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One-Pot Synthesis of Cyclic Triamides with a Triangular Cavity from *trans*-Stilbene and Diphenylacetylene Monomers

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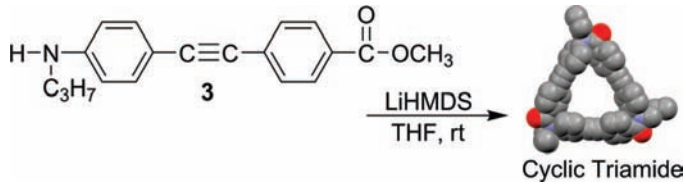
ABSTRACT



Base-promoted self-condensation reactions of *trans*-stilbene and diphenylacetylene monomers bearing 4-alkylamino and 4′-methoxycarbonyl groups were investigated. Reactions of *N*-propyl monomers under pseudohigh-dilution conditions (a THF solution of monomer was added dropwise to a THF solution of LiHMDS) afforded the corresponding cyclic triamides in good yields. X-ray crystallographic analysis showed that these cyclic triamides possessed an almost equilateral triangle structure with a cavity surrounded by tilted benzene rings.

Cyclic molecules composed of a rigid backbone and a noncollapsible nanometer lumen are classified as shape-persistent macrocycles[1] and have attracted increasing attention due to their potential use as scaffolds and building blocks of supramolecules. These compounds are frequently constructed of arylene units connected by unsaturated linkages, such as ethynylene. When the arylene units are directed vertical to the macrocycle plane, the molecule possesses a belt-shaped structure, with an intriguing cavity surrounded by the arylene wall.[2] Herges and co-workers synthesized such belt-shaped molecules via metathesis reaction with tetradehydrodianthracene,[3] and Kawase, Oda, and co-workers reported the synthesis and complex formation of [6]- and [8]paraphenylacetylenes with fullerenes.[4]

The amide linkage has been often used as a building block of macrocycles, and its hydrogen-bonding ability

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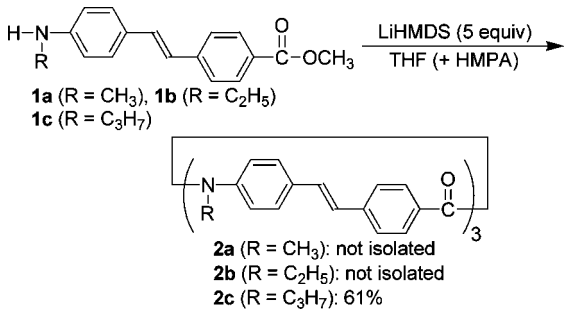
plays a crucial role in the function and structure of the macrocycles. For instance, organic nanotubes were constructed by taking advantage of intermolecular hydrogen bonding of cyclic oligopeptides,[5] and folded conformation assisted by intramolecular hydrogen bonding led to easy formation of aromatic oligoamide macrocycles.[6,7] On the other hand, the *N*-alkylated aromatic amide linkage preferentially takes a cis conformation,[8] and its intrinsic curved structure has been utilized to achieve one-pot synthesis of aromatic oligoamide macrocycles.[9,10] Furthermore, the *N*-alkylated cyclic triamides of 4-(alkylamino)benzoic acids adopt a beltlike triangle structure, because steric repulsions between the aromatic rings connected with *N*-alkylated *cis*-amide linkages cause the aromatic rings to take conformations almost vertical to the amide plane.[11,12] However, the cyclic triamides do not have a cavity large enough to incorporate another molecule. In the course of our study of controlled synthesis of *N*-alkylated aromatic polyamides,[13] we found that polycondensation of *trans*-stilbene and diphenylacetylene monomers bearing both 4-alkylamino and 4′-alkoxycarbonyl groups afforded the corresponding polyamides, accompanied with cyclic oligoamides.[14] These cyclic oligoamides are expected to have larger cavities, although they were byproducts in the polycondensation. Here, we report a selective and convenient synthesis of cyclic triamides containing *trans*-stilbene or diphenylacetylene units by base-promoted condensation reaction of the corresponding aminoester monomers. X-ray analysis of the crystal structures of the obtained macrocycles revealed that the macrocycles possess a beltlike triangular structure with a larger cavity than that of the cyclic trimer of 4-(alkylamino)benzoic acid.

