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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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^{(1) (}a) Gutsche, C. D. In *Calixarenes*; Stoddart, J. F., Ed.; Royal Society of Chemistry: Cambridge, 1989. (b) Gutsche, C. D. In *Calixarenes Revisited*; Stoddart, J. F., Ed.; Royal Society of Chemistry: Cambridge, 1998.

⁽²⁾ Calixarenes: A Versatile Class of Macrocyclic Compounds; Vicens, J., Böhmer, V., Eds.; Kluwer: Dordrecht, 1991.

⁽³⁾ *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Saadioui, M., Eds.; Kluwer: Dordrecht, 2001.

⁽⁴⁾ For a review on heteroatom-bridged calixarenes: (a) König, B.; Fonseca, M. H. *Eur. J. Inorg. Chem.* **2000**, 2303. (b) Lhoták, P. *Eur. J. Org. Chem.* **2004**, 1675.

⁽⁵⁾ König, B.; Rödel, M.; Bubenitschek, P. J. Org. Chem. 1995, 60, 7406.
(6) (a) Kumagai, H.; Hasegawa, M.; Miyanari, S.; Sugawa, Y.; Sato, Y.; Hori, T.; Ueda, S.; Kamiyama, H.; Miyano, S. Tetrahedron Lett. 1997, 38, 3971. (b) Lhoták, P.; Himl, M.; Stibor, I.; Sykora, J.; Lang, J.; Petricková, H. Tetrahedron 2003, 59, 7581.

⁽⁷⁾ Katz, J. L.; Feldman, M. B.; Conry, R. R. Org. Lett. 2005, 7, 91.

^{(8) (}a) Ito, A.; Ono, Y.; Tanaka, K. New J. Chem. 1998, 779. (b) Ito,
A.; Ono, Y.; Tanaka, K. J. Org. Chem. 1999, 64, 8236. (c) Miyazaki, Y.;
Kanbara, T.; Yamamoto, T. Tetrahedron Lett. 2002, 43, 7945. (d) Wang,
M.-X.; Zhang, X.-H.; Zheng, Q.-Y. Angew. Chem., Int. Ed. 2004, 43, 838.
(e) Wang, M.-X.; Yang, H.-B. J. Am. Chem. Soc. 2004, 126, 15412.

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 hydrogenbonding 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.



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 reaction¹¹ 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 palladiumcatalyzed 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

(9) Tsue, H.; Ohmori, M.; Hirao, K. J. Org. Chem. **1998**, 63, 4866. (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 $5 + 6 \rightarrow 7$ and $7 + 8 \rightarrow 9$.



presence of 20 mol % Pd(dba)₂, 16 mol % P(*t*-Bu)₃, and 2 equiv of *t*-BuONa to give azacalix[4]arene **2** in 30% yield. FD MS, ¹H NMR, ¹³C NMR, and elemental analysis fully confirmed the structure of this new azacalix[4]arene **2**.

In the ¹H NMR spectrum of **2** (Figure 1), only four sharp



Figure 1. ¹H NMR spectrum (500 MHz, CDCl₃) of azacalix[4]-arene 2 at 25 °C.

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

⁽¹¹⁾ For reviews on the palladium-catalyzed aryl amination: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. Acc. Chem. Res. **1998**, *31*, 805. (b) Hartwig, J. F. Acc. Chem. Res. **1998**, *31*, 852. (c) Hartwig, J. F. Angew. Chem., Int. Ed. **1998**, *37*, 2046. (d) Muci, A. R.; Buchwald, S. L. Top. Curr. Chem. **2002**, *219*, 133.

^{(12) (}a) Wolbers, M. P. O.; van Veggel, F. C. J. M.; Snellink-Ruël, B. H. M.; Hofstraat, J. W.; Geurts, F. A. J.; Reinhoudt, D. N. J. Am. Chem. Soc. 1997, 119, 138. (b) Breitfelder, S.; Cirillo, P. F.; Regan, J. R. (Boehringer Ingerlheim Pharmaceuticals, Inc.). PCT Int. Appl. WO 200283642, 2002; Chem. Abstr. 2002, 137, 325421. (c) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. Organometallics 1995, 14, 3081.



Figure 2. ORTEP¹⁹ drawing of azacalix[4]arene **2**. The displacement ellipsoids are drawn at the 50% probability level. Hydrogen atoms are omitted for clarity.

the methoxy protons characteristic of the cone and 1,3alternate 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 $(\Delta \delta = -0.85 \text{ ppm}^{15})$ agrees well with that of 1,3-alternate 3 ($\Delta \delta = -0.8 \text{ ppm}^{15}$) rather than that of cone 3 ($\Delta \delta =$ +0.1 ppm¹⁵), 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 analysis¹⁶ was obtained by slow crystallization from CH₂Cl₂. Unsolvated azacalix[4]arene **2** crystallizes in a monoclinic form, space group C2/m (Z = 4). Just from appearance



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.

(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

^{(13) (}a) Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer,
L. J. *Tetrahedron* **1983**, *39*, 409. (b) Harada, T.; Rudzinski, J. M.; Shinkai,
S. J. Chem. Soc., Perkin Trans. 2 **1992**, 2109. (c) Grootehuis, P. D. J.;
Kollman, P. A.; Groenen, L. C.; Reinhoudt, D. N.; van Hummel, G. J.;
Ugozzoli, F.; Andreetti, G. D. J. Am. Chem. Soc. **1990**, *112*, 4165.

⁽¹⁴⁾ Armitage, B. J.; Kenner, G. W.; Robinson, M. J. T. Tetrahedron 1964, 20, 723.

⁽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, $\beta = 116.40(3)^\circ$, V = 4535(3) Å³, Z = 4, $\rho_{calc} = 1.120$ g cm⁻³, $2\theta_{max} = 57.4^\circ$, Mo K α ($\lambda = 0.71075$ 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 crystal-lographic data in CIF format.

were reported for tetrazacalix[2]arene[2]triazine^{8e} and benzenederived 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 onedimensional 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. ¹H 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*-tertbutylcalix[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.

⁽¹⁸⁾ Messina, M. T.; Metrangolo, P. M.; Pappalardo, S.; Parisi, M. F.; Pilati, T.; Resnati, G. *Chem. Eur. J.* **2000**, *6*, 3495.

⁽¹⁹⁾ Farrugia, L. J. J. Appl. Crystallogr. 1997, 30, 565.

⁽²⁰⁾ CrystalStructure, version 3.6.0; Rigaku and Rigaku/MSC: The Woodlands, TX, 2004.