AZA-CROWN MACROCYCLES

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AZA-CROWN MACROCYCLES

This is the Fifty-First Volume in the Series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

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A SERIES OF MONOGRAPHS

EDWARD C. TAYLOR, *Editor*

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The Chemistry of Heterocyclic Compounds
Introduction to the Series

The chemistry of heterocyclic compounds constitutes one of the broadest and most complex branches of chemistry. The diversity of synthetic methods utilized in this field, coupled with the immense physiological and industrial significance of heterocycles, combine to make the general heterocyclic arena of central importance to organic chemistry.

The Chemistry of Heterocyclic Compounds, published since 1950 under the initial editorship of Arnold Weissberger, and later, until Dr. Weissberger's death in 1984, under our joint editorship, has attempted to make the extraordinarily complex and diverse field of heterocyclic chemistry as organized and readily accessible as possible. Each volume has dealt with syntheses, reactions, properties, structure, physical chemistry, and utility of compounds belonging to a specific ring system or class (e.g., pyridines, thiophenes, pyrimidines, three-membered ring systems). This series has become the basic reference collection for information on heterocyclic compounds.

Many broader aspects of heterocyclic chemistry are recognized as disciplines of general significance which impinge on almost all aspects of modern organic and medicinal chemistry, and for this reason we initiated several years ago a parallel series entitled *General Heterocyclic Chemistry*, which treated such topics as nuclear magnetic resonance, mass spectra, photochemistry of heterocyclic compounds, the utility of heterocyclic compounds in organic synthesis, and the synthesis of heterocyclic compounds by means of 1,3-dipolar cycloaddition reactions. These volumes are of interest to all organic and medicinal chemists, as well as to those whose particular concern is heterocyclic chemistry.

It has become increasingly clear that this arbitrary distinction created as many problems as it solved, and we have therefore elected to discontinue the more recently initiated series *General Heterocyclic Chemistry* and to publish all forthcoming volumes in the general area of heterocyclic chemistry in *The Chemistry of Heterocyclic Compounds* series.

EDWARD C. TAYLOR

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Preface

We have been interested in the synthesis and complexing properties of macrocyclic ligands since 1968. Our work concerns, in general, the crown ethers and thioethers and their diester analogs. Our interest in the aza-crowns started in 1987 and was prompted by a desire to have macrocycles that formed very strong interactions with all types of metal ions. The 1987 Nobel Prize was awarded jointly to Charles Pedersen, Jean Marie Lehn, and Donald J. Cram for their elegant pioneering work on the synthesis and properties of macrocyclic ligands. Their work, perhaps more than any other, made people realize that molecules that have the property to recognize other molecules could be synthesized. Our own work showed that metal and organic cations could be recognized by the appropriate crown ether or thioether.

Our *Chemical Reviews* article in 1989 on aza-crown compounds made us realize the wealth of great chemistry available in the aza-crown macrocycles field. This review prompted us to look more fully into this field and has resulted in writing this book. As with any endeavor where one looks at the predecessors and current practitioners in one's area of expertise, one finds some tremendous individuals who have made or are making great strides in the field. We know that a list of important people in the aza-crown field will most likely be incomplete, but that shouldn't keep one from mentioning some individual researchers whose names come quickly to mind. Some of these are as follows:

E. Blasius (polymer-containing macrocyclic ligands)
A. V. Bogatskii and I. G. Lukyanenko (prepared hundreds of aza-crown macrocycles)
D. H. Busch (template syntheses of the aza-crown macrocycles)
N. F. Curtis ("Curtis" reaction—first to report the aza-crown macrocycles)
G. W. Gokel (lariat aza-crown macrocycles)
E. Kimura (syntheses of numerous peraza-crown macrocycles)
J. M. Lehn (biological-like aza-crown macrocycles)
L. F. Lindoy (numerous benzoaza-crown macrocycles)
M. Okahara (ring closure of diols with tosyl chloride)
P. Paoletti (complexing properties of peraza-crown macrocycles)
J. E. Richman and T. J. Atkins (tosylamide ring-closure reactions)
H. Stetter (first prepared macrocyclic diamides)
I. Tabushi ("Tabushi" synthesis using diamines and diesters)
F. Vögtle (great variety of aza-crown macrocycles)

This book contains four introductory chapters covering uses of the aza-crown macrocycles, the synthesis of starting materials, and general ring-closure reactions. The remaining chapters cover the synthesis of aza-crown macrocycles containing one or more ring nitrogen atoms, benzene rings, and those macrocycles containing other heteroatoms such as sulfur. Two lengthy chapters on the peraza-crown macrocycles come next followed by a chapter on macromolecular systems containing the aza- and peraza-crown macrocycles. A final short chapter containing practical information on the synthesis of the aza-crown macrocycles is also included. A complete listing of all aza-crown macrocycles prepared through about July, 1991 is given in tables at the end of Chapters V–XII. We estimate that over 3800 individual aza-crown macrocycles are included. We apologize for the few macrocycles we may have overlooked. The tables are arranged first by ring size and then by the complexity of the various substituents attached to ring atoms.

We wish to thank the many people who helped us along the way. Daria Zamecka-Krakowiak helped in every phase of the work. She found material in the library, put together most tables, compiled and checked all the references, and, most importantly, made all the drawings on CHEM DRAW™. This work could not have been done without Daria's expert help. Two part-time secretaries, Laura Sullivan and Devin Greenhalgh, did the bulk of the typing. The Chemistry Department secretaries, particularly Debbie Smith and Peggy Erickson, also helped in so many ways.

We express our gratitude to Professor E. C. Taylor and the editorial people at John Wiley and Sons for their patience and help during this work.

JERALD S. BRADSHAW
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Provo, Utah
November, 1992

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CHAPTER I

Aza-crown Macrocycles: An Overview

A. INTRODUCTION

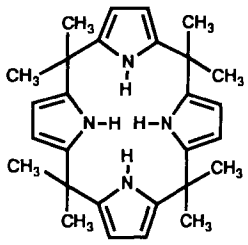
Macrocyclic ligands containing heteroatoms are important complexing agents for cations, anions, and neutral molecules. The aza-crown macrocycles, which are the subject of this book, play an important role in the macrocyclic ligand field. Macrocycles included in this book have ring sizes of at least nine members and have three or more heteroatoms with at least one nitrogen atom in the ring. We estimate that about half of all synthetic macrocycles belong to this class. The nitrogen atom has a much stronger association with transition-metal ions than does the oxygen atom. Nitrogen is less electronegative, so the electron pair is more available for complexing purposes.

