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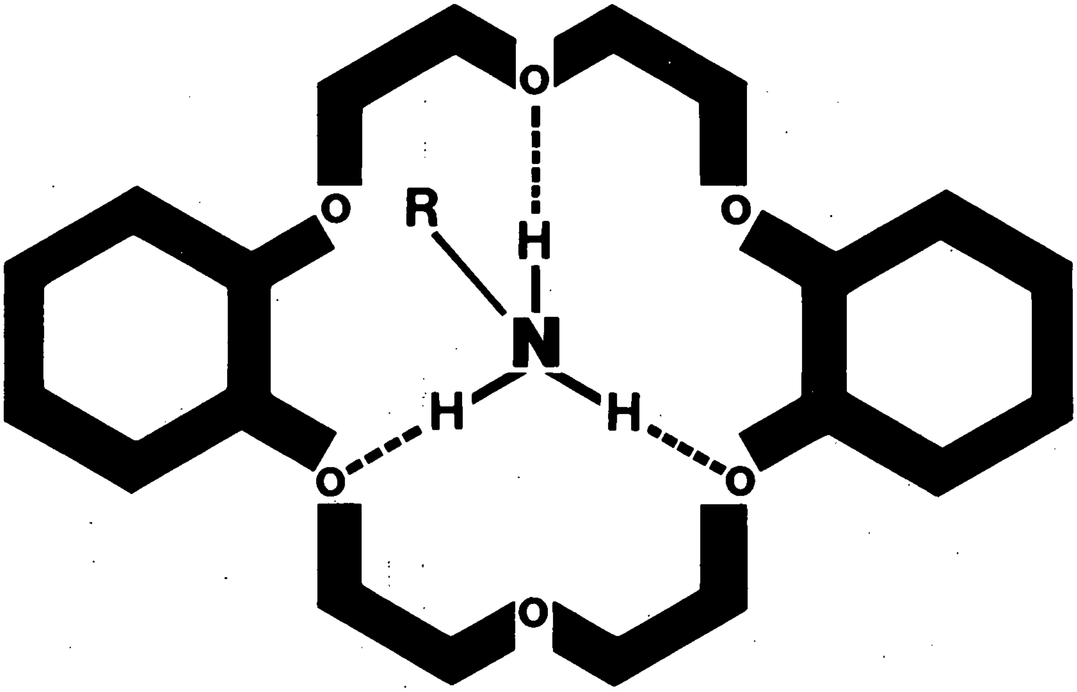
Second
Symposium
on

Macrocyclic Compounds

August 14-16, 1978
Program and Abstracts



Sponsored by the
Thermochemical Institute
in cooperation with the
Department of Special Courses and Conferences
Brigham Young University
Provo, Utah 84602,
U.S.A.

The Second Symposium on Macrocyclic Compounds to be held at Brigham Young University, Provo, Utah, 14-16 August is one of a planned series of annual symposia dealing with various aspects of macrocyclic compounds.

The objective of this symposium is to provide a forum for the presentation and discussion of research activities in the macrocyclic compound field. Both theoretical and experimental aspects of the properties and behavior of synthetic and naturally occurring macrocyclic compounds are to be covered. The symposium will consist of a series of invited lectures as well as the presentation of accepted contributed papers. The papers presented at the symposium will not be published as it is desired to retain an atmosphere of informality in which results of a preliminary nature may be presented.

We acknowledge the financial support of the Research Division, the College of Engineering and Technology, the Chemistry Department, and the Thermochemical Institute all of Brigham Young University, the Parish Chemical Company of Provo, Utah, and the United States Department of Energy, Washington, D.C. Their support has helped greatly to make this conference possible.

We welcome you and hope that your stay will be both pleasant and useful. We encourage you to participate actively in the symposium both in formal and informal discussions as the success of the meeting will in large measure be determined by the involvement of you and the other participants.

Reed M. Izatt
James J. Christensen

LIST OF SPEAKERS

Speaker	Session	Speaker	Session
T. O. Alvik	II.3.	W. J. McDowell	I.4.
K. Andoh	II.1.	A. P. Merz	IV.5.
R. A. Bartsch	II.8.	M. E. Newcomb	IV.7.
A. V. Bogatsky	IV.3.	G. R. Newkome	IV.2.
E. Borowski	IIIC.1.	N. Ōtake	IIIB.2.
H. S. Brown	IV.9.	Yu. A. Ovchinnikov	IIIB.1.
L. R. Caswell	II.5.	B. C. Pressman	IIIA.1.
A. A. Casselman	IIIA.2.	E. Pretsch	I.7.
J. J. Christensen	V.5.	J. K. Rasmussen	II.7.
S. G. Collins	V.3.	M. F. Richardson	IIID.2.
F. L. Cook	II.4.	J. E. Richman	IV.6.
N. K. Dalley	V.4.	B. Sarkar	IIID.1.
M. W. Davis, Jr.	I.3.	A. Shanzer	I.6.
J. L. Dye	I.1.	L. A. Sternson	IIIA.3.
G. Eisenman	IIIC.1.	P. E. Stott	II.6.
G. Folcher	I.5.	A. K. Tashmukhamedova	IIIB.3.
R. M. Izatt	V.1.	F. Vögtle	IV.1.
T. E. Jones	V.2.	D. M. Walba	IV.4.
J. D. Lamb	I.2.	R. F. Ziolo	II.2.
A. J. Mayr	IV.8.		

THE SECOND SYMPOSIUM ON MACROCYCLIC COMPOUNDS
14-16 August 1978
Brigham Young University
Provo, Utah 84602

PROGRAM - 321 Ernest L. Wilkinson Center (ELWC)

Monday, 14 August

7:30 a.m. Registration Finalization, Pick up packets (321 ELWC)

8:00 J. J. Christensen, Welcome and Introduction

8:10 L. P. Vernon, Assistant Academic Vice President-Research

SESSION I: INORGANIC REACTIONS, R. M. Izatt, presiding

Session Lecture:

8:15 I.1. STABILIZATION OF UNUSUAL OXIDATION STATES WITH MACROCYCLIC POLYETHERS. J. L. Dye, Department of Chemistry, Michigan State University, East Lansing, MI 48824.

8:55 I.2. THE EFFECT OF SOLVENT ON BINDING OF METAL CATIONS OF SIMILAR SIZE TO CYCLIC POLYETHERS. J. D. Lamb, R. M. Izatt, and J. J. Christensen, Departments of Chemistry and Chemical Engineering and the Thermochemical Institute, Brigham Young University, Provo, UT 84602.

9:15 I.3. THE USE OF 24-CROWN-8'S IN THE SOLVENT EXTRACTION OF $CsNO_3$ AND $Sr(NO_3)_2$. Irene H. Gerow and Milton W. Davis, Jr., College of Engineering, University of South Carolina, Columbia, SC 29208.

9:35 I.4. SIZE-SPECIFIC SYNERGISTIC EXTRACTION OF METAL IONS BY MIXTURES OF CROWN ETHERS AND ORGANIC-PHASE-SOLUBLE ACIDS. W. J. McDowell and R. R. Shoun, Chemical Technology Division, Oak Ridge National Laboratory, Oak Ridge, TN 37830.

9:55 I.5. STRUCTURAL AND NMR STUDY OF URANIUM MACROCYCLIC COMPOUNDS. G. Folcher, Division de Chimie, Departement de Genie Isotopique, Centre D'Etudes Nucleaires, Saclay, France.

10:15 Break

10:35 I.6. METALLOID DERIVATIVES FOR MACROCYCLES. A. Shanzer, N. Mayer-Shochet, and E. Schwartz, The Weizmann Institute for Science, Rehovot, Israel.

10:55 I.7. CHEMICAL ARCHITECTURE OF IONOPHORES: DESIGN AIDED BY AB INITIO CALCULATIONS. E. Pretsch, W. Simon, G. Corongiu, and E. Clementi, Department of Organic Chemistry, Swiss Federal Institute of Technology, Zurich, Switzerland, and Institute "G. Donegani", Soc. Montedison, Novara, Italy.

SESSION II: INDUSTRIAL APPLICATIONS, W. Wes Parish, presiding

Session Lecture:

11:15 II.1. INDUSTRIAL APPLICATION OF MACROTETROLIDE ANTIBIOTIC. K. Andoh and Y. Nawata, Research Laboratories, Chugai Pharmaceutical Company, Ltd., Toshima, Tokyo 171, Japan.

11:55 II.2. SYNTHESIS AND STRUCTURAL CHARACTERIZATION OF NOVEL MULTIMACROCYCLIC POLYETHER ALKALI METAL PHTHALOCYANINE COMPLEXES. R. F. Ziolo and W. H. H. Günther, Xerox Corporation, Webster Research Center, Webster, NY 14580.

12:15 Lunch, ELWC Dining Mezzanine

2:00 II.3. THE EFFECT OF WATER IN SOME 18-CROWN-6 CATALYSED SOLID-LIQUID PHASE TRANSFER REACTIONS. G. Ulsaker, S. Strandberg, G. Teien, and T. Alvik, Norwegian Institute of Drug Control, Oslo, Norway. Borregaard Industries Ltd., 1700 Sarpsborg, Norway.

2:20 II.4. EFFECT OF CROWN ETHERS IN ANIONIC POLYMERIZATIONS. F. L. Cook and T. N. Montgomery, Jr., Textile Engineering, Georgia Tech, Atlanta, GA 30332.

2:40 II.5 ABSORPTION SPECTRA OF UNSOLVATED ANIONS. Lyman R. Caswell, Karen A. McDowell, Cynthia A. Mahan, and Glenna Lynch, Department of Chemistry, The Texas Woman's University, Denton, TX 76204.

3:00 II.6. THE SYNTHESIS AND PROPERTIES OF ALKANOYL AND α-HYDROXY ALKANYL BENZO CROWNS. P. E. Stott and J. S. Bradshaw, Department of Chemistry, Brigham Young University, Provo, UT 84602 and W. W. Parish and C. W. McCausland, Parish Chemical Company, 812 West Columbia Lane, Provo, UT 84601.

3:20 II.7. KINETICS OF DECOMPOSITION OF AQUEOUS POTASSIUM PERSULFATE IN THE PRESENCE OF 18-CROWN-6. Jerald K. Rasmussen, Steven M. Heilmann, and Paul E. Toren, Central Research Laboratories, 3M Company, 3M Center, St. Paul, MN 55133.

3:40 II.8. COMPLEXATION OF ARYLDIAZONIUM IONS BY MACROCYCLIC COMPOUNDS. R. A. Bartsch and P. N. Juri, Department of Chemistry, Texas Tech University, Lubbock, TX 79409.

