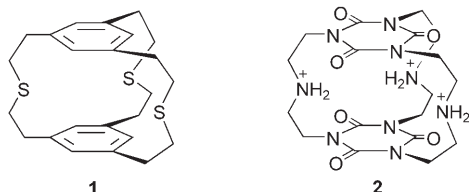


Fluoride-Selective Host Based on Anion- π Interactions, Ion Pairing, and Hydrogen Bonding: Synthesis and Fluoride-Ion Sandwich Complex**

Mark Mascal,* Ilya Yakovlev, Edward B. Nikitin, and James C. Fetting

The theoretical description of the anion- π interaction by Frontera, Deyà, and co-workers;^[1] Alkorta and co-workers;^[2] and our group^[3] has, in the five years since the publication of these studies, given rise to a large body of work describing physical observations of close anion- π contacts as well as further theoretical investigations.^[4] Such reports are often accompanied by the suggestion that this phenomenon could form the basis for anion recognition and binding, and indeed, this is turning out to be the case.^[5] For example, a synthetic halide-ion channel composed of electron-deficient aromatic rings has recently been reported,^[6] as well as a chloride- π complex formed in a calix-like cavity within a dendrimer.^[7] We ourselves described a hypothetical series of purpose-designed fluoride receptors that took advantage of the cylindrophane effect, that is, the high conformational stability and limited vertical flexibility of [1,3,5]cyclophanes bridged by chains with odd numbers of atoms, such as **1** (Scheme 1).



Scheme 1. Structures of cation host **1** and the proposed anion host **2**.

While **1** has been shown to be a selective silver(I) and copper(I) host,^[8] it was demonstrated that an inversion of its electronic character from electron-rich to electron-poor, such as in **2**, would produce an anion host.^[9] In the theoretical treatment of this receptor, the complexation of fluoride ion was shown to benefit from intrinsically stronger $\pi \cdots X^- \cdots \pi$ and $^+NH \cdots X^-$ interactions than for chloride. This difference, in

addition to acute steric issues associated with accommodating the larger chloride anion in the cavity, led to a calculated 23.5 kcal mol⁻¹ difference in binding energy between the two halides in aqueous solution.^[9] Herein, we present the proof of principle behind the design of **2**.

The synthesis of a cyanuric acid based cylindrophane is shown in Scheme 2. Although **2** itself was useful for modeling purposes, it was anticipated that substitution at the chain nitrogen atoms would be required to eventually be able to work with the tricationic receptor in common organic solvents. Thus, commercially available diethanolamine (**3**) was alkylated with *n*-hexyl bromide to give **4**. Statistical monoprotection of **4** as the triisopropylsilyl (TIPS) ether and subsequent conversion of the remaining hydroxy group to chloride gave **6**. Installation of the first cyanuric acid ring could be accomplished in good yield by simply heating the components together in DMF in the presence of the base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Desilylation of **7** and subsequent chlorination gave the cage precursor **9**. Heating trichloride **9** with cyanuric acid in the presence of DBU at high dilution gave the macrocyclic product **10** in good yield for this type of reaction.

