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First Cryptand-Like Calixpyrrole: Synthesis, X-ray Structure, and Anion Binding Properties of a Bicyclic[3,3,3]nonapyrrole

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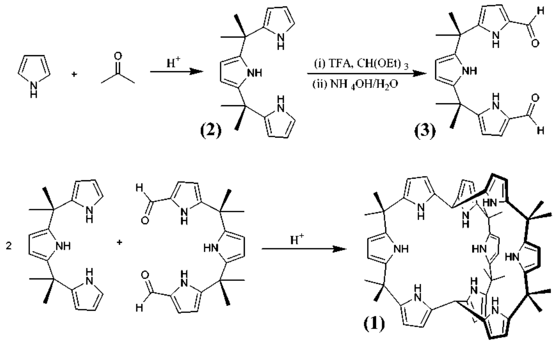
Calix[*n*]pyrroles, formally a macrocyclic succession of pyrrole subunits and sp^3-hybridized bridging carbon atoms, are known to be readily accessible hosts for fluoride and other anions both in solution and in the solid state.[1] This anion-binding ability, well documented in the case of the simple-to-make calix[4]pyrroles,[2] has spawned recent efforts to design and synthesize new homologues. By varying the number of pyrrole moieties, the nature of the meso-like or β-pyrrolic substituents, the binding selectivity and strength of calix[*n*]pyrroles may be tuned appreciably.[3] Still, recognizing what has proved true for cation recognition, namely that topographically nonplanar systems can display very distinctive stabilities and selectivities,[4] we have been keen for some time to synthesize and investigate the binding abilities of three-dimensional polypyrrolic receptors. Despite some rare examples of expanded porphyrins,[5] Schiff-base cryptands,[6] and tripod-like open chain derivatives,[7] three-dimensional pyrrole-containing systems remain virtually unknown.[8]

We report here the synthesis and solid-state structure of a calixpyrrole-like cryptand, the bicyclic[3,3,3]nonapyrrole **1**, and show that this system displays anion-binding behavior that differs substantially from that of simple calix[*n*]pyrroles.

The synthesis of **1** is summarized in Scheme 1. Briefly, Clezy formylation of the α-free tripyrrane **2**,[9] readily obtained from pyrrole and acetone, is used to prepare the tripyrrane dialdehyde **3** in 20% yield. Then, an acid-catalyzed condensation between this diformyl derivative **3** and 2 equiv of **2** is used to produce the three-dimensional bicyclic product **1**, in 15% yield.[10] To the best of our knowledge, **1** is the first cryptand-like calixpyrrole to be constructed uniquely from pyrrole subunits and bridging carbon atoms. Because of the bridge-head carbon atoms, compound **1** can exist, in principle, in the form of three configurational isomers. In the present instance, only one product was actually isolated, and its ^{1}H NMR spectral characteristics were consistent with its being a highly symmetric species. In particular, both meso-like hydrogen atoms appear as a singlet at 4.69 ppm, while three signals attributed to the β-pyrrolic protons are observed between 5.3 and 6 ppm (CD_2Cl_2). Interestingly, the NH protons that resonate at 7.49 and 7.67 ppm (CD_2Cl_2) as two broad signals in a 6:3 relative intensity, shift downfield to 9 and 9.2 ppm, respectively, when recorded in deuterated acetone. This observation is consistent with relatively strong solvent−pyrrole NH hydrogen-bonding interactions.[1]

Scheme 1



The structure of **1** was determined by X-ray diffraction analysis. As shown in Figure 1, the molecule adopts an *in*−*in* configuration wherein both meso-like bridging carbon atoms are pointing in toward the center of the molecule. The distance between these atoms (C15−C30) is 4.3 Å.

The fact that the two bridging CH hydrogen atoms point inward serves to close up the inner core. On the other hand, the resulting configurational, and it is assumed conformational rigidity, coupled with the overall three-dimensional structure serves to define three identical cavities with three calixpyrrole-like NH motifs that could serve as potential binding sites. In the solid state, three different solvent species are observed in these cavities (Figure 2). Two water molecules, bound to each other, are located in one of these sites, whereas a dichloromethane interacts with the pyrrole moieties of a second cavity through three N−H···Cl hydrogen bonds and two C−H···π interactions.[12] The third cavity, not shown in Figure 2, contains only one water molecule hydrogen bonded to two pyrrole NHs (N(3)H and N(1)H).

