A Novel Calixarene-Analogous Macrocyclic Metacyclophane, "Molecular Pendulum"

Takehiko Yamoto,* Louis Korbla Doamekpor, Hirohisa Tsuzuki,† and Masashi Tashiro††
Department of Applied Chemistry, Faculty of Science and Engineering, Saga University, Honjo-machii, Saga, Saga 840
†*Center of Advanced Instrumental Analysis, Kyushu University, Kasuga-kohen 6-1, Kasuga, Fukuoka 816*
††*Institute of Advanced Material Study, Kyushu University, Kasuga-kohen 6-1, Kasuga, Fukuoka 816*

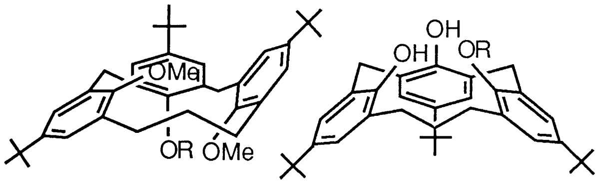
(Received October 3, 1994)

Hydroxy[3.1.1]metacyclophane, which is regarded as an unsymmetric or uncomplete "homocalixarene" bearing a propane bridge, has been synthesized using Nafion-H catalyzed cyclobenzylation. A novel "pendulum" type motion steered by intramolecular hydrogen bonding has been observed.

Conformational characteristics of macrocyclic cyclophanes, especially those of calix[n]arenes, have been extensively investigated in the past decade.[1] Their phenolic hydroxyl groups are ordered in well-shaped cyclic arrays due to strong intramolecular hydrogen bonds. Recently, Kanters *et al.* have reported that 27,28-diethoxy-*p*-*tert*-butylcalix[4]arene exhibited interconversion of equivalent partial cone conformers steered by intramolecular hydrogen bondings.[2] However, due to the low energy barrier in the conformational process, this process has been frozen on the IR time scale, but not on the ^{1}H NMR time scale. Considering the role of hydrogen bond in this study, it is surprising that reports on the preparation of calix[3]arenes and their analogs containing three benzene rings and characterization of their hydrogen bondings have been very limited.[3-5] Although the first success of preparation of *p*-halocalix[3]arenes was reported in 1982,[3] nobody has followed it so far. This fact seems to be due to the much more strained structure of calix[3]arenes than calix[n]-arenes containing the larger ring. In this paper, we describe the preparation and "pendulum" type conformational properties of [3.1.1]metacyclophanes ([3.1.1]MCP) as a propane-bridged calixarene-analogous macrocyclic MCP.

We have recently demonstrated[6] for the first time a convenient synthesis of 10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene and [2.1.1]MCPs using Nafion-H (solid perfluorinated resinsulfonic acid) catalyzed cyclobenzylation, in which a benzene molecule is directly incorporated in the cyclic system as a phenylene unit. This strategy can be employed for the preparation of hydroxyMCPs containing three benzene rings. The cyclobenzylation reaction of 3,3'-bis(methoxymethyl)-5,5'-di-*tert*-butyl-2,2'-dimethoxy-1,3-diphenylpropane **1**[7] with 4-*tert*-butylphenol **2** carried out in the presence of Nafion-H under chloroform reflux for 72 h afforded the desired 16-hydroxy-9,23-dimethoxy-6,13,20-tri-*tert*-butyl[3.1.1]MCP **3** in 17% yield. Chloroform gave the optimum yield for **3** whereas other solvents (*e.g.* methylene dichloride, 1,2-dichloroethane, 1,4-dioxane, sulfolane) either gave trace quantities or none of the desired product **3**. [3.1.1]MCP **3** was easily separated from the crude reaction mixture by column chromatography over silica gel using benzene as an eluent.

The structure of **3** has been elucidated on the basis of its elemental analyses and spectral data. For instance, the mass spectral data for **3** ($M^+ = 542$) strongly supports intramolecular cyclobenzylated macrocyclic structure. The calixarenes show concentration-independent hydroxyl stretching bands in the 3200 cm^{-1} region of the infrared spectrum and a signal at δ 9-10 in the ^{1}H-NMR spectrum, indicative of very strong intramolecular hydrogen bonding and the cyclic nature of calixarenes.[1] The IR (KBr) spectra of **3** shows the absorption for the hydroxyl stretching vibration around 3350 cm^{-1}. The ^{1}H-NMR spectra (in $CDCl_3$) exhibit the signals for hydroxyl groups around δ 7.39. These data show the existence of the intramolecular hydrogen bonding between the hydroxy group and methoxy groups of cyclic product **3**. ^{1}H NMR spectrum of macrocycle **3** presents two sets



3; R = H **5**; R = Me
4; R = Me **6**; R = H
"partial cone" "cone"

Figure 1. Schematic illustration of conformers.

