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Cone Calix[4]arene Diethyl Ester Strapped Calix[4]pyrrole: A Selective Receptor for the Fluoride Anion

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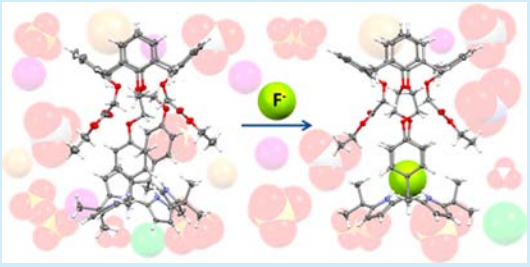
Supporting Information

ABSTRACT: A calix[4]pyrrole strapped by a bulky calix[4]arene diester locked in its cone conformation has been prepared. On the basis of ^{1}H NMR spectroscopic analyses carried out in $CDCl_3$, it is concluded that this hybrid system, receptor **2**, binds only the fluoride anion and does so with remarkably high affinity even in the presence of an excess of various potentially competing environmentally and biologically ubiquitous anions (studied as the tetrabutylammonium, cesium, or lithium salts). Solid state structural analyses provide support for the notion that receptor **2** interacts well with the fluoride anion in the solid state.



As our understanding of the importance of anions in natural phenomena and industrial processes has increased, the benefits of receptors capable of recognizing, binding, and sensing anions selectively have become commensurately apparent.[1−4] Among the various anions targeted for selective recognition, the fluoride anion has attracted particular attention. It underlies a number of biological, environmental, and chemical processes and is important in public health and medicine.[5−7] For example, the fluoride anion has been utilized in many countries as an additive to water supplies and toothpaste because of its beneficial but still controversial effects on dental health.[8] In addition, the fluoride anion has been reported as a potential treatment of osteoporosis.[9] On the other hand, high levels of the fluoride anion, as found in certain well waters and other environmental sources, have been implicated in several types of human pathologies, including dental and skeletal fluorosis, osteoporosis, metabolic and neurological dysfunctions, and kidney failure.[10] This conflict between benefit and risk makes it important to be able to recognize and detect the fluoride anion across a range of environments. In this context, synthetic anion receptors could have an important role to play, particularly if they allow the selective binding of the fluoride anion within environments that are rich in competing anions.[5−7]

The fluoride anion is the smallest halide anion and is characterized by a high charge density and Lewis basicity. This makes it a particularly challenging target in terms of receptor design. Moreover, for an artificial anion receptor to be applied for practical use it must be able to recognize and bind the fluoride anion very strongly and with high selectivity relative to other potentially competing anions that may be present at much higher concentrations in solution. A good receptor should also display reversible binding such that removal of the bound fluoride is possible subsequent to the recognition event, thereby allowing for reusability of the receptor in question.

For construction of fluoride anion receptors the calix[4]-pyrrole core (**1**) is an attractive starting point. This is a system that shows inherent fluoride anion specificity in halogenated solvents. It is also an attractive building block because it is relatively easy to modify synthetically.[11,12] For instance, both the *β*-pyrrolic carbon and *meso*-carbon atoms can be substituted with various functional groups.[11] The calix[4]pyrrole framework also has a well-defined three-dimensional geometry and typically adopts a cone conformation upon anion binding. Taking advantage of these properties, in recent years a variety of so-called strapped calix[4]pyrroles have been designed and synthesized that rely on connecting two diagonal meso-carbons atoms via various linkers.[11] Most of the resulting systems have been found to possess anion affinities that are substantially greater than the parent calix[4]pyrrole, **1**.[10−13] The increased anion affinity observed in the case of many strapped systems is attributed to additional interactions between the straps and anions, as well as to better protection from solvation. A further attractive feature of strapped calix[4]pyrroles is that, in principle, their specificity for a given anion could be tuned by varying the length and nature of the straps. For instance, an increased selectivity for small anions, such as F^-, could potentially be achieved by introducing rigid and bulky groups into the straps.[12] As a specific test of this particular design expectation, we have prepared the rigid strapped-calix[4]pyrrole **2** and, as detailed below, demonstrated that in $CDCl_3$ this system acts as a highly selective receptor for the fluoride anion in the presence of an excess of other potentially competing anions, when studied in the form of their tetrabutylammonium (TBA^+) or cesium cation salts.

