Stereoselective Synthesis of Dimethoxy[*n*.2]metacyclophanes[1)]

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Synopsis. Dimethoxy[*n*.2]metacyclophanes were obtained in 5—45% yields through [2+2] photocycloaddition of corresponding styrene derivatives. These cyclobutane-fused metacyclophanes were assigned to be of only *syn* conformation (n=6, 8, 10, and 12). The cyclobutane ring exclusively took the opposite direction to the alkyl bridged chain.

[2+2] Photocycloaddition of styrene derivatives is one of the excellent methodology for cyclobutane-fused [*n*.2]ortho-,[2)] meta,-[3)] and paracyclophanes.[4)] Since this method can give [*n*.2]cyclophanes differing inch-by-inch from each other, one can use them for the systematic study of their static or dynamic molecular structures and functions. The homologs of [*n*.2]metacyclophanes and methoxyl group-substituted ones were investigated on their conformer distribution.[3,5)] Consequently the effect of methoxyl group was clarified to force the skeletons to take *syn* conformation exclusively, when the group was substituted on *ortho* position of the benzene ring adjacent to the fused cyclobutane ring.[5)] This result, however, is easily understood because of a severe steric repulsion between the methoxyl group and the cyclobutane methylene group in *anti* conformer. The methoxyl group located at *meta* or *para* position of the cyclobutane bridge would exert different effect on the conformation of [*n*.2]metacyclophanes. So, we were prompted to study the substituent effect at *para* position. In this note, we would like to report the synthesis and structural analysis of dimethoxyl derivatives of cyclobutane-fused [*n*.2]metacyclophanes having cyclobutane ring bridge and methoxyl groups at *para* position to each other (Scheme 1).

Experimental

General Procedure of [*n*.2]Metacyclophane Syntheses. 1,6-Bis[2-methoxy-5-(1-hydroxyethyl)phenyl]hexane (2a). A solution of acetic anhydride (56.1 g, 0.550 mol) in 1,1,2,2-tetrachloroethane (54 cm^3) was gradually added into a mixture of 1,6-bis(2-methoxyphenyl)hexane **1a** (68.0 g, 0.228 mol) and $AlCl_3$ (125 g, 0.935 mol) in nitrobenzene (109 cm^3) and 1,1,2,2-tetrachloroethane (54 cm^3) at 0 °C and stirred for 12 h at room temperature. The reaction mixture was poured into cold 10% HCl solution and extracted with benzene (1.2 dm^3). After drying over Na_2SO_4 and evaporation, 1,6-bis(2-methoxy-5-acetylphenyl)hexane was isolated in a 63% yield by column chromatography (SiO_2, benzene/ethyl acetate=9/1 as an eluant). ^{1}H NMR ($CDCl_3$, 60 MHz) δ=1.42 (8H, m), 2.50 (6H, s), 2.58 (4H, m), 3.83 (6H, s), 6.77 (2H, d, J=9.0 Hz), 7.65 (2H, d, J=2.2 Hz), and 7.71 (2H, dd, J=9.0 and 2.2 Hz). A solution of 1,6-bis(2-methoxy-5-acetylphenyl)hexane (54.7 g, 0.143 mol) in THF (500 cm^3) was added dropwise into a suspension of $LiAlH_4$ (7.48 g, 0.197 mol) in THF (200 cm^3) below 10 °C. After stirring for 20 h, the mixture was poured into cold 10% HCl solution and extracted with benzene (3 dm^3). After drying over Na_2SO_4 and evaporation, the crude product **2a** was obtained in a quantitative yield and used in a next step without further purification. ^{1}H NMR ($CDCl_3$, 60 MHz) δ=1.44 (8H, m), 1.45 (6H, d, J=6.2 Hz), 1.72 (2H, bs), 2.75 (4H, m), 3.77 (6H, s), 4.78 (2H, q, J=6.2 Hz), 6.73 (2H, d, J=9.0 Hz), 7.06 (2H, d, J=2.2 Hz), and 7.12 (2H, dd, J=9.0 and 2.2 Hz).

