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Elite New Anion Ligands: Polythioamide Macrocycles

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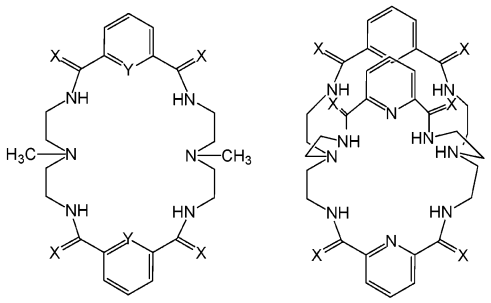
Prototypes for a new class of polythioamide-based macrocycles have been synthesized and anion-binding capabilities assessed. Results indicate higher anion binding for $H_2PO_4^-$, HSO_4^-, and F^- for monocycles, but somewhat lessened binding capabilities for bicycles compared with amide corollaries.

While a natural progression in anion coordination chemistry has been the design and synthesis of neutral amide-based receptors for anions,[1] to our knowledge thioamide-based macrocyclic anionophores have not been reported. Thioamides have been known for a long time as excellent chelating agents for heavy metal ions[2−4] and in therapeutic applications.[5] They have also been used in ferrocenoyl-based anion receptors.[6] Hence, the design of thioamide macrocycles for anion recognition appeared to be a promising strategy toward achieving enhanced anion binding. We have now synthesized prototypes for this elite new class of macrocycles, monocycles **1** and **2**, and bicycle **3**, by converting simple amide-based precursors, **4**−**6**,[7] to thioamides. Herein are described preliminary findings for anion binding for the first thioamide-based macrocycles, **1**−**3**, and crystal structures of the free bases of **1** and **3**.

In earlier work we explored monocyclic and bicyclic polyamine receptors with isophthalaldehyde and related spacers for anion recognition, focusing on the role of dimensionality on binding.[8] More recently we have broadened the scope of our ligands for anions to include similar amide-base receptors,[7,9] acyclic analogues of which were successfully introduced by others as effective recognition frameworks.[10] Compared to amides, however, thioamide ligands are predicted to display enhanced acidities, the result of the increased polarizability of the sulfur with a concomitant decrease in the N−H bond energy (∼10 kcal mol^{-1}).[11−13] This subtle change, when magnified by multiple thioamide sites, was anticipated to lead to enhancement of the hydrogen-bonding capabilities so important in anion recognition.



1 X = S, Y = CH
2 X = S, Y = N
4 X = O, Y = CH
5 X = O, Y = N

3 X = S
6 X = O

Compounds **1** and **2** were prepared from the reaction of the amide precursors, **4** and **5**,[7] with 2 equiv of Lawesson's reagent[14] in toluene. The bicyclic amide-based cryptand **6**

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Table 1. Association Constants (log K_a) of the Ligands with Anions in DMSO-d_6[a]

	log K_a/dm^3 mol^{-1}					
ligand	$H_2PO_4^-$	HSO_4^-	F^-	Cl^-	Br^-	I^-
			Monocycles			
1	4.97[b]	3.15	2.85	2.02	2.00	1.44
2	4.63[c]	4.99[c]	4.11[c]	2.60	1.40	<1.0
4	2.92	2.89	2.63	1.39	1.30	<1.0
5	4.05	2.03	2.61	2.69	2.71	<1.0
			Bicycles			
3	3.40	1.69	4.50[c]	1.54	<1.0	<1.0
6	3.31	1.83	5.90[c]	3.48	1.60	1.30

[a] Estimated deviations less than 5% unless otherwise noted. [b] Estimated deviation 10%. [c] Slow exchange; estimated error less than 15%.

was synthesized in CH_2Cl_2 from the condensation of 2 equiv of tris(2-aminoethyl)amine with 3 equiv of 2,6-pyridinedicarbonyl dichloride in the presence of Et_3N as a base. The product was isolated in 10% yield after column chromatography (neutral Al_2O_3, 5% CH_3OH in CH_2Cl_2). The thioamide cryptand, **3**, was prepared from **6** by reaction with 3 equiv of Lawesson's reagent in toluene. Crystals of the thioamide free base **1** were obtained from slow evaporation of a DMSO solution of the ligand,[15] and crystals of **3** were grown from CH_3OH/CH_3CN at room temperature.[16]

