Inorganica Chimica Acta, 34 (1979) L245–L246

Solution Equilibrium in the Ternary Copper(II)–L-Histidine–Diglycyl-L-histidine System

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Received February 2, 1979

It has been considered that the copper(II) bound to serum albumin is in equilibrium with copper in tissues through some specific amino acid complexes [1–7]. Among such amino acids L-histidine (His) has been thought as the most probable one to form a ternary Cu(II)–albumin–amino acid complex, which participates in an intermediate stage for copper-transport between blood and tissues. Although some workers have attempted to clarify the copper-transport mechanism by use of diglycyl-L-histidine (GlyGlyHis) as a model for the copper transport site of serum albumin, even the solution equilibrium of the binary Cu(II)–GlyGlyHis system [8–10] has been a subject of controversy, hence that of the ternary Cu(II)–GlyGlyHis–His system [11] even more.

Potentiometric titrations were performed at 25 ± 0.05 °C and I = 0.1 M KNO_3 for the binary Cu(II)–GlyGlyHis and the ternary Cu(II)–GlyGlyHis–His system, and the available data were treated using the computer program SCOGS [12]. The procedure was carried out as previously described [13]. The Table lists the stability constants of the complexes, which are represented as the overall formation constants (β_{pqrs}) of the following equilibrium reaction,

$$pM + qH + rA + sB \rightleftharpoons^{\beta_{pqrs}} M_pH_qA_rB_s$$

where p, q, r and s are numbers of M(Cu^{2+}), H(H^+), A (GlyGlyHis anion), and B (His anion), respectively.

TABLE. Logβ for the Species $M_pH_qA_rB_s$ (M = Cu^{2+}, H = H^+, A = GlyGlyHis Anion, and B = His anion) at 25 ± 0.05 °C and Ionic Strength I = 0.1 (KNO_3). Standard deviations are given in parentheses.

Species				Stability
p	q	r	s	log β_{pqrs}
0	1	1	0	8.01 (0.01)
0	2	1	0	14.88(0.01)
1	−2	1	0	−1.98(0.01)
1	1	1	1	22.41(0.03)
1	0	1	1	17.06(0.04)
1	−1	1	1	9.93(0.04)

For the binary Cu(II)–GlyGlyHis system, the calculation satisfactorily converged only by taking into account $CuH_{-2}A$ species (the charge of each species is omitted for simplicity) over acid to alkaline pH region, indicating that the highly square planar complex where amino, two deprotonated amides, and imidazole nitrogens are coordinated to central Cu(II) ion, is as much as *ca.* 10^4 times more stable than other Cu(II)–tripeptide complexes. Analyses including any other binary species such as CuHA, CuA, $CuH_{-1}A$, $CuH_{-3}A$ failed to converge contrary to the results obtained by other workers [8–10].

For the ternary Cu(II)–GlyGlyHis–His (1:1:1) system, there exist in total *ca.* 45% of the ternary species $CuH_{-1}AB$ and CuAB and His-containing binary species CuB_2 at physiological pH. However, the population of the binary species $CuH_{-2}A$ increases with increasing pH and at extremely high pH the binary species is predominant (Fig. 1). This result is successfully in line with absorption, CD, and ESR spectral behaviors for the system [14], to which the solution equilibrium study by Kruck and Sarkar [11], who suggested predominant formation of ternary species at neutral to alkaline pH, is in contradiction. Whatever the structural factors in stabilization for the ternary complexes that are taken into consideration the ternary complexes illustrated by Kruck and Sarkar [11] could not be equal to the highly square planar complex