ADVANCES IN INORGANIC CHEMISTRY, VOL. 45

THE TRANSITION METAL ION CHEMISTRY OF LINKED MACROCYCLIC LIGANDS

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I. Introduction

In recent times there has been a trend toward the synthesis of larger molecular entities that are multicomponent in nature. One category of this type involves linked macrocyclic ligand ring systems. Macrocyclic systems often show unique complexation properties; for example, they usually give rise to very kinetically and thermodynamically stable complexes and hence retain their integrity under a variety of conditions (*1*). In this review the transition metal ion chemistry of linked macrocyclic ring systems will be discussed. Linked macrocyclic systems that are capable of binding simultaneously to two or more metal ions yield the prospect of generating unusual electronic, catalytic, and/or redox properties (associated with the proximity of the metal centers). Heterometallic complexes are also a possibility and if rigid spacers are employed then the distance between metal centers can be tuned. The latter may enable the selective control of electronic properties. Further, such complexes are of interest as potential models for charge transfer, electron transport, and other processes found in a number of metal-containing natural systems such as the active sites of particular di- or polynuclear proteins (*2*).

0898-8838/98 $25.00

Many covalently linked bis(macrocyclic) ligands incorporating synthetic rings have now been reported and a number of linked porphyrin systems are also known (*3*); however, compounds of this latter type are not discussed in this review. A monograph by Bradshaw *et al.* has comprehensively reviewed the synthetic procedures for obtaining aza-containing macrocyclic and bis(macrocyclic) ligands (*4*) and less emphasis is given to this aspect in the present discussion.

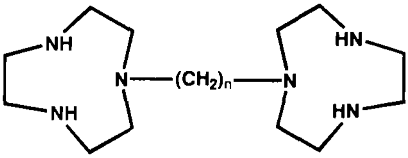
A range of bis(crown) and bis(azacrown) rings have also been synthesized but the metal ion chemistry of these species has largely involved the alkali and alkaline earth metals (*5*). As such, such systems fall outside of the scope of the present review.

Interest in linked macrocyclic ligands has increased very greatly by the finding that bis(cyclam) derivatives (*6*) [including nickel and zinc metal complex derivatives (*7*)], incorporating either alkyl or aromatic linking groups between the rings, are effective in inhibiting several strains of human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2) with low levels of cytotoxicity. Interaction with the bis(macrocycle) species was shown to occur at an early stage in the HIV reproduction cycle.

II. Linked Aza Macrocyclic Ring Systems

A. Linked Triaza Ring Systems

Examples of linked cyclic amine systems have been known for a considerable time. For example, the synthesis of the bis-linked system (**1**; $n = 2$), consisting of two potentially tridentate macrocycles, was reported in 1977 (*8*). Potentiometric measurements have been employed to obtain the stability constants for the 1:1 complexes of this ligand system with Mn(II), Ni(II), Co(II), Zn(II), and Cd(II). All these metals are bound strongly, with the binding constants varying from a log K_{ML} value of 15.0 for the Mn(II) species to 21.5 for the Ni(II) species. Although the respective structures are not



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discussed by the authors, there seems little doubt that **1**(n = 2) acts as a sexadentate ligand toward each of these metals under the conditions employed. The flexibility of the ligand should allow coordination to a single metal, whereby all chelate rings will be five-membered.

Subsequent studies by Wieghardt *et al.* (*9*) were successful in using **1**(n = 2) to obtain dinuclear complexes in which the ligand occupied three facial coordination sites on each of two metal centers—a mode of coordination well documented to occur for the single ring analogue, 1,4,7-triazacyclononane (*10*). In the course of these studies, a range of stable mononuclear complexes of type $[ML]^{n+}$ [M = Cr(III), Mn(II), Fe(III), Co(III), Ni(II), Ni(III), Cu(II), and Zn(II)] were isolated as their bromide, hexafluorophosphate, or perchlorate derivatives. Spectrophotometric measurements were in accord with the adoption of a distorted octahedral geometry for each of the complex cations. An electrochemical study indicated that the Ni(III) species is a strong one-electron oxidant. The structure of low-spin $[FeL]Br_3 \cdot 4H_2O$ has since been shown to be monomeric (Fig. 1) (*11*).

Reaction of **1** with the metal carbonyls of chromium, molybdenum, and tungsten in dimethylformamide (DMF) gives air-stable, binuclear complexes of type $[(CO)_3MLM(CO)_3]$ (*9*). These proved to be useful starting species for generating (via oxidative decarbonylation reac-

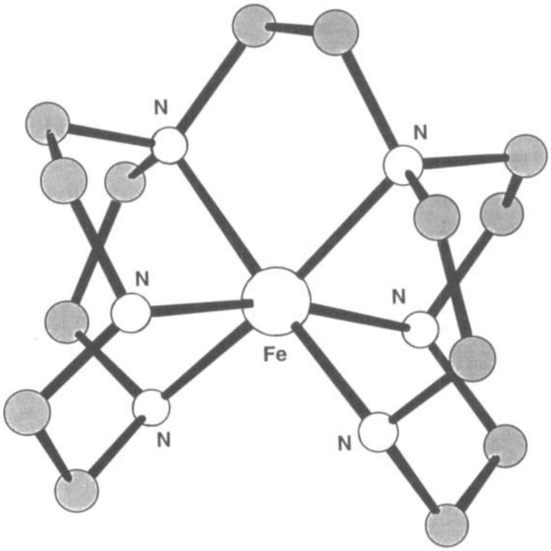


FIG. 1. The structure of the complex cation in $[FeL]Br_3 \cdot 4H_2O$.

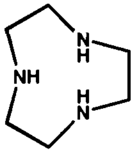
tions) related binuclear species containing the metals in higher oxidation states. For example, $[CO]_3CrLCr(CO)_3$ reacts with bromine in chloroform to yield $[Br_3CrLCrBr_3]$. However, the related complexes $[Cl_3MLMCl_3]$ [M = Cr(III), Fe(III), and Co(III)] are generated on direct reaction of **2** with the corresponding metal chloride in a 1:2 (ligand:metal) ratio. The divalent metal species $[Cl_2CuLCuCl_2]$ and $[Cl_2MnLMnCl_2]$ were also prepared by direct means.

If $Mn(ClO_4)_2$ is reacted with **1** in alkaline solution in the presence of air, a black precipitate of the oligomeric oxo-bridged species, $[Mn_4(L)_2O_6](ClO_4)_4$, forms. This unusual (Mn(IV) species has been assigned an adamantane-like structure.

The synthesis of the related bis(macrocycle) incorporating a three-carbon bridge between the two 1,4,7-triazacyclononane rings has also been reported (*12*) as well as, in a separate study, an efficient procedure for incorporating longer linkages between the rings (*13*). The latter procedure is also applicable to the preparation of analogous linked 1,5,9-triazacyclododecane macrocyclic systems. Subsequently, Sessler *et al.* (*14*) published a further synthesis for the bis(1,4,7-triazacyclononane) derivative incorporating a four-methylene linkage between the nine-membered rings.

The formation of Cu(II) complexes with bis(1,4,7-triaza-1-cyclononyl) ligands incorporating tri- and tetramethylene bridging groups (*15*) has been investigated. Both ligands form stable 1:1 and 2:1 Cu(II) complexes. Potentiometric studies in aqueous media indicate that the 1:1 copper complex of the ligand incorporating a trimethylene bridge is more stable than its tetramethylene analogue (although the stabilities of these complexes differ by only 0.5 log K units); the reverse order applies for the 2:1 species (whose stabilities differ by 2.4 log units). Such behavior has been rationalized in terms of the relative ease of breaking a six- versus a seven-membered chelate ring in the respective monomeric 1:1 species, a process that must occur on formation of the dinuclear species.

The UV–vis spectra of the respective 1:1 and 2:1 complexes have been determined. Comparison of the spectra suggested that slightly



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different coordination environments may be present in the 1 : 1 complexes whereas the 2 : 1 species clearly have similar environments.

Crystals of the Cu(II) chloride complexes of each ligand were obtained and were employed for X-ray diffraction studies. The structures of $[Cu_2LCl_4] \cdot 2H_2O$ (L = **1**; $n = 3$) and $[Cu_2LCl_4]$ (L = **1**; $n = 4$) are shown in Figs. 2 and 3, respectively. The Cu(II) ions in both complexes have five-coordinate geometries; two chloride ions and two secondary amine nitrogens occupy the base of a square pyramid that has the tertiary nitrogen in the apical position. The ligands adopt somewhat different conformations in each complex; the pair of chloride ions attached to the two Cu(II) are effectively syn for $Cu_2LCl_4 \cdot 2H_2O$ (L = **1**; $n = 3$) but anti for Cu_2LCl_4 (L = **1**; $n = 4$). The copper atoms are displaced 0.18 and 0.20 Å above the respective planes toward the axial amine groups. Related square pyramidal stereochemistries are found in the 1 : 1 Cu(II) chloride (*16*) and Cu(II) bromide complexes (*17*) of triazacyclononane. It is of interest that the Cu–Cu distances in $[Cu_2LCl_4] \cdot 2H_2O$ (L = **1**; $n = 3$) and $[Cu_2LCl_4]$ (L = **1**; $n = 4$) are 8.6 and 8.3 Å, respectively. Thus, for these systems the compound with the longer bridging chains shows, at least in the solid state, a shorter intramolecular metal–metal distance.

Linked complexes incorporating second-row transition ions have been prepared. In a comparative study, ruthenium complexes of mono- and dinuclear complexes of 1,4,7-triazacyclononane (**2**) and its ethane-linked derivative (**1**; $n = 2$) have been synthesized starting from $[Ru(DMSO)_4Cl_2]$ (where DMSO is dimethyl sulfoxide) (*18*). The resulting Ru(III) products are of type $[RuLCl_3]$ (L = **2**), $[Ru_2LCl_6]$ (L = **1**; $n = 2$), and $[Ru_2LBr_6]$ (L = **1**; $n = 2$). These products readily undergo hydrolytic conversion in aqueous sodium carboxylate or so-

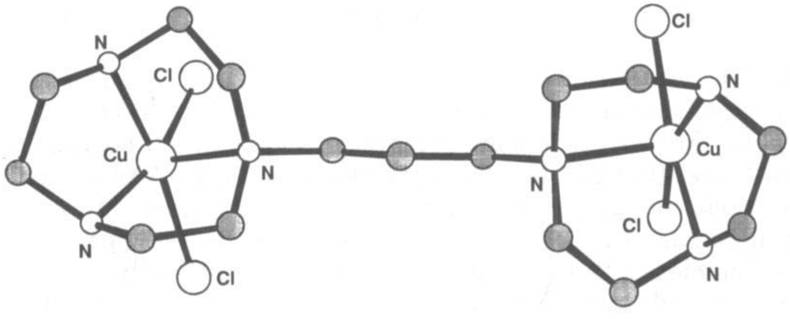


FIG. 2. The structure of $[Cu_2LCl_4]$ (L = **1**; $n = 3$).

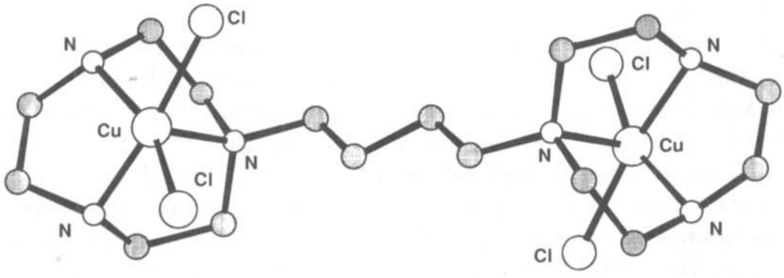


FIG. 3. The structure of $[Cu_2LCl_4]$ (L = **1**; n = **4**).

dium carbonate to hydroxo/oxo-bridged dinuclear species incorporating Ru(III) or Ru(III)/Ru(IV). In recent years the coordination chemistry of such oxo- or hydroxo-bridged dinuclear ruthenium species has been much studied. A motivation for this interest has been the discovery that in edge- and face-sharing dioctahedral compounds, the metal oxidation states can range between +2 and +5, and include mixed-valent species (*19*, *20*).

The formation of bridged dinucleating species of the above type can often be promoted by the use of a tridentate cyclic amine, such as **2**, as a "blocking group" for three facial sites on each metal ion; the process is further aided by the very considerable kinetic and thermodynamic stabilities of the macrocyclic species generated (*18*). The complexes $[Ru_2L(\mu\text{-}OH)_2(\mu\text{-}PhCO_2)][PF_6]_3$ (L = **1**; n = 2), $Ru_2L_2(\mu\text{-}OH)_2(\mu\text{-}CO_3)Br_2 \cdot 3.75H_2O$ (L = **2**), and $[Ru_2L)(\mu\text{-}O)_2(\mu\text{-}CO_3)]PF_6 \cdot 5H_2O$ (L = **1**; n = 2) have been isolated. The latter two have been investigated by X-ray diffraction and were shown to contain octahedral edge-sharing ruthenium units of types $Ru_2(\mu\text{-}OH)_2(\mu\text{-}CO_3)^{2+}$ and $Ru(\mu\text{-}O)_2(\mu\text{-}CO_3)^+$, respectively; the structure of $[Ru_2L(\mu\text{-}O)_2(\mu\text{-}CO_3)]^+$ (L = **1**; n = 2) is shown in Fig. 4. The Ru–Ru metal–metal distance in this latter cation is 2.469 Å. Binuclear Ru(IV) analogues of the above three complexes may be readily generated in solution using either chemical or electrochemical oxidation.

