Electrochemical Switching in Reducible Lariat Ethers: from Cation Binding Enhancements to Electrochemically-Mediated Transport

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Abstract. The evolution of lariat ethers from relatively simple, substituted crown ethers into electrochemically sensitive ligands is presented. Although nitrogen-pivot lariats were observed to be better binders than the corresponding parent crowns and to retain considerable flexibility after complexation, overall stability constants were not favorable for cation transport applications. This led to the syntheses of nitrobenzene- and anthraquinone-substituted systems capable of reversible redox behavior and drastically enhanced cation binding abilities when reduced. Application of these in enhanced cation transport processes has been demonstrated.

Key words. Cation transport, electrochemical reduction, EPR, lariat ethers.

1. Introduction

The 1987 Nobel prize in chemistry was awarded to Charles J. Pedersen, Donald J. Cram, and Jean-Marie Lehn not for a single discovery, but for the invention of macrocyclic 'crown' polyethers [1] and their elaboration into cryptands [2], spherands, cavitands [3], and other, related macrocycles. Although very closely related, each of these structures has a unique character. The original monocyclic crown ethers are moderately strong binders of alkali and alkaline earth metal cations and they exhibit a modest cation selectivity. Binding dynamics in crown ether complexation reactions is relatively high. Evolution along the cryptand line gave spherands which, like their predecessors, are very strong and selective cation binders, but the rates of their decomplexation reactions are generally slow.

Cryptands are thus relatively rigid, three-dimensional structures while monocyclic crown ethers are generally flexible, two-dimensional structures [4]. The former exhibit high binding constants and the latter more modest ones under similar circumstances. These considerations led us to develop a class of compounds we call the 'lariat ethers' [5] that were designed to have high binding while retaining considerable flexibility. Structural comparisons of a crown, a cryptand, and a lariat ether are shown in Figure 1 below. In order to emulate the properties of the cryptands, however, the lariat ethers had to be elaborated into systems that could exhibit enhanced cation binding and increased rigidity [6]. This was done by incorporating an electrochemically reducible function [7].
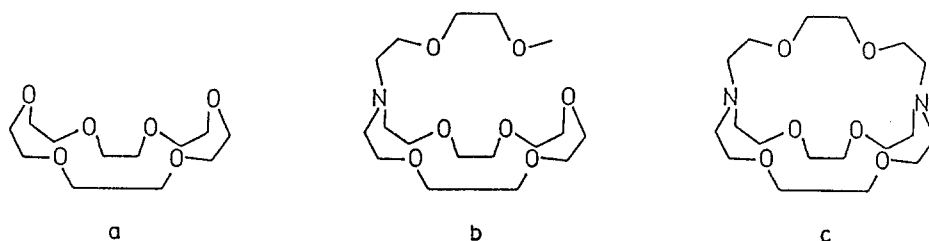
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Fig. 1.   Structural comparisons between (a) crown ether, (b) lariat ether, and (c) cryptand.

Based on these considerations, we have developed, in an evolutionary fashion reminiscent of the crown, cryptand, spherand series, compounds that have become increasingly more specialized in their structural variations and corresponding functions. One of the important considerations guiding this development has been the potential application of these systems in membrane transport. At the beginning of a transport step, strong binding is required. At the end of the transport step, week binding and high dynamics are required. Throughout, good binding strength is needed and this is often accompanied by rigidity and slow kinetics.

The stages of this development are described below along with an assessment of the directions still to be followed.

2. Results and Discussion

2.1. STRUCTURE AND FLEXIBILITY

Initially, two classes of lariat ethers were prepared, the carbon-pivot [5, 8] and the nitrogen-pivot [9] compounds. These differ by the atom to which the donor-group-bearing sidearm is attached to the macroring. Although the cation binding strengths for the carbon-pivot compounds were generally disappointing, the nitrogen-pivot lariat ethers exhibited significant enhancements over structures such as 15-crown-5 or 18-crown-6. For example, aza-15-crown-5 having a $CH_3OCH_2CH_2OCH_2CH_2$ sidearm attached to the macroring nitrogen, binds Na^+ in anhydrous methanol with an equilibrium constant (expressed hereinafter as log K_S) of 4.54. This compares to a binding constant of 3.29 [10] for Na^+ with 15-crown-5 and to a value of 4.34 for Na^+ with 18-crown-6 in methanol. Of course, this is several powers of ten lower than the value of 7.8–8.0 reported for 2.2.2.[cryptand] binding Na^+ [11]. Nevertheless there is a clear binding enhancement when compared to the parent crown ethers. Additional evidence for this was obtained from the solution of several solid state structures of lariat ether-cation complexes showing clear sidearm participation in binding to the cation [12].

