Metal-ion-controlled Transamination in the Synthesis of Macrocyclic Schiff-base Ligands. Part 1. Reactions of 2,6-Diacetylpyridine and Dicarbonyl Compounds with 3,6-Dioxaoctane-1,8-Diamine

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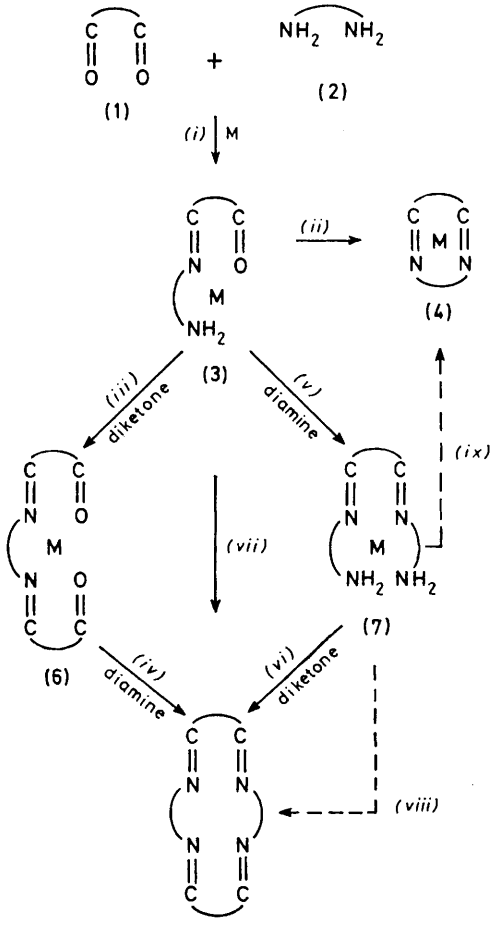
Possible routes to the metal-ion-controlled synthesis of [2 + 2] macrocyclic ligands derived from the Schiff-base condensation of two molecules of 2,6-diacetylpyridine (or related dicarbonyl) with two molecules of 3,6-dioxaoctane-1,8-diamine are considered. It is proposed that in the presence of Ba^{2+} ion, macrocycle formation proceeds *via* the open-chain intermediate derived from one molecule of dicarbonyl and two molecules of diprimary amine. The intermediates, isolated as their barium(II) complexes, are shown to undergo ring closure in anhydrous MeOH on treatment with a further mol of dicarbonyl to give complexes of the 30-membered macrocyclic ligands, including an ' asymmetric ' ligand containing both pyridyl and furyl moieties. In one case, reversible ring closure occurs in the absence of added dicarbonyl and a transamination mechanism involving a sequence of nucleophilic additions (followed by deamination) of NH_2 to co-ordinated C=N groups is proposed. Further evidence for transamination as a route to macrocycle synthesis is provided by the ring closure, with elimination of four molecules of *e.g.* n-propylamine, observed on treatment of some six-co-ordinate copper(II) or zinc(II) bis complexes of pyridine-2,6-bis(*N*-propylcarbaldimine) (or related open-chain ligand) with 3,6-dioxaoctane-1,8-diamine. An analogous transamination mechanism is proposed for the conversion of a 30-membered macrocyclic ligand to an 18-membered macrocycle co-ordinated to Pb^{II}, and for the conversion of a magnesium(II) complex of the same 30-membered ring to a magnesium(II) complex of a 15-membered ring.

CONDENSATION reactions between dicarbonyl compounds and diprimary amines have played an important role in the development of synthetic macrocyclic ligands.[1-5] Usually such syntheses are carried out in the presence of a suitable metal ion which serves to direct the steric course of reaction preferentially towards cyclic rather than oligomeric/polymeric products, the kinetic template effect, and/or to stabilise the macrocycle, once formed, the thermodynamic template effect.[2] For a few such metal-ion-assisted syntheses metal complexes of non-macrocyclic intermediates have been isolated. Examples are found in the reactions of some complexed quadridentate open-chain ligands containing *cis* oriented carbonyl groups with suitable diprimary amines.[6-8] Also, the Curtis type reactions between complexed bi- and quadri-dentate amines with carbonyl compounds are well known.[2,3] [The classical example [9] of controlled stepwise synthesis is the ring closure obtained on reaction of bis(mercaptoethylimino)(pentane-2,3-dione)nickel(II) with α,α′-dibromo-*o*-xylene.] However, it is true that most syntheses of macrocyclic Schiff-base ligands involve reactions between the amine and carbonyl precursors in the presence of a metal without the isolation of any intermediate.[4] This *in situ* synthetic method, powerful though it is, therefore remains very empirical. While the essential nature of the Schiff-base reaction is well understood [10] there is a clear need for further understanding of the mechanism and sequence of steps leading to macrocycle formation in different cases and of the influence thereon of the metal ion. This is particularly true of syntheses involving the cyclic condensation of two molecules of dicarbonyl with two molecules of diprimary amine (designated [2 + 2] syntheses) for which a greater number of mechanistic pathways may be envisaged. We have previously demonstrated how the size (among other factors) of the template ion may be used to direct the condensation between 2,6-diacetylpyridine and some polyfunctional diprimary amines either towards [1 + 1] or [2 + 2] macrocyclic products.[11-13] In this paper we describe the isolation and subsequent chemical reactions of intermediates in the template synthesis of some [2 + 2] macrocycles derived from 2,6-diacetylpyridine (and related dicarbonyls) and 3,6-dioxaoctane-1,8-diamine, and demonstrate the importance of nucleophilic attack by amine not only at the carbonyl function but also at co-ordinated imine groups in the sequence of reaction steps leading to macrocycle formation. The potential application of this type of reaction to the synthesis of new macrocycles is indicated.

