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Formation and Conformational Conversion of Flattened Partial Cone Oxygen Bridged Calix[2]arene[2]triazines

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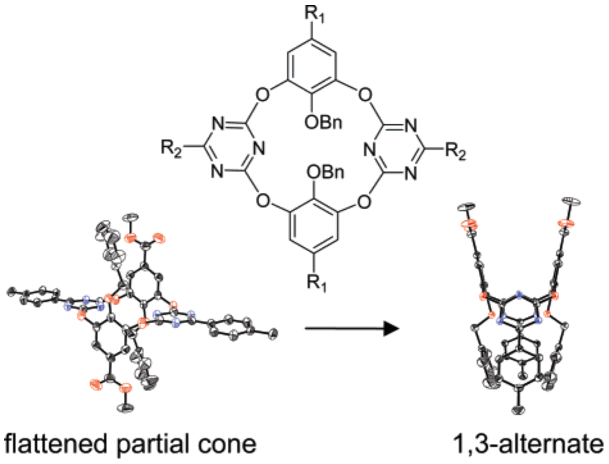
ABSTRACT



A stepwise fragment coupling reaction starting with substituted dichlorotriazine and resorcinol derivatives gave rise to thermodynamically favored 1,3-alternate tetraoxacalix[2]arene[2]triazines and kinetically controlled flattened partial cone tetraoxacalix[2]arene[2]triazines. The flattened partial cone conformer, which was stable due to the steric effect, converted into the 1,3-alternate conformer via ether bond cleavage upon treatment with an inorganic base.

There is a growing interest in the chemistry of heteroatom-bridged calixaromatics.[1−4] Being different from conventional calixarenes[5] in which the aromatic rings are linked by methylene units, heteroatom-bridged calixaromatics have been shown to exihibit different structure characteristics and unique molecular recognition properties. The nitrogen-bridged calix[*n*]pyridines[4d−f] and their protonated macrocycles,[4g] for instance, are able to self-regulate their conformation and cavity in order to achieve the strongest interaction with guest species, because the bridging nitrogen atoms can adopt different electronic configurations and form various degrees of conjugation with their adjacent pyridine rings.

In 2004, we[3a] reported the efficient and high-yielding synthesis of the oxygen- and/or nitrogen-bridged calix[2]arene[2]triazines from cyanuric chloride and various 1,3-bisnucleophiles based on a fragment coupling strategy. By reacting 1,3-dihydroxybenzenes with reactive 1,5-difluoro-2,4-dinitrobenzene, Katz[3b] in 2005 reported a very useful one-pot synthesis of symmetric tetraoxacalix[4]arenes. The chemical yield was dramatically improved in comparison to the reaction with 1,5-dichloro-2,4-dinitrobenzene.[6] Since then a number of tetraoxacalix[4]aromatics have been prepared in either a one-pot synthesis fashion[3c−j] or a [3+1] fragment coupling approach[3k,l] with use of activated 1,3-dihalogenated

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(1) For a useful overview of heteroatom-bridged calixarenes, see: König, B.; Fonseca, M. H. *Eur. J. Inorg. Chem.* **2000**, 2303.

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

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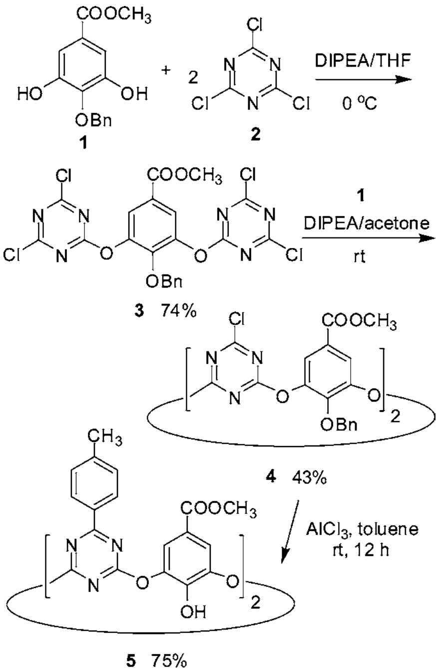
aroamtic compounds. It is interesting to note that, except for only one case,[3j] all of the tetraoxacalix[4]aromatics reported to date have been shown to adopt the 1,3-alternate conformation.[3a−n] To explore their applications in molecular recognition and molecular assembly, however, it is highly challenging and desirable to construct tetraoxacalix[4]-aromatics of different conformations. Our ongoing project[3l,4d−h] to study the functionalizations of heteroatom bridged calix-aromatics has led us to obtain accidentally the oxygen-bridged calix[2]arene[2]triazines of partial cone conformation. Here we report their synthesis, structure, and conformational conversion into 1,3-alternate conformers.

