Synthesis and Molecular Recognition Studies of Pyrrole Sulfonamides

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General Methods: Nuclear magnetic resonance (NMR) spectra were measured in $CDCl_3$ with tetramethylsilane (TMS) as internal reference standard at 300 MHz on a Varian MercuryPlus. Chemical shifts are reported in δ (ppm) referenced to TMS. $CDCl_3$ was obtained from Cambridge Isotope Labs, and stored over CaH_2 to remove water and HCl. The solvent was filtered immediately prior to use. The reported melting points are uncorrected. Ethyl 3,4-dimethylpyrrole-2-carboxylate was prepared via standard methods. All other solvents and materials were purchased from common sources (Fisher, Acros or Aldrich) and used as received. Radial chromatography was carried out on Merck Silica Gel PF_{254} with gypsum preparative layer grade, using a Chromatotron (Harrison Research, Inc., Palo Alto, CA).

^{1}H-NMR Host-Guest Titration Method: Host:guest titrations were performed using ^{1}H-NMR spectroscopy. A 0.02 M stock solution of the respective pyrrole sulfonamides **1-4** was prepared in deuteriochloroform. Guest solutions ranged in concentration from 0.08M to 0.35M dissolved in 0.02M respective pyrrole sulfonamides **1-4** stock solution. A standard addition titration was performed with aliquots of guest solutions ranging from 15mL to 100mL added directly to stock solution in the NMR tube, and the ^{1}H-NMR spectra measured in order to track the change in chemical shift of the pyrrole and sulfonamide N-H protons until such time as the saturation point was reached. The reported K_a values are the average calculated from both the sulfonamide and pyrrole NHs from multiple titrations (2-4 total). Errors are estimated to be no large than 10%. All anions used were in their tetrabutylammonium salt form. All analysis resulted in R^2 values of 0.98 or better.

Molecular Modeling Studies: All molecular mechanics calculations were performed using Materials Studio, c4.1.0.0; Acceleys Software Inc.: 2006; forcefield – Dreiding; charges – Gasteiger; Electrostatics & van der Waals – atom based.

Synthetic Procedures

5-Carboethoxy-3,4-dimethyl-1*H*-pyrrole-2-sulfonyl chloride (6): To a 100 mL RBF, pyrrole **5** (30 mmol) was added, and the solid material was cooled in an ice bath. Chlorosulfonic acid (25 mL) was added, and the solution was heated to 60°C. (Note: It is important for the reaction temperature to never exceed 65°C due to excessive decomposition and substantially lower yields.) The reaction was heated for ~10 minutes (no longer then 15 min). After heating, the resulting solution was added to a beaker of 150 g of crushed ice dropwise, carefully and quickly. (Caution: The excess chlorosulfonic acid decomposes vigorously!) The solid precipitate **6**, was collected by vacuum filtration. The crude product was used in the next step without further purification or characterization due to the hydrolysis of the sulfonyl chloride.

Preparation of mono-sulfonamides: Sulfonyl chloride **6** and 100 ml of methylene chloride were placed in a 250 mL RBF, and the desired amine (92 mmol) was added in one portion. After stirring for 24 hours at room temperature, the resulting solution was washed with saturated aqueous $NaHCO_3$ (2 x 100 mL), water (2 x 100 mL), and 10% aqueous HCl (2 x 100 mL). The organic solution was dried over anhydrous sodium sulfate, and the solvent removed by rotovap to give the desired crude product. The crude product was purified by recrystallization from CH_2Cl_2/hexanes followed by radial chromatography (CH_2Cl_2/methanol) to provide pure product.

Preparation of Di-sulfonamides: Sulfonyl chloride **6** and 60 ml of methylene chloride were placed in a 250 mL RBF, and the desired amine (11 mmol) was added in one portion. After stirring for 24 hours at room temperature, the resulting solution was washed with saturated aqueous $NaHCO_3$ (2 x 60 mL), water (2 x 60 mL), and 10% aqueous HCl (2 x 60 mL). The organic solution was dried over anhydrous sodium sulfate, and the solvent removed by rotovap to give the desired crude product. The crude product was purified by recrystallization from CH_2Cl_2/hexane followed by radial chromatography (CH_2Cl_2/hexane) to provide pure product. The di-sulfonamide was purified by recrystallization from methanol and water for **3**, and CH_2Cl_2/hexanes for **4**.

5-Carboethoxy-2-phenylaminosulfonyl-3,4-dimethyl-1*H*-pyrrole(1): Yield = 30%; It had a mp of 154-156^{o}C; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 8.96, 10.14, 14.26, 60.96, 121.62, 122.53, 124.92 125.34, 126.00, 127.11, 129.29, 135.67, 160.99 ppm; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.34 (t, 3 H, 6.0H z), 1.94 (s, 3 H), 2.17 (s, 3H), 4.31 (q, 2 H, 6.0 Hz), 7.17 (m, 5 H), 9.55 (bs, 1 H) ppm; IR (KBr) 1354, 1593, 1658, 2934, 2978, 3210, 3429 cm^{-1}; MS (EI+) (base peak) m/z; and HR-MS (EI+) $C_{15}H_{18}N_2O_4S_1$ Calc'd 322.0987 amu; found 322.0987 amu.

