

Sixth Progress Report for Division of Basic Energy Sciences,
Department of Energy, Contract AT(04-3)34, P. A. 218

MULTIHETEROMACROCYCLES THAT COMPLEX METAL IONS

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MASTER

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I. Objectives and Background of Research

The overall objective of this research is to design, synthesize, and evaluate cyclic and polycyclic host organic compounds for their abilities to complex and lipophilize guest metal ions, their complexes, and their clusters. Host organic compounds consist of strategically placed solvating, coordinating, and ion-pairing sites tied together by covalent bonds through hydrocarbon units around cavities shaped to be occupied by guest metal ions or by metal ions plus their ligands. Specificity in complexation is sought by matching the following properties of host and guest: cavity and metal ion sizes; geometric arrangements of binding sites; number of binding sites; character of binding sites; and valences. The hope is to synthesize new classes of compounds useful in the separation of metal ions, their complexes, and their clusters.

The Fifth Progress Report for the Division of Basic Energy Sciences, Department of Energy, summarizes the research done under this contract since its inception. Full length papers have been published that cover all of the work done during the first four years of this contract (see section VI of this report). They provide a context for the current work.

II. Personnel

1. Dr. Donald J. Cram, the principal investigator, devoted one full time summer month and 20% of each of the nine academic months to the project.

2. Dr. Roger Helgeson, Assistant Research Chemist II, was employed 89% of full time for 8 months and 100% of full time for 2 months on this project. He has had ten postdoctoral years' previous experience in the synthesis of macrocyclic compounds, five of which were with multiheteromacrocycles.

3. Mr. George Lein, a Ph.D. degree candidate at UCLA, worked as a Postgraduate Research Chemist III on this project at 40% of full time for

12 months

4. Mr. Steve Artz, a Ph.D. degree candidate at UCLA, worked on this project as a Postgraduate Research Chemist II at 40% of full time for 4 months.

5. Mr. Ira Dicker, a Ph.D. degree candidate at UCLA, worked on this project as a Postgraduate Research Chemist III at 40% of full time for 4 months.

6. Dr. Woo Young Lee, Department of Chemistry, Seoul National University, Korea; Korean Visiting Scholar at UCLA; supplies paid out of contract. His salary was paid by SNU-AID funds.

7. Ms. Cindy Franz, a third year undergraduate student at UCLA, worked on this contract as a laboratory helper; she was paid \$160.16 from this contract on an hourly basis.

III. Research Results Obtained for the Reporting Period 1 May 1979 through 30 April 1980

Our past work indicates the most promising ligand systems are the spherands, defined as hosts containing roughly spherical holes lined with binding sites that are organized fully by the support system rather than by bound guests. Hemispherands are defined as ligand systems composed of units which rigidly orient binding sites in a hemispherical array. These binding sites are not required to reorganize upon complexation.

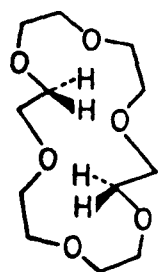
A. Hemispherands Based on Cyclotrimetaaryloxyethylene Units (George Lein)

The hemispherand concept is simply illustrated by contrasting the X-ray structures (done by others) of uncomplexed and complexed crowns, cryptands, and hemispherands. Crown 1 and cryptand 2 fill up their own holes by methylene groups turning inward and oxygens turning outward. Upon complexation, the oxygens turn inward and the methylenes turn outward. In hemispherand 3, the three aryloxy oxygens line a hemispherical cavity in both the free ligand and its complex, 4 (K. N. Trueblood and I. Goldberg, private communications). Reorganization of the ligand system upon complexation to give 4 occurs only in the ethylene glycol units of the ligand system and not in the triarylene units. The aryloxy oxygens are similarly placed in both uncomplexed and complexed ligand systems.

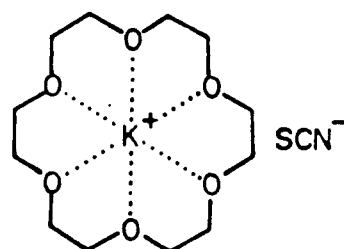
The free energies of complexation of standard picrate salts in CHCl_3 at 25 °C have now been determined for these hemispherands and are tabulated.

Conclusions derived from the data are as follows. (1) Standard crowns 4 and 5 are close to one another, and substitution of one ArOCH_3 for a CH_2OCH_2 unit in 6 decreases $-\Delta G^\circ$ values markedly. (2) Two aryloxy units adjacent to one another substantially enhance binding compared to their being placed opposite to one another (compare 7 and 8). (3) Three adjacent aryloxy units (as in 3)

