

Preparation of Lower Rim Functionalized Tetrahomodiazap-Phenylcalix[4]arenes

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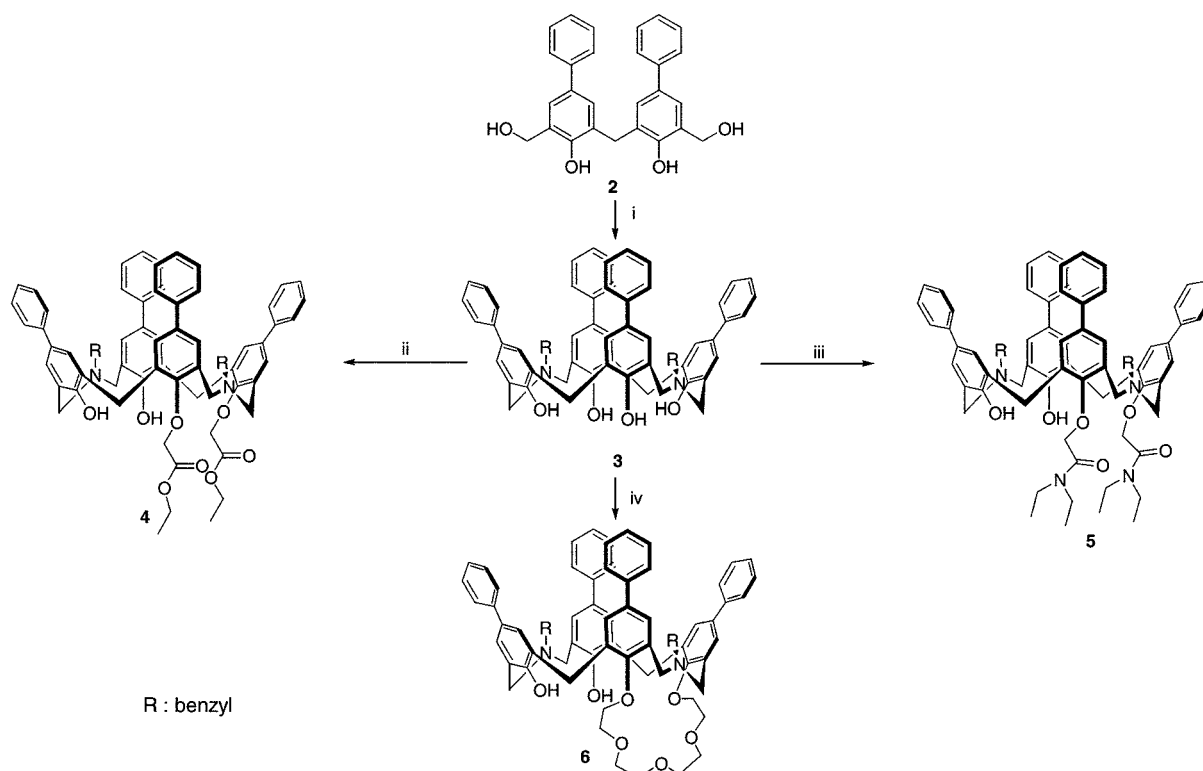
Calixarenes are synthetic macrocycles that are available in a variety of ring sizes. They have long been of interest both as complexation hosts for ions and molecules and as frameworks for elaborating more complex structures, and have received a great deal of attention in recent years.¹⁻⁴ Homoazacalixarenes, which are derived from calixarenes by replacement of at least one methylenic carbon atom by a dimethyleneaza (-CH₂N(R)CH₂-) link, have been the subject of relatively few investigations up to now.⁵ In particular, in spite of their potential richness and versatility as ligands, the structural studies of their complexes are scarce⁶ compared to those of calixarenes and even homooxacalixarenes, which are another closely related family of expanded calixarenes. Azacalixarenes could have great utility as receptors for a large variety of guests. The dimethyleneaza linkages introduce flexibility to the receptor, a feature that may be desirable for binding guests in an induced-fit fashion. Since the synthesis and conformation of *N*-benzyl-tetrahomodiazap-*t*-butylcalix[4]arene were reported by Khan and coworkers⁷ several *p*-substituted azacalix[4]arenes were synthesized and their solid structures and complexation behavior were investigated.⁶ Takemura and coworkers prepared *N*-alkyl tetrahomodiazap-*p*-*tert*-butylcalix[4]arenes in 20% yield by refluxing the mixture of bis(hydroxymethyl) phenol dimer and various amine in toluene or xylene for 4 days in reasonable yield.⁷ However the introduction of functional groups, which can be utilized as recognition or binding sites, into the lower or/and upper rim of calixarene was not reported yet. Therefore in this paper we describe the first synthesis and molecular structure determination of three *N*-benzyl-tetrahomodiazap-*p*-phenylcalix[4]arene derivatives.

