## Highly efficient construction of large molecular cavity using 1,3-alternate tetraoxacalix[2]arene[2]triazine as a platform<sup>†</sup>

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In the presence of  $K_2CO_3$  in refluxing THF, dichloro-substituted tetraoxacalix[2]arene[2]triazine, a readily available macrocyclic compound from cyanuric acid chloride and benzyl 1,3-dihydroxy-benzoate, underwent highly efficient nucleophilic displacement reactions with bis-nucleophilic reagents of different geometry, length and chirality in a 2+2 fashion to produce large and size-tunable cavity bis-tetraoxacalix[2]arene[2]triazines in good to excellent yields.

For more than three decades, calix[n]arenes have been one of the most important and attractive macrocyclic host molecules in the study of supramolecular chemistry owing to their easy preparation and functionalization, various conformational structures and powerful binding ability towards different guest species.<sup>1-3</sup> Along with the rapid development of calix[n] arenes, recent years have also witnessed a fast growing interest in heteroatom bridged calix(hetero)aromatics.<sup>4–8</sup> In comparison with calix[n]arenes<sup>1–3</sup> and calixheteroarenes such as calixpyrroles,9 calixpyridines10 and other calixaromatics,<sup>11</sup> in which the (hetero)arene units are linked by methylenes, introduction of heteroatoms into the bridging positions has generated a number of novel macrocyclic molecules.<sup>4-8</sup> Based on the fragment coupling strategy, for example, we<sup>6a,6k,6l,7d,7e</sup> have efficiently synthesized aza- and/or oxacalix[2]arene[2]triazines and azacalix[m]arene[n]pyridines (m = 0, n = 4, 5, 8, 10; m = n = 2, 4, 5, while Katz<sup>6b-d,6m</sup> and others<sup>6e,6f,6j,6n</sup> reported the preparation of symmetrically substituted oxacalix[4]aromatics using a very convenient one-pot reaction method. Because of the different electronic nature of heteroatoms from carbon, the heteroatom bridged calix(hetero)aromatics exhibit interesting structural and molecular recognition properties.<sup>4-8</sup> It has been demonstrated that the cavity of azaand/or oxa-calix[2]arene[2]triazines can be regulated by using different combinations of heteroatoms<sup>6a</sup> or varied substituents on the bridging nitrogen atoms.<sup>6k</sup> It has also been shown that, due to the intrinsic nature of nitrogen which can adopt  $sp^2$  and/or  $sp^3$ electronic configurations to form or not form conjugation with adjacent aromatic rings, azacalix[n]pyridines its and azacalix[m]arene[n]pyridines are able to pre-organize into different conformational and cavity structures to interact with metal ions,<sup>7</sup> anions,<sup>7e</sup> fullerenes<sup>7d,e</sup> and both aromatic and aliphatic diols and monools.71

Although the syntheses and the structures of a number of heteroatom bridged calixaromatics have been documented, functionalization and application studies of these novel hosts are just emerging.<sup>6k,6l,7d-f,12</sup> Being analogous to calixarenes, heteroatom bridged calixaromatics can act as platforms for the construction of functionalized and more sophisticated molecular architectures. Dichloro-substituted heteroatom bridged calix[2]arene[2]triazines, which were readily obtained from cyanuric chloride and different aromatic bisnucleophilic agents, for instance, have indeed been chemically modified at the positions of both the triazine ring<sup>12</sup> and the nitrogen bridge.<sup>5k</sup> We report herein the highly efficient construction of a larger and size-tunable molecular cavity by the nucleophilic displacement reaction of dichlorotetraoxacalix[2]arene[2]triazine 1 with bis-nucleophilic reagents 2 of varied geometry and length in a 2+2 fashion.

We started our investigation by examining the reaction of  $1^{6a}$ with 1,3-bis(aminomethyl)benzene 2a under various conditions. As summarized in Table 1, the use of di(isopropyl)ethylamine (DIPEA) (entry 1) or Cs<sub>2</sub>CO<sub>3</sub> (entries 2-4) as a base did not give the desired product. The combination of  $K_2CO_3$  with a polar solvent including dimethylsulfoxide (DMSO) and N.N-dimethylformamide (DMF) afforded a mixture of inseparable oligomers (entries 5 and 6). When the reaction was carried out in dry acetonitrile, a small amount of bis-tetraoxacalix[2]arene[2]triazine 3 was isolated from oligomers (entry 7). Gratifyingly, the chemical yield of 3 was improved drastically to 90% when the reaction was refluxed in dry tetrahydrofuran (THF) (entry 8). It is evident that both the base and the solvent play an important role in facilitating the macrocyclization reaction. The efficient formation of macrocycle 3 in  $K_2CO_3$ -THF suggests the polarity of the reaction medium and the template effect of potassium ion are most likely in favor of intramolecular cyclization over oligomerization.

