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Twelve diaza-15-crown-5 and 18-crown-6 macrocycles containing different side arms on the nitrogen atoms have been prepared. These diaza-*N,N'*-di pivot lariat crown ethers were prepared either from *N,N'*-bishydroxyethyl-1,4-diaza-15-crown-5 or 18-crown-6 ligands or from the corresponding unsubstituted diaza-crowns.

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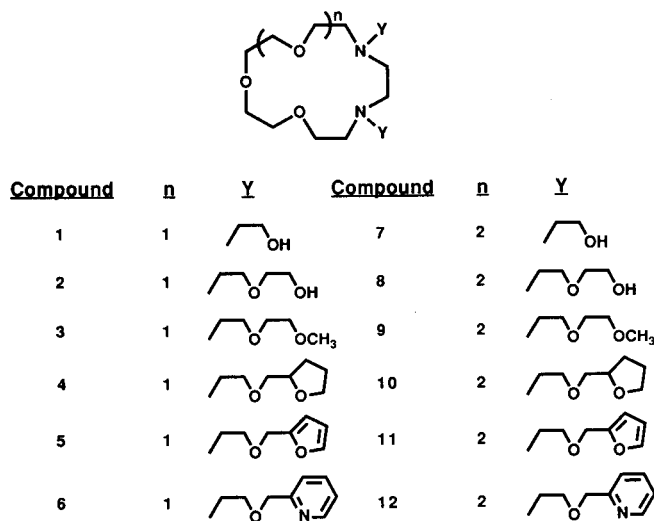
Introduction.

The lariat crown ethers recently have attracted much scientific attention [1-4]. These compounds are characterized by a macrocyclic polyether skeleton with one or more flexible donor arm groups. They mimic naturally occurring ionophores by presenting a cation with a three-dimensional, intramolecular array of binding sites as do the cryptands and spherands [5-8]. A variety of carbon [8] and nitrogen pivot lariat crown ethers with single [5,7,9-12] and double [6,13-21] side arms have been prepared to enhance cation binding properties of the parent crown ethers. Most of these lariat crown ethers exhibited increased cation binding abilities over the parent crown ether because of the coordination of the side-arm groups. Gokel and co-workers [7] demonstrated that the nitrogen pivot molecules bind sodium cation more strongly than do the corresponding carbon pivot lariat crown ethers. It was also found [5,22] that nitrogen pivot lariat ethers with two donor atoms in the side arms have stronger complexing abilities for sodium and potassium ions than do the lariats with side arm(s) containing only one donor atom. However, binding constants decrease with longer side arms. Also, complexing properties of the *N*-pivot lariats are related to both the cavity size of the parent crown and the nature of the side arms, thus, a "hole-size relationship" is somewhat oversimplified with these compounds. Some double armed lariats, especially those bearing furane, pyridine and quinoline groups, exhibited specific cation transport abilities and excellent catalytic activities [15,16,23]. In general, introducing neutral oxygen donor atoms into the side arms leads to an increase in selectivity of the ligand for large metal ions over small metal ions. Addition of 2-hydroxyethyl groups or pyridinyl groups to the crown ether increases the $\text{Pb}^{2+}/\text{Zn}^{2+}$ selectivity by 5.7 and 4.7 log units, respectively [2,17,24]. Generally, as the polarity of the side arm increases, the binding constant increases, especially for Ca^{2+} [6]. Okahara and co-workers [10] demonstrated that compounds having a methoxy group at the end of the side chain have similar or better complexing abilities as compared to the corresponding compounds containing a hydroxy function.

Several methods can be used to synthesize *N*-pivot lariat crown ethers. First, the lariat ethers may be prepared directly from substituted amines by cyclization [5-7,9]. Second, parent aza-crown ethers were first prepared, then the side arm(s) were attached [9,15-17,20,21]. The lariat ethers with hydroxyl functions can be prepared from the aza-crown starting materials with [25] or without [10-13] protecting the hydroxy function.

In order to more fully understand the influence of side arms with varying lengths and different donor atoms on the complexing properties of the lariat crown ethers, we have prepared a series of *N,N'*-di pivot lariat 1,4-diaza-15-crown-5 (**1-6**) and 18-crown-6 (**7-12**) macrocycles (Figure 1). We have reported previously a high yield synthesis of double armed lariat crown ethers with the pendant arms on nitrogen atoms on opposite sides of the macroring [11]. In this paper, we present the synthesis of new *N,N'*-di pivot lariat 1,4-diaza-crown ethers.

