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A *p-tert*-butylcalix[6]arene capped with a triethanolamine-derived triple bridge

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Abstract—The C_3-symmetrically lower-rim capped *p-tert*-butylcalix[6]arene **6** has been synthesized and its solid-state structure has been determined by X-ray diffraction analysis. The triethanolamine-derived triple bridge fixes the calixarene part in the cone conformation. Mass spectrometry studies (MALDI-TOF) indicate that host–guest interaction of **6** with alkali metal ions decreases in the order Cs>K≫Na, Li.
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1. Introduction

Calix[*n*]arenes are a class of $[1_n]$metacyclophanes consisting of phenolic units linked by methylene groups. They have been studied intensely as three-dimensional molecular receptors in host–guest chemistry and for the construction of supramolecular assemblies.[1] The conformational flexibility of these macrocycles is a major criterion for their ability to act as receptor molecules. Although calixarenes have been reported to change conformation during their complex formation with a suitable guest molecule and therefore can be considered as induced-fit type host molecules, it may be helpful in other cases to restrict the conformational mobility in order to obtain molecular geometries and receptor sites of well-defined size and shape.[2]

Due to their higher conformational flexibility as compared to calix[4]arenes, calix[6]arenes are still limited in their application as molecular receptors.[3] The complex dynamics of phosphoryl derivatives of *p-tert*-butylcalix[6]arene **1** has been elucidated only recently.[4] The introduction of appropriate bridges at the lower or upper ring of calix[6]arenes is suited to lowering the conformational freedom or to completely immobilizing the conformation of the macrocyclic skeleton. Today, we know molecular architectures in which phenol functions of calix[6]arenes such as **1** and **2** are connected by one bridge (A,D-[5a–g,6] and A,C-bridging,[6] where the letters A–F in this study denote the six phenol units), by two bridges (A,C; D,E[7]), and by three bridges (A,E; B,C; F,G).[5g] Bridging of the upper or lower rim with a multipodal cap is a particularly suitable strategy to suppress the ring inversion of the calixarene skeleton. The connection of the six phenol groups of **1** by two triply bridging phosphate groups (A,B,C; D,E,F) was the first example of a calix[6]arene with immobilized conformation.[8] Other examples include upper-rim bridging with a tripodal cap,[9] and lower-rim capping with C_3-symmetrical tripodal caps to give A,C,E-bridged systems such as **3**,[10] **4**,[6] and **5**[11] (Scheme 1) as well as calix[6]cryptands which are A,C,E- or A,B,D-bridged by a $EtC(CH_2OCH_2CH_2OCH_2CH_2)_3$ unit.[12] A lower-rim A,B,D,E-bridged system with a C_4-symmetrical cap has also been reported.[13]

In this communication, we present a novel calix[6]arene which is bridged at the lower rim with a tripodal cap derived from triethanolamine.[14]

2. Results and discussion

The triply bridged calixarene **6** was obtained by deprotonation of calix[6]arene **2**[15] with sodium hydride and subsequent triple alkylation with alkyl chloride **7** (Scheme 2). After column chromatography, **6** was obtained in 25% yield. The ^{1}H NMR spectrum (500 MHz) at 303 K shows two signals for the *t*Bu groups (δ=0.88 and 1.37, 1:1 intensity), one signal for the OMe groups (δ=2.96), an AB quartet (δ=3.45 and 4.40) for the $ArCH_2Ar$ methylene protons, and two sharp singlets for the aromatic protons. These observations are consistent with a C_3-symmetrical cone conformation of the calixarene moiety. In the temperature-dependent ^{1}H NMR spectra, the mentioned AB quartet

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Keywords: calix[6]arenes; macrocycles; MALDI mass spectrometry.

