Synthesis and inclusion properties of *O*-tris(benzyloxy) hexahomotrioxacalix[3]arenes

Takehiko Yamato*, Shofiur Rahman, Fumika Kitajima, Zeng Xi and Jeong Tae Gil

Department of Applied Chemistry, Faculty of Science and Engineering, Saga University, Honjo-machi 1, Saga 840-8502 Japan

O-benzylation of hexahomotrioxacalix[3]arene with benzyl bromide gave tri-*O*-benzylated products with cone and partial-cone conformation, in a ratio governed by the base used. *cone*-Tris-*O*-benzyloxy derivative shows a selectivity for the *n*-butylammoniun ion.

Keywords: calix[3]arenes, alkylation, conformation, template effect, ammonium recognition

Introduction of larger alkyl groups on the phenolic oxygens of calix[4]arenes led to a situation in which the OR groups within a cyclophane ring cannot pass each other by oxygen-through-the-annulus rotation.[1,2] Although there exist four possible conformational isomers in calix[4]arenes; *i.e.* cone, partial-cone, 1,2-alternate and 1,3-alternate, only two different conformational isomers, "cone" and "partial-cone" are expected in hexahomotrioxacalix[3]arene. Thus, the conformational isomerism is much simpler than that of *O*-alkylated calix[4]arenes.

Recently, Shinkai *et al.* reported on the influence of *O*-substituents on the conformational isomerism of hexahomotrioxacalix[3]arenes **1** in detail.[3] They have established that interconversion between conformers, which occurs by oxygen-through-the-annulus rotation, is sterically possible for methyl, ethyl, and propyl groups but it is inhibited by butyl group.[3d] In their studies on the conformer distribution of hexahomotrioxacalix[3]arene Shinkai *et al.* reported that the partial-cone is sterically less crowded than the cone and therefore formed predominantly in spite of choosing the *O*-alkylation conditions. On the other hand, the cone results only when template metal, which strongly interacts with phenolic oxygens, such as ethoxycarbonylmethyl or *N,N*-diethylaminocarbonylmethyl group, is present in the reaction system.[3a,d] However, the selective introduction of benzyl group on the phenolic groups has not yet been accomplished.

We report here on the selective synthesis of tris(benzyloxy)-hexahomotrioxacalix[3]arenes **3** with cone and partial-cone conformation by *O*-benzylation of hexahomotrioxacalix[3] arene **1** and on the inclusion properties with alkyl ammonium ions.

Results and discussion

Hexahomotrioxacalix[3]arene **1**[4] was *O*-alkylated with benzyl bromide in the presence of Cs_2CO_3 to yield one pure conformational isomer, *partial-cone*-**3** as a major product, while the other possible isomer *cone*-**3** was not observed. In contrast, a similar reaction was carried out in the presence of K_2CO_3 to yield a mixture of two conformers of the tri-*O*-alkylated product **3** in a ratio of 4: 96 (*cone*-**3**: *partial-cone*-**3**) in 70% yield. The cone-to-partial-cone ratio of **3** increased in the presence of NaH to 75: 25 (*cone*-**3**: *partial-cone*-**3**) in the *O*-substitution of triol **1**. However, attempted *O*-benzylation of triol **1** with a large excess of benzyl bromide (20 equiv.) in the presence of Na_2CO_3 failed. Only the starting compound was recovered in almost quantitative yield. Thus, the template effect of the alkali metal cations plays an important role in this *O*-benzylation reaction like *O*-alkylation with bromoethylacetate or *N,N*-diethylchloroacetamide.[3a,d] The regioselective introduction of one or two benzyl groups onto the phenolic oxygens of triol **1** was not possible in spite of tuning the reaction conditions.