RESULTS AND DISCUSSION

General Consideration of Possible Mechanisms.—Possible generalised routes to the formation of both [1 + 1] and [2 + 2] Schiff-base macrocyclic complexes are indicated diagrammatically in Scheme 1. In both cases the initial product of reaction between the dicarbonyl (1) and diprimary amine (2) is presumed to be the monoimine complex (3) containing one unreacted carbonyl and one unreacted primary amine function [step (*i*)]. Whether the reaction then proceeds *via* an intramolecular condensation [step (*ii*)] to give the [1 + 1] macrocycle (4) or *via* one or other of the bimolecular steps shown in the Scheme leading to the [2 + 2] macrocycle (5) is expected to depend on one or more of a number of factors. First, if the diamine (2) has insufficient chain length to span the two carbonyl groups of (1) then a [1 + 1] ring cannot be formed.[14] Secondly, if the template ion is large in relation to the cavity size of the [1 + 1] ring, a [2 + 2] condensation may occur as in the cases cited above.[11-13] Thirdly, the electronic nature of the metal ion and the conformation of the monoimine

ligand in (3) may be expected to influence the subsequent course of reaction in ways that are difficult to probe. For example, a strongly co-ordinated NH_2 group in (3) may preclude intramolecular nucleophilic attack at the carbonyl group, thereby eliminating step (*ii*). Again,

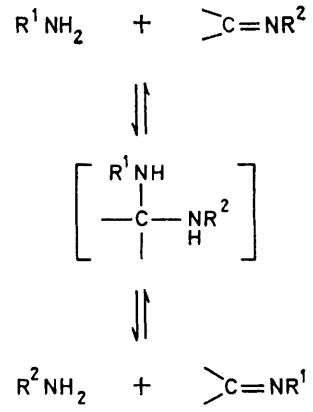


SCHEME 1

depending on the nature of the diamine (2), in particular the number, nature, and disposition of other potential donor atoms it may possess, the structure of intermediate (3) may be such that the NH_2 and C=O groups are not in the necessary *cis* relationship for ring closure.

As shown in Scheme 1 there are a number of possible routes from the initially formed intermediate (3) to the [2 + 2] macrocyclic complex (5). First, intermediate (3) may condense with a molecule of dicarbonyl (1) to form a new dicarbonyl species (6) which, in turn, reacts with a molecule of diamine (2) to give the macrocyclic product [route A: steps (*iii*) + (*iv*)].* Alternatively, the reverse sequence of condensation steps may occur, passing through the diamino-species (7) [route B: steps (*v*) + (*vi*)]. Thirdly, a bimolecular self-condensation of (3) is, in principle, possible [route C: step (*vii*)]. A fourth alternative [route D: steps (*v*) + (*viii*)] involves a self-condensation of two molecules of the diamine–diimine species (7) leading through to an overall amine exchange (transamination). The operation of route D (as well as route B) to [2 + 2] macrocycle formation is discussed below in relation to condensations between **2,6**-diacetylpyridine (and related dicarbonyls) with **3,6**-dioxaoctane-1,8-diamine in the presence of Ba^{2+} ion.

The Addition of Amines to Imines.—The susceptibility of the C=N group to nucleophilic attack is well known.[10,15] Addition of water regenerates the carbonyl



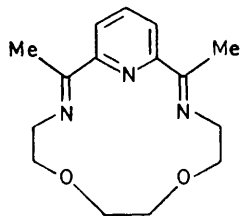
SCHEME 2

and primary amine *via* the (usually) unstable carbinolamine intermediate. Additions of alcohol, alkoxide, thiol, or thiolate to the imine group to give isolable products is also known, particularly when the imine nitrogen is co-ordinated to a metal ion.[16-18] When the nucleophile is a primary amine the *gem*-diamine (aminal) addition compound is not generally isolable although it is known to be stabilised by co-ordination in a few cases.[17] Two means of breakdown of the aminal are possible (Scheme 2).[15] The deamination may regenerate the starting materials or it may lead to a new amine and a new imine. Amine exchange (transamination) reactions were first used by Reddelien [19] as a route to new imines. The equilibria in Scheme 2 can be displaced in favour of the exchanged products by removal *e.g.* by distillation of the lower boiling amine and if the displacing amine has the higher basicity.[20] A few examples of amine exchange at co-ordinated imine centres, generating new imines, have been reported.[21] Transamination is also believed to be implicated in amino-acid metabolism mediated by pyridoxal phosphate (vitamin B_6).[22] Where the nucleophile is a secondary amine no amine exchange is possible because the aminal addition compound can only deaminate to re-form the reactants. In such cases evidence for attack may rest on the isolation of the aminal addition compound. We have recently reported some

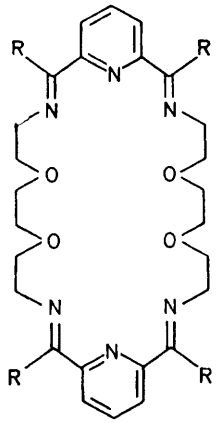
* The formation and structure of a barium(II) complex of type (6) derived from two molecules of 2,6-diacetylpyridine and one molecule of 3,6-diazaoctane-1,8-diamine have been described (M. G. B. Drew, C. V. Knox, and S. M. Nelson, *J. Chem. Soc., Dalton Trans.*, 1980, 942). This complex does not ring close on reaction with a range of diprimary amines possibly because of an unfavourable mutual positioning of the two carbonyl groups.

macrocyclic examples wherein the *gem*-diamino-addition product is stabilised by co-ordination.[23]

Condensation between 2,6-Diacetylpyridine and related Dicarbonyls with 3,6-Dioxaoctane-1,8-diamine.—Evidence for route B. It has previously been shown [24] that reaction of 2,6-diacetylpyridine (dap) with 3,6-dioxaoctane-1,8-diamine (dod) in the presence of salts of Mg^{II}, Mn^{II}, Fe^{II}, Fe^{III}, Zn^{II}, or Cd^{II} leads to the formation of seven-co-ordinate complexes of the 15-membered [1 + 1] quinquedentate macrocycle L^1, whereas when Pb^{II} or Ag^{I} are the template ions the products are binuclear complexes of the 30-membered [2 + 2] macrocycle L^2.[11,12] Further study now shows that when dap and dod are mixed together in MeOH in 1 : 1 molar proportions in the presence of one equivalent of $Sr[ClO_4]\cdot 6H_2O$ or $Ba[ClO_4]_2$ the complexes $[ML^4][ClO_4]_2$ are obtained in 15—20% yield (M = Sr^{II} or Ba^{II} and L^4 is the open-chain condensate of two molecules of dod with



L^1

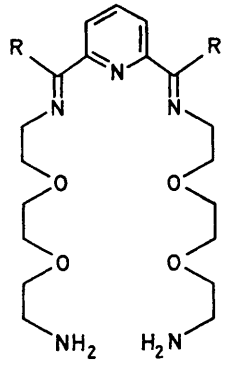


L^2 : R = Me

L^3 : R = H

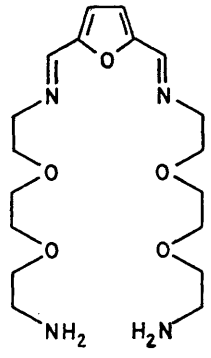
one molecule of dap). Yields are significantly increased (up to *ca.* 65% calculated on dap) by the use of a one equivalent excess of dod (see Experimental section for details). No macrocyclic products were obtained under these conditions. The complexes $[BaL^5][ClO_4]_2$ and $[BaL^6][ClO_4]_2\cdot 2H_2O$ were also obtained in good yield by reaction of dod (two equivalents) with one equivalent of 2,6-diformylpyridine (dfp) or 2,5-diformylfuran (dff) respectively.

