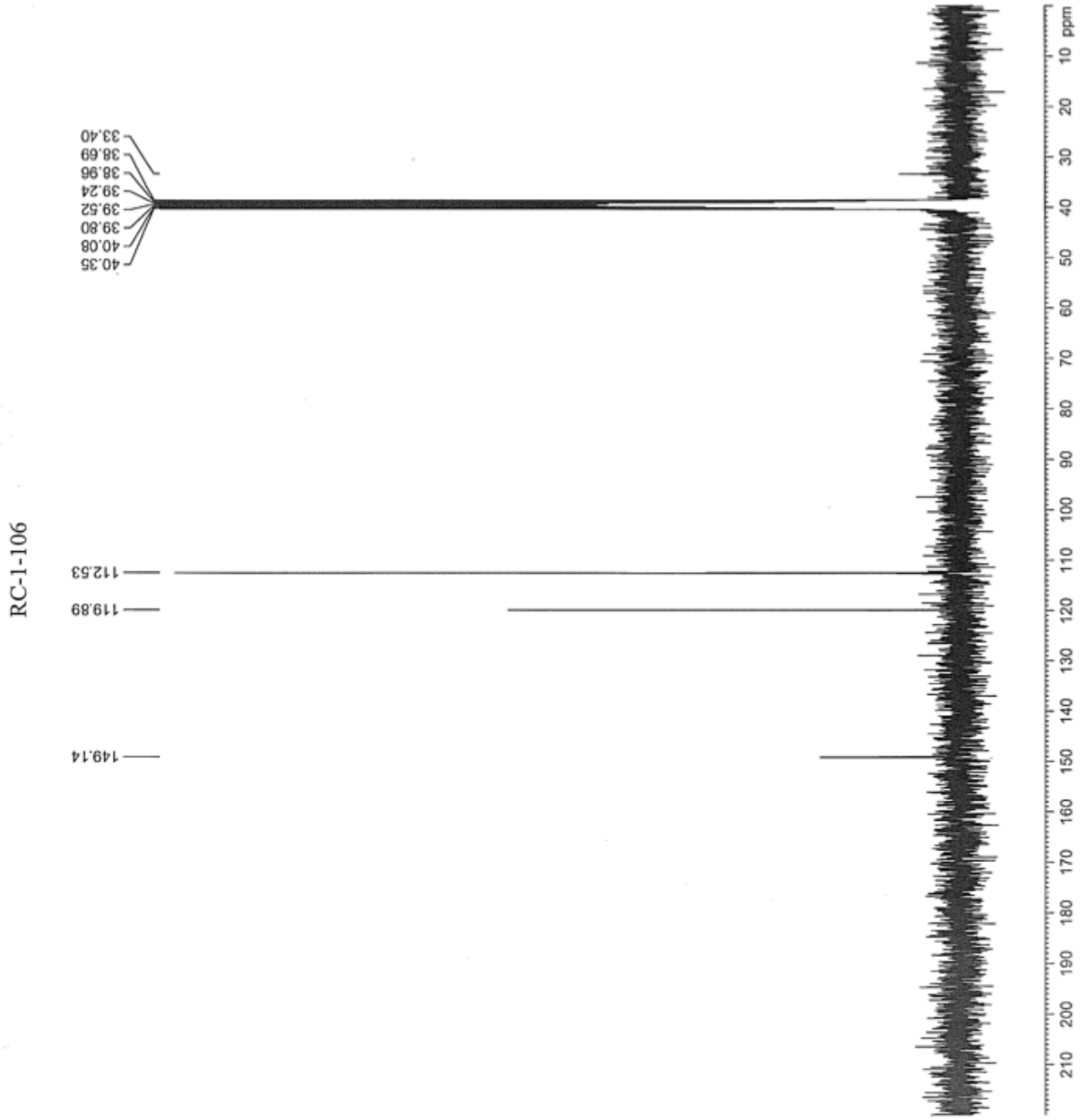
^{1}H NMR (300 MHz) of host **1** in CD_3CN.



^{13}C NMR (75 MHz) of host **1** in DMSO-d_6.



^{1}H NMR (500 MHz) of host **2** in DMSO-d_6.



^{13}C NMR (125 MHz) of host **2** in DMSO-d_6.

Experimental procedure — NMR studies

^{1}H NMR titrations were done on a Bruker DRX 500 MHz spectrometer using CD_3CN purchased from Cambridge Isotope Laboratories. Guests were used as their Bu_4N^+ salts and were dried *in vacuo* over P_2O_5 before use. Binding constants were determined by duplicate or triplicate titrations using host solutions of 0.5–4 mM. Guest solutions were prepared using the host solutions themselves to ensure that [host] remained constant during the titrations. Guest concentrations were 8–20 times the concentration of host solutions, and were added into the host solutions beginning with 10 uL increments and increasing to a final incremental volume of 500 uL. Titration curves were generated by plotting the change in chemical shift of protons on the host molecule against the concentration of guest. The chemical shift data was fit to 1:1 or 1:2 binding isotherms using a Microsoft Excel macro by Dr. J.M. Sanderson and the Centre for Bioactive Chemistry, Department of Chemistry, Durham University, Durham, UK, which is freely available at http://dur.ac.uk/j.m.sanderson/science/downloads. Job plots were carried out in CD_3CN using total concentrations of ([host] + [guest]) as indicated.

Representative ^{1}H titration data and fits for each of 1 and 2 with different guests

Only pyrrole N*H* signal titration curves are shown graphically. Results of replicate titrations are indicated below each figure.

