Anion Binding Studies of Fluorinated Expanded Calixpyrroles

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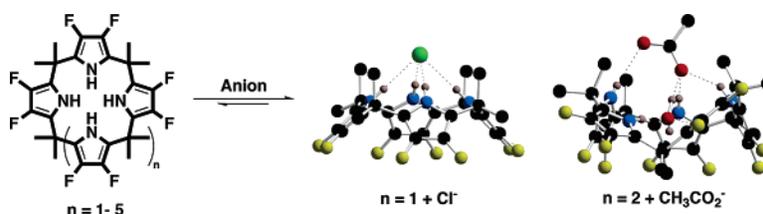
The anion binding properties of fluorinated calix[*n*]pyrroles (*n* = 4−6) in aprotic solvents (acetonitrile and DMSO) and modified reaction conditions allowing for the synthesis and isolation of the hitherto missing dodecafluorocalix[6]pyrrole from the condensation of 3,4-difluoro-1*H*-pyrrole and acetone are described. In acetonitrile solution containing 2% water, the association constants for the 1:1 binding interaction between octafluorocalix[4]pyrrole and chloride anion obtained with isothermal titration calorimetry (ITC) and ^{1}H NMR titration methods were found to match reasonably well. As compared to its nonfluorinated congener, octafluorocalix[4]pyrrole was found to display enhanced binding affinities for several representative anions in pure acetonitrile as judged from ITC analyses. Similar analyses of the fluorinated calix[*n*]pyrroles revealed an increase in the relative affinity for bromide over chloride with increasing macrocycle size, as manifest in a decrease in the binding ratio $K_{a(Cl)}/K_{a(Br)}$. Anion binding studies in the solid state, involving single-crystal X-ray diffraction analyses of the chloride and acetate anion complexes of octafluorocalix[4]pyrrole and decafluorocalix-[5]pyrrole, respectively, confirmed the expected hydrogen bond interactions between the pyrrolic NH protons and the bound anions.

Introduction

Over the last several decades, considerable effort has been devoted to developing efficient artificial receptors capable of forming complexes with selectively targeted guests. Within the context of this work, many groups are focusing on the synthesis of rationally designed anion binding agents. Inspired in part by the ubiquity of anions in biology, as well as various practical applications such systems might permit, considerable effort has been devoted to the preparation of receptors displaying high binding affinities and selectivities.[1] Here, much of the emphasis has been on neutral hosts. This is because neutral receptor systems often show better selectivities than charged receptors as the result of (as a general rule)

possessing more precisely oriented (i.e., directional) hydrogen bond donor groups. One of the more attractive neutral anion receptors is octamethylcalix[4]pyrrole (**1**). First synthesized by Bayer in 1886, this system has been found to bind fluoride, chloride, and phosphate anions in organic solvents, albeit with relatively low affinities.[2,3] Efforts to enhance the anion binding affinities, as well as to modulate the selectivities of calix[4]pyrrole, have spawned various structural modifications and have led to the synthesis of inter alia strapped calix[4]pyrroles,[4,5]

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deep cavity calix[4]pyrroles,[6,7] and calixpyrroles containing nonpyrrolic building blocks.[8,9] Another attractive approach involves the use of so-called higher order systems, calix[4]pyrrole analogues that contain a larger central core. In early work along these latter lines, a calix[5]pyrrole motif was prepared as a calix[5]pyrrole–calix[5]arene pseudodimer with a templated approach.[10] Separately, Eichen and co-workers synthesized a phenyl-substituted calix[6]pyrrole; this first free-standing higher order system showed an enhanced affinity for larger anions such as I$^-$ and BF$_4^-$.[11] Shortly thereafter, Kohnke and co-workers reported the synthesis of calix[n]pyrroles (n = 5, 6) prepared from the corresponding calix[n]furan analogues.[12]

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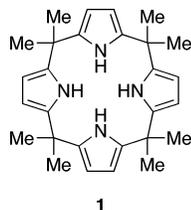
More recently, our group found that higher order fluorinated calix[n]pyrroles (n = 4, 5, and 8) could be prepared via the acid-catalyzed condensation of 3,4-difluoropyrrole and acetone at room temperature.[13,14] While a preliminary report detailing some aspects of their

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SCHEME 1. Synthesis of Fluorinated Calix[n]pyrroles (n = 4−8)^a

