in size of the incubated "monomeric" vesicles.

The vesicular suspensions of ω-MA were not colloidally stable, whereas the poly(ω-MA) suspensions were stable. Within hours of centrifugation the mean size was significantly increasing, and the suspensions appeared flocculent after incubation overnight. The initial sizes indicate a slightly smaller size than the α-MA vesicles, in the 170–250-Å range. After incubation, the nonpolymerized vesicles could not be fitted to a single experimental relaxation function. This generally indicates a bimodal distribution, i.e., two major sizes, with few intermediately sized particles. Again, the smaller of the two sizes is usually predominant.

Polymerization of the vesicle membrane alters the predominant radius of the vesicles prepared by sonication to ~300–400 Å. Although larger particles are present, they do not represent a significant fraction of material as little material pelletted upon centrifugation, which yielded the small predominant apparent mean-sized vesicles.

Conclusions

Thermally initiated polymerization of bilayer membranes of α-MA and ω-MA gave polymers with retention of the vesicle structure. The mean size distribution of the colloidal suspension was not significantly altered by the polymerization. The membranes still sequestered [^{3}H]glucose, and the permeability of the bilayer membrane decreased to about 0.5 of that of the nonpolymerized membranes. The number-average molecular weights estimated for poly(α-MA) and poly(ω-MA) suggest that the average polymer chain consists of 500 units.[27] These data coupled with the radii of the vesicles show that there are 20 to a few hundred polymer chains per vesicle of poly(α-MA) or poly(ω-MA).

The observed moderate reduction in permeability on polymerization is probably a consequence of the large number of polymer chains per vesicle. Differential scanning calorimetry of these membranes shows that the phase transition has been shifted only a few degrees; thus the lipid chain mobility in both poly(α-MA) and poly(ω-MA) is not greatly reduced. Membrane permeability may be further reduced by cross-linking the polymer chains, either with appropriately designed lipids, which contain multiple reactive groups, or by the addition of membrane-soluble cross-linking agents to lipids such as ω-MA.

The first approach is exemplified by poly(butadiene PC) vesicles, which showed a significant reduction in glucose permeability. These vesicles successfully encapsulated glucose for several days and were not disrupted by the addition of surfactant. Photopolymerization of butadiene taurine vesicles only moderately reduced membrane permeability. The difference in permeability properties of polymerized membranes of each of these suggests that effective reduction in membrane permeability is more likely with lipid molecules that contain reactive groups arranged to enhance intermolecular rather than intramolecular reaction.

Finally, caution must be exercised in describing the materials formed upon polymerization of lipids in vesicle structures. In many instances the vesicles will consist of several polymer chains, which enhance the stability of the vesicle to various reagents and conditions, without necessarily producing a major change in membrane permeability. However, polymerization of appropriately designed lipids, e.g., butadiene PC, can yield vesicles with enhanced stability and significantly reduced permeability to nonionic water-soluble species.

Registry No. α-MA, 81571-93-9; poly(α-MA), 87279-13-8; ω-MA, 87279-14-9; poly(ω-MA), 87279-15-0; butadiene PC, 88589-84-8; poly(butadiene PC), 88589-85-9; butadiene taurine, 88589-82-6; poly(butadiene taurine), 88589-83-7; D-glucose, 50-99-7; dioctadecylamine, 112-99-2; acrylonitrile, 107-13-1; 3-(dioctadecylamino)propionitrile, 28288-18-8; *N*,*N*-dioctadecyl-1,3-propanediamine, 15337-59-4; methacryloyl chloride, 920-46-7; *N*-[3-(dioctadecylamino)propyl]methacrylamide, 76282-14-9; 12-hydroxydodecanoic acid methacrylate, 63439-30-5; 6-(dimethylamino)-1-hexanol, 1862-07-3; 12-methacryloyloxydodecanoic acid *N*,*N*-dimethylhexanamine ester, 88589-86-0; octadecyl bromide, 112-89-0; triethyl 4-phosphonocrotonate, 10236-14-3; dodecylaldehyde, 112-54-9; (*E*,*E*)-2,4-hexadecadienoic acid ethyl ester, 59404-47-6; 2,4-hexadecadienoic acid, 59404-48-7; *N*,*N*-bis(2-hydroxyethyl)-2-sulfoethylamine, 10191-18-1; 2,4-hexadecadienoic anhydride, 88589-87-1.

