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Unusual cone conformation retention in calix[4]arenes

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Abstract—Use of a regioselective *O*-alkylation, *C*-dealkylation synthetic sequence generates an 'ABAB' calix[4]arene, **4**, which contains only two upper rim *t*-butyl groups and yet retains the cone conformation. Further substitutions can then be carried out independently on the upper and/or lower rims of the A and/or B subunits, with retention of conformation. Complexation studies show that **4** retains its cone conformation in the presence of alkali metals from sodium to cesium. Thus **4** remains in the cone conformation in solid state, in solution and on complexation.

The spectacular development of calixarenes is related to the possibilities that this class of molecules offers in terms of structural and functional modifications.[1] Calix[4]arenes are highly ordered structures and are known to exist in a range of conformations including the cone, the partial cone, the 1,2-alternate and the 1,3-alternate structures. It is critical that the conformation adopted by a given calixarene is known, as this determines its recognition properties.

In order to obtain calix[4]arenes suitable for selective supramolecular interactions with small molecules, it is desirable to be able to substitute both rims regioselectively. One possible route is to selectively alkylate the phenolic functions of the lower rim. The higher reactivity *para* to the free phenolic groups—as compared to the phenol ether positions—can then be utilised to introduce functionality.[2,3] Another possibility is to fix the conformation of the calix[4]-arene by tetra-*O*-alkylation and then introduce substituents in the upper rim. While the latter strategy is appealing, it requires regioselective O-functionalisation if compounds other than symmetrically tetrasubstituted derivatives are to be obtained.

The alkylation of all the hydroxy groups is well known, both with simple alkyl halides, RX, or those with further functionality, for example, XCH_2CO_2R.[1] A wide variety of tetra-alkyl calixarenes have been prepared, using an excess of alkylating agent in the presence of either sodium hydride or potassium carbonate, and characterised by either NMR spectroscopy or X-ray crystallography.[4–8] In this paper, we have developed these strategies to build a synthon capable of incorporating a variety of functionalities at both the upper and lower rims, but with retention of cone conformation. The retention of cone conformation may not appear unexpected or surprising since one would expect strong hydrogen bonding to exist between the free phenol hydrogens and the ester groups. However, See et al. have reported that selective de-*tert*-butylation of the diester, 5,11,17,23-tetra-*tert*-butyl-25,27-bis((3,5-dinitrobenzoyl)oxy)-26,28-dihydroxycalix[4]arene, in the cone conformation, yielded 11,23-bis-*tert*-butyl-25,27-bis((3,5-dinitrobenzoyl)oxy)-26,28-dihydroxycalix[4]arene, in the 1,3-alternate conformation, suggesting that more than hydrogen bonding is responsible for defining the conformation of the calixarene, since one would expect the hydrogen bonding to be similar in both cases.[9]

The reaction of *p-tert*-butylcalix[4]arene with a two-fold molar quantity of the bromo compound, ethyl bromoacetate, under conventional conditions for A,C-dialkylation[†] (K_2CO_3 as base in acetonitrile solvent)[1] resulted in the expected A,C-dialkyl derivative **1**, with a single recrystallisation from methanol necessary to obtain the pure compound. Further reaction with a two-fold molar quantity of either *tert*-butyl bromoacetate or ethyl bromoacetate resulted in further alkylation of the lower rim to give compounds **2** and **3** (see Scheme 1). All of these compounds have been previously prepared, although **3** was synthesised

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† Naming the rings A, B, C, D after the reference of Gutsche[4] rather than 1,2,3,4 avoids confusion with assignment of calixarene conformations as for example 1,2-alternate and 1,3-alternate.

