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A Novel Strained Undecadiyne Cyclophane with Interesting Dienophilic Character

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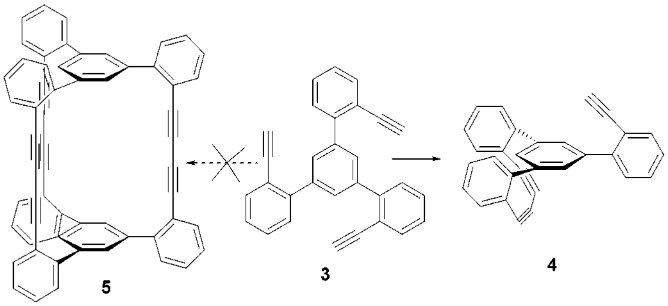
ABSTRACT



Copper-mediated oxidative coupling of 3 afforded the strained product 4 from intramolecular cyclization rather than the triply bridged cyclophane 5 from dimerization. X-ray analysis of the bromo derivative 15 confirmed the distorted nature of the butadiyne bridge (bond angles 164.1° and 153.4°). The distortion in the strained triple bond is reflected in its cycloaddition reactivity. Cyclopentadiene and 1,3-cyclohexandiene afforded the new adduct macrocycles 16 and 17, respectively.

The synthesis and design of new cyclophanes[1] and assorted cage compounds[2] with novel shapes and supramolecular geometries[3] continue to be topics of current interest. We have established previously that the *para*-cyclophanes with eneyne bridges composed of double bonds[4] and/or benzene rings[5] may be readily prepared by sequential palladium(0)- and copper(II)-mediated couplings. The combination of the number and type of unsaturated linkages in these molecules creates a twisted conformation that imparts helical chirality[6] to the assembled molecule, and yet the free rotation of the central aryl ring is not restricted by the bridge.

Previously, our initial attempts to synthesize a triply bridged member of these families failed.[7] It was hoped that the increased stability of the phenyl-yne bridges in the triyne

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[†] For enquiries regarding X-ray analysis.

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[5] (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.

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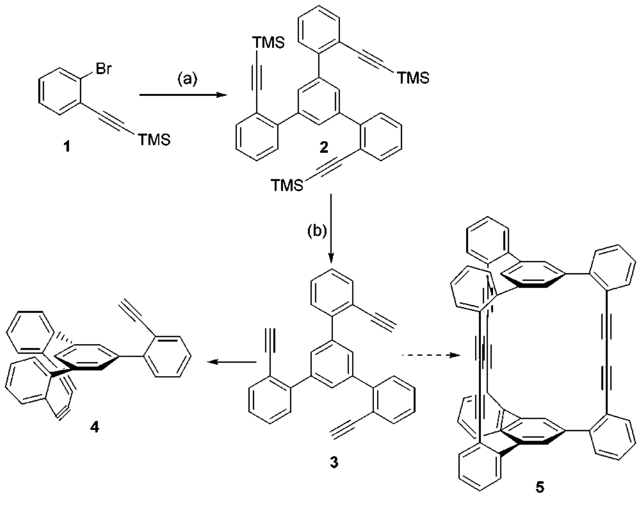
Scheme 1[a]



[a] (a) (1) *n*-BuLi, THF, −78 °C, 30 min;. (2) $ZnBr_2$, THF, 0 °C, 15 min; (3) $Pd(PPh_3)_4$, 1,3,5-tribromobenzene, THF, 65 °C, 15 h, 90%; (b) K_2CO_3, MeOH, THF, H_2O, 3 h, 85%.

system **3** (Scheme 1) might assist the dimerization to **5**. The intramolecular reaction to generate **4**, frequently encountered as a competing pathway[8,9] in related compounds, appeared to be precluded due to the strained nature of the diyne unit. Consequently, it was anticipated that **5** could be assembled by intermolecular coupling in the presence of copper acetate. Two related intermolecular isomers (not illustrated) could arise from joining either one or two of the terminal acetylenes.

