15 mmol) was cooled to −30 °C and the corresponding alkyl fluoride (3 mmol) was then added. While the solution was stirred, a slow stream of boron trifluoride was introduced for 30 s. It was then allowed to warm up to 25 °C and further reacted for 30 min. The reaction mixture was subsequently quenched with ice water and extracted with ether (10 mL). The organic layer was separated, washed with water, dried over $MgSO_4$, and analyzed by GC-MS.

**Competitive Alkylation of $\alpha,\alpha,\alpha$-Trifluoromethoxybenzene and Benzene with Alkyl Halides.** To an equimolar mixture of benzene (5 mmol) and $\alpha,\alpha,\alpha$-trifluoromethoxybenzene (5 mmol) was added $AlCl_3$ (2 mmol) in 2 mL of nitromethane. While the solution was kept at 25 °C with vigorous stirring, alkyl halide (2 mmol) dissolved in 1 mL of nitromethane was added. The reaction mixture was reacted at 25 °C for 30 min. It was thereafter quenched with ice water, extracted with ether, dried over $MgSO_4$, and analyzed by GC-MS.

**Analyses.** GLC analyses were carried out on a Varian Associates Model 3300 gas-liquid chromatograph, using a 50-m glass column coated with OV 1018 oven temperature from 90 to 190 °C, He pressure 30 psi, and FID detector. Peak areas were determined by the use of a Varian 4270 integrator system.

Separation of isomeric methyl- and ethylfluorobenzenes was carried out on a 50-m carbovax fused silica column at 45 °C, 30 psi He pressure, using a FID detector.

Mass spectrometric analyses were carried out with a Hewlett-Packard Model 5985A GC-MS spectrometer and a Finnigan MAT Ion Trap Detector.

$^1H$ NMR spectra were obtained on a 60-MHz Varian EM-360 spectrometer. $^{13}C$ NMR spectra were obtained on Varian Model FT-80 and XL-200 NMR spectrometers equipped with variable temperature broad-band and $^1H/^{19}F$ probes.

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# Determination of Thermodynamic Parameters in Lariat Ether Complexes Using Ion-Selective Electrodes

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**Abstract:** Ion-selective electrodes were used to determine $Na^+$ and $K^+$ equilibrium stability (binding) constants (expressed within as log $K_S$) for a series of carbon-pivot lariat ethers in anhydrous methanol over the temperature range 15-41 °C. A plot of ln $K_S$ vs. $1/T$ gives a slope of $-\Delta H/R$ and the intercept is $\Delta S/R$. This method for determining $\Delta H$ and $\Delta S$ for complexation reactions requires less than 0.5 g of sample, can be conducted in 8 h, utilizes inexpensive equipment, and affords acceptable precision for the compounds examined. The binding phenomenon has been assessed from the thermodynamic perspective by using the following 2-substituted derivatives of 15-crown-5: **1**, $CH_2OC_6H_4$-2-$OCH_3$; **2**, $CH_2OC_6H_4$-4-$OCH_3$; **3**, $CH_2OCH_2CH{=}CH_2$; **4**, $CH_2OH$; **5**, $CH_2O$-*t*-Bu; **6**, $CH_2OCH_2CHOHCH_3$; **7**, $CH_2OCH_2C_6H_4$-2-$OCH_3$; **8**, $CH_2OCH_2C_6H_5$. The differences in enthalpic and entropic contributions reveal surprising differences in the cooperativity between macroring and sidearm when cations are bound.

The importance of thermodynamic measurements in understanding cation complexation by macrocycles is obvious from the huge number of reports which have addressed this subject during the past two decades. These data were catalogued in a massive review published in 1985 by Izatt, Christensen, and their coworkers.[1] We have recognized in our own work with lariat ethers that a better understanding of the complexation process would result from thermodynamic data combined with the equilibrium cation binding data (log $K_S$ values) which we have previously obtained.[2] Unfortunately, thermodynamic parameters determined by calorimetric measurements require special, sophisticated, and often expensive equipment, a considerable amount of sample, complicated computer fitting programs, and a good deal of effort even by the most skilled workers. We present here a method for obtaining both $\Delta H$ and $T\Delta S$ for the complexation process which (1) requires less than half a gram of sample, (2) can be completed in a single day, (3) utilizes inexpensive equipment, and (4) affords acceptable precision for a variety of macrocyclic compounds when binding either $Na^+$ or $K^+$. We present here the results of a systematic study of carefully selected carbon-pivot lariat ethers based on the 2-substituted 15-crown-5 framework which demonstrate the value of this approach.

