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Bromination of Cycloparaphenylenes: Strain-Induced Site-Selective Bis-Addition and its Application for Late-Stage Functionalization

Eiichi Kayahara, Rui Qu, and Shigeru Yamago*[a]

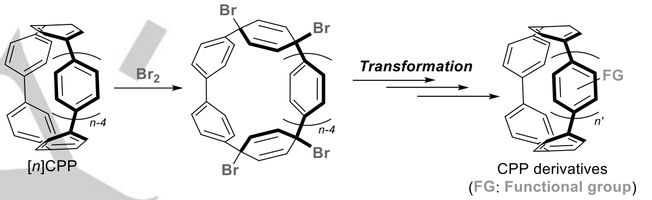
Dedicated to Professor Teruaki Mukaiyama in celebration of his 90th birthday (Sotsuju)

Abstract: Bromination of [*n*]cycloparaphenylenes (CPPs) is herein reported. Small [*n*]CPPs ($n < 8$) underwent a bis-bromine-addition reaction with high site-selectively producing tetrabromo-adducts in moderate to excellent yields. Theoretical calculations revealed that thermodynamic stability dictates both the reactivity and site-selectivity of the reaction. The addition product was further converted to the octabromo product by a $FeBr_3$-catalyzed site-selective bromination reaction. The tetra- and octa-bromine adducts were then transformed to mono- to tetrabromo CPPs, which were further converted to several CPP derivatives. Therefore, bromination and subsequent transformations provide a path for late-stage functionalization of CPPs.

Hoop-shaped π-conjugated molecules have attracted growing interest not only for their fascinating structures but also for their potential applications in material science.[1] Cycloparaphenylenes (CPPs, Scheme 1), which have the shortest sidewall structure of armchair carbon nanotube, have acquired a prominent position[2] because of their availability by bottom-up organic synthesis recently reported by Jasti and Bertozzi et al.,[3] Itami et al.,[4] and Yamago et al.[5] These synthetic endeavors not only enabled the synthesis of CPPs of different sizes,[6],[7],[8] CPP derivatives,[9] and their analogues,[10] but also unveiled the unique physical properties of CPPs including their photophysical[11] and redox properties[8a, 12] and host–guest chemistry.[13] In addition, CPPs have been used as seeds for the synthesis of structurally defined carbon nanotubes.[14]

The synthesis of CPP derivatives is among the most important research subject because the introduction of functional groups could enable fine-tuning of the electronic properties of CPPs and their use as functional materials. However, CPP derivatives were so far synthesized by early-stage functionalization starting from functionalized precursors by tedious multistep syntheses. Therefore, the development of a new method for late-stage functionalization of CPPs is required.

Recently, the gram-scale synthesis of several CPPs[6c, 8e, 8f] has been achieved by Jasti and Yamago. These findings open a new possibility for the late-stage functionalization of CPPs that allows access to a variety of CPP derivatives. On the other hand, late-stage functionalization poses a new challenge of site-selectivity for the functionalization when multi-functionalization is necessary, because all paraphenylene units in CPPs are chemically equivalent. Here we report the site-selective late-stage functionalization of CPPs based on the electrophilic bromination as a key step (Scheme 1). Recently, Itami and co-workers reported the late-stage functionalization of [9]- and [12]CPPs based on the formation of a chromium complex.[15] However, the desired complex was formed in low yield. Furthermore, the method was used only for mono-functionalization.



Scheme 1. Bromination of CPP and its application for the synthesis of CPP derivatives.

Bromination of [5]CPP was examined by adding a solution of bromine (1.0 equiv.) to a suspension of [5]CPP in CCl_4 at -15 °C (Table 1, entry 1). Analysis of the crude reaction mixture indicated the formation of bis-bromine adduct **1a** in 46% yield together with 42% recovery of [5]CPP. Surprisingly, no brominated [5]CPP, which is an expected product from an electrophilic aromatic substitution reaction, was detected. The addition of bromine over an isolated benzene ring was already reported for highly strained [6]paracyclopahanes by Tochtermann[16] and Tobe,[17] and the release of the strain is the driving force of this unexpected result (see below). When 2.0 equivalents of Br_2 was used, nearly quantitative formation of **1a** was observed (entry 2). Increasing the Br_2 amount to 3.0 equivalents did not produce any other addition products (entry 3).

