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Editor's Choice

[9]Cycloparaphenylene: Nickel-mediated Synthesis and Crystal Structure

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Nickel-mediated synthesis of [9]cycloparaphenylene ([9]CPP) is described. L-shaped diphenylcyclohexane monomers underwent cyclotrimerization under the influence of [Ni(cod)$_2$]/bipy. X-ray crystal-structure analysis and VT NMR analysis of the thus-formed cyclic trimer confirmed its triangle structure and interesting cyclohexane-flipping behavior in solution. Cyclic trimer was converted to [9]CPP by acid-mediated aromatization. The first X-ray crystal structure of [9]CPP is also described.

Highly symmetric macrocyclic structures have fascinated chemists for decades and centuries. Cycloparaphenylenes ([*n*]CPPs) (Figure 1), simple and beautiful ring-shaped compounds in which *n* benzene rings are bound to each other at their para positions, have been targeted by synthetic chemists.[1] Recently, three groups included our own successfully achieved the synthesis of CPPs with strain-attenuating strategies utilizing cyclohexa-2,5-diene-1,4-diyl (Bertozzi et al.),[2] cyclohexane-1,4-diyl (Itami et al.),[3] and platinum (Yamago et al.).[4] To date, [*n*]CPP where *n* is 8, 9, 12, 14, 15, 16, or 18 has been synthesized.

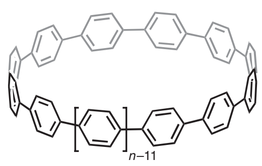
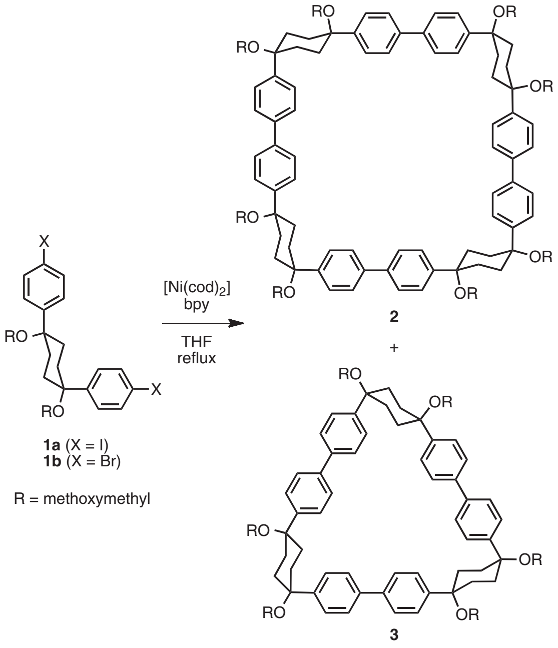


Figure 1. [*n*]Cycloparaphenylene ([*n*]CPP).

In an effort to provide CPP in useful quantities by a more concise, cost-effective, and scalable route, we recently developed a nickel-mediated synthesis of [12]CPP.[3c] One of the key reactions en route to [12]CPP has been the Ni^0-mediated "shotgun" macrocyclization of *cis*-1,4-bis(4-halophenyl)cyclohexane monomer **1a** or **1b** furnishing square-shaped tetramer **2** in moderate yield (20–25%, up to 1 g) as shown in Scheme 1. During our investigation trying to identify by-products in the Ni-mediated reaction of **1**, we found that the triangle-shaped trimer **3** could be also generated in the "shotgun" macrocyclization reaction. We herein report the synthesis and structure of cyclic trimer **3** and its conversion to [9]CPP. The ring structure of [9]CPP•2THF is also confirmed by X-ray crystallography.



Scheme 1. "Shotgun" synthesis of macrocycles **2** and **3**.

A single crystal generated from a by-product fraction in the macrocyclization was subjected to X-ray crystallography. Counter to our initial approximation, the compound was found not to be an acyclic oligomeric product but to be the cyclic trimer **3**.[5] During the crystallization, one EtOAc molecule was incorporated into **3** without any disorder. As shown in Figure 2, all three cyclohexane moieties in **3** adopt chair conformations with included angles of ca. 70°. To gain understanding of the stability of cyclic trimer **3**, strain energy was estimated by DFT calculation using B3LYP with a 6-31G(d) basis set. Strain energy of the framework of **3** was estimated to be 8.0 kcal mol^{-1}, which is 6.3 kcal mol^{-1} higher than that of **2** (see Supporting Information for detail[8]).

