Receptor That Can Capture a Discrete Monohydrated Fluoride Anion
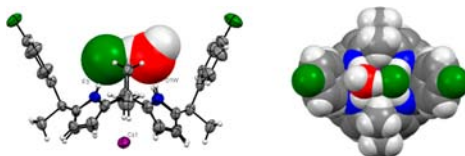
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ABSTRACT

A 'picket calix[4]pyrrole' bearing a well-defined binding domain has allowed the stabilization of a monohydrated fluoride anion. The monohydrated F^{−} was observed only when CsF (not the TBAF) was treated with a host in aqueous acetonitrile. The structure of the receptor-bound, monohydrated F^{−} was fully characterized by single crystal X-ray diffraction analysis as well as by low temperature ^{1}H and ^{19}F NMR spectroscopy. Further analysis revealed that the complex formed a three-dimensional, salt mediated organic framework in the solid state.

The design and synthesis of neutral anion receptors with high affinity and selectivity for a variety of targeted anions represents a significant challenge in supramolecular chemistry. The use of H-bonding interactions as recognition motifs for specific anions has been studied extensively because of the potential applications of the technologies in the biological and environmental sciences.[1] Applications

that have received particular interest in recent years include ion selective electrodes, fluorescence chemosensors, and electrochemical signaling devices.[2] The development of novel and more specifically functionalized receptors showing enhanced selectivity requires fine-tuning of the interactions with targeted guest molecules. Although H-bonding interactions are weak noncovalent interactions that are strongly affected by both pH and solvent, they are commonly used as the driving force in anion recognition. Thus, the effective design of anion receptors is more challenging than the design of the corresponding cation receptors.[3] Among the various anion recognition motifs reported in the literature,[4] calix-[4]pyrroles, which are readily accessible from the condensation of pyrrole and ketones, have been identified as versatile hosts for anion recognition and for halide anions especially.[5] We have reported several strapped calix[4]pyrroles as new homologues for anion-binding and ion-pair recognition motifs.[6] Three-dimensional cyclic oligopyrroles

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have been reported by several groups that are engaged in research aimed at improving anion binding affinity and selectivity.[7] It is envisaged that calix[4]pyrroles bearing preorganized and flexible binding domains will exhibit enhanced affinity and selectivity.

Although considerable progress has been made in the area of supramolecular chemistry, it remains a challenge to design host molecules that allow for the specific incorporation of targeted analytes. In the particular case of anion selective receptors and capsules,[4] it has proved difficult to generate systems that capture and stabilize hydrated forms of the fluoride anion, which are considered as discrete species that are fundamentally different from the naked fluoride anion.[5] In recent pioneering work, Bowman-James et al.[6] described the first example of a fluoride anion based cascade complex in which a water molecule bridges two fluoride anions $[F^- \text{---} H\text{---}O\text{---}H \text{---} F^-]$ within an aza-cryptand cavity.[7] More recently, Ghosh et al.[8] synthesized a tripodal receptor and demonstrated through structural means the existence of a hydrated fluoride anion cluster $(F_2(H_2O)_6^{2-})$. In this case, formation of the dimeric capsule structure was templated by the presence of this particular fluoride−water cluster. However, to the best of our knowledge, a discrete monohydrated fluoride anion has not been characterized in both the solid state and solution in the same system; however Gale et al. have previously observed monohydrated fluoride bound to an anion receptor in the solid state.[9]

Calix[4]pyrroles are a class of simple tetrapyrrolic non-aromatic macrocycles that are well recognized for their ability to recognize anions in organic media.[10] The recent discovery that these systems can be used to affect simultaneous anion and cation recognition (ion-pair binding) has made these systems and their functionalized derivatives of further interest in the context of supramolecular recognition and self-assembly.[11] The versatile binding ability of calix[4]pyrroles can be explained by their tendency to adopt a cone conformation in the presence of Lewis basic anions such that the four pyrrolic N−H's can form a H-bond with the anion. Adopting this conformation

provides, in turn, an electron-rich tetrapyrrolic cup that can interact with appropriately sized cations. Motivated by a desire to generate improved receptors for the fluoride anion, which is known to be toxic in living systems,[12] we have recently prepared a modified calix[4]pyrrole bearing cis-4-fluorophenyl "pickets" **1**.