4:00 Break

5:30 Tour of Brigham Young University, Provo, and surrounding area, and bus to Sundance in Provo Canyon.

6:45 Dinner at Sundance.

8:30 Outdoor Show at Sundance.

Tuesday, 15 August SESSION III: BIOLOGY AND BIOCHEMISTRY

SESSION IIIA: J. J. Christensen, presiding

Session Lecture:

8:10 a.m. IIIA.1. BIOLOGICAL AND PHARMACOLOGICAL PROPERTIES OF CARBOXYLIC IONOPHORES. Berton C. Pressman, Department of Pharmacology, School of Medicine, P.O. Box 520875, Biscayne Annex, University of Miami, Miami, FL 33152.

8:50 IIIA.2. AN EXAMINATION OF MACROCYCLIC ETHER-ALKALI METAL SALT COMPLEXES AS REAGENTS FOR THE DESTRUCTION OF TOXIC ORGANIC COMPOUNDS. A. A. Casselman, H. Gail Thompson, and R. A. B. Bannard, Department of National Defence, Defence Research Establishment, Ottawa, Canada K1A 0Z4.

9:10 IIIA.3. INTERACTION OF BIOGENIC AMINES WITH IONOPHORE X-537A Larry A. Sternson, Siegfried Lindenbaum, and Jane Kinsel, Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, KS 66045.

SESSION IIIB: N. K. Dalley, presiding

Session Lecture:

9:30 IIIB.1. SELECTIVE BINDING AND TRANSMEMBRANE ION TRANSPORT IN BIOLOGICAL SYSTEMS: CARRIERS AND CHANNELS. Professor Yu. A. Ovchinnikov, Shemyakin Institute of Bio-Organic Chemistry, U.S.S.R. Academy of Sciences, Moscow, U.S.S.R.

10:10 Break

10:30 IIIB.2. THE STRUCTURES OF SEVERAL NATURALLY OCCURRING POLYETHERS AND THEIR CATION SELECTIVITY PATTERNS. N. Ōtake, Institute of Applied Microbiology, University of Tokyo, Bunkyo-ku, Tokyo 113, Japan.

10:50 IIIB.3. SOME NEW DERIVATIVES OF 2,3,11,12-DIBENZO-18-CROWN-6. WAYS OF PREPARATION AND BIOLOGICAL EFFECT. A. K. Tashmukhamedova, Institute of Bioorganic Chemistry, Academy of Sciences of Uzbekistan, Tashkent, U.S.S.R.

SESSION IIIC: N. Ōtake, presiding

Session Lecture:

11:10 IIIC.1. AMPHOTERIC COMPLEXES OF NEUTRAL IONOPHORES HAVING TERTIARY AMIDE LIGANDS -- IMPLICATIONS FOR ANION BINDING TO THE POLYPEPTIDE BACKBONE. G. Eisenman, R. Margalit, and K. -H. Kuo, Department of Physiology, UCLA Medical School, Los Angeles, CA 90024.

11:50 IIIC.2. POLYENE MACROLIDE ANTIBIOTICS AND SPECIFIC MEMBRANE PERMEABILITY CHANGES: STRUCTURE-BIOLOGICAL EFFECTS RELATIONSHIPS. E. Borowski, B. Cybulska, B. Malewicz, and T. Zieniawa, Department of Pharmaceutical Technology and Biochemistry, Technical University, 80-952, Gdansk, Poland.

12:10 Lunch, ELWC Dining Mezzanine

SESSION IIID: L. D. Hansen, presiding

Session Lecture:

2:00 IIID.1. DESIGN AND SYNTHESIS OF CYCLIC PEPTIDES TO MIMIC THE METAL BINDING SEGMENT OF THE ACTIVE SITES OF METALLOENZYMES. B. Sarkar, The Research Institute of The Hospital for Sick Children, Toronto, Ontario and The Department of Biochemistry, University of Toronto, Toronto, Ontario, Canada M5G 1X8.

2:40 IIID.2. SYNTHESIS OF LIGANDS FOR BINDING METHYLMERCURY CATIONS. Mary Frances Richardson and Bibudhendra Sarkar, The Research Institute of The Hospital for Sick Children, Toronto, Ontario, Canada M5G 1X8.

SESSION IV: ORGANIC SYNTHESIS AND REACTIONS, Richard Bartsch, presiding

Session Lecture:

3:00	IV.1.	NEW POLAROPHILIC AND LIPOPHILIC MOLECULAR CAVITIES. F. Vögtle, L. Rossa, W. Wehner, E. Buhleier, P. Dix, N. Wester, H. Sieger, E. Hammerschmidt, J. Winkel, St. Karbach, W. Bieber, and R. Wingen, Institut für Organische Chemie und Biochemie der Universität, Gerhard-Domagk-Str. 1, D-5300 Bonn, Bundesrepublik Deutschland.
3:40		Break
4:00	IV.2.	SYNTHESIS, TEMPERATURE DEPENDENT CONFORMATIONAL PREFERENCES, AND COMPLEXATION OF POLYETHERAL MACROCYCLES CONTAINING THE NEUTRAL BIPYRIDYL SUBUNIT. George R. Newkome, Ashutosh Nayak, Toshio Kawato, and Frank Fronczek, Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803.
4:20	IV.3.	THE SYNTHESIS AND COMPLEXING PROPERTIES OF NOVEL MACROHETEROCYCLES CONTAINING ESTER AND AMIDE MOIETIES. A. V. Bogatsky and N. G. Lukyanenko, Ukranian Academy of Sciences, Physico-Chemical Institute, Odessa, U.S.S.R. 270080.
4:40	IV.4.	METHODS DIRECTED TOWARDS THE SYNTHESIS OF LARGE CAGE MOLECULES CONTAINING MACROCYCLIC POLYETHER SUBUNITS. D. M. Walba, S. Sherwood, P. M. Macintosh, Department of Chemistry, University of Colorado, Boulder, CO 80309.
5:00	IV.5.	2,3,11,12-TETRAPHENYL-1,4,7,10,13,16-HEXAOXA-2,11-CYCLOOCTADECADIENE. A NEW UNSATURATED CROWN ETHER FROM BENZOIN. Andreas P. Merz, Institut für Chemie der Universität, D-8400 Regensburg, West Germany.
5:20	IV.6.	AROMATIC DERIVATIVES OF HEXACYCLEN. J. E. Richman and M. R. Asirvatham, Department of Chemistry, University of Idaho, Moscow, ID 83843.
5:40		Break
6:15		Dinner, ELWC Dining Mezzanine
7:30-10:00		Informal Discussion or tour Temple Square, Salt Lake City

Wednesday, 16 August

7:30 a.m.	Breakfast, ELWC Dining Mezzanine

8:30 IV.7. MACROCYCLIC POLYSTANNANES. M. Newcomb, Department of Chemistry, Texas A & M University, College Station, TX 77843.

8:50 IV.8. MACROCYCLIC POLYETHER-BROMINE COMPLEXES AS STEREOSELECTIVE BROMINATING AGENTS. Keith Pannell and Armin Mayr, Department of Chemistry, University of Texas at El Paso El Paso, TX 79968.

9:10 IV.9. FIELD INDUCED PI POLARIZATION OF NAPHTHALENE CROWN ETHERS AND CROWN ETHER CONFORMATIONAL CHANGES STUDIED BY ^{13}C NMR. Lynn R. Sousa, Mark R. Johnson, and Houston S. Brown, Department of Chemistry, Michigan State University, East Lansing, MI 48824.

SESSION V: THERMODYNAMICS AND KINETICS, D. J. Eatough, presiding

Session Lecture:

9:30 V.1. ALKALI AND ALKALINE EARTH CATION SELECTIVITY BY CYCLIC POLYETHER TYPE LIGANDS. R. M. Izatt, J. D. Lamb, and J. J. Christensen, Departments of Chemistry and Chemical Engineering and the Thermochemical Institute, Brigham Young University, Provo, UT 84602.

10:10 Break

10:30 V.2. KINETICS AND THERMODYNAMICS OF MACROCYCLIC TETRATHIAETHER COMPLEXES. Thomas E. Jones, Jeff Dill, and Wang Yu, Department of Chemistry, The University of New Mexico, Albuquerque, NM 87131.

10:50 V.3. REACTIONS OF PRIMARY, SECONDARY, AND TERTIARY AMMONIUM IONS WITH 12-CROWN-4, 15-CROWN-5, 18-CROWN-6, AND 21-CROWN-7. S. Collins, R. M. Izatt, and J. J. Christensen, Department of Chemistry, Brigham Young University, Provo, UT 84602.

11:10 V.4. CORRELATION OF STRUCTURAL AND THERMODYNAMIC DATA FOR SOME CATION-CYCLIC POLYETHER COMPLEXES. N. K. Dalley and S. B. Larson, Department of Chemistry, Brigham Young University, Provo, UT 84602.

11:25 V.5. CARRIER FACILITATED TRANSPORT OF CATIONS AND ANIONS THROUGH THICK AND THIN MEMBRANES. J. J. Christensen, S. R. Izatt, M. Astin, K. Bedke, J. D. Lamb, K. Stimpson, and R. M. Izatt, Departments of Chemical Engineering and Chemistry and the Thermochemical Institute, Brigham Young University, Provo, UT 84602.

11:40 Lunch

ABSTRACTS

STABILIZATION OF UNUSUAL OXIDATION STATES WITH MACROCYCLIC POLYETHERS,

J. L. Dye, Department of Chemistry, Michigan State University,
East Lansing, MI 48824

Macrocyclic polyethers of the crown and cryptand classes are very resistant to reduction. Because of this, they can be used in the presence of strong reducing agents such as solvated electrons and alkali metal atoms. By enhancing the stability of the included cation, concentrated solutions of alkali metals in amines and ethers can be prepared. By appropriate choice of the complexing agent, solvent, and metal, either solvated electrons or alkali metal anions are produced as the counter-ions. By either rapid evaporation of the solvent, or, in favorable cases, simply permitting crystals to grow, one can prepare solvent-free salts which contain metal anions and complexed alkali metal cations. The metal anions may be one of the alkali metal anions Na^-, K^-, Rb^- or Cs^-, or poly-anions of such amphoteric elements as Pb, Sb, Te and Sn. In all of these salts the complexing agent serves to stabilize the included alkali metal cation and thus to prevent its reduction to the metal. It may even be possible to prepare stoichiometric compounds in which the anion is the trapped electron.

