

Preparation and Conformational Behavior of Trimethoxyl [2.2.3] metacyclophanes

Sawada, Tsuyoshi
Institute of Advanced Material Study Kyushu University

Tsukinoki, Takehito
Tohwa Institute for Science Tohwa University

Tashiro, Masashi
Tohwa Institute for Science Tohwa University

Mataka, Shuntaro
Institute of Advanced Material Study Kyushu University

<https://doi.org/10.15017/7877>

出版情報：九州大学機能物質科学研究所報告．11（2），pp.131-134，1997-12-15．九州大学機能物質科学
研究所
バージョン：
権利関係：

Preparation and Conformational Behavior of Trimethoxyl-[2.2.3]metacyclophanes

Tsuyoshi SAWADA, Takehito TSUKINOKI,*¹ Masashi TASHIRO[¶],
and Shuntaro MATAKA

Trimethoxyl[2.2.3]metacyclophanes **5** and **8** were prepared and it was proved by ¹H-NMR spectra that the conformational change between 2,3-alternate and the cone conformers. The comparison between the dynamic NMR spectra of **8** and the computer-simulated spectra led to the energy barrier ($\Delta G^\ddagger_{298\text{K}} : 78.67 \pm 4.02 \text{ KJ mol}^{-1}$) from 2,3-alternate to cone conformers of **8**.

Introduction

The conformational study of macrocyclic metacyclophanes (MCPs) is of interest because the application for a host molecule and MCPs having four aromatic rings, for example calix[4]arenes, has been well studied.¹⁾ On the other hand, the study on the conformational behavior of MCPs having three aromatic rings is limited.²⁻⁶⁾ Recently, both 1,2-alternate and 2,2-alternate conformers were isolated in the case of trimethoxyl[2.2.1]MCPs⁷⁾ and the tri-*tert*-butyl derivative. Also, it was found that tri-*tert*-butyl-trimethoxy-,⁸⁾ and trimethoxy[2.2.2]MCP⁹⁾ take a 2,2-alternate conformation in a solution. In both MCPs, however, the corresponding cone conformer could not be detected by ¹H NMR.

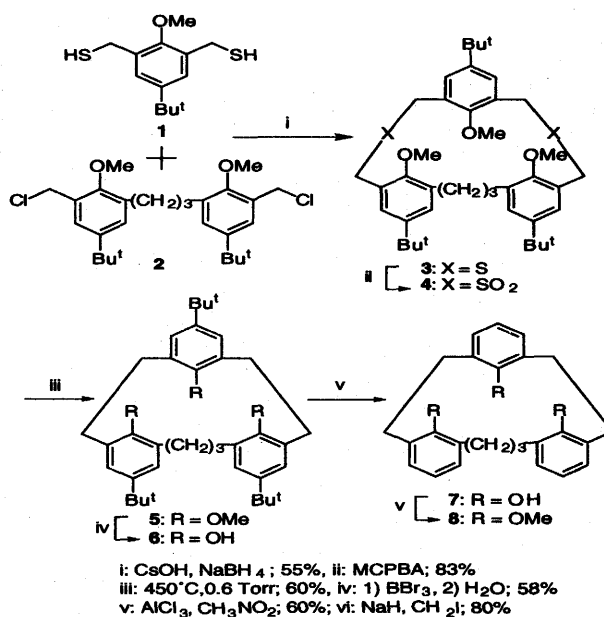
It is expected that [2.2.3]MCPs may be more flexible than [2.2.1]- and [2.2.2]MCPs to take a cone conformation, which can afford a cavity to accept a guest molecule and ions of a small size. The present paper reports the preparation and the conformational behavior of trimethoxyl[2.2.3]MCPs.