3 n = 1 (30%)
4 n = 2 (30%)
5 n = 3 (20%)
6 n = 4 (trace)
7 n = 5 (15%)
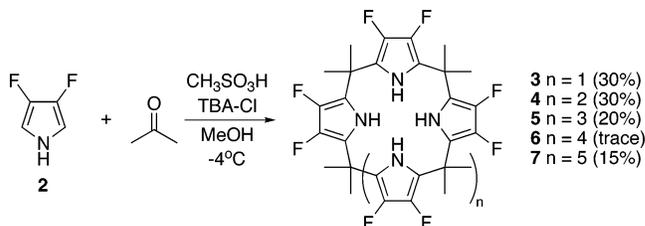
^{a} The numbers in parentheses are isolated yields.

extraction properties has appeared,[15] as yet, their anion binding behavior has yet to be fully described. In this paper we report a detailed anion binding study of the fluorinated calix[n]pyrrole family (n = 4, 5, and 6), including octamethylcalix[4]pyrrole (**1**) as a control system, using isothermal titration calorimetry (ITC). We also report the synthesis and isolation of the hitherto "missing" dodecafluorocalix[6]pyrrole (**5**), as well as reaction conditions that permit the formation, albeit not isolation, of tetradecafluorocalix[7]pyrrole (**6**) (cf. Scheme 1 for structures).

Results and Discussion

Synthesis. In our initial communication detailing the synthesis of decafluorocalix[5]pyrrole (**4**) and hexa-decafluorocalix[8]pyrrole (**7**), the conditions reported (reaction of acetone with 3,4-difluoropyrrole **2** at room temperature in the presence of H$^+$) were optimized to favor the formation of these two higher order species. While **4** and **7** were obtained in yields of 23% and 14%, respectively (up to 31% and 16% yield, as calculated by HPLC), along with **3** in 52% yield, we were unable to isolate the corresponding fluorinated calix[6]pyrrole (**5**) or calix[7]pyrrole (**6**). However, peaks ascribed to these species were observed in the mass spectra of the crude reaction mixture. After publication, a detailed inspection of the HPLC data revealed the presence of two peaks corresponding to compounds with greater polarity than **7** that appeared to grow in during the early stages of the reaction but which subsequently disappeared. Follow-up mass spectrometric analysis led us to attribute these two unresolved peaks to the two "missing" fluorinated calix-pyrroles, **5** and **6**. Parallel analyses confirmed that both **5** and **6** are thermodynamically unstable under the room-temperature reaction conditions used to obtain calixpyr-roles, **3**, **4**, and **7**. In light of this inherent instability, we chose to carry out our synthesis of fluorinated calix[n]-pyrroles at lower temperatures in the hope that decomposition of **5** and **6** could be slowed if not halted. As detailed below, this has allowed for the isolation of fluorinated calix[6]pyrrole (**5**) but not its higher order congener **6**.

After optimization, it was found that a mixture of fluorinated calixpyrroles (**3**−**7**) favoring the higher order species (**4**, **5**, and **7**) could be obtained by condensing 3,4-difluoro-1H-pyrrole (**2**)[16] with acetone at −4 °C in the presence of methanesulfonic acid and tetrabutylammo-

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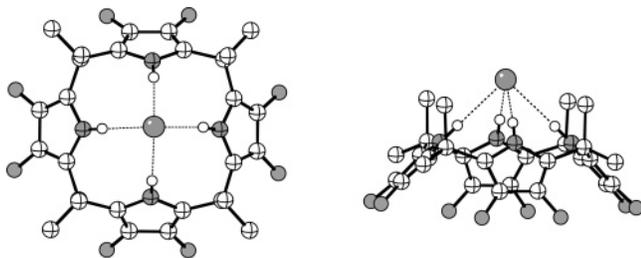
FIGURE 1. Two different views of the single-crystal structure of the 1:1 complex formed between octafluorocalix[4]pyrrole (**3**) and chloride anion. The countercation, tetrabutylammonium (TBA⁺), is not involved in the binding interactions and is not shown.

FIGURE 2. Two different views of the X-ray crystal structure of the complex formed between decafluorocalix[5]pyrrole (**4**), acetate anion, and a water molecule. The countercation, TBA⁺, is not involved in the binding interactions and is not shown.

nium chloride (TBA-Cl) for 6 days. These conditions produced dodecafluorocalix[6]pyrrole (**5**) in 20% isolated yield, as well as a trace of tetradecafluorocalix[7]pyrrole (**6**) as judged by positive CI-MS analysis. Without TBA-Cl, the yield of **5** dropped to ca. 8%. Although not investigated in detail, the higher yield with TBA-Cl is consistent with an anion template effect.