A promising application of macrocyclic polyethers is stabilization of particular oxidation states of cations trapped within the cavity and protection of these cations from solvolysis reactions. For example the lanthanides form stable complexes with cryptand (221) which do not precipitate even in basic solutions and the potential of the Eu^{3+}/Eu^{2+} couple shifts in favor of Eu^{2+} compared with aqueous solutions.

THE EFFECT OF SOLVENT ON BINDING OF METAL CATIONS OF SIMILAR SIZE TO CYCLIC POLYETHERS. Reed M. Izatt, John D. Lamb, C. Samuel Swain, James J. Christensen, Departments of Chemistry and Chemical Engineering and the Thermochemical Institute, Brigham Young University, Provo, UT 84602.

The thermodynamic parameters log K, ΔH, and TΔS for the interaction of cyclic polyethers with metal cations in water, methanol, and water-methanol mixtures of varying proportion at 25°C have been determined by titration calorimetry. Comparison of results for cations of similar size but differing charge, namely Na^+, Ca^{2+}, and Ce^{3+}; and K^+ and Ba^{2+}, reveal that solvation terms are primarily responsible for cation selectivity sequences in these two groups. The selectivity of a single ligand for these cations can be altered and even reversed by a change in solvent, ΔH being primarily responsible for this effect.

THE USE OF 24-CROWN-8'S IN THE SOLVENT EXTRACTION OF $CsNO_3$ AND $Sr(NO_3)_2$,

Irene H. Gerow and Milton W. Davis, Jr., College of Engineering, University of South Carolina, Columbia, South Carolina 29208.

The objective of this work is to develop a solvent extraction system for treating acidic high activity nuclear wastes in order to remove 99.9% of the cesium and strontium. A corollary objective is to develop a process compatible with the Purex process currently being used at the Savannah River Plant. The removal of 99.9% of the cesium and strontium would lower the relative toxicity of nuclear waste which has aged for ten years by a factor of 10^3. This objective is being pursued by measuring the distribution coefficients of both Cs^{+1} and Sr^{+2} between two phases, one phase being principally dilute aqueous HNO_3 and the other being an organic phase consisting of a CCl_4 or kerosene diluent containing tributyl phosphate and the 24-crown-8 complexing agent. Both aqueous and organic soluble materials capable of contributing anions have also been tested in order to increase the distribution coefficient in favor of the organic phase.

In several of the systems tested the Cs^{+1} distribution coefficient D (o/a) has exceeded unity while the Sr^{+2} distribution coefficient D (o/a) has been as high as 200. The extractions were found to be reversible and the development of a suitable solvent extraction system is therefore possible pending results of selectivity tests from mixed fission products and radiation stability tests of the complexing agents.

SIZE-SPECIFIC SYNERGISTIC EXTRACTION OF METAL IONS BY MIXTURES OF CROWN ETHERS AND ORGANIC-PHASE-SOLUBLE ACIDS,

W. J. McDowell and R. R. Shoun, Chemical Technology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee 37830

Although crown ethers are often spoken of as "phase transfer agents" for metal ions, they have not shown much usefulness as solvent extraction reagents in hydrometallurgical processes because the common mineral acid anions (Cl^-, NO_3^-, SO_4^{2-}) that must be used in these processes are difficult to solubilize in the organic phase. The inclusion of alcohols or phenols with the crown ether in the organic diluent ameliorates this situation somewhat; however, the most promising arrangement tried so far is the addition of a long-chain, organic-phase-soluble acid to the crown ether solution. An organic phase salt of the aqueous phase metal can then be formed by cation exchange across the aqueous-organic interface, and the crown ether can provide part or all of the coordination for the metal ion. Carboxylic, phosphoric, and sulfonic acids have been tried, and in all cases a synergistic extraction of potassium nitrate was observed when dicyclohexyl 18-crown-6 was the crown ether. The largest effect was observed with a crown ether--sulfonic acid mixture. Here a solution 0.10 M in sulfonic acid and 0.20 M in crown ether extracted potassium nitrate with a coefficient of 20.3. This amounts to a synergistic factor of 50.

Research sponsored by the Division of Chemical Sciences, U.S. Department of Energy under contract W-7405-eng-26 with the Union Carbide Corporation.

STRUCTURAL AND NMR STUDY OF URANIUM MACROCYCLIC COMPOUNDS. G. Folcher,
Division de Chimie, Department de Genie Isotopique, Centre D'Etudes
Nucleaires, Saclay, France.

We wish to present the structure of this first complex in which an actinide ion is inserted in a macrocyclic polyether namely: dicylohexyl 18-crown-6 (dcc). An x-ray crystallographic study shows that the asymetric unit is composed of $UCl_6[UCl_3dcc]_2$ units. Two uranium atoms are bonded to the oxygen atoms with three Cl atoms as neighbors and one uranium atom is surrounded by six Cl atoms.

NMR studies have been performed on several analogous complexes. Large induced shifts provide structural information on the conformation of uranium IV crown ether and cryptate complexes in solution. The analysis of these spectra show that the complexation ability of the various macrocyclic ligands is slightly size dependent: <222> and <221> crypts for instance form insertion complexes but in the <211> cryptate the cation is located outside of the macrocyclic cavity.

Evidence for intramolecular rearrangements of the $[UCl_3\ 18\text{-crown-}6]^+$ unit is provided by dynamic NMR. The rate of these movements appears to depend on the coordinance saturation of the U^{4+} cation. On the other hand, a conformational exchange between the pseudo axial and pseudo equatorial protons of the crown can be observed in some complexes. Activation parameters were measured in two cases.

Intermolecular exchange in these macrocyclic complexes is always slow on an NMR time scale.

$UO_2(ClO_4)_2$ 18-crown-6 (or dcc) complexes have been prepared and isolated. Structural determination on a single crystal is in progress.

The 250MHz spectrum of $[UO_2dcc]^{2+}$ can be assigned using the McConnell Robertson formula and the calculated susceptibility anisotropy of uranyl ion. This assignment is in a good agreement with the hypothesis of a time averaged plane ligand perpendicular to the UO_2^{2+} ion.

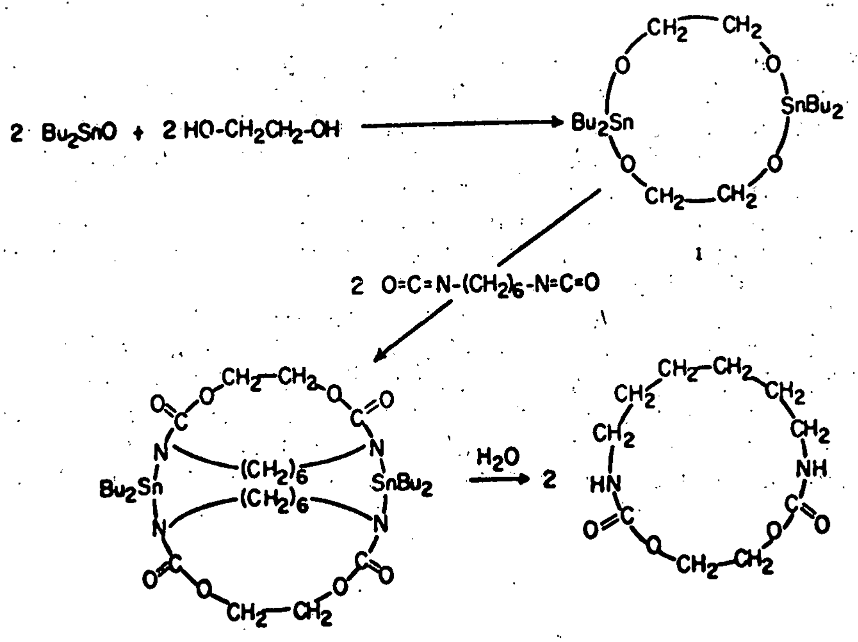
I.6.

METALLOID DERIVATIVES FOR MACROCYCLES. A. Shanzer, N. Mayer-Shochet and E. Schwartz, Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel

A novel method for the efficient synthesis of macrocyclic compounds is introduced. The method is based on the use of metalloid derivatives (stannum or silicon derivatives) as covalent templates, around which the desired ring compounds are being constructed from acyclic precursors. Once the construction of the organic shell has been completed, the metalloid template is removed by mild hydrolytic cleavage of the weak metalloid-heteroatom bonds.

Following this approach, macrocyclic polycarbamates have been prepared from common starting materials in a smooth and simple three step procedure.

The basic reaction scheme is exemplified below for the preparation of the 14-membered dicarbamate III from ethylene glycol and diisocyanato hexane.



I

II

III

The glycol is first reacted with dibutyl stannum oxide to afford the stannum heterocycle I. Subsequent treatment with the diisocyanate induces transannular ring closure to give the polycyclic intermediate II. The latter is then freed from its metalloid template by addition of a few drops of water to provide the macrocyclic dicarbamate III in good yield and purity.

While the use of such difunctional stannum derivatives furnished non-symmetric macrocyclic compounds, application of tetrafunctional silicon derivatives as templates provided entrance into symmetric macrocyclic polycarbamates.

The scope and limitation of these and related transformations will be illustrated and the advantages of this method over conventional ones discussed.

CHEMICAL ARCHITECTURE OF IONOPHORES: DESIGN AIDED BY AB INITIO CALCULATIONS.

E. Pretsch, W. Simon, G. Corongiu and E. Clementi, Department of Organic Chemistry, Swiss Federal Institute of Technology, Zurich, Switzerland, and Institute "G. Donegani", Soc. Montedison, Novara, Italy

Although the description with simple electrostatic models of the interaction of hard cations, such as IA and IIA ions, and small monodentate ligands leads to relevant interaction energies and coordination numbers, this model can give at best semiquantitative results where the interaction with larger multidentate ligands is concerned. Ab initio calculations were shown to give a correct description of the complexation of such cations; for practically important ionophor: cation complexes with relative molar masses of up to 1500 and higher, however, ab initio calculations are still utopic.

