SAN-34/P218 X4

MASTER

Fourth Progress Report for ERDA Contract AT(04-3)34, P. A. 218

MULTIHETEROMACROCYCLES THAT COMPLEX METAL IONS

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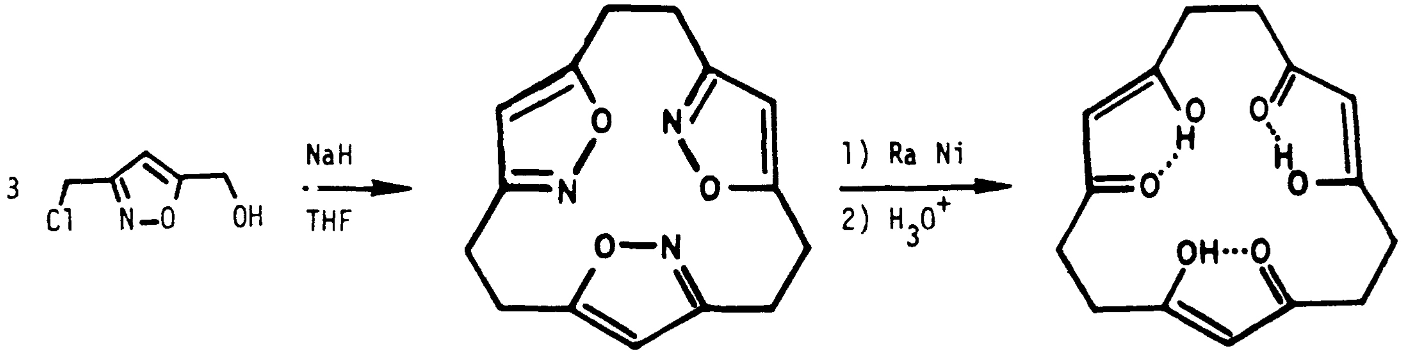
The 1977-1978 Research Accomplishments
Supported by ERDA Contract AT(04-3)34, P. A. 218

Synopsis of Research Done Under the Grant Since its Inception

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 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 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; numbers of binding sites; characters of binding sites; valences. In the 44.5 months since the inception of this contract (1 May 1974) and in the remaining 3.5 months of this project year, the specific goals and accomplishments are as follows. (1) We have synthesized in small quantities and have characterized macrorings $(OCH_2CH_2CH_2COCH_2COCH_2CH_2CH_2)_n$ (1) and $(CH_2C_6H_4\text{-}\underline{m}\text{-}CH_2CH_2COCH_2COCH_2)_n$ (2) as well as their noncyclic model compounds $O(CH_2CH_2CH_2COCH_2COCH_3)_2$ (3) and $\underline{m}\text{-}C_6H_4(CH_2CH_2COCH_2COCH_3)_2$ (4). The stability constants ($K^f_{av.}$) in dioxane-water at 25^o of these ligand assemblies with divalent ions were determined. Their values decreased for 1-4 (except where noted, see below) in the order $Cu^{2+} > UO_2^{2+} > CO^{2+} > Zn^{2+} > Pb^{2+} > Cd^{2+} > Mg^{2+} > Ca^{2+} > Sr^{2+} > Ba^{2+}$. Exceptions involved 1 where $Ca^{2+} > Cd^{2+}$, 2 where $Cd^{2+} \sim Ca^{2+} > Mg^{2+}$. Log $K^f_{av.}$ values ranged from 12.0 to 2.5. Values of log $K^f_{av.}$ for 1 and 2 were greater than for acetylacetone by amounts that ranged from 1.6 to 4.1. The differences between cycles 1 and 2 and models 3 and 4 ranged from 0.6 in one direction (e.g., model better complexer than cycle) to 0.9 in the other (e.g., cycle better than model). (2) We prepared cycle 5 which we had hoped would be a precursor of 6, a potential ligand assembly for the lanthanides. However, we abandoned this approach to 6 because of the high dermatological toxicity of the chloroalcohol starting material and the resistance of 5's reduction to 6. (3) Ligand assemblies 7 and 8 have been prepared. Whereas 7 was only moderately good, 8 was superb as a complexer and lipophilizer of a variety of metal ions. A practical synthesis



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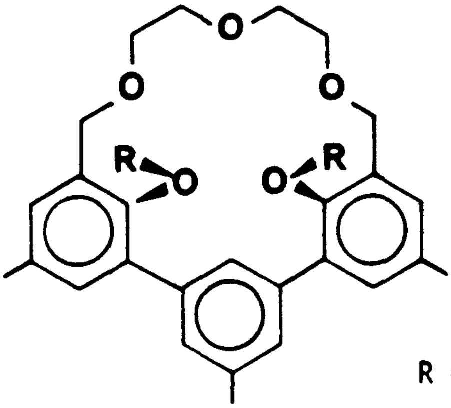
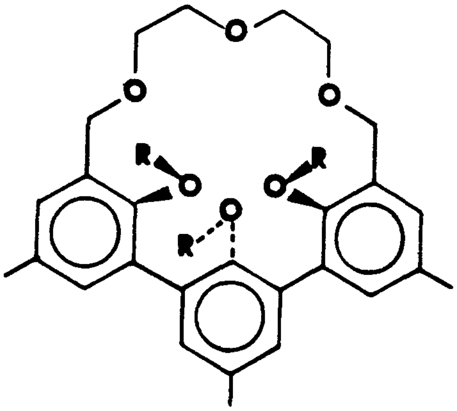


R = CH_3

7



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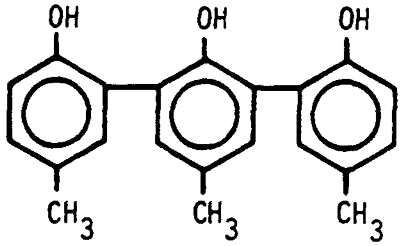
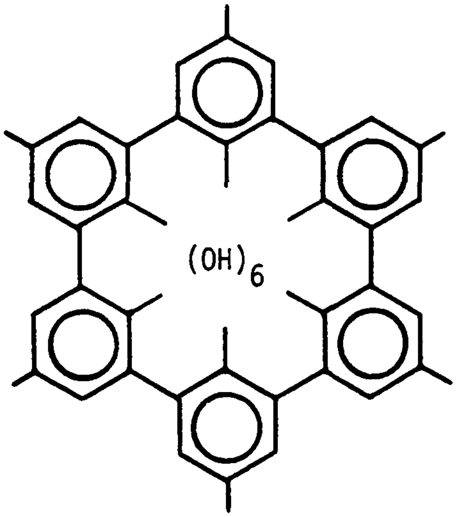


9

of 9 has been developed which is a key intermediate for synthesis of many important ligand systems. A concerted effort to convert 9 to 10 by oxidative coupling involving many oxidants has led to 10 in amounts observable only by mass spectrometry (< 0.001% yields). In another approach to the greatly desired metahexaarylene system, 9 was converted to 11 which was subjected to a large number of Ullmann-type coupling reactions. Only < 0.001% yields of cycles 12, 13, and 14 were obtained, characterized by their mass spectra. The excellent complexing properties of 8, coupled with the formations and stabilities of 13-15 to the high temperatures in the spectral inlet, indicate that 12 will be the supreme metal-ion complexing agent. Its perfectly enforced octahedral arrangement of oxygens whose 12 electron pairs form a cavity of 1.2 to 3.0 Å diameter (depending on aryl-aryl dihedral angles) makes it mandatory that we synthesize it and study it and its analogues. In an attempt to prepare 16, its isomer 17 was obtained. Compound 17 proved to be a poor complexer, which confirmed expectations based on molecular model examination. A practical synthesis of 18 has been developed which we expect will lead to 10 and 12. (4) Compounds 19 and 20 have been prepared (the former,



