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Synthesis, Structure, and Functionalization of Homo Heterocalix[2]arene[2]triazines: Versatile Conformation and Cavity Structures Regulated by the Bridging Elements

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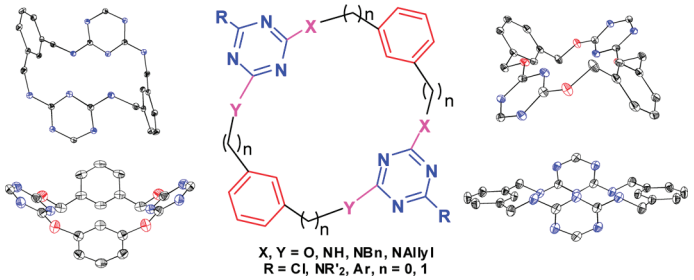

A number of homo[2] and homo[4] heterocalix[2]arene[2]triazines were synthesized through a general and good-yielding fragment coupling approach starting from cyanuric halides, aromatic and aliphatic diols, and diamines under very mild reaction conditions. While homo[2] tetraazacalix[2]arene[2]triazine gave a twisted and pinched 1,2-alternate conformer, almost all homo[2] heterocalix[2]arene[2]triazines adopted different partial cone conformations in the solid state. Homo[4] heterocalix[2]arene[2]triazines yielded more diverse conformational structures including partial cone, pinched partial cone, 1,2-alternate and twisted 1,2-alternate, depending on the nature of bridging moieties. On the basis of ^{1}H NMR spectra, homo[2] and homo[4] heterocalix[2]arene[2]triazines were fluxional macrocycles in solution, and they underwent rapid conformation interconversion at different temperatures. Efficient and straightforward nucleophilic aromatic substitution reaction and palladium-catalyzed cross-coupling reactions on chlorotriazine rings, and the nucleophilic alkylation reaction on the bridging nitrogen atoms led to the construction of various highly functionalized homo heterocalix[2]arene[2]triazine derivatives.

Introduction

One of the challenging tasks in supramolecular chemistry is the design and synthesis of novel and functional macrocyclic molecules. Historically, the emergence of crown ethers,[2] spherands,[3] and cryptands[4] promoted tremendous advances in supramolecular science.[1] One of the recent examples is calixarenes.[5] Following Gutsche's pioneering work[6] of synthesis and structural elucidation, calix[*n*]arenes have become classic macrocyclic molecules because of their easy availability, unique conformational and cavity structures, and powerful recognition properties.

(1) *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, D., MacNicol, D. D., Vögtle, F., Lehn, J.-M., Eds.; Elsevier: Amsterdam, 1996.
(2) Pedersen, C. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1021.
(3) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009.
(4) Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89.
(5) (a) Gutsche, C. D. *Calixarenes Revisited*; The Royal Society of Chemistry: Cambridge, 1998. (b) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Saadioui, M., Eds.; Kluwer Academic Publishers: Amsterdam, 2001.
(6) For a monograph, see : Gutsche, C. D. *Calixarenes*; The Royal Society of Chemistry: Cambridge, 1989.
(7) For reviews of heterocalixaromatics, see: (a) Wang, M.-X. *Chem. Commun.* **2008**, 4541. (b) König, B.; Fonseca, M. H. *Eur. J. Inorg. Chem.* **2000**, 2303.

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As a novel type of [1$_n$]metacyclophanes, heterocalixaromatics or the heteroatom-bridged calix(hetero)arenes[7−11] have recently been emerging as a unique type of macrocyclic host molecules in supramolecular chemistry. Based on the stepwise fragment coupling strategy[8e,9d] and one-pot macrocyclic condensation reaction approach,[9j] a number of dissymmetric and symmetric heterocalixaromatics have been synthesized in good yields. Functionalized heterocalixaromatics are also obtained conveniently either from starting materials containing functional groups[9g,h,11] or from postmacrocyclization functionalizations on aromatic rings[8m,n,9d,f,i,o] and bridging heteroatoms.[8h,n] Owing to the bridging heteroatoms such as nitrogen, oxygen, and sulfur that can adopt different electronic configurations and form different degrees of conjugation with their neighboring aromatic rings, heterocalixaromatics are able to form fine-tunable conformation and cavity structures.[8f] Furthermore, the various electronic effects of the heteroatoms also regulate the electron density of aromatic rings, producing the cavity of varied electronic features.[9d,12] Heterocalixaromatics have been shown to act as versatile macrocyclic host molecules to recognize metal cations,[8g,l,13] halides,[12] neutral molecules,[8f,i,14] including fullerenes.[8e,j,k]

Our continuous interest[7a] in exploring the supramolecular chemistry of macrocyclic host molecules has led us to design and construct novel and functional homo heterocalixaromatics.[15] By the insertion of methylene units into the bridging position of heterocalixaromatics, we envisioned that homo heterocalixaromatics would give an enlarged cavity and varied conformations other than 1,3-alternate. Remaining the direct connectivity between heteroatoms and aromatic rings, the electronic features of the aromatic surfaces of the homo heterocalixaromatic macrocycles might be regulated by the bridging nitrogen and oxygen atoms. We report herein a general and high-yield fragment coupling method for the synthesis of nitrogen and oxygen bridged homo calix[2]arene[2]triazines. Depending on the nature of the bridging units, the macrocycles adopt indeed versatile conformational structures and give varied cavity sizes. We will also demonstrate that the homo heterocalix[2]arene[2]triazines prepared from cyanuric chloride are amenable to facile functionalizations on triazine rings simply via nucleophilic aromatic substitution reaction and palladium-catalyzed cross-coupling reaction. Functionalization on the bridging positions was accomplished through exclusive and exhaustive *N*-allylation reaction of homo[4] tetraazacalix[2]arene[2]triazine.

Results and Discussion

Synthesis. We initiated our study with the synthesis of homo[2] diazadioxacalix[2]arene[2]triazine **3a**.[16] In the presence of diisopropylethylamine (DIPEA) as an acid scavenger, a linear trimer **1a**, which was prepared in a good yield from the reaction of resorcinol with 2 equiv of cyanuric chloride,[9d] underwent macrocyclic condensation reaction with 1,3-phenylenedimethaneamine **2a** in acetonitrile at room temperature to give a hardly soluble white solid product **3a** in 40% yield. To increase its solubility and therefore to facilitate its characterization, the chloro substituent on triazine ring was replaced by a diethylamino group via nucleophilic aromatic substitution reaction with diethylamine to afford homo[2] diazadioxacalix[2]arene[2]triazine product **4a** in 78% yield (Scheme 1). Without the isolation of **3a**, the product **4a** was synthesized readily in 31% yield from the reaction between **1a** and **2a** in acetonitrile at

(8) For examples of *N*-bridged calixaromatics, see: (a) Tsue, H.; Ishibashi, K.; Tamura, R. *Top. Heterocycl. Chem.* **2008**, *17*, 73. (b) Ito, A.; Ono, Y.; Tanaka, K. *New J. Chem.* **1998**, 779. (c) Ito, A.; Ono, Y.; Tanaka, K. *J. Org. Chem.* **1999**, *64*, 8236. (d) Selby, T. D.; Blackstock, S. C. *Org. Lett.* **1999**, *1*, 2053. (e) Wang, M.-X.; Zhang, X.-H.; Zheng, Q.-Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 838. (f) Gong, H.-Y.; Zhang, X.-H.; Wang, D.-X.; Ma, H.-W.; Zheng, Q.-Y.; Wang, M.-X. *Chem.—Eur. J.* **2006**, *12*, 9262. (g) Gong, H.-Y.; Zheng, Q.-Y.; Zhang, X.-H.; Wang, D.-X.; Wang, M.-X. *Org. Lett.* **2006**, *8*, 4895. (h) Wang, Q.-Q.; Wang, D.-X.; Ma, H.-W.; Wang, M.-X. *Org. Lett.* **2006**, *8*, 5967. (i) Gong, H.-Y.; Wang, D.-X.; Xiang, J.-F.; Zheng, Q.-Y.; Wang, M.-X. *Chem.—Eur. J.* **2007**, *13*, 7791. (j) Liu, S.-Q.; Wang, D.-X.; Zheng, Q.-Y.; Wang, M.-X. *Chem. Commun.* **2007**, 3856. (k) Zhang, E.-X.; Wang, D.-X.; Zheng, Q.-Y.; Wang, M.-X. *Org. Lett.* **2008**, *10*, 2565. (l) Gong, H.-Y.; Wang, D.-X.; Zheng, Q.-Y.; Wang, M.-X. *Tetrahedron* **2009**, *65*, 87. (m) Yao, B.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *Chem. Commun.* **2009**, 2899. (n) Yao, B.; Wang, D.-X.; Gong, H.-Y.; Huang, Z.-T.; Wang, M.-X. *J. Org. Chem.* **2009**, *74*, 5361. (o) Miyazaki; Kanbara, T.; Yamamoto, T. *Tetrahedron Lett.* **2002**, *43*, 7945. (p) Suzuki, Y.; Yanagi, T.; Kanbara, T.; Yamamoto, T. *Synlett* **2005**, *2*, 263. (q) Fukushima, W.; Kanbara, T.; Yamamoto, T. *Synlett* **2005**, *19*, 2931. (r) Tsue, H.; Ishibashi, K.; Takahashi, H.; Tamura, R. *Org. Lett.* **2005**, *7*, 2165. (s) Ishibashi, K.; Tsue, H.; Tokita, S.; Matsui, K.; Takahashi, H.; Tamura, R. *Org. Lett.* **2006**, *8*, 5991. (t) Ishibashi, K.; Tsue, H.; Sakai, N.; Tokita, S.; Matsui, K.; Yamauchi, J.; Tamura, R. *Chem. Commun.* **2008**, 2812. (u) Tsue, H.; Ishibashi, K.; Tokita, S.; Takahashi, H.; Matsui, K.; Tamura, R. *Chem.—Eur. J.* **2008**, *14*, 6125. (v) Tsue, H.; Matsui, K.; Ishibashi, K.; Takahashi, H.; Tokita, S.; Ono., K.; Tamura, R. *J. Org. Chem.* **2008**, *73*, 7748. (w) Vale, M.; Pink, M.; Rajca, S.; Rajca, A. *J. Org. Chem.* **2008**, *73*, 27. (x) Touil, M.; Lachkar, M.; Siri, O. *Tetrahedron Lett.* **2008**, *49*, 7250. (y) Konishi, H.; Hashimoto, S.; Sakakibara, T.; Matsubara, S.; Yasukawa, Y.; Morikawa, O.; Kobayashi, K. *Tetrahedron Lett.* **2009**, *50*, 620.