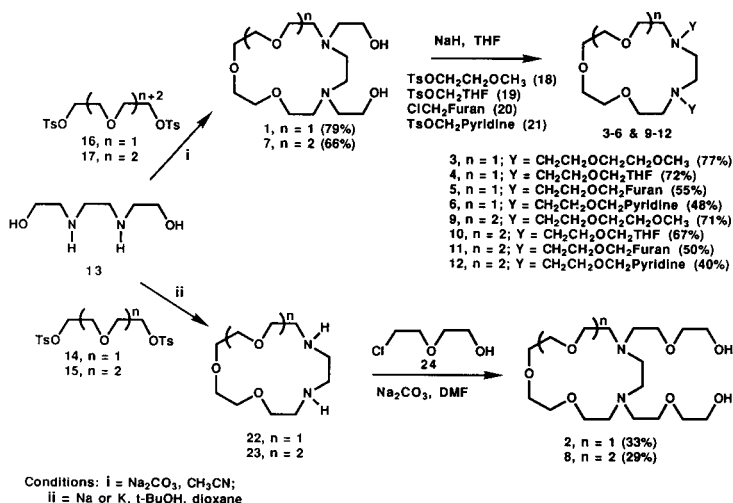
Figure 1. New Diaza-*N,N'*-dipivot Lariat Crown Ethers



Results and Discussion.

Up to now, the double armed *N*-pivot lariat crown ethers have the pivot arms on nitrogen atoms on opposite sides of the diaza-crown. We have prepared twelve new double

Scheme I. Preparation of Double Armed Lariat Crown Ethers (1-12)



armed *N*-pivot diaza-crowns with the pivot groups on neighboring nitrogen atoms (Figure 1). Having the lariat arms on the same side of the diaza-crown molecule may give these ligands unique complexing properties.

The new double armed lariat crowns were synthesized from *N,N'*-bis(2-hydroxyethyl)ethylenediamine (**13**) as shown in Scheme I. We previously reported the preparation of **1** and **7** by the reaction of **13** with bis(2-chloroethyl) ether and ditosylate **17** respectively [13]. Lariat crown **1** was also obtained from the corresponding ditosylate **16**. Our procedure to prepare **1** and **7** with hydroxyethyl side arms is a superior method because only one step is necessary. As we have reported previously, the sodium carbonate base does not remove protons from the hydroxyl groups so that the amine functions rather than the alcohols react with the alkyl tosylates [13]. Then, under strong basic conditions, the pendant alcohols of crown ethers **1** and **7** were reacted with the appropriate tosylate or chloro compound **18-21** to give the double armed lariats **3-6** and **9-12** which have terminal donor groups five atoms away from the ring nitrogen atoms. The side arms also include an additional oxygen donor atom. These eight double armed lariat crown ethers were produced in good yields as shown.

Diaminodiol **13** reacted with ditosylates **14** and **15** using strong base to form diaza-15-crown-5 (**22**) and diaza-18-crown-6 (**23**), respectively. Again, the ditosylate (**14** or **15**) reacted with the dialkoxide formed from **13** and strong base rather than with the amine functions [13]. Chloroalcohol **24** was then reacted with the diaza-crowns **22** or **23** to form the *N,N'*-bis[2-(2-hydroxyethoxy)ethyl]diaza-crown compounds **2** or **8** in moderate yields.

The double armed lariat crown-ethers prepared in this study should provide interesting complexing agents for various metal ions. The results of this complexation study will be reported when the work is completed.