The ^1H NMR spectrum of *cone*-**3** shows a singlet for the *tert*-butyl protons at δ 1.09 and a singlet for ArO*CH$_2$*Ph and the aromatic protons at δ 4.62 and 6.97 ppm, respectively indicating a C_{3V}-symmmetric structure of *cone*-**3**. On the other hand, ^1H NMR spectrum of *partial-cone*-**3** shows two singlets for the *tert*-butyl protons at δ 0.93, 1.20 ppm (relative intensity 2:1). Furthermore, the resonance for the ArO*CH$_2$*Ph methylene protons appeared as two singlets at δ 3.40 and 4.19 ppm (relative intensity 1:2). On the basis of the ^1H NMR studies and the consideration of CPK model of *partial-cone*-**3**, two benzyl groups in the compound point upwards and the other one is folded into the π-cavity formed by two benzene rings and is thus shielded giving upfield signals at δ 3.40 ppm for methylene protons and at δ 6.72–6.78 ppm for the aromatic protons at the 2,6-positions, respectively. The remarkable shielding effect experienced by the ortho protons of the inverted benzene ring suggests that this benzene ring is tightly accommodated inside the hydrophobic cavity in a sort of self-inclusion complex. Interestingly, two *tert*-butyl groups are located on the benzene ring of the inverted benzyl group in spite of the sterically crowded environment. This finding might be attributed to the C-H-π-interaction[5] between methyl groups of the *tert*-butyl group and the benzene ring. The same self-inclusion phenomenon was observed in the partial-cone structure for tris(benzyloxy)hexahomotrioxacalix [3]arene as in tris[(2-pyridylmethyl)oxy] derivative.[5]

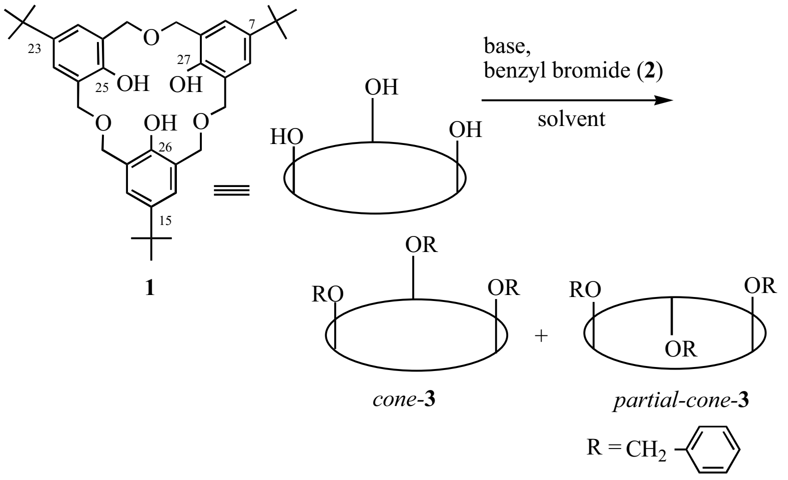
Table 1 O-Benzylation reaction of hexahomotrioxaocalix[3]arene 1 with benzyl bromide 2

			Distribution /%[a,b]	
Run	Base	Solvent	Cone	Partial-cone
1	NaH	THF	75 (45)	25 (16)
2	Na_2CO_3	Acetone	0[c]	0
3	K_2CO_3	Acetone	4	96 (82)
4	Cs_2CO_3	Acetone	0	100 (86)

[a]Relative yields determined by HPLC. [b]Isolated yields are shown in parentheses. [c]Starting compound **1** was recovered in quantitative yield.

---

* Correspondent. E-mail: yamatot@cc.saga-u.ac.jp



Scheme 1

It has been known that calixarenes can be converted to be neutral ligands by the introduction of ester or amide groups. The affinity and the selectivity depended on the calix[n]arene ring size and the substituents.[1] To obtain a quantitative insight into the metal and alkylammonium ion affinity of *cone*-tris(benzyloxy)hexahomotrioxacalix[3]arene *cone*-**3**, we have determined the association constants by ^{1}H NMR titration experiments according to the literature.[6, 7] The K_a values for alkali metals and Ag^+ could not be evaluated since the addition of 5 equiv. of Li^+, Na^+, K^+ and Ag^+ into solutions of *cone*-**3** did not cause any significant chemical shift changes. Thus, *cone*-**3** shows no complexation ability for alkali metal ions and Ag^+. Interestingly, *cone*-**3** shows almost same association constant for *n*-butylammonium ion (K_a = 25.3 × 10^3 M^{-1} in $CDCl_3$–CD_3CN 10:1) as that of the corresponding tris[(*N,N*-diethylaminocarbonyl) methoxy] derivative (K_a = 23.5 × 10^3 M^{-1} in $CDCl_3$–CD_3CN 10:1), which also shows high association constants for alkali metal ions.

