Synthesis, Structure, and Ion-Binding Properties of New Tetraoxacalix[3]arenes

Kazunori Tsubaki,† Tatsuya Morimoto,† Tadamune Otsubo,† Takayoshi Kinoshita,‡ and Kaoru Fuji*,†,§

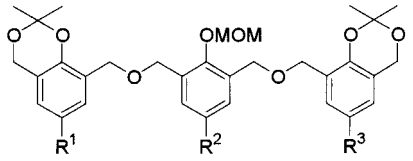
Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan, and Exploratory Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., Tokodai, Tsukuba, Ibaragi 300-2698, Japan

fuji@scl.kyoto-u.ac.jp

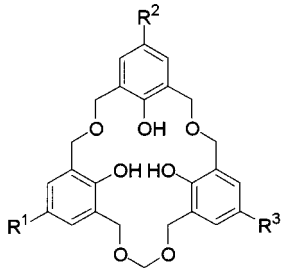
Received January 17, 2001

Introduction

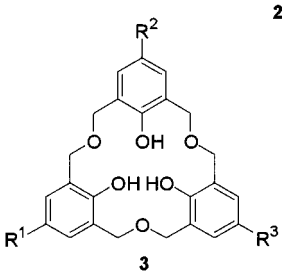
Since the monumental work on the one-step synthesis of calix[4,6,8]arenes by Gutsche, calixarenes have been extensively investigated in supramolecular chemistry as host compounds.[1] To develop more specific function or recognition, supramolecular chemists have widely used calixarene as a platform and have selectively introduced a variety of groups into the upper and lower rims. At the same time, many analogues of calixarene have also been synthesized, for example, homocalixarenes,[2] heterocalixarenes,[3] heteracalixarenes,[4] and calixarene derivatives with combinations of these properties.[5] With regard to the oxacalixarene family, we recently published a stepwise construction of hexahomotrioxacalix[3]arenes **3** based on cyclization of the corresponding linear trimers **1**.[6] In the course of our studies, we noticed that an irregular cyclic compound, heptahomotetraoxacalix[3]arene **2**, was formed as a byproduct. This tetraoxacalix[3]arene **2** is not only a new skeleton but has unique structural features such as pseudo-C_2-symmetry and a 20-membered ring consisting of three aromatic rings. This ring size is comparable to that of calix[5]arene, which has recently attracted a great deal of interest as a new host skeleton. In this paper, we describe the synthesis of the new skeleton of tetraoxacalix[3]arenes, the X-ray crystal structure, and preliminary binding studies toward alkali metal cations.



1



2



3

For compounds **1** - **3**;
a: $R^1 = R^3 = t$-Bu, R^2 = H
b: $R^1 = t$-Bu, R^2 = H, R^3 = Et
c: $R^1 = R^3 = t$-Bu, R^2 = Me
d: $R^1 = R^3 = t$-Bu, R^2 = Et
e: $R^1 = R^3 = t$-Bu, $R^2 = i$-Pr
f: $R^1 = R^2 = R^3 = t$-Bu

Results and Discussion

Synthesis of Tetraoxacalix[3]arenes 2a−f. Although the mechanism for the formation of irregular tetraoxacalix[3]arene **2** is not clear, a CH_2O fragment derived from a methoxymethyl group of linear trimer **1** should be caught in the middle of normal cyclization. Thus, we fixed linear trimer **1a** and trioxane as starting substrates to optimize the yield of **2a** and the ratio of **2a** and **3a** (Table 1). In entries 1−3, pretreated wet $CHCl_3$ was used as a solvent.[7] The selectivity of **2a**/**3a** was poor despite a large excess of trioxane, especially when a small

† Kyoto University.
‡ Fujisawa Pharmaceutical Co., Ltd.
§ Phone: +81-774-38-3190. Fax: +81-774-38-3197.

(1) For reviews on calixarenes, see: (a) Gutsche, C. D. *Calixarenes*; The Royal Society of Chemistry: Cambridge, 1989. (b) Ikeda, A.; Shinkai, I. *Chem. Rev.* **1997**, *97*, 1713−1734. (c) Gutsche, C. D. *Calixarenes Revisited*; The Royal Society of Chemistry: Cambridge, 1998.

(2) Homocalixarenes are defined as having two or more carbons forming one or more bridges between the aryl moieties. Ibach, S.; Prautzsch, V.; Vögtle, F.; Chartroux, C.; Gloe, K. *Acc. Chem. Res.* **1999**, *32*, 729−740 and references therein.

