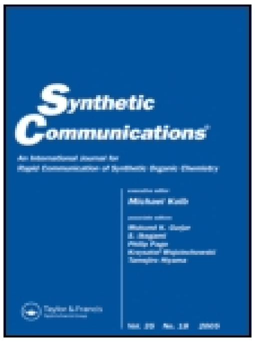

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NOVEL CALIX[4]ARENE DIBENZOCROWN ETHERS BEARING LIPOPHILIC ALKYL GROUPS SYMMETRICALLY BRANCHED

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ABSTRACT: 1,3-dialkyloxycalix[4]arene dibenzocrown ether in which two lipophilic butyl groups are symmetrically attached were successfully synthesized in the fixed 1,3-alternate conformation (**12** and **13**) of which structure was characterized by X-ray crystal structure.

Calix[4]arene molecule has long been proven to be a useful three dimensional molecular building block for the synthesis of molecules with specific properties.[1] Several groups have succeeded in demonstrating that calix[4]arenes serve as an excellent receptor for the specific binding of guest atoms and molecules.[2,3] Reinhouldt and Ungaro have reported that 1,3-dialkoxycalix[4]arene-crown-6 derivatives were successfully prepared and they are exceptionally selective ionophores for cesium ion when they are fixed in the 1,3-alternate conformation.[4]

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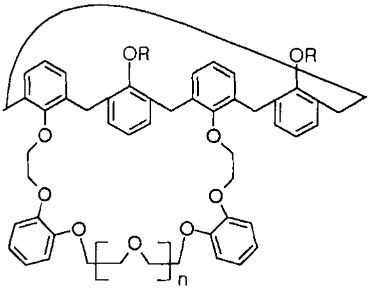
It has been known that introducing aryl substituents such as phenyl or naphtyl into the polyether ring greatly enhance the metal ion selectivity and efficiency.[5] So, recently, we reported that the successful synthesis of calix[4]arene crown ethers (**1-4**) containing dibenzo unit on the downward ether linkage and they showed a selective complexation with cesium ion over alkali metal ions.[6] To further investigate an influence of lipophilicity of organic ligand and the corresponding stereochemistry, now we report synthetic methods for the preparation of dibutyl substituted 1,3-dialkyloxycalix[4]arene dibenzocrown ethers.

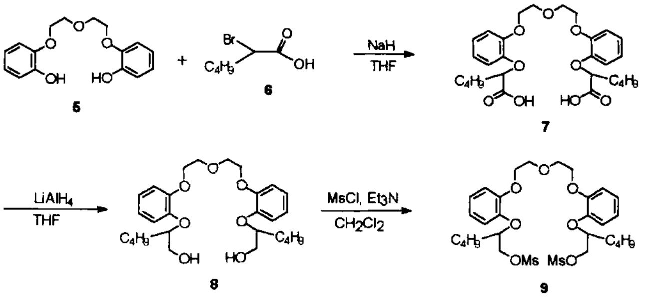


	n	R
1	1	n-propyl
2	1	allyl
3	2	n-propyl
4	2	allyl

Synthetic route for the preparation of dibenzodimesylate (**9**) is described in Scheme 1. Reaction of 1,2-bis(2-hydroxyphenoxy)ethane (**5**) as a starting material with 2-bromohexanoic acid (**6**) in the presence of sodium hydride as a base in THF provided 1,5-bis[2-(2-carboxypentyloxy)phenoxy]-3-oxapentane (**7**) as over 79% yield. Subsequently, reduction of corresponding diacid with lithium aluminum hydride in THF gave a corresponding diol (**8**) with 75 % yield. Number of attempts including varied solvents for tosylation of the diol in this case was found to give a product with a low yield (below 20 %). Instead, dimesylation of diol with methanesulfonyl chloride in the presence of triethylamine gave a desired product over 95 % yields.

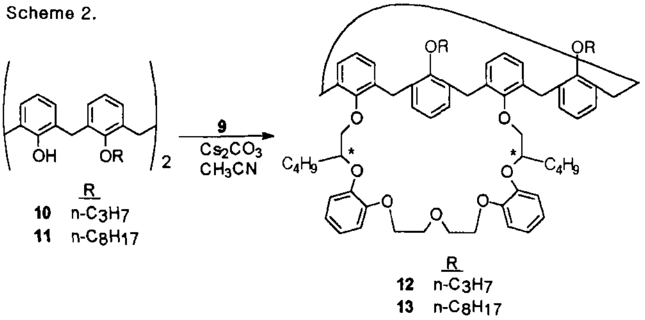
Dialkylation of calix[4]arene using the reported method[4] was successfully conducted to give compounds **10** and **11** with an over 80 % yield. Compounds **10** and **11** appeared AB quartet splitting pattern (J=12.8 Hz, $\triangle$v= 199 Hz, chemical shift difference value) in ^{1}H NMR spectra, indicating a characteristic cone conformation.

