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Triptycene-Derived N(H)-Bridged Azacalixarenes: Synthesis, Structure, and Encapsulation of Small Neutral Molecules in the Solid State

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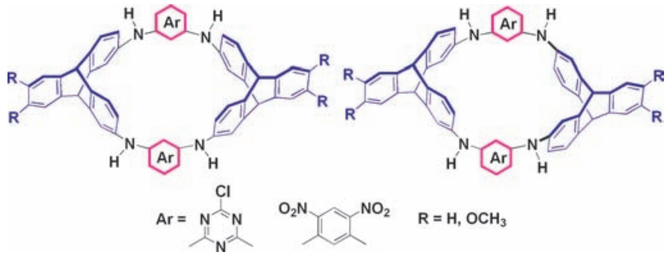
ABSTRACT



Four pairs of novel N(H)-bridged azacalixarenes derived from triptycene were synthesized by both one-pot and two-step fragment-coupling approaches. Due to the unique 3D rigid structure of triptycene, the macrocycles all adopted fixed conformations in both solution and solid state. X-ray crystallographic analyses also revealed that the *cis* isomers with boat conformations showed the capability of encapsulating methanol and acetone molecules inside.

Azacalixarenes or aza[1_n]metacyclophanes,[1] an important class of heterocalixarenes,[1,2] have attracted increasing interest in recent years due to the unique feature of bridging nitrogen atoms. Consequently, a few types of *N*-substituted azacalixarenes have been synthesized independently by Tanaka,[3] Wang,[4] Kanbara,[5] and Tsue.[6] Owing to the hydrogen-bonding ability of NH groups and their possible tunable functionalization, the N(H)-bridged azacalixarenes can be especially attractive hosts for molecular recognition and molecular assembly. However, they are still in the stage of synthesis with very few examples until now, and their properties remain largely unexplored[4b,7] possibly due to their small cavities or nonfixed conformations.[7b,8]

During the past several years, we have proven that a triptycene[9] with a unique 3D rigid structure could be used as a useful building block for the design and synthesis of novel macrocyclic hosts with specific structures and properties.[10] Thus, we supposed that if a proper triptycene derivative instead of *m*-phenylenediamine was used as the nucleophilic reagent for the direct nucleophilic aromatic substitution (S_NAr) reactions,

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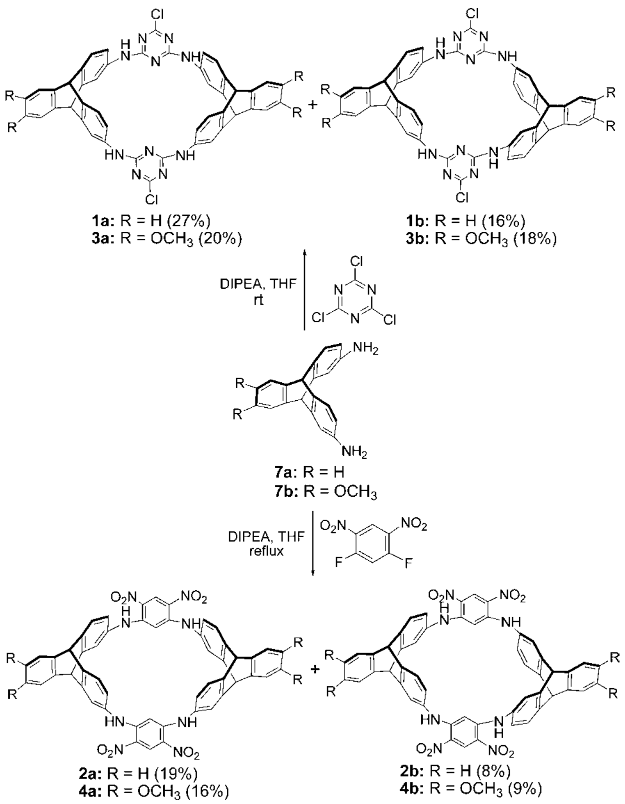
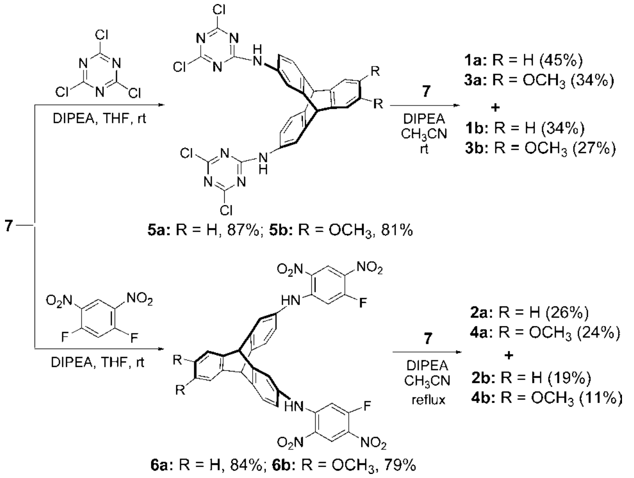
a new kind of N(H)-bridged azacalixarenes with fixed conformation and large cavities could thus be obtained. Herein, we report the synthesis of four pairs of novel triptycene-derived N(H)-bridged azacalixarenes by both one-pot and two-step fragment-coupling approaches and their structures in both solution and solid state. Moreover, we also find that the large cavities and unique boat conformations of the *cis* isomers, in addition to their aromatic motifs and heteroatom binding sites, can make them available to encapsulate small neutral molecules inside the solid state.