Host **1** in anhydrous CD_3CN

Cl^-

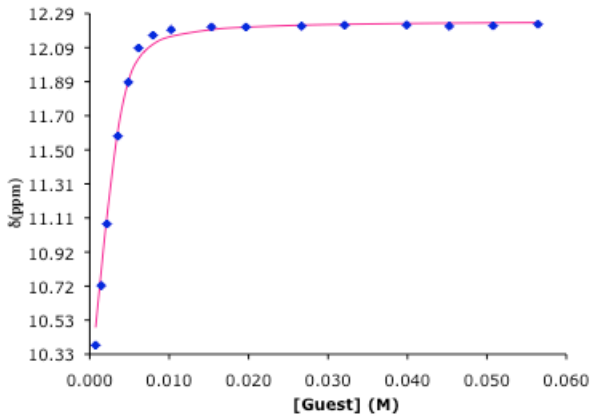


Figure S1.
[Host **1**] = 0.0041 M
Pyrrole N*H*: K_{assoc} = 4856.0 M^{-1}; Min % bound = 41 % ; Max % bound = 99%; δ free =10.14; δ bound 1 = 12.24.
Other signals tracked: tetrazole N*H* = 2300.6 M^{-1}; CH_a = 4811.6 M^{-1}, CH_b = 2033.8 M^{-1}
Duplicate titration: pyrrole N*H* = 3521.9 M^{-1}; tetrazole N*H* = 2145.9 M^{-1}; C*H*$_a$ = 4150.2 M^{-1}; C*H*$_b$ = 2287.8 M^{-1}

Br^-

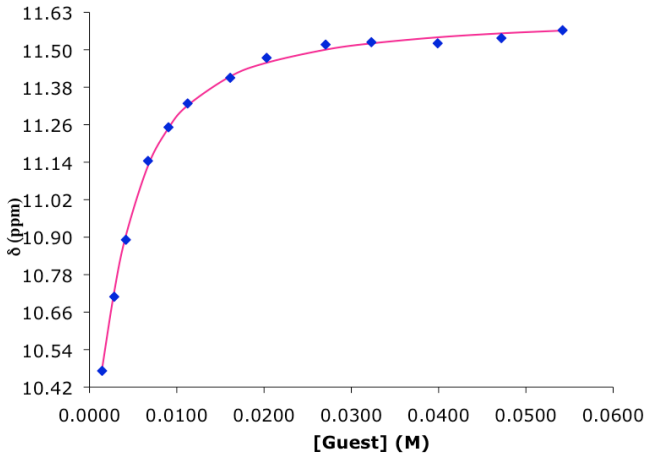


Figure S2.
[Host **1**] = 0.0039 M
Pyrrole N*H*: K_{assoc} = 480.31 M^{-1}; Min % bound = 21 % ; Max % bound = 96%; δ free =10.15; δ bound 1 = 11.62.
Other signals tracked: tetrazole N*H* = 419.5 M^{-1}; CH_a = 452.7 M^{-1}, CH_b = 380.5 M^{-1}
Duplicate titration: pyrrole N*H* = 499.6 M^{-1}; tetrazole N*H* = 479.4 M^{-1}; C*H*$_a$ = 473.6 M^{-1}; C*H*$_b$ = 379.5 M^{-1}

I^-

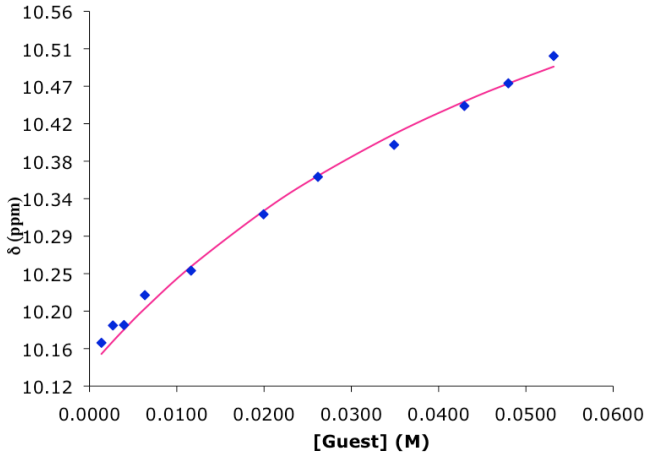


Figure S3.
[Host **1**] = 0.0035 M
Pyrrole N*H*: K_{assoc} = 16.33 M^{-1}; Min % bound = 4 % ; Max % bound = 46%; δ free =10.14 δ bound 1 = 10.91.
Other signals tracked: CH_a = 10.98 M^{-1}, CH_b = 17.45 M^{-1}
Duplicate titration: pyrrole N*H* = 18.30 M^{-1}; C*H*$_a$ = 18.72 M^{-1}; C*H*$_b$ = 20.72 M^{-1}

TsO^-

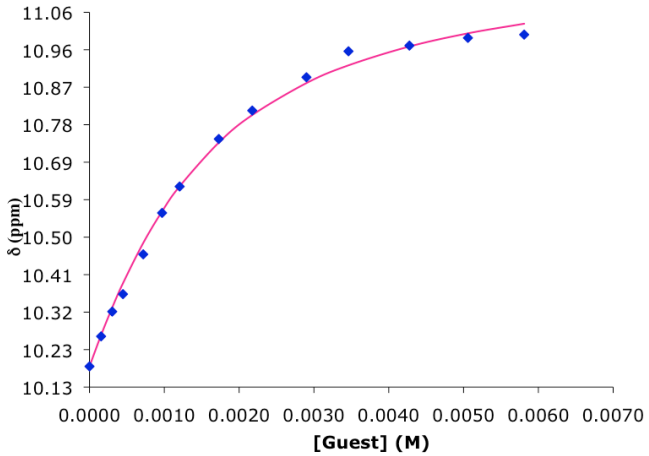


Figure S4.
[Host **1**] = 0.00092 M
Pyrrole N*H*: K_{assoc} = 959.20 M^{-1}; Min % bound = 0% ; Max % bound = 80%; δ free = 10.18; δ bound 1 = 11.20.
Other signals tracked: CH_a = 820.50 M^{-1}, CH_b = 911.48 M^{-1}
Duplicate titration: pyrrole N*H* = 913.65 M^{-1}; C*H*$_a$ = 836.20 M^{-1}; C*H*$_b$ = 932.56 M^{-1}

