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Triple helical structure constructed by covalent bondings: effective synthesis by a pre-organized partial structure and helicity induced by aromatic–aromatic interactions

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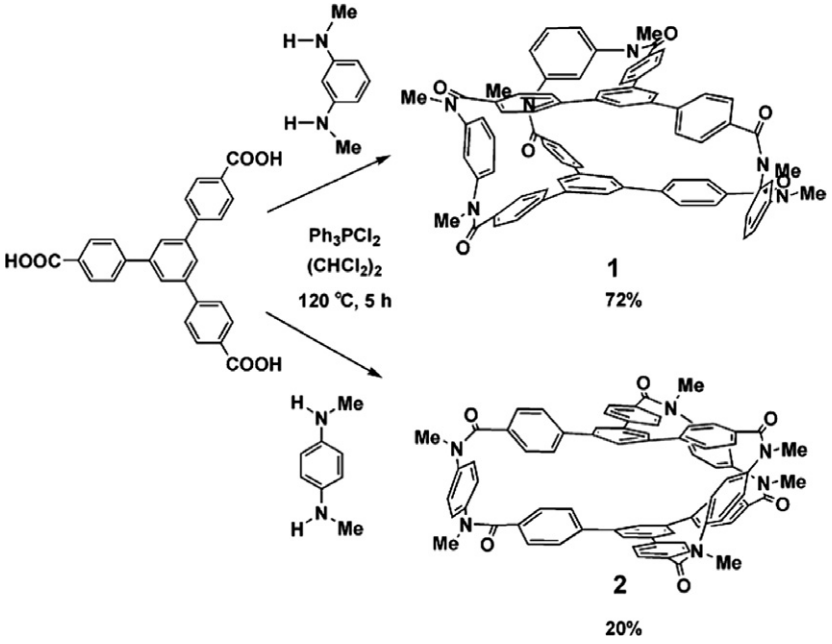
Abstract—Discotic helical macrocycle constructed by aromatic tertiary amide was effectively synthesized using dichlorotriphenylphosphorane as the condensation reagent. The yield was significantly higher when *meta*-substituted diaminobenzene was used as the linkage for a two 1,3,5-tris(4-carboxyphenyl)benzene moiety than when *para*-substituted diaminobenzene was used. The yield is thus dependent on whether the pre-organized partial diamide structure suits the construction of the macrocyclic structure.

Recently, huge three-dimensional macrocyclic compounds have received attention as skeletons for functionalized molecules such as cation receptors,[1] anion receptors,[2] and substrate-specific artificial receptors.[3] Synthetic strategies for such macrocyclic compounds have been based on, for example, template synthesis as seen in crown ether or cryptand,[4] self-assembly of small bi- or multi-dentate ligands by metal coordination,[5] and others.[6] A number of macromolecules with a repeating unit such as a helical oligomer or a large cyclic molecule



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have been synthesized via a strategy that includes pre-organization of the bonding direction of a small partial structure regulated by hydrogen bonding[7] or by metal coordination performed in advance. In this context, it is of great interest whether intramolecular interactions such as a CH–π or aromatic–aromatic interaction, which is weaker than metal coordination and hydrogen bonding, can work to correctly set several bond directions in the construction of macrocyclic compounds. In the course of our investigations into an effective synthesis of amide containing macrocycles,[8] we found that a simple partial structure pre-organized by aromatic–aromatic interaction, that is, a preferable *syn* conformation of aromatic tertiary diamides, was extremely effective for constructing huge covalently bonded macrocyclic compounds. In this Letter, we report on the synthesis and crystal structure of macrocylic compound **1** with a helical structure.