The aza-crowns have metal ion complexing properties that are intermediate between those of the all-oxygen crowns, which strongly complex alkali and alkaline-earth metal ions, and those of the peraza-crowns (cyclic amines), which strongly complex heavy-metal cations. These complexing properties make the nitrogen-containing macrocycles interesting to researchers in many

areas (Izatt et al., 1985, 1991; Lindoy and Baldwin, 1989; Kimura, 1986). The macrocycles have important uses as synthetic receptors in molecular recognition processes (Sutherland, 1986) and, in some cases, anion complexing properties that are similar to those in certain biological systems (Hosseini et al., 1987; Lehn, 1985; Yohannes et al., 1985). They have an enhanced complexing ability for ammonium salts (Lehn and Vierling, 1980; Izatt et al., 1985, 1991) and for transition-metal ions over the all-oxygen crown compounds (Izatt et al., 1985; Lamb et al., 1979; Hancock, 1986).

The era of macrocycles containing amine functions started over 100 years ago when Baeyer (1886) prepared tetraazaquaterene (**1**). Hinsberg and Kessler (1905) prepared similar nitrogen-containing macrocycles. Cyclic amines (like **2**) were first reported by Alphen (1937), and the dibenzoaza-crowns (**3**) were first prepared by Krässig and Greber (1953, 1956). The important complexing properties of the peraza macrocycles were known before the milestone discovery of the all oxygen-containing crown ligands (**4**) by Pedersen (1967, 1988).

The metal-ion-templated synthesis of a peraza macrocycle was reported more than 30 years ago. The macrocycle resulted from the reaction of tris(1,2-diaminoethane)nickel(II) perchlorate with acetone to form a 14-membered macrocyclic ligand–Ni(II) complex (**5**) (Curtis, 1960; Curtis and House, 1961). Numerous examples of this and other metal-ion-templated reactions have been investigated in the intervening years (Black and Hartshorn, 1972–1973; Busch, 1964; Curtis, 1968). Slightly earlier, the methyl-substituted peroxa-12-crown-4 (**6**) was reported along with unambiguous evidence for its ability to solubilize the alkali metal ions in organic solvents (Down et al., 1959).



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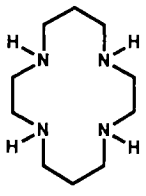

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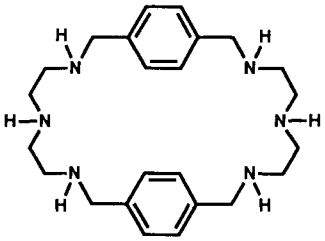

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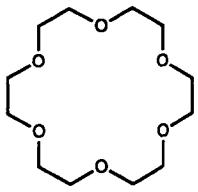

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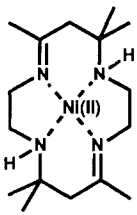

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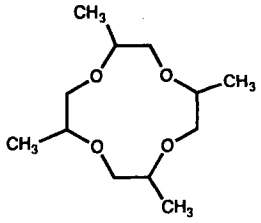

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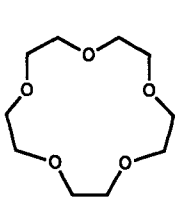
This chapter contains information on the nomenclature of the aza-crown macrocycles and a brief review of their complexing abilities and selectivities for various cations, anions, and neutral organic molecules. Some information on important medicinal uses for these compounds is also included. The last section gives a few general comments about the compounds that are covered in this book.

B. NOMENCLATURE OF THE AZA-CROWN MACROCYCLES

Two types of nomenclature for these macrocycles are used in this book. Mainly, we use the crown nomenclature proposed by Pedersen (1967) in his article on the crown ether compounds. In his nomenclature, the total number of ring members is given first followed by the word "crown." Then the number of heteroatoms is given. The 18-membered ring containing 6 oxygen atoms is 18-crown-6 (see **4** above) and the 15-membered ring is 15-crown-5 (**7**). The position of nitrogen heteroatoms that replace the oxygen atoms in the aza-crown macrocycles is numbered in Pedersen's crown nomenclature. Thus, 1,10-diaza-18-crown-6 (**8**) is the 18-crown-6 macrocycle where two oxygen atoms on opposite sides of the macroring have been replaced by NH groups. The sulfur-containing macrocycles are named in the same manner. Compound **9** is thia-15-crown-5.

The second method used to name the nitrogen-containing macrocycles was proposed by Busch and coworkers (Dabrowiak et al., 1972). The size of the macrocycle is given in a bracket followed by the number and types of heteroatoms. Structure **10** is [14]N_4. This macrocycle is often called *cyclam*. The 15-membered ring with four nitrogen atoms and one oxygen atom is [15]N_4O (see **11**). We have modified this nomenclature by leaving out the "ane" following the brackets. The original proposal used "ane" to denote a saturated macrocycle. This book is devoted to saturated macrocycles, so the "ane" part of the Busch et al. nomenclature is not needed. This nomenclature method does not indicate the position of the nitrogen atoms in the ring. For example, there can be two [15]N_2O_3 structures. The crown nomenclature discussed above does distinguish between the two structures as 1,4-diaza- or 1,7-diaza-15-crown-5 (**12** and **13**, respectively).



