The Syntheses and Characterization of Aza Coronands and Cryptands Containing the 2,6-Pyridino And/Or the 1,8-Naphthyridino Subunits.

Veronica Katherine Majestic
Louisiana State University and Agricultural & Mechanical College

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The Louisiana State University and Agricultural and Mechanical Col. Ph.D. 1982

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THE SYNTHESES AND CHARACTERIZATION
OF AZA CORONANDS AND CRYPTANDS CONTAINING
THE 2,6-PYRIDINO AND/OR THE 1,8-NAPHTHYRIDINO SUBUNITS

A Dissertation
Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy

in

The Department of Chemistry

by
Veronica Katherine Majestic
B.S., McNeese State University, 1974
May 1982
for Mom, Dad, the Family
and
W. B. Pearce III
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<td>XVI.</td>
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ABSTRACT

The syntheses of coronands and cryptands containing the 2,6-pyridino and 1,8-naphthyridino subunits have been accomplished. These macrocycles may contain only nitrogen heteroatoms while others contain both nitrogen and oxygen heteroatoms. Transition metal complexes have been formed only with the macrocycles which contain strictly nitrogen heteroatoms; no complexes have been found for the macrocycles which contain oxygen and nitrogen atoms. A diprotonated cobalt(II) tetrachloride salt was formed from the dimeric macrocycle which results from the reaction of 2,6-dichloropyridine with \( \text{N,N-bis-2-hydroxyethylpiperazine} \). Several analogous systems have also been synthesized.

A hexaaza-18-crown-6 analogue has also been synthesized by the treatment of 2,6-bis(chloromethyl)pyridine with \( \text{N,N'-dimethylethlyenediamine} \). This compound was found to form octahedral complexes with either cobalt(II) or copper(II) chloride, wherein all of the coordination sites of the metal ion are occupied by a ligating atom of the macrocycle. In addition several other compounds of this type have been synthesized and their complexation properties studied.

A few cryptands have been reported, accompanied by data on their complexation properties. Two main reaction
pathways were utilized to acquire the desired macrocycles: 1) a one-pot nucleophilic substitution reaction where six bonds are formed in one reaction, and 2) a quaternization-demethylation sequence where in a stepwise manner the bridges are introduced into the macrocyclic framework. The demethylations were accomplished by the use of L-Selectride® which quantitatively and selectively removes methyl groups from a quaternary ammonium salt.

Some of the cryptands synthesized have exhibited unusual structural properties and the effect of these structural properties on these macrocycles complexation properties have been studied. Their spectral and physical properties have also been reported.
I. Introduction

Man is limited only by his imagination. Fifty years ago it was difficult to imagine a world such as we live in today. The things that are now accepted as commonplace, i.e., silicon chips, computers, space shuttles, heart transplants, television, nuclear reactors, monoclonal antibodies and such movies as "Star Wars" and "The Empire Strikes Back", which bring to life strange and wonderful new worlds, were once the material of dreams. In light of these marvels, it is not too difficult to imagine the synthesis of molecules which might: selectively remove precious metals such as gold from sea water; purify metals which are at present extremely difficult to obtain in pure form; mimic biological substances (i.e., proteins or antibiotics); detoxify organisms poisoned by heavy metals; catalyze reactions which ordinarily do not occur; or stabilize oxidation states which are usually unstable. The heteromacrocycles and heteromacropolycycles appear to be the answer to these flights of fancy.

The current interest in heteromacrocycles and cryptands stems primarily from a desire to design ligands which selectively complex cations. A number of factors influence cation selectivity. With regard to the ligand, there are several structural considerations: the cavity
size, the nature and number of coordination sites, the ligand thickness, the lipophilicity, and the ligand conformation and flexibility. Other factors which influence cation selectivity and complex stability include the reaction environment (i.e., solvent polarity and temperature) and the counterion. Usually, a change from a polar solvent to a less polar one results in the formation of more stable complexes; in most cases, the sequences of relative selectivity do not change.\(^1\) As far as the counterion is concerned, nucleophilicity and steric bulk must be considered. Once these factors are weighed along with the charge density of the metal ion, it is possible to predict whether a particular complex will form and, if so, the preferred stoichiometry of the resulting complex. The effects of these factors on complexation properties will be realized as the synthesis of the macropolycyclic mesomolecules are discussed in terms of their type of structure.

A number of macropolycyclic structures may be envisioned, depending on the nature of the subunits and on the number of connecting bridges employed for their construction. These include: the connection of two chelate subunits leading to a coronand; the coaxial positioning of two tripodal units resulting in the axial macrobicyclic (bis-tripodal) systems; and the bridging of a coronand by
a chelating subunit to afford a lateral macrobicyclic cryptand. The face-to-face bridging of two macrocyclic units by two chelating subunits results in the formation of a cylindrical tricyclic cryptand; and the face-to-face bridging of two coronands by three chelating subunits resulting in the formation of a cylindrical tetracyclic cryptand. Finally, there exists the spheroidal macrotricyclic systems which result when a macrocycle is bridged across the top and bottom by chelating subunits. The diverse architecture that characterizes these systems offers the opportunity for significant control over the complexing abilities of these mesomolecules.
II. Coronands Containing Nitrogen Heteroatoms

Myriad polydentate aza macrocycles have been reported. The extent of the subject forces limitation of this discussion to only macrocycles containing a pyridino, dipyridino, or phenanthrolino subunit. Most of these coronands have been synthesized by a Schiff base condensation of an aldehyde or ketone with a bis-primary amine in the presence of a metal ion. The metal ion acts as a template, resulting in dramatic increases in yield of the desired cyclic product over linear polymerization products. Lindoy and Busch have described this effect in two ways, kinetic and thermodynamic. If the metal ion controls the steric course of a series of step-wise reactions, the template effect is considered to be kinetic. If the metal ion influences an equilibrium in an organic reaction sequence by coordination with one of the reactants, the template effect is termed thermodynamic. It is the kinetic effect that is believed to be operative in most metal ion-assisted (in situ) syntheses of macrocycles, although, it is difficult to ascertain which of the two effects is dominate in a specific synthesis.

As in most synthetic schemes, there are advantages and disadvantages to these in situ macrocyclic syntheses. The advantages include increased yields by virtue of the
elimination or reduction of side reactions and macrocyclic product control by steric influence of the metal ion. The disadvantages include the fact that the steric requirements of the metal ion may preclude formation of the desired macrocyclic product and the occasional inability to remove the metal ion from the resulting complex due to the inherent instability of the free ligand.

Some of the important factors influencing these reactions are: polarization effects, kinetic liability, thermodynamic stability, and stereochemistry of both the metal atom(s) and the reactants. In general, these syntheses are more metal ion specific than are complexations of the metal ion with a preformed macrocyclic ligand.10

A. Coronands Derived From the Schiff's Base Condensation of Polyamines with 2,6-Diacetyl- or 2,6-Diformylpyridine

The in situ synthesis of macrocyclic ligands by condensation of 2,6-diacetylpyridine with polyamines in the presence of metal ions represents one of the early demonstrations of the "template effect". Curry and Busch reported the first penta- and hexa-dentate macrocycle (1 and 2),11 both of which are cyclized in the presence of iron(II) chloride tetrahydrate. The two ligands were
isolated as highly crystalline, spin-paired, iron(III) complexes, and were characterized by magnetic, conductive, and spectral measurements.\textsuperscript{11,12} Because these complexes cannot be protonated, it is believed that all of the nitrogen atoms in the ligand are coordinated to the metal atom.\textsuperscript{13} Other metals for which complexes of ligand 1 have been isolated are: iron(II),\textsuperscript{14-18} iron(III),\textsuperscript{14-18} zinc(II),\textsuperscript{17-19} cadmium(II),\textsuperscript{17,18,20} mercury(II),\textsuperscript{17,20} magnesium(II),\textsuperscript{17,21} manganese(II),\textsuperscript{18} nickel(II),\textsuperscript{22} and lead(II).\textsuperscript{23} The reduction of \textit{bis}-amine 1 has been reported to afford ligand 3. In addition, the transition metal complexes of iron(III), cobalt(III), nickel(II), and copper(II) with ligand 3 have been prepared and characterized.\textsuperscript{24}

Complexes of 4 have also been formed by the reaction of 2,6-diacetylpyridine and \textit{N},\textit{N}-\textit{bis}(3-aminopropyl)ammine in the presence of nickel(II) and copper(II) chloride.\textsuperscript{25}
Other metals that have been used include: iron(II),\textsuperscript{26,27} copper(II),\textsuperscript{28,29} nickel,\textsuperscript{29,30} cobalt(II),\textsuperscript{31} cobalt(III),\textsuperscript{32-37} manganese(II),\textsuperscript{38} zinc(II),\textsuperscript{38} and ruthenium(II).\textsuperscript{39} Karn and Busch\textsuperscript{40} have reported the catalytic hydrogenation of the nickel(II) perchlorate complex of 4 to afford two nickel(II) complexes of 5: a yellow minor component and a red major component which preliminary studies indicate to be the meso form (6). The isomeric ligands can be displaced from the respective reduced complexes by cyanide ion. Ligand 6 has also been isolated and characterized as the copper(II) complex.\textsuperscript{41,42}

Treatment of other amines with 2,6-diacetylpyridine in the presence of nickel(II), copper(II), or cobalt(II) salts has generated a wide variety of new macrocyclic complexes (7-11). It is interesting to note that 9 forms complexes with nickel(II) and copper(II) but not with cobalt(II); no explanation for this observation has been forwarded.\textsuperscript{43}

Studies by Stotter indicate that: (1) the template formation of macrocyclic complexes of 12 requires a minimum
ring size of $x=y=3$; (2) it depends upon strong complexation of the metal at the pH of the reaction by the triamine reactant, such that the solubility product of the metal hydroxide is never exceeded; and (3) it proceeds through a ternary intermediate complex. If $x=3$ and $y=4$, the yields are lower and the complexes are less stable due to the presence of a seven-membered chelate ring in the complex. In contrast when complexes containing five- or six-membered chelate rings are formed the yields are usually much
higher, a result of the greater stability of such systems. Since no reaction occurs when the metal ion is present as a suspension of its hydroxide (and thus is not coordinated by the triamine) it is believed that the reaction between the triamine and 2,6-diacetylpypridine is a true template reaction in which both reactants are coordinated to the metal ion.44

![Complexes of macrocycles](image)

Complexes of macrocycles 13 and 14 have been prepared in situ from 2,6-diacetylpypridine and the necessary diamine. Transition metal complexes of 13 with iron(II),15,16,18,45,46 iron(III),18 magnesium(II),21 cadmium(II),18,20,47 mercury(II),20,48 silver(I),47 manganese(II),17,18,38,46 manganese(III),38 nickel(II),22 and zinc(II)18,38,46 have been isolated and characterized. The isolated complexes of 14 include those of iron(II),18 iron (III),18 silver(I),47,48 manganese(II),17,18,38 manganese(III),38 zinc(II),18,38 cadmium(II),18,20,47 mercury(II),20,47 nickel(II),22 lead(II),23,49 magnesium, calcium, strontium, and barium50. Complexes of ligands 1 and 13 possess structures that are approximately
pentagonal bipyramidal with the macrocycle defining the equatorial plane and the axial positions being occupied by a unidentate anion or water. The complexes of 14 are somewhat different, in that the five donor nitrogen atoms do not lie in one plane: there is a distortion which causes one face of the macrocycle to be more sterically crowded than the other.\textsuperscript{18,20,22} The coordination number ranges from five to seven depending on the occupancy of the two axial positions.

The nickel(II) complex of ligand 14 cannot be prepared directly via the template method, but can be prepared by a transmetallation procedure. Synthesis of the macrocycle in the presence of one of the metal ions known to be effective as a template is followed by a metal exchange process in solution to insert the nickel(II) ion. This cation exhibits a strong preference for the square planar, square pyramidal, and octahedral geometries.\textsuperscript{22} Thus the failure of the nickel(II) cation to behave as a template ion in the synthesis of ligand 14 is probably due to the disinclination of the metal to accommodate the pentagonal array of donor nitrogen atoms necessary for reaction to occur.

Attempts to prepare the nickel(II) complex of ligand 13 by transmetallation have resulted instead in the formation of addition products 15 or the ring-opened
product 16. In this case, the stereochemical preferences of the metal impose a new conformation on the ligand and thereby enhance its reactivity. 

![Chemical structures](image)

\[15 \text{ (R=Me, Et)} \quad 16\]

Judging from molecular models, the size of ligand 13 is not sufficient for its complexes to possess a planar conformation without experiencing a great deal of strain. The strong preference of nickel(II) for octahedral geometry provides the driving force for addition across one of the azomethine bonds, which in turn introduces the flexibility necessary for achievement of the optimum conformation. It is important to point out that pentagonal bipyramidal complexes of 13 with other metal ions of similar size and charge, such as iron(II), are relatively stable to nucleophilic attack by alcohols or water. The opposite effect has also been well documented; the steric requirements of the ligand may impose an unusual or irregular coordination geometry on a metal ion.

If 2,6-diacetylpyridine is condensed with \(N,N\)-bis(3-aminopropyl) amine in the presence of a large metal ion
such as silver, dimer 17 is the only observed product and exists as the disilver(I) complex. The Ag---Ag distance is 6.0 Å: clearly, there is no interaction between the metal atoms. It appears that in this case the size metal ion is the dominant factor in determining the course of the reaction.\textsuperscript{53} Thus far, 17 is the only dimeric complex synthesized by the in situ template procedure.

Stotz and Stoufer\textsuperscript{54} reported the first example of a binuclear complex of a macrocyclic ligand 18, which holds the two metal ions in sufficiently close proximity to permit metal–metal interactions, as indicated by magnetic susceptibility and esr measurements. The dinuclear complex of ligand 18 (40–45\%) is formed by the copper(II) assisted Schiff base condensation of 2,6-diacetylpyridine with o-phenylenediamine. Although calcium, strontium, barium, lead(II), lanthanum(III),\textsuperscript{55,56} and cerium(III)\textsuperscript{55} have all been successfully used as templating ions in the synthesis of 19, attempts to effect cyclization in the presence of magnesium, manganese(II), iron(II), nickel(II), copper(II), silver(I), cadmium(II), and mercury(II) have
These complexes of 19 appear to be the first in which the "hard" alkaline earth metal ions are bound to a macrocyclic ligand containing only "soft" nitrogen donors. Efforts to prepare a barium complex of 18 have failed, whereas calcium, strontium, barium, and lead(II) have been used successfully in the synthesis of 20 by the Schiff base condensation of 2,6-diformylpyridine with o-phenylenediamine.

Transmetallation reactions in methanol, intended to form the manganese(II) (ionic diameter: 1.84 Å), iron(II) (1.84 Å), cobalt(II) (1.80 Å), or zinc (I) (1.80 Å) complexes of 20 (cavity radius: 2.7 Å), have led to the isolation of a new series of complexes where the ligand has undergone a ring contraction to better accommodate the smaller cations. The ring-contraction was initiated by following the metal ion or cavity, respectively.) The ring-contraction was initiated by addition of methanol across one of the azo-methine bonds during transmetallation, and subsequent formation of a five-membered imidazoline ring to afford ligand 21. Evidence to support the belief that the ring-
contraction is due to a disparity in the sizes of the metal ion and ligand 20 is provided by the fact that exchange of cadmium(II)(2.20 Å) for barium(II) does not invoke ring-contraction, but forms the desired complex.59

![Structure 21]

In an analogous fashion complex 22 may be obtained by condensation of 2,6-diformylpyridine with 23 in the presence of manganese(II) or zinc(II). According to crystallographic data, the coordination geometry of 22 is distorted pentagonal bipyramidal.60

![Structure 22]

B. Coronands Containing Appendages Capable of Complexation

Several derivatives of 4 have been synthesized in which an additional functional group has been attached to the secondary sp³ nitrogen atom. Such compounds are less rigid in terms of the geometrical requirements of the
coordinated metal ion and are thus especially interesting for structural studies. Condensation of \( N,N\text{-bis}(3\text{-amino-propyl})-N',N'\text{-dimethylethlenediamine} \) with \( 2,6\text{-diacetyl-pyridine} \) in the presence of nickel(II) ions results in the formation of \( 24 \), which upon subsequent reduction of the imine groups affords the nickel(II) complexes of \( 25 \).\(^{61}\) Ligands \( 26 \) and \( 27 \), in which the terminal amino groups have been replaced by hydroxide, have also been synthesized as the nickel(II) complexes. Ligands \( 24-27 \) may exist in one of two forms depending on the pH of the solution. At low pH protonation of the dimethylamino or hydroxy groups results in binding of the metal ion by the four nitrogen atoms of the macrocycle in a square planar ligand field. At higher pH the dimethylamino or hydroxy groups can coordinate in one of the axial positions to produce a pseudo-octahedral coordination geometry.\(^{62}\)
Interest in these ligands stems from a desire to synthesize improved analogues of the cobalamines. With this in mind, 2,6-diacetylpyridine was condensed with N,N,N-tris(aminopropyl)amine in the presence of nickel(II) or copper(II) to afford the complex of 28. Cobalt(II) and zinc(II) have also been employed as templating agents in the synthesis of 28. The reaction of the nickel(II) complex of 28 with acetone results in a dimeric complex, 29, by a process that is well established for primary amines.

\[ \text{C. Coronands Containing the 1,10-Phenanthroline Subunit.} \]

There have been reports of several macrocycles which contain a 1,10-phenanthrolino subunit. The first (30) was synthesized in 94% yield by the reaction of 2,9-diaminophenanthroline (32) and 2,9-dichlorophenanthroline (31) in nitrobenzene, with potassium carbonate present as an acid acceptor. The solid state IR spectrum indicated that 30 possesses intramolecular hydrogen bridging. The copper(II) (94%) and nickel(II) complexes (33) have also been
reported. They may be formed in one of two ways: either by reaction of $31$ and $32$ in the presence of the metal salt or by reaction of $30$ with the metal salt.\textsuperscript{66}

\[
\begin{align*}
\text{Cl} & \quad 31 \\
\text{H}_2\text{N} & \quad k_2\text{CO}_3 \\
\text{NH}_2 & \quad \Delta \quad 30 \\
\text{M}^{2+} & \quad \text{Co, Cu, Ni}
\end{align*}
\]

Incorporation of the 1,10-phenanthroline moiety into a macrocyclic framework is of importance because of the great stability of the complexes it forms with transition metals. It also has been found to stabilize unusual metal ion oxidation states.\textsuperscript{67} As a result of the considerable electron delocalization between the metal ion and the nitrogen base system, these phenanthroline complexes are potential electron acceptors,\textsuperscript{68} and may therefore prove to be useful porphyrin mimics. These complexes should certainly exhibit interesting redox reactions and result in unusual oxidation states for the metal ions. The condensation of 1,10-phenanthroline-2,9-dicarboxaldehyde ($34$) with dihydrazone, diethylenetriamine, or $N,N$-iminobispropylamine ($35$) results in the formation of macrocycles $36$ (50%), $37$ (50%), and $38$ (10%). The metal ions effective in
the synthesis of 36 include: nickel(II), iron(II), and cobalt(II). In contrast 37 and 38 have only been prepared in the presence of manganese(II).69

\[ \text{The macrocyclic complexes of 41 have been prepared by the condensation of 2,6-diacetylpyridine (40) with the 2,9-dihydrazino-1,10-phenanthroline (39) in the presence of zinc(II) (60%) cadmium(II) (55%), or manganese(II) (75%) as templates. The X-ray structure determination of the manganese complex of 41 shows the coordination geometry around the metal ion to be an unusual distorted pentagonal pyramid, consistent with a } \pi \text{-delocalization process. The five nitrogen atoms all lie in approximately the same} \]
plane, above which rests the manganese atom capped by an apical chlorine.\(^{69}\)

\[
\begin{array}{c}
\text{Me} \\
\text{N-NH}_2 \\
\text{N-NH}_2 \\
\text{Me}
\end{array}
\begin{array}{c}
\text{Me} \\
\text{N-NH}_2 \\
\text{N-NH}_2 \\
\text{Me}
\end{array}
\begin{array}{c}
\text{Me} \\
\text{N-NH}_2 \\
\text{N-NH}_2 \\
\text{Me}
\end{array}
\]

Lewis and O'Donoghue have subjected the zinc complexes of 41 and 42 to sodium borohydride reduction; NMR data indicate that trans hydrogenation occurs across both hydrazone bonds.\(^{70}\) The iron(II) complex of 41 has also been reported and bears certain structural similarities to the porphyrins. The geometrical form of the complex is that of a slightly distorted pentagonal bipyramid: the metal atom is coplanar with the nitrogen atoms of the ligand cavity and water molecules occupy the two axial

\[
\begin{array}{c}
\text{R} \\
\text{R} \\
\text{R} \\
\text{MeN} \\
\text{Zn} \\
\text{NMe}
\end{array}
\begin{array}{c}
\text{H} \\
\text{H} \\
\text{H} \\
\text{MeN} \\
\text{Zn} \\
\text{NMe}
\end{array}
\begin{array}{c}
\text{R} \\
\text{R} \\
\text{R} \\
\text{MeN} \\
\text{Zn} \\
\text{NMe}
\end{array}
\begin{array}{c}
\text{R} \\
\text{R} \\
\text{R} \\
\text{MeN} \\
\text{Zn} \\
\text{NMe}
\end{array}
\]

\[
\begin{array}{c}
1) \text{NaBH}_4 \\
2) \text{H}^+ \\
\text{R}=\text{H} \\
\text{R}=\text{Me}
\end{array}
\begin{array}{c}
\text{R}=\text{H} \\
\text{R}=\text{Me}
\end{array}
\]
positions. The complex is relatively rigid and appears to possess some π-delocalization.71

D. Coronands Containing the Triazine and/or Isoindolinylidene Subunits.

Borodkin et al. have reported the syntheses of a series of macrocycles containing isoindoline and triazine subunits with 2,6-diaminopyridine (48).72-77 The first macrocycle of this type reported involves the treatment of 4-chloro-2,6-bis[(1-imino-3-isooindolinylidine)amino]-triazine with 2,6-diaminopyridine to afford 45 (25%).
Complexes of 45 have been isolated for copper(II), cobalt(II), and nickel(II) cations. Condensation of
2,6-diaminopyridine with 46 affords the dimeric macrocycle 49 (73%). No complexes have been reported with ligands 4973 or 50.74,75 In addition, the reaction of 1,3-bis[(1-imino-4,5,6,7-tetrahydro-3 isoindoline) amino]-benzene with 2,6-diaminopyridine gives 51a (70%).76

These authors have also reported the preparation of a series of chlorotriazines 52-55 with 2,6-diaminopyridine to generate the corresponding dimeric macrocycles 56-59. The copper(II) complexes of these macrocycles (56-59) have also been synthesized and characterized.77

E. Coronands Bridged by Hydrazine Moieties

Lewis and Wainwright78 have prepared a new thirteen-membered macrocycle by treating the nickel(II) or cobalt(II) complexes of 6,6'-dihydrazino-2,2'-dipyridine (60) with acetone. In the case of 60 the metal chelates very strongly to the dipyridine moiety and bonds only weakly at the terminal nitrogen sites of the hydrazine moiety, rendering these atoms unusually labile and nucleophilic. Treatment of the nickel(II) complex of 60 with refluxing aqueous acetone results within a few minutes in the quantitative formation of the Curtius-type macrocycle, (61).65 These are the mildest conditions yet observed for such a transformation. The metal ion can be displaced with sodium cyanide to afford the free ligand 62. The
iron(II) and cobalt(II) complexes of 62 have also been isolated. 78

\[
\text{Ni(CO}_4\text{)}_2\cdot6\text{H}_2\text{O} \rightarrow \begin{array}{c}
\text{EtOH} \\
\end{array}
\]

An analogous system involves the condensation of pentane-2,4-dione (63) with 6,6'-bis(N-methylhydrazino)-2,2'-dipyridine (64) in the presence of nickel(II) to afford the thirteen-membered complex 65. Treatment of the complex with sodium cyanide does not release the ligand,
nor does the complex form when copper is used as the metal template.\(^7\)

Treatment of oxovanadium(IV) complexes of 2,6-di-picolinoyl dihydrazine with \(\beta\)-diketones results in the formation of macrocyclic complexes \(^{66-68}\). These products have been characterized on the basis of their elemental analyses, electrical conductance, magnetic susceptibility and infrared spectral data.\(^8\)

\[\begin{align*}
&66 \quad R=\text{Me}; R'=\text{Me} \\
&67 \quad R=\text{Et}; R'=\text{Me} \\
&68 \quad R=\text{Bz}; R'=\text{Me}
\end{align*}\]

The only other example of a Schiff base condensation with bipyridyl to form a macrocyclic complex has been reported by Tasker et al.\(^{81}\) in which 2,6-diformyl-or 2,6-diacetyl-pyridine is condensed with 6,6'-dihydrazino-2,2'dipyridine (60) in the presence of zinc(II) to

\[\begin{align*}
&\text{R=Me or H} \\
&\text{NHNH}_2 \quad \text{NH}_2
\end{align*}\]
afford pentagonal bipyramidal complexes. The rigidity of the system results in an equatorial 'N$_5$' donor set that is essentially planar; water molecules occupy the axial positions.

An iron(II) complex of a completely conjugated fourteen-membered hexa-aza ligand has been prepared by the condensation of 2,6-diacetylpyridine with hydrazine in acetonitrile. There are two possible isomers, 70 and 71. X-ray data show that the structure of this complex is best represented by 70 in which the macrocycle is completely planar and the coordination geometry is pentagonal bipyramidal. This iron(II) complex of 70 is extremely labile to nucleophiles. The cobalt(II), magnesium(II), zinc(II), and scandium(III) complexes of this hexa-aza quadridentate ligand have also been prepared.

\[ X = \text{CH}_3\text{CN} \]

Rana and Teotia have reported the synthesis of a novel tridentate macrocycle (72) by the reaction of 2,6-dipicolinic acid hydrazide and acetylacetone in the presence of cobalt(II), nickel(II), and copper(II) salts. As is
frequently the case, water occupies the axial positions of these trigonal bipyramidal complexes and the chelating nitrogen atoms are essentially coplanar. 85

\[ \text{Diagram 72} \]

Vögtle et al. have employed the reaction of 2,6-bis-(chloroformyl)pyridine with various polyamines to synthesize a number of coronands, including 73-75. Copper(II) complexes have been reported for ligands 73 and 74. 86

\[ \text{Diagrams 73, 74, and 75} \]

In 1976, Weber and Vögtle also reported the syntheses of 76, obtained by treatment of the same substrate with 2,6-diaminopyridine. 87 To date, no complexes of 76 have been reported. Similar macrocyclic compounds which have been prepared by Vögtle et al.,
include 77-79;\textsuperscript{88} however, no complexes of these ligands have yet been reported.

\begin{align*}
\text{In view of the affinity of transition metals for dipyridine, this moiety has been incorporated in macrocyclic systems in lieu of pyridine. Vögtle has utilized this new entity in the synthesis of ligands 80 (41\%) and 81 (19\%), but to date no complexes of these two ligands have been isolated.}
\end{align*}

However, several intriguing macrocyclic ligands which form dinuclear complexes have been synthesized by Lehn and coworkers. Ligands 82 and 83 are synthesized by a route which results in the formation of uncomplexed ligands (Scheme I). Both ligands form dinuclear copper(II)
complexes, the copper-copper distance in $\text{82}$ being 4.79 Å.

III. Coronands Containing Both Oxygen and Nitrogen

As with the aza coronands previously discussed, the majority of the coronands containing oxygen and nitrogen have been synthesized by Schiff base condensation or via a nucleophilic substitution of halide from a compound possessing either pyridine or dipyridine subunits. The first part of this discussion will deal with the synthesis of these coronands by the Schiff base condensation.

A. Synthesis by Schiff's Base Condensation

Analogous to the preparation of strictly nitrogen containing macrocycles, ligands $\text{84, 18, 20, 22, 46, 90 85, 46, 90}$ $\text{86, 91, 92}$ and $\text{87, 91, 92}$ have been synthesized by condensation of 2,6-diacetyl- or 2,6-diformylpyridine with the desired diaminopolyether in the presence of a metal ion. The metal ions which have been utilized in the synthesis of ligand $\text{84}$ are iron(III), $\text{20, 46}$ manganese(II), $\text{18, 20, 46}$ iron(II), $\text{18, 20}$ zinc(II), $\text{18, 20, 46}$ magnesium(II), $\text{18, 20, 90}$ iron(II), $\text{18, 20}$ cobalt(II), $\text{90}$ and cadmium. $\text{18}$ In the case of ligand $\text{85}$, only iron(III), $\text{46}$ manganese(II), $\text{46}$ magnesium (II), $\text{90}$ and
Scheme I

\[
\begin{align*}
\text{Ts} \quad \text{N} \quad \text{Ts} \quad \text{COCl} &\quad \stackrel{\text{NH}_3, \text{THF}}{\longrightarrow} &\quad \text{Ts} \quad \text{N} \quad \text{Ts} \quad \text{CONH}_2 \\
\text{Ts} \quad \text{N} \quad \text{Ts} \quad \text{COCl} &\quad \text{90\%} &\quad \text{Ts} \quad \text{N} \quad \text{Ts} \quad \text{CONH}_2 \\
\end{align*}
\]

\[\text{1} \text{B}_2\text{H}_6 \quad \text{2} \text{TsCl}\]

\[
\begin{align*}
\text{Ts} \quad \text{N} \quad \text{Ts} \quad \text{N} \quad \text{Ts} \quad \text{Br} &\quad \text{Br} \quad \text{DMF} &\quad \text{Ts} \quad \text{N} \quad \text{Ts} \quad \text{NTs} \\
\text{Ts} \quad \text{N} \quad \text{Ts} \quad \text{N} \quad \text{Ts} \quad \text{N} \quad \text{Ts} &\quad \text{conc. H}_2\text{SO}_4 \quad 75\% &\quad \text{82} \\
\end{align*}
\]
Zinc(II), have been employed. Complexes of 86 and 87 have been prepared with barium, strontium, calcium, and lead(II). The crystal structure determination of the lead complex of 86 indicates that the lead ion is located within the macrocyclic cavity and appears to interact preferentially with the nitrogen atoms.

Manganese(II) and zinc(II) metal ions have been used to synthesize ligands 88 and 89. The coordination geometry of these complexes is distorted pentagonal bipyramidal. If manganese(II) chloride in ethanol is utilized, 88 was isolated. However, if magnesium(II) perchlorate or magnesium(II) isothiocyanate in alcohol is
employed, $89$ is isolated. Because both ligands can be formed even in the absence of metal ions, there arise several questions about the factors that control the cyclization. The metal ion may indeed act as a template, or the macrocycle formation may be governed strictly by entropic considerations.$^{95}$

The calcium, strontium, barium, and lead$^{23}$ complexes of $90$ and $91$ have also been reported. In these two ligands the six donor atoms are essentially confined in a plane; these complexes thus permit study of unusual coordination geometries in species of high coordination number. Attempts to form alkali metal complexes with $90$ and $91$ under the same conditions as employed for the alkaline earth metal complexes have failed. The successful syntheses of complexes of the latter type indicate that the higher charge to radius ratio is of consequence when spherically charged cations are employed. Such metal ions have no apparent coordinative discrimination as the template ion.$^{93}$

A bimetallic complex of a thirty-membered decadentate macrocyclic ligand $92$ was synthesized in greater than 80% yield when lead(II) thiocyanate was used as the template. No monomeric complex has yet been isolated from the lead(II) template reaction. The x-ray crystal structure shows that the coordination geometry of the metal is basically hexagonal bipyramidal with one equatorial site
unoccupied. The axial positions are occupied by thio-
ecyanate molecules. Because the metal ions are associated
more strongly with the nitrogen atoms than with the oxygen
atoms indicates that the weakly coordinating ethereal oxy-
gens may not be able to compete effectively with solvent
molecules for coordination sites. As a result, the termi-
nal amine and carbonyl functions are not constrained into
close proximity, and there is a preferential self-conden-
sation to afford the dimeric dinuclear complex.23,96

The dinuclear copper(II) complex of 92 has also been
isolated by transmetallation. This copper complex adopts a
folded conformation which allows for intramolecular
bridging of the metal ions by small anions such as azide
and hydroxide. The structure of the μ-azide complex has
been determined by x-ray crystal analysis. It shows each
copper atom to be bound only to the nitrogen atoms of the
macrocycle and an azide molecule bridging the two metal
ions. There is also a terminal azide ion bound to each
copper atom in the plane of the pyridine ring.97 The
transmetallation of complex 92 has also been successfully utilized for iron(II), cobalt(II), cobalt(III), and nickel(II). On the basis of preliminary X-ray data, all of these complexes are believed to be octahedral, the nitrogen atoms being coordinated to the metal ion.98

Complex 94 has been obtained by the sodium borohydride reduction of 93, whereas 95 is formed by N-methylation of ligand 94. Copper(I) complexes of 94 and 95 rapidly absorbs dioxygen in equimolar amounts; the ligand then undergoes a slower anaerobic oxidative dehydrogenation to regenerate the copper(I) centers so that the cycle may be repeated at least once again, although more slowly.

Evidence indicates that the -CH$_2$-NH- bond is initially oxidized to the imine, then the second, slower dehydrogenation is believed to be that of -CH$_2$-CH$_2$-, which has a higher activation energy for dehydrogenation than do the -CH$_2$-NH- groups. Attempts to isolate pure samples of the oxidized complex have proven fruitless.99
B. Synthesis by Condensation of a Diacid Halide with a Diaminoether

Another method employed for the synthesis of these types of macrocycles involves the reaction of a bis-acid chloride with a diaminoether. Weber and Vögtle have reported the synthesis of a series of these macrocycles and their complexes. The first examples included ligands $96-101^{100}$ which were obtained in yields varying from 3% to 61%; no metal complexes have as yet been reported for these lactam-type macrocycles.$^{86,100}$

\[ \text{Diagram} \]

In 1978, Vögtle et al. reported the synthesis of a different series of lactams, which were achieved by the treatment of 2,6-bis(aminomethyl)pyridine with various

\[ \text{Diagram} \]
polyether-bis-acid chlorides. Among the coronands reported were ligands 102 and 103; to date, only the magnesium complex of ligand 103 has been prepared.

A slight modification of reactants has led to the synthesis of ligand 104. In this case, 2,6-bis(aminomethyl)pyridine was treated with bis(chloroformyl)diethyl-eneglycol ether to afford 104 (66%); to date, there have been no complexes reported for this ligand.

This class of macrocycles has recently been expanded to include 2,2'-dipyridine subunits within the macrocyclic framework. Vögtle et al. have synthesized 105 (59%) and 106 (24%); again, no complexes of these two ligands have been reported.

This discussion has covered all the coronands synthesized to date which contain nitrogen and oxygen heteroatoms in the macrocyclic framework. It has also included a discussion of any complexes which may have been reported. Much of the work has been centered about two synthetic strategies; the amide reduction and the formation of Schiff's bases. In addition, most of the complexes formed have been with Schiff's bases involving transition
metals or with the amide type macrocycles utilizing alkali metals or the alkaline earth metals. Therefore, it is more than evident from the information presented herein that much work remains to be done on determining the general structure of these compounds along with studying their complexation properties.
IV. Cryptands

A. Bis-tripodal Macrobicycles

In 1968, Simmons and Park\textsuperscript{102} reported the synthesis of the first bis-tripodal cryptands. These diazacycloalkanes (107), prepared by the procedure of Stetter and Marx,\textsuperscript{103} were subsequently converted to the diazacycloalkane cryptands (108) by an extension of the same procedure. The yields of 108 depend on the number of methylene units in the bridges: when $x$, $y$, and $z$ are equal to seven the yield is 20%; however, when $x$, $y$, and $z$ are equal to eight the yield is 75%. Simmons and Park also discuss the in-out isomerization and the encapsulation of ammonium ions by these compounds, as evidenced by proton NMR spectroscopy measurements. These compounds have been shown also to form inclusion complexes with halide ions. Determination of the crystal structure of 108 for $x$, $y$, and $z$ equal to nine proves that the chloride anion is held
within the intramolecular cavity of the diprotonated diamine.104

Dietrich et al.,105 with the expressed purpose of complexing diverse metal cations, decided to incorporate several heteroatoms in a macrobicyclic system analogous to that of Simmons and Park. Utilizing essentially the same procedure, Lehn reported the condensation of bis-aminoether

![Chemical Structures]

110 111 m=1 (80%)

112 m=1 (75%)

113 m=n=1 (45%)

1. B₂H₆
2. HCl
3. ion exchange resin

114a m=0; n=1 [2.1.1]
114b m=1; n=0 [2.2.1]
114c m=n=1 [2.2.2]
114d m=1; n=2 [3.2.2]
114e m=2; n=1 [3.3.2]
114f m=n=2 [3.3.3]
(109) with bis-acid chloride (110) to afford coronand 111 as the major product. Reduction of the coronand followed by condensation with another equivalent of the bis-acid chloride and subsequent reduction resulted in the formation of the cryptands 114a-f. Variation of the length of the glycol units, allows regulation of the size of the macrobicycles, thereby altering their complexation properties.

