Toward the Synthesis of a Belt-Shaped Cyclic π-Conjugated System Comprising para-Phenylene Framework and Amide Bridging Unit

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Abstract
Belt-shaped π-conjugated systems have been attracting more and more attention in recent years from the synthetic interest as well as their mysterious properties that linear counterparts do not have. In this paper, the stepwise condensation of 2-bromo-4-(octylamino)benzoic acid and subsequent macrocyclization was carried out to obtain a cyclic hexamer (c6mer). The palladium-catalyzed direct arylation was then performed to get the target belt-shaped molecule (b6mer) although the isolation of b6mer did not meet with success because of the contamination of structural defects. Theoretical calculation of b6mer indicated the strain energy of ca. 100.9 kcal mol⁻¹ and revealed the electronic transition from degenerate HOMO-1 and HOMO-2 orbitals to LUMO similar to that of parent cyclo-paraphenylene derivatives.

Keywords: Belt-shaped molecule | Amide bond | Direct arylation

Introduction
Cyclic π-conjugated systems have been drawing much attention due to their end-free structures,1 in which the cyclic framework may provide nano-sized interior space suitable for host-guest interaction and molecular recognition.2 Cycloparaphenylenes (CPPs) are regarded as the shortest segment of armchair carbon nanotubes. Not only the beautiful structure but also the theoretical, photophysical, electrochemical, and material aspects of CPPs have been fascinating many researchers for the past several decades3-5 since Jasti and Bertozzi firstly reported the preparation of CPPs (carbon nano hoops) in 2008.7 For example, in stark contrast to linear paraphenylenes oligomers, the energy gap of CPPs between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) becomes narrower with the decrease of the number of phenylene rings as indicated by the theoretical calculation.8 Several research groups have developed the elegant synthesis of CPPs with various size and ring strain based on their original strategies. Segawa and Itami have investigated theoretically the strain energies of CPPs and revealed that constituent phenylene rings in [12]CPP can rotate rather freely at room temperature.9

In relation to CPPs solely constructed from benzene rings, cyclic π-conjugated systems with larger aromatic units have been also developed aiming at tubular architecture.10,11 This kind of synthetic challenge was provoked by Hitosugi and Isebe in 2011,12 to the best of our knowledge, in which the bottom-up synthesis of [4]cyclo-2,8-chryseneylene ([4]CC) was achieved through the preparation of intermediate platinum complex. Subsequently, π-extended cyclic conjugated systems with the cylindrical shape having naphthalene,13 phenanthrene,14 anthanthrene,15 pyrene,16 and dibenzoanthrylene17 panels have been synthesized. In these cases, rotational barriers of aromatic units around the carbon-carbon single bond were influenced due to the steric factor, particularly for small-membered congeners. In addition to this approach, belt-shaped cyclic π-conjugated compounds could be synthesized by covalently bridging neighboring phenylene rings. Segawa and Itami have debuted carbon nanobelts consisting solely of fused benzene rings to figure out their unique structural and optoelectronic features.18,19 These compounds can be also considered as the CPP analog, in which each phenylene ring is connected...
by the carbon-carbon double bonds. The same research group also synthesized a methylene-bridged carbon nanobelt later.20 Cheung and Miao have succeeded in the synthesis of armchair and chiral carbon nanobelts through Scholl reactions.21

We have previously reported the synthesis of ladder poly(para-phenylene) via palladium-catalyzed polymer direct arylation using bromo-functionalized poly(N-alkyl-p-benzamide) as a precursor (Figure 1A).22 Because of the preferential cis conformation of tertiary aromatic amide bonds,23 24 two benzene rings attached to the amide group are positioned in close proximity to enable the aryl-aryl coupling. The obtained π-conjugated ladder polymer has para-linked phenylene rings which are forced to adopt the nearly planar and rigid conformation owing to the presence of the fused lactam unit. On the other hand, cyclic trimer and hexamer could be synthesized and successfully isolated by the condensation reaction of 4-(methylamino)benzoic acid.25 With these results in hand, we came up with the synthesis of a bent-shaped cyclic π-conjugated system comprising para-phenylene framework and amide bridging unit (Figure 1B). In this paper, the synthetic effort toward the target molecule and theoretical analyses are described.

