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Articles

Methoxymetacyclophanes from 2,6-Dimethylanisole

Robert B. Bates,*[1] Sanjeev Gangwar,[1] Vinayak V. Kane,[2] Kessara Suvannachut,[1] and
Stuart R. Taylor[1]

Department of Chemistry, University of Arizona, Tucson, Arizona 85721, and Department of Chemistry, Johns Hopkins University, Baltimore, Maryland 21218

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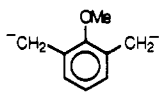
[*n*]Metacyclophanes 2 (n = 8–15), [*n.n*]metacyclophanes 3 (n = 2,5–10), and [5.5.5]metacyclophane 4 were obtained by reacting dianion 1 from 2,6-dimethylanisole with α,ω-dihalides. The favored conformations of these cyclophanes were deduced from their NMR spectra and molecular mechanics calculations. An X-ray study showed dimeric cyclophane 3 (n = 9) to crystallize in essentially the conformation calculated to be of lowest energy. The methoxyl groups move through the large ring rapidly on the NMR time scale when the ring is larger than 18-membered for monomeric cyclophanes 2, 16- or 17-membered for dimeric cyclophanes 3, and in trimeric cyclophane 4 with its 24-membered ring.

We recently reported a rearrangement of anions such as 1 in which an alkyl group moves from oxygen to carbon.[3] It was shown that when the alkyl group is methyl, this rearrangement can be largely avoided by working at room temperature, since at room temperature dianion 1 gave the simple diethyl sulfate quench product (2,6-dipropylanisole) in 62% yield. We now report that reactions of dianion 1 with α,ω-dihalides provide direct routes to [*n*]metacyclophanes 2(n = 8–15), [*n.n*]metacyclophanes 3(n = 2, 5–10), and [5.5.5]metacyclophane 4, and discuss the preferred conformations of and rotation barriers in these cyclophanes. Though these methoxycyclophanes have not been prepared previously, some of the corresponding phenols have been made by considerably longer routes.[4] Certain cyclophanes with methoxyl groups have proved to be valuable host molecules,[5] and cyclophanes like 2 mercuriated para to the alkoxyl group have been suggested as components for perforated monolayers.[6]



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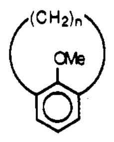

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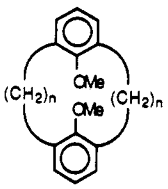

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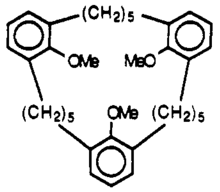

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Preparation of Cyclophanes 2–4. Table I shows the yields of cyclophanes 2–4 from 2,6-dimethylanisole via dianion 1. From its yield on quenching with diethyl sulfate, the yield of dianion 1 from 2,6-dimethylanisole is at least 62%,[3] but due to competing reactions such as oligomerization the cyclophane yields are 20% or less. The yield of monomeric cyclophanes 2 peaks at n = 10 and the smallest monomeric cyclophane 2 prepared had n = 8. When diiodides $I(CH_2)_mI$ were used instead of dibromides in efforts to make 2(n = 6, 7), 2m methylene groups were incorporated to give 2(n = 10, 12) in trace amounts; these unexpected products may result from radical couplings.

The yields of dimers 3 were small except when n = 10 (but see Table I, footnote *a*); dimers 3(n = 3, 4), though not notably strained, were not found when $ClCH_2Cl$ and $ClCH_2CH_2Cl$ were the dihalides used. Dimers were no doubt formed when $n > 10$, but were not isolated. Trimers were presumably formed in all reactions, but only 4 was isolated.

Dianion 1 was oxidized by either 1,2-dibromoethane or cuprous bromide to the dimeric cyclophane 3(n = 2). The low yield of 2% as compared to the 25% obtained in the corresponding oxidation of the dianion from *m*-xylene[7] is no doubt largely a reflection of the extra steric hindrance with the methoxyls present. As was the case with the corresponding phenol, demethyl-3(n = 2),[8] ring strain causes a reaction not seen with larger rings: 3(n = 2) decomposes completely by an unknown path upon standing in $CDCl_3$ in an NMR tube for a week. Unlike any of the other cyclophanes, 3(n = 2) gives a series of peaks in the MS at m/z 202–206 for hydrocarbons with the pyrene skeleton.

