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X-ray Evidence for the Lysyl Lateral Amine Group Coordination in the (L-Lysyl-L-tyrosine)Cu(II)·$2H_2O$ Complex

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Abstract

X-ray evidence for the lysyl lateral amine group coordination to cupric ion is presented for the Cu(II) complex with L-lysyl-L-tyrosyl dipeptide. The dipeptide molecule is coordinated to the metal ion via all its functions. The α-amine, N^- and COO^- donors bind the metal ion forming two small chelate rings while ε-NH_2 is coordinated to the other copper ion related by the screw axis and the polymeric complex is formed.

Introduction

A number of amino acid residues have polar side groups which are potential binding sites for metal ions. The coordination ability of such potent side chain donors as imidazole of histidine or thiol sulfur of cysteine residues has been quite well established [1–5] by various physicochemical methods. Also their biological importantce, e.g. in many metalloproteins in which they serve as main binding sites, is evident. Recent studies have shown that, although less specific, the side groups of the other amino acids may influence considerably the coordination equilibria in the metal oligopeptide systems, e.g. β-COO^- of aspartic acid [5, 6–9]. In the latter case the binding of β-carboxylate leads to the formation of the stable six-membered chelating ring which makes such coordination more favourable. In the case of a lysine or arginine lateral amine group, however, the relatively long methylene chains render any chelation much less likely [1, 5, 10]. On the other hand the spectroscopic and thermodynamic studies of the coordination ability of some specific oligo- and polypeptides strongly indicated that lateral amine groups of both lysine and arginine residues may be of critical importance for metal ion coordination and the direct involvement of the lateral nitrogen in the metal binding has been suggested [11–14]. In this communication we present the X-ray evidence for such bond formation.

Experimental

Monocrystals were obtained from solutions containing equimolar amounts of metal and ligand at pH 11 in 0.2 M KCl. The ligand concentration was 0.002 mol dm^{-3}.

A single crystal (deep blue air stable plate) with approximate dimensions of 0.15 X 0.20 X 0.25 mm was used: preliminary crystal data obtained from oscillation and Weissenberg photographs were refined by setting angles of 15 reflections with $15° < 2\theta < 24°$. A Syntex $P2_1$ computer-controlled four-circle diffractometer with scintillation counter and graphite-monochromated Mo Kα radiation was used.

The crystal data are: $a = 8.787(5)$, $b = 9.753(5)$, $c = 10.525(5)$ Å, $\beta = 101.69(5)°$, $V = 883.5$ Å^3, space group $P2_1$, $D_{calc} = 1.53$ g cm^{-3}, $Z = 2$, formula weight = 406.9, $F(000) = 426$ and $\mu = 13.2$ cm^{-1}. 2167 reflections were measured with h 0 to 11, k 0 to 12 and l −13 to 13 with $4.0° < 2\theta < 55.0°$. 1726 of these reflections with $I > 2.0$ were used in analysis; other detals: variable θ–2θ scan, scan rate 2.0 to 29.3° min^{-1} depending on intensity, two standard reflections (224 and 231) monitored at intervals of 100 measurements indicated no significant fluctuations; correction for Lorentz-polarization effects was used. The structure was solved by the heavy atom method and refined by full-matrix least-squares [minimizing $\Sigma w(|F_o| - |F_c|)^2$ where $w = 1/\sigma^2(F_o)$] with anisotropic temperature factors for non-H atoms; H atoms located by means of difference Fourier syntheses are included in calculated positions with isotropic thermal parameters of 5.0 Å^2. 50 atoms and 225 variables were considered. Final R, R_w and S values were 0.056, 0.055 and 2.321 respectively. Scattering factors for neutral atoms and corrections for anomalous dispersion (for Cu) were taken from the International Tables for X-ray Crystallography [15].

All calculations were performed on a Nova 1200 computer with the locally modified XTL/XTLE system (Syntex, 1976). An absorption correction following the DIFABS procedure [16] was applied

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on isotropically refined data; minimal and maximal absorption corrections were 0.793 and 1.210 respectively.

Results and Discussion

Final positional and equivalent isotropic thermal parameters for non-H atoms are listed in Table 1. Relevant bond distances and angles are given in Table 2. A perspective view of the molecule with the numbering of atoms is shown in Fig. 1.

