Binding of Neutral Substrates by Calix[4]pyrroles

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Molecular recognition of neutral compounds presents a challenge in the area of supramolecular chemistry.[1] Binding of substrates such as short-chain alcohols[2] and simple monoamides[3] is particularly difficult because these molecules have few functionalized sites available for hydrogen bonding, and they lack the large hydrocarbon surfaces necessary to participate in efficient hydrophobic or $\pi-\pi$ stacking interactions. Association constants for neutral substrate/synthetic receptor complexes are thus generally modest,[4] even though the architectural complexity of the receptors is often high. Previously, we found that the R_8-calix[4]pyrroles (*i.e.*, *meso*-octaalkylporphyrinogens), readily made by acid-catalyzed condensation of pyrrole with symmetrical ketones,[5] act as receptors for anionic substrates such as fluoride, chloride, dihydrogen phosphate, and carboxylate.[6] In this paper, we report that these macrocycles also bind neutral substrates, both in the solid state and in solution.

Structural flexibility is a characteristic of the calix[4]pyrroles.[7] In the solid state, the known octamethyl derivative Me_8-calix[4]pyrrole (**1**) adopts a 1,3-alternate conformation in the absence of substrates and a cone conformation when bound to F^- or Cl^-.[6] On this basis, it was considered likely that **1** would modify its shape to accommodate different neutral substrates,[8] provided that these can act as hydrogen-bonding acceptors. In accord with this expectation, the calixpyrrole unit in **1**·2(MeOH) was found to assume a 1,3-alternate conformation in the solid state, as judged from single-crystal X-ray diffraction analysis[9] (Figure 1). Single molecules of the alcohol lie above and below the macrocycle, each one held in place by hydrogen bonds to two pyrrolic NH groups.[10] The four symmetry-equivalent H-bonds ($N_{pyrrole}\cdots O_{MeOH}$) are 3.155(4) Å long, a value which is very close to the $N_{pyrrole}\cdots O_{MeOH}$ distances (*ca.* 3.0−3.2 Å) found in a methanol complex of a tetrapyrrolic "expanded porphyrin."[2c] Further evidence that methanol is bound to **1**, rather than merely occupying space in the lattice, is given by the inward tilt of the pyrroles of **1**·2(MeOH). This effect compresses the "cross ring" $N_1\cdots N_{1C}$ and $N_{1A}\cdots N_{1B}$ distances by *ca.* 0.15 Å relative to those in free **1**,[6] although it is not sufficient to allow for a linear alignment of the three hydrogen-bonding atoms ($N_{pyrrole}-H\cdots O_{MeOH} = 152.1(4)°$).

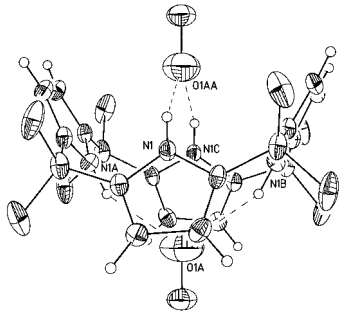
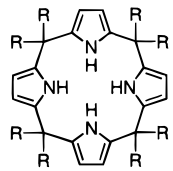


Figure 1. View of **1**·2(MeOH). Thermal ellipsoids are scaled to the 30% probability level.



Complex **1**·2(DMF) (DMF = *N*,*N*-dimethylformamide) has also been studied by X-ray crystallography.[11] As in the methanol adduct, individual symmetry-equivalent guests are found above and below the host, but in this case each amide is hydrogen bonded to *adjacent* pyrroles (Figure 2). The conformation of the calixpyrrole is therefore 1,2-alternate. Structurally characterized examples of 1,2-alternate calix[4]*arenes* are scarce,[12] and to our knowledge **1**·2(DMF) is the first calixpyrrole in this conformation to be unambiguously characterized. The $N_{pyrrole}\cdots O_{DMF}$ distances are 2.908(2) Å and 2.924(2) Å, with associated N−H···O angles of 167(2)° and 166(2)°, respectively. The unsaturated portion of the amide lies 3.363(3) Å above the plane of a third pyrrole ring (the planar twist angle between these two moieties is 7.1(1)°), leading to the proposal that a $\pi-\pi$ stacking interaction helps to stabilize **1**·2(DMF).

