ORGANIC
LETTERS

2003
Vol. 5, No. 11
1911−1914

Molecular Folding of C60 Acetylenic Cyclophanes: π-Stacking of Superimposed Aromatic Rings

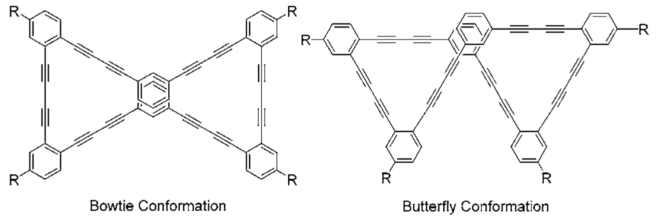
Matthew A. Heuft, Shawn K. Collins,[†] and Alex G. Fallis*

Department of Chemistry, University of Ottawa, 10 Marie Curie,
Ottawa, Ontario, Canada K1N 6N5

afallis@science.uottawa.ca

Received March 31, 2003

ABSTRACT



Bowtie Conformation

Butterfly Conformation

The syntheses of two distinct families of phenylyne helical cyclophanes with potential for organic materials are described. The *meta*-bonded atropisomers afford interesting bowtie-like and butterfly-like conformers from a palladium(0), copper-mediated coupling sequence. Molecular modeling revealed the contrasting stereochemistry in these systems from differential molecular folding pathways during cyclization. The interplanar separation of the superimposed aromatic rings is $\sim$3.5 Å.

Carbon-rich molecules with 60 or more carbon atoms are currently of widespread interest, particularly if they have potential to eventually generate new fullerenes and related structures.[1]

Experience has demonstrated that despite careful design of suitable building blocks, the experimental realization of these goals is frequently thwarted by nature.[2] This is reflected in recent reports describing the synthesis and design of new cyclophanes[3] and assorted cage compounds[4] with novel shapes and supramolecular geometries.[5] These investigations have encompassed the incorporation of molecular architectures with shape-persistent characteristics[6] for liquid crystals[7] and nonlinear optics applications, as well as π-stacking between aromatic systems.[8]

We have established previously that *para*-cyclophanes with eneyne bridges composed of double bonds and/or benzene rings may be prepared by sequential palladium(0) and copper(II)-mediated coupling reactions.[7b,9] The combination

---

[†] Present Address: Department of Chemistry, University of California−Irvine, Irvine, CA.

(1) (a) Hirsh, A. *Fullerenes and Related Structures*; Springer-Verlag: Berlin, 1999. (b) Scott, L. T.; Boorum, M. M.; McMahon, B. J.; Hagen, S.; Mack, J.; Blank, J.; Wegner, H.; de Meijere, A. *Science* **2002**, *295*, 1500.

(2) (a) Rubin, Y.; Parker, T. C.; Timothy, 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. J.; Jalisatgi, S.; Boulle, C.; Wilkins, C. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 1353. (c) Tobe, Y.; Nakagawa, N.; Naemura, K.; Wakabayashi, T.; Shida, T.; Achiba, Y. *J. Am. Chem. Chem.* **1998**, *120*, 4544. (d) Fallis, A. G. *Can. J. Chem.* **1999**, *77*, 159. (e) Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Org. Lett.* **2002**, *4*, 11. (f) Manini, P.; Amrein, W.; Gramlich, V.; Diederich, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4339.

(3) (a) Vögtle, F. *Cyclophane Chemistry*; Wiley: New York, 1999. (b) Bodwell, G. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2085. (c) de Meijere, A.; König, B.; *Synlett* **1997**, 1221. (d) Hopf, H. *Classics in Hydrocarbon Chemistry*; Wiley-VCH: Weinheim, Germany, 2000. (e) Bodwell, G. J.; Saton, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 4003.

(4) (a) König, B. *Top. Curr. Chem.* **1998**, *196*, 91. (b) Tsuji, T. In *Advances in Strained Interesting Organic Molecules*; Halton, B. Ed.; JAI Press: Greenwich, CT, 1999; pp 103−152.

