Unusual Host–Guest π-Arene···H Bonding in a 'Hooded' Cavitand: the First Solid-state Structure of a Calix[4]resorcinarene with Underivatised Hydroxy Groups

David A. Leigh,*[a] Patrick Linnane,[a] Robin G. Pritchard[a] and Graham Jackson[b]

[a] *Department of Chemistry, University of Manchester Institute of Science and Technology, PO Box 88, Manchester, UK M60 1DQ*

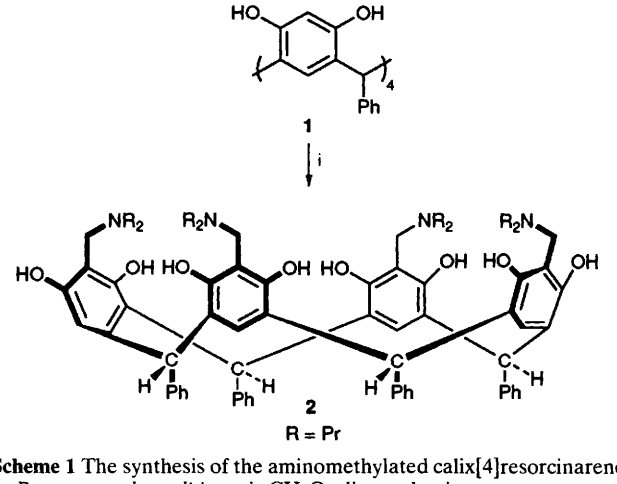
[b] *Exxon Chemical Limited, PO Box 1, Milton Hill, Abingdon, Oxfordshire, UK OX13 6BB*

Treatment of phenylcalix[4]resorcinarene **1** with dipropylamine and paraformaldehyde leads to the formation of a deep cleft cavitand **2**, in which the cavity is extended by a collar of exquisite intramolecular donor–acceptor hydrogen bonding networks which all proceed in the same direction around the upper rim imparting chirality on the individual cavitands; the amine groups involvement in intramolecular hydrogen bonding draws the *N*-alkyl substituents inward to form an encapsulating 'hood' over an included CH_2Cl_2 guest molecule.

In the early 1980s Cram coined the term 'cavitand' to describe synthetic molecules possessing an enforced cavity[1,2] of a size large enough to accommodate other molecules, atoms or ions. Calix[4]resorcinarenes (*e.g.* **1**) are conformationally mobile macrocycles generally possessing ephemeral rather than permanent cavities. However, bridging the hydroxy groups of adjacent aromatic rings of such structures with covalent linkages of one or two atoms leads to rigid, bowl-shaped receptors capable of forming supramolecular complexes with many different guest species.[3–5]

We have recently prepared a new class of extended deep cleft cavitands (*e.g.* **2**) where the rigidity of the cavity is enforced by non-covalent forces, namely donor–acceptor hydrogen bonding networks.[6] Here we report the solid-state of **2** which confirms both the geometry of the cavity and the nature of the hydrogen-bonding network. Included in each cavitand is a molecule of methylene chloride. One of the hydrogen atoms of the included methylene chloride points directly toward the centre of the aromatic ring of one of the resorcinal units of the calixarene, forming a strong π-arene···H bond (C···ring centroid 3.68 Å) which stabilises the host–guest complex. Also clathrated in the structure is an equal number of well ordered acetone molecules which are located outside the calix[4]resorcinarene cavities and not hydrogen bonded to any other molecules. Fig. 1 shows the solid-state structure of **2** from a side and top view with both included methylene chloride and clathrated acetone.

The aminomethylated phenylcalix[4]resorcinarene **2** was prepared by condensation of **1** with dipropylamine and formaldehyde (Scheme 1).† The tetra-substituted Mannich base was recrystallised from a 1 : 1 solution of methylene chloride and acetone to give colourless single crystals suitable for study by X-ray crystallography‡ and which proved to be a 1 : 1 : 1 clathrated inclusion complex of **2**, methylene chloride and acetone.



Scheme 1 The synthesis of the aminomethylated calix[4]resorcinarene **2**. *Reagents and conditions*: i, CH_2O, dipropylamine.