Synthesis of the novel macrocycles through a one-pot approach is depicted in Scheme 1. Reaction of 2,7-diaminotriptycene **7a**[10f] with cyanuric chloride in dry THF in the presence of DIPEA at room temperature gave the macrocycles **1a** and **1b** in 27% and 16% yield, respectively. Similarly, the macrocycles **3a** and **3b** could also be synthesized in total 38% yield. However, under the same conditions, compounds **2a** and **2b** could not be afforded until the mixture was refluxed for 5 days under argon atmosphere. While the macrocycles **4a** and **4b** could also be synthesized after refluxing the mixture for 7 days. Besides the one-pot synthesis, the macrocycles could also be afforded by a two-step fragment-coupling method in total higher yields (Scheme 2). When 2,7-diaminotriptycene **7a** was reacted with 3 equiv of cyanuric chloride, the linear trimer products **5a** was obtained in high yield. Then the macrocyclization from reaction between **5a** and **7a** afforded the target molecules **1a** and **1b** in 45% and 34% yield, respectively. Accordingly, compounds **2**−**4** were produced respectively in moderate total yields. It was found that owing to the 3D rigid structure of triptycene, each cyclization reaction formed two different macrocyclic products **a** and **b** as a pair of diastereomers, which have been confirmed by the NMR, MALDI-TOF mass spectra, and elemental analysis.

Scheme 1. Synthesis of the Triptycene-Derived N(H)-Bridged Azacalixarenes by a One-Pot Approach



Scheme 2. Synthesis of the Triptycene-Derived N(H)-Bridged Azacalixarenes by a Two-Step Fragment-Coupling Approach



The structural characterization of the macrocycles was first studied by the NMR experiments. The ^{1}H NMR spectrum of **1a** in DMSO-d_6 exhibited two singlets (5.44, 5.50 ppm) for the bridgehead (or benzylic) protons in triptycenes and

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one singlet (9.78 ppm) for the protons of N−H bridged groups (Figure 1a), which indicated that isomer **1a** has a high symmetry. Close chemical shifts of the aromatic protons and small different shifts for the benzylic protons with $\Delta\delta$ of 0.06 ppm are highly characteristic of a *cis* isomer with boat conformation in solution.[11] Compared with **1a**, the bridgehead protons in triptycenes of **1b** showed four singlets (4.08, 5.45, 5.85, 6.10 ppm) with significant different chemical shifts ($\Delta\delta = 2.02$ ppm) and the protons of N−H bridged groups showed two singlets (10.12, 10.16 ppm) in its ^{1}H NMR spectrum (Figure 1b). These observations suggested that **1b** does not have a high symmetry structure and does not adopt the chair conformation but fixed curved-boat conformation at room temperature, which is different from the *trans* isomer of the relative triptycene-based oxacalixarenes.[11] Moreover, the ^{13}C NMR experiments provided more evidence for the different conformations of the two diastereomers.[12] For example, compound **1b** displayed more complicated signals than **1a** in the ^{13}C NMR spectra in DMSO-d_6. Similar results were also found for other pairs of macrocycles **2** and **3** by using NMR spectra. However, under the same tested conditions, it was found that the ^{1}H NMR and ^{13}C NMR spectra of isomers **4a** and **4b** are all consistent with their high symmetrical structures, which suggested that the *cis* isomer **4a** adopts a boat conformation and the *trans* isomer **4b** adopts a normal chair conformation in solution. The different conformations between **4b** and **1b**−**3b** may possibly result from their different properties of dynamic conformational interconversion.[11]

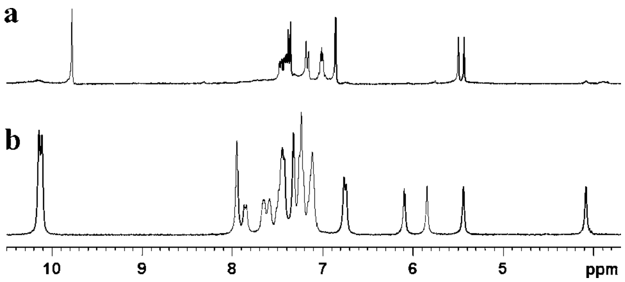

Figure 1. ^{1}H NMR spectra (300 MHz, DMSO-d_6) of (a) **1a** and (b) **1b**.