(3) Heterocalixarenes, the phenolic units of calixarene, can be substituted by heterocyclic units. For calix[4]furan, see: Musau, R. M.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2881−2888. For calix[4]pyrrole, see: Gale, P. A.; Sessler, J. L.; Král, V.; Lynch, V. *J. Am. Chem. Soc.* **1996**, *118*, 5140−5141.

(4) Heteracalixarenes, the methylene bridges of calixarene, can be substituted by heteroatoms. For oxacalix[3]arenes, see: (a) Hultzsch, K. *Kunststoffe* **1962**, *52*, 19−24. (b) Mukoyama, Y.; Tanno, T. *Org. Coat. Plast. Chem.* **1979**, *40*, 894−897. (c) Araki, K.; Inaba, K.; Otsuka, H.; Shinkai, S. *Tetrahedron* **1993**, 9465−9478. (d) Araki, K.; Hashimoto, N.; Otsuka, H.; Shinkai, S. *J. Org. Chem.* **1993**, *58*, 5958−5963. (e) Takeshita, M.; Shinkai, S. *Chem. Lett.* **1994**, 125−128. (f) Matsumoto, H.; Nishio, S.; Takeshita, M.; Shinkai, S. *Tetrahedron* **1995**, *51*, 4647−4654. (g) Masci, B. *Tetrahedron* **1995**, *51*, 5459−5464. (h) Araki, K.; Inada, K.; Shinkai, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 72−74. (i) Ikeda, A.; Suzuki, Y.; Yoshimura, M.; Shinkai, S. *Tetrahedron* **1998**, *54*, 2497−2508. (j) Ohkanda, J.; Shibui, H.; Katoh, A. *Chem. Commun.* **1998**, 375−376). (k) Tsubaki, K.; Tanaka, K.; Kinoshita, T.; Fuji, K. *Chem. Commun.* **1998**, 895−896. (l) Ashram, M.; Mizyed, S.; Georghiou, P. E. *J. Org. Chem.* **2001**, *66*, 1473−1479. (m) Masci, B. *J. Org. Chem.* **2001**, *66*, 1497−1499. For oxacalix[4]arenes, see: (n) Zerr, P.; Mussrabi, M.; Vicens, J. *Tetrahedron Lett.* **1991**, *32*, 1879−1880. (o) Masci, B.; Saccheo, S. *Tetrahedron* **1993**, *49*, 10739−10748. (p) Masci, B.; Finelli, M.; Varrone, M. *Chem. Eur. J.* **1998**, *4*, 2018−2030. For thiacalix[4]arenes, see: (q) Akdas, H.; Bringel, L.; Graf, E.; Hosseini, M. W.; Mislin, G.; Pansanel, J.; De Cian, A.; Fischer, J. *Tetrahedron Lett.* **1998**, *39*, 2311−2314. (r) Sone, T.; Ohba, Y.; Moriya, K.; Kumada, H.; Ito, K. *Tetrahedron* **1997**, *53*, 10689−10698.

(5) For examples, see: (a) Komatsu, N.; Taniguchi, A.; Suzuki, H. *Tetrahedron Lett.* **1999**, *40*, 3749−3752. (b) Lee, G.; Oka, M.; Takemura, H.; Miyahara, Y.; Shimizu, N.; Inazu, T. *J. Org. Chem.* **1996**, *61*, 8304−8306.

(6) (a) Tsubaki, K.; Otsubo, T.; Tanaka, K.; Fuji, K.; Kinoshita, T. *J. Org. Chem.* **1998**, *63*, 3260−3265. (b) Tsubaki, K.; Mukoyoshi, K.; Otsubo, T.; Fuji, K. *Chem. Pharm. Bull.* **2000**, *48*, 882−884. For one-step construction of hexahomotrioxacalix[3]arenes, see: (c) Dhawan, B.; Gutsche, C. D. *J. Org. Chem.* **1983**, *48*, 1536−1539. (d) Zerr, P.; Mussrabi, M.; Vicens, J. *Tetrahedron Lett.* **1991**, *32*, 1879−1880. (e) Hampton, P. D.; Bencze, Z.; Tong, W.; Daitch, C. E. *J. Org. Chem.* **1994**, *59*, 4838−4843. (f) Komatsu, N. *Tetrahedron Lett.* **2001**, *42*, 1733−1736.

