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FINAL REPORT

Novel Macrocyclic Carriers for

Proton-Coupled Liquid Membrane Transport

Principal Investigator: John D. Lamb
Professor of Chemistry

Co-Principal Investigators: Reed M. Izatt
Professor of Chemistry

Jerald S. Bradshaw
Professor of Chemistry

Randall B. Shirts
Associate Professor of Chemistry

Brigham Young University
Provo, Utah 84602

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TABLE OF CONTENTS

I. ABSTRACT

The objective of our research program is to elucidate the chemical principles which are responsible for the cation selectivity and permeability of liquid membranes containing macrocyclic carriers. Several new macrocyclic carriers were synthesized during the last three year period. In addition, new, more convenient synthetic routes were achieved for several nitrogen-containing bicyclic and tricyclic macrocycles. The cation binding properties of these macrocycles were investigated by potentiometric titration, calorimetric titration, solvent extraction and NMR techniques. In addition, hydrophobic macrocycles were incorporated into dual hollow fiber and other membrane systems to investigate their membrane performance, especially in the proton-coupled transport mode. A study of the effect of methoxyalkyl macrocycle substituents on metal ion transport was completed. A new calorimeter was constructed which made it possible to study the thermodynamics of macrocycle-cation binding to very high temperatures. Measurements of thermodynamic data for the interaction of crown ethers with alkali and alkaline earth cations were achieved to 473 K. Molecular modeling work was begun for the first time on this project and fundamental principles were identified and developed for the establishment of working models in the future.

II. RESEARCH RESULTS FOR PERIOD 1 DEC. 1991 - 31 MAY 1994

II.A. SUMMARY OF ACTIVITY

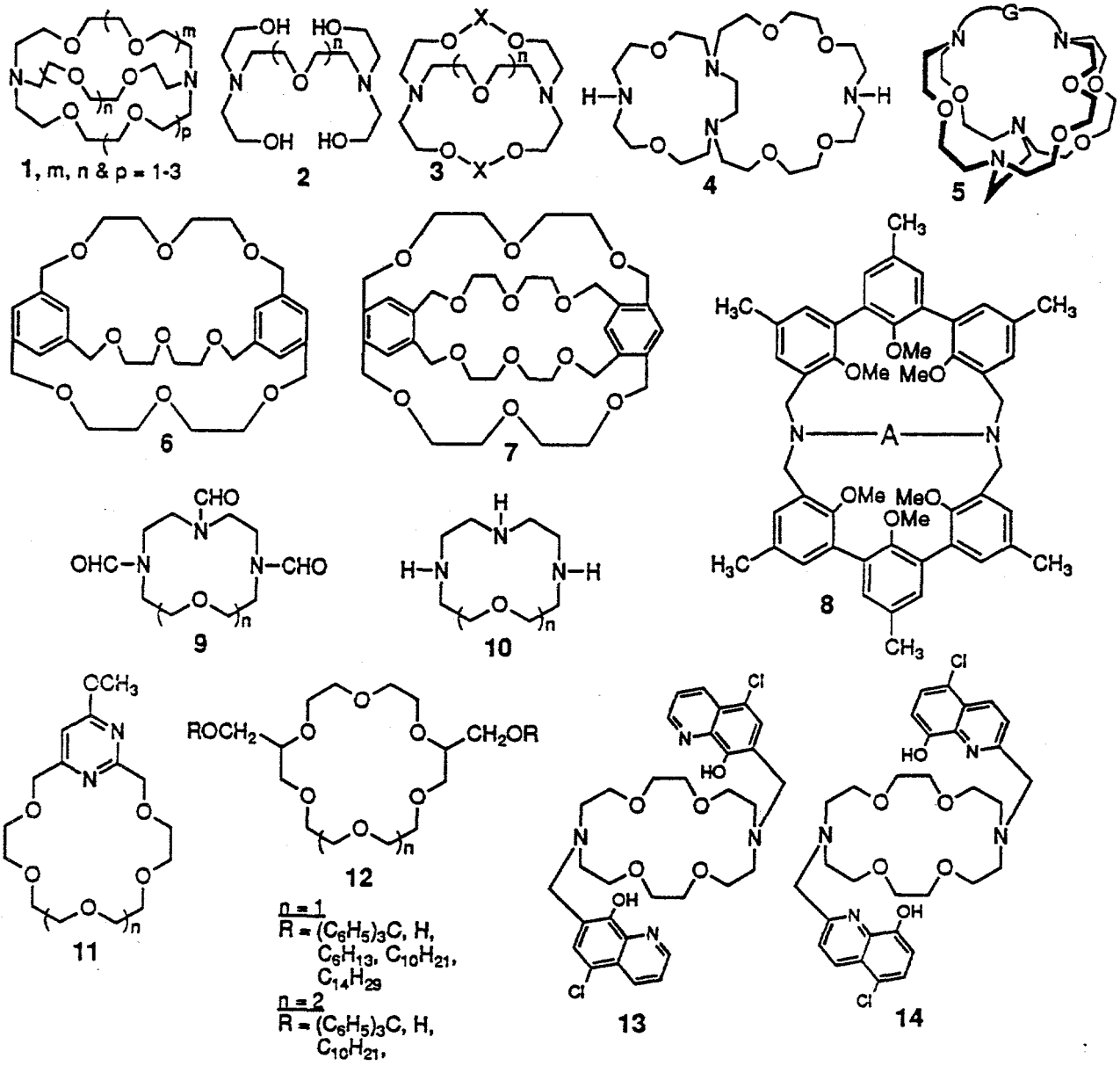
The following table summarizes activities during the reporting period with respect to publication of results, presentation of results, and personnel:

1.	Number of refereed papers published	23
2.	Number of refereed papers in press or submitted	4
3.	Number of oral presentations	19
4.	Number of undergraduate students involved on project	9
5.	Number of graduate students involved on project	5
6.	Number of post-doctoral fellows involved on project	7
7.	Number of faculty involved on project	4

