TEMPLATE REACTIONS

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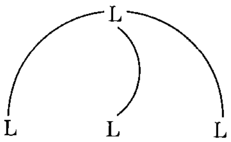
I. Introduction

During the past decade there has been a growing interest in the synthesis of multidentate ligands and in the complexes such ligands form with metal ions. The principal types of multidentate ligand are illustrated for quadridentate ligands, e.g., the tripod (**I**), the open chain (**II**), and the closed chain or macrocycle (**III**). Macrocycles may be single-ring systems, e.g., structures **IV–VIII**, or multiring systems, e.g., the cryptates (**IX** and **X**). The obvious resemblance between a



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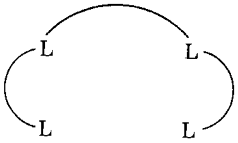

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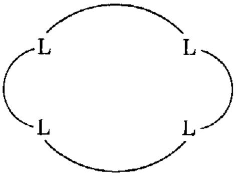

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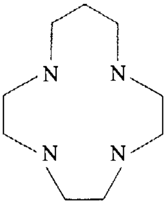

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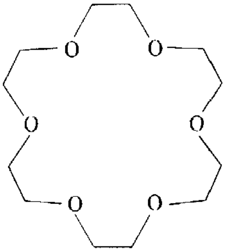

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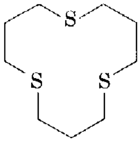

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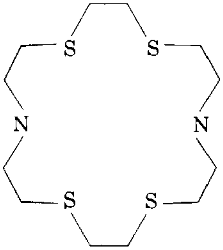

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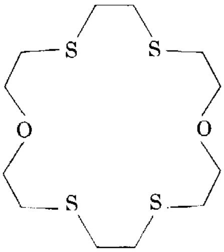

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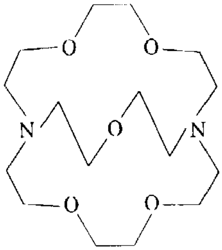

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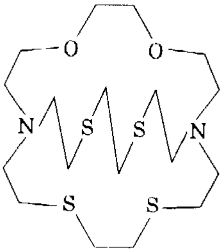
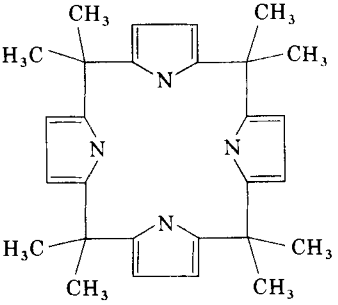


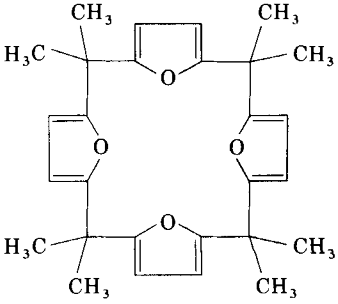
(X)

planar metal complex of structure **(IV)** and the prosthetic groups in hemoglobin, chlorophyll, and vitamin B_{12} has stimulated research on the synthesis of macrocycles and on the structure, bonding, and reactions of macrocycle–metal complexes.

For many years the synthesis of macrocycles has been a largely unsuccessful and wasteful endeavor because of the low yields, the many side products of the reactions, and the large volumes of solvents that were required to give sufficient dilution to minimize polymerization and encourage cyclization. Two exceptions were compounds **XI** and **XII**. Von Baeyer first reported the formation of **XI** from the violent reaction of pyrrole with dry acetone on the addition of *one* drop of hydrochloric acid (*142*). Subsequently, the reaction was made less violent (*44–46*) and eventually compound **XI** was obtained with an 88% yield (*121*). Ackman, Brown, and Wright condensed furan with acetone in the presence of concentrated hydrochloric acid and produced an 18–20% yield of **XII** (*1*), but attempts to broaden the scope of the reaction, by using other carbonyl compounds and a variety of furans (*8*, *22*), or to obtain mixed donor macrocycles from pyrrole and furan (*21*), gave low yields of macrocycles.

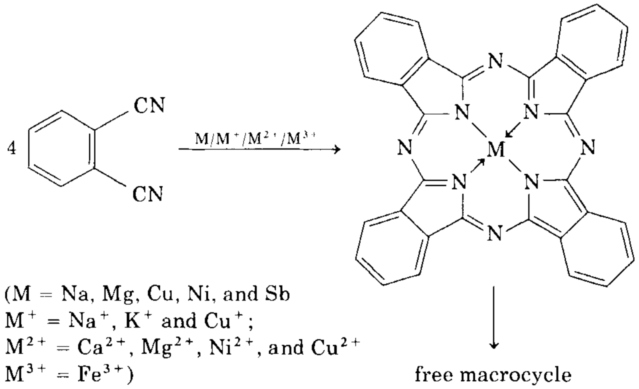


(XI)



(XII)

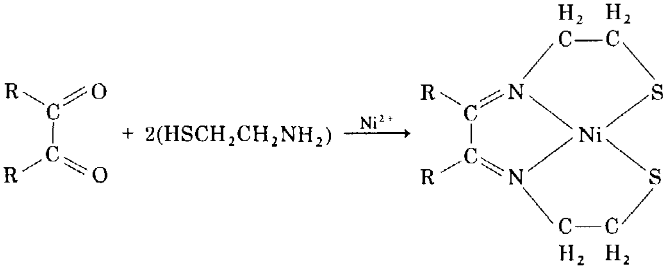
One of the first examples of a metal or metal salts facilitating the formation of a macrocycle was the self-condensation of *o*-phthalonitrile to give metal phthalocyanine complexes from which the free ligand was easily displaced (*89*):



(1)

(M = Na, Mg, Cu, Ni, and Sb
$M^+ = Na^+$, K^+ and Cu^+;
$M^{2+} = Ca^{2+}$, Mg^{2+}, Ni^{2+}, and Cu^{2+}
$M^{3+} = Fe^{3+}$)

The role of the metal ions in promoting cyclization was not understood until much later when Hurley *et al.* (*74*) isolated a series of intermediates in the reaction between 1,3-diiminoisoindoline with nickel chloride. The widespread utilization of metal ions in the synthesis of macrocycles was developed largely through the work of the group led by Busch. The formation of macrocycles using Ni(II) ions (*136*) and complexes (*138*), e.g.,



(2)

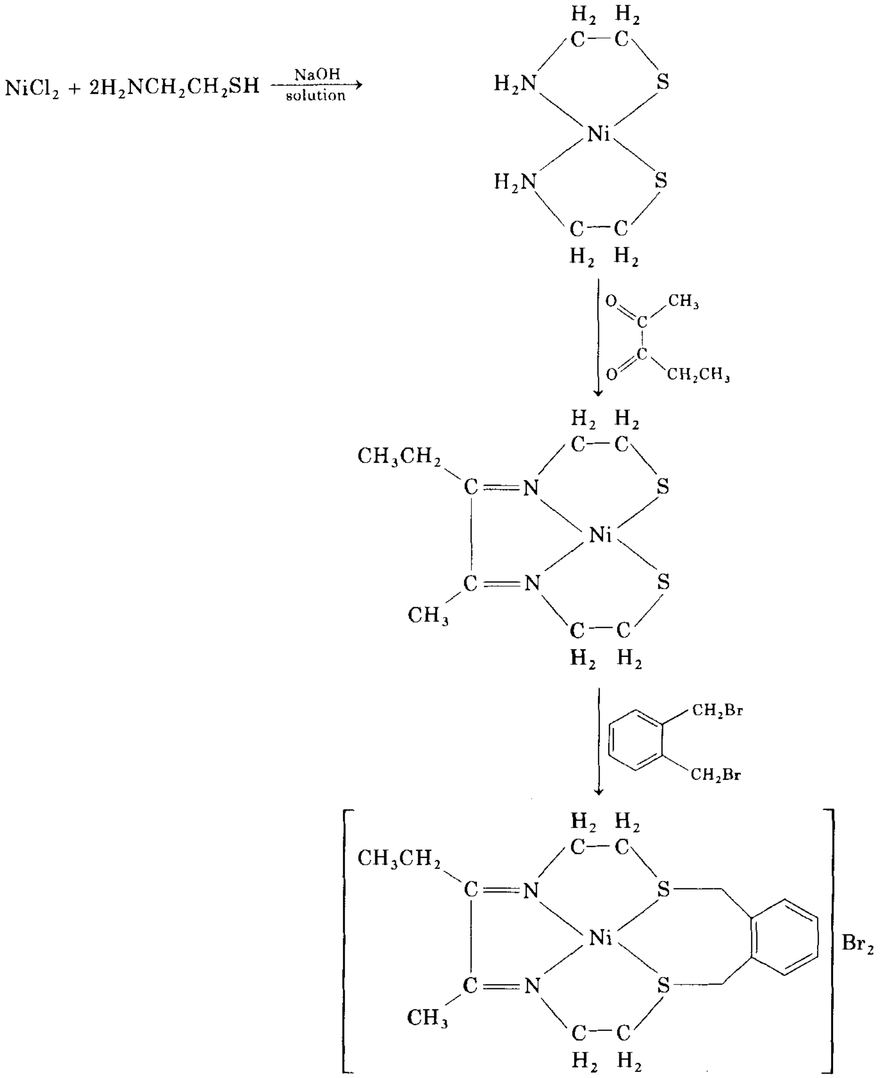
$$\mathrm{Ni(H_2NCH_2CH_2S)_2 + 2CH_3I \rightarrow Ni(H_2NCH_2CH_2SCH_2)I_2} \tag{3}$$

led Busch to recognize that the coordination sphere of the metal ion would hold the reacting groups in the correct positions for cyclization reactions, i.e., the metal ion acts as a "template." Since the time of these observations, many more examples of template reactions have been discovered; these are quoted in reviews on macrocycle synthesis and the properties of macrocycle–metal complexes (*9, 12, 23, 24, 30, 39, 85, 86, 88, 94, 110*).

