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TEMPLATE REACTIONS

MARIA DE SOUSA HEALY and ANTONY J. REST

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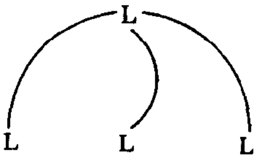
I. Introduction

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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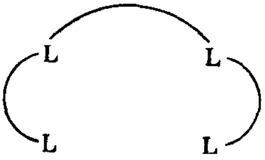

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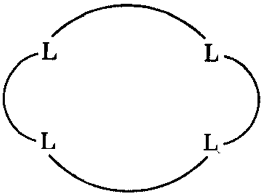

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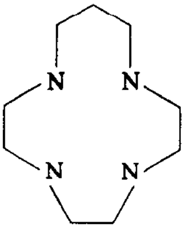

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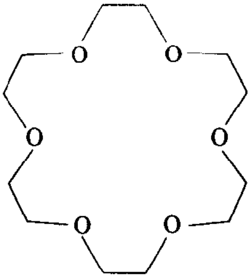

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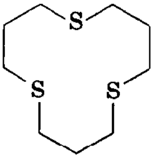

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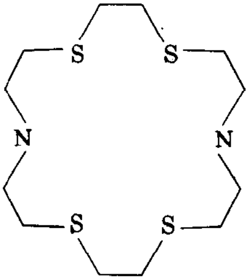

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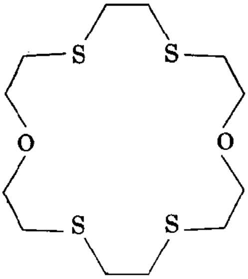

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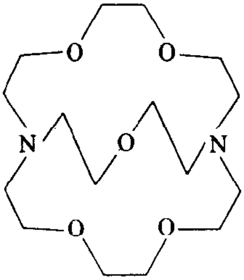

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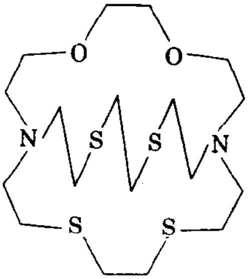
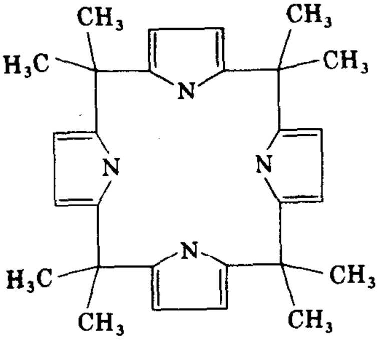


(X)

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.



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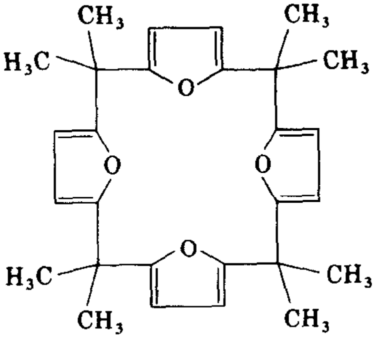
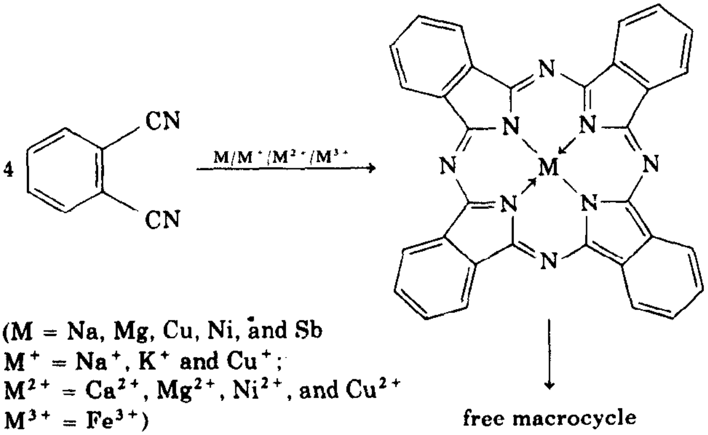


(XII)

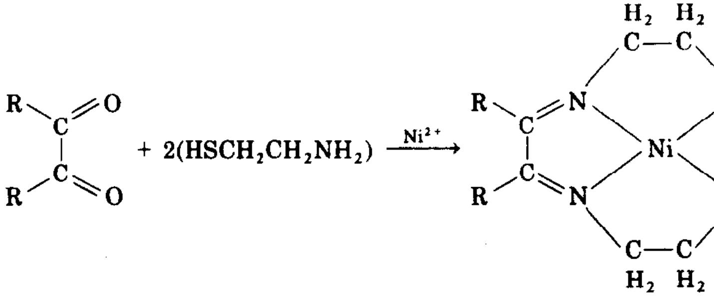
One of the first examples of a metal or metal salts facilitating the formation of a macrocycle was the self-condensation of o-phthalonitrile to give metal phthalocyanine complexes from which the free ligand was easily displaced (*89*):