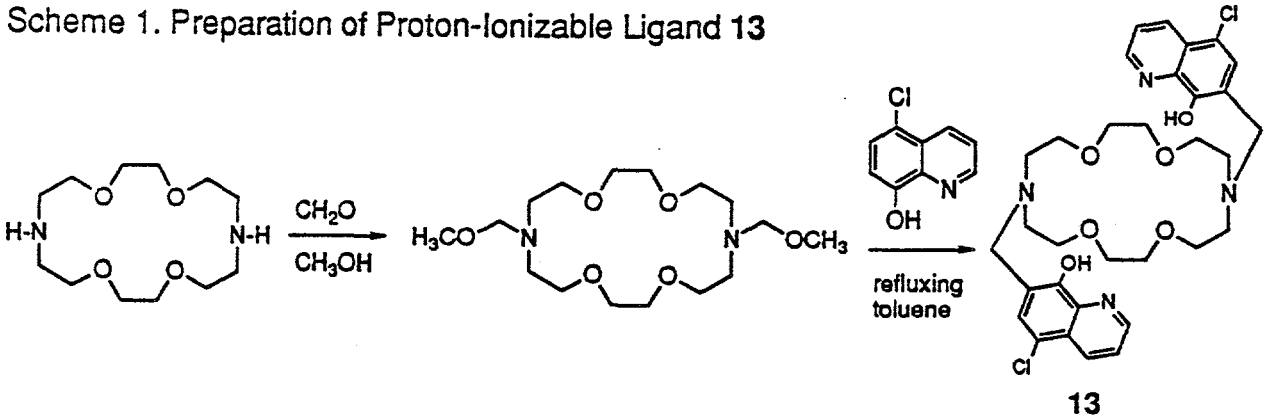
II.B. LIGAND SYNTHESIS

Many new ligands have been prepared for this project in the laboratory of Professor Jerald Bradshaw since December 1, 1991. Figure 1 shows the new macrocycle types that have been prepared. In addition to preparing specific ligands to transport metal ions across lipophilic membranes, we have been developing new and convenient methods to prepare nitrogen-containing macrocycles. Cryptands **1** were prepared by a one-step process from commercially

Figure 1. New Macrocyclic Ligands Prepared in the Past Three Years



Scheme 1. Preparation of Proton-Ionizable Ligand **13**



available oligoethylene glycol ditosylates and the appropriate diamine. Yields for this reaction were 36% to 50% which are a great improvement over the overall yields of 5% to 15% for the usual multistep process. More details are found in *Tetrahedron Lett.* **34**, 777 (1993). An X-ray structure analysis for the [3.3.3] (**1**, m, n, p = 2)-KI complex showed that all nine oxygen atoms and the two nitrogen atoms were coordinated to the potassium ion [see *Tetrahedron* **50**, 2721 (1994)].

Unsymmetrical cryptands **3** were prepared by treating tetraalcohol **2** with various dihalide or ditosylate compounds. Structure **3** represents a dozen compounds where X = CH_2, $CH_2CH(=CH_2)CH_2$, CH_2-pyridine-CH_2 and CH_2-benzene-CH_2 and n = 1-3. Complete details including complexation properties for these new unsymmetrical cryptands can be found in *Tetrahedron Lett.* **33**, 4871 (1992) and *J. Org. Chem.* **57**, 6112 (1992).

Some very interesting bicyclic and tricyclic polyazaethers have been prepared. Bicycle **4** was prepared by first treating the tritosylate derivative of 6-aza-3,9-dioxa-1,11-undecanediol with 3,5-diaza-1,8-octanediol using a carbonate base. The resulting N, N′-bis(2-hydroxyethyl)-N″-tosyl-15-crown-5 was then treated with the same tritosylate derivative followed by reductive cleavage of the two N-tosyl groups. Bicycle **4** was then treated with three different X-G-X groups to give three suitcase-shaped cage compounds **5**. More details on the syntheses of **4** and **5** and information on their complexation with various cations are given in *J. Org. Chem.* **57**, 543 (1992).

Benzene-bridged macrobi- and macrotricyclic polyether ligands (**6** and **7**) were prepared in two steps by treating 1,3,5-tris(hydroxymethyl)benzene and 1,2,4,5-tetrakis(hydroxymethyl)benzene with THP-protected 5-bromo-3-oxa-1-pentanol followed by deprotection, tosylation and another mole of the oligo(hydroxymethyl)benzene. Complete details of these syntheses are found in *J. Org. Chem.* **58**, 7694 (1993).

In our research for better ways to prepare the polyazacrown ethers, we found that the per(N-formyl)polyamines were good synthons to form the per(n-formyl)polyazacrowns (**9**). The cyclization reaction is straight forward and removal of the N-formyl protecting groups gave the desired azacrowns (**10**). Complete details can be found in *J. Heterocyclic Chem.* **29**, 1429 (1992).

Several new synthetic ligands are reported in papers that are in press. Spherocryptands **8** [A = $(CH_2)_2O(CH_2)_2O(CH_2)_2$ and $(CH_2)_3O(CH_2)_2O(CH_2)_3$] were prepared by treating the aliphatic diamine with 2 moles of the bis(bromomethyl)-substituted tribenzene compound (see *J. Org. Chem.*, in press). Methoxy-substituted pyrimidinocrown ethers (**11**, n = 1-3) have now been prepared and characterized (*J. Heterocyclic Chem.*, in press). These materials, when treated with strong base, will be converted to the proton-ionizable pyrimidonocrowns. The octyl-substituted pyrimidonocrowns will be useful for the proton-assisted transport of metal ions. Bis(alkoxymethyl)-substituted 18-crown-6 and 21-crown-7 ligands (**12**) have been prepared by first preparing the bis(trityloxymethyl)-crowns, removing the trityl groups and treating the resulting bis(hydroxymethyl)-crowns with the appropriate alkyl halide and base.

Bisdecoxymethyl-18-crown-6 (**12**, n = 1, R = $C_{10}H_{21}$) has a better selectivity for K^+ than does unsubstituted 18-crown-6. Complete details of this work are in *Sep. Sci. Technol.*, in press.

We have also prepared two new proton-ionizable ligands **13** and **14**. Ligand **13** was prepared as shown in Scheme 1. A great number of new proton-ionizable ligands can be prepared by this process as described in the accompanying proposal. Ligand **13** has unique complexing properties in that it is selective for Mg^{2+}, Ca^{2+}, and Cu^{2+} over Na^+ and K^+. The selectivity can be dramatically changed in these types of ligands. Ligand **14**, an analogue of **13** and prepared in a different way , is selective for Ba^{2+} over other alkali and alkaline earth cations.

