

## COMMUNICATION

# Diastereoselective Cyclization of Aminobenzoic Acid Derivative and Chiroptical Properties of Triple-Stranded Helical Bis(phenylethynyl)benzene

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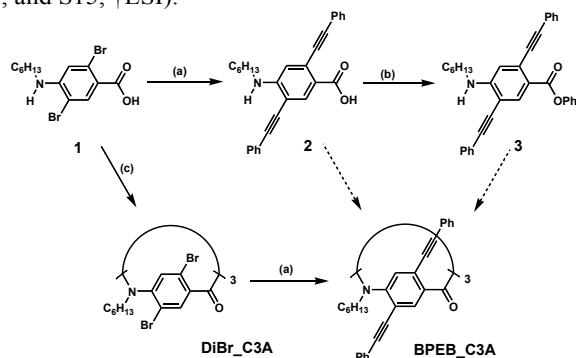
The diastereoselective cyclization of 2,5-dibromo-4-hexylaminobenzoic acid was achieved by the microwave-assisted condensation using SiCl<sub>4</sub>. Moreover, the triple-stranded helical structure of bis(phenylethynyl)benzene units embedded in the cyclic tri(benzamide) scaffold was obtained by Sonogashira-Hagihara coupling reaction. Two optically active enantiomers that do not racemize even at the elevated temperature were separated by chiral HPLC. The chiral helical topology was revealed by the spectroscopic data and theoretical calculation.

Cyclic oligomers including calixarene, pillararene, and cyclodextrin with unique cavities have been attracting much attention in the field of host-guest chemistry.<sup>1</sup> On the other hand, the definite conformation of these cyclic oligomers are useful as the template for nano architectures; for example, the scaffold for the alignment of  $\pi$ -conjugated systems<sup>2</sup> or the building block for nanotubes.<sup>3</sup> The design of an intertwining helical structure is a challenging issue for the construction of well-defined three-dimensional architectures, as exemplified by naturally-occurring DNA. One possible strategy for obtaining such helical structures relies on the non-covalent self-assembly including the hydrogen bonding<sup>4</sup> and metal coordination.<sup>5</sup> In contrast, there are not many reports to attain the helical structure using the covalent bond approach despite of the robustness over the external environmental change. In particular, the helical structure of  $\pi$ -conjugated chromophores are restricted to a few examples,<sup>6</sup> probably owing to the rigidity or reactivity of the building unit. We have recently succeeded at the triple helical alignment of bithiophene chromophores using two calix[3]amides, a cyclic oligomer consisted of meta-linked tri(benzamide).<sup>7</sup> The inherent chirality of calix[3]amide<sup>8</sup> induced a helicity in the arrangement of bithiophenes without the help of chiral sources. However, the helicity of bithiophenes was dynamic to only show the strong Cotton effect in selected

solvents or at low temperature. In this communication, we report the synthesis and chiroptical properties of a new cyclic tri(benzamide) carrying bis(phenylethynyl)benzene chromophores (**BPEB\_C3A**) arranged in a triple-stranded helical conformation.

The synthetic route to **BPEB\_C3A** is shown in Scheme 1. We initially tried the cyclization of phenyl 2,5-bis(phenylethynyl)-4-hexylaminobenzoate **3** using lithium 1,1,1,3,3,3-hexamethylidisilazide (LiHMDS) following to previous reports<sup>9</sup> (Table 1, Entry I). The reaction did not proceed to recover **3** although the solution colour changed from yellow to red indicating the generation of aminyl anion. We considered that the nucleophilicity of aminyl anion was decreased because of the steric hindrance and/or the charge delocalization by the phenylethynyl group. We subsequently examined the cyclization of 2,5-bis(phenylethynyl)-4-hexylaminobenzoic acid **2** using dichlorotriphenylphosphorane (Entry II) or tetrachlorosilane (Entry III) as condensation reagents,<sup>10</sup> but the monomer was not consumed at all. The cyclization of 2,5-dibromo-4-hexylaminobenzoic acid **1** was finally performed using tetrachlorosilane for 1 day (Entry V). The cyclic tri(benzamide) **DiBr\_C3A** was detected by the matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) of the crude reaction mixture. In the <sup>13</sup>C nuclear magnetic resonance (NMR) spectra, the chemical shift of the carbonyl carbon of **1** (168.5 ppm) appeared in the lower magnetic field region compared with that of **2** (166.5 ppm), indicating the electron-positive character of the carbonyl carbon in **1**. This might be plausible reason for the increased reactivity of **1**. The cyclization under the same condition for 3 days gave **DiBr\_C3A** in 45% yield after purifying by the preparative gel permeation chromatography (GPC) (Entry VI). On the other hand, when the cyclization was carried out under the single-mode microwave irradiation, the monomer was almost consumed after 1 day to obtain **DiBr\_C3A** in 40% yield. The

