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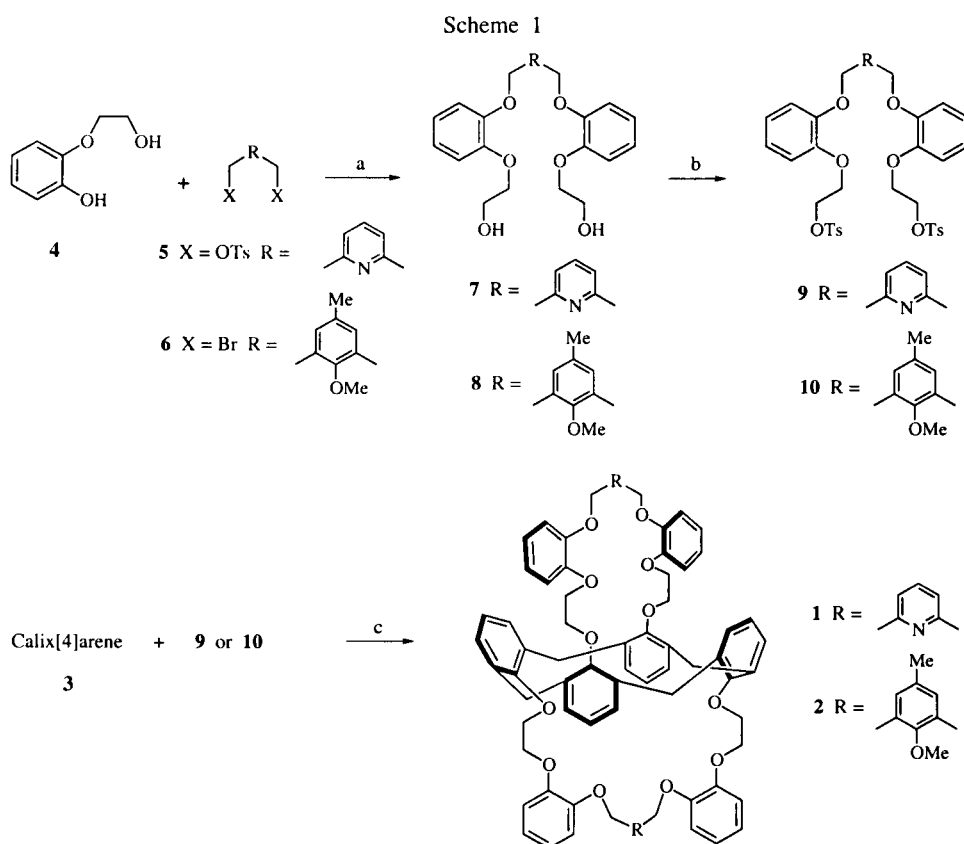
Syntheses of 1,3-2,4-calix[4]bis-crown ethers (**1** and **2**) fixed in the 1,3-alternate conformation by 1,3- and 2,4-bridges made of two modified polyether chains each containing two 1,2-phenylene residues and one pyridine or anisole unit are reported. The structures of compounds **1** and **2** were established by ^1H nmr, ^{13}C nmr, hrms and elemental analyses.

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Much attention has been paid in recent years to chemical separation techniques and the design and synthesis of new extraction reagents for metal ions. This attention results in part from environmental concerns, efforts to save energy, and recycling at the industrial level. Progress in the development of new extraction agents has resulted from advances in the field of "supramolecular chemistry," which has provided a variety of new reagents with the capacity to substantially improve the selectivity efficiency of many separations techniques [1]. Solvent extraction is of special interest for the selective removal of cesium ions (one of the major radionuclides) in nuclear waste treatment. It is very

difficult to separate cesium from nuclear waste solutions that also have high concentrations of sodium and other alkali-metal cations [2]. Thus, the achievement of a very high selectivity for cesium over other alkali-metal cations, especially sodium, is a worthy goal.

1,3-2,4-Calix[4]bis-crown ethers fixed in the 1,3-alternate conformation by polyether linkages have recently been reported to be highly selective as cesium ion carriers [3-5]. It has been shown that introducing benzo or 1,2-naphtho units into the polyether ring of a calix[4]crown ether greatly enhances metal ion affinity and selectivity [6]. For example, having a 1,2-phenylene (benzo) residue



a) Potassium carbonate, acetonitrile, reflux; b) Tosyl chloride, pyridine, 0°; c) Potassium carbonate, acetonitrile, reflux

in the middle of the crown-6 loop favored selectivity for cesium over the other alkali metal ions, especially sodium. The observed higher Cs^+/Na^+ selectivity was attributed to the replacement of sp^3 carbons in the middle of the polyether loop by sp^2 carbons which cause flattening of the polyether chains [7-10]. However, 1,3-2,4-calix[4]bis-crown ethers having not only two benzo moieties, but also having other rigid groups such as pyridine or anisole, have not been studied. According to Cram's preorganization principle, introduction of rigid anisole or pyridine units into macrocyclic polyether rings may provide preorganized ligating donor sites and enhance the binding properties of the ligands toward alkali metal cations [11-13].

