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Novel Calixarene Hemisphere Synthesized via Pinacol Rearrangement of [2.1.2.1]Metacyclophane

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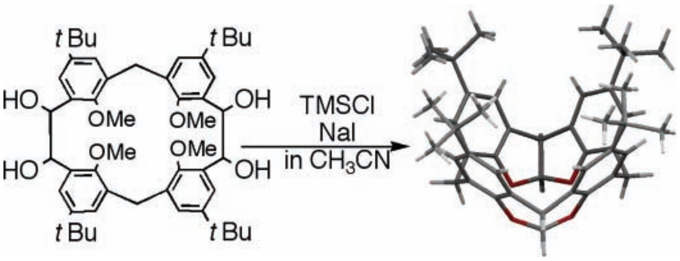
ABSTRACT



Tetramethoxy[2.1.2.1]metacyclophane ([2.1.2.1]MCP) was prepared by the pinacol coupling reaction of diphenylmethane dialdehyde. The treatment of [2.1.2.1]MCP with trimethylsilyl chloride and sodium iodide yielded two unexpected calixarene derivatives, cone (hemisphere) and 1,2-alternate types, instead of octahydroxy[2.1.2.1]MCP. The X-ray structure of the cone-type derivative and its inclusion property with acetonitrile were also discussed.

The development of macrocyclic compounds is still an attractive topic in organic synthesis because of their application in molecular recognition.[1] Recently, many researchers have shown interest in the three-dimensional structure of macrocyclic compounds. They have attempted to design molecular capsules or their hemisphere for the purpose of molecular recognition.[2]

Previously, we have reported the development of a pinacol coupling method to yield [2.2]metacyclophanes (MCPs) that have pinacol units.[3] Pinacols widely occur in many biologically active molecules such as Taxol[4a] and (−)-grayanotoxin III.[4b] They have also been used as versatile synthetic intermediates.[5]

In this study, we prepared tetramethoxy[2.1.2.1]MCP **2** from diphenylmethane dialdehyde **1** by using the pinacol coupling method. From the study of the demethylation

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(1) For recent reviews, see: (a) Gleiter, R.; Hopf, H. *Modern Cyclophane Chemistry*; Wiley-VCH Verlag GmbH & Co. KgaA: Germany, 2004; p 566. (b) Yoon, K.; Kim, K. *J. Org. Chem.* **2005**, *70*, 427. (c) Sawada, T. In *New Trends in Structural Organic Chemistry*; Takamura, H., Ed.; Research Signpost: Kerala, India, 2005; p 85.

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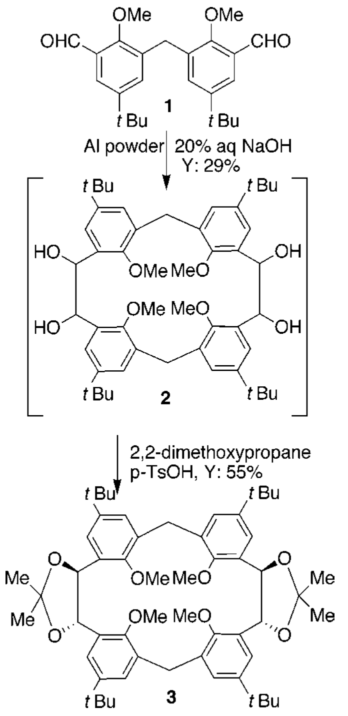
reaction of the internal methoxy groups of **2** by treatment with trimethylsilyl chloride and sodium iodide, we found that unexpected calixarene derivatives **5**, cone (hemisphere) and 1,2-alternate types, were produced instead of the expected octahydroxy[2.1.2.1]MCP **4**. In this paper, the synthesis and structure of the novel hemisphere-shaped calixarene derivative **5a** are reported.

The preparation of **2** is shown in Scheme 1.

Scheme 1. Pinacol Coupling and Ketal Condensation



Because the ^{1}H NMR spectrum of **2** was observed as unidentified broad peaks, we performed the ketal condensation of **2** using 2,2-dimethoxypropane to freeze its molecular movements. The diketal derivative **3** was formed with a yield of 55%. The structure of **3** was determined by ^{1}H NMR spectroscopy and X-ray crystallography[6] (Figure 1).

The X-ray crystallography of **3** indicated its 1,2-alternate conformation that was alternated at ethylene bridges. Both sides of the pinacol units were protected by the dimethylketal structure, and pinacol units formed dl-type bonds. Two dl-type pinacol units were placed at plane symmetrical positions, and **3** formed a meso structure. Therefore, it was suggested that the stereostructure of **2** would assume a meso-type structure similar to that of **3**.

