The aqueous-phase synthesis of sulfonylthioureas and a study of their properties as anion receptors

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Abstract

A series of mono- or bis-sulfonylthioureas has been synthesized via nucleophilic substitution of potassium sulfonamides and sodium dithiocarbamate in water under mild conditions, and their properties as anion receptors in the absence and presence of K^+ have been investigated by ^1H NMR spectroscopy. It was found that calix[4]crown-5 derivative **10** shows much higher selective complexation capability with $H_2PO_4^-$ in the presence of K^+ than in the absence of K^+, which indicates the physical dimension of K^+ and $H_2PO_4^-$, respectively, matched the corresponding cavity of the host compound.

Keywords: Synthesis, sulfonylthiourea, sulfonamide, dithiocarbamate, anion receptor, water

Introduction

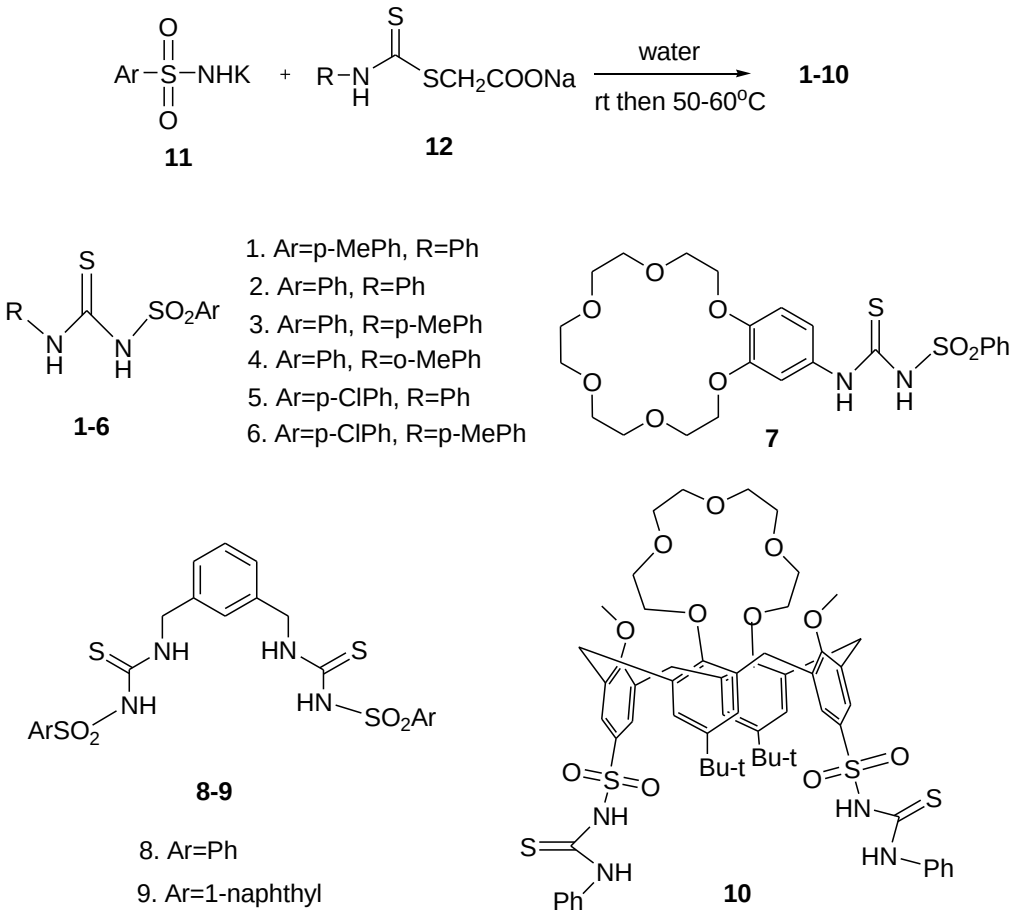
Thioureas are useful reagents for f. ex. anion complexation[1] and sensing[2], asymmetric catalysts[3] and solar cell construction[4]. The derived sulfonylthioureas display a broad spectrum of biological and pharmacological properties with action as antidiabetics[5], enhancers of parasympathetic system function[6], anticonvulsants[7], antiarrhythmics[8] or herbicides[9]. Furthermore, they are often used as synthetic intermediates[10] for a variety of guanidine drugs and also as building blocks[11] in the synthesis of heterocycles. Direct condensation of sulfonylisothiocyanate with amine in dry $CHCl_3$ or CH_2Cl_2 is the general procedure for the synthesis of sulfonylthioureas.[12] Another synthetic route[13] is nucleophilic addition of sulfonamide and isothiocyanate in the presence of inorganic bases in anhydrous acetone, DMF or DMSO. The two methods are frequently limited by harsh reaction conditions, lower yields, longer reaction times, and use of toxic solvents. To the best of our knowledge, the voluminous literature about applications of sulfonylthioureas does not mention the use of sulfonylthioureas as anion receptors probably due to their inaccessibility