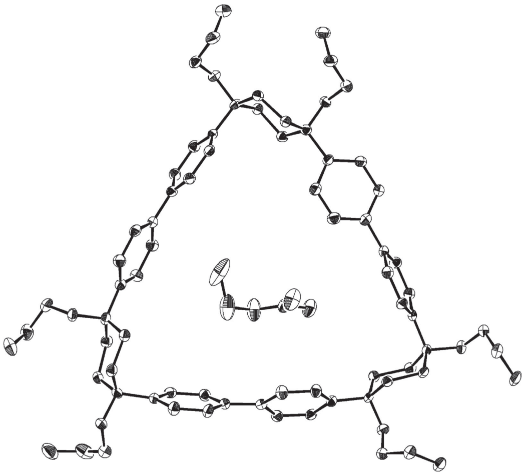


Figure 2. Crystal structure of **3**•EtOAc (50% thermal ellipsoids. All hydrogen atoms are omitted for clarity.).

Having identified the existence of a pathway forming cyclic trimer **3**, we re-examined the conditions of Ni-mediated macrocyclization (Table 1). The halogen atom of monomer (I for **1a**, Br for **1b**) did not affect the ring-size selectivity significantly

Table 1. Effect of halogen and concentration in Ni-mediated macrocyclization of **1**[a]

Entry	X (**1**)	[**1**]/mM	Yield of **2**[b]/%	Yield of **3**[b]/%
1	I (**1a**)	10	20	23
2	Br (**1b**)	10	22	25
3	Br (**1b**)	33	13	12
4	Br (**1b**)	5	23	32

[a]Reaction conditions: **1a** (X = I) or **1b** (X = Br) (0.82 mmol), [Ni(cod)$_2$] (1.64 mmol), 2,2′-bipyridyl (1.64 mmol), THF, reflux, 24 h. [b]Isolated yield.

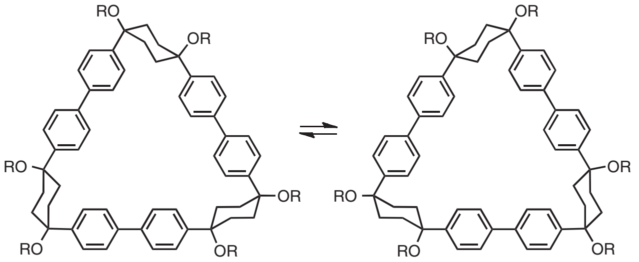


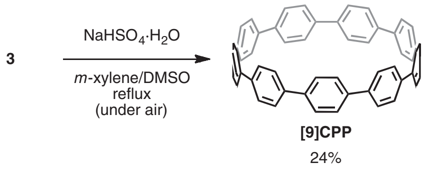
Figure 3. Ring flipping of cyclohexane moieties in **3** (R = methoxymethyl).

(Entries 1 and 2). In both reactions, **2** and **3** were formed in similar yields. However, concentration of monomer **1** had a certain effect (Entries 2–4). As somewhat expected, both the combined yield of macrocycles and the selectivity of trimer increased at lower concentration. It should be noted that under optimized conditions (5 mM of **1b**), more than half of **1b** could be converted into CPP precursors **2** (23%) and **3** (32%) by the "shotgun" method.

We then investigated the chair-flipping behavior of cyclohexane units of cyclic trimer **3** (Figure 3) by using VT NMR. As the flipping barrier of cyclohexane units of cyclic tetramer **2** has been already estimated (11 kcal mol^{-1}),[3c] knowing the relationship of thermodynamic behavior and macrocyclic ring size is important. The methyl signals of **3** in ^{1}H NMR was observed as one singlet (δ 3.43) at 50 °C and it became two singlets (δ 3.40 and 3.57) upon cooling to −60 °C. By simulating the spectral change observed from −20 to −40 °C, the flipping barrier of **3** was calculated to be the following values [$\Delta H^‡ = 10.1$ kcal mol^{-1}, $\Delta S^‡ = -7.6$ cal mol^{-1} K^{-1}]. Counter to our initial approximation, the cyclohexane units within the triangle structure of **3** were found to be very flexible.

Cyclic trimer **3** was then treated with $NaHSO_4 \cdot H_2O$ in refluxing *m*-xylene/DMSO under air to afford [9]CPP in 24% isolated yield (Scheme 2). Lower yield compared to 65% attained in the synthesis of [12]CPP may be due to higher strain energy of [9]CPP (65.6 kcal mol^{-1}) than that of [12]CPP (48.1 kcal mol^{-1}) calculated with B3LYP/6-31G(d).[6] ^{1}H and ^{13}C NMR spectra of [9]CPP showed the same chemical shifts (δ_H 7.52, δ_C 127.3, 137.9) as previously reported by Bertozzi.[2]

