Calix[4]pyrroles Containing Deep Cavities and Fixed Walls. Synthesis, Structural Studies, and Anion Binding Properties of the Isomeric Products Derived from the Condensation of *p*-Hydroxyacetophenone and Pyrrole

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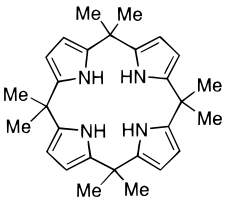
The inclusion chemistry of receptors with extended cavities has attracted the attention of an increasing number of research groups.[1] Extension of the cavity of a preexisting receptor molecule may confer new binding properties on the molecule and/or modulate the existing affinity of the receptor for guest species. Our recent discovery that calix[4]pyrroles (e.g., **1**), a class of tetrapyrrolic macrocycle known for over a century,[2] are effective and selective receptors for anions[3] and, to a lesser extent, neutral guest species[4] led us to produce a number of calixpyrroles that have found application in anion sensing[5] and separation[6] technologies. Additionally, we have found that it is possible to tune the anion binding affinity of these receptors by substitution at either the β-positions of the pyrrole rings or the *meso*-carbons of the calixpyrrole[3,7] or by fusing a calixarene scaffold onto the basic calixpyrrole framework.[8] Separately, Eichen and co-workers have succeeded in preparing calix[4]pyrroles with flat, extended aryl "wings" as well as "expanded" calix[6]pyrroles.[9] In this Communication, we report the first examples of a new class of calix[4]pyrroles containing deep cavities and fixed walls. These systems, represented by prototypical systems **2** and **3**, are easily obtained from the condensation of *p*-hydroxyacetophenone with pyrrole.[10,11] Surprisingly and unexpectedly, these systems show lower affinities for small anions, specifically Cl^- and $H_2PO_4^-$, in acetonitrile−water (99.5:0.5) than do simple unsubstituted calix[4]pyrroles such as **1**. On the other hand, increased selectivities and other binding effects ascribable to the "walls" of the cavities are observed.



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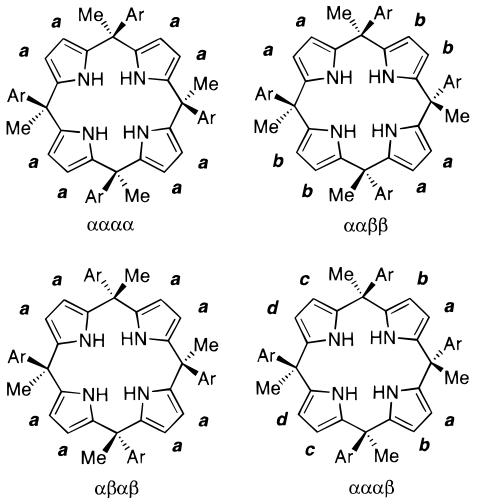

2 Ar = 4-hydroxyphenyl, **3** Ar = 4-methoxyphenyl.

Figure 1. Structures of calix[4]pyrroles (**2**, Ar = 4-hydroxyphenyl; **3**, Ar = 4-methoxyphenyl). Inequivalent CH positions are labeled with different letters (thus in αααα all the CH protons are equivalent while in αααβ there are four inequivalent sets of protons, a, b, c, and d).

Calixpyrrole **2** was prepared using a modification of standard literature methods.[12] Briefly, *p*-hydroxyacetophenone (13.62 g, 100 mmol), pyrrole (6.71 g, 100 mmol), and methanesulfonic acid (4.81 g, 50 mmol) were dissolved in methanol (300 mL) and stirred at room temperature for 6 h under an inert atmosphere. After this mixture was neutralized with ammonia gas and passed through a short silica gel precolumn, the desired calix[4]pyrrole was isolated, as a mixture of four configurational isomers, via column chromatography (silica gel, 6−8% methanol in chloroform v/v) in 62% yield. The relative yields of these latter isomers, denoted $\alpha\beta\alpha\beta$, $\alpha\alpha\beta\beta$, $\alpha\alpha\alpha\beta$, and αααα to indicate the relative position of the bulky substituted phenyl substituent (cf. Figure 1), were on the order of <5%, 25%, 30%, and 45%, respectively. They were readily separated from one another during the chromatographic purification and, as would be expected on the basis of considerations of relative polarity, found to elute in the same order as the atropoisomers of 2,2′,2″,2‴-substituted tetraphenylporphyrins, namely (in order of decreasing R_f) $\alpha\beta\alpha\beta$ > $\alpha\alpha\beta\beta$ > $\alpha\alpha\alpha\beta$ > αααα.[13] Once isolated, the individual isomers of **2** were converted to their respective 4-methoxyphenyl con-

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(10) The first examples of unsymmetrical, as opposed to the present deep-cavity, calixpyrroles were produced by the Russian chemists Chelintzev and Tronov. Among other accomplishments, they isolated a pure sample of a single configurational isomer of *meso*-tetramethyltetraethylcalix[4]pyrrole: (a) Chelintzev, V. V.; Tronov, B. V. *J. Russ. Phys. Chem. Soc.* **1916**, *48*, 105−155. (b) Chelintzev, V. V.; Tronov, B. V. *J. Russ. Phys. Chem. Soc.* **1916**, *48*, 1197−1209.