Pedersen's Crowns

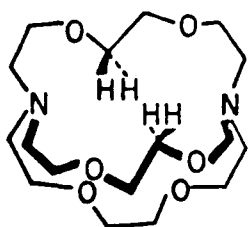


1

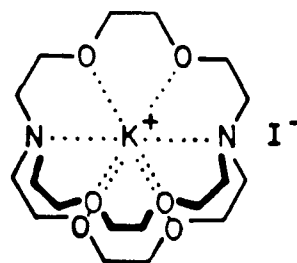


Dunitz' X-ray structures

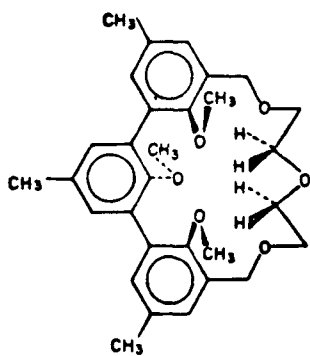
Lehn's Cryptands



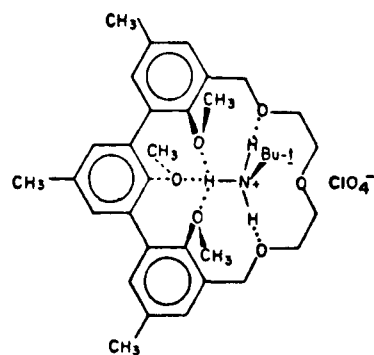
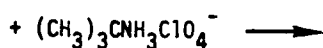
2



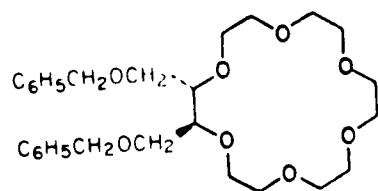
Weiss' X-ray structures



3



provide enough enforced conformation for their systems to surpass in binding power the standard crowns, 4 and 5. (4) An additional aryloxy unit positioned nonrigidly (as in 9) with its OCH_3 group occupying the hole drastically reduces

