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Tribracchial Lariat Ethers: Syntheses, Binding, and Formation of an Intramolecular Macroring-Sidearm Complex in the Absence of Any Cation

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Abstract. Details of a new synthetic approach to 4,10,16-triaza-18-crown-6 ('triaza-18-crown-6') are reported, along with the preparation and binding properties of the following derivatives having the indicated sidearms: $CH_2C{\equiv}CH$, CH_2CH_2OH, $CH_2CH_2OCH_3$, $COCH_2OCH_3$,$CH_2COOCH_2CH_3$, $CH_2C_6H_5$, and $CH_2C_6H_4$-2-NO_2. A key intermediate in the synthesis of triaza-18-crown-6 is 4-*N*-toluenesulfonyl-1,7,13-trioxa-4,10,16-triazacyclooctadecane-9,17-dione. This compound is found by solid state structure analysis to fold to form an intramolecular, doubly-hydrogen bonded complex in which the two N—H protons interact with the two tosyl group oxygens. Details of the structure are reported.

Key words. Cation binding, crown ether, crystal structure, lariat ether, synthesis, triaza-18-crown-6.

Ave Charles Pedersen

In this issue dedicated to the memory of Charles Pedersen, it is fitting to recall a personal interaction with this fine scientist. One of the authors (GWG) was an employee at the du Pont Experimental Station during the Summer of 1974. At that time, the crown ethers were becoming very important subjects of research throughout the world and were of great interest at du Pont because of a project involving their antiviral activity then underway. It was my impression, however, that Pedersen was not very well known (except by reputation) among my contemporaries at the Central Research Department. This was for two reasons. Pedersen made the Elastomer Chemical Department his home during his career and, by 1974 when I arrived, he had already retired. It was only several years later when a Professor visiting my group from the Soviet Union asked to meet Pedersen that I made personal contact. It was a very pleasant meeting, both socially and scientifically, but the strongest recollection I have of it is Pedersen's comment to me that he felt like a father who was forced to give up a child for adoption. He meant, I believe, that he had many ideas that he could not try because of his retirement.

This paper is dedicated to the memory of the late Dr C. J. Pedersen.

One wonders what direction crown chemistry might have taken had Pedersen been involved longer in orchestrating its development.

1. Introduction

As our lariat ether [1] program has evolved over the last decade [2], we gradually increased the number of sidearms present on the macroring in the hope of enhancing the binding strength and selectivity as well as the versatility of this class of compounds. The two-armed or bibracchial lariat ethers (BiBLEs) [3] utilize both sidearms in complexing cations [4] and these sidearms may interact either from the same or opposite sides of the macroring. It seemed a natural question to ask what role a third arm would play since two arms already provided octa-coordination [4]. We set as our target the parent macrocycle 4,10,6-triaza-18-crown-6, previously prepared by Lehn and coworkers [5]. We report here the details [6] of synthesis, homogeneous binding properties, and an unusual intramolecular 'complex' of a key intermediate in the synthesis.

2. Experimental

^{1}H-NMR spectra were recorded on a Varian VXR-400 NMR spectrometer or on a Hitachi Perkin-Elmer R-600 high resolution NMR spectrometer in $CDCl_3$ solvents and are reported in ppm (δ) downfield from internal Me_4Si. ^{13}C-NMR were recorded on a JEOL EX90Q or Varian VXR-400 NMR spectrometer. Infrared spectra were recorded on a Perkin-Elmer 1310 Infrared Spectrophotometer. Melting points were determined on a Thomas Hoover apparatus in open capillaries and are uncorrected. Thin layer chromatographic (TLC) analyses were performed on aluminum oxide 60 F-254 neutral (Type E) with a 0.2 mm layer thickness or on silica gel 60 F-254 0.2 mm layer thickness. Preparative chromatography columns were packed with activated aluminum oxide (MCB 80–325 mesh, chromatographic grade, AX 611) or with Kieselgel 60 (70–230 mesh).

All reactions were conducted under dry nitrogen unless otherwise noted. All reagents were the best grade commerically available and were distilled, recrystallized, or used without further purification, as appropriate. Molecular distillation temperatures refer to the oven temperature of a Kugelrohr apparatus. Combustion analyses were performed by Atlantic Microlab, Inc., Atlanta, GA, and are reported as percentages.

