Novel Macrocyclic Carriers
For Proton-Coupled Liquid Membrane Transport

Progress Report

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NOVEL MACROCYCLE CARRIERS FOR PROTON-COUPLED LIQUID MEMBRANE TRANSPORT

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I. Ligand Synthesis

We have devised important new methods to prepare the cryptands. These bicyclic ligands form very strong complexes with the alkali metal ions. One method is the reaction of preformed tetraol **1-3** (Figure 1) with the appropriate dihalide or ditosylate to give unsymmetrical cryptands **4-15**. It is most interesting that cryptand **13**, a cryptand [2.2.2] containing two acetal linkages, exhibited selectivity of sodium over potassium ions with a selectivity factor of over 1000. A complete report of this work can be found in *J. Org. Chem.* **57**, 6112-6118 (1992).

The most convenient method for the preparation of the cryptands is one-step reaction of two moles of the ditosylate derivative of tri-or-tetraethylene glycol with one mole of an appropriate diamine. Both starting materials can be purchased. This process gave remarkably good yields - 36% to 50%. A preliminary report of this work can be found in *Tetrahedron Lett.* **34**, 777 (1993). It is important to note that this synthesis will allow the preparation of long chain alkyl-substituted cryptands in a more straightforward manner.

A new method to protect nitrogen atoms during the synthesis of aza-crowns was studied. Aza-crown ligands **22-28** were prepared by treating per(N-formyl)-substituted polyamines with the appropriate dihalide or ditosylate. The yields for the cyclization reaction were over 40%. Per(N-formyl) macrocycles **26-28** were hydrolyzed under acidic conditions to give unsubstituted ligands **29-31** in yields of over 77%. A complete report on this work can be found in *J. Heterocyclic Chem.*, **29**, 1429-1432 (1992).

Figure 1. New Macrocyclic Ligands and Starting Materials

1, $n = 1$

2, $n = 2$

3, $n = 3$

4-6; $X = \text{CH}_2\text{C}(\text{=CH}_2)\text{CH}_2$; $n = 1, 2$ and 3

7-9; $X = 2,6\text{-pyridinediCH}_2$; $n = 1, 2$ and 3

10-12; $X = 1,2\text{-benzenediCH}_2$; $n = 1, 2$ and 3

13,14; $X = \text{CH}_2$; $n = 2$ and 3

15; $X = 1,3\text{-benzenediCH}_2$; $n = 3$

16; 2.2.1 $m, n = 1$

17; 2.2.2 $m = 1, n = 2$

18; 3.3.1 $m = 2, n = 1$

19; 3.2.2 $m = 1, n = 3$

20; 3.3.2 $m = 2, n = 2$

21; 3.3.3 $m = 2, n = 3$

22

23

24

25, $n = 1$

26, $n = 2$

27, $n = 3$

28, $n = 4$

29, $n = 2$

30, $n = 3$

31, $n = 4$

II. Extraction and Liquid Membrane Experiments

We have been studying the effect of the addition of hydrophobic side chains on crown ethers used in separation systems. Crowns containing side chains of various lengths were studied in back extraction and dual module hollow fiber membrane separation experiments. The back extraction experiments characterize the cation selectivity of ligands while the dual module hollow fiber membrane experiments monitor the membrane separation behavior of ligands. Representative back extraction results for two ligands containing side chains $C_{11}H_{23}O$ and $C_{10}H_{21}$ are shown in Table 1. Figure 2 shows representative results for the latter of these crowns in a dual module hollow fiber membrane system.

The $\log K$, ΔH , and ΔS values in 100% methanol were determined for these ligands using Tronac titration calorimetry. The results for one ligand are shown in Table 2, as a comparison with the parent compound, 18-Crown-6.

We have also characterized proton-ionizable ligands using potentiometric titrations. The pK_a of a ligand is important in the development of membrane transport systems because proton gradients can be used with concentration gradients to perform membrane transport of specific ions. When the transport system is driven by these two factors, transport efficiency should increase. The pK_a also identifies the pH ranges which can be used in the transport system. The Metrohm titration system is controlled through an interface to a personal computer using a BASIC program which permits both experimental control and data collection from the titration system. The pK_a of a proton-ionizable phosphorous-containing crown, phosphono-crown-6, was measured as $2.5 \pm .02$. This very acidic crown ether is very promising for use in membrane separations.

