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Small triiminopyrrolic molecular cage with high affinity and selectivity for fluoride

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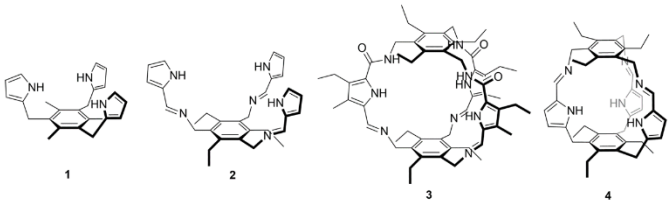
A small molecular cage (4) with high affinity and complete selectivity for fluoride to the limit of detection over other competing small anions was synthesized. Cage 4 was also found to retain the encapsulated fluoride anion within its cavity even after one or two pyrrolic NH protons were subject to deprotonation.

The fluoride anion plays important roles in a range of environmental, biological, and chemical processes and is the subject of policy debates involving public health and medicine. Not surprisingly, therefore, this small, Lewis basic species has become a special target for selective anion receptor design.[1-3] Although numerous efforts have been devoted to the development of anion receptors with high affinity and selectivity for the fluoride anion,[4-6] few anion receptors have been reported that demonstrate exclusive selectivity, especially, in the presence of other competing anions.[7] The design of such a receptor is particularly challenging because of the small size, high charge density of fluoride, and exceptional Lewis basicity of the fluoride anion. To achieve high affinity and selectivity for the fluoride anion, we believe that good size matching between the receptor and the anion, as well as a high degree of spatial preorganization is essential. Structural rigidity and an appropriate geometry of the receptor are likewise expected to be critical design elements if better anion selectivity is to be achieved.[8] In this vein, cage-like molecules have attracted increasing attention as supramolecular hosts; many have proved effective in forming strong and selective complexes with guests, presumably as the result of encapsulating them within the essentially shielded cavities.[9-11] For instance, tripodal receptors **1** and **2** were reported to recognize halide anions and oxyanions, respectively, but with relatively low affinity and selectivity.[12,13] In contrast, molecular cage **3**, possessing both hydrogen bonding donor and acceptor sites, was found to bind tetrahedral oxyanions as well as spherical halide anions with significantly enhanced affinity, albeit without appreciable selectivity.[14] Based on these prior advances, we designed and synthesized the relatively small molecular cage (**4**).[11] Cage **4** contains three iminopyrrole groups and was designed to act as a structurally contracted analogue of cage **3**. As described in detail below, this new system was found to bind the fluoride anion *via* hydrogen bonding interactions with high affinity and complete selectivity in chloroform as well as in relatively polar solvent, DMSO, as inferred from ^{1}H NMR, and ^{19}F NMR spectroscopic analyses. A combination of ^{1}H and ^{19}F NMR spectral data also provides support for the conclusion that the mono- and doubly deprotonated forms of cage **4**, obtained by treatment with an excess of tetrabutylammonium fluoride (e.g., >1.66 equiv.), were able to bind the fluoride anion, presumably as the result of residual NH-F^{-} hydrogen bonding interactions.



The synthesis of cage **4** is shown in Scheme 1. Briefly, the trispyrrolic benzene derivative **5** was synthesized by means of an electrophilic substitution reaction involving pyrrole and 1,3,5-tribromomethyl-2,4,6-triethylbenzene carried out in the presence of K_2CO_3 as a base.[15] Subsequently, the pyrrole groups of compound **5** were subject to Vilsmeier-Haack formylation using DMF and $POCl_3$ to give compound **6**. Finally, the formyl groups of **6** were condensed with the 1,3,5-triaminomethyl-2,4,6-triethylbenzene to give the [1 + 1] molecular cage **4** in essentially quantitative yield. The structure of cage **4** was confirmed by standard spectroscopic means, including ^{1}H and

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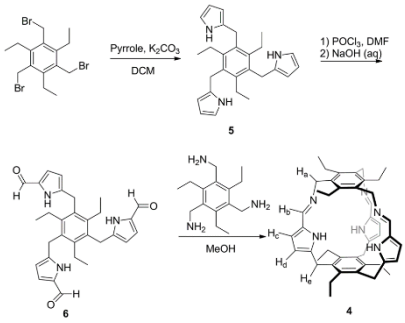
^{13}C NMR spectroscopy and high resolution mass spectrometry (HRMS).



