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Crystal and molecular structure of 1,3-(dis/tal) derivatives of *p-tert*-butyl calix[4]arene. Evidence for conformational control and self-inclusion involving weak C-H ... π interactions

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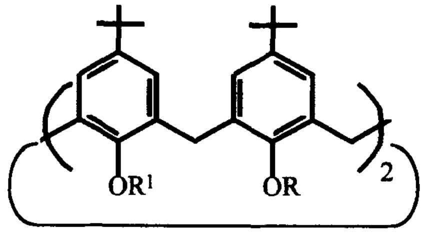
X-Ray crystallographic analyses of four *p-tert*-butylcalix[4]arenes in which two 1,3-(distal)phenolic groups on the lower rim have been derivatised with cyanomethyl, amino ester and alkyl acetate residues, are reported. Intramolecular hydrogen bonding between the free phenolic groups and their proximal ethereal oxygen atoms is evident in all four compounds. With the exception of the ethyl ester, these calixarenes adopt very distorted cone conformations in the solid state. The ethyl ester adopts a much less distorted cone conformation with the distinguishing feature of self-inclusion of an ethoxy residue of one ester group on the lower rim within the hydrophobic cavity of a neighbouring molecule within the crystal. Factors which control the conformations of these molecules are discussed.

INTRODUCTION

Introduction of two substituents on the phenolic groups of the lower rim of calix[4]arenes *via* alkylation using a moderately strong base occurs preferentially at the 1,3-(distal) positions[1] (Equation 1). This regioselectivity can be explained on the grounds that the more stable anion formed from the product of the first alkylation should be that resulting from deprotonation of the opposite (distal) phenolic group where stabilisation by *two* intramolecular hydrogen bonds is possible; steric factors may also favour the distal position. 1,3-(Distal) derivatisation has been used to prepare various calix[4]arene diethers, diesters, amino esters, cyanomethyl and pyridinylmethyl derivatives. Several of these compounds are useful precursors for the synthesis of other, more extensively derivatised calixarenes, including compounds with crown and azacrown bridges. Because of their usefulness in calixarene modification[1,2], we have undertaken a study of the crystal and molecular structures of several 1,3-(distal) derivatives using X-ray diffraction to determine the influence of substituent type on the conformations adopted in the solid state.

In a recent paper we described the crystal and molecular structure of the biscyanomethyl derivative 1[1b]. We have now extended the list of solid state structures to include the bis-ethyl ester **2**, the bis-*tert*-butyl ester **3** and the bisamino ester **4**. ^{1}H-NMR measurements established that all four derivatives exist in stable cone conformations in solution at room temperature.



1 $R = CH_2CN$ $R^1 = H$
2 $R = CH_2CO_2Et$ $R^1 = H$
3 $R = CH_2CO_2Bu^t$ $R^1 = H$
4 $R = CH_2CH_2N(CH_2CO_2Bu^t)_2$ $R^1 = H$
5 $R = R^1 = CH_2CO_2Et$
6 $R = R^1 = CH_2CONEt_2$

RESULTS AND DISCUSSION

In all four compounds the aromatic rings bearing the two substituents are labelled A and C while the two free phenolic rings are labelled B and D. The interplanar angles between each pair of distal rings define the calix conformations (**Table 1**). In **1**, for example, rings A and C bearing OCH_2CN moieties are almost parallel to each other (interplanar angle 13°) while rings B and D are close to normal (interplanar angle 102°); all rings are tilted so that their *tert*-butyl groups on the upper rim are pitched away from the calix cavity. Table 2 contains the proximal O ... O distances. The principal structural feature common to all four molecules is the presence of the cone conformation, albeit with differing degrees of distortion from the four-fold symmetry of the parent *tert*-butyl-calix[4]arene in the solid state.

