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Synthesis and Characterization of Rigid, Deep-Cavity Calix[4]arenes

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One of the major goals of calixarene chemistry has been the development of compounds which mimic the structure or function of enzymes.[1,2] To that end, considerable effort has been expended in elaborating the cavity of calix[4]arene by derivatization at the "upper rim". One of the most interesting compounds in this regard is *p*-phenylcalix[4]arene (**1**), which, because of its rigid, extended hydrophobic cavity, should be capable of binding large organic guest molecules. However, the chemistry of the deep-cavity calix[4]arenes has been slow to develop because of the lack of high-yield synthetic pathways to even the simplest of such compounds. Gutsche and No reported the synthesis of **1** by a stepwise route in 2.6% overall yield starting from the phenol,[3,4] and later noted the failure of the direct substitution route starting from calix[4]arene.[5] More recently, Arduini et al. have achieved a maximum of 15% yield by employing mercury- or thallium-containing calix[4]arenes.[6] In this communication we report a general synthetic strategy for rigid, deep-cavity calix[4]arenes, which affords **1a** (the tetramethyl ether of **1**) in 75% yield from the readily available bromocalix[4]arene tetramethyl ether,[5,7] and the characterization of several such derivatives by NMR, mass spectroscopy, and single crystal X-ray diffraction techniques.

The synthetic method, shown in Scheme I, involves the palladium-catalyzed reaction of arylboronic acids[8] with *p*-bromocalix[4]arene tetramethyl ether.[5,7] The compounds thus far isolated include those with R = phenyl (**1a**, 75%), *p*-biphenyl (**2**, 43%), *p*-tolyl (**3**, 62%), 3-pyridyl (**4**, 25%), 2-thiophenyl (**5**, 69%), and C_6H_4-O-C_6H_5 (**6**, 63%).[9] All of these new derivatives exhibit the parent ion in the electron impact mass spectrum and are further characterized by complex ^1H and ^{13}C NMR spectra. Compounds **1a**, **2**, **5**, and **6** have been subjected to single crystal X-ray structure determination.

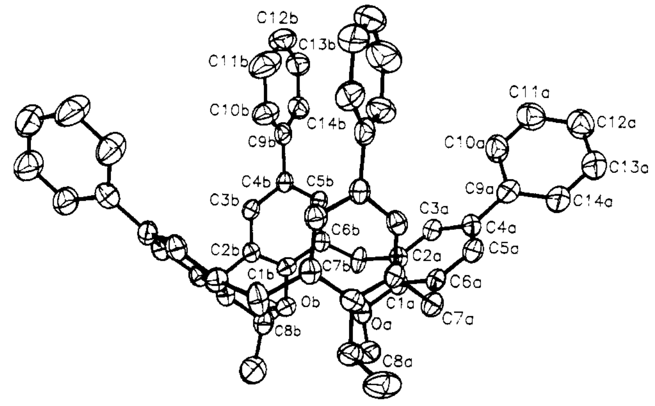
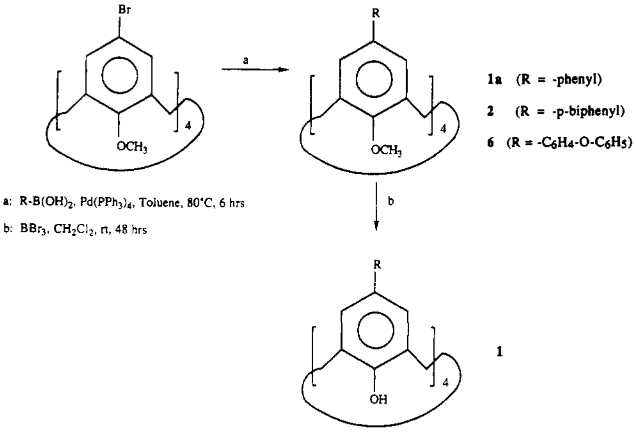


Figure 1. Structure of *p*-phenylcalix[4]arene tetramethyl ether (**1a**). The molecule resides on a crystallographic twofold axis.

Scheme I



1a (R = -phenyl)
2 (R = -p-biphenyl)
6 (R = -C_6H_4-O-C_6H_5)

a: R-$B(OH)_2$, $Pd(PPh_3)_4$, Toluene, 80°C, 6 hrs
b: BBr_3, CH_2Cl_2, rt, 48 hrs

p-Phenylcalix[4]arene tetramethyl ether (**1a**) (Figure 1) crystallizes in the cone conformation and resides on a crystallographic twofold axis.[10] The envelope-shaped conformation with C12a···C12a′ = 15.8 Å and C12b···C12b′ = 4.2 Å does not provide a cavity. Indeed, the two lower aromatic rings which face each other are nearly parallel (they are inclined toward one another by 11°) and show a centroid···centroid separation of 5.1 Å, while their phenyl substituents exhibit a centroid···centroid distance of 4.4 Å.