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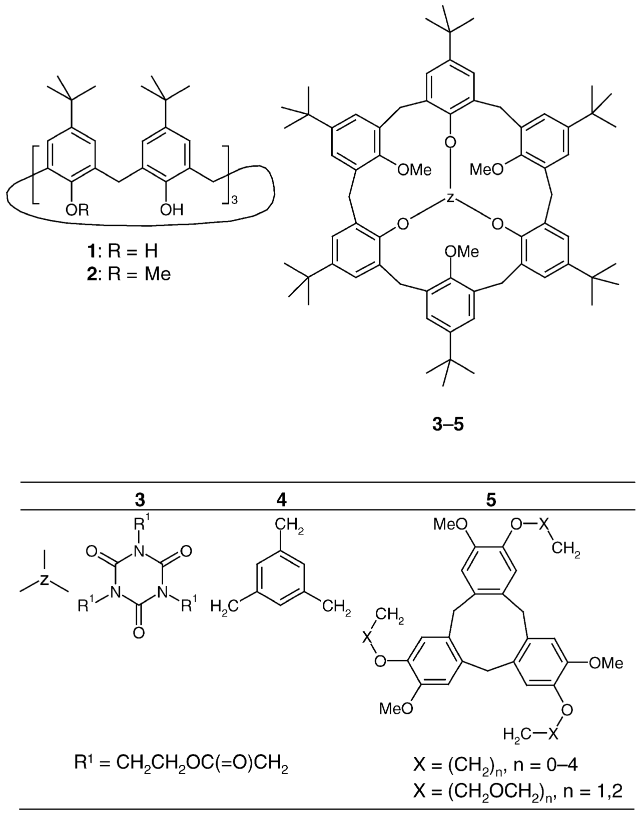
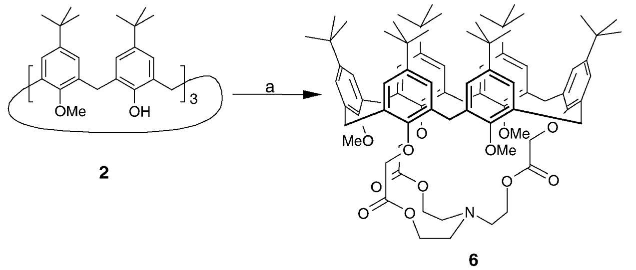


Scheme 1.

can be observed over the temperature range 220–328 K, indicating that ring inversion in the calixarene part does not occur on the NMR time-scale. Nevertheless, dynamic NMR spectra are found below ambient temperature (Fig. 1). In particular, the methoxy signal shifts downfield, goes through coalescence and reappears at $\delta=3.75$ as a rather sharp singlet at 220 K. The chemical shift of the OMe groups at low temperature is nearly the same as in triply bridged calixarene **4** ($\delta=3.84$ at 30°C); in the latter case, molecular mechanics calculations provided an energy-minimized structure in which the methyl groups of the anisyl rings are located at the periphery of the molecule.[6] On the other hand, δ values in the range 2.1–2.7 were assigned to methoxy protons reaching into the calixarene cavity.[6,16a] Thus, the dynamic behavior of the methoxy groups in **6** can be interpreted as follows (Scheme 3): at low temperature, the methyl groups of the anisyl rings prefer a position directed away from the calixarene moiety ('methyl out'); rotation around the C_{aryl}—O bond brings them into the cavity of the calixarene, and this equilibrium conformation dominates at elevated temperature. Fig. 1 also indicates dynamic processes for the flexible bridges at the lower rim. They are attributed in part to conformational changes within the bridge (perhaps including inversion of the bridgehead nitrogen) and in part to the change of the magnetic environment accompanying the positional equilibrium of the methoxy groups. Evidence for the latter contribution comes from the observation that the largest chemical shift change is observed for the methylene protons closest to the lower rim [$\Delta\delta(ArOCH_2)=+0.4$ ppm upon lowering the temperature to 220 K].



Scheme 2. (a) 1) NaH, THF/DMF; 2) $N[CH_2CH_2OC(=O)CH_2Cl]_3$ (**7**).