The linked tetra-N-methylated derivative (**3**) and its tri-N-methylated single-ring analogue (**4**) each react with $RhCl_3 \cdot 3H_2O$ in ethanol to yield the corresponding uncharged complexes: $[Rh_2Cl_6L] \cdot 2H_2O$ (L = **3**) and $[RhCl_3L]$ (L = **4**) (*21*). Because the 1,4,7-triazacyclononane backbone in both **3** and **4** will coordinate facially to an octahedral metal, structures in which this was the case were proposed for these complexes. If these species are then (individually) suspended in water and treated with sodium borohydride, followed by the addition of hexafluorophosphate anion, then red–brown crystals of

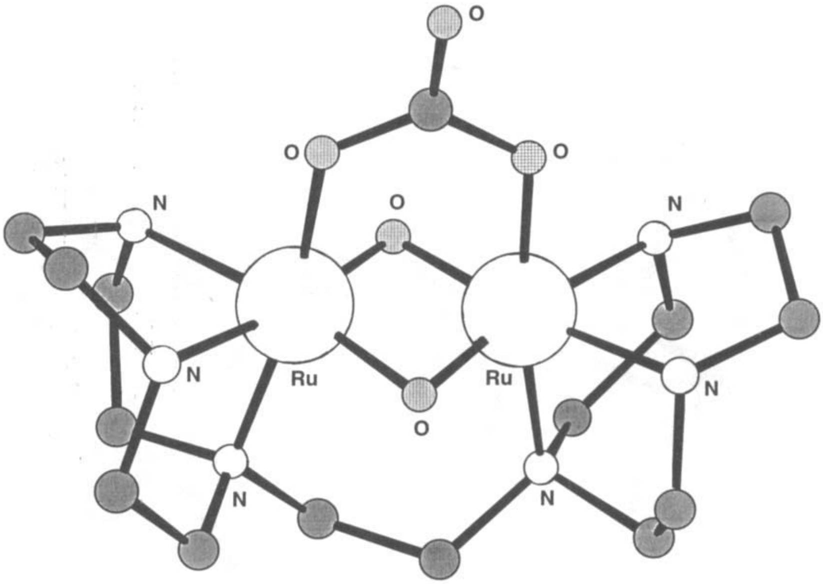
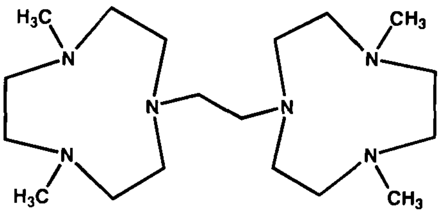


FIG. 4. The structure of $[Ru_2L(\mu\text{-}O)_2(\mu\text{-}CO_3)]^+$ (L = **1**; n = 2).

syn-$[Rh_2(H)_2(\mu\text{-}H)_2L](PF_6)_2$ (L = **4**) and *anti*-$[Rh_2(H)_2(\mu\text{-}H)_2L_2](PF_6)_2$ (L = **3**) form.

The X-ray structure of the latter complex (Fig. 5) shows that it contains a $[HRh(\mu\text{-}H)_2RhH]^+$ core. Both complexes may be considered classical rhodium hydride species, although they are of a less common variety in that the ancillary amine ligands are purely σ-donor in nature. The presence of the linkage in **3** is reflected in the ^1H NMR spectra of these complexes. At room temperature, the complex of **4** is fluctional whereas that of **3** is rigid.

The cyclic voltammograms for the above complexes each show a



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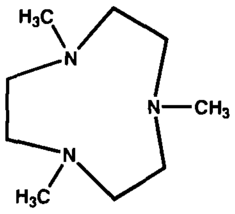

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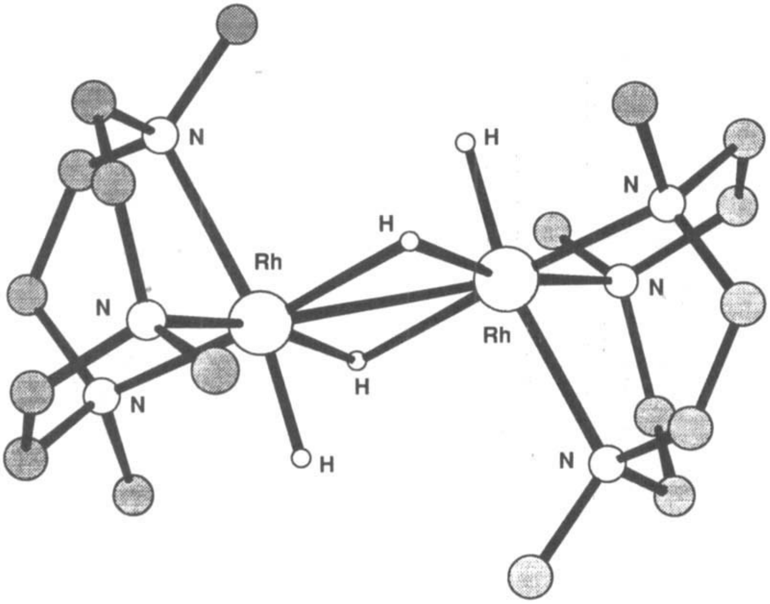
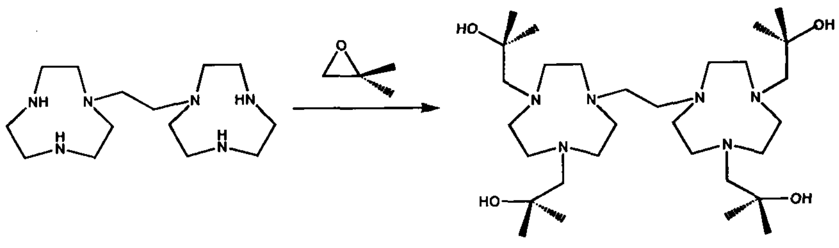


FIG. 5. The structure of *anti*-$[Rh_2(H)_2(\mu\text{-}H)_2L_2]^{2+}$ (L = **3**).

reversible one-electron transfer wave that was assigned to a one-electron reduction process. Thus in the case of **3** a mixed-valence Rh(II)/Rh(III) species is accessible electrochemically, although attempts to obtain such a complex in the solid state were unsuccessful.

The dinucleating pendant arm ligand (**5** in Fig. 6), incorporating 10 potential donor sites, has been synthesized and used to prepare the following complexes: $[Co_2(LH_4)(OH_2)_2](NO_3)_4 \cdot 5H_2O$, $[Ni_2(LH_4)(NCMe)_2](PF_6)_4 \cdot 4H_2O$, $[Zn_2(LH_4)(NO_3)_2](NO_3)_2$, and $[Cu_2(LH_2)](BPh_4)_2$ (where LH_4 = **5**) (*22*). The X-ray structures of each of these complexes have



(5)

FIG. 6. Synthesis of a tetra alcohol pendant arm derivative.

been determined. All have anti (transoid) configurations except the Cu(II) species, which adopts a syn configuration and is accompanied by intramolecular hydrogen bonding. The structure of $[Co_2(LH_4)(OH_2)_2]^{4+}$ is shown in Fig. 7. Ligands such as **5** can be used to control the availability of vacant site(s) at a metal center by varying the number of pendant arms as well as the donicity of the cyclic core. In the present case, coordination to two octahedral metal ions will leave one vacant site at each metal center.

In the case of the Co(II) complex, the sixth coordination site on each metal is occupied by a water molecule. The stability toward oxidation of this complex is unusual because the Co(II) complex of the corresponding 1,4,7-triazacyclononane derivative, incorporating three pendant alcohol arms, readily oxidizes in air at neutral pH to form the corresponding Co(III) species (*23*).

The dark blue copper complex formed by reaction of Cu(II) acetate with **5** has the ligand bound in its doubly deprotonated form; protons have been lost from two of the pendant arm alcohol groups. This loss of an alcohol proton at each copper site is unusual in the complex of a divalent cation. This is particularly so in the present case because the complex was crystallized at neutral pH. Two O · · · H · · · O bridges are present between the two halves of the bound ligand dimer. Each copper site has a distorted square pyramidal coordination geometry.

The Wieghardt study discussed earlier (*9*) also encompassed the preparation of an acetato-bridged Fe(III) complex of **1**; (n = 2). Such

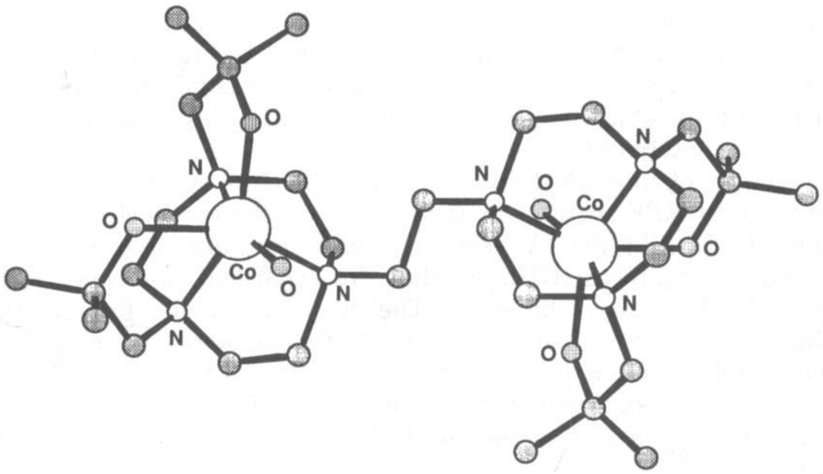


FIG. 7. The structure of $[Co_2(LH_4)(OH_2)]^{4+}$ (LH_4 = **5**).

species are of interest because oxo-bridged dinuclear Fe(III) cores occur at the active sites of a number of metalloproteins (including hemerythrin, ribonucleotide reductase, purple acid phosphatase, methane monooxygenase, and rubrerythrin).

The respiratory protein hemerythin (Hr) incorporates a triply bridged diiron core (*24*). In its deoxy form, two iron atoms are bridged by hydroxo and two carboxylate groups attached to the side chains of glutamate and aspartate residues, and five imidazole ligands cap the diiron core. This arrangement leaves one iron coordination site vacant for the binding of a dioxygen molecule. In oxyhemerythrin, dioxygen binds in the form of its hydroperoxide to the binuclear oxo-bridged Fe(III) core, which retains its bridging carboxylates and imidazole capping ligands.

It was postulated (*9*) that the use of **1**(n = 2) could result in stabilization of a hemerythrin model complex, incorporating a (μ-oxo)bis(μ-acetato)diiron(III) core. However, it was subsequently proposed (*25*) that this complex might be better formulated as a tetranuclear species. Based on this, it was suggested by Sessler *et al.* (*14*) that steric influences might favor the formation of a dinuclear species if the length of the link between the triaza rings was increased to four methylene groups. The preparation of the required ligand (**1**; n = 4) was carried out. However, this derivative was also found to yield an Fe(III) tetranuclear species, $[Fe_4O_2(acetato)_4L_2](PF_6)_4$ (L = **1**; n = 4), rather than stabilizing the required diiron core complex of the type present in hemerythrin. The structure of the tetranuclear species is shown in Fig. 8.

In an attempt to gain greater rigidity (and possibly, stability) of tetrameric complexes of the above type, it was decided to attempt the synthesis of the tetranuclear species in which the four acetates were replaced by two dicarboxylic acids of the required length to span adjacent iron centers (*26*).

Reaction of glutonic acid with $[Fe_2Cl_6L]$ (L = **1**; n = 4) in the presence of KPF_6 results in two forms of the tetranuclear species $\{[Fe_2O(C_5H_6O_4)_2L]_2\}(PF_6)_4$, each of which contains two (μ-oxo)bis(μ-carboxylato)diiron(III) cores that are separated from each other by 7.748 Å in the solid state. The structure of one form of this "dimer of dimers" is shown in Fig. 9; the arrangement present is very similar to that found in $[Fe_4O_2(acetato)_4L_2](PF_6)_4$ (L = **1**; n = 4). Despite this, electrochemical studies indicate that the former complex is more stable toward electrochemical reduction than the latter.

Based on the above results it appears that bis(macrocycle) ligands

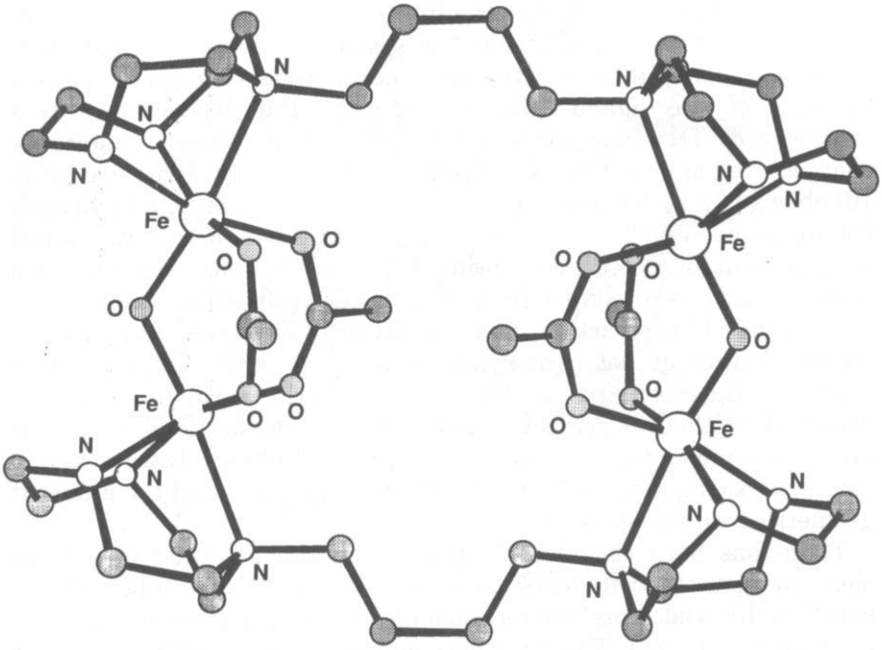


FIG. 8. The structure of $[Fe_4O_2(acetato)_4L_2](PF_6)_4$ (L = **1**; *n* = 2).