We first examined the oligomerization of the *N*-methyl *trans*-stilbene monomer **1a** (Scheme 1), expecting that the

Scheme 1. Condensation of *trans*-Stilbene Monomer **1**



cyclic triamide **2a** would show high crystallinity to afford a single crystal suitable for X-ray analysis. Following the reaction conditions for the polymerization of a *trans*-stilbene monomer with other *N*-alkyl groups,[14] lithium 1,1,1,3,3,3-hexamethyldisilazide (LiHMDS) was used as a base to deprotonate the monomer amino group. As in the case of cyclic trimerization of 4-(alkylamino)benzoic acid dimer esters,[10] the reaction was carried out under pseudohigh-dilution conditions; i.e., a solution of the monomer **1a** was added dropwise to a THF solution of LiHMDS (5 equiv to the monomer) over 4 h. Because of the low solubility of **1a**, we used a mixture of THF and HMPA as a solvent for the monomer. When the oligomerization was carried out at −30 °C, the monomer **1a** was not fully consumed even after 65 h. On the other hand, dropwise addition of the monomer at −30 °C, followed by stirring at −10 °C for 60 h, resulted in higher conversion of **1a**. The elution curve obtained by size exclusion chromatography (SEC) analysis of the crude product showed a sharp peak in the oligomeric-molecular-weight region and a broad peak in the higher-molecular-weight region (Figure 1a). MALDI-TOF mass spectra of

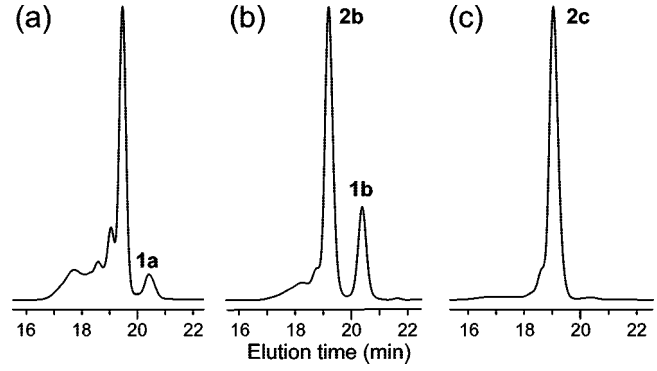


Figure 1. SEC profiles of the crude product obtained by the oligomerization of (a) **1a** at −10 °C for 60 h, (b) **1b** at rt for 1 h, and (c) **1c** at rt for 45 min.

the product obtained after precipitation in diethyl ether showed the formation of **2a** accompanied by the cyclic tetramer and hexamer.[15] However, the products showed poor solubility, and it was difficult to separate them.

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(15) See Supporting Information for details.

To increase the solubility of the reaction product, the *N*-alkyl group of the monomer was replaced with an ethyl group. Oligomerization of the *N*-ethyl monomer **1b** was carried out at −30 °C under the same conditions, and the SEC profile suggested that the conversion of **1b** was lower than that of **1a**. We thought that the nucleophilicity of the deprotonated **1b** might have been lowered due to the introduction of the bulkier *N*-ethyl group, and therefore the oligomerization of **1b** was examined at higher temperature than that of **1a**. Reaction of **1b** at room temperature proceeded smoothly, and the SEC profile of the product obtained after 1 h showed a sharp peak, like that in the case of the reaction of **1a** at −10 °C (Figure 1b). The crude product exhibited good solubility in common organic solvent, and the product corresponding to the sharp peak in the SEC elution curve was isolated by silica gel column chromatography. The ^{1}H NMR spectrum showed only one series of signals assignable to a repeating unit, without any signals assignable to the terminal units of linear oligomers, and the lower field shift of the N-C$\underline{H}_2$ signal to 3.99 ppm suggested amide bond formation. These results indicated that the isolated product was the cyclic amide (41% yield). However, MALDI-TOF MS analysis of the product showed a signal corresponding to the cyclic triamide **2b** as a major peak, accompanied by signals of the cyclic tetramer and hexamer as minor peaks.[15]

When oligomerization of the *N*-propyl monomer **1c** at room temperature was conducted using a mixture of THF and HMPA, the SEC analysis of the crude product showed an elution profile similar to that of the *N*-ethyl monomer **1b**, and separation with silica gel column chromatography gave a mixture of cyclic tri- and tetraamides. In contrast to the *N*-methyl and *N*-ethyl monomers, the *N*-propyl monomer **1c** showed higher solubility in THF, and homogeneous reaction could be carried out in the absence of HMPA. Oligomerization of **1c** in THF at room temperature resulted in complete consumption of the monomer, and the SEC elution curve showed only a sharp signal in the oligomer-molecular-weight region, indicating selective cyclic oligoamide formation (Figure 1c). The crude product was separated by means of preparative HPLC, and MALDI-TOF MS analysis revealed the product to be the pure cyclic triamide **2c** (61% yield).

