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Macrocyclic Cyclophane Belts via Double Diels-Alder Cycloadditions: Macroannulation of Bisdienes by Bisdienophiles. Synthesis of a Key Precursor to an [8]Cyclacene[1]

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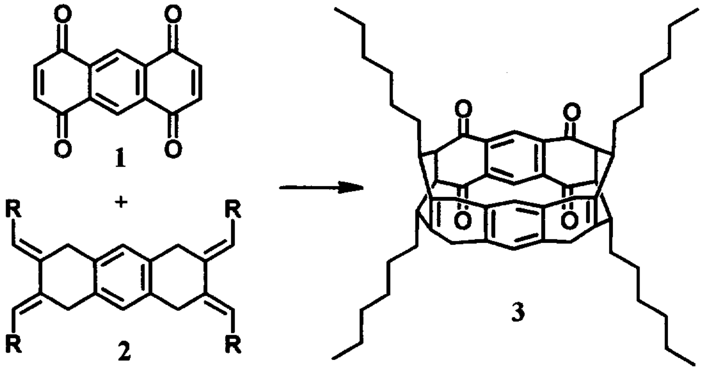
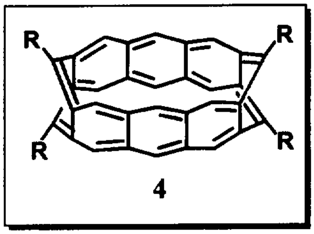
Abstract: A synthesis of macrocyclic cyclophanes is accomplished by double Diels-Alder cycloaddition of two bisdienophiles, 1,4,5,8-anthradiquinone and *p*-phenylenedimaleimide, to a bisdiene, 2,3,6,7-tetraheptylidene-1,2,3,4,5,6,7,8-octahydroanthracene. The structure of the macrocyclic cyclophane derived from the diquinone has been determined by single crystal x-ray diffraction, in addition to ^{1}H and ^{13}C NMR, HRMS and IR spectroscopic data.

A convergent synthesis of [8]cyclacene **4** (R = hexyl) via a key step involving stereospecific double Diels-Alder macroannulation of a *rigid planar* bisdienophile, diquinone **1**, by a *flexible non-planar* bisdiene, **2**, to give macrocyclic cyclophane **3** is currently under investigation in our laboratories.[2,3,4] Comparison of space-filling models indicated that diquinone **1** is shorter than bisdiene **2**, so the flexibility of the bisdiene is crucial for the success of this reaction. In contrast, the related approach of the Stoddart group employed *rigid* non-planar bisdienes and rigid *non-planar* bisdienophiles in the synthesis of *rigid* macrocyclic cyclophanes[5] which are also potential precursors of cyclacenes.[3] Cyclophane **3** not only has two aromatic rings already in place, but also has sufficient functionality to facilitate aromatization of the remaining six rings in the belt.



1 **2** **3**



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DOUBLE DIELS ALDER MACROANNULATION WITH DIQUINONE 1

Synthesis of Cyclophane Belt 3. It was reasonable to predict that the reaction of **1** with **2** would give a polymer, but we were hopeful that conditions could be found which would favor macroannulation.[6] We now report the remarkable finding that double Diels-Alder cycloaddition of diquinone **1**[2] to bisdiene **2**[2] to give cyclophane **3** occurs when separate solutions of **1** and **2** in dioxane are slowly added simultaneously to refluxing dioxane. Cyclophane **3** was obtained in 69% yield as a white crystalline solid (mp 186-188 °C) by flash chromatography and crystallization from dichloromethane/methanol.

