Novel structure of a macrocyclic dioxotetraamine copper(II) complex

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An unprecedented singly deprotonated macrocyclic dioxotetraamine copper(II) complex is prepared and characterized by IR, UV-VIS, EPR and X-ray crystallography; it is established that the enolic tautomer of the amide is present; two double deprotonated copper(II) complexes are prepared for comparison.

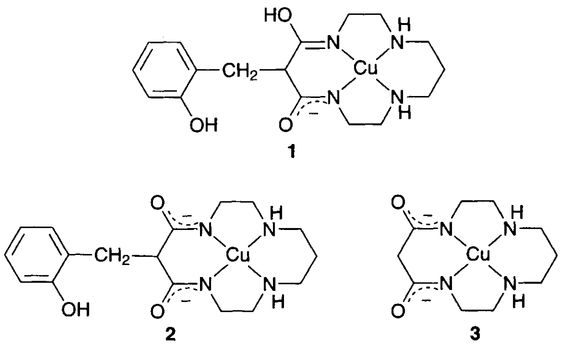
Macrocyclic oxopolyamines are unique metal chelators, their structure bearing the dual features of macrocyclic polyamines and oligopeptides.[1–4] Because of their important biological functions and some unusual properties, oxopolyamines have been extensively studied, and structural features for their biological significance are well recognized.[1–11] The two amido groups in macrocyclic dioxotetraamines are equivalent upon coordination to a 3d metal ion and both are deprotonated simultaneously.[11] As for dioxotetraamines, the presence of non- or singly-deprotonated ligands was considered unlikely,[11] and therefore, such complexes have generally not been considered in previous studies.[2–5] Recently, in a study of formation constants and dissociation kinetics and mechanisms, Kaden and Hay predicted that a singly deprotonated dioxocyclam copper(II) complex may exist in solution[12] and such singly deprotonated species have been observed seen with other tripeptides[13] and diamides.[14] Until now, however, no X-ray structural evidence has been obtained.

Here we report an unprecedented complex, in which both amido (peptide) nitrogen atoms are coordinated to copper(II). One amido group is deprotonated, the other amido hydrogen having migrated to amido oxygen to form a C-hydroxy Schiff-base (enolic tautomer) instead of deprotonation. An enolic tautomer of amide coordinated to a metal centre is thus established. This is a novel conceptual advance in the knowledge of macrocyclic dioxotetraamines.

The ligands 12-(2′-hydroxy)-benzyl-1,4,8,11-tetraazacyclotetradecane-12,14-dione(L^1) and 1,4,8,11-tetraazacyclotetradecane-12,14-dione(L^2) were synthesized according to a novel method recently developed by us.[1b] Elemental analysis, IR, NMR and MS are in good agreement with the structure. To prepare the singly deprotonated complex, ligand L^1 (335 mg, 1 mmol) was dissolved in 20 ml of an aqueous solution of $Cu(ClO_4)_2$ (1 mmol). The solution was filtered, and the filtrate was allowed to stand at room temperature for several days during which red crystals of $[Cu(C_{17}H_{25}N_4O_3)]ClO_4{\cdot}H_2O$ **1** suitable for X-ray structure analysis‡ were obtained in 80% yield. When ligand L^1 reacted with $Cu(ClO_4)_2$ under neutral conditions (adjusted by NaOH solution to pH=7–8), a doubly deprotonated pink complex $[Cu(C_{17}H_{24}N_4O_3)]{\cdot}2H_2O$ **2** was obtained in 60% yield.§

For comparison, ligand L^2 reacted with $Cu(ClO_4)_2$ under the same conditions as in the preparation of **1** (*i.e.* without adjusting pH) to give a purple complex $[Cu(C_{10}H_{18}N_4O_2)]{\cdot}4.5H_2O$ **3** in 60% yield.¶ The proposed structures of complexes **1–3** are shown in Scheme 1.