Results and Discussion

Preparation of trimethoxyl[2.2.3]MCPs

The preparation of trimethoxyl[2.2.3]MCP **5** and **8** is shown in Scheme 1. High-diluted coupling reaction of **1** and **2** gave dithia[3.3.1]MCP **3** in 55% yield. Oxidation of **3** with *m*-chloroperbenzoic acid (MCPBA), and subsequent pyrolysis of the resulted sulfone **4** at 450°C (0.6 torr) afforded the desired tri-*tert*-butyl-trimethoxyl[2.2.3]MCP **5** in 50% yield. As *trans-tert*-butylation of **5** leading to **8** afforded only tarry products, **5** was de-methylated to give trihydroxy derivative **6**; then, *tert*-butyl groups of **6** were removed by using AlCl₃-CH₃NO₂ in toluene, giving the expected trihydroxy[2.2.3]MCP **7**. Methylation of **7** gave

the desired trimethoxyl[2.2.3]MCP **8** in 80% yield.



Scheme 1

Conformational behavior of [2.2.3]MCP **5** and **8**

The ¹H-NMR spectrum showed that [2.2.3]MCP **5** takes two conformations in a solution. The methoxyl groups of the major conformer were observed, each as a singlet of equal intensity in a higher magnetic region than those of the minor conformer and also the methoxyl group of 4-*tert*-butyl-2,6-dimethyl-anisole (Figure 1). Especially, one methoxyl group of the major conformer showed remarkable up-field shift to δ 2.72 ppm, probably due to the shielding effect of the two opposing benzene rings.⁷⁾ Thus, the major conformer was elucidated to take a '2,3-alternate' conformation. On the other hand, the *tert*-butyl

Received October 3, 1997

*¹ Tohwa Institute for Science, Tohwa University

[¶] Present address: Tohwa Institute for Science, Tohwa University

and the methoxyl protons of the minor conformer were observed each as a pair of singlets of relative intensity of 2 : 1. One methoxyl group shifted to down-field (δ 4.22 ppm), as compared with the other two. On the basis of the inspection of molecular models, the shift was apparently due to the location of methoxyl protons (δ 4.22 ppm) in the region where the deshielding effect of the two equivalent benzene rings arises. Thus, it is deduced that the minor conformer is present as a 'cone' conformation (Fig. 1).

From the $^1\text{H-NMR}$ spectrum, [2.2.3]MCP **8** is determined to take the '2,3-alternate' and the 'cone' conformation in a solution, where the former is predominant, similarly to **5**. In the solid state, **8** was confirmed, by X-ray crystallographic analysis, to take the 2,3-alternate conformation (Fig. 2).

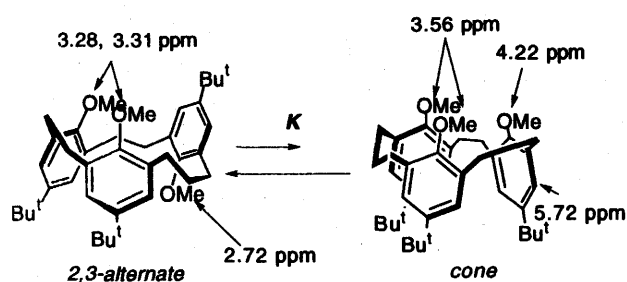


Fig. 1 Conformation and $^1\text{H-NMR}$ shifts of **5**.

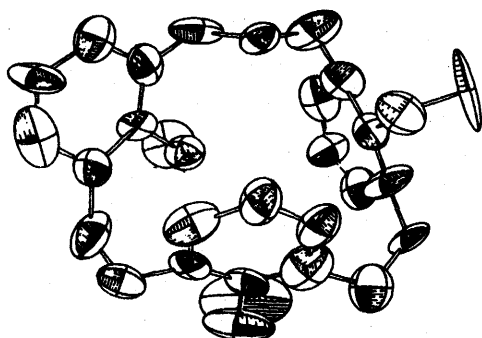


Fig. 2 ORTEP View of trimethoxyl[2.2.3]MCP **8**

The interconversion between the 2,3-alternate and the cone conformations of [2.2.3]MCP **5** and **8** was studied by dynamic NMR method at low temperature and it was found that the ratio of the cone conformer decreases with lowering of the temperature.