The binding of the new receptors **1**−**3** with a variety of inorganic anions was investigated in DMSO-d_6 and compared with that observed for the amide precursors. The addition of aliquots of the Bu_4N^+ salts of $H_2PO_4^-$, HSO_4^-, NO_3^-, ClO_4^-, F^-, Cl^-, Br^-, and I^- to solutions of the receptors led to downfield shifts of all the ligand proton resonances. Determination of the binding constants for several of the anions was complicated by slow exchange on the NMR time scale for the thioamide pyridine macrocycle **2**.[17] This was also the case in binding studies of the cryptands **3** and **6** with F^-. Association constants are presented in Table 1.[17,18] The titration data gave the best fit for 1:1 stoichiometries of host to guest, in agreement with the Job plots, which indicated a maximum $\Delta\delta$ at ca. 0.5 = [**L**]/([**L**] + [A$^-$]). Examples of the titration curves for **1** are shown in Figure 1. The results indicated that, for monocycles, the thioamide ligands **1** and **2** are superior in binding the two oxo acids, $H_2PO_4^-$ and HSO_4^-, and F^- compared to the amide-based receptors **4** and **5**. Binding was negligible for NO_3^- and ClO_4^-. The thioamide bicycles in general exhibited lessened binding compared to the amide corollaries.

As noted previously, the trend in higher affinities for the tetrahedral oxo acid anions may be linked to acid−base properties of both the ligand and the anion.[7] The absence of significant binding with ClO_4^- indicates geometry is not the predominant factor. The presence of the basic tertiary amines can facilitate extraction of the proton from the oxo acid, bringing the anion in position for docking with the ligand. The high binding of **2** with HSO_4^- is particularly striking, since sulfate does not usually exhibit strong hydrogen-bonding capabilities compared to phosphate. Earlier work with the *m*-xylyl derivative **4** also indicated strong and selective binding of HSO_4^- in $CHCl_3$. Crystallographic results for **4** indicated a sandwich-like structure with the sulfate held by eight hydrogen bonds emanating from two different macrocycles, i.e., a type of "macrocyclic effect".[7] It may be that a similar situation is occurring for the interaction of **2** with HSO_4^- in DMSO.

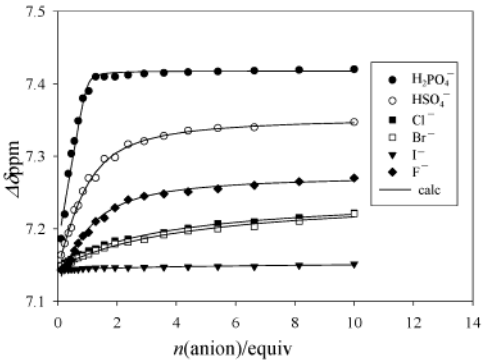

Figure 1. ^{1}H NMR titration curves following chemical shifts of the aromatic Y = C*H* proton of **1** with various anions.

Results for the bicyclic systems were at first glance somewhat surprising, since, in polyammonium anion receptors, bicyclic aza cryptands usually exhibit higher affinities for anions than monocycles.[8,19] While the thioamide **3** and the amide **6** cryptands show high affinities for F^-, decreased affinities compared to the monocycles are seen for most of the other anions. This may be a result of the presence of the C═O or C═S moieties, which could be involved in internal hydrogen bonding with amides in adjacent arms. Others have seen this type of conformation in a small urea-based cryptand,[20] and we have also seen it in acyclic tren-based amides.[21] Although the crystallographic data for **3** indicate internally oriented amide hydrogens (vide infra), this does not preclude solution changes of conformation.

Although 1:1 stoichiometries are observed in the titrations, we suspect that, at high concentrations of F^-, ditopic complexes may be formed. This is evidenced by the NMR titration of **3** with *t*-BuN^+F^-. As initial equivalents of F^- are added, the singlet amide signal at 10.62 ppm is replaced by a new doublet at 13.01 ppm, the result of coupling with a single F^- nucleus (I = $^1/_2$) (Figure 2). At the same time two new aromatic signals appear at 8.19 and 8.92 ppm, replacing the original signals at 7.94 and 8.41 ppm, respectively. This trend continues up to 1.0 equiv of F^-, at which