NO_3^-

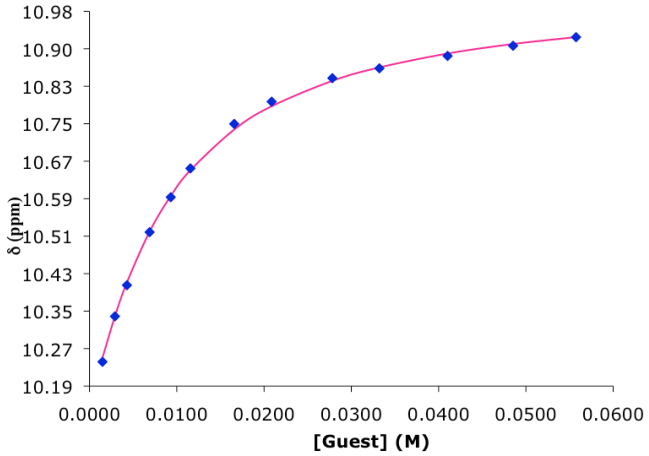


Figure S5.
[Host **1**]= 0.0043 M
Pyrrole N*H*: K_{assoc} = 142.64 M^{-1}; Min % bound = 11% ; Max % bound = 88%; δ free = 10.14; δ bound 1 = 11.04.
Other signals tracked: CH_a = 159.81 M^{-1}, CH_b = 134.94 M^{-1}
Duplicate titration: pyrrole N*H* = 171.87 M^{-1}; C*H*$_a$ = 179.10 M^{-1}; C*H*$_b$ = 146.87 M^{-1}

Host **1** in 1% (v/v) H_2O in CD_3CN

Cl^-

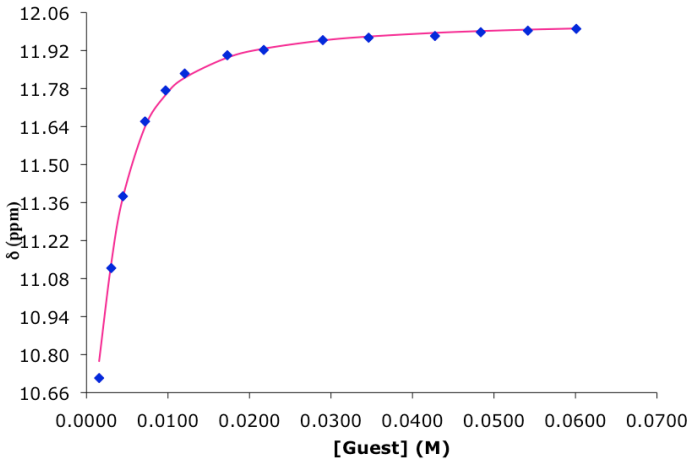


Figure S6.
[Host **1**] = 0.0039 M
Pyrrole N*H*: K_{assoc} = 803.6 M^{-1}; Min % bound = 24 % ; Max % bound = 98%; δ free =10.30; δ bound 1 = 12.04.
Other signals tracked: CH_a = 910.3 M^{-1}, CH_b = 842.8 M^{-1}
Duplicate titration: pyrrole N*H* = 957.9 M^{-1}; CH_a = 1054.4 M^{-1}, CH_b = 792.6 M^{-1}

Br^-

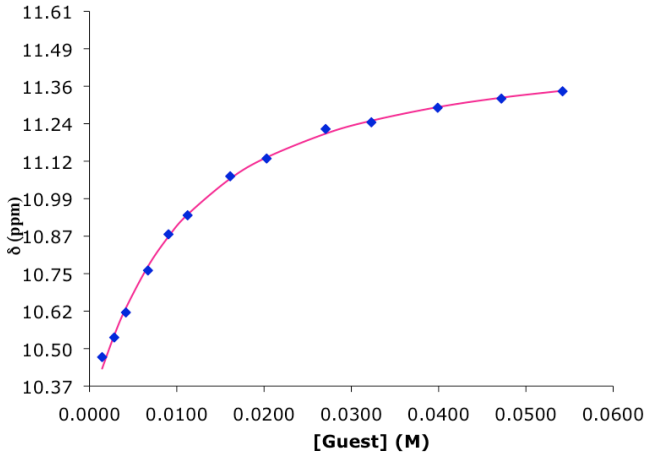


Figure S7.
[Host **1**] = 0.0037 M
Pyrrole N*H*: K_{assoc} = 118.8 M^{-1}; Min % bound = 14 % ; Max % bound = 86%; δ free =10.30; δ bound 1 = 11.52.
Other signals tracked: CH_a = 117.6 M^{-1}, CH_b = 92.7 M^{-1}
Duplicate titration: pyrrole N*H* = 123.1 M^{-1}; CH_a = 122.3 M^{-1}, CH_b = 93.8 M^{-1}

I^-

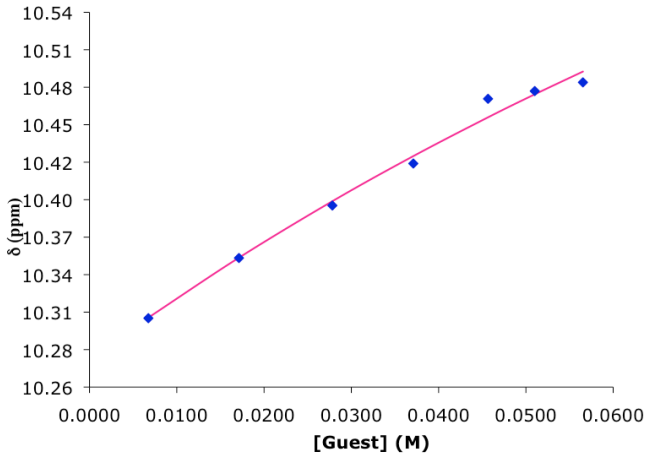


Figure S8.
[Host **1**] = 0.0035 M
Pyrrole N*H*: K_{assoc} = 4.74 M^{-1}; Min % bound = 3 % ; Max % bound = 21%; δ free =10.28; δ bound 1 = 11.31.
Other signals tracked: tetrazole CH_a = 3.13 M^{-1}, CH_b = 0.017 M^{-1}
No duplicate titration done.

