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Tricyclic Host for Linear Anions

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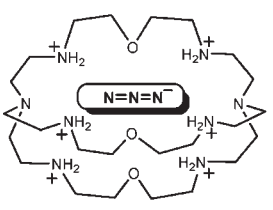
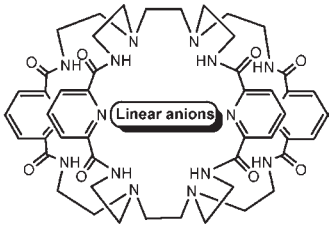
A tricyclic host for anions consisting of two tetraamide monocycles attached by two ethylene chains was designed and synthesized. Structural and binding results indicate that the receptor is selective for linear triatomic anions. Crystallographic data for two hydrated free bases, along with FHF^-, N_3^-, and SO_4^{2-} complexes indicate that there are at least two preferred gross conformations for the host, one of which possesses pseudo-D_2 symmetry and the other pseudo-C_{2h} symmetry. Both FHF^- and N_3^- are encapsulated in the pseudo-D_2 symmetric complex, bridging the two tetraamido macrocyclic halves. The pseudo-C_{2h} octahydrate structure shows an ice-like H-bonded $(H_2O)_6$ array of water molecules embedded in the host cavity. The SO_4^{2-} structure has a nearly superimposable host conformation to the octahydrate but with the SO_4^{2-} anions lying outside the host. Binding studies in DMSO-d_6 indicate selectivity for FHF^-, with lesser affinity for other inorganic anions.

Introduction

In the past decade, anion coordination chemistry has been established as an independent field,[1−3] and the wide selection of ligand sizes, shapes, and H-bond donor groups is impressive. In part, this is because host design is a key factor to targeting H-bond directionality preferences for anions that differ in shape and size. Spherical anions were early targets of anion researchers,[4] and even more recently F^- is still of great interest.[5] However, the first example of a structural report of an encapsulated multiatomic anion with more complex H-bonding needs was for the triatomic N_3^- ion.[6] The host in this case was a relatively simple bicyclic azacryptand, bis-tren, reported by Lehn and co-workers. Because of its cylindrical shape, bis-tren was considered to be a perfect fit for linear anions, suggesting that FHF^- might also be a candidate for encapsulation. Since then other hosts for N_3^- have been reported.[7] However, despite the reported physical evidence for FHF^- encapsulation in solution,[8] no crystallographic confirmation of sequestration had been obtained for FHF^- until our earlier communication.[9]



[bis-tren(N_3)]$^{5+}$



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In a systematic study over the past decade of the influence of dimensionality on anion binding, we have designed a series

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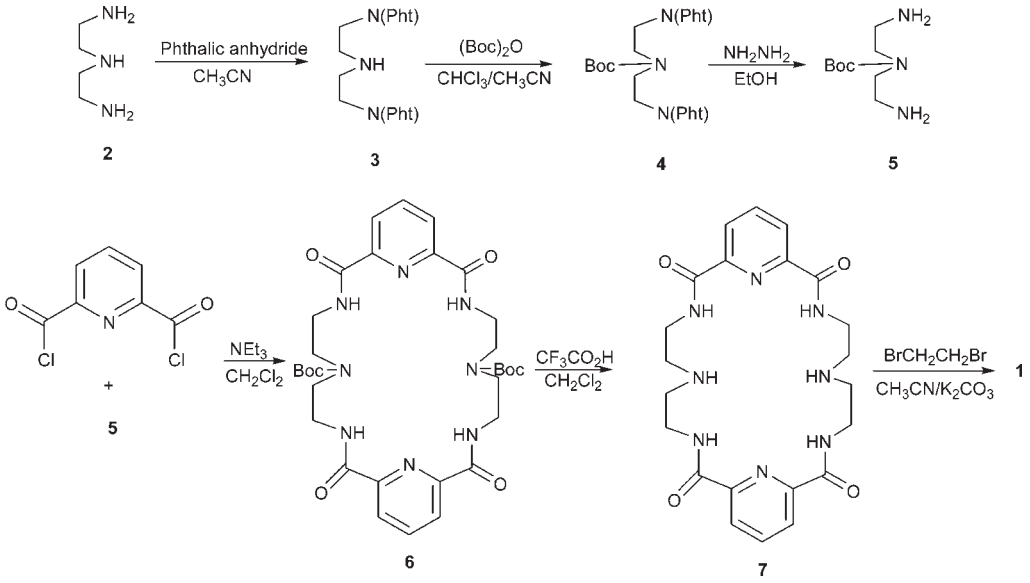
Scheme 1. Synthesis of Tricycle **1**



of mixed amide/amine-containing hosts of expanding complexity. Monocycles appear to be selective for oxo acids,[10] while bicyclic cryptands show higher affinities for halides, especially F^-.[11] By connecting two monocycles with an ethylene bridge, the tricycle **1** materialized. Only a limited number of higher-order multicyclic amide anion hosts have been reported[12−16] even though these more complex hosts show great potential for anion coordination. Binding properties of the new tricycle **1** indicated a preference for the small triatomic FHF^- ion, and crystallographic studies indicated encapsulation between the two macrocyclic units.[9] Subsequent experimentation led to the isolation of an almost identical structure of an encapsulated N_3^- ion. Crystal structure determination and solution chemistry are reported herein for the new anion host, the tricyclic receptor **1**, and its anion complexes.

