

Tribracchial Lariat Ethers, 'TriBLEs,' based on 4,10,16-Triaza-18-Crown-6: An Apparent Limit to Sidearm Contributions in Lariat Ether Molecules

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The development of an improved synthesis of 4,10,16-triaza-18-crown-6 (crystal structure shown) has permitted the synthesis of several novel derivatives of this well-known but little-studied compound and the finding that two-armed and three-armed derivatives exhibit comparable rather than markedly different cation binding strengths and selectivities.

Since our first report of lariat ether compounds in 1980,¹ we have striven to understand and increase both the binding strengths and selectivities of this interesting group of macrocycles. In so doing, we have elaborated the original carbon-pivot^{1,2} lariat ethers into single-armed, nitrogen-pivot³ lariat ethers and further into two-armed, diaza-bibracchial lariat ethers (BiBLEs).⁴ The latter compounds exhibit generally useful and interesting cation binding strengths and some selectivities that are significantly higher than observed for the one-armed macrocycles. We now report that our effort to extend the lariat ether series of compounds to include three-armed triaza-tribracchial lariat ether (TriBLE) systems has proved successful, but a limit to ring-sidearm co-operativity has apparently been reached.

4,10,16-Triaza-18-crown-6, (**1**), was first reported by Lehn and coworkers⁵ and was an important precursor in the synthesis of the first spherand.⁶ A key step in this synthesis involves conversion of $\text{TsN}(\text{CH}_2\text{CH}_2\text{OH})_2$ into $\text{TsN}(\text{CH}_2\text{CH}_2\text{OCH}_2\text{CO}_2\text{H})_2$ by chloromethylation, substitu-

tion of chloride by cyanide, and barium hydroxide mediated hydrolysis. We found it difficult to implement scale-up of this sequence and instead accomplished the conversion by treatment of $\text{TsN}(\text{CH}_2\text{CH}_2\text{OH})_2$ with the sodium salt of chloroacetic acid. This alteration in the synthetic strategy was achieved experimentally only after considerable effort to overcome the solubility properties that prevent facile conversion. Full details of the experimental procedure will be published in due course. Using the procedure outlined in Scheme 1, we have obtained more than 15 g of the title compound.[†]

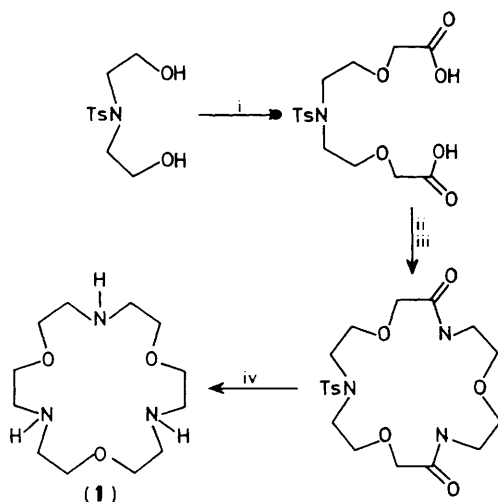
The hitherto unreported crystal structure of (**1**) is shown in Figure 1. The compound adopts the D_{3d} conformation even in the absence of a cation as does 4,13-diaza-18-crown-6.⁷ In addition, the hydrogen atoms must be turned inward but could not be located because of a 50% disorder in the structure such

[†] M.p. of (**1**) 132.5–135.5 °C; lit.⁶ m.p. 134–135 °C.

Table 1. Cation binding affinities ($\log K_s$) for aza-lariat ethers in anhydrous methanol solution at 25 °C.^a

Sidearm	Aza-18-crown-6			Diaza-18-crown-6			Triaza-18-crown-6		
	Na ⁺	K ⁺	Ca ²⁺	Na ⁺	K ⁺	Ca ²⁺	Na ⁺	K ⁺	Ca ²⁺
H	2.69	3.98	3.96	1.5	1.8	ND	1.8	<1.5	<1.5
Me	3.93	5.33	—	3.7 ^b	5.3 ^b	—	3.11 ^c	2.78 ^c	—
CH ₂ CH=CH ₂	3.58	5.02	3.65	3.04	4.04	2.84	—	—	—
CH ₂ C≡CH	—	—	—	3.61	4.99	3.52	4.03	5.10	4.12
CH ₂ CH ₂ OH	4.75 ^d	5.49 ^d	—	4.83	5.07	6.02	4.15	4.45	5.58
CH ₂ CH ₂ OMe	4.58	5.67	4.34	4.75	5.46	4.48	4.19	4.93	4.07
CH ₂ CO ₂ CH ₂ Me	4.67	5.92	—	5.51	5.78	6.78	5.13	5.87	6.70

^a Ref. 8. ^b Values determined potentiometrically in anhydrous methanol in the presence of 0.01 M Me₄NBr.¹⁰ ^c Values determined in 90% methanol.¹¹ ^d Ref. 12.



