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# Improved Synthesis of 5,11,17,23,29-Penta-*t*-butylcalix[5]arene-31,32,33,34,35-pentol and Immobilization of the Conformation by *O*-Alkylation

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**Synopsis.** The synthetic method of the title compound was improved to 16.1% yield. The $^1$H NMR studies established that the oxygen-through-the-annulus rotation is not inhibited by the butyl group but inhibited by the bulkier octyl group.

Calix[*n*]arenes are cavity-shaped macrocycles which are very attractive for designing functionalized host molecules. To thoroughly investigate if the hole-size selectivity is operative in a calix[*n*]arene family, calix[*n*]arenes with a variety of ring sizes are needed. Syntheses of "even-number" calix[*n*]arenes ($n$=4, 6, and 8) have been established by Gutsche.[1] In contrast, the efforts to synthesize "odd-number" calix[*n*]arenes ($n$=5 and 7) have been very limited and the yields are generally low.[2,3] Probably, this is why they attract little attention. We considered, however, that if the yields are significantly enhanced, they will attract more attention as starting materials for designing penta-coordinative or hepta-coordinative metal ligands,[4] medium-size inclusion spheres between "even-number" calix[*n*]arenes, etc. The difficulty is mainly related to the isolation process: Under every reaction condition known so far "even-number" calix[*n*]arenes are yielded in great excess over "odd-number" calix[*n*]arenes, so that one has to isolate minor products in the presence of major products. 5,11,17,23,29-Penta-*t*-butylcalix[5]arene-31,32,33,34,35-pentol (**1**) was first synthesized by Ninagawa and Matsuda[2] from 4-*t*-butylphenol (4-BP) and paraformaldehyde in the presence of potassium *t*-butoxide (*t*-BuOK) in 6.2% yield. In this paper we examined the reaction conditions and isolation methods. Eventually, we succeeded in enhancing the yield up to 16.1%. By using **1** thus synthesized we investigated which *O*-substituent can inhibit the rotation of the phenyl units (Chart 1).

## Results and Discussion

**Improved Synthesis of 1.** It is known that the reaction of 4-BP and paraformaldehyde in the presence of *t*-BuOK in tetralin gives pentameric **1** in addition to tetramer, hexamer, heptamer, octamer, and dihomooxacalix[4]arene.[2,4,5] First, we carefully checked the reaction conditions, monitoring the yields of concerned products by an HPLC technique. The results are summarized in Table 1. Surprisingly, it is seen from Table 1 that when the reaction mixture is heated at 55 °C for 2 h and then at 150 °C for 3 h, the HPLC yield of **1** is 22.5%, the high yield next to octamer (35.6%). Even when the reaction mixture was immediately heated at 150 °C, the yield of **1** was pretty high (17.2—18.5%). The results indicate that the low yield of **1** is due to the difficulty in the isolation process.

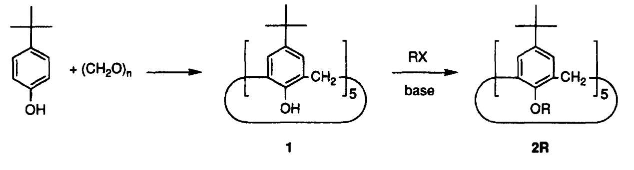

Chart 1.

Next, we attempted several isolation methods. After trial-and-error we reached a conclusion that the following isolation method, which is more convenient than the previous methods,[2,4,5] affords the highest isolation yield. The product mixture was cooled at room temperature. The precipitate was removed by filtration. The HPLC analysis established that the precipitate contains tetramer, hexamer, octamer, and polymeric products, indicating that "even-number" calix[*n*]arenes are less soluble in tetralin than "odd-number" calix[*n*]arenes. The filtrate was concentrated to 100 ml and then left at room temperature. The precipitate at this stage contains tetramer, hexamer, octamer, and dihomooxacalix[4]arene. These products were scarcely detected in the filtrate which contained **1** and heptamer. The filtrate was concentrated to dryness. Recrystallization of the residue from ethanol gave pure **1**, indicating that **1** is less soluble in ethanol than heptamer. As shown in Table 1, 60—90% of **1** could be recovered from the product mixture.