(5) Diederich, F.; Gobbi, L. *Top. Curr. Chem.* **1999**, *201*, 43.

(6) (a) Haley, M. M.; Pak, J. J.; Brand, S. C. *Top. Curr. Chem.* **1999**, *201*, 81. (b) Grave, C.; Schlüter, A. D. *Eur. J. Org. Chem.* **2002**, 3075. (c) Höger, S.; Rosselli, S.; Ramminger, A.-D.; Enkelmann, V. *Org. Lett.* **2002**, *4*, 4269.

(7) (a) Schmidt-Mende, L.; Fechtenkotter, A.; Mullen, K.; Moons, E.; Friend, R. H.; MacKenize, J. D. *Science* **2001**, *293*, 1119. (b) Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Org. Lett.* **2000**, *2*, 3189.

(8) (a) Shetty, A. S.; Zhang, J.; Moore, J. S. *J. Am. Chem. Chem.* **1996**, *118*, 1019. (b) Tobe, Y.; Utsumi, N.; Kawabata, K.; Nagano, A.; Adachi, K.; Araki, S.; Sonoda, M.; Hirose, K.; Naemura, K. *J. Am. Chem. Chem.* **2002**, *140*, 4544. (c) Cozzi, F.; Annunziata, R.; Benaglia, M.; Cinquini, M.; Raimondi, L.; Baldridge, K. K.; Siegel, J. S. *Org. Biomol. Chem.* **2003**, *1*, 157.

10.1021/ol0345576 CCC: $25.00

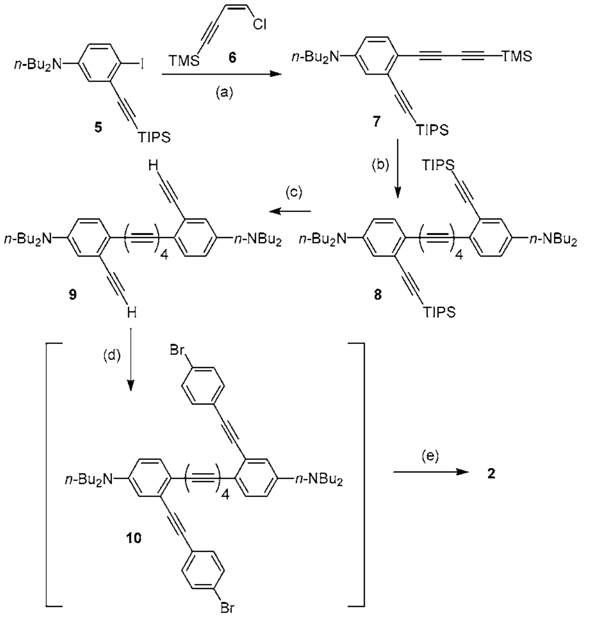
of the number and type of unsaturated linkages in these compounds creates a twisted conformation that imparts helical chirality to the assembled molecule.[10] Consequently, the preparation of C60 acetylenic cyclophanes that possess different molecular conformations and variable through-space interactions are also of interest.

Compounds **1** and **3** each possess 60 carbons but differ in the acetylene bridges employed and the point of attachment to the benzene cap. Cyclophane **1** possesses a *para*-(1,4)-bridged phenyl skeleton, while cyclophane **3** is composed of *meta*-(1,3)-bridged benzene caps. Due to the frequent insolublity of these unsaturated hydrocarbons, we and others, have circumvented this difficulty by alkylamine substitution.[10d,11] Consequently, we decided to synthesize and investigate the properties of the more soluble amine-substituted cyclophanes **2** and **4** in order to gain further understanding of various features, including their helical geometry, through-space interactions, and preferred conformations from various molecular folding pathways.