5-Carboethoxy-2-butylaminosulfonyl-3,4-dimethyl-1*H*-pyrrole(2): Yield = 57%; It had a mp of 63-66^{o}C; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 9.46, 10.41, 13.75, 14.58, 19.91, 31.62, 42.85, 60.98, 121.34, 123.82, 126.74, 127.44 161.24 ppm; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.83 (t, 3 H, 7.2 Hz), 1.34 (m, 7 H), 2.17 (s, 3 H), 2.23 (s, 3 H), 2.90 (q, 2 H, 6.9 Hz), 4.31 (q, 2 H, 7.2 Hz), 5.36 (t, 1 H, 6.0 Hz), 9.69 (bs, 1H) ppm; IR (KBr) 901, 1239, 1317, 1723, 2958, 3286 cm^{-1}; MS (EI+) (base peak) m/z; and HR-MS (EI+) $C_{13}H_{22}N_2O_4S_1$ Calc'd 302.1300 amu; found 302.1302 amu.

N,N'-bis(5-Carboethoxy-3,4-dimethyl-1*H*-pyrrole-sulfonyl)-1,2-diaminoethane(3): Yield = 57%; It had a mp decomposed at ~ 130°C; ^{13}C-NMR (75 MHz, DMSO) δ 9.11, 10.09, 14.39, 41.96, 60.31, 121.06, 122.90, 125.93, 127.54, 160.58 ppm; ^{1}H-NMR (300 MHz, D-Acetone) δ 1.31 (t, 3 H, 7.2 Hz), 2.08 (s, 3 H), 2.17 (s, 3 H), 2.81 (s, 2 H), 4.26 (q, 2 H, 6.9 Hz), 7.36 (bs, 1 H), 11.67 (bs, 1 H) ppm; IR (KBr) 595, 1240, 1689, 2930, 3203, 3320 cm^{-1}; MS (EI+) (base peak) m/z; and HR-MS (EI+) $C_{20}H_{30}N_4O_8S_2$ Calc'd 518.1505 amu; found 518.1518 amu.

N,N'-bis(5-Carboethoxy-3,4-dimethyl-1*H*-pyrrole-sulfonyl)-1,4-diaminobutane(4): Yield = 35%; It had a mp decomposed at 124°C; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 9.51, 10.47, 14.58, 26.46, 42.42, 61.13, 121.56, 123.88, 126.54, 127.48, 161.32 ppm; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.39 (t, 3 H, 7.5 Hz), 1.48 (s, 2 H), 2.18 (s, 3 H), 2.24 (s, 3 H), 2.88 (s, 2 H), 4.34 (q, 2 H, 7.5 Hz), 6.74 (t, 1 H, 6.0 Hz), 10.53 (bs, 1 H) ppm; IR (KBr) 599, 1242, 1699, 2934, 3271 cm^{-1}; MS (EI+) (base peak) m/z; and HR-MS (EI+) $C_{22}H_{34}N_4O_8S_2$ Calc'd 546.1818 amu; found 546.1813 amu.