**Immobilization of Conformation.** In calix[4]arenes it has been established that the para-substituent-through-the-annulus rotation does not take place whereas the oxygen-through-the-annulus rotation is allowed but becomes inhibited by introduction of *O*-substituents bulkier than an ethyl group into the OH groups.[6—8] For example, the oxygen-through-the-annulus rotation is completely inhibited by a propyl group and one can thus isolate four isomers (cone, partial-cone, 1,2-alternate, and 1,3-alternate) as stable conformational isomers.[6—8] In calix[5]arenes, in contrast, it is totally unknown if these rotations are allowed or not. To obtain insights into a correlation between the bulkiness of *O*-substituents and the oxygen-through-the-annulus rotation, we introduced several alkyl groups into the OH groups.

We first synthesized 5,11,17,23,29-penta-*t*-butyl-31,32,33,34,35-pentabutoxycalix[5]arene (**2Bu**) from **1** and butyl bromide because the butyl group is bulky enough

Table 1. Synthesis and Isolation of **1**[a)]

| *t*-BuOK | Temperature | Product distribution/HPLC %[c)] | | | | | Isolated yield |
|---|---|---|---|---|---|---|---|
| mmol | °C(h) | [4]+[Oxa][b)] | [5] | [6] | [7] | [8] | % |
| 65 | 55(6)→150(6) | 12.3 | 15.2 | 17.1 | 8.6 | 46.9 | 14.6 |
| 65 | 55(2)→150(3) | 16.8 | 22.5 | 10.3 | 14.8 | 35.6 | 16.1 |
| 65 | 150(6) | 9.6 | 18.5 | 20.4 | 5.4 | 46.1 | 11.2 |
| 130 | 150(6) | 13.1 | 17.2 | 45.9 | 15.5 | 8.3 | 3.3 |
| 130 | 180(6) | 21.1 | 8.8 | 54.6 | 11.9 | 3.6 | 1.1 |

a) 250 mmol 4-BP and 630 mmol $(CH_2O)_n$ in 500 ml tetralin. b) In HPLC tetramer and dihomooxacalix[4]arene appeared together. c) HPLC % was estimated on the basis of the peak area in UV-detection at 254 nm.

to inhibit the oxygen-through-the-annulus rotation of calix[4]arenes.[6,7)] In calix[4]arenes the reaction in the presence of NaH gave the cone and the partial-cone approximately in a 1 : 1 ratio whereas the reaction in the presence of $Cs_2CO_3$ gave the partial-cone, 1,2-alternate, 1,3-alternate but no cone.[6)] The product distribution was rationalized in terms of the template effect of $Na^+$ which holds four OH groups in the same side of the calix[4]arene cavity.[6)] In penta-*O*-butylation of **1**, on the other hand, the product **2Bu** prepared in the presence of NaH was the same compound as that prepared in the presence of $Cs_2CO_3$. In $^1$H NMR spectroscopy (Fig. 1: 400 MHz, $Cl_2CDCDCl_2$) the $ArCH_2Ar$ methylene protons appeared as a broad singlet above room temperature and a complex multiplet at −20 °C. The results show that in **2Bu** ring inversion can take place in a speed comparable with the NMR time-scale: that is, the calix[5]arene ring is large enough for a butoxyl group to rotate through the annulus.

Here, we decided to introduce a bulkier substituent. We thus synthesized 5,11,17,23,29-penta-*t*-butyl-31,32,33,34,35-pentakis(octyloxy)calix[5]arene (**2Oct**) from **1** and octyl bromide in the presence of NaH. In $^1$H NMR spectroscopy (Fig. 2: 400 MHz, $Cl_2CDCDCl_2$) the spectral pattern of **2Oct** was scarcely changed at wide temperature range (−40—130 °C). The result allows us to conclude that the oxygen-through-the-annulus rotation is sterically inhibited in **2Oct**.[9)] At the same time, this finding establishes that the para-substituent-through-the-annulus rotation is also inhibited by the *t*-butyl groups.

