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Selective Inclusion of Fluoride within the Cavity of a Two-Wall Bis-calix[4]pyrrole

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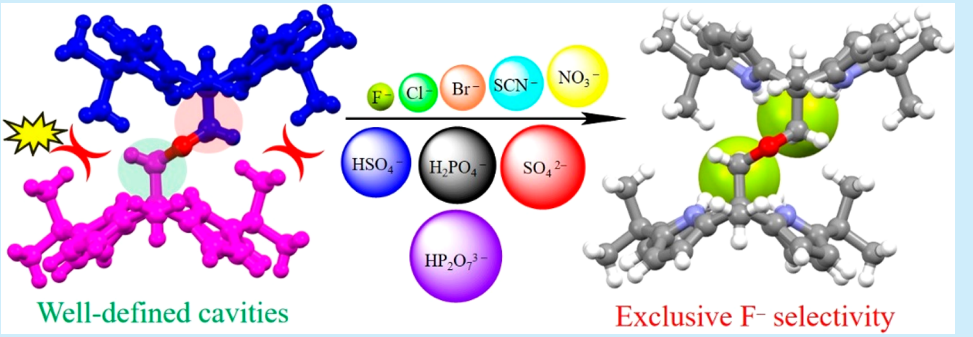

ABSTRACT: We report what to our knowledge is the smallest bis-calix[4]pyrrole (**2**). It proved capable of trapping fluoride anions exclusively relative to other anions (Cl^-, Br^-, SCN^-, NO_3^-, $H_2PO_4^-$, HSO_4^-, SO_4^{2-}, and $HP_2O_7^{3-}$; tetrabutylammonium salts), as confirmed by ^1H NMR spectroscopy ($CDCl_3$), X-ray diffraction analysis, DFT calculations, and molecular dynamics simulations. The F^- selectivity is ascribed to the small size of the cavity in **2**.

Molecular recognition remains a central focus of supramolecular and host–guest chemistry.[1−7] However, synthetic molecular recognition systems that perform with near-idealized specificity are rare,[8] notwithstanding the fact that they are commonplace in nature. A specific challenge involves increasing the inherent selectivity of a given class of receptor. Here, we show that linking formally two calix[4]pyrrole subunits via two single atom oxygen bridges creates a receptor with essentially exclusive selectivity for the fluoride anion relative to other standard test anions, including Cl^-, Br^-, SCN^-, NO_3^-, $H_2PO_4^-$, HSO_4^-, SO_4^{2-}, and $HP_2O_7^{3-}$, as inferred from ^1H NMR spectroscopic studies carried out in $CDCl_3$, as well as supporting X-ray diffraction analyses and DFT calculations.

Calix[4]pyrrole (octamethylporphyrinogen) and its derivatives have been extensively studied as both anion receptors and ion-pair receptors.[9−17] In the context of this effort, it was found that strapped calix[4]pyrroles, wherein one face of the macrocyclic core is bridged by a connecting linker, are particularly effective as both anion and ion pair receptors displaying, inter alia, relatively enhanced affinities and selectivities.[18,19] In most cases, the observed selectivity reflects a greater affinity for a given targeted species over other comparative guests. Nevertheless, examples that show exclusive selectivity toward targeted guests over other species are rare.[20] In 2015, Panda and co-workers[20] reported a series of calix[4]pyrroles with what may well be the shortest possible strap and showed that the systems in question displayed exclusively selective toward the fluoride anion. This selectivity is attributed to the conformational restriction imposed by the small strap on the calix[4]pyrrole moiety, which prevents the calix[4]pyrrole from accessing the cone conformation considered most favorable for anion binding (Figure 1a). Other approaches to achieving high fluoride anion selectivity, including the use of small pyrrolic cages, are also known.[21] However, the importance of fluoride as a target justifies continued efforts to capture it with high fidelity.

Fluoride (F^-) is the smallest anion except for hydride (H^-). Our thinking, therefore, was that a three-dimensional cavity slightly larger than the volume of fluoride anion capable of supporting hydrogen-bonding interactions would reject anions larger than fluoride, resulting the exclusive fluoride selectivity. With such a predicative postulate in mind, we designed what we believe is the smallest two-walled bis-calix[4]pyrrole (**2**) reported to date.[23,24] It consists of two simple calix[4]pyrroles (**1**) formally linked via two oxygen bridges.