**Table I.** Thermodynamic Parameters for the Reactions of $Na^+$ and $K^+$ with 15-Crown-5 and 18-Crown-6 in Methanol

| study | $\Delta H$ | $T\Delta S$ | log $K_S$ |
|---|---|---|---|
| | 15-Crown-5 with Sodium Cation | | |
| this study | −4.19 ± 0.05 | 0.30 ± 0.03 | 3.29 |
| Michaux and Reisse[a] | −5.50 ± 0.20 | −1.23 ± 0.24 | 3.14 |
| Izatt et al.[b] | −4.99 ± 0.03 | −0.24 | 3.48 |
| Izatt et al.[c] | −5.40 ± 0.05 | −0.90 | 3.30 |
| Okahara[d] | | | 3.27 |
| | 18-Crown-6 with Sodium Cation | | |
| this study | −7.40 ± 0.11 | −1.50 ± 0.09 | 4.34 |
| Michaux and Reisse[a] | −7.50 ± 0.07 | −1.55 ± 0.11 | 4.37 |
| Izatt et al.[b] | −8.40 ± 0.30 | −2.4 | 4.36 |
| | 18-Crown-6 with Potassium Cation | | |
| this study | −11.3 ± 0.02 | −3.03 ± 0.04 | 6.09 |
| Michaux and Reisse[a] | −12.70 ± 0.10 | −4.30 ± 0.15 | 6.16 |
| Izatt et al.[b] | −13.41 ± 0.06 | −5.14 | 6.06 |
| Frensdorff[e] | | | 6.08 |

[a] See ref 5. [b] See ref 4. [c] See ref 6. [d] See ref 7. [e] See ref 3.

## Results and Discussion

Our method is based on the well-known temperature dependence of the equilibrium constant. Within a relatively narrow temperature range (15-41 °C over which $\Delta H$ is assumed to be constant), log $K_S$ values for complexation between either $Na^+$ or $K^+$

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0002-7863/87/1509-3713$01.50/0

**Table II.** Thermodynamic Parameters for the Reaction of $Na^+$ with 15-Crown-5-Derived Lariat Ether Compounds in Methanol

| compd no. | sidearm[a] | $\Delta H$ | $T\Delta S$ | log $K_S$ | extn const[b] |
|---|---|---|---|---|---|
| **1** | $CH_2OC_6H_4$-2-$OCH_3$ | −4.47 ± 0.07 | −0.05 ± 0.05 | 3.25 | 15.7 |
| | | −5.34 ± 0.03[c] | −0.92 | 3.24 | |
| **2** | $CH_2OC_6H_4$-4-$OCH_3$ | −4.23 ± 0.08 | −0.15 ± 0.07 | 3.00 | 6.4 |
| | | −5.41 ± 0.08[c] | −1.46 | 2.90 | |
| **3** | $CH_2OCH_2CH{=}CH_2$ | −4.40 ± 0.17 | −0.14 ± 0.19 | 3.12 | 7.0 |
| **4** | $CH_2OH$ | −4.17 ± 0.07 | 0.06 ± 0.05 | 3.10 | 2.7 |
| **5** | $CH_2O$-*t*-Bu | −3.75 ± 0.25 | 0.28 ± 0.29 | 2.95 | 7.3 |
| **6** | $CH_2OCH_2CHOHCH_3$ | −4.43 ± 0.07 | −0.08 ± 0.10 | 3.9 | 10.0 |
| **7** | $CH_2OCH_2C_6H_4$-2-$OCH_3$ | −1.80 ± 0.20 | 2.34 ± 0.23 | 3.04 | |
| **8** | $CH_2OCH_2C_6H_5$ | −1.54 ± 0.08 | 2.34 ± 0.03 | 2.97 | 7.9 |

[a] 2-Substituted derivatives of 15-crown-5. [b] Determined as described in ref 8. [c] Data on this line from ref 9.