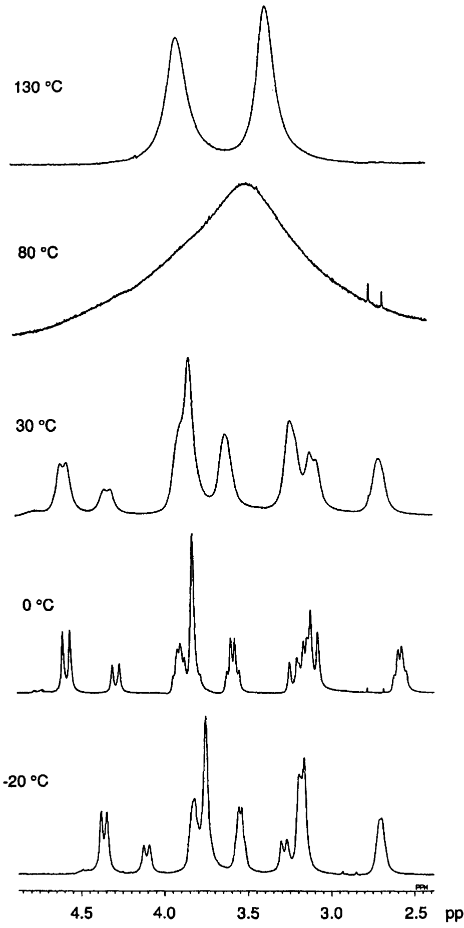

Fig. 1. $^1$H NMR spectra of **2Bu** for $ArCH_2Ar$ region (400 MHz, $Cl_2CDCDCl_2$).

In conformationally-immobilized calix[5]arenes there exist four conformational isomers (Fig. 3). Their $^1$H NMR splitting patterns are summarized in Table 2. From splitting patterns of calix[4]arene derivatives it has been established that the $ArCH_2Ar$ methylene protons flanked by two *syn* phenyl groups give a pair of doublets with $\Delta\delta$=ca. 1 ppm whereas those flanked by two *anti* phenyl groups give a pair of doublets with a small $\delta$ difference and sometimes appear as a singlet.[6—8)] Table 2 shows that one can discriminate the cone and the 1,3-alternate but the splitting pattern for the partial-cone and the 1,2-alternate is basically same. We attempted to isolate each conformational isomers by a TLC method or column chromatography but failed because of the small difference in their $R_f$ values. We thus decided to estimate the conformer distribution directly from the $^1$H NMR spectrum of the conformer mixture. As shown in Fig. 2, the mixture contains cone-**2Oct** with a pair of doublets for $ArCH_2Ar$ and a singlet resonance for ArH. It also contains partial-cone-**2Oct** and 1,2-alternate-**2Oct** with two pairs of doublets (1 : 2 ratio) and a singlet for $ArCH_2Ar$ and four doublets and a singlet for ArH but to identify which is which is difficult. We here noticed that the $^1$H NMR spectrum of

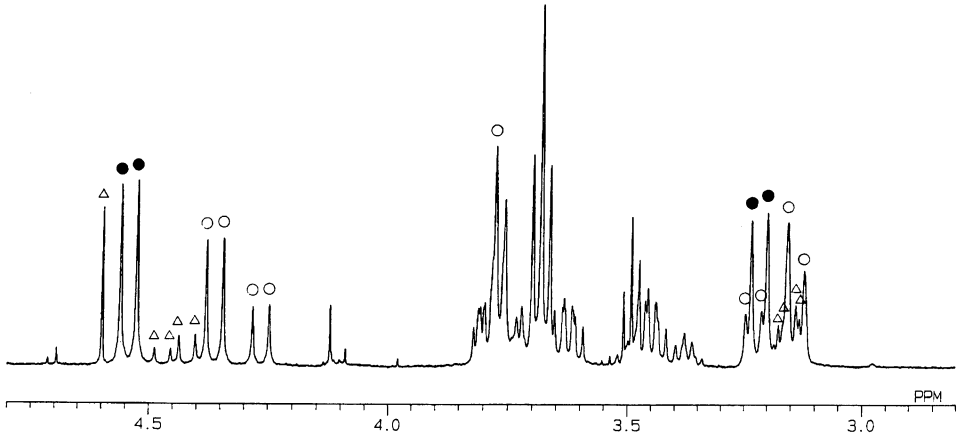

Fig. 2. $^1$H NMR spectrum of **2Oct** for $ArCH_2Ar$ region (400 MHz, $Cl_2CDCDCl_2$, 130 °C): ● cone, ○ partial cone, △ 1,2-alternate.

