

## Lithium Isotope Discrimination by the Anion Radical of an Anthraquinone-15-crown-5 Lariat Ether

Servando Muñoz and Luis Echegoyen\*

Department of Chemistry, University of Miami, Coral Gables, FL 33124, USA

The reduction potentials, or solution electron affinities, of the  ${}^6\text{Li}^+$  and the  ${}^7\text{Li}^+$  complexes of (9,10-dioxoanthracen-1-yloxymethyl)-15-crown-5 have been measured in acetonitrile, and in mixtures of acetonitrile and dichloromethane, to include 50 and 75%, by volume, of the latter cosolvent. While in acetonitrile the reduction potentials are the same within experimental error, in the presence of 50 and 75% dichloromethane, the  ${}^6\text{Li}^+$  complex is anodically shifted relative to its  ${}^7\text{Li}^+$  counterpart, by  $7 \pm 3$  and  $12 \pm 3$  mV, respectively. The preceding differences in the reduction potentials suggest equilibrium constant values of *ca.*  $1.3 \pm 0.1$  and  $1.6 \pm 0.2$ , in turn, for electron exchange between  ${}^7\text{Li}^+$  and  ${}^6\text{Li}^+$  complexes of the macrocyclic donor, whereby the anionic charge resides preferentially in the latter electrophore.

The study of equilibrium isotope effects is of both fundamental and practical importance. Twenty years ago Chang and Coombe<sup>1</sup> observed, using electron paramagnetic resonance, that perdeuterated naphthalene dissolved in tetrahydrofuran is reduced with more difficulty than its unsubstituted counterpart; that is, they found that the perdeuterated material has the lower electron affinity in solution. Still, their contribution was not appreciated until a recent investigation by Stevenson<sup>2</sup> and his collaborators revealed, also by means of EPR, that the solution electron affinity of perdeuterated benzene is in fact lower than that of the unsubstituted molecule.

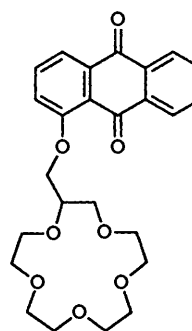
The existence of a large equilibrium hydrogen-deuterium isotope effect for benzene and benzenoid hydrocarbons has been confirmed by ion-cyclotron resonance<sup>3</sup> and cyclic voltammetric methods.<sup>4,5</sup> Typically, perdeuterated aromatic radical anions are found to be 200–400 cal mol<sup>-1</sup> less stable at ambient temperature than the corresponding non-deuterated species.† Or, equivalently, the reduction potential of perdeuterated aromatic electrophores is 7–16 mV lower, that is, cathodically shifted, with respect to the <sup>1</sup>H-substituted molecules.

Similarly, Stevenson<sup>6</sup> and co-workers have extended their investigation further and observed equilibrium isotope effects in the case of aromatic arrays that incorporate heavy isotopes such as <sup>13</sup>C, <sup>15</sup>N and <sup>17</sup>O. In this regard, it is noteworthy that reduction of an aromatic electrophore by means of a metallic mirror that includes <sup>22</sup>Na and <sup>23</sup>Na in a comparatively non-polar medium like tetrahydrofuran, in the presence of 18-crown-6, yields an isotopic distribution which differs from that found originally on the metallic monolayer; as the adjacent solution becomes enriched in the lighter <sup>22</sup>Na<sup>+</sup> isotope.<sup>7</sup> The provocative and important application from such experiments concerns the fact that mixtures of alkali metal isotopes may be resolved efficiently by the appropriate combination of an electrophore with a macrocyclic polyether.<sup>7</sup>

While Stevenson and associates studied sodium and potassium isotope effects, they did not investigate the case of lithium. Yet equilibrium isotope effects involving lithium have fundamental importance in such widely different fields as nuclear fusion technology and psychopharmacology. As an example, when <sup>6</sup>Li captures a thermal neutron and thereafter emits an alpha particle, tritium, one of the fuels in a fusion reactor is obtained.<sup>8</sup> On the other hand, while there is generally little chemical or physiological differentiation between the

isotopes of an element, Lieberman<sup>9</sup> and his collaborators have demonstrated that lithium is an exception. Thus, of the two species that make up naturally occurring lithium, they observed that the lighter <sup>6</sup>Li<sup>+</sup> isotope is translocated more readily across the membrane of human erythrocytes (red blood cells) and across the blood-brain barrier of adult cats.<sup>10</sup> Furthermore, lithium is effective in the treatment of psychopathy. Consequently, the existence of lithium isotope effects has therapeutic and toxicological implications of the utmost importance.