The dipeptide is coordinated to the metal ion via all its functions, *i.e.* the α- and ϵ-NH_2 groups, the N^- of a peptide bond and carboxyl oxygen. The $\{\alpha\text{-}NH_2, N^-, COO^-\}$ donor set binds cupric ion forming two small chelate rings as usually found in metal ion dipeptide systems (see for example ref. 17), while ϵ-NH_2 is coordinated to the other metal ion related by the screw axis parallel to b. The latter bonding leads to the formation of the polymeric copper(II)–dipeptide complex. The copper is five-coordinated in a distorted square-pyramidal geometry with the water molecule occupying the apical position (Fig. 1). The bond lengths and the

TABLE 1. Positional Parameters and Equivalent Isotropic Temperature Factors ($Å^2$)[a]

	x	y	z	B_{eq}[b]
Cu	0.0296(1)	0.3500(0)	0.1626(1)	2.21(1)
O(1)	−0.1002(7)	0.4940(6)	0.0610(6)	2.7(2)
O(2)	−0.3047(7)	0.5107(7)	0.0982(6)	3.4(2)
O(3)	−0.2552(7)	0.0265(7)	0.1184(7)	3.5(2)
W(1)	0.1273(9)	0.2927(7)	−0.0223(7)	4.9(2)
O(H)	−0.4177(8)	0.5822(8)	0.5439(6)	4.1(2)
W(2)	−0.5458(7)	0.4380(8)	−0.2816(6)	3.7(2)
N(1)	−0.1537(8)	0.2433(7)	0.1181(7)	2.1(2)
N(2)	0.1253(8)	0.1751(8)	0.2518(7)	2.6(2)
N(3)	−0.1959(8)	−0.0121(8)	0.7730(7)	2.9(2)
C(1)	−0.2255(10)	0.4458(9)	−0.0089(8)	2.3(2)
C(2)	−0.2778(10)	0.3006(9)	0.0229(8)	2.0(2)
C(3)	−0.4374(9)	0.3111(9)	0.0661(8)	2.4(2)
C(4)	−0.1484(10)	0.1136(10)	0.1535(9)	2.7(2)
C(5)	0.0001(10)	0.0655(9)	0.2389(9)	2.7(2)
C(6)	−0.0142(11)	0.0005(12)	0.3627(9)	3.6(3)
C(7)	−0.0699(12)	0.0912(12)	0.4569(9)	3.7(3)
C(8)	−0.1105(14)	0.0075(13)	0.5660(10)	5.1(4)
C(9)	−0.1604(14)	0.0836(12)	0.6720(11)	4.5(4)
C(11)	−0.4284(9)	0.3854(9)	0.1929(8)	2.4(3)
C(12)	−0.4407(11)	0.3115(9)	0.3025(9)	2.9(3)
C(13)	−0.4378(10)	0.3751(11)	0.4190(8)	2.9(3)
C(14)	−0.4210(10)	0.5123(11)	0.4303(9)	3.2(3)
C(15)	−0.4061(12)	0.5919(10)	0.3209(9)	3.3(3)
C(16)	−0.4121(11)	0.5270(10)	0.2038(9)	2.9(3)

[a] e.s.d.s are given in parentheses. [b] $B_{eq} = \frac{1}{3}\sum_i B_{ii}$.

TABLE 2. Selected Intramolecular Distances (Å) and Angles (°)