(9) For examples of *O*-bridged calixaromatics, see: (a) Maes, W.; Dehaen, W. *Chem. Soc. Rev.* **2008**, *37*, 2393. (b) Chambers, R. D.; Hoskin, P. R.; Khalil, A.; Richmond, P.; Sandford, G.; Yufit, D. S.; Howard, J. A. K. *J. Fluorine Chem.* **2002**, *116*, 19. (c) Chambers, R. D.; Hoskin, P. R.; Kenwright, A. R.; Khalil, A.; Richmond, P.; Sandford, G.; Yufit, D. S.; Howard, J. A. K. *Org. Biomol. Chem.* **2003**, 2137. (d) Wang, M.-X.; Yang, H.-B. *J. Am. Chem. Soc.* **2004**, *126*, 15412. (e) Wang, Q.-Q.; Wang, D.-X.; Zheng, Q.-Y.; Wang, M.-X. *Org. Lett.* **2007**, *9*, 2847. (f) Yang, H.-B.; Wang, D.-X.; Wang, Q.-Q.; Wang, M.-X. *J. Org. Chem.* **2007**, *72*, 3757. (g) Hou, B.-Y.; Wang, D.-X.; Yang, H.-B.; Zheng, Q.-Y.; Wang, M.-X. *J. Org. Chem.* **2007**, *72*, 5218. (h) Hou, B.-Y.; Zheng, Q.-Y.; Wang, D.-X.; Wang, M.-X. *Tetrahedron* **2007**, *63*, 10801. (i) Hou, B.-Y.; Zheng, Q.-Y.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *Chem. Commun.* **2008**, 3864. (j) Katz, J. L.; Feldman, M. B.; Conry, R. R. *Org. Lett.* **2005**, *7*, 91. (k) Katz, J. L.; Selby, K. J.; Conry, R. R. *Org. Lett.* **2005**, *7*, 3505. (l) Katz, J. L.; Geller, B. J.; Conry, R. R. *Org. Lett.* **2006**, *8*, 2755. (m) Katz, J. L.; Geller, B. J.; Foster, P. D. *Chem. Commun.* **2007**, 1026. (n) Maes, W.; Van Rossom, W.; Van Hecke, K.; Van Meervelt, L.; Dehaen, W. *Org. Lett.* **2006**, *8*, 4161. (o) Van Rossom, W.; Maes, W.; Kishore, L.; Ovaere, M.; Van Meervelt, L.; Dehaen, W. *Org. Lett.* **2008**, *10*, 585. (p) Van Rossom, W.; Ovaere, M.; Van Meervelt, L.; Dehaen, W.; Maes, W. *Org. Lett.* **2009**, *11*, 1681. (q) Li, X. H.; Upton, T. G..; Gibb, C. L. D.; Gibb, B. C. *J. Am. Chem. Soc.* **2003**, *125*, 650. (r) Hao, E.; Fronczek, F. R.; Vicente, M. G. H. *J. Org. Chem.* **2006**, *71*, 1233. (s) Konishi, H.; Tanaka, K.; Teshima, Y.; Mita, T.; Morikawa, O.; Kobayashi, K. *Tetrahedron Lett.* **2006**, *47*, 4041. (t) Yang, F.; Yan, L.-W.; Ma, K.-Y.; Yang, L.; Li, J.-H.; Chen, L.-J.; You, J.-S. *Eur. J. Org. Chem.* **2006**, 1109. (u) Zhang, C.; Chen, C.-F. *J. Org. Chem.* **2007**, *72*, 3880. (v) Ma, M.-L.; Li, X.-Y.; Wen, K. *J. Am. Chem. Soc.* **2009**, *131*, 8338.

(10) For a review of thiacalixarenes, see: Morohashi, N.; Narumi, F.; Iki, N.; Hattori, T.; Miyano, S. *Chem. Rev.* **2006**, *106*, 5291.

(11) For a recent example of calixaromatics bridged by a mixture of heteroatoms, see: Wu, J.-C.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *Tetrahedron Lett.* **2009**, *50*, 7209. Other examples can be found in ref 9d.

(12) Wang, D.-X.; Zheng, Q.-Y.; Wang, Q.-Q.; Wang, M.-X. *Angew. Chem., Int. Ed.* **2008**, *47*, 7485.

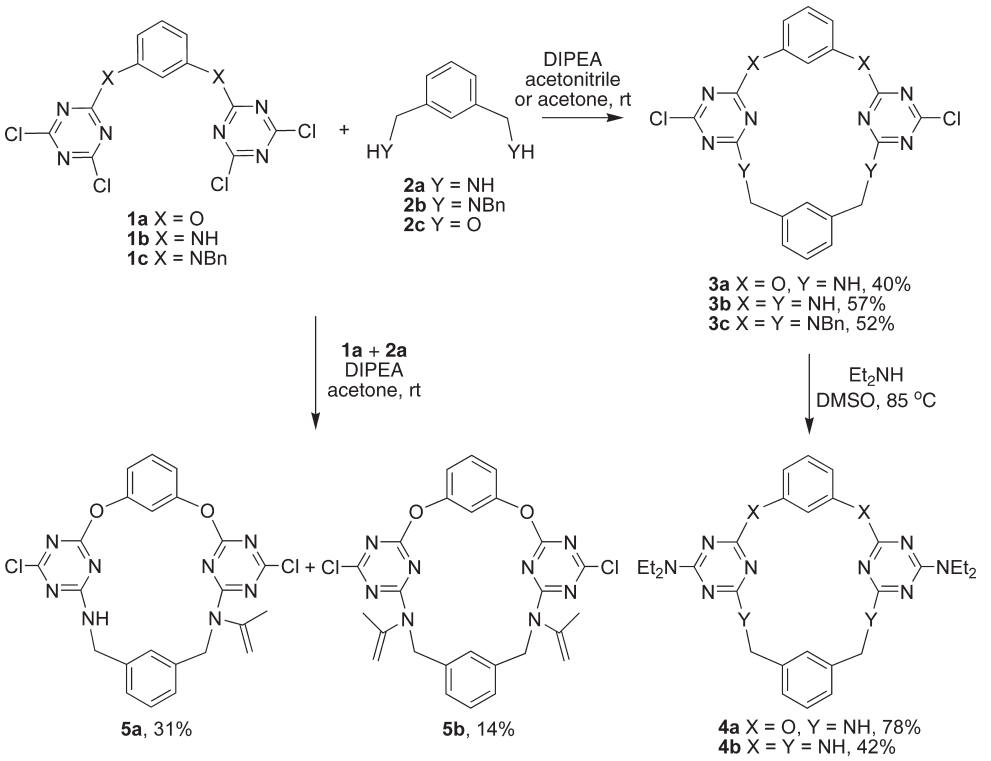
(13) Gong, H.-Y.; Wang, D.-X.; Zheng, Q.-Y.; Wang, M.-X. *Tetrahedron* **2009**, *65*, 87.

(14) Gong, H.-Y.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *Sci. China Ser. B: Chem.* **2009**, *52*, 1646.

(15) A few examples of homocalixarenes, ethylene-bridged phenol derivatives, are known. Ibach, S.; Prautzsch, V.; Vögtle, F. *Acc. Chem. Res.* **1999**, *32*, 729. To the best of our knowledge, however, no homo heterocalixaromatics have been reported.

(16) There are two different types of homo heterocalixaromatics synthesized in this study. Homo[2] and homo[4] heterocalixaromatics refer to macrocycles having two methylene and four methylene units in bridging positions, respectively. Based on cyclophane nomenclature, they are also named, respectively, as [2.2.1.1]metacyclophanes and [2.2.2.2]metacyclophanes.

SCHEME 1. Synthesis of Homo Heterocalix[2]arene[2]triazines from Macrocyclic Condensation Reactions of 1,3-Phenylenedimethylamine and 1,3-Phenylenedimethanol with Trimers 1 Derived from Resorcinol and 1,3-Phenylenediamines



room temperature followed by the treatment of the resulting precipitate with diethylamine at 85 °C in dimethyl sulfoxide (DMSO). It is very interesting to note that when the reaction of **1a** with **2a** was performed in acetone, the macrocyclic condensation reaction yielded *N*-prop-1-en-2-yl-substituted homo-[2] diazaoxacalix[2]arene[2]triazines **5a** and **5b** in 31% and 14%, respectively. Under the identical conditions for the preparation of **5a** and **5b**, however, the homo[2] diazadioxacalix-[2]arene[2]triazine **3a** was not converted into its *N*-prop-1-en-2-yl-substituted derivatives **5**. It might suggest that the reaction of bridging nitrogen atom(s) with acetone occurred prior to the macrocyclization step.