Symmetrical double dissection between the tetrayne bridges of cyclophane **2** suggested that dimerization of a suitable C30 precursor would be an attractive building block. However, when this C30 precursor was subjected to our one-pot desilylation/coupling procedure, only the intramolecular product was formed.[12]

Consequently, a stepwise approach to the C60 cyclophane core with early assembly of the tetraoctyne moiety was investigated (Scheme 1). Iodide **5** underwent a Negishi coupling with the organozincate derived from *cis*-4-chloro-1-trimethylsilyl-but-3-en-1-yne (**6**)[13] upon treatment with *n*-BuLi (2 equiv) and quenching with $ZnBr_2$ to give **7**. Subsequent one-pot desilylation/coupling with K_2CO_3 and $Cu(OAc)_2{\cdot}H_2O$ in pyridine/methanol (1:1)[14] led to tetrayne **8** in 92% yield. Exposure to tetrabutylammonium fluoride afforded chromatographically (SiO_2) unstable acetylene **9** that was reacted directly with 1-bromo-4-iodobenzene (2 equiv, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N) to give the desired dibromide **10**. This compound also decomposed during chromatography. Therefore, the coupling with 1-bromo-4-iodobenzene was repeated and its disappearance was monitored. Once all of the iodobenzene was consumed, $Pd(PhCN)_2Cl_2$ and $P(t\text{-}Bu)_3$[15] were added and the reaction was heated to reflux. Dropwise addition of a second equivalent of **9** led to cyclophane **2** as desired. The use of this improved ligand for Pd(0) coupling reactions greatly facilitated the stepwise construction of this cyclophane macrocycle. This protocol is also useful for the synthesis of unsymmetrical cyclophanes with nonlinear optical potential.

Scheme 1. Synthesis of Cyclophane **2**[a]



[a] Conditions: (a) (1) **6**, *n*-BuLi (2 equiv), THF, −78 °C, 2 min; (2) $ZnBr_2$, 0 °C, 15 min; (3) **5**, $[Pd(PPh_3)_4]$, Δ, 48 h, 80%. (b) K_2CO_3, $Cu(OAc)_2$ (6 equiv), MeOH/py (1:1), 6 h, 92%. (c) TBAF, THF, 18 h, 97%. (d) 1-Bromo-4-iodobenzene, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, THF, Δ, 13 h. (e) **9**, $Pd(PhCN)_2Cl_2$, $P(t\text{-}Bu)_3$, 17 h, 4%.

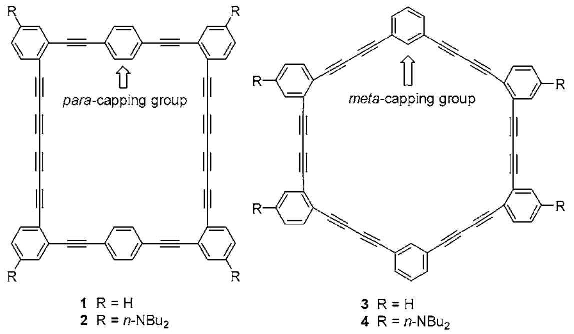


Figure 1. Aceylenic, 60-carbon atom macrocyclic cyclophanes with (*para*- and *meta*-substituted capping groups).

Proton and carbon NMR spectra revealed that **2** adopted a highly symmetrical conformation in solution (Figure 2). In contrast to our experience with related cyclophanes,[9,10e] cyclophane **2** was conformationally stable at room temper-

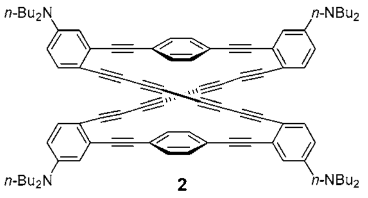


Figure 2. Proposed conformation of cyclophane **2**.

---

[9] (a) Romero, M. A.; Fallis, A. G. *Tetrahedron Lett.* **1994**, *35*, 4711. (b) Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 385.

