

DEVELOPMENTS IN THE SYNTHESIS AND COORDINATION CHEMISTRY OF MACROCYCLIC
 SCHIFF BASE LIGANDS

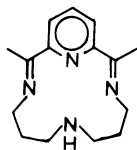
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Abstract - The use of metal ions as templates in the synthesis of a range of macrocyclic Schiff base ligands varying in size (15-30 member atoms), in the number and nature of the potential donor atoms, and in flexibility is described. Factors controlling the course of the reactions are discussed. Open-chain intermediates have been isolated in several cases and mechanisms for the cyclizations are proposed. The structures, properties and reactions of the macrocyclic complexes, including the use of some binuclear copper complexes as receptors for small bridging molecules and ions (e.g. pyrazine, imidazolate ion), are reported.

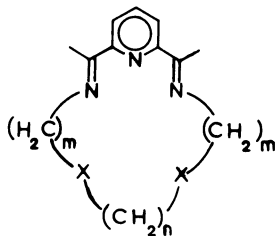
INTRODUCTION

Condensation reactions between carbonyl compounds and primary amines have played a central role in the synthesis of new macrocyclic ligands (Ref. 1-5). Usually, though not necessarily, such reactions are conducted in the presence of a suitable metal ion which may serve to direct the condensation preferentially to cyclic rather than oligomeric/polymeric products - the kinetic template effect, or to stabilise the macrocycle once formed - the thermodynamic template effect (Ref. 2, 4 & 6). A particularly useful precursor dicarbonyl is 2,6-diacetylpyridine (DAP), which having a good donor atom (the pyridine nitrogen), may be held to (and possibly activated by) the template ion while nucleophilic attack at the carbonyl carbon atom occurs (Ref. 2). Among the first macrocycles of this class to be synthesised is the 14-membered tetradentate 'N₄' ligand (L¹) obtained by *in situ* reaction of DAP with 3,3'-diaminodipropylamine in the presence of Ni(II), Cu(II), Mn(II), Co(II) and



L¹

Zn(II) salts (Ref. 7). This paper surveys more recent work over the last decade on macrocyclic Schiff base ligands based on the use of DAP and related dicarbonyl precursors. Attention is focussed on four aspects: (i) synthesis via metal ion template methods, (ii) structures and physical properties of the metal complexes, (iii) the chemical consequences of a mis-match in the geometrical preferences of metal ion and macrocycle, and (iv) the use of binuclear complexes of macrocyclic ligands as receptors for small bridging substrate molecules and ions.



L ²	m = n = 2,	X = NH
L ³	m = 2, n = 3,	X = NH
L ⁴	m = 3, n = 2,	X = NH
L ⁵	m = n = 2,	X = O
L ⁶	m = 2, n = 3,	X = S
L ⁷	m = 3, n = 2,	X = S

PENTADENTATE MACROCYCLES

In 1964 Curry and Busch (Ref. 8) reported the *in situ* synthesis of the pentadentate 15-membered 'N₅' macrocycle (L²) from DAP and 3,6-diazaoctane-1,8-diamine in the presence of iron(II). The macrocycle was isolated as the iron(III) complex originally formulated as [FeL²(OH)]₂[(ClO₄)₂]₂, in which the folded ring occupies five octahedral sites. However, further study (Ref. 9), including an X-ray investigation (Ref. 10), showed the complex to be the μ -oxo dimer [(FeL²(ClO₄)₂O)]₂[(ClO₄)₂]₂·H₂O in which each metal ion has a pentagonal bipyramidal geometry with the five nitrogens of the ring defining the equatorial plane. Subsequently, it was shown that other d⁵ and d¹⁰ ions, Mn(II) and Zn(II), also are effective template ions for the formation of L², and closely related 15-membered 'N₅' rings, the complex products ML²X₂ (X = halide, H₂O, etc) having essentially the same pentagonal bipyramidal coordination (Ref. 11-13). Similar complexes of the 16-membered 'N₅' macrocycle L³ with Fe(III) were also prepared and structurally characterised (Ref. 14). The discovery of the 7-coordinate geometry in these macrocyclic complexes was of interest because of the rarity (at that time) of this coordination number particularly among metal ions of the first transition series. The structural investigations referred to above had shown that the preferred conformation of both L² and L³ is pentagonal planar. Thus both these rings are ideal for the purpose of imposing a pentagonally based stereochemistry on metal ions of differing electron configurations. A systematic investigation of the capacity of a wide variety of metal ions to accommodate to a pentagonal disposition of donor atoms was therefore undertaken. Two synthetic approaches were employed. In the first the efficacy of the metal ion as a template for the *in situ* synthesis of the 15-, 16- and 17-membered 'N₅' macrocycles (L², L³ and L⁴), and of the 15-membered 'N₃O₂' macrocycle (L⁵) was examined. In the second, the possibility of exchanging the complexed template metal ion for other metal ions not effective as templates was investigated (see later).

Template synthesis of the macrocyclic ligands

In most cases the macrocycles were prepared by reacting DAP (or related dicarbonyl) with the appropriate diprimary amine in equimolar proportions in the presence of a metal salt. Various solvents were used, most commonly MeOH or EtOH. The optimum reaction temperatures and reaction periods, found by experiment, varied widely from ca. 30 min. at 20°C to 48 h at 65°C. The importance of the metal ion is shown by the fact that in its absence only viscous oils were obtained, these having indefinite composition and properties suggestive of an oligomeric/polymeric constitution. The macrocycles were isolated as crystalline complexes of the metal ion used as a template in their formation. It appears that the metal ion has a stabilising effect on the macrocycle. Attempts to isolate the free macrocycles after displacement of the metal ion proved unsuccessful.

Not all metal ions have proved to be effective as templates for the four macrocycles (L²-L⁵) under discussion. Table 1 summarises our results to date in this regard. The entry 'No' means that the synthesis has been attempted but has proved unsuccessful under the conditions employed. The Table shows that a few metal ions lead to the synthesis of the smaller macrocycles (15-membered L² and L⁵ and 16-membered L³) but not to the largest (17-membered L⁴). A probable reason for this is the compatibility or otherwise of the sizes of the metal ion and the 'hole' of the macrocycle. Thus, ions of radius less than ca. 0.80 Å appear not to form macrocyclic complexes with L⁴. However, the converse does not always apply since a large metal ion such as Hg²⁺ does complex with e.g. L². There is structural evidence that in some such cases the metal is displaced from the plane of the ring (Ref. 16) and in others that a 'double' rather than a 'single' ring is formed via a [2+2] condensation of two moles of diketone with two moles of diprimary amine (see later). It is surprising, at first sight, that neither Ni(II) nor Cu(II) are templates for any of the macrocycles (L²-L⁴) since both ions are commonly used as templates in the synthesis of tetradentate 'N₄' macrocycles (Ref. 5). This is probably due to the preference of these ions for stereochemistries (octahedral, tetragonal, square pyramidal and square planar) in which the bonding orbitals are in orthogonal relationships as is apparent, for example, from a comparison of the crystal field stabilisation energies of the d⁸ and d⁹ ions in fields of O_h and D_{5h} symmetry (Ref. 17). Although a few pentagonal bipyramidal complexes of these ions are known (Ref. 18 and below) there is clear evidence, at least for Ni(II), that this is an unstable stereochemistry relative to the octahedron (see below)

Synthesis by metal exchange (transmetalation)

Since the macrocyclic Schiff base ligands appear to be unstable in the uncomplexed state it might appear that synthesis of metal complexes is restricted to those of metals which are effective as templates. However, it has been found that the complexes are usually kinetically labile and that the complexed template ion may be readily exchanged in very many cases for other metal ions present in solution. Thus, if the complex [AgL³]₂[(ClO₄)₂]₂, for example is treated with MX (M = alkali metal, X = halide or thiocyanate ion) precipitated AgX together with macrocycle decomposition products are obtained. However, if the reaction is carried out in the presence of a second metal ion the liberated macrocycle is 'captured' and stabilised by coordination to the new metal ion before decomposition. In this way a range of Ni(II) and Cu(II) complexes of L³, and other macrocycles, have been obtained which are not accessible by the direct template route (Ref. 19 & 20).