Initially, we targeted the synthesis of functionalized tetraoxacalix[2]arene[2]triazines with hydroxyl groups attached to the lower rim. Following our previously established method,[3a,l] we prepared tetraoxacalix[2]arene[2]triazine **4** readily starting from methyl 4-benzoxy-3,5-dihydroxybenzoate **1** and cyanuric chloride. To obtain the desired dichloro-dihydroxy-tetraoxacalix[2]arene[2]triazine, we tried a number of well-established methods to remove the benzyl protecting groups of **4**. Unfortunately, no deprotection reaction was observed. Only under conditions that used a large amount of $AlCl_3$ (30 equiv) in toluene did the reaction proceed to afford 75% yield of **5**, a product containing both two free hydroxy groups at the low rim of the benzene rings and the two *p*-tolyl groups of the upper rim of the triazine rings (Scheme 1).

Scheme 1. Synthesis of Functionalized Tetraoxacalix[2]arene[2]triazine **5**



Intrigued by the deprotection−arylation reaction, we prepared tetraoxacalix[2]arene[2]triazine **8** bearing both *p*-tolyl and *O*-benzyl groups with the intention of further mechanistic study. As summarized in Table 1, the reaction between **1** and **7** was strongly influenced by the base and the solvent used. No reaction was observed when a mixture of **1** and **7** was heated at reflux in THF or 1,4-dioxane in the presence of DIPEA as a base. The use of acetone or acetonitrile as a solvent gave rise to a moderate yield of product **8a** and a very small amount of a second product **8b**. Interestingly, on the basis of mass spectroscopy and microanalysis, both products **8a** and **8b** have identical chemical constitutions. The combination of triethylamine as a base and acetonitrile as a solvent led to a slight increase of the chemical yield of product **8b**. When an inorganic base such as K_2CO_3 or Cs_2CO_3 was used, the reaction afforded exclusively **8a** in excellent yields (entries 8−10 in Table 1).

The NMR spectra of **8a** and **8b** (Figure 1), which showed only marginal differences, did not give conclusive evidence for the assignment of their structures. Fortunately, both **8a** and **8b** gave high-quality single crystals which allowed us to determine their structures unambiguously. Surprisingly, the X-ray crystallography revealed that products **8a** and **8b** are actually a pair of conformers. As illustrated in Figure 2, compound **8a**, the major product from the reaction, adopted a 1,3-alternate conformation. However, it is worth noting that, compared to the structure of **4** (see Figure S1 in the Supporting Information), the introduction of two *p*-tolyl groups caused the upper rim of triazine rings and the lower rim of benzene rings to get closer, generating a cavity formed by four benzene rings (Figure 2). In contrast to **8a**, product **8b** gave a flattened partial cone (u, uo, d, uo) conformation.[7] To the best of our knowledge, such a flattened partial cone

