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Ion Binding by Synthetic Macrocyclic Compounds

Selective ion binding in the interior of ring structures characterize these compounds.

J. J. Christensen, J. O. Hill, R. M. Izatt

Many synthetic macrocyclic polyethers, polyamines, polythioethers, and other related molecules have very interesting and unusual ion binding properties (*1*). These novel macrocycles typically contain central hydrophilic cavities ringed with either electronegative or electropositive binding atoms and exterior flexible frameworks exhibiting hydrophobic behavior. They show a pronounced ability to bind a wide variety of cations or anions and, in many cases, to undergo marked conformational changes during binding. Their hydrophobic exteriors allow them to solubilize ionic substances in nonaqueous solvents and in membrane media. Particularly interesting is the strong affinity shown by the polyethers for alkali and alkaline earth metal ions and their selective binding of these cations resulting in their use as models for carrier molecules in the study of active ion transport phenomena in biological systems. The synthetic macrocyclic compounds are promising agents for use in removing or separating metals in solution in processes such as saline water purification and solution mining. They may also be possible tools in the development of new areas of synthetic coordination chemistry.

The principal classes of macrocyclic compounds considered here are illustrated by structures **1** to **21**, and include, in general, synthetic macrocycles having multiple binding sites which complex either cations or anions in their interiors and which have been prepared as the free molecule (that is, not complexed with a given cation or anion). Many macrocycles have been synthesized by means of the so-called coordination template effect. This effect consists of a metal ion being used in a reaction to direct the steric course of the process leading to the synthesis of species not readily obtained in the absence of the metal ion. Many macrocycles formed in this manner have only been isolated in the form of their complexes with the templating metal ion. Representative complexes of this nature have been included, although in many cases the free macrocycle has not been obtained. In a few instances, we have included macrocycles that have, in our opinion, the potential of forming complexes with either anions or cations although no complex has yet been reported.

The macrocyclic compounds shown in structures **1** to **21** differ in types and number of ion binding sites and thus generally exhibit widely different affinities for a given ion. Various macrocyclic molecules have been shown to bind with a wide variety of cations, including ammonium ion, and, in a few specific cases, with selected anions. The factors affecting the formation and stability of these ion-macrocycle complexes include (i) the type or types of binding sites in the ring, (ii) the number of binding sites in the ring, (iii) the relative sizes of the ion and the macrocyclic cavity, (iv) the physical placement of the binding sites, (v) steric hindrance in the ring, (vi) the solvent and extent of solvation of the ion and the binding sites, and (vii) the electrical charge of the ion. Thus, there exist unusual opportunities for the synthesis of macrocyclic molecules that exhibit a high degree of selectivity in metal binding. For example, certain cyclic polyethers not only strongly bind particular alkali and alkaline earth metal ions but selectively bind one or more of these ions in preference to the others in each series. It is our purpose in this article to discuss the selective ion binding characteristics of synthetic macrocyclic compounds and to indicate some present and possible future applications.

Cyclic Polyethers and Polyoxides

Of all the macrocyclic compounds, the cyclic polyethers have been the most extensively investigated with respect to ion binding. Over 60 cyclic polyethers have been synthesized with ring structures containing from 9 to 60 total atoms, from 3 to 20 oxygen atoms, and from 1 to 4 attached hydrocarbon rings. The polyethers have been found to form primarily one to one (1:1) polyether-metal complexes with a large array of metal ions. However, there are some indications that, depending on the ratio of the cavity to metal ion diameter, two to one (2:1) and three to two (3:2) complexes are also formed.

The 1:1 complexes are generally assumed to consist of the metal ion bound in the cavity of the polyether ring (*2*–*6*). This "metal in the hole"

Dr. Christensen is professor of chemical engineering and Dr. Izatt is professor of chemistry, and both are affiliated with the Center for Thermochemical Studies, at Brigham Young University, Provo, Utah 84601. Dr. Hill was a postdoctoral fellow at Brigham Young University (1969–1970) and is now a research fellow at La Trobe University, Bundoora, Victoria, Australia.

picture has been substantiated by an x-ray crystallographic study (*7*) of the complex formed by the cyclic polyether dibenzo-18-crown-6 (**2**) [see (*8*) for information concerning nomenclature used in this article] with rubidium thiocyanate which showed that the rubidium ion was located in the exact center and slightly above a planar ring with the thiocyanate ion nearly perpendicular to the plane of the ring (structure **22**). Other x-ray studies of the sodium complexes of dibenzo-18-crown-6 and benzo-15-crown-5 (*9*) have also shown that the metal ion occupies a position in the center of the plane of the oxygen atoms. It was also found (*9*) that, for the potassium complex of dibenzo-30-crown-10 and apparently for other large ring cyclic polyethers, the complex consists of a wrap-around structure where all the oxygen atoms are approximately equidistant from the potassium ion but not in the same plane.

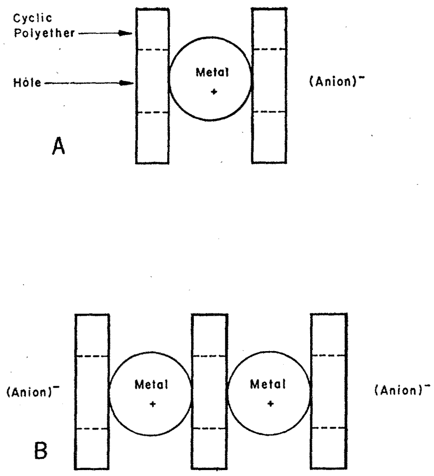


Fig. 1. (A) A sandwich complex; (B) a club sandwich complex.

