
Kwanghyun No∗ and Young Ja Park

Department of Chemistry, Sookmyung Women’s University, Seoul 140-742, Korea
Received September 13, 2002

Reaction of tetrahomodioxa p-phenylcalix[4]arene with alkyl halide and NaH in DMF leads to the title tetraalkylated derivatives, 7,13,21,27-tetra-phenyl-29,30,31,32-tetraalkyloxy-2,3,16,17-tetrahomo-3,17-dioxacalix[4]arenes, their preferred conformations were determined by NMR spectra as C-1,2-alternate. The molecular structure of allyl derivative has been solved by X-ray diffraction methods. The molecules have a conformation with pseudo center of symmetry. The benzene ring A is up, ring C is down, B and D rings are flat with respect to the plane of the macrocyclic ring.

Key Words: Homooxacalix[4]arene, Conformation, Crystal structure

Introduction

Calixarenes are synthetic macrocycles with varying ring sizes that have received a great deal of attention in recent years.1-3 They are of interest both as complexation hosts for ions and molecules and as frameworks for elaborating more complex structures. In contrast to calix[4]arenes, tetrahomodioxacalix[4]arenes which contain two extra oxygen atoms in the macrocyclic ring have received little attention, mainly because they can be synthesized only in relatively low overall yields.4-6 There have only been limited studies of the solution conformations, solid-state structures and complexation properties of tetrahomodioxacalix[4]arenes.7-10

Shaping of cavity plays a potentially vital role in the design of calixarenes, for host-guest interaction depends on complementarity in shape as well as functionality. The interconversion between conformers of calix[4]arene can be sterically inhibited by O-substituents bulkier than ethyl group.11 By using n-propyl bromide as an alkylation reagent, one can thus synthesize a variety of conformational isomer from calix[4]arene. Conformational isomerism in tetrahomodioxacalix[4]arene compounds is expected to be more complicated than in calix[4]arenes, due to reduced symmetry as well as greater mobility. Tetrahomodioxacalix[4]arene containing free intraannular OH groups is conformationally flexible in solution at room temperature and exists five limiting conformations as illustrates in Figure 1.

Masci and coworker12 reported that the main conformation of tetrahomodioxia-p-tert-butylcalix[4]arene tetramethyl ether is C-1,2-alternate based on temperature dependent NMR spectral analysis. However the X-ray crystal structure was not reported. In the X-ray crystal structure determination study, Thuery and coworkers13 reported that p-alkyl tetrahomodioxacalix[4]arene is crystallized as distorted cone-like

Figure 1. Conformations of Tetrahomodioxia calix[4]arene.
conformation with or without solvent molecules.

Recently, we described a facile two-step synthesis of tetrahomodioxa-p-phenyl calix[4]arene by refluxing bis-hydroxymethylated p-phenylphenol in xylene\(^{14}\) and the solid-state structure of its tetraester.\(^{15}\) We also reported the synthesis of tetrahomodioxa-p-phenyl calix[4]arene tetraamide, its two-phase metal picrate extraction behavior and the solid-state structure of its complex with lead picrate.\(^{16}\) In a continuation of the homooxacalixarene research, series of tetrahomodioxacalix[4]arene tetraalkyl ethers \(^4\) have been prepared and their conformations were studied by NMR spectral analysis.

**Results and Discussion**

As shown on the following Scheme 1 tetrahomodioxacalix[4]arene tetraalkyl ethers \(^4\) can be obtained in a good yield by treatment of a DMF solution of the homooxacalix[4]arene \(^3\) with NaH followed by the alkyl halide (bromide or iodide). Judging from \(^1\)H and \(^13\)C NMR spectroscopy, compounds \(^4\) were found to be in the C-1,2-alternate conformation.

The NMR spectrum of \(^4a\) could not be obtained due to lack of solubility to most deuterated organic solvent including DMSO. Therefore its conformation can not be determined.

