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Triple Helicate Constructed by Covalent Bondings: Crystal Structure and Effective Synthesis Based on Propeller-like Substructures

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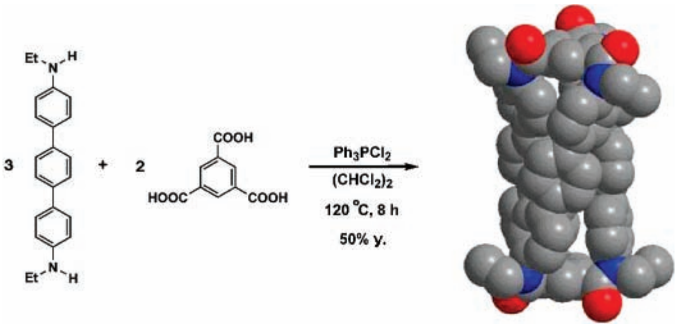
ABSTRACT



A triple helicate, having a macrocyclic aromatic amide structure, was synthesized in high yield because of a preorganized component of the tertiary benzenetrianilide moieties in a propeller-like syn conformation at both ends. The helicity was derived from tilted T-shaped aromatic–aromatic (CH–π) interactions between each of the *N*-phenyl rings.

The helical structure is a common, attractive topological feature that is widely observed in synthetic or biological molecules.[1] Helical structures have been constructed by various methodologies; for example, metal coordination in self-assembled nanomolecules,[2] hydrogen bonding in helices of β-peptides,[3] hydrogen bonding associated with parallel aromatic−aromatic interaction in some discoidal compounds[4] or in DNA, solvent effect or guest inclusion in phenylene ethynylene foldamers,[5] or weak internal CH−π interactions in tertiary aromatic polyamides.[6] In this context, there are

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[4] (a) Lightfoot, M. P.; Mair, F. S.; Pritchard, R. G.; Warren, J. E. *Chem. Commun.* **1999**, 1945−1946. (b) Azumaya, I.; Uchida, D.; Kato, T.; Yokoyama, A.; Tanatani, A.; Takayanagi, H.; Yokozawa, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 1360−1363.

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few examples in which a *pre-organized helical moiety* is utilized to construct the entire helical structure in covalently bonded macrocycles. In the course of our investigation of the stereochemistry of an aromatic tertiary amide,[7] we found that *N*,*N*′,*N*″-trimethyl-*N*,*N*′,*N*″-triphenyl-1,3,5- benzenetricarboxyamide (**1**) exists in a propeller-like chiral conformation due to intramolecular tilted T-shaped aromatic−aromatic (CH−π) interactions (Figure 1).[8] We have applied this moiety as a helically preorganized structural fragment to construct helicate **2**. In this paper, we report the crystal structure of this helicate and its synthesis.

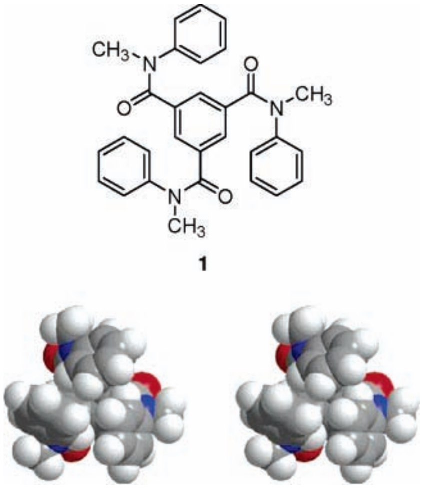

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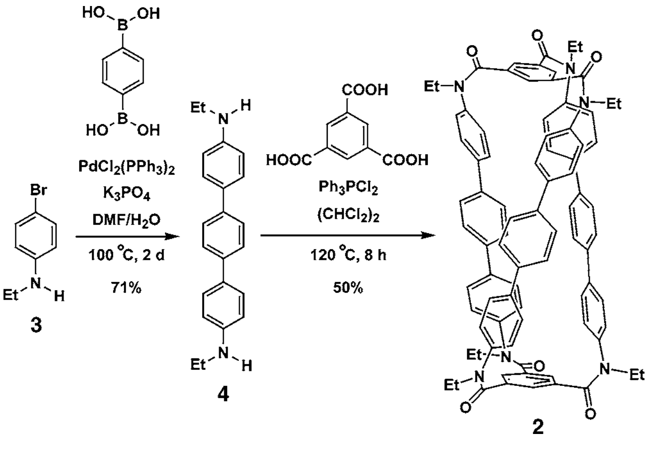
Figure 1. Structural formula and stereoview of the crystal structure[8] in a space-filling model of **1**.