Spectroscopic Evidence for the Macrocyclic Structure of Cyclophane 3. In view of the high probability that this reaction could have produced a polymer, a full description of the spectral data for **3** is included here as proof that this product was not polymeric and was the desired cyclophane. The highly symmetric, macrocyclic structure of the product was immediately evident upon examination of the ^{13}C and ^{1}H NMR spectra. Cyclophane **3** has 56 carbon atoms and two planes of symmetry. The ^{1}H-decoupled ^{13}C NMR spectrum cleanly consisted of 15 sharp singlets (indicating the presence of 15 non-equivalent sets of carbon atoms) rather than a complex spectrum of broadened peaks which would be expected for a polymer. DEPT identified these carbon atoms as giving rise to one methyl absorption, six methylene absorptions, two aliphatic and two aromatic methine signals, three (two aromatic and one olefinic) ipso signals, and one carbonyl absorption, as expected for **3**.

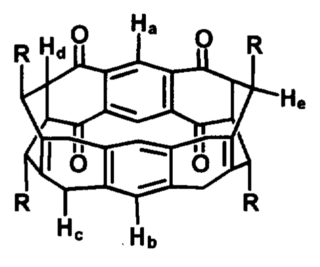


Figure 1. Labeling of protons of cyclophane **3**

The symmetry of **3** also results in a very simple ^{1}H NMR spectrum. Cyclophane **3** is expected to give rise to two sharp singlets in the aromatic region, and in $CDCl_3$ these appeared at 7.75 ppm and at 6.44 ppm, assigned to H_a (2 protons) and H_b (2 protons), respectively (Figure 1). The singlet at 6.44 ppm is approximately 0.5 ppm upfield from the corresponding signal arising from the aromatic protons of bisdiene **2** (6.90 ppm). This shift can be attributed to transannular shielding by the opposing aromatic ring in cyclophane **3**, supporting its macrocyclic structure. ^{1}H-^{1}H (COSY) and ^{13}C-^{1}H (HETCOR) correlations were employed to assign absorptions to the aliphatic protons of **3**. The 8 methylene protons labeled H_c give rise to a singlet at 3.00 ppm, which splits apart into a roughly symmetric pattern of multiplets in benzene-d_6. The methine protons, H_d and H_e, each give rise to a 4 proton multiplet correlated to only one carbon absorption: H_d at 3.37 ppm and H_e at 2.72 ppm. In the mass spectrometer the molecular ion of cyclophane **3** undergoes a facile double retro-Diels-Alder fragmentation, with loss of diquinone **1**, to give the second most intense peak, at 571, corresponding to bisdiene **2**.

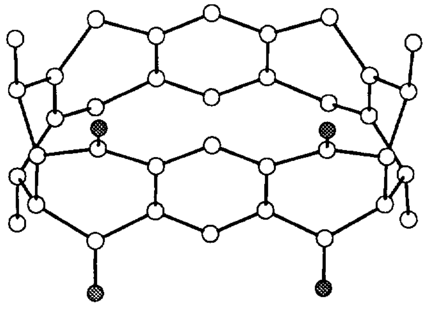
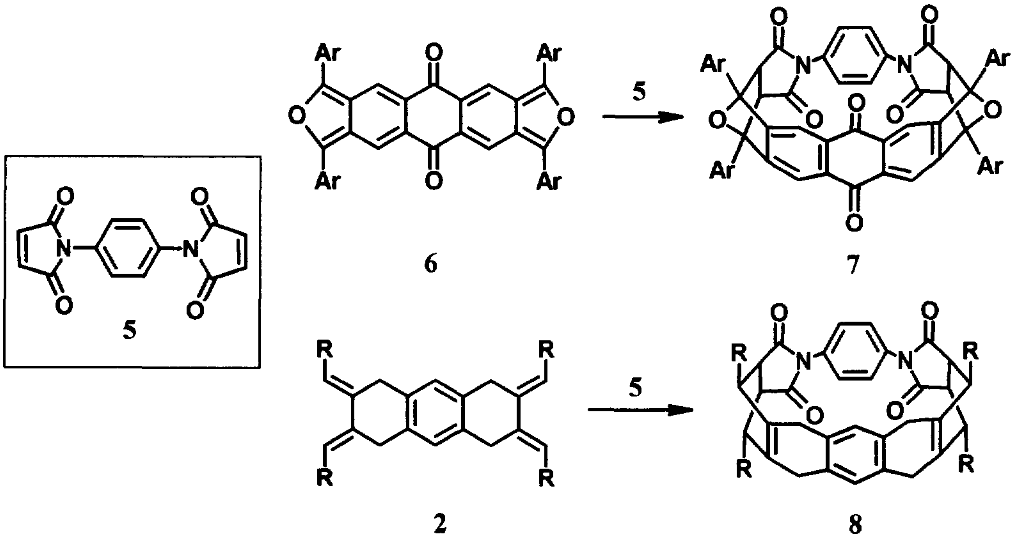


