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Synthesis of Tetraazacalix[2]arene[2]triazines: Tuning the Cavity by the Substituents on the Bridging Nitrogen Atoms

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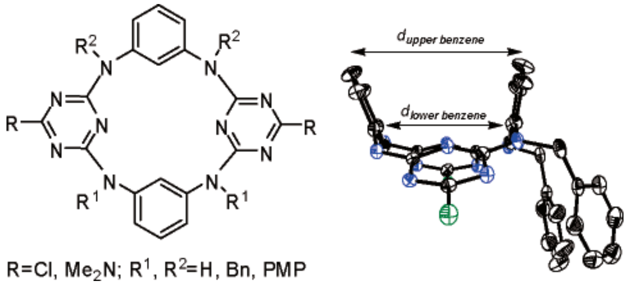
ABSTRACT



A number of tetraazacalix[2]arene[2]triazines bearing different substituents on the bridging nitrogen atoms were synthesized efficiently using a fragment coupling strategy. The N-arylation of the parent azacalix[2]arene[2]triazine afforded tetra(arylaza)calix[2]arene[2]triazine in 91% yield. The introduction of different substituents on the bridging positions led to the regulation of the cavity of the resulting macrocyclic molecules.

There is an increasing interest in heteroatom-bridged calix(hetero)aromatics.[1−4] Compared with calixarenes and calixheteroarenes such as calixpyrroles,[5] calixpyridines,[6] and other calixaromatics[7] in which the (hetero)arene units are linked by methylenes, introduction of heteroatoms into the bridging positions would lead to a wide variety of macrocyclic molecules. Because of the electronic nature of

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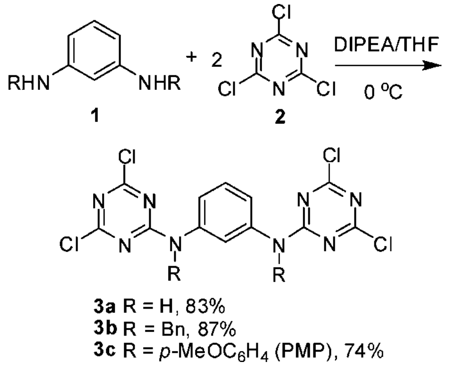
heteroatoms which is different from that of carbon, the heteroatom-bridged calix(hetero)aromatics exhibit interesting structure and molecular recognition properties.[1−4] For example, we[3a,4d−f] have shown that, due to the intrinsic nature of nitrogen which can adopt sp^2 and/or sp^3 electronic configurations to form or not to form conjugation with its adjacent aromatic rings, azacalix[*n*]pyridines and azacalix[*m*]arene[*n*]pyridines are able to preorganize into different conformational and cavity structures to interact with metal ions,[4f] anions,[4e] fullerenes,[4d,e] and other small neutral molecules.

The control of conformational structures, particularly the fine-tuning of the cavity size of the macrocyclic rings, is essential for the design of tailor-made host molecules. We[3a] have previously shown that the cavity of oxygen- and/or nitrogen-bridged calix[2]arene[2]triazines, which ranges from 4.724 to 6.928 Å, was determined by the combined effect of bridging oxygen and nitrogen atoms. We envisioned that the presence of the different substituents on the bridging nitrogen atoms would lead to the tuning of the cavity of the calix[2]arene[2]triazines because the electronic and steric effects of different substituents might perturbate the electronic configuration and conjugation states of the bridging nitrogen atoms. We report herein the highly efficient synthesis of various bridge-N-substituted calix[2]arene[2]triazines and the regulation of their cavity through the introduction of different numbers of aliphatic and/or aromatic groups on the bridging nitrogen atoms.

To synthesize tetraazacalix[2]arene[2]triazines bearing the desired substituents on the bridging nitrogen atoms, the condensation reaction of 1,3-phenylenediamine derivatives **1** with cyanuric acid chloride was first performed. In the presence of di(isopropyl)ethylamine, diamines **1** reacted with 2 equiv of cyanuric acid chloride **2** at 0 °C to give intermediates **3a**−**c** in good yields (Scheme 1). Macrocyclic coupling reaction of **3a**−**c** with 1,3-phenylenediamine proceeded smoothly at ambient temperature to furnish the corresponding tetraazacalix[2]arene[2]triazines **5aa**−**ac** (Scheme 2) in the yield of 43−61%. The reaction time was shortened and the chemical yields were improved when the reaction was carried out in refluxing acetone (Table 1). At room temperature, the reaction between **3a**−**c** and *N*,*N*′-dibenzyl-1,3-phenylenediamine was very slow. For example, it took 3 days for *N*,*N*′-dibenzyl-1,3-phenylenediamine to react with **3a** to form **5ab** in 13% yield, whereas the reaction with **3b** or **3c** at room temperature gave mainly the linear products **6bb** and **7bb** or **6bc** and **7bc**, respectively. The macrocyclic coupling reaction between *N*,*N*′-dibenzyl-1,3-phenylenediamine and **3a**−**c** was facilitated at an elevated temperature to produce tetraazacalix[2]arene[2]triazines in good yields (Table 1). Intramolecular cyclization of the linear intermediates **6bb** and **6bc** in refluxing acetone led to the formation of macrocyclic molecules **5bb** and **5bc** efficiently (Scheme 3). It was noticeable that *N*,*N*′-di(*p*-methoxyphenyl)-1,3-phenylenediamine did not interact with intermediates **3**, and no reaction at all was observed even under more forceful conditions (Table 1).