Table 1. Extraction Equilibrium Constants (Chloroform/water) for the Interaction of Two Crown Ligands with Alkali Cations

Macrocycle	K_{ex}			
	Na^+	K^+	Rb^+	Cs^+
Decyl-18-Crown-6	.94	1.2	.83	.57
2-(decyloxymethyl)-18-Crown-6	.09	2.5	.45	.02

Table 2. Comparison of 18-Crown-6 with Decyl-18-Crown-6.

18 Crown-6 Values at 25°C in MeOH

	LogK	$\Delta H(kJ/Mol)$	$\Delta S(J/KMol)$
Na^+	4.32	-34.0	-32
K^+	> 5	-54.9	-68
Rb^+	> 5	-49.6	-64
Cs^+	4.44	-49.9	-83

Decyl-18-Crown-6 Values at 25°C in MeOH

	LogK	$\Delta H(kJ/Mol)$	$\Delta S(J/KMol)$
Na^+	2.75	-66.6	-170.8
K^+	5.74	-53.87	-71.3
Rb^+	4.03	-65.96	-190.2
Cs^+	3.22	-74.99	-32

Figure 2

**Na⁺, K⁺, Rb⁺, and Cs⁺ Transport with Decyl18C6
in a DMHF Membrane System**

Transport in a 250 ml, 0.1M NaNO₃, KNO₃, RbNO₃, and CsNO₃ source phase/
30 ml, 1mM decyl-18-Crown-6 in 2-octanone membrane/
250 ml H₂O receiving phase system

III. High Temperature Isothermal Flow Calorimetry: Thermodynamics of Macrocycle-Cation Reactions at High Temperature

Crown ether-cation complex reactions are very temperature dependent and this characteristic can be exploited in making separations. This phase of the project is designed to study these reactions at high temperature. In order to determine the thermodynamic quantities for macrocycle-cation reactions at different temperatures, we have completed construction of an isothermal flow calorimeter. This calorimeter retains all of the desirable operating characteristics and advantages of previous isothermal flow calorimeters, while offering the additional advantages of operation at temperatures from 25°C up to 325°C. It can be operated at pressures from 0.1 to 25.5 MPa, and at solution pH ranging from 3 to 14. The data can be collected and displayed in digital form by a Macintosh Plus computer and/or obtained on a strip chart recorder.

The calorimeter has been calibrated by measuring the heat of mixing for ethanol and water and the heat of dilution of aqueous NaCl at 50°C and 200°C, respectively. The results in Table 3 and Table 4 show that our calorimeter can give reliable results in the temperature range we measured.

Log K, ΔH , and ΔS values for the interaction of 18C6 with Ba^{2+} , Sr^{2+} , and K^+ have been determined at different temperatures up to 200°C. The results in Table 5 show that as the temperature increases, the log K value decreases. This is because the reaction is exothermic. As the temperature increases, both ΔH and ΔS decrease. Figures 3 and 4 show these specific macrocycle and cation interactions; ΔH is a linear function of the temperature. From this linear relationship, we can predict the log K value at other temperatures by integration using the Van't Hoff equation. Table 6 shows that the predicted log K values are very close to the experimentally measured values. The thermodynamic quantities measurements for macrocycle-

Table 3. Chemical Calibrations of the Flow Calorimeter

Heat of dilution of aqueous NaCl at 200°C and 2.6 MPa

m_i^e (mol/Kg)	m_f^f (mol/Kg)	ΔH^a (J/mol)		n^c	Δ^d
		Literature ^b	This study		
1.000	0.7067	-1062.9	-1043.3±0.5	3	0.018
1.000	0.6138	-1711.8	-1633±1.4	3	0.046
1.000	0.5144	-2211.7	-2241.7±0.8	3	-0.013
1.000	0.4182	-2794.0	-2739.4±0.9	3	0.019
1.000	0.3095	-3522.6	-3505.1±0.6	3	0.004
1.000	0.2330	-4193.8	-4206.1±1.3	3	0.003

^a ΔH is the heat of dilution of aqueous NaCl.

^b Literature values are obtained by interpolation from reference.

^c Number of duplicate runs.

^d $\Delta = (\Delta H \text{ literature} - \Delta H \text{ this study})/\Delta H \text{ literature}$.

^e Initial concentration of NaCl.

^f Final concentration of NaCl.