Our belief that dynamics and flexibility are both retained in N-pivot lariat ether complexes derives from two sources. First, we have studied the relaxation times (T_1) for a variety of N-pivot lariat ethers using ^{13}C-NMR [6]. The ^{13}C-NMR results show essentially no change in the mobility of detectable nuclei whether or not the lariat ether is complexed by sodium or potassium cations. Second, ultrasound relaxation time studies conducted collaboratively with Petrucci and Eyring [13] have confirmed high binding rates for a two-step complexation mechanism.

From these lines of evidence, it is clear that lariat ethers of this general type do offer enhanced cation binding capability while retaining much of the fast cation exchange dynamics inherent to the monocyclic crown ethers.

2.2. ELECTROCHEMICAL PROPERTIES AND ENHANCED CATION BINDING: THE PRINCIPLE OF SWITCHABILITY

Once the essential structures and dynamics of the lariat ether interactions were established, we began our quest for enhanced cation binding strengths. Our approach was to replace the polyethyleneoxy donor groups in the lariat ether sidearms by systems capable of reversible, electrochemical reduction. The first series of compounds were based on the nitrobenzene system. In the neutral state, the nitrobenzene oxygens served as neutral donors for a ring-bound cation. After electrochemical reduction, a nitrobenzene radical anion was formed, substantially increasing the donicity of the sidearm. As a consequence, the overall binding constant was increased dramatically.
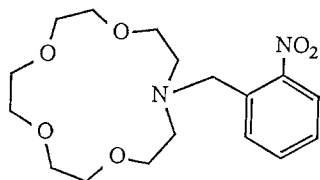
Nitrobenzene-substituted lariat ether

The cyclic voltammogram for the compound illustrated above appeared essentially identical to that observed for 2-nitrotoluene in the absence of any cation. When Na^+ was added to the solution, a significant change in the voltammogram was observed. This change was not observed when the nitro group was in the *para*-position, indicating the importance of proper geometry. The new cyclic voltammogram exhibited a new, quasi-reversible redox couple at a more positive potential than the original one. This was surprising to us since a shift of the existing peak was expected rather than the appearance of a new peak, the intensity of which depended upon the cation concentration (see Figure 2).

The appearance of simultaneous redox pairs, a rather unusual observation, instead of a shift of the existing peak, has not been fully rationalized and is under current investigation in our laboratories. At least part of this behavior can be attributed to the numerical value of K_1 for the neutral ligand. When K_1 is larger than 10 000, two waves are always observed. When K_1 is less than 1, a single peak is observed which appears to be the original peak shifted to a new position as a result of added cation. At K_1 values in the range 1–10 000, the behavior, as expected, is intermediate between the two extremes noted above and depends on the ratio K_2/K_1. Computer simulations based purely on thermodynamic considerations (no kinetic parameters) permit us to simulate the behavior described above. In order to further evaluate all of the chemical and structural contributions to this behavior, we are currently synthesizing the carboxylic acid lariat ether shown below.
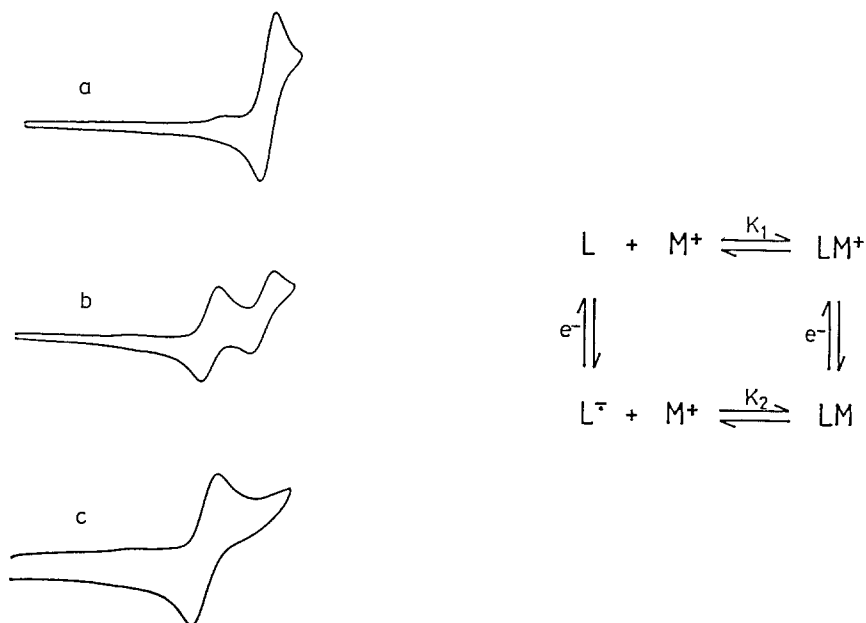
$$L \; + \; M^+ \; \underset{}{\overset{K_1}{\rightleftharpoons}} \; LM^+$$