Electrochemically Switched Cation Binding in Nitrobenzene-Substituted, Nitrogen-Pivot Lariat Ethers

Deborah A. Gustowski,[†] Luis Echegoyen,*[‡,⊥] Deepa M. Goli,[†] Angel Kaifer,[⊥] Rose Ann Schultz,[†] and George W. Gokel*[†]

Contribution from the Departments of Chemistry, University of Maryland, College Park, Maryland 20742, University of Miami, Coral Gables, Florida 33124, and University of Puerto Rico, Rio Piedras, Puerto Rico 00931. *Received September 19, 1983*

Abstract: *N*-2-Nitrobenzylmonoaza-15-crown-5 (**2**) and *N*-4-Nitrobenzylmonoaza-15-crown-5 (**4**), representatives of a new class of N-pivot lariat ethers bearing reducible nitroaromatic side arms, have been prepared and examined by cyclic voltammetric techniques. When the nitro group is sterically disposed to permit interaction with the ring-bound cation (**2**), intramolecular ion pairing occurs. This is not the case when the side arm is remote from the macroring (**4**) nor when the side arm is detached. A thermochemical cycle is used to determine that the binding constant (K_s) enhancement in MeCN solution is 25000-fold upon electrochemical switching.

We have previously reported the synthesis of macrocyclic polyether compounds having donor-group-bearing side arms attached at both carbon[1] and nitrogen pivot points.[2] These lariat ethers exhibit a variety of interesting properties, but in general, the N-pivot compounds have proved more versatile as enhanced cation binders than the C-pivot structures. We believe that this is due, at least in part, to the geometrical requirements of cation binding. In the N-pivot structures, cation binding by the macroring involves the nitrogen lone pair and forces the side arm into a more or less perpendicular position appropriate for a secondary

[†] University of Maryland.
[‡] University of Miami.
[⊥] University of Puerto Rico.

(1) Dishong, D. M.; Diamond, C. J.; Cinoman, M. I.; Gokel, G. W. *J. Am. Chem. Soc.* **1983**, *105*, 586.

(2) (a) Schultz, R. A.; Dishong, D. M.; Gokel, G. W. *Tetrahedron Lett.* **1981**, 2623. (b) Schultz, R. A.; Dishong, D. M., Gokel, G. W. *J. Am. Chem. Soc.* **1982**, *104*, 625. (c) Schultz, R. A.; Schlegel, E.; Dishong, D. M.; Gokel, G. W. *J. Chem. Soc., Chem. Commun.* **1982**, 242.

0002-7863/84/1506-1633$01.50/0

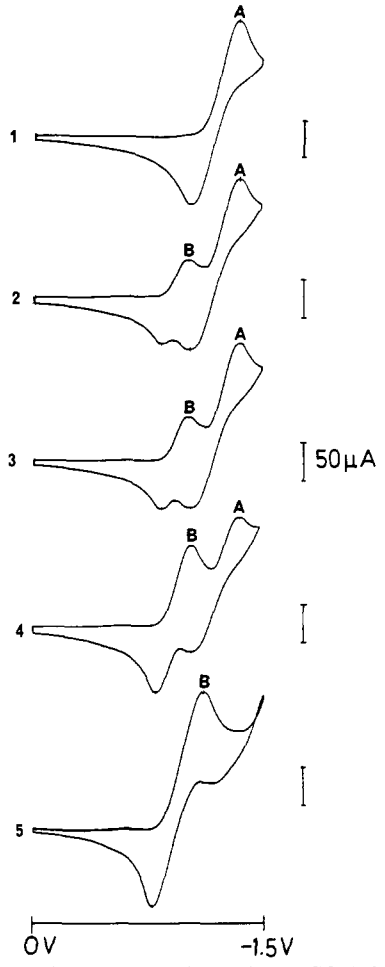


Figure 1. Cyclic voltammograms (potential vs. SCE) for *N*-(2-nitrobenzyl)monoaza-15-crown-5 (**2**) alone (1) and in the presence of (2) 0.25, (3) 0.33, (4) 0.50, and (5) 1.00 equiv of $NaClO_4$.

interaction of the donor group with the ring-bound cation.[3]

Typically, C-pivot lariat ethers bearing ethyleneoxy side chains show much smaller incremental binding than do the corresponding N-pivot structures. When compounds having nitroaromatic side chains are compared, there is little difference in the binding between *o*-nitro vs. *p*-nitro or between C-pivot and N-pivot structures. This is because the cations we have studied do not interact strongly with neutral nitroaromatic moieties. In contrast, when the nitroaromatic side arm is electrochemically reduced to form a radical anion, the side arm and ring-bound cation interact approximately 10^3 times more strongly.[4] Since the cation binding interactions with N-pivot molecules have generally proved stronger than those with C-pivot structures, we anticipated that the electrochemically reduced N-pivot lariat ethers having nitroaromatic side arms would show an even higher degree of cation binding enhancement than noted above. We report here the first evidence for dramatically enhanced sodium cation binding by electrochemically switched nitroaromatic N-pivot lariat ethers.

