Synthesis of [6.6]Metacyclophane via the Suzuki Coupling

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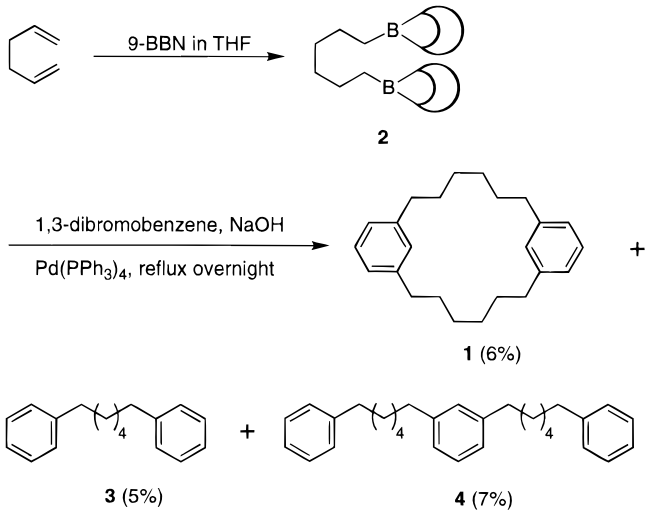
Cyclophane chemistry has contributed greatly to the understanding of fields as varied as molecular and cationic recognition to fundamental principles of NMR.[2] To date, the largest all-carbon [*n.n*]metacyclophane prepared is [5.5]metacyclophane, which was synthesized by the acid-catalyzed dimerization of δ-2-methoxyphenylvaleric acid, yet no conformational information is available about this system.[3] [4.4]Metacyclophane has been prepared by a combination of an intramolecular photocycloaddition followed by Birch reduction,[4] and molecular mechanics calculations predict that the *anti* conformer is energetically preferred.[5] The most in-depth study of an [*n.n*]metacyclophane was performed on [3.3]-metacyclophane, which was synthesized by the chromium hexacarbonyl complex method.[6] Variable-temperature NMR studies and X-ray crystallography revealed that [3.3]metacyclophane has a thermodynamic preference for the *syn* conformation rather than the *anti* conformation of [2.2]metacyclophane.[7] While the Wurtz coupling was the first method employed to make [2.2]metacyclophane,[8] the most common procedure for preparing the smaller [*n.n*]metacyclophanes and their derivatives has been the oxidation of the sulfide precursor to the corresponding sulfone, followed by flash vacuum thermolysis, or photolysis, to extrude SO_2 in the ring contraction.[9] Additionally, a highly strained mono(Dewar benzene) isomer of [1.1]metacyclophane has been prepared, possibly paving the way to the fully aromatic system.[10]

Scheme 1



Recently, we demonstrated that the palladium-catalyzed coupling of an alkyl-9-borabicyclononane (alkyl-9-BBN) derivative with an aryl bromide (the Suzuki coupling) could be used to prepare a silicon-containing cage system.[11] As an extension of this work, we have also been examining a general synthesis of all-carbon [*n*]- and [*n.n*]metacyclophanes. We report here the synthesis and structure determination of [6.6]metacyclophane (**1**), which is formed according to Scheme 1 in a single reaction vessel.

The bis-9-BBN adduct **2** was formed at room temperature by adding 1,5-hexadiene to a solution of 2.05 equiv of 9-BBN in THF (Scheme 1). The reaction mixture containing **2** was then added to a solution of 1,3-dibromobenzene, NaOH, and $Pd(PPh_3)_4$ in THF. This mixture was refluxed overnight under an inert atmosphere to provide **1** in 6% isolated yield. No [6]metacyclophane was detected by GC/MS.

The efficiency for this cyclization process is relatively low because the conditions are not entropically favorable: we have formed an 18-membered ring in which the four carbon−carbon bonds are created sequentially. Consequently, formation of the acyclic systems **3** (5%) and **4** (7%) effectively compete with the cyclization process. It is also likely that large amounts of polymeric material were formed in the reaction, but no effort was made to identify these. No 1,3-dibromobenzene or other starting materials were detected in the reaction mixture. When the coupling was carried out using different Suzuki conditions[12] (a 3 M aqueous NaOH solution) a similar yield of **1** was obtained.

Compound **1** was crystallized from pentane and gave clear, colorless crystals suitable for X-ray study.[13] One ORTEP view of [6.6]metacyclophane, **1a** shows the symmetry in the molecule as well as a cavity that measures 6.6 Å in length by 5.3 Å in width. Another ORTEP representation, **1b**, clearly shows the *anti* conformation of the 18-membered ring in which the benzene rings are nearly perpendicular to the plane of the methylene bridges (Figure 1). Thermodynamic preference for the

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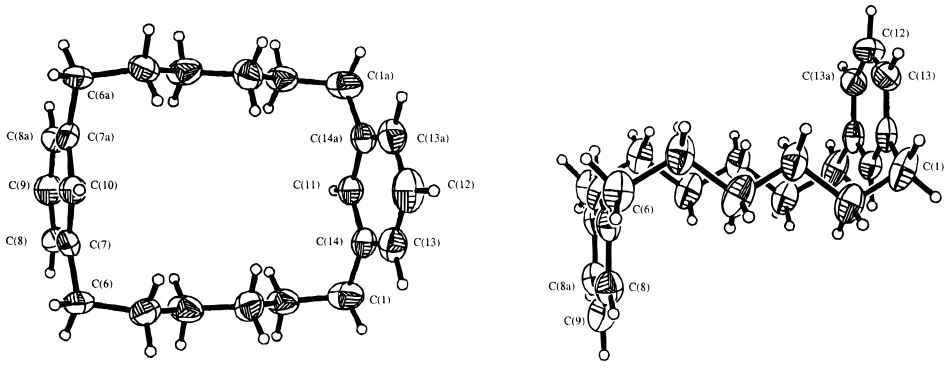