Scheme 1. Formation of two different ion-pair complexes whose structure depends on the nature of the countercation

[1•CsF•H₂O]   1   [1•TBAF]
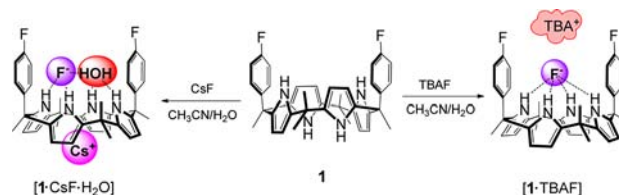
We found that this receptor displays a remarkable enhanced affinity for the fluoride anion relative to other anions (Supporting Information (SI)).[13] We have shown that receptor **1** binds to F^- (as its tetrabutylammonium salt) in a 1:1 fashion with a binding affinity of $K_a = (5.22 \pm 0.18) \times 10^6$ M^{-1} in acetonitrile. The high affinity for F^- was ascribed to a favorable anion-π and strong NH-anion H-bond. We have now found that this receptor (i.e., **1**) will stabilize a hydrated F^- in the presence of an appropriately chosen countercation. Surprisingly, we found that receptor **1** can form two different types of supramolecular anion complexes, involving the naked fluoride anion (F^-) and a monohydrated fluoride anion $[F(H_2O)]^-$, resespectively, depending on the choice of countercation (Scheme 1). To the best of our knowledge, a receptor that can discriminate between these two species has not been reported.

A diffraction grade single crystal of the complex of receptor **1** with CsF(H₂O) was obtained via the slow diffusion of a solution of excess cesium fluoride in wet acetonitrile into a solution of receptor **1** in dichloromethane (see SI for details). The resulting structure revealed a novel complex, [**1**•CsF•H₂O], wherein a monohydrated fluoride anion is trapped within the cavity (Figure 1). This single X-ray crystal analysis served to confirm that the calix-[4]pyrrole **1** adopts a cone-like conformation with the four pyrrolic NH protons involved in H-bonding to the entrapped monohydrated fluoride anion. The receptor-bound F^- to N distances are 2.762 and 2.774 Å. The water-bound N-to-O distances are 2.898 and 2.939 Å, respectively. The distance between the Cs^+ and F^- is 2.896 Å. The distance between the F^- anion and the H-atom of the bound water molecule is 1.588 Å. The complexed Cs^+-pyrrole π surface distances range from 3.59 to 3.97 Å. All the values indicate the existence of the strong ion-pair interaction. Careful analysis of the crystal structure also revealed that the complex exists in the form of a well-ordered, 3-D array

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that can be considered as a kind of salt organic framework. In this extended arrangement, a receptor and [CsF·H$_2$O] are stacked one by another with the spatial arrangement such that the [CsF·H$_2$O] salt and receptor are almost diagonal to one another.
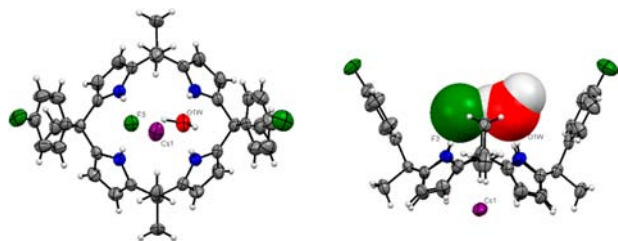
Figure 1. Single crystal X-ray structure of the [CsF•H$_2$O] complex of **1** showing receptor-bound hydrated fluoride anion [F(H$_2$O)]$^-$. Top view (left) and side view (right). Thermal ellipsoids are shown at the 30% probability level.

The crystal structure also revealed that the monohydrated fluoride [F$^-$·(H$_2$O)] is tightly held by four pyrrole N−H's through H-bonding, while the Cs$^+$ ion is firmly included in the cup-like cavity of the receptor **1**. Two such cone-shaped, receptor-shared ion-pair complexes are held together *via* ion-pair interactions between the F$^-$ and Cs$^+$ ions, interactions that result in a well-ordered framework. The cavity generated by the two phenyl groups in **1** seems to provide a perfect match for the bound monohydrated fluoride anion, a substrate that appears held in place *via* a fortuitous combination of anion−π and N−H H-bonding interactions. The view presented in Figure 2 is meant to underscore the fact that the hydrated fluoride ion (F$^-$━H−OH) resides in the center of the cavity and that the water molecule is a structural unit. Based on the metric parameters, this water molecule appears to play a key role in the binding processes, stabilizing in particular what appear to be favorable anion−π interactions.