by traditional synthetic methods.We now report the aqueous-phase synthesis of sulfonylthioureas and a study of their properties as anion receptors.

Results and Discussion

Aqueous-phase synthesis of sulfonylthioureas

The aqueous-phase synthetic method we offered holds many advantages such as mild reaction conditions, free organic solvent, high isolated product yields and very short reaction time. Thus it provided a better and more practical alternative to existing procedures. The synthetic route is outlined in Scheme 1. C=S of **12** has been activated by $ClCH_2COONa$. The reaction time is shorter for the preparation of **7** and **10**. It is because that benzo-18-crown-6 and calix[4]crown-5 can effectively bind K^+ from **11**. $ArSO_2NH^-$ become unsheltered, which makes nucleophilicity of **11** strengthened.



Scheme 1. Aqueous-phase synthesis of derived sulfonylthioures **1-10** under mild conditions.

Sulfonylthioureas **1-10** has been synthesized via nucleophilic substitution of potassium sulfonamides **11** and dithiocarbamate **12** at rt to 50-60 °C within 1.0 h in water. Aqua **11** were prepared from $ArSO_2NH_2$ and equivalent KOH in water. Corresponding $ArSO_2NH_2$ for the

synthesis of compound **10** was obtained based on the modified procedures.[14a,15] Aqua **12** were afforded from sodium dithiocarbamate and $ClCH_2COONa$ in water following the method.[14b] All new compounds were characterized by IR, ^1H NMR, ^{13}C NMR, mass spectra and elemental analysis.

In conclusion, we have designed and developed a convenient, efficient, economically and environmentally benign procedure for the synthesis of sulfonylthioureas which will be studied below for their properties as anion receptors.

Sulfonylthiourea-based properties as anion receptors.

2 and **7**−**10** were selected as test objects. Their properties as anion receptors were investigated by standard ^1H NMR titration using a ligands concentration (0.1−2.0 mM) and an increasing concentration of appropriate anion to obtain different host : guest ratios (0.1−20 : 1). To ensure the solubility of both organic ligands and inorganic anions, a mixed solvent system ($CDCl_3$−CD_3CN 4:1, v/v) was used. All anions were added as their tetrabutylammonium salts to minimize possible interactions of sulfonylthioureas with counter cations. The addition of anions led to the down-field shifts of $-SO_2NH-$ signals. Another experiment was carried out repeatedly in the presence of 2 eq. of $KBPh_4$ by the same procedure as described above.

Results are summarized in Table 1 and 2 where diphenylthiourea is taken as a reference. The binding constants of **8** and **10** towards some anions are too large to be determined accurately by ^1H NMR spectroscopy and the values given are rough estimations.

Table 1. Binding constants of **2**, **7**−**10**, and Ph-TU[a] ϕϕtowards anions[b] (^1H NMR titration, 400 MHz, $CDCl_3$−CD_3CN = 4 : 1, v/v, 25 °C, Kass, M^{-1})

anion[b]	Ph-TU	Receptor **2**	Receptor **7**	Receptor **8**	Receptor **9**	Receptor **10**
$H_2PO_4^-$	420	740	720	51000	1600	350000
HSO_4^-	170	260	220	1300	350	1470
I^-	6	8	11	9	5	165
Br^-	10	17	15	14	16	2000
Cl^-	13	26	19	18	25	2500

[a]Ph-TU: diphenylthiourea. [b]Counter-cation: NBu_4^+.