TABLE 1. Efficacy of various metal ions as templates in the synthesis of 'N₅' and 'N₃O₂' macrocycles

Ion	Ionic radius ^a (Å)	L ²	L ³	L ⁴	L ⁵	Ref.
Mg ²⁺	0.72	Yes	Yes	No	Yes	21
Ca ²⁺	1.00	No	-	-	No	21
Sr ²⁺	1.16				Yes ^b	22
Ba ²⁺	1.36				Yes ^b	22
Al ³⁺	0.53	No				21
La ³⁺	1.05		Yes	No		26
Mn ²⁺	0.82	Yes	Yes	Yes	Yes	23,24
Fe ³⁺	0.65	Yes	Yes		Yes	9,14,23
Fe ²⁺	0.78	Yes	Yes		Yes	25
Co ²⁺	0.74	Yes	Yes		Yes	26
Ni ²⁺	0.70	No	No	No	No	19
Cu ²⁺	0.73	No	No	No	No	19
Ag ⁺	1.15	?	Yes	Yes	Yes ^b	16
Zn ²⁺	0.75	Yes	Yes	No	Yes	13
Cd ²⁺	0.95	Yes	Yes	Yes	Yes	16,27
Hg ²⁺	1.02	Yes	Yes	Yes	No	16,27
Sn(IV)	0.69	Yes	Yes	Yes	No	28
Pb ²⁺	1.18	Yes	No	Yes	Yes ^b	29,30,31

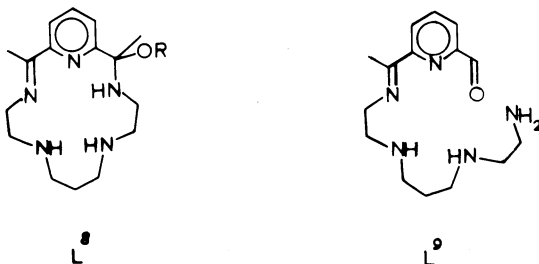
^a Radii refer to the high-spin hexacoordinate ions (Ref. 15)

^b In these cases a 30-membered 'N₆O₄' macrocycle is formed

Structures of complexes of the pentadentate macrocycles

Complexes of L², L³ and L⁵. Single crystal X-ray structure determinations (carried out by Dr. M.G.B. Drew, University of Reading) of a wide range of metal complexes of the potentially pentadentate macrocycles L²-L⁷ have shown that the preferred conformation of the 15-membered (L² and L⁵) and the 16-membered (L³) rings is that in which the five donor atoms define a pentagonal plane but that the more flexible 17-membered rings may adopt a variety of conformations. Thus, 7-coordinate (pentagonal bipyramidal) geometries have been demonstrated for Mg(II), Mn(II), Fe(III), Fe(II), Zn(II), Cd(II) and Sn(IV), and 6-coordinate (pentagonal pyramidal) structures for Co(II), Ag(I), Cd(II) and Hg(II) complexes containing L², L³ or L⁵ (Ref. 10, 13, 14, 16, 19, 21, 23-28). Properties of the complexes are described in the references cited.

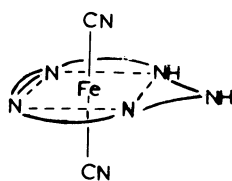
In a few cases, however, octahedral rather than pentagonal-based geometries are obtained. Reference has already been made to the greater crystal field stabilisation energy (CFSE) of Ni(II) in O_h compared to D_{5h} symmetry. When Ag(I) in [AgL³]₂[ClO₄]₂ is exchanged by Ni(II) in dry ROH (R = Me or Et) the product is an octahedral complex of the new more flexible macrocycle (L⁸) derived from L³ by addition of ROH across one of the azomethine bonds. If the reaction is carried out in the presence of water, hydrolysis occurs to give an



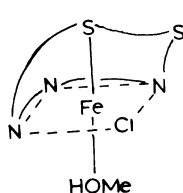
octahedral complex of the ring-opened ligand (L⁹). Molecular models and various structural analysis show that L³ cannot fold so as to occupy five octahedral positions. Thus, it is the strong preference of Ni(II) for an orthogonal disposition of metal-ligand bonds which is the driving force for this macrocycle, after replacement of Ag(I) by Ni(II), to add ROH across one C = N bond thereby acquiring the necessary flexibility to coordinate on an octahedron (Ref. 19). The ability of pentadentate macrocycles such as L², L³ and L⁵ to impose an unusual (pentagonal bipyramidal) geometry on a metal ion is amply illustrated by results obtained for e.g. Mn(II), Fe(III), Fe(II), Co(II), etc. In this reaction we see the opposite effect in operation, namely, the imposition on the macrocycle of a new conformation,

via chemical modification, because of the stereochemical preferences of the metal ion.

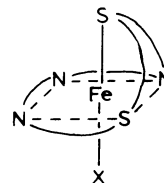
A second example where a metal ion forces a new coordination mode upon a 'pentagonal' macrocycle is drawn from the chemistry of some Fe(II) complexes of L^2 , L^3 and L^5 . As noted above a range of pentagonal bipyramidal complexes $FeLX_2$ ($X =$ axial monodentate ligand) of these ligands have been characterised (Ref. 23, 25 & 32).² In contrast the dicyano derivatives $[FeL(CN)_2] \cdot xH_2O$ ($L = L^2$ or L^3 ; $x = 0, 0.5$ or 1) are diamagnetic. Since a spin singlet ($S = 0$) ground state for a d^6 system is precluded in D_{5h} symmetry it is concluded that those complexes have the trans octahedral structure (1) in which one of the secondary amine groups is uncoordinated. Once again it appears to be the large CFSE advantage of the $t_{2g}^6 e_g^0$ configuration which is responsible for the adoption of the somewhat strained 'square' coordination of L^2 and L^3 in these complexes. The complex $FeL^5(CN)_2 \cdot H_2O$



(1)



(2)



(3)

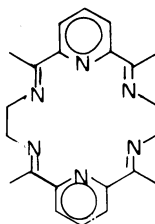
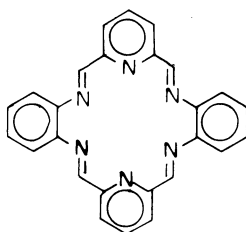
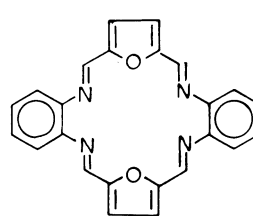
is high spin at 293K ($\mu_{eff} = 5.09$ B.M.) but the moment falls to 3.57 B.M. at 93K. Parallel Mossbauer effect experiments show that at this temperature half the metal ions are in the $S = 0$ spin state and half in the $S = 2$ spin state. The spin change-over is accompanied by marked hysteresis effects suggesting considerable lattice reorganization and it may be that the $(S = 2) \rightarrow (S = 0)$ spin transition involves a stereochemical rearrangement from a pentagonal bipyramidal to an octahedral structure in the solid state.

Complexes of L^4 and L^7 . Increase in size of the pentadentate macrocycles to the 17-membered ring (L^4) leads to a considerable increase in flexibility allowing a readier response to the geometrical preferences of the central metal ion. Thus, L^4 can fold so as to occupy five octahedral sites without addition of ROH when complexed to Ni(II) (Ref. 19), while for Mn(II) complexes, for example, a (slightly folded) pentagonal disposition of donor atoms is retained (Ref. 24). In $[AgL^4][ClO_4]$ the Ag(I) is 5-coordinate, the macrocycle having a distorted pentagonal planar conformation (Ref. 16).

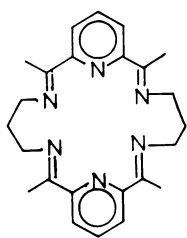
For the case of the sulphur-containing macrocycle (L^7) an even greater variety of coordination modes is observed. Not only has this ring the flexibility associated with 17-member atoms, it also contains two sulphur atoms which may or may not be coordinated depending on the nature of the metal ion. In $[CuL^7]^+$ and $[AgL^7]^+$ both sulphur atoms are strongly bonded to the d^{10} metal ion giving 5-coordinate (distorted trigonal bipyramidal) arrangements (Ref. 33). In $[CuL^7(NCS)][ClO_4]$, on the other hand, one sulphur atom is uncoordinated while in $[CuL^7(NCS)_2]$ neither thioether group is bonded (Ref. 20). Again, the high spin ($S = 2$) complex cation $[FeL^7Cl(MeOH)]^+$ contains one bonded sulphur structure (2) while in the low spin ($S = 0$) complexes $[FeL^7X]^+$ ($X = NCS$ or I) both sulphur atoms are coordinated [structure (3)] (Ref. 34).