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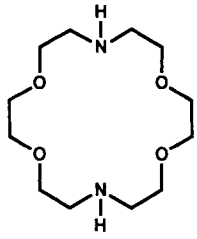

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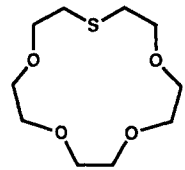

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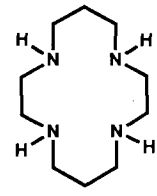

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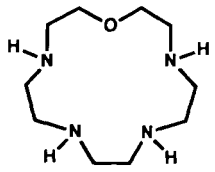

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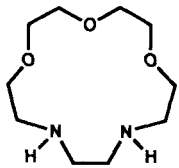

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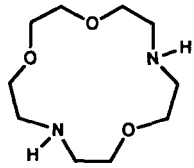

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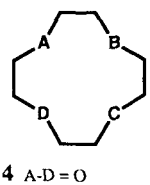
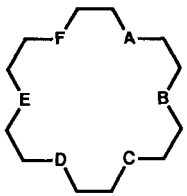
C. COMPLEXING ABILITIES OF THE AZA-CROWN MACROCYCLES

1. Introduction

The most important characteristic of the polyether and polyamine macrocycles is their ability to form complexes with cations, anions, and neutral organic molecules. There are many reviews on the complexing abilities of the crowns and aza-crowns (Bianchi et al., 1991; Hiraoka, 1982; Izatt and Christensen, 1978, 1987a, 1987b; Izatt et al., 1985, 1991; DeLong and Reinhoudt, 1981; Lindoy, 1989a; Melson, 1979; Patai, 1980). The aza-crown macrocycles generally form 1:1 complexes with metal ions with the ion located in the central cavity of the macrocycle. However, there are bi- and trinuclear complexes where two or three metal ions complex with one macrocycle, especially where the macrocycle is large and the cation small. Substitution of oxygen by nitrogen in ligands such as 18-crown-6 and dibenzo-18-crown-6 results in macrocycles that have less affinity for the alkali metal ions, such as K^+, than did the parent peroxa-crown. The log K values in these cases decrease in the order of decreasing electronegativity of the heteroatom O > N (containing an alkyl substituent) > N (containing a proton) (Frensdorff, 1971). However, replacing the oxygen donor atom by nitrogen resulted in increased affinities for the heavy-metal ions such as Ag^+ and Pb^{2+}. For example, the log K values in water for Pb^{2+} interactions with the 12- and 18-membered macrocycles are as follows: [12]O_4(**14**), 2.0; [12]NO_3(**15**), 4.1; [12]N_2O_2(**16**), 6.3; [12]N_3O(**17**), 10.5; [12]N_4(**18**), 15.9 and [18]O_6(**19**), 4.4; [18]N_2O_4(**20**), 6.9; [18]N_4O_2(**21**), 9.0; [18]N_6(**22**), 14.1 (Hancock and Martell, 1989). Increased interactions for



14 A-D = O
15 A = NH; B-D = O
16 A, C = NH; B,D = O
17 A-C = NH; D = O
18 A-D = NH

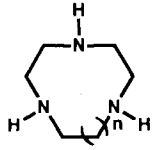


19 A-F = O
20 A, D = NH; B, C, E, F = O
21 A, D = O; B, C, E, F = NH
22 A-F = NH

Ca^{2+}, Sr^{2+}, and Ba^{2+} also have been observed for $[15]N_2O_3$(**13**) where the two ring nitrogen atoms contain substituents that have alkyl chains containing hydroxy functions (Wester and Vögtle, 1978). These examples of changing the macrocycle–metal ion interaction by changing the macrocycle cavity size, type of donor atoms, and substituents show some of the reasons for the great interest in these compounds. The design and synthesis of macrocycles having selectivity for a desired cation or group of cations are now possible. Some features of aza-crown macrocycle interactions with metal ions and the specific types of aza-crown macrocycles needed for specific applications are given as follows.

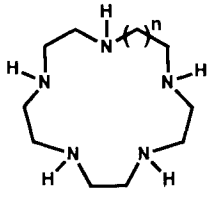
2. The Macrocyclic Effect

The peraza macrocycles, in general, form more stable complexes with a variety of metal ions than do the open-chain polyamines containing the same number of amine groups. This characteristic is called the *macrocyclic effect*. Triaza-crown macrocycles, in nearly every case, form 1:1 complexes with metal ions that are thermodynamically more stable than those with diethylenetriamine. Only complexes of the open-chain triamine with Cu^{2+} and Hg^{2+} are more stable than those with the cyclic triamines (Bianchi et al., 1991). Triaza-9-crown-3 (**23**) forms stronger complexes with most cations than the larger triazacyclodecane (**24**), triazacycloundecane (**25**), or triazacyclododecane (**26**) (Bhula et al., 1988; Chaudhuri and Wieghardt, 1987).



23 n = 1
24 n = 2
25 n = 3
26 n = 4

The tetraazacycloalkanes, particularly the 14-membered cyclic tetraamine (cyclam) (**10**), exhibit the macrocyclic effect due to a more favorable enthalpy contribution to complex stability (Hancock and Martell, 1988). Complexes of the pentaaza-crown macrocycles have been studied extensively from a thermodynamic point of view (Bianchi et al., 1991). With the exception of Ni^{2+}, $[15]N_5$ formed the most stable complexes with all the metal ions studied with the stability order as follows $[15]N_5$(**27**) > $[16]N_5$(**28**) > $[17]N_5$(**29**) (Bianchi et al., 1991).



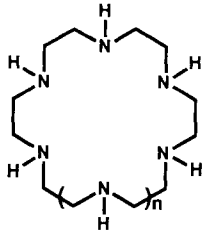
27 n = 1
28 n = 2
29 n = 3

The hexaazacycloalkanes have complexing properties that lie between those of the smaller peraza-crown macrocycles, which exhibit the macrocyclic effect and the large peraza macrocycles, which do not. Compound $[18]N_6$(**22**) forms complexes in water with the transition metals and also with K^+, Sr^{2+}, Ca^{2+}, and La^{3+} ions. It is interesting that $[18]N_6$(**22**) has a higher affinity for Ca^{2+} than does $[18]O_6$(**19**) (Bianchi et al., 1991).

3. Large Cavity Peraza-crown Macrocycles

The peraza-crown macrocycles that have large cavities do not exhibit the macrocyclic effect. These large macrocycles have several features in common: (1) they are polybases producing highly charged protonated species in solution in the neutral pH range that could serve as model reagents for the study of nucleotide complexation; (2) they are suitable for anion-coordination studies; and (3) because of the large number of donor atoms, they can form polynuclear metal ion complexes that could prove useful in the search for more effective catalysts.