An interesting 1:1 complex is the one formed between barium difluorenyl and the cyclic polyether dimethyldibenzo-18-crown-6 in tetrahydrofuran. In this complex, absorption spectral data (*5*) showed that the barium is located in the cavity of the ring and sandwiched symmetrically between the two fluorenyl moieties. The spectral data indicate that the solvation is asymmetric and this, coupled with the likelihood that the barium ion rapidly moves up and down through the hole of the polyether ring (*5*), results in a complex that, at any one time, has one fluorenyl ring close to the barium ion while the other fluorenyl ring is separated from the barium ion by the cyclic polyether. However, the fact that a metal ion forms a 1:1 complex with a cyclic polyether does not always indicate that the metal ion is located in the cavity of the polyether. The metal ion may have directed valencies which preclude bonding to all the oxygen atoms or it may be too large or too small to fit "exactly" in the hole. Apparently, the former is the case for the solid complex of cobalt dichloride and the cyclic polyether dicyclohexyl-18-crown-6 (**1**) where, on the basis of infrared and magnetic moment data (*10*), two possible structures were postulated: a sandwich-type structure with two cobalt ions located between two cyclic polyether molecules (**23**) and a chain-type polymer with an alternating array of cobalt cations and cyclic polyether molecules (**24**). These structures are possible only if each cyclic polyether contributes three oxygen atoms to each cobalt ion to form an octahedral complex. In the absence of x-ray crystallographic data, it cannot be predicted which, if either, of these structures is correct.

Table 1. Diameters of selected cations and cyclic polyether cavities (*4, 11*).

Cation		Polyether	
Type	Ionic diameter (Å)	Type	Diameter of cavity (Å)
Lithium	1.20	All 14-crown-4	1.2–1.5
Sodium	1.90	All 15-crown-5	1.7–2.2
Potassium	2.66	All 18-crown-6	2.6–3.2
Ammonium	2.84	All 21-crown-7	3.4–4.3
Rubidium	2.96		
Cesium	3.34		
Silver	2.52		
Barium	2.70		

Table 2. Preferential metal ion binding exhibited by cyclic polyethers. See Table 1 for diameters of metal ions and polyether cavities.

Alkali metal ion	Cyclic polyether showing preference for given alkali metal ion over other ions	Approximate ratio of metal ion diameter to hole diameter
Lithium	bis-*tert*-Butylcyclohexyl-14-crown-4*	0.89
Sodium	*tert*-Butylcyclohexyl-15-crown-5*	0.97
Potassium	Dicyclohexyl-18-crown-6*	0.90
Rubidium	asym-Dicyclohexyl-21-crown-7†	0.77
Cesium	Dicyclohexyl-24-crown-8†	0.83

* See (*15*). † See (*4*).

There is also structural evidence indicating that, in many cases, the relative sizes of the polyether cavity and the metal ion control the stoichiometry of the resulting complex. The ionic diameters of some cations and the estimated sizes of the holes of selected cyclic polyethers are given in Table 1. The alkali metal thiocyanate complexes of the cyclic polyether dibenzo-18-crown-6 (**2**) were found (*11*) to have, for a given metal, the following ratios of polyether to metal ion—potassium, 1:1; rubidium, 1:1 and 2:1; and cesium, 2:1 and 3:2. A "sandwich" structure, in which the metal ion is located between two cyclic polyether molecules was suggested as the most probable for the 2:1 complex. An x-ray study of the 2:1 rubidium dibenzo-18-crown-6 complex (*12*), however, has shown that the complex has a stoichiometry of 3:2 with a unit cell containing one 1:1 complex and one uncomplexed polyether. A 2:1 complex, potassium benzo-15-crown-5, has been synthesized and found by x-ray analysis (*12*) to have a "sandwich" structure. A "club sandwich" structure was postulated for the 3:2 complex where three polyether molecules are arranged as planes in three tiers, each separated from the next by a metal ion. Rough approximations of these structures are depicted in Fig. 1A (sandwich complex) and Fig. 1B (club sandwich complex). Similarly, where the metal ion was larger than the hole in the ring, other cyclic polyethers have been found to give 2:1 (*11, 13*), 3:2 (*11, 13*), and 3:1 (*14*) complexes with various metal ions. Thus, it seems evident that the relative sizes of the hole and the metal ion have much to do with determining the stoichiometry of the complex. However, it has also been found that silver forms a 1:1 complex with the cyclic polyether benzo-15-

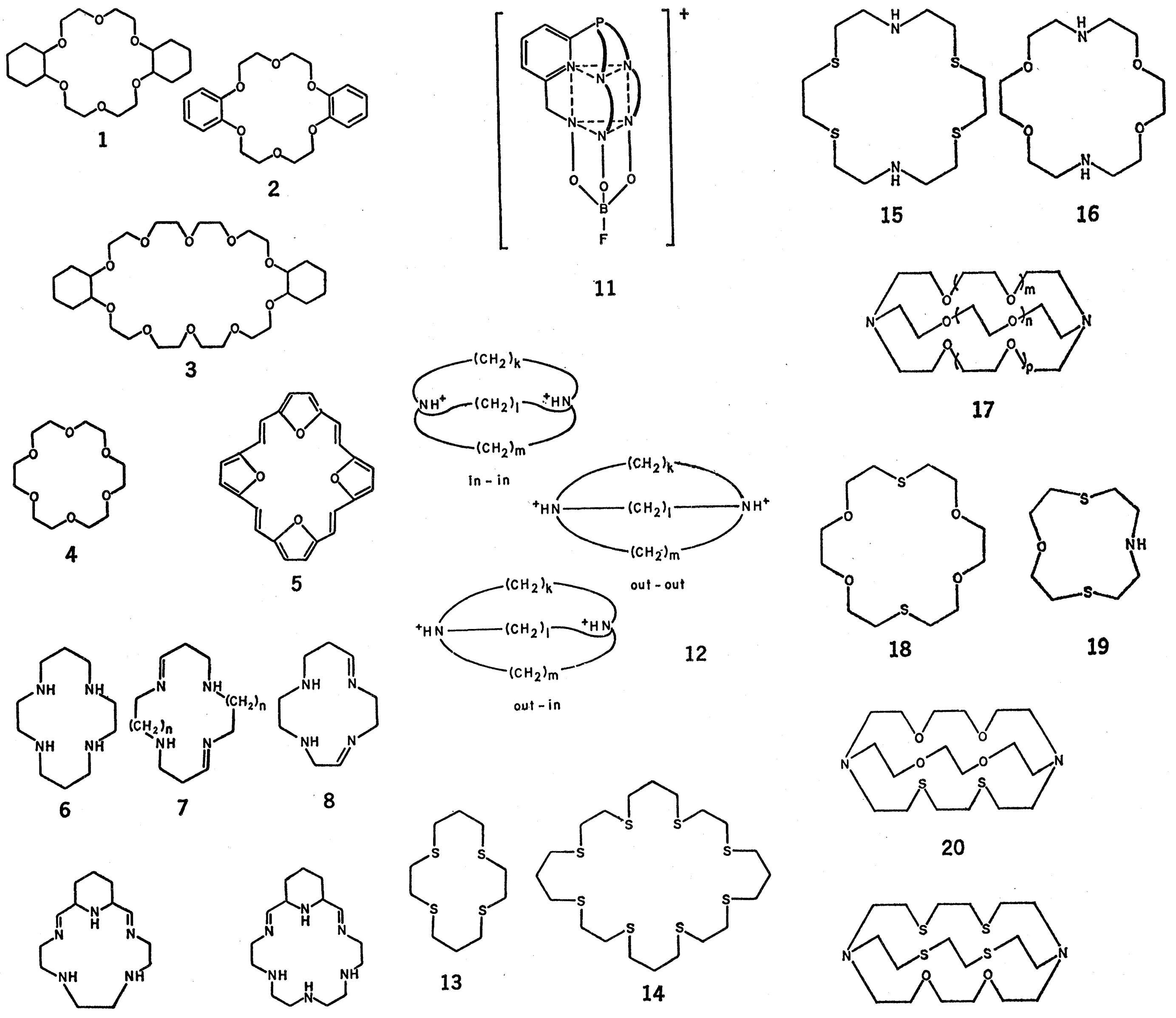
crown-5, yet the silver ion diameter is larger than the diameter of the hole in the cyclic polyether (Table 1). This indicates that relative size is not the only factor influencing the configuration of the complexes.