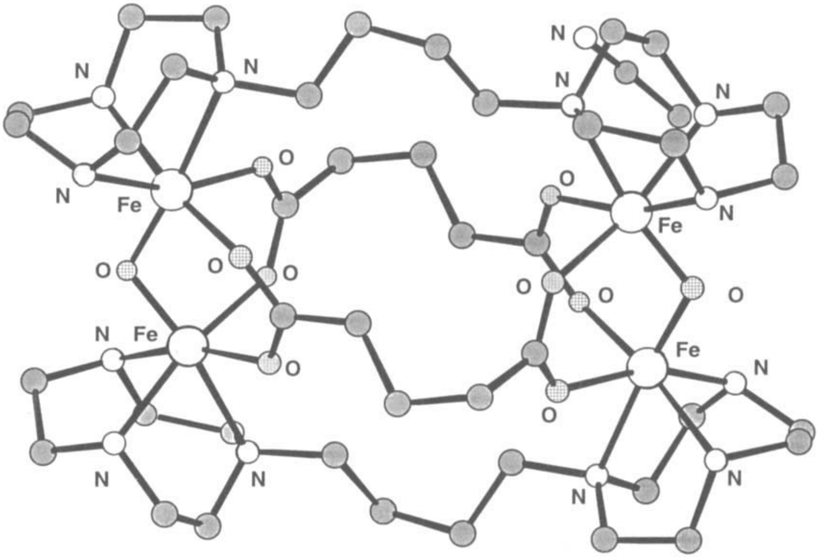
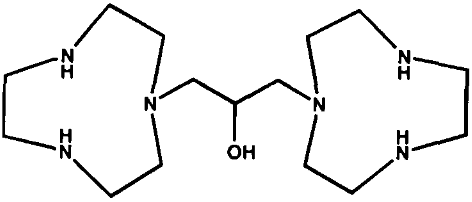


FIG. 9. The structure of one form of the cation $[Fe_2O(C_5H_6O_4)L]_2^{4+}$.

of type **1**, containing a flexible hydrocarbon linkage, tend to promote tetranuclear rather than dinuclear species. It was reasoned that, in part, this might reflect the absence of a ligating group in this bridging of the ligand (*26*). Accordingly, the derivative **6** was synthesized. However, once again, the yield was a quadruply charged, tetranuclear Fe(III) species whose X-ray structure (Fig. 10) shows two molecules of **6** acting as ditopic, heptadentate ligands bound to an Fe_4O_6 core. The core is composed of a tetrahedral arrangement of Fe(III) ions bridged by six oxygens (two oxo, two hydroxo, and two alkoxo from **6** (*27*). Overall, this core has an adamantane-like structure; it is of interest that a similar species forms whether or not carboxylate ions are present in the reaction mixture. The respective Fe(III) atoms in the structure adopt a distorted octahedral geometry made up of a facially binding triazacyclononone moiety, a μ-alkoxo group, a μ-hydroxo ligand, and a single μ-oxo ligand. The four N_3 rings adopt two slightly different geometries in the structure.

There has been considerable interest in the potential of polynuclear manganese complexes to oxidize water to molecular oxygen catalytically and thus act as models for the manganese center in photosystem II (*28*). The binuclear complex $[Mn_2L(\mu\text{-OAc})_2]^{2+}$, where L = **7**, has been investigated using a number of techniques—including EPR, magnetic susceptibility measurements, and electrochemical measurements. The X-ray structure (Fig. 11) confirmed the presence of a mixed ("valence-trapped") Mn(II)/Mn(III) cation. Both manganese ions adopt a distorted octahedral coordination geometry, with each metal bound to the three nitrogens of one ring, a bridging phenoxy ion, and two oxygens from each of two bridging acetate groups. The adoption of this unusual geometry clearly reflects the inherent structural features of the bis(macrocyclic) ligand system (**7**). Electrochemical studies (in acetonitrile) indicated that the above mixed-valence species undergoes one-electron oxidation



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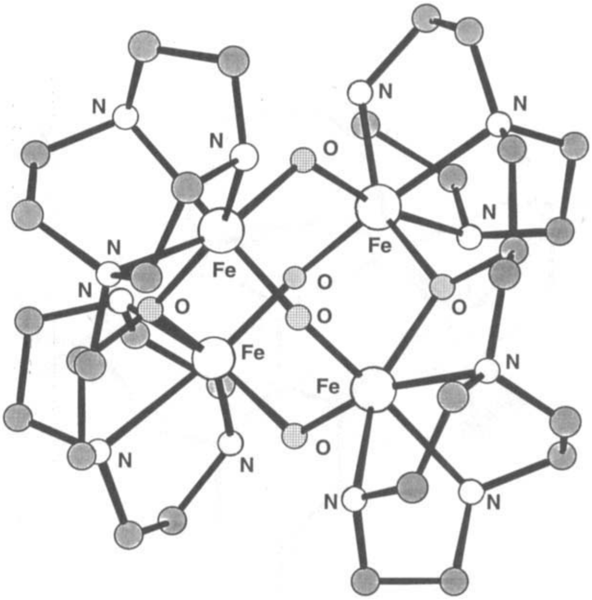
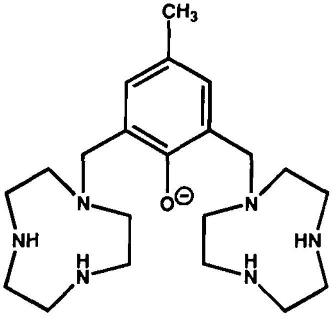


FIG. 10. The structure of tetranuclear Fe(III) complex of **6**.

as well as one-electron reduction to yield Mn(III)/Mn(III) and Mn(II)/Mn(II) species, respectively.

B. LINKED TETRAAZA AND HIGHER AZA RING SYSTEMS

A considerable number of linked tetraaza macrocyclic systems have now been reported. An early example, first isolated in low yield as its



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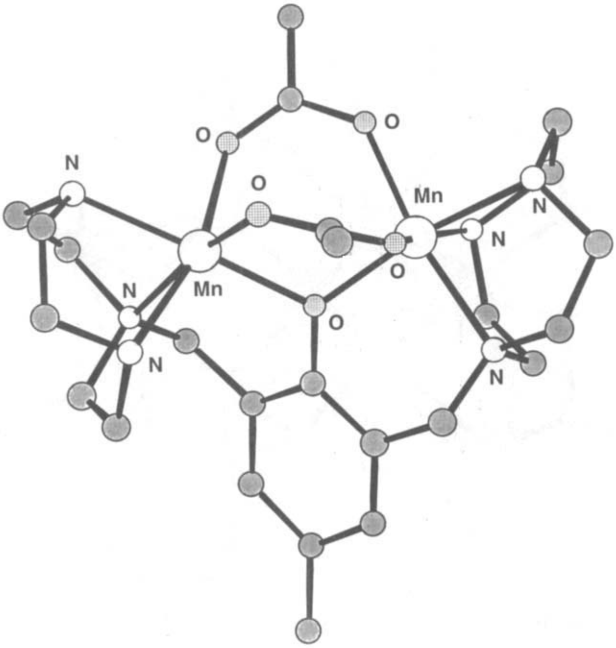
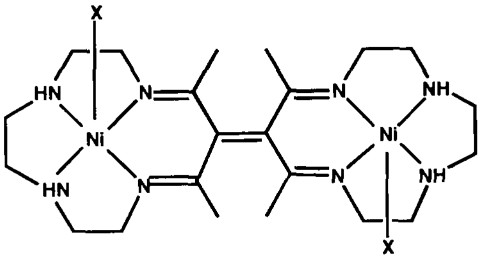


FIG. 11. The structure of $[Mn_2L(\mu\text{-acetato})_2^{2+}$.

di-Ni(II) iodide complex (**8**) (*29*), was formed by direct condensation of two molecules of the related monomeric nickel complex (**9**) (*30*).

The mechanism of formation of the dimer has been suggested to involve the combination of radicals generated at the γ position of the six-membered chelate ring derived from acetylacetone in **9** (*31*). That is, a one-electron oxidation of the monomeric complex takes place at the γ carbon followed by dimerization; further oxidation of the initial bridging C—C bond formed leads to formation of a C=C bond. The



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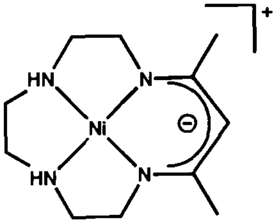


(9)

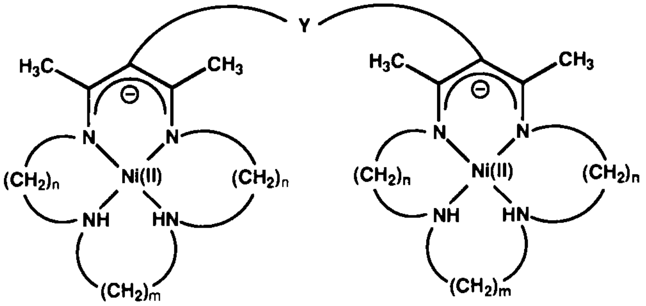
low yield obtained in the original preparation presumably reflects the occurrence of side reactions such as ligand dehydrogenation and/or oxidation. Indeed, reactions of this type have been documented for the oxidation of **9** with bromine (*32*).

An improved method for synthesizing the above dinuclear complex has been reported (*33*). Oxidation of **9** in deoxygenated acetonitrile using Fe(III) perchlorate gives the dinuclear species in approximately 70% yield. Cyclic voltametry on the starting Ni(II) monomeric complex, as well as on the corresponding Cu(II) complex, gave evidence for radical formation on oxidation. The crystal structure of the dinuclear Ni(II) complex, in which an acetonitrile ligand is coordinated to each nickel, has been determined. The configuration adopted by the ligand in this structure is quite similar to that found in the corresponding diiodide complex mentioned above (*29*). Steric interaction between the methyl substituents surrounding the double bond linkage joining the rings results in this link being quite strained. As a consequence, the respective double bonds in the dimer are almost completely localized.

A new family of bis(macrocyclic ligand) nickel complexes of type **10** has been synthesized (*34*). The procedure involved electrophillic substitution of **9** or its 14-membered analogue (*35*) at their respective γ carbons, using two difunctional electrophiles, terephthaloyl chloride or isophthaloyl chloride. This procedure was based on a previous study describing electrophillic attack by benzoyl chloride on the above starting complexes (*36*).

The visible spectra of each of the new (dinuclear) complexes confirmed the presence of a square planar coordination environment for the Ni(II) ions.

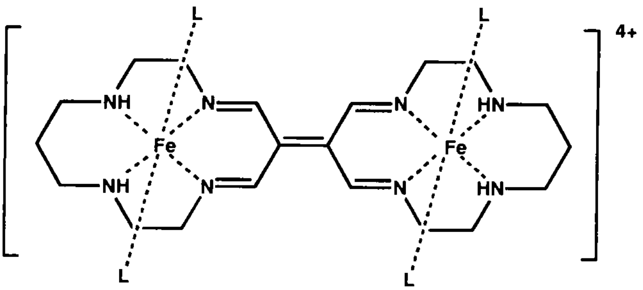
The related Fe(II) dinuclear complex of type **11** (L = acetonitrile) has been reported (*37*). This complex is generated by the reaction of 1,4,8,11-tetraazacyclotetradecane (cyclam) with $Fe(OH_2)_6(ClO_4)_2$ in



(10)

oxygenated acetonitrile. An X-ray study (Fig. 12) reveals that the iron atoms and the tetraimine moiety joining the two centers are essentially coplanar. The length of the C–C link between the rings is 1.41 Å; this corresponds to about 40% double bond character. Thus, unlike the complexes of **8**, delocalization of the double bond character occurs in this species.

The nature of the axial ligands in the low-spin complexes of types **11** and **12** has been shown to have a marked effect on the redox properties of the corresponding complexes (*38*). For example, for **12** (X = Cl), dioxygen removes an electron such that a valance-averaged, mixed-valence species with a charge of +5 is formed. However, for **11** (X = DMF), dioxygen attacks the C=C link to generate two doubly charged keto-β-diimine monomeric complexes. For X = CH_3CN in the presence of wet acetonitrile, oxidative dehydrogenation occurs to yield a new di-Fe(II) species with a charge of +4 incorporating two keto-β-diimine moieties, one at each end of the bis(macrocycle). Under other redox conditions, a number of other metal-containing products have



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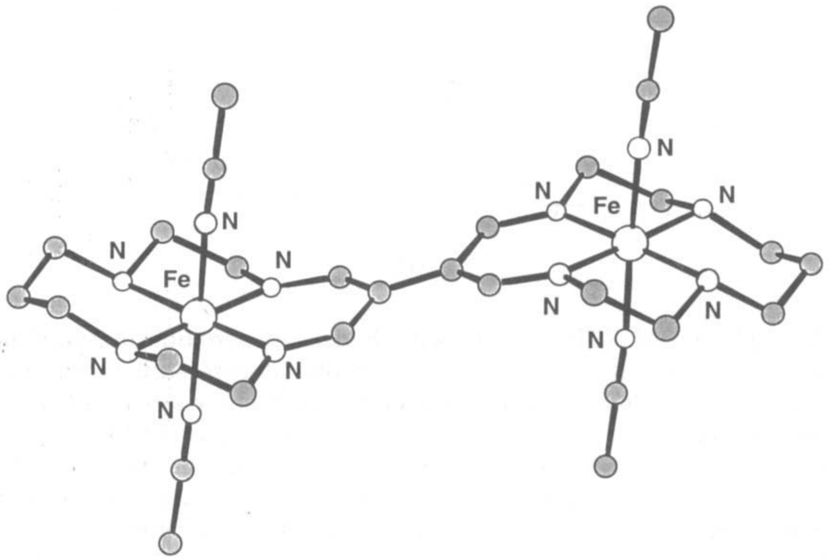
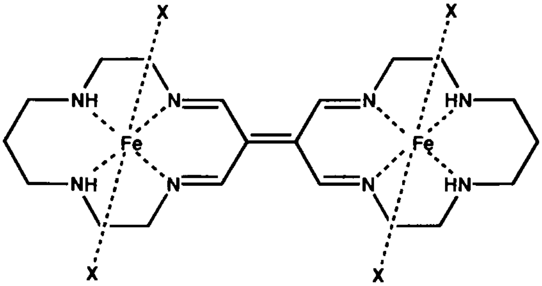


FIG. 12. The structure of the dinuclear Fe(II) complex of type **11**. Acetonitrile ligands occupy the axial coordination positions.

also been demonstrated to form. In a parallel study, the synthesis and properties of a ruthenium dinuclear mixed-valence complex has also been investigated (*39*).