10.1021/jo0100502 CCC: $20.00
Published on Web 04/27/2001

Table 1. Optimization of the Reaction Conditions for the Synthesis of 2a

entry[a]	equiv of trioxane	$HClO_4$[b] (μL/mg of **1a**)	H_2O (μL/mg of **1a**)	time	yield **2a**[c] (%)	yield **3a**[c] (%)
1	50	0.20	*d*	1.5 h	9	50
2	100	0.20	*d*	18 h	8	44
3	70	1.00	*d*	1 h	21	12
4[e]	70	1.00	none	10 min	0	0
5[e]	70	1.00	0.25	10 min	40	8
6[e,f]	70	1.00	0.25	10 min	37	9
7[e]	70	1.00	0.50	30 min	19	5
8[e]	70	1.00	1.00	20 h	10	4

[a] Approximately 100 mg of **1a** was used. [b] A 60% aqueous solution. [c] Isolated yield. [d] Pretreated $CHCl_3$ was used; see ref 7. [e] $CHCl_3$ stabilized with amylenes was used. [f] 2.0 g of **1a** was used.

Table 2. Cyclization of Linear Trimer to Tetraoxacalix[3]arenes

entry	linear trimer **1**	R^1	R^2	R^3	yield **2**[a] (%)	yield **3**[a] (%)
1	**1a**	*t*-Bu	H	*t*-Bu	40	8
2	**1b**	*t*-Bu	H	Et	25	8
3	**1c**	*t*-Bu	Me	*t*-Bu	23	7
4	**1d**	*t*-Bu	Et	*t*-Bu	26	8
5	**1e**	*t*-Bu	*i*-Pr	*t*-Bu	29	8
6	**1f**	*t*-Bu	*t*-Bu	*t*-Bu	30	10

[a] Isolated yield.

amount of $HClO_4$[8] was used (entries 1 and 2). Increasing the amount of $HClO_4$ reversed the ratio of **2a** to **3a** (entry 3). $CHCl_3$ was then changed to a commercially available solvent (stabilized with amylenes). The reaction did not proceed in the absence of water. Surprisingly, a small amount of water (0.25 μL for 1 mg of **1a**) affected the distribution of the products and the reaction time. The reaction was completed within 10 min, and the selectivity of **2a**/**3a** was improved to 40/8 (compare entries 3 and 5). Furthermore, we were also able to scale-up the reaction without any decrease in the yield of **2a** (entry 6). Increasing the amount of water decreased both the yield of **2a** and the ratio of **2a**/**3a** (entries 7 and 8).

The results of the formation of a variety of tetraoxacalix[3]arenes **2a**−**f** under the optimized conditions are summarized in Table 2. Tetraoxacalix[3]arenes **2a**−**f** were generated in preference to formation of hexahomotrioxacalix[3]arenes **3a**−**f** in every case. Although the selectivity **2b**−**f**/**3b**−**f** and yields of **2b**−**f** were decreased slightly, the yields (23−40%) are tolerable for a 20-membered ring-closure reaction. Tetraoxacalix[3]arene **2** was not formed with other aldehydes. Thus, *n*-butyraldehyde or paraldehyde gave **5** and **6** generated from ketal−actal exchange in respective yields of 79% and 65%.

Conformation of Tetraoxacalix[3]arene 2 in the Solid State. The four singlet signals corresponding to the methylene bridge protons were slightly broadened at −90 °C, but no coalescence temperature was observed in temperature-dependent 400 MHz ^1H NMR spectra of **2a** in CD_2Cl_2. This means that the inversion barrier of the hydroxy group through the annulus of **2a** was less than 8 kcal/mol due to flexibility of the skeleton. This inversion barrier is smaller than that of calix[5]arene (13.2 kcal/mol) and comparable to that of hexahomotrioxacalix[3]arene (<9 kcal/mol).[1a]

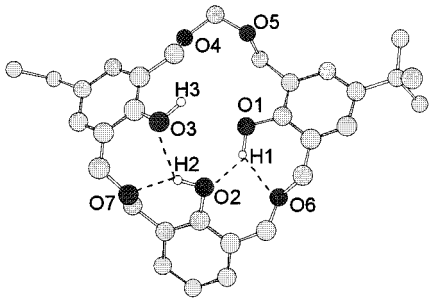
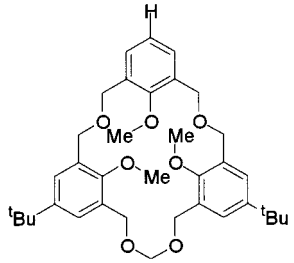
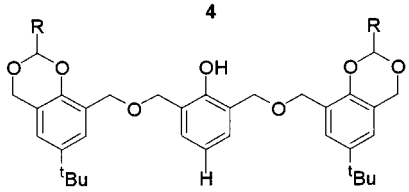


Figure 1. Crystal structure of **2b**, showing the atom-labeling scheme for the oxygens. Hydrogen atoms except phenolic hydrogen atoms are excluded for clarity.