$-\Delta G^{\circ}$ (kcal/mol), CHCl_3 , 25°C
Li⁺Na⁺K⁺Rb⁺Cs⁺

4

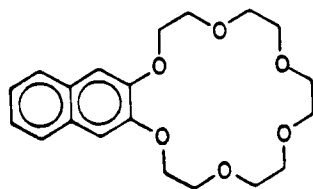
6.3

8.4

11.4

9.9

8.5



5

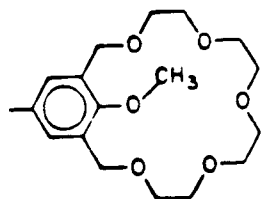
5.9

8.3

10.8

8.3

9.5



6

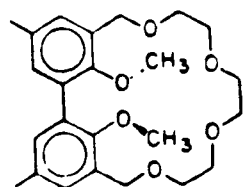
5.5

6.4

8.5

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6.9



7

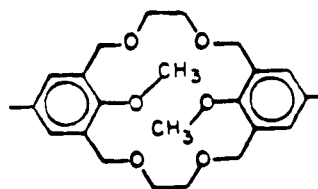
6.5

8.7

9.8

8.6

7.8



8

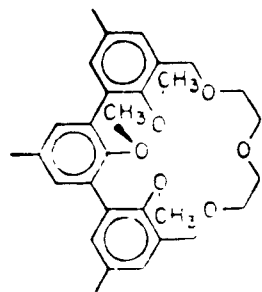
4.0

4.5

4.9

4.6

4.5

$-\Delta G^{\circ}$ (kcal/mol), CHCl_3 , 25°C
Li⁺Na⁺K⁺Rb⁺Cs⁺

7.2

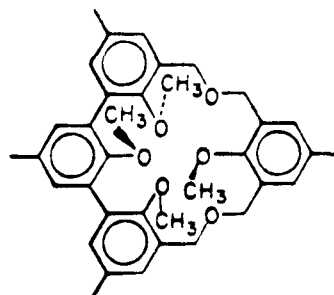
12.5

12.4

10.5

9.0

3



4.0

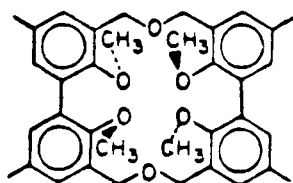
7.7

6.6

5.4

5.4

9



< 4.0

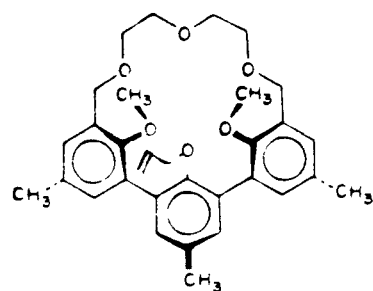
5.2

4.6

4.0

3.9

10



7.0

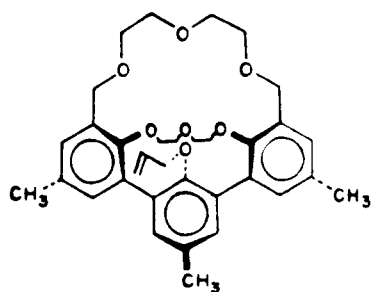
12.2

11.9

8.7

7.1

11

$-\Delta G^{\circ}$ (kcal/mol), CHCl_3 , 25°C
Li⁺Na⁺K⁺Rb⁺Cs⁺

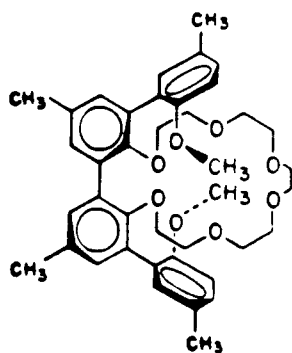
7.6

14.5

14.2

10.0

8.2

12
~ ~

6.8

10.5

11.6

8.6

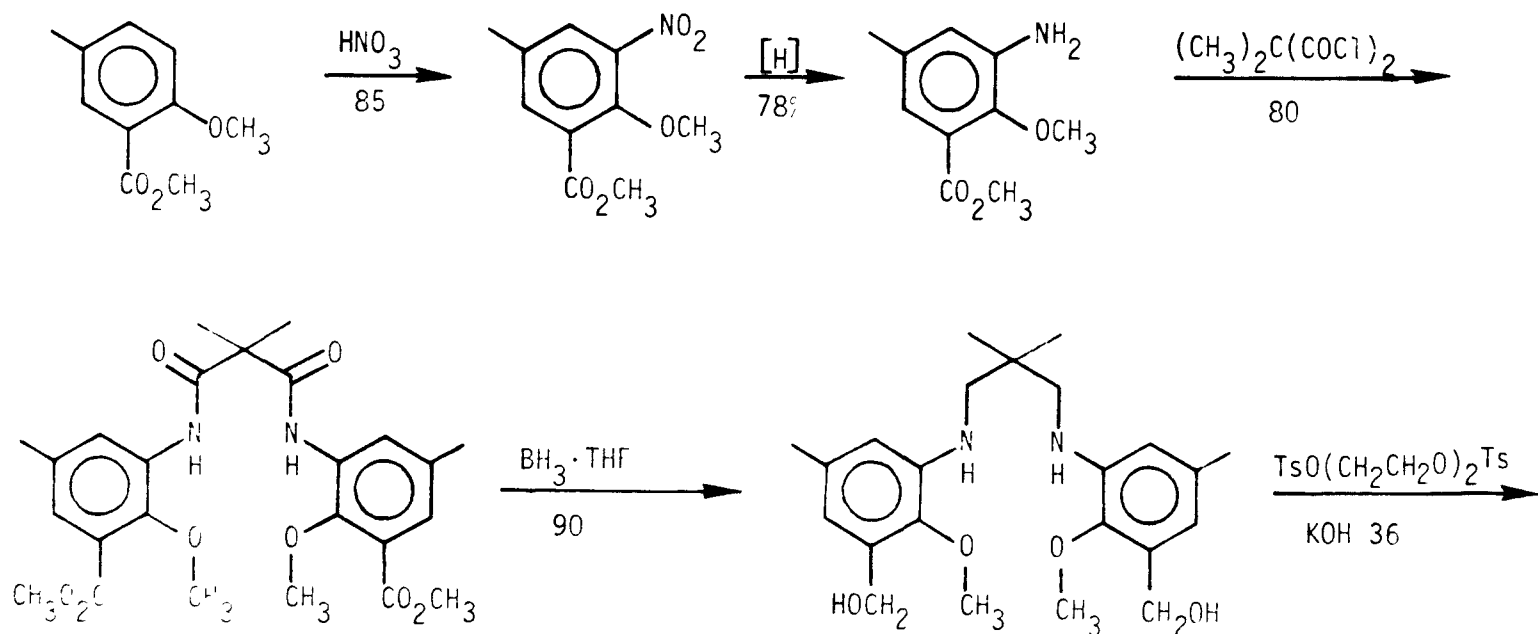
7.5

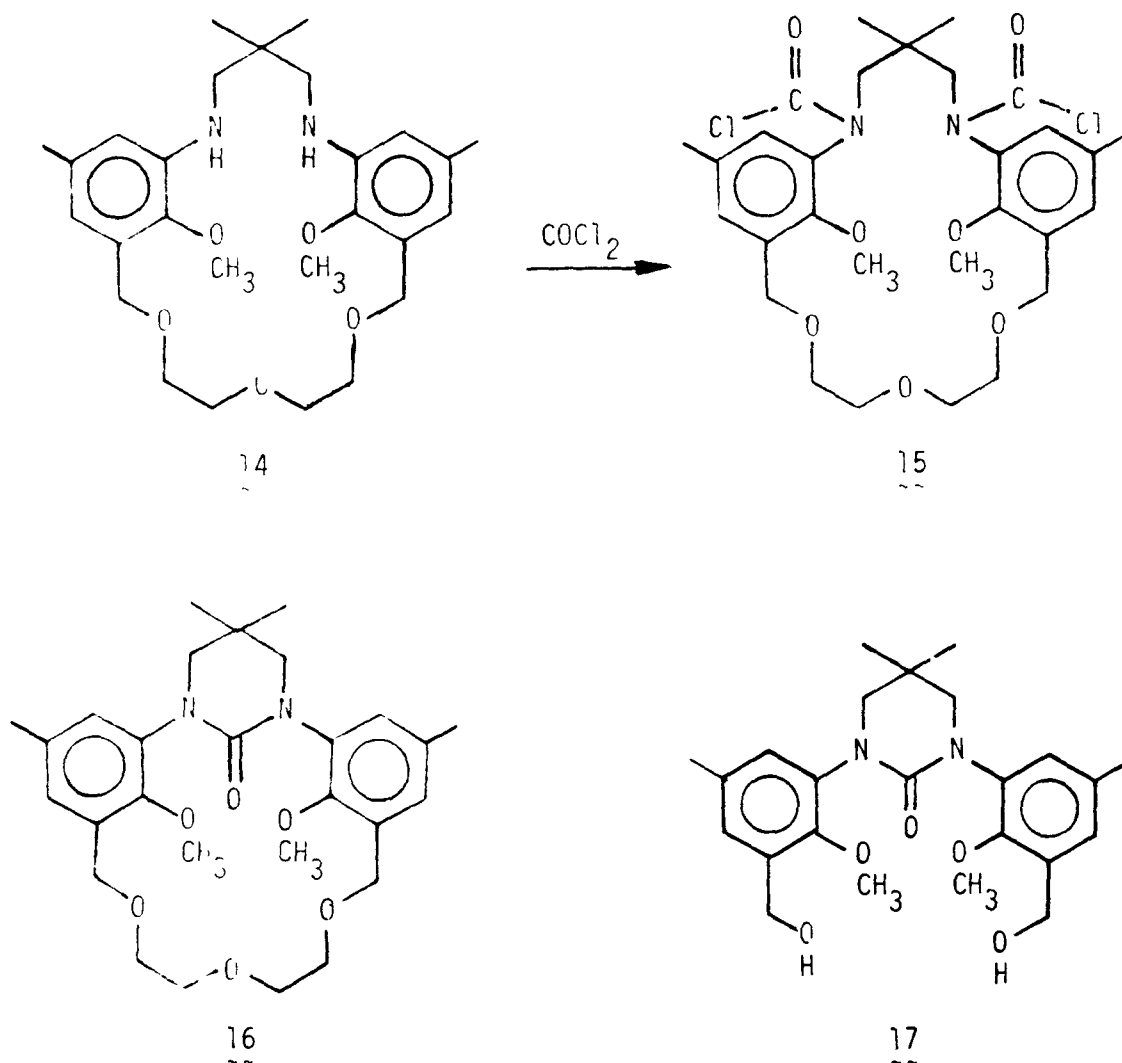
13
~ ~

binding. (5) Four aryloxy units arranged in pairs (as in 10) also greatly depress binding free energies. (6) Appending of an extra oxygen in the additional bridge of 12 increases binding considerably over 11 or 3. System 12 is the best hemispherand binder prepared thus far. (7) Although 13 contains eight oxygens, it is a poorer binder than the hemispherands because this flexible ligand system lacks the organization of the hemispherands. The overall conclusion is that the greater the similarity in organization of the free ligand system and of the complex, the greater the binding free energy.

B. Hemispherands that Include a Cyclic Urea Unit (Ira Dicker)

Some progress has been made in attempts to introduce a cyclic urea unit into a hemispherand in place of the central aryloxy unit of prototype hemispherand 3. Attempts to make target compound 16 by the sequence formulated failed in the last step. Attempts to convert either 14 or 15 to 16 were unsuccessful. Progress has been made toward making 17, a reasonable precursor of 16.