The nature of the ligands L^4, L^5, and L^6 in these complexes was deduced from elemental analysis, i.r., and ^1H n.m.r. spectra (Tables 1 and 2) and from the chemical reactions of the complexes (see below). All exhibit a strong doublet between 3 300 and 3 380 cm^{-1} in the i.r. attributable to the asymmetric and symmetric NH_2 stretching vibrations, a medium intensity band at *ca.* 1 600 cm^{-1}, attributable to the NH_2 bending mode, and a strong band at 1 630—1 660 cm^{-1} due to the ν(C=N) stretch. The spectra also show features expected for the pyridine (or furan) and aliphatic ether moieties. The ν_3 and ν_4 modes of the perchlorate ions occurring at 1 090 and 620 cm^{-1} are unsplit suggesting that they are unco-ordinated. All four complexes are 2 : 1 electrolytes in acetonitrile solution. Hydrogen-1 n.m.r. spectra in CD_3CN solution confirm the conclusions relating to the



L^4 : R = Me

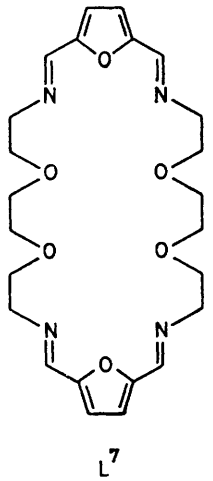
L^5 : R = H



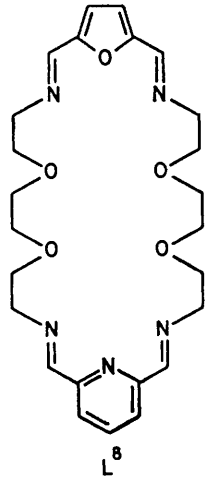
L^6

constitution of the ligands; assignments are given in Table 2.

When $[BaL^4][ClO_4]_2$ was dissolved in MeOH containing one equivalent of dap a new complex was formed in 30—40% yield within minutes at room temperature. This was shown by chemical analysis and i.r. spectra (Table 1) to be $[BaL^2][ClO_4]_2$ where L^2 is the [2 + 2] macrocyclic ligand referred to above. The i.r. spectrum is similar to that of $[BaL^4][ClO_4]_2$ except for the absence of $\nu(NH_2)$ and $\delta(NH_2)$ vibrations at 3 300—3 400 and *ca.* 1 600 cm^{-1} respectively. Due to its low solubility it was not possible to obtain a ^1H n.m.r. spectrum of $[BaL^2][ClO_4]_2$. However, confirmation of the occurrence of the macrocycle L^2 in this complex was obtained by metal exchange (transmetallation) with Cu^{II} to give the previously



L^7



L^8

characterised [25,26] complexes $[CuL^2][ClO_4]_2\cdot H_2O$ and $Cu_2L^2(ClO_4)_4\cdot 3H_2O$.

Similarly, treatment of $[BaL^6][ClO_4]_2\cdot 2H_2O$ with dff afforded the complex $[BaL^7][ClO_4]_2\cdot H_2O$ of the new 30-

TABLE 1

Analytical, i.r. (cm^{-1}), and electrical conductance data for the complexes

Complex	Analysis (%) Found C	Found H	Found N	Calc. C	Calc. H	Calc. N	$\nu(NH_2)$	$\delta(NH_2)$	$\nu(C{=}N)$	Λ^* / S cm^2 mol^{-1}
$[BaL^2][ClO_4]_2$	40.8	4.7	9.5	40.6	4.8	9.5			1 650 1 632	286
$[BaL^3][ClO_4]_2 \cdot 2H_2O$	34.6	3.9	8.8	34.6	4.2	9.3			1 650	251
$[BaL^4][ClO_4]_2$	33.3	4.9	9.2	33.2	4.9	9.2	3 382 3 320	1 604	1 645	335
$[SrL^4][ClO_4]_2$	35.6	5.4	9.7	35.5	5.3	9.9	3 360 3 302	1 602	1 642	319
$[BaL^5][ClO_4]_2$	31.3	4.6	9.5	31.2	4.6	9.6	3 360 3 298	1 598	1 652	282
$[BaL^6][ClO_4]_2 \cdot 2H_2O$	28.4	4.6	7.6	28.6	4.8	7.4	3 372 3 304	1 602	1 634	296
$[BaL^7][ClO_4]_2 \cdot H_2O$	34.5	4.0	6.5	34.8	4.2	6.8			1 634	310
$[BaL^8][ClO_4]_2 \cdot H_2O$	35.7	4.1	8.0	35.8	4.2	8.3			1 632	322
$[MgL^2][ClO_4]_2 \cdot H_2O$	45.9	5.7	10.4	45.5	5.6	10.6				
$[MgL^2][BPh_4]_2$	76.9	6.8	6.7	77.2	6.8	6.9			1 644	
$[Cu(L^9)_2][ClO_4]_2$	44.1	5.6	10.3	44.1	5.7	10.3			1 630	321
$[Cu(L^{10})_2][ClO_4]_2$	47.7	6.2	11.0	47.8	6.2	11.2			1 640	321
$[Cu(L^{11})_2][ClO_4]_2 \cdot H_2O$	42.9	5.2	11.5	43.6	5.6	11.7			1 639	325
$[Zn(L^{11})_2][ClO_4]_2 \cdot H_2O$	43.6	5.3	11.7	43.6	5.6	11.7			1 645	337
$[CuL^2][ClO_4]_2 \cdot H_2O$	43.4	5.3	10.2	43.4	5.3	10.1			1 640	320
$Cu_2L^2(ClO_4)_4 \cdot 3H_2O$	32.0	4.3	7.3	31.9	4.3	7.4			1 625	463
$[CuL^2][BPh_4]_2$	74.8	6.8	6.9	74.8	6.8	6.7			1 633	264
$[CuL^3][BPh_4]_2 \cdot H_2O$	73.4	6.4	7.2	73.2	6.3	6.9			1 642	
$[ZnL^3][BPh_4]_2$	74.1	6.4	7.1	74.2	6.2	7.0			1 638	
$[PbL^{12}(NCS)(SCN)]$	41.2	3.8	15.6	40.3	3.9	14.9			1 635	
$[Pb_2(L^{12})_2(en)][ClO_4]_4 \cdot 2H_2O$	33.0	3.8	11.7	33.3	3.9	11.8	3 320 3 275		1 635	