Compound **1** [(2-bromophenylethynyl)trimethylsilane)] was converted to its organozincate[10] in situ by halogen−metal exchange with *n*-BuLi, followed by transmetalation with $ZnBr_2$ and addition of tetrakistriphenylphosphine−palladium(0) and 1,3,5-tribromobenzene (15 h reflux) to afford **2** in 90% yield. Deprotection of **2** with K_2CO_3 in MeOH/THF provided **3** (85%), which was subjected to the different Cu-mediated oxidative coupling conditions summarized in Table 1.[9c,11,12]

Table 1. Oxidative Coupling Conditions to **4**

entry	conditions	yield (%)
1	CuCl, TMEDA, PhH, 15 h	2
2	$Cu(OAc)_2$ (9 equiv), 3:1 pyr:Et_2O, 3 d	6
3	$Cu(OAc)_2$ (9 equiv), 3:1 pyr:Et_2O, 3 h	52
4	$Cu(OAc)_2$ (9 equiv), 3:1 pyr:Et_2O, Δ, 3 h	26
5	$Cu(OAc)_2$ (18 equiv), 3:1 pyr:Et_2O, 4 h	62
6	$Cu(OAc)_2$ (25 equiv), CuCl (20 equiv), pyr, Δ, 3 d	0

Exposure of **3** to $Cu(OAc)_2$-mediated coupling (3 equiv/acetylene) afforded the unexpected product, the highly strained cyclophane **4** in 52% yield (entry 3)! Extension of the reaction time to 3 days led to decomposition and a diminished yield of 6%. Similarly, increasing the rate of reaction by heating at reflux also reduced the yield (26%). Doubling the number of equivalents of $Cu(OAc)_2$ from 3 per acetylene to 6 per acetylene increased the yield to 62% (entry 5). Unfortunately, oxidative coupling using modified conditions[6b] produced no isolatable products (entry 6) and exposure of **3** to CuCl-mediated oxidation gave only traces of **4** (entry 1).

Thus, the only product observed from the attempted dimerization of **3** was the unusual strained cycle **4**. There is considerable interest in strained cycloalkenes and bent polyynes. In these molecules, the normal linear geometry for the C−C≡C bond is often severely distorted (165−155°). However, previous studies have confirmed that large deviations from the idealized bond angle of 180° can be tolerated, and consequently these bonds are significantly more flexible than their C−C≡C and C−C−C counterparts. Figure 1 illustrates some early examples (**6**,[13] **7**,[14] and **8**[15]) as well as

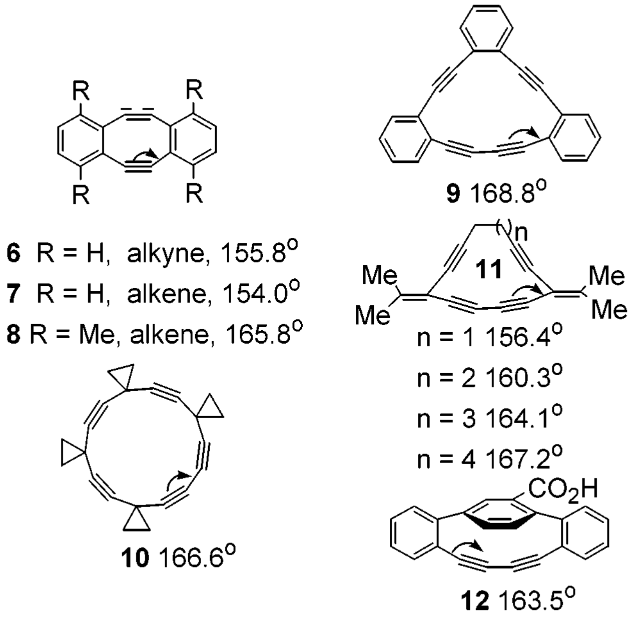


Figure 1.

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[8] For some tribridged carbocyclic systems, see: (a) Wu, Z.; Lee, S.; Moore, J. S. *J. Am. Chem. Soc.* **1992**, *114*, 8730. (b) Yu, Z.; Kahr, M.; Walker, K. L.; Wilkins, C. L.; Moore, J. S. *J. Am. Chem. Soc.* **1994**, *116*, 4537. (c) R. Faust, *Angew. Chem., Int. Ed.* **1998**, *37*, 2825. (d) Rubin, Y.; Parker, T. C.; Khan, S. I.; Holliman, C. L.; McElvany, S. W. *J. Am. Chem. Soc.* **1996**, *118*, 5308. (e) Tobe, Y.; Nakagawa, N.; Naemura, K.; Wakabayashi, T.; Shida, T.; Achiba, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4544. (f) Rubin, Y.; Parker, T. C.; Pastor, S. J.; Jalisatgi, S.; Boulle, C.; Wilkins, C. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 1226.