Table 4. Chemical Calibrations of the Flow Calorimeter
Heats of Mixing for Ethanol and Water at 50°C

Pressure (MPa)	EtOH Mole Fraction	ΔH^a (J/mol)		n ^c	Δ^d
		Literature ^b	This study		
0.4	0.0300	-179.0	-179.5±0.5	3	0.002
0.4	0.0646	-330.6	-330.2±1.0	3	-0.001
0.4	0.1044	-415.8	-413.9±0.6	3	-0.004
0.4	0.1550	-430.6	-428.3±1.3	3	-0.005
0.4	0.2188	-385.3	-385.3±0.8	3	0.000
0.4	0.2982	-302.9	-301.5±0.9	3	-0.004
0.4	0.4041	-193.0	-193.3±1.1	3	0.002
0.4	0.5290	-104.0	-102.4±1.2	3	-0.015
0.4	0.6342	-62.3	-61.2±1.0	3	-0.017
0.4	0.7098	-52.1	-51.5±1.4	3	-0.012
0.4	0.8267	-53.5	-56.8±0.9	3	-0.029

^a ΔH is the heat of mixing for ethanol and water.

^b Literature values are obtained by interpolation from reference.

^c Number of duplicate runs.

^d $\Delta = (\Delta H \text{ literature} - \Delta H \text{ this study})/\Delta H \text{ literature}$.

Table 5. Thermodynamic values for the indicated reaction

System	Temp. (K)	LogK	ΔH (kJ mol ⁻¹)	ΔS (J mol ⁻¹ K ⁻¹)
18C6 + Ba ²⁺	298.2 ^a	3.87	-37.71	-32.21
	374.2	2.73	-33.03	-37.08
	423.2	2.03	-35.06	-43.97
	473.2	1.53	-42.74	-61.21
18C6 + Sr ²⁺	298.2 ^a	2.80	-15.10	2.97
	374.2	2.04	-18.90	-11.44
	423.2	1.59	-22.82	-23.48
	473.2	1.28	-25.93	-30.28
18C6 + K ⁺	298.2 ^a	2.23	-19.00	-21.02
	423.2	0.91	-29.84	-53.08
	473.2 ^b	0.28	-67.94	-138.13

^a Literature values

^b Since the log K is too low, the results at this temperature may not be accurate.

Figure 3

Plot of calculated and experimental log K values
as a function of temperature for
the interaction of 18-Crown-6 with Strontium

0.3 M $\text{Sr}(\text{NO}_3)_2$ reacted with 0.3 M 18-Crown-6

Figure 4

Plot of calculated and experimental log K values
as a function of temperature for the
interaction of 18-Crown-6 with Barium

0.3 M $\text{Sr}(\text{NO}_3)_2$ reacted with 0.3 M 18-Crown-6

Table 6. Comparison of Experimental and Calculated Log K Values for the Interaction of 18-Crown-6 with Ba²⁺ and Sr²⁺ at Different Temperatures

System	Temp	LogK(exp)	LogK(calc) ^a
18C6 + Ba ²⁺	374.2	2.73	2.72
	423.2	2.03	2.12
	473.2	1.53	1.57
18C6 + Sr ²⁺	374.2	2.04	2.13
	423.2	1.59	1.50
	473.2	1.28	1.12

^a From the Van't Hoff equation.

cation interactions in other solvents are currently underway. Chuan Wang, the graduate student who has been working on this project, is due to graduate soon and is preparing two manuscripts for publication based on this work.

IV. Computer Modelling of Ligand-Cation Interaction

In the new computational portion of this project, we are making rapid progress. We trained a very good undergraduate research assistant during the winter semester of 1993. During spring and summer, Mr. Lloyd Stolworthy has been working on the molecular mechanics simulation of macrocycle binding of alkali metal ions in the gas phase. We are working to understand the gas phase binding first for two reasons:

1. The gas phase binding is simpler, and
2. Experimental results are beginning to become available.^{1,2,3}

Experimental binding affinities for crown ethers with alkali metal ions in the gas phase are now being studied. Experimental studies of crown ether binding have included mass spectrometric fragmentation information,^{2,3} and relative binding affinities.¹ One of the innovative experimenters in this field, D. V. Dearden, will be joining this department and will be available for consultation and collaboration. We hope to extend our initial gas phase investigations during this calendar year to the point that we can move to liquid phase molecular dynamics simulations during the next project year.

Using this year's project funds, CERIUS, a commercial software package noted for its flexibility in designing and modifying molecular mechanics force fields, was purchased. Figure 5 is output from CERIUS showing high quality graphics of 18-crown-6 bound to Rb^+ with the Rb ion bound out of the plane of the macrocycle. Learning is rapid and efficient using this

Figure 5.

visualization tool running on a Silicon Graphics PI/35 workstation made available for full-time use on this project by the chemistry department.