Cation binding constants were measured in absolute MeOH at 25.0 ± 0.1°C using a Corning 476210 electrode and an Orion model 701A 'Ionalyzer' meter according to the method of Frensdorff [7] as described recently in detail [8]. Values for the equilibrium constants are reported as $\log_{10} K_S$.

N,N,-bis(2-Hydroxyethyl)-p-toluenesulfonamide, **1**

Prepared by the method of Lehn and coworkers [5] in 85% yield, mp 100–101°C, and had spectral properties identical to those reported.

N-p-Toluenesulfonyl-2,8-dioxa-5-aza-1,9-nonanedicarboxylic acid, **2**

The disodium salt of **1** (90.0 g, 0.347 mol) was prepared from 10.2 g of NaH (60% in oil) in 2500 mL of THF by stirring the reagents together for 24 h at room temperature with 500 g of 3 mm glass beads in the flask. Chloroacetic acid, sodium salt (101.1 g, 0.867 mol) was added to the reaction flask. The reaction was stirred at reflux temperature for 2 d. The reaction was allowed to cool and 20 mL of water was added. CH_2Cl_2 (400 mL) was added to the reaction mixture, which was then filtered. The filtered solid was dissolved in 600 mL of CH_2Cl_2 and 1200 mL of 1M NaOH. The resulting two-phase system was poured through a Buchner funnel (no filter paper, to remove the glass beads) into a separatory funnel, shaken, and the phases were separated. The organic layer was extracted with 1M NaOH (2×100 mL). The combined aqueous phases were extracted with CH_2Cl_2 (100 mL). $BaCl_2 \cdot 2H_2O$ (180 g) was added to the aqueous portion with vigorous stirring. The resulting precipitate was filtered. The precipitate was dissolved in 1200 mL of CH_2Cl_2 and 600 mL of 3M HCl, shaken, and the phases were separated. The organic portion was extracted with 3M HCl (2×100 mL). The aqueous portions were extracted with CH_2Cl_2 (3×100 mL). The combined organic portions were dried over Na_2SO_4 and evaporated *in vacuo*. Recrystalization (300 mL CH_2Cl_2) afforded 98.0 g (75%) of a white solid, mp 85–87°C (lit. [5c] 87–88°C). The product had spectral properties identical to those reported [5].

N-p-Toluenesulfonyl-2,8,dioxa-5-aza-1,9-nonanedicarboxylic acid chloride, **3**

Oxalyl chloride (24.0 g, 0.189 mol) was added to a suspension of **2** (20.0 g, 0.053 mol) in benzene (200 mL) containing 4 drops of pyridine. The reaction mixture was stirred for 2 d at room temperature, concentrated *in vacuo* and any remaining HCl and oxalyl chloride were removed at high vacuum during 24 h. The pale yellow oil (100% crude yield) had spectral properties identical to those reported [5] and was used in the next step without further purification.

N-p-Toluenesulfonyl-4,10,16-triaza-1,7,13-trioxacyclooctadecane-9,17-dione, **4**

A solution of **3** (21.0 g, 0.050 mol) in benzene (170 mL) was prepared. A second solution of bis(2-aminoethyl)ether (10.48 g, 0.100 mol) in benzene (170 mL) was prepared. Both solutions were pumped into a 3L flask, containing 1L of benzene, during 8 h using a Sage Model 352 syringe pump. The reaction mixture was warmed to 30°C, filtered through celite, and the filtrate was concentrated *in vacuo*. The product was used without further purification and had spectral properties identical to those reported [5]. One sample was purified and the yield was 65%.

Crystal data for compound **4** [mp (after recrystallization from $CHCl_3 : C_6H_6$ 1 : 5 v/v) 115–116°C, lit. [5] mp 117–118°C]: $C_{19}H_{33}O_7N_3S$, FW = 447.55, space group $P\bar{1}$, $a = 7.1357(5)$, $b = 10.1681(4)$, $c = 15.5037(7)$ Å, $z = 2$, $d_c = 1.349$ g cm^{-1}, CuK_α ($\mu = 16.65$ cm^{-1}) $R = 0.021$ for 2119 unique reflections with $I > 2\sigma(I)$ (of 2130 unique data) measured by an Enraf-Nonius CAD4 X-ray diffractometer by $\omega-2\theta$ scans, $2° < \theta < 50°$.

