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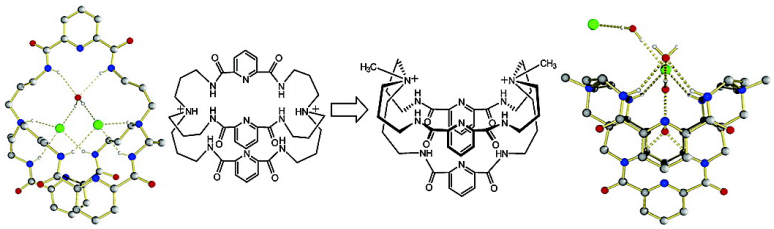

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Anion Binding Motifs: Topicity and Charge in Amidocryptands

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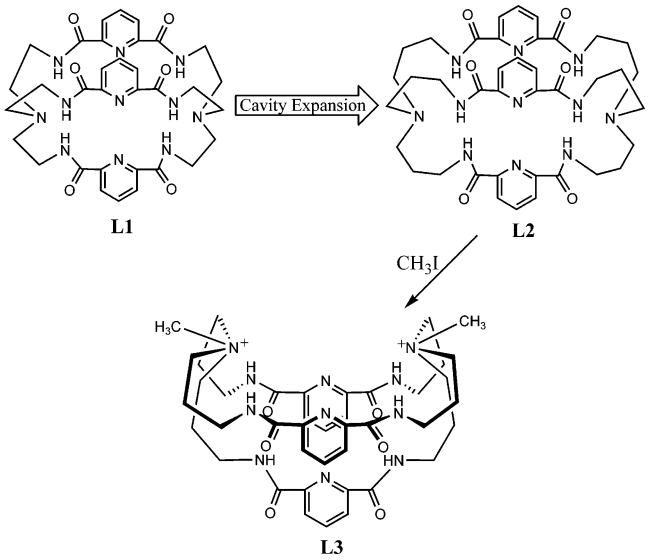
In a systematic approach to probe the influence of hydrogen bonding, dimensionality, and charge on structure and selectivity in anion binding, we designed a series of amide-based macrocycles and cryptands. Acyclic,[1] monocyclic,[2,3] and bicyclic[4−6] receptors were synthesized, and structural and binding aspects with anions were explored. In monocycles, the addition of charge by quaternization of tertiary amines enhanced binding considerably,[3] so a similar effect was anticipated for the cryptands. Furthermore, bicyclic cryptands, such as **L1** (Scheme 1), offer advantages compared to their monocyclic analogues due to the cage-like structure that can capture and sequester anions. Attempts at quaternizing **L1**, however, resulted in disappointingly low yields. A slight modification using tris(3-aminopropyl)amine (trpn) instead of the ever popular tris(2-aminoethyl)amine (tren) for the bridgehead tripod resulted in a new amidocryptand, **L2**. The expanded cryptand also provides a better template for quaternization because of the larger cavity, which leads to **L3** (Scheme 1). Preliminary results bring significant insight to anion binding and structure in these capsule-like receptors. These are the first examples of multitopic inclusion of anions in amide-based cryptands and of quaternized amidocryptands.

L2 was synthesized from the condensation of 2 equiv of trpn and 3 equiv of 2,6-pyridinedicarbonyl dichloride in CH_2Cl_2 in the presence of Et_3N as a base. **L2** was isolated in 10% yield after chromatography through two columns (silica gel, 15% CH_3OH in CH_2Cl_2, followed by basic aluminum oxide, 5% CH_3OH in CH_2Cl_2). Both "neutral" amidocryptand complexes crystallized as the diprotonated salts: $[H_2\mathbf{L2}(Cl)_2(H_2O)]\cdot CH_3OH$, grown from slow evaporation of a $CHCl_3$/MeOH solution of **L2**, and $[H_2\mathbf{L2}(SO_4)(H_2O)_2]\cdot 3H_2O\cdot CH_3CN$, grown from a $CHCl_3/CH_3CN$ solution of **L2** in the presence of excess of n-$Bu_4N^+HSO_4^-$. **L2** was quaternized using CH_3I to give **L3** in 80% yield. The chloride complex was obtained from a solution of **L3** in CH_3CN in the presence of excess n-$Bu_4N^+Cl^-$. The oxalate complex was obtained by adding a stoichiometric amount of oxalic acid to a solution of **L3** in CH_3CN. Crystals were grown from a water solution of the isolated oxalate salt.

