

Self-Assembled Hydrogen-Bonded Molecular Cages of Calix[6]arenetricarboxylic Acid Derivatives

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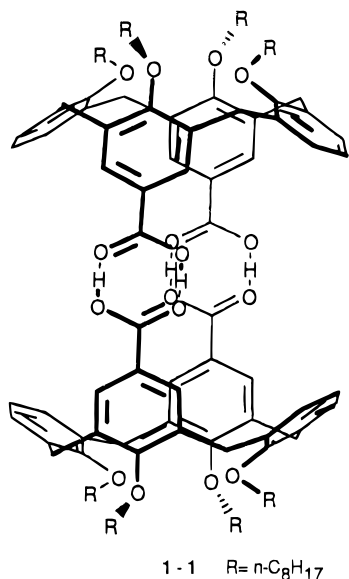
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Introduction

The formation of molecular cages able to encapsulate neutral or charged species is a topic of current interest in supramolecular chemistry. Following the pioneering work of Cram, who first synthesized the extreme case of a carcerand where the guest is irreversibly trapped into the host,¹ several cage molecules have been synthesized, mainly through covalent links between two cavitated subunits.²

Only recently, the reversible formation of a molecular capsule through hydrogen bonding³ or metal-assisted⁴ dimerization has been reported. Hydrogen-bonded calix-arene dimers so far reported refer to urea derivatives of calix[4]arene, which have a strong tendency to aggregate via hydrogen bonding between NH and CO functions present at the upper rim⁵ and to head-to-tail adducts of calix[4]arenes blocked in the cone conformation.⁶

We have recently found that the tetrakis(octyloxy)-calix[4]arenedicarboxylic acid **1** in the cone conformation is able to reversibly form a dimeric structure in solution via intermolecular association of the carboxylic acid functions.⁷ (See following formula).



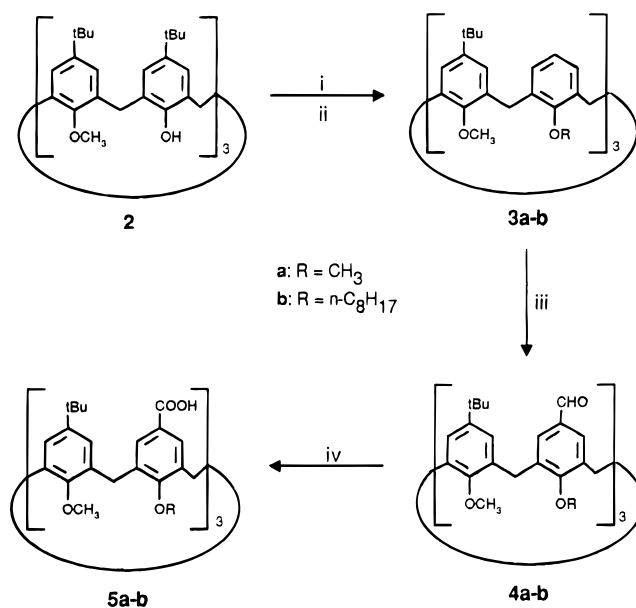
We have now extended these studies to conformationally more mobile calix[6]arene derivatives to verify the possibility of rigidifying these derivatives via dimeriza-

(1) Cram, D. J.; Karbach, S.; Kim, Y. H.; Baczyński, L.; Kallemeyn, G. W. *J. Am. Chem. Soc.* **1985**, *107*, 2575–2576.

(2) See, for example: Cram, D. J.; Cram, M. J. In *Container Molecules and their Guests*, Monographs in Supramolecular Chemistry; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Letchworth, UK, 1994.

(3) See, for example: Rebek, J., Jr. *Chem. Soc. Rev.* **1996**, 255–264.

Scheme 1^a



^a (i) AlCl₃, toluene; (ii) CH₃I or nC₈H₁₇Br, Cs₂CO₃, DMF; (iii) HMTA, CF₃COOH; (iv) NaClO₂, NH₂SO₃H, acetone/CHCl₃.

tion and thus to enhance their binding properties in solution, especially toward organic cations.