identity of **DiBr\_C3A** was confirmed by the MALDI-TOF MS (Figure S2, †ESI) and NMR spectrometry (Figures S10, S11, and S12, †ESI). Thus the microwave irradiation facilitated the cyclic trimerization with minimum side reactions. Then, Sonogashira-Hagihara coupling reaction of **DiBr\_C3A** with phenylacetylene in the presence of  $\text{Cu}_2(\text{OAc})_4$  and  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$  was performed to obtain **BPEB\_C3A** having six phenylethynyl groups as a pale yellow solid in 28% yield. Because of the large steric hindrance, a compound with five phenylethynyl groups, lacking one phenylethynyl group, was also detected as the side product. The identity of **BPEB\_C3A** was also confirmed by the spectroscopic data and MALDI-TOF MS (Figure S3, †ESI) and NMR spectrometry (Figures S13, S14, and S15, †ESI).



**Scheme 1** Preparation of cyclic tri(benzamide) **BPEB\_C3A**. (a) Phenylacetylene,  $\text{Cu}_2(\text{OAc})_4$ ,  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ , TEA, (b)  $\text{SOCl}_2$ , Phenol, (c)  $\text{SiCl}_4$ , Pyridine.

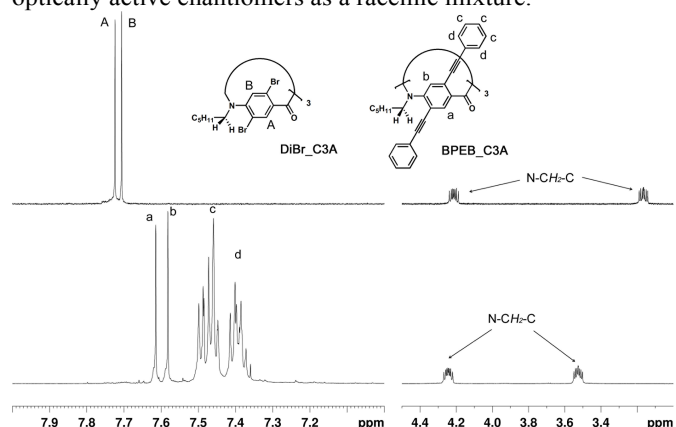
**Table 1** Conditions and results of the cyclization.

Entry	Monomer	Reagents <sup>a</sup>	Time	Yield <sup>c</sup>
I	3	A	1 day	-
II	2	B	↓	-
III	2	C	↓	-
IV	1	B	↓	-
V	1	C	↓	<5%
VI	1	C	3 day	45%
VII	1	C <sup>b</sup>	1 day	40%

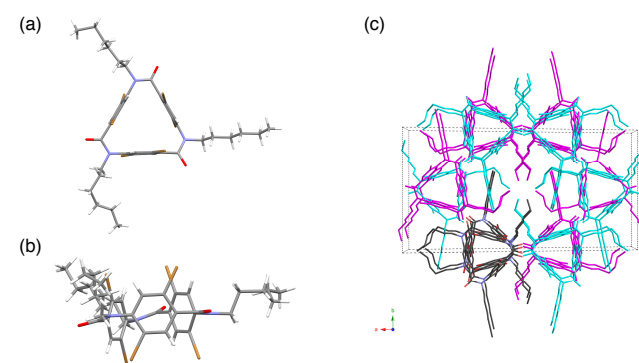
*a* (A) LiHMDS (1 M in THF), THF, 50 °C, (B)  $\text{Ph}_3\text{PCl}_2$ ,  $(\text{CHCl}_2)_2$ , 150 °C, (C)  $\text{SiCl}_4$ , Pyridine, 115 °C, *b* Microwave heating, *c* Isolated yield.