Although each cavitand is chiral by virtue of the helical nature of its cavity, the four molecules in the unit cell form a racemic mixture because of the centrosymmetric space group. The two-tiered hydrogen bonding network extends the cone conformation from 6 to 7.5 Å. The upper tier of intra-residue hydrogen bonding, between the hydroxy group of the resorcinol unit and the nitrogen of the aminoalkyl group (OH···N) are very strong (O···N 2.48–2.54 Å) and unique to this class of cavitand. The lower tier, between the hydroxy groups on adjacent aromatic rings almost certainly occurs to enforce the cavity in other calix[4]resorcinarenes with underivatised hydroxy groups (although to our knowledge there are no crystal structures or experimental evidence actually confirming this). However, in these other structures there is virtually no driving force for the hydrogen bonding networks to proceed round the rim in the same direction.[6] In the aminomethylated calix[4]resorcinarene **2**, if the hydrogen bonding networks are not unidirectional within each molecule a hydrogen bond is lost and therefore those structures are of significantly higher energy. This imparts both a helical twist to the cavity and greatly increases the rigidity of the cone conformation, illustrated by the strength of the inter-residue OH···O hydrogen bonding (O···O 2.68–2.76 Å) which are maximised by alternate hydroxy groups acting as both hydrogen bond donors and acceptors, preventing unfavourable electon density build up on the oxygen atom. Such donor–acceptor hydrogen bonding networks occur extensively throughout nature, particularly in determining the conformational and binding properties of oligo- and poly-saccharides, proteins, and nucleic acids.

One molecule of methylene chloride is bound within each calixarene cavity. Although methylene chloride has previously been shown to form inclusion complexes with resorcinol-based calixarenes,[4,5] this is the first example of such a complex being stabilised by π-arene···H–C hydrogen bonds. A methylene chloride hydrogen is bonded in this way to one of the aromatic rings of the cavity with a ring centroid···H distance of 2.84 Å. Three of the four aminomethylated side chains cover the top of the cavity almost completely encapsulating the halogenated hydrocarbon within the cavity. A protruding chlorine atom forces the final chain away from the top face.

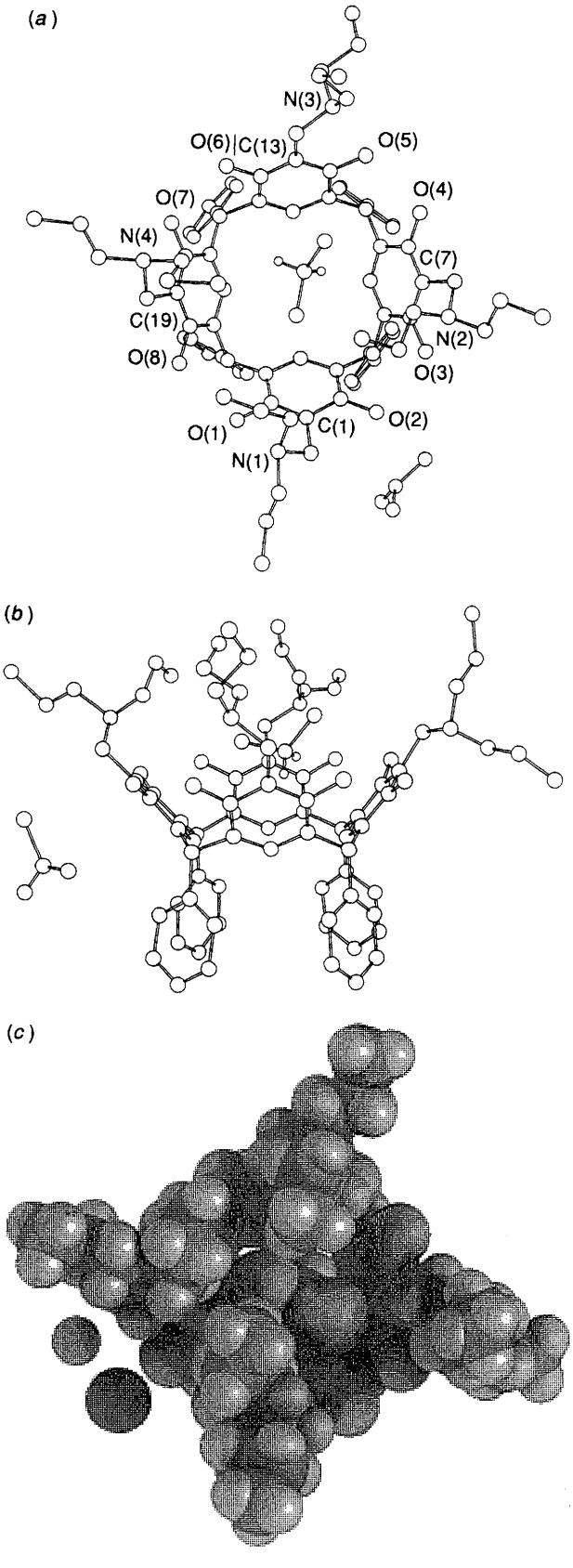
An unusual feature of this crystalline composite is that it is both an inclusion complex and a clathrate. The acetone present in the clathrate is not hydrogen bonded, presumably because all the potential hydrogen bond donors in the structure are all satisfied by strong intramolecular networks.