Experimental Section

N-Nitrobenzylation of Monoaza-15-crown-5. Monoaza-15-crown-5, obtained by hydrogenolysis of *N*-benzylmonoaza-15-crown-5 (9 mmol) as previously described,[5] Na_2CO_3 (18 mmol), MeCN (30 mL), and either 2- or 4-nitrobenzyl bromide (9 mmol) were heated at reflux for 24 h. The reaction mixture was cooled and filtered, the solvent evaporated, the residue dissolved in $CHCl_3$ (20 mL), cooled, filtered, and the solvent evaporated. This residue was then purified as described below.

(3) Fronczek, F. R.; Gatto, V. J.; Schultz, R. A.; Jungk, W. J.; Colucci, R.; Gandour, R. D.; Gokel, G. W. *J. Am. Chem. Soc.* **1983**, *105*, 6717.
(4) Kaifer, A.; Echegoyen, L.; Gustowski, D. A.; Goli, D. M.; Gokel, G. W. *J. Am. Chem. Soc.* **1983**, *105*, 7168.
(5) Gokel, G. W.; Garcia, B. J. *Tetrahedron Lett.* **1977**, 317.

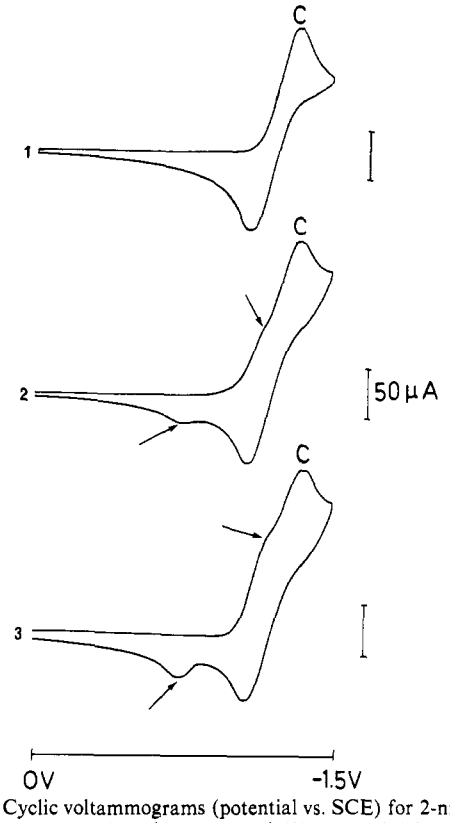


Figure 2. Cyclic voltammograms (potential vs. SCE) for 2-nitrotoluene (**3**) in the absence (1) and presence of (2) 0.5 and (3) 1.0 equiv of $NaClO_4$. Arrows indicate the presence of a new, irreversible redox couple.

***N*-2-Nitrobenzylmonoaza-15-crown-5 (2).** Compound **2** was isolated (35%) as a yellow oil after chromatography (200 g, Al_2O_3, 2% 2-PrOH/hexanes) and Kugelrohr distillation (156 °C (0.05 torr)). NMR δ 2.75 (t, 4 H), 3.60 (m, 16 H), 3.95 (s, 2 H), 7.50 (m, 4 H); IR (neat) 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.