4



5; R = *n*-Pr
6; R = Me

X-ray crystallographic analysis of some hexahomotrioxacalix[3]arenes **3** showed that **3** adopts a cone conformation due to intramolecular hydrogen bonding between each phenolic hydroxy group.[6a,9] In addition, calix[4]arene[10] and calix[5]arene[11] also exist in a cone conformation in the solid state. Therefore, it should be interesting to investigate the conformation of the flexible new skeleton of tetraoxacalix[3]arenes **2**. The crystal structure of **2b** is shown in Figure 1. The tetraoxacalix[3]arene **2b** exists in an unusual conformation in the crystalline state. The conformation is neither a cone nor a partial cone, but rather a so-called "flattened cone". Two phenolic hydrogen atoms H1 and H2 are shared with the phenolic oxygen and the ethereal oxygen (H1 by O2 and O6, H2 by O3 and O7). This kind of bifid intramolecular hydrogen bonding is also observed in the crystal structure of hexahomotrioxacalix[3]arene.[6a] However, no hydrogen bonding was observed for H3, as judged from the distances between the phenolic hydrogen atom and the two adjacent oxygen atoms (Table 3). Thus, the bifurcated intramolecular hydrogen bond network, which was ob-

(7) $CHCl_3$ was washed with water, allowed to stand for at least 6 h in a separatory funnel, and then separated. This process is required to supply H_2O for deprotection as well as to remove trace amounts of ethanol added as a stabilizer.

(8) Particular caution should be given when handling perchloric acid and related compounds; heating the reaction mixture might cause a hazardous explosion.

(9) Suzuki, K.; Minami, H.; Yamagata, Y.; Fujii, S.; Tomita, K. *Acta Crystallogr.* **1992**, *C48*, 350−352.

(10) Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Chem. Soc., Chem Commun.* **1979**, 1005−1007.

(11) (a) Coruzzi, M.; Andreetti, G. D.; Bocchi, V.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1133−1138. (b) Gallagher, J. F.; Ferguson, G.; Böhmer, V.; Kraft, D. *Acta Crystallogr.* **1994**, *C50*, 73−77.

Table 3. Distances (Å) between the Selected Oxygens and Hydrogens in 2b[a]

doner	hydrogen	acceptor	D[b]−A[c](Å)[d]	D−H (Å)	H−A (Å)
O1	H1	O2	2.866(4)	1.054(3)	1.999(3)
O1	H1	O6	2.834(4)	1.054(3)	2.019(3)
O2	H2	O3	3.011(4)	1.032(3)	2.281(3)
O2	H2	O7	2.753(4)	1.032(3)	1.860(3)
O3	H3	O1	3.728(4)	1.088(3)	3.362(3)
O3	H3	O4	4.193(4)	1.088(3)	3.791(3)
O3	H3	O5	5.036(4)	1.088(3)	4.254(3)

[a] The symmetry operations are applied to the acceptors. [b] D indicates donor. [c] A indicates acceptor. [d] Estimated standard deviations (esd's) are shown in the parentheses. They are not calculated when one of the atoms has an esd = 0.00.

served in crystalline **3**, was interrupted in **2** in the solid state. Hence, tetraoxacalix[3]arene **2** should exist in the "flattened cone" conformation.

Two-Phase Solvent Extraction of Alkali Metal Cations. Binding of the tetraoxacalix[3]arene skeleton **2a** to alkali metal cations was investigated by a two-phase solvent picrate extraction method. In the case of **2a**, negligible absorption derived from picrate in the CH_2Cl_2 layer was observed. In general, calixarene derivatives, such as calix[4,6,8]arenes[12] and hexahomotrioxacalix[3]-arenes[6e] with free phenolic hydroxy groups, did not have complexation affinities toward alkali metal cations by the two-phase extraction method. Therefore, we synthesized the neutral host **4** by methylation of the phenolic hydroxy groups of **2a** to estimate the ability of compounds with a tetraoxacalix[3]arene skeleton to complex with alkali metal cations. Metal complexation to **4** was studied by the pictrate extraction method. Percent extraction of the alkali metals to dichloromethane were found to be Li^+ (1.3%), Na^+ (3.3%), K^+ (7.2%), Rb^+ (8.5%), and Cs^+ (9.5%). Although percent extraction showed a tendency to increase as the size of the ions increases, it was not significant.