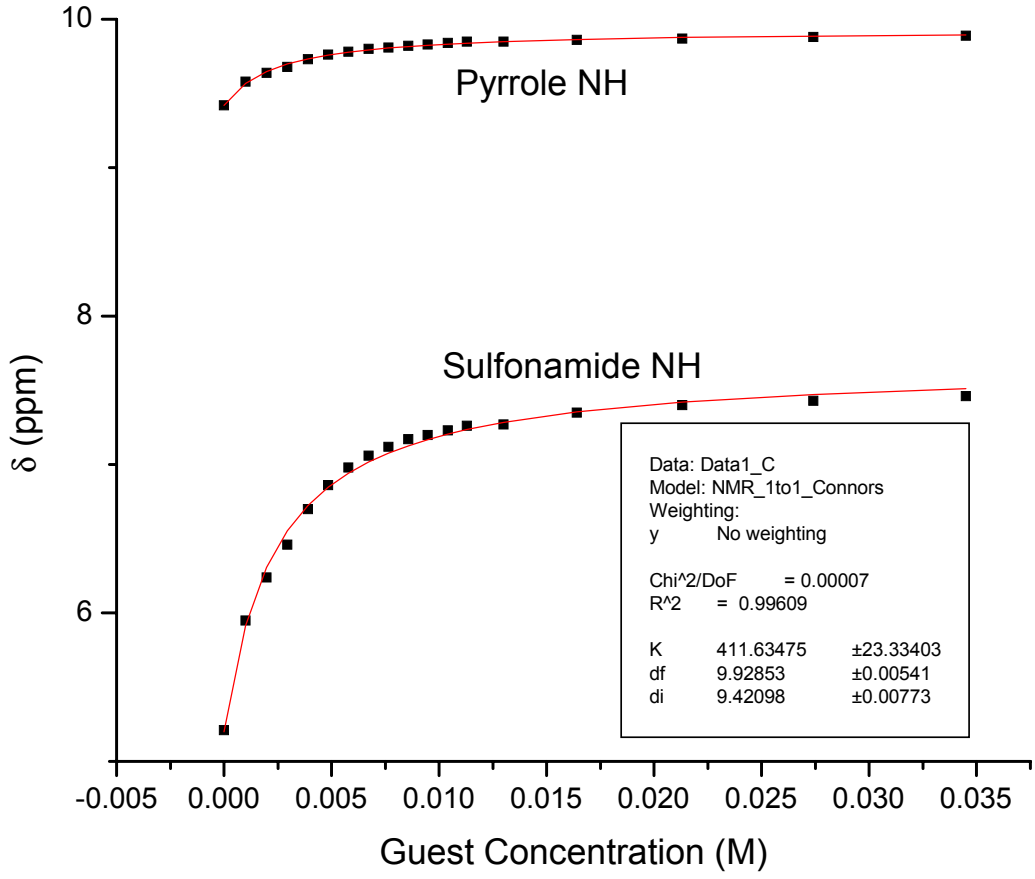
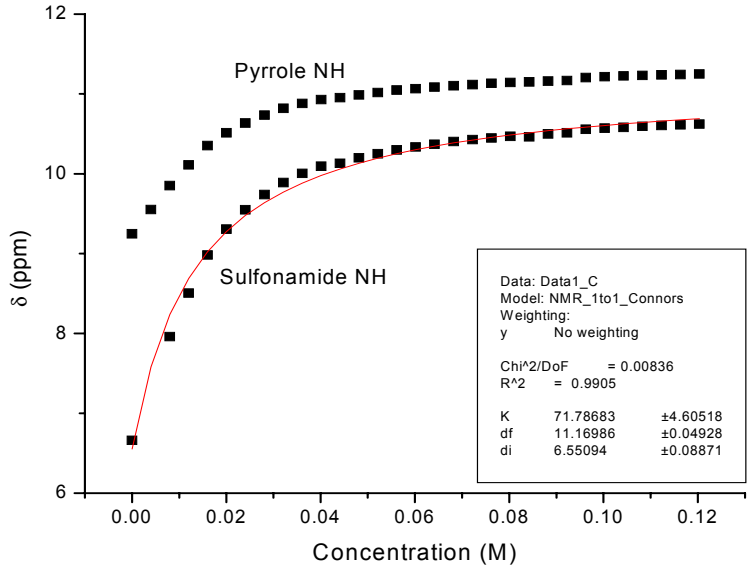


Figure1. Titration curves for disulfonamide **3** with TBA Br^- in $CDCl_3$ at 25°C.



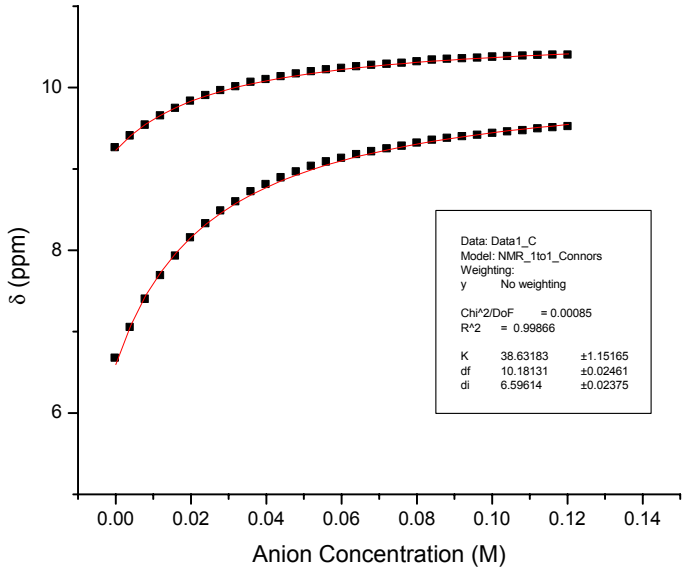


Figure 1. Titration curves for sulfonamide **1** with TBA Cl^- in $CDCl_3$ at 25°C.

Figure 2. Titration curves for sulfonamide **1** with TBA Br^- in $CDCl_3$ at 25°C.

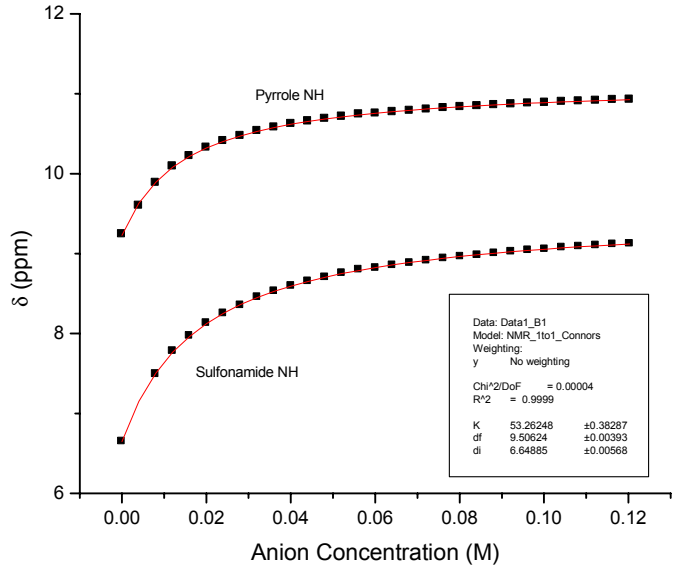


Figure 3. Titration curves for sulfonamide **1** with TBA hydrogen sulfate in $CDCl_3$ at 25°C.

