Synthesis of 5,5′-Bicalix[6]arene and 5,5′-Bicalix[8]arene Systems

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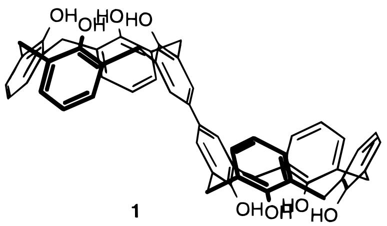
Design and construction of high-order di- or polytopic receptors is a current goal of supramolecular chemistry for the investigation of high-level host properties such as cooperativity, allostery, regulation, etc.[1] Consequently, also in the calixarene field[2] double or multiple macrocyclic structures have received, in recent years, increased attention, and several preorganized structures have been described. The majority of work has been focused on double calix[4]arenes[3] in which the two subunits are linked at their upper (*head*) or lower (*tail*) rim through various spacer elements to give three basic combinations commonly known as *head-to-head*, *head-to-tail*, and *tail-to-tail*.[4] As concerns the larger members of the family, to the best of our knowledge, only two examples are known, both relating to double calix[6]arenes. They are a molecular capsule reported by Shinkai[5] having two units linked head-to-head through six sulfur bridges and a dixanthylene derivative, described by Biali, in which two calix[6]arenes are connected at the level of $ArCH_2$-Ar groups.[6] No example is presently available of double or multiple calix[8]arenes.

Recently we have reported the first example of a bridgeless, head-to-head double calix[4]arene, 5,5′-bicalix[4]arene **1**, with a direct biphenyl-like para-para linkage.[7] Its structural features readily evoke a potential host cooperativity which was confirmed by preliminary studies.[7] This result prompted us to a deeper investigation of chemical[8] and host properties of 5,5′-bicalix[4]arenes and to tackle the synthesis of larger bicalix[*n*]arene systems, very promising novel molecular architectures. In the present paper we report the synthesis, spectroscopic characterization, and conformational features of the first 5,5′-bicalix[6]arene **2** and 5,5′-bicalix[8]arene **3**.



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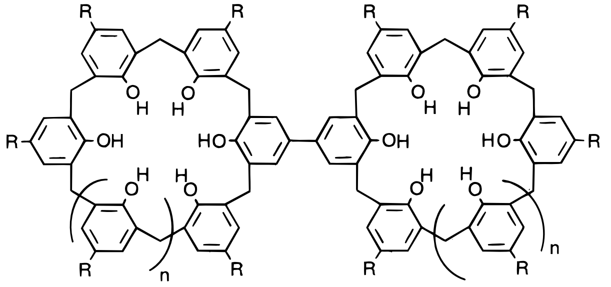

2 n = 1, R = H
3 n = 3, R = Bu^t

As concerns the synthesis of **2**, by analogy with the synthesis of 5,5′-bicalix[4]arene **1**,[7] we first attempted the direct oxidative coupling with ferric chloride of *p*-H-calix[6]arene **2a** which proved useless, probably because of extensive polymerization and polyoxidation. Therefore, to circumvent this difficulty, we resorted to a protection−deprotection procedure using a pentaprotected calix[6]arene. The absence in the literature of a useful procedure for the preparation of this kind of derivative[2] induced us to pursue a careful investigation of the benzoylation of *p*-H-calix[6]arene **2a**. Thus, pentabenzoylcalix[6]arene **2b** was prepared in 93% yield by treatment of **2a** with benzoyl chloride in pyridine (Scheme 1).[9] At room temperature the hitherto unreported **2b** [MALDI-TOF(+) MS 1158 *m*/*z*, MH^+] shows an extremely broad NMR spectrum, since introduction of five benzoyl groups causes a considerable reduction of conformational mobility in solution. However, on heating at 360 K in C_6D_6 the ^1H NMR spectrum shows three diagnostic sharp singlets of equal intensity at 3.81, 3.85, and 3.90 ppm for the $ArCH_2$-Ar groups, as expected by the molecular symmetry of **2b**.

Pentabenzoylcalix[6]arene **2b** was then subjected to oxidative coupling by treatment with $FeCl_3{\cdot}6H_2O$ in refluxing CH_3CN, under the conditions previously adopted for bicalix[4]arene,[7] to give decabenzoyl-5,5′-bicalix[6]arene. This was directly hydrolyzed without purification to give, after column chromatography on Si gel, 5,5′-bicalix[6]arene **2** in 20% yield (Scheme 1).[10] Its structure was established by elemental analysis, MALDI-TOF(+)

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(8) For a preliminary report on the *O*-alkylation of 5,5′-bicalix[4]arene see: Bottino, A.; Cunsolo, F.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* **1998**, *39*, 9549.

