Anion Binding by Calix[n]bipyrroles

Calix[*n*]bipyrroles: Synthesis, Characterization, and Anion-Binding Studies**

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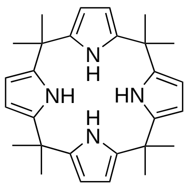
Anion-binding chemistry has emerged in recent years as one of the most intensely explored areas of supramolecular chemistry.[1,2] As a consequence, a number of elegant anion-binding systems are now known. Nonetheless, there remains a need for new receptors, particularly ones that are easy to make or which display unusual anion-binding characteristics. In 1996, the calix[4]pyrroles (for example, **1**), a venerable set of macrocycles dating from the late 1880s, were put forward as a new class of neutral anion-binding agents.[3] These simple-to-make, conformationally flexible macrocycles were found to bind small anions, such as fluoride, phosphate, and chloride, well in common aprotic solvents.[4–7] This observation has made the calix[4]pyrroles and their homologues of interest in a range applications that include anion sensing,[8] extraction,[9] and transport.[10] They have also been attached to solid supports and used to effect anion-specific separations.[11] In spite of their potential utility, the calix[4]pyrroles are plagued by binding "cavities" that are too small to make them efficient receptors for most larger anions, including specifically bromide and iodide in the halide series. Given this shortcoming, several research groups have worked to prepare so-called "higher order" calix[*n*]pyrroles ($n > 4$). In 1998, Eichen and co-workers reported the first syntheses of *meso*-substituted calix[6]pyrroles (for example, **2** and **3**).[12] Shortly thereafter, Kohnke and co-workers detailed a novel route based on the opening of the furan ring that permitted the synthesis of both calix[6]pyrrole **4** and calix[5]pyrrole **5**.[13] Contemporaneous with these latter efforts, our group reported one-pot syntheses of both β-decafluorocalix[5]pyrrole (**6**) and β-hexadecafluorocalix[8]pyrrole (**7**).[14] More recently, we have succeeded in isolating the corresponding β-dodecafluorocalix[6]pyrrole system (**8**).[15] Surprisingly, several of these larger systems did not show improved binding affinities for larger anions.[13d,16] This raises the question of whether other kinds of "expanded" calixpyrroles could be made that would indeed display enhanced selectivities for large anions. Here, we report the synthesis of calix[3]bipyrrole **10** and calix[4]bipyrrole **11**, representatives of a new class of calixpyrrole analogue containing bipyrrole (rather than pyrrole), and show that the first of these displays an affinity for bromide anions in dry acetonitrile that is greatly enhanced in both absolute and relative terms (that is, relative to the affinities of **1** and **10** for bromide and chloride anions, respectively).

The synthesis of **10** and **11** is shown in Scheme 1. By analogy to the procedure used to prepare the parent calix[4]pyrrole **1**,[3–6] 2,2′-bipyrrole **9** was condensed with acetone in methanol in the presence of a catalytic amount of methanesulfonic acid. Bipyrrole **9** was synthesized in two steps from pyrrole and 2-pyrrolidinone as described previously in the literature.[17] Optimal conditions for the condensation involved stirring at room temperature for 2 h, followed by quenching with saturated aqueous sodium bicarbonate. The target macrocycles **10** and **11** were obtained in 24 and 29 % yields, respectively, after purification by column chromatography (silica gel; dichloromethane eluent for **10**, followed by dichloromethane/ethyl acetate (98:2 v/v eluent) for **11**). Attempts to condense β-substituted bipyrroles, for example, 3,3′,4,4′-tetraethyl-2,2′-bipyrrole, proved unproductive. We attribute this latter lack of success to steric effects: interactions between the acetone-derived incipient *meso*-methyl groups and the β-alkyl substituents could be serving to inhibit both the various condensation steps and the ultimate ring-forming macrocyclization process.