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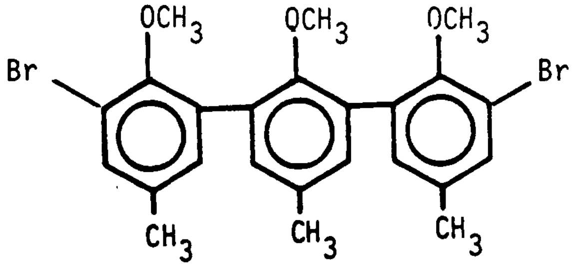

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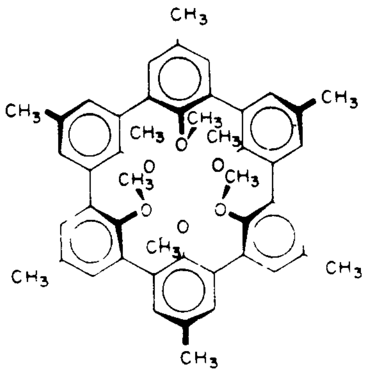

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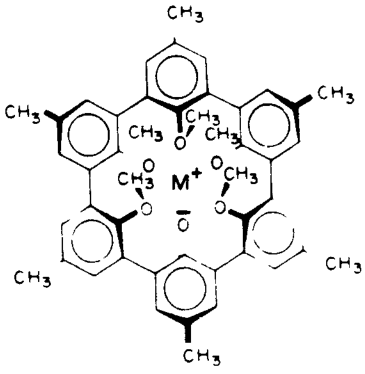
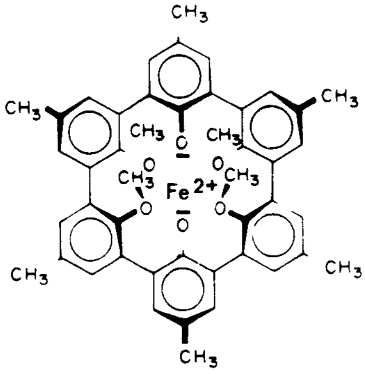


13, M = Li

14, M = Na



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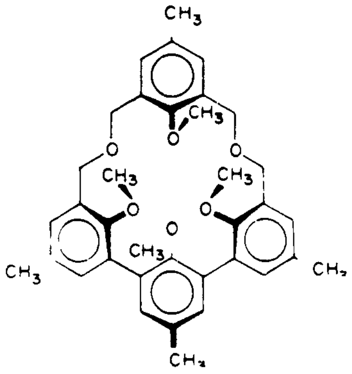

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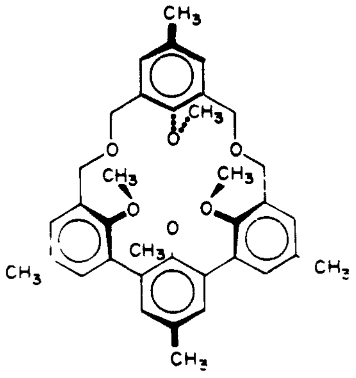
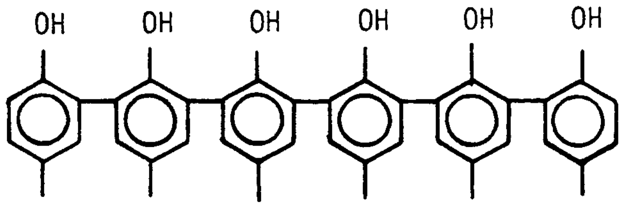
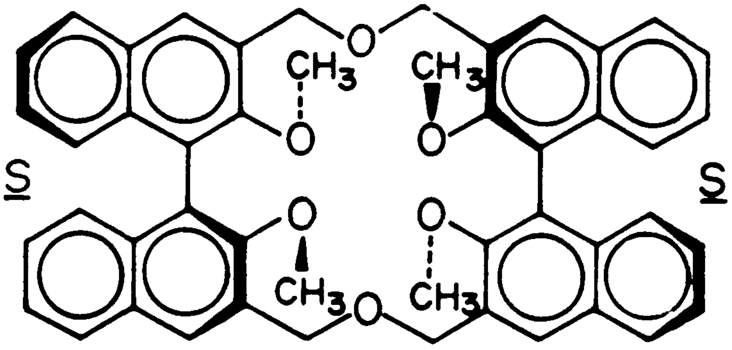


17



18

pure, the latter, as a mixture of diastereomers) for testing as potential small ion binders and lipophilizers. Molecular models indicate that the four OCH_3 oxygens of 19 and 20 of the right configurations form a cavity surrounded by eight electron pairs arranged in an elongated tetrahedron. Attempts to encapsulate Li^+ ion in the cavity are in progress. (5) Compounds 22-27 have been prepared, and their complexation constants determined in $CHCl_3$ with Li^+, Na^+, K^+, Rb^+, and Cs^+ picrates. Although not superb binders, interesting differences in the binding properties of the above ions were observed. (6) Prototype compounds 28 and 29 have been prepared and found



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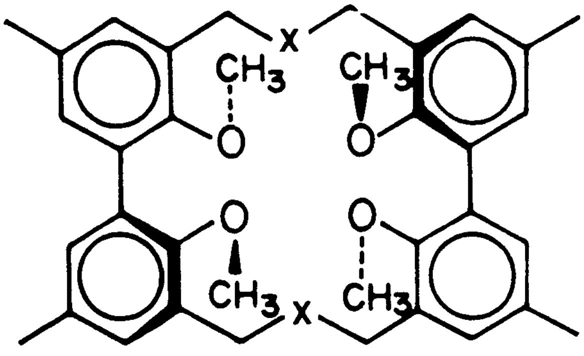
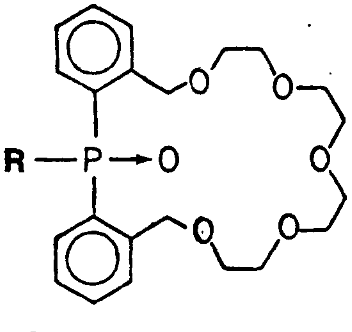
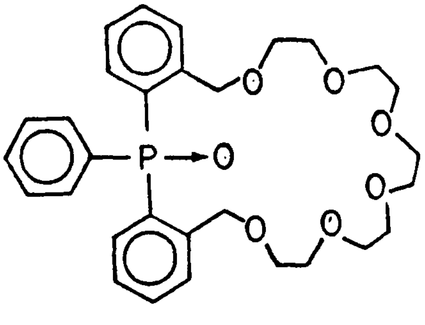


20, X = O
21, X = S



22, R = C_6H_5
23, R = $o\text{-}HO_2CC_6H_4$
24, R = $o\text{-}CH_3O_2CC_6H_4$
25, R = OCH_3



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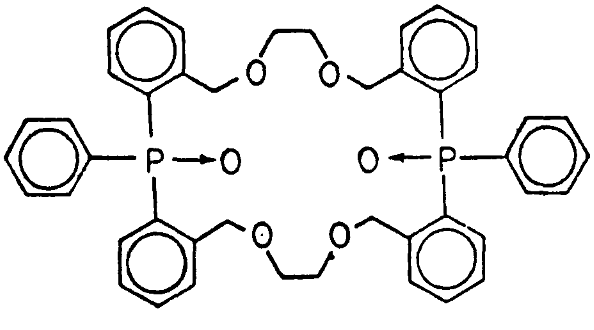
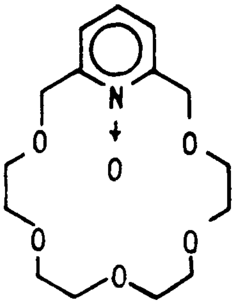


27 (both isomers)

to be only average metal complexers. (7) Macrocycles 30-32 and model compound 33 have been prepared, and their binding and lipophilizing properties toward metal ions compared. Compounds 30 and 31 are among the best binders and lipophilizers we have tested, and 30 shows a spread of about 5 kcal/mol in binding energies in $CHCl_3$ between our standard monovalent ions. These two compounds and 7 are the best metal binders and lipophilizers we have yet prepared. Compounds 34 and 35 prepared on other grants for other purposes, and compound 36 prepared on this grant, were also examined for their complexing abilities and were found to be very good, but not excellent, metal complexers and lipophilizers.