Table 1 shows that the association constants follow the trend $H_2PO_4^- > HSO_4^- > Cl^- > Br^- > I^-$ for **2** and **7**−**10** as well as Ph-TU. The observed binding selectivity can be roughly explained by the anion basicity order. **2** and **7**−**10** lead to much higher complexation constants if compared with the reference. This can be understood by considering the electron-withdrawing effect of SO_2 groups. The influence of the naphthyl group of **9** is less beneficial for complexation likely because of a decrease in electron delocalization energy. **10** showed higher selective

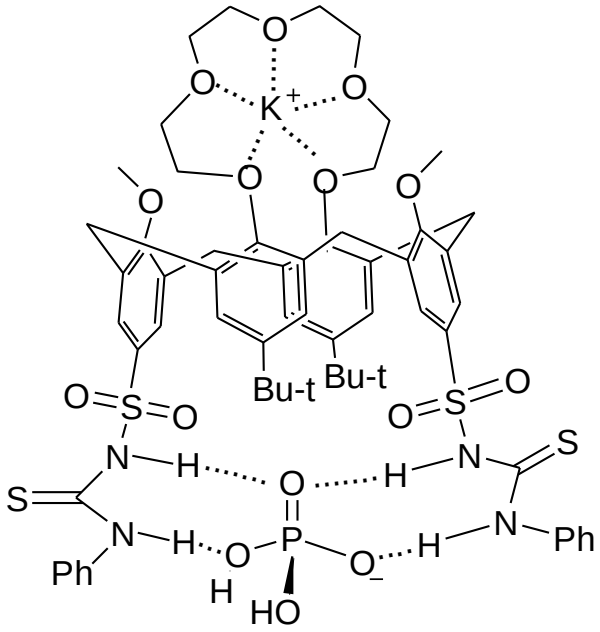
affinity for $H_2PO_4^-$ due to the enhanced hydrogen bonding ability of the sulfonylthiourea −N*H* protons. Most important of all, the cavity of **10** matched the size and shape of given $H_2PO_4^-$.

Table 2 indicates that **7** and **10** work as a novel bifunctional receptor for simultaneous complexation of K^+ and anions, where the ability of **7** and **10** to bind anions is significantly enhanced when K^+ is bound to the crown moiety. This is supported by their ^{1}H NMR spectroscopy, in which downfield shifts for sulfonylthiourea protons were observed upon complexation of K^+ at the crown moiety. But, no complexes of crown moiety can be detected when K^+ is replaced by the other metal ion such as Na^+, Rb^+, and Cs^+. By contrast, Ph-TU, **2**, **8**, and **9**, which lack crown ether moiety for K^+ binding, shows a small decrease for anions. **10** can act as a better bifunctional receptor. Selective complexation model of **10** with $H_2PO_4^-$ in the presence of K^+ is depicted in Scheme 2.

Table 2. Binding constants of **2**, **7**−**10**, and Ph-TU[a] towards anions[b] (^{1}H NMR titration, 400 MHz, $CDCl_3$−CD_3CN 4 : 1, v/v, 25 ºC, Kass, M^{-1}) in the presence of (2eq.) K^+ [c]

Anion[b]	Ph-TU	Receptor **2**	Receptor **7**	Receptor **8**	Receptor **9**	Receptor **10**
$H_2PO_4^-$	418	735	7500	50000	1590	3700000
HSO_4^-	165	255	600	1250	340	9470
I^-	5	4	110	7	4	1650
Br^-	9	16	150	12	14	2100
Cl^-	11	23	190	15	22	2800

[a]Ph-TU: diphenylthiourea. [b]Counter-cation: NBu_4^+. [c]Counter-anion: BPh_4^-



