The Synthesis of an *N,N′*-Diformylated 36-Membered N_8O_4 Oxaazamacrocycle

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N-formylation of a secondary aliphatic amine has been achieved through the in situ reaction of potassium *o*-nitrophenolate, generated from *o*-nitrophenol, K_2CO_3, KOH, and bis(2-chloroethyl)amine hydrochloride in hot DMF. The initial product, *N,N*-bis[2-(2-nitrophenoxy)ethyl]formamide has been reduced to provide *N,N*-bis[2-(2-aminophenoxy)ethyl]formamide which after an Mn^{II}-templated cyclocondensation reaction with 2,6-diformylpyridine followed by reductive demetallation with $NaBH_4$ gives an *N,N′*-diformylated 36-membered N_8O_4 oxaazamacrocycle.

N-Formylation is frequently used for amino group protection because of the ease by which deprotection can be accomplished.[1] *N,N*-Dimethylformamide (DMF) has been shown to be a convenient reagent for the base-catalysed formylation of aromatic[2] and primary aliphatic amines[3][4] whereas the analogous reaction of secondary aliphatic amines has received less reference.[5][6] During the course of an investigation into the synthesis of oxaazamacrocycles we have noted that *N,N*-bis[2-(2-nitrophenoxy)ethyl]formamide (**1**) is readily prepared via the in situ reaction of potassium *o*-nitrophenolate, generated from *o*-nitrophenol and potassium carbonate in hot DMF, potassium hydroxide, and bis(2-chloroethyl)amine hydrochloride (Scheme 1). In this instance DMF has served as a reagent in the base-catalysed formylation of the secondary aliphatic amine. Reduction of **1** with hydrazine hydrate and 5% palladium-carbon in absolute ethanol gave **2** which was then used in a metal-templated cyclocondensation reaction with 2,6-diformylpyridine − manganese(II) nitrate was used as the metal template.

In previous studies concerning the manganese-templated cyclocondensation of 1,5-bis(2-aminophenoxy)-3-oxapentane with 2,6-diformylpyridine the [1+1][7] 18-membered N_3O_3 oxaazamacrocycle **4** was obtained as its metal complex.[8][9] In situ reductive demetallation of the Schiff base macrocyclic complex with $NaBH_4$ then gave the corresponding metal-free aminic macrocycle **5**.

On ring size analogy a [1+1] macrocyclic product was anticipated from the corresponding reactions involving **2**. However, the mass spectrum of the reaction product, **3**, *m/z* = 837 indicated that a [2+2] macrocycle had been formed and this was confirmed by the X-ray crystal structure (Figure 1) which also revealed a *trans*-arrangement of the formyl groups giving rise to conformer **3a**. The bond lengths and angles in the macrocyclic framework are all within the normal ranges. The disposition of the hydrogen bonding leading to the *trans*-arrangement is evidenced from the N(4)H···O(6) and the N(8)H···O(5) separations which are 2.38 and 2.88 Å respectively as compared with separations greater than 3.7 Å for both N(2)H···O(6) (4.02 Å) and N(6)H···O(5) (3.77 Å).

The ^{1}H-NMR spectrum of **3** run at room temperature in [D_6]DMSO shows the presence of two different isomers, **3a** and **3b**, of the ligand which are made available by slow rotation of the formyl group. Two signals are observed for the formyl group at δ = 8.37 and 8.39; the intensity of the signals is almost the same indicating that the concentration of the isomers in solution is similar.

The spectrum shows three triplets for the gamma proton of the pyridine. The most intense of these triplets, at δ = 7.51, belongs to isomer **3a** in which these two protons are equivalent. the remaining triplets, at δ = 7.47 and 7.50, in which the intensity is approximately one half of that of the first triplet, are assigned to isomer **3b** in which the corresponding two protons are not equivalent.

The remaining protons from the pyridine ring should give rise to four doublets in the room temperature spectrum. Unfortunately, the signals appear to be two triplets due to the accidental overlap of the doublets. The signals, analysed as four doublets are at δ = 7.11, 7.08, 7.06, and 7.04. The COSY-45 spectrum was only partially resolved, but it appears that the triplet at δ = 7.51 is coupled to the doublets at δ = 7.11 and 7.06 while the triplet at δ = 7.50 is coupled to the doublet at δ = 7.08 and the triplet at δ = 7.47 to the doublet at δ = 7.04. This situation arises as in isomer **3a** both protons of the second pyridine ring whereas in isomer **3b** both protons of one pyridine ring are equivalent but different to the protons of the second pyridine ring.

