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Synthesis and Structural Analysis of Dimethoxy[2.n]metacyclophanes[1)]

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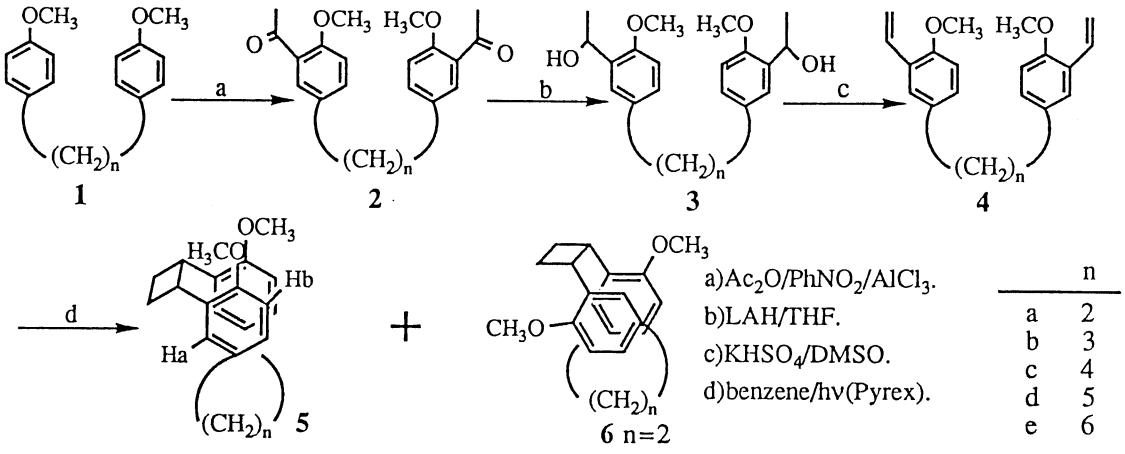
Dimethoxy[2.n]metacyclophanes were obtained in 46 - 68% yields through [2 + 2] photocycloaddition of corresponding styrene derivatives. These metacyclophanes were assigned to be of syn-conformation (n=3, 4, 5, and 6) or the mixture of syn- and anti-conformers with the syn/anti ratio of 4/3 (n=2).

Ortho,[1)] meta,[1,2)] and paracyclophanes[3)] having cyclobutane rings were readily prepared from the corresponding styrene derivatives through [2 + 2] photocycloaddition. In our previous work,[2)] the stable conformation of 1,2-ethano[2.n]metacylophanes (n=2, 3, 4, 5, and 6) was concluded to be anti except n=5. The configuration of cyclobutane ring was of cis form in [2.2]-, [2.5]-, and [2.6]metacyclophanes. But [2.3]- and [2.4]metacyclophanes contained trans one as a minor product.

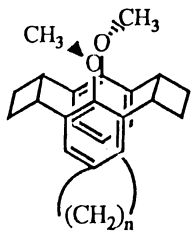
We also showed that the methoxyl group remarkably suppressed the formation of isomers in a synthesis of three-bridged cyclophanes **7** as reported previously.[4)] On the basis of these results, we investigated the steric effect of methoxyl group (anisol type) on the product distribution, which was introduced at vicinal position of cyclobutane for metacyclophane system. The conformation of metacyclophanes can be readily determined by the $\Delta\delta$ value defined by Lehner et al.[5,6)]



Scheme 1.

In this paper, we would like to report the synthesis and structural analysis of 1,2-ethano-dimethoxy[2.n]-metacyclophanes.

The synthesis of cyclophane was shown in Scheme 1. α,ω-Bis(*p*-methoxyphenyl)alkanes **1** were used as starting materials. Diketones **2** were obtained by the treatment with $AlCl_3$ and acetic anhydride in nitrobenzene at room temperature for 26 h in 32 - 55% yields. Diols **3** were obtained by the reduction with LAH in THF at room temperature for 20 h in 72 - 99% yields. Diolefins **4** were obtained by the dehydration with $KHSO_4$/DMSO at 180 °C for 3.5 min in 53 - 70% yields. [2 + 2] Photocycloaddition of diolefins **4** was carried out by the irradiation with a 400 W Hg high pressure lamp (Pyrex filter) in benzene for 16 - 92 h.[3] After evaporation, [2.n]metacyclophanes **5b**, **5c**, **5d**,[1] and **5e** were isolated with column chromatography (SiO_2, benzene) in 46 - 68% yields. [2.2]Metacyclophanes **5a** and **6**, however, became an equilibrium mixture, so that they could not be separated with either HPLC or TLC. The ^{1}H-NMR peaks for each isomers, however, could be detected separately.