Conformations of the Cyclophanes. The NMR parameters of cyclophanes 2–4 in Tables II and III give clues as to their favored conformations, and further information was gained through molecular mechanics calculations. In

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(1) University of Arizona.

(2) Johns Hopkins University.

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Table I. Products and Yields (in Parentheses[a]) of Cyclophanes 2–4 from 2,6-Dimethylanisole via Reactions of Dianion 1 with Dihalides $X(CH_2)_mX$

m	X	2	ring size	3	ring size	4	ring size
2	Br			*n* = 2 (2)	10		
3	Br			*n* = 5 (2)	16	*n* = 5 (1)	24
4	Br			*n* = 6 (3)	18		
4	I	*n* = 10 (1)	13	*n* = 6 (1)	18		
5	Br			*n* = 7 (3)	20		
5	I	*n* = 12 (2)	15	*n* = 7 (2)	20		
6	Br	*n* = 8 (5)	11	*n* = 8 (3)	22		
7	Br	*n* = 9 (11)	12	*n* = 9 (2)	24		
8	Br	*n* = 10 (20)	13	*n* = 10 (14)	26		
9	Br	*n* = 11 (14)	14				
10	Br	*n* = 12 (7)	15				
11	Br	*n* = 13 (4)	16				
12	Br	*n* = 14[b]	17				
13	Br	*n* = 15[b]	18				

[a] These yields, except where *m* = 8, are for simultaneous additions into 500 mL of THF at 0 °C rather than into 150 mL of THF at 25 °C. Where *m* = 8, the yields were raised from 13% yield of 2(*n* = 10) and 4% of 3(*n* = 10) to the values given in the table by changing from the former to the latter conditions. The other yields could probably be raised correspondingly by making these changes. [b] Yield not determined.

Table II. ^{1}H NMR Parameters for Monomeric Cyclophanes 2(*n* = 8–15)

	chemical shifts (δ) for *n* =							
	8	9	10	11	12	13	14	15
3	6.94	6.98	7.01	6.95	6.98	6.98	6.98	6.98
4	6.98	6.98	7.01	6.95	6.98	6.98	6.98	6.98
Me	3.63	3.67	3.66	3.69	3.66	3.67	3.67	3.69
α	2.95	3.04	2.97	3.06	2.96	2.98	2.91	2.63
α′	2.43	2.41	2.46	2.28	2.39	2.38	2.39	
β	2.02	1.93	1.97	1.89	1.82	1.72	1.66	1.61
β′	0.98	1.41	1.44	1.45	1.49	1.62	1.53	
γ	1.08	0.95	1.26	0.94	1.05	1.08	1.14	1.20
γ′	1.56	1.26	1.11	1.13	1.08	1.32	1.35	
δ	−0.02	0.35	0.57	1.08	1.07	1.21	1.17	
δ′	0.88	0.98	0.95	1.25	1.21	1.11		
ε		1.16	1.16	1.13	1.07			
ε′		0.87	0.87	1.13	1.25			
ζ				0.66	1.07			
ζ′				0.66	0.96			
η								
η′						0.97		
θ,θ′								
	coupling constants (*J*, in hertz)							
αα′		12.3	13.3	13.2	13.2	13.3	13.5	13.2
αβ		4.1	4.7	4.2	3.6	3.6	4.2	4.7
αβ′		11.9	9.1	10.5	6.8	9.6	9.3	8.9
α′β,		4.4	5.7	4.2,	3.4,	3.7,	4.4,	6.2
α′β′				5.9	10.1	7.6	7.4	

Table III. ^{1}H NMR Chemical Shifts (δ) and Coupling Constants[a] for Dimeric Cyclophanes 3(*n* = 2, 5–10) and Trimeric Cyclophane 4

	3, *n* =							
H	2	5	6	7	8	9	10	4
3	7.06	6.79	6.92	6.92	6.96	6.96	6.98	6.96
4	6.87							
Me	2.93	3.60	3.61	3.60	3.64	3.65	3.69	3.60
α	2.66	2.84	2.54	2.58	2.56	2.58	2.60	2.57
α′		2.34						
β		1.70	1.49	1.50	1.56	1.56	1.58	1.62
β′		1.39						
γ, γ′		0.78	1.15	1.10	1.27	1.20	1.27	1.33
δ, δ′				1.10	1.27	1.20	1.27	
ε, ε′						1.20	1.27	