II.C. MACROCYCLE CHARACTERIZATION

Titration Calorimetry

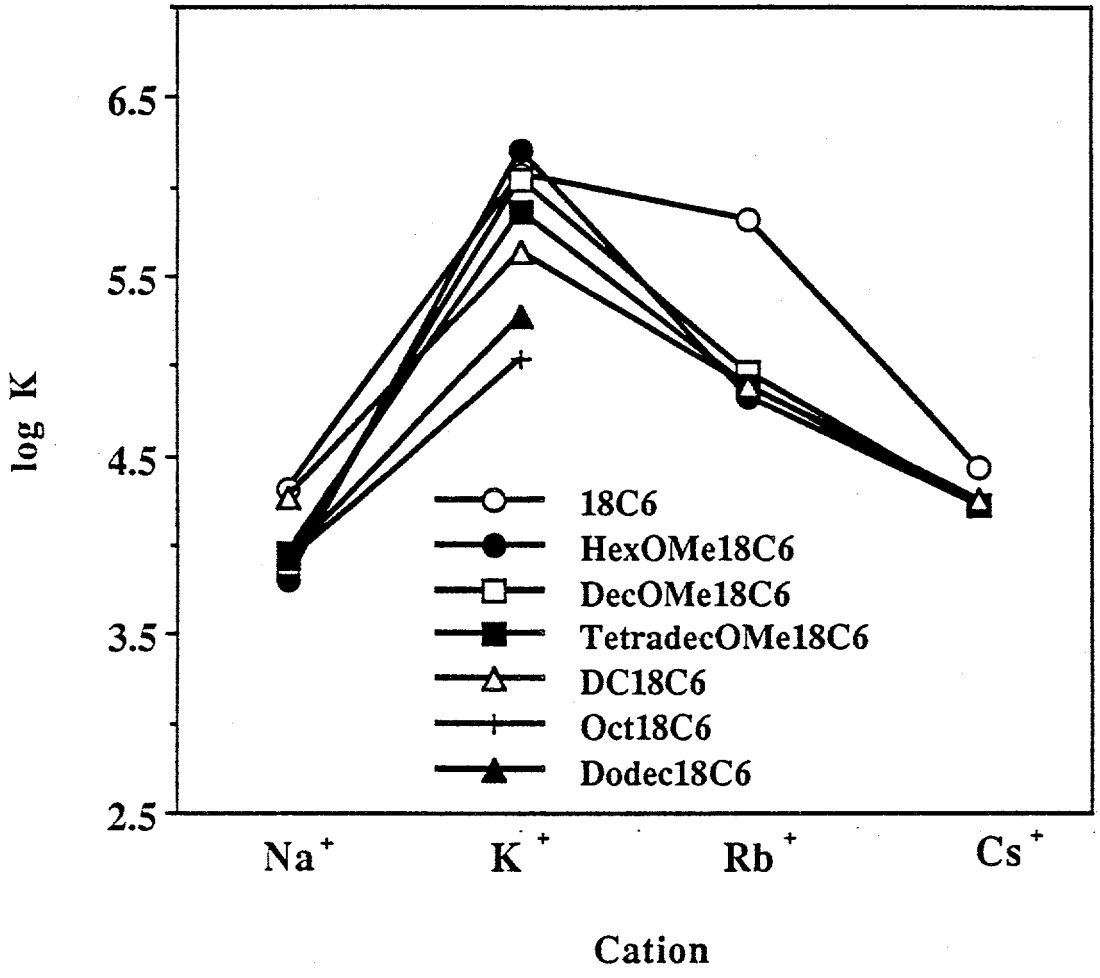
Titration calorimetry was used in the characterization of two classes of macrocylic ligands in the laboratories of Professors John Lamb and Reed Izatt. The first class of compounds studied were sulfur containing crown thioethers: benzodithia-18-crown-6, benzodithia-15-crown-5, and bis-(1,4-dioxa-7,11-dithiacyclotridecen-9-yl)glutarate. The heats of interaction of these three macrocyles with Pb^{2+}, Cd^{2+} and Hg^{2+} were measured in methanol at 25 °C using a Tronac 450 isoperibol titration calorimeter. From the titration data, log *K*, ΔH, and ΔS values were calculated using a VAX 11/780 computer employing previously developed programs. The log *K* values for the interaction of Hg^{2+} with all three of the macrocycles were shown to be higher than the other metal ions tested, confirming the advantage of S-containing ligands for Hg^{2+} selectivity.

The second class of compounds studied were alkoxymethyl-substituted 18-crown-6 and 21-crown-7 ligands to determine the effect on binding of hydrophobic substituents. Log *K*, ΔH, and ΔS values in methanol at 25 °C were determined for the interaction of the ligands with the alkali metal cations. Figure 1 shows that the 18-crown-6 based macrocyles displayed an increase in the log *K* value for K^+ over that of the parent 18-crown-6, while showing a decrease in log *K* values for the other alkali metal cations. This phenomenon was attributed to the activity of the neutral oxygen donor atom in the alkoxymethyl side chain. Since the atomic radius of K^+ best matches the cavity size of the 18-crown-6 ligands, the oxygen atom in the side chain participates in the binding process.

Construction of the High Temperature Calorimeter

A flow calorimeter was built which is suitable for use with high-temperature aqueous or organic solutions containing macrocylic ligands and metal salts. Experiments in a wide range of concentrations, flow rates, temperatures, and pressures can be explored via this calorimeter (see next section). The calorimeter is based on the use of a controlled heat-leak path between the reaction zone and the surrounding concentric container, which allows the reaction zone to be maintained at a constant temperature during the course of the reaction.

Figure 2. Comparison of alkali metal log K values for various ligands in methanol at 25 °C



The main components of the calorimeter are the reaction vessel, the isothermal cylinder, the thermal shields and insulating container, the fluid delivery system containing high-pressure pumps, and the pressure control system. The temperature control system for the calorimeter consists of four Tronac PTC-41 controllers and a Hart Scientific 3704 isothermal control unit. The data acquisition system consists of a strip chart recorder. A diagram showing the main components of the calorimeter is given in Figure 3. Platinum-rhodium alloy tubing was used in the fluid delivery system to give the calorimeter excellent resistance to hot, corrosive solutions, including acidic chlorides. The addition of a preheating system and the increase in heat exchange areas have reduced the amount of time required to reach thermal equilibrium.

High Temperature Calorimetry

Thermodynamic data for a large number of macrocylic ligand-metal ion interactions at or near room temperature are presently available. However, there is little or no information available concerning the variation of thermodynamic quantities as a function of temperature.