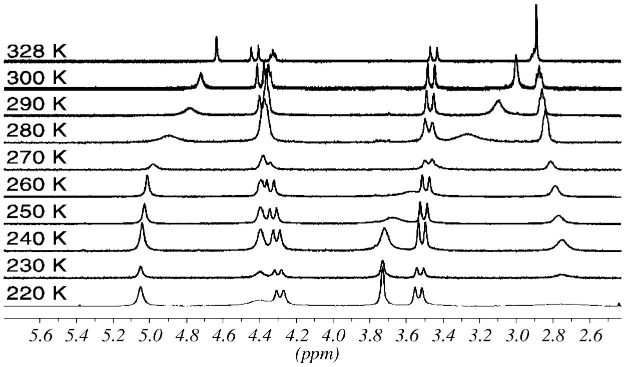
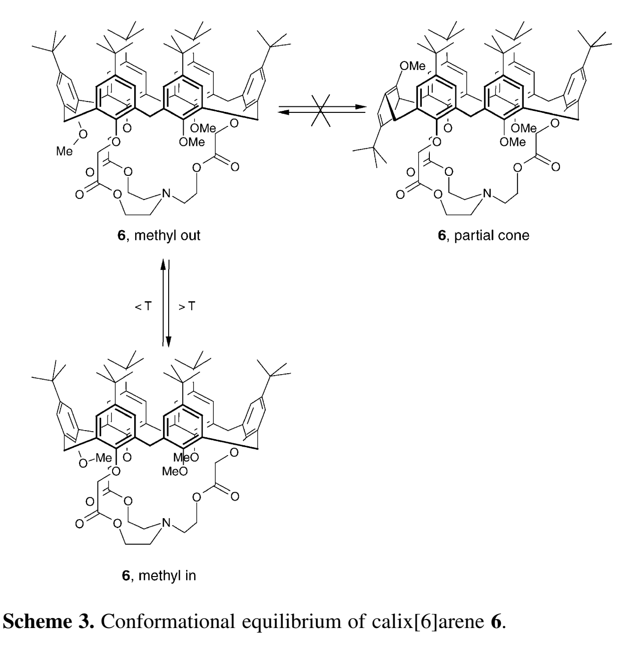


Figure 1. Temperature-dependent ^{1}H NMR spectra (400 MHz) of **6** in $CDCl_3$.

In terms of rigidification of the cone conformation, triply bridged calixarene **6** resembles the structurally related molecules **3**[10] and **4**[6] which do not undergo a ring flip up to 383 K (note, however, that NMR spectra of **6** were recorded only up to 328 K). On the other hand, the observation of an equilibrium between the cone and a partial-cone conformer of calixarenes **5**[11] depended on the length and flexibility of the three bridges.

2.1. Crystal structure determination of calix[6]arene 6

Crystals suitable for an X-ray diffraction crystal structure



Scheme 3. Conformational equilibrium of calix[6]arene **6**.

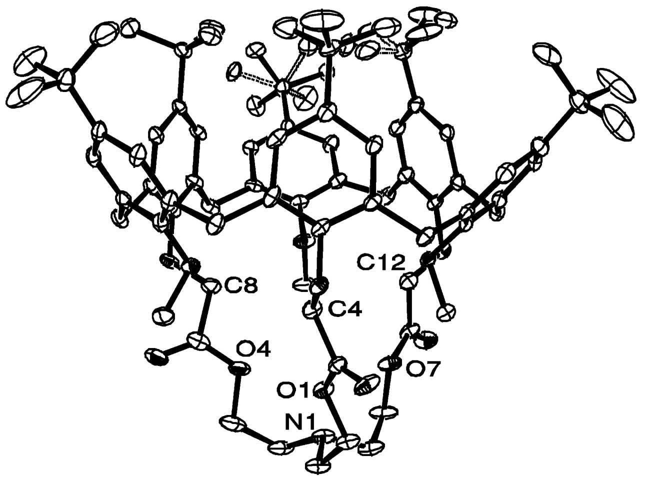


Figure 2. Structure of calix[6]arene **6** in the crystal. Hydrogen atoms and solvent molecules are omitted for clarity. Two *t*Bu groups were found to be disordered over two positions.[23]