[a] Coupling constants were not determined for 3(*n* = 2) from the complex pattern observed. For 3(*n* = 5), $J_{\alpha\alpha'}$ = 13.3, $J_{\alpha\beta}$ = 3.7, $J_{\alpha\beta'}$ = 10.1, $J_{\alpha'\beta}$ = 6.4, $J_{\alpha'\beta'}$ = 3.7 Hz. For 3(*n* > 5) and 4, $J_{\alpha\beta}$ and $J_{\beta\gamma}$ are averaged to 6.9–7.6 Hz.

these tables, Greek letters with primes are used to indicate protons on the same side of the large ring as the nearest methoxyl group. All of the cyclophanes **2–4** were readily located in chromatography fractions by the upfield locations of the singlets for their methyl groups in the ^{1}H NMR spectra (Tables II and III) as compared to acyclic byproducts (~δ 3.72). The lowest energy conformations calculated for **2**(*n* = 7–15) are shown in Figure 1 and for **3**(*n* = 2–5, 9) in Figure 2. These are not of course the *only* conformations present in solution for these molecules, but they would be expected to contribute heavily to the NMR spectrum.

It is apparent from the equivalence or nonequivalence of the proton NMR absorptions of the α-methylenes in

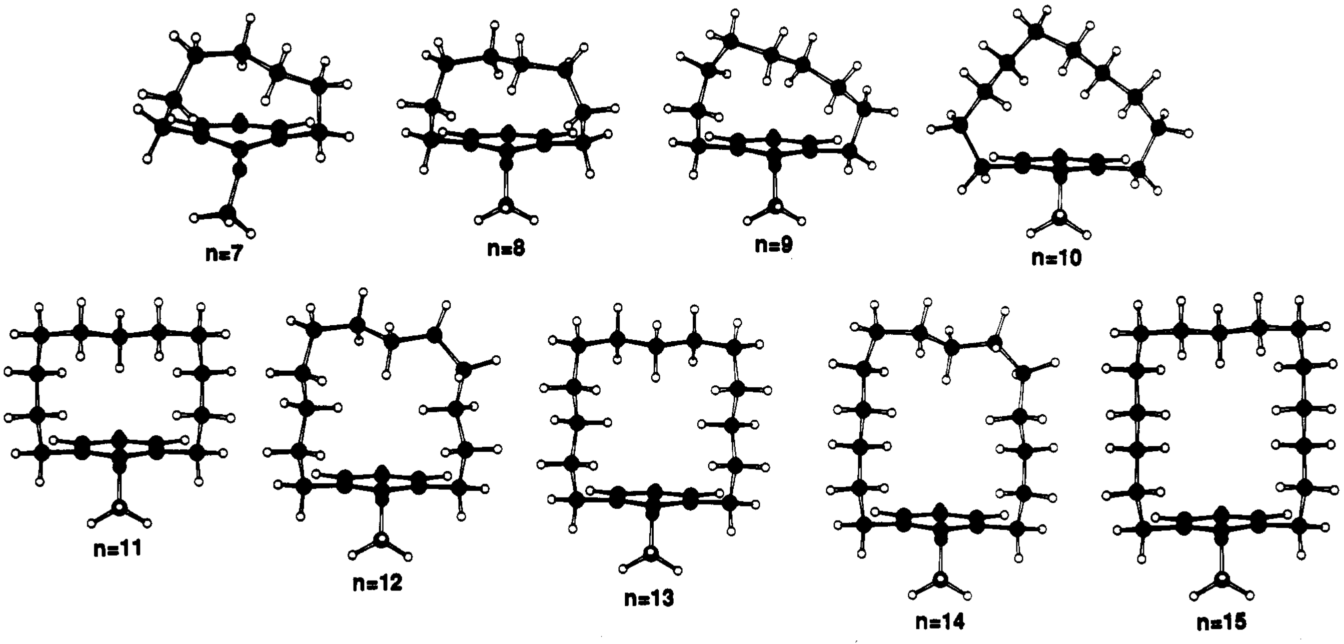

Figure 1. Lowest energy conformations calculated for monomeric cyclophanes **2**(n = 7–15).