The F$^-$ anion is tetrahedrally coordinated in a slight distorted way. Specifically, the F$^-$ is bound by three strong intramolecular H-bonds, while its charge is presumably balanced by electrostatic interactions with a Cs$^+$ cation bound in the cup of another calix[4]pyrrole lying above it. A diffraction grade crystal of [**1**•TBAF] was also prepared *via* the slow evaporation of a dichloromethane/wet aceto-nitrile solution of receptor **1** in the presence of excess TBAF. The resulting structure is shown in Figure 2. Interestingly, the structure reveals two different conformations of the TBA cation: In one, the TBA cation resides between the cup generated by the receptor **1**, whereas, in the other, it is sitting on top of the F$^-$-containing cavity. The structures shown in Figure 2 lead us to suggest that the countercation

can undertake a critical role in the complex formation. Some calix[4]pyrroles have previously been recognized as versatile ion-pair receptors also.[14,15]

To understand the solution state behavior of **1** in the presence of CsF, quantitatively ^{1}H NMR spectroscopic analyses were carried out in dry CD$_3$CN at rt. Here, the addition of 1 equiv of CsF was found to produce downfield shifts in the NH signal to ca. 12.55 ppm ($\Delta\delta$ = 4.74 ppm). This latter signal appears as a doublet (J = 50 Hz), as would be expected for the strong H-bonding between F$^-$ and pyrrole NHs. The single set of aromatic protons appearing at δ = 6.95 ppm shifts slightly upfield and becomes split into two well-defined signals that appear at δ = 6.89 and 6.68 ppm. The well-ordered splitting of the pyrrole N−H and Ar−H resonance is taken as evidence that the F$^-$ is symmetrically oriented inside the cavity. The slightly longer NH−F distance compared to what is seen in the case of octamethyl calix[4]pyrrole clearly indicates that an anion−π interaction is involved in anion binding. Upon complexation of Cs$^+$ ions within the cup of receptor **1**, the signals ascribable to the β-pyrrolic protons were found to undergo a slight downfield shift ($\Delta\delta$ = 0.04 ppm). Evidence for complete binding was observed upon addition of only 1 equiv of CsF, indicating a 1:1 binding stoichiometry between **1** and CsF. No evidence was found for the formation of a monohydrated fluoride complex in dry acetonitrile. Standard titrations using absorption spectros-copy and associated curve fitting[16] provided support for the conclusion that CsF·H$_2$O (K = (2.36 ± 0.48) × 10^7 M^{-1}) is bound more strongly to receptor **1** than TBAF (K = (5.22 ± 0.18) × 10^6 M^{-1}) in wet acetonitrile. This result leads us to suggest that the stabilizing cation−π interaction is more effective in the case of CsF binding.

No diagnostic evidence was seen in the rt ^{1}H NMR spectrum for the formation of monohydrated fluoride in wet CD$_3$CN. Although a broad signal at δ 3.78 ppm was observed, that may or may not reflect such a species (Figure 2, top) present. However, a ^{1}H NMR spectrum recorded at −40 °C showed clear evidence for the existence of the monohydrated fluoride anion. For example, The doublet appearing at δ 12.35 ppm is typical of a proton resonance associated with NH━F$^-$ H-bonding, while the singlet observed at 8.41 ppm is assigned as NH━OH$_2$ H-bonding. The observation of these two signals with a 1:1 integration ratio provided strong support for the conclu-sion that two different sets of H-bonding motifs are present. Two new signals appearing at δ 8.44 and 4.65 ppm were thought to reflect the presence of water molecules under a different environment. The broad signal appearing at 4.65 ppm was considered to be a fluoride-bound water molecule (Figure 2, bottom).