Scheme 2. Possible complexation model of **10** with $H_2PO_4^-$ in the presence of $K.^+$

Conclusions

In this study, a series of mono- or bis-sulfonylthioureas as potential hydrogen bond donors to bind some anions, has been synthesized via nucleophilic substitution of potassium sulfonamides and sodium dithiocarbamate in water under mild conditions, and the anion complexation in the absence and presence of K^+ has been examined by ^{1}H NMR spectroscopy. The presence of electron withdrawing sulfonyl group results in very high binding affinity towards anions compared with reference Ph-TU. **7** and **10** bearing crown ether moiety are found to work as a novel bifunctional receptor for simultaneously selective complexation of K^+ and $H_2PO_4^-$, where the ability of **7** and **10** to bind $H_2PO_4^-$ is significantly enhanced when K^+ is bound to the crown moiety, whereas receptor **10** shows a much higher complexation degree with $H_2PO_4^-$ due to the cavities of crown moiety and calixarene matching the physical dimensions of K^+ and $H_2PO_4^-$, respectively.

Experimental Section

General. The reagents used were of reagent grade and used as purchased. Melting points were measured by using a XT-4A Electrothermal micro-melting-point apparatus and are uncorrected. NMR spectra were recorded at 400 (^{1}H) and 100 (^{13}C) MHz, respectively, on a Bruker Avance III Plus 400 spectrometer in DMSO-d_6 using TMS as internal reference. Infrared spectra were obtained on a Bio-Rad spectrophotometer using KBr pellets. Mass spectra were measured using Agilent 6100B and Agilent 6220 Time-of-Flight LC/MS. Elemental analysis was determined on a Vario EL III elemental analyzer.

Typical procedure to synthesize sulfonylthioureas (1-10). To the aqueous solution of $ArSO_2NHK$ **11** (1 eq.) was dropwise added an aqueous solution of sodium dithiocarbamates **12** (1eq.). After the addition was completed, the reaction mixture was stirred for about 30 min at room temperature and was subsequently heated to 50-60 ^{o}C for another 30 min or so. Finally, the mixture was cooled to room temperature.The resulting precipitate was collected by suction filtration and washed successively with H_2O, then dried under vacuum over P_4O_{10} to afford sulfonylthioureas **1-10** in high purity and yields.

Sulfonylthiourea 1. Yield, 85%, white crystalline powder, mp 146-148 ^{o}C (lit.[16]: 144-146 ^{o}C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 9.75 (brs, 1H), 8.41 (brs, 1H), 7.82 (d, J = 8.3 Hz, 2H), 7.47-7.26 (m, 7H), 2.46 (s, 3H). IR (KBr, cm^{-1}) ν: 3302, 1597, 1518, 1481, 1381, 1178, 1146, 1082 cm^{-1}. HRMS (ESI) calcd for $C_{14}H_{15}N_2O_2S_2$ ($M + H^+$) 307.0575, found 307.0566.

Sulfonylthiourea 2. Yield, 82%, white crystalline powder, mp 135-137 ^{o}C (lit.[17]: 120 ^{o}C). ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 9.76 (brs, 1H), 8.80 (brs, 1H), 7.96 (d, J = 7.5 Hz, 2H),

7.74-7.29 (m, 8H). IR (KBr, cm^{-1}) ν: 3285, 1593, 1537, 1481, 1447, 1383, 1084 cm^{-1}. ESI-MS *m/z*: 293.2 (M＋H^+). Anal. calcd for $C_{13}H_{12}N_2O_2S_2$: C 53.40, H 4.14, N 9.58; found C 53.14, H 4.35, N 9.70.

Sulfonylthiourea 3. Yield, 82%, white crystalline powder, mp 149-151 ºC (lit.[17]: 124 ºC). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.68 (brs, 1H), 8.55 (brs, 1H), 7.95 (d, *J* = 7.3Hz, 2H), 7.71-7.57 (m, 3H), 7.28 (d, *J* = 8.4 Hz, 2H),7.19 (d, *J* = 8.4 Hz, 2H), 2.35 (s, 3H). IR (KBr, cm^{-1}) ν: 3298, 1595, 1533, 1474, 1448,1385, 1337, 1186, 1142, 1084 cm^{-1}. ESI-MS *m/z*: 307.1(M＋H^+). Anal. calcd for $C_{14}H_{14}N_2O_2S_2$: C 54.88, H 4.61, N 9.14; found C 54.58, H 4.99, N 9.14.

