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Crystal Structures of Mixed Ligand Copper(II) Complexes Containing L-Amino Acids. II. (L-Alaninato)aqua(L-histidinato)-copper(II) Trihydrate

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Copper(II) complex containing L-alanine and L-histidine crystallizes from aqueous solution at pH 7.0. Crystals of (L-alaninato)aqua(L-histidinato)copper(II) trihydrate are monoclinic, space group $P2_1$, $a=10.980(4)$, $b=7.362(3)$, $c=9.700(2)$ Å, $\beta=101.45(3)°$, and $Z=2$. There is some disorder for the location of three water molecules of crystallization. Four coordinating atoms in an approximately planar arrangement around copper are the α-amino nitrogen and imidazole δ-nitrogen of L-histidine, and α-amino nitrogen and α-carboxyl oxygen of L-alanine. They take a *cis* conformation with respect to the amino groups. The axial site is occupied with oxygen atom of water, so that the coordination geometry is square-pyramidal. Similarity and difference are discussed in comparison with the coordination mode in copper complexes containing L-histidine and L-asparagine.

Histidine-containing ternary amino acid copper(II) complexes in serum have attracted wide attention in relation to the copper(II) transport in biological systems, and the preferred second amino acids are asparagine, glutamine and threonine.[1,2] In the previous paper,[3] we have reported the crystal structure of (L-asparaginato)(L-histidinato)copper(II) and its hydrate, in which the coordination mode is the same as that of aqua(L-histidinato)(L-threoninato)copper(II) hydrate.[4] It is interesting to examine the structures of the ternary copper complexes of which the second amino acid is thought less cooperative. We have prepared (L-alaninato)aqua(L-histidinato)copper(II) trihydrate and determined the three-dimensional structure by X-ray analysis.

Experimental

1 mmol of L-alanine (0.0891 g) and 1 mmol of L-histidine (0.1552 g) were dissolved with 10 ml of ion-exchanged water. The solution, into which 1 mmol of copper(II) hydroxide (0.0976 g) prepared by the same manner as in the previous paper was added, turned blue by stirring. After removing the precipitate of copper(II) oxide, small amount of methanol was poured. Blue plate crystals of (L-alaninato)aqua(L-histidinato)copper(II) trihydrate were grown by standing the solution for a few days at room temperatures. Elemental analysis. Found: C, 28.95; H, 5.81; N, 15.28%. Calcd for $C_9H_{22}N_4O_8Cu$: C, 28.61; H, 5.87; N, 14.82%.

Crystal data are: Monoclinic, $a=10.980(4)$, $b=7.362(3)$, $c=9.700(3)$ Å, $\beta=101.45(3)°$. $D_m=1.63$ g cm^{-3} (by floatation), $D_x=1.63$ g cm^{-3}, $Z=2$. Systematic absence, $0k0$ for odd k. Space group, $P2_1$ or $P2_1/m$.

Accurate unit cell dimensions were obtained from a least-squares fit to 2θ data of 18 reflexions measured on a Rigaku automated four-circle diffractometer. Intensity data were collected on the diffractometer with graphite monochromated Mo $K\alpha$ radiation at room temperature. A θ-2θ scan technique was employed, and reflexions for $2\theta \leq 55°$ were recorded. A total of 1746 non-zero reflexions out of 1897 were obtained. Intensities were corrected for the Lorentz and polarization factors but not for absorption and secondary extinction.

Structure Determination

Since this crystal contains L-amino acid, the space group $P2_1/m$ was certainly excluded. The x and z coordinates of a copper atom were obtained from the Harker section in the sharpened three-dimensional Patterson map. Its y coordinate was taken arbitrarily as 0.25. The Fourier map phased with the copper atom has shown a pseudo-symmetry due to a mirror plane at $y=0.25$. Most of atoms in the amino acids were near this plane. Four atoms coordinated to the central copper atom were selected to be in accordance with the stereochemistry of the remaining part of the complex. All the non-hydrogen atoms except for three oxygen atoms of water of crystallization were assigned by successive Fourier syntheses. When the R factor was 0.11, the difference Fourier map showed a disorder about these three water molecules in the space along the two-fold screw axis at

Table 1a. The fractional coordinates ($\times 10^4$) with B_{eq} for the complex

Estimated standard deviations are in parentheses.