Results and Discussion

Because Azumaya and co-workers have reported the successful synthesis of cyclic hexamer from the self-condensation of 4-(methylamino)benzoic acid,25 we have initially tried the condensation of 2-bromo-4-(octylamino)benzoic acid (monomer) using PPh3/Cl2CCl3 as a dehydrating reagent in pyridine at 120 °C (Scheme S2). Although cyclic trimer (c3mer) was isolated, target cyclic hexamer (c6mer) could not be obtained. Aside from our final purpose, we have briefly investigated the stereochemistry of c3mer. As indicated in Figure S7, six sets of methylene proton signals adjacent to the amide nitrogen and nine sets of aromatic proton signals were observed in the same integral ratio. This signal splitting is most probably due to the diastereotopic environment related to the fixed chirality of the substituted aromatic cyclic triamide skeleton.26 27 Thus the isolated c3mer was determined to have the anti-isomer, namely, the racemic mixture of R,R,S and S,S,R isomers. Accordingly, we have applied the second strategy to get c6mer that utilizes the cyclic trimerization of dimer. To this end, the stepwise condensation was carried out through the protection-deprotection method (Scheme S3). Double-protected dimer 7 was obtained in 76% yield by the condensation of 4 and 6 using SiCl4/pyridine as a dehydrating reagent at 60 °C. Other reagents such as PPh3/Cl2CCl328 and NMP/BEP29 did not work well and the starting materials were considerably recovered. The higher reaction temperature at 90 °C and 120 °C decreased the isolated yield to 60% and 19%, respectively. After trimming two protecting groups, dimer was obtained in high yield. In the 1H NMR spectrum, inner ArN-(CH2-R)-CO- protons were clearly observed at 3.87 ppm (Figure S14). As for a similar dimer having the bromine group at the ortho position relative to the nitrogen atom, on the other hand, corresponding prochiral methylene protons were separately observed at 3.54 ppm and 4.05 ppm in the 1:1 integral ratio (not shown here), which is due to the higher energy barrier for the phenylene-amine plane rotation. Dimer was then subjected to the cyclic condensation using SiCl4/pyridine as a dehydrating reagent at 90 °C (Scheme S4). The GPC profile of crude product indicated that several oligomers having different molecular weight were generated (Figure S16). When we take a close look at the HR ESI-MS, cyclic tetramer (c4mer) as well as linear hexamer and octamer are detected in addition to c6mer (Figure S17). Because the isolation of c6mer was impossible by the standard chromatographic technique, we alternatively decided to perform the iterative addition of dimer to get hexamer followed by macrocyclization to obtain c6mer (Scheme S5 and Scheme 1). In order to suppress the intermolecular coupling of hexamer, the cyclization at the last stage was carried out under dilute conditions using the SiCl4/pyridine system.26 The crude product was treated with Silica gel 60 NH2 to remove unreacted hexamer and/or higher linear oligomers with a CO2H terminal group. The purification by preparative GPC resulted in the isolation of c6mer in 51% yield (Figure S35). In the 1H NMR spectrum (Figure S30), the

![Scheme 1. Synthetic route to c6mer. See Supplementary Information (Scheme S5) for the details.](image-url)
integral ratio of aromatic proton signals and methylene proton signals adjacent to the amide nitrogen agreed well with the theoretical value (18:12). These signals were broadly observed in contrast to that of $c3$mer, which is likely ascribed to the rotation of phenylene rings and the existence of various diastereomeric conformations due to the fixed chirality. When the spectrum of $c6$mer was collected at 70°C in C$_2$D$_2$Cl$_4$, aromatic proton signals were observed in three parts (Figure S31). At the higher measuring temperature (120°C), methylene proton signals adjacent to the amide nitrogen coalesced and were broadly observed indicating that the conformational transition between different diastereomers slowly occurred (Figure 2, top). We also carried out the variable-temperature $^1$H NMR spectroscopic analysis for hexamer (Figure S27).

