Non-template Synthesis of 'N_4' Macrocyclic Imine Ligands with Variable Ring Sizes: The Importance of Intramolecular Hydrogen-bonding. *X*-Ray Crystal Structures of Three Macrocyclic and Two Open-chain Ligands

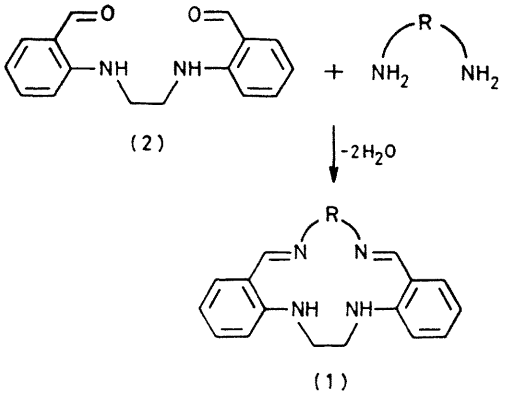
By PHILIP G. OWSTON, ROGER PETERS, EDWARD RAMSAMMY, PETER A. TASKER,* and JILL TROTTER†
(*Department of Chemistry, Polytechnic of North London, Holloway, London* N7 8DB
and †*Department of Chemistry, Queen Mary College, Mile End Road, London* E1 4NS)

Summary Di-imine tetra-aza macrocycles with an extensive range of ring sizes can be isolated by simple condensations without recourse to 'metal-ion template' or 'high-dilution' reactions, provided the rings can form intramolecular hydrogen bonds to reduce unfavourable lone-pair–lone-pair interactions between the nitrogen atoms

THE 'template' approach[1] to the synthesis of metal complexes of macrocyclic ligands has serious limitations for complexes of a number of metals, notably iron.[2] It is also unsuitable when it is necessary to examine the physical properties of the free ligands in order to interpret the properties of the metal complexes. We have therefore investigated the conditions which allow the isolation of the metal-free tetra-aza ligands (**1**) and analogues of (**1**) which have different levels of hydrogenation of the inner great-ring.

Previously, condensation reactions of the type shown in the Scheme have been conducted in the presence of metal(II) acetates to yield an extensive range[3,4] of neutral Co^{II}, Ni^{II}, and Cu^{II} complexes of (**1**) or of related systems[5] having a trimethylene link between the anilino-nitrogen atoms. In only a few cases have the related free macrocycles been isolated by performing the condensation (Scheme) in the presence of Zn^{II} salts,[4,6] or by using conditions of 'high dilution',[5] or by displacement of the metal ion from a suitable metal complex.[7]

We have now prepared the series of macrocycles (**1**)† by varying the conditions for the condensation, see the Scheme. No catalysts were required for reactions giving the 14- to



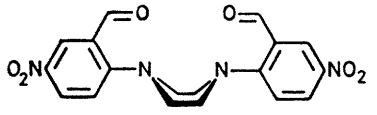
	R	Conditions	Yield/%
(**1a**)	$-[CH_2]_2-$	i	86
(**1b**)	$-[CH_2]_3-$	ii	94
(**1c**)	$-[CH_2]_4-$	ii	88
(**1d**)	$-[CH_2]_5-$	iii	85
(**1e**)	$-[CH_2]_7-$	iii	73
(**1f**)	$-[CH_2]_8-$	iii	89
(**1g**)	$-[CH_2]_{10}-$	iii	75
(**1h**)	$-[C_6H_4\text{-}o]-$	iv	83
(**1i**)	$-C(CN)=C(CN)-$	v	87
(**1j**)	$-(C_6H_4\text{-}o)NH(C_6H_4\text{-}o)-$	vi	76
(**1k**)	$-(C_6H_4\text{-}o)-O-[CH_2]_2-O-(C_6H_4\text{-}o)-$	vi	80

SCHEME *Reaction conditions*: i, 10% molar excess of diamine in sufficient refluxing $CHCl_3$ for dissolution of (**2**), addition of EtOH after 18 h, and reduction of solvent volume at 45 °C; ii, 10—20% molar excess of diamine with refluxing methanolic suspension of (**2**); iii as ii but in EtOH; iv, (**2**) diamine, and $Zn(MeCO_2)_2\,2H_2O$ in molar ratio 1 : 1 : 2 in refluxing MeOH; v, (**2**), diamine and toluene-*p*-sulphonic acid in molar ratio 1 : 1 : 0.1 in refluxing tetrahydrofuran; vi, as v, but in MeOH.

