Communications to the Editor

Enhanced Sodium Cation Binding by Electrochemically Reduced Nitrobenzene-Substituted Lariat Ethers

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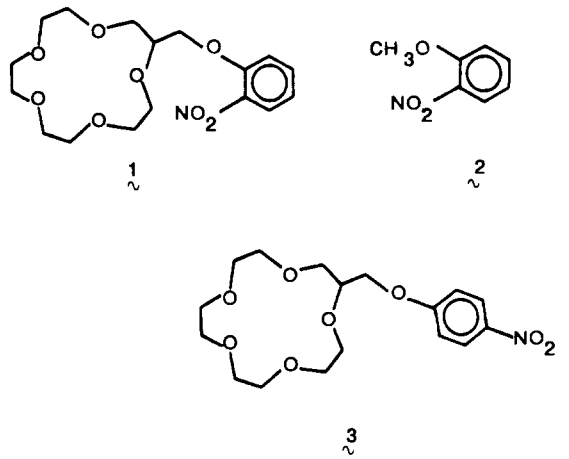
An important advantage of lariat ethers[1] over monocyclic crown ethers is the presence of a side arm whose properties may be varied to control binding and, it is hoped, selectivity. Moreover, the potential exists for reversibly switching the ligand and altering its binding strength on demand. Photoswitching,[2] ionization of acidic functions,[3] protonation of amines,[4] and oxidative dimerization of sulfhydryl-substituted crowns[5] have all been utilized to one degree or another as reversible switching mechanisms. We report here the first evidence for electrochemically controlled electron-transfer switching and intramolecular ion-pair formation in nitrobenzene-derived lariat ethers.

2-(2-Nitrophenoxy)methyl-15-crown-5 (**1**) was prepared by treating the anion (NaH, THF) of 2-hydroxymethyl-15-crown-5[6] with 1 equiv of 1-chloro-2-nitrobenzene (25 °C, 4 h). The crown was a pale yellow oil isolated (55%) by chromatography over alumina.[7] 2-(4-Nitrophenoxy)methyl-15-crown-5 (**3**) was prepared analogously and isolated (bp 175 °C (0.1 mm)) as a yellow oil in 74% yield.[7] All electrochemical experiments were conducted under dry N_2 in MeCN 0.1 M in Bu_4NClO_4. A standard three-compartment cell, glassy carbon (0.35-cm^2 surface), and Pt wire electrodes were used. $E^{\circ\prime}$ values are reported vs. an aqueous Na^+-saturated calomel electrode (SSCE). Measurements



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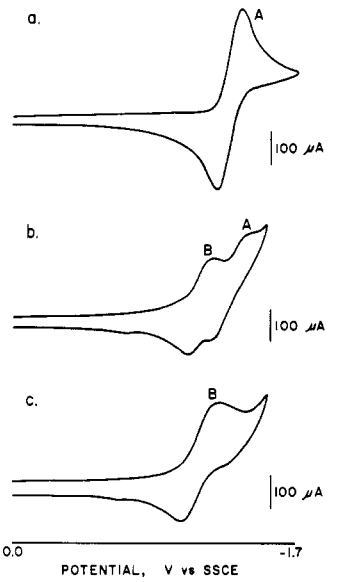

Figure 1. Cyclic voltammograms for 2-(2-nitrophenoxy)methyl-15-crown-5 (**1**) in the (a) absence and (b) presence of 0.5 equiv and (c) presence of 1 equiv of $Na^+ClO_4^-$.

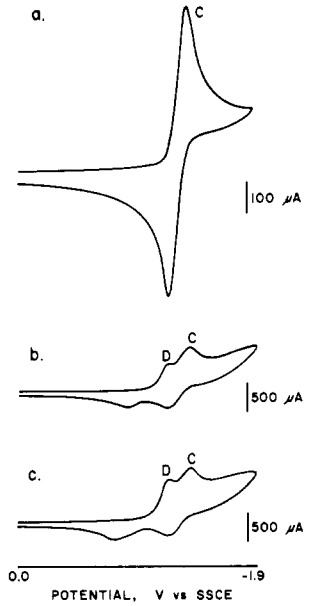

Figure 2. Cyclic voltammograms for 2-nitroanisole (**2**) in the (a) absence and (b) presence of 0.5 equiv and (c) presence of 1.0 equiv of $Na^+ClO_4^-$.