Scheme 1.



Cyclization reaction of 1,3-dialkyloxy calix[4]arene with dibutylated dibenzomesylate (**9**) in the presence of Cs_2CO_3 provided the desided products (**12** and **13**) with 64 % and 58 % yield, respectively. It has been known that when calix[4]arene crown ether takes an 1,3-alternate conformation, due to magnetical equivalence on NMR time scale, singlet peak (8 hydrogens of methylene bridge) is shown in ^{1}H NMR.[4]

Scheme 2.



With an accordance of this phenomenon, 1,3-dlalkyloxy calix[4]arene dibenzocrown ethers (**12** and **13**) showed an singlet peak at around 3.58 ppm ($CDCl_3$) for the bridging methylene hydrogens in ^{1}H NMR, indicating the characteristic of 1,3-alternate conformation in both cases. No other isomers were observed. Fortunately, we were able to obtain the solid state structure of compound **12** in methylene chloride as shown in Figure 1. Refinement converged with R_f (R_w)=0.0613 (0.0847). The two butyl group attached on crown ether linkage stretched toward same direction, indicating that compound **12** is of apparent symmetry, namely achiral property although it has two chiral carbons in ether linkage. Complexation studies upon the ion transport of alkali metal ions through bulk liquid membrane and supported liquid membrane using **12**, **13**, and their structural derivatives are now in progress and will be reported soon.

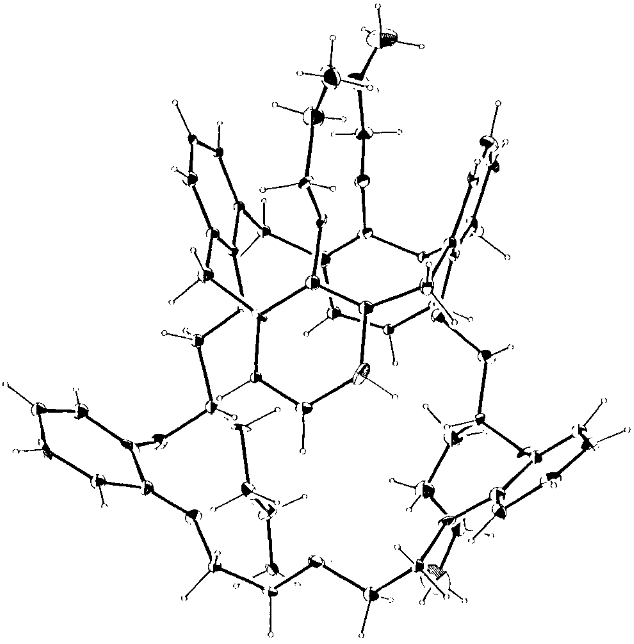


Figure 1. X-ray crystal structure of compound **12**.

Experimental

Melting points were taken by the use of a Mel-Temp of Fisher-Johns melting point apparatus without any correction. IR spectra were obtained with a Perkin-Elmer 1600 Series FT-IR on potassium bromide pellet and on deposited KBr window in the case of soild product and oil, respectively, are recorded in reciprocal centimeters. ^1H spectrum was recorded with a 400 MHz (Bruker ARX-400) spectrometer, the chemical shifts (δ) reported downfield from the internal standard, tetramethylsilane. Elemental analysis was performed by Vario EL of

Elemental Analyzer in Korea Basic Science Institute in Seoul, Korea. FAB^+ mass spectra was obtained from JEOL-JMS-HX 110A/110A High Resolution Tendem Mass Spectrometry in Korea Basic Science Institute in Taejon, Korea.

Unless specified otherwise, reagent grade reactants and solvents were obtained from chemical suppliers and used as received. Dry solvents were prepared as follows: tetrahydrofuran was freshly distilled from sodium metal ribbon or chunks; benzene and pentane were stored over sodium ribbon, respectively; dichloromethane was freshly distilled from lithium aluminum hydride. Acetonitrile was pre-dried from molecular seives (3Å) and distilled over diphosphorous pentaoxide. Compounds **5**,[7] **10**,[4] and **11**,[4] were prepared as described in the literatures.