[10] For examples of helical chirality in cyclophanes, see: (a) Boese, R.; Matzger, A. J.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1997**, *119*, 2052. (b) Marsella, M. J.; Kim, I. T.; Tham, F. *J. Am. Chem. Soc.* **2000**, *122*, 974. (c) Baxter, P. N. W. *J. Org. Chem.* **2001**, *66*, 4170. (d) Heuft, M. A.; Fallis, A. G. *Angew. Chem., Int. Ed.* **2002**, *41*, 4520.

ature. This is expected since isomerization requires the adoption of a strained, planar, rectangular-like intermediate. Molecular modeling (Figure 3) and NMR data were consistent with a C_2-symmetric conformation of **2**.

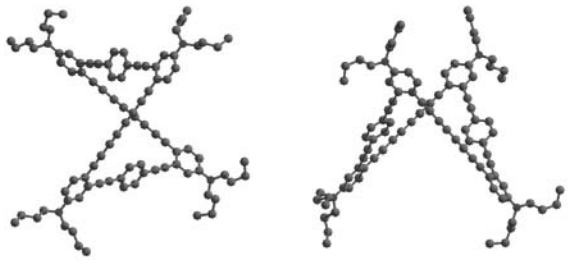
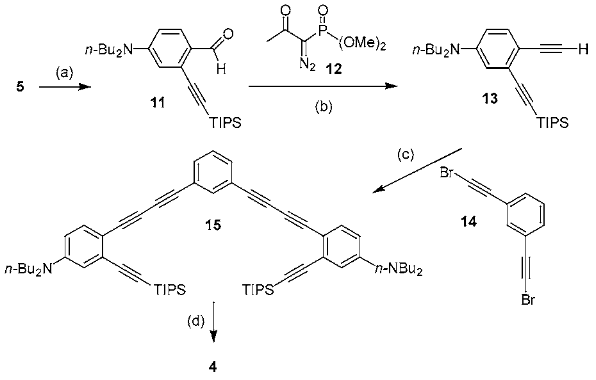


Figure 3. Molecular modeling representations of the C_2-symmetric, helical conformation of cyclophane **2**.

Our previous observations regarding the competition between acetylenic intramolecular and dimerization reactions revealed that the favored reaction was dictated by the termini separation.[16] The intramolecular alternative was inhibited when the reactive acetylenic termini were separated by more than 7.5 Å. Consequently, the dimerization strategy toward cyclophane **4** was particularly attractive, as the termini separation was approximately 10.7 Å. Cyclophane **4** was synthesized by our established dimerization protocol. Unfortunately, iodide **5** failed to undergo a direct Sonogashira coupling reaction with trimethylsilylacetylene under a variety of reaction conditions (Scheme 2). To overcome this challenge, iodide **5** was converted to aldehyde **11** by halogen−metal exchange with *t*-BuLi (2 equiv) and quenching with dimethylformamide (DMF). Aldehyde **11** was then treated with Ohira's reagent (**12**),[17] followed by K_2CO_3 in MeOH to yield acetylene **13**. A Cadiot−Chodkiewicz alkyne cross-coupling reaction of **13** with dibromide **14** gave the amino-substituted C30 precursor **15** required for the dimerization experiment. This hexyne was then transformed by our in situ disilylation/coupling protocol with TBAF and $Cu(OAc)_2$[12] to afford two new molecules (15% yield) that were consistent with the generic cyclophane structure **4**. However, this flat cyclic representation of **4** does not accurately reflect the actual conformation of these molecules.

Scheme 2. Synthesis of Cyclophane **4**[a]



[a] (a) (1) *t*-BuLi (2 equiv), THF, −78 °C, 5 min; (2) DMF, Δ, 12 h, 97%. (b) **12**, K_2CO_3, MeOH, 48 h, 61% conversion. (c) **14**, $Pd_2(dba)_3$, CuI, 1,2,2,6,6-pentamethylpiperidine, THF, 16 h, 30%. (d) TBAF, $Cu(OAc)_2$ (6 equiv), Et_2O/py (1:3), 18 h, 15%.

