Calix[4]pyrroles: Old Yet New Anion-Binding Agents

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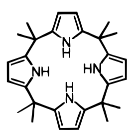
Anions play essential rôles in biological processes; indeed, it is believed that they participate in 70% of all enzymatic reactions.[1] There is, therefore, intense effort being devoted to the problem of anion complexation and recognition.[2] In the molecular recognition arena, a number of research groups have followed nature's lead[3] and have designed and synthesized receptors that use hydrogen bonds alone,[4] or in concert with electrostatic interactions,[5,6] to coordinate to anions. Nonetheless, there remains at present a critical need for additional anion-complexing agents that are either easy to make or inherently selective in their substrate-binding properties. Recently, as the result of our work with polypyrrole macrocycles,[5] it occurred to us that the porphyrinogens, a venerable class of molecules, might serve as such easy-to-make anion-binding agents. We now report that this is indeed the case.

Porphyrinogens are macrocyclic species composed of four pyrrole rings linked in the α-position via sp^3-hybridized carbon atoms. Porphyrinogens which carry *meso*-hydrogen atoms are prone to oxidation to the corresponding porphyrin. On the other hand, fully *meso*-substituted porphyrinogens are generally not only stable crystalline materials but also readily obtainable.[7] In fact, the first such species, an octamethyl derivative, was obtained over a century ago by Baeyer[7a] as the result of an acid-catalyzed condensation between acetone and pyrrole. Subsequently, this synthesis was refined by a number of research groups.[7b−d] In 1971 Brown and co-workers condensed cyclohexanone with pyrrole in a 1:1 ratio in the presence of acid to produce tetraspirocyclohexylporphyrinogen **2**.[7e] Recently Floriani and co-workers have made an extensive study of the chemistry of metal complexes of various deprotonated octaalkylporphyrinogens.[8]

While the term porphyrinogen is now widely accepted in the literature, octaalkylporphyrinogens are not *bona fide* precursors of the porphyrins and might, therefore, be better considered as being *calixpyrroles*. Such a renaming, which has precedent in the chemistry of other heterocyclic ring systems,[9] would allow the analogy to calixarenes[10] to be more fully stressed. Interestingly, while functionalized calixarenes have been shown to be capable of binding anions,[11] unmodified calixarene frameworks show no affinity for anionic guests.

1 and **2** were prepared in one step using known literature procedures.[7] Single crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation of acetone[12] and acetone/dichloromethane[13] (1:1 v/v) solutions of macrocycles **1** and **2**, respectively. As illustrated in Figure 1, the molecules adopt a 1,3-alternate conformation in the solid state wherein adjacent rings are oriented in opposite directions just as is true in the case of the previously reported octaethyl analogue.[8b] This is a less common conformation for calixarenes, only a few structurally characterized examples having been reported.[14]



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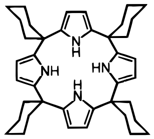

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Crystals of the tetrabutylammonium chloride complex of calixpyrrole **1** were obtained by slow evaporation of a dichloromethane solution containing an excess of the chloride salt.[15] Crystals of the tetrabutylammonium fluoride complex of **2** were obtained using a similar procedure.[16] X-ray crystal analysis revealed that in both cases the calix[4]pyrrole ligand adopts a conelike conformation such that the four NH protons can hydrogen bond to the halide anion (Figure 2).[17] While these two structures are thus grossly similar, in the case of the chloride complex (Figure 2a) the nitrogen-to-anion distances are in the range of 3.264(7)−3.331(7) Å, while for the corresponding fluoride complex they are 2.790(2) Å (Figure 2b) (the four pyrrole groups are equivalent by symmetry). As a result, in these two complexes the chloride and fluoride anions reside 2.319(3) and 1.499(3) Å above the N_4 root-mean-square planes of calixpyrroles **1** and **2**, respectively. Thus, fluoride anion appears to be more tightly bound, at least in the solid state.

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[12] Crystallographic summary for **1**. Pale yellow crystals, tetragonal, $P4_1$, $Z = 2$ in a cell of dimensions $a = 10.097(1)$ Å, $c = 23.764(1)$ Å, $V = 2422.7(4)$ Å^3, $\rho_{calc} = 1.18$ g cm^{-3}, $F(000) = 928$. 3733 unique reflections, 2552 with $F_o > 4(\sigma(F_o))$. The final $R = 0.0556$, $R_w = 0.132$, goodness of fit = 0.999 for 290 parameters.