EXPERIMENTAL

Infrared (ir) spectra were obtained on a Perkin-Elmer FT1600 spectrometer. Nuclear magnetic resonance (¹H nmr) spectra were obtained on a Varian Gemini-200 spectrometer in deuteriochloroform. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. Molecular weights were determined by the electron impact method on a Finnegan 8430 High Resolution Mass spectrometer. Starting materials were purchased from Aldrich Chemical Company. Di-, tri-, tetra- and pentaethylene glycol ditosylates **14-17** were prepared from the corresponding oligoethylene glycols and *p*-toluenesulfonyl chloride according to the reported procedure [26]. 2-Methoxyethyl tosylate (**18**) and 2-(tosyloxymethyl)tetrahydrofuran (**19**) [27] were obtained using the same procedure [26] in yields of 89% and 96%, respectively. 2-Pyridylmethyl tosylate (**21**) [28] was prepared using a similar procedure at -10°. 2-Chloromethylfuran (**20**) was obtained in the same manner as reported for 2,5-bis(chloromethyl)furan [29]. 13,16-Bis(2-hydroxyethyl)-1,4,7,10-tetraoxa-13,16-diazacyclooctadecane (**7**) was prepared as reported [13]. 10,13-Bis(2-hydroxyethyl)-1,4,7-trioxa-10,13-diazacyclopentadecane (**1**) was obtained by the same procedure from **13** and tetraethylene glycol ditosylate (**16**) rather than the corresponding dichloride [13]. 1,4,7-Trioxa-10,13-diazacyclopentadecane (**22**) and 1,4,7,10-tetraoxa-13,16-diazacyclooctadecane (**23**) were synthesized as reported [30], but purified by chromatography on neutral alumina using toluene/ethanol: 60/1, 20/1 and 10/1 as the eluents.

General Procedure for the Preparation of 2-(2-Hydroxyethoxy)ethyl Derivatives of 1,4-Diaza-15-crown-5 (**2**) and 1,4-Diaza-18-crown-6 (**8**).

A mixture of 2.3 mmoles of **22** or **23**, 2 g (16 mmoles) of 2-chloroethoxyethanol (**24**), 50 ml of DMF and 10 g of anhydrous powdered sodium carbonate was stirred under reflux for 2 days. The cooled mixture was filtered and the solid was washed with chloroform. The solvent was evaporated under reduced pressure. The residue was purified by chromatography on neutral alumina using toluene/ethanol: 50/1, 20/1 and 10/1 as the eluents, and then on the silica gel using methanol/ammonium hydroxide: 30/1 and 10/1 as the eluents. After evaporation of the solvent, the purified product was dissolved in chloroform, filtered to remove inor-

ganic material and evaporate. Product yields and spectral properties are as follows:

Macrocycle **2** (33%) was isolated as an oil; ¹H nmr (δ) 2.60-2.90 (m, 14 H), 3.52-3.75 (m, 24 H).

Anal. Calcd. for C₁₈H₃₈N₂O₇: C, 54.80; H, 9.71; mol wt, 394.509. Found: C, 54.62; H, 9.63; mol wt, 394.

Macrocycle **8** (29%) was isolated as an oil; ¹H nmr (δ) 2.50-2.85 (m, 14 H), 3.40-3.62 (m, 28 H).

Anal. Calcd. for C₂₀H₄₂N₂O₈: C, 54.77; H, 9.65; mol wt, 438.562. Found: C, 54.87; H, 9.60; mol wt, 438.

General Procedure for the Preparation of Bis[2-(2-methoxyethoxy)ethyl]- and Bis(2-tetrahydrofurfuryloxyethyl) Derivatives of 1,4-Diaza-15-crown-5 (**3,4**) and 1,4-Diaza-18-crown-6 (**9,10**).

THF (20 ml) was added dropwise into a dry flask containing 0.5 g sodium hydride under a nitrogen atmosphere. A solution of **1** or **7** (2 mmoles) in 30 ml of dry THF was added to the stirred mixture. The resulting mixture was stirred for 2 hours under reflux and a nitrogen atmosphere. A solution of tosylate **18** or **19** (8 mmoles) in 50 ml of THF was added at 50-60°. The reaction mixture was stirred for 18 hours under reflux. The cooled mixture was filtered and the solid was washed with THF. The solvent was removed under reduced pressure. The residue was purified by chromatography on neutral alumina using toluene/ethanol: 100/1 and 60/1, as the eluents. If necessary, the product can be further purified by chromatography on silica gel using methanol/30% aqueous ammonium hydroxide: 30/1 and 10/1 as eluents. After evaporation of the solvent, the purified product was dissolved in chloroform, filtered to remove inorganic material and evaporated to give an oil. Product yields and spectral properties are as follows:

Macrocycle **3** (77%) was an oil; ¹H nmr (δ) 2.69-2.82 (m, 12 H), 3.39 (s, 6 H), 3.52-3.70 (m, 24 H).

Anal. Calcd. for C₂₀H₄₂N₂O₇: C, 56.85; H, 10.02; mol wt, 422.563. Found: C, 56.82; H, 9.97; mol wt, 422.