The actual conformation adopted by any calixarene in the solid state is clearly the result of a subtle interplay of intramolecular interactions, intermolecular packing effects and the presence of appropriate solvent molecules to fill what might otherwise have been voids in the crystal lattice. For the calixarene derivatives under discussion here, a common intramolecular interaction is the existence of hydrogen bonds between the phenolic groups and the proximal ethereal oxygen atoms. The hydrogen atoms in these bonds were located in compounds **1** and **4**. In compounds **2** and **3** the O ... O separations are entirely consistent with the presence of hydrogen bonds, although the hydrogen atoms could not be located because of the paucity of data for these two compounds. However, hydrogen bonding in itself is not sufficient to ensure that all four compounds adopt similar distorted cone conformations. In fact, there are several fully substituted calix[4]arenes which lack intramolecular hydrogen bonds but which adopt distorted cone conformations in the solid state[3]. The tetraethyl ester **5**[3] and tetra diethyl amide **6**[4] are notable examples.

A further illustration of interplay between conformation-determining factors is the spatial relationship within each pair of aromatic rings AC and BD. The distortion is greatest in dinitrile **1** where the almost parallel disposition of rings A and C leads to a more closed cavity at the upper rim. Compounds **3** and **4** share the distortion of **1** but to a lesser extent. In contrast, diethyl ester **2**, with interplanar angles of 49 and 72° for rings AC and BD, respectively, adopts a much more open, regular cone-shaped conformation which enclathrates the ethoxy residue of one of the ester groups of a neighbouring molecule (Figures 1a, 1b). This self-inclusion (with repetition along the b-glide direction) produces a one-dimensional polymeric chain with the molecules aligned in a zig-zag fashion and alternating in opposite directions between successive chains. In compound **3** (Fig. 2), on the other hand, in which the relatively small ethyl residues of ester **2** are replaced by bulky *tert*-butyl residues, this form of self inclusion is precluded on steric grounds. The upper rim calix cavity of **3**, however, enclathrates a small solvent molecule, dichloromethane, a guest which forces the calixarene to assume a more open distorted cone, though not to the same extent as that of the ethyl ester **2**. In contrast, compound **4** (Fig. 3), which also possesses bulky *tert*-butyl residues on rings A and C, does not have any solvent guest molecules in the calix cavity. Here the phenolic rings are almost normal to one another (interplanar angle 87°) and while the substituted rings are opened out slightly (29°) from being parallel, the arrangement still precludes the encapsulation of a solvent molecule, as is also the case with dinitrile **1**.

Table 1 Interplanar Angles in **1–4**[a]

	1	2	3	4
Angles A/C	13	49	41	29
Angles B/D	102	72	94	87

[a]Rings A and C are derivatised rings Rings B and D are phenolic

Table 2 Proximal O ... O Distances Å

Rings	1	2	3	4
A-B	2.9	3.2	2.7	2.8
B-C	3.1	2.9	2.8	3.1
C-D	2.9	3.1	2.8	2.8
D-A	3.1	2.7	2.8	3.1

The major driving forces in the enclathration of the ester residues in the molecular cavity of diester **2** and the dichloromethane solvent molecule in the cavity of diester **3** are the favourable though weak C-H...π(arene) hydrogen-bond interactions that exist between the hydrogen atoms of the terminal methyl group of the ester moiety of **2**, and the methylene hydrogen atoms of the dichloromethane molecule in **3**, with the π-arene electron cloud of the aromatic rings of the calix. This self-inclusion in **2** is supported by the distances of the terminal methyl carbon C16A to the aromatic carbon atoms of the calix core of a glide-related molecule, (the shortest of which is 3.60 Å). We have previously noted this C-H...π(arene) effect in the structure of a calix[4]arene guest-host complex, where the guest CH_2Cl_2 molecule uses both C-H bonds to bind to two different arene rings, in the absence of any other stabilising intermolecular interaction[2f]. Atwood and co-workers have described X-H...π(arene) interactions, X = O or C, in calix[4]arene guest-host complexes, where the hydrogen bonds from H_2O[5] or CH_2Cl_2[6] to the arene rings are the sole form of intermolecular interactions. These observations are of interest in the light of the studies reported by Aoyama and co-workers, where the primary stabilisation of the guest in the host cavity is O-H...O