Experimental Section

General. Melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were taken at 200 MHz in $CDCl_3$ with chemical shifts being reported as δ ppm from tetramethylsilane as an internal standard and couplings expressed in hertz. Flash column chromatography was carried out with silica gel 60 spherical (150−325 mesh).

Preparation of Linear Trimers 1a−f. The linear trimers **1a−f** were prepared according to the previously reported procedure.[6a]

1a and **1f**: known.[6a]

1b. IR (neat) cm^{-1}: 2960, 2865, 1605, 1455. ^1H NMR δ: 1.20 (t, J = 7.6, 3H), 1.28 (s, 9H), 1.52 (s, 6H), 1.53 (s, 6H), 2.57 (q, J = 7.6, 2H), 3.53 (s, 3H), 4.57 (s, 2H), 4.58 (s, 2H), 4.68 (s, 4H), 4.83 (s, 2H), 4.85 (s, 2H), 5.02 (s, 2H), 6.74 (d, J = 1.7, 1H), 6.91 (d, J = 2.4, 1H), 7.15 (d, J = 1.7, 1H), 7.17 (t, J = 7.6, 1H), 7.33 (d, J = 2.4, 1H), 7.47 (d, J = 7.6, 2H). HRMS: calcd for $C_{38}H_{50}O_8$ (M^+) 634.3505. Found: 634.3503. Anal. Calcd for $C_{38}H_{50}O_8$: C, 71.90; H, 7.94. Found: C, 71.56; H, 8.02.

1c. IR (neat) cm^{-1}: 2952, 1606, 1484, 1384. ^1H NMR δ: 1.28 (s, 18H), 1.53 (s, 12H), 2.32 (s, 3H), 3.50 (s, 3H), 4.59 (s, 4H), 4.63 (s, 4H), 4.84 (s, 4H), 4.98 (s, 2H), 6.90 (d, J = 2.0, 2H), 7.25 (s, 2H), 7.34 (d, J = 2.0, 2H). HRMS: calcd for $C_{41}H_{56}O_8$ (M^+) 676.3975. Found: 676.3954. Anal. Calcd for $C_{41}H_{56}O_8$: C,72.75; H, 8.34. Found: C,72.86; H, 8.46.

1d. IR (neat) cm^{-1}: 2962, 1606, 1485, 1373. ^1H NMR δ: 1.23 (t, J = 7.6, 3H), 1.28 (s, 18H), 1.52 (s, 12H), 2.62 (q, J = 7.6, 2H), 3.51 (s, 3H), 4.59 (s, 4H), 4.64 (s, 4H), 4.84 (s, 4H), 4.98 (s, 2H), 6.90 (d, J = 2.4, 2H), 7.27 (s, 2H), 7.34 (d, J = 2.4, 2H). HRMS: calcd for $C_{42}H_{58}O_8$ (M^+) 690.4132. Found: 690.4153. Anal. Calcd for $C_{42}H_{58}O_8$: C, 73.01; H, 8.46. Found: C, 72.90; H, 8.59.

1e: mp 74−75 °C. IR (KBr) cm^{-1}: 2954, 1485, 1272, 1102. ^1H NMR δ: 1.24 (d, J = 6.8, 6H), 1.28 (s, 18H), 1.52 (s, 12H), 2.89 (hep, J = 6.8, 1H), 3.51 (s, 3H), 4.60 (s, 4H), 4.64 (s, 4H), 4.84 (s, 4H), 4.99 (s, 2H), 6.90 (d, J = 2.0, 2H), 7.30 (s, 2H), 7.35 (d, J = 2.0, 2H). HRMS: calcd for $C_{43}H_{60}O_8$ (M^+) 704.4288. Found: 704.4288. Anal. Calcd for $C_{43}H_{60}O_8$: C, 73.26; H, 8.58. Found: C, 73.03; H, 8.70.