Results and Discussion

The plan for synthesis took advantage of our recent studies on the selective functionalization of calix[6]arenes both at the lower and upper rim.⁸ The selective 1,3,5-methoxylation of *p*-*tert*-butylcalix[6]arene at the lower rim to give **2**^{8a,b} induces a reactivity of the *para* position of phenolic units different from that of the anisole units of this macrocycle. Selective removal of *tert*-butyl groups, followed by methylation of the free OH groups and formylation, gave compound **4a**,^{8c} which was oxidized to give the corresponding tricarboxylic acid **5a** (see Scheme 1). To enhance the solubility of this compound we have also synthesized the *n*-octyl derivative **5b** through a similar reaction sequence. Both compounds show a similar behavior in different solvents, but for brevity we describe only **5a**, which is also more interesting, being conformationally more mobile than **5b**.

The ¹H NMR spectrum of **5a** in CD₃OD taken at *T* = 300 K shows, in addition to two singlets for the aromatic protons at $\delta = 7.76$ and 6.95 ppm, two distinct signals for the methoxy groups at $\delta = 3.34$ and 3.05 ppm as well as a singlet for the 12 methylene protons, indicating its great mobility in this solvent. On the contrary the ¹H

(4) Hunter, C. A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1079–1080.

(5) (a) Hamman, B. C.; Shimizu, K. D.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1326–1328. (b) Castellano, R. K.; Rudkevich, D. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1996**, *118*, 10002–10003.

(6) Vreekamp, H. V.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1996**, *61*, 4282–4288.

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(8) (a) Casnati, A.; Minari, P.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1991**, 1413–1414. (b) Janssen, R. G.; Verboom, W.; Reinhoudt, D. N.; Casnati, A.; Freriks, M.; Pochini, A.; Uguzzoli, F.; Ungaro, R.; Nieto, P. N.; Carramolino, M.; Cuevas, F.; Prados, P.; de Mendoza, J. *Synthesis* **1993**, 380–386. (c) Casnati, A.; Domiano, L.; Pochini, A.; Ungaro, R.; Carramolino, M.; Magrans, J. O.; Nieto, P. N.; López-Prados, J.; Prados, P.; de Mendoza, J.; Janssen, R. G.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1995**, *51*, 12699–12720.

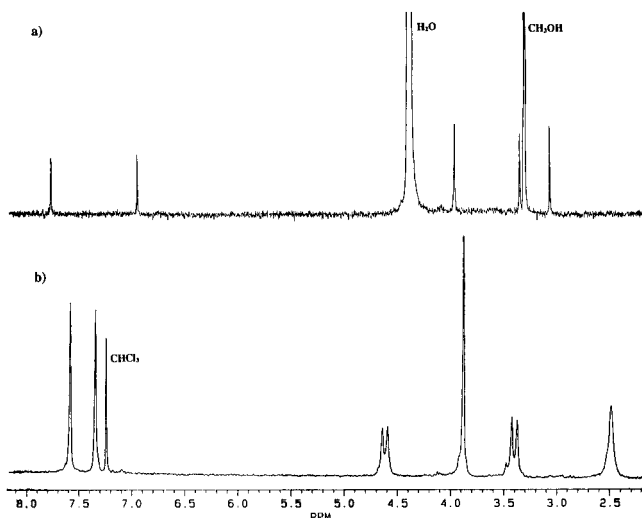
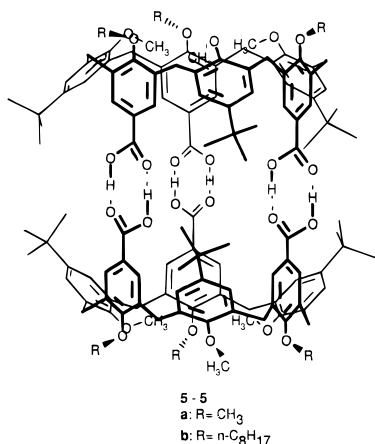


Figure 1. (a) ^1H NMR (300 MHz) spectrum of **5a** in CD_3OD at 300 K; (b) ^1H NMR (300 MHz) spectrum of **5a·5a** in CDCl_3 at 300 K.

NMR spectrum of **5a** taken in CDCl_3 at the same temperature shows, in addition to two singlets for the aromatic protons at $\delta = 7.61$ and 7.37 ppm, two singlets for the methoxy groups at $\delta = 3.89$ and 2.51 ppm as well as two distinct doublets at $\delta = 4.63$ and 3.42 ppm for the bridging methylene protons. These data are in agreement with a rigidified flattened cone structure⁹ and strongly support the hypothesis of a **5a·5a** dimer formation (see Figure 1).