Upon increasing the measuring temperature, aromatic and N-CH$_2$ methylene proton signals became sharp as compared with those observed at room temperature. At 120°C, aromatic proton signals at the N terminal were detected at 6.37, 6.66, and 6.80 ppm, while those at the C terminal were detected at 7.45 ppm and 7.67 ppm in the theoretical integral ratio (Figure 2, bottom). The N-CH$_2$ methylene proton signals at the N and C termini were also clearly detected at 3.05 and 3.80 ppm, respectively. The difference in the NMR spectra between $c6$mer and hexamer can be ascribed to the ring structure and the absence of the terminal groups in $c6$mer. Figure 3A shows the MALDI-ToF MS, in which the observed spectral pattern is almost coincident with the simulated one (Figure S33). The exact mass number in the HR ESI-MS also agreed with the theoretical value (Figure S34). These results strongly support the identity and purity of $c6$mer. The elution time of $c6$mer in the GPC analysis was shifted from that of hexamer (Figure 3B). This fact implies the smaller hydrodynamic volume of cyclic architecture as generally observed for cyclic polymers although the influence of terminal polar groups of hexamer cannot be completely ruled out.

In the final step, the intramolecular direct arylation of $c6$mer was carried out under the conventional conditions using Pd(OAc)$_2$, Ph$_3$P, Ph$_3$P, BF$_3$, and K$_2$CO$_3$ in DMAc (Scheme S7). Heating with microwave irradiation was applied by reference to previous reports, and the reaction was performed at 120°C for 12 h. The crude product was purified by preparative GPC and the unimodal chromatogram in the analytical GPC indicates that no product derived from the intermolecular direct arylation is included (Figure S37). In the $^1$H NMR spectrum (Figure S36), the integral ratio of aromatic proton signals and methylene proton signals adjacent to the amide nitrogen was 14:12, which deviates from the theoretical value (12:12). The simulated MS pattern of pure $b6$mer (Figure S38) indicates that the most intense peak should be observed at m/z = 1397.84. On the other hand, the MALDI-ToF MS of obtained product exhibited the maximum peak at m/z = 1399.85 (Figure 4). Taking into consideration the simulated MS pattern of $b6$mer(H$_2$) having one carbon-carbon bond defect (Figure S40), the intramolecular direct arylation of $c6$mer did not proceed in a perfect manner and the obtained product most likely contains approximately one carbon-carbon bond defect. By assuming the equal ionization efficiency, the calculated abundance ratio of $b6$mer and $b6$mer(H$_2$) was 23:77. The higher reaction temperature at 150°C provided a product with more carbon-carbon bond defects. When we performed the reaction using Pd(dbq)$_2$, Ph$_3$P, Ph$_3$P, and C$_6$H$_5$CO$_3$ in THF at 100°C for 12 h, and $c6$mer was detected in the MALDI-ToF MS (Figure S41). $b6$mer(H$_2$) was not observed and, instead, $b6$mer(HBr) with the incomplete carbon-carbon bond formation was confirmed at m/z = 1453.7747.

Furthermore, the direct arylation using the phosphine ligand-free system, namely, in the presence of PdCl$_2$, Ph$_3$P, and K$_2$CO$_3$ in DMAc at 100°C also resulted in the recovery of $c6$mer (Figure S42). Under this condition, neither $b6$mer(H$_2$) nor $b6$mer(HBr) was formed. We could not succeed in the crystal structure analysis of $c6$mer because of the semi-flexible characteristic, however, the energy-minimized conformation suggested by the density functional theory (DFT) calculation indicates that $c6$mer can be an appropriate precursor for obtaining $b6$mer (Figure S45). The debromination is responsible
for the contamination of this defect, which has been often observed in the palladium-catalyzed direct arylation.\textsuperscript{35,36}