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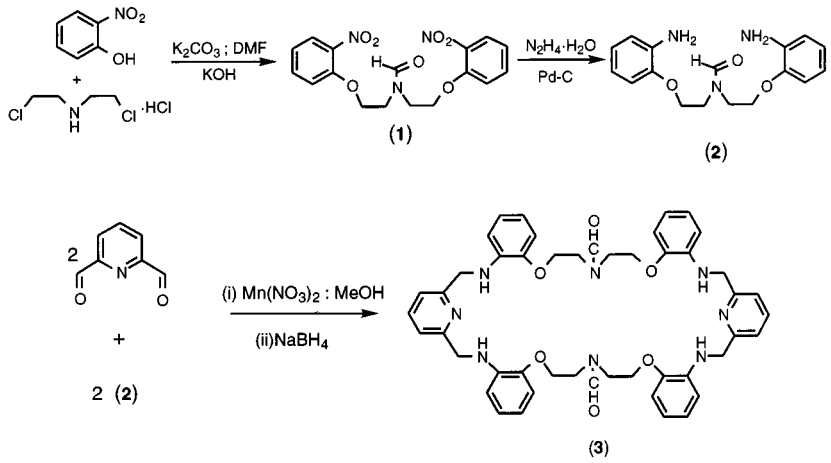
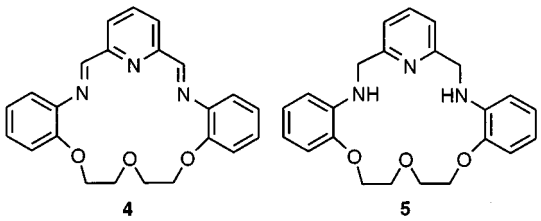


Scheme 1. The synthesis of precursors **1** and **2**, and of macrocycle **3**



Scheme 2. Macrocycles **4** and **5**

The aromatic region of the spectrum is quite complicated and we observe a series of multiplets between δ = 6.32 and 6.82. There are signals due to 16 protons in this region of the spectrum and analysis was not possible. There are four NH groups at δ = 5.53, 5.58, 5.72, 5.72. The signal at δ = 5.72 is of double intensity, but is consistent with the overlap of two triplets as it broader than the other two. The triplets arise from coupling to the benzylic CH_2 groups.

The benzylic CH_2 signals appear in the region δ = 4.3−4.55. The COSY-45 spectrum establishes the coupling between the NH and CH_2 protons. The triplet at δ = 5.53 is coupled to a doublet at δ = 4.33; 5.58 to 4.44; 5.72 to 4.33 and 4.40. This coupling confirms the accidental overlap of the two signals at δ 5.72 and of two at δ = 4.33.

The ethylenic bridge protons signals give multiplets at δ = 4.09−4.17 and δ = 3.77−3.87 due to coupling between