Encouraged by the highly efficient and high-yielding synthesis of **3** from **1** and **2a**, other bis-nucleophiles of different geometry, length and chirality were employed in order to obtain macrocyclic molecules with a size-tuned cavity. Under conditions identical to those for the synthesis of **3**, the reaction between **1** and benzyl 3,5-dihydroxybenzoate **2b** proceeded equally well to furnish resorcinol-connected cavity molecule **4** in excellent yield (Fig. 1). *N*,*N'*-Dimethylethylenediamine **2c**, a secondary diamine species with the shortest aliphatic chain, was also able to react with **1** in a 2+2 fashion, yielding a rigid macrocyclic cavity **5** in an acceptable yield (41%) (Fig. 1). The chiral molecules can also be incorporated into the macrocyclic bis-tetraoxacalix[2]are-ne[2]triazine cavity. Thus, the interaction between enantiomerically pure 1*R*,2*R*-1,2-diphenylethylenediamine **2d** and 1*R*,2*R*-1,2-cyclohexanediamine **2e** with **1** afforded the corresponding

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Entry	Conditions	Oligomer	<b>3</b> (%) <sup>b</sup>
1	DIPEA, 1.4-dioxane, reflux, 24 h	+	
2	Cs <sub>2</sub> CO <sub>3</sub> , DMSO, reflux, 24 h	+	
3	Cs <sub>2</sub> CO <sub>3</sub> , 1,4-dioxane, reflux, 24 h	+	
4	Cs <sub>2</sub> CO <sub>3</sub> , THF (dry), reflux, 24 h	+	
5	$K_2CO_3$ , DMSO, rt to reflux, 24 h	+	
6	$K_2CO_3$ , DMF, rt to reflux, 24 h	+	
7	K <sub>2</sub> CO <sub>3</sub> , CH <sub>3</sub> CN (dry), reflux, 24 h	+	19
8	K <sub>2</sub> CO <sub>3</sub> , THF (dry), reflux, 24 h	-	90
$a \Delta mix$	ture of <b>1</b> (1 mmol) and <b>2a</b> (1 mmol) wa	is stirred or re	-fluxed in

solution (880 mL). <sup>b</sup> Isolated yield.

chiral cavity molecules 6 and 7, respectively, in good yields (Fig. 1).

The structures of bis-tetraoxacalix[2]arene[2]triazines 3-7 were supported by their spectroscopic data and microanalyses (see Supporting Information<sup>†</sup>). Both mass spectrometry and elemental analysis indicated a 2+2 reaction between dichloro-substituted tetraoxacalix[2]arene[2]triazine 1 and a bis-nucleophilic reactant 2 with the loss of two equivalents of HCl. To understand the cavity structure on the molecular level, a single crystal of 5<sup>±</sup> was cultivated from the slow evaporation of the solvent from its solution in a mixture of methanol and chloroform. Since the Xray diffraction analysis was performed at room temperature, disorder of the atoms of the benzyl moieties was observed (see CIF of 5<sup>†</sup>). As illustrated in Fig. 2, the larger cavity in 5 is composed of two 1,3-alternate tetraoxacalix[2]arene[2]triazine segments which are head-to-head (upper-rim-to-upper-rim) con-N, N'-dimethyl-ethylenediamine nected by two moieties. Compared with its parent 1,3-alternate tetraoxacalix[2]arene[2]triazine,<sup>12b</sup> the distance between two triazine rings



Fig. 1 Structures of larger and size-tunable cavity molecules prepared.