Although the purity of b6mer was insufficient at the present stage, the optical properties were preliminarily investigated in THF solution. The broad absorption shoulder at around 400 nm and the fluorescence maximum at 464 nm were detected (Figure 5). Because both [6]CPP\textsuperscript{17} and methylene-bridged [6]CPP\textsuperscript{20} are non-fluorescent due to the systematically forbidden S\textsubscript{1}→S\textsubscript{0} transition, the observed blue emission might originate from b6mer(H\textsubscript{1}) having the structural defect (\textit{vide infra}). We have finally performed the quantum chemical calculation to gain insight into the structural features and photophysical properties of b6mer. The DFT calculation was implemented on the Gaussian 09 program, where octyl chains of b6mer were replaced with methyl groups for computational cost. The ground state structure was optimized using a B3LYP density functional and a 6-31G(d,p) basis set to obtain a stable minimum with no imaginary frequency part (Figure S46). The ring strain energy of b6mer calculated on the basis of the homodesmotic reaction scheme (Scheme S8 and Table S1) was 100.9 kcal mol\textsuperscript{−1}, which is larger than [6]CPP (96.0 kcal mol\textsuperscript{−1})\textsuperscript{9} and smaller than the methylene-bridged [6]CPP (110.2 kcal mol\textsuperscript{−1}).\textsuperscript{20} Thus the bridge formation is considered to increase the ring strain of [6]CPP, and amide and methylene bridges have a different perturbation effect. For reference, the ring strain energy of a virtual belt-shaped cyclic octamer (b8mer) having the larger ring size was estimated as 73.6 kcal mol\textsuperscript{−1}. The time-dependent DFT calculation was then performed in the same level. Singlet excited energies and states of b6mer are summarized in Table S2, and related frontier molecular orbitals are indicated in Figure 6. The electronic transition from HOMO to LUMO is completely forbidden with a zero oscillator strength similar to [6]CPP\textsuperscript{36} and methylene-bridged [6]CPP.\textsuperscript{20} On the other hand, the theoretical absorption band can be assigned to the electronic transition from HOMO-1 to LUMO and from HOMO-2 to LUMO. HOMO-1 and HOMO-2 orbitals were almost degenerate. It was found that the calculated electronic transition band corresponds to the wavelength at 402 nm. Additionally, the theoretical calculation of b6mer(H\textsubscript{1}) was also investigated. The optimized structure and frontier molecular orbitals (Figures S47 and S48) as well as the time-dependent DFT results (Table S3) are provided in the Supplementary Information. In sharp contrast to b6mer, the HOMO–LUMO transition at 468 nm is allowed with an oscillator strength of 0.1490, whereas other electronic transitions are relatively small. Related calculations were also performed for b6mer(H\textsubscript{2}) and b6mer(H\textsubscript{3}) with more defects. From b6mer(H\textsubscript{2}) to b6mer(H\textsubscript{3}) and b6mer(H\textsubscript{4}), the lower excitation energy exhibited a blue-shift and the oscillator strength increased (Figures S49–S52, Tables S4 and S5.). Although HOMO and LUMO surfaces were delocalized over the whole molecule in the case of b6mer, the structural defect brought about the localization of orbital surfaces. These theoretical calculations demonstrate the unique photophysical properties of cyclic belt-shaped architecture of b6mer and the influence of the structural defect.

Conclusions

We have investigated the synthesis of a belt-shaped cyclic π-conjugated system comprising the para-phenylene framework and amide bridging unit. Cyclic aromatic amide hexamer obtained through the stepwise condensation of 2-bromo-4-(octyl-amino)benzoic acid was subjected to the palladium-catalyzed direct arylation. MALDI-ToF MS suggested the formation of target compound and DFT calculation revealed the unique photophysical properties. We believe that these findings can contribute to the advancement of chemistry of belt-shaped cyclic π-conjugated systems.

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Supporting Information

Syntheses, GPC chromatograms, ESI-MS charts, NMR spectra, and computational results. This material is available on https://doi.org/10.1246/bcsj.20210340.

References


\textbf{Figure 5.} UV-vis absorption and photoluminescence spectra of b6mer (solid line) and b6mer (dotted line) in THF solution (10\textsuperscript{−5} M). Inset is a photograph of a solution of b6mer under the irradiation with UV light at 365 nm.

\textbf{Figure 6.} A and B: CPK model structures of b6mer (gray; carbon, white; hydrogen, red; bromine). C: Frontier molecular orbitals of b6mer.
24 The terms “cis” and “trans” are conventionally used to show the relative positions of aromatic groups connected to the amide unit. Based on an IUPAC definition, the cis conformation corresponds to the E-isomer.
36 Preliminary spectroscopic characterization of 6mer (mixture) is provided in the Supporting Information (Figures S43 and S44).