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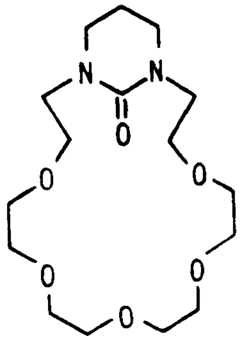

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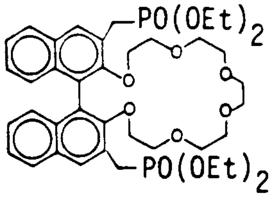

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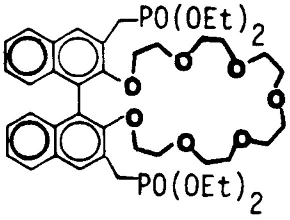

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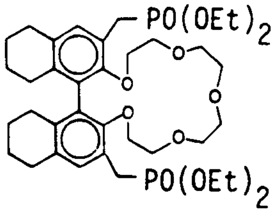

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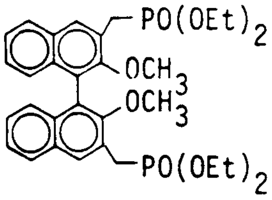
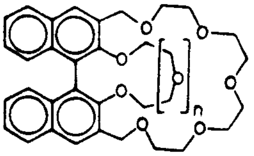
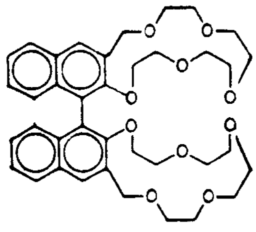


33



34, n = 6



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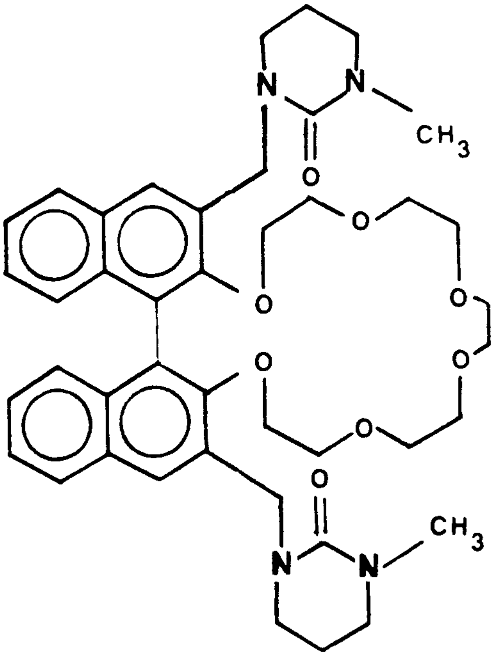

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Personnel

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 C. Helgeson, Assistant Research Chemist I, was employed 100% of full time on this project for four months. He has had eight post-doctoral years' previous experience in the synthesis of macroring compounds, three of which were with multiheteromacrocycles.

3. Dr. Takahiro Kaneda, Postgraduate Research Chemist I, was employed 73% of full time on this project for twelve months. He obtained his Ph.D. degree at the University of Osaka in 1974.

4. Mr. Alan Laibelman, Postgraduate Research Chemist III, was employed 41% of full time on this project for seven months.

5. Mr. John Toner, Postgraduate Research Chemist IIIand Ph.D. candidate at UCLA, was employed 43% of the time for 10 months.

6. Mr. Lester Kaplan, Postgraduate Research Chemist III, was employed 41% of full time on this project for five and one-half months.

7. Dr. Peter Stuckler, who obtained his Ph.D. degree at the Munich Technical University in 1976, spent eight months of his time on this project, although he was supported on a NATO Fellowship. Part of his storeroom bill was paid out of this contract.

8. Mr. George Lein, a Ph.D. candidate at UCLA supported on a departmental fellowship, spent about 20% of his time on this project, and part of his storeroom bill was paid out of this contract.

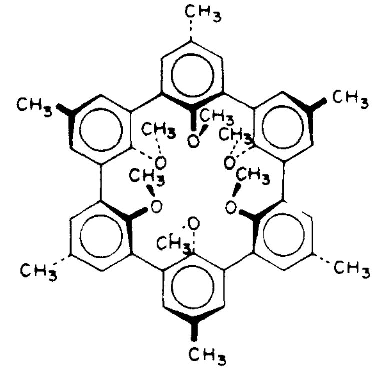
9. Mr. Paul Cheng, Research Assistant and Ph.D. candidate at UCLA, was employed 47% of full time on this project for three months.