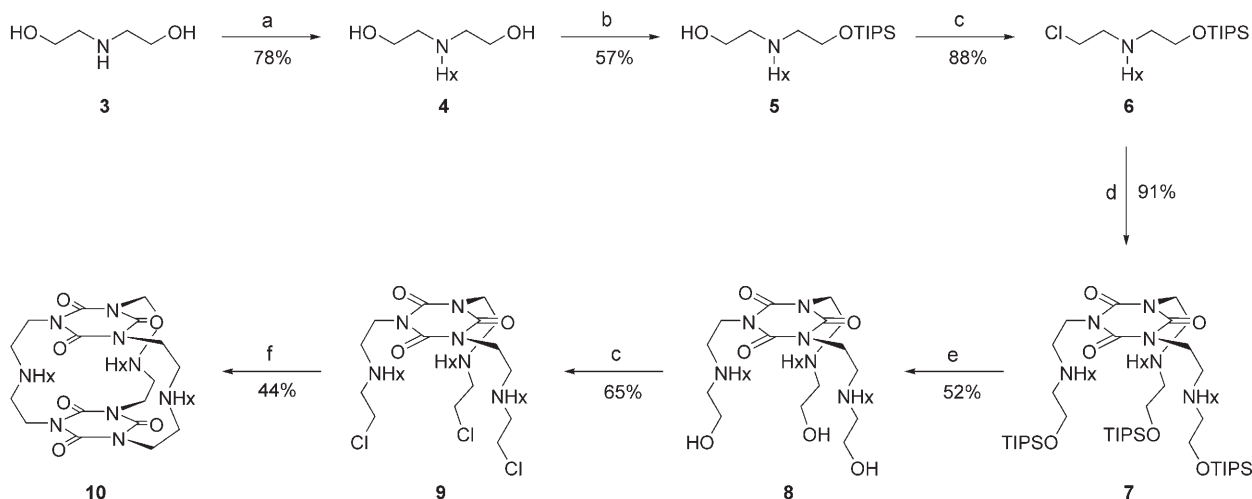
Cylindrophane **10** is freely soluble in dichloromethane but only poorly so in methanol and crystallizes from a mixture of these solvents. An X-ray crystal structure of the empty cage is shown in Figure 1. Unexpectedly, the conformation of one of the three bridging chains is *gauche-anti-gauche-gauche*, deviating from the *gauche-anti-anti-gauche* conformation of the other chains. There are two molecules in the asymmetric unit of the crystal ($Z' = 2$), and this distortion appears in both of them, causing the cyanuric acid rings to tilt relative to each other such that the height of the cylinder varies from 4.30 to 4.91 Å.^[10] In one of the structures (not shown), one of the three hexyl sidechains also has a *gauche* kink.

The cage was armed for the binding of fluoride by protonation. Thus, **10** was suspended in methanol, and an excess of concentrated aqueous hydrochloric acid was added to give a clear solution, the evaporation of which gave [H₃**10**]Cl₃ as a white solid. The corresponding tetrafluoroborate salt could similarly be prepared by the use of aqueous HBF₄. Redissolution of either [H₃**10**]³⁺ salt in methanol and treatment with an excess of aqueous HF gave a white solid after evaporation of the solvent. The first evidence of a fluoride complex in this material came from the electrospray mass spectrum, which showed a base peak at *m/z* 370, corresponding to the [H₃**10**F]²⁺ ion.^[12] Also present in the spectrum were signals corresponding to [H₂**10**]²⁺ (*m/z* 360), [H**10**]⁺ (*m/z* 718), and [H₂**10**F]⁺ (*m/z* 738). No

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Scheme 2. Reagents and conditions: a) $n\text{-C}_6\text{H}_{13}\text{Br}$, Na_2CO_3 , MeCN, reflux, 48 h (Hx = n -hexyl); b) NaH, THF, RT, 30 min; TIPSCl, 10 h; c) SOCl_2 , CH_2Cl_2 , RT, 16 h; d) cyanuric acid, DBU, DMF, 70°C , 16 h; e) $[\text{Bu}_4\text{N}]\text{F}$, THF, RT, 4 h; f) cyanuric acid, DBU, DMF, 90°C , slow addition over 10 h, then 16 h.

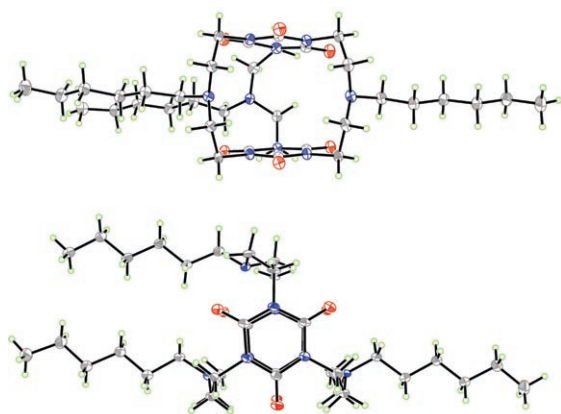


Figure 1. Views of the X-ray crystal structure of **10**.^[11] Only one of the two molecules in the asymmetric unit is shown. Thermal ellipsoids are shown at the 50% probability level. N blue, O red, C gray.

peaks containing chloride were ever observed, even in the spectrum of the $[\text{H}_3\text{10}]\text{Cl}_3$ salt.