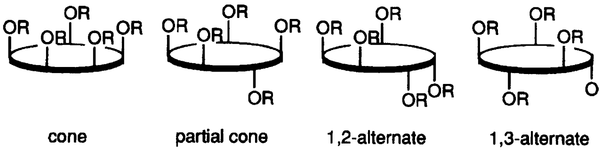

Fig. 3. Four conformational isomers derivable from calix[5]arenes.

**2Bu** at 0 °C shows the same splitting pattern, indicating that **2Bu** adopts either a partial-cone conformation or a 1,2-alternate conformation although the conformation is not immobilized. In this spectrum one $CH_3CH_2$ group appears at unusually higher magnetic field (0.40 ppm for $CH_3$ and −0.10 ppm for $CH_2$). This suggests that **2Bu** is the partial-cone with one inverted phenyl unit, undergoing the shielding effect of the neighboring benzene rings. Based on this information we could successfully identify the stronger peaks to partial-cone-**2Oct** and the weaker peaks to 1,2-alternate-**2Oct**. The integral intensity ratio of cone : partial-cone : 1,2-alternate is 32 : 55 : 13.[9]

**Conclusions.** The present study established that (i) by improving the synthetic method and the isolation method the yield of **1** can be enhanced up to 16.1% and (ii) the oxygen-through-the-annulus rotation cannot be suppressed by the butyl group which was effective in calix[4]arenes but can be inhibited by the bulkier octyl group whereas the para-substituent-through-the-annulus rotation can be inhibited by the *t*-butyl group. We believe that these findings are important in extending various concepts obtained in calix[4]arenes to calix[5]arenes.

## Experimental

**Synthesis of 1.** *p*-*t*-Butylphenol (37.5 g; 0.25 mol), paraformaldehyde (25 g; 0.63 mol), and *t*-BuOK (8.5 g; $6.5\times10^{-2}$ mol) were mixed in tetralin (500 ml). The reaction mixture was heated under stirring for the period in Table 1. After cooling, a small portion was taken out and subjected to HPLC analysis (Zorbax ODS, chloroform : methanol=1 : 8 v/v). The precipitate was removed by filtration. The filtrate was concentrated to 100 ml and the precipitate formed here was removed by filtration, the filtrate being concentrated to dryness. Finally, recrystallization from ethanol gave **1** in the yield recorded in Table 1.

Table 2. $^1$H NMR Splitting Patterns of Conformational Isomers of 5,11,17,23,29-Penta-*t*-butylcalix-[5]arenes

| Conformation | ArH | $ArCH_2Ar$ | *t*-Bu |
|---|---|---|---|
| Cone | s(10H) | d×2(10H) | s(45H) |
| Partial-cone | s (2H) | d×2 (4H)$^{a)}$ | s(18H) |
| | d (2H) | d×2 (4H) | s(18H) |
| | d (2H) | d×2 (2H) | s (9H) |
| | d (2H) | | |
| | d (2H) | | |
| 1,2-Alternate | s (2H) | d×2 (4H)$^{a)}$ | s(18H) |
| | d (2H) | d×2 (4H) | s(18H) |
| | d (2H) | d×2 (2H) | s (9H) |
| | d (2H) | | |
| | d (2H) | | |
| 1,3-Alternate | s (2H) | d×2 (4H)$^{a)}$ | s(18H) |
| | d (2H) | d×2 (4H)$^{a)}$ | s(18H) |
| | d (2H) | d×2 (2H) | s (9H) |
| | d (2H) | | |
| | d (2H) | | |

a) Basically, these protons should give a pair of doublets with a small δ difference but sometimes appear as a singlet resonance.