One of the most interesting features of the cyclic polyethers is the ability of these compounds to selectively bind various metal ions. Because of the unique way in which metal ions are bound in the cavities of the polyethers, it is not surprising that the stabilities of the complexes formed are strongly influenced by the relative cavity and metal ion sizes. Solvent extraction studies (*4*, *15*) indicate preferential metal ion binding of alkali metal ions by cyclic polyethers as shown in Table 2. The selectivity was thought to be related to the relative sizes of the cations and the holes of the cyclic polyethers. Furthermore, the alkali metal ions are generally regarded as poor complexing cations, and the cyclic polyethers appear to be the only neutral class of compounds except the macrocyclic antibiotics which complex appreciably with these metals. In fact, the stability sequence for the alkali metal ion complexes with the cyclic polyether dicyclohexyl-18-crown-6 has been found (*16*, *17*) to be

Potassium > rubidium >
cesium, sodium > lithium

This sequence is essentially the same as the permeability sequence of the alkali metal ions in the presence of certain antibiotics for the transport of metal ions through natural and synthetic membranes.

In Fig. 2 is shown the relation as found by us (*16*, *17*) between (i) the magnitude of the binding constant and (ii) the relative sizes of the polyether cavity and the metal ion for the reaction of the cyclic polyether dicyclohexyl-18-crown-6 with several uni- and bivalent cations. Below a ratio of cation to cavity diameters of 0.5 little complex formation occurs, whereas at ratios greater than 0.5 there is a rapid increase in the degree of interaction with a maximum between a diameter ratio of 0.75 and 0.9; this increase is followed by a decrease in the extent of interaction as the ratio of cation to cavity increases. A charge effect is also seen in that the 2+ ions generally have larger binding constants than the 1+ ions have for the same ratio value and also the 2+ ions are more selectively



Structures 1 to 21

complexed than the 1+ ions. We postulated that the metal-oxygen bond in cyclic polyether complexes is predominantly ionic, but with increasing covalent character as the charge on the metal increases. The charge effect is manifested primarily in the change of enthalpy on complexation, with larger negative values for enthalpy change signifying increasing covalent bonding. For example, more covalent bonding would be expected in barium than in cesium complexes, and this is indicated in that the enthalpies of complexation for these two metal ions in aqueous solution are −4.87 and −2.0 kilocalories per mole for barium and cesium, respectively.