 $(d_{C30-C33} = 8.818 \text{ Å}, d_{C43-C46} = 8.747 \text{ Å})$  in two of the 1,3alternate tetraoxacalix[2]arene[2]triazine units in 5 decreased while the distance between two benzenes ( $d_{C9-C15} = 5.867$  Å,  $d_{C49-C63}$ = 6.122 Å) increased. The distance between two 1,3-alternate tetraoxacalix[2]arene[2]triazines, which are slightly twisted, is 6.668 Å  $(d_{C18-C66})$  to 7.104 Å  $(d_{C12-C52})$ . It is interesting to note that the cavity in 5 is formed by four electron-deficient triazine walls. Furthermore, in the solid state, two bis-tetraoxacalix[2]arene[2]triazine molecules form a non-covalently bonded dimer structure with each large cavity including one of the benzyl moieties of the other molecule. As judged from the distances between the included benzene ring and benzene and triazine rings of the large cavity, there are multiple C–H– $\pi$  interactions between host and guest (see CIF of 5 and structure in ESI<sup>†</sup>). Moreover, there is an apparent  $\pi$ - $\pi$  stacking interaction between two benzene rings of each bistetraoxacalix[2]arene[2]triazine, as the distance between two benzene planes was 3.395 Å (Fig. 3).

The construction of stable cavity molecules of tunable sizes is of great importance in materials and life sciences. The functionalized cavity hosts have been widely used in molecular recognition, enzyme mimics and supramolecular assemblies. The bis-tetraoxacalix[2]arene[2]triazine compounds synthesized in this study have distinct structural features. By using bis-nucleophilic reagents of different structures, for example, the macrocyclic cavity can be



**Fig. 2** X-ray structure of **5** (top view). 50% Thermal ellipsoids are shown for the non-hydrogen atoms. Selected atomic distances:  $d_{C30-C33} = 8.818$  Å;  $d_{C43-C46} = 8.747$  Å;  $d_{C9-C15} = 5.867$  Å;  $d_{C49-C63} = 6.122$  Å;  $d_{C18-C66} = 6.668$  Å; and  $d_{C12-C52} = 7.104$  Å.



**Fig. 3** X-ray structure of a non-covalently bonded dimer formed in the solid state, with one molecule at (x,y,z) being shown in spacefill and the other at (1-x, -y, 1-z) in capped sticks. All hydrogen atoms are omitted for clarity. While two bis-tetraoxacalix[2]arene[2]triazine molecules interact with each other through  $\pi$ - $\pi$  stacking interaction between two benzene rings (d = 3.395 Å), each large cavity includes one benzyl group of the other molecule.

tuned in size. In addition, the macrocyclic framework contains multiple triazine and secondary amine moieties, which are potential hydrogen bond acceptors and donors, respectively. Most noticeably, the cavity of bis-tetraoxacalix[2]arene[2]triazines such as **4** is composed of all four electron-deficient triazine walls. It might be useful in complexation with highly electron-rich species.

In summary, we have shown that dichloro-substituted tetraoxacalix[2]arene[2]triazine 1, a readily available macrocyclic scaffold, is a useful building block for the construction of the higher level polytopic macrocycles. The treatment of 1 with different bisnucleophilic reagents including chiral diamines in the presence of K<sub>2</sub>CO<sub>3</sub> in refluxing THF afforded bis-tetraoxacalix[2]arene[2]triazines in good to excellent yields. In the solid state, a dimeric structure was formed through the  $\pi$ - $\pi$  stacking interaction and mutual inclusion complexation between two large macrocyclic molecules 5. The electron-deficient triazine-walled large cavity of tunable size, the presence of multiple hydrogen-bonding sites and the incorporated chirality would render the bis-tetraoxacalix[2]arene[2]triazines obtained unique and interesting receptors in molecular recognition and supramolecular assembly. Their applications in molecular recognition are being actively investigated in this laboratory.

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## Notes and references

‡ *Crystal data* **5**: C<sub>76</sub>H<sub>60</sub>N<sub>16</sub>O<sub>16</sub>·3CHCl<sub>3</sub>, M = 1811.52, triclinic,  $P\bar{1}$ , a = 14.1173(4), b = 15.7356(3), c = 20.9053(6) Å,  $\alpha = 101.255(1)$ ,  $\beta = 98.513(1)$ ,  $\gamma = 96.039(1)^\circ$ , V = 4461(2) Å<sup>3</sup>, Z = 2,  $\mu$ (Mo-K $\alpha$ ) = 0.078 mm<sup>-1</sup>. The structure was solved by Sir97 and refined by SHELXL-97 in the WinGX package. The excess electron density was smoothed out by the SQUEEZE option in PLATON. Final residuals (1005 parameters) R1 = 0.0787 for 7760 reflections with  $I > 2\sigma(I)$ , and R1 = 0.1462, wR2 = 0.2495, GoF = 0.945 for all 17233 data. CCDC 682855.

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