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Ring Contraction in Schiff Base Macrocycles: The X-Ray Crystal Structure of an Imidazolidine-Containing Macrocycle

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Abstract. Cyclocondensation of benzene-1,3-dicarbaldehyde and 3-azapentane-1,5-diamine in acetonitrile leads to isolation of an 18-membered imidazolidine-containing Schiff base macrocycle rather than the anticipated 24-membered tetraimine Schiff base macrocycle. This has occurred as a consequence of internal nucleophilic addition of the secondary amine functions across adjacent azomethine bonds. The X-ray crystal structure of the imidazolidine-containing Schiff base macrocycle is reported.

Key words. Macrocycle, Schiff base, imidazolidine ring contraction.

Supplementary Data relating to this article have been deposited with the British Library as Supplementary Publication No. SUP 82112 (7 pages).

1. Introduction

The template cyclocondensation of heterocyclic dicarbonyls and α, ω-diamines has been exploited in the preparation of metal complexes of '2 + 2' tetraimine Schiff base macrocycles (TSBM) [1]. It has, however, not been possible to achieve facile release of the metal and recover the intact metal-free macrocycle although there have been some reports of tetraimine Schiff base macrocycle formation in the absence of templating devices. Metal-free tetraimine Schiff base macrocycles derived from thiophene-2,5-dicarbaldehyde [2] and from pyrrole-2,5-dicarbaldehyde [3] have been prepared using similar reaction conditions – alcoholic solvent media – to the template cyclocondensations. If a non-protic medium is used – benzene, tetrahydrofuran, acetonitrile – then TSBM derived from pyridine-2,6-dicarbaldehyde [4, 5], benzene-1,3-dicarbaldehyde [6] and 4,4′-methylene-bis-benzaldehyde [7] may be prepared. Use of a diamine containing a reactive –XH function in metal templated reactions giving tetraimine Schiff base macrocycles has led to ring contraction reactions through addition of the –XH across an imine bond. Crystal structures of the lead and barium complexes have confirmed the nature of ring contractions leading to oxazolidine- [8] and imidazolidine-containing [9, 10] Schiff base macrocycles derived from the template cyclocondensation of 2,6-diacetylpyridine with 1,3-diamino-2-propanol and 3-azapentane-1,5-diamine, respectively. In these reactions it was thought that the presence of the metal ion aided the

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ring-contraction, particularly as attempts to demetallate the complexes generally resulted in a breakdown of the ligand. In this paper we report the synthesis of a ring-contracted, but metal-free, imidazolidine-containing macrocycle, together with its X-ray crystal structure [11].

2. Experimental

2.1. NON-TEMPLATE SYNTHESIS OF THE RING CONTRACTED '2 + 2' MACROCYCLE [6, 7]

A solution of benzene-1,3-dicarbaldehyde (2.01 g, 15 mmol) in acetonitrile (250 mL) was added dropwise to a stirred solution of 3-azapentane-1,5-diamine (1.62 mL, 15 mmol) in acetonitrile (250 mL) over a period of 2 h. A white precipitate formed over a period of 12 h and was recrystallised from a dichloromethane/acetonitrile mixture. Colourless crystals. Yield 70–75%; m.p. 156–8°C.; IR (KBr disc): ν_{NH} 3240 cm^{-1}, $\nu_{C=N}$ 1640 cm^{-1}; MS (e.i.): 402 amu.; Microanalysis (%) found (required) for $C_{24}H_{30}N_6$: C 68.73 (68.27), H 7.25 (7.40), N 19.83 (19.95).

2.2. CRYSTAL STRUCTURE DATA AND DETERMINATION

Crystal data for (**2**)·0.25 CH_2Cl_2, $C_{24.25}H_{30}Cl_{0.5}N_6$, M = 423.77: crystallises from dichloromethane/acetonitrile as colourless blocks; crystal dimensions 0.45 × 0.20 × 0.20 mm. Monoclinic, $a = 17.448(21)$, $b = 17.028(24)$, $c = 18.190(23)$ Å, $\beta = 118.16(9)^\circ$, $U = 4765(11)$ Å^3, $D_c = 1.181$ g cm^{-3}, $Z = 8$, space group $C2/c$ (C_{2h}^6, No. 15), MoK_α X-radiation ($\lambda = 0.71069$ Å), μ(MoK_α) = 1.23 cm^{-1}, $F(000) =$ 1811.58.