Azacalix[4]arene **3** and their derivatives were obtained as outlined in scheme. Treatment of bis(hydroxymethyl)-*p*-phenylphenol dimer **2**⁸ with benzylamine in refluxing xylene with continuous azeotropic removal of water afforded tetrahomodiazacalix[4]arene **3** in 52% yield. An additional pure product was obtained from the flash chromatographic separation of the residue which was resulted by the evaporation of solvent from the combined solution of filtrate and washing. The total yield was 62%. In the ¹H NMR spectrum of compound **3** at 25 °C the benzylic bridge protons appear as three singlets, which indicates the free interconversion between conformational isomers. The ¹³C NMR spectrum of **3** shows one peak at 58.68 ppm for the ArCH₂N bridged methylene carbons and one peak at 31.73

ppm for the ArCH₂Ar bridge carbons. These NMR spectral data of **3** show more flexible conformation of this molecule compared with analogous *p*-*t*-butylazacalix[4]arene. In the ¹H NMR of tetrahomodiazap-*p*-*t*-butylcalix[4]arene at room temperature the benzylic protons appears as two pairs of doublet.⁷ The conformation of tetrahomodiazacalix[4]arenes can be described along the same categories as those of tetrahomodioxacalix[4]arenes, *i.e.*, cone, partial cone, COC-1,2-alternate, C-1,2-alternate and 1,3-alternate.⁹

Ethyl acetate groups at lower rim of calix[4]arene can be converted to the various other useful functional groups such as acid,¹⁰ hydroxy¹¹ or amide,¹² therefore we tried to introduce alkyl ester function into the lower rim of tetrahomodiazacalix[4]arene **3**. When the tetrahomodiazacalix[4]arene **3** was treated with 4 equivalents ethyl bromoacetate in acetone in the presence of K₂CO₃, the di-*O*-alkylated compound **4** was isolated in 87% yield as crystalline solid. The structure of compound **4** was confirmed by ¹H and ¹³C NMR spectra and elemental analysis. In the ¹H NMR spectrum, the methylenic protons from ArCH₂Ar bridges appear as one pair of doublet at δ 4.82 and 3.48 (Δν = 536 Hz) with a geminal coupling constant of 15.5 Hz and the methylenic protons from ArCH₂N(R)CH₂Ar appear as two pairs of doublet at δ 4.71 and 2.96 (Δν = 700 Hz) with a geminal coupling constant of 11.6 Hz and at δ 4.65 and 3.48 (Δν = 468 Hz) with a geminal coupling constant of 14.6 Hz. The methylenic protons from ArCH₂N of benzyl amine appear as two broad peaks at δ 4.22 and 3.97 (Δν = 100 Hz). In the ¹³C NMR spectrum, two peaks are observed at 60.91, 59.68 ppm for the ArCH₂N(R)CH₂Ar bridged methylene carbons and one peak at 29.89 ppm for the ArCH₂Ar bridge carbons. The methylene carbons of ArCH₂N from benzyl amine appear as two peaks at 53.62 and 50.49 ppm. These NMR spectra for **4** indicate that two adjacent aryl moieties joined by a CH₂ group and CH₂NCH₂ group are in syn orientation, respectively, therefore, **4** is in the cone conformation in solution. The NMR spectral data support the symmetrical 1,2-dialkylation at lower rim of azacalix[4]arene. Tetrahomodiazacalix[4]arene has only two plane of symmetry compared to calix[4]arene which has four, therefore selective 1,3-dialkylation will eliminate the remaining symmetry of tetrahomodiazacalix[4]arene and the resulting compound is chiral,¹³ which gives much more complex NMR peak pattern. When the same reaction was carried with large excess of ethyl bromoacetate and extended refluxing time (6 days), the same result was obtained. We tried to prepare tetra *O*-alkylated product by using NaH as

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Scheme 1. reagents: i) benzylamine, ii) $\text{BrCH}_2\text{CO}_2\text{Kt}/\text{K}_2\text{CO}_3$, iii) $\text{ClCH}_2\text{CON}(\text{Et})_2/\text{K}_2\text{CO}_3$, iv) tetraethyleneglycol ditosylate/ K_2CO_3

base. When the compound **3** was treated with large excess of ethyl bromoacetate in THF and DMF mixture in the presence of NaH as a base, tetra *O*-alkylated product was not produced even when the reaction time was extended up to 4 days. The origin of this phenomenon is not clear at present.