The work reported herein is concerned with differentiation between, or recognition of, the naturally occurring lithium ion isotopes, <sup>6</sup>Li<sup>+</sup> and <sup>7</sup>Li<sup>+</sup>, by the reducible, macrocyclic, anthraquinone-15-crown-5 lariat ether below. In analogy to Stevenson's work, this molecule contains an electrophoric portion (the anthraquinone) and a macrocyclic polyether.<sup>6</sup> The main difference is that both are covalently linked in the present case.



The extent of isotopic recognition is determined from the corresponding reduction potentials or solution electron affinities derived directly from cyclic voltammetric measurements in non-polar media made up of acetonitrile and dichloromethane.

### Results

Tables 1 and 2 list the pertinent formal potentials,  $\Delta E$ , for reduction of anthraquinone-15-crown-5 lariat ether in the presence of <sup>6</sup>Li<sup>+</sup> and <sup>7</sup>Li<sup>+</sup>, respectively, in three different media: acetonitrile, 50:50 acetonitrile-dichloromethane, and 25:75 acetonitrile-dichloromethane (by volume); measured in

† 1 cal = 4.184 J.

**Table 1** Formal reduction potentials for the cationic complexes of anthraquinone-15-crown-5 lariat ether with lithium ions relative to the ferrocene–ferricinium couple at 23 °C<sup>a,b,c</sup>

Solvent composition		$\Delta E/\text{mV}$		$\Delta\Delta E/\text{mV}$	$K^d$
$\text{CH}_3\text{CN}$	$\text{CH}_2\text{Cl}_2$	${}^6\text{Li}^+$	${}^7\text{Li}^+$		
100	0	-1173	-1172	$-1 \pm 3$	$1.0 \pm 0.1$
50	50 <sup>e</sup>	-1195 $\pm 3$	-1202 $\pm 2$	$7 \pm 3$	$1.3 \pm 0.1$
50	50	-1175 $\pm 2$	-1183 $\pm 1$	$8 \pm 2$	$1.4 \pm 0.1$

<sup>a</sup> The potentials listed are measured relative to the saturated calomel electrode which is isolated from the test solution by means of a double bridge filled with the supporting electrolyte, 0.100 mol dm<sup>-3</sup> tetrabutylammonium perchlorate in acetonitrile. The working electrode is a carbon disc supported in a glassy matrix, while the auxiliary electrode is a platinum coil. The electrochemical domain spans the range between +750 and -1650 mV and is swept at a rate of 200 mV s<sup>-1</sup>. Typically, the concentration of reducible macrocycle is 1.1 mmol dm<sup>-3</sup> and that of the internal standard ferrocene *ca.* 2.0 mmol dm<sup>-3</sup>. <sup>b</sup> Two equivalents of lithium ions are added, unless noted to the contrary. <sup>c</sup> The uncertainty limits represent standard deviations. <sup>d</sup>  $K$  represents the equilibrium constant for electron exchange between the  ${}^7\text{Li}^+$  and  ${}^6\text{Li}^+$  complexes of the reducible macrocycle, as defined in the text. <sup>e</sup> One equivalent of lithium ions is added.

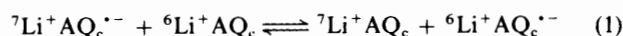
**Table 2** Formal reduction potentials for the cationic complexes of anthraquinone-15-crown-5 lariat ether with lithium ions relative to the ferrocene–ferricinium couple at 23 °C<sup>a,b</sup>

Solvent composition		$\Delta E/\text{mV}$		$\Delta\Delta E/\text{mV}$	$K^c$
$\text{CH}_3\text{CN}$	$\text{CH}_2\text{Cl}_2$	${}^6\text{Li}^+$	${}^7\text{Li}^+$		
25	75	-1163	-1172	$12 \pm 3$	$1.60 \pm 0.20$
		-1160	-1175		
		-1165	-1174		
		-1166	-1175		
		-1164	-1178		
		-1161	-1175		
		-1160	-1172		
		-1157	-1171		
		-1164	-1174		
		-1166	-1174		
		-1159	-1175		
Mean		-1162 $\pm 3$	-1174 $\pm 2$		