Three-dimensional, room temperature X-ray data were collected in the range $3.5 < 2\theta < 40^\circ$ on a Nicolet R3 4-circle diffractometer by the omega scan method.

The 1116 independent reflections (of 2422 measured) for which $|F|/\sigma(|F|) > 3.0$ were corrected for Lorentz and polarisation effects, but not for absorption. The structure was solved by multiple solution direct methods and refined by blocked cascade least squares. A molecule of dichloromethane was found to be equally disordered, in low occupancy, across a crystallographic C_2 axis and each component was given a population of 0.25 and was refined with constrained bond lengths and angles in such a way that the hydrogen bonds which it formed were geometrically optimised: unconstrained refinement led to an unacceptably asymmetric pair of hydrogen bonding interactions and several disorder models were tried before the one reported was finally accepted. Hydrogen atoms were included in calculated positions, with isotropic thermal parameters related to those of the supporting atom, and refined in riding mode. Refinement converged at a final R 0.1185 (289 parameters; mean and maximum final Δ/σ 0.001 and 0.004 respectively), with allowance for the thermal anisotropy of all non-hydrogen atoms, with the exception of those of the components of the disordered dichloromethane molecule. A final difference electron density synthesis showed minimum and maximum values of -0.55 and $+0.67$ e Å^{-3}. Complex scattering factors were taken from the programme package SHELXTL [12] as implemented on the Data General Nova 3 computer. Unit weights were used throughout the refinement. Table I lists atomic positional parameters with estimated standard deviations and Table II lists bond lengths and angles.

Table I. Atom coordinates ($\times 10^4$) and temperature factors ($\text{Å}^2 \times 10^3$)

Atom	x	y	z	U_{eq}
N(1)	1798(8)	2528(6)	3380(7)	61(7)*
N(2)	2084(7)	4217(6)	3955(7)	54(6)*
N(3)	2818(8)	5286(7)	4836(8)	74(8)*
C(1)	2702(10)	1176(9)	4359(10)	60(9)*
C(2)	3157(10)	516(9)	4799(9)	56(9)*
C(3)	3675(11)	95(9)	4543(10)	68(11)*
C(4)	3815(11)	358(11)	3902(11)	79(11)*
C(5)	3356(11)	1029(10)	3457(11)	69(11)*
C(6)	2817(10)	1452(9)	3694(10)	57(9)*
C(7)	2378(9)	2161(9)	3252(10)	61(9)*
C(8)	1343(10)	3201(9)	2854(9)	73(10)*
C(9)	1259(9)	3884(9)	3373(9)	60(8)*
C(10)	2549(10)	4625(9)	3551(10)	66(10)*
C(11)	3117(12)	5240(10)	4201(11)	91(12)*
C(12)	1992(9)	4825(8)	4494(9)	60(9)*
N(1a)	5250(8)	4106(6)	−1073(8)	66(8)*
N(2a)	4740(7)	3031(7)	−29(8)	65(7)*
N(3a)	3958(10)	2768(9)	672(10)	117(11)*
C(1a)	4813(9)	5768(7)	−1288(9)	52(8)*
C(2a)	4590(11)	6537(8)	−1495(12)	63(10)*
C(3a)	3927(14)	6760(11)	−2307(15)	89(14)*
C(4a)	3500(12)	6165(15)	−2896(10)	81(11)*
C(5a)	3695(11)	5398(10)	−2697(10)	63(10)*
C(6a)	4378(10)	5191(7)	−1911(10)	49(9)*
C(7a)	4574(9)	4357(9)	−1719(9)	64(8)*
C(8a)	5401(10)	3243(8)	−977(9)	62(9)*
C(9a)	5526(10)	2954(8)	−130(10)	70(10)*
C(10a)	4011(11)	2490(11)	−596(12)	97(12)*
C(11a)	3432(14)	2430(13)	−188(13)	127(16)*
C(12a)	4852(11)	2823(9)	806(10)	72(10)*
Cl(1)	3621(18)	1532(17)	1624(17)	190(9)
Cl(2)	5482(17)	1542(17)	2989(16)	190(9)
C(13)	4577(28)	925(20)	2265(52)	190(9)

*Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor.
The two independent half-macrocycles comprise atoms N(1)–N(3), Cl(1)–C(12) and N(1a)–N(3a), C(1a)–C(12a), and their associated hydrogen atoms. Atoms Cl(1), Cl(2), C(13) comprise a dichloromethane molecule of crystallisation which has total occupancy of 50%, but is disordered equally across a crystallographic C_2 axis.