Macrocyclic compound **1** is synthesized by the direct amide coupling of 1,3,5-tris(4-carboxyphenyl)benzene with *N*,*N*′-dimethyl-1,3-phenylenediamine using dichlorotriphenylphosphorane as a very effective coupling reagent, to construct macrocyclic aromatic amide, as reported previously.[9] A mixture of 1,3,5-tris(4-carboxyphenyl)benzene and *N*,*N*′-dimethyl-1,3-phenylenediamine (2:3 in molar ratio) was treated with 2.4 equiv of Ph_3PCl_2 in 1,1,2,2-tetracholoroethane (50 mM for amine) at 120 °C for 5 h. The crude product was purified by gel permeation chromatography to give the macrocyclic aromatic amide **1** in 72% yield. The yield in the macrocyclic reaction was much higher than those of other multi-component amide coupling reactions from acid chlorides and amines. In contrast to the high yield obtained in the synthesis of **1**, 1,3,5-tris(4-carboxyphenyl)benzene was treated with *N*,*N*′-dimethyl-1,4-phenylenediamine under the same conditions to give macrocyclic compound **2** in only 20% yield.

X-ray crystallographical analysis was performed on a single crystal of compound **1** obtained from a mixture of chloroform and cyclohexane solution by slow evaporation of the solvent.[10] Figure 1a shows a stereoview of the sole molecule, 8 Å in length and ca. 19 Å in diameter, in the crystal. Four sets of aromatic–aromatic interactions are observed in the molecule; two are parallel aromatic–aromatic interactions and are observed between the central benzene rings and one of the three sets of benzene rings in the side arms of the molecule. In the other two side arms, tilted T-shaped aromatic–aromatic interactions are observed (Fig. 1b), resulting in a helical conformation for macrocycle **1**. The crystal belongs to the space group $P2_1/c$ containing two pairs of enantiomeric helical conformers per unit cell. Both enantiomers of macrocycle **1** alternate along both the *b*- and *c*-axes, and the racemic row of the macrocycle piles up along the *a*-axis (Fig. 2a and b). The unit cell contains eight

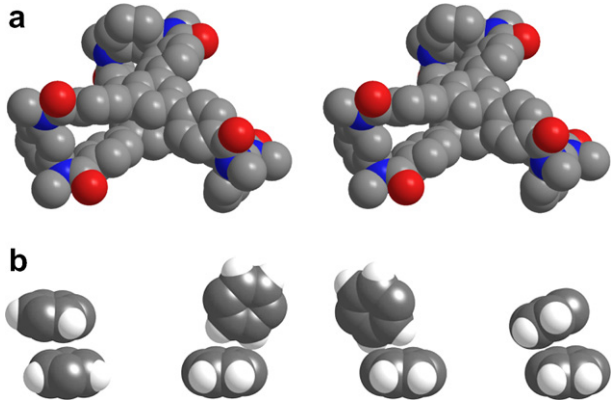

Figure 1. (a) Stereoview of the crystal structure of macrocycle **1** in a space-filling model. Hydrogen atoms are omitted. (b) Relative positions of each set of two benzene rings of **1**. The first set shows the relative position of the central benzene rings of the molecule. The other three sets show the relative positions of benzene rings in the side arms of the molecule.