TsO^-

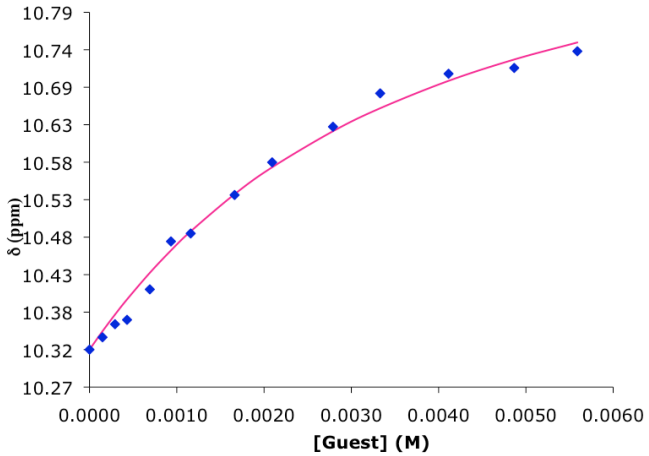


Figure S9.
[Host **1**] = 0.00092 M
Pyrrole N*H*: K_{assoc} = 344.74 M^{-1}; Min % bound = 0% ; Max % bound = 80%; δ free =10.32; δ bound 1 = 10.99.
Other signals tracked: CH_a = 493.35 M^{-1}, CH_b = 291.96 M^{-1}
Duplicate titration: pyrrole N*H* = 520.57 M^{-1}; CH_a = 567.75 M^{-1}, CH_b = 291.25 M^{-1}

NO_3^-

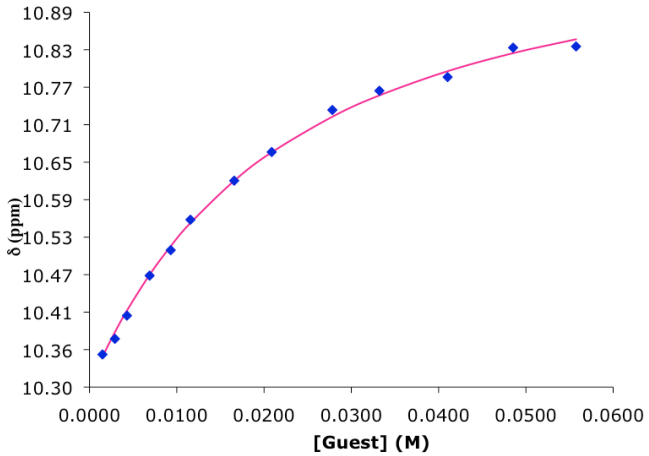


Figure S10.
[Host **1**] = 0.0043 M
Pyrrole N*H*: K_{assoc} = 51.49 M^{-1}; Min % bound = 6 % ; Max % bound = 73%; δ free =10.30; δ bound 1 = 11.05.
Other signals tracked: CH_a = 60.31 M^{-1}; CH_b = 48.95 M^{-1}
Duplicate titration: pyrrole N*H* = 63.17 M^{-1}; C*H*$_a$ = 73.76 M^{-1}, C*H*$_b$ = 62.45 M^{-1}

Host **2** in anhydrous CD_3CN

Cl^-

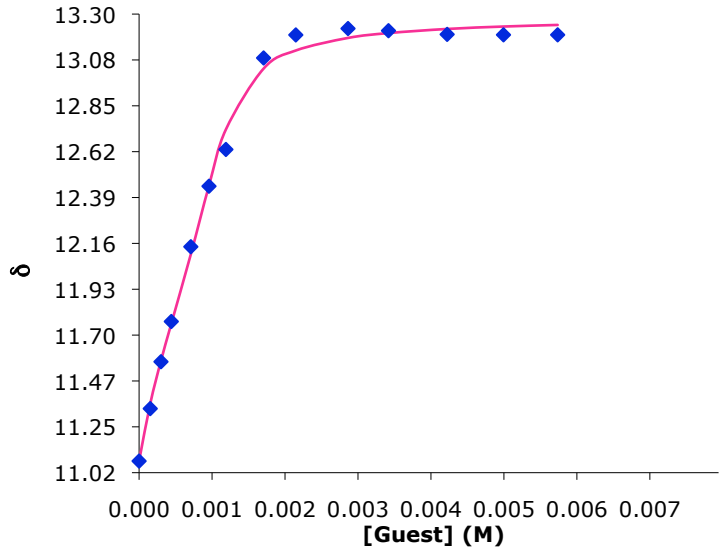


Figure S11.
[Host **2**] = 0.0011 M
Pyrrole N*H*: K_{11} = 24,672 M^{-1}, K_{12} = 656 M^{-1}; Min % bound = 0 % ; Max % bound = 99%; δ free =11.08; δ bound 1 = 13.29, δ bound 2 = 11.30,
Duplicate titration: pyrrole N*H*: K_{11} = 27,904 M^{-1}, K_{12} = 899 M^{-1};

