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Facile Intramolecular Cyclization in Oxidative Coupling of Acetylenes Linked to 1,3-Positions of Benzene: Strained [12]Metacyclophanedienetetrayne System

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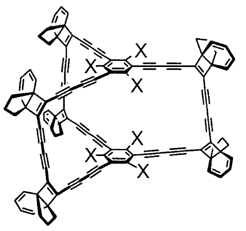
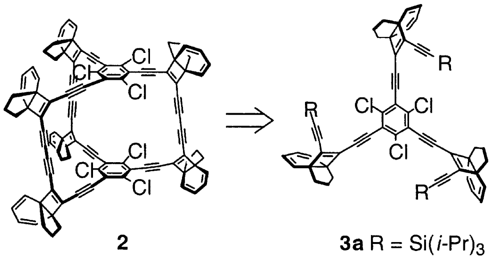
Abstract: Oxidative coupling of ethynylpropellane linked to 1,3,5-position of a benzene core **3b** did not give the cage dimer **2** but the dimer **4** having a strained [12]metacyclophanedienetetrayne system. The spectral and structural features of the novel ring system were revealed for the simple dibenzo derivative **6**, which was also prepared efficiently by the intramolecular cyclization of the open-chain precursor.

Three-dimensional, cagelike cyclophanes have been attracting a great deal of interest as receptors of organic molecules[1] and as precursors of carbon cage fullerenes.[2] Rubin[3] and we[4] reported the individual endeavor to produce C_{60} from [16.16.16](1,3,5)cyclophanetetracosayne and its chloro derivative, which were formed from their appropriate precursors having cyclobutenedione or [4.3.2]-propelladiene units (compounds **1a**, **1b**) as masking groups of a triple bond, by the cyclization of the polyyne chains.[5] Although C_{60}^{+} and C_{60}^{-} ions were formed in the laser-desorption mass spectra (LDMS) of the precursors, preparative-scale synthesis of C_{60} has not been achieved by this method.[6] We extended this method to the formation of [12.12]paracyclophanedodecayne from the corresponding propellane precursor and the stepwise dechlorination to form of C_{36}^{-} in the LDMS.[7,8] We also designed a C_{48} precursor **2** which would be prepared by dimerization of **3b** by oxidative *intermolecular* coupling of each alkyne terminals anchored by a 1,3,5-substituted benzene (Scheme 1). This paper reports the formation of unexpected dimer **4**, having a strained [12]metacyclophanedienetetrayne ring system, derived by *intramolecular* coupling followed by dimerization. To confirm the generality of the mode of cyclization, we also investigated the oxidative coupling of simple benzo-fused diyne **5b** which furnished [12]metacyclophanedienetetrayne **6** in a high yield. The spectroscopic and structural features of **6** and the relationship between the mode of cyclization and the structure of the precursory alkynes are discussed.



1a X = H
1b X = Cl

SCHEME 1



2

3a R = Si(*i*-Pr)$_3$
3b R = H

The Sonogashira coupling of trichlorotriiodobenzene **7**[4b] with the monoprotected propellatriene **8**[4b] gave the triad **3a** in 59% yield (Scheme 2).[9] After deprotection of the TIPS group, the terminal acetylene **3b** was subjected to oxidative coupling with $Cu(OAc)_2$ under high dilution conditions just like the preparation of **1a** and **1b**, forming a dimeric product in 85% yield. However, the ^{13}C NMR of the product exhibited 7 and 12 groups of peaks due to sp and sp^2 carbons, respectively, which were far more than those expected for the cage dimer **2**. Moreover, the presence of an sp^2 signal at 152 ppm suggested the presence of a distorted benzene ring.[10] Such a low field resonance was not observed in the cage compounds **1a** and **1b**. These results indicated that the product was not **2** but **4** which was formed by *intramolecular* oxidative

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[1] For a review: Diederich, F. *Cyclophanes*; The Royal Society of Chemistry: Cambridge, 1991.

[2] For reviews: (a) Rubin, Y. *Chem. Eur. J.* **1997**, *3*, 1009. (b) Bunz, U. H. F.; Rubin, Y.; Tobe, Y. *Chem. Soc. Rev.* **1999**, *28*, 107. (c) Tobe, Y. In *Advances in Strained and Interesting Organic Molecules*; Halton, B., Ed.; JAI Press: Greenwich, 1999; Vol. 7, p 153.

[3] (a) Rubin, Y.; Parker, T. C.; Khan, S. I.; Holliman, C. L.; McElvany, S. W. *J. Am. Chem. Soc.* **1996**, *118*, 5308. (b) Rubin, Y.; Parker, T. C.; Pastor, S.; Jalisatgi, S.; Boulle, C.; Wilkins, C. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 1226.