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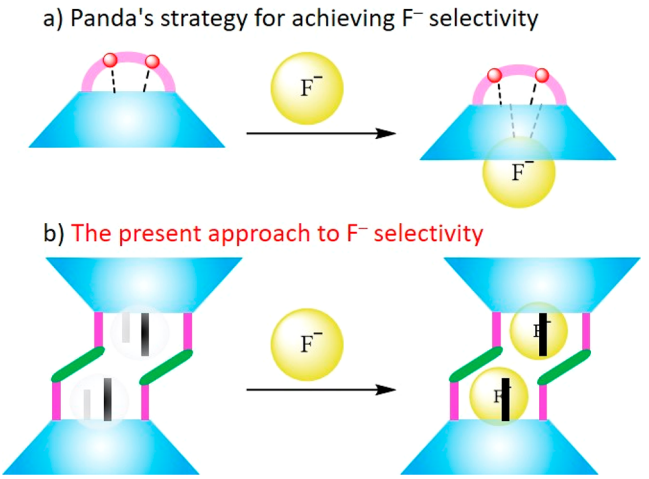
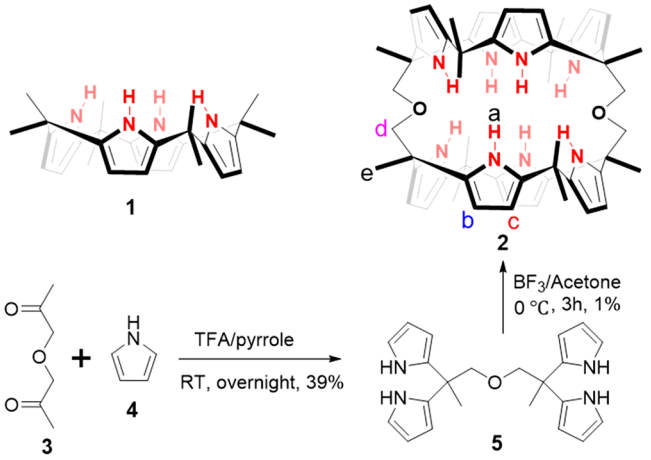


Figure 1. Two strategies leading to exclusive selectivity for the fluoride based on calix[4]pyrroles: (a) strategy used by Panda and co-workers;[20] (b) strategy reported here. Color codes in (b): thick pink lines, methylene units; gray/black lines, methyl groups; green lines, bridging oxygen atoms; and blue cones, calix[4]pyrrole units.

To prepare bis-calix[4]pyrrole **2**, we started with commercially available 2-propynyl ether. Hydrolysis catalyzed by HgO/H_2SO_4 (Kucherov's reaction) yielded 2-propanone ether (**3**) (Scheme S1).[22] Condensation between **3** and pyrrole (**4**) gave the key O-linked bis-dipyrrolemethane intermediate (**5**) in a yield of 39% (Scheme 1). A one-pot, BF_3-catalyzed, multi-ring-forming condensation of **5** with acetone then gave the desired trimacrocyclic bis-calix[4]pyrrole **2** in 1% yield. Compound **2** was characterized by NMR spectroscopy and high-resolution mass spectrometry (Figures S1−S3) as well as via single-crystal X-ray diffraction analysis (Figure S4).

Scheme 1. Chemical Structure of Calix[4]pyrrole 1 and the Synthetic Route Used to Prepare Receptor 2



Initial evidence that receptor **2** could act as an effective receptor for the fluoride ion came from an X-ray diffraction analysis of single crystals obtained by allowing a CH_2Cl_2/CH_3CN solution of **2** to undergo slow evaporation in the presence of excess tetrabutylammonium fluoride (TBAF) (Figure 2). The resulting structure revealed an encapsulated 1:2 complex in the solid state. As is common for solid-state TBA anion complexes of calix[4]pyrroles, the TBA counter cations were found to be partially bound to the electron-rich