A single crystal of **2c** was obtained by recrystallization from $CH_3CN-CH_2Cl_2$ and analyzed by X-ray crystallography (Figure 2). The asymmetric unit contained two independent molecules, both of which showed an almost equilateral triangle structure with a cavity. The aromatic rings were inclined from the perpendicular plane to the triangle but acted as walls of the cavity, as expected. The side length of the triangles is approximately 13 Å, indicating that the cavity would be able to accommodate a sphere with a diameter of 7.5 Å. This estimation is consistent with the fact that the distances between the carbon atoms of the neighboring vinylene units are 7−8 Å. In the crystal, *N*-alkyl amide moieties of one independent molecule, whose carbon atoms are dark gray in Figure 2, are directed toward the cavity of neighboring molecules. The *N*-propyl groups of the other independent macrocycle shown in light gray in Figure 2 fill the space between the molecules.

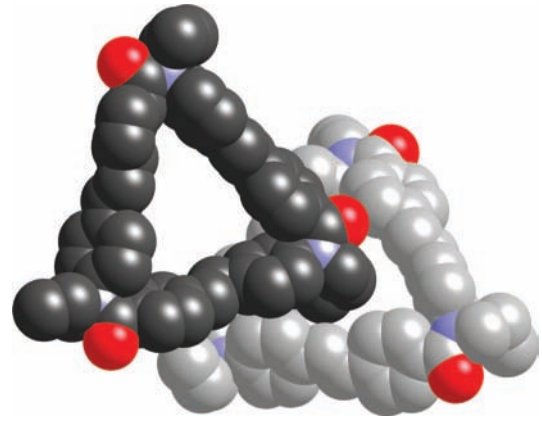
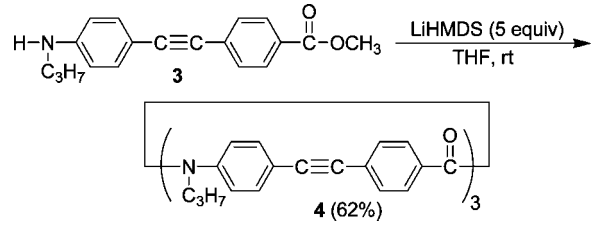


Figure 2. Two independent molecules in an asymmetric unit of the crystal structure of **2c** shown in a space-filling representation. Hydrogen atoms are omitted for clarity, and the carbon atoms of each molecule are represented in different colors so that the molecules can be easily distinguished.

Scheme 2. Condensation of Diphenylacetylene Monomer **3**



We next carried out the oligomerization of *N*-propyl diphenylacetylene monomer **3** (Scheme 2). On the basis

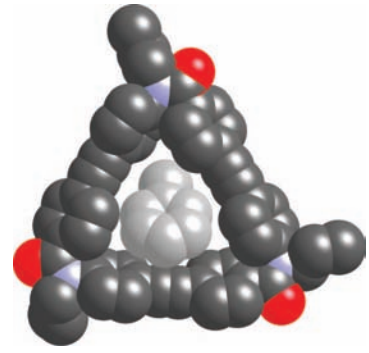


Figure 3. Space-filling representation of **4** with the solvent molecule (toluene). Hydrogen atoms are omitted for clarity.