Scheme 1. Reagents and conditions: i, ClCH₂CO₂H, NaH, tetrahydrofuran (THF), 25 °C, 24 h, 75%; ii, ClCOCOCl, C₆H₆ plus pyridine (cat.), quantitative; iii, H₂NCH₂CH₂OCH₂CH₂NH₂ in C₆H₆, high dilution, product used directly in step iv; iv, LiAlH₄, THF, reflux, 36 h, 65%. Ts = *p*-MeC₆H₄SO₂.

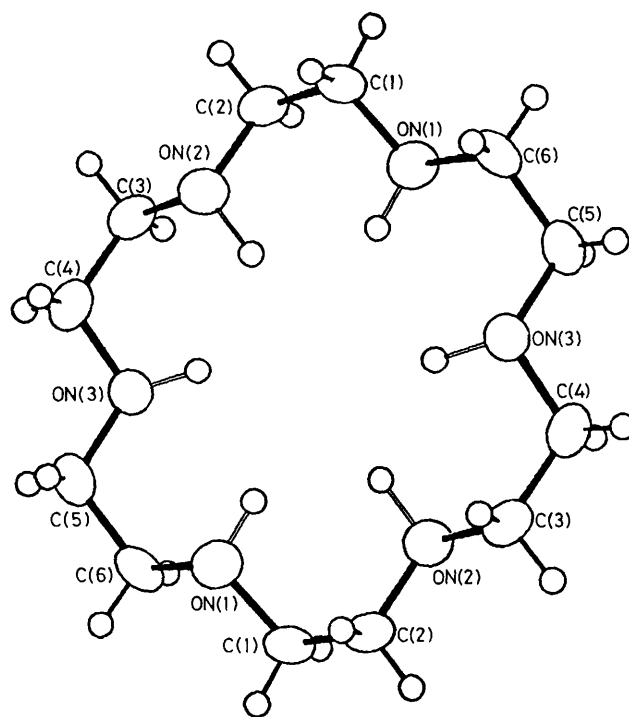


Figure 1. ORTEP drawing showing the solid state structure of 4,10,16-triaza-18-crown-6 (**1**) in which the three >N-H hydrogens are turned inward. The crystal is 50% disordered, because the macrocycle alternates orientation so that >N-H and -O- are superimposed in successive molecular layers.

that NH and O atoms alternate throughout the crystal. Full details of the structure will be reported separately.[‡]

A major motivation for preparing the series of *N,N',N''*-trisubstituted derivatives of (**1**) was to assess the enhancement of ring-sidearm co-operativity anticipated based on previous studies of one- and two-armed azalariat ethers.¹⁻⁴ Thus, we compared binding for the 18-membered ring, *N*-pivot lariat ethers having the following substituents on nitrogen: H, Me, CH₂CH=CH₂, CH₂C≡CH, CH₂CH₂OH, CH₂CH₂OMe, and CH₂CO₂CH₂Me. The Na⁺, K⁺, and Ca²⁺ cation binding constants (reported in Table 1 as $\log K_s$ for anhydrous methanol solution at 25 °C) were determined as previously described.^{8,9}

Because of the paucity of data for the compounds in this

study which lack sidearm donors, little insight can be gained from a discussion of their cation binding strengths. For di- and tri-aza-18-crown-6 derivatives having donor-containing-sidearms, the comparisons are interesting. In all three cases (final three lines in Table 1) Na⁺ cation binding strength is greater for the two-armed than for the three-armed systems. The same is true for K⁺ binding except for the triester derivative of diaza-18-crown-6 which binds K⁺ slightly less strongly than does the triaza-analogue. Divalent calcium cation is bound more strongly by the two-armed systems than by the three-armed ones, although the difference in the glycine ester case is marginal. The data in Table 1 thus demonstrate that an apparent limit in cation binding co-operativity has been reached at the BiBLE stage and that little

[‡] Crystal data for (**1**): C₁₂H₂₇N₃O₂, *M* = 261.4, monoclinic, space group *P*2₁/*c*, *a* = 10.319(2), *b* = 8.591(3), *c* = 9.150(3) Å, β = 190.70(2)°, *U* = 763.7(8) Å³, *Z* = 2, *D*_c = 1.137 g cm⁻³, μ = 0.8 cm⁻¹, *T* = 23 °C. At convergence, *R* = 0.049. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

or no further advantage is realized by addition of a third arm at an additional nitrogen pivot point. Of course, there are many instances in which binding by diaza-BiBLEs is comparable to aza-lariat ethers. Indeed, an example of this can be seen in line 4 of Table 1. This is because the enhancement afforded by an additional sidearm donor is reduced by the cost of replacing a macroring oxygen donor by nitrogen. The latter is costly only for alkali metal cations and may show great advantage when complexation is attempted with transition or coinage metals. These observations apply only to the 18-membered ring system in which the macroring makes a significant contribution to binding. Three arms present on a smaller macrocycle may exhibit a much larger binding increment. Of course, the special symmetry of this molecule makes its affinity for NH_4^+ particularly high and applications specific to ammonium ion complexation are currently underway.

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