II. Types of Template Effect

A. Kinetic

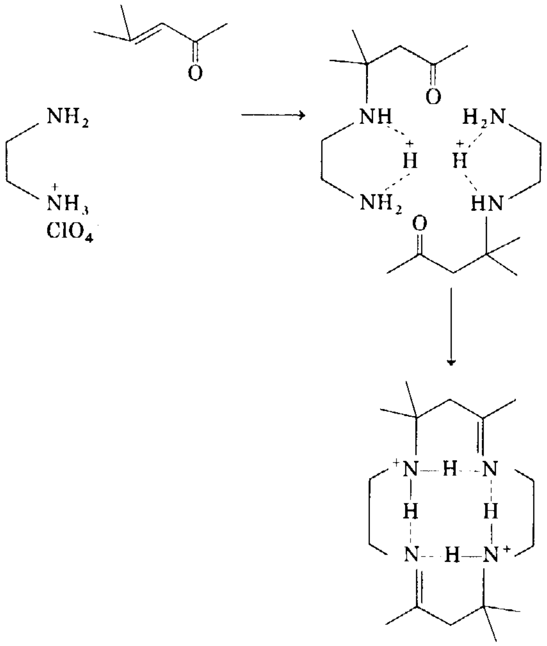
A reaction is described as proceeding by a kinetic template effect if it provides a route to a product that would not be formed in the absence of the metal ion and where the metal ion acts by coordinating the reactants. An alternative description for this process is the coordination template effect that more aptly describes how the stereochemistry imposed by the metal ion, through coordination, promotes a series of controlled steps in a multistep reaction, e.g., Scheme 1 (*17, 136, 137*).



SCHEME 1

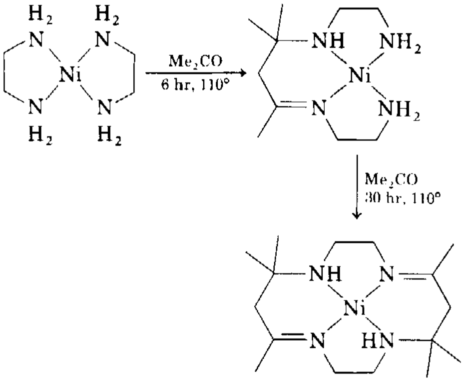
B. THERMODYNAMIC

Macrocycles formed by reactions that are described as proceeding by the thermodynamic template effect can take place in the absence of metal ions (*40*),



(4)

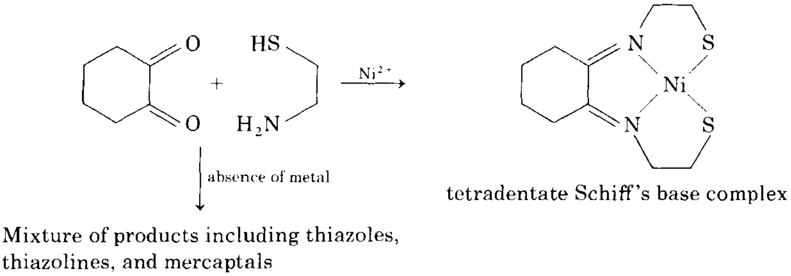
but in this case the metal promotes the formation of macrocycle by removing it from the equilibrium as a macrocycle-metal complex (*39*), e.g.,



(5)

C. Equilibrium

The equilibrium template effect, so named by Thompson and Busch (*137*), is a combination of the two previous effects. In this case the reactants react reversibly to give an intermediate that forms a stable complex with the metal so that all the reactants proceed to a macrocycle–metal complex. The distinctive feature of the equilibrium effect is the formation of *different* products in the metal-assisted and metal-free reactions (*137*), e.g.,



(6)

whereas in the thermodynamic effect the two reactions give the *same* products.

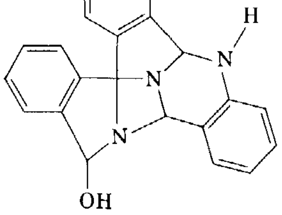
III. Template Synthesis of Macrocycles

A requirement for a metal ion template has been established for the majority of reactions described in this section. Other reactions described are those in which metal ions, particularly Na^+, are part of the stoichiometry of the reactions but for which a template function has not been identified.

A. NITROGEN-DONOR MACROCYCLES

1. *Macrocycles with Benzenoid Units*

The self-condensation of *o*-aminobenzaldehyde has been the most studied reaction under this heading. In the absence of metal ions, self-condensation was found (*6*, *127*) to be a very slow reaction that gave a mixture of products including a bisanhydrotrimer and a trisanhydrotetramer. The same reaction was repeated by McGeachin (*95*) and by Taylor *et al.* (*135*) and a structure (**XIII**) was assigned (*135*) to the bisanhydrotrimer. When compound **XIII** is heated with an equimolar amount of $[Ni(H_2O)_6](NO_3)_2$ in absolute ethanol for 3 hr, a complex of macrocycle **XIV** is formed. Eichhorn and Latif (*50*)



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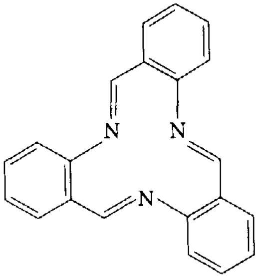

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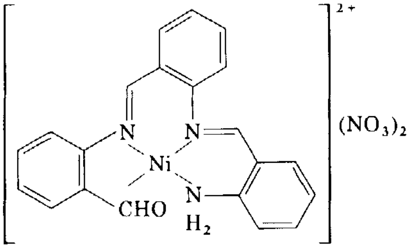

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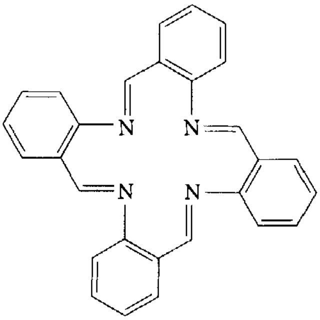
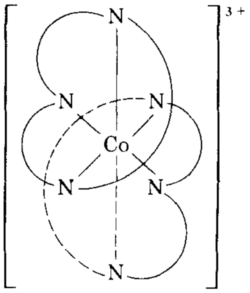


(XVI)

carried out the self-condensation of *o*-aminobenzaldehyde in the presence of divalent metal nitrates and found that Ni and Co formed M(II) complexes of the trisanhydrotrimer (**XIII**), which were assigned as having structure **XV**; Cu gave Cu(I) complex of **XIII**, and Mn gave uncomplexed **XIII**. Later investigation (*54, 96, 97, 135*) of the self-condensation of *o*-aminobenzaldehyde in the presence of Ni(II) salts showed that a mixture of complexes containing trimeric (**XIV**) and tetrameric (**XVI**) macrocycles {tribenzo[*b,f,j*][1,5,9]triazacycloduodecine (TRI) and tribenzo[*b,f,j,n*][1,5,9,13]tetraazacyclohexadecine (TAAB), respectively} was formed. Nickel(II) complexes of **XIV**, i.e., $[Ni(TRI)(H_2O)X_2]$, with pseudo-octahedral geometry around nickel, and of **XVI**, i.e. $[Ni(TAAB)]X_2$, with square planar geometry around nickel, have been obtained with a variety of counteranions (X^- or Y^{2-}). In general, the nature of the complexes depends on the coordination geometry preference of the metal ion, e.g., self-condensation in the presence of Cu(II) ions gives only the square planar complex $[Cu(TAAB)]^{2+}$, whereas the same reaction with Co(II) ions [from $CoBr_2$ and with subsequent oxidation of Co(II) to Co(III) by concentrated HBr] has led to the isolation of both complexes **XIV** and **XVI** and also to the formation of octahedral complexes $[Co(TRI)_2]^{3+}$ **(XVII)** and $[Co(TAAB)X_2]^{+}$ **(XVIII)** (*34, 35*). Chemical reactions can be carried out on a macrocycle while it is bound to the metal, e.g., $[Ni(TAAB)]^{2+}$ reacts (*134*) with alkoxide ions to give compound **XIX**, and nucleophilic attack on $M(TAAB)^{2+}$ by bis(2-hydroxyethyl)methylamine or bis(2-hydroxyethyl)sulfide has led (*80*) to the formation of square pyramidal complexes **(XX)**.



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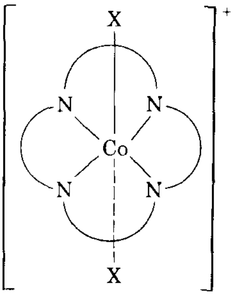

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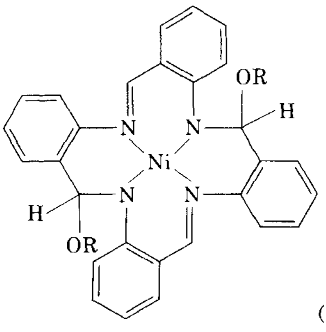
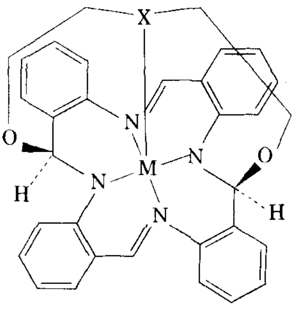


$(R = CH_3—, CH_3CH_2—)$

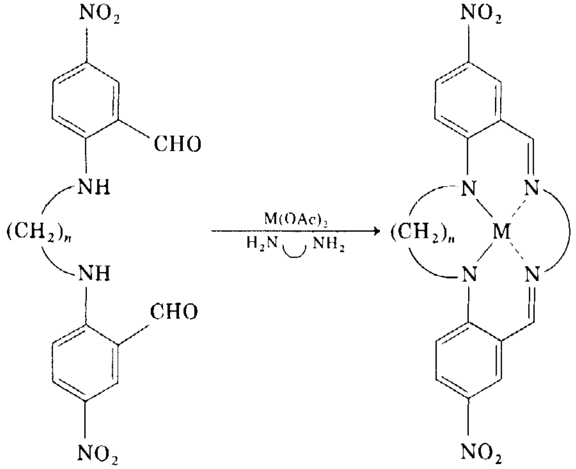
(XIX)



(M = Ni, Cu
X = S, NCH_3)

(XX)

