

Selective N,N-Functionalisation of Cyclam: Crystal Structure of the Cu²⁺ Complex of 1,4,8,11-Tetra-azacyclotetradecane-1,8-diacetic Acid and the Tricyclic Lactam 15,18-Dioxo-1,5,8,12-tetra-azatricyclo[10.2.2.2^{5,8}]tetradecane

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A general synthetic method for the synthesis of 1,8-disubstituted derivatives of the 14-membered tetra-aza macrocycle, 'cyclam', involves selective ditosylation: in the Cu²⁺ complex of the 1,8-diacetic acid derivative, the copper is six-co-ordinate with elongated Cu–O interactions and this macrocycle undergoes lactamisation to form a paracyclophane-like tricyclic lactam which is resistant to acidic hydrolysis.

The selective functionalisation of the parent [14]-membered tetra-aza-macrocycle 'cyclam', has been sought recently.¹ Approaches to different C-5 and C-6 substituted derivatives have been established^{2,3} and the synthesis of monosubstituted N-functionalised ligands has been defined.^{4,5} The formation of 1,8-N,N-disubstituted derivatives is important as the ligand may then be hexadentate, for example with the four ring nitrogens binding in the equatorial plane and the two ligating N-substituents occupying axial sites in an octahedral complex. The 4,11-functionalisation of the C-hexamethyl [14]-tetra-aza-macrocycle (**6**) has been described, relying upon steric inhibition of alkylation at the nitrogens proximate to the 7,14-*gem*-dimethyl substituents.⁶ A general method for the functionalisation of the parent tetra-aza macrocycle 'cyclam' is now described. The 1,8-diacetic acid derivative has been prepared and it undergoes lactamisation readily to form the tricyclic lactam (**2**). The lactam and the neutral copper(II) complex of (**1**) have been characterised crystallographically.

Reaction of 1,4,8,11-tetra-azacyclotetradecane (cyclam) with tosyl chloride (1 equiv., 0°C, CH₂Cl₂, Et₃N) yielded the tritosylamide (**3**), (54%), which was readily separated from the ditosylamides (**4a**) and (**4b**). The 1,8-derivative (**4a**) was the major component of this mixture and was isolated by flash chromatography on silica (m.p. 256–257°C, 30%). Ethoxy-carbonylmethylation of (**4a**) (Na₂CO₃/MeCN/BrCH₂CO₂Et) afforded (**5**) (m.p. 128–129°C, 75%) and treatment with HBr/AcOH/PhOH permitted ester hydrolysis and detosylation to yield (**1**) as the hydrobromide salt (70%). In aqueous solution (**1**) lactamises readily to afford the bis-lactam (**2**) [ν_{CO} 1660 cm⁻¹, m/z (NH₃, chemical ionisation) 281 ($M^+ + 1$)].

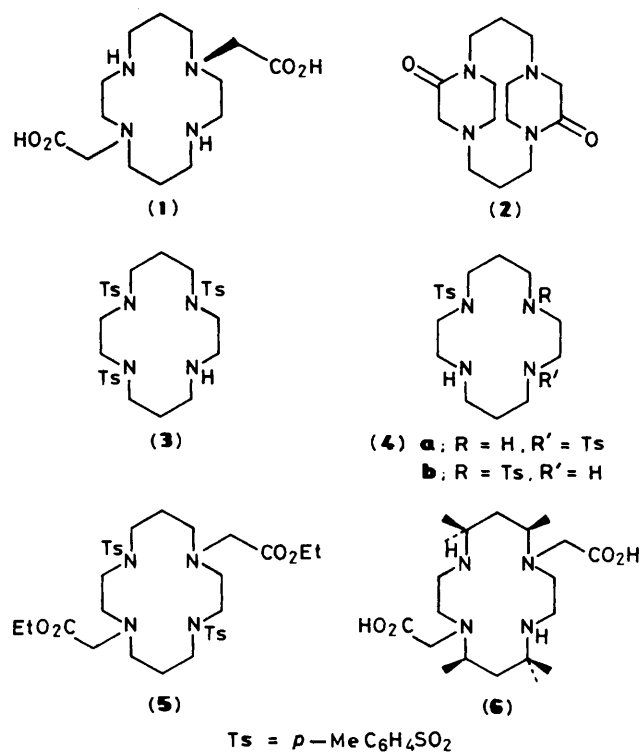
Complexation of (**1**) with copper perchlorate in aqueous solution gave a blue solution from which pale blue crystals of a copper complex were obtained by slow evaporation. The structure of the complex [λ_{max} 565 nm (70); m/z (fast-atom bombardment, 3-nitrobenzyl alcohol) 377, 379 (M^+)] was determined by X-ray crystallography.[†]