Figure 2. X-ray structure of the core of cyclophane **3**

Single Crystal X-ray Structure of Cyclophane 3. A single crystal x-ray structure determination was also carried out in order to establish the macrocyclic core structure beyond any possible doubt (Figure 2).[7] The hexyl chains of **3** are disordered in the crystal lattice, but this is of minimal importance, as far as this study is concerned, since the hexyl groups serve only to help solublize the compound, and only the macrocyclic portion, which is not disordered, is of interest. The central cavity of the macrocyclic core, a thin slot, is small enough that no guest molecule, such as solvent of crystallization, can be incorporated within it. (Later on in our proposed synthesis of cyclacene **4**, as more sp^3 hybridized carbon atoms are converted to sp^2, the cavity is predicted to open up as the structure becomes more hoop-like.)

DOUBLE DIELS-ALDER MACROANNULATION WITH BISMALEIMIDE 5

Synthesis of Cyclophane Belt 8. Miller has reported that addition of bisdienophile **5** to *rigid* bisisobenzofuran **6** gives cyclophane 7 (Ar = *p*-*tert*-butylphenyl).[8] Comparison of space-filling models of **5**, **6** and bisdiene **2** indicated that they all are very similar in length, so it was of interest to compare the macroannulation of bisdiene **2** by the shorter diquinone **1** (to give cyclophane **3**) with macroannulation of bisdiene **2** by bisdienophile **5**. In the event, when a solution of **2** in chloroform was added to a solution of **5** in a 1:3 mixture of methanol and chloroform at room temperature, cyclophane **8** (R = hexyl) was obtained as a white crystalline solid (mp 175-177 °C) in 76% yield.



Spectroscopic Evidence for the Macrocyclic Structure of Cyclophane 8. As discussed for cyclophane **3**, the symmetry of cyclophane **8** was consistent with its ^{13}C and ^{1}H NMR spectra. Again, ^{1}H-^{1}H COSY was helpful in assigning absorptions and confirming the structure. The ^{1}H NMR spectrum of cyclophane **8** showed two distinct aromatic signals: a two proton singlet at 6.69 ppm (approximately 0.2 ppm upfield from the chemical shift of the analogous protons in bisdiene **2**), and a four proton singlet at 6.81 ppm arising from the *p*-phenylene moiety. The upfield shift effect is attributable to the transannular shielding effect of the opposing aromatic ring. Even though molecular modeling indicated that the *p*-phenylene ring should preferably assume a skewed conformation, in which it is not parallel to the opposing aromatic ring, the equivalency of its four aromatic protons could not be removed upon cooling to −80 °C.

CONCLUSIONS

Not unexpectedly, the degree of success of the macro-annulation seems to depend on how easily each of the corresponding molecular termini of the bisdiene and bisdienophile can reach each other during the double Diels-Alder process. However, the most important lesson to be learned from the successful synthesis of macrocyclic cyclophane **3** is that even if the two reacting species are not of exactly the same length, flexibility in one or both of the reactants can be sufficient to favor macrocycle formation. This discovery gives us more versatility in the variety of macrocycle sizes and shapes that we can produce.

Our efforts are now focused on functionalization and aromatization of the remaining non-aromatic rings of macrocycle **3**, with the ultimate goal of obtaining [8]cyclacene **4**. Considerable progress has already been made, and some of these results are reported in the following paper in this issue.