4,10,16-*Triaza*-1,7,13-*trioxacyclooctadecane*, '*triaza*-18-*crown*-6', **5**

Compound **4** (16.0 g, 0.036 mol) was slowly added as a solid to a stirred suspension of lithium aluminum hydride (27 g, 0.7 mol) in THF (600 mL). The reaction was stirred for 36 h at reflux temperature and was then allowed to cool. Water (50 mL) was added during 1 h and a LiOH solution (15%, 30 mL) was added during 30 min. Anhydrous $MgSO_4$ (35 g) was added followed by 20 g of celite. The reaction was filtered through filter paper and the filtrate was saved. The filtered solid was placed in 500 mL of CH_2Cl_2 in a 1 L beaker. The suspension was stirred with a 20-cm long, 3-cm diameter, 4-blade stirrer at 1200 rpm for 1 min. The suspension was filtered through filter paper. This procedure was repeated a second time. The combined filtrates were concentrated *in vacuo*. The solid residue was recrystallized from hexanes (400 mL) to give a light yellow-green crystalline solid which was then sublimed (0.02 torr, 130–135°C) using an Aldrich Kugelrohr apparatus. The sublimed solid was recrystallized from 300 mL of hexanes by refluxing hexanes through the Kugelrohr receiver bulb until the solid material dissolved in the refluxing hexanes. The title compound was obtained as a white crystalline solid, 6.1 g (65%), m.p. 132.5–135.5°C (lit. [5] 134–135°C), when the hexane solution was cooled to −5°C. The compound had spectral properties identical to those reported [5].

N,N'N''-tris(*Propargyl*)-4,10,16-*triaza*-18-*crown*-6, **6**

To a solution of **5** (1.95 g, 7.5 mmol) and Na_2CO_3 (3.18 g, 30 mmol) in MeCN (35 mL) was added propargyl bromide (2.85 g, 24 mmol). The reaction was stirred at reflux temperature for 16 h. The reaction was cooled, concentrated *in vacuo*, dissolved in CH_2Cl_2 (200 mL), and filtered through celite. The organic solution was extracted with 1M HCl (100 mL). The aqueous layer was then basified with Li_2CO_3 to pH 10 and extracted with CH_2Cl_2 (3 × 50 mL). The organic portions were dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil. The oil was distilled (Kugelrohr apparatus, bp 160–165°C, 0.1 torr) to give 1.0 g (36%) of a pale yellow oil. ^{1}H-NMR: 2.17 (*t*, 3H, C≡CH), 2.78 (*t*, 12H,CH_2N), 3.48 (*s*, 6H, NCH_2C≡C), 3.58 (*t*,12H, CH_2O); IR (neat): 3320, 2950, 2880, 2100, 1460, 1370, 1330, 1130(s), 1060, 1000, 900, 640 cm^{-1}; High res. mass. spec. *calcd.* for $C_{21}H_{33}N_3O_3$: 375.2522. *Found*: 375.2530.

N,N'N''-tris(2-*Hydroxyethyl*)-4,10,16-*triaza*-18-*crown*-6, **7**

Alkylated using the method of Kulstad and Malmsten [9]. Ethylene oxide (1.02 g, 23 mmol) was added to a solution of **5** (1.02 g, 3.9 mmol) in MeOH (10 mL) at 0°C. The reaction was heated at reflux temperature for 2 h while the condenser was maintained at 0°C. The condenser was then operated at 20°C and the reaction was heated at reflux temperature for an additional hour. The reaction mixture was cooled and concentrated *in vacuo*. The resulting oil was distilled (bp 210–220°C, 0.1 torr) to give 1.2 g (78%) of a colorless oil. ^{1}H-NMR: 270 (*t*, 18H, CH_2N), 3.55 (*t*, 18H, CH_2O), 3.75 (*s*, broad, 3H, OH); IR (neat): 3370(b), 2960, 2900, 2840, 1450, 1360, 1120(s), 1080, 940, 740 cm^{-1}; High res. mass. spec. *Calcd.* for $C_{18}H_{39}N_3O_6$: 393.2838. *Found*: 393.2823.