Cu–O(1)	1.981(6)	O(1)–Cu–N(3)^i	90.4(3)
Cu–N(1)	1.895(7)	W(1)–Cu–N(1)	95.7(3)
Cu–N(2)	2.045(8)	W(1)–Cu–N(2)	89.8(3)
Cu–N(3)^i	2.001(8)	W(1)–Cu–N(3)^i	94.4(3)
Cu–W(1)	2.348(8)	N(1)–Cu–N(2)	84.6(3)
O(1)–Cu–W(1)	89.3(3)	N(1)–Cu–N(3)^i	168.2(3)
O(1)–Cu–N(1)	83.6(3)	N(2)–Cu–N(3)^i	101.6(3)
O(1)–Cu–N(2)	168.0(3)		
O(1)–C(1)	1.282(11)	Cu–O(1)–C(1)	112.6(5)
O(2)–C(1)	1.226(11)	Cu–N(1)–C(2)	116.5(5)
O(3)–C(4)	1.264(12)	Cu–N(1)–C(4)	118.6(6)
O(H)–C(14)	1.372(12)	Cu–N(2)–C(5)	108.7(5)
N(1)–C(2)	1.437(11)	Cu–N(3)^i–C(9)^i	114.7(6)
N(1)–C(4)	1.317(12)	O(1)–C(1)–O(2)	122.6(8)
N(2)–C(5)	1.521(12)	O(1)–C(1)–C(2)	118.0(7)
N(3)–C(9)	1.494(14)	O(2)–C(1)–C(2)	119.5(8)
C(1)–C(2)	1.547(12)	C(1)–C(2)–N(1)	106.9(7)
C(2)–C(3)	1.562(12)	C(1)–C(2)–C(3)	109.1(7)
C(3)–C(11)	1.507(12)	C(2)–C(3)–C(11)	113.6(7)
C(11)–C(12)	1.382(11)	C(3)–C(11)–C(12)	119.3(8)
C(12)–C(13)	1.371(13)	C(3)–C(11)–C(16)	122.4(8)
C(13)–C(14)	1.349(15)	C(11)–C(12)–C(13)	121.4(8)
C(14)–C(15)	1.418(14)	C(12)–C(13)–C(14)	120.6(9)
C(15)–C(16)	1.377(14)	C(13)–C(14)–C(15)	119.9(9)
C(16)–C(11)	1.391(13)	C(14)–C(15)–C(16)	118.9(9)
C(4)–C(5)	1.502(13)	C(15)–C(16)–C(11)	121.0(9)
C(5)–C(6)	1.474(14)	O(H)–C(14)–C(13)	123.5(9)
C(6)–C(7)	1.484(15)	O(H)–C(14)–C(15)	116.6(9)
C(7)–C(8)	1.509(16)	O(3)–C(4)–N(1)	125.5(9)
C(8)–C(9)	1.480(16)	O(3)–C(4)–C(5)	118.0(8)
N(1)–C(4)–C(5)	116.5(8)	C(5)–C(6)–C(7)	115.6(9)
C(4)–C(5)–N(2)	111.1(7)	C(6)–C(7)–C(8)	110.2(9)
N(2)–C(5)–C(6)	114.4(8)	C(7)–C(8)–C(9)	117.0(10
C(4)–C(5)–C(6)	116.3(8)	C(8)–C(9)–N(3)	111.1(9)

Symmetry code: (i) $-x, \frac{1}{2}+y, 1-z$.

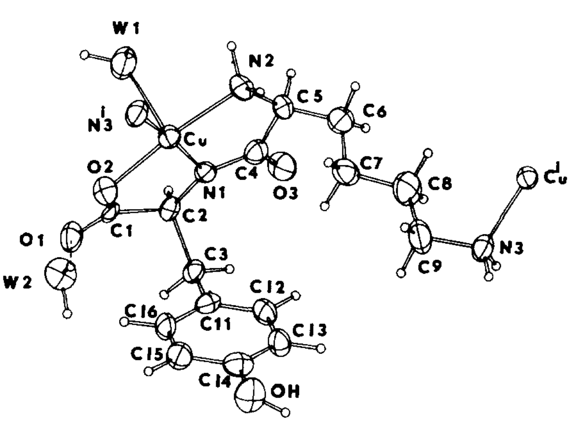

Fig. 1. A perspective view of the molecule of the Cu(Lys–Tyr) complex with numbering scheme.

TABLE 3. Selected Torsion Angles (°)

Angle	Descriptions	
φ_1	Cu–N(2)–C(5)–C(4)	6.3(7)
ψ_1	N(2)–C(5)–C(4)–N(1)	–8.3(9)
χ_1^1	N(2)–C(5)–C(6)–C(7)	66.7(11)
χ_1^2	C(5)–C(6)–C(7)–C(8)	168.5(9)
χ_1^3	C(6)–C(7)–C(8)–C(9)	176.9(11)
χ_1^4	C(7)–C(8)–C(9)–N(3)	–179.8(10)
χ_1^5	C(8)–C(9)–N(3)–Cu^{i}	50.5(10)
ω	C(5)–C(4)–N(1)–C(2)	171.2(10)
φ_2	C(4)–N(1)–C(2)–C(1)	–169.6(9)
χ_2^1	N(1)–C(2)–C(3)–C(11)	53.4(1)
χ_2^{21}	C(2)–C(3)–C(11)–C(16)	74.3(9)
χ_2^{22}	C(2)–C(3)–C(11)–C(12)	–107.4(8)
φ_2	N(1)–C(2)–C(1)–O(1)	–8.3(8)
	Cu–N(1)–C(4)–C(5)	6.3(8)
	Cu–N(1)–C(2)–C(1)	–4.4(7)
	Cu–O(1)–C(1)–C(2)	16.4(8)