Atom	x	y	z	B_{eq}/Å^2 a)
Cu	1951(1)	2501(4)	1467(1)	2.98
C(1)	5075(13)	3568(17)	4986(12)	3.51
C(2)	4373(10)	3155(15)	3414(9)	2.83
C(3)	4776(12)	4518(18)	2409(10)	3.56
C(4)	4337(10)	3984(16)	885(10)	2.80
C(5)	3132(10)	2962(14)	−1016(9)	2.76
C(6)	4956(13)	4233(17)	−204(10)	3.29
N(1)	3033(9)	3215(16)	3297(8)	3.76
N(2)	3218(8)	3175(12)	391(8)	2.60
N(3)	4159(9)	3576(13)	−1367(8)	3.02
O(1)	4387(10)	3763(16)	5850(7)	5.29
O(2)	6188(9)	3664(19)	5201(9)	5.86
C(11)	−329(10)	1507(16)	−149(11)	3.08
C(12)	−634(11)	1477(18)	1351(10)	3.33
C(13)	−1825(11)	2461(35)	1416(12)	4.88
N(11)	462(8)	2141(17)	2345(9)	3.71
O(11)	767(7)	1829(13)	−256(7)	3.77
O(12)	−1162(8)	1212(14)	−1153(8)	4.16
O(1′)	2751(9)	−664(13)	2033(8)	4.42

a) $B_{eq}=8\pi^2(U_1+U_2+U_3)/3$ where U_1, U_2, and U_3 are the principal components of U matrix.

Table 1b. The fractional coordinate $(\times 10^3)$, isotropic thermal factors and occupancies for the disordered water molecules

Estimated standard deviations are in parentheses.

Atom	x	y	z	B/Å^2	Occupancy
O(2′)	991(2)	114(4)	648(2)	10.2(6)	0.7
O(3′)	778(3)	102(5)	455(3)	11.9(9)	0.6
O(4′)	189(2)	112(4)	533(3)	10.3(7)	0.6
O(5′)	171(8)	407(15)	570(9)	19.3(33)	0.3
O(6′)	1008(7)	293(17)	641(8)	18.9(31)	0.3
O(7′)	856(4)	480(8)	512(5)	8.9(13)	0.3
O(8′)	790(9)	410(17)	459(10)	13.5(31)	0.2

$0, y, 0.5$. Seven sites with appropriate occupancies were given for three oxygen atoms. Later stage of refinement was achieved by the full-matrix least-squares. Contributions from hydrogen atoms were not included. The R factor dropped to 0.078 for observed reflexions. Atomic scattering factors used were taken from "International Tables for X-Ray Crystallography."[5] The final atomic parameters are listed in Table 1.[6]

Description of the Structure and Discussion

Figure 1 shows the packing of the molecules in the crystal, the hydrogen bonds being indicated by broken lines. Each complex molecule is connected along b through the axial coordination of the carboxyl oxygen of alanine related by the two-fold screw, which is hydrogen-bonded to the coordinated water in the next complex. α-Carboxyl group of histidine forms two hydrogen bonds, O(2) with water O(1′) of the complex at $1-x$, $0.5+y$, $1-z$ and O(1) with N(3) of imidazole of the complex at x, y, $1+z$. Three-dimensional network is constructed by the bridging coordination of alanine and these hydrogen bonds. The network leaves the cavities along $0, y, 0.5$, in which three water molecules take randomly some of seven sites. These random water molecules form hydrogen bonds with the cavity wall and with each other, although details of the hydrogen bonds of this kind need not be discussed. The possible hydrogen bonds are listed in Table 2. Other than hydrogen bonds, all non-bonded intermolecular distances are normal.