NMR experiments show that the intramolecular hydrogen bonding networks and the resulting helical nature of the cavity of **2** and other aminomethylated calix[4]resorcinarenes are maintained in nonpolar solvents such as [$^2H_8$]toluene and $CDCl_3$§. The ability of these 'hooded cavitands' to form complexes in solution and the solid state is currently under investigation in our laboratories. Initial results reveal that **2** is able to discriminate very effectively between the three isomeric phthalic acids [$C_6H_4(CO_2H)_2$] in solution, solubilising only the σ-substituted derivative in $CDCl_3$. NMR studies

reveal a fast exchange regime of free vs. bound guest at 298 K. Attempts to utilise the helical chirality of the hosts to discriminate between the different enantiomers of amino acid esters in solution has thus far proved unsuccessful.

We gratefully acknowledge support of this work from the SERC, Nestlé (CH) and Exxon Chemical Ltd.

Received, 28th May 1993; 3/03054G



Footnotes

† To a stirred solution of phenylcalix[4]resorcinarene **1** (198 mg, 0.25 mmol) in ethanol (15 ml) was added paraformaldehyde (45 mg, 1.5 mmol) and dipropylamine (151 mg, 1.5 mmol). On addition of the amines the solution turned a deep burgundy-colour and was brought to reflux; an orange precipitate began to form after a couple of hours. After 24 h, TLC indicated that no starting material remained. the precipitate was filtered off and washed with a small quantity of cold ethanol before being subjected to flash column chromatography (silica gel, ethyl acetate as eluent) to give **2** (260 mg, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.61 (s, 24H, 8 × CH_3), 1.48 (m, 16H, 4 × $N(CH_2CH_2CH_3)_2$), 2.45 [bt, 16H 2 × $N(CH_2CH_2CH_3)_2$], 3.88 (AB system, 8H, 4 × $ArCH_2N$), 5.95 (s, 4H, Ar_3CH), 6.67 (s, 4H, arH), 7.05 (t, 4H ArH, J_o 10 Hz J_m 2 Hz, H-11), 7.13 (t, 8H ArH J_o 10 Hz J_m 2 Hz, H-9 and H-13), 7.27 (d, 8H ArH, J_o 10 Hz, H-10 and H-12); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.73 (8 × CH_3), 19.26 [4 × $N(CH_2CH_2CH_3)_2$], 39.60 (Ar_3CH C-25), 52.88 [4 × $N(CH_2CH_2CH_3)_2$], 55.37 ($ArCH_2N$) C-29), 107.83 (C-1), 122.93–123.67 (C-3, C-5), 125.33 (C-84), 127.34 (C-83 and C-85), 128.03 (C-4), 129.20 (C-82 and C-86), 143.37 (C-81), 151.67–154.37 (C-2, C-6); MS *m/z* calc. for $C_{80}H_{100}N_4O_8$: 1244, found 1244.