Results and Discussion

Synthesis. The tricycle was synthesized by bridging two tetraamido macrocycles with two ethylene spacers. The monocycle **7**, the key precursor to **1**, was synthesized using selective protection and deprotection techniques (Scheme 1) since the condensation reaction of diethylenetriamine without the central amine protection did not give the desired macrocycle. The terminal amines of diethylenetriamine **2** were protected with phthaloyl (Pht) groups, followed by protection of the central secondary amine with a tert-butoxycarbonyl (Boc) group. Deprotection of the terminal amines with hydrazine gave the Boc-protected triamine **5** which yielded **6** upon condensation with an equimolar amount of pyridine-2,6-dicarbonyl chloride in the presence of Et_3N as a base. This key macrocyclization reaction also yielded 1x1 and 3x3 adducts as minor products. Better yields of the desired product were obtained with high dilution conditions. The deprotected macrocycle **7** resulted after **6** was reacted with trifluoroacetic acid. The tricycle **1** was obtained in 30% yield by coupling two of the macromonocycles, **7**, at the unprotected amine sites using dibromoethane. The overall yield for the entire sequence was 2.8%.

Structural Considerations. Two different preferred conformations were found for **1** (one with pseudo-D_2 symmetry and one with pseudo-C_{2h} symmetry). In the hexahydrated free base and the FHF^- and N_3^- complexes, the two folded macrocycles were rotated from each other by 90° about a pseudo-S_4 axis running through the center of the two monocycles. However, the integrity of this axis is broken in the free base **1**·6H_2O because of intramolecular C═O···HN H-bonds. For the octahydrated free base and the bis-SO_4^{2-} complex, pseudo-C_{2h} symmetry was observed for the once again folded macrocycles. These two conformational classes are discussed separately below. Selected H-bond distances are provided in Tables 1 and 2, and perspective views of the hosts are shown in Figures 1 and 2, for the pseudo D_2 and C_{2h} symmetry classes, respectively.

Pseudo-D_2 Structures (S_4-like Symmetry): [1]·6H_2O, [1(FHF^-)], and [1(N_3^-)]. The prototype host structure for the pseudo-D_2 conformation is the hexahydrated free base structure, [**1**]·6H_2O, which crystallized in the monoclinic space group $C2/c$. The N_3^- complex, [nBu$_4$N$^+$][**1**(N_3^-)]·3H_2O, crystallized in the monoclinic space group $C2_1$,

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Table 1. Selected H-Bonding Distances for [**1**], [**1**(N_3^-)], and [**1**(FHF^-)][a]

D−H···A	*d*(D···A)	∠(DHA)	D−H···A	*d*(D···A)	∠(DHA)
		[**1**]·6H_2O			
N(4)−H(4)···N(1)	2.814(2)	104(1)	N(19)−H(19)···N(22)	2.576(1)	115(2)
N(4)−H(4)···N(7)	2.710(2)	108(1)	N(13)−H(13)···O(4)	2.905(1)	159(2)
N(19)−H(19)···N(16)	2.689(1)	111(2)			
		[**1**(N_3^-)][nBu$_4$N]$^+$·3H_2O			
N(4)−H(4)···N(1)	2.842(4)	102	N(51)−H(51)···N(48)	2.944(5)	100
N(4)−H(4)···N(7)	2.771(5)	105	N(51)−H(51)···N(54)	2.748(5)	105
N(19)−H(19)···N(16)	2.883(5)	101	N(13)−H(13)···N(1A)	2.895(5)	143
N(19)−H(19)···N(22)	2.760(5)	104	N(28)−H(28)···N(1A)	2.873(5)	144
N(36)−H(36)···N(33)	2.854(4)	102	N(45)−H(45)···N(3A)	2.906(5)	145
N(36)−H(36)···N(39)	2.772(5)	104	N(60)−H(60)···N(3A)	2.854(5)	149
		[**1**(FHF^-)][nBu$_4$N]$^+$·3H_2O[b]			
N(4)−H(4)···N(1)	2.839(2)	98(2)	N(13)−H(13)···F(1)	2.754(3)	155(3)
N(4)−H(4)···N(7)	2.755(3)	111(2)	N(28)−H(28)···F(1)	2.724(3)	154(2)
N(19)−H(19)···N(16)	2.896(4)	114(4)	F(1)−H(1)···F(1′)#1	2.475(4)	168(4)
N(19)−H(19)···N(22)	2.734(4)	102(3)			

[a]In this table and the subsequent Table 2, standard deviations are only reported for H-bond angles where the positional parameters of the hydrogen atom were refined. [b]Symmetry transformations used to generate equivalent atoms: [a]1: x, $-y+1$, $-z+1$.

Table 2. Selected H-Bonding Distances for [**1**(H_2O)$_6$] and [H_4**1**(SO_4)$_2$(H_2O)$_2$]

D−H···A	*d*(D···A)	∠(DHA)	D−H···A	*d*(D···A)	∠(DHA)
		[**1**(H_2O)$_6$]·2H_2O [a]			
N(4)−H(4)···O(1w)	2.903(1)	150(2)	O(1w)−H(1w2)···O(3w)#1	2.839(1)	178(2)
N(13)−H(13)···O(1w)	2.922(1)	150(2)	O(2w)−H(2w1)···N(1)	2.963(1)	175(2)
N(19)−H(19)···O(2w)	3.148(1)	167(2)	O(2w)−H(2w2)···O(3w)	2.878(1)	174(2)
N(28)−H(28)···O(2w)	3.272(1)	165(2)	O(3w)−H(3w1)···O(3)#2	2.796(1)	169(2)
O(1w)−H(1w1)···O(2w)	2.913(1)	148(2)	O(3w)−H(3w2)···O(4)#3	2.745(1)	166(2)
		[H_4**1**(SO_4)$_2$(H_2O)$_2$]·10H_2O [b]			
N(1)−H(1)···O(12)#1	2.704(7)	168(6)	N(19)−H(19)···O(6w)#1	2.854(7)	159
N(4)−H(4)···O(11)	2.874(7)	154	N(28)−H(28)···O(6w)#1	2.937(7)	156
N(13)−H(13)···O(11)	2.891(6)	154	O(6w)−H(6w1)···O(1)#2	2.836(6)	174
N(16)−H(16)···O(12)	2.638(6)	165(6)	O(6w)−H(6w2)···O(14)	2.672(6)	171