**Penta-*O*-alkylation.** The alkylation method is the same as that described for tetra-*O*-alkylation of calix[4]-arene.[6] We treated one equiv of **1** with 50 equiv of butyl bromide or octyl bromide in the presence of NaH (25 equiv) or $Cs_2CO_3$ (50 equiv) at room temperature for 3 h and at 50 °C for 2 h. The product isolation method was also described previously.[6] **2Bu**: Yield 85%; mp 168.5—169.5 °C; $^1$H NMR ($Cl_2CDCDCl_2$, 0 °C) $\delta$=0.50, 0.69, 0.93 (3H, 6H and 6H, t each, $CH_3$ in *n*-butyls), 0.40, 1.00, and 1.40 (2H, 4H and 4H, m each, $\underline{CH_2}CH_3$), −0.10, 1.40, 1.68, and 1.82 (2H, 4H, 2H and 2H, m each, $\underline{CH_2}CH_2CH_3$), 1.13, 1.37, and 1.42 (18H, 18H and 9H, s each, *t*-Bu), 2.00, 2.75, 3.19, 3.57, and 3.80 (2H each, t, m, m, m and m, $OCH_2$), 3.15, 3.29, 3.76, 4.10, and 4.36 (2H, 1H, 4H, 1H and 2H, d, d, s, d and d, ArCH$_2$), 6.98, 7.02, 7.21, 7.29, and 7.54 (2H each, s each, ArH). Found: C, 81.62; H, 10.10%. Calcd for $(C_{15}H_{22}O)_5\cdot 0.1CHCl_3$: C, 81.73; H, 10.05%. Inclusion of $CHCl_3$ was confirmed by $^1$H NMR spectroscopy. **2Oct**: Yield 70%; colorless oil; $^1$H NMR ($Cl_2CDCDCl_2$, 130 °C) $\delta$ for cone-**2Oct**=0.88 (15H, t ($J$=8 Hz), CH$_3$ in octyls), 1.04 (54H, s, *t*-Bu), 1.27 (60H, m, CH$_2$ in octyls), 3.22, and 4.54 (5H each, d each ($J$=14 Hz), ArCH$_2$), 3.68 (10H, t ($J$=7 Hz), OCH$_2$), 6.90 (10H, s, ArH). $\delta$ for partial-cone-**2Oct**=0.09, 0.68, and 1.35 (2H, 2H, and 56H, m each, CH$_2$ in octyls), 0.86 (15H, t, *t*-Bu), 1.11, 1.36, and 1.41 (18H, 18H, and 9H, s each, *t*-Bu), 2.20, 3.45, and 3.60 (2H, 4H, and 4H, t ($J$=7 Hz), m, and m, OCH$_2$), 3.14, 3.23, 3.78, 4.27, and 4.36 (2H, 1H, 4H, 1H, and 2H, d ($J$=14 Hz), d ($J$=14 Hz), s, d ($J$=14 Hz), and d ($J$=14 Hz), ArCH$_2$), 6.86, 7.03, 7.20, 7.21, and 7.44 (2H each, d ($J$=2 Hz), d ($J$=2 Hz), d ($J$=2 Hz), s, and d ($J$=2 Hz), ArH). $\delta$ for 1,2-alternate-**2Oct**=0.84 (15H, t, CH$_3$ in octyls), 1.00, 1.22, and 1.38 (18H, 18H, and 9H, s each, *t*-Bu), 1.35 (60H, m, CH$_2$ in octyls), 3.15, 3.16, 4.42, 4.47, and 4.60 (1H, 2H, 2H, 1H, and 4H, d ($J$=14 Hz), d ($J$=14 Hz), d ($J$=14 Hz), d ($J$=14 Hz), and s, ArCH$_2$), 3.36, 3.45, and 3.75 (2H, 4H, and 4H, t, m, and m, OCH$_2$), 6.70, 7.06, 7.07, 7.08, and 7.23 (2H, 1H, 2H, 1H, and 4H, d ($J$=2 Hz), d ($J$=2 Hz), d ($J$=2 Hz), d ($J$=2 Hz), and s, ArH). Found: C, 83.55; H, 10.88%. Calcd for $(C_{19}H_{30}O)_5$: C, 83.15; H, 11.02%.

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9) This observation is not enough to propose that the rotation is definitely inhibited because the same result is obtained when the rotation is much slower than the NMR time-scale and the conformer distribution is the thermodynamically-controlled one. It is known that under such conditions the conformer distribution changes with temperature. e.g., see: K. Araki, K. Iwamoto, S. Shinkai, and T. Matsuda, *Chem. Lett.*, **1989**, 1747. In the present system the conformer distribution was not affected by temperature at −40—130 °C. This supports the inhibition of the rotation.