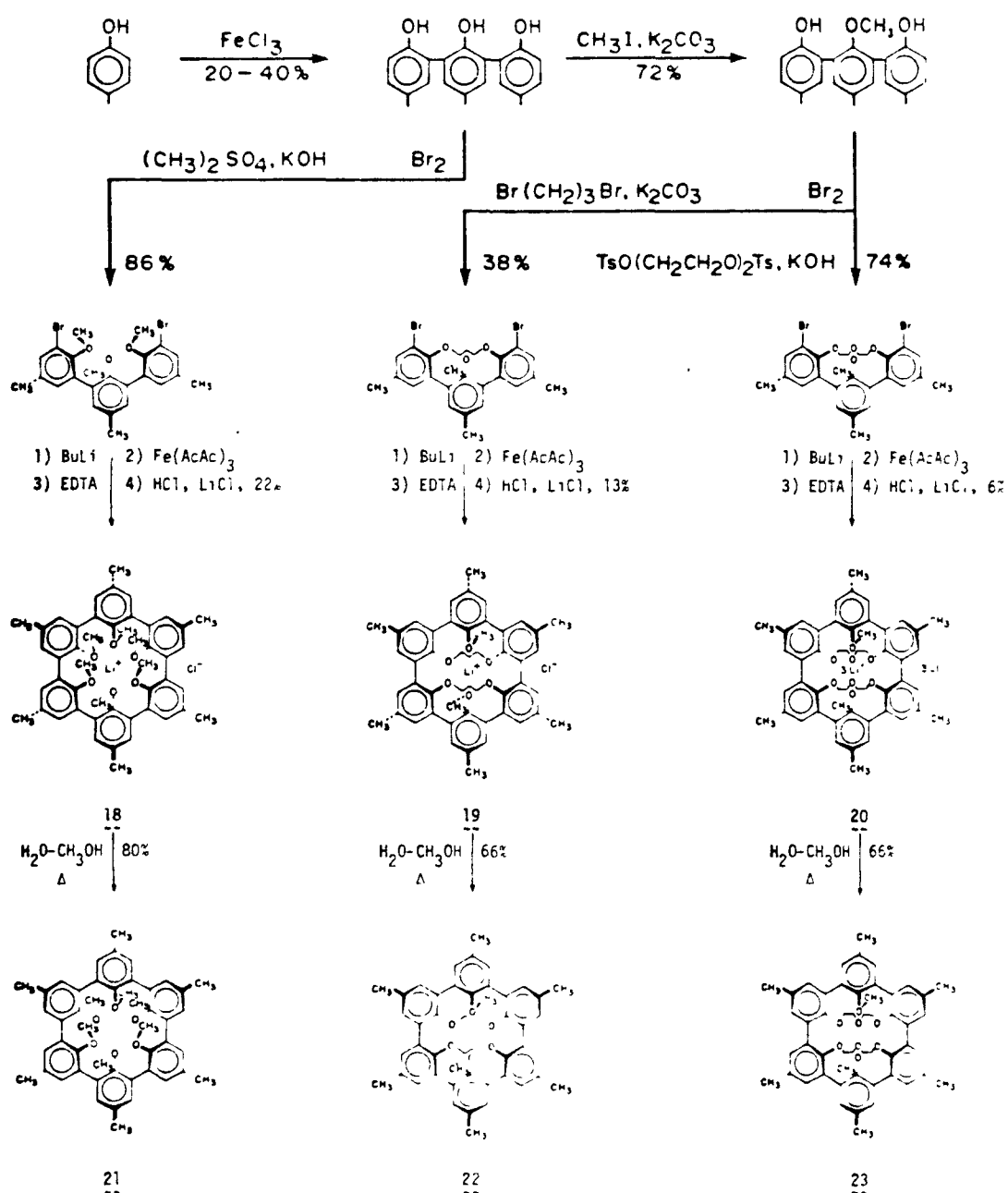




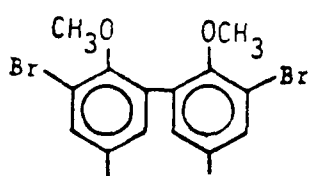
C. Spherands Based on Aryloxy Units Only (Roger Helgeson and George Lein)

Workable quantities of lithiospherium salts 18-20 have been synthesized by the sequence shown. They were freed of LiCl by heating them in CH₂OH-H₂O to give the free spherands, 21-23. The driving force for decomplexation was the crystallization of the free ligand system in each case. The free ligands are very insoluble in the media. Different temperatures and times were required for the decomplexation. Complex 18 required 150 °C for 5 days, whereas 19 and 20 decomplexed in a few hours at 70-100 °C. The complexes, particularly 18, are stable to anion exchange and other common laboratory mani-

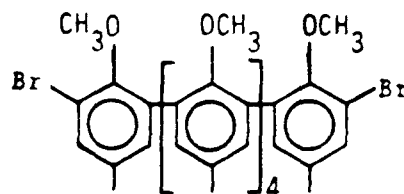
pulations. The overall yield in the synthesis of 21 from p-cresol is about 6%. Lithiospherium chloride 18 has also been prepared in lower ring-closing yields from 24 and 25, although the low yield from 25 involved mechanical difficulties. These ring closures involved invention of a new reaction, the oxidation of ArLi with Fe(AcAc)₃ to give Ar-Ar. Many, many oxidizing agents were tried, of which only Fe(AcAc)₃ gave reasonable yields. The yields increase



with high dilution, and undoubtedly the ring-closing reaction is templated by Li^+ .