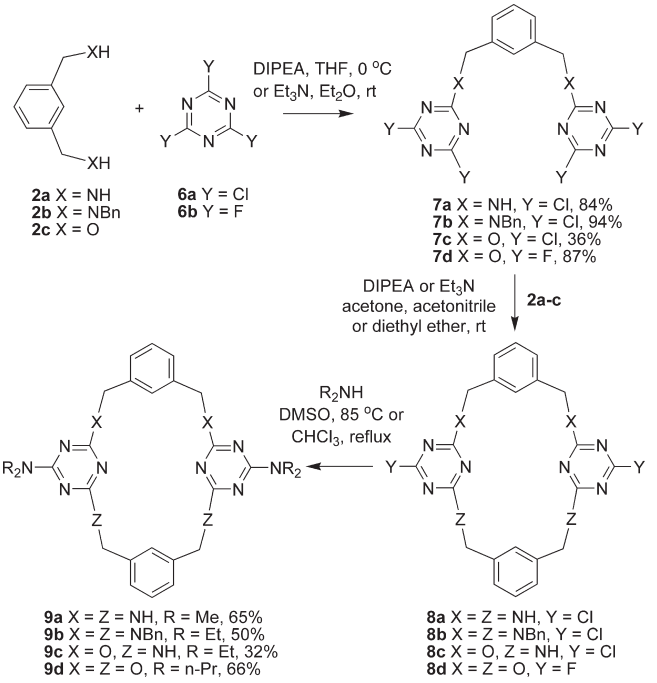
Applying the same reaction conditions for the synthesis of **5a** and **5b**, the macrocyclic condensation reaction between **1b** and **2a** gave homo[2] tetraazacalix[2]arene[2]triazine **3b**, which underwent nucleophilic aromatic substitution reaction with diethylamine to afford product **4b** in an overall yield of 24%. *N*-Benzylated homo[2] tetraazacalix[2]arene-[2]triazine **3c** was prepared in 52% yield from the reaction of linear trimer **1c** with *N*,*N*′-(1,3-phenylenebis(methylene))bis-(1-phenylmethaneamine) **2b** (Scheme 1). It should be noted that the reaction of linear trimer **1a**−**c** with 1,3-phenylene-dimethanol **2c** under the identical conditions did not produce the desired macrocyclic products, due to probably the low nucleophilicity of aliphatic diol **2c**.

Encouraged by the facile synthesis of homo[2] heterocalix-[2]arene[2]triazines **3**−**5** (Scheme 1), we then attempted the synthesis of homo[4] heterocalix[2]arene[2]triazines[16] that contained four methylene units in the bridging positions using the fragment coupling approach. In the presence of a base such as DIPEA or K_2CO_3 in tetrahydrofuran (THF) or acetonitrile at 0 °C, diamines **2a** and **2b** reacted efficiently with 2 equiv of cyanuric chloride **6a** to produce the corresponding linear trimers **7a** and **7b** in 84% and 94%, respectively (Scheme 2). Oxygen-linked linear trimer **7c** has been prepared by Krische[17] from 1,3-phenylenedimethanol **2c** and cyanuric chloride using lutidine as a base. Following the literature method,[17] we found it difficult to get pure product **7c**. Employing the conditions for the synthesis of **7a** and **7b**, reaction between cyanuric chloride and 1,3-phenylenedimethanol **2c** proceeded very sluggishly, probably due to the low nucleophilicity of aliphatic diol. Interestingly, changing the solvent from THF to chloroform, the reaction proceeded exothermically to afford pure **7c** as white solid in 34% yield. Starting with cyanuric fluoride **4b** instead of cyanuric chloride **4a**, the reaction in THF afforded the oxygen-linked linear trimer **7d** in 55% yield. A much improved chemical yield (87%) of **7d** was obtained when the reaction was performed in diethyl ether at room temperature (Scheme 2). Macrocyclic condensation reaction of the resulting linear trimers **7** proceeded effectively with dinucleophiles **2** in the presence of a base at ambient temperature to form targeted homo[4] heterocalix[2]arene[2]triazines **8**. Since the parent homo[4] heterocalix[2]arene[2]triazines **7** were not soluble in most of the organic solvents, they were transformed into products **8** simply through the nucleophilic displacement of chloro substituent on triazine ring by a dialkylamine. For example, nitrogen-linked linear trimers **7a** and **7b** underwent macrocyclic condensation reaction with diamines **2a** and **2b**, respectively, in acetone at room temperature with the aid of DIPEA as an acid scavenger to

(17) Archer, E. A.; Caube, D. F., Jr.; Lynch, V.; Krische, M. J. *Tetrahedron* **2002**, *58*, 721.

give intermediates **8a** and **8b**. Treatment of **8a** with dimethylamine in *N*,*N*-dimethylformamide (DMF) at 85 °C led to the formation of homo[4] NH-bridged calix[2]arene[2]triazine **9a** in an overall yield of 65%. Homo[4] NBn-bridged calix[2]arene[2]triazine **9b** was obtained after intermediate **8b** was interacted with diethylamine in DMSO at 85 °C. The room temperature reaction of oxygen-linked linear trimer **7c** with diamine **2a** using DIPEA as a base and acetonitrile as the solvent resulted in the formation of intermediate **8c** which underwent further reaction with diethylamine to afford homo[4] diazadioxacalix[2]arene[2]triazine **9c** in 32% yield. Synthesis of homo[4] tetraoxacalix[2]arene[2]triazine from the reaction between **7c** and 1,3-phenylenedimethanol **2c** met with failure. Various reaction conditions such as using different inorganic and organic base, different organic solvent and reaction temperature yielded no desired product. Either macrocyclic condensation reaction did not proceed or the reaction gave a mixture of inseparable and insoluble oligomers (see the Supporting Information). Fortunately, all

SCHEME 2. Fragment Coupling Approach for the Synthesis of Homo Heterocalix[2]arene[2]triazines from 1,3-Phenylenedimethylamine and 1,3-Phenylenedimethanol with Trimers 1 Derived from Resorcinol and 1,3-Phenylenediamines



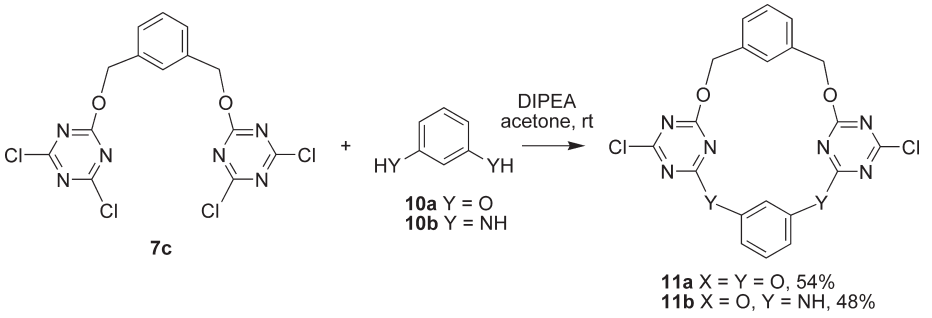
oxygen-linked homo[4] calix[2]arene[2]triazine product **9d** was isolated in 66% from the reaction of fluoro-substituted trimer **7d** with 1,3-phenylenedimethanol **2c** in diethyl ether utilizing triethylamine as a base, followed by the treatment with di-*n*-propylamine in refluxing chloroform (Scheme 2).

The linear trimers **7** derived from 1,3-phenylenedimethaneamine **2a** and 1,3-phenylenedimethanol **2c** were also very useful fragments for the construction of homo[2] heterocalix[2]arene[2]triazines. More importantly, they provided a complementary approach to homo[2] heterocalix[2]arene[2]triazines **3** that can not be accessed using the method described in Scheme 1. This has been evidenced by the synthesis of homo[2] tetraoxacalix[2]arene[2]triazine **11a** and homo[2] diazadioxacalix[2]arene[2]triazine **11b**. As aforementioned, the reactions between 1,3-phenylenedimethanol **2c** and linear trimers **1a** and **1b** gave no desired macrocyclic products at all owing probably to the diminished nucleophilic activity of aliphatic diol (Scheme 1). In stark contrast, the oxygen-linked linear trimer **7c** underwent macrocyclic condensation reaction with resorcinol **10a** to produce homo[2] tetraoxacalix[2]arene[2]triazine **11a** in 54% yield. Homo[2] diazadioxacalix[2]arene[2]triazine **11b** was also synthesized successfully in 48% yield from the reaction of **7c** with 1,3-phenylenediamine **10b** (Scheme 3). It seems apparent that the careful design of the reaction partners, viz. linear trimer and dinucleophile, on the basis of their reactivity would enable the construction of all nitrogen- and oxygen-bridged homo[2] calix[2]arene[2]triazines.

Structure. The structures of homo heterocalix[2]arene[2]triazines synthesized were elucidated on the basis of spectroscopic date and microanalysis. All products are crystalline and many of them gave high-quality single crystals suitable for X-ray diffraction analysis. The X-ray crystallographic data (see Supporting Information) then allowed us to study the molecular structures of homo heterocalix[2]arene[2]triazines in the solid state.

It has been reported that heterocalix[4]aromatics[7a,9d] adopt predominantly the 1,3-alternate conformation in the solid state. Surprisingly, by the introduction of methylene linkages into the bridging positions, the homo calix[2]arene[2]triazines gave various different conformational structures other than 1,3-alternate. More interestingly and remarkably, the conformational structures and the cavity sizes of the macrocycles changed with the variations of both bridging heteroatoms and methylene units and of their combinations. For example, having two methylene groups inserted into the bridging positions, homo[2] tetraoxacalix[2]arene[2]triazine **11a** (Figure 1), homo[2] diazadioxacalix[2]arene[2]triazine **4a**

SCHEME 3. Synthesis of Homo Heterocalix[2]arene[2]triazines from Macrocyclic Condensation Reactions of Resorcinol and 1,3-Phenylenediamine with Trimers 7 Derived from 1,3-Phenylenedimethylamine and 1,3-Phenylenedimethanol



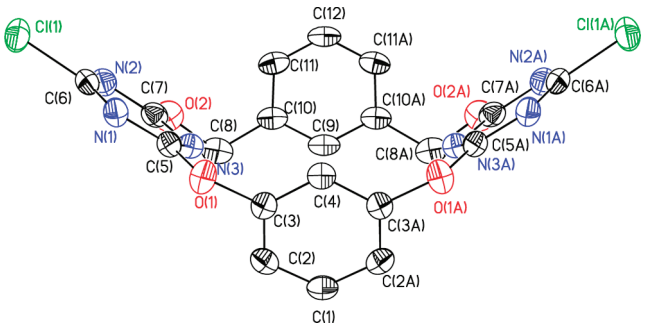


FIGURE 1. X-ray crystal structure of homo[2]tetraoxacalix[2]-arene[2]triazine **11a**. Selected bond lengths (Å): O(1)−C(5) 1.336, O1−C3 1.413, O(2)−C(7) 1.320, O(2)−C(8) 1.457. Selected interatomic distances (Å): C(6)−C(6A) 9.757, N(3)−N(3A) 5.696, C(4)−C(9) 4.577, C(6)−C(12), 6.702, C(6A)−C(12) 6.702.

