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Selective and Unusual Fluoride Ion Complexation by A Steroidal Receptor Using OH...F$^-$ and CH...F$^-$ Interactions: A New Motif for Anion Coordination?

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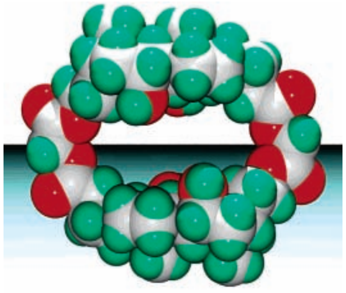
ABSTRACT



A novel cholaphane has been synthesized from a naturally occurring bile acid in just two steps. It has an ability to bind two fluoride ions selectively utilizing the glycolate motif in chloroform. This “inside-out” cyclodextrin analogue encapsulates fluoride through O–H...F$^-$ and C–H...F$^-$ interaction.

The binding and recognition of anions with synthetic systems has received considerable interest in recent years. Although such receptors have been known for several decades,[1] the structural diversity exhibited by this class of molecules is not as varied as has been demonstrated for cation receptors. During the last two decades, anion binding by various pyrrole derivatives[2] and aza cryptands[3] has been demonstrated. In general, most of these receptors bind anions through H-bonding involving N−H groups, with supplementary interaction through (cationic) charge[4] and OH groups.[5] The C−H...F$^-$ type of interaction reported so far involves interaction either with an aromatic hydrogen[6] or with an aliphatic hydrogen attached to a perfluoroalkyl chain.[7] Here, we report selective and unusual fluoride binding utilizing

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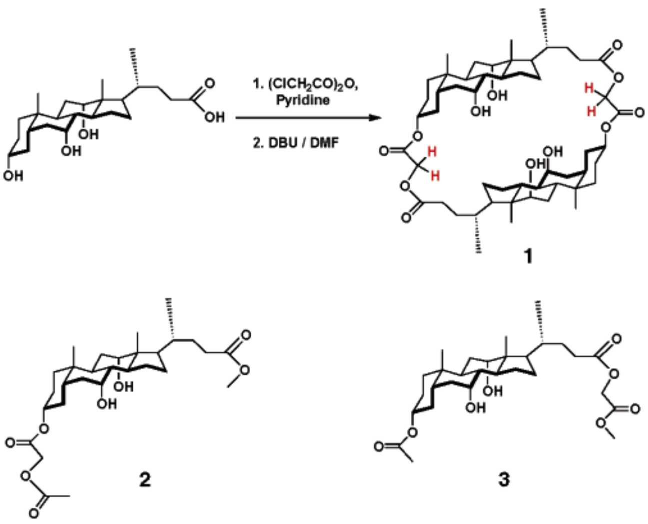
Scheme 1



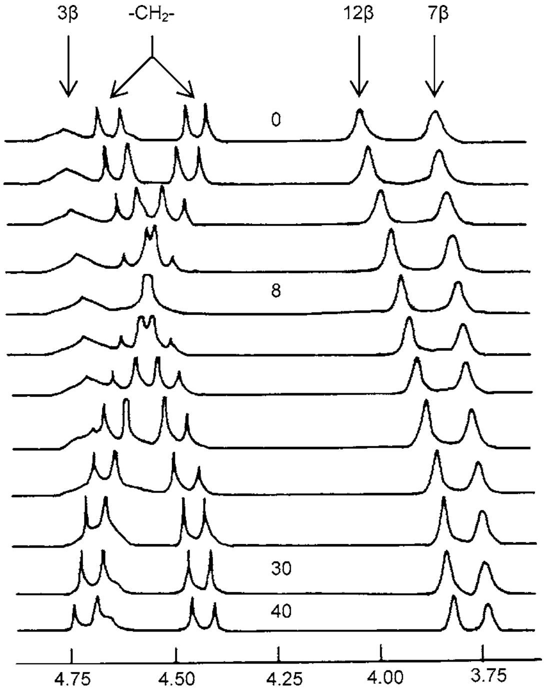


Figure 1. Unusual behavior of glycolate methylene doublets with increasing F$^-$ concentration (mM). *x*-Axis represents NMR chemical shift in parts per million.

simultaneous O−H...F$^-$ and C−H...F$^-$ interactions from a readily synthesized bile acid-derived receptor. To the best of our knowledge, this is unprecedented.