The  $^1\text{H}$  NMR spectra of **DiBr\_C3A** are shown in Figure 1a. In the higher magnetic field region, the methylene proton signals on the amide nitrogen were clearly split in two positions. This signal separation would be ascribed to the diastereotopic environment of the methylene proton due to the axial chirality of **DiBr\_C3A**. If benzene rings rotate around the amide bond, **DiBr\_C3A** would exist in the equilibrium between four diastereomers; (*S,S,S*), (*R,R,R*), (*R,S,S*), and (*R,R,S*). In the lower magnetic field region, however, only two sharp aromatic proton signals assignable to A and B were observed implying the highly symmetrical structure of **DiBr\_C3A**, namely (*S,S,S*) and (*R,R,R*) isomers. These proton signals showed ignorable shifts at 50 °C to suggest that the aforementioned benzene

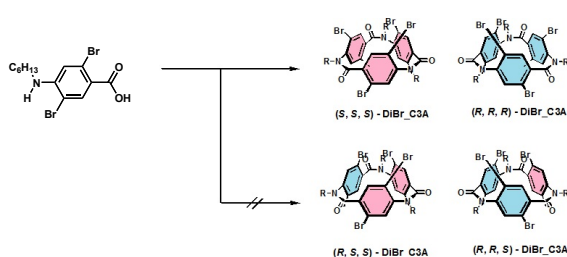
rotation is blocked due to the steric repulsion (Figure S16, †ESI). In addition, the solid-state structure of **DiBr\_C3A** was investigated by single-crystal X-ray analysis, showing racemic crystal including (*S,S,S*) and (*R,R,R*) isomers (Figures 2 and S20, space group= $C2/c$ ,  $Z=8$ ). Three benzene rings are standing in the direction perpendicular to the amide bond and, hence, the C-O bond length (ca. 1.22 Å) corresponds to the typical C=O bond length (ca. 1.23 Å). Two enantiomers are alternatively stacked to form the columnar structure along the *c* axis (Figure 2c). The enantiomers having the different chirality in the neighboring columns are associated by the two non-covalent  $\text{C}=\text{O}\cdots\text{Br}$  (halogen bonding) interactions<sup>11</sup> with the length of ca. 2.98 Å which contributes to the formation of the crystal network structure (Figure S21). Thus, the cyclization of **1** was found to proceed in a diastereoselective manner (Figure 3). This may be caused by the steric bulkiness of the bromine atom and the axial chirality was transmitted in the cyclization process. The methylene proton signals on the amide nitrogen and the aromatic proton signals of **BPEB\_C3A** were likewise observed as two sharp signals (Figure 1b) indicating that the partial rotation of the benzene ring of **DiBr\_C3A** (epimerization) did not take place during Sonogashira-Hagihara coupling reaction. Therefore, **BPEB\_C3A** would be expected to contain two optically active enantiomers as a racemic mixture.<sup>12</sup>



**Figure 1.**  $^1\text{H}$  NMR spectra (600 MHz,  $\text{CD}_2\text{Cl}_2$ , rt) of (a) **DiBr\_C3A** and (b) **BPEB\_C3A**.



**Figure 2.** Crystal structure of **DiBr\_C3A**. (a) Top view, (b) side view, and (c) packing structure along the *c* axis. Hydrogen atoms are omitted for clarity in c. Magenta- and cyan-colored molecules are enantiomers of each other.