The possibility for these polyaza-crown macrocycles to bind more than one metal ion in the macrocyclic framework has aroused the interest of several research groups. The work to date has been limited to the first-row transition elements, Zn^{2+} and Cd^{2+}. Since second- and third-row transition elements are important as catalysts and since several of these elements have large affinities for nitrogen, it is likely that future work may involve them. In general, large polyazacycloalkanes can form mono-, di-, and trinuclear (with copper) species, as well as polyprotonated complexes. The dinucleating and trinucleating abilities of these ligands increase as ring size increases. Mononuclear and dinuclear complexes are formed by Cu^{2+} with $[21]N_7$(**30**); Ni^{2+}, Zn^{2+}, and Cd^{2+} with $[24]N_8$(**31**); and by Co^{2+} with $[27]N_9$(**32**) (Bencini et al., 1987a, 1987b). All macrocycles with rings larger than these form only binu-



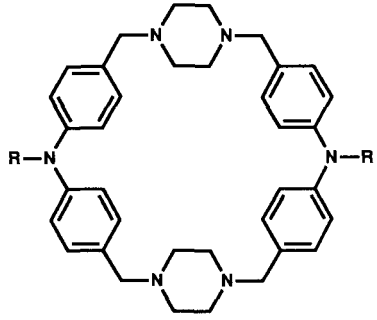
30 n = 2
31 n = 3
32 n = 4
33 n = 5
34 n = 6
35 n = 7

clear complexes with these specific metal ions. In addition, Cu^{2+} forms both binuclear and trinuclear species with $[33]N_{11}$(**34**) and $[36]N_{12}$(**35**) (Bencini et al., 1988). The general trend of stability of binuclear complexes is: $Co^{2+} < Zn^{2+} < Ni^{2+} < Cu^{2+}$ (Bencini et al., 1989a). Co_2L^{4+} type complexes with $[30]N_{10}$(**33**), **34**, and **35** predominate over a rather wide pH range, which is a favorable condition for study of O_2 uptake (Bencini et al., 1989a).

The stability of mononuclear complexes of Ni^{2+} with azacycloalkanes increases from [9]N_3(**23**) to [18]N_6(**22**), and then decreases for [21]N_7(**30**) and [24]N_8(**31**) (Bencini et al., 1989b). Crystallographic data show that Ni^{2+} is coordinated by six of the nitrogen atoms of **30**. The fact that only the monoprotonated form of Ni^{2+}-[21]N_7 is present in solution supports this idea (Bencini et al., 1989b).

4. Aza-cyclophanes

Azacyclophanes, macrocycles with cyclophane subunits incorporated into the ring, have sizable internal cavities and are able to interact with neutral molecules (Schneider et al., 1988, Murakami et al., 1989a), cations (Kihara et al., 1989; Schneider and Junker, 1986), and anions (Murakami et al., 1989b; Murakami and Kikuchi, 1988) through hydrophobic host–guest interactions that are scarcely affected by external factors such as pH, temperature, and ionic strength. A novel azacyclophane consisting of diphenylamine and piperazine skeletons (see **36**) was synthesized and was found to be an effective ligand for alkali metal and ammonium cations; thus, the log $K(CHCl_3)$ value for Li^+ interaction is 8.06. This ligand is effective in the selective extraction



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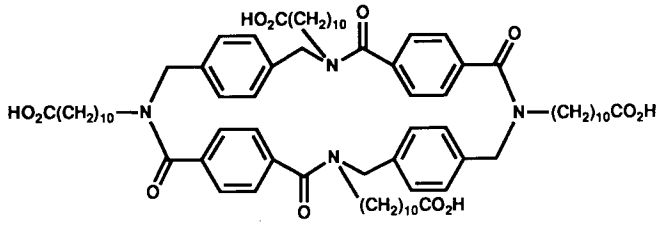
of Li^+ from H_2O to $CHCl_3$. Corey–Pauling–Koltun (CPK) molecular models showed that the cavity of this ligand is too large to include the bare Li^+, but $Li(H_2O)_6^+$ could fit into the cavity forming hydrogen bonds with the piperazine moieties and two molecules of the coordinated water (Kihara et al., 1989).

Macrocycles consisting of crown ether and cyclophane subunits and having properties of both crown ethers and cyclophanes have been synthesized (Saigo, 1990; Saigo et al., 1990; Ferguson et al., 1989). Attachment of long alkyl chains on the macrocycle skeleton provides a deeper cavity and allows the introduction of catalytically active groups not only into the cyclic skeleton but also into each alkyl chain (see **37**). These properties of azacyclophanes, as well as their high substrate specificity due to their intrinsic geometric



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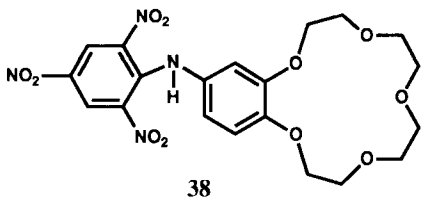
requirements for host–guest interactions, give them the potential to be superior enzyme models (Murakami, 1983).

5. Chromogenic Macrocycles

The idea of designing crown ether dyes that have chromogenic functional groups within the molecules and are able to serve as photometric reagents selective for alkali and alkaline-earth metal ions arose over a decade ago (Takagi et al., 1977). During the 1980s, a substantial number and variety of these compounds were prepared (Takagi and Ueno, 1984; Takagi and Nakamura, 1986). In these compounds, the chromogenic groups bear a dissociable proton (or protons) and ion exchange between the proton and appropriate metal cations causes the color change (Nakashima et al., 1983; Shiga et al., 1983; Takagi and Nakamura, 1986). The chromogenic groups can also be uncharged. In this case, both the electron donor and acceptor are within the chromogenic crown ether dye and the metal cation coordinated to either the donor or acceptor site induces a change in the charge-transfer band of the dye (Dix and Vögtle, 1980, 1981; Hollmann and Vögtle, 1984; Takagi and Ueno, 1984; Takagi et al., 1989).