(9) Under similar conditions Gutsche and co-workers have isolated hexabenzoyl-*p*-H-calix[6]arene (Gutsche, C. D.; Lin, L.-g. *Tetrahedron* **1986**, *42*, 1633), while in the presence of NaH, the tetrabenzoyl derivative was obtained (Rogers, J. S.; Gutsche, C. D. *J. Org. Chem.* **1992**, *57*, 3152).

(10) The complete IUPAC name for this compound is 5,5′-bicalix[6]arene-37,37′,38,38′,39,39′,40,40′,41,41′,42,42′-dodecaol.

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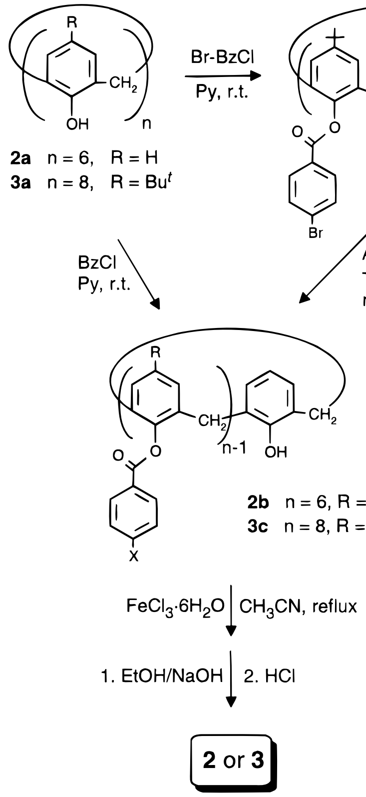
Scheme 1



MS (1272 m/z, MH^+), and ^1H and ^{13}C NMR spectroscopy. In this case also the ^1H NMR spectrum at room temperature exhibited broad signals because of the stabilizing cyclic hydrogen bond involving the free OH groups of the two macrocycles that accordingly give rise to a broad 12 H resonance at 10.40 ppm.[11] In C_6D_6 at 369 K the peaks sharpen, and three signals for $ArCH_2Ar$ are seen at 3.75, 3.76, and 3.81 ppm, in agreement with the molecular symmetry. Formation of the biphenyl bond was confirmed by a characteristic singlet at 135.0 ppm in the ^{13}C NMR spectrum for quaternary carbons (DEPT) involved in the Ar−Ar bond.[7]

As in the previous case, synthesis of a bicalix[8]arene system by direct oxidative coupling of *p*-H-calix[8]arene (**3a** with R = H) proved unsatisfactory. Therefore, to also apply in this case a protection−deprotection procedure, we resorted to heptakis(*p*-bromobenzoyl)-*p*-*tert*-butylcalix[8]arene **3b**, easily obtained from **3a** in good yield without chromatographic purification (Scheme 1).[12] Obviously, in this instance (selective) removal of the *tert*-butyl group of the free phenolic moiety is required to allow oxidative coupling. This was accomplished by treatment of **3b** with $AlCl_3$ (30 equiv) in anhydrous toluene (Scheme 1), which gave mono-de-*tert*-butylated heptabenzoylcalix[8]arene **3c** in 98% yield.[13] Compound **3c** was fully characterized by ^1H and ^{13}C NMR spectroscopy in C_6D_6 at 365 K. In particular, mono-de-*tert*-butylation was proved by a typical *ortho*-coupled triplet at 6.73 ppm (8.3 Hz) in the ^1H NMR spectrum and by the appearance of a doublet at 120.0 ppm in the ^{13}C NMR spectra. It is worth mentioning here that the preparation of **3c** is the first example of a selective reaction at the upper rim of a preformed calix[8]arene.[14]

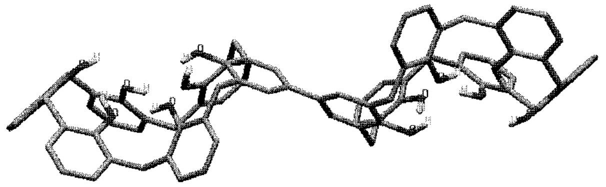


Figure 1. Polytube computer model (H-atoms omitted) of the *anti*-pinched-cones conformation of 5,5′-bicalix[6]arene **2**.