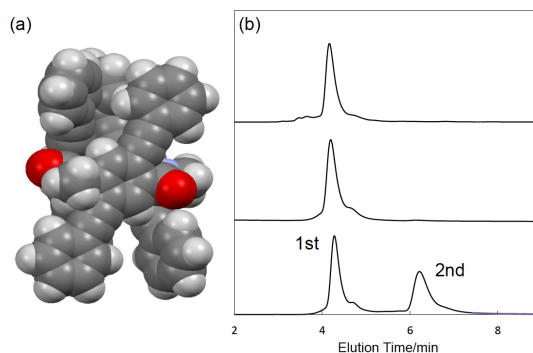


**Figure 3.** Diastereoselective cyclization to give **DiBr\_C3A**.

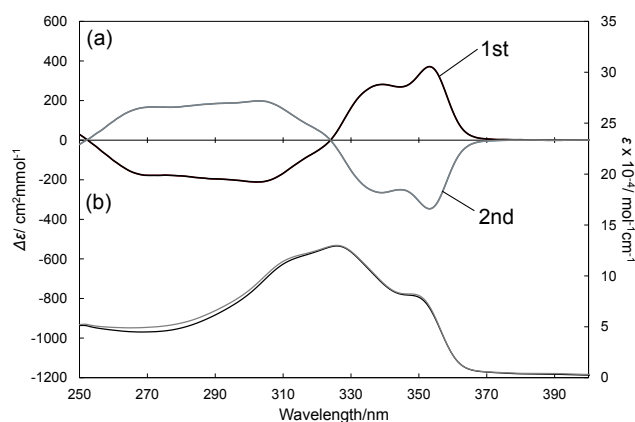
Because we could not obtain single crystals suitable for the X-ray analysis, the conformation of **BPEB\_C3A** was investigated by optimizing the structure with the density functional theory (DFT) calculation at the B3LYP/6-31G(d) level of theory. As shown in Figure 4a, bundled bis(phenylethynyl)benzene units form the triple-stranded helical conformation. The optical resolution of racemic **BPEB\_C3A** was carried out by the chiral high-performance liquid chromatography (HPLC) on ChiralPAK IA using 2-propanol/*n*-hexane (20:80) as the mobile phase (Figure 4b). The stability of the chiral conformation was examined by heating the solution of the first fraction at 50 °C for 10 min. No peak derived from the paired enantiomer (second fraction) was detected in the chiral HPLC analysis (Figure 4b) indicating that the racemization of **BPEB\_C3A** was inhibited by the bulky phenylethynyl groups. To investigate the chiral helical topologies in solution, the circular dichroism (CD) spectra of isolated chiral **BPEB\_C3A** was studied, and the mirroring Cotton effect was observed in THF (Figure 5). The CD spectra of the first fraction showed a positive Cotton effect at 353 nm and 339 nm followed by a negative Cotton effect at 302 nm. The CD anisotropy factors ( $\Delta\epsilon/\epsilon$ ) at these wavelengths were found to be  $10^3 g_{\text{abs}} = 5.4, 3.0,$  and  $2.4,$  respectively. These values are more than ten times larger than our previous report ( $10^3 g_{\text{abs}} = 0.2$ )<sup>7</sup> and the solvent character influenced CD spectra only a little (Figure S17, †ESI) to suggest the robust chromophore arrangement within **BPEB\_C3A**. We also found that the CD intensity around 353 nm was increased with lowering temperature (Figure S18, †ESI). This result may indicate that the rotation around the carbon-carbon triple bond and/or the swinging motion of bis(phenylethynyl)benzene units are suppressed at the low temperature.

The UV-vis absorption and fluorescence emission spectra of **BPEB\_C3A** in a deaerated THF solution and solid state were obtained (Figure S19, †ESI). The emission spectrum in solution exhibited a broad peak at 440–650 nm in addition to the emission around 340–400 nm having the vibronic structure. The broad emission at the longer wavelength region can be explained by the intramolecular interaction between three bis(phenylethynyl)benzene units<sup>13</sup> and **BPEB\_C3A** had a low fluorescence quantum yield (< 1%). We could not measure the circularly-polarized luminescence (CPL) spectra owing to the low quantum yield of the material. In the solid state, the monomer emission at the shorter wavelength was almost

disappeared indicating the intermolecular interaction between **BPEB\_C3A**.



**Figure 4.** (a) Energy-minimized structure of **BPEB\_C3A** at B3LYP/6-31G(d) level. (b) Chiral HPLC chromatograms of racemic **BPEB\_C3A** (bottom), the isolated 1<sup>st</sup> fraction of **BPEB\_C3A** (center), and that after heating 50 °C for 10 min (top).