Compounds **10** and **11** were characterized by standard spectroscopic techniques (see Supporting Information). They



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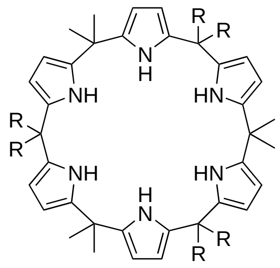
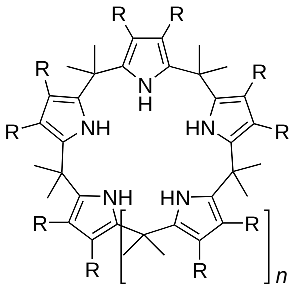


2 R = phenyl
3 R = 4-pyridyl
4 R = CH_3



5 R = H, *n* = 1
6 R = F, *n* = 1
7 R = F, *n* = 4
8 R = F, *n* = 2

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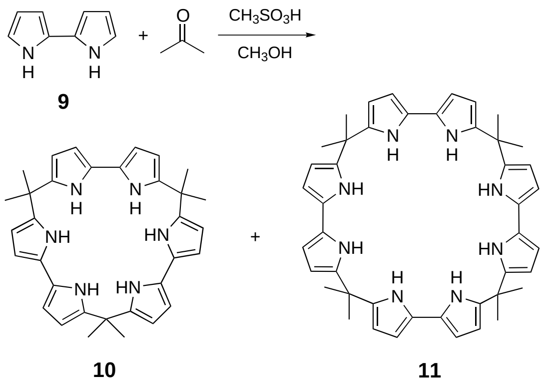

Scheme 1. Synthesis of calix[3]bipyrrole **10** and calix[4]bipyrrole **11**.

were also characterized by X-ray diffraction analysis.[18] In the case of the calix[3]bipyrrole **10**, attempts to obtain diffraction grade crystals in the absence of an anion proved unsuccessful. However, crystals of the chloride anion complex of **10** were obtained by allowing a dichloromethane solution containing an excess of tetrabutylammonium chloride to undergo slow evaporation. X-ray structural analysis revealed that the calix[3]bipyrrole ligand adopts a conelike conformation, and that the six pyrrole NH protons are involved in hydrogen-bonding interactions to the chloride ion (Figure 1). The nitrogen-to-anion distances are in the range of 3.338(7)–3.382(8) Å, and the nitrogen-hydrogen-anion angles are in the range of 147.5–175.5°. As a result, the chloride anion resides 1.189(5) Å above the N_6 root-mean-square plane of the calix[3]bipyrrole core.

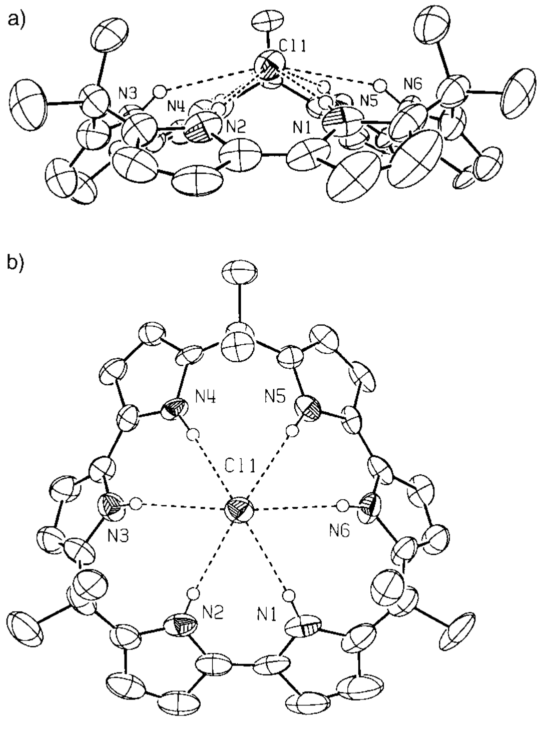

Figure 1. View of the molecular structure of the chloride complex of compound **10**·Cl. a) Side view; b) top view. Thermal ellipsoids are scaled to the 30% probability level. The molecule adopts a conelike conformation in the solid state. The chloride anion is bound to the calix[3]bipyrrole core through six NH···Cl bonding interactions (indicated by dashed lines).