Research Results Obtained for this Reporting Period Only

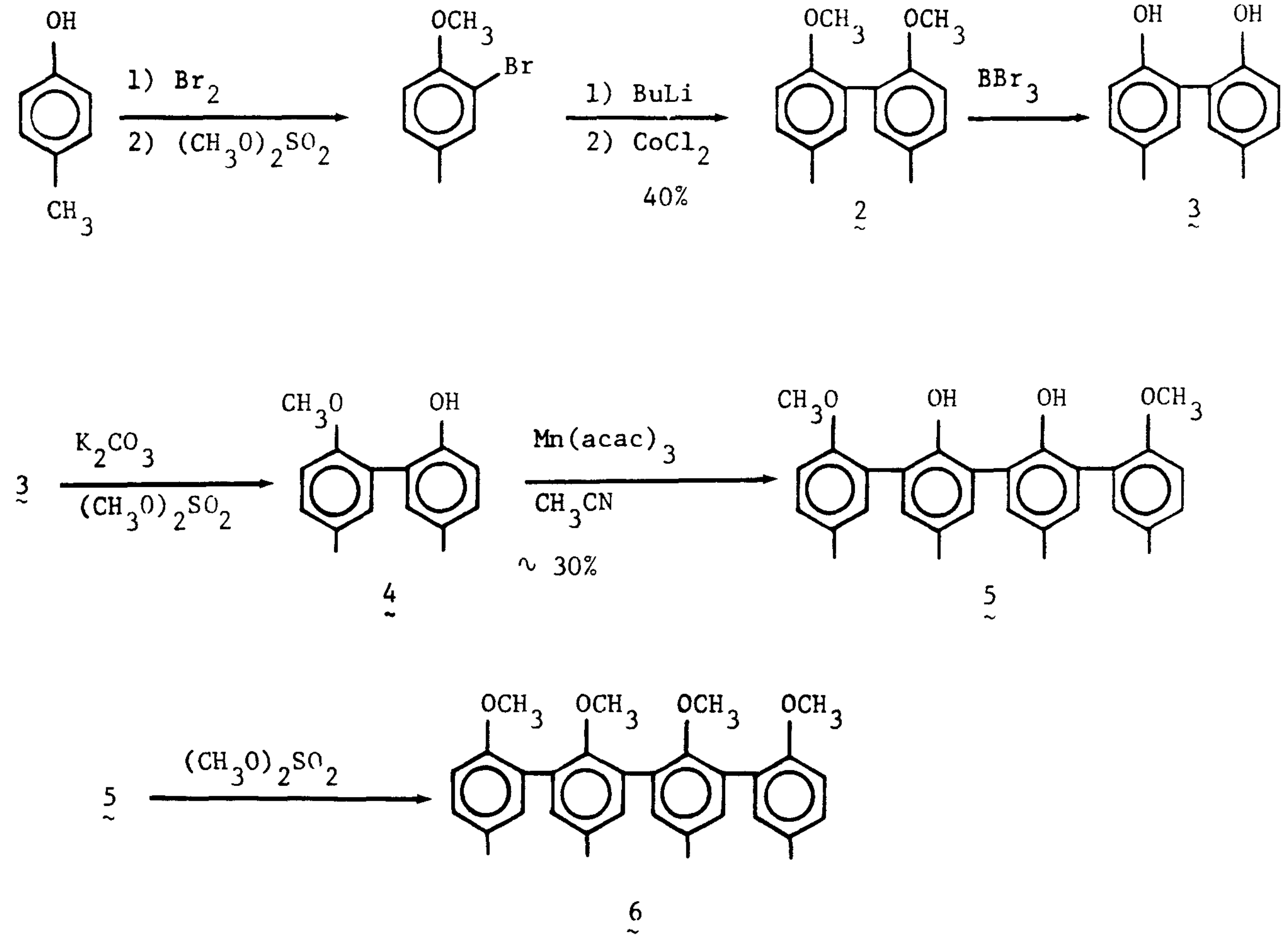
1 May 1977 through 30 April 1978

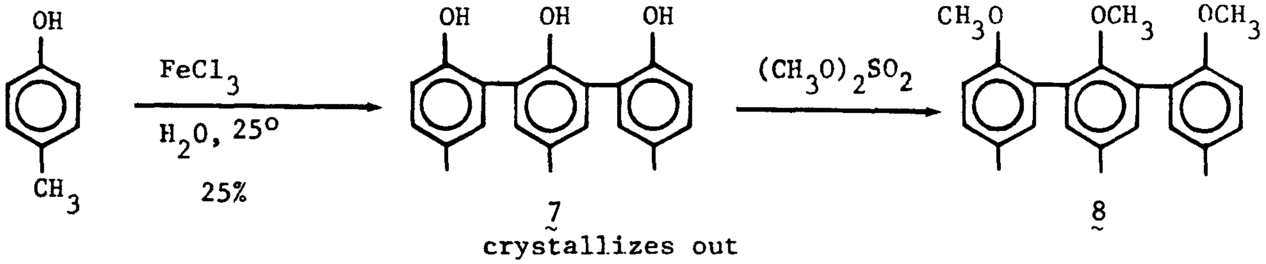
A. Synthesis and Study of Substituted Cyclohexametaphenylenes (with Takahiro Kaneda, Peter Stuckler, Roger Helgeson, and George Lein)

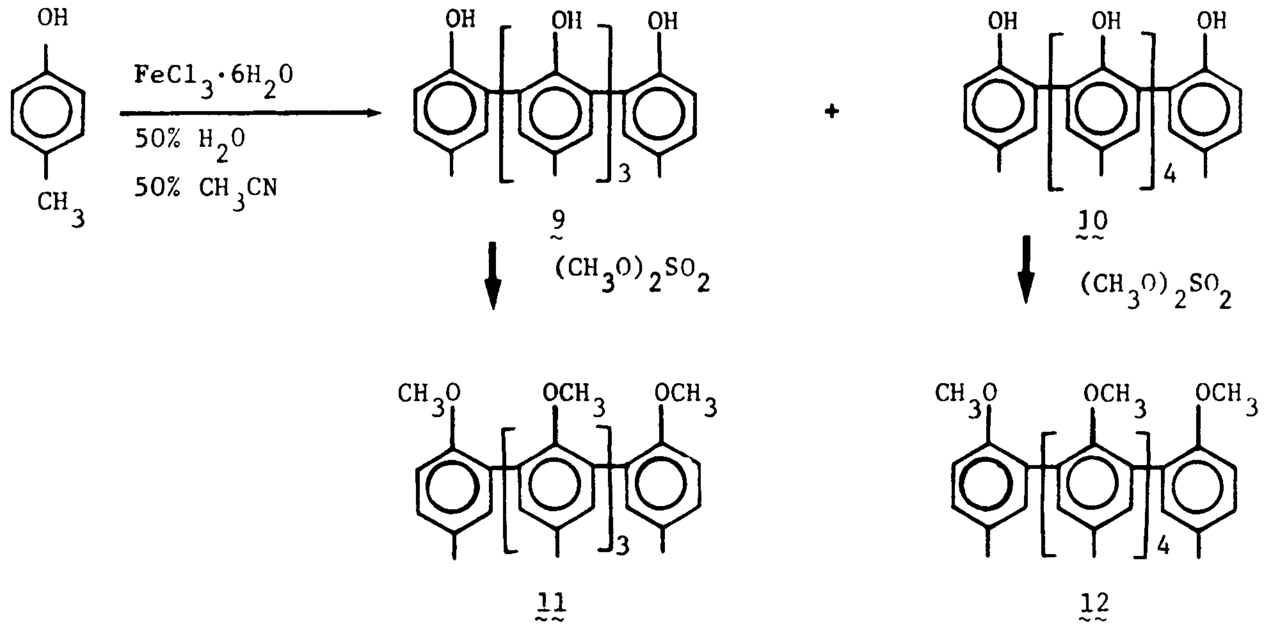
Phenoxides and their ether derivatives are good ligands for metal ions, and aryl groups resist radiation damage. We have made a concerted effort to incorporate phenols and their ether derivatives into macrocycles whose covalent bonds provide good organizations of ligands and valence sites. The protype compound to prepare is **1**. Molecular models (CPK) of **1** indicate an enforced structure in which six oxygens alternate up and down and form a perfect octahedral cavity composed entirely of oxygen electron pairs. The cavity size depends on the dihedral angles between the benzene rings, and in CPK molecular models can vary from about 1.2 to 3.0 Å in diameter. The least strained diameter appears to be about 2 Å. We believe that **1**, its derivatives and analogues, will strongly complex and lipophilize most of the metal ions of the periodic table. Accordingly, a major effort has been made to prepare in the best possible yields from the cheapest starting materials, the key intermediate compounds for preparing **1** and its analogues. Past results have demonstrated that only by direct attachment of aryl-to-aryl units is it possible to get the sterically enforced preorganization of binding sites necessary to good complexation and lipophilization of metal ions. Therefore, we have tried hard to develop viable methods of preparing from *p*-cresol (inexpensive) compounds **2**-**12**. Compounds **3**, **4**, **7**, **8**, **10**, and **12** can be made relatively easily, **5** requires more steps, and **9** has been obtained in only very small quantities.