At this point hepta-*tert*-butylcalix[8]arene **3c** was subjected to oxidative coupling by treatment with $FeCl_3 \cdot 6H_2O$ followed by alkaline hydrolysis to yield *p*-*tert*-butyl-5,5′-bicalix[8]arene **3** in 25% yield (Scheme 1).[15] Its dimeric nature was proved by a *pseudo*molecular peak at 2482 m/z in the MALDI-TOF(+) mass spectrum and by a singlet at 135.8 ppm for biphenylic quaternary carbons in the ^{13}C NMR spectra. As expected, NMR spectra of **3** showed broad resonances because of the reduced conformational mobility due to the cyclic hydrogen bond present in each macrocycle, evidenced by broad ^1H NMR signals at δ 9.50 (2 H), 9.54 (4 H), 9.57 (8 H), and 9.78 (2 H).[11] The observation of the signal patterns expected from the molecular symmetry of **3** is made difficult by the overlapping of NMR resonances occurring even under different conditions. For example, a partially resolved four-singlet pattern in a 2:2:2:1 ratio expected for the *tert*-butyl groups is only observed in $(CD_3)_2SO$ at $T > 400$ K.

The conformational mobility of 5,5′-bicalix[6]arene **2** and *p*-*tert*-butyl-5,5′-bicalix[8]arene **3**, pointed out by dynamic NMR spectra, can be due to two main conformational processes, passage of phenol rings through the annulus, and rotation around the biphenyl-like junction.[7] In the case of **2** molecular modeling[16] indicates that it should prefer the *pinched-cone* conformation[17] for the two subunits, which can be *syn* or *anti* oriented according to the torsion angle around the biphenyl bond (32.8° or 132.0°, respectively). Evaluation of MM3 energy in chloroform−model−solvent indicates that the *anti* orientation (Figure 1) should be preferred since it is slightly more stable than the *syn* one. Therefore, the molecule in solution should turn rapidly from the *anti* to the *syn* orientation and *vice versa* while the *cone-to-cone* interconversion has to be within the NMR time scale, as confirmed by the coalescence at 276 K for $ArCH_2Ar$

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[11] Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 6052.

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[13] For examples of selective trans-de-*tert*-butylation in smaller calixarenes see: van Loon, J. D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S. and Reinhoudt, D. N. *J. Org. Chem.* **1990**, *55*, 5639. See, K. A.; Fronczek, F. R.; Watson, W. H.; Kashyap, R. P.; Gutsche, C. D. *J. Org. Chem.* **1991**, *56*, 7256. de Mendoza, J.; Carramolino, M.; Cuevas, F.; Nieto, P. M.; Prados, P.; Reinhoudt, D. N.; Verboom, W.; Ungaro, R.; Casnati, A. *Synthesis* **1994**, 47.

[14] An example of calix[8]arene selectively functionalized at the upper rim was recently obtained by condensation of fragments already bearing different functions: Tsue, H.; Ohmori, M.; Hirao, K. *J. Org. Chem.* **1998**, *63*, 4866.

[15] The complete IUPAC name for this compound is 11,11′,17,17′,23,23′,29,29′,35,35′,41,41′,47,47′-tetradeca-*tert*-butyl-5,5′-bicalix[8]arene-49,49′,50,50′,51,51′,52,52′,53,53′,54,54′,55,55′,56,56′-hexadecaol.

[16] Energies were evaluated with the MM3 force field with GB/SA chloroform−model−solvent as implemented in the program MacroModel V4.5: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

[17] Molins, M. A.; Nieto, P. M.; Sanchez, C.; Prados, P.; de Mendoza, J.; Pons, M. *J. Org. Chem.* **1992**, *57*, 6924. van Hoorn, W. P.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *J. Org. Chem.* **1996**, *61*, 7180.

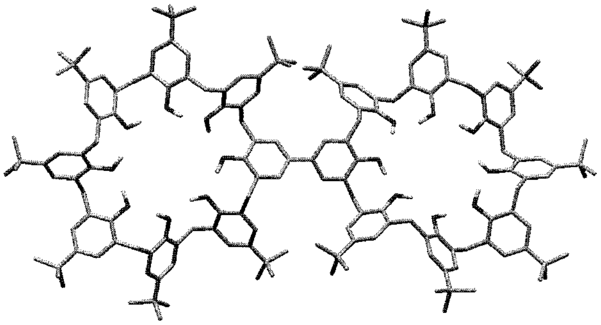

Figure 2. Polytube computer model (H-atoms omitted) of the quasi-planar-pleated-loops conformation of *p*-*tert*-butyl-5,5′-bicalix[8]arene **3**.

signals which give a roughly estimated energy barrier of ca. 13 kcal/mol. Interestingly, at low temperature the ^{1}H NMR spectrum of **2** becomes reminiscent of that of *p*-*tert*-butylcalix[6]arene[17] (**2a** with R = Bu^t), indicating a similar conformation, thus lending support to modeling studies.