(11) Early studies of unsymmetrical *meso*-aryl-substituted calix[4]pyrroles were presented in the following: Sessler, J. L.; Anzenbacher, P., Jr.; Jursíková, K.; Miyaji, H.; Genge, J. W.; Tvermoes, N. A.; Allen, W. E.; Shriver, J. A.; Gale, P. A.; Král, V. *Pure Appl. Chem.* **1998**, *70*, 2401−2408.

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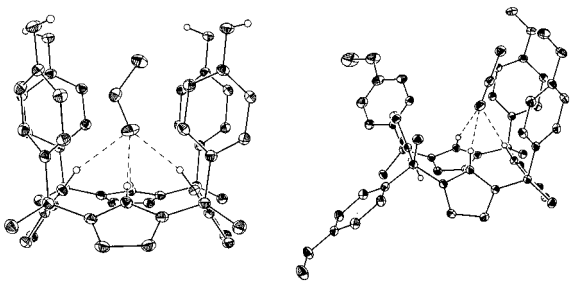

Figure 2. View of the molecular structures of the ethanol adduct of the αααα isomer of **2** in the cone conformation (left) and the acetonitrile adduct of the ααα*β* isomer of **3** in the partial cone conformation (right). Thermal elipsoids are scaled to the 30% probability level. Dashed lines are indicative of a hydrogen-bonding interaction. The encapsulated ethanol in **2** is disordered about two positions.

geners **3** by reaction with iodomethane in acetonitrile in the presence of potassium carbonate.

While the α*β*α*β* isomer was not obtained in sufficient quantities to allow its detailed study, the configurations of the αα*ββ*, ααα*β*, and αααα isomers were confirmed unambiguously by X-ray crystallographic analysis (cf. Figure 2 and Supporting Information). In the specific case of the αααα isomer of **2**, a deep cavity structure was observed in the solid state, wherein the calixpyrrole core is in a so-called cone conformation (Figure 2).[14] Structures of lower symmetry are seen in the case of the other isomers, with conformations other than pure cone (e.g., 1,3-alternate, partial cone) being observed in certain instances (e.g., the ααα*β* isomer of **3**; Figure 2).

Proton NMR spectroscopy was used to confirm the configurational assignments and to analyze conformational effects in solution. As a general rule, it was found that free rotation around the pyrrole-bridging *meso*-like carbons and *ipso*-aryl bonds pertains at room temperature in acetonitrile-d_3−D_2O 99.5:0.5 (v/v) in the absence of an added anionic substrate. Thus, the symmetries of the various isomers were reflected directly in their ^{1}H NMR spectra, particularly in the number of pyrrole CH resonances. The αααα isomers of **2** and **3** have one type of CH group, represented by an "a" in Figure 1, while the αα*ββ* isomer has two types of pyrrolic CH group (represented by "a" and "b"), and the ααα*β* isomer possesses four different CH groups ("a", "b", "c', and "d"), and in all cases the requisite number of signals were observed.

Proton NMR spectroscopy was also used to probe the effect of anion binding in solution. Here, it was found that under conditions of strong binding, such as proved true for fluoride, phosphate, and chloride anions interacting with the αααα isomers of **2** and **3** and fluoride anion interacting with the αα*ββ* isomer of **2**, addition of the substrate served to lock the system into the expected[3] cone conformation. In the case of the ααα*β* isomer of **2** and the αα*ββ* isomer of **3**, high concentrations of fluoride anion served to lock the system into two separate, well-defined conformations that, on the basis of symmetry considerations, were assigned as being the two conformationally accessible conelike forms and the cone and partial cone conformations, respectively. In other systems, where weaker anion binding occurred, the addition of anions did not serve to lock the fluxional calixpyrrole core into a single conformation.