**Figure 5.** (a) CD and (b) UV-vis spectra of the first and second fractions ( $3.7 \times 10^{-6}$  M) in THF at rt.

## Conclusions

In summary, we demonstrated efficient and diastereoselective synthesis of cyclic tri(benzamide) having six bromo groups **DiBr\_C3A** using the microwave irradiation. After Sonogashira-Hagihara coupling reaction with phenyl acetylene, cyclic tri(benzamide) carrying three bis(phenylethynyl)benzene units **BPEB\_C3A** could be prepared. The optical resolution was performed by chiral HPLC. The novel cyclic tri(benzamide) forms the triple-stranded helical conformation, in which the racemization was not occurred even at the elevated temperature. The enantiomeric pure sample showed the strong Cotton effect in CD spectra. The study about chiroptical properties in the solid state and electrochemical properties are currently underway.

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## Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details, characterization data, chromatography chart, and electronic spectra. CCDC 1045865. For ESI and crystallographic data in CIF format see DOI: 10.1039/c000000x/

- 1 For reviews on host-guest chemistry, see; J. M. Lehn, *Supramolecular Chemistry-Concepts and Perspective*, VCH: Weinheim, 1995; A. Ikeda and S. Shinkai, *Chem. Rev.*, 1997, **97**, 1713; L. Mutihac, J. H. Lee, J. S. Kim, and J. Vicens, *Chem. Soc. Rev.*, 2011, **40**, 2777; G. Wenz, *Angew. Chem. Int. Ed.*, 1994, **33**, 803; J. L. Atwood, J. E. D. Davies, D. D. MacNicol, and F. Vögtle, *Comprehensive Supramolecular Chemistry, Vol. 3 Cyclodextrins*, Pergamon, Oxford, 1996; F. Hapiot, S. Tilloy, and E. Monflier, *Chem. Rev.*, 2006, **106**, 767; T. Ogoshi, *J. Incl. Phenom. Macrocycl. Chem.*, 2012, **72**, 247; P. J. Cragg and K. Sharma, *Chem. Soc. Rev.*, 2012, **41**, 597.
- 2 M. Larsen, F. C. Krebs, M. Jørgensen, and N. Harrit, *J. Org. Chem.*, 1998, **63**, 4420; A. Alemán, D. Zanuy, and J. Casanovas, *J. Org. Chem.*, 2006, **71**, 6952; X. H. Sum, C. S. Chan, M. S. Wong, and W. Y. Wong, *Tetrahedron*, 2006, **62**, 7846; C. Hippus, I. H. M. van Stokkum, M. Gsänger, M. M. Groeneveld, R. M. Williams, and F. Würthner, *J. Phys. Chem. C*, 2008, **112**, 2476; K. Takagi, S. Sugimoto, R. Yamakado, and K. Nobuke, *J. Org. Chem.*, 2011, **76**, 2471.
- 3 A. Harada, J. Li, and M. Kamachi, *Nature*, 1993, **364**, 516; A. Ikeda and S. Shinkai, *Chem. Commun.*, **1994**, 2375; S. E. Matthews, P. Schmitt, V. Felix, M. G. Drew, and P. D. Beer, *J. Am. Chem. Soc.*, 2002, **124**, 1341; J. Morales-Sanfrutos, M. Ortega-Muñoz, J. Lopez-Jaramillo, F. Hernandez-Mateo, and F. Santoyo-Gonzalez, *J. Org. Chem.*, 2008, **73**, 7768.