The focus of our investigation in the three months that this work has been pursued full-time has been the conformational analysis of 18-crown-6 and its alkali metal ion complexes together with the energetics of the complexation. This problem has previously been examined using different methods by several different researchers.^{4,5,6,7} In early work, Yamabe⁴ used the semiempirical CNDO method to predict the structure and electrostatic potential. This early work was not sophisticated, but the results of this study were sufficient to indicate that the specificity of alkali metal ions binding to crown ethers is determined not by the binding energy of the ion to the macrocycle, but by differential solvation free energies. More recent work was used more sophisticated ab initio SCF calculations^{8,9} and density functional theory.^{10,11}

Many recent examinations of the 18-crown-6:metal ion complex have been performed by molecular mechanics methods.^{12,13,14,15,16,17,18} These methods are well developed and very accurate for hydrocarbon systems, but all of the researchers in the field agree that the conformational energy of polyethers is controlled by the electrostatic interactions between polar oxygen atoms and other parts of the molecule. The MM2 force field of Allinger and coworkers¹⁹ uses bond dipoles to represent these interactions. Other force fields like AMBER²⁰ use partial charges on each atom (or possibly also in lone pairs). In addition, however, there is disagreement about how the intramolecular dielectric constant should be handled²¹ and how to determine the partial atomic charges.²² Some researchers use the charges calculated from ab initio calculations. These seem to work reasonably well, except the partial charges must necessarily be held constant as the conformation of the molecule changes. Some researchers use charges from good quality semi-empirical calculations. These have the advantage

of being able to be recalculated for each conformation, but are not necessarily reliable. A new method called charge equilibration due to Rappe⁷ and Goddard²³ has promise. This method uses atomic information about ionization potential, electron affinity and Coulomb integrals to iteratively solve a set of equations which equalize the chemical potential in all atoms of the molecule subject to the constraint of total charge. This new method has an advantage over similar methods in that it takes geometry and distance into account rather than just bonding relationships. This method has proved very illuminating in our investigations so far, but will need to be compared to more accurate calculational methods.

One of the major products of the computational part of this project in the few months of operation is a small software package. In order to sort out and analyze the several contributions to the steric energy of a macrocycle (or any other molecule), a new program, ANLIZE, was written by Mr. Stolworthy. This extremely illuminating program runs on a personal computer. It takes the output of a molecular mechanics program such as CERIUS and displays graphically the interactions which are parameterized by the force field chosen. One can rotate the molecule using a mouse and interactively examine the contribution of each term in the force field to the energy. This capability is not available on any of the commercial packages that we have seen, so we are investigating the patentability or salability of this software or even the concept by itself. In the meantime, we are using this program to understand the details of the molecular mechanics calculations we are performing. Much of the knowledge we have gained about the conformational behavior of macrocycles has been developed using this program. Figures 6-7 illustrate the utility of the ANLIZE program. Figure 6 shows a screen dump of ANLIZE as it analyzes dimethyl ether. On the left is a mouse palette of options. In the center is a wire-frame rendition of dimethyl ether with the largest van der Waals contribution to the

steric energy (a 1-4 C-O interaction with energy 0.5974 kcal/mole) and the largest bond stretching interaction (a C-O stretch with harmonic energy 0.1112 kcal/mole) highlighted. Also indicated are the equilibrium bond stretch for the highlighted bond and the van der Waals radius parameter for the highlighted nonbonding interactions. In the center of the picture is the calculated dipole moment of the molecule in this conformation (in units of electronic charge $\times$ Ångstroms). On the left of the figure is a stack chart of the contributions to the energy (van der Waals, Coulomb, angle bending, and bond stretching in order bottom to top, torsional strain is negligible). Figure 7 illustrates a similar rendition of sodium ion (whose position is indicated by the + sign) bound to 18-crown-6. In Fig. 7, the highlighted contributions to the steric energy are the largest Coulomb interaction (between Na^+ and an O atom), and the largest bond stretch (a C-O). Although we have only exhibited the largest of several contributions to the steric energy in the figure, the program allows one to cycle through all the contributions of any term in the energy expression (there may be several hundred of each).