The calix[4]pyrrole-derived receptor **2** is capped by a cone-calix[4]arene diethyl ester subunit and contains two phenyl spacers in the straps to increase rigidity. The synthesis of receptor **2** is shown in Scheme S1. Compound **2** was fully characterized by

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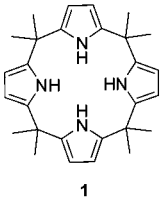

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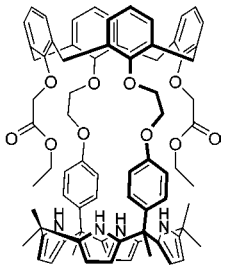

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standard spectroscopic techniques, as well as by single crystal X-ray diffraction analysis. Two different crystals of **2** were obtained in its anion-free form. Crystals suitable for single crystal X-ray diffraction analysis were grown by subjecting solutions of **2** in a 1:1 (v/v) mixture of chloroform/methanol (1/1) and ethyl acetate, respectively, to slow evaporation. The resulting structures revealed that the calix[4]pyrrole unit of **2** adopts either a partial cone or a flattened 1,2-alternate conformation in the solid state depending on the nature of the solvent molecules bound to the pyrrolic NH protons (Figures S1 and S2). In accord with design expectations, the calix[4]arene moiety is found to be fixed in the cone conformation in both structures. Evidence that the conformation of the calix[4]arene is retained in solution came from the observation of two doublet peaks corresponding to the methylene protons at 3.23 and 4.55 ppm in the ^{1}H NMR spectrum recorded in $CDCl_3$ in the absence of an added anion salt (Figure S3).

The ability of **2** to bind anions in solution was investigated via ^{1}H NMR spectroscopy using $CDCl_3$ as the solvent. In the anion-free form of **2**, the aromatic proton signals (H_a and H_b) of the calix[4]arene resonate around 6.5 ppm. They are thus considerably upfield-shifted relative to those for H_c and H_d (Figure S1). This shift is attributable to the shortened distance between the two facing calix[4]arene aromatic rings linked to the rigid phenoxy spacers. Such a structural interpretation is consistent with what was seen in the X-ray diffraction analysis (Figures S1−S3).

When receptor **2** was exposed to various anions, such as F^-, Cl^-, Br^-, I^-, NO_3^-, SO_4^{2-}, $H_2PO_4^-$, and $HP_2O_7^{3-}$ (as the tetrabutylammonium (TBA^+) salts), only the fluoride anion gave rise to spectroscopic changes consistent with anion binding (Figures S3 and S4). Whereas no discernible changes in the proton resonances were seen in the ^{1}H NMR spectrum recorded in $CDCl_3$ in the presence of other test anions, when receptor **2** was subject to titration with TBAF in chloroform-d_1, two sets of distinguishable resonances were seen for all proton signals in the ^{1}H NMR spectrum before saturation was achieved (Figure S3). These peaks are attributed to the anion-free form and the fluoride complex of **2**, respectively, leading us to conclude that the fluoride binding/release equilibrium is slow on the ^{1}H NMR time scale. The observed slow exchange kinetics reflects a strong binding interaction between the receptor and the bound fluoride anion. This latter presumption was further supported by the observation of large, anion-induced chemical shift changes in both the β-pyrrolic proton signals and, particularly, the NH proton resonance. The singlet seen for the pyrrolic NH protons in free **2** undergoes a significant downfield shift (by 5.70 ppm) when exposed to the fluoride anion. Furthermore, this signal also becomes split into a doublet (J = 44.8 Hz) as the result of coupling with the bound fluoride anion.[14] In contrast to what is seen for the NH proton signals, the β-pyrrolic CH proton resonances experience a more modest (ca. 0.3 ppm) upfield shift. This is consistent with an increase in the electron density of the pyrrole rings resulting from hydrogen bonding interactions with the fluoride anion.

