Synthesis of Novel Expanded Calixphyrins: Anion Binding Properties of a Calix[6]phyrin with a Deep Cavity

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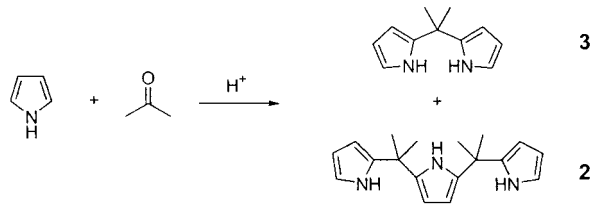
Chemical hybrids of the porphyrins and calixpyrroles, calix[*n*]phyrins, are polypyrrolic macrocycles that contain at least one sp^3 hybridized meso-like bridging carbon atom. While examples of calix[4]phyrin derivatives, represented by such classic structures as the phlorins,[1] isoporphyrins,[2] 5,10- or 5,15-dihydroporphyrins,[3] and porphomethenes,[4] abound, the chemistry of higher order calix[*n*]phyrins ($n > 4$) remains virtually unexplored.[3f,5] Recently, we reported the synthesis of calix[6]- and calix[9]phyrin, macrocycles that contain a succession of conjugated dipyrromethene subunits linked via sp^3 hybridized meso-like bridging carbon atoms.[3f] We have now found that, by using appropriate acyclic polypyrrolic precursors, it is possible to modify the ratio of oxidized to non-oxidized meso-like carbon atoms in higher order calix[*n*]phyrins as well as the distribution of these bridging centers within the macrocyclic skeleton. Specifically, we report here the synthesis of 5,5-10,10-20,20-25,25-octamethylcalix[6]phyrin **1**, obtained from 5,5,10,10-tetramethyltripyrrane **2**, and show that this non-planar species acts as an anion receptor both in solution and in the solid sate.

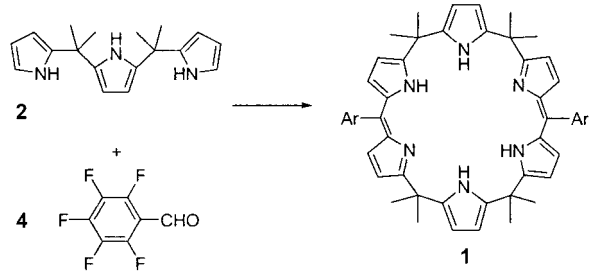
The synthesis of tripyrrane **2** is shown in Scheme 1.[6] It is obtained from the TFA acid-catalyzed condensation of pyrrole and acetone. Optimal conditions involved stirring at room temperature for 2 h followed by the addition of triethylamine. Removal of excess pyrrole by distillation followed by column chromatographic purification (silica gel; hexane−dichloromethane eluent) yielded **2** in an approximate yield of 5%, along with substantial quantities of the known dipyrromethane **3** (ca. 25% yield).[7] While the yield of **2** is low, the ready availability of the starting materials allows this key precursor to be made easily in ≥10 g batches.

Scheme 1



Initial attempts to react tripyrrane **2** with benzaldehyde in the presence of various Brønsted or Lewis acids proved unproductive. In our hands, the only products obtained were ones in which the integrity of the starting polypyrrole was degraded. Considering that these observations could reflect the fact that tripyrrane **2** is inherently unstable in the presence of acid, pentafluorobenzaldehyde was chosen as the reaction partner; this electron-deficient aryl aldehyde is known to react with pyrrole derivatives in the absence of any catalyst.[8] Condensation of **2** with **4** in dichloromethane at room temperature followed by DDQ oxidation gave calix[6]phyrin **1** in ca. 10% yield (Scheme 2, Ar = C_6F_5).

Scheme 2



Compound **1** displayed spectroscopic properties in accord with the proposed structure and was characterized by X-ray diffraction analysis. The resulting Ortep views (Figure 1) revealed the presence of a water molecule bound to the macrocycle through two N···H_w and two N−H···O_W intramolecular interactions. Considering the deep cavity structure observed in the solid state as well as the existence of two calixpyrrole-like pyrrole moieties pointing in toward the center of the cleft, it was considered likely that macrocycle **1** would act as an efficient anion receptor.

