12-, 15-, and 18-Membered-Ring Nitrogen-Pivot Lariat Ethers: Syntheses, Properties, and Sodium and Ammonium Cation Binding Properties†

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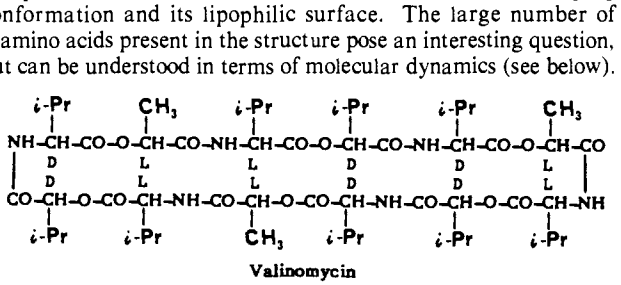
Abstract: Nitrogen-pivot lariat ethers of varying ring sizes can be prepared by cyclization of an amine or appropriately substituted diol. Twelve-membered-ring nitrogen-pivot lariat ethers were synthesized by one of two approaches. The method used by Calverley and Dale primarily for the synthesis of nonlariat azamacrocycles involves cyclo-bis-dialkylation of an amine with 1,11-diiodo-3,6,9-trioxaundecane (method C). Several monoaza-12-crown-4 derivatives did not form in high yield by this method or were more conveniently prepared by alkylation of monoaza-12-crown-4 (method A). The latter was prepared from *N*-benzylmonoaza-12-crown-4 (C, 53%) by hydrogenolysis (H_2, EtOH, Pd/C, 95%). The following monoaza-12-crown-4 derivatives were thus prepared: *N*-benzyl- (**2**, C, 53%); *N*-(2-methoxyphenyl)- (**3**, C, 26%); *N*-(4-methoxyphenyl)- (**4**, C, 40%); *N*-(2-methoxybenzyl)- (**5**, C, 47%); *N*-(2-nitrobenzyl)- (**6**, A, 86%); *N*-(3-hydroxypropyl)- (**7**, C, 56%); *N*-[2-(dimethylamino)ethyl]- (**8**, C, 21%); *N*-(3-oxabutyl)- (**9**, C, 60%); *N*-(3,6-dioxaheptyl)- (**10**, A, 66%); *N*-(3,6,9-trioxadecyl)- (**11**, A, 52%); *N*-(3,6,9,12-tetraoxatridecyl)- (**12**, A, 54%); and *N*-(11-allyloxy-3,6,9-trioxaundecyl)- (**13**, A, 50%). Monoaza-15-crown-5 **14** was prepared by hydrogenolysis (98%) of *N*-benzylmonoaza-15-crown-5 (**19**, overall yield, 45%). The following N-substituted, monoaza-15-crown-5 derivatives were prepared for this study by cyclization of the appropriate N-substituted diethanolamine derivative (method C) or alkylation of monoaza-15-crown-5 (method A): *N*-methyl (**15**, A, 37%); *N*-allyl (**16**, C, 61%); *N*-(*n*-butyl)- (**17**, C, 65%); *N*-(*tert*-butyl)- (**18**, C, 28%); *N*-benzyl (**19**, C, 46%); *N*-(2-methoxyethyl)- (**20**, C, 55%); *N*-(3,6-dioxaheptyl)- (**21**, C, 47%); *N*-(3,6,9-trioxadecyl)- (**22**, A, 34%); *N*-(3,6,9,12-tetraoxatridecyl)- (**23**, A, 55%); *N*-(3,6,9,12,15-pentaoxahexadecyl)- (**24**, A, 78%); *N*-(3,6,9,12,15,18,21,24-penteicosyl)- (**25**, C, 49%); *N*-(2-methoxyphenyl)- (**26**, C, 38%); *N*-(4-methoxyphenyl)- (**27**, C, 30%); *N*-(2-methoxybenzyl)- (**28**, C, 40%); *N*-(2-nitrobenzyl)- (**29**, A, 35%); *N*-(4-nitrobenzyl)- (**30**, A, 22%); *N*-(*tert*-butoxycarbonylmethyl)- (**31**, A, 66%). N-Substituted derivatives of monoaza-18-crown-6 (**32**, prepared from *N*-benzylmonoaza-18-crown-6 by hydrogenolysis in 39% overall yield) were synthesized for this study as described above: *N*-methyl- (**33**, A, 29%); *N*-benzyl- (**34**, C, 40%); *N*-(2-methoxyethyl)- (**35**, C, 53%); *N*-(3,6-dioxaheptyl)- (**36**, C, 50%); *N*-(3,6,9-trioxadecyl)- (**37**, A, 46%); *N*-(3,6,9,12-tetraoxatridecyl)- (**38**, A, 18%); *N*-(3,6,9,12,15-pentaoxahexadecyl)- (**39**, A, 15%); *N*-(3,6,9,12,15,18,21,24-penteicosyl)- (**40**, A, 60%); *N*-(2-methoxyphenyl)- (**41**, C, 41%). The 12-, 15-, and 18-membered-ring nitrogen-pivot lariat ethers bind a variety of cations, and data are presented for ammonium and sodium cations. Studies involving ammonium cation binding show that the interaction of ring and sidearm with the cation is intramolecular in methanol solution. X-ray crystal structure evidence confirms this for the solid state in the complex **35**·KI. Sodium cation binding data demonstrate intramolecularity as well. The strongest binding for sodium occurs when six oxygens are present in the lariat ether regardless of ring size. This suggests that a flexible macrocycle is directed by the cation to envelop and solvate in the geometry most appropriate for the cation and not for the macrocycle. An estimate of strength is made for the N–H–O or N–H–N interaction in ammonium ion complexes. Some observations concerning these structures as valinomycin models are also made.

Valinomycin,[1] a naturally occurring ionophore, is remarkable for several properties. First, it is a 36-membered ring which seems physically too large to effectively accommodate K^+ in its cavity. Nevertheless, it is highly selective for K^+ over Li^+, Na^+, or Ca^{2+}.[2] It is a depsipeptide and one might expect the six polar amide donors rather than the six ester carbonyl groups to bind the alkali metal cation. X-ray crystal structure analysis shows that instead it is the six ester carbonyl groups which bind K^+ in the macrocycle's cavity.[3] This apparent contradiction of expectations based upon donor group basicities or dipole moments can be understood in conformational terms. The six amide residues hydrogen bond about the perimeter of uncomplexed valinomycin's "tennis ball seam" conformation.[4] Valinomycin's ability to function as an ionophore can be understood in terms of its cation-enveloping conformation and its lipophilic surface. The large number of D-amino acids present in the structure pose an interesting question, but can be understood in terms of molecular dynamics (see below).



Valinomycin

Several attempts have been made to model valinomycin activity by using synthetic macrocycles. Cryptands offer a bound cation a three-dimensional donor group array similar to that found in valinomycin. While this affords a cation a high homogeneous stability (binding) constant ($K_S = k_{complex}/k_{decomplex}$), these compounds lack the binding dynamics (i.e., forward and reverse cation binding rates are slow) necessary to realistically model the natural ionophore.[5] Simple, monocyclic crown ether esters (cyclic mono- or dilactones) have been studied in this context as well.[6] The latter compounds are not the best valinomycin models since many of the ring sizes studied have been too small to permit the ester carbonyl groups to turn inward.[7] As a result, cation binding by the dilactone analogue of 18-crown-6 and 18-crown-6 itself showed

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†Dedicated to Professor Donald J. Cram on the occasion of his 65th birthday.

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(6) (a) Asay, R. E.; Bradshaw, J. S.; Nielsen, S. F.; Thompson, M. D.; Snow, J. W.; Masihdas, D. R. K.; Izatt, R. M.; Christensen, J. J. *J. Heterocycl. Chem.* **1977**, *14*, 85. (b) Izatt, R. M.; Lamb, J. D.; Maas, G. E.; Bradshaw, J. S.; Christensen, J. J. *J. Am. Chem. Soc.* **1977**, *99*, 2365.
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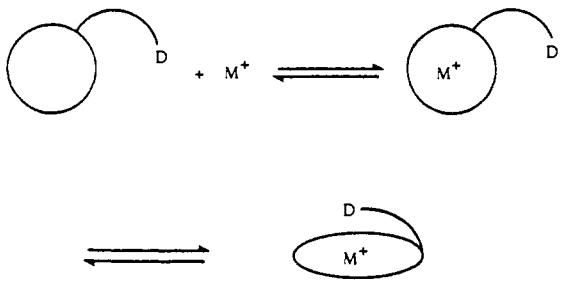
Scheme I



similar affinities for K^+ and other cations.[8]

Our approach to modeling valinomycin was to use a monocyclic crown ether to enforce what we believed was "hole-size" selectivity on the system and then attach one or more sidearms bearing neutral donor groups. Charged donor groups were avoided because they are not present in valinomycin, although other ionophores contain them.[9] It was expected that such a compound would have the rapid binding kinetics observed for valinomycin and many monocyclic crown ethers.[5,10] Once bound in the macroring, the sidearm should provide a third dimension of solvation. Note that the process could be reversed (sidearm first, then macroring binding) but a primary cation–macroring interaction seems more likely on statistical grounds. The notion is illustrated in Scheme I.

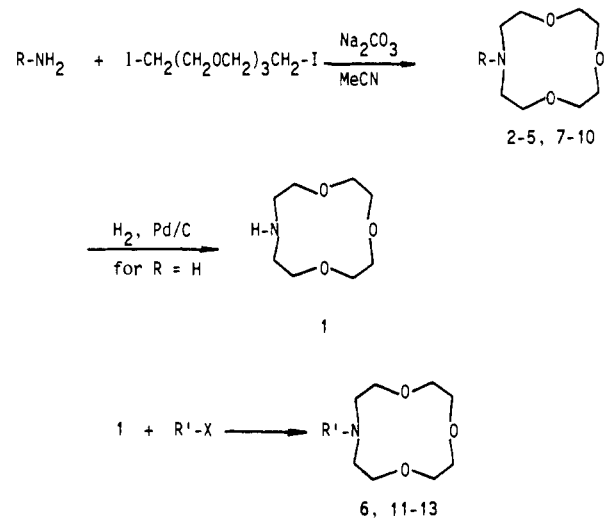
The compounds envisioned for these studies have both a macroring and a sidearm. The physical resemblance of CPK molecular models of these compounds to rope lassoes coupled with the concept of "roping and tying" a cation suggested the name "lariat ether." We report here the synthesis of nearly 50 lariat ethers. They represent rings containing from 12 to 18 members. All have a single arm attached at a nitrogen atom. We refer to this class of structures as nitrogen-pivot lariat ethers to distinguish them from the carbon-pivot series.[11]

Results and Discussion

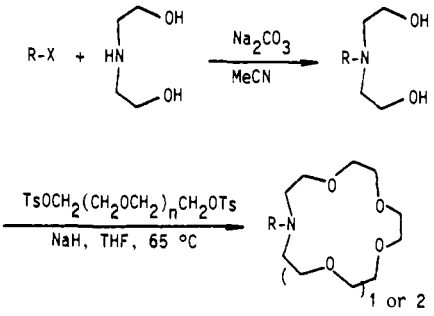
Syntheses. The nitrogen-pivot lariat ethers described here were prepared in three different ways. First, the substituted azacrown may be prepared directly from an amine by cyclization. This was the method of choice for 12-membered-ring systems. Second, the parent azacrown can be prepared, usually in a protected form. The most common protecting group in our work is the benzyl group which is removed by hydrogenolysis. The macrocycle having a free, 2° N–H can be alkylated to add the sidearm. Finally, diethanolamine can be alkylated and the substituted diol, $R–N(CH_2CH_2OH)_2$, cyclized in the usual fashion.[12] These approaches are discussed and exemplified below.