CH₃
CH₃
CH₃
CH₃
CH₃
CH₃
CH₃O
CH₃O
CH₃O
CH₃O
CH₃O
CH₃O

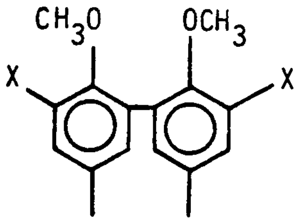
1


OH
CH3
1) Br2
2) (CH3O)2SO2
OCH3
Br
1) BuLi
2) CoCl2
40%
OCH3 OCH3
2
BBr3
OH OH
3
3
K2CO3
(CH3O)2SO2
CH3O OH
4
Mn(acac)3
CH3CN
∿ 30%
CH3O OH OH OCH3
5
5
(CH3O)2SO2
OCH3 OCH3 OCH3 OCH3
6

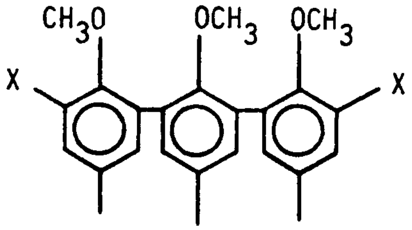

OH
CH3
FeCl3
H2O, 25°
25%
OH OH OH
7
crystallizes out
(CH3O)2SO2
CH3O OCH3 OCH3
8



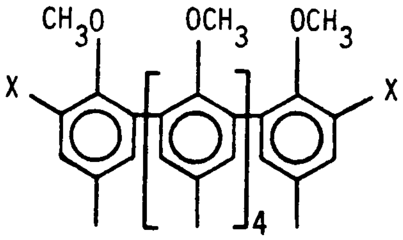
From 2, 7, and 10 by conventional conversions, we have prepared 13-18. Attempts to form cycle 19 from 14 and various metal reducing agents failed, probably for steric reasons.



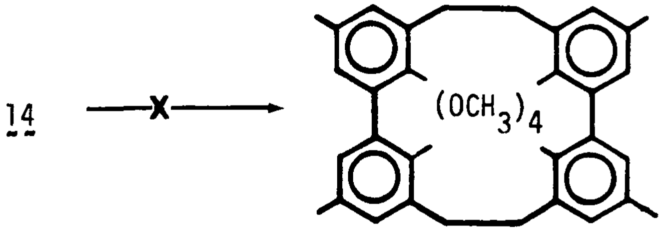
13, X = CH_2OH
14, X = CH_2Br
15, X = CH_2SH



16, X = Br
17, X = CH_2OH



18, X = Br



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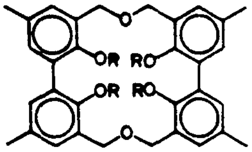
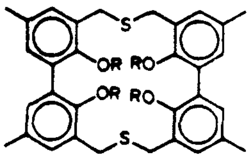
Cycles 20 and 21 were prepared as shown in 18% yields, 20 as a mixture of diastereomers, and 21 as a single diastereomer. We do not as yet know the configurations of the compounds. We do know, however, that if they complex Li^+ picrate$^-$ well in $CDCl_3$, we have not yet been able to get the metal into its encapsulated state.

$$13 + 14 \xrightarrow[18\%]{NaH}$$



20, R = CH_3

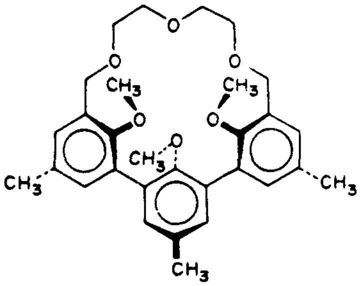
$$14 + 15 \xrightarrow[18\%]{NaH}$$



21, R = CH_3

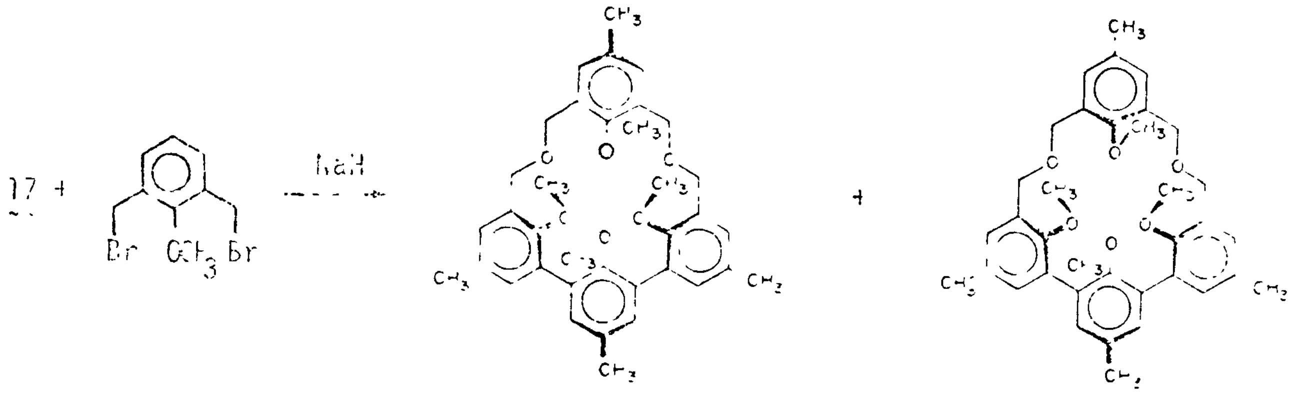
From 17 has been prepared cycles 22 and 23, both of which have been fully characterized and examined for their metal ion binding abilities. Host 22 is the best metal complexer-lipophilizer we have prepared thus far, whereas 23 is only moderately good. Molecular models (CPK) indicate that 23 should be a poor complexer. We had hoped to get 24, an isomer of 23, which should be an excellent binder (molecular model examination), but none was produced. We have not been able to thermally isomerize 23 to 24.

$$17 \xrightarrow[NaH]{TsOCH_2CH_2OCH_2CH_2OTs}$$



22

~ 35%



23

25%

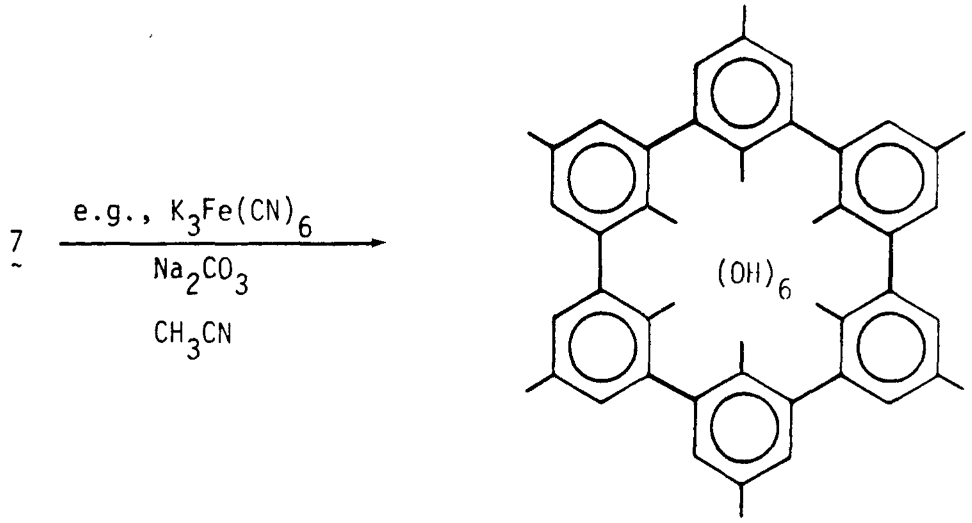
24

0%

Our association constants and free energies of binding picrate salts in $CHCl_3$ at 25^o for 22 and 23 are as follows.