While studies of the anion binding behavior of **1** are still in progress, in preliminary work this receptor has been found to bind a wide range of anions (as their tetrabutylammonium salts) in dichloromethane-d_2 in the absence of air, including fluoride, chloride, bromide, nitrate, dihydrogen phosphate, and thiocyanate, as judged from shifts seen in the ^{1}H NMR spectrum of **1**.

The existence of three identical binding cavities, as observed in the solid state, led us to consider that receptor **1** might stabilize anion complexes of 1:1, 1:2, and 1:3 stoichiometry in solution. This, and the multiplicity of the possible equilibria has impeded

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(4) Lehn, J.-M. *Supramolecular Chemistry, Concepts and Perspectives*; VCH: New York, 1995.

(5) Sessler, J. L.; Král, V.; Hoehner, M.; Chin, K. O.; Dávila, R. M. *Pure Appl. Chem.* **1996**, 1291; Sessler, J. L.; Dávila, R. M.; Král, V. *Tetrahedron Lett.* **1996**, *37*, 6469; Andrievsky, A., Ahuis, F.; Sessler, J. L.; Vögtle, F.; Gudat, D.; Moini, M. *J. Am. Chem. Soc.* **1998**, *120*, 9712.

(6) Lu, Q.; McKee, V.; Nelson, J. *Chem. Commun.* **1994**, 649.

(7) Sessler, J. L.; Hoehner, M.; Johnson, D. W.; Gebauer, A.; Lynch, V. *Chem. Commun.* **1996**, 2311 and references therein.

(8) This stands in marked contrast to what is true for other heterocyclic systems. See, for example: Seel, C.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 528 and references therein.

(9) Bucher, C.; Zimmerman, R. S.; Lynch, V.; Král, V.; Sessler, J. L. *J. Am. Chem. Soc.* **2001**, 123, 2099.

(10) Compound **1** was found to be moderately unstable when exposed to acid, air, and light. Current efforts are devoted to ascertaining the nature of the decomposition products.

(11) Crystal Data for **1**. $C_{56}H_{65}N_9 - CH_2Cl_2 - 3H_2O$, monoclinic, space group $P2_1/n$ (No. 14), $a = 12.0515(6)$ Å, $b = 22.1214(13)$ Å, $c = 20.1491(9)$ Å, $\beta = 94.062(3)°$, $V = 5358.2(5)$ Å^3, $Z = 4$, $D_c = 1.24$ g/cm^3, $\mu = 0.174$ mm^{-1}. The structures were refined on F^2 to a wR2 = 0.206 with an R1 [for 4253 reflections with $F_o > 4(\sigma(F_o))$] = 0.119 and a goodness of fit = 1.21. Full X-ray experimental details are located in the Supporting Information.

(12) These types of weak hydrogen-bonding interactions are often observed in structures containing more hydrogen bond donors than acceptors. See Desiraju, G. R.; Stiener, T. *The Weak Hydrogen Bond in Structural Chemistry and Biology*; Oxford University Press: Oxford, 1999. In the present instance, the distances between the calculated positions of the dichloromethane hydrogen atoms and the center of the pyrrolic aromatic systems, $d(C-H\cdots\pi_c)$ are 2.42 and 2.35 Å.

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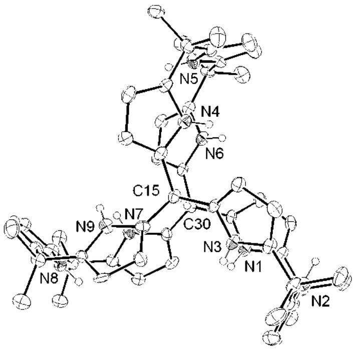

Figure 1. Ortep views of **1** showing the heteroatom-labeling scheme. Bound solvent molecules have been omited for clarity.[11]

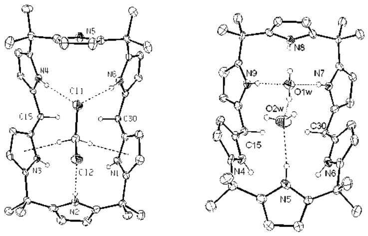

Figure 2. Partial Ortep views of two cavities present in **1,** showing bound neutral species. All protons are shown in calculated positions. Hydrogen bonding interactions are indicated by dashed lines.

quantitative analyses. Additionally, depending on the anion, receptor **1** was found to bind either via a slow or fast equilibrium-binding process.[13] Still, with nitrate as the guest, a fast equilibrium-binding process corresponding to the formation of a 1:2 cryptand nitrate complex was observed, with the two relevant binding constants K_1 and K_2 being 1740 and 420 M^{-1}, respectively. Attempts to form a trianionic species, corresponding to [**1**•3A^-], by adding a large excess of tetrabutylamonium nitrate proved unsuccessful. Instead, complex spectroscopic features were observed that are thought to reflect the binding of multiple anions to a single calixpyrrole-like face or the formation of complexes where more than one stoichiometric equivalent of **1** is bound to a single nitrate anion.