Bile acids are naturally occurring steroidal molecules that are rigid, chiral, and a rare class of molecules exhibiting facial amphiphilicity. Bile acid-derived cyclic oligomers (cyclocholates or cholaphanes)[8] have been shown to be supramolecular hosts.[9] Davis et al. have described bile acid-derived monomeric and cyclic dimeric structures for anion binding and recognition.[10] We synthesized a bile acid-based cyclic dimer **1** with a glycolate spacer by a remarkably simple synthetic route (Scheme 1).[11] This cholaphane **1** has a polar interior with four hydroxyl groups and a hydrophobic outer surface, implying that it could be used for anion encapsulation in a relatively nonpolar solvent. Preliminary NMR screening in CDCl$_3$ revealed that **1** selectively bound F$^-$ ion.

When host **1** was titrated with varying concentrations of ^{n}Bu$_4$N$^+$F$^-$ (TBAF), the 7β-H and 12β-H signals shifted upfield (Figure 1). In addition, the pair of doublets from the glycolate CH$_2$ gradually collapsed to a singlet with increasing concentrations of fluoride. Further addition of fluoride split the singlet back into two doublets (Figure 1). The most reasonable explanation is that the F$^-$ is held by two O−H and *one* of the two C−H hydrogens. Since the receptor can in principle hold two F$^-$, a 1:2 stoichiometry would be expected, which was confirmed by Job plot[12] analysis. For the estimation of binding constants, NMR titration was carried out with 10 mM **1** using 2−40 mM TBAF at 22 °C. Nonlinear least-squares fitting for 7β-H, 12β-H, and both glycolate CH$_2$s was performed (Figure 2). The average values are $K_1 = 1.8\ (\pm 0.1) \times 10^3\ \mathrm{M}^{-1}$ and $K_2 = 2.5\ (\pm 0.35) \times 10^2\ \mathrm{M}^{-1}$.[13] To understand this unusual behavior of the

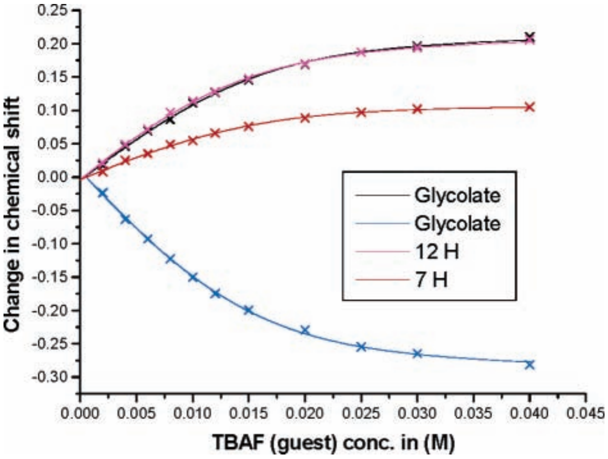


Figure 2. Fit for change in steroidal hydrogen chemical shift of **1** with varying concentration of F$^-$.

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(13) The lower value of K_2 is consistent with the statistical factor plus electrostatic repulsion between the two bound F$^-$.

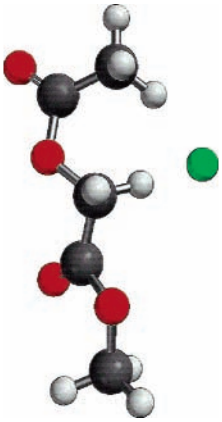

Figure 3. Interaction of F^- with theoretical model.

glycolate methylene group, we studied the possible interaction of F^- with $MeCO_2\mathbf{CH_2}CO_2Me$ as a model (Figure 3).[14] In the presence of F^-, the electron density on the hydrogen involved in H-bonding with the fluoride *decreases*, while that on the other geminal hydrogen *increases*. This is consistent with our observation of the fluoride-induced chemical shifts (*up*field shift for one, *down*field shift for the other). Additionally, the C−H bond involved in H-bonding with F^- was found to be elongated by 32 mÅ, and the H...F^- distance was estimated to be 1.68 Å.[15]

