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BINDING OF LITHIUM ION ISOTOPES WITH REDOX-ACTIVE MACROCYCLIC AND MACROBICYCLIC CROWN ETHERS

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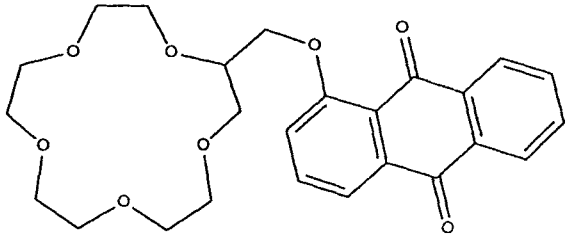
Three anthraquinone-containing crown ether macrocycles and one macrobicycle were reduced coulometrically to their corresponding anion radicals under vacuum. The resulting anion radical solutions in CH_2Cl_2 were stirred with an excess of a solid $^6LiClO_4$–$^7LiClO_4$ mixture of known isotropic composition in order to form the appropriate Li^+ complexes. After equilibration, the solution was separated from the excess solid and the $([^6Li^+]/[^7Li^+])$ ratio was determined by atomic absorption spectrometry. The values were converted into the corresponding separation factors (α) after division by the original composition ratio of the solid mixture. The values were in the range 1·04–1.18. Except for one compound, 2, all of the reduced systems studied exhibited a much larger α value than the 1·057 reported for 12.crown-4 at 0 °C in a liquid–liquid extraction system.

INTRODUCTION

The idea of using cyclic polyethers and cryptands as agents for the discrimination of metal ion isotopes is not new.[1] The first report of such an application using crown ethers appeared over 25 years ago for calcium isotope separations.[2] Although some work is still ongoing in this general area, the most comprehensive account of the subject was published in 1985.[3] The present level of effort in this area seems to be low.

The largest separation factor (α) reported for a $^{6,7}Li^+$ separation system employing a crown ether is 1·057, which was obtained using 12-crown-4 (12-C-4) at 0 °C in a two-phase extraction experiment.[4] Industrial-scale processes for lithium isotope enrichment that use mercury amalgam and lithium salt exchange technologies have α values which are only barely above 1·05.[5] Therefore, synthetic ligands such as the crowns and the cryptands may play an important role in the separation of metal ion isotopes, especially if α value enhancements can be achieved via chemical and electrochemical fine tuning of the structures and properties of the crowns and cryptands.

In a related development, we recently reported[6] a notable difference in the cyclic voltammetric behavior of the complexes of **1** with $^6Li^+$ or $^7Li^+$. In a 75 : 25 CH_2Cl_2–CH_3CN solvent mixture it was possible to detect a 12 ± 3 mV difference in the corresponding reduction potentials of these isotopic complexes. The potential for the $^7Li^+$ complex was cathodically shifted relative to that for the $^6Li^+$ complex. Such a potential difference was converted into an α value of 1·6 ± 0·2 in favor of the lighter isotope.[6] Stated more directly, the $^6Li^+$ complex of **1** is 12 mV easier to reduce than is



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its $^7Li^+$ counterpart. Therefore, the unpaired electron in the anion radical attaches itself to the lighter complex preferentially, with an equilibrium factor of 1·6. Such a large α value is theoretically provocative and potentially very important for real applications involving metal ion isotope separations.

Two other relevant (although widely different) lines of observation need at least to be mentioned in this introduction. One is the characterization of *in vivo* and *in vitro* differential effects of $^6Li^+$ and $^7Li^+$ in biological tissues.[7] When equal doses of $^6Li^+$ and $^7Li^+$ are administered to rats, the animals receiving $^6Li^+$ are initially less active than those receiving $^7Li^+$.[7a] It has

