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Exhaustively Methylated Azacalix[4]arene: Preparation, Conformation, and Crystal Structure with Exclusively CH/π-Controlled Crystal Architecture

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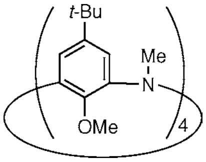
ABSTRACT



Described are the preparation, conformation, and crystal structure of exhaustively methylated azacalix[4]arene involving nitrogen atoms as bridging units. NMR and X-ray crystallographic analysis have demonstrated that this novel azacalix[4]arene adopts a 1,3-alternate conformation both in solution and in the solid state. The crystal structure has been characterized solely by intermolecular CH/π interactions, by which the azacalix[4]arenes mutually interact with each other outside the cavity to furnish a two-dimensional network structure.

The name "calixarene" was initially coined for a family of macrocyclic phenol condensates linked via methylene bridges.[1−3] In recent years, the name has been gradually extended to express structurally related compounds designated as "heterocalixarenes",[3] in which aromatic systems other than phenol are incorporated into the $[1_n]$metacyclophane skeleton. More recently, much attention has been attracted to the preparation of "heteroatom-bridged calixarenes",[3,4] in which methylene bridges are replaced by heteroatoms such as silicon, boron, germanium, tin, nitrogen, oxygen, phosphorus, and sulfur. Among these, only silicon-, sulfur-, and oxygen-bridged calixarenes[5,6a,7] incorporate phenols as building blocks, whereas others consist of benzene rings and/or heteroaromatics rather than phenol.[3,4a]

Very recently, Tanaka,[8a,b] Yamamoto,[8c] and Wang[8d,e] independently succeeded in preparing nitrogen-bridged deoxycalixarenes, which exhibited intriguing structure−property relationships reflecting the introduction of nitrogen atoms as bridging units. These calixarene analogues consist of aromatic systems other than phenol, while we are interested

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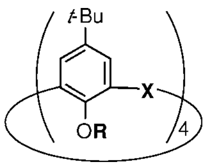
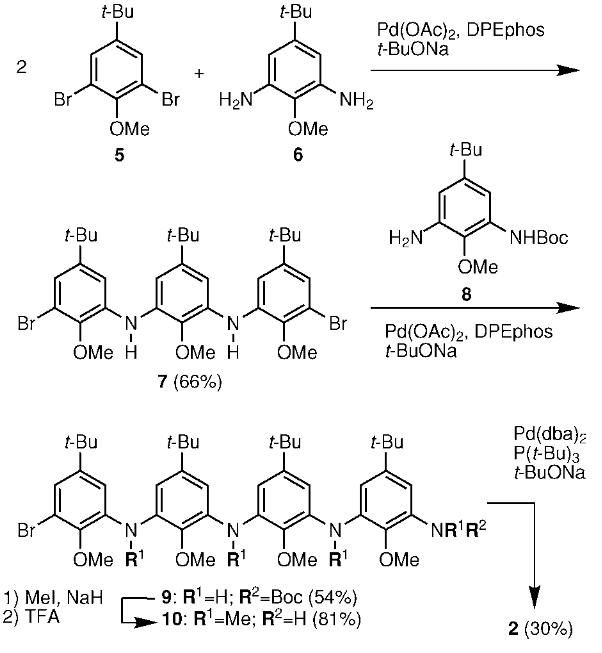
in employing phenol rings as aromatic motifs because of the attractive prospect that the incorporation of phenol rings would enhance conformational stability due to the formation of intramolecular hydrogen-bonding cyclic array.[1,9] With this in mind, to develop a new and versatile host molecule, we have designed a novel calix[4]arene **1** consisting of phenol rings and nitrogen bridges, by which additional hydrogen-bonding and functionalization sites would be provided. In addition, the bridging nitrogen atoms may conjugate with aromatic rings to increase the electron density of the π cloud. From the synthetic point of view, the fully methylated derivative **2** rather than **1** has been preliminarily selected as a target molecule in the present study to establish the synthetic pathway leading to the construction of the basic skeleton. As an eventual outcome, azacalix[4]arene **2** in a 1,3-alternate conformation could be prepared from readily available starting materials. Moreover, X-ray crystallographic analysis clearly revealed that molecules of **2** mutually interacted outside the cavity to furnish an unique crystal structure solely stabilized by virtue of the intermolecular CH/π interactions. In this paper, we report the synthesis and structural features of the novel phenol-derived azacalix[4]arene **2** involving nitrogen atoms as bridging units.