Sulfonylthiourea 4. Yield, 82%, white crystalline powder, mp 168-170 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.47 (brs, 1H), 8.80 (brs, 1H), 7.99 (d, *J* = 7.5Hz, 2H), 7.76-7.58 (m, 3H), 7.29-7.20 (m, 4H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 177.8, 138.4, 135.8,134.5, 134.3, 131.0, 129.7, 128.3, 127.2, 126.9, 126.8, 17.7. IR (KBr, cm^{-1}) ν: 3316, 3288, 1510, 1476, 1447, 1375,1186, 1167, 1144, 1084 cm^{-1}. ESI-MS *m/z*: 307.1 (M＋H^+). Anal. calcd for $C_{14}H_{14}N_2O_2S_2$: C 54.88, H 4.61, N 9.14; found C 54.49, H 5.00, N 9.13.

Sulfonylthiourea 5. Yield, 84%, white crystalline powder, mp 138-140 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.70 (brs, 1H), 8.72 (brs, 1H), 7.89 (d, *J* = 8.6 Hz, 2H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.51-7.27 (m, 5H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 176.6, 141.3, 137.0, 136.7, 130.1, 129.2, 128.6, 127.5, 124.4. IR (KBr, cm^{-1}) ν: 3304, 1574, 1516, 1475, 1454, 1385, 1186, 1172, 1146, 1082 cm^{-1}. ESI-MS *m/z*: 327.0 (M＋H^+). Anal. calcd for $C_{13}H_{11}ClN_2O_2S_2$: C 47.78, H 3.39, N 8.57; found C 47.62, H 3.54, N 8.38.

Sulfonylthiourea 6. Yield, 84%, white crystalline powder, mp 174-176 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.63 (brs, 1H), 8.49 (brs, 1H), 7.88 (d, *J* = 8.7 Hz, 2H), 7. 56 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 176.6, 141.3, 137.6, 136.7, 134.5, 130.1, 129.8, 128.6, 124.4, 21.1. IR (KBr, cm^{-1}) ν: 3310, 1578, 1522, 1475, 1387, 1178, 1146, 1080 cm^{-1}. ESI-MS *m/z*: 341.0 (M＋H^+). Anal. calcd for $C_{14}H_{13}ClN_2O_2S_2$: C 49.33, H 3.84, N 8.22; found C 49.33, H 3.69, N 8.12.

Sulfonylthiourea 7. Yield, 81%, white crystalline powder, mp 104-106 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.61 (brs, 1H), 8.46 (brs, 1H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.70-7.25 (m, 4H), 7.17 (d, *J* = 8.9 Hz, 1H), 7. 06 (d, *J* = 8.9 Hz, 1H), 6.89 (d, *J* = 5.8 Hz, 1H), 4.25 (m, 4H), 4.21 (m, 8H), 4.11 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 179.6, 147.0, 142.6, 139.7, 132.5, 129.3, 129.1, 127.3, 118.7, 115.3, 110.4, 71.2, 70.6, 70.5, 69.4, 69.3. IR (KBr, cm^{-1}) ν: 3280, 3220, 1576, 1520, 1477, 1389, 1176, 1144, 1082 cm^{-1}. ESI-MS *m/z*: 527.14 (M＋H^+). Anal. calcd for $C_{23}H_{30}N_2O_8S_2$: C 52.46, H 5.74, N 5.32; found C 52.43, H 5.79, N 5.29.