Cyclization To Form 12-Membered Rings. Twelve-membered-ring nitrogen-pivot lariat ethers were synthesized by the method of Calverley and Dale.[13] The method involves cyclo-bis-dialkylation of an amine with 1,11-diiodo-3,6,9-trioxaundecane in the presence of Na_2CO_3 in MeCN solution at reflux for 18 h. Yields for the compounds reported here ranged from 20 to 60%. Certain compounds did not form in high yield by this method or were more conveniently prepared by alkylation. In such cases, *N*-benzylmonoaza-12-crown-4 was prepared (53%), hydrogenolyzed (95%), and monoaza-12-crown-4 alkylated with the appropriate sidearm. In this way, the monoaza-12-crown-4 derivatives shown in Table I were prepared by alkylation (A) or cyclization (C): *N*-benzyl- (**2**, C, 53%); *N*-(2-methoxyphenyl)- (**3**, C, 26%); *N*-(4-methoxyphenyl)- (**4**, C, 40%); *N*-(2-methoxybenzyl)- (**5**, C, 47%); *N*-(2-nitrobenzyl)- (**6**, A, 86%); *N*-(3-hydroxypropyl)- (**7**, C, 56%); *N*-[2-(dimethylamino)ethyl]- (**8**, C, 21%); *N*-(3-oxabutyl)- (**9**, C, 60%); *N*-(3,6-dioxaheptyl)- (**10**, A, 66%); *N*-(3,6,9-trioxadecyl)- (**11**, A, 52%); *N*-(3,6,9,12-tetraoxatridecyl)- (**12**, A, 54%); and *N*-(11-allyloxy-3,6,9-trioxaundecyl)- (**13**, A, 50%).

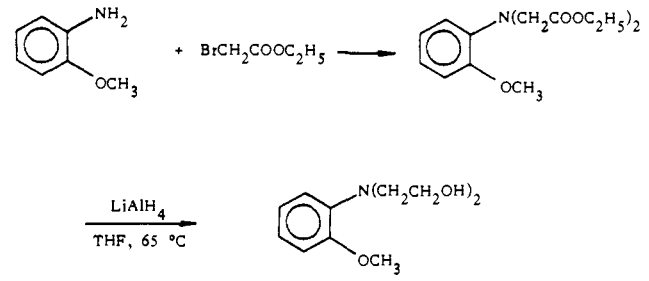
Scheme II



Scheme III



Scheme IV



Alkylation of Diethanolamines. Diethanolamine was treated with an alkylating agent in the presence of Na_2CO_3 at ca. 80 °C for a period of 24 h. After workup and fractional distillation, the N-substituted diethanolamines were obtained in 50–80% yields. When polyethyleneoxy-derived alkylating agents having more than two (CH_2CH_2O) units were used, it was difficult to remove residual salts from the reaction mixture which, in turn, made distillation very difficult. In such cases, the sidearm was added by alkylation of the preformed monoazacrown as shown in Scheme II, see above.

Alkylation of Primary Amines. In cases such as described above, or when R in $R–N(CH_2CH_2OH)_2$ is an aromatic ring, alkylation of diethanolamine is impractical. An alternative is to treat the primary amine or aniline with ethyl bromoacetate (2.2 equiv, steam bath) in the presence of Na_2CO_3. After the mixture was stirred

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Table I. Ammonium and Sodium Binding Constants for 12-, 15-, and 18-Membered-Ring Nitrogen-Pivot Lariat Ethers

compd no.	sidearm	method[a]	% yield	no. of oxygens	stability constants Na^+	stability constants NH_4^+
		12-Membered Rings				
1	H	B	95	3	*b*	ND
2	benzyl	C	53	3	2.08	ND
3	2-MeO-Ph	C	26	4	2.75	ND
4	4-MeO-Ph	C	40	4	1.38	ND
5	2-methoxybenzyl	C	47	4	2.49	ND
6	2-nitrobenzyl	A	86	5[c]	1.77	ND
7	MMM-OH	C	56	4	2.35	ND
8	E-NMe_2	C	21	3	ND	ND
9	EOMe	C	60	4	3.17	ND
10	EOEOMe	A	66	5	3.60	ND
11	EOEOEOMe	A	52	6	3.97	ND
12	EOEOEOEOMe	A	54	7	3.76	ND
13	EOEOEOEOallyl	A	50	7	3.97	ND
		15-Membered Rings				
14	H	B	98	4	1.70	2.99
15	Me	A	37	4	3.39	3.22
16	allyl	A	61	4	3.14	ND
17	*n*-Bu	A	65	4	3.02	ND
18	*t*-Bu	C	28	4	2.15	ND
19	benzyl	C	46	4	2.77	ND
20	EOMe	C	55	5	3.88	3.14
21	EOEOMe	C	47	6	4.54	3.19
22	EOEOEOMe	A	34	7	4.32	3.38
23	EOEOEOEOMe	A	55	8	4.15	3.48
24	EOEOEOEOEOMe	A	78	9	4.19	3.49
25	EOEOEOEOEOEOEOEOMe	C	49	12	3.52	3.04
26	2-methoxyphenyl	C	38	5	3.86	ND
27	4-methoxyphenyl	C	30	5	2.12	ND
28	2-methoxybenzyl	C	40	5	3.54	ND
29	2-nitrobenzyl	A	35	6[c]	2.40 3.20[d]	ND
30	4-nitrobenzyl	A	22	6[c]	2.30 3.21[d]	ND
31	CH_2COO-*t*-Bu	A	66	6[c]	4.20	2.51
		18-Membered Rings				
32	H	B	98	5	2.69	ND
33	Me	A	29	5	3.93	4.08
34	benzyl	C	40	5	3.41	ND
35	EOMe	C	53	6	4.58	4.21
36	EOEOMe	C	50	7	4.33	4.75
37	EOEOEOMe	A	46	8	4.28	4.56
38	EOEOEOEOMe	A	18	9	4.27	4.40
39	EOEOEOEOEOMe	A	15	10	4.22	4.04
40	OEOEOEOEOEOEOEOEMe	A	60	13	3.44	3.58
41	2-methoxyphenyl	C	41	6	4.57	ND

[a] A stands for alkylation. B refers to hydrogenolysis of the corresponding *N*-benzyl derivative. C stands for cyclization. E stands for ethylene, i.e., $-CH_2-CH_2-$. M stands for methylene, i.e., $-CH_2-$. ND means not determined. [b] This compound forms ligand-to-cation complexes with sodium in the ratio NaL_2. [c] Not all of the oxygen atoms in the functional group are capable of interacting simultaneously with a ring-bound cation. [d] Value determined in MeCN solution by NMR methods.

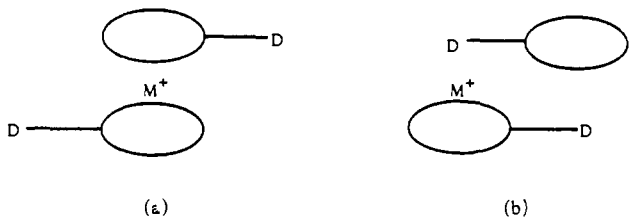
and heated for an additional 20 h followed by workup and fractional distillation, the pure diesters were obtained in 50–60% yield. The diesters were reduced ($LiAlH_4$/THF, 65 °C) to N-substituted diethanolamines in approximately 80% yield.

Cyclization To Form 15- and 18-Membered Rings. In each case, an N-substituted diethanolamine (described above) was dissolved in THF along with either triethylene glycol ditosylate (TrEGTs) or tetraethylene glycol ditosylate (TEGTs). The mixture was added dropwise to a refluxing THF solution containing NaH (2.1 equiv). The product was obtained by alumina chromatography followed by bulb-to-bulb distillation with a Kugelrohr apparatus. Cyclization yields were generally 30–50%. As in the 12-membered-ring case, above, certain compounds were more readily synthesized from the parent monoaza-15-crown-5 or -18-crown-6 compounds by alkylation. The monoaza-15-crown-5 derivatives prepared for this study were the following: *N*-methyl (**15**, A, 37%); *N*-allyl (**16**, C, 61%); *N*-(*n*-butyl)- (**17**, C, 65%); *N*-(*tert*-butyl)- (**18**, C, 28%); *N*-benzyl (**19**, C, 46%); *N*-(2-methoxyethyl)- (**20**, C, 69%); *N*-(3,6-dioxaheptyl)- (**21**, C, 47%); *N*-(3,6,9-trioxadecyl)- (**22**, A, 34%); *N*-(3,6,9,12-tetraoxatridecyl)- (**23**, A, 55%); *N*-(3,6,9,12,15-pentaoxahexadecyl)- (**24**, A, 78%); *N*-(3,6,9,12,15,18,21,24-penteicosyl)- (**25**, C, 49%); *N*-(2-methoxyphenyl)- (**26**, C, 38%); *N*-(4-methoxyphenyl)- (**27**, C, 30%); *N*-(2-methoxybenzyl)- (**28**, C, 40%); *N*-(2-nitrobenzyl)- (**29**, A, 35%); *N*-(4-nitrobenzyl)- (**30**, A, 22%); *N*-(*tert*-butoxycarbonylmethyl)- (**31**, A, 66%).

The derivatives of monoaza-18-crown-6 synthesized for this study were the following: *N*-methyl- (**33**, A, 29%); *N*-benzyl- (**34**, C, 40%); *N*-(2-methoxyethyl)- (**35**, C, 53%); *N*-(3,6-dioxaheptyl)- (**36**, C, 50%); *N*-(3,6,9-trioxadecyl)- (**37**, A, 46%); *N*-(3,6,9,12-tetraoxatridecyl)- (**38**, A, 18%); *N*-(3,6,9,12,15-pentaoxahexadecyl)- (**39**, A, 15%); *N*-(3,6,9,12,15,18,21,24-penteicosyl)- (**40**, A, 60%); *N*-(2-methoxyphenyl)- (**41**, C, 41%).

Cyclization Yields and the Template Effect. The nitrogen-pivot lariat ethers can be classified into three groups based on the cyclization yields. Compounds which have sidearms incapable for geometric reasons of coordinating a cation or lacking a donor group on the sidearm were generally formed in 30% yield. Those compounds having relatively rigid aryl sidearms containing ether donor groups cyclized in approximately 40% yield. Lariat ethers having donor groups on flexible sidearms afforded product in 50% or greater yield.

Scheme V



Cyclization of 15-crown-5 is reported to occur in yields ranging from 14% to 50% depending on conditions.[14] When only macroring (no sidearm or no appropriate sidearm donor group) donors are available for templating, cyclization yields are nearly the same. Higher yields are realized for those compounds capable of forming more highly organized transition states. Although questions about the template effect have been raised, it seems clear that some additional organization is occurring during cyclization. The higher cation binding constants for those lariat ethers affording higher cyclization yields affirms a template effect. The variation in alkylation yields often reflects the difficulty in working up and purifying particular samples, and no trends are discerned in the yield variations.

Homogeneous Stability Constants. An important goal of the present study was to understand how structural variations affect the ability of these species to bind cations. According to the notions upon which design was based, binding selectivities were expected to reflect ring sizes. In addition, the number, identities, and geometric disposition of sidearm donor groups was expected to affect cation binding.

Sodium, potassium, and ammonium cation binding was determined with cation-selective electrodes according to the method of Frensdorff.[15] A sodium-specific glass electrode was used for the determination of Na^+, and a univalent cation electrode was used for the NH_4^+ ion determinations. The procedure was as follows. The cation, as its chloride, was dissolved in anhydrous methanol and its conductivity determined with use of a sensitive millivolt meter (Orion Ionalyzer, Model 701). The ligand was added, the solution stirred and allowed to equilibrate, and a second voltage reading taken. The conductivity difference was converted to an equilibrium binding constant by using the equations developed by Frensdorff.[15] The homogeneous binding constants reported here are the average of at least two independent determinations.