Scheme 1. Synthesis of cage **4**

Initial studies involving the anion recognition features of cage **4** were carried out in $CDCl_3$ and DMSO-d_6 solution by means of ^{1}H NMR spectroscopy. In $CDCl_3$, the ^{1}H NMR spectrum of cage **4** in its as-prepared form is characterized by one singlet at δ = 7.70 and a pair of doublets at δ = 6.61 ppm and 6.11 ppm corresponding to the imine CH and the pyrrolic CH proton resonances, respectively (Figures S1 and S2). In analogy to what was seen with cage **3**, the proton signal of the pyrrolic NH protons were not seen in the ^{1}H NMR spectrum in $CDCl_3$, a finding attributed to peak broadening by intra- or inter-molecular hydrogen bonding interactions (Figure S1). When cage **4** was exposed to a variety of anions including F^-, Cl^-, Br^-, I^-, HCO_3^-, SO_4^{2-}, $H_2PO_4^-$, and $HP_2O_7^{3-}$ (as the tetraethylammonium (TEA) salt for HCO_3^- and the tetrabutylammonium (TBA^+) salts for all other anions), only fluoride produced an appreciable change in ^{1}H NMR spectrum (Figures S1). The F^--induced spectral changes (discussed in detail below) proved similar to those seen in the case of **3**. We thus suggest that cage **4** binds fluoride with complete selectivity over other test anions, at least to the limits of ^{1}H NMR spectral detection. This binding behaviour stands in sharp contrast to what was seen with tripodal receptors **1** and **2** and cage **3** that lacked selectivity for specific anions.[12-14] We ascribe the evident selectivity for fluoride to the increased rigidity and contracted cavity size of cage **4** relative to **3**.

When cage **4** was subjected to an ^{1}H NMR spectral titration with TBAF in chloroform-d_1, two sets of distinct resonances were seen for proton signals of the pyrrolic CHs, the imine CHs, and the methylene CHs bonded to the imine nitrogen atoms before saturation was reached upon the addition of ≈1 equiv. of fluoride (Figure S3). These peaks are derived from the anion-free form and the fluoride complex of cage **4**, respectively. Such a finding is consistent with the suggestion that the binding/release equilibrium between cage **4** and fluoride is slow on the ^{1}H NMR time scale. Although not a proof, in our experience such slow exchange kinetics are characteristic of strong anion binding in the case of pyrrole-based receptors.

Further support for the proposed high affinity and selectivity for fluoride displayed by of cage **4** came from a ^{1}H NMR spectral titration experiment carried out in $CDCl_3$ in the presence of an excess of various other competitive anions (>10 equiv. for each anion). Upon subjecting cage **4** to titration with TBAF in $CDCl_3$ in the presence of Cl^-, Br^-, I^-, and SO_4^{2-}, two separate sets of proton signals were again visible for all observable protons in the ^{1}H NMR spectra recorded before saturation was attained (at ca. 1.01 equiv. of TBAF; Figure 1). Indeed, the spectral changes matched those seen when **4** was titrated with TBAF in the absence of any potential competing anions (Figure S3). The binding constant (K_a) corresponding to the interaction of cage **4** with the fluoride anion was approximated from this ^{1}H NMR spectroscopic titration to be >10,000 M^{-1} even when the various potentially competing anions were present in the solution.[16]