We also investigated other anions such as chloride and bisulfate. While chloride showed weak binding[16] ($K \sim 100$ M^{-1}), bisulfate did not show any binding, which is in agreement with the size of the cavity suggested by X-ray diffraction data (vide supra). A control experiment carried out with **2** did not show any appreciable fluoride binding. However, with regioisomeric **3**, NMR titration with TBAF showed binding with F^- ($K = 76$ M^{-1}), suggesting that the 7α OH and 12α OH from the steroid and a glycolate methylene hydrogen attached to the side chain of the steroid were necessary to bind a F^- ion. A possible mode of binding is shown in Figure 4. Two such binding sites are present in host **1**, enabling it to accommodate *two* F^- ions. Extrapolating this idea, we propose the possible mode of binding of F^- with **1** to be as shown in Figure 4.

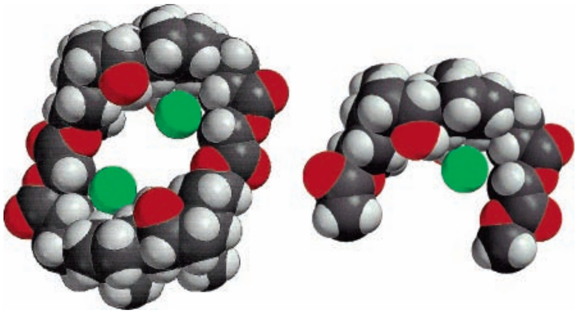

Figure 4. Mode of F^- binding with host **1** (left) and monomeric model **3** (right).

To structurally characterize host **1** and its F^- complex, crystallization was carried out in $CHCl_3$ and in DCM/CH_3CN, in the presence and absence of TBAF, respectively. Polymorph I (Figure 5) crystallized from $CHCl_3$ by slow evaporation at room temperature. This form showed several electron density peaks, indicating disordered solvent molecules in the difference Fourier map. Identification of individual solvent molecules was not possible due to a lack of sufficient data (crystal quality not being good). Hence, the program SQUEEZE/BYPASS[17] was used to eliminate the solvent contribution[18] and thus disordered solvents were ignored in the further refinement cycles.

The unique conformations at the O11−C51−C52−O1−C1−C2−C3−C4 and O5−C25−C26−O7−C27−C28−C29−C30 sites makes the molecule circular in shape and allows solvent molecules to reside in the cavity thus formed. The distances between the O atoms pointing inward are in the range 6.24−7.13 Å, and the distance between O1 and O7 is 12.63 Å; that between O11 and O5 is 12.22 Å. The carbonyl groups C1═O2 and C27═O8 point away (I, Figure 5) from the ring in this polymorph. Interestingly, a different polymorph of **1** was formed (II, Figure 5) when **1** was crystallized from CH_2Cl_2/CH_3CN in the presence of 2.5 equiv of TBAF by slow evaporation at room temperature. This structure did not contain any solvent of crystallization had a *different* molecular conformation. The conformation at the O11−C51−C52−O1−C1−C2−C3−C4 and O5−C25−C26−O7−C27−C28−C29−C30 sites makes the molecule elliptical in shape and hence does not allow solvent molecules to reside in the cavity. The distances between the O atoms pointing inward are in the range 3.14−5.91 Å, and the distance between O1 and O7 is 14.47 Å; the distance between O11 and O5 is 13.21 Å. The carbonyl groups C1═O2 and C27═O8 point toward the interior of the cavirty. The torsion angles in O11−C51−C52 O1−C1−C2−C3−C4 and O5−C25−C26−O7−C27−C28−C29−C30 sites in polymorphs I and II are very different. Despite many attempts, we were not successful in crystallizing the $\mathbf{1}\cdot(F^-)_2$ complex, possibly because of the moderate association constants. It is interesting to note that, in the solid-state structure of polymorphs I and II (Figure 5), both pairs of methylene hydrogens (H26a/H26b and H52a/H52b) point away from the molecular cavity, but in solution, they must turn around to interact with the bound F^- in its molecular cavity.

In conclusion, a bile acid-based selective fluoride ion receptor has been synthesized in two steps from commercial

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[14] MP2 calculation at the 6-31+G* level was performed using SPARTAN '04 for Windows (Wavefunction, Inc.: Irvine, CA).