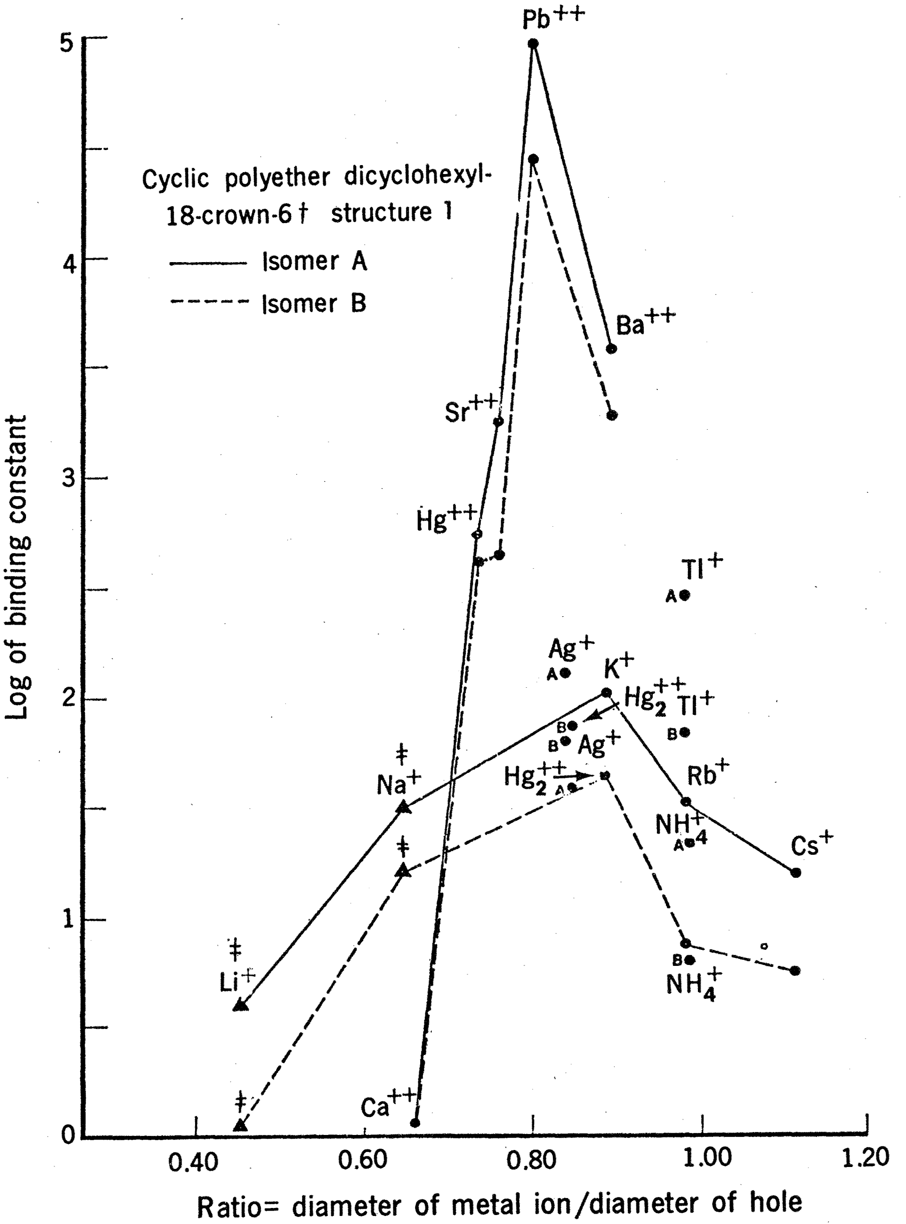


Fig. 2. Relation between magnitude of binding constant and relative sizes of the polyether cavity and the metal ion for the cyclic polyether dicyclohexyl-18-crown-6 (**1**). † The diameter of the hole is assumed to be 3.0 Å (Table 1). ‡ The data are taken from (*13*).

Binding constants for the reaction of more than 20 cyclic polyethers (12- to 60-membered rings) with numerous metal ions [alkali, alkaline earth, ammonium, silver(I), mercury(I), mercury(II), thallium(I), and lead(II)] have been determined at various temperatures and in various solvents (*13*, *16–19*). The effect of solvent and dielectric constant on the thermodynamics of interaction of alkali metal and cyclic polyether is indicated in Table 3. The sharp increases in both the binding constant and the heat of interaction as the dielectric constant of the solvent decreases suggests that, in aqueous media, most of the water molecules in the first hydration sphere of the metal ion are replaced on complexation with the cyclic polyether. Similarly, nuclear magnetic resonance (NMR) and ultraviolet spectroscopic studies (*6*) of the complexing of fluorenyl alkali salt ion pairs by cyclic polyethers in ethereal solvents and pyridine indicate that the relative magnitudes of the equilibrium constants are functions of the solvent composition. The selectivity shown by the cyclic polyether dimethyldibenzo-18-crown-6 toward alkali metal ions in tetrahydrofuran was found to be

Sodium ≫ potassium > cesium > lithium

The sequence, however, was dependent on the solvent medium; for example, in oxetane potassium is preferred to sodium. It has been proposed that the stability order in tetrahydrofuran differed from other reported stability orders where potassium, as compared to sodium, complexes 18-crown-6 derivatives more readily because of differences in the solvation of the metal ions. In most solvents sodium binds the solvent more strongly than does potassium but in tetrahydrofuran the difference is expected to be much less, and thus the order of stability of sodium and potassium is reversed compared to that in more polar solvents, such as water and alcohol.

Although the synthesis of several cyclic polyoxides (**5**) have been reported (*20*) no metal complexes of this class of macrocycles are known.

Cyclic Polyamines

Monocyclic. A large variety of cyclic polyamines having three to six functional groups in the ring have been synthesized. However, most of the cyclic polyamines have four functional groups which are more or less evenly spaced in a ring containing between 12 and 16 atoms. Representative formulas of the main classes of polyamine macrocycles are illustrated by structures **6** to **10**. No attempt is made here either to indicate the many variations that exist in these structures resulting from the attachment of side groups, functional groups, and the like, or to name each of the complexes systematically [see (*8*)]. In general, cyclic polyamines are formed by one of a number of different kinds of condensation reactions in which a transition metal ion functions as a template and holds the condensing molecules in a suitable orientation to facilitate the formation of products. This so-called coordination

Table 3. Thermodynamic properties for the interaction of alkali metals with dicyclohexyl-18-crown-6 (**1**) in different solvents at 25°C. Data taken from (*13, 16, 19*).

Solvent	Dielectric constant	Cation	Heat of interaction (kcal/mole)		Log of binding constant (liter/mole)	
			Isomer A	Isomer B	Isomer A	Isomer B
Water	78	Sodium	~ 0	~ 0	1.5	1.2
Water	78	Potassium	− 3.9	− 5.1	2.02	1.6
Methanol	33	Sodium		− 5.6	4.08	3.7
Methanol	33	Potassium		− 10.5	6.01	5.4
Ethanol	24	Sodium		~ − 8.6		~ 4.5
Ethanol	24	Potassium		~ − 12.6		~ 6.0

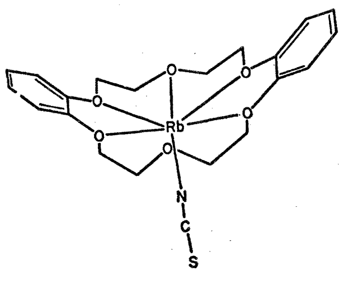
template effect is very influential in most of the syntheses of macrocyclic ligands containing nitrogen binding atoms.

Typical of macrocycles prepared by condensation in the presence of transition metal salts are those formed by reaction of certain metal-amine complexes with aliphatic carbonyl compounds. For example, with acetone as the carbonyl compound and diaminoethane as the amine in the metal complex, a macrocycle characterized by the structure shown by **7**, where $n = 2$ is obtained (the methyl side groups are not indicated in the drawing). This reaction provides a convenient route to complexes of macrocyclic ligands with four nitrogen donor atoms. The size of the macrocycle can be changed either by replacing one or both of the diaminoethane residues by 1,3-diaminopropane residues, or by cyclization of triethylenetetramine complexes by a single amine-imine bridge. The ring substituents can be changed by replacing diaminoethane with a substituted diaminoethane, or by replacing acetone with some other aliphatic carbonyl compound. The macrocyclic complexes formed have two imine and two secondary amine donor groups, but it is possible to vary the unsaturation of the macrocycle from the tetraimine to the tetra-amine by oxidation or reduction, respectively.