Br^-

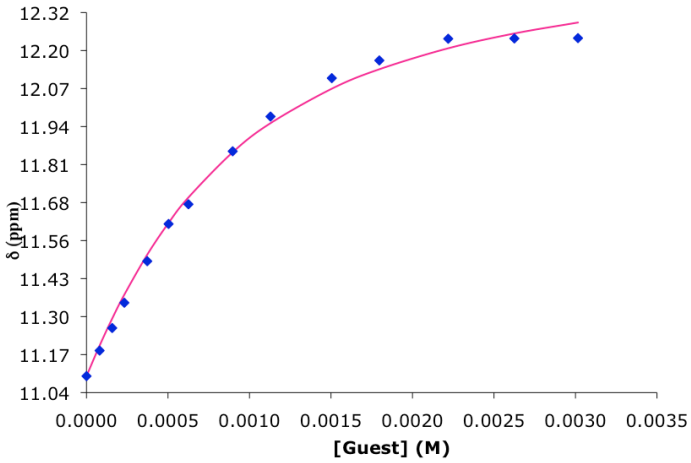


Figure S12.
[Host **2**] = 0.00049 M
Pyrrole N*H*: K_{assoc} = 1632.46 M^{-1}; Min % bound = 0 % ; Max % bound = 81%; δ free =11.10; δ bound 1 = 12.57.
Duplicate titration: pyrrole N*H* = 2010.4 M^{-1}

I^-

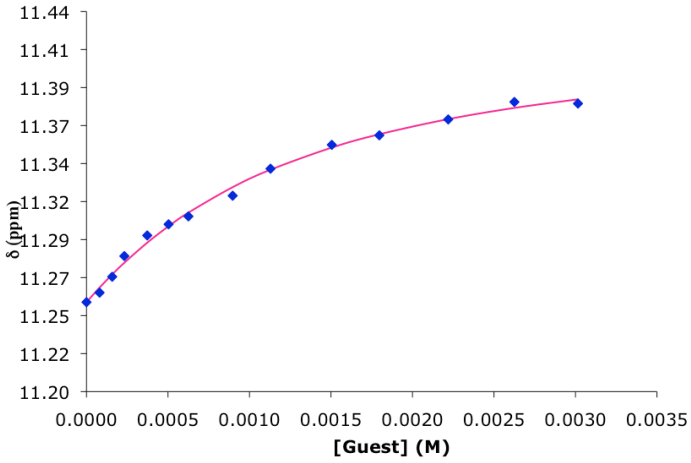


Figure S13.
[Host **2**] = 0.00049 M
Pyrrole N*H*: K_{assoc} = 1016.8 M^{-1}; Min % bound = 0 % ; Max % bound = 73%; δ free =11.25; δ bound 1 = 11.43.
Other signals tracked: pyrrole C*H* = 1264.9 M^{-1}
Duplicate titration: pyrrole N*H* = 1096.88 M^{-1}; pyrrole C*H* = 413.2 M^{-1}

NO_3^-

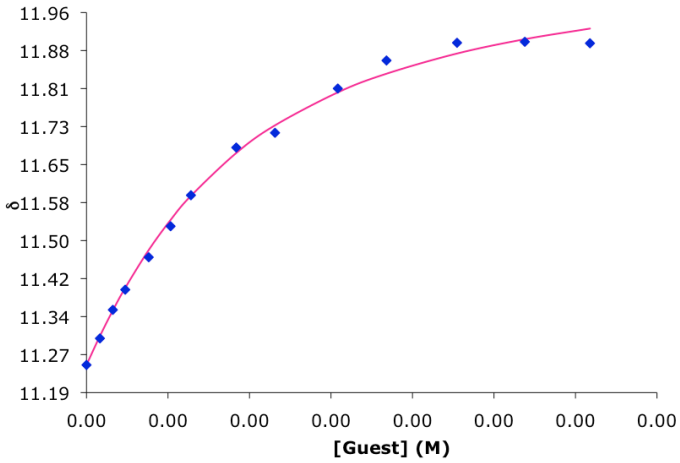


Figure S14.
[Host **2**] = 0.00049 M
Pyrrole N*H*: K_{assoc} = 1538.87 M^{-1}; Min % bound = 0 % ; Max % bound = 81%; δ free =11.25; δ bound 1 = 12.09.
Other signals tracked: pyrrole C*H* = 1374.53 M^{-1}
Duplicate titration: pyrrole N*H* = 2004.11 M^{-1}; pyrrole C*H* = 1374.54 M^{-1}

BzO^-

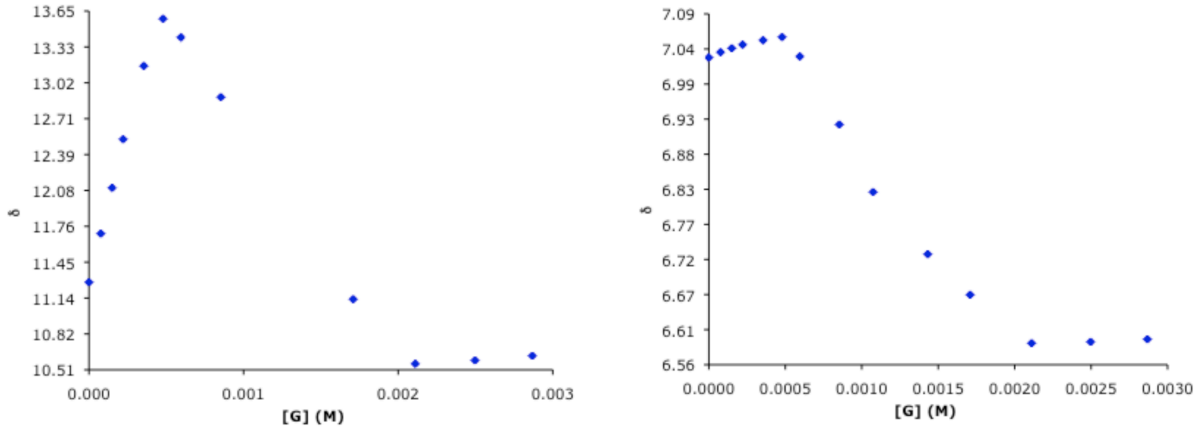


Figure S15.
[Host **2**] = 0.00049 M
Pyrrole NH (left) and pyrrole CH (right) could not be fit to any 1:1, 1:2, or 2:1 binding isotherm. The trends observed for pyrrole NH are consistent with initial strong binding followed by transfer of the tetrazole proton from host to BzO^-. See main text.

