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Cyclophane Capsule Motifs with Side Pockets

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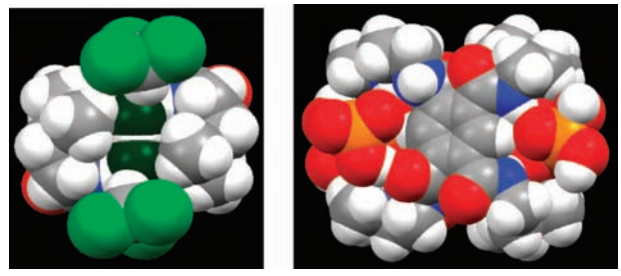
ABSTRACT



Neutral and charged multitopic cyclophane-capped anion hosts connected by three or four diamide/monoamine chains and a decomposition product with two chains have been synthesized and characterized. The chains in the two former hosts fold together to form one or two binding pockets, respectively, and FHF^- and several phosphate complexes have been obtained with the anions nestled in these pockets. The decomposition product also shows propensity for binding dicarboxylates, as evidenced by an isophthalate crystal structure.

The architectural design of multidimensional and multitopic supramolecular hosts has had a major impact in synthetic organic chemistry.[1,2] Efforts in our research group in supramolecular design have centered primarily on targeting the selective recognition of anions.[3] Our basic design pattern is to incorporate two different H-bonding functionalities, one of which is always an amine, with the second often being an amide. As a result we have explored a series of neutral amine/amide-based anion hosts of varying dimension (mono-,[4] bi-,[5] and tricyclic[6]) (Scheme 1, A−C) as well as the charged, quaternized analogues of A and B.[7,8] Herein is reported an expansion of this design concept centered around the use of the aromatic group as a template for new scaffolded bicyclic and tricyclic hosts, (Scheme 1, D and E). A similar strategy was used quite effectively by Anslyn and co-workers using 1,3,5-substituted phenyl groups as caps, but with more rigid spacers.[9] Similar strategies (linking phenyl rings with different spacers) have been adopted by others.[10]

The prototype for these receptors was the monocycle **1**, (Scheme 2) based on *N*′-methyl-2,2′-diaminodiethylamine

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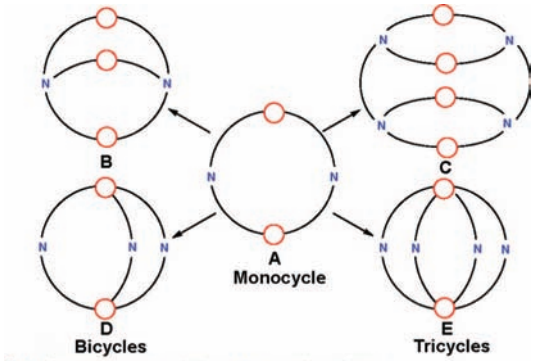
Scheme 1. Schematic Representation of Host Systems



[a] O = benzene or pyridine, N = amine linker.

linkers bridging two aromatic or heterocyclic groups.[3,6] By adding one and two linkers to the aromatic group, i.e., 1,3,5- and 1,2,4,5-substituents, **2** (Scheme 1, triad D) and **3** (Scheme 1, tetrad E) were isolated, respectively. Once again the presence of amines in the new hosts allows for greater flexibility compared to hosts containing only amide groups. While the triad **2** has only one possible condensation product, the tetrad **3** can give both eclipsed (**3-E**) and staggered (**3-S**) isomers. Furthermore, the proximity of the chains in **3** leads to an interesting acid-catalyzed decomposition product, a two-chain (or diad) host, **4**.

Hosts **2** and **3** were synthesized from the condensation of 2 equiv of trimesoyl chloride or tetramethyl 1,2,4,5-benzene-tetracarboxylate with 3 or 4 equiv of *N*′-methyl-2,2′-diaminodiethylamine, respectively. Two isomers were isolated for **3** (see Supporting Information). An unexpected find was the decomposition product containing two linking chains, **4**, the diad. Due to the electrophilic attack of one of the amide lone pairs on an adjacent carbonyl, the resulting molecule has two pyromellitimide caps and a single amine in the resulting five-membered spacer. Others have noted similar decomposition reactions in adjacent amides.[11]

The binding properties of **2** and **3** were studied in DMSO-d_6 by ^{1}H NMR titrations for the nBu$_4$N$^+$ salts of F$^-$, FHF$^-$, $H_2PO_4^-$, and $HP_2O_7^{3-}$. Binding constants were calculated from the resulting titration data using EQNMR (Table 1).[12]

Table 1. Association Constants (K, M^{-1})[a] of **1**, **2**, and **3-E** in DMSO-d_6

anion	**1**[6]	**2**	**3-E**
F$^-$	260	21 000 (>10^{5c})	[b]
FHF$^-$	–	110	19
$H_2PO_4^-$	830	3000	2300 (280[c])
$HP_2O_7^{3-}$	–	9800 (280[c])	[b]

[a] At room temperature (errors >15%). [b] Calculation not possible due to peak broadening. [c] The association constant of the 1:2 L/A complex (LA + A = LA$_2$).