3. Results and Discussion

The reaction of benzene-1,3-dicarbaldehyde with 3-azapentane-1,5-diamine in acetonitrile at high dilution gives a white precipitate, analysis of which corresponds to that of the anticipated metal-free tetraimine Schiff base macrocycle (**1**). The IR spectrum gave bands at *ca.* 3240 cm^{-1} and at 1640 cm^{-1} indicative of the presence of secondary amines and imines. No bands corresponding to carbonyls or primary amines were observed thus suggesting that cyclisation had occurred. A parent ion at $m/z = 402$ in the MS confirmed this. The ^1H NMR in $CDCl_3$, in which there are five signals attributable to imine protons, suggests the presence of an isomeric

Table II.

(a) Bond lengths (Å)

N(1)—C(7)	1.301(24)	N(1)—C(8)	1.464(18)
N(2)—C(9)	1.442(16)	N(2)—C(10)	1.498(24)
N(2)—C(12)	1.485(21)	N(3)—C(11)	1.477(29)
N(3)—C(12)	1.495(19)	C(1)—C(2)	1.389(21)
C(1)—C(6)	1.398(28)	C(2)—C(3)	1.395(28)
C(2)—C(12)^{I}	1.540(27)	C(3)—C(4)	1.375(30)
C(4)—C(5)	1.410(23)	C(5)—C(6)	1.404(29)
C(6)—C(7)	1.452(20)	C(8)—C(9)	1.548(24)
C(10)—C(11)	1.539(21)	N(1a)—C(7a)	1.284(16)
N(1a)—C(8a)	1.489(17)	N(2a)—C(9a)	1.472(25)
N(2a)—C(10a)	1.514(19)	N(2a)—C(12a)	1.482(24)
N(3a)—C(11a)	1.505(25)	N(3a)—C(12a)	1.463(26)
C(1a)—C(2a)	1.366(18)	C(1a)—C(6a)	1.419(19)
C(2a)—C(3a)	1.432(25)	C(2a)—C(12)^{II}	1.598(21)
C(3a)—C(4a)	1.406(29)	C(4a)—C(5a)	1.356(30)
C(5a)—C(6a)	1.407(20)	C(6a)—C(7a)	1.464(20)
C(8a)—C(9a)	1.532(26)	C(10a)—C(11a)	1.513(38)
Cl(1)—C(13)	1.836(47)	Cl(2)—C(13)	1.836(52)
Cl(1)..N(3a)	2.955	Cl(1)..H(N3c)	2.02
Cl(2)..N(3a)^{III}	2.999	Cl(2)..H(N3c)^{III}	2.12

(b) Bond angles (deg.)