- 4 I. Huc, *Eur. J. Org. Chem.*, **2004**, 17; H. Katagiri, Y. Tanaka, Y. Furusho, and E. Yashima, *Angew. Chem. Int. Ed.*, 2007, **46**, 2435; H. Iida, M. Shimoyama, Y. Furusho, and E. Yashima, *J. Org. Chem.*, 2010, **75**, 417.
- 5 A. Ikeda, H. Udzu, Z. Zhong, S. Shinkai, S. Sakamoto, and K. Yamaguchi, *J. Am. Chem. Soc.*, 2001, **123**, 3872; A. Orita, T. Nakano, D. L. An, K. Tanikawa, K. Wakamatsu, and J. Otera, *J. Am. Chem. Soc.*, 2004, **126**, 10389; L. Yan, Z. Wang, M.T. Chen, N. Wu, J. Lan, X. Gao, J. You, H.-M. Gau, and C.-T. Chen, *Chem. Eur. J.*, 2008, **14**, 11601; F. Cui, S. Li, C. Jia, J. S. Mathieson, L. Cronin, X.-J. Yang, and B. Wu, *Inorg. Chem.*, 2012, **51**, 179.
- 6 M. Tominaga, H. Masu, K. Katagiri, T. Kato, and I. Azumaya, *Org. Lett.*, 2005, **7**, 3785; M. Tominaga, H. Masu, K. Yamaguchi, and I. Azumaya, *Chem. Lett.*, 2006, **35**, 718; R. Shomura, S. Higashibayashi, H. Sakurai, Y. Matsushita, A. Sato, and M. Higuchi, *Tetrahedron Lett.*, 2012, **53**, 783.
- 7 R. Yamakado, K. Mikami, K. Takagi, I. Azumaya, S. Sugimoto, S. Matsuoka, M. Suzuki, K. Katagiri, M. Uchiyama, and A. Muranaka, *Chem. Eur. J.*, 2013, **19**, 11853.
- 8 H. Masu, K. Katagiri, T. Kato, H. Kagechika, M. Tominaga, I. Azumaya, *J. Org. Chem.*, 2008, **73**, 5143; K. Katagiri, T. Ikeda, A. Muranaka, M. Uchiyama, M. Tominaga, and I. Azumaya, *Tetrahedron: Asymmetry*, 2009, **20**, 2646; N. Fujimoto, M. Matsumura, I. Azumaya, S. Nishiyama, H. Masu, H. Kagechika, and A. Tanatani, *Chem. Commun.*, 2012, **48**, 4809.
- 9 A. Yokoyama, T. Maruyama, K. Tagami, H. Masu, K. Katagiri, I. Azumaya, and T. Yokozawa, *Org. Lett.*, 2008, **10**, 3207; R. Yamakado, S. Sugimoto, S. Matsuoka, M. Suzuki, Y. Funahashi, and K. Takagi, *Chem. Lett.*, 2012, **41**, 249; R. Yamakado, S. Matsuoka, M. Suzuki, D. Takeuchi, H. Masu, I. Azumaya, and K. Takagi, *RSC Adv.*, 2014, **4**, 6752.
- 10 I. Azumaya, H. Kagechika, K. Yamaguchi, and K. Shudo, *Tetrahedron Lett.*, 1996, **37**, 5003; I. Azumaya, T. Okamoto, F. Imabeppu, and H. Takayanagi, *Tetrahedron*, 2003, **59**, 2325; F. Imabeppu, K. Katagiri, H. Masu, T. Kato, M. Tominaga, B. Therrien, H. Takayanagi, E. Kaji, K. Yamaguchi, H. Kagechika, and I. Azumaya, *Tetrahedron Lett.*, 2006, **47**, 413.
- 11 J. P. M. Lommerse, A. J. Stone, R. Taylor, F. H. Allen, *J. Am. Chem. Soc.*, 1996, **118**, 3108; S. Muniappan, S. Lipstman, I. Goldberg, *Chem. Commun.*, **2008**, 1777; F. C. Pigge, V. R. Vangala, P. P. Kapadia, D. C. Swenson, N. P. Rath, *Chem. Commun.*, **2008**, 4726.
- 12 T. Ogoshi, D. Yamafuji, T. Aoki, K. Kitajima, T. Yamagishi, Y. Hayashi, S. Kawauchi, *Chem. Eur. J.*, 2012, **18**, 7493; Y. Morisaki, M. Gon, T. Sasamori, N. Tokitoh, Y. Chujo, *J. Am. Chem. Soc.*, 2014, **136**, 3350.
- 13 T. Ogoshi, K. Umeda, T. Yamagishi, and Y. Nakamoto, *Chem. Commun.*, **2009**, 4874.