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Dedicated to the memory of Professor Roland K. Robins

The synthesis of two *N*-(2-allyloxy)ethyl-substituted diaza-crowns and two *C*-pivot (allyloxy)methyl-substituted cryptands is described. Controlled etherization of *N,N'*-bis(2-hydroxyethyl)-4,13-diaza-18-crown-6 with allyl bromide and sodium hydride gave *N*-(2-allyloxy)ethyl-*N'*-(2-hydroxyethyl)-4,13-diaza-18-crown-6 in a good yield. This macrocycle was reacted with sodium hydride and tetrahydrofurfuryl chloride or 3,3-dimethylbutyl tosylate to give expected *N*-(2-allyloxy)ethyl-*N'*-tetrahydrofurfuryloxy)ethyl-[or (3,3-dimethylbutoxy)-ethyl]-substituted products **3** or **4**. 6,13-Dimethylenyl-14-crown-4 (**9**) and 9,19-dimethylenyl-20-crown-6 (**10**) were treated with mercuric acetate, followed by sodium borohydride in strong base to give macrocyclic diols **11** and **12**, respectively. These diols were reacted with sodium hydride and the ditosylate derivative of allyloxymethyl-substituted triethyleneglycol **13** to produce the *C*-pivot (allyloxy)methyl-substituted macrotricycles **6** and **7**.

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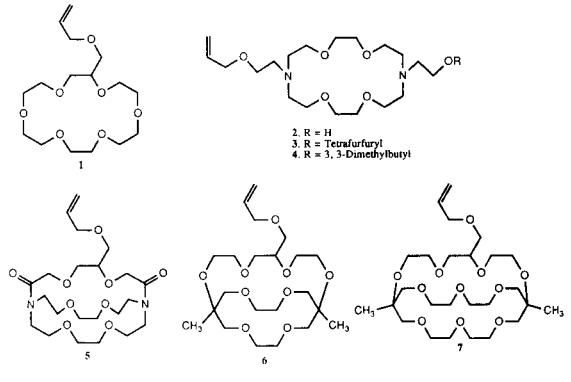
Monoalkenylated crown ethers can be conveniently bonded to polyhydromethylsiloxanes by a hydrosilylation reaction to produce crown-substituted polymethylsiloxanes. These polymers can be used as stationary phases in gas and supercritical fluid chromatography [1]. The crown polymers are of interest because of the hydrophilic cavity containing electronegative heteroatoms in the crown ether ring [2]. We are interested in the development of these polymers for use in capillary electrophoresis (CE), an important technique for the separation of complex mixtures of large biomolecules.

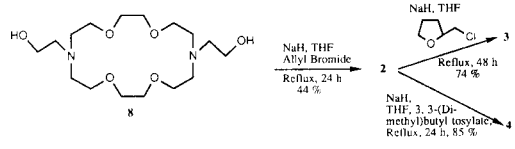
Crown ethers and cryptands form strong complexes with metal ions [3]. Crown- (or cryptand)-substituted polymethylsiloxanes can be used to chemically tailor the inner surfaces of fused silica capillary columns to vary, and even reverse, the electroosmotic flow in CE [4].

In order to prepare polysiloxanes containing aza-crown or cryptand ligands, three functionalized crown compounds and three functionalized cryptands have been prepared (see Figure 1). (Allyloxy)methyl-18-crown-6 (**1**) was prepared from (allyloxy)methyl-substituted triethylene glycol and triethylene glycol ditosylate in a yield of 37% as reported [5]. (Allyloxy)methyl-substituted cryptand diamide **5** was synthesized from 4-(allyloxy)methyl-3,6-dioxasuberoyl dichloride and 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane in a yield of 62% following the procedure reported by Bartsch and coworkers [6]. The physical and spectral properties of the above macrocycles were identical to that reported [5,6]. 1-[2-(Allyloxy)ethyl]-10-[2-(tetrahydrofurfuryloxy)ethyl]-4,7,13,16-tetraoxa-1,10-diazacyclooctadecane (**3**) and 1-[2-(allyloxy)ethyl]-10-{2-[(3',3'-dimethyl)butoxy]ethyl}-4,7,13,16-tetraoxo-1,10-diazacyclooctadecane (**4**) were prepared by two-step processes from **8** as shown in Scheme I. 6-(Allyloxy)methyl-1,12-dimethyl-2,5,8,11,14,17,20,23-octaoxabicyclo[10.6.6]tetracosane (**6**) and 6-(allyloxy)methyl-1,12-dimethyl-2,5,8,11,14,17,20,23,26,29-decaoxabicyclo[10.9.9]triacontane (**7**) were prepared by two-step processes from **9** and **10**, respectively, as shown in Scheme II.