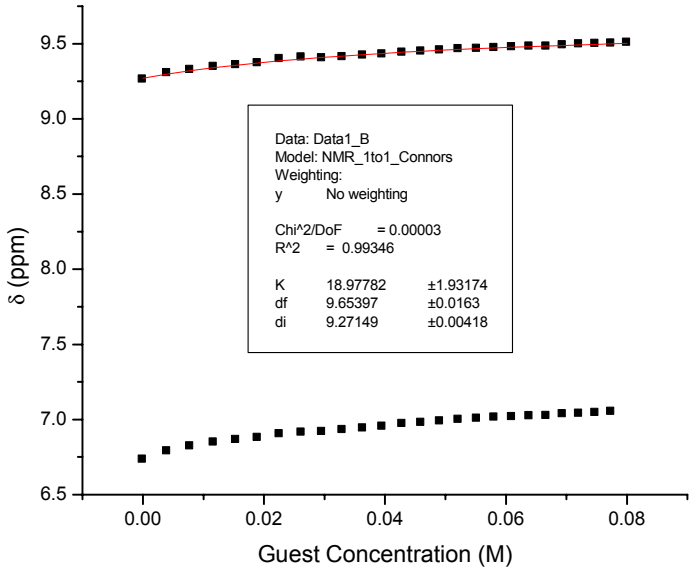


Figure 4. Titration curves for sulfonamide **1** with benzoic acid in $CDCl_3$ at 25°C.

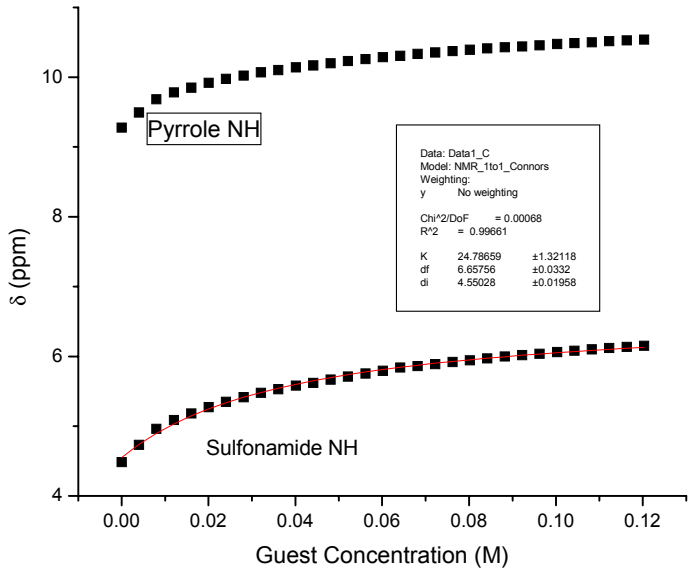


Figure 5. Titration curves for sulfonamide **2** with TBA HSO_4^- in $CDCl_3$ at 25°C.

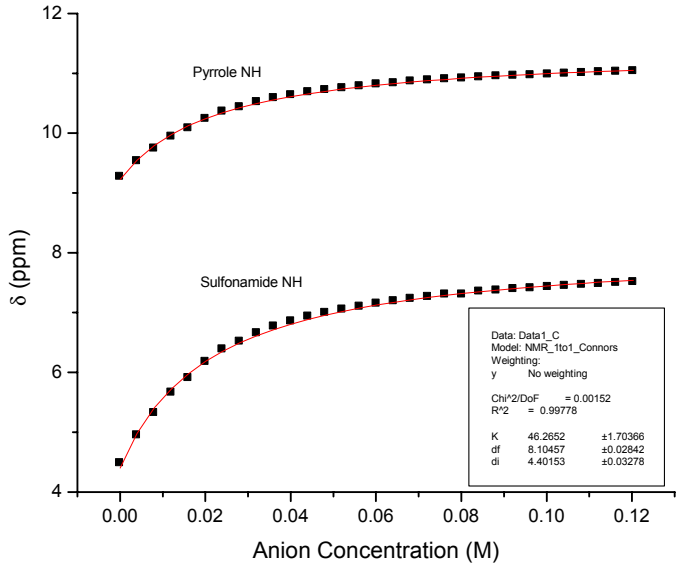
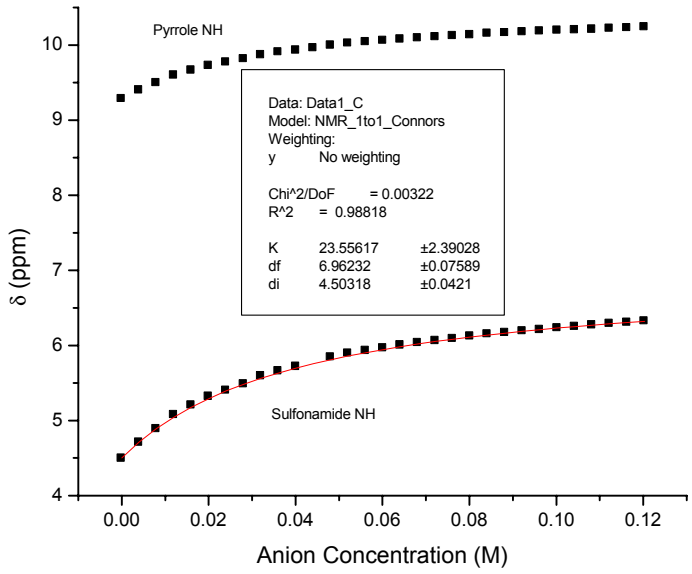


Figure 6. Titration curves for sulfonamide **2** with $TBACl^-$ in $CDCl_3$ at 25°C.