The structure of **1a** was unambiguously determined by NMR spectroscopy. In the ^{1}H NMR spectrum, the protons of the cyclohexadiene moieties appeared at $\delta = 6.13$ and 6.58 ppm as two doublet ($J = 10.0$ Hz). The protons on the paraphenyl ring between the two cyclohexadiene moieties resonated at $\delta = 6.57$ ppm as a singlet, and those on the remaining biphenyl unit appeared at $\delta = 7.29$ and 7.39 ppm as two doublets ($J = 8.8$ Hz). In the ^{13}C NMR spectrum, only ten signals were observed; the C-H cyclohexadiene carbons resonated at $\delta = 127.0$ and 127.3 ppm, and the *ipso*-carbons appeared at 51.4, 59.0 ppm. The highly symmetrical spectra are consistent with the proposed structures. Furthermore, two dimensional NMR analyses (HMQC and HMBC) enables assignment of all hydrogens and carbons of **1a**

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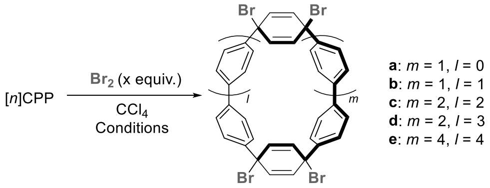
Table 1. Bromination of [*n*]CPP.



1

a: *m* = 1, *l* = 0
b: *m* = 1, *l* = 1
c: *m* = 2, *l* = 2
d: *m* = 2, *l* = 3
e: *m* = 4, *l* = 4

Entry	[*n*]CPP	Br_2 (x equiv.)	Conditions	1	Yield (%)[a]	Recovery of [*n*]CPP (%)[a]
1	[5]CPP	1.0	-15 °C /15 min	**1a**	46	42
2	[5]CPP	2.0	-15 °C /15 min	**1a**	94	0
3	[5]CPP	3.0	-15 °C /15 min	**1a**	90	0
4	[6]CPP	1.0	-15 °C /15 min	**1b**	34	21
5	[6]CPP	2.0	-15 °C /15 min	**1b**	82	1
6	[8]CPP	2.0	-15 °C /15 min	**1c**	17	22
7	[9]CPP	2.0	50 °C / 10 h	**1d**	0	95
8	[12]CPP	2.0	50 °C /14 h	**1e**	0	100

[a] NMR yield.

(See Supporting Information).

The scope of the bromination reaction was examined next. The reaction of [6]CPP with 1.0 equivalent of Br_2 selectively afforded bis-adduct **1b** in 34% yield with 21% recovery of [6]CPP (Table 1, entry 4). The yield of **1b** also increased to 82% by employing 2.0 equivalents of Br_2 (entry 5). [8]CPP also selectively gave bis-addition adduct **1c**, but the yield dropped to 17% even with 2.0 equivalents of Br_2 (entry 6). While side product(s) was formed, characterization was unsuccessful due to its low solubility. On the contrary, [9] and [12]CPPs were completely inert to Br_2 and were recovered quantitatively even being heated at 50 °C (entries 7 and 8). All bromine adducts **1a~c** are stable at ambient temperature but decompose above 200 °C.

To clarify the size-dependency of the addition reaction, the heat of formation (ΔH) of the mono-bromine addition reactions of [*n*]CPPs forming mono-bromine adduct **2** was calculated using the density functional theory (DFT) method at the B3LYP/6-31G* level of theory (Figure 1, black line). The ΔH values are strongly affected by the size of the CPPs. The addition reaction is exothermic for [*n*]CPPs with *n* smaller than 9 despite the loss of aromaticity, and the exothermicity increases as the CPP becomes smaller. For example, the ΔH of [5]CPP adduct **2a** is -87 kJ mol^{-1}, whereas the addition reaction becomes endothermic when the CPP size exceeds [9]CPP. These results are consistent with the experimental observation.