McAuley and Xu (*40*) have investigated the formation and redox chemistry of the corresponding di-Ni(II) species (**13**). Although a number of previous studies have shown that the oxidation of the Ni(II) complex of cyclam produces corresponding Ni(III) species, under the conditions used in the present study the oxidation reaction was seen to proceed further. This dinuclear complex cation (**13**) results from



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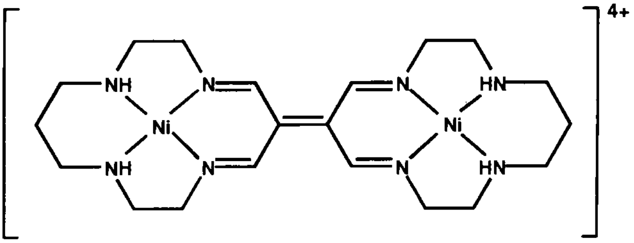


(13)

the oxidation of Ni(II) cyclam with hydrogen peroxide in acidic perchlorate media; it was isolated as its perchlorate salt. Once again, evidence for π-electron delocalization between the rings was obtained and the nature of the overall structure was confirmed by X-ray diffraction (Fig. 13). Each Ni(II) lies in the plane of its macrocyclic donors, with planarity being maintained across the carbon bridge framework. For this system, both chemical and electrochemical reduction were demonstrated to result in cleavage of the link between the macrocyclic rings, yielding a pair of mononuclear radical ions.

The Ni(II) complex of **14** is another system that has been shown to undergo dimerization on electrochemical oxidation (via π-cation radical formation). The dimerization process was found to be rapid in acetonitrile. The initial product (**15**) is readily deprotonated to yield **16** (*41*).

The versatility of this general procedure is further illustrated by the synthesis of the bis system (**17**) (*42*). This dinuclear complex was obtained by template condensation of the precursor complex, [Ni_2L] {LH_4 = tetrakis[1-(3-methylisothiosemicarbazono)ethyl]-ethane}, with 3-ethoxyacrylaldehyde in DMF and followed by the usual oxidative coupling/deprotonation process. The X-ray structure of the diamag-

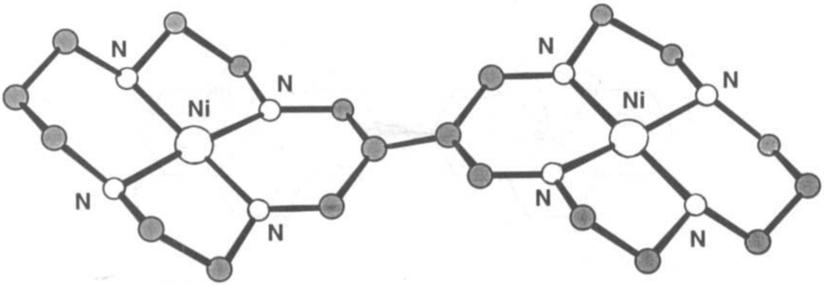
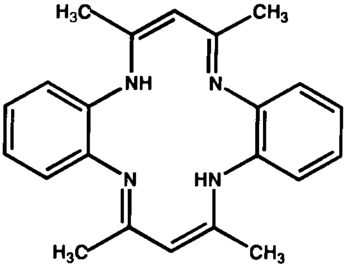


FIG. 13. The structure of the tetra cation **13**.



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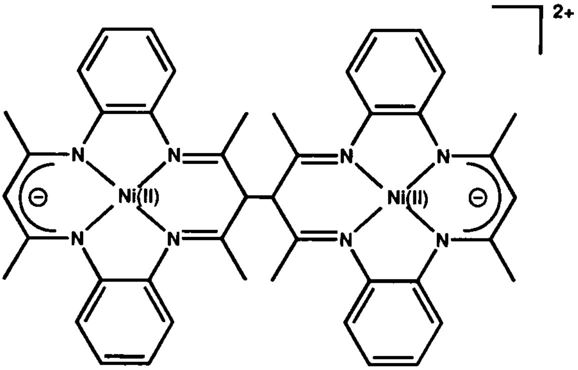

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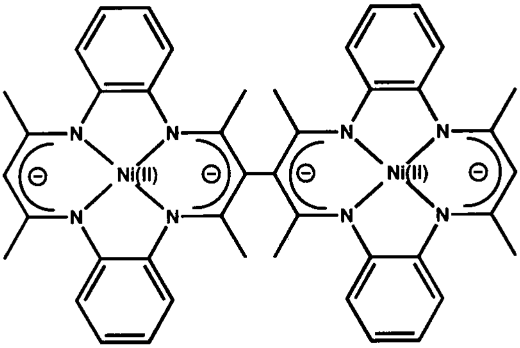

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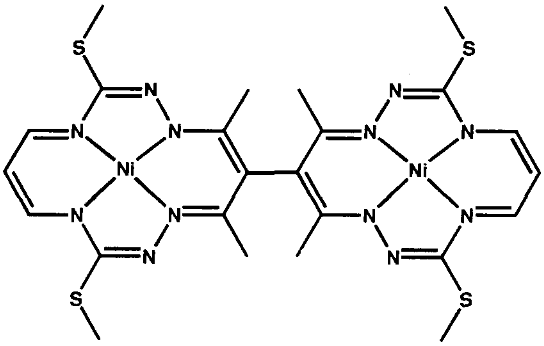


(17)

netic product (Fig. 14) has been obtained. Both macrocyclic components are equivalent and are orientated nearly perpendicular to each other (the dihedral angle between adjacent planes is 80.6°). The twist around the single C–C bonds largely reflects steric interactions between the appended methyl groups and effectively inhibits delocalization of the π systems between the rings.

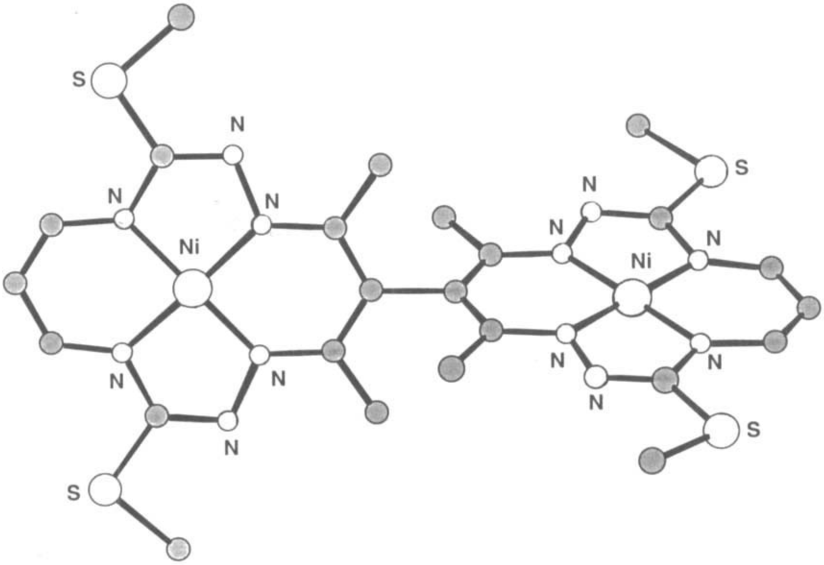
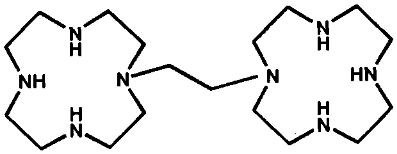


FIG. 14. The structure of **17**.



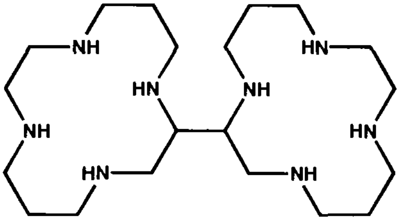
(18)

Ligand **18**, in which two 12-membered (cyclen) subunits are linked by a $-CH_2CH_2-$ bridge, yields a di-Cu(II) complex of type $[Cu_2L](ClO_4)_4$ (L = **18**) in which a weak ferromagnetic interaction between the Cu(II) sites is present *(43)*.

There are a number of reports of studies involving dinucleating ligands incorporating linked subunits of the 14-membered ring, cyclam (or its derivatives). Linked systems based on cyclam are expected to yield complexes with d^n metals that show elevated kinetic and thermodynamic stabilities, because the latter are well-documented properties of the complexes of cyclam *(1)*.

A small yield of the linked cyclam derivative (**19**) was identified as a minor product in the Ni(II) template synthesis of cyclam *(44)*. It is noted that the two cyclam subunits are linked via carbons in their respective backbones; in general, this is expected to cause less perturbation of the coordination properties of the individual rings than would occur if the link was via nitrogen atoms in each ring. An X-ray structure of the nickel(II) perchlorate derivative, $[Ni_2L](ClO_4)_4$ (L = **19**), has been obtained. Each of the nickel ions in this complex is in a (low-spin) square planar environment, with both halves of the ligand adopting the low-energy trans III configuration *(45)*.

Like $[Ni(cyclam)]^{2+}$, the above dinuclear nickel complex exists in aqueous solution as a mixture of low-spin, four-coordinated and high-spin, six-coordinated species, with the equilibrium between the two being dependent on the ionic strength. In the presence of excess per-



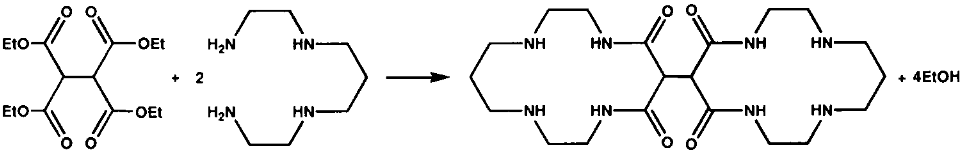
(19)

chlorate ion, the equilibrium is shifted toward the low-spin form. Thus, the presence of a direct linkage between individual cyclam rings in **19** does not appear to affect markedly this aspect of this ring's coordination behavior toward Ni(II).

The dimeric derivative of dioxocyclam (**20** in Fig. 15) has also been synthesized by means of a single-step reaction between the appropriate tetraester and linear tetraamine in a 1 : 2 molar ratio (*46*). This double-ring macrocycle complexes with two Cu(II) ions in aqueous solution, with the simultaneous release of four protons. EPR evidence indicates that the very stable di-Cu(II) complex exhibits weak metal–metal interaction. The Cu(II) ions were demonstrated to be readily oxidized to their trivalent state by means of two consecutive one-electron steps; the latter are separated by only approximately 100 mV. This is only slightly greater than the value of 36 mV expected from a purely statistical basis. Because many redox processes in organic and bioorganic chemistry involve two-electron single-step processes, the quasi-independent redox behavior of the two connected metal centers in the present system suggests that it may be considered as a potential two-electron redox reagent.

An investigation of the effect of ring size on ring-to-ring effects in dimetallic complexes of the above type has been carried out (*47*). The analogous bis(macrocyclic) ligand incorporating 13-membered subunits has been synthesized and its complexation behavior toward Cu(II) compared with that of the corresponding 14-membered ring species. A detailed potentiometric investigation of Cu(II) binding by both these ligand species has been performed. The incorporation of two Cu(II) ions into these bis(rings) involves three pH-controlled steps. In general, greater ring-to-ring effects are seen for the bis(13-membered system) and this was ascribed to the presence of less shielded electrostatic interactions between the metal centers in this case. In turn, this may indirectly reflect the lower coordination ability of the 13-membered subunit toward Cu(II) relative to the 14-membered analogue.

The neutral (fully deprotonated) di-Cu(II) complex of the bis(13-



(20)

FIG. 15. The synthesis of a bis(dioxocyclam) derivative.

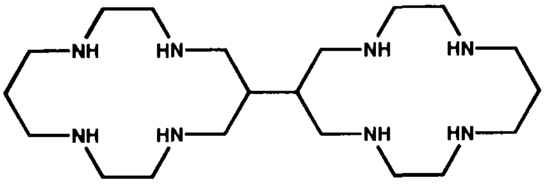
membered ring species) undergoes a reversible oxidation process via two one-electron steps; these are again separated by 100 mV, giving evidence for the presence of a small interaction between copper sites. As mentioned previously, similar behavior was observed for the bis(14-membered ring) system.

