Crystal Structures of Three Complexes of Copper(II) with Mixed Imidazole and Glycine Peptide Ligands

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Summary The crystal structures of three mixed-ligand complexes of copper(II) with glycine peptide and imidazole ligands are reported.

THE binding of a metal atom by a protein molecule may involve peptide groups or functional side chains which are separated by many amino-acid residues along the protein chain. For instance, sperm whale metmyoglobin has Cu^{II}- and Zn^{II}-binding sites in which the residues His–A10, Lys–A14, Asn–GH4 and Lys–A14, His–GH1, Asn–GH4, respectively, participate.[1] With respect to the metal, the donor groups may then be considered as acting independently of one another except for steric interactions between them. To a first approximation, this situation is present also in complexes containing mixed amino-acid and/or peptide ligands. The crystal structure of one such complex, Cu(L-His)(L-Thr),$2H_2O$, has already been described.[2]

A number of complexes in which Cu^{II} is co-ordinated simultaneously by glycine peptides and by imidazole (the functional group of histidine) have been reported.[3,4] Similar Ni^{II} and Cd^{II} complexes can be prepared.[5] The importance of these complexes lies in their use as models for protein–metal–amino-acid interactions[3] such as those which may be responsible for the binding of histidine and threonine to human serum albumin.[6] We now report crystal structure analyses of $[Cu(Gly–GlyH)(ImH)_2]ClO_4$ (I), $[Cu(Gly–Gly)(ImH)(H_2O)],1\frac{1}{2}H_2O$ (II) and $[Cu(Gly–Gly–GlyH)(ImH)(H_2O)],H_2O$ (III).†

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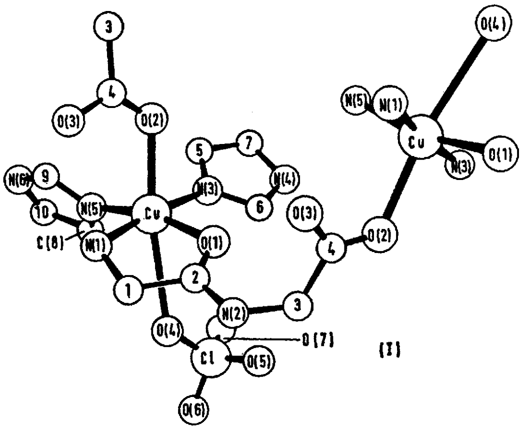
† Gly–GlyH = $NH_2{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CO_2^-$, ImH = $C_3N_2H_4$, Gly–Gly = $NH_2{\cdot}CH_2{\cdot}CON^-{\cdot}CH_2{\cdot}CO_2^-$, Gly–Gly–GlyH = $NH_2{\cdot}CH_2{\cdot}CON^-{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CO_2^-$.

Complex (I) is prepared at pH < 5. As predicted from potentiometric titrations of Cu^{II}–glycylglycine mixtures,[7] the metal is co-ordinated by the terminal N(amino) and O(peptide) atoms. The same type of co-ordination is found in a Cu^{II} complex of diglycylglycine crystallised at low pH[8] and in the Zn^{II} complex of glycylglycine.[9] As in both these complexes, the terminal carboxyl group of the peptide in (I) is bonded to the Cu-atom of a symmetry-related complex. With respect to this atom, the O(carboxyl) atom occupies one of the axial positions of a distorted co-ordination octahedron. The opposite axial position is occupied by a perchlorate oxygen atom. As usual, the four closest ligand atoms N(1), O(1), N(3), and N(5) have a square-planar arrangement.[10] They deviate from their plane of best fit to form a highly flattened tetrahedron about the Cu.



(I)

(Atoms are carbons except where marked otherwise.)