Helicate **2** is synthesized by a direct condensation reaction of aromatic diamine **4** with 1,3,5-benzenetricarboxylic acid using dichlorotriphenylphosphorane as a condensation reagent (Scheme 1), a very effective method for macrocyclic aromatic amide construction.[9] The synthesis of diamine **4** was based on the Miyaura−Suzuki coupling to extend the phenylene chain. First, 4-bromoaniline was acetylated and *N*-ethylated by a usual method, followed by deacetylation by 4 M HCl at reflux to give 4-bromo-*N*-ethylaniline (**3**). The coupling reaction of **3** and 1,4-benzenediboronic acid using $PdCl_2(PPh_3)_2$ with K_3PO_4 in DMF−H_2O at 100 °C for 2 days gave **4** in 71% yield. The mixture of **4** and 1,3,5-benzenetricarboxylic acid (3:2 in molar ratio) was treated with 2.4 equiv of Ph_3PCl_2 in 1,1,2,2-tetracholoroethane (50 mM for **4**) at 120 °C for 8 h. The crude product was purified by gel permeation chromatography (GPC) to give the macrocyclic aromatic amide **2** in 50% yield.

Scheme 1



3

4

2

The yield in the macrocyclic reaction was much higher than that of the other multicomponent amide condensation reaction from acid chlorides and amines.[10] This is because the trianilide moieties at both ends of the macromolecule tend to exist in a syn conformation as shown in trianilide **1**; that is, the fragments would work as a preorganized structure during the macrocylic amide formation.

Prismatic single crystals of compound **2** were obtained from a chloroform solution by slow evaporation of the solvent. X-ray crystallographic analysis showed that the crystal belonged to the space group $Pca2_1$, which contains two sets of enantiomeric helical conformers per unit cell (Figure 2).[11] Both enantiomers of helicate **2** alternate along the *c*-axis, and the racemic row of the helicates piles up with chloroform molecules along the *b*-axis. Therefore, the crystal is achiral, as opposed to the other 1,3,5-benzenetricarboxylic acid derivatives with no fixed chiral element that frequently show spontaneous resolution.[4,12] The unit cell contains 16 molecules of chloroform to fill the space among the macrocyclic amide molecules.

Figure 3a shows a stereoview of the sole molecule in the unit cell. The molecule is 18 Å in length and ca. 10 Å in diameter. The tricarbonyl trianilide moieties exist in similar conformations as observed in the triamide **1** reported previously,[8] except that each has slightly larger torsion angles where the torsion angle of the six amide bonds (C_{Ph}−C−N−C_{Ph}) are 18.3°, 15.6°, 27.4°, 23.5°, 21.1°, and 20.0°, those

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(11) X-ray data were collected on a Bruker Smart1000 CCD detector. The crystal structure was solved by direct methods SHELXS-97 (Sheldrick, 1997) and refined by full-matrix least-squares SHELXL-97 (Sheldrick, 1997). All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included as their calculated positions. Crystal data for **2**: $C_{84}H_{72}N_6O_6{\cdot}4CHCl_3$; $M = 1738.95$ g mol^{-1}, orthorhombic, $Pca2_1$, colorless prism measuring 0.30 × 0.25 × 0.25 mm, $T = 150$ K, $a = 33.749(12)$ Å, $b = 12.982(5)$ Å, $c = 19.167(7)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 8398(5)$ Å^3, $Z = 4$, $D_{calcd} = 1.375$ Mg m^{-3}, $\mu = 0.453$ mm^{-1}, $T_{max} = 0.8952$, $T_{min} = 0.8761$, GOF on $F^2 = 0.950$, R1 = 0.0892, wR2 = 0.2229 ([$I > 2\sigma(I)$], R1 = 0.1618, and wR2 = 0.2679 (all data). CCDC-275835.