* For 10^{-3} mol dm^{-3} solutions at 25 °C.

TABLE 2

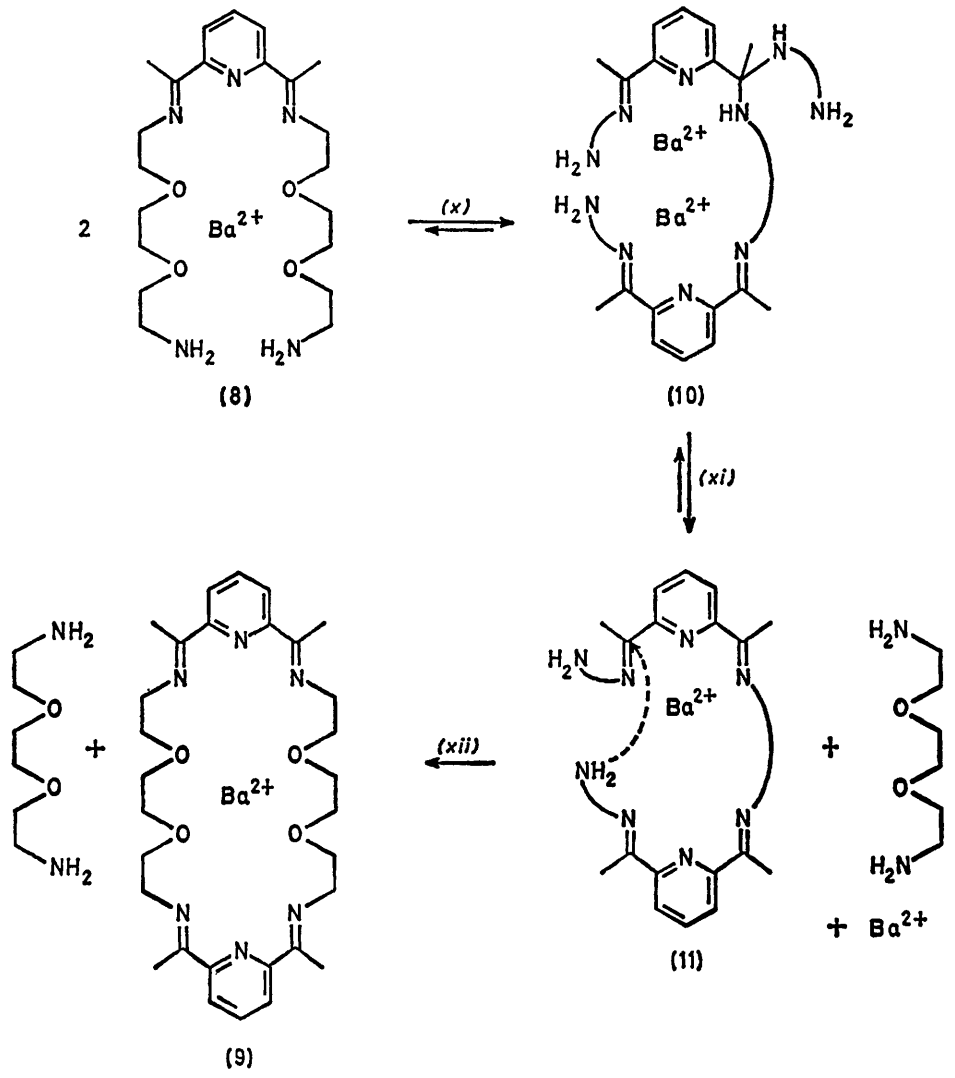
Hydrogen-1 n.m.r. spectral data [a] for the barium(II) complexes in CD_3CN

Complex	*HC*=N	Ring protons	CH_2–O	CH_2–C=N	CH_2–NH_2	CH_3–C=N	CH_3–NH_2 [b]
$[BaL^4][ClO_4]_2$		8.02 (m)[3]	3.86 (s)[16]	3.62 (t)[4]	2.83 (t)[4]	2.42 (s)[6]	0.18 (s)
$[BaL^5][ClO_4]_2$	8.54 (s)[2]	7.85 (m)[3]	3.84 (s)[16]	3.63 (t)[4]	2.85 (t)[4]		0.93 (s)
$[BaL^6][ClO_4]_2 \cdot 2H_2O$	8.20 (s)[2]	6.98 (s)[2]	3.85 (s)[16]	3.55 (t)[4]	2.87 (t)[4]		1.05 (s)
$[BaL^3][ClO_4]_2 \cdot 2H_2O$	8.50 (s)[4]	7.88 (m)[6]	3.2—3.9 (m)[24]				
$[BaL^7][ClO_4]_2 \cdot H_2O$	8.10 (s)[4]	7.04 (s)[4]	3.2—3.8 (m)[24]				
$[BaL^8][ClO_4]_2 \cdot H_2O$	8.45 (s)[2] [c] 8.12 (s)[2] [d]	7.88 (m)[3] [c] 7.05 (s)[2] [d]	3.2—3.9 (m)[24]				

[a] Chemical shifts (δ/p.p.m.) with multiplicities in parentheses. Relative intensities are given in square brackets. [b] Variable position and intensity due to exchange with H_2O. [c] dfp moiety. [d] dff moiety.

membered 'N_4O_6' macrocycle L^7, while treatment of $[BaL^5][ClO_4]_2$ with dff gave $[BaL^8][ClO_4]_2 \cdot H_2O$ containing the new 'asymmetric' 'N_5O_5' macrocycle having one pyridyl and one furan moiety. The nature of L^7 and L^8 in these complexes was again deduced from analytical and i.r. data (Table 1), and because of their greater solubility in acetonitrile, from ^1H n.m.r. data also (Table 2). The latter clearly show the presence of the furan group in $[BaL^7][ClO_4]_2 \cdot H_2O$ and of both the furan and pyridine groups in $[BaL^8][ClO_4]_2 \cdot H_2O$. Significantly, too, the triplets present in the spectra of the complexes of L^6 and L^5 at *ca.* 2.85 p.p.m., attributable to CH_2 adjacent to NH_2, are absent in the spectra of the complexes of L^7 and L^8. Instead, the multiplet at 3.2—3.9 p.p.m., due to CH_2 protons adjacent to C=N and ether oxygen groups, had increased in relative intensity.