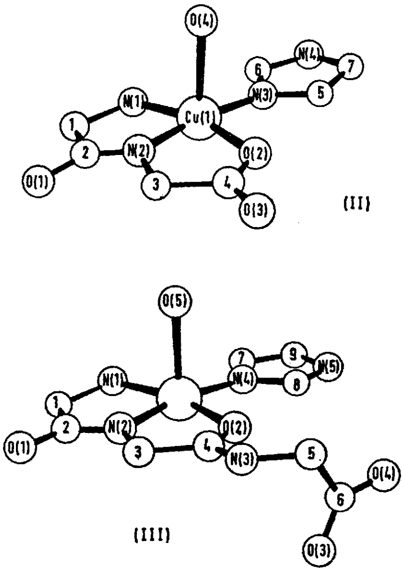


FIGURE.

A coplanar arrangement of *cis*-co-ordinated imidazole groups is sterically impossible.[3,11] The planes of the two imidazole rings in (I) make angles of 31° and 57°, respectively, with the plane of best fit of the four closest ligand atoms. The Cu atom lies in the plane of the first imidazole ring, and is displaced 0·20 Å from the plane of the other.

There is overwhelming evidence from potentiometric titrations,[7,12] calorimetric measurements,[13] i.r. spectra[14] and n.m.r. spectra[15] that the peptide proton dissociates from glycyclglycine in the presence of Cu^{II} ion at pH > 5. The N(peptide) simultaneously replaces the O(peptide) as a donor atom, thereby bringing the carboxyl group into a favourable position for the formation of an additional bond from the metal to an O(carboxyl) atom. Similar pH-dependent chelation reactions occur with Ni^{II} and Co^{III}.

The predicted behaviour of glycylglycine as a tridentate chelating ligand is illustrated in the crystal structures of Cu(Gly–Gly),$3H_2O$,[16] Na_2Ni(Gly–Gly)$_2$,$8H_2O$,[17] Na_2Ni(Gly–Gly)$_2$,$9H_2O$[17] and (NH_4)Co(Gly–Gly)$_2$,$2H_2O$.[18] We now report the same mode of chelation in complex (II), which is effectively formed by raising the pH of a solution containing (I). The composition of this complex is that predicted from a kinetic study of glycylglycine-Cu^{II}-imidazole equilibria in the range $5{\cdot}9 < \text{pH} < 7{\cdot}1$.[3] The asymmetric unit in the crystals of (II) contains *two* complex molecules (only one of which is shown in the Figure). The two independent complexes have almost identical dimensions. In each complex the imidazole ring is approximately coplanar with the peptide ligand, and the Cu atom is displaced from the co-ordination square in the direction of the axial water molecule.

Complex (III) fills an interesting gap in the structural chemistry of Cu^{II}-diglycylglycine interaction. Co-ordination at low pH *via* the N(amino) and the first O(peptide) atoms is known from the structure of Cu(Gly–GlyH–GlyH) Cl,$1\frac{1}{2}H_2O$;[8] and co-ordination at high pH *via* the N(amino) and two deprotonated N(peptide) atoms has been found in NaCu(Gly–Gly–Gly),H_2O.[19] The present complex is the first example of diglycylglycine behaving as a tridentate chelate *via* the N(amino), one N(peptide) and the second O(peptide) atoms. As in complex (II), the imidazole and peptide ligands in (III) are approximately coplanar. The Cu atom is again displaced from their plane towards the co-ordinated axial water molecule.

The tendency of the peptide and imidazole ligands in (II) and (III) to be coplanar suggests that an imidazole ring prefers to lie close to the plane of the four strongest Cu-ligand bonds unless it is rotated out of the plane (as in I) by steric hindrance or by hydrogen bond formation. The Cu–N(imidazole) bond-lengths (see Table) agree with that recently found in Cu(L-His)(L-Thr),$2H_2O$,[2] but are significantly shorter than values reported earlier.[10,20] In other respects, the complexes (I), (II), and (III) have dimensions close to those found in similar structures.[10] On examining all the recorded Cu–N(imidazole) bonds, we have found no correlation between their lengths and (i) the rotations of the imidazole rings about the Cu–N bonds, (ii) the deviations of the co-ordinated Cu atoms from the imidazole planes, and (iii) the Cu–N–C angles at the donor nitrogen atoms. Those Cu–N(imidazole) bonds which are longer than 1·95 Å may reflect the influence of ring-strain or other steric effects.