General Procedure for the Preparation of Tetraoxacalix-[3]arenes 2a−f. The preparation of **2a** is typical. A solution of trioxane (20.0 g), 60% $HClO_4$ (2.0 mL), and water (0.5 mL) in $CHCl_3$ (300 mL, stabilized with amylenes) was stirred at room temperature for 30 min. This reaction mixture was added to a solution of the linear trimer **1a** (2.0 g) in $CHCl_3$ (100 mL), the mixture was stirred at room temperature for 10 min, and then water was added to the solution. The organic layer was separated, washed with aqueous sodium hydrogen carbonate, dried over sodium hydrogen carbonate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with hexane/EtOAc = 10/1 as an eluent to afford tetraoxacalix[3]arene **2a** (329 mg) and hexahomotrioxacalix[3]-arene **3a** (111 mg) and unseparated mixture. The mixture was further purified by recycling preparative HPLC (Japan Analytical Industry Co., Ltd. LC-908) connected with JAIGEL-1H (20 × 600 mm) and JAIGEL-2H (20 × 600 mm) under the conditions of 3.5 mL/min of flow rate with $CHCl_3$ detected by UV (254 nm) and RI (refractive index) to afford another 292 mg of **2a** and 29 mg of **3a**. In the case of small reaction scale, the residue was purified by PTLC. Yields of **2a−f** and **3a−f** are given in Table 2.

2a: mp 89 °C. IR (KBr) cm^{-1}: 3358, 2960, 1602, 1489, 1216, 1070. ^1H NMR δ: 1.28 (s, 18H), 4.74 (s, 4H), 4.75 (s, 4H), 4.84 (s, 4H), 4.92 (s, 2H), 6.76 (t, J = 7.4, 1H), 7.07 (d, J = 7.4, 2H), 7.18 (d, J = 2.4, 2H), 7.24 (d, J = 2.4, 2H), 8.05 (s, 2H), 9.12 (s, 1H). HRMS: calcd for $C_{33}H_{42}O_7$ (M^+) 550.2931. Found: 550.2915. Anal. Calcd for $C_{33}H_{42}O_7$: C, 71.97; H, 7.69. Found: C, 71.64; H, 7.72.

2b: mp 92−93 °C. IR (KBr) cm^{-1}: 3353, 2957, 1603, 1484. ^1H NMR δ: 1.19 (t, J = 7.6, 3H), 1.28 (s, 9H), 2.49 (q, J = 7.6, 2H), 4.72 (s, 2H), 4.74 (s, 4H), 4.75 (s, 2H), 4.82 (s, 2H), 4.84 (s, 2H), 4.91 (s, 2H), 6.76 (t, J = 7.4, 1H), 7.00 (d, J = 2.2, 1H), 7.06 (d, J = 2.2, 1H), 7.07 (d, J = 7.4, 2H), 7.18 (d, J = 2.3, 1H), 7.24 (t, J = 2.3, 1H), 8.06 (s, 2H), 9.11 (s, 1H). HRMS: calcd for $C_{31}H_{38}O_7$ (M^+) 522.2618. Found: 522.2629. Anal. Calcd for $C_{31}H_{38}O_7$: C, 71.24; H, 7.33. Found: C, 71.10; H, 7.42.

2c: mp 207−208. IR (KBr) cm^{-1}: 3511, 3356, 2962, 1613, 1488. ^1H NMR δ: 1.28 (s, 18H), 2.21 (s, 3H), 4.71 (s, 4H), 4.72 (s, 4H), 4.83 (s, 4H), 4.91 (s, 2H), 6.87 (s, 2H), 7.18 (d, J = 2.2, 2H), 7.23 (d, J = 2.2, 2H), 8.05 (s, 2H), 8.89 (s, 1H). HRMS: calcd for $C_{34}H_{44}O_7$ (M^+) 564.3087. Found: 564.3068. Anal. Calcd for $C_{34}H_{44}O_7 \cdot H_2O$: C, 70.08; H, 7.96. Found: C, 69.75; H, 7.58.

2d: mp185−186 °C. IR (KBr) cm^{-1}: 3514, 3348, 2961, 1488, 1217. ^1H NMR δ: 1.14 (t, J = 7.6, 3H), 1.28 (s, 18H), 2.51 (q, J = 7.6, 2H), 4.72 (s, 8H), 4.83 (s, 4H), 4.91 (s, 2H), 6.90 (s, 2H), 7.18 (d, J = 2.2, 2H), 7.23 (d, J = 2.2, 2H), 8.05 (s, 2H), 8.90 (s, 1H). HRMS: calcd for $C_{35}H_{46}O_7$ (M^+) 578.3244. Found: 578.3250. Anal. Calcd for $C_{35}H_{46}O_7 \cdot 0.5H_2O$: C, 71.52; H, 8.06. Found: C, 71.71; H, 7.89.