Chromogenic macrocycles that are useful for selective extraction of cations and for determining cation concentrations, particularly Na^+ and K^+ at the parts per million (ppm) level, have been synthesized (Nakashima et al., 1986; Nakamura et al., 1981, 1982a, 1982b; Takagi et al., 1977) (see **38** for example). Takagi and coworkers synthesized chromogenic macrocycles that are selective for Ca^{2+} (see **39**) and extract other alkaline-earth cations in the order $Ca^{2+} > Sr^{2+} > Ba^{2+} >> Mg^{2+}$ (Shiga et al., 1983). Kaneda and coworkers synthesized chromogenic macrocycles and developed a sensitive spectropho-



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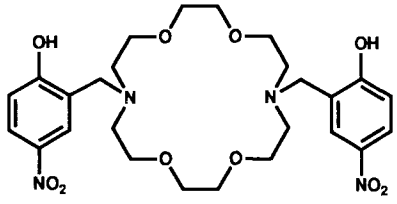
tometric method for their use in the colorimetric determination of Rb^+ and Cs^+ (see **40**)(Nakashima et al., 1983). The same group of scientists reported



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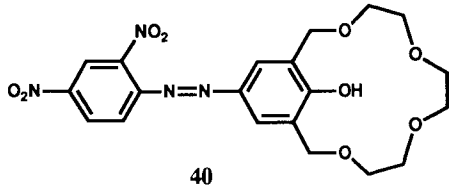

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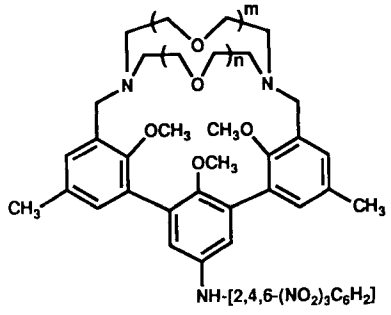
the first examination of amine-selective (Kaneda et al., 1989a) and enantiomeric-amine-selective (Kaneda et al., 1989b) coloration properties of chromogenic macrocycles.

Recently, creativity in chromogenic macrocycle synthesis has expanded. New spherand species have been synthesized that act as highly preorganized chromogenic-specific indicators for Li^+ and Na^+ (Cram et al., 1985), and an azophenol dye has been prepared with "perfect" selectivity for Li^+ (Kaneda et al., 1985). Many of these chromogenic macrocycles and more complicated species such as the hemispherands and cryptohemispherands have found commercial use for Na^+ and K^+ assays in body fluids (see **41**) (Helgeson et al., 1989; Czech et al., 1990).



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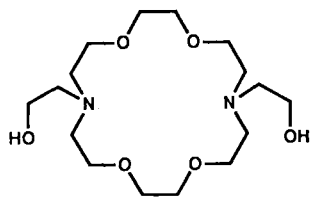
6. Lariat Crown Ethers

The number of reported lariat crown ethers bearing one, two, or more side arms has increased dramatically in the past few years. The lariat crowns are crown ethers with side arms containing donor atoms at the end. These lariat donor atoms can complex with cations above and/or below the complex, thereby increasing complex stability (Gokel et al., 1987). Macrocycles bearing pendant carboxylic acid functions are good examples of the lariat crowns. Carboxylate groups interact with metal cations; for example, $[12]N_4$ containing pendant carboxylates forms the most stable lanthanide complexes known (log K = 22.86–29.2) (Cacheris et al., 1987; Loncin et al., 1986). The cavity of the ligand is too small to accommodate a lanthanide cation, so the ligand ring acts as a frame to constrain the nitrogen atoms and the carboxylate groups into a nearly spherical arrangement.

In general, side arms, especially those containing donor groups, enhance the binding strength of the lariat crown ethers toward cations, in comparision with the crown ether analogs without side arms, by cooperative ring–side arm interaction (Gatto et al., 1986). Gokel and coworkers showed by X-ray crystallography that the two-armed lariat crown ether of 4,13-diaza-18-crown-6 (see **42**) enveloped Na^+ and K^+ cations in a three-dimensional manner displaying cryptand-like behavior (Arnold et al., 1987). Side arms without donor



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groups do not interact directly with ring-bound cations, but influence the binding by their interaction with the solvent (Arnold et al., 1988a). The complexation phenomena exhibited by lariat crown ethers are influenced by the cavity size–cation size relationship, ligand flexibility and conformation, total number of donor atoms, and solvation energies for the cation, macrocycle, and complex (Arnold et al., 1988b).

D. COMPLEX SELECTIVITIES OF THE AZA-CROWN MACROCYCLES

1. Introduction

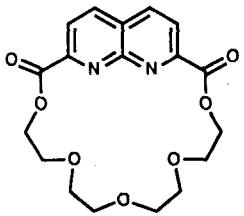
The main target in macrocycle ligand design is to synthesize macrocycles that are able to discriminate among different cations. Many factors influencing

the selectivities of macrocycles for cations have been determined. These factors may be divided roughly into several groups, including macrocycle cavity dimensions; shape and topology; substituent effects; conformational flexibility/rigidity; and donor atom type, number, and arrangement (Bianchi et al., 1991; Cram, 1988; Izatt et al., 1985, 1991; Izatt and Christensen, 1987a, 1987b; Lindoy, 1989b; Pedersen, 1988; Raevskii, 1990; Vögtle and Weber, 1989).

2. Rigidity, Side Arms, and Donor Atoms

Macrocycles of the "rigid" type (e.g., small cryptands and other preorganized macrocycles) discriminate between cations that are either smaller or larger than the one that exactly fits into the cavity (peak selectivity). Macrocycles of the "flexible" type (e.g., larger polyether crowns and cryptands) discriminate principally among smaller cations (plateau selectivity) (Vögtle and Weber, 1989).