Evidence for route D. It was observed that when $[BaL^4][ClO_4]_2$ (8) was dissolved in MeOH at room temperature in the *absence* of dap or other dicarbonyl the macrocyclic complex $[BaL^2][ClO_4]_2$ (9) separated out in 25—35% yield. The possibility that the ring closure might have resulted from a hydrolysis of L^4 followed by recombination of hydrolysis products to give L^2 was excluded by carrying out the reaction in dried solvent without loss in yield. To account for the ring closure of the co-ordinated diamine L^4 without dicarbonyl the sequence of reactions shown in Scheme 3 is proposed. Step (*x*) is a bimolecular reaction between two molecules of (8) involving nucleophilic attack by an unco-ordinated NH_2 group of one molecule at a co-ordinated C=N group of a second molecule to give the aminal addition compound (10). Regeneration of the imino-group can occur by elimination of one molecule of dod forming (11) [step (*xi*)]. A second nucleophilic attack, intramolecular this time, of an unco-ordinated NH_2 group of (11) at a neighbouring imino-carbon atom leads to the product (9) with elimination of a second molecule of dod [step (*xii*)]. The proposed mechanism thus comprises two trans-



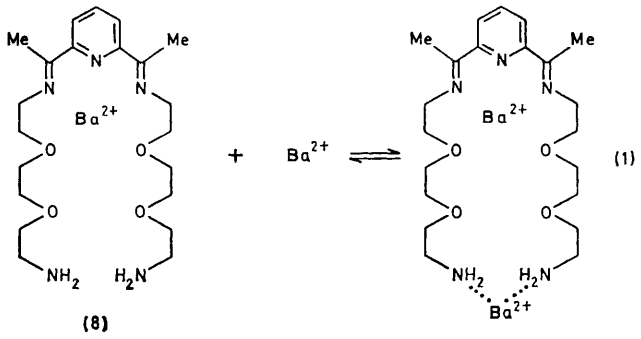
SCHEME 3

aminations, one intermolecular and one intramolecular. The sequences (8) ⟶ (11) and (11) ⟶ (9) are specific cases of the generalised transamination process shown in Scheme 2.

Since the non-macrocyclic diamine complex (8) appears to be an intermediate in the formation of the ring-closed product (9) it is at first sight surprising that the condensation stops at this stage in the initial experiments which employed dap and dod in 1 : 1 molar ratio. Under these conditions an excess of dap will be present, and available for ring closure, once (8) is formed. However, it should be noted that the yields of (8) under these conditions were always low (15—20%) so that there is also a substantial concentration of primary amine present. Whether the NH_2 groups are present as unreacted dod or in some partially condensed Schiff-base species with dap is probably unimportant provided the NH_2 groups are not strongly co-ordinated. Free NH_2 functions in these species are therefore available for nucleophilic attack at the imino-carbon atoms of (8) thereby competing with the self-condensation of (8) [step (*x*)]. To test this hypothesis the effect of added dod on the transamination sequence (8) ⟶ (9) was examined. It was found that the presence of the free amine dod completely suppressed the ring closure even at the relative concentration level of one mole per mole of (8). Moreover, the ring closure reaction (8) ⟶ (9) is reversible since it was found that (8) could be recovered in *ca.* 30% yield by treatment of (9) with two equivalents of dod (30 min at 65 °C in MeOH).

It was also observed that the presence of an excess of Ba^{2+} ion suppressed the formation of (9) from (8), although less effectively. For example, addition of one mole of $Ba[ClO_4]_2$ reduced the rate of formation of (9) by a factor of *ca.* 50. A possible reason for the reduced rate of macrocycle formation in the presence of free Ba^{2+} ion may be the occurrence of an equilibrium such as (1) involving a binuclear species (12) in which the terminal primary amine functions are less available for nucleophilic attack.

In contrast to the behaviour of $[BaL^4][ClO_4]_2$ the corresponding strontium(II) complex $[SrL^4][ClO_4]_2$ does not undergo ring closure to yield a complex of L^2 either in the absence of free dod or in its presence. Once again, the strength of interaction of the metal ion with the NH_2 groups may be a contributory cause for the different behaviour since Sr^{2+}, having a higher charge density than



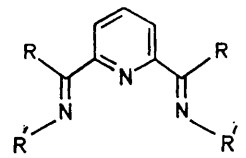
Ba^{2+}, may bond more effectively. Also, in contrast to $[BaL^4][ClO_4]_2$, the complexes $[BaL^5][ClO_4]_2$ and $[BaL^6][ClO_4]_2 \cdot 2H_2O$ do not undergo ring closure in the absence of dap. We believe that the varying behaviour is determined largely by the relative solubilities of the complexes of the open-chain and ring-closed ligands. That the nature of the solvent is important is demonstrated by the observation that $[BaL^4][ClO_4]_2$ can be recovered unchanged from MeCN solution.

The Magnesium(II) *Ion as a Template for both the* [1 + 1] *and* [2 + 2] *Macrocycles.*—Experiments employing calcium(II) salts did not lead to Schiff-base formation. Instead the products obtained appeared to be complexes of dod as judged by their i.r. spectra. They were not investigated further.