Fortunately, we obtained single crystals of **1a** and **1b** for X-ray analysis.[13] The crystal structures showed that compounds **1a** and **1b** are a pair of diastereomers, in which **1a** is a *cis* isomer with a C_2 axis and **1b** is a *trans* isomer without a high symmetrical structure (Figure 2). These results are consistent with those of NMR experiments. For compound **1a**, a cavity with dimensions of 9.113 × 12.527 Å^2 (wider rim[14]) and 6.369 × 8.227 Å^2 (narrower rim) was surrounded by two triptycene subunits and two triazine ring subunits. The dihedral angle between the two triazine rings was 109.10°, and the dihedral angles of 49.55° and 51.24° between two face-to-face benzene rings in triptycene existed, respectively, while for compound **1b** it adopted a curved-boat conformation. Compared with the normal chairlike conformation of the previously *trans* isomer of triptycene-based oxacalixarene,[11] one of the triptycene subunits on **1b** changed its position, which provided a strong shielding effect for one of the bridging benzylic proton on the other triptycene. That is the reason for its dramatical upfield chemical shift ($\delta = 4.08$ ppm) in ^{1}H NMR spectrum in DMSO-d_6. Furthermore, the N−H sites of both **1a** and **1b** which linked the four building blocks pointed out of the cavity and the bridging nitrogen atoms adopted a sp^2 configuration and conjugated with the triazine rings rather than triptycene subunits, which was confirmed by C−N bond lengths and bond angles.[14]

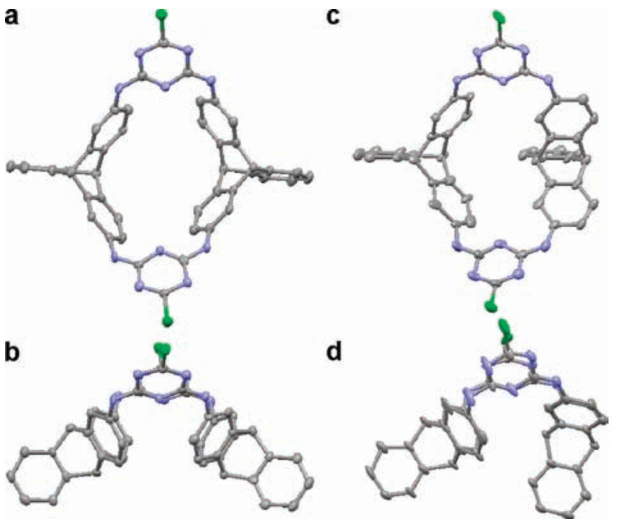

Figure 2. Crystal structures. (a) Top view and (b) side view of **1a**; (c) top view and (d) side view of **1b**. Solvent molecules and hydrogen atoms are omitted for clarity.

We also obtained single crystals of **2a** and **3a** for X-ray analyses.[12] As we can see from Table 1, compared with **1a**, although there exists a little difference for the cavities of **2a** and **3a**, these *cis* isomers all have the similar boat conformations. It is indicated that either alternating another aromatic subunits or derivatization on the triptycene moiety, as long as the triptycene subunits exist, cannot change the boat conformations of these macrocycles. The crucial effect of this fixed conformation comes from the rigid triptycene moieties. In the unique structure, the wider rim of triptycenes and the wider rim of the heteroaromatics point to the same direction, which is striking different from that of reported azacalixarenes.[1c] Similar to the macrocycles with cone conformation, it is easy for these *cis* isomers to encapsulate guest molecules inside the cavity.

As expected, macrocycle **1a** could encapsulate one methanol molecule through the O−H···N hydrogen-bonding interaction ($d_{\mathrm{N}\cdots\mathrm{H}} = 2.18$ Å, $\theta_{\mathrm{O-H}\cdots\mathrm{N}} = 155.21°$) between the hydroxyl of methanol and N atom in the triazine ring and the O−H···π hydrogen bond ($d_{\mathrm{H}\cdots\pi} = 2.88$ Å, $\theta_{\mathrm{O-H}\cdots\pi} =$

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[11] Zhang, C.; Chen, C.-F. *J. Org. Chem.* **2007**, *72*, 3880.

[12] See the Supporting Information for details.