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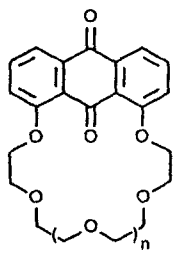
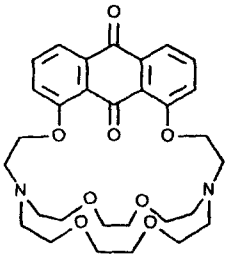
also been observed that $^{6}Li^{+}$ is transported across the membranes of human erythrocytes 5–8% faster than $^{7}Li^{+}$.[7b] It thus seems likely that lithium isotope effects play an important biological role and these may be related to their differential transport across cell membranes. Such a situation suggests that specific binding and transport processes exist and that these are potentially useful within the context of lithium isotope separations. This is not an unreasonable idea in view of the fact that the naturally occurring ionophore monactin has been shown to exhibit differential binding towards the isotopes of Na^{+}.[7c]

The second line of observation is related to equilibrium isotope effects associated with electron transfer reactions.[8–10] Stevenson and co-workers[8] have accumulated considerable evidence to support the idea that larger than expected equilibrium isotopic effects are present in the solution electron affinities of a variety of organic compounds. One example that illustrates their findings is represented by the reaction shown below. When the number of deuterium atoms (x) in the benzene ring is equal to the number of ^{13}C atoms (y) and both are equal to zero, then the equilibrium constant is 1 by definition. Using ESR spectroscopy, Stevenson and co-workers have shown that the deviation of K_{eq} from 1 is a function of x and y. When $y = 0$ and $x = 1, 2, 3$ or 6, K_{eq} values are 0·86, 0·55, 0·37 and 0·26, respectively. These monotonically decreasing values of K_{eq} show that successive increases in deuteration of the benzene group disfavor the formation of the correspondingly heavier anion radical ion pair. Further heavier isotope substitution with ^{13}C ($x = y = 6$) results in $K_{eq} = 0{\cdot}10$. Although theoretical explanations are still lacking, these unusual isotopic effects have now been confirmed by many methods such as ESR, NMR, mass spectra, cyclotron resonance and cyclic voltammetry.[8–11]

In order to test the validity of the voltammetric results described previously[6] and to explore the potential isotopic fractionation properties of reducible crown ethers and cryptands, compounds **1–4** were reduced to their corresponding anion radicals and reacted with a solid salt mixture containing $^{6,7}LiClO_4$. These results are presented here.



2, n=0
3, n=1



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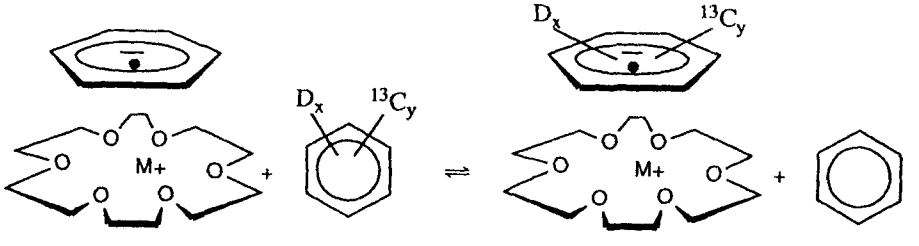
EXPERIMENTAL

Solvents and reagents. Acetonitrile (Aldrich) was refluxed over CaH_2 under a dry nitrogen atmosphere and stored over P_2O_5 under vacuum until needed. Dichloromethane (HPLC grade, Aldrich) was dried over CaH_2 under vacuum. $^{7}LiClO_4$ (99·984%) and $^{6}LiClO_4$ (95·5%) were prepared from the isotopically pure lithium metals.

Atomic absorption spectrometry. Atomic absorption spectra were measured with a Varian SpectrAA-300 spectrometer. An air–acetylene flame was used at flow rates set by the instrument. The emission sources used were a natural hollow-cathode lamp and an enriched ^{6}Li hollow-cathode lamp. The lamps were operated at 10 mA. The spectral band pass was set at 0·2 nm for the 670·8 lithium line.