$$L^{\overline{\cdot}} \; + \; M^+ \; \underset{}{\overset{K_2}{\rightleftharpoons}} \; LM$$

Fig. 2. *Left*: Cyclic voltammograms for N-(2-nitrobenzyl)aza-15-crown-5 in the (a) absence, (b) presence of 0.5 equiv., and (c) presence of 1 equiv. of $NaClO_4$. *Right*: Corresponding electrochemical cycle.

This compound can form an anion by deprotonation and its complexation can be followed in solution using NMR techniques [6]. We believe this compound is the ideal diamagnetic analog of the nitrobenzene lariat ether in its radical ion form. It should provide information on the effect of rigidity on the overall complexation process.
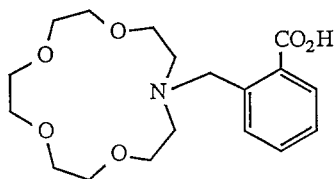
Benzoic acid-substituted lariat ether

Despite these mechanistic intricacies and uncertainties, it is possible to extract considerable information from the electrochemical behavior. When two separate redox couples are observed, it is possible to determine the ratio K_2/K_1, the factor of electrochemically-enhanced cation binding that occurs upon electrochemical switching. The enhancements observed always follow the trend $Li^+ > Na^+ > K^+$. This result is expected in view of coulombic considerations. Factors as high as 10^6 were observed for Li^+ cation and lower values, typically 10^2 were observed for K^+ [7]. Although these enhancement factors exhibit a clear selectivity, the overall binding

ability is actually leveled. The latter is due to the fact that K_1 for typical, neutral crowns and lariat ethers is in the order $K^+ > Na^+ > Li^+$, the reverse of the order observed for electrochemical enhancement [14]. This levelling effect can be overcome by imposing a more rigid binding structure on the reduced ligand. This was demonstrated in a reducible aza-cryptand [15].

At this stage it was demonstrated that reduced lariat ethers could bind cations more strongly than the neutral, parent compounds. These structures, when reduced, exhibit cation binding affinities much closer to those of cryptands than do the neutral lariat ethers and behave as if they are more rigid, cryptand-like structures as well. In contrast to the cryptands, they can be switched back to their low-binding, flexible structures on demand using electrochemical or chemical oxidation.
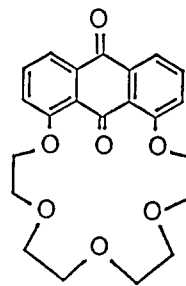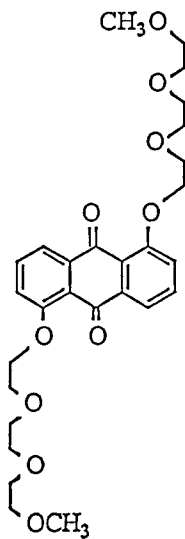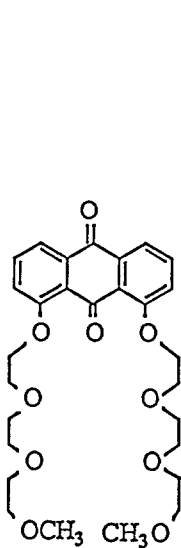
2.3. ANTHRAQUINONE SUBSTITUENTS FOR ONE AND TWO ELECTRON REDUCTION IN AQUEOUS MEDIA: AN ELEMENT OF TUNABILITY