When $Mg[ClO_4]_2$ was used as template for reactions between dap and dod in MeOH two products were obtained depending on the method of isolation. Slow concentration of reactant solutions at room temperature yielded the complex $[MgL^2][ClO_4]_2 \cdot H_2O$ in 25% yield which could be converted into $[MgL^2][BPh_4]_2$ by metathesis. However, if the reactant solution was treated with $Na[BPh_4]$ before crystallisation of the ClO_4^- salt a white precipitate was obtained which on recrystallisation from MeOH–MeCN gave white crystals of $[MgL^1(OH_2)_2][BPh_4]_2$. Identification of the [1 + 1] and [2 + 2] macrocyclic ligands L^1 and L^2 in these complexes was achieved by chemical analysis (Table 1) and as follows. The i.r. spectrum of $[MgL^1(OH_2)_2][BPh_4]_2$ was identical to that of an authentic sample described previously.[27] The spectrum of $[MgL^2][BPh_4]_2$, although generally very similar, differed markedly in the 1 000—1 150 cm^{-1} region. In the spectrum of $[MgL^2][BPh_4]_2$ the dominant features in this region are two bands at 1 072 and 1 100 cm^{-1} whereas in $[MgL^1(OH_2)_2][BPh_4]_2$ two strong bands occur at 1 110 and 1 148 cm^{-1}. We assign these bands to the C–O–C stretching vibrations, unco-ordinated in the former complex (of the [2 + 2] ring) and co-ordinated in the latter (containing the [1 + 1] ring). Confirmation for the occurrence of the [2 + 2] macrocycle in $[MgL^2][ClO_4]_2 \cdot H_2O$ was obtained by a transmetallation reaction with Fe^{II} to give the known complex $[FeL^2][ClO_4]_2 \cdot H_2O$, as determined by chemical analysis and comparison of i.r. and Mössbauer spectra with those of an authentic sample.[25]

No complexes of open-chain condensates, such as (7), were isolated in these reactions even when an excess of dod was employed. However, it seems likely that (7) is a common intermediate to both the 15- and 30-membered macrocycles since when $[MgL^2][ClO_4]_2 \cdot H_2O$ was treated with two equivalents of dod in dry MeOH followed by an excess of $Na[BPh_4]$, the complex $[MgL^1(OH_2)_2][BPh_4]_2$ was recovered in 30% yield. Once again, the transamination mechanism appears to be operative.

Macrocycle Formation via *Transamination Reactions of Copper*(II) *and Zinc*(II) *Schiff-base Complexes.*—As a further test of the proposal of facile imine–amine exchange as an integral step leading to macrocycle formation some experiments designed to demonstrate transamination more directly were carried out. For this purpose some copper(II) and zinc(II) complexes of the open-chain Schiff-base ligands L^9, L^{10}, and L^{11} derived from the metal-free condensation of dap or dfp with the monoamines n-propylamine or 2-methoxyethylamine were prepared. These ligands form 2 : 1 $[ML_2]^{2+}$ com-



L^9: R = Me, R' = $CH_2CH_2OCH_3$

L^{10}: R = Me, R' = $CH_2CH_2CH_3$

L^{11}: R = H, R' = $CH_2CH_2CH_3$

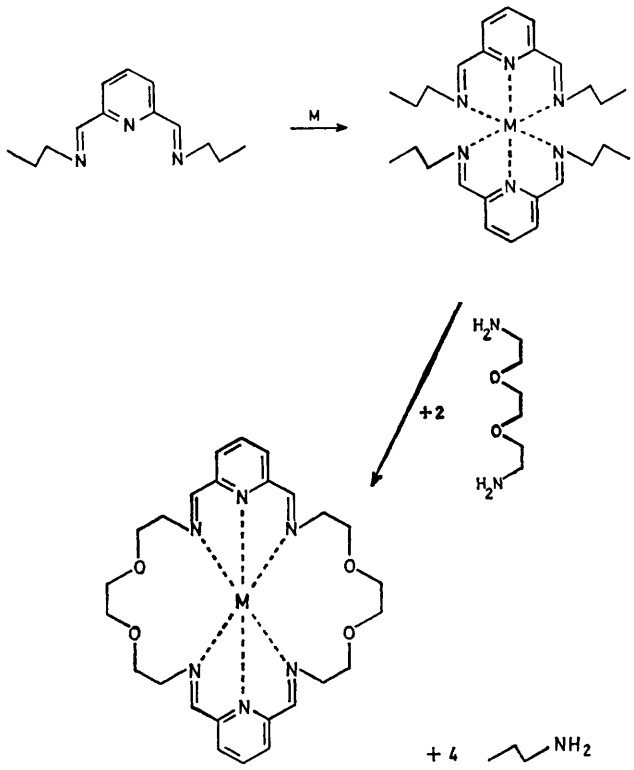
plexes with Cu^{II} and Zn^{II} (Table 1) analogous to some previously reported iron(II), cobalt(II), and nickel(II) complexes shown [25] to have six-co-ordinate, approximately octahedral structures comprising two co-ordinated and mutually perpendicular trimethine units, the ether oxygen atoms being unco-ordinated in the case of complexes of L^9.

Treatment of the copper(II) complex $[Cu(L^9)_2][ClO_4]_2$ with a five-fold excess of dod in dried MeOH (55 °C, 30 min) gave emerald green crystals of the known complex $[CuL^2][ClO_4]_2 \cdot H_2O$ in 70% yield on cooling and concentration. Although there are only trivial differences in the analytical figures calculated for the reactant and product complexes, and only small (although definite) differences in their i.r. spectra, proof that transamination had occurred was obtained by treatment of the mononuclear product complex in solution with an excess of $Cu[ClO_4]_2 \cdot 6H_2O$ to yield blue crystals of the known [26] binuclear complex $Cu_2L^2(ClO_4)_4 \cdot 3H_2O$ and shown to be identical with an authentic sample prepared from $[Ag_2L^2]^{2+}$.

The amine exchange reactions occurring at the imine centres co-ordinated to Cu^{II} were extended to copper(II) complexes of L^{10} and L^{11} containing different R' groups and to the zinc(II) complex $[ZnL^{11}][ClO_4]_2 \cdot H_2O$. Re-

actions were conducted in similar fashion in open-neck flasks, to allow ready escape of liberated n-propylamine, but using smaller excesses of dod and different solvents in some cases (see Experimental section). Products were isolated as $[BPh_4]^-$ salts rather than $[ClO_4]^-$ salts to allow identification of the ν(C–O) vibrations at 1 050—1 150 cm^{-1} present in the i.r. spectra of the products but absent in reactants.