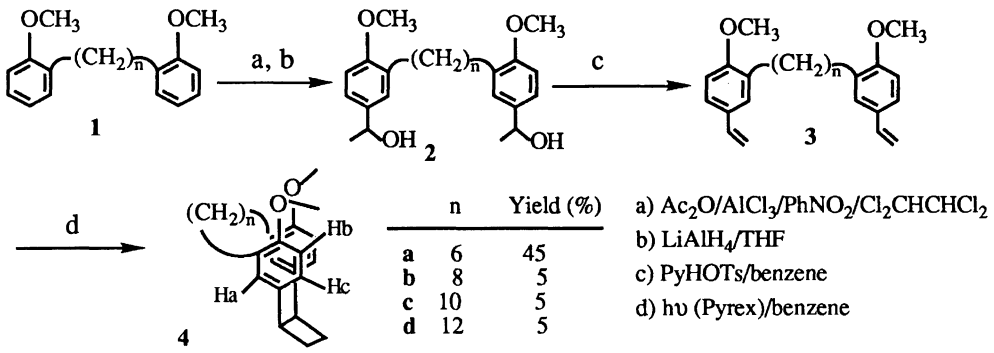
1,6-Bis(2-methoxy-5-vinylphenyl)hexane (3a). A mixture of **2a** (54.7 g, 0.142 mol) and pyridinium *p*-toluenesulfonate (3.76 g, 15.0 mmol) in benzene (1.8 dm^3) was refluxed with Dean–Stark apparatus for 12 h. After extraction with benzene (2 dm^3), drying over Na_2SO_4, and evaporation, **3a** was isolated in a 69% yield by column chromatography (SiO_2, benzene as an eluant). ^{1}H NMR ($CDCl_3$, 60 MHz) δ=1.42 (8H, m), 2.57 (4H, m), 3.75 (6H, s), 5.02 (2H, dd, J=10 and 1.6 Hz), 5.48 (2H, dd, J=17 and 1.6 Hz), 6.59 (2H, dd, J=17 and 10 Hz), 6.70 (2H, d, J=9.0 Hz), 7.07 (2H, d, J=1.8 Hz), and 7.14 (2H, dd, J=9.0 and 1.8 Hz).

1, 8- Bis(2- methoxy- 5- vinylphenyl)octane (3b). ^{1}H NMR ($CDCl_3$, 60 MHz) δ=1.35 (12H, m), 2.53 (4H, m), 3.75 (6H, s), 5.03 (2H dd, J=11 and 1.6 Hz), 5.51 (2H, dd, J=17 and 1.6 Hz), 6.62 (2H, dd, J=17 and 11Hz), 6.71 (2H, d, J=7.8 Hz), 7.05 (2H, d, J=1.8 Hz), and 7.08 (2H, dd, J=7.8 and 1.8 Hz).

1, 10- Bis(2- methoxy- 5- vinylphenyl)decane (3c). ^{1}H NMR ($CDCl_3$, 60 MHz) δ=1.06—1.93 (16H, m), 2.56 (4H, m), 3.73 (6H, s), 5.02 (2H, dd, J=10 and 1.9 Hz), 5.50 (2H, dd, J=18 and 1.9 Hz), 6.58 (2H, dd, J=18 and 10 Hz), 6.65 (2H, d, J=7.2 Hz), 7.07 (2H, d, J=1.8 Hz), and 7.13 (2H, dd, J=7.2 and 1.8 Hz).

1,12-Bis(2-methoxy-5-vinylphenyl)dodecane (3d). ^{1}H NMR ($CDCl_3$, 60 MHz) δ=1.00—1.92 (20H, m), 2.56 (4H, m), 3.88 (6H, s), 5.02 (2H, dd, J=10 and 1.6 Hz), 5.50 (2H, dd, J=17 and 1.6 Hz), 6.59 (2H, dd, J=17 and 10 Hz), 6.64 (2H, d, J=9.0 Hz), 7.10 (2H, d, J=2.0 Hz), and 7.14 (2H, dd, J=9.0 and 2.0 Hz).

8, 18- Dimethoxy[$2^{13,14}$][6.2]metacyclophane (4a). Diolefin **3a** (17.0 g, 48.6 mmol) was dissolved in dry benzene (1.6 dm^3) under nitrogen atmosphere in a Pyrex glass apparatus (2 dm^3) for photoreaction. The solution was stirred and irradiated with a 400 W high-pressure Hg lamp for 16 h. The disappearance of vinyl groups was confirmed by ^{1}H NMR. After photoreaction, the mixture was evaporated and separated by column chromatography (SiO_2, benzene as an eluant). Pure cyclophane **4a** was obtained in a 45% yield; mp 26—28 °C. Found: C, 81.62; H, 8.46%. Calcd for $C_{24}H_{30}O_2 \cdot 0.2H_2O$: C, 81.41; H, 8.65%. EIMS (70 eV) m/z 350 (M^+). IR ν (neat) 2925, 1500, 1243, 1030, and 802 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz) δ=0.96 (4H, m), 1.62



Scheme 1.

(4H, m), 2.30—2.68 (8H, m), 3.70 (6H, s), 3.96 (2H, m), 6.61 (2H, d, J=8.1 Hz), 6.79 (2H, d, J=2.1 Hz), and 6.82 (2H, dd, J=8.1 and 2.1 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ=23.92, 27.22, 28.33, 30.13, 44.36, 55.12, 109.68, 125.49, 129.63, 130.31, 133.54, and 155.93.