	22		23	
M^+	K_a	ΔG(Kcal/mol)	K_a	ΔG(Kcal/mol)
Li	1.79×10^5	-7.16	812	-5.36
Na	1.46×10^9	-12.5	4.86×10^5	-7.75
K	1.15×10^9	-12.4	6.62×10^4	-6.57
Rb	4.57×10^7	-10.4	8.70×10^3	-5.37
Cs	3.68×10^6	-8.95	8.86×10^3	-5.35
NH_4	1.45×10^7	-9.77	1.03×10^4	-5.47
CH_3NH_3	5.70×10^5	-7.80	7.7×10^3	-5.30
t-$BuNH_3$	4.2×10^5	-7.67	73	-2.54

Many attempts to oxidatively ring close two moles of **7** to give cycle **25** gave only traces of product, characterizable only by its sublimation and mass spectrum (less than 1 mg). Many attempts to reductively ring close two moles of **16** by Ullmann-type reactions led to trace amounts of **1** and its demethylated salts, **26**-**28**, characterized only mass spectrometrically.



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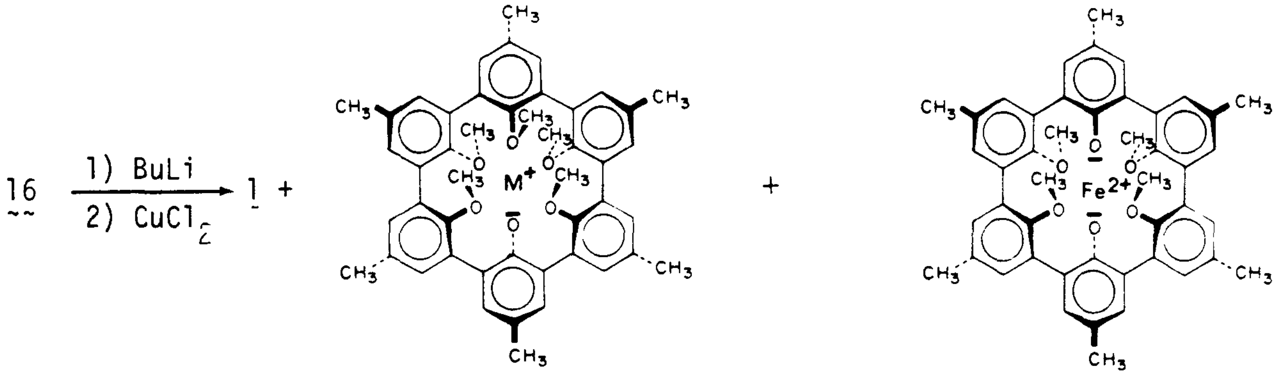


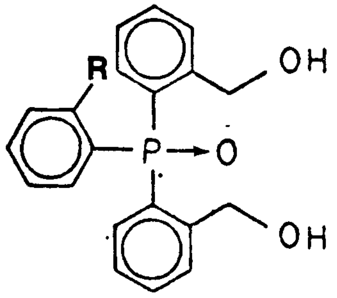
26, M = Li

27, M = Na

28

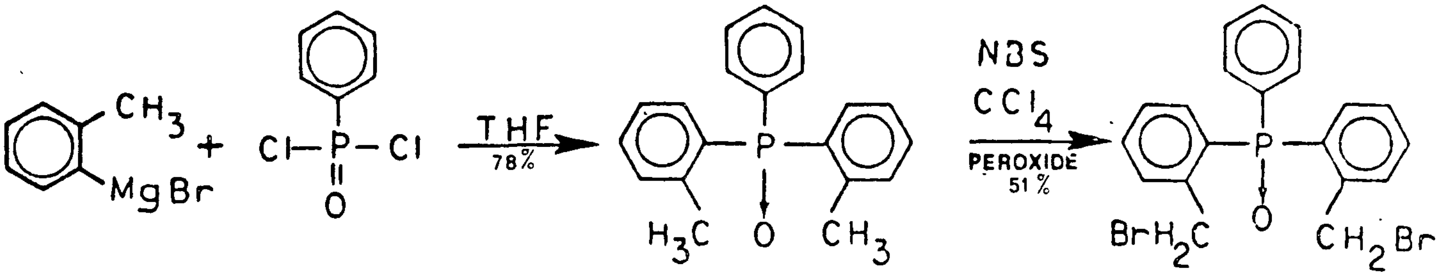
B. Synthesis and Study of Cyclic Phosphine Oxides (with Lester Kaplan)

The phosphoryl group (abcP=O) has been shown to be a good ligand for alkali, alkaline earth, transition and actinide metal salts, particularly when a, b, and c are alkyl or aryl groups. Examination of CPK molecular models indicated that the placement of oxygens in unit A is spacially about the equivalent of their placement in a diethylene glycol unit. Consequently, we incorporated this unit into six macrocyclic rings and determined the binding constants and lipophilizing abilities of these ligand assemblies toward a standard set of metal ions.

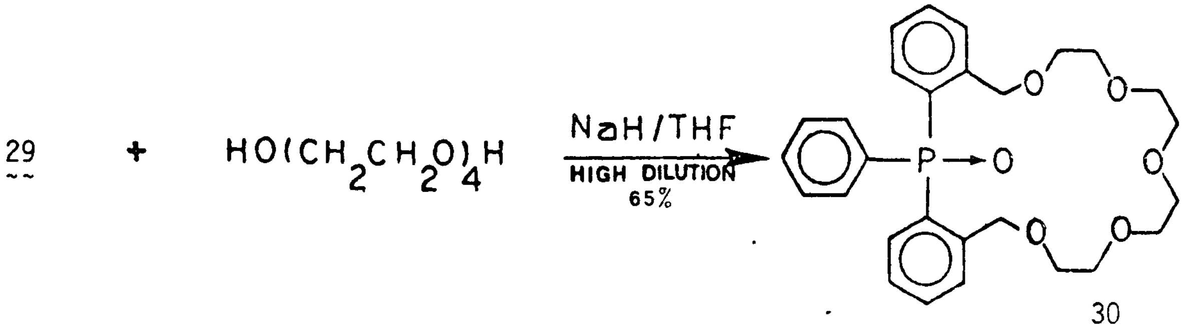


A

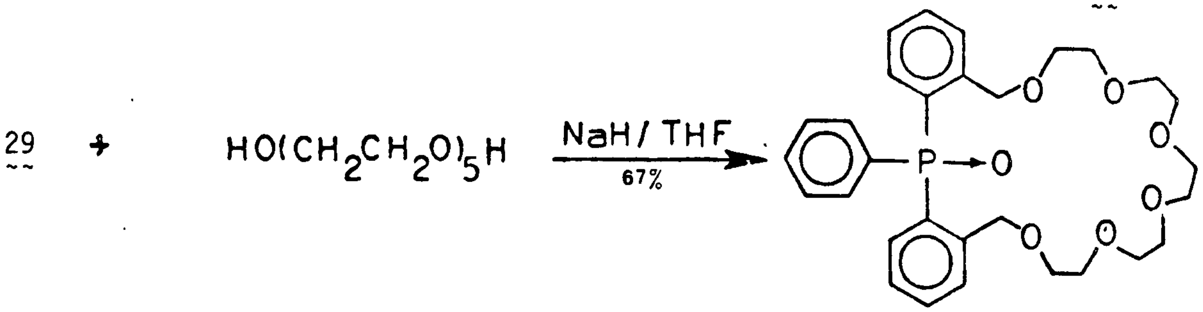
The syntheses were carried out as outlined on the next page, with the yields written under the arrows.