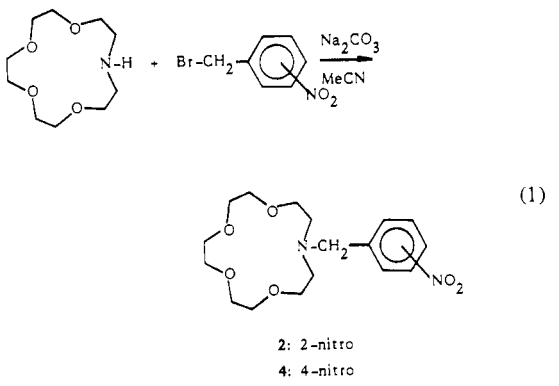
***N*-4-Nitrobenzylmonoaza-15-crown-5 (4).** Compound **4** was isolated (22%) as a yellow oil after chromatography over Al_2O_3 (200 g, 2% 2-PrOH/hexanes), then Kieselgel 60 Silica (300 g, 18:1 $CHCl_3$/MeOH), and finally Chromatotron chromatography (0.75 g partially purified **4** in 10 mL of $CHCl_3$ applied to a 4-mm rotating silica plate, eluted with $CHCl_3$, collecting 5-mL fractions). Compound **4** solidified to a glass on standing for 500 h. NMR δ 2.75 (t, 4 H), 3.65 (m, 18 H), 7.85 (dd, 4 H); IR (Nujol) 2900, 1600, 1520, 1350, 1310, 1260, 1125, 860, 750 cm^{-1}. Anal. Isomer of **2**. Found: C, 57.38; H, 7.58; N, 7.80.

2-Nitrotoluene (**3**) and 4-nitrotoluene (**5**) were purchased from Eastman Organic Chemicals and the former was used as obtained. Compound **5** was recrystallized from 90% EtOH and dried in vacuo prior to use.

The electrochemical experiments were performed under dry N_2 in MeCN 0.1 M in Bu_4NClO_4. The supporting electrolyte was recrystallized twice from EtOAc and then dried in vacuo. Glassy carbon was used as the working electrode and a Pt wire as the counterelectrode. $E^{0\prime}$ values are reported vs. a saturated aqueous calomel electrode (SCE). The measurements were done on a Bioanalytical Systems (Model CV-1B) apparatus and recorded on a Hewlett-Packard Moseley 7035-B *x*–*y* recorder.

Results and Discussion

Monoaza-15-crown-5 (**1**) was prepared from the corresponding *N*-benzylmonoaza-15-crown-5, which in turn derives from *N*-benzyldiethanolamine.[5] Reaction of **1** with either 2-nitrobenzyl chloride or 4-nitrobenzyl chloride in the presence of Na_2CO_3 and DMF yields *N*-(2-nitrophenylmethyl)monoaza-15-crown-5 (**2**) or *N*-(4-nitrophenylmethyl)monoaza-15-crown-5 (**4**), respectively. This is illustrated in eq 1. Cyclic voltammograms in anhydrous MeCN were obtained for **2**, 2-nitrotoluene (**3**), **4**, and 4-nitrotoluene (**5**). Incremental addition of $NaClO_4$ (0–1 equiv) produced the changes observed in the cyclic voltammograms shown in Figures 1 and 2 and summarized in Table I.



(1)

2: 2-nitro
4: 4-nitro

The electrochemical results observed when Na^+ is added to a solution of **2** are similar to the results previously reported for 2-(2-nitrophenoxy)methyl-15-crown-5,[4] but the results are much more striking. In the present case, the initial redox couple for neutral **2** is observed at −1.16 V vs. SCE. When Na^+ is added, a new redox couple appears at −0.90 V, a 0.26 V displacement. The corresponding displacement in the C-pivot system[4] was 0.17 V or substantially less than observed in the present case.

The clear relationship between the relative peak intensities of the respective couples for **2** as the Na^+ concentration is increased shows that the new, quasireversible redox couple corresponds to the Na^+-lariat ether complex. When 2-nitrotoluene (**3**) is reduced in MeCN solution as described above, a quasireversible couple is observed at −1.17 V. As expected, this potential is almost identical with that of 2-nitrophenoxymethyl-15-crown-5. When Na^+ is added, a new redox couple is observed, but in this case, the couple is quite irreversible (see Figure 2). The current intensity of this new couple depends on the amount of Na^+ present as it does with **2**.

There are two important differences observed between these two systems. First, the peak potentials of the new redox couple observed with **3** are not much different from the original couple. This suggests a relatively weak interaction when Na^+ interacts with the side arm (**3**) but no polyether ring is present. Second, the difference in reversibility of the new redox couple (**2** compared to **3**) suggests that Na^+ is kinetically available to interact with the reduced nitroaromatic side arm when it is already bound by the macroring. This is not the case when the side arm is not attached to a ring and the nitroaromatic must compete with solvent for Na^+ in this case. This is clear evidence for cooperative binding involving both the side arm anion radical and macroring in **2**.