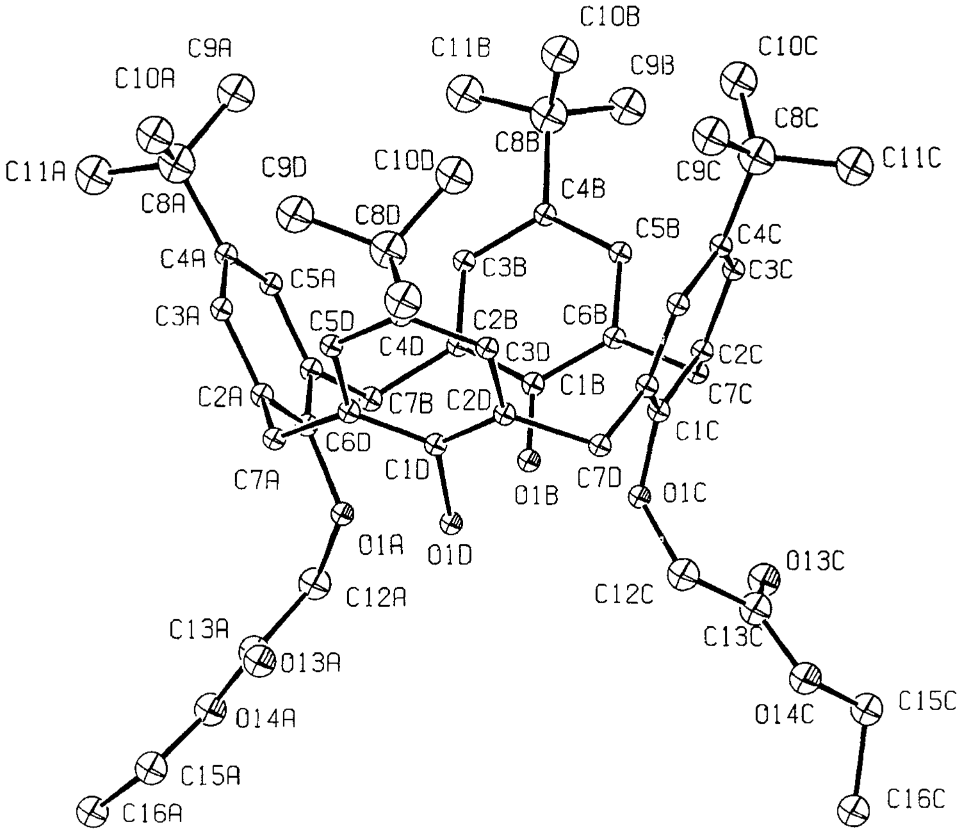


Figure 1a. A view of (**2**) with the carbon and oxygen atoms drawn as small spheres of an arbitrary size with our numbering scheme.

hydrogen bonding with weak cooperative C-H... π(arene) interactions.[7]

We have also recently observed the C-H...π(arene) interaction manifesting itself as an unusual self-inclusion phenomenon in the structures of calix[6]arene[8] and calix[5]arene[9] derivatives. In the former, the structure adopts polymeric self-inclusion chains as a result of complementary C-H...π(arene) interactions involving