These compounds do indeed form inclusion complexes with metal cations. Because the cation is completely encapsulated by the macrocycle, in a sort of molecular vault or crypt, the term cryptand has been coined for these systems. (The cryptand nomenclature, [2.2.2], was proposed by Lehn and is commonly accepted; the three numerals indicate the number of heteroatoms in the three bridging subunits between the nitrogen bridgehead atoms.) The metal-ligand complex is referred to as a cryptate.

Table I. Complexation Stability Based on The Size Relationship Between the Cation and Cryptand

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Solvent</th>
<th>Li⁺</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Rb⁺</th>
<th>Ca⁺</th>
<th>Mg²⁺</th>
<th>Ca²⁺</th>
<th>Sc²⁺</th>
<th>Ba²⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td><a href="0.8">2.1.1</a></td>
<td>W</td>
<td>5.5</td>
<td>3.2</td>
<td>&lt;2.0</td>
<td>&lt;2.0</td>
<td>2.0</td>
<td>0.3</td>
<td>2.5</td>
<td>&lt;2.0</td>
<td>&lt;2.0</td>
</tr>
<tr>
<td><a href="1.15">2.2.1</a></td>
<td>W</td>
<td>2.50</td>
<td>5.4</td>
<td>3.95</td>
<td>2.55</td>
<td>&lt;2.0</td>
<td>&lt;2.0</td>
<td>6.95</td>
<td>7.35</td>
<td>6.30</td>
</tr>
<tr>
<td><a href="1.4">2.2.2</a></td>
<td>W</td>
<td>&lt;2.0</td>
<td>3.9</td>
<td>5.4</td>
<td>4.35</td>
<td>&lt;2.0</td>
<td>&lt;2.0</td>
<td>4.4</td>
<td>8.0</td>
<td>9.5</td>
</tr>
<tr>
<td><a href="1.8">3.2.2</a></td>
<td>W</td>
<td>&lt;2.0</td>
<td>1.65</td>
<td>2.2</td>
<td>2.05</td>
<td>2.0</td>
<td>&lt;2.0</td>
<td>&lt;2.0</td>
<td>3.4</td>
<td>6.0</td>
</tr>
<tr>
<td><a href="2.1">3.3.2</a></td>
<td>W</td>
<td>&lt;2.0</td>
<td>&lt;2.0</td>
<td>&lt;2.0</td>
<td>&lt;0.7</td>
<td>&lt;2.0</td>
<td>&lt;2.0</td>
<td>&lt;2.0</td>
<td>&lt;2.0</td>
<td>&lt;2.0</td>
</tr>
<tr>
<td><a href="2.4">3.3.3</a></td>
<td>W</td>
<td>&lt;2.0</td>
<td>&lt;2.0</td>
<td>&lt;2.0</td>
<td>&lt;0.5</td>
<td>&lt;2.0</td>
<td>&lt;2.0</td>
<td>&lt;2.0</td>
<td>&lt;2.0</td>
<td>&lt;2.0</td>
</tr>
<tr>
<td>Ionic Radius (Å)</td>
<td>1.86</td>
<td>1.12</td>
<td>1.44</td>
<td>1.58</td>
<td>1.84</td>
<td>0.87</td>
<td>1.18</td>
<td>1.32</td>
<td>1.49</td>
<td></td>
</tr>
</tbody>
</table>
In general the complex achieves maximum stability when the cation diameter is approximately the same as the ligand cavity diameter. This has been clearly demonstrated by the stability sequence of the alkali and alkaline earth complexes of compounds 114a-f, as shown in Table I.\textsuperscript{106} The larger macrocycles show less pronounced selectivities, most probably due to an increase in ligand flexibility.\textsuperscript{10} A complete discussion of these cryptands\textsuperscript{108} and their cryptates\textsuperscript{109} has been published.

Although acyclic polyethers will bind cations, the cyclic polyethers form much more stable complexes (Figure I). This phenomenon is known as the macrocyclic effect,\textsuperscript{110} and the cryptates exhibit a similar, but much larger, effect. The potassium complex of cryptand [2.2.2] is more stable by a factor of 10\textsuperscript{5} than the potassium complex of its coronand analogue. This cryptate effect is generally characterized by high complex stability, high complex selectivity, and shielding of the complexed cation from the environment. These factors are ascribed to the complete sequestration of the cation inside the macrocyclic cavity. Both the macrobicyclic and macrocyclic effects are enthalpic in origin, and result from the strong interaction of the cation with a weakly solvated polydentate macrocyclic structure. In contrast, the chelate effect of acyclic systems is due to a strong positive entropy of complexation.\textsuperscript{111}
<table>
<thead>
<tr>
<th>Macrocyclic Effect</th>
<th>Cryptate Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Cyclic Compound" /></td>
<td><img src="image2" alt="Cryptate Compound" /></td>
</tr>
<tr>
<td>2.2</td>
<td>4.8</td>
</tr>
<tr>
<td>6.1</td>
<td>9.75</td>
</tr>
<tr>
<td>Δ</td>
<td>Δ</td>
</tr>
<tr>
<td>3.7</td>
<td>4.95</td>
</tr>
</tbody>
</table>

**Figure 1.** The macrocyclic and cryptate effects (Δ) on complex stability; the values given are the stability constants, log $K_s$ of the $K^+$ complex.

Lehn *et al.*,\(^{112}\) in 1970, also reported the analogous series of cryptands in which some of the oxygen atoms were replaced by sulfur atoms. The same synthetic scheme was followed: starting with the desired dioxa- or dithiadiamine or dicarboxycyclic acid dichloride, the macrocyclic diamines (115-117) were obtained in 75%, 55%, and 45% yield, respectively. Repeating the sequence of condensation and reduction once again resulted in the formation of the macrobicyclic diamines 118-120.
These compounds (118-120) form various metal complexes which are similar to those of their oxygen relatives. The ease of complexation with potassium, barium, silver(I), thallium(I), lithium, sodium, lead(II), and rubidium decreases in the order 118 > 119 > 120. Only a few complexes of 119 and 120 have been obtained.

Generally, macrocyclic and macrobicyclic ligands form more stable complexes with the alkaline earth cations than with alkali cations of about the same diameter. The ratio of selectivities for alkali versus alkaline earth cations [M(I)/M(II)] can be regulated by altering ligand thickness and lipophilicity or by changing the number of coordination sites while maintaining the cavity size.113,114
It is expected that an increase in the thickness of the organic layer, which separates the complexed cation from the solvent, will decrease the interaction between the two moieties, thereby destabilizing the complex. This effect has been shown to be much larger for the divalent cations than for the monovalent cations. To this end, Lehn and coworkers\textsuperscript{115} have synthesized ligands 121-123 by the previously described condensation and reduction sequence. In practice, the stability constants of the inclusion complexes formed by 121-125 are measured and compared to that of nonactin (126), a natural macrolide antibiotic (Table II). The data indicate that incorporation of a benzo group in ligand 123 (to form an analogue of ligand 121) does not appreciably affect the barium to potassium selectivity ratio. However, the incorporation of two benzo groups into the ligand structure as in 122 greatly reduces the complex stability of barium: the barium/potassium ratio becomes approximately one. When two of the oxygen atoms in 123 are replaced by methylene
groups to afford 124, the selectivity of potassium over barium exceeds that of nonactin. 114

Table II. Stability constants, log Ks, of 121-125.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Cation</th>
<th>121</th>
<th>122</th>
<th>123</th>
<th>124</th>
<th>125</th>
<th>126 (nonactin)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Na⁺</td>
<td>7.40</td>
<td>7.30</td>
<td>6.95</td>
<td>3.0</td>
<td>3.26</td>
<td>2.40</td>
</tr>
<tr>
<td></td>
<td>K⁺</td>
<td>9.05</td>
<td>8.60</td>
<td>9.45</td>
<td>4.35</td>
<td>4.38</td>
<td>3.60</td>
</tr>
<tr>
<td></td>
<td>Ba²⁺</td>
<td>11.05</td>
<td>8.50</td>
<td>11.5</td>
<td>&lt;2.0</td>
<td>6.67</td>
<td>1.70</td>
</tr>
<tr>
<td></td>
<td>Ba²⁺ /K⁺</td>
<td>100</td>
<td>1</td>
<td>110</td>
<td>1/&gt;200</td>
<td>200</td>
<td>1/80</td>
</tr>
</tbody>
</table>

A change in the nature of the heteroatoms in macrocyclic and macrobicyclic ligands also greatly influences the complexation selectivities. The relatively hard, polar oxygen atoms complex strongly with the hard alkali and alkaline earth cations; the softer sulfur and nitrogen atoms prefer the softer transition metal cations and heavy metal cations. The ultimate goal of these alterations is the selective complexation of the very toxic heavy metal cations such as thallium, cadmium, mercury, and lead with minimal effect on the biologically important metal ions such as sodium, potassium, magnesium, calcium, and zinc. This would allow control of toxic heavy metals in organisms and the environment. Cryptand [2.2.2] has already been employed for the removal of radioactive strontium and radium from contaminated rats, 116 and has also been shown to be effective for the removal of lead. 117
Lehn and Montavon\textsuperscript{118} have described the synthesis and properties of these "softer" cryptands. The same general procedure was employed, necessitating the protection of the amine functions in the bridging units by a group which was resistant to the condensation and reduction conditions usually maintained, yet which could be easily removed without introducing a cation capable of forming a stable complex with the resultant cryptand. After several attempts the $p$-toluenesulfonyl group was finally selected as the appropriate protecting group for the nitrogen atoms. Cryptands 134, 137, 140, and 145 were isolated in acceptable yields (see Schemes II, III, and IV).

Studies indicate that the stability of the complexes of 134, 137, 140, and 145 is influenced by the number of nitrogen sites and the size of the cavity. Ligand 140, the smallest one studied, forms the most stable complexes with the comparably small cobalt(II), nickel(II), copper(II), and zinc(II) cations. Ligands 134, 137, and 145 form more stable complexes with lead(II) than with cadmium(II); they also have a much larger cadmium(II)/zinc(II) selectivity ratio than 140. These results are attributed mainly to the size relationship. The effects of altering the number of nitrogen sites can be seen by comparing the ratio of thallium to potassium selectivities for ligands 114c and
Scheme II

1. NaOH/toluene  
2. BrCH₂CO₂Me

1. HCl  
2. TsCl/NaOH

127

X=OH  
129  
X=Cl  
130

HN
NH

Benzene/NE₃

131

Li/THF  
2. HCl

134

1. ClCO₂Me  
LiOH aq.  
2. LAH/Et₂O
Scheme III

1. B₂H₆
2. HCl
3. Li/NH₃

1. CO₂Me
2. LiOH/H₂O
3. LAH

1. HCO₂H
2. HCl
3. KOH
Scheme IV

1. \( \text{B}_2\text{H}_6 \)
2. \( \text{HCl} \)

1. \( \text{B}_2\text{H}_6 \)
2. \( \text{HCl} \)
3. \( \text{Li/\text{NH}_3} \)

1. \( \text{ClCO}_2\text{Me}/\text{LiOH} \)
2. \( \text{LAH} \)
they differ by a factor of approximately 80, exhibiting the largest thallium/potassium ratio.

Ligands 137 and 145 also show the highest observed selectivities for cadmium(II) over zinc(II) and very high selectivities for cadmium(II) over calcium(II). Due to the presence of the softer nitrogen atoms, 137 and 145 form very strong complexes with cadmium(II), mercury(II), and lead(II) and much weaker complexes with the biologically important sodium, potassium, magnesium, calcium, and zinc(II) cations.

Lehn et al., in 1977, extended the bis-tripodal cryptand system by incorporating two $\text{N(CH}_2\text{CH}_2\text{NH}_2)_3$ units into the macrobicyclic framework and bridging them with $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2$ units as in 150 (Scheme V). Binuclear complexes of 151 have been reported for zinc(II), copper(II), cobalt(II), silver(I), and nickel(II), although no crystal structures have yet been determined. Studies indicate that when sodium azide is added to an aqueous solution of cryptand 151 at pH 5 a 1:1 complex (152, where Z=H) results. It has been proposed that azide
ion is bound within the cavity by six hydrogen bonds, with three of them surrounding each terminal nitrogen atom of the azide anion.\textsuperscript{121}

**Scheme V**

\[
\begin{align*}
\text{Scheme V} & \\
\text{1. } & + \\
\text{2. } & + \\
\text{3. } & + \\
\text{4. } & + \\
\end{align*}
\]

Vögtle et al. has also reported the synthesis of a series of cryptands and catapinands, \textsuperscript{153-155}, which contain aromatic rings in their bridging units. These types of macropolycyclic systems may exhibit endolipophilic-exo-
lipophilic properties indicating that these compounds may be useful as membrane transport model systems. The synthetic procedure utilized was similar to that of Lehn in that it involved the high dilution condensation of a bis-acid chloride with a diamine to afford a diamide which was subsequently reduced. Repetition of the sequence resulted in the formation of the desired cryptands in 5%, 60-70%, and 41% yields, respectively. Compound was N-alkylated with "Magic Methyl" to afford the bis-quaternary ammonium salt. Proton NMR spectroscopy
studies indicated that the counterions of the bis-ammonium salt of 155 are included within the cavity of the cryptand. 123

Few of the cryptands which have been synthesized contain the pyridino subunit, notable exceptions being 156, 157, 159, and 160. Reported by Vögtle and Wehner in 1976, these cryptands were synthesized by the condensation of 2,6-bis(chloroformyl)pyridine with the appropriate diamino crown ether macrocycle. 124 Compound 160 was the only amide reduced with diborane to afford the diamino ligand (157). The only dimeric ligand (162) isolated was the benzo-substituted tetraamide. Ligand 157 was found to form complexes with LiClO₄, NaSCN, and

\[ 156 \quad 157 \quad 158 \quad 159 \quad 160 \quad 161 \]
KSCN, whereas 156 complexed with only LiClO₄. However, cation selectivity and stability measurements were made for several cations the order of stability being as indicated for both of the ligands: barium > strontium > calcium > sodium > potassium > lithium > rubidium > cesium ~ magnesium with the order of stability as indicated for both of the ligands.¹²⁴

Vögtle et al. have also reported the synthesis of an analogous system (163 and 164) which possesses a bipyridyl bridging unit. The only complexes of 163 reported thus far are of NaSCN, LiClO₄, and NaClO₄.¹²⁵

In 1979, Weiss and coworkers¹²⁶ reported the synthesis of several macrocyclic and macrobicyclic ligands which form bimetallic copper complexes and which mimic some of the properties exhibited by the copper metalloproteins. The synthesis of 165 and 166 is accomplished by the
standard cyclization procedure developed by Lehn:102 a condensation and reduction sequence which eventually leads to the cryptand (166). Both of these systems form 1:2 (ligand to metal) complexes with copper(I) and copper(II) salts. According to molecular models, the metal to metal distances may vary from 4 to 8 Å, depending on the conformation of the ligand. Therefore, insertion of a substrate molecule which could bridge the two metal atoms should be feasible. The crystal structure determination of the dicopper(II) complex of 165 shows the metal-metal separation to be 7.228(1) Å. Also, addition of an aqueous solution of sodium azide to a methanolic solution of 165 and copper nitrate resulted in dark green crystals of 

\[ [\text{Cu}_2^2+(\text{N}_3)_4] \text{Cl}_{165} \]. (This symbolism was proposed by Lehn and Stubbs127 with \( \subset \) being the mathematical symbol of inclusion. Thus, \([S\subset L]\), means that substrate \( S \) is included in ligand \( L \). Wehner and Vögtle127 have also proposed a system of nomenclature for such macrocycles which describes the type of bridging units present. The latter method of nomenclature will be predominately utilized.) The X-ray crystal structure indicates that the two copper atoms are bridged by two azide molecules and that each copper atom is also bound to a third terminal azide nitrogen, two sulfur atoms, and one nitrogen atom of the ligand, as shown in structure 167. Such studies of 166 have not yet been published.126
The macrobicycles and their complexes are known to stabilize unusual species. The most extraordinary example is the isolation by Dye et al., of [Na⁺\(\text{c}_{2.2.2}\)Na⁻], the first salt containing an alkali metal anion, as indicated by X-ray analysis and NMR data. The salt exists as gold colored, shiny metallic crystals. The electride (\([\text{Na}^+\text{c}_{2.2.2}]e^-\)) and \([\text{K}^+\text{c}_{2.2.2}]\text{K}^-\) have also been observed. The isolation and determination of the crystal structures of the unstable ionic clusters of Sb\(_3\)\(^{3-}\), Pb\(_5\)\(^{2-}\), and Sn\(_9\)\(^{4-}\) with \([\text{Na}^+\text{c}_{2.2.2}]\) as the counterion have been achieved. Another example is the stabilization of Ln(III), Eu(III), and Gd(III) by complexation with cryptand [2.2.2]. The Eu(III) and Gd(III) cryptates show remarkable kinetic stability in aqueous solution and appear to be the first truly substitutionally inert lanthanide complexes. These lanthanide complexes may find use in NMR spectroscopy, electrochemistry, synthesis, and medicine.

These heteromacrocylocycles have also proved useful in the solubilization of salts: complexation of the cation leads to dissociation or separation of cation-anion pairs, increasing the concentration of the reagent in solution and
concomitantly enhancing the reactivity of the anion. This augmentation of reagent concentration coupled with anion activation frequently results in significant rate enhancement, as observed in the hydrolysis of hindered esters. The highly hindered methyl mesitoate is hydrolyzed at room temperature in the presence of cryptand [2.2.2] and powdered potassium hydroxide suspended in anhydrous benzene. Here the anion is activated by complexation of the potassium cation by the cryptand, resulting in separation of the ion pair. If dimethyl sulfoxide is used as the solvent instead of benzene, the reaction occurs much more rapidly.131

Complexation or cryptation also allows determination of the extent of cation participation in ionic reactions.132,133 An increase in reaction rate upon complexation of the cation indicates that the cation is not important in the mechanism of the reaction; rather, ion pair separation and the resulting anion activation governs the course of the reaction. Conversely, a decrease in reaction rate upon complexation of the cation indicates cation stabilization of the transition state or at least stabilization of the developing charge. This can be seen in the inhibition of lithium aluminum hydride reductions of carbonyl compounds by the presence of cryptand [2.2.2].132 Thus, the heteromacrocycles may become powerful tools in the study of ionic mechanisms.
B. Lateral Macrobicycles

When a macrocycle is bridged by a chelating subunit, the resulting macrobicyclic molecule may be able to form a binuclear complex: one cation complexed by the macrocycle and a second cation complexed by the bridging subunit. Such complexes may be referred to as lateral macrobicyclic dinuclear cryptates. Dinuclear complexes are of particular interest for: the study of cation interaction at short distance; as bio-inorganic models of the metalloproteins when larger intercation distances permit insertion of a substrate molecule; as a means of complexing two different cations, allowing for the possible stabilization of different oxidation states; for the selective fixation and transport of substances (i.e., gases); and for the catalysis of multicenter-multielectronic processes.

The first example of this type of chelate-bridged cryptand is 168, which forms a cryptate containing two copper(II) ions. The reduction potentials of the two ions would be expected to be vastly different, because the copper(II) complex of 169 is reduced at a potential 500 mV less positive than the copper(II) complex of 170. This is indeed found to be the case. The dinuclear copper(II) complex of 168 undergoes a monoelectronic reduction at +550 mV. The second copper(II) ion is reduced at +70 mV.
Therefore, the first reduction must be that of the copper(II) ion complexed by the [12]-N_{2} subunit, resulting in the facile formation of a Cu(I)-Cu(II) mixed valence dinuclear cryptate (171). This system suggests at the possibility of the formation of heterometallic dinuclear complexes.^{134}

Gunter and coworkers\(^{135}\) have synthesized a lateral macrobicyclic molecule 172 where a porphyrin ring is capped by a bridging unit which contains a pyridino subunit. This model system for cytochrome \(c\) oxidase is in fact a heterobinuclear complex with iron(III) complexed to the porphyrin unit and copper(II) complexed to the lateral pyridino bridge. A series of these complexes have been made with varying counterions. Mössbauer, ESR, and magnetic moment studies have been conducted to determine if there is any coupling between the two complexed metal atoms, and the data indicate that exchange coupling effects are minimal for the complexes studied.\(^{135}\)
C. Cylindrical Macrotricycles

An extension of these systems is exemplified by the synthesis of the cylindrical macrotricycles and macrotetra-cycles. The cylindrical tricycles are formed when two macrocycles are bridged by two chelating subunits. The intramolecular cavity of the mesomolecules can be altered by changing the size of the bridging units, thereby allowing some control over the complexation properties of the ligand. The general synthetic pathway is shown in Scheme VI.136 The tosyl groups are removed by treatment of 186 with sodium in liquid ammonia/ethylamine (1:1) to give 188 in 70% yield. A macrotetracyclic diamide 189 is formed when 188 is condensed under high dilution conditions with dodecanediyl dichloride. Reduction of 189 affords the expected diamine 190.137,138 Compound 187 was also formed by the same procedure as ligand 186.137
Scheme VI

173 \( X = H \)
174 \( X = \text{CO}_2 \text{CH}_2 \text{Ph} \)

175 \( X = \text{CO}_2 \text{CH}_2 \text{Ph}; \ Y = \text{CH}_2 \)
176 \( X = \text{CO}_2 \text{CH}_2 \text{Ph}; \ Y = O \)
177 \( X = \text{CO}_2 \text{CH}_2 \text{Ph}; \ Y = \text{NTs} \)
178 \( X = \text{H}; \ Y = \text{CH}_2 \)
179 \( X = \text{H}; \ Y = O \)
180 \( X = \text{H}; \ Y = \text{NTs} \)

181 \( Y = \text{CH}_2 \)
182 \( Y = O \)
183 \( Y = \text{NTs} \)
184 \( Y = \text{CH}_2 \)
185 \( Y = O \)
186 \( Y = \text{NTs} \)
Lehn and Stubbs\textsuperscript{127} have studied, via variable temperature proton NMR, the intramolecular cation exchange rate in cryptand \textsuperscript{185} for the alkaline earth metals. This exchange is a result of the large distance between the lateral cavities. Their results indicate that \textsuperscript{185} forms a "fluxional" type complex with the cations investigated. In other words, the cation migrates from one end of the cryptand molecule to the other as demonstrated in Figure II. Thus, one can envision the synthesis of molecules
which could function as channels for the flow of metal cations.

\[ \text{Figure II. The intramolecular cation exchange as indicated by variable temperature } ^1\text{H NMR data.} \]

The x-ray crystal structure of the silver nitrate complex of 185 indicates that the two silver(I) ions are included in the tricyclic macrocycle.\(^{139}\) Also, the x-ray structure of a complex of 185 with sodium iodide has been reported:\(^{140}\) there are two sodium cations encompassed by the cryptand, because the iodide ions are separated by more than 5 Å from the sodium ions, no interaction between them is possible. The distance between the two encapsulated sodium ions is 6.40 Å.

The lateral cavities of these tricyclic cryptands appear to function as units independent of each other.\(^{111}\) This feature may permit the formation of heterodinuclear complexes by these cylindrical tricycles. Such a complex of lead and silver cations has been observed with ligand 192. The heterodinuclear complex, \([\text{Pb}^{2+}\text{Ag}^+\text{c192}]\), exists in
equilibrium with the two corresponding homodinuclear complexes, \([2\text{Pb}^{2+}\text{192}]\) and \([2\text{Ag}^+\text{192}]\).\(^{141}\)

\[
\begin{array}{c}
\text{N} & \text{O} & \text{N} \\
\text{X} & \text{O} & \text{X} \\
\text{N} & \text{O} & \text{N}
\end{array}
\]

\[
\begin{array}{c}
\text{191} \ X=\text{CH}_2 \\
\text{192} \ X=\text{O} \\
\text{193} \ X=\text{NH}
\end{array}
\]

The polythia cylindrical macrotricycles, \(\text{194 and 195}\), were formed via the same synthetic sequence as the polyoxa species. However, ligand \(\text{196}\) had to be synthesized by a modified procedure in which two appendages were attached at diagonally opposed positions on the macrocycle, followed by activation of the free termini of the appendages, and condensation with the second macrocycle (Scheme VII).\(^{142}\)

\[
\begin{array}{c}
\begin{array}{c}
\text{N} \quad \text{S} \quad \text{N} \\
\text{O} \quad \text{S} \quad \text{O} \\
\text{N} \quad \text{S} \quad \text{N}
\end{array} & \\
\begin{array}{c}
\text{N} \quad \text{S} \quad \text{N} \\
\text{O} \quad \text{S} \quad \text{O} \\
\text{N} \quad \text{S} \quad \text{N}
\end{array} & \\
\begin{array}{c}
\text{N} \quad \text{S} \quad \text{N} \\
\text{O} \quad \text{S} \quad \text{O} \\
\text{N} \quad \text{S} \quad \text{N}
\end{array}
\end{array}
\]

\[
\begin{array}{c}
\text{194} & \\
\text{195} & \\
\text{196}
\end{array}
\]

Regulation of the size of the central cavity by variation of the length of the bridging units may incur strong cation-cation interactions at short distances upon complexation; at greater distances, the formation of
Scheme VII

\[ \text{Reaction 197} \]

\[ \text{Reaction 198 (70\%)} \]

\[ \text{Reaction 199 (50\%)} \]

\[ \text{Reaction 196} \]
cascade complexes by inclusion of a substrate molecule (e.g., $O_2$, $N_2$, superoxide, etc,) between the two complexed metal cations may lead to mimics of the copper proteins or of superoxide dismutase. No direct evidence for such an occurrence has been obtained, but spectral changes due to the reaction of $[2\text{Cu(II)}c_{194}]$ with potassium superoxide and of $[2\text{Cu(I)}c_{194}]$ with oxygen have been observed. Additionally, the electrochemical reduction potential of $[2\text{Cu(II)}c_{194}]$ is similar to that measured for the copper proteins.\(^{143}\)

Sutherland and colleagues reported the synthesis of a series of cylindrical macrotricycles similar to those reported by Lehn. These compounds were prepared by the reaction of the appropriate diaza crown macrocycle with the desired bis-bromomethyl arene. The authors also studied the formation of inclusion complexes of the macrotricyclic molecules (200-204) with bis-primary alkyl ammonium salts of various chain lengths (205). Competition experiments
indicated that the length of the host cavity dictates the preferential selection of the bis-ammonium salt of appropriate length to span the cavity.\textsuperscript{144}

According to proton NMR spectroscopy data, 202 forms a 1:1 inclusion complex with the bis-ammonium salts when n=2 or n=3, 203 forms a 1:1 inclusion complex when n=4, and 204 forms 1:1 inclusion complexes when n=4, 5, 6, or 7. Competition experiments on 204 and four different bis-ammonium salts (n=4-7) show that 90 preferentially complexes two salts (n=5 and n=6).

Complexes of copper(II) chloride with 202-204 were also prepared. The results indicate that 202 forms a 1:1 complex, 203 forms both a 1:1 complex and a 2:1 complex, and 204 forms only a 2:1 complex. These stoichiometries were expected, on the basis of the cavity size and the steric requirements of the ligands.\textsuperscript{144}

Vögtle and Dix prepared cryptand 207 (12\%) by the reaction of dimethyl squarate (206) with the monocyclic
crown ether amine and reported the cryptates of $^{207}$ with KSCN, RbI, and CsCl.\(^{145}\)

\[
\begin{align*}
\text{O} & \text{O} \\
\text{O} & \text{O} \\
\text{OMe} & \text{OMe} \\
\end{align*}
\begin{align*}
\text{NH} & \text{HN} \\
\end{align*}
\begin{align*}
\text{N} & \text{N} \\
\text{N} & \text{N} \\
\text{N} & \text{N} \\
\text{N} & \text{N} \\
\text{O} & \text{O} \\
\text{O} & \text{O} \\
\end{align*}
\]

The step-by-step bridging sequence generally employed should allow for the incorporation of two different bridging subunits into the macrocyclic framework. Lehn \textit{et al.} have reported just such an example in which two macrocycles are bridged by an ethylene glycol subunit and a binaphthol subunit (208), which is chiral and exhibits some degree of chiral recognition.\(^{146}\)

\[
\begin{align*}
\text{N} & \text{N} \\
\text{N} & \text{N} \\
\text{N} & \text{N} \\
\text{N} & \text{N} \\
\text{O} & \text{O} \\
\text{O} & \text{O} \\
\text{O} & \text{O} \\
\end{align*}
\]

208 (50\%)

\[\text{D. Cylindrical Macrotetracycles}\]

In 1981, Lehn \textit{et al.}\(^{147}\) reported the synthesis of previously unknown, triply bridged, cylindrical macrotetra-
cycles which are built by sequentially bridging two [18]-
$\text{N}_3\text{O}_3$ coronands. The three bridges maintain the macrocyclic
subunits at fixed distances and delineate a central intra-
molecular cavity which may be rather rigid and insulated
from its surroundings, depending on the type of bridging
subunits. Cavity 210 is much more insulated from its
external environment than the cavity of 209. The formation
of complexes of these molecules with primary bis-alkyl-
ammonium salts was studied by proton NMR spectroscopy.
Complexation with chain length descritimation for
H_3N^+-(CH_2)_n-NH_3^+ substrates was observed; ligand 210 binds
the n=5 and n=6 species, but no complexes with n=4 and n=8
cations were observed under the same reaction conditions.
Further studies indicated that the substrate binding is
more restricted in 210 and 211 than in 212, indicating that
these new systems may exhibit a very high selectivity of
complexation.147
E. Spherical Macrotricycles

The ideal organic ligand to effect molecular recognition of spherical cations is a macrocyclic system which contains a spherical intramolecular cavity into which the cation may be included, resulting in a complex of optimum stability. Graf and Lehn\(^{148}\) reported the synthesis of such a spherical ligand (221) with ten coordination sites. It contains four nitrogen atoms located at the corners of a tetrahedron and six oxygen atoms located at the corners of an octahedron. This spheroid was synthesized by a stepwise sequence in which a macrocycle is converted to a macrobicycle and finally to the spherical macrotricyclic molecule (Scheme VII). Diol 213 is converted to 217, one of the major building blocks used to construct cryptand 221. The proton NMR spectrum of 221 demonstrates the high symmetry of the molecule: there are two triplets (J = 5.5 Hz) for the CH\(_2\)-N and CH\(_2\)-O protons at 2.70 ppm and 3.65 ppm, respectively.

Cationic complexes of 221 have much higher stability constants than for the other cryptates; the Cs\(^+\) complex appears to be the most stable Cs\(^+\) complex known to date. The cation exchange rate of this cryptate is slow, and the activation energy of dissociation of the complex is high (~16 Kcal/mol).\(^{148}\) The tetrahedral array of nitrogen atoms in 221 ensures the formation of inclusion complexes
Scheme VIII

\[ \text{Scheme VIII} \]

\[ \text{NTs} \rightarrow \text{Ts} \]

\[ \text{X=Cl} \]

\[ \text{X=CN} \]

\[ \text{X=CO}_2\text{H} \]

\[ \text{X=COCl} \]

\[ \text{Ts} \rightarrow \text{B}_2\text{H}_6 \]

\[ \text{Ts} \rightarrow \text{B}_2\text{H}_6 \]

\[ \text{1) Na, NH}_3/\text{E1NH}_2 \]

\[ \text{2) Cl} \]

\[ \text{3) B}_2\text{H}_6 \]
with ammonium cations,\textsuperscript{149} and the diprotonated species complexes a water molecule.\textsuperscript{150} In other words, these spherical cryptands can act as molecule receptors which display tetrahedral recognition of small inorganic molecules.

There exist only a few synthetic sequestering agents for organic and inorganic anions, although at least seventy-five percent of all enzymes act on anionic substrates. Therefore, the synthesis and complexation properties of abiotic receptors for anions is of interest, and the study of such systems should lead to a better understanding of the mechanism of the biological processes.

The tetraprotonated spherical macrotricycles have been used to complex anions of appropriate size. The crystal structure of a chloride complex has been reported:\textsuperscript{50} the chloride anion is held in a tetrahedral network of N\textsuperscript{+}-H---Cl\textsuperscript{-} hydrogen bonds. The most stable anion complex is formed with chloride, although fluoride and bromide also form complexes; furthermore, chloride/bromide selectivity is high. This is believed to be due to the size relationship and to the inability of the rigid cavity to adapt by deformation to larger or smaller anions; as a result, there is a very large spherical macrotricyclic effect.\textsuperscript{150}

Another series of spherical macrotricyclic ligands was reported in which the final ether linkage was replaced by a
simple methylene bridge. Macrobicycle 223 was condensed
with a series of methylenic bis-acid chlorides 223-225
under high dilution conditions and reduced with diborane to
afford the spherical cryptands 226-228, respectively. The
stability and cation selectivity of the complexes of these
three spherical macrocycles with alkali and alkaline earth
metals (sodium, potassium, rubidium, cesium, calcium,
strontium, and barium) were also investigated. None of the
complexes formed with 226, 227, or 228 were found to be as
stable as the comparable complexes of ligand 221. However,
the most stable complex with ligands 226 and 227 was with
barium.151

Schmidtchen152 also reported the synthesis of
macroyclic quaternary ammonium salts which form inclusion
complexes with anions. Compound 229 was produced by
quaternization of the spherical cryptand 221 with methyl-p-
toluenesulfonate. Spherical macrotricycles 236 and 237
were synthesized by an alternate route (Scheme IX).
Quaternization of 236 and 237 with methyl fluorosulfate or
methyl-p-toluenesulfonate resulted in the tetraammonium salts 230 and 231.

According to the molecular models of 229-231, they should be able to bind chloride and bromide; 230 and 231 should also be able to bind iodide. In fact, a comparison of the stability constants of the halide complexes indicates that the bromide and iodide complexes are considerably more stable than the chloride complex. Since the solvation shell of the anion is removed during complexation, the more strongly solvated anion should result in the more labile complex. The observed order of stabilities supports this belief. Even so, the bromide and iodide complexes of 230 and 231 are, as yet, the most...
Scheme IX

\[ \text{Br} + \text{CH}_2\text{CO}_2\text{CH}_3 \xrightarrow{1) \text{TsNH}_2} \xrightarrow{2) \text{HCl}} \xrightarrow{3) \text{oxalyl chloride}} \text{Ts-} \begin{array}{l} \text{(CH}_2\text{)}^{n-1}\text{-COCl} \\ \text{(CH}_2\text{)}^n \end{array} \]

\[ \xrightarrow{1) \text{NH}_2(\text{CH}_2)^n \text{NH}_2} \xrightarrow{2) \text{B}_2\text{H}_6} \]

\[ \text{NH}_2(\text{CH}_2\text{)}^n\text{NH}_2 \xrightarrow{2) \text{B}_2\text{H}_6} \]
stable inclusion complexes observed for these anions in aqueous solutions. The halide ion inclusion complexes of ligands 230 and 231 also allow for them to be studied independently of the configurational and protonation equilibria at the nitrogen atoms as seen for Lehn's spherical cryptands.¹⁵⁰

A spherical octa-aza cryptate 238 has been synthesized in greater than 95% yield by condensation of tris(ethylene-diamine)cobalt(II) with formaldehyde and ammonia.¹⁵³ The crystal structure indicates that the synthesis occurs with retention of chirality of the Co(en)₃³⁺ ion and shows the hexadentate nature of the ligand with tris(methylene)-amino caps at both ends of the molecule. The ethylene diamine rings have the lel (λλλ) conformation and the overall symmetry is very close to D₃. The free ligand has, as yet, to be isolated.
Experimental

Reagents. Unless otherwise indicated in a specific experiment, all of the chemicals utilized were reagent grade and no purification steps were undertaken. The solvents [benzene, cyclohexane, diethyl ether, petroleum ether (bp 30-60°C), xylene, and tetrahydrofuran] were dried over sodium and distilled prior to use. N,N-Dimethylformamide was distilled from calcium hydride at reduced pressure and stored over activated molecular sieves (Linde Type, 4Å) under argon atmosphere in the dark.

Thin layer chromatography (TLC) was performed on 20cm glass plates with a 0.25mm coating of Brinkmann HF-254+366 silica gel, with the eluents indicated. The plates were activated for a minimum of 1 hour at 120°C before use. Alumina TLC plates were prepared from Brinkmann EM Aluminum Oxide 60 F-254, neutral Type E. Preparative thick layer chromatography (ThLC) utilized 20cm X 40cm glass plates with a 2mm thick coating of Brinkmann PF-254+366 silica gel and activated for a minimum of 4 hours at 120°C before use. The eluents and number of elutions are indicated in the specific experiment. Certain mixtures required ThLC plates made with 2mm of Brinkmann EM Aluminum Oxide PF-254 Type E (neutral alumina). Multiple elutions are indicated when necessary. Column chromatography procedures involved
either silica gel (Baker, 60-200 mesh) or aluminum oxide (Brinkmann EM, neutral, activity D, 70-230 mesh).