1: **X** = NH; **R** = H
2: **X** = NMe; **R** = Me
3: **X** = CH_2; **R** = Me
4: **X** = S; **R** = Me

Scheme 1. Preparation of Azacalix[4]arene **2**



After our numerous attempts to prepare this novel azacalix[4]arene **2**, the convergent, stepwise approach shown in Scheme 1 was finally devised.[10] Buchwald−Hartwig aryl amination reaction[11] of dibromoanisole **5**[12a] with *m*-phenylenediamine **6**[12b] by using $Pd(OAc)_2$ as a catalyst in the presence of bis[2-(diphenylphosphino)phenyl] ether (DPEphos)[12c] and *t*-BuONa gave nitrogen-bridged linear trimer **7** in moderate yield (66%). The same palladium-catalyzed aryl amination reaction was again applied for the cross-coupling reaction of the trimer **7** with monoprotected *m*-phenylenediamine **8** to furnish linear tetramer **9** in 54% yield. Treatment of the resultant **9** with methyl iodide in the presence of NaH, followed by the removal of the Boc group with TFA, cleanly afforded linear tetramer **10** in 81% yield in two steps. The final cyclization reaction of **9** was achieved by heating **10** under reflux in anhydrous toluene in the presence of 20 mol % $Pd(dba)_2$, 16 mol % $P(t\text{-}Bu)_3$, and 2 equiv of *t*-BuONa to give azacalix[4]arene **2** in 30% yield. FD MS, ^{1}H NMR, ^{13}C NMR, and elemental analysis fully confirmed the structure of this new azacalix[4]arene **2**.

In the ^{1}H NMR spectrum of **2** (Figure 1), only four sharp singlet signals appeared at δ 1.29, 2.83, 3.29, and 6.66 ppm for the *tert*-butyl, methoxy, *N*-methyl, and aromatic hydrogens, respectively, suggesting that azacalix[4]arene **2** adopts either a cone or 1,3-alternate conformation. The chemical shift of the methoxy protons was used as a diagnostic for elucidating the conformation of **2** in solution. Methoxy hydrogens of **2** at δ 2.83 ppm experienced an upfield shift, as compared with that of a reference compound, 4-*tert*-butyl-2,6-bis(methylamino)anisole, at δ 3.68 ppm. A similar upfield shift is reported for the carbocyclic calix[4]arene **3**;[13]

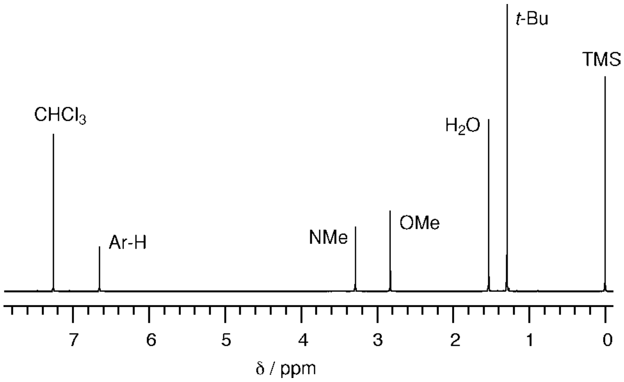


Figure 1. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of azacalix[4]arene **2** at 25 °C.