N,N',N''-tris(Methoxymethylcarbonyl)-4,10,16-*triaza*-18-*crown*-6, **8**

To a vigorously stirred solution containing **5** (1.50 g, 5.74 mmol) and triethylamine (0.59 g, 5.8 mmol) in benzene (30 mL) was added a solution containing methoxyacetyl chloride (0.53 g, 5.8 mmol) in benzene (25 mL) during 30 min. After the addition, the reaction mixture was stirred at room tepmerature for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was distilled in a Kugelrohr apparatus (b.p. 210–220°C, 0.02 torr) to give 1.2 g (44%) of a pale yellow oil. ^{1}H-NMR: 3.40 (*s*, 9H, OCH_3), 3.60 (*m*, 24H, crown ring), 4.10 (*s*, 6H, $COCH_2OR$); IR (neat): 2960, 2910, 1670(s), 1490, 1440, 1370, 1210, 1120(s), 1020, 940 cm^{-1}; High res. mass. spec. *Calcd.* for $C_{21}H_{39}N_3O_9$; 477.26863. *Found*: 477.26538.

N,'N''-tris(2-*Methoxyethyl*)-4,10,16-*triaza*-18-*crown*-6, **9**

Compound **8** (1.0 g, 2.1 mmol) was dissolved in a solution of $BH_3 \cdot THF$ (50 mL, 1.0 M). The reaction was heated at reflux temperature for 24 h, cooled, and then concentrated *in vacuo*. The residue was dissolved in 3M HCl (40 mL) and heated at reflux temperature for 24 h. Water (50 mL) was added and the reaction was extracted with CH_2Cl_2 (3 × 50 mL). The aqueous layer was basified with solid LiOH to pH 10 and was extracted with CH_2Cl_2 (300 mL) in a continuous extraction apparatus for 3 d. The organic phase was concentrated *in vacuo* and the residue was distilled (b.p. 160–165°C, 0.02 torr) in a Kugelrohr apparatus. Column chromatography on neutral alumina (40 g, hexanes/CH_2Cl_2/EtOH, increasingly polar solvent gradient) followed by another distillation (b.p. 160–165°C, 0.02 mm) resulted in 250 mg (31%) of a non-viscous pale yellow oil. ^{1}H-NMR: 2.75 (*t*, 18H, NCH_2R), 3.25 (*s*, 9H,OCH_3), 3.45 (*t*, 18 H, OCH_2R); IR (neat): 2960, 2900, 1470, 1370, 1310, 1210, 1130, 1080, 960, 830 cm^{-1}; High res. mass. spec. *Calcd.* for $C_{21}H_{45}N_3O_6$: 435.3308. *Found*: 435.3328.

N,N',N''-tris(*Carbethoxymethyl*)-4,10,16-*triaza*-18-*crown*-6, **10**

A solution of **5** (2.0 g, 7.65 mmol), ethyl chloroacetate (2.91 g, 23.7 mmol) and Na_2CO_3 (2.52 g, 23.8 mmol) in MeCN (50 mL) was heated at reflux temperature for 100 h. The reaction was then cooled, filtered, and concentrated *in vacuo*. The brown residue was dissolved in CH_2Cl_2 (50 mL) and washed with water (50 mL). The compound was then extracted into 1M HCl (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The aqueous layer was basified to pH 10 with solid LiOH, extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic portions were concentrated *in vacuo*. The resulting yellow oil was filtered through alumina (30 g) and then distilled (b.p. 195–200°C, 0.01 torr) to give 1.2 g (30%) of a colorless oil. ^{1}H-NMR: 1.28 (*t*, 9H, CH_3), 2.92 (*t*, 12H, CH_2N), 2.5 (*s*, 6H, NCH_2CO), 3.55 (*t*, 12H, CH_2O), 4.15 (*q*, 6H, OCH_2CH_3); IR (neat): 2950, 2900, 1750, 1460, 1370, 1200, 1120, 930 cm^{-1}; *Anal. Calcd.* for $C_{24}H_{45}N_3O_9$; C, 55.47: H, 8.73. *Found*: C, 55.55; H, 8.76%.