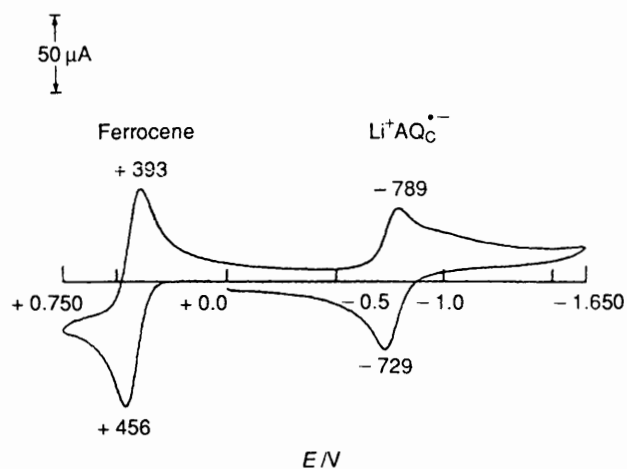
<sup>a</sup> The experimental conditions are summarized in Table 1, except that the concentration of the inert electrolyte is 0.200 mol dm<sup>-3</sup>. <sup>b</sup> The uncertainty limits represent standard deviations. <sup>c</sup>  $K$  represents the equilibrium constant for electron exchange between the  ${}^7\text{Li}^+$  and the  ${}^6\text{Li}^+$  complexes of the reducible macrocycle, as defined in the text.

each case against the saturated calomel electrode. Since the formal potentials are expressed relative to that of the ferrocene–ferricinium couple in the same medium,  $\Delta E$  provides a convenient means to circumvent the uncertainty that liquid junction electromotive forces introduce into voltammetric measurements.<sup>11</sup> It follows that the ability of the macrocyclic donor to distinguish between  ${}^6\text{Li}^+$  and  ${}^7\text{Li}^+$  is determined readily from the double voltage difference  $\Delta\Delta E$ . When  $\Delta\Delta E$  is zero, the isotopic recognition is negligible.

The data in Tables 1 and 2 also include  $K$ , the isotopic recognition factor which is defined by the equilibrium (1) in



which the single electron is exchanged between the  ${}^7\text{Li}^+$  and the  ${}^6\text{Li}^+$  complexes of the reducible lariat ether. Accordingly, in the



**Fig. 1** Representative cyclic voltammogram for  $1 \times 10^{-3}$  mol dm<sup>-3</sup> anthraquinone-15-crown-5 lariat ether in 50:50 acetonitrile–dichloromethane, in the presence of two equivalents of lithium perchlorate at 23 °C. The potentials are measured against the saturated calomel electrode; the working electrode is a glassy carbon disc.

absence of isotopic discrimination, the value of  $K$  is unity. On the other hand, when  $K$  is different from unity, the equilibrium diverges from the limit of a symmetrical, one electron exchange.

It should be pointed out that the voltammetric data included in Table 1 are derived from multiple measurements, which are not specified here in the interest of brevity. A complete set of data is presented in Table 2 in the case of 25:75 acetonitrile–dichloromethane for illustration. Thus, in pure acetonitrile, in the presence of one equivalent of lithium ions, the data are based on four independent measurements: one determination is carried out in the presence of  ${}^6\text{Li}^+$  while the other three are obtained in the presence of  ${}^7\text{Li}^+$ . In 50:50 acetonitrile–dichloromethane, in the presence of one equivalent of lithium ions, the voltammetric data are based on seventeen independent measurements: eight determinations are carried out in the presence of  ${}^6\text{Li}^+$  while the remaining nine are obtained in the presence of  ${}^7\text{Li}^+$ . Further, in 50:50 acetonitrile–dichloromethane, in the presence of two equivalents of lithium ions, the data are based on sixteen separate measurements: eight of these are recorded in the presence of  ${}^6\text{Li}^+$  while the remaining eight are determined in the presence of  ${}^7\text{Li}^+$ . In 25:75 acetonitrile–dichloromethane the data are based on twentyfour separate measurements, which as Table 2 shows, are distributed equally between both isotopes.

A representative cyclic voltammogram showing the electrochemical events for the lithium complex of the anthraquinone lariat ether and the ferrocene–ferricinium internal standard is presented in Fig. 1.

## Discussion

As Table 1 indicates, when  $\Delta\Delta E$  is measured in acetonitrile, its magnitude is small, *ca.*  $-1 \pm 3$  mV. In this case, the isotopic recognition factor is very near unity to indicate that in a polar medium the macrocyclic receptor shows little tendency to distinguish  ${}^6\text{Li}^+$  from its heavier counterpart,  ${}^7\text{Li}^+$ .