Slow diffusion of dichloromethane into a solution of $[\text{H}_3\text{10F}](\text{BF}_4)_2$ in acetonitrile produced good-quality crystals. As can be seen in the X-ray crystal structure (Figure 2), the fluoride ion occupies the cavity. As in the crystal of **10**, the asymmetric unit contains two independent structures which differ in the conformations of the n -hexyl chains. One of the structures is associated with two well-ordered BF_4^- counterions, while the other has two multiply disordered BF_4^- ions. Interestingly, both of the disordered BF_4^- sites also include centrally located, partial-occupancy chloride anions. The observation of this adventitious chloride is attributed to the presence of a trace amount of $[\text{H}_3\text{10F}]\text{Cl}_2$ in the crystallization sample.

The relationship of the fluoride ion to its host in $[\text{H}_3\text{10F}]^{2+}$ is nearly identical to that of the modeled complex $[\text{2F}]^{2+}$, which appeared in the theoretical study that preceded this work.^[9] The key structural parameters are presented in

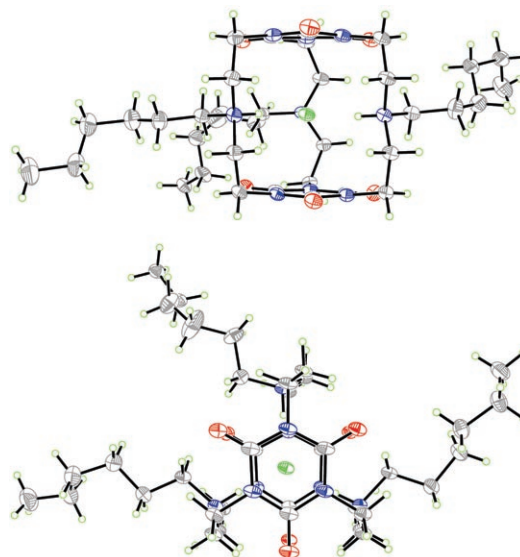


Figure 2. Views of the X-ray crystal structure of $[\text{H}_3\text{10F}][\text{BF}_4]_2$.^[13] Only one of the two molecules in the asymmetric unit is shown. Counterions, sidechain disorder components, and solvate molecules are omitted for clarity. Thermal ellipsoids are shown at the 50% probability level. F green, N blue, O red, C gray.

Table 1 and show that the design of the cage is nearly optimal for fluoride inclusion. Although $[\text{H}_3\text{10F}]^{2+}$ lacks the C_{3h} symmetry of the $[\text{2F}]^{2+}$ model, the fluoride ion in the former compound is located less than $0.1 \text{ \AA}$ from the center of the trigonal plane described by the ammonium nitrogen atoms and is equidistant between the two cyanuric acid rings to within $0.01 \text{ \AA}$ (distance from F^- to the least-squares ring planes). The data for the $[\text{2X}]^{2+}$ complexes are included in Table 1 for comparison purposes. As can be seen, the distance between the centroid of a trimethylcyanuric acid model and the fluoride ion is $0.14 \text{ \AA}$ less than that within **2**. The free hydrogen-bond length between a trimethylammonium model and fluoride ion is likewise $0.10 \text{ \AA}$ less than the corresponding

Table 1: Selected structural parameters from the X-ray crystal structure of the $[\text{H}_3\text{10F}]^{2+}$ complex, the modeled $[\text{2X}]^{2+}$ complexes, trimethylcyanuric acid (Me_3CA)–halide sandwich complexes, and tris(trimethylammonium)–halide complexes.^[a]