(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)

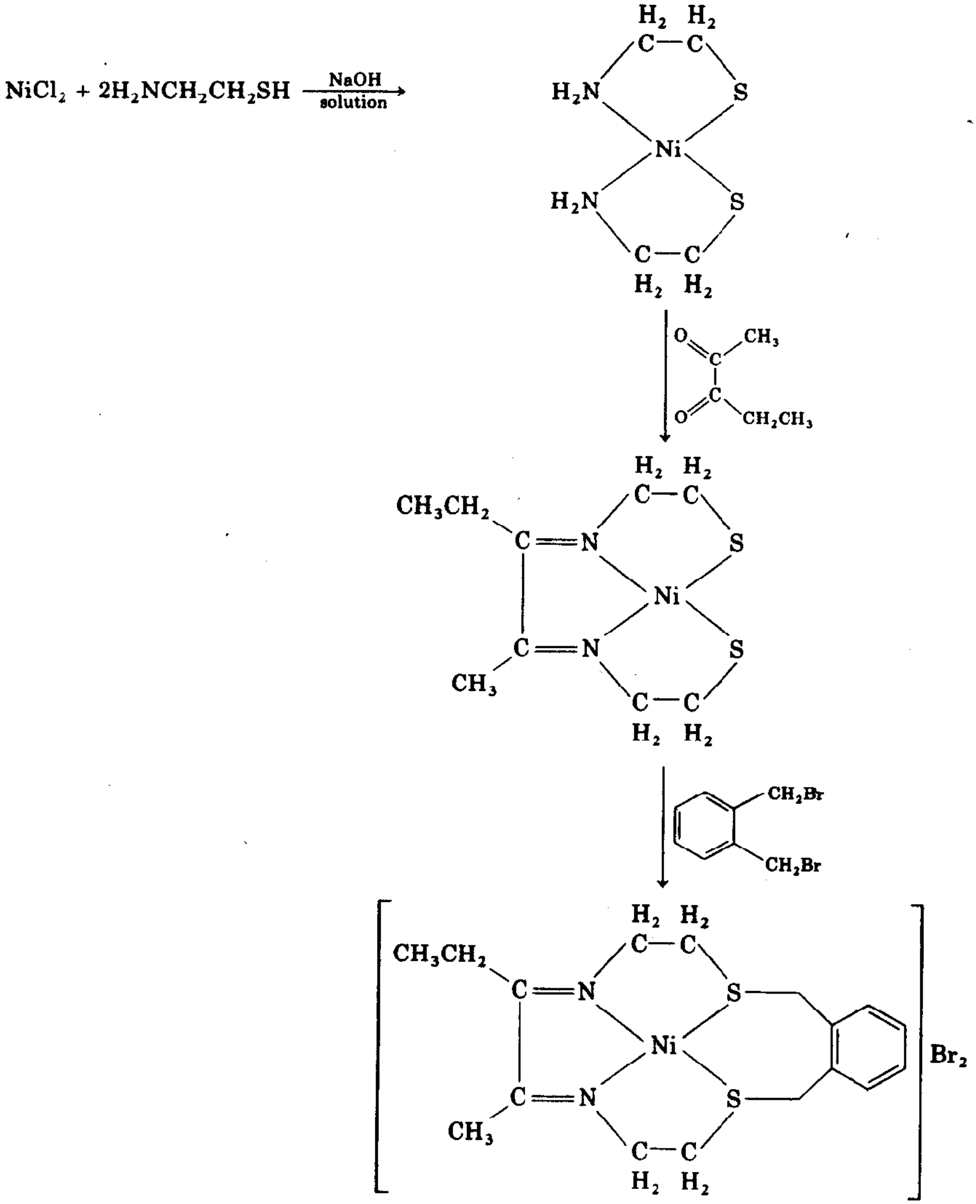
$$\mathrm{Ni(H_2NCH_2CH_2S)_2 + 2CH_3I \rightarrow Ni(H_2NCH_2CH_2SCH_2)I_2} \qquad (3)$$