These reactions clearly establish the exchange of four molecules of unidentate amine in the reactant complex by two molecules of bidentate dod to yield the 30-membered macrocycles as represented diagrammatically in Scheme 4. A sequence of steps can be postulated



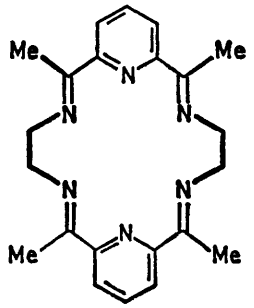
SCHEME 4

similar to those in Scheme 3, each involving addition of dod to the imine groups and elimination of the unidentate amine from the *gem*-diamine intermediates.

The importance of the nature of the metal ion in the amine exchange was revealed in experiments involving treatment of $[FeL^{11}][ClO_4]_2$ with dod. Here the reactant complex ion was recovered (as the BPh_4^- salt) unchanged. It is probable that the non-reaction in this case is a consequence of the low-spin ($S = 0$) nature of the metal ion in this complex which renders the imino-carbon less electrophilic as a result of the $d_\pi \rightarrow p_\pi^*$ back co-ordination.

Formation of an 18-*Membered* ' N_6 ' *Macrocycle from a* 30-*Membered* ' N_6O_4 ' *Macrocycle Co-ordinated to* Pb^{II}.—In principle, the synthetic strategy summarized in Scheme 4 is capable of extension to transamination by other diprimary amines leading to new macrocycles. Investigations towards this end are in progress. Preliminary results indicate that not only is it possible to exchange the amine moieties of an open-chain Schiff base by a suitable diprimary amine to form a macrocycle, as described above, it is also possible in favourable instances to convert one macrocycle into another. An example is given below.

We have previously described some metal complexes of the 18-membered ' N_6 ' macrocycle L^{12} derived from the [2 + 2] condensation of dap with 1,2-diaminoethane (en) in the presence of Pb^{II} or the heavier alkaline-earth metal ions, and the structure (approximately hexagonal bipyramidal) of the complex $[PbL^{12}(NCS)(SCN)]$ has been determined by *X*-ray methods.[14] We now find that the same complex can be obtained in good yield by treatment of $[Pb_2L^2(SCN)_4]$ (dry MeOH, 65 °C, 2.5 h) with a ten-fold excess of en. If $Na[ClO_4]\cdot H_2O$ is added to the reaction mixture before separation of $[PbL^{12}(NCS)(SCN)]$ the product is the complex of stoicheiometry $Pb_2L^{12}{}_2(en)(ClO_4)_4\cdot 2H_2O$ thought to have a dimeric structure in which two lead(II) ions are bridged by one en molecule.



L^{12}

This complex was compared with the product of reaction of $[PbL^{12}(NCS)(SCN)]$ prepared directly from dap and en, with $Na[ClO_4]\cdot H_2O$ + en and found to have identical properties.

Conclusions.—The results show that reactions between 3,6-dioxaoctane-1,8-diamine with 2,6-diacetylpyridine and related dicarbonyls in the presence of Ba^{2+} conducted under very mild conditions allow the isolation of complexes of open-chain ligands derived from the condensation of one molecule of dicarbonyl with two molecules of diprimary amine. It is further shown that the open-chain complexes subsequently undergo ring closure in the presence of added dicarbonyl (route B). The isolation of these species provides a route to new ' asymmetric ' macrocycles *via* ring closure with a different dicarbonyl. In the case of one of the open-chain complexes ring closure is also observed to occur in the absence of added dicarbonyl and a mechanism (route D) involving a sequence of inter- and intra-molecular nucleophilic additions, followed by deamination, of NH_2 to co-ordinated C=N groups is proposed.

It is implicit in our discussions so far that the open-chain complexes such as (8) are actual intermediates in the formation of the macrocyclic complexes. In the

light of the collected results presented in this and in the following paper we believe that this assumption has strong justification. However, it must be stated that proof that this is so in all cases is lacking. This is because the rapidity and reversibility of many of the reactions described in this paper point to their being under thermodynamic rather than kinetic control. Relevant observations are the ring closure (in the absence of dap) in one case and not in others, the influence of solvent, and the co-existence in solution of both [1 + 1] and [2 + 2] macrocyclic complexes of Mg^{II}. Under such circumstances the isolation of a particular complex may be determined largely by the relative solubilities of the various species present in equilibrium. For the closely related reactions described in the following paper, where there are measurable differences in the rates of formation of the open-chain complexes and their subsequent ring-closure reactions, the intervention of kinetic factors is apparent. Thus, for these systems more direct evidence for the intermediacy of open-chain complexes in the pathway leading to macrocycle formation is available.

Strong support for the proposals relating to transamination steps in the macrocycle synthesis has been obtained by the direct observation of amine exchange in copper(II), zinc(II), and lead(II) complexes of both open-chain and macrocyclic Schiff-base ligands. The results clearly demonstrate the importance in these systems of reversible nucleophilic addition of amines to the C=N bond as well as to the C=O bond.

EXPERIMENTAL

2,6-Diacetylpyridine was used as supplied. 2,6-Diformylpyridine was prepared by the method of Papadoupoulos *et al.*,[28] 2,5-diformylfuran by the method of Oleinik and Novitskii,[29] and 3,6-dioxaoctane-1,8-diamine by the method of Dwyer *et al.*[30]

Preparation of the Complexes.—$[BaL^4][ClO_4]_2$. 2,6-Diacetylpyridine (5 mmol) in methanol (150 cm^3) was treated with $Ba[ClO_4]_2$ (5 mmol) and 3,6-dioxaoctane-1,8-diamine (5 mmol). Reaction was allowed to proceed for *ca.* 1 h at room temperature. The solution was concentrated to *ca.* 50 cm^3 by rotary evaporation. White crystals of the product separated on standing in 10—15% yield in different preparations. The use of one equivalent excess of amine increased the yield to 55—60%.

$[SrL^4][ClO_4]_2$. This complex was prepared similarly. Yields were *ca.* 20% when 1 : 1 : 1 molar proportions of reactants were employed but substantially higher when an excess of amine was present.

$[BaL^5][ClO_4]_2$. 2,6-Diformylpyridine (5 mmol) in methanol (150 cm^3) was treated with $Ba[ClO_4]_2$ (5 mmol) and 3,6-dioxaoctane-1,8-diamine (10 mmol) and allowed to stand for 45 min at room temperature. On concentration, white crystals of product separated in 60% yield.