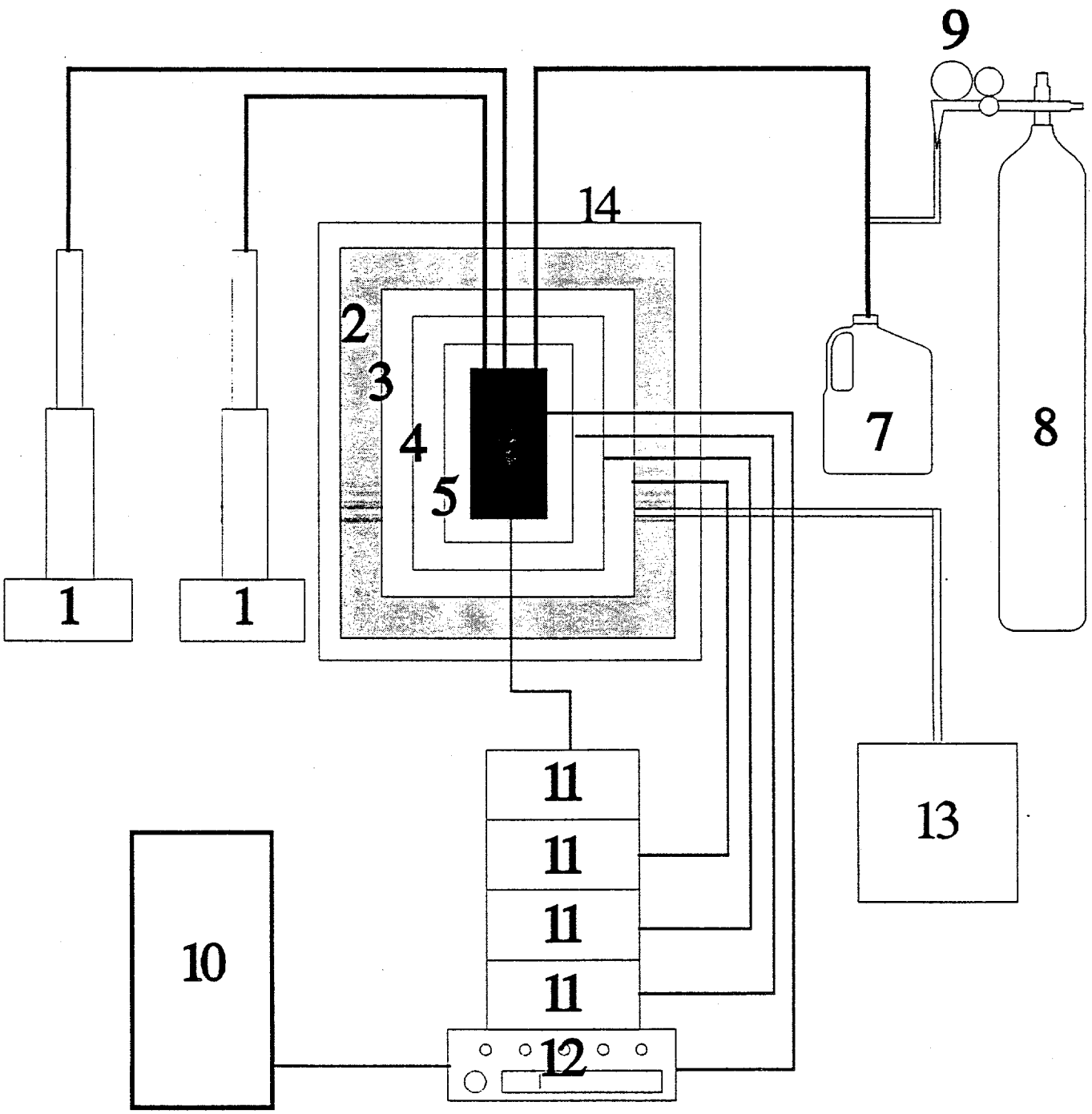
The thermodynamic quantities for the interactions of 18-crown-6 with K^+, Ba^{2+}, and Sr^{+2} at 324.2 K, 374.2 K, 423.2 K and 473.2 K were determined using the high temperature flow calorimeter. The pressure of the calorimeter system in all the experiments was 12.4 MPa. Figure 4 shows that a linear variation exists between the ΔH values and temperature over the temperature range studied. For each of the cations studied, log K values decreased as the temperature increased due to the exothermic nature of the macrocyle-cation complexation reaction. The thermodynamic quantities determined in this study can be used for evaluating the effects of temperature on the thermodynamic values of cation-macrocylic ligand interactions.

II.D. MEMBRANE TRANSPORT STUDIES

Liquid Membrane Experiments

Figure 5 shows a Dual Module Hollow Fiber (DMHF) membrane system which was used under the direction of Professors Lamb and Izatt to study the separation of metal cations using several classes of macrocylic ligands. This system involves a double extraction, with the membrane solvent in contact with the fibers containing both the source and receiving aqueous phases. In all the DMHF membrane experiments, 2-octonone was used as the membrane solvent. All of the experiments were run for a period of 24 hours with samples being taken from the receiving phase hourly. These samples were analyzed by a Perkin Elmer Model Plasma II ICP. A more detailed description of the DMHF membrane system and some representative results can be found in the article in *Separation Science and Technology* **28**, 383 (1993).

Figure 3. Schematic of the various components of the high-temperature flow calorimeter.



1, pump; 2, insulation; 3, outer shield; 4, inner shield; 5, reaction vessel; 6, isothermal cylinder; 7, waste container; 8, nitrogen tank; 9, pressure gauge; 10, strip chart recorder; 11, temperature controller (Tronac PTC-41); 12, isothermal control unit (Hart Scientific 3704); 13, isotemp refrigerated circulator (Fisher Scientific 9500); 14, outer can

Figure 4. Enthalpy values for the reaction of metal cations and 18-Crown-6 as a function of temperature.