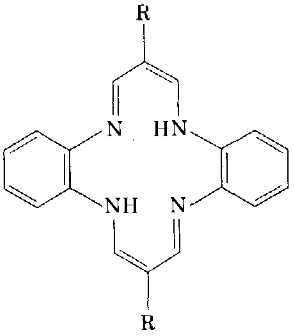
Condensation of a series of diaminodialdehydes with ethylenediamine, *o*-phenylenediamine, or 1,8-diaminonaphthalene in the presence of Ni(II), Co(II), and Cu(II) acetates has afforded a series of macrocyclic quadridentate complexes containing 14-, 15-, or 16-membered rings (*10, 11, 16*):



$n = 2,3$

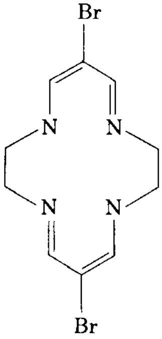
(7)

A template synthesis (*28*) has been used to form the macrocycle **XXI** by heating 1,1,3,3-tetramethoxypropane with concentrated HCl in ethanol, adding the templating agent ($CuCl_2 \cdot 2H_2O$), and refluxing for 8 hr. A yellow-green solid is obtained from this solution and refluxing this with an ethanolic solution of *o*-phenylenediamine affords the copper complex of the macrocyclic ligand. Bromomalondialdehyde has been found to react rapidly with the diacetate metal complexes of *o*-phenylenediamine (*72*) to give the macrocycle **XXII**. The yield of

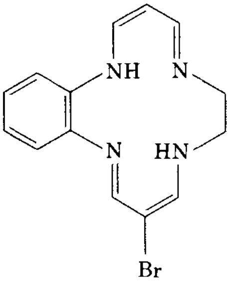


R = H **(XXI)**
R = Br **(XXII)**

complex **XXII** is 60% when Co(II) ions are used as the template agent, and almost quantitative when Cu(II) ions are used. This is a vast improvement in the yield of macrocycle and in the simplicity of the reaction over the alternative synthesis starting from propynal and using no metal ions (*68*). Macrocycles **XXIII–XXVI** can all be prepared by similar template reactions using bromomalonaldehyde with ethylenediamine, namely, with a mixture of ethylenediamine and *o*-phenylenediamine, with a mixture of 1,3-diaminopropane and *o*-phenylenediamine, and with bis(1,8-diaminonaphthalene)copper(II) acetate, respectively. The bromine atoms provide centers in which side chains can be substituted to yield macrocycle complexes that resemble metalloporphyrins.



(XXIII)



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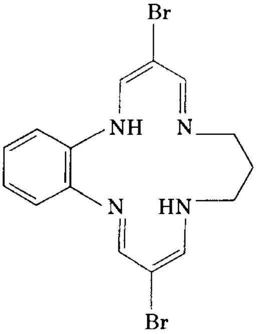

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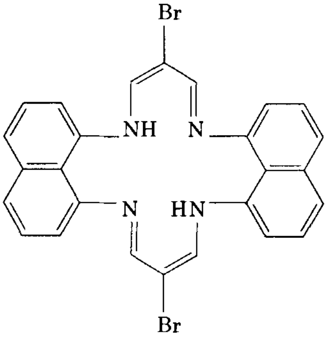
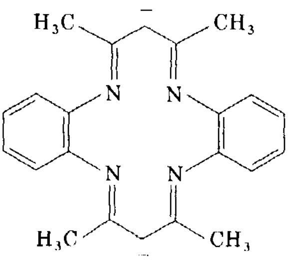


(XXVI)

The free ligand (**XXVII**) was first prepared by a template condensation of *o*-phenylenediamine with pentane-2,4-dione in the presence of Ni(II) ions (*56*), with removal of the metal ion by subsequent reaction with anhydrous HCl in ethanol, and then isolated as the hydrochloride salt. A slight modification (**XXVIII**) can be achieved as a complex of Fe(II) or Fe(III) (*57*), and a Zn(II) complex of **XXIX** is also known (*99*). The original analog (**XXX**) was prepared by Jager (*75*). At high dilution and in the presence of a trace of H_2SO_4, *o*-phenylenediamine reacts with 2,6-diacetylpyridine to yield a hexadentate macrocycle (**XXXI**) which is known to form a binuclear Cu(II) complex (*130*).



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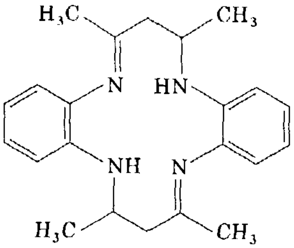

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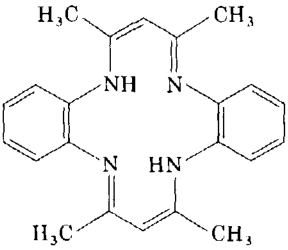

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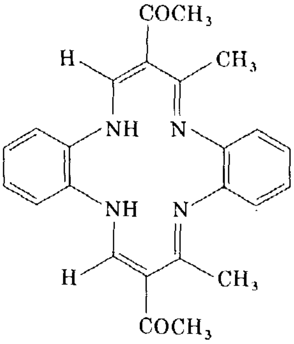

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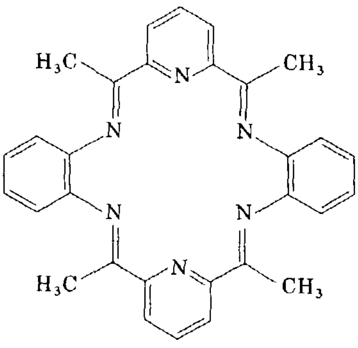
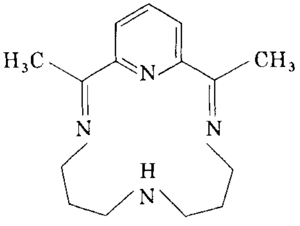
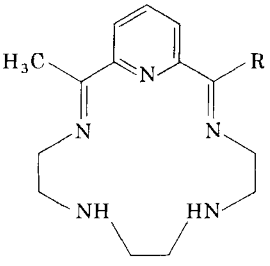


(XXXI)

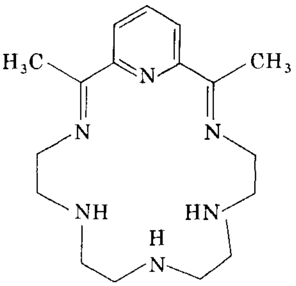
Ochai and Busch (*101*) briefly mention the synthesis of a macrocycle containing a pyridyl unit (**XXXII**) from the condensation of 2,6-diacetylpyridine with bis(3-aminopropyl)imine in the presence of Ni(II) ions. A similar condensation (*38*), using the same pyridyl source, with tetraethylaminetetramine in the presence of Fe(II) ions produces macrocycles **XXXIII** and **XXXIV**, containing five and six donor atoms, respectively. Macrocycle **XXXII** acts as a ligand with a number of metals, e.g. Cu(II) (*116*), Ni(II) complexes of the reduced ligand that give rise to meso and racemic forms (*79*), and Co(II) (*91*). The interesting complexes [RCo(**XXXII**)X]Y [R = alkyl, X = halide, Y = $B(C_6H_5)_4^-$ or PF_6^-] have been isolated; they can be considered as model compounds for vitamin B_{12} because reduction affords neutral Co(I) complexes from which Co(III) complexes can be obtained by oxidative alkylation (*52*). Macrocycle **XXXIII** forms unusual seven-coordinate Fe(III) complexes (*53*, *98*). A comprehensive study of the formation of ligands of the types **XXII**–**XXXIV** gives independent confirmatory evidence for the operation of the template effect (*113*).



(XXXII)

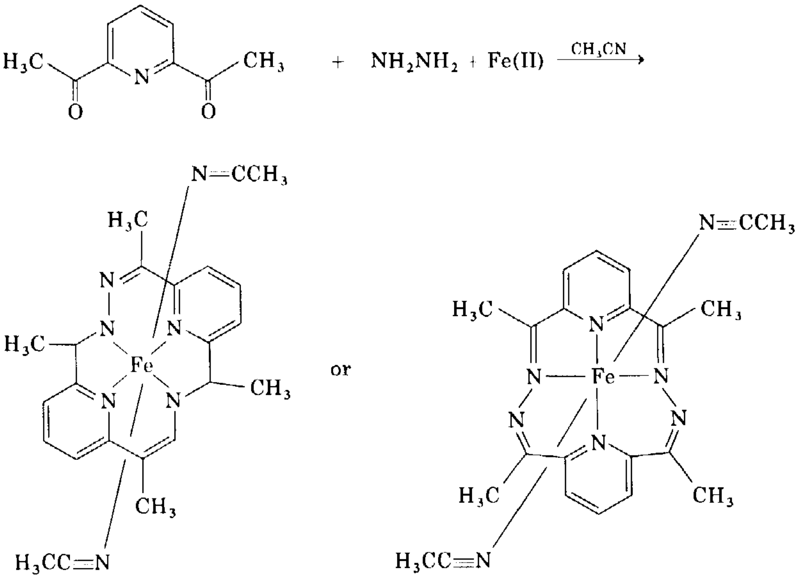


(XXXIIIa) R = Me
(XXXIIIb) R = H



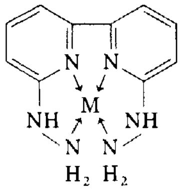
(XXXIV)

Other macrocycles containing pyridyl units (**XXXV**–**XXXVIII**) have been synthesized on Co(II) and Ni(II) templates by Lewis and Wainwright (*84*). In the case of Ni(II) the free macrocycle **XXXVIII** can be generated; it reacts almost quantitatively with Fe(II) ions to give an air-stable high-spin complex. However, most macrocycles containing pyridyl units are derived from 2,6-diacetylpyridine (*58*), e.g.,



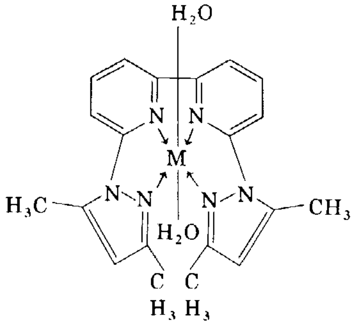
(8)

In the synthesis of **XXXIX** when using an Mg(II) template (*49*), the key reagent is 2,6-diacetylpyridine. The formation of **XXXIX** is a particularly significant result because in nature Mg(II) is bound to a porphyrin in chlorophyll, and in this reaction Mg(II) has been used successfully to cyclize a nitrogen macrocycle, thereby giving a possible indication of the conditions required for the biological synthesis of chlorophyll. The macrocycles were produced in 40–60% yield in the presence of Mg(II) ions, but in the absence of metal ions the products were of a polymeric nature.