2e: mp 174−175 °C. IR (KBr) cm^{-1}: 3368, 2958, 1613, 1487, 1362. ^1H NMR δ: 1.16 (d, J = 6.8, 6H), 1.28 (s, 18H), 2.78 (hep, J = 6.8, 1H), 4.73 (s, 8H), 4.83 (s, 4H), 4.91 (s, 2H), 6.92 (s, 2H), 7.18 (s, 2H), 7.22 (s, 2H), 8.04 (s, 2H), 8.90 (s, 1H). HRMS: calcd for $C_{36}H_{48}O_7$ (M^+) 592.3400. Found: 592.3403. Anal. Calcd for $C_{36}H_{48}O_7$: C, 72.94; H, 8.16. Found: C, 72.61; H, 8.24.

2f: mp 83−84 °C. IR (KBr) cm^{-1}: 3369, 2958, 1611, 1488, 1216. ^1H NMR δ: 1.24 (s, 9H), 1.28 (s, 18H), 4.74 (s, 8H), 4.84 (s, 4H), 4.91 (s, 2H), 7.08 (s, 2H), 7.18 (d, J = 2.3, 2H), 7.23 (d, J = 2.3, 2H), 8.05 (s, 2H), 8.91 (s, 1H). HRMS: calcd for $C_{37}H_{50}O_7$ (M^+) 606.3556. Found: 606.3542. Anal. Calcd for $C_{37}H_{50}O_7$: C, 73.24; H, 8.31. Found: C, 72.97; H, 8.52.

3a: known.[6a]

3b and **3f**: known.[6b]

3c: mp 72−73 °C. IR (KBr) cm^{-1}: 3356, 2957, 1612, 1487. ^1H NMR δ: 1.24 (s, 18H), 2.21 (s, 3H), 4.68 (s, 4H), 4.70 (s, 4H),

(12) Chang, S.-K.; Cho, I. *J. Chem. Soc., Perkin Trans. 1* **1986**, 211−214.

4.73 (s, 4H), 6.92 (s, 2H), 7.13 (s, 4H), 8.57 (s, 3H). HRMS: calcd for $C_{33}H_{42}O_6$ (M^+) 534.2981. Found: 534.2997. Anal. Calcd for $C_{33}H_{42}O_6 \cdot 0.5H_2O$: C, 72.90; H, 7.97. Found: C, 73.27; H8.17.

3d: mp 170−171 °C. IR (KBr) cm^{-1}: 3360, 2959, 1612, 1488. ^1H NMR δ: 1.14 (t, J = 7.6, 3H), 1.24 (s, 18H), 2.51 (q, J = 7.6, 2H), 4.70 (s, 4H), 4.71 (s, 4H), 4.73 (s, 4H), 6.95 (s, 2H), 7.13 (s, 4H), 8.57 (s, 3H). HRMS: calcd for $C_{34}H_{44}O_6$ (M^+) 548.3138. Found: 548.3157. Anal. Calcd for $C_{31}H_{38}O_7 \cdot H_2O$: C, 72.06; H, 8.18. Found: C, 71.71; H, 8.01.

3e: mp 213-214 °C. IR (KBr) cm^{-1}: 3359, 2954, 1487, 1210. ^1H NMR δ: 1.16 (d, J = 7.0, 6H), 1.24 (s, 18H), 2.78 (hep, J = 7.0, 1H), 4.72 (s, 12H), 6.98 (s, 2H), 7.13 (s, 4H), 8.57 (s, 3H). HRMS: calcd for $C_{35}H_{46}O_6$ (M^+) 562.3294. Found: 562.3291. Anal. Calcd for $C_{35}H_{46}O_6$: C, 74.70; H, 8.24. Found: C, 74.41; H, 7.99.