Intramolecularity of the Sidearm–Cation Interaction. Although the lariat ethers were designed so that the sidearm donor group(s) would be involved intramolecularly with a ring-bound cation, the possibility clearly existed that dimer complexes might form. One possible dimer complex is the well-known "sandwich" structure in which a cation is bound between two macrorings. This is exemplified by the $(12\text{-crown-4})_2{\cdot}Na^+$ and $(12\text{-crown-4})_2{\cdot}Ag^+$ complexes whose X-ray crystal structures are known.[16] Indeed, unsubstituted monoaza-12-crown-4 also forms a sandwich complex with Na^+.[17] Another likely complex is that in which the sidearm donor(s) of one lariat ether would interact with a cation bound in the macroring of another lariat ether. The two possibilities are illustrated schematically in Scheme V.

Intramolecularity of complexation was demonstrated by determining homogeneous, equilibrium stability constants, K_S, for

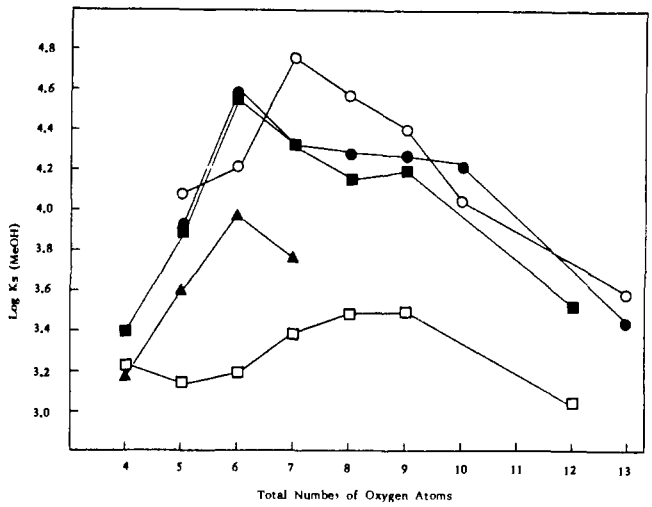
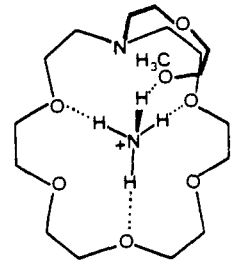


Figure 1. Plot of homogeneous stability constants (log K_S, in anhydrous methanol) vs. total number of oxygen atoms in each ligand. Open symbols: ammonium ion binding. Filled symbols: sodium ion binding. Triangles: monoaza-12-crown-4 derivatives. Squares: monoaza-15-crown-5 derivatives. Circles: monoaza-18-crown-6 derivatives.

the 15- and 18-membered-ring N-pivot lariat ethers having $-(CH_2{-}CH_2{-}O)_n{-}CH_3$ substituents on nitrogen. Binding constants were measured for compounds **15**, **20**, **21**, **22**, **23**, **24**, **25**, **33**, **35**, **36**, **37**, **38**, **39**, and **40** with NH_4^+ and Na^+ cations in anhydrous methanol solution. Ammonium cation differs from sodium by being tetrahedral rather than spherical. It binds to donor groups by discrete hydrogen bonds. Ammonium is a "directional" cation while Na^+ is not.

An examination of CPK molecular models suggested that only two of the NH_4^+ ion's hydrogen bonds could be accommodated by a 15-membered ring. Binding by these lariats was expected to be weak but gradually increasing as the sidearm length increased. It was assumed that intramolecular sidearm participation would enhance ammonium cation binding at longer sidearm lengths and this would be evidence for intramolecular participation. Both CPK molecular models and X-ray crystal structures show that with NH_4^+, 18-membered rings typically form three hydrogen bonds to alternating macroring donor atoms.[18] The fourth hydrogen on ammonium ion is perpendicular to the macroring plane. Models suggested that the 2-methoxyethyl sidearm of **35** was too short to hydrogen bond the perpendicular N–H, but the second sidearm oxygen in **36** was appropriately placed to form such a hydrogen bond.



The overall predictions for intramolecular sidearm involvement in ammonium cation binding were, therefore, as follows. Binding by 15-membered rings should be generally weak, but it should gradually increase with increasing sidearm length. Ammonium cation binding by the 18-membered-ring compounds was expected to be stronger than that for the 15's, and a plot of log K_S vs. the total number of oxygen atoms in the 18-membered-ring compounds should peak at seven oxygens. Confirmation of these predictions is found in the graph shown in Figure 1 (open circles and squares). Thus, for methanol solution and ammonium cation, intramolecular

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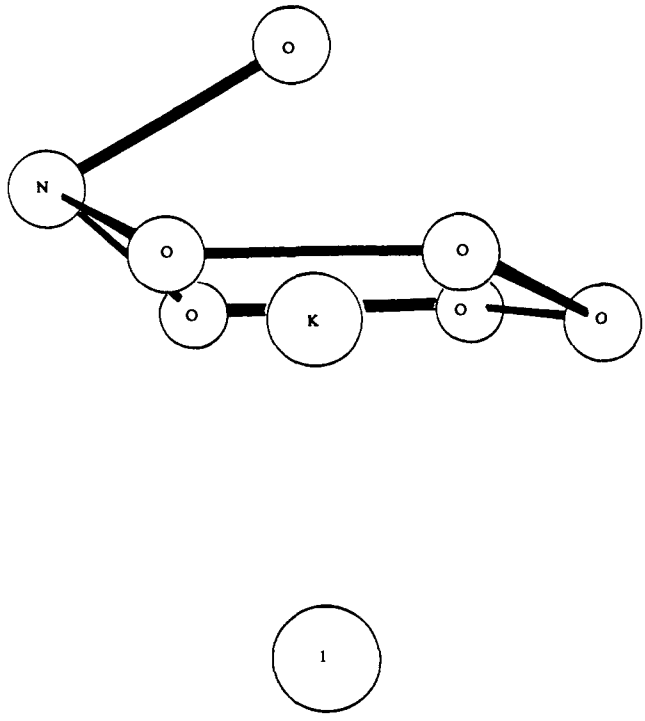

Figure 2. Framework structural diagram of the complex between KI and *N*-(2-methoxyethyl)monoaza-18-crown-6 (**35**) (*see* ref 20).

participation in complexation by the sidearm is confirmed.

A plot similar to that described above was prepared for log $K_S(Na^+)$ vs. total oxygens in the 12-, 15-, or 18-membered-ring ligands. A clear peak at six oxygens for all three ring systems suggested two things. First, it seemed that the desirable octahedral array about sodium cation was being provided by either set of ligands. This, in turn, suggested intramolecularity. Second, the indifference of log K_S to ring size for these systems showed clearly that the much discussed "hole-size relationship" does not apply to flexible macrocycles. We have recently reported a more detailed and general discussion of this latter point.[19]

Finally, intramolecularity was demonstrated for the solid phase. We have reported single-crystal X-ray analysis of the complex between *N*-(2-methoxyethyl)monoaza-18-crown-6 and KI.[20] In this case, the macroring adopts the well-known D_{3d} conformation and the sidearm reaches over and oxygen solvates potassium cation from above. The arm is a little too short for oxygen to be perpendicular to the macroring plane and the I^- counterion is offset on the bottom by a nearly equal amount. Potassium is thus surrounded by a distorted hexagonal bipyramid of donor atoms.

Trends in Sodium and Ammonium Cation Binding. Sodium cation binding by N-substituted monoaza-12-crown-4,[21] -15-crown-5, and -18-crown-6 lariat ethers is plotted (filled triangles, squares, and circles, respectively) in Figure 1. The trend in all three cases is identical: Poor binding when only four or five oxygen atoms are present but a clear peak at six oxygen atoms. It is quite striking that the sodium cation binding constants for the 15- and 18-membered rings are superimposable (within experimental error) on each other. Binding is generally lower for the 12-membered rings, but for the compounds having from four to seven oxygen atoms, the trend exactly parallels that noted above. This suggests an ability of these lariat ethers to adjust their binding arrays in accord with the cation's requirements.

The binding for seven, eight, and nine oxygen lariats having 15- or 18-membered rings appears to be level. One can imagine that if the first oxygen in the sidearm can provide solvation to a ring-bound cation, two oxygens could afford bifurcated solvation. A plateau in the graph can thus be rationalized. On the other hand, using the stability constant values for the range 6–13 oxygens, the trend can be rationalized, using linear regression analysis with a high degree of confidence, as a straight line having a negative slope. It seems to us that the peak in binding is more important than whether the apparent plateau results from experimental error and we have not pursued this point further.

As in previous studies, we note that when no donor is present on the sidearm, cation binding is low. This is clear in compounds **14–19** and in **32–34**. An especially interesting point is that binding by **17** and **20** differs by nearly a power of 10. Both are 15-membered-ring compounds and both have four-atom side chains. The key difference is the presence of an oxygen donor atom in **20**. This is further evidence for intramolecularity. In addition, when the donor group does not have the appropriate geometry for intramolecular interaction with a ring-bound cation, binding is also reduced. 2-Methoxyphenylmonoaza-15-crown-5 (**26**) has a Na^+ binding constant of 3.86. The binding constant for the corresponding para isomer is only 2.12. It should be noted that when a donor, such as nitro, is especially weak, binding is low irrespective of geometry (see **29** vs. **30**).

Of all the compounds reported here, the only realistic valinomycin model is *N*-(*tert*-butoxycarbonylmethyl)monoaza-15-crown-5 (**31**). Its carbonyl donor group interacts strongly with ring-bound sodium as shown by its binding constant and the crystal structure of its ethyl ester analogue.[22] The geometric requirements for NH_4^+ binding are again apparent from the binding constants for this ester lariat: $K_S(Na^+) = 4.20$; $K_S(NH_4^+) = 2.51$.

We have noted above the characteristics of ammonium cation binding by the 15- and 18-membered-ring compounds.[23] It is also interesting to note that the binding peak for the 18-membered-ring lariat ethers (log K_S) is 4.8. Four hydrogen bonds should be involved in each complex so one N–H–O interaction is estimated to be worth a log K_S value of 1.2. Using this extremely simple approach, we might predict that peak binding for the 15-membered rings, which models suggest should involve only three hydrogen bonds, will be observed at log $K_S = 3.6$. Peak ammonium ion binding is observed in the 15-membered-ring series for **23** and **24** at about 3.5.

We have not determined ammonium ion binding constants for the 12-membered rings since models suggest that not more than two hydrogen bonds could conveniently form at any given time. The prediction is thus that 12-membered ring lariats should have binding constants in the range 1–3. This presumption seems correct since our simple model above predicts ammonium ion binding of 1.2 log units per hydrogen bond and we have previously found that 12-crown-4 has a binding constant of 1.3.[19] Indeed, the model predicts binding of ammonium by 15-crown-5 and 18-crown-6 to be 2.4 and 3.6. The actual values are 3.03 and 4.14, respectively. Larger ring compounds 21-crown-7 and 24-crown-8 might be better models since they have more degrees of freedom and do not enjoy the especially favorable D_{3d} arrangement possible for 18-crown-6. Their binding constants are 3.27 and 2.63, respectively.[19]

Diminished Binding in Long-Sidearm Lariat Ethers. A phenomenon we have consistently noted in our binding studies (see Figure 1) is the fall off in log K_S with long sidearms (approximately eight ethyleneoxy units). Although we have no evidence which allows us to explain this, it seems reasonable to assume that hydrogen bonding by solvent is playing a role. The long sidearms have many hydrogen bond acceptor sites, and their conformational and translational mobility should both be reduced. We believe that ^{13}C NMR relaxation time measurements[24] made on the methyl groups may be informative, and we will report the results of these studies when they are complete.

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Flexibility and Selectivity. For a molecule like valinomycin to be effective in cation transport, it must retain binding dynamics. Transport across a membrane involves three steps. First, the cation must be bound in the source phase. Second, it must translocate the cation from source to receiving phase through the membrane. Finally, it must release the cation. Compounds which fail to release the cation at an appreciable rate will be ineffective as ionophores. Another way of saying this is that if $k_{decomplex}$ is small, the ligand is not a dynamic cation binder.

