Calix[4]bipyrrole—a big, flexible, yet effective chloride-selective anion receptor†

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Anion binding studies reveal that, in spite of its big size and flexible structure, calix[4]bipyrrole shows strong anion binding in general and good selectivity towards chloride anion in acetonitrile.

The anion binding chemistry of calixpyrroles (*e.g.*, **1**) has been intensely explored since 1996.[1–3] The relatively small "cavity" size of the calix[4]pyrroles enables them to bind small anions, such as fluoride, chloride, and dihydrogen phosphate, reasonably efficiently in common aprotic solvents, such as dichloromethane and acetonitrile.[4] On the other hand, larger anions, such as bromide and iodide, are not bound well. This has led to consideration that expansion of the pyrrole NH hydrogen bond donor cavity would lead to receptors appropriately sized to accommodate larger anions. Therefore, we and others have worked to prepare so-called "higher order" calix[*n*]pyrroles (n = 5, 6, and 8), several of which display enhanced binding affinities for larger anions.[5–7] In the context of this work, our group recently reported two new compounds, namely calix[3]bipyrrole **2** and calix[4]bipyrrole **3** that rely on the use of bipyrrole, rather than pyrrole, as the basic building block.[8] Associated anion binding studies revealed that macrocycle **2** binds large halide anions (*e.g.*, Br^-) with affinities that are substantially enhanced relative to those of calix[4]pyrrole **1**. Excluded from this initial study, however, was compound **3**, since it appeared too large and too flexible to complex various standard test anions (*e.g.*, the larger halides). However, we have now carried out an X-ray structural analysis of crystals of compound **3** grown in the presence of tetrabutylammonium chloride and found that this octapyrrolic system stabilizes the formation of well-defined chloride and bromide anion complexes in the solid state. Solution phase anion binding studies, carried out using standard ^{1}H NMR spectroscopic and isothermal titration calorimetry (ITC) methods, reveal that in acetonitrile solution compound **3** acts as a highly effective chloride anion receptor.

Previously, we reported the crystal structure of **3**·4C_4H_8O, in which **3** is bound to four tetrahydrofuran molecules. The macrocycle adopts a square conformation, in which the two bipyrroles at the 1,3- (or 2,4-) positions are parallel to each other and in a *cis*-like orientation. The presence of hydrogen bonding interactions in this structure led us to consider that this system might act as an effective anion receptor, provided a more suitable conformation (or set of conformations) could be stabilized. As a test of this proposal, crystals of an adduct, formally analyzed as [**3**·Cl^-][TBA] (TBA = tetrabutylammonium), were grown from a dichloromethane–ether solution containing a 1 : 1 mixture of **3** and TBACl.‡ The resulting structure is shown in Fig. 1. It reveals the presence of a bound chloride anion that is nested within the binding "cavity" as opposed to perched above it, as seen in the case of **1**·Cl^-,[1] and to a lesser extent, **2**·Cl^-.[8] In **3**·Cl^-, the macrocycle adopts a V-shaped (D_{2d}) conformation with the chloride ion sitting in the center and bound to eight pyrrole units *via* eight NH···Cl^- hydrogen bond interactions, the highest number so far observed in any structurally characterized calixpyrrole or calixpyrrole-like anion complex. The range of N···Cl^- and H···Cl^- distances (Å) are 3.422(4)–3.572(4) and 2.53–2.70 respectively; the N–H–Cl^- angles range between 161.7° and 173.9°. The counter ion, TBA, resides more or less at the side of the cleft-like macrocycle. By contrast, in **2**·Cl^- this cation sits above and below the receptor.