We compared the energies of the 30 lowest energy conformations of uncomplexed 18-crown-6 as determined using the AMBER force field by Sun and Kollman²⁴ to the relative energies of the same conformations as determined using the DREIDING force field²⁵ from the program CERIUS. We used several different methods of determining the charges. In all cases, the major differences in energy were controlled by the electrostatic interactions, as expected. Figure 8 shows the results of this calculation in which we fully minimized the energy of the 42 atom 18-crown-6 molecule from an initial configuration with bond angles and lengths at their equilibrium values and torsion angles set at $\pm 60^\circ$, or 180° as assigned by Sun and Kollman. The abscissa of this plot is the conformation number in order of increasing energy as determined by Sun and Kollman, and the ordinate is energy in kcal/mole. Conformation #14 is the symmetrical

Figure 1. All dipole moment plots. 1. with a hydrogen bond transition

Figure 2. All dipole moment plots. 2. with a hydrogen bond transition

D_{3d} structure. In Sun and Kollman's calculation, conformation #1 was the lowest energy. All calculations are reported relative to the energy of this conformation. This conformation was also the lowest energy in our calculation where we used the DREIDING force field with the same constant charges that Billeter and Kollman¹⁶ used. However, the ordering of the other conformations was not the same. For example, #15 was the second lowest. When we used the charge equilibration method which allows the partial atomic charges to adjust, conformation #15 was the lowest, with #30 being the second and #11 third. The red line shows the relative energy of the same configurations with the electrostatic forces turned off. What was surprising to us was that the ordering of conformations was entirely different even though the force fields are very similar. Another important result was that when the charge equilibration algorithm was used to determine the charges, the oxygen charges were quite different in the different conformations. The changes from one formation to another were 10 to 15%. Since the electrostatic interactions, in fact, control which conformation is of minimum energy, a 15% error in assigning the charge can change the energy ordering of conformations. This change would probably affect the kinetics or even the thermodynamics of binding specificity. Thus, before any definitive progress can be made in the theoretical description of polyethers such as 18-crown-6, additional, good quality calculations must be performed in determining the electrostatic interactions between the nuclei in these systems. The calculations demonstrating these conclusions will be submitted shortly.²⁶

Figure 8.

V. A. Papers Published Since the Last Progress Report

1. J. S. Bradshaw, K. E. Krakowiak, H.-Y. An, T.-M. Wang, C.-Y. Zhu and R. M. Izatt "A Novel Two-step Method to Prepare New Unsymmetrical Cryptands," Tetrahedron Lett., **33**, pp. 4871-4874, (1992).
2. J. S. Bradshaw, H.-Y. An, K. E. Krakowiak, T.-M. Wang, C.-Y. Zhu and R. M. Izatt, "Synthesis and Complexation Properties of New Unsymmetrical Cryptands," *J. Org. Chem.*, **57**, pp. 6112-6118, (1992).
3. J.S. Bradshaw, K.E. Krakowiak, H.-Y. An and R.M. Izatt, "A New Synthetic Route to Polyaza-crown Macrocycles Through the Per(N-formyl)polyaza-crowns," *J. Heterocyclic Chem.*, **29**, pp. 1429-1432, (1992).
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5. H.-Y. An, J.S. Bradshaw, K.E. Krakowiak, C.-Y. Zhu, N.K. Dalley, and R.M. Izatt, "Synthesis and Complexation Properties of Suitcase-shaped Macrotricyclic and Butterfly-shaped Macrobicyclic Polyether Ligands," *J. Org. Chem.*, **57**, 4998-5005, (1992).
6. R. M. Izatt, J. D. Lamb, R. L. Bruening, C. Wang, N. Edge, and J. S. Bradshaw, "Cation Separations Using a Proton-Ionizable Macrocycle in a Dual Module Hollow Fiber Membrane System," *Sep. Sci. Technol.*, **28**, 383-396, (1993)
7. K. E. Krakowiak and J. S. Bradshaw, "Syntheses of the Cryptands. A Short Review," *Israel J. Chem.*, **32**, pp. 3-14, (1992). (DOE acknowledgement inadvertently left out.)

B. Papers in Press or Submitted

1. G. Wu, R.M. Izatt, M.L. Bruening, W. Jiang, H. Azab, K.E. Krakowiak and J.S. Bradshaw, "NMR and Potentiometric Investigations of Portonation Sites of Dipyrindino-28-Crown-8 and Its Oxa-Anion Binding Properties With Selenate, Sulfate and Nitrate Ions in Aqueous Solution", *J. Incl. Phenom.*, in press.
2. K.E. Krakowiak, J.S. Bradshaw and R.M. Izatt, "Improved Methods for the Synthesis of Aza-crown Macrocycles and Cryptands," *Syn Lett.*, in press.

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