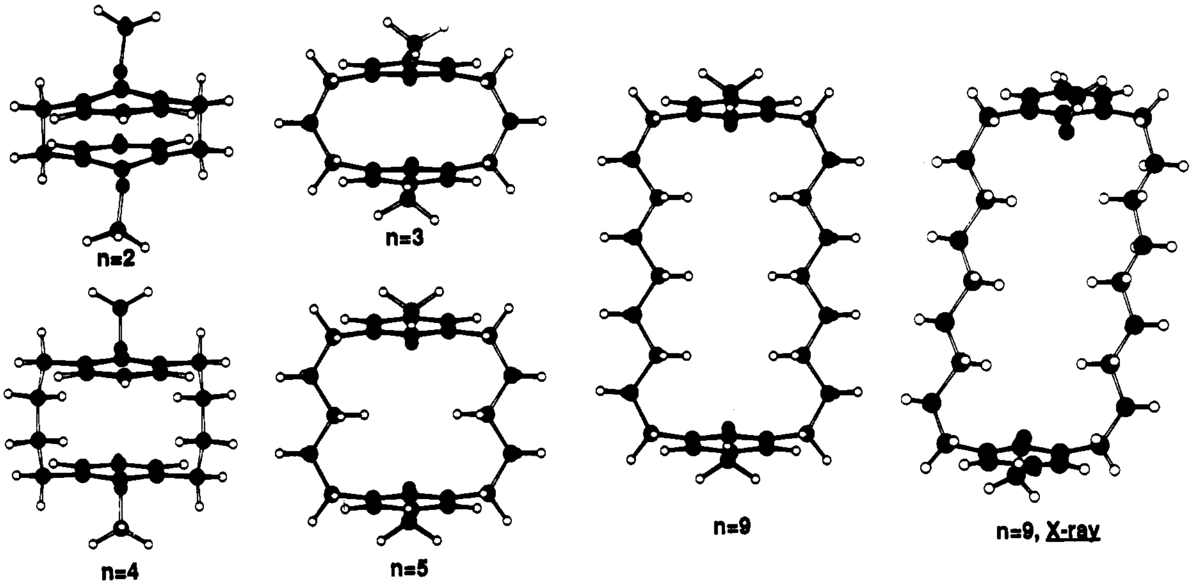

Figure 2. Lowest energy conformations calculated for dimeric cyclophanes **3**(n = 2–5, 9), and X-ray conformation of **3**(n = 9).

these cyclophanes whether or not the loop of methylenes is able to move from one side of the aromatic ring to the other rapidly on the NMR time scale. In the monomeric cyclophanes **2** the change from a tight loop in small rings to a loose loop in large ones comes at the 18-membered ring compound **2**(n = 15). For this compound, probe temperature coincides with the coalescence temperature for the α-methylene protons, whereas in the dimeric cyclophanes **3** the change comes between the 16- (**3**,n = 5) and 18-membered (**3**,n = 6) ring compounds.

Dimers **3** show alternation between two types of structures (Figure 2), depending on whether n is even or odd (the n = 6–8, 10 structures are not depicted but fit this pattern). Those with even values of n have methoxyls on opposite sides of the large ring, whereas those with odd values have methoxyls on the same side. Support for this alternation in structure comes from alternations in NMR parameters (Table III), especially the chemical shifts of the γ hydrogens, which are upfield in the n = odd dimers in accordance with structures which put the γ hydrogens more over the π cloud of the benzene ring.

Strong support for the reasonableness of the n = odd conformations depicted was obtained via an X-ray study of **3**(n = 9). Although there is a 2-fold disorder in which half the molecules are turned 180° about the vertical axis of the molecule as depicted in Figure 2, giving 14 of the 17 atoms 0.5–1.0 Å away from atoms in the other molecule, the crystal structure was solved and refined with all atoms at occupancy $^1/_2$ to R_w = 12.2%. Visual comparison (Figure 2) of the resulting structure with that of the conformation calculated to be of lowest energy shows them to be essentially the same, with torsion angles changed slightly in the crystal for better packing.