Scheme 1. Synthesis of Linear Trimers



The results summarized in Table 1 provided us with the guidelines to construct calix[2]arene[2]triazines from the macrocyclic coupling reaction between the linear trimer and

Scheme 2. Synthesis of Azacalix[2]arene[2]triazines

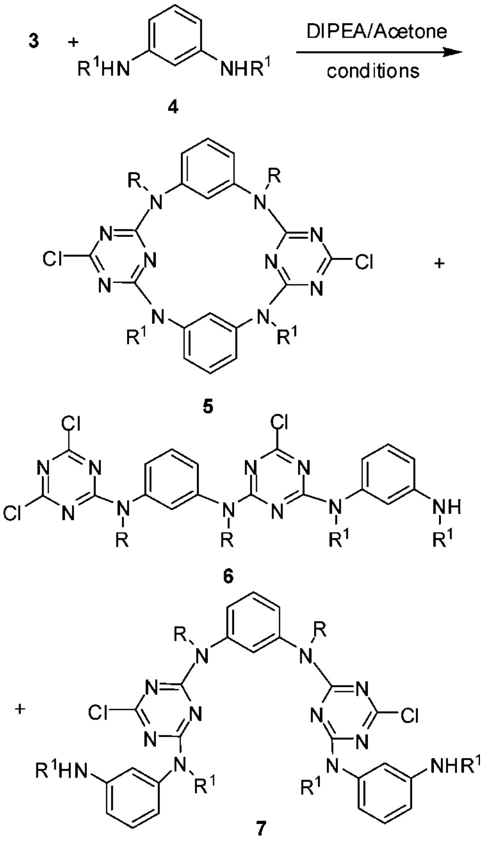


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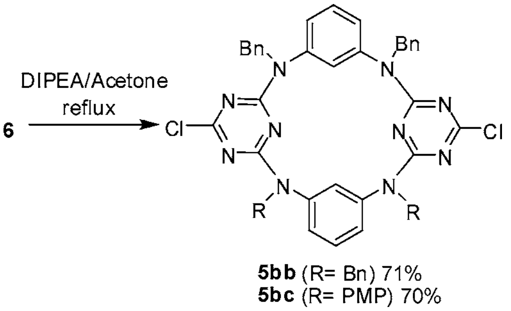
Table 1. Synthesis of Tetraazacalix[2]arene[2]triazines **5**

entry	**3**	R	**4**	R^1	temp	time^d	**5** (%)	**6** (%)
1	**3a**	H	**4a**	H	rt	8 + 48 h	**5aa** (58)	–
2	**3b**	Bn	**4a**	H	rt	5 + 41 h	**5ab** (61)	–
3	**3b**	Bn	**4a**	H	reflux	5 + 31 h	**5ab** (82)	–
4	**3c**	PMP	**4a**	H	rt	5 + 43 h	**5ac** (43)	–
5	**3c**	PMP	**4a**	H	reflux	5 + 72 h	**5ac** (54)	–
6	**3a**	H	**4b**	Bn	rt	5 + 72 h	**5ab** (13)	–
7	**3a**	H	**4b**	Bn	reflux	5 + 58 h	**5ab** (70)	–
8[a]	**3b**	Bn	**4b**	Bn	rt	8 + 81 h	–	**6bb** (46)
9[b]	**3b**	Bn	**4b**	Bn	reflux	7 + 90 h	**5bb** (60)	**6bb** (3)
10	**3c**	PMP	**4b**	Bn	rt	2 + 94 h	–	**6bc** (68)
11[c]	**3c**	PMP	**4b**	Bn	rt	5 + 9 days	**5bc** (26)	**6bc** (26)
12	**3c**	PMP	**4b**	Bn	reflux	4 + 80 h	**5bc** (67)	–
13	**3a**	H	**4c**	PMP	reflux	6 days	–	–
14	**3b**	Bn	**4c**	PMP	reflux	11 days	–	–
15	**3c**	PMP	**4c**	PMP	reflux	10 days	–	–

[a] **7bb** was obtained in 23% yield. [b] **7bb** was obtained in 22% yield. [c] **7bc** was obtained in 27% yield. [d] The period of mixing reactants + reaction time.