Incorporating benzene, cyclohexane or pyridine rings, and/or other constituents into macrocyclic skeletons leads to a more rigid macroring and may alter the strength and selectivity of ligand interaction with a cation. An example is that of a 20-membered crown ether with an incorporated 1,8-naphthyridine ring (see **43**), which shows excellent selectivity for Ba^{2+} (log K = 7.16) over Ca^{2+} (log K = 4.91) in $CDCl_3$ (Chandler et al., 1988). Chiral groups incorporated into the correct location of a macrocyclic framework may allow separation of optically active enantiomeric cations (see **44**) (Bradshaw et al., 1990; Huszthy et al., 1991; Izatt et al., 1985; Stoddart, 1981; Vögtle and Weber, 1989; Zhu et al., 1992). Selectivities may be modified also by variation of the side arms. 4,13-Diaza-18-crown-6 containing two carboxylate groups on side arms shows unique selectivity toward lanthanide cations as a group (Chang and Rowland, 1983). 18-Crown-6 derivatives with amine-containing substituents (see **45**) are effective in K^+ transport through a CH_2Cl_2 membrane and are highly selective in transport experiments for K^+ over Na^+ (Nakatsuji et al., 1986).



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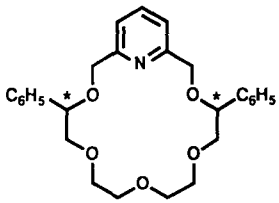

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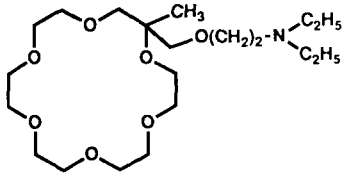

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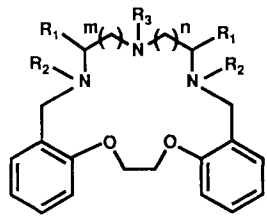
The number, kind, and arrangement of donor atoms also play important roles in macrocycle selectivities. Oxygen donor atoms in classical crown ethers have the largest affinities for alkali, alkaline-earth, and lanthanide cations;

nitrogen donor atoms favor transition-metal cations; and sulfur donor atoms interact preferentially with Ag^+, Pb^{2+}, and Hg^{2+} (Vögtle and Weber, 1989). For example, the extremely large stability differential among macrocycles (e.g., up to 10^{10} for Cu^{2+}) may be achieved solely through variation of number, kind, and location of donor atoms within the specific ligand frame employed (Adam et al., 1987).

3. Structural Dislocations

Recently, Lindoy and Adam and their coworkers conducted a series of investigations on cation discrimination by structural dislocation (Adam et al., 1983a, 1983b, 1986, 1987, 1988; Lindoy, 1989b). Structural dislocation is associated with a sudden change in the K value for cation–macrocycle interaction for a particular metal ion with a series of closely related macrocyclic ligands (Adam et al., 1983b, 1986). In one example, the interaction of 17-, 18-, and 19-membered dibenzo macrocycles (see **46**–**52**) containing three nitrogen and two oxygen atoms in the ring with Cd^{2+} and Zn^{2+} in 95% CH_3OH was examined. The log K values of Cd^{2+} with the 19-membered macrocycles were considerably lower than expected from the log K values for the 17- and

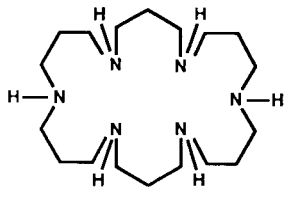


46 R_1, R_2, R_3 = H; m, n = 1
47 R_1 = CH_3; R_2, R_3 = H; m, n = 1
48 R_1 = H; R_2, R_3 = CH_3; m, n = 1
49 R_1, R_2, R_3 = H; m = 1, n = 2
50 R_1, R_2, R_3 = H; m, n = 2
51 R_1, R_2 = H; R_3 = CH_3; m, n = 2
52 R_1, R_2, R_3 = H; m = 1; n = 3

18-membered macrocycles. The observed dislocation along the Cd^{2+} series appears to be a crossover from coordination of the ether groups in the 17- and 18-membered macrocycles to their lack of coordination in the 19-membered macrocycle (Adam et al., 1988; Chen et al., 1984; Buschmann, 1988, 1989; Soong et al., 1990; Gholivand and Shamsipur, 1986). The influence of solvent (Marolleau et al., 1990; Schmidt et al., 1983) and counteranion (Bünzli and Giorgetti, 1985; Pett et al., 1988; Kim et al., 1987a, 1987b; Zavada et al., 1985; Solovev et al., 1987; Stover et al., 1985; Motekaitis et al., 1982) on macrocycle selectivities are also well known and have been studied thoroughly.

4. Selectivity For Anions

Macrocyclic polyamines that can be fully or nearly fully protonated in the neutral pH range appear to be the best ligands for the biologically important carboxylate and adenosine phosphate anions because the formation of these anions occurs in these pH regions. Lehn and Dietrich and their coworkers have synthesized macrocyclic polyamines [24]N_6(**53**) and [32]N_8(**54**), based on propylene units (Dietrich et al., 1981), and macrocycles with mixed nitrogen–oxygen donor atoms connected by ethylene units, [27]N_6O_3(**55**) (Dietrich et al., 1981) and [24]N_6O_2(**56**) (Hosseini and Lehn, 1987; Hosseini et al., 1983). These macrocycles are similar to those found in natural systems.



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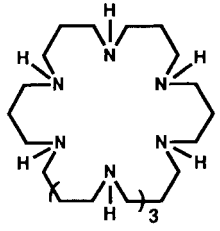

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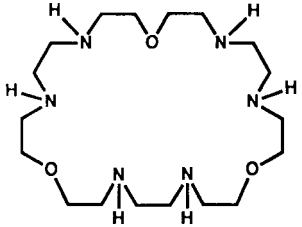

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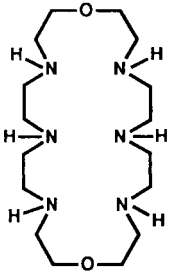

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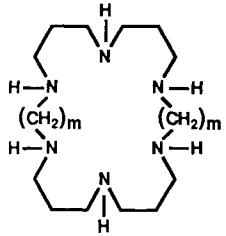
Both types of protonated macrocycles were found to form stable and selective complexes with both inorganic [i.e., SO_4^{2-}, $Co(CN)_6^{3-}$, and $Fe(CN)_6^{4-}$] and organic (i.e. carboxylate and nucleotide) polyanions in aqueous solution in the neutral pH range. Since selectivity in these systems depends on electrostatic and geometric effects, modification of macrocyclic cavity shape and size should allow one to control the selectivity sequence (Dietrich et al., 1981). The interactions of **53** and **54** in their less than fully protonated forms with carboxylate and nucleotide anions have been investigated recently (Hosseini and Lehn, 1988).