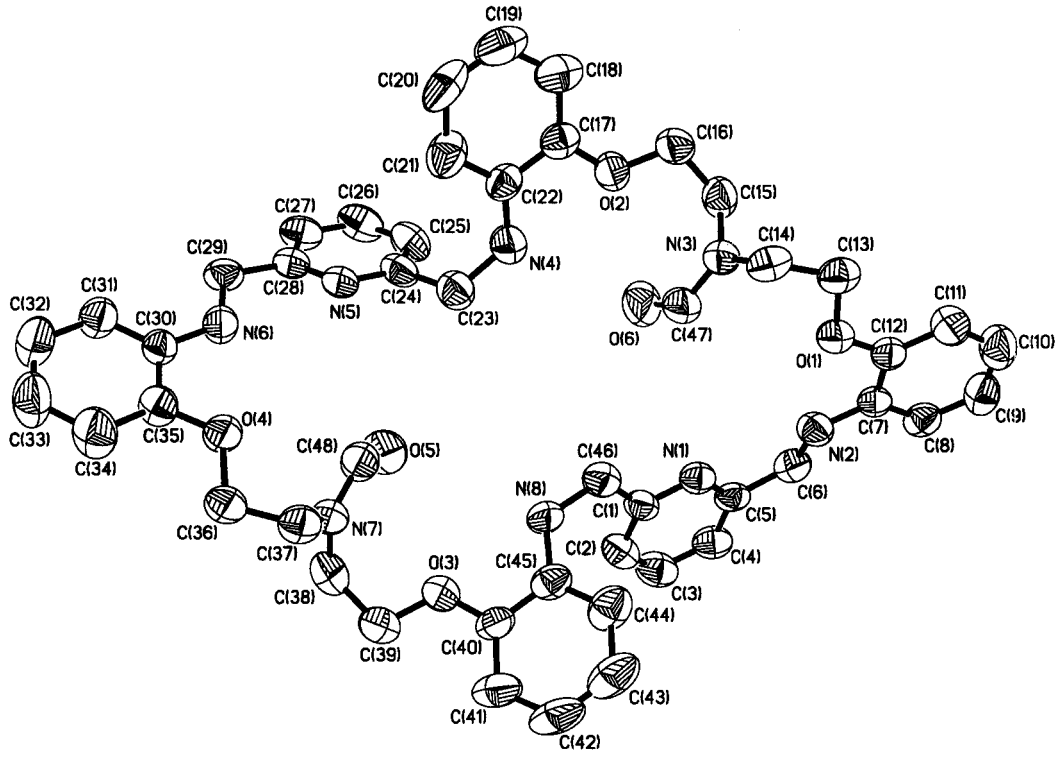
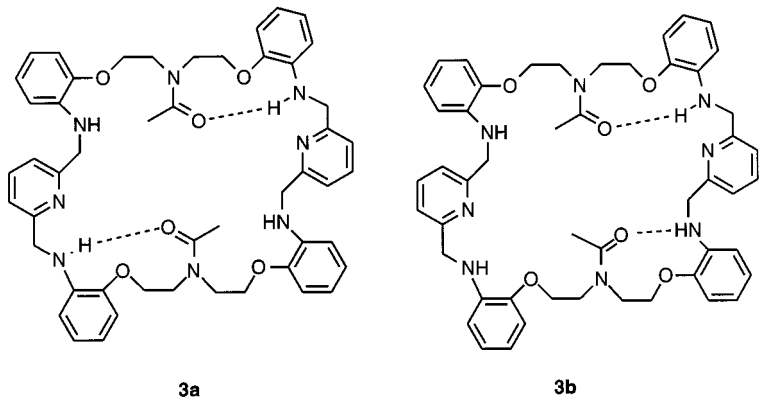


Figure 1. An ORTEP representation of the molecular struture of conformer **3a**



3a **3b**

Scheme 3. The conformers of macrocycle **3**

Table 1. Assignment of NMR spectra

Assignment	^{1}H signal	^{13}C signal
CH=O	8.39	169.30
CH=O	8.37	169.16
γ-pyr	7.51, 7.50, 7.47	142.83, 142.78
β−pyr	7.11, 7.08, 7.06, 7.04	124.60, 124.20, 123.95
o-to O	6.80, 6.79, 6.76, 6.74	116.19, 116.00, 115.89
m-to N	6.75, 6.69, 6.69, 6.65	126.66,126.38
m-to O	6.52, 6.51, 6.47, 6.47	124.60, 124.20, 123.95
o-to N	ca6.50, 6.42, 6.42, 6.33	115.03, 114.81
$NHCH_2Ar$	4.44, 4.41, 4.33	53.08, 52.80
OCH_2	4.13	71.04, 70.63
NCH_2	3.85, 3.81	51.88, 46.88
α-pyr		163.89, 163.34, 163.18, 162.51
Ar−O		150.67, 150.43, 150.40
Ar−N		142.27, 142.16

these protons. The signal at low frequency is due to the protons nearest to the NH group and that at high frequency is due to the protons nearer to the ether O atoms. The ^{13}C-NMR spectrum also shows the presence of the two isomers. A two dimensional HMQC ^{1}H-^{13}C NMR spectrum was acquired to correlate the ^{1}H- and ^{13}C-NMR signals and the results are summarised in Table 1.

A possible way of forming the second conformer **3b** can be suggested after looking at the bond lengths associated with interactions at the formyl group on C(48). The hydrogen bond length between N(8)H···O(5) is 2.88 Å and the separation between N(6)H···O(5) is 3.77 Å. The separation of the hydrogen atoms C(48)H and N(6)H is 2.76 Å so hinting that if the formyl group was turned through 180° juxtaposing O(5) and C(48)H then there would be a close enough approach of the realigned O(5) with N(6)H to permit the occurrence of a hydrogen-bonded interaction which in turn would generate **3b**.