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

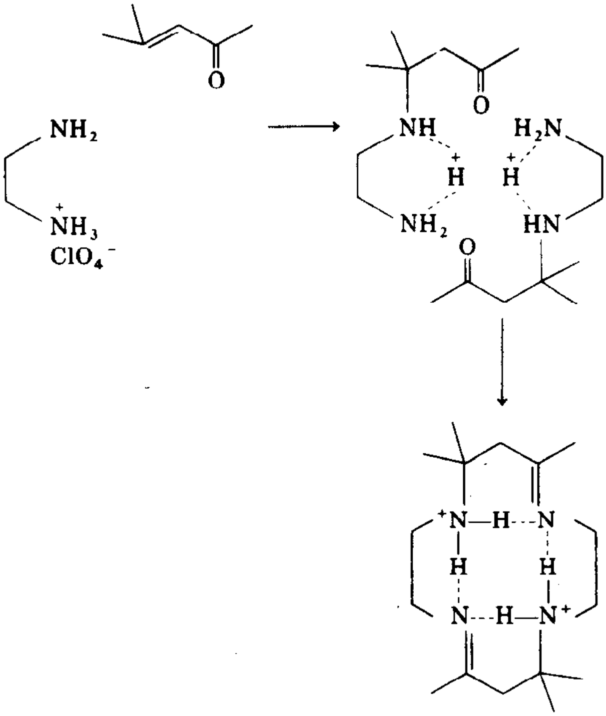
A reaction is described as proceeding by a kinetic template effect if it provides a route to a product that would not be formed in the absence of the metal ion and where the metal ion acts by coordinating the reactants. An alternative description for this process is the coordination template effect that 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

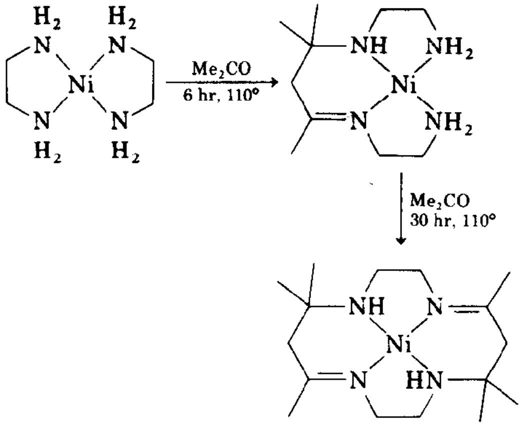
B. THERMODYNAMIC

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)

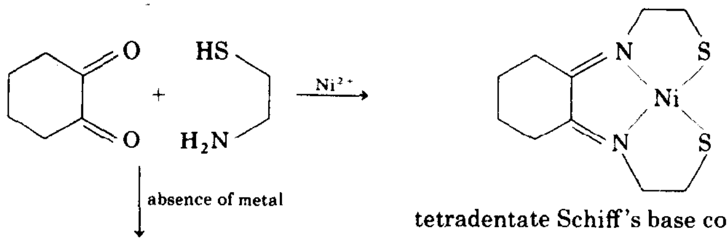
but in this case the metal promotes the formation of macrocycle by removing it from the equilibrium as a macrocycle-metal complex (*39*), e.g.,



(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.,



Mixture of products including thiazoles, thiazolines, and mercaptals

tetradentate Schiff's base complex

(6)

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

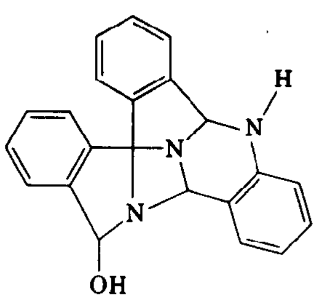
III. Template Synthesis of Macrocycles

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.

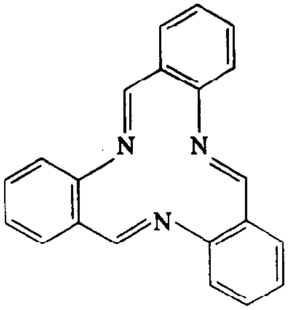
A. NITROGEN-DONOR MACROCYCLES

1. Macrocycles with Benzenoid Units

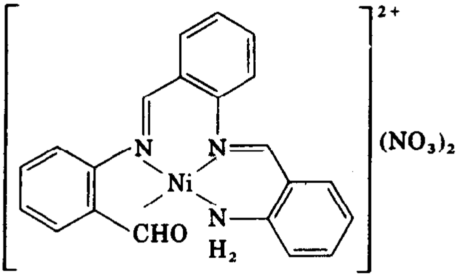
The self-condensation of *o*-aminobenzaldehyde has been the most studied reaction under this heading. In the absence of metal ions, self-condensation was found (*6, 127*) to be a very slow reaction that gave a mixture of products including a bisanhydrotrimer and a trisanhydrotetramer. The same reaction 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*)