Molecular modeling[16] for **3** indicates that the *pleated-loop* should be the most favored conformation for each calix[8]arene subunit.[11,14,18] In this case, rotation around the biphenyl bond does not give rise to a *syn*−*anti* equilibrium because of the planarity of each pleated-loop. In fact, two conformations are found in which the two pleated-loops are quasi-orthogonal (biphenyl torsion angle 125.0°) or quasi-planar (biphenyl torsion angle 36.6°), the latter being 4.5 kcal/mol more stable. In the quasi-planar structure (Figure 2) the *tert*-butyls of the rings adjacent to the biphenyl system give rise to favorable van der Waals interactions as well as to additional steric encumbrance to the biphenyl rotation. Therefore, *p*-*tert*-butyl-5,5′-bicalix[8]arene **3** should preferentially adopt in solution the quasi-planar-pleated-loops conformation, which can also interconvert to its mirror image by the "normal" through-the-annulus flipping of phenol rings, as confirmed by a typical coalescence at 330 K for $ArCH_2$-Ar signals (energy barrier of ca. 13 kcal/mol).[11]

The new members of the 5,5′-bicalixarene family described here open up further potentialities in the field of host−guest chemistry, in particular as ditopic receptors, and constitute versatile skeletons for the construction of various and interesting three-dimensional molecular architectures, with peculiar stereochemical features, exploitable in supramolecular chemistry. Work along these lines is currently in progress in our laboratory.

Experimental Section

General Comments. Elemental analyses were obtained from the Department of Pharmaceutical Sciences, University of Catania. All chemicals were reagent grade and used without further purification. *p*-H-calix[6]arene[9] **2a** and heptakis(*p*-bromobenzoyl)-*p*-*tert*-butylcalix[8]arene **3b**[12] were prepared following literature procedures. NMR spectra were acquired at 250.13 (^{1}H) and 62.9 (^{13}C) MHz under specified conditions. MALDI-TOF mass spectra were acquired using dithranol (1,8,9-trihydroxyanthracene) as matrix.

Preparation of Pentabenzoyl-*p*-H-calix[6]arene 2b. *p*-H-calix[6]arene (**2a**) (1 g, 1.57 mmol) was added to a solution of benzoyl chloride (1.35 mL, 11.6 mmol) in anhydrous pyridine (20 mL), and the suspension was stirred at room temperature for 5 h. The reaction was then quenched by pouring the mixture into 2 N HCl (100 mL), and the precipitate was collected by filtration and washed sequentially with 2 N NaOH, H_2O, and MeOH to give 37,38,39,40,41-pentakis(benzoyloxy)calix[6]aren-42-ol (**2b**): 1.7 g, 93% yield; ^{1}H NMR (250 MHz, C_6D_6, 363 K) δ 3.81, 3.85, 3.90 (s, 4 H each), 6.60−7.20 (m, 33 H), 7.71−8.00 (m, 10 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 31.2 (t), 119.9, 126.1, 127.0 (s), 128.4, 130.1 (d), 132.2, 132.5, 147.0, 153.2, 164.3 (s); MALDI-TOF(+) MS 1158 *m/z* (MH$^+$). Anal. Calcd for $C_{77}H_{56}O_{11}$: C, 79.91; H, 4.88. Found: C, 79.89; H, 4.86.