The direct condensation between metal-amine complexes and carbonyl compounds is satisfactory only for nickel(II) and copper(II), but isolation of some of the macrocycles from the nickel(II) complexes has made it possible to prepare complexes of other metal ions. Recently, some of the macrocycles have been prepared by direct condensation of diamines and carbonyl compounds in the absence of metal ions, and this method can be used to prepare complexes of metal ions. The synthesis of cyclic polyamines has been described and reviewed (*21, 22*).

Each of the representative cyclic polyamine compounds (structures **6** to **10**) has formed complexes with one or more of the following metal ions: nickel(II), nickel(I), copper(II), copper(I), cobalt(III), cobalt(II), iron(III), iron(II), platinum(II), paladium(II), magnesium(II), and manganese(II). Most of these complexes have structures similar to that given by **25**, where four more-or-less equivalent nitrogen atoms are coordinated in a single plane about the metal ion, while two variable ionic groups are bound in the axial sites above and below that plane. X-ray crystallographic analyses on several macrocycles containing four and five nitrogen atoms indicate that the metal ion is located in the cavity of the ring. Perspective views of two such structures are shown by **26** and **27**. In **26** is represented dicyanocyclic polyamine **8** complexed to cobalt(III) (*23*), and in **27** is represented dithiocyclic polyamine **9** complexed to iron(III) (*24*).

Most of the work to date on cyclic polyamines has been related to synthesis, classification of the metal complexes, and the chemistry of the reaction of the metal complex with other monodentate ligands. Comparatively little has been done to measure metal binding constants in the reactions of these macrocycles or to investigate the various factors which affect these constants. This is due in part to the covalent bonding between the nitrogen atoms and the metal ion which, because of the template effect, results in a macrocycle being synthesized with a strongly bonded metal ion in the cavity. The complexes are in general remarkably inert to dissociation, and, in many cases, it is not possible to obtain the metal-free macrocycle. In fact, it has been suggested that because of the high



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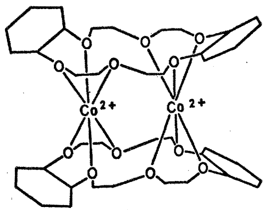

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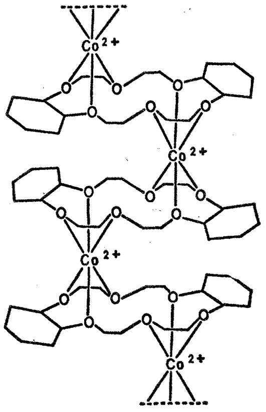

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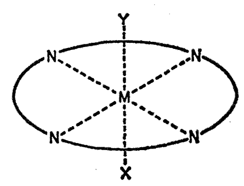

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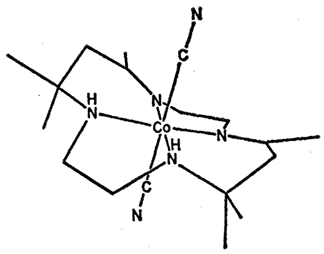

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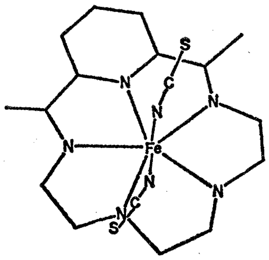

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Structures 22 to 27

Table 4. Binding constants for the 1 : 1 complexes of tetra-amines with copper(II) (*26*).

Ligand	Log of binding constant (liter/mole)	Temperature (°C)
	Macrocyclic	
Structure **6** (blue)	20	25
Structure **6** (red)	28	25
	Noncyclic	
$N[(CH_2)_3NH_2]_3$	13.1	25
$NH_2(CH_2)_3NH(CH_2)_2NH(CH_2)_3NH_2$	17.3	20
$N[(CH_2)_2NH_2]_3$	18.8	20
$NH_2(CH_2)_2NH(CH_2)_2NH(CH_2)_2NH_2$	20.1	25
$NH_2(CH_2)_2NH(CH_2)_3NH(CH_2)_2NH_2$	23.9	25

Table 5. Halide radii, cavity diameters, and binding constants for the encapsulation of halide ions by bicyclic amines in 50 percent trifluoroacetic acid (*29*).

Halide	Ionic radii (Å)	Binding constant * (liter/mole) for bicyclic amine [*k*, *l*, *m*] (see **12**):			
		[7.7.7] 1.6†	[8.8.8] 2.8†	[9.9.9] 3.6†	[10.10.10] 4.5†
Chloride	1.81	0	0	4	> 10
Bromide	1.95	0	0	1	> 10
Iodide	2.16	0	0	0	> 10

* This is the constant for hte following reaction: in-in (bicyclic amine)$^{2+}$ + halide$^-$ = in-in (bicyclic amine) halide$^+$. † This figure is the bicyclic amine cavity diameter in angstrom units.

stability of the complexes it might be possible to trap some of the more uncommon oxidation states of the transition metals by reduction or oxidation of the complexes containing the metals in their normal oxidation states (*25*). In some cases, the free macrocycle can be obtained by introduction of a stronger metal binding molecule. For example, the macrocycle shown in **6** can be readily removed intact from the nickel(II) ion by the action of aqueous cyanide ion (*22*).

$$Ni(L)^{2+} + 4CN^- \rightarrow Ni(CN)_4^{2-} + L$$

(where L is the ligand). This reaction also establishes the binding constant for the nickel macrocycle complex to be less than that for the $Ni(CN)_4^{2-}$ complex, which is log $K = 30.1$.