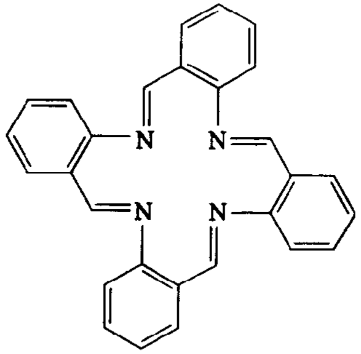
(XIII)



(XIV)

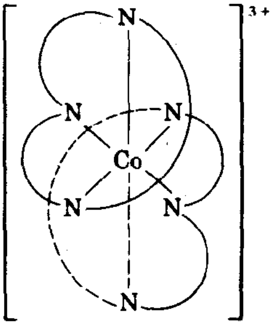


(XV)

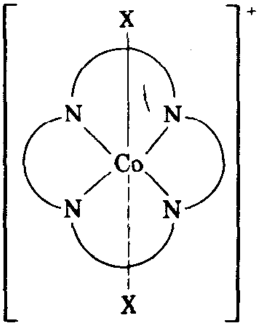


(XVI)

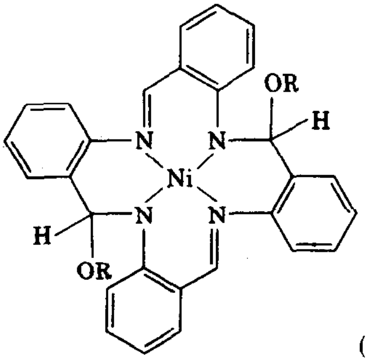
carried out the self-condensation of *o*-aminobenzaldehyde in the presence of divalent metal nitrates and found that Ni and Co formed M(II) complexes of the trisanhydrotrimer **(XIII)**, which were assigned as having structure **XV**; Cu gave Cu(I) complex of **XIII**, and Mn gave uncomplexed **XIII**. 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]triazacyclododecine (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**).



(XVII)

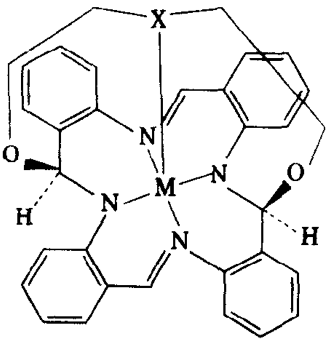


(XVIII)



(R = CH_3—, CH_3CH_2—)

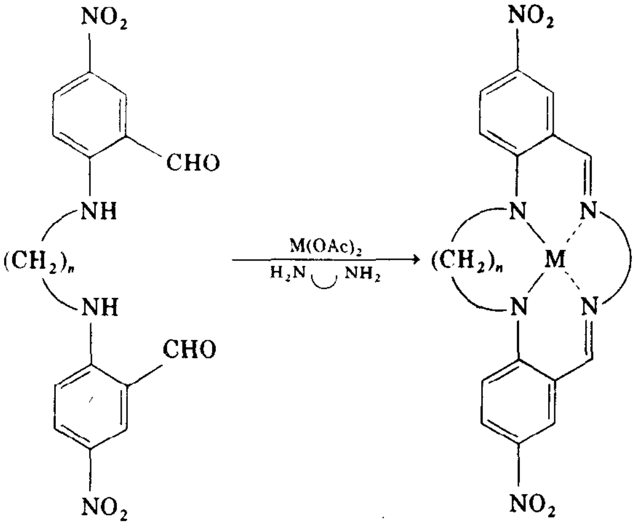
(XIX)



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

(XX)

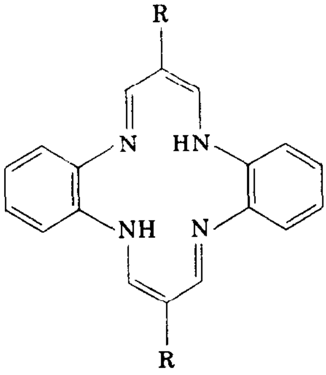
Condensation of a series of diaminodialdehydes with ethylenediamine, *o*-phenylenediamine, or 1,8-diaminonaphthalene in the presence of Ni(II), Co(II), and Cu(II) acetates has afforded a series of macrocyclic quadridentate complexes containing 14-, 15-, or 16-membered rings (*10, 11, 16*):



$n = 2,3$

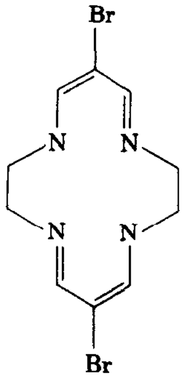
(7)