Stock solutions (100 mM) of the isotopic standards were prepared by dissolving the ^{6}Li- and ^{7}Li-enriched $LiClO_4$ in deionised water. Isotopic standard solutions were prepared by quantitative dilutions of these stock solutions to 0·01–0·04 mM.

Calibration was accomplished by plotting the ultimate absorbance ratio of each of the isotopic standard solutions against the ^{6}Li abundance in the sample, following well established procedures.[12] This method is known as the 'ultimate absorbance-ratio technique' and the theory behind it can be found elsewhere.[13] The plotted ratios are obtained by extrapolation of the



linear portion of the total lithium concentration vs absorbance ratio curves for each standard to zero concentration.[12,13] Isotopic compositions of sample solutions were determined by comparison of their ultimate absorbance ratios with those of the isotopic standards. The main advantage of this method is that the results do not depend on the total lithium concentration in the sample solutions. The uncertainty of the final α values determined using this method is 5–6%.

Sample preparation. Typically, about 10 mg of the ligand (**1–4**) and enough tetrabutylammonium perchlorate (TBAP) (or $TBAPF_6$) are added to compartment B of the apparatus shown in Figure 1 in order to make a 10 mM ligand and a 0.1 M supporting electrolyte solution after solvent addition. There is a high-vacuum stopcock between E and the vacuum line, which allows removal of the complete system from the line.

The same amount of the supporting electrolyte is then added to compartment A. The working and counter electrodes were both platinum mesh and a silver wire was used as a pseudo-reference in the B compartment. A 1 mL volume of aqueous solution containing 20 mg of a mixture of $^6LiClO_4$ and $^7LiClO_4$ (of known composition) was added to D. The system was then coupled to the vacuum line via E and evacuated until all of the water had been evaporated. The final pressure was about 10^{-3} mmHg. Approximately 5 ml of acetonitrile were then vapor-transferred directly through the vacuum line, keeping the system under vacuum at all times. After the ligand and supporting electrolyte had dissolved, controlled potential bulk electrolysis was conducted using a BAS-100 electrochemical analyzer. The reduction potential was maintained at $-1{\cdot}0$ V. Electrolysis was continued until the current dropped to 10% of its original value. The solution in B (which contained the anion radical of the ligand and TBA^+ as a counter cation) was then transferred to C, from where the acetonitrile was removed by distillation through the vacuum line. Dichloromethane was then added by vapor transfer directly into C and the newly formed solution was transferred to D and allowed to react with the solid salt mixture for 30 min while vigorously stirred. The solution, which now contained $^6Li^+$ and $^7Li^+$ complexed to the anion radical of the ligand, was transferred back to C through the frit that separates C and D. The excess of solid salt remained in the D compartment. Oxygen was then bubbled through the CH_2Cl_2 solution and the $^{6,7}Li^+$ was extracted into water (300 ml total) by repeated washes. The samples used for the isotopic atomic absorption spectrometric analyses were prepared directly from these water extracts.

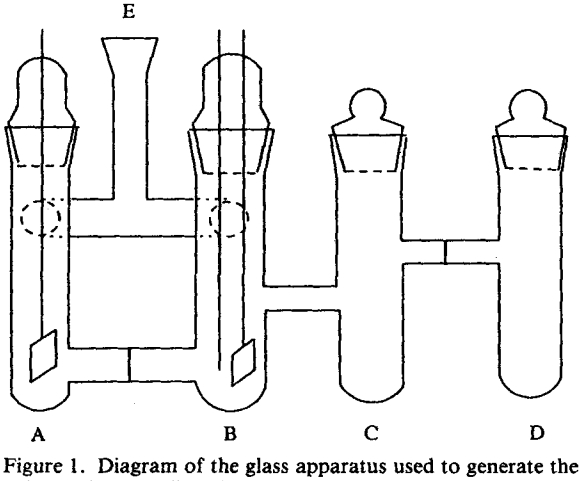


Figure 1. Diagram of the glass apparatus used to generate the anion radicals of ligands **1–4** under high vacuum and also to react them with $^6LiClO_4$–$^7LiClO_4$