Reduction of **20** with diborane in bis(2-methoxyethyl)ether yields the bis(cyclam) derivative (**21**) (*48*). Addition of one equivalent of nickel(II) nitrate to an aqueous solution of **21** at pH 7, followed by one equivalent of copper(II) nitrate, is expected to result in a mixture of complexes in the proportion of 1:1:2 [di-Cu(II) complex: di-Ni(II) complex: Cu(II)/Ni(II) complex] (provided the two rings behave independently toward both metals). Separation of these three species was achieved by ion-exchange chromatography. Spectral and electrochemical investigations on the above binuclear complexes were undertaken. The visible spectra are very similar to those of the corresponding (mononuclear) cyclam complexes and, for example, the spectrum of the binuclear complex is virtually equal to the sum of the spectra of $[Cu(cyclam)]^{2+}$ and $[Ni(cyclam]^{2+}$. Despite this, electrochemical studies confirm the presence of a weak interaction between the coordinated metals in each dinuclear complex. This is manifested by a shift in the second oxidation potential [M(II) → M(III)] to a more positive value in each case.

The dinuclear species $[Ni_2L]^{4+}$ (L = **21**) has also been demonstrated to exist as an equilibrium mixture of yellow (low-spin) and blue (high-spin) forms in aqueous solution, further demonstrating the parallel between the metal-ion chemistry of the present binuclear species relative to that of cyclam.

The EPR spectra of $[Cu(cyclam)]^{2+}$ and $[CuNiL]^{4+}$ (L = **21**) in a water/DMF glass at ~120°C are almost identical, indicating that any interaction between the metals in the binuclear complex is not strong. Both spectra are typical of the presence of axial symmetry and show a $g_{\parallel}$ signal that is split into a quartet by the hyperfine coupling constant of the copper.

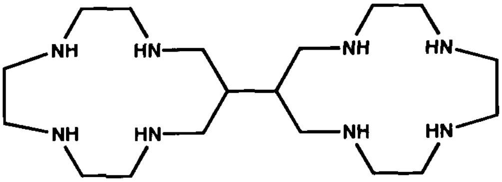
The relative electrocatalytic abilities of $[Ni(cyclam)]^{2+}$ and $[Ni_2L]^{4+}$



(21)

(L = **21**) toward CO_2 and H_2O reduction have been investigated (*49*). Because the latter complex possesses two metal sites, the prospect that these could bind two substrates simultaneously in such a manner that different reaction products might result {relative to the use of $[Ni(cyclam)]^{2+}$} was considered. In particular, for CO_2 activation, the possibility that the dinuclear species might favor a coupling reaction to yield a C_2 product provided a motivation for the study. Namely, it was thought feasible that the proposed sequence would involve the reduction of the nickel centers, leading to simultaneous reaction with two CO_2 molecules and formation of a C–C bond. However, on electroreduction, both the mononuclear and binuclear compounds were found to react similarly with CO_2 in aqueous media, yielding only a C_1 product (CO); no coupling reaction was observed with the binuclear complex. A feature of both systems is that they are exceptionally selective in reducing CO_2, i.e., no product other than CO is produced. On the other hand, the systems differ with regard to the electroreduction of water to produce hydrogen. The dinuclear species was found to be a much more efficient catalyst for this potentially important reaction than is $[Ni(cyclam)]^{2+}$.

The electrocatalytic capabilities of the above type of bis(macrocycle) have been the subject of further study (*50*). In this extension, the effect of replacing the 14-membered rings of **21** with 13-membered rings was investigated. The corresponding binucleating systems incorporating two 13-membered rings (**22**), as well as one 13- and one 14-membered ring (**23**), were synthesized using procedures related



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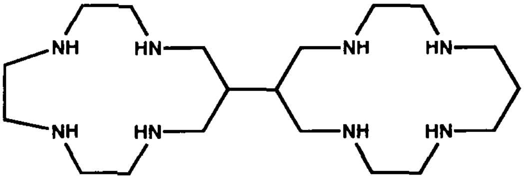
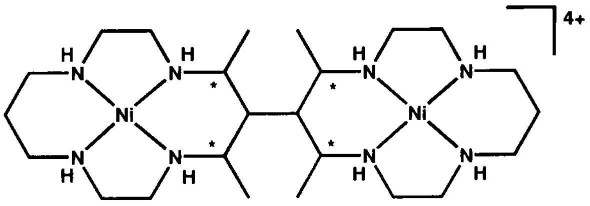


(23)

to that employed previously for the bis(cyclam) species (**21**) (*48*). The relative behavior of the di-Ni(II) complexes of each of the above bis(macrocycles), along with those of **21**, was then studied with regard to serving in electrocatalysis for hydrogen generation. Not surprisingly, the spectral and electrochemical properties of the dinickel complex of the mixed-ring-size ligand (**23**) seemed characteristic of both the 13- and 14-membered ring systems. Each dimetallic system was demonstrated to serve as an electrocatalyst for hydrogen production; the efficiency, at −1.5 V, for the respective dinuclear Ni(II) complexes followed in the ligand order of (14–14) > (13–14) ≫ (13–13). The efficiency thus drops as 13-membered rings replace 14-membered rings.

The related bis(macrocyclic ligand) Ni(II) complex (**24**), incorporating the meso–meso form of the ligand, has also been synthesized—this time from the corresponding monomeric Ni(II) complex (**9**) by again taking advantage of the reactivity of the γ-carbon position (*51*). Oxidative coupling was achieved with Fe(III) in acetonitrile and this was followed by reduction of the resulting imine-containing intermediate with sodium borohydride. The dinuclear Ni(II) species (**24**) formed is a significantly better catalyst for carbon dioxide reduction than is its corresponding mononuclear (single-ring) derivative (**25**). It is also superior to the corresponding bis(cyclam) species (**21**), even though the latter incorporates the same bis(macrocycle) skeleton (but without the methyl substituents).



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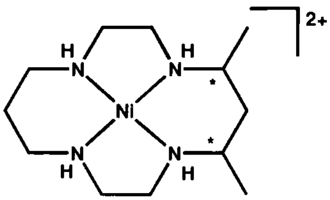
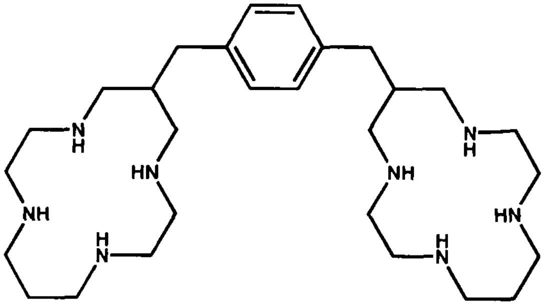


(25)

A complex of type $[Ni_2L](ClO_4)_4 \cdot 4H_2O$ has been isolated containing the xylyl-bridged biscyclam (**26**) (*52*). Under the conditions employed, cyclic voltammetry gave no evidence for any interaction between the bound nickel centers in this complex. However, in the presence of CO_2, electrocatalytic reduction of this species to CO appears to be promoted. The X-ray structure of the di-Ni(II) complex confirms that the metal sites are widely separated. Each cyclam ring is held in a stable trans III square planar arrangement with the nickel occupying the central cavity; no unusual bond distances or angles are present. The respective cyclam coordination planes are almost parallel and are orientated on opposite sides of the bridging xylyl group.

It is noted that the general procedure (involving the corresponding bi-dioxomacrocycle as precursor) has been employed for the synthesis of the pentaaza ligands of type **27** (*53*). In this study, protonated forms of **27** were demonstrated to form 1:1 complexes with a range of anions, including citrate^{3-}, AMP^{2-}, ATP^{4-}, HPO_4^{2-}, $[Fe(CN)_6]^{4-}$, and $[Fe(CN)_6]^{3-}$ anions.

A novel procedure for the production of bis(polyazamacrocycles) has recently been reported. Bis(chromium) alkoxycarbene complexes incorporating bridging alkoxy groups have been shown to undergo photochemical cycloaddition to protected imidazolines to yield protected bis(azapenams) (*54*). Deprotection, followed by acid treatment, leads to selective dimerization to produce bis(dioxocyclams) that are bridged at either end with 4-, 5-, 6-, or 12-atom α,ω-diol links. A representative example is given by **28**. These bis(oxocyclam) products were shown to form both mononuclear and dinuclear Ni(II) complexes. The structure of the 5-atom, doubly bridged complex of **28** has been confirmed by X-ray crystallography (Fig. 16).



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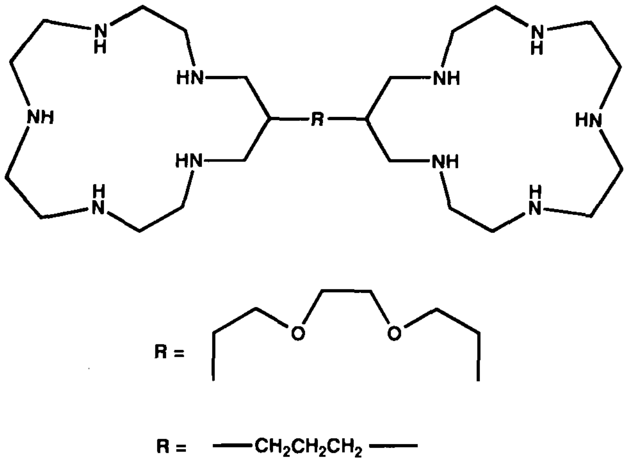

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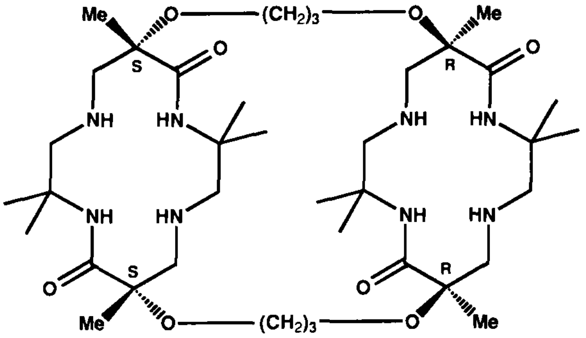


(28)

The characterization of a series of Cu(II) complexes of the binucleating bis(isocyclam) ligands of type **29**, in which a flexible linear polymethylene chain ($n = 2$–4) links a nitrogen of each macrocyclic ring, has been reported (*55*). These species were obtained by detosylation of the corresponding protected macrocycles (Fig. 17). The complexes are of type $Cu_2LX_4 \cdot xH_2O$ (where X = ClO_4 or NCS). The magnetic moments of all complexes are normal. Nevertheless, the hyperfine structure of the EPR spectra in frozen DMF clearly demonstrated the presence of magnetic coupling between the Cu(II) ions.

In an independent study, Kaden *et al.* (*56*) have also undertaken an

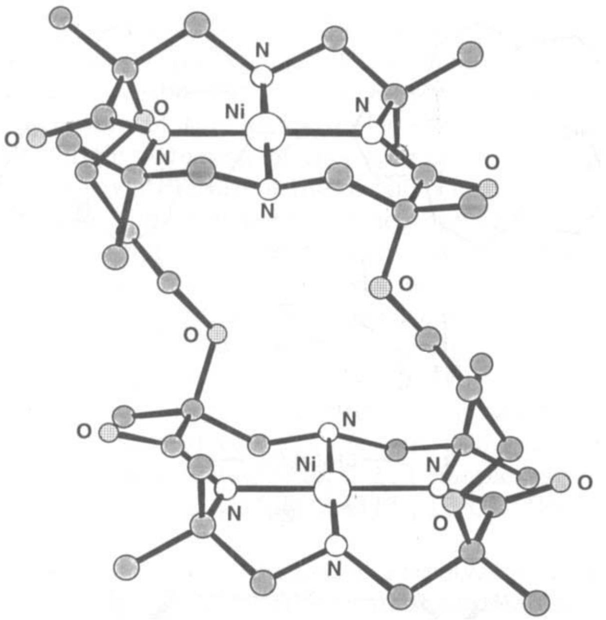


FIG. 16. The structure of the doubly bridged dinuclear Ni(II) complex **28**.

investigation of the complexation of both **29** ($n = 2$) and the related xylyl bridged species (**30**) toward Ni(II) and Cu(II). Both ligand species were demonstrated to yield complexes of type $[M_2L]^{4+}$. Spectrophotometric titration of **29** ($n = 2$) or **30** with Cu^{2+} at constant pH also confirmed the formation of binuclear species. The slopes of the respective titration plots remained constant between 0 and 2 equivalents of Cu(II), indicating that both copper sites give rise to analogous spectral properties; a sharp end point was observed at 2 equivalents of Cu(II) in each case. The visible spectra of the respective Ni(II) and Cu(II) complexes suggest that the metals in these derivatives are in square planar environments. EPR studies on the Cu(II) species con-

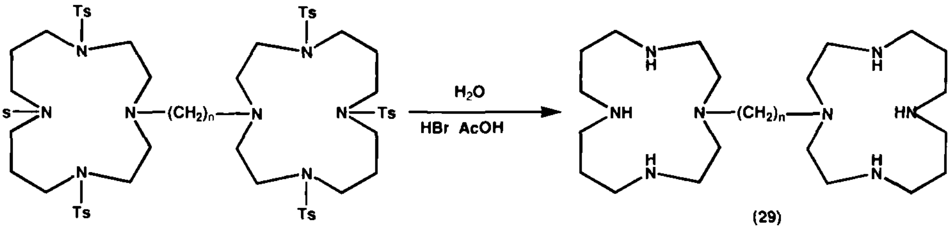
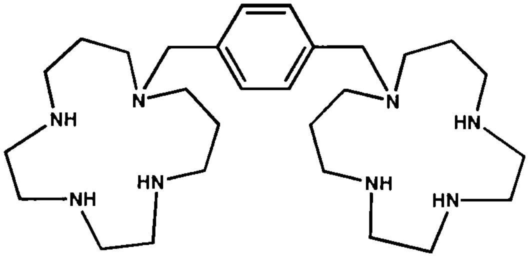


FIG. 17. The synthesis of linked isocyclam derivatives via detosylation of the tosylated precursors.