[13] Crystallographic summary for **2**·(CH_2Cl_2). Colorless crystals, monoclinic, $P2_1/c$, $Z = 4$ in a cell of dimensions $a = 10.993(2)$ Å, $b = 14.250(3)$ Å, $c = 23.466(4)$ Å, $\beta = 97.254(14)°$, $V = 3646.5(11)$ Å^3, $\rho_{calc} = 1.23$ g cm^{-3}, $F(000) = 1448$. 5562 unique reflections, 2285 with $F_o > 4(\sigma(F_o))$. The final $R = 0.0762$, $R_w = 0.141$, goodness of fit = 0.995 for 424 parameters.

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[15] Crystallographic summary for **1**·($^nBu_4NCl$)·CH_2Cl_2. Colorless crystals, orthorhombic, $Pna2_1$, $Z = 4$ in a cell of dimensions $a = 21.247(3)$ Å, $b = 19.937(2)$ Å, $c = 10.691(1)$ Å, $V = 4528.7(9)$ Å^3, $\rho_{calc} = 1.16$ g cm^{-3}, $F(000) = 1720$. 6027 unique reflections, 3566 with $F_o > 4(\sigma(F_o))$. The final $R = 0.0959$, $R_w = 0.246$, goodness of fit = 1.224 for 478 parameters.

[16] Crystallographic summary for **2**·($^nBu_4NF$). Colorless crystals, tetragonal, $P4/nnc$, $Z = 4$ in a cell of dimensions $a = 15.732(1)$ Å, $c = 20.076(1)$ Å, $V = 4968.7(5)$ Å^3, $\rho_{calc} = 1.14$ g cm^{-3}, $F(000) = 1872$. 3634 unique reflections, 2220 with $F_o > 4(\sigma(F_o))$. The final $R = 0.064$, $R_w = 0.171$, goodness of fit = 1.029 for 152 parameters.

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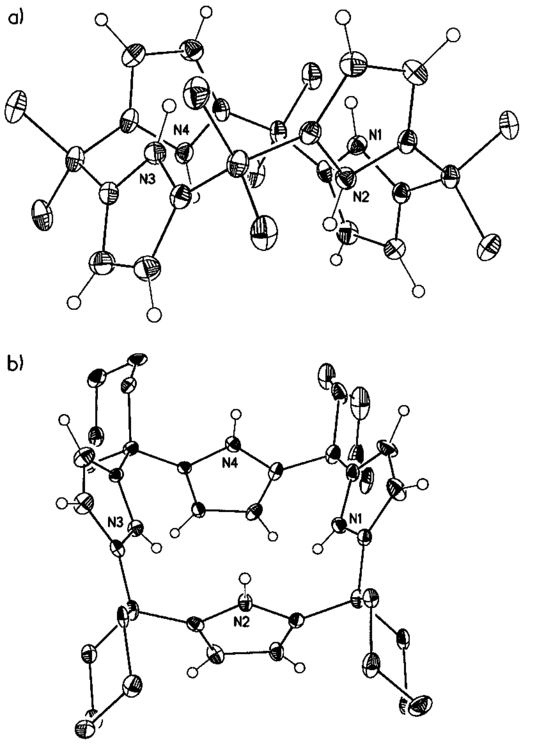

Figure 1. View of the molecular structures of (a) **1** and (b) **2**. Thermal ellipsoids are scaled to the 30% probability level. Both compounds adopt a 1,3-alternate conformation in the solid state.

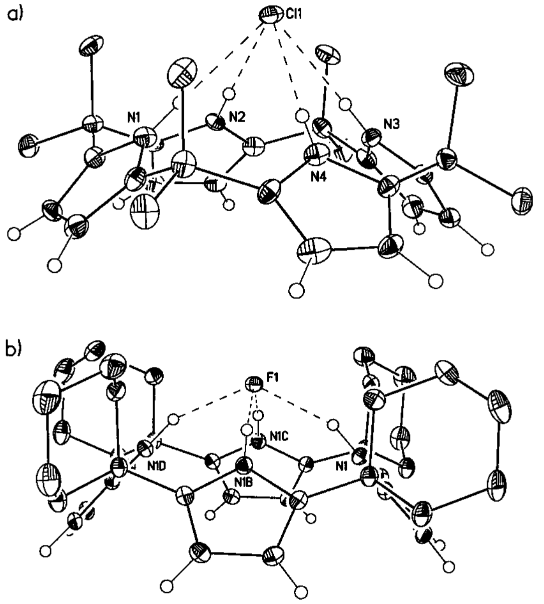

Figure 2. View of the molecular structures of (a) the chloride complex of compound **1** and (b) the fluoride complex of compound **2**. Thermal ellipsoids are scaled to the 30% probability level. Both complexes adopt a cone conformation in the solid state.

