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# SYNTHESES AND CATION BINDING PROPERTIES OF 12-MEMBERED RING NITROGEN-PIVOT LARIAT ETHERS

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Summary: The efficient synthesis of several 12-membered ring, N-pivot lariat ethers are reported and it is shown that binding to sodium cations is generally weak except when an oligoethyleneoxy sidearm is long enough to provide additional solvation.

In studies reported during the past several years, we[1] and others[2] have shown that lariat ethers have a variety of interesting properties. Notable among these is the flexibility which results in cation-induced organization of the ligand. As a result of this, all-aliphatic, 15- and 18-membered ring, nitrogen-pivot lariat ethers having the same total number of oxygen atoms show identical (within experimental error)[3] equilibrium binding constants (Ks) for $Na^+$ in anhydrous methanol. We were interested to know if this ring-size independence could be extended to include 12-membered rings as well. We therefore undertook the syntheses of several new lariat ether compounds and we report our findings here.

Calverly and Dale[4] showed that primary amines react with 1,11-diiodo-3,6,9-trioxaundecane in the presence of $Na_2CO_3$ (MeCN solution) to give N-substituted monoaza-12-crown-4 molecules in a single step. We have utilized this reaction, shown in the equation below, to prepare the compounds listed in the Table.

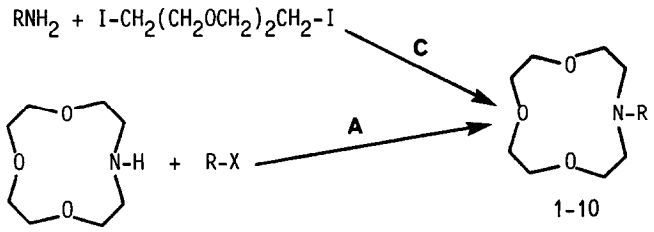
Note that both aliphatic and aromatic amines have been used in this study. Further, hydrogenation[5] of N-benzylmonoaza-12-crown-4 affords the parent system, monoaza-12-crown-4, to which a variety of sidearms can be added by alkylation. The methods of preparation are shown in the Table as A for alkylation and C for cyclization. The symbol B means that the amine was

Table: Syntheses and Binding Comparisons for 12-Membered Ring N-Pivot Lariat Ethers[a]

| Cpd. No. | Sidearm | Method of Prep'n | Yield (%) | MP or (BP)°C | Log Ks ($Na^+$) for Ring Size 12 | 15 | 18 |
|---|---|---|---|---|---|---|---|
| 1 | H | B | 95 | 60 (subl)/0.05[b] | ----[c] | 1.72 | 2.69 |
| 2 | $CH_2$-Ph | C | 53 | (122-125/0.03)[d] | 2.08 | 2.77 | 3.41 |
| 3 | 2-MeO-$C_6H_4$ | C | 26 | (130-135/0.03) | 2.75 | 3.86 | 4.59 |
| 4 | 4-MeO-$C_6H_4$ | C | 40 | (142-146/0.03) | 1.38 | 2.12 | ND |
| 5 | $CH_2$-2-MeO-$C_6H_4$ | C | 47 | (150-153/0.03) | 2.49 | 3.43 | 4.59 |
| 6 | $CH_2$-2-$NO_2$-$C_6H_4$ | A | 86 | 37-38 | 1.77 | 2.40 | ND |
| 7 | $CH_2CH_2CH_2$-OH | C | 56 | (110-112/0.03) | 2.35 | NA | NA |
| 8 | $CH_2CH_2NMe_2$ | C | 21 | (85-90/0.05) | ND | NA | NA |
| 9 | $(CH_2CH_2O)_3Me$ | A | 52 | (155-160/0.03) | 3.97 | 4.32 | 4.28 |
| 10 | $(CH_2CH_2O)_4$-allyl | A | 50 | (160-165/0.03) | 3.97 | NA | NA |

Notes: Preparation of compounds was accomplished by A = alkylation of monoaza-12-crown-4, B = hydrogenolysis of N-benzylmonoaza-12-crown-4, or C = cyclization. ND = Not determined. NA = Compound not available. (a) All compounds had proton NMR and IR spectra as expected and all new compounds gave satisfactory combustion analyses for C, H, and N. (b) Literature (ref. 4) mp 59-60°C. (c) 2:1 Complex forms, see text. (d) Literature (ref. 4) bp 140-143°C/0.05 torr.

obtained by hydrogenation of the corresponding N-benzyl crown.




There are three points which are of considerable interest in this work. First, a variety of lariat ether compounds can readily be prepared by the Dale method and these substances have quite interesting properties. As with the larger ring lariat ether compounds, steric accessibility of the sidearm donor group continues to be important. This is apparent from a comparison of 4 with either 3 or 5. Note that 5 is a poorer $Na^+$ binder than 3 despite its more basic ring nitrogen. Second, compound 9 which has six oxygen atoms, is nearly as effective a $Na^+$ cation binder as its 15-membered ring analog. It is a somewhat poorer $Na^+$-binder than either $CH_3(OCH_2CH_2)_2N$-15-crown-5 or $CH_3OCH_2CH_2N$-18-crown-6, both of which contain six oxygens. In a previously reported study,[3] we found that these lariat ethers exhibited peak $Na^+$ binding with log Ks values in anhydrous methanol of 4.54 and 4.58 respectively. We believe that $K^+$ is enveloped by donor atoms in both the macroring and on the sidearm. Single crystal x-ray analysis confirms this and a structure of the $K^+$ complex of 9 will be published shortly.[6]

The third point concerns the binding of monoaza-12-crown-4. We note the report of Calverly and Dale[4b] that the interaction between $Na^+$ and N-methylmonoaza-12-crown-4 is of the 2:1 (ligand:cation) variety. They determined this by $^{13}C$-NMR studies using 0.5 M solutions of ligand in $CD_3OD$ and adding a solution of $Na^+$. Our own binding constant studies were conducted on 1 at nine different concentrations in anhydrous MeOH in the range 0.51 - 5.08 x $10^{-3}$ M using ISE techniques. The concentrations ($10^{-3}$ M) and apparent log Ks values (calculated assuming a 1:1 complex) are as follows: 0.51, 2.42±0.17; 0.61, 2.40±0.13; 1.02, 2.17±0.14; 1.83, 2.10±0.06; 2.03, 2.00±0.11; 2.44, 1.96±0.08; 3.05, 1.84±0.04; 4.07, 1.75±0.08; and 5.08, 1.70±0.11.[7] When the observed conductivity readings were graphed as a function of ligand/salt ratio, a curve was obtained which fell between the values anticipated for either 1:1 or 2:1 complexes. For most 15-membered ring and larger macrocycles, 2:1 ligand:cation complexation is minor, but in the present case, it seems likely that since each monoaza-12-crown-4 molecule contains three oxygen

donor groups, the two crowns form a 2:1 complex in which the six oxygen atoms form an octahedron about $Na^+$.[3] This favorable arrangement accounts for the broad concentration range (5 mM - 0.5 M[4b]) over which the 2:1 complex is observed for these two ligands. Indeed, NaI forms a crystalline (mp 182°C) complex having the stoichiometry (determined by combustion analysis) $crown_2NaI$.

The differences in apparent binding constants for the series of compounds monoaza-12-crown-4, monoaza-15-crown-5, and monoaza-18-crown-6 are intriguing. We are currently attempting to obtain evidence which will resolve the binding and structural issues more thoroughly.

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