

Synthesis and Structure of a New [6.6]Metacyclophane with Eneidyne Bridges[†]

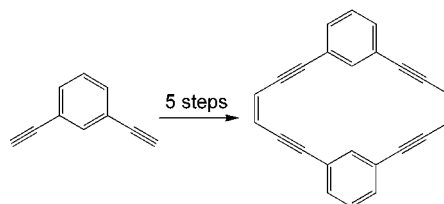
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ABSTRACT



Synthesis and structure of a novel [6.6]metacyclophane with eneidyne bridges is reported.

The chemistry of eneidyne gained prominence among synthetic and theoretical chemists and also biologists after the discovery of eneidyne antibiotics during the late 1980s.¹ Several synthetic model systems have been prepared incorporating the basic eneidyne skeleton, namely, the hexa-3-ene-1,5-diyne unit, in order to study the mechanism of thermally induced cycloaromatization, commonly known as the Bergman cyclization.² Synthesis of extended cyclophanes is another area³ that is actively pursued by synthetic chemists, and in recent years several cyclophanes bearing extended acetylenic units as bridges have been constructed.⁴ Some of these cyclophanes serve as precursors for the synthesis of

fullerenes, their subunits, graphyne subunits, and nanotubes.⁵ Cyclophanes bearing eneidyne units as the bridges (eneidynephanes) offer enormous potential to study both of these areas in a single system. For example, the strain and the distance between the termini of the eneidyne unit, which is

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[†] Dedicated to Professor Dr. Henning Hopf on the occasion of his 60th birthday.

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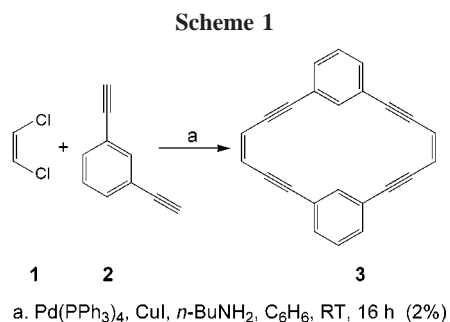
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one among the factors responsible for its reactivity, and the structure and conformation of the extended cyclophanes can be easily manipulated by the phane connectivity and substituents present in the aromatic and the bridging units. Besides, synthesis of isomeric [6.6] enediynephanes and multibridged [6_n] enediynephanes offers challenge to the synthetic chemists. Although several enediynephanes are known, the enediyne units in these cyclophanes are invariably connected to the aromatic units through a heteroatom, either oxygen, nitrogen, or sulfur.⁶ Cyclophanes in which the enediyne bridges are directly connected to the aromatic unit through C–C bonds are rare, although they have been postulated as intermediates in Bergman cyclization. In their classical work on cycloaromatization of polyenyne systems Sondheimer⁷ and Masamune⁸ have proposed aromatic enediyne intermediates during the Bergman cyclization. These intermediates could well be regarded as ortho enediynephanes, and as a result of the strain associated with these cyclic enediyne they undergo cyclization spontaneously at ambient conditions. Herein we report the synthesis and structure of a novel [6.6]metaenediynephane, namely, [6.6]metacyclophan-3,15-diene-1,5,13,17-tetrayne.

The Pd(0)-mediated coupling of (*Z*)-1,2-dichloroethene (**1**) with 1,3-diethynylbenzene (**2**) under high dilution condition yielded the desired metaenediynephane (**3**) albeit in very low yield of 2% (Scheme 1).

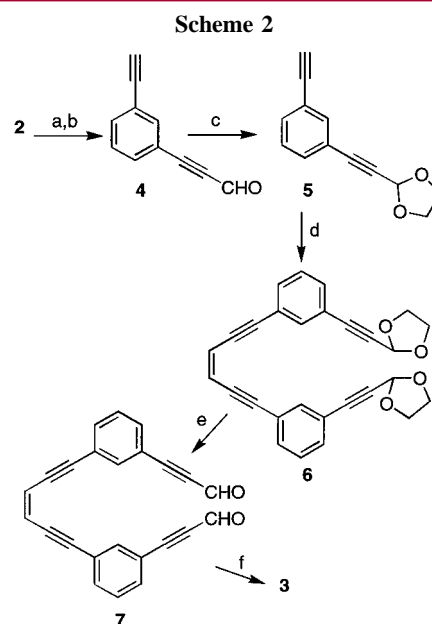


Therefore, an alternative five-step route was executed in which the enediyne bridges were constructed in a stepwise manner (Scheme 2). 1,3-Diethynylbenzene (**2**) was converted into the monoaldehyde **4** using ethylmagnesium bromide and DMF in 52% yield along with the corresponding bisaldehyde (16%). Attempted McMurry coupling of the bisaldehyde to **3** lead to intractable material. Also, attempted Pd(0)-mediated coupling of the monoaldehyde **4** with **1** resulted in unidentifiable mixture of products, and none of the desired dialdehyde **7** was obtained.