MACROCYCLES DERIVED FROM 2 + 2 CONDENSATIONS

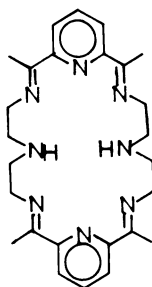
The synthesis of the 14-membered 'N₄' macrocycle (L^1) employing Mn(II), Co(II), Ni(II), Cu(II) or Zn(II) as template ion (Ref. 7) has been mentioned above. When the synthesis is carried out in the presence of Ag(I), however, the product is the binuclear complex $[Ag_2L^{16}]X_2$ ($X = ClO_4$ or BPh_4) in which L^{16} is the 28-membered macrocycle derived from the

 L^{10}  L^{11}  L^{12}

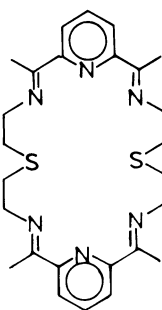
(Ca²⁺, Sr²⁺, Ba²⁺, Pb²⁺)



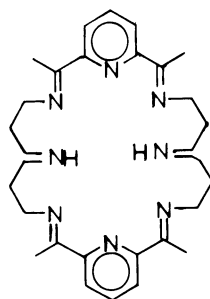
L¹³
(Ba²⁺)



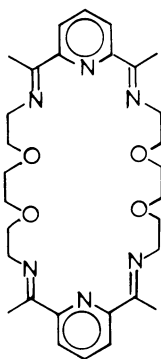
L¹⁴
(Ca²⁺, Sr²⁺, Ba²⁺)



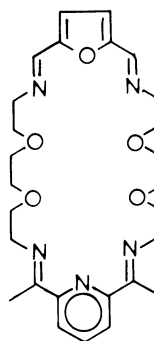
L¹⁵
(Ag⁺)



L¹⁶
(Ag⁺)



L¹⁷
(Sr²⁺, Ba²⁺, Ag⁺, Pb²⁺)



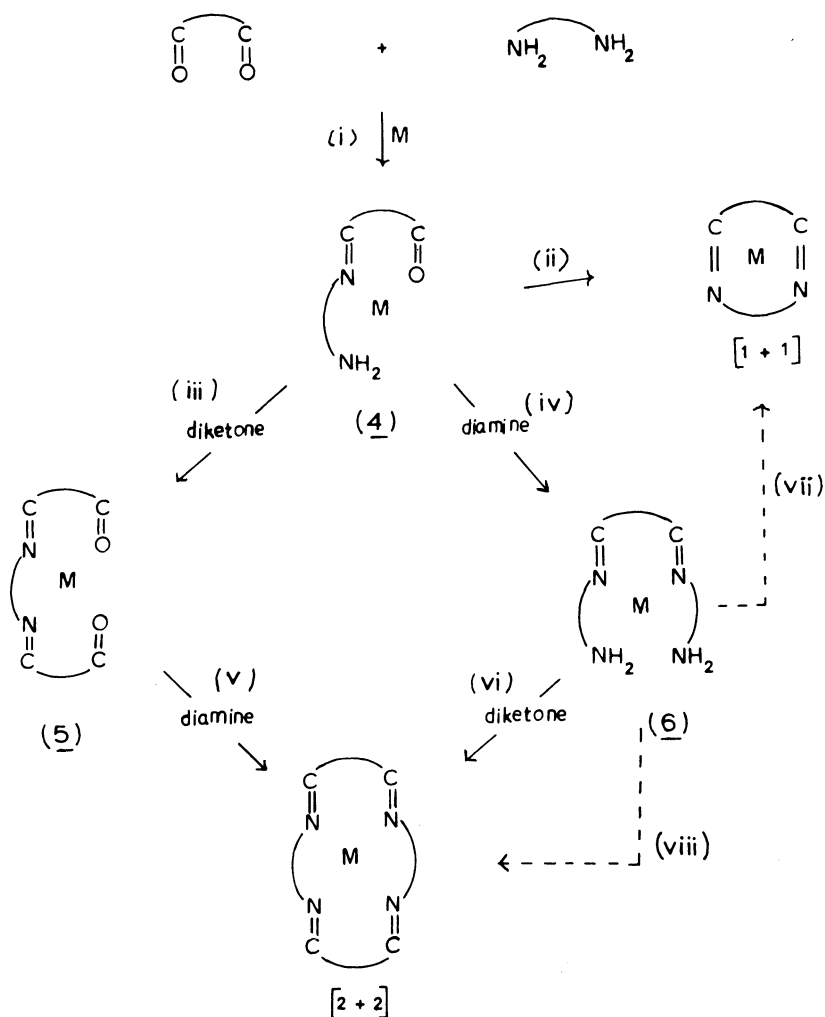
L¹⁸

condensation of two moles of DAP with two moles of diprimary amine - [2 + 2] condensation. The structure of the [BPh₄]⁻ salt has been determined (Ref. 35). Each Ag(I) ion is 4-coordinate being bonded to three nitrogens of one trimethine unit and to one secondary amine nitrogen in an irregular environment intermediate between tetrahedral and square planar. It is probable that it is the relatively large size of the Ag⁺ ion which is responsible for directing the condensation to the [2 + 2] rather than the [1 + 1] product. This result prompted the further investigation of large metal ions as templates for the synthesis of [2 + 2] macrocycles. A selection of those which have been prepared is shown above (L¹⁰ - L¹⁸). It can be seen that among the ions used as templates (indicated below

the structural formulae of the macrocycles) the larger alkaline earth metal ions are particularly useful. As before, the macrocycles are isolated in good yield as crystalline complexes of the template ion. Replacement of the complexed template ion by other metal ions not effective as templates is usually readily achieved by the transmetalation method described above. In this way a wide range of mono- and binuclear complexes of the macrocycles $L^{10} - L^{18}$ have been prepared. Structures of the complexes have been elucidated by chemical analysis and by means of physical properties (i.r., uv/vis, e.s.r., mass, n.m.r. and Mossbauer spectra, magnetic susceptibilities and electrical conductances, as appropriate) and by single crystal X-ray structure determinations in selected cases. Before describing structures and properties possible mechanisms for the formation of the macrocyclic ligands are considered in a general way.

Mechanistic aspects of the template syntheses

Possible routes to the formation of $[1 + 1]$ and $[2 + 2]$ Schiff base macrocycles are indicated in Scheme 1. In all cases the initial product of reaction of the dicarbonyl and diprimary amine [step (i)] is presumed to be the monocarbonyl monoamine species (4).



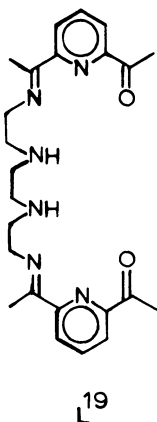
Scheme 1

Whether the reaction then proceeds via an intramolecular condensation [step (ii)] to give the $[1 + 1]$ ring or by a second intermolecular condensation [steps (iii) or (iv)] followed by an intermolecular ring closure [steps (v) or (vi)] to give the $[2 + 2]$ ring will be decided by a number of factors. Clearly, if the diamine has insufficient chain length to span the two carbonyl groups of DAP i.e. if the NH_2 groups are linked by a chain having fewer than six or seven atoms, then a $[1 + 1]$ ring cannot be formed. Secondly, if the template ion is large in relation to the cavity size of the $[1 + 1]$ ring, a $[2 + 2]$ condensation may occur. Thirdly, the conformation of the non-macrocyclic intermediate (4) may be expected to influence the subsequent course of reaction. This, in turn, will depend

on the nature and stereochemical demands of the template ion. Also, as shown in Scheme 1, there are two possible routes, [(iii) + (v)] and [(iv) + (vi)], from the initially formed intermediate (4) to the [2 + 2] product.

To date, the use of metal ions as templates in macrocycle synthesis has been largely empirical. It is clearly desirable to improve our understanding of the sequence and mechanism of the stepwise macrocycle formation reactions, which, hopefully, might be applied to the synthesis of new macrocycles having particularly coordinating properties. Some insight into the nature of these reactions has been gained by the isolation of intermediates and the study of their subsequent reactions. From results obtained it appears that both routes [(iii) + (v)] and [(iv) + (vi)] may occur in different cases but, also, that a third mechanism involving transamination steps (vii) and (viii) may be equally important. Some evidence relating to the mechanistic pathways in several systems is summarised below.

Complexes of an open-chain 'N₆O₂' ligand. Reaction of DAP with 3,6-diazaoctane-1,8-diamine in the presence of Sr²⁺ or Ba²⁺ salts yielded complexes ML¹⁹(ClO₄)₂ where M = Sr or Ba and L¹⁹ is the non-macrocylic, potentially octadentate ligand derived from the condensation of 2 molecules DAP with one molecule of diprimary amine species (5) in Scheme 1.