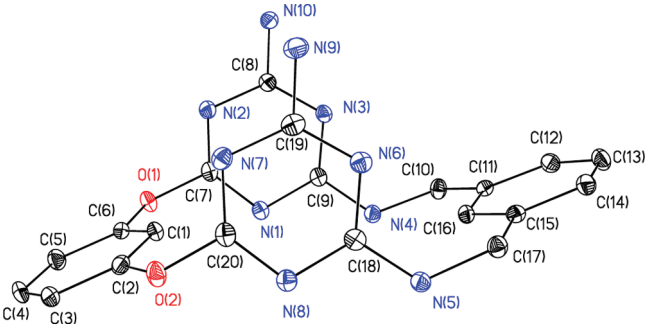


FIGURE 2. X-ray crystal structure of homo[2]diazadioxacalix-[2]arene[2]triazine **4a**. Ethyl substituents on N(9) and N(10) atoms were omitted for clarity. Selected bond lengths (Å): O(1)−C(7) 1.385, O(1)−C(6) 1.390, N(4)−C(9) 1.343, N(4)−C(10) 1.451. Selected interatomic distances (Å): N(5)−N(4) 4.981, C(8)−C(19) 5.222, N(1)−N(8) 4.900, C(8)−C(13) 7.132, C(13)−C(19) 6.272.

(Figure 2), and homo[2] tetraazacalix[2]arene[2]triazine **3c** (Figure S3, Supporting Information) adopted a partial cone conformation with the benzene ring linked to methylenes orientating to the same direction as two triazine rings. All four bridging heteroatoms were found to locate almost on the same plane. The cavity size, which was defined by the upper rim distance between two triazine rings, varied, however, from 5.222 Å of **4a** to 9.755 Å of **3c** and to 10.419 Å of **11a**. In the case of homo[2] diazadixoacalix[2]arene-[2]triazines **11b** (Figure 3, and Figure S4, Supporting Information) and **5a** (Figure S5, Supporting Information), twisted partial cone conformations were observed. No planarity was evidenced for four bridging heteroatoms in these cases. Moreover, being different from the structures of **3c**, **4a**, and **11a**, in both molecular structures **5a** (Figure S5, Supporting Information) and **11b** (Figure 3 and Figure S4, Supporting Information), it was the triazine rings that were alternately orientated. Most noticeably, however, when two oxygen bridges in **4a** or in **11b** units were changed into two NH moieties, NH-bridged homo[2] tetraazacalix[2]arene-[2]triazine **4b** gave surprisingly a twisted and pinched 1,2-alternate conformer (Figure 4 and Figure S6, Supporting Information).

When another two methylene units were introduced into the linking positions between heteroatoms and benzene rings, the resulting homo[4] heterocalix[2]arene[2]triazines

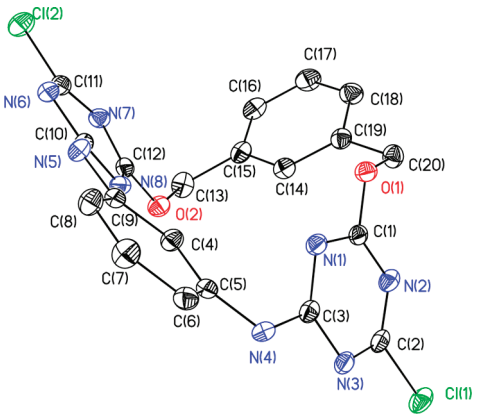


FIGURE 3. X-ray crystal structure of homo[2]diazadioxacalix-[2]arene[2]triazine **11b**. Selected bond lengths (Å): O(2)−C(12) 1.333, O(2)−C(13) 1.443, O(1)−C(1) 1.333, N(4)−C(3) 1.337, N(4)−C(5) 1.425, N(5)−C(10) 1.347, N(5)−C(9) 1.409. Selected interatomic distances (Å): N(8)−N(1) 4.307, C(14)−C(4) 5.391, C(11)−C(17) 6.138, C(11)−C(7) 7.062.

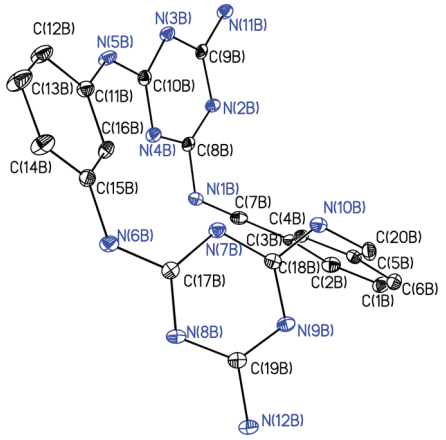


FIGURE 4. X-ray crystal structure of homo[2]tetraazacalix-[2]arene[2]triazine **4b**. Only one of two discrete molecules in a unit cell was shown. Ethyl substituents on N(11B) and N(12B) atoms were omitted for clarity. Selected bond lengths (Å): N(1B)−C(7B) 1.444, N(5B)−C(10B) 1.356, N(5B)−C(11B) 1.412, N(11B)−C(9B) 1.351. Selected interatomic distances (Å): C(1B)−C(19B) 6.788, C(9B)−C(13B) 6.788, C(1B)−C(13B) 10.989, N(4B)−N(7B) 4.259.

9a−**d** adopted even more diverse conformational structures in the solid state. Partial cone, pinched partial cone, 1,2-alternate, and twisted 1,2-alternate conformational structures were yielded depending on the heteroatoms and on the substituents attaching at the nitrogen bridges. For example, homo[4] tetraazacalix[2]arene[2]triazine **9a** gave a typical 1,2-alternate conformation (Figure 5 and Figure S7, Supporting Information). Two triazine rings and two benzene rings in **9a** were nearly perpendicular to the plane formed by four bridging nitrogen atoms, with the dihedral angles being 80.7° and 75.46°, respectively. The upper rim and the lower rim distances between proximal benzene and triazine rings were 5.183 Å ($d_{C(1)-C(7)}$) and 4.587 Å ($d_{C(4)-N(5)}$), respectively (see the caption in Figure 5). The replacement of four NH bridges with oxygen atoms resulted in a slightly twisted 1,2-alternate conformation of homo[4] tetraoxacalix[2]-arene[2]triazine **9d** (Figure S8, Supporting Information). The dihedral angles of benzene and triazine rings to the plane

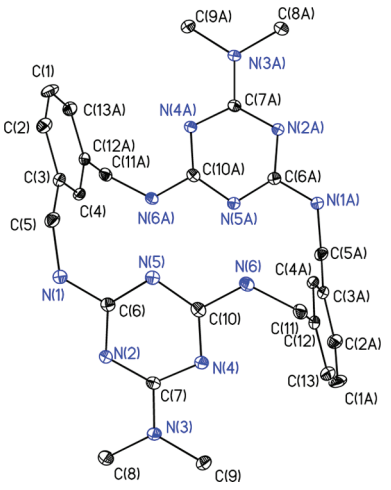


FIGURE 5. X-ray crystal structure of homo[4]tetraazacalix[2]arene-[2]triazine **9a**. DMSO molecule was omitted for clarity. Selected bond lengths (Å): N(1)−C(6) 1.349, N(1)−C(5) 1.444, N(5)−C(6) 1.338. Selected interatomic distances (Å): C(1)−C(7A) 5.183, C(4)−N(5A) 3.734, C(4)−C(4A) 6.457, C(4A)−C(7A) 5.365, N(1)−N(6A) 5.345, N(5)−N(5A) 5.317.

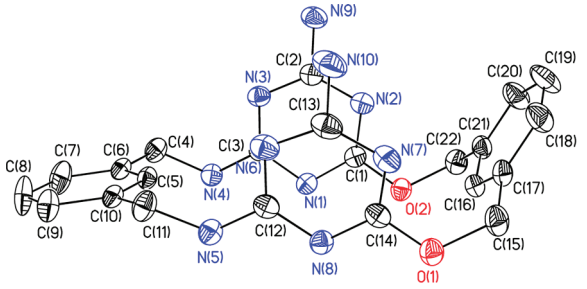


FIGURE 6. X-ray crystal structure of homo[4]diazadioxacalix-[2]arene[2]triazine **9c**. Ethyl substituents on N(9) and N(10) atoms were omitted for clarity. Selected bond lengths (Å): O(1)−C(14) 1.347, O(1)−C(15) 1.441, N(4)−C(3) 1.335, N(4)−C(4) 1.446. Selected interatomic distances (Å): C(2)−C(19) 5.450, C(13)−C(19) 5.708, N(1)−C(16) 4.263, N(8)−C(16) 4.684, C(5)−C(16) 7.133, C(2)−C(13) 5.416, N(1)−N(8)4.953, O(1)−O(2) 5.007, N(4)−N(5) 4.989.

defined by four oxygen bridges were, respectively, 46.11° and 45.21°. The cavity of homo tetraoxacalix[2]arene[2]triazine **9d** was larger than that of homo tetraazacalix[2]arene-[2]triazine **9a**, as the upper rim and the lower rim distances between benzene and triazine rings in proximity were 6.506 Å ($d_{C(1)-C(7)}$) and 3.332 Å ($d_{C(4)-N(5)}$), respectively (see caption in Figure S8, Supporting Information). Interestingly, the combination of two nitrogen atoms and two oxygen atoms as the bridging elements gave rise to a typical partial cone conformer of homo[4] diazadioxacalix[2]arene[2]triazine **9c** in the solid state (Figure 6 and Figure S9, Supporting Information). One benzene ring and two almost face-to-face paralleled triazine rings were nearly perpendicular to the plane of heteroatom bridges, whereas the other benzene ring tended to be coplanar with the plane of bridging hetero-atoms. Very interestingly, introduction of four benzyl groups onto the bridging nitrogen atoms of **9a** led macrocycle **9b** to adopt a flattened partial cone conformation (Figure 7 and Figure S10, Supporting Information). It was noteworthy

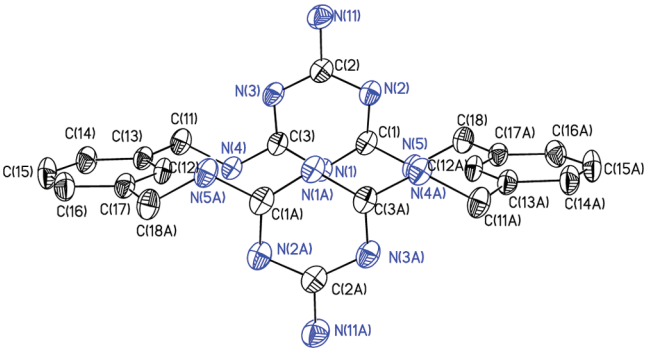


FIGURE 7. X-ray crystal structure of homo[4]tetraazacalix[2]-arene[2]triazine **9b**. Ethyl substituents on N(11) and N(11A) atoms and benzyl substituents on N(4), N(5), N(4A), and N(5A) were omitted for clarity. Selected bond lengths (Å): N(4)−C(3) 1.353, N(4)−C(11) 1.451. Selected interatomic distances (Å): C(12)-C-(12A) 7.287, C(2)−C(15) 7.076, C(15)−C(15A) 12.761, N(1)−C-(2A) 4.802.

that two benzene rings were edge-to-edge orientated and they located almost in the same plane. On the other hand, two triazine rings, which were alternately orientated, were almost perpendicular to the two benzene plane with the dihedral angle being around 82°.