(M = Ni, Co)

(XXXV)



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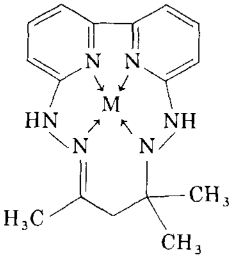
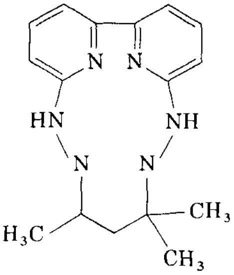
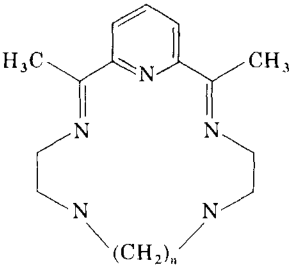


(XXXVII)

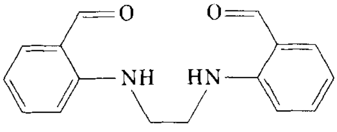


(XXXVIII)

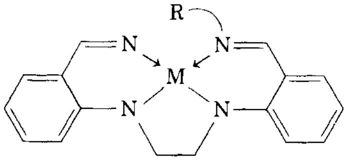


(XXXIX)

Condensation of the symmetric dialdehyde XL with diamines affords quadridentate complexes (**XLI**) when M(II) (M = Co, Ni, Cu) acetates are used as template agents, and hexadentate complexes (**XLII**) in the

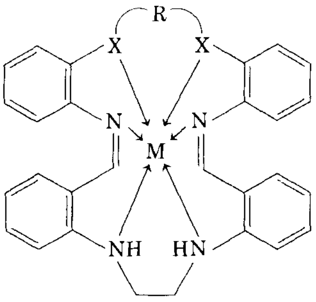


(XL)

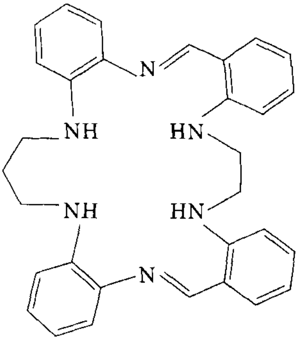


(R = —(CH$_2$)$_n$—, n = 2,3,4, and o-C$_6$H$_4$)

(XLI)

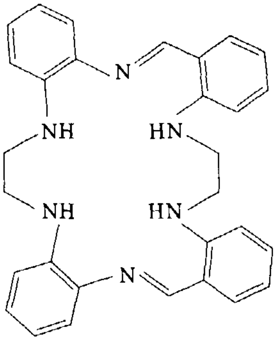


(XLII)

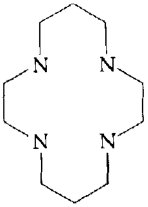


(XLIII)

presence of M′(II) (M′ = Fe, Co, Ni, Zn) perchlorates (*55*, *133*). In the absence of metal ions, the dialdehyde (**XL**) gives no detectable amounts of macrocyclic ligands when condensation reactions with diamines are attempted, and, hence, a kinetic template effect (Section II,A) is operating in these reactions. A detailed study of the reactions leading to the formation of complexes of the type **XLI** presented confirmatory evidence for template effects and also the occurrence of Lewis acid catalysis (*62*). The free ligands, e.g., **XLIII** and **XLIV**, may be liberated by reacting acetone solutions of the complexes with excess pyridine (*54*, *122*).



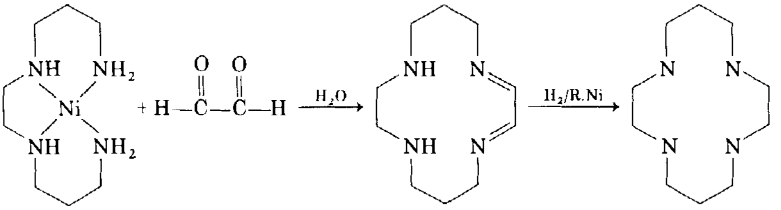
(XLIV)



(XLV)

2. *Nonbenzenoid Macrocycles*

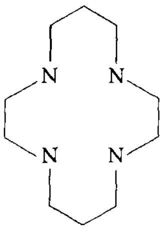
One of the simplest examples of a nitrogen-containing macrocycle is cyclam (**XLV**), which was synthesized with a 3% yield from the condensation of 1,3-bis(2′-aminoethylamino)propane and 1,3-dibromoethane in alcoholic KOH at high dilution (*18*). A more recent synthesis,



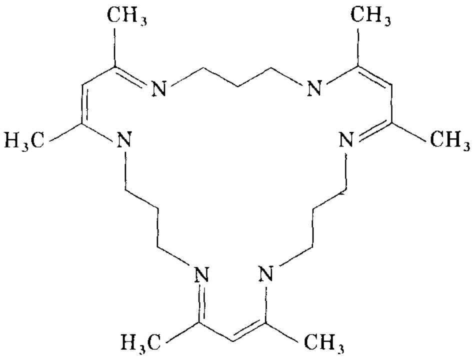
(XLV)

(9)

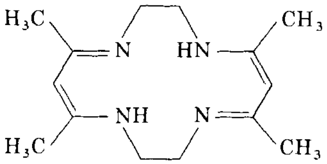
still only achieved a 20% yield (*7*). These moderate yields are typical of syntheses carried out in the absence of templating metals, although some elegant syntheses have been designed to give macrocycles, e.g., **XLVI–XLVIII**, which have subsequently formed complexes with



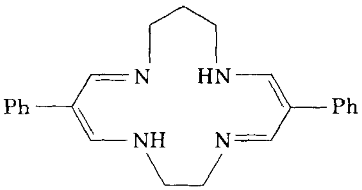
(XLV)



(XLVI)

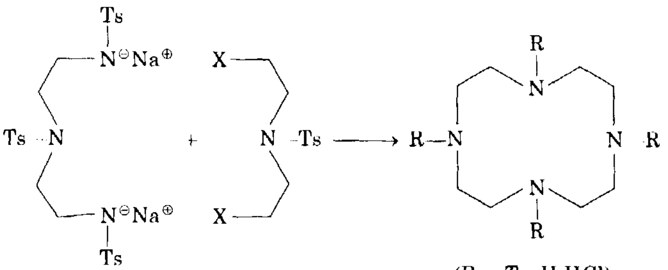


(XLVII)



(XLVIII)

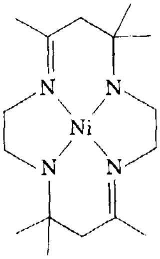
transition metals (*132*). Nitrogen analogs of crown ethers (Section III,B) containing 9- to 21-membered rings with 3–7 heteroatoms have also been synthesized by nontemplate means (*117*), e.g.,



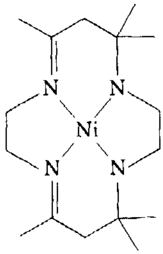
(X = OTs, OMs, halide) (R = Ts, H·HCl) (10)

and in some cases, depending on the nature of X, very respectable yields (40–90%) have been obtained.

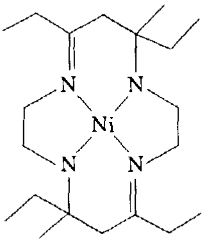
Most of the template syntheses of nonbenzenoid macrocycles originated with Curtis (*39*) and involve the condensation of metal–amine complexes with aliphatic carbonyl compounds, e.g., the reaction of acetone with tris(diaminoethane)nickel(II) perchlorate at ambient temperature leads to the isolation of three products, two of which may be represented as *cis*-**XLIX** and *trans*-**L** and the other is formed by a further interconversion of complex **L** in solution (*39*, *143*). With Cu(II) diaminoperchlorates, a mixture of cis and trans complexes analogous to **XLIX** and **L** is formed, but with Co(II) only the trans analog of **L** has been isolated. When ketones containing bulky groups are used, the reaction is much slower, e.g., there is only a small yield of **LI** from tris(diaminoethane)nickel(II) perchlorate and 2-butanone after heating at 100°C for many hours. A variety of carbonyl compounds may be used for condensation, e.g., isobutyraldehyde gives a 13-membered ring macrocycle (**LII**). A Curtis-type macrocycle (**LIII**) has been reported to form low-spin five-coordinate Co(II) and six-coordinate



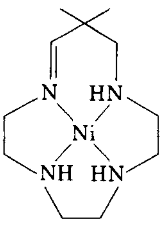
(L)



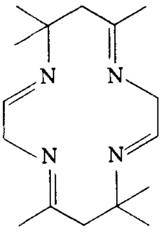
(XLIX)



(LI)



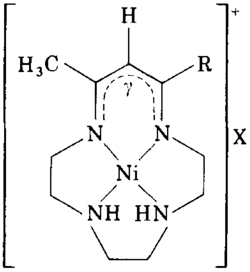
(LII)



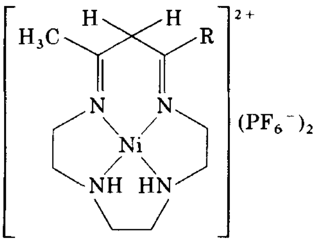
(LIII)

Co(III) complexes and also Fe(II) complexes of 13-, 14-, 15-, and 16-membered ring compounds related to macrocycle **LIII** have been prepared (*131*).