The last step in Scheme I has been effected with BBr_3 and *p*-phenylcalix[4]arene has been structurally characterized.[11] Interestingly, the cavity is opened by the demands of the intramolecular O—H···O hydrogen bonding among the phenol groups to produce a rather symmetrical cone (C12a···C12c = 14.9 Å; C12b···C12d = 12.2 Å) (Figure 2). The spacious cavity contains a $CHCl_3$ molecule.

The partial cone conformation exhibited by *p*-biphenylcalix[4]arene tetramethyl ether[12] (**2**) (Figure 3) shows intramolecular attractive aromatic···aromatic interactions between the two arms

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[1] Gutsche, C. D.*Calixarenes*; Royal Society of Chemistry: Cambridge, 1989.

[2] *Calixarenes: a Versatile Class of Macrocyclic Compounds*; Bohmer, V., Vicens, J., Eds.; Kluwer: Dordrecht, 1990.

[3] Gutsche, C. D.; No, K. H. *J. Org. Chem.* **1982**, *47*, 2708.

[4] No, K. H.; Gutsche, C. D. *J. Org. Chem.* **1982**, *47*, 2713.

[5] Gutsche, C. D.; Pagoria, P. F. *J. Org. Chem.* **1985**, *50*, 5795.

[6] Arduini, A.; Pochini, A.; Rizzi, A.; Sicuri, A. R.; Ungaro, R. *Tetrahedron Lett.* **1990**, *31*, 4653. This reference also contains the synthesis of *p*-phenylcalix[4]arene tetraethoxyethyl ether from *p*-iodocalix[4]arene tetraethoxyethyl ether in 95% yield using PhZnCl and $Ni(PPh_3)_4$.

[7] Hamada, F.; Bott, S. G.; Orr, G. W.; Coleman, A. W.; Zhang, H.; Atwood, J. L. *J. Incl. Phenom.* **1990**, *9*, 195.

[8] Thompson, Y. J.; Guadino, J. *J. Org. Chem.* **1984**, *49*, 5237.

[9] The synthesis of *p*-phenylcalix[4]arene tetramethyl ether (**1a**) is accomplished as follows: to a stirred solution of 1.194 g (1.5 mmol) of *p*-bromocalix[4]arene tetramethyl ether in 10 mL of toluene was added 2.31 g (2.0 mmol) of $Pd(PPh_3)_4$ under N_2. Aqueous 2 M Na_2CO_3 (5 mL) and 0.83 g (1.7 mmol) of phenyl boronic acid in 5 mL of MeOH were then added. The vigorously stirred mixture was heated to 80 °C for 6 h. It was then partitioned between 100 mL of CH_2Cl_2 and 50 mL of 2 M Na_2CO_3 containing 5 mL of concentrated NH_3. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and evaporated to dryness under reduced pressure. Column chromatography of the crude product over silica gel afforded pure *p*-phenylcalix[4]arene tetramethyl ether (**1a**) (1.10 g, 75%). Recrystallization from chloroform produced X-ray diffraction quality crystals. All of the new compounds exhibited the parent ion in their electron impact mass spectra.

[10] *p*-Phenylcalix[4]arene tetramethyl ether (**1a**) belongs to the monoclinic space group *C*2/*c* with $a = 12.827(2)$, $b = 18.941(3)$, and $c = 18.301(2)$ Å, $\beta = 100.57(1)°$, and $d_{calc} = 1.20$ g cm^{-3} for $Z = 4$. Refinement based on 1136 observed reflections led to $R = 0.065$.

[11] *p*-Phenylcalix[4]arene·$2CHCl_3$ (**1**·$2CHCl_3$) crystallizes in the triclinic space group $P\bar{1}$ with $a = 12.830(3)$, $b = 13.320(3)$, and $c = 16.394(3)$ Å, $\alpha = 68.65(1)$, $\beta = 76.20(1)$, $\gamma = 63.14°$, and $Z = 2$. Refinement based on 4124 observed reflections has given $R = 0.091$. One of the two $CHCl_3$ molecules resides within the cavity, and the other is positioned in the lattice external to the cavity. Preparation of **1**: 20 mL of a solution of BBr_3 in CH_2Cl_2 was added dropwise to a solution of 0.50 g of **1a** in 25 mL of CH_2Cl_2, and the mixture was stirred under N_2 at room temperature for 48 h. Formation of the product was monitored by TLC. The reaction mixture was poured into H_2O and stirred for 30 min. The organic layer was then evaporated. The residue was dissolved in $CHCl_3$, and methanol was added to the solution. Brownish crystals of **1** were grown by slow evaporation of the solution. Yield, 0.20 g, 43%; mp > 300 °C dec.