Sulfonylthiourea 8. Yield, 79%, white crystalline powder, mp 184-186 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.80 (brs, 2H), 8.82 (brs, 2H), 7.98 (d, *J* = 8.1 Hz, 2H), 7. 93-7.54 (m, 8H), 7.02 (dd, *J* = 7.3 Hz, 1H), 6.87 (d, *J* = 7.3 Hz, 2H), 6.86 (d, *J* = 5.3 Hz, 1H), 4.79 (d, *J* = 5.1 Hz, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 184.1, 141.5, 139.7, 132.0, 129.1, 128.4, 127.3, 126.7, 125.4, 51.3. IR (KBr, cm^{-1}) ν: 3376, 3276,

3162, 3059, 2933, 2869, 1579, 1385, 1168, 1149, 1080, 707, 694 cm^{-1}. ESI-MS *m/z*: 535.05 (M ＋H^+). Anal. calcd for $C_{22}H_{22}N_4O_4S_4$: C 49.42, H 4.15, N 10.48; found C 49.41, H 4.19, N 10.45.

Sulfonylthiourea 9. Yield, 78%, white crystalline powder, mp 180-182 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.79 (brs, 2H), 8.72 (brs, 2H), 7. 97-7.64 (m, 14H), 7.01 (dd, *J* = 7.3 Hz, 1H), 6.85 (d, *J* = 7.3 Hz, 2H), 6.82 (d, *J* = 5.3 Hz, 1H), 4.76 (d, *J* = 5.1 Hz, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 184.1, 141.9, 141.5, 134.0, 131.5, 130.9, 128.4, 128.3, 126.7, 126.6, 126.3, 125.0, 124.5, 51.3. IR (KBr, cm^{-1}) ν: 3376, 3182, 3054, 2972, 2929, 1596, 1541, 1501, 1437, 1396, 1272, 1236, 1084, 763, 522 cm^{-1}. ESI-MS *m/z*: 635.08 (M＋H^+). Anal. calcd for $C_{30}H_{26}N_4O_4S_4$: C 56.76, H 4.13, N 8.83; found C 56.74, H 4.15, N 8.81.

Sulfonylthiourea 10. Yield, 75%, white crystalline powder, mp 260-162 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.23 (brs, 2H), 8.86 (brs, 2H), 7.50 (s, 4H), 7.45 (m, 10H), 6.47 (s, 4H), 4.38 (d, $J_{ax,\,eq}$ = 14.6 Hz, Hax, 4H,), 4.41–3.87 (m, 16H), 3.17 (d, $J_{ax,\,eq}$ = 14.6 Hz, Heq, 4H), 1.62 (s, *J* = 7.5 Hz, 6H), 1.39 (s, 18H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 206.1, 157.5, 152.3, 147.3, 146.3, 137.7, 135.4, 127.8, 127.3, 125.6, 125.3, 123.4, 123.3, 73.9, 73.5, 72.4, 72.2, 71.9, 36.5, 33.3, 32.4 ; IR (KBr, cm^{-1}) ν: 3283, 3225, 1578, 1521, 1145, 1086, 765, 523 cm^{-1}. ESI-MS *m/z*: 1151.39 (M ＋H^+). Anal. calcd for $C_{60}H_{70}N_4O_{11}S_4$: C 62.58, H 6.13, N 4.87; found C 62.57, H 6.15, N 4.85.

Measurement of sulfonylthiourea-based properties as anion receptors

The measurements were performed by ^{1}H NMR titration experiments in $CDCl_3$-CD_3CN (v/v=4 : 1) at 298 K using a constant host concentration of 2.0 mM and a varying guest concentration of 0.1-20 mM. For each K_{ass} value determination, 5-10 different guest concentrations were taken As a probe, the chemical shift of the SO_2NH signal was used.

In the presence of K^+, anion complexation was measured analogously to the above procedure.

The K_{ass} values were calculated by the equation below as described in literature[18].

$$K_{ass} = \alpha / [(1-\alpha)([G]-\alpha[H])]$$

where $\alpha=(\delta-\delta_0)/(\delta_{max}-\delta_0)$,$\delta_0$ is the initial chemical shift (host only), δ is the chemical shift at each titration point, andδ_{max} is the chemical shift when the receptor is entirely bound.

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