With this in mind, we have synthesized two 1,3-2,4-calix[4]bis-crown ethers **1** and **2** consisting of a calix[4]arene fixed in the 1,3-alternate conformation by 1,3- and 2,4-bridges made of two modified polyether chains in which two 1,2-phenylene residues and one pyridine or anisole unit have been introduced. This may enable their utilization in the field of nuclear waste treatment, which is important given current environment concerns.

The synthesis of **1** and **2** is illustrated in Scheme 1. The synthesis began by reacting an excess of 2-(2-hydroxyethoxy)phenol **4** with 2,6-bis[(tosyloxy)methyl]pyridine **5** or 2,6-bis(bromomethyl)-4-methylanisole **6** in acetonitrile in the presence of potassium carbonate to produce bis(2-ethoxyphenoxy) compounds **7** and **8** in 80-82% yields. Compounds **7** and **8** were transformed into ditosylate derivatives **9** and **10** according to well established procedures for the preparation of 1,2-bis[2-(tosyloxy)ethoxy]benzene [14]. Calix[4]arene **3** was reacted with 2.0 equivalents of ditosylate **9** or **10** in the presence of 20.0 equivalents of potassium carbonate in refluxing acetonitrile for 10 days to form the desired polycyclic ligands **1** and **2** in 25-30% yields without the need for high dilution. It is likely that cation template effects influence the outcomes of these reactions.

1,3-2,4-Calix[4]bis-crown ethers **1** and **2** have been fully characterized by ^1H nmr, ^{13}C nmr, hrms spectrometry and elemental analyses. Compounds **1** and **2** are locked in the 1,3-alternate conformation according to their ^1H nmr spectra, which show singlet peaks at 3.44 ppm and 3.81 ppm for the ArCH_2Ar methylene protons for **1** and **2**, respectively. In the ^{13}C nmr spectra, single peaks at 36.1 ppm and 37.5 ppm for **1** and **2**, respectively, strongly imply the characteristic 1,3-alternate conformation due to the magnetic equivalence of the exo and endo protons on the nmr time-scale.

In summary, two 1,3-calix[4]bis-crown ethers with 1,3-alternate conformations made by 1,3- and 2,4-bridges composed of two modified polyether chains in which two 1,2-phenylene residues and one pyridine or anisole unit were introduced.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. ^1H and ^{13}C nmr spectra were recorded on Varian Gemini 200 MHz or Varian 300 MHz spectrometers. Tetramethylsilane was used as an internal standard. The ms spectra were obtained on a Finnegan 8430 high resolution mass spectrometer using the fast atom bombardment (FAB) technique. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. All solvents were purified by standard procedures. Starting materials were used without further purification. 2,6-Bis[(tosyloxy)methyl]pyridine **5** [15] and 2,6-bis(bromomethyl)-4-methylanisole **6** [16] were prepared according to the literature procedures.

Bis(2-ethoxyphenoxy) Compounds **7** and **8**; General Procedure.

A mixture of 2-(2-hydroxyethoxy)phenol **4** (6.15 g, 0.04 mole), potassium carbonate (55.2 g, 0.4 mole) and 2,5-bis[(tosyloxy)methyl]pyridine **5** or 2,6-bis(bromomethyl)-4-methylanisole **6** (0.01 mole) in acetonitrile (300 ml) was refluxed for 24 hours under nitrogen. After cooling to room temperature, the solvent was removed by evaporation under reduced pressure. The residue was mixed with methylene chloride and water. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by recrystallized from ethanol to give pure products.

Compound **7** was isolated as white crystals in an 80% yield; mp 105-106°; ^1H nmr (deuteriochloroform): δ = 3.92-4.17 (m, 10H), 5.25 (s, 4H), 6.96 (m, 8H), 7.47 (d, 2H), 7.76 (t, 1H); ^{13}C nmr (deuteriochloroform): δ = 61.2, 71.6, 72.3, 115.3, 116.3, 121.2, 122.1, 122.7, 138.1, 148.8, 149.4, 157.0; ms (FAB): m/z = 434 ($\text{M}+\text{Na}$) $^+$.

Anal. Calcd. for $\text{C}_{23}\text{H}_{25}\text{NO}_6$: C, 67.14; H, 6.13. Found: C, 67.29; H, 6.03.

Compound **8** was isolated as white crystals in an 82% yield; mp 124-125°; ^1H nmr (deuteriochloroform): δ = 2.32 (s, 3H), 3.84-4.07 (m, 8H), 3.86 (s, 3H), 5.12 (s, 4H), 6.97 (m, 8H), 7.30 (s, 2H); ^{13}C nmr (deuteriochloroform): δ = 21.0, 61.4, 63.4, 67.1, 71.5, 115.3, 115.4, 122.2 (2C), 130.1, 131.3, 134.3, 149.2, 149.3, 154.8; ms (FAB): m/z = 477 ($\text{M}+\text{Na}$) $^+$.

Anal. Calcd. for $\text{C}_{26}\text{H}_{30}\text{O}_7$: C, 68.70; H, 6.65. Found: C, 68.59; H, 6.54.

Ditosylate Compounds **9** and **10**; General Procedure.

A mixture of compounds **7** or **8** (0.01 mole) and pyridine (12 ml) was cooled to 0°. Then, *p*-toluenesulfonyl chloride (4.19 g, 0.022 mole) was added at such a rate that the temperature did not exceed 15°. The mixture was stirred for 5 hours at room temperature. A chilled solution of concentrated hydrochloric acid (12 ml) in water (20 mL) was added dropwise to the mixture. Solid ditosylates **9** and **10** were filtered and recrystallized from ethanol.

Compound **9** was isolated as white crystals in an 85% yield; mp 81-82°; ^1H nmr (deuteriochloroform): δ = 2.40 (s, 6H), 4.24-4.42 (m, 8H), 5.22 (s, 4H), 6.96 (m, 8H), 7.30-7.80 (m, 11H); ^{13}C nmr (deuteriochloroform): δ = 21.7, 67.3, 68.4, 71.6, 114.7, 115.8, 120.4, 121.9, 122.8, 128.2, 130.1, 133.1, 138.2, 145.2, 148.2, 149.1, 156.9; ms (FAB): m/z = 742 ($\text{M}+\text{Na}$) $^+$.

Anal. Calcd. for $\text{C}_{37}\text{H}_{37}\text{NO}_{10}\text{S}_2$: C, 61.73; H, 5.18. Found: C, 61.82; H, 5.24.

Compound **10** was isolated as white crystals in an 88% yield; mp, 82-84°; ¹H nmr (deuteriochloroform): δ = 2.30 (s, 3H), 2.39 (s, 6H), 3.83 (s, 3H), 4.19-4.34 (m, 8H), 5.10 (s, 4H), 6.90 (m, 8H), 7.23-7.78 (m, 10H); ¹³C nmr (deuteriochloroform): δ = 21.0, 21.7, 63.2, 66.5, 67.2, 68.4, 115.2, 115.6, 121.8, 122.7, 128.1, 130.0, 130.1, 130.7, 133.0, 134.3, 145.1, 148.4, 149.3, 154.5; ms (FAB): m/z = 785 (M+Na)⁺.

Anal. Calcd. for C₄₀H₄₂O₁₁S₂: C, 62.97; H, 5.55. Found: C, 62.83; H, 5.47.

1,3-2,4-Calix[4]bis-crown Ethers **1** and **2**; General Procedure.

A mixture of calix[4]arene **3** (0.43 g, 1.0 mmole), ditosylate **9** or **10** (1.0 mmole) and anhydrous potassium carbonate (1.38 g, 10.0 mmole) in acetonitrile (150 ml) was refluxed for 5 days under nitrogen. Then the same quantities of ditosylate **9** or **10** and potassium carbonate were added and the mixture was refluxed for 5 additional days. After removal of the solvent, the residue was stirred in methylene chloride (100 ml) and 1N hydrochloric acid (25 ml) for 1-2 hours. The solution was then neutralized with 1N sodium hydroxide to pH~7-8 and the organic layer was dried over magnesium sulfate, filtered, and evaporated. The residue was purified by column chromatography (silica gel, methylene chloride/acetone 20:1) to give the pure products.

Compound **1** was isolated as white crystals in a 25% yield; mp 242-244°; ¹H nmr (deuteriochloroform): δ = 3.44 (s, 8H), 3.99 (t, 8H), 4.21 (t, 8H), 5.31 (s, 8H), 6.16 (t, 4H), 6.92-7.03 (m, 20H), 7.15 (m, 4H), 7.68 (d, 4H), 7.84 (t, 2H); ¹³C nmr (dimethyl sulfoxide-d₆): δ = 36.1, 67.5, 69.7, 72.1, 113.5, 113.6, 121.0, 121.3, 122.7, 124.3, 130.5, 132.6, 138.1, 147.8, 148.6, 155.3, 155.6; hrms (FAB): m/z = 1197.4512 [(M+Na)⁺, calcd, 1197.4516].

Anal. Calcd. for C₇₄H₆₆N₂O₁₂: C, 75.62; H, 5.66. Found: C, 75.66; H, 5.55.

Compound **2** was isolated as white crystals in a 30% yield; mp 240-242°; ¹H nmr (deuteriochloroform): δ = 2.38 (s, 6H), 3.53 (t, 8H), 3.81 (s, 6H), 3.82 (t, 8H), 3.95 (t, 8H), 5.12 (s, 8H), 6.02 (t, 4H), 6.89-7.07 (m, 22H), 7.18-7.42 (m, 6H); ¹³C NMR (deuteriochloroform): δ = 21.0, 37.5, 65.4, 67.7, 69.2, 69.9, 116.0, 116.1, 122.1, 122.4 (2C), 130.4, 130.7 (2C), 133.1, 133.6, 133.9, 149.9, 155.9, 157.0; hrms (FAB): m/z = 1283.5132 [(M+Na)⁺, calcd, 1283.5135].

Anal. Calcd. for C₈₀H₇₆O₁₄: C, 76.17; H, 6.07. Found: C, 76.25; H, 6.27.

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