[a]Symmetry transformations used to generate equivalent atoms: #1: $-x+1$, $-y+1$, $-z+1$; #2: $-x$, $-y+1$, $-z+1$; #3: $-x$, $-y+2$, $-z+1$. [b]Symmetry transformations: #1: $-x+1$, $-y+1$, $-z+1$; #2: $-x$, $-y+1$, $-z+1$.

and the FHF^- complex, [nBu$_4$N$^+$][**1**(FHF^-)]·3H_2O, crystallized in the orthorhombic space group $C222_1$. The choice of space group for the N_3^- complex [an alternate nonstandard setting of $P2_1 - C_2^2$ (No. 4)] was made to facilitate easy comparisons between the rigorously monoclinic (but pseudo-orthorhombic) N_3^- complex and the orthorhombic FHF^- complex with nearly identical lattice constants.

In each of these three structures, the host tetraamide macrocycles are folded at the bridgehead amines and the pyridine units are canted slightly from parallel with N_{py}---N_{py} and *para*-C_{py}---C_{py} distances of about 3.5 and 4.5 Å, respectively. A crystallographic C_2 axis passes through the midpoints of the C−C bonds in the two secondary ethylene units of both [**1**]·6H_2O and **1**(FHF^-). In comparison, the N_3^- complex possesses only pseudo-C_2 symmetry. However, in all three structures the four diamidopyridine groups are related by a pseudo-S_4 axis perpendicular to the crystallographic C_2 (or pseudo-C_2) axis, adopting alternate up/down orientations with each 90° rotation (Figure 1). This conformation is achieved by twisting the molecules like a towel or rope about the two secondary ethylenediamine linkers until the two folded tetraamido macrocycles form an elongated tetragonal "pocket" with the four diamidopyridine groups defining the four "long" sides. If the host is considered to be roughly an elongated ellipse, it is approximately 14 Å long (along the S_4 axis) with a diameter of about 7 Å (between the two bridgehead amine nitrogen atoms in the same tetraamido macrocycle) for all three structures. These gross elliptical dimensions for the tricycle are shorter and thicker than the pseudo-C_{2h} structures described later.

Each tetraamido macrocyclic component in the three structures is, as noted above, folded, and the diamidopyridine groups form internal multiatom H-bonding networks involving the pyridine nitrogen, amido hydrogen, and amine nitrogen atoms ($N_{py}\cdots H_{amide}\cdots N_{amine}$). These linkages provide additional rigidity and stability as well as preorganized H-bonding "pockets," as best seen in Figure 1a−c. The structural similarities of the tricycle in the free base, [**1**]·6H_2O, with the linear FHF^- and N_3^- complexes are the result of the placement of two carbonyl oxygen atoms in the free base structure (one on each macrocycle) into the "pocket" near the sites occupied by FHF^- fluorine atoms or N_3^- nitrogen atoms in the two