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n=2, 3, and 4

Structural determination was carried out by NMR spectroscopy, including COSY, NOESY, ^{13}C, and DEPT methods. ^{1}H-NMR chemical shifts of Ha and Hb aromatic protons were listed in Table 1. Physical and analytical data are summarized in Table 2.

According to the molecular framework examination, these dimethoxymetacyclophanes are apt to take syn conformation. It is because, in the anti-conformation, the steric interaction between methoxyl group and methylene protons of ethano-bridge seems to be severe. The conformation was determined experimentally by Lehner's Δδ value as shown in Table 1.[2] It was also confirmed by ^{1}H-NMR spectrum, since syn conformer showed a symmetrical spectral pattern of C_s symmetry, whereas anti conformer did an unsymmetrical one due to C_1 symmetry. The anisotropic shielding effect of CH_3O group on the chemical shift of Hb was estimated by using 2,4-dimethylanisol as a model, whose proton chemical shifts corresponding to Ha and Hb are δ6.9 and 6.7, respectively. Hence, the chemical shift deviation due to the effect of CH_3O group is calculated 0.2 ppm.

Table 1. Conformational Analysis of Cyclophanes **5** and **6**

	Observed			Corrected	Assignment
Compound	Ha	Hb	Δδ[a]	Δδ[b]	
5a	7.03	6.08	1.0	0.8	syn
6	4.38, 5.18	6.83, 6.89	-2.5 - -1.7	-2.7 - -1.9	anti
5b	7.05	6.24	0.8	0.6	syn
5c	7.04	6.32	0.7	0.5	syn
5d	7.04	6.43	0.6	0.4	syn
5e	6.98	6.49	0.5	0.3	syn

a) $\Delta\delta=\delta_{Ha} - \delta_{Hb}$. b) Corrected by -0.2 ppm.

Dimethoxy[2.n]metacylophanes (**5b-e**) are concluded to be of syn conformation by the corrected $\Delta\delta$ value of +0.3 - +0.6. According to ^{1}H-NMR and COSY spectra, [2.2]metacyclophanes **5a** and **6** formed a mixture of syn- and anti-isomers with the ratio of 4:3. *syn*-Dimethoxy[2.2]metacyclophane has a highly strained structure, so that the repulsion between benzene rings overcomes the steric hindrance between the methoxyl groups and ethano bridge. In fact, the MM2 calculation shows that the steric energy difference of *syn*-[2.2]metacyclophane **5a** (ΔSE=27 kcal/mol) is larger than that of *syn*-[2.3]metacyclophane **5b** (ΔSE=7 kcal/mol), based on the energy of *syn*-[2.6]metacyclophane **5e**.

The cyclobutane ring of metacyclophanes **5** and **6** was assigned to be of cis configuration by ^{1}H-NMR chemical shifts (δ3.7 - 4.7) of cyclobutane methine protons.[1,2,4)]

The direction of the cyclobutane ring to the methoxyl group in these syn-metacyclophane structures was easily confirmed by NOESY experiments; i.e., the methylene protons of the cyclobutane ring clearly show an NOE interaction with Ha aromatic protons. The methoxyl groups possess NOE interactions with not only methine protons of the cyclobutane ring but also Hb aromatic protons. Accordingly, the cyclobutane ring faces to the opposite direction of the methoxyl groups as shown in Scheme 1.