In both **L2** structures, the ligand folds with two of the diamide loops directed in one direction, while the third points in the opposite direction, depicted as an inverted Y-shape (Figure 1, B and D). This face-to-face orientation of bridges containing pyridine spacers has been seen by us[3] and others[8] in pyridine-containing amido- and azacryptands, respectively, and may be influenced by π stacking interactions. The two **L2** complexes each contained three species within the cryptand cavity. In the chloride complex, two chlorides (scavenged from small amounts of HCl in the $CHCl_3$ used for crystallization)[4] are bridged by a "cascading" water molecule (Figure 1, A and B). The binding is similar to that observed in a related protonated azacryptand,[7] with each halide in a pseudo-tetrahedral coordination geometry. The bridging (or cascade) effect is reminiscent of that observed with transition metals bound in neutral azacryptands, where the bridging species is an anion.[9] The

Scheme 1. Schematic Design Strategy



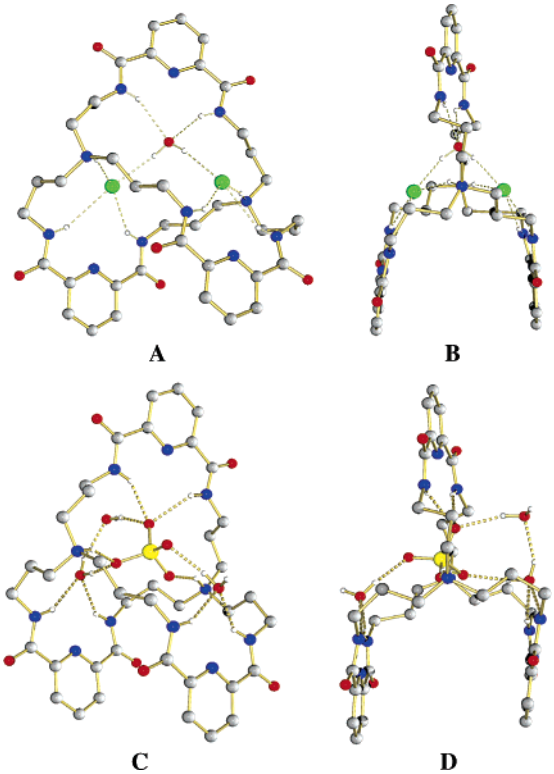


Figure 1. Two views each of the anion complexes of **L2**: (A) and (B), the chloride complex; (C) and (D) the sulfate complex.

sulfate structure, containing two independent but similar cryptand units, more closely parallels this latter scenario by containing a bridging anion (Figure 1, C and D). Two water molecules, instead

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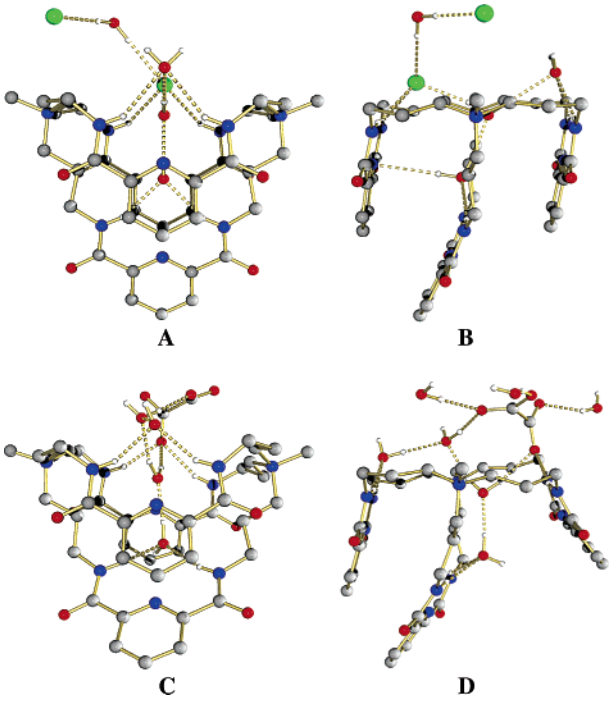