N,N′N″-tris(Benzyl)-4,10,16-*triaza*-18-*crown*-6, **11**

A solution of triaza-18-crown-6 (200 mg, 0.77 mmol) and Na_2CO_3 (250 mg, 2.38 mmol) in CH_3CN (10 mL) was prepared. A solution of benzyl chloride (280 mg, 2.2 mmol) in CH_3CN (5 mL) was added during 20 min. The reaction was heated at reflux temperature for 12 h, cooled, filtered, and concentrated *in vacuo*. Chromatography over alumina (10% *i*-PrOH in hexane) gave 370 mg (91%) of a pale yellow oil. ^{1}H-NMR: 2.70 (*t*, 12h, $J = 5$ Hz, CH_2N), 3.45 (*s* + *t*, 18H, $J = 5$ Hz, CH_2O and NCH_2Ar), 7.10 (*s*, 15H, Ar); IR (neat): 3080, 3060, 3030, 2900, 1500, 1455, 1120, 1060, 730, 700 cm^{-1}; *Anal. Calcd.* for $C_{33}H_{45}N_3O_3$: C, 74.58; H, 8.47; N, 7.91. *Found*: C, 74.26; H, 8.70; N, 7.78.

N,N′,N″-tris(2-Nitrobenzyl)-4,10,16-*triaza*-18-*crown*-6, **12**

Compound **5** (0.50 g, 1.9 mmol), 2-nitrobenzyl chloride (1.00 g, 5.8 mmol), and Na_2CO_3 (1.52 g, 14.3 mmol) were combined in MeCN (13 mL) and stirred at reflux for 20 h. The reaction was cooled, filtered, and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL) and was then washed with water (20 mL). The organic portion was extracted with 1M HCl (30 mL). The aqueous portion was basified to pH 10 with LiOH and extracted with CH_2Cl_2 (2 × 20 mL). The organic portions were dried ($MgSO_4$), and concentrated *in vacuo* to give 0.60 g (50%) of an orange oil. ^{1}H-NMR ($CDCl_3$) 2.77 (*t*, 12H, CH_2N), 3.50 (*t*, 12H, CH_2O), 3.96 (*s*, 6H, $ArCH_2N$), 7.10–8.00 (*m*, 12H, Ar); ^{13}C-NMR: 54.3, 56.58, 69.48, 124.03, 127.48, 130.88, 132.32, 135.33, 149.41; *Anal. Calcd.* for $C_{33}H_{42}N_6O_9$; C, 59.45; H, 6.35%.

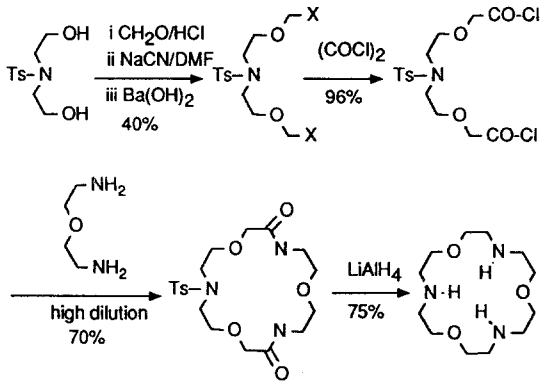
N,N′,N″-tris(n-Hexyl)-4,10,16-*triaza*-18-*crown*-6, **13**

To a refluxing solution of triaza-18-crown-6 (200 mg, 0.77 mmol) and Na_2CO_3 (250 mg) in CH_3CN (10 mL) was added a solution of 1-bromohexane (370 mg, 2.2 mmole) in CH_3CN (5 mL) dropwise over 20 min. The mixture was then left to reflux for 24 h. The mixture was cooled, filtered, the solvent removed *in vacuo* and the residue chromatographed over alumina (5% 2-propanol/hexanes) to yield 200 mg (51%) of *N,N′,N″-tris-(n-hexyl)*-4,10,16-*triaza*-18-*crown*-6. ^{1}H-NMR: 5.5 (*t*, 12H, $J = 5$), 2.4 (*m*, 18H), 1.4–1.7 (*m*, 33H). *Anal. Calcd.* for $C_{30}H_{63}N_3O_3$: C, 70.18; H, 12.28; N, 8.19%. *Found*: C, 70.08; H, 12.50; N, 8.05%.

3. Results and Discussion

The Lehn procedure deserves great credit because it was the first to afford triaza-18-crown-6. The procedure is serviceable on a small scale but, in our hands at least, proved cumbersome on a multi-gram scale. Moreover, Lehn's approach to the $C-C-X$ unit in $TsN(CH_2CH_2O-C-C-X)_2$ involved chloromethylation of $TsN(CH_2CH_2OH)$ to give $TsN(CH_2CH_2OCH_2Cl)_2$ followed by reaction with cyanide to give $TsN(CH_2CH_2OCH_2C{\equiv}N)_2$. This, in turn, had to be hydrolyzed to the corresponding diacid. We attempted a more direct route, although the

influence of the Lehn approach will be obvious. It is summarized schematically below.