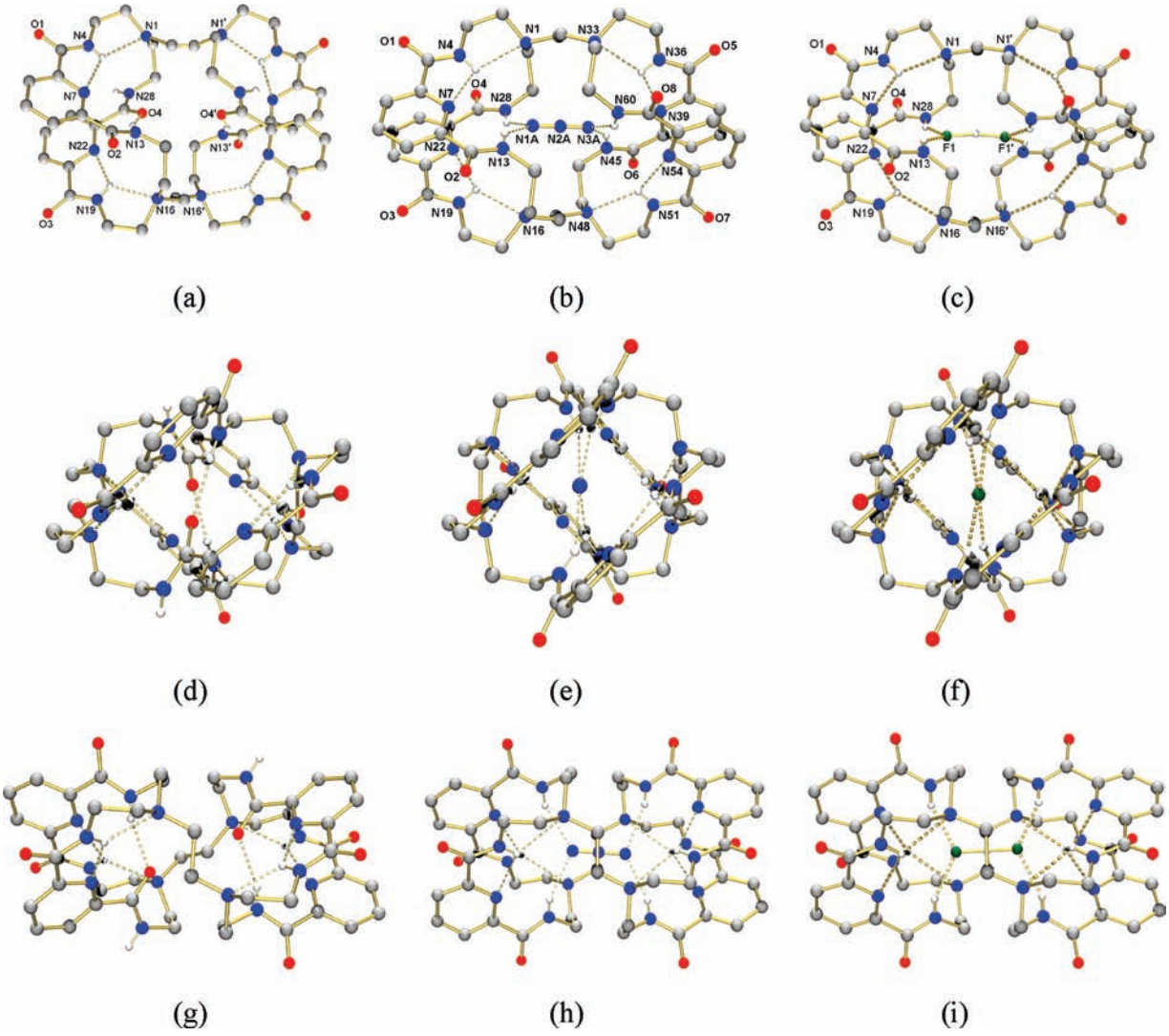

Figure 1. Perspective views of [**1**] (a, d, and g), [**1**(N_3^-)] (b, e, and h), and [**1**(FHF^-)] (c, f, and i). For clarity, water molecules and the nBu_4N^+ ions were omitted in the views of [**1**(N_3^-)] and [**1**(FHF^-)].

anion structures. The four amide groups used to form these two additional free base H-bonds were not used for the ($N_{py}\cdots H_{amide}\cdots N_{amine}$) interactions. Rotation of these two carbonyl groups into the "pocket" therefore does not interfere with the (normal) internal H-bonding networks and provides additional structural stabilization/rigidity by forming two additional internal H-bonds across the "pocket" as best seen in Figure 1g. The carbonyl oxygen atoms are, in fact, serving as surrogate guests. In summary, the host tricycles are virtually superimposable for all three structures.

For the anionic complexes, the tricyclic macrocycle holds the linear triatomic N_3^- ion as well as the earlier reported FHF^-[9] anion via four H-bonds from the four amido hydrogen atoms. These hydrogen atoms do not participate in the intraligand H-bond network but are rather directed toward the interior "cavity." The presence of four H-bonds elongates the F···F distance to 2.475(4) Å relative to FHF^- salts which range from about 2.23 to 2.34 Å.[17] On the other hand, the N=N=N separation is a short 2.355(5) Å with nearly equal N−N distances of 1.162(6) and 1.193(6) Å. The shortness of the N_3^- end-to-end distance is probably an artifact caused by that bond lying perpendicular to the twin axis (see Supporting Information for more detail), but may also be related to the rather imperturbable strength of the azide double/triple bond system (compared to the much weaker H-bonded FHF^-). While the FHF^- ion may be slightly bent, the N_3^- ion is clearly linear (168(4)° for FHF^- and 179.3(4)° for N_3^-).

Pseudo C_{2h} Structures: [1(H_2O)$_6$]·2H_2O and [$H_4$1-(SO_4)$_2$(H_2O)$_2$]·10H_2O. In addition to the hexahydrate free base described above, the tricycle also forms an octahydrate, [**1**(H_2O)$_6$]·2H_2O. This free base crystallizes with an interesting ice-like arrangement for six of the H_2O molecules (Figure 2a,c,e), as previously communicated.[18] Both the octahydrate free base and bis-SO_4^{2-} complex crystallize in the triclinic space group $P\bar{1}$, with the center of the tricycle coincident with a crystallographic inversion center. Again the tetraamido macrocyclic units fold, and

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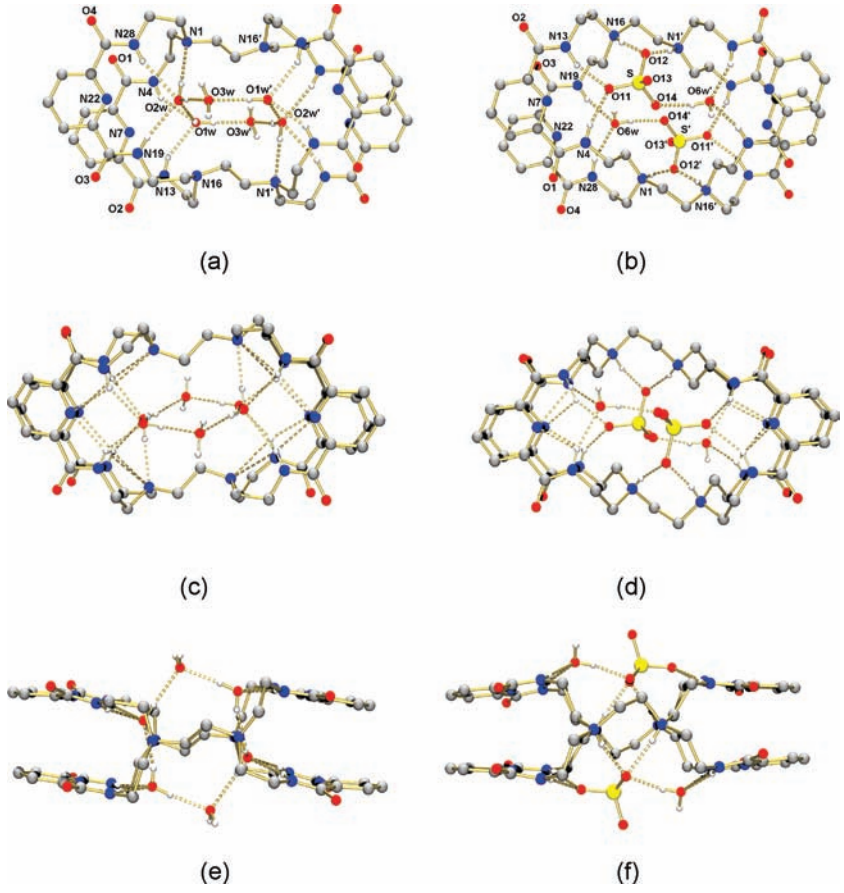