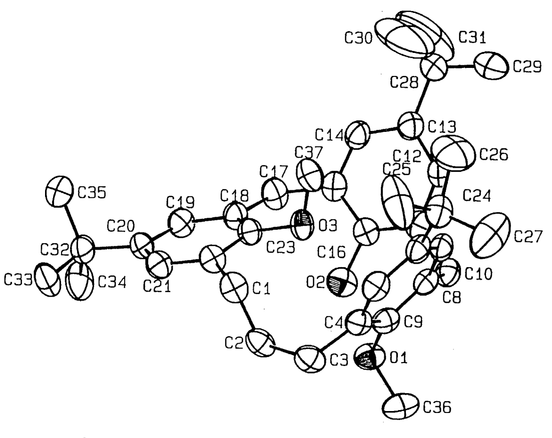
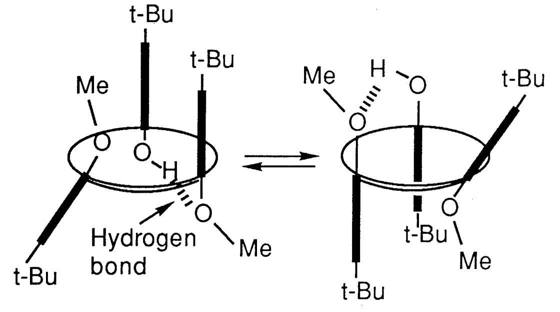


Figure 2. X-ray structure of [3.1.1]MCP **3**.



— Methylene bridge; ═ Propane bridge

Figure 3. Schematic representation of the ring inversion of hydroxy[3.1.1]MCP **3**.

of doublets at δ 3.41, 4.12 (J = 12.7 Hz) and 3.71, 4.09 (J = 16.1 Hz) for the $ArCH_2Ar$ methylene protons and two single peaks at δ 2.29 and 3.62 for methoxy protons. The dimethoxy compound **3** is fixed to form an asymmetric "partial cone" conformation at room temperature by the observation of two sets of doublets for the methylene protons. Thus, in this conformation the two methoxy groups in the compound point up and down with one of them folded into the π-cavity by two benzene rings and thus shielded greater upfield at δ 2.29. The crystal structure of **3** is shown in Fig. 2.[9] It is clear that one methoxy group is present between two aromatic rings that are forced towards each other as predicted from the ^{1}H NMR data.

The conformations of the present system have also been evaluated by means of dynamic ^{1}H-NMR spectroscopy. From the observation of resonances arising from the $ArCH_2Ar$ methylene protons and the methoxy protons, the pattern of the spectra becomes a sharp singlet above 80°C. This behavior indicates that the rate of conformational ring flipping of macrocycle **3** is faster than the NMR time scale above this temperature. The coalescence temperature (T_c) for methylene protons of $ArCH_2Ar$ is 80°C in $CDBr_3$ and the free energy of activation for inversion ($\Delta G^{\neq}$) is estimated to be 16.7 kcal/mol. As indicated above two possible structures could be drawn for this conformation based on the position of the OH group which could form a hydrogen bond with either of the methoxy oxygens like a "molecular pendulum". This phenomenon is shown in Fig. 3.

Demethylation of compound **3** with BBr_3 in dichloromethane was carried out at room temperature for 3 h to afford the dihydroxy[3.1.1]MCP **5** in 74% yield along with the triol **6** in 25% yield. The IR (KBr) spectra of diol **5** and triol **6** show the OH stretching absorption around 3300 and 3267 cm^{-1}, respectively. The ^{1}H-NMR spectra (in $CDCl_3$) show the signals for hydroxy groups around δ 3.49, 4.20 for diol **5** and δ 4.20, 5.89 for triol **6**, respectively. ^{1}H NMR spectrum of macrocycle **6** presents a set of doublets at δ 3.60 and 4.13 (J =14.7 Hz) for the $ArCH_2Ar$ methylene protons, two singlet peaks at δ 1.26 and 1.28 for *tert*-butyl protons (relative intensity 1:2). The aromatic protons appeared as a singlet (δ 7.13) and a set of broad singlets (δ 7.00 and 7.08)(relative intensity 1:1:1). From these data, it is deduced that triol **6** adopts a symmetric "cone" conformation (C_2 symmetry) at room temperature.