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a. EtMgBr, THF, -40 °C to RT; b. DMF, -20 °C to RT, 18 h, (52%); c. ethylene glycol, PTSA, MgSO₄, C₆H₆, reflux, 1 h, (93%); d. **1**, Pd(PPh₃)₄, CuI, *n*-BuNH₂, C₆H₆, RT, 12 h, (67%); e. FeCl₃·6H₂O, CH₂Cl₂, acetone, RT, 3 h, (32%); f. TiCl₃·DME_{1.5}, Zn–Cu, DME, -78 °C, 5 h, (69%);

Therefore, aldehyde **4** was protected using ethylene glycol to the acetal **5** (93%), which underwent coupling reaction with **1** smoothly to furnish the bisacetal **6** (67%). Hydrolysis of the bisacetal **6** using hydrated ferric chloride yielded the dialdehyde **7**, although in a moderate yield of 32%. The bisacetal **6** was resistant to hydrolysis with aqueous oxalic acid and 3 N HCl. The dialdehyde **7** in which one of the enediyne bridge is already in place in the *cis* configuration is ideally suited for the construction of the second bridge through McMurry coupling, which offers a convenient methodology for the construction of medium- and large-ring alkenes in good yields.⁹ The McMurry coupling of **7** using TiCl₃ and Zn–Cu couple in DME at -78 °C yielded the target metaenediynephane **3** as the sole product in 69% yield.

Enediynephane **3** is a pale yellow solid and is highly fluorescent, as would be expected for a fully conjugated rigid planar system. In the electronic absorption spectrum of **3** well resolved absorption bands at 224, 244, 300, 316 (sh), 328 (sh), 338, 350, and 363 nm are observed in cyclohexane. Excitation of **3** at any one of the absorption bands above 300 nm gives identical fluorescence spectra showing emission maxima at 384 (sh), 398, 408, 434, and 446 (sh) nm, and the fluorescence quantum yield (Φ_f) is 0.42. In the ¹H NMR spectrum of **3** the intra-annular protons appear as a singlet at δ 7.82, more deshielded than the rest of the aromatic protons, which appear between δ 7.15 and 7.4, and the olefinic protons appear as a singlet at δ 6.05. In the mass spectrum of **3** the molecular ion peak at *m/z* 300 appears as

(9) McMurry, J. E.; Fleming, M. P.; Kees, K. L.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 3255–3266. Baumstark, A. L.; McClosky, C. J.; Witt, K. E. *J. Org. Chem.* **1978**, *43*, 3609–3611.

the base peak, and the salient feature of the spectrum is that the intensity of the fragment ions are very weak. The structure of **3** was confirmed by single-crystal X-ray diffraction data,¹⁰ and Figure 1 shows the structure of **3** in the crystal.

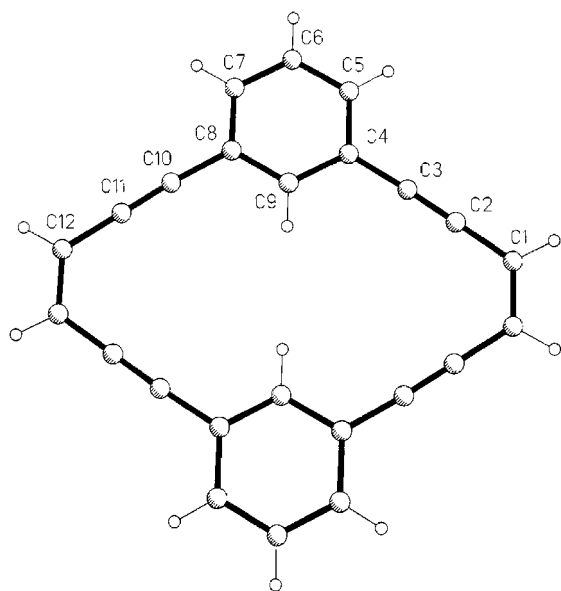


Figure 1. Structure of **3** in the crystal.

The structure is nearly planar, and it belongs to D_{2h} point group symmetry. The distance between the intra-annular hydrogens is 251.7 pm. The distance between the acetylenic termini of the bridge is 427.6 pm. In the crystal lattice there are layers in the packing, and along the Y -axis the molecules are stacked exactly on one another. The mean distance

between the layers is 547.7 pm. Along the Z -axis an ABAB arrangement of two layers is observed, and the angle between the two layers is 71.18° . The calculated energy minimized structure based on semiempirical AM1 calculations is nearly identical to the X-ray structure.

Currently we are investigating the synthesis of the corresponding ortho and para isomers of **3** and the effect of intra-annular substituents (C-9, Figure 1) on the structure and conformation of the phane and the reactivity of the enediyne bridge.

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Supporting Information Available: Experimental procedure for the synthesis of **3**, excitation and emission spectra of **3**, and complete spectroscopic characterization data for compounds **3**–**7**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(10) Crystallographic data for **3**. Data collection was performed on a Siemens P4 diffractometer with the ω -scan method using a graphite monochromator for Mo $K\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$). The structure was solved by direct method and refined anisotropically on F^2 using all reflections.¹¹ $C_{24}H_{12}$, MW = 300.34, monoclinic, space group $P2_1/n$, $a = 1002.0$ (3), $b = 545.72$ (16), $c = 1501.3$ (4) pm, $\alpha = \gamma = 90^\circ$, $\beta = 102.934(6)^\circ$, $V = 0.8001$ (4) nm^3 , $Z = 2$, $\rho_{\text{calc}} = 1.247 \text{ Mg m}^{-3}$, $\mu = 0.071 \text{ mm}^{-1}$, reflections measured 4836, unique reflections 1631, $2\theta_{\text{max}} = 52^\circ$, $T = 143 \text{ K}$, $R_{\text{int}} = 0.0397$, $R = 0.0613$ and $R_w = 0.0889$. Further details of the crystal structure investigation may be obtained from the Director of the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K. on quoting the full journal citation.¹¹ Sheldrick, G. M. *SHELXL-97 A Program for Crystal Structure Refinements*, University of Gottingen, 1997.