Figure 2. Perspective views of $[\mathbf{1}(H_2O)_6]$ (a, c, and e) and $[H_4\mathbf{1}(SO_4)_2(H_2O)_2]$ (b, d, and f) complexes. Additional H_2O molecules outside the cavity were omitted for clarity.

although the structures possess crystallographic C_i symmetry, they approximate C_{2h} symmetry with the pseudo-C_2 axis bisecting the two ethylene linkers and the pseudomirror passing through the four pyridine nitrogen atoms (pseudo-C_2 axis perpendicular to page and pseudomirror in page of Figure 2e,f). The molecular dimensions, averaging about 16.4 × 6.4 Å for this conformation of the tricycle, are longer and thinner than those for the more compact pseudo-S_4 conformation. The pseudo-C_{2h} conformation also places the two pyridines of each tetraamido macrocycle closer together, slightly canted toward each other (instead of away from each other as in the D_2 structures) with N_{py}---N_{py} and *para*-C_{py}---C_{py} separations of about 3.9 and 3.7 Å, respectively (Figure 2e,f). The internal H-bonding networks are also different for the pseudo-C_{2h} structures. All of the potentially semicircular five-nitrogen H-bonding units, $N_{amine}\cdots H_{amide}\cdots N_{py}\cdots H_{amide}\cdots N_{amine}$ in the pseudo-C_{2h} conformation, are utilized in the water complex, if one includes a rather weak (3.16 Å) interaction between one of the amine nitrogen atoms and the adjacent amide (Figure 2c). For the bis-SO_4^{2-} complex this longer network is broken down into just three H-bonds, $H_{amide}\cdots N_{py}\cdots H_{amide}$, since the protonated amines break the chain.

The H_2O array is one of the more interesting aspects of the octahydrate structure. The H_2O network forms a chairlike hexagonal pattern with four of the H_2O molecules, two for each tetraamido macrocycle, embedded within the tricycle framework.[18] Two of the H_2O molecules [O(3w) and O(3w)′] lie outside the cavity, above and below the ethylene linkers as seen best in Figure 2e. Each of the four embedded H_2O molecules serve as H-bond acceptors to a pair of amide groups attached to the same pyridine. These interactions are significantly stronger for water molecule O(1w) than for O(2w). O(1w) also serves as a H-bond donor to O(2w) and the C_i-related O(3w), and O(2w) is a H-bond donor to N(1) and O(3w). O(3w) serves as a H-bond donor to O(3w) and O(4w) in symmetry-related $[\mathbf{1}(H_2O)_6]\cdot 2H_2O$ moieties. The angles between the oxygen atoms in the H-bonded $(H_2O)_6$ hexagon, O(1w)···O(2w)···O(3w), O(2w)···O(3w)···O(1w)′, and O(2w)···O(1w)···O(3w)′, are 129.52(4), 105.52(4), and 119.15(4)°, respectively.

As opposed to the FHF^- and N_3^- complexes, which crystallize as the nBu$_4$N$^+$ salts, the bis-SO_4^{2-} complex of **1** achieves neutrality by tetraprotonation of the four bridgehead amines of the tricycle. Two SO_4^{2-} ions and two H_2O molecules are associated with each host but outside the cavity. Each of the SO_4^{2-} oxygen atoms is H-bonded to one or two other atoms: O(11) to the two amide hydrogen atoms; O(12) to two protonated amines of a single secondary ethylenediamine linker; O(13) to oxygen atoms of two different H_2O molecules; and O(14) to a H_2O oxygen atom (Table 2). Interestingly, SO_4^{2-} oxygen atoms O(11) and O(14) and the H_2O oxygen atom O(6w) in the bis-SO_4^{2-} structure are approximate structural counterparts of the H_2O oxygen atoms, O(2w), O(3w), and O(1w), respectively, in $[\mathbf{1}(H_2O)_6]\cdot 2H_2O$. A chain of

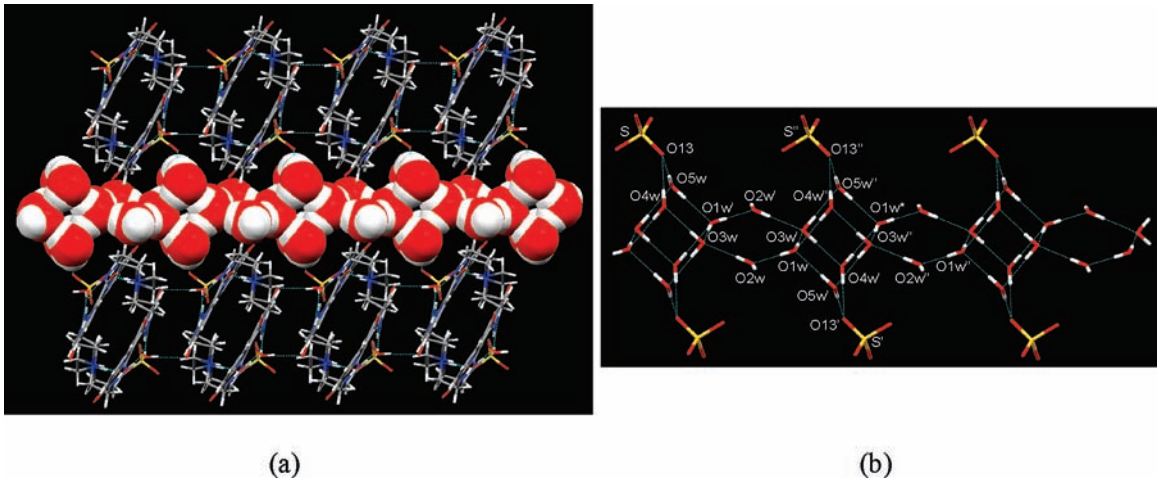

Figure 3. Packing diagrams for $[H_4\mathbf{1}(SO_4)_2(H_2O)_2]\cdot 10H_2O$ showing: (a) the orientation of the (space filling) fused cube-hexameric arrays of H-bonded H_2O molecules and (b) the labeled SO_4^{2-} and H_2O molecules without **1**. Additional superscripts to atomic labels refer to the following symmetry transformations: (') is $1-x, -y, -z$; (") is $1+x, y, z$; and (*) is $2-x, -y, -z$.