Figure 2. Two views each of the anion complexes of **L3**: (A) and (B), the chloride complex; (C) and (D) the oxalate complex.

of two metal ions, are bridged by the sulfate inside the cavity in both cryptand units. The geometry in both units is a distorted monocapped trigonal pyramid similar to that observed in the seven-coordinate sulfate binding protein.[10]

The quaternized $\mathbf{L3}^{2+}$ structures reveal a totally different conformation compared to that of **L2**, with all three loops pointing in the same direction to give the receptor a bowl-like shape (Figure 2). The chloride and oxalate complexes crystallize with multiple solvent molecules, $\mathbf{L3}\cdot 2Cl\cdot 5H_2O\cdot 4CH_3CN$ and $\mathbf{L3}\cdot C_2O_4\cdot 15H_2O$, respectively. In both these structures, water appears to play an important structural role, with a number of waters being held within the "bowl", and the anions floating on top. Solvent can play a critical role in stabilizing host−guest complexes, as recently noted by Burns and co-workers.[11] In neither complex, however, are the anions encapsulated. Rather, in the chloride structure (Figure 2, A and B), one chloride is centered between the two quaternized amines at the top of the bowl (Figure 2, A) and tied by four hydrogen bonds to amide hydrogens and water molecules. In the oxalate structure, the oxalate also lies centered between the two charged sites (Figure 2, C). One oxygen of the dicarboxylate anion is held by three hydrogen bonds to two amide hydrogens and a water molecule in the bowl, while the second oxygen is hydrogen bonded to two water molecules. The two carbonyl oxygens of the oxalate are also hydrogen bonded to surrounding water molecules (Figure 2, D). The centered anions in both structures result in an almost symmetrical balance of negative charge between the two positive "poles", which may be the driving force in promoting the bowl-like structure.

Preliminary binding studies of **L2** and **L3** were performed by ^{1}H NMR titrations in DMSO-d_6 (Table 1). Results indicated that **L2** is extremely selective for fluoride as also observed for **L1**.[4] On the other hand, **L3** is selective for $H_2PO_4^-$ and possibly F^-, the latter determination being complicated due to signal broadening. The best curve fits were obtained for 1:1 binding modes in all cases. Binding studies are currently being expanded to other anions, including carboxylates.

Table 1. Association Constants (K) of **L2** and **L3** with Anions

	K/M^{-1}[a]					
L	F^-	Cl^-	Br^-	HSO_4^-	$H_2PO_4^-$	NO_3^-
L1[4]	$>10^5$ [b]	3000	40	68	2000	85
L2	$>10^5$ [b]	180	7	2700	170	<5
L3	*c*	3100	1300	340	12000	92

[a] In DMSO-d_6 at room temperature. Standard deviations are less than 10%. Constant ionic strength was not maintained. [b] Slow equilibrium. [c] Calculation not possible due to peak broadening and irregular shift of NH protons.

In conclusion, the cascade-type crystal structures of **L2** are the first examples of multitopic anion inclusion in amidocryptands, with binding in the sulfate complex resembling that seen in the sulfate binding protein.[10] **L3** represents a new addition to amidocryptands. Although charge complementarity was expected to enhance binding, the quaternized cryptand binds anions with magnitudes similar to that of **L1** and **L2**. However, **L3** complexes display a folded bowl-like geometry quite different from the conformation observed in other amidocryptand structures.[4−6] Furthermore, in both **L2**, but especially **L3**, water seems to play an important role in connecting anions to binding sites. Hence, cavity size and flexibility appear to be the operative factors determining topicity, seen in comparing the tritopic **L2** structures with monotopic **L1** complexes.[4−6] On the other hand, charge positioning seems to be the major shape-determining factor in the quaternized systems. Hence, while **L2** brings insight to size and topicity considerations, the quaternized **L3** adds another structural motif that could be important for the further development of highly selective capsules and bowls for anion chemistry.

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Supporting Information Available: Crystallographic data (CIF), synthetic procedures, analytical data, ^{1}H NMR spectra, and binding curves with anions, crystallographic information, and ORTEP drawings for **L2** and **L3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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