It has recently been reported (*36, 37*) that the condensation of triethylenetetramine with a β-diketone in the presence of Ni(II) ions gives rise to macrocyclic complexes (**LIV**) that undergo protonation at the methine carbon in acid solution to give a complex with a neutral macrocycle (**LV**), characterized as the PF_6^- salt. Analogous Cu(II)



(LIV)

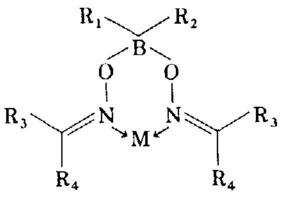


(LV)

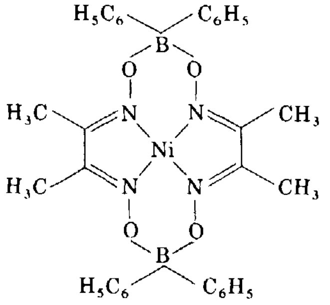
complexes, [Cu(AT)]X and $[Cu(ATH)]X_2$ ($R = CH_3$), have been obtained (*92*) from the reaction of equimolar amounts of triethylenetetramine and acetylacetone in the presence of Cu(II) ions. Reduction of **LIV** and **LV** with Raney Ni/H_2 affords saturated macrocycle complexes of Ni(II) (*71*).

3. Unusual Macrocycles

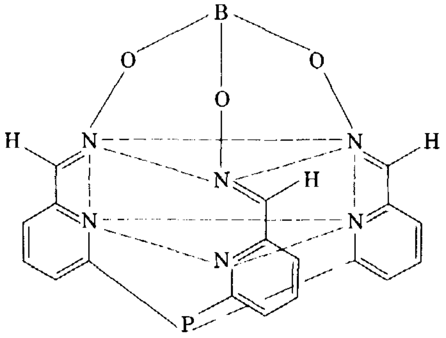
Nitrogen-donor macrocycles have also been prepared with other heteroatoms in the ring but not coordinated to the metal. Schrauzer (*124*) observed that chelate complexes (**LVI**) could be obtained when certain metal salts were present in the reaction of borinic acid ester or anhydride with oximes. Umland and Thierig (*141*) obtained a macrocycle (**LVII**) by mixing solutions of aqueous nickel(II) salts, amyl alcohol, methanolic dimethylglyoxime, and diphenylborinic acid aminoethyl ester and boiling for 1 to 2 min. The same macrocycle can be obtained as complexes with Fe(II), Cu(II), and Pd(II) ions, and these reactions can be described as kinetic template reactions. Ligand **LVIII** was synthesized (*104*) from tris(2-aldoximo-6-pyridyl)phosphine reacting with $M(BF_4)_2$ [where M = Fe(II), Co(II), Ni(II), Zn(II)] and, on distilling with BF_3, a cation is encapsulated. This synthesis was modeled on that for the clathro-chelate (**LIX**), where Co(III) was the encapsulated ion (*19*).



(LVI)

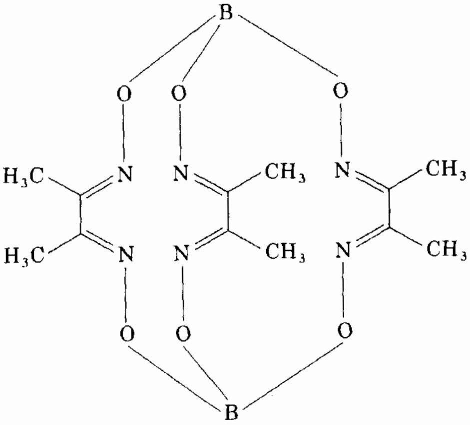


(LVII)

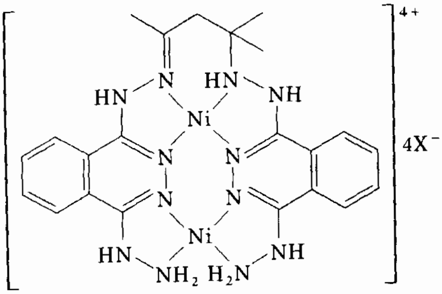


(LVIII)

Nitrogen-donor macrocycles can bind two metal ions, e.g., the reaction between acetone and 1,4-dihydrazinophthalazine is promoted by Ni(II) ions and can give two products: $[Ni_2(daph)]^{4+}$ (**LX**) and $[Ni_2(taph)]^{4+}$ (**LXI**), depending on the solvent and temperature used for the reaction (*119*).

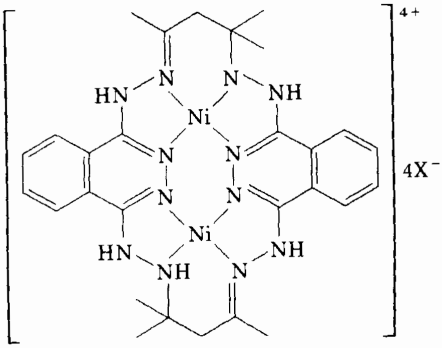


(LIX)



(X$^-$ = NCS$^-$, ClO$_4$$^-$)

(LX)

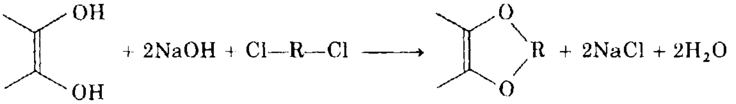


(X$^-$ = BF$_4$$^-$, NCS$^-$)

(LXI)

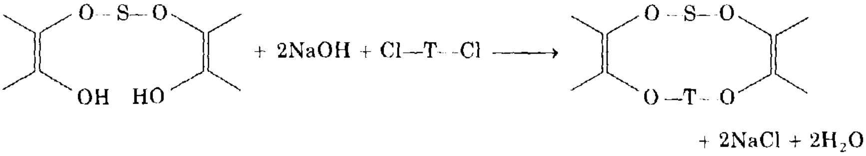
B. OXYGEN-DONOR MACROCYCLES

A great variety of polyether macrocycles, containing from 3 to 20 oxygen atoms and with ring sizes from 9 to 60, have been prepared by Pedersen (*105–108*). The synthetic routes used in cyclic polyether formation all require NaOH, but a template role for the Na^+ ion has not been established:



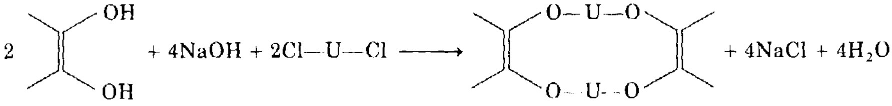
(11)

e.g., 2,3-benzo-1,4,7,10,13-pentaoxacyclopentadeca-2-ene $[R = -(CH_2CH_2O)_3CH_2CH_2]$



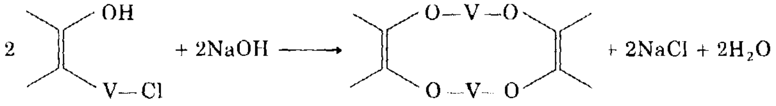
e.g., 2,3,9,10-dibenzo-1,4,8,11-tetraoxacyclotetradeca-2,9-diene $[S = T = -(CH_2)_3-]$

(12)



e.g., 2,3,11,12-dibenzo-1,4,7,10,13,16-hexaoxacyclooctadeca-2,11-diene $[U = -(CH_2CH_2O)_3CH_2CH_2$

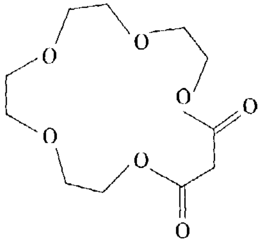
(13)



(14)

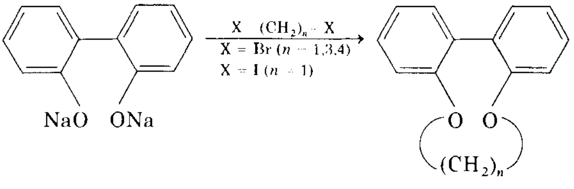
e.g., 2,3,16-17-dibenzo-1,4,15,18-tetraoxacyclooctadeca-2,16-diene $[V = -(CH_2)_{10}-]$

An interesting type of macrocycle containing ether–ester ligands (**LXII**) has been synthesized by Bradshaw (*20*), and other nontemplate



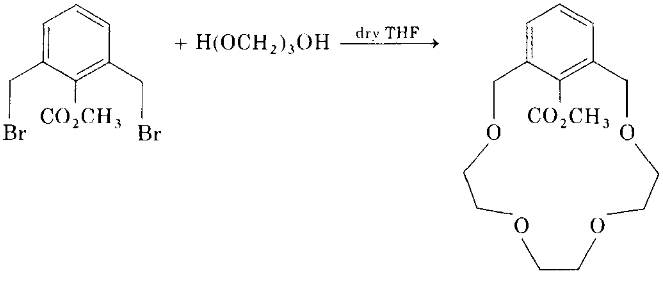
(LXII)

routes to oxygen donor macrocycles, e.g., **LXIII** (*3*) and **LXIV** (*100*) are shown by the following reactions:



(LXIII)

(15)



(LXIV)

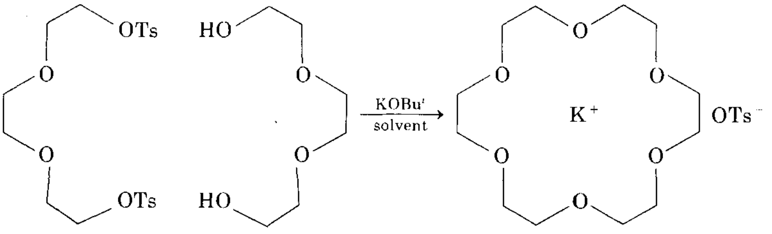
(16)