determination of calixarene **6** were obtained from a mixture of chloroform and methanol leading to a **6**×5 $CHCl_3$×1 CH_3OH clathrate. The molecule has an approximate C_3-symmetrical shape and adopts a cone (*ui*, *uo*, *ui*, *uo*, *ui*, *uo*)[5a] conformation with the methyl groups of the anisole functions pointing away from the calixarene cavity (Fig. 2). This geometry is probably due to the steric strain imposed by the tripodal ligand at the lower rim. In contrast, comparable 5,11,17,23,29,35-hexa-*tert*-butyl-37,39,41-trimethoxy-38,40,42-trisubstituted calix[6]arenes show a distinct self-complexation, i.e. the methoxy groups are embedded in the cavity and stabilize the cone conformation by CH···π interactions with the opposite phenyl rings.[16] The six *t*Bu groups at the upper rim occupy an inner and an outer sector alternately; hereby, the *t*Bu groups of the bridged phenyl rings are in the inner sector and form a lid over the calixarene cavity. This geometry corresponds to the structure proposed for **3**,[10] which has a similarly large and flexible tripodal cap as **6**, but is opposite to the structure of **4** obtained from molecular mechanics calculations.[6]

The lone pair of electrons at the bridging N atom points inside, in agreement with force field calculations (see below) predicting this geometry to be more stable than the *exo*-cone conformation. It should be noted that triethanolamine itself also prefers the C_3-symmetrical *endo*-conformation according to quantum chemical calculations.[17] The diameter of the cavity formed by the substituents at the lower rim is approximately 4–6 Å (distances between oxygen atoms O1, O4, O7: 3.98–4.32 Å; distances between methylene carbon atoms adjacent to carbonyl: 5.26–5.88 Å). Given these dimensions, it should be possible that included guests (e.g. all alkali ions, Ag^+, etc.) do not only reside in the calixarene cavity but slip down deep into the appended basket.

Table 1. Potential energies *E* and symmetry of typical conformations of calix[6]arene **6** (force field calculations)

Conformation	E^a	E_{rel}^a	Symmetry
endo-cone[b,c]	429.7	0.0	C_3
endo-cone[b,d]	435.4	5.7	C_1
1,3,5-alternate	436.7	7.0	C_3
Partial cone	448.4	18.7	C_1
exo-cone[b]	465.0	35.3	C_1
Pseudo partial cone	469.0	39.3	C_1
1,2-alternate	470.3	40.6	C_1
1,3-alternate	470.6	40.9	C_1

[a] Kilocalories per mol (kcal mol^{-1}).

[b] *Endo* and *exo* refer to direction of lone pair of electrons at N.

[c] Methyl groups of OMe pointing outwards.

[d] Methyl groups of OMe pointing inside calixarene cavity.

The solvent molecules in the crystal serve to fill the void between calixarene molecules in the crystal lattice. As in similar cases, high thermal motion and disorder did not allow determination of their positions accurately. Only one $CHCl_3$ molecule seems to maintain a weak interaction with the calixarene through C—H···Cl contacts with the three *t*Bu groups forming the lid above the upper rim (see above).

2.2. Molecular modeling studies

These studies were performed to obtain an estimate of the differences in energy of typical conformers of triply bridged calixarene **6**. Due to the size of the macrocyclic system, force field calculations (Merck94 force field as implemented in PC Spartan Pro)[18,19] were carried out. The C_3-symmetrical cone conformation was identified as the most stable one; in agreement with the solid-state structure (see Fig. 2), the arrangement with the OMe groups pointing away from the calixarene cavity is somewhat more favorable than the opposite direction (Table 1). The 1,3,5-alternate arrangement of the calixarene moiety is not much higher in energy than the energy-minimized conformation. Both calixarene conformations have C_3 symmetry and show a very compact overall shape of the molecule.