Melting points were measured in capillary tubes with a Thomas-Hoover Unimelt and are uncorrected. Mass spectral (MS) (70eV) (ass., rel. int.) data were obtained on either a Hitachi Perkin-Elmer RMS-4 or a Hewlett Packard Model 5986 GC/MS system. A fluorocarbon was employed as a counting reference. Proton nuclear magnetic resonance (\(^1\)H NMR) spectra were recorded on either a Varian Associates A-60A spectrometer or a Bruker WP-200 spectrometer as indicated. Tetramethysilane (TMS) was used as an internal standard and chemical shift values are reported in parts per million (§) downfield from TMS. Carbon-13 nuclear magnetic resonance (\(^{13}\)C NMR) spectra were obtained on a Bruker WP-200 spectrometer. Infrared spectra (IR) were recorded on either a Perkin Elmer IR-137 or an IR-621 grating spectrophotometer. Ultraviolet (UV) spectra were recorded on a Cary-14 spectrophotometer, in the stipulated solvent. The spectra were obtained in 1cm matched quartz cells and were corrected by a solvent blank.

Elemental analyses were performed by Mr. R. L. Seab in these laboratories. The X-ray structural analyses were performed by Dr. Frank R. Fronczek on Enraf-Nonius CAD4 automatic diffractometer, using programs MULTAN,\(^{155}\) SHELEX,\(^{156}\) and the Enraf-Nonius Structure Determination Package on IBM 3033 and Digital PDP 11/34 computers.
1,2-Bis(β-chloroethoxy)ethane. To a solution of triethylene glycol (10g, 66mmol) in refluxing chloroform (500mL) under nitrogen, thionyl chloride (22mL, 300mmol) in chloroform (75mL) was added dropwise over one hour. After refluxing for 12 hours, the solvent and excess thionyl chloride were removed in vacuo. The residue was treated with 10% sodium carbonate solution and extracted several times with methylene chloride (3 X 50mL). The combined extract was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give a liquid which was distilled under vacuum to afford 240: 10.98g (89%); bp 110°C (0.8mm); MS m/e 187 (M⁺, 4.4), 107 (C₆H₄OCl, 39.5), 93 (C₃H₅OCl, 100), 63 (C₂H₄Cl, 76.1).


1,2-Bis(β-iodoethoxy)ethane by the Finkelstein Reaction. A solution of 1,2-bis(β-chloroethoxy)-ethane (20g, 107mmol) and sodium iodide (32g, 214mmol) in acetone (250mL) was refluxed for 72 hours. The reaction was cooled, filtered, and concentrated in vacuo, affording
the crude product, which was vacuum distilled to give the desired diiodo compound 241: 31g (79%); bp 110°C (1mm); $^1$H NMR (200MHz, CDCl$_3$) $\delta$ 3.27 (t, $\alpha$-CH$_2$, J=6.5 Hz, 4H), 3.67 (s, $\gamma$-CH$_2$, 4H), 3.79 (t, $\beta$-CH$_2$, J=6.5 Hz, 4H); MS m/e 370 (M$^+$, 0.2); 198 (C$_4$H$_7$I, 21.7); 155 (C$_2$H$_4$I, 100).

Anal. Calcd. for C$_{12}$H$_{12}$O$_2$I$_2$: C, 19.46; H, 3.24.

Found: C, 19.79; H, 3.22.

Methyl 2,6-Pyridinedicarboxylate. A suspension of 2,6-pyridinedicarboxylic acid (167g, 1mol) in anhydrous methanol (1.5L) was saturated with anhydrous hydrochloric acid. After refluxing for 2 days, the solvent was removed in vacuo. The residue was suspended in a 10% sodium carbonate solution and extracted with chloroform (3 x 200mL). The combined organic extract was dried over anhydrous magnesium sulfate and concentrated in vacuo to afford methyl 2,6-pyridinedicarboxylate, as a colorless solid: 190g (98%); mp 122-123°C (lit. 158 mp 124-125°C); $^1$H NMR (CDCl$_3$) $\delta$ 4.00 (s, CH$_3$, 6H), 7.85-8.45 (m, 3,5-PyH, 3H); IR(KBr) 1740, 1570, 1245, 1195, 1140, 995 cm$^{-1}$. 
2,6-Bis(hydroxymethyl)pyridine. Similar to published methods, sodium borohydride (18.9g, 0.5mol) was slowly added to a solution of 2,6-dicarboxymethoxypyridine (19.5g, 0.10mol) in anhydrous methanol (500mL) via a solid addition funnel. The reaction temperature was maintained below 50°C with the aid of an ice bath. Methanol (30mL) was added and the temperature was maintained at 45°C with an ice bath for several hours until the reaction subsided. The mixture was then refluxed for 10 hours, cooled, and acetone (50mL) was added. After evaporation, the mixture was heated for 1.5 hours in 10% sodium carbonate (40mL) and upon cooling the diol precipitated to give 2,6-bis(hydroxymethyl)pyridine; 13.6g (98%); mp 111-112°C.159,160

2,6-Bis(chloromethyl)pyridine. 2,6-Bis(hydroxymethyl)pyridine (24g, 0.17mol) was slowly added to thionyl chloride (100mL) which was cooled to 0°C. The temperature was maintained at 0° for 30 minutes, then warmed to 25°C
and refluxed for 2.5 hours. The condenser was replaced
with a distillation head and the excess thionyl chloride
was removed. The thionyl chloride was removed in vacuo and
the residue was washed with benzene, filtered, and dried
under vacuum. The product was freed from its salt by the
careful addition of 10% sodium bicarbonate (300mL). The
2,6-bis(chloromethyl)pyridine was filtered, dried, and
recrystallized [petroleum ether (bp 30-60°C)] to give 245,
as a crystalline solid: 23.1g (71.5%); mp 74.5-75.5°C; $^1$H
NMR (CDCl$_3$) $\delta$ 4.88 (s, CH$_2$, 4H), 7.25-7.95 (m, PyH, 3H).
2,6-Dichloropyridine with N,N-Dimethyl-3-hydroxypropylamine. To a stirred suspension of sodium hydride (9.6g, 0.2mol) in dry xylene, N,N-dimethyl-3-hydroxypropylamine (20.6g, 0.2mol) was slowly added under nitrogen. The solution was stirred at 25°C for 30 minutes then, 2,6-dichloropyridine (14.8g, 0.1mol) in xylene (100mL) was added dropwise. The reaction was refluxed for 24 hours, cooled, and carefully quenched with water. The organic layer was separated from the aqueous layer, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The resulting liquid was distilled collecting two fractions:

Fraction A contained the monosubstituted product 246:

712mg (2%); bp 120°C (0.3mm); ¹H NMR (CDCl₃) δ 1.90 (m, β-CH₂, 2H), 2.22 (s, -CH₃, 6H), 2.42 (t, γ-CH₂, J=6.5 Hz, 2H), 4.28 (t, α-CH₂, J=6.5 Hz, 2H), 6.66 (d, 3- or 5-PyH, J=8 Hz, 1H), 6.86 (d, 5- or 3-PyH, J=8 Hz, 1H), 7.46 (t, 4-PyH, J=8 Hz, 1H); IR (neat) 3000, 1600(b), 1260, 1245, 1170, 1150, 1050, 950 cm⁻¹.

Anal. Calcd. for C₁₁H₁₁N₂OICl: C, 37.08; H, 5.06; N, 7.86. Found: C, 37.32; H, 5.18; N, 7.83.
Fraction B was shown to be the diether 247: 20.5g (73%); bp 140°C (0.3mm); $^1$H NMR (CDCl$_3$) δ 1.90 (m, $\beta$-CH$_2$, 4H), 2.22 (s, N-CH$_3$, 12H), 2.42 (t, $\gamma$-CH$_2$, J=6.5 Hz, 4H), 4.28 (t, $\alpha$-CH$_2$, J=6.5 Hz, 4H), 6.22 (d, 3,5-PyH, J=8 Hz, 2H), 7.42 (t, 4-PyH, J=8 Hz, 1H); IR (neat) 2900, 1590, 1230, 1150 cm$^{-1}$; MS (70mV) m/e 281 (M$^+$, 6), 85 (C$_5$H$_{11}$N, 100).

Anal. Calcd. for C$_{15}$H$_{27}$N$_2$0: C 64.06; H, 9.61; N, 14.95. Found: C, 63.94; H, 9.64; N, 14.86.

2,6-Dichloropyridine with N,N-Dimethylamino-2-propanol.

The above procedure was followed except for the substitution of N,N-dimethylamino-2-propanol (4.10g, 40mmol). After workup, the liquid residue was distilled to afford two fractions:

Fraction A contained the monoether 248: 172mg (4%) bp 66°C (0.1mm); $^1$H NMR (CDCl$_3$) δ 1.30 (d, C-CH$_3$, J=6 Hz, 3H), 2.29 (s, N-CH$_3$, 6H), 2.41 (d, $\beta$-CH$_A$, J=5 Hz, 1H), 2.54 (d, $\beta$-CH$_B$, J=6.5 Hz, 1H), 5.34 (m, $\alpha$-CH$_1$, 1H), 6.58 (d, 3- or 5-PyH, J=8 Hz, 1H), 6.80 (d, 5- or 3-PyH, J=8 Hz, 1H), 7.45 (t, 4-PyH, J=8 Hz, 1H); IR (neat) 3000, 1600, 1275, 1050, 970 cm$^{-1}$; MS (70eV) m/e 214 (M$^+$, 6), 85 (C$_5$H$_{11}$N, 100).
Anal. Calcd. for C_{10}H_{13}N\textsubscript{12}OCl: C, 56.07; H, 7.01; N, 13.08. Found: C, 55.94; H, 7.03; N, 12.88.

Fraction B afforded the diether 249: 4.27g (76%) bp 130°C (0.3mm); $^1$H NMR (CDCl\textsubscript{3}) $\delta$ 1.30 (d, C-CH\textsubscript{3}, J=6 Hz, 6H), 2.42 (d, $\beta$-CH, J=5 Hz, 2H), 2.50 (s, N-CH\textsubscript{3}, 12H), 2.54 (d, $\beta$-CH, J=6.5 Hz, 2H), 5.25 (m, $\alpha$-CH\textsubscript{2}, 2H), 6.20 (d, 3,5-PyH, J=8 Hz, 2H), 7.37 (t, 4-PyH, J=8 Hz, 1H); IR (neat) 3000, 1600, 1425, 1260, 1050, 790 cm$^{-1}$; MS m/e 281 (M$^+$, 9), 85 (C-H-N, 100).

Anal. Calcd. for C_{15}H_{27}N_{12}O\textsubscript{5}: C 64.06; H, 9.61; N, 14.95. Found; C, 64.02; H, 9.43; N, 14.98.

\[
\begin{align*}
\text{N} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Cl} & \quad + \quad \text{HO-} \text{NMe}_2 \\
\text{Cl} & \quad \text{NMe}_2 \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\hline
\text{250} & \quad \text{251}
\end{align*}
\]

2,6-Dichloropyridine with N,N-Dimethyl-2-hydroxyethylamine. The same procedure as described above was followed except for the substitution of N,N-dimethyl-2-hydroxyethylamine (17.8g, 0.2mol). After workup, the liquid residue was distilled to afford two fractions:

Fraction A was the low-boiling monosubstituted amine 250: 601mg (3%); bp 81°C (0.1mm); $^1$H NMR (CDCl\textsubscript{3}) $\delta$ 2.32 (s, N-CH\textsubscript{3}, 6H), 2.69 (t, $\beta$-CH, J=6 Hz, 2H), 4.39 (t, $\alpha$-CH\textsubscript{2}, J=6 Hz, 2H), 6.65 (d, 3- or 5-PyH, J=8 Hz, 1H), 6.86 (d, 5- or 3-PyH, J=8 Hz, 1H), 7.47 (t, 4-PyH, J=8 Hz, 1H);
IR (neat) 3000, 1610, 1580, 1275, 1070 cm\(^{-1}\); MS m/e 200 (M\(^+\), 4), 71 (C\(_4\)H\(_9\)N, 100).

Analytical: Calculated for C\(_9\)H\(_{13}\)N\(_2\)OCl: C, 53.86; H, 6.48; N, 13.96. Found: C, 53.73; H, 6.42; N, 13.78.

Fraction B was the diether 251: 21.5g (85%); bp 125°C (0.3mm); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 2.32 (s, N-CH\(_3\), 12H), 2.69 (d, \(\beta\)-CH\(_2\), J=6 Hz, 4H), 4.39 (t, \(\alpha\)-CH\(_2\), J=6 Hz, 4H), 6.29 (d, 3,5-PyH, J=8 Hz, 2H), 7.43 (t, 4-PyH, J=8 Hz, 1H); \(^{13}\)C NMR (200MHz, CDCl\(_3\)) \(\delta\) 45.70 (-CH\(_3\)), 58.14 (N-CH\(_2\)), 63.46 (O-CH\(_2\)), 101.65 (3,5-C), 140.61 (4-C), 162.29 (2,6-C); IR (neat) 3000, 1600, 1260, 1245, 1170, 1075 cm\(^{-1}\); MS m/e 253 (M\(^+\), 9), 71 (C\(_4\)H\(_9\)N, 100).

Analytical: Calculated for C\(_{13}\)H\(_{23}\)N\(_2\)O (253): C, 61.66; H, 9.09; N, 16.60. Found: C, 61.68; H, 9.16; N, 16.34.

\[
\begin{align*}
\text{I} & \quad \text{EIOH} & \quad \Delta \\
\text{O} & \quad \text{N} & \quad \text{N} \\
\text{N} & \quad \text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{Me} & \quad \text{Me}
\end{align*}
\]

5,5,10,10-Tetramethyl-15\(\langle\text{O}(2,6)\text{pyridino,ON}^+\text{O}_2\text{.2.4.2-}
\text{coronand-5\rangle diiodide (252). Step A. A solution of bis-2,6-
[2-(N,N'-dimethylamino)ethoxy]pyridine (710mg, 2.8 mmol) and 1,4-diiodobutane (865mg, 2.8mmol) in ethanol (500mL) was refluxed under nitrogen for three days. The solution was cooled and the solvent was removed in vacuo. The crude product was demethylated without purification.
Step B. The diquaternary coronand (1.5g, 2.8mmol) in L-Selectride® (30mL) was refluxed for two hours, then cooled and carefully quenched with 6 N hydrochloric acid (20mL). The two phase system was, subsequently, extracted with dichloromethane (2 X 50mL) and the combined organic extract was discarded. The aqueous layer was neutralized with 6 N sodium hydroxide and extracted with dichloromethane (2 X 100mL). The organic extract was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give a residue which was chromatographed (ThLC) on alumina. Elution with chloroform afforded the macrocycle 253: 105mg (13.5%); mp 45-46°C; R_f=0.30; ¹H NMR (CDCl₃) δ 1.48 (m, δ-CH₂, 4H), 2.32 (s, N-CH₃, 6H), 2.43 (m, γ-CH₂, 4H), 2.75 (t, β-CH₂, J=6 Hz, 4H), 4.37 (t, α-CH₂, J=6 Hz, 4H), 6.33 (d, 3,5-PyH, J=8 Hz, 2H), 7.43 (t, 4-PyH, J=8 Hz, 1H); IR (KBr) 2980, 1595, 1430, 1045, 1060, 795 cm⁻¹; MS m/e 279 (M⁺, 50), 112 (C₅H₆NO₂, 100).

Anal. Calcd. for C₁₅H₂₅N₃O₂: C, 64.52; H, 8.96; N, 15.05. Found: C, 64.66; H, 8.72; N, 14.88.
Quaternization of 253 (172mg, 0.60 mmol) with 1,4-diiodobutane (191mg, 0.60mmol) in absolute ethyl alcohol (250 mL) under nitrogen was performed in the same manner as previously described. After workup, the crude product refluxed with L-Selectride® (25mL) for two hours and worked up as previously described. The crude product was chromatographed (ThLC) on alumina. Elution with chloroform afforded 253, according to NMR and TLC analysis.

\[
\text{5,10-Dimethyl[N(0(2,6)pyridino,0)N-2,4,2-cryptand-5].}
\]

5,5,14,14-Tetramethyl-19\(\text{O(2,6)pyridino,ON}^+\text{O,N}^+\text{-}
\]
coronand-7\text{diiodide (254). A mixture of 1,2-\text{bis(β-iodo-}
\]
ethoxymethylenediyldimethylamino)ethoxy]pyridine (2.0g, 7.9mmol) in acetonitrile
\]
was refluxed for 72 hours, and after cooling the solvent
\]
was removed in vacuo. The crude product 254 (4.63g) mp
\]
208-209°C (dec); \text{\textsuperscript{1}H NMR (D}_2\text{O)} \delta 3.25 (s, NMe}_2\text{) was
\]
demethylated without further purification.
Step B. 5,14-Dimethyl-19\((2,6)\)pyridino,ONO\_2N-\(7\times(255)\) coronand-7\(\rightarrow\) (255). Method A. Thiophenoxide Anion. Thiophenoxide was generated by careful addition of thiophenol (240mg, 2mmol) in anhydrous benzene (50mL) to a suspension of sodium hydride (56mg, 2mmol) in benzene (25mL). The mixture was stirred for several hours at 25°C, then 254 (740mg, 2mmol) in 2-butanone (25mL) was added dropwise. The reaction was refluxed for 36 hours. After cooling, hydrochloric acid (3N, 10mL) was added, and the solution was extracted with methylene chloride (2 \times 20mL). The aqueous layer was then neutralized with sodium hydroxide and extracted with methylene chloride (2 \times 50mL). The combined organic extract was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. No demethylated products could be detected from the organic extracts.

Method B. L-Selectride\textsuperscript{®}. To a suspension of 254 (2g, 4.73mmol) in tetrahydofuran (25mL), L-Selectride\textsuperscript{®} (30mL) was added dropwise under nitrogen. After addition, the reaction was refluxed for two hours, cooled, and carefully quenched with 6N hydrochloric acid (20mL). The two phase
system was subsequently extracted with dichloromethane (2 X 50mL) and the organic extract was discarded. The aqueous layer was neutralized with 6N sodium hydroxide and was extracted with dichloromethane (2 X 100mL). The organic extract was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give a residue which was column chromatographed on neutral alumina. Sequential elution with cyclohexane/ethyl acetate (1:1) followed by methylene chloride gave the 1:1 macrocycle 255 as a colorless oil: 271mg (40%); 1H NMR (200MHz, CDCl₃) δ 2.41 (s, N-CH₃, 6H), 2.71 (t, γ-CH₂, J=6 Hz, 4H), 2.87 (t, β-CH₂, J=6.5 Hz, 4H), 3.54 (s, ε-CH₂, 4H), 3.55 (t, δ-CH₂, J=6 Hz, 4H), 4.46 (t, α-CH₂, J=6.5 Hz, 4H), 6.27 (d, 3,5-PyH, J=8 Hz, 2H), 7.39 (t, 4-PyH, J=8 Hz, 1H); IR (neat) 1590, 1255, 1150, 1060, 970 cm⁻¹; MS m/e 339 (M⁺, 11), 70 (C₄H₈N, 100).


\[
\text{255} + \text{I₂} \xrightarrow{\Delta} \text{256} + 2\text{I}^+ \quad \text{CH₃CN}
\]

5,14-Dimethyl<N⁺[O(2,6)pyridino,0][O₂]₂N⁺cryptand-9>-diiodide (256). Step A. The quaternization procedure of macrocycle 255 (1.05g, 3.1mmol) with 1,2-bis(β-iodoethoxy)-
Step B. \(<\text{N}[\text{O}(2,6)\text{pyridino},\text{O}]\text{O}_2\text{N}-\text{cryptand-9}>\) (257).

Macrocycle 256 was reduced with L-Selectride\(^\circledR\) (30mL), and after standard workup the solution was cooled and carefully quenched with 6N hydrochloric acid (20mL). The two phase system was subsequently extracted with dichloromethane (2 X 100mL) and the combined organic extract was dried over anhydrous magnesium sulfate, filtered, and concentrated \textit{in vacuo} to give a residue, which was column chromatographed on neutral aluminum oxide (elution with cyclohexane/ethyl acetate (1:1), then methylene chloride). The eluent was further purified by chromatography (ThLC) on neutral aluminum oxide. Elution with cyclohexane/ethyl acetate (1:1) gave cryptand 257, as a colorless oil: 184mg (14%); \(^1\text{H NMR (200MHz, CDCl}_3\) \(\delta 2.82 \) (t, \(\gamma-\text{CH}_2\), J=6 Hz, 8H), \(2.93 \) (t, \(\beta-\text{CH}_2\), J=7 Hz, 4H), \(3.59 \) (t, \(\delta-\text{CH}_2\), J=6 Hz, 8H), \(3.64 \) (s, \(\epsilon-\text{CH}_2\), 8H), \(4.49 \) (t, \(\alpha-\text{CH}_2\), 4H), \(6.27 \) (d, 3,5-PyH, J=8 Hz, 2H), 7.46 (t, 4-PyH, J=8 Hz, 1H); IR (neat) 2980, 2910,
1580, 1555, 1435, 1455, 1310, 1230, 1150, 1020, 780 cm\(^{-1}\); MS m/e 425 (M\(^+\), 18), 69 (C\(_4\)H\(_7\)N, 100).

Anal. Calcd. for C\(_{21}\)H\(_{35}\)N\(_3\)O\(_6\): C, 59.29; H, 8.24; N, 9.88. Found: C, 59.08; H, 8.02; N, 10.07.

![Chemical Structure](image)

Attempted Preparation of 5,15-Dimethyl-20<\(\{\text{O(2,6)-pyridino, O,N}\}_{2}\)-coronand-8> (261). Method A. To a stirred suspension of sodium hydride (1.96g, 40mmol) in dry xylene (100mL), amine 258 (2.38g, 20mmol) in xylene (50mL) was added dropwise for one hour at 25°C under nitrogen. Then 2,6-dichloropyridine (2.96g, 20mmol) in xylene (100mL) was slowly added. The reaction was refluxed for 72 hours, cooled, and carefully quenched with water. After the solvent was removed in vacuo, the resulting solid was washed with methylene chloride (3 X 100mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The crude products were purified by chromatography (ThLC) on silica gel. Elution with 10% ethanol in chloroform afforded two fractions:
Fraction A afforded an open-chain compound 259: 126mg (1.8%); Rf = 0.71; mp 56°C; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \delta 2.48 (s, N-CH\textsubscript{3}, 3H), 2.92 (t, \beta-CH\textsubscript{2}, J=5 Hz, 4H), 4.46 (t, \alpha-CH\textsubscript{2}, J=5 Hz, 4H), 6.64 (d, 3-PyH, J=8 Hz, 2H), 6.87 (d, 5-PyH, J=8 Hz, 2H), 7.50 (t, 4-PyH, J=8 Hz, 2H); IR (KBr) 2960, 2760, 1575, 1350, 1285, 1255, 1150, 940, 855, 780 cm\textsuperscript{-1}.

Anal. Calc. for C\textsubscript{15}H\textsubscript{17}N\textsubscript{3}O\textsubscript{2}Cl\textsubscript{2}: C, 52.63; H, 4.79; N, 12.88. Found: C, 52.40; H, 4.69; N, 12.63.

Fraction B was 260: 784mg (22%); mp 77-78°C; Rf = 0.54; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \delta 2.48 (s, N-CH\textsubscript{3}, 6H), 2.96 (t, \beta,\beta'-CH\textsubscript{2}, J=6 Hz, 8H), 4.42 (t, \alpha-CH\textsubscript{2}, J=6 Hz, 8H), 4.46 (t, \alpha'-CH\textsubscript{2}, J=6 Hz, 8H), 6.28 (d, 3,5-PyH, J=8 Hz, 2H), 6.64 (d, 3'- or 5'-PyH, J=8 Hz, 2H), 6.88 (d, 5'- or 3'-PyH, J=8 Hz, 2H), 7.45 (t, 4-PyH, J=8 Hz, 1H), 7.50 (t, 4'-PyH, J=8 Hz, 2H); IR (KBr) 2955, 2760, 1565, 1255, 1150, 780 cm\textsuperscript{-1}.

Anal. Calc. for C\textsubscript{25}H\textsubscript{31}N\textsubscript{5}O\textsubscript{4}Cl\textsubscript{2}: C, 55.97; H, 5.78; N, 13.06. Found: C, 55.62; H, 5.54; N, 12.88.

\[
\begin{align*}
\text{Cl} & \quad \text{OH} \\
\text{NMe} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{Cl} & \quad \text{MeN} \\
\text{NMe} & \quad \text{MeN}
\end{align*}
\]

5,15-Dimethyl-20<\text{O}(2,6)\text{pyridino},O,N\text{>}_2\text{-coronand-8}>(261). Method B. A suspension of oil-free sodium hydride (1.96g, 40mmol), N-methyldiethanolamine (2.38g, 2.3mL,
20mmol), and 2,6-dichloropyridine (2.96g, 20mmol) in DMF (700mL) was stirred under nitrogen for 84 hours at 50°C. After cooling, water was added and the solvent was removed in vacuo. The resulting residue was washed with methylene chloride (4 X 100mL), filtered, and concentrated in vacuo. The residue was chromatographed (ThLC) on silica gel. Elution with 10% ethanol in chloroform gave two products:

**Fraction A** was 259 as found from procedure A, according to TLC and NMR.

**Fraction B** was dimer 261, a white solid; 375 mg (4.8%); R_f =0.68 (silica 10% ethanol in chloroform); mp 41-42°C; 1H NMR (CDCl3) δ 2.49 (s, N-CH₃, 6H), 2.87 (t, β-CH₂, J=6 Hz, 8H), 4.40 (t, α-CH₂, J=6 Hz, 8H), 6.23 (d, 3,5-PyH, J=8 Hz, 4H), 7.40 (t, 4-PyH, J=8 Hz, 2H); IR (KBr) 2970, 2765, 2790, 1580, 1540, 1430, 1255, 1160, 790 cm⁻¹; MS m/e 388 (M⁺, 8), 83 (C₅H₉N, 100).


\[ \text{Me-N} \quad \overset{\text{I}}{\underset{\text{I}}{\text{O}}} \quad \text{O} \quad \text{N} \quad \text{Me} \quad \overset{\text{I}}{\text{O}} \quad \text{N} \quad \overset{\text{+2I}^-}{\text{O}} \quad \text{Me} \]

\[ \text{Me-N} \quad \overset{\text{I}}{\text{O}} \quad \text{N} \quad \overset{\text{CH₃CN, } \Delta}{\text{O}} \quad \text{Me} \]

\[ \text{Me-N} \quad \overset{\text{+2I}^-}{\text{O}} \quad \text{N} \quad \overset{\text{O}}{\text{N}} \quad \text{Me} \]
5,15-Dimethyl<\textit{N}^+\textit{[O(2,6)pyridino,0]_2[O]_2}\textit{N}^{+}\textit{cryptand-10}>-diiodide (262). A mixture of coronand (276\textit{mg}, 0.7\textit{mmol}) and the 1,2-bis(\textit{\beta}-idoethoxy)ethane (263\textit{mg}, 0.7\textit{mmol}) in acetonitrile (750\textit{mL}) was refluxed for 72 hours. After cooling, the solvent was removed \textit{in vacuo} and the crude product was dried \textit{in vacuo}, affording the crude \textit{bis}-quaternary salt which was demethylated.

\[
\begin{align*}
\text{Me} & \quad \text{N}^+ \quad \text{O} \quad \text{O} \quad \text{N} \quad \text{Me} \\
\text{N} & \quad \text{O} \quad \text{O} \quad \text{N} \quad \text{Me} \\
\end{align*}
\]

\text{"L-Selectride"}

\[
\begin{align*}
+ 2 \text{I}^- \\
\end{align*}
\]

\[
\begin{align*}
\text{262} & \quad \text{263} \\
\end{align*}
\]

<\textit{N}[\textit{O(2,6)pyridino,0]_2[O]_2}\textit{N-cryptand-10}> (263). After refluxing the \textit{bis}-quaternary compound 262 (500\textit{mg}, 0.7\textit{mmol}) in a tetrahydrofuran solution of L-Selectride® (25\textit{mL}) for two hours, the solution was cooled, hydrolyzed with 3N hydrochloric acid (10\textit{mL}), and extracted with methylene chloride (3 \times 50\textit{mL}). The aqueous layer was neutralized with sodium hydroxide (3N) and extracted with methylene chloride (3 \times 50\textit{mL}). The methylene chloride was removed \textit{in vacuo}, and the product was chromatographed (ThLC) by elution with cyclohexane/ethyl acetate (4:1) to afford the cryptand 322 as an oily solid: 12\textit{mg} (0.3\%); \textit{R}_f =0.32; ^1\text{H} NMR (200\text{MHz}, \textit{CDCl}_3) \delta 2.92 (t, \textit{\gamma}-\textit{CH}_2, \textit{J}=6 \text{ Hz}, 4\textit{H}), 3.00 (t, \textit{\beta}-\textit{CH}_2, \textit{J}=6.7 \text{ Hz}, 8\textit{H}), 3.61 (t, \textit{\delta}-\textit{CH}_2, \textit{J}=6 \text{ Hz}, 4\textit{H}), 3.64 (s,
<N[O(2,6)Pyridino, O]_3 N-cryptand-11> (264). To a mixture of triethanolamine (1.5g, 10mmol) and oil-free sodium hydride (1.44g, 30mmol) in xylene (500mL), 2,6-dichloropyridine (2.22g, 15mmol) in xylene (100mL) was added dropwise. The solution was refluxed for 72 hours, after which, the solution was cooled and carefully quenched with water. The organic extract was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give a crude product which was triturated with cyclohexane/ethyl acetate (2:1) and filtered. The resultant solid was recrystallized from a mixture of chloroform and ethyl alcohol to afford 264, as colorless crystals: 140mg (3%); mp 228°C (dec); ¹H NMR (200MHz, CDCl₃) δ 3.08 (t, β-CH₂, J=6 Hz, 12H), 4.32 (t, α-CH₂, J=8 Hz, 12H), 6.13 (d, 3,5-PyH, J=8 Hz, 6H), 7.30 (d, 4-PyH, J=8 Hz, 3H); ¹³C NMR (200MHz, CDCl₃) δ 55.09 (N-CH₂), 65.42 (O-CH₂), 101.65 (3,5-C), 141.00 (4-C), 162.21 (2,6-C); IR (KBr) 1580, 1250, 1145 cm⁻¹; UV (CH₃CN) λ_max 276 (3.10 X 10⁶), 258
(sh, 2.36 x 10^6), 225 (7.50 x 10^6); MS m/e 523 (M^+, 0.1), 95 (C_5H_5NO, 100).

Anal. Calcd. for C_{27}H_{33}N_5O: C, 61.95; H, 6.31; N, 13.28. Found: C, 61.84; H, 6.42; N, 13.26.

![Chemical structure](image)

6,6,11,11-Tetramethyl-17\(\text{O}(2,6)\)pyridino,ON^+\text{-3.4.3-c coronand-5>diiodide (265). The same quaternization procedure was followed except bis-2,6\((3\text{-N,N-dimethyl-}

N_{\text{amino propoxy}]}\text{pyridine (1g, 3.6mmol) was used. After cooling, the solvent was reduced to 75mL, upon which white precipitate formed. The precipitate was filtered and dried in vacuo to afford 265 (1.16g), which was directly demethylated.

![Chemical structure](image)

6,11-Dimethyl-17\(\text{O}(2,6)\)pyridino,ON^-\text{-3.4.3-coronand-5> (266). The general demethylation procedure was employed except 265 (1.16g, 1.96mmol) was used. The crude product was chromatographed (ThLC) on alumina. Elution with
chloroform gave 266, as a white powder: 120mg (20%); mp 41-42°C; R_f=0.28; 1H NMR (CDCl_3) δ 2.17 (m, -CH_2, 4H), 2.62 (m, β-CH_2, 4H), 2.90 (s, N-CH_3, 6H), 3.01 (m, δ-CH_2, 4H), 3.15 (t, γ-CH_2, J=6 Hz, 4H), 4.37 (t, α-CH_2, J=6 Hz, 4H), 6.25 (d, 3,5-PyH, J=8 Hz, 2H), 7.45 (t, 4-PyH, J=8 Hz, 1H); IR (KBr) 2960, 1585, 1550, 1440, 1250, 1140, 780 cm⁻¹; MS m/e 307 (M⁺, 100); 221 (C_{12}H_{17}N_2O_2, 53); 98 (C_6H_{12}N, 54); 84 (C_5H_{10}N, 85).

Anal. Calcd. for C_{17}H_{29}N_2O_2: C, 66.66; H, 9.15; N, 13.73. Found: C, 66.38; H, 9.07; N, 13.43.

\[
\begin{align*}
\text{Attempted Preparation of } & 6,11\text{-Dimethyl}<N[O(2,6)\text{pyridino,0}]N-3.4_2.3\text{-cryptand-5>diiodide. Quaternization of } \\
266 & \text{ (240mg, 0.78mmol) with } 1,4\text{-diiodobutane (216mg, 0.78mmol) in anhydrous ethyl alcohol (250mL) under nitrogen was performed as described above. After workup, the crude product was demethylated with L-Selectride® (25mL) by refluxing for two hours. The crude product was chromatographed (ThLC) on alumina eluting with chloroform to afford } \\
266 & \text{, the starting material.}
\end{align*}
\]
6,6,15,15-Tetramethyl-21<0(2,6)pyridino,ON<sup>+</sup>O<sub>2</sub>N<sup>-</sup>-3.2.3-coronand-7>diiodide (267). The same quaternization procedure as described above was followed, except bis-2,6-[3-(N,N-dimethylamino)propoxy]pyridine 247 (2g, 7.0mmol) was used. The crude product [4.32g; mp 178-179°C (dec)] was demethylated without further purification.

6,15-Dimethyl-21<0(2,6)pyridino,ONO<sub>2</sub>N-3.2.3-coronand-7> (268). The demethylation procedure as described above was used except 267 (1.86g, 4.12mmol) was substituted for 265. The crude product was chromatographed (ThLC) on alumina. Elution with cyclohexane/ethyl acetate (1:1) gave the 1:1 macrocycle 268, as a colorless oil: 1.29g (43%); <sup>1</sup>H NMR (200MHz, CDCl<sub>3</sub>) δ 1.95 (m, β-CH<sub>2</sub>, 4H), 2.28 (s, N-CH<sub>3</sub>, 6H), 2.56 (t, γ-CH<sub>2</sub>, J=6.8 Hz, 4H), 2.58 (t, δ-CH<sub>2</sub>, J=5 Hz, 4H), 3.56 (t, ε-CH<sub>2</sub>, J=5 Hz, 4H), 3.56 (s, ζ-CH<sub>2</sub>, 4H), 4.36 (t, α-CH<sub>2</sub>, J=6.8 Hz, 4H), 6.25 (d,
3,5-PyH, J=8 Hz, 2H), 7.43 (t, 4-PyH, J=8 Hz, 1H); IR (neat) 2985, 2915, 1585, 1440, 1320, 1240, 1155, 780 cm⁻¹; MS m/e 367 (M⁺, 6.0), 84 (C₅H₁₀N, 100).


6,15-DimethylN⁺[O(2,6)pyridino,0][O₂]₂N⁺-cryptand-9>diiodide (269). A solution of 268 (1.02 g, 2.78 mmol) and bis(2-iodoethoxy)ethane (1.03 g, 2.78 mmol) in acetonitrile (600 mL) was refluxed under nitrogen for three days. After cooling, the solvent was removed in vacuo to afford 6,15-dimethylN⁺[O(2,6)pyridino,0][O₂]₂N⁺-cryptand-9>diiodide [mp 202-203°C (dec); ¹H NMR (D₂O) δ 3.23 (s, N-Me)] which was demethylated without further purification.

6,15-DimethylN⁺[O(2,6)pyridino,0][O₂]₂N⁺-cryptand-9>diiodide (269). A solution of 268 (1.02 g, 2.78 mmol) and bis(2-iodoethoxy)ethane (1.03 g, 2.78 mmol) in acetonitrile (600 mL) was refluxed under nitrogen for three days. After cooling, the solvent was removed in vacuo to afford 6,15-dimethylN⁺[O(2,6)pyridino,0][O₂]₂N⁺-cryptand-9>diiodide [mp 202-203°C (dec); ¹H NMR (D₂O) δ 3.23 (s, N-Me)] which was demethylated without further purification.

6,15-DimethylN⁺[O(2,6)pyridino,0][O₂]₂N⁺-cryptand-9>diiodide (269). A solution of 268 (1.02 g, 2.78 mmol) and bis(2-iodoethoxy)ethane (1.03 g, 2.78 mmol) in acetonitrile (600 mL) was refluxed under nitrogen for three days. After cooling, the solvent was removed in vacuo to afford 6,15-dimethylN⁺[O(2,6)pyridino,0][O₂]₂N⁺-cryptand-9>diiodide [mp 202-203°C (dec); ¹H NMR (D₂O) δ 3.23 (s, N-Me)] which was demethylated without further purification.