However, these complexes are not intermediates in the formation of [2 + 2] macrocycles since further reaction with a range of diprimary amines of varying chain length failed to effect ring closure (Ref. 36). A possible reason for the failure of the ring closure reactions is suggested by the results of an X-ray structure analysis of [BaL¹⁹(ClO₄)₂]. The Ba²⁺ ion is 10-coordinate being bonded to all eight donor atoms of L¹⁹ and, monodentately, to two ClO₄⁻ ions. As shown in Fig. 1 the conformation of the ligand is such that the two keto-pyridyl-imine segments are inclined at 80.2° to each other forming a

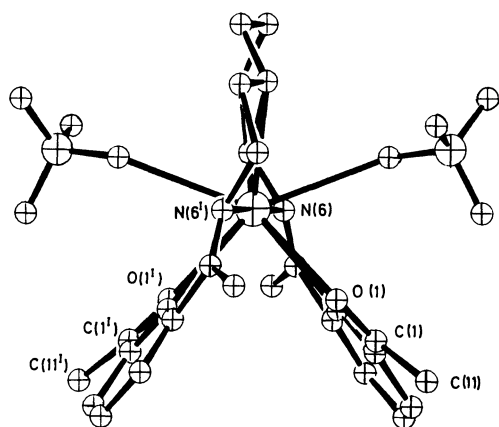
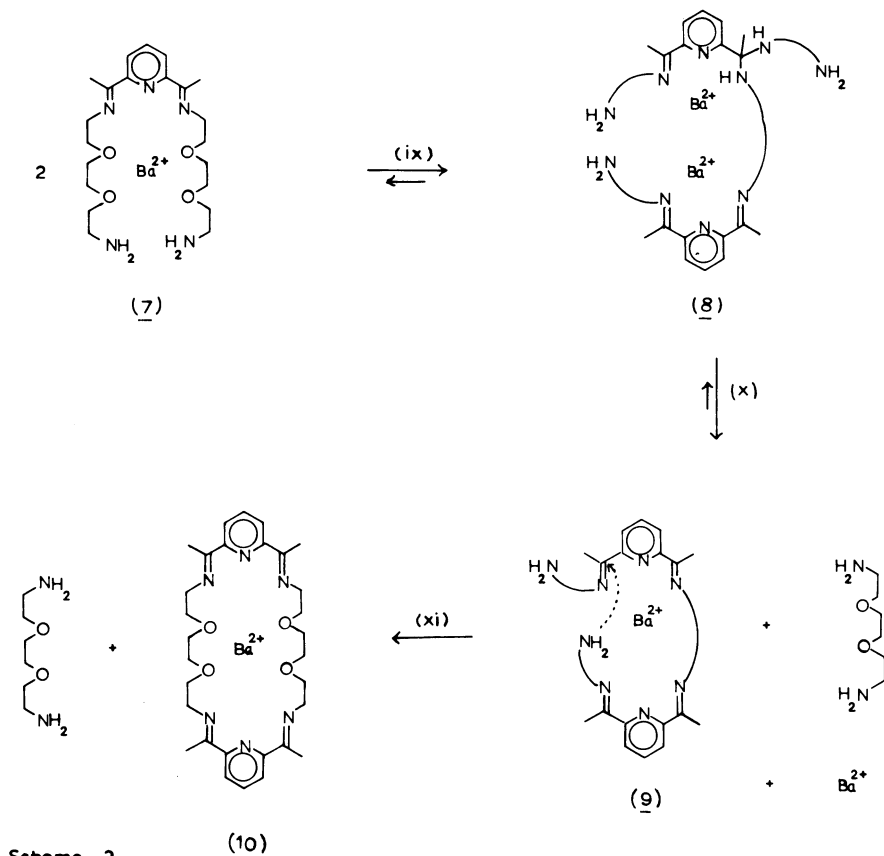


Fig. 1. Projection of [BaL¹⁹(ClO₄)₂] showing the cleft between the two keto-pyridyl-imine planes.

cleft in which the two ketonic carbon atoms are separated by 5.21 Å. Thus, assuming a similar conformation in solution, it may be that the failure to ring close is due to a steric barrier to the entry of the difunctional nucleophile into the cleft. If this is correct it illustrates the importance of ligand conformation in relation to chemical reactivity. The Ba^{2+} ion in $[BaL^{19}(ClO_4)_2]$ may be replaced by a number of transition metal ions to give both mononuclear complexes $[ML^{19}]^{2+}$ [$M = Fe(II), Co(II)$ and $Ni(II)$] in which the carbonyl groups are uncoordinated, and some binuclear $Cu(II)$ complexes containing an intramolecular hydroxo bridge (Ref. 36).

Transamination in the synthesis of macrocyclic ligands

A more commonly observed open chain Schiff base condensate in alkaline earth metal ion controlled reactions carried out under mild conditions is that of type (6) in Scheme 1. An example is the complex (7) shown in Scheme 2. That this complex is an intermediate in the formation of the $[2 + 2]$ macrocyclic complex (10) is strongly indicated by the fact that

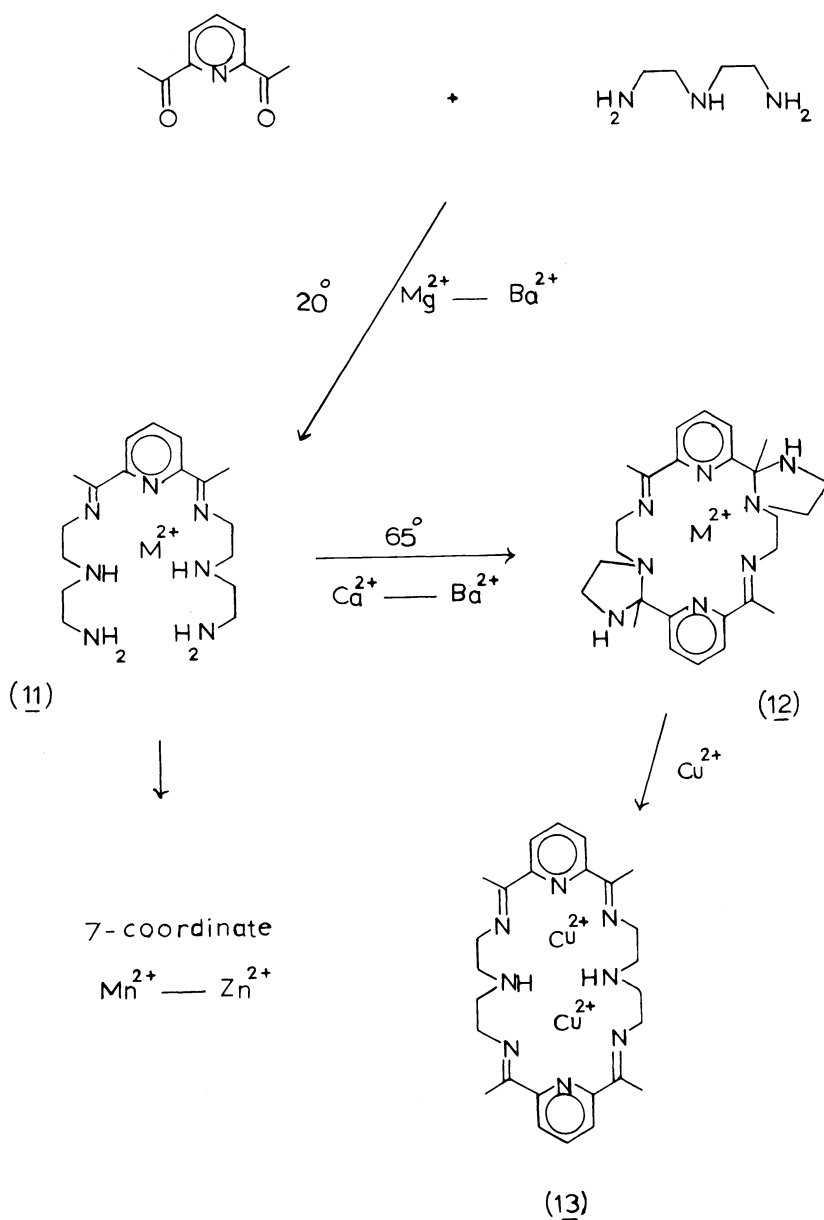


Scheme 2

(10) is obtained on reaction of (7) with DAP. Moreover, reaction of (7) with 2,6-diformylfuran (DFF) gives the $Ba(II)$ complex of the macrocycle L^{18} containing both pyridyl and furan moieties. Thus, we now have a potential route to the synthesis of asymmetric macrocycles better suited to the formation of hetero-binuclear complexes.