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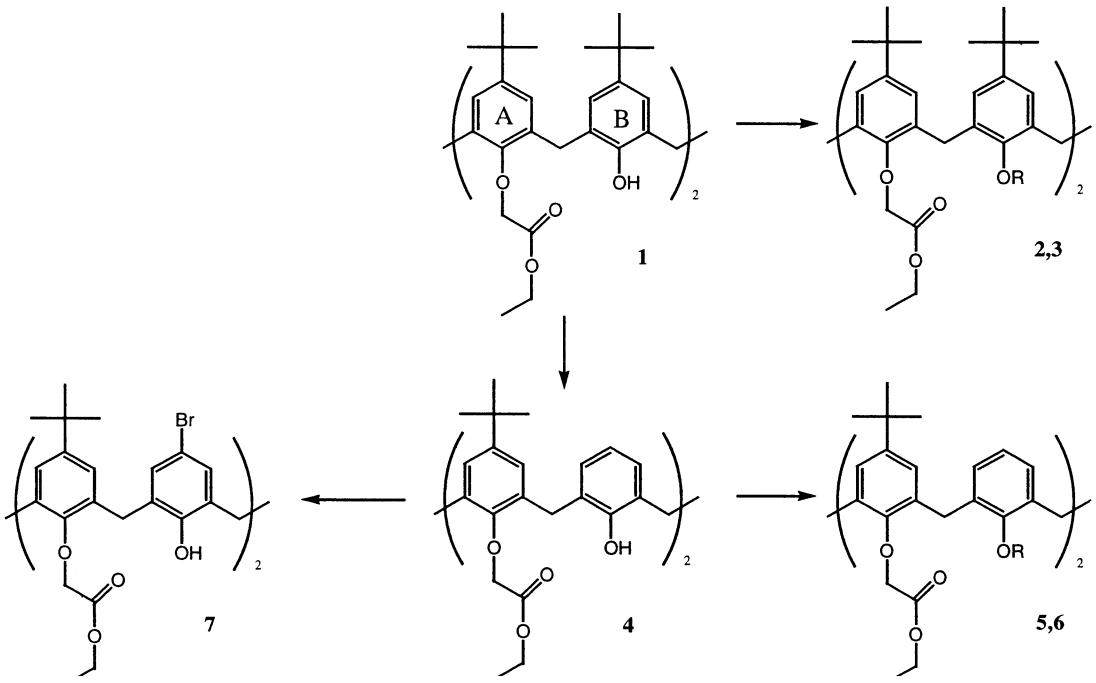

Scheme 1. **2**,**5** R=$CH_2CO_2(t\text{-}C_4H_9)$; **3**,**6** R=$CH_2CO_2C_2H_5$.

directly by alkylation of the commercially available *tert*-butyl calix[4]arene, as opposed to the two-step synthesis used here.[4,8]

The removal of the two *tert*-butyl groups *para* to the free phenolic groups in **1** by electrophilic dealkylation with $AlCl_3$ in toluene led to **4**, which was found to exist exclusively, both in the solid state and solution, in the cone conformation. Reaction of **4** with a two-fold molar quantity of either *tert*-butyl or ethyl bromoacetate resulted in the complete functionalisation of the lower rim to give compounds **5** and **6**, both in the cone conformation. Furthermore, the reaction of **4** with a two-fold excess of bromine led to the complete functionalisation of the upper rim to give compound **7**, also in the cone conformation. Thus, the new compound **4** opens up routes to a wide variety of calix[4]-arenes, with or without upper or lower rim substituents in the B and D rings, with the conformation fixed as cone by the substituents in the A and C rings. In contrast, the removal of two of the *p-tert*-butyl groups from the A,C-bis(3,5-dinitrobenzoyl) ester of *p-tert*-butylcalix[4]arene changed the conformation from pinched cone to 1,3-alternate.[9] It is also interesting to note that partially etherified calix[4]arenes are often less conformationally flexible than their fully etherified counterparts, due to the synergistic intramolecular hydrogen bonding.[1]

It is well-known that the ^1H NMR spectrum of *p-tert*-butylcalix[4]arene in solution reflects an apparently four-fold symmetric cone conformation for the molecule,[1] specifically shown by the doublets observed for the axial and equatorial protons of the bridging methylene groups. This signature for the cone conformation is usually retained even when functionalisation of the calixarene removes the four-fold rotational symmetry. Thus, the observation of methylene proton doublets at δ 4.45 and 3.32 for **1**, δ 4.49 and 3.35 for **4** and δ 4.46 and 3.31 for **7** is taken as evidence that these compounds adopt a cone conformation in solution. Similarly, the observation of two sets of doublets in all other compounds also suggests that the cone conformation is retained on further reaction, either at the upper rim, the lower rim, or on complexation.