By contrast, in a medium made up of 50:50 acetonitrile–dichloromethane, in the presence of one equivalent of  ${}^6\text{Li}^+$  and  ${}^7\text{Li}^+$ , respectively, the value of  $\Delta\Delta E$  measures *ca.*  $7 \pm 3$  mV; the  ${}^7\text{Li}^+$  complex being at the more negative potential. Interpretation of this result is complicated by the fact that the binding affinity of  $\text{Li}^+$  for the neutral macrocycle is small. Under this condition, it is well known that the position of the reduction wave is sensitive to the stoichiometric ratio between the alkali metal cation and the complexing macrocycle.<sup>12</sup>

Accordingly, the data in Table 1 describe an independent experiment carried out in 50:50 acetonitrile–dichloromethane, yet in the presence of two equivalents of  ${}^6\text{Li}^+$  and  ${}^7\text{Li}^+$ , respectively. While both reduction waves become more positive, by 20 mV each, an anodic shift typical of that found in the limit of low binding affinity towards the neutral macrocycle, observe that the value of  $\Delta\Delta E$  is maintained at  $8 \pm 2$  mV. It follows, therefore, that the magnitude of  $\Delta\Delta E$  is independent of the stoichiometric ratio between the alkali metal ion and the macrocyclic donor; hence the difference in the corresponding reduction potentials is genuine.

The fact that the  ${}^7\text{Li}^+$  complex accepts an electron at the lower applied voltage indicates, following the electrochemical convention, that its reduction is more difficult to accomplish than that of its  ${}^6\text{Li}^+$  isomer. Clearly then, because reduction of the heavier complex,  ${}^7\text{Li}^+\text{AQ}_c$ , occurs at the more negative voltage,  ${}^7\text{Li}^+\text{AQ}_c^{\cdot-}$  is thermodynamically less stable than its lighter analogue,  ${}^6\text{Li}^+\text{AQ}_c^{\cdot-}$ . Moreover, electron exchange from  ${}^7\text{Li}^+\text{AQ}_c^{\cdot-}$  into  ${}^6\text{Li}^+\text{AQ}_c$  implies a decrease in Gibbs free energy. Therefore, the equilibrium stated in eqn. (1) above is exothermic, and the isotopic recognition factor  $K$  must exceed unity. The foregoing analysis may be put into more quantitative form by transforming the magnitude of  $\Delta\Delta E$ , at  $7 \pm 3$  mV, into the corresponding equilibrium constant by invoking the Nernst equation. The appropriate value of  $K$  is calculated to be  $1.3 \pm 0.1$ .

Consider the strength of the isotopic recognition in a comparatively non-polar medium made up of 25:75 acetonitrile–dichloromethane, as indicated by the data recorded in Table 2. In particular, note that in this medium the magnitude of  $\Delta\Delta E$  becomes  $12 \pm 3$  mV; the  ${}^7\text{Li}^+$  complex is still at the more negative potential. Thus, electron transfer from  ${}^7\text{Li}^+\text{AQ}_c^{\cdot-}$  into  ${}^6\text{Li}^+\text{AQ}_c$  involves a decrease in Gibbs free energy which, in turn, implies an equilibrium constant in excess of unity. Invoking the Nernst equation again, the value of  $K$  is  $1.6 \pm 0.2$ . It is noteworthy that while a value of 1.6 for the equilibrium constant is apparently small, it corresponds to a difference in free energy of  $-300$  cal mol $^{-1}$  at 23 °C. This is an appreciable thermicity, reminiscent of that found in the case of isotopically substituted aromatic, benzenoid arrays.<sup>1,2,3,6</sup>

The value of 1.6 for an equilibrium isotope effect exceeds the upper limit that can be satisfactorily explained by theoretical treatments.<sup>13</sup> Because the theory of equilibrium isotope effects is firmly established, we anticipate that our experimental observations are likely to stir considerable controversy. Nevertheless, the evidence which shows the existence of large deviations from the limit of a symmetrical one-electron exchange is strong, and it comes from several groups employing widely different methodologies. In the beginning, of course, there was the trailblazing, nearly forgotten, work of Chang and Coombe<sup>1</sup> regarding the non-degeneracy in the solution electron affinities of unsubstituted and perdeuterated naphthalene. Subsequently, their EPR work was refined and extended most notably by Stevenson<sup>2</sup> and his co-workers who, in addition to EPR employed ion-cyclotron resonance<sup>3</sup> to confirm the existence of large hydrogen–deuterium equilibrium isotope effects in electron exchange between aromatic radical anions. Alternatively, Morris<sup>5</sup> and co-workers confirmed Stevenson's observations by employing the cyclic voltammetric method. Then Kaifer and Goodnow<sup>4</sup> found, also by means of cyclic voltammetry, that the solution electron affinity of perdeuterated anthracene is lower than that of its unsubstituted analogue by ca. 15 mV, which corresponds to an isotopic recognition factor,  $K$ , of 1.80 at 23 °C.