Under these optimized reaction conditions (i.e., low temperature in the presence of tetrabutylammonium chloride), calix[6]pyrrole **5** proved stable, whereas appreciable decomposition of **6** was still observed. While isolation of **5** proved somewhat challenging (repeated chromatography over silica gel was required), it proved relatively stable once obtained. As such, it could be characterized by standard spectroscopic means. Whereas the ^{1}H NMR and ^{13}C NMR spectra were analogues to those of other fluorinated calixpyrroles, the HRMS of compound **5** was found to differ according to the molecular weights of **3**, **4**, and **7**. The molecular mass of **5** was found to match the expected mass exactly (i.e., m/z 859.33590 vs m/z calculated 859.33576).

Anion Binding in the Solid State. To date, crystals of two anion complexes suitable for X-ray diffraction analysis have been obtained, namely of the chloride anion complex of **3** and the acetate anion complex of **4**.[17] The resulting structures are shown in Figures 1 and 2, respectively. In the presence of chloride anion, compound **3** adopts the expected cone conformation and produces a 1:1 complex in the solid state that is stabilized by four hydrogen bonding interactions between the bound chloride anion and the pyrrolic NH protons. The distance between the pyrrolic NH and the chloride anion was on
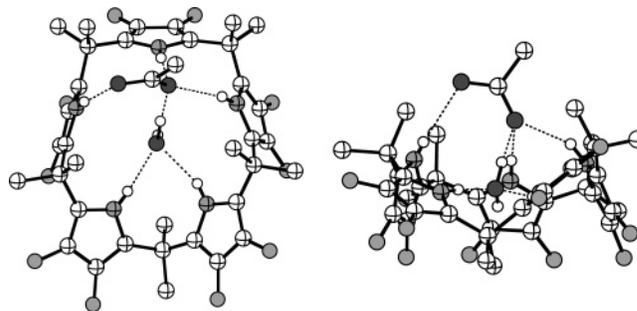
average NH⋯Cl = 2.42 Å, nearly the same as in the chloride anion complex of calix[4]pyrrole (**1**)[3] (i.e., considerably longer than in the corresponding fluoride complex case; cf. NH⋯F = 1.82 Å[13]).

In contrast to the above, a partial cone conformation is seen in the acetate anion complex of **4** (Figure 2). Here, the upper three pyrrolic NH protons are oriented in the same direction, while the two "bottom" pyrrole units are orientated in a perpendicular direction. Three of the five pyrrole NH units are involved in what appear to be strong hydrogen bond interactions with the bound acetate anion (the NH⋯O distances are in the range of 1.94−2.38 Å). The remaining pyrrolic NH protons also participate in the binding of acetate via water mediated hydrogen bond interactions.

Solution Phase Anion Binding Properties. The anion binding properties of fluorinated calix[4]pyrrole (**3**) in solution were studied initially with standard ^{1}H NMR titration methods, using tetrabutylammonium chloride as the anion source and a solvent mixture consisting of CD_3CN containing 2% D_2O.[7,18] Increasing the concentration of chloride anion in the host−guest mixture solution induced a clear downfield shift in the N*H* peak of around 3 ppm (cf. Figure 3). Fitting the observed data points to a 1:1 binding profile, using the Wilcox equation,[19] provided a chloride anion binding constant (K_a) of 50 000 M^{-1} for **3**, a value that is around 7 times higher than that of the control calix[4]pyrrole (**1**) (cf. Table 1). Under identical conditions, ITC analysis provided K_a values for **1** and **3** that matched reasonably well those from the NMR titrations (cf. Table 1). Since ITC allows for analysis of higher K_a values than ^{1}H NMR methods, the other compounds in this study were analyzed via ITC. It should be noted, however, that as yet we have been unable to obtain reliable K_a values for fluoride anion binding by ITC. Therefore, this latter species has been excluded from the present study.