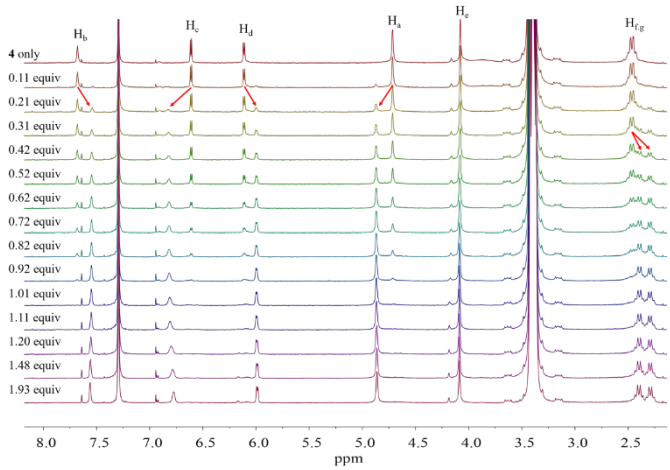


Figure 1. Partial ^{1}H NMR spectra recorded during the titration of cage **4** (3 mM) with TBAF (tetrabutylammonium fluoride) in the presence of TBACl, TBABr, TBAI, and $(TBA)_2SO_4$ (>10 equiv. each) in $CDCl_3$.

In marked contrast to what was seen in $CDCl_3$, the ^{1}H NMR spectrum of cage **4** measured in DMSO-d_6 proved complex. In this relatively polar solvent, sharp and split signals were seen for all the protons of cage **4**, even the NH protons (Figures 2 and S4). This finding leads us to suggest that the DMSO solvent interacts with cage **4** so as to retard conformational motion of the cage on the NMR time scale. As a result, ostensibly equivalent protons are placed in different magnetic environments giving rise to different chemical shifts. In contrast, the addition of fluoride produces a simplified ^{1}H NMR spectrum analogous to that recorded in $CDCl_3$ (cf. Figures 2 and S1). We interpret this finding in terms of the fluoride anion being bound within the middle of the cavity leading to a system that is both symmetric and conformationally locked on the NMR time scale. These changes occur in a concentration dependent fashion. Specifically, when cage **4** was titrated with TBAF in DMSO, a new set of readily discernible proton signals begin to appear in ^{1}H NMR spectra while the original proton signals corresponding to anion-free cage **4** gradually disappear before saturation occurs upon the addition of ca. 1.20 equiv. of TBAF. The presence of signals for both the anion-bound and free receptor forms of **4** seen at intermediate fluoride anion concentrations is, as above, taken as evidence for a strong binding interaction. Further support for the strong fluoride binding by cage **4** came from the observations that the NH proton signals appear to be downfield-shifted with splitting into doublet (J = 54.6 Hz) as the result of coupling between the NH protons and the bound fluoride anion (Figure 2).[7,9] H-F coupling was also seen in the corresponding ^{19}F NMR spectrum (Figure 3). For example, in the presence of the fluoride anion, a fluoride

resonance at δ = -97.52 ppm is seen. This signal appears in the form of an apparent quartet (*J* = 55.6 ppm) as a result of the coupling between the bound fluoride and the three pyrrolic NH protons (Figure 3). This finding lends credence to the notion that the fluoride anion sits in the middle of cage **4** and is bound with a 1:1 stoichiometry, as would be inferred from the ca. 1.2 equiv. needed to produce saturation in the ^{1}H NMR spectral titration discussed above.

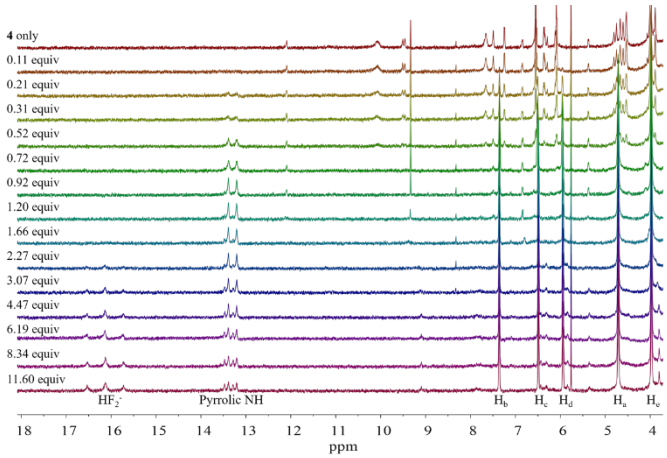


Figure 2. ^{1}H NMR spectra recorded during the titration of cage **4** (3 mM) with TBAF in DMSO-d_6.

