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Direct Synthesis of Expanded Fluorinated Calix[*n*]pyrroles: Decafluorocalix[5]pyrrole and Hexadecafluorocalix[8]pyrrole

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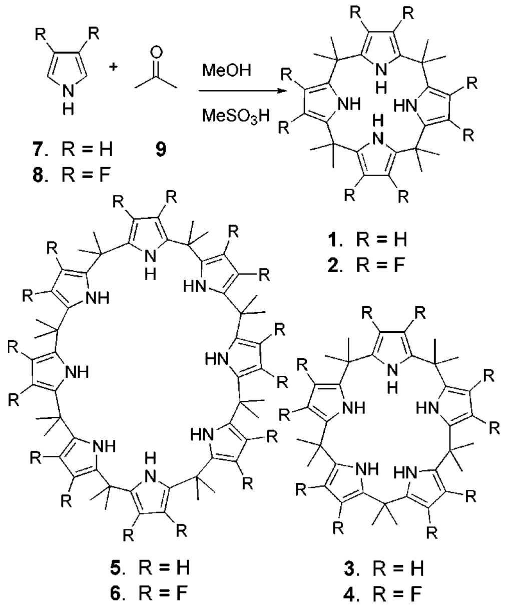
First synthesized by Baeyer in 1886,[1] calix[4]pyrroles (e.g., **1**) have recently attracted attention as simple-to-make receptors for anionic and neutral substrates.[2−8] To date, they have been used to prepare both optical anion sensors[3] and anion selective HPLC supports.[4] They also show promise as anion carriers for use in medicinal applications.[5] By contrast, the chemistry of so-called higher order calix[*n*]pyrroles ($n > 4$) has remained virtually unexplored.[6−8] In early work, we succeeded in preparing a covalently linked calix[5]pyrrole−calix[5]arene pseudodimer using the calixarene fragment as a synthetic scaffold.[6] Unfortunately, as the result of the specific templating strategy employed, cleavage to the free calix[5]pyrrole could not be effected. More recently, calix[6]pyrroles have been obtained in pure form as the result of elegant syntheses involving the use of either sterically encumbered dipyrrane[7] or calix[6]furan[8] intermediates. Syntheses of higher order mixed calix[*n*]furan[*m*]pyrrole species ($n = 3, 4, 6, 8$; $m = 2, 4$) from polyheterocyclic intermediates have also been reported.[9] However, to date it has not proved possible to prepare either these latter products or, indeed, any kind of higher order calix[*n*]pyrrole (e.g., **3**, **5**) using the direct acid-catalyzed ketone + pyrrole (furan) condensation methods first introduced by Baeyer over 100 years ago.[1,10] Here, we report the synthesis of β-decafluoro-*meso*-octamethylcalix[5]pyrrole **4** and β-hexadecafluoro-*meso*-octamethylcalix[8]pyrrole **6**;[11] under carefully optimized conditions, these products are obtained in fair to decent yield from the 1-step condensation procedure used to prepare octafluorocalix[4]pyrrole **2** from 3,4-difluoro-1*H*-pyrrole **8** and acetone **9**.[12]

Scheme 1. Synthetic Procedure



The standard conditions[1,2,10] used to produce calix[4]pyrroles involve condensing pyrrole **7** with acetone (or another ketone) in methanol in the presence of a Lewis or Brønsted acid. In general, the reaction is relatively fast, with the calix[4]pyrrole product (e.g., **1**) precipitating out within a matter of hours. While this solid material is as a rule quite pure, in a number of instances mass spectrometric analysis of the remaining supernatant revealed peaks that could be ascribed to higher order species (e.g., **3** and **5**).[13] However, all efforts to isolate these putative products via standard methods proved unsuccessful; apparently, a fast equilibrium in favor of the calix[4]pyrrole product (e.g., **1**) is set up under even the most mild of conditions, including those associated with chromatography over silica gel.

By contrast, to the above, we have recently found that the preparation of **2** from 3,4-difluoro-1*H*-pyrrole **8** requires substantially longer reaction times ($\geq$1 week at room temperature).[12] This led us to consider that any higher order calix[*n*]pyrrole products, were they present in the reaction mixture, would likely be stable under the conditions of acid catalysis and hence readily isolable.[14] This indeed proved to be the case. Specifically, we have found that the methane-sulfonic acid-catalyzed condensation between difluoropyrrole **8** and acetone (methanol, ambient temperature) gives, in addition to octafluorocalix[4]pyrrole **2**, the dominant reaction product, appreciable quantities of both the corresponding calix[5] and calix[8] products **4** and **6** (Scheme 1); in contrast to what is true for congeners **3** and **5**, compounds **4** and **6** proved kinetically stable under the reaction conditions

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(14) The specific reasoning here was that any kinetic barrier hindering calix[*n*]pyrrole formation would also impede its subsequent rearrangement into other ($m \neq n$) calix[*m*]pyrrole species.