Figure 1. The Structure of Monoalkenated Crown Ethers and Cryptands

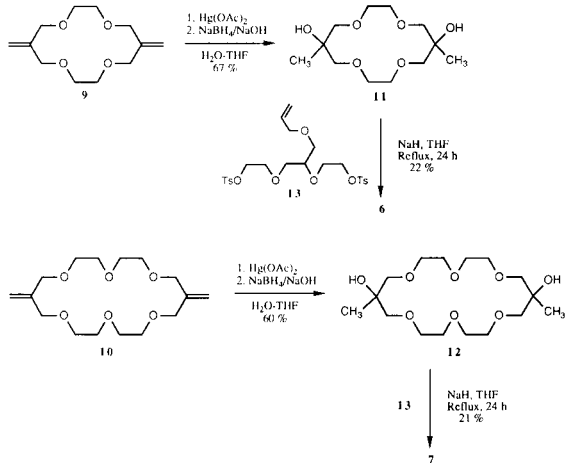


Scheme I. Preparation of Monoallyloxyethyl-diaza-18-crown-6 Ethers



1-[2-(Allyloxy)ethyl]-10-(2-hydroxyethyl)-4,7,13,16-tetraoxa-1,10-diazacyclooctadecane (**2**), needed for the preparation of **3** and **4**, was prepared in a yield of 44% by treating two-armed lariat ether **8** with allyl bromide and sodium hydride (Scheme I). A by-product of this reaction, 1,10-bis-[2-(allyloxy)ethyl]-4,7,13,16-tetraoxa-1,10-diazacyclooctadecane, was separated by column chromatography. The intermediate diazacrown **2** reacted with tetrahydrofurfuryl chloride and sodium hydride in THF to give *N*-pivot lariat **3**, and with 3,3-dimethylbutyl tosylate and sodium hydride to give lariat **4**. Both groups, *N*-(2-furfuryloxyethyl) and

Scheme II. Preparation of C-Pivot Allyloxymethyl-Cryptands



N-{2-[(3′,3′-dimethyl)butyloxy]ethyl} could increase the complexing ability of these lariat ethers with sodium or potassium ion, and decrease the interaction of the crown ether ring or complexed metal ion with the solute being analyzed in CE.

Diolefins **9** and **10** were oxidized to produce diols **11** and **12** in yields of 67% and 60%, respectively, using the solvomercuration-demercuration process [7] (Scheme II). A mixture of the *anti*- and *syn*-diols **11** or **12**, which were not further purified, were treated with 4-(allyloxy)methyl-3,6-dioxa-1,8-octanediyl ditosylate (**13**) to give *C*-pivot cryptands **6** and **7** in yields of 21-22%. This preparation of a *C*-pivot non-benzo-containing cryptand is reported for the first time.

The monoalkenylated crowns and cryptands were bonded to polyhydromethylsiloxane following the reported procedure [1a]. Free-radical crosslinking was used to immobilize the cryptand-containing polymer on the inner walls of fused silica capillary columns used in capillary electrophoresis. The cryptand-containing polymers were unique as coatings in capillary electrophoresis because they provided switchable electroosmotic flow, depending on the *p*H, because of the complexing ability of the cryptand groups with metal ions in the buffer solution. For such columns at low *p*H, the net charge on the capillary surface is positive due to the complexed metal ions, and the movement of the bulk solution in the capillary is toward the anode. A typical fused silica column has a negatively charged surface because of the silanol groups, and the bulk solution moves toward the cathode. This reversal in electroosmotic flow is extremely useful for certain peptides, proteins, and other biomolecules. The details of this work is reported elsewhere [4].

EXPERIMENTAL

Infrared (ir) spectra were obtained on a Perkin-Elmer 1600 series FTIR spectrometer. The proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on a Varian Gemini 200 spectrometer using deuteriochloroform. Elemental analyses were performed by MHW Laboratories, Phoenix, Arizona. All starting materials were purchased from Aldrich Chemical Co. 1,10-Bis(2-hydroxyethyl)-4,7,13,16-tetraoxa-1,10-diazacyclooctadecane (**8**) [8], 6,13-dimethylenyl-1,4,8,11-tetraoxacyclotetradecane (**9**) [9], 9,19-dimethylenyl-1,4,7,11,14,17-hexaoxacycloeicosane (**10**) [8], and 4-(allyloxy)methyl-3,6-dioxa-1,8-octanediyl ditosylate (**13**) [10] were prepared as reported.