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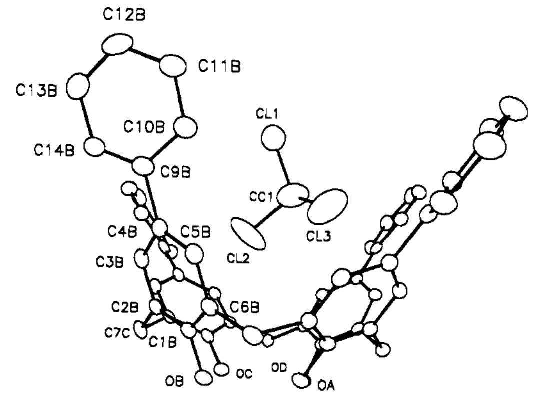

Figure 2. Structure of *p*-phenylcalix[4]arene (1) with the guest $CHCl_3$ molecule.

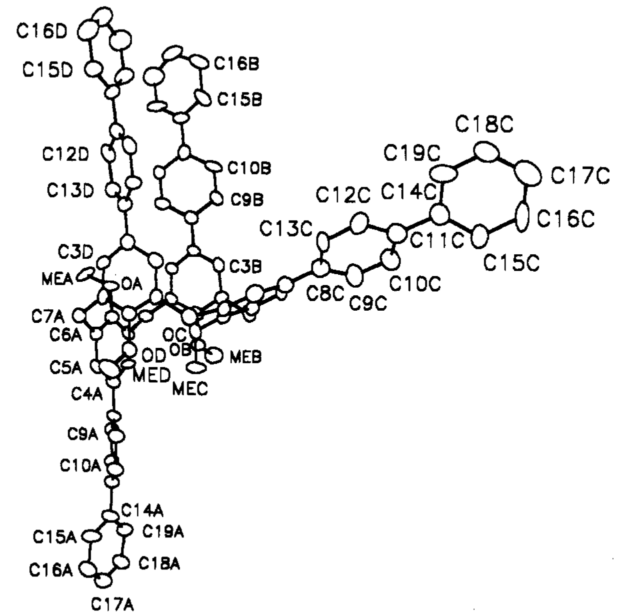

Figure 3. Partial cone conformation of *p*-biphenylcalix[4]arene tetramethyl ether (2).

which face each other.[13] The two aromatic rings at the base of the cavity are almost exactly parallel, while the central ones exhibit a dihedral angle between phenyl-ring planes of 72° and the ones at the top show a similar value of 78°. The centroid···centroid separations are 5.29, 5.23, and 5.04 Å, respectively, which indicate that the edge-to-face π-π stacking at the top of the cavity is of sufficient strength to completely close the cavity. Indeed, these values are within the range found for intermolecular π-π interactions and the 5.04 Å, 78° values are close to the 5.02 Å, 87° values in crystalline benzene.[14]

p-Biphenylcalix[4]arene (**2**), C_6H_5-O-*p*-C_6H_4calix[4]arene (**5**), and 2-thiophenylcalix[4]arene (**6**) tetramethyl ethers are all found in the partial cone conformation.[2,7,15] For the former two compounds, a new type of partial cone is obtained in which the arm directed down is almost exactly parallel to the two arms directed up from the cavity.

It should be noted that the methyl ethers of calix[4]arenes are conformationally mobile in solution at room temperature. Gutsche et al. have interpreted a complex pattern of resonances in both the aromatic and the -CH_2-/-OMe regions of the ^1H NMR spectra of calix[4]arene tetramethyl ether and *p-tert*-butylcalix[4]arene tetramethyl ether in terms of a partial cone conformation.[16] Compounds **1a**, **2**, **5**, and **6** exhibit spectra similar to those found by Gutsche et al. We must therefore assume at this stage that **1a**, **2**, **5**, and **6** all exist predominantly in the partial cone conformation in solution. The crystallization of **1a** in the cone conformation may be driven by crystal packing considerations.

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Supplementary Material Available: Procedure for data collection, structure solution, and refinement; tables of crystal data, final fractional coordinates, thermal parameters, bond lengths, and bond angles for **1**, **1a**, **2**, and **5**; and a diagram showing the structure of **5** (27 pages). Ordering information is given on any current masthead page.

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(12) *p*-Biphenylcalix[4]arene tetramethyl ether (**2**) crystallizes in the triclinic space group $P\bar{1}$ with $a = 10.832(3)$, $b = 15.008(2)$, and $c = 25.347(3)$ Å, $\alpha = 94.42(1)$, $\beta = 92.57(2)$, $\gamma = 98.91(2)°$, and $Z = 2$. Refinement based on 3624 observed reflections led to $R = 0.098$. Preliminary structural data for **5** is available in the supplementary material.

(13) Burley, S. K.; Petsko, G. A. *Science* **1985**, *229*, 23.

(14) Cox, E. G.; Cruickshank, D. W. J.; Smith, J. A. S. *Proc. R. Soc. A* **1958**, *247*, 1.

(15) Rizzoli, C.; Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Mol. Struct.* **1982**, *82*, 133.

(16) Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983**, *39*, 409.