Diffraction-grade crystals of calix[4]bipyrrole **11** were grown from a tetrahydrofuran solution of the macrocycle layered between water and methanol. In this case, X-ray crystal analysis revealed that the calix[4]bipyrrole adopts a 1,3-alternate conformation in the solid state, with adjacent bipyrrole units oriented in opposite directions and each bipyrrole unit bonded to a tetrahydrofuran molecule through two NH(pyrrole)···O(THF) hydrogen bonds (Figure 2).[18] The two bipyrrole units at opposite positions are almost parallel to each other, while the plane of each bipyrrole unit is perpendicular to the plane of the tetrahydrofuran molecule hydrogen bonded to it.

The observation of a bound chloride anion in the solid-state structure of **10** led us to consider that it could act as an anion receptor in solution. Initial analyses were made by carrying out standard ^{1}H NMR titrations in [D$_3$]acetonitrile using the tetrabutylammonium chloride, bromide, and iodide salts (TBACl, TBABr, and TBAI) as the anion source. These analyses revealed evidence of very strong anion binding. For example, addition of approximately 0.1 equivalents of TBACl to an approximately 2 mM solution of calix[3]bipyrrole in [D$_3$]acetonitrile caused the pyrrole NH signal, originally

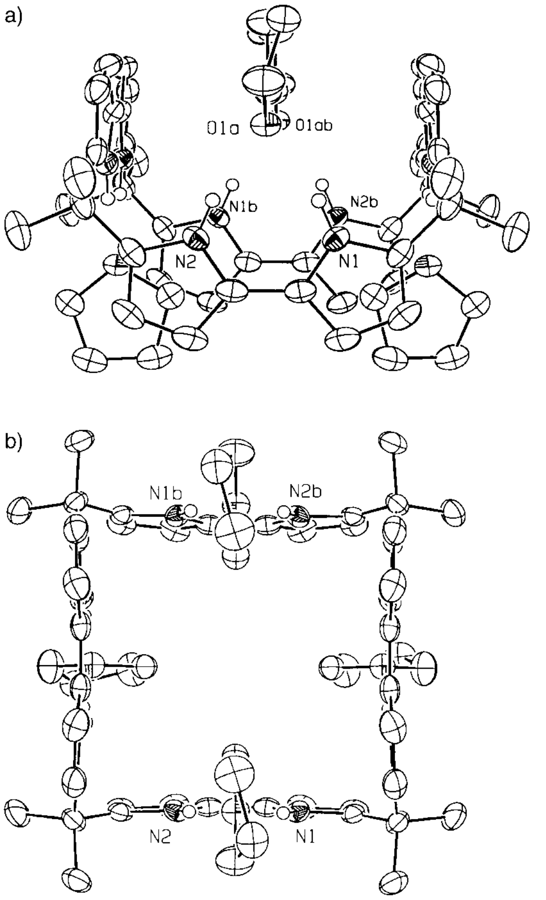

Figure 2. View of the molecular structure of **11**·4THF. a) Side view; b) top view. Thermal ellipsoids are scaled to the 30% probability level. The molecule adopts a 1,3-alternate conformation in the solid state, with each bipyrrole unit being bound to a tetrahydrofuran molecule through two NH···O hydrogen bonds.