The shorter the bridge chain is, the larger $\Delta\delta$ value becomes. This is considered to be due to the increase of shielding of methoxyl group, which is caused by the increase of the torsional angle θ (see Fig. 1). Angle θ

Table 2. Physical and Analytical Data of Cyclophanes **5** and **6**

Compd.	Mp/°C: Anal. Calcd (Found)[a)]: MS (M^+)[b)]: IR (υ)[c)]: ^{1}H NMR δ (intensity, multiplicity, J in Hz)[d)]
5a/6	105 - 109: For $C_{20}H_{22}O_2$; C, 81.60 (81.74), H, 7.48 (7.66): m/z 294: 1260, 1050 cm^{-1}: 1.73 - 2.15 (m), 2.30 - 2.64 (m), 2.83 - 3.22 (m), 3.50 (s), 3.72 (m), 3.81 (s), 3.85 (s), 4.38 (d, 2.1), 4.74 (m), 5.18 (d, 2.1), 6.08 (d, 8.1), 6.44 (dd, 8.1 & 2.1), 6.72 (d, 2.1), 6.83 (d, 8.1), 6.89 (d, 8.1), 7.03 (dd, 8.1 & 2.1).
5b	153 - 155: For $C_{21}H_{24}O_2$: C, 81.80 (81.74), H, 7.85 (7.58): m/z 308: 1260, 1042 cm^{-1}: 2.22 (1H, m), 2.55 (7H, m), 2.95 (2H, m), 3.55 (6H, s), 4.64 (2H, m), 6.24 (2H, d, 8.3), 6.62 (2H, dd, 8.3 & 2.2), 7.05 (2H, d, 2.2).
5c	125 - 130: For $C_{22}H_{26}O_2$; C, 81.95 (81.95), H, 8.13 (8.15): m/z 322: 1255, 1040 cm^{-1}: 1.42 (2H, bt), 1.91 (2H, bt), 2.28 (2H, bt), 2.52 (6H, m), 3.59 (6H, s), 4.57 (2H, m), 6.32 (2H, d, 8.1), 6.55 (2H, dd, 8.1 & 2.2), 7.04 (2H, d, 2.2).
5e	46 - 50: For $C_{24}H_{30}O_2$; C, 82.24 (82.04), H, 8.63 (8.42): m/z 350: 1260, 1040 cm^{-1}: 0.98 (4H, m), 1.20 - 1.86 (4H, m), 2.48 (8H, m), 3.63 (6H, s), 4.43 (2H, m), 6.49 (2H, d, 8.2), 6.76 (2H, dd, 8.2 & 2.1), 6.98 (2H, d, 2.1).

a) Microanalytical Center, Faculty of Engineering, Gunma University. b) A JEOL JMS-DX302 mass spectrometer. c) A Hitachi 270-50 infrared spectrometer with KBr-disc method. d) A Varian Gemini-200 FT NMR spectrometer. In $CDCl_3$, using TMS as an internal standard.

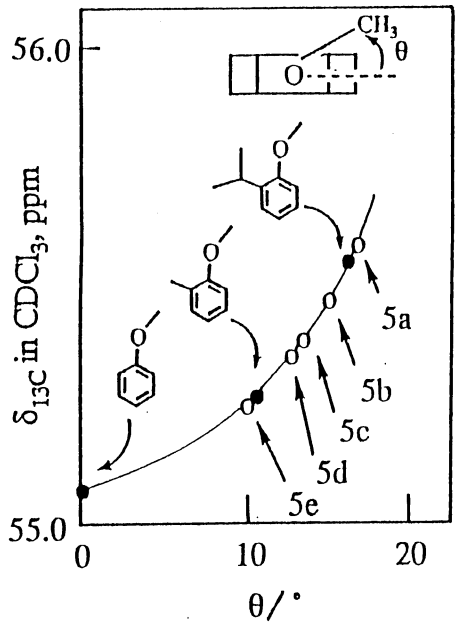

Fig. 1. Torsional angle of CH_3O group.

of methoxyl group can be calculated by its ^{13}C NMR chemical shifts.[7] The obtained data together with substituted anisols are shown in Fig. 1. The torsional angles of substituted anisols and cyclophanes gathered in the range of 10 -17 °. Generally speaking, the torsional angle becomes larger when n decreases.

In conclusion, dimethoxy[2.n]metacyclophanes (n=2, 3, 4, 5, and 6) were obtained in 46 - 68% yields. Their conformations, when n=3 - 6, are exclusively syn, while dimethoxy[2.2]metacylophane exists as a mixture of syn and anti isomers with the ratio of 4:3. Further investigation is in progress and will be reported elsewhere.

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