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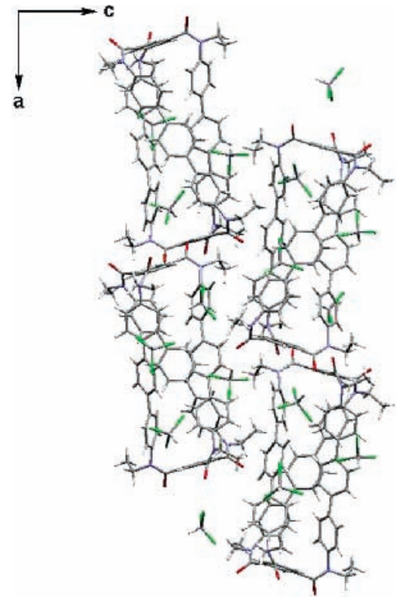

Figure 2. Projection on the *ac* plane of the unit cell of **2**.

of Ar−CO are 58.1°, 57.9°, 50.9°, 52.5°, 51.0°, and 54.0°, and those of Ar−NC_{Et} are 72.6°, 68.5°, 85.4°, 81.1°, 77.3°, and 61.2° (averaged torsion angles in **1** are 3°, 52°, and 63°, respectively). These means that two sets of tricarbonyl trianilide, with the same chirality in the propeller-like conformation in one macromolecule, were joined through three phenylene groups at their para positions without any large conformational change, which holds the macrocyclic amide in a helicate. The angle of the twist between two benzenetricarbonyl moieties at both ends of the molecule is 101°. The observed intermolecular tilted T-shaped aromatic−aromatic (CH−π) interaction between the two phenylene groups of both trianilide moieties is shown in Figrue 3b; this is the driving force to form the helical structure for the macrocyclic amide.

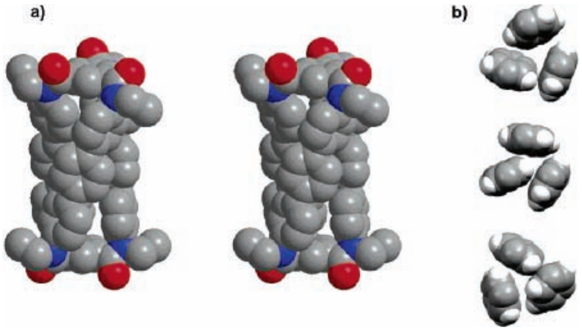

Figure 3. (a) Stereoview of molecule **2** in a space-filling model (hydrogens were omitted for simplicity). (b) Relative positions of each of the three phenylene groups in the upper, middle, and bottom part of molecule **2**. The ring center−ring center distances of each two phenylene groups from the left in a clockwise direction are 5.40, 5.14, 5.17 Å (upper), 5.31, 4.71, 4.71 Å (middle), and 5.05, 5.45, 5.08 Å (bottom).

^{1}H NMR measurements of **2** at ambient temperature showed that the equilibrium between the two enantiomeric helical conformers is fast because the two ortho protons on the N side of each phenylene ring or two prochiral methylene protons of the *N*-ethyl group are not distinguished (see the Supporting Information). Preliminary DNMR measurements in dichloromethane-d_2 revealed that an equilibrium between the two enantiomeric helical conformers was definitely slower at low temperatures because the signals became broader as the temperature was lowered, but did not split into two sets of peaks at 178 K (data not shown). Therefore, even at low temperatures, the lifetime of enantiomeric helical conformers is too short on an NMR time scale. These dynamic behaviors of helicate **2** are caused by the inherently weak nature of the aromatic−aromatic interaction, and so the structure in a helicate with one chirality is not tightly fixed.

In conclusion, we have designed and synthesized a triple helicate, a macrocyclic aromatic amide with a helical structure. The yield in the macrocyclization reaction is very high due to the preorganized propeller-like structure of tertiary trianilide moieties. It is notable that the helicity of the helicate was induced by intramolecular tilted T-shaped aromatic−aromatic (CH−π) interactions, which were observed in the crystal structure. Because the interaction was sufficiently weak, the helicate came to have dynamic features, such as the helical structures being able to interconvert to each other at an ambient temperature. We could create a "softly constrained" helical structure using a tilted T-shaped aromatic−aromatic (CH−π) interaction. We are now applying this concept to construct a chiral architecture with dynamic behavior.

Supporting Information Available: Synthetic procedures, NMR spectra, and mass spectrum of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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