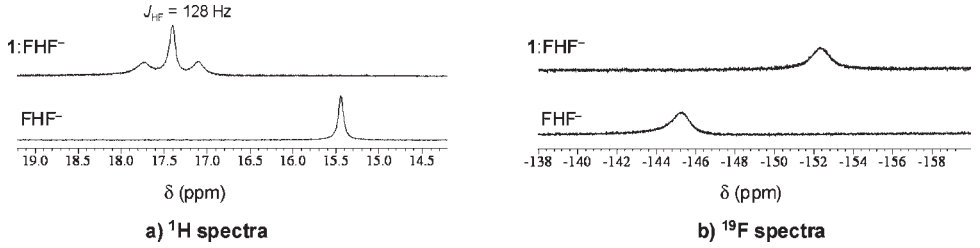

Figure 4. (a) ^{1}H NMR and (b) ^{19}F NMR spectra of $[n\text{Bu}_4\text{N}^+][\text{FHF}^-]$ and $[\mathbf{1}(\text{FHF}^-)]$ in DMSO-d_6.

water "cubes" (from the 10 "external" H_2O molecules of hydration) forms a channel between tricycles parallel to the *a* axis of the unit cell by fusing with hexagonal "rings" of H_2O molecules (Figure 3).

Solution and Binding Studies. The FHF^- complex was further characterized by ^{1}H and ^{19}F NMR spectroscopy in solution (Figure 4). In the ^{1}H NMR of a 1:1 L:A complex in DMSO-d_6, the free FHF^- signal at 15.4 ppm shifts downfield ($\Delta\delta$ = 2.1 ppm) to 17.5 ppm. The new signal appears as a triplet (J_{HF} = 128 Hz) due to well-resolved coupling of the central proton with the two adjacent fluoride ions (Figure 4a). In the ^{19}F NMR of $[\mathbf{1}(FHF^-)]$ in DMSO-d_6, however, the free FHF^- signal at −145.3 ppm shifts upfield ($\Delta\delta$ = −6.8 ppm) to −152.1 ppm. The signal remains broad, possibly due to unresolved coupling with both the amide and FHF^- hydrogen atoms.[9]

Binding affinities of the tricyclic host **1** for anions were determined by NMR titrations of the *n*-Bu_4N^+ salts of selected anions in DMSO-d_6. Results revealed selectivity for FHF^- compared to the other simple inorganic anions exained. FHF^- affinity in $CDCl_3$ is close to the calculation limit by NMR methods (log $K \sim 4-5$). The amide signal at 8.55 ppm was shifted downfield by 0.83 ppm upon addition of 1.0 equiv of FHF^- in $CDCl_3$, indicative of strong H-bonding between amide hydrogen atoms and FHF^- (Figure 5). Results indicated strong and selective binding for FHF^- (log K = 3.74), moderate binding for $H_2PO_4^-$ (2.87), N_3^- (2.53), and CH_3COO^- (2.00), and negligible binding for HSO_4^-, Cl^-, Br^-, I^-, NO_3^-, SCN^-, and ClO_4^- in DMSO-d_6 (Figure 6). Determination of the affinity of **1** for F^- was hampered due to severe

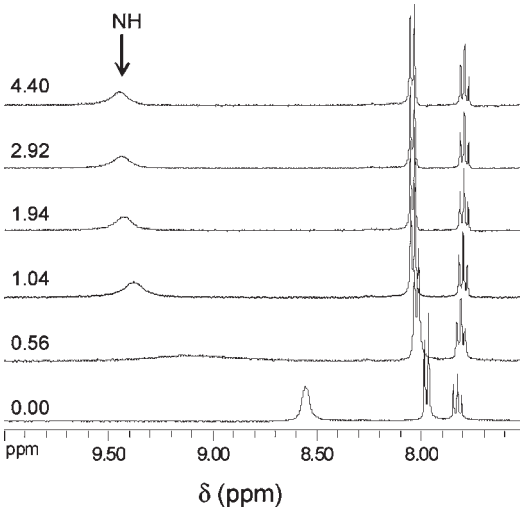

Figure 5. ^{1}H NMR titration spectra of **1** with $[n\text{Bu}_4\text{N}^+][\text{FHF}^-]$ in $CDCl_3$. Numbers at the left side indicate the equivalent amounts of FHF^- added.

broadening of the amide signals, which could be the result of both multiple stoichiometries and FHF^- formation. It is known that F^- ion can facilitate the hydrogen ion extraction from amide-,[9,11,19] urea-,[20] thiourea-,[21] and pyrrole-based[22] anion hosts, which often results in the