In the present context ab initio calculations for a large number of Li^+- and Na^+-complexes of some selected ligands were carried out. The interaction energies E_{int} are given by

$$E_{int} = E_{complex} - E_{ion} - E_{ligand}$$

and were fitted by the following expression:

$$E_{int} = \sum_i (-A_{iM}/r_{iM}^{6} + B_{iM}/r_{iM}^{12} + C_{iM}q_i q_M/r_{iM})$$

where A_{iM}, B_{iM} and C_{iM} are adjustable constants, r_{iM} is the distance between an atom i on the ligand and M, q_M and q_i are the net charges of M and the atom i calculated for the isolated species. In this way pair potentials A_i, B_i and C_i for the interaction of Li^+ and Na^+ with 27 classes of atoms of the ligand molecules investigated were obtained. The entire potential surface of an ion in the field of these model ligands may be easily described with these potential functions. Furthermore, the pair potentials are shown to be transferable, so that they may be applied for the corresponding atoms in a similar chemical environment in other molecules. In this way the potential surface of an ion around large ionophor molecules may be calculated if the pair potentials of all the atoms involved are known. Results obtained on actual ionophores are in very good agreement with X-ray data.

INDUSTRIAL APPLICATION OF MACROTETROLIDE ANTIBIOTIC. K. Andoh and Y. Nawata, Research Laboratories, Chugai Pharmaceutical Co. LTD., Toshima, Tokyo 171, Japan.

Environmental pollution of pesticides is a serious problem all over the world, especially in Japan where amount of pesticides used per unit area is the most abundant. On the other hand, pesticides are essential for harvesting enough crops in modern agriculture.

There are a number of desirable properties for future pesticides; we consider the following two are very important among them; one is specificity in activity and the other readily decomposable property in nature. Antibiotics possess such ideal properties, since they are produced by microorganisms.

A decade ago, we undertook research and development project of pesticidal antibiotics. During the course of our screening program, a new macrotetrolide antibiotic, tetranactin, was selected due to its specific pesticidal activity against mites and safety towards warm-blooded animals.

Since then, much effort had been focussed on the R & D of tetranactin. In this report, we will summarize the progress of the R & D, including (1) the miticidal property and possible mode of action, (2) structure elucidation, (3) the method for the quantitative determination, (4) toxicological properties and (5) absorption, distribution, metabolism and excretion in rodents. We will also refer to the complex-forming property and its potential industrial application.

SYNTHESIS AND STRUCTURAL CHARACTERIZATION OF NOVEL MULTIMACROCYCLIC POLYETHER ALKALI METAL PHTHALOCYANINE COMPLEXES.

R.F. Ziolo, and W.H.H. Günther, Xerox Corporation, Webster Research Center, Webster, New York 14580.

The highly colored macrocycle phthalocyanine (Pc) and its numerous metal complexes are generally quite insoluble in common solvents. These properties, together with a high degree of environmental stability, have led to the extensive use of these compounds in the pigment industry. Relative to the transition metal phthalocyanines, little characterization of the alkali metal phthalocyanines has been reported. We have observed that ready solubility in organic solvents is imparted to disodium and dipotassium phthalocyanines by complexation with macrocyclic polyethers. Treatment of M_2Pc (M = Na, K) suspensions in benzene with various crown ethers yielded transparent, green solutions. From these we have isolated green crystalline complexes of K_2Pc with 18-crown-6 and 15-crown-5. The K_2Pc 18-crown-6 complex has been identified as $K_2Pc(18\text{-crown-}6)_2 \cdot 1.5C_6H_6$, and has been characterized by single-crystal X-ray diffraction techniques. The compound consists of two independent trimacrocyclic sandwich-type units. Two potassium ions separate the three plane-parallel macrocyclic rings and flank the central phthalocyanine dianion normal to the plane of the ring. This compound represents one in a series of macrocyclic and small-molecule oxygen-donor K_2Pc complexes that we have isolated and found to contain free-core dianionic phthalocyanine, $C_{32}H_{16}N_8^{2-}$. The synthesis, properties and structural characteristics of these novel multimacrocyclic complexes will be reported.

THE EFFECT OF WATER IN SOME 18-CROWN-6 CATALYSED SOLID-LIQUID PHASE TRANSFER REACTIONS.

G. Ulsaker, S. Strand-Berg, G. Teien and T. Alvik, Norwegian Institute of Drug Control, Oslo, Norway. Borregaard Industries Ltd., 1700 Sarpsborg.

Macrocyclic polyethers have shown excellent catalytic properties in solid-liquid phase transfer reactions.

However in practical synthetic applications low reaction speeds often tend to be a limiting factor.

This is due to the fact that the rate determining step in such reactions seems to be the dissolution of the solid salt by the crown ether.

We will present some data showing that addition of small controlled amounts of water to solid-liquid phase transfer systems helps to overcome the lattice forces in the crystals and thus speed up the reactions. This can in some cases be done without significant deactivation of the anions in the salts.

We also will present some results which shows how the addition of water affects the product distribution in a nucleophilic substitution reaction with F^-.

Interesting effects from anion activation by sandwich complexes will be discussed.

EFFECT OF CROWN ETHERS IN ANIONIC POLYMERIZATIONS.

F.L. Cook and T.N. Montgomery, Jr., Textile Engineering, Georgia Tech, Atlanta, GA 30332.

The effects of catalytic quantities of unsubstituted crown ethers on anionic-initiated polymerization systems were investigated. Dramatic modifications in the polymerization characteristics of the *n*-BuLi-styrene-benzene and *n*-BuLi-isoprene-heptane polymerization systems occurred upon addition of either 15-crown-5 or 12-crown-4. Both rates of polymerization increased dramatically on crown addition, approaching instantaneous conversion for polystyrene. The molecular weight of polystyrene increased to an optimum value as the molar ratio of crown ether to *n*-BuLi approached 0.5:1, after which further crown additions resulted in proportionately-decreasing molecular weights. A theory based on monomer depletion resulting from the increased polymerization rate was developed to explain the molecular weight dependence on the crown: *n*-BuLi ratio. Increases in the molecular weight of polyisoprene were more moderate. In all cases, 15-crown-5 gave more substantial rate and molecular weight increases than did 12-crown-4 under the same polymerization conditions.

II.5.

ABSTRACT SPECTRA

ABSORPTION SPECTRA OF UNSOLVATED ANIONS. Lyman R. Caswell, Karen A. McDowell, Cynthia A. Mahan and Glenna Lynch. Department of Chemistry, The Texas Woman's University, Denton, Texas 76204.

The anions are believed to be unsolvated in solutions of salts solubilized in nonpolar solvents by crown ether-complexation of the cations. The absorption spectra of anions in such solutions will therefore not be influenced by ion-dipole effects. If such a spectrum can be obtained under conditions in which ion-pairing is also minimized, then the spectrum will measure the excitation energy of the anion, free from external influences other than the comparatively small dispersion effect of the solvent. In a pilot study of these possibilities, the visible absorption spectra of the permanganate, 2-nitrophenoxide and 4-nitrophenoxide anions have been examined, using the potassium or thallium(I) salts, in water, in acetonitrile, and solubilized in benzene with 18-crown-6 or dicyclohexano-18-crown-6 complexation of the cation. The initial findings suggest that the desired measurement of the unsolvated anion spectrum may be best approximated with the potassium salt solubilized in benzene in the presence of an excess of crown ether, rather than with a solution of the pure 1:1 crown-salt complex.

THE SYNTHESIS AND PROPERTIES OF ALKANOYL AND α-HYDROXY ALKANYL BENZO CROWNS.

P. E. Stott and J. S. Bradshaw, Department of Chemistry, Brigham Young University, Provo, UT 84602; and W. W. Parish and C. W. McCausland, Parish Chemical Company, 812 West Columbia Lane, Provo, UT 84601.

The ability of crown ethers to catalyze reactions between organic substrates and alkali metal salts is dependent on the formation of a complex between the metal salt and the crown ether. The complex is brought into the organic solvent where it is able to react with the organic substrate. The rate at which this process proceeds is dependent on both the ability of the crown ether to form a complex with the metal salt, and on the solubility of the complex in the organic solvent.

In an effort to produce more efficient catalysts a program was undertaken to increase the lipophilicity of the crown for the purpose of making the crown ether - metal salt complex more soluble in the organic solvent. The acylation of readily available benzocrown ethers with fatty acids and their derivatives was extensively explored. With most systems difficulties with opening of the macrocyclic ring and/or extensive polymerization of the products was encountered. Systems based on phosphorous pentaoxide as condensing agent, however, were found to be generally useful for the synthesis of a broad range of acylated benzocrown ethers. The carbonyl moiety of the resulting acylated compounds was further modified.

The new compounds are being investigated with regard to their ability to solubilize inorganic salts in organic solvents, transact salts across a lipid like membrane, and catalyze nucleophilic displacement reactions in non-polar solvents.

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KINETICS OF DECOMPOSITION OF AQUEOUS POTASSIUM PERSULFATE IN THE PRESENCE OF 18-CROWN-6

Jerald K. Rasmussen, Steven M. Heilmann and Paul
E. Toren, Central Research Laboratories, 3M Company,
3M Center, St. Paul, Minn. 55133.

The influence of 18-crown-6 on the thermal decomposition of potassium persulfate in aqueous solution has been investigated. Kinetic studies have shown the decomposition to be second order in basic media, but zero order in acidic media. In basic media (0.1N KOH), the rate of decomposition is dependent upon crown ether concentration up to a certain point, after which there is no further accelerating effect. Activation parameters have been measured. The results are interpreted in terms of a modified mechanism for persulfate decomposition, and of anion and ion-association effects on complexation. Implications of the results in other areas of chemistry will be considered.

COMPLEXATION OF ARYLDIAZONIUM IONS BY MACROCYCLIC COMPOUNDS.

R. A. Bartsch and P. N. Juri, Department of Chemistry, Texas Tech University, Lubbock, Texas 79409

In our continuing efforts to probe the parameters of macrocyclic compounds which provide the strongest complexation (and best thermal and photochemical stabilization) of aryldiazonium ions, the effects of approximately fifty macrocyclic compounds upon the rate of thermal decomposition of p-tert-butylbenzenediazonium fluoroborate in 1,2-dichloroethane have been measured. Effects of ring size, nature of the heteroatoms, and other factors have been assessed. Complexation (and stabilization) of aryldiazonium salts by open-chain polyethers have also been examined.

Preliminary results concerning the isolation and properties of protonated complexes of aryldiazonium salts and crown ethers will also be presented.

IIIA.1.

