Synthesis of a Strapped Calix[4]pyrrole: Structure and Anion Binding Properties**

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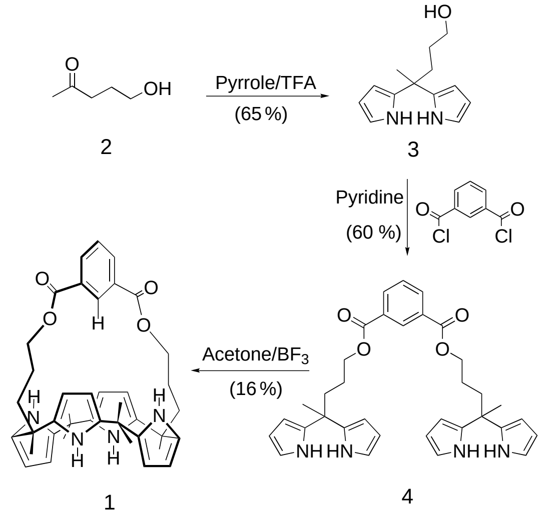
Anion binding chemistry using neutral host molecules has been extensively studied as a result of its potential biological applications, and has emerged as one of the key areas in the field of molecular recognition.[1] The application of anion receptors to molecular devices, such as ion-selective electrodes, fluorescence sensors, and electrochemical signaling devices has received particular attention.[2] The development of newer and more specifically functionalized receptors with enhanced selectivity requires maximized interactions with guest molecules, and this remains a critical goal in the synthesis of neutral receptors for anions. Anion recognition is often affected by hydrogen-bonding interactions; such interactions are weak and this is one of the reasons that anion recognition is more challenging to achieve than cation complexation.[3, 4] Among the various neutral anion receptors described in the literature, calix[4]pyrroles, which are readily accessible from pyrrole and acetone, have been identified as one of the more attractive hosts for the binding of halide anions, especially for fluoride ions.[5] A number of new homologues have been synthesized recently by Sessler and coworkers and subsequently applied in anion sensing[5] and separation.[6] In most cases, the design is based on the modification of either the β-pyrrolic positions or the *meso* substituents.[7–10] A three-dimensional cyclic oligopyrrole unit as well as expanded calixpyrroles have also been reported as part of the efforts to tune the binding abilities of the receptors.[6] However, the synthesis of calix[4]pyrrole receptors bearing preorganized and adjustable binding domains has not been attempted, although the idea has been documented,[4] and encapsulated calixpyrroles prepared by template-based methods have been reported.[10, 11]

Herein we report the first example of a new class of calix[4]pyrroles bearing *trans*-substituted straps on one side of the molecule. We also report the solid-state structure and chloride and fluoride anion binding behavior of this prototypical system. In the design of the receptor (**1**) a flexible strap was used to enable isolation and encapsulation of the binding site. The strap was expected to provide additional hydrogen-bonding sites and allow specific modulation of the inherent anion affinities. Furthermore, it was anticipated that further modifications in affinities could be engendered by using different sizes of straps or by introducing various functional groups into the straps. Ultimately, different kinds of straps could be used to probe the relationships between structure, guest size, and binding affinity.

The synthesis of host (**1**) was accomplished in three steps (Scheme 1). The condensation of 5-hydroxy-2-pentanone (**2**) with pyrrole in the presence of an acid catalyst afforded dipyrromethane **3**.[12] The reaction of isophthaloyl dichloride with two equivalent of **3** in the presence of pyridine gave **4**. The acid-catalyzed condensation of **4** in the presence of excess acetone afforded the desired receptor **1** in 16% yield. The separation of the desired product was straightforward and purification by column chromatography on silica gel (single column) gave a sample of analytical purity. A crystallographic analysis of **1** (Figure 1) reveals that the compound is surprisingly asymmetric at least in the solid state. The overall



Scheme 1. Synthesis of the strapped calix[4]pyrrole **1**. TFA = trifluoroacetic acid.

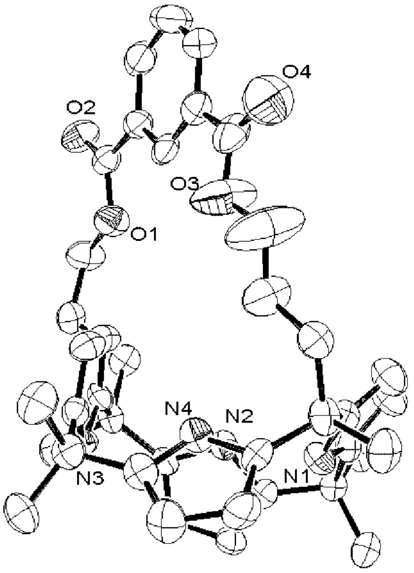


Figure 1. ORTEP view of the molecular structure of **1**. Four pyrrole rings are distorted and form an irregular 1,3-alternating conformation.