The binding constants for the red and blue forms of the copper(II) complex of the macrocycle shown by **6** have been measured and compared with similar constants for copper binding with noncyclic nitrogen-containing molecules (*26*). These results are given in Table 4 and indicate the high stabilities of the macrocyclic complexes. The effect of increased stability of a metal complex coordinated to a tetra-amine macrocyclic ligand over that of similar noncyclic tetra-amine ligands has been called the macrocyclic effect. Aside from that provided by the above study, little information is available with respect to the effect of the various factors influencing the relative binding of metals to cyclic polyamines.

Bicyclic. Several macrobicyclic complexes of the general type shown by **11** containing completely encapsulated metal ions have been synthesized and characterized (*27, 28*). Encapsulated metal ions include iron(II), cobalt(II), nickel(II), and zinc(II). Rigid cage structures are characteristic of this class of complexes. No metal binding constants have been reported for the bicyclic complexes.

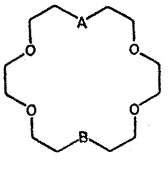
Macrobicyclic diamines with bridgehead nitrogen atoms have been reported (*29*) to exhibit an unprecedented ion pairing phenomenon. These macrocycles can exist in the three configurations illustrated by **12**. As indicated by NMR studies the out-out isomer (**12**, $k = l = m = 9$) dissolved in 50 percent deuteriotrifluoroacetic acid was slowly converted to the in-in isomer until an equilibrium condition of approximately 40 percent in-in isomer and, 60 percent out-out isomer was obtained. The equilibrium constant, K = in-in/out-out, was found to be equal to 0.41. Also, halide ions react with the in-in form to produce a new cation consistent with the encapsulation of the halide ions in the molecular cavity of the bicyclic amine. This process, which involves the diffusion of halide ions into the cavity of a bicyclic amine, has been defined as katapinosis, and the resulting ion pairs have been termed katapinate ions.

The structure of the katapinate ion formed by the encapsulation of chloride ion by the macrobicyclic diamine **12** is given by **28**, and the binding constants for halide ion encapsulation by these macrocyclic compounds are given in Table 5. It was postulated (*29*) that the stability of the complexes must be in part due to the high positive potential of the hole with respect to anions and to hydrogen bonding within the cavity. Experiment showed that, for chloride ions, the encapsulated chloride ion exchanged rapidly with the external chloride ion.

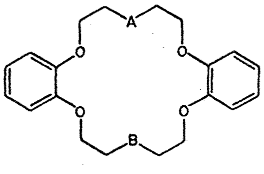
Table 6. Binding constants for the interaction of potassium and silver(I) with mixed dentate macrocycles at 25°C (*13*).

Ligand type*	Donor atom		Log of binding constant (liter/mole)	
	A	B	Potassium in methanol	Silver(I) in water
1	O	O	6.10	1.60
2	O	O	5.00	
2	NR†	O	4.10	
1	NH	O	3.90	3.3
2	NH	O	3.20	
1	NH	NH	2.04	7.8
2	NH	NH	1.63	

* Type 1 =



Type 2 =



† R = *n*-Octyl.

Cyclic Polythioethers

Metal chelates, primarily nickel(II) and cobalt(III), of several cyclic polythioethers containing three, four, six, and eight sulfur atoms have been prepared (*30–32*) and representative structures of two of these macrocycles are shown by **13** and **14**. The configuration of the metal ion-ligand complex is a function of the ring size and number of sulfur groups. A tridentate macrocycle (*13*) with nickel(II) gave a complex with a 2 : 1 ligand-metal ratio, indicating the formation of a sandwich-type structure with the metal ion located between the two ligands (Fig. 1a). Tetradentate macrocycles contain the metal ion in the plane of the ring for ring sizes over 14 members (*33*), but form complexes with 3:2 ratios of ligand to metal for ring sizes of 13 members or less. Sexadentate ligands having 18- and 20-member rings have four of the sulfur atoms in a plane with the metal ion, with the other two sulfur atoms occupying positions above and below the plane (octahedral geometry). An octadentate thioether yields nickel(II) complexes in which four sulfur atoms are bound to each of the two nickel atoms or, in other words, the ligand circumscribes completely two metal ions. Spectral evidence indicates that each nickel(II) ion is located in a plane of the four sulfur atoms coordinated to it. With palladium(II) and platinum(II), however, the complexes formed had a metal to ligand ratio of 4:1, indicating that two sulfur atoms bind with each metal ion. The metal-free cyclic polythioether ligands can usually be obtained because, in most cases, the complexes react with water or ethanol to liberate the free ligand. No metal binding constants have been reported for the cyclic polythioethers.

Mixed Dentate Macrocycles

Metal complexes of cyclic mixed dentate ligands are discussed according to the types of donor atoms in the macrocycle.

Sulfur-nitrogen donor groups. Metal complexes of nickel(II) and cobalt(II) with ligands of the types shown by **15** have been synthesized (*34*) and usually the metal-free ligand has also been obtained. The metal ion in macrocycles of this type occupies, in most cases, a position in the plane of the sulfur atoms with the nitrogen atoms above and below the plane. No metal binding constants have been reported in the cases of these ligands.

Oxygen-nitrogen donor groups. The effect of substituting nitrogen for oxygen (**16**) on the metal binding properties of the cyclic polyethers 18-crown-6 and dibenzo-18-crown-6 with potassium and silver ions has been studied (*13*) and the results are shown in Table 6. The complexes formed were all 1:1 macrocycle:metal ion with the metal ion located in the cavity of the macrocycle. Complexing of potassium is weakened appreciably as nitrogen is substituted in the ring, the stability constant falling in the order of decreasing electronegativity of the substituted group, O > NR > NH. The effects on silver(I) complexing were exactly the opposite with the stability increasing with substitution. It was concluded that only electrostatic bonding exists in the potassium complexes whereas the silver(I) complexes have both electrostatic and covalent bonding.