[15] Similar methodology has recently been employed for theoretically studying the complexation of di- and trihalomethanes with F^-. See: Kryachko, E. S.; Zeegers-Huyskens, T. *J. Phys. Chem. A* **2002**, *106*, 6832.

[16] Job plot analysis showed 1:1 binding. Modeling suggested that there is no space in the interior for two chloride ions.

[17] Van der Sluis, P.; Spek, A. L. *Acta Crystallogr., Sect. A* **1990**, *46*, 194.

[18] SQUEEZE/BYPASS has been used to solve crystal structure of cyclocholates or cholaphanes because they often crystallize along cylindrical channels, which are filled with disordered solvent molecules. For details, see: Dias, J. R.; Pascal, R. A., Jr.; Morrill, J.; Holder, A. J.; Gao, H.; Barnes, C. *J. Am. Chem. Soc.* **2002**, *124*, 4647.

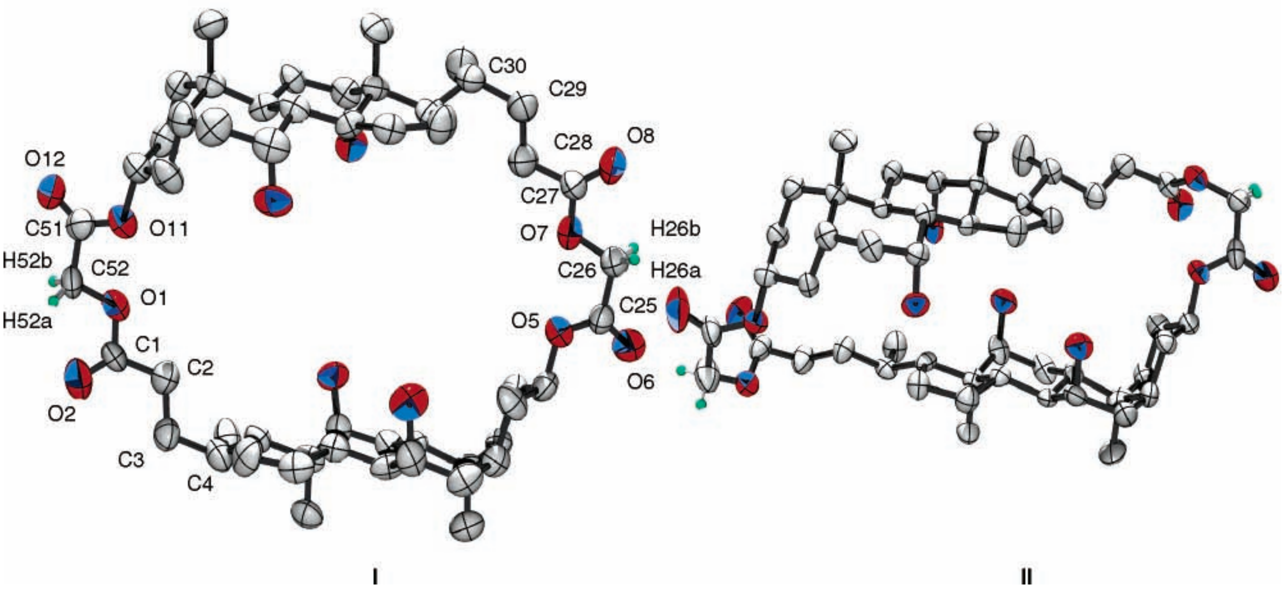

Figure 5. Solid-state structure of polymorphs. Atom numbering shown in I is applicable for II.

starting materials and characterized by crystallography. It showed a remarkable ability to bind *two* fluoride ions in its molecular cavity using OH and CH groups present in its interior surface. An unusual C−H...F$^-$ interaction with a glycolate hydrogen has been observed. We feel that such C−H...F$^-$ interactions have not been adequately exploited in supramolecular chemistry. Thus, anion receptors utilizing the glycolate motif are likely to enrich the structural diversity of anion binding chemistry. We are currently using the motif shown in Figure 3, and its derivatives with increased acidity of the CH$_2$ group, for the design of new anion receptors that may be used in competing solvents. The results of these investigations will be published elsewhere.

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Supporting Information Available: CIF files, Job plot, synthetic procedure, and Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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