In order to gain further insight into the driving force of the addition reaction, the relief of ring strain (ΔE_s) was also calculated (Figure 1, red line). The ΔE_s is quite substantial for small CPPs; for example, ΔE_s = -164 kJ mol^{-1} for [5]CPP. ΔE_s decreases as the CPP size increases, and there is always a difference of 78 kJ mol^{-1} between ΔH and ΔE_s for every CPP, which corresponds to ΔH for the mono-bromine addition to terphenylene at the 1,4-position in the central paraphenylene unit (Figure S6). Thus, the reactivity of CPPs is determined by the balance between the exo- and endo-thermicity resulting from the relief of strain and the loss of aromaticity, respectively.

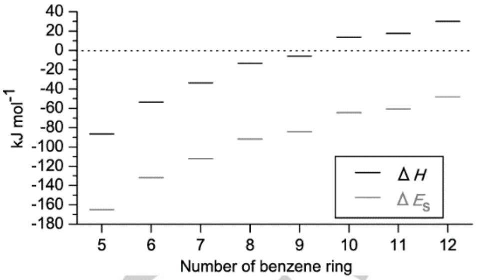


Figure 1. Heat of formation (ΔH, black line) and relief of ring strain (ΔE_s, red line) upon the addition of bromine to CPPs forming mono-bromine adduct **2** obtained by the DFT calculations at the B3LYP/6-31G(d) level of theory. The relief of ring strain (ΔE_s) is defined as ΔE_s = Strain energy (**2**) - Strain energy ([*n*]CPP).

The origin of the site-selective formation of **1a** was also clarified by the DFT calculation. The ΔH of the second addition of Br_2 to **2a** giving **1a** is -108 kJ mol^{-1} (Figure 2), which is more exothermic than the first addition, suggesting that **2a** spontaneously undergoes second addition giving **1a**. In contrast, the formation of isomer **1a′** is endothermic. Furthermore, further addition of bromine to **1a** giving **3a** or its isomer **3a′** is almost thermo-neutral or endothermic. When entropy is taken into consideration, while the addition reactions giving **2a** and **1a** are still highly exothermic, those affording **1a′**, **3a**, and **3a′** are endothermic at 298.15 K. Similar energy diagrams were also obtained for the addition reaction of [6] and [8]CPPs (Figures S7 and S8). These results clearly indicate that thermodynamics control the reaction.

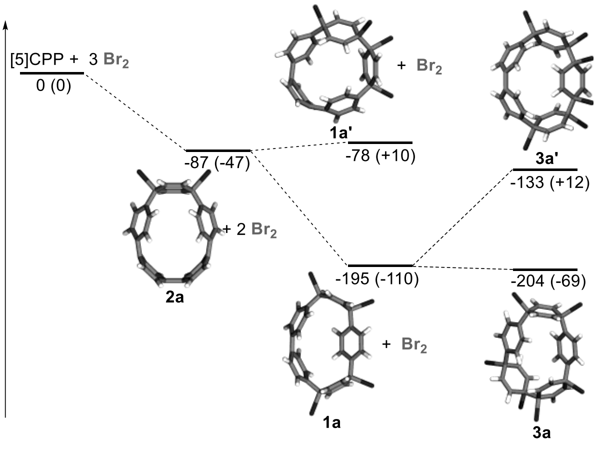


Figure 2. Relative energies of mono, bis, and tris-bromine adducts obtained by the DFT calculations. The given energy values (kJ mol^{-1}) are the relative heat of formation with respect to [5]CPP + 3 Br_2. The values in parentheses are the relative Gibbs energy (kJ mol^{-1}) at 298.15 K. Gray, white, and black represent carbon, hydrogen, and bromine atoms, respectively.