$[BaL^6][ClO_4]_2 \cdot 2H_2O$. 2,5-Diformylfuran (2.5 mmol) in ethanol (150 cm^3) was treated with $Ba[ClO_4]_2$ (2.5 mmol) and 3,6-dioxaoctane-1,8-diamine (5 mmol) at room temperature. After *ca.* 10 min, a pale yellow solid separated. Yield 75%.

$[BaL^2][ClO_4]_2$. The complex $[BaL^4][ClO_4]_2$ (0.39 mmol) was added to dry methanol (150 cm^3) and the solution stirred at room temperature. The reactant complex gradually dissolved. Shortly after the solution became clear (*ca.* 30 min) a cloudiness developed followed by separation of a fine white solid. Yield 25—35% in different experiments. Yields were increased, but not substantially, if free 2,6-diacetylpyridine was present.

$[BaL^3][ClO_4]_2 \cdot 2H_2O$. The complex $[BaL^5][ClO_4]_2$ (0.41 mmol) in dry methanol (150 cm^3) was treated with 2,6-diformylpyridine (0.82 mmol) and the solution allowed to stand for 30 min. On concentration, a fine white solid was obtained in 35% yield. The reactant complex was recovered unchanged in the absence of added diformylpyridine. This complex was also obtained by direct reaction from dicarbonyl and diamine. 2,6-Diformylpyridine (2.5 mmol) was treated with $Ba[ClO_4]_2$ (2.5 mmol) and 3,6-dioxaoctane-1,8-diamine (2.5 mmol) in methanol (150 cm^3). Refluxing for 30 min followed by concentration gave the product in 35% yield.

$[BaL^7][ClO_4]_2 \cdot H_2O$. The complex $[BaL^6][ClO_4]_2 \cdot 2H_2O$ (0.676 mmol) was dissolved in a refluxing solvent mixture made up of ethanol (150 cm^3) and methanol (20 cm^3). 2,5-Diformylfuran (1.35 mmol) was added and the solution refluxed for 30 min. On cooling and concentration, pale yellow crystals of the product were obtained in 60% yield. Alternatively this complex could be obtained in 45% yield from the dicarbonyl, diamine, and $Ba[ClO_4]_2$ (1 : 1 : 1 molar ratio).

$[BaL^8][ClO_4]_2 \cdot H_2O$. The complex $[BaL^5][ClO_4]_2$ (0.41 mmol) in dry methanol (150 cm^3) was treated with 2,5-diformylfuran (0.41 mmol) at room temperature. After 30 min the solution gave the very pale pink product in *ca.* 40% yield.

$[Cu(L^9)_2][ClO_4]_2$, $[Cu(L^{10})_2][ClO_4]_2$, $[Cu(L^{11})_2][ClO_4]_2 \cdot H_2O$. *and* $[Zn(L^{11})_2][ClO_4]_2 \cdot H_2O$. These complexes were prepared by the method outlined previously.[25]

Conversion of $[Cu(L^9)_2][ClO_4]_2$ *into* $[CuL^2][ClO_4]_2 \cdot H_2O$.—To a stirred solution of $[Cu(L^9)_2][ClO_4]_2$ (0.37 mmol) in warm MeOH (30 cm^3) was added a solution of dod (2 mmol) in MeOH (15 cm^3). On warming to *ca.* 60 °C for 30 min the colour changed to dark brown. The solution was maintained at 60 °C for a further 30 min and then cooled, whereupon the colour became green once more. On concentration to 10 cm^3, emerald green crystals of $[CuL^2][ClO_4]_2 \cdot H_2O$ separated. These were characterised by analysis and i.r. spectra, and by conversion into the binuclear complex $[Cu_2L^2][ClO_4]_4 \cdot 3H_2O$ previously described.[26]

Conversion of $[Cu(L^{10})_2][ClO_4]_2$ *into* $[CuL^2][BPh_4]_2$.—To a green solution of $[Cu(L^{10})_2][ClO_4]_2$ (0.48 mmol) in refluxing EtOH (250 cm^3), was slowly added a solution of dod (1.2 mmol) in EtOH (10 cm^3). After *ca.* 1 min the colour began to darken to a dark brown. Heating was continued for a further 3 min and the solution was then allowed to cool to room temperature, whereupon the colour reverted to green. To this stirred solution a solution of $Na[BPh_4]$ (1.4 mmol) in MeCN (50 cm^3) was added. On standing, green crystals of $[CuL^2][BPh_4]_2$ separated in *ca.* 60% yield.

Conversion of $[Cu(L^{11})_2][ClO_4]_2 \cdot H_2O$ *into* $[CuL^3][BPh_4]_2 \cdot H_2O$.—To a stirred solution of $[Cu(L^{11})_2][ClO_4]_2 \cdot H_2O$(0.18 mmol) in dry MeCN (100 cm^3) was added a solution of dod (0.6 mmol) in dry MeCN (10 cm^3) at room temperature. The mixture was gently heated over 30 min during which it changed colour to brown. On cooling the colour lightened somewhat. A solution of $Na[BPh_4]$ in MeCN was slowly added. Then EtOH (50 cm^3) was added dropwise to precipitate a pale brown material. This was recrystallised from MeCN to give the product as green crystals.

Conversion of $[Zn(L^{11})_2][ClO_4]_2 \cdot H_2O$ *into* $[ZnL^3][BPh_4]_2$.—This was carried out similarly.

Conversion of $[Pb_2L^2(SCN)_4]$ *into* $[PbL^{12}(SCN)_2]$.—To a pale yellow solution of $[PbL^2(SCN)_2]$ (1.7 mmol) in refluxing MeOH (900 cm^3) was slowly added 1,2-diaminoethane (17 mmol). The mixture was refluxed for 2.5 h with no visible colour change and then concentrated to 50 cm^3 by rotary evaporation. Yellow needles of product separated in 65% yield on standing. If an excess of $Na[ClO_4] \cdot H_2O$ is added to the reaction mixture before isolation of the dithiocyanate the complex $[Pb_2L^{12}{}_2(en)][ClO_4]_4 \cdot 2H_2O$ separates in 45% yield.

[0/1880 *Received, 5th December*, 1980]

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