Evidence for a different kind of binding mode was seen when **1** was treated with fluoride anion. In this instance, the signals located at 7.49 and 7.67 ppm in the ^{1}H NMR spectrum of pure **1** (CD_2Cl_2), accounting for six and three NH protons, respectively, were seen to disappear after the addition of 0.3 equiv of tetrabutylammonium fluoride, giving rise, after the addition of three full anion equivalents, to four different signals at 6.78, 7.97, 10.56, and 11.99 ppm in a 1:2:2:4 relative intensity, respectively. Among these new NH signals, only those located at lower field were attributed to pyrrolic protons directly involved in the anion-binding process. The downfield nature of these shifts along with the integration values are consistent with the formation of a 1:1 complex such as that illustrated in Figure 3. In this complex, two of the three cryptand arms combine to form a single large pocket that allows six calixpyrrole-like N−H groups to be hydrogen-bonded to the anionic species.

The assumption that six of the NH protons interact with the fluoride anion was further supported by low temperature (−10 °C) ^{1}H NMR experiments, which revealed $^{19}F-^1H$ splitting (J = 32 and 11 Hz) only for these signals. No splitting was observed for the other three NH protons. Unfortunately, even at this low temperature, no peaks from both **1** and [**1**•F^-] were observed concurrently. As a result, no reliable affinity constants for F^- binding could be deduced.[14]

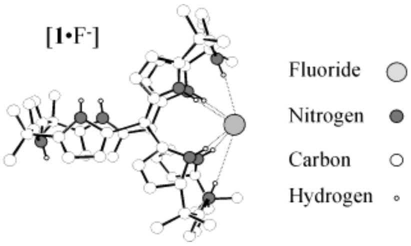

Figure 3. Simulated representation of [**1**•F^-].

A somewhat similar binding behavior was observed upon addition of tetrabutylammonium chloride to an anaerobic solution of **1** in deuterated dichloromethane. In this case, the two initial peaks located at 7.49 and 7.67 ppm attributed to the NH protons decrease in intensity as Cl^- is added. Concurrently, four new NH peaks are seen to grow in at 6.86, 7.84, 10.51, and 10.94 ppm. The apex CH signal at 4.69 ppm is also seen to decrease in intensity, while a new peak, ascribed to the same proton, begins to appear at 5.20 ppm. Although this spectral evolution compares roughly to what is observed in the course of the corresponding fluoride titration, the fact that saturation is observed upon the addition of only 0.7 mol equiv in dichloromethane-d_2 and tetrahydrofuran-d_8[15] leads us to propose that, in these solvents, two cryptand-like hosts are binding one guest. Specifically, it is suggested that the chloride anion is encapsulated between two cryptand-like molecules, adopting the same binding pattern as is observed for [**1**•F^-], with the exception that the bound species is now hydrogen-bonded to 12 calixpyrrole-like NH protons. An internal standard, bicyclo[2.2.1]hepta-2,5-diene, was used to ensure a direct correlation between the integration and the concentration of **1** and that of the presumed 2:1 receptor−anion species.[16] Calculations revealed a binding constant for the formation of [**1**•Cl^-•**1**] of 3.08×10^6 M^{-2}.

The present results provide further support for the proposal that pyrrole NH subunits can act as an "umpolung ether group" complementing the known cation-recognition function of ethers and polyethers by acting as a viable anion-binding motif. The use of three-dimensional systems, such as reported here, adds an increasing level of complexity to the anion-recognition process but could lead to receptors with greater affinity, specificity, and fine-tuned binding stoichiometries.

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Supporting Information Available: Crystallographic data, synthetic experimental for **1** and **3,** binding data for **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Relative to the ^{1}H NMR time scale.

(14) Unpublished experimental data available to a reviewer leads him or her to suggest that dodecamethylcalix[6]pyrrole displays similar binding behavior. For previous calix[6]pyrrole binding studies, see: Turner, B.; Sheterenberg, A.; Kapon, M.; Suwinska, K.; Eichen, Y. *Chem. Commun.* **2001**, 13.

(15) In acetone-d_6, however, saturation does not occur until such time as ≥1.1 mol equiv are added.

(16) T_1 values were calculated to determine the relaxation delay necessary to achieve an accurate integration.