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(10) A simpler [3 + 1] cyclization of **6** with **7** afforded a complicated reaction mixture under essentially the same reaction conditions as those used for the cross-coupling reactions $\mathbf{5} + \mathbf{6} \rightarrow \mathbf{7}$ and $\mathbf{7} + \mathbf{8} \rightarrow \mathbf{9}$.

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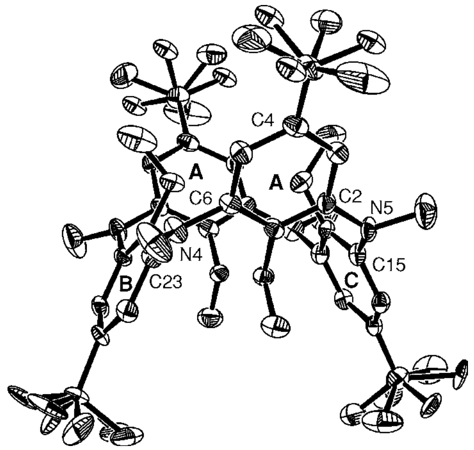

Figure 2. ORTEP[19] drawing of azacalix[4]arene **2**. The displacement ellipsoids are drawn at the 50% probability level. Hydrogen atoms are omitted for clarity.

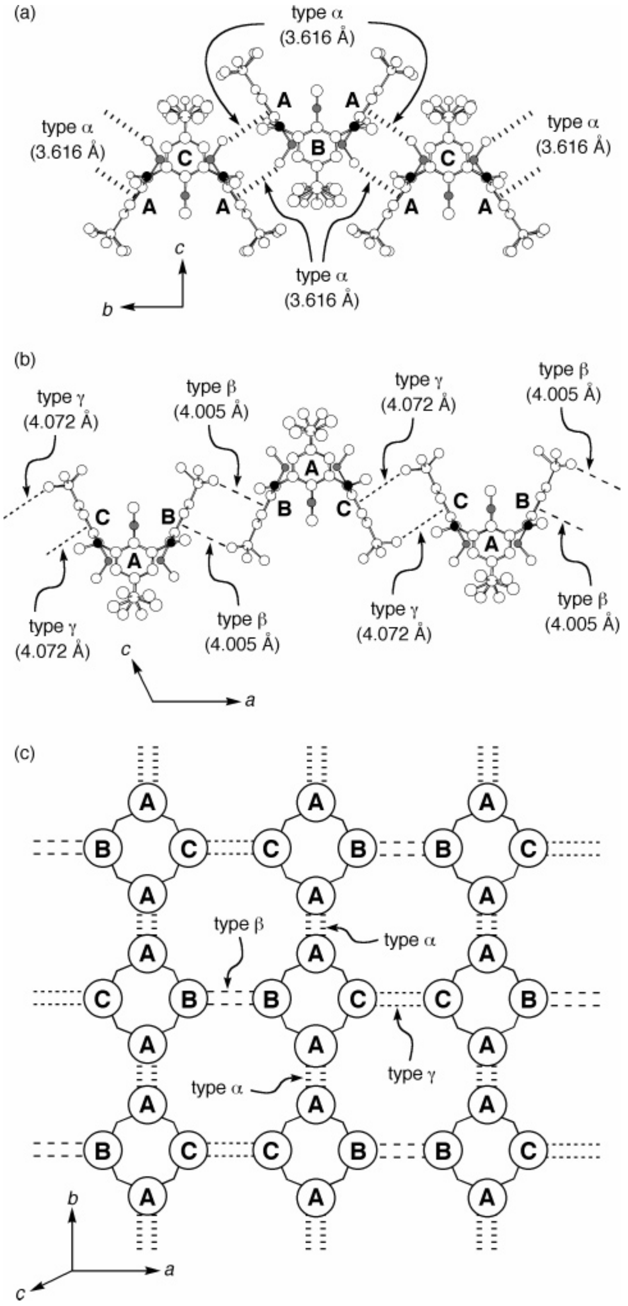

Figure 3. Crystal structure of azacalix[4]arene **2** viewed down (a) the *a* axis and (b) the *b* axis. The carbon, nitrogen, and oxygen atoms are represented by open, closed, and shaded circles, respectively. The two-dimensional structure on the *ab* plane is schematically illustrated in panel c, where aromatic rings **A**, **B**, and **C** are represented by open circles with lettering.