Several polyoxa macrobicyclic diamines represented by the structure given by **17** where $m = n = p = 1$; $m = n = 1$, $p = 2$; $m = 1$, $n = p = 2$; and $m = n = p = 2$ have recently been synthesized (*35, 36*). These compounds are able to form metal ion complexes in which the metal ion is located within the central cavity of the macrocycle. The crystal structure of the rubidium complex of the macrobicycle, $m = n = p = 1$, has been determined by x-ray crystallography (*37*) and confirms the proposal that the rubidium ion is located in the cavity of the macromolecule (**29**). The two nitrogen atoms participate with the six oxygen atoms in bonding to the rubidium. Binding constants for the formation of several metal complexes of the macrocycle, $m = n = p = 1$ in water at 35°C are given in Table 7 (*36, 38*). All the complexes showed 1:1 stoichiometry with the metal being positioned in the center of the ligand cavity. It can be seen that these macrocycles demonstrate a very strong tendency to form remarkably stable complexes with, and to differentiate between, various metal ions.

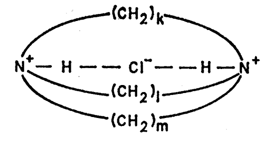
Table 7. Binding constants for metal-bicyclic mixed dentate (**17**, $m = n = p = 1$) complexes in aqueous solution at 35°C (*36, 38*).

Metal	Log of binding constant (liter/mole)
Barium	≧ 15.0
Strontium	13.0
Potassium	5.1
Calcium	4.1
Rubidium	3.7
Sodium	3.6
Lithium	≃ 0
Cesium	≃ − 0.7

Oxygen-sulfur donor groups. A tetrathioether, **18**, has been synthesized as a white crystalline solid but it was impossible to complex the macrocycle with either nickel(II) or cobalt(II), even though the similar all-sulfur sexadentate macrocycle readily yielded complexes with both metals (*32*). This same tetrathioether was found, however, to form complexes with potassium and silver(I) and the binding constants are given in Table 8 (*13*). The fact that silver(I) forms the stronger complex is due to its ability to form both ionic bonds with the oxygen and covalent bonds with the sulfur whereas the potassium forms predominantly ionic bonds.

Table 8. Binding constants for the formation of 1 : 1 complex of potassium and silver(I) with a tetrathioether (**18**) (*13*).

Metal	Log of binding constant (liter/mole)	Solvent
Potassium	1.15	Methanol
Silver	4.34	Water



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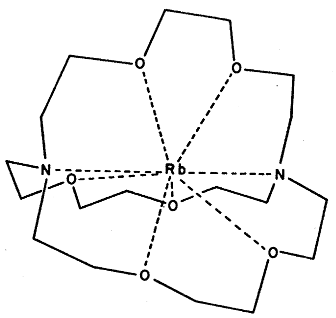

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Structures 28 and 29

Three different donor groups. The 12-membered dithioether, **19**, containing oxygen, sulfur, and nitrogen atoms readily forms 1:1 metal complexes with nickel(II) and cobalt(II), with the metal and ligand in an octahedral configuration rather than in a plane (*32*). This octahedral configuration is at least partially due to the relatively small hole available in the ring for insertion of the metal.

Macrobicyclic diamines containing oxygen, sulfur, and nitrogen atoms have been prepared (**20** and **21**); these form predominantly 1:1 cryptate type complexes with a series of metal ions (*39*). Some of the metal ions which complex in chloroform include potassium, barium, silver(I), thallium(I), lithium, and sodium; and in water they include sodium, potassium, rubidium, thallium(I), silver(I), barium, and lead(II). No equilibrium constants have been reported for the reaction of metal ions with macrocycles containing three different donor groups.

Present and Future Areas of Application

The unique ion binding properties of the macrocyclic compounds coupled with their special configuration and structural properties suggest several applications for these molecules. Relatively few applications have been reported because major interest has centered on the synthesis of new macrocyclic com-

Table 9. Metal ion selectivities exhibited by antibiotics and macrocyclic polyethers. ATPase, adenosine triphosphatase.

Selectivity sequence	Type of measurement	Ref.
	Valinomycin	
K > Rb > Cs >> Na > Li	ATPase activity in mitochondria	(*43*)
Rb > K > Cs >> Na > Li	Membrane permeability	(*44*)
K > Na	Equilibrium constants	(*45*)
K > Rb > Cs > Na	Extraction	(*46*)
	Nonactin	
K > Cs > Rb > Na > Li	ATPase activity in mitochondria	(*45*)
K > Na	Membrane permeability	(*47*)
K > Na	Equilibrium constants	(*48*)
	Monactin	
K > Rb > Cs > Na > Li	ATPase activity in mitochondria	(*43*)
K > Na	Membrane permeability	(*47*)
K > Na	Equilibrium constants	(*48*)
	Dicyclohexyl-18-crown-6	
K > Na	ATPase activity in mitochondria	(*49*)
K > Rb > Cs > Na > Li	Membrane permeability	(*50*)
K > Rb > Cs, Na > Li	Equilibrium constants	(*16*)
K > Rb > Cs > Na	Extraction	(*46*)
	Dicyclohexyl-24-crown-8	
K > Rb > Li > Na	ATPase activity in mitochondria	(*49*)
K > Na	Membrane permeability	(*51*)

pounds and the thermodynamic studies of their metal binding properties. However, we see great potential use for the synthetic macrocyclic compounds as models for biological studies of active ion transport, as selective complexing agents, as agents for solubilizing ionic substances in nonaqueous solvents, and as drugs. In addition, they open for study a new field of coordination chemistry. Of the applications that have been reported, most refer to the cyclic polyether macromolecules primarily because of their unique ability to complex alkali and alkaline earth metal ions. Each of these applications is now discussed briefly. However, many of the applications given for one class of macrocyclic compounds are theoretically valid for other classes, and there are many fascinating possibilities to explore.