From the van't Hoff plot, ΔH° and ΔS° are determined as 822 J mol^{-1} and $-7.98 \text{ J mol}^{-1}\text{K}^{-1}$, respectively, for *tert*-butyl-trimethoxyl[2.2.3]MCP **5**. The difference in free energy (ΔG°) between the 2,3-alternate and the cone conformers of **5** is calculated as 3.20 kJ mol^{-1} at 25°C .

The parameters for the interconversion of trimethoxyl[2.2.3]MCP **8** are given in Fig. 3.

As shown below, ΔH° of **8** (6.73 kJ mol^{-1}) is almost eight times larger than that of **5** (822 J mol^{-1}) and ΔS° of **8** is positive ($1.37 \text{ J mol}^{-1}\text{K}^{-1}$), while that of **5** is negative ($-7.98 \text{ J mol}^{-1}\text{K}^{-1}$). These differences may be due to the

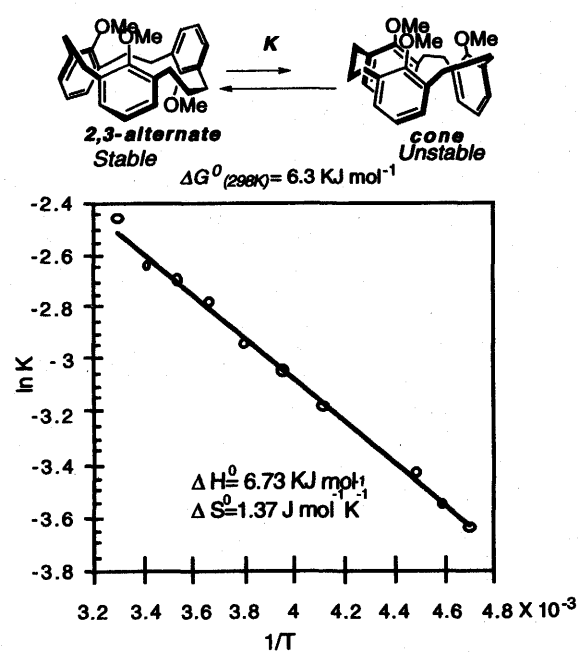


Fig. 3 Conformation and van't Hoff plot of **8**

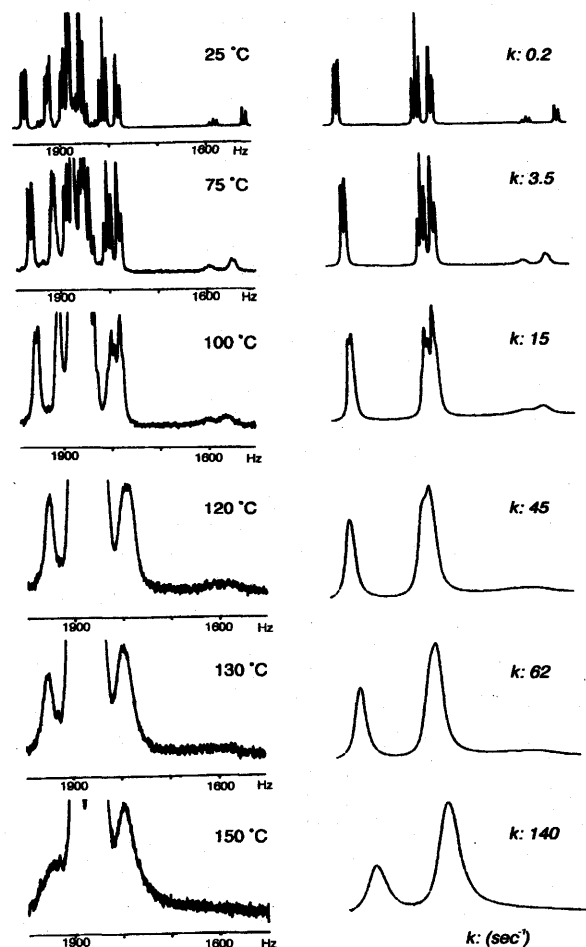


Fig. 4 Dynamic $^1\text{H-NMR}$ spectra (in nitrobenzene- d_5 , 270 MHz) and the simulated spectra of aromatic protons of **8**