6,15-DimethylN⁺[O(2,6)pyridino,0][O₂]₂N⁺-cryptand-9>diiodide (269). A solution of 268 (1.02 g, 2.78 mmol) and bis(2-iodoethoxy)ethane (1.03 g, 2.78 mmol) in acetonitrile (600 mL) was refluxed under nitrogen for three days. After cooling, the solvent was removed in vacuo to afford 6,15-dimethylN⁺[O(2,6)pyridino,0][O₂]₂N⁺-cryptand-9>diiodide [mp 202-203°C (dec); ¹H NMR (D₂O) δ 3.23 (s, N-Me)] which was demethylated without further purification.

6,15-DimethylN⁺[O(2,6)pyridino,0][O₂]₂N⁺-cryptand-9>diiodide (269). A solution of 268 (1.02 g, 2.78 mmol) and bis(2-iodoethoxy)ethane (1.03 g, 2.78 mmol) in acetonitrile (600 mL) was refluxed under nitrogen for three days. After cooling, the solvent was removed in vacuo to afford 6,15-dimethylN⁺[O(2,6)pyridino,0][O₂]₂N⁺-cryptand-9>diiodide [mp 202-203°C (dec); ¹H NMR (D₂O) δ 3.23 (s, N-Me)] which was demethylated without further purification.
of 5,14-dimethyl<sup>N⁺</sup>[O(2,6)pyridino,O]<sub>2</sub>N⁺-cryptand-9>di-
iodide to afford cryptand 270, as a colorless oil; 189mg
(15%): ¹H NMR (200MHz, CDCl₃) δ 1.81 (m, β-CH₂, 4H), 2.54
(s, γδ-CH₂, 12H), 3.46 (s, ετ-CH₂, 16H), 4.38 (m, α-CH₂,
4H), 6.20 (d, 3,5-PyH, J=8 Hz, 2H), 7.41 (t, 4-PyH, J=8 Hz,
1H); IR (neat) 2985, 2900, 1585, 1260, 1155, 1045, 780
cm⁻¹; (MS) m/e 453 (M⁺, 5), 84 (C₅H₁₀N, 100).

Anal. Calcd. for C₂₃H₃₉N₄O: C, 60.93; H, 8.61; N, 9.27. Found: C, 61.15; H, 8.64; N, 9.01.

2,6-Bis(chloromethyl)pyridine with N,N-Dimethyl-2-
hydroxyethylamine. To a suspension of sodium hydride
(1.10g, 46mmol) in N,N-dimethylformamide (DMF, 500mL),
N,N-dimethyl-2-hydroxyethylamine (4.05g, 46mmol) in DMF
(100mL) was added dropwise under nitrogen. The mixture was
stirred at 25°C for one hour and then 245 (4g, 23mmol) in
DMF (100mL) was added dropwise. The reaction was stirred
at 25°C for three days, after which, the solvent was
removed in vacuo. The residue was extracted with
chloroform (2 x 250mL), filtered, and concentrated in vacuo
to give the crude product, which was chromatographed
through a short alumina column eluting with chloroform.
After concentration the oil was vacuum distilled \(\text{[bp 156°C (0.5mm)]}\) to afford the disubstituted product 271: 8.79g (68%); \(^1\text{H NMR (CDCl}_3\) \(\delta 2.30 \text{ (s, N-CH}_3\), 12H), 2.58 \text{ (t, } \gamma-\text{CH}_2, J=6 \text{ Hz, 4H)}, 3.67 \text{ (t, } \beta-\text{CH}_2, J=6 \text{ Hz, 4H)}, 4.67 \text{ (s, } \alpha-\text{CH}_2, 4H), 7.27-7.84 \text{ (m, PyH, 3H)}; \(^{13}\text{C NMR (200MHz, CDCl}_3\) \(\delta 45.70 \text{ (CH}_3\), 58.77 \text{ (N-CH}_2\), 68.86 \text{ (O-CH}_2\), 73.87 \text{ (Py-CH}_2\), 119.72 \text{ (3,5-C), 136.93 \text{ (4-C)}, 157.83 \text{ (2,6-C); IR (neat) 2950, 1595, 1250, 1160, 1080 cm}^{-1}\); (MS) m/e 281 \((M^+, 2), 95 \text{ (C}_5\text{H}_5\text{NO, 100)}\).

Anal. Calcd. for C\(_{15}\)H\(_{27}\)N\(_3\)O: C, 64.06; H, 9.61; N, 14.95. Found: C, 64.32; H, 9.62; N, 15.16.

\[\begin{array}{c}
\text{N} \\
\text{Me} \text{Me} \text{Me} \text{Me}
\end{array}\] \(\xrightarrow{\text{I, CH}_3\text{CN, }\Delta}\) \[\begin{array}{c}
\text{N}^+ \text{O}^- \\
\text{Me} \text{Me} +2\text{I}^-
\end{array}\]  

\text{Attempted Preparation of 6,6,15,15-Tetramethyl-21<O(2,6)pyridino,ON\(_2\)N\(_2\)-1,2,2,2,2,1-coronand-7>diiodide (272). To a solution of 271 (2g, 7.12mmol) in acetonitrile (500mL), 1,2-bis(\beta-iodoethoxy)ethane (2.63g, 7.12mmol) in acetonitrile (50mL) was slowly added. The solution was refluxed for 72 hours, and after cooling, the acetonitrile was removed in vacuo. The crude product was demethylated without further purification.}
Attempted Preparation of 6,15-Dimethyl-21\(\text{O}(2,6)-\)pyridino,\(\text{ONO}_2\)N-1.2.2.2.1-coronand-7\(>\). A suspension of 272 in tetrahydrofuran with L-Selectride® was stirred under nitrogen until all the material dissolved. The reaction mixture was carefully quenched with dilute hydrochloric acid (10mL), extracted with methylene chloride (50mL), and the aqueous layer neutralized with sodium hydroxide (3N). The aqueous solution was then extracted with methylene chloride (3 x 50mL), the combined organic extract was dried over anhydrous magnesium sulfate, and concentrated in vacuo. The crude product was purified by chromatography (ThLC) on alumina. Elution with cyclohexane/ethyl acetate (1:1) afforded only open-chain demethylated products, according to \(^1\text{H} \text{NMR} \) data. The \(^1\text{H} \text{NMR} \) spectrum indicated the appearance of a methyl group at 2.55 ppm, in general, methyl groups located in the 2 or 6 position of a pyridine ring resonate at \(\delta\) 2.46 as seen for lutidine while the \(\text{N}\)-methyl groups resonate from \(\delta\) 2.28 to 2.38 as seen for 268 and 271. The aromatic region is also complicated indicative of an unsymmetrically substituted pyridine ring, normally \(\text{H}(3,5)\) exhibits a doublet at ca. \(\delta\) 7.30 as for 274
and 276; however, in all fractions there were two doublets at approximately δ 7.03 and 7.24. Because of the large number of very small fractions obtained, further characterization was not attempted.

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{N} & \quad \text{N} \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\]

6,19-Dimethyl-25<[O(2,6)pyridino,ON-1.2.1]_2-coronand-8> (274). To a stirred suspension of sodium hydride (969mg, 20mmol) in dry N,N-dimethylformamide (DMF; 100mL), 2,6-bis(chloromethyl)pyridine (1.76g, 10mmol) in DMF (200mL) and N-methyldiethanolamine (1.19g, 10mmol) in DMF (200mL) were added simultaneously dropwise over four hours under nitrogen. After addition, the reaction was stirred at 25°C for 96 hours. Thereafter, the suspension was carefully quenched with water (10mL), then the solvent was removed in vacuo. The residue was chromatographed (ThLC) on alumina by elution with ethyl acetate/cyclohexane (1:1) to afford dimer 274, as a colorless oil: 460mg (5.2%); \( R_f = 0.34; \)

\[ ^1H \text{NMR (200MHz, CDCl}_3 \delta 2.38 (s, N-CH}_3, 6H), 2.70 (t, \gamma-\text{CH}_2, J=6 \text{ Hz}, 8H), 3.63 (t, \beta-\text{CH}_2, J=6 \text{ Hz}, 8H), 4.57 (s, \alpha-\text{CH}_2, 8H), 7.29 (d, 3,5-\text{PyH}, J=8 \text{ Hz}, 4H), 7.51 (t, \]
4-PyH, J=8 Hz, 2H); IR (neat) 2995, 1595, 1250, 1165, 1030, 775 cm⁻¹; MS m/e 444 (M⁺, 0.4), 83 (C₅H₉N, 100).

Anal. Calcd. for C₂₄H₃₄N₄O₄: C, 64.86; H, 8.11; N, 12.61. Found: C, 64.89; H, 8.13; N, 12.99.

6,19-Dimethyl-25N⁺[O(2,6)pyridino,0-2.1₂2]₂[O₂⁻]⁻N⁺-cryptand-10>diiodide (275). The mixture of 274 (386mg, 1mmol) and 1,2-bis(β-iodoethoxy)ethane (370mg, 1mmol) in acetonitrile (500mL) was refluxed for 72 hours. After cooling, the solvent was removed in vacuo, and the resulting residue was dried under vacuum. The crude material was demethylated without further purification.

Attempted Preparation of 24N[O(2,6)Pyridino,0-
2.1₂2]₂[O₂⁻]⁻N-cryptand-10>. The above crude residue was
stirred under nitrogen in tetrahydrofuran (30mL) with L-Selectride® until all the starting material dissolved, after which the reaction was carefully quenched with dilute hydrochloric acid (10%, 10mL). The solution was extracted with methylene chloride (2 x 25mL), then the aqueous layer was neutralized with sodium hydroxide (3N), and extracted with methylene chloride (2 x 50mL). The organic solvent was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford product (338mg), which was chromatographed (ThLC) on alumina. Elution with ethyl acetate/cyclohexane (1:1) gave four fractions all of which were shown via $^1$H NMR to be ring-opened demethylated material. This was determined by the appearance of a methyl signal at δ 2.55 indicative of a methyl group substituted in the 2 or 6 position on a pyridine ring. In addition, the aromatic region has become more complicated and the pattern of two doublets at δ 7.05 and 7.24 is indicative of an unsymmetrically substituted pyridine ring. Further purification and identification was not undertaken.

![Chemical Reaction Image]
a stirred suspension of sodium hydride (960mg, 20mmol) in dry N,N-dimethylformamide (DMF; 500mL) 2,6-bis(chloro-
methyl)pyridine (1.76g, 10mmol) in DMF (125mL) and tri-
ethanolamine (983mg, 875 L, 6.6mmol) in DMF (125mL) were
added simultaneously dropwise. After the addition was
complete, the reaction was stirred at 25°C for three days.
The solvent was removed in vacuo, and the residue was
triturated with methylene chloride (3 X 100mL), filtered,
and concentrated in vacuo to give a crude product, which
was column chromatographed (neutral alumina, activity III,
1:1 cyclohexane/ethyl acetate) to afford cryptand 276, as
colorless crystals (chloroform/ethanol): 135 mg (2%); mp
118-119°C; Rf=0.29; $^1$H NMR (200MHz, CDCl$_3$) δ 2.82 (t,
N-CH$_2$, J=5 Hz, 12H), 3.56 (t, O-CH$_2$, J=5 Hz, 12H), 4.52 (s,
Pyr-CH$_2$, 12H), 6.90 (t, 4-PyH, J=8 Hz, 3H), 7.30 (d,
3,5-PyH, J=8 Hz, 6H); $^{13}$C NMR (200MHz, CDCl$_3$) δ 57.67
(N-CH$_2$), 70.19 (O-CH$_2$), 73.48 (PyCH$_2$), 119.33 (3,5-C),
136.62 (4-C), 157.83 (2,6-C); IR (KBr) 1600, 1460, 1355,
1120, 1050, 970 cm$^{-1}$; MS m/e 607 (M$^+$, 1.9); 578
(C$_{32}$H$_{42}$N$_4$O$_6$, 1) 487 (C$_{26}$H$_{39}$N$_4$O$_5$, 1); 120 (C$_7$H$_6$NO, 78); 106
(C$_7$H$_8$N, 96); 97 (C$_5$H$_7$NO, 73); 95 (C$_5$H$_5$NO, 100).

Anal. Calcd. for C$_{33}$H$_{45}$N$_5$O: C, 65.24; H, 7.41; N,
Attempted Formation of the Manganese(II) Perchlorate Complex of \(\text{N[O}(2,6)\text{Pyridino,0-2.1.2]}_3\text{N-cryptand-11}]\).

Manganese(II) perchlorate (3.9mg, 1.08x10^-5mmol) and 2,2-dimethoxypropane (500 L) were stirred in a minimum amount of ethanol (5mL) for one hour, after which 276 (3.3mg, 5.40x10^-6mmol) in ethanol (1mL) was added. Upon addition, a white solid precipitated, which was recrystallized from methanol to afford crystals suitable for X-ray structure determination. The product was shown to be the diprotonated perchloric salt 277.

\[
\text{N(CH}_2\text{CH}_2\text{OH)}_3
\]

\[
\text{NaH, DMF}
\]

Attempted Preparation of \(\text{N[O}(6,6')2,2'\text{-dipyridino,0-2.1.2]}_3\text{N-cryptand-14}]\) (279). To a suspension of sodium hydride (500mg, 10mmol) in \(\text{N,N-dimethylformamide (DMF, 200mL)}\), triethanolamine (490mg, 3.3mmol, 437 L) in DMF (200mL) was slowly added. After stirring at 25°C under
nitrogen for 30 minutes, 6,6'-bis(chloromethyl)-2,2'-dipyridine (1.27 g, 5 mmol) in DMF (200 mL) was added dropwise over a period of four hours. The mixture was stirred at 25°C for 72 hours, after which the solvent was removed in vacuo. The resulting crude product was triturated with chloroform (300 mL), filtered, and the solvent was removed in vacuo. The desired cryptand should have a significant $R_f$ value on alumina TLC; however, nothing moved from the baseline using 10% ethanol in chloroform. This leads one to conclude that none of the desired macrocyclic product was formed.

Reaction of 2,7-Dichloro-1,8-naphthyridine with Triethanolamine. To a stirred suspension of sodium hydride (2.16 g, 45 mmol) in $\text{N,N}$-dimethylformamide (DMF, 150 mL), triethanolamine (2.24 g, 15 mmol) in DMF (150 mL) was added under nitrogen. The heterogeneous solution was stirred for one hour at 25°C and 280 (2.0 g, 10 mmol) in DMF (200 mL) was added dropwise. After addition, the suspension was warmed to 80°C via an oil bath for 72 hours. Then, the solution was cooled, carefully quenched with water, and the solvent
removed in vacuo. The resulting residue was washed with methylene chloride (2 X 100mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo, to give the crude product, which was chromatographed (ThLC) on alumina by elution with 5% methanol in chloroform to afford two fractions:

**Fraction A** was 281, a pale yellow viscous oil; 128mg (3%); \( R_f = 0.23 \); \(^1\)H NMR (CDCl\(_3\)) \( \delta \): 2.60 (m, \( \gamma\)-CH\(_2\), 8H), 2.85 (t, \( \beta\)-CH\(_2\), J=6 Hz, 4H), 3.76 (m, \( \delta\)-CH\(_2\), 8H), 4.74 (t, \( \alpha\)-CH\(_2\), J=6 Hz, 4H), 6.88 (d, 3,5-NaphH, J=8 Hz, 2H), 7.95 (d, 4,5-NaphH, J=8 Hz, 2H); IR (neat) 1600, 1255, 1160, 1050, 975 cm\(^{-1}\).


**Fraction B** was 282, isolated as a viscous oil; 250mg (9%); \( R_f = 0.33 \); \(^1\)H NMR (CDCl\(_3\)) \( \delta \): 2.80 (t, \( \gamma\)-CH\(_2\), J=5 Hz, 4H), 3.19 (t, \( \beta\)-CH\(_2\), J=6 Hz, 8H), 3.70 (t, \( \delta\)-CH\(_2\), J=5 Hz, 4H), 4.66 (t, \( \alpha\)-CH\(_2\), J=6 Hz, 8H), 6.61 (d, 3,5-NaphH, J=8.5 Hz, 4H), 7.65 (d, 4,5-NaphH, J=8.5 Hz, 2H); IR (neat) 1610, 1260, 1155, 1045, 970 cm\(^{-1}\).

**Anal. Calcd. for C\(_{28}\)H\(_{34}\)N\(_6\)O\(_6\)·HCl:** C, 57.34; H, 5.97; N, 14.32. Found: C, 57.68; H, 5.99; N, 14.24.
284. The dianion of $\text{N},\text{N}^\prime$-bis-2-hydroxyethylpiperazine was generated by the dropwise addition of 283 (3.48g, 20mmol) in xylene (100mL) to a suspension of sodium hydride (1.92g, 40mmol) in xylene (100mL). The solution was stirred for 45 minutes at 25°C and then 2,6-dichloropyridine (2.96g, 20mmol) in xylene (50mL) was added dropwise. The mixture was refluxed for 24 hours under nitrogen, cooled, and carefully quenched with water. The xylene layer was removed and the aqueous layer was extracted with methylene chloride (3 X 50mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was dry column chromatographed (5% methanol in chloroform; silica gel) to give 26$\langle0(2,6)$-pyridino,0(1,4)piperazino$\rangle_2$-coronand-10$\rangle$ 284: 996mg (10%); $R_f$=0.62; mp 240°C (dec); $^1$H NMR (CDCl$_3$) $\delta$ 2.67 (s, $\gamma$-CH$_2$, 16H), 2.78 (m, $\beta$-CH$_2$, 8H), 4.46 (m, $\alpha$-CH$_2$, 8H), 6.27 (d, 3,5-PyH, J=$8\text{ Hz}$, 4H), 7.45 (t, 4-PyH, J=$8\text{ Hz}$, 2H); IR (KBr) 2970, 2900, 1590, 1560, 1430, 1450, 1300, 1230, 1145, 1010, 780 cm$^{-1}$; MS m/e 498 (M$^+$, 2), 83 (C$_5$H$_9$N, 100).

Anal. Calcd. for C$_{26}$H$_{38}$N$_6$O$_4$: C, 62.67; H, 7.62; N, 16.86. Found: C, 62.64; H, 7.49; N, 16.75.
ill

285

30<[O(2,6)Pyridino,O,(1,4)piperazino-1.2.1]-coronand-
10> (285). N,N'-Bis-2-hydroxyethylpiperazine (992mg, 5.7mmol) in anhydrous tetrahydrofuran (THF, 100mL) was slowly added to a stirred suspension of sodium hydride (55mg, 11.4mmol) in THF (200mL). Subsequently the solution was stirred with heating for one hour. After cooling, 2,6-bis(chloromethyl)pyridine (1g, 5.7mmol) in THF (100mL) was added dropwise. The reaction was stirred at 25°C for five days, after which, the solvent was removed in vacuo. Water was carefully added and extracted with methylene chloride (300mL). The organic extract was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give a crude product which was chromatographed (ThLC) on alumina. Elution with 2% ethanol in chloroform afforded \( \text{285} \): 200mg; mp 122-123°C; \( R_f =0.47 \); \(^1\)H NMR (200MHz, CDCl\(_3\)) \( \delta \) 2.48 (s, 5-CH\(_2\), 16H), 2.57 (t, 6-CH\(_2\), J=6 Hz, 8H), 3.04 (t, \( \beta \)-CH\(_2\), J=6 Hz, 8H), 4.54 (s, 8-CH\(_2\), 8H), 7.30 (d, 3,5-PyH, J=8 Hz, 4H), 7.54 (t, 4-PyH, J=8 Hz, 2H); IR (KBr) 2980, 1590, 1240, 1155, 1020, 780 cm\(^{-1}\); MS m/e 554 (M\(^+\), 0.4), 136 (C\(_8\)H\(_{14}\)N\(_2\), 100).

Anal. Calcd. for C\(_{30}\)H\(_{46}\)N\(_4\)O\(_2\): C, 64.98; H, 8.30; N, 15.16. Found: C, 65.24; H, 8.59; N, 15.45.
Attempted Preparation of 14<[(S(2,6)Pyridino,S)]₂-coronand-6>. Method A. To a stirred suspension of ethanedithiol (940mg, 10mmol) and sodium hydride (960mg, 20mmol) in N,N-dimethylformamide (DMF, 200mL), 2,6-dichloropyridine (1.48g, 10mmol) in DMF (100mL) was added dropwise under nitrogen. The reaction was stirred at 25°C for 24 hours, then warmed to 75°C for 48 hours. After cooling, water was carefully added, and the solvent removed in vacuo to give a residue, which was washed with chloroform (2 x 150mL) and filtered. The combined chloroform extract was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude product was passed through a short silica gel column. Elution with cyclohexane/ethyl acetate (1:1) afforded only one fraction (359mg), which was rechromatographed (ThLC) on silica gel by elution with acetone/petroleum ether (1:9) to give two major fractions.

Fraction A afforded 287: mp 100-101°C; 38.4mg (2%); R_f=0.63; ^1H NMR (200MHz, CDCl₃) δ 3.14 (bs, β-CH₂, 4H), 3.28 (bs, α-CH₂, 4H), 6.90 (d, 3,5-PyH, J=8 Hz, 2H), 7.31 (t, 4-PyH, J=8 Hz, 1H); IR (KBr) 2960, 1620, 1540, 1410, 1155, 1140, 780 cm⁻¹; MS m/e 229 (M⁺, 62), 201 (C₇H₇NS₃, 30), 168 (C₇H₆NS₂, 44), 143 (C₅H₅NS₂, 100).
**Anal. Calcd. for C9H11NS3:** C, 47.16; H, 4.80; N, 6.11. Found: C, 46.86; H, 4.88; N, 5.81.

*Fraction B afforded 288:* mp 151-152°C; 57.8mg (2%); Rf = 0.52; 1H NMR (200MHz, CDCl3) δ 2.82 (m, β-CH2, 4H); 2.85 (s, γ-CH2, 4H); 3.51 (m, α-CH2, 4H); 6.88 (d, 3,5-PyH, J=8 Hz, 2H); 7.27 (t, 4-PyH, J=8 Hz, 1H); IR (KBr) 2960, 1615, 1415, 1270, 1195, 1120, 770, 695, 675 cm⁻¹; (MS) m/e 289 (M⁺, 33), 261 (C9H11NS4, 14), 230 (C9H12NS3, 21), 203 (C7H9NS3, 75), 168 (C7H6NS2, 56), 143 (C5H5NS2, 100).

**Anal. Calcd. for C11H15NS4:** C, 45.67; H, 5.19; N, 4.84. Found: C, 45.38; H, 5.23; N, 4.61.

\[ \text{F-N-F} + \text{SH-SH} \xrightarrow{\text{NaH, DMF}} \text{SSSS} + \text{SSSS} \]

**Attempted Preparation of 14(S2,6)Pyridino,S1₂-coronand-6.** Method B. To a stirred suspension of sodium hydride (960mg, 20mmol) in anhydrous N,N-dimethylformamide (DMF, 350mL), 2,6-difluoropyridine (1.12g, 10mmol) in DMF (100mL) and ethanediithiol (940mg, 10mmol) in DMF (100mL) were added dropwise simultaneously under nitrogen. After 48 hours at 25°C the solvent was removed in vacuo to give a residue which was washed with chloroform and filtered. The solvent was removed in vacuo to give a crude product which was chromatographed (ThLC) on silica gel by eluting
with 2% acetone in petroleum ether to afford two fractions.

Fraction A (5%): the $R_f$, NMR spectrum, and mp were consistent with those of 287.

Fraction B (3%): spectral and physical data were in accordance with those of 288.

\[
\begin{align*}
\text{Cl} & \quad \text{H} \\
\text{N} & \quad \text{MeNCH}_2\text{CH}_2\text{NMMe}
\end{align*}
\]

2,5,8,12-Tetramethyl-14\(\text{[N}(2,6)\text{pyridino,} \text{N}]_2\)-coronane-6> (291). Method A. To a stirred solution of $\text{N,N'}$-dimethylethlenediamine (4.4g, 50mmol) in anhydrous benzene (250mL), n-butyllithium (60mL, 2.17M in hexane, 100mmol) was added dropwise under nitrogen. The suspension was stirred for one hour at 25°C, then 2,6-dichloropyridine (7.45g, 50mmols) in benzene (100mL) was added slowly. After stirring at 25°C for five days, the mixture was carefully quenched with water and the organic layer was concentrated in vacuo to afford a residue which was column chromatographed [silica gel, cyclohexane/ethyl acetate (1:1)]. The product was further purified by chromatography (ThLC) by elution with cyclohexane/ethyl acetate (9:1) to afford two fractions:
Fraction A was the open-chain 2:1 compound \(290\); 3.78 g (25%); mp 90-91°C; \(R_f = 0.81\); \(^1H\) NMR (CDCl\(_3\)) \(\delta \) 3.0 (s, N-CH\(_3\), 6H), 3.68 (s, N-CH\(_2\), 4H), 6.36 (d, 3-PyH, J=8 Hz, 2H), 6.45 (d, 5-PyH, J=8 Hz, 2H), 7.26 (t, 4-PyH, J=8 Hz, 1H); IR (KBr) 2940, 1585, 1490, 1400, 1255, 1155, 765 cm\(^{-1}\); MS m/e 311 (M\(^+\), 0.3), 155 (C\(_7\)H\(_8\)Cl, 100).

Anal. Calcd. for C\(_{14}\)H\(_{16}\)N\(_2\)Cl: C, 54.02; H, 5.15; N, 18.00. Found: C, 53.95; H, 5.32; N, 17.69.

Fraction B was the desired 2:2 macrocycle (291):
326 mg (2%); mp 240°C (dec); \(R_f = 0.75\); \(^1H\) NMR (200MHz, CDCl\(_3\)) \(\delta \) 3.00 (s, N-CH\(_3\), 12H), 3.75 (s, -CH\(_2\), 8H), 5.73 (d, 3,5-PyH, J=8 Hz, 4H), 7.30 (t, 4-PyH, J=8 Hz, 2H); IR (KBr) 2990, 1575, 1485, 1310, 1190, 1160, 1045, 965, 770, 720 cm\(^{-1}\); MS m/e 326 (M\(^+\), 20), 150 (C\(_8\)H\(_{12}\)N\(_3\), 100).

Anal. Calcd. for C\(_{18}\)H\(_{26}\)N\(_6\): C, 66.26; H, 7.96; N, 25.77. Found: C, 65.95; H, 8.03; N, 25.51.

\[
\text{Cl} \quad \text{N} \quad \text{Cl} \quad \xrightarrow{\text{MeNCH}_2\text{CH}_2\text{NMe}} \quad \text{H} \quad \xrightarrow{\text{NaH, xylene, } \Delta} \quad \text{Cl} \quad \text{N} \quad \text{Cl} \quad \text{N} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me}
\]

\(290\)

Attempted Preparation of 2,5,8,12-Tetramethyl-14\(^<\text{[N-(2,6)pyridino,N]}_2\) coronand-6\(>\) (291). Method B. To a stirred suspension of oil free NaH (4.80g, 100mmol) in xylene (250mL), N,N'-dimethylethlenediamine (4.4g, 50mmol) in xylene (50mL) was slowly added. The solution was
maintained at 25°C for 30 minutes, then 2,6-dichloro-
pyridine (7.4g, 50mmol) in xylene (50 mL) was added
dropwise. After refluxing under nitrogen for four days,
the mixture was cooled and carefully quenched with water.
The organic layer was concentrated and the aqueous layer
was extracted with methylene chloride (3 x 50mL). The
combined organic extract was dried over anhydrous
magnesium sulfate, filtered, and concentrated in vacuo.
The crude product (6.94g) was purified by column chromatography by elution with cyclohexane/ethyl acetate (1:1) and the resultant product was recrystallized from absolute
ethanol to give 290, as white crystals: 5g (35%); mp
90-91°C; 1H NMR (CDCl₃) δ 3.0 (s, N-CH₃, 6H), 3.68 (s,
-CH₂, 4H), 6.36 (d, 3-PyH, J=8 Hz, 2H), 6.45 (d, 5-PyH,
J=7.5 Hz, 2H), 7.26 (t, 4-PyH, J=7.5 Hz, 1H); IR (KBr)
2940, 1585, 1535, 1430, 1255, 1155, 1100, 990, 765
cm⁻¹; MS m/e 311 (M⁺, 9.5), 155 (C₇H₆N₂Cl, 100).

Anal. Calcd. for C₁₄H₁₆N₄Cl₂:  C, 54.02; H, 5.15; N,
18.00. Found: C, 53.95; H, 5.32; N, 17.69.
2,5,8,12-Tetramethyl-14<\text{[N}(2,6)\text{pyridino,N]}_2^{-}\text{coronand}-6>\text{)} (291). Method C. The same procedure as in Method B was used except that LiH was substituted for NaH. After workup, the crude product was chromatographed (ThLC) on alumina by elution with cyclohexane/ethyl acetate (8:2) to give two fractions:

**Fraction A** was dimer 291, as shown by physical and spectral data.

**Fraction B** was trimer 292, a colorless, viscous oil:

- 120mg (2%); $R_f = 0.68$; $^1$H NMR (CDCl$_3$) $\delta$ 2.92 (s, N-CH$_3$, 18H), 3.68 (s, -CH$_2$, 12H), 5.69 (d, 3,5-PyH, $J=8$ Hz, 6H), 7.23 (t, 4-PyH, $J=8$ Hz, 3H); IR (KBr) 2995, 2960, 1580, 1490, 1420, 1190, 1155, 985, 770 cm$^{-1}$; MS m/e 489 ($M^+$, 2), 150 (C$_8$H$_{12}$N$_2$, 100).

**Anal. Calcd.** for C$_8$H$_{12}$N$_2$: C, 66.26; H, 7.96; N, 25.77. **Found:** C, 65.98; H, 7.92; N, 25.57.

![Chemical Structure](image)

**Attempted Preparation of 2,5,8,12-Tetramethyl-14<\text{N-}\text{(2,6)pyridino,N]}_2^{-}\text{coronand-6}>\text{)} (291).** To a stirred suspension of NaH (154mg, 7.6mmoles) in dry xylene (50mL) N,N'-dimethylenediamine (141mg, 1.9mmol) was slowly added under nitrogen. The solution was maintained at 25°C for 30
minutes, then 290 (500mg, 1.9mmoles) in xylene (50mL) was added dropwise. The solution was refluxed for 7 days, then carefully quenched with water and the organic layer was separated. The aqueous layer was extracted with methylene chloride (2 x 50mL) and the combined organic extract was dried over anhydrous magnesium sulfate and concentrated in vacuo. NMR and TLC showed the resulting residue to be starting material.

![Chemical structure](image)

3,6,12,15-Tetramethyl-18<N(2,6)pyridino,N-1.2.1>2-coronand-6> (293). Method A. A solution of 2,6-bis-(chloromethyl)pyridine (1.76g, 10mmol), N,N'-dimethyl-ethylenediamine (880mg, 10mmol), and potassium carbonate (3.66g, 20mmol) in N,N-dimethylformamide (600mL) was stirred at 25°C for 72 hours. The solution was filtered and the solvent was removed in vacuo to afford crude product (2.85g), which was chromatographed (ThLC) on alumina by elution with cyclohexane/ethyl acetate (1:1) to afford two fractions:

Fraction A was dimer 293: 65mg (3%); mp 80-81°C; 
R_f=0.56; \(^1\)H NMR (200MHz, CDCl\(_3\)) \(\delta\) 2.39 (s, N-CH\(_3\), 12H), 2.48 (s, N-CH\(_2\), 8H), 3.57 (s, Py-CH\(_2\), 8H), 7.15 (d,
3,5-PyH, J=7.6 Hz, 4H), 7.52 (t, 4-PyH, J=7.6 Hz, 2H); IR (KBr) 2960, 2900, 1580, 1445, 1135, 1000, 830, 800, 740 cm⁻¹; MS m/e 383 (M²⁺, 14), 382 (M⁺, 25), 204 
(C₁₂H₁₈N₂, 83), 178 (C₁₀H₁₆N₂, 92), 149 (C₁₀H₁₃N₂, 100), 107 (C₉H₇N, 68).


Fraction B was trimer 294, a viscous oil: 62mg (1%);
R = 0.45; ¹H NMR (200MHz, CDCl₃) δ 2.27 (s, N-CH₃, 18H), 2.54 (s, N-CH₂, 12H), 3.60 (s, Py-CH₂, 12H), 7.21 (d, 3,5-PyH, J=7.6 Hz, 6H), 7.47 (t, 4-PyH, J=7.6 Hz, 3H); IR (neat) 2970, 2905, 1585, 1140, 1010, 840, 800, 745 cm⁻¹; MS m/e 572 (M⁺, 12), 149 (C₁₀H₁₃N₂, 100), 107 (C₉H₇N, 100).


\[
\begin{align*}
\text{Cl} & \quad \text{MeNCH}_2\text{CH}_2\text{NMe} \\
\text{LiH, DMF} & \quad \text{MeNCH}_2\text{CH}_2\text{NMe} \\
\text{Cl} & \quad \text{MeNCH}_2\text{CH}_2\text{NMe} \\
\end{align*}
\]

\[
\begin{align*}
3,6,12,15\text{-Tetramethyl}-18\langle]\text{N(2,6)pyridino,N-1.2.1}_2\text{-coronand-6}\rangle \quad (293). \quad \text{Method B}. \quad \text{To a stirred suspension of lithium hydride (160mg, 20mmol) in N,N-dimethylformamide (DMF, 300mL), N,N'-dimethylthelylendiamine (880mg, 10mmol) in DMF (50mL) was added under nitrogen. After stirring at 25°C for one hour, 2,6-bis(chloromethyl)pyridine (1.76g,}
\]
10 mmol) in DMF (300 mL) was added dropwise. The solution initially turned blue green, but after stirring for several minutes the color dissipated. The mixture was stirred for 72 hours at 25°C, after which the solution was filtered and the solvent was removed in vacuo. The resulting crude product (1.70 g) was chromatographed (ThLC) on alumina by elution with cyclohexane/ethyl acetate (1:1) to afford dimer 293 (7.8%) and trimer 294 (8%), both were characterized by TLC, NMR, and MS and shown to be identical to previously prepared samples.

Complexation of 293 with Cobalt(II) Chloride. The dimeric macrocycle 293 (45.6 mg, 1.2 X 10^{-2} mmol) was dissolved in methanol and a solution of cobalt(II) chloride (28 mg, 1.2 X 10^{-2} mmol) in methanol was added. After slow evaporation of the methanol, crystals suitable for x-ray structure determination were obtained: mp >300°C.
Attempted Preparation of \(14\left[(2,6)\text{Pyridino,}(1,4)\text{-piperazino}\right]_2\text{-coronand-6}\) (331). Method A. To a stirred suspension of sodium hydride (2.0g, 50mmol) in dry xylene (250mL), piperazine (2.15g, 25mmol) in xylene (50mL) was added under nitrogen. The solution was stirred for one hour, then 2,6-dichloropyridine (3.7g, 25mmol) was added. The reaction was refluxed for 72 hours, cooled, and carefully quenched with water. The organic layer was concentrated in vacuo to give a residue (5.16g), which was chromatographed (ThLC) on silica gel. Elution with methanol/chloroform (1:9) afforded two products:

Fraction A was the 1:1 open-chain compound 298, a colorless viscous oil: 104mg (12%); \(R_f=0.35\); \(^1\text{H NMR (CDCl}^3\) \(\delta 1.81 (s, -\text{NH}, 1H), 2.93 (m, \alpha-\text{CH}_2, 4H), 3.49 (m, \beta-\text{CH}_2, 4H), 6.40 (d, 3,5-\text{PyH}, J=7.5 \text{Hz, 1H}), 6.53 (d, 3,5-\text{PyH}, J=7.5 \text{Hz, 1H}); IR (neat) 2940, 2920, 1580, 1460, 1240, 1160, 1130, 970, 790, 770 cm\(^{-1}\); MS m/e 197 (M\(^+\), 25), 155 (C\(_9\)H\(_8\)N\(_2\)Cl, 100).


Fraction B afforded the 2:1 compound 299: 49.5mg (3.8%); mp 142-143\(^\circ\)C; \(R_f=0.75\); \(^1\text{H NMR (CDCl}^3\) \(\delta 3.67 (s, -\text{CH}_2, 8H), 6.48 (d, 3,5-\text{PyH}, J=8 \text{Hz, 2H}), 6.59 (d, 3,5-\text{PyH}, J=8 \text{Hz, 2H}); IR (KBr) 2940, 2920, 1580, 1540, 1460, 1430, 1240, 1160, 1130, 970 cm\(^{-1}\); MS m/e 309 (M\(^+\), 2), 141 (C\(_6\)H\(_5\)N\(_2\)Cl, 100).
Anal. Calcd. for C_{14}H_{14}N_{4}Cl_{2}: C, 54.37; H, 4.53; N, 18.12. Found: C, 54.48; H, 4.54; N, 18.03.

Attempted Preparation of 14<(2,6)pyridino, (1,4)-piperazino]_{2}-coronand-6>. Method B. To a stirred solution of piperazine (2.15g, 25mmol) in anhydrous benzene (250mL), butyllithium (23mL, 50mmol) was added dropwise under nitrogen. The mixture was refluxed for one hour, then 2,6-dichloropyridine (3.70g, 25mL) in benzene (25mL) was slowly added. After refluxing for 24 hours, the mixture was cooled, and water was carefully added. The solvent was removed dried over anhydrous magnesium sulfate and concentrated in vacuo. Other than butylated products, only one product was isolated and shown to be the 2:1 compound 299 (2g, 52%), according to physical and spectral data.