C(7)—N(1)—C(8)	119.1(15)	C(9)—N(2)—C(10)	114.0(12)
C(9)—N(2)—C(12)	112.2(12)	C(10)—N(2)—C(12)	104.7(11)
C(11)—N(3)—C(12)	105.9(12)	C(2)—C(1)—C(6)	119.7(18)
C(1)—C(2)—C(3)	120.4(17)	C(1)—C(2)—C(12)^{I}	120.7(17)
C(3)—C(2)—C(12)^{I}	118.4(13)	C(2)—C(3)—C(4)	121.2(15)
C(3)—C(4)—C(5)	118.1(19)	C(4)—C(5)—C(6)	121.4(19)
C(1)—C(6)—C(5)	118.9(14)	C(1)—C(6)—C(7)	120.4(17)
C(5)—C(6)—C(7)	120.8(18)	N(1)—C(7)—C(6)	123.5(17)
N(1)—C(8)—C(9)	111.5(12)	N(2)—C(9)—C(8)	113.3(13)
N(2)—C(10)—C(11)	103.9(15)	N(3)—C(11)—C(10)	107.5(16)
N(2)—C(12)—N(3)	104.9(14)	N(2)—C(12)—C(2)^{I}	113.6(12)
N(3)—C(12)—C(2)^{I}	111.1(11)	C(7a)—N(1a)—C(8a)	118.1(11)
C(9a)—N(2a)—C(10a)	113.2(14)	C(9a)—N(2a)—C(12a)	115.3(11)
C(10a)—N(2a)—C(12a)	102.4(13)	C(11a)—N(3a)—C(12a)	106.2(18)
C(2a)—C(1a)—C(6a)	117.9(12)	C(1a)—C(2a)—C(3a)	121.7(14)
C(1a)—C(2a)—C(12)^{II}	116.6(13)	C(3a)—C(2a)—C(12)^{II}	121.6(13)
C(2a)—C(3a)—C(4a)	118.3(17)	C(3a)—C(4a)—C(5a)	121.0(15)
C(4a)—C(5a)—C(6a)	119.9(14)	C(1a)—C(6a)—C(5a)	121.0(12)
C(1a)—C(6a)—C(7a)	120.3(12)	C(5a)—C(6a)—C(7a)	118.4(12)
N(1a)—C(7a)—C(6a)	123.5(12)	N(1a)—C(8a)—C(9a)	111.6(14)
N(2a)—C(9a)—C(8a)	113.5(12)	N(2a)—C(10a)—C(11a)	104.4(16)
N(3a)—C(11a)—C(10a)	105.2(16)	N(2a)—C(12a)—N(3a)	103.3(11)
N(2a)—C(12a)—C(2)^{II}	112.2(14)	N(3a)—C(12a)—C(2)^{II}	112.5(16)
Cl(1)—C(13)—Cl(2)	110.5(22)	H(N3a)—N(3)—H(N3b)	109.5
H(N3a)—N(3)—C(11)	110.4	H(N3b)—N(3)—C(11)	110.4
H(N3a)—N(3)—C(12)	110.4	H(N3b)—N(3)—C(12)	110.4
H(N3c)—N(3a)—C(11a)	108.9	H(N3c)—N(3a)—C(12a)	109.1

Symmetry operations are as follows: I [$0.5-x$, $0.5-y$, $1-z$]; II [$1-x$, $1-y$, $-z$]; III [$1-x$, y, $0.5-z$].

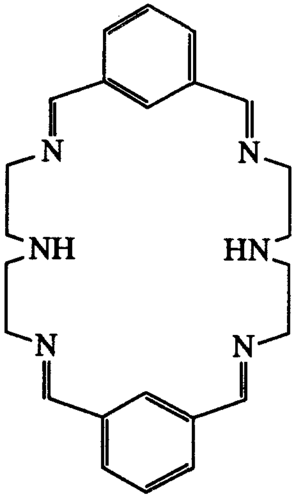
mixture in solution. If ring contractions have occurred both structural and stereoisomers would be available. ^1H NMR studies in $CDCl_3$ have also indicated the formation of an imidazolidine-containing Schiff base macrocycle derived from the condensation of 3-azapentane-1,5-diamine with thiophene-2,5-dicarbaldehyde [2] and with pyridine-2,6-dicarbaldehyde [13] but suitable crystals for an X-ray structural investigation were not available. In the present study it was possible to grow crystals from a CH_2Cl_2/CH_3CN mixture and an X-ray crystal structure determination was undertaken in order to establish the nature of the solid product.

The crystal structure consists of two sets of independent, macrocyclic molecules, each molecule having crystallographically imposed inversion symmetry, utilising both sets of inversion centres in the space group $C2/c$. Approximately half of the molecules of one set are linked in pairs by the formation of hydrogen bonds to a dichloromethane molecule which is disordered across a crystallographic C_2 axis. Thus the asymmetric unit comprises two half macrocycles and a 25% occupancy dichloromethane. The structure of one macrocycle, with atom labelling, is illustrated in the Figure: bond lengths and angles with estimated standard deviations are listed in Table II. The structure confirms that a ring contraction from the 24-membered tetraimine Schiff base macrocycle (**1**) to the 18-membered macrocycle (**2**) has occurred and that internal nucleophilic addition of the two secondary amine functions in the lateral units across the adjacent azomethine bonds leads to expulsion of two imidazolidine rings. This takes place in a symmetric manner which places the imidazolidine rings diametrically opposite in the macrocycle and permits the adoption of inversion symmetry. The hydrogen atoms of the protonated nitrogen atom of one set are ordered to allow hydrogen bond formation, but those of the second molecule are equally disordered into the two sterically possible sites.