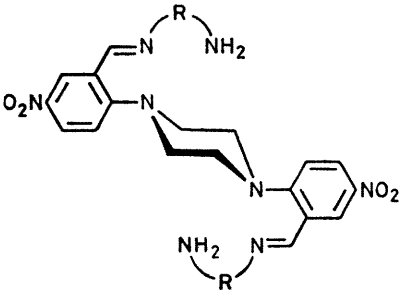
† The compounds (**1**) gave satisfactory C, H, and N analyses, relative molecular masses were determined by electron-impact mass spectrometry for all compounds and additionally by field-desorption mass spectrometry (*m/e* 404, no other peaks in the range 300—1000) for (**1g**); ^1H n.m.r. spectra were mutually consistent for the whole series of compounds. Reaction of (**2**) with 1,6-diaminohexane appears to proceed similarly to that with 1,2-diaminoethane, but is still under study. Condensation of (**2**) with 1,9-diaminononane was not attempted.

22-membered rings (**1a**)—(**1g**) when the bridges were aliphatic, though (**1a**) was found to be unstable, being converted into a species of higher relative molecular mass on prolonged heating in methanol. The formation of compounds (**1h**)—(**1k**) with unsaturated bridges R requires the addition of an acid catalyst, *e.g.* toluene-*p*-sulphonic acid. Zinc(II) acetate is an effective catalyst for the formation of (**1h**), but not for (**1i**) because it reacts preferentially with diaminomaleonitrile.

The isolation of di-imine macrocycles with such a range of ring sizes is remarkable and is dependent on a number of factors. Two which appear to be important for the series (**1**) are (i) the choice of reaction conditions and solvents which allow the free ligands to separate from solution before conversion into species which are thermodynamically more stable and (ii) the stabilization of the imine bond by intramolecular hydrogen-bonding. An indication of the importance of the latter is provided by a comparison of the condensations of the Scheme with those of a related dialdehyde (**3**) which has no anilino-hydrogen atoms. From the reactions of (**3**) so far attempted (with 1,2-diaminoethane, 1,2-diaminobenzene, and 1,3-diaminopropane) the 1 : 2 linear condensation products (**4a**), (**4b**),

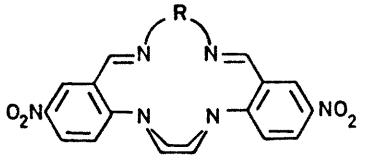


(3)



(4)

a; R = $-[CH_2]_2-$
b; R = $-(C_6H_4-o)-$
c; R = $-[CH_2]_3-$



(5)

and (**4c**) were obtained instead of the macrocyclic di-imines (**5**). Structure determinations of (**4a**) and (**4b**) show that these adopt an extended configuration which minimises nitrogen lone-pair–lone-pair repulsion (see Figure 1). Molecular models indicate that in the di-imines (**5**) there would be a very unfavourable interaction in the centre of the ring between the lone-pairs on the four nitrogen atoms.