Consistent with the strong binding inferred from the slow exchange kinetics is the observation that saturation behavior was seen in the ^{1}H NMR spectral titration of **2** upon the addition of ~1 equiv. Based on the spectral changes, an association constant (K_a) for F^- binding could be estimated as $>10^4$ M^{-1} via use of standard curve fitting protocols.[15]

Over the course of the spectral titration, the multiplet peaks corresponding to the aromatic proton resonances of H_a and H_b converged into a singlet while undergoing a noticeable upfield shift (Figure S3). Such observations are also consistent with fluoride anion binding, which serves to bring closer the two rigid facing aromatic rings in the linking arms (Figure 1). In contrast,

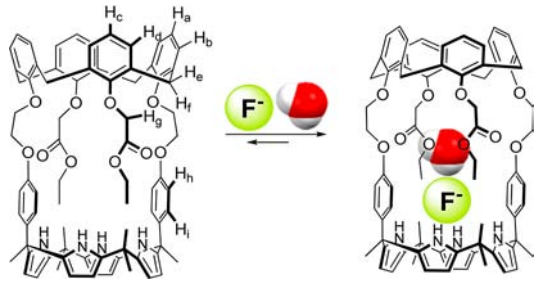

Figure 1. Putative binding interactions present in the monohydrated fluoride anion complex of **2** as inferred from NMR spectroscopic studies carried out in $CDCl_3$ and solid state structural analyses.

the signal (H_g) corresponding to the methylene protons adjacent to the carbonyl groups undergo a significant downfield shift ($\Delta\delta_{H_g}$ = 0.64 ppm) during the course of the titration. These latter changes are ascribed to interactions between the methylene protons in question (H_g) and a water molecule that originates with the fluoride anion source ($TBA{\cdot}F{\cdot}3H_2O$) and which presumably serves to hydrate the bound fluoride anion (Figure 1).

The observation of the fluoride anion-only recognition that was seen in the case of **2** stands in marked contrast to what was observed in the case of the parent calix[4]pyrrole **1**, as well as other calix[4]pyrrole analogues that have been found to bind various anions.[11,13] The selectivity of **2** under the present standard conditions of analysis is ascribed to the increased rigidity of the calix[4]pyrrole core imparted by the relatively inflexible phenyl linkers, as well as to the bulky nature of the calix[4]arene strap. Presumably, these components act as steric blocking moieties that prevent anions larger than fluoride from either reaching the interior of the cavity or interacting favorably with the calix[4]pyrrole core.

Single crystal X-ray diffraction analyses provided further insights into the fluoride anion binding behavior of **2** (Figure 2). Crystals suitable for such analyses were obtained by allowing pentane to diffuse slowly into a chloroform solution of receptor **2** in the presence of excess tetraethylammonium fluoride (TEAF). The resulting single crystal structure revealed that the F^- anion is hydrogen-bonded to the NH protons of the calix[4]pyrrole substituent at distances between 2.74 and 2.75 Å (N---F^- interactions) and is also monohydrated. The fluoride−water separation is 2.78 Å (O---F^- interaction) (Figure 2). The tetraethylammonium cation (TEA^+) is bound within the electron-rich calix[4]pyrrole cup present in the cone conformation, presumably as the result of electrostatic interactions.

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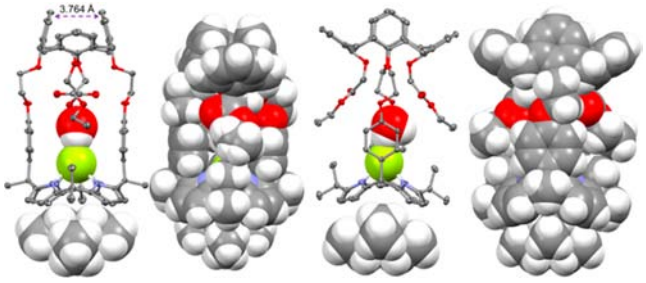

Figure 2. Two different views of the single crystal X-ray diffraction structure of **2**·TEAF·H_2O. Most hydrogen atoms and solvent molecules not involved in stabilization of the ion pair complex have been removed for clarity. Displacement ellipsoids are scaled to the 50% probability level.