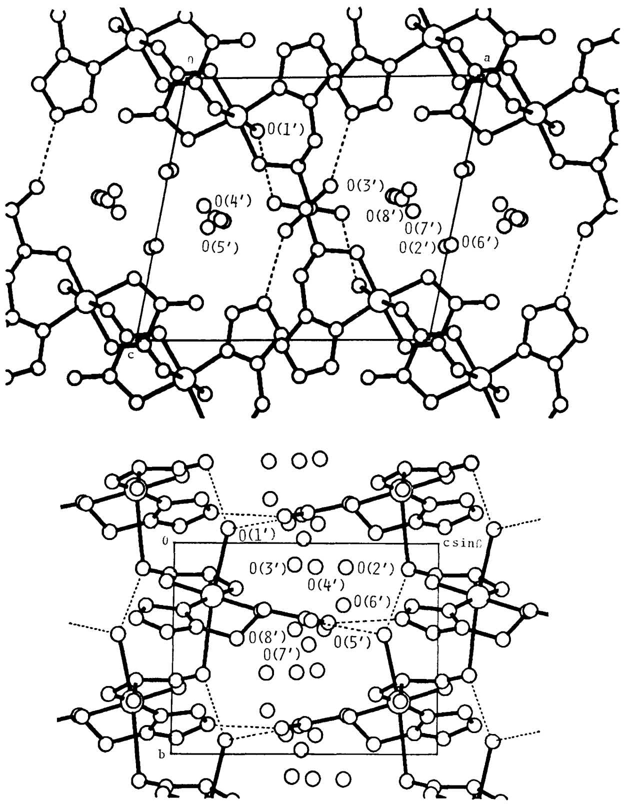

Fig. 1. Crystal structure of (L-alaninato)aqua(L-histidinato)copper(II) trihydrate projected along **b** (upper) and **a** (lower).

Figure 2 shows the stereo pair of the diagram of the complex. Bond lengths and angles are given in Fig. 3 and Table 3, respectively. L-Alanine molecule coordinates to the central copper through α-amino nitrogen N(11) and α-carboxyl oxygen O(11), while L-histidine links through α-amino nitrogen N(1) and imidazole δ-nitrogen N(2). These four atoms occupy

Table 2. Distances of hydrogen bonds

X at a	Y	at	Distance X···Y (l/Å)	X at a	Y	at	Distance X···Y (l/Å)
N(1)	O(1)	a	2.654(14)	O(2)	O(7′)	a	2.755(53)
N(3)	O(1)	c	2.763(14)	O(2)	O(8′)	a	2.108(108)
O(1′)	O(2)	h	2.749(14)	O(12)	O(2′)	e	2.781(26)
O(1′)	O(12)	f	2.910(13)	O(2′)	O(3′)	a	2.687(41)
N(1)	O(4′)	a	2.975(31)	O(2′)	O(4′)	b	2.634(38)
N(11)	O(7′)	h	3.021(53)	O(2′)	O(5′)	h	2.908(100)
O(1)	O(3′)	g	2.865(34)	O(2′)	O(7′)	i	2.690(58)
O(1)	O(5′)	a	2.922(97)	O(3′)	O(7′)	a	2.934(62)
O(2)	O(3′)	a	2.777(34)	O(4′)	O(6′)	d	2.768(103)
O(2)	O(4′)	g	2.900(31)	O(6′)	O(8′)	a	2.805(146)