1a **1b**

Figure 1. ORTEP representations showing the cavity of the macroring **1a** and the *anti* conformation **1b**. The crystallographic numbering is not the same as the systematic numbering scheme.

anti conformation over the syn was predicted by molecular mechanics calculations.[14] In the *anti* conformation, the methylene bridges of both the [2.2]metacyclophane and **1** are nicely staggered and show no sign of Pitzer strain, which is present in the syn conformers of both of these ring systems.[5] In addition, the [4.4]metacyclophane, which belongs to the same C_{2v} point group, also appears to adopt the *anti* conformation.

Experimental Section[15]

[6.6]Metacyclophane (1). To a flame-dried 250 mL round-bottom flask under a nitrogen atmosphere was added 127.8 mL of 0.3 M 9-BBN (37.52 mmol, 2.05 equiv) in THF. The solution was stirred for a short time before 2.17 mL of 1,5-hexadiene (18.26 mmol, 1 equiv) was rapidly added. The reaction mixture was stirred at room temperature for 3 h to form the bis-9-BBN adduct **2**. The borane intermediate **2** was then cannulated to a previously flame-dried 500 mL, two-necked round-bottom flask equipped with a condenser that contained 2.21 mL of 1,3-dibromobenzene (18.26 mmol, 1 equiv), 633 mg of $Pd(PPh_3)_4$ (0.55 mmol, 0.03 equiv), and 3.84 g of dry NaOH pellets (95.88 mmol, 5.25 equiv) in 100 mL of THF and refluxed for 12 h under nitrogen. The reaction mixture was then poured into 100 mL of hexanes and extracted with 1 M HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL). Following drying ($MgSO_4$) and solvent removal, the crude material was filtered through a plug of silica gel with hexanes. The product was isolated by flash column chromatography on silica gel with 0.5% Et_2O/hexanes as a crystalline solid in 6% (167 mg) yield: mp (uncorrected) 92−93 °C. Evaporative recrystallization of **1** from pentane gave crystals suitable for X-ray analysis: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (m, 2H), 6.97 (s, 2H), 6.96 (d, J = 7.2 Hz, 4H), 2.57 (t, J = 7.14 Hz, 8H), 1.60 (m, 8H), 1.29 (m, 8H); ^{13}C NMR (100 MHz, benzene-d_6)[16] δ 142.7, 128.4, 128.3, 126.5, 35.3, 30.8, 27.6; IR (KBr) 759 cm^{-1}; MS (70 eV), m/z 321 (M + 1, 27), 320 (M^+, 100). Anal. Calcd for $C_{24}H_{32}$: C, 89.93; H, 10.07. Found: C, 89.96; H, 10.02.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR for compound **1** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(13) Crystal structure analysis of **2**: crystal dimensions 0.40 × 0.20 × 0.21 mm; crystal system, orthorhombic; space group, *Pbcm*; unit cell dimensions and volume, a = 7.085(2) Å, b = 15.978(3) Å, c = 17.349(3) Å, V = 1964.0(8) Å^3, Z = 4, R = 0.0775 (wR = 0.0551), r_{calcd} = 1.084 g/cm^3, 2 < 2q < 51, l (Mo Kα) = 0.710 73 Å, 26 °C, ω data collection, 2059 w/1796 unique of which 570 > 4I/σ and used for least-squares refinement. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: Int. code + (1223) 336−033; e-mail: teched@chemcrys.cam.ac.uk).

(14) CSC's Chem3D Pro, Version 3.1 makes use of Allinger's MM2 force field approach to energy minimization. Cambridge Scientific Computing, 875 Massachusetts Ave., Sixth Floor, Cambridge, MA 02139. Internet: support@camsci.com.

(15) All reagents were purified prior to use. Anhydrous THF was obtained by distillation from Na/benzophenone. The 9-BBN was titrated using Brown's method (see: Brown, H. C. *Organic Synthesis via Boranes*; Wiley-Interscience: New York, 1975). All reactions were performed in flame-dried glassware under an inert atmosphere of argon. ^{1}H and ^{13}C NMR were obtained on either a Bruker 400 MHz NMR or a Varian 200 MHz NMR. Infrared spectra were obtained on a Beckman IR-33. Ultraviolet spectra were recorded on a Perkin-Elmer Model 552A UV-vis spectrophotometer. Gas chromatography was performed on a Hewlett-Packard 5890 gas chromatograph using a 30 m J + W Scientific SE-30 fused silica capillary column. GC/MS analyses were carried out on a Hewlett-Packard 5895B GC/MS system. Flash chromatography was performed on silica gel 60, 230−400 mesh ASTM, obtained from Baxter Scientific. The aluminum-backed TLC plates used were cut from sheets of Whatman AL AIL G/UV plates. Visualization of the TLC plates was done by dipping the plate in 10% phosphomolybdic acid/ethanol and heating with a heat gun. Melting points were taken using a Laboratory Devices MEL-TEMP apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, GA.

(16) The signals due to C-9/12 and C-10/11 were coincident when this spectrum was recorded in $CDCl_3$.