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(17) X-ray Crystal Structure Determination. **Compound 3·C₁₆H₃₆NCl**: C₄₄H₆₄ClF₈N₅; crystals grew as large colorless prisms by vapor diffusion of acetone into an ethanol solution of compound **3** and tetrabutylammonium chloride. The data crystal was cut from a large crystal and had approximate dimensions 0.47 × 0.20 × 0.16 mm³. Triclinic, space group $P\bar{1}$, a = 13.6372(2) Å, b = 17.3214(2) Å, c = 21.0872(3) Å, α = 65.928(1)°, β = 85.442(1)°, γ = 81.976(1)°, V = 4502.01(11) Å³, Z = 4, ρ_{calcd} = 1.255 mg/m³, μ = 0.154 mm^{-1}, $F(000)$ = 1808. A total of 524 frames of data were collected using ω-scans with a scan range of 1° and a counting time of 139 s per frame. **Compound 4·C₁₆H₃₆NC₂H₃O₂·2C₂H₅OH·H₂O**: C₅₇H₈₈F₁₀N₆O₅; crystals grew as long colorless needles by vapor diffusion of acetone into an ethanol solution of compound **4** and tetrabutylammonium acetate. The data crystal was cut from a large crystal and had approximate dimensions 0.48 × 0.21 × 0.20 mm³. Triclinic, space group $P21/n$, a = 11.4814(1) Å, b = 36.1664(5) Å, c = 14.6605(2) Å, α = 90°, β = 99.361(1)°, γ = 90°, V = 6006.57(13) Å³, Z = 4, ρ_{calcd} = 1.247 mg/m³, μ = 0.100 mm^{-1}, $F(000)$ = 2408. A total of 513 frames of data were collected using ω-scans with a scan range of 1° and a counting time of 117 s per frame.

(18) This solvent mixture was chosen because the K_a values in pure CD_3CN were too large to determine accurately by ^{1}H NMR titration methods. This is also proved true for the nonfluorinated calix[4]pyrrole **1**. In previous work, we estimated a K_a > 5 000 M^{-1} in CD_3CN (0.5% v/v D_2O) at 22 °C.[7] Repeated analyses have served to extend this lower bound to >1 × 10^5 M^{-1} (CD_3CN, 22 °C).

(19) Wilcox, C. S. In *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H.-J., Dürr, H., Eds.; VCH: Weinheim, Germany, 1991; p 123.

(20) The effect of dilution is greater for the TBA-salt than for the host macrocycle; such effects are thought to account for the apparent differences in the calculated affinity constants. Representative dilution traces are included in the Supporting Information.
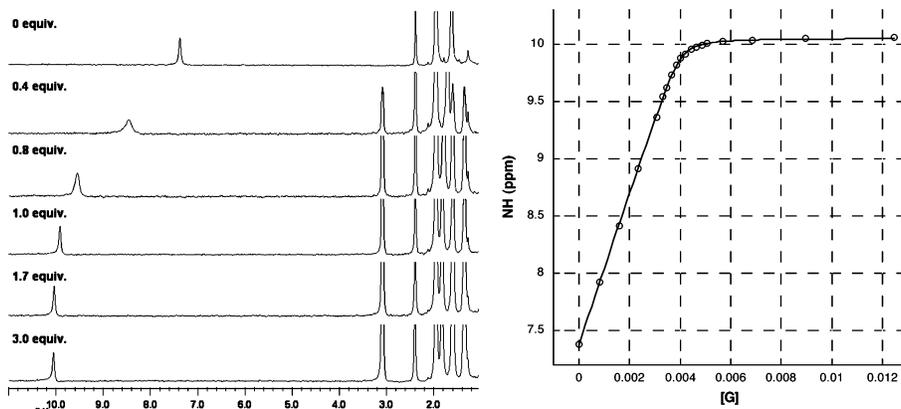
FIGURE 3. Left side: ^{1}H NMR spectral changes observed for the NH protons upon the addition of TBACl to a CD_3CN (2% D_2O) of **3**. Right side: observed and calculated 1:1 binding profile associated with these shifts.

TABLE 1. Association Constants (K_a, M^{-1}) of 1 and 3 for Chloride Anion (tetrabutylammonium salt) in CH_3CN (2% v/v H_2O) As Obtained from ITC^a Analysis and NMR Titrations Carried out in the Corresponding Deuterated Solvents^b

	1	3
NMR	7 600	50 000
ITC	5 400	31 000

^{a} The host (macrocycle) solution was titrated with the guest (anion) solution to obtain the heat effects corresponding to complexation. The net heat effect was determined by subtracting the heat traces for the appropriate background titration. ^{b} Both sets of measurements were made at 22 °C.