and a variety of macrocycles can be readily determined by using the ion-selective electrode technique developed originally by Frensdorff.[3] Thus far, we have applied the method only to $Na^+$ by using a $Na^+$-specific glass electrode (Corning 476210) and $K^+$ by using a monovalent cation electrode (Corning 476220). Typically, the macrocycle was dissolved in anhydrous methanol (1 mmolar cation, 1.5–2.5 mmolar macrocycle in 20 mL of MeOH). The potential was determined to within 0.1 mV by using an Orion 701A voltmeter (five separate trials each at 15, 21, 25, 31, 37, and 41 °C). The equilibrium constants ($K_S$) were calculated by using the equations shown in the Experimental Section. A plot of ln $K_S$ vs. $1/T$ (K) gives a slope of $-\Delta H/R$ and the intercept is $\Delta S/R$.

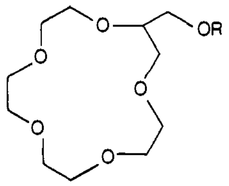
**Calibration of the Method.** Because calorimetry is such a high precision technique and because equilibrium variable temperature measurements are sometimes suspect, we determined thermodynamic parameters for 15-crown-5 with $Na^+$ and for 18-crown-6 with both $Na^+$ and $K^+$. Data for these reactions were also available from the work of Izatt et al.[4] as well as by Michaux and Reisse[5] and are included in the comparisons shown in Table I.

The determinations made by Izatt et al.[4] and Michaux and Reisse[5] differ in an important respect. In the former case, $K_S$ was determined indirectly as part of the overall data reduction process, and, in the latter, $K_S$ was determined experimentally and data reduction afforded $\Delta H$ and $T\Delta S$. Our agreement with the Michaux and Reisse data for the reaction 18-crown-6 + $Na^+$ = complex is excellent. We agree with neither value for the reactions 15-crown-5 + $Na^+$ = complex and 18-crown-6 + $K^+$ = complex, but this is probably due to the disparity in cation binding constants (see Table I).

Note that for the 15-crown-5 + $Na^+$ case, our $K_S$ value agrees well with Izatt's second value[6] and with that reported independently by Okahara.[7] The $K_S$ value determined potentiometrically by Michaux and Reisse[5] differs substantially from ours and from Izatt's, yet their thermodynamic parameters agree well with the latter. Since enthalpy, entropy, and equilibrium constants are all related, such a partial agreement indicates an error in one of the values.

For the 18-crown-6 + $K^+$ = complex case, our $K_S$ value agrees well with Izatt's value and with that reported by Frensdorff. We have found that if we subtract our $\Delta H$ and $T\Delta S$ values for 15-crown-5 + $Na^+$ and 18-crown-6 + $K^+$ from those reported by Michaux and Reisse, we obtain a $\Delta G$ which corresponds to the difference in binding constants within 0.02 log $K_S$ units. We are certain that if our binding constants were the same as Michaux and Reisse's, our thermodynamic data would also be the same as it was in the $Na^+$ and 18-crown-6 case.

**Enthalpy–Entropy Variations in 15-Membered Ring Carbon-Pivot Lariat Ethers.** The family of structurally related carbon-pivot lariat ethers (compounds **1–8**) shown below are all based on the 15-crown-5 macroring and were prepared as previously described.[2a] They were selected for study because a variety of direct comparisons can be made within each group. For example, **1** and **2** differ by the placement of the methoxy group. Previous studies and an examination of molecular models have shown that an *ortho*-methoxy, but not a *para*-methoxy, group on an aromatic ring can interact with a macroring-bound cation. Compounds **1** and **7** differ not in the methoxy group's placement on the aromatic ring, but in its distance from the macroring. The methoxy group of **7** is completely lacking in **8**. Other variations will be obvious from an examination of the structures.



1, R = 2-$CH_3OC_6H_4$
2, R = 4-$CH_3OC_6H_4$
3, R = $CH_2CH{=}CH_2$
4, R = H
5, R = *t*-Bu
6, R = $CH_2$—CHOH—$CH_3$
7, R = $CH_2C_6H_4$—2-$OCH_3$
8, R = $CH_2C_6H_5$

The thermodynamic parameters are summarized below in Table II. As with the calibration data shown above (see Table I) for 15-crown-5 and 18-crown-6, there is a systematic variation in our and Izatt's values of about 1 kcal/mol, but the trends are all in the same direction.