Macrocycle **9** (71%) was an oil; ¹H nmr (δ) 2.68-2.82 (m, 12 H), 3.38 (s, 6 H), 3.49-3.74 (m, 28 H).

Anal. Calcd. for C₂₂H₄₆N₂O₈: C, 56.63; H, 9.93; mol wt, 466.616. Found: C, 56.58; H, 9.82; mol wt, 466.

Macrocycle **4** (72%) was an oil; ¹H nmr (δ) 1.50-1.66 (m, 2 H), 1.76-2.01 (m, 6 H), 2.66-2.81 (m, 12 H), 3.39-4.08 (m, 26 H).

Anal. Calcd. for C₂₄H₄₆N₂O₇: C, 60.73; H, 9.77; mol wt, 474.639. Found: C, 60.55; H, 9.53; mol wt, 474.

Macrocycle **10** (67%) was an oil; ¹H nmr (δ) 1.53-1.68 (m, 2 H), 1.79-2.03 (m, 6 H), 2.68-2.84 (m, 12 H), 3.42-4.12 (m, 30 H).

Anal. Calcd. for C₂₆H₅₀N₂O₈: C, 60.21; H, 9.72; mol wt, 518.692. Found: C, 59.98; H, 9.85; mol wt 518.

General Procedure for the Preparation of Bis(2-furfuryloxyethyl) and Bis[2-(2-pyridylmethoxy)ethyl] Derivatives of 1,4-Diaza-15-crown-5 (**5,6**) and 1,4-Diaza-18-crown-6 (**11,12**).

These compounds were prepared in a manner similar to the procedure for **3**, **4**, **9** and **10** above. After refluxing for 2 hours under a nitrogen atmosphere, 7-8 mmoles of **20** or **21** in 100 ml of THF were added very slowly over a period of 1 hour at -10° to -5°. The resulting mixture was stirred for 5 hours at 5° and then 12 hours at room temperature. The solid was filtered and washed with THF. The solvent was evaporated under reduced pressure. The residue was purified by chromatography on neutral alumina using toluene/ethanol: 100/1 and 80/1 as the eluents, and then on silica gel using methanol/30% aqueous ammonium

hydroxide: 30/1 and 10/1 as the eluents. An oil product was obtained using the same procedure as above. Product yields and spectral properties are as follows:

Macrocycle **5** was isolated in a 55% yield; ¹H nmr: (δ) 2.64-2.82 (m, 12 H), 3.48-3.68 (m, 16 H), 4.44 (s, 4 H), 6.28-6.34 (m, 4 H), 7.49 (d, 2 H).

Anal. Calcd. for C₂₄H₃₈N₂O₇: C, 61.78; H, 8.21; mol wt, 466.575. Found: C, 61.88; H, 8.32; mol wt, 466.

Macrocycle **11** was isolated in a 50% yield; ¹H nmr: (δ) 2.60-2.81 (m, 12 H), 3.46-3.73 (m, 20 H), 4.46 (s, 4 H), 6.27-6.36 (m, 4 H), 7.50 (d, 2 H).

Anal. Calcd. for C₂₆H₄₂N₂O₈: C, 61.15; H, 8.29; mol wt, 510.628. Found: C, 61.38; H, 8.22; mol wt, 510.

Macrocycle **6** was isolated in a 48% yield; ¹H nmr: (δ) 2.74-2.90 (m, 12 H), 3.73-3.59 (m, 16 H), 4.64 (s, 4 H), 7.12-7.23 (m, 2 H), 7.46 (d, 2 H), 7.63-7.76 (m, 2 H), 8.65 (d, 2 H).

Anal. Calcd. for C₂₆H₄₀N₄O₅: C, 63.91; H, 8.25; mol wt, 488.629. Found: C, 63.96; H, 8.07; mol wt 488.

Macrocycle **12** was isolated in a 46% yield; ¹H nmr: (δ) 2.60-2.85 (m, 12 H), 3.43-3.68 (m, 20 H), 4.68 (s, 4 H), 7.07-7.18 (m, 2 H), 7.40 (d, 2 H), 7.58-7.70 (m, 2 H), 8.50 (d, 2 H).

Anal. Calcd. for C₂₈H₄₄N₄O₆: C, 63.13; H, 8.32; mol wt, 534.682. Found: C, 63.02; H, 8.15 mol wt, 534.

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