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(9) Crystal data for **1**·2(MeOH): yellow prisms from CH_2Cl_2/MeOH, tetragonal space group $I\bar{4}$, $Z = 2$, $a = 10.383(2)$ Å, $b = 10.383(2)$ Å, $c = 13.232(5)$ Å, $V = 1426.6(6)$ Å^3, $\rho_{calc} = 1.15$ g cm^{-1}, $F(000) = 536$. Final $R = 0.0787$, $R_w = 0.205$, GOF = 1.099 for 84 parameters. The NH proton of **1**·2(MeOH) was calculated in an idealized postion (N−H = 0.90 Å) with U_{iso} set to 1.2 × U_{eq} for the attached N atom.

(10) A similar structural motif has been observed in the adduct formed between an oxidized porphyrin and water: Golder, A. J.; Milgrom, L. R.; Nolan, K. B.; Povey, D. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1751−1753.

(11) Crystal data for **1**·2(DMF): colorless prisms from DMF, triclinic space group $P\bar{1}$, $Z = 1$, $a = 9.473(1)$ Å, $b = 9.573(1)$ Å, $c = 10.316(1)$ Å, $\alpha = 66.428(4)°$, $\beta = 80.987(5)°$, $\gamma = 72.025(4)°$, $V = 815.00(14)$ Å^3, $\rho_{calc} = 1.17$ g cm^{-1}, $F(000) = 312$. Final $R = 0.0390$, $R_w = 0.0952$, GOF = 1.061 for 291 parameters. The NH protons of **1**·2(DMF) were obtained from a ΔF map and refined with isotropic thermal parameters.

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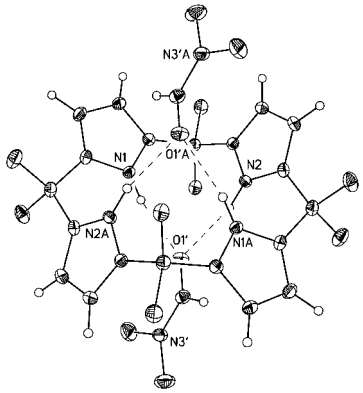

Figure 2. View of **1**·2(DMF). Thermal ellipsoids are scaled to the 30% probability level.

Table 1. Association Constants for **1** with Neutral Substrates[a]

substrate added	K_a (M^{-1})	substrate added	K_a (M^{-1})
methanol	12.7 ± 1.0	dimethyl sulfoxide	16.2 ± 1.1
ethanol	10.7 ± 0.7	1,2-dimethylimidazole	5.4 ± 0.3
benzyl alcohol	9.7 ± 0.7	acetone	2.2 ± 0.2
isopropyl alcohol	7.0 ± 0.4	nitromethane[b]	
sec-butanol	6.2 ± 0.4		
N-formylglycine ethyl ester	13.3 ± 1.0		
N,*N*-dimethylformamide	11.3 ± 0.8		
N,*N*-dimethylacetamide	9.0 ± 0.9		
1,1,3,3-tetramethylurea	2.2 ± 0.1		

[a] In benzene-d_6 at 298 K. For each titration, the concentration of **1** was held constant (at *ca.* 4×10^{-3} M) as aliquots of the substrate in benzene-d_6 (*ca.* 1 M) were added. [b] In this instance, the induced shifts in the NH proton(s) of **1** were too small (<0.15 ppm) to afford a reliable K_a value.

Octabenzylcalix[4]pyrrole (**2**) was prepared by reaction of pyrrole and 1,3-diphenylacetone,[13] and crystals suitable for X-ray study[14] were grown from acetone. The conformation of the macrocycle in **2**·2(acetone)·acetone$_{lattice}$ is 1,3-alternate (as in **1**·2(MeOH)), but the two acetone guests are both located on the *same* face of the ligand, held in place by single H-bonds (figure included in the Supporting Information). One of the acetone moieties lies much closer to the macrocycle than the other ($N_{pyrrole}\cdots O_{acetone} = 2.972(6)$ Å *vs* 3.359(6) Å), reflecting an almost collinear (177(5)°) arrangement of $N_{pyrrole}-H\cdots O_{acetone}$ atoms in the former case. In contrast, the N−H···O angle formed with the more distant ketone measures 159(4)°.