Before attempting to apply these structures directly in cation transport experiments across lipid membranes, it was necessary to replace the nitrobenzene group by one that would afford a water-stable anion radical. After careful consideration of synthetic possibilities, the anthraquinone residue was chosen. This selection afforded an additional flexibility in the switching scheme, namely the possibility of one- and/or two-electron reduction. The latter can be regarded as a tunability feature of the overall system. Several of the anthraquinone derivatives that were prepared as part of this study are shown below.
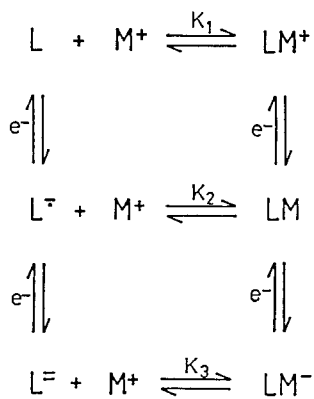
As anticipated, two reversible redox waves were observed for all of these compounds in the absence of a bound cation [16]. Addition of Li^+, Na^+, or K^+, results in most cases in the appearance of additional redox waves. All electrochemical observations are consistent with those presented in the previous section for nitrobenzenes except that they contain an additional redox wave. By controlling the potential, it is possible to observe binding enhancement in two distinct stages: K_2/K_1 and K_3/K_2 (see scheme below).

In contrast to the nitrobenzene derivative results, the observed enhancements are typically lower for the anthraquinone cases. This was expected in view of the fact that charge and spin are much more delocalized in the latter case. Typical enhancement values for Li^+ are 10^3–10^4 for one electron reduction in the case of anthraquinones and 10^2 for Na^+ or K^+. The second electron reduction results in a further enhancement (K_3/K_2). The binding enhancement of the anthraquinone anion is reduced by the more diffuse charge relative to nitrobenzene, but this is compensated by addition of a second electron, a step not easily accessible in the nitrobenzene system.

We have outlined the electrochemical and electron spin resonance properties of several of these systems in a recent series of papers [17]. Results with the anthraquinone lariat ether were successful but unremarkable. Likewise, the single-armed anthraquinone podands behaved as expected. Unexpected behavior was observed for the anthraquinone bis(podands) having the arms arranged either *syn* or *anti*. The anion radical of the *anti* compound bound two cations as expected but the *syn* two-armed anthraquinone podand radical anion did so as well. This behavior was not anticipated and is surprising. The capability of these anion
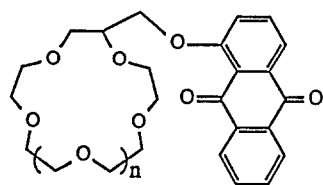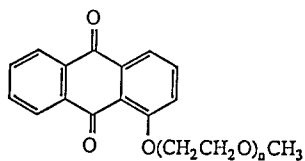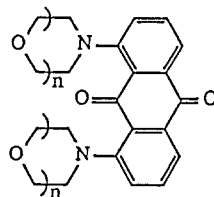
$n = 1,2$ $n = 0-5$ $n = 1,4$

Anthraquinone derivatives

$$L + M^+ \underset{\longleftarrow}{\overset{K_1}{\rightleftharpoons}} LM^+$$

$$L^{\overline{\cdot}} + M^+ \underset{\longleftarrow}{\overset{K_2}{\rightleftharpoons}} LM$$

$$L^{=} + M^+ \underset{\longleftarrow}{\overset{K_3}{\rightleftharpoons}} LM^-$$

Scheme 1. Electrochemical cycle for anthraquinone derivatives.

radicals to bind one and/or two cations adds an extra dimension in the degree of flexibility, if not tunability of these systems [18]. EPR results also indicate that the cyclic anthraquinone compound possesses an exceptionally high affinity for Na^+ when reduced.

Preliminary results with the morpholino and aza-15-crown-5 compounds illustrated above have shown interesting cation selectivities upon electrochemical reduction. It appears, for example, that the bis-crown is unaffected by K^+ although the electrochemical behavior is more normal in the presence either of Li^+ or Na^+. The morpholino case exhibits a gradual disappearance of the second redox couple as the cation concentration is increased. This apparently indicates the formation of a strong 2:1 ligand-to-metal complex. Further synthetic, voltammetric, and EPR experiments are underway.

2.4. APPLICATIONS IN CATION TRANSPORT

An important advantage of the anthraquinone system is the stability of its radical anion in the presence of water at neutral pH. When an anthraquinone radical anion podand was added to a two-phase, CH_2Cl_2–water system containing Li^+, the cation was transported into the organic phase. This was demonstrated unequivocally using electron spin resonance spectroscopy by detection of a 0.33 G Li-hyperfine splitting.