present at $\delta = 8.52$ ppm, to split into two distinct signals, one at $\delta = 8.52$ ppm corresponding to the free calix[3]bipyrrole, and one at $\delta = 10.29$ ppm ascribed to the complex formed between calix[3]pyrrole and a chloride anion. Further additions of TBACl caused the siganl at $\delta = 8.52$ ppm to decrease in intensity, with a concomitent increase in the size of the signal at $\delta = 10.29$ ppm. The presence of the signal at $\delta = 8.52$ ppm could no longer be discerned after the addition of about 0.7 equivalents, with further additions causing no apparent changes, either in the NH region, or in the spectrum as a whole. Such observations, which were seen also when TBABr was used as the anion source, preclude accurate assignments of either binding stoichiometry or association constants. However, they are consistent with strong binding and an equilibrium exchange process that is slow on the ^{1}H NMR time scale. In the case of TBAI in [D$_3$]acetonitrile, however, as well as in the cases of TBACl and TBABr in [D$_6$]DMSO, fast exchange was observed, with the NH signal moving to lower field in a monotonic manner upon the addition of increasing equivalents of anions. Good fits to 1:1 binding equilibria were obtained,[19] which allowed association constants K_a to be calculated in the usual way.[20] The resulting values (Table 1) provide support for the conclusion that receptor **10** displays affinities for bromide and iodide anions that are greatly enhanced relative to those of the parent system **1**.

Table 1: Association constants (M^{-1}) for the interaction of **10** and **1** with halide anions in acetonitrile and DMSO.[a]

Anion	Solvent	**10**	**1**	K_{rel}[e]
Cl^-	CH_3CN	110000[b]	140000[b]	0.79
	DMSO	9600[b]	1300[b]	
	[D$_6$]DMSO	15000[c]	1025[d]	14.6
Br^-	CH_3CN	100000[b]	3400[b]	29.4
	DMSO	440[b]	N.D.	
	[D$_6$]DMSO	450[c]	17[c]	26.5
I^-	CH_3CN	[f]	N.D.	
	[D$_3$]CH_3CN	9300[c]	17[c]	547
	[D$_6$]DMSO	N.D.	N.D.	

[a] Anions used in this assay were in the form of their tetrabutylammonium salts; values are the average of at least three separate measurements and are considered reproducible to ±15%; N.D.: not determined. [b] Value obtained from ITC titrations at 30 °C. [c] Determined from ^{1}H NMR titrations carried out at 25 °C. [d] From ref. [21]. [e] Represents the ratio of the association constants for **10** and **1**, respectively, recorded under identical conditions. [f] No reliable fit could be obtained.

Further studies of the anion-binding properties of receptor **10** were made using isothermal titration calorimetry (ITC). The advantages of this method in terms of permitting, for example, the analysis of calix[4]pyrrole···anion interactions characterized by high affinity have recently been highlighted by Schmidtchen.[7] In the present case, it allowed the association constants for the binding of both Cl^- and Br^- ions to **10** in dry acetonitrile to be determined, while also providing an independent confirmation of a representative subset of the K_a values originally determined by ^{1}H NMR titration as described above (see Table 1). In all cases, good fits to 1:1, but not 1:2 or 2:1, receptor:anion stoichiometries were obtained. Thus, the ITC measurements provide support for the notion that **10** binds a single halide anion (Cl^- or Br^-) under the solution-phase conditions of the ITC experiments, just as one would infer from the solid-state structure shown in Figure 1.[22] They also reinforce the conclusion drawn from the ^{1}H NMR analyses that calix[3]bipyrrole **10** is a good receptor for Br^- and I^- ions, both in absolute terms and when considered in comparison to calix[4]pyrrole **1**. Presumably, this observation reflects a better size- and geometry-based matching between the macrocyclic receptor and these larger anions, as well as the greater number of hydrogen-bond donor sites system **10** provides relative to **1**. Interestingly, detailed analysis of the ITC curves for **10** leads to the inference that in DMSO, but not CH_3CN, the binding process is dominated by entropic factors. Efforts to understand the origin of these observations, which are not seen for **1**, are ongoing.

In summary, we have described a new class of macrocyclic anion receptors, as well as a new member of the generalized calixpyrrole family. Current work is devoted to studying further the anion-binding properties of **10**, analyzing those of **11**, and preparing new macrocycles based on bipyrroles, terpyrroles, or combinations of these units and other heterocyclic building blocks, including simple, monomeric pyrroles.