The cation of complex **1** is characterized by an essentially square-planar coordination around the metal centre, comprising two secondary amino nitrogens and two peptide nitrogens (Fig. 1) and the phenolic oxygen is uncoordinated. The Cu^{II}–N (amido) bond distance is much shorter than the Cu^{II}–N (secondary amine) bond distance, indicating comparatively strong coordination for the former. In a complex with two deprotonated amido groups, the two Cu–N(amido) bond distances are nearly equivalent.[13] However, in complex **1**, the Cu–N(1) distance is obviously shorter than Cu–N(2); this is because the N(1) site has been deprotonated, and a negative charge is delocalized over N(1)–C(1)–O(1), which increases the coordination ability of N(1). On the other hand, the hydrogen



Scheme 1 Structures of complexes **1–3**

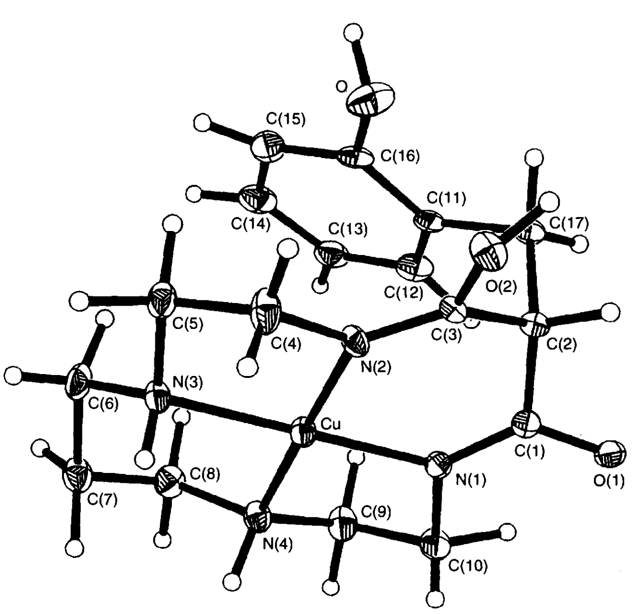


Fig. 1 Structural representation of complex cation in **1** with hydrogen atoms omitted. Selected bond lengths(Å) and angles(°): Cu–N(1) 1.921(6), Cu–N(2) 1.941(4), Cu–N(3) 1.999(6), Cu–N(4) 2.004(5), O(1)–C(1) 1.273(8), O(2)–C(3) 1.327(7), N(1)–C(1) 1.289(8), N(2)–C(3) 1.273(8), O–C(16) 1.373(8), C(11)–C(17) 1.508(10), C(2)–C(17) 1.577(8), C(1)–C(2) 1.543(8), C(2)–C(3) 1.492(9). N(1)–Cu–N(2) 93.5(2), N(1)–Cu–N(4) 85.1(2), N(2)–Cu–N(3) 85.2(2), N(3)–Cu–N(4) 96.3(2), O(1)–C(1)–N(1) 125.1(5), O(2)–C(3)–N(2) 120.1(6), O(1)–C(1)–C(2) 115.9(5), N(1)–C(1)–C(2) 119.0(6), O(2)–C(3)–C(2) 117.1(5), N(2)–C(3)–C(2) 122.7(5), C(2)–C(17)–C(11) 114.9(5), C(1)–C(2)–C(17) 108.1(4), C(3)–C(2)–C(17) 110.7(5).

originally bound to N(2) has migrated to the carbonyl oxygen O(2), so that no net negative charge exists on N(2)–C(3)–O(2). Because of the hydrogen migration, a double bond forms between N(2) and C(3), and the N(2)–C(3) bond distance is shorter than that of C(1)–N(1) or equivalent amide C–N bonds in similar compounds.[1a,13] The IR spectrum of complex **1** in the region 2400–2700 cm^{-1} indicastes that it has a enolic tautomeric structure,[15] which strongly supports the migration of the amido hydrogen to carbonyl oxygen in agreement with the X-ray crystal structure. Such IR spectra do not occur for complexes **2** and **3**. It is this migrated amido hydrogen atom that allows the formation of a C(3)–O(2)–H···O(1)′ hydrogen bond, which binds two molecules together, and stabilizes the crystal. The protonation constant of the uncoordinated phenolic OH group (log *K*) is *ca.* 10,[1b] while the solution pH of **1** is 4.3, indicating non-deprotonation of phenol group. Also, owing to the presence of an anion in complex **1**, phenolic OH deprotonation is even less likely.