Attempts to use dimeric cyclophane **3**(n = 9) as a host molecule for 1,2-, 1,3-, and 1,4-dihydroxybenzenes and 1,3-propanediol showed (UV and NMR) no interaction in any case. Models indicate the possibility of complex formation in each case, but Cram's principle of preorganization[5] apparently keeps this cyclophane from being a good host since the larger cavity conformation required for complexation is calculated to be several kilocalories/mole above the conformation calculated to be most stable.

The conformations calculated to have lowest energies for monomers **2**($n = 7$–15) fall into *four* groups as depicted in Figure 1. The conformations of **2**($n = 11$) and **2**($n = 13$) look superficially alike, but the central methylene points away from the viewer in the former and toward the viewer in the latter; **2**($n = 12$) and **2**($n = 14$) share a similar relationship to one another. **2**($n = 11$) and **2**($n = 15$) are homologues differing by two methylenes in each vertical chain, and **2**($n = 8$) and **2**($n = 12$) are similarly homologues of one another. On the other hand, **2**($n = 7, 9, 10$) are special conformations *not* related to **2**($n = 11, 13, 14$) by such homology. All of the conformations depicted in Figure 1 have either five or six approximately gauche arrangements in the methylenes, with the additional arrangements essentially anti.

The NMR parameters in Table II generally support these calculated conformations for monomers **2**. The additional NMR parameters available when the loop is tight ($n < 15$) aided the conformational analysis. In the conformations which lack planes of symmetry ($n = 8$–10, 12, 14), the enantiomers interconvert through rotations about single bonds faster than the NMR measurement. The upfield position (δ −0.02) of the δ proton for **2**($n = 8$) is in accord with its position above the center of the aromatic ring. Examination of the conformations in Figure 1 similarly reveals why when $n = 11$–13, the furthest upfield absorptions are from the highest lettered protons, whereas when $n = 9$–10, they are from the δ protons.

Experimental Section

For general techniques, see ref 9.

Cyclophanes 2–4. 2,6-Dimethylanisole (1.4 mL, 10 mmol) was added to a magnetically stirred suspension of potassium *tert*-butoxide (4.5 g, 40 mmol) and 1.6 M *n*-BuLi (40 mmol, 25 mL) in 100 mL of dry, degassed hexane (0 °C, Ar). The yellow suspension turned orange after stirring for 5 h at 0 °C. After being stirred an additional 17 h at 25 °C, the suspension was Schlenk-filtered (Ar), washed with 100 mL of pentane, and suspended in 100 mL of pentane at 25 °C for dropwise cannulation (1 h) into 150 mL of stirring tetrahydrofuran at 25 °C[10] while an α,ω-dihalide (8.1 mmol) in 50 mL of THF was simultaneously being added dropwise. After stirring for 22 h, water (100 mL) and then 3 M HCl (75 mL) were added, and the mixture was extracted 3 × 100 mL of pentane. After drying ($MgSO_4$), filtering, and evaporating, the residue was purified by preparative thin layer chromatography on silica gel, eluting with $CHCl_3$–hexane mixtures.

Yields estimated from the ^1H NMR spectra of the crude product using 100 μL of CH_2Cl_2 as an internal standard are given in Table I. All cyclophanes **2–4** were characterized by 250- or 500-MHz ^1H NMR (Table II). ^{13}C NMR spectra were obtained on all monomers **2**. High-resolution mass spectrometry aided the characterization of **2**($n = 9$), **3**($n = 2, 9$), and **4**. Melting points are given below for cyclophanes which solidified.

2($n = 8$): ^{13}C NMR δ 159.2 (C1), 136.3 (C2), 128.0 (C3), 124.9 (C4), 61.5 (Me), 31.7, 30.5, 27.7, 23.3.

2($n = 9$): MS m/z (rel intensity, assignment) 232.1832 (100, calcd 232.1827 for $C_{16}H_{24}O$), 175 (21, $C_{12}H_{15}O$), 161 (24, $C_{11}H_{13}O$), 135 (29, $C_9H_{11}O$), 121 (51, C_8H_9O), 105 (30, C_8H_9), 91 (43, C_7H_7), 55 (21, C_4H_7); ^{13}C NMR δ 158.3 (C1), 135.0 (C2), 128.7 (C3), 123.9 (C4), 61.3 (Me), 29.3 (C_α), 26.6, 2 × 24.9, 26.1 (C_ϵ).