Compound \(^4b\) shows temperature dependent \(^1\)H NMR spectra for the methylene protons of \(\text{ArCH}_2\text{OCH}_2\text{Ar}\) and \(\text{ArCH}_2\text{Ar}\). At \(0^\circ\)C in chloroform, the methylene protons of the \(\text{ArCH}_2\text{Ar}\) showed two doublets at \(\delta \text{ 4.56 and 3.46 with a geminal coupling constant of 13.7 Hz. An AB pattern for the dimethylenoxy protons of } \text{ArCH}_2\text{OCH}_2\text{Ar]\ appeared at } \delta \text{ 4.60 and 4.54 with a geminal coupling constant of 10.7 Hz. The methylene protons from propyl groups showed two sets of quartet at } \delta \text{ 3.54, 3.37 and two sets of sextet at } \delta \text{ 1.52, 1.37 and methyl protons appeared as a triplet at } \delta \text{ 0.63. When the temperature was raised, the spectrum became less well resolved and, at 25 \(^{\circ}\)C, AB quartets from bridge methylene protons of } \text{ArCH}_2\text{OCH}_2\text{Ar}\) collapsed into one broad singlet at \(\delta \text{ 4.57, and AB quartets from bridge methylene protons of } \text{ArCH}_2\text{Ar}\) collapsed into two broad singlet at \(\delta \text{ 4.57 and 3.45. Obviously, the ease of transformation between conformations via the oxygen-through-the-annulus rotation should be different between } \text{ArCH}_2\text{Ar}\) rotation and \(\text{ArCH}_2\text{OCH}_2\text{Ar}\) rotation. In propyl ether, the interconversion between conformations could occur through both the \(\text{ArCH}_2\text{Ar}\) and \(\text{ArCH}_2\text{OCH}_2\text{Ar}\) rotation, however \(\text{ArCH}_2\text{OCH}_2\text{Ar}\) rotation is much easier than \(\text{ArCH}_2\text{Ar}\) rotation. At \(50^\circ\)C, protons from propyl groups also became three broad singlets at \(\delta \text{ 3.45, 1.47 and 0.63. CH}_3\) signal is upfield shifted with respect to the typical value. The shielding effect experienced by the \(\text{CH}_3\) protons of \(^4b\) is not compatible with the cone structure. The obvious interpretation is that the corresponding methyl groups face the benzene ring of \(p\)-substituted aromatic ring. The \(^13\)C NMR spectrum showed a single peak at 75.46 ppm for the \(\text{ArCH}_2\text{OCH}_2\text{Ar}\) bridge methylene carbons and one peak at 30.70 ppm for the \(\text{ArCH}_2\text{Ar}\) bridge carbons. On extending the criterion first established for calix[4]arenes and successfully applied also to larger homologues to homooxacalixarenes,\(^{17,18}\) a syn arrangement of the aromatic rings can be predicted for the \(\text{ArCH}_2\text{Ar}\) moieties of \(^4b\). For the partial cone, COC-1,2-alternate and 1,3-alternate conformers, in which two adjacent benzene rings are in an anti orientation, an additional methylene bridge carbon peak at around 37 ppm would be anticipated. Thus, the spectral pattern for \(^4b\) is consistent with a C-1,2-alternate conformation in which the two adjacent phenyl rings connected by a dimethylenoxy group are inverted. The position of the methylenic bridge carbons of \(\text{ArCH}_2\text{Ar}\) at 30.70 ppm indicates that these two adjacent benzene-rings are in syn orientation.

Compound \(^4c\) shows a similar NMR spectral pattern with
At -25 °C in chloroform, the methylene protons of the ArCH₂Ar showed two AB doublets at δ 4.58 and 3.48 with a geminal coupling constant of 13.6 Hz. An AB pattern for the dimethyleneoxy protons of ArCH₂OCH₂Ar appeared at δ 4.60 and 4.45 with a geminal coupling constant of 10.3 Hz. When the temperature was raised, the spectrum became less well resolved and, at 0°C, AB quartets from bridge methyleneoxy protons of ArCH₂OCH₂OAr collapsed into broad doublets at δ 4.53 and 3.50. When the temperature was raised to room temperature, the protons of the ArCH₂Ar and ArCH₂OCH₂OAr appeared as singlets, respectively. Obviously, the transformation between conformations via the oxygen-through-the-annulus rotation should be faster than NMR time scale at room temperature. The 13C NMR spectrum showed a single peak at 75.89 ppm for the ArCH₂OCH₂Ar bridge methylene carbons and one peak at 32.27 ppm for the ArCH₂Ar bridge carbons. Thus, the spectral pattern for 4c is also consistent with a C-1,2-alternate conformation. The X-ray crystal structure of 4c is also a positive proof for the C-1,2-alternate conformation.