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[16] Recently a detailed analysis of the chloride anion binding behavior of octafluorocalix[4]pyrrole and **6** was carried out in dry acetonitrile by isothermal calorimetry, and revealed association constants of 760000 and 47000 M^{-1} in the case of octafluorocalix[4]pyrrole and **6**, respectively: W.-S. Cho, J. L. Sessler, unpublished results. We consider these values more reliable than those determined by ^{1}H NMR titration methods as reported previously.[14]

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[18] a) Crystallographic summary for [**10**·Cl]·TBA·CH_2Cl_2. Very thin, light brown plates were grown by slow evaporation from dichloromethane, monoclinic, space group $P2_1/c$ (no. 14), $Z = 4$ in a cell of dimensions: $a = 12.6394(3)$, $b = 25.0959(6)$, $c = 16.5497(5)$ Å, $\beta = 108.614(1)°$, $V = 4974.9(2)$ Å^3, $\rho_{\text{calcd}} = 1.17\ \text{g cm}^{-3}$, $\mu = 0.225\ \text{mm}^{-1}$, $F(000) = 1896$. A total of 15672 reflections were measured ($2\theta_{\max} = 50°$), 8657 unique ($R_{\text{int}} = 0.148$), on a Nonus Kappa CCD using graphite monochromatized $\text{Mo}_{\text{K}\alpha}$ radiation ($\lambda = 0.71073$ Å) at −120 °C. The structure was refined on F^2 to an $R_w = 0.169$, with a conventional $R = 0.142$ (3449 reflections with $F_o > 4[\sigma(F_o)]$), and GOF = 1.40 for 550 refined parameters. b) Crystallographic summary for **11**·4THF. Light brown square plates were grown by layering a THF solution of the macrocyle over water and topping the THF with methanol, tetragonal, space group $I\bar{4}$ (no. 14), $Z = 4$ in a cell of dimensions $a = b = 16.4069(3)$, $c = 15.5522(2)$ Å, $V = 2840.51(9)$ Å^3, $\rho_{\text{calcd}} = 1.14\ \text{g cm}^{-3}$, $\mu = 0.072\ \text{mm}^{-1}$, $F(000) = 1056$. A total of 10600 reflections were measured ($2\theta_{\max} = 55°$), 3277 unique ($R_{\text{int}} = 0.037$), on a Nonus Kappa CCD using graphite monochromatized $\text{Mo}_{\text{K}\alpha}$ radiation ($\lambda = 0.71073$ Å) at −120 °C. The structure was refined on F^2 to an $R_w = 0.0833$, with a conventional $R = 0.0391$ (2548 reflections with $F_o > 4[\sigma(F_o)]$), and a GOF = 1.03 for 249 refined parameters. CCDC-201040 ([**10**·Cl]·TBA·CH_2Cl_2) and CCDC-201041 (**11**·4THF) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[19] Binding stoichiometries were confirmed by independent Job plots; see the Supporting Information.

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[22] In the course of review, a referee noted with interest the fact that the affinity of calix[3]bipyrrole **10** for chloride anions is actually lower than that of calix[4]pyrrole **1** in acetonitrile, in spite of the greater number of potential NH donor sites in receptor **10** than in **1**. We rationalize this observation in terms of the poor size match between receptor **10** and a Cl^- ion. Specifically, we believe that the corresponding incommensurate binding geometry, as evidenced more by the unfavorable Cl-H-N angles seen in the solid state (ranging from 147.5–175.5°) than by the Cl···H-N hydrogen bond lengths, outweighs in an adverse sense the binding advantage that an increased number of hydrogen bonds would be expected to impart, at least in this relatively less polar solvent. This is not the case in DMSO. Here, the increased number of hydrogen-bond donor groups serves to overcome competition from the solvent, with the net result that stronger binding of a chloride anion is displayed by **10** relative to **1** in DMSO.