We next examined the reactivity of the addition product using **1a** as a model compound (Scheme 2). A substitution

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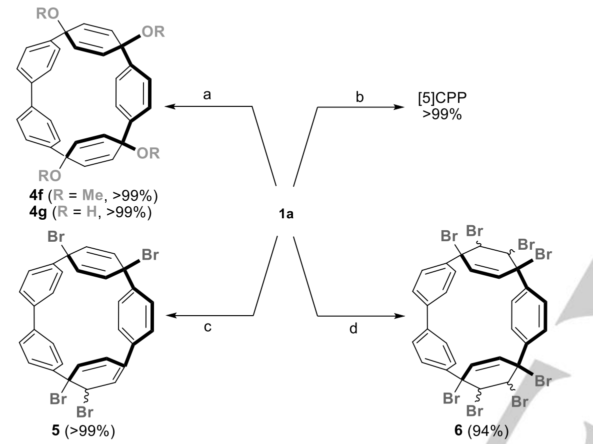
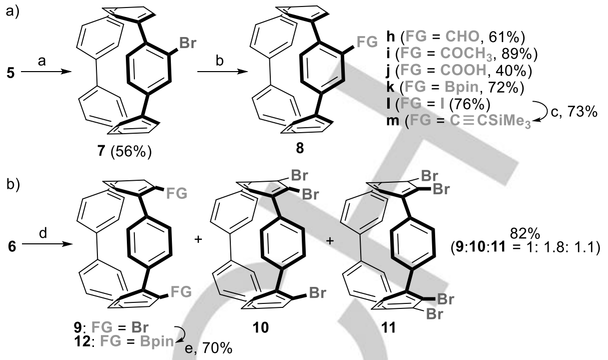
reaction took place when **1a** was treated with excess MeOH or H_2O in the presence of $NaHCO_3$ giving **4f** or **4g** quantitatively. When **1a** was treated with organometallic reagents or strong bases (2.0 equiv.), such as BuLi, lithium dibutylcuprate, lithium diisopropylamide (LDA), or *t*-BuOK, [5]CPP was quantitatively reformed despite its high strain energy. During the investigation, isomerization of one of the four bromine atoms on **1a** was observed at room temperature giving isomer **5**, which is 4 kJ mol^{-1} more stable than **1a** as determined by the DFT calculation. The isomerization completed quantitatively at 100 °C within 3 min. Moreover, when **1a** was treated with Br_2 (6.0 equiv.) in the presence of Fe powder (2.5 mol%), further bromination occurred to the already brominated rings giving octa-bromide **6** in 94% yield. While a 3:1 mixture of two stereoisomers were formed, the site-selectivity of the addition was completely controlled.



Scheme 2. Reactivity of bis-adduct **1a**. Reagents and conditions: (a) $NaHCO_3$ (5.0 equiv.), THF/MeOH or H_2O = 1:1, rt, 24 h. (b) R-M (BuLi, Bu_2CuLi, LDA, or *t*-BuOK, 2.0 equiv.), THF, -78 °C to rt, 15 min. (c) 100 °C, 3 min. (d) Fe (2.5 mol%), Br_2 (6.0 equiv.), CCl_4, rt, 1 h.

Tetra- and octabromides **5** and **6**, respectively, were then selectively converted to CPP derivatives (Scheme 3). When **5** was treated with a phosphazene superbase, *t*-BuN=P[N=P(NMe_2)$_3$]$_3$[18] (P_4-*t*-Bu, 2.0 equiv.), monobrominated [5]CPP **7** was obtained in 56% yield (Scheme 3a). Several bases were examined, but only P_4-*t*-Bu was successful for this transformation. Transmetallation of **7** with BuLi gave the corresponding lithiated [5]CPP, which was reacted with various electrophiles to give acyl- (**8h-j**), boryl- (**8k**), and iodo- (**8l**) [5]CPPs in good to high yields. Moreover, **8l** was coupled with alkyne in the presence of a Pd catalyst[19] affording mono-alkynylated [5]CPP **8m** in 73% yield. Multi-functionalized CPP derivatives could be also synthesized (Scheme 3b). When **6** was treated with P_4-*t*-Bu, (4.0 equiv.), a 1:1.8:1.1 mixture of bis- (**9**), tris- (**10**), and tetra- (**11**) bromo [5]CPPs were obtained in 82% combined yield. The products were easily separated in pure form by high-pressure liquid chromatography. While formation of regioisomers is possible for di- and tri-bromides, only a single isomer was observed in both compounds. Dibromide **9** was transformed to diborylated



