



Influence of the Size of Upper and Lower Rim Substituents on the Fluxional and Complexation Behaviour of Calix[5]arenes

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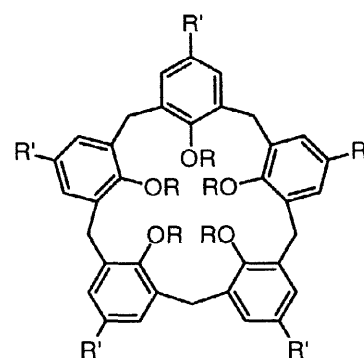
Abstract: A comparative study on a series of penta-*O*-alkylated *p*-H-calix[5]arenes **1b–e** and *p*-*tert*-butylcalix[5]arenes **1g–m** shows that the former are inherently mobile and adopt in solution non-cone conformations. The 1,2-alternate conformation for penta-*O*-benzyl ether **1c** was proven by single-crystal X-ray analysis. VT-NMR studies on **1c–e** have provided the first experimental evidence that conformational interconversion occurs via the *p*-phenyl-through-the-annulus mechanism with ΔG^\ddagger in the range 17.9–18.8 kcal mol⁻¹. Unlike the corresponding *tert*-butylated counterparts, *p*-H-calix[5]arenes are unable to form 1:1 *endo*-calix complexes with primary unbranched alkylammonium cations. © 1998 Elsevier Science Ltd. All rights reserved.

The conformational characteristics and complexation properties of calix[4]arenes have been extensively investigated.¹ On the contrary, little is known about the behaviour of the corresponding calix[5]arenes. Very recently, we have shown that conformationally preorganized (1,3)-*p*-*tert*-butylcalix[5]crown-6 triethers and simple penta-*O*-alkylated *p*-*tert*-butylcalix[5]arenes are able to discriminate linear from branched alkylammonium cations, selectively forming 1:1 inclusion complexes only with the former.^{2,3}

In order to investigate a possible influence of the upper and lower rim substituents on the observed selectivities, we have undertaken a comparative study on the conformational and complexation behaviour of a series of *p*-H-calix[5]arene **1b–e** and *p*-*tert*-butylcalix[5]arene **1g–m** derivatives and a *p*-nitrocalix[5]arene pentaether **1n** (shown in the Table). We now wish to present our findings.

New de-*tert*-butylated calix[5]arene derivatives **1b–e** and *tert*-butylated **1l,m** were obtained in 47–80% yield by exhaustive alkylation of the parent calix[5]arene pentols **1a**⁴ or **1f**⁵ with an excess of the appropriate electrophile (MeOTs, BnBr, ^tPrOCH₂CH₂OTs, BrCH₂CO₂^tBu, BrCH₂CO₂Me, and EtOCH₂CH₂OTs, respectively) and K₂CO₃ in refluxing CH₃CN. *p*-Nitrocalix[5]arene pentaether **1n** was prepared (34%) by *ipso*-nitration⁶ of **1i**.⁷

With the exception of **1c**, the conformation of all new compounds was assigned from distinctive ¹H and ¹³C NMR patterns of the bridging methylenes,⁸ using the signals of the terminal groups of the lower rim substituents as an additional diagnostic probe (see Table).



1a : R = R' = H

1f : R = H, R' = ^tBu

The 1,2-alternate conformation of **1c** was proven by X-ray analysis,⁹ since the NMR data could not rule out the alternative partial cone conformation. The Figure shows the conformation of **1c** in the solid state. Three adjacent aromatic rings (C11-C16, C21-C26, C31-C36) of the calix[5]arene system are oriented with their phenolic O atoms on one side of the best plane through the five methylene groups which link them, while the remaining two rings (C41-C46, C51-C56) have their O atoms on the opposite side of the methylene plane. The interplanar angles which the calix[5] aromatic rings make with the bridging methylene plane are 82.6(1), 139.7(1), 87.6(1), 109.3(1) and 88.4(1)° for rings C11-C16 to C51-C56, respectively. Interplanar angles <90° indicate that these rings are inclined in towards the center of the molecule, and values >90° show that the rings are tipped away from the calix center.