In fact, to ensure the best stereochemical arrangement between the two interacting carboxylic groups, two connected aromatic nuclei belonging to different subunits adopt an almost coplanar orientation. This implies that the six aromatics blocked by hydrogen bonding define a trigonal prism perpendicular to the mean plane containing the methylene groups of the calix[6]arene, forcing the other six to be more flattened (See following formula).



In this structure the three methoxy groups on the *tert*-butyl-containing aromatic nuclei appear as "locked" (on the NMR time scale) in the aromatic cavity of the calix, thus experiencing a high field shift at $\delta = 2.51$ ppm. This behavior is typical of rigidified 1,3,5-trimethoxy-2,4,6-trialkoxycalix[6]arenes.^{8a,9}

(9) van Duynhoven, J. P. M.; Janssen, R. G.; Verboom, W.; Franken, S. M.; Casnati, A.; Pochini, A.; Ungaro, R.; de Mendoza, J.; Nieto, P. N.; Prados, P.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1994**, *116*, 5814–5822.

In CHCl_3 , the more soluble **5b** is also present as dimer **5b·5b** and shows ^1H NMR spectra in CDCl_3 similar to the dimer **5a·5a**. Osmometric molecular weight determination of **5b** in CHCl_3 solution ($\text{MW} = 2770 \pm 550$; calcd 2628) as well as desorption chemical ionization mass spectrometry (see the Experimental Section) confirm this hypothesis.

The rigidification of the host, through this self-assembly process, strongly influences its molecular recognition properties. We have evaluated these properties using several *N*-methylpyridinium iodides as guests.

By adding variable amounts of the host to a saturated solution of *N*-methylpyridinium iodide in CDCl_3 , a significant upfield shift of all signals of the guest (0.5–0.8 ppm) was observed in the ^1H NMR spectra, supporting the hypothesis of an *endo*-cavity complex formation. On the contrary, when using trialdehyde **4b** no significant variation of the chemical shift of the guest was observed. At 300 K, fast exchange between complexed and free guest was observed, giving a single averaged signal. Assuming a dimer formation, the nonlinear least-squares analysis of the ^1H NMR titration data gave a stability constant of 347 ± 8 ($\text{dm}^3 \cdot \text{mol}^{-1}$).¹⁰ The Job's plot¹¹ analysis of the titration data shows that the binding stoichiometry between **5b·5b** and *N*-methylpyridinium iodide in CDCl_3 is 1:1, further supporting the dimeric structure of the host.

With the aim of studying the effect of the size and shape of the guest on the selectivity of complexation of host **5b·5b**, *N*-methylpicolinium iodide isomers were employed. Interestingly, while with *N*-methyl-2-picolinium iodide no evidence of complexation was obtained, with *N*-methyl-4-picolinium iodide a stability constant of 234 ± 6 ($\text{dm}^3 \cdot \text{mol}^{-1}$) was observed. These data indicate a strong influence of the size and shape of the guest on the complexation process.

Conclusions

In conclusion, we have verified the possibility of preparing efficient hosts by the more rigid and extended cavity hydrogen-bonded dimers obtained via self-assembly of tricarboxy derivatives of calix[6]arenes. To compare the efficiency of these systems, we are currently synthesizing similar double calix[6]arenes bridging the two subunits by covalent bonds to obtain carrier systems able to transport cations through membranes.

Experimental Section

General. All reactions were carried out in a nitrogen atmosphere. All reagents and solvents were of reagent grade quality, were obtained from commercial suppliers, and were used without further purification. Chemical shifts (δ) are expressed in ppm relative to internal tetramethylsilane (TMS). Mass spectra were determined in the CI mode (CH_4). Melting points are uncorrected. The calixarene **2^{8a,b}** was synthesized according to literature procedures. Osmometric measurements were carried out in chloroform at 37°C using a vapor pressure osmometer. Calibration curves were obtained using the trimethyl esters of **5b**.¹² The molecular weight determination of **5b·5b**

(10) Preliminary data obtained measuring the association constant in CDCl_3 in the 288–313 K range indicate that the complexation process is driven by enthalpy gain ($\Delta H^\circ = -13.8 \pm 0.5$ kJ/mol; $T\Delta S^\circ = 0.8 \pm 0.5$ kJ/mol).