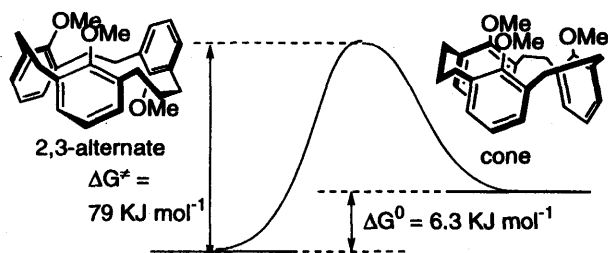


Fig. 5 Conformational behavior of **8**

presence of *tert*-butyl groups, although no definitive explanation is available at the present stage. For MCP **8**, ΔG^0 between the conformers was calculated as 6.32 kJmol⁻¹ at 25°C.

The dynamic ¹H NMR spectra and the computer-simulated spectra (DNMR2)¹⁰ of aromatic protons of **8** are shown in Fig. 4. As shown in the spectrum, [2.2.3]MCP **8** exists as a 13 : 1 mixture of 2,3-alternate and cone conformers at 25°C. As the temperature increases, the signals of the aromatic protons of the two conformers become broad, coalesce, and finally emerge as two singlets at 150°C. The rate constant (*k*) at each temperature was calculated by simulation. Arrhenius plot of 1/*T* vs ln(*k*/*T*) afforded ΔS^\ddagger (-67.45 ± 5.72 Jmol⁻¹K⁻¹) and ΔH^\ddagger (58.57 ± 2.31 KJ mol⁻¹). Thus, the energy barrier (ΔG^\ddagger) of the conformational change from 2,3-alternate to the cone at 25°C is estimated as 78.67 ± 4.02 KJ mol⁻¹ and the energy barrier from the cone to 2,3-alternate as 73 KJ mol⁻¹.

Compared with trimethoxyl[2.2.1]⁻⁷, trimethoxyl-[2.2.2]MCP⁸, [2.2.3]MCPs **5** and **8** are flexible, allowing interconversion between the 2,3-alternate and the cone conformers. The C3-carbon bridge of [2.2.3]MCP makes the flipping motion of the methoxyl-substituted benzene rings possible, even in the case of *tert*-butyl substituted [2.2.3]MCP **5**.

In the case of calix[4]arenes, the cone conformer is well recognized to show strong sodium ion-selectivity, while the other conformers do not.¹¹ Since three methoxyl groups at the internal positions of **5** and **8** point the same direction in the cone conformation, [2.2.3]MCP can be expected to be useful as a host molecule. Study in this context is of interest and now under investigation.

Experiments

General- All m.p.s were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a Nippon Bunko IR-700 spectrometer as KBr pellets. ¹H NMR spectra (internal Me₄Si) were measured on a JEOL EX270 NMR spectrometer unless stated otherwise. Mass spectra were recorded on a JEOL JMS-01SA-2 spectrometer at 75eV using direct-inlet system. Column chromatography was carried out on silica gel (Wako gel, C300).

6,15,24-tri-*tert*-butyl-9,18,27-trimethoxyl-2,11-dithia-[3.3.3]metacyclophane (3**)**: To a stirred mixture of CsOH (4.3 g, 26 mmol) and NaBH₄ (0.49 g, 13 mmol) in EtOH (4 L) under reflux, a solution of **1** (1.6 g, 6.5 mmol) and **2** (3.0 g, 6.5 mmol) in a mixed solvent of benzene (100 mL) and EtOH (400 mL) was added dropwise from a Hershberg funnel. After the addition was complete (90 h), the reaction mixture was concentrated, and extracted with dichloromethane. The extract was washed with water, dried (MgSO₄), and evaporated under reduced pressure to leave a residue, which was chromatographed with an 8 : 2-mixture of hexane-ethyl acetate as eluent to afford **3** (2.3 g, 55%); as colorless prisms (hexane), m.p. 121-124°C; IR ν (cm⁻¹) 2960 2866 1601 1480 1462 1432 1393 1299 1203; ¹H-NMR (CDCl₃, 25°C) δ (ppm) 1.24 (s, 9H), 1.28 (s, 18H), 1.60-1.96 (m, 2H), 2.40-2.68 (m, 4H), 2.94 (s, 3H), 3.31 (s, 6H), 3.55 (s, 4H), 3.62 (s, 4H), 6.99 (d, *J*=2.4Hz, 2H), 7.17 (s, 2H), 7.19 (d, *J*=2.4Hz, 2H); MS (*m/z*) 648 (M⁺). *Anal.* Found: C, 73.76; H, 8.94%. Calcd. for C₄₀H₅₆O₃S₂: C, 74.03; H, 8.70%;