2.3. Complexation properties studied by MALDI-TOF mass spectrometry

Mass spectrometry is a feasible method to elucidate cation···π-interactions[20] of a receptor molecule with charged guests in the gas phase.[21] In this work MALDI-MS techniques were used to study the non-covalent intermolecular interactions between calixarene **6** and alkali metal ions. Samples of the receptor–metal ion mixtures were prepared by mixing a solution of the matrix (4-hydroxy-α-cyanocinnamic acid) in THF with solutions of **6** and metal ions in acetonitrile. Ionization was achieved using a pulsed laser (λ=377 nm). When mixtures of **6** with individual metal ions were prepared, the main peak was $[LM]^+$ (L=**6**, M=Li, Na, K, Cs) indicating a 1:1 ratio for the complex formed in the gas phase. In the case of Cs^+, $[LCs_4]^{4+}$ was observed with high relative intensity together with $[LCs]^+$. In the presence of a mixture of all four metal ions, the calixarene exhibited a very high selectivity for Cs^+ ions (Fig. 3).

3. Conclusion

With calixarene **6**, we have added a novel example to the so far small set of calix[6]arenes which are rigidified by C_3-symmetrical A,C,E-bridging at the lower rim and we

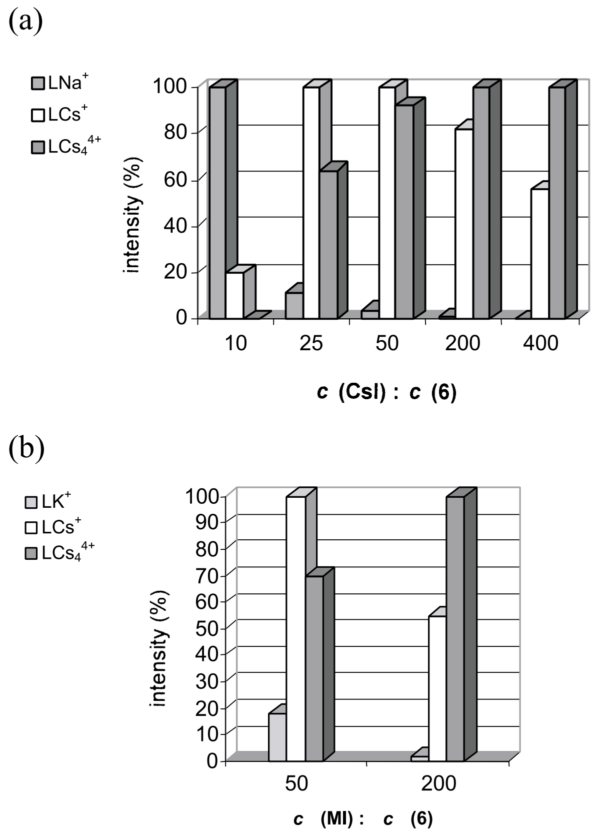


Figure 3. Complexation properties of calix[6]arene **6** towards alkali metal ions (studied by MALDI-TOF mass spectrometry). (a) Complexation with CsI at different concentration ratios; (b) selectivity towards MI (M=K, Cs; Li and Na not shown due to negligible intensities).

have provided the first solid-state structure for this structural type. The temperature-dependent NMR spectra in solution do not give evidence for ring inversion in the calixarene part of the molecule, but they indicate a positional equilibrium for the protons of the methoxy groups: they point away from the calixarene cavity at low temperature, in complete agreement with the solid-state structure, and prefer the inward orientation at ambient temperature and above. According to MALDI-MS experiments, calixarene **6** shows a distinct selectivity for Cs as compared to K, Na, and Li ions. These observations should encourage a closer look at the complexation properties of the capsule-like molecules of **6** in solution.