As a corollary to the preceding discussion, there are reported examples of experiments in which either mixtures of the isotopes of an element or isotopic isomers are resolved efficiently by means of electron exchange equilibria. Most recently in this

respect, there is the elegant work of Shi and Guthrie<sup>14</sup> regarding the one-electron-promoted cleavage of naphthylmethyl phenyl ethers. They report that when equimolar mixtures of naphthalene-ring-deuterated and -undeuterated ethers are reversibly reduced by a single electron donor, such as the fluoroanthene radical anion, the product is found to contain an excess of undeuterated methyl-naphthalene. Conversely, the remaining unchanged material contains an excess of naphthalene-ring-deuterated ether. They suggested that in the rate-determining step, namely scission of the  $\text{CH}_2\text{-O}$  bond, the corresponding transition state resembles a naphthalene radical anion whereby the added electron remains localized in a  $\pi^*$  molecular orbital. Clearly, to the extent that naphthalene-ring-deuteriation raises the energy of the transition state relative to that of its unsubstituted isotopic isomer, fractionation must occur on proceeding from the reactant ether to the product methyl-naphthalene molecules.

With respect to our work, recall that the reduced species  ${}^6\text{Li}^+\text{AQ}_c^{\cdot-}$  is found to be more stable than its isotopic isomer. In particular, note that the greater charge density, or enhanced electrophilicity, of the  ${}^6\text{Li}^+$  isotope acts to stabilize the excess anionic charge on the anthraquinone nucleus to a greater extent than  ${}^7\text{Li}^+$  in the corresponding  ${}^7\text{Li}^+\text{AQ}_c^{\cdot-}$  complex. Similarly, the observation that the equilibrium constant,  $K$ , varies inversely as the dielectric constant of the medium, from  $1.0 \pm 0.1$  in acetonitrile, to  $1.3 \pm 0.1$  in 50:50 acetonitrile–dichloromethane, and  $1.6 \pm 0.2$  in 25:75 acetonitrile–dichloromethane, may be interpreted in terms of the binding enhancement that occurs on complexation of alkali metal ions by reducible macrocyclic polyethers.<sup>12,15</sup>

The binding enhancement can be defined as the anodic displacement, that is, toward more positive reduction potentials, that takes place when electroactive macrocyclic polyethers are reduced in the presence of alkali metal ions. For example, when anthraquinone-15-crown-5 lariat ether is reduced in an organic solvent such as acetonitrile, the potential is ca.  $-970$  mV, relative to the saturated calomel electrode. However, in the presence of two equivalents of lithium ions, the charge transfer process occurs at  $-760$  mV. Hence, addition of  $\text{Li}^+$  brings about an anodic displacement of 210 mV. An anodic displacement of 210 mV implies an increase of  $10^3$  in the formation constant of the complex.<sup>15</sup> As a result, the difference in the reduction potentials of the anthraquinone polyether upon isotopic substitution may be attributed to variations in the strength of ion-pairing between the carbocyclic donor and lithium ions.

To illustrate, in a polar medium, such as acetonitrile, that can function as an electron donor, the solvent will compete with the reduced anthraquinone donor to complete the solvation sphere of the lithium ions. As a consequence of this competition, the extent of ion-pairing with the carbocyclic nucleophile is diminished such that isotopic recognition is negligible. Conversely, in a comparatively non-polar medium, the solvent will compete to a smaller extent against the anthraquinone donor such that the latter alone will complete the solvation sphere of the lithium acceptor. It follows that intramolecular ion-pairing with the carbocyclic nucleophile predominates in order to result in strong isotopic discrimination. The preceding analysis is demonstrated by the fact that the anodic shift in the reduction potential of  ${}^6\text{Li}^+\text{AQ}_c$  in 50:50 acetonitrile–dichloromethane, ca.  $7 \pm 3$  mV, increases to  $12 \pm 3$  mV when the fraction of dichloromethane becomes 75% by volume.