In contrast to the nontemplate function of Na$^+$ ions, the K$^+$ ion acts as a template when an equimolar mixture of diol and a ditosylate (Ts) of the same or a different diol dissolved in benzene is added slowly to potassium-*t*-butoxide to give polyethers (*42*, *43*) with $n = 5$ (20% yield), $n = 6$ (33% yield), $n = 7$ (26% yield), and $n = 8$ (15% yield), e.g.,

$$HO(CH_2CH_2O)_{n-m}\text{—}H + TsO\text{—}(CH_2CH_2O)_m\text{—}Ts \xrightarrow[\text{benzene}]{KOBu^t} \overline{\lfloor(CH_2CH_2O)_n\rfloor} + 2KOTs$$

$$(m > 1) \tag{17}$$

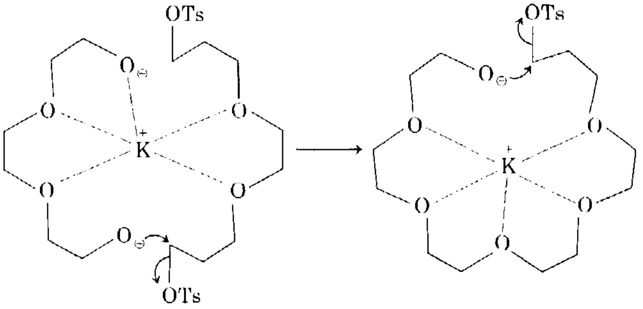
The K$^+$ ion has been shown (*63*) to act as a template in the synthesis of three crown ethers, e.g., 18-crown-6 (**V**) according to the reaction



(V)

(18)

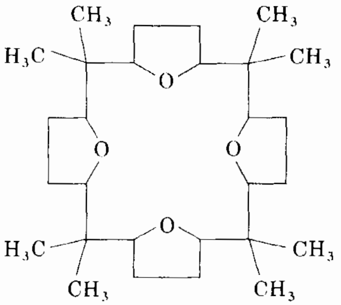
Because complex **V** binds strongly to K^+, the template synthesis may be considered to occur via **XLV** and **XLVI** that undergo ring-closure reactions. An alternative template synthesis of complex **V** has been described (*59*), which uses more readily available reagents and eliminates the need to synthesize tosylates as starting materials. Triethylene glycol and triethylene glycol dichloride are condensed together in a 10% aqueous solution of tetrahydrofuran in the presence of KOH, with the K^+ ion as the template.



(LXV) **(LXVI)**

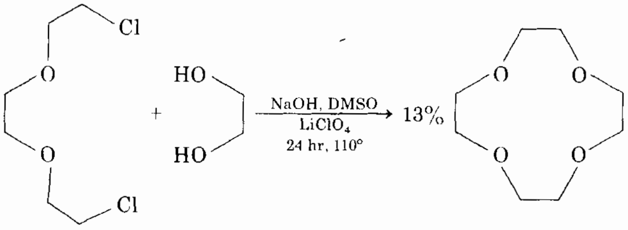
An improved synthesis of crown ethers that involves the cyclization of ethylene oxide using BF_3 in the presence of fluoroborate, fluorophosphate, and fluoroantimonate salts of the alkali, alkaline earth, and transition metals has been described (*41*). Cyclic tetramers, pentamers, and hexamers are formed in a template reaction where the ring sizes favored are those which complex most strongly with a particular cation, e.g., $Ca(BF_4)_2$ gives 50% tetramer, $Cu(BF_4)_2$ and $Zn(BF_4)_2$ gives 90% pentamer, and $Rb(BF_4)$ and $Cs(BF_4)$ give exclusively hexamer. Presumably the cation coordinates to the chain to facilitate cyclization and, because such a complex is already positively charged, complex formation prevents secondary reactions via oxonium salts that would degrade the growing chain to dioxane.

The reaction between acetone and furan in the presence of strong acid has been shown to exhibit a pronounced increase in the yield of complex **XII** with the addition of Group I and Group II metal salts (*27*). Yields of **XII** have been improved, e.g., 40–45% by the addition of $LiClO_4$ and 39–43% by the addition of perchlorates of calcium, magnesium, and zinc, from the 18–20% yield obtained (*1*) without added metal salts. No increase in yield was obtained when tetrabutylammonium perchlorate was added, thus proving the template action of the Group I and Group II metal ions (*27*). Hydrogenation of **XII** gives the saturated macrocycle **LXVII** that shows much stronger donor properties than the unsaturated macrocycle (**XII**). Recently, transition metal templates have been found to give enhanced yields of **XII** with $Ni(ClO_4)_2$ affording a yield comparable to $Mg(ClO_4)_2$ (*115*).

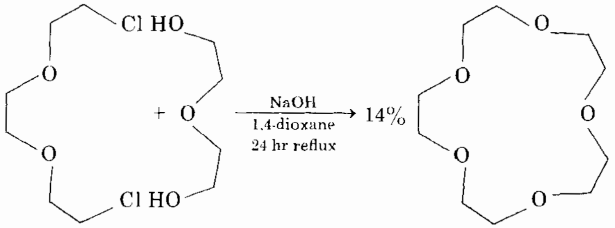


(LXVII)

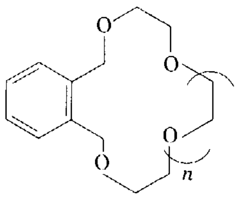
The use of a Li^+ ion template (*27*) has been extended (*31*) to the synthesis of a crown compound,

 (19)

and the same workers have also described the use of a Na^+ ion template,

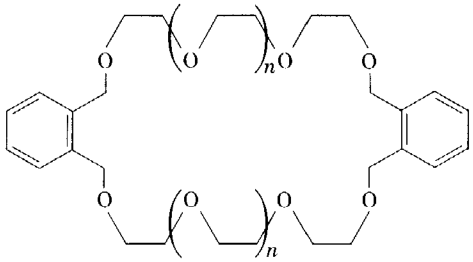
 (20)

A template synthesis using Group I metal ions has recently been developed (*114*) for producing crown ether compounds from substituted benzenes, furans, and thiophenes, e.g., the reactions of 1,2-bis(bromoethyl)benzene with disodium or dipotassium glycolates produced polyethers (**LXVIII** and **LXIX**) together with polymeric material,



($n = 0$–6)
yields 1–50%

(LXVIII)



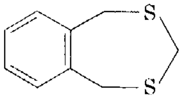
($n = 0$–2)
maximum yield 24%

(LXIX)

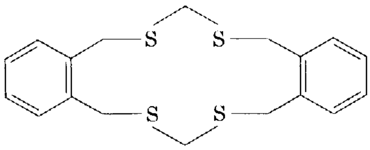
whereas with dilithium glycolates only complex **LXVIII** was obtained and the reaction was much slower.

C. Sulfur-Donor Macrocycles

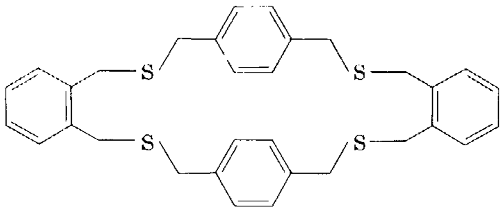
A wide range of macrocyclic polythioethers are known and have been obtained by elegant synthetic routes (*102*), yet relatively few of these macrocycles have been by template methods, unless the sodium ion serves to coordinate the sulfur atom in the reactions of disodium salts of thiols with dihalides. Some examples of macrocycles prepared by this route are **LXX–LXXII** (*3*), **LXXIII** and **LXXIV** (*120*), and **LXXV** (*15*).



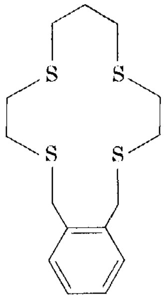
(LXX)



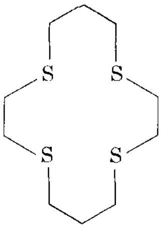
(LXXI)



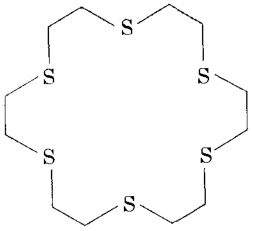
(LXXII)



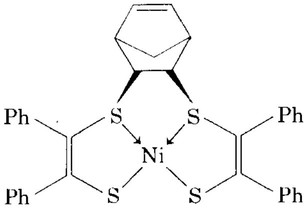
(LXXIII)



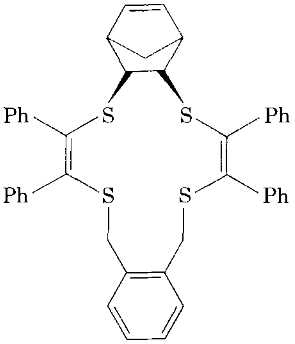
(LXXIV)



(LXXV)



(LXXVI)



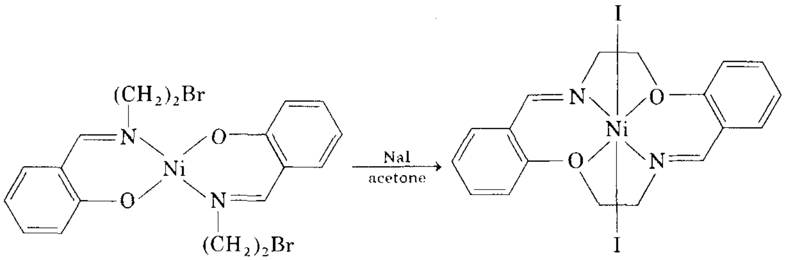
(LXXVII)

A definite template requirement does, however, exist in one case (*125*). The intermediate **LXXVI** had first to be obtained, and it was refluxed with a calculated amount of α,α'-dibromo-*o*-xylene to give a green crystalline solid. The free macrocycle (**LXXVII**) was liberated by dissolving the solid in methanol.