[4] (a) Tobe, Y.; Nakagawa, N.; Naemura, K.; Wakabayashi, T.; Shida, T.; Achiba, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4544. (b) Tobe, Y.; Nakagawa, N.; Kishi, J.; Sonoda, M.; Naemura, K.; Wakabayashi, T.; Shida, T.; Achiba, Y. *Tetrahedron* **2001**, *57*, 3629.

[5] A similar mechanism was proposed: Fallis, A. G. *Can. J. Chem.* **1999**, *77*, 159.

[6] Recently, preparative scale synthesis of C_{60} was accomplished by flash vacuum pyrolysis of a polycyclic chlorinated hydrocarbon: Scott, L. T.; Boorum, M. M.; McMahon, B. J.; Hagen, S.; Mack, J.; Blank, J.; Wagner, H.; de Meijere, A. *Science* **2002**, *295*, 1500.

[7] Tobe, Y.; Furukawa, R.; Sonoda, M.; Wakabayashi, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 4072.

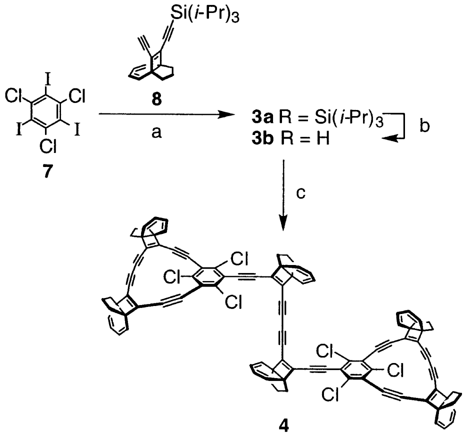
[8] For representative examples for the formation of small carbon clusters from organic precursors: (a) Prinzbach, H.; Weiler, A.; Landenberger, P.; Wahl, F.; Wörth, J.; Scott, L. T.; Gelmont, M.; Olevano, D.; Issendorff, B. v. *Nature* **2000**, *407*, 60. (b) Manini, P.; Amrein, W.; Gramlich, V.; Diederich, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4339.

[9] Compounds **3a**, **3b**, and **4** were unseparable mixtures of diastereomers, of which one isomer is drawn for clarity.

[10] (a) Both sp and sp^2 carbon signals of highly strained, acetylene-bridged metacyclophanes exhibit downfield shifts: (a) Kawase, T.; Ueda, N.; Darabi, H. R.; Oda, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1556. (b) Kawase, T.; Ueda, N.; Oda, M. *Tetrahedron Lett.* **1997**, *38*, 6681. (c) Kawase, T.; Hosokawa, Y.; Kurata, H.; Oda, M. *Chem. Lett.* **1999**, 745. (d) Hosokawa, Y.; Kawase, T.; Oda, M. *Chem. Commun.* **2001**, 1948.

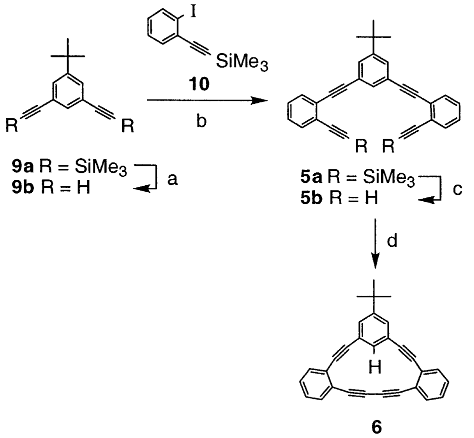
10.1021/jo0268299 CCC: \$25.00

SCHEME 2[a]



[a] Reaction conditions: (a) $Pd(PPh_3)_4$, CuI, $(i\text{-}Pr)_2NH$, THF, reflux, 59%; (b) TBAF, AcOH, THF, rt; (c) $Cu(OAc)_2$, pyridine, toluene, rt, 85% from **3a**.

SCHEME 3[a]



[a] Reaction conditions: (a) K_2CO_3, MeOH, THF, rt, 99%; (b) $Pd(PPh_3)_4$, CuI, Et_3N, toluene, 45 °C, 58%; (c) K_2CO_3, MeOH, THF, rt; (d) $Cu(OAc)_2$, pyridine, toluene, rt, 83% from **5a**.

coupling followed by dimerization. To confirm the generality of the mode of cyclization, we investigated the oxidative coupling of simple benzo-fused diyne **5b**, which was prepared from diethynylbenzene **9b**[11] and iodoalkyne **10**[12] (Scheme 3). As a result, *intramolecular* coupling of **5b** proceeded smoothly to afford cyclophane **6** in 83% yield. No dimer was detected (LCMS).