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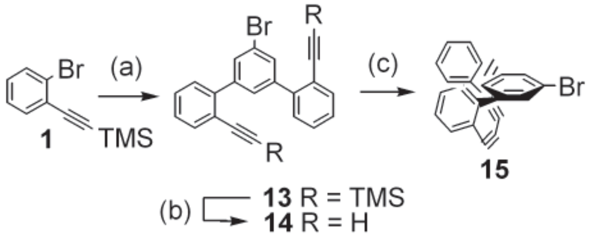
more recent diyne systems by Vollhard (**9**),[16] Scott, Smith, and de Meijere (**10**),[17] and Tykwinski (**11**)[18] and their respective co-workers and ourselves (**12**).[5]

The cyclophane **4** was isolated as a reddish-orange powder, which decomposed slowly upon standing (3 days). This property precluded growing crystals suitable for X-ray analysis. Consequently, a more stable derivative of **4**, compound **15**, containing an aromatic bromine substituent to aid crystallization and structure elucidation, was constructed from **1** in a parallel manner to that used above (Scheme 2).

Scheme 2[a]



[a] (a) (1) *n*-BuLi, THF, −78 °C, 30 min; (2) $ZnBr_2$, THF, 0 °C, 15 min. (3) $Pd(PPh_3)_4$, 1,3,5-tribromobenzene (0.5 equiv), THF, 65 °C, 15 h, 67%; (b) K_2CO_3, MeOH, THF, H_2O, 3 h, 99%; (c) $Cu(OAc)_2$ (6 equiv), pyr:Et_2O 3:1, 3 h, 60%.

Oxidative dimerization of **14** gave exclusively the strained undecadiyne **15**, corresponding to the intramolecular cyclization observed previously. Crystals of **15** were obtained as thin needles from the slow evaporation of a dichloromethane solution. This process created a dark film from competitive decomposition which was removed from the crystals prior to analysis.

The crystal structure (Figure 2) revealed the strained nature of the acetylene linkages within the cyclophane. The phenyl units remain free of any distortion and adopted an orientation that forced the acetylene linkages below the plane of the central benzene ring. This conformation places the *para* hydrogen atom just above the diacetylene bridge. The ^1H NMR signal for this hydrogen in **14** appears as a triplet at 7.89 ppm, but experiences a significant deshielding effect upon cyclization to **15**, shifting to 8.25 ppm. This hydrogen occupied the space between the bridge and the central benzene ring and thus no cavity is evident, despite the appearance of the diagram.

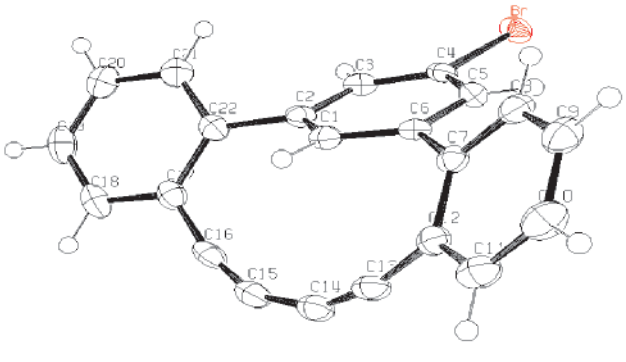


Figure 2. X-ray crystal structure of **15**.[19]

The adjacent acetylene units are distorted, as a consequence of the cyclization, and deviate ~16−26.6° from the normal 180° angle. The bond angles of the triple bonds are C(12)−C(13)−C(14) 164.1° and C(14)−C(15)−C(16) 153.4°. These bond angle distortions are greater than those observed previously for most other related diyne systems (Figure 1). Additional values for the largest angle deviation for related diynes are 165.8°,[20] 172.8°,[21] 168.0°,[22] and 164.5.[23] The other acetylene bond angles in **15**, C(13)−C(14)-C(15) and C(15)−C(16)-C(17), have similar values of 153.5° and 164. 6°, respectively.

The ^{13}C NMR chemical shifts of the sp carbons also experience a deshielding due to ring strain. The chemical shifts of the acetylenic carbons in **15** are 87.1 and 107.4 ppm. These values are consistent with the trend described by Tykwinski and co-workers[18] for strain in butadiyne bridges as the chemical shifts for the sp carbons in **11** ($n = 1$) appeared at 86.5 and 108.1 ppm for bond angles of 159.4° and 156.2°.

