A cylindrical cavity with two different hydrogen-binding boundaries: the calix[4]arene skeleton screwed onto the *meso*-positions of the calix[4]pyrrole†

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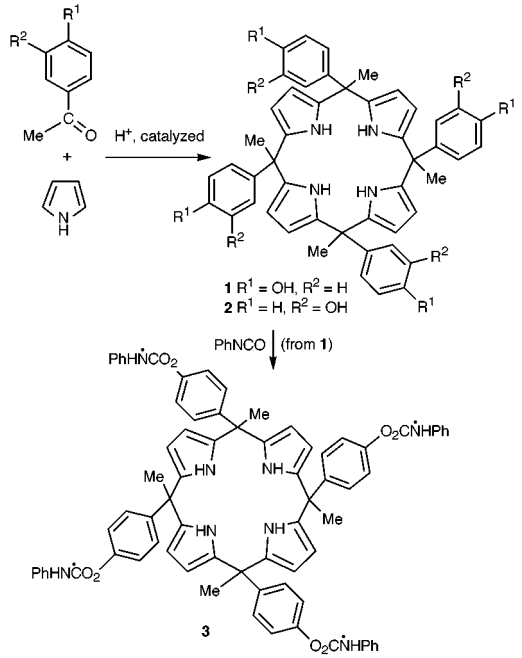
The acid-catalyzed condensation of pyrrole with *p*- or *m*-hydroxyacetophenone led to the formation of *meso*-tetramethyltetrakis(hydroxyphenyl)calix[4]pyrroles occurring in three isomeric forms, with the cone conformer displaying topologically variable multi-site or multi-point surfaces for binding neutral or anionic substrates.

There has been a recent explosive development in the realm of molecular recognition of polar, and often uncharged, multifunctional organic molecules in which multi-point hydrogen bonds provide stabilization.[1–3] Multi-point hydrogen bonding molecules are appropriate devices for the maintenance of the function and structure of complex biomolecules.[4] Many of them are bifunctional molecules, *i.e.* amino acids[5a] and steroids,[5b,3c] all requiring bifunctional hosts which have two chemically different binding areas. The present report deals with the discovery of a class of compounds particularly appropriate to play a role in multi-point or multi-site host–guest interactions. An important factor in any artificial receptor is simplicity of synthesis, and this is the case reported here. The general synthetic procedure is shown in Scheme 1. The acid-catalyzed condensation of pyrrole with *p*- or *m*-hydroxyacetophenones led to the formation of the expected *meso*-octaalkylporphyrinogen derivatives[6,7] **1**‡ and **2**,† occurring in three isomeric forms (the cone **a**, the partial cone **b** and the 1,2 alternate conformation **c**) in a 7:2:1 ratio.



Scheme 1

The separation of the three isomers was performed either by crystallization or chromatography.†‡ The identification of the three isomers is conveniently made by ^{1}H NMR spectroscopy. Compound **1** in its cone conformation **a** is associated into dimers or trimers, the molecular complexity being determined by the guest molecule.[1–3,8] In the presence of hydrogen-binding substrates such as DMF or acetic acid, the isomer **1a** is assembled into closed two-basket cavity dimers,[1] **1a**·DMF (Fig. 1),§ or into cyclic trimeric units, **1a**·AcOH (Fig. 2),§ displaying C_3 symmetry. The trimeric cavity hosts nine molecules of AcOH, three of them being associated to the porphyrinogen moieties while the other six establish an intermolecular hydrogen bonding network with other trimers.

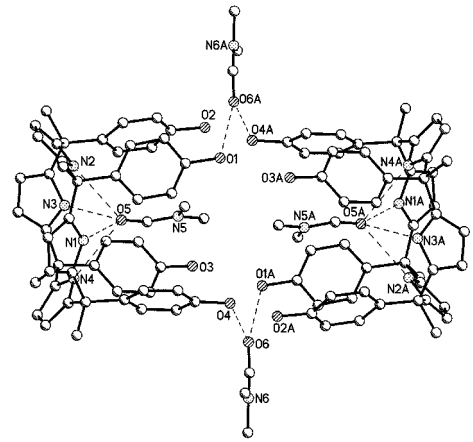


Fig. 1 A plot of **1a**·DMF linked into pairs by hydrogen bonds. Selected bond distances (Å) and angles (°): N–H···O [H···O$_{av}$ = 2.15, N···O$_{av}$ = 3.013(7), N-H···O$_{av}$ = 170.0]. Letter *A* denotes the symmetry transformation −*x*, −*y*, −*z*.¶