BIOLOGICAL AND PHARMACOLOGICAL PROPERTIES OF CARBOXYLIC IONOPHORES,

B.C. Pressman, Dept. of Pharmacology, Univ. of Miami

Although ionophores in general are capable of major perturbations of transmembrane gradients *in vivo*, the carboxylic ionophores as a class are remarkably well tolerated. This permits them to evoke rather specific responses of considerable potential interest for therapeutic applications. We have become particularly interested in their cardiovascular effects which appear to consist of: (1) an increase in cardiac contractility mediated through the release of adrenal catecholamines; (2) a direct increase in cardiac contractility mediated through an alteration of the role of calcium in triggering the contractile process; (3) a strong and persistent dilation of the coronary arteries mediated by the release of adenosine from the heart. In general, many of the biological effects of carboxylic ionophores are mediated via calcium, however this cation can be indirectly modulated by ionophore-induced increases in sodium permeability. Thus monensin which has a high affinity for sodium and an extremely low affinity for calcium can stimulate a variety of calcium-dependent cellular secretion processes. The biological effects of ionophores are becoming of ever-increasing significance to man as they currently enter his food supply via livestock feed supplements for poultry and cattle.

AN EXAMINATION OF MACROCYCLIC ETHER-ALKALI METAL SALT COMPLEXES AS REAGENTS FOR THE DESTRUCTION OF TOXIC ORGANIC COMPOUNDS.

A. A. Casselman, H. Gail Thompson, and R. A. B. Bannard, Department of National Defence, Defence Research Establishment, Ottawa, Canada, K1A 0Z4.

The ease of conducting nucleophilic substitution and oxidative reactions with organic substrates at or near room temperature with solutions of "naked" anions generated by the complexation of alkali metal salts with macrocyclic ethers in non-aqueous solvents appeared to be of considerable interest in the context of a novel approach to effect the destruction of toxic organic compounds. The feasibility of this approach has been briefly examined using 18-crown-6, 15-crown-5, and cryptand 2,2,2 in conjunction with alkali metal salts such as sodium and potassium hydroxide, potassium superoxide and potassium acetate in a wide variety of solvent systems. The effect of macrocyclic ether type, reaction media and nucleophiles on the destruction of toxic organic substrates will be illustrated and discussed.

INTERACTION OF BIOGENIC AMINES WITH IONOPHORE X-537A. Larry A. Sternson, Siegfried Lindenbaum, and Jane Kinsel, Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, KS 66045.

Previous work in this laboratory has shown that the ionophore antibiotic X-537A binds strongly with biogenic amines in hydrocarbon solvents. Complexation constants were evaluated from measurements of the quenching of the native fluorescence of the sodium salt of X-537A upon the addition of amine hydrochloride. For epinephrine and norepinephrine binding was found to be a function of solvent polarity, with the complexation constant decreasing by almost two orders of magnitude in going from isooctane to 2-octanol.

Complexation constants based on the partition of catecholamine between an aqueous buffer solution and an organic phase containing X-537A will be presented. In this case norepinephrine is found to complex more strongly than epinephrine. But in both cases complexation is much weaker than that previously determined in anhydrous nonaqueous environment. Presumably this difference arises from solvation of the ionophore, amine and the resulting complex by water.

SELECTIVE BINDING AND TRANSMEMBRANE ION TRANSPORT IN BIOLOGICAL SYSTEMS: CARRIERS AND CHANNELS. Yu. A. Ovchinnikov, Shemyakin Institute of Bioorganic Chemistry, Academy of Sciences, 117312 Moscow, U.S.S.R.

The present state of the chemistry of naturally occurring transmembrane metal ion carriers is reviewed. New developments in the depsipeptide ionophores are discussed particularly with the following valinomycin analogs:

$$\text{cyclo}[-(\text{D-Ile-Hyi-Ile-Hyi})_n-]$$

$$\text{cyclo}[-(\text{D-Val-Pro-Val-D-Hyi})_n-]$$

$$\text{cyclo}[-(\text{D-Val-Lac-Val-D-Pro})_n-]$$

$$n = 2,\ 3,\ \text{or}\ 4$$

The Ile-containing analogs proved more efficient in extraction experiments than the parent antibiotic, the 16-membered derivative (n = 4) being a good ionophore for cesium quaternary amines.

A new view is presented on the conformational equilibrium of the channel forming polypeptide gramicidin A, based on the comparison of experimental and calculated IR spectra of various spatial forms.

In conclusion recent structural findings in the proton channel forming protein bacteriorhodopsin will be discussed.

IIIB.2.

THE STRUCTURES OF SEVERAL NATURALLY OCCURING POLYETHERS AND THEIR CATION SELECTIVITY PATTERNS.

N. Ōtake, Institute of Applied Microbiology, University of Tokyo, Bunkyo-ku, Tokyo 113, Japan

A number of the antibiotics belonging to the family of monocarboxylic polyethers have been reported and their biological activities have attracted considerable interests.

In the course of our studies on the bioorganic chemistry of the ionophore antibiotics, we have established the structures of a number of the naturally occuring polyethers, e.g., salinomycin and its minor congeners, lysocellin, lonomycin, etheromycin (CP-38295) and carriomycin by means of X-ray analysis or chemical procedure and carried out the investigations of ion-complexing properties thereof across an organic solvent barrier layer and biological membranes.

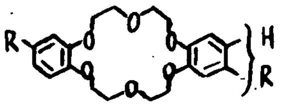
The structures and the cation selectivity patterns of several newer members of the polyether antibiotics will be reported.

IIIB.3.

SOME NEW DERIVATIVES OF 2,3,11,12-DIBENZO-18-CROWN-6. WAYS OF PREPARATION AND EFFECT.

A. K. Tashmukhamedova, B. A. Tashmukhamedov, Institute of Bioorganic Chemistry and Institute of Biochemistry, Uzbek Academy of Sciences, Tashkent, USSR.

Macrocyclic polyethers are synthetic membrane active ligands. We have modified the molecule of 2,3,11,12-dibenzo-18-crown-6 to make the molecule more lipophilic and hydrophilic. The way of preparation of diacyl derivatives of 2,3,11,12-dibenzo-18-crown-6 has been worked out. The reaction products - geometrical isomers - have been separated by fractional crystallization. The structures of isomers have been proved by two counter synthesis and spectral methods. The "trans"-structure has been found to be the low-melting isomer. Diacyl derivatives have been used as initial compounds to obtain some new dialkyl- and di-α-oxyalkyl derivatives of 2,3,11,12-dibenzo-18-crown-6.



R = $COCH_3$ COC_2H_5 COC_3H_7
COC_4H_9 COC_5H_{11} COC_6H_{13}
COC_7H_{15} COC_6H_5 C_2H_5
C_3H_7 C_4H_9 C_5H_{11} C_6H_{13}
C_7H_{15} C_8H_{17} $CH_2C_6H_5$
$CH(OH)CH_3$ $CH(OH)C_2H_5$
$CH(OH)C_3H_7$ $CH(OH)C_4H_9$
$CH(OH)C_5H_{11}$ $CH(OH)C_6H_{13}$
$CH(OH)C_7H_{15}$

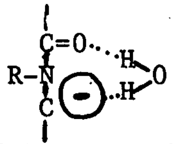
All compounds have been tested on biological (rat liver mitochondria) and model (phospholipid bilayer) membranes. Some of them show high activity and selectivity to some mono- and bivalent ions. The synthesis and membrane properties of these compounds will be reported.

IIIC.1.

AMPHOTERIC COMPLEXES OF NEUTRAL IONOPHORES HAVING TERTIARY AMIDE LIGANDS--IMPLICATIONS FOR ANION BINDING TO THE POLYPEPTIDE BACKBONE.

G. Eisenman, R. Margalit and K.-H. Kuo, Dept. Physiol., UCLA Medical School, Los Angeles, Ca. 90024.

We find that Simon's neutral Li$^+$ selective complexone, N,N'-diheptyl-N,N',5,5-tetramethyl-3,7-dioxanonan-diamide, is not only a Li$^+$ carrier in lipid bilayers but also can carry monovalent anions selectively. Similar behavior is seen with his neutral Na$^+$ selective complexone, N,N,N',N',-tetrabenzyl-3,6-dioxaoctan-diamide, which also functions in bilayers as an "equilibrium domain" carrier for cations or anions. The stoichiometry of the charged complexes has been analyzed in detail for the Li$^+$ carrier (and less completely for the Na$^+$ carrier) by characterizing the dependence of membrane conductance on salt and carrier concentration and by measuring the charge of the permeant complexes from dilution potentials. Positively charged 1:1 and 2:1 carrier:ion complexes have been found for monovalent cations and negatively charged 1:1, 2:1 and 2:2 complexes have been found for monovalent anions. Singly positively charged 4:2:1 carrier:cation:anion mixed complexes of 2 monovalent cations together with 1 monovalent anion have also been identified. Consistent with electron withdrawing tendency of aromatic groups, the selectivity sequence observed for cations with the Na$^+$ carrier (Na>K>Rb>Cs>Li) is the intermediate one, VII, expected for lower field strength oxygens than the high field strength sequence XI (Li>Na>K>Rb>Cs) observed for the Li$^+$ carrier. The observed cation vs. anion selectivity is also consistent with the electron withdrawing tendency of the aromatic groups since the anion:cation selectivity of the Na$^+$ carrier is greater than that of the Li$^+$ carrier. (The sequence for the Li$^+$ carrier is ClO_4^->Li^+=SCN^->Tl^+>I^->Na^+>NH_4^+>NO_3^-=K^+>Br^->Rb^+>Cl^-=Cs^+>F^->Ac^- while for the Na$^+$ carrier it is Na^+>NO_3^->K^+>Cl^->Rb^+>Cs^+>Li^+). Since these molecules contain no classical anion binding group (the amide is tertiary), we propose, as indicated schematically,



that a water molecule, interposed between the amide carbonyl (or ether oxygen) and the anion, forms a major component of the anion binding site (via H-bonds), the anion also being coordinated to positive π electron regions at the N (or C) atoms of the backbone. The selective anion binding by this model for a peptide suggests that anions can bind selectively to the peptide backbone even in regions where no amide H's are available (e.g. owing to intramolecular H-bonding or to the presence of tertiary amides). We speculate that this may be the basis for anion binding to the H-bonded backbone of the gramicidin channel as well as to proteins.

POLYENE MACROLIDE ANTIBIOTICS AND SPECIFIC MEMBRANE PERMEABILITY CHANGES: STRUCTURE-BIOLOGICAL EFFECTS RELATIONSHIPS.

E. Borowski, B. Cybulska, B. Malewicz, T. Zieniawa, Department of Pharmaceutical Technology and Biochemistry, Technical University, 80-952, Gdańsk, Poland.

Polyene macrolide antibiotics induce broad range of membrane permeability changes in eucaryotic cells, consequent to the formation of hydrofobic complexes with membrane sterols. Their action was supposed to be cytocydal and irreversible.