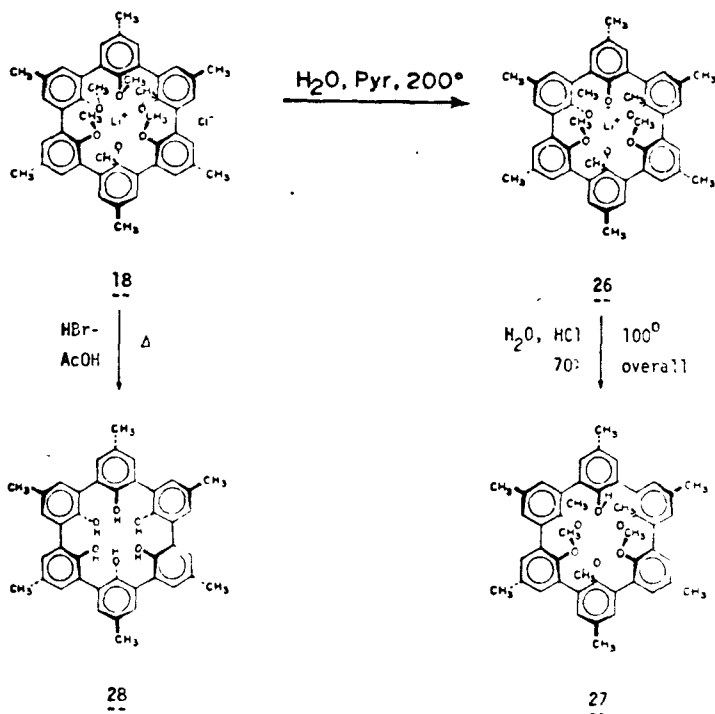


24

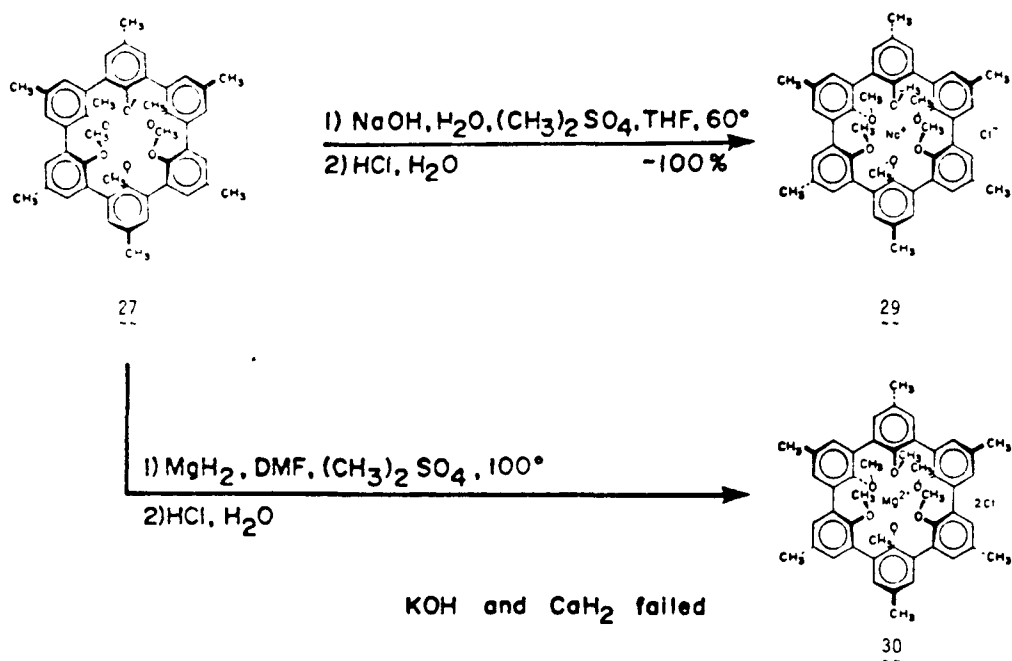


25

When lithiospherium chloride 18 was heated in water-pyridine at 200° , methyl chloride and lithium spheride 26 was formed, which gave the spheranol 27 when heated with $\text{HCl-H}_2\text{O}$ at 100° . When heated with HBr-AcOH , 18 gave the completely demethylated compound 28, which has not yet been thoroughly characterized. The substance is incredibly insoluble and attempts to methylate or acetylate it have produced mixtures of products. The chemistry of 28 should prove interesting.



Sodio- and magnesiospherium chlorides 29 and 30 were formed by encapsulation of the corresponding metallospheride. Attempts to encapsulate K^+ and Ca^{2+} failed and resulted only in scavenging of Na^+ from bulk KOH and CaH_2 .



The X-ray structure of lithiospherium chloride 18 has been completed (K. N. Trueblood, private communication, work not done on this contract), and possesses the C_3 axis indicated in the structure drawn. The 1H NMR spectra of 18-23, 26 and 27 are beautifully simple and unique, and 1H NMR has provided an invaluable tool for following reactions of the compounds. All six compounds are crystalline, are fully characterized, possess high melting points, and all but 21 are reasonably soluble in organic solvents. Spherand 21 is only slightly soluble in organic media.

When $CDCl_3$ solutions of 21, 22, and 23 were mixed with ClO_4^- salts of metals in $(CD_3)_2SO$ to give homogeneous solutions containing about 5% (v) of the latter solvent, complexation of $LiClO_4$ and $NaClO_4$ occurred before the solutions could be observed by 1H NMR. Thus the complexation rate is fast on the human time scale.

In the presence of excess spherand, no observable metal ion exchange occurred between free spherand and metallospherium perchlorate with ^1H NMR as probe. Hence, decomplexation-complexation is slow on the ^1H NMR time scale. With KClO_4 , RbClO_4 , CsClO_4 , $\text{Mg}(\text{ClO}_4)_2$, $\text{Ca}(\text{ClO}_4)_2$, $\text{Sr}(\text{ClO}_4)_2$, $\text{La}(\text{ClO}_4)_3$, and HClO_4 , no complexation was observed. Hence 21, 22, and 23 all show high kinetic or thermodynamic (or both) discrimination between ions, and complex only Li^+ and Na^+ . When 1-mL samples of D_2O that were 3 to 6M in LiBr , NaBr , KBr , RbBr , CsBr , MgBr_2 , CaBr_2 , or SrBr_2 were shaken violently for 24 hr with 1-mL samples of CDCl_3 that were 0.0028M in spherands 21, 22, and 23, only LiBr and NaBr were complexed. For all three spherands, 1:1 complexes were formed and no free spherand was left. With the other salts, Li^+ and Na^+ were scavenged. The free spherands and each metallospherium complex exhibit different chemical shifts in their ^1H NMR spectra. These experiments indicate that only Li^+ and Na^+ have reasonable extraction-complexation rates.