the methoxy protons characteristic of the cone and 1,3-alternate conformations appear at δ 3.8 and 2.9 ppm, respectively,[13b] whereas that of 4-*tert*-butyl-2,6-dimethylanisole at 3.71 ppm.[14] The upfield shift observed in **2** ($\Delta\delta = -0.85$ ppm[15]) agrees well with that of 1,3-alternate **3** ($\Delta\delta = -0.8$ ppm[15]) rather than that of cone **3** ($\Delta\delta = +0.1$ ppm[15]), clearly indicating that azacalix[4]arene **2** adopts a 1,3-alternate conformation with D_{2d} symmetry. Whether the conformation is frozen or not in solution remains unclear at this moment because the NMR spectral pattern shown in Figure 1 was virtually independent of both the solvent and the temperature (see Figure S4 in Supporting Information). Nontheless, conclusive evidence for the conformational preference for the 1,3-alternate conformation over the others was provided by NOE measurements (Figure S5) as well as X-ray crystallography.

A single-crystal suitable for X-ray crystallographic analysis[16] was obtained by slow crystallization from CH_2Cl_2. Unsolvated azacalix[4]arene **2** crystallizes in a monoclinic form, space group $C2/m$ ($Z = 4$). Just from appearance (Figure 2; see also Figure S6), azacalix[4]arene **2** is in a highly symmetrical 1,3-alternate conformation that is similar to that reported for thiacalix[4]arene **4**[4b,6b] rather than that for the carbocyclic analogue **3**.[2,13c] On the other hand, this conformation of **2** is in striking contrast to those reported for analogous nitrogen-bridged calixarenes incorporating benzene rings and/or heteroaromatics in place of phenol; for example, "clip-like" and almost flat conformational structures

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(15) Plus and minus signs indicate downfield and upfield shifts, respectively, compared to the chemical shift of the relevant reference compound.

(16) X-ray data were collected on a Rigaku RAXIS RAPID imaging plate area detector. The crystal structure was solved by direct methods and refined by full-matrix least-squares. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were refined using the riding model. All calculations were performed using a crystallographic software package, CrystalStructure version 3.6.0.[20] Crystal data for **2**: $M_r = 765.09$, monoclinic, space group $C2/m$, $a = 23.64(1)$, $b = 16.890(6)$, $c = 12.682(5)$ Å, $\beta = 116.40(3)°$, $V = 4535(3)$ Å^3, $Z = 4$, $\rho_{calc} = 1.120$ g cm^{-3}, $2\theta_{max} = 57.4°$, Mo Kα ($\lambda = 0.71075$ Å), $\mu = 0.71$ cm^{-1}, $\theta - \omega$ scans, $T = 173$ K, 25 100 independent reflections, 6370 observed reflections ($I > 3.0\sigma(I)$), 340 refined parameters, $R = 0.092$, $R_w = 0.136$, $\Delta\rho_{max} = 2.38$ e Å^{-3}, $\Delta\rho_{min} = -2.26$ e Å^{-3}; CCDC 263006. See Supporting Information for crystallographic data in CIF format.