We have demonstrated that very specific membrane changes may occur and that the action of polyene macrolide can be reversed and the damage done to the membrane can be repaired by the cell/Nature, 213, 1034/1967. We have also proved that polyene macrolide can induce permeability changes in membranes not containing sterols/FEBS Letters, 76, 81/1977.

In our continuing studies on the structure-biological properties relationships in polyene macrolides, the structure of the following antibiotics representative for various groups of properties have been elucidated: rimocidin, flavomycoin, nystatin A_1, nystatin A_3, polyfungin B, amphotericin B, mycoheptin, candidin, levorin A_2, candicidin D, perimycin A, lienomycin. Chemical modifications aimed at the modification of properties have been done also.

The correlation of structures with biological properties will be discussed including the following effects: reversibility of membrane changes and the ability to repair the membrane damage, selective toxicity effects in animal and fungal cells. Characteristics of permeability pathways induced by specifically acting polyene macrolides will be discussed also.

IIID.1.

DESIGN AND SYNTHESIS OF CYCLIC PEPTIDES TO MIMIC THE METAL BINDING SEGMENT OF THE ACTIVE SITES OF METALLOENZYMES.

B. Sarkar, The Research Institute of The Hospital for Sick Children, Toronto, Ontario and The Department of Biochemistry, University of Toronto, Toronto, Ontario, Canada.

In recent years, the three dimensional structures of several metalloenzymes have been elucidated at the atomic level. The metal-binding amino acid residues are assembled from the distant polypeptide chains because of the folding of the protein. As part of our investigation on the molecular design of the functional sites of biological molecules, we have undertaken to study the metal-binding segment of the active sites of two Zn(II)-metalloenzymes: carboxypeptidase and carbonic anhydrase. In these studies we have embarked on the design of peptides in order to closely resemble the protein character of the molecule. A linear peptide has considerable conformational flexibility, however, it was considered that if the same peptide could be conformationally fixed by cyclization, it could provide a suitable geometry for the Zn(II)-binding. Taking into account the various features as well as the geometry of the Zn(II)-binding at the active site, a cyclic octapeptide:

Gly-L-Glu-Gly-Gly-L-His-Gly-L-His-Gly

was designed to mimic the Zn(II)-binding site of carboxypeptidase. Similarly, a cyclic heptapeptide:

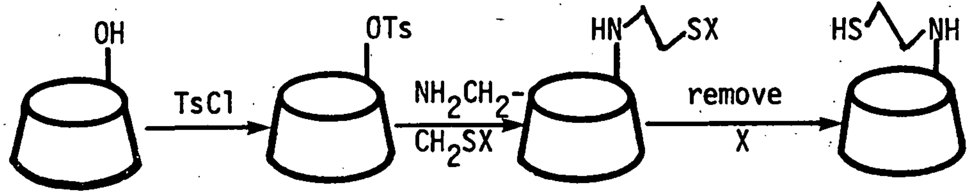
Gly-L-His-Gly-L-His-Gly-L-His-Gly

was designed to mimic the Zn(II)-binding site of carbonic anhydrase. In both these designs, the natural Zn(II)-binding ligands were maintained. Both these peptides have been synthesized and their detailed Zn(II)-binding studies are currently underway. (The research was supported by a grant (MT 1800) from the Medical Research Council of Canada).

SYNTHESIS OF LIGANDS FOR BINDING METHYLMERCURY CATIONS.

Mary Frances Richardson and Bibudhendra Sarkar, The Research Institute, The Hospital for Sick Children, Toronto, Ontario, M5G 1X8.

A ligand capable of binding CH_3Hg^+ should provide two things: a hydrophobic cavity for the methyl group, and an — SH group for the free coordination site of the mercury. Cyclodextrins (cyclohexaamylose and cycloheptaamylose) posess ready-made hydrophobic cavities, as evidenced by their ability to encapsulate a variety of nonpolar molecules (W. Saenger, in B. Pullman, ed., "Environmental Effects on Molecular Structure and Properties", D. Reidel Publishing Co., Boston, 1976, pp. 265-305). Cyclodextrins can be functionalized to provide a mercapto group by the following reaction scheme:



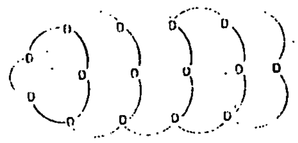
The — SH protecting group is dihydropyran. Methylmercury binding to the cyclodextrins is being investigated.

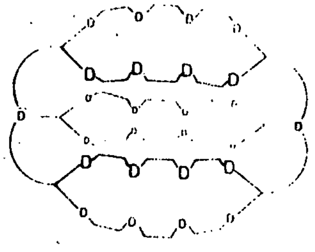
This research has been supported by a grant from the Ontario Provincial Ministry of Health.

NEW POLAROPHILIC AND LIPOPHILIC MOLECULAR CAVITIES.

F. Vögtle, L. Rossa, W. Wehner, E. Buhleier, P. Dix, N. Wester, H. Sieger, E. Hammerschmidt, J. Winkel, St. Karbach, W. Bieber and R. Wingen, Institut für Organische Chemie und Biochemie der Universität, Gerhard-Domagk-Str. 1, D-5300 Bonn, Bundesrepublik Deutschland.

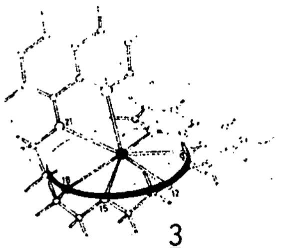
a) Synthetic strategies were developed for nonskid-chain analogous ligand molecules of type 1 and for multicyclic cryptand systems 2:





1 (D = donor site) 2

b) The "cyclisation" of open-chain oligoethylene glycol ethers with cations as templates leads to crystalline, helical complexes 3,4; with thiourea complexes of type 5 displaying interesting hydrogen bondings crystallize out:



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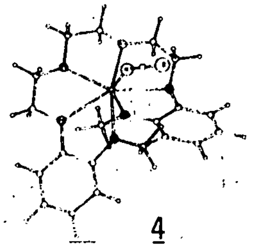

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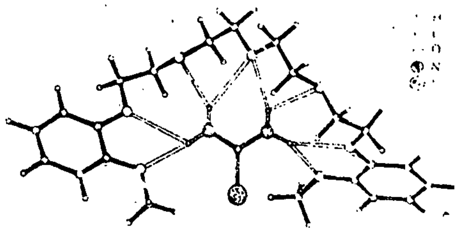

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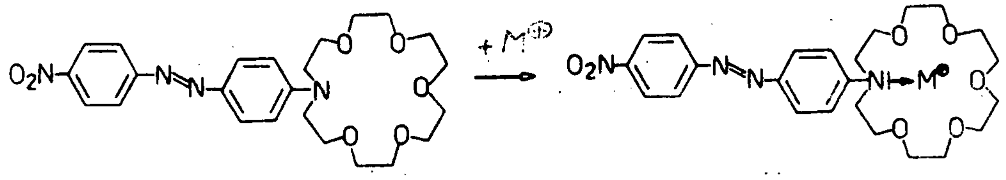
c) Ionsensitive crown ether dyes like 6 selectively alter their light absorption on addition of alkali/alkaline earth ions:



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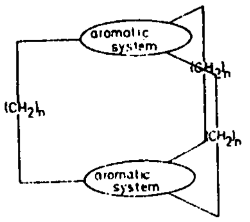
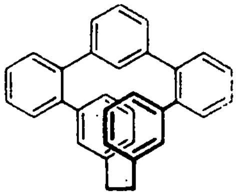
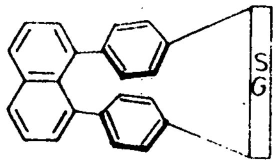
d) New multiply clamped polycycles 7, new helically shaped "arenicenes" (8) and the "spreading group concept" (cp. 9) are discussed:







7 8 9

e) New synthetic methods are represented: e.g. Thioacetamide cyclisation, Sulfide pyrolysis.

SYNTHESIS, TEMPERATURE DEPENDENT CONFORMATIONAL PREFERENCES, AND COMPLEXATION OF POLYETHEREAL MACROCYCLES CONTAINING THE NEUTRAL BIPYRIDYL SUBUNIT.

George R. Newkome, Ashutosh Nayak, Toshio Kawato, and Frank Fronczek, Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803.

At the turn of the century, Blau's discovery of iron complexation by 2,2'-bipyridyl has sparked the imagination to numerous chemists to devise more selective ligands, which have been based on the alteration of the Schiff base moiety of these bipyridyls. Although x-ray data of bipyridyl have demonstrated that in the crystal state the free ligand possesses an antiperiplanar conformation, dipole moment studies suggest an anticlinal orientation, and recently MINDO-3 calculations indicate a synclinal orientation, all metal bipyridyl complexes have the synperiplanar configuration. We will report the syntheses of macrocycles, which possess the 2,2'-bipyridyl subunit(s) and in selected cases possess a macrocyclic bridge capable of satisfying the inner coordination sphere of selected transition metals. The conformational mobility of these ligands can be varied with the dihedral angle of ca.30° to 180° prior to complexation. These macrocycles can also possess a preselected cavity size. Synthetic aspects and chemical properties will be considered. The unique ligands also demonstrate a temperature dependent anti to syn conformational rotation at low temperatures; variable temperature NMR and UV studies support an increasing rigidity of the macrocyclic bridge at diminished temperatures. Various metal complexes, in which the bipyridyl unit and the polyfunctionalized bridge satisfies the equatorial positions of the metals, will be presented.

IV.3.

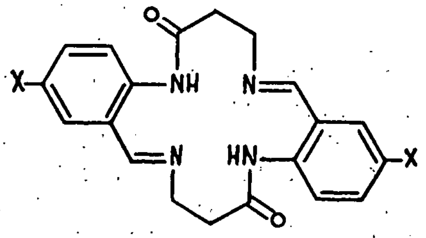
THE SYNTHESIS AND COMPLEXING PROPERTIES OF NOVEL MACROHETEROCYCLES CONTAINING ESTER AND AMIDE MOIETIES,

A.V. Bogatsky and N.G. Lukyanenko, Ukranian Academy of Sciences, Physico-Chemical Institute, Odessa, U.S.S.R. 270080

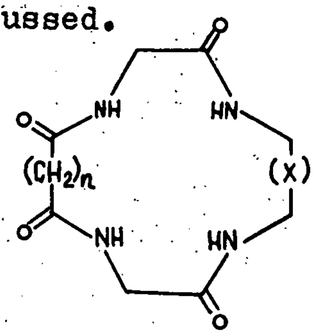
A great deal of interest has been focused on macroheterocycles because of the possible chemical and biological applications of their unusual complexing and solvating properties. The most completely investigated in this aspect are the macrocyclic polyethers (crown ethers). The properties less studied are those of macroheterocycles containing different functional groups of the ester, amide, carbonyl type etc.