Synthesis of 4. To a solution of **2a** (220 mg) in DMF (4 mL) was added portionwise sodium hydride (240 mg, 60% mineral oil) at 0 °C, and the suspension was stirred for 10 min. Methyl iodide (0.37 mL) was added to the suspension, and the resulting mixture was stirred for 2 h at 0 °C. The reaction mixture was poured into ice-cold water and extracted with EtOAc (three times). The organic layer was combined, washed with water (4 times) and brine, and dried over sodium sulfate. Concentration of the extract under reduced pressure gave the residue, which was subjected to silica gel column chromatography with hexane/EtOAc = 10/1 to afford desired product **4** (186 mg, 79%): mp 115 °C. IR (KBr) cm^{-1}: 2956, 1488, 1101, 1048. ^1H NMR δ: 1.29 (s, 18H), 3.14 (s, 6H), 3.44 (s, 3H), 4.47 (s, 4H), 4.59 (s, 4H), 4.59 (s, 4H), 4.86 (s, 2H), 7.06 (t, J = 7.8, 1H), 7.31 (d, J = 2.6, 2H), 7.36 (d, J = 7.8, 2H), 7.37 (d, J = 2.6, 2H). HRMS: calcd for $C_{36}H_{48}O_6$ (M^+) 592.3400. Found: 592.3409. Anal. Calcd for $C_{36}H_{48}O_7$: C, 72.94; H, 8.16. Found: C, 72.55; H, 8.14.

Trimers 5 and 6. The reaction carried out in a manner similar to the preparation of tetraoxacalix[3]arenes.

5. IR (neat) cm^{-1}: 3372, 2960, 2871, 1487. ^1H NMR δ: 0.8−1.1 (4H), 0.98 (t, J = 7.2, 6H), 1.28 (s, 18H), 1.4−1.7 (2H), 1.7−1.9 (2H), 4.58 (d, J = 11.6, 2H), 4.66 (d, J = 11.6, 2H), 4.72 (s, 4H), 4.83 (d, J = 14.8, 2H), 5.00 (d, J = 14.8, 2H), 5.04 (t, J = 5.0, 2H), 6.84 (t, J = 7.6, 1H), 6.92 (d, J = 2.2, 2H), 7.19 (d, J = 7.6, 2H), 7.27 (d, J = 2.2, 2H), 7.83 (br s 1H). HRMS: calcd for $C_{40}H_{54}O_7$ (M^+) 646.3870. Found: 646.3904. Anal. Calcd for $C_{40}H_{54}O_7$: C, 74.27; H, 8.41. Found: C, 73.95; H,8.73.

6. IR (neat) cm^{-1}: 3370, 2960, 1599, 1487. ^1H NMR δ: 1.28 (s, 18H), 1.57 (d, J = 5.2, 6H), 4.57 (d, J = 11.6, 2H), 4.66 (d, J = 11.6, 2H), 4.72 (s, 4H), 4.82 (d, J = 14.6, 2H), 5.01 (d, J = 14.6, 2H), 5.19 (q, J = 5.2, 2H), 6.84 (t, J = 7.6, 1H), 6.92 (d, J = 1.6, 2H), 7.20 (d, J = 7.6, 2H), 7.27 (d, J = 1.6, 2H), 7.84 (br s 1H). HRMS: calcd for $C_{36}H_{46}O_7$ (M^+) 590.3243. Found: 590.3240. Anal. Calcd for $C_{36}H_{46}O_7$: C, 73.19; H, 7.85. Found: C, 72.92; H, 7.94.

X-ray Crystallographic Analysis of 2b. $C_{31}H_{38}O_7$, M = 522.64, monoclinic, a = 25.463(6) Å, b = 9.090(5) Å, c = 25.216(4) Å, β = 107.44(1)°, V = 5568(2) Å^3, space group $C_{2/C}$ (No. 15), Z = 8, D_{calcd} = 1.247 g cm^{-3}, μ(Cu Kα) = 7.11 cm^{-1}, λ(Cu Kα) = 1.54178 Å, T = 293 K, 5213 reflections measured, 4750 unique (R_{int} = 0.026) which were used in all calculations. R_1 = 0.076, Rw = 0.120. Further details of the crystal structural investigation are available on request from the Director of the Cambridge Crystallographic Data Centre.

Picrate Extraction. Two-phase solvent extraction was carried out between water (5.0 mL, [MOH] = 0.1 M, [MCl] = 0.5 M, and [PicOH] = 5.0 × 10^{-4} M; alkali metal picrates were generated in situ) and dichloromethane (2.5 mL, [host **4**] = 1.25 × 10^{-3} M). The mixture was stirred for 30 min at 25 °C. The mixture was centrifuged (3000 rpm, 2 min, 25 °C). The extractability was determined by UV−vis spectroscopy from the decrease in the absorbance of the picrate ion in the aqueous phase.

Acknowledgment. We are grateful to Prof. Araki, Kyushu Institute of Technology, for providing us the exact values of percent extraction of alkali metal picrates. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan.

JO0100502