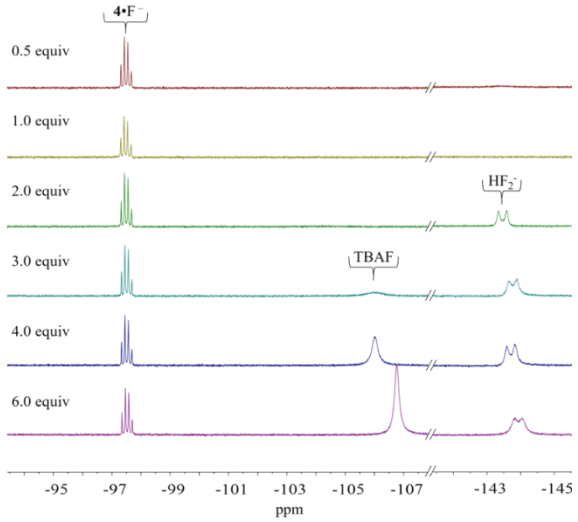


Figure 3. Partial ^{19}F NMR spectra recorded during the titration of **4** (27 mM) with TBAF in DMSO-d_6. Fluorobenzene (C_6H_5F, 16.2 mM) was used as an internal reference.

Adding quantities of fluoride to cage **4** beyond those needed to achieve saturation of the CH signals in the ^{1}H NMR spectrum recorded in DMSO-d_6 (ca. 1.2 equiv.; vide supra) leads to the appearance of a new signal in the range of 15.5-16.5 ppm. This new resonance appears in the form of a triplet with a large coupling constant (*J* = 121 Hz) and its relative integration increases as a function of fluoride anion concentration (Figure 2). This triplet peak is attributable to the formation of the bifluoride anion (HF_2^-) as the result of pyrrole NH deprotonation by the Lewis basic fluoride anion. A signal corresponding to HF_2^- at δ = -144 ppm is also seen in the ^{19}F NMR spectrum (Figure 3).

After allowing a sample of cage **4** to stand overnight in the presence of 6.0 equiv of fluoride in DMSO-d_6, a new triplet signal at δ = -98.3 ppm was observed in the ^{19}F NMR spectrum. This peak appears at slightly higher field (Δδ = 0.78 ppm) than the original quartet seen in the presence of ca. 1 equiv of F^- (Figure 4). Based on the inferred coupling to two protons (giving rise to the observed triplet) and the chemical shift value, this new signal is ascribed to a cage complex wherein a fluoride anion is bound within the cavity of a mono-deprotonated form of cage **4** ([**4** - H^+]). In the ^{1}H NMR spectrum, the pyrrolic NH proton signals of [**4** - H^+]•F^- appear in the form of slightly downfield-shifted doublet. This signal is distinct from that ascribed to the neutral fluoride-bound complex of cage **4** (Figures 2 and 4). Such findings lead us to suggest that, after deprotonation, cage **4** is still able to encapsulate the fluoride *via* strong hydrogen bonds as shown schematically in Figure 5.

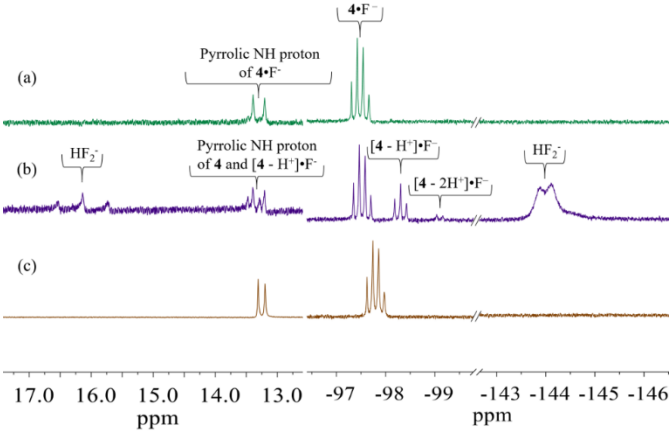


Figure 4. Partial ^{1}H (left) and ^{19}F (right) NMR spectra of cage **4** (27 mM) recoreded (a) with 1.0 equiv. of TBAF in DMSO-d_6, (b) with 6.0 equiv. of TBAF in DMSO-d_6, and (c) after adding 10% water to (b). NMR spectra were recorded after the samples were allowed to stand overnight at room temperature. Fluorobenzene was used as an internal reference.