The downfield-shifted, sp^2 ^{13}C NMR signal of **6** appeared at 142.3 ppm.[13] The most characteristic feature of the ^{1}H NMR spectrum of **6** is the remarkable downfield shift of the intraannular aromatic proton which appears at 8.58 ppm owing to the anisotropic deshielding effect of the transannular triple bonds.[14] To clarify the deformation of the triple bonds of **6**, an X-ray crystallographic analysis was carried out. A crystal suitable for the X-ray analysis was grown from dichloromethane. An ORTEP drawing is shown in Figure 1.[15] Although the diyne moiety is not deformed (bond angles 177−179°) the acetylene carbons (C(12), C(13), C(24), and C(25)) are moderately distorted from linearity (165−172°). The *tert*-butyl-substituted benzene ring is not much distorted ($\alpha = 2.3°$ (for plane C(14)−C(22)−C(23)) and 0.6° (for plane C(15)−C(16)−C(21)), $\beta = 4.6°$ (for bond C(13)−C(14)) and 4.9° (for bond C(22)−C(24))).[16] The distance between H(9) and the transannular sp carbons (C(3) and C(4)) is relatively short (2.76 and 2.74 Å, respectively). In the crystal, owing to the bulky *tert*-butyl group, the molecules of **6** do not pack in such a manner that topochemical polymerization would give poly(diacetylene) or onion-like carbon materials upon heating as observed in the related molecules.[17] A packing diagram is shown in the Supporting Information.

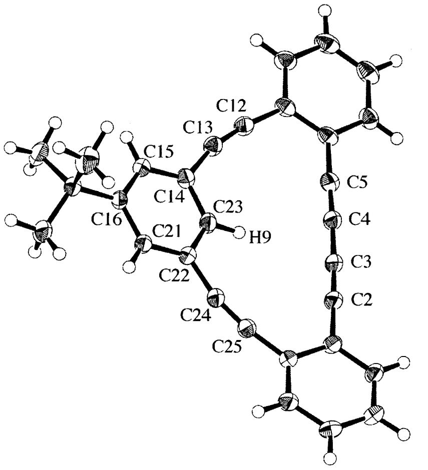


FIGURE 1. ORTEP drawing of compound **6**.

With regard to the distance between the reacting terminals, the 1,3,5- or 1,3-[(*o*-ethynylphenyl)ethynyl]benzene systems such as **3b** and **5b** must be allotted the place between 1,3,5-[(*o*-ethynylphenyl)butadiynyl]benzene **11**,[2a,18] which formed the cage dimer related to **1a** and **1b**, and 1,3,5-(*o*-ethynylphenyl)benzene **12**,[14] which underwent intramolecular oxidative coupling (Table 1). These results clearly indicate that the distance between the alkyne terminals is critical to the mode of oxidative coupling. In the 1,4-disubstituted benzene system, however, the oxidative coupling of [(*o*-ethynylphenyl)ethynyl]benzene **13**[19,20] gave the corresponding dimer while (*o*-

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(11) Shultz, D. A.; Lee, H.; Kumar, R. K.; Gwaltney, K. P. *J. Org. Chem.* **1999**, *64*, 9124.

(12) (a) Baxter, P. N. W. *J. Org. Chem.* **2001**, *66*, 4170. (b) Lavastre, O.; Cabioch, S.; Dixneuf, P. H.; Vohlidal, J. *Tetrahedron* **1997**, *53*, 7595.

(13) The lowest-field signal of **6** which appeared at 152 ppm was due to the aromatic carbon attached to the *tert*-butyl group.

(14) (a) Similar deshielding effect was observed in a [8]metacyclophanedienediyne system: Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Org. Lett.* **2002**, *4*, 11.

(15) X-ray crystal structural analysis for **6**: 0.30 × 0.30 × 0.50 mm^3, space group $P\bar{1}$, scan range $4 < 2\theta < 60°$, $a = 9.5375(1)$ Å, $b = 11.4548(2)$ Å, $c = 11.7388(4)$ Å, $\alpha = 100.819(1)°$, $\beta = 110.902(2)°$, $\gamma = 109.536(2)°$, $V = 1058.23(5)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.194$ g cm^{-3}, $\mu = 0.68$ cm^{-1}, 20651 unique reflections at −100 °C, of which 6160 were taken as observed [$I_o \geq 2.0\sigma(I)$], $R = 0.116$, $R_w = 0.188$.