A significant observation is that the macrocyclic complex (10) is also obtained in good yield merely by warming it in dried solvents in the absence of added DAP. The sequence of reactions shown in Scheme 2 is proposed to account for the ring closure under these conditions. Step (ix) is a bimolecular reaction between two molecules of (7) involving nucleophilic attack by an NH_2 group of one molecule at an imino carbon atom of a second molecule to give the addition compound (8). Regeneration of the imine bond can occur by elimination of a molecule of 3,6-dioxaoctane-1,8-diamine forming (9) [step (x)]. A second nucleophilic attack of an uncoordinated NH_2 group at a neighbouring $C = N$ group, intramolecular this time, leads to the macrocyclic product (10) with elimination of a second molecule of 3,6-dioxaoctane-1,8-diamine [step (xi)]. The proposed mechanism involves two transaminations, one intermolecular and one intramolecular, processes known to be important in amino acid metabolism mediated by pyridoxal phosphate (Vitamin B6) (Ref. 37). The suggested mechanism is consistent with the observation that macrocycle formation is suppressed by the presence of an excess of free 3,6-dioxaoctane-1,8-diamine or of free Ba^{2+} ion.

Similar effects are observed in the reaction of DAP with diethylenetriamine and with 1,2-diaminoethane. In the former system (Scheme 3) reaction at 20° in the presence of Mg(II), Ca(II), Sr(II) or Ba(II) the initial products are again complexes (11) of the open-chain

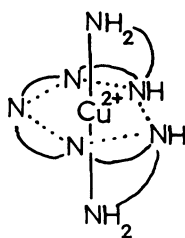


Scheme 3

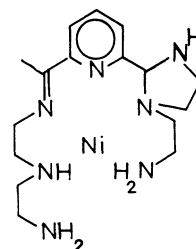
Schiff base containing two terminal primary amine groups. When these complexes (the Mg(II) complex excepted) are redissolved in dry methanol and heated to reflux macrocyclic complexes (12) are obtained in high yield, again in the absence of added DAP. The structure of the Ba(II) complex has been solved by X-ray crystallography (Ref. 38). It can be seen that the secondary amine groups have added across neighbouring imine bonds with concomitant expulsion of two 5-membered imidazolidine rings from the inner large ring of the macrocycle to give, in these cases, an 18-membered (hexadentate) macrocycle instead of the expected 24-membered (octadentate) macrocycle (L¹⁴). The failure of the ring closure in the case of the Mg(II) complex may be attributed to stronger metal-nitrogen bonds which suppress the availability of the secondary amine groups for nucleophilic attack.

The Ba²⁺ ion in (11) can be exchanged for the ions Mn(II) - Zn(II) to give a series of 7-

coordinate (pentagonal bipyramidal) complexes. The structure of the Cu(II) complex has been solved (Ref. 38). The pentagonal equatorial plane is made up of the three trimethine nitrogens together with the two secondary amine groups while the primary amine groups occupy the axial positions [structure (14)]. As expected for a ground state in which the d_{z^2} orbital is singly occupied the $\text{Cu}-\text{N}_{\text{ax}}$ distance is short at 1.93 Å (cf. the average



(14)



(15)

Cu - N distance of 2.37 Å). E.s.r. spectra gave $g_{\parallel} = 2.00$, $g_{\perp} = 2.22$, $A_{\parallel} = 127\text{G}$ and $A_{\perp} = 52\text{G}$. Two spin-allowed electronic transitions, ${}^2A_{1g} \rightarrow {}^2E_{2g}$ and ${}^2A_{1g} \rightarrow {}^2E_{1g}$, are predicted for the d^9 ion in D_{5h} symmetry and these are observed at $8,200\text{ cm}^{-1}$ and $13,400\text{ cm}^{-1}$ respectively.

The Ni(II) complex, isomorphous with the Cu(II) complex, is interesting. Reference has already been made to the disinclination of Ni(II) to adopt D_{5h} symmetry. This is again illustrated in a virtually quantitative isomerization of the green 7-coordinate complex to a brown octahedral complex (ca. 4 days at 20° in MeCN). X-ray analysis (Ref. 38) shows that a ligand rearrangement has occurred to give structure (15), one NH group having added across the adjacent C = N bond thereby reducing the number of available donor atoms from seven to six.

Unlike the alkaline earth metal ion complexes (11), none of the 7-coordinate complexes of the transition metal ions undergoes ring closure to give macrocyclic complexes. However, such complexes, both mono- and binuclear, may be obtained by transmetalation from (12). Full structural details for these are not available but it is clear from their properties, at least for the binuclear complexes, that a macrocycle ring expansion ($[18] \rightarrow [24]$) occurs during the metal exchange [see Scheme 3 for the case of the bi-Cu(II) complex (13)].

Parallel behaviour is found for condensation reactions between DAP and 1,2-diaminoethane in the presence of the ions Ca^{2+} , Sr^{2+} and Ba^{2+} (Scheme 4). The initial reaction product at 20° is a complex in which the ligand is made up of two DAP and three 1,2-diaminoethane moieties. Properties suggest structure (16) in the solid state but this may exist in equilibrium with structure (17) in solution. As for the systems described above ring closure to give (18) is effected simply by heating in the absence of DAP. Routes to binuclear Cu(II) complexes [(19) and (20)] of both the open-chain and macrocyclic ligands are indicated in Scheme 3.

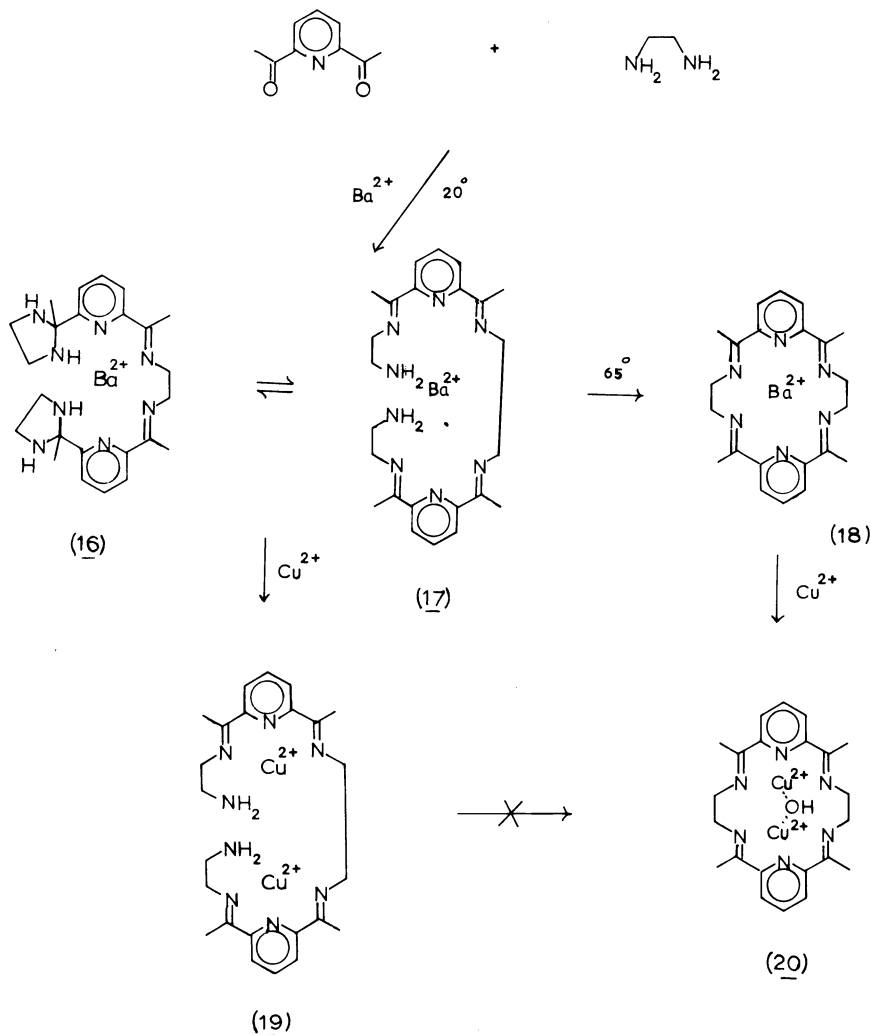
It is clear from the foregoing examples that nucleophilic attack by primary and secondary amino functions at coordinated imino centres is a facile process. Nucleophilic attack by alcohols, alkoxides, thiols and thiolates, often yielding stable addition products, is well known (Ref. 39, 40 & 41). In the reactions described here the isolation of the addition products can be attributed to stabilisation by coordination.