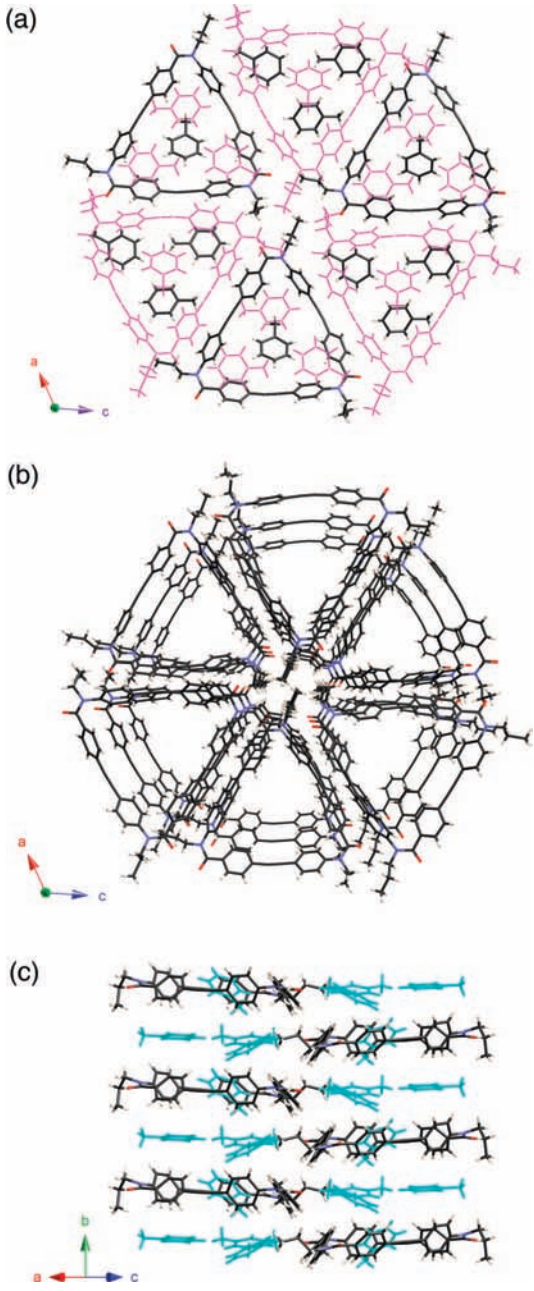


Figure 4. Packing structure of **4**. (a) Layer form of **4** and toluene molecules. The magenta-colored line is the layer above. (b) Channel structure of **4**. Toluene molecules are omitted for clarity. (c) Side view of the channel structure. Toluene molecules are cyan-colored.

of the optimized conditions for the oligomerization of **1c**, a THF solution of **3** was added dropwise over 4 h to a THF solution of 5 equiv of LiHMDS at room temperature, and the mixture was stirred at that temperature. The monomer was consumed completely 0.5 h after the addition, and separation with silica gel column chromatography afforded the cyclic triamide **4** in 62% yield. Reaction at 0 °C also proceeded smoothly, but the yield of **4** was reduced to 32% due to increased formation of higher-molecular-weight products, as judged from the SEC profile of the crude product.

Recrystallization of **4** from toluene gave a single crystal, which was analyzed by X-ray crystallography (Figure 3). The crystal structure of **4** was similar to that of **2c**: the shape was an equilateral triangle whose side length was approximately 13 Å, and the benzene rings were tilted. However, unlike **2c**, the crystal contained four molecules of the recrystallization solvent, toluene, in an asymmetric unit, and the cavity of **4** was filled with a toluene molecule (Figure 3). Furthermore, the packing of **4** occurred in layers along the *a* and *c* axes of the unit cell (Figure 4a). The toluene molecules filled the space between the molecules of **4**. The layers stacked along the *b* axis and formed channels filled with solvent molecules (Figure 4b and 4c).

In conclusion, we have demonstrated that cyclic triamides can be obtained from the *N*-propyl *trans*-stilbene and diphenylacetylene monomers **1c** and **3**, respectively, in good yield by one-pot condensation reaction. X-ray crystallographic analysis revealed that the cycles **2c** and **4** possess triangular cavities surrounded by tilted benzene rings. This one-pot trimeric cyclization approach has potential for the synthesis of macrocycles possessing larger cavities and functional units in the backbone and side chain. Studies along this line are in progress.

Supporting Information Available: Synthesis and condensation reaction of the monomers **1a**−**c** and **3**, MALDI-TOF mass spectra of the products obtained by the reaction of **1a** and **1b**, NMR spectra and X-ray crystallographic data for **2c** and **4**, and CIFs. This material is available free of charge via the Internet at http://pubs.acs.org.

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