4. Experimental

4.1. Calixarene 6

5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-trimethoxy-38,40,42-trihydroxycalix[6]arene[15] (**2**) (507 mg, 0.49 mmol) was dissolved in anhydrous THF (50 mL) and anhydrous DMF (10 mL). The solution was cooled at 0°C, and sodium hydride (80%, 200 mg, 3.5 mmol) was added. The solution was brought to rt, stirred for 30 min, then heated to reflux for 10 min. A solution of tris(chloromethylcarbonyloxyethyl)-amine[22] (**7**) (150 mg, 0.63 mmol) in DMF (10 mL) was added dropwise, and the reaction mixture was refluxed for 16 h. The mixture was cooled and poured into cold 1N aq. HCl (100 mL). The water solution was extracted with $CHCl_3$ (3×50 mL). The extract was washed with water and brine, and dried (Na_2SO_4). Column chromatography on silica gel using chloroform/ethyl acetate (20:1) as the eluent yielded compound **6** as a white powder. Yield: 150 mg (23%); mp >300°C. IR (KBr): ν=2962, 1763, 1482 cm^{-1}. MS (MALDI-TOF): *m*/*z*=1284.6 [MH^+]. ^1H NMR (500.13 MHz, $CDCl_3$, 303 K): δ=0.88 (s, 27 H), 1.37 (s, 27 H), 2.88 (t, 6 H, NCH_2), 2.96 (broadened s, 9 H, OCH_3), 3.45 (d, *J*=15.3 Hz, 6 H, $ArCH_2Ar$), 4.34 (t, 6 H, OCH_2CH_2), 4.40 (d, *J*=15.3 Hz, 6 H, $ArCH_2Ar$), 4.69 (broad, 6 H, OCH_2CO), 6.81 (s, 6 H, ArH), 7.29 (s, 6 H, ArH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=30.30 ($ArCH_2Ar$), 31.33 (CMe_3), 31.56 (CMe_3), 34.04 (CMe_3), 34.23 (CMe_3), 52.19 (NCH_2), 60.87 (OMe), 61.91 (NCH_2CH_2), 69.49 ($ArOCH_2$), 124.46, 128.47, 132.77, 132.89, 146.29, 146.32, 151.13, 154.65, 170.02. Anal. calcd. for $C_{81}H_{105}NO_{12}$: C 75.72, H 8.24, N 1.09; found C 74.61, H 8.08, N 1.00.

4.2. X-Ray crystal structure determination of 6

Crystal data: $C_{81}H_{105}NO_{12} \times 5\,CHCl_3 \times CH_3OH$; *M*=1913.5 g mol^{-1}; triclinic space group $P\bar{1}$, *a*=13.852(1), *b*=16.227(2), *c*=22.565(3) Å, α=84.26(1), β=87.67(1), γ=88.86(1)°; *V*=5041(9) $Å^3$; *Z*=2; d_{calcd}=1.260 Mg m^{-3}; μ(Mo-K_α)=0.463 mm^{-1}. *Data collection*: *T*=173 K, crystal size 0.69×0.54×0.38 mm^3, imaging-plate instrument STOE IPDS; radiation Mo-K_α; Θ range 1.76–24.11°; 32,699 reflections collected, 15,034 independent reflections (R_{int}=0.0676). *Structure solution and refinement*: structure solution by direct methods (program SHELXS-86), full-matrix least-squares refinement on F^2 (program SHELXL-97) with 15,034 data, 1190 variables, and 21 restraints. Hydrogen atoms are in calculated positions and were treated as riding atoms. The thermal parameters of most of the *tert*-butyl groups and solvent molecules suggested some degree of disorder. For two *tert*-butyl groups and one chloroform molecule, this disorder was resolved by refining two sets of positions for the Me groups and chlorine atoms, respectively; for the methanol molecule, three orientations of the C—O bond were refined. *R*=0.0978 for 5689 observed reflections [$I>2\sigma(I)$], R_w=0.3177 for all reflections, residual electron density between 0.98 and −0.68 electrons $Å^{-3}$.[23]

4.3. MALDI-TOF-MS study of complexation

The mass spectrometer used was a KOMPACT MALDI III laser desorption reflectron time-of-flight instrument (Shimadzu/Kratos). 4-Hydroxy-α-cyanocinnamic acid (HCCA) was used as the matrix. Samples were deposited on target surfaces after mixing 100 μL of a THF solution of HCCA (10 mg in 1 mL) and 200 μL of an acetonitrile solution of **6** (2.0×10^{-5} M) with the proper volume of a metal salt solution in acetonitrile (5.0×10^{-4} M). Ionization was achieved by using a pulsed nitrogen laser operating at 377 nm. All spectra were obtained in positive-ion reflector mode; 200 single shots were accumulated in order to obtain a good signal-to-noise ratio.

Acknowledgements

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