Finally, it should be pointed out that the tendency of the macrocyclic, anionic donor to ion-pair more tightly with the electrostatically denser  ${}^6\text{Li}^+$  acceptor is consistent with the well known fact that extraction of lithium isotopes by macrocyclic polyethers into non-polar organic media, such as dichloromethane, invariably results in enrichment with respect to this

**Table 3** The statistical *t*-test at the 99% confidence level to compare the mean reduction potentials of the  ${}^6\text{Li}^+$  and the  ${}^7\text{Li}^+$  complexes of anthraquinone-15-crown-5 lariat ether at 23 °C<sup>a,b</sup>

Solvent composition		${}^6\text{Li}^+$ Isotope		${}^7\text{Li}^+$ Isotope		$ t $	$t_0$	Conclusion
$\text{CH}_3\text{CN}$	$\text{CH}_2\text{Cl}_2$	$\Delta E_1/\text{mV}$	$n_1$	$\Delta E_2/\text{mV}$	$n_2$			
100	0	-1173	1	$-1172 \pm 3$	3	0.3	10	$\Delta E_1 = \Delta E_2$
50	50 <sup>c</sup>	$-1195 \pm 3$	8	$-1202 \pm 2$	9	6	3	$\Delta E_1 \neq \Delta E_2$
50	50	$-1175 \pm 2$	8	$-1183 \pm 1$	8	10	3	$\Delta E_1 \neq \Delta E_2$
25	75	$-1162 \pm 3$	12	$-1174 \pm 2$	12	11	2.8	$\Delta E_1 \neq \Delta E_2$

<sup>a</sup> The mean values  $\Delta E$  and the number of measurements,  $n$ , for each isotope are obtained from the respective data listed in Tables 1 and 2. The parameter  $|t|$  represents the absolute value of the test coefficient for each collection of data, while  $t_0$  indicates the upper limit for the test coefficient at the 99% confidence level. The latter parameter is obtained from the tabulated *t*-distribution in ref. 16. <sup>b</sup> Two equivalents of lithium ions are added unless noted to the contrary. <sup>c</sup> One equivalent of lithium ions is added.

isotope. Nevertheless, the typical partition constants, or fractionation coefficients observed using liquid-liquid extraction are small; reaching a maximum value of only 1.057 in the presence of neutral 12-crown-4.<sup>8</sup> Isotopic fractionation by direct reduction of anthraquinone-15-crown-5 lariat ether in non-polar media, using naturally occurring lithium metal, is currently under investigation in this laboratory.

#### Discussion of Errors

In anticipation of potential controversy, we include here a relatively detailed analysis to determine the statistical difference between the reduction potentials upon isotopic substitution. This section also considers some possible sources of error in the voltammetric measurements including such variables as the cation to macrocyclic donor stoichiometric ratio, and the influence of uncompensated resistance. Additional sources of error are discussed in the experimental section, as appropriate.

**The Statistical *t*-Test.**—Although voltammetric parameters can be determined with high precision, it is significant that the inherent uncertainty in the potentiometric measurements reported herein, *ca.* 3 mV, is comparable to the difference,  $\Delta\Delta E$ , in the position of the reduction waves of  ${}^6\text{Li}^+\text{AQ}_c$  and  ${}^7\text{Li}^+\text{AQ}_c$ . Consequently, the question arises as to whether the mean values of these potentials are statistically different.

The data recorded in Table 3 describe the *t*-statistical analysis, at the 99% confidence level, applied to the mean values  $\Delta E$  corresponding to the reduction potentials of  ${}^6\text{Li}^+\text{AQ}_c$  and  ${}^7\text{Li}^+\text{AQ}_c$ . In acetonitrile, the calculated absolute value of  $t$  is 0.3; that derived from the tabulated<sup>16</sup> distribution,  $t_0$ , is *ca.* 10. Because  $t$  is less than the upper limit  $t_0$ , the mean values under consideration must be the same; the null, or identity condition,  $H_0$ , is correct in 99 out of every 100 observations.

Now, in 50:50 acetonitrile-dichloromethane, in the presence of one equivalent of lithium ions, the calculated absolute value of the test parameter  $t$  is *ca.* 6; that derived from the tabulated *t*-distribution,  $t_0$ , is *ca.* 3. Because the calculated estimate of  $t$  exceeds the upper limit  $t_0$ , the mean values under consideration are different; that is, the inequality condition,  $H_1$ , is correct in 99 out of every 100 observations. The same conclusion holds true in the presence of two equivalents of lithium.

Likewise, when the voltammetric measurements are carried out in 25:75 acetonitrile-dichloromethane, the corresponding  $\Delta E$  values for reduction of both isomers are different at the 99% confidence level.

**Voltammetry.**—An important variable in the potentiometric measurements described above is the stoichiometric ratio between the macrocyclic donor and the alkali metal ion acceptor.<sup>12</sup> In the presence of a comparatively small concentration of lithium ions, the resulting voltammogram is the superposition of one- and two-electron waves from the free and complexed forms of the reducible donor. To deconvolute

the voltammogram, it is necessary to utilize a stoichiometric excess of lithium perchlorate such that only a single, reversible, one-electron event remains to be observed.