The binding studies reported here demonstrate that the nitrogen-pivot lariat ethers effectively mimic valinomycin in terms of flexibility. We have previously[16] shown that flexible crowns select potassium cation from the group sodium, potassium, calcium, and ammonium. If valinomycin's K^+ selectivity is due primarily to its flexibility, is there any special structural feature which is important for this? Indeed, there is. In order for valinomycin to fold over into the "tennis-ball-seam" arrangement, it must have bends in the depsipeptide chain. Bends in peptide chains often result from the presence of proline which would reduce flexibility in the ionophore. It thus appears that nature incorporates alternating D- and L-amino acids to permit such bends while retaining conformational flexibility.

Summary

Nitrogen-pivot lariat ethers can be synthesized by cyclization of an amine or appropriately substituted diol. They may also be prepared by alkylation of the parent monoaza-12-crown-4, -15-crown-5, or -18-crown-6 compound. These compounds bind a variety of cations, and data are presented for ammonium and sodium cations. Ammonium cation binding data show that the interaction of ring and sidearm with the cation is intramolecular in methanol solution. X-ray crystal structure evidence shows that the sidearm is intramolecularly involved in the complex of **35** with KI. Sodium cation binding data demonstrate intramolecularity as well. More important, however, is the observation that peak binding for sodium occurs when six oxygens are present in the lariat ether regardless of ring size. This suggests that a flexible macrocycle is directed by the cation to envelop and solvate in the geometry most appropriate for the cation and not for the macrocycle. Ammonium ion binding is more sterically demanding and involves hydrogen bonds. As a result, these trends are not apparent, although a simple analysis reveals that each N–H–O hydrogen bond is worth about 1.2 log units in binding under these conditions despite differences in ring size and arm length.

Experimental Section

Melting points (Thomas-Hoover apparatus, open capillaries) are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 281 spectrophotometer as neat samples unless otherwise noted. Spectral bands are reported in cm^{-1} and calibrated against the 1601-cm^{-1} band of polystyrene. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at 60 MHz as ca. 15 wt % solutions in $CDCl_3$ unless otherwise specified. Chemical shifts in parts per million (δ) downfield from internal Me_4Si are reported in the following order: chemical shift, spin multiplicity (br = broad; s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet), and integration. Proton-decoupled ^{13}C NMR spectra were recorded at 25.2 MHz on a Varian Associates XL 100 instrument in $CDCl_3$. The chemical shifts are reported in parts per million (δ) downfield from Me_4Si. Solvent provided the internal deuterium lock signal. Gas chromatographic (GLC) analyses were conducted on a Varian Model 920 analytical gas chromatograph (TC detector), having a column 5 ft × 0.25 in, 1.5% OV-101 on 100/120 mesh, Chromosorb G. Helium (60 mL/min) was the carrier gas. Combustion analyses (C, H, N) were performed at the University of Maryland.

All reagents were the best grade commercially available and were used without further purification unless otherwise specified. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ or sodium-benzophenone and benzene and dioxane were dried by distillation from sodium-benzophenone under a dry N_2 atmosphere immediately before use. *N,N*-Dimethylformamide (DMF) was dried by distillation from CaO prior to use. Oven temperatures are given for bulb-to-bulb distillations conducted in a Kugelrohr apparatus. Preparative chromatography columns were packed with MCB activated Al_2O_3 (80–325 mesh, chromatographic grade, AX-611) or Fluka silica gel 60 (70–230 mesh, chromatographic grade). Precoated sheets (aluminum oxide 60 F-254 neutral-Type E or silica gel 60 F-254) 0.2 mm thick were used for TLC analyses.

General Procedure for the Preparation of 12-Membered-Ring Nitrogen-Pivot Lariat Ethers by Cyclization of Primary Amines, Procedure A. The N-substituted monoaza-12-crown-4 lariat ethers were prepared according to the procedure of Dale.[13b] A stirred solution of 1,11-diiodo-3,6,9-trioxaundecane (4.3 g, 0.01 mol) and the primary amine (0.011 mol) in MeCN (150 mL) containing anhydrous Na_2CO_3 (5.3 g, 0.05 mol) was heated to reflux under an atmosphere of N_2 for 18 h. The mixture was then allowed to cool and was filtered. The filtrate was concentrated. The residue was stirred in CH_2Cl_2 (150 mL) and filtered to remove the residual salts. The solvent was removed in vacuo. The pure product was obtained after chromatography (Al_2O_3) and molecular distillation in a Kugelrohr apparatus.

General Procedure for the Alkylation of Monoaza-12-crown-4, Procedure B. The parent monoaza crown (1.0 g, 0.006 mol) was dissolved in MeCN (25 mL) containing anhydrous Na_2CO_3 (0.7 g, 0.007 mol) and heated to reflux under an atmosphere of N_2. A solution of the incipient sidearm as its tosylate or chloride (0.006 mol) in MeCN (10 mL) was then added dropwise. Reflux was continued for 20–24 h, the mixture was cooled and filtered, and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 or $CHCl_3$ (30 mL) and was washed with H_2O (30 mL), brine (30 mL), and again with H_2O (30 mL). The organic layer was dried (Na_2SO_4 or $MgSO_4$) and concentrated in vacuo to yield the crude N-substituted monoaza crown ether. The pure crown was obtained after column chromatography (Al_2O_3) and subsequent Kugelrohr distillation.

Preparation of Monoaza-12-crown-4 (1). **1** was obtained by hydrogenolysis (H_2, 10% Pd-C, absolute EtOH) of the corresponding *N*-benzylmonoaza-12-crown-4 (**2**).

Preparation of *N*-Benzylmonoaza-12-crown-4 (2). *N*-Benzylmonoaza-12-crown-4 was prepared by the method of Dale[13b] except that the crown compound was isolated by chromatography over a column of Al_2O_3 (10% EtOAc/hexane). Pure **2** was obtained after Kugelrohr distillation in 54% yield, bp 122–125 °C (0.05 torr) (lit.[13b] bp 140–143 °C (0.05 torr)), and had properties identical with those previously reported.

Preparation of *N*-(2-Methoxyphenyl)monoaza-12-crown-4 (3). Compound **3** was prepared according to procedure A. The amine used was 2-methoxyaniline (1.4 g, 0.011 mol). Pure crown was isolated in 26% yield after chromatography (Al_2O_3, 6% EtOAc/hexane) and molecular distillation, bp 130–135 °C (0.05 torr): ^1H NMR δ 3.30 (m, 4 H), 3.67 (m, 15 H); 6.90 (m, 4 H); IR 3060, 2850, 1595, 1500, 1460, 1360, 1240, 1130, 1024, 975, 930, 910, 830, 745 cm^{-1}. Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.02; H, 8.26; N, 4.98. Found: C, 63.62; H, 8.52; N, 4.93.

Preparation of *N*-(4-Methoxyphenyl)monoaza-12-crown-4 (4). Compound **4** was prepared as described in procedure A from 4-methoxyaniline (1.4 g, 0.011 mol). Pure **4** was obtained in 40% yield after chromatography (Al_2O_3, 1% 2-PrOH/hexane) and molecular distillation, bp 142–143 °C (0.03 torr): ^1H NMR δ 3.70 (m, 19 H), 6.77 (m, 4 H); IR 3060, 2850, 1595, 1500, 1460, 1360, 1250, 1130, 1020, 975, 930, 910, 830, 750 cm^{-1}. Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.02; H, 8.26; N, 4.98. Found: C, 64.41; H, 8.06; N, 4.88.

Preparation of *N*-(2-Methoxybenzyl)monoaza-12-crown-4 (5). *N*-(2-Methoxybenzyl)monoaza-12-crown-4 was isolated in 47% yield from the cyclization reaction described in procedure A with (2-methoxybenzyl)amine (1.5 g, 0.011 mol). The crude mixture was chromatographed over a column of Al_2O_3 (1% 2-PrOH/hexane) and distilled to give pure **5**, bp 150–153 °C (0.03 torr): ^1H NMR 2.73 (t, 4 H), 3.67 (m, 17 H), 7.10 (m, 4 H); IR 2903, 2340, 1600, 1590, 1490, 1450, 1350, 1230, 1120, 1050, 1020, 910, 830, 750, 700 cm^{-1}. Anal. Calcd for $C_{16}H_{25}NO_4$: C, 65.05; H, 8.55; N, 4.74. Found: C, 65.35; H, 8.80; N, 4.79.

Preparation of *N*-(2-Nitrobenzyl)monoaza-12-crown-4 (6). Compound **6** was prepared according to procedure B with 2-nitrobenzyl chloride (1.0 g, 0.006 mol) as the alkylating agent. The product was isolated as a solid. Recrystallization of the solid from 50% MeOH–H_2O gave **6** as shiny needles (1.6 g, 86%), mp 37–38 °C: ^1H NMR δ 7.68 (m, 4 H), 3.95 (s, 2 H); 3.67 (m, 12 H); 2.73 (t, 4 H); IR 3010, 2090, 2860, 1620 (w), 1580 (w), 1530, 1450, 1360, 1300, 1130, 1060, 920, 860 cm^{-1}. Anal. Calcd for $C_{15}H_{22}N_2O_5$: C, 58.04; H, 7.16; N, 9.03. Found: C, 57.98; H, 7.25; N, 8.94.

Preparation of *N*-1-(3-Hydroxypropyl)monoaza-12-crown-4 (7). Compound **7** was prepared as described in procedure A with 3-amino-1-propanol (0.8g, 0.011 mol) as the amine. The crude product was chromatographed over a column of Al_2O_3 (20% 2-PrOH/hexane). Pure **7** was obtained in 56% yield after distillation, bp 112–115 °C (0.1 torr): ^1H NMR δ 1.67 (m, 2 H), 2.67 (t, 6 H), 3.70 (m, 14 H), 4.42 (s, 1 H); IR 3380, 2920, 2840, 1450, 1360, 1300, 1250, 1120, 1090, 1050, 910, 840 cm^{-1}. Anal. Calcd for $C_{11}H_{23}NO_4$: C, 56.61; H, 9.96; N, 6.00. Found: C, 56.38; H, 10.24; N, 6.13.

Preparation of *N*-1-[2-(Dimethylamino)ethyl]monoaza-12-crown-4 (8). Compound **8** was prepared according to procedure A from *N,N*-di-

methylethylenediamine in 21% yield, bp 85–95 °C (0.05 torr): ^{1}H NMR δ 2.13 (s, 6 H), 2.54 (m, 8 H), 3.60 (m, 12 H); IR 2940, 2850, 1460, 1360, 1290, 1260, 1130(s), 1040, 920, 860, 840 cm^{-1}. Anal. Calcd for $C_{12}H_{26}N_2O_3$: C, 58.51; H, 10.64; N, 11.37. Found: C, 58.57; H, 10.96; N, 11.12.

Preparation of *N*-1-(3-Oxabutyl)monoaza-12-crown-4 (9). Compound **9** was prepared according to the procedure of Dale[13b] except that the crown was isolated as a solid. Recrystallization of the resulting solid (THF) gave 2.3 g of **9** as its NaI complex (mp 202–203 °C): ^{1}H NMR δ 2.63 (m, 6 H), 3.53 (s, 3 H), 3.70 (m, 14 H); IR (Nujol) 2860, 2820, 1450, 1360, 1290, 1250, 1230, 1150, 1130, 1110, 1090, 1070, 1030, 1010, 855, 835 cm^{-1}. Anal. Calcd for $C_{11}H_{23}NO_4NaI$: C, 34.47; H, 4.06; N, 3.66. Found: C, 34.56; H, 6.20; N, 3.57. The solid material was dissolved in H_2O (150 mL) and lariat ether **9** was extracted with CH_2Cl_2 (4 × 150 mL). The combined organic layers were reduced to a minimum volume. The pure product was obtained after distillation (Kugelrohr, 1.4 g, 60%) as a colorless oil; bp 70–72 °C (0.05 torr) [lit.[13b] bp 100–102 °C (0.005 torr)]. Anal. Calcd for $C_{11}H_{23}NO_4$: C, 56.61; H, 9.95; N, 6.00. Found: C, 56.50; H, 10.10; N, 5.99.