In the final example of metal-controlled reactions of this class the transamination is applied rather differently to the synthesis of macrocyclic ligands. Reaction of DAP (or related dicarbonyl) with an excess of a simple mono-primary amine such as n-propylamine in the absence of metal ion affords tridentate Schiff bases such as (21) (see Scheme 5) which can then be reacted with a range of metal ions. With the transition metal ions Mn(II) - Zn(II) 6-coordinate octahedral complexes (22) are readily obtained. For $M = \text{e.g. Cu(II)}$ or Zn(II) the macrocyclic complexes (23) are produced in good yield by treatment of (22) with two moles of 3,6-dioxaoctane-1,8-diamine with elimination of four moles of propylamine. In principle, this synthetic strategy may be applied to the synthesis of new $[2 + 2]$ macrocycles.

MONONUCLEAR COMPLEXES OF $[2 + 2]$ MACROCYCLES

Complexes of L^{17}

Although the 30-membered 'N₆O₄' macrocycle L^{17} is well suited to the formation of binuclear complexes (see next Section) it also forms very stable mononuclear octahedral complexes with certain metal ions in which only the six trimethine nitrogen atoms are coordinated

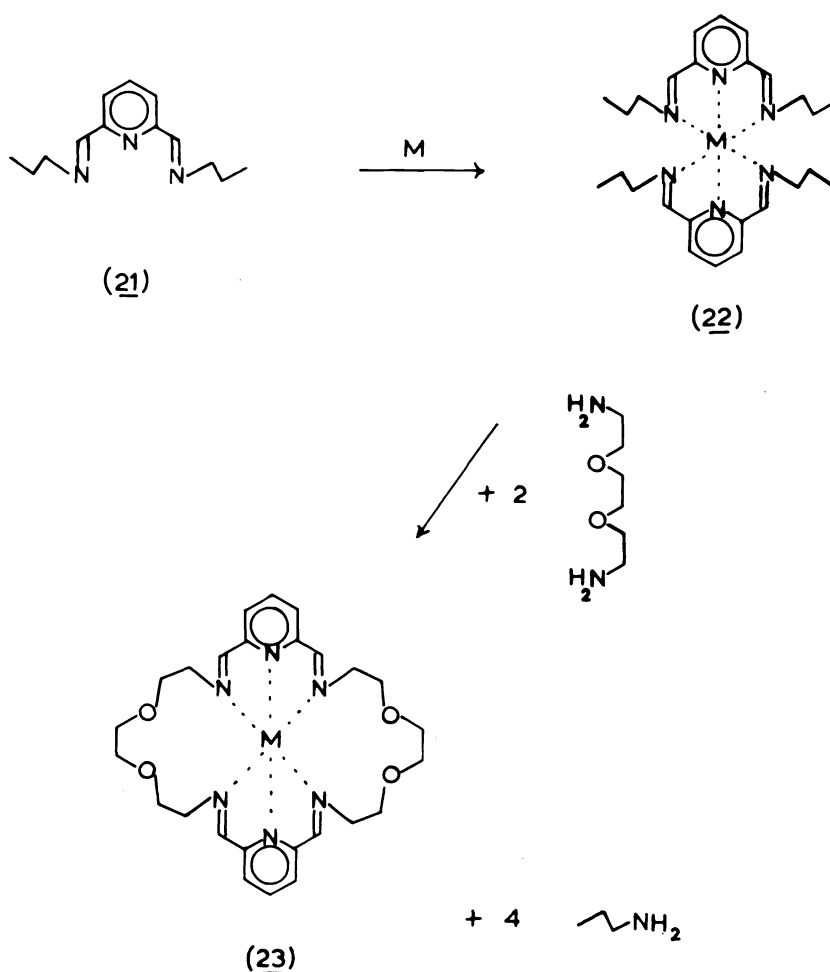


Scheme 4

[structure 23] . The Fe(II), Co(II) and Co(III) complexes are all low spin and it is almost certainly the large CFSE stabilisation which is the major thermodynamic driving force for the adoption of this coordination mode in these cases (Ref. 42). The effectiveness of the trimethine moiety as a coordinating group is illustrated by the results of cyclic voltammetry measurements on the iron and cobalt complexes both of which display a series of reversible one-electron redox waves (Ref. 42). For the iron system the most positive wave is ascribed to the Fe(III)/Fe(II) couple while the two waves occurring at -1.0 and -1.5V (versus the s.c.e.) are attributed to the formation of radical anions in which the added electrons are delocalised onto the trimethine units. For the cobalt system the successive addition of electrons to Co(III) is best described in terms of the formation of a Co(II) complex, a Co(I) complex and Co(I) complex of a radical anionic macrocycle.

Complexes of L¹⁰, L¹¹ and L¹²

As mentioned above the Ca^{2+} , Sr^{2+} , Ba^{2+} and Pb^{2+} ions are effective templates for the synthesis of the 18-membered hexadentate macrocycles L¹⁰, L¹¹ and L¹² (Ref. 43 & 44). The Mg^{2+} ion, the transition metal ions Mn(II) - Zn(II), Ag(I) and Cd(II) are ineffective as templates although a Cd(II) complex of L¹¹ has been obtained by transmetalation. In addition, Na^+ , K^+ and NH_4^+ complexes of L¹² have been prepared (Ref. 45). In all cases the complexes have a 1:1 metal: macrocycle stoichiometry with the exception of the Ba^{2+} complexes of the conjugated macrocycles L¹¹ and L¹² which have a 1:2 stoichiometry, viz. $[\text{BaL}_2]^{2+}$. In view of the planarity of these conjugated macrocycles the 1:2 Ba^{2+} complexes



Scheme 5

are believed to have a sandwich structure. They are surprisingly stable and do not dissociate in solution. The structures of several of the 1:1 complexes have been solved by X-ray analysis (Fig. 2). In all cases the macrocycle is near planar, the overall coordination geometry being a slightly distorted hexagonal bipyramid ($[\text{SrL}^{10}\text{Cl}_2]$, $[\text{PbL}^{10}(\text{SCN})(\text{NCS})]$ and $[\text{CdL}^{11}(\text{H}_2\text{O})(\text{ClO}_4)]$ $[\text{ClO}_4] \cdot \text{MeOH}$) or, in the case of $[\text{PbL}^{11}(\text{H}_2\text{O})]$ $[\text{ClO}_4]_2 \cdot \text{H}_2\text{O}$, a hexagonal pyramid with the 'vacant' axial position probably containing a stereochemically active lone pair of electrons.

The differing stoichiometries and stabilities (as judged by the success or otherwise in the preparation) of the complexes can be nicely accounted for in terms of the sizes of the metal

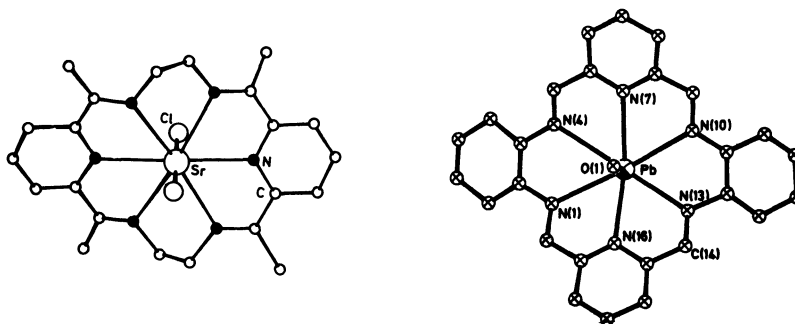


Fig. 2. The structures of $[\text{SrL}^{10}\text{Cl}_2]$ and $[\text{PbL}^{11}(\text{H}_2\text{O})]^{2+}$.

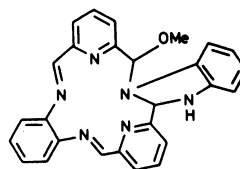
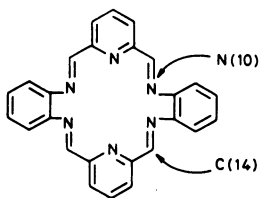
ions and the size of the macrocycle hole. Thus, for the case of the planar conjugated 'N₆' macrocycle L¹¹, the structural analyses show that the radius of the hole is ca. 2.7 Å. Therefore, it is not expected that Ba²⁺, of octa-coordinate diameter 2.84 Å, (Ref. 46) would sit within the cavity, a prediction consistent with the proposed sandwich structure. For Ca²⁺, Sr²⁺, Cd²⁺ and Pb²⁺ (octa-coordinate diameters 2.24, 2.52, 2.20 and 2.58 Å, respectively) the metal ion can now be readily accommodated within the planar 'N₆' ring, as found. The Mg²⁺ ion and the first row transition metal ions Mn²⁺ - Zn²⁺ (octa-coordinate diameters 1.80-1.92 Å) are clearly too small to be effectively bonded to all six nitrogen atoms of the planar macrocycle, thus accounting for their ineffectiveness as templates.