(30)

firmed the presence of an interaction between the metal centers, with the strength of interaction depending on the length of the bridge.

Cyclic voltammetry and differential pulse polarography have been used to investigate the redox properties of the di-Ni(II) species in acetonitrile. Effectively, a two-electron step was observed for the complex of **30**, whereas that of **29** ($n = 2$) yielded two clear one-electron steps. This is in accord with the occurrence of an interaction between the nickel sites for the latter system containing the shorter link between the isocyclams.

The X-ray structures of the dinickel perchlorate complexes of **29** ($n = 2$) and **30** have been determined (Figs. 18 and 19). A square planar coordination geometry for the Ni(II) in each complex was confirmed. For both complexes, the nickel atoms are separated by the greatest possible distance [7.05 Å in the complex of **29** ($n = 2$; 11.56 Å in the complex of **30**]. It is worth noting that the closely related

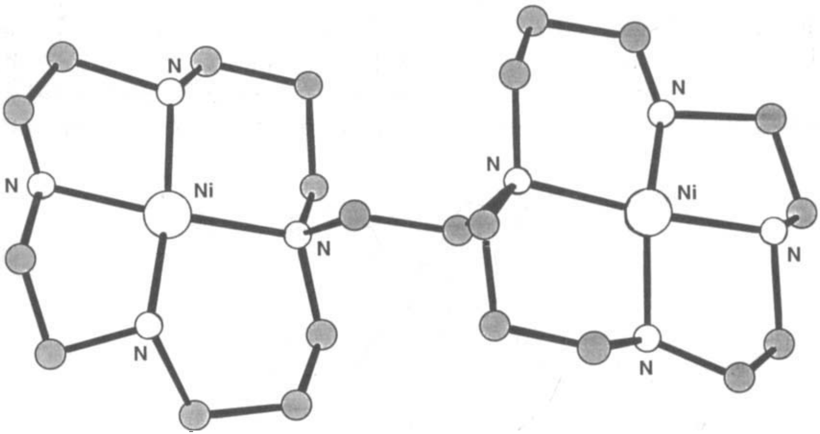


FIG. 18. The structure of the dinuclear Ni(II) complex of **29** ($n = 2$).

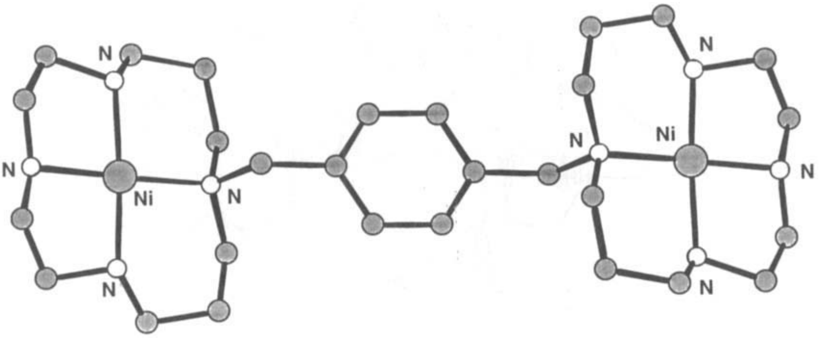


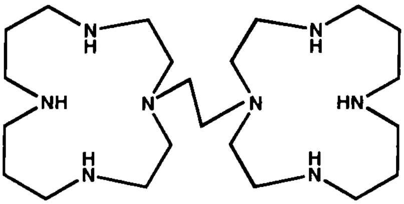
FIG. 19. The structure of the dinuclear Ni(II) complex of **30** (n = 2).

isomeric bis(isocyclam) derivative (**31**) has also been reported and demonstrated to yield a dinuclear Cu(II) complex on reaction with copper perchlorate in hot propanol (*57*).

The family of bis(cyclam macrocycles) represented by **32**, in which the cyclam subunits are linked through nitrogen atoms by $-(CH_2)_n-$ (n = 2–4), *m*-xylyl, or *p*-xylyl groups, has been synthesized (*58*). The di-Ni(II) and di-Cu(II) complexes of these bis(macrocycles) have been used in an investigation of the effects of mutual electrostatic interaction on the redox behavior of the respective metal centers.

The electrochemistry of the above systems once again involves a two-electron process, involving two reversible one-electron steps. The difference in potential between these steps is given by $\Delta E°$. This value is made up of a statistical component associated with a "valence scrambling" equilibrium as well as a component that reflects the electrostatic repulsion between the metal centers.

For the present series of complexes, because of the presence of extended bridges between the macrocycle subunits, it was assumed that any nonelectrostatic effect between metal centers is negligible. Accordingly the systems were treated in terms of a simple electrostatic



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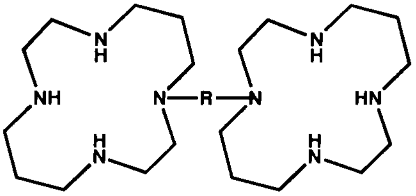
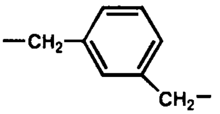


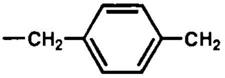
(32)

R = $—CH_2CH_2—$

$—CH_2CH_2CH_2—$

$—CH_2CH_2CH_2CH_2—$

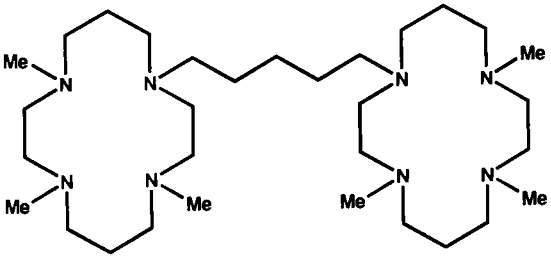




model. On this basis, the observed redox behavior is in accord with the electrostatic repulsion decreasing as the distance between metal sites increases.

An alternative synthesis for the *p*-xylyl-linked system of type **32**, employing a facile *de novo* procedure has been published (*59*). Interest in new syntheses for this compound was motivated by the report that this was the compound of choice for further development in the search for new anti-HIV compounds (*6*).

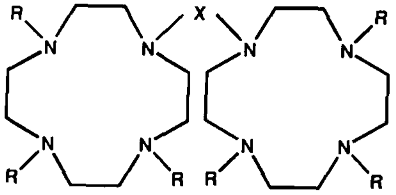
The bis(trimethylated cyclam) derivative (**33**) has been prepared in



(33)

low yield by the reaction of glutaryl dichloride with two equivalents of the corresponding (parent) tri-N-methylated cyclam ring, followed by reduction of the diamide derivative produced with diborane in THF. Reaction of **33** with nickel perchlorate in ethanol yields a dinuclear species of the usual type, $[Ni_2L](ClO_4)_4$ (*60*). Urfer and Kaden (*61*) have described procedures for obtaining a number of mixed-ring bis(macrocycles), starting from tri-N-protected tetraaza rings and employing bromoacetyl bromide as the bridging reagent. The reaction sequence involves the use of the latter reagent to acylate the first tri-N-protected ring (at its nonprotected secondary nitrogen) followed by the employment of this acylated product for alkylation of a second triprotected tetraaza ring. The heteroditropic bis(macrocycle) is then obtained by diborane reduction of the amide moiety followed by deprotection. Structures **34–36** illustrate the range of products (including protected derivatives) obtained in this study, where R is tosyl, H, CH_3; R′ is H, CH_3; and X is $-CH_2CH_2$ or $-C(O)-CH_2CH_2-$ or $C(O)C(O)-$.

Both the symmetric and nonsymmetric bis(macrocyclic) ligands were titrated at constant pH with Cu(II) to confirm that two Cu(II) per ligand can be bound and, if so, to determine whether the complexation process involves two steps or one. For the symmetric sys-



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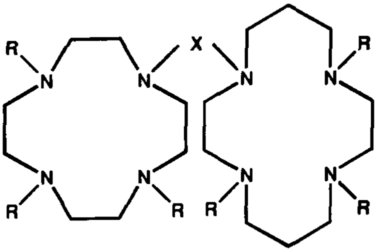

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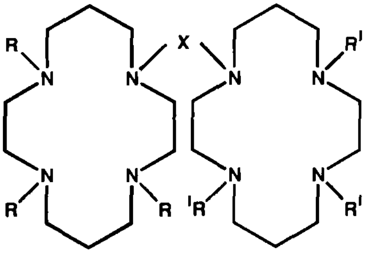

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tems **34** (R = H, X = CH_2CH_2) and **36** (R = R′ = H, X = CH_2CH_2) there was a steady increase in absorption at 610 and 530 nm, respectively, until a sharp end point occurs at a 2:1 (metal:ligand) ratio. This is strong evidence that the respective binding sites are equivalent, or close to equivalent. Unexpectedly, the nonsymmetric system **35** (R = H, X = CH_2CH_2) also gave a similar result, suggesting that the differences in binding constant, as well as the ligand field strength of each site, are not sufficiently different to observe stepwise binding.

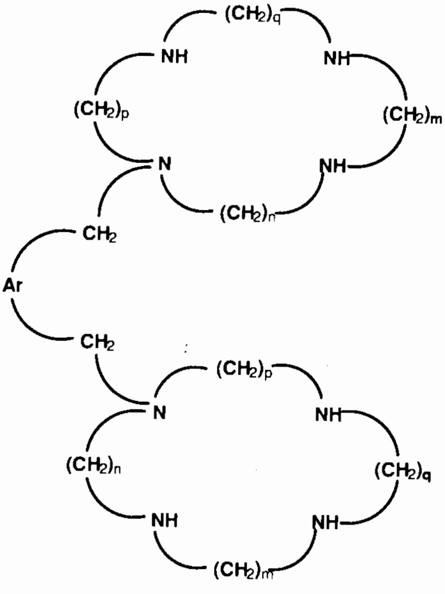
In contrast to the above observations, the ligand incorporating an unsubstituted cyclam bridged to a trimethyl-substituted cyclam undergoes selective metal-ion binding, with the first metal ion being incorporated into the unsubstituted cyclam site and the second being bound by the trimethyl ring derivative. Thus sequential addition of two metal ions in the correct proportions has been demonstrated to provide a means of preparing heterometallic complexes in some instances, without the subsequent need for chromatographic separation of such species from their dinucleating, single-metal analogues. Zn/Cu and Cu/Zn isomers with **36** (R = H, R′ = Me, X = CH_2CH_2) have been prepared.

As part of this study, it was shown that particular binuclear Ni(II) complexes yielded $E^{\circ}_{1/2}$ values that are shifted by 50–150 mV to more positive values relative to the values for the corresponding mononuclear complexes, in agreement with the results from previous studies. This shift may be rationalized in terms of the additional positive charge on the dinuclear complex, resulting in the oxidation of Ni(II) to Ni(III) being less favored. A similar reasoning may be used to explain the 90–100 mV separating the values for the homodinuclear nickel complex of the symmetrical ligand (**36**; R = R′ = H, X = CH_2CH_2). As expected, the related dinuclear Ni(II) complex of the unsymmetrical system (**35**; R = H, X = CH_2CH_2) gave a much greater separation.

The EPR spectra of the dinuclear Cu(II) complex of **36** (R = H, R′ = CH_3, X = CH_2CH_2) have been obtained and, as for related systems of this type studied previously (see earlier), the presence of a weak interaction between the Cu(II) ions was again clearly indicated.

In the context of HIV drug research, the syntheses of a range of other N,N′-linked bis(macrocycles), many obtained in small yields, have been described recently (*6*).

Recent reports also describe the use of *tert*-butyloxycarbonyl (Boc) protecting groups in the preparation of a number of bis(polyazamacrocyclic) ligands of general type **37** (*62*, *63*). As discussed above, a



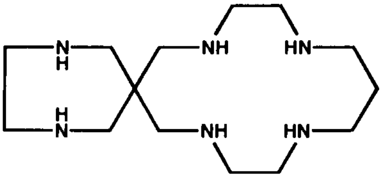
(37)

preferred method for linking two tetraaza macrocyclic units is to start from the corresponding triprotected tetraaza species and condense this with a difunctional electrophile. Frequently tosyl groups have been employed as protecting groups for secondary amines, but the detosylation procedure has often proved not straightforward and its success can depend on the nature of the species involved. In general, the removal of Boc protecting groups tends to be more facile, requiring gentler conditions than is necessary for the detosylation reaction. As a result, there is less chance of unwanted side products being generated.

Using a trial-and-error procedure, it was found that 2.4 equivalents of Boc_2O yielded optimum yields of the corresponding triprotected derivatives when reacted with the tetraaza macrocycles, cyclen (12-membered), cyclam (14-membered), and the corresponding symmetrical 16-membered macrocycle. These partially protected products were then reacted with an aromatic "spacer" group, namely, dibromo *o*-, *m*-, or *p*-xylyl or anthracenyl derivatives. The Boc groups were removed by treatment of the resulting linked systems with 6 *M* HCl for 1 hr. A number of such *o*-xylyl and anthracenyl derivatives were also obtained by reaction of phthaloyl dichloride or anthracene-1,8-dicarbonyl dichloride with the protected macrocycles. In these cases reduction of the intermediate diamides was carried out using diborane in THF. Deprotection of the secondary amines by acid treatment then yielded the required products in near 60% yield.

In an attempt to obtain close-linked bis(macrocycles) related to the systems just discussed, McAuley *et al.* (*64*) were successful in synthesizing the spiro-linked derivatives **38** and **39** in which an sp^3 carbon atom is common to both macrocyclic rings. Although the number of such spiro-linked systems remains small, examples of both open-chain (*65*) and other macrocyclic systems (*66–70*) incorporating such a linkage are known. When the shared atom is an sp^3 carbon then the resulting tetrahedral arrangement will dispose the respective macrocyclic rings to adopt a mutually orthogonal alignment. Unlike most linked systems, free rotation around the linkage joining the macrocyclic subunits is thus not possible for such systems.