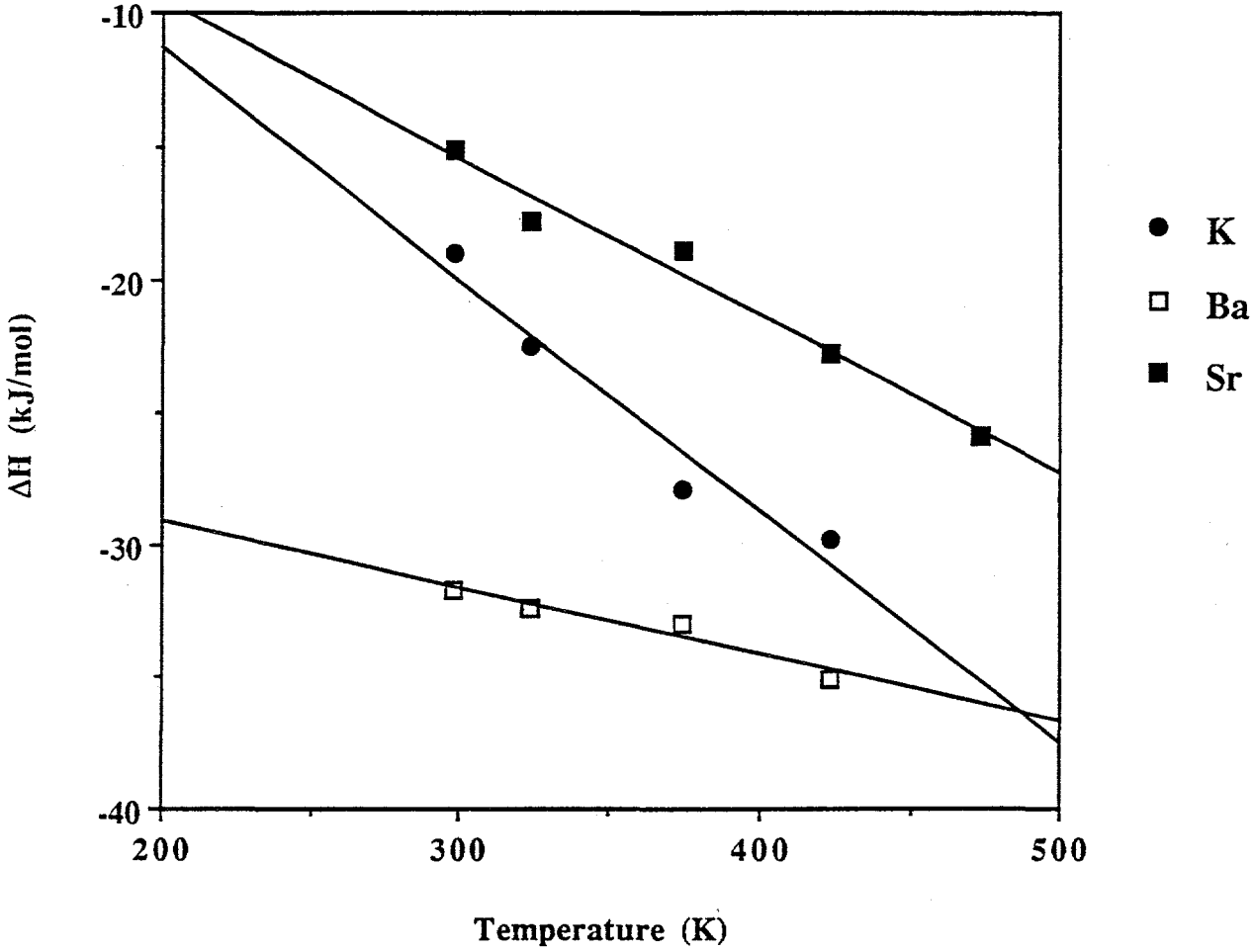
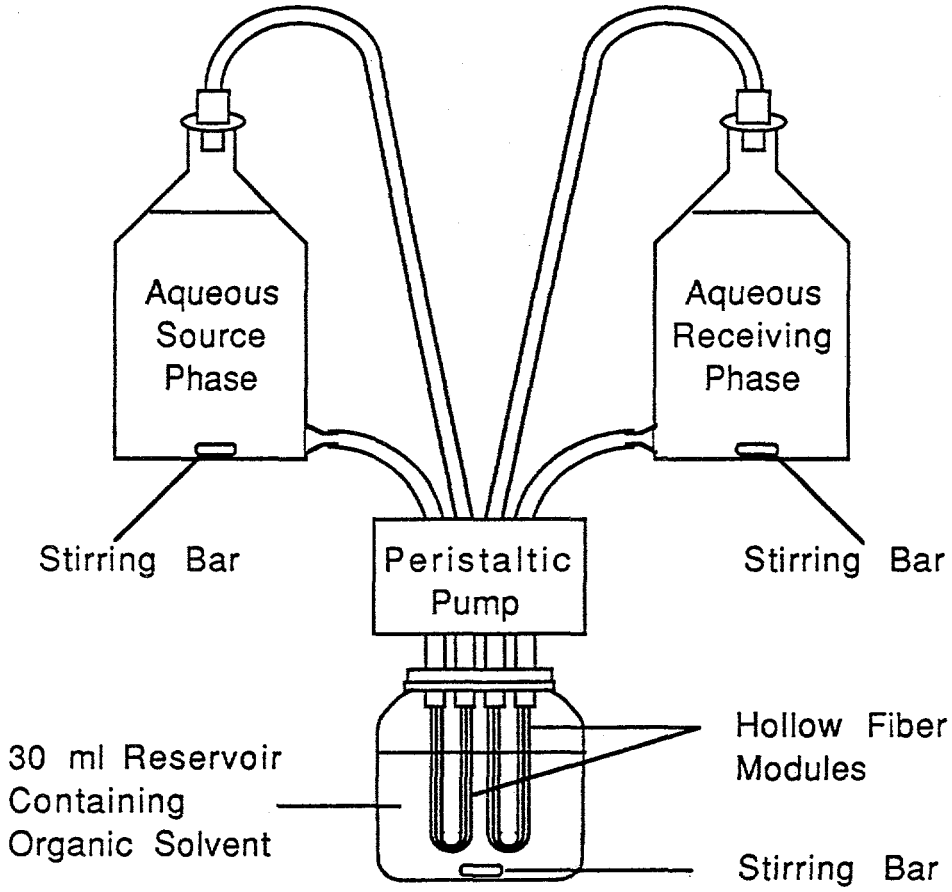


Figure 5. Schematic of Dual Hollow Fiber Membrane System



One class of macrocylic ligands which were tested in the DMHF system were sulfur containing crown thioethers: benzodithia-18-crown-6, benzodithia-15-crown-5, and bis-(1,4-dioxa-7,11-dithiacyclotridecen-9-yl)glutarate. The metal ions studied were Pb^{2+}, Cd^{2+} and Hg^{2+}. Flux values for each metal ion were calculated from the slope of the transport curve, and it was found that the flux for Hg^{2+} was the greatest with each ligand. These results correlated well with the thermodynamic results from calorimetric titration.

Transport of alkali metal cations in the DMHF membrane system using alkoxymethyl-substituted 18-crown-6 and 21-crown-7 ligands was studied. Table 1 shows cation fluxes for all the ligands studied using a neutral source solution containing equal molar concentrations of the alkali metal nitrate salts. In each case, the selectivities determined by titration calorimetry were maintained. Experiments showed that alkoxymethyl-substituted ligands showed greater selectivity than simple alkyl-substituted macrocycles, while maintaining desirable partition characteristics. Other series of ligands studied include a set of three tetrathia macrocycles, as well as a series of lariat ethers. These results are summarized in the representative papers included in Appendix A.

Work is presently being carried out to develop a liquid membrane system which can use temperature as a variable in facilitating the binding and release of cations by macrocylic ligands. Through the use of high temperature flow calorimetry we have seen that log K values decrease as temperature increases. By using heat in the receiving phase of a membrane system, the release of cations is thermodynamically favored.

Solvent Extractions

Back extractions using macrocylic ligands as extractants were performed using several classes of macrocyclic ligands. The stripping phases of the extractions were analyzed by a Perkin Elmer Model Plasma II ICP for the metal ions being studied. From the analysis, extraction equilibrium (K_{ex}) constants were calculated. Table 2 shows representative results of extraction equilibrium constants for the interaction of four alkoxymethyl-substituted ligands with alkali metal cations.