The two independent six-membered rings are each planar (rms deviations 0.017 and 0.017Å). The two five-membered rings are each hinged about the $C(10) \cdots C(12)$ line by 34 and 39°: the four-atom fragments of these rings are approximately planar (rms deviations 0.048 and 0.065Å). Notwithstanding the limited precision of the structural analysis the bond lengths are acceptable. There are no further noteworthy intermolecular contacts.

The NMR spectra suggest that in solution it is likely that (**1**) and (**2**) coexist together with isomers (**3**), in which only one secondary amine has added across its adjacent imine bond, and (**4**). It is also interesting to note that whilst the above reaction leads to a ring contraction which provides an example of the usually disfavoured 5-*endo*-trig ring closure [14], the reaction of benzene-1,3-dicarbaldehyde with 4-azaheptane-1,7-diamine, which could have been expected to proceed with a favoured 6-*endo*-trig ring closure, has not given a macrocyclic product.

Although a pattern is emerging for the non-template formation of ring-contracted Schiff base macrocycles it is too early to state that any general behavioural principle has been established. It has previously been noted [3] that there is an intriguing coincidence between the nature of the conformer distribution in heterocyclic dialdehydes and the need for a metal template in cyclocondensation reactions to produce tetraimine Schiff base macrocycles. Thiophene-2,5-dicarbaldehyde, which has the *cis,cis*-conformer predominating, underwent non-template cyclocondensations with diamines in alcoholic media whereas pyridine-2,6-dicarbaldehyde, in which the only important conformer is *trans,trans*-, gave only polymers and the



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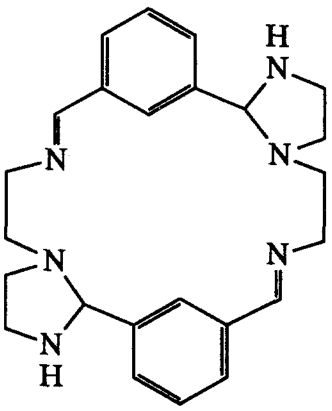

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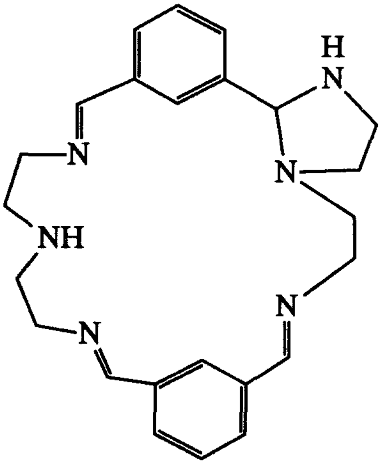

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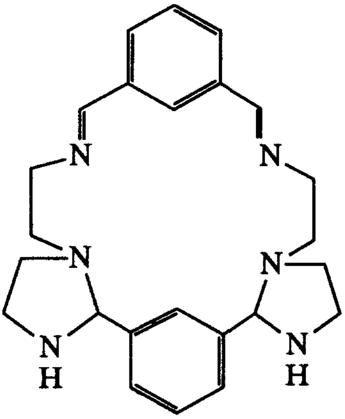

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presence of a metal was required to effect cyclocondensation. It is presumed that in the latter case there is an initial complexation of the pyridine-2,6-dicarbaldehyde to the metal ion, via the pyridine nitrogen atom, which orientates the dicarbaldehyde into the correct conformer for cyclisation. If the conformer distribution is markedly different in acetonitrile solution from that in alcohol then this could significantly affect the reaction pathway and the need for a metal template.

3.1. POSTSCRIPT

At the point of submitting this paper the X-ray structure of $(\mathbf{2})_2\cdot CH_3OH$ was reported and shows that the two structures are closely similar [15]. The space group was the same and the unit cell dimensions for $(\mathbf{2})_2{\cdot}0.5\ CH_2Cl_2$ were marginally larger than those for $(\mathbf{2})_2{\cdot}CH_3OH$. The presence of a methanol solvate rather than that of a disordered dichloromethane solvate appears to have produced better quality crystals and so an improved R-factor has been obtained for the structure. An analytical comparison of the two structures has shown that the conformation of the macrocycle in the two independent molecules is essentially identical and so it would appear that the presence of the different included solvents has not influenced these conformations.

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