Table 1. Summary of Crystal Data of tetrahomodioxa p-phenylcalix[4]arene tetraallyl ether 4c

<table>
<thead>
<tr>
<th>Crystal data</th>
<th>C₆₆H₆₀O₆</th>
<th>D_x = 1.229 (calc.) g cm⁻³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mw</td>
<td>949.14</td>
<td>Mo Kα radiation</td>
</tr>
<tr>
<td>Triclinic, P(-1)</td>
<td>a = 13.354(7) Å</td>
<td></td>
</tr>
<tr>
<td></td>
<td>b = 14.163(5) Å</td>
<td>µ = 0.077 mm⁻¹</td>
</tr>
<tr>
<td></td>
<td>c = 15.026(3) Å</td>
<td>T = 293(2) K</td>
</tr>
<tr>
<td></td>
<td>alpha = 76.21(3)°</td>
<td>gamma = 76.76(5)°</td>
</tr>
<tr>
<td></td>
<td>beta = 70.32(2)°</td>
<td>V = 2564.2(17) Å³</td>
</tr>
<tr>
<td></td>
<td>Colorless</td>
<td>0.6 × 0.4 × 0.1 mm</td>
</tr>
<tr>
<td></td>
<td>Z = 2</td>
<td></td>
</tr>
</tbody>
</table>

Data collection

<table>
<thead>
<tr>
<th>Enraf-Nonius CAD-4</th>
<th>θ_max = 25°</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffractometer</td>
<td>h = 0 → 16</td>
</tr>
<tr>
<td>ω/2θ scan type</td>
<td>k = -16 → 16</td>
</tr>
<tr>
<td>Absorption correction: none</td>
<td>l = -16 → 17</td>
</tr>
<tr>
<td>9015 measured reflections</td>
<td>3 standard reflections</td>
</tr>
<tr>
<td>Frequency: 60 min</td>
<td></td>
</tr>
<tr>
<td>3186 reflections with I &gt; 2σ(I)</td>
<td>Intensity decay: negligible</td>
</tr>
</tbody>
</table>

Refinement

<table>
<thead>
<tr>
<th>Refinement on F²</th>
<th>w = 1/[σ²(Fo²)² + (0.0762P)² + 0.7341P]</th>
</tr>
</thead>
<tbody>
<tr>
<td>R(F² &gt; 2σ(F²))</td>
<td>0.077</td>
</tr>
<tr>
<td>wR(F²)</td>
<td>0.215</td>
</tr>
<tr>
<td>S</td>
<td>0.958</td>
</tr>
<tr>
<td>(ΔA/σ)_mean</td>
<td>0.052</td>
</tr>
<tr>
<td>9015 reflections</td>
<td>Δρ_max = 0.47 eÅ⁻³</td>
</tr>
<tr>
<td>649 parameters</td>
<td>Δρ_min = -0.32 eÅ⁻³</td>
</tr>
</tbody>
</table>

Extinction correction: none

Atomic scattering factors from International Table for Crystallography

Figure 2. View of the molecular structure and atomic numbering of compound 4c. Hydrogen atoms have been omitted for clarity.

(a)

(b)

(c)
are thus essentially parallel (interplanar angle 9.2° and 10.3 respectively) and rings A and C are tilted so that their allyl ether groups are oriented toward the cavity, while B and D rings are approximately normal to the least-square plane of 18-membered macrocyclic ring. The C-1,2-alternate conformation of the 4c is also shown in Table 2 of conformational angles.

In 1H NMR spectrum of compound 4d, at room temperature, the peak from protons of ArCH2Ar splits into AB system, however that from protons of ArCH2OCH2Ar appears as a singlet which splits into AB system on cooling to lower temperature (0°C). For propyl ether, the ease of conformational interconversion should be different between ArCH2Ar and ArCH2OCH2Ar rotation. In case of butyl ether, it can occur only through the CH2OCH2 rotation at room temperature. The rotation through ArCH2Ar is not so fast in NMR time scale even at 50°C, which showed two singlets in 1H NMR spectrum at that temperature. The 13C NMR spectrum of 4d showed a similar spectral pattern with 4b.

For hexyl ether 4e, in the 1H NMR spectrum, the singlet at 4.56 from bridge methyleneoxy protons of ArCH2OCH2OAr at 50°C splits on cooling to room temperature into AB system at 4.57 and 4.53 which indicates the conformational transformation through the ArCH2OCH2 rotation does not occur at room temperature. The AB pattern of ArCH2Ar protons remains unchanged up to 50°C, suggesting the transformation through ArCH2Ar rotation does not occur even at that temperature. The 13C NMR spectrum of 4e showed similar spectral pattern with 4b.