Reaction of **3** with excess *N,N*-diethyl chloroacetamide and in MeCN in the presence of K_2CO_3 afforded a 48% yield of diamide **5** as a crystalline solid. In the ^1H NMR spectrum of **5**, the methylenic protons from ArCH_2Ar bridges appear as one pair of doublet at δ 4.73 and 3.49 ($\Delta\nu = 496$ Hz) with a geminal coupling constant of 14.1 Hz and the methylenic protons from $\text{ArCH}_2\text{N}(\text{R})\text{CH}_2\text{Ar}$ appear as two pairs of doublet at δ 4.57 and 2.97 ($\Delta\nu = 648$ Hz) with a geminal coupling constant of 11.9 Hz and at δ 4.15 and 3.59 ($\Delta\nu = 224$ Hz) with a geminal coupling constant of 13.6 Hz. The methylenic protons from ArCH_2N of benzyl amine appear as one pair of doublet at δ 4.60 and 4.46 ($\Delta\nu = 56$ Hz) with a geminal coupling constant of 13.0 Hz. In the ^{13}C NMR spectrum, two peaks were observed at 57.98 and 55.54 ppm for the ArCH_2N bridged methylene and benzylic carbons and one peak at 30.00 ppm for the ArCH_2Ar bridge carbons. These NMR spectral data support the symmetrical vicinal 1,2-alkylation at lower rim of azacalix[4]arene **3**.

Calix[4]crown in which the proper-sized crown rings are incorporated into the calix[4]arene framework have also been attractive as specific metal-selective extractant.¹⁴ Compound **3** was treated with 2 equivalents of tetra(ethyl-ene glycol) ditosylate and 2 equivalents of K_2CO_3 in refluxing acetonitrile for 48 h. After evaporation of solvent,

the resulting crude residue was purified by flash chromatographic separation to produce tetrahomodiazacalix[4]mono-crown-5 **6** in 56% yield. Judging from ^1H and ^{13}C NMR spectroscopy, azacalix[4]crown-5 was in cone conformation in solution. Two AB doublets were observed in the ^1H NMR spectrum corresponding to the dimethyleneaza protons of the $\text{ArCH}_2\text{N}(\text{R})\text{CH}_2\text{Ar}$ bridge at δ 4.37 and 2.98 ($\Delta\nu = 556$ Hz) with a geminal coupling constant of 11.9 Hz and at δ 4.13 and 3.49 ($\Delta\nu = 256$ Hz) with a geminal coupling constant of 13.4 Hz, as well as one AB doublet peak at δ 4.89 and 3.45 ($\Delta\nu = 576$ Hz) with a geminal coupling constant of 14.2 Hz for the methylene protons of ArCH_2Ar . The methylenic protons from ArCH_2N of benzyl amine appear as two multiplet peaks at δ 4.22 and 3.98 ($\Delta\nu = 96$ Hz). In the ^{13}C NMR spectrum, two peaks were observed at 58.51 and 55.80 ppm for the ArCH_2N bridged methylene and benzylic carbons and two peaks at 29.94 and 29.18 ppm for the ArCH_2Ar bridge carbons. These NMR spectra for **6** indicate that two adjacent aryl moieties joined by a CH_2 group and $\text{CH}_2\text{N}(\text{R})\text{CH}_2$ group are in syn orientation, respectively. Studies are currently underway to exploit the full potential of these functionalized tetrahomodiazacalix[4]arenes.

Experimentals

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. ^1H and ^{13}C NMR spectra

were recorded with a Bruker AMX 400 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.⁸

***N,N*-Dibenzyl-7,13,21,27-tetraphenyl-29,30,31,32-tetrahydroxy-2,3,16,17-tetrahydro-3,17-diazacalix[4]arene (3)**. A solution of 2,2'-methylenebis(4-phenyl-6-hydroxymethylphenol) (2.47 g, 5.99 mmol) and benzylamine (1.4 mL, 12.8 mmol) in 80 mL of xylene was heated under reflux for 20 h. After partial removal of solvent under reduce pressure, the reaction mixture cooled to room temperature and then collected the precipitated solid to afford 1.49 g (52%) of the desired product as pale yellow crystal. After the combined filtrate and washing were evaporated, the resultant oily material was subjected to flash chromatography (3 : 1 mixture of hexane and acetone as an eluent) to afford an additional 300 mg (10%) of the desired product. The total yield is 62%. mp 238 °C; ¹H NMR (CDCl₃) δ 7.51-7.16 (m, 42, ArH & OH), 3.82 (br. 4, ArCH₂N), 3.78 (br. 4, ArCH₂N), 3.56 (br. 8, ArCH₂N & ArCH₂Ar); ¹³C NMR (CDCl₃) δ 141.19, 133.36, 130.07, 129.01, 128.87, 128.24, 127.93, 127.66, 126.98, 126.77, 123.29 (Ar), 58.68 (ArCH₂N), 31.73 (ArCH₂Ar). Anal. Calcd. for C₆₈H₅₈O₄N₂: C, 84.44; H, 6.04. Found: C, 84.12; H, 6.10.