The chloromethylation reaction followed by cyanide treatment and then barium hydroxide catalyzed hydrolysis is obviously an indirect approach to the diacid. Even so, the reaction is successful and the overall yield for Lehn's sequence is 20%.

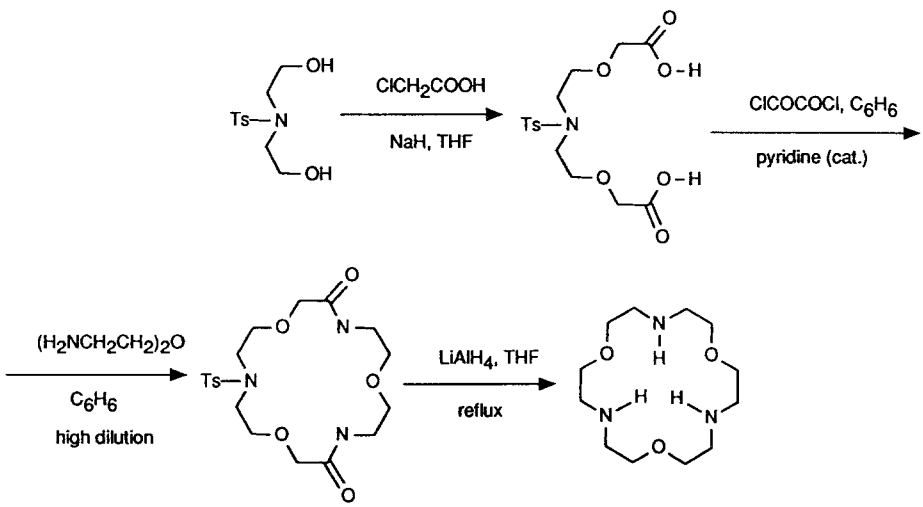
The previously unreported but obvious reaction sequence:

$$TsN(CH_2CH_2OH)_2 + ClCH_2C{\equiv}N \rightarrow TsN(CH_2CH_2OCH_2C{\equiv}N)_2$$

proved impractical in our hands. We therefore attempted to circumvent all three steps, i.e. chloromethylation, reaction with cyanide, and hydrolysis by using the following sequence:

$$TsN(CH_2CH_2OH)_2 + ClCH_2COONa \rightarrow TsN(CH_2OCH_2COOH)_2.$$

This sequence succeeded, although vigorous agitation (glass beads were present in the reaction mixture) was required for best yields. Once the diacid was in hand, the strategy followed that described by Lehn with some modifications to the experimental procedure. The latter are detailed in the experimental section. The overall procedure reported here is as shown below. This approach has permitted the accumulation of tens of grams of this versatile material [3].



The yields for the formation of each product are as follows: **2**, 75–85% (many replicates); **3**, ~100%; **4**, 65% and **5**, 65%. The overall yield for this sequence is thus 32%, compared to the yield Lehn reported of 20%. Note that we have not been able to achieve quite such high yields as Lehn reported for the penultimate and final steps. Were we able to do so, our overall yield would improve to nearly 40%. All of our yield estimates are based on 75% in the first step although we have sometimes realized 85% in this step. As indicated above, the yield is sensitive to agitation.

3.1. TRIBRACCHIAL LARIAT ETHERS

The three-armed lariat ether (TriBLE) derivatives of triaza-18-crown-6 were prepared by alkylation of the parent compound in acetonitrile. The incipient sidearm was introduced in electrophilic form, usually as its chloride. Sodium carbonate was used as base. Compound **8**, which has three $CH_2CH_2OCH_3$ sidearms, was prepared by acylation of **7** followed by reduction. Using this approach, the yields shown in Table I were obtained.

3.2. CATION BINDING PROPERTIES

The cation binding constants recorded in Table I were determined by ion selective electrode techniques [8] in anhydrous methanol solution at 25.0 ± 0.1°C. The parent crown (**5**, sidearm = H) and the tris(methyl) derivative of **5** exhibit generally low binding. This is expected for **5** since the solid state structure of **5** [6] shows that all three N—H bonds may be focussed into the cavity's center even in solution. The data for the tris(methyl) derivative of **5** were taken from the literature and while

Table I. Cation binding properties of TriBLEs.