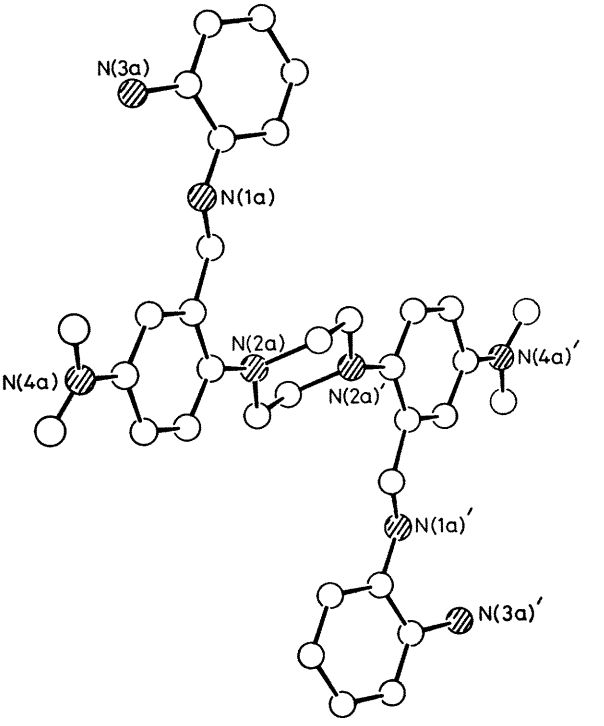


FIGURE 1. The extended configuration of (**4b**) in the solid state.

In the series (**1**) the presence of anilino-hydrogen atoms allows intramolecular hydrogen-bonding which reduces such lone-pair interactions in the centres of the rings. Almost planar hydrogen-bonded units (Figure 2) are observed in the *X*-ray structures of (**1a**), (**1b**), (**1c**),[8] and (**1h**), (see the Table). The overall configurations of the macrocycles differ considerably (see Figure 3) and appear to be determined by the requirement of preserving the planarities of the units shown in Figure 2, while minimising contact between the 'chelated' anilino-protons in the two halves of the molecules.

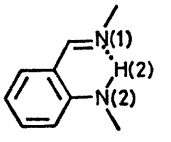


FIGURE 2. Hydrogen-bonded units in (**1a**), (**1b**), (**1c**),[8] and (**1h**). Bond lengths N(1) . . . N(2) 2·65—2·75 and N(1) . . . H(2) 1·87—2·04 Å; bond angles N(2)–H(2) . . . N(1) 125·0—139·4°. Root-mean-square deviations from the 'best' plane through the atoms of this unit (excluding H's) fall in the range 0·031—0·055 Å in all cases.

These results suggest that an important consideration in devising methods for preparing metal-free tetra-aza macrocycles (particularly those with relatively planar 'N_4' donor sets) is the potential occurrence of unfavourable intra-annular interactions of lone pairs of electrons. Significantly, there have been no reports[1] of successful ring-closure reactions to give metal-free 14-, 15-, or 16-membered 'N_4' macrocycles, unless there are at least two secondary amine hydrogen atoms present. These can apparently

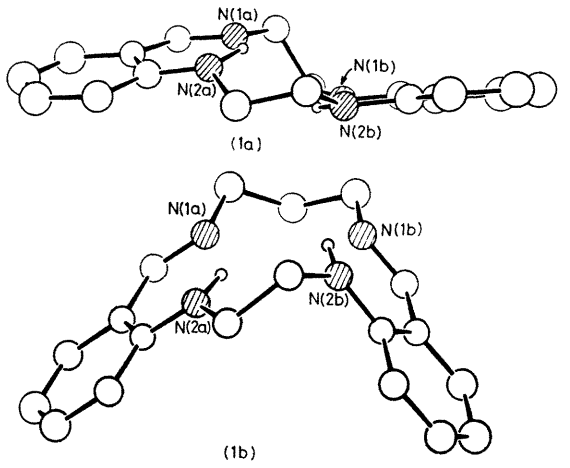


FIGURE 3 The molecular configurations of the 14- and 15-membered macrocycles (**1a**) and (**1b**)

operate as an alternative to a metal ion as a 'thermodynamic template'[9] in stabilizing the molecule by reducing the lone-pair repulsions