1,5-Bis[2-(2-carboxypentyloxy)phenoxy]-3-oxapentane (7). After removal of the protecting mineral oil from NaH (50% dispersion in mineral oil, 6.00 g, 0.34 mol) by washing with n-pentane under nitrogen, a solution of bisphenol **5** (10.0 g, 34.4 mmol) in 150 mL of dry THF was added. The mixture was stirred for 2 hours at room temperature. 2-Bromohexanoic acid (14.1 g, 72.2 mmol) in 100 mL of dry THF was added dropwise at room temperature during a period of 2 hours. Upon the complete addition, the reaction mixture was allowed to reflux for additional 10 hours. After careful addition of water to the reaction mixture in an ice bath to destroy the unreacted excess NaH, which gave a homogeneous solution, THF was removed *in vacuo* leaving an aqueous mixture. Into this basic solution was poured 100 mL of ethyl acetate to extract the unreacted diphenol and organic impurities. The aqueous layer was washed with ethyl acetate (2 × 50 mL). Upon the acidification with conc. HCl to pH 1, crude product was extracted with methylene chloride (3 × 50 mL) and dried over $MgSO_4$. Removal of methylene chloride *in vacuo* provided colorless oil followed by recrystallization from 100 mL of diethyl ether gave 13.6 g of white crystal with mp 140 ℃ in 79 % yield. Mp: 158-162 ℃. IR (KBr pellet): 3445 (O-H); 1709 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.94 (s, 8 H), 6.11 (s, 2 H), 4.55 (t, 2 H), 3.73-4.24 (m, 8 H), 1.85-2.12 (m, 4 H), 1.45-1.75 (m, 8 H), 0.90 (t, 6 H). Anal. calculated for $C_{28}H_{38}O_9$: C, 64.70; H, 7.32. Found: C, 64.72; H, 7.25.

1,5-Bis[2-(1-butyl-2-hydroxyethyloxy)phenoxy]-3-oxapentane (8). Under nitrogen, to a suspension of $LiAlH_4$ (2.8 g, 73.9 mmole) in 150 mL of THF was added dropwise a solution of 7 (8.50 g, 16.4 mmole) dissolved in 100 mL of THF during a period of 30 min at 0 ℃. Upon the complete addition, reaction mixture was refluxed for 20 hr under nitrogen atmosphere. After cooling down to 0 ℃ with ice-bath, 10 mL of ethyl acetate and 10 mL of 10% NaOH aqueous solution were added dropwise to destroy the unreacted $LiAlH_4$. The reaction mixture was allowed to stir for an additional 1 h at room temperature. White solid was filtered and washed with 100 mL of THF. After the organic solvent of filtrate was removed *in vacuo*, the residue was poured into a separatory funnel with 100 mL of CH_2Cl_2. The organic layer was separated and washed with 10 % HCl solution followed by washing with 100 mL of brine and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to give a colorless oil. Recrystallization from 100 mL of diethyl ether provided 6.08 g (75%) of a white solid. Mp 121-122 ℃: IR (KBr pellet, cm^{-1}) 3400 (O-H), 1110 (C-O); ^1H NMR ($CDCl_3$) δ 6.91 (s, 8 H, Ar-*H*), 4.57 (br s, 2 H, -O*H*), 4.47 (t, 2 H, -$HOCH_2CH(C_4H_9)$-O), 4.25-4.19 (m, 8 H), 3.99-3.84 (m, 4 H, $HOCH_2CH(C_4H_9)$-O), 1.25-1.84 (m, 12 H), 0.87 (t, 6 H); Anal. Calcd for $C_{28}H_{42}O_7$: C, 68.50; H, 8.56. Found: C, 68.47; H, 8.60.

