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Lariat ethers: from cation complexation to supramolecular assemblies

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Abstract - Lariat ethers are now well-known as macrocycles having one or more sidearms that contain donor groups and can interact with ring bound cations. Variations in structure and donor group arrangements lead to variation in cation binding strengths and selectivities. Such systems exhibit enhanced cation complexation and generally high complexation dynamics. The binding dynamics and strength may readily be altered by reductive switching. This process has been accomplished using both reducing metals and electrochemical techniques. Cyclic voltammetry and EPR techniques confirm the redox switching and the formation of intramolecular ion pairs. Redox-switched lariats have been utilized in cation transport through bulk liquid membranes. When the sidearms are highly lipophilic systems such as cholesteryl, they readily form completely synthetic lipid bilayers or micelles and can assemble into vesicle systems of considerable size and stability.

INTRODUCTION

Lariat ethers are macrocyclic polyether compounds having one or more donor-group-bearing sidearms (ref. 1). In the systems prepared to date, sidearms are attached either to carbon (carbon-pivot lariat ethers) (ref. 2) or to nitrogen (nitrogen-pivot lariat ethers) (ref. 3). When more than one sidearm is attached, the number of them is designated using standard prefixes and the Latin word bracchium which means arm. A two-armed compound is thus a bibracchial lariat ether and the name is abbreviated BiBLE (ref. 4, 5). Cations such as Na^+, K^+, Ca^{2+}, and NH_4^+ are strongly bound by these ligands. The intramolecularity of the interaction has been conclusively demonstrated in the solid state by X-ray methods (ref. 6), in solution using complexation studies (ref. 7) and by NMR relaxation time studies (ref. 8). Electrochemical switching has been demonstrated using cyclic voltammetric techniques (ref. 9). We have now expanded the concept of lariat ethers to encompass podands as well as macrocycles and to include molecules having sidearms that contain no donor groups. In the latter case, the sidearms serve an important purpose different from bearing a Lewis basic donor group as described below.

In an effort to understand cation complexation in detail, we have surveyed a large number of systematically varied structures. The sidearms have contained one or more neutral donor groups. We have also surveyed systems in which the donor groups were more polar than simple ethers, such as hydroxyl, ester, or amide (ref. 4). We have also elaborated the system to include macrocycles having two sidearms which we expected to cooperate with the ring in cation binding (ref. 4,5). The combination of techniques along with the array of compounds available, have permitted a detailed evaluation of cation binding strengths and selectivities. As this work progressed, we wished to broaden the scope of applications for sidearm-containing structures and to deepen our understanding of their interactions with cation and each other.

THERMODYNAMICS OF CATION COMPLEXATION

The complexation of cations by lariat ethers is, like cation complexation by all ligands, a process that depends on several variables. The number of variables can be minimized by determining the homogeneous cation stability constants, that is, the equilibrium constant K_S for the reaction ligand + M^+ = complex$^+$. Our own work has centered on anhydrous methanol at 25 °C. Although we have determined numerous cation binding constants, the measured values were not always in accord with our intuition. We felt the need to dissect the equilibrium constant into its thermodynamic components and have done so by determining K_S in the range of temperatures 15-41 °C (ref. 10). Using the well-known van't Hoff relationship, we have obtained the following thermodynamic data for N,N-disubstituted 4,13-diaza-18-crown-6 derivatives.

The value of such thermodynamic studies lies in the fact that equilibrium constant studies show only the ultimate position of the equilibrium and not the contributions of enthalpy and entropy. Most discussions of cation binding have focused on enthalpic interpretations and this seems quite reasonable. From the data presented above, it is clear that a much more detailed analysis is required.

TABLE 1. Thermodynamic parameters for N,N'-disubstituted 4,13-diaza-18-crown-6 compounds[a]