Metal-induced ring contraction in L¹¹. Although L¹¹ is too large to form stable complexes with first row transition metal ions it was found that treatment of [BaL¹¹]₂[ClO₄]₂ with Mn(II), Fe(II), Co(II) and Zn(II) salts in refluxing methanol gave a series of new complexes in 40-80% yield (Ref. 44). I.r. and mass spectra, together with an X-ray analysis of a Co(II) complex, showed that the inner large ring of L¹¹ has contracted from 18- to 15-member atoms as a result of covalent bond formation between N(10) and C(14) to give the new pentadentate macrocycle L²⁰. The resulting complex has a pentagonal bipyramidal geometry, the axial positions being filled, in this example, by a water and by a methanol molecule. The ring contraction can be seen as proceeding in two steps. The first is the addition of a molecule of MeOH across one C = N bond as a result of the strain generated by the attempt of the macrocycle L¹¹, by folding or other distortion, to bond effectively via all six nitrogens to a too-small metal ion. The gain in flexibility gained by the conversion of a double into a single carbon-nitrogen bond then allows nucleophilic attack of the secondary amino nitrogen N(10), so formed, at the imino carbon C(14) of the adjacent azomethine group. The ring contraction may be viewed as an example of the entatic effect (Ref. 47) in which a mis-match in the geometrical requirements of the metal ion and ligand activates the system to chemical reaction leading to, in this case, to a new macrocycle of improved fit for the incoming metal ion.

BINUCLEAR COMPLEXES OF THE [2 + 2] MACROCYCLES

Binuclear complexes of macrocyclic ligands are of interest for several reasons including the study of metal-metal exchange interaction, electron transfer properties, the binding and possible activation of small substrate molecules between the metal centres, and as synthetic models for some metalloproteins in which the biological function is believed to be associated with the occurrence of the metal centres in pairs (Ref. 48). Examples are bovine superoxide dismutase and cytochrome C oxidase which contain imidazolate-bridged copper ... zinc and copper ... iron units, respectively, and haemocyanin and haemerythrin containing O₂-linked bi-copper and bi-iron centres, respectively (Ref. 49-51). Some bi-Cu(II) macrocyclic complexes capable of the intramolecular binding of small substrate molecules and ions are briefly described below.

The macrocycle L¹⁵ has been prepared as the di-Ag(I) complex in ca. 60% yield. While the detailed structure is not known it is thought that each Ag(I) is 4-coordinate being bonded



to three nitrogens and one sulphur atom. A di-Cu(II) complex may be obtained by transmetalation which has the capacity to bind bridging ligands between the Cu(II) ions (Ref. 52). The bridging ligands include the imidazolate anion (im), pyrazine and azide ion. The structure of the μ -Imidazolate complex is shown in Fig. 3. Each Cu(II) ion is strongly bonded to three nitrogens of one trimethine unit and to one nitrogen atom of the bridging imidazolate [Cu-N 1.90(2) - 1.93(2) Å] in a square planar arrangement. In addition, both Cu(II) ions are weakly bonded to ClO₄⁻ or H₂O [Cu-O 2.45(3) - 2.70(3) Å] in axial positions (not shown in Fig. 3). The two planar trimethine units intersect at an angle of 42.2°. The plane of the bridging imidazolate ion intersects the two trimethine planes at angles of 88.6° and 90.0°. The sulphur atoms are not coordinated and the Cu ... Cu separation is 5.87 Å. A somewhat similar imidazolate bridged bi-Cu(II) macrocyclic complex has recently been reported (Ref. 53).

Magnetic susceptibility measurements have revealed an antiferromagnetic exchange coupling between the Cu(II) ions with the exchange energy $J = \text{ca. } -23 \text{ cm}^{-1}$. This value is close to that observed (-26 cm⁻¹) for some (non-macrocyclic) imidazolate-bridged Cu(II) dimers in which, as here, the plane of the imidazolate ring is perpendicular to the plane of the

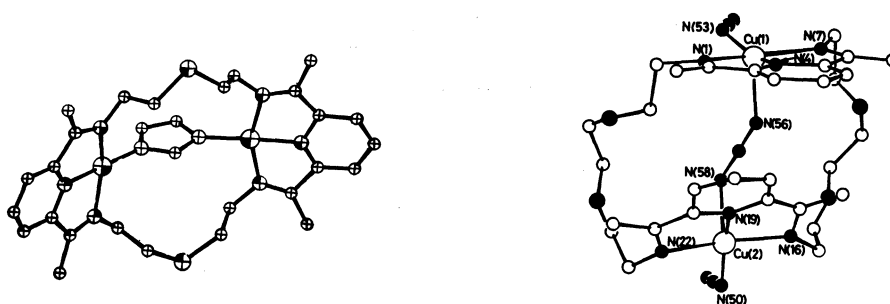


Fig. 3. The structures of $[\text{CuL}_2\text{L}^{15}(\text{im})]^{3+}$ and $[\text{Cu}_2\text{L}^{17}(\text{N}_3)_3]^+$.

coordination square planes (Ref. 54). It is interesting, also, that the J value is close to that (-26 cm^{-1}) found for the Cu(II) derivative of bovine superoxide dismutase from the temperature dependence of the e.s.r. spectra (Ref. 55). These results lend encouragement to the view that further study of synthetic binuclear complexes may lead to an improved understanding of structure/function relationships in the natural systems.

Some mononuclear complexes of the 30-membered 'N₆O₄' macrocycle L¹⁷ have been mentioned above. This large ring forms binuclear complexes with several metal ions including Pb(II), Ag(I) (Ref. 56) and Cu(II). For the bi-Cu(II) complexes a series of antiferromagnetically coupled derivatives incorporating small bridging ligands between the metal centres have been prepared and structurally characterized (Ref. 57 and 58). These include μ -azido, μ -hydroxo and μ -imidazolato complexes. The structure of the μ -azido complex is shown in Fig. 3. Here, the macrocycle is folded so that the bridging 1,3-azido group is positioned axially with respect to two 'CuN₄' square planes each made up of three macrocycle nitrogen donors and one nitrogen atom of a terminally bonded azide ion. The oxygen atoms are not bonded to the metal and the Cu ... Cu separation is 6.02 Å.

Since these macrocycles can adopt conformations suitable to the accommodation of single-atom bridging ligands (e.g. OH⁻) and three-atom bridging ligands (e.g. im, N₃⁻) they should also be structurally adaptable to the intramolecular binding of two-atom bridging ligands. It is therefore of interest to study the interaction of dioxygen with e.g. bi-Cu(I) complexes. Recent work in other laboratories, using macrocyclic ligands of the cryptate class (Ref. 59 and 60) as well as some non-macrocyclic Schiff base ligands (Ref. 61), indicates that O₂-carrying synthetic bi-Cu(I) models for the haemocyanins may be obtained. Preliminary studies show that some bi-Cu(I) complexes of the hydrogenated macrocycles, derived from L¹⁷ and analogues by borohydride reduction, absorb one mole O₂ per bi-Cu(I) centre very rapidly and that this is followed by a slower anaerobic oxidative dehydrogenation of the ligand by the bound dioxygen to regenerate the Cu(I) centres so that the process may be repeated at least once again (Ref. 62). The results demonstrate a clear separation between the initial coordination of O₂ (to two Cu(I) centres) and its subsequent anaerobic utilisation. This, together with the observation of a Cu(I)/Cu(II) cycle, suggests possible application to the catalytic reduction of dioxygen to water and to the catalytic oxidation of added organic substrates.