Diffraction-grade crystals of **3**·Br^- were also obtained using a procedure analogous to that used to prepare crystals of **3**·Cl^-. X-Ray diffraction analysis revealed the existence of two structurally-similar macrocycles in the unit cell, both of which bear resemblance to the structure of **3**·Cl^- (Fig. 2).‡ In molecular structure 1, the nitrogen-to-bromide distances are in the range 3.492(4)–3.608(3) Å, the NH proton-to-bromide distances are in

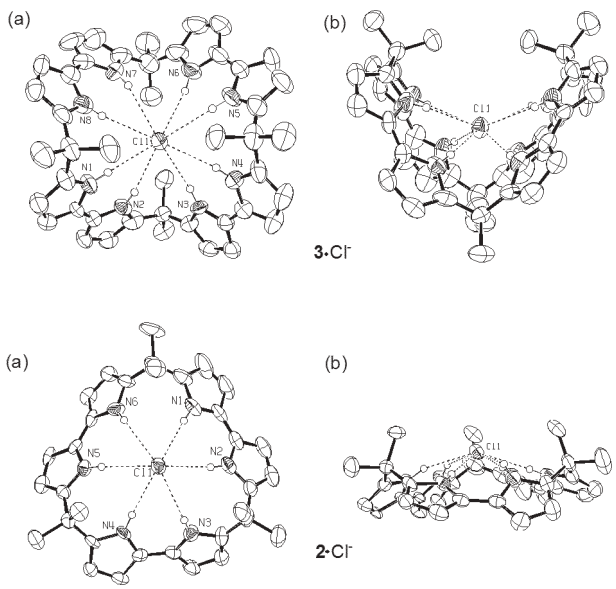

Fig. 1 X-Ray crystal structures of **3**·Cl^- and **2**·Cl^- (ORTEP, displacement ellipsoids scaled to the 30% probability level for **3**·Cl^-; most hydrogen atoms have been removed for clarity). (a) Top view, (b) side view. Dashed lines are indicative of NH···Cl^- hydrogen bonds. The structure of **2**·Cl^- was generated from coordinates first published in ref. 8.

† Electronic supplementary information (ESI) available: ^{1}H NMR and ITC titration data for **1–3** and crystal data for **3**·Cl^- and **3**·Br^-. See http://www.rsc.org/suppdata/cc/b4/b412737d/

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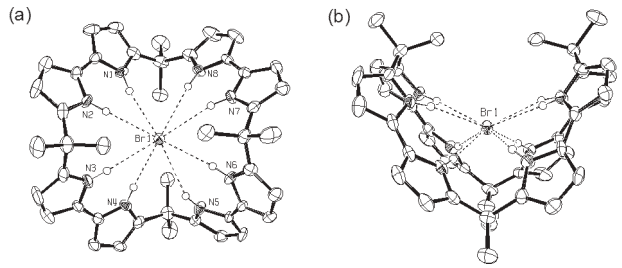

Fig. 2 X-Ray crystal structure of **3**·Br^- (molecular structure 1 of 2; ORTEP, displacement ellipsoids scaled to the 50% probability level; most hydrogen atoms have been removed for clarity). (a) Top view, (b) side view. Dashed lines are indicative of NH···Br^- hydrogen bonds.

the range 2.60–2.73 Å, and the nitrogen-hydrogen-bromide angles are in the range 154.7°–174.6°. In molecular structure 2, the nitrogen-to-bromide distances are in the range 3.430(3)–3.583(4) Å, the NH proton-to-bromide distances (Å) are in the range 2.54–2.73 Å, and the nitrogen-hydrogen-bromide angles are in the range 158.5°–177.2°.

The finding that **3** stabilizes the formation of "encapsulated" complexes with chloride and bromide anion complexes in the solid state led us to consider that system **3** might prove to be an effective halide anion receptor in organic solution. As a test of this consideration, the binding of selected anions was studied in acetonitrile solution using ^{1}H NMR spectroscopic titration and ITC methods. The results of these studies are shown in Table 1.

Inspection of Table 1 reveals that, compared to **1** and **2**, the octapyrrolic macrocycle **3** displays an enhanced affinity for chloride anion, binding this species over 20 times more effectively than either **1** or **2**. In the case of bromide, receptor **3** shows an affinity that is substantially increased, by a factor of roughly 33, compared to **1**, but which is essentially similar to that displayed by **2**. For the larger anions, nitrate and iodide, it is actually the latter species (*i.e.* **2**), not **3**, that displays the highest affinity, although for both receptors the actual K_a values are low.