18<[[(2,6)Pyridino, (1,4)piperazino]_{2}-coronand-6] (300). To a stirred suspension of anhydrous potassium
carbonate (3.66g, 20mmol) in N,N-dimethylformamide (DMF; 500mL), piperazine (860mg, 10mmol) in DMF (25mL) and 2,6-
bis(chloromethyl)pyridine (1.76g, 10mmol) in DMF (25mL)
were slowly added under nitrogen. The reaction was stirred
at 25°C for 72 hours, filtered, and the solvent was removed
in vacuo. The resulting residue was dissolved in
chloroform, filtered, and concentrated in vacuo to give a
crude product which was column chromatographed on neutral
alumina. Elution with 2% methanol in chloroform afforded
three fractions:

Fraction A afforded dimer 300: 50mg (2.6%); 275°C
dec; Rf =0.89 (2% methanol in chloroform, alumina); 1H NMR
(200MHz, CDCl3) δ 2.58 (s, β-CH2, 16H), 3.77 (s, α-CH2,
8H), 7.01 (d, 3,5-PyH, J=7.3 Hz, 4H), 7.52 (t, 4-PyH,
J=7.3 Hz, 2H); IR (KBr) 2960, 2900, 1580, 1445, 1135, 1000,
830, 800, 740 cm⁻¹; MS m/e 378 (M⁺, 26), 190 (C11H7N3,
25), 107 (C7H9N, 100).

Analytical. Calcd. for C22H30N6: C, 69.84; H, 7.94; N,
22.22. Found: C, 69.89; H, 7.97; N, 22.52.

Fraction B afforded trimer 301: 155mg (18%); Rf =0.73
(2% methanol in chloroform, alumina); 1H NMR (200MHz,
CDCl3) δ 2.48 (s, β-CH2, 24H), 3.64 (s, α-CH2, 12H), 7.24
(d, 3,5-PyH, J=7.3 Hz, 6H), 7.57 (t, 4-PyH, J=7.3 Hz, 3H);
IR (neat) 2965, 2910, 1585, 1445, 1134, 1010, 830, 810
cm⁻¹; MS m/e 567 (M⁺, 60), 379 (C22H31N6, 22), 190
(C11H6N3, 22), 106 (C7H8N, 100).
Anal. Calcd. for C$_{33}$H$_{45}$N$_9$: C, 69.84; H, 7.94; N, 22.22. Found: C, 69.65; H, 7.89; N, 21.98.

Fraction C afforded tetramer 302: 270mg (14%);
$R_f$ = 0.61; $^1$H NMR (200MHz, CDCl$_3$) $\delta$ 2.51 (s, $\beta$-CH$_2$, 32H), 3.65 (s, $\alpha$-CH$_2$, 16H), 7.25 (d, 3,5-PyH, J = 7.9 Hz 8H), 7.57 (t, 4-PyH, J = 7.9 Hz, 4H); IR (neat) 2970, 2900, 1590, 1450, 1135, 1015, 835, 810 cm$^{-1}$; MS m/e 756 (M$^+$, 8); 567 (C$_{33}$H$_{45}$N$_9$, 4); 190 (C$_{11}$H$_{16}$N$_3$, 35); 133 (C$_{8}$H$_9$N$_2$, 33); 107 (C$_{7}$H$_9$N, 100).

Anal. Calcd. for C$_{44}$H$_{60}$N$_{12}$: C, 69.84; H, 7.94; N, 22.22. Found: C, 69.99; H, 7.80; N, 21.95.

Complexation of 18<[(2,6)Pyridino,(1,4)piperazino,-1,2,1,-coronand-6> (300) with Copper(II) Chloride. To a solution of coronand 300 (21mg, 5.56 $\times$ 10$^{-5}$mmol) in methanol (5mL), copper(II) chloride (7.47mg, 5.56 $\times$ 10$^{-5}$ mmol) in methanol (2mL) was added. The slow evaporation of the methanol lead to the formation of amber crystals 303 (mp >300°C) suitable for X-ray analysis.

$$\text{NH}_2 \text{NH}_2$$

Complexation of 18<[(2,6)Pyridino,(1,4)piperazino,-1,2,1,-coronand-6> (300) with Copper(II) Chloride. To a solution of coronand 300 (21mg, 5.56 $\times$ 10$^{-5}$mmol) in methanol (5mL), copper(II) chloride (7.47mg, 5.56 $\times$ 10$^{-5}$ mmol) in methanol (2mL) was added. The slow evaporation of the methanol lead to the formation of amber crystals 303 (mp >300°C) suitable for X-ray analysis.
Attempted Preparation of 2,6-Bis(aminomethyl)pyridine.

Method A. Sodium Borohydride. Sodium borohydride (18.9 g, 0.50 mol) was slowly added to a solution of 2,6-pyridinedicarboxamide (1.65 g, 0.10 mol) in anhydrous methanol (500 mL) via a solid addition funnel. The temperature was maintained below 50°C. After the addition was completed, additional methanol (30 mL) was introduced and the temperature was monitored at 45°C for several hours until the reaction subsided. The mixture was refluxed for 10 hours, cooled, and acetone (50 mL) was added. After evaporation, the mixture was heated for 1.5 hours in 10% sodium carbonate (4 mL), then taken to dryness, and the resulting solid was continuously extracted with chloroform to afford exclusively starting material.

\[
\begin{align*}
\text{LAH} &\rightarrow \text{NR} \\
\text{Q} &\begin{array}{c}
\text{N} \\
\text{H}_2 \\
\text{N} \\
\text{H}_2
\end{array}
\end{align*}
\]

Method B. Lithium Aluminum Hydride. To a suspension of 2,6-pyridinedicarboxamide (2 g, 12 mmol) in anhydrous tetrahydrofuran (THF, 500 mL), lithium aluminum hydride (2 g, 53 mmol) was slowly added under nitrogen. The reaction was stirred at 25°C for twelve hours and then refluxed for twelve hours. After cooling, ice water (3 mL) was cautiously added. The slurry was filtered and the resulting solid was washed with cold THF. The organic layer was
dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was washed with hydrochloric acid (10%), filtered, and neutralized with 3N sodium hydroxide. The aqueous solution was filtered to afford starting material according to melting point data, mp 319-320°C (lit.161 mp 320-321°C).

2,6-Bis(chloromethyl)pyridine with N,N'-Bis(3-aminopropyl)piperazine. To a stirred suspension of anhydrous potassium carbonate (960mg, 20mmol) in N,N-dimethylformamide (DMF, 500mL), 2,6-bis(chloromethyl)pyridine (1.76g, 10mmol) in DMF (25mL) and N,N'-bis(3-aminopropyl)piperazine (2g, 10mmol) in DMF (25mL) were slowly added simultaneously. After 72 hours under nitrogen at 25°C the solvent was removed in vacuo. The resulting residue was washed with chloroform, filtered, and concentrated in vacuo to afford only polymeric material which would not redissolve in chloroform.
2-Amino-7-hydroxy-1,8-naphthyridine (304). A mixture of malic acid (3.0g, 22mmol) and 2,6-diaminopyridine (2.2g, 20mmol) was ground to an intimate powder, cooled in an ice bath, and concentrated sulfuric acid (10mL) was added dropwise. The solution was heated to 110°C for two to three hours, then poured over ice, and made alkaline with concentrated ammonium hydroxide (pH8). 2-Amino-7-hydroxy-1,8-naphthyridine was isolated: mp > 350°C (lit.162 mp > 360°C); 3.56g (97%); $^1$H NMR (DMSO-$d_6$) $\delta$ 6.12 (d, 3-NaphH, J=9 Hz, 1H), 6.35 (d, 6-NaphH, J=9 Hz, 1H), 6.94 (s, $-\text{NH}_2$, 2H), 7.65 (d, 4,5-NaphH, J=9 Hz, 2H).

2,7-Dihydroxy-1,8-naphthyridine. 2-Amino-7-hydroxy-1,8-naphthyridine (4.7g, 29mmol) was ground to a fine powder and added to concentrated sulfuric acid (40mL), then sodium nitrite (2.4g) was added. The mixture was allowed to stand for five minutes, poured over crushed ice and allowed to stand for ten minutes. Excess sodium nitrite was neutralized with sodium carbonate, then the solution
was acidified with glacial acetic acid (pH 3) giving 305, as a pale green powder: mp 321-323°C (lit. 320-330°C); 4.1 g (87%); 1H NMR (DMSO-d₆) δ 3.15 (bs, -OH, 2H), 6.25 (d, 3,6-NaphH, J=9 Hz, 2H), 7.75 (d, 4,5-NaphH, J=9 Hz, 2H).

![Chemical structure of 2,7-Dichloro-1,8-naphthyridine](image)

**2,7-Dichloro-1,8-naphthyridine.** A mixture of 2,7-dihydroxy-1,8-naphthyridine (500 mg, 3.1 mmol), phosphorus pentachloride (1.25 g, 7 mmol), and phosphorus oxychloride (1.12 g, 7 mmol) was refluxed for two hours, then ice was carefully added. The solution was made alkaline with sodium carbonate. A brown precipitate was collected and recrystallized from acetone to give 306, as a white powder: subl pt 258°C (lit. 259°C); 500 mg (81%); 1H NMR (CDCl₃) δ 7.50 (d, 3,5-NaphH, J=9 Hz, 2H); 8.10 (d, 4,5-NaphH, J=9 Hz, 2H).

![Chemical structure of 2,7-Dicyano-1,8-naphthyridine](image)

**2,7-Dicyano-1,8-naphthyridine.** Method A. Potassium Cyanide. To a stirred solution of potassium cyanide (1.3 g, 20 mmol) in dry N,N-dimethylformamide (250 mL), 2,6-dichloro-
1,8-naphthryidine (2g, 10mmol) was added under nitrogen. The solution was heated at 80°C for 24 hours. After cooling, the solvent was removed in vacuo to afford only black insoluble material (3.3g).

Method B. Cuprous Cyanide. Finely powdered 2,7-dichloro-1,8-naphthryidine (2g, 10mmol) was added to a stirred solution of cuprous cyanide (4.33g, 50mmol) in dry pyridine (100mL). After refluxing for 24 hours, the solution was cooled and a saturated solution of sodium cyanide (100mL) was added and the mixture was stirred for 8 hours at room temperature to afford black insoluble crude (2.98g).

2,7-Dichloro-1,8-naphthryidine with Diethylene Glycol.
To a stirred suspension of sodium hydride (960mg, 20mmol) in dry N,N-dimethylformamide (DMF, 10mL), diethylene glycol (1.06g, 10mmol) in DMF (25mL) was slowly added. The mixture was stirred at 25°C for one hour and 306 (2g,
10mmol) in DMF (100mL) was slowly added. The reaction was heated at 80°C for 72 hours, cooled, and then water was cautiously added. The solvent was removed in vacuo, and the resultant solid was washed with methylene chloride (3 x 100mL), filtered, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give an oil, which was chromatographed (ThLC) on alumina by eluting twice with chloroform to afford two macrocycles:

**Fraction A** afforded 307, as colorless needles (chloroform/2-propyl alcohol): mp 254-255°C; 78mg (1.6%); $R_f$ = 0.46 (chloroform, alumina); $^1$H NMR (200MHz, CDCl$_3$) $\delta$ 4.04 (m, $\beta$-CH$_2$, 8H), 4.82 (m, $\alpha$-CH$_2$, 8H), 6.58 (d, 3,6-NaphH, J=8.5 Hz, 4H), 7.67 (d, 4,5-NaphH, J=8.5 Hz, 4H); IR (neat) 1630, 1510, 1330, 1130, 800 cm$^{-1}$; MS m/e 464 ($M^+$, 5), 259 (22), 231 (51), 189 ($C_{10}H_9N_2O_2$, 100), 162 (52), 145 (37).

**Anal. Calcd. for C$_{24}$H$_{26}$N$_4$O$_7$: C, 59.76; H, 4.97; N, 11.62. Found: C, 59.85; H, 4.99; N, 11.56.**

**Fraction B** afforded 308, as colorless microcrystals (chloroform-propyl alcohol): 36mg (0.5%); mp 230-230.5°C; $R_f$ = 0.46 (chloroform, alumina); $^1$H NMR (200MHz, CDCl$_3$) 3.97 (m, $\beta$-CH$_2$, 12H), 4.69 (m, $\alpha$-CH$_2$, 12H), 6.78 (d, 3,6-NaphH, J=9 Hz, 6H), 7.79 (d, 2,5-NaphH, J=9 Hz, 6H); IR (neat) 1610, 1510, 1340, 1270, 1135, 1025, 850, 805 cm$^{-1}$; MS m/e 696 ($M^+$, 12), 189 ($C_{10}H_9N_2O_2$, 100).

2,7-Dichloro-1,8-naphthyridine with Triethylene Glycol. Triethylene glycol (1.5 g, 10 mmol) in dry N,N-dimethylformamide (DMF, 25 mL) was added to a stirred suspension of sodium hydride (960 mg, 20 mmol) in dry DMF (10 mL). The mixture was stirred at 25°C for one hour, then 306 (2 g, 10 mmol) in DMF (100 mL) was added dropwise. The reaction was heated at 80°C for 72 hours, cooled, and then water (50 mL) was cautiously added. The solvent was removed in vacuo and the resulting solid was washed with methylene chloride (3 x 100 mL) and filtered. The filtrate was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give an oil, which was chromatographed (ThLC) on alumina by eluting once with chloroform to give dimer 309, as a white solid: 110 mg (2%); mp 219-220°C (ethanol); R$_f$ = 0.36; $^1$H NMR (CDCl$_3$) δ 3.74 (s, γ-CH$_2$, 8H), 3.89 (m, β-CH$_2$, 8H), 4.70 (m, α-CH$_2$, 8H), 6.77 (d, 3,6-NaphH, J=9 Hz, 4H), 7.78 (d, 4,5-NaphH, J=9 Hz, 4H); IR (neat) 1600, 1495, 1430, 1320, 1250, 1105, 1050,
940, 845, 800 cm\(^{-1}\); MS m/e 552 (M\(^+\), 2), 275 (30), 231 (19), 189 (C\(_{10}\)H\(_{9}\)N\(_{2}\)O\(_2\), 100), 162, (98), 145 (37).

Anal. Calcd. for C\(_{28}\)H\(_{34}\)N\(_{4}\)O\(_9\): C, 58.98; H, 5.61; N, 9.82. Found: C, 59.12; H, 5.81; N, 9.89.

\[
\begin{align*}
\text{Cl} & \quad \text{Me} \\
\text{N} & \quad \text{OH} \\
\text{N} & \quad \text{OH} \\
\text{N} & \quad \text{Me} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{Me} \\
\end{align*}
\]

5,17-Dimethyl-24\([O(2,7)1,8\text{-naphthyridino,ON}\]_2-coronand-10> (310). To a stirred suspension of sodium hydride (120mg, 5mmol) in dry N,N-dimethylformamide (DMF, 10mL), N-methyldiethanolamine (298mg, 2.5mmol) in DMF (50mL) was slowly added under nitrogen. The mixture was stirred at 25°C for one hour and 306 (500mg, 2.5mmol) in DMF (100mL) was added dropwise. Then the reaction was heated at 80°C for 72 hours, cooled, and water was cautiously added. The solvent was removed in vacuo, and the resulting solid was washed with methylene chloride (3 X 100mL) and filtered. The filtrate was dried over anhydrous magnesium sulfate and concentrated in vacuo to give an oil, which was chromatographed (ThLC) on alumina by eluting with chloroform to afford the dimer 310: 56mg (4.6%); \(R_f=0.64\) (chloroform, alumina); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 2.57 (s, N-CH\(_3\), 6H), 3.04 (t, β-CH\(_2\), 8H), 4.73 (t, α-CH\(_2\), J=6 Hz, 8H), 6.76 (d, 3,6-NaphH, J=8 Hz, 4H), 7.67 (d, 4,5-NaphH, J=8 Hz,
4H); IR (KBr) 1620, 1520, 1345, 1280, 850 cm\(^{-1}\); MS m/e 490 (M\(^+\), 2), 189 (C\(_{10}\)H\(_9\)N\(_2\)O\(_2\), 100).

Anal. Calcd. for C\(_{26}\)H\(_{30}\)N\(_4\)O\(_4\)HCl: C, 59.26; H, 5.69; N, 15.95. Found: C, 59.00; H, 5.85; N, 15.60.

2-Methyl-1,8-naphthyridine. Skraup Reaction of 2-Amino-6-methylpyridine with Glycerol. A mixture of sodium m-nitrobenzenesulfonate (70g, 0.36mol), sulfuric acid (320g, 98%), boric acid (9.6g, 0.16mol), and ferrous sulfate heptahydrate (5.6g, 0.02mol) was chilled to 0-5°C via an ice/aceton bath. Anhydrous glycerol [vacuum distilled (bp 125°C/3 torr); 50mL] was added and the slurry stirred for 15 min., after which 2-amino-6-methylpyridine (17.28g, 0.16mol) in warm water (50°C, 100mL) was added dropwise. The mixture was stirred for five hours at 135°C, then made basic with 50% sodium hydroxide and extracted with methylene chloride. The organic extract was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give 2-methyl-1,8-naphthyridine (312): 11.2g (49%); mp 98-99°C (cyclohexane); lit.\(^{163,164}\) mp 99-100°C; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 2.79 (s, \(-\text{CH}_3\), 3H), 7.38 (d,
3-NaphH, J=8 Hz, 1H), 7.43 (dd, 6-NaphH, J=8, 4 Hz, 1H),
8.09 (d, 4-NaphH, J=8 Hz, 1H), 8.17 (dd, 5-NaphH J=8, 2 Hz,
1H), 9.13 (dd, 7-NaphH, J=4, 2 Hz, 1H).

2,7-Dimethyl-1,8-naphthyridine. A solution of
2-methyl-1,8-naphthyridine (7.87, 0.055mol) in anhydrous
diethyl ether was cooled to -60°C via a dry ice/acetone
bath. Methyllithium (102mL, 1.55M, 158mmol) was added
dropwise at a rate such that the temperature was maintained
< -50°C. After two hours, the solution was warmed to 25°C
for an additional two hours and then carefully quenched
with water. The organic layer was dried over anhydrous
magnesium sulfate, filtered, and concentrated in vacuo.
The resulting orange solid was oxidized with a solution of
potassium permanganate in acetone. The solution was
filtered, dried over anhydrous magnesium sulfate, and
concentrated in vacuo to afford 2,7-dimethyl-1,8-naphthyridine (313), as a pale yellow solid: 7.3g (84%); mp
193-195°C (cyclohexane); lit.165,166 mp 194-195°C; 1H
NMR (CDCl₃) δ 2.80 (s, -CH₃, 6H); 7.31 (d, 3,5-NaphH, J=8
Hz, 2H); 8.03 (d, 4,5-NaphH, J=8 Hz, 2H).
2,7-Dimethyl-1,8-naphthyridine with Tetraethylene Glycol Ditosylate. A solution of 2,7-dimethyl-1,8-naphthyridine (500mg, 3.16mmol) in tetrahydrofuran (THF, 500mL) was cooled to -70°C via a dry ice/acetone bath, after which methyllithium (9ml, 1.6M, 12.64mmol) was added dropwise under nitrogen maintaining the temperature at -70°C. After addition, the dark red solution was stirred for 3 hours at -70°C, then tetraethylene glycol ditosylate (3.35g, 6.66mmol) in THF (100mL) was added over a period of one hour maintaining that temperature. The reaction was slowly warmed to 25°C and stirred for two days. After carefully quenching with water, the solvent was removed in vacuo. The crude product was chromatographed (ThLC) on neutral aluminum oxide. Elution with cyclohexane/ethyl acetate (1:1) afforded starting material according to physical and spectral data.

2,7-Dimethyl-1,8-naphthyridine with Methyllithium and Subsequent Trapping with Dimethyldisulfide. A solution of
2,7-dimethyl-1,8-naphthyridine (313) (250mg, 1.58mmol) in anhydrous diethyl ether (100mL) was cooled to -60°C. Methyllithium (1.98ml, 1.6M, 3.16mmol) was added dropwise at such rate as to maintain the temperature at -60°C. After addition, the solution was stirred for 2 hours and dimethyl disulfide (297mg, 3.16mmol) in diethyl ether (50mL) was added dropwise. The solution was then allowed to warm to 25°C and stirred for several hours before carefully quenching with water. The organic layer was extracted, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The resulting crude product was shown to be starting material via TLC and NMR.

![Chemical Reaction Diagram]

2,7-Bis(dichloromethyl)-1,8-naphthyridine (315). A suspension of 313 (500mg, 3.16mmol), 324 (1.69g, 13mmol) and a catalytic amount of benzoyl peroxide (100mg) in carbon tetrachloride (75mL) was refluxed for two hours, cooled, filtered, and the solvent was removed in vacuo. The exclusive product was 2,7-bis(dichloromethyl)-1,8-naphthyridine 315: 906mg (97%); mp 179-180°C; H NMR (CDCl₃) δ 6.98 (s, α-CHCl₂, 2H), 8.15 (d, 3,6-NaphH, J=8 Hz, 2H), 8.28 (s, 4,5-NaphH, 2H); IR (KBr) 3000, 1590,
1490, 1245, 1020, 830, 770 cm\(^{-1}\); MS (70eV) m/e 268 
(M\(^+\), 2), 231 (C\(_{10}\)H\(_{5}\)N\(_2\)Cl\(_3\), 100).

Anal. Calcd. for C\(_{10}\)H\(_6\)N\(_2\)Cl\(_4\): C, 40.54; H, 2.03; N, 9.46. Found: C, 40.26; H, 1.97; N, 9.28.

\[
\begin{array}{c}
\text{Cl}_2\text{HC} \quad \text{N} \quad \text{N} \\
\text{CHCl}_2 \quad \xrightarrow{\text{H}_2\text{SO}_4} \quad \Delta 2\text{hrs} \quad \text{NR}
\end{array}
\]

2,7-Bis(dichloromethyl)-1,8-naphthyridine with Sulfuric Acid. A mixture of 2,7-Bis(dichloromethyl)-1,8-naphthyridine (830mg, 2.8mmol) and concentrated sulfuric acid (1mL) were heated on an oil bath at 110°C with stirring for two hours. After cooling, the reaction was neutralized with a saturated solution of sodium bicarbonate (pH 7-8). Starting material was recovered, according to TLC and NMR data.

\[
\begin{array}{c}
\text{Cl}_2\text{HC} \quad \text{N} \quad \text{N} \\
\text{CHCl}_2 \quad \xrightarrow{(\text{Bu})_3\text{SnH}} \quad \text{NR}
\end{array}
\]

Tributyltin Hydride and 2,7-Bis(dichloromethyl)-1,8-naphthyridine. To a stirred solution of 2,7-bis(dichloromethyl)-1,8-naphthyridine (906mg, 3.06mmol) in anhydrous benzene (10mL), tributyltin hydride (1.78g, 6.12mmol) was added dropwise. The reaction was stirred at 25°C for 2 hours and, subsequently, refluxed for 24 hours. After
cooling, the solvent was removed in vacuo and the mixture was shown by TLC to contain only starting material, which was recovered in quantitative yield.

\[
\begin{array}{c}
\text{H}_2\text{C} \quad \text{8 eq NCS} \quad \text{Cl}_3\text{C} \\
\text{N} \quad \text{benzoyl peroxide} \quad \text{N} \\
\text{Cl}_3\text{CCl}_3, \quad \Delta 24 \text{ hrs}
\end{array}
\]

2,7-Bis(trichloromethyl)-1,8-naphthyridine (316).

To a stirred solution of 2,7-dimethyl-1,8-naphthyridine (1g, 6.23mmol) in carbon tetrachloride (100mL), N-chlorosuccinimide (6.7g, 50mmol) was added and benzoyl peroxide (100mg) were added, then the mixture was refluxed for 24 hours. Periodically, small amounts of benzoyl peroxide were added over this period. After cooling, the reaction was filtered and the solvent was removed in vacuo to afford 2,7-bis(trichloromethyl)-1,8-naphthyridine 316: 2.6g (98%); mp 233-234°C; \( R_f = 0.68 \) [silica, eluted three times in cyclohexane/ethyl acetate (2:1)]; \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 7.27 (d, 3,6-NaphH, J=8 Hz, 2H), 7.53 (d, 4,5-NaphH, J=8 Hz, 2H); IR (KBr) 1590, 1485, 1400, 870, 820, 780 cm\(^{-1}\); MS m/e 365 (M\(^+\), 4), 328 (C\(_{10}\)H\(_3\)N\(_2\)Cl\(_5\), 100).

Anal. Calcd. for C\(_{10}\)H\(_3\)N\(_2\)Cl\(_5\): C, 32.88; H, 1.10; N, 7.67. Found: C, 32.69; H, 0.98; N, 7.39.
Hydrolysis of 2,7-Bis(trichloromethyl)-1,8-naphthyridine with Sulfuric Acid. Sulfuric acid (1mL, 1.7g) and 2,7-bis(trichloromethyl)-1,8-naphthyridine (2.26g, 6.2mmol) were heated on an oil bath at 110° C for 3 hours. The reaction was cooled and methanol (3mL) was added. The solution was refluxed for several hours, after which the reaction was neutralized with 10% sodium carbonate and filtered. The crude product was chromatographed (ThLC) on silica by eluting with cyclohexane/ethyl acetate (2:1) to afford three fractions:

Fraction A was shown to be starting material 316 (10%) according to melting point, TLC, and $^1$H NMR data.

Fraction B was shown to be the monoester 317: 19%; mp 158-159°C; R$_f$ = 0.51; $^1$H NMR $\delta$ 4.08 (s, -CH$_3$, 3H), 8.25 (d, 6-NaphH, J=8 Hz, 1H), 8.33 (d, 3-NaphH, J=8 Hz, 1H), 8.48 (d, 4,5-NaphH, J=8 Hz, 2H); IR (KBr) 3000, 2970, 1730, 1585, 1290, 1140, 870 cm$^{-1}$; MS m/e 306 (M$^+$, 2), 248 (C$_9$H$_5$NCl$_3$, 100).
Anal. Calcd. for $C_{11}H_7N_2O_2Cl_3$: C, 43.14; H, 2.29; N, 9.15. Found: C, 42.97; H, 2.21; N, 8.92.

Fraction C was diester 318: 42%; mp 212-213°C; $R_f = 0.31$; $^1H$ NMR $\delta$ 4.07 (s, $-CH_3$, 6H), 7.32 (d, 3,6-NaphH, $J=8$ Hz, 2H), 7.50 (d, 4,5-NaphH, $J=8$ Hz, 2H); IR (KBr) 3000, 2960, 1725, 1580, 1280, 1150, 880 cm$^{-1}$; MS m/e 346 ($M^+$, 2), 188 ($C_{10}H_8N_2O_2^+$, 100).

Anal. Calcd. for $C_{12}H_{10}N_2O_4$: C, 41.26; H, 2.89; N, 8.09. Found: C, 40.99; H, 2.79; N, 7.88.
Results and Discussion

Introduction. In an effort to delineate the relationship between a macrocyclic structure and its complexation properties, our research endeavors have been directed toward the synthesis of "crown ether" macrocycles which contain the 2,6-pyridino, 6,6'-(2,2'-bipyridino), and 2,7-(1,8-naphtyridino) subunits. The initial work centered primarily on the preparation of coronands, attention was thereafter directed toward cryptands which possess these same subheterocyclic moieties. Prior to the work described herein, only the 2,6-pyridino and 6,6'-(2,2'-bipyridino) subunits had been incorporated within cryptands.

A. Coronands

A number of years ago the synthesis of cyclophane was reported by Newkome et al. They have also studied the variable temperature NMR of this compound and

![Chemical Structures](image_url)
initially proposed a syn $\leftrightarrow$ anti isomerization. The $\Delta G^\ddagger$ value of 13.5 ± 0.3 kcal/mol determined for this syn-anti interconversion was comparable to values determined for the metacyclophane systems.\textsuperscript{170} such

\[
\begin{array}{c}
\text{syn} \\
\xrightarrow{\quad}
\end{array}
\]
\[
\begin{array}{c}
\text{anti}
\end{array}
\]

isomerizations are inferred from \textsuperscript{1}H NMR data by a distinct upfield shift for the aromatic protons of the syn isomer due to the anisotropy of the juxtaposed ring; however, this upfield shift is not observed in the NMR spectra of macrocycle \textsuperscript{325}. An "anti, longitudinal" isomerization (Scheme X) has since been proposed in which structures \textsuperscript{c} and \textsuperscript{d} represent an energy minima. The 3,5-pyridine proton signal for \textsuperscript{325} at 223°K appears as two resolved doublets of equal intensity; these data support the "anti, longitudinal" isomerization. The "anti, transverse" isomerization (\textsuperscript{a} $\leftrightarrow$ \textsuperscript{b}) should afford a single doublet for the 3,5-pyridine hydrogens, which are equivalent by symmetry. At low temperatures macrocycles such as \textsuperscript{325} possess a nearly coplanar geometry so that the pyridine subunits satisfy the rigid angular constraints imposed by the imidate groups (dihedral angle of 0 ± 10°) and symmetry considerations as previously seen.\textsuperscript{171}
To substantiate these findings, bis-amide 326 was synthesized. In this case the free energy of activation ($\Delta G^\ddagger$) for "anti, longitudinal" isomerization is $14.5 \pm 0.1$ kcal/mol. In addition, the 5-pyridine hydrogen signal appears as two doublets of equal intensity indicative of longitudinal isomerization with approximately equal populations of c and d.\textsuperscript{171}

Therefore, it is of interest whether this same effect is operative when other heteroatoms are directly attached to the pyridine ring in these positions. Macrocycle 291 was synthesized by the treatment of 2,6-dichloropyridine
with N,N'-dimethylethylene diamine and lithium hydride or butyllithium as the base. Utilization of sodium hydride afforded only ring-opened products (mainly 290). This difference in products is believed to be due to the template effect: the smaller lithium atom should be able to fit in the cavity of this macrocycle much better than the larger sodium atom.

Dimer 291 (2%) and trimer 292 (2%) were isolated by elution of ThLC plates (silica gel) with 10% methanol in chloroform. The $^1$H NMR of 291 showed a singlet at δ 3.00 for the methyl groups, a doublet at δ 5.73 for the 3,5-pyridine hydrogens, and a triplet at δ 7.30 for the 4-pyridine hydrogens. The signal for the methylene hydrogens was coalesced at 300°K, but when the sample was warmed to 330°K, a singlet at δ 3.75 appeared (Scheme XI). Lowering the probe temperature to 227°K resulted in the appearance of two triplets at δ 2.69 and 4.80 for these methylene hydrogens. The free energy of activation ($\Delta G^\dagger$) for the isomerization is 12.5 ± 0.3 kcal/mol, which is comparable to the value of 13.5 kcal/mol obtained for 325. Macr-
Scheme XI

Variable temperature $^1$H NMR study for 291
cycle 291 apparently undergoes the same "anti, longitudinal" isomerization which is operable with 325. However, at 227°K instead of the two doublets of equal intensity observed for 325, 291 exhibits only one doublet at $\delta$ 5.75 for the 3,5-pyridine hydrogens. This difference is probably due to the insulating effect of the N-methyl groups. The nitrogen atoms attached to the pyridine rings are most likely sp$^2$ hybridized due to the amidine nature of this substitution pattern, the overall structure being nearly planar with a dihedral angle <30°. Two of the methylenes have hydrogen atoms pointing inside the cavity of the macrocycle and the other two methylenes have their hydrogen atoms oriented outside the cavity as evidenced in 328. The triplet at $\delta$ 2.69 corresponds to the methylene hydrogens located inside the cavity; whereas, the triplet at $\delta$ 4.80 corresponds to the methylene hydrogens oriented outside the cavity. The downfield shift for the protons external to the cavity is due to a deshielding effect by the sp$^2$ nitrogen atoms substituted in the 2 and 6 positions on the pyridine rings. The methylene hydrogens projected inside the cavity are also deshielded.
by the sp2 nitrogen atoms, but the effect of the pyr-
idine N-lone pair results in a net chemical shift similar
to that of the methyl protons.

It was noted that upon exposure to light 291 was
transformed into a different compound which was dark blue
in color. This phenomenon occurs in the solid state as
well as in solution, thus hindering attempts to obtain an
analytically pure sample of 291. The blue compound
(> 300°C) was found to be most soluble in methyl alchol and
only slightly soluble in chloroform.

291 in dry, degassed THF was photolyzed for four hours
with a 450 watt Hg arc at which point no starting material
could be detected by TLC and a dark blue precipitate had
formed on the walls of the reaction vessel. Due to the
lack of volatility of this substance, the mass spectrum
could not be obtained, in addition, attempts to procure a
1H NMR spectrum in CDCl3 and methanol-d4 were in vain. The
lack of a spectrum in CDCl3 was due mainly to the limited
solubility of the sample in the solvent; and the spectrum
which was obtained in methanol-d4 showed solvent peaks at
chemical shifts where some of the protons from the sample
resonated, limiting the usefulness of methanol as a
solvent. All attempts to obtain crystals suitable for
X-ray analysis of this material has proven to be futile;
therefore, the identity of this substance, as yet, remains
a mystery.
The macrocyclic trimer 292 does not exhibit a temperature dependent NMR spectrum. Signals for the methyl hydrogen atoms and the methylene hydrogen atoms appear as singlets at δ 2.92 and 3.68, respectively. The signals for the 3,5-pyridine hydrogens appear as a doublet at δ 5.69 whereas the signal for the 4-pyridine hydrogen appears as a triplet at δ 7.23.

Another related macrocycle of interest, due to the fact that it is a hexaaza "18-crown-6", is 293, which was synthesized by treatment of 2,6-bis(chloromethyl)pyridine with \( \text{N, N'}-\text{dimethylethlenediamine} \) in DMF in the presence of potassium carbonate or lithium hydride. One also obtains trimer 294 from this reaction. This particular synthetic pathway is a unique method to achieve these azamacrocycles. Normally, hexaazadentate macrocyclic ligands possessing the 2,6-pyridino subunit(s) have been prepared by the \textit{in situ} Schiff's base cyclocondensation of either 2,6-diacetyl- or 2,6-diformylpyridine with an \( \alpha, \omega \)-diamine in the presence of an appropriate metal ion, which acts as a template for cyclization. Disadvantages of this template procedure include the fact that the steric requirements of a specific
metal ion may preclude formation of the desired macrocycle, the occasional inability to remove the metal ion from the resultant complex, and the inability to transform the imine groups to the respective $N$-alkyl moieties. In a few cases the free imine has been reduced to the free secondary amine.

An alternate procedure to acquire these macrocyclic amines involves the high-dilution cyclocondensation of an $\alpha,\omega$-diamine with a bis-acyl halide to afford a cyclic bis-amide which subsequently may be reduced with difficulty to the amine. This acylation-reduction procedure directly affords the desired macrocycle albeit in relatively low yield (10%), depending on the base utilized. If potassium carbonate is employed the yields are 3% and 1% for 293 and 294, respectively; however, if lithium hydride is utilized as the base the yields are 8% for both macrocycles.

Macrocycles 293 and 294 have very similar $^1H$ NMR spectra, differing slightly in chemical shifts. The $^1H$ NMR spectrum of 293 shows three singlets at $\delta$ 2.39, 2.48, and 3.57 corresponding to the methyl groups, the $\beta$-methylene protons, and the $\alpha$-methylene protons, respectively. The aromatic region consists of a doublet at $\delta$ 7.15 for the 3,5-pyridine hydrogens and a triplet at $\delta$ 7.45 for the 4-pyridine hydrogen.

CPK models indicate that 293 could easily complex a metal ion with either tetrahedral or octahedral geometry.
To ascertain if the ligand would indeed form a complex and, if so, the preferred geometry thereof, 293 was treated in methanol with either cobalt(II) or copper(II) chloride. A blue-green complex, 295, was isolated in the case of cobalt(II) chloride and an emerald green complex, 296, was isolated in the case of copper(II) chloride. Both 295 and 296 were found to have melting points greater than 300°C and their elemental analyses indicated that for each complex there were two cobalt(II) or copper(II) chloride molecules associated with each ligand.

Two modes of complexation (A or B) are possible for an octahedral geometry; however, CPK models indicate that configuration A would not be favored due to the rigidity imposed by the directed pyridine nitrogen atoms. In order to determine which configuration is predominate, an X-ray structural determination was performed. Crystals of each suitable for X-ray analysis were obtained by slow evaporation of the respective methanol solutions.

Both complexes have approximate $D_2$ symmetry supportive of configuration B, in which the pyridine N-orthog-anol electrons occupy the axial positions and the tertiary
amino groups occupy the equatorial positions. In Co-N(Py) distance [ca. 2.052(4) Å] and the equatorial Co-N distances [ca. 2.233(3) Å] are almost identical (Figure III). Distortion from perfect octahedral geometry may be envisioned in two steps: 1) bending of the Co-N bonds cis to pyridine towards pyridine, due to meridional spanning and 2) twisting the two meridional NNN planes away from 90°, due to the equatorial chelate rings. The dihedral angle in 295 is 79.1°.