Temperature dependant 1H NMR spectral patterns of ArCH2OCH2Ar and ArCH2Ar protons of compound 4 are summarized in Table 3.

**In conclusion,** five tetrahomodioxacalix[4]arene tetra alkylethers were synthesized by the treatment of tetrahomodioxa-p-phenylcalix[4]arene with alkyl halide and NaH in DMF. From 1H, 13C NMR and crystal structure they were found to be in the C-1,2-alternate conformation. The butyl group is not bulky enough for the sterical inhibition of the conformational interconversion of tetrahomodioxacalix[4]arene at room temperature.

**Experiments Section**

Unless otherwise noted, reagents were obtained from commercial suppliers and used without further purification. Melting points were taken in evacuated and sealed capillary tubes with a Mel-Temp apparatus. IR spectra were determined with a Nicolet Impact 400 FT-IR spectrometer as KBr pellets. 1H and 13C NMR spectra were recorded with a Bruker AMX 600 spectrometer. Chemical shifts are recorded in parts per million relative to TMS as an internal standard.

The 3-(3-hydroxymethyl-5-phenylsalicyl)-5-phenyl-2-hydroxybenzyl alcohol (2) was prepared in 55% yield following the published procedure. The 7,13,21,27-tetraphenyl-29,30,31,32-tetrahydroxy-2,3,16,17-tetrahomo-3,17-dioxacalix[4]arene (3) was prepared in 79% yield from bishydroxymethylated dimer of p-phenylphenol as described elsewhere.

**General method for the synthesis of 7,13,21,27-tetraphenyl-29,30,31,32-tetraalkyloxy-2,3,16,17-tetrahomo-3,17-dioxacalix[4]arenes 4a-d.** To heated suspension of compound 3 (1.00 mmole) and NaH (537 mg, 60% oil dispersion) in dry DMF (30 mL), alkyl iodide or bromide (12.0 mmole) was added under Ar and then the reaction mixture was heated at 70°C for 24-48 h. After small amount of methanol was added to destroy the excess NaH, solvent was removed in vacuo and then the organic material was extracted with methylene chloride. The organic layer was washed with water, dried and evaporated to afford slightly brown colored residue, which was subjected to purification.

7,13,21,27-Tetraphenyl-29,30,31,32-tetramethyloxy-2,3,16,17-tetrahomo-3,17-dioxacalix[4]arene 4a. The reaction residue was stirred with methylene chloride. The methylene insoluble material was collected by filtration, washed with water and then dried to afforded 724 mg (84.5%) of the colorless crystalline material. The filtrate and washing were washed with water, dried and evaporated to afford additional 85 mg of colorless solid. The total yield.
Conformations of Tetrahomo-1,4-phenylcalix[4]arene Alkyl Ethers


was 94.4%. Analytical sample was obtained by recrystallization from CH₂Cl₂ and methanol to produce 1.08 g (89%) of the product 4b as crystalline solid. mp 250-251 °C; 'H NMR (CDCl₃, 0 °C) δ 7.56-7.27 (m, 28, ArH), 4.60 (d, 4, ArCH₂O, J = 10.7 Hz), 4.56 (d, 2, ArCH₂Ar, J = 13.7 Hz), 4.54 (d, 4, ArCH₂O, J = 10.7 Hz), 3.54 (q, 4, CH₂, J = 7.0 Hz), 3.46 (d, 2, ArCH₂Ar, J = 13.7 Hz), 3.37 (q, 4, CH₂, J = 7.0 Hz), 1.52 (sextet, 4, CH₂, J = 6.8 & 7.3 Hz), 1.37 (sextet, 4, CH₂, J = 6.8 & 7.3 Hz), 0.63 (t, 12, CH₂, J = 7.3 Hz). (25 °C) 7.55-7.26 (m, 28, ArH), 4.57 (s, 10, ArCH₂O & ArCH₂Ar), 3.53-3.39 (br, 10, OCH₃ & ArCH₂Ar), 1.50 (br, 4, 8, CH₂), 1.37 (br, 4, 8, CH₂), 0.62 (br, s, 12, CH₂). 'C NMR (CDCl₃): δ 156.50, 140.71, 136.02, 131.60, 129.09, 128.58, 126.74 (Ar), 76.89, 66.80 (OCH₃), 30.70 (ArCH₂O, 23.03 (CH₃), 3.10 (CH₃). Anal. Calcd. For C₆H₄O₆C₆: C, 82.81; H, 7.16. Found: C, 82.88; H, 7.04.