After titration with an equivalent of the *n*-butylammonium ion in deuterated chloroform, the signals of *cone*-**3** appeared separately for the complex and the free host, respectively. With increasing amounts of ammonium ion, the signals of *cone*-**3** decreased and finally only the complex signals were observed. In comparison with the free host, in the complex the axial protons in the bridge methylene, which was related to the conformation of calixarene, were shifted to lower magnetic field ($\Delta\delta$ = + 0.16 ppm) while the equatorial protons shifted to upper field ($\Delta\delta$ = –0.33 ppm). The methylene protons $ArOCH_2Ph$ and calix-benzene protons were also shifted to lower field, respectively ($\Delta\delta$ = + 0.54 and + 0.25 ppm). These phenomena also established the conformation of complex of *cone*-**3** with *n*-butylammonium ion. The ammonium ion was encapsulated into the cavity formed by the benzene rings and changed the conformaton of *cone*-**3**. The NH_3 protons interact with three phenyl groups and phenolic oxygens and the *n*-butyl chain remains in the cavity of calix benzene rings.

The protons of ammonium ion encapsulated into the concave cavity were shifted to the upper field (δ 5.76 ppm) compared to that of free ones (δ 8.79 ppm) because of the shielding effect of the calix-benzene rings. The NH proton on *n*-butylammonium ions was shifted to higher magnetic field ($\Delta\delta$ = –3.03 ppm) when it was encapsulated into the calix cavity. The maximum upper field shift was observed among the protons of $CH_2CH_2NH_3^+$ ($\Delta\delta$ = –2.81 ppm) and it then decreased with the sequence of alkyl length. The proton in $CH_2CH_2NH_3^+$ was shifted to upper field by more than 2.0 ppm while the protons in CH_3CH_2 were shifted to upper field only by δ 0.72 ppm and 1.17 ppm, respectively. The calix cavity of homooxacalix[3]arene can include *n*-butylammonium ion totally, and the terminal $CH_2CH_2NH_3^+$ was located deep into the cavity, while CH_3CH_2 was located on the edge of the cavity.

On the contrary, the signals of the *partial-cone*-tris (benzyloxy) derivative *partial-cone*-**3** did not show any significant change upon addition of 5 equiv. of *n*-butyl ammonium picrate. Only the original signals for *partial-cone*-**3** remained. These results indicate that the C_{3v}-symmetric structure of *cone*-**3** plays a significant role in the complexation of tris(benzyloxy) derivative **3** and C_3-symmetric guest molecules, alkyl ammonium ions.

In conclusion, an interesting result was obtained by introduction of benzyl groups into the hydroxy groups of triol **1**. We have demonstrated for the first time that *O*-alkylation of the flexible macrocycle **1** with benzyl bromide gave tri-*O*-alkylated products with cone and partial-cone conformation which show promising complexation properties and interesting stereochemistry. The alkali metal cation can play an important role for the confomer distribution based on the template effect. Interestingly, *cone*-**3** shows high association constants for alkyl ammonium ions, but not silent for alkali metal ions. *Cone*-**3** has single complexation abilities for alkyl ammonium ions without the introduction of ester or amide groups. Further studies of the inclusion properties of *cone*-**3** and *partial-cone*-**3** for the biological active ammonium ions such as dorpamine and serotonin are in progress.

Experiment

All melting points (Yanagimoto MP-S1) were uncorrected. ^{1}H NMR spectra were recorded at 300 MHz on a Nippon Denshi JEOL FT-300 NMR spectrometer in deuteriochloroform with Me_4Si as an internal reference. IR spectra were measured as KBr pellets on a Nippon Denshi JIR-AQ2OM spectrometer. Mass spectra were obtained on a Nippon Denshi JMS-01SA-2 spectrometer at 75 eV using a direct-inlet system. Elemental analyses were performed by Yanaco MT-5. UV spectra were measured by Hitachi 220A spectrophotometer.