Preparation of *N*-1-(3,6-Dioxaheptyl)monoaza-12-crown-4 (10). Compound **10** was prepared as described in procedure B with 3,6-dioxaheptyl tosylate (1.6 g, 0.006 mol). Chromatography of the crude product (Al_2O_3, 50% EtOAc/hexane) and distillation (Kugelrohr) gave pure **10** (1.1 g, 66%) as a colorless oil: bp 96–101 °C (0.7 torr); ^{1}H NMR δ 2.70 (t, 6 H), 3.30 (s, 3 H), 3.60 (m, 18 H); IR 2850, 1455, 1360, 1310, 1300, 1250, 1130, 1025, 970, 930, 840 cm^{-1}. Anal. Calcd for $C_{13}H_{27}NO_5$: C, 56.28; H, 9.83; N, 5.05. Found: C, 56.34; H, 9.90; N, 5.25.

Preparation of *N*-1-(3,6,9-Trioxadecyl)monoaza-12-crown-4 (11). Compound **11** was prepared as described in procedure B with 3,6,9-trioxadecyl tosylate (1.9 g, 0.006 mol) as the alkylating agent. Chromatography of the crude product (Al_2O_3, 50% EtOAc/hexane) and molecular distillation afforded the pure crown (1.0 g, 52%), bp 155–160 °C (0.03 torr): ^{1}H NMR δ 2.73 (t, 6 H), 3.35 (s, 3 H), 3.62 (m, 22 H); IR 2906, 1450, 1350, 1300, 1290, 1280, 1240, 1190, 1120, 1030, 970, 960, 920, 830 cm^{-1}. Anal. Calcd for $C_{15}H_{31}NO_6$: C, 56.04; H, 9.74; N, 4.36. Found: C, 56.24; H, 9.89; N, 4.21.

Preparation of *N*-1-(3,6,9,12-Tetraoxatridecyl)monoaza-12-crown-4 (12). Compound **12** was prepared according to procedure B described with 3,6,9,12-tetraoxatridecyl tosylate (2.2 g, 0.006 mol). Chromatography of the crude product (Al_2O_3, 50% EtOAc/hexane) and molecular distillation yielded 54% of the pure crown, bp 138–141 °C (0.05 torr): ^{1}H NMR δ 2.73 (t, 6 H), 3.33 (s, 3 H), 3.67 (m, 26 H); IR 2900, 1460, 1360, 1300, 1290, 1250, 1200, 1120, 1030, 920, 840 cm^{-1}. Anal. Calcd for $C_{17}H_{35}NO_7$: C, 55.86; H, 9.67; N, 3.83. Found: C, 5.50; H, 9.90; N, 3.70.

Preparation of *N*-1-(11-(Allyloxy)-3,6,9-trioxaundecyl)monoaza-12-crown-4 (13). Compound **13** was prepared as described in procedure B with 11-(allyloxy)-3,6,9-trioxaundecyl tosylate (2.3 g, 0.006 mol). After chromatography (Al_2O_3, 50% EtOAc/hexane) and molecular distillation, the pure crown was obtained in 51% yield, bp 160–165 °C (0.03 torr): ^{1}H NMR δ 2.75 (t, 6 H), 3.87 (m, 28 H), 5.52 (m, 3 H); IR 2840, 1680, 1440, 1350, 1290, 1240, 1110, 920, 830 cm^{-1}. Anal. Calcd for $C_{19}H_{37}NO_7$: C, 58.28; H, 9.54; N, 3.58. Found: C, 58.01; H, 9.80; N, 3.46.

General Procedure for the Preparation of Nitrogen-Pivot Lariat Ethers from Diethanolamine, Procedure C. (a) Preparation of $CH_3(OCH_2CH_2)_nOTs$. A slurry of *p*-TsCl (205 g, 1.1 mol) and pyridine (200 mL) was mechanically stirred in a three-necked, N_2-flushed flask. The temperature was maintained at 5 °C (ice-water bath), while the desired ethylene glycol monomethyl ether (1 mol) was added slowly from an addition funnel. After addition was complete, the mixture was stirred for 15 min. The mixture was poured into ice water (900 mL) and washed with CH_2Cl_2 (900 mL). The organic layer was washed with ice-cold 6 N HCl (3 × 500 mL) and reduced to minimum volume by evaporation in vacuo. Tosylates thus prepared were at least 90% pure and were used as obtained.

(b) Alkylation of Diethanolamine. Diethanolamine (52.5 g, 0.5 mol) and Na_2CO_3 (29 g, 0.275 mol) were placed in a three-necked, N_2-flushed flask. This mixture was held at ca. 80 °C while the tosylate (0.55 mol) was added over 2 h. The reaction mixture was stirred vigorously (80 °C) for 20 h and cooled to room temperature, CH_2Cl_2 (100 mL) was added, and the salts were filtered and then washed with additional CH_2Cl_2 (150 mL). The CH_2Cl_2 was evaporated in vacuo. The crude alkylated diethanolamine thus obtained was vacuum distilled through a 10-cm Vigreux column.

(c) Cyclization. Formation of the lariat ether was accomplished as follows. A 1-L three-necked, N_2-flushed flask was purged with N_2. NaH (50% in oil, 5 g, 0.21 mol) was added to the reaction vessel and washed with hexanes (4 × 100 mL). THF (250 mL) was then added to the flask. This suspension was heated to reflux with vigorous stirring. A solution of the *N*-alkoxyethylated diethanolamine (0.1 mol) and either triethylene glycol dimesylate (TrEGMs) or tetraethylene glycol dimesylate (TEGMs) (0.1 mol) in THF (100 mL) was added dropwise. Reflux was continued for 20 h. The reaction mixture was cooled and quenched with H_2O, and the solvent was evaporated in vacuo. The residue was dissolved in H_2O (400 mL) which was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were reduced to a minimum volume. The pure product was obtained as a colorless oil after chromatography (Al_2O_3) and Kugelrohr distillation.

General Procedure for the Preparation of Nitrogen-Pivot Lariat Ethers from Primary Amines, Procedure D. (a) Alkylation of Primary Amines. The amines were alkylated according to the procedure of Burnett[25] with the following modifications. The appropriate amine (1 equiv) and Na_2CO_3 (1.2 equiv) were mixed in a three-necked flask. Ethyl bromoacetate (2.2 equiv) was added over a 1-h period. The reaction mixture was heated (steam bath) during an additional 20 h of stirring. The salts were filtered and washed with CH_2Cl_2. The filtrate was acidified (pH 2) with 6 N HCl. The product was extracted with Et_2O (2 × 100 mL). The combined organic phases were dried ($MgSO_4$) and filtered, and the solvent was evaporated in vacuo. The crude material was vacuum distilled to provide the pure diester in a range of 50–60% for seven different preparations.

(b) Reduction of the Diesters. The amine diester was reduced to the corresponding diethanolamine. $LiAlH_4$ (4 hydrides per ester group,[26] 0.8 mol) was suspended in THF (1000 mL) in a three-necked, N_2-flushed flask. The suspension was cooled to ca. 0 °C (ice-water bath) while a solution of the amine diester (0.40 mol) in THF (500 mL) was added over a 2-h period. After the addition was complete, the reaction mixture was slowly warmed to reflux, held there for 12 h, and then cooled to room temperature. A saturated aqueous solution of Na_2SO_4 was added to quench the excess $LiAlH_4$. Solid anhydrous Na_2SO_4 was added to absorb any water. Dichloromethane (1000 mL) was added and the mixture was stirred for 0.5 h. The solid was removed by filtration through a Celite pad. The solvent was evaporated in vacuo, and the residue was vacuum distilled to yield (78%) the pure diethanolamine.

(c) Cyclization. The diethanolamine was cyclized to the lariat ether according to the method described in procedure C.

General Procedure for the Preparation of Nitrogen-Pivot Lariat Ethers by *N*-Alkylation of the Parent Monoazacrown, Procedure E. Monoaza-15-crown-5 (**14**) and monoaza-18-crown-6 (**32**) were obtained by hydrogenolysis (H_2, 10% Pd–C, absolute EtOH) of the corresponding *N*-benzylmonoaza-15-crown-5 (**19**) or *N*-benzylmonoaza-18-crown-6 (**34**) as previously described.[27] The parent monoazacrowns were treated with various alkylating agents in the presence of Na_2CO_3 in either THF, CH_3CN, or DMF solvent. Details of individual syntheses are given below.

Preparation of Monoaza-15-crown-5. Compound **14** was prepared by hydrogenolysis of *N*-benzylmonoaza-15-crown-5 (**19**, see below). A solution of **19** (9.5 g, 0.03 mol) in absolute EtOH (90 mL) was added to 10% Pd–C (0.9 g) in a Parr hydrogenation apparatus under H_2 (60 psi) and the mixture was shaken for 24 h at 25 °C. The reaction mixture was filtered through a bed of Celite and the solvent evaporated. Distillation of the residue in a Kugelrohr apparatus (bp 76 °C (0.05 torr)) gave pure **14** 6.5 g, 98%) as a colorless oil which solidified to a soft, white hygroscopic solid: ^{1}H NMR δ 2.53 (s, 1 H), 2.72 (t, 4 H), 3.57 (m, 16 H).

Preparation of *N*-Methylmonoaza-15-crown-5 (15). A 100-mL flask was charged with monoaza-15-crown-5 (**14**, 3.0 g, 0.014 mol), Na_2CO_3 (3.0 g, 0.028 mol), CH_3CN (50 mL), and dimethyl sulfate (1.8 g, 0.014 mol). The reaction mixture was magnetically stirred at reflux for 24 h, cooled, and filtered, and the solvent was evaporated. The residue was swirled with CH_2Cl_2, cooled, and filtered, and the solvent evaporated in vacuo. The residue was distilled (Kugelrohr, 110 °C (0.07 torr)) to afford **15** (1.2 g, 37%) as a pale yellow oil: ^{1}H NMR δ 2.32 (s, 3 H), 2.68 (t, 4 H), 3.65 (m, 16 H); ^{13}C NMR δ 44.44, 57.17, 69.50, 70.28, 70.57, 70.99; IR 2880, 1450, 1350, 1125 cm^{-1}. Anal. Calcd for $C_{11}H_{23}NO_4$: C, 56.63; H, 9.94; N, 6.00. Found: C, 56.79; H, 10.20; N, 5.82.

Preparation of *N*-Allylmonoaza-15-crown-5 (16). Compound **16** was prepared as described in procedure C. Allyl chloride (168.3 g, 2.2 mol) was allowed to react with diethanolamine (210 g, 2 mol) according to the general procedure. *N*-Allyldiethanolamine was obtained after vacuum distillation (242.4 g, 83%): bp 124 °C (0.1 torr); ^{1}H NMR δ 2.65 (t, 4 H), 3.20 (d, 2 H), 3.70 (t, 4 H), 3.85 (s, 1 H), 5.10 (m, 2 H), 5.85 (m, 1 H). The *N*-allyl crown was obtained from the reaction of *N*-allyldiethanolamine (116.2 g, 0.8 mol) with TrEGTs (245.1 g, 0.8 mol) as described in procedure C. The crude mixture was chromatographed (Al_2O_3, 0–2% 2-PrOH/petroleum ether) to give the lariat ether (**16**, 126.8 g, 61%) as a pale yellow oil after evaporation of the volatile solvents from the crown: ^{1}H NMR δ 2.72 (t, 4 H), 3.15 (d, 2 H), 3.65 (m, 16

H), 5.13 (m, 2 H), 5.80 (m, 1 H); IR 2860, 1640, 1450, 1350, 1290, 1250, 1125, 990, 870, 860 cm^{-1}. Anal. Calcd for $C_{13}H_{25}NO_4$: C, 60.21; H, 9.72; N, 5.40. Found: C, 60.21; H, 10.00, N, 5.23.