A series of novel macrocycles (I-V) have been prepared. Type I compounds have been obtained by the interaction of ß-alanine chloride with o-aminobenzophenones. Lengthy boiling of equimolar quantities of dimethyl ester of succinyl (or adipayl) diglycine and the corresponding diamine in methanol yielded (II). III-V substances have been obtained by the reaction of 2,2-dimethylpropane bis-(hydrogensuccinate) dichloride with glycols or diamines.

The complexing properties of these novel macrocyclic compounds will be discussed.

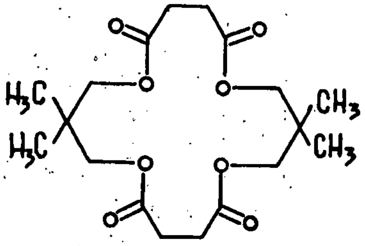


I

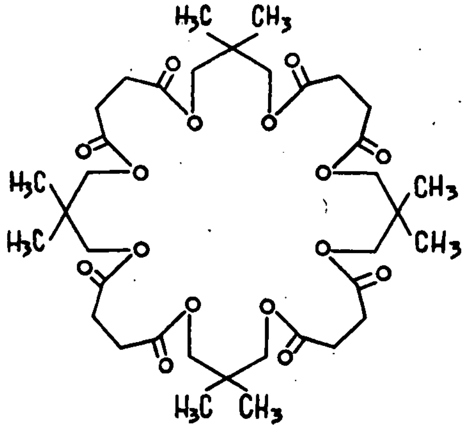


II

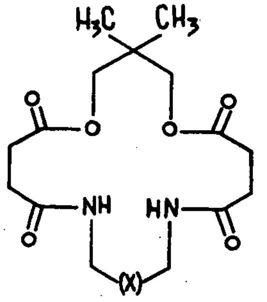
n = 2-4;
X = $(CH_2)_n$
or $(CH_2OCH_2)_n$



III



IV



V

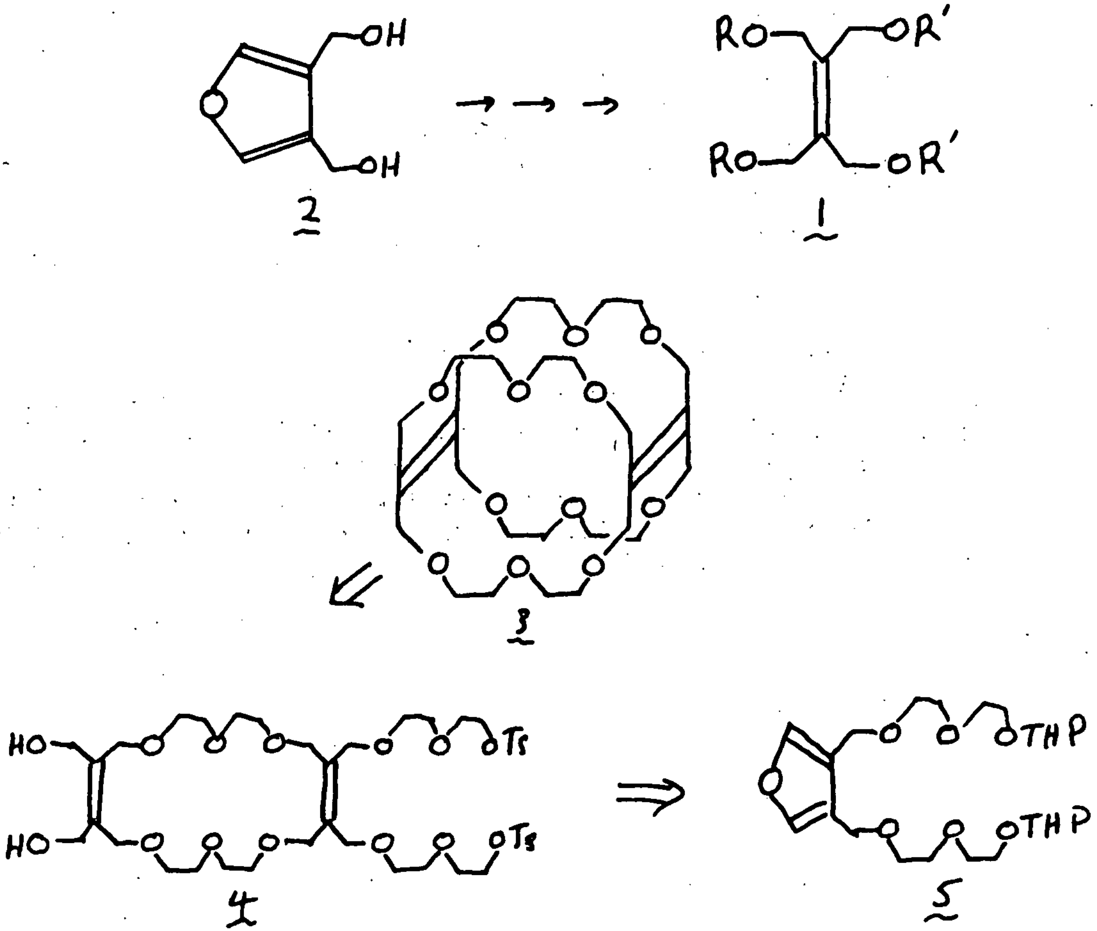
X = $(CH_2)_n$ or $(CH_2OCH_2)_n$

METHODS DIRECTED TOWARDS THE SYNTHESIS OF LARGE CAGE MOLECULES CONTAINING MACROCYCLIC POLYETHER SUBUNITS.

D.M. Walba, S. Sherwood, P.M. Macintosh, Department of Chemistry, University of Colorado, Boulder, CO 80309.

Methods have been developed which allow the synthesis of tetrahydroxymethyl ethylene derivatives 1 from readily available 3,4-dihydroxymethyl furan (2). Application of this methodology to the construction of large cage molecules containing macrocyclic polyether subunits is being investigated. The initial goal of this work is the synthesis of tricyclic cage compound 3, which is envisioned as resulting from base induced cyclization of diol-ditosylate precursor 4. Progress on the preparation of compound 4 from the readily available bis-THP ether 5 will be reported.

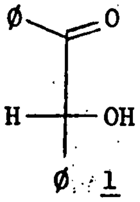
Extension of these methods is hoped to allow synthesis of larger homologues of cage 3 which would contain three tetrahydroxymethyl ethylene units. Examination of CPK molecular models indicates that such a cage may form lipophilic complexes with sugar molecules stabilized by hydrogen-bonding and entropic effects in a manner similar to the binding of aromatic substrates to the cyclodextrins to form hydrophilic complexes.



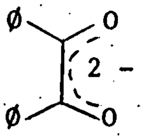
2,3,11,12-TETRAPHENYL-1,4,7,10,13,16-HEXAOXA-2,11-CYCLOOCTADECADIENE. A NEW UNSATURATED CROWN ETHER FROM BENZOIN.

Andreas P. Merz, Institut fuer Chemie der Universitaet, D-8400 Regensburg, West-Germany.

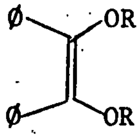
In the two-phase system benzene/50 per cent aqueous sodium hydroxide, benzoin (1) is converted into stilbenediol dianion (2) which can be bis-alkylated to E and Z dialkoxystilbenes (3) with dialkyl sulfates or alkyl sulfonates and to oxygen heterocycles (3a) with bifunctional alkylating agents



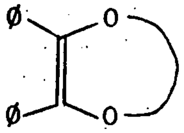
1



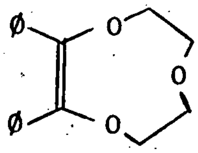
2



E,Z-3

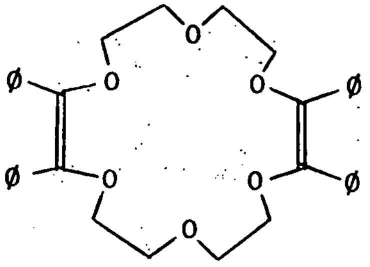


3 a

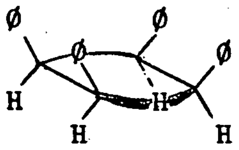


4

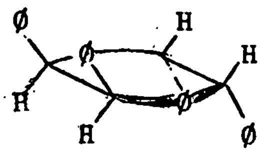
From (1) and ethylene glycol ditosylate the crown ethers (4) (14%), and (5) (title compound, 20-25%) are obtained.



5



6 (syn)



7 (anti)

Catalytic hydrogenation of (5) (5% Pd on $BaSO_4$/DMF) yields two achiral saturated [18]crown-6 species (6) and (7). Alkali metal and ammonium ion com plexes from (5), (6) and (7) are eradily available.

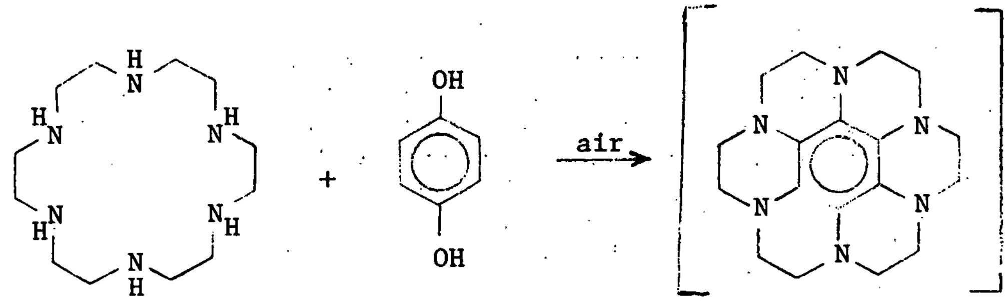
(5) is the first crown ether containing reactive prochiral double bonds within the ring system. Chemical modification of (5) by reactions at the double bonds are discussed.

IV.6.

AROMATIC DERIVATIVES OF HEXACYCLEN.

J. E. Richman and M. R. Asirvatham, Department of Chemistry, University of Idaho, Moscow, Idaho 83843.

Air oxidation of a mixture of hydroquinone and hexacyclen (the aza analogue of 18-crown-6) produces a rapid progression of color changes.



hexacyclen

1

Evidence suggesting that the various oxidation states of the benzene derivative, 1, are involved in this reaction will be presented. Alternative synthetic routes to 1 and the rich redox chemistry of this novel system will be discussed.