Table 1. Stability Constants for **1** and **2** with Anionic Substrates[a] in CD_2Cl_2 at 298 K

anion added	stability constant (M^{-1})	
	calix[4]pyrrole **1**	calix[4]pyrrole **2**
fluoride[b,c]	17 170 (±900)	3600 (±395)
chloride	350 (±5.5)	117 (±4.0)
bromide	10 (±0.5)	*e*
iodide	<10	*e*
dihydrogen phosphate[d]	97 (±3.9)	<10
hydrogen sulfate	<10	*e*

[a] Anions were added as 0.1 M CD_2Cl_2 solutions of their tetrabutylammonium salts to 10 mM solutions of the receptor in CD_2Cl_2 with concentration changes being accounted for by EQNMR.[18] In determining the stability constants, the possible effects of ion pairing (if any) were ignored. [b] Tetrabutylammonium fluoride was added as the trihydrate. [c] A repeat titration with **1** at 1.0 mM concentration gave concordant results. [d] A repeat titration with **1** at 100 mM concentration gave concordant results. [e] Not determined.

Analyses of the solution phase anion-binding properties of calix[4]pyrroles **1** and **2** were made using ^1H NMR titrations carried out in dichloromethane-d_2. Data analysis and stability constant determinations were then made using the EQNMR computer program.[18] The findings, summarized in Table 1, revealed that both compounds **1** and **2** are not only effective 1:1 anion-binding agents in solution,[19] they are also selective ones; they show a marked preference for F^- relative to other putative anionic guests (*viz.* Cl^-, Br^-, I^-, $H_2PO_4^-$, and HSO_4^-).[20] On the other hand, control titrations carried out using simple monomeric 2,5-dimethylpyrrole and, e.g., fluoride anion showed but little evidence for anion binding (see the supporting information). Thus, the anion-binding behavior displayed by **1** and **2** appears to be a direct consequence of having available for hydrogen bonding a polypyrrolic macrocycle of appropriate size and shape. The present findings are thus reminiscent of what has been found earlier in the case of protonated expanded porphyrin-type systems.[5] However, in the present instance, the receptor itself is neutral, not charged. And, in contrast to many of the expanded porphyrins, it is quite easy to make.

The present results lead us to suggest that there could be a rich molecular recognition chemistry associated with the calixpyrroles. Presently, we are exploring whether the calix[4]pyrroles might also serve as receptors for neutral substrates[21] or as chelating agents for more complex negatively charged materials (e.g., polyanions such as DNA). We are also working to produce yet-larger (i.e., expanded) calixpyrroles based on the incorporation of more than four pyrrolic substrates into a porphyrinogen-like framework[22] or the use of bi- or terpyrrolic starting materials. The results of these investigations will be reported in due course.

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Supporting Information Available: A listing of observed and calculated binding profiles for NMR titrations, Job plots, high-resolution mass spectral data, X-ray experimental details for the four crystal structures, atomic positional parameters, bond distances, angles and atomic thermal parameters for **1**, **2**, and their chloride and fluoride complexes respectively (90 pages). Ordering information is given on any current masthead page.

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(17) The N-H proton for $2\cdot F^-$ was obtained from a ΔF map and refined with an isotropic temperature parameter. The N−H protons for $1\cdot Cl^-$ were located in a ΔF map but did not refine to geometrically reasonable positions and were, therefore, calculated in idealized positions with U_{iso} set to 1.2 × U_{eq} for the attached N atom.

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(19) Receptor-to-anion stoichiometries were determined from molar-ratio plots (as opposed to simple curve-fitting procedures; cf. the supporting information).

(20) ^1H NMR titrations were carried out with the starting concentration of receptor at 10 mM. In order to discount aggregation effects caused by hydrogen bonding between dihydrogen phosphate anions in solution, a repeat titration at a starting concentration of 100 mM **1** was carried out; it gave concordant results. Similarly, a titration involving fluoride anion but with a starting concentration of 1.0 mM **1** was carried out. It gave results identical within error to those obtained from titrations carried out with an initial receptor concentration of 10 mM.

(21) Preliminary structural data confirms that the calixpyrrole **1** will bind methanol in the solid state.

(22) Preliminary mass spectrometric evidence confirms that calix[5], [6], and [7]pyrroles are formed in trace quantities under certain conditions (see the supporting information).