The crystal structures of **3**·Cl^- and **3**·Br^-, to the extent that they reflect the dominant species present in solution, help provide a rationale for the high relative and absolute chloride anion affinity seen in the case of **3**, namely an ability to adopt a conformation wherein eight pyrrole NH hydrogen bond donor groups can interact with the anionic center. Presumably, the entropic cost associated with adopting such a cavity-producing conformation is outweighed by the enthalpic advantages it provides. These conformation related costs are expected to be less in the case of the more flexible system than in its more rigid congener **2**. In the case of the larger bromide anion, the advantages of the additional hydrogen bonds are presumably less significant given the greater anion-to-pyrrole NH separations that are likely to exist under solution phase conditions. By contrast, the price of conformational organization is expected to be similar to what is seen in the case of **3**·Cl^-, albeit, again, presumably lower than in the case of **1**·Br^- or **2**·Br^-. In **3**·Cl^-, the deep "walls" of the receptor are also expected to provide greater protection from solvation than in either the corresponding bromide complex, or in the chloride anion complexes of **1** and **2**.

Table 1 Association constants (K_a, M^{-1}) for the interaction of receptors **1–3** with different anions in acetonitrile[a]

Anions	3	2	1
Cl^-	2 900 000[b]	110 000[b,d]	140 000[b,d]
Br^-	110 000[b]	100 000[b,d]	3 400[b,d,e]
I^-	56[c]	9 300[c,d]	17[c,d]
NO_3^-	450[c]	11 000[c]	52[c]

[a] Anions were studied in the form of their corresponding tetrabutylammonium salts; values are the average of at least three measurements and are considered reproducible to ±15%. [b] Value obtained from ITC titrations in dry CH_3CN at 30 °C. [c] Value obtained from ^{1}H NMR titrations carried out in $[D_3]CH_3CN$ at 25 °C. [d] Data from ref. 8. [e] At 22 °C, K_a = 5900 M^{-1} and 4500 M^{-1} in dry acetonitrile, as determined by ^{1}H NMR spectroscopic titrations and ITC methods, respectively.

When DMSO was used as a solvent, compound **3** failed to show any appreciable interaction with either chloride or bromide anion. This stands in marked contrast to what is true for its "lower order" calix[3]bipyrrole **2**; this more rigid anion receptor displays K_a values of 9600 and 440 M^{-1} for these two anions, respectively.[8] The reduced level of preorganization present in **3** is expected to allow this system to be highly solvated. As a result of this solvation and the associated DMSO-to-NH interactions, the relative enthalpic benefit associated with chloride or bromide anion binding seen in the case of acetonitrile is diminished and is no longer sufficient to overcome the entropic penalty needed to form the V-shaped conformation that favors halide anion complexation.

In conclusion, calix[4]bipyrrole **3**, in spite of being both large and conformationally flexible, is found to bind chloride anions well and with high selectivity in acetonitrile. This is thought to reflect its ability to support the formation of V-shaped "nesting" complexes that are very different from those seen for calix[4]pyrrole **1** or calix[3]bipyrrole **2**.

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Notes and references

‡ Crystal data for **3**·Cl^-: $C_{68}H_{104}ClN_9O_2$, M = 1115.05, T = 153 K, orthorhombic, space group $P2_12_12_1$, a = 15.1706(3), b = 20.1092(4), c = 21.6320(5) Å, V = 6599.2(2) Å^3, Z = 4, ρ_{calcd} = 1.122 g cm^{-3}, μ(Mo–Kα) = 0.107 mm^{-1}, F(000) = 2432, 11 343 reflections measured, 11 343 unique, $R1$ = 0.0754, $wR2$ = 0.1322. CCDC reference number 247496; for **3**·Br^-: $C_{52.50}H_{69}BrClN_9$, M = 941.53, T = 153 K, monoclinic, space group $P2_1/c$, a = 21.4853(3), b = 15.7904(2), c = 29.3770(5) Å, β = 91.265(1), V = 9964.1(3) Å^3, Z = 8, ρ_{calcd} = 1.255 g cm^{-3}, μ(Mo–Kα) = 0.923 mm^{-1}, F(000) = 3992, 31 386 reflections measured, 17 418 unique (R_{int} = 0.1174), $R1$ = 0.0647, $wR2$ = 0.0916. CCDC reference number 247497. See http://www.rsc.org/suppdata/cc/b4/b412737d/ for crystallographic data in .cif or other electronic format.

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