Figure 7. Titration curves for sulfonamide **2** with TBA NO_3^- in $CDCl_3$ at 25°C.



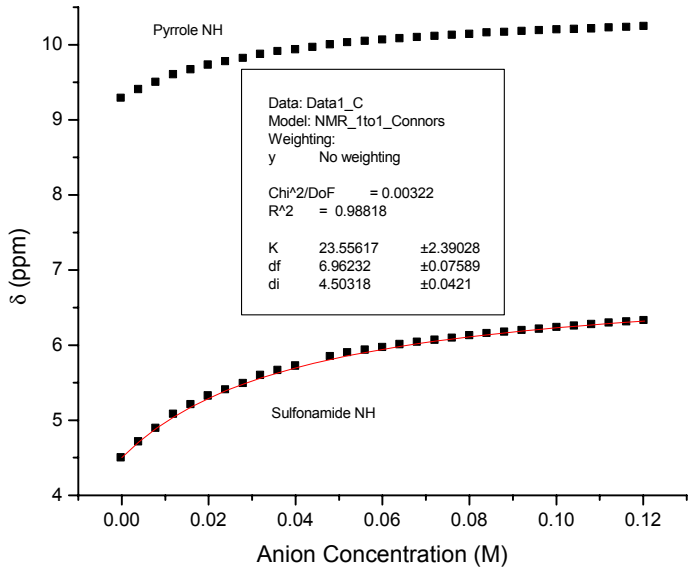


Figure 8. Titration curves for sulfonamide **2** with TBA Br^- in $CDCl_3$ at 25°C.

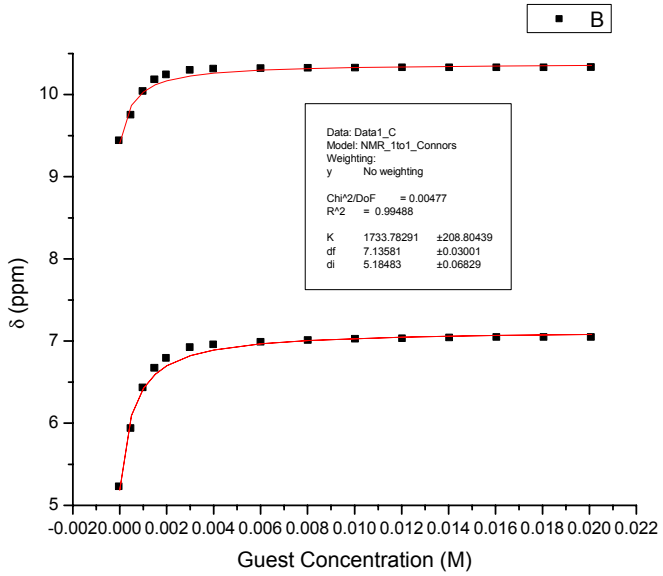


Figure 9. Titration curves for sulfonamide **3** with TBA HSO_4^- in $CDCl_3$ at 25°C.

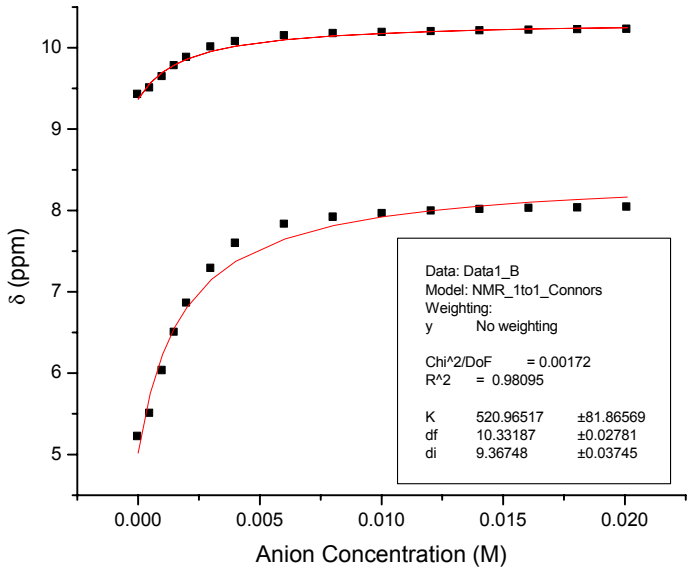
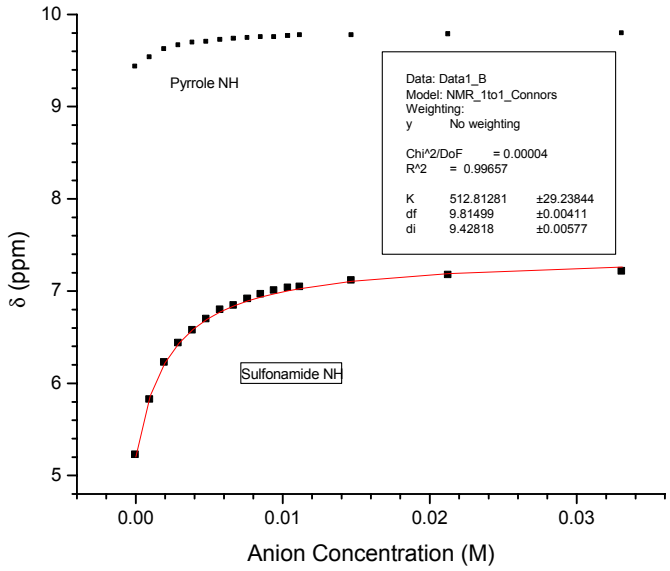