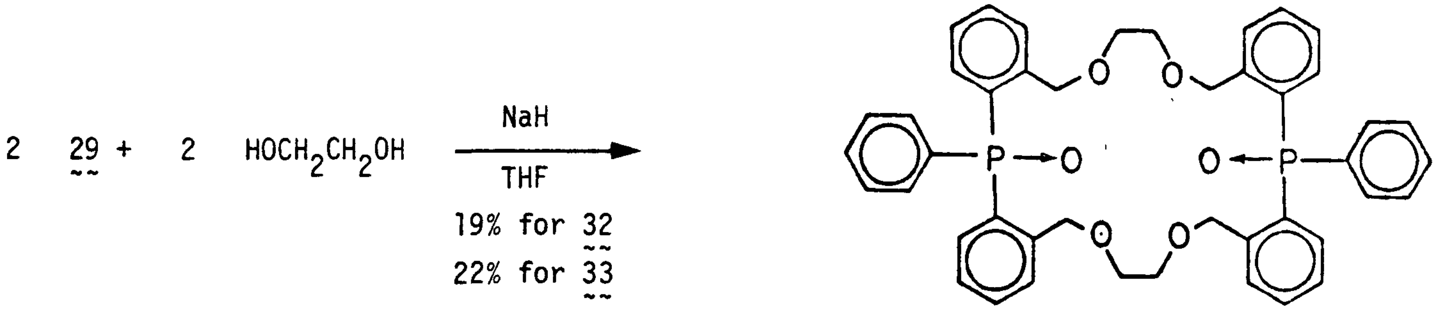
29



30

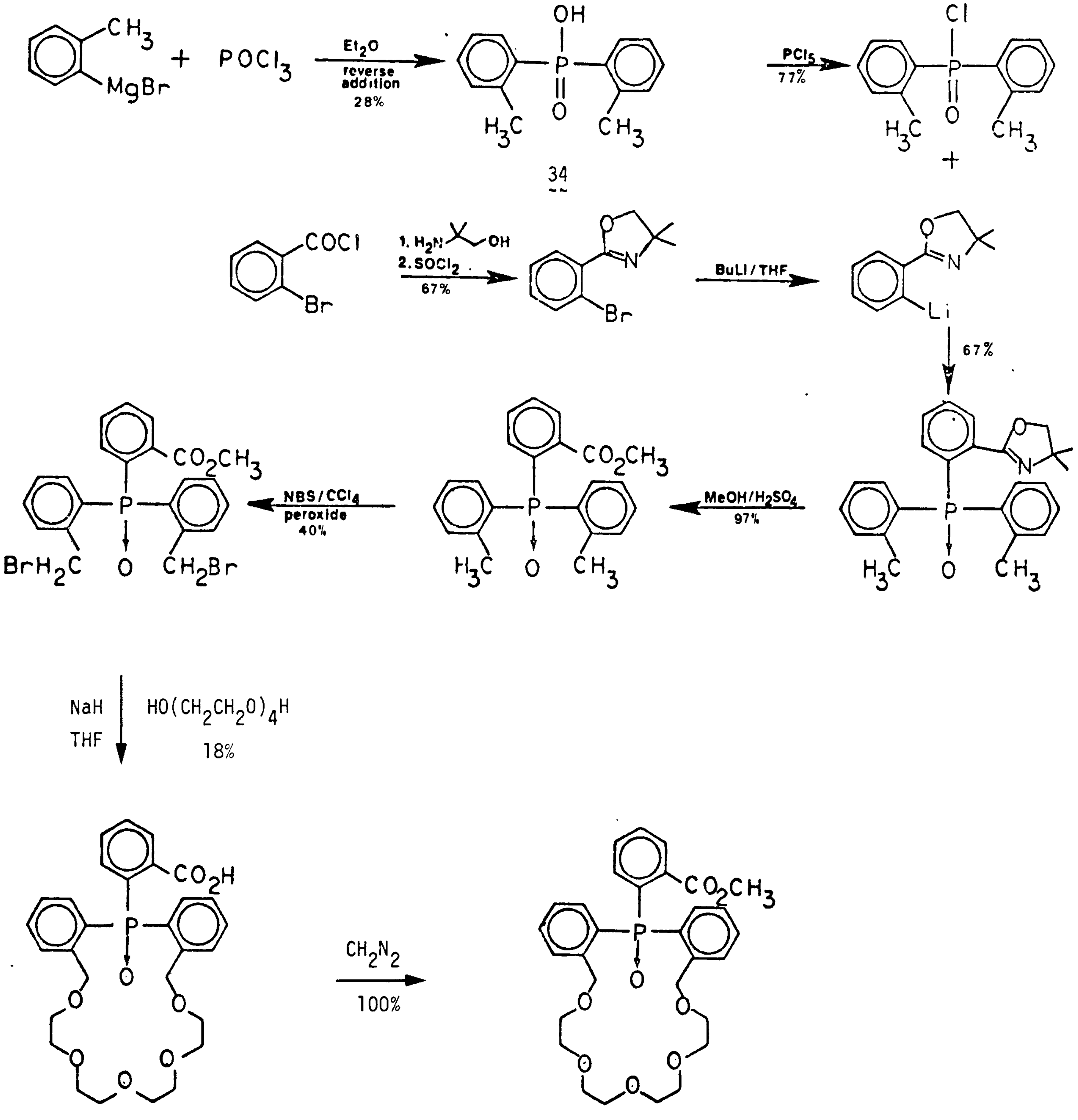


31



32, isomer mp 199-202°

33, isomer mp > 320°

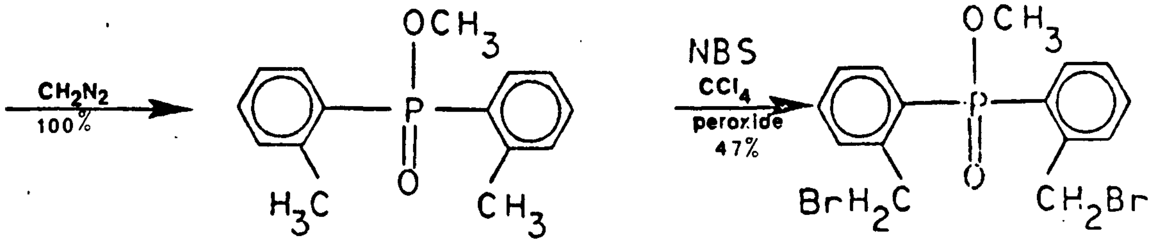

CH3
MgBr
+
POCl3
Et2O
reverse addition
28%
OH
P
O
H3C
CH3
PCl5
77%
Cl
P
O
H3C
CH3
+
COCl
Br
1. H2N OH
2. SOCl2
67%
O
N
Br
BuLi/THF
O
N
Li
67%
O
N
P
O
H3C
CH3
MeOH/H2SO4
97%
CO2CH3
P
O
H3C
CH3
NBS/CCl4
peroxide
40%
CO2CH3
P
O
BrH2C
CH2Br
NaH
THF
HO(CH2CH2O)4H
18%
CO2H
P
O
O
O
O
O
O
CH2N2
100%
CO2CH3
P
O
O
O
O
O
O