The first point of interest concerns the affinity of each lariat ether for $Na^+$. By using equilibrium stability constant measurements ($K_S$), one can discern some sidearm structure-dependent differences. For example, the placement of the *o*- vs. *p*-methoxy group in **1** and **2** makes a difference of 0.25 log units in cation binding strengths. This is in the expected direction, but the magnitude is small by any assessment. If we evaluate these binding data critically, there is relatively little variation with changes in sidearm structure. In contrast, the extraction constants, determined by partitioning salt and ligand between chloroform and water,[8] show a marked dependence on sidearm structure. The difference in extraction constants between **1** and **2** is large indeed. Unlike the equilibrium binding constants, the extraction constants are significantly affected by lipophilicity. Note that **4**, the least lipophilic compound in Table II, is far below any other compound in extraction constant but only marginally different in $K_S$. It is important to distinguish binding strength information reflected in equilibrium constant data ($K_S$) from extraction constant data which reflects lipophilicity and partitioning between two different solvents. Extraction constants are clearly important for understanding transport but should not be used as a basis for classifying selectivity except in the latter context.

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(3) Frensdorff, H. K. *J. Am. Chem. Soc.* **1971**, *93*, 600.

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(5) Michaux, G.; Reisse, J.; *J. Am. Chem. Soc.* **1982**, *104*, 6895.

(6) Davidson, R. B.; Izatt, R. M.; Christensen, J. J.; *J. Org. Chem.* **1984**, *49*, 5080.

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(8) Gokel, G. W.; Dishong, D. M.; Diamond, C. J. *J. Chem. Soc., Chem. Commun.* **1980**, 1053.

We have previously assessed flexibility in free and cation-bound lariat ethers by using C-13 NMR relaxation times ($T_1$s).[10] For compounds **1** and **2**, relaxation time changes were similar. This confirms the similarity in $K_S$ rather than the differences in extraction constant.

If our understanding of the cation complexation phenomenon for these structures was based exclusively on $K_S$ values, we would conclude that there is little difference in the modes of binding for this series. By using the thermodynamic parameters obtained from the present method, significant differences in the contributions of enthalpy and entropy to the overall binding are apparent. All $\Delta H$ values for the reaction

$$L_{(\text{solvated})} + M^+_{(\text{solvated})} = LM^+_{(\text{solvated})}$$

in the series **1**–**8** are negative indicating that macrocycle binding is favored over solvation by methanol. Within this generalization, two situations are apparent. Enthalpy ($\Delta H$) values for compounds **1**–**6** are the same and essentially identical with those observed for 15-crown-5 (see Table I). This indicates that macroring solvation of the cation dominates the binding phenomenon and that sidearm participation in these cases is essentially irrelevant.

Such a grouping by similar enthalpic contributions is paralleled by similarities in entropies. For compounds **1**–**6**, entropy values are all near zero ($\Delta S$ range: +0.9 to −0.5 eu). The near-zero entropy values in these cases suggest that solvation of the cation and solvation of the complexed cation is similar. This is in marked contrast to compounds **7** and **8**.

Compounds **7** and **8** differ from **1** in the placement of a methylene ($CH_2$) between sidearm oxygen and the macroring. Of course, **1** and **7** have an *o*-methoxy group present which is missing in **8**. The benzyl methylene group must significantly alter the macroring conformation compared to that of **1**–**6**, because macroring enthalpy is considerably less negative for **7** and **8** (−1.80 and −1.54 kcal/mol) than observed for the series **1**–**4** (−3.8 to 4.5 kcal/mol). Likewise, the entropies for **7** and **8** are significantly larger (7.9 and 8.2 eq, respectively) than for the series **1**–**6**. The entropy differences must reflect a less solvated complex in the case of **7** and **8** compared to **1**–**6**. This is expected based on the greater length and flexibility of the sidearms in **7** and **8**.