II.E. MOLECULAR MODELING

The computational portion of this project, directed by Prof. Randall B. Shirts, is developing the widely used molecular mechanics (MM) method for design of macrocyclic ligands. We have chosen to first simulate macrocycle binding of alkali metal ions in the gas phase. The gas phase binding must first be understood as a prerequisite to the more difficult condensed phase binding. In addition, gas phase experimental results are now beginning to be available[1,2,3] for comparison purposes. Experimental gas phase 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, has recently joined the BYU Chemistry department and has been a valuable consultant and collaborator.

Table 1. Competitive Transport of Metal Cations Across a 2-Octanone Membrane from a Neutral Source Phase[a]

Carrier Transport	Average Cation Flux and Standard Deviation $(mol \cdot s^{-1} \cdot m^{-2}) \times 10^{-7}$	Total Cation Flux $(mol \cdot s^{-1} \cdot m^{-2}) \times 10^{-7}$	Selectivity Order
HexOMe18C6	$K^+(2.7\pm0.2)$ $Rb^+(0.57\pm0.04)$ $Na^+(0.33\pm0.05)$ $Cs^+(0)$	3.6	$K^+>Rb^+>Na^+>Cs^+$
DecOMe18C6	$K^+(2.2\pm0.2)$ $Rb^+(1.0\pm0.7)$ $Na^+(0.067\pm0.004)$ $Cs^+(0)$	3.3	$K^+>Rb^+>Na^+>Cs^+$
TetradecOMe18C6	$K^+(2.8\pm0.4)$ $Rb^+(0.44\pm0.03)$ $Na^+(0.065\pm0.004)$ $Cs^+(0)$	3.3	$K^+>Rb^+>Na^+>Cs^+$
DecOMe21C7	$Cs^+(1.6\pm0.5)$ $Rb^+(0.96\pm0.04)$ $K^+(0.45\pm0.04)$ $Na^+(0.10\pm0.03)$	3.1	$Cs^+>Rb^+>K^+>Na^+$

[a]Transport in a 0.1 M $NaNO_3$, 0.1 M KNO_3, 0.1 M $RbNO_3$ or 0.1 M $CsNO_3$/1.0 mM ligand in a 2-octanone/H_2O liquid membrane system.

Table 2. Extraction Equilibrium Constants for Interaction of Some Alkoxymethyl-substituted 18-Crown-6 and 21-Crown-7 Ligands with Alkali Metal Cations

Macrocycle	K_{ex}[a]			
	Na^+	K^+	Rb^+	Cs^+
HexOMe18C6	0.09	2.04	0.51	0.10
DecOMe18C6	0.09	2.04	0.52	0.10
TetradecOMe18C6	0.19	2.10	0.53	0.13
DecOMe21C7	0.10	0.04	0.13	1.76

[a]Extraction equilibrium constant, $M^+(aq) + A^-(aq) + L(org) = MLA(org)$

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 next year.

Our computational efforts are of several types. We have used CERIUS, a commercial software package noted for its flexibility in designing and modifying molecular mechanics force fields, as well as GAUSSIAN and SPARTAN *ab initio* quantum chemistry programs running on Silicon Graphics workstations made available for use on this project by the chemistry department. HYPERCHEM and QUANTA/CHARMM are also available to us.

The initial focus of our investigation is 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, Yamabe, *et al.*[4] used the semiempirical CNDO method to predict the structure and electrostatic potential. Results indicated that the specificity of alkali metal ions binding to crown ethers is determined not by the raw binding energy of the ion to the macrocycle, but by differential solvation free energy. That is, a metal ion-macrocycle complex will be stable if it, when solvated, is more stable than the species when separately solvated. For example, Li^+/18-crown-6 complexation is much more exoergic than K^+/18-crown-6 complexation; however, the Li^+ ion has a higher energy of solvation than the K^+ ion. The preference of 18-crown-6 for K^+ over Li^+ in solution comes from a difference of these effects (also taking account of the solvation of the bare ligand and the ligand-metal ion complex).

More recent work has used more sophisticated *ab initio* SCF calculations[8,9] and density functional theory.[10,11] This work has been used to directly investigate relative energies of crown ether conformations and also to fit the parameters which are used in molecular mechanics force fields. Some work has even shown solvation effects.[8] Our own results are in agreement with these investigators in concluding that the electrostatic interactions between oxygen atoms and between oxygen atoms and bound metal ions are the most important contributors to conformational preference and to relative binding.

Many recent examinations of metal ion/18-crown-6 complexes have been performed by molecular mechanics methods.[12,13,14,15,16,17,18] These methods are well developed and very reliable for hydrocarbon systems, but as stated above, the conformational energy of polyethers is controlled by the electrostatic interactions between polar oxygen atoms and other parts of the system. The MM2 force field of Allinger and coworkers[19] uses bond dipoles to represent these interactions. Other force fields like AMBER[20] use partial charges on each atom (or possibly also in lone pairs). In addition to differences in the form of the electrostatic interaction, there is also disagreement about how the intramolecular dielectric constant should be handled[21] and how to determine the partial atomic charges.[22]

One of the major products of the computational part of this project 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, a student participant. 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 in 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 available commercial package, and we are using this program to understand the details of our molecular mechanics calculations. Much of the knowledge we have gained about the conformational behavior of macrocycles has been developed using this program. Sample ANLIZE output was included in last year's progress report.

Several groups are presently involved in developing suitable MM parameter sets appropriate for polyethers.[9,11,23,24,25] This is still an open problem. One approach, that of Hay and coworkers[18] approaches the interaction of a metal ion with a ligand as if it were a covalently bound atom. For example, K^+ is considered to be covalently bound to all six oxygens in 18-crown-6 when complexed. This treatment requires stretching, bending and torsion parameters for those coordinates involving a K^+ ion. This approach may be empirically justified when sufficient data is available; however, it will not give correct dynamical behavior when solution phase simulations are done.

Another approach pursued by several groups is to model the interaction of metal ion and oxygen (or other) atoms as a standard nonbonded interaction, a combination of van der Waals and electrostatic terms. The problem here is the determination of partial atomic charges. Some researchers use the charges calculated from *ab initio* calculations.[11,12,15,25] Yet another variant is to empirically fit the charges to reproduce computed relative energies of several conformations.[9] These methods seem to work reasonably well, except the partial charges must necessarily be held constant as the conformation of the molecule changes. A new method called charge equilibration due to Rappé and Goddard[26] has promise because it is fast. This method uses atomic information about ionization potentials, electron affinites 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 accurate *ab initio* methods. An additional effect, not yet included in most force fields is atomic polarization, but inclusion of polarization into the charge equilibration algorithm is, in principle, well-defined.[15,27]

To illustrate the importance of this effect, 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 Kollman[28] to the relative energies of the same conformations as determined using the DREIDING force field[29] 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. However, 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 conformation to another were

10 to 15%. This effect is seen in the best *ab initio* calculations, though not to the same degree.[8] 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. 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. Calculations demonstrating these conclusions are submitted for publication.[30] This paper represents the major progress for the computational portion of this project. Additional progress consists of refinements to polyether force field parameters, but is not yet completed.