***N,N*-Dibenzyl-7,13,21,27-tetraphenyl-29,30-bis(ethoxycarbonyl)methoxy-31,32-dihydroxy-2,3,16,17-tetrahydro-3,17-diazacalix[4]arene (4)**. To a solution of **3** (705 mg, 0.729 mmol) in acetonitrile (70 mL) was treated with 720 mg of anhydrous K₂CO₃. To this suspension ethyl bromoacetate (1.0 mL) was added, then the reaction mixture was refluxed 24 h. After cooling to room temperature the insoluble material was collected by filtration, washed with acetonitrile and then water several times to afford the desired compound (720 mg, 87%) as a TLC pure crystalline solid. A recrystallization from ethyl acetate and ethanol provides the analytical sample. mp 230 °C (decompose); ¹H NMR (CDCl₃) δ 10.18 (br. 2, OH) 7.59 (d. 1, ArH, *J* = 1.6 Hz), 7.58 (s. 2, ArH), 7.49 (s. 2, ArH), 7.42 (t. 2, ArH, *J* = 7.4 Hz), 7.41 (t. 2, ArH, *J* = 7.4 Hz), 7.31-7.14 (m. 27, ArH), 7.05 (br. 2, ArH), 4.82 (d. 2, ArCH₂Ar, *J* = 15.5 Hz), 4.71 (d. 2, ArCH₂N, *J* = 11.6 Hz), 4.65 (d. 4, ArCH₂N, *J* = 14.6 Hz), 4.26 (q. 4, OCH₂, *J* = 7.2 Hz), 4.22 (br. 2, ArCH₂N), 3.97 (br. 2, ArCH₂N), 3.48 (d. 2, ArCH₂Ar, *J* = 15.5 Hz), 3.48 (d. 4, ArCH₂N, *J* = 14.6 Hz), 2.96 (d. 2, ArCH₂N, *J* = 11.6 Hz), 1.34 (t. 3, CH₃, *J* = 7.2 Hz), 1.33 (t. 3, CH₃, *J* = 7.2 Hz); ¹³C NMR (CDCl₃) δ 168.58 (C=O), 156.25, 154.95, 150.48, 147.85, 140.73, 136.98, 134.28, 133.46, 130.59, 129.25, 129.09, 128.78, 128.56, 127.06 (Ar), 71.69 (OCH₂CO), 69.35 (OCH₂), 60.91, 59.68, 53.62, 50.49 (ArCH₂N), 29.89 (ArCH₂Ar), 14.11 (CH₃). Anal. Calcd. for C₇₆H₇₀O₈N₂. EtOH: C, 79.03; H, 6.46. Found: C, 79.36; H, 6.39.

***N,N*-Dibenzyl-7,13,21,27-tetraphenyl-29,30-bis(diethylcarbamoyl)methoxy-31,32-dihydroxy-2,3,16,17-tetrahydro-3,17-diazacalix[4]arene (5)**. To a solution of **3** (900 mg, 0.931 mmol) in dry acetone (100 mL) was added anhydrous