Once again, the di-Ni(II) complexes of the bis(cyclam) system **40** exhibits the characteristic robustness that is a feature of $[\mathrm{Ni(cyclam)}]^{2+}$ (*71*). The X-ray structure of the dinuclear Ni(II) complex has been determined (Fig. 20). Nickel atoms fully occupy each of the cyclam cavities in a low-strain coordination arrangement; each ring adopts the low-energy trans III form found for $[\mathrm{Ni(cyclam)}]^{2+}$. An interesting feature of the solid-state structure is that the angle between the rings is not 90°, but rather 84°. The resulting reduction in orthogonality between the d_z^2 orbitals may increase the prospect



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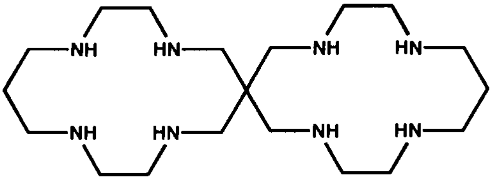


(39)

of communication between the metal sites. As expected, the above dinuclear Ni(II) complex is readily oxidized (both chemically and electrochemically) to the corresponding [Ni(III)–Ni(III)] species; attempts to isolate the intermediate [Ni(II)–Ni(III)] species were unsuccessful.

The dinucleating bis(dimethylcyclam) ligand **40** has been synthesized and its complexes with Ni(II) and Zn(II) isolated (*72*). The employment of an *ortho*-dihalo-xylyl group for condensation with two molecules of **9**, by the usual electrophilic attack mechanism, followed by sodium borohydride reduction, gives an arrangement in which the macrocyclic rings are oriented face to face. The resulting complex, $[Ni_2(\mu\text{-}Br)Br_2L]Br \cdot H_2O$ (L = **40**), was obtained in 60–70% yield. Treatment of this species with sodium cyanide in water/ethanol results in demetalation to yield the free bis(macrocycle). Treatment of this metal-free species with Zn(II) perchlorate, followed by slow crystallization of the resulting product over several weeks, gave the carbonato-bridged species **41**. The structures of the dinucleating ligand in the above di-Ni(II) complex and in **41** are very similar, with the cyclam rings adopting stable trans III arrangements in each case. The two methyl substituents on each ring are orientated equatorially with respect to the corresponding chair-form chelate ring. In contrast, the xylylene group is arranged axially; it is this orientation of the *ortho*-xylylene moiety that directs the adoption of a face-to-face configuration. The structure of a chloro-bridged complex of **40**, related to the bromo derivative mentioned above, has also been reported (*73*).

Based on a related procedure for synthesizing single-ring complexes (*74*), template condensation of $[Ni(2,3,2\text{-tet})]^{2+}$ (2,3,2-tet = 1,9-

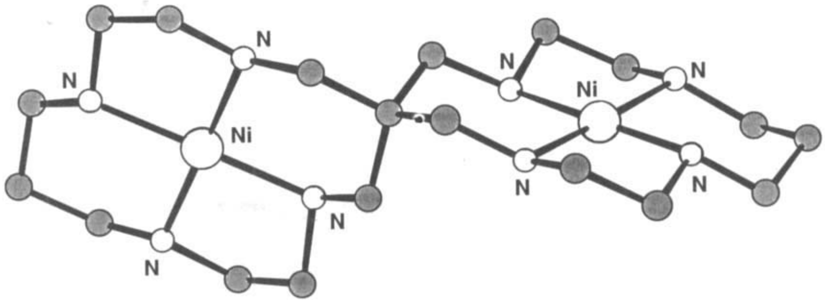
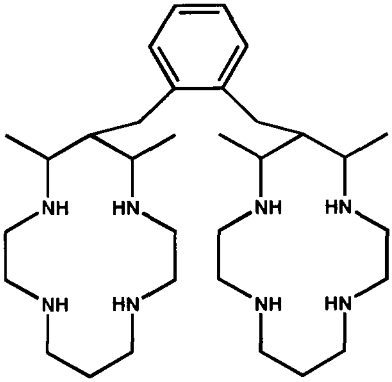


FIG. 20. The structure of the di-Ni(II) complex of a spiro-linked bis(cyclam) derivative (**39**).



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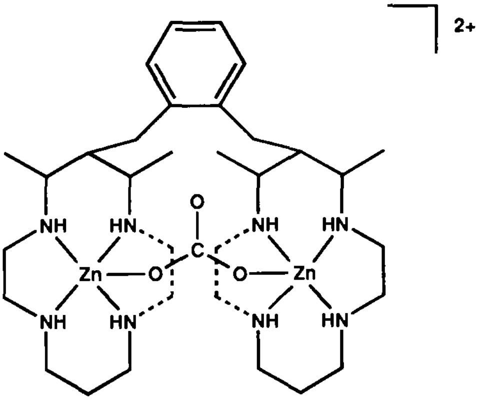
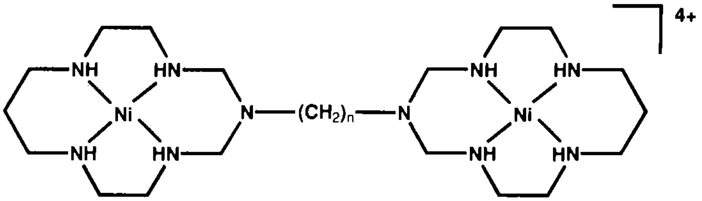


(41)

diamino-3,7-diazanonane) with formaldehyde and aliphatic diamines was demonstrated to yield bis(pentaaza-macrocyclic) complexes of type **42** ($n = 2$–5) in a one-pot reaction (*75*, *76*). The new ligand systems have their macrocyclic subunits linked by polymethylene chains of various length via noncoordinating, bridge-head nitrogens in each ring.

The electrochemical and spectral data for the dinuclear Ni(II) complexes were found to be very similar to those of the corresponding mononuclear species (**43**). The visible spectrum of each complex indicated the presence of low-spin, square planar Ni(II). Interestingly,



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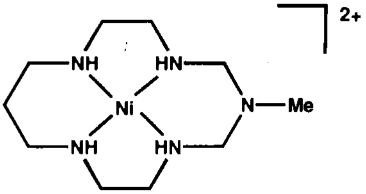


(43)

these complexes are quite stable to pH over the range 2–12. The voltammograms for the individual complexes contain single anodic and cathodic peaks that are separated by ~100 mV. The number of methylene groups linking the rings has almost no effect on the respective $E_{1/2}$ values; this provides strong evidence for the absence of interaction between the metal sites.

Oxidation of the above complexes to the corresponding Ni(III) species was found to occur readily using either chemical or electrochemical means (under acidic conditions). EPR spectral data for the bis(macrocyclic) Ni(III) complexes are very similar and confirm the presence of a d^7 electronic configuration in which the metal is in a tetragonally distorted environment.

Rate data for the oxidation of the respective Ni(II) complexes to their Ni(III) analogues have been obtained. The formation of the latter was observed to be first order in Ni(II) and oxidant ($S_2O_8^=$ or H_2O_2), with the rate constants being several times greater for the dinuclear complexes than for the single-ring analogue.

The analogous series of Cu(II) complexes have also been prepared by a procedure similar to that for the Ni(II) species starting from the 1:1 Cu(II) complex of 2,3,2-tet.

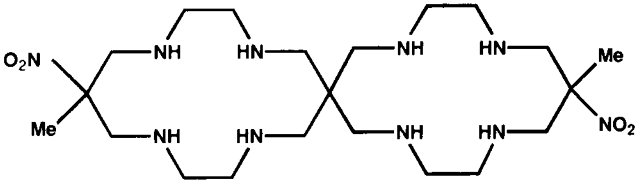
In other studies, a related *in situ* procedure has been employed to produce a di-Cu(II), bis(macrocyclic ligand) system linked by an ethylene bridge through noncoordinating N atoms (*77*). The ligand in this case incorporates a 1,3-diazacyclohexane ring in each macrocyclic subunit.

An *in situ* procedure involving condensation of the appropriate open-chain, spiro-linked amine with nitromethane and formaldehyde in water in the presence of copper perchlorate has been employed to obtain the dinuclear Cu(II) perchlorate complex of **44** (*78*). The visible spectrum of this complex is very similar to that of its mononuclear analogue. In solution, the metal in each complex was assigned a tetragonally distorted octahedral environment in which axial solvation completes the coordination sphere. As with other complexes of this general type, the addition of dilute acid did not affect the spectrum of this species.

Electrochemical studies, related to those discussed previously, gave clear evidence for the presence of interaction between the metal sites. A detailed investigation of the EPR spectrum of this complex has been undertaken, enabling structural parameters to be deduced.

An extension of the template reaction mentioned above [involving condensation of the Cu(II) complex of a tetradentate amine with formaldehyde and a nitroalkane] was employed to prepare the Cu(II) complexes of the series of bis(tetraaza macrocyclic) ligands given by **45** (*79*). Reduction of the nitro groups in these species with Zn/HCl produced the corresponding metal-free bis(pendant amino) derivatives (**46**).

EPR studies gave no evidence for interaction between the Cu(II) centers in the bis(nitro) derivative incorporating 14-membered macrocyclic rings when the latter are joined by an ethylene bridge. In accordance with this, molecular mechanics calculations coupled with simulated EPR data suggested that this complex will adopt a "stretched" arrangement in solution. The absence of interaction in this complex contrasts with the behavior of the related di-Cu(II) complex corresponding to **43**; (n = 2) for which a weak interaction was demonstrated to be present (*76*). For this latter species the calculations suggest that it exists largely in a face-to-face configuration in solution.



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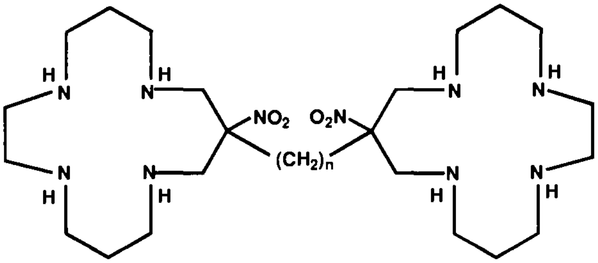

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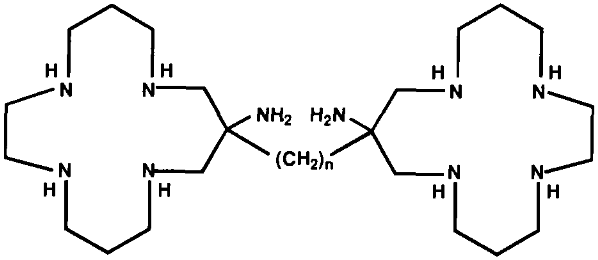
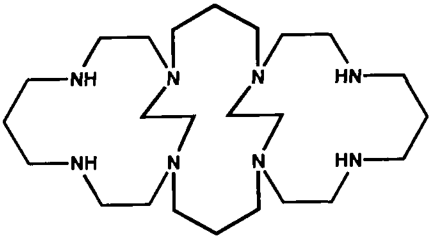


(46)

Co(II), Ni(II), and Cu(II) binuclear complexes of the dilinked species (**47**), incorporating 13-membered macrocycle subunits, have been reported (*80*). The X-ray structure of one such product, $[Cu_2(Tos)L]$ $(ClO_4)_2 \cdot 4H_2O$ (where Tos is the tosylate anion and L = **47** has been determined (Fig. 21). This complex has a distorted square pyramidal coordination geometry; four nitrogen donors coordinate in the basal plane with a tosylato oxygen occupying the axial site. The basal nitrogens deviate from their mean plane by ±0.12 Å. Each of the macrocycles adopts a dish-shaped arrangement, with the Cu(II) coordinating on the outer side of the dish. This complex reacts with F^-, Cl^-, Br^-,



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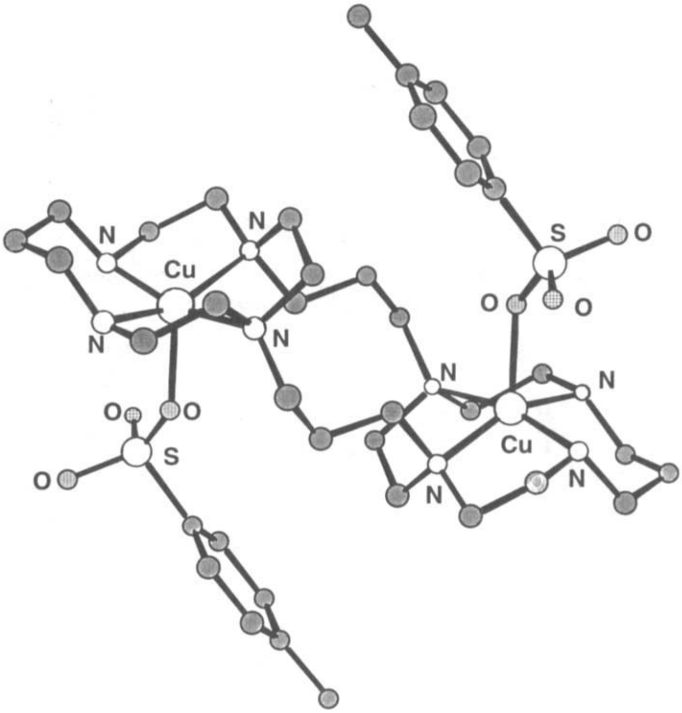


FIG. 21. The structure of $[Cu_2(Tos)L]^+$ (Tos = tosylate anion, L = **47**).