Crystal data: Glycylglycinatobis-imidazolecopper(II) perchlorate (I) was prepared as described previously.[4] The structure analysis has not confirmed the reported presence of one molecule of water of crystallisation. Monoclinic crystals, $a = 7{\cdot}72$, $b = 18{\cdot}91$, $c = 11{\cdot}66$ Å, $\beta = 94{\cdot}6°$, *Metal-ligand bond lengths in three peptide–Cu–imidazole complexes. Standard deviations are all* ca. 0·01 Å.

Bond	Bondlengths (Å) (I)	(II)	(III)	Previously reported average[10]
Cu–N(amino)	2·02	2·04, 2·04	2·03	2·00
Cu–N(peptide)	—	1·90, 1·90	1·90	1·92
Cu–N(imidazole)	1·96, 1·95	1·96, 1·95	1·95	2·00
Cu–O(peptide)	2·01	—	2·01	1·99
Cu–O(carboxylate)	2·36*	2·01, 2·02	—	1·98
Cu–OH_2*	—	2·40, 2·36	2·38	2·42
Cu–O(perchlorate)	2·97*	—	—	—

* Indicates ligand in axial co-ordination position.

D_m = 1·71 g.cm.$^{-3}$, D_c = 1·69 g.cm.$^{-3}$, $Z = 4$ for $C_{10}H_{15}N_6O_7ClCu$. Space group *Cc*. 1451 Reflexions (311 unobservably weak) measured photometrically on integrated Weissenberg photographs, Cu-K_α radiation.

Glycylglycinato-aquo-imidazolecopper(II),$1\frac{1}{2}$-water (II) crystallised as blue plates.[4] Triclinic, reduced cell has $a = 7{\cdot}94$, $b = 17{\cdot}12$, $c = 10{\cdot}91$ Å, $\alpha = 109{\cdot}5°$, $\beta = 116{\cdot}7°$, $\gamma = 97{\cdot}7°$, D_m = 1·78 g.cm.$^{-3}$, D_c = 1·75 g.cm.$^{-3}$, $Z = 4$ for $C_7H_{15}N_4O_{5\frac{1}{2}}Cu$. Space group $P\bar{1}$. 4129 Reflexions (804 unobservably weak) recorded on an automated Buerger–Supper equiinclination diffractometer, Cu-K_α radiation.

Diglycylglycinato-aquo-imidazolecopper(II)-water (III) was prepared from a mixture of freshly precipitated and washed copper(II) hydroxide (0·5 g), diglycylglycine (0·9 g.) and imidazole (0·34 g.) in water (25 ml.). After digestion on a water-bath for thirty minutes, the deep violet solution was filtered. Blue-violet crystals were deposited during the next three days. Triclinic, Delaunay cell has $a = 10{\cdot}46$, $b = 10{\cdot}16$, $c = 8{\cdot}47$ Å, $\alpha = 113{\cdot}7°$, $\beta = 90{\cdot}7°$, $\gamma = 119{\cdot}1°$, D_m = 1·69 g.cm.$^{-3}$, D_c = 1·69 g.cm.$^{-3}$, $Z = 2$ for $C_9H_{17}N_5O_6Cu$. Space group $P\bar{1}$. 2318 Reflexions (206 unobservably weak), recorded as for preceding compound.

Structure analyses by three-dimensional Patterson and Fourier methods. Refinements of overlapping blocks of parameters by full-matrix least squares. Anisotropic thermal parameters. Hydrogen atoms of the organic ligands located in all three structures. Final residuals, *R* (observed reflexions) for (I), (II), and (III) are 0·059, 0·055, and 0·044, respectively.

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