angles in the neighbourhood of the Cu atom agree well with the average values given by Freeman [18]. The basal plane is a highly distorted tetrahedron. The least-squares plane containing the α-NH_2, ε-NH_2^{i}, amide N^- and carboxyl oxygen atoms forms a distorted square plane with deviations: α-NH_2 0.099(7), ε-NH_2^{i} 0.096(7), N^- 0.109(7) and O(1) 0.074(6) Å. Cu is displaced from this mean plane by 0.070(1) Å in the direction of the apically coordinated water molecule. The angles at the copper ion which are included in the chelated rings are decreased significantly from the value of 90° expected for a square pyramid. The aromatic ring is situated over the basal complex plane as usually found in this type of complex [17, 19–21]. Although the equatorial plane of the complex is severely distorted from a square planar geometry the distance between the aromatic ring and the metal ion (3.923 Å) excludes any interaction between these two moieties. This result is in contradiction to the earlier general conclusion stating a relation between the geometry of the equatorial plane and the aromatic ring–metal ion distance [17, 20].

The torsional angles of a bound peptide molecule are presented in Table 3. The peptide bond plane is slightly distorted (ω = 171°). The lysine side chain has an extended *trans* conformation which is the most favourable and the most common structure of this amino acid residue [22–25]. This conformation is essentially the same as in the free peptide [25] with the exception of the torsional angle χ_1^2 which, due to the coordination of the backbone donors, is somewhat lower in the case of the copper(II) complex. The coordination to the metal ion causes, however, the distinct change of the conformational angle χ_1^1 which defines the orientation of the side chain with respect to the amine nitrogen atom. Binding of the ε-NH_2 group does not influence significantly the lysine side chain conformation. The bound metal ion is in the gauche position to the C_6 of the lysine side chain. The conformation of the tyrosine residue is essentially the same as that found for similar Cu(II) complexes with Gly–Tyr [26], Leu–Tyr [17] and Val–Tyr [19]. In all these complexes the aromatic ring faces the Cu(II) basal plane even if there is no metal–aromatic ring interaction.

The metal nitrogen bond lengths differ from each other. The shortest bond (1.895 Å) is that between copper and amide nitrogen and is comparable to the values obtained earlier for similar structures [17, 19]. The other two amine group nitrogens are almost at the same distance from the metal ion, although the lateral amine nitrogen is at a slightly shorter distance than the α-amine one (Table 2). This clearly indicates that the lateral amine group can be involved in the regular coordination of the metal ion even though the chelate ring is not formed. The lysine side chain cannot compete with the set of backbone donors of the same peptide molecule where coordination is additionally stabilized by the formation of small chelate rings. It is, however, possible to favour lysine side group coordination by, for example, the introduction of the 'break-point' proline residue as was suggested earlier [11].

There is a network of hydrogen bonds between the water molecule ant the hydroxyl group of the tyrosine residue, as well as between the water molecule and carboxyl and carbonyl oxygens of the peptide molecule (Table 4). Thus, the water molecules act in this structure as both donor and acceptor.

Supplementary Materials

Lists of observed and calculated structure factors, anisotropic temperature factors, hydrogen atom parameters and selected least-square planes are available from the authors on request.

TABLE 4. Geometry of the Hydrogen Bonds

X–H...Y	X...Y (Å)	H...Y (Å)	X–H...Y (°)
W(1)–H(1)W(1)...O(3)^{i}	2.819(10)	2.00	143
W(1)–H(2)W(1)...O(1)^{ii}	2.945(9)	2.26	125
W(2)–H(1)W(2)...O(3)^{iii}	2.824(9)	1.90	163
W(2)–H(2)W(2)...O(2)	2.657(9)	1.75	162
O(H)–H(0)...W(2)^{iv}	2.730(10)	1.83	174

Symmetry code: (i) $-x, \frac{1}{2} + y, -z$; (ii) $-x, y - \frac{1}{2}, -z$; (iii) $-x - 1, \frac{1}{2} + y, -z$; (iv) $x, y, 1 + z$.

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