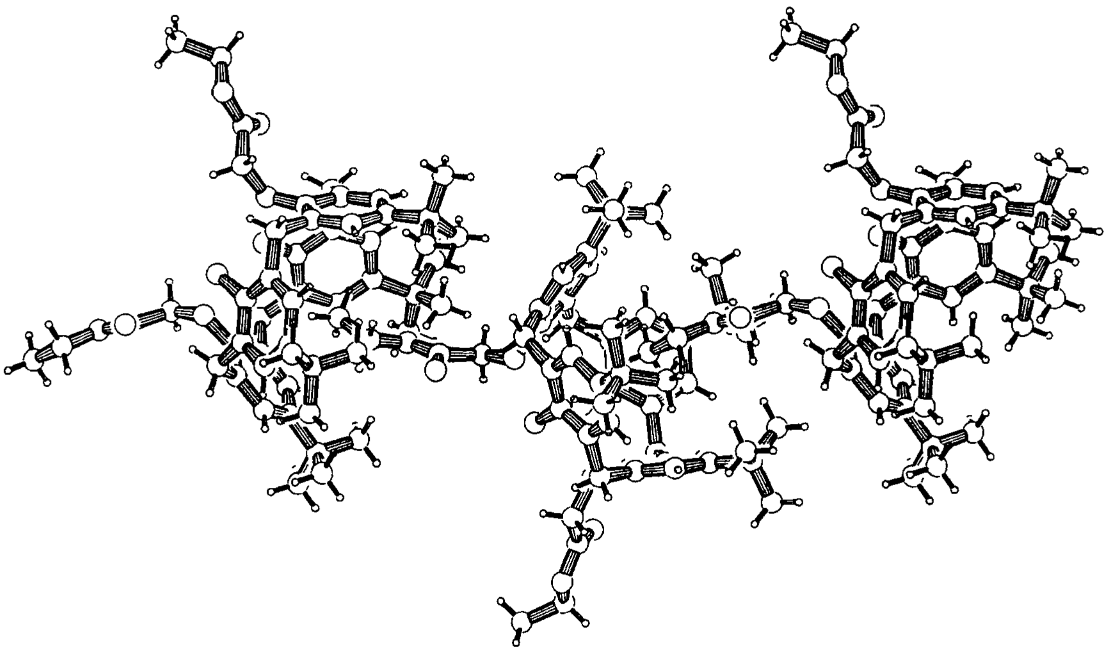


Figure 1b. A view showing three molecules of (**2**) and the enclathration of ester moieties in the molecular cavity of a neighbouring molecules in a polymeric *self*-inclusion assembly.

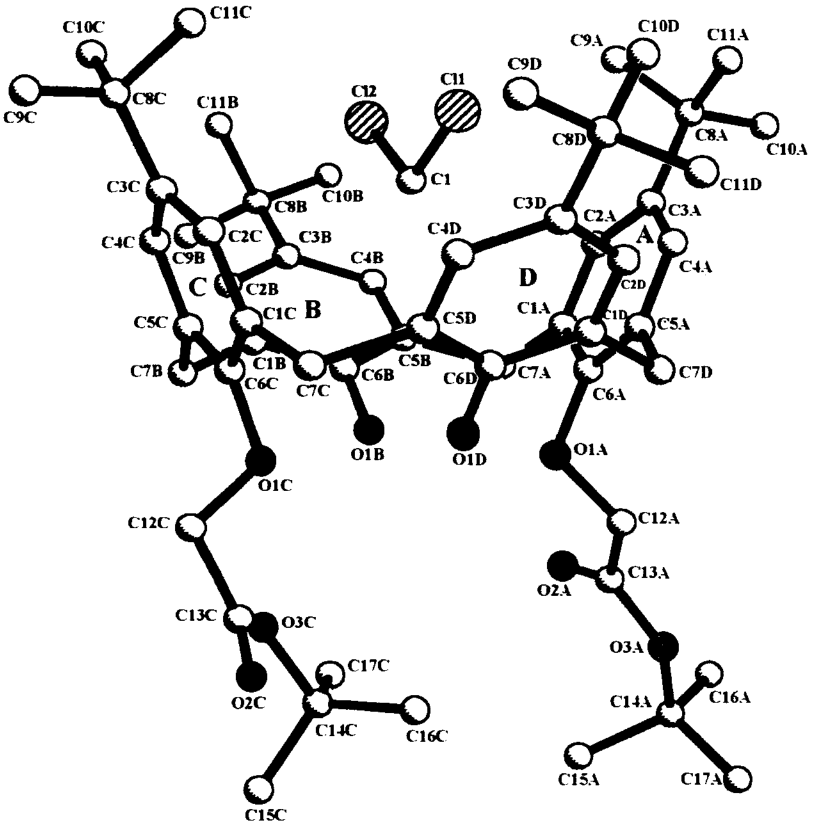


Figure 2 A view of molecule 3 depicting the enclathration of a CH_2Cl_2 guest molecule within the calix cavity.

arene...arene groups and *tert*-butyl...arene groups, while in the latter there exists a relay of C-H...π(arene) hydrogen-bonding between *tert*-butyl and aromatic groups. In the solid state structures of these two calixarenes the stronger intramolecular O-H...O hydrogen-bonding determines the calixarene conformation and