The copper complex 296 is more distorted from ideal octahedral geometry. The Cu-N(Py) distances [ca. 1.985(4) Å] are identical; however, the equatorial Cu-N distances range from 2.214(6) to 2.307(6) Å. The dihedral angle between the two meridional planes is 78.7°. Copper(II), a Jahn-Teller ion, is expected to form a distorted complex, but the mode of distortion in 296 is unexpected. The anticipated axial elongation does not occur with the pyridine donors, but rather with the "equatorial" tertiary amine donors (N3 and N6). This effect probably results from the fact that the pyridine subgroups occupy the "meridional positions", bridging trans donors, while the other nitrogen atoms occupy "facial positions", bridging cis donors. Elongation of a bond to a fac position invokes primarily changes in torsion angles, and thus requires less bond-stretching energy than elongation of a bond to a mer position.
**Figure III.** Structure of the complexes 295 and 296. Distances and angles in the coordination sphere for the cobalt <copper> complex are: M(1)-N(1) 2.050(5) <1.987(5)> A, M(1)-N(2) 2.234(6) <2.307(6)> A, M(1)-N(3) 2.237(5) <2.244(6)> A, M(1)-N(4) 2.054(5) <1.983(5)> A, M(1)-N(5) 2.225(5) <2.214(6)> A, M(1)-N(6) 2.235(5) <2.289(5)> A. N(1)-M(1)-N(4) 178.4(2) <178.2(2)> A, N(1)-M(1)-N(2) 76.8(2) <77.5(2)> A, N(1)-M(1)-N(6) 76.7(2) <77.7(2)> A, N(4)-M(1)-N(3) 76.6(2) <78.0(2)> A, N(4)-M(1)-N(5) 77.1(2) <77.8(2)> A, N(2)-M(1)-N(6) 153.5(2) <155.1(2)> A, N(3)-M(1)-N(5) 153.7(2) <155.7(2)> A. The cobalt complex is illustrated.
The tetrachlorocobaltate(2-) counterion is a nearly perfect tetrahedron with cobalt-chloride bond distances ca. 2.282(7) Å, whereas the tetrachlorocuprate(2-) counterion is a flattened tetrahedron with copper-chloride bond distances ranging from 2.226(2) to 2.254(2) Å.

Sulfur system 327, analogous to 291, has proven to be more elusive. Bottino and Pappalardo\textsuperscript{179} have reported attempts to synthesize 327 by the treatment of 2,6-dimercaptopyridine with 1,2-dibromoethane in ethanol. The product isolated is thione 329 (15%). There are several
fragmentation possibilities for these systems other than the one which forms the thione (329).\textsuperscript{182}

In these laboratories the synthesis of 327 was approached in a different manner:\textsuperscript{180} 2,6-dihalo-pyridine was treated with 1,2-ethanedithiol in xylene or DMF in the presence of sodium hydride as the base. Newkome \textit{et al.}\textsuperscript{180} have reported the isolation of four compounds from the reaction of 2,6-dichloropyridine with 1,2-ethanedi-thiol in refluxing xylene. Three of these components were oligomerized 2:1 adducts 330a-c; the only macrocycle isolated was 288, which arose from the dianion of 3,6-dithiaoctane-1,8-dithiol. The desired product 327 was not detected. It thus appears that the cyclization process under these reaction conditions is much slower relative to competitive reactions such as oligomerization, fragmentation, and oxidation. The greater difficulty in cyclization of poly(thiaethylene) can be attributed to the increase in C-X bond length and the decrease in C-X-C angle when X is changed from an oxygen to a sulfur atom.\textsuperscript{181}

\[
\begin{align*}
\text{Cl} & \quad \text{HS} \quad \text{SH} \\
\text{Cl} & \quad \text{S} \quad \text{S} \\
\text{Cl} & \quad \text{S} \quad \text{S} \\
\end{align*}
\]
\[\text{330a n=1, 330b n=2, 330c n=3}\]
When DMF was employed as the solvent and the temperature was lowered to 75°C, two macrocyclic products (287 and 288) were isolated. Macrocycle 287 showed a broad singlet at δ 3.14 for the β-methylene and a broad singlet at 3.28 for the α-methylene. The aromatic region of the

\[
\begin{align*}
\text{X} & \quad \text{HS} \quad \text{SH} \\
\text{X} & \quad \text{NaH, DMF} \\
\text{X*Cl, F} & \quad \text{287} \\
\text{S} & \quad \text{S} \\
\text{S} & \quad \text{S} \\
\text{288}
\end{align*}
\]

\(^1\)NMR spectrum consisted of a doublet at δ 6.90 with a coupling constant of 8 Hz corresponding to the 3,5-pyridine hydrogens and a triplet at δ 7.31 corresponding to the 4-pyridine hydrogen. The \(^1\)H NMR spectrum of 288 was considerably different from that of 287, in that the signal for the β-methylene hydrogens appears as a multiplet at δ 2.82 with a multiplet at δ 3.51 for the α-methylene, and a singlet at δ 2.85 for the γ-methylene hydrogens. These data are supportive of the symmetry associated with three thiaether units in the macrocycle. The aromatic region for 288 is similar to that of 287 in that there appears a doublet at δ 6.88 for the 3,5-pyridine hydrogens and a triplet at δ 7.27 for the 4-pyridine hydrogen. The mass spectra of 287 and 288 substantiates the NMR structural assignments with a parent peak for 287 at 229 (M⁺, 62) and for 288 at 289 (M⁺, 33), indicating the presence of a single subheterocyclic ring. This MS
evidence is, however, far from conclusive since one may be seeing only half of the total mass. To prove the structure of these macrocycles crystals of 288 suitable for X-ray analysis were grown.

The molecule is disordered such that it and its mirror image occupy the same position in the unit cell with approximately 72% and 28% populations. The pyridine ring and sulfur atoms coincide in both structures while the other carbon atoms occupy the partially populated positions (Figure IV).

According to the crystal structure determination of 288, it is evident that 287 is also probably monomeric and that both are derived from the cyclization of oligomers of 1,2-ethanediol. In addition, it appears that oligomerization of 1,2-ethanediol can occur even at 25°C under basic conditions.\textsuperscript{180,182}

The question then arose as to whether the analogous piperazine macrocycle 331 could be synthesized and, if so,
what is the conformation of the piperazine subunits. There are several possible conformations include the boat-boat, the chair-chair, and the boat-chair as suggested by CPK models.

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{N} & \quad \text{N} \\
\text{HN(CH₂CH₂)₂NH} & \quad \text{HN} \\
\text{NOH, xylene, } \Delta & \quad \text{Cl} \\
\text{Cl} & \quad \text{N} \\
\end{align*}
\]

2,6-Dichloropyridine was treated with piperazine in refluxing xylene in the presence of sodium hydride as the base. Only open-chain products 298 (12%) and 299 (3.8%) were isolated. Both were characterized by \(^1\)H NMR data and by their mass spectra. The amine hydrogen of 298 appears as a singlet at \(\delta 1.81\) while the \(\beta\)- and \(\alpha\)-methylene hydrogens appear as multiplets at \(\delta 2.93\) and \(\delta 3.49\), respectively. The 3-pyridine hydrogens appear as a doublet at \(\delta 6.40\), the 5-pyridine hydrogen appears as a doublet at \(\delta 6.53\), and the 4-pyridine hydrogen appears as a triplet at \(\delta 7.34\). The 2:1 compound 299 exhibits a much simpler \(^1\)H NMR spectrum in which the piperazine methylene hydrogens appear as a singlet at \(\delta 3.67\), and the 3,5-pyridine hydrogens appear as a doublet at \(\delta 6.59\), and the 4-pyridine hydrogens appear as a triplet at \(\delta 7.34\).

It was hoped that utilization of butyllithium as the base would assist in the preparation of the 2:2 macrocycle
in a fashion analogous to the generation of 291. However, substitution of benzene as the solvent and use of butyllithium afforded only 299 (52%), the 2:1 compound.

Macrocyle 331 has not been isolated from any of its attempted preparations and according to CPK models it is impossible to form this dimeric species. Therefore, enlarging the ring-size of the macrocycle by insertion of a methylene unit between the pyridine ring and the piperazine ring was undertaken. The CPK models of the dimeric macrocycle 300 indicate that the piperazine rings should be able to assume the boat conformation, resulting in a unique hexadentate ligand for complexation of metal ions. The procedure chosen involves the treatment of 2,6-bis(chloro-methyl)pyridine with piperazine in DMF and potassium carbonate. From this mixture dimer (300), trimer (301), and tetramer (302) can be isolated by chromatography on alumina. In general, for dimer 300 the NMR spectrum exhibits a singlet at δ 2.48 for the β-methylene hydrogens and a singlet at δ 3.64 for the α-methylene hydrogens. The 3,5-pyridine hydrogen atoms and the 4-pyridine hydrogen
appear as a doublet at δ 7.24 and a triplet at δ 7.57, respectively.

Once again, an interest in the conformation of the piperazine rings (chair or boat) led to the preparation of crystals suitable for X-ray analysis. Slow evaporation of a chloroform solution of 300 afforded ideal crystals.

The piperazine rings in 300 in the crystalline state exist in the chair conformations and are parallel to one another. The distance between the parallel N2 and N3 atoms is ca. 4.984 Å. The pyridine rings are anti in relation to one another and the distance between the two pyridine nitrogen atoms is 6.083 Å (Figure V).

![Figure V. ORTEP stereopairs of macrocycle 300.](image)

The copper(II) chloride complex of 300 was easily formed in refluxing methanol. Slow evaporation of the methanol solution afforded amber crystals suitable for X-ray analysis. It seems that the complexed copper ion is
a copper(III) ion and coordinated to one of the pyridine nitrogen atoms and a chloride with a chloride counterion; however, the R value is currently 5, but there appear to be several systematic errors in the collected data.

Once again it was hoped that ring enlargement of the macrocycle by utilization of \( \text{N,N'}-\text{bis-(2-hydroxyethyl)-piperazine} \) (283) would afford the 2:2 macrocycle 284. The piperazine rings should be able to assume the boat conformations. CPK models of 284 suggest that a novel cavity could be realized if the piperazine rings possessed the boat conformation: all four piperazine nitrogens would be able to coordinate a transition metal ion and form at least a stable tetradeutate complex.

\[
\begin{align*}
\text{Cl} & \quad \text{N} \\
\text{N} & \quad \text{OH} \\
\text{Cl} & \quad \text{N} \\
\text{OH} & \quad \text{N} \quad \text{OH}
\end{align*}
\]  

\[
\xrightarrow{\text{NaH}} \text{xylene, } \Delta
\]

Macrocyle 284 (10%) was synthesized by the treatment of 2,6-dichloropyridine with the dianion of \( \text{N,N'}-\text{bis-(2-hydroxyethyl)piperazine} \) 283 in refluxing xylene. The \( ^1\text{H} \) NMR spectra was as expected with a singlet at \( \delta \) 2.67 for the \( \gamma \)-methylene hydrogens. The multiplets at \( \delta \) 2.78 and 4.47 are assigned to the \( \beta \)- and \( \alpha \)-methylene hydrogen atoms, respectively. The aromatic region exhibits a doublet at \( \delta \) 6.27 for the 3,5-pyridine hydrogens and a
triplet at $\delta$ 7.45 ppm for the 4-pyridine hydrogens. Crystals of 284 for X-ray analysis were obtained by slow evaporation of a methylene chloride solution.

The piperazine rings are in the chair conformation, and the conformation of the 2,6-substituents of the pyridine subrings is essentially cis to the pyridine nitrogen atom, as uniformly found in all related compounds recently investigated.\textsuperscript{172}

Dr. Frank Fronczek has attempted to prepare the cobalt(II) chloride complex of 284 by dissolving the macrocycle and metal salt in hot ethyl acetate-methanol (3:1). The solution was refluxed for four hours, after which dark blue crystals formed on the walls of the reaction vessel.

The complex was shown to be the diprotonated cobalt salt 332 of the macrocycle 284. Each macrocyclic cation is surrounded by six cobalt(II) tetrachloride dianions and is hydrogen-bonded to two of them. The hydrogen bonds are linear, and nitrogen to chlorine distances fall within the
range 3.09(4)-3.17(4) Å, indicative of the strength of these forces. Each complex anion forms contacts to portions of six macrocyclic cations, accepting hydrogen bonds from two of them. The acid responsible for protonation of 284 is undoubtedly an aquocobalt(II) complex.

\[
\text{Cl} \quad \text{Cl} \quad + \quad \text{HO-NNNHO} \quad \text{NaH} \quad \text{THF} \quad \rightarrow \quad \text{N-N-NO} \\
\text{285}
\]

In order to increase the complexing ability of the pyridine rings and at the same time increase the flexibility of the macrocycle, 285 was synthesized. This was accomplished by treatment of 2,6-bis(chloromethyl)pyridine with the dianion of N,N'-bis(2-hydroxyethyl)piperazine in THF to afford 285 (13%). The \(^1\)H NMR spectral data show a singlet at δ 2.48 for the δ-methylene protons of the piperazine ring, while triplets appear at δ 2.57 and 3.64 for the β- and γ-methylene protons, respectively. The singlet at δ 4.54 for the α-pyridine methylene protons is reasonable, whereas a doublet at δ 7.30 and a triplet at 7.54 for the 3,5-pyridine hydrogens and the 4-pyridine hydrogen, respectively, are equally reasonable. It was envisioned that this increase in the flexibility of the macrocycle gained by insertion of a methylene unit between each pyridine ring and the oxygen heteroatom might allow
the piperazine rings to assume the boat configuration in which all four piperazine nitrogen atoms participate in the complexation process. No complexes of 285 have as yet been prepared.

There are only a limited number of macrocycles containing the 1,8-naphthyridine moiety; thus we were interested in incorporating this entity into such systems. At this time only crown ether macrocyclic analogues containing these subunits have been synthesized. Therefore, the target molecule for a macrocyclic system which contains oxygen and nitrogen heteroatoms was 310.

Realization of this goal necessitated the synthesis of 2,7-dichloro-1,8-naphthyridine. This was accomplished in several steps the first of which was the Skraup reaction of malic acid and 2,6-diaminopyridine in concentrated sulfuric acid to afford 2-amino-7-hydroxy-1,8-naphthyridine (304) (97%). Diazotization of 304 by sodium nitrite and subsequent hydrolysis gave 2,7-dihydroxy-1,8-naphthyridine (305) (87%). Treatment of the 305 with phosphorus pentachloride and phosphorus oxychloride resulted in the
formation of 2,7-dichloro-1,8-naphthyridine 306 (81%) (Scheme XII). 162

Scheme XII

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{H}_2\text{SO}_4 \quad \text{molar acid} \quad \text{H}_2\text{N} \quad \text{H}_2\text{SO}_4 \\
\text{H}_2\text{H}_2 & \quad \text{304} \\
\text{Cl} & \quad \text{PCl}_3 \quad \text{PCl}_5 \\
\text{Cl} & \quad \text{306}
\end{align*}
\]

Macrocycle 310 (4.6%) was prepared by treatment of 2,7-dichloro-1,8-naphthyridine and N-methyldiethanolamine in DMF with sodium hydride. The symmetry and the integration of the $^1H$ NMR spectrum are indicative of macrocyclic properties. The singlet at $\delta$ 2.57 for the nitrogen methyl group and the triplets at $\delta$ 3.04 and 4.73 for the the $\beta$- and $\alpha$-methylene protons, respectively, support the assignment. The aromatic region consists of two doublets: one at $\delta$ 6.76 and the other at $\delta$ 7.67 for the 3,6- and 4,5-naphthyridine protons, respectively. No other macrocyclic products were detected.

All attempts to form metal complexes with 310 proved fruitless and it thus appears that, as in the case of pyridine, the direct substitution of oxygen atoms on the
subhetero ring greatly diminishes the N-complexing ability as a result of the imidate character. Therefore, to enhance the ability of these ligands to include metal ions, again insertion of a methylene unit between the oxygen atom and the naphthyridine ring was deemed necessary. This incorporation could be envisioned to proceed by several proposed synthetic pathways. One such pathway involves treatment of 2,7-dichloro-1,8-naphthyridine with cuprous cyanide in dry pyridine or with potassium cyanide in DMF and subsequent reduction or hydrolysis of the 2,7-dicyano-1,8-naphthyridine (332) intermediate (Scheme XIII).

Diacid 333 may be esterified and subsequently reduced to give the diol, which can be transformed into the dihalide. Compound 332 could also be reduced to the diamine, which would be useful in the synthesis of the related macrocycles.

Scheme XIII

![Scheme XIII diagram]

1. Treatment of 2,7-dichloro-1,8-naphthyridine with KCN or CuCN.
2. Reduction or hydrolysis of the 2,7-dicyano-1,8-naphthyridine (332) intermediate.
3. Esterification of diacid 333.
4. Reduction of diacid 333 to diol.
5. Transformation of diol into dihalide.
6. Reduction of compound 332 to diamine.
Unfortunately, all attempts to synthesize the 2,7-dicyano-1,8-naphthyridine resulted in the isolation of insoluble black material which could not be further characterized. Therefore, an alternate pathway was used in which 2,7-dimethyl-1,8-naphthyridine 313 would be subsequently functionalization. The only reported route to the desired precursor 313 was by a Skraup reaction,\textsuperscript{165} in which 2-amino-6-methylpyridine and crotonaldehyde afforded 313 in poor\textsuperscript{165} and erratic\textsuperscript{166} yields (5-15\%).

\[
\begin{align*}
\text{CH}_3 \text{N} \text{NNH}_2 & \quad \text{O} \text{N} \text{C} \text{SO}_3 \text{Na} \quad \text{H}_2 \text{SO}_4 \\
& \quad \text{H}_3 \text{BO}_3 \quad \text{FeSO}_4 \cdot 7\text{H}_2\text{O} \quad \text{glycerol} \\
\rightarrow & \\
\text{H} \text{O} \text{O} \text{O} \text{O} \text{O} & \quad \text{CH}_3
\end{align*}
\]

Although the synthesis of 313 leaves much to be desired, 2-methyl-1,8-naphthyridine 312 (50\%) can be easily prepared by the Skraup reaction of 2-methyl-6-aminopyridine and glycerine.\textsuperscript{163,164} A mixture of sodium m-nitrobenzenesulfonate, sulfuric acid, boric acid, ferrous sulfate heptahydrate, glycerol, and 2-methyl-6-aminopyridine is stirred for five hours at 135\(^\circ\)C; after a very messy workup procedure 2-methyl-1,8-naphthyridine (49\%) is obtained. To ensure high yields of 312 the glycerine must be anhydrous and the reaction temperature must be maintained below 135\(^\circ\)C.
The only remaining problem is the introduction of a methyl group in the open \( \alpha \)-position. Kauffmann et al.\(^{184} \) have reported the methylation of \( 2,2' \)-dipyridine with methyllithium, whereby \( 6,6' \)-dimethyl-\( 2,2' \)-dipyridine may be obtained from this two-step process. The first methylation affords \( 6 \)-methyl-\( 2,2' \)-dipyridine (59\%) and the second methylation affords \( 6,6' \)-dimethyl-\( 2,2' \)-dipyridine (64\%).

\[
\begin{array}{c}
\text{N} \quad \text{N} \\
\text{H}_3 \quad \text{C} \quad \text{N} \quad \text{H}_3 \\
\text{CH}_3
\end{array}
\rightarrow
\begin{array}{c}
\text{H}_3 \quad \text{C} \quad \text{N} \quad \text{H}_3 \\
\text{N} \quad \text{N} \\
\text{CH}_3
\end{array}
\]

\[313\]

Methylation was accomplished by slow addition of three equivalents of methyllithium to a solution of \( \text{312} \) in anhydrous diethyl ether cooled to \(-50^\circ\text{C}\). The resulting dihydronaphthyridine intermediate was then oxidized with potassium permanganate in acetone to afford \( 2,7 \)-dimethyl-\( 1,8 \)-naphthyridine (\( \text{313} \)) (84\%). The overall yield was 43\% and represented a significant improvement in the synthesis of \( \text{313} \).

\[\text{Scheme XIV}\]

\[
\begin{array}{c}
\text{NR} \\
\text{1) MeLi} \\
\text{2) Me-SS-Me}
\end{array}
\rightarrow
\begin{array}{c}
\text{H}_3 \quad \text{C} \quad \text{N} \quad \text{H}_3 \\
\text{N} \quad \text{N} \\
\text{CH}_3
\end{array}
\rightarrow
\begin{array}{c}
\text{NR} \\
\text{1) MeLi} \\
\text{2) OTs}
\end{array}
\]

\[\text{Scheme XIV}\]
Two methods of functionalizing the methyl groups of 313 which have been attempted are shown in Scheme XIV. Unfortunately, both procedures afforded only starting material. Attempts to halogenate these methyl groups with N-chlorosuccinimide (NCS) with benzoyl peroxide initiator resulted in the formation of various products which depended on the stoichiometry and reaction conditions. If 313 is treated with four equivalents of NCS in CCl₄ and refluxed for two hours, 2,7-bis(dichloromethyl)-1,8-naphthyridine (315) is isolated quantitatively. However, if 313 is treated with eight equivalents of NCS in CCl₄ and refluxed for twenty-four hours, 2,7-bis(trichloromethyl)-1,8-naphthyridine 316 is the sole product.

Typically, organotin hydrides RₙSnH₄₋ₙ can be used to reduce one halogen of a gem-dihalide or a 1,1,1-trihalide. With this in mind the tetrachloro naphthyridine derivative, 315, was treated with tributyltin hydride to afford quantitative recovery of starting
material. In addition, gem-dihalides may be hydrolyzed with either acid or base to give aldehydes or ketones. However, for aldehydes, strong bases may not be used, due to the possibilities of further aldol condensations or Cannizzaro reactions. The tetrachloro derivative was subjected to acid hydrolysis conditions, (concentrated sulfuric acid at 110° C for two hours) starting material was once again recovered quantitatively. The hexachloro derivative 316 was also subjected to hydrolysis conditions and immediately treated with methanol to afford the monester 317 (19%), the diester 318 (42%), and some 316.

\[
\begin{align*}
&\text{Cl}_2\text{HC} & \text{N} & \text{N} & \text{CHCl}_2 \\
&\text{(Bu)}_3\text{SnH} & \rightarrow & & \text{NR}
\end{align*}
\]

Future work in this field should deal primarily with the reduction of the diester to the diol, and then subsequent conversion of the diol to the dichloro derivative. As with methyl 2,6-pyridinedicarboxylate, sodium borohydride may be used in the reduction of 318, while thionyl chloride readily converts a diol to a dichloro substituent.
Cryptands. Although several cryptands have been quaternized to form bis- and tetra-quaternary ammonium salts, they were not cyclized by a quaternization procedure but were quaternized after cyclization.\textsuperscript{151,152} In contrast, we have employed a quaternization-demethylation sequence (Scheme XV) to effect cyclization and to afford a new series of cryptands. Initially, the key 2,6-disubstituted pyridine was obtained, by reaction of 2,6-di-
chloropyridine with either N,N-dimethyl-3-hydroxypropylamine or N,N-dimethyl-2-hydroxyethylamine. According to Newkome et al. in 1975, 2,6-dihalopyridines are subject to nucleophilic substitution by alkoxides, the result being direct attachment of the oxygen atom to the heteroaromatic ring. Generation of the alkoxide by the action of sodium hydride precludes unwanted side products which may be formed if sodium hydroxide or other hydroxylic bases are employed. This procedure has been used extensively to synthesize a series of pyridino crown ethers which contain the oxygen heterocyclic linkage.

The facile reaction of 2,6-dichloropyridine with each of the homologous hydroxyamines resulted in the formation of both the disubstitution products, 251 and 247 (73% and 85% yield, respectively), and the monosubstituted products, 250 and 246 (2% and 3% yield, respectively). These compounds were isolated and purified by vacuum distillation.

Of particular interest was an unusual phenomenon which was observed during the synthesis of these disubstituted compounds: when a large excess of sodium hydride was used,
a minute amount of monosubstituted product was detected by NMR spectroscopy (by the appearance of the 6-pyr-H at δ 8.10). In order to determine the source and structure of 320, 251 was treated with a five molar excess of sodium hydride in refluxing xylene; after 24 hours 320 was isolated in 41% yield. This reduction product can be postulated to arise through intermediate 319 which subsequently loses chloride ion, a better leaving group than hydride.

2,6-Dichloropyridine was also subjected to the same reaction conditions with the exception that N,N-dimethyl-ethanolamine was omitted from the reaction. Starting material was quantitatively recovered from the reaction, indicating the necessity of complexing the sodium hydride by the 2-substituted pyridine derivative. In addition, treating 246 with sodium hydride in refluxing xylene afforded the hydride substituted product (ca. 30%).

The passing resemblance of intermediate 321 to the dihydronicotinamides, which have in the past been used to reduce various substituted acetophenones, prompted
tests of the new compound as a reducing agent. Unfortunately all attempts to reduce \( \alpha, \alpha, \alpha \)-trifluoroacetophenone and benzophenone resulted in the quantitative recovery of starting materials in both instances.

Initially, \( \overset{247}{n=3} \) and \( \overset{251}{n=2} \) were each quaternized with 1,4-diiodobutane in refluxing ethanol. The reaction mixtures were not purified but demethylated directly with L-Selectride® in refluxing tetrahydrofuran, resulting in the formation of macrocycles \( \overset{253}{n=3} \) and \( \overset{266}{n=2} \) in 13% and 20% yield, respectively. Attempts to quaternize further and demethylate \( \overset{253}{n=3} \) and \( \overset{266}{n=2} \) resulted in the quantitative recovery of the initial macrocycles according to TLC and NMR data. In retrospect this was not surprising, since the space filling molecular models (CPK) of the expected cryptands cannot be readily formed.
Treatment of 251 in acetonitrile with 1,2-bis(2-iodoethoxy)ethane, prepared by the Finkelstein reaction on the corresponding chloride,\textsuperscript{152,153} gave the bis-quaternary salt 254 [mp 208-209°C (dec); NMR δ 3.25 (s, -NMe\textsubscript{2})]. Both 1,2-bis(2-iodoethoxy)ethane and the dichloro analogue were used in this dialkylation procedure; the former was generally preferred on the basis of increased cyclization products and diminished deliquescence of the iodide salt. Replacement of acetonitrile as the solvent by ethanol resulted in a 10% reduction in yield. Macrocycle 267 [mp 178-179°C (dec); NMR δ 3.30 (s, -NMe\textsubscript{2})] was prepared in the same manner. Although not a problem with these ammonium salts, it should be noted that certain bis-quaternary ammonium salts with separated (13-15 Å) cationic centers usually exhibit curare-like properties.\textsuperscript{188}
Generally, the bis-quaternary ammonium macrocycles were not isolated, but were directly demethylated by L-Selectride® to afford the desired azacrown ethers 255 [oil; 40% (overall); NMR δ 2.28 (N-Me)] and 268 [oil; 43% (overall); NMR δ 2.30 (N-Me)]. The only other attempted demethylation employed the sodium salt of thiophenol in 2-butanol; no demethylated products were isolated.

Purification of azacrown ethers 255 and 268 was best accomplished by thick layer chromatography on alumina: elution with cyclohexane/ethyl acetate (1:1); efficiently removed any residual salts or bridge-fragmented contaminants. All attempts at distillation of these macrocycles resulted in their partial decomposition.

It appears that prolonged heating during the demethylation step (24 hours) results in a significant degree of fragmentation of the macrocyclic product. Proton NMR spectroscopy indicates that most of the fragmentation occurs between the oxygen atom and the pyridine ring, as evidenced by the presence of a 6-pyridyl proton signal at 8.10.

Quaternization of macrocycles 255 and 268 with 1,2-bis(2-iodoethoxy)ethane afforded the bis-quaternary ammonium salts 256 [mp 232-233°C (dec); NMR (D$_2$O) δ 3.37 (s, N-Me)] and 269 [mp 202-203°C (dec); NMR (D$_2$O) δ 3.23 (s, N-Me)]. X-ray analysis of crystals of 256 obtained
from an acetonitrile solution demonstrates the **exo-exo** orientation of the amine methyl groups (Figure VI). Two other structural characteristics should be noted for 256: 1) the dihedral angles of C(5)-C(4)-O(1)-C(3) and C(7)-C(8)-O(2)-C(9) are essentially 0°, and 2) the N(1)-N(3) distance is approximately 5.69 Å.

![Figure VI. ORTEP drawing of the bis-quaternary ammonium salt 256.](image)

Although no crystal suitable for X-ray analysis was obtained for 269, cryptands 256 and 269 have very similar
In the absence of variable temperature NMR spectroscopy studies one can only speculate as to the preferred conformation of both cryptands in solution.

Cryptands 256 and 269 were subjected to L-Selectride® in refluxing tetrahydrofuran for two hours to afford 257 and 270 in 14% and 15% yield, respectively. These cryptands are both colorless oils that decompose upon attempted vacuum distillation. The structure of these cryptands was easily confirmed by 1H NMR spectroscopy. For cryptand 257 a doublet at δ 6.27 for the 3,5-pyridyl hydrogens and a triplet at δ 7.46 for the 4-pyridyl hydrogen resulted from the symmetrical pyridine substitution pattern. Disappearance of the spike for the N-methyl group at δ 2.41 in macrocycle 321 in conjunction with the presence of the appropriate integration expected for this cryptand is the most conclusive evidence for the structure of 257.

The NMR spectrum of 270 exhibited a doublet at δ 6.20 for the 3,5-pyridyl protons and a triplet at δ 7.41 for the 4-pyridyl proton. In addition, there was no N-methyl singlet at δ 2.28 as there was for macrocycle 269. These spectroscopy data along with an acceptable elemental analyses and mass spectra indicate that the structures drawn are the correct ones.

An extension of these systems was attempted in which a methylene unit would be inserted between the pyridine ring
and the ethereal oxygen atom. The reaction of 2,6-bis-(chloromethyl)pyridine with \textit{N,N}-dimethyl-2-hydroxyethylamine and sodium hydride in \textit{N,N}-dimethylformamide at room temperature resulted in the isolation of the disubstituted product 271 (86%). Diamine 271 was then treated with 1,2-bis(2-iodoethoxy)ethane in refluxing acetonitrile for 48 hours. The solvent was removed \textit{in vacuo} and the resulting crude product was dried under vacuum and subjected to demethylation by L-Selectride®.

Unfortunately, only demethylated ring-opened products could be detected. Most of the cleavage apparently occurred between the \(\alpha\)-methylene and the adjacent oxygen atom, indicating that these 2,6-methylene groups are very susceptible to nucleophilic attack by L-Selectride®. The limited amount of sample precluded further characterization. This enhanced reactivity may be due to
complexation of the pyridine nitrogen atom by lithium, which places the hydride ion in close proximity to the methylenes adjacent to the pyridine ring.

The next logical compounds in this series were the cryptands containing two pyridine bridging units and only one triethylene glycol bridging unit between the bridgehead nitrogen atoms and the cryptand containing only pyridine bridging units as in structures 322 and 264, respectively. The reaction of 2,6-dichloropyridine with N-methyldiethanolamine and sodium hydride as the base in refluxing xylene afforded two products (259 and 260), which were each purified by alumina thick layer chromatography and characterized by $^1$H NMR spectroscopy. In 259 the two doublets at $\delta$ 6.64 and 6.87 for the 3,5-pyridyl protons and the triplet at $\delta$ 7.50 for the 4-pyridyl proton appear at reasonable positions. Macrocycle 260 exhibited three doublets at $\delta$ 6.28, 6.64, and 6.88 for the 3,5-pyridyl protons. Each doublet integrated for two protons. The
4-pyridyl protons exhibited two triplets at $\delta$ 7.45 (one proton) and at $\delta$ 7.50 (two protons). This datum indicates that of the three pyridine rings in this molecule, two of the rings underwent monosubstitution and the central ring underwent disubstitution. When the reaction was performed in N,N-dimethylformamide at 50°C, the two products isolated were 259 and 261. The triplet at $\delta$ 7.40 was for the 4-pyridyl protons while the doublet at $\delta$ 6.23 was for the 3,5-pyridyl protons. In general, when the heteroatom is located directly on the pyridine ring there is an upfield chemical shift for the aromatic protons in the open-chain products as compared with the macrocyclic products.
Macrocyle 261 was treated with 1,2-bis(2-iodoethoxy)ethane according to the general procedure for quaternization and, subsequent demethylation. Unfortunately, no macrocyclic products or starting material could be isolated or detected in the resulting crude material.

Cryptand 264 was formed directly in 3% yield by the reaction of 2,6-dichloropyridine with triethanolamine using sodium hydride as the base for generating the glycolate.

\[
\text{Cl}_2\text{N} + \text{N(CH}_2\text{CH}_2\text{OH)}_3 \xrightarrow{\text{NaH, xylene}} \text{264}
\]

The NMR spectrum of 264 is very simple due to the symmetry of the cryptand; the two sets of triplets at δ 3.08 and 4.32 were assigned to the β- and α-methylene. The 3,5-pyridyl proton signal appears at δ 6.13 and the 4-pyridyl proton signal appears at δ 7.30. These chemical shifts are analogous to those of similar macrocycles (257, 270, and 261).

Crystals of 264 suitable for X-ray structure determination were obtained from a solution of chloroform and ethanol. The cryptand was found to possess D₃ symmetry in the crystal, deviating from ideal D₃h.
symmetry by a slight twist about the $C_3$ axis (Figure VII).

![Figure VII. ORTEP drawing of 264 projected down the N-N axis.]

The most surprising aspect of this crystal structure is that the bridgehead nitrogen atoms possess a planar configuration with crystallographically equivalent $120^\circ$ bond angles. Figure VIII shows this unusual phenomenon as well as the expected bond distances and angles for this molecule. In addition, the N1-N2 bridgehead distance is 7.0 Å and each pyridine nitrogen atom is located 3.9 Å from the center of the molecule.

Since the nitrogen atoms in 264 are planar $sp^2$ hybridized, rather than the anticipated $sp^3$ configuration-
tion, the generally accepted in-in and out-out pictorial representation need not adequately represent these macro-polycyclic structures. Data indicates that skeletal rigidity is imposed in the molecule by the imidate entity which is associated with a low dihedral angle of 0 ± 10°. Synthetic and theoretical studies have shown that heteroatoms adjacent to the pyridine moiety retard metal ion complexation due to steric problems caused by this preferred conformation of the integrated imidate units and the reduced N-electron densities on the pyridine nitrogen atoms (Figure IX). Figure X shows the stereoscopic representation of 264.

Figure VIII. Bond angles and distances for 264.
Because of an interest in studying the effects of structural constraints on the complexing ability of macrocyclic ligands,\textsuperscript{160} it was deemed of interest to attempt the synthesis of 276, a structural analog of 264, in which a methylene group was inserted between each pyridine ring and oxygen atom. It was expected that the increased flexibility and the removal of the steric constraints caused by the imidate moieties (in 264) would allow the bridgehead N-lone pairs of electrons to assume a nonplanar (sp\textsuperscript{3}) configuration and to thus be available for internal complexation. Cryptand 276 was synthesized by the reaction
of sodium hydride with triethanolamine and 2,6-bis(chloro-methyl)pyridine. The best yields (2%) were achieved when the two reactants were added simultaneously as dilute solutions at a very slow rate (not so high dilution). The use of tetrahydrofuran or xylene as a solvent proved to be fruitless; cyclization was only observed to occur in N,N-dimethylformamide. The $^1$H NMR spectrum of cryptand 276 showed a large upfield shift for the 4-pyridyl proton signal at $\delta$ 6.90, while the 3,5-pyridyl protons resonated at $\delta$ 7.30, comparable to similar compounds (264, 285, 293, 300). Molecular models (CPK) of 276 showed that the pyridine rings could freely rotate through the cavity, but that only one pyridine ring could be accommodated within the cavity at any time. Variable temperature NMR spectroscopy studies of 276 suggested that, at least in solution (CD$_2$Cl$_2$), the prediction of the molecular models are borne out. On the NMR time scale, a rapidly rotating structure of this type appears to possess average C$_3$ symmetry. Although coalescence of the 4-pyridyl proton
occurs at -78°C, $\Delta G^+$ cannot be calculated because the sample freezes before the peaks reappear.

**Figure XI.** ORTEP drawing of 276.

Well formed single crystals were obtained for X-ray diffraction by slow evaporation of a chloroform solution of 276. Figure XI illustrates the in-in configuration of cryptand 241, in contrast with the planar nitrogen configuration previously reported for 264. The surprising structural aspect of 276 is the relative orientation of the pyridine rings. The plane normals of two of the pyridine rings point toward the center of the molecule, while the third pyridine ring is located within the cavity. The center of the molecule is occupied by a pyridine 4-hydrogen atom, which lies within 1 Å of the midpoint between the two bridgehead nitrogen atoms. Whereas in cryptand 264 linkage to the aromatic ring is cis to the nitrogen atom with the
N-C-O-C torsion angle near zero, such a linkage in cryptand 276, described by torsion angles equivalent to N(4)-C(19)-C(20)-O(4), is in all cases within 30° of the trans configuration. The low symmetry of 276 and the presence of different conformations for each of its three bridging chains attests to its greater flexibility with respect to cryptand 264.