III. COMPLIANCE WITH AGREEMENT REQUIREMENTS

The research effort is proceeding in compliance with the objectives and procedures set forth in the original proposal.

IV. INTERACTION WITH OTHER DOE CONTRACTORS

During the contact period we have exchanged information and insights with several other DOE contractors such as Dr. B. Moyer at Oak Ridge National Laboratory, Prof. R. Bartsch at Texas Tech University, Prof. S. Alexandratos at the University of Tennessee and Dr. P. Horwitz at Argonne National Laboratory.

V. EDUCATIONAL BENEFITS

The concept of applying membrane technology and macrocycles of novel design to making inorganic separations is being developed in this work. The success of the project requires involvement from many disciplines - inorganic chemistry, coordination chemistry, membrane science, organic chemistry, physical chemistry, macrocycle chemistry and chemical engineering. This project has stimulated the intellectual involvement of professors, post-doctoral students, graduate students, and undergraduate students participating in the project from widely separated fields. A sizeable number of individuals have contributed to the research effort, as indicated in Section II.A.

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VII. PUBLICATION AND PRESENTATION OF RESULTS

VII.A. PAPERS PUBLISHED 1992-1994

The following publications reporting results obtained under this contract were published during the last three year funding period. Copies of papers published during the last year, which have not previously been submitted, are submitted for DOE internal use.

1. U. Olsher, K.E. Krakowiak, N.K. Dalley and J.S. Bradshaw, "Syn-Bishydroxymethyl-14-Crown-4: A Possible Preorganized Molecule for Simultaneous Lithium Complexation and Anion Solvation," Tetrahedron, **47**, 2947-2956 (1991).

2. U. Olsher, R.M. Izatt, J.S. Bradshaw and N.K. Dalley, "Coordination Chemistry of Lithium Ion: A Crystal and Molecular Structure Review," Chem. Rev., **91**, 137-164 (1991).

3. J.S. Bradshaw, K.E. Krakowiak, P. Huszthy, and R.M. Izatt, "Proton-Ionizable Crown Compounds. 20. The Synthesis of Polyazatriazolo-, Polyazabistriazolo- and Bispyridino-Crown Ligands Containing Lipophilic Hydrocarbon Substituents," J. Heterocyclic Chem., **28**, 773-775 (1991).

4. G. Wu, W. Jiang, J.D. Lamb, J.S. Bradshaw and R.M. Izatt, "High Specificity Thiacrown Ether Reagents for Silver (I) over Bivalent Mercury and Lead. Thermodynamic and ^{13}C NMR Relaxation Time Studies," J. Am. Chem. Soc., **113**, 6538-6541 (1991).

5. R.M. Izatt, K. Pawlak, J.S. Bradshaw and R.L. Bruening, "Thermodynamic and Kinetic Data for Macrocycle Interactions with Cations and Anions," Chem. Rev., **91**, 1721-2085 (1991).

6. K. E. Krakowiak, J. S. Bradshaw, N. K. Dalley, C.-Y. Zhu, G.-L. Yi, J. C. Curtis, D. Li and R. M. Izatt, "Preparation and Cation Complexing Properties of Some Macropolycyclic Ligands," J. Org. Chem., **57**, 3166-3173 (1992).

7. H.-Y. An, J. S. Bradshaw, and R. M. Izatt, "Macropolycyclic Polyethers (cages) and Related Compounds," Chem. Rev., **92**, 543-572 (1992).

8. G. Wu, R. M. Izatt, M. L. Bruening, W. Jiang, H. Azab, K. E. Krakowiak and J. S. Bradshaw, "NMR and Potentiomeric Investigations of Protonation Sites of Dipyridino-28-Crown-8 and Its Oxa-Anion Binding Properties With Selenate,Sulfate and Nitrate Ions in Aqueous Solution", J. Incl. Phenom., **13**, 121-127 (1992).

9. 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**, 4871-4874 (1992).

10. 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 Novel Butterfly-shaped Macrobicyclic Polyether Ligands," J. Org. Chem., **57**, 4998-5005 (1992).

11. 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**, 6112-6118 (1992).

12. Nazarenko, A.Y.; Izatt, R.M.; Lamb, J.D.; Desper, J.M.; Matysik, B.E.; Gellman, S.H. "Thermodynamics of Copper(II) Complexation by Macrocyclic Tetrathioethers at 25°C in Water-methanol Mixtures and Acetonitrile: Correlations of Complexation Enthalpy and Ligand Conformational Preferences"; Inorg. Chem., **31**, 3990-3993 (1992).

13. 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**, 1429-1432 (1992).

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15. K. E. Krakowiak, P. A. Krakowiak and J. S. Bradshaw, "The Most Convenient Method for the Preparation of Aliphatic Cryptands," Tetrahedron Lett., **34**, 777-778 (1993).

16. 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**, 383-395 (1993).

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19. K. E. Krakowiak, J. S. Bradshaw and R. M. Izatt, "Improved Methods for the Synthesis of Aza-crown Macrocycles and Cryptands," Syn Lett., 611-620 (1993).

20. H.-Y. An, J. S. Bradshaw, K. E. Krakowiak, B. J. Tarbet, N. K. Dalley, X.-L. Kou, C.-Y. Zhu and R. M. Izatt, "Novel Benzene-bridged Macrobi- and Macrotricyclic Polyethers," J. Org. Chem., **58**, 7694-7699 (1993).

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22. N. K. Dalley, K. E. Krakowiak, J. S. Bradshaw, M. M. England, X. Kou, and R. M. Izatt, "Crystal Structure of the Cryptand [3.3.3]-Potassium Iodide Complex: A Large Coordination Number for Potassium Ion," Tetrahedron, **50**, 2721-2728 (1994).

23. R. M. Izatt, X.-X. Zhang, H.-Y. An, C.-Y. Zhu and J. S. Bradshaw, "Thermodynamics of Macrocycle Complexation Chemistry. Interactions of Metal Ions with Double Armed N-Pivot Lariat Ethers in Methanol and Methanol Water Solutions at 25°C," Inorg. Chem., **33**, 1007-1010 (1994).