In contrast to the 1,3-alternate conformation of almost all heterocalixaromatics reported,[7a] the formation of diverse conformational structures of homo heterocalix[2]arene-[2]triazines in the solid state was intriguing. Conventional calix[4]arenes adopt cone conformation mainly because of intramolecular circular hydrogen-bond interactions.[5,6] No intramolecular hydrogen-bond interaction is present, however, between aromatic rings within heterocalixaromatics and homo heterocalix[2]arene[2]triazines. The preference of heterocalixaromatics to forming the 1,3-alternate conformation is most probably due to the dipole−dipole interactions among aromatic rings. This is also in agreement with the observation of the two bridging heteroatom-conjugated triazine rings of heterocalix[2]arene[2]triazines tending to be edge-to-edge aligned.[9d] The presence of methylene segments as extra bridging units in addition to heteroatoms in homo calix[2]arene[2]triazines most likely reduced the dipole−dipole repulsion between the neighboring benzene and triazine rings, leading therefore to conformations other than 1,3-alternate. The formation of a variety of conformations also reflected the subtle but important role played by the bridging elements such as the nature of heteroatoms, the substituents on the nitrogen, and the number of methylenes. In other words, the conformation and the cavity structures of homo calix[2]arene[2]triazines were regulated by the combination of the heteroatoms and methylene units. The careful selection of the bridging elements would give macrocycles with tailor-made conformation and cavity. Last, but not least, although homo calix[2]arene-[2]triazine macrocycles adopted a range of diverse conformational structures, it should be pointed out that four bridging heteroatoms in all cases formed conjugation with triazine rings. This has been judged by the shorter bond length between the heteroatom and its attaching carbon atom of the triazine ring (see captions in Figures S1−S10, Supporting Information). This conjugation pattern, which was similar to that of hetero-calix[2]arene[2]triazines,[9d] enabled the tuning of the electron density of triazine ring by the bridging heteroatoms, a unique

feature very useful in molecular recognition, particularly in anion−π complexation.[12]

A few interesting features of intermolecular interactions of some homo calix[2]arene[2]triazines in the crystalline state were worth addressing. For the homo heterocalix[2]arene[2]-triazines containing NH-bridges such as **4a** (Figure S2, Supporting Information), **4b** (Figure S6, Supporting Information), **5a** (Figure S5, Supporting Information), **9c** (Figure S9, Supporting Information), and **11b** (Figure S4, Supporting Information), one or two pairs of intermolecular hydrogen bonds were formed to give dimeric structures. In the case of 1,2-alternate NH-bridged homo[4] calix[2]arene[2]triazine **9a** (Figure S7, Supporting Information), however, each bridging NH unit formed a hydrogen bond with one DMSO solvent molecule through the formation of hydrogen bonds. Each DMSO molecule, which was included in the cavity, used its oxygen atom as a hydrogen-bond bridge to link another macrocycle, yielding an infinite two-dimensional assembly. While the NBn-bridged homo[2] tetraazacalix[2]arene-[2]triazine molecules **3c** assembled via mainly intermolecular Ar−H···Cl and C−H···π interactions (Figure S3, Supporting Information), a two-dimensional assembly of NBn-bridged homo[4] tetraazacalix[2]arene[2]triazine **9b** was obtained from different Ar−H···π interactions (Figure S10, Supporting Information). The oxygen-linked 1,2-alternate homo[4] calix-[2]arene[2]triazine **9d** was assembled into a one-dimensional molecular wire because of the formation of four pairs of Ar−H···$N_{triazine}$ interactions (Figure S8, Supporting Information). A network of intermolecular halogen bond between two chloro substituents and lone-pair electron−π interactions between the chloro and triazine ring was most probably responsible for the formation of one-dimensional molecular assembly of homo[2] tetraoxacalix[2]arene[2]triazine **11a** in the solid state (Figure S1, Supporting Information).

Although in the solid state homo calix[2]arene[2]triazines existed in certain conformations with different conjugation systems being observed, these macrocycles might not be able to retain these stable conformational structures in the solution. As evidenced by the ^{1}H and ^{13}C NMR spectra (see the Supporting Information), most of them were fluxional at certain temperatures and the rates of interconversion of various conformational structures might be very rapid relative to the NMR time scale. For instance, all homo[2] heterocalix[2]arene[2]triazines including **4**, **5**, and **11** gave only one set of the ^{1}H and ^{13}C signals at ambient temperature in the ^{1}H and ^{13}C NMR spectra, respectively. While home[4] tetraoxacalix[2]arene[2]-triazine **9d** showed nicely a single set of signals at room temperature, homo[4] tetraazacalix[2]arene[2]triazine **9a** and diazadioxacalix[2]arene[2]triazine **9c** gave descent NMR spectra at an elevated temperature (around 380 K). Only with the *N*-benzyl-substituted homo[2] tetraazacalix[2]arene[2]triazine **3c** and homo[4] tetraazacalix[2]arene[2]triazine **9b** were no very well resolved ^{1}H NMR spectra observed at 385 K. It was interesting to address that the flexibility of macrocycles decreased with the increase of methylene linkages and with the increase of the NH bridges. The presence of a benzyl substituent on the bridging nitrogen atom greatly decreased the conformational mobility of the macrocycle. The influence of the bridging elements on the flexibility of conformational structures was most probably attributable to the conjugation effect of the bridging heteroatoms with triazine rings and the steric effect of the substituent on the bridging nitrogen atoms. Compared to the formation of dual conjugations of heteroatom with its adjacent aromatic rings in heterocalixaromatics,[7a,9d] heteroatoms, especially nitrogen, in homo heterocalix[2]arene-[2]triazines formed stronger conjugation with only their neighboring triazine rings in solution. This enhanced conjugation effect probably resulted in the rigidification of the macrocycles, leading to relatively slow interconversion of conformational structures in solution. Bulky substituents on the bridging nitrogen atoms further inhibited the conformational mobility of the macrocycle because of the steric effect.

Functionalization. Homo heterocalix[2]arene[2]triazines synthesized from the fragment coupling approach starting with cyanuric halides provided a unique platform for the elaboration of functionalized macrocyclic host molecules. As we have already shown in Schemes 1 and 2, the electrophilicity of chlorotriazine moiety in macrocycles **3** and **8** was utilized to introduce a dialkylamino group in order to improve the solubility of homo heterocalix[2]arene[2]triazines in organic solvents. When an amine containing a functional group is applied, the functionalized homo calix-[2]arene[2]triazines are feasible. Scheme 4 depicts the efficient synthesis of allyl-functionalized homo[2] tetraozacalix-[2]arene[2]triazine using allylamine as a nucleophile. One of the further examples of functionalizations illustrated in Scheme 4 was the arylation on the upper rim position of the triazine rings. The Suzuki coupling reaction[18] of homo[2] tetraoxacalix[2]arene[2]triazine **11a** and homo[4] tetraaza-calix[2]arene[2]triazine **8b** with 4-chlorophenylboronic acid furnished the corresponding diarylated products **13** and **15** in 85% and 82% yield, respectively. Further reaction of **13** with bis(pinacolato)diboron under palladium catalysis[19] afforded boronate product **14**.