10,20-Dimethoxy[2^{15,16}][8.2]metacyclophane (4b); Liquid. Found: C, 80.24; H, 8.69%. Calcd for $C_{26}H_{34}O_2 \cdot 0.5H_2O$: C, 80.58; H, 9.10%. EIMS (70 eV) m/z 378 (M^+). IR ν (neat) 2936, 1500, 1248, 1038, and 820 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz) δ=1.08 (4H, m), 1.26 (4H, m), 1.48 (4H, m), 2.44 (4H, m), 2.52 (4H, m), 3.73 (6H, s), 3.93 (2H, m), 6.64 (2H, d, J=8.0 Hz), 6.73 (2H, d, J=2.0 Hz), and 6.88 (2H, dd, J=8.0 and 2.0 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ=24.62, 26.29, 27.08, 27.80, 28.71, 44.51, 55.30, 109.89, 126.18, 128.48, 129.78, 133.74, and 155.68.

12,22-Dimethoxy[2^{17,18}][10.2]metacyclophane (4c); Liquid. Found: C, 81.50; H, 9.34%. Calcd for $C_{28}H_{38}O_2 \cdot 0.3H_2O$: C, 81.63; H, 9.44%. EIMS (70 eV) m/z 406 (M^+). IR ν (neat) 2930, 1500, 1255, 1040, and 803 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz) δ=1.30 (12H, m), 1.30—1.64 (4H, m), 2.25—2.64 (8H, m), 3.74 (6H, s), 3.90 (2H, m), 6.63 (2H, d, J=8.1 Hz), 6.67 (2H, d, J=2.1 Hz), and 6.73 (2H, dd, J=8.1 and 2.1 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ=24.80, 25.87, 26.45, 27.00, 27.84, 29.48, 44.45, 55.21, 109.65, 126.01, 128.75, 130.06, 133.59, and 155.60.

14,24-Dimethoxy[2^{19,20}][12.2]metacyclophane (4d); Liquid. Found: C, 83.32; H, 9.83%. Calcd for $C_{30}H_{42}O_2$: C, 82.90; H, 9.74%. EIMS (70 eV) m/z 434 (M^+). IR ν (neat) 2930, 1500, 1248, 1038, and 804 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz) δ=1.20—1.68 (20H, m), 2.40 (8H, m), 3.73 (6H, s), 3.89 (2H, m), 6.62 (2H, d, J=8.1 Hz), 6.67 (2H, d, J=2.1 Hz), and 6.77 (2H, dd, J=8.1 and 2.1 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ=24.31, 26.52, 26.67, 27.29, 28.39, 28.86, 29.69, 44.65, 55.16, 109.59, 125.88, 129.76, 130.45, 133.50, and 155.52.

Results and Discussion

The synthetic sequence is shown in Scheme 1. α,ω-Bis(o-methoxyphenyl)alkanes **1** were used as starting materials. Diketones were obtained in 63—91% yields by the treatment with acetic anhydride and $AlCl_3$ in nitrobenzene/1,1,2,2-tetrachloroethane at room temperature for 12 h. Diols **2** were obtained in 96—100% yields by the reduction with $LiAlH_4$ in THF at room temperature for 20 h. Diolefins **3** were obtained in 46—69% yields by the dehydration with pyridinium p-toluenesulfonate under reflux in benzene. The [2+2] photocycloaddition of diolefins **3** was carried out by the irradiation with a 400 W high-pressure Hg lamp (Pyrex filter) in benzene for 16—100 h.[4] After evaporation, [n.2]metacyclophanes **4a—d** were isolated in 5—45% yields as a sole product by column chromatography.

Their structures were determined by NMR spectroscopy, including COSY, NOESY, ^{13}C, and DEPT experiments. The cyclobutane ring of metacyclophanes **4** was assigned to be of *cis* configuration by comparing ^{1}H NMR chemical shifts (δ=3.89—3.96) of cyclobutane methine protons with ones prepared previously.[2,5]

The *syn* conformation of these dimethoxymetacyclophanes was confirmed by ^{1}H NMR spectrum; i.e., *syn* conformer showed a simple spectral pattern of C_s symmetry, but *anti* conformer should give a complex one due to the lack of symmetry. It was also confirmed by Lehner's $\Delta\delta$ value[6,7] shown in Table 1,[5] because these $\Delta\delta$ values were small and nearly zero. These results suggest that a steric repulsion between methoxyl groups and methylene groups of alkyl bridge suppresses the formation of *anti* conformer. In fact, if **4** takes *anti* conformer, it becomes unstable due noteable to high strain energy by the MM2 calculations.