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(7) (a) Compound **1**: ^1H NMR ($CDCl_3$, ppm) 3.9 (m, 21 H), 6.9–8.1 (m 4 H). Anal. Calcd for $C_{17}H_{25}NO_8$: C, 54.98; H, 6.78; N, 3.77. Found: C, 54.62; H, 6.91, N, 3.78. (b) Compound **3**: ^1H NMR ($CDCl_3$, ppm) 3.7 (m, 21 H), 7.0–8.2 (dd, 4 H). Anal. (Isomer of **1**) found: C, 54.99; H, 6.95; H, 3.90.

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Table I. Electrochemical Data for Na^+ Effect on Nitroaromatics

compd	couple[a]	Na^+/L ratio[b]	E_p^{red}, V	E_p^{ox}, V	$E^{\circ\prime}$, V[c]
1	A	0	−1.36	−1.21	−1.28
	A	1/2	−1.38	−1.18	−1.28
	A	1			
	B	0			
	B	1/2	−1.17	−1.04	−1.11
	B	1	−1.22	−1.00	−1.11
2	C	0	−1.36	−1.22	−1.29
	C	1/2	−1.37	−1.21	−1.29
	C	1	−1.37	−1.21	−1.29
	D	0			
	D	1/2	−1.20	−0.87	
	D	1	−1.20	−0.78	
3		0	−1.28	−1.15	−1.22
		1/2	−1.28	−0.99	
4		0	−1.29	−1.17	−1.23
		1/2	−1.33	−1.17	−1.25

[a] See figure. [b] L = nitroaromatic (ligand). [c] Diffusion coefficients for reduced and oxidized forms were assumed to be equal.

were done with a Princeton Applied Research apparatus (Models 173 and 176) and recorded on an H-P 7045A x-y recorder.

The cyclic voltammograms (cvs) for **1** and 2-nitroanisole (**2**) in the presence and absence of Na^+ are shown in Figures 1 and 2. The data for **1**, **2**, **3**, and 4-nitroanisole (**4**) are summarized in Table I. The quasi-reversible, one-electron redox couples for **1** and **2** (A and C, respectively) exhibit virtually identical $E^{\circ\prime}$ values (see figures) indicating that CH_3O- or crown-CH_2O- has a similar effect on the nitroaromatic nucleus. When $NaClO_4$ (0.5 equiv) is added to solutions of **1** or **2**, a new redox couple (quasi-reversible for **1**/B; irreversible for **2**/D, see figure) appears in each case. Couple A disappears when a full equivalent of Na^+ is added to **1** and only couple B is observed, with an enhanced current. The oxidation peak of D moves to more positive potential when **1** equiv of Na^+ is added to **2**, the reduction potential does not change, and C is not dissipated. In the absence of Na^+, the single redox couples observed for **3** and **4** are nearly identical. The similarity continues when 0.5 equiv of Na^+ is present in solutions of **3** or **4**. No new redox couple is observed in either case although additional Na^+ increases irreversibility (see table).

The results described clearly suggest an intramolecular interaction between the macroring-bound cation and the reduced nitroaromatic side arm of **1**. The intramolecularity of this interaction is clear from two lines of evidence. First, **3**, which has all the structural elements of **1**, behaves differently because the nitro group is inappropriately situated. Second, the significant intermolecular interaction between Na^+ and $\mathbf{2}^-$ (a surprising, but not difficult to rationalize, observation), which leads to electrochemically irreversible behavior, contrasts nicely with the weaker interaction observed between Na^+ and $\mathbf{1}^-$. The latter process is quasi-reversible, indicative of kinetically fast electrode processes for couple B. This probably results from the ready availability of macroring-bound Na^+ to intramolecularly ion pair with the reduced nitroaromatic side arm.