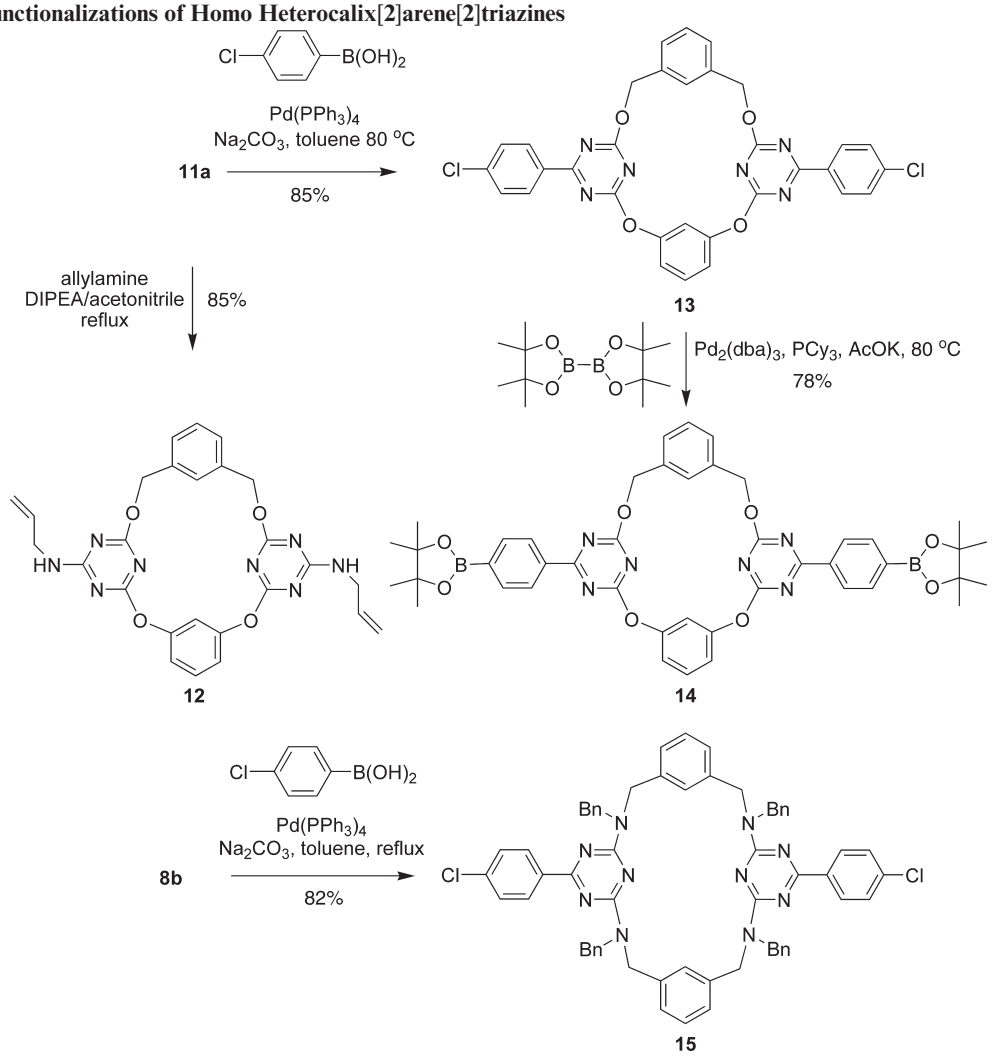
One of the unique and distinguishable features of heterocalixaromatics from conventional calixarenes is the reactivity of bridging moieties.[8h,n] Facile reactions on the bridging positions of NH-linked homo calix[2]arene[2]triazines would generate novel heterocalixaromatics with functional groups specifically installed on the bridging elements. As a demonstration, we prepared exhaustive *N*-allylated homo[4] tetraazacalix[2]arene[2]triazine **16** in 64% yield from alkylation reaction of **9a** with allyl bromide in the presence of NaH (Scheme 5). Both allyl and boronate are versatile functional groups amenable to further chemical manipulations.

Conclusion

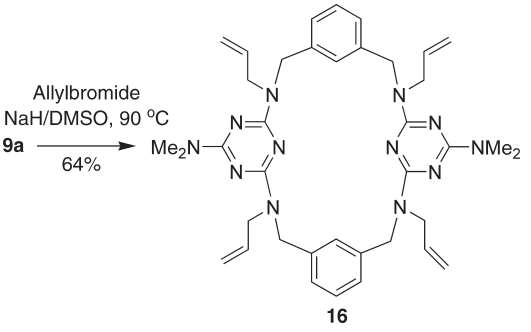
In summary, we have devised a novel type of macrocyclic molecules, namely, homo heterocalixaromatics. Through a general and good-yielding fragment coupling approach, a number of homo[2] and homo[4] aza- and oxa-calix[2]arene-[2]triazines were synthesized under very mild conditions from simple and readily available starting materials. All heteroatoms formed strong conjugation with triazine rings. The combination of methylene, heteroatom such as nitrogen and oxygen, and substituent as the bridging units enabled the generation of tunable diverse conformational structures of homo heterocalix[2]arene[2]triazines in the solid state. Homo heterocalix[2]arene[2]triazines were fluxional macrocycles in

(18) Janietz, D.; Bauer, M. *Synthesis* **1993**, 33.
(19) Ishiyama, T.; Ishida, K.; Miyaura, N. *Tetrahedron* **2001**, *57*, 9813.

SCHEME 4. Functionalizations of Homo Heterocalix[2]arene[2]triazines



SCHEME 5. Synthesis of *N*-Functionalized Homo[4]tetraazacalix[2]arene[2]triazine 16



solution, and they underwent rapid conformation interconversion at different temperatures depending on the nature of the bridging elements. Efficient and straightforward chemical manipulations on triazine rings and the bridging NH units led to functionalized homo heterocalix[2]arene[2]triazine derivatives. The easy availability, versatile conformational and cavity structures, and amenability to functionalization would render homo calix[2]arene[2]triazines useful macrocyclic host molecules in supramolecular science.

Experimental Section

Synthesis of 3c. To a solution of DIPEA (1.22 g, 9.6 mmol) in acetone (200 mL) at room temperature were added dropwise both solutions of **1c** (2.33 g, 4 mmol) in acetone (75 mL) and **2b** (1.26 g, 4 mmol) in acetone (75 mL) at nearly the same rate during 5 h. The resulting mixture was allowed to stir for another 20 h. After removal of the solvent, the residue was mixed with silica gel (6 g) and subjected to silica gel chromatography with dichloromethane as an eluent. Product **3c** (1.71 g, 52%) was obtained as a white powder. **3c**: mp 237−238 °C; MS (MALDI-TOF) m/z 827.2 [M + H$^+$] (100), 829.2 (73), 849.2 [M + Na$^+$] (54), 851.2 (40); ^{1}H NMR (300 MHz, o-$C_6H_4Cl_2$, 340 K) δ 7.10−6.70 (m, 24H), 6.55 (d, J = 7.4 Hz, 2H), 6.33 (br s, 2H), 4.75 (br, s, 8H), 4.14 (br, s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 169.7, 165.4, 165.3, 142.4, 137.6, 137.4, 137.4, 128.6, 128.5, 128.3, 128.2, 128.0, 127.9, 127.6, 127.4, 124.7, 122.7, 53.2, 51.5, 50.4; IR (KBr) ν 3027, 1596, 1561 cm^{-1}. Anal. Calcd for $C_{48}H_{40}Cl_2N_{10}$: C, 69.64; H, 4.87; N, 16.92. Found: C, 69.69; H, 4.88; N, 16.67.

Synthesis of 4a. To a solution of DIPEA (3.1 g, 24 mmol) in acetonitrile (300 mL) at room temperature were added dropwise solutions of **1a** (4.04 g, 10 mmol) in acetonitrile (100 mL) and **2a** (1.4 g, 10 mmol) in acetonitrile (100 mL) at nearly the same rate during 5 h. The resulting mixture was allowed to stir for another 12 h, and the white precipitate was formed gradually. Filtration gave 1.88 g of crude product as the white solid. The crude

product (0.93 g) was mixed with diethylamine (0.36 g, 5 mmol) and DIPEA (0.64 g, 5 mmol) in DMSO (50 mL), and then the mixture was allowed to stire at 85 °C for 12 h. Water (150 mL) was added, and the mixture was extracted with chloroform (3 × 50 mL). After drying with anhydrous Na_2SO_4 and removal of the solvent, the residue was chromatographed on a silica gel column eluting with a mixture of petroleum ether and acetone (4:1) to afford product **4a** as a white powder (0.84 g, 31% overall yield based on **1a**). **4a**: mp 271 °C; MS (MALDI-TOF) *m*/*z* 543.4 [M + H$^+$] (100); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 8.07 (t, J = 12.5 Hz, 2H, NH), 7.45 (t, J = 8.2 Hz, 1H), 7.05−7.17 (m, 5H), 6.89 (s, 1H), 6.68 (s, 1H), 4.13 (d, J = 5.7 Hz, 4H), 3.51 (q, J = 6.3 Hz, 4H), 1.1 (t, J = 6.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 170.2, 166.7, 165.5, 152.7, 140.2, 128.1, 128.0, 127.3, 125.2, 119.8, 115.1, 43.9, 40.5, 13.2; IR (KBr) ν 3263, 1602, 1551 cm^{-1}. Anal. Calcd for $C_{28}H_{34}N_{10}O_2$: C, 61.98; H, 6.32; N, 25.81. Found: C, 61.75; H, 6.31; N, 25.68.

Synthesis of 4b. To a solution of DIPEA (3.1 g, 24 mmol) in acetone (300 mL) at room temperature were added dropwise solutions of **1b** (4.06 g, 10 mmol) in acetone (100 mL) and **2a** (1.4 g, 10 mmol) in acetone (100 mL) at nearly the same rate during 5 h. The resulting mixture was allowed to stir for another 20 h, and the white precipitate was formed gradually. Filtration gave 2.64 g of crude product as the white solid. The crude product (0.94 g) was mixed with diethylamine (0.36 g) and DIPEA (0.64 g) in DMSO (50 mL), and then the mixture was kept stirring at 85 °C for 12 h. Water (150 mL) was added, and the mixture was extracted with chloroform (3 × 50 mL). After drying with anhydrous Na_2SO_4 and removal of the solvent, the residue was chromatographed on a silica gel column eluting with a mixture of petroleum ether and acetone (5:1) to afford product **4b** as a white powder (0.84 g, 24% overall yield based on **1b**). **3b** was also synthesized in 19% overall yield from **7a** and **11b**. Product **4b** (recrystallized from chloroform and *n*-hexane). **4b**: mp 232−233 °C; MS (MALDI-TOF) *m*/*z* 541.0 [M + H$^+$] (100); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 9.28 (s, 1H), 7.21−7.31 (m, 3H), 7.08 (m, 3H), 6.70 (s, 2NH), 6.48 (q, J = 2.2 Hz, 2H), 5.28 (t, J = 6.6 Hz, 2NH), 4.70 (d, J = 6.6 Hz, 4H), 3.50 (q, J = 7.1 Hz, 8H), 1.09 (br, s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 165.4, 163.6, 163.4, 140.1, 138.7, 127.4, 126.9, 123.5, 119.8, 112.2, 111.1, 42.1, 39.8, 12.1; IR (KBr) ν 3259, 3113, 1590, 1543, 1508 cm^{-1}. Anal. Calcd. for $C_{30}H_{38}N_{10}O_2 \cdot CHCl_3$: C, 52.77; H, 5.65; N, 25.47. Found: C, 53.22; H, 5.69; N, 25.66.