TABLE 2. Association Constants (K_a, M^{-1}) for Anion Binding by Fluorinated Calixpyrroles 3−5 and Calix[4]pyrrole 1 in CH_3CN or DMSO As Determined by ITC Analysis at 30 °C, Using the Corresponding Tetrabutylammonium Salts as the Anion Source^a

anion	solvent	1	3	4	5
Cl^-	CH_3CN	140000^b	530000^b	41000	280000
	DMSO	1300^b	1500^b		
Br^-	CH_3CN	3400^b	8500^b	4500	110000
I^-	CH_3CN	c	c	c	610
$CH_3CO_2^-$	CH_3CN	290000^d	1900000	e	e
	CH_3CN^f	350000	2400000	520000	1000000
	DMSO	6100	48000		
$C_6H_5CO_2^-$	CH_3CN	120000^d	1200000	52000	e
	CH_3CN^f	170000	1400000	83000	580000
$H_2PO_4^-$	DMSO	5100	17000	9600	15000
$H_2PO_2^-$	DMSO	c	3300	13000	35000
$K_{rel} = K_a(Cl^-)/K_a(Br^-)$		41	62	9	3

^{a} The host (macrocycle) solution was titrated with the guest (anion) solution unless otherwise indicated. ^{b} Reference 5. ^{c} Association constant too low to be determined by ITC. ^{d} Reference 9. ^{e} A good fit of the data to a 1:1 binding profile could not be made. ^{f} The guest solution was titrated with the host solution (reverse titration).[20]

Table 2 provides a summary of the association constants recorded for compounds **1** and **3**−**5** in the presence of several classic test anions as determined from ITC studies carried out under slightly more "convenient" conditions than those used above (e.g., dry acetonitrile and DMSO). In general, octafluorocalix[4]pyrrole **3** shows the highest association constants toward all the anions investigated except phosphate and bromide. In addition, and very much in line with expectations, fluorinated calix[4]pyrrole **3** displays higher binding affinities across

the board than does calix[4]pyrrole **1**. This difference is ascribed to the highly electron withdrawing groups on the β-pyrrolic position present in **3**. The electron withdrawing effects improve the ability of the pyrrolic NH protons to act as hydrogen bond donors. In acetonitrile, all compounds show a high preference toward carboxylate anions (e.g., acetate and benzoate) over halide anions. It was also found that the relative association constant (K_{rel} = $K_{a(Cl)}/K_{a(Br)}$) decreases with increasing macrocycle size (Table 2). This represents a reversal of what would be expected based on anion electronegativity and charge density considerations. Specifically, chloride anion, being more electronegative and possessing a higher charge density, was expected to be bound more strongly than bromide anion. While this is true in an absolute sense, in the case of **5**, the K_{rel} value is rather small, presumably reflecting the fact that the relatively large cavity present in dodecafluorocalix[6]pyrrole (**5**) is better able to accommodate a bromide anion than a chloride anion. Interestingly, in the case of $H_2PO_2^-$, an inherently less spherical anion, the association constants were seen to increase as the number of β-fluorinated pyrrolic subunits increased. Within the series of fluorinated calixpyrroles, the calix[5]pyrrole **4** was generally seen to display the lowest anion binding affinities, a finding that can presumably be attributed to its distorted structure.

Conclusion

With these results, we have demonstrated that careful optimization of the reaction conditions can lead to higher order calixpyrroles when 3,4-difluoropyrrole is used as the reactant. In this case, the use of TBA-Cl, as an apparent anion template at reduced temperatures (−4 °C), allowed us to obtain dodecafluorocalix[6]pyrrole in a respectable 20% yield. X-ray crystal structures of the chloride and acetate anion complexes of **3** and **4**, respectively, provide support for the notion that fluorinated calixpyrroles can bind anions in the solid state. Anion binding in the solution phase was assessed by ^{1}H NMR spectroscopic and ITC titration methods, using several test anions and three different solvent systems (CH_3CN; CH_3CN + 2% H_2O; DMSO). While octafluorocalix[4]-pyrrole (**3**) displays anion binding affinities that are generally enhanced relative to the other higher order fluorinated calixpyrroles, these latter species show a preference for larger anions, at least in a relative sense.

Taken in concert, these results provide support for the intuitively appealing notion that size effects play a role in modulating the anion binding process in oligopyrrole anion receptors. In accord with such thinking, we are currently looking at anion template effects in the hope of isolating calix[n]pyrroles where $n > 8$.

Supporting Information Available: Crystallographic data for the chloride anion complex of **3** and the acetate anion complex of **4**; spectroscopic data for **5**; NMR spectroscopic and ITC titration plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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