(16) For the definition of the deformations angles of strained cyclophanes, see: Bickelhaupt, F.; de Wolf, W. H. In *Advances in Strain in Organic Chemistry*; Halton, B., Ed.; JAI Press: Greenwich, 1993; Vol. 3, p 185.

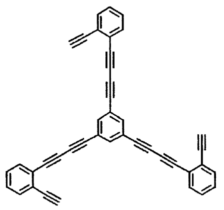
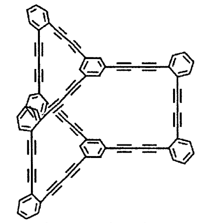
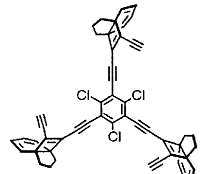
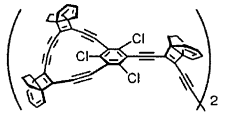
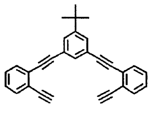
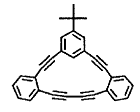
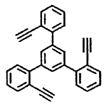
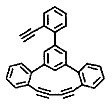
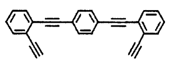
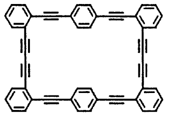
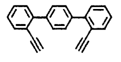
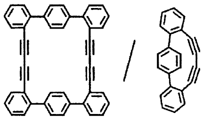
(17) (a) Boese, R.; Matzger, A. J.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1997**, *119*, 2052. (b) Baldwin, K. P.; Matzger, A. J.; Scheiman, D. A.; Tessier, C. A.; Vollhardt, K. P. C.; Youngs, W. J. *Synlett* **1995**, 1215.

(18) For the corresponding cyclobutenyl case, see refs 3 and 4.

(19) (a) Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 385. (b) Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Org. Lett.* **2000**, *2*, 3189.

(20) For the corresponding cyclobutenyl case, see ref 7.

TABLE 1. Relationship between the Structure and the Mode of Cyclization of Acetylenes Linked to a Benzene Core

Compound	Mode of Coupling	Ref.
 **11**	 Intermolecular	2a
 **3b**	 Intramolecular	this work
 **5b**	 Intramolecular	this work
 **12**	 Intramolecular	14
 **13**	 Intermolecular	19
 **14**	 Intermolecular / Intramolecular	19

ethynylphenyl)benzene **14**[19] underwent both inter- and intramolecular coupling, because the distance between the reacting terminals are larger than those of the corresponding meta-substituted benzenes.

Experimental Section

1,3,5-Trichloro-2,4,6-tris[[11-(triisopropylsilyl)ethynyl-[4.3.2]propella-2,4,10-trien-10-yl]ethynyl]benzene (3a). To a mixture of $Pd(PPh_3)_4$ (156 mg, 0.135 mmol), CuI (51 mg, 0.27 mmol), chloroiodobenzene **7**,[21,4b] and diisopropylamine (0.75 mL) was added a solution of diethynyl[4.3.2]propellatriene **8**[4b] (2.35 g, 6.75 mmol) in THF (10 mL) under a nitrogen atmosphere. The mixture was stirred at 70 °C for 24 h. Additional solution of **8** (523 mg, 1.50 mmol) in THF (2 mL) was added, and the solution was stirred for an additional 20 h. The reaction mixture was diluted with dilute HCl and ether and extracted. The extract was washed with saturated $NaHCO_3$ solution followed by brine and dried over $MgSO_4$. After removal of the solvent, purification by flash chromatography followed by preparative HPLC afforded **3a** as a brown solid (1.08 g, 59%): mp 78−80 °C; ^{1}H NMR (270 MHz, $CDCl_3$, 30 °C) δ 5.93−5.82 (m, 12H), 2.03 (dt, $J = 12.9$, 5.4 Hz, 6H), 1.67−1.49 (m, 6H), 1.35−1.22 (m, 6H), 1.09 (s, 63H); ^{13}C NMR (67.5 MHz, $CDCl_3$, 30 °C) δ 138.1 (s), 135.8 (s), 130.8 (s), 128.4 (d), 128.3 (d), 122.6 (s), 121.9 (d), 121.8 (d), 99.7 (s), 98.5 (s), 93.2 (s), 87.5 (s), 56.7 (s), 56.1 (s), 33.1 (t), 33.0 (t), 18.9 (t), 18.7 (q), 11.3 (d).

