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LARIAT ETHERS. 3. MACROCYCLIC POLYETHERS BEARING DONOR GROUPS ON FLEXIBLE ARMS ATTACHED AT A NITROGEN PIVOT POINT[1]

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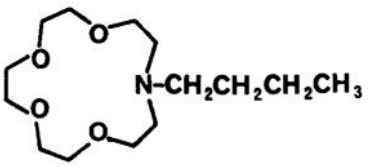
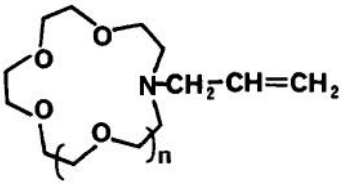
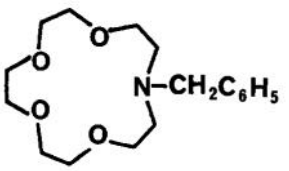
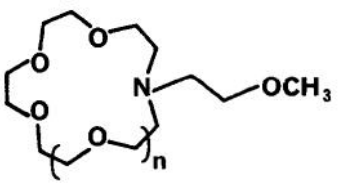
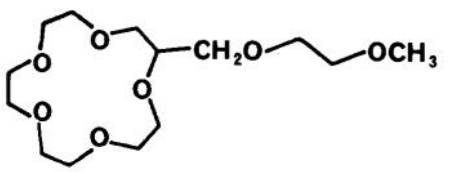
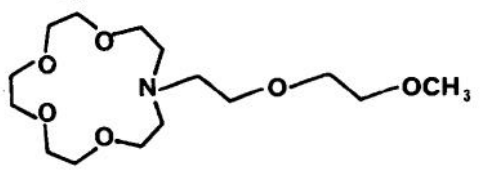
Abstract: The binding of lariat ethers utilizing a nitrogen pivot atom for the donor sidearm is enhanced considerably relative to the carbon-based systems and this may be explicable in terms of diminished "sidedness."

Although the lariat ethers have already proven themselves to be interesting macrocycles[2] and to possess surprising binding properties, albeit solvent dependent ones,[1] they suffer from the inherent disadvantage of "sidedness." In the compounds we have reported previously, the sidearm bearing the donor group(s) has been bound to the macroring through an alkoxymethyl linkage. Since the stereochemistry of the sidearm is fixed, one side of the macrocycle is never blocked by it, while the other side may be shielded often or even most of the time from an incoming cation. Logically, this predicts that the number of collisions between cation and crown which lead to complexation must inherently be smaller than in cases where neither side of the macroring is blocked.

Although we have not conducted any kinetic analysis which would tell us clearly whether or not this orientation factor should be of consequence, we sought to confirm the thesis by attaching the sidearm at a flexible molecular pivot atom, namely, nitrogen. We reasoned that facile inversion about nitrogen[3] should reduce the potential problem of sidedness in these systems and we have therefore prepared the molecules illustrated in the table.

Table: Sodium Cation Binding by Nitrogen-based Lariat Ethers[7]

Cpd. No.	Structure[9]		Binding Constant Ks	Log Ks
1	15-Crown-5		927±32	2.97±0.01
2			414	2.62
3		n=1	661	2.82
4		n=2	1255	3.10
5			303	2.48
6		n=1	4587	3.66
7		n=2	15056	4.18
8			669	2.82
9			14630	4.16

The nitrogen-lariats were prepared by reaction of the appropriate N-alkylated diethanolamine with triethylene glycol ditosylate and sodium hydride in THF solution. Alkylation of the diethanolamine was accomplished as previously described using the incipient sidearm as its tosylate and sodium carbonate as base.[4] Alternatively, monoaza-15-crown-5 or monoaza-18-crown-6 could be prepared as reported[5] and alkylated. "One-pot" procedures are also available.[6]

$$(HOCH_2CH_2)_2NH + R\text{-}OTs \longrightarrow (HOCH_2CH_2)_2N\text{-}R \xrightarrow[TsO(CH_2CH_2O)_nTs]{NaH/THF} \textbf{2-7,9}$$

From the data presented in the table, several interesting facts emerge. First, it is not surprising that substitution of N-Bu for O in 15-crown-5 (i.e., **1** vs. **2**) diminishes the binding constant (Ks) for sodium cation. Sodium is clearly a "hard" cation and exchange of "hard" oxygen for "softer" nitrogen has the anticipated effect on binding. The binding constants of N-allylmonoaza-15-crown-5 (**3**) and N-benzylmonoaza-15-crown-5 (**5**) are likewise lower than 15-crown-5. On the other hand, the corresponding N-allylmonoaza-18-crown-6 (**4**) still presents five oxygen atoms for complexation so the binding constant is considerably increased, and even slightly better than for 15-crown-5.

The most interesting data are apparent for compounds **6-9**. Clearly, the nitrogen - pivot molecules bind sodium cation more strongly than do the corresponding carbon-based systems.[7] This contrast is especially vivid for compounds **6** and **8** which are quite similar in shape, size and available binding sites, but differ in binding constant by almost an order of magnitude. It is especially interesting to note that the very high binding constant of **9**, a five-heteroatom ring with two oxygen donors in the sidearm, is essentially matched by a six-heteroatom ring system having only one donor atom in the sidearm. It is probably not a coincidence that the number of oxygen donors is identical in **7** and **9** and the binding constants differ by less than 3%.

We recognize that the considerably higher binding constants found for the nitrogen-based lariats compared to the all-oxygen systems do not confirm the design

criterion noted above, but these results are suggestive of such an effect. Indeed, we have found that the nitrogen-based systems may also have disadvantages, and will report on this shortly.

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NOTES AND REFERENCES

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3. See Lehn, J.-M.; Structure and Bonding, 1973, 16, 1.

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6. a) Kuo, P.-L., Miki, M., Ikeda, I., Okahara, M.; Tetrahedron Letters, 1978, 4273.
   b) Kuo, P.-L., Miki, M., Ikeda, I., Okahara, M.; J. Am. Oil. Chem. Soc.; 1980, 227.

7. Binding constants were measured in 90% (w/w) aq. MeOH at 25.0±1.0°C using a Corning 476210 electrode and an Orion model 501 "Ionalyzer" meter according to the method of Frensdorff. We have previously reported a standard deviation for these measurements of ±3% (of Ks). Frensdorff has estimated the error to be as high as ±10%.[8]

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9. All new compounds were pure by gas chromatographic analysis and gave satisfactory C and H analyses as well as acceptable IR and NMR spectra.

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