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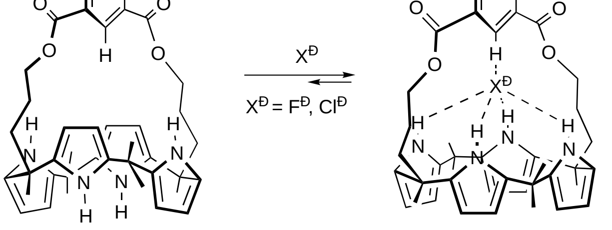
conformation is close to the cyclic 1,3-alternate form seen in other calix[4]pyrroles. However, all four pyrrole rings are tilted at different angles.[13] The two pyrrolic nitrogen atoms (N2 and N4) point toward the strap while the other two (N1 and N3) point downward. The N3 pyrrolic proton points almost outward and is nearly parallel with the N1 pyrrole ring. Close inspection of the 3D-packing structure indicates that the N3 pyrrolic proton is involved in intermolecular hydrogen bonding with one of the carbonyl groups in the neighboring molecule. The observed distance between N3 and O2′ atoms is 3.008 Å. The strap also adopts a slight tilt to compensate for the steric interactions incurred by this intermolecular hydrogen-bonding interaction. These latter features contrast those of other reported calix[4]pyrroles, which, as a general rule, display completely symmetric conformations.[14]

In spite of the asymmetric nature of the solid-state structure, the ^{1}H NMR spectra of **1** recorded in [D$_6$]DMSO displayed a single NH resonance as a sharp singlet at $\delta = 9.39$ and two distinctive β-pyrrolic resonances at $\delta = 5.76$ and 5.74. ^{1}H NMR spectroscopy was also used to study the anion binding behavior of host **1** in [D$_6$]DMSO. The extremely slow nature of the binding/release equilibrium has enabled the direct observation of the complexation phenomenon. Quantitative binding titrations with fluoride and chloride ions reveal distinctive resonances for all the proton signals, as well as dramatic shifts in the NH resonances. The singlet for the NH resonance at $\delta = 9.39$ was split into two distinctive singlets and shifted to $\delta = 13.03$ and 13.07 on addition of fluoride anions. The splitting of the pyrrole NH resonance is thought to reflect a coupling of the bound fluoride anion with the NH protons.[15] The β-pyrrolic resonance originally appearing as two doublets at $\delta = 5.76$ and 5.74 ($J = 2.5$ Hz) was also shifted to $\delta = 5.40$. The integrals of the new resonance signals observed were proportional to the concentration to the amount of added fluoride anions (see Supporting Information). The inner aromatic proton located between the two carbonyl groups on the strap originally resonating at $\delta = 8.65$ was shifted to $\delta = 9.06$ upon addition of fluoride anions while those of the other aromatic protons remained almost unchanged. This large downfield shift is consistent with the presence of a hydrogen-bonding interaction between the inner aromatic proton and fluoride anion in addition to the expected normal strong hydrogen-bonding interaction between the pyrrolic NH protons and the fluoride anion found in simple calix[4]pyrroles. The binding of a fluoride ion to the pocket locks the calixpyrrole into the cone conformation (Scheme 2).



Scheme 2. Controlling the conformation of the strapped calix[4]pyrrole **1**.

The inner aromatic proton located between the two carbonyl groups in **1** showed an even larger downfield shift (to $\delta = 9.52$) upon addition of chloride anions. The other ring protons were shifted to higher field ($\delta = 7.54$ and 8.00). The pyrrolic NH resonance was also shifted to $\delta = 11.33$ and appeared as a broad singlet in the presence of chloride anions. These results provide support for the contention that chloride anions form a stronger hydrogen-binding interaction than fluoride anions with the inner aromatic proton. Such a conclusion is rationalized in terms of a better match of the size between the chloride ion and the binding site defined by the presence of the strap. The smaller fluoride anion sits snuggly within the cavity generated by the four pyrrolic NH protons and, accordingly, the bound fluoride anion must be further away from the aromatic proton than the chloride anion is. The slow equilibrium exchange seen in the strapped system is also noteworthy (this is not seen in the unstrapped calix[4]pyrroles) and provides a further indication that the use of a flexible strap bearing potential hydrogen bonding elements may allow for the generic design of optimized anion receptors.

Qualitative assessments of anion binding affinity were made by following the chemical shift changes or integrated intensity changes of the corresponding resonance signals as a function of anion concentration in the evolving ^{1}H NMR spectra. These binding studies clearly indicate that one fluoride (or one chloride) anion binds with one host molecule,[16] even though the two discrete binding sites (upper and lower part) may have different affinities towards anionic substrates. The ^{1}H NMR spectra indicate that the smaller fluoride anion binds more tightly with the pyrrolic NH proton and thus forms a loose hydrogen bond with the inner aromatic proton. On the other hand, the relatively large chloride anion interacts less well with the pyrrolic NH proton but forms a stronger hydrogen bond with the inner aromatic proton. No appreciable binding interaction is observed with bromide, iodide, sulfate, and phosphate anions. The 1:1 binding stoichiometry for both the fluoride and chloride anions was confirmed by Job plots. The encapsulated binding site in **1** should modulate the inherent affinity of calixpyrroles towards specific anions by differentiating them on the basis of their size. The cavity generated in the presence of the strap may not have enough room to accommodate larger anions.