(11) Job, A. *Liebigs Ann. Chem.* **1928**, *9*, 113.

(12) The corresponding trimethyl ester was obtained by treating an ether suspension of the tricarboxy acid derivative **5b** with an excess of diazomethane. The spectral data are in agreement with those expected.

was performed in three separate series of measurements and gave a molecular weight of 2770 ± 550 D (calculated 2628 D). The ^1H NMR titrations with ammonium salts ($(5.00 \pm 0.05) \times 10^{-3}$ M) in CDCl_3 were performed at 300 K using methods reported elsewhere.¹³ Fast exchange between the complexed and free guest was observed, giving a single signal averaged between the two forms, the chemical shift of which varies with the ratio between host and guest.

5,17,29-Tris(1,1-dimethylethyl)-37,39,41-trimethoxy-38,40,42-tris-(*n*-octyloxy)calix[6]arene (3b). To a solution of **2** (0.50 g, 0.59 mmol) dissolved in DMF (25 mL) were added Cs_2CO_3 (1.16 g, 3.56 mmol) and *n*- $\text{C}_8\text{H}_{17}\text{Br}$ (0.69 g, 3.59 mmol). The reaction mixture was heated at 90 °C for 16 h. The solvent was evaporated under reduced pressure, and the residue was taken up with a solution of HCl (10% w/v, 100 mL) and extracted with CH_2Cl_2 (2×100 mL). The combined organic solutions were washed with water (2×60 mL) and brine (50 mL) and dried over Na_2SO_4 . After removal of the solvent, the resulting crude product was purified by column chromatography (silica gel, hexane:THF = 99:1) and gave **3b** in a quantitative yield as a viscous oil: ^1H NMR (300 MHz, CDCl_3) δ = 0.98 (t, 9H, J = 6.9 Hz), 1.4–1.8 (m, 63H), 2.74 (s, 6H), 2.98 (s, 3H), 3.8 (bs, 4H), 4.1 (bs, 10H), 4.16 (t, 2H, J = 6 Hz), 4.21 (t, 2H, J = 6 Hz), 6.7–6.8 (m, 9H), 7.30 (s, 6H); ^{13}C (75 MHz, CDCl_3) δ = 14.0, 22.6, 26.2, 29.2, 29.5, 30.4, 30.5, 31.5, 31.7, 59.8, 65.3, 67.8, 72.7, 123.1, 127.0, 127.4, 133.4, 134.7, 145.7, 154.4, 154.6; mass spectrum m/e 1183 (MH^+ , 100). Anal. Calcd for $\text{C}_{81}\text{H}_{114}\text{O}_6$: C, 82.18; H, 9.71. Found: C, 81.83; H, 10.25.

11,23,35-Triformyl-5,17,29-tris(1,1-dimethylethyl)-37,39,41-trimethoxy-38,40,42-tris-(*n*-octyloxy)calix[6]arene (4b). To a solution of **3b** (0.40 g, 0.34 mmol) in CF_3COOH (9 mL) was added hexamethylenetetramine (2.00 g, 14.30 mmol). The reaction was refluxed for 6 h, quenched by pouring it into a stirred cooled solution of HCl (10% w/v, 100 mL), and extracted with CH_2Cl_2 (2×100 mL). The combined organic solutions were then washed with water (2×100 mL) and brine (100 mL) and dried over Na_2SO_4 . After the solvent was evaporated, the resulting crude product was purified by column chromatography (silica gel, hexane:THF = 85:15) to give 0.28 g (65% yield) of **4b** as a white solid: mp = 119–120 °C; ^1H NMR (300 MHz, CDCl_3) δ = 0.8–0.9 (m, 9H), 1.1–2.0 (m, 63H), 2.7 (bs, 9H), 3.6 (bs, 6H), 3.8 (bs, 6H), 4.3 (bs, 6H), 7.2 (bs, 12H), 9.6 (bs, 3H); ^{13}C (75 MHz, CDCl_3) δ = 14.0, 22.6, 26.1, 29.2, 29.5, 30.3, 30.7, 31.5, 31.8, 59.9, 65.3, 73.5, 127.4, 131.9, 132.7, 135.6, 146.5, 154.5, 191.5; mass spectrum m/e 1267 (MH^+ , 100); IR (cm^{-1}) 1685 (s). Anal. Calcd for $\text{C}_{84}\text{H}_{114}\text{O}_9$: C, 79.58; H, 9.06. Found: C, 79.25; H, 9.58.