Distances and angles compare quite well with corresponding values found in cryptand 264, except for the bridgehead C-N-C angle, which is 114.0°. No unusual bond distances or angles exist, and no unusually short intramolecular contacts are present. Figure XIV illustrates the bond distances and angles found for this cryptand. The N1-N2 bridgehead distance is 9.598 Å.

It is not unexpected that cryptand 276 is able to collapse to fill its own cavity, since to maintain the cavity as a void would be energetically unfavorable. If there is an inherent structural rigidity as in 264 the
cavity may exist as a void, as evidenced by X-ray analysis but in solution the cavity most likely will contain solvent molecules. In numerous cases water and various other neutral molecules (acetonitrile, ethyl alcohol, methyl alcohol, etc.) have been shown to form complexes which may

Figure XIV. Bond angles and distances for 276.
be obtained as crystalline solids from which yield to X-ray analysis.¹⁹⁵

Treatment of 276 with manganese(II) perchlorate in ethanol in a ratio of 2:1 (metal salt to ligand) resulted in the immediate precipitation of a white solid 277. Crystals suitable for X-ray analysis were obtained by evaporation of a methanolic solution of the resultant material.

The most surprising feature of this structure determination was the absence of a metal ion within the cavity. The compound isolated was shown to be the bis-quaternary perchlorate salt 277. The two bridgehead

![Structure diagram](image)

nitrogen atoms are in the in-in configuration with the hydrogen atoms on the bridgehead nitrogens located inside the cavity of the macrocycle. Both of these protons are held in a tetrahedral array (bond distances are shown in Figure XV) by a nitrogen atom and three oxygen atoms. All of the O-H-N and O-H-O angles range from 105° to 116°. In addition, the three oxygen atoms have turned such that
their electron density is located inside the cavity in contrast with the non-protonated cryptand where the oxygen atoms are oriented such that their electron density is outside the cavity. Neither is the pyridine ring located inside the cavity: the three pyridine rings now form an equilateral triangle around the center of the molecule in a head-to-tail fashion. The molecule has become more elongated with a bridgehead N1-N2 distance of 10.40 Å for 277, while the N1-N2 distance for 276 is 9.598 Å. The symmetry of the molecule is approximately C3.

The center of the molecule was found in two ways and the distance between the two centers is only 0.029 Å. The first method for finding the center of the molecule was simply by averaging the coordinates of the two bridgehead nitrogen atoms; each of these nitrogen atoms is located 5.202 Å from the center of the molecule. The second center was obtained by averaging coordinates of all six atoms in each ring to obtain the centroid of the ring; the
coordinates of these centroids of each ring were then averaged to obtain the center of the molecule. From these data was calculated the distance of each centroid from the
center and, also, the angles between the centroid to center vectors.

Figure XVIII. Stereopairs of 277.

The copper(II) and cobalt(II) chloride complexes of 276 were prepared; elemental analyses indicate that in both cases there are two metal atoms associated with each cryptand molecule. To date, however, no crystals suitable for X-ray structural determination studies have been obtained.

In an effort to determine the configuration of 264 in solution, the carbon-13 NMR spectra were acquired for cryptands 264 and 276. In the case of a nitrogen bridgehead that is planar in solution (264), the adjacent methylenes should have a significantly different chemical shift from the methylenes in 276. However, for cryptand 264 the N-CH₂ carbon appears at 55.09 Hz, while in cryptand
The N-CH₂ methylenes appear at 57.67 Hz. The difference (Δ) of only 2.58 Hz is not significant enough to indicate planarity of the bridgehead nitrogen atoms in 264 in solution.

Vögtle and Engel have performed pKa measurements on 264 and 276 using a pH-electrode and tritratting with hydrochloric acid (10⁻² N). The basicity of cryptand 264 was measured in water/methanol (4:1) and the data indicate that the compound is only monoprotonated at a pKa of approximately 7.5 despite the fact that there are two nitrogen atoms. The pH measurement of 276 was performed in water and indicates only one equivalence point at pKa 7.8 with two moles of proton being taken up at once. In contrast, Lehn's [2.2.2] cryptand shows two pKa values, 9.6 and 7.28; and cryptand [3.3.3] exhibits pKa values of 6.96 and 7.70, similar to the value seen for 276. Complex constant measurements made with ion selective electrodes on these two cryptands are currently underway in their laboratories.¹⁹⁶

As a means of comparison, it was of interest to synthesize 323. This could be accomplished by synthesis of 274, subsequent, quaternionization with 1,2-bis(2-iodoethoxy)-ethane and demethylating to afford the desired cryptand (Scheme XVI). The reaction of 2,6-bis(chloromethyl)-pyridine with the sodium glycolate of N-methyldiethanolamine in N,N-dimethylformamide afforded 274 (52%) as a
colorless oil after purification by alumina thick layer chromatography.

The \(^1\text{H}\) NMR spectrum showed a triplet at \(\delta 7.51\) for the two 4-pyridyl protons. 274 was then quaternized with 1,2-bis(2-iodoethoxy)ethane in refluxing acetonitrile; after workup the resulting viscous oil was directly treated with L-Selectride\textsuperscript{®} to effect demethylation. No macrocyclic products could be detected only ring-opened demethylated materials appear to be present, but these numerous miniscule fractions were not characterized.

Scheme XVI

Because of the nonexistence of cryptands containing 1,8-naphthyridino moieties and the varied interesting
structural properties of the cryptands thus far synthesized (264 and 276), we were interested in incorporating this entity within a cryptand. The reaction of the relatively insoluble 2,7-dichloro-1,8-naphthyridine with triethanolamine was performed at 80°C in N,N-dimethylformamide. As usual, sodium hydride was enlisted as the base to generate to glycolate. Two products were isolated and purified by alumina thick layer chromatography. 281 was formed in 3% yield and identified as the open-chain

\[
\begin{align*}
\text{Cl} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\end{align*}
\]

\[
\text{N(CH}_2\text{CH}_2\text{OH)}_3
\]

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\end{align*}
\]

\[
\text{281}
\]

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{O} & \quad \text{N} \\
\text{O} & \quad \text{N} \\
\text{O} & \quad \text{N} \\
\end{align*}
\]

\[
\text{282}
\]

disubstituted naphthyridine compound. The macrocyclic product 282 was isolated (9%) and identified by normal physical methods. All attempts to isolate the desired cryptand 324 have failed, this is believed to be due to the expected insolubility of this cryptand and the intermediates; the synthesis of 324 is left as an exercise to the reader.
Attempts were made to incorporate the 6,6'-dimethyl-2,2'-dipyridine moiety into a cryptand by treatment of triethanolamine with 6,6'-bis(chloromethyl)-2,2'-dipyridine. The desired cryptand should have a significant frontal retention value on alumina TLC, however, no eluant, even 10% ethanol in chloroform, would move anything from the baseline. This leads one to conclude that the desired macrocycle was not formed. In retrospect this is not unexpected since calculations show that dipyridine prefers the anti conformation over the syn conformation.\textsuperscript{194}

In addition, there is also an entropy problem since five molecules must be constrained in proximity in order for reaction to occur. Perhaps a metal ion may be utilized to complex the dipyridine in the syn conformations, thereby,
allowing the cyclization to occur. At present it appears that zinc(II) chloride may be useful in selected instances. However, the lability\textsuperscript{197} of the zinc(II) chloride-dipyridine complex to water may preclude the utility of such a complex under glycolate reaction conditions.
Conclusion

The major thrust of this research project has been the study of molecular structure versus complexation ability, the ultimate aim being the synthesis of metal specific chelates capable of selectively complexing a particular metal ion. The latter goal remains an elusive dream at this time in history; however, significant strides have been made towards understanding the effects of structural modification of a chelate on its complexation abilities. The ones discussed here may be monocyclic (coronands) or polycyclic (cryptands) and may complex one or more metal ions.

Most of the previous work with aza coronands has centered primarily on the in situ Schiff's base cyclo-condensation of a dialdehyde or a diketone with a diamine, with a transition metal as the template ion. These reactions are very metal ion specific and in most instances removal of the metal ion from the resulting macrocyclic complex is difficult, if not impossible to accomplish without fragmentation of the macrocycle. Only a few isolated cases have been reported in which the free imine has been isolated and subsequently reduced to the free amine.
We were interested in utilizing a different approach: the macrocyclic ligand is synthesized first and then the metal ion complex is formed. All of the macrocycles reported in this dissertation contain either pyridine or 1,8-naphthyridine. Of the various coronands reported, some contain only nitrogen heteroatoms while others contain both nitrogen and oxygen heteroatoms. However, transition metal ion complexes have been formed only for the macrocycles which contain strictly nitrogen heteroatoms; no complexes have been found for the macrocycles which also contain oxygen and nitrogen atoms. Furthermore, if the heteroatom is directly substituted on the pyridine nucleus, the macrocycle does not form metal ion complexes. A diprotonated cobalt(II) tetrachloride salt was formed from 284, which contains both oxygen and nitrogen atoms.

Another macrocycle, 293, an analogue of "18-crown-6", was synthesized by the treatment of 2,6-bis(chloromethyl)-pyridine with N,N'-dimethylethlenediamine. This compound
was found to form an octahedral complex with either cobalt(II) or copper(II) chloride, wherein all of the coordination sites of the metal ion are occupied by a ligating atom of the macrocycle. The counterion of this complex is tetrachlorocobaltate(2-). The interesting complexation properties of 293 have led to the synthesis of the piperazine derivative 300. If the the piperazine rings of this compound can assume the boat conformation, all four of these nitrogen atoms should be able to participate in complexation of a metal ion. The copper(II) chloride complex of 300 has been prepared and the structure determined by X-ray analysis. It appears that a copper atom occupies the cavity of the macrocycle, but that only the pyridine nitrogen atoms are involved in complexation of the metal. Another copper ion is also present in the unit.
cell; however, the exact nature of this species is not known because a disordered solvent sphere about this metal ion prevents further refinement of the data.

Numerous cryptands have been reported, accompanied by data on their complexation properties. It has been determined that there is a direct relationship between complex stability and the relative sizes of the cation and the cavity: the most stable complex is formed when there is a good fit of the guest within the host. Cryptands containing oxygen atoms in the bridging units preferentially complex the alkali and alkaline earth metals; cryptands containing nitrogen atoms in the bridging units prefer the transition metals.

Cryptands have primarily been synthesized by the cyclocondensation of a diacid halide with a diamine, followed by reduction to the cyclic diamine, and then cyclocondensation and reduction once again to afford the desired cryptand. The cyclocondensations are performed under high-dilution conditions and the yields are generally very good.

Prior to our work in the cryptand field there were only a few examples of cryptands containing pyridino subunits. We essentially doubled the number of cryptands in this category containing this subunit. To attain our target molecules we utilized alternative schemes: on one hand, "brute" force reactions were performed in which all
six bonds were formed in a one-pot reaction as for 264 and 276. X-ray diffraction studies of these macrocycles demonstrate that both possess somewhat unusual, but not unduly surprising, structures. The bridgehead nitrogen atoms of 264 are $sp^2$ hybridized in the solid state, but do not exhibit any unusual spectral properties to indicate this to be the case in solution. However, the 4-pyridyl proton of 276 exhibits an unusual chemical shift in the $^1H$ NMR spectrum which shows all of the pyridine rings to be equivalent on the NMR time scale. The X-ray crystal analysis provides some insight into this abnormal chemical shift: in the solid state, one of the pyridine rings occupies the cavity created by the rest of the molecule. That this is so seems quite reasonable in retrospect, since it would be energetically unfavorable for the cavity

![Diagram of 264 and 276]

to remain a void. 264 cannot occupy its own cavity due to the rigidity associated with the imidate nature of the heteroatoms which are substituted directly onto the pyridine nucleus. This substitution is also responsible for the planarity of the bridgehead nitrogen atoms. In
solution the cavity of 264 is probably occupied by solvent molecules.

No complexes have been formed with 264, 276 forms complexes with cobalt(II) and copper(II) chloride but crystals suitable for X-ray analysis have been unattainable. A cadmium(II) chloride complex has also been formed with 276, and elemental analysis indicates that there are three cadmium ions associated with each cryptand molecule.

A quaternization-demethylation sequence was also developed to obtain some of the desired cryptands. A dihalide was treated with a diamine to form a macrocyclic quaternary ammonium salt which was demethylated with L-Selectride®; repetition of the, quaternization and demethylation afforded the cryptand. 257 and 270 were obtained by this reaction sequence. That no complexes were acquired for these two compounds was ascribed to the inability of macrocycles containing heteroatoms directly substituted on the pyridine ring to form metal complexes. It must be pointed out that for 257 and 270 the glycol
portion of these cryptands should be able to complex alkali or alkaline earth ions.

The observation that pyridine and naphthyridine compounds which have a heteroatom directly substituted onto the aromatic ring do not form complexes at all is believed to be due to the imidate nature of this section of the molecule. This substitution results in a dihedral angle of essentially $0^\circ$ which in turn produces a steric effect: the $\alpha$ protons are forced to orient themselves inside the cavity, blocking the pyridine nitrogen from participating in complexation. In addition, because of the restricted dihedral angle, the free electrons of the heteroatoms are pointing outside the cavity and are also unavailable for complexation.

In summary, a number of factors influence cation selectivity. With regard to the ligand, there are several structural considerations: cavity size, nature and number of coordination sites, lipophilicity, and ligand conformation and flexibility. Other factors which influence cation selectivity and complex stability include the reaction environment (solvent polarity and temperature)
and the counterion. As far as the counterion is concerned, nucleophilicity and steric bulk must be considered. Once these factors are weighed along with the charge density of the metal ion, it is possible to predict whether a particular complex will form and, if so, the preferred stoichiometry thereof.

Future work in the area of the aza macrocycles should include modification of the coronand size to form compounds such as 325 and 326 to see if they will complex cobalt(II) and copper(II) chloride in the same fashion as 293. It would also be interesting to alter the nature of the ligating atoms and investigate the types of complexes, if any, that are formed. It is more than evident from the information presented herein that much work remains to be done with regard to the general structure of these two-dimensional ligands and their complexation properties.

As far as the polycyclic systems are concerned, further work should attempt to determine the exact nature of the complexes that have been formed with ligand 276 and the effects on its complexation properties of altering the
structure of this cryptand. It is also evident that these systems present a greater opportunity for selective metal ion complexation than the coronand systems. Although great strides have been made in studying ligand design versus complexation properties, the surface has only been scratched. The diverse architecture that characterizes these systems offers the opportunity for significant control over the complexing abilities of these macrocycles. The design and synthesis of new and varied cryptands and studies of their complexation properties offers a unique challenge to chemists, the ultimate goal being the synthesis of molecules which would rival biological systems in their complexation selectivities.
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Appendix I

X-Ray Data
Crystal data for 295 \([\text{Co}_{22}\text{H}_{34}\text{N}_6][\text{CoCl}_4]\), FW=642.2,
monoclinic space group P2\(1\)/n, \(a=9.944(3)\), \(b=17.214(4)\),
\(c=16.347(4)\) Å, \(\beta=94.32(2)^\circ\), \(Z=4\), \(d_c=1.529\) g cm\(^{-3}\),
\(\mu(\text{MoK}\alpha)=16.0\) cm\(^{-1}\), \(R=0.042\) for 1738 observed data.

Bond Distances for 295

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Bond Angles of 295
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C10-N3-C11  109.0(6)  C11-C12-C13  122.9(7)
Co1-N4-C12  119.9(5)  C12-C13-C14  118.4(7)
Co1-N4-C16  119.3(5)  C13-C14-C15  121.2(7)
C12-N4-C16  120.7(6)  C14-C15-C16  117.9(7)
Co1-N5-C17  107.8(4)  N4-C16-C15  121.1(7)
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Co1-N5-C19  103.8(4)  C15-C16-C17  124.1(7)
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C17-N5-C19  109.2(5)  N5-C19-C20  111.0(5)
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Coordinates for 295

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Bond Distances of 296

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**Bond Distances for 288**

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![Diagram of a molecule](image)
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Bond Distances for 300

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Bond Angles of 300

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Coordinates for 300
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Bond Distances for 284

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Bond Angles for 284
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Coordinates for 284

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$\beta$ = 107.18(3)$^\circ$, $U$ = 6495(4) Å$^3$, $Z$ = 8, $d_c$ = 1.432(1) g cm$^{-3}$, 
$\mu$(MoKa) = 8.96 cm$^{-1}$, $R$ = 0.108 for 2,239 observed data 
having $2^\circ$ $\leq 2\theta$ $\leq$ 42$^\circ$.

Coordinates for [CoCl$_4$]$^{2-}$
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Crystals of $\text{[C}_\text{48} \text{H}_{52} \text{N}_{14} \text{O}_{14}\text{]}^{2+} \text{CH}_3 \text{CN}$, 256, are monoclinic and the space group is $P2_1/n$, $a=11.355(2)$, $b=23.291(3)$, $c=12.161(6)$ Å, $\beta=97.72(1)^\circ$, $Z=4$. Data were collected using MoK$_\alpha$ radiation on an Enraf-Nonius CAD4 diffractometer to $\Theta=22^\circ$ and the intensities were corrected for absorption.

### Bond Distances for 256

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N3-C10  1.535(5)  C15-O4  1.424(6)
N3-C11  1.479(6)  O4-C16  1.437(6)
N3-C17  1.531(5)  C16-C17  1.464(7)
N3-C23  1.492(5)  C18-C19  1.488(6)
C2-C3  1.516(5)  C19-O5  1.396(5)
C3-O1  1.444(5)  O5-C20  1.426(6)
O1-C4  1.360(5)  C20-C21  1.385(9)
C4-C5  1.361(6)  C21-O6  1.497(8)
C5-C6  1.374(7)  O6-C22  1.284(9)
C6-C7  1.363(6)  C22-C23  1.542(11)
C7-C8  1.387(6)  C1s-N1s  1.181(12)
C8-O2  1.359(5)  C1s-C2s  1.319(12)

Bond Angles for 256

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C11-N3-C17 111.4(3) C15-O4-C16 112.7(4)
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C17-N3-C23 111.1(3) C16-C17-N3 116.5(4)
N1-C2-C3 116.8(3) N1-C18-C19 117.2(3)
C2-C3-O1 113.9(3) C18-C19-O5 112.1(3)
C3-O1-C4 117.5(3) C19-O5-C20 112.5(4)
O1-C4-C5 118.3(4) O5-C20-C21 109.7(5)
N2-C4-C5 124.0(4) C20-C21-O6 107.7(6)
N2-C4-O1 117.7(3) C21-O6-C22 112.1(7)
C4-C5-C6 117.4(4) O6-C22-C23 110.1(6)
C5-C6-C7 121.2(4) C22-C23-N3 115.2(4)
C6-C7-C8 116.7(4) N1s-C1s-C2s 178.1(10)
C7-C8-N2 123.6(4)

Coordinates for 256

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Crystal data: C<sub>27</sub>H<sub>33</sub>N<sub>5</sub>O<sub>6</sub>; trigonal space group R<sup>3</sup>c, with rhombohedral axes \( a = 10.939(1) \) Å, \( \beta = 83.325(1) ^\circ \), \( z = 2 \), \( d_c = 1.353 \) g cm\(^{-3} \), \( R = 0.031 \) for 738 unique observed data collected on an Enraf–Nonius CAD4 diffractometer.

Bond Distances for 264

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Bond Angles for 264

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### Coordinates for 264

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Crystal data: \( \text{C}_3 \text{H}_4 \text{N}_2 \text{O}_5 \), triclinic, space group \( \overline{P}\overline{1} \),

\[ a=8.762(1), \quad b=9.198(1), \quad c=23.122(3)\AA, \quad \alpha=75.70(1), \quad \beta=76.17(1), \quad \gamma=67.27(1)^\circ, \quad Z=2, \quad d=1.228 \text{ gcm}^{-3}, \quad R=0.045 \]

for 2154 observed data having \( 2^\circ \leq \theta \leq 25^\circ \), \( \lambda=0.71073\AA \) for \( \mu(\text{MoK}\alpha) \) radiation. Intensity data were collected by the \( \theta-2\theta \) scan method on an Enraf-Nonius CAD4 automatic diffractometer.

Bond Distances for 276

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Coordinates for 276

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Bond Distances for 277
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<td>0.5285(5)</td>
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</table>
Appendix II

Convenient Dealkylation

of Quaternary Ammonium Salts
CONVENIENT DEALKYLATION OF QUATERNARY AMMONIUM SALTS

George R. Newkome*, Veronica Majestic
Department of Chemistry, Louisiana State University
Baton Rouge, Louisiana 70803

Joe D. Sauer*
Research and Development, Ethyl Corporation
Baton Rouge, Louisiana 70821

Over the past twenty years, numerous new procedures have been devised to dealkylate various quaternary ammonium compounds. The early dealkylations of quaternary ammonium halides via pyrolysis gave low yields of the corresponding tertiary amines along with decomposition products. More recently, reagents with enhanced nucleophilicity have been utilized. As a consequence, it has become possible to reduce reaction temperatures and times and ultimately product degradation can be reduced. In 1950, Kenner and Murray suggested that demethylation of quaternary ammonium salts occurred via an SN2 attack by hydride ion from lithium aluminum hydride; subsequently, Cope et al. demonstrated the generality of this reagent. Sodium borohydride in polar aprotic solvents has also been shown to remove reductively an alkyl group from quaternary ammonium salts in smooth fashion. The use of "Super-Hydride" to dealkylate ammonium compounds has been reported and high selectivity for removal of a methyl group from PhN(C2H5)(CH3)2I was demonstrated. We herein describe a convenient procedure to dealkylate quaternary ammonium compounds with
"L-Selectride" (lithium tri-sec-butylborohydride) and via application of this procedure to mixtures of quaternary ammonium salts, a near quantitative analyses can be realized.

To evaluate the dealkylation procedure, samples of commercial* dodecyl-, tetradecyl-, and hexadecyldimethylamine were initially quaternized with methyl bromide in ethanol to give, in quantitative yield, the expected methyl quats. Although the commercial amines were >95% a single component, in order to maintain the initial amine distribution, the resultant quat mixture was not purified, but rather was treated with "L-Selectride" in refluxing toluene (General Procedure). The reaction conditions described appear to be more rigorous than necessary; however slight modifications of these conditions produced little or no variance in the resulting amine distributions. In all cases, analyses showed that dealkylation was highly selective for a methyl group. The recovered dealkylated amine mixtures were shown to be, within experimental error, nearly identical to the starting amine distribution.

\[
\text{LiB}(2-\text{C}_4\text{H}_9)\text{BH} \\
\text{RN(CH}_3\text{)}_2 + \text{CH}_3\text{Br} + \text{RN(CH}_3\text{)}_3\text{Br}
\]

Dealkylation of commercial quat formulations by this procedure proved to be a convenient route to the tertiary amines as well as demonstrated the utility under difficult conditions.

*Ethyl Corporation ADMATM products.
Subsequent analyses of the mixtures by standard GLC techniques resulted in reliable descriptions of the compositions of these often complex commercial products. Experimental values obtained for several of these products are compared with the compositions announced by their producers in Table II. Cetramide®, tetradecyltrimethylammonium bromide, was selectively demethylated to give quantitatively a predominant (99.2%) amine in favorable correlation with the reported composition. Bardac®, a mixture of dioctyldimethyl-, octyldecylmethyl-, and didecyldimethylammonium chlorides, also underwent selective demethylation, quantitatively yielding the expected distribution of dialkylmethyldamines. Hyamine 3500®, a mixture of alkylidimethylbenzylammonium chlorides, afforded, upon dealkylation, products arising from loss of either a methyl or a benzyl group. Although the resulting tertiary amine mixture in this case was more complex, the agreement between the reported composition and the observed analysis was excellent.

This dealkylation procedure provides a quantitative, general procedure to liberate tertiary amines from their corresponding quaternary salt. Application to the demethylation or debenzylation of simple or complex mixtures of tetra-alkyl ammonium salts has been demonstrated to be convenient procedure to accurately ascertain amine distributions.
General Procedure for Quaternization of Tertiary Amines. A flask equipped with mechanical stirrer, gas inlet, addition funnel, and dry ice-cooled condenser was charged with absolute ethanol (150 mL) and methyl bromide (0.5 mol). To this stirred solution, commercial alkyldimethylamine (ca. 0.5 mol) was slowly added under a nitrogen atmosphere. After addition was complete, the extremely thick mixture was stirred thirty minutes, then allowed to stand at ambient conditions overnight. The semi-solid mass was broken up with absolute ether (500 mL) and the solid product (alkyltrimethylammonium bromide) was collected by filtration. This procedure resulted in practically quantitative (95+% theoretical) yields of the expected products.

General Procedure for Dealkylation of Quaternary Amines. To a stirred suspension of the anhydrous\textsuperscript{1} quaternary ammonium salt (2.5 mmol) in dry toluene (25 mL), "L-Selectride" in THF (5 mL, 5 mmol) was slowly added under a nitrogen atmosphere. The mixture was refluxed for one hour, then cooled, and aqueous hydrochloric acid (10%, 10 mL) was added slowly. After neutralization with aqueous sodium hydroxide (3N), the mixture was extracted with methylene chloride (2 x 15 mL). The combined extract was dried over anhydrous magnesium sulfate and concentrated in vacuo to give the corresponding amine in nearly quantitative yield. GLC analysis

\textsuperscript{1}Since many commercial "quats" are supplied in aqueous, ethanolic solution, a practical method for pre-drying the sample was necessary. Simply refluxing a solution of the commercial material in excess toluene with a Dean-Stark trap in place proved to be satisfactory with all of the samples examined. No further drying or sample preparation was required prior to treatment with "L-Selectride".
of the amine mixtures are given in Tables 1 and 2. All amine
structures were ascertained by mass spectral comparison to known
compounds.⁹

Acknowledgement

We gratefully acknowledge the National Institute of Health
(G. R. N.) and the Ethyl Corporation for their partial support of
this work.

REFERENCES AND NOTES.


2. For review see (reference 16, therein): Hutchins, R. O.,
   Kandasamy, D., Dux III, F., Maryanoff, C. A., Rotstein, D.,
   Goldsmith, B., Burgoyne, W., Cistone, F., Dalessandro, J.,

3. Other pertinent references not included in reference 2:
   Co(I) reagents: Costa, G., Puxeddu, A., Reisenhofer, E.
   Tetrahedron Lett. 1972, 2167; Carboxylic Acid Anhydrides:
   Fereczberg, S., Gaona, R. T., Lopez, R. T., Comin, J.
   Tetrahedron Lett. 1973, 1269; Potassium tert-butoxide:
   1972, 4787; Trimethylamine: Lane, T. H., Speier, J. L. J.


5. Cope, A. C., Ciganek, E., Fleckenstein, L. J., Meisinger,

   1669.


   7159; available from Aldrich Chemicals.

9. Amine distributions and structural analyses were conducted
   on a Finnigan 4021 Mass Spectrometer (70 eV, 2 sec scan) coupled
   with a Hewlett Packard 5710 A gas chromatographed equipped with
   a flame ionization detector using a 1/4" O.D. (2 mm I.D.) x 15'
   glass column packed with 10% Carbowax 20M on 80/100 mesh
   Gas Chrom Q.
### TABLE I. DEMETHYLATION OF QUATERNARY SALTS DERIVED FROM COMMERCIAL FATTY AMINES

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<th>R&lt;sup&gt;1&lt;/sup&gt;R&lt;sup&gt;2&lt;/sup&gt;R&lt;sup&gt;3&lt;/sup&gt;N Compound&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Starting Amine Mixture (prior to methylation)</th>
<th>Reaction Conditions&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Recovered Amine Mixture (after demethylation)</th>
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<tbody>
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<td>Dodecyl-dimethylamine</td>
<td>R&lt;sup&gt;1&lt;/sup&gt; CH&lt;sub&gt;3&lt;/sub&gt; CH&lt;sub&gt;3&lt;/sub&gt; 0.3</td>
<td>(a) Time (min) 60, Temp. (°C) 111</td>
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<td>(b) Time (min) 10, Temp. (°C) 111</td>
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<sup>a</sup>Ethyl Corporation ADMA™ Products.

<sup>b</sup>Various reaction conditions gave similar product distribution.
TABLE II. DEALKYLATION OF COMMERCIAL ALKYL AMMONIUM SALTS.

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aComposition as stated on chemical sample. bTrademark of tetraalkyl ammonium salt. cVarious reaction conditions gave similar product distributions. dDanchemo, Copenhagen, Denmark. eLonza, Inc., Fair Lawn, N.J. fRohm & Haas, Co., Philadelphia, PA.
Appendix III

Chemistry of Heterocyclic Compounds.

Synthesis and Conformational Studies of

Macrocycles Possessing 1,8- or 1,5-Naphthyridino

Subunits Connected by Carbon-Oxygen Bridges
Chemistry of Heterocyclic Compounds. 61. Synthesis and Conformational Studies of Macrocycles Possessing 1,8- or 1,5-Naphthyridino Subunits Connected by Carbon-Oxygen Bridges.\textsuperscript{1a}

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Received

During our recent studies in the synthesis of hetero-macrocycles,\textsuperscript{2} we have evaluated macroligands containing 2,6-pyridino,\textsuperscript{3} 2,4-pyrimidino,\textsuperscript{4} 2,6-pyrazino,\textsuperscript{5} and 3,6-diazino\textsuperscript{6} in order to ascertain a better molecular picture of multifunctional cyclic ligands. The successful inclusion of a site-localized complexing region within a macroligand has recently been reported\textsuperscript{1a,7} however, these subunits have been limited generally to a bis-Schiff base moiety, best represented by 1. In view of the limited examples of naphthyridine complexes,\textsuperscript{8} the nonexistence of macrocycles containing a naphthyridino subunit,\textsuperscript{2} and the practical application as medicinals,\textsuperscript{9} we herein report the synthesis, spectral studies, and x-ray data on macrocycles possessing either a 1,8- or 1,5-naphthyridino moiety.
Synthesis of Naphthyridine Starting Materials. A. 2,6-Dichloro-1,5-naphthyridine \( (2) \). Hart\(^1\) initially prepared \( 2 \) from 1,5-naphthyridine di-N-oxide \( 3 \) upon treatment with phosphorus oxychloride, whereas equally attractive routes have been employed such as the treatment of 1,5-dimethyl-1,5-naphthyridine-2,6(1H,5H)-dione with a mixture of phosphorus pentachloride and phosphorus oxychloride\(^1\) and the reaction of 2-hydroxy-1,5-naphthyridine 5-oxide\(^2\) under Hart's conditions.\(^1\) In view of the differing physical properties reported for \( 2, \)\(^1\)^{11-13} the authenticity of \( 2 \) was recently established.\(^1\) Repetition of Hart's procedure (Scheme 1) has afforded (36\%) \( 2 \), which conforms to the desired physical and spectral data.

Scheme 1
2,7-Dichloro-1,8-naphthyridine. - Treatment of 2,6-diaminopyridine with malic acid in concentrated sulfuric acid gave (97%) 2-amino-7-hydroxy-1,8-naphthyridine (4), which was diazotized with sodium nitrite in concentrated sulfuric acid to give (87%) 2,7-dihydroxy-1,8-naphthyridine (5). Upon treatment of 5 with refluxing phosphorus oxychloride and phosphorus pentachloride for two hours, the desired 6 was isolated in 81% yield (Scheme 2). The NMR spectrum of 6 showed an anticipated AB pattern with doublets at δ 7.5 and 8.1 for the H-3,6 and H-4,5 protons, respectively.

Scheme 2

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{N} & \quad \text{NH}_2 \\
\rightarrow & & \rightarrow \\
\text{H}_2\text{N} & \quad \text{N} & \quad \text{O} & \quad \text{H} & \quad \text{OH} & \quad \rightarrow \\
& & \rightarrow \\
& & \text{Cl} & \quad \text{N} & \quad \text{N} & \quad \text{Cl} \\
\end{align*}
\]

2,6-(1,5-Naphthyridino) Macrocycles. Reaction of 2,6-dichloro-1,5-naphthyridine (2) with the dianion, generated from anhydrous hexaethylene glycol and two equiv. of sodium hydride, afforded the desired 1:1-macrocycle 7a as well as the 2:2-compound 8a. Numerous open-
chain compounds were detected but not characterized further since they were deemed similar to those previously isolated.\textsuperscript{1c} Reactions of $\mathcal{Z}$ with hexa- to diethylene glycols were conducted, in which 1:1-macrocycles ($\mathcal{Z}_a$ and $\mathcal{Z}_b$) were isolated only from hexa- and pentaethylene glycols, respectively; whereas, 2:2-macrocycles ($\mathcal{Z}_c$-$\mathcal{Z}_g$) were isolated from the respective reactions. Inspection of the space-filling CPK models of $\mathcal{Z}_e$ supports the fact that the 13-membered bridge is too short to span the 2,6-positions of the naphthrydine nucleus only when the restrictive, near zero, dihedral angle caused by the imidate moiety\textsuperscript{17} is imposed. Therefore the bridging distance is not to be considered between the two $\alpha$-positions (first
atoms from the subheterocyclic unit) but rather between the two β-bridge positions. Without this constraint, dictated by the presence of the two imidate groups, the tetrathylene glycol (13-membered) bridge may be constructable, for example, in the 2,6-bridging of the related naphthylene nucleus.

The structures of these C,0-macrocycles were confirmed by molecular weight determinations (mass spectrometry and/or osmometry) and 1H NMR spectroscopy. The 3(7),4(8)-naphthyridine hydrogens appear as doublets (J = 9 Hz) at δ 7.0-7.1 and 7.6-8.6, respectively. The bridging methylenes in 7 possess varying degrees of ring anisotropy as the bridge spans the face of the naphthyridine subunit. Figure 1 shows the separation of the different methylenes by ring current proximity. The corresponding 2:2-macrocycles (8) show considerably less discrimination between the various methylenes, since they are not subjected to the effects of the ring currents. Further evidence for the existence of the bridged conformation in 7 was derived from variable temperature NMR. At -80°C, the 2-methylene proton signal coalesced, indicative of a specific conformation imposed by the rigidity of the non-mobile bridging glycol moiety, very similar to that recently demonstrated in the 2,2'-dipyridyl series. The imidate moiety also imposes an additional spanning distance. The ε- and β-CH2 protons exhibit a shielding of 1.4 ppm caused
by their direct juxtaposition to the naphthyridine ring current. Recently similar bridging discrimination of the methylene groups caused by the magnetically anisotropic benzene$^{19}$ and naphthalene$^{20}$ groups has been reported. The $\beta,\gamma$-methylene protons showed a deshielding of 0.7 ppm at $-80^\circ$C, which further indicates that these protons are more nearly coplanar with the aromatic nucleus.

2,7-(1,8-Naphthyridino) Macrocycles. The reaction of 9 with various dianions of polyethylene glycols was conducted in a similar fashion to that described above. Three new 1:1 macrocycles 2a-c were isolated and characterized. The supportive NMR data of 2a-c for the macrocyclic structure are the doublets ($J = 9$ Hz) at $\delta$ 6.7-7.0 and 7.7-7.8 for the H-3,6 and H-4,5 protons, respectively (see Figure 2). The bridging methylenes are less clearly separated [$\delta = 4.7(a), 3.8-3.2 (b-c)$] due the lack of proximal ring current. The orthogonal N-electron density is lessened in magnitude due to their inclusion in the imidate moiety. In order to ascertain the site of ion complexation, Eu(FOD); shift reagent was added to 9b. From the downfield shift of the spike for the $\epsilon$-methylene protons, the shift reagent is predominantly associated with the central region of the polyetherreal bridge and not with the naphthyridine nucleus.

Attempts to increase the yields of macrocyclic products were made by templation about a transition metal
cation. Slight increases (ca. 5%) were realized but these minor increases could not be attributed exclusively to the usage of the metal ion.

Open-chain compounds (11) were also isolated from these reactions. Since the IR spectrum of 6 contained an absorption band at 748 cm\(^{-1}\) for the C-Cl vibrational mode, which was not present in the parent 1,8-naphthyridine or macrocyclic derivatives, the presence of the absorption at 750 ± 10 cm\(^{-1}\) in these 2:1-compounds supports the presence of the C-Cl bond. Further spectral support was provided by MS and NMR data. The NMR spectra of 11 show two close doublet of doublets at δ 6.55 and 6.59-6.65 for the H-3 and H-6 protons, respectively; the unsymmetrical nature of the ring and the complexity of the NMR spectrum further substantiate mono-oxygen substitution.