Host **2** in 1% (v/v) H_2O in CD_3CN

Cl^-

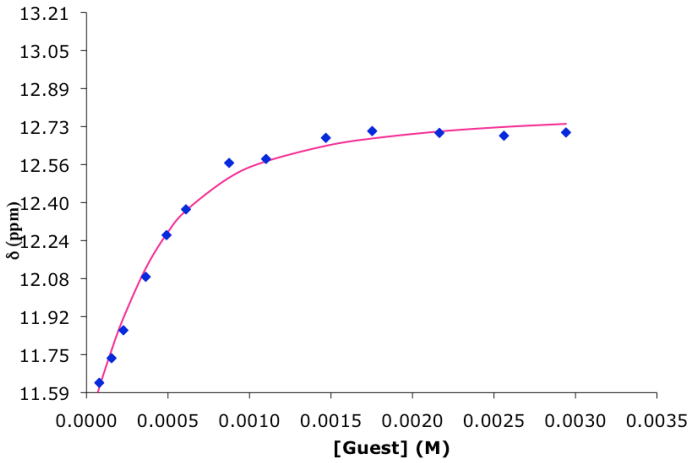


Figure S16.
[Host **2**] = 0.00041 M
Pyrrole N*H*: K_{assoc} = 6203.05 M^{-1}; Min % bound = 0 % ; Max % bound = 94%; δ free =11.43; δ bound 1 = 12.82
Duplicate titration: pyrrole N*H* = 6680.5 M^{-1}

Br^-

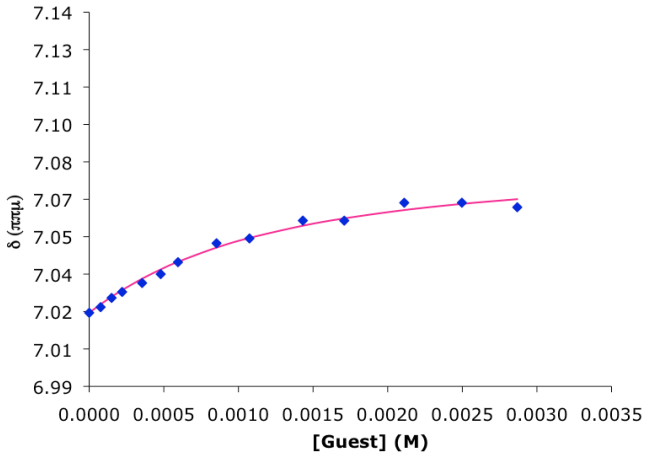


Figure S17.
[Host **2**] = 0.00041 M
Pyrrole C*H*: K_{assoc} = 1061.62 M^{-1}; Min % bound = 0 % ; Max % bound = 80%; δ free =7.02; δ bound 1 = 7.08.
Duplicate titration: pyrrole C*H* = 1081.89 M^{-1}

I^-

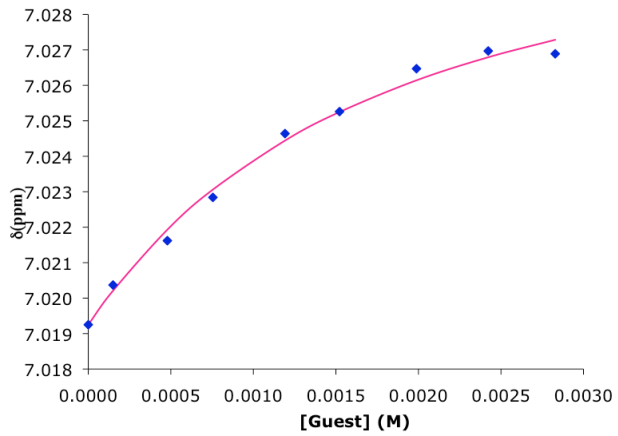


Figure S18.
[Host **2**] = 0.00041 M
Pyrrole C*H*: K_{assoc} = 648.60 M^{-1}; Min % bound = 0 % ; Max % bound = 80%; δ free =7.02; δ bound 1 = 7.03.
Duplicate titration: pyrrole C*H* = 648.6 M^{-1}

TsO^-

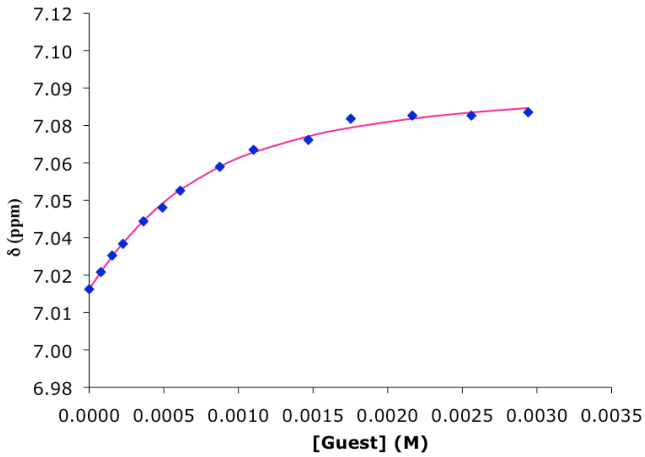


Figure S19.
[Host **2**] = 0.00041 M
Pyrrole C*H*: K_{assoc} = 2302.62 M^{-1}; Min % bound = 0 % ; Max % bound = 80%; δ free =7.02; δ bound 1 = 7.09.
Duplicate titration: pyrrole C*H* = 3771.8 M^{-1}