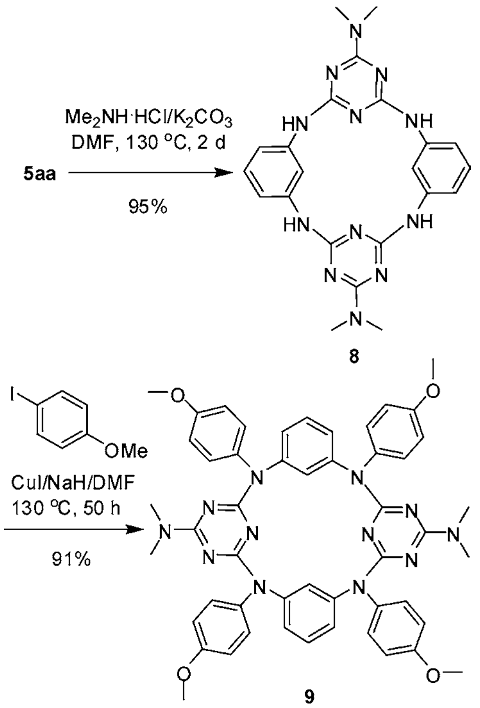
1,3-phenylenediamine derivatives. The less sterically hindered and more nucleophilic diamines including phenylenediamine and *N,N′*-dibenzylphenylenediamine are reactive toward all linear trimers, whereas the more sterically hindered and less nucleophilic diamines such as *N,N′*-di(*p*-methoxyphenyl)phenylenediamine are inert. For the preparation of calix[2]arene[2]triazines having two different N-substituents, it is apparently advantageous to couple diamines bearing two smaller substituents on amino with the trimers that are N-substituted with two larger groups. Higher reaction temperature is beneficial to effect cyclization.

Scheme 3. Cyclization of **6**



To synthesize tetra(arylaza)calix[2]arene[2]triazine, an alternative approach was employed starting with parent macrocyclic ring compound **5aa**. The chloro substituents on the triazine rings of **5aa** were first replaced by two dimethylamino groups. The resulting compound **8** was efficiently N-arylated by 4-iodoanisole in the presence of CuI and NaH at 130 °C to afford the desired calix[2]arene[2]triazine **9** with four *p*-methoxyphenyl (PMP) moieties on the bridging nitrogens in an excellent yield (Scheme 4).

Scheme 4. Synthesis of Fully N-Arylated Calix[2]arene[2]triazine



All macrocyclic compounds, which were characterized with spectroscopic data and microanalysis, were in crystalline form, and they easily gave X-ray quality single crystals. The molecular structures of **5** and **9** in the solid state, which are depicted in Figures 1 and 2 and Supporting Information Figures S1−S3, showed that they adopted a 1,3-alternate conformation with two benzene rings in a face-to-face position and two triazine rings in an edge-to-edge orientation. Four bridging nitrogen atoms sat nearly on the same plane. The bond lengths and bond angles of the bridging nitrogen

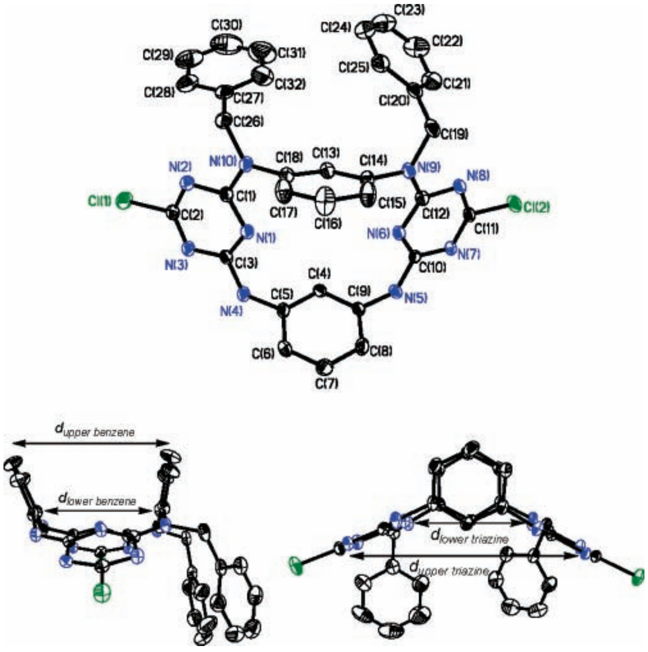


Figure 1. X-ray structure of **5ab**: top and side views.