In most circumstances, very reactive inverse demand dienes such as cyclopentadieneones are required to effect [4 + 2] cycloadditions with diphenylacetylene and 1,4-diphenylbutadiynes.[24] In the case of the cyclic “dibutynyl” system **15**, the very strained nature of the butadiyne bridge was confirmed via standard Diels−Alder reactions with 1,3-cyclohexadiene and cyclopentadiene (Scheme 3). The cyclophane **15** underwent cycloaddition with cyclopentadiene (sealed tube, 120 °C) to give the bicycloadduct **16** in 28% yield. The low yield was attributed to the thermal instability of **15**. The cycloaddition reaction was not observed at room

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(19) X-ray data for compound **15** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 147868. Copies of the data may be obtained free of charge from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223−336−033; e-mail: deposit@ccdc.cam.ac.uk). In the packing diagram these slightly concave molecules sit on top of each other as a disklike set of “twined coins”. Compare: Bunz, U. H. F.; Enkelmann, V. *Chem. Eur. J.* **1999**, *5*, 263.

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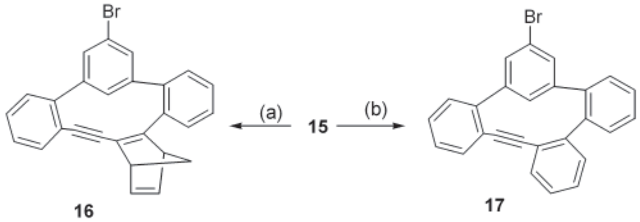
Scheme 3[a]

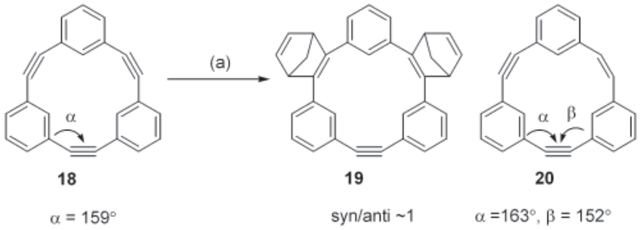


[a] (a) Cyclopentadiene, PhMe, Δ, sealed tube, 24 h, 28%; (b) 1,3-cyclohexadiene, PhMe, Δ, sealed tube, 24 h, 22%.

temperature (21 °C), nor after 24 h at reflux (110 °C) at atmospheric pressure. A second addition was not detected, as the first cycloaddition relieves the strain in the butadiyne unit and reinstates an approximately linear bond angle geometry in the remaining triple bond. In a parallel fashion, **15** underwent initial cycloaddition with 1,3-cyclohexadiene, followed by a retro-Diels−Alder reaction involving the thermal expulsion of ethylene to give the interesting acetylenic-tetraphenyl product **17**. These results established the olefinic nature of this distorted triple bond and it's rare dienophilic characteristics.

The symmetrical, nearly planar triyne **18** also displayed dienophilic character.[25a] Exposure to excess cyclopentadiene resulted in double addition to give **19** (Scheme 4). The measured alkyne angle α in **18** was 159°, although AM-1 calculations of enediyne **20** revealed that a significant degree of strain would still remain in the triple bonds ($\beta = 152°$) after an initial cycloaddition. Consequently, the second cycloaddition to afford **19** was observed, consistent with the sole formation of the diadduct.

Scheme 4[a]



[a] (a) Cyclopentadiene, 22 °C, $CHCl_3$, 76%.

In summary, a palladium coupling/oxidative dimerization sequence provided a rapid route to novel cyclophanes. Intramolecular coupling of **3** occurred in preference to intermolecular dimerization to **5**. A parallel cyclization afforded the strained **15** despite the bending required in the adjacent triple bonds. The most distorted bond deviated ∼26° from the normal C−C═C bond angle of ∼180°. The Diels−Alder reactions of the strained butadiyne bridge in **15** established its reactivity and provided the novel macrocycles **16** and **17**, respectively. Collectively, these results imply that with appropriate substitution patterns the synthesis of more highly distorted and strained unsaturated systems may be feasible.

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Supporting Information Available: Experimental procedures and spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, and MS) for compounds **3**, **4**, and **13**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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