34

35

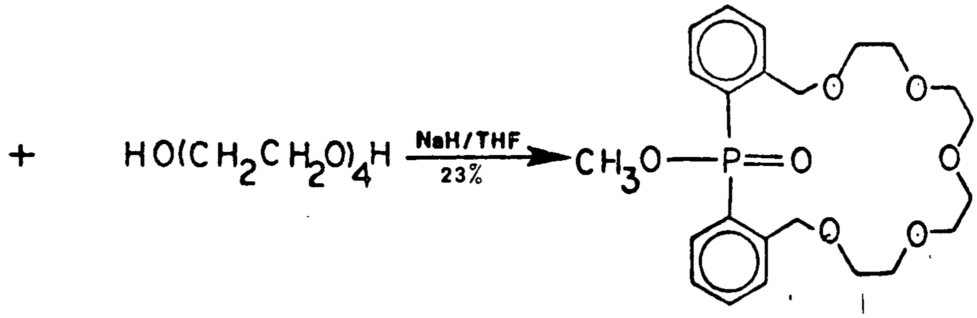
36

34



37

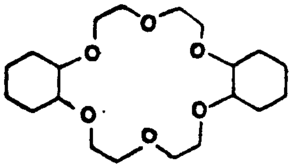
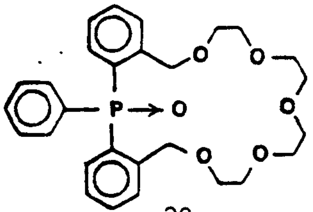
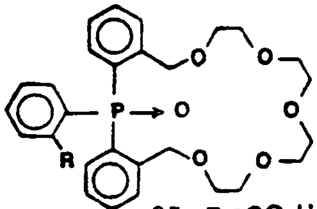
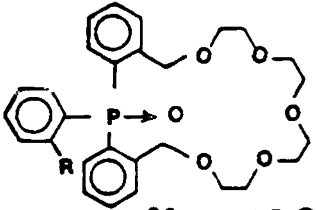
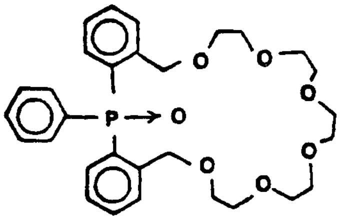
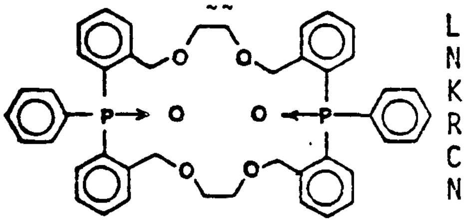
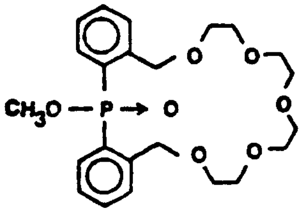
37



38

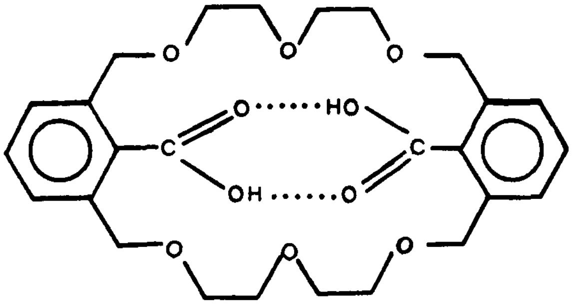
The association constants and free energies of complexation of cycles **30**, **35**, **36**, **31**, **32**, and **38** with M^+ picrates$^-$ in $CHCl_3$ at 25°C are listed, along with those of the dicyclohexyl-18-crown-6 standard. Disappointingly, the results indicate that in all cycles containing the P=O unit in place of a CH_2OCH_2 unit, the binding decreases. We believe this inferiority arises out of the lack of enforced preorganization of the P=O group in these new cycles rather than in intrinsically poorer binding capacity of the P=O linkage.

Association Constants (K_a) and Free Energies of Association of
M^+ Picrates$^-$ in $CHCl_3$ at $25^\circ C$

	M^+	R_{org}	K_a	ΔG° (kcal/mole)
 ISOMERS A + B	Li	0.053	192,000	- 7.20
	Na	0.308	2,340,000	- 8.68
	K	0.809	200,000,000	-11.32
	Rb	0.636	5,050,000	- 9.14
	Cs	0.497	1,790,000	- 8.53
	NH_4	0.768	67,100,000	-10.67
 30	Li	0.008	25,600	- 6.01
	Na	0.061	189,000	- 7.19
	K	0.221	815,000	- 8.06
	Rb	0.058	109,000	- 6.87
	Cs	0.017	32,300	- 5.95
	NH_4	0.179	358,000	- 7.57
 35 R=CO_2H	Li	0.022	75,000	- 6.64
	Na	0.146	599,000	- 7.88
	K	0.298	1,500,000	- 8.42
	Rb	0.117	372,000	- 7.59
	Cs	0.052	113,000	- 6.89
	NH_4	0.154	281,000	- 7.42
 36 R=CO_2CH_3	Li	0.012	38,000	- 6.24
	Na	0.123	466,000	- 7.72
	K	0.394	3,100,000	- 8.85
	Rb	0.136	461,000	- 7.72
	Cs	0.034	882,000	- 6.70
	NH_4	0.329	1,200,000	- 8.29
 31	Li	0.013	41,000	- 6.29
	Na	0.041	117,000	- 6.91
	K	0.241	961,000	- 8.16
	Rb	0.223	1,040,000	- 8.20
	Cs	0.321	1,900,000	- 8.56
	NH_4	0.262	721,000	- 7.99
 32	Li	0.024	80,000	- 6.68
	Na	0.036	103,000	- 6.83
	K	0.026	50,000	- 6.41
	Rb	0.007	15,000	- 5.69
	Cs	0.004	7,500	- 5.28
	NH_4	0.027	32,500	- 6.15
 38	Li	0.003	10,000	- 5.45
	Na	0.023	63,900	- 6.55
	K	0.098	233,000	- 7.13
	Rb	0.027	64,600	- 6.55
	Cs	0.009	18,000	- 5.80
	NH_4	0.057	75,500	- 6.60

C. Synthesis and Study of Compounds Containing Inward-turning Carboxyl Groups (with Paul Cheng)

The fact that the carboxyl group is a good metal ion ligand led us to synthesize the prototype compound 39 in which two carboxyl groups are brought face-to-face with one another and might nicely embrace metal ions. The compound has been prepared and characterized, but its affinity for metal ions has not yet been examined.



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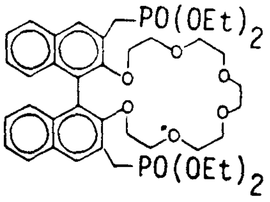
Cooperation With Other ERDA Contractors

We have sent experimental procedures to Mr. Bernard Jepson of Mound Laboratories for the synthesis of a considerable quantity of compound 40 for testing as an extracting agent for Li^+ in the separation of Li^+ isotopes from one another.



40

Educational Profit from this Contract

A new field of organic host-inorganic guest chemistry is being developed under this contract. Two carefully chosen postdoctoral research chemists, several graduate students and the principal investigator are learning the science and art of multiheteromacrocycle synthesis and enough inorganic chemistry to design our ligand assemblies. As time goes on, the 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 it is our belief that we are cultivating a field that will attract many other research groups.

Research Publications Resulting from Grant

As mentioned in the text, the results of some of the research done under this grant are reported in more thorough form in the following three papers which have appeared in the journals. Two copies of each of these papers accompany this report.

(1) Syntheses and Binding Characteristics of Macrocyclic Systems Containing One to Three β-Diketone Units, J. C. S. Chem. Commun., 958 (1976), by A. H. Alberts and D. J. Cram.

(2) Synthesis and Binding Characteristics of Macrocyclic Polyethers Containing Convergent Methoxyaryl or Phenolic Groups, J. Amer. Chem. Soc., **98**, 4018 (1976), by K. E. Koenig, R. C. Helgeson and D. J. Cram.

(3) Templated Syntheses of Cyclic Acetylacetone Hosts, Their Affinities for Divalent Ions, and an Example of a Slow Proton Transfer from Enol to Hydroxide Ion, J. Amer. Chem. Soc., **99**, 3880 (1977), by A. H. Alberts and D. J. Cram.

Results for several more papers are in hand, and these will be written up during the upcoming grant period.