The electrochemically enhanced binding constant, K_s, for $\mathbf{1}^-$ with Na^+ can be assessed by a simple, thermochemical cycle since the $E^{\circ\prime}$ values are known and $Ks_{\mathbf{1}\cdot Na^+}$ has been measured by previously described methods.[1,8] Redox couples A and B correspond to eq 2 and 1, respectively. The difference (eq 2 − eq 1 = eq 3) gives K_{ee} for electron exchange between $\mathbf{1}^-$ and $\mathbf{1}\cdot Na^+$.

$$\mathbf{1}\cdot Na^+ + e \rightarrow \mathbf{1}\cdot Na \quad (1)$$

$$\mathbf{1}^- \rightarrow \mathbf{1} + e \quad (2)$$

$$\mathbf{1}\cdot Na^+ + \mathbf{1}^- \rightarrow \mathbf{1}\cdot Na + \mathbf{1} \quad (3)$$

K_{ee}, when multiplied by $Ks_{\mathbf{1}\cdot Na^+}$, gives the stability constant for the $Na^+\cdot\mathbf{1}^-$ complex. From the $E^{\circ\prime}$ values, the electrochemically reduced ligand binds Na^+ 750 times more strongly than does the neutral ligand. Therefore, log $Ks_{\mathbf{1}\cdot Na}$ = 6.33.

To our knowledge, this is the first time an intramolecular complex between Na^+ and a radical anion crown ether ligand has been detected. This is also the first direct evidence for enhanced binding by an electrochemically reduced macrocyclic ligand. The latter is especially important since it represents a new switching mechanism for lariat ether complexes. The generality of these observations and this approach, especially the potential for reversible, electrochemically switched cation transport, are currently under investigation.

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Registry No. 1, 87453-20-1; $Na^+\mathbf{1}^-$, 87453-19-8; **2**, 91-23-6; **3**, 87453-21-2; **4**, 100-17-4; Na, 7440-23-5; 2-hydroxymethyl-15-crown-5 anion, 87453-22-3; 1-chloro-2-nitrobenzene, 88-73-3.

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Glutathiohydroxyacetone: ^1H NMR Determination of the Stereochemistry of Proton Exchange by Glyoxalase I. Evidence for a *cis*-Enediol Intermediate Based on Mirror-Image Catalysis

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We have recently reported that (glutathiomethyl)glyoxal (**1**) is an inverse substrate for glyoxalase I [(*S*)-lactoylglutathione methylglyoxal-lyase (isomerizing) EC 4.4.1.5; GX I].[2] The reaction is characterized by a loss of specificity for glutathione in thioester **3** formation *via* thiohemiacetal **2** and by the production of the *S* isomer of **3** (Scheme I). We have termed the effect "mirror-image catalysis". The key implication of this finding is the uncoupling of the two functions of glutathione: activation of the C-1 proton by thiohemiacetal formation and binding of the thiohemiacetal to the enzyme. Since the role of RSH in the inverse processing of **1** is essentially activation and not binding, one might intuit that the increased acidity of the C-1 proton could be accomplished by a variety of structures that are intrinsically more stable and better defined than the stereochemically ambiguous thiohemiacetal **2**. To this end, we have found that glutathiohydroxyacetone **6**[2] undergoes a stereospecific GX I catalyzed exchange of one hydroxymethyl proton and have established the absolute stereochemistry by the unambiguous synthesis of both monodeuterated diastereomers of **6**. The analysis relies on the nonequivalence of the hydroxymethyl proton resonances by 500-MHz ^1H NMR. The results strongly suggest the selective processing of one of the diastereomeric thiohemiacetals and are consistent with the intermediacy of a *cis*-enediol.

The synthesis of **6** was accomplished by the reaction of chlorohydroxyacetone[3] and glutathione (GSH) under aqueous conditions (Scheme II).[4] At 500 MHz the hydroxymethyl protons

(1) American Cancer Society Faculty Research Awardee (1983–1988).

(2) Kozarich, J. W.; Chari, R. V. J. *J. Am. Chem. Soc.* **1982**, *104*, 2655. The proper (current *Chemical Abstracts* Index) name for **1** is *N*-[*N*-L-γ-glutamyl-*S*-(2,3-dioxopropyl)-L-cysteinyl]glycine and for **6**, *N*-[*N*-L-γ-glutamyl-*S*-(3-hydroxy-2-oxopropyl)-L-cysteinyl]glycine.

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(4) In a typical reaction, chlorohydroxyacetone (15 μmol) and GSH (15 μmol) were added to ^2H_2O (>95%) containing 0.2 M potassium phosphate (pD 7.2; 0.6-mL total volume). Formation of **6** was monitored at 293 nm ($\epsilon_{293} \cong 200\ M^{-1}\ cm^{-1}$) and was complete in 15 min.

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