Materials

Synthesis of 7,15,23-tri-*tert*-butyl-25,26,27-trihydroxy-2,3,10,11,18, 19-hexahomo-3,11,19-trioxacalix[3]arene **1**, was carried out according to the reported procedure.[4a,b]

Alkylation of **1** *with benzyl bromide* **2** *in the presence of NaH to afford* **3**: A mixture of **1** (100 mg, 0.174 mmol) and NaH (227 mg, 5.25 mmol, 60%) in dry tetrahydrofuran (10 cm^3) was heated under reflux for 1 h under N_2. Benzyl bromide (0.21 cm^3, 1.74 mmol) was added and the mixture heated under reflux for an additional 17 h. After cooling the reaction mixture to room temperature, it was filtered. The filtrate was concentrated to give a yellow oil, which was then distilled under the reduced pressure to remove the excess unreacted benzyl bromide using a Kugelrohr apparatus. ^{1}H NMR analyses of the residue was accord with its being a mixture of *cone*-**3** and *partial-cone*-**3** in the ratio of 75:25. The residue was washed with methanol to give the crude *partial-cone*-**3** (22 mg, 16%) as a colourless solid. The filtrate was concentrated to give a yellow oil, which was chromatographed over silica gel (Wako, C-300; 100 g) with hexane-benzene (1:1) as eluent to give *cone*-**3** (66 mg, 45%) as a colourless solid. Recrystallisation from MeOH afforded *cone*-7,15,23-tri-*tert*-butyl-25,26,27-tris(benzyloxy)-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (*cone*-**3**) as colourless prisms, m.p. 163–165°C; ν_{max} (KBr)/cm^{-1} 2975, 2915, 2867, 1758, 1483, 1456, 1363, 1234, 1199, 1094 and 1058; δ_H ($CDCl_3$) 1.09 (27 H, s, *tBu*), 4.59 (12 H, s, ArCH_2O), 4.62 (6 H, s, OCH_2Ph), 6.97 (6 H, s, Ar–*H*) and 7.13–7.39 (15 H, s, Ph-*H*); δ_C ($CDCl_3$) 31.5, 34.2, 69.1, 125.7, 127.7, 127.8, 128.3, 131.0, 137.5, 146.2 and 152.2; *m/z* 846 (M^+) (Found C, 80.61; H, 7.93. $C_{57}H_{66}O_6$ (847.16) requires C, 80.82; H, 7.85%).

The splitting pattern in ^{1}H NMR shows that the isolated compound is *cone*-**3**.

Benzylation of **1** *with benzyl bromide in the presence of* Cs_2CO_3: A mixture of **1** (100 mg, 0.174 mmol) and Cs_2CO_3 (567 mg, 1.74 mmol) in acetone (10 cm^3) was heated under reflux for 1 h. Then benzyl bromide (0.21 cm^3, 1.74 mmol) was added and the mixture heated under reflux for 17 h. After cooling the reaction mixture to room temperature, it was filtered. The filtrate was concentrated and the residue was extracted with CH_2Cl_2 (100 cm^3 × 2) and washed with water (50 cm^3 × 2), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was washed with methanol to give the crude *partial-cone*-**3** (127 mg, 86%) as a colourless solid. Recrystallisation from MeOH-$CHCl_3$ (3: 1) gave *partial-cone*-7,15,23-tri-*tert*-butyl-25,26,27-tris(benzyloxy)-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (*partial-cone*-**3**) as colourless prisms, m.p. 180–185°C; ν_{max} (KBr)/cm^{-1} 2975, 2915, 2867, 1758, 1483, 1456, 1363, 1234, 1199, 1094 and 1058; δ_H ($CDCl_3$) 0.93 (18 H, s, *tBu*), 1.20 (9 H, s, *tBu*), 3.40 (2 H, s, OCH_2Ph), 4.07 (2 H, d, J = 12.7 Hz, ArCH_2O), 4.19 (4 H, s, OCH_2Ph), 4.27 (2 H, d, J = 9.3 Hz, ArCH_2O), 4.28 (2 H, d, J = 12.7 Hz, ArCH_2O), 4.46 (2 H, d, J = 12.7 Hz, ArCH_2O), 4.53 (2 H, d, J = 12.7 Hz, ArCH_2O), 4.54 (2 H, d, J = 9.3 Hz, ArCH_2O), 6.72–6.78 (2 H, m, Ph–*H*), 7.01–7.14 (17 H, m, Ar–*H* and Ph–*H*) and 7.29 (2 H, s, Ar–*H*); *m/z* 846 (M^+) (Found C, 80.53; H, 7.73. $C_{57}H_{66}O_6$ (847.16) requires C, 80.82; H, 7.85%).