D. MIXED DONOR MACROCYCLES

1. *Nitrogen and Oxygen*

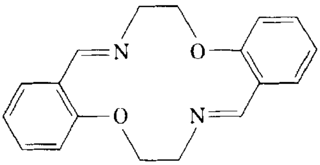
The template synthesis of mixed nitrogen and oxygen donor macrocycles are mainly based on substituted salicylaldehydes or salicylaldehyde–metal complexes (*82*), e.g.,



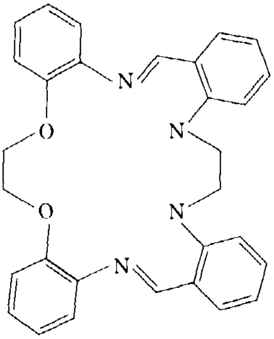
(21)

(LXXVIII) **(LXXIX)**

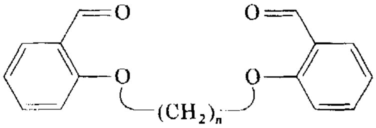
The imine ether (**LXXIX**) can also be formed by heating the iodo analog of **XXVIII** in acetone, but the scope of the reaction is limited by proximity of the side-chain halide to the coordinated phenoxide and to ethyl and *n*-propyl side chains. The free macrocycle (**LXXX**) is obtained by hydrolyzing **LXXIX** with water—a reaction that occurs rapidly at room temperature. The macrocyclic ligand (**LXXXI**) was obtained (*55*, *133*) using Zn(II) perchlorate as the template for reacting 4,7-diaza-2,3:8,9-dibenzodiene-1,10-dione with 1,2-di(*o*-aminophenoxy)-ethane. Reaction of the dialdehyde (**LXXXII**) with diamines in the presence of Ni(II) ions followed by hydrolysis of the intermediate complex, which is analogous to **LXXIX**, affords **LXXXIII** (*4*, *5*). Ligand **LXXXIV** can be obtained according to Equation (22)



(LXXX)

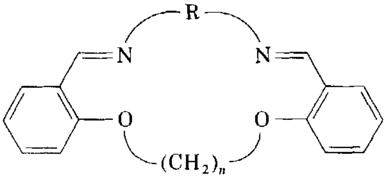


(LXXXI)



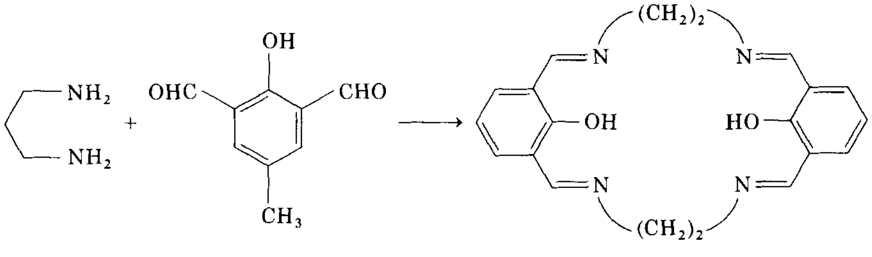
(n = 2,3)

(LXXXII)



(n = 2,3; R = $-(CH_2)_3-$, $-CH_2CH(CH_3)-$, C_6H_4-)

(LXXXIII)



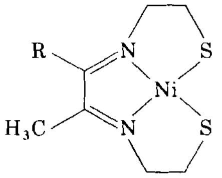
(LXXXIV)

(22)

only when a metal salt is present for complexation (*112*). In the form shown, it forms mononuclear complexes with Ni(II), but when the hydroxyl groups are deprotonated it forms binuclear complexes (*73*) with the metal ions Mn(II), Fe(II), Ni(II), Cu(II), and Zn(II).

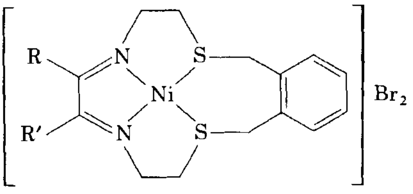
2. *Nitrogen and Sulfur*

The most common template syntheses have been for macrocycles containing the donor atoms in the ratio of 2:2, e.g., reaction of the Ni(II) complexes (**LXXXV**), formed by condensation of α-diketones with β-mercaptoamines in the presence of Ni(II) ions, with α,α′-dibromo-*o*-xylene affords **LXXXVI** through a kinetic template effect (see Section II,A) (*136–138*). Reaction with acetone links the coordinated amine groups of dithiodiamine to form the macrocycle complex **LXXXVII** (*23*).

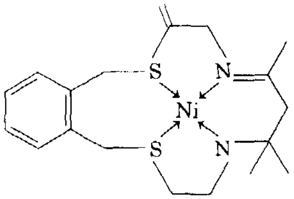


[R = CH_3, Ni(BE)
= C_5H_{11}, Ni(OE)
= C_2H_5, Ni(PE)
= C_6H_5, Ni(PPE)]

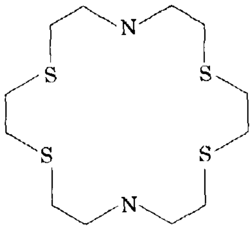
(LXXXV)



(LXXXVI)

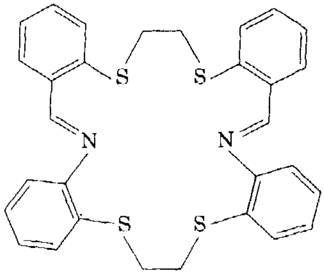


(LXXXVII)

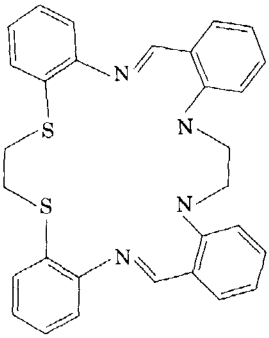


(LXXXVIII)

Macrocycle **LXXXVIII** was prepared (*13*) in an 8% yield from the reaction of the disodium salt of ethane-1,2-dithiol with di(2-bromoethyl)amine in ethanol at high dilution, and it was found to complex with Ni(II) and Co(II) ions when these were added as salts. A macrocycle containing the same donor atoms (**LXXXIX**) has been obtained in the form of complexes (*87*) by the template reactions of 1,2-bis(2-aminophenylthio)ethane and 1,4-bis(2-formylphenyl)-1,4-dithiabutane with Ni(II) and Co(II) perchlorates. Iron, cobalt, nickel, and zinc as their M(II) perchlorates have been used as templates in the formation of **XC** (*55*, *133*).

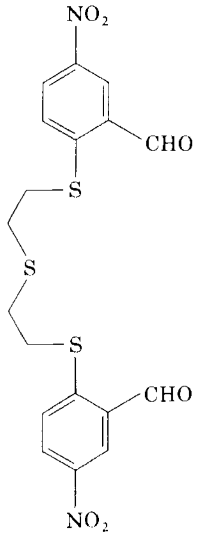


(LXXXIX)

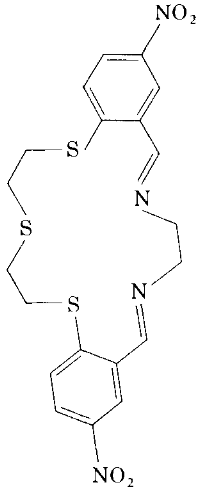


(XC)

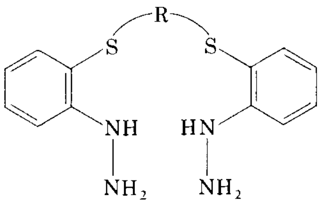
Macrocycles with 2 nitrogen and 3 sulfur donors have been prepared (*14*) by a template synthesis in which the dialdehyde (**XCI**) is condensed with primary diamines, e.g., ethylenediamine gives **XCII** in boiling acetonitrile containing Fe(II) perchlorate. The reaction is typical of template condensation between carbonyl compounds and primary amines. An unusual monanionic macrocyclic ligand was produced (*2*) when formaldehyde was condensed with the hydrazine (**XCIII**) instead of a primary amine in the presence of Ni(II) salts, and complexes **XCIV** have been characterized.



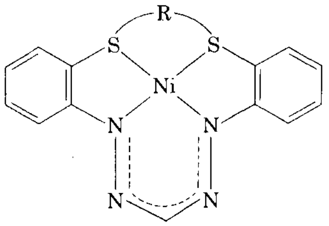
(XCI)



(XCII)



(XCIII)

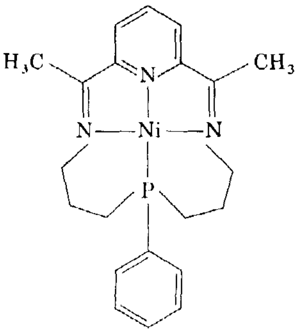


(R = $-(CH_2)_2-$, $-(CH_2)_3-$)

(XCIV)

3. Nitrogen and Phosphorus

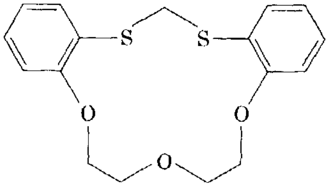
The first macrocyclic ligand containing nitrogen and phosphorus donors has been prepared (*118*) by refluxing bis(3-aminopropyl)phenylphosphine with 2,6-diacetylpyridine in an ethanolic solution containing $NiCl_2 \cdot 6H_2O$. A four-coordinate complex $[Ni(pn_3)]$ (**XCV**) is obtained, but, if $NiBr_2 \cdot 6H_2O$ or $NiI_2 \cdot 6H_2O$ are used as templates followed by addition of NH_4PF_6, a five-coordinate complex $[Ni(pn_3)X]$ (X = Br, I) results.



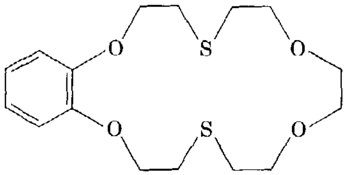
(XCV)

4. *Oxygen and Sulfur*

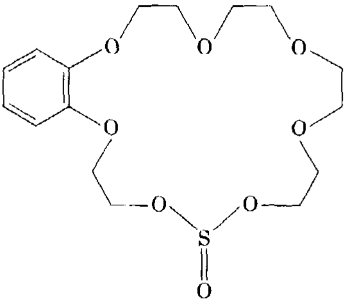
A number of mixed macrocycles have been prepared. A template requirement has not been established unless the sodium ion serves to coordinate to sulfur and oxygen in the reaction of cyclic vicinal mercaptophenols or dithiols with equivalent proportions of terminal-substituted ether dichlorides in the presence of sodium hydroxide (*109*) and in the reaction of 1,2-dibromoethane with the disodium salt of 3-oxapentane-1,5-dithiol at high dilution (*15*). Macrocycles **XCVI–XCVIII** were prepared by the former route, and **XCIX**, in low yield due to extensive polymerization, by the latter.