The removal of the two *tert*-butyl groups in compound **4** resulted in only one signal for the remaining *tert*-butyl group at δ 1.12 and also the appearance of a triplet at δ 6.53, due to the hydrogen *para* to the free phenolic groups, and a doublet at δ 7.05, due to the hydrogens *meta* to the free phenolic groups. Similar signals are also present in compounds **5** and **6**, as expected. The spectrum of compound **7** shows two sharp singlets in the aromatic region, replacing the doublet and triplet of compound **4**, indicating that bromination has occurred *para* to the free phenol group. The spectra of compounds **1**, **4**, and **7** show sharp singlets at δ 7.08, 8.05 and 7.84, respectively, for the hydroxyl protons while these signals are absent in the spectra of compounds **2**, **3**, **5**, and **6** as expected.

The electrospray mass spectrum of solids **4** and **7** showed a signal corresponding to the molecular ion plus sodium in each case. The sodium ion was picked up from the conditions used to operate the spectrometer, as is common in this type of mass spectrometry, and was not present in the actual compounds themselves.

Preliminary nuclear Overhauser effect difference (NOE-dif) experiments have aided in assigning the ring system to which the free hydroxyl group is attached in compound **4** as well as providing conclusive evidence for the correct assignment of the hydrogen atoms *meta* to both the free phenolic groups and the ether linkages. In compound **1**, the signals at 7.02, 4.72, 4.30/1.33, and 1.26 ppm are found on the A subunit of the calixarene while those at 7.12, 6.83 and 0.98 are found on the B subunit, where A

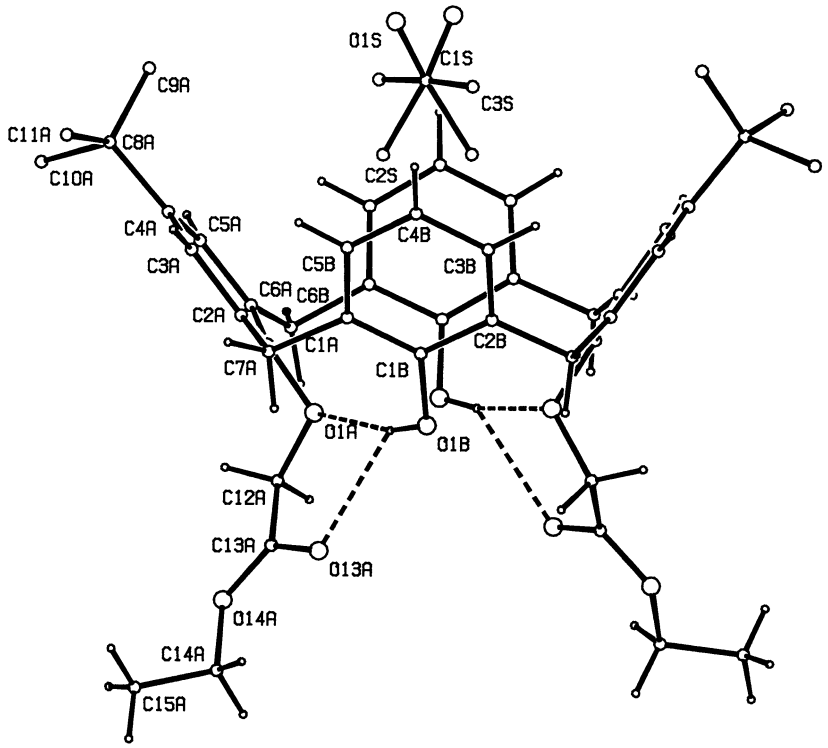

Figure 1. A PLATON view of the calix[4]arene (**4**) with the atomic labelling scheme. For clarity, all atoms are drawn as small spheres of arbitrary size and the hydrogens atoms are omitted from the *tert*-butyl groups and acetone molecule. The acetone solvent molecule is disordered about the two-fold axis.