NO_3^-

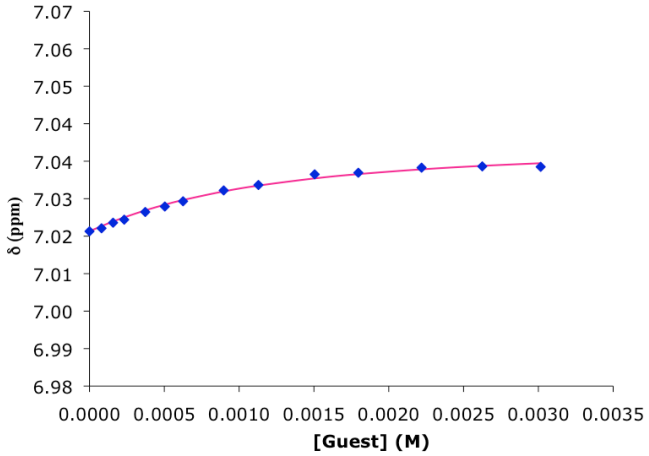


Figure S20.
[Host **2**] = 0.00041 M
Pyrrole C*H*: K_{assoc} = 1166.78 M^{-1}; Min % bound = 0 % ; Max % bound = 80%; δ free =7.02; δ bound 1 = 7.04.
Duplicate titration: pyrrole C*H* = 705.44 M^{-1}

Selected Job plots

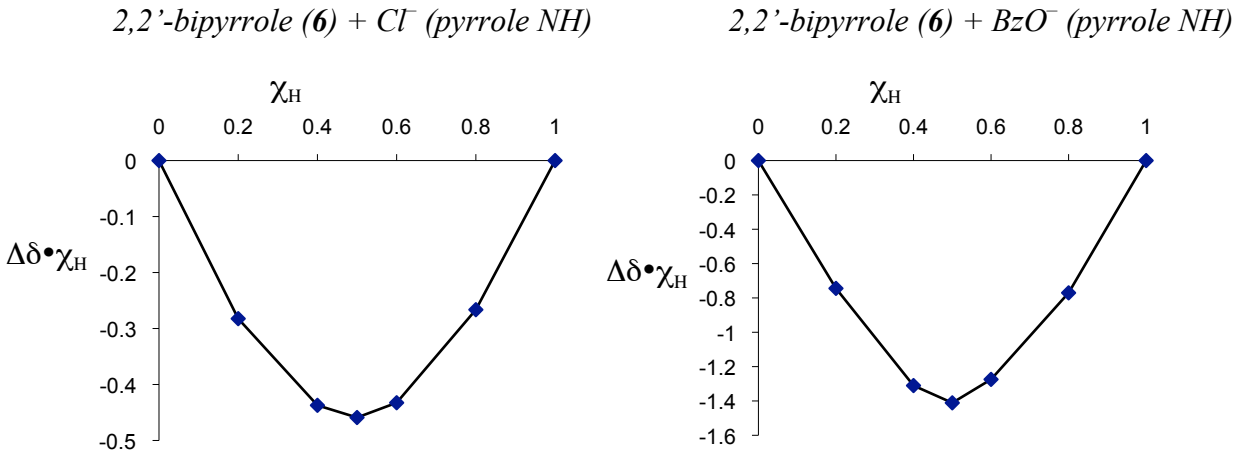


Figure S21. Job plots for bipyrrole **6**. ([**6**]+[Bu_4NCl] or [Bu_4NOBz) = 5 mM. Bipyrrole forms 1:1 complexes with both Cl^- and BzO^-.

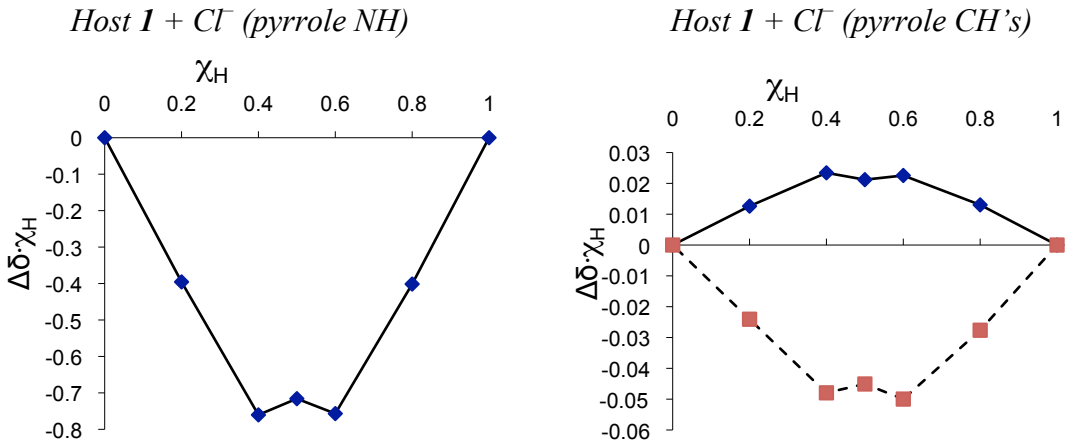


Figure S22. Job plots for complex **1**•Cl^-. ([**1**]+[Bu_4NCl]) = 5 mM. All host signals that shift significantly indicate 1:1 complex formation with Cl^-. The origin of the slight deviation from ideal 1:1 curves at the extrema is unclear, but we have seen this behavior previously for other tetrazole-based hosts.