Confirmation of this intramolecular cooperativity is also obtained by comparing the 2- and 4-nitrophenyl lariat ethers (**2** and **4**). In the latter case, the nitro group is too remote to interact with a ring-bound cation and no second redox couple is observed at all, even when a full equivalent of Na^+ is present. As Na^+ is added to a solution of **4**, the only change observed in the cyclic voltammogram is a slight displacement of the redox couple to more positive potential accompanied by a slight increase in irreversibility. This behavior is almost exactly paralleled by 4-nitrotoluene (**5**).

It was of interest to us to determine the stability constant (K_s) for the reaction shown in eq 1.

$$\text{crown}^- + Na^+ \xrightarrow{K_s} \text{complex}$$

If K_s(radical anion) is much larger than K_s(neutral lariat ether), and the redox conversion is efficient and reversible, a facile switching mechanism exists which may be exploited in transport phenomena. Since the $E^{0\prime}$ values are known for all of the compounds of interest, we applied the following series of equations to obtain a measure of K_s for the radical anion system.

$$2^- \rightarrow 2 + e \qquad E^{0\prime} = +1.16 \text{ V} \tag{2}$$

$$2{\cdot}Na^+ + e \rightarrow 2{\cdot}Na \qquad E^{0\prime} = -0.90 \text{ V} \tag{3}$$

$$2{\cdot}Na^+ + 2^- \rightarrow 2{\cdot}Na + 2 \qquad E^{0\prime} = +0.26 \text{ V} \tag{4}$$

An $E^{0\prime}$ value of +0.26 V corresponds to a K_s value of 2.48×10^4. Since K_s for neutral **2** with Na^+ is known from independent measurements, eq 5, the binding constant for 2^- with Na^+, eq 6, can easily be determined.

$$2 + Na^+ \rightarrow 2{\cdot}Na^+ \qquad K = 1.58 \times 10^3 \tag{5}$$

$$2^- + Na^+ \rightarrow 2{\cdot}Na \qquad K = 3.93 \times 10^7 \tag{6}$$

The increase in stability constant when **2** is in the radical anion form compared to the neutral form is approximately 25 000. This enormous increase in cation binding strength exceeds that observed for the C-pivot systems in which the analogous increase was only 750-fold. This superior binding strength is anticipated for N-pivot systems as noted in the introduction. More important, however, it suggests that not only can these compounds be used as effective switches, but also they exhibit constants which have values previously observed only for three-dimensional binders like cryptands.

The search for compounds that exhibit even higher levels of switched binding, enhanced or switched selectivities, and applications of these structures in transport is ongoing.

Table I. Effect of Na^+ on Nitroaromatic Electrochemistry[a]

compd no.	couple code	Na^+/L, equiv	Ep(c), V	Ep(a), V	E°, V
2	A	0	−1.28	−1.05	−1.16
	A	0.25	−1.28	−1.04	−1.16
	A	0.33	−1.29	−1.04	−1.17
	A	0.50	−1.26	−1.05	−1.16
	A	1.00			
	B	0			
	B	0.25	−0.97	−0.82	−0.90
	B	0.33	−0.98	−0.82	−0.90
	B	0.50	−0.98	−0.82	−0.90
	B	1.00	−1.00	−0.80	−0.90
3	C	0	−1.29	−1.05	−1.17
	C	0.50	−1.30	−1.05	−1.18
	C	1.00	−1.29	−1.05	−1.17
4		0	−1.18	−0.97	−1.08
		0.50	−1.17	−0.95	
		1.0	−1.15	−0.92	
5		0	−1.24	−1.00	−1.12
		0.50	−1.25	−1.01	
		1.00	−1.25	−1.01	

[a] Abbreviations: L = ligand; Ep(c) = cathode potential; Ep(a) = anode potential.

Summary

Representatives of a new class of N-pivot lariat ethers bearing reducible nitroaromatic side arms have been prepared and examined by cyclic voltammetric techniques. When the nitro group is sterically disposed to permit interaction with the ring-bound cation, intramolecular ion pairing occurs. This is not the case when the side arm is remote from the macrocycle nor when the side arm is detached. A thermochemical cycle is used to determine that the binding constant (K_s) enhancement is 25000-fold upon electrochemical switching.

Registry No. **2**, 88548-59-8; **3**, 88-72-2; **4**, 88548-60-1; **5**, 99-99-0; monoaza-15-crown-5, 66943-05-3; 2-nitrobenzyl bromide, 3958-60-9; 4-nitrobenzyl bromide, 100-11-8; sodium(1+), 17341-25-2.