Preparation of *N*-(*n*-Butyl)monoaza-15-crown-5 (17). Compound **17** was prepared as described in procedure C. *n*-Butyl bromide (151 g, 1.1 mol) was treated with diethanolamine (105 g, 1.0 mol) to afford *n*-butyldiethanolamine (113.5 g, 71%) after vacuum distillation: bp 103–105 °C (0.1 torr); ^1H NMR δ 0.87 (t, 3 H), 1.37 (m, 4 H), 2.57 (t, 6 H) 3.53 (t, 4 H), 3.73 (s, 2 H). The *n*-butyl crown **17** was prepared by cyclization of *n*-butyldiethanolamine (16.1 g, 0.1 mol) with TrEGMs (30.6 g, 0.1 mol). The crude mixture was chromatographed (alumina, 0–4% 2-PrOH/petroleum ether) to give the lariat ether (**17**, 17.8 g, 65%) as an oil after evaporation of the volatile solvents: ^1H NMR δ 0.88 (t, 3 H), 1.37 (m, 4 H), 2.72 (t, 6 H), 3.67 (m, 16 H); IR 2940, 2920, 2840, 1460, 1350, 1290, 1240, 1120, 980, 930, 830 cm^{-1}. Anal. Calcd for $C_{14}H_{29}NO_4$: C, 61.06; H, 10.61; N, 5.09. Found: C, 61.08; H, 10.85; N, 5.18.

Preparation of *N*-(*tert*-Butyl)monoaza-15-crown-5 (18). Commercially available *N*-(*tert*-butyl)diethanolamine (16 g, 0.1 mol) was cyclized with TrEGMs (30.6 g, 0.1 mol) according to procedure C. The crude mixture was chromatographed (alumina, 0–4% 2-propanol/hexanes) and then distilled (Kugelrohr, 90 °C (0.02 torr)) to yield colorless **18** (18.8 g, 28%): ^1H NMR 1.15 (s, 9 H), 2.78 (t, 4 H), 3.65 (m, 16 H); ^{13}C NMR 26.92, 51.15, 54.78, 69.91, 70.34, 71.28, 72.86; IR: 2950, 1450, 1360, 1120 cm^{-1}. Anal. Calcd for $C_{14}H_{29}NO_4$: C, 61.06; H, 10.61; N, 5.09. Found: C, 61.23; H, 10.90; N, 4.78.

Preparation of *N*-Benzylmonoaza-15-crown-5 (19). Compound **19** was prepared as described in procedure C. Benzyl chloride (557 g, 4.4 mol) was allowed to react with diethanolamine (420 g, 4 mol) according to the general procedure. *N*-Benzyldiethanolamine was obtained after vacuum distillation (609 g, 78%): bp 143–145 °C (0.1 torr); ^1H NMR 2.63 (t, 4 H), 3.60 (m, 8 H), 7.30 (s, 5 H). *N*-Benzylmonoaza-15-crown-5 (**19**) was prepared by cyclization of *N*-benzyldiethanolamine (195 g, 1 mol) with TrEGTs (458 g, 1 mol) as described in procedure C. The crude mixture was chromatographed (Al_2O_3, hexanes) and distilled (Kugelrohr, 125 °C (0.1 torr)) to give the lariat ether (**19**, 142 g, 46%) as a colorless oil: ^1H NMR δ 2.77 (t, 4 SH), 3.67 (m, 18 H), 7.30 (s, 5 H); IR 3060, 3030, 2860, 1600, 1500, 1455, 1350, 1300, 1250, 1125, 740, 700 cm^{-1}.

Preparation of *N*-(3-Oxabut-1-yl)monoaza-15-crown-5 (20). Compound **20** was prepared as described in procedure C from methoxyethanol (76 g, 1.0 mol). The crude tosylate, obtained in 90% yield (126 g, 0.55 mol), was treated with diethanolamine (25.5 g, 0.5 mol) to afford *N*-(3-oxabut-1-yl)diethanolamine after vacuum distillation (10-cm Vigreux column): 57 g; 70%; bp 105–107 °C (0.03 torr); ^1H NMR δ 2.7 (m, 6 H), 3.3 (s, 3 H), 3.55 (t, 6 H), 3.80 (br s, 2 H).

N-(3-oxabut-1-yl)crown (**20**) was obtained from the reaction of *N*(3-oxabut-1-yl)diethanolamine (16.3 g, 0.1 mol) with TrEGMs (30.6 g, 0.01 mol). The crude mixture was chromatographed (alumina, 0–4% 2-PrOH/petroleum ether) to give **20** (15 g, 55%) as a pale yellow oil which was distilled (Kugelrohr, 127 °C (0.15 torr)) to yield a colorless oil: ^1H NMR δ 2.8 (m, 6 H), 3.3 (s, 3 H), 3.65 (m, 18 H); ^{13}C NMR δ 54.96, 55.78, 58.54, 69.94, 70.00, 70.32, 70.87, 71.13; IR 2860, 1450, 1350, 1120 cm^{-1}. Anal. Calcd for $C_{13}H_{27}NO_5$: C, 56.30; H, 9.81; N, 5.05. Found: C, 56.47; H, 10.08; N, 4.87.

Preparation of *N*-(3,6-Dioxahept-1-yl)monoaza-15-crown-5 (21). Compound **21** was prepared according to procedure C. 2-(2-Methoxyethoxy)ethanol (120 g, 1 mol) was tosylated as described in the general procedure. The crude tosylate (151 g, 0.55 mol) was treated with diethanolamine (52.5 g, 0.5 mol) to afford *N*-(3,6-dioxahept-1-yl)diethanolamine after vacuum distillation (10-cm Vigreux column): 50 g, 48%; bp 128–130 °C (0.04 torr). *N*-(3,6-Dioxahept-1-yl) crown was obtained from the reaction of *N*-(3,6-dioxahept-1-yl)diethanolamine (21 g, 0.1 mol) with TrEGMs (30.6 g, 0.1 mol). The crude mixture was chromatographed (alumina, 0–4% 2-PrOH/petroleum ether) to give the lariat ether (**21**, 15 g, 47%) which was distilled (Kugelrohr, 130 °C (0.07 torr)) to yield a colorless oil: ^1H NMR δ 2.85 (m, 6 H), 3.35 (s, 3 H), 3.65 (m, 22 H); ^{13}C NMR δ 55.11, 55.86, 58.80, 69.70, 70.00, 70.17, 70.32, 70.87, 71.83; IR 2860, 1450, 1350, 1120 cm^{-1}. Anal. Calcd for $C_{15}H_{31}NO_6$: C, 56.05; H, 9.72; N, 4.36. Found: C, 56.24; H, 10.00; N, 4.50.

Preparation of *N*-(3,6,9-Trioxadec-1-yl)monoaza-15-crown-5 (22). 3,6,9-Trioxadecanol (82 g, 0.5 mol) was treated with *p*-TsCl (105 g, 0.55 mol) in the presence of pyridine (61 mL) to afford 3,6,9-trioxadecyl tosylate (134 g, 84%) as described in procedure C. A 100-mL flask was charged with monoaza-15-crown-5 (**14**, 4.4 g, 0.02 mol), Na_2CO_3 (1.6 g, 0.015 mol), THF (75 mL), and the tosylate (6.4 g, 0.02 mol). The reaction mixture was stirred at reflux for 24 h, cooled, and filtered, and the solvent was evaporated. The residue was chromatographed (Al_2O_3, 2% 2-PrOH/hexanes) and then distilled (Kugelrohr, 155 °C (0.05 torr)) to yield lariat ether **22** (2.50 g, 34%) as a colorless oil: ^1H NMR δ 2.80 (m, 6 H), 3.35 (s, 3 H), 3.65 (m, 26 H); ^{13}C NMR δ 55.08, 55.84, 58.81, 69/74, 70.03, 70.35, 70.90, 71.84; IR 2860, 1450, 1350, 1120 cm^{-1}. Anal. Calcd for $C_{17}H_{35}NO_7$: C, 55.87; H, 9.65; N, 3.83. Found: C, 55.65; H, 9.90; N, 3.86.

Preparation of *N*-(3,6,9,12-Tetraoxatridec-1-yl)monoaza-15-crown-5 (23). 3,6,9,12-Tetraoxatridecanol (52.0 g, 0.25 mol) was treated with *p*-TsCl (53.0 g, 0.275 mol) in pyridine (32 mL) to afford 3,6,9,12-tetraoxatridecyl tosylate (293.0 g, 81%). A 500-mL flask was charged with monoaza-15-crown-5 (**14**, 17.5 g, 0.08 mol), Na_2CO_3 (6.4 g, 0.06 mol), THF (200 mL), and the tosylate (29.0 g, 0.08 mol). The reaction mixture was stirred at reflux for 24 h, cooled, and filtered, and the solvent was evaporated in vacuo. The residue was taken up in H_2O (200 mL) which was then washed with CH_2Cl_2 (2 × 200 mL). The CH_2Cl_2 was evaporated in vacuo. The crude mixture was chromatographed (Al_2O_3, 0–6% 2-PrOH/hexanes) to give a pale yellow oil (18.7 g, 55%), which was distilled (Kugelrohr, 175 °C (0.07 torr)) to yield **23** as a colorless oil: ^1H NMR δ 2.30 (m, 6 H), 3.40 (s, 3 H), 3.65 (m, 30 H); ^{13}C NMR δ 55.36, 56.04, 58.63, 70.17, 70.29, 70.40, 50.55, 71.05, 71.94; IR 2860, 1450, 1350, 1120 cm^{-1}. Anal. Calcd for $C_{19}H_{39}NO_8$: C, 55.73; H, 9.60; N, 3.42. Found: C, 56.00; H, 9.86; N, 3.65.

Preparation of *N*-(3,6,9,12,15-Pentaoxahexadec-1-yl)monoaza-15-crown-5 (24). 3,6,9,12,15-Pentaoxahexadecanol (63.0 g, 0.25 mol) was treated with *p*-TsCl (53.0 g, 0.276 mol) in pyridine (32 mL) as described in procedure C to afford 3,6,9,12,15-pentaoxahexadecyl tosylate (83.0 g, 81%). A 500-mL flask was charged with monoaza-15-crown-5 (**14**, 17.5 g, 0.08 mol), Na_2CO_3 (6.4 g, 0.06 mol), THF (200 mL), and the tosylate (33 g, 0.08 mol). The reaction mixture was stirred at reflux for 24 h, cooled, and filtered, and the solvent was evaporated in vacuo. The residue was dissolved in H_2O (200 mL), which was then washed with CH_2Cl_2 (2 × 200 mL). The CH_2Cl_2 was evaporated in vacuo. The crude mixture was chromatographed (Al_2O_3, 0–6% 2-PrOH/hexanes) to give a pale yellow oil (23 g, 78%), which was distilled (Kugelrohr, 185 °C (0.07 torr)) to yield the colorless lariat **24**: ^1H NMR δ 2.80 (m, 6 H), 2.40 (s, 3 H), 3.65 (m, 34 H); ^{13}C NMR δ 55.08, 55.86, 58.78, 69.73, 70.02, 70.35, 70.46, 70.87, 71.83; IR 2869, 1450, 1350, 1120 cm^{-1}. Anal. Calcd for $C_{21}H_{43}NO_9$: C, 55.61; H, 9.56; N, 3.09. Found: C, 55.65; H, 9.83; N, 2.98.

