

# Formation of 1,11-bis(pendant donor)-cyclam derivatives *via* the formamidinium salt (cyclam = 1,4,8,11-tetraazacyclotetradecane)

Philip J. Davies, Max R. Taylor and Kevin P. Wainwright\*†

Department of Chemistry, The Flinders University of South Australia, GPO Box 2100, Adelaide, South Australia 5001, Australia

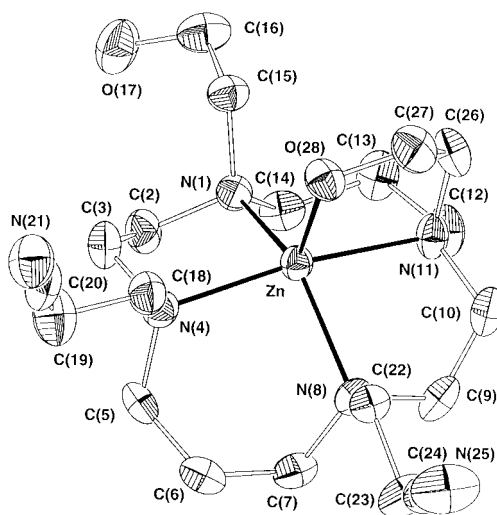
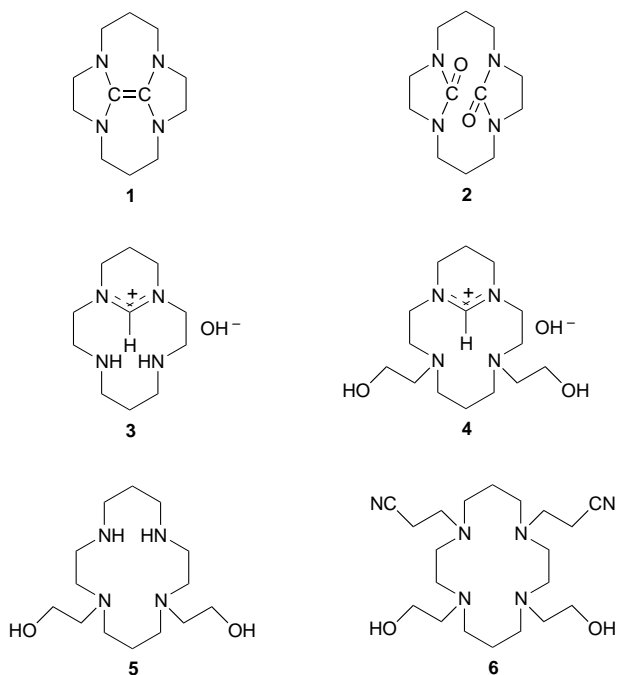
When reacted in chloroform, the dimethyl acetal of dmf and cyclam (1,4,8,11-tetraazacyclotetradecane) forms a stable formamidinium salt which can be used as an intermediate for very simple formation of 1,11-bis(pendant donor)-cyclam derivatives.

Some years ago we reported that reaction of the dimethyl acetal of dmf, dmfdma, with 1,4,8,11-tetraazacyclotetradecane (cyclam) in ethanol generates the electron rich alkene **1** which can subsequently undergo atmospheric oxidation to the bis(urea) derivative of cyclam **2**.<sup>1</sup> In a recent adaptation of that work we had cause to change the solvent from ethanol to chloroform and found that the outcome of the reaction is totally changed. The serendipitous result of this is that we have now found a simple means for producing 1,11-dialkylated derivatives of cyclam which upon deprotection can be used to afford mixed pendant donor ligands.

Reaction of cyclam with an equimolar amount of dmfdma in refluxing chloroform (instead of ethanol) for a period of 18 h gives a 75% yield, after crystallisation from aqueous acetonitrile, of the previously unreported formamidinium salt, **3**.<sup>‡</sup> The formation of stable formamidinium salts from triaza macrocycles having secondary amines separated by trimethylene units (1,5,8-triazacyclododecane and some derivatives) has been reported,<sup>2</sup> but those derived from tetraaza macrocycles have only been invoked as reactive intermediates formed along the hydrolysis pathways between the orthoamide and formyl structures.<sup>3</sup> In the case of the triaza ligands the formamidinium salt forms upon treatment of the similarly stable orthoamide with HCl, but in the case of cyclam we did not observe the orthoamide, despite vigorous attempts to dehydrate **3**.

Formation of **3** affords protection of one pair of 1,11-related amine sites on the cyclam moiety whilst allowing alkylation at the other two. Thus, in reaction with ethylene oxide the substituted salt **4** was generated quantitatively and then converted to the free base, **5**, in 79% yield, by reaction with 10 M sodium hydroxide for 6 h.