Mono-de-*tert*-butylation of Heptakis(*p*-bromobenzoyl)-*p*-*tert*-butylcalix[8]arene 3b To Give 3c. $AlCl_3$ (7.5 g, 56.2 mmol) was added to a suspension of **3b** (5 g, 1.9 mmol) in anhydrous toluene (130 mL), and the mixture was kept under stirring for 2 h at room temperature. The reaction was then quenched by adding 1 N HCl (100 mL). The organic phase was evaporated in vacuo, leaving 11,17,23,29,35,41,47-hepta-*tert*-butyl-49,50,51,52,53,54,55-heptakis[(4-bromobenzoyl)oxy]calix[8]aren-56-ol (**3c**): white powder, 4.7 g, 98% yield; ^{1}H NMR (250 MHz, C_6D_6, 360 K) δ 1.01, 1.03, 1.05, 1.09 (s, 18 H, 9 H, 18 H, 18 H), 3.83, 3.88, 3.95 (bs, 4 H, 8 H, 4 H), 6.73 (t, J = 8.3 Hz, 1 H), 6.97 (d, J = 8.3 Hz, 2 H), 7.07−7.22 (m, 14 H), 7.41−7.61 (m, 28 H);^{13}C NMR (62.9 MHz, C_6D_6 375 K) δ 31.4, 31.5 (q), 33.0, 33.8 (t), 34.4 (s), 120.7, 125.7, 126.6, 126.9, 130.8, 131.9, 132.0, 132.2 (d), 146.1, 146.2, 146.4, 149.3, 149.4, 153.4, 163.9, 164.0, 164.3 (s); MALDI-TOF(+) MS 2524 *m/z* (MH$^+$). Anal. Calcd for $C_{133}H_{125}O_{15}Br_7$: C, 63.32; H, 4.99. Found: C, 63.38; H, 5.00.

General Procedure for Oxidative Coupling of 2b and 3c. A suspension of **2b** or **3c** (1 mmol) and $FeCl_3{\cdot}6H_2O$ (8 mmol) in CH_3CN (50 mL) was refluxed under stirring. Additional aliquots of $FeCl_3{\cdot}6H_2O$ (8 mmol) were added at 1-h intervals, until the starting material was no longer detected by TLC. The solvent was then removed by evaporation in vacuo, 2 N HCl was added to the residue, and the solid material was collected by filtration. This crude product was suspended in EtOH (85 mL), and after addition of 15% aqueous NaOH (13 mL) the mixture was refluxed under stirring for 7 h. Most of the EtOH was removed by evaporation in vacuo, the resulting suspension was neutralized with 1 N HCl, and the solid material was collected by filtration.

5,5′-Bicalix[6]arene-37,37′,38,38′,39,39′,40,40′,41,41′,42,42′-dodecaol (2). Compound **2** was obtained (0.25 g, 20% yield) after purification by flash chromatography on Si gel (CH_2Cl_2/petroleum ether, 45:55 v/v): mp dec 250 °C; R_f 0.5 (CH_2Cl_2/petroleum ether, 1:1 v/v); ^{1}H NMR (250 MHz, C_6D_6, 363 K) δ 3.75, 3.76, 3.81 (s, 8 H each), 6.68 (t, J = 7.5 Hz, 4 H), 6.70 (t, J = 7.5 Hz, 4 H), 6.71 (t, J = 7.5 Hz, 4 H), 6.97−7.00 (m, 18 H), 7.27 (s, 4 H), 10.23 (br s, 12 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 32.2, 32.3 (t), 121.9 (d), 127.2, 127.4, 127.6 (s), 128.2, 129.5 (d), 135.0, 148.9, 149.6 (s); MALDI-TOF(+) MS 1272 *m/z* (MH$^+$). Anal. Calcd for $C_{84}H_{70}O_{12}$: C, 79.35; H, 5.55. Found: C, 79.30; H, 5.56.

11,11′,17,17′,23,23′,29,29′,35,35′,41,41′,47,47′-Tetradeca-*tert*-butyl-5,5′-bicalix[8]arene-49,49′,50,50′,51,51′,52,52′,53,-53′,54,54′,55,55′,56,56′-hexadecaol (3). Compound **3** was isolated (0.62 g, 25% yield) by flash chromatography on Si gel (CH_2Cl_2/petroleum ether, 1:3 v/v); mp dec 235 °C; R_f 0.4 (CH_2Cl_2/petroleum ether, 1:4 v/v); ^{1}H NMR [250 MHz, $(CD_3)_2SO$, 390 K] δ 1.25, 1.28, 1.29, 1.30 (s, 18 H, 36 H, 36 H, 36 H), 3.16 (br s, 32 H), 7.13 (br s, 32 H), 9.20 (br s, 16 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 31.5, 31.6 (q), 32.4 (t), 34.1 (s), 125.6, 126.0, 127.6 (d), 128.3, 128.7 (s), 128.8 (d), 129.4, 135.8, 144.8, 144.9, 146.6, 146.7, 148.4 (s); MALDI-TOF(+) MS 2482 *m/z* (MH$^+$). Anal. Calcd for $C_{168}H_{206}O_{16}$: C, 81.32; H, 8.37. Found: C, 81.35; H, 8.34.

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