In accord with what was found in solution, in the fluoride complex of **2**, the distance between two diagonal aromatic rings of the calix[4]arene unit linked to the rigid phenyl units was considerably reduced relative to what was seen in the anion-free form of **2** (5.32 Å for the methanol complex vs 3.76 Å for the TEAF complex; cf. Figures 2 and S1).

Evidence for high affinity and selectivity of receptor **2** for the fluoride anion came from a ^{1}H NMR spectroscopic titration experiment carried out in $CDCl_3$ in the presence of other competitive anions at high concentrations (>5 equiv for each anion relative to F^-). During the titration of **2** with TBAF in the presence of Cl^-, Br^-, I^-, NO_3^-, and SO_4^{2-} (TBA^+ salts) two sets of distinguishable resonances were seen for all observable proton signals in ^{1}H NMR spectra before saturation was achieved upon the addition of 1.11 equiv of TBAF (Figure 3). The spectral

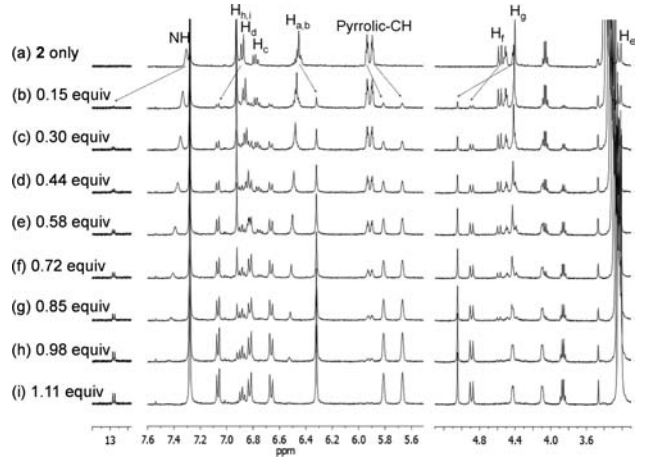

Figure 3. ^{1}H NMR spectra recorded during the titration of receptor **2** (4.18 mM) with TBAF (tetrabutylammonium fluoride) in the presence of TBACl, TBABr, TBAI, $TBANO_3$, and $(TBA)_2SO_4$ (>5 equiv each) in $CDCl_3$.

features were entirely analogous to what was seen during the course of the ^{1}H NMR spectral titration of **2** with TBAF alone (i.e., in the absence of any potentially competing anions) (Figure S3). This leads us to suggest that receptor **2** responds to the fluoride anion with high sensitivity and selectivity even in the presence of other anions. Based on the changes in the chemical shifts seen during this ^{1}H NMR spectroscopic titration, a binding constant for interaction with the fluoride anion could be calculated and was found to be higher than 10^4 M^{-1}.[15] The extent of this reduction (less than a factor of 2.5) places an upper bound on the effective affinity constant for any of the competing anions.

In a complementary study, TBAF (1.5 equiv) was added to a $CDCl_3$ solution of **2** containing excess quantities of the relatively basic CH_3COO^-, $H_2PO_4^-$, and $HP_2O_7^{3-}$ anions (as the TBA^+ salts) in $CDCl_3$. The resulting ^{1}H NMR spectra proved identical to those measured during titrations of **2** with F^- alone (Figure S5). This finding provides further support for the high F^- selectivity of **2** relative to other potentially competitive anions (Figure S5).

The effect of the countercation on the anion selectivity of **2** was also investigated. This was done using various lithium and cesium salts and standard ^{1}H NMR spectroscopic analysis carried out in 10% CD_3OD in $CDCl_3$ for reasons of solubility. In the case of most calix[4]pyrrole-based anion and ion pair receptors reported to date, especially, those strapped with rigid linkers, the observed selectivity for the F^- anion decreases remarkably when the analyses are carried out in the presence of the cesium cation. This reduction in selectivity has been ascribed to the fact that the Cs^+ cation is cocoordinated to the calix[4]pyrroles along with anions to form relatively strong ion pair complexes.[11,12] The strength of these complexes acts as an effective buffer against what might otherwise be a higher inherent fluoride anion selectivity.