Ligands 1–4. The syntheses and characterizations of the four ligands have been reported previously.[14–16]

RESULTS AND DISCUSSION

Most isotopic separation experiments conducted with crown ethers and cryptands involve biphasic extraction systems, typically chloroform–water.[3] The total metal ion concentration in the aqueous phase is relatively high while the ligand concentration in the organic phase is relatively low. Therefore, after extraction of the isotopes into the organic phase and attainment of equilibrium, the isotopic ratio measured in the organic phase relative to the original ratio in the aqueous phase represents directly the α value, since the relative ratio remains essentially unchanged for the water phase. The equation defining α is

$$\alpha = \frac{\left(\frac{[^6Li^+]}{[^7Li^+]}\right)_{org.}}{\left(\frac{[^6Li^+]}{[^7Li^+]}\right)_{aq.}}$$

This definition can also be applied to a heterogeneous system such as that used in this work. Instead of the isotope ratio in the aqueous phase, one can substitute the corresponding ratio in the solid salt sample. Thus the α value is defined as the lithium isotope ratio measured in the organic phase relative to the original solid salt sample ratio. Treated in this manner the data yielded the α values presented in Table 1.

Even when taking into consideration the degree of uncertainty of these measurements, the α values for all of the ligands studied, except **2**, are much larger than previously reported for any crown ether or cryptand system. Assuming the maximum experimental error on these measurements leading to the lowest possible α values, compound **4** would still exhibit an α of $1{\cdot}11$, much larger than the $1{\cdot}057$ value reported for 12-C-4.[4] Under a similar assumption, compound **1** would have a

Table 1. Isotope separation factors (α) determined for ligands **1–4**

Ligand	α[a]
1	1·16 ± 0·07
2	1·04 ± 0·06
3	1·15 ± 0·07
4	1·18 ± 0·07

[a] Values are for $[^6Li^+]/[^7Li^+]$.

value of 1·09 and **3** would have a value of 1·08. Therefore, all of these ligands are better lithium isotope discriminators than 12-C-4, even when considering experimental uncertainties. As does 12-C-4, all of these favor extraction of the lighter lithium isotope.

Within experimental error, compounds **1**, **3** and **4** exhibit essentially the same α value. At present, it is not entirely clear why **2** behaves so differently. One possible explanation is that the polyether ring of **2**, which is considerably twisted owing to the strain resulting from its small size and the rigidity imposed by the anthraquinone group, is not able to interact well with the cation. This seems to be evident when CPK models are constructed. The oxygen atoms are simply unable to adopt a favourable conformation to interact well to complex the lithium cation. The other three compounds possess more flexibility and are able to interact more strongly with the lithium cation isotopes.

It is not difficult to rationalize why these systems exhibit more favorable α values than the simple crown ethers by simply invoking the added ionic interactions. It is well known that the magnitude of an isotopic fractionation reaction depends critically on the type of chemical bond of the investigated species involved in the process.[3] Larger isotopic fractionation are found for exchange reactions where the isotopes are covalently bound than in the cases where they are ionically bound.[3] An excellent example of this is presented in Ref. 3, p. 83. Although complexation of Li^+ by the reduced ligands in the present cases is not covalent, the added intramolecular ion-pair formation must contribute significantly to strengthening the interaction between the cation and the crown ether. It is therefore reasonable to argue that the increased strength of the interaction results in a more pronounced isotopic discrimination effect.

Whether or not there is some kind of 'anomalous' effect due to the presence of the unpaired electron in these systems is not clear yet. Stevenson *et al.*[10] recently pointed out that there are pronounced environmental (solvent) effects on the ΔG° value for the electron transfer reaction between an anion radical and its perdeuterated analogue. These effects are larger than can be accounted for on the basis of standard theories.

Further work is in progress in order to establish if anomalous isotopic behavior is being observed with these reducible macrocycles and macrobicycles.

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