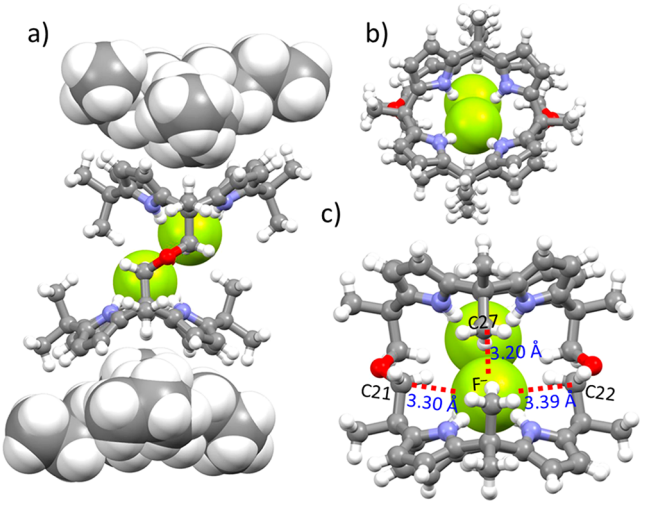


Figure 2. Single-crystal structures of **2**·2TBAF: (a) side on view; (b) and (c) top and side views of the core **2**·2F⁻ complex. For (a), TBA^+ and F^- ions are shown in space-filling form. For (b) and (c), the F^- anions are shown in space-filling form while the counter cations are omitted for clarity.

cup of the calix[4]pyrrole domain through presumed cooperative C−H···π interactions and cation···π interactions (Figure 2a).[9,25−29] Each of the two fluoride anions concurrently trapped within the inner cavity of **2** is bound to one calix[4]pyrrole unit in its corresponding cone conformation. The top calix[4]pyrrole moiety was found tilted at ∼26 degrees relative to the lower one (Figure S5); presumably, this reflects steric clashes between the peripheral methyl groups attached to the *meso* positions. The net result is the formation of two relatively independent small pockets defined by the conelike calix[4]pyrrole subunits, the *meso* methyl groups, and the two linking ether groups.

The two bound fluoride anions are nestled into the pockets of **2** in spite of the potential electrostatic repulsion such cobinding is likely to engender (Figure 2b,c). The $F^-\cdots F^-$ distance was estimated to be 3.02 Å, which is consistent with a degree of anion−anion repulsion interaction. However, this repulsion is apparently stabilized by multiple cooperative hydrogen bonding interactions, as has been seen in the case of other dianion complexes.[30] For instance, average pyrrole N···F^- distances of 2.69 Å are seen. In addition, C···F^- distances of 3.30 Å (C21···F^-), 3.39 Å (C22···F^-), and 3.20 Å (C27···F^-) are seen for the methylene CHs and methyl CHs subunits, respectively (Figure 2c). These are very short distances and could reflect strong CH···F^- interactions. For instance, a search of the Cambridge Crystallographic Data Centre (CCDC) revealed roughly 40 calix[4]pyrrole−fluoride anion structures. Most of the C···F^- distances (where C refers to either a methylene or methyl carbon atom) were found to fall in the 3.50−4.00 Å range.[26,31−33] Only few with C···F^- distances in the 3.50−3.45 Å range were found.[34−36] No examples with C···F^- distances as short as 3.20 Å (as in the present instance) were found. This contrast was taken as an indication that the cavity provided by **2** is restricted and was thus likely to provide for size-dictated selectivity in favor of fluoride. While not a proof of binding exclusivity, all efforts to obtain diffraction grade crystals of **2** with larger anions (than F^- ion), i.e., Cl^-, Br^-, SCN^-, NO_3^-, $H_2PO_4^-$, HSO_4^-, SO_4^{2-},

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and $HP_2O_7^{3-}$ as their TBA salts failed. This was true in spite of the fact that a variety of crystallization conditions were tested.