The structure revealed that the copper complex of (**1**) and the diprotonated lactam tricycle, (**2**), were both present in the unit cell with the carboxy oxygens of the copper complex, O(11), hydrogen-bonded to the protonated tertiary amine N(1) of the tricycle. The copper complex resided at the four corners of the unit cell with the tricycle in the centre of the cell, lying about an inversion centre. The copper is strongly

co-ordinated by the four nitrogen atoms [bond lengths 2.014(3) and 2.095(3) Å] and is more weakly bound to the axial carboxylate oxygen atoms [Cu–O(10) 2.263(3) Å] in the slightly distorted octahedral complex (Figure 1). The structure therefore resembles that of the copper complex of cyclam, in which all of the copper–nitrogen bond lengths are equal (2.02 Å),⁷ and two perchlorate counterions occupy the Jahn–Teller elongated axial sites. It differs however from the structure of the copper complexes of 1,4,8,11-tetra-azacyclotetradecanetetra-acetic acid (TETA),^{8,9} in which a primary N₂O₂ co-ordination occurs. The reported structure of the nickel(II) complex of the di-acetic acid derivative, (**6**), is also somewhat dissimilar: the macrocycle is folded and the two carboxylate oxygens are *cis*-disposed.⁶ This neutral copper complex of (**1**) may therefore be expected to be insensitive to acid-catalysed decomplexation, like the copper complex of cyclam.

The tricyclic lactam, (**2**), which bears a topological similarity to a paracyclophane, is fairly resistant to acid hydrolysis, (recovered unchanged after boiling in 6 M HCl, 12 h) and this may be related to steric inhibition for the approach of an attacking water molecule at C(9) (Figure 1).

The ligand (**1**) and its congeners may be expected to form a



[†] Crystal data: C₂₈H₅₂CuCl₂N₈O₁₄, $M = 859.22$, triclinic, space group $P\bar{1}$, $a = 9.547(2)$, $b = 12.014(2)$, $c = 8.929(1)$ Å, $\alpha = 98.97(1)$, $\beta = 114.56(1)$, $\gamma = 80.44(2)^\circ$, $U = 914.2$ Å³, $Z = 1$, $D_c = 1.56$ g cm⁻³, $F(000) = 451$, $T = 294$ K, $\lambda = 0.71073$ Å, $\mu(\text{Mo-K}\alpha) = 8.2$ cm⁻¹. Data were collected with an Enraf-Nönius CAD-4 diffractometer and at convergence $R = 0.053$ ($R_w = 0.081$) for the 2643 observed reflections. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

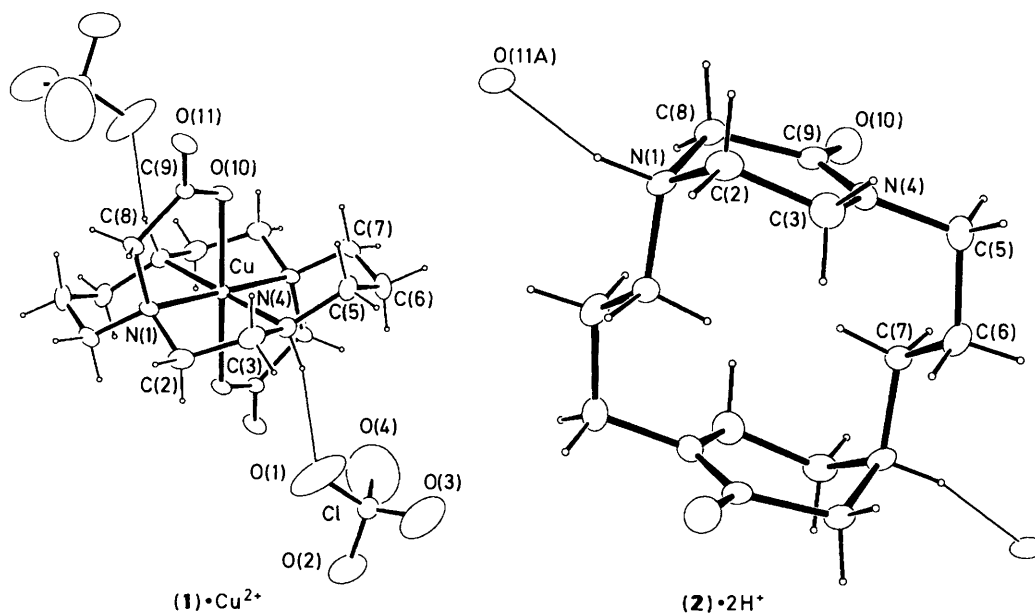


Figure 1. Structures of $[(1) \cdot \text{Cu}^{2+}]$ and $[(2) \cdot 2\text{H}^+]$. Copper co-ordination geometry Cu–N(1A) 2.095(3), Cu–N(4A) 2.014(4), Cu–O(10A) 2.263(3) Å; N(1A)–Cu–N(4A) 86.3(1), N(1A)–Cu–N(4A*) 93.7(1), N(4A)–Cu–O(10A) 90.0(1), N(1A)–Cu–O(10A) 100.3(1), N(1A)–Cu–O(10A) 79.7(1)°. Lactam ring bond lengths: N(1B)–C(2B) 1.489(7), N(1B)–C(8B) 1.485(5), C(2B)–C(3B) 1.510(7), C(3B)–N(4B) 1.456(5), N(4B)–C(9B) 1.341(7), C(9B)–C(8B) 1.508(6), C(9B)–O(10B) 1.216(5) Å.

wide range of relatively lipophilic complexes with divalent metal ions.

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