2($n = 10$): ^{13}C NMR δ 157.9 (C1), 135.4 (C2), 128.5 (C3), 124.1 (C4), 61.2 (Me), 29.3 (C_α), 28.0, 26.7, 26.5, 26.1.

2($n = 11$): ^{13}C NMR δ 157.6 (C1), 135.2 (C2), 129.4 (C3), 123.1 (C4), 60.5 (Me), 30.6 (C_α), 2 × 26.5, 26.3, 24.3, 24.2 (C_ζ).

2($n = 12$): ^{13}C NMR δ 157.5 (C1), 135.1 (C2), 128.5 (C3), 123.6 (C4), 60.8 (Me), 29.4 (C_α), 29.1, 27.3, 27.0, 25.9, 25.6.

2($n = 13$): ^{13}C NMR δ 157.5 (C1), 135.0 (C2), 128.2 (C3), 123.6 (C4), 60.7 (Me), 29.4 (C_α), 28.7, 27.4, 27.0, 26.8, 26.0, 26.4 (C_η).

2($n = 14$): ^{13}C NMR δ 157.4 (C1), 135.3 (C2), 128.1 (C3), 123.8 (C4), 60.8 (Me), 29.4 (C_α), 30.4, 28.2, 27.8, 27.4, 26.7, 26.3.

2($n = 15$): ^{13}C NMR δ 157.2 (C1), 135.6 (C2), 128.2 (C3), 123.7 (C4), 60.7 (Me), 30.0, 29.8, 28.0, 27.6, 2 × 27.5, 27.3, 27.1 (C_θ).

3($n = 2$): mp 218–220 °C; MS m/z 268.1479 (78, calcd 268.1463 for $C_{18}H_{20}O_2$), 237 (100, $C_{17}H_{17}O$), 236 (12, $C_{17}H_{16}O$), 206 (31, $C_{16}H_{14}$), 205 (32, $C_{16}H_{13}$), 202 (28, $C_{16}H_{10}$), 165.0660 (34), 147 (13, $C_{10}H_{11}O$), 133 (33, C_9H_9O), 121 (18, C_8H_9O), 105 (39, C_8H_9), 91 (57, C_7H_7).

3($n = 5$): mp 148–151 °C.

3($n = 6$): mp 97–99 °C.

3($n = 7$): mp 62–65 °C.

3($n = 9$): mp 124–126 °C; MS m/z 464.3666 (100, calcd 464.3654 for $C_{32}H_{48}O_2$), 161 (10, $C_{11}H_{13}O$), 147 (10), 135 (35, $C_9H_{11}O$), 121 (24, C_8H_9O), 105 (20, C_8H_9), 91 (13, C_7H_7).

3($n = 10$): mp 63–64 °C.

4: MS m/z 528.3579 (100, calcd 528.3603 for $C_{36}H_{48}O_3$), 189 (17, $C_{13}H_{17}O$), 175 (31, $C_{12}H_{15}O$), 135 (34, $C_9H_{11}O$), 121 (31, C_8H_9O), 105 (28, C_8H_9).

Calculations of Strain Energies. Using PCMODEL 4.0,[11] the lowest energy conformations found for cyclophanes **2**($n = 7$–15), depicted in Figure 1, had strain energies of 24.2, 22.2, 16.7, 14.1, 11.6, 14.0, 10.8, 14.6, and 10.8 kcal/mol, respectively. The strain energies for dimeric cyclophanes **3**($n = 2$–10), with calculated lowest energy conformations in Figure 2, were 36.4, 21.8, 16.7, 14.3, 15.2, 13.5, 14.3, 12.1, and 13.7, respectively.

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Supplementary Material Available: 500-MHz proton NMR spectra ($CDCl_3$) of **2**($n = 8$–15) and 250-MHz spectra of **3**($n = 2, 5$–10) and **4**; coordinates of the lowest energy conformations calculated for cyclophanes **2**($n = 7$–15) and **3**($n = 2$–10); and details of the X-ray study on **3**($n = 9$) (40 pages). Ordering information is given on any current masthead page.

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[9] Bates, R. B.; Siahaan, T. *J. Org. Chem.* **1986**, *51*, 1432.

[10] See Table I, footnote *a*.

[11] PCMODEL 4.0, Serena Software, Bloomington, IN 47407-3076.