The ability of receptor **2** to bind fluoride anions in solution was probed via ^{1}H NMR spectroscopy using $CDCl_3$ as the solvent. Although receptor **2** exhibits only a *1,3-alternate* conformation in solid state, spectroscopic analysis of compound **2** revealed only one set of resonances in $CDCl_3$ at room temperature (Figure S1), as would be expected for a relatively flexible system that is in conformational equilibrium. When excess TBAF was added into a 1.0 mM solution of **2** in $CDCl_3$, the broad singlet ascribed to the pyrrolic NH signals at 7.49 ppm (designated as ***a*** in Scheme 1) in free **2** disappeared completely presumably as the result of fast exchange induced by anion binding (Figure S6). Concurrently, the two peaks ascribed to the *β*-pyrrolic protons, located at 6.01 ppm (***c***) and 5.86 ppm (***b***), respectively, were found to shift to around 5.71 ppm. These changes are consistent with the conclusion that one or more fluoride anions is being bound effectively by **2**.

To obtain greater insights into the binding of fluoride by **2**, ^{1}H NMR spectroscopic titrations were carried out in CD_3Cl using TBAF as the fluoride anion source (Figure 3). Under the

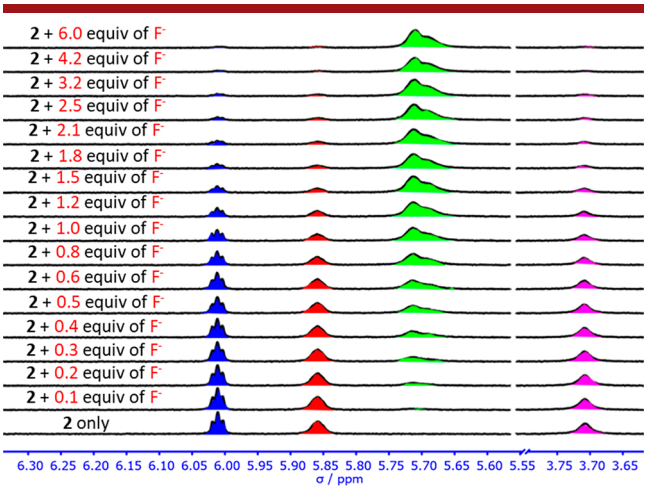

Figure 3. Selected regions of ^{1}H NMR spectra ($CDCl_3$, 298 K) acquired during the titration of **2** with increasing quantities of TBAF: 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.8, 1.0, 1.2, 1.5, 1.8, 2.1, 2.5, 3.2, 4.2, and 6.0 equiv. The resonances of the *β*-pyrrolic protons (peaks in blue and red) undergo an upfield shift to 5.71 ppm (peaks in green) upon the addition of TBAF to a solution of **2**, while the signals of the methylene protons (in pink) disappear in monotonic fashion.

conditions of the titration, new peaks (in green) around 5.71 ppm are seen to increase in intensity, while those of the original *β*-pyrrolic proton signals (in blue and red) decrease. Such changes are thought to reflect a fluoride anion binding process that is slow on the NMR time scale. Additionally, the signals for the methylene protons at 3.71 ppm (***d***, in pink) in the ether bridge were seen to disappear upon the incremental addition of TBAF. This disappearance could be attributed to an increase in the rigidity of this otherwise flexible portion of the molecule brought about as the result of fluoride anion binding to **2** (Figure S7) such that local motions are intermediate on the NMR time scale.

The ^{1}H NMR data corresponding to the pyrrolic C−H proton signals were fitted to a 1:2 binding model and the resulting binding constants were estimated to be $K_{11} = (5.2 \pm 0.4) \times 10^3$ and $K_{12} = (4.4 \pm 1.4) \times 10^2$ M^{-1}, respectively (Figures S8 and S9). These values are in accord with the intuitively appealing inference that the sequential binding of two F^- anions is subject to negative cooperativity ($a = 4K_{12}/K_{11} = 0.34 < 1$).[37,38] In other words, the binding of a first fluoride anion serves to reduce the affinity for the second F^- guest. This is in line with the repulsive anion−anion interaction inferred from the solid-state structural studies (vide supra). Moreover, under conditions of HRMS analysis, evidence for only a 1:1 **2**·F^- complex is seen; this finding is interpreted in terms of the binding of a second fluoride anion in the gas phase being unfavorable (Figure S10), a conclusion further supported by gas-phase DFT calculations (Table S1).