Host **2** showed the highest binding for 1:1 stoichiometries among the amido hosts **l**,[7] **2**, and **3-E**. Additional fit with 2:1 A$^-$/L stoichiometries was observed for F$^-$and $HP_2O_7^{3-}$. Host **3-E** showed slightly less but comparable affinity for $H_2PO_4^-$; however, binding studies were hampered by line-broadening in most cases. Further studies are warranted to determine if the double pockets truly enhance the binding capabilities of the host.

Crystallographic results were obtained for the FHF$^-$ complex of neutral **2**; the $H_2PO_4^-$, $H_2P_2O_7^{2-}$, and $H_3P_3O_{10}^{2-}$ complexes of tetraprotonated $\mathbf{H_4}$**3-E**$^{4+}$; and the isophthalate complex of diprotonated $\mathbf{H_2}$**4**$^{2+}$.[13] The FHF$^-$ complex of **2** represents the second crystallographic example of FHF$^-$ within a macrocyclic receptor.[6] The structures of the phosphate complexes are especially meaningful because of the widespread prevalence of phosphate in biological systems.[14] The diad also crystallizes in the diprotonated form $\mathbf{H_2}$**4**$^{2+}$, making it a charge- and site-complementary host for dicarboxylates such as isophthalate. These five crystal structures lend insight to binding propensities of the new multitopic hosts.

The structure of FHF$^-$ with **2** gave the first indication of the pocketlike folding of the arms in the new bicyclic receptor. The complex, [**2**(FHF)]$^-$, crystallizes as the Me$_4$N$^+$ salt with two disordered CHCl$_3$ molecules of crystallization. Two of the amide/amine-containing bridges of **2** point in the same direction, forming a pocketlike cavity for a guest and with the phenyl groups stacked at a distance of 3.70 Å in a staggered conformation (Figure 1a). The FHF$^-$ ion is held by two weak H-bonds to **2** (N···F = 2.831(5) Å) with an F−F$^-$ distance of 2.177(12) Å, a distance reflective of that found in noncomplexed FHF$^-$ salts,[15] and significantly shorter than that observed in the encapsulated F−H−F$^-$ recently reported by us.[6] The role of two symmetry-related CHCl$_3$ molecules as "caps" for the FHF$^-$ ion, holding it in the pocket (Figure

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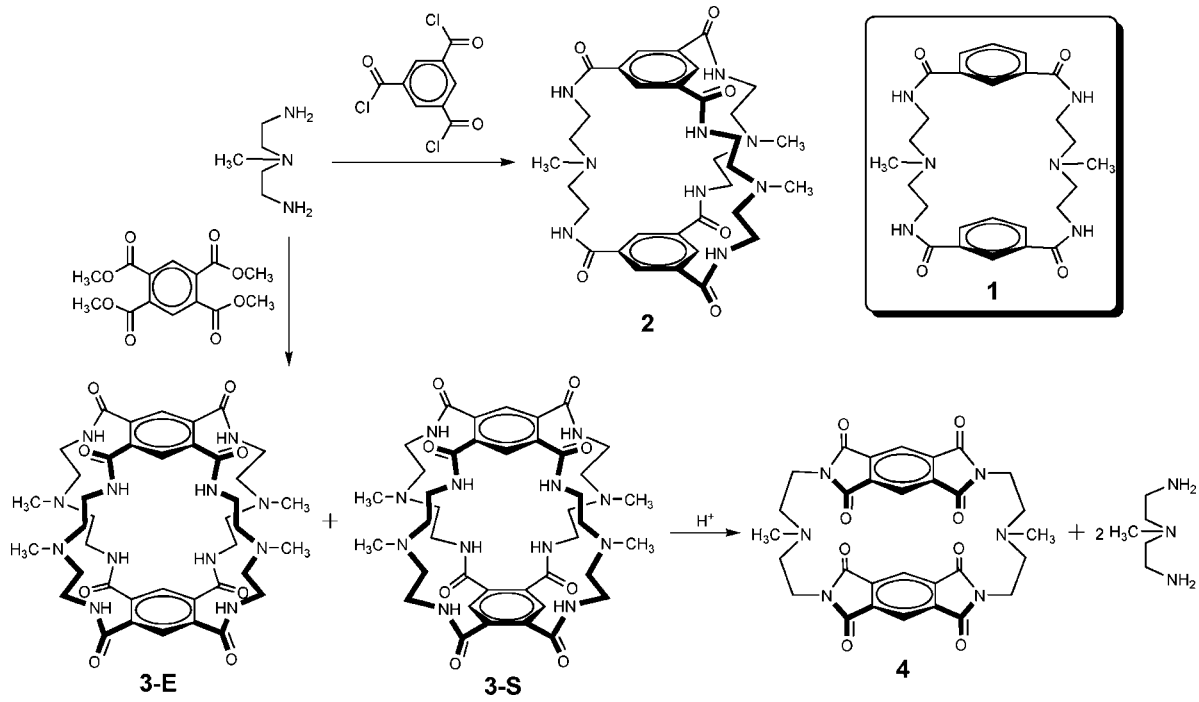
(13) Crystals of FHF$^-$ with **2** suitable for X-ray diffraction were grown by slow evaporation of a solution of CHCl$_3$ and EtOAc in the presence of excess Me$_4$NF. The phosphate salts of H_4**3-E**$^{4+}$ were isolated after adding the corresponding phosphoric acids ($Na_5P_3O_{10}$ and TsOH for the triphosphate salts) to a CHCl$_3$/MeOH solution of **3-E**. Crystals were grown by slow evaporation of DMF/H_2O solutions of the isolated products. Crystals of the isophthalate complex of the diad **4** were grown by slow evaporation of a DMF/H_2O solution of **4** in the presence of excess isophthalic acid.