Code of symmetry-related position

a : x, y, z d : $-1+x, y, z$ g : $1-x, 0.5+y, 1-z$
b : $1+x, y, z$ e : $-1+x, y, -1+z$ h : $1-x, -0.5+y, 1-z$
c : $x, y, -1+z$ f : $-x, -0.5+y, -z$ i : $2-x, -0.5+y, 1-z$

the corners of the planar coordination square, taking a *cis* conformation with respect to the amino groups. The coordination distances, 2.006(10), 1.966(8), 2.000 (10), and 1.961(9) Å, are in agreement with those in the related complexes.[3,7,8] The axial coordination sites are occupied with a water molecule and a carboxyl oxygen of L-alanine in the neighbouring complex as mentioned above. These oxygen atoms, O(1′) and O(12)$^{\mathrm{a}}$ where superscript a denotes the neighbouring alanine, are at 2.512(9) and 2.864(9) Å from copper, respectively. It has been reported that the in-plane covalent radius of copper is 1.30 Å and the out-of-plane radius is 1.90 Å.[9] If the covalent radius of oxygen is taken as 0.66 Å, Cu–O length should be 2.56 Å which is very close to the value of Cu–O(1′) in the present complex. On the other hand, Cu–O (12)$^{\mathrm{a}}$ is considerably longer than the expected value. If the fact that the copper atom is 0.09 Å out of the best plane for the equatorial coordinating atoms toward the axial water molecule is also taken into account, it seems that the present complex is five-coordinated square-pyramidal.

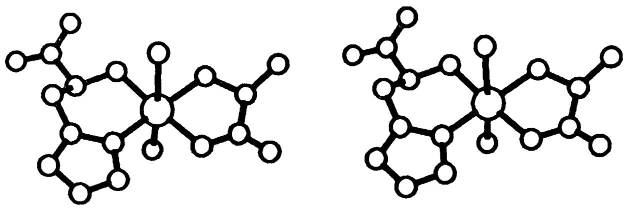

Fig. 2. Stereoview of the structure of (L-alaninato)-aqua(L-histidinato)copper(II).

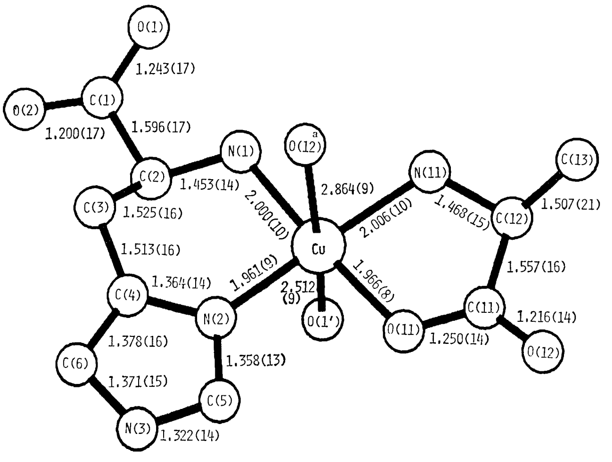

Fig. 3. Bond lengths (l/Å) in (L-alaninato)aqua(L-histidinato)copper(II).
Estimated standard deviations in the last digits are in parentheses.

The imidazole ring is planar within the experimental errors, whose mean plane makes a dihedral angle of 4.1(0.4)° with the plane of N(1)–Cu–N(2).

Common feature observed among Cu(ala his), Cu-(asn his), its hydrate and Cu(his thr) is a *cis* conformation with respect to the amino groups. In terms of electrostatic repulsion of two carboxyl groups which coordinate to copper at the oblique axial and equatorial positions in the latter three complexes, the *cis* form may be more favourable. In fact, the O···O distances between these carboxyl groups are over 4.0 Å in the observed *cis* form. If the *trans* form were constructed with the same molecular dimensions, short contacts between carboxyl oxygen atoms would be 3.38, 3.25, and 3.15 Å. In the Cu(ala his) complex, however, there is no approach between the carboxyl groups of histidine and alanine. Therefore, the steric hindrance between hydrogen atoms at imidazole moiety and equatorial amino group should be more important. The distances in question were calculated for a hypothetical *trans* form, the smallest being 1.92 and 1.65 Å for Cu(asn his) and its hydrate, respectively.