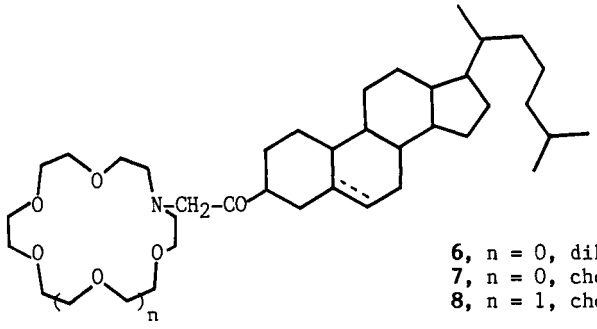
Compound Number	Ring Size	Sidearm	Cation	Log K_S	ΔH (kcal/mol)	$T\Delta S$ (kcal/mol)
1	18	4-methoxybenzyl	Na^+	2.79	-3.02±0.09	0.79±0.07
2	18	benzyl	Na^+	2.68	-3.28±0.28	0.37±0.30
3	18	4-chlorobenzyl	Na^+	2.40	-3.34±0.14	-0.07±0.11
4	18	4-cyanobenzyl	Na^+	2.07	-3.91±0.01	-1.09±0.01
5	18	2-hydroxybenzyl	Na^+	2.30	-5.34±0.21	-2.21±0.25

[a]Values determined in anhydrous methanol as described in ref. 10.

The compounds identified above as **1-5** were chosen because the substituents are expected to exert a predictable effect on the cation binding. Compared to benzyl, 4-methoxybenzyl is expected to be a better binder because of the electron donating effect of CH_3O. Cyano is expected to diminish cation binding when present in the 4-position. Indeed, the trend for binding in 4-substituted benzyl derivatives is -MeO > -H > -CN. The thermodynamic data tell quite a different story. Enthalpically, the 4-cyano group contributes substantially to binding and even benzyl is better than 4-MeO-benzyl in terms of enthalpic contribution. Remarkably, the 2-hydroxybenzyl derivative shows quite a large enthalpic contribution to the overall binding. It is not our intention here to offer a detailed interpretation of these data, only to call attention to the considerable variation that can occur in a closely related series.

LIPOPHILIC LARIAT ETHERS

When carbon-pivot or nitrogen-pivot lariat ethers containing steroidal sidearms are evaluated for cation binding properties, the results are generally disappointing. On the other hand, these compounds exhibit several remarkable properties. We describe here the preparation and characterization of a new class of liposomes formed from, among others, the steroidal lariat ethers, **6-8**, shown below.



6, n = 0, dihydrocholesterol
7, n = 0, cholesterol
8, n = 1, cholesteryl

Several reports have recently appeared which describe the preparation and properties of nonionic liposomes (ref. 11-14). The surfactants used in these reports have two features in common: polyoxyethylene head groups and long hydrocarbon tails. Cholesterol has been used as an additive in some of these preparations to increase vesicle stability (ref. 12,13). Two other reports which are peripherally related to the present work are as follows. Graetzel *et al.* demonstrated in 1980 that a dialkyldiaza-crown ether-silver complex formed cationic vesicles (ref. 15). Shinkai and collaborators reported the formation of lamellar and rod-like aggregates from surfactants bearing an anion-capped crown ether (ref. 16). Several reports, including the work of Okahara, Kuwamura, Turro, and others, confirm the ability of lipophilic crown ethers to form micelles rather than vesicles. The polyether macroring functions as head group and the lipophilic portion serves as the tail. The present work is, to our knowledge, the first report of neutral vesicles formed from steroidal lariat ethers (ref. 17). The syntheses of these novel lariat ethers, their cation binding behavior, and a crystal structure of one of them, are reported elsewhere (ref. 18). It is important to note that the aggregation state can be altered from vesicle to micelle by addition of or

alteration of the bound cation. These steroidal lariat ethers possess the unique ability to form micelles, niosomes, or vesicles depending on simple and apparently minor alterations in structure and complexed cation.

Supramolecular assemblies from lipophilic crown ethers

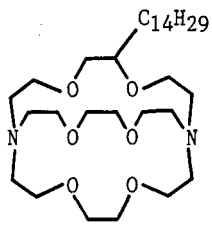
When **6** or **7** (1-5 mM) was dispersed in deionized H_2O (Branson Cell Disruptor, model 185, 40 w, 10 °C), the turbidity of the dispersion decreased until a plateau was reached (3-6 min) indicating the formation of vesicles. Solutions were centrifuged and filtered to remove titanium particles released by the sonicator probe. The pH of the solution (ca. 8.5) was unchanged after dispersion confirming the absence of proton transfer. Similar vesicles were also prepared in the presence of KCl (0.1-1.0 M) and NaCl (0.1 M). In contrast, dispersion of **6** in aqueous LiCl (0.1 M) did not afford vesicles. Instead, micelles were formed under these conditions. An unexpected result was our failure to form vesicles from lithium, sodium, or potassium perchlorate salts. Such anion dependence is known for cationic micelles (ref. 19). The liposomes were characterized by dynamic laser light scattering and electron microscopy. The results of the light scattering measurements for vesicles formed from **6** in the presence and absence of KCl suggest an average size of 700 Angstroms. Vesicle diameter varies with KCl concentration.