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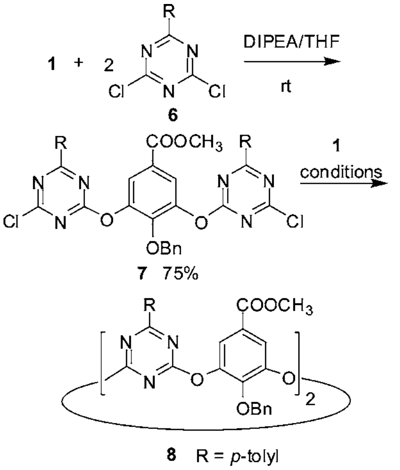
(3) For recent examples of oxygen-bridged calixarene derivatives, see: (a) Wang, M.-X.; Yang, H.-B. *J. Am. Chem. Soc.* **2004**, *126*, 15412. (b) Katz, J. L.; Feldman, M. B.; Conry, R. R. *Org. Lett.* **2005**, *7*, 91. (c) Katz, J. L.; Selby, K. J.; Conry, R. R. *Org. Lett.* **2005**, *7*, 3505. (d) Katz, J. L.; Geller, B. J.; Conry, R. R. *Org. Lett.* **2006**, *8*, 2755. (e) Katz, J. L.; Geller, B. J.; Foster, P. D. *Chem. Commun.* **2007**, 1026. (f) Maes, W.; Van Rossom, W.; Van Hecke, K.; Van Meervelt, L.; Dehaen, W. *Org. Lett.* **2006**, *8*, 4161. (g) Hao, E.; Fronczek, F. R.; Vicente, M. G. H. *J. Org. Chem.* **2006**, *71*, 1233. (h) 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. (i) Zhang, C.; Chen, C.-F. *J. Org. Chem.* **2007**, *72*, 3880. (j) Konishi, H.; Tanaka, K.; Teshima, Y.; Mita, T.; Morikawa, O.; Kobayashi, K. *Tetrahedron Lett.* **2006**, *47*, 4041. (k) Konishi, H.; Mita, T.; Morikawa, O.; Kobayashi, K. *Tetrahedron Lett.* **2007**, *48*, 3029. (l) Yang, H.-B.; Wang, D.-X.; Wang, Q.-Q.; Wang, M.-X. *J. Org. Chem.* **2007**, *72*, 3757. (m) 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. (n) 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. (o) Li, X. H.; Upton, T. G.; Gibb, C. L. D.; Gibb, B. C. *J. Am. Chem. Soc.* **2003**, *125*, 650.

(4) For recent examples of nitrogen-bridged calixarene derivatives, see: (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; 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) Gong, H.-Y.; Zheng, Q.-Y.; Zhang, X.-H.; Wang, D.-X.; Wang, M.-X. *Org. Lett.* **2006**, *8*, 4895. (f) Gong, H.-Y.; Zhang, X.-H.; Wang, D.-X.; Ma, H.-W.; Zheng, Q.-Y.; Wang, M.-X. *Chem. Eur. J.* **2007**, *13*, in press. (g) Gong, H.-Y.; Zhang, X.-H.; Wang, D.-X.; Ma, H.-W.; Zheng, Q.-Y.; Wang, M.-X. *Chem. Eur. J.* **2006**, *12*, 9262. (h) Wang, Q.-Q.; Wang, D.-X.; Ma, H.-W.; Wang, M.-X. *Org. Lett.* **2006**, *8*, 5967. (i) Tsue, H.; Ishibashi, K.; Takahashi, H.; Tamura, R. *Org. Lett.* **2005**, *7*, 11. (j) Fukushima, W.; Kanbara, T.; Yamamoto, T. *Synlett* **2005**, *19*, 2931. (k) Selby, T. D.; Blackstock, S. C. *Org. Lett.* **1999**, *1*, 2053. (l) Suzuki, Y.; Yanagi, T.; Kanbara, T.; Yamamoto, T. *Synlett* **2005**, *2*, 263.

(5) (a) Gutsche, C. D. *Calixarenes*; The Royal Society of Chemistry: Cambridge, UK, 1989. (b) Gutsche, C. D. *Calixarenes Revisited*; The Royal Society of Chemistry: Cambridge, UK, 1998.

(6) (a) Sommer, N.; Staab, H. A. *Tetrahedron Lett.* **1966**, 2837. (b) Lehmann, F. P. A. *Tetrahedron* **1974**, *30*, 727.

