Synthesis of a Ternary Copper(II) Complex Containing L-Histidine and L-Asparagine and Optical Resolution of DL-Histidine *via* the Complex Formation

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Summary L-Asparaginato-L-histidinatocopper(II) has been isolated as crystals in two different forms from aqueous solutions containing $Cu(ClO_4)_2$, L-histidine, and L-asparagine in the molar ratio of 1:1:1; the use of DL-histidine in place of L-histidine has shown that the L-enantiomer is preferentially incorporated into the ternary complex.

HISTIDINE-CONTAINING ternary amino-acid–copper(II) complexes have attracted wide attention because of their occurrence and involvement in copper(II) transport in biological systems,[1] where histidine (His) has been shown to form copper(II) complexes preferentially with asparagine (Asn), glutamine, and threonine.[1c] In fact, L-histi-

dinato-L-threoninatocopper(II) was detected in human blood serum,[1a] and its monohydrate was later revealed by *X*-ray crystal analysis to have His co-ordinated as a terdentate ligand.[2] Although the aqueous solution equilibria of copper(II)–His–amino-acid systems have been studied in detail,[3] the structures of the species present in solution are still controversial,[3b,4] and proper explanations of the preferential formation of certain ternary complexes in blood serum seem to be lacking.

In a series of attempts to prepare His-containing ternary copper(II) complexes, we isolated [Cu(L-Asn)(L-His)] in two modifications and observed a remarkable difference in crystallisation between [Cu(L-Asn)(L-His)] and [Cu(D-Asn)(L-His)] or [Cu(L-Asn)(D-His)]. We here report synthesis of [Cu(L-Asn)(L-His)] and optical resolution of racemic histidine *via* formation of this complex.

TABLE. Optical resolution of DL-histidine *via* complex formation.

System	Complex isolated	Yield/%[a]	Optical purity/%[b] Complex isolated[c]	His isolated[d]
Cu(II)–L-Asn–DL-His (1 : 1 : 1·5)	[Cu(L-Asn)(His)]·0·25H_2O	25	98	98
	[Cu(L-Asn)(His)]·3·5H_2O	24	84	88

[a] The yield of the isolated complex is based on the amount of copper(II) used. [b] The optical purity of L-histidine incorporated. [c] Estimated by the c.d. calibration curve. [d] Calculated from the specific rotations ($[\alpha]_{589}^{20}$). The samples contained a small amount (*ca.* 4%) of inorganic impurities, which were not removed by recrystallisation.

The complex [Cu(L-Asn)(L-His)]·0·25H_2O (**1**) was obtained as deep blue prismatic crystals by adding methanol or ethanol to an aqueous solution containing $Cu(ClO_4)_2$, L-His, and L-Asn in the molar ratio of 1 : 1 : 1 at pH 7·5—8·0. Crystallisation from aqueous solution gave blue needles of [Cu(L-Asn)(L-His)]·4H_2O (**2**). The i.r. spectral pattern of (**1**) was entirely different from that exhibited by (**2**), which, on dehydration at 60 °C *in vacuo*, gave the same i.r. spectrum as (**1**). On the other hand, the system involving $Cu(ClO_4)_2$, L-His, and D-Asn in the same molar ratio as above always gave the slightly soluble binary complex [Cu(D-Asn)$_2$] as crystals, and the ternary complex was not isolated under these conditions.

Because of the difference between [Cu(L-Asn)(L-His)] and [Cu(D-Asn)(L-His)], DL-His was resolved into enantiomers *via* isolation of [Cu(L-Asn)(His)] from a neutral solution of $Cu(ClO_4)_2$ (5 mmol), DL-His (7·5 mmol), and L-Asn (5 mmol) in water or aqueous methanol. Depending on the conditions used for crystallisation, the mixture gave the analytically pure complex, similar to (**1**) or (**2**). The optical purities of the histidine residue incorporated into the complexes were estimated by the calibration curve based on the c.d. spectra of the ternary systems with known amounts of copper(II), L-Asn, and His with different optical purities.[5] They were further checked by measuring the specific rotations of His isolated from the complexes. Both data clearly show that the L-enantiomer of His has been preferentially incorporated into the ternary copper(II) system with L-Asn (Table).

In our previous studies, electrostatic ligand–ligand interactions within complex molecules have been shown to lead to the ternary complex formation and fix the complex in a particular configuration.[5,6] Since Asn and His offer polar groups that can form hydrogen bonds with each other around copper(II), the present findings may point to the existence of intramolecular as well as intermolecular ligand–ligand interactions between the polar groups. Formation of (**1**) and (**2**) seems to reflect a structural difference due to such interactions affected by hydration of the complex.

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