Figure 10. Titration curves for sulfonamide **3** with TBA Cl^- in $CDCl_3$ at 25°C.



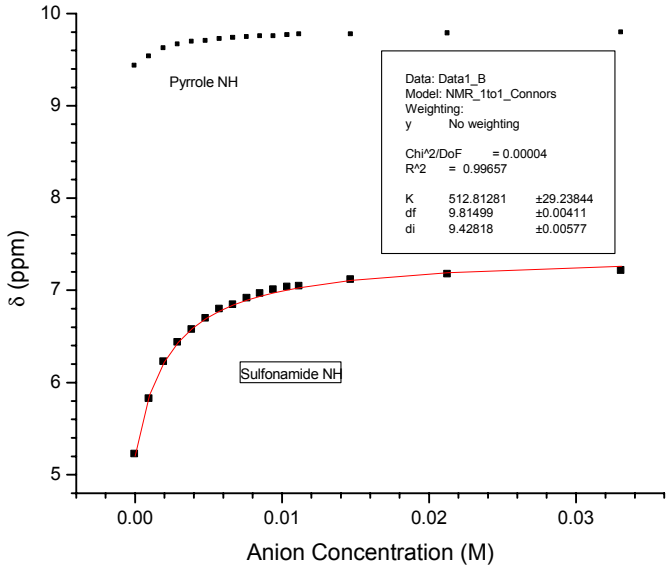
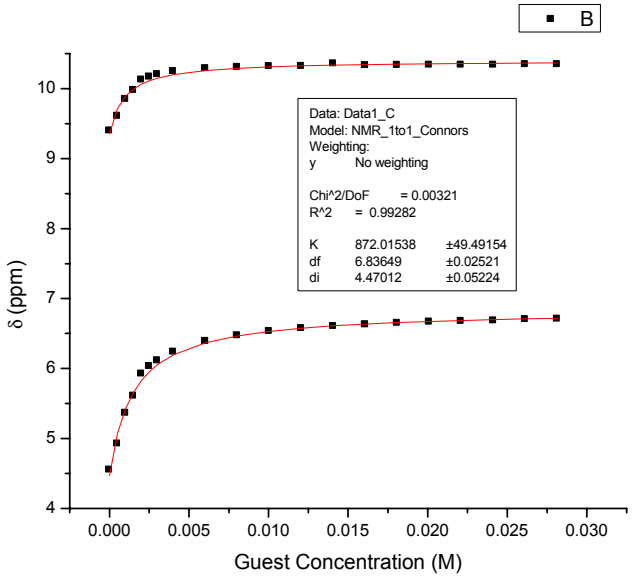


Figure 11. Titration curves for sulfonamide **3** with TBA NO_3^- in $CDCl_3$ at 25°C.

Figure 12. Titration curves for sulfonamide **3** with TBA Br^- in $CDCl_3$ at 25°C.


B
Data: Data1_C
Model: NMR_1to1_Connors
Weighting:
y No weighting
Chi^2/DoF = 0.00321
R^2 = 0.99282
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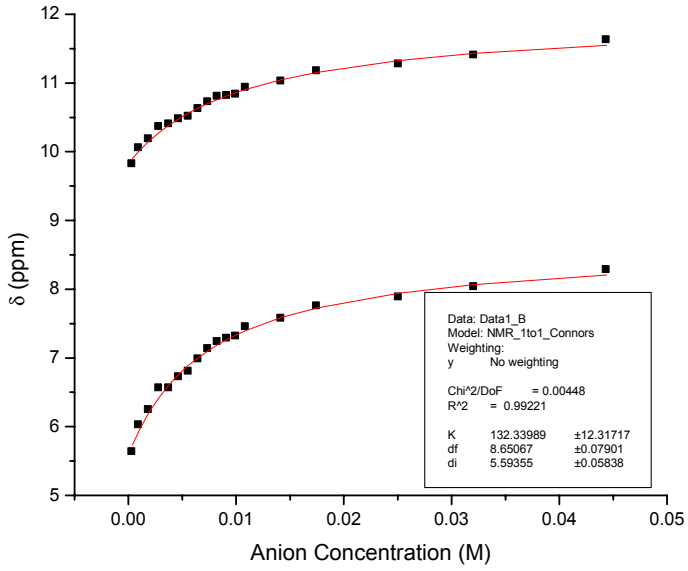
df 6.83649 ±0.02521
di 4.47012 ±0.05224
δ (ppm)
Guest Concentration (M)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Weighting:
y No weighting
Chi^2/DoF = 0.00448
R^2 = 0.99221
K 132.33989 ±12.31717
df 8.65067 ±0.07901
di 5.59355 ±0.05838
δ (ppm)
Anion Concentration (M)

Figure 13. Titration curves for sulfonamide **4** with TBA HSO_4^- in $CDCl_3$ at 25°C.