Scheme 3. Transformation to CPP derivatives. Reagents and conditions: (a) P_4-*t*-Bu (2.0 equiv.), THF, -45 °C, 18 h. (b) 1) BuLi (1.2 equiv.), 2) DMF, $(CH_3CO)_2O$, CO_2/H^+, *i*-PrOBpin (pin = pinacol), or ICl, (1.2–1.4 equiv.), THF, -78 °C to rt. (c) Pd-PEPPSI-IPent[19] (5 mol%), $Me_3SnC{\equiv}CSiMe_3$ (1.4 equiv.), THF, rt, 6 h. (d) P_4-*t*-Bu (4.0 equiv), THF, -45 °C, 18 h. (e) 1) BuLi (2.4 equiv.), 2) *i*-PrOBpin (3.0 equiv.), THF, -78 °C to rt.

[5]CPP **12** in 70% yield by a bromine-lithium exchange reaction and subsequent borylation. To our knowledge, this is the first example of late-stage functionalization for the synthesis of multi-functionalized CPPs.

The effect of substituents on [5]CPP was investigated next. In the UV-vis spectra measured in CH_2Cl_2 (Supporting Information), all compounds exhibited intense absorption bands with the absorption maximum wavelengths (λ_{max}s) around 330–340 nm, which was nearly identical to that of the parent [5]CPP.[8d] A weak absorption band in the long-wavelength region of around 450–650 nm observed in each compound was assigned as a HOMO-LUMO transition by the time-dependent DFT calculations. No fluorescence was observed in any of the compounds.

The redox properties of **7**–**12** were investigated by cyclic voltammetry (CV) and differential pulse voltammetry (DPV) (Supporting Information). In the CV measurements, all derivatives showed irreversible oxidation and reduction waves, except for the boryl derivatives (**8k** and **12**) which did not exhibit clear redox behavior. In the DPV measurements, two oxidation events were observed in every compound, and the oxidation potentials were higher than that of [5]CPP. Among the bromine-substituted CPPs (**7** and **9**–**11**), the oxidation potential becomes higher as the number of bromine atom increases. The relative order of the oxidation potentials is in good agreement with that of the HOMO energies obtained by the DFT calculation. In contrast, the reduction potentials do not have good correlation with the calculated LUMO energies probably due to the participation of the functional groups for the reduction. Further studies are needed to clarify this point.

In summary, we have disclosed that the small [*n*]CPPs (*n* < 8) undergo a site-selective bis-bromine addition reaction instead of a substitution reaction. Furthermore, the addition products can be transformed to several substituted CPPs. While the transformation is limited to small CPPs, it is still valuable and beneficial considering unique electronic properties of small CPPs.[8a, 8d] These results not only unveil the novel reactivity of CPPs but also provide a new synthetic route to various CPP derivatives by late-stage functionalization

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Keywords: Cycloparaphenylene • Late-stage functionalization • Bromination • Addition • Strained molecule

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COMMUNICATION

Small [*n*]CPPs ($n < 8$) underwent a bis-bromine-addition reaction with high site-selectively producing tetrabromo-adducts in moderate to excellent yields. The [5]CPP-adduct was further converted to the octabromo product by a $FeBr_3$-catalyzed site-selective bromination reaction. The tetra- and octa-bromine adducts were then transformed to mono- to tetrabromo CPPs, which were further converted to several CPP derivatives.

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