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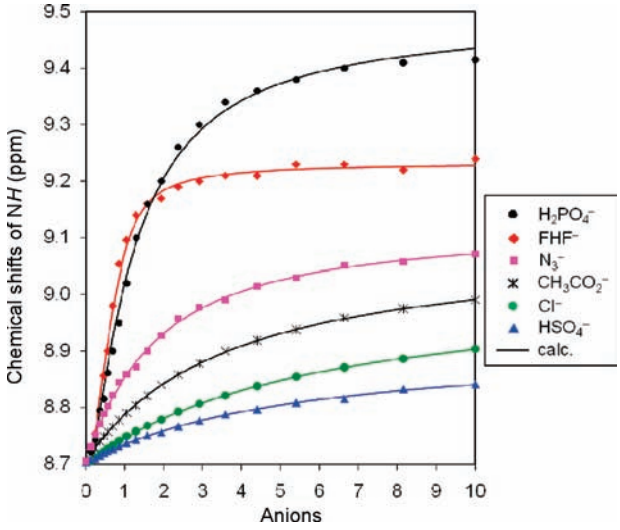

Figure 6. Plots of the chemical shift of the NH proton of **1** (2 mM) upon increasing the concentration of $[n\mathrm{Bu_4N^+}][\mathrm{X^-}]$ in DMSO-d_6.

formation of FHF^-. The titration data of **1** with all of the anions were consistent with 1:1 L:A^- stoichiometries.

Conclusions

The new tricyclic host provides a surprisingly rigid framework for both the free base forms and for the binding of linear anions, especially for the simple triatomic FHF^- and N_3^- ions. Primarily two conformations are observed, one with pseudo-D_2 symmetry, and the other with pseudo-C_{2h} symmetry. These two conformations are stabilized by a "semi-rigid" or organized structural motif consisting of semicircular internal H-bonding networks incorporating the amide, pyridine, and amine groups to different extents. In the D_2 symmetric host, a 3-fold H-bonding semicircle between the pyridine, amide, and amine groups is observed. In the pseudo-C_{2h} case either an expanded five-atom network - amine, amide, pyridine, amide, and amine - is observed (in the free base) or a shortened amide, pyridine, amide in the protonated bis-SO_4^{2-} complex. (Protonation of the amines disrupts the network.) The host also offers an ideal internal cylindrical cavity with four appropriately positioned amide H-bond donors for binding the ends of either the N_3^- or FHF^- ion. The semicircular H-bond preorganization promotes planar H-bonding "pockets" that can adapt to bind the triatomic guests in a 4-fold vice grip. Thus, in summary, while the amido bicyclic cryptand receptors we reported earlier tend to bind a single fluoride anion very nicely by encapsulation,[11] the tricyclic host with an expanded cylindrical-like cavity between the monocyclic lids shaped by the semicircular H-bonding network is preorganized to accommodate linear triatomic anions such as FHF^- and N_3^-. Further studies are underway to expand on the chemistry of tricyclic hosts with mixed amine/amide functionalities.

Experimental Section

All chemicals were reagent grade and were used as received without further purification. NMR spectra were recorded on a Bruker Avance 400 spectrometer. Chemical shifts are reported as δ values relative to the TMS signal (δ = 0.00) at 23 °C. Mass spectra were obtained on a ZAB HS mass spectrometer (VG Analytical Ltd., Manchester, UK) equipped with an Opus data system. Fast-atom bombardment (FAB) experiments were performed using a Xenon gun operated at 8 keV energy and 0.8 mA emission. Samples were added to mNBA as the matrix. Elemental analyses were obtained from Desert Analytics, Tucson, AZ.

Bis(phthalimidylethyl)amine (3). Phthalic anhydride (10.0 g, 67.5 mmol) was added to a solution of diethylenetriamine **2** (3.20 g, 31.0 mmol) in CH_3CN (200 mL). The reaction mixture was stirred under reflux for 2 days. The solvent was evaporated and 200 mL of EtOH was added to the residue. After stirring for 5 h, the precipitate was filtered, collected, and dried to give **3** (yield: 80%). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.72 (m, 4H; ArH), 7.66 (m, 4H; ArH), 3.79 (t, J (H,H) = 6 Hz, 4H; CH_2), 2.99 (t, J (H,H) = 6 Hz, 4H; CH_2).

***N′*-Boc-2,2′-bis(phthalimidylethyl)amine (4).** Di-*tert*-butyldicarbonate (1.44 g, 6.60 mmol) was added to a solution of **3** (2.00 g, 5.50 mmol) with K_2CO_3 (2.00 g, 14.5 mmol) in CH_2Cl_2/CH_3CN (100 mL/100 mL). The reaction mixture was stirred for 1 day at room temperature. The solvent was evaporated and the residue was dissolved in 200 mL of CH_2Cl_2. The organic phase was washed with H_2O (2 × 200 mL), dried with Na_2SO_4, and concentrated. The crude product was recrystallized from a mixture of MeOH/*n*-hexane to give **4** (yield: 80%) as a white power. ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS): δ = 7.83 (m, 4H; ArH), 7.73 (m, 2H; ArH), 7.68 (m, 2H; ArH), 3.89 (t, J (H,H) = 6 Hz, 2H; CH_2), 3.85 (t, J (H,H) = 6 Hz, 2H; CH_2), 3.57 (t, J (H,H) = 6 Hz, 2H; CH_2), 3.52 (t, J (H,H) = 6 Hz, 2H; CH_2), 1.07 (s, 9H; CH_3).

***N′*-Boc-2,2′-diaminodiethylamine (5).** *N′*-Boc-2,2′-bis(phthalimidylethyl)amine **4** (1.00 g, 2.16 mmol) and hydrazine monohydrate (2.00 mL, 41.2 mM) in EtOH (100 mL) were stirred for 1 day at room temperature. After the reaction, the precipitate was removed by filtration, and the filtrate was evaporated and extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were evaporated to give **5** as a light yellow oil (yield: 70%) which was used for the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.27 (br s, 4H; CH_2), 2.84 (t, J (H,H) = 6 Hz, 4H; CH_2), 1.45 (s, 9H; CH_3).