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REFERENCES

1. D.H. Busch, *Rec. Chem. Prog.*, **25**, 107 (1964); *Helv. Chim. Acta*, **50**, 174 (1967).
2. L.F. Lindoy and D.H. Busch, *Preparative Inorganic Reactions*, ed. W. Jolly, vol. 6, p.1, Interscience, New York (1971).
3. D.H. Busch, K. Farmery, V. Goedken, V. Katovic, A.C. Melnyk, C.R. Sperati and N. Tokel, *Adv. Chem. Ser.* **100**, 44 (1971).
4. N.F. Curtis, *Coord. Chem. Rev.* **3**, 3 (1968).
5. L.F. Lindoy, *Quart Rev.* **25**, 379 (1971).
6. M.C. Thompson and D.H. Busch, *J. Amer. Chem. Soc.* **84**, 1762 (1962).
7. J.L. Karn and D.H. Busch, *Nature*, **211**, 160 (1966); R.L. Rich and G.L. Stucky, *Inorg. Nucl. Chem. Lett.*, **1**, 61 (1965); J.C. Dabrowiak, L.A. Nafie, P.S. Bryan and A.T. Torkelson, *Inorg. Chem.* **16**, 540 (1977); K.M. Long and D.H. Busch, *Inorg. Chem.*, **9**, 505

8. J.D. Curry and D.H. Busch, J. Amer. Chem. Soc. **86**, 592 (1964).
9. S.M. Nelson, P. Bryan and D.H. Busch, Chem. Comm. 641 (1966); S.M. Nelson and D.H. Busch, Inorg. Chem. **8**, 1859 (1969).
10. E. Fleischer and S. Hawkinson, J. Amer. Chem. Soc. **89**, 720 (1967).
11. M.D. Alexander, A. Van Heuvelen and H.G. Alexander, Inorg. Nucl. Chem. Lett. **6**, 445 (1970); A. Van Heuvelen, M.D. Lundeen, H.G. Hamilton and M.D. Alexander, J. Chem. Phys. **50**, 489 (1969).
12. N.W. Alcock, D.C. Liles, M. McPartlin and P.A. Tasker, J. Chem. Soc. Chem. Comm. 727 (1974).
13. M.G.B. Drew and S.M. Nelson, Acta Cryst. **A31**, S140 (1975).
14. M.G.B. Drew, A.H. bin Othman, P.D.A. McIlroy and S.M. Nelson, J. Chem. Soc. Dalton Trans. 2507 (1975).
15. R.D. Shannon and C.T. Prewitt, Acta Cryst. **B25**, 925 (1969).
16. S.M. Nelson, S.G. McFall, M.G.B. Drew, A.H. bin Othman and N.B. Mason, J.C.S. Chem. Comm. 167 (1977).
17. F. Basolo and R.G. Pearson, Mechanisms of Inorganic Reactions, p. 146, Wiley, New York (1968).
18. D. Wester and G.J. Palenik, J. Amer. Chem. Soc. **96**, 7566 (1974); T.J. Giordano, G.J. Palenik, R.C. Palenik and D.A. Sullivan, Inorg. Chem. **18**, 2445 (1979).
19. C. Cairns, S.G. McFall, S.M. Nelson and M.G.B. Drew, J.C.S. Dalton, 446 (1979).
20. C. Cairns, M.G.B. Drew, J. Nelson and S.M. Nelson, J.C.S. Dalton, in press.
21. D.H. Cook, D.E. Fenton, M.G.B. Drew, S.G. McFall and S.M. Nelson, J.C.S. Dalton, 446 (1977).
22. V. Knox and S.M. Nelson, unpublished work.
23. M.G.B. Drew, A.H. bin Othman, S.G. McFall, P.D.A. McIlroy and S.M. Nelson, J.C.S. Dalton, 1173 (1977).
24. M.G.B. Drew, A.H. bin Othman, S.G. McFall and S.M. Nelson, J.C.S. Dalton, 438 (1977).
25. M.G.B. Drew, A.H. bin Othman and S.M. Nelson, J.C.S. Dalton, 1394 (1976).
26. C. Cairns and S.M. Nelson, unpublished work.
27. M.G.B. Drew, S.G. McFall and S.M. Nelson, J.C.S. Dalton, 575 (1979).
28. S.M. Nelson and A. Rodgers, Second International Conference on The Organometallic and Coordination Chemistry of Germanium, Tin and Lead, Nottingham, 1977.
29. M.G.B. Drew, A. Rodgers, M. McCann and S.M. Nelson, J.C.S. Chem. Comm. 415 (1978).
30. D.H. Cook, D.E. Fenton, M.G.B. Drew, A. Rodgers, M. McCann and S.M. Nelson, J.C.S. Dalton, 414 (1979).
31. M.G.B. Drew and S.M. Nelson, Acta Cryst. **B35**, 1594 (1979).
32. M.G.B. Drew, J. Grinshaw, P.D.A. McIlroy and S.M. Nelson, J.C.S. Dalton, 1388 (1976).
33. M.G.B. Drew, C. Cairns, S.G. McFall and S.M. Nelson, J.C.S. Dalton, in press.
34. C. Cairns, M.G.B. Drew and S.M. Nelson, unpublished results.
35. M.G.B. Drew, S.G. McFall, S.M. Nelson and C.P. Waters, J. Chem. Research, (S) 16-17, (M) 0360-0378 (1979).
36. M.G.B. Drew, C.V. Knox and S.M. Nelson, J.C.S. Dalton, 942 (1980).
37. G.A. Hamilton, in "Progress in Bioorganic Chemistry", ed. E.T. Kaiser and F.J. Kezdy, vol. 1, p. 95, Wiley, New York (1971).
38. M.G.B. Drew, J. Nelson and S.M. Nelson, unpublished results.
39. D.H. Busch and J.C. Bailar, J. Amer. Chem. Soc. **78**, 1139 (1956); M. Cressey, E.D. McKenzie and S. Yates, J. Chem. Soc. (A) 2677 (1971); D.H. Cook and D.E. Fenton, Inorg. Chim. Acta, **25**, L95 (1977).
40. L.F. Lindoy and D.H. Busch, Inorg. Chem. **13**, 2494 (1974).
41. V. Katovic, L.T. Taylor and D.H. Busch, J. Amer. Chem. Soc. **91**, 2122 (1969); L.T. Taylor, F.L. Urbach and D.H. Busch, J. Amer. Chem. Soc. **91**, 1072 (1969).
42. S.M. Nelson, M. McCann, C. Stevenson and M.G.B. Drew, J.C.S. Dalton, 1477 (1979).
43. J. de O. Cabral, M.F. Cabral, M.G.B. Drew, A. Rodgers and S.M. Nelson, Inorg. Chim. Acta, **30**, L 313 (1978); M.G.B. Drew, J. de O. Cabral, M.F. Cabral, F.S. Esho and S.M. Nelson, J.C.S. Chem. Comm. 1033 (1979).
44. S.M. Nelson, F.S. Esho, M.G.B. Drew and P. Bird, J.C.S. Chem. Comm. 1035 (1979).
45. F.S. Esho and S.M. Nelson, unpublished work.
46. R.D. Shannon, Acta Cryst. **A32**, 751 (1976).
47. B.L. Vallee and R.J.P. Williams, Proc. Nat. Acad. Sci. U.S.A. **59**, 498 (1968).
48. J. Peisach, P. Aisen and W. Blumberg, Eds. "The Biochemistry of Copper", Academic Press, New York (1966).
49. J.S. Richardson, K.A. Thomas, B.H. Rubin and D.C. Richardson, Proc. Nat. Acad. Sci. U.S.A. **72**, 1349 (1975); K.M. Beem, D.C. Richardson and K.V. Rajagopalan, Biochemistry, **16**, 1930 (1977).
50. G. Palmer, G.T. Babcock and L.E. Vickery, Proc. Nat. Acad. Sci. U.S.A. **73**, 2206 (1976) M.F. Tweedle, L.J. Wilson, L. Garcia-Iniguez, G.T. Babcock and G. Palmer, J. Biol. Chem. **252**, 8065 (1978).
51. M.Y. Okamura, I.M. Klotz, C.E. Johnson, M.R.C. Winter and R.J.P. Williams, Biochemistry, **8**, 1951 (1969).
52. C. Cairns, M.G.B. Drew, A. Lavery and S.M. Nelson, unpublished results.
53. P.K. Coughlin, J.C. Dewan, S.J. Lippard, E. Watanabe and J.-M. Lehn, J. Amer. Chem. Soc. **101**, 266 (1979).

54. C.-L. O'Young, J.C. Dewan, H.R. Lilienthal and S.J. Lippard, J. Amer. Chem. Soc. 100, 7291 (1978).
55. J.A. Fee and R.G. Briggs, Biochem. Biophys. Acta, 400, 439 (1975).
56. M.G.B. Drew, A. Rodgers, M. McCann and S.M. Nelson, J.C.S. Chem. Comm. 415 (1978).
57. M.G.B. Drew, M. McCann and S.M. Nelson, J.C.S. Chem. Comm. 481 (1979).
58. M.G.B. Drew, unpublished results.
59. A.H. Alberts, R. Annunziata and J.-M. Lehn, J. Amer. Chem. Soc. 99, 8502 (1977).
60. Y. Agnus, R. Louis and R. Weiss, J. Amer. Chem. Soc. 101, 3381 (1979).
61. M.G. Simmons and L.J. Wilson, J.C.S. Chem. Comm. 634 (1978).
62. M.G. Burnett, V. McKee and S.M. Nelson, J.C.S. Chem. Comm. in press.