Quantitative assessments of anion binding affinity were made by following the induced changes in the ^{1}H NMR spectra as a function of anion concentration.[15,16] From these analyses (Table 1) it becomes clear that, despite what might be inferred from the open cavities seen in the solid-state X-ray diffraction structures, the affinities of **2** and **3** for chloride and dihydrogenphosphate anions are actually *lower* than those of **1**. This, presumably, is due to a combination of electronic effects and steric interactions between the *meso*-aryl groups and the anion. Nonetheless, it is important to appreciate that variations in the structure of receptors **2** and **3** do serve to modulate the anion binding affinities. For example, the αααα isomer of **3** has the highest affinity for anions among the three isomers of **3**, a finding that, presumably, reflects the fact that this system is able to adopt easily a cone conformation. On a separate level, it is observed that the anion binding affinities of **2** are greater across the board than those of **3**. We interpret this result in terms of the hydroxy groups present in **2** being able to serve as secondary hydrogen-bonding recognition elements that further stabilize the calixpyrrole−anion complex.[17] In the case of the αααα isomer of **2**, this effect reverses the intrinsic fluoride > chloride > phosphate selectivity that has previously been observed for calixpyrroles.[3]

Table 1. Stability Constants for Compounds **1**−**3** (M^{-1}) with Anionic Substrates[a] in Acetonitrile-d_3 (0.5% v/v D_2O) at 22 °C

		2			3		
	1	αα*ββ*	ααα*β*	αααα	αα*ββ*	ααα*β*	αααα
fluoride	>10 000	>10 000	5 000[c]	>10 000[b]	4 600	1 100[c]	>10 000
chloride	>5 000	1400[d]	260	320	<100	220	300
phosphate	1 300	520[d]	230	500	<100	<80	<100

[a] Acetonitrile-d_3 (0.5% v/v D_2O) solutions of receptors **2** and **3** (4.5 and 4.6 mM, respectively) were titrated by adding concentrated acetonitrile-d_3 (0.5% v/v D_2O) solutions of the anions in question (in the form of their tetrabutylammonium salts) that, to account for dilution effects, also contained receptors **2** and **3** at their initial concentrations. The data were fit according to the method of Wilcox[16] using changes in both the NH and *β*-C*H* pyrrolic resonances unless otherwise indicated. Estimated errors were <15%. Binding stoichiometries, determined by Job plots, were 1:1 unless otherwise noted. [b] At high [F^-]/[calixpyrrole] ratios, a second binding process, involving presumably interactions between the fluoride and the phenolic OH residues, is observed. [c] Fit by following the change of two different *β*-pyrrole C*H* resonances. [d] Fit by following the change of *meso*-aryl C*H* and *β*-pyrrole C*H* resonances.

The present results lead us to suggest that there could be a rich molecular recognition chemistry associated with calixpyrroles containing built-in cavities and rigid walls. Not only does the introduction of *meso*-aryl groups allow the intrinsic anion selectivity of the calixpyrrole skeleton to be altered, but also the ease of synthesis and facile functionalization of systems such as **2** opens up the possibility of producing calixpyrroles with an endless variety of secondary binding sites that may allow for the optimized recognition of cationic, anionic, and neutral guests.

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Supporting Information Available: Binding profiles for NMR titrations, spectral data for new compounds, X-ray experimental details, atomic positional parameters, bond distances, angles and atomic thermal parameters for the αααα isomer of **2** (ethanol adduct), the exocyclic fluoride complex of the αααα isomer of **2** (acetonitrile adduct), the αα*ββ* isomer of **2** (methanol adduct), and the ααα*β* isomer of **3** (acetonitrile adduct) (PDF). X-ray crystallographic data, in CIF format, is also available. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Crystallographic summary: monoclinic, $P2_1/c$, $Z = 4$ in a cell of dimensions $a = 10.8820(5)$, $b = 20.2050(6)$, and $c = 19.7400(6)$ Å, $\beta = 105.134(2)°$, $V = 4189.7(3)$ Å^3, $\rho_{calc} = 1.28$ g cm^{-3}, $F(000) = 1712$. The structure was refined on F^2 to an $R_w = 0.111$, with a conventional $R = 0.0582$ (6309 reflections with $F_o > 4[\sigma(F_o)]$), and a goodness of fit = 1.08 for 641 refined parameters.

(15) In many cases, the NH proton resonance broadened considerably upon addition of anions. In these instances, the anion induced resonance shifts of the pyrrolic *β*-protons were used to calculate stability constants.

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(17) Evidence for this kind of ancillary interaction is seen in the case of the αααα isomer of **2** in that a second discrete binding process is identified in the NMR titrations at very high F^-/**2** ratios. For this same system, fluoride−hydroxyl interactions have also been observed in the solid state; cf. Supporting Information.