Figure 14. Titration curves for sulfonamide **4** with TBA Cl^- in $CDCl_3$ at 25°C.

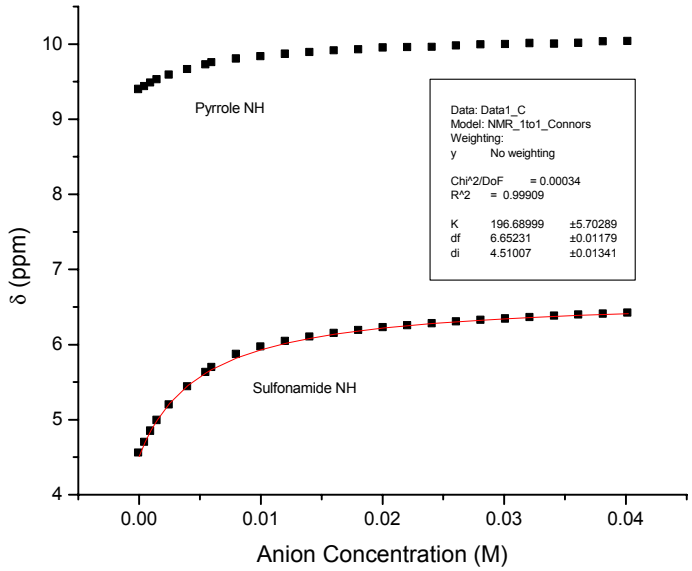
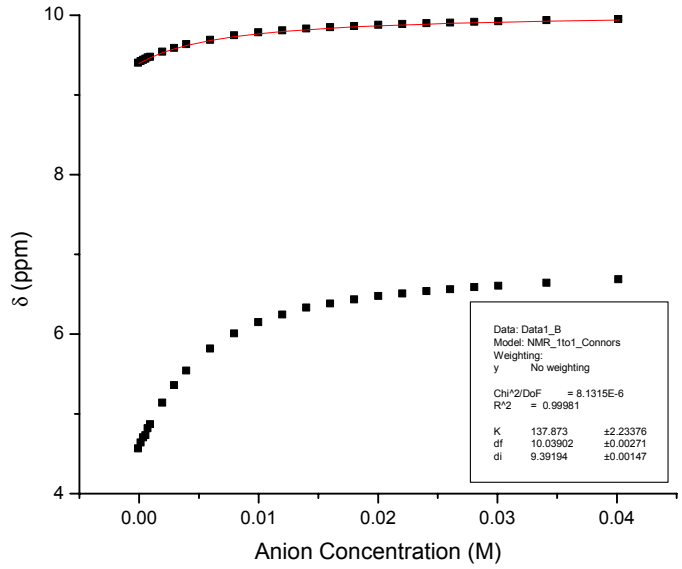


Figure 14. Titration curves for sulfonamide **4** with TBA NO_3^- in $CDCl_3$ at 25°C .

Figure 14. Titration curves for sulfonamide **4** with TBA Br^- in $CDCl_3$ at 25°C.



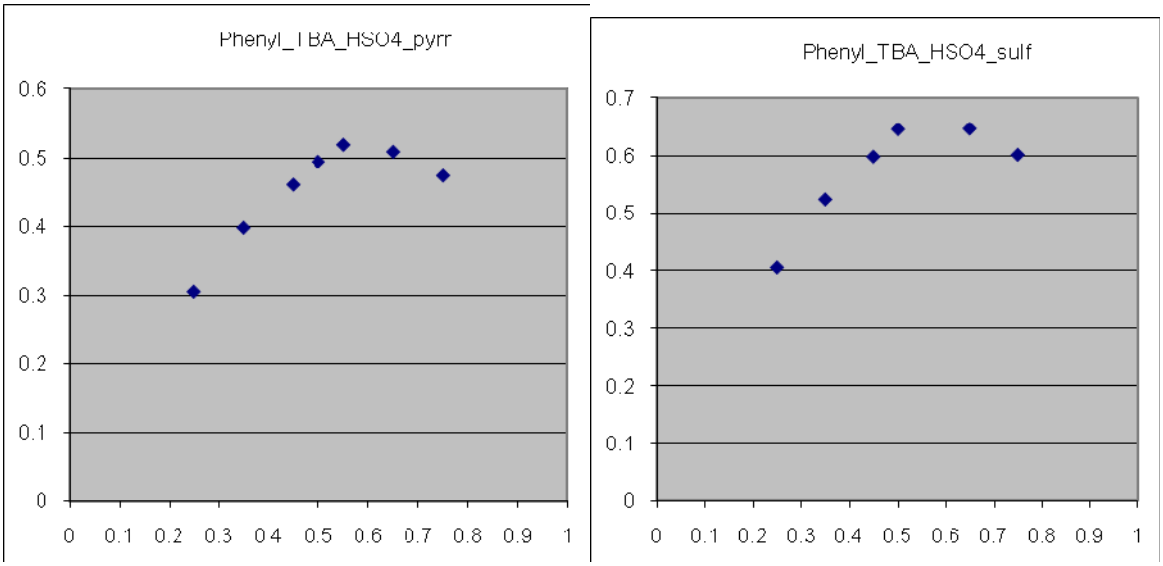


Figure 15. Job Plots for **1** with TBA HSO_4^- in $CDCl_3$ at 25°.