1,5-Bis[2-(1-butyl-2-methanesulfonyloxyethyloxy)phenoxy]-3-oxapentane (9). Under nitrogen, to a solution of 5.0 g (6.40 mmol) of **8** and 1.88 mL (1.35 g, 13.4 mmol) of triethylamine in 100 mL of dry CH_2Cl_2 was added dropwise 1.24 mL (1.53 g, 13.4 mmol) of methanesulfonyl chloride during a period of 30 min at 0 ℃. Upon the complete addition, reaction mixture was stirred for 5 h at 0 ℃. Reaction temperature was slowly rasied upto room temperature and stirred for additional 10 hr. 50 mL of 10 % aqueous sodium bicarbonate solution was added and CH_2Cl_2 layer was separated. The organic layer was washed with water

(2 × 20 mL) and brine (2 × 20 mL) followed by drying over anhydrous magnesium sulfate. Removal of CH_2Cl_2 *in vacuo* provided 4.92 g (95 %) of desired product as a colorless oil. IR (KBr pallet, cm^{-1}) 1597, 1516, 1350 (SO_2), 1180 (SO_2); ^1H NMR ($CDCl_3$) δ 6.99-6.88 (m, 8 H, Ar-*H*), 4.43-4.35 (m, 6 H), 4.16 (t, 4 H), 3.92 (t, 4 H), 3.03 (s, 6 H, CH_3SO_2O), 1.64-1.85 (m, 4 H), 1.31-1.42 (m, 8H), 0.89 (s, 6 H). Anal. Calcd for $C_{30}H_{46}O_{11}S_2$: C, 55.60; H, 7.11. Found: C, 55.62; H, 7.13.

General Procedures for the Synthesis of Lipophilic Calix[4]arene Dibenzocrown-7. 25,27-dialkyloxycalix[4]arene (2.0 mmol) was dissolved in 100 mL of acetonitrile and added to an excess of Cs_2CO_3 (1.62 g, 5.0 mmol) and compound **9** (1.94 g, 2.1 mmol) under nitrogen atmosphere. The reaction mixture was refluxed for 24 hr. Then acetonitrile was removed *in vacuo* and the residue extracted with 100 mL of methylene chloride and 50 mL of 10% aqueous HCl solution. The organic layer was separated and washed twice with water. After the organic layer was separated and dried over $MgSO_4$ followed by removing the solvent *in vacuo* to give a brownish oil. Filtration column chromatography with ethyl acetate : hexane = 1 : 6 as eluents provided pure product as a white solid.

25,27-Bis(1-propyloxy)calix[4]arene dibenzo(dibutyl) crown-7, 1,3-alternate (12) was recrystallized from the oil residue with 5/1 diethyl ether-hexanes: 64 % yield; mp 179-181 ℃; IR (KBr pellet, cm^{-1}); 3068 (Ar-H), 1501, 1451, 1254, 1196; ^1H NMR ($CDCl_3$) δ 7.04-6.83 (m, 16 H), 6.78-6.70 (m, 4 H), 4.29 (t, J = 5.1 Hz, 2 H, -OC*H*(C_4H_9)CH_2O-), 4.33-4.19 (m, J = 5.1 Hz, 4 H), 4.07-4.00 (m, 4 H), 3.86-3.82 (m, 2 H), 3.64-3.40 (m, 6 H), 3.56 (s, 8 H, ArCH_2Ar), 1.66-1.27 (m, 16 H), 0.92-0.85 (m, 12 H). FAB MS *m/z* (M^+) calcd 962.52, found 962.50. Anal. Calcd for $C_{62}H_{74}O_9$: C, 77.29; H, 7.68. Found: C, 77.30; H, 7.60.

25,27-Bis(1-octyloxy)calix[4]arene dibenzo(dibutyl) crown-7, 1,3-alternate (13) was obtained as an oil: 58 % yield; IR (KBr window, cm^{-1}); 3068 (Ar-H), 1504, 1455, 1258, 1208; ^1H NMR ($CDCl_3$) δ 7.04 (m, 20 H), 4.20 (t, J =

5.1 Hz, 4 H), 4.38 (t, *J* = 5.1 Hz, 2 H, -OC*H*(C_4H_9)CH_2O-), 4.37-4.18 (m, *J* = 5.1 Hz, 4 H), 4.07-4.01 (m, 4 H), 3.86-3.82 (m, 2 H), 3.63-3.49 (m, 6 H), 3.55 (s, 8 H, ArCH_2Ar), 1.60-1.47 (m, 8 H), 1.31 (br s, 28 H), 0.73-0.91 (m, 12 H). FAB MS *m/z* (M^+) calcd 1102.51, found 1102.43. Anal. Calcd for $C_{72}H_{94}O_9$: C, 78.40; H, 8.53. Found: C, 78.29; H, 8.58.

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