were reported for tetrazacalix[2]arene[2]triazine[8e] and benzene-derived deoxyazacalix[4]arene,[8a] respectively. To be more accurate, conformation of **2** is slightly distorted from the ideal 1,3-alternate conformation with D_{2d} symmetry to one with C_s symmetry. There exists only one symmetry plane bisecting the two opposite aromatic units, eventually lowering the symmetrical arrangement of the aromatic systems to three different types designated as **A**, **B**, and **C** (Figure 2; see also Figure S6). Indeed, the dihedral angles between the aromatic rings **A**, **B**, and **C** and the mean plane defined by the four nitrogen bridges are 56.7, 64.2, and 61.9°, respectively. Moreover, the bond alternation of the N−C(sp^2) bonds was observed, of which the distances were 1.407, 1.417, 1.416, and 1.425 Å for N4−C23, N4−C6, N5−C2, and N5−C15, respectively. Nonuniform packing forces arising from the unique crystal structure of **2** (vide infra) must be a reason for the observed decline in the symmetry of **2** from D_{2d} to C_s in the solid state.

Of further interest is that the crystal structure is solely characterized by three types of intermolecular CH/π interactions between azacalix[4]arenes **2**; the first one is formed between the methoxy groups located on the rings **A** and the centroid of the rings **A** belonging to the nearest molecules (type α, C···centroid, 3.616 Å; CH···centroid, 3.121 Å and 114.30°; H···centroid···C4, 103.79°; Figure 3a), the second one between the *tert*-butyl groups bound to the rings **B** and the centroid of the rings **B** of another neighboring **2** (type β, C···centroid, 4.005 Å;[17] Figure 3b), and the third one between the *tert*-butyl groups of the rings **C** and the centroid of the rings **C** of another adjacent molecules (type γ, C···centroid, 4.072 Å;[17] Figure 3b). By virtue of the intermolecular CH/π interactions of type α, a one-dimensional infinite chain structure is formed along the *b* axis in an antiparallel direction, as shown in Figure 3a. Besides, the one-dimensional chains interact with each other along the *a* axis by a combination of the CH/π interactions of types β and γ, as depicted in Figure 3b. As a consequence of these intermolecular interactions, a two-dimensional sheet structure of **2** is eventually formed on the *ab* plane, as schematically illustrated in Figure 3c (see also Figures S7−S9).

Similar two-dimensional network structures have precedent in azacalix[2]arene[2]triazine[8e] and the clathrate complex of a pyridine-appended *p-tert*-butylcalix[4]arene,[18] in which two-dimensional structures are formed by intermolecular hydrogen bonding interactions in the former and by the cooperation of intermolecular π/π and halogen/nitrogen interactions in the latter. Likewise, a combination of π/π and CH/π interactions was reported to build up the crystal structure of thiacalix[4]arene **4**.[6b] On the other hand, the crystal structure of **2** is established exclusively by the intermolecular CH/π interactions of **2**, which behaves as both CH/π donor and acceptor at once. From this experimental result, it is reasonable to presume that the incorporation of nitrogen atoms as bridging units increases the π-basic character of the aromatic rings, thereby allowing the prominent contribution of intermolecular CH/π interactions to the control of the crystal structure of **2**.

In summary, we have described the synthesis of the novel phenol-derived azacalix[4]arene **2** in four steps from readily available starting materials. ^{1}H NMR and X-ray crystallographic analysis clearly demonstrated that azacalix[4]arene **2** adopts a 1,3-alternate conformation both in solution and in the solid state. In the crystal, azacalix[4]arene **2** was found to enjoy its simultaneous role as both CH/π donor and acceptor in the formation of the two-dimensional crystal structure as a result of the enforced π-basic character of aromatic rings. Our ongoing preliminary study for preparing completely demethylated azacalix[4]arene **1** has revealed that demethylation of **2** and the synthetic precursors is feasible, though partial at this moment for the former. Further work aimed at synthesizing **1**, a perfect analogue of *p-tert*-butylcalix[4]arene, is currently underway in our laboratory in order to construct a versatile and efficient host molecule.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds (including NMR spectra and crystal structure for azacalix[4]arene **2**) (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[17] CH···centroid distance and angle are omitted for the positional disorder of *tert*-butyl groups.

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