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(15) Crystal data for **1**, $C_{26}H_{34}N_6S_4$: monoclinic; $P2_1/n$; a = 7.7444(6) Å, b = 20.3145(15) Å, c = 9.0829(7) Å, β = 102.658(2)°, V = 1394.22(18) Å^3; Z = 2; d_{calc} = 1.331 g cm^{-3}.
(16) Crystal data for **3**, $C_{33}H_{39}N_4S_6$: triclinic; $P\bar{1}$; a = 12.0283(12) Å, b = 12.1094(12) Å, c = 14.0344(13) Å, α = 84.9792(2)°, β = 79.876(2)°, γ = 78.866(2)°, V = 1971.4(3) Å^3; Z = 2; d_{calc} = 1.387 g cm^{-3}.
(17) The titration was done by 20 measurements in DMSO-d_6 at room temperature on a Bruker AM500 spectrometer. Aliquots from a stock solution of *n*-BuN^+ salts (20 mM) were gradually added to the solution of ligand (2 mM). Association constants K were calculated as in refs 7 and 17, or by using the integration of the NH signals for free and complexed ligands to calculate binding in the case of slow exchange.
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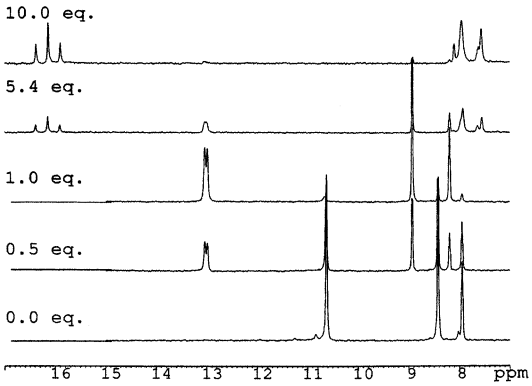

Figure 2. Partial ^{1}H NMR spectra of **3** in the presence of *n*-$Bu_4N^+F^-$ in DMSO-d_6.

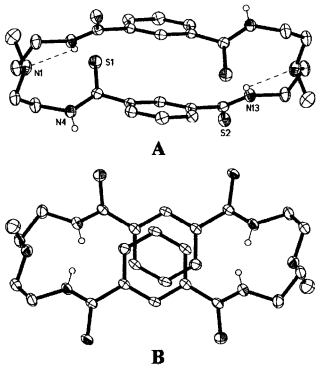

Figure 3. ORTEP drawing of the structure of **1** showing both a side view (A) and an overhead view (B) of the free base. Thermal ellipsoids are at 50% probability.

time the original amide and aromatic proton signals have almost disappeared. As the titration continues, new amide and aromatic signals appear, the former a triplet way downfield at 16.14 ppm (*J* ca. 120 Hz). We have assigned this signal to a complex in which the amide protons are symmetrically coupled to two F^- nuclei. Several new aromatic signals appear upfield, which may be indicative of a breakdown of the symmetry of the complex. From integration of the signals, we suspect that the two fluorides are only coupling with four amide protons. These findings are currently being probed further.

Crystal structures for the free bases of the monocycle **1** and bicycle **3** have been obtained (Figures 3 and 4, respectively). In the X-ray structure of the neutral, uncomplexed **1**, the macrocycle sits on a crystallographic center of symmetry, with an elongated bridgehead axis (N(1)···N(1)′ = 10.602(3) Å). The *m*-xylyl groups are coplanar, with offset $\pi-\pi$ stacking at 3.522(6) Å (Figure 3B). Two of the

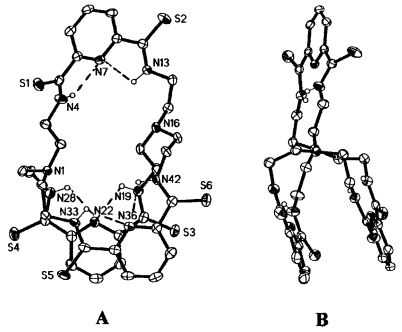

Figure 4. ORTEP drawing of the structure of **3** showing both a side view (A) and a view down the bridgehead amine axis (B). Thermal ellipsoids are at 50% probability.

thioamide hydrogens point to the center of the cavity and are hydrogen bonded with N(1) and N(1)′ at 2.686(2) Å.

In the structure of **3** (Figure 4), the receptor is elongated along the axis perpendicular to the bridgehead axis. Two of the spacer arms are pointed in relatively the same direction, while one is in the opposite direction. The net result of this elongation is a very short distance between the bridgehead amines (5.687 Å). All of the thioamide nitrogens point inside the cavity, stabilized by hydrogen bonding with the pyridine spacers.

In conclusion, prototypes for a new class of elite polythioamide-based macrocyclic receptors have been prepared by straightforward synthetic procedures. Increased binding in DMSO is observed for the monocycles **1** and **2** for $H_2PO_4^-$, HSO_4^-, and F^- compared with the amide corollaries. Selectivity is observed for **3** (and **6**) with F^-, **1** (and **5**) with $H_2PO_4^-$, and **2** with HSO_4^-. By virtue of the enhanced acidities of the NH groups as well as the presence of the soft, polarizable sulfur atoms, these new ligands may open the door to a whole new area of chemistry.

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Supporting Information Available: Synthetic procedures and NMR titration (PDF) and two crystallographic files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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