The two isomers of cyclophane **4** were separated via size-exclusion semiprep HPLC. The major isomer **4a** displayed higher symmetry than the minor isomer **4b** (**4a**/**4b** 3:1) on the basis of their proton and carbon NMR spectra. Unfortunately, crystalline samples suitable for X-ray analysis could not be obtained. However, computer-based molecular modeling revealed that two different isomeric conformers were possible.[18] These symmetrical isomeric "bowtie-like" and "butterfly-like" structures, **4a** and **4b**, respectively, are illustrated in Figures 4−6.

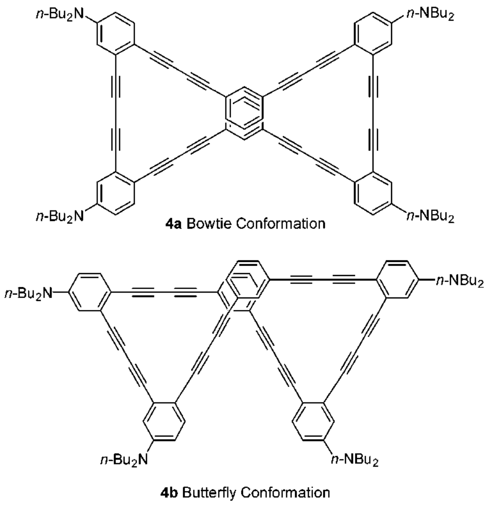


Figure 4. Figure 4. Proposed conformations of cyclophanes **4a** and **4b**.

Cyclophane conformer **4a** possesses C_{2h} symmetry, while cyclophane **4b** belongs to the lower symmetry C_2 point group. This creates an environment in which the aromatic

---

(11) Pak, J. J.; Weakley, T. J. R.; Haley, M. M. *J. Am. Chem. Soc*. **1999**, *121*, 8182.

(12) Heuft, M. A.; Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Org. Lett*. **2001**, *3*, 2883.

(13) (a) Lu, Y.-F.; Harwig, C. W.; Fallis, A. G. *J. Org. Chem*. **1993**, *58*, 4202. (b) Lu, Y.-F.; Harwig, C. W.; Fallis, A. G. *Can. J. Chem*. **1995**, *73*, 2253.

(14) Haley, M. M.; Bell, M. L.; Brand, S. C.; Kimball, D. B.; Pak, J. J.; Wan, W. B. *Tetrahedron Lett*. **1997**, *38*, 7483.

(15) Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett*. **2000**, *2*, 1729.

(16) Collins, S. K. Ph.D. Thesis, University of Ottawa, Ottawa, Ontario, Canada, December 2001.

(17) Ohira, S. *Synth. Commun*. **1989**, *19*, 561.

(18) Universal force field (UFF) calculations were obtained using the Cerius^2-Dmol^3 molecular modeling suite from Molecular Simulations, Inc. (San Diego, 1999). We thank S. Drouin and Prof. D. Fogg (University of Ottawa) for assistance.

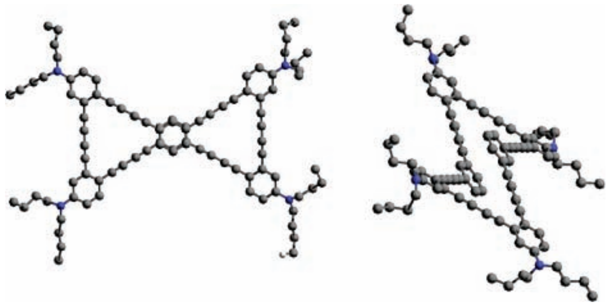


Figure 5. Figure 5. Molecular modeling representation of the bowtie-like, C_{2h}-symmetric conformation of cyclophane **4a**.