When an H-shaped cell was constructed, the neutral anthraquinone podand failed to transport Li^+. Upon coulometric reduction to the corresponding anion radical, the podand was able to transport Li^+ at a rate of 2.2×10^{-7} moles/hour [19]. This electrochemically-enhanced transport scheme, clearly shows that it is possible to
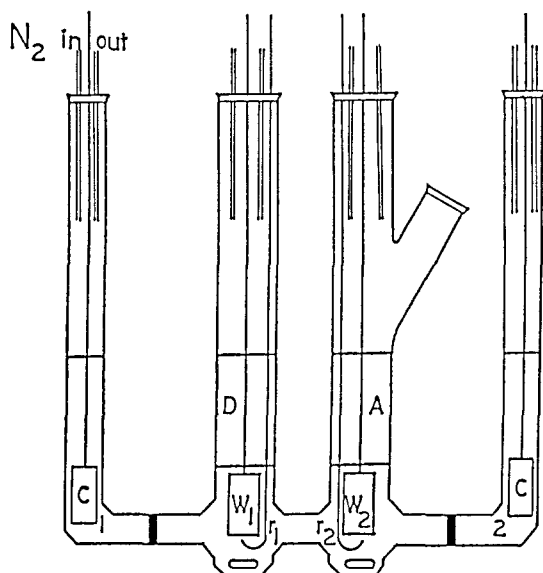

Fig. 3. Diagram of modified transport cell: (D) aqueous donor phase; (A) aqueous receiving phase; (W_1) and (W_2) working electrodes for reduction and oxidation respectively; (r_1) and (r_2) reference electrodes; (C_1) and (C_2) counter electrodes.

attain both enhanced cation binding and enhanced cation transport ability upon reduction.

More recent results have been obtained using a modified version of the previously reported H cell (see Figure 3 below). Two potentiostats are used simultaneously, one to reduce the anthraquinone ligand near the donor organic interface and the other to oxidize the complexed, neutral species near the receiving interface. Such an experimental arrangement has been reported by Saji [20] and is clearly not without its problems. Nevertheless, we have recently shown further cation transport rate enhancements using this approach. Refinements in this approach are still required.

2.5. THE FUTURE FOR CHEMICAL REDOX-DRIVEN SYNTHETIC ION PUMPS

Our efforts to prepare suitable switchable carriers have suffered from several difficulties that did not become apparent until actual transport experiments were attempted. It now appears that the combination of a macroring or podand, an anthraquinone, and a lipophilic residue are all required. The lipophilic residue must be attached through a non-hydrolytically-sensitive linkage and best results seem likely when the lipophilic residue and cation binding portions of the molecule are non-adjacent. We have already begun studies of switchable transport in lipid bilayers but for these experiments, highly lipophilic carriers are imperative. Furthermore, reduction and oxidation must be accomplished by chemical rather than electrochemical means. Suitable redox agents are currently under evaluation. Another important but currently remote goal is to develop ion channel structures which would incorporate reducible groups capable of providing on–off gating in these channels.

3. Experimental

3.1. GENERAL METHODS

Preparations for the compounds described herein are given in the references cited above. All new compounds were characterized by NMR, IR, and combustion analysis as a minimum as described in those references.

3.2. REAGENTS FOR ELECTRON SPIN RESONANCE AND CYCLIC VOLTAMMETRY

Tetrahydrofuran (THF, Aldrich) was flask-to-flask distilled from the vacuum line immediately prior to use. Dichloromethane (Aldrich) was distilled from CaH_2. All solutions were prepared either under vacuum or under an atmosphere of dry N_2. Tetrabutylammonium perchlorate (TBAP, Fluka) was twice recrystallized from EtOAc and stored in a desiccator. Alkali metal perchlorate salts (Aldrich) were recrystallized from deionized water and dried in a vacuum oven at 100°C for 24 h.

3.3. ELECTRON PARAMAGNETIC RESONANCE

EPR spectra were recorded for dry THF solutions by using the X-band of an IBM ER-200D SRC spectrometer. Samples were prepared under vacuum (10^{-3} mm)

by reaction of a 10^{-3} M solution of the compound with either sodium or potassium metal. Spectra in the presence of Li^+ were obtained in purified CH_2Cl_2 by controlled-potential electrolysis by using TBAP as the supporting electrolyte and 1 M $LiClO_4$ aqueous solution directly in the ESR cavity.

3.4. CYCLIC VOLTAMMETRY EXPERIMENTS

The electrochemical experiments were performed at 25°C under N_2 in MeCN 0.1 M in TBAP. The electroactive species was present in millimolar concentrations. Glassy carbon was used as the working electrode and a Pt wire as the counter electrode. E^0 values are reported vs. saturated calomel electrode (SCE). The measurements were done on a Bioanalytical Systems (Model 100) electrochemical analyzer, equipped with IR compensation.

Acknowledgement

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