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Table 1. Study of the Effect of Reaction Parameters on the Formation of Fluorinated Calix[*n*]pyrroles **2**, **4**, and **6**[a]

temp, °C	time,[b] h	[**9**], mM	[**8**], mM	yield of **4**, %	yield of **6**, %
25	193	50	50	21.0	4.3
25	73	75	50	31.5	8.8
25[c]	388	100	50	23.2	0
25	40	200	200	27.2	16.0
64	23	50	50	0	0

[a] All reaction runs were monitored by HPLC with the absolute yields (based on **8)** and relative product concentrations being determined via standardization with 1,3-dibromobenzene. Methanesulfonic acid was used as the catalyst in all cases and the reactions were run in methanol. [b] The optimum time was arbitrarily chosen as that when the concentration of **2** was at a maximum. [c] Appreciable peaks corresponding to starting material and open chain oligomer products were noted under these reaction conditions.

and could be purified by column chromatography (silica gel, hexanes−acetone 4:1 v/v eluent).

As revealed by the data collected in Table 1, the yields of **4** and **6** are not high when reaction conditions optimized for the formation of **2** are employed. However, increasing the relative and absolute concentration of acetone was found to increase the yield of **4** (up to 31% HPLC; 23% isolated), whereas increasing the concentration of both starting materials was found to increase the yield of **6** (up to 16%, HPLC; 14% isolated). On the other hand, carrying out the reaction at higher temperatures was found to give exclusively the calix[4] product, **2**.

This latter finding is consistent with compounds **4** and **6** being kinetically stable at ambient temperature but not at higher ones. In accord with this supposition was the finding that purified samples of both **4** and **6** remained completely intact for ≥24 h when subject to conditions of acid catalysis identical to those used to effect their preparation. This, however, was not the case at higher temperature (64 °C); here, nearly complete conversion to **2** was observed within 24 h.

Compounds **4** and **6** displayed spectroscopic properties in accord with their proposed structures (see Supporting Information). They were further characterized by X-ray diffraction analysis. The resulting structures, shown as Figures 1 and 2, respectively, reveal the presence of bound solvent as well as obvious distortions from planarity. In both cases the calix[*n*]pyrrole cores exist in what are perhaps best described as distorted alternate conformations. As a consequence, many but not all of the pyrrolic NH moieties in **4** and **6** point into what appears to be a large hydrogen bond donor rich substrate binding cavity.

Studies of the substrate binding properties of **4** and **6** are currently in progress. In preliminary work it has been found that, under conditions identical to those used to study **2** (viz., deuterated acetonitrile containing 0.5% v/v D_2O), the decafluorocalix[5]pyrrole **4** displays an affinity for chloride anion ($K_a = 41000 \pm 6000$ M^{-1}) that is increased by a factor of ca. 4 relative to the corresponding octafluorocalix[4]pyrrole **2**. It also displays an affinity for DMSO that is slightly enhanced ($K_a = 29 \pm 3$ M^{-1} vs 20 ± 2 M^{-1} for **2**). Such findings, which are in accord with those of Kohnke for *meso*-dodecamethylcalix[6]pyrrole,[8] lead us to suggest that higher order calix[*n*]pyrroles, including the ones described here, will have an important role to play as receptors for a range of anionic and neutral substrates.

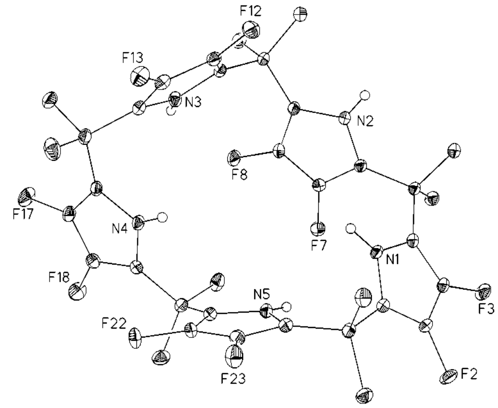

Figure 1. View of **4** showing the heteroatom labeling scheme. Thermal ellipsoids are scaled to the 30% probability level. Hydrogen atoms shown are drawn to an arbitrary scale.

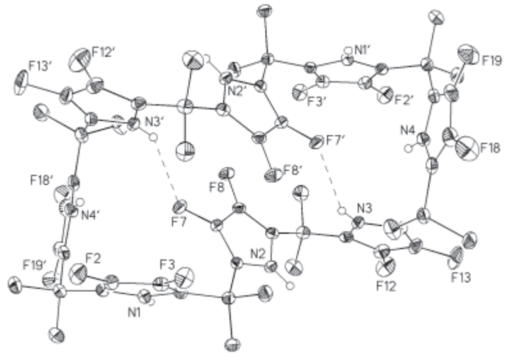

Figure 2. View of **6** showing the heteroatom labeling scheme. Thermal ellipsoids are scaled to the 30% probability level. Hydrogen atoms shown are drawn to an arbitrary scale. There are two N−H···F intramolecular interactions as indicated by dashed lines. There are also four molecules of acetone H-bound to the macrocycle as well as an inversion center (see Supporting Information).

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Supporting Information Available: Crystallographic data for β-decafluoro-*meso*-octamethylcalix[5]pyrrole **4** and β-hexadecafluoro-*meso*-octamethylcalix[8]pyrrole **6**, synthetic experimental data for **4** and **6**, binding data for **4**, and output results from HPLC studies (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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