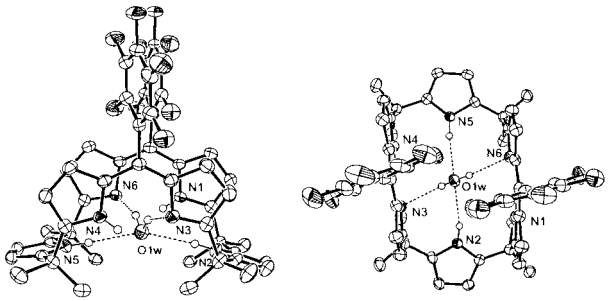


Figure 1. Ortep[10] views of **1**·H_2O showing the heteroatom labeling scheme. Hydrogen bonding interactions are indicated by dashed lines.

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(1) For examples of phlorins, see: Sugimoto, H. *J. Chem. Soc., Dalton Trans.* **1982**, 1169. Setsune, J.; Ikeda, T.; Iida, T.; Kitao, T. *J. Am. Chem. Soc.* **1988**, *110*, 6572. Segawa, H.; Azumi, R.; Shimidzu, T. *J. Am. Chem. Soc.* **1992**, *114*, 7564. Setsune, J.; Wada, K.; Higashino, H. *Chem. Lett*. **1994**, 213. Jiang, X.; Nurco, D. J.; Smith, K. M. *Chem. Commun.* **1996**, 1759. Krattinger, B.; Callot, H. J. *Eur. J. Org. Chem.* **1999**.

(2) For examples of isoporphyrins, see: Dolphin, R.; Felton, R. H.; Borg, D. C.; Fajer, C. *J. Am. Chem. Soc.* **1970**, *92*, 743. Fuhrhop, J.-H.; Lumbantobing, T. *Tetrahedron Lett.* **1970**, *32*, 2815. Xie, H.; Smith, K. M. *Tetrahedron Lett.* **1992**, *33*, 1197. Barkigia, K. M.; Renner, M. W.; Xie, H.; Smith, K. M.; Fajer, J. *J. Am. Chem. Soc.* **1993**, *115*, 7894.

(3) 5,10-Dihydroporphyrins: (a) Krattinger B.; Callot, H. J. *Tetrahedron Lett*. **1998**, *39*, 1165. (b) Krattinger, B.; Callot, H. J. *Eur. J. Org. Chem*. **1999**, 1857. (c) Bucher, C.; Seidel, D.; Lynch, V.; Král, V.; Sessler, J. L. *Org. Lett.* **2000**, *2*, 3103. For examples of 5,15-dihydroporphyrins, see: (d) Buchler, J. W.; Lay, K. L.; Smith, P. D.; Scheidt, W. R.; Rupprecht, G. A.; Kenny, J. E. *J. Organomet. Chem.* **1976**, *110*, 109. (e) Bonomo, L.; Solari, E.; Scopelliti, R.; Floriani, C.; Re, N. *J. Am. Chem. Soc.* **2000**, *122*, 5312. (f) Král, V.; Sessler, J. L.; Zimmerman, R. S.; Seidel, D.; Lynch, V.; Andrioletti, B. *Angew. Chem., Int. Ed.* **2000**, *39*, 1055. (g) Harmjanz, M.; Gill, H. S.; Scott, M. J. *J. Am. Chem. Soc.* **2000**, *122*, 10476.

(4) For examples of porphomethenes, see: Benech, J.-M.; Bonomo, L.; Solari, E.; Scopelliti, R.; Floriani, C. *Angew. Chem., Int. Ed.* **1999**, *38*, 1957 and references therein.

(5) Khoury, R. G.; Jaquinod, L.; Nguyen, L. T.; Smith, K. M. *Heterocycles* **1998**, *47*, 113. Wytko, J. A.; Michels, M.; Zander, L.; Lex, J.; Schmickler, H.; Vogel, E. *J. Org. Chem.* **2000**, *65*, 8709.