The two distinctive H-bonding interactions also in-curred the splitting of the aromatic protons and one set of *meso*-methyl protons (Figure 2, boxed region); these findings provide additional support for the conclusion drawn above. These conclusions are fully consistent with

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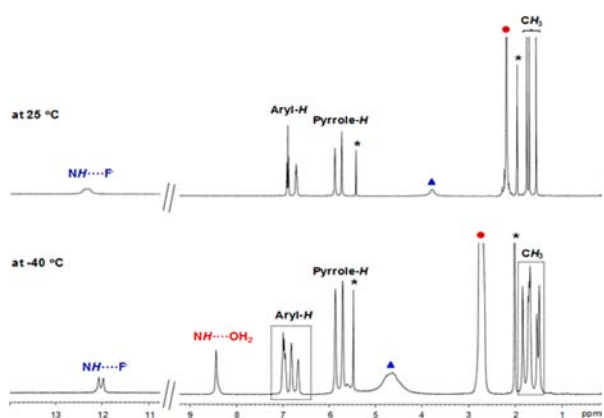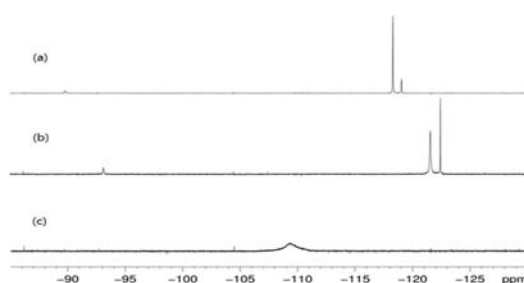
Figure 2. Comparison of the ^{1}H NMR (400 MHz) spectra of receptor **1** + CsF (1 equiv) at 25 °C (top) and at −40 °C (bottom) in 80% CD$_3$CN/20% CD$_2$Cl$_2$/2% H$_2$O. (●) Solvated H$_2$O; (▲) F$^-$·H$_2$O. [**1**] = [CsF] = 8.49 mM.

Figure 3. ^{19}F NMR (300 MHz) spectra of (a) **1** + CsF (1 equiv), (b) **1** + TBAF (1 equiv), and (c) CsF (1 equiv) taken at −40 °C in CD$_3$CN/H$_2$O (2%).

the binding picture inferred from the single crystal X-ray crystallographic analysis. On the other hand, the ^{1}H NMR spectra of the [**1**•TBAF] complex did not reveal any indication for the binding of water at either rt or −40 °C. In addition, the single crystal X-ray analysis of the [**1**•TBAF]-complex grown from dichloromethane and wet acetonitrile clearly indicates that no water molecules are associated with the bound fluoride anion (see SI).

The monohydrated fluoride complex was further characterized by ^{19}F NMR spectrocopy. The results indicate that the signal associated with the receptor-bound, monohydrated fluoride anion shows a clear distinction from the receptor-bound simple fluoride anion (Figure 3). In ^{19}F NMR spectra recorded at −40 °C in CD$_3$CN, the signal of the encapsulated monohydrated fluoride anion is seen as a singlet at −118.34 ppm while the singnal of a simple fluoride anion appeared at −122.47 ppm. The singal of the Ar−F initially observed at −89.46 ppm at rt is shifted to −119.10 ppm at −40 °C. This is attributed to the conformational changes associated with a strong $\pi-\pi$ interaction between a bound anion and the two aryl groups. On the other hand, the signal of the unbound fluoride anion (CsF) appears at −109.23 ppm.

In conclusion, we have reported a receptor that can trap the elusive monohydrated fluoride anion both in the solid state and in solution. The ion-pair complex formed from the receptor **1** and the monohydrated fluoride anion complex exists in the form of a well-ordered 3-D salt-mediated organic framework. The key factors for the formation of the complex appear to be the ability of receptor **1** to stabilize a bound ion pair via a combination of multiple interactions, including a H-bond, anion−π interactions, cation−π interactions, and the specific dimensions of the binding domain. Moreover, the size of the hydrated fluoride anion seems to be well matched with the binding domain provided by receptor **1** in its cation-bound cone conformation. As a result, the water molecule and counter-cations play a key role in the binding. Such capturing of a monohydrated fluoride over its higher hydrated forms would allow us to visualize and interrogate not only the basic docking modes of anion-calix[4]pyrrole interactions but also the geometrical arrangement of the ''solvent'' molecules around the anion at the binding site. We expect that the present findings may provide further insight in the transition metal and anion coordination chemistry as proposed by Bowman-James.[17] We expect that other associated species, including the higher hydrates of the fluoride anion, will prove amenable to capture using appropriately designed synthetic hosts. Work toward the realization of this goal is currently in progress.

Supporting Information Available. Experimetnal procedures, spectroscopic data. and X-ray crystal data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.