6,15,24-tri-*tert*-butyl-9,18,27-trimethoxyl-11,20-dithia[3.3.3]metacyclophane-11,11,20,20-tetraoxide (4**)**: After a solution of **3** (1.0 g, 1.5 mmol) and *m*-CPBA (1.8 g, 8.5 mmol) in dichloromethane (100 mL) was stirred at room temperature for 1 h, it was washed with 10% aqueous Na₂CO₃ and water, dried over MgSO₄, and evaporated *in vacuo* and washed with hexane to give compound **4** (0.95 g, 83%) as a colorless powder, m.p. >300°C decomp.; Mass. (*m/e*) 712(M⁺); E.A. Found: C, 65.36; H, 8.05%. Calcd. for C₄₀H₅₆O₇S₂: C, 67.38; H, 7.92%; IR ν (cm⁻¹) 2956 2866 1486 1312 1258 1202 1173 1115 1007 889; ¹H-NMR (CDCl₃, 25°C) δ (ppm) 1.28 (s, 9H), 1.30 (s, 18H), 1.60-2.10 (m, 2H), 2.40-3.00 (m, 7H), 3.50 (s, 6H), 3.80-4.60 (m, 8H), 7.18 (d, *J*=2.5Hz, 2H), 7.38 (d, *J*=2.5Hz, 2H), 7.60 (s, 2H).

5,13,22-tri-*tert*-butyl-8,16,25-trimethoxyl[2.2.3]metacyclophane (5**)**: After compound **4** (4.00 g, 5.57 mmol) was pyrolyzed at 450°C under reduced pressure (0.6-0.8 Torr) according to the reported method,¹² the crude product was dissolved in CH₂Cl₂ and chromatographed over silica gel with 8 : 2 mixture of hexane-ethyl acetate as an eluant (R_f value 0.48), giving compound **5** (1.9 g, 60%) as colorless prisms (from EtOH); m.p. 145-147°C; Mass. 584(M⁺); E.A. Found: C, 82.06; H, 9.94%. Calcd. for C₄₀H₅₆O₃: C, 82.14; H, 9.65%; IR ν (cm⁻¹) 2964 2818 1482 1361 1291 1205 1173 1007; ¹H-NMR (CDCl₃) δ (ppm) cone: 2,3-alternate = 1 : 6, cone: 0.62 (s, 9H), 1.33 (s, 18H), 1.80-3.50 (m, 10H), 3.56 (s, 6H), 4.22 (s, 3H), 5.72 (s, 2H), 6.80 (d, *J*=2.4Hz, 2H), 7.13 (d, *J*=2.4Hz, 2H), 2,3-alternate : 1.18 (s, 9H), 1.28 (s, 9H), 1.33 (s, 9H), 1.80-3.50 (m, 10H), 2.72 (s, 3H), 3.28 (s, 3H), 3.31 (s, 3H), 6.56 (d, *J*=2.5Hz, 1H), 6.85 (d, *J*=2.5Hz, 1H), 6.92 (d, *J*=2.5Hz, 2H), 7.09 (d, *J*=2.5Hz, 1H), 7.16 (d, *J*=2.5Hz, 1H)