[13] Although the quality and resolution of the diffraction data of **1b** are limited, they allow for unambiguous assignment of the macrocyclic conformation.

[14] See Figure S37 in Supporting Information for the definition of the wider rim and the narrower rim and also the C−N bond lengths.

Table 1. Cavity of the *cis* Isomeric Macrocycles

compd	$d_{\mathrm{widertriptycene}}$ (Å)	$d_{\mathrm{narrowertriptycene}}$ (Å)	$d_{\mathrm{wideraromatics}}$ (Å)	$d_{\mathrm{narroweraromatics}}$ (Å)
1a	9.113	6.369	12.527	8.227
2a	9.040	6.401	13.283	8.667
3a	8.760	6.581	12.666	8.742

135.77°) between the hydroxyl of methanol and a phenyl ring in triptycene motif (Figures 3a and 3b). Similarly, one acetone molecule was also found to be encapsulated inside the cavity of macrocycle **2a** (Figure 3c). The interactions between this host and guest include the C−H···O hydrogen bond ($d_{\mathrm{H \cdots O}} = 2.66$ Å, $\theta_{\mathrm{C-H \cdots O}} = 116.61°$) between the acetone and the dinitrobenzene subunit and two pairs of C−H···π interactions ($d_{\mathrm{H \cdots \pi}} = 2.59$ and 2.61 Å, respectively) between the methyl protons of the acetone and benzene rings of the triptycene subunit. In the process of recognition, the aromatic subunits provide the binding sites, while the unique structures provide the large cavities and the fixed boat conformations, which totally result in the whole guest molecules inside. A similar case has never been shown in the reported N(H)-bridged azacalixarenes. Moreover, it was also interestingly found that two molecules of **2a** can form a dimer through the O$^{\delta-}$···N$^{\delta+}$ and O$^{\delta-}$···C$^{\delta+}$ interactions,[15] and two acetone molecules and two dichloromethane molecules were situated in its cavity (Figure 3d). The aggregates of nitro groups have been ascribed to the electrostatic stabilization of multiple O···N/C interactions between the oxygen atom of one nitro group and the C−NO$_2$ fragment of another one.

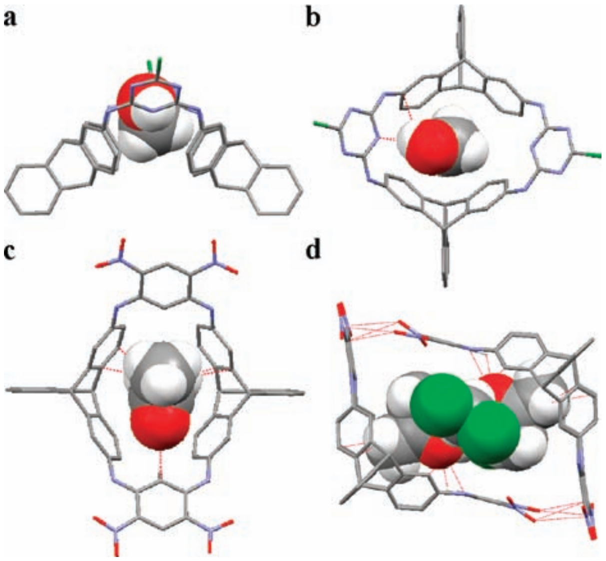

Figure 3. Molecular structure of **1a**·CH$_3$OH complex: (a) side view, (b) top view. Molecular structure of **2a**·acetone complex: (c) top view of the monomer, (d) side view of the dimer also with CH$_2$Cl$_2$ inside. The guest molecules are shown by a space-filling model. Hydrogen atoms not involved in the interactions are omitted for clarity. Red dashed line means the intermolecular interactions.

In summary, we have synthesized four pairs of novel triptycene-derived N(H)-bridged azacalixarenes by both one-pot and two-step fragment-coupling approaches and also demonstrated that owing to the 3D rigid structure of triptycene, the macrocyclic compounds all adopted fixed conformations in both solution and solid state. Moreover, the X-ray crystallographic analyses further revealed that the *cis* isomers with boat conformations and large enough cavities showed the capability of encapsulating methanol and acetone molecules inside their cavities. These new types of N(H)-bridged azacalixarenes we presented here promise well as host molecules. Further work will focus on preparation of their analogues with different functional groups to allow for recognition of larger guests and exploring their potential applications in supramolecular assemblies via the intrinsic hydrogen bonding interactions, which are now underway in our laboratory.

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Supporting Information Available: Experimental procedures and characterization data for new compounds. Comparison of NMR spectra. Crystal structures and the X-ray crystallographic files (CIF) for compounds **1a**, **1b**, **2a**, and **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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