Macrocyclic penta- and hexaamines [15]N_5(**27**) and [18]N_6(**22**), based on ethylene units, are selective in their triprotonated forms at neutral pH for polycarboxylate anions that occur in the catabolic tricarboxylic acid cycle in

which the two carboxylate groups are near each other, and are ineffective toward other carboxylate and monocarboxylate anions (Kimura et al., 1981). These macrocyclic polyamines also form stable 1:1 complexes at neutral pH with phosphate anions such as the inorganic phosphates, AMP, ADP, and ATP (Kimura et al., 1982a) and with physiologically essential CO_3^{2-} (Kimura et al., 1982b). Bis(macrocyclic polyamine) ligands synthesized recently by Kimura and coworkers show enhanced polyanion binding due to probable formation of sandwich-type complexes (Kimura et al., 1990). Gelb and coworkers studied the interactions of tetraprotonated macrocyclic hexaamines with inorganic anions (tri- and tetraprotonated forms in the case of SO_4^{2-}) and found that the process of desolvating macrocycle and anion solvation spheres is a driving force in complexation (Cullinane et al., 1982; Gelb et al., 1985, 1986).

Large polyazacycloalkanes produce highly charged protonated species in the neutral pH range. Complexation of such large polyazacycloalkanes as [27]N_9(**32**), [30]N_{10}(**33**), and [33]N_{11}(**34**) with large polyanions, $Fe(CN)_6^{4-}$ and $Co(CN)_6^{3-}$, have been examined (Garcia-Espana et al., 1985; Bencini et al., 1987c). It was found that these macrocycles did not show selectivity toward the anions studied. This result is consistent with strong interactions, mainly Coulombic in nature, between the anion and the protonated ligand. The greater the extent of protonation of the ligand, the more stable is the complex. An X-ray crystallographic study of the octaprotonated **33**–$Co(CN)_6^{3-}$ complex shows that the anion lies outside the ligand cavity (Bencini et al., 1987c). The same authors reported recently how small structural modifications in highly organized tricarboxylic acid molecules cause drastic changes in the degree of complexation with the polyaza-crown macrocycle **32** (Bencini et al., 1991a).

Ditopic macrocyclic polyamines containing 1,3-diamine and longer units, [24]N_6(**53**), [32]N_6(**57**), and [38]N_6(**58**), were designed as receptors for dianions (Hosseini and Lehn, 1982, 1986). All of the polyamines studied form

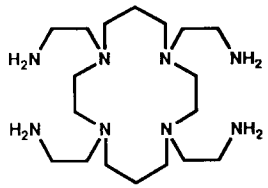


57 n = 7
58 n = 10

stable and highly selective complexes with organic dicarboxylate anions, $^-O_2C\text{-}(CH_2)_m\text{-}CO_2^-$. These macrocycles display linear molecular recognition based on ditopic binding between two triammonium units of the macrocycle and the two terminal CO_2^- groups of the dicarboxylate anion. The most stable

complex is formed when the macrocycle is fully protonated and the length of the dicarboxylate anion complements the site separation of the macrocycle.

Recently it was reported that the small macrocycle *N*,*N*′,*N*″,*N*‴-tetrakis(2-aminoethyl)[14]N_4(**59**) can interact with anions. It was proposed that protons attach first to the primary amino groups of the side arms and second to the tertiary nitrogens of the macrocycle. Thus, because of the initial protonation



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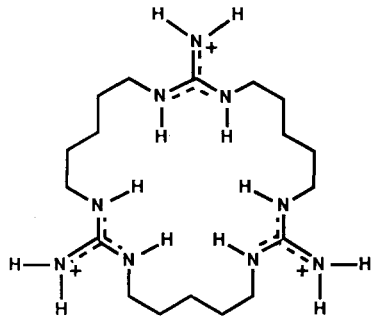
in the side arms, the flexibility of this receptor might lead to better matching in its interaction with anions (Bencini et al., 1991b).

5. Selectivity for Organic Molecules

Aza-cyclophane-type macrocycles possess large cavities of different sizes that have pronounced hydrophobic character and form host–guest inclusion complexes with charged or uncharged organic compounds in aqueous solution by hydrophobic and/or electrostatic interactions. In these complexes, the matching of the shape and size of the macrocycle hydrophobic cavity to the shape of the hydrophobic anion is important for optimum complex stability. In addition, increasing the hydrophobic volume of the cavity improves complex formation (Koga and Odashima, 1989). Aza-cyclophane-type macrocycles are able to select guests by recognition of the steric structure and charge of the guests. Their complexes with dianions are stronger than those with corresponding monoanions. They form strong complexes with anions having naphthalene rings, weaker but relatively strong complexes with anions having benzene rings, and only weak complexes with anions having nonaromatic structures (Odashima et al., 1981). Macrocycles bearing quaternary $^{+}$N charges in the cavity bind aromatic guests, including anions, 60 times stronger than aliphatic guests of similar shape. The differences in log *K* values are much smaller with the same macrocycles bearing no charges (Schneider et al., 1989).

Macrocycles containing guanidinium moieties as binding sites (see **60**) were synthesized by Lehn and coworkers (Dietrich et al., 1978). These macrocycles were expected to be effective and selective ligands for phosphate, di- and triphosphate, AMP, ADP, and ATP anions. However, the PO_4^{3-} complex was found to have low stability and there was almost no macrocyclic effect (Dietrich, 1984; Dietrich et al., 1978).