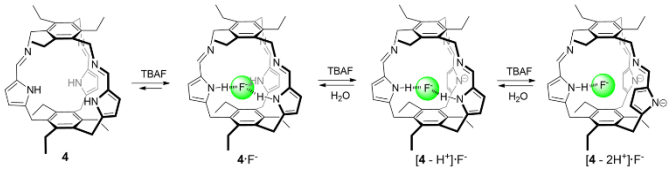


Figure 5. Proposed binding interactions between various forms of cage **4** and the fluoride anion as inferred from ^{1}H and ^{19}F NMR spectral studies.

Further treatment with fluoride anion led to the production of a new signal, a doublet at δ = -99.2 ppm, in the ^{19}F NMR spectrum that is distinct from the quartet and the triplet signals ascribed to the fluoride anion complexes of the neutral and mono-deprotonated forms of **4** (Figure 4(b)). Again, this finding is ascribed to the formation of a fluoride anion bound complex involving a doubly deprotonated species ([**4** - 2H^+]) as shown schematically in Figure 5. To the extent this interpretation of the ^{19}F-^{1}H splitting is valid, it leads to the inference that cage **4** is able to bind the fluoride anion even after loss of two pyrrolic NH protons and the formation of a formally dianionic cage species. This, in turn, implies that the specific structure of cage **4**, as well as hydrogen bonding, plays a crucial role in fluoride anion binding. In contrast, the addition of water (10%) to solutions of [**4** - H^+]•F^- or [**4** - 2H^+]•F^- gave rise to similar ^{1}H NMR and ^{19}F

NMR spectra as those of **4**•F^- (Figure 4(c)). This is consistent with the deprotonated pyrrolic subunits being re-protonated in the presence of water.

The binding affinity of cage **4** for fluoride in DMSO was quantified by UV/Vis spectroscopic analyses. Cage **4** in its ion-free form exhibits two absorption peaks at 310 nm and 360 nm, respectively (Figure S8). When cage **4** was exposed to increasing amounts of fluoride, the absorption band at 360 nm undergoes a gradual hypochromic shift and then reaches saturation quickly (Figure S8). By fitting the UV/Vis spectroscopic titration data to a standard 1:1 binding profile, an association constant (K_a) of 1.01×10^7 M^{-1} could be derived.[18] This value is significantly higher than the corresponding values recorded for receptors **1**-**3** (K_a < 5 M^{-1} for **1** and **2** vs $K_a = 1.57 \times 10^6$ M^{-1} for **3** vs 1.01×10^7 M^{-1} for **4**).[12-14] This marked difference is ascribed to the well-defined and preorganized structure of cage **4**, as well as a cavity size that is presumably nearly optimal for fluoride anion encapsulation.

Conclusions

In conclusion, a molecular cage (**4**) possessing a small, rigid cavity was synthesized in high yield via a [1 + 1] condensation reaction involving 1,3,5-triaminomethyl benzene and an α-formylated-1,3,5-tripyrrolyl benzene. ^{1}H NMR and UV/Vis spectroscopic analyses provided support for the conclusion that cage **4** is capable of binding the fluoride anion with high affinity and selectivity in chloroform and DMSO. ^{1}H and ^{19}F NMR spectroscopic studies proved consistent with the suggestion that cage **4** is able to encapsulate the fluoride anion not only in its neutral form, but also after being subject to mono- and even double deprotonation. The present work thus serves to highlight the importance of structural design in the creation of systems that are capable of capture specific anions with both high affinity and selectivity.

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Conflicts of interest

There are no conflicts to declare.

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