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The Synthesis of Macrocycles Derived from Pyridine-2,6-dicarbaldehyde in the Absence of Metal Ions

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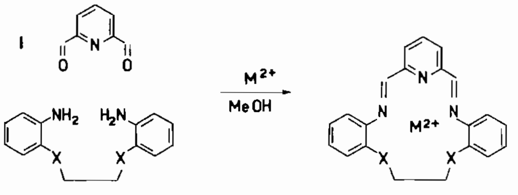
Metal complexes of quinquedentate macrocyclic ligands have been isolated from Schiff base condensations of pyridine-2,6-dicarbaldehyde (I) with a series of α,ω-diamines (II) in methanol in the presence of Mn^{++} and Zn^{++} perchlorates or nitrates [1].



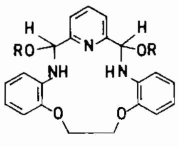
I

IIa, X = O
b, X = NH
c, X = S

III a,b,c

As part of an investigation into the coordination chemistry of the alkaline earth cations [2, 3] we have reinvestigated the above reaction and also attempted to introduce Mg^{++} as the templating cation in view of our success with related reactions of (I) with α,ω-polyfunctional dimaines [3].

Using (IIa) as the diamine we were able to repeat the above reactions successfully in both MeOH and EtOH. It was noticeable however that the products crystallised out more readily from EtOH than from MeOH. If $MnCl_2$ was used, in EtOH, as the template then a modified reaction sequence was observed. Although the first product isolated was [(IIIa), $Mn(H_2O)_2Cl_2$], as a bright orange–yellow powder, it was noted that on removal of this compound from solution, long, very fine needles were formed. This compound was shown by analysis*, i.r., ^{1}H and ^{13}C nmr to be 2,21-diethoxy-10,13-dioxa-3,20,26-triazatetracyclo[20.3.1.$0^{4,9}0^{14,19}$]hexacosa-1(26),4,6,8,14,16,18,22,24-nonaene, (IVa). If these crystals were returned to the filtrate and warmed for a few minutes a red–brown microcrystalline product, [(IVa), $MnCl_2$] was obtained.



IVa, R = Et
b, R = Me
c, R = nBu

The use of $Mg(ClO_4)_2$ or $Mg(NCS)_2$ as the potential template led to the precipitation of (IVa) from ethanolic solutions. It was further found that the presence of the metal was not required for the formation of (IVa) as the reaction of (I) with (IIa) in EtOH led directly to the crystallisation of (IVa). If this latter reaction was carried out in MeOH or nBuOH then (IVb) or (IVc) were isolated respectively. The use of i-propanol, t-butanol or benzyl alcohol as the solvent gave no isolable macrocyclic products.

The i.r. spectra of (IV) showed no bands corresponding to $\nu_{C=O}$ or $\nu_{C=N}$, but gave sharp secondary amine ν_{NH}'s *ca.* 3300 cm^{-1}. The ^{1}H nmr of (IVa) in $CDCl_3$ showed no signals attributable to imino- or formaldehydo-protons, but gave the very characteristic multiplets ascribed to ethoxy groups adjacent to chiral centers (δ_{CH_2}, 3.00 and 3.35). A sharp doublet was observed at δ 5.96, and is assigned to the –CH proton of the carbon–nitrogen bond, the doublet arising from coupling with the secondary amine proton. Shaking with D_2O causes the doublet to collapse to a single line, as does irradiation at the broad resonance at δ 7.31, assigned as the secondary amine proton.

It was noticed that chloroform solutions of (IVa) became yellow on standing for a short time, and following the addition of D_2O the ^{1}H nmr undergoes several changes. A steady ingrowth of signals ascribed to free ethanol is observed together with the appearance of a signal at δ 8.17, due to an imino-proton. The changes were also monitored by ^{13}C nmr and the imine carbon is observed at δ 159.9. After 24 hours a small peak is observed at δ 192.3 and this is assigned to the appearance of a carbonyl group, showing that after initial loss of ethanol the imine group is hydrolysed to open up the macrocycle.

The m.s. of (IV) gave no parent-ion peaks but only those corresponding to (P – 2ROH). This behaviour parallels that found for the alcohol adducts of 8-azobenzo-[4,5]cycloheptal[1,2,3-de]naphthalene [4]. For this compound the addition of alcohols across the carbon–nitrogen double bond occurs with surprising ease and it was proposed that the driving force

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*Analytical data: [(IIIa)$Mn(H_2O)_2Cl_2$]: found (calc)%: C 51.1 (49.9); H 3.9 (4.1); N 8.4 (8.3); Cl 14.0 (14.1). [(IVa)$MnCl_2$]: C 53.4 (53.5); H 4.7 (5.2); N 8.0 (7.5); Cl 13.3 (12.7). [(IVa)]: C 69.3 (69.0); H 6.4 (6.7); N 9.6 (9.7). [(IVb)]: C 67.3 (67.8); H 6.2 (6.1); N 10.7 (10.3). [(IVc)]: C 70.6 (70.8); H 7.9 (7.5); N 8.5 (8.6).

for the reaction was the relief of angular strain. The use of models suggests that a similar proposition be advanced for the facile syntheses of (IV a–c), *i.e.* that the relief of an angularly strained >C=N moiety leads to the formation of the alcohol adducts.

By extending the aliphatic bridge to a three carbon unit ($-CH_2CH_2CH_2-$) compounds analogous to (IV) may be made. In these a much more facile loss of alcohol occurs in solution: models indicate that there is less strain in the diimine precursors of these compounds than for the precursors of (IV) and it is probable that the relief of strain by the introduction of a more flexible bridge inhibits the formation of stable adducts. Further extension of the bridge length to five atoms ($-CH_2CH_2OCH_2CH_2-$) gave no isolable alcohol adducts, and so lends support to this proposition.

The formation of compounds such as (IV) may be interpreted as strongly suggesting that the macrocyclic diimine precursors are readily formed in a non-template synthesis; they are also formed in solutions of moderate concentration and not at high dilution. It has been proposed that cyclisation occurs in systems where there is an unusually small loss of internal entropy on ring closure [5]. In our case the nature of the starting materials is such that after the formation of a C=N bond to provide an open-chain intermediate, the relatively rigid nature of the components and the restricted rotation about the C=N bond would facilitate only a small entropy loss. It is pertinent therefore to question the role of the metal in the formation of compounds such as (III). The metal may participate in a thermodynamic template effect and complex the preformed macrocycle removing it from the equilibrium; or it may have no organisational influence at all with cyclisation being governed by entropy factors and the metal merely complexing the product.

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