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

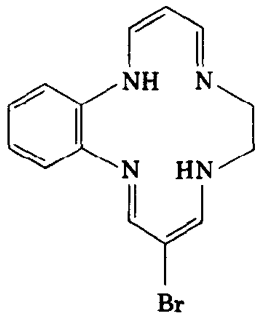


R = H **(XXI)**
R = Br **(XXII)**

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



(XXIII)



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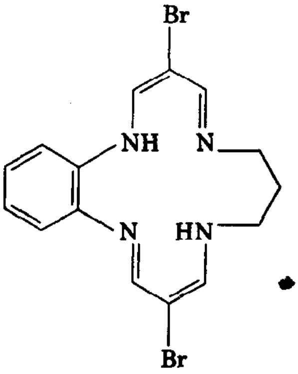
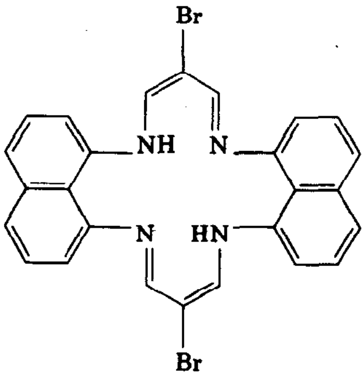


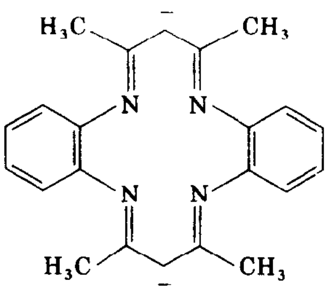
(XXV)



(XXVI)

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.

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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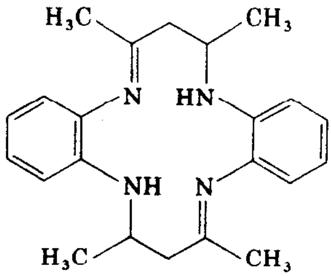
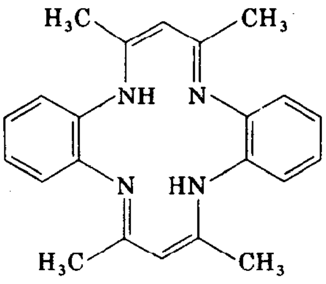


(XXVIII)



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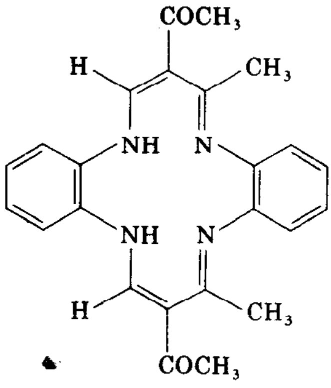

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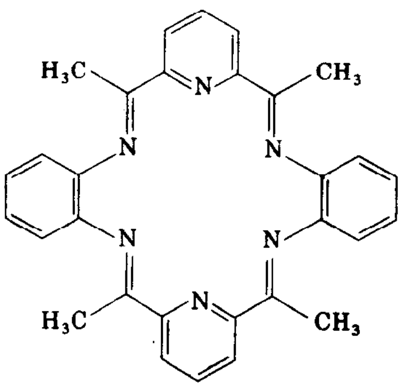
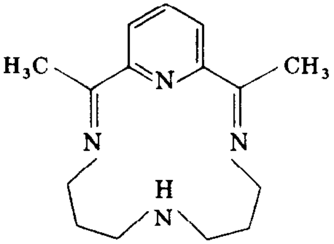
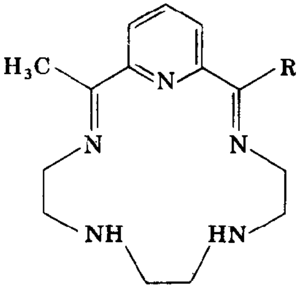


(XXXI)

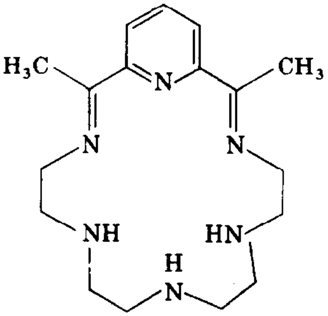
Ochai and Busch (*101*) briefly mention the synthesis of a macrocycle containing a pyridyl unit (**XXXII**) from the condensation of 2,6-diacetylpyridine with bis(3-aminopropyl)imine in the presence of Ni(II) ions. A similar condensation (*38*), using the same pyridyl source, with tetraethylaminetetramine 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