The steroidal lariat ether niosomes are stable for several weeks in the light at ambient temperature. Heating the preparations to temperatures just below the melting points of the surfactants did not affect solution opalescence.

Monoaza-18-crown-6 steroidal lariat ether **8** behaves in a surprisingly different way. Either in the absence or presence of LiCl, NaCl, or KCl, it aggregates into micellar form and shows no evidence for vesicle formation. This difference in behavior is likely due to the larger surface area of the macroring of **8** compared to the 15-membered ring systems. The change in behavior for **6** when the cation is altered from Na^+ or K^+ to Li^+, can be accounted for in terms of complexation and solvation strength. Lithium cation exhibits the highest solvation enthalpy of the three cations and the lowest complexation constant with macrocycles. It is therefore likely that solvated lithium cation will be loosely associated with the crown ring while strongly associated to water molecules. The reverse would be true for the other cations thus reducing the surface area of the polar head group.

Supramolecular assemblies from lipophilic cryptands

Montanari, Tundo, and coworkers prepared the first examples of a remarkable class of lipophilic cryptands and have studied their properties in phase transfer catalytic reactions (ref. 20). We have prepared two compounds of this class, one previously reported (**9**) and one having the cholestanyl sidearm attached to the macrobicyclic system (**10**). To our knowledge, the aggregation properties of these compounds have never been studied.



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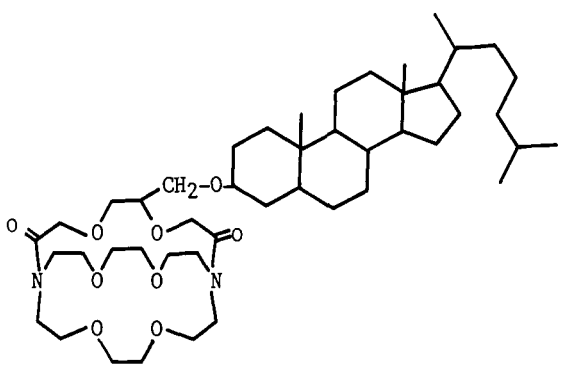

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Treatment (as described above) of **9** results in the formation of micellar aggregates. The cloud point of the micelle is approximately 12.5 °C either alone or in the presence of one added equivalent of Li^+ (13.5 °C). When one equivalent of either Na^+ or K^+ is added, the cloud points increase to 21.0 and 49.0 °C respectively. In previous studies of lipophilic crown ethers, excess cation was often required to observe altered cloud points. The high binding constants and slow cation release rates exhibited by cryptands permit the assumption of single cation complexation and the high likelihood that the cation is retained by the

ligand during aggregation. The lipophilic cryptands thus promise a more controlled type of molecular aggregate in which the relationship of polar head group to cation is better characterized. Critical micelle concentrations for **9** in H_2O are 0.13 mM for Na^+ and 0.11 mM for K^+. Studies of cholestanyl cryptand **10**, a waxy solid exhibiting phase transitions at 63-66 °C and 78-81 °C, are underway. The aggregation states and CMC values are summarized in Table 2.

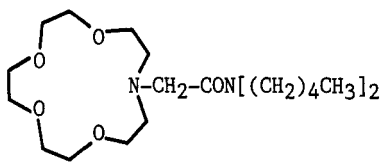
TABLE 2. Aggregation of steroidal lariat ether and cryptand compounds

No.	Compound	Aggregation State			
		Water	0.1M KCl	0.1M NaCl	0.1M LiCl
6	15-crown-5-CH2-CO-O-cholestanyl	niosomes	vesicles	vesicles	micelles
7	15-crown-5-CH2-CO-O-cholesteryl	niosomes	vesicles	vesicles	vesicles
8	18-crown-6-CH2-CO-O-cholesteryl[a]	micelles	micelles	micelles	micelles
9	[2.2.2]-n-$C_{14}H_{29}$[b]	micelles	micelles	micelles	micelles
10	[2.2.2]-CH_2-O-cholestanyl[c]				

[a]Critical micelle concentrations (cmc) were found to be 0.88 mM in water and 0.42 mM in the presence of 0.1M KCl.
[b]CMC for 0.1M KCl, 0.11 mM; 0.1M NaCl, 0.13 mM.
[c]No data yet available.