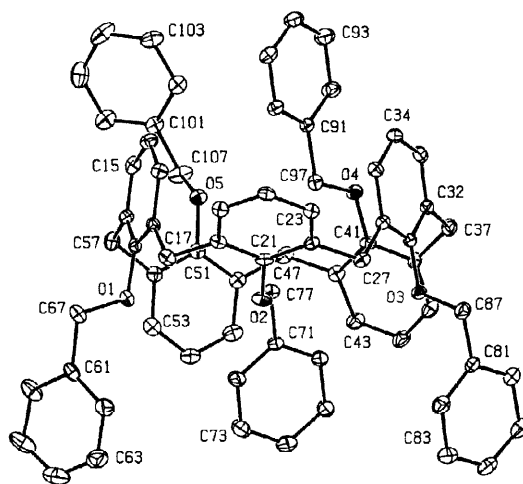


Figure. A view of molecule **1c** with an indication of our number scheme. Aromatic ring C atoms are labelled C*i*1-C*i*6 (*i* = 1-10). For clarity, anisotropic displacement ellipsoids are drawn at the 10% probability level and H atoms are not shown.

Compound **1c** maintains the 1,2-alternate conformation also in solution. However, the presence of additional peaks of minor intensity strongly suggests the existence in solution of at least one other non-cone structure with *C_s* symmetry. Upon heating in CDCl₂CDCl₂ (TCE), the two sets of signals first broaden and then coalesce (*T_c* = 408 K), indicating that the two species are in slow conformational equilibrium at room temperature. It is known that the introduction of very bulky substituents at the lower rim of **1f** suppresses the oxygen-through-the-annulus rotation, and affords conformationally immobilized derivatives.^{8b} Since the *p*-*tert*-butylcalix[5]arene **1h** adopts a fixed cone arrangement at ordinary temperatures,^{8b} conformational interconversion of **1c** must necessarily occur via the *p*-phenyl-through-the-annulus pathway. Although the swinging of an unsubstituted phenol residue through the annulus has been predicted by Gutsche on the basis of molecular modelling,^{8b} this study provides the first experimental evidence for conformational interconversion in *p*-H-calix[5]arenes through this mechanism.¹³ For this dynamic process, a free energy barrier of about 18.8 kcal mol⁻¹ was calculated ($\Delta\nu$ = 351 Hz, *T_c* = 408 K). Analogous VT-NMR experiments on **1d** and **1e** in TCE have shown a similar trend with ΔG^\ddagger values of 18.3 and 17.9 kcal mol⁻¹, respectively.

As can be seen from the Table, overcrowding at the lower rim by bulky substituents (Bn, (CH₂)₂O^{*i*}Pr, and CH₂CO₂^{*i*}Bu), if not counterbalanced by the presence of *t*-butyl groups at the upper rim, results in the loss of preorganized cone conformations (*i.e.*, **1c** vs **1h**, **1d** vs **1i**, and **1e** vs **1j**). The Table shows also that groups larger than CH₂CH₂OEt or CH₂CO₂Et must be introduced at the lower rim in order to inhibit the conformational mobility of *p*-*tert*-butylcalix[5]arenes. Derivatives **1k-m** all show temperature dependent ¹H NMR spectra, due to cone-non-cone fluxionality.

The host-guest properties and selectivities of the calix[5]arenes shown in the Table were tested by ¹H NMR (CDCl₃-CD₃OD 9:1, v/v), using the four isomeric butylammonium picrates as potential guests. In agreement with the results previously found for **1i,j**,³ all *p*-*tert*-butylcalix[5]arene derivatives (**1g,h** and **1k-m**) exhibit a remarkable discrimination for the *n*-BuNH₃⁺ cation, while surprisingly the de-*tert*-butylated (**1b-e**)

Table. Selected NMR Data (300 MHz, CDCl₃, 293 K) and Conformation of Calix[5]arenes **1**, and their Percentage of *endo*-Cavity Complexation with *n*-BuNH₃⁺ (1 equiv).