5,14,22-tri-tert-butyl-8,17,25-trihydroxy[2.2.3]metacyclophane (6): To a solution of compound 5 (204 mg, 0.349 mmol) in 15 mL of dry CH_2Cl_2 in an ice bath was added dropwise a solution of BBr_3 (2.62 g, 10.5 mmol) in 5 mL of dry CH_2Cl_2 , and the reaction mixture was stirred at room temperature for 23 h. It was poured into ice-water (50 mL) and extracted with CH_2Cl_2 . The extract was washed with water, dried over MgSO_4 , and evaporated *in vacuo* to give a residue, which, on recrystallization from EtOH, gave compound 6 (110 mg, 60%) as colorless prisms; m.p. 197-201 °C; Mass. (m/e) 542 (M^+); E.A. Found: C, 81.87; H, 9.29%. Calcd. for $\text{C}_{37}\text{H}_{50}\text{O}_3$: C, 82.07; H, 9.47%; IR ν (cm^{-1}) 3466 2956 1484 1363 1291 1175 1101 868 815; $^1\text{H-NMR}$ (CDCl_3) δ (ppm) 0.80 (s, 9H), 1.30 (s, 18H), 1.30-2.00 (m, 2H), 2.30-2.60 (m, 4H), 2.70-3.10 (m, 8H), 4.83 (brs, 1H), 4.90 (brs, 2H), 6.60 (s, 2H), 6.81 (d, $J=2.5\text{Hz}$, 2H), 7.60 (d, $J=2.5\text{Hz}$, 2H).

8,17,25-trihydroxy[2.2.3]metacyclophane (7): To a solution of compound 6 (150 mg, 0.28 mol) in dry toluene (30 mL) was added a solution of AlCl_3 (2 g) in CH_3NO_2 (4 mL). After the reaction mixture was stirred for 14 h at room temperature, it was poured into ice-water (100 mL) and extracted by CH_2Cl_2 . The extract was washed, dried over MgSO_4 and evaporated *in vacuo* to leave a residue, which, on recrystallization from Et_2O , gave compound 7 (60 mg, 58%) as colorless plate, m.p. 178-179 °C; Mass (m/e) 374 (M^+); E.A. Found: C, 80.19; H, 7.00%. Calcd. for $\text{C}_{25}\text{H}_{26}\text{O}_3$: C, 79.77; H, 7.01%; IR ν (cm^{-1}) 3368, 2930, 1461, 1203, 1072, 743; $^1\text{H-NMR}$ δ (ppm) 1.10-1.52 (m, 2H), 2.49 (t, $J=7\text{Hz}$, 4H), 2.70-3.20 (m, 8H), 4.68 (s, 2H), 5.00 (s, 1H), 6.40-7.20 (m, 9H).

8,17,25-trimethoxy[2.2.3]metacyclophane (8): To a suspension of NaH (130mg, 2.7mmol) in 10 mL dry DMF was added a solution of compound 7 (100 mg, 0.27 mmol) in 20 mL dry DMF under a nitrogen atmosphere. After the mixture was stirred for 3h, MeI (40 mg, 2.7 mmol) was added and the mixture was stirred at room temperature for 10h. It was poured into ice-water and extracted with CH_2Cl_2 . The extract was washed with water, dried over MgSO_4 , and evaporated *in vacuo*. The residue was chromatographed, using a mixture of hexane - CH_2Cl_2 (4 : 1) as eluant, to give compound 8 (90 mg, 80%), colorless prisms. m.p. 187-190 °C (EtOH). Mass. 416 (M^+); E.A. Found: C, 81.03; H, 7.75%. Calcd. for $\text{C}_{28}\text{H}_{32}\text{O}_3$: C, 80.73; H, 7.74%; IR ν (cm^{-1}) 2934 1464 1255 1212 1165 1074 1013 766; $^1\text{H-NMR}$ δ (Nitrobenzene- d_5 , 25°C) 2,3-alternate : cone = 13 : 1, 2,3-alternate; 1.19-1.26 (m, 1H), 1.70-1.83 (m, 1H), 1.98-2.17 (m, 2H), 2.37-2.46 (m, 1H), 2.58-2.86 (m, 6H), 2.98-3.42 (m, 3H), 3.06 (s, 3H), 3.26 (s, 6H), 3.42 (s, 6H), 6.46 (dd, 1H, $J=7.6$, 1.4 Hz), 6.70 (dd, 1H, $J=7.6$, 7.6 Hz), 6.79-6.97 (m, 5H), 7.12 (dd, 1H, $J=4.7$, 4.7Hz), 6.27 (dd, 1H, $J=4.7$, 1.3 Hz). cone 1.00-1.20 (m, 2H), 2.20-3.56 (m, 12H), 3.52 (s, 6H), 4.15 (s, 3H), 5.62 (d, $J=7.6\text{Hz}$, 2H), 5.85 (t, $J=7.6\text{Hz}$, 1H), 6.60-7.20 (m, 6H).