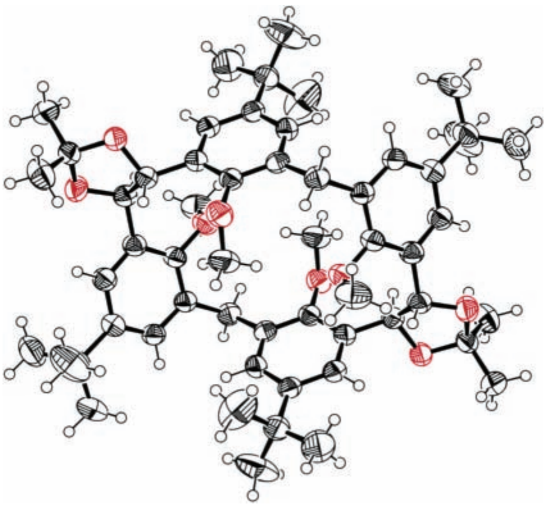
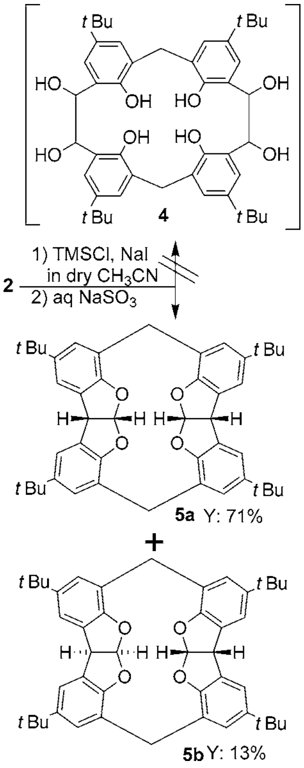


Figure 1. ORTEP view of **3**.

The treatment of trimethylsilyl chloride and sodium iodide in the demethylation of **2** yielded two unexpected products **5a** and **5b** instead of **4**. **5a** and **5b** were isolated by recrystallization and silica gel column chromatography in the ratio of 6:1 (Scheme 2). The ^{1}H NMR spectrum of **5a** is almost the same as that of **5b**; however, instead of a singlet peak of the methylene bridge positions of **5b**, a pair of doublets for the bridge protons of **5a** was identified.[7]

Scheme 2. Pinacol Rearrangement of **2**



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[6] Crystallographic data: $C_{56}H_{76}O_8$, triclinic, space group $P\bar{1}$, a = 10.585(4) Å, b = 12.668(4) Å, c = 9.841(4) Å, α = 97.61(3), β = 99.46(3), γ = 92.88(3), U = 1286.7(8) Å^3, D_c = 1.132 mg m^{-3}, Z = 1, T = 298.1 K, colorless rod, 0.30, 0.30, 0.10 mm^3. Data collection was carried out using a Rigaku AFC7R diffractometer, and the SIR92 and SHELXL97 programs were used for the structure solution and refinement. The number of reflections collected was 7146, of which 5902 were independent [R(int = 0.049)], giving R1 = 0.0710 and wR2 = 0.2260 for the observed unique reflections [$F2 > 2\sigma(F2)$]. The maximum and minimum residual electron densities on the final difference Fourier map were 0.28 and −0.25 eÅ^{-3}, respectively. Supplementary data have been deposited with the CCDC in the CIF format with the deposition number CCDC 277666.

X-ray crystallography revealed that **5a** had a $[1_4]$MCP (calix[4]arene) skeleton (Figure 2).[8]

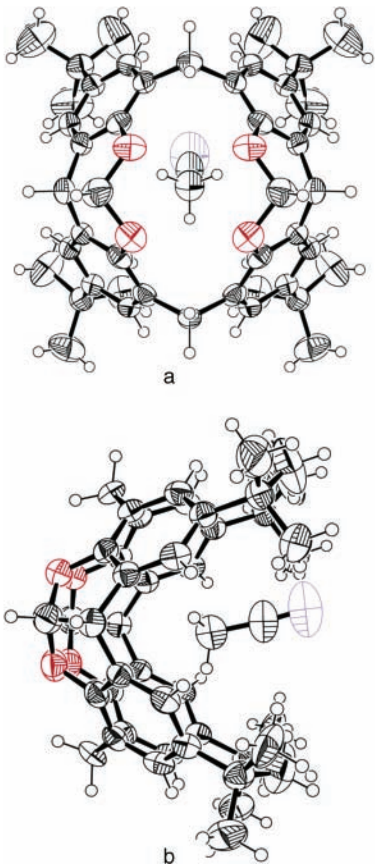

Figure 2. ORTEP view of calixarene derivative **5a**.