Cpd. No.	Sidearm on 5	% yield	log K_S^a Na^+	K^+	Ca^{2+}
5	H	20–30[b]	1.8	<1.5	<1.5
–	CH_3	—	3.11[c]	2.78[c]	—
6	$CH_2C{\equiv}CH$	36	4.03	5.10	4.12
7	CH_2CH_2OH	78	4.15	4.45	5.58
8	$CO{-}CH_2{-}O{-}CH_3$	44	—	—	—
9	$CH_2CH_2{-}O{-}CH_3$	31[c]	4.19	4.93	4.07
10	$CH_2CO{-}O{-}CH_2CH_3$	30	5.13	5.87	6.70
10	$CH_2CO{-}O{-}CH_2CH_3$	30	1.9[d]	—	4.62[d]
11	$CH_2{-}C_6H_5$	91	—	—	—
12	$CH_2{-}C_6H_4{-}2{-}NO_2$	50	—	—	—
13	*n*-hexyl	51%	—	—	—

[a]All binding data were determined at 25.0 ± 1.0°C in anhydrous methanol.
[b]Yield range given for the present procedure and that reported in Ref. [5], see text.
[c]Binding constants determined in 90% MeOH–10% H_2O and are from Ref. [11].
[d]Binding constants determined in water.

they are presumed to have been determined under comparable conditions, this is not certain. We did not prepare this derivative nor did we check these values as the sidearms cannot contribute to binding in the anticipated way.

Cation binding strengths for the remaining derivatives, namely **6–13**, are fairly high. It is interesting that Na^+ binding differs little whether the sidearm is $CH_2—C\equiv CH$, CH_2CH_2OH or $CH_2CH_2OCH_3$. One is tempted to account for this in terms of a π-contribution from the sidearm. Previous studies of π-sidearm BiBLEs have shown that a combination of differences in the entropic and enthalpic contributions can account for these similarities [10].

Two features of the cation binding deserve special note. First, as the sidearm donor groups increase in polarity, cation binding generally rises. This is true for the polarity sequence **8** < **7** < **10**. For this series, Ca^{2+} binding (log K_S) increases in the same order: 4.07, 5.58, and 6.70. Second, cation binding strength for these derivatives is considerable, even in water (log K_S 4.62). This must be due to participation by one or more sidearms.

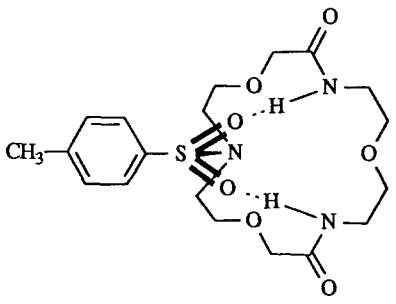
Although we have no solid state structure of any TriBLE complex, we believe that only two of the three sidearms participate in binding. We draw this conclusion from a comparison of cation binding strengths for two- and three-armed systems in which the sidearms are the same. For the series of compounds noted above, i.e. CH_2CH_2OH (**7**), $CH_2CH_2OCH_3$ (**8**), and $CH_2COOCH_2CH_3$ (**10**), log K_S for Na^+ is, respectively, 4.83, 4.75, and 5.51 for the two-armed compounds compared to 4.15, 4.19, and 5.13 for the TriBLEs. Two possible explanations for the lower binding strength of TriBLEs compared to BiBLEs are obvious. It may be that the TriBLEs use the macroring relatively little and most of the binding strength derives from sidearm donors. Alternately, binding by TriBLEs may occur just as in the BiBLE case (i.e. ring and two sidearms) but the third arm 'gets in the way'. Such interference by the third arm could lower the effectiveness of the remaining two binders. Both of these explanations are essentially enthalpic and entropy must play a greater role when three arms are present in otherwise analogous systems.

The parallel in binding strengths for the Na^+, K^+, and Ca^{2+} ions by the BiBLE and TriBLE (**10**) having $CH_2COOCH_2CH_3$ sidearms is striking. The respective binding constants are: Na^+, 5.51 vs. 5.13; K^+, 5.78 vs. 5.87; and 6.78 vs. 6.70. Again, it is presumptuous to interpret these values using pure enthalpic arguments but one might easily surmise that binding in both cases relies on two sidearms. The data for these systems are summarized in Table I.