Compd	R	R'	δ_{H} ArCH ₂ Ar, ppm	δ_{C} ArCH ₂ Ar, ppm	δ_{H} (terminal groups), ppm	Conformation	Complex (%)
1b	Me	H	3.88 (s,10 H)	30.0		flexible	<i>a</i>
1c ^{b,c,d}	Bn	H	3.15, 4.25 (AX, <i>J</i> = 14.5 Hz, 2 H)	26.6		1,2-alternate	<i>a</i>
			3.22, 4.38 (AX, <i>J</i> = 14.6 Hz, 4 H)	29.4			
			3.61, 3.67 (AB, <i>J</i> = 13.3 Hz, 4 H)	36.0			
CH(CH₃)₂							
1d ^{c,d}	(CH ₂) ₂ O ⁱ Pr	H	3.33, 4.29 (AX, <i>J</i> = 14.0 Hz, 2 H)	27.1	0.96 (d, <i>J</i> = 6.1 Hz, 6 H)	partial cone	<i>a</i>
			3.24, 4.33 (AX, <i>J</i> = 14.9 Hz, 4 H)	30.3	1.19 (d, <i>J</i> = 6.0 Hz, 12 H)		
			3.91 (pseudo s, 4H)	35.3	1.24 (d, <i>J</i> = 5.9 Hz, 12 H)		
C(CH₃)₃							
1e ^{c,d}	CH ₂ CO ₂ ⁱ Bu	H	3.33, 4.31 (AX, <i>J</i> = 15.4 Hz, 4 H)	28.9	1.18 (s, 9 H)	partial cone	<i>a</i>
			3.40, 4.51 (AX, <i>J</i> = 14.5 Hz, 2 H)	32.0	1.52 (s, 18 H)		
			4.01, 4.11 (AB, <i>J</i> = 12.9 Hz, 4 H)	33.8	1.55 (s, 18 H)		
1g	Me	ⁱ Bu	<i>e</i>	<i>e</i>		flexible	6
1h	Bn	ⁱ Bu	<i>e</i>	<i>e</i>		fixed cone	38
1i	(CH ₂) ₂ O ⁱ Pr	ⁱ Bu	<i>f</i>	<i>f</i>		fixed cone	68 ^f
1j	CH ₂ CO ₂ ⁱ Bu	ⁱ Bu	<i>g</i>	<i>g</i>		fixed cone	90 ^f
1k ^d	CH ₂ CO ₂ Et	ⁱ Bu	<i>g</i>	<i>g</i>		cone	32
1l ^d	CH ₂ CO ₂ Me	ⁱ Bu	3.34, 4.76 (AX, <i>J</i> = 14.4 Hz, 10 H)	30.0		cone	30
CH₂CH₃							
1m ^{c,d}	(CH ₂) ₂ OEt	ⁱ Bu	3.19, 4.37 (AX, <i>J</i> = 14.1 Hz, 4 H)	29.1	0.94 (t, <i>J</i> = 7.0 Hz, 3 H)	partial cone	23
			3.31, 4.21 (AX, <i>J</i> = 14.0 Hz, 2 H)	27.2	1.21 (t, <i>J</i> = 7.0 Hz, 6 H)		
			3.82, 3.90 (AB, <i>J</i> = 13.5 Hz, 4 H)	37.0	1.25 (t, <i>J</i> = 7.0 Hz, 6 H)		
1n	(CH ₂) ₂ O ⁱ Pr	NO ₂	3.52, 4.76 (AX, <i>J</i> = 15.0 Hz, 10 H)	30.8		fixed cone	<i>a</i>