Complex	$\pi\cdots\text{X}^-\cdots\pi$ [$\text{\AA}$] ^[b]	$^+\text{NH}\cdots\text{X}^-$ [$\text{\AA}$] ^[c]	$^+\text{N}-\text{H}\cdots\text{X}^-$ [$^\circ$] ^[d]
$[\text{H}_3\text{10F}]^{2+}$	2.68 ± 0.0091 ^[d] 2.69 ± 0.0042 ^[e]	2.79 ± 0.038 ^[d] 2.80 ± 0.053 ^[e]	178.3 ± 0.47 ^[d] 175.6 ± 0.78 ^[e]
$[\text{2F}]^{2+}$	2.62	2.80	176.2
$\text{Me}_3\text{CA}\cdots\text{F}^-\cdots\text{Me}_3\text{CA}$	2.48	–	–
$[(\text{Me}_3\text{NH}^+)_3\cdots\text{F}]^{2+}$	–	2.70	179.7
$[\text{2Cl}]^{2+}$	2.72	3.03	164.1
$\text{Me}_3\text{CA}\cdots\text{Cl}^-\cdots\text{Me}_3\text{CA}$	3.15	–	–
$[(\text{Me}_3\text{NH}^+)_3\cdots\text{Cl}]^{2+}$	–	3.24	179.7

[a] Modeled complexes optimized at B3LYP/6-31+G(d,p), see reference [9] for a full description of the computational methods. [b] Distance from the centroid of the cyanuric acid ring to the anion. [c] Distance from nitrogen to the anion. [d] Structure 1 of the asymmetric unit. [e] Structure 2 of the asymmetric unit.

distance in **2**, and the hydrogen-bond angle 3.5° less acute. The fit of chloride in **2** is much inferior to that of fluoride, with the preferred trimethylcyanuric acid– Cl^- distance $0.43 \text{ \AA}$ greater than that within $[\text{2Cl}]^{2+}$ and the hydrogen-bond length and attendant angle $0.21 \text{ \AA}$ and 15.6° less than optimal, respectively. With such violations of the unconstrained bond lengths and angles in $[\text{2Cl}]^{2+}$, it is no surprise that $[\text{H}_3\text{10Cl}]^{2+}$ is not observed.

In conclusion, we report herein the first practical application of anion– π bonding in a purpose-designed macrocyclic anion host. The cyanuric acid based cylindrophane **10** can be synthesized in seven steps from cheap, commercially available diethanolamine. The triprotonated receptor $[\text{H}_3\text{10}]^{3+}$ forms an inclusion complex with fluoride by a combination of anion– π interactions and ion-pair-reinforced hydrogen bonding. $[\text{H}_3\text{10}]^{3+}$ shows no affinity for chloride in the electrospray mass spectrum and indeed has been predicted by comparative binding energetics in models to be completely fluoride-selective. Although a number of halide complexing agents have been described,^[14] cage **10** introduces a new genre of anion binding, wherein anion– π interactions operate alongside conventional ion pairing, hydrogen bonding, and the classic “preorganization” effect.^[15] An X-ray crystal structure of the $[\text{H}_3\text{10F}]^{2+}$ sandwich complex shows the fluoride ion occupying the center of the cavity, in very close agreement with published theory.^[9] A detailed study of the solution-state binding of fluoride by $[\text{H}_3\text{10}]^{3+}$ and some related receptors is being undertaken and will be the subject of a later report.

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- [11] Crystal data for **10** is given in the Supporting Information. CCDC-659002 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [12] HRMS (ESI) m/z calcd for $\text{C}_{36}\text{H}_{66}\text{FN}_9\text{O}_6$ 369.75599; found 369.75555.
- [13] Crystal data for the $[\text{H}_3\text{10F}]^{2+}$ complex is given in the Supporting Information. CCDC-659003 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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