Preparation of *N*-(Methoxypoly[ethyleneoxy(*n* ~ 8)]ethyl)monoaza-15-crown-5 (25). Compound **25** was prepared according to procedure C. Polyethylene glycol monomethyl ether (average MW = 350, 350 g, 1 mol) was tosylated as described in the general procedure. The crude tosylate (332.7 g, 0.66 mol) was treated with diethanolamine (63 g, 0.6 mol) to afford *N*-(methoxypoly[ethyleneoxy(*n* ~ 8)]ethyl)diethanolamine. *N*-(Methoxypoly[ethyleneoxy(*n* ~ 8)]ethyl) crown **25** was obtained from the reaction of the diethanolamine (43.7 g, 0.1 mol) with TrEMs (30.6 g, 0.1 mol). The crude mixture was chromatographed (Al_2O_3, 0–6% 2-PrOH/Skellysolve-F) to give lariat ether (**25**, 25 g, 49%) which was distilled (Kugelrohr, 185 °C (0.05 torr)): ^1H NMR δ 2.82 (m, 6 H), 3.38 (s, 3 H), 3.67 (m, 46 H).

Preparation of *N*-(2-Methoxyphenyl)monoaza-15-crown-5 (26). Compound **26** was prepared as described in procedure D from *o*-anisidine (12.3 g, 0.1 mol) alkylated with ethyl bromoacetate (36.7 g, 0.22 mol). After vacuum distillation the amine diester was obtained as a yellow oil (19 g, 64%): bp 137–140 °C (0.06 torr); ^1H NMR δ 1.25 (t, 6 H), 3.80 (s, 3 H), 4.15 (s, 4 H), 4.20 (q, 4 H), 6.90 (s, 4 H). The diester (121 g, 0.41 mol) was reduced with $LiAlH_4$ (31 g, 0.32 mol) to give *N*-(2-methoxyphenyl)diethanolamine as a pale yellow oil (67 g, 78%) after vacuum distillation: bp 144–146 °C (0.1 torr) [lit.[28] bp 161 °C (4 torr)]: ^1H NMR δ 3.40 (m, 10 H), 3.90 (s, 3 H), 7.10 (m, 4 H). *N*-(2-Methoxyphenyl) crown **26** was prepared by cyclization of the above diethanolamine (25 g, 0.1 mol) with TrEGMs (30.6 g, 0.1 mol) as described in procedure C. The crude mixture was chromatographed (Al_2O_3, 0–2% 2-PrOH/hexanes) and then distilled (Kugelrohr, 134 °C (0.05 torr)) to yield lariat ether **26** (12.5 g, 38%) as a pale yellow oil: ^1H NMR δ 3.65 (m, 23 H, 6.9 (m, 4 H); ^{13}C NMR δ 52.98, 55.20, 70.12, 70.20, 70.41, 70.82, 111.67, 120.59, 121.84, 139.91, 152.53; IR 3050, 2860, 1590, 1500, 1460, 1350, 1240, 1120, 745 cm^{-1}. Anal. Calcd for $C_{17}H_{27}NO_5$: C, 62.75; H, 8.36; N, 4.30. Found: C, 63.04; H, 8.61; N, 4.58.

Preparation of *N*-(4-Methoxyphenyl)monoaza-15-crown-5 (27). Compound **27** was prepared as described in procedure D from *p*-anisidine (6.2 g, 0.05 mol) which was alkylated with ethyl bromoacetate (16.7 h,

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0.1 mol). After vacuum distillation the amine diester was obtained as a yellow oil (6.5 g, 44%): bp 154–156 °C (0.02 torr); ^{1}H NMR δ 1.18 (t, 6 H), 3.60 (s, 3 H), 3.95 (s, 4 H), 4.10 (q, 4 H), 6.50 (m, 4 H). This amine diester (6 g, 0.02 mol) was reduced with $LiAlH_4$ (1.7 g, 0.044 mol) to give *N*-(4-methoxyphenyl)diethanolamine as a tan crystalline solid after recrystallization (CCl_4, mp 69–70 °C): ^{1}H NMR δ 3.40 (m, 6 H), 3.78 (m, 7 H), 6.83 (s, 4 H). *N*-(**4**-Methoxyphenyl) crown **27** was prepared by cyclization of diethanolamine (3.3 g, 0.013 mol) with TrEGMs (4 g, 0.013 mol) as described in procedure C. The crude mixture was chromatographed (Al_2O_3, 0–2% 2-PrOH/hexanes) and distilled (Kugelrohr, 139 °C (0.05 torr)). Lariat ether **27** was obtained as a white crystalline solid (1.3 g, 30%) after recrystallization from petroleum ether (mp 55–56.5 °C): ^{1}H NMR δ 3.55 (m, 23 H), 6.55 (s, 4 H); ^{13}C NMR δ 52.66, 55.69, 68.87, 70.12, 71.19, 112.76, 114.82, 142.36, 150.84; IR (Nujol mull) 3040, 3000, 2860, 1620, 1520, 1440, 1350, 1260, 1190, 1130, 1120, 1040, 980, 810 cm^{-1}. Anal. Calcd for $C_{17}H_{27}NO_5$: C, 62.75; H, 8.36; N, 4.30. Found: C, 62.64; H, 8.65; N, 4.36.

Preparation of *N*-(2-Methoxybenzyl)monoaza-15-crown-5 (28). Compound **28** was prepared as described in procedure D from (2-methoxybenzyl)amine (10 g, 0.073 mol) which was alkylated with ethyl bromoacetate (26.8g, 0.16 mol). After vacuum distillation, the amine diester was obtained as a yellow oil (9.8 g, 43%): bp 120 °C (0.02 torr); ^{1}H NMR δ 1.23 (t, 6 H), 3.47 (s, 4 H), 3.77 (s, 3 H), 3.85 (s, 2 H), 4.07 (q, 4 H), 7.07 (m, **4** H). The amine diester (9.5 g, 0.031 mol) was reduced with $LiAlH_4$ (2.35 g, 0.062 mol) to give *N*-(2-methoxybenzyl)-diethanolamine as a pale yellow oil (5.3 g, 76%) after vacuum distillation: bp 163–165 °C (0.02 torr); ^{1}H NMR δ 2.62 (t, 4 H), 3.48 (m, 8 H), 3.77 (s, 3 H), 6.98 (m, 4 H). *N*-(2-Methoxybenzyl) crown **28** was prepared by cyclization of the diethanolamine (5.0 g, 022 mol) with TrEGMs (6.74 g, 0.022 mol) as described in procedure C. The crude mixture was chromatographed (Al_2O_3, 0–2% 2-PrOH/hexanes) and distilled (Kugelrohr, 140 °C (0.04 torr)) to yield lariat ether **28** (3.0 g, 40%) as a pale yellow oil: ^{1}H NMR δ 2.85 (t, 4 H), 3.65 (m, 21 H), 7.20 (m, 4 H); ^{13}C NMR δ 53.74, 54.38, 55.06, 69.91, 70.09, 50.44, 70.88, 109.96, 120.06, 127.44, 129.94, 157.34; IR 3060, 2860, 1600, 1585, 1490, 1460, 1240, 1120, 755 cm^{-1}. Anal. Calcd for $C_{18}H_{29}NO_5$: C, 63.69; H, 8.61; N, 4.13. Found: C, 63.89; H, 8.35; N, 4.20.

Preparation of *N*-(2-Nitrobenzyl)monoaza-15-crown-5 (29). Monoaza-15-crown-5 (**14**, 2.0 g, 0.009 mol), Na_2CO_3 (1.9 g, 0.018 mol), CH_3CN (30 mL), and 2-nitrobenzyl chloride (1.6 g, 0.009 mol) were stirred at reflux for 24 h, cooled, and filtered, and the solvent was evaporated in vacuo. The residue was taken up in $CHCl_3$ (20 mL), cooled, and filtered, and the solvent was evaporated. The residual oil was chromatographed (Al_2O_3, 2% 2-PrOH/hexanes) and distilled (Kugelrohr, 155 °C (0.05 torr)) to afford lariat ether **29** (1.1 g, 35%) as a yellow oil: ^{1}H NMR δ 2.75 (t, 4 H), 3.60 (m, 16 H), 3.95 (s, 2 H), 7.50 (m, 4 H); ^{13}C NMR δ 54.99, 57.32, 69.79, 70.17, 70.55, 70.99, 123.79, 127.32, 131.05, 132.19, 135.39; IR 2860, 1530, 1450, 1355, 1300, 1125, 935, 740 cm^{-1}. Anal. Calcd for $C_{17}H_{26}N_2O_6$: C, 57.61; H, 7.39; N, 7.90. Found: C, 57.81; H, 7.58; N, 8.09.

Preparation of *N*-(4-Nitrobenzyl)monoaza-15-crown-5 (30). Monoaza-15-crown-5 (**14**, 2.0 g, 0.009 mol), Na_2CO_3 (1.9 g, 0.018 mol), CH_3CN (50 mL), and 4-nitrobenzyl bromide (1.95 g, 0.009 mol) were stirred at reflux for 24 h, cooled, and filtered, and the solvent was evaporated in vacuo. The residue was dissolved in $CHCl_3$ (20 mL) and filtered, and the solvent was evaporated. The residual oil was chromatographed twice (Al_2O_3, 2% 2-PrOH/hexanes) (silica gel, 18:1 $CHCl_3$/MeOH). The lariat ether was further purified by Chromatotron chromatography (0.75 g of compound/10 mL of $CHCl_3$ applied to a 4-mm silica gel rotating plate, eluted with $CHCl_3$, collected 5-mL fractions) to provide pure **30** (0.7 g, 22%), which solidifed upon standing for 500 h: ^{1}H NMR δ 2.75 (t, 4 H), 3.65 (m, 18 H), 7.85 (dd, 4 H); ^{13}C NMR δ 54.82, 59.83, 69.79, 70.20, 70.50, 70.99, 123.09, 129.07, 146.96, 148.01; IR (Nujol) 2900, 1600, 1520, 1350, 1310, 1260, 1125, 860, 750 cm^{-1}. Anal. Calcd for $C_{17}H_{26}N_2O_6$: C, 57.61; H, 7.39; N, 7.90. Found: C, 57.38; H, 7.58; N, 7.80.

Preparation of *tert*-Butyl 2-(*N*-Monoaza-15-crown-5)acetate (31). *tert*-Butyl chloroacetate was prepared according to the procedure of Westheimer and Shookhoff[29] from chloroacetyl chloride (35 g, 0.31 mol), dimethylaniline (40 g, 0.33 mol), and *tert*-butyl alcohol (25 g, 0.34 mol). After vacuum distillation through a 10-cm Vigreux column, *tert*-butyl chloroacetate was obtained as a colorless oil (24.5 g, 52%): bp 53–55 °C (10 torr) [lit.[29] bp 60 °C (15 torr)]; ^{1}H NMR δ 1.50 (s, 9 H), 3.93 (s, 2 H).

Monoaza-15-crown-5 (**14**, 8.0 g, 0.0365 mol), Na_2CO_3 (7.7 g, 0.073 mol), and DMF (300 mL) were added to a 1-L round-bottomed flask. This was mechanically stirred and heated to ca. 95 °C. Then the *tert*-butyl chloroacetate (5.5 g, 0.0365 mol) was added to the flask and this was heated at ca. 95 °C for an additional 24 h. The reaction mixture was filtered, and the solvent was evaporated in vacuo. The residue was dissolved in H_2O (150 mL) and washed with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvent was evaporated in vacuo. This yellow oil was then chromatographed (Al_2O_3, 0–1% 2-PrOH/ hexanes) to provide the pure **48** (8.0 g, 66%) as a pale yellow oil: ^{1}H NMR δ 1.45 (s, 9 H), 2.93 (t, 4 H), 3.35 (s, 2 H) 3.65 (m, 16 H); ^{13}C NMR δ 28.15, 54.67, 58.02, 70.06, 70.26, 70.85, 80.43, 170.65; IR 2860, 1670, 1450, 1370, 1130 cm^{-1}. Anal. Calcd for $C_{16}H_{31}NO_6$: C, 57.64; H, 9.37; N, 4.20. Found: C, 57.65; H, 9.60; N, 4.22.