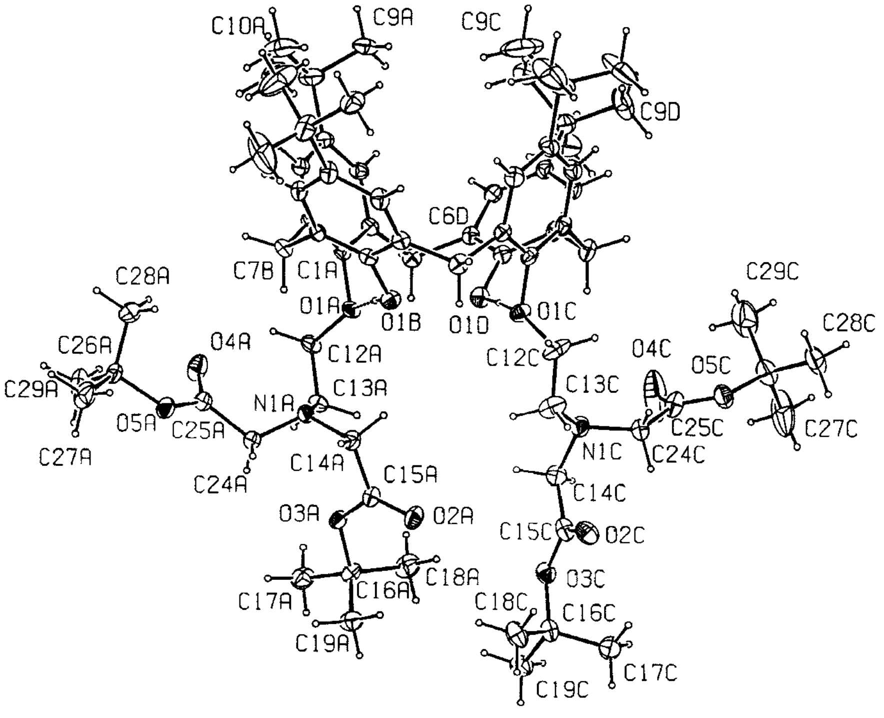


Figure 3 A view of molecule 4.

facilitates the formation of the weaker C-H...π(arene) hydrogen bonds. This arises because the strongest hydrogen bond donors pair off with the strongest hydrogen bond acceptors. Similar pairing processes are repeated until all of the donors and acceptors have been utilised. The weaker C-H...π(arene) interactions, which sometimes may form under favourable conditions, can ultimately determine the overall molecular packing of the calixarene; hence the formation of a molecular chain and 'zipper' in these solid state structures. Cram and his co-workers have described the structures of 'saddle-shaped' dibenzofuran-based hosts which form dimers in the solid state.[10] The 'V' shaped cleft of each host is mostly filled in a mutual fashion by the other host's 'wings' and the dimerisation was attributed to π(arene)...π interactions. The structural chemistry of several carceplexes which form four-fold host-guest dimers has also been described by Cram.[11] The binding forces in these dimers were attributed to dipole-dipole, van der Waals and solvophobic interactions in the absence of hydrogen bonds, ion pairs and metal ligation sites.

EXPERIMENTAL

Dinitrile **1b**[1] and diethyl ester **2** were known compounds.[1b] Synthetic details for compounds **3**[12] and **4**[13] will be published separately as part of a synthesis program.

Structure analysis for compounds **2**, **3** and **4**.
Details of the X-ray experimental conditions, cell data, data collection and refinement for molecules **2**, **3** and **4** are summarised in Table 3. The corresponding data for compound **1** are given in reference 1b. The various

Table 3 Summary of Crystal Data, Data Collection, Structure Solution and Refinement Details