Synthesis of 5a and 5b. To a solution of DIPEA (0.75 g, 6 mmol) in acetone (200 mL) at room temperature were added dropwise solutions of **1a** (1.01 g, 2.5 mmol) in acetone (75 mL) and **2a** (0.35 g, 2.5 mmol) in acetone (75 mL) at nearly the same rate during 3 h. The resulting mixture was allowed to stir for another 5 h. After removal of the solvent, the residue was mixed with silica gel (3 g) and subjected to silica gel chromatography with a mixture of petroleum ether and acetone (4:1) as eluent. Both products **5a** (0.18 g, 14%) and **5b** (0.37 g, 31%) were obtained as a white powder. **5a**: mp > 300 °C; MS (MALDI-TOF) *m*/*z* 509.2 [M + H$^+$] (100), 511.2 (61); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 8.12 (m, 2NH) 7.41 (t, J = 8.0 Hz, 1H), 6.9−7.2 (m, 7H), 5.11 (s, 1H), 4.93 (s, 1H), 4.63 (br s, 2H), 4.39 (d, J = 6.0 Hz, 1H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 171.6, 170.7, 170.4, 167.2, 165.1, 152.1, 152.0, 145.4, 138.0, 137.4, 128.9, 128.7, 125.2, 120.5, 119.8, 115.0, 113.2, 54.0, 45.4, 20.9; IR (KBr) ν 3260, 3126, 1568, 1507 cm^{-1}. Anal. Calcd for $C_{23}H_{18}N_8O_2Cl_2$: C, 54.24; H, 3.56; N, 22.00. Found: C, 54.28 H, 3.64; N, 21.88. **5b**: mp > 300 °C; MS (MALDI-TOF) *m*/*z* 549.2 [M + H$^+$] (100), 551.2 (71); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 7.37 (t, J = 8.1 Hz, 1H), 7.14 (t, J = 8.1 Hz, 1H), 7.01−7.06 (m, 5H), 6.87 (s, 1H), 5.17 (s, 2H), 5.02 (s, 2H), 4.65 (br s, 4H), 2.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 171.4, 170.3, 165.2, 152.2, 145.7, 137.1, 128.9, 128.4, 126.5, 125.4, 120.0, 114.9, 113.3, 54.3, 20.8; IR (KBr) ν 1559, 1541, 1506 cm^{-1}. Anal. Calcd for $C_{26}H_{22}N_8O_2Cl_2$: C, 56.84; H, 4.04; N, 20.40. Found: C, 56.66; H, 4.14; N, 20.46.

Synthesis of 9a. To a solution of DIPEA (3.1 g, 24 mmol) in acetone (300 mL) were added at room temperature dropwise solutions of **7a** (4.3 g, 10 mmol) in acetone (100 mL) and **2a** (1.37 g, 10 mmol) in acetone (100 mL) at nearly the same rate during 5 h. The mixture was reacted for another 20 h, and a white precipitate was formed. After filtration, the crude product (4.19 g) was collected as a white solid. A mixture of crude product (1.0 g) and aqueous dimethylamine (30%, 1.5 mL) in DMF (50 mL) was allowed to stir at 85 °C for 12 h. After being cooled to room temperature, the product **9a** (0.86 g, 65% overall yield based on **7a**), which was complexed with 1 equiv of DMF, was precipitated. **9a**: mp 265−266 °C; MS (ESI) *m*/*z* 513.2 [M + H$^+$] (100); ^{1}H NMR (300 MHz, DMSO, TMS, 370 K) δ 7.28 (s, 2H), 7.15 (t, J = 7.1 Hz, 2H), 7.05 (d, J = 7.1 Hz, 4H), 6.55 (br, s, 4NH), 4.40 (br, s, 8H), 2.94 (s, 12H); ^{13}C NMR (75 MHz, CF_3CO_2D, TMS) δ 165.8, 165.3, 141.0, 127.1, 126.2, 125.1, 43.1, 35.4; IR (KBr) ν 3379, 1550, 1511 cm^{-1}. Anal. Calcd for $C_{26}H_{32}N_{12} \cdot 2DMSO$: C, 53.87; H, 6.63; N,25.13. Found: C, 53.72; H, 6.67; N, 25.04.

Synthesis of 9b. To a solution of DIPEA (2.1 g, 16.8 mmol) in acetone (200 mL) were added at room temperature dropwise solutions of **7b** (4.30 g, 7 mmol) in acetone (75 mL) and **2b** (2.10 g, 7 mmol) in acetone (75 mL) at nearly the same rate during 5 h. The mixture was reacted for another 12 h, and a white precipitate was formed. After filtration, the crude product (3.7 g) was collected as a white solid. The crude product (1.3 g), diethylamine (0.36 g, 5 mmol), and DIPEA (0.64 g, 5 mmol) were mixed in DMSO (50 mL). The reaction mixture was stirred at 85 °C for 12 h. Water (150 mL) was added, and the product was extracted with chloroform (3 × 50 mL). After drying with anhydrous Na_2SO_4 and the removal of the solvent, the residue was chromatographed on a silica gel column eluted with a mixture of petroleum ether and dichloromethane (1:1) to afford pure product **9b** (1.14 g, 50% overall yield based on **7b**) as a white solid. **9b**: mp 218−219 °C; MS (MALDI-TOF) *m*/*z* 929.6 [M + H$^+$] (100); ^{1}H NMR (300 MHz, *o*-$C_6H_4Cl_2$, 385K) δ 6.77−7.05 (m, 28H), 3.6−6.0 (m, 16H), 3.28 (s, 8H), 0.86 (s,12H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 166.4, 165.1, 139.6−140.0, 122.8−130.9, 49.6, 48.5−48.6, 41.7−42.2, 13.7−14.2; IR (KBr) ν 2927, 1537, 1492 cm^{-1}. Anal. Calcd for $C_{58}H_{64}N_{12}$: C, 74.97; H, 6.94; N, 18.09. Found: C, 74.78; H, 6.82; N, 17.95.

Synthesis of 9c. To a solution of DIPEA (3.1 g, 24 mmol) in acetonitrile (300 mL) were added at room temperature dropwise solutions of **7c** (4.3 g, 10 mmol) in acetonitrile (100 mL) and **2a** (1.38 g, 10 mmol) in acetonitrile (100 mL) at nearly the same rate during 5 h. A white precipitate was formed, and the mixture was reacted for another 12 h. After filtration, the crude product (3.01 g) was collected as white solid. The crude product (0.96 g), diethylamine (0.36 g, 5 mmol), and DIPEA (0.64 g, 5 mmol) were mixed in DMSO (50 mL). The reaction mixture was stirred at 85 °C for 12 h. Water (150 mL) was added, and the product was extracted with chloroform (3 × 50 mL). After drying with anhydrous Na_2SO_4 and the removal of the solvent, the residue was chromatographed on a silica gel column eluted with a mixture of petroleum ether, dichloromethane, and acetone (4:8:1) to afford pure product **9c** (0.58 g, 32% overall yield based on **7c**) as a white solid. **9c**: mp 260−262 °C; MS (MALDI-TOF) *m*/*z* 571.1 [M + H$^+$] (100), 572.2 (53); ^{1}H NMR (300 MHz, DMSO-d_6, 380K, TMS) δ 7.37 (s, 1H), 7.07−7.27(m, 7H) 6.92 (s, 2NH), 5.32 (s, 4H), 4.42 (d, J = 6.2 Hz, 4H), 3.43 (q, J = 6.7 Hz, 8H), 1.02 (t, J = 6.7 Hz, 12H); ^{13}C NMR (75 MHz, CF_3CO_2D, TMS, 380 K) δ 157.5, 156.7, 154.4, 139.6, 137.3, 133,3, 132.9, 131.9, 131.4, 130.2, 73.6, 49.2, 49.0, 46.9, 14.5, 14.3; IR (KBr) ν 3256, 3117, 1618, 1590, 1556 cm^{-1}. Anal. Calcd for $C_{30}H_{38}N_{10}O_2$: C, 63.14; H, 6.71; N, 24.54. Found: C, 63.04; H, 6.72; N, 24.52.

Synthesis of 9d. To a solution of triethylamine (2.1 g, 21 mmol) in dry diethyl ether (300 mL) were added at room temperature dropwise solutions of **7d** (3.70 g, 10 mmol) in dry ether (200 mL) and **2c** (1.39 g, 10 mmol) in dry ether (200 mL) at nearly the same rate during 10 h. The mixture was reacted for another 12 h. After filtration, the crude product (4.8 g) was collected as a white solid. The crude product (0.47 g) was refluxed with dipropylamine (0.51 g, 5 mmol) in chloroform (50 mL) for 2 h. Water (50 mL) was added, chloroform was separated, and the aqueous layer was extracted with an additional 50 mL of chloroform. After drying with anhydrous Na_2SO_4 and the removal of the solvent, the residue was chromatographed on a silica gel column eluted with a mixture of petroleum ether and dichloromethane (2:1) to afford pure product **9d** (0.42 g, 66% overall yield based on **7d**) as a white solid. **9d**: mp 205 °C; MS (MALDI-TOF) m/z 629.1 [M + H^+] (100), 630.1 (30); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 7.73 (s, 2H), 7.30 (m, 6H), 5.40 (s, 4H), 3.43 (t, J = 7.7 Hz, 8H), 1.58 (m, J = 7.5 Hz,8H), 0.87 (t, J = 7.4 Hz,12H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 171.4, 166.9, 137.1, 128.4, 128.1, 127.8, 68.0, 49.1, 20.9, 11.4; IR (KBr) ν 1583, 1533 cm^{-1}. Anal. Calcd for $C_{34}H_{44}N_8O_4$: C, 64.95; H, 7.05; N, 17.82. Found: C, 64.58; H, 7.15; N, 17.44.