X-ray crystallography of [9]CPP was then performed. A pale green single crystal of [9]CPP was obtained by recrystallization with THF/pentane at 10 °C. In the solid state, [9]CPP was slightly distorted to form an ellipsoid (Figure 4) unlike the circular structure of [12]CPP.[3c] Two THF molecules were incorporated in the [9]CPP ring with disordering. Averaged bond lengths of [9]CPP and [12]CPP are summarized in Table 2. From the lengths of C_{ipso}–C_{ipso}, C_{ipso}–C_{ortho}, and C_{ortho}–C_{ortho} bonds, the benzenoid characters are reasonably preserved in [9]CPP. However, one can see that C_{ipso}–C_{ipso} and C_{ortho}–C_{ortho} bond lengths of [9]CPP are shorter than those of [12]CPP. This clearly shows that the contribution of the "quinoid" property of CPP becomes larger as the ring size of CPP decreases.[7]



Scheme 2. Synthesis of [9]CPP by deprotection/aromatization of **3**.

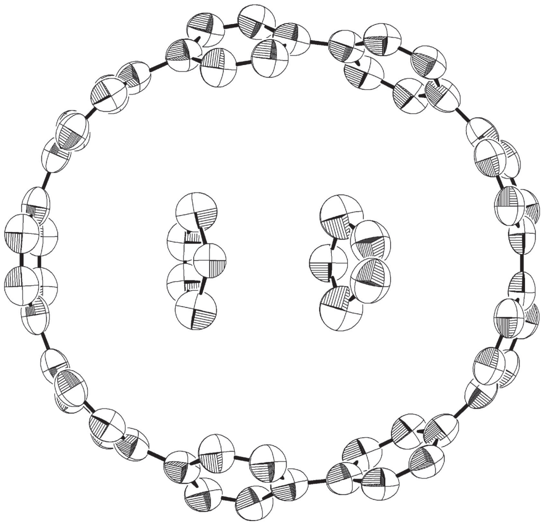


Figure 4. Crystal structure of [9]CPP•2THF (50% thermal ellipsoids. All hydrogen atoms and a minor part of disordered THF molecules are omitted for clarity. Half of the entire structure constitutes an asymmetric unit.).

Table 2. Average bond lengths (Å) of [9]CPP and [12]CPP

	C_{ipso}–C_{ipso}	C_{ipso}–C_{ortho}	C_{ortho}–C_{ortho}
[9]CPP	1.468(6)	1.398(6)	1.362(6)
[12]CPP[3c]	1.481(5)	1.394(5)	1.381(5)

In summary, we have synthesized [9]CPP through the Ni-mediated cyclotrimerization of L-shaped unit **1a** and **1b** and follow-up aromatization. Overall yield of [9]CPP from commercially available materials (1,4-dihalobenzene and cyclohexane-1,4-dione) is 6.2% in four steps. The X-ray crystal-structure analysis of [9]CPP not only confirmed that benzenoid characters are reasonably preserved in [9]CPP, but also uncovered the emergence of a "quinoid" property in smaller CPP.

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References and Notes

1 a) V. C. Parekh, P. C. Guha, *J. Indian Chem. Soc.* **1934**, *11*, 95. b) R. Friederich, M. Nieger, F. Vögtle, *Chem. Ber.* **1993**, *126*, 1723.

2 R. Jasti, J. Bhattacharjee, J. B. Neaton, C. R. Bertozzi, *J. Am. Chem. Soc.* **2008**, *130*, 17646.

3 a) H. Takaba, H. Omachi, Y. Yamamoto, J. Bouffard, K. Itami, *Angew. Chem., Int. Ed.* **2009**, *48*, 6112. b) H. Omachi, S. Matsuura, Y. Segawa, K. Itami, *Angew. Chem., Int. Ed.* **2010**, *49*, 10202. c) Y. Segawa, S. Miyamoto, H. Omachi, S. Matsuura, P. Šenel, T. Sasamori, N. Tokitoh, K. Itami, *Angew. Chem., Int. Ed.* **2011**, *50*, in press. doi:10.1002/anie.201007232

4 S. Yamago, Y. Watanabe, T. Iwamoto, *Angew. Chem., Int. Ed.* **2010**, *49*, 757.

5 Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-809162 (**3**•EtOAc) and CCDC-809161 ([9]CPP•2THF). Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html.

6 Y. Segawa, H. Omachi, K. Itami, *Org. Lett.* **2010**, *12*, 2262.

7 a) K. Tahara, Y. Tobe, *Chem. Rev.* **2006**, *106*, 5274. b) M. N. Jagadeesh, A. Makur, J. Chandrasekhar, *J. Mol. Model.* **2000**, *6*, 226.

8 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.