From the observation of the dynamic ^{1}H-NMR spectroscopy of triol **6**, the coalescence temperature of the methylene protons of $ArCH_2Ar$ is 140°C and the free energy of activation for inversion is estimated to be 19.5 kcal/mol (T_c = 140°C, $\Delta\upsilon$ = 143.3 Hz) in hexachloro-1,3-butadiene-$CDCl_3$ (3:1). The value of the free energy of activation for inversion is greater than that of calix[4]arene (15.7 kcal/mol).[10] In pyridine solution the intramolecular hydrogen bonding is disrupted, and the value for the free energy of activation for inversion decreases [17.2 kcal/mol (T_c = 100°C, $\Delta\upsilon$ = 223.9 Hz) in pyridine[D_5]-$CDCl_3$ (3:1)]. This result strongly suggests that the intramolecular hydrogen bonding among the hydroxyl groups between the diarylmethane units and the diarylpropane unit may fix the "cone" conformation like calix[4]arenes.[1, 10]

On the other hand, the spectra of trimethoxy derivative **4**, which was prepared by methylation of triol **6** with MeI, showed three kinds of methoxy protons, each as a singlet at δ 2.71, 3.37 and 3.41. The methylene protons appeared as two sets of doublets [δ 3.20, 4.21 (J =12.0 Hz) and 3.76, 3.90 (J =16.1 Hz)] and three single peaks at δ 1.20, 1.28 and 1.32 for *tert*-butyl protons (relative intensity 1:1:1). These signals correspond to an asymmetric structure. From these data, it is deduced that **4** adopts an unsymmetric "partial cone" conformation. It was also found that the methyl group is large enough to inhibit the oxygen-through-the-annulus rotation based on the dynamic ^{1}H-NMR spectroscopy of macrocycle **4** [T_c > 140°C, $\Delta G^{\neq}$ > 25 kcal/mol in hexachloro-1,3-butadiene-$CDCl_3$ (3:1)]. This result strongly suggests that in macrocycle **3** the introduction of two methyl groups on the phenolic oxygens should lead to a situation, where neither of the two OMe groups within the propane-bridge can undergo the oxygen-through-the-annulus rotation like a "molecular pendulum". This motion could only be possible for the OH group through an intramolecular hydrogen bonding between the hydrogen of this group (OH) and either of the methoxy oxygens.

In conclusion, we have demonstrated a novel "pendulum" type motion steered by intramolecular hydrogen bonding by ^{1}H-NMR method, the first of its kind in the calixarene field.

References and Notes

1 For a comprehensive review of all aspects of calixarene chemistry, see: C. D. Gutsche, *Calixarenes*, Royal Society of Chemistry, Cambridge, **1989**.

2 J. A. Kanters, A. Schouten, E. Steinwender, J. H. van der Maas, L. C. Groenen, and D. N. Reinhoudt, *J. Mol. Struct.*, **269**, 49 (1992).

3 A. A. Moshfegh, F. Beladi, L. Radnia, A. S. Hosseini, S. Tofigh, and G. H. Hakimelahi, *Helv. Chim. Acta.*, **65**, 1264 (1982).

4 K. Araki, N. Hashimoto, H. Otsuka, and S. Shinkai, *J. Org. Chem.*, 58, 5958 (1993); K. Araki, K. Inada, H. Otsuka, and S. Shinkai, *Tetrahedron*, **49**, 9465 (1993).

5 A. Tsuge, T. Sawada, S. Mataka, N. Nishiyama, H. Sakashita, and M. Tashiro, *J. Chem. Soc., Perkin Trans. 1*, **1992**, 1498.

6 T. Yamato, C. Hideshima, G. K. S. Prakash, and G. A. Olah, *J. Org. Chem.*, **56**, 2089 (1991); T. Yamato, N. Sakaue, Hideshima, T. Furusawa, M. Tashiro, G. K. S. Prakash, and G. A. Olah, *J. Chem. Res.*, **1991**, *(S)* 242; *(M)* 2414.

7 Compound **1** was prepared by treatment of 3,3'-bis(chloromethyl)-5,5'-di-*tert*-butyl-2,2'-dimethoxy-1,3-diphenylpropane[8] with sodium methoxide in methanol in 90% yield.

8 T. Yamato, J. Matsumoto, K. Tokuhisa, K. Suehiro, and M. Tashiro, *Chem. Ber.*, **125**, 2443 (1992).

9 Recrystallized from chloroform-methanol. Crystal data: chemical formula $C_{37}H_{50}O_3$; Fw 542.81, crystal system, triclinic; space group P_1 (No. 2); Z = 2; Dc = 1.124 gm^{-3}; cell dimensions, a = 12.829 (1), b = 13.810 (1), c = 10.071 (6) Å; α = 105.229 (6), β = 110.278 (6), γ = 78.787 (7) deg; V = 1604.4 (2) Å^3; R = 0.0657, R_w = 0.0949 for 4947. The distance between H (OH) and O_1 (OMe) is 2.05 (3) Å, which is reasonable value for the intramolecular hydrogen bonding [H (OH) - O_3 (OMe) = 2.92 (3) Å].

10 C. D. Gutsche and L. J. Bauer, *J. Am. Chem. Soc.*, **107**, 6052 (1985).