I^-, and N_3^- in aqueous solution to form a range of anion-bridged complexes of type $[Cu_2XL](ClO_4)_3 \cdot xH_2O$ (X = halide). All these have magnetic moments that fall in the normal range. The Ni(II) complex, $[Ni_2L](ClO_4)_4$, is essentially diamagnetic and each nickel was assigned a square planar coordination geometry.

The di-Co(II) species, $[Co_2OHL](ClO_4)_3$, rapidly binds CO_2 in aqueous solution to yield $[Co_2CO_3L](ClO_4)_2 \cdot 3H_2O$. An X-ray diffraction study of this product revealed that each Co(II) ion has a distorted octahedral geometry made up of four nitrogens from **47** and two oxygens from the carbonate anion (Fig. 22).

A variety of linked, Schiff base macrocyclic ligands and their metal complexes have been isolated. An early ligand of this type is given by **48** (*81*). Reaction of the free ligand with Ni(II) or Cu(II) acetate yields the corresponding dimetallic complexes. In contrast, the nickel(II) complexes of type **49** were obtained by means of a Schiff base condensation *in situ* in which the required amine and dialdehyde reagents were reacted in hot DMF in the presence of nickel acetate (*82*).

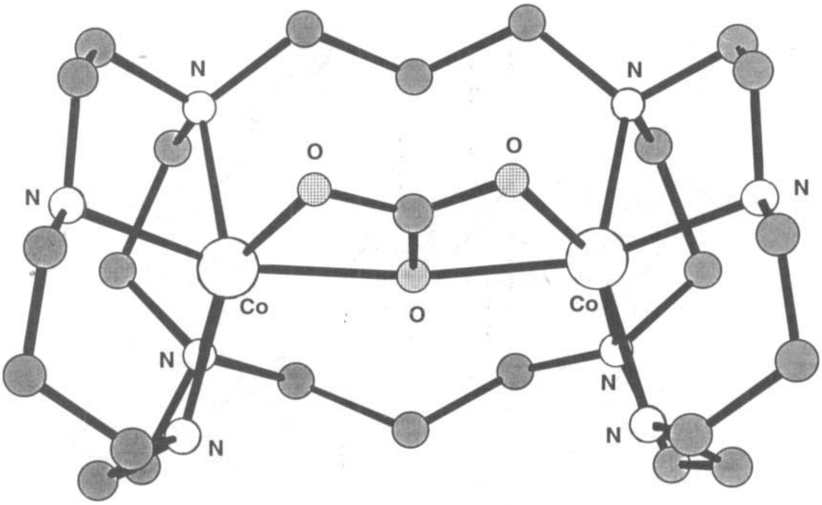
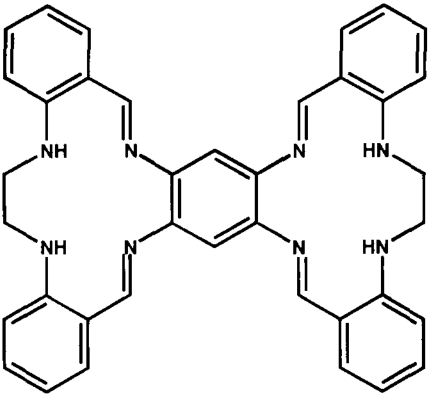


FIG. 22. The structure of $[Co_2CO_3L]_2$ (L = **47**).

The *in situ* Schiff base condensation of 2,6-diacetylpyridine with *N,N,N′,N′*-tetrakis(3-aminopropyl)-1,2-diaminoethane in the presence of copper(II) chloride was demonstrated to yield the dinuclear cation **50** (n = 2; R = CH_3) as its perchlorate salt (*83*). The corresponding single-ring, mononuclear copper(II) complex **51** (R = CH_3) had been reported previously (*84*). Both this and the dinuclear species yield similar visible spectra, suggesting that similar copper coordination



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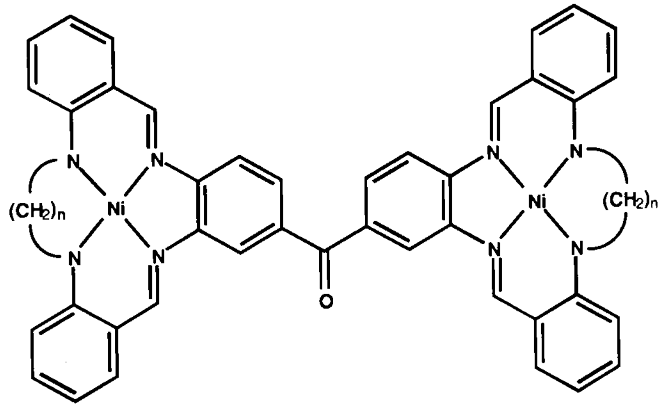

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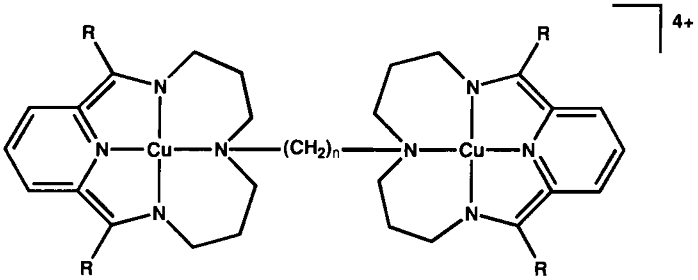
environments are present in each complex. For the dinuclear species, variable-temperature magnetic studies indicated that some antiferromagnetic interaction occurs between the Cu(II) sites; Curie–Weiss behavior was observed over the temperature range 290–87 K, with θ =



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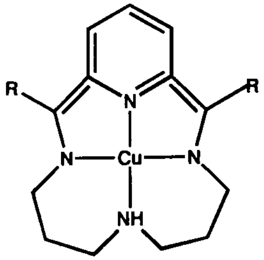


(51)

−14 K. ESR studies (DMF glass) gave clear evidence for interaction between the sites, particularly when the spectrum was compared with the similar spectrum of the above mononuclear species. The coupling of two ^{63}Cu nuclei ($I = \frac{3}{2}$) is expected to give rise to two sets of seven hyperfine lines whose separation ($A_{\|}$) is one-half of that for the hyperfine lines in the spectrum of the corresponding mononuclear complex. This situation is closely approximated by the present system.

In an extension of the above study (*85*), Cu(II) complexes of ligands of type **50** incorporating from three to six methylene groups linking the macrocyclic subunits have been prepared. Two dinuclear Ni(II) complexes were also isolated. The properties of the copper complexes were found to be generally similar to those discussed above for the parent complex. Nevertheless, as the link between the macrocyclic rings becomes longer, the respective negative Weiss constants decrease, suggesting that the already weak antiferromagnetic interaction present in the parent complex decreases further along the series. Heterobinuclear [Ni(II)/Cu(II)] complexes of the above ligand series (n = 2–6) have been prepared by *in situ* condensation in the presence of a mixture of these metals (*86*). A mixture of Cu(II)/Cu(II), Cu(II)/Ni(II), and Ni(II)/Ni(II) species was obtained, but the individual complexes were able to be separated by chromatography using an SP-Sephadex C-25 ion-exchange column.

An X-ray diffraction study of the di-Ni(II) complex **50** (n = 4; R = CH_3) shows that it adopts an open configuration in the solid state, in which the macrocyclic subunits are widely spaced (*87*). The X-ray structures of two Cu(II) complexes of this ligand have also been determined (*88*). $[Cu_2(H_2O)_2L](ClO_4)_4 \cdot 4H_2O$ also adopts an open structure in which the copper sites are widely separated. In contrast, $[Cu_2Cl_2L](ClO_4)_2 \cdot H_2O$ crystallizes in a closed configuration in which the tetramethylene chain is folded such that the two macrocyclic subunits face each other. In part, the difference between the structures of these complexes appears to reflect the reduced electrostatic repulsion between the copper centers when the latter are each bound to a chloro ligand, rather than to an uncharged water ligand, as occurs in $[Cu_2(H_2O)_2L]^{4+}$.

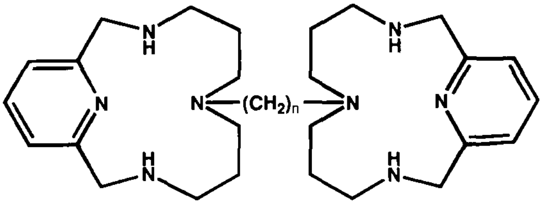
The square planar/octahedral equilibrium commonly observed for the Ni(II) complexes of tetraaza ligands in aqueous solutions has once again been shown to occur for the Cu(II)/Ni(II) and Ni(II)/Ni(II) systems (*89*). The equilibria for both systems show the usual dependence on temperature, with the percentage of square planar form increasing as the temperature is increased. It was found that the position of the equilibrium was also dependent on the length of the polymethylene bridge—shortening the bridge had an effect similar to lowering the temperature—for both the homo- and heterobinuclear species. That is, formation of the octahedral form is favored as the bridge is shortened.

A parallel study of the Ni(II)/Ni(II) complexes of related reduced forms of the above ligand series (namely, of type **52**) in aqueous solution has been carried out (*90*). Once again, as the length of the methylene chain between the macrocyclic subunits decreases, the proportion of octahedral over square planar complex present increases.

A heterobinuclear [Cu(II)/Ni(II)] complex of **52** ($n = 3$) has been isolated {after chromatographic separation from the corresponding [Cu(II)/Cu(II)] and [Ni(II)/Ni(II)] products also formed} following reaction of a mixture of both metals with this dinucleating ligand (*91*). It has been possible to reduce the Cu(II) selectively in the hetereobinuclear complex by electrolysis (at −0.6 V), using a mercury pool as working electrode. After loss from the macrocyclic cavity, the Cu(O) generated presumably forms an amalgam with the mercury. From the resulting solution the complex of **52** ($n = 3$), containing one Ni(II), was isolated. Addition of one equivalent of Cu(II) to a solution of this product was shown to regenerate the original heterodinuclear species.

The above study has been extended to encompass the synthesis of a new system incorporating differentially substituted macrocyclic subunits (*92*). Starting from the mononuclear Ni(II) complex of **52** ($n = 3$) described above, it proved possible to obtain a selective Michael addition reaction between acrylonitrile and the secondary amine groups of the vacant macrocyclic ring. Reaction of the product with Ni(II) yielded the nonsymmetrical complex **53**. Based on comparative visible spectral studies, one nickel atom in this complex was assigned a four-coordinate geometry; the second appears to be five-coordinate.

In wide ranging studies, Bush *et al.* (*93, 94*) have investigated an extended series of binuclear complexes of type **54** incorporating dilinked tetraimine macrocyclic subunits. These systems adopt face-to-



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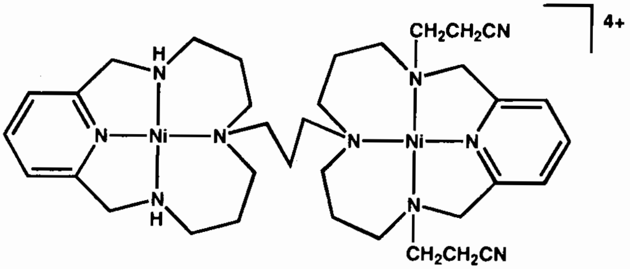
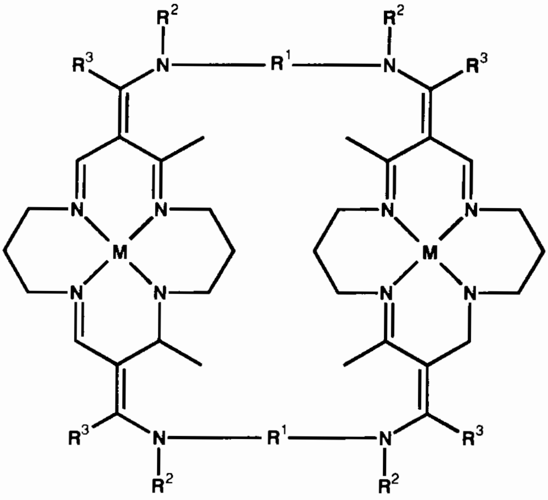


(53)

face orientations, although the rings may be displaced somewhat with respect to each other in some complexes. These systems incorporate large flexible cavities between the macrocycle rings, which can be varied in size by changing the nature of the linking ($-R^1-$) groups. For example, in one study dinuclear Ni(II) complexes were prepared in which R^1 varied over the range: $-N(CH_3)(CH_2)_2N(CH_3)-$, $-NH(CH_2)_2NH-$, $-NH(CH_2)_3NH-$, $-NH(CH_2)_5NH-$, $-N(CH_2CH_2)_2N-$, and $-NHCH_2C_6H_4CH_2NH-$ (*94*). Dinuclear Co(II) and Fe(II) complexes of such cofacial dimers have been investigated as dioxygen binders and, for example, particular Fe(II) species are excellent reversible dioxygen carriers. The dinuclear complexes of the above metals also exhibit a range of interesting redox properties that have



(54)

been studied in detail. The chemistry of these interesting and well-studied systems has been reviewed elsewhere (*95*) and will not be discussed further here.

III. Concluding Remarks

Synthetic routes for compounds of the type discussed in this review have been developed over the past 25 years or so. Interest in this area has stemmed, in part, from the intellectual and practical challenge arising from design and synthesis aspects, but also because particular compounds might provide models for dimetallic protein centers found in biology. However, as often happens interest in such compounds has been engendered by a recently discovered medical relevance—namely, that some compounds are active against HIV. In this context, it is likely that there will be an acceleration of new chemistry in the area. It is hoped that the present review will be helpful in this enterprise.

ACKNOWLEDGMENTS

The author thanks the Australian Research Council for support and I. M. Atkinson and J. Kim for technical assistance in the preparation of this review.

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