General Procedure for the Synthesis of Calix[6]arene-carboxylic Acids 5a and 5b. The appropriate calix[6]arene trialdehyde (**4a** or **4b**) (0.195 mmol) was dissolved in a mixture

of CHCl_3 (10 mL) and acetone (10 mL) and cooled at 0 °C. In a separate flask, $\text{NH}_2\text{SO}_3\text{H}$ (0.17 g, 1.75 mmol) and NaClO_2 (0.16 g, 1.46 mmol) were dissolved in H_2O (ca. 1 mL), and the resulting solution was quickly poured into the calixarene solution. After 6 h at room temperature, the solvent was completely evaporated under reduced pressure. The residue was taken up with a HCl solution (10% w/v, 15 mL), filtered on a Buchner funnel, and washed twice with water.

11,23,35-Tricarboxy-5,17,29-tris(1,1-dimethylethyl)-37,38,39,40,41,42-hexamethoxycalix[6]arene (5a). The crude product was triturated with ethyl acetate and filtered, affording 0.17 g (85% yield) of **5a** as a white solid: mp > 300 °C; ^1H NMR (300 MHz, CDCl_3) δ = 1.44 (s, 27H), 2.51 (s, 9H), 3.42 (d, 6H, J = 15 Hz), 3.89 (s, 9H), 4.63 (d, 6H, J = 15 Hz), 7.37 (s, 6H), 7.61 (s, 6H), 13.30 (bs, 3H); ^1H NMR (400 MHz, CD_3OD) δ = 1.09 (s, 27H), 3.05 (s, 9H), 3.34 (s, 9H), 3.96 (s, 12H), 6.95 (s, 6H); 7.76 (s, 6H); mass spectrum m/e 985 ($\text{MH}^+ - 2\text{H}_2\text{O}$, 100); IR (cm^{-1}) 1690 (s). Anal. Calcd for $\text{C}_{63}\text{H}_{72}\text{O}_{12}$: C, 74.09; H, 7.11. Found: C, 74.15; H, 7.62.

11,23,35-Tricarboxy-5,17,29-tris(1,1-dimethylethyl)-37,39,41-trimethoxy-38,40,42-tris-(*n*-octyloxy)calix[6]arene (5b). The crude product was triturated in methanol and filtered, affording 0.23 g (90% yield) of **5b** as a white solid: mp 172–174 °C; ^1H NMR (300 MHz, CDCl_3) δ = 0.93 (t, 9H, J = 6.2 Hz), 1.34 (s, 24H), 1.46 (s, 27H), 1.5–1.6 (m, 6H), 1.9–2.0 (m, 6H), 2.5 (bs, 9H), 3.4 (bd, 6H, J = 13.5 Hz), 3.94 (t, 6H, J = 6.4 Hz), 4.6 (bs, 6H), 7.41 (s, 6H), 7.63 (s, 6H), 11.90 (bs, 3H); ^{13}C (75 MHz, CDCl_3) δ = 14.1, 22.6, 26.2, 29.5, 30.4, 31.5, 31.8, 34.4, 61.0, 73.6, 124.8, 128.2, 129.8, 132.3, 134.4, 146.3, 154.5, 159.0, 172.3; mass spectrum m/e 1315 (MH^+ , 20), 1279 ($\text{MH}^+ - 2\text{H}_2\text{O}$, 100), 2629 (2MH^+ , 20), 2593 ($2\text{MH}^+ - 2\text{H}_2\text{O}$, 20); IR (cm^{-1}) 3438 (w), 1690 (s). Anal. Calcd for $\text{C}_{84}\text{H}_{114}\text{O}_{12}$: C, 76.68; H, 8.73. Found: C, 76.74; H, 9.27.

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Supporting Information Available: ^1H NMR spectra of all new compounds **3b**, **4b**, and **5a,b** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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