7.13,21,27-Tetraphenyl-29,30,31,32-tetrapropoxy-2,3,16,17-tetrahydro-3,17-dioxacalix[4]arene 4b. The reaction residue was recrystallized from CH₂Cl₂ and methanol to produce 792 mg (82.3%) of the product 4 as crystalline solid. mp 244-245 °C; 'H NMR (CDCl₃, 50 °C) δ 7.50-7.25 (m, 28, ArH), 5.75 (m, 4, CH =), 4.98 (d, 4, =CH₂, J = 17.2 Hz), 4.82 (d, 4, =CH₂, J = 10.4 Hz), 4.53 (s, 8, ArCH₂O), 4.00 (br, 4, ArCH₂Ar), 3.96 (d, 8, OCH₃C =, J = 5.6 Hz); (25 °C) 7.50-7.25 (m, 28, ArH), 5.75 (m, 4, CH =), 5.01 (d of d, 4, =CH₂, J = 17.2 & 1.6 Hz), 4.84 (d, 4, =CH₂, J = 10.4 Hz), 4.60 (d, 4, ArCH₂O, J = 10.3 Hz), 4.58 (d, 2, ArCH₂Ar, J = 13.6 Hz), 4.45 (d, 4, ArCH₂O, J = 10.3 Hz), 4.05 (br, 4, OCH₃C =), 3.89 (br, 4, OCH₃C =), 3.84 (d, 2, ArCH₂Ar, J = 13.6 Hz). 'C NMR (CDCl₃): δ 156.30, 140.11, 136.77, 135.48, 134.29, 131.11, 129.59, 120.03, 128.69, 127.18, 126.93 (Ar H₂C =), 116.99 (=CH₂), 75.89, 67.14 (OCH₃), 32.27 (CH₃). Anal. Calcd. For C₆H₄O₆C₆: C, 83.52; H, 6.37. Found: C, 83.45; H, 6.29.

7.13,21,27-Tetraphenyl-29,30,31,32-tetrahexyloxy-2,3,16,17-tetrahydro-3,17-dioxacalix[4]arene 4d. The reaction residue was recrystallized from CH₂Cl₂ and methanol to produce 968 mg (94%) of the product 4 as crystalline solid. mp 227-228 °C; 'H NMR (CDCl₃, 25 °C) δ 7.57-7.25 (m, 28, ArH), 4.53 (s, 8, ArCH₂O), 4.55 (d, 2, ArCH₂Ar, J = 13.6 Hz), 3.58 (t, 4, CH₂, J = 7.2 Hz), 3.42 (t, 4, CH₂, J = 7.2 Hz), 3.38 (d, 2, ArCH₂Ar, J = 13.6 Hz), 1.45 (quintet, 4, CH₂, J = 7.2 & 8.0 Hz), 1.35 (quintet, 4, CH₂, J = 7.2 & 8.0 Hz), 1.05 (sextet, 8, CH₂, J = 7.2 & 8.0 Hz), 0.54 (t, 12, CH₂, J = 7.2 Hz). (0 °C) δ 7.56-7.28 (m, 28, ArH), 4.56 (d, 4, ArCH₂O, J = 10.6 Hz), 4.55 (d, 2, ArCH₂Ar, J = 13.7 Hz), 4.52 (d, 4, ArCH₂O, J = 10.6 Hz), 3.59 (t, 2, CH₂, J = 7.2 Hz), 3.58 (t, 2, CH₂, J = 7.2 Hz), 3.45 (d, 2, ArCH₂Ar, J = 13.7 Hz), 3.39 (t, 2, CH₂, J = 7.2 Hz), 3.38 (t, 2, CH₂, J = 7.2 Hz), 1.46 (m, 4, CH₂), 1.36 (m, 4, CH₂), 1.05 (sextet, 8, CH₂, J = 7.2 Hz), 0.54 (t, 12, CH₂, J = 7.2 Hz). ‘C NMR (CDCl₃): δ 156.61, 140.59, 135.87, 135.20, 130.60, 128.96, 128.81, 128.57, 126.76 (Ar), 75.46, 67.03 (OCH₃), 32.11 (ArCH₂Ar), 30.85 (CH₂), 19.15 (CH₃), 13.77 (CH₃). Anal. Calcd. For C₆H₄O₆C₆: C, 82.97; H, 7.56. Found: C, 82.88; H, 7.62.

Acknowledgment. The authors are grateful to the KISTEP for the financial support (M10022010001-01G0506-00210).

References