X-ray crystallographic analysis of 8: Crystal data: $\text{C}_{28}\text{H}_{32}\text{O}_3$, Formula weight 416, Orthorhombic; $a=14.575(1)\text{\AA}$, $b=8.836(2)\text{\AA}$, $c=17.742(2)\text{\AA}$, $V=2285.6\text{\AA}^3$, $Z=4$, space group $\text{Pna}2_1$, Cu-K α radiation $\lambda=1.54184\text{\AA}$, colorless prism. Data were collected on Enraf-Nonius CAD4 diffractometer, ω -2 θ scan type, graphite-monochromatic Cu-K α radiation, $\lambda=1.54184\text{\AA}$. Of 2236 independent reflections collected in the range $1 < \theta < 65^\circ$ 1132 with $I_o > 3\sigma(I_o)$ were taken as observed. The crystal did not show any significant decay during the data collection. Positional parameters were determined by direct methods using SIR 88¹³⁾, and were reflected by full-matrix least-squares calculations with all non-hydrogen atoms treated anisotropically and hydrogen atoms treated isotropically using scheme $w = 4F_{\text{obs}}^2 / [(\sigma I_o)^2 + 0.0016 F_{\text{obs}}^4]$ to give the final results: $R = 0.103$, $R_w = 0.112$.

References

1. For example, Gutsche, C. D., *Calixarenes*, in "Monographs in Supramolecular Chemistry", Ed. Stoddart, J. F., The royal society of chemistry; Cambridge, 1990.
2. Yamato, T., Doamekpor, L. K., Tsuzuki, H., Tashiro, M., *Chem. Lett.*, **1995**, 89.
3. Vögtle, F., Schmitz, J., Nieger, M., *Chem. Ber.*, **1992**, 125, 2523.
4. Moshfegh, A. A., Belagi, F., Radnia, L., Hosseini, A. S., Tofigh, S., Hakimelahi, G. H., *Helv. Chim. Acta*, **1982**, 65, 1264.
5. Sato, T., Wakabayashi, M., Hata, K., Kainosho, M., *Tetrahedron*, **1971**, 27, 2737.
6. Vögtle, F., *Ann.*, **1969**, 728, 728.
7. Tsuge, A., Sawada, T., Mataka, S., Nishiyama, N., Sakashita, H., Tashiro, M., *J. Chem. Soc., Perkin Trans. I*, **1992**, 12, 1489.
8. Tsuge, A., Sawada, T., Mataka, S., Tashiro, M., *Chem. Lett.*, **1992**, 3, 345.
9. Sawada, T., *thesis*, **1993**, Kyushu Univ..
10. Binsch, G., Kleier, D. A., *DNMR2*, QCPE, **1969**, No.140.
11. Shinkai, S., *Tetrahedron*, **1993**, 49-40, 8933.
12. Mitchell, R. H., *Cyclophanes*; Keehn, P. M., Rosenfeld, S. M., Eds. Academic Press: New York, I, Chapter 4, (1983), 296.
13. Burla, M. C., Camalli, M., Cascano, G., Giacobozzo, C., Polidori, G., Spagna, R., Viterbo, D., *J. Appl. Cryst.*, **1989**, 22, 389.