## Summary

This carefully selected series of compounds illustrates for the first time that considerable insight into macroring–sidearm cooperatively can be gained by using a combination of $K_S$ values and thermodynamic parameters. The large number of compounds we have prepared as part of our ongoing study in the chemistry of lariat ethers should provide a basis for a detailed understanding of this otherwise difficult to assess interplay of ring and sidearm. The present method permits a rapid, precise, and inexpensive means for obtaining the crucial thermodynamic information.

## Experimental Section

**Reagents.** Reagent grade methanol was distilled from magnesium turnings through a 20-cm Vigreux column. Either $ClO_4^-$ or $Cl^-$ salts were used. $NaClO_4$, $KClO_4$, NaCl, and KCl were the purest available from Aldrich Chemical Co. and were recrystallized from water and dried in a vacuum oven (60 °C, 0.05 torr) for 2 days.

**Syntheses.** Compounds **1**–**8** were prepared as follows. The appropriate phenol or alcohol was converted into its allyl ether or glycidyl ether. Glycidyl ethers were hydrolyzed to the corresponding diols, and allyl ethers were oxidized directly to the diols by using $OsO_4$. The diols were then cyclized by using tetraethylene glycol ditosylate and NaH in THF as previously described. Complete details and full characterization for these compounds can be found in ref 2a.

**Apparatus.** Potentials to within ±0.1 mV were measured by using an Orion Model 701A voltmeter. Sodium activity was determined by using a sodium ion-selective electrode (ISE, Corning Model no. 476210). Potassium cation activities were determined by using Corning monovalent cation electrode Model no. 476220. A Corning Ag/AgCl reference electrode (476029) was used with each of the ion-selective electrodes. A water bath, placed on a magnetic stirrer, was maintained at the desired temperature by using a Cole Parmer circulator heater (Model 125200). Sample cells were constructed as previously described.[11]

**Procedure.** New electrodes were conditioned in 1 M salt solutions stepwise to 100% MeOH over a 10-day period, starting with 1 M salt in 90% $H_2O$:10% MeOH solution. The MeOH was increased by 10% per day while the $H_2O$ was decreased by 10%. The salt concentration was kept constant at 1 M. NaCl was used to condition the $Na^+$ ISE, and KCl was used for the monovalent ISE. Once at 100% MeOH, the electrodes were thereafter kept in a 4 mM salt solution. Each ion-selective electrode was tested as described in its manual for Nernstian response.

A 1.00 mM salt reference sample (20 mL) was prepared. Five crown plus salt samples (20 mL) were prepared. The samples ranged from 2.50–1.50 mM with respect to crown and were 1 mM with respect to cation. The potentials of the reference and crown plus salt samples with respect to crown were measured at 15, 21, 25, 31, 37, and 41 °C by taking readings at 5-min intervals until three successive readings differed by 0.3 mV or less. The solution was stirred except while recording a voltage. At least two trials of all samples were measured.

**Calculations.** The stability constant for a 1:1 crown–metal complex is defined as $K_S = [MCr^+]/[M^+][Cr]$ assuming activity coefficients of one. The concentration of free $[M^+]$ was calculated at the desired temperature by using the Nernst equation as follows

$$\Delta E = E_{\text{ref}}(V) - E_{\text{crown}}(V)$$

$$[M^+]_{\text{free}} = e^{-\Delta EnF/RT} \times [M^+]_{\text{ref}}$$

The complex concentration is calculated by subtracting $[M^+]_{\text{free}}$ from the total salt concentration added to the sample. In the samples described, the total salt concentration was 0.00100 M.

$$[MCr^+] = [M^+]_{\text{total}} - [M^+]_{\text{free}}$$

From the total crown concentration and the complex concentration, $[Cr]_{\text{free}}$ was calculated.

$$[Cr]_{\text{free}} = [Cr]_{\text{total}} - [MCr^+]$$

The equilibrium constant, $K_S$, was calculated by using the values of $[M^+]_{\text{free}}$, $[Cr]_{\text{free}}$, and $[MCr^+]$. The ln $K_S$ values of all the trials were averaged. If the standard deviation was more than ±0.08 log units, then the experiment was repeated. If the values still had a standard deviation >0.08, then the situation was probably complicated by the presence of second order or higher equilibria. In such a case, the titration method and calculations described by Frensdorff[3] must be used.

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