In an extraction-complexation time study, 1-mL portions of D_2O that were 0.2M in LiCl or NaCl were shaken violently at 30° with 1-mL portions of CDCl_3 solutions that were 0.0026M in 21, 22, or 23. Shaking was continued until equilibrium was reached. With LiCl and 21, equilibrium was reached in 763 hr with $\sim 100\%$ ligand complexed; LiCl and 22 took 769 hr, with 93% complexation; LiCl and 23 took 669 hr, with 68% complexation; NaCl with 21 took 76 hr, with $\sim 100\%$ complexation; NaCl with 22 took 20 hr, with 7% complexation; and NaCl with 23 took 124 hr, with $\sim 100\%$ complexation.

In an extraction-decomplexation time study, 1-mL portions of CDCl_3 that were 0.0026 M in lithiospherium chloride complexes 18-20 and their sodiospherium chloride counterparts were violently shaken at 30° with 1-mL portions of D_2O until equilibrium was reached. In 444 hr, 18 was $\sim 0\%$ decomplexed; in 770 hr, 19 was $\sim 100\%$ decomplexed; in 605 hr, 20 was $\sim 100\%$ decomplexed; in

731 hr, the NaCl complex of 21 was 93% decomplexed; in 21 hr, the NaCl complex of 22 was 100% decomplexed; in 84 hr, the NaCl complex of 23 was 15% decomplexed.

These last results provide very rough relative complexation free energy values that fall in the following orders: 21·LiCl is >9 kcal/mol more stable than 22·LiCl, which is ~1 kcal/mol more stable than 23·LiCl; 23·NaCl is 3 kcal/mol more stable than 21·NaCl, which is 4 kcal/mol more stable than 22·NaCl. In preliminary extraction-complexation experiments involving sodium and lithium picrates in water and spherand 22 in CDCl₃, we estimate that $-\Delta G^{\circ}$ of complexation at 30° in CDCl₃ for formation of 22·NaCl is very roughly 14 kcal/mol, and that the value for 22·LiCl is greater than 19 kcal/mol. Very crude estimates for the $-\Delta G^{\circ}$ values (kcal/mol) for complexation are therefore as follows: 22·NaCl, 14; 21·NaCl, 18; 23·NaCl, 21; 23·LiCl, >18; 22·LiCl, >19; 21·LiCl, >28.

These results dramatically illustrate the spherands to be vastly better ligand systems for complexing Li⁺ and Na⁺ than the crowns, and probably better than the cryptands, although direct comparisons with the latter have not yet been made. These spherands are very highly selective for Na⁺ and Li⁺ ions. High selectivity to favor one or the other of these two ions by bridge manipulation can be tailored into the systems. These spherands exclude all other ions tried except Mg²⁺, which can only be complexed by encapsulation.

In the X-ray structure of 18, Li⁺ has a diameter of 1.48 Å. Normally, Na⁺ has a diameter of 1.96 Å, Mg²⁺, one of 1.45 Å, and Ca²⁺, one of 2.05 Å. It appears that our spherands contain enforced holes capable of complexing metal ions only with diameters of less than 2.05 Å, but up to 1.95 Å, and as small as 1.45 Å and possibly less. The results also suggest that only monovalent ions undergo thermal complexation at rates fast enough to be conveniently observed.

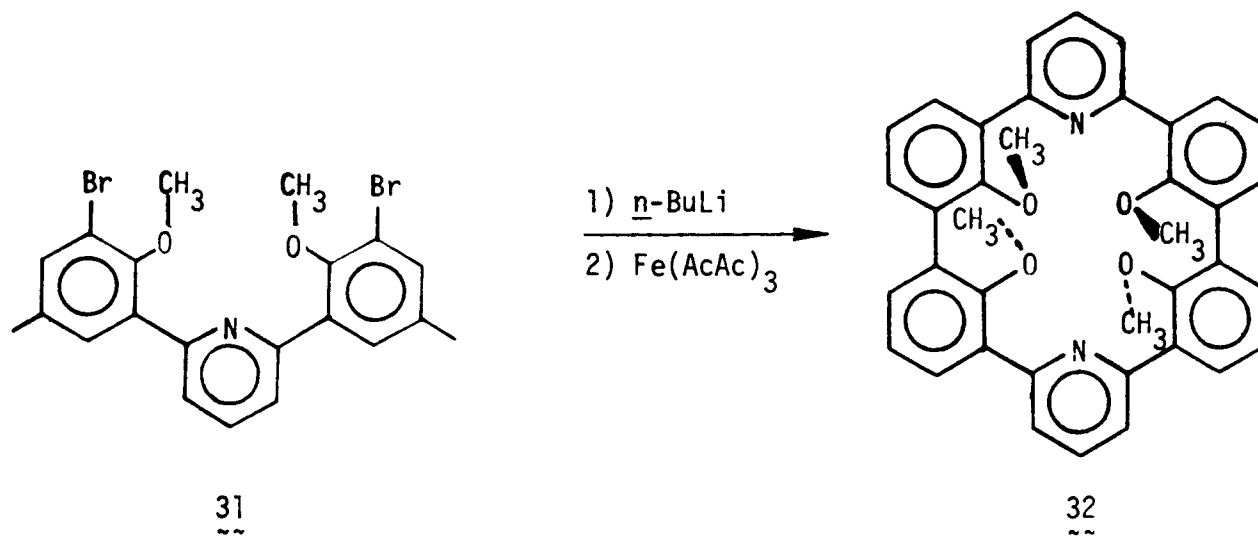
Since anisole units are intrinsically poor ligands, we believe the superb complexing and selecting abilities of the aryloxy spherands reflect