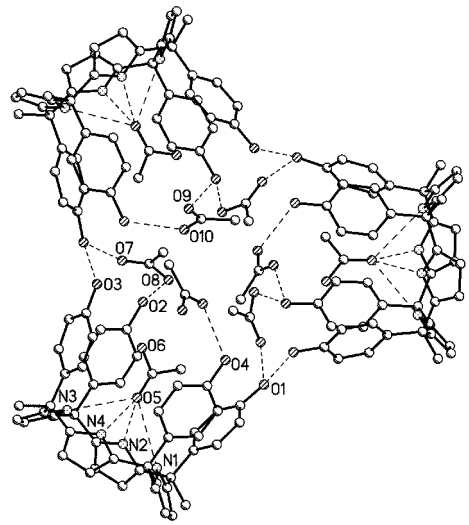


Fig. 2 A plot of **1a**·AcOH associated into trimers by hydrogen bonds and viewed down the three-fold axis. Selected bond distances (Å) and angles (°): N–H···O [H···O$_{av}$ = 2.26, N···O$_{av}$ = 3.140(5), N–H···O$_{av}$ = 174.0].¶

† Details of the synthesis and characterisation of **1**–**3** are available from the RSC web site, see http://www.rsc.org/suppdata/cc/1999/2413/

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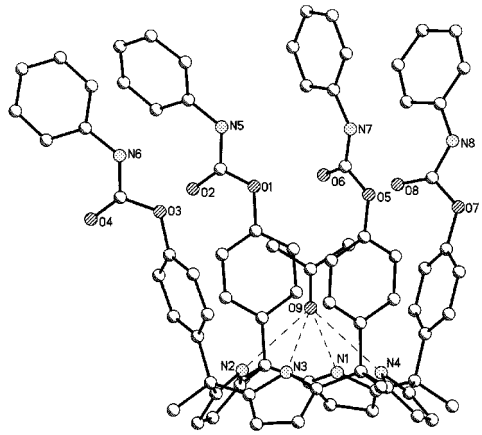

Fig. 3 A plot of **3** showing the interaction with the inner acetone. Selected bond distances (Å) and angles (°): N–H···O [H···O$_{av}$ = 2.26, N···O$_{av}$ = 3.12(1), N–H···O$_{av}$ = 168.1].¶

Therefore the overall structure of **1a**·AcOH is a tridimensional cylindrical cavity. Compound **1a** has been converted into the corresponding *N*-phenylcarbamate **3**,† which was crystallized from acetone (Fig. 3).§ The structure of **3** shows the same conformation of the monomeric unit in **1**. The guest molecules, except those bonded to the porphyrinogen moiety,[9] are loosely bonded and easily lost on gentle heating *in vacuo* or in solution, as shown by the ^{1}H NMR spectra.

Unlike other attempts,[10] our approach maintained in **1**–**3** both the OH and NH surfaces associated with the cone conformation of calix[4]arene and calix[4]pyrrole, thus, depending on the tunable spacer, being appropriate hosts of functionalizable molecules.

The overall structures of **1**–**3** deserve some additional comments concerning the calix[4]arene fragment, since the calix[4]pyrrole moieties are structurally very close to that of the well known *meso*-octaalkylporphyrinogens.[7] In our case, we are dealing in fact with an upside down flexible calix[4] unit cavity, the connectivity between the phenol groups being assured through the *p*-carbons of the phenyl substituent rather than through the *o*-carbons. In the three compounds the most significant structural parameters related to the monomeric building block are very close: (*i*) the planarity of the N_4 and O_4 set of atoms; (*ii*) the distance between the two parallel O_4 and N_4 planes [5.482(4), **1a**·DMF; 5.492(7), **1a**·AcOH; 5.53(2) Å, **3**]; (*iii*) the size of the slightly elliptical cavity, which can be roughly estimated from the opposite oxygen's distance [9.915(7) and 8.14(1), **1a**·DMF; 10.146(5) and 8.435(6), **1a**·AcOH; 10.478(9) and 8.19(1) Å, **3**]. The general synthesis outlined in Scheme 1, with an appropriate choice of acetophenone derivatives and the various conformations associated both with the porphyrinogen and the calix[4]arene moieties, will allow us to obtain topologically variable (tubes, cylinders *etc.*) multi-site or multi-point surfaces for binding neutral or anionic substrates.