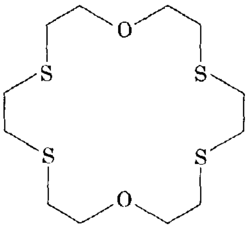
(XCVI)



(XCVII)



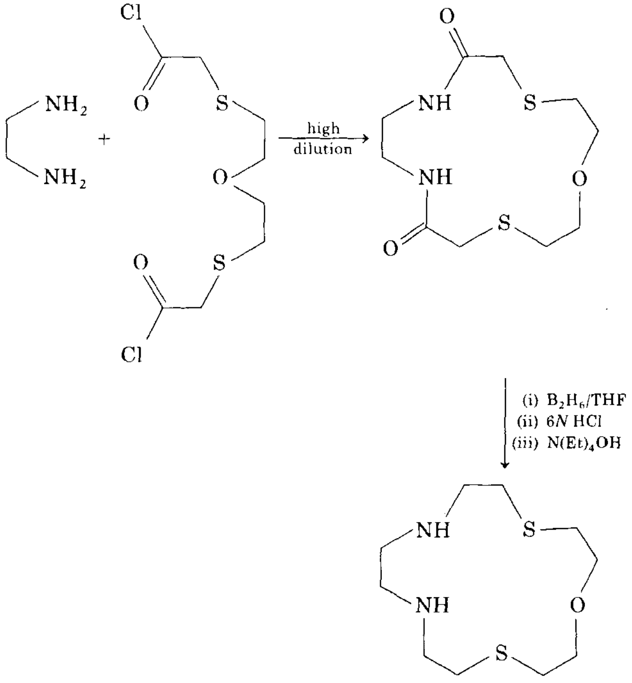
(XCVIII)



(XCIX)

5. *Nitrogen, Oxygen, and Sulfur*

A few compounds containing N, O, and S atoms have been synthesized (*29*, *47*, *48*), but no template requirement has been established. The following is a typical preparation (*111*):



(23)

IV. Choice of Templates for Specific Syntheses

The metals that have been most widely used as templates are shown in Table I. Two correlations arise from the syntheses described in Section III.

1. An effective template metal ion binds strongly to the donor atoms of the macrocycle or its precursors, e.g., K^+ is the most common template for synthesis of crown ethers and forms definite complexes with a wide variety of crown ethers.

2. The preferential coordination geometry of the template metal ion determines the nature of the macrocycle that is formed, e.g., Ni^{2+} and Cu^{2+} are particularly effective template ions for the synthesis of N-donor macrocycles containing 4 nitrogen atoms that can be arranged in a plane and, hence, form a square planar macrocycle-metal complex.

The preference of a metal for a particular ligand is not always the overriding consideration as was demonstrated (*115*) for **XII** where

TABLE I

SECTION OF THE PERIODIC TABLE SHOWING METALS KNOWN TO ACT AS TEMPLATES (ENCIRCLED)

IA	IIA	IIIA	IVA	VA	VIA	VIIA	VIII	IB	IIB
H									
Li	Be								
Na	Mg								
K	Ca	Sc	Ti	V	Cr	Mn	Fe Co Ni	Cu	Zn
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru Rh Pd	Ag	Cd

Ni(II) ions, most commonly used in the synthesis of N-donor macrocycles, were found to be as effective as Mg(II) ions.

The significance of the counteranion in metal template reactions has received little attention. Where reactions are carried out in solvents with low polarities and low dielectric constants, namely, most organic solvents, the effectiveness of the metal template ion will be related to its availability in solution, i.e., dissociation of the salt. For the Li^+ ion in the template synthesis of **XII**, the order of yields, $LiClO_4 > LiCl > Li_2SO_4$ (*27*, *115*), has been correlated with the dissociation energies of the salts (*115*).

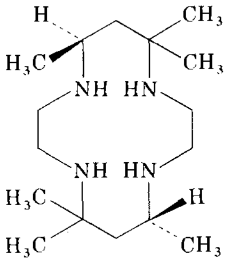
V. Physical Studies of Template Reactions

Claims that metal ions are exercising a template effect are obviously justified in situations where enhanced yields of macrocycle are obtained or partially cyclized, macrocycle–metal complexes, which react further to give macrocycles, are isolated. In other situations, especially the formation of crown ethers, whether the metal ion is exercising a template effect is hard to determine, e.g., Eq. (18) (Section III,B). In this case the template action of the K^+ ion was established (*63*) by allowing 1 mole each of tri- and tetraethylene glycol to compete for 1 mole of the tosylate in the presence of either potassium tertiary butoxide or tetra-*n*-butylammonium hydroxide. In both reactions, the same ratio of the two possible macrocycles was obtained but the yield was greatly diminished in the reaction containing tetra-*n*-butylammonium hydroxide. The fact that the ratio of products was the same for the nontemplate reaction and the reaction where the K^+ ions acted as templates was interpreted (*63*) as showing that the oxygen cannot be bound to the potassium ion when the first tosyl group is lost because such a situation would not lead to the equal probability of macrocycles as observed. The metal acts by complexing to the oxygen before the second tosyl group is lost so that cyclizing groups are held in close proximity and ring closure is aided.

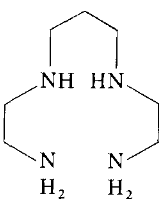
Template reactions have been monitored by NMR spectroscopy (*126*) for the reaction of Na^+ ions with dibenzo-18-crown-6 in *N*,*N*-dimethylformamide. One drawback of this technique is that the presence of paramagnetic ions, i.e., many transition metal ions, would cause appreciable broadening of the resonances.

The kinetic nature of the template effect for the reaction of 2,3-pentanedionebis(mercaptoethylimino)Ni(II) with α,α'-dibromo-*o*-xylene and benzyl bromide, i.e., the final step in Scheme 1 (see Section II,A) has been demonstrated using UV/visible spectroscopy (*17*). Spectrophotometric scans as a function of time while the reaction was taking place showed a single isosbestic point for the dibromoxylene with no evidence of any other absorption. For the benzyl bromide reaction, the scans showed the formation of an intermediate in a large enough amount to dominate the spectrum. The lack of intermediates in the dibromoxylene reaction was taken to suggest that a single rate-determining step dominates the reaction; it is, thus, an example of the kinetic template effect.

The driving force toward formation of a macrocycle has been related to stability constants by Cabbiness and Margerum (*25*). In aqueous solution it was found that compound **C** formed a more stable complex with Cu(II) than did compound **CI**, and it was concluded that differences in configuration and solvation properties of the free ligands must in some way contribute to the difference in stability of the two complexes. Similar studies were carried out for the complexation of cyclam (**XLV**) and **CI** with Ni(II) ions, and again an enhanced stability of the cyclic ligand (**XLV**) was observed (*69*, *70*). Comparison between any conformations, bond strengths, ΔH and ΔS values for the two



(C)



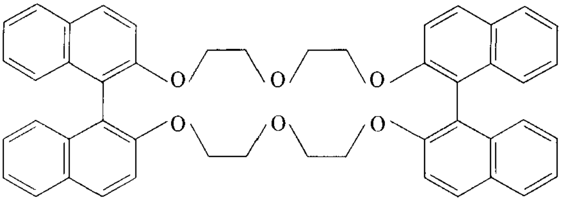
(CI)

ligands were made. In terms of ΔS changes, complexation of the open-chain ligand (**CI**) is more favorable since a greater loss of entropy results for this ligand than for the cyclic ligand. Equilibrium and calorimetric studies show that a very negative ΔH for the cyclam complex is enough to overcome the ΔS handicap. The extra stability of the macrocyclic–metal complex, which has been described as the "macrocyclic effect" (*25*), has been explained in terms of solvation differences: For cyclam, steric hindrance limits hydrogen bonding of the solvent molecules to the N-donors, whereas in **CI** the open chain makes the N-atoms relatively more accessible. In consequence of the hydrogen-bonding differences, cyclam is less solvated and less energy is required to break the hydrogen bonds with the solvent than for the open-chain ligand. If the macrocyclic effect depends on the solvation properties, it should be independent of the metal ions, providing the metal ion coordination geometry is suitable, as was found for Cu(II) and Ni(II) ions which both have a tendency to form square planar complexes. Similarly, if the hydrogen-bonding potential of the solvent is reduced then the solvation of the macrocycle should diminish giving only a small macrocyclic effect for this situation. Experiments with the sulfur analog of **XLV** and **CI** complexing to Ni(II) ions in nitromethane, which is a relatively poor hydrogen-bonding solvent, indeed showed a decreased macrocyclic effect (*128*).

VI. Applications of Template Reactions

The use of metal ions as templates for macrocycle synthesis has an obvious relevance to the understanding of how biological molecules are formed *in vivo*. The early synthesis of phthalocyanins from phthalonitrile in the presence of metal salts (*89*) has been followed by the use of Cu(II) salts as templates in the synthesis of copper complexes of etioporphyrin-I (*32*), tetraethoxycarbonylporphyrin (*26*), etioporphyrin-II (*78*), and coproporphyrin-II (*81*). Metal ions have also been used as templates in the synthesis of corrins, e.g., nickel and cobalt ions in the synthesis of tetradehydrocorrin complexes (*64*) and nickel ions to hold the two halves of a corrin ring system while cyclization was effected (*51*), and other biological molecules (*67, 76, 77*).

The ability of crown ethers to bind selectively to particular Group IA and Group IIA metal ions, because of the relationship between hole size and metal ion radius, has led to considerable interest in them in relation to membranes (models for selective ion transport), antibiotics (similar polyether structure), organic synthesis [solubilization of inorganic reagents leading to milder routes for oxidation (*122*), nucleophilic substitution (*123*), fluoridation (*90*)] and extraction of alkali cations (*140*). Crown ethers have also been used catalytically by solubilizing the active agent (*93*, *103*). A crown ether, dibinaphthyl-22-crown-6 (**CII**), has recently been synthesized by a template synthesis that is able to extract α-phenylethylammoniumhexafluorophosphate from chloroform and has the ability to distinguish between *R* and *S* enantiomers of phenylethylamine. The fact that such separations can be achieved in a separating funnel emphasizes the considerable potential of the chiral crown ethers (*33*, *60*, *61*, *65*, *66*, *83*, *129*, *139*).



(CII)

The variety of macrocycles that have already been prepared by template reactions (see Sections III and VI) suggest that, in designing a macrocycle synthesis to meet a future need, the use of a metal ion template should not be ignored.

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