This research is supported by a grant from The Petroleum Research Fund of the American Chemical Society.

MACROCYCLIC POLYSTANNANES. M. Newcomb, Department of Chemistry, Texas A&M University, College Station, Texas, 77843

Synthetic approaches to macrocyclic polystannanes will be reported. The potential for these compounds to act as anion and neutral donor complexing agents and the results of preliminary complexation experiments will be discussed.

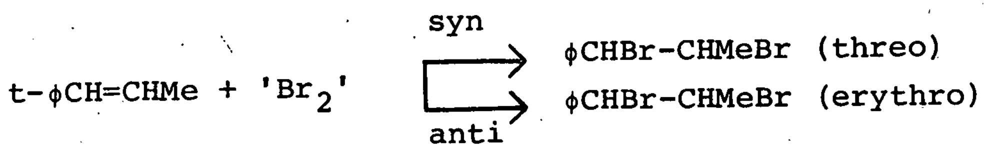
IV.8.

Macrocyclic Polyether-Bromine Complexes as Stereoselective Brominating Agents.

Keith Pannell and Armin Mayr, Department of Chemistry, University of
Texas at El Paso, El Paso, Texas 79968.

Molecular bromine forms stable complexes with macrocyclic polyethers. We have utilized these complexes for the bromination of olefins and find them to exhibit a high degree of stereoselectivity. This is illustrated in the table where we have compared the stereoselectivity of bromine addition in various solvents to trans-methylstyrene using molecular bromine and the pyridine bromine complex as comparisons to illustrate the stereospecificity of the dibenzo-18-crown-6 bromine complex.

The reasons for the stereospecificity illustrated will be discussed along with information concerning the stability constants for the various crown ether bromine complexes.



% erythro

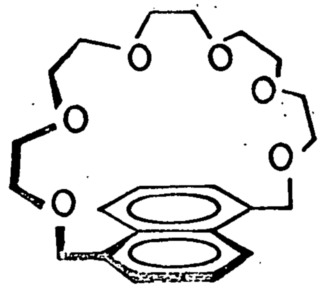
Solvent	Br_2	$Py.Br_2$	$DBC.Br_2$
CH_2Cl_2	90	89	100
CH_3NO_2	81	86	100
Dioxane	79	89	100

Research supported by the Robert A. Welch Foundation Houston, Texas.

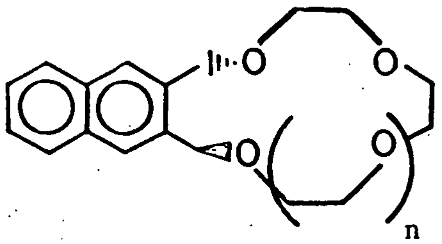
IV.9.

FIELD INDUCED PI POLARIZATION OF NAPHTHALENE CROWN ETHERS AND CROWN ETHER CONFORMATIONAL CHANGES STUDIED BY ^{13}C NMR. Lynn R. Sousa, Mark R. Johnson and Houston S. Brown, Department of Chemistry, Michigan State University, East Lansing, Michigan 48824.

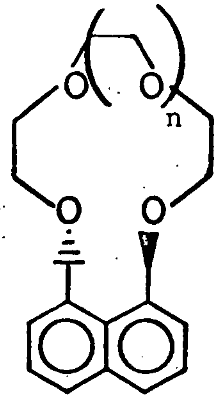
Naphthalene crown ether compounds 1 through 7 have been synthesized for use in a systematic study of the interactions of an oriented positive monopole with a reasonably extensive pi system. The changes in naphthalene and crown ether ^{13}C NMR chemical shifts caused by complexed cations (Na^+, K^+, Rb^+, Cs^+, Ca^{+2}, Ba^{+2}, etc.) give new information about electric field induced pi polarization and also an indication of complexation induced conformational changes, in solution, of the crown ring.



1



	n+3
2	6
3	5
4	4



	n+3
5	6
6	5
7	4

For a given crown, 2 for example, most of the naphthalene carbon chemical shift changes are independent of the size, polarizability, polarizing strength, but not charge, of the complexed cation. This indicates that dispite large changes in cation size (Na^+, r = 0.95Å to Cs^+, r = 1.69 Å) the cation is effecitvely centered in the crown ring of 2 such that the cation-pi system distance is not changed much as the cation is varied. The observed naphthalene chemical shift changes correlate rather well with changes in electron densities calculated by the INDO method.

Those naphthalene carbons <u>ortho</u> to a carbon of attachment do respond differently to different sized cations. This is presumably due to the γ effect which is related to, and thus gives information about, conformational changes in the crown ether ring near the aromatic system. Changes are also observed in the ether ring carbons. In some cases the data indicates that drastic changes in the crown ether conformation are caused by the complexation of small cations.

ALKALI AND ALKALINE EARTH CATION SELECTIVITY BY CYCLIC POLYETHER TYPE LIGANDS. R. M. Izatt, J. D. Lamb, and J. J. Christensen, Departments of Chemistry and Chemical Engineering and the Thermochemical Institute, Brigham Young University, Provo, UT 84602.

The availability of macrocyclic compounds of the cyclic antibiotic and cyclic polyether types which complex alkali and alkaline earth metal ions has provided increased opportunity for the systematic investigation of the coordination chemistry of these cations. Selectivity sequences for both of these groups of cations are affected by changes in ligand structural parameters such as donor atom number and type, ring substituents, and ring cavity size. Log K, ΔH, and $T\Delta S$ data for the interaction of several alkali and alkaline earth cations with 12-crown-4, 15-crown-5, 18-crown-6, 21-crown-7, and several of their substituted derivatives have been determined by us. These data provide several examples of changes in cation selectivity within and between these groups of cations resulting from changes in ligand structure. Certain of these ligands have been found to react with certain of the trivalent lanthanide cations, Cu^{2+}, and post-transition heavy metal cations. Corresponding thermodynamic data have been determined in the cases of several of these cations allowing comparisons to be made with the alkali and alkaline earth cations.

KINETICS AND THERMODYNAMICS OF MACROCYCLIC TETRATHIAETHER COMPLEXES.

Thomas E. Jones, Jeff Dill, and Wang Yu, Department of Chemistry,
The University of New Mexico, Albuquerque, NM 87131.

Metal ion complexes of macrocyclic amines and crown ethers have been widely studied. Sulfur donor macrocycles represent the third class of cyclic ligands capable of forming metal ion complexes. However, they have received far less attention. In contrast to the oxoethers, the thiaethers show a distinct preference for the "softer" metal ions such as Hg(II), Pd(II), Pt(II), and Cu(II). Kinetics and thermodynamics of heavy metal macrocyclic thiaether complexes will be reviewed. Recent studies on solvent extraction of Hg(II) from aqueous solutions utilizing macrocyclic and open chained tetrathiaethers will be discussed in terms of the underlying equilibria which controls the efficiency of the extraction process. Equilibrium studies of Pd(II) macrocyclic thiaethers will be discussed. An attempt will be made to contrast and compare the behavior of macrocyclic thiaethers with the more widely studied crown ethers.

Financial support of this work by Sandia Laboratories is gratefully acknowledged.

REACTIONS OF PRIMARY, SECONDARY, AND TERTIARY AMMONIUM IONS WITH 12-CROWN-4, 15-CROWN-5, 18-CROWN-6, AND 21-CROWN-7. Scott Collins, Reed M. Izatt, and James J. Christensen, The Thermochemical Institute and Departments of Chemistry and Chemical Engineering, Brigham Young University, Provo, UT 84602.

Log K, ΔH, and TΔS values have been determined for the reaction at 25° in methanol of several macrocyclic polyethers with NH_4^+ and several mono-, di-, and trialkyl ammonium ions. These reactions are studied in an effort to discriminate among the structural features which impart selectivity in host-guest interactions. The number of hydrogen bonds between the protonated amine and the oxygen atoms of the polyether is the main factor in determining the extent of these interactions. Ligand cavity size and donor atom symmetry as well as guest steric factors are important in determining the extent of hydrogen bonding.

CORRELATION OF STRUCTURAL AND THERMODYNAMIC DATA FOR SOME CATION-CYCLIC POLYETHER COMPLEXES.

N. K. Dalley and S. B. Larson, Department of Chemistry, Brigham Young University, Provo, UT 84602.

Several correlations between structural and thermodynamic data for cation-macrocycle interaction will be presented and discussed. Among the earliest correlations found was that between log K for metal complex formation and the ratio of cavity size to cation radius. However, this correlation appears to break down in certain instances. More recently our study of cation complexes of cyclic ether esters has shown that TΔS favors the reaction in methanol of K^+ with 2,6-diketo-18-crown-6 over the corresponding reaction involving 18-crown-6. This result can be understood from the crystal data of the free ligands and their K^+ complexes. Less ordering of the ether ester ring is required for complex formation in the case of the 2,6-diketo-18-crown-6.

CARRIER-FACILITATED TRANSPORT OF CATIONS AND ANIONS THROUGH THICK AND THIN MEMBRANES.

J. J. Christensen, S. R. Izatt, M. Astin, K. Bedke, J. D. Lamb, K. Stimpson, and R. M. Izatt, Departments of Chemical Engineering and Chemistry and the Thermochemical Institute, Brigham Young University, Provo, UT 84602.

The macrocycles dibenzo-18-crown-6 and *tert*-butylbenzo-15-crown-5 have been used to study the carrier-facilitated transport of cations and anions through both thick and thin liquid and thin microporous membranes.

The thick liquid membranes used consisted of a layer of $CHCl_3$ containing the macrocycle separating two aqueous solutions. The liquids were well stirred and the amount of transport of the metal ions from one aqueous solution to the other together with their counter ion was measured as a function of time. The thin liquid membranes consisted of an emulsion in water of small droplets of aqueous solution encapsulated in a thin film of oil. The metal ions and their counter ions were transferred from the surrounding aqueous solution through the oil film which contained the macrocycle. The thin microporous membranes were microporous polypropylene films containing a hydrophobic organic phase. The organic phase contained the macrocycle carrier.

A wide variety of anions including Cl^-, Br^-, I^-, $PO_4^{\equiv}$, $HPO_4^{=}$, $H_2PO_4^-$, OH^-, NO_3^-, picrate and acetate were used. Metal ion concentrations were determined by atomic absorption and where applicable, by spectroscopy. The rate of transport of metal ions was found to be highly dependent on the type of anion used. The factors which determine the rate of transfer of a metal ion under the conditions studied will be discussed.