K₂CO₃ (370 mg) followed by 0.8 mL of *N,N*-diethylchloroacetamide. The mixture was refluxed for 3 days and evaporated *in vacuo*. The mixture was extracted with CH₂Cl₂ and water. The organic layer was washed with water, dried over MgSO₄ and evaporated *in vacuo*. The residue, which showed one major spot on TLC analysis, was triturated with MeOH to give 396 mg (35%) of dialkylated product as a white, crystalline solid. An additional 147 mg (13%) of pure product was isolated by flash chromatography of the residue obtained by evaporation of filtrate on silica gel with acetone-hexane as eluent. Analytical sample was recrystallized from ethanol. mp 183 °C; ¹H NMR (CDCl₃): δ 9.87 (s. 2, OH), 7.61 (d. 2, ArH, *J* = 1.2 Hz), 7.59 (d. 2, ArH, *J* = 1.2 Hz), 7.50 (d. 2, ArH, *J* = 2.4 Hz), 7.43 (t. 6, ArH, *J* = 7.6 Hz), 7.32-7.12 (m. 24, ArH), 7.04 (br. 2, ArH), 4.73 (d. 2, ArCH₂Ar, *J* = 14.1 Hz), 4.60 (d. 2, CH₂N, *J* = 13.0 Hz), 4.57 (d. 2, ArCH₂N, *J* = 11.9 Hz), 4.46 (d. 2, CH₂N, *J* = 13.0 Hz), 4.15 (d. 2, ArCH₂N, *J* = 13.6 Hz), 3.59 (d. 2, ArCH₂N, *J* = 13.6 Hz), 3.50 (q. 4, NCH₂, *J* = 7.0 Hz), 3.49 (d. 2, ArCH₂Ar, *J* = 14.1 Hz), 3.47 (s. 4, OCH₂CO), 3.45 (q. 4, NCH₂, *J* = 7.0 Hz), 2.97 (d. 2, ArCH₂N, *J* = 11.9 Hz), 1.34 (t. 6, CH₃, *J* = 7.0 Hz), 1.20 (t. 6, CH₃, *J* = 7.0 Hz). ¹³C NMR (CDCl₃): δ 167.66 (C=O), 156.33, 155.95, 141.57, 140.61, 136.52, 136.18, 135.19, 131.46, 130.69, 130.53, 129.83, 129.03, 128.94, 128.64, 128.29, 127.50, 127.31, 127.07, 126.97, 126.88, 126.52, 123.08 (Ar), 72.70 (OCH₂CO), 57.98, 55.54 (ArCH₂N), 41.79, 40.55 (NCH₂), 30.00 (ArCH₂Ar), 14.86, 13.28 (CH₃). Anal. Calcd. for C₈₀H₈₂O₆N₄. 1/2EtOH: C, 78.94; H, 7.03. Found: C, 78.72; H, 7.39.

***N*-Benzyl tetrahomodiazacalix[4]monocrown-5 (6)**. To a solution of **3** (1.45 g, 1.50 mmol) in dried acetonitrile was added 2.26 g of anhydrous K₂CO₃ followed by 0.75 g (1.50 mmol) of tetra(ethyleneglycole) ditosylate. The reaction mixture was refluxed for 5 days under argon atmosphere and cooled to room temperature. The precipitated solid was collected by filtration, washed with water several times and then dried. The product mixture, which showed one major spot with long tailing on TLC analysis, was separated with flash chromatography (eluent was 4 : 1 mixture of hexane and acetone) to afford 950 mg (56%) of **6** as a white solid. mp 230 °C (decompose); ¹H NMR (CDCl₃): δ 9.69 (s. 2, OH), 7.59 (d. 2, ArH, *J* = 1.2 Hz), 7.57 (d. 2, ArH, *J* = 1.2 Hz), 7.51 (d. 2, ArH, *J* = 2.0 Hz), 7.41 (t. 4, ArH, *J* = 7.6 Hz), 7.29-7.05 (m. 28, ArH), 4.89 (d. 2, ArCH₂Ar, *J* = 14.2 Hz), 4.37 (d. 2, ArCH₂N, *J* = 11.9 Hz), 4.22 (m. 2, CH₂N), 4.13 (d. 2, ArCH₂N, *J* = 13.4 Hz), 4.08 (d of t. 8, OCH₂, *J* = 7.8 Hz), 3.98 (m. 2, CH₂N), 3.88 (d of t. 4, OCH₂, *J* = 7.8 Hz), 3.64 (t. 2, OCH₂, *J* = 10.4 Hz), 3.49 (d. 2, ArCH₂N, *J* = 13.4 Hz), 3.45 (d. 2, ArCH₂Ar, *J* = 14.2 Hz), 3.30 (br t. 2, CH₂O, *J* = 10.4 Hz), 2.95 (d. 2, ArCH₂N, *J* = 11.9 Hz). ¹³C NMR (CDCl₃): δ 155.89, 155.65, 141.65, 140.78, 136.59, 136.35, 135.49, 131.40, 130.55, 130.51, 129.90, 129.18, 128.93, 128.68, 128.53, 127.79, 127.62, 127.11, 126.98, 126.90, 123.28 (Ar), 74.98, 72.65, 71.35, 70.00 (OCH₂), 58.51, 55.80 (ArCH₂N), 29.94, 29.18 (ArCH₂Ar). Anal. Calcd. for C₇₆H₇₂O₇N₂: C, 81.11; H, 6.45. Found: C, 80.95; H, 6.39.

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