3.3. SOLID STATE STRUCTURE OF **4**

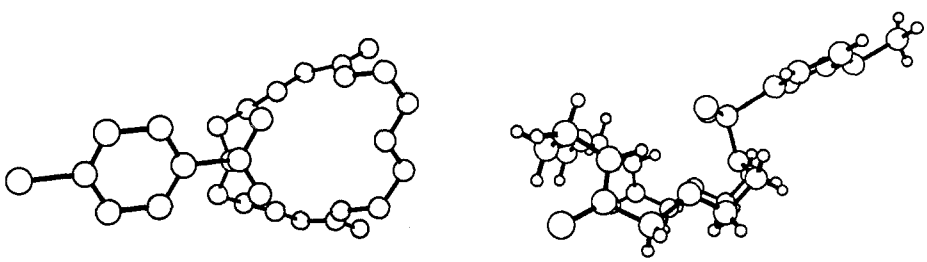
A key intermediate in our approach is 4-*N*-tosyloxy-9,17-dioxo-4,10,16-triaza-18-crown-6, **4**, which is, in turn, prepared from the *N*-tosyldiacid chloride, Ts-$N(CH_2CH_2OCH_2COCl)_2$ by high dilution reaction with 2,2,′-diaminodiethyl ether. Compound **1** is critical to our plans since we wish to attach two different kinds of sidearms to this tribracchial lariat ether. We now report X-ray crystal structure data showing that this important intermediate is the first example of a

cation-free lariat ether compound that exhibits specific, if weak, sidearm-macroring interaction.



Two views of the solid state structure are shown below. Rather than being planar or nearly so, the macroring is puckered so that the sidearm can reach over the ring. The sidearm is tilted but the ring and amide oxygens approximate a plane and the aromatic ring is almost parallel to it. The two S → O bonds are oriented directly toward the amide nitrogens which are intrannular and at a distance of 3.28 Å and 3.41 Å respectively. The O—H—N angle in the former case is 161° and in the latter it is 154°. The more acute angle is consistent with the longer O···N distance and the clearly weaker interaction. It is, of course, well known that the vast majority of N—H···O hydrogen bonds in amino acids fall within the range 155–175° and relatively few are actually 180° [12].

On the other hand, these hydrogen bonds are long by any standard. The N—H distance in the shorter case is 0.94 Å and in the longer case the corresponding distance is 1.01 Å. The corresponding H···O distances are 2.37 Å and 2.45 Å. There is no obvious packing force that would make this crown pucker so severely were there not some stabilizing interaction present between ring and sidearm. It should be noted that a similar phenomenon is observed in valinomycin which folds into a 'pre-binding' conformation by virtue of hydrogen bond stabilization. Even so, we believe this neutral ring-sidearm interaction to be unique in crown ether chemistry.



The present structure compares with three other reports of similar compounds or similar interactions. Buchanan, Ripmeester and coworkers [13] have reported a 1 : 1

complex of 18-crown-6 which has a melting point similar to a previously reported [14] complex but differs in stoichiometry from it. The 1 : 1 complex (**14**) is stabilized by hydrogen bond formation between sulfonamide amino nitrogen and two oxygen atoms of 18-crown-6. Thus the O(1)—N and O(7)—N distances are reported to be 3.003 Å and 3.002 Å, respectively [13]. Stoddart, Williams, and coworkers [15] have reported the solid state structure of a diazadibenzo-30-crown-10 disulfonamide which failed to form complexes with 'diquat^{2+}'. In this case, edge-to-face aromatic interactions apparently dominate the structure. No hydrogen bond formation is possible in any event since there are no >NH bonds either in the host or guest. Malinovsky and coworkers [16] have recently reported the structure of **15** which forms a dimer in which the aromatic amine group of one molecule complexes more or less as shown for **14**. Intermolecular distances for the amino nitrogen of one molecule to the macroring of a second molecule are, for three of the five oxygen atoms in the latter, 2.95–3.15 Å (six distances reported) [16].

Despite the somewhat long hydrogen bond distances in the present complex, the sidearm-macroring interaction is clear and, in the most general sense, precedented. This is the first such interaction observed but may presage other observations of this type. The triaza-18-crown-6 system should now prove more accessible and holds forth the promise of considerable interesting complexation chemistry.

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