Synthesis of 11a. To a solution of DIPEA (1.5 g, 12 mmol) in acetone (300 mL) were added at room temperature dropwise solutions of **7c** (2.1 g, 5 mmol) in acetone (100 mL) and **10a** (0.55 g, 5 mmol) in acetone (100 mL) at nearly the same rate during 5 h. The mixture was reacted for another 5 h. After removal of solvent, the residue was chromatographed on a silica gel column eluted with a mixture of petroleum ether and acetone (4:1) to afford pure product **11a** (1.26 g, 54%) as a white solid. **11a**: mp > 300 °C; MS (MALDI-TOF) m/z 492.8 [M + Na^+] (100), 494.8 (64); ^{1}H NMR (300 MHz, CDCl3, TMS) δ 7.61 (t, J = 8.3 Hz, 1H), 7.23−7.28(m, 3H), 7.21 (d, J = 2.2 Hz, 2H), 6.87 (t, J = 2.2 Hz,1H), 6.62(s, 1H), 5.28 (s, 1H); ^{13}C NMR (75 MHz, CDCl3, TMS) δ 173.9, 172.1, 171.9, 152.1, 135.5, 129.6, 129.5, 126.6, 125.0, 120.7, 115.0, 70.0; IR (KBr) ν 1551 cm^{-1}. Anal. Calcd for $C_{20}H_{12}Cl_2N_6O_4$: C, 50.97; H, 2.57; N, 17.83. Found: C, 50.79; H, 2.61; N, 17.48.

Synthesis of 11b. To a solution of DIPEA (1.5 g, 12 mmol) in acetone (200 mL) were added at room temperature dropwise solutions of **7c** (2.1 g, 5 mmol) in acetone (75 mL) and **10b** (0.54 g, 5 mmol) in acetone (75 mL) at nearly the same rate during 5 h. The mixture was reacted for another 12 h. After removal of solvent, the residue was chromatographed on a silica gel column eluted with a mixture of petroleum ether and acetone (4:1) to afford pure product **11b** (1.14 g, 49%) as white solid. **11b**: mp > 300 °C; MS (MALDI-TOF) m/z 469.3 [M + H^+] (83), 471.3 (77), 491.2 [M + Na^+] (100), 493.2 (84), 507.2 [M + K^+] (84); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 10.73 (s, 2H, NH), 8.61 (s, 1H), 7.56 (s, 1H), 7.38−7.34 (m, 4H), 7.05(q, J = 1.5 Hz, 2H), 5.46 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 170.5, 169.7, 165.3, 137.9, 136.6, 129.1, 128.7, 127.1, 126.3, 119.4, 116.3, 67.8; IR (KBr) ν 3287, 1576, 1551 cm^{-1}. Anal. Calcd for $C_{20}H_{14}Cl_2N_8O_2$: C, 51.19; H, 3.01; N, 23.88. Found: C, 50.98; H, 2.97; N, 23.52.

Synthesis of 12. A mixture of **11a** (68 mg, 0.15 mmol), allylamine (20 mg, 0.35 mmol), and DIPEA (0.12 g, 0.95 mmol) in acetonitrile (20 mL) was refluxed for 4 h, and white precipitates were generated. The solvent was concentrated to around 5 mL, and the white solid product **12** (56 mg, 85%) was obtained through filtration. **12**: mp > 300 °C; MS (MALDI-TOF) m/z 513.3 [M + H^+] (9), 535.2 [M + Na^+] (100), 536.2 (52), 551.2 [M + K^+] (57), 552.2 (28); ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 8.25 (q, J = 5.6 Hz, 2NH), 7.53 (t, J = 8.2 Hz, 1H), 7.15−7.26 (m, 5H), 7.03 (s, 1H), 6.82 (s, 1H), 5.85 (m, 2H), 5.06−5.17 (m, 8H), 3.92 (d, J = 4.6 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, TMS) δ 172.0 (br), 171.5 (br), 168.9 (br), 152.9 (br), 137.8 (br), 135.3 (br), 129.5, 129.1, 126.6, 126.1, 125.7, 120.4, 115.8, 68.0 (br), 43.0; IR (KBr) ν 3264, 3138, 3021, 1622, 1578 cm^{-1}. Anal. Calcd for $C_{26}H_{24}N_8O_6 \cdot CH_3CN$: C, 60.75; H, 4.92; N, 22.77. Found: C, 60.30; H, 5.03; N, 23.02.

Synthesis of 13. Under argon protection, **11a** (0.13 g, 0.3 mmol), *p*-chlorobenzoboric acid (0.10 g, 0.65 mmol), and Pd-$(PPh_3)_4$ (17 mg, 5% mol) were mixed in dry toluene (30 mL). An aqueous solution of Na_2CO_3 (1 M, 2 mL) was added, and the resulting mixture was allowed to stir at 80 °C for 4 h. Water (50 mL) was then added, and product was extracted with dichloromethane (3 × 50 mL). After drying with anhydrous Na_2SO_4 and the removal of the solvent, the residue was chromatographed on a silica gel column eluted with a mixture of petroleum ether and dichloromethane (1:1) to afford pure product **13** (0.14 g, 85%) as a white powder. **13**: mp > 300 °C; MS (MALDI-TOF) m/z 623.4 [M + H^+] (100), 625.4 (70) [M + Na^+] (645.4); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 8.39 (d, J = 8.6 Hz, 4H), 7.41 (d, J = 8.6 Hz, 4H), 7.53 (t, J = 7.2 Hz, 1H), 7.27 (t, J = 7.3 Hz, 1H), 7.24−7.30 (m, 4H), 6.89 (s, 1H), 6.66 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 175.5, 172.5, 172.4, 152.5, 139.6, 136.6, 133.1, 130.5, 129.3, 129.1, 128.9, 126.5, 125.3, 120.5; IR (KBr) ν 1566, 1522 cm^{-1}. Anal. Calcd for $C_{32}H_{20}Cl_2N_6O_4$: C, 61.65; H, 3.23; N, 13.48. Found: C, 61.26; H, 3.25; N, 13.37.

Synthesis of 14. Under protection of argon, $Pd_2(dba)_3$ (9 mg, 5% mol), a solution of PCy_3 in toluene (20%, 50 mg), and newly distilled 1,4-dioxane (5 mL) were mixed for 20 min. A mixture of reactant **13** (125 mg, 0.2 mmol), bis(pinacolato)diboron (130 mg, 0.5 mmol), and KOAc (100 mg, 1 mmol) was added followed by the addition of newly distilled 1,4-dioxane (20 mL). The resulting mixture was allowed to stir at 80 °C for 10 h. After removal of solvent, water (30 mL) was added, and the mixture was extracted with dichloromethane (2 × 25 mL). After drying with anhydrous Na_2SO_4 and removal of the solvent, the residue was chromatographed on a silica gel column eluted with a mixture of petroleum ether and ethyl acetate (5:1) to afford pure product **14** (98 mg, 78%) as a white powder. **14**: mp > 300 °C; MS (MALDI-TOF) m/z 807.5 [M + H^+] (12), 829.5 [M + Na^+] (100), 830.5 (52), 845.4 [M + K^+] (37); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 8.53 (d, J = 7.7 Hz, 4H), 7.96 (d, J = 7.7 Hz, 4H), 7.60 (t, J = 7.2 Hz, 1H), 7.37 (d, J = 7.7 Hz, 1H), 7.24−7.30(m, 4H), 7.01(s, 1H), 6.76 (s, 1H), 5.34 (s, 4H), 1.38 (s, 24H) ; ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 176.5, 172.2, 172.4, 152.8, 136.8, 136.3, 134.9, 129.2, 129.0, 128.2, 126.5, 125.4, 120.5, 115.5, 84.2, 69.2, 24.9; IR (KBr) ν 2978, 1564, 1525, 1471 cm^{-1}. Anal. Calcd for $C_{44}H_{44}B_2N_6O_8$: C, 65.53; H, 5.50; N, 10.42. Found: C, 65.52; H, 5.48; N, 10.48.

Synthesis of 15. Following the same procedure for the preparation of **13**, the reaction of **8b** (0.65 g, 0.75 mmol) for 12 h afforded product **15** (0.6 g, 82%). **15**: mp 176−178 °C; MS (MALDI-TOF) m/z 1009.6 [M + H^+] (100), 1007.6 (41), 1010.6 (62); ^{1}H NMR (300 MHz, *o*-$C_6H_4Cl_2$, 385 K) δ 8.5−7.6 (m, 4H), 6.6−7.3 (m, 32H), 6.0−5.0 (m, 8H), 4.0−3.6 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 169.11, 166.2 (br), 137−139 (br), 124−130 (br), 48 (br); IR (KBr) ν 3028, 2920, 1586, 1538 cm^{-1}. Anal. Calcd for $C_{62}H_{52}Cl_2N_{10}$: C, 73.87; H, 5.20; N, 13.89. Found: C, 73.85; H, 5.30; N, 13.87.

Synthesis of 16. A mixture of **9a**·2DMSO (purified from the recrystallization from DMSO) (121 mg, 0.2 mmol), NaH (40 mg), and DMF (8 mL) was allowed to stir at 80 °C for 0.2 h. 3-Bromopropene (100 mg, 0.83 mmol) was added, and the resulting mixture was reacted at 80 °C for another 1 h. After removal of DMF under vacuum, water (20 mL) was added very slowly, and the mixture was extracted with dichloromethane (2 × 30 mL). After drying with anhydrous Na_2SO_4 and removal of the solvent, the residue was chromatographed on a silica gel column eluted with a mixture of *n*-pentane and ethyl acetate (5:1) to afford pure product **16** (89 mg, 64%) as pale yellow oil. **16**: MS (MALDI-TOF) m/z 673.4 [M + H^+] (100), 674.4 (40); ^{1}H NMR (300 MHz, DMSO-d_6, TMS, 385K) δ 7.19−7.05

(br m, 8H), 5.72 (br, s, 6H), 4.96 (br, s, 11H), 3.97 (br, s, 11H), 2.94 (br, s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9 (br), 165.5 (br), 139.6 (br), 134.9 (br), 127.3 (br), 125.9 (br), 124.3 (br), 115.9 (br), 49.5−47.1 (br), 35.8 (br); IR (KBr) ν 3264, 3138, 3021, 1622, 1578 cm^{-1}; ESI (M + H^+) calcd for $C_{38}H_{48}N_{12}$ + H^+ 673.4198, found 673.4196 .

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Supporting Information Available: Experimental procedures and analytical and spectral characterization data for compounds **7**; copies of ^{1}H and ^{13}C NMR spectra of **4**, **5**, **9**, and **11**−**16**; X-ray crystallographic data and molecular structures of homo heterocalix[2]arene[2]triazines (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.