1-[2-(Allyloxy)ethyl]-10-(2-hydroxyethyl)-4,7,13,16-tetraoxa-1,10-diazacyclooctadecane (**2**).

A mixture of sodium hydride (95%, 0.13 g, 5 mmoles) and lariat crown ether **8** (2.50 g, 7.13 mmoles) was stirred in 150 ml of THF at room temperature for 1 hour, and a solution of 0.61 g (5 mmoles) of allyl bromide in 50 ml of THF was added dropwise. The reaction mixture was refluxed for 24 hours. After cooling, the reaction mixture was neutralized with 30% sulfuric acid in methanol to a *p*H = 6-7 and concentrated under reduced pressure. The residue was dissolved in chloroform and the organic mixture was washed twice with water, dried, and evaporated under reduced pressure. The yellowish oil was chromatographed on silica gel (isopropyl alcohol/chloroform, 1:9) to give 1.22 g (44%) of **2** as an oil; ^{1}H nmr: (δ) 5.84 (m, 1 H), 5.17 (m, 2 H), 4.37 (t, J = 5.2 Hz, 1 H, OH), 4.0 (d, J = 5.7 Hz, 2 H), 3.80-3.36 (m, 20 H), 2.79-2.47 (m, 12 H); ms: [m/z (%)] 390 (16), 372 (17), 359 (35), 319 (100). Satisfactory elemental analyses were obtained for **3** and **4** which are derivatives of **2**.

1-[2-(Allyloxy)ethyl]-10-[2-(tetrahydrofurfuryloxy)ethyl]-4,7,13,16-tetraoxa-1,10-diazacyclooctadecane (**3**).

A solution of **2** (1.95 g, 5 mmoles) in 100 ml of THF was treated with sodium hydride (95%, 0.132 g, 5.5 mmoles) until hydrogen was no longer produced. Then, a solution of tetrahydrofurfuryl chloride (0.60 g, 5 mmoles) in 50 ml of THF was added dropwise to the refluxed reaction mixture. The mixture was refluxed for 48 hours, cooled to 0°, neutralized with 30% sulfuric acid in methanol to a *p*H of 7, and concentrated under reduced pressure. The residue was added to a mixture of chloroform and water, mixed, and the aqueous layer was separated. The organic layer was washed with water, dried, and concentrated under reduced pressure. Product **3** (1.76 g, 74%) was isolated on a silica gel column using ethanol/chloroform (7:93) as eluant; ^{1}H nmr: (δ) 5.90 (m, 1 H), 5.23 (m, 2 H), 4.37 (m, 1 H), 4.02 (m, 2 H), 3.94-3.40 (m, 24 H), 2.91-2.70 (m, 12 H), 1.90 (m, 2 H), 1.60 (m, 2 H); ms: [m/z (%)] 474 (14), 417 (40), 403 (36), 359 (100).

Anal. Calcd. for $C_{24}H_{46}N_2O_7$: C, 60.72; H, 9.77. Found: C, 60.55; H, 9.63.

1-[2-(Allyloxy)ethyl]-10-[2-(3′,3′-dimethyl)butyloxy]ethyl-4,7,13,16-tetraoxa-1,10-diazacyclooctadecane (**4**).

Macrocycle **4** was prepared as above for **3** from 1.95 g (5 mmoles) of **2**, 0.13 g (5.5 mmoles) of 95% sodium hydride and 1.30 g (5 mmoles) of 3,3-dimethylbutyl tosylate. Column chromatography (ethanol/chloroform 7:93) of the product gave 2.01 g (85%) of **4** as an oil; ^{1}H nmr: (δ) 5.90 (m, 1 H), 5.23 (m, 2 H), 3.98 (d, J = 5.7 Hz, 2 H), 3.78-3.38 (m, 22 H), 2.93-2.68 (m, 12 H), 1.50 (t, J = 6.2 Hz, 2 H), 0.92 (s, 9 H); ms: [m/z (%)] 474 (9), 403 (30), 359 (39), 256 (37), 172 (100).

Anal. Calcd. for $C_{25}H_{50}N_2O_6$: C, 63.26; H, 10.62. Found: C, 63.42; H, 10.50.

6,13-Dimethyl-1,4,8,11-tetraoxa-6,13-cyclotetradecanediol (**11**) (Scheme II).