	2[a,b]	**3**[c]	**4**[a,b]
(a) **Crystal Data**			
formula	$C_{52}H_{68}O_8.0.88(CHCl_3)$	$C_{56}H_{76}O_8.CH_2Cl_2$	$C_{72}H_{106}N_2O_{12}$
molar mass	950.2	962.1	1191.6
color, habit	colorless, block	colorless, block	colorless, block
crystal size, mm	0.25 × 0.20 × 0.20	0.40 × 0.40 × 0.38	0.41 × 0.33 × 0.27
crystal system	Orthorhombic	Monoclinic	Triclinic
a, Å	17.771(2)	20.104(5)	12.865(2)
b, Å	20.463(2)	13.399(5)	13.673(3)
c, Å	32.004(2)	22.355(6)	22.836(9)
α, °	90	90	107.20(2)
β, °	90	111.30(2)	95.58(2)
γ, °	90	90	92.047(14)
V, $Å^3$	11638.2(19)	5606.7(3)	3810.2(18)
space group	*Pbca*	$P2_1/c$	$P\bar{1}$
Z	8	4	2
F(000)	3960	2072	1296
d_{calc}, g cm^{-3}	1.06	1.14	1.04
μ, mm^{-1}	0.18	0.17	0.07
(b) **Data acquisition**[ac]			
temp, K	294(1)	294(1)	294(1)
unit-cell reflcns (θ-range°)	25 (8.0 12.0)	25 (7–21)	25 (9.5 17.5)
max. θ (°) for reflcns	20	25	21
hkl range of reflcns	0 17; 0 19; 0 30	−24 24; −16 16; 0 27	−12 12; 0 13; −22 21
decay in 3 standard reflcns	1.0%	no decay	2.9%
reflcns measured	5397	11867	8132
unique reflcns	5397	9938	8132
R_{int}	-	0.1507	-
reflcns with $I > n\sigma(I)$, n	752 2	4074 2.5	5635 2
(c) **Structure Solution and Refinement**[bc]			
refinement on	F^2	F	F^2
solution method	SHELXS86	SHELXS86	SHELXS86
H-atom treatment	riding	riding	riding
no. of variables in L.S.	115	607	921
weights: either			
k in $w = 1/(\sigma^2Fo + kFo^2)$ or		0.01691	-
k in $w = 1/(\sigma^2Fo^2 + k)$	$(0.1690P)^2$	-	$(0.1589P)^2 + 0.8783P$
$[P = (Fo^2 + 2Fc^2)/3]$			
R, R_w, *gof*	0.201, 0.508, 0.92	0.090 0.108	0.075, 0.256, 1.15
density range in final Δ-map, e A^{-3}	−0.50, 0.45	−0.24, 0.24	−0.30, 0.70
final shift/error ratio	−0.072	0	−0.021

[a] Data collection on an Enraf Nonius CAD4 diffractometer with graphite monochromatised Mo-Kα radiation (λ 0.7107A). [b] All calculations were done on a Silicon Graphics 4D-35TG computer system with the NRCVAX system of programs (E.J. Gabe, Y. Le Page, J-P. Charland, F.L. Lee and P.S. White, *J. Appl. Cryst.* (1989), **22**, 384–389) for refinement with observed data on F, or with SHELXL-93 (G.M. Sheldrick, 1993) for refinement with all data on F^2. [c] For **3** data collection was with a Siemens P3/V2000 diffractometer and refinement was with SHELX76 (G.M. Sheldrick, 1976).

figures were prepared with the aid of *ORTEPII*[14] and *PLUTON*.[15]

Compound 2. The data crystal diffracted *very* weakly (only 16% of the measured data could be labelled "observed" in the 2 to 20° θ range, (I > 2σ(I)). The structure was solved by direct methods with difficulty using *SHELXS86*[16a] which revealed the non-hydrogen atoms of the calixarene core. The subsequent F_o-maps were almost "protein-like" because of the effective low resolution of the data, but it was possible to determine unequivocally the gross conformation of the molecule. It was evident at an early stage of the analysis that partial occupancy disordered chloroform molecules were also present in two different locations, *exo* to the calix cup. These were allowed for by the *SQUEEZE* option in *PLATON-94*[17]. All aromatic rings were treated as rigid hexagons and all C-C and C-O bonds were restrained to appropriate values.

Compound 3. The structure was solved by direct methods using *SHELXS86*[16a] and refined by blocked least squares using *SHELX76*[16b]. The location of the phenoxy (O1B and O1D) hydrogen atoms could not be unequivocally located but a molecule of dichloromethane was found to be present, encapsulated by the upper rim calix cavity. Hydrogen atoms were included at positions calculated from the geometry of the molecule with common isotropic temperature factors for methyl, methylene and aromatic hydrogens.

Compound 4. All four *tert*-butyl groups bonded to the aromatic rings in **4** were disordered unequally over two orientations and one of the four side-chain *tert*-butyl groups was similarly affected. This disorder was allowed for and refined using the features available in *SHELXL93*[16c].

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