Deprotection Followed by Oxidative Coupling of 3a by the Eglinton's Method:[22] **Metacyclophane Dimer 4.** To a solution of acetic acid (1.3 mL, 2.3 mmol) and **3a** (183 mg, 0.150 mmol) in THF (10 mL) was added dropwise 1.5 mL of a solution of tetrabutylammonium fluoride (1.0 M, 1.5 mmol) in THF under a nitrogen atmosphere. The mixture was stirred at room temperature for 2 h. The reaction mixture was extracted with toluene and worked up as usual. The extract was concentrated to ca. 100 mL in vacuo. To an another flask charged with $Cu(OAc)_2$ (2.72 g, 15.0 mmol) and pyridine (225 mL) under a nitrogen atmosphere was added dropwise the above toluene solution (100 mL) through a Hershberg dropping funnel at room temperature during 32 h, and the mixture was stirred for 10 h. During the reaction, the flask was covered with an aluminum foil to protect the product from the room light. After removal of the solvent in vacuo, the residue was passed through a short plug of SiO_2 and the solvent was removed to afford a crude product. Purification by flash chromatography followed by preparative HPLC afforded **4** as a yellowish brown solid (95 mg, 85%): ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C) δ 5.93−5.76 (m, 24H), 2.08−2.00 (m, 8H), 1.95−1.91 (dd, $J = 12.8$, 5.7 Hz, 4H) 1.69−1.62 (m, 6H), 1.59−1.48 (m, 6H), 1.35−1.21 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, 30 °C) δ 152.38 (s), 152.29 (s), 139.98 (s), 139.89 (s), 135.13 (s), 134.88 (s), 132.39 (s), 128.02 (d), 127.90 (d), 127.44 (d), 127.40 (d), 127.31 (d), 127.26 (d), 124.76 (s), 122.18 (d), 121.07 (s), 98.33 (s), 95.73 (s), 92.78 (s), 89.32 (s), 85.16 (s), 83.01 (s), 82.99 (s), 80.21 (s), 57.25 (s), 56.76 (s), 56.37 (s), 55.81 (s), 55.79 (s) 33.34 (t), 33.22 (t), 33.13 (t), 29.73 (t), 18.97 (t), 18.90 (t); MS (APCI) *m/z* 1494−1504 (the most abundant peak at 1496, M^-).

Deprotection Followed by Oxidative Coupling of 5a by the Eglinton's Method:[22] **Dibenzo[12]metacyclophane-tetrayne (6).** Metacyclophanetetrayne **6** was prepared in a manner similar to that of the synthesis of metacyclophane dimer **4** using K_2CO_3 (83 mg, 0.60 mmol), MeOH (10 mL), and THF (10 mL) for deprotection of **5a** and $Cu(OAc)_2$ (5.45 g, 30.0 mmol), pyridine (450 mL), and toluene (200 mL) for intramolecular oxidative coupling of **5b**. Purification by flash chromatography followed by preparative HPLC afforded **6** as a colorless solid (95 mg, 83%): dec >220 °C; ^{1}H NMR (270 MHz, $CDCl_3$, 30 °C) δ 8.58 (t, $J = 1.5$ Hz, 1H), 7.56−7.53 (m, 2H), 7.43−7.39 (m, 2H), 7.36 (d, $J = 1.5$ Hz, 2H), 7.33 (td, $J = 7.3$, 1.7 Hz, 2H), 7.29 (td, $J = 7.3$, 1.7 Hz, 2H), 1.33 (s, 9H); ^{13}C NMR (67.5 MHz, $CDCl_3$, 30 °C) δ 151.94 (s), 142.29 (d), 132.61 (d), 129.62 (d), 129.00 (d), 127.92 (d), 127.20 (s), 126.26 (s), 124.67 (d), 123.47 (s), 96.28 (s), 91.88 (s), 82.30 (s), 78.43 (s), 34.98 (s), 31.30 (q); UV ($CHCl_3$, 30 °C) λ_{max} (log ϵ) 289 (4.90), 328 (4.12), 339 (3.99), 390 (3.67) nm; MS (FAB) *m/z* 380 (M^+); HRMS calcd for $C_{30}H_{20}$ 380.1565, found 380.1558.

Supporting Information Available: Experimental procedure for compounds **5a** and **9b**, ^{1}H NMR and ^{13}C NMR spectra of compounds **3a**, **4**, **5a**, **6**, and **9b**, UV/vis spectrum of compound **6**, details of the X-ray diffraction data, and structure of compound **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0268299

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(22) (a) Eglinton, G.; Galbraith, A. R. *Proc. Chem. Soc.* **1957**, 350. (b) Behr, O. M.; Eglinton, G.; Galbraith, A. R.; Raphael, R. A. *J. Chem. Soc.* **1960**, 3614.