Macrocyclic molecules have been used as models for carrier molecules to study the phenomena of active ion transport across membranes. A large variety of naturally occurring macrocyclic antibiotics have been shown to exhibit differing degrees of ion selectivity as related to the processes of active ion transport, photosynthesis, oxidative phosphorylation, and metal binding. The synthesis of cyclic polyethers aroused immediate interest because they are the first synthetic organic molecules that clearly discriminate among sodium, potassium, and other cations. In this essential feature they are similar to the biologically produced cyclic antibiotics of the valinomycin and nonactin types, and, like them, affect ionic transport across cell membranes. Thus the polyethers can serve as convenient synthetic model compounds for their biological counterparts. In Table 9 are listed several antibiotics and cyclic polyethers, together with the metal ion selectivities which they show under various experimental conditions. The similarity between the metal ion selectivity exhibited by the antibiotics and by some macrocyclic compounds is striking and important in that a new class of model compounds has become available for the systematic investigation of active ion transport phenomena. Other potential model compounds are the macrocyclic polyamines which could very well serve as models for large cyclic molecules; for example, enzymes containing nitrogen complexing groups. It has been suggested (*40*) that metal complexes of certain macrocyclic polyamines, notably the tetradentate ligands, may serve as models for similar naturally occurring systems such as the porphyrin ring. The model compounds would be expected to exhibit unusual redox behavior, and the electrochemistry of such complexes may be of particular importance in providing the basic foundation necessary to understand the more complicated native systems. Macrocyclic tetradentate ligands have been used (*26*) as model compounds for porphyrins to study the rate of formation and dissociation of copper(II) complexes.

The selectivity demonstrated by many of the macrocyclic compounds, notably the polyethers, could lead to their use, for example, in selective ion electrodes, as selective complexing agents and as ion chelating resins. Potassium electrodes have been described (*41*) based on the cyclic polyethers dicyclohexyl-18-crown-6 and dibenzo-18-crown-6. Although these polyethers showed a 10 : 1 preference for potassium over sodium, neither gave a theoretical Nernstian electrode response. An electrode based on valinomycin was found to be superior with respect both to theoretical Nernstian response and to selectivity to the cyclic polyethers and other antibiotics tested. Macrocyclic compounds would seem to be ideally suited for applications as complexing agents and ion chelating resins in that ring size, number and kind of complexing groups, and side groups can be altered to give a wide variety of properties. For instance, as illustrated in Table 2, cyclic polyethers can be made which will selectively complex one alkali metal ion over the others.

The macrocyclic compounds in general offer a unique way of carrying out many ionic reactions in nonaqueous solvents because of the central hydrophilic cavities and the hydrophobic exteriors. Cyclic polyethers have been used to dissolve alkali metals in solvents in which they are ordinarily either insoluble or only slightly soluble (*42*). Polymerization catalysts can be made consisting of homogeneous solutions of macrocyclic complexed metal salts in the same nonpolar solvent in which the monomer is dissolved. Organic substances can be analyzed in organic solvents by solubilizing the reagent through complexation with a macrocyclic compound. The use of cyclic polyethers in organic synthesis has been demonstrated (*15*) by complexing potassium permanganate with the cyclic polyether dicyclohexyl-18-crown-6 for oxidation of olefins to carboxylic acids in benzene or toluene at room temperatures. Complexed potassium hydroxide saponifies esters more efficiently in toluene than potassium hydroxide itself does in 1-propanol (*15*). Less than 10 percent of the methyl ester of 2,4,6-trimethylbenzoate is saponified after 5 hours at 77°C when potassium hydroxide is used in 1-propanol, but 99 percent is saponified by cyclic polyether complexed potassium hydroxide after 6 hours at 100°C in toluene. In general, in these studies completely saturated polyethers such as dicyclohexyl-18-crown-6 were favored over unsaturated polyethers because of their greater solubility in organic solvents and their greater complexing efficiency.

The potential use of artificial macrocyclic compounds as drugs is obvious from the similarity of many of the macrocycles to known drugs. The cyclic polyethers are very similar to the valinomycin-nonactin type of antibiotic, both in structure and in metal selectivity and ion transport characteristics. Other antibiotics of the nigericin-monensin types are normally classified as open-chain compounds but can in solution form a macrocyclic ring through intramolecular hydrogen bonding between the OH^- and COO^- groups at the two ends of the chain. It has been postulated (*15*) that from the cyclic polyethers may come drugs combining therapeutic activity with sodium-potassium regulating capability.

The study of the chemistry of macrocyclic molecules opens up a new field of coordination chemistry in which a systematic examination of ion binding becomes possible. Since it is possible to synthesize the desired macrocycles, it is feasible to examine systematically such variables as the size, charge, and stereochemical requirements of the cation; the ring size, ring substituents, and type, number, and arrangement of ring donor atoms of the ligand; and the solvent type and solvent dielectric constant. Preliminary data indicate that in many cases the results of such studies give rise to very intriguing information. For instance, the introduction of two nitro groups on the benzene rings of the cyclic polyether dibenzo-18-crown-6 sufficiently decreases the stability of the cesium-iodide complex so that its formation cannot be measured. From the data in Table 3 it can be seen that there are large stability increases of the order of 10^2 to 10^4 as the solvent is changed from water to methanol or ethanol. Also it has been found (*18*) that the replacement of oxygen donor atoms by sulfur donor atoms in cyclic polyethers decreases the complex stability, except in the case of cations having particular affinity for sulfur, such as mercury(II).

Summary

The existence of synthetic macrocyclic molecules with hydrophilic cavities containing multiple binding atoms and with hydrophobic exteriors gives rise to extraordinary possibilities with respect to the design and synthesis of molecules with specific cation and anion binding properties. The preparation of many new macrocyclic compounds has recently been reported, but few practical applications for them have been suggested. From the information available, it is becoming clear that it should be possible to synthesize macrocycles that will have specified, or selected, ion binding properties. Cavity size can be varied to accommodate only those cations or anions within a specified narrow band of sizes. Numbers and types of coordinating atoms can be chosen to give essentially electrostatic or covalent bonding or a combination of the two in a metal-macrocycle complex. The metal ligand bond appears to be predominantly ionic in the case of the cyclic polyethers but the covalent character increases on substitution of sulfur or nitrogen for oxygen donor atoms. The essential hydrophobic exteriors of the macrocycles can be modified by the addition of side chains and groups to facilitate the solution of anions and cations in organic solvents. The structures of many macrocycles can be made to approximate naturally occurring molecules, that is, cyclic polyethers similar to macrocyclic antibiotics of the valinomycin and nonactin types and cyclic polyamines similar to porphyrins. Macrocycles are also useful as model compounds for the study of metal interactions with biological systems. The synthetic macrocycles thus represent an intriguing new area of coordination chemistry, the systematic study of which should lead to many interesting and useful chemical applications in the field of metal complexation in solution.

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