(6) Although tripyrrane **2** appears to be a new compound, analogous materials have been reported; see: Brückner, C.; Sternberg, E. D.; Boyle, R. W.; Dolphin, D. *Chem. Commun.* **1997**, 1689. Ka, J.-W.; Lee, C.-H. *Tetrahedron Lett.* **2000**, *41*, 4609.

(7) Brown, W. H.; French, W. N. *Can. J. Chem.* **1958**, *36*, 371. Littler, B. J.; Miller, M. A.; Hung, C.-H.; Wagner, R. W.; O'Shea, D. F.; Boyle, P. D.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 1391.

(8) Gross, Z.; Galili, N.; Simkhovitch, L.; Saltsman, I.; Botoshansky, M.; Bläser, D.; Boese, R.; Goldberg, I. *Org. Lett.* **1999**, *1*, 599.

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However, perhaps as a consequence of the strongly bound water located inside the cavity, little evidence of anion binding was observed upon the addition of various anions (e.g., Cl^-, Br^-, I^-, NO_3^-, HSO_4^-). On the other hand, as has proved to be the case with a variety of other polypyrrolic macrocycles, anion binding was observed following protonation.[9]

The monoprotonated form of **1**, [**1**·H]$^+$·Cl^-, was obtained in the form of single crystals via the slow evaporation of a dichloromethane solution previously washed with aqueous 1 N HCl. The resulting X-ray diffraction structure (Figure 2) revealed

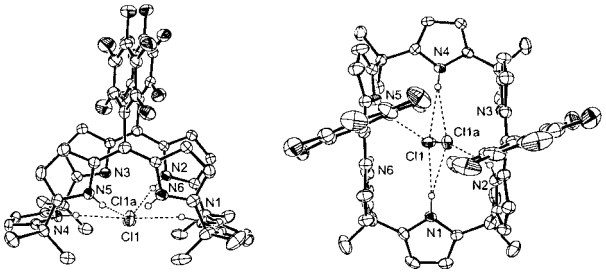

Figure 2. Ortep[10] views of [**1**·H]$^+$·Cl^- showing the heteroatom labeling scheme. N−H···Cl intramolecular interactions are indicated by dashed lines. The bound chloride anion is disordered.

that, as expected, one of the dipyrromethene subunits is protonated and that the chloride counteranion is located in the cavity, hydrogen bonded by both calixpyrrole-like NHs (Figure 2, N2−H···Cl and N5−H···Cl).

For solution-phase studies carried out in acetone, full conversion to the diprotonated form, [**1**·2H]$^{2+}$, was effected by the addition of 90 molar equiv of H_2SO_4·30% SO_3 to ca. 9.3×10^{-3} mM solutions of **1**. Upon this addition, the intensity of the absorption band at 449 nm is seen to decrease, whereas that at 499 nm is seen to increase. The solutions also change color from yellow to pink. Significant shifts in the UV−visible absorbance spectrum were also seen upon the addition of tetrabutylammonium salts of chloride, bromide, and iodide to these latter pink solutions. Under the conditions of this experiment, full saturation (as determined from a lack of subsequent spectral response) was observed in the presence of ca. 13, 6, and 60 molar equiv of these three anions, respectively (Figure 3). While such findings are consistent with [**1**·2H]$^{2+}$ acting as a protonated "molecular box" and binding bromide anion with the greatest affinity, only in the case of iodide anion was a clean fit to a 1:1 binding equilibrium observed, as judged from Job plots and Benesi−Hildebrand analysis.[11] From the latter, an equilibrium constant of 25 500 ± 900 was calculated, corresponding to either direct binding of I^- by [**1**·2H]$^{2+}$ or displacement of hydrogen sulfate from [**1**·2H]$^{2+}$·$2HSO_4^-$ or [**1**·2H]$^{2+}$·HSO_4^-.