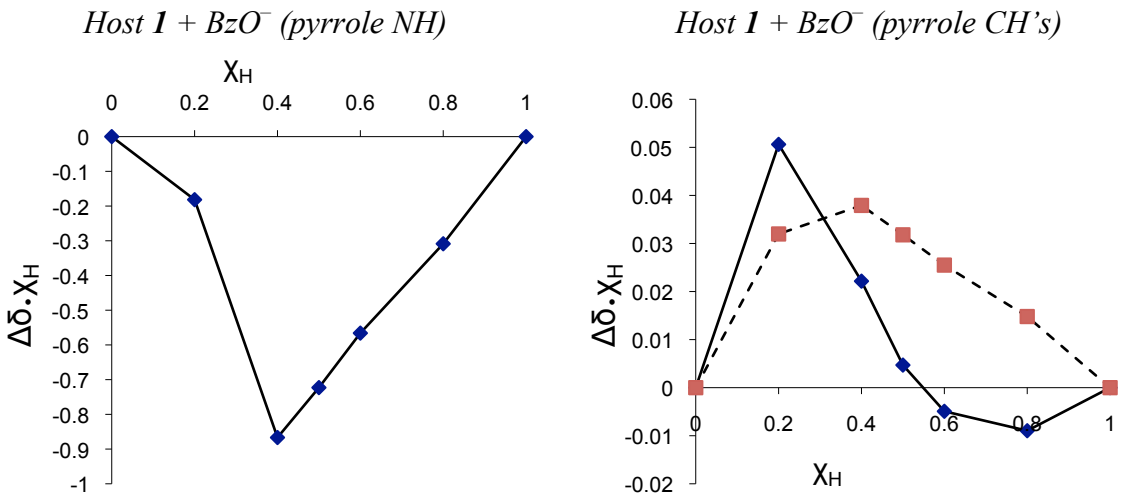


Figure S23. Job plots for addition of BzO^- to **1**. ([**1**]+[Bu_4NOBz]) = 5 mM. The titration data for this pair indicate a mixture of binding *and* proton transfer between host and guest. The diverse and non-ideal trends observed in these Job plots (especially the sigmoidal curve at right) are consistent with the conclusion that no simple n:m binding model can explain the behavior of **1** and BzO^-.

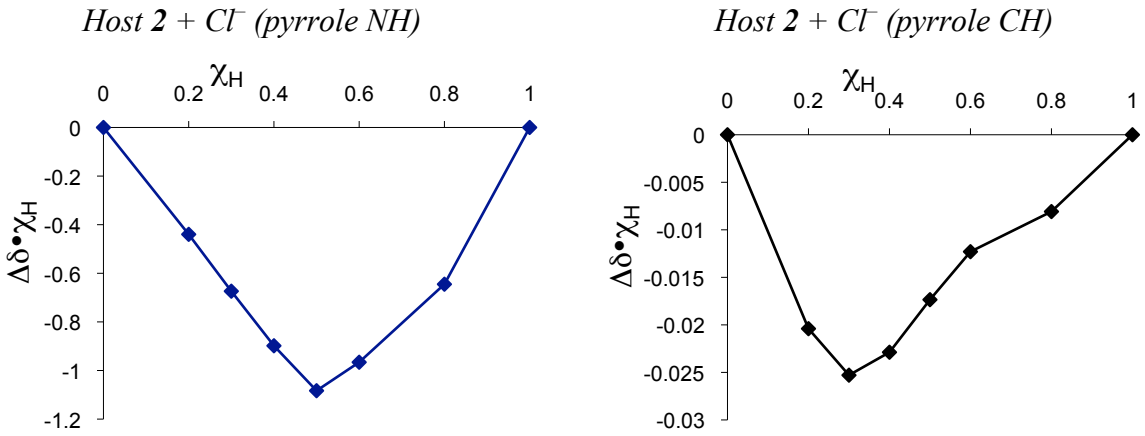


Figure S24. Job plots for addition of Cl^- to **2**. ([**2**]+[Bu_4NCl]) = 0.5 mM. These plots indicate in an unconventional way the mixed participation of 1:1 and 1:2 binding for this host/guest pair. See main text.

Calculations and discussion of conformational and acidity differences between amide 4 and tetrazole 1.

The relatively low affinities of each of these pyrrole-amide hosts arises because their global minimum energy conformations are governed by the antiparallel orientation of pyrrole and amide dipoles (that also can be considered a weak intramolecular NH---O=C hydrogen bond) that hold them in an *anti* conformation in which pyrrole NH and amide NH are divergent (Figure S25).[27-32] We calculated the relative energies of **1** and **4** in their NH-divergent ("*anti*") and NH-convergent ("*syn*") conformations by energy minimizations at the HF/6-311+G** level of theory as implemented in Spartan '06 (Wavefunction, Inc.) (Figure S25). Both prefer the *anti* conformation, but **1** pays a smaller penalty (+5.5 kcal mol^{-1}) than **4** (+6.1 kcal mol^{-1}) to reorient itself into the *syn* conformation required for anion binding. This difference of 0.6 kcal mol^{-1} makes up ~25% of the ≥44-fold difference ($\Delta\Delta G \geq 2.2$ kcal mol^{-1}) observed between **1**•Cl^- and **4**•Cl^-; the remainder likely arises as a result of the inherently greater acidity and H-bonding capability of the tetrazole relative to the amide, which we probed experimentally by comparisons to 2,2'-bipyrrole **6** (see main text).

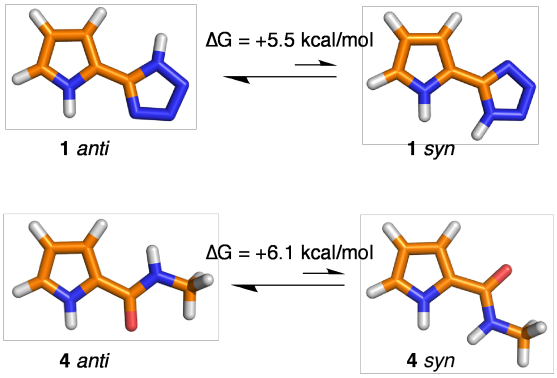


Figure S25. Calculated conformational preferences of host **1** and reference host **4** (alkyl chain truncated). All calculations done using Spartan '06 V1.0.2 (Wavefunction, Inc.) at the HF/6-311+G** level of theory.