ACKNOWLEDGMENTS

Financial support of this work by the Natural Sciences and Engineering Research Council (NSERC) of Canada is gratefully acknowledged. We are indebted to Dr. P. J. Carroll and Prof. D. H. Berry, University of Pennsylvania, U.S.A. for the x-ray data collection and processing and for solving the structure prior to final refinement. CLM thanks NSERC for a Postgraduate Scholarship.

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7. Colorless transparent crystals were grown from a dichloromethane/methanol mixture by diffusion; $C_{56}H_{72}O_4$, $M = 809.18$, triclinic, space group $P\bar{1}$, $a = 14.936(1)$ Å, $b = 22.140(1)$ Å, $c = 14.175(1)$ Å, $\alpha = 92.113(5)°$, $\beta = 92.349(3)°$, $\gamma = 90.636(4)°$, $V = 4680(1)$ Å^3, $Z = 4$, $d_{calcd} = 1.148$, $d_{obsd} = 1.137(5)$ g cm^{-3}, $\lambda = 0.71073$ Å, $\mu = 0.067$ mm^{-1}, $F(000) = 1760$, and $T = 296$ K. The final refinements, performed using the SHELXL-93 programs (G.M. Sheldrick, University of Göttingen, Germany), based on all 14520 independent reflections and 839 variables, led to $R1 = 0.1472$, $wR2 = 0.3623$. The asymmetric unit contains two independent molecules, in which all eight of the hexyl groups (four in each molecule) are disordered, with the exception of the first carbon atom in each of the hexyl chains. This disorder limits the overall precision of the structure (in terms of agreement factors), but the structure of the macrocyclic core has been determined with good precision for each of the independent molecules.
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SPECTROSCOPIC DATA

Cyclophane 3: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (m, 12 H), 1.2-1.9 (m, 40 H), 2.72 (m, 4 H), 3.00 (s, 8 H), 3.37 (m, 4 H), 6.44 (s, 2 H), 7.75 (s, 2 H); ^{1}H NMR (300 MHz, C_6D_6) δ 1.00 (m, 12 H), 1.3-2.0 (m, 40 H), 2.34 (m, 4 H), 2.7-3.0 (m, 8 H), 3.02 (m, 4 H), 6.06 (s, 2 H), 8.00 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (CH_3), 22.8 (CH_2), 28.6 (CH_2), 29.0 (CH_2), 29.7 (CH_2), 31.3 (CH_2), 31.9 (CH_2), 42.4 (CH), 51.0 (CH), 125.6 (CH), 125.7 (CH), 135.1 (C), 136.3 (C), 139.7 (C), 196.0 (C); MS *m/z* 809, 571, 301, 243, 154; HRMS, calcd for $C_{56}H_{72}O_4$, 808.543; found, 808.537; IR (CCl_4) 1684 cm^{-1}.

Cyclophane 8: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (m, 12 H), 1.2-1.7 (m, 32 H), 2.06 (m, 8 H), 2.48 (m, 4H), 3.19 (s, 12 H), 6.69 (s, 2 H), 6.81 (s, 4 H); ^{1}H NMR (300 MHz, C_6D_6) δ 1.01 (m, 12 H), 1.2-1.8 (m, 32 H), 2.06 (m, 8 H), 2.34 (m, 4H), 2.59 (s, 4 H), 3.09 (m, 8 H), 6.19 (s, 2 H), 6.99 (s, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.7 (CH_2), 28.2 (CH_2), 28.5 (CH_2), 29.6 (CH_2), 30.6 (CH_2), 31.8 (CH_2), 40.7 (CH), 43.4 (CH), 123.7 (CH), 126.6 (CH), 130.5 (C), 132.8 (C), 133.1 (C), 176.8 (C); MS *m/z* 838, 837, 836; HRMS calcd for $C_{56}H_{74}N_2O_4$, 838.565; found, 838.556; IR (CCl_4) 1713 cm^{-1}.

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