In conclusion, the reaction of potassium *o*-nitrophenolate with bis(2-chloroethyl)amine in basic DMF provides an unexpected route to *N*-formylation of the secondary aliphatic amine. Reduction of the product **1** gave a diamine 2 which has been used, via a metal-templated cyclocondensation reaction, to produce a [2+2] macrocycle **3**. As this [2+2] product is formed rather than the anticipated [1+1] macrocycle it is proposed that *N*-formylation of the linker unit in the diamine has a significant influence on the reaction pathway. Further investigations are in progress in order to resolve this.

Experimental Section

NMR spectra were measured in [D_6]DMSO using a Bruker AMX-400 NMR spectrometer.

***N,N*-Bis[2-(2-nitrophenoxy)ethyl]formamide (1):** *N,N*-Bis[2-(2-nitrophenoxy)ethyl] formamide was prepared by a modification of the method of Cannon et al.[10] *o*-Nitrophenol (48 g) in hot DMF (75 mL) was treated with potassium carbonate (24 g) slowly in 5 g portions. The solution was boiled and when the effervescence stopped, potassium hydroxide (19.28 g) was added. The solution was refluxed during 30 min and bis(2-chloroethyl)amine·HCl (30.6 g) dissolved in 80 mL of DMF was dropped during 30 min. Gentle reflux was maintained for 5 hours and then allowed to cool. The mixture was then poured into water (500 mL). The granular yellow solid was filtered off and extracted with $CHCl_3$ and H_20. The organic phase was dried with $MgSO_4$ anhydrous and evaporated to dryness in a rotary evaporator. The product was recrystallized from absolute ethanol to give 21 g of product. − IR (KBr disc): $\tilde{\nu}$ = 1674 (NC=O) cm^{-1}, 1607 $(C=C)_{ar}$, 1355 (NO_2). − MS (FAB: NOBA): *m/z* = 376. − ^{1}H NMR ($CDCl_3$): δ = 8.28 (s, 1 H), 7.84 (m, 2 H), 7.55 (m, 2 H), 7.05 (m, 4 H), 4.31 (m, 4 H), 3.94 (m, 4 H). − $C_{17}H_{17}N_3O_7$ (375): calcd. C 54.40, H 4.57, N 11.20; found C 54.02, H 4.61, N 11.18.

***N,N*-Bis[2-(2-aminophenoxy)ethyl]formamide (2):** *N,N*-Bis[2-(2-nitrophenoxy)ethyl] formamide (1 g) in absolute ethanol (50 mL) was heated under reflux with 5% palladium-carbon (0.025 g). Hydrazine hydrate (5 mL) was dropped and the mixture was refluxed for 2 h. After filtration the solution was evaporated to dryness and crystallized from hot ethanol. − IR (KBr disc): $\tilde{\nu}$ = 3361 and 3454 cm^{-1} (NH_2), 1659 (NC=O), 1617 $(C=C)_{ar}$. − MS (FAB: NOBA): *m/z* = 316. − ^{1}H NMR ($CDCl_3$): δ 8.16 (s, 1 H), 6.72 (m, 8 H), 4.15 (m, 4 H), 3.75 (m, 4 H), 3.66(bd) (s, 4 H). − $C_{17}H_{21}N_3O_3$ (315): calcd. C 64.76, H 6.66, N 13.33; found: C 64.82, H 6.31, N 13.27.

The Macrocycle 3:[11] 2,6-Diformylpyridine (0.135 g) and manganese(II) nitrate hexahydrate (0.287 g) were dissolved in methanol (25 mL). The solution was refluxed for 30 min, and *N,N*-bis[2-(2-aminophenoxy)ethyl]formamide (0.315 g), dissolved in methanol (25 mL), was added. The solution was gentle refluxed for 2 h, and allowed to cool. Then $NaBH_4$ (0.37 g) was carefully added. Precipitated products were filtered off and dissolved in hot dichlorometh-

ane. The solution was filtered off and concentrated to dryness in a rotary evaporator. The product was recrystallized in hot acetonitrile to give 0.25 g of the macrocycle. − IR (KBr disc): $\tilde{\nu}$ = 3384 cm^{-1} (NH), 1670 (NC=O) and 1603 $(C=C)_{ar}$. − MS (FAB: NOBA): *m*/*z* = 837 − $C_{48}H_{52}N_8O_6$ (836): calcd. C 68.89, H 6.22, N 13.39; found: C 68.15, H 6.32, N 13.41.