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Notes and references

‡ *Synthesis* of **1**: MeOH (10 ml) was added to a solution of *p*-hydroxyacetophenone (80.0 g, 588 mmol) and pyrrole (40 cm^3, 588 mmol) in MeOH (200 cm^3). The reaction was refluxed for 3 h and then quenched with water (700 cm^3). A yellow solid precipitated, which was collected and dissolved in Et_2O (400 cm^3). A black residue was filtered off and the solution was evaporated to dryness to give a light pink powder, which was dried *in vacuo* (10^{-7} Mbar) at 90 °C for 24 h (65.3 g, 60%). The ^{1}H NMR spectrum of this powder showed a mixture of the three isomers **1a**–**c** in a 7:2:1 ratio. Each isomer was isolated by flash chromatography (CH_2Cl_2–*n*-hexane–MeOH, 8:1.4:0.6). All the fractions were dried *in vacuo* (10^{-7} Mbar) at 90 °C for 24 h. The third fraction [R_f = 0.193 (UV)] contained the major isomer **1a**: δ_H (acetone-d_6, 400 MHz, 298 K) 8.74 (s br, 4H, NH),8.15(s br, 4H, OH), 6.76 (d, *J* 8.8, 8H, ArH), 6.65 (d, *J* 8.8, 8H, ArH), 5.94 (d, *J* 2.45, 8H, C_4H_2N), 1.8 (s, 12H, CH_3). The major isomer **1a** (30.0 g) was also isolated by crystallization of the isomeric mixture from AcOH (19.4 g, 59%); δ_H(THF-d_8, 200 MHz, 298 K) 8.35 (s br, 4H, NH), 6.90 (d, *J* 8.8, 8H, ArH), 6.56 (d, *J* 8.8, 8H, ArH), 5.63 (d, *J* 2.45, 8H, C_4H_2N), 1.88 (s, 12H, CH_3 overlapping with s, 3H, CH_3COOH). Acetic acid elimination from **1a**·AcOH was carried out by azeotropic distillation with Bu_2O. Crystals suitable for X-ray diffraction, grown from a THF–AcOH solution, contain AcOH in a **1a**:AcOH = 1:3 molar ratio. Crystals of **1a**·DMF suitable for X-ray analysis and containing DMF in a **1a**: DMF = 1:3 molar ratio were obtained from a DMF–THF solution of the isomeric mixture; δ_H(THF-d_8, 200 MHz, 298 K) 9.14 (s br, 4H, NH), 8.12 (s br, 3H, CHO), 6.69 (d, *J* 8.8, 8H, ArH), 6.48 (d, *J* 8.8, 8H, ArH), 5.90 (d, *J* 2.6, 8H, C_4H_2N),2.70 (s br, 18H, CH_3), 1.75 (s, 12H, CH_3); (THF-d_8, 200 MHz, 330 K) 9.12 (s br, 4H, NH), 7.91 (s br, 3H, CHO), 6.70 (d, *J* 8.8, 8H, ArH), 6.48 (d, *J* 8.8, 8H, ArH), 5.90 (d, *J* 2.6, 8H, C_4H_2N), 2.60 (s, 12H, CH_3), 2.25 (s br, 6H, CH_3), 1.76 (s, 12H, CH_3).

§ *Crystal data* for **1a**·DMF: $C_{48}H_{44}N_4O_4{\cdot}C_4H_8O{\cdot}3C_3H_7NO$, *M* = 1032.26, monoclinic, space group $P2_1/c$, *a* = 10.960(2), *b* = 21.081(4), *c* = 24.039(5) Å, β = 90.42(3)°, *V* = 5554.0(19) Å^3, *Z* = 4, D_{calc} = 1.235 g cm^{-3}, *F*(000) = 2208, λ(Mo-Kα) = 0.71070 Å, μ(Mo-Kα) = 0.082 mm^{-1}; crystal dimensions 0.20 × 0.13 × 0.10. Diffraction data were collected on a mar345 Imaging Plate at 143 K. For 3355 observed reflections [$I > 2\sigma(I)$] and 686 parameters, the conventional *R* is 0.0942 (*wR2* = 0.2662 for 6736 independent reflections). For **1a**·AcOH: $C_{48}H_{44}N_4O_4{\cdot}C_4H_8O{\cdot}3C_2H_4O_2$, *M* = 993.13, trigonal, space group $P3_2$, *a* = 20.054(5), *b* = 20.054(5), *c* = 11.079(3) Å, *V* = 3858.6(17) Å^3, *Z* = 3, D_{calc} = 1.282 g cm^{-3}, *F*(000) = 1584, λ(Mo-Kα) = 0.71070 Å, μ(Mo-Kα) = 0.089 mm^{-1}; crystal dimensions 0.25 × 0.23 × 0.22. Diffraction data were collected on a mar345 Imaging Plate at 143 K. For 4394 observed reflections [$I > 2\sigma(I)$] and 659 parameters, the conventional *R* is 0.0459 (*wR2* = 0.1105 for 5796 independent reflections). For **3**: $C_{76}H_{64}N_8O_8{\cdot}5C_3H_6O$, *M* = 1507.74, monoclinic, space group $P2_1/c$, *a* = 11.3580(19), *b* = 19.927(3), *c* = 35.860(4) Å, β = 94.400(12)°, *V* = 8093(2) Å^3, *Z* = 4, D_{calc} = 1.238 g cm^{-3}, *F*(000) = 3200, λ(Mo-Kα) = 0.71070 Å, μ(Mo-Kα) = 0.083 mm^{-1}; crystal dimensions 0.17 × 0.13 × 0.06. Diffraction data were collected on a KUMA CCD at 143 K. For 4534 observed reflections [$I > 2\sigma(I)$] and 1009 parameters, the conventional *R* is 0.1119 (*wR2* = 0.3308 for 9923 independent reflections). CCDC 182/1457.

¶ Hydrogens and some solvent molecules have been omitted for clarity, while labels have been used only for oxygen and nitrogen atoms.

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11 For the structural parameters, see the Captions of the Figures in the supplementary data (see note †).

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