Unfortunately, the association constants for host **1** with fluoride and chloride anions proved too large to determine accurately from the titration curves obtained by ^{1}H NMR spectroscopy.[10, 16, 17] Thus, we attempted to obtain accurate binding constant by using isothermal titration calorimetry (ITC). Here, DMSO was chosen as the solvent because of the limited solubility of the host compound in other solvents. It was also thought that the high dielectric constant of DMSO combined with the low concentrations of the guest and host required for these experiments would eliminate aggregation effects. The calorimetric traces in DMSO for fluoride anion did not show constant baseline and heat pulses. However, the calorimetric traces measured for chloride anions (Bu$_4$NCl) revealed progressive changes in the heat pulses, and a K_a value of $1.01 \times 10^5 (\pm 1.01 \times 10^4)$ M for the formation of the 1:1 complex $[(\mathbf{1})\mathrm{Cl}^-]$ was calculated.

Since accurate determination of the binding constant for a fluoride anion proved to be problematic by ITC, we performed a competition experiment by using ^{1}H NMR spectroscopy. Specifically, an equimolar amount of fluoride anions was added to a premixed [(**1**)Cl$^-$] complex (1:1 molar ratio) in [D$_6$]DMSO. The spectra obtained indicated the rapid replacement of the precomplexed chloride anion by a fluoride anion. Integration of the spectra at equilibrium gave a ratio of 6.3:1 for the two complexes ([(**1**)F$^-$]/[(**1**)Cl$^-$]). A binding constant of approximately $3.87 \times 10^6\,\mathrm{M}^{-1}$ for the formation of [(**1**)F$^-$] was calculated from the observed ratio and assuming that a negligible amount of free host **1** was present in the final equilibrium mixture.[9a] This assumption is reasonable because the measured association constant for the chloride anion is large and the competition experiment indicates that the affinity constant for a fluoride anion is even larger. In both cases the derived association constants in DMSO are larger than those reported for normal calix[4]pyrroles, as well as for various deep cavities or chromophore-functionalized calix[4]pyrroles measured in acetonitrile.[9b, 17, 18]

Given the above findings and cognizant of the dangers of comparing K_a values in different solvents, we elected to measure the binding constant of unstrapped calix[4]pyrrole with chloride anions in DMSO by using ITC. We obtained a value of $1.270 \times 10^3\,\mathrm{M}^{-1}$ for the binding of a chloride anion, a value that agrees well with that ($K_a = 1.025 \times 10^3\,\mathrm{M}^{-1}$) determined by NMR titration in [D$_6$]DMSO.[18a] The concordance between these old and new values, measured by different methods, lends credence to the argument that strapping the calixpyrrole increases its anion binding affinity significantly, at least for chloride anions where good values for comparison are available. Apparently, encapsulation of the binding domain and the introduction of straps with weak hydrogen-bonding donors acts to reduce the matrix–host interaction and enhance the host–guest interaction. Less well determined at the present time is whether the inherent selectivity of the calixpyrrole system is being modulated. Further studies of this issue using a range of other strapped calixpyrroles bearing various chromophores and different length of strap are in progress.

In conclusion, we have succeeded in synthesizing a strapped calix[4]pyrrole for the first time. The current results support the use of super-structured elements to generate calix[4]pyrrole systems with affinities and selectivities that are modified relative to normal calix[4]pyrroles. As such, the approach detailed here could provide a new and useful complement to other affinity modulations currently being pursued in the context of calixpyrrole chemistry.

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[13] X-ray data of a crystal with dimensions of $0.3 \times 0.3 \times 0.4$ mm were collected on a Nonius CAD4 mach 3 diffractometer equipped with graphite-monochromated $\mathrm{Mo}_{\mathrm{K}\alpha}$ radiation ($\lambda = 0.71373$ Å) at room temperature. The unit cell was determined to be monoclinic, $P2_{1/n}$ (No. 14), $a = 10.335(2)$, $b = 16.519(3)$, $c = 20.329(3)$ Å, $\beta = 95.297(14)$, $V = 3455.9(9)$ Å^3, $\rho_{\mathrm{calcd}} = 1.243\,\mathrm{g\,cm^{-3}}$ $Z = 4$, on the basis of 25 reflections. A total of 7467 reflections were measured, 6990 unique ($R_{\mathrm{int}} = 0.0646$). The structure was refined on F^2 to $R_w = 0.3248$, $R = 0.1013$ (3162 reflections with $F_o > 4\sigma F_o$), and GOF = 1.125 for 433 refined parameters. The data were collected by using the ω-2θ scan technique in the range $2.14 < \theta < 26.29°$. No absorption corrections were applied. The structure was solved by direct methods and refined by full-matrix least-squares calculation with SHELXL-97. Anisotropic thermal parameters were used for all non-hydrogen atoms.

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