TABLE 3. BOND ANGLES (ϕ/°)

N(1)-Cu-N(2)	92.7(4)	C(1)-C(2)-C(3)	109.8(9)
N(11)-Cu-O(11)	82.6(4)	N(1)-C(2)-C(3)	110.4(9)
N(1)-Cu-N(11)	92.8(4)	C(2)-C(3)-C(4)	112.1(10)
N(2)-Cu-O(11)	91.7(4)	C(3)-C(4)-N(2)	123.2(10)
N(1)-Cu-O(11)	175.2(4)	Cu-N(2)-C(4)	127.4(7)
N(2)-Cu-N(11)	169.6(4)	C(3)-C(4)-C(6)	127.2(10)
N(1)-Cu-O(1′)	86.0(4)	N(2)-C(4)-C(6)	109.6(10)
N(2)-Cu-O(1′)	95.6(3)	C(4)-C(6)-N(3)	104.6(10)
N(11)-Cu-O(1′)	93.7(4)	C(6)-N(3)-C(5)	110.3(9)
O(11)-Cu-O(1′)	95.5(3)	N(3)-C(5)-N(2)	109.1(9)
N(1)-Cu-O(12)$^{\mathrm{a}}$ a)	87.6(3)	C(5)-N(2)-C(4)	106.4(9)
N(2)-Cu-O(12)$^{\mathrm{a}}$	86.2(3)	Cu-N(2)-C(5)	126.2(7)
N(11)-Cu-O(12)$^{\mathrm{a}}$	85.2(4)	Cu-N(11)-C(12)	113.3(7)
O(11)-Cu-O(12)$^{\mathrm{a}}$	90.8(3)	N(11)-C(12)-C(11)	108.0(9)
O(1′)-Cu-O(12)$^{\mathrm{a}}$	173.4(3)	C(12)-C(11)-O(11)	118.0(10)
Cu-N(1)-C(2)	118.3(7)	C(12)-C(11)-O(12)	118.6(10)
N(1)-C(2)-C(1)	111.0(9)	O(11)-C(11)-O(12)	123.4(11)
C(2)-C(1)-O(1)	115.0(11)	C(11)-C(12)-C(13)	112.4(11)
C(2)-C(1)-O(2)	117.4(11)	N(11)-C(12)-C(13)	114.7(11)
O(1)-C(1)-O(2)	127.6(13)	Cu-O(11)-C(11)	117.5(7)

a) O(12)$^{\mathrm{a}}$ denotes O(12) in the complex at the symmetry-related position, $-x,\ 0.5+y,\ -z$.

These are of course formidable values. In Cu(ala his), the closest approach is 2.06 Å, which may also enough to exclude the *trans* form. It should be added that the *cis* form of the complexes of Cu(asn his) and Cu(his thr) would be further stabilized by the possible ligand-ligand interaction in the solution proposed by Nakahara *et al.*[10,11]

The principal difference between the present and previously reported mixed-ligand complexes is the coordination mode of histidine. In Cu(asn his), its hydrate and Cu(his thr), L-histidine coordinates to copper as a tridentate ligand, while in Cu(ala his) it behaves as a bidentate ligand, that is to say, α-carboxyl group of L-histidine does not coordinate to copper but extends to form the hydrogen bonds with the neighbouring complexes. Neumann *et al.*[1] has reported that mixed-ligand copper complexes, Cu(asn his), Cu(gln his), and Cu(his thr), are preferably formed in serum. These observations can be related to the higher stability of the chelation of histidine as tridentate ligand. Difference in the coordination mode of histidine might be interpreted by pK_a's of the second amino acids, which are 2.34, 2.02, 2.15 and 2.17 for L-alanine, L-asparagine, L-threonine, and L-glutamine, respectively.[12] L-Alanine has distinctly higher pK_a than those of the remaining three amino acids. The high pK_a means the large electron density of carboxyl oxygen. Therefore, it is suggested that amino acid with higher pK_a donates more electron to copper ion, and the electrostatic interaction of copper with axial carboxyl group is not enough to hold the distorted coordination of α-carboxyl group of histidine.

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