We have not been able to obtain a hydrogen-migrated dioxocyclam–copper(II) complex although such a complex may exist. This means that the phenol-containing pendant arm introduced as a functional group is an important factor in the observed complex formation. As for dioxotetraamines, the formation of non- or singly-deprotonated complexes should not be excluded;[11] electronic spectra show the d–d transitions in both aqueous solution and in the solid state to be the same for each of the three copper(II) complexes. This implies that there is no obvious difference in coordination environment in solution and in the solid state and the proton of complex **1** appears to bind to the complex in solution without significant dissociation. The two doubly deprotonated complexes **2** and **3** have similar coordination environments in the *x* and *y* directions of the equatorial plane and their $g_\perp$ values are nearly the same. Owing to the different coordination environment, $g_\perp$ of complex **1** differs from those of complexes **2** and **3**. Furthermore, complexes **1** and **2** have the same $A_\parallel$ and $g_\parallel$ values which differ from that of complex **3**, because the axial (*z*) environments of complexes **1** and **2** are similar. The Cu–C(11) and Cu–C(12) distances of 3.504 and 3.684 Å, differ slightly, possibly due to some interaction between the phenol-containing pendant arm and the central copper(II) ion. This is potentially of interest and quantum calculations for this interaction are in progress.

The present work shows that a singly deprotonated dioxotetraamine copper(II) complex exists both in the solid state and in aqueous solution. The complex deprotonates in a stepwise manner and not simultaneously. This is a novel conceptual advance. From this point of view, previous work, especially with regard to macrocyclic dioxotetraamines, may need reinvestigation. This structure provides critical evidence and enables discussion of the detailed mechanism of complex formation and acid dissociation.[12,16]

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Footnotes

† **CAUTION.** Perchlorate salts of metal complexes with organic ligands are potentially explosive. Only small amounts of material should be prepared, and these should be handled with care. The complex described in this report has, so far, been found to be safe when used in small quantities.

Spectroscopic data for **1**: IR(KBr pellet): 3558, 3509, 3264, 3232; 3025w (Ar–H), 2400–2700m (enolic tautomer), 1683s [νC=N)], 1597s [ν(C=O)], 1107s (ClO_4), 995, 762, 626s cm^{-1}; EPR (110 K, methanol), $A_\parallel$ = 210 G, $g_\parallel$ = 2.168, $g_\perp$ = 2.048. UV–VIS (H_2O): 495(77), 275(700), 225 nm (1600 dm^3 mol^{-1} cm^{-1}); reflectance spectrum: 490, 293, 238 nm.

‡ *Crystal data*: $C_{17}H_{25}ClCuN_4O_7 \cdot H_2O$ **1**, monoclinic, space group $P2_1/a$, a = 15.554(3), b = 8.478(2) c = 17.250(3) Å, β = 111.1(1)°, U = 2117(1) $Å^3$, Z = 1, D_c = 1.611 g cm^{-3}, F(000) = 1068, μ(Mo-Kα) = 0.71073 Å. Data for the red crystals having approximate dimensions of 0.2 × 0.3 × 0.3 mm were collected at 299 K on an Enraf-Nonius CAD4 diffractometer using the ω–2θ scan mode (θ range 2.0–23.0). A total of 2976 unique reflections were measured, of which 1982 with $I > 3\sigma(I)$ were considered observed. The structure was solved by direct methods. The positions of all non-hydrogen atoms were refined with anisotropic displacement factors. Apart from two water hydrogens that could not be located, all other H-atom positions were refined but their isotropic thermal parameters were fixed. The convergence of the last stage of full-matrix least-squares refinement reached R = 0.040 and R_w = 0.044. The maximum peak in the final difference electron density synthesis was 0.52 e $Å^{-3}$. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

§ *Spectroscopic data for* **2**: IR(KBr pellet): 3357(br) (H_2O), 3188, 3127 (OH, HN), 3042(Ar–H), 1596s [*ν*(C=O)], 1486, 1384, 1252, 1075, 937, 760 cm^{-1}; EPR (110 K, methanol), $A_\parallel$ = 211 G, $g_\parallel$ = 2.168, $g_\perp$ = 2.035. UV–VIS (H_2O): 505(115), 275(500), 225 nm (1200) dm^3 mol^{-1} cm^{-1}); reflectance spectrum: 517, 290, 238 nm.

¶ *Spectroscopic data for* **3**: IR(KBr pellet): 3371(br), (H_2O), 3138 (NH), 1604 (C=O), 1547, 1399, 1265, 1078, 935, 717 cm^{-1}. EPR (110 K, methanol), $A_\parallel$ = 215 G, $g_\parallel$ = 2.172, $g_\perp$ = 2.038. UV–VIS (H_2O): 515 (158), 240 (900 dm^3 mol^{-1} cm^{-1}) nm; reflectance spectrum: 517, 290, 238 nm.

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