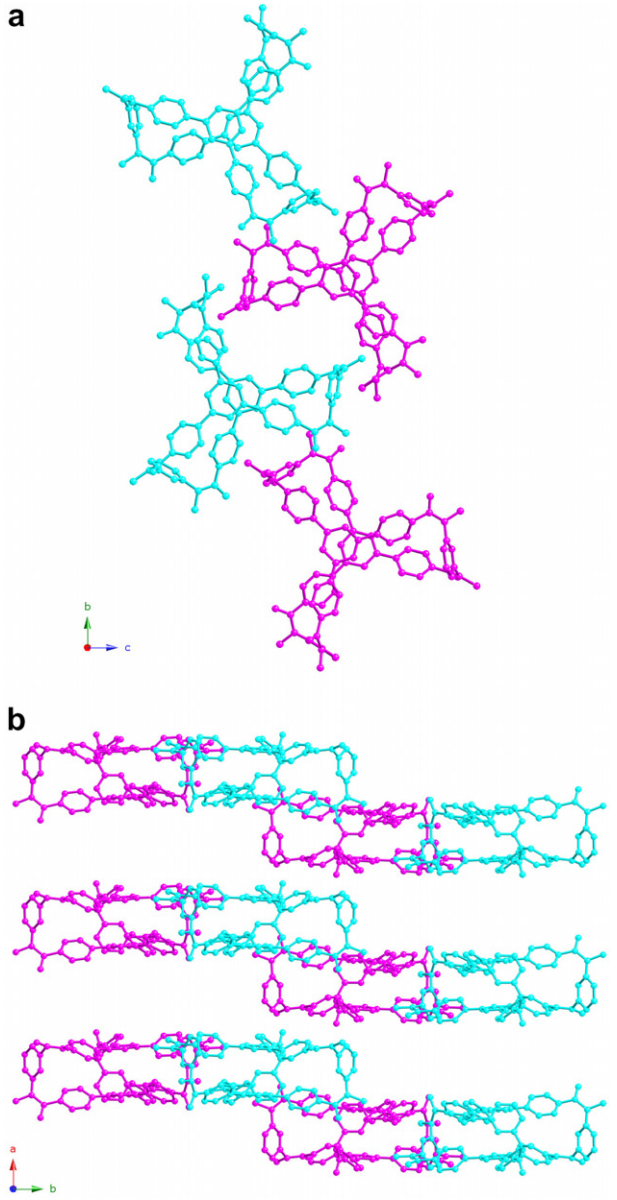

Figure 2. (a) Projection on the *bc* plane of the unit cell of **1**. (b) Projection on the *ab* plane. Magenta- and cyan- colored molecules are enantiomeric helical conformers that are mirror images of each other. The hydrogen atoms and chloroform molecules are omitted.

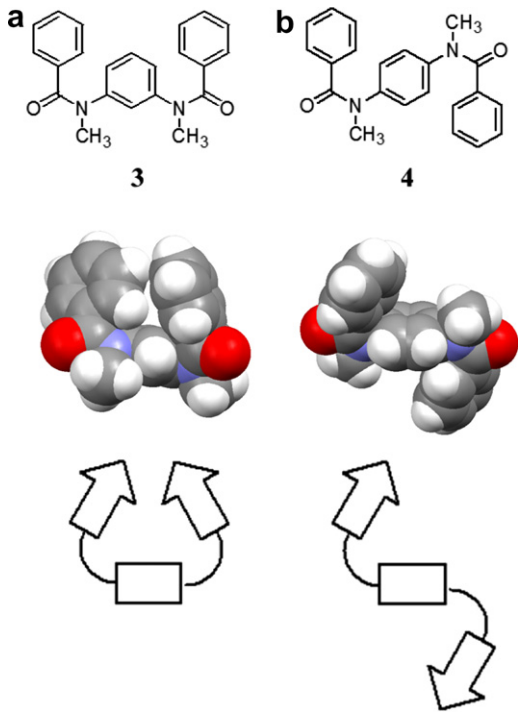

Figure 3. Crystal structures of (a) *meta*-substituted diamide **3** and (b) *para*-substituted diamide **4** in space-filling models and schematic representations of the directions of their terminal phenyl rings.[10]

molecules of chloroform to fill the spaces among the macrocycles.

The yield on the macrocyclization reaction using *meta*-diamine is much higher than that achieved using *para*-diamine because the diamide moieties at both ends of macromolecule **1** tend to exist in a *syn* conformation, as shown in diamide **3** (Fig. 3a); that is, the fragments work as a pre-organized structure in the formation of macrocylic amide. By contrast, the macrocyclization reaction using *para*-diamine resulted in a low yield because the diamide moieties at both ends of macromolecule **2** tend to exist in an anti conformational way, as shown in diamide **4** (Fig. 3b).[11]

In conclusion, we designed and synthesized a macrocyclic aromatic amide with a helical structure in high yield. The yield in the coupling reaction is dependent on the pre-organized structure of the bis-amide moieties. The helicity of macrocycle **1** was induced by the intramolecular tilted T-shaped aromatic–aromatic interactions observed in the crystal structure. We are now using this strategy of construction by covalent bondings to synthesize various huge macrocycles with interesting topological properties.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.089.