Note as well, that voltammetry in a comparatively non-polar medium made up of 75% dichloromethane, is complicated by the fact that the inert electrolyte, tetrabutylammonium perchlorate, has a small tendency to dissociate and provide charge carriers. Yet, the comparatively high resistance of this medium is reduced effectively by doubling the concentration of the inert electrolyte. Routinely, 0.200 mol dm<sup>-3</sup> tetrabutylammonium perchlorate is needed to maintain the resistance in the range that makes it possible for the BAS-100 electrochemical analyser to exclude uncompensated resistance effects.

#### Conclusions

We recall, as stated by Holmes,<sup>17</sup> that 'it is a capital mistake to theorize before one has data. Insensibly, one begins to twist facts to suit theories, instead of theories to suit facts.' Our data and those reported elsewhere, which demonstrate clearly the existence of unsymmetrical electron exchange between isotopic isomers, await theoretical exploration.

#### Experimental

**Instrumentation and Chemicals.**—The voltammetric measurements were carried out using a Bioanalytical Systems electrochemical analyser (BAS-100) equipped with IR compensation and connected to a Houston DMP-40 plotter. The micro-volumetric measurements were performed using a Gilson Model P-200D digital microlitre pipette.

(9,10-dioxoanthracen-1-yloxymethyl)-15-crown-5, or anthraquinone-15-crown-5 lariat ether was available from other work.<sup>18</sup> Acetonitrile, 99.9%, was purchased from EM Science and used after drying by standing over molecular sieves. Dichloromethane, 99.9% HPLC grade, was obtained from the Aldrich Chemical Company and it, similarly, was used after drying by standing over molecular sieves.

Ferrocene was used as received from the Aldrich Company, while tetrabutylammonium perchlorate was purchased from the Fluka Chemical Co. and recrystallized twice from ethyl acetate, prior to use.  ${}^7\text{LiClO}_4$  was prepared from isotopically pure lithium metal, 99.984% by mass as provided by the National Bureau of Standards, as follows: the lithium metal is reacted with water and the solution acidified by using perchloric acid. Upon evaporation of the solvent,  ${}^7\text{LiClO}_4$  may be recrystallized from 80:20 chloroform-ethanol (v/v). The crystals obtained are dried under a vacuum at 110 °C and stored in a dessicator. In the case of  ${}^6\text{LiClO}_4$ , the procedure is similar except that the starting material is 95.5% isotopically pure  ${}^6\text{LiOH}$  monohydrate, which was bought from the Stable Isotopes Division of ICN Biomedicals.

Finely powdered alumina made up of 0.05  $\mu\text{m}$  particles,

and the micropolishing cloth to clean the surface of glassy carbon electrodes, as well as vycor glass sections to construct a double salt bridge, were supplied by the Buehler Limited Company.

**Voltammetric Measurements.**—The formal electrode potentials of the reducible macrocycle and the internal standard ferrocene are determined under an atmosphere of argon, and are measured relative to the saturated calomel electrode. The auxiliary electrode is made up of a platinum coil while the working electrode is a carbon disc supported in a glassy matrix. To precede the potentiometric measurements, the glassy carbon disc is polished by using an aqueous suspension, or slurry, of powdered alumina. Thereafter, the electrode is rinsed with deionized water, sonicated for 2–3 min in an immersion tank filled with water, and dried by means of a hot air fan. On cooling down to ambient temperature, the surface of the electrode is inspected under a bright source of light to verify that the carbon disc is stainless.

In order to circumvent the uncertainties introduced by liquid junction potentials across the interface with the reference electrode, the internal standard ferrocene is added to the analyte to make it possible to express the reduction potential of the lariat ether electrophore relative to that of the ferrocene–ferricinium couple. Moreover, the saturated calomel electrode is kept separate from the test solution by utilizing a double bridge equipped with a porous vycor glass; the double bridge is filled with a solution of the supporting electrolyte in the solvent of interest.

The function of the double bridge is twofold: it inhibits the passage of potassium ions and to some extent water from the reference electrode into the analyte. Note that the reference electrode is immersed into the double bridge only briefly, at the time the cyclic voltammogram is recorded. In addition, the double bridge precludes contamination of the reference electrode by adsorption of electrophores dissolved in the analyte.