5a formed a fixed cone-type structure that shows a hemispherical shape and an inclusion complex with an acetonitrile molecule from the recrystallization solvent at the center of its cavity. The methyl group of acetonitrile determined the direction of the calixarene cavity, and it was placed at the center of the cavity.

These results suggest that a CH-π interaction existed between the methyl group of acetonitrile and the benzene ring of **5a**, although the distances between the acetonitrile and benzene planes were approximately 3.60−3.66 Å. The diameter of the upper and lower rims of **5a** was measured as 8.0 Å between the ipso positions of the *tert*-butyl groups and as 3.9 Å between the oxygen atoms at the internal position of calix[4]arene. These results suggest that the host−guest properties of **5a** with ammonium cations due to the cation-π interraction[9] can be observed by ^{1}H NMR spectra or UV spectra. **5a** was constructed with a couple of 5*a*,10*b*-dihydrobenzofuro[2,3-*b*]benzofuran[10] units. The rigid structure of **5a** was suggested by the dynamic NMR spectra of **5a**; the spectra indicated no remarkable variation up to 160 °C in DMSO-d_6.

On the other hand, **5b** was expected to be a stereoisomer of **5a** on the basis of a similar pattern of the ^{1}H NMR spectra of **5a** and **5b**. In the ^{1}H NMR spectrum of **5b**, the singlet peak of methylene bridge protons suggested an alternate structure of aromatic rings at the methylene bridges, and it was indicated that **5b** assumes a 1,2-alternate conformation.

Although the details of this reaction mechanism have been under investigation, a type of pinacol rearrangement was expected to proceed toward a couple of 1,2-dihydroxyl diphenyl ethane moieties in **2**. This was verified when the rearrangement reaction of 1,2-dihydro-1,2-bis(2-phenoyl)-ethane was reported to produce benzofura[2,3-*b*]- and [3,2-*b*]benzfuran.[11]

There are some reports on the tandem Claisen rearrangement applied in macrocyclic syntheses;[12] this is the first example of the pinacol rearrangement to produce a macrocyclic compound.

In conclusion, we have developed a novel hemisphere-shaped calixarene derivative **5a** and its isomer **5b** by a single-step rearrangement reaction from tetramethoxy[2.1.2.1]MCP **2**. This reaction would be regarded as a new synthetic method for calix[4]arenes, and **5a** could be applied as a new type of cage compound or as a part of molecular capsules.

Acknowledgment. We are grateful to Kumamoto University for supporting this work.

Supporting Information Available: Experimental procedures, compound characterization data, FAB-MS, and ^{1}H NMR spectra of all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) ^{1}H NMR data of **5a**: ^{1}H NMR (400 MHz, CDCl$_3$, 25C, TMS) δ = 1.23 (s, 36H, *t*BuH), 3.40 (d, ^2J(H,H) = 13 Hz, 2H, CH$_2$), 4.44 (d, ^2J(H,H) = 13 Hz, 2H, CH$_2$), 4.95 (d, ^3J(H,H) = 6 Hz, 2H, CH), 7.01 (d, ^3J(H,H) = 6 Hz, 2H, CH), 7.07 (d, ^4J(H,H) = 2 Hz, 4H, ArH), 7.08 (d, ^{4}J(H,H) = 2 Hz, 4H, ArH). ^{1}H NMR data of **5b**: δ = 1.31 (s, 36H, *t*BuH), 4.04 (s, 4H, CH$_2$), 4.76 (d, ^3J(H,H) = 7 Hz, 2H, CH), 6.37 (d, ^3J(H,H) = 8 Hz, 2H, CH), 7.02 (d, ^4J(H,H) = 2 Hz, 4H, ArH), 7.25 (d, ^4J(H,H) = 2 Hz, 4H, ArH).

(8) Crystallographic data: $C_{48}H_{55}NO_4$, orthorhombic, space group *Pnma*, a = 11.365(5) Å, b = 21.338(6) Å, c = 16.49(2) Å, U = 3999(5) Å^3, D_c = 1.179 mg m^{-3}, Z = 4, T = 298.1 K, colorless rod, 0.50, 0.30, 0.10 mm^3. Data collection was carried out using the Rigaku AFC7R diffractometer, and the SIR92 and SHELXL97 programs were used for the structure solution and refinement. The number of reflections collected was 4708, of which 2934 were independent [R(int = 0.049)], giving R1 = 0.0770 and wR2 = 0.2440 for observed unique reflections [$F2 > 2\sigma(F2)$]. The maximum and minimum residual electron densities on the final difference Fourier map were 0.41 and −0.22 eÅ^{-3}, respectively. Supplementary data have been deposited with the CCDC in the CIF format with the deposition number CCDC 277667.

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