$\pi-\pi$ stacking interactions between the capping phenyl rings in each structure are quire similar despite their pictorial appearance.[19] The interplanar separations for the superimposed aromatic rings in **4a** and **4b** are 3.55 and 3.52 Å, respectively. These "sandwich-like" arrangements are clearly evident, and these values are similar to theoretical numbers calculated for the parallel dimer of benzene itself.[20]

Cyclophanes **4a** and **4b** constitute a pair of atropisomers due to their restricted rotation. They are both conformationally and configurationally stable even upon heating to 100 °C. Interconversion of **4a** to **4b** involves a significant energy barrier, which requires one of the capping benzene rings to undergo a "skipping rope" type rotation through the other cyclophane macrocycle ring en route to the second isomer.

In conclusion, we have synthesized two novel C60 cyclophanes. The stereochemistry of these compounds is governed by the *para*-(1,4) or *meta*-(1,3) substitution of the capping phenyl ring. Both series are geometrically distinct but adopt helical conformations in which the benzenoid caps π-stack. The *meta* isomer follows different molecular folding pathways during the macrocyclization reaction to generate two atropisomers, **4a** and **4b**, as depicted in Figures 4−6.

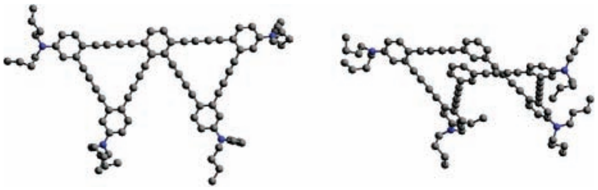


Figure 6. Figure 6. Molecular modeling representation of the butterfly-like, C_2-symmetric conformation of cyclophane **4b**.

These acetylenic, shape-persistent, π-stacked C60 cyclophanes with modified functional groups possess interesting potential. New families can be designed with different molecular conformations, variable through-space interactions, and modified levels of unsaturation. These features hold promise, with appropriate substitutents, for the preparation of different types of discotic,[21] nematic, and ferroelectric liquid crystals,[22] metallomesogens,[23] and electronic devices.[24]

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support of this research. S. K. Collins and M. A. Heuft thank NSERC and the University of Ottawa for Graduate Scholarships.

Supporting Information Available: Experimental details and characterization for cyclophanes **2**, **4a**, and **4b** and characterization for intermediates **9**, **10**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0345576

---

[19] For recent benzenoid examples, see: Tobe, Y.; Utsumi, N.; Kawabata, K.; Nagano, A.; Adachi, K.; Araki, S.; Sonoda, M.; Hirose, K.; Naemura, K. *J. Am. Chem. Chem*. **2002**, *140*, 4544. For a thiophene example, see: Marsella, M. J.; Wang, Z.-Q.; Reid, R. J.; Yoon. K. *Org. Lett*. **2001**, *3*, 885.

[20] (a) Tsuzuki, S.; Honda, K.; Uchimaru, T.; Mikami, M.; Tanaba, K. *J. Am. Chem. Soc.* **2000**, *124*, 104. (b) Hobza, P.; Selzle, H. L.; Schlag, E. W. *J. Phys. Chem*. **1996**, *100*, 18790.

[21] Bushby, R. L.; Lozman, O. R. *Curr. Opin. Colloid Interface Sci.* **2002**, *7*, 343.

[22] Hird, M.; Goodby, J. W.; Hindmarsh, P.; Lewis, R. A.; Toyne, K. J. *Ferroelectronics* **2002**, *276*, 219.

[23] Costisor, O.; Schweifer, J.; Grunert, M.; Linert, W. *Recent Res. Dev. Mater. Sci.* **2001**, *2*, 1.

[24] Ito, K.; Suzuki, T.; Sakamoto, Y.; Kubota, D.; Inoue, Y.; Sato, F.; Tokito, S. *Angew. Chem., Int. Ed*. **2003**, *42*, 1159.