The splitting pattern in ^{1}H NMR shows that the isolated compound is *partial-cone*-**3**.

^{1}H NMR complexation experiment: To a $CDCl_3$ solution (1.53 × 10^{-3} M, 400 μl) of **3** in the NMR tube was added a CD_3CN solution (1.53 × 10^{-3} M, 40 μl) of an equivalent of *n*-$BuNH_3^+Pic^-$. The spectrum was registered after addition and the temperature of NMR probe kept constant at 27°C. The association constants values were calculated by the integral intensity of CH_2 protons of the benzyl protons [ArOCH_2Ph] signal in the complex and free host molecules according to the literature.[7]

Received 28 October 2005; accepted 24 January 2006
Paper 05/3600

References

1 For a comprehensive review of all aspects of calixarene chemistry, see: (a) C.D. Gutsche, *Calixarenes*, Royal Society of Chemistry, Cambridge, 1989; (b) J. Vicens and V. Böhmer, *CALIXARENES*: *A Versatile Class of Macrocyclic Compounds*, Kluwer Academic Publishers, Cambridge, 1990; (c) C.D. Gutsche, *Calixarenes Revisited*, Royal Society of Chemistry, Cambridge, 1998.

2 (a) S.G. Bott, A.W. Coleman and J.L. Atwood, *J. Chem. Soc., Chem. Commun.,* 1986, 610; (b) A. Anduni, A. Pochini, S. Reverber, R. Ungaro, G.D. Andretti and F. Ugozzoli, *Tetrahedron,* 1986, **42**, 2089.

3 (a) K. Araki, N. Hashimoto, H. Otsuka and S. Shinkai, *J. Org. Chem.*, 1993, **58**, 5958; (b) K. Araki, K. Inaba, H. Otsuka and S. Shinkai, *Tetrahedron*, 1993, **49**, 9465; (c) M. Takeshita and S. Shinkai, *Chem. Lett.*, 1994, 125; (d) H. Matsumoto, S. Nishio, M. Takeshita and S. Shinkai, *Tetrahedron*, 1995, **51**, 4647; (e) K. Araki, K. Inada and S. Shinkai, *Angew. Chem. Int. Ed. Engl.,* 1996, **35**, 72.

4 (a) H. Ninagawa and H. Matsuda, *Makromol. Chem. Rapid Commun.*, 1982, **3**, 65; (b) B. Dhawan and C.D. Gutsche, *J. Org. Chem.*, 1983, **48**, 1536; (c) P.D. Hampton, Z. Bencze, W. Tong and C.E. Daitch, *J. Org. Chem.*, 1994, **59**, 4838; (d) C.E. Daitch, P.D. Hampton, E.N. Duesler and T.M. Alam, *J. Am. Chem. Soc.*, 1996, **118**, 7769.

5 (a) T. Yamato, M. Haraguchi, J. Nishikawa, S. Ide and H. Tsuzuki, *Can. J. Chem.,* 1998, **76**, 989; (b) T. Yamato, M. Haraguchi, J. Nishikawa and S. Ide, *J. Chem. Soc., Perkin Trans. 1*, 1998, 609; (c) T. Yamato and F. Zhang, *J. Inclusion Phenom.,* 2001, **42**, 55.

6 (a) T. Yamato, F. Zhang, H. Tsuzuki and Y. Miura, *Eur. J. Org. Chem.*, 2001, 1069; (b) T. Yamato, F. Kitajima and J. Tae Gil, *J. Inclusion Phenom.,* 2005, **53**, 257.

7 H.A. Benesi and J.H. Hildebrand, *J. Am. Chem. Soc.,* 1949, **71**, 2073.