CATION TRANSPORT BY LIPOPHILIC LARIAT ETHERS

Lithium cation transport has been investigated across lecithin vesicles using the method of Springer, et al. (ref. 21). Lecithin vesicles are prepared by dialysis of a phospholipid:surfactant (5:1) solution in the presence of 150 mM LiCl using a Lipoprep-GD-1 system. Further dialysis vs. 150 mM NaCl affords total exchange of extravesicular Li^+ for Na^+. Dysprosium tripolyphosphate (3.5 mM) is then added to shift the ^7Li NMR signal of extravesicular cation by approximately 5 PPM. The lipophilic carrier is added and Li^+ efflux is monitored by direct integration of the ^7Li signals. Transport rates for **6** and **7** are shown in Table 2. Compound **12** was prepared primarily for comparative purposes since **6** was expected to afford high transport rates. Indeed, the transport of Li^+ by **11** in the vesicular system described above exceeds that for **12** by four powers of ten.



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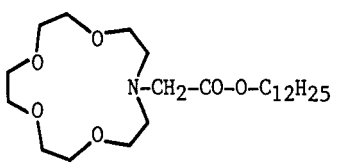

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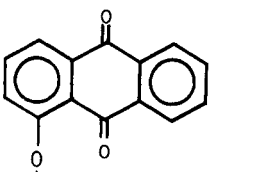
Our studies of these neutral carriers will help define the inherent ability of these compounds to bind and transport a variety of cations. Simultaneous with these efforts, we are studying a variety of electrochemically switched systems and eventually hope to merge these efforts and develop a redox-based, chemically-switched transport system.

ELECTROCHEMICALLY-SWITCHED TRANSPORT

In previously published studies, we have demonstrated that appropriately substituted lariat ethers and podands can be reduced to radical ions capable of strongly binding cations. The presence of intramolecular ion pairs was confirmed by cyclic voltammetric analysis and by EPR spectroscopy. This electrochemical switching ability constitutes the basis of a cation transport pump system, especially if the carrier involved is stable in its reduced form at aqueous interfaces. Using these notions, Saji has recently demonstrated the feasibility of such an electrochemically operated cation pump, if only in a preliminary way (ref. 22). We, on the other hand, have demonstrated enhanced transport rates for lithium cation for an electrochemically reduced quinone podand system compared to its neutral counterpart. We have yet to demonstrate a true pump which requires an oxidation step at the second interface.

Quinone podand **13** exhibits a negligible Li^+-transport rate in its neutral form but, when reduced, transports Li^+ at a rate of $2.2x10^{-7}$ M/h (ref. 23). When **13** is reduced, it turns intensely red, fading to orange within about ten minutes. The orange species transports lithium at the above noted rate and its radical anion structure was confirmed by EPR spectroscopy. Direct observation of Li^+-splitting in the EPR spectrum confirms the strong ion pair formed from reduced **13.** As Saji also noted, these non-lipophilic species gradually partition into water when reduced thus diminishing their effectiveness in transport. It is clear that the combination of a crown or podand for cation association in the neutral state, an electrochemical switch such as provided by the quinone, and enhanced lipophilicity are all crucial to the success of these transport experiments. Compound **14** was prepared for this reason and studies of it and its relatives are currently underway. We anticipate that these ligands will be effective in our goal of developing a usable electrochemically (and later, chemically) switched cation pump system.



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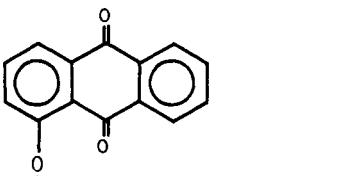

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The progression from simple ligands that complex cations, to molecules that conduct cations across membranes, and finally to molecules that can assemble into membranes is obvious from the above discussion. Our work continues in this direction in the hope that well-characterized and well behaved molecular and supramolecular structures will result.

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