Scheme 2. Synthesis of Anion Hosts[a]



[a] **3-E** = eclipsed conformation, **3-S** = staggered conformation.

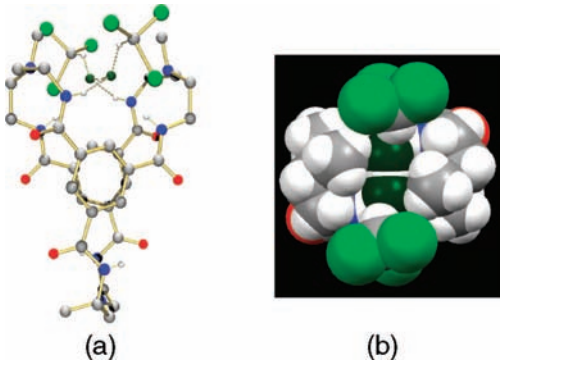


Figure 1. Views of [**2**·FHF]$^-$: (a) perpendicular to the phenyl rings and (b) space-filling model viewed parallel to the phenyl rings that show the FHF^- buried in the pocket with $CHCl_3$ caps. The Bu_4N^+ counterion is not shown for clarity.

1b) by a weak H-bond (C···F = 3.001 Å), is particularly noteworthy.

The presence of the lone dangling chain in **2** led to the synthesis of **3**, designed to provide two binding pockets. Crystallographic findings for **3-E** indicated a general propensity for the ligand to protonate, thereby obviating the need to add charge via quaternization. As anticipated, $\mathbf{H_4}$**3-E**$^{4+}$ forms two pocketlike cavities as seen in the crystal structures of the $H_2PO_4^-$, $H_2P_2O_7^{2-}$, and $H_3P_3O_{10}^{2-}$ complexes (Figure 2). The phenyl rings stack at distances of 4.17, 3.94, and 3.87 Å, respectively, with eclipsed conformations. However, in this host the cis position of the two phenyl arm pairs facilitates preorganization of the ligand through the formation of an intramolecular H-bond between one of the amide hydrogen atoms on one arm and a carbonyl oxygen atom on the adjacent arm. Hence, only three amide hydrogen atoms in each pocket are available for H-bonding with an anion. Just two of them actually do H-bond to these particular anionic guests. Two additional H-bonds per pocket are instead provided by the protonated amines.

In [$\mathbf{H_4}$**3-E**·4H_2PO_4], one of the two crystallographically independent $H_2PO_4^-$ ions exhibits 3-fold H-bonding with $\mathbf{H_4}$**3-E**$^{4+}$, with two H-bonds to the protonated amines and one to an amide. This anion is also linked to the second $H_2PO_4^-$ ion by an O−H···O linkage. This second $H_2PO_4^-$ ion is held to the host by only one H-bond to an amide hydrogen atom. In the $H_2P_2O_7^{2-}$ structure, one PO_3H^- end is linked to the host via four H-bonds, two from amide hydrogen atoms and two from the protonated amines. The second PO_3H^- group is not directly H-bonded to the macrocycle. Disorder observed in the vicinity of the $H_2P_2O_7^{2-}$ anion ultimately proved to be due to a $H_3P_3O_{10}^{2-}$ impurity that was bound in the pocket (see Supporting Information). The fact that a very minor impurity is captured in the solid state 17% of the time is strong indication of the selectivity of **3-E** for the longer chain triphosphate ion. Competition studies are currently