Despite this precedent, it was found that when receptor **2** was exposed to a range of lithium and cesium salts in $CD_3OD/CDCl_3$ (1/9, v/v), a ^{1}H NMR spectral response was seen only in the case of CsF (Figures S7–S9). Nearly identical spectral changes were seen as during the course of the titration with TBAF in $CDCl_3$. On this basis, it was inferred that receptor **2** is able to bind CsF selectively and does so with a fluoride anion binding mode that is analogous to that seen in the case of the TBAF complex (Figure S7). Such fidelity has not been seen in the case of previous ion pair receptors based on calix[4]pyrrole.

Slight chemical shift changes in the ^{1}H NMR spectrum of **2** were observed in the presence of excess LiCl in $CD_3OD/CDCl_3$ (1/9, v/v) (Figure S8). However, a detailed ^{1}H NMR spectral titration of **2** with LiCl revealed no appreciable spectral changes upon the addition of up to 6.22 equiv of LiCl, leading us to suggest that the binding interaction between **2** and LiCl, if any, is very weak (Figure S10).

Further evidence for the CsF selectivity of receptor **2** came from competition studies. Specifically, it was found that the ^{1}H NMR spectrum of **2** recorded in the presence of CsF, CsCl, CsBr, $CsNO_3$, $CsClO_4$, LiF, LiCl, and $LiClO_4$ (~10 equiv each) in $CD_3OD/CDCl_3$ (1/9, v/v) was identical to that recorded in the presence of CsF only (Figure S7). Such a finding provides support for the notion that receptor **2** binds the CsF with remarkably high selectivity over other cesium and lithium salts. A detailed ^{1}H NMR spectral titration of receptor **2** with CsF in 10% CD_3OD in $CDCl_3$ gave results analogous to those seen with TBAF in $CDCl_3$, leading us to propose that the binding modes are similar. Moreover, in the presence of the CsF the binding and release kinetics likewise proved slow on the ^{1}H NMR time scale (Figure S11). The K_a value for the interaction of **2** with CsF determined from the spectral titration was found to be ~4000 M^{-1} in $CD_3OD/CDCl_3$ (1/9, v/v).[15]

Further support for the CsF binding mode of receptor **2** inferred from the solution phase NMR spectroscopic studies came from a single crystal X-ray diffraction analysis. Suitable single crystals of the CsF complex, **2**·CsF·CH_3OH, were obtained by slow evaporation of a chloroform/methanol solution of **2** containing excess cesium fluoride. The resulting structure

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revealed that the cesium cation is bound within the cone-shaped calix[4]pyrrole cavity formed by the fluoride anion binding to the pyrrolic NH protons (N---F^- distances of 2.74−2.78 Å) (Figure S12). The distances between Cs^+ and the centroids of the pyrrole rings were found to be between 3.37 and 3.69 Å. These values fall within the range of π−cation interactions. The cesium cation bound to the calix[4]pyrrole cavity is also coordinated with the carbonyl O-atom of the ester group from a different molecule. This interaction results in the formation of a coordination polymer found in the solid state (Figure S12). Meanwhile, the bound F^- is also solvated by a methanol molecule with a distance of 2.71 Å (O---F^- interaction). The distance between Cs^+ and F^- was found to be 3.87 Å.

In conclusion, a calix[4]pyrrole receptor **2** strapped by a bulky calix[4]arene diester subunit locked in its cone conformation has been synthesized. ^{1}H NMR spectroscopic studies and single crystal X-ray diffraction analyses reveal that **2** binds F^- with high affinity and near-complete selectivity in the presence of an excess of other competitive anions, including Cl^-, Br^-, I^-, OAc^-, NO_3^-, SO_4^{2-}, $H_2PO_4^-$, and $HP_2O_7^{3-}$. We thus propose that **2** will have a role to play in the construction of fluoride-anion-selective sensors, extractants, electrodes, and polymeric materials. Work along these lines is in progress.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic details, NMR spectroscopic data, and X-ray structural data for **2**·CH_3OH·H_2O (CCDC 1026518), **2**·ethyl acetate (CCDC 1026517), **2**·TEAF·H_2O·$(CH_2Cl_2)_2$ (CCDC 1026519), and **2**·CsF·CH_3OH·$CHCl_3$ (CCDC 1026516). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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