The direction of the cyclobutane ring to the alkyl bridge in these *syn*-metacyclophanes was easily confirmed by NOESY experiments; i.e., Ha protons possess NOE interactions with the benzyl protons of the alkyl bridge. And also, the methoxyl groups exhibit NOE interactions with Hb aromatic protons and the benzyl protons of the alkyl chain. The methylene protons of the cyclobutane ring clearly show an NOE interaction

Table 1. Conformational Analysis of Cyclophanes **4**

Compound	Observed Ha	Observed Hb	$\Delta\delta$[a]	Corrected $\Delta\delta$[b]	Assignment
4a (n=6)	6.79	6.61	0.18	−0.02	*syn*
4b (n=8)	6.73	6.64	0.09	−0.11	*syn*
4c (n=10)	6.67	6.63	0.04	−0.16	*syn*
4d (n=12)	6.67	6.62	0.05	−0.15	*syn*

a) $\Delta\delta=\delta_{Ha}-\delta_{Hb}$. b) Corrected by −0.2 ppm, since 2,4-dimethylanisole gives the chemical shift difference between Ha (3-) and Hb (6-) positions.

Table 2. Strain Energy (SE) and Strain Energy Difference (ΔSE) of Cyclophane **4**

	SE/kcal mol^{-1}	ΔSE/kcal mol^{-1}
4a	54.4	25.7
4b	54.6	25.9
4c	58.8	30.1
4d	64.7	36.0

a) Strain energy was calculated by the MM2 method. Strain energy difference (ΔSE) is based on *cis*-diphenylcyclobutane (SE=28.7 kcal mol^{-1}) as a standard.

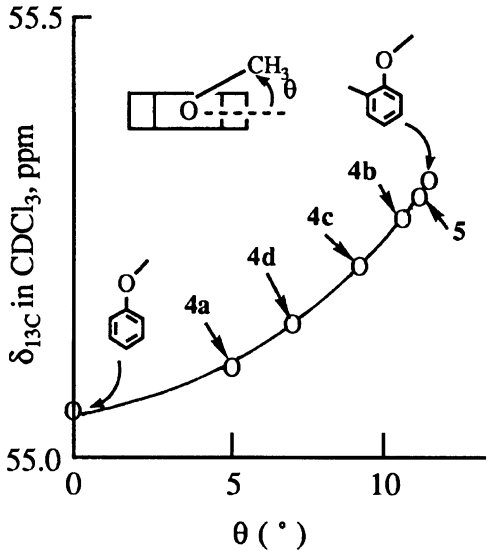


Fig. 1. Torsional angle of CH_3O group.

with Hc aromatic protons. The methine protons possess NOE interactions with Ha aromatic protons. Based on these observations, the cyclobutane ring faces to the opposite direction of the bridge as shown in Scheme 1.

The MM2 calculations also suggest the direction of cyclobutane ring. In fact, the isomers having the cyclobutane ring facing toward the bridge are ca. 1.5 kcal mol^{-1} higher in strain energy than those isolated. Accordingly, we conclude that **4** is the most stable isomer. The strain energy of **4** gradually increases from **4a** (n=6, ΔSE=25.7 kcal mol^{-1}) to **4d** (n=12, ΔSE=36.0 kcal mol^{-1}) in the range of 10 kcal mol^{-1} (see Table 2). Actually, **4a** is the most stable one among them. The dihedral angle of Ph–C–C–Ph at the fused cyclobutane ring of **4b** is larger than that of **4a** by 8°, according to the MM2 calculations. These results suggest that vinyl groups of **3** having longer bridge are difficult to approach each other. This seems to reflect the lower yields of **4** with increasing the chain length.

The methoxyl group which is attached on the bulky cyclophane skeleton exhibits the restricted conformation as reported previously[5]; i.e., the increase of methoxyl group shielding caused by the increase of the torsional angle θ. Angle θ of methoxyl group can be calculated by its ^{13}CNMR chemical shifts.[8] The obtained data together with those of substituted anisoles are shown in Fig. 1. The torsional angles of cyclophanes gathered in the range of 5—11° compared with those of substituted anisoles. Interestingly, the torsional angle of [6.2]metacyclophane **4a** is smaller than that of [6.2]-metacyclophane **5** (see Fig. 1, Chart 1). This result shows that the conformational freedom of the methoxyl group increases by replacing the position of the cyclobutane ring bridge as that of the methylene bridge relative to the methoxyl group.

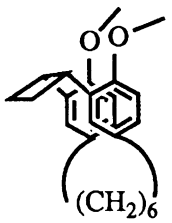


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Chart 1.

In conclusion, dimethoxy[n.2]metacyclophanes **4** (n= 6, 8, 10, and 12) were obtained in 5—45% yields. They were assigned to be exclusively of *syn* conformation.

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