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10. X-ray data were collected on a Bruker ApexII (for **1** and **4**) or Bruker Smart1000 (for **3**) CCD detector. The crystal structure was solved by direct methods SHELXS-97 (SHELDRICK, 1997) and refined by full-matrix least-squares SHELXS-97 (SHELDRICK, 1997). All non-hydrogen atoms were refined anisotropically. Crystal data for **1**: $C_{78}H_{60}N_6O_6{\cdot}2(CHCl_3)$; $M = 1416.06$ g mol^{-1}, monoclinic, $P2_1/c$, colorless plate measuring $0.15 \times 0.10 \times 0.05$ mm, $T = 90$ K, $a = 12.758(2)$, $b = 40.960(6)$, $c = 17.349(2)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 9066(2)$ Å^3, $Z = 4$, $D_c = 1.037$ mg m^{-3}, $\mu = 0.236$ mm^{-1}, $T_{max} = 0.9883$, $T_{min} = 0.9655$, GOF on $F^2 = 1.061$, $R_1 = 0.0759$, $wR_2 = 0.1943$ ($[I > 2\sigma(I)]$),

$R_1 = 0.1159$, and $wR_2 = 0.2095$ (all data). CCDC-608988. Crystal data for **3**: $C_{22}H_{20}N_2O_2$; $M = 344.40$ g mol^{-1}, monoclinic, $P2_1/n$, colorless prism measuring $0.20 \times 0.20 \times 0.20$ mm, $T = 150$ K, $a = 9.2617(14)$, $b = 21.453(3)$, $c = 9.4451(14)$ Å, $\alpha = \gamma = 90$, $\beta = 105.337(2)°$, $V = 1809.9(5)$ Å^3, $Z = 4$, $D_c = 1.264$ mg m^{-3}, $\mu = 0.082$ mm^{-1}, $T_{max} = 0.9838$, $T_{min} = 0.9838$, GOF on $F^2 = 1.051$, $R_1 = 0.0438$, $wR_2 = 0.1106$ ($[I > 2\sigma(I)]$), $R_1 = 0.0653$, and $wR_2 = 0.1211$ (all data). CCDC-608989. Crystal data for **4**: $C_{22}H_{20}N_2O_2$; $M = 344.40$ g mol^{-1}, orthorhombic, *P*bca, colorless plate measuring $0.40 \times 0.30 \times 0.05$ mm, $T = 150$ K, $a = 13.4373(5)$, $b = 9.2656(4)$, $c = 14.8039(6)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 1843.15(13)$ Å^3, $Z = 4$, $D_c = 1.241$ mg m^{-3}, $\mu = 0.080$ mm^{-1}, $T_{max} = 0.9960$, $T_{min} = 0.9686$, GOF on $F^2 = 1.058$, $R_1 = 0.0489$, $wR_2 = 0.1061$ ($[I > 2\sigma(I)]$), $R_1 = 0.0848$, and $wR_2 = 0.1209$ (all data). CCDC-608990.

11. Dynamic ^{1}H NMR measurements of **3** (see Supplementary data) showed that the *syn* conformation of **3** is more preferable in solution than the *anti* conformation, as in the case for *N*,*N*′-dimethyl-1,3-benzenedicarboxanilide: (a) Yamaguchi, K.; Matsumura, G.; Kagechika, H.; Azumaya, I.; Ito, Y.; Itai, A.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 5474–5475; (b) Azumaya, I.; Kagechika, H.; Yamaguchi, K.; Shudo, K. *Tetrahedron* **1995**, *51*, 5277–5290.