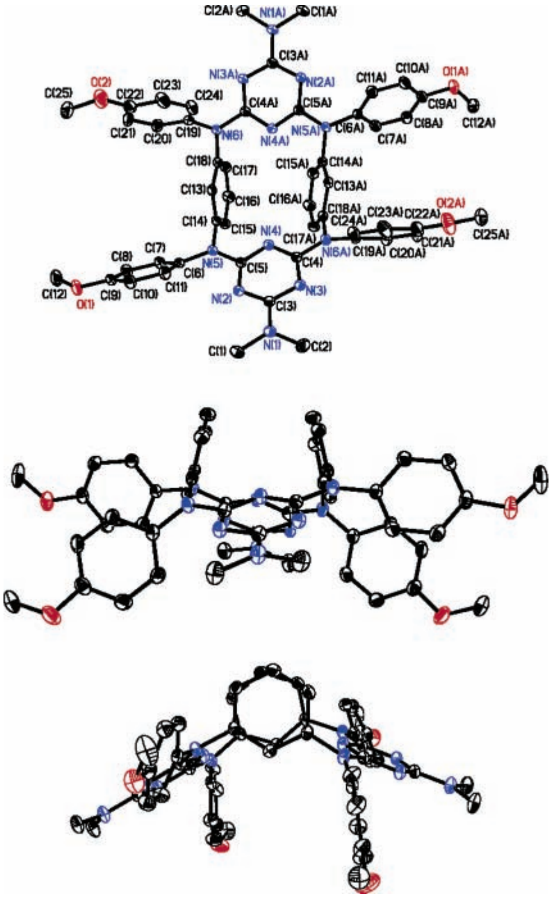


Figure 2. X-ray structure of **9**: top and side views.

atoms indicated that four linking nitrogen atoms adopted an sp^2 configuration, and each of them formed a conjugation with their neighboring triazine ring. The cavity of calix[2]-arene[2]triazines can be viewed as resulting from cyclic arrangement of two isolated benzene units and two diamino-conjugated triazine segments in an alternate fashion. It is very interesting to note that the cavity or the cleft size of the molecule, defined by the distance between two benzene rings at the upper rim ($d_{\text{upper benzene}}$) (Figure 1), is tuned by the substituents on the bridging positions. As tabulated in Table 2, $d_{\text{upper benzene}}$ values varied from 3.514 to 7.392 Å depending on both the number and the nature of the N-substituents. For example, the cavity decreased in the order of **5aa** (7.392 Å), **5ac** (7.245, 6.763 Å), **5ab** (5.993 Å), **5bc** (4.269 Å), **5bb** (4.031 Å), and **9** (3.514 Å) with an increase of the number and bulkiness of the substituents.

Table 2. Cavity of Azacalix[2]arene[2]triazines[a]

5	substituent	d_{upper} benzene	d_{lower} benzene	d_{upper} triazine	d_{lower} triazine
5aa	$R = R^1 = H$	7.392	4.217	9.050	4.632
5ab	$R = Bn, R^1 = H$	5.993	4.404	9.474	4.727
5ac[b]	$R = PMP, R^1 = H$	6.763	4.480	9.690	4.684
5ac[b]	$R = PMP, R^1 = H$	7.245	4.366	9.483	4.678
5bb	$R = R^1 = Bn$	4.031	4.650	9.344	4.816
5bc	$R = PMP, R^1 = Bn$	4.269	4.572	9.863	5.095
9	$R = R^1 = PMP$	3.514	4.776	9.621	4.830

[a] The distances were given in Å. [b] Two discrete molecules of slightly different cavity sizes crystallized in the solid state.

In summary, we have shown an efficient fragment coupling approach for the synthesis of calix[2]arene[2]-triazines bearing different N-substituents. The cross-coupling reaction of tetraazacalix[2]arene[2]triazine with aryl iodide afforded fully N-arylated azacalix[2]arene[2]triazine in excellent yield. The synthetic methods are useful for the functionalization of calix[2]arene[2]triazines on the bridging positions. We have also demonstrated that by introducing different numbers and different substituents on the bridging nitrogen atoms the cavity of the resulting macrocyclic molecules can be regulated. This might open a new avenue to the tailor-made cavity host molecules.

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Supporting Information Available: ^{1}H NMR spectra and X-ray structures of **5** and **9** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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