Experimental support for the notion that receptor **2** was capable of binding fluoride in solution with exclusive selectivity came from ^{1}H NMR spectroscopic analyses performed in $CDCl_3$ (Figure 4). It was found that adding 50 equiv of Cl^-,

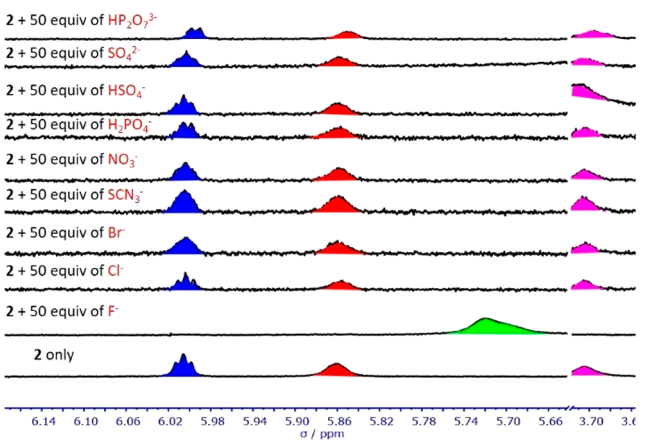

Figure 4. Selected regions of the ^{1}H NMR spectra ($CDCl_3$, 298 K) of solutions of **2** recorded in the absence or presence of 50 equiv of F^-, Cl^-, Br^-, SCN^-, NO_3^-, $H_2PO_4^-$, HSO_4^-, SO_4^{2-}, or $HP_2O_7^{3-}$, respectively, as their TBA salts.

Br^-, SCN^-, NO_3^-, $H_2PO_4^-$, HSO_4^-, SO_4^{2-}, or $HP_2O_7^{3-}$, respectively, as their TBA salts to solutions of **2** in $CDCl_3$ failed to produce any noticeable changes in the proton signals of **2**. This is consistent with the absence of any appreciable interaction between **2** and any of these anionic species in question. In contrast, dramatic changes in the *β*-pyrrole proton signals (i.e., from 6.01 and 5.86 ppm to 5.71 ppm, respectively) were seen in the case of TBAF under otherwise identical conditions. Meanwhile, the presence of one or more potentially competing anions in excess had no adverse effect on the presumed fluoride anion binding (Figure S11). Taken together, these findings lead us to conclude that receptor **2** is able to bind F^- exclusively in the presence of not only larger spherical Cl^- and Br^- but also the more structurally complex SCN^-, NO_3^-, $H_2PO_4^-$, HSO_4^-, SO_4^{2-}, and $HP_2O_7^{3-}$ anions.

To provide further support for the hypothesis that the exclusive F^- selectivity was dictated by the very limited three-dimensional (3D) space within receptor **2**, density functional theory (DFT) calculations were carried out in the gas phase at the X3LYP/6-31g* level. Only in the case of the calculated **2**·2F^- and **2**·F^- complexes did the optimization converge to give rational structures (Figures S12 and S13). Conversely, in the cases of various other putative complexes, including **2**·2Cl^-, **2**·2Br^-, **2**·2SCN^-, and **2**·2NO_3^-, all attempts to force the convergence to structures with anions entrapped within the expected cavities of **2** failed(Figures S14 and S15). Further

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support for this notion came from gas-phase molecular dynamics simulation studies (Figures S16–S21).

In summary, we describe here a small two-wall bis-calix[4]pyrrole (**2**) formally linked by two single oxygen atom bridges. This putative anion receptor was characterized by standard spectroscopic protocols, as well as by single X-ray crystal diffraction analysis. Bis-calix[4]pyrrole **2** was found capable of binding the fluoride anion in a 1:2 manner in the solid state as evidenced by a single crystal structural analysis. In $CDCl_3$ solution, receptor **2** was found to bind the F^- anion well but not interact appreciably with the Cl^-, Br^-, SCN^-, NO_3^-, $H_2PO_4^-$, HSO_4^-, SO_4^{2-}, and $HP_2O_7^{3-}$ anions, as inferred from ^1H NMR spectroscopic analyses, a conclusion supported by DFT calculations and gas-phase molecular dynamics simulation studies. This study paves the way to the design of functional receptors with high or exclusive selectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01440.

Synthetic procedures, NMR, HRMS, titration studies, X-ray crystallography, and DFT calculations of the inclusion complexes (PDF)

Accession Codes

CCDC 1949125–1949127 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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