There were no 2:2-macro cyclic products, e.g., 10, isolated when our general\(^3\) xylene was used; however when N,N-dimethylformamide (DMF) was utilized, not only were the 1:1-macrocycles isolated but also the desired 2:2-macro cycles were realized. The NMR data for 10\(_d\) and 6 show an anticipated symmetrical pattern for the naphthyridine subunits. Furthermore, the trimer 12 was isolated and characterized from the reaction of 6 with sodium diethylene glycolate.

In order to ascertain the dimensions of these cavities and the actual hindrance to the naphthyridine
N-electrons, the x-ray crystal structure of 2b was undertaken. Two independent molecules exist in the asymmetric unit of the crystal. One is illustrated in Figure 3; average interatomic distances and average angles are given in Figure 4 and 5, respectively. Two distinct molecules lie in almost identical orientations with respect to the crystal axes and have very similar conformations. The only substantial differences in conformation exist in the portion of the polyetheral bridge between 04 and 06, which is also the only portion of the molecule in which statistically significant differences in distances and angles exist between the primed and unprimed molecules. The sixteen-atom bridge is apparently quite flexible and subject to quite subtle packing effects.

Insert Figures 3-5
Substitution of the polyethereal bridge to the naphthyridyl moiety (the imidate group) is in all cases essentially cis to the nitrogen atom. Torsion angle N1-C2-C11-C11 is 3.8° and N8-C7-C6-C20 is 0.2°. The corresponding values for the primed molecule are 6.7° and -1.8°, respectively. This conformation is universally found in N-heterocycles, e.g., pyridine, pyrimidine, substituted by an α-oxygen atom ortho to the N-atom. The 1,8-naphthyridyl fragment exhibits marked structural differences from the parent 1,8-naphthyridine, many of which can be understood as consequences of the polyethereal disubstitution. Naphthyridine has a clearly nonplanar, twisted structure, in which the two nitrogen atoms lie on opposite sides of the best plane of the molecule. The N-C-N angle in naphthyridine is 115.3(2)°, which is significantly larger than the corresponding angle found in complexed naphthyridines. These facts have been rationalized in terms of repulsion between the nitrogen lone pairs. The naphthyridyl fragment of 9b does not have the twisted structure of the parent molecule, but exhibits only marginally significant deviations from planarity. The N1-C9-N8 angle has an average value of 113.0(5)°. Both of these geometrical features coupled with the lanthanide shift studies (Figure 2) indicated a reduced electron density for the N-lone pairs due to their inclusion in the imidate moiety. Such reduced N-electron density has also been observed in polyethereal substituted pyridine and bipyridyls. The twisting of naphthyridine also causes the central bond (e.g. C9-C10) to be lengthened relative to the two bonds parallel to it. 9b showed no such lengthening. In general, the naphthyridyl subunit of 9b more closely exhibits the pattern of lengths expected from the resonance description than does naphthyridine.
Experimental Section.

General Comments. All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. IR spectra were measured on a Perkin-Elmer 621 Grating Spectrophotometer and the UV spectra were recorded on a Cary 14 Spectrophotometer. Unless otherwise noted, NMR spectra were obtained in CDCl₃ solutions with Me₄Si, as the internal standard (δ = 0 ppm) and recorded on either a Varian Associates A-60A or Bruker WP 200. Low temperature (40° to -80°C) NMR studies were conducted in CD₂Cl₂; whereas with the high temperature range (40° to 100°C), perchlorobutadiene was used. MS data were measured on a Hitachi-Perkin-Elmer RMS-4 mass spectrometer by Mr. J. Murphy or a Hewlett-Packard model 5985 gc/ms spectrometer by Mr. D. Patterson. Elemental analyses were performed by Mr. R. L. Seab in these laboratories.

The recorded Rf values were determined by a standardized thin-layer chromatography (TLC) procedure: 0.25 mm Brinkman silica gel HF-254+366 plates eluting with the stipulated solvents. For preparative ThLC, 2 mm Brinkman silica gel P/UV-254-366 or aluminum oxide (Type T) HF-254-366 plates were used. Xylene was distilled from sodium wire under a nitrogen atmosphere, while DMF was purified by specific condition to retard cyanide formation. Sodium hydride (57% oil dispersion) was washed with anhydrous petroleum ether (bp 30-60°C) and then dried in vacuo prior to the reaction. Ethylene glycol and di-, tri-, and tetraethylene glycols were purchased from Aldrich Chemical Co.; whereas, penta- and hexaethylene glycols were purchased from Columbia Organic Chemicals, Inc.
**1,5-Naphthyridine. Series**

2,4-Dichloro-1,5-naphthyridine (2) was prepared from 1,5-naphthyridine in 35% yield by a previously described procedure:\textsuperscript{14} mp 250-251°C.

**Reaction of 2,4-Dichloro-1,5-naphthyridine (2) with Hexaethylene Glycol.** - A General Macrocyclic Preparation. Under a nitrogen atmosphere an oil suspension of sodium hydride (120 mg) was washed with anhydrous hexane (75 mL), then dried \textit{in vacuo}. Sodium dried xylene (100 mL) was added, stirred 10 minutes, then hexaethylene glycol (370 mg, 1.3 mmol) was added carefully. The suspension was stirred for one hour, then 2 (250 mg, 1.3 mmol) was added with additional xylene (100 mL). The mixture was refluxed for 24 hours under a nitrogen atmosphere. After cooling, the excess sodium hydride was carefully hydrolyzed with water (75 mL). The water layer was extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated \textit{in vacuo} to afford a yellow paste, which was chromatographed (ThLC) eluting with cyclohexane-ethyl acetate (1:1) to give two major fractions.

Extraction A was recrystallized from absolute ethanol to give 7\textsubscript{A} as white needle-like crystals: mp 125-125.5°C; 320 mg (60%); NMR \textit{δ} 2.98 (t, \(\text{CH}_2\), J=4Hz, 4H), 3.15 (t, \(\text{CH}_2\), J=4Hz, 4H), 3.46 (m, \(\text{CH}_2\), 4H), 3.65 (m, \(\text{CH}_2\), 4H), 3.91 (m, \(\text{CH}_2\), 4H), 4.78 (m, \(\text{CH}_2\), 4H), 7.09 (d, 3,7-Naph-H, J=9Hz, 2H), 7.98 (d, 4,8-Naph-H, J=9Hz, 2H); IR (KBr) 1620, 1340, 1260, 1170 cm\textsuperscript{-1}; UV (EtOH) \(\lambda_{\text{max}}\) (ε) 344 nm (2.0 x 10\textsuperscript{4}), 336 (1.7 x 10\textsuperscript{4}), 329 (2.0 x 10\textsuperscript{4}), 316 (1.3 x 10\textsuperscript{4}), 241 (1.8 x 10\textsuperscript{4}); MS m/e (assign., rel.
Intensity: 408 (M+, 53), 300 (C₁₅H₂₀N₂O₄, 30), 256 (C₁₄H₁₆N₂O₃, 32)
208 (C₁₀H₁₂N₂O₃, 90) 194 (C₁₀H₁₂N₂O₂, 80), 160 (C₈H₄N₂O₂, 100).

Anal. Calcd. for C₂₉H₂₈N₂O₇: C, 58.58; H, 6.86; N, 6.86.
Found: C, 58.72; H, 6.88; N, 6.68.

Fraction B was recrystallized from absolute ethanol to afford 8a, as white microcrystals: mp 87-88.5°C; 21 mg (2%); NMR δ 3.68 (m, ζ-γ-CH₂, 32H), 3.96 (m, η-CH₂, 8H), 4.59 (m, α-CH₂, 8H), 7.03 (d, 3,7-Naph-Η, J=9Hz, 4H), 7.94 (d, 4,8-Naph-Η, J=9Hz, 4H); MS m/e 816 (M+, 14), 704 (11), 680 (20), 560 (37), 404 (M²/2, 64), 300 (C₁₆H₂₀N₂O₄, 18), 194 (C₁₀H₁₂N₂O₂, 23), 160 (C₈H₄N₂O₂, 100).

Anal. Calcd. for C₄₀H₅₆N₄O₁₄: C, 58.58; H, 6.86; N, 6.86.
Found: C, 58.75; H, 6.88; N, 6.70.

Reaction of 4-Nitro-α-naphthylidine with Pentaethylene Glycol. - The above general procedure was used except for the substitution of pentaethylene glycol (600 mg, 2.5 mmol) and the following two major macrocyclic fractions were isolated.

Fraction B was recrystallized from absolute ethanol to afford 7b, as colorless needle-like crystals: mp 94-95°C; 100 mg (19%); Rf 0.5; NMR δ 2.65 (s, e-CH₂, 4H), 3.44 (m, γ-η-CH₂, 8H), 3.83 (m, ζ-γ-CH₂, 4H), 4.95 (m, α-CH₂, 4H), 7.11 (d, 3,7-Naph-Η, J=9Hz, 2H), 8.03 (d, 4,8-Naph-Η, J=9Hz, 2H); IR (KBr) 1610, 1520, 1250, 1140 cm⁻¹; UV (EtOH) λ_max (ε) 345 nm (2.3 x 10⁴), 337 (2.0 x 10⁴), 330 (2.4 x 10⁴), 317 (1.4 x 10⁴), 242 (2.2 x 10⁴); MS m/e 364 (M⁺, 6.2), 216 (5.2), 180 (C₁₀H₅N₂O₃, 57), 160 (C₈H₄N₂O₂, 20), 128 (C₃H₄N₂, 4), 44 (C₂H₄O, 100).
Anal. Calcd. for C_{18}H_{24}N_{2}O_{6}:  C, 59.37; H, 6.59; N, 7.69.
Found:  C, 59.10; H, 6.88; N, 7.52.

Fraction B was recrystallized from absolute ethanol to give 8b, as white microcrystals: mp 101-103°C; 250 mg (26%); R_f 0.13; NMR δ 3.5-4.1 (m, 8-CH2, 32H), 4.6 (t, α-CH2, J=8Hz, 8H), 7.0 (d, 3,7-Naph-H, J=9Hz, 4H), 7.9 (d, 4,8-Naph-H, J=9Hz, 2H); IR (KBr) 1630, 1510, 1280, 1130 cm⁻¹; UV (EtOH) λ_max (ε) 340 (6.5 x 10^4), 332 (5.2 x 10^4), 325 (6.7 x 10^4), 319 (4.7 x 10^4), 312 (3.9 x 10^4), 300 (2 x 10^4); MS m/e 728 (M⁺, 32), 568 (24), 408 (27), 364 (M⁺/2, 100), 336 (36), 320 (86), 276 (73), 248 (96), 232 (95), 160 (14).

Anal. Calcd. for C_{38}H_{46}N_{4}O_{12}:  C, 59.39; H, 6.59; N, 7.69.
Found:  C, 59.67; H, 6.64; N, 7.39.

Reaction of 1,6-Dichloro-1,5-naphthyridine with Tetraethylene Glycol. - The general procedure was followed except for the substitution of tetraethylene glycol (490 mg, 2.5 mmol). After work-up, the xylene layer gave one major macrocycle fraction which was recrystallized from absolute ethanol to afford 8c, as white microcrystals: mp 153-153.5°C; 390 mg (49%); R_f 0.18; NMR δ 3.73 (δ, γ,δ-CH2, 16H), 3.92 (m, β-CH2, 8H), 4.54 (m, α-CH2, 8H); 6.97 (d, 3,7-Naph-H, J=9Hz, 4H), 7.80 (d, 4,8-Naph-H, J=9Hz, 4H); IR (KBr) 1620, 1550, 1340, 1280, 1150 cm⁻¹; UV (EtOH) λ_max (ε) 340 (4 x 10^4), 325 (4 x 10^4), 317 (2.9 x 10^4), 311 (2.9 x 10^4), 266 (3.5 x 10^4); MS m/e 640 (M⁺, 86), 596 (19), 320 (M⁺/2, 43), 232 (C_{12}H_{12}N_{2}O_{3}, 15), 204 (C_{10}H_{8}N_{2}O_{3}, 100), 160 (C_{6}H_{4}N_{2}O_{2}, 93), 128 (C_{8}H_{4}N_{2}, 24).

Anal. Calcd. for C_{32}H_{40}N_{4}O_{10}:  C, 60.00; H, 6.24; N, 8.75.
Found:  C, 59.88; H, 6.47; N, 8.61.
Reaction of 2,6-Dichloro-1,5-naphthyridine with Triethylene Glycol: - The general procedure was followed except for the substitution of triethylene glycol (200 mg, 1.5 mmol). After work-up, the organic layer gave one major macrocyclic fraction, which was recrystallized from absolute ethanol to afford 8g, as a white microcrystal: mp 215-216°C; 140 mg (20%); Rf 0.16; NMR δ 3.74 (s, γ-CH₂, 8H), 3.88 (m, ω-CH₂, 8H), 4.58 (m, α-CH₂, 8H), 7.01 (d, 3,7-Naph-H, J=9Hz, 4H), 7.91 (d, 4,8-Naph-H, J=9Hz, 4H); IR (KBr) 1630, 1560, 1290, 1150 cm⁻¹; MS m/e 276 (M⁺/2, 43), 232 (3), 204 (C₁₀H₈N₂O₂, 78), 160 (C₆H₄N₂O₂, 100), 128 (C₆H₄N₂, 30).

Anal. Calcd. for C₂₁H₁₂N₂O₆: C, 60.50; H, 5.80; N, 10.20.
Found: C, 60.20; H, 5.64; N, 9.99.

Reaction of 2,6-Dichloro-1,5-naphthyridine with Diethylene Glycol: - The general procedure followed except for the substitution of diethylene glycol (140 mg, 1.3 mmol). After work-up, the organic layer gave one major cyclic fraction, which was recrystallized from absolute ethanol, to give 8g, as microcrystals: mp 133-134°C; 20 mg (7%); Rf 0.14; NMR δ 3.88 (m, ω-CH₂, 8H), 4.60 (m, α-CH₂, 8H), 7.01 (d, 3,7-Naph-H, J=9Hz, 4H), 7.91 (d, 4,8-Naph-H, J=9Hz, 4H); IR (CHCl₃) 1610, 1430, 1230, 1150 cm⁻¹; MS m/e 232 (M⁺/2, 64), 188 (C₁₈H₁₆N₂O₂, 86), 160 (C₆H₄N₂O₂, 100), 128 (C₆H₄N₂, 36).

Found: C, 61.98; H, 5.27; N, 11.93.
Malic acid (3.0 g, 22 mmol) and 2,6-diaminopyridine (2.2 g, 20 mmol) were ground to an intimate powder, cooled in an ice bath, then concentrated sulfuric acid (10 mL) was added dropwise. The solution was heated to 110°C for 2-3 hours, poured over ice, and made alkaline with concentrated ammonium hydroxide (pH 8). 2-Amino-7-hydroxy-1,8-naphthyridine was isolated: mp > 350°C (lit.15 mp > 360°C; 3.52 g (97%); NMR (DMSO-d$_6$) $\delta$ 6.12 (d, 3-Naph-H, $J$=9Hz, 1H), 6.35 (d, 6-Naph-H, $J$=9Hz, 1H), 6.94 (s, NH$_2$, 2H), 7.65 (d, 4,5-Naph-H, $J$=9Hz, 2H).

2-Amino-7-hydroxy-1,8-naphthyridine (4.7 g, 29 mmol) was ground to a fine powder and added to concentrated sulfuric acid (40 mL), then sodium nitrite (2.4 g) was added. The mixture was allowed to stand for five minutes, poured over crushed ice and allowed to stand for ten minutes. Excess sodium nitrite was neutralized with sodium carbonate, then the solution was acidified with glacial acetic acid (pH 3) giving $\xi$, as a pale green powder: mp 321-323°C (lit.$^{16}$ mp 320-330°C); 4.1 g (87%); NMR (DMSO-d$_6$) $\delta$ 3.15 (m, OH, 2H), 6.25 (d, 3,6-Naph-H, $J$=9Hz, 2H), 7.75 (d, 4,5-Naph-H, $J$=9Hz, 2H).

A mixture of 2,7-dihydroxy-1,8-naphthyridine (500 mg, 3.1 mmol), phosphorus pentachloride (1.25 g, 6 mmol) and phosphorus oxychloride (1.12 g, 7 mmol) was refluxed for two hours, then ice was carefully added and the solution was made alkaline with sodium carbonate. A brown precipitate
was collected and recrystallized from acetone to give \( \bar{g}_2 \), as a white powder; subl. pt. 258°C (lit.\(^6\) subl. pt. 259°C); 500 mg (81%); NMR \( \delta \) 7.5 (d, 3,5-Naph-H, J=9Hz, 2H), 8.1 (d, 4,5-Naph-H, J=9Hz, 2H).

**Reaction of \( \bar{g}_2 \)-Dichlorocyclohexylmethyldiimine (\( \bar{g}_2 \)) with Hexaethyleneglycol.** The General \( \bar{g}_2 \)-Macro cyclic Procedure. - Sodium dried xylene (600 mL) was added to the oil-free sodium hydride, stirred for 10 minutes, then hexaethyleneglycol (1.5 g, 5.2 mmol) was added. After 30 minutes, \( \bar{g}_2 \) (1.0 g, 5.2 mmol) was added in additional xylene (150 mL). The resultant mixture was refluxed for twenty-four hours, cooled to 25°C, and the excess sodium hydride was hydrolyzed with water (150 mL). The aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined halocarbon extract was dried over anhydrous magnesium sulfate and concentrated in vacuo to afford a yellow oil, which was chromatographed (ThLC) eluting twice with an ethyl acetate-cyclohexane (4:1) mixture to afford \( 11a \), as white microcrystals: mp 98-100°C [benzene-cyclohexane (1:1)]; 35 mg (4%); \( R_f \) 0.19; NMR \( \delta \) 3.6-4.0 (m, 8-\( \bar{g}_2 \)-CH2, 18H), 4.5 (t, \( \bar{g}_2 \)-CH2, J=5Hz, 4H), 6.55 (d, 3-Naph-H, J=10Hz, 2H), 6.6 (d, 6-Naph-H, J=8Hz, 2H), 7.6 (d, 4-Naph-H, J=10Hz, 2H), 7.7 (d, 5-Naph-H, J=8Hz, 2H); IR (KBr) 3500, 1540, 1350, 1120 cm\(^{-1}\).

**Anal. Calcld. for C\(_{28}\)H\(_{32}\)N\(_2\)O\(_7\)Cl\(_2\):** C, 55.35; H, 5.27; N, 9.23. Found: C, 55.04; H, 5.35; N, 9.50.

After work-up, the water layer gave a brown oil, which was chromatographed (ThLC) eluting twice with ethyl acetate-cyclohexane (4:1) to give \( 9a \), as colorless crystals: mp 73.5-75°C; 306 mg (30%).
Rf 0.35; NMR δ 3.49 (s, δ-γ-CH₂, 8H), 3.79 (m, γ-δ-CH₂, 8H), 3.95 (t, δ-CH₂, J=5Hz, 4H), 4.84 (t, γ-CH₂, J=5Hz, 4H), 6.84 (d, 3,6-Naph-H, J=9Hz, 2H), 7.91 (d, 4,5-Naph-H, J=9Hz, 2H); IR (CHCl₃) 1640, 1530, 1250, 1050 cm⁻¹; UV (EtOH) λ_max (ε) 326 nm (2.5 x 10⁴), 318 (1.8 x 10⁴), 313 (1.8 x 10⁴), 299 (1.3 x 10⁴), 251 (5 x 10⁴); MS m/e 404 (M⁺, 39), 364 (31), 320 (26), 276 (21), 232 (35), 204 (C₁₀H₆N₂O₃, 96), 160 (C₉H₆N₂O₂, 100).

Anal. Calcd. for C₂₀H₂₈N₂O₇: C, 58.62; H, 6.86; N, 6.86.
Found: C, 58.73; H, 6.99; N, 6.73.

Reaction of 2,4,7-Triethyl-2,4,7-Naphthyridine with Pentaethylene Glycol. - The general 1,8-procedure was followed except for the substitution of pentaethylene glycol (1.2 g, 5.2 mmol). After work-up, the xylene layer gave a yellow oil, which was chromatographed (ThLC) eluting once with ethylacetate-cyclohexane (5:1) to give 9b, as white microcrystals: mp 77-78°C [diethyl ether-hexane (3:1)]; 360 mg (38%); Rf 0.45; NMR δ 3.39 (s, δ-CH₂, 4H), 3.52 (m, γ-CH₂, 4H), 3.79 (m, γ-δ-CH₂, 4H), 3.94 (t, δ-CH₂, J=5Hz, 4H), 4.87 (t, γ-CH₂, J=5Hz, 4H), 6.86 (d, 3,6-Naph-H, J=9Hz, 2H), 7.89 (d, 4,5-Naph-H, J=9Hz, 2H); IR (CHCl₃) 1630, 1520, 1350, 1250, 1050 cm⁻¹; UV (EtOH) λ_max (ε) 325 (1.5 x 10⁴), 319 (1.1 x 10⁴), 311 (7.3 x 10³), 294 (7.3 x 10³), 254 (7.3 x 10³); MS m/e 364 (M⁺, 28), 320 (38), 276 (17), 232 (33), 188 (96), 160 (C₉H₆N₂O₂, 100).

Found:  C, 59.62; H, 6.81; N, 7.64.
The water layer gave a yellow oil, which was chromatographed (ThLC) eluting twice with ethyl acetate to give 11b, as white needles: mp 101-103°C [benzene-cyclohexane (1:1)]; 22 mg (1%); Rf 0.16; NMR δ 3.5-4.0 (m, 8-CH₂, 16H), 4.6 (t, α-CH₂, J=4Hz, 4H), 6.57 (d, 3-Naph-H, J=9.5Hz, 2H), 6.62 (d, 6-Naph-H, J=8Hz, 2H), 7.60 (d, 4-Naph-H, J=9.5Hz, 2H), 7.69 (d, 5-Naph-H, J=8Hz, 2H); IR (KBr) 1640, 1340, 1230, 1110 cm⁻¹; UV (EtOH) λmax (ε) 341 nm (1.1 x 10⁴), 328 (1.5 x 10⁴), 315 (9.8 x 10³), 307 (6.2 x 10³), 299 (4.1 x 10³).


Reaction of 2,7-Dihalo-1,8-naphthyridine with Tetraethylene Glycol. - The general 1,8-procedure was followed except for the substitution of tetraethylene glycol (1.0 g, 5.1 mmol). The xylene layer afforded an oil, which was chromatographed (ThLC) eluting twice with ethyl acetate to give 10c: mp 65-67°C [diethyl ether-hexane (3:1)]; 37 mg (2%); Rf 0.51; NMR (DMSO-δ₆) δ 3.46 (t, δ-CH₂, J=5Hz, 4H), 3.84 (t, γ-CH₂, J=5Hz, 4H), 4.03 (t, δ-CH₂, J=5Hz, 4H), 4.98 (t, α-CH₂, J=5Hz, 4H), 7.10 (d, 3,6-Naph-H, J=9Hz, 2H), 7.89 (d, 4,5-Naph-H, J=9Hz, 2H); IR (CHCl₃) 1620, 1490, 1240, 1060 cm⁻¹; UV (EtOH) λmax (ε) 325 nm (1.3 x 10⁴), 319 (1.1 x 10⁴), 312 (1.0 x 10⁴), 297 (6.6 x 10⁴), 250 (6.6 x 10³); MS m/e 320 (M⁺, 49), 276 (32), 232 (40), 204 (C₁₀H₇N₂O₂, 95), 160 (C₈H₄N₂O₂, 100).

The water layer gave a yellow oil which was chromatographed (ThLC) eluting twice with ethyl acetate to give 11c: mp 34-35°C [benzene-
cyclohexane (1:1); 40 mg (2%); Rf 0.19; NMR δ 3.6-4.1 (m, 8-CH2, 12H), 4.5 (t, α-CH2, J=4Hz, 4H), 6.55 (d, 3-Naph-H, J=9.5Hz, 2H), 6.63 (d, 6-Naph-H, J=8Hz, 2H), 7.62 (d, 4-Naph-H, J=9.5Hz, 2H), 7.74 (d, 5-Naph-H, J=8Hz, 2H); IR (KBr) 1640, 1350, 1220, 1110 cm⁻¹; UV (EtOH) λmax (ε) 345 (1.7 x 10³), 330 (2.3 x 10³), 315 (1.5 x 10³), 307 (8 x 10³), 300 (4 x 10³).

Anal. Calcd. for C26H21N5O5Cl2: C, 57.46; H, 4.42; N, 10.31.
Found: C, 57.18; H, 4.41; N, 10.39.

Reaction of 2,4,7-Trichloro-1,8-naphthyridine with Triethylene Glycol. Method A. - The general 1,8-procedure was followed except for the substitution of triethylene glycol (1.0 g, 6.2 mmol). The xylene layer gave no macrocyclic products. The aqueous layer gave a yellow oil which was chromatographed (ThLC) eluting twice with ethyl acetate to give mp 93-94°C [benzene-cyclohexane (1:1)]; 71 mg (3%); Rf 0.17; NMR δ 3.6-4.0 (m, 8-γ-CH2, 8H), 4.6 (t, α-CH2, J=4Hz, 4H), 6.55 (d, 3-Naph-H, J=10Hz, 2H), 6.59 (d, 6-Naph-H, J=8Hz, 2H), 7.65 (d, 4-Naph-H, J=10Hz, 2H), 7.70 (d, 5-Naph-H, J=8Hz, 2H), IR (KBr) 1630, 1450, 1220, 1120, 1040 cm⁻¹; UV (EtOH) λmax (ε) 342 nm (1.5 x 10³), 329 (1.9 x 10³), 316 (1 x 10³), 306 (6 x 10³), 299 (2.6 x 10³); MS m/e 479 (M+ + 4, 5), 477 (M+ + 2, 30), 475 (M+, 46), 312 (C13H16N2OCl, 57), 268 (C13H15N2O2Cl, 30), 224 (C15H8N2O2Cl, 36), 180 (C6H4N2OCl, 100).

Anal. Calcd. for C26H21N5O5Cl2: C, 55.60; H, 4.23; N, 11.80.
Found: C, 55.49; H, 4.55; N, 11.70.

Method B. - To a stirred suspension of NaH (960 mg, 20 mmol) in dry DMF (10 mL), triethylene glycol (1.5 g, 10 mmol) in DMF (25 mL)
was slowly added. The mixture was stirred at room temperature for 1 hour and $\text{g} (2 \text{ g}, 10 \text{ mmol})$ in DMF (100 mL) was slowly added. The reaction was heated at $80^\circ\text{C}$ for 72 hours, was cooled and water (50 mL) was cautiously added. The solvent was removed in vacuo and the resulting solid was washed with methylene chloride (3 x 100 mL) and filtered. The filtrate was dried over magnesium sulfate, filtered, and concentrated in vacuo to give an oil, which was chromatographed (ThLC) on alumina eluting once with chloroform to give $\text{Iod}$, as a white solid: 

mp 219-220°C (ethanol); 67 mg (2%); $R_f$ 0.36; NMR 3.74 (s, $\gamma$-CH$_2$, 8H), 3.89 (m, $\alpha$-CH$_2$, 8H), 4.70 (d, 3,6-Naph-H, $J$=9Hz, 4H), 7.76 (d, 4,5-Naph-H, $J$=9Hz, 4H); IR (neat), 1,600, 1,495, 1,430, 1,320, 1,250, 1,105, 1,050, 940, 845, 800 cm$^{-1}$; MS m/e 552 (M$^+$, 1.4), 275 (30), 231 (18.9), 189 (C$_8$H$_6$N$_2$O$_2$, 100), 162 (97.6), 145 (36.9).

Anal. Calcd. for C$_8$H$_{32}$N$_4$O$_6$: C, 58.94; H, 5.61; N, 9.82.

Found: C, 59.12; H, 5.81; N, 9.89.

Reaction of 2,7-Dichloro-1,8-naphthryidine with Diethylene Glycol. Method A. - The general 1,8-procedure was followed except for the substitution of diethylene glycol (270 mg, 2.5 mmol). The water layer gave an oil, which was chromatographed (ThLC) eluting three times with ethyl acetate to afford $\text{Ile}$, as white microcrystals: 

mp 87-88°C; 54 mg (5%); $R_f$ 0.16; NMR 3.8-4.1 (m, $\gamma$-CH$_2$, 4H), 4.5 (m, $\alpha$-CH$_2$, 4H), 6.55 (d, 3-Naph-H, $J$=10Hz, 2H), 6.60 (d, 6-Naph-H, $J$=8Hz, 2H), 7.63 (d, 4-Naph-H, $J$=10Hz, 2H), 7.71 (d, 5-Naph-H, $J$=8Hz, 2H); IR (KBr) 1,630, 1,325, 1,220, 1,130 cm$^{-1}$; UV (EtOH) $\lambda_{max}$ (e) 344 (1.4 x 10$^4$), 328 (2 x 10$^4$), 314 (1.2 x 10$^4$), 305 (6.5 x 10$^3$), 298 (3 x 10$^3$); MS m/e 435 (M$^+$ +4, 65), 433 (M$^+$ +2, 40), 431 (M$^+$, 62), 268 (29), 224 (180 (C$_8$H$_4$N$_2$OCl, 85), 164 (C$_8$H$_4$N$_2$Cl, 100).
Anal. Calcd. for C\textsubscript{2}H\textsubscript{12}N\textsubscript{4}O\textsubscript{2}Cl\textsubscript{2}: C, 55.68; H, 3.71; N, 12.99.
Found: C, 55.45; H, 3.91; N, 12.69.

Method B. - The general 1,8-procedure as above was followed except for the substitution of diethylene glycol (1.06 g, 10 mmol). The resulting oil was chromatographed (ThLC-alumina) eluting twice with chloroform to give two macrocycles. Fraction A afforded \(10e\) as colorless needles: mp 254-255°C [chloroform-isopropanol]; 78 mg (28): \(R_f\) 0.46 (chloroform-alumina). NMR \(\delta\) 4.04 (m, \(\beta-\text{CH}_2\), 8H), 4.82 (m, \(\alpha-\text{CH}_2\), 8H), 6.59 (d, 3,6-Naph-H, J=8.5Hz, 4H), 7.67 (d, 4,5-Naph-H, J=8.5Hz, 4H); IR (neat) 1630, 1510, 1330, 1270, 1130, 800 cm\(^{-1}\); MS m/e 464 (M\(^{+}\), 4.5), 259 (22), 231 (51), 189 (C\textsubscript{6}H\textsubscript{4}N\textsubscript{2}O\textsubscript{2}, 100), 162 (50), 145 (36.5).

Anal. Calcd. for C\textsubscript{26}H\textsubscript{24}N\textsubscript{4}O\textsubscript{6}H\textsubscript{2}O: C, 59.75; H, 4.97; N, 11.62.
Found: C, 59.85; H, 4.99; N, 11.56.

Fraction B afford \(12\), as colorless microcrystals: mp 230-230.5°C; 36 mg (1%): \(R_f\) 0.37 (chloroform-alumina). NMR \(\delta\) 3.97 (m, \(\beta-\text{CH}_2\), 12H), 4.69 (m, \(\alpha-\text{CH}_2\), 12H), 6.78 (d, 3,6-Naph-H, J=9Hz, 6H), 7.79 (d, 2,5-Naph-H, J=9Hz, 6H); IR (neat) 1610, 1510, 1340, 1270, 1135, 1025, 850, 805 cm\(^{-1}\).

Anal. Calcd. for C\textsubscript{36}H\textsubscript{36}N\textsubscript{6}O\textsubscript{9}: C, 62.07; H, 5.17; N, 12.07.
Found: C, 61.77; H, 5.40; N, 11.99.

X-Ray Experimental. - Prismatic, colorless crystals of \(9b\) were grown from a mixture of diethyl ether-petroleum ether (bp 30-45°C). A crystal of dimensions 0.33 x 0.45 x 0.52 mm was used for data collection on an Enraf-Nonius CAD 4 diffractometer equipped with a graphite-monochromatized Mo x-ray tube (\(\lambda = 0.71069\) Å for MoK\(_{\alpha}\)).
**Crystal Data**: \( \text{C}_{16}\text{H}_{24}\text{N}_{2}\text{O}_{6} \) (9b), \( \text{MW} = 364.4 \), triclinic space group \( \text{P}\bar{1} \), \( a = 8.969(3) \), \( b = 10.325(3) \), \( c = 20.107(5) \) Å, \( \alpha = 86.02(2) \), \( \beta = 90.01(2) \), \( \gamma = 79.15(2) \)°, \( Z = 4 \), \( \rho_{\text{c}} = 1.327 \) g cm\(^{-3} \), \( \mu \) (MoK\(_\alpha\)) = 0.93 cm\(^{-1} \). Intensity data were collected by the \( \omega\)-2θ scan technique. Scan speeds varied from 0.60 deg. min\(^{-1} \) to 20.0 deg. min\(^{-1} \) in order to measure all reflections with approximately equal precision. A maximum of 120 sec. was spent on the measurement of any reflection, and reflections judged to be insignificantly intense in a rapid pre-scan were flagged as "unobserved" and were not scanned slowly. No significant decrease in the intensities of periodically measured reflections was noted. All reflections within one hemisphere having \( 1° \leq 2θ \leq 20° \) were measured, yielding 3732 data. Averaging equivalent reflections led to 2374 "observed" data, which were used in further calculations. Background, Lorentz, and polarization corrections were applied to these data, but absorption corrections were deemed insignificant.

**Structure Solution and Refinement**: The structure of 9b was solved routinely by use of MULTAN78\(^{26} \), and completed by Fourier methods using program SHELX\(^{27} \). The model was refined by least-square techniques, treating C, N, and O atoms anisotropically, and fixing H atoms in calculated positions. Aromatic hydrogen atoms were refined with a common isotopic temperature factor, and methylene hydrogen atoms were treated similarly. Convergence was achieved with \( R = 0.055 \). Coordinates of nonhydrogen atoms are listed in Table 1, anisotropic thermal parameters and hydrogen atoms parameters are given in the supplementary material.
Supplementary Materials Available: Anisotropic thermal parameters and hydrogen atom parameters for the x-ray structure of 9b (2 pages). Ordering information is given on any current masthead page.

Acknowledgments are made to the National Institutes of Health and the A. P. Sloan Foundation to the S.R.E.B. (travel grant) for partial support of this research and to Professor J. L. Atwood (University of Alabama) for his assistance in obtaining the x-ray data.
References:

1. (a) For the previous paper in this series, see: Newkome, G. R.; Onishi, M.; Puckett, W. E.; Deutsch, W. A. J. Am. Chem. Soc. 1980, 102, 4551. (b) Part of work was from the M. S. thesis of S. J. G. (c) On leave from the Institute Di Mineralogia, via San Massimo 24, 10123 Torino (Italy).


25. Samples of penta- and hexaethylene glycols should be analyzed (HPLC) prior to use due to the variability in purity. Professor K. Potts (Rensselaer Polytechnic Institute) personal communication, 1980.
Figure 1. The 200 MHz $^1$H NMR spectrum of 7a in CD$_2$Cl$_2$ at 40°C.
Figure 2. The 200 MHz $^1$H NMR spectrum of 9b in CD$_2$Cl$_2$ at 40°C with 0-3% added Eu(FOD)$_3$. 
Figure 3. Prospective drawing of macrocycle 2. Nonhydrogen atoms are represented by thermal ellipsoids drawn at the 30% probability level, and hydrogen atoms are drawn as spheres of arbitrary radius.
Figure 4. Average interatomic distances and numbering scheme.

Standard deviations in individual distances are about 0.008 Å within the naphthyridyl subunit and from 0.008-0.012 Å within the polyetheral bridge. Where distances differ by more than 2σ between the two independent molecules, both are given.
Figure 5. Average bond angles. Standard deviations are about 0.4-0.6°. Both angles are given if they differ by more than 2σ.
TABLE 1. Coordinates ($\times 10^4$) for the nonhydrogen atoms in 9b.

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Table Al. Coordinates ($x \times 10^3$) assigned to the hydrogen atoms in

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Vita

Veronica Katherine Majestic was born May 13, 1952 at Fort Polk, Louisiana. She attended elementary school in DeRidder, Louisiana and graduated from LaGrange Senior High School in Lake Charles, Louisiana in 1970. That same year she entered McNeese State University and was awarded a B.S. in Chemistry in 1974. She began graduate work at Lousiana State University in 1975, where she was employed as a Teaching Assistant. In 1980 she was appointed a Research Assistantship under a National Institutes of Health grant. Currently, she is a candidate for the Doctor of Philosophy degree with a major in Organic Chemistry and a minor in Inorganic Chemistry. She has accepted a position as Research Chemist with Nalco Chemical Company in Sugar Land, Texas to begin May 8, 1982.
EXAMINATION AND THESIS REPORT

Candidate: Veronica Katherine Majestic

Major Field: Organic Chemistry

Title of Thesis: The Syntheses And Characterization Of Aza Coronands And Cryptands Containing The 2,6-Pyridino And/Or The 1,8-Naphthyridino Subunits

Approved:

[Signature]

Major Professor and Chairman

[Signature]

Dean of the Graduate School

EXAMINING COMMITTEE:

[Signature]

N. B. Thompson

D. K. Carpenter

[Signature]

R. A. Feddersen

Date of Examination: April 27, 1982