Table 1. Synthesis of Tetraoxacalix[2]arene[2]triazine **8**[a]



entry	solvent	base	time	**8a** (%)[b]	**8b** (%)[b]
1	acetone	DIPEA	53 h	17	n.d.
2	acetone	DIPEA	6 days	31	6
3	THF	DIPEA	6 days	no reaction	
4	1,4-dioxane	DIPEA	7 days	no reaction	
5	MeCN	DIPEA	1 day	53	3
6	MeCN	Et_3N	2 days	49	5
7[c]	MeCN	Et_3N	7 h	42	14
8	MeCN	K_2CO_3	20 h	91	0
9[c]	MeCN	K_2CO_3	12 h	92	0
10	MeCN	Cs_2CO_3	16 h	88	0

[a] **1** (1 mmol) and **7** (1 mmol) were added at the same rate to a mixture of an organic base (2.5 mmol) or inorganic base (1.25 mmol) in solvent. For the reaction procedure, see the Supporting Information. [b] Isolated yield. [c] Starting materials were mixed and heated.

structure was only noted once in a substituted tetraoxacalix[4]arene derivative.[3j] More interestingly, two triazine rings located on the same plane and were orientated outward, whereas the benzene rings were anti-positioned and perpendicular to the plane formed by the two triazine rings (Figure 3). As indicated by the bond lengths (Figures S2 and S3, Supporting Information), the bridging oxygen atoms conjugated with their neighboring triazine rings rather than benzene rings in both conformational structures **8a** and **8b**.

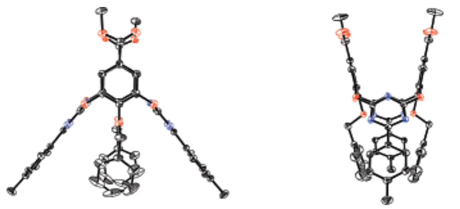


Figure 2. X-ray structure of **8a**: side views.

Figure 3. X-ray structure of **8b**: side views.

To understand the formation of different conformers from the reaction, the mutual conversions of two isomers **8a** and **8b** were investigated. The 1,3-alternate tetraoxacalix[2]arene[2]triazine **8a** was very stable, and no transformation was effected when it was treated with either DIPEA in acetone or K_2CO_3 in acetonitrile under heating. The partial cone tetraoxacalix[2]arene[2]triazine **8b** was stable too. For example, it did not undergo change under neutral conditions even at an elevated temperature. Only a small portion of **8b** was converted into the 1,3-alternate conformer **8a** within 16 days, when **8b** was heated at reflux with DIPEA in acetone. However, heating **8b** at reflux in acetonitrile in the presence of K_2CO_3 (the conditions for exclusive formation of **8a** from the reaction between **1** and **7** [entries 8 and 9 in Table 1]) resulted in the complete transformation of **8b** into **8a** rapidly (within 15 min). These outcomes indicated convincingly that **8a** was a thermodynamically controlled product whereas **8b** was the kinetic product from the reaction of **7** with **1**. Although the exact mechanism needs more study, the conversion of **8b** into **8a** likely proceeds through ether bond scission.

The stability of the flattened partial cone conformation in the case of **8b** is intriguing. We rationalized that the stability most probably originates from the steric effect of the substitutents on the aromatic rings. In other words, bulky groups such as *p*-tolyl and benzyloxy prohibit the free rotation of the benzene and triazine rings around the *meta*−*meta* axes or through the annulus, and therefore inhibit

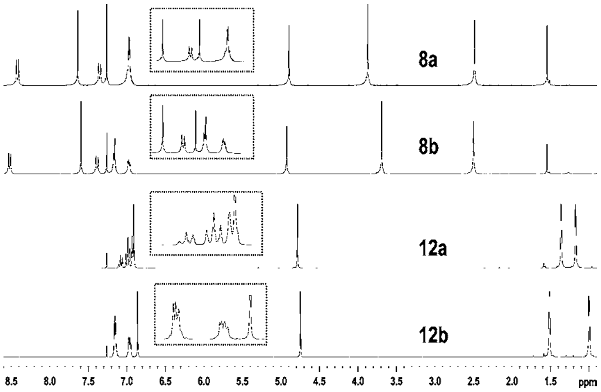


Figure 1. ^1H NMR of **8a**, **8b**, **12a**, and **12b** in $CDCl_3$. The insets are expansions.