It is also noteworthy that in acetonitrile, two equivalents of  $\text{LiClO}_4$  must be present to observe a single, Nernstian, electron transfer. Alternatively, in the less polar media lithium ions are more strongly bound to the macrocyclic donor; hence, one equivalent of  $\text{LiClO}_4$  is sufficient to yield a comparatively simple voltammogram. Yet care is needed in interpreting the voltammetric displacement,  $\Delta\Delta E$ , upon isotopic substitution, because of the fact that the binding affinity of the cationic alkali metal for the neutral macrocycle is comparatively low. Under this condition, the position of the reduction wave is sensitive to the stoichiometric ratio between the cation guest and the macrocyclic host.<sup>12</sup> In order to demonstrate that the measured value of  $\Delta\Delta E$  is genuine, it becomes necessary to perform independent experiments using different cation to ligand ratios. The data in Table 2 show that doubling the concentration of added  $\text{LiClO}_4$  in 50:50 acetonitrile–dichloromethane shifts the corresponding reduction potentials of the  $^6\text{Li}^+$  and the  $^7\text{Li}^+$  complexes anodically by *ca.* 20 mV. Nevertheless, their initial separation,  $\Delta\Delta E$ , is maintained at *ca.*  $7 \pm 3$  mV. Therefore, provided the stoichiometric ratio of metal cation to macrocycle is controlled with precision, the magnitude of  $\Delta\Delta E$  can be determined accurately.

By comparison, in 25:75 acetonitrile–dichloromethane, the positions of the respective reduction waves are independent of the concentration ratio between the metal cation and the lariat polyether, because the binding affinity of lithium ions for the neutral macrocycle in that medium is strong.

**Procedure.**—In a representative experiment, 10 mg of anthraquinone-15-crown-5 lariat ether (21.9  $\mu\text{mol}$ ) together with 7 mg (37.6  $\mu\text{mol}$ ) of ferrocene and 0.700 g (2.05 mmol) of tetrabutylammonium perchlorate are dissolved into 20  $\text{cm}^3$  of

the appropriate solvent. Hence, the corresponding concentrations of the reducible macrocycle, ferrocene, and the supporting electrolyte are, in turn, 1.10, 2.00 and 100  $\text{mmol dm}^{-3}$ . In the case of the least polar solvent made up of 25:75 acetonitrile–dichloromethane, it is necessary to increase the concentration of the supporting electrolyte up to 0.200  $\text{mol dm}^{-3}$ , to compensate for the decreasing electrical conductivity of the medium. Note in this respect that the uncompensated resistance in the electrochemical circuit is maintained at zero ohms in all of the voltammetric experiments herein reported.

Initially, a 10  $\text{cm}^3$  aliquot of the analyte solution is deoxygenated by passing argon gently through the solution for about 45 min. Note that to minimize evaporation, the sparging gas is saturated with vapour by first directing the argon stream through a large, deoxygenated reservoir of the solvent that makes up the analyte solution. After deoxygenation, the saturated calomel electrode is brought into contact with the test solution *via* the double salt bridge, to complete the electrochemical circuit. Then the voltammogram is recorded at ambient temperature by cycling the potential of the working electrode once in the range between 750 and  $-1650$  mV at a rate of 200  $\text{mV s}^{-1}$ . The starting point for the voltammogram is zero and the initial scan direction is positive.

Once the voltammetric profile is recorded, the reference electrode is withdrawn from the auxiliary or double bridge and an aliquot of the corresponding  $^6\text{LiClO}_4$  or  $^7\text{LiClO}_4$  stock solution is added. The stock solutions are prepared by dissolving approximately 10 mg of the respective dry salts into 0.500  $\text{cm}^3$  of acetonitrile; that is, the concentrations of  $^6\text{LiClO}_4$  and  $^7\text{LiClO}_4$  are about 0.200  $\text{mol dm}^{-3}$ . Thus, in the presence of  $1.1 \times 10^{-3}$   $\text{mol dm}^{-3}$  anthraquinone-15-crown-5 lariat ether, it is necessary to utilize 55 and 110  $\text{mm}^3$  of the stock  $\text{LiClO}_4$  solution to provide one or two equivalents of lithium ions, as required. Subsequently, the analyte is deaerated further with argon for an additional 10 min at which time the reference electrode is reconnected into the electrochemical circuit and the voltammogram recorded in the manner described above.

The voltammetric data listed in Tables 1 and 2 are replicates after the following protocol: using the same test solution; using the same test solution after repolishing the glassy carbon electrode; using the same test solution with different polished glassy carbon electrodes; finally, using separate test solutions of the same chemical composition. In addition, data are included which correspond to voltammograms before and after signal averaging by the BAS-100 algorithm. Observe that in all cases the inherent uncertainty in the voltammetric measurements holds at 3 mV or better.

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