Table 1. Changes in chemical shift on complexation of **4** with various alkali metal salts

Functional group	Change in ^{1}H NMR chemical shifts ($\Delta\delta$ (ppm)) of **4** upon complexation of MX							
	MX							
	NaI	$NaClO_4$	KI	$KClO_4$	RbI	$RbClO_4$	CsI	$CsClO_4$
CH_2 bridge								
H_b	0.07	0.08	0.09	0.07	0.06	0.17	0.07	0.07
H_a	−0.17	−0.17	−0.14	−0.11	−0.13	0.00	0.05	−0.09
OCH_2CO	−0.09	−0.09	−0.08	−0.06	−0.09	0.04	−0.05	0.06
Ar_A–H	0.25	0.25	0.22	0.26	0.22	0.35	0.26	0.26

denotes the subunit containing the ethyl ester linkage and B denotes the subunit containing the phenolic linkage. Similarly in **4**, the signals at 6.89, 4.79, 4.31/1.31, and 1.06 ppm are found on the A subunit of the calixarene while those at 7.47, 6.99, and 6.62 are found on the B subunit.

The calixarene **4** adopts a distorted cone conformation in the solid state (Fig. 1). The major conformation-determining feature in this molecule is the presence of an intramolecular O–H···O hydrogen bond between the phenolic O–H group O1B and a proximal ethereal oxygen O1A; a *para*-substituted *t*-butyl group is also attached to this substituted aromatic ring together with the ester functionality at O1A. The overall conformation adopted by **4** is broadly similar to related calixarene systems which have a solvent molecule present in the calix[4]arene cavity, e.g. dichloromethane,[10] methanol,[11] ethanol[12] and acetonitrile.[13]

The conformation of **4** is defined by the angles which the aromatic rings make with the plane of the four methylene carbon atoms which link them, viz 125.95(7)° (A/A*) and 114.65(8)° (B/B*).[‡] All four rings (A, B, A* and B*) are tilted back, opening up the molecular cavity and leading to O···O separations between O1A···O1A* and O1B···O1B* across the calixarene cavity of 3.993(4) and 4.219(4) Å, respectively. This conformation adopted by **4** effectively allows a solvent molecule to be enclathrated and this is what is observed with the acetone molecule in the calix[4]arene cavity.[10–15] Only the sp^2 carbon of the acetone resides on the axis and thus the acetone is disordered about the two-fold axis. The *t*-butyl group is disordered over two sites, 0.67(1) and 0.33(1) respectively: this is not uncommon in calixarene systems.[10–15] There is some disorder in the ester group with the C═O disordered over two sites with equal occupancies for the major and minor orientations, respectively.

[‡] Here we denote rings C and D as A* and B* respectively, reflecting the symmetry of the molecule.

Preliminary cation co-ordination properties of the receptors **1** and **4** with sodium, potassium, rubidium, and cesium cations were investigated by ^{1}H NMR titration experiments[6,16] in $CDCl_3$ solution. In a typical experiment, the calixarene receptor (**1** or **4**) (0.002 mmol) was dissolved in $CDCl_3$ (approx. 1 cm^3) and the ^{1}H NMR chemical shifts were measured after sequential additions (0.1 mol equiv.) of the alkali metal salt. The results for **4** are shown in Table 1 and the same trend in peak movement was also found for compound **1**. The addition of the metal typically caused the Ar–CH_aH_b–Ar signal and the Ar–H signals to shift over the course of the addition of 1 equiv., suggesting that complexes of 1:1 metal/calixarene are being formed in solution, even in the case of cesium where a weak interaction was observed. In all cases, however, the cone conformation was retained despite the difference in ion size on going down the group from sodium to cesium. This is in contrast with the findings of Ungaro et al.[18] who showed that, when cesium picrate was complexed with a 1,3-dialkoxycalix[4]arenecrown-6, the conformation of the calixarene changed from a cone conformation to that of a 1,3-alternate conformation. This then establishes the unusual cone conformation retention which we are observing for this calix[4]arene, not only in the solid state and in solution but also on complexation with all alkali metals.

