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. 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. [4,4]Metacyclophane has been prepared by a combination of an intramolecular photocycloaddition followed by Birch reduction, and molecular mechanics calculations predict that the anti conformer is energetically preferred. 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. 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. While the Wurtz coupling was the first method employed to make [2,2]metacyclophanes, 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 SO₂ in the ring contraction. 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

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Recently, we demonstrated that the palladium-catalyzed coupling of an alkyl-9-borabicyclononene (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(PPh₃)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 acrylic 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 conditions12 (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

Scheme 1
anti conformation over the syn was predicted by molecular mechanics calculations. 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. In addition, the [4.4]metacyclophane, which belongs to the same point group, also appears to adopt the anti conformation.

Experimental Section

[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(PPh3)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 NaHCO3 (50 mL), and brine (50 mL). Following drying (MgSO4) 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% Et2O/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, CDCl3) 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-$d_6$) 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 and 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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(16) The signals due to C-9/12 and C-10/11 were coincident when this spectrum was recorded in CDCl$_3$. 

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.