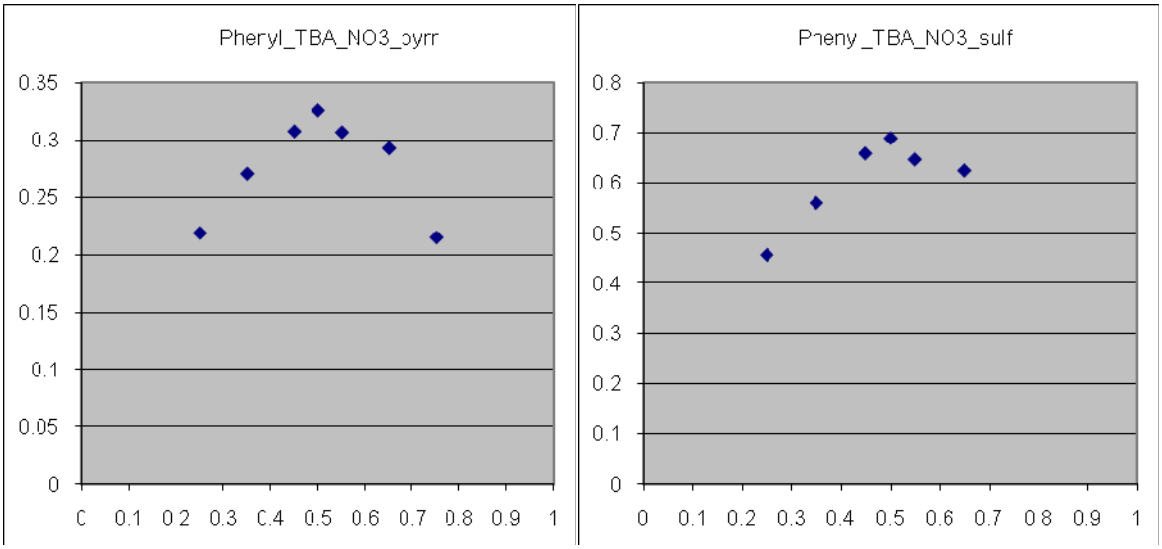


Figure 16. Job Plots for **1** with TBA NO_3^- in $CDCl_3$ at 25°.

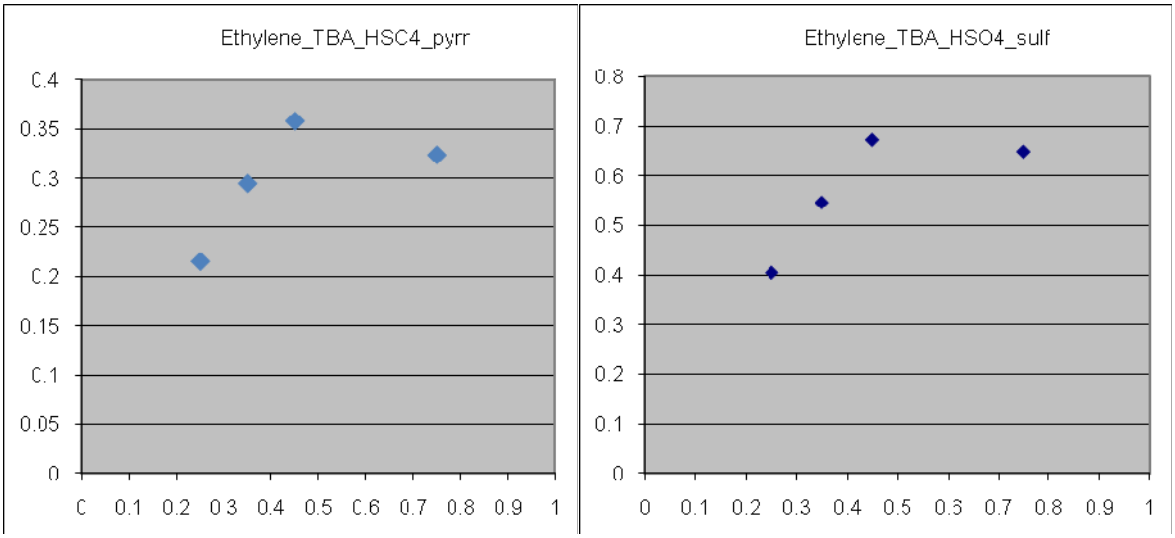


Figure 17. Job Plots for **3** with TBA HSO_4^- in $CDCl_3$ at 25°.