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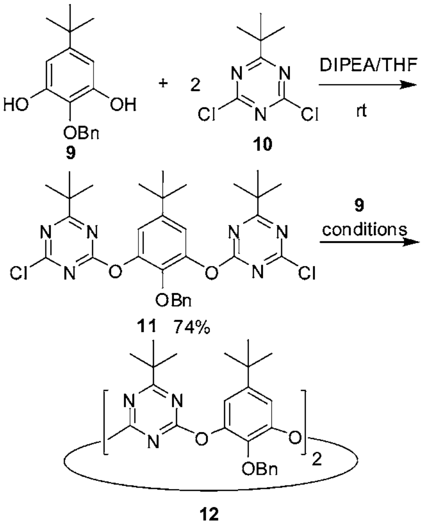
(7) For the nomenclature, see ref 5b, pp 41−46.

Table 2. Synthesis of Tetraoxacalix[2]arene[2]triazine **12**[a]



entry	solvent	base	time	**12a** (%)[b]	**12b** (%)[b]
1	acetone	DIPEA	4 days	no reaction	
2	MeCN	K_2CO_3	12 h	87	0
3	MeCN	Cs_2CO_3	9 h	82	0
4	MeCN	DIPEA	12 h	7	17
5	MeCN	Et_3N	12 h	trace	10

[a] **9** (0.5 mmol), **11** (0.5 mmol), and an organic base (1.25 mmol) or inorganic base (0.63 mmol) were used. For the reaction procedure, see the Supporting Information. [b] Isolated yield.

conversion of the flattened partial cone conformation into the 1,3-alternate conformation without breaking the ether bond linkage. To test our hypothesis of steric effects on the conformations, we then synthesized the tetraoxacalix[2]arene[2]triazines bearing tertiary butyl groups on the aromatic rings from the reaction of **9** and **11** (Table 2). Although the reaction yielded the thermodynamically favored 1,3-alternate product **12a** (Figure 4, left) with use of an inorganic base (entries 2 and 3 in Table 2), the flattened partial cone conformational product **12b** (Figure 4, right) was indeed obtained as the major product, albeit in a low yield, under the kinetically controlled conditions (entries 4 and 5 in Table 2). Product **12b** showed the same conformational stability as **8b**. Only under the conditions such as heating **12b** with an inorganic base in acetonitrile did a flattened partial cone conformation convert into a 1,3-alternate conformation.

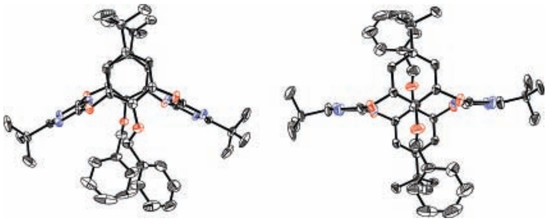


Figure 4. X-ray structure of **12a** (left) and **12b** (right). The disorder of *tert*-butyl groups has been omitted for clarity.

In summary, we have shown that the introduction of sterically bulky groups on the aromatic rings in the [1+3] fragment coupling reaction can lead to the formation of both thermodynamically favored 1,3-alternate and kinetically controlled flattened partial cone tetraoxacalix[2]arene[2]-triazines. The flattened partial cone conformer, which was very stable under neutral conditions due to the steric effect, underwent conversion to 1,3-alternate conformer via the ether bond cleavage upon treatment of an inorganic base. The study of the conformation control and the molecular recognition property of the functionalized heteroatom bridged calixaromatics is in progress and will be reported in due course.

Acknowledgment. The project was supported by grants from NNSFC, MOST, and CAS.

Supporting Information Available: Synthesis and characterization of tetraoxacalix[2]arene[2]triazines, ^{1}H and ^{13}C NMR spectra of all new compounds, and X-ray structures of **4**, **8a**, **8b**, **12a**, and **12b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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