Control experiments involving the addition of Bu_4NHSO_4 to solutions of [**1**·2H]$^{2+}$, formed by the addition of 90 molar equiv

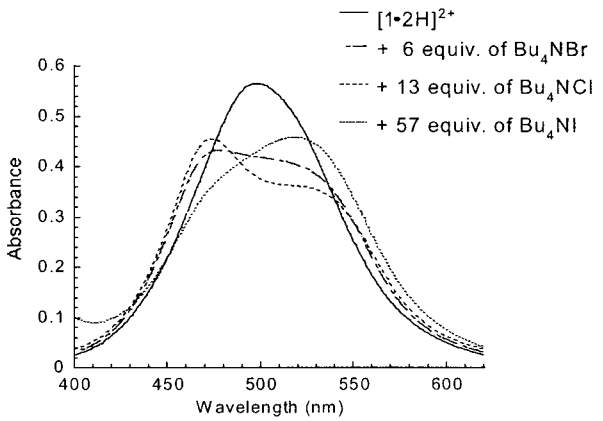

Figure 3. Absorpsion spectra of [**1**·**2**H]$^{2+}$, generated by the addition of 90 molar equiv of H_2SO_4·30% SO_3 to ca. 9.8×10^{-3} mM solutions of **1**, in the absence and presence of anions. The concentrations shown correspond to ones at which the addition of further molar equivalents induced no additional spectral changes.

of H_2SO_4·30% SO_3 to **1**, revealed that hydrogen sulfate is bound with a K_a for 1:1 complexation of 3500 ± 390 M^{-1}. On this basis[12] it is estimated that, to the extent it could be prepared in the absence of a coordinating counteranion, receptor [**3**·2H]$^{2+}$ would bind I^- in acetone solution with an affinity constant $K_a = 8 \times 10^7$ M^{-1}. While not established by the present solution-phase experiments, in analogy to what is seen in the solid state, it is assumed that 1:1 binding of iodide anion takes place within the positively charged, NH hydrogen bond donor rich cavity.

Current work is focused on probing in greater detail the molecular recognition characteristics of calix[6]phyrin **1** and in using analogous strategies to prepare other calix[*n*]phyrin-type macrocycles. In preliminary work, it has been found that a [3 + 3] cyclization product may be isolated as a side product in the reaction used to prepare **1**. X-ray diffraction analysis of this calix[9]phyrin **5** reveals the same deep cavity structure as present in **1** (Figure 4). Further studies of this new product are in progress.

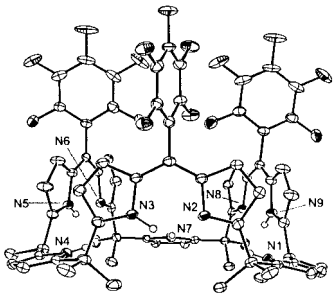

Figure 4. Ortep[10] view of **5** showing the heteroatom labeling scheme.

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Supporting Information Available: Crystallographic data, synthetic experimental for **1**, **2**, **3**, and **5**, and binding data for **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Sessler, J. L.; Gebauer, A.; Weghorn, S. J. In *The Porphyrin Handbook*; Kadish, K., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, 1999; Vol. 2, p 55.

(10) Thermal ellipsoids are scaled to the 40% probability level.

(11) While clean isosbestic behavior was observed through the addition of 13 and 1 molar equiv of anion in the case of chloride and bromide, respectively, deviations from such behavior, reflecting higher order receptor-to-anion binding stoichiometries or competition from hydrogen sulfate anions in the formation of, for example, [**1**·2H]$^{2+}$·$2X^-$ complexes, is observed at higher anion-to-receptor ratios. Even in the case of titrations of [**1**·2H]$^{2+}$·$2HSO_4^-$ with iodide, deviations from isosbestic behavior are seen at higher anion-to-receptor ratios.

(12) In calculating this value, the effects of possible sulfuric acid ionization were ignored. The 2 molar equiv of HSO_4^- generated by protonation of **1** were, however, accounted for. See Supporting Information.