Preparation of Monoaza-18-crown-6 (32). The title compound was prepared by hydrogenolysis of *N*-benzylmonoaza-18-crown-6 (98%) for an overall yield of 39% rather than 25% as previously reported.[27]

Preparation of *N*-Methylmonoaza-18-crown-6 (33). A 100-mL flask was charged with monoaza-18-crown-6 (**32** 2.6 g, 0.01 mol), Na_2CO_3 (0.53 g, 0.005 mol), THF (50 mL), and dimethyl sulfate (1.3 g, 0.01 mol). The mixture was stirred at reflux for 24 h, cooled, and filtered, and the solvent was evaporated in vacuo. The residue was chromatographed (Al_2O_3, 2% 2-PrOH/Skellysolve-F) to afford lariat ether (0.8 g, 29%) as a pale yellow oil: ^{1}H NMR δ 2.32 (s, 3 H), 2.70 (t, 4 H), 3.67 (m, 20 H); IR 2870, 1450, 1350, 1120 cm^{-1}. Anal. Calcd for $C_{13}H_{27}NO_5$: C, 56.30; H, 9.81; N, 5.05. Found: N, 5.11.

Preparation of *N*-Benzylmonoaza-18-crown-6 (34). Compound **34** was prepared as described in procedure C and as above for **19**, except that cyclization was effected with TEGTs (502 g, 1 mol). The crude mixture was chromatographed (Al_2O_3, hexanes) and distilled (Kugelrohr, 130 °C/0.05 torr) to give **34** (140 g, 40%) as a colorless oil: ^{1}H NMR δ 2.70 (t, 4 H), 3.57 (m, 22 H), 7.07 (s, 5 H); IR 3060, 3030, 2860, 1600, 1495, 1450, 1350, 1295, 1250, 1120, 735, 700 cm^{-1}.

Preparation of *N*-(3-Oxabut-1-yl)monoaza-18-crown-6 (35). Compound **35** was prepared as described for **20**, except that cyclization was effected with TEGMs (35 g, 0.1 mol). The crude mixture was chromatographed (Al_2O_3, 0–4% 2-PrOH/petroleum ether) to give the lariat ether **35** (17 g, 53%) which was distilled (Kugelrohr, 129 °C (0.07 torr)) to yield a colorless oil: ^{1}H NMR δ 2.8 (m, 6 H), 3.3 (s, 3 H), 3.6 (m, 22 H); ^{13}C NMR δ 54.49, 54.96, 58.58, 69.85, 70.29, 70.64, 71.14; IR 2860, 1450, 1350, 1120 cm^{-1}. Anal. Calcd for $C_{15}H_{31}NO_6$: C, 56.05; H, 9.72; N, 4.36. Found: C, 56.29; H, 10.01; N, 4.14.

Preparation of *N*-(3,6-Dioxahept-1-yl)monoaza-18-crown-6 (36). Compound **36** was prepared as described for **21**, except that cyclization was effected with TEGMs (35 g, 0.1 mol). The crude mixture was chromatographed (Al_2O_3, 0–4% 2-PrOH/petroleum ether) to give the lariat ether **36** (18 g, 50%), which was distilled (Kugelrohr, 143 °C (0.05 torr)) to yield a colorless oil: ^{1}H NMR δ 2.8 (m, 6 H), 3.4 (s, 3 H), 3.65 (m, 26 H); ^{13}C NMR δ 54.99, 58.84, 69.76, 69.88, 70.29, 70.67, 71.86; IR 2860, 1450, 1350, 1120 cm^{-1}. Anal. Calcd for $C_{36}H_{35}NO_7$: C, 55.87; H, 9.65; N, 3.83. Found: C, 56.00; H, 9.90; N, 3.97.

Preparation of *N*-(3,6,9-Trioxadec-1-yl)monoaza-18-crown-6 (37). A 250-mL flask was charged with monoaza-18-crown-6 (**32**, 5.0 g, 0.019 mol), Na_2CO_3 (4.0 g, 0.038 mol), DMF (125 mL), and 3,6,9-trioxadecyl tosylate (6.0 g, 0.019 mol). The reaction mixture was maintained at 100 °C for 48 h, cooled, and filtered, and the solvent was evaporated in vacuo. The residue was taken up in H_2O (100 mL) which was then washed with CH_2Cl_2 (2 × 100 mL). The CH_2Cl_2 was removed by evaporation in vacuo. The crude mixture was chromatographed (Al_2O_3, 0–2% 2-PrOH/hexanes) and distilled (Kugelrohr, 152 °C (0.04 torr)) to provide lariat ether **37** (3.6 g, 46%) as a colorless oil: ^{1}H NMR δ 2.80 (m, 6 H), 3.35 (s, 3 H), 3.65 (m, 30 H); ^{13}C NMR δ 54.61, 55.02, 58.84, 69.82, 69.94, 70.34, 70.70, 71.86; IR 2860, 1450, 1350, 1120 cm^{-1}. Anal. Calcd for $C_{19}H_{39}NO_8$: C, 55.73; H, 9.60; N, 3.42. Found: C, 55.45; H, 9.65; N, 3.69.

Preparation of *N*-(3,6,9,12-Tetraoxatridec-1-yl)monoaza-18-crown-6 (38). A 100-mL flask was charged with monoaza-18-crown-6 (**32**, 5.3 g, 0.02 mol), Na_2CO_3 (1.6 g, 0.015 mol), THF (50 mL), and 3,6,9,12-tetraoxatridecyl tosylate (7.3 g, 0.02 mol). This mixture was magnetically stirred at reflux for 24 h, cooled, and filtered, and the solvent was evaporated in vacuo. The residue was taken up in H_2O (50 mL), which was then washed with CH_2Cl_2 (2 × 60 mL). The CH_2Cl_2 was evaporated in vacuo. The crude mixture was chromatographed (Al_2O_3, 0–3% 2-PrOH/hexanes) and distilled (Kugelrohr, 192 °C (0.15 torr)) to provide the lariat ether (**38**, 1.6 g, 18%) as a colorless oil: ^{1}NMR 2.80 (m, 6 H), 3.40 (s, 3 H), 3.65 (m, 37 H); ^{13}C NMR δ 54.60, 55.01, 58.83, 69.76, 69.91, 70.32, 70.52, 70.69, 71.86; IR 2860, 1450, 1350, 1120 cm^{-1}. Anal. Calcd for $C_{21}H_{43}NO_9$: C, 55.61; H, 9.56; N, 3.09. Found: C, 55.50; H, 9.80; N, 3.05.

Preparation of *N*-(3,6,9,12,15-Pentaoxahexadec-1-yl)monoaza-18-crown-6 (39). Monoaza-18-crown-6 (**32**, 5.0 g, 0.019 mol), Na_2CO_3 (4.0

(29) Westheimer, F. H.; Shookhoff, M. W. *J. Am. Chem. Soc.* **1940**, *62*, 269.

g, 0.038 mol), DMF (125 mL), and 3,6,9,12,15-pentaoxahexadecyl tosylate (7.7 g, 0.019 mol) were added to a 250-mL flask. This mixture was stirred and heated (ca. 100 °C) for 48 h, cooled, and filtered, and the solvent was evaporated in vacuo. The residue was taken up in H_2O (100 mL) which was then washed with CH_2Cl_2 (2 × 100 mL). The CH_2Cl_2 was evaporated in vacuo. The residue was chromatographed (Al_2O_3, 0–1% 2-PrOH/hexanes) and distilled (Kugelrohr, 180 °C (0.05 torr)) to provide lariat ether **39** (2.5 g, 26%) as a colorless oil: ^1H NMR δ 2.82 (m, 6 H), 3.40 (s, 3 H), 3.65 (m, 38 H); ^{13}C NMR δ 54.58, 55.02, 58.83, 69.79, 69.91, 70.35, 70.49, 70.67, 71.86; IR 2880, 1450, 1350, 1120 cm^{-1}. Anal. Calcd for $C_{23}H_{47}NO_{10}$: C, 55.51; H, 9.52; N, 2.81. Found: C, 55.54; H, 9.80; N, 2.75.

Preparation of *N*-(Methoxypoly[ethyleneoxy(*n* ~8)]ethyl)monoaza-18-crown-6 (40). As described in procedure C polyethylene glycol monomethyl ether (average MW = 350, 24.5 g, 0.07 mol) was treated with *p*-toluenesulfonyl chloride (14.7 g, 0.077 mol) in pyridine (40 mL) to afford the tosylate (30.0 g, 85%). To a 50-mL round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser, was added monoaza-18-crown-6 (**32**, 3.0 g, 0.0114 mol), Na_2CO_3 (1.2 g, 0.0114 mol), CH_3CN (10 mL), and the tosylate (5.8 g, 0.0114 mol). The reaction mixture was stirred at reflux for 24 h, cooled, and filtered, and the solvent was evaporated in vacuo. The residual oil was then chromatographed over a column of Al_2O_3 (5% 2-PrOH/hexanes) to give lariat ether **25** as a yellow oil (4.3 g, 60%): ^1H NMR δ 2.80 (m, 6 H), 3.40 (s, 3 H), 3.65 (m, 36 H). Anal. Calcd for $C_{29}H_{59}NO_{13}$: C, 55.31; H, 9.44; N, 2.22. Found: C, 55.46; H, 9.70; N, 2.30.

Preparation of *N*-(2-Methoxyphenyl)monoaza-18-crown-6 (41). Compound **41** was prepared as described above for **26** except that cyclization was effected with TEGMs (35 g, 0.1 mol). The crude mixture was chromatographed (Al_2O_3, 0–2% 2-PrOH/hexanes) and then distilled (Kugelrohr, 135 °C (0.02 torr)) to give the lariat ether **41** (15 g, 41%) as a pale yellow oil: ^1H NMR 3.65 (m, 27 H), 6.9 (m, 4 H); ^{13}C NMR δ 52.66, 55.16, 69.74, 70.24, 70.52, 70.70, 111.70, 120.12, 122.10, 139.35, 152.80; IR 3060, 2860, 1590, 1500, 1460, 1350, 1240, 1120, 750 cm^{-1}. Anal. Calcd for $C_{19}H_{31}NO_6$: C, 61.77; H, 8.46; N, 3.79. Found: C, 61.91; H, 8.75; N, 3.71.

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Methyl Transfers. 10. The Marcus Equation Application to Soft Nucleophiles

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Abstract: The Marcus equation applied to methyl transfers is shown to cover reactions of "soft" nucleophiles, although small discrepancies occur. Rates and equilibria are reported for a series of reactions of arylmethylselenides with (*p*-chlorophenyl)dimethylselenonium ion. Experimental reaction rates between "hard" methylating agents and "soft" nucleophiles show small deviations from the calculated values, mostly but not always in the direction predicted by the HSAB principle. The Marcus equation fails to explain the previously reported "inversion" of reaction rates of 4-nitrothiophenoxide and of 4-nitrophenoxide with methyl iodide and dimethyl sulfate. Identity rates for dimethyl sulfate, methyl methanesulfonate (using ^3He), methyl iodide (using ^{125}I), and methyl triflate (using ^{35}S) in sulfolane are reported.

The Marcus equation was developed to correlate electron-transfer reactions[1] and later found application to hydrogen atom transfers,[2] proton transfers,[3] and group transfers, especially methyl-transfer reactions.[4,5] The first critical evaluation of the Marcus equation is predicting methyl-transfer reactions, where identity reactions, equilibria, and cross reactions were directly measured, found the Marcus equation fitted the data within experimental error.[6] These reactions with oxygen leaving groups were transfers of methyl between various arenesulfonates.

Limitations on the application of the Marcus equation to group transfers might be found in those cases with participation of special transition-state interactions not present to the same extent in the identity reactions or in the ground states.

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