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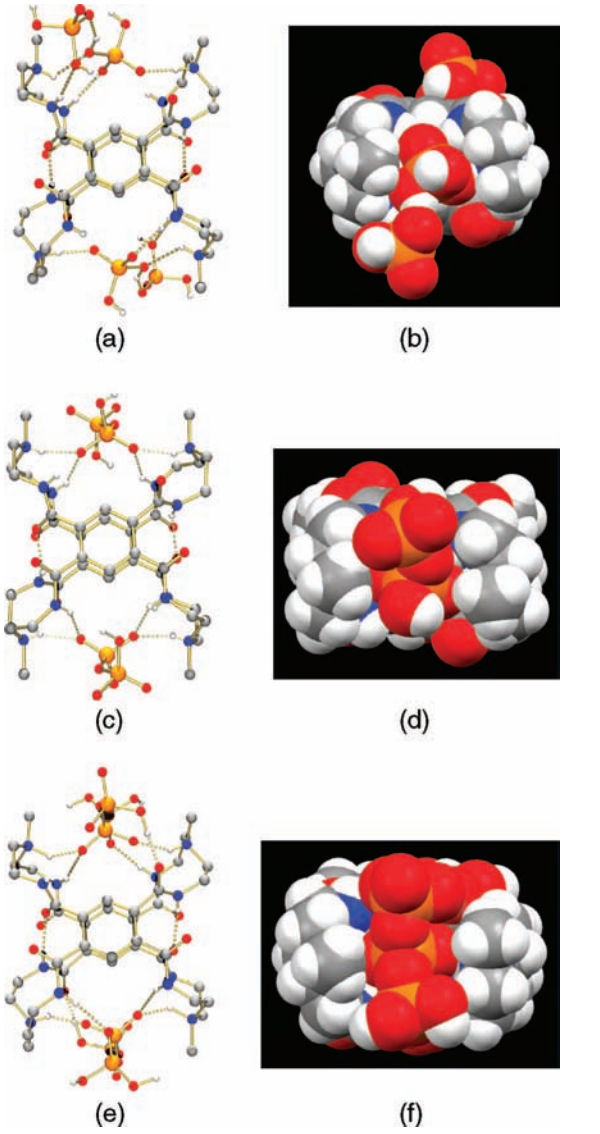

Figure 2. Views of [$\mathbf{H_4}$**3-E**·$4H_2PO_4$] (a and b), [$\mathbf{H_4}$**3-E**·$2H_2P_2O_7$] (c and d), and [$\mathbf{H_4}$**3-E**·$2H_3P_3O_{10}$] (e and f): (a, c, and e) perpendicular to the phenyl rings and (b, d, and f) space filling views parallel to phenyl rings. Water molecules are not shown for clarity.

underway to investigate this possibility. In the $H_3P_3O_{10}^{2-}$ complex crystallized by design, the triphosphate is bound to the host via five H-bonds, two from amide hydrogen atoms, two from the protonated amines, and one to a carbonyl oxygen atom.

The diad decomposition product **4** also binds anions. In this case, when protonated, the two amines are perfectly situated to bind aromatic 1,3-dicarboxylates. In the crystal structure, the two 16-atom fused-ring caps are within 42° of being parallel. The two protonated amines are H-bonded to the oxygen atoms of the isophthalate at distances of 2.664 and 2.714 Å. The decomposition of **3**-**E** can be followed by ^{1}H NMR studies in the presence of isophthalic acid (see Supporting Information).

In conclusion, new multitopic, pocket-containing anion hosts have been synthesized and characterized by adding dimension to the prototype monocycle **1**. Results confirm the feasibility of increasing the host's capacity by using a cyclophane-capped scaffold to incorporate multiple binding sites. Furthermore, these multicyclic, multitopic hosts can be obtained by straightforward one- or two-step synthetic routes. These flexible hosts provide promising new receptors with external pockets or clefts for enfolding a variety of anions, and especially longer anions such as triphosphate.

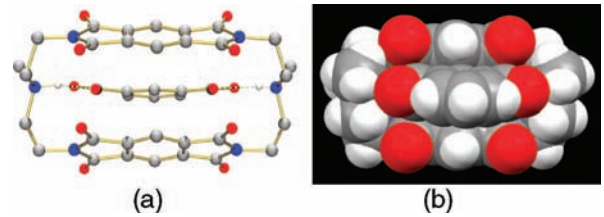

Figure 3. Crystal structure of [H_2**4**·($C_6H_4(CO_2)_2$)] viewed parallel to the phenyl rings as (a) ball-and-stick and (b) space-filling models. Solvent molecules and external isophthalic acid were omitted for clarity.

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Supporting Information Available: Synthetic and analytical details, crystallographic data (CIF), and crystallographic information. This material is available free of charge via the Internet at http://pubs.acs.org.

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