Macromonocycle (6). A 3-neck round-bottom flask equipped with two dropping funnels was filled with dry CH_2Cl_2 (500 mL) under argon in a dry ice/acetone bath. The funnels were charged with 2,6-pyridinedicarbonyldichloride (1.00 g, 4.90 mmol) in CH_2Cl_2 (150 mL) in one and *N′*-Boc-2,2′-diaminodiethylamine **5** (1.00 g, 4.90 mmol) and NEt_3 (2.28 mL, 16.24 mmol) in CH_2Cl_2 (150 mL) in the other. The reagents in the two dropping funnels were added into the flask simultaneously at equal rates over 1 h and the reaction mixture was stirred for 24 h. The solvent was evaporated and the residue was redissolved in 300 mL of CH_2Cl_2. The organic phase was washed with H_2O (2 × 200 mL), dried with Na_2SO_4, and concentrated. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2/CH_3COCH_3, 10:3) to give pure monocycle **6** (yield: 30%). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS): δ = 9.34 (m, 4H; NH), 8.11 (m, 6H; ArH), 3.52 (m, 8H; CH_2), 3.37 (m, 8H; CH_2), 1.41 (s, 18H; CH_3). FAB MS m/z 669.3 $[MH]^+$.

Deprotected Macromonocycle (7). The protected macromonocycle **6** (0.50 g, 0.75 mmol) was dissolved in CH_2Cl_2 (5 mL) and treated with 2 mL of CF_3COOH. The reaction mixture was stirred for 5 h at room temperature, followed by evaporation of

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the solvent under reduced pressure. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH/NH_3(aq), 20:4:1) to give deprotected macromonocycle **7** (yield: 70%). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS): δ = 9.21 (br t, 4H; NH), 7.98 (m, 6H; ArH), 3.44 (br q, 8H; CH_2), 2.83 (s, 8H; CH_2). FAB MS m/z 469.2 $[MH]^+$.

Tricycle (1). 1,2-Dibromoethane (1.00 mL, 11.6 mmol) was added to a solution of the deprotected macromonocycle **7** (0.20 g, 0.43 mmol) with K_2CO_3 (0.50 g, 3.62 mmol) in CH_3CN (200 mL), and the reaction mixture was refluxed for 2 days. The solvent was evaporated and 100 mL of H_2O was added to the residue. After stirring for 3 h, the precipitates were filtered, collected, and dried. This crude product was purified by column chromatography (basic Al_2O_3, 2% MeOH in CH_2Cl_2) to give a pure macrotricycle **1** (yield: 30%). ^{1}H NMR (400 MHz, DMSO-d_6, 23 °C, TMS): δ = 8.70 (br s, 8H; NH), 7.88 (t, J (H,H) = 7.0 Hz, 4H; ArH), 7.79 (d, J (H,H) = 7.4 Hz, 8H; ArH), 3.35 (m, 16H; CH_2), 2.79 (m, 24H; CH_2); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.8 (C=O), 149.1, 138.5, and 124.6 (Ar), 54.7, 53.0, and 38.1 (CH_2). FAB MS m/z 989.7 $[MH]^+$; Anal. Calcd for $C_{48}H_{60}N_{16}O_8 \cdot CH_2Cl_2 \cdot H_2O$: C, 53.89; H, 5.91; N, 20.52. Found: C, 53.69; H, 5.66; N, 20.77.

NMR Studies. Each titration was performed by 20 measurements in DMSO-d_6 at room temperature. Aliquots from a stock solution of the nBu$_4$N$^+$ salts (20 mM) were gradually added to the initial solution of ligand (2 mM). Up to 10 anion equivalents were added during the titrations. All proton signals were referenced to a TMS standard. The association constants K were calculated by EQNMR.[23] All titration curves fit best in 1:1 binding modes of the ligand to anions.

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For ^{19}F NMR spectra, the aqueous NaF signal (δ = −122.4) was used as an external standard. All ^{19}F spectra were recorded at 23 °C and $[F^-]$ of 10 mM.

X-ray Crystallographic Studies. A detailed experimental description is provided in the Supporting Information. Complete hemispheres of intensity data were collected for crystals of all five compounds at 100(2) K using 0.30°-wide ω scans with graphite-monochromated MoK_α radiation (λ = 0.71073 Å) on a Bruker SMART APEX CCD area detector mounted on a Bruker D8 goniometer. Crystals of the hexahydrated free ligand, [**1**]·6H_2O, suitable for X-ray diffraction were grown by slow evaporation of a $CHCl_3$ solution. Crystals of [**1**(N_3^-)]-[nBu$_4$N]$^+$·3H_2O and [**1**(FHF^-)][nBu$_4$N]$^+$·3H_2O, were grown by slow evaporation of a CH_3CN solution of **1** in the presence of excess [nBu$_4$N$^+$][N_3^-] and [nBu$_4$N$^+$][F^-], respectively. The octahydrated H_2O complex of **1**, [**1**(H_2O)$_6$]·2H_2O, was obtained from a CH_3CN solution of **1** in the presence of excess [nBu$_4$N$^+$]-[Cl^-]. The resulting crystalline product was not the anticipated anion complex but was instead the neutral hydrated ligand, [**1**(H_2O)$_6$]·2H_2O that contained an encapsulated ring of six H-bonded H_2O molecules.[18] The bis-SO_4^{2-} complex, [H_4**1**(SO_4)$_2$-(H_2O)$_2$]·10H_2O, was obtained by adding excess H_2SO_4 to a solution of **1** in DMSO.

Acknowledgment. The authors thank the National Science Foundation, CHE-0316623, for support of this work and CHE-0079282 for purchase of the X-ray diffractometer.

Supporting Information Available: Detailed crystallographic description of the structural determination for all five complexes. This material is available free of charge via the Internet at http://pubs.acs.org.