1. Experimental

1.1. Data for compounds

1.1.1. 5,17-Di-*tert*-butyl-25,27-diethoxycarbonylmethoxy-26,28-dihydroxycalix[4]arene (4). The diester (**4**) was prepared in 88% yield from the diethyl ester (**1**) following a procedure similar to that described by Arduini et al.[17] Recrystallisation from acetone afforded **4** as a colourless crystalline material, yield 88%, mp 150–154°C; [Found: C, 72.60; H, 7.62. $C_{44}H_{52}O_8{\cdot}C_3H_6O$ requires C, 72.75; H, 7.33]; ν_{max}(KBr) 3390, 1749, 1585, 1218, 1184, 1055, 752 cm^{-1}; δ_H (300 MHz, $CDCl_3$):[§] 7.45 (2H, s, O*H*), 6.99 (4H, d, J=7.5 Hz, Ar_B–H_m), 6.89 (4H, s, Ar_A–*H*), 6.62 (2H, t, J=7.5 Hz, Ar_B–H_p), 4.78 (4H, s, OCH_2CO_2), 4.49 (4H, d, J=12.8 Hz, Ar–CH_aH_b–Ar), 4.31 (4H, q, J=7.1 Hz, CH_2Me), 3.35 (4H, d, J=13.0 Hz, Ar–CH_aH_b–Ar), 2.09 (6H, s, $(Me)_2CO$), 1.31 (6H, t, J=7.0 Hz, CH_2Me), 1.05 (18H, s, *t-Bu*$_A$); δ_C (300 MHz, $CDCl_3$) 169.4, 152.4, 150.9, 147.5, 132.7, 128.9, 128.2, 125.9, 119.5, 72.2, 61.2, 34.0, 31.9, 31.2, 14.2; LRMS (ES): *m/z* calcd for $C_{44}H_{52}O_8Na$ $[M+Na]^+$ 731.8, found 731.4; Crystal data for **4**: $C_{44}H_{52}O_8{\cdot}C_3H_6O$, M=766.93, monoclinic, a=24.377(3), b=16.6098(16), c=10.6842(17) Å, β=93.808(11)°, V=4316.5(9) Å^3, T=296(2) K, space group $C2/c$, Z=4, Dc=1.18 g cm^{-3}, μ(Mo-Kα)=0.081 mm^{-1}. Crystal dimensions 0.40×0.28×0.20 mm^3. 5969 reflections measured, 3810 unique ($R_{(int)}$=0.026). The final R=0.063. Crystallographic data has been deposited with the Cambridge Crystallographic Data Centre as CCDC-166197.

1.1.2. Compound 7. It was prepared from the diethyl ester (**4**) (0.11 g, 0.14 mmol) in chloroform (20 cm^3) with 2 equiv. of bromine (0.044 g, 0.28 mmol) in chloroform (20 cm^3) at 0°C. The solution was stirred at 0°C for 1 h and then at room temperature for 2 h. Dichloromethane (40 cm^3) and water (60 cm^3) were added and the organic phase was washed with water (50 cm^3), brine (50 cm^3), and dried with $MgSO_4$. The solvent was removed under pressure to give a yellow material. Recrystallisation from methanol afforded **7** as a colourless microcrystalline material, yield 85%; mp 208–212°C; [Found: C, 60.75; H, 5.74. $C_{44}H_{50}Br_2O_8$: C, 60.98; H, 5.81]; ν_{max}(KBr) 3360, 1749, 1585, 1218, 1183, 750 cm^{-1}; δ_H (300 MHz, $CDCl_3$)[¶]: 7.85 (2H, s, O*H*), 7.09 (4H, s, Ar–*H*), 6.96 (4H, s, Ar–*H*), 4.78 (4H, s, OCH_2CO_2), 4.46 (4H, d, J=13.2 Hz, Ar–CH_aH_b–Ar), 4.31 (4H, q, J=7.1 Hz, CH_2Me), 3.31 (4H, d, J=13.2 Hz, Ar–CH_aH_b–Ar), 1.34 (6H, t, J=7.2 Hz, CH_2Me), 1.14 (18H, s, *t-Bu*); δ_C (300 MHz, $CDCl_3$) 169.3, 151.5, 150.9, 148.2, 132.4, 130.9, 130.8, 126.3, 111.2, 72.1, 61.4, 34.2, 31.8, 31.2, 14.2; LRMS (ES): *m/z* calcd for $C_{44}H_{52}Br_2O_8Na$ $[M+Na]^+$ 889.6, found 889.1.

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[§] The subscripts A and B refer to the relevant rings as in Scheme 1.

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