X-Ray Data for 3: Crystal data for $C_{48}H_{54}N_8O_6$; *M* = 838.99. The compound crystallises from acetonitrile/dichloromethane as colourless blocks; crystal dimensions 0.70 × 0.34 × 0.22 mm. Triclinic, *a* = 11.270(5), *b* = 13.802(6), *c* = 15.975(7) Å, α = 66.96(3)° β = 86.88(2)° γ = 75.94(3)°, *U* = 2216(2) $Å^3$, *Z* = 2, D_c = 1.257g cm^{-3}, space group *P*1, Mo-K_α radiation (= 0.71073 Å), μ(Mo-K_α) = 0.085 mm^{-1}, *F*(000) = 892.

Three-dimensional, room temperature X-ray data were collected in the range 3.5 < 2θ < 50° on a Siemens P4 diffractometer by the omega scan method. Of the 8816 reflections measured, all of which were corrected for Lorentz and polarisation effects but not for absorption, 4204 independent reflections exceeded the significance level $|F|/\sigma(|F|) > 4.0$ The structure was solved by direct methods and refined by full matrix least squares methods on F^2. Hydrogen atoms were included in calculated positions and refined in riding mode. Refinement converged at a final *R* = 0.0759 (*wR*2 = 0.3392 for all 7534 unique data, 560 parameters, mean and maximum δ/σ 0.000, 0.000), with allowance for the thermal anisotropy of all non-hydrogen atoms. Minimum and maximum final electron density −0.347 and 0.236 $eÅ^{-3}$ A weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.1021\times P)^2 + 0.7556\cdot P]$ where $P = (F_o^2 + 2\times F_c^2)/3$ was used in the latter stages of refinement. Complex scattering factors were taken from the program package SHELXL97[12] as implemented on the Viglen 486dx computer.

Crystallographic data (excluding structure factors) for the structure(s) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-120664. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk].

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[1] T. W. Greene, P. G. Wuts, *Protective Groups in Organic Synthesis,* 2nd ed., Wiley & Sons, New York, **1991**.
[2] G. R. Pettit, E. G. Thomas, *J. Org. Chem*. **1965**, *24*, 895−896.
[3] M. A. Kraus, *Synthesis* **1973**, 361−362.
[4] M. Iwata, *Chem. Lett*. **1989**, 2029−2030.
[5] S. W. Djuric, *J. Org. Chem*. **1984**, *49*, 1311−1312.
[6] M. B. Berry, J. Blagg, D. Craig, M. C. Willis, *Synlett* **1992**, 659−650.
[7] A [1+1] macrocycle is formed by the cyclo-condensation of 1 molecule of diamine precursor with 1 molecule of dicarbonyl precursor; a [2+2] macrocycle is formed by the cyclo-condensation of 2 molecules of diamine precursor with 2 molecules of dicarbonyl precursor
[8] R. Bandin, R. Bastida, A. de Blas, P. Castro, D. E. Fenton, A. Macias, A. Rodriguez, T. Rodriguez, *J. Chem. Soc., Dalton Trans.* **1994**, 1185−1188.
[9] L. Valencia, R. Bastida, A. de Blas, D. E. Fenton, A. Macias, A. Rodriguez, T. Rodriguez-Blas, A. Castineiras, *Inorg. Chim. Acta* **1998**, *282*, 42−49.
[10] R. D. Cannon, B. Chiswell, L. M. Venanzi, *J. Chem. Soc (A)*. **1967**, 1277−1281.
[11] **3** = 10,16,38,44-tetraoxa-3,13,23,31,41,51,57,58-octaazaheptacyclo[51.3.1.$1^{25,29}$.$0^{4,9}$.$0^{17,22}$.$0^{32,37}$.$0^{45,50}$]octapentaconta-1(57),4(9),5,7,17(22),18,20,25(58),26,28,32,34,36,45,47,49,53,55-octadecaene-13,41-dicarbaldehyde.
[12] G. M. Sheldrick, *SHELXL97*, An integrated system for solving and refining crystal structures from diffraction data, University of Göttingen, Germany **1997**.

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