their ideal enforced preorganization in which 24 electrons line a spherical cavity. Complexation probably releases considerable electron-electron repulsion. The results suggest that spherands can be structurally "fine-tuned" to complex selectively a variety of metal ions for a variety of purposes.

An attempt was made to fractionate ${}^6\text{Li}^+$ and ${}^7\text{Li}^+$ by gel permeation chromatography of lithiospherium chloride, 18. The idea involved the tiny differences in the diameters of these isotopes which would be molecularly leveraged into larger differences in diameters of their respective complexes. The ${}^6\text{Li}/{}^7\text{Li}$ ratio in a sample of 18 was measured by mass spectrometry (both Li^+ and lithium spheride ion peak intensities were examined). The sample was then submitted to chromatography on a Waters High Pressure machine on a column with 17,000 plates. The peak that emerged from the column was cut into lead, middle, and tail fractions. The ${}^6\text{Li}/{}^7\text{Li}$ ratios of 18 isolated from each fraction were identical within experimental error to one another, and to the ratio of the starting material. Thus no fractionation was observed.

D. Attempt to Prepare a Spherand Containing Two Pyridine Oxide Units (Roger Helgeson)

Examinations of CPK molecular models for spherand candidates suggest that pyridine oxide units substituted for one or more of the aryloxy units of 18 should lead to interesting new complexing agents. Attempts to convert 31 to 32 failed, possibly due to addition of $n\text{-BuLi}$ to the substituted pyridine unit.



IV. Cooperation with other DOE Contractors

Because of the slow extraction-decomplexation rates of LiCl and 21-23, we doubt that they will be useful in the Mound Laboratory isotope separation process without structural modification (Bernard Jepson). When we have increased these rates by structural modification, we will communicate with him on possible uses of our compounds for this purpose.

V. Educational Profit from this Contract

A new field of organic host-inorganic guest chemistry is being developed under this contract. One carefully chosen postdoctoral research chemist, several graduate students, and the principal investigator are learning the science and art of multiheteromacrocyclic synthesis and enough inorganic chemistry to design their own ligand assemblies. As time goes by, this same group will develop new test systems to determine the complexing properties of the systems synthesized. A whole new way of thinking about organic-inorganic chemistry is evolving, and this research group is cultivating a field that will attract many other research groups.

VI. Research Publications Resulting from Work Done Under this Contract

1. Host-Guest Complexation. 15. Macrocyclic Acetylacetone Ligands for Metal Cations, J. Amer. Chem. Soc., 101, 3545 (1979), by A. H. Alberts and D. J. Cram.

2. Host-Guest Complexation. 16. Synthesis and Cation Binding Characteristics of Macrocyclic Polyethers Containing Convergent Methoxyaryl Groups, J. Amer. Chem. Soc., 101, 3553 (1979), by K. E. Koenig, G. M. Lein, P. Stuckler, T. Kaneda, and D. J. Cram.

3. Host-Guest Complexation. 17. Design, Synthesis and Complexation of Macrocycles Containing Phosphoryl, Pyridine Oxide, and Urea Binding Sites, J. Org. Chem., 44, 2226 (1979), by L. J. Kaplan, G. R. Weisman, and D. J. Cram.

4. Host-Guest Complexation. 18. Effects on Cation Binding of Convergent Ligand Sites Appended to Macrocyclic Polyethers, J. Amer. Chem. Soc., 101, 4928 (1979), by R. C. Helgeson, G. R. Weisman, J. L. Toner, T. L. Tarnowski, Y. Chao, J. M. Mayer, and D. J. Cram.

5. Host-Guest Complexation. 19. Cyclic, Bicyclic, and Tricyclic Polyether Systems, J. Org. Chem., 44, 2538 (1979), by R. C. Helgeson, T. L. Tarnowski, and D. J. Cram.

6. Spherands-Ligands whose Binding of Cations Relieves Enforced Electron-Electron Repulsions, J. Amer. Chem. Soc., 101, 6752 (1979), by D. J. Cram, T. Kaneda, R. C. Helgeson, and G. M. Lein.

7. A Spherand Containing an Enforced Cavity that Selectively Binds Lithium and Sodium Ions, J. Chem. Soc. Chem. Commun., 21, 948 (1979), by D. J. Cram, T. Kaneda, G. M. Lein, and R. C. Helgeson.

Papers 1-5 are full length and summarize all of the work done in the first three years of this contract and much of the fourth. Communications 6 and 7 report work done partly during the fourth and largely during the fifth years of this contract.