Crystal data (**1a**) $C_{18}H_{20}N_4$, 7,8,15,16,17,18-hexahydrodibenzo[*e*,*m*][1,4,8,11]tetra-azacyclotetradecine, M = 292·4, orthorhombic, space group *Pbca*, a = 29·158(60), b = 27·311(20), c = 7·849(7) Å, U = 6250·4 Å^3, Z = 16, D_c = 1·24 g cm^{-3}, 1356 data with $F > 4\sigma(F)$, R 0·121, R_w (= $\Sigma w^{\frac{1}{2}}\Delta/\Sigma w^{\frac{1}{2}}|F_o|$) 0 087 (**1b**) $C_{19}H_{22}N_4$, 8,9,16,17,18,19-hexahydro-7*H*-dibenzo[*e*,*n*][1,4,8,12]tetra-azacyclopentadecine, M = 306·4, orthorhombic, $Pna2_1$, a = 15·806(4), b = 20·580(19), c = 4 967(1) Å, U = 1615·7 Å^3, Z = 4, D_c = 1·26 g cm^{-3}, 1737 data with $F > 4\sigma(F)$, R 0 071, R_w 0·063 (**1h**) $C_{22}H_{20}N_4$, 17,18,19,20-tetrahydrotribenzo[*e*,*i*,*m*][1,4,8,11]tetra-azacyclotetradecine, M = 340·4, monoclinic, $P2_1/n$, a = 20 924(11), b = 4 772(1), c = 18·302(11) Å, β = 106 32(1)°, U = 1753 8 Å^3, Z = 4, D_c = 1·29 g cm^{-3}, 1321 data with $F > 5\sigma(F)$, R 0·073, R_w 0 064 (**4a**) $C_{22}H_{28}N_8O_4$, 1,4-bis-[2-(2-aminoethyliminomethyl)-4-nitrophenyl]piperazine, M = 468 5, monoclinic, $P2_1/c$, a = 9 619(5), b = 10 072(3), c = 12·444(4) Å, β = 106·88(1)°, U = 1153 7 Å^3, Z = 2, D_c = 1·35 g cm^{-3}, 731 data with $F > 4\sigma(F)$, R 0 091, R_w 0 087 (**4b**) $C_{30}H_{28}N_8O_4\ 2H_2O$, 1,4-bis-[2-(*o*-aminophenyliminomethyl)-4-nitrophenyl]piperazine, M = 600·6, monoclinic, $C2/c$, a = 16·708(5), b = 7·805(10), c = 24·113(7) Å, β = 92·81(2)°, U = 3140·7 Å^3, Z = 4, D_c = 1 27 g cm^{-3}, 734 data with $F > 4\sigma(F)$, R 0·116, R_w 0 113 ‡

We thank the S R C for a studentship (to R P) and for diffractometer equipment and computing facilities

(*Received*, 22*nd July* 1980, *Com* 794)

‡ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW Any request should be accompanied by the full literature citation for this communication

[1] G A Melson in 'Co-ordination Chemistry of Macrocyclic Compounds,' ed G A Melson, Plenum Press, 1979 Ch 2.
[2] S C Tang, S Koch, G N Weinstein, R W Lane, and R H Holm, *Inorg Chem*, 1973, **12**, 2589
[3] M Green and P A Tasker, *Inorg Chim Acta*, 1971, **5**, 65
[4] D St C Black, C H Bos Vanderzalm, and L C H Wong, *Aust J Chem*, 1979, **32**, 2303
[5] D St C Black, A J Hartshorn, M Horner, and S Hunig, *Aust J Chem*, 1977, **30**, 2493
[6] M Green, J Smith, and P A Tasker, *Inorg Chim Acta*, 1971, **5**, 17
[7] P A Tasker and E B Fleischer, *J Am Chem Soc*, 1970, **92**, 7072
[8] G M Sheldrick and J Trotter, *Acta Crystallogr*, *Sect B*, 1978, **34**, 3122
[9] P B Donaldson, P A Tasker, and N W Alcock, *J Chem Soc*, *Dalton Trans*, 1976, 2262