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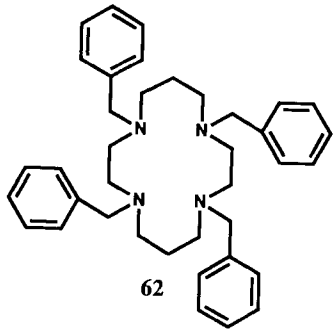
Achieving selective complexation between receptors and substrates of biochemical interest has been a driving force in the design of macrocycles suitable for selective binding of organic anions. As in the case of cations, selectivities of macrocycles toward anions are governed by many parameters. An important parameter involving spherical anions is the match between anion size and macrocycle cavity diameters. The geometry and topology of macrocyclic cavities are other parameters that influence selectivity. Arrangement of and distance between binding sites in ditopic polyammonium macrocycles, such as [38]N_6(**58**) and [24]N_6(**53**), result in a selectivity pattern toward dicarboxylate anions corresponding to a process of linear molecular recognition (Hosseini and Lehn, 1982, 1986). Usually, macrocycle selectivities for anions are governed by several factors simultaneously. Macrocyclic penta- and hexaamines were found to recognize only the dicarboxylates having suitable geometry and electronic arrangement (Kimura et al., 1981).

E. MEDICINAL USES OF THE AZA-CROWN MACROCYCLES

There are important new applications of the aza-crown macrocycles for medicinal purposes. The perturbation of metabolic processes based on biological metal ion–ligand coordination can produce a disease or even death. Conversely, undesirable biological processes can be prevented by using certain metal ion–ligand interactions. For example, the weak complexing ability of chlorine to the central platinum ion of *cis*-platin (**61**) allows *cis*-platin to have antitumor activity (Haiduc and Silvestru, 1989). When applied in a biological

61

system, the labile chlorine dissociates, allowing the platinum ion to interact with the DNA molecules of the cancer tissue. This is a common mode of antitumor activity by a chelating agent. Other drugs such as metallocene dichloride and diorganotin dihalide use this type of antitumor action (Reedijk et al., 1987). Up to the mid 1980s, only metal ion complexes of linear ligands had been tested. More recently, tetrabenzyl[14]N_4(**62**) complexes containing copper, gold, and silver have been tested for antitumor activity (Farrell, 1989; Haiduc and Silvestru, 1989).



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Other antitumor active compounds such as the bleomycin, antracycline, and streptomycin antibiotics have a different mode of action. Antitumor activity is manifested by DNA binding to the antibiotics followed by DNA strand cleavage. Cleavage requires oxygen and a metal ion that can form a complex. Fe^{2+} is the most effective metal ion in vivo and in vitro (Farrell, 1989; Sugiura et al., 1986). Busch and Cairns (1987) have taken the first steps in finding the right ligands to bind Fe^{2+} and dioxygen.

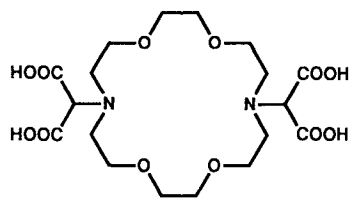
A novel method to localize and treat tumors by means of a ligand–radioisotope complex attached to an antibody is now being tested. The cyclic polyamines are ideal ligands for this purpose because they can be attached to an antibody and form strong complexes with the appropriate radioactive metal ions (Cox et al., 1989; Craig et al., 1989; Kaden et al., 1989; Moi et al., 1987, 1988; Morphy et al., 1988, 1989; Parker et al., 1989; Riesen et al., 1989). The cyclic amines form complexes with radioactive metal ions that are kinetically inert with respect to dissociation either by the pH of body fluids or reaction with the common metal ions in body fluids.

Early experiments in tumor localization and treatment using C-functionalized EDTA and DTPA chelates were not promising because the complexes with Cu^{2+} and In^{3+} were labile in body fluids and mixed complexes with Ca^{2+}, Mg^{2+}, and Zn^{2+} formed. Since the radioactive metal ions can damage liver and bone marrow, it is very important to use ligands that form very strong complexes with those cations. Recently, a complex of Bi^{3+} and a DTPA incorporating rigid cyclohexane rings between the nitrogen atoms has exhib-

ited good in vivo stability and has promise for ^{212}Bi-radioimmunotherapy (Brechbiel et al., 1991). Aza-crown macrocycles of 9–14 ring members and with acetic or phosphoric acid groups attached to each nitrogen atom appear to be good candidates to replace DTPA or EDTA for this application. A number of these macrocycles were tested and the only inefficient labeling was found for the complex of [12]N_4-tetraacetate and ^{90}Y where divalent cations such as Ca^{2+} and Zn^{2+} effectively competed for the ligand (Broan et al., 1991). The aza-crown macrocycles do show great promise, but more work is needed (Gansow et al., 1991). More detailed discussions concerning the complexation of radioisotopes for radioimmunotherapy have been published in recent reviews (Jankowski and Parker, 1992; Liu and Wu, 1991; Parker, 1990).

Aza-crown macrocycle–metal ion complexes are effective proton relaxation enhancement agents in aqueous solution and in rat tissue. The magnitude of enhancement is such that proton relaxation is detectable in magnetic resonance images obtained by clinical nuclear magnetic resonance (NMR) imagers (Jackels et al., 1986). Recent work shows promise for the use of paramagnetic complexes with macrocycles as contrast agents in medicinal NMR imaging. The best metal ions appear to be Fe^{3+}, Gd^{3+} and Mn^{2+} because of their high magnetic moments and relaxation efficiencies (Comblin et al., 1991; Geraldes et al., 1991; Kumar et al., 1991; Lauffer, 1987).

The oldest medicinal application for chelating agents is the immobilization of toxic metal ions such as arsenic, lead, mercury, and nickel. Immobilization of excess amounts of essential metal ions such as iron or copper has also been done by chelating agents. In general, the linear chelating agents are being used for these purposes (Bulman, 1987; Jones, 1991), but the aza-crown macrocycles are now being tested. The tetrasodium salt of [18]N_2O_4-*N*,*N*′-dimalonic acid (**63**) is capable of promoting the excretion of radiostrontium



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and radiocerium that had been administered into animal bodies (Varga et al., 1990). Derivatives of [14]N_4(**10**) (cyclam) even in low doses have a good efficiency in reducing the lethal response to nickel. These macrocycles significantly enhance the urinary and biliary excretion of Ni^{2+} and restore the altered levels of other trace metal ions such as Cu^{2+}, Zn^{2+}, and Fe^{3+}. They are more efficient in this application than linear chelating agents such as EDTA or triethylenetetraamine (Athar et al., 1987; Misra et al., 1988).