Proton NMR titrations were performed to quantify the binding characteristics of **1** in solution. Benzene-d_6 solutions of **1** were treated with the substrates listed in Table 1, while following the shifts in the NH proton(s) of the calixpyrrole. Association constants K_a (with respective errors) were then calculated using the EQNMR computer program.[15] For all substrates, the data were best fit to a 1:1 binding model,[16] despite the exclusively 2:1 ratio seen in the crystal structures. Calixpyrrole **1** was found to have a measurable affinity for all of the studied substrates except nitromethane, which is a notoriously poor hydrogen-bond acceptor.[17] A trend is evident across both the alcohol and amide series, in which the association constants uniformly decrease with increasing bulk near the substrate oxygen atom. Methanol is therefore bound most strongly among the alcohols, with $K_a = 12.7 \pm 1.0$ M^{-1},[18] the two primary alcohols cluster about $K_a \approx 10$ M^{-1}, and the secondary alcohols fall near $K_a \approx 7$ M^{-1}. For the amides, the K_a values are sensitive to changes in substituents on the nitrogen atom and on the carbonyl carbon. Thus, receptor **1** has a higher affinity for a secondary formamide (*N*-formylglycine ethyl ester) than for a tertiary one (DMF) and forms a more robust complex with DMF than with *N*,*N*-dimethylacetamide. The low K_a value of 2.2 ± 0.1 M^{-1} recorded for 1,1,3,3-tetramethylurea indicates that the presence of *two* sets of *N*-bound methyl groups severely hinders approach of the amide oxygen atom to the calixpyrrole pseudocavity.[19] The molecular structure of **2**·2(acetone)·acetone$_{lattice}$ demonstrates that the carbonyl portion of acetone can be accessed by the NH groups of *bulky* calixpyrrole **2**; thus, the weak solution binding of acetone by unhindered **1** ($K_a = 2.2 \pm 0.2$ M^{-1}) cannot be explained on steric grounds. In this case, adventitious water could not be completely removed from the solution used in the titrations, and the presence of this competing H-bonding material could account for the low apparent K_a.

The present results confirm that the calixpyrroles, very simple molecules to make, can be used to bind neutral species both in solution and in the solid state. Planned extensions to the calixpyrrole "library" include electron-poor calixpyrroles with improved H-donor capability, chiral calixpyrroles to effect resolutions, and calixpyrrole dimers for binding of difunctional substrates.

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Supporting Information Available: Details of the synthesis and characterization of **2**, a listing of observed and calculated binding profiles for NMR titrations, a Job plot, and X-ray experimental details, atomic positional parameters, bond lengths and angles, and atomic thermal parameters for **1**·2(MeOH), **1**·2(DMF), and **2**·2(acetone)·acetone$_{lattice}$ (60 pages). See any current masthead page for ordering and Internet access instructions.

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(13) Compound **2** is a new substance. See the Supporting Information for synthetic experimental and characterization data.

(14) Crystal data for **2**·2(acetone)·acetone$_{lattice}$: colorless prisms from acetone, triclinic space group *P*1, $Z = 2$, $a = 9.832(2)$ Å, $b = 18.535(5)$ Å, $c = 19.910(6)$ Å, $\alpha = 69.96(2)°$, $\beta = 86.49(2)°$, $\gamma = 86.70(2)°$, $V = 3399.6(15)$ Å^3, $\rho_{calc} = 1.18$ g cm^{-1}, $F(000) = 1296$. Final $R = 0.0766$, $R_w = 0.217$, GOF = 1.002 for 846 parameters. The NH protons of **2**·2(acetone)·acetone$_{lattice}$ were obtained from a ΔF map and refined with isotropic thermal parameters.

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(16) A Job analysis for **1** with DMF confirmed the 1:1 binding stoichiometry in benzene-d_6 (see the Supporting Information). Complexes of 2:1 guest−host stoichiometry with $K_1 \gg K_2$ may also be formed: Lenkinski, R. L.; Elgavish, G. A.; Reuben, J. *J. Magn. Reson.* **1978**, *32*, 367−376.

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(18) For the binding of **2** with methanol, $K_a = 4.1 \pm 0.5$ M^{-1} in benzene-d_6.

(19) *A priori*, tetramethylurea was expected to be the most strongly bound of the amides based upon electronic considerations (see ref 17).