VII.B. PAPERS IN PRESS OR SUBMITTED

1. C. Wang, P. Huszthy, J. S. Bradshaw, J. D. Lamb, B. Olenyuk, D. Bearss and R. M. Izatt, "Alkoxymethyl-substituted 18-Crown-6 and 21-Crown-7 Ligands: Synthesis, Complexation Properties and Metal Ion Membrane Separations," Sep. Sci. Technol., in press.

2. K. E. Krakowiak, J. S. Bradshaw, C.-Y. Zhu, J. K. Hathaway, N. K. Dalley and R. M. Izatt, "New Cryptaspherands and Their Complexation Properties with the Alkali Metal Ions," J. Org. Chem., in press.

3. J. T. Redd, J. S. Bradshaw, P. Huszthy and R. M. Izatt, "New Pyrimidino-crown Ether Ligands", J. Heterocyclic Chem., in press.

4. R.B. Shirts and L.D. Stolworthy, "Predicting the Conformation of Polyether Macrocycles: Sensitivity to Potential Form and Partial Atomic Charge Determination," to be submitted.

VII.C. PRESENTATION OF RESULTS

1. R. M. Izatt, R. L. Bruening, C. Wang, N. Edge, J. S. Bradshaw and J. D. Lamb, "Cation Separations Using a Proton Ionizable Macrocycle in a Dual Module Hollow Fiber Membrane," Seventh Symposium on Separation Science and Technology for Energy Application," Knoxville, TN, October 20-24, 1991.

2. J. D. Lamb, "Thermodynamics of Cation Complexation by Crown Thiaethers," IUPAC Conference on Chemical Thermodynamics, Snowbird, Utah, August 1992.

3. J. S. Bradshaw, "New Syntheses of the Aza-crown Ethers and Their Use in Removing and Concentrating Metal Ions from Water," Invited Lecture, Ethyl Corporation, Baton Rouge, LA, January 23, 1992. This lecture was also given at LSU and Texas, Austin during this trip.

4. K. E. Krakowiak, J.S. Bradshaw, N. K. Dalley, C.-Y. Zhu, G.-L. Yi, J. C. Curtis, D. Li and R. M. Izatt, "A Most Convenient Method to Synthesize the Cryptands," 203rd National Meeting of the American Chemical Society, San Francisco, CA, April 8, 1992.

5. J. S. Bradshaw, "Important New Methods for the Preparation of Aza-crowns and Cryptands," Seminars given at 1) Institute of Chemistry, Academia Sinica, Beijing, China; 2) Henan Academy of Sciences, Zhengzhou, China; 3) Department of Chemistry, Nanjing University, Nanjing, China; and 4) Shanghai Institute of Organic Chemistry, Shanghai, China, July 1992.

6. K. E. Krakowiak, J. S. Bradshaw, H.-Y. An and R. M. Izatt, "Simple Methods to Prepare the Cryptands," Invited Lecture, XVII International Symposium on Macrocyclic Chemistry, Provo, Utah, August 9-14, 1992.

7. X.-X. Zhang, R. M. Izatt, H.-Y. An, C.-Y. Zhu and J. S. Bradshaw, "The Values of Log K, ΔH, and $T\Delta S$ for Metal Ion Interactions with Double Armed N-Pivot Lariat Ethers in Methanol at 25°," XVII International Symposium on Macrocyclic Chemistry, Provo, Utah, August 9-14, 1992.

8. R.M. Izatt, J.S. Bradshaw, J.L. Oscarson, and C.Y. Zhu, "Thermodynamics of Cation Macrocyclic Interaction," International Symposium Macrocylic Ligands for The Design of New Materials, Guildford, Surrey, U.K., 14-16 September, 1992.

9. R. M. Izatt, C.-Y. Zhu, T.-M. Wang, P. Huszthy and J. S. Bradshaw, "Quantitation of Chiral Host-Guest Interaction," Invited Lecture, 48th Southwest Regional Meeting of the American Chemical Society, Lubbock, Texas, October 21-23, 1992.

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11. N. K. Dalley, U. Olsher, R. M. Izatt, R. M. Bartsch and J. S. Bradshaw, "Dibenzo-14-crown-4 and Other Small Crown Ethers as Possible Preorganized Ligands for Lithium Cations," Invited Lecture, 48th Southwest Regional Meeting of the American Chemical Society, Lubbock, Texas, October 21-23, 1992.

12. R.B. Shirts, "Molecular Mechanics of Macrocyclic Polyether Ligands: To Bond or Not to Bond?" Seminar at Molecular Sciences Research Center, Battelle Pacific Northwest Laboratory, Richland, Washington, 22 November 1993.

13. J. T. Redd, J. S. Bradshaw, P. Huszthy and R. M. Izatt, "New Pyrimidino-crown Ether Ligands," 205th National Meeting of the American Chemical Society, Denver, Colorado, March 28-April 2, 1993.

14. J. S. Bradshaw, K. E. Krakowiak and R. M. Izatt, "New Syntheses of Aza-crown Macrocycles and Cryptands and Their Use in Separating Metal Ions," Invited Lecture at the U.S.-Korean Inorganic Conference sponsored by NSF, Seoul, Korea, April 27-May 1, 1993.

15. K. E. Krakowiak, J. S. Bradshaw, R. M. Izatt and C.-Y. Zhu, "Cryptasperands - New Strong Binding Macrocycles," XVIII International Symposium on Macrocyclic Chemistry, Enschede, The Netherlands, June 27-July 2, 1993.

16. J. S. Bradshaw, K. E. Krakowiak and R. M. Izatt, "New Syntheses of Aza-crowns and Cryptands," Plenary Lecture. Eleventh Symposium on Chemistry of Heterocyclic Compounds, Prague, Czechoslovakia, August 29-September 4, 1993.

17. J. S. Bradshaw, J. D. Lamb, R. M. Izatt, P. Huszthy, C. Wang and B. Olenyuk, "New Lipophilic Crown Ethers and Their Complexation with Metal Ions for Selective Transport Through Liquid Membranes," Eighth Symposium in Separation Science and Technology for Energy Applications, Gatlinburg, Tennessee, October 24-28, 1993.

18. L.D. Stolworthy and R.B. Shirts, "The Importance of Electrostatic Forces in Determining the Conformation of Polyether Macrocycles," Oral presentation at the Spring Research Conference, Brigham Young University, College of Physical and Mathematical Sciences. Provo, Utah, March 26, 1994.

19. J. S. Bradshaw, "Novel Separations of Industrial, Nuclear Waste and Environmental Interest using Solid-supported Superlig Materials," Invited Lecture, Donald J. Cram Symposium, UCLA, March 11-12, 1994.