^aNot observed. ^bIn CDCl₂CDCl₂. ^cAssignments follow from COSY, HETCOR, and homo-decoupling experiments. ^dSpectral data of the predominant conformer. ^eSee ref. 8b. ^fSee ref. 3. ^gSee ref. 14.

are unable to recognize and/or include any of the RNH₃⁺ cations tested, irrespective of the conformation adopted. *p*-*tert*-Butylcalix[5]arene-*n*-BuNH₃⁺ *endo*-cavity complex formation is attested by dramatic upfield shifts for the cavity-included *n*-alkyl chain protons. Free and complexed species are in slow exchange in the NMR time-scale, and consequently the 1:1 host-guest stoichiometry and percentages of *endo*-cavity complex were determined by direct ¹H NMR analysis³ of equimolar solutions (5 × 10⁻³ M) of host and guest (see Table).

Degrees of complexation are mainly related to the extent of preorganization of the calix cup, ranging from 6% for the highly flexible compound **1g** to 90% for compound **1j** locked in a regular cone conformation. It is remarkable that compound **1m**, which is present in solution (CDCl₃-CD₃OD, 9:1) as a 97:3 mixture of partial cone and cone conformers, forms 23% of *endo*-cavity complex with 1 equiv of *n*-BuNH₃⁺. This result indicates that the cone conformer is the active species responsible for complexation. This implies also that **1m** undergoes a conformational rearrangement (partial cone → cone)¹⁵ - a sort of "guest induced fit" - to accommodate the incoming alkylammonium cation inside a more suitably preorganized cavity. *p*-Nitrocalix[5]arene pentaether **1n**, on the contrary, although blocked in a cone conformation, is unable to form inclusion complexes with any of the BuNH₃⁺ isomers presumably because the *p*-nitro groups drastically

reduce the π electron density of the calixarene cavity. The failure of *p*-H-calix[5]arene derivatives **1b-e** to form inclusion complexes with alkylammonium cations can then be attributed to both their unfavourable conformational arrangement (all of them adopt in solution non-cone conformations) and to the lack of an electron-donating effect of the *p*-H substituents as compared to the *p*-*tert*-butyl groups.

In conclusion, we have established the minimum size of the lower rim substituents required to inhibit the oxygen-through-the-annulus rotation in *p*-*tert*-butylcalix[5]arenes, and proved the *p*-phenyl-through-the-annulus rotation in *p*-H-calix[5]arenes. Our results emphasize the central role played by the *tert*-butyl substituents on the upper rim of calix[5]arenes both in the control of the conformation, and in the recognition of linear RNH_3^+ cations *via endo*-cavity complexation.

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- Crystal data for **1c**: $\text{C}_{70}\text{H}_{60}\text{O}_5 \cdot 0.35 (\text{CH}_3\text{CN})$, $M_r = 1029.2$, trigonal, space group $R\bar{3}a = 50.301(6)$, $c = 12.325(2)$ Å, $V = 27007(6)$ Å³, $Z = 18$, $F(000) = 9792$, $d_{\text{calc}} = 1.139$ g cm⁻³, $\mu = 0.070$ mm⁻¹. Data were collected with monochromated Mo-K α radiation to a maximum θ of 25°. Of the 10619 unique reflections measured, 3139 had $I > 2\sigma(I)$. The structure was solved using NRCVAX¹⁰ and refined using NRCVAX and SHELXL93¹¹ using all F^2 data. A set of disordered solvent molecules clustered around sites of $\bar{3}$ symmetry in the crystal required the use of the SQUEEZE option in PLATON.¹² Refinement of the modified data set then proceeded normally with anisotropic displacement parameters for all non-H atoms and H atoms treated and allowed for as riding atoms. The final R factor for the observed data is 0.067. Complete crystallographic details have been deposited with the Cambridge Crystallographic Data Centre and are also available from the authors in CIF format.
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