‡ *Crystal data*: **2** $C_{80}H_{100}N_4O_8 \cdot CH_2Cl_2 \cdot C_3H_6O$, M = 1388.7, monoclinic, space group $P2_1/n$, a = 12.752(8), b = 42.83(1), c = 15.063(5) Å, β = 112.36(9)°, V = 7608(8) Å^3, D_x = 1.212 g cm^{-3}, Z = 4; 12 909 reflections measured, 12 211 unique (R_{int} = 0.032), 2065 observed with $I > 3\sigma(I)$. Diffractor Rigaku AFC6S, $2\theta_{max}$ = 48°, Mo-Kα radiation, α = 0.71069, T = 296. The structure was solved by direct-methods (SHELLXS-86[7]) and subjected to least-squares refinement (TEXSAN[8]) to yield final residuals of R = 0.093 and R_w = 0.085 for 491 parameters. The chlorine atoms and some of the carbons in the isopropyl chains were subjected to anisotropic refinement; the remainder were treated isotropically. The phenyl rings were constrained to be regular hexagons and all hydrogens attached to carbons were placed in chemically reasonable positions.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1, 1994.

§ The ^{13}C NMR spectra of the aminomethylated calix[4]resorcinarenes in nonpolar solvents possess two distinct signals for the dissimilar phenyl ring carbon atoms attached to the hydroxy groups.In polar solvents, where the intramolecular hydrogen bonding networks are broken and the carbon atoms are thus in identical environments, only one signal is observed for these nuclei. Similarly, the methylene protons attached to the aromatic ring appear separated as an AB system in the ^{1}H NMR spectra of the aminomethylated calix[4]resorcinarenes in nonpolar solvents and as a simple, sometimes broad, singlet in the analogous spectra in polar solvents.

References

1 J. Moran, S. Karback and D. Cram, *J. Am. Chem. Soc.*, 1982, **104**, 5826.
2 D. Cram, *Science*, 1983, **219**, 1177.
3 D. Cram and S. Karbach, Y. Kim, L. Baczynskyj, K. Martin, R. Sampson and G. Kalleymeyn, *J. Am. Chem. Soc.*, 1988, **110**, 2554.
4 J. Tucker, C. Knobler, K. Trueblood and D. Cram, *J. Am. Chem. Soc.*, 1989, **111**, 3688.
5 L. Tunstad, J. Tucker, E. Dalcanale, J. Weiser, J. Bryant, J. Sherman, R. Helgeson, C. Knobler and D. Cram, *J. Org. Chem.*, 1989, **54**, 1305.
6 D. Leigh, P. Linnane, A. Murphy and G. Jackson, in preparation.
7 G. Sheldrick, SHELLXS-86, *Crystallographic computing 3*, pp. 175, OUP, Oxford, 1985.
8 Molecular Structure Corporation, TEXSAN, Texray Structure Analysis Package, 1985, MSC 3200A Research Forest Drive, The Woodlands, TX 77381, USA.

Fig. 1 Three alternative views (*a*, *b*, *c*) of the calix[4]resorcinarene **2** to show the bound dichloromethane. Selected bond lengths (Å) for **2**: O(1)–C(2), 1.42(2); O(2)–C(6), 1.37(2); O(3)–C(8), 1.37(2); O(4)–C(12), 1.39(2); O(5)–C(14), 1.38(2); O(6)–C(18), 1.41(2); O(7)–C(20), 1.35(3); O(8)–C(24), 1.40(2); N(1)–C(29), 1.51(3); N(2)–C(30), 1.50(2); N(3)–C(31), 1.49(3); N(4)–C(32), 1.50(3) and selected bond angles (°) for **2**: C(29)–N(1)–C(33); 104(2); C(29)–N(1)–C(36); 109(2); C(30)–N(2)–C(39); 115(1); C(30)–N(2)–C(42); 113(1); C(31)–N(3)–C(45); 112(1); C(31)–N(3)–C(48); 105(1); C(32)–N(4)–C(51); 105(1); C(32)–N(4)–C(54); 108(1); C(1)–C(29)–N(1); 109(2); C(7)–C(30)–N(2); 108(1); C(13)–C(31)–N(3); 113(2); C(19)–C(32)–N(4); 111(2); C(3)–C(27)–C(91); 119(1); C(5)–C(25)–C(81); 114(1); C(15)–C(26)–C(61); 118(1); C(17)–C(28)–C(71); 112(1).