As an illustration of the utility of this sequence, **5** was quantitatively derivatised by reaction with acrylonitrile giving the bis(cyanoethyl) ligand, **6**. The zinc(II) complex of **6** was formed through the reaction of **6** with  $\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  in ethanol. Recrystallisation of the crude complex from hot water gave crystals of sufficiently high quality for structure determination by X-ray diffraction.<sup>§</sup> This revealed that the complex is a rare example of a macrocyclic complex in which a pendant hydroxyethyl group coordinated to a divalent metal ion has undergone deprotonation at neutral pH.<sup>4</sup> The complex has the trigonal bipyramidal structure, shown in Fig. 1, in which the four nitrogen atoms of the macrocycle and one deprotonated pendant hydroxyl group coordinate. The macrocycle is in the *trans*-I configuration (the four pendant arms project in the same direction). The axial sites are occupied by a nitrogen atom [N(4)] carrying a pendant 2-cyanoethyl group and by the nitrogen atom [N(11)] carrying the pendant alkoxide. The N(4)–Zn–N(11) angle is 169.8(2)° and the equatorial angle, N(1)–Zn–N(8), internal to the macrocycle, is 138.7(2)°. The Zn–O<sup>−</sup> bond length is 1.923(4) Å which is significantly shorter than the 1.994 Å separation seen for a Zn–neutral pendant alcohol bond in the zinc(II) complex of



**Fig. 1** Molecular structure of the cation in  $[\text{Zn}(\mathbf{6} - \text{H})]\text{ClO}_4 \cdot \text{H}_2\text{O}$ . Displacement ellipsoids are drawn at the 50% probability level. Important bond distances (Å) and angles (°): Zn–N(1) 2.155(5), Zn–N(4) 2.200(4), Zn–N(8) 2.204(5), Zn–N(11) 2.187(4), Zn–O(28) 1.923(4); N(1)–Zn–N(4) 85.0(2), N(1)–Zn–N(8) 138.7(2), N(1)–Zn–N(11) 93.4(2), N(1)–Zn–O(28) 110.0(2), N(4)–Zn–N(8) 91.6(2), N(4)–Zn–N(11) 169.8(2), N(4)–Zn–O(28) 104.3(2), N(8)–Zn–N(11) 83.0(2), N(8)–Zn–O(28) 110.7(2), N(11)–Zn–O(28) 85.7(2).

*N*-(2-hydroxyethyl)cyclen (cyclen = 1,4,7,10-tetraazacyclododecane).<sup>5</sup>

## Notes and References

† E-mail: chkpw@flinders.edu.au

‡ IR (Nujol) 1650 cm<sup>-1</sup> [amidinium ν(C–N)]; <sup>13</sup>C (D<sub>2</sub>O), δ 155.8 (amidinium C), 51.8, 47.0, 45.5, 42.3, 26.2, 18.8; <sup>1</sup>H NMR (D<sub>2</sub>O), δ 7.96 (s, amidinium H), 3.60 (t, 4 H), 3.37 (t, 4 H), 2.95 (t, 4 H), 2.69 (t, 4 H), 2.15 (qnt., 2 H), 1.71 (qnt., 2 H).

§ *Crystal data* for [Zn(6 –H)]ClO<sub>4</sub>·H<sub>2</sub>O: C<sub>20</sub>H<sub>39</sub>ClN<sub>6</sub>O<sub>7</sub>Zn, *M* = 576.4, orthorhombic, space group *P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>, *a* = 8.409(1), *b* = 16.180(1), *c* = 18.886(1) Å, *U* = 2569.6(4) Å<sup>3</sup>, *Z* = 4, *F*(000) = 1216, *T* = 293(1) K, *D*<sub>c</sub> = 1.490 Mg m<sup>-3</sup>, μ(Mo-Kα) = 1.11 mm<sup>-1</sup>, λ(Mo-Kα) = 0.71069 Å. Data were measured on an Enraf-Nonius CAD/PC diffractometer using graphite-monochromated Mo-Kα X-radiation, θ<sub>max</sub> = 27.5°. Absorption corrections were calculated by Gaussian integration, crystal size 0.10 × 0.13 × 0.41 mm, *T*<sub>min</sub>, *T*<sub>max</sub> = 0.710, 0.906. Reflections measured; 6468 (ω–2θ scans), unique 3347, *R*<sub>int</sub> = 0.039. The structure was solved by direct methods and refined using XTAL 3.5 (ref. 6). Hydrogen atoms were placed at geometrically calculated positions, but the hydroxyl and the water molecule hydrogen atoms were not included. The perchlorate ion was found to be disordered in two orientations and was modelled as two rigid groups.

Refinement of a group population parameter indicated equal occupancy of the two orientations. Refinement on *F*<sup>2</sup>, with individual anisotropic displacement parameters for all atoms except hydrogen, which were held fixed, converged at *R*(*F*) = 0.069, *wR*(*F*<sup>2</sup>) = 0.093, *S* = 1.063 for 3100 reflections with *F*<sup>2</sup> > 0 and 345 variable parameters. Final shift/σ(max.) = 0.001 and Δρ(min., max.) = –0.62, +0.62 e Å<sup>-3</sup>.

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