A solution of mercuric acetate (12.75 g, 40 mmoles) in a mixture of 40 ml of water and 40 ml of THF was stirred at 25° for 10 minutes. Macrocycle **9** (4.57 g, 20 mmoles) was slowly added to the ice-cold reaction mixture. The reaction temperature was kept below 25°. The reaction mixture was then stirred at room temperature for 20 minutes to complete the oxymercuration reaction. Sodium hydroxide (40 ml of 3 *M*) was added dropwise to the cooled mixture (temperature below 25°), then 40 ml of 0.5 *M* sodium borohydride in a 3.0 *M* sodium hydroxide solution was added dropwise. The mixture was stirred for 3 hours. The mixture was decanted to remove mercury, and the organic layer was separated. The aqueous layer was saturated with sodium chloride and extracted three times with methylene chloride. The organic layer was combined, washed with saturated brine, dried over magnesium sulfate, and concentrated. Column chromatography on alumina oxide (methylene chloride/methanol, 100:1) of the residue gave 3.52 g (67%) of **11** as an oil which slowly solidified on standing; ^{1}H nmr: (δ) 3.66 (s, 8 H), 3.46 (t, J = 7.0 Hz, 4 H), 3.41 (t, J = 7.0 Hz, 4 H), 2.65 (s, 2 H, OH), 1.15 (s, 6 H); ms: [m/z (%)] 264 (40), 101 (100).

Macrotricycle **6**, a derivative of **11** gave a satisfactory elemental analysis.

6-(Allyloxy)methyl-1,12-dimethyl-2,5,8,11,14,17,20,23-octaoxabicyclo[10.6.6]tetracosane (**6**) (Scheme II).

A mixture of **11** (1.32 g, 5 mmoles) and sodium hydride (0.72 g, 30 mmoles) in 150 ml of THF was stirred at room temperature for 2 hours, and 2.64 g (5 mmoles) of **13** in 100 ml of THF was added dropwise. The reaction mixture was stirred at room temperature for 24 hours, refluxed for 24 hours, and evaporated under reduced pressure. The residue was titurated between chloroform and water. The organic layer was washed with water twice, dried, and concentrated. The residue was subjected to column chromatography on silica gel (methanol/ammonium hydroxide 10:1) to give **6** (0.50 g, 22%) as an oil; ^{1}H nmr: (δ) 5.89 (m, 1 H), 5.16 (m, 2 H), 3.98 (d, J = 5.2 Hz, 2 H), 3.84-3.25 (m, 29 H), 1.08 (s, 3 H), 1.06 (s, 3 H); ms: [m/z (%)] 448 (100), 407 (7), 377 (4), 290 (6).

Anal. Calcd. for $C_{22}H_{40}O_9$: C, 58.91; H, 8.99. Found: C, 58.81; H, 8.76.

9,19-Dimethyl-1,4,7,11,14,17-hexaoxa-9,19-cycloeicosanediol (**12**) (Scheme II).

Macrocycle **12** was prepared as above for **11** from 3.74 g (11.8 mmoles) of **10** and 7.52 g (23.6 mmoles) of mercuric acetate. Column chromatography on alumina oxide (hexane/methylene chloride/methanol 70:30:3) of the residue gave 2.50 g (60%) of **12** as an oil which also slowly solidified on standing; ^{1}H nmr: (δ) 3.94 (s, 2 H, OH), 3.82-3.29 (m, 24 H), 1.12 (s, 3 H), 1.08 (s, 3 H); ms: [m/z (%)] 352 (36), 308 (7), 219 (25), 151 (98), 101 (100).

Anal. Calcd. for $C_{16}H_{32}O_8$: C, 54.53; H, 9.15. Found: C, 54.52; H, 8.96.

6-(Allyloxy)methyl-1,12-dimethyl-2,5,8,11,14,17,20,23,26,29-decaoxadicyclo[10.9.9]triacontane (**7**) (Scheme II).

Macrotricycle **7** was prepared as above for **6** from 0.86 g (2.4 mmoles) of **12** and 1.27 g (2.4 mmole) of **13**. The residue was subjected to column chromatography on silica gel (methanol/ammonium hydroxide 10:1) to give 0.27 g (21%) of **7** as an oil; ^{1}H nmr: (δ) 5.90 (m, 1 H), 5.18 (m, 2 H), 4.00 (d, J = 5.2 Hz, 2 H), 3.88-3.35 (m, 37 H), 1.15 (s, 3 H), 1.14 (s, 3 H); ms: [m/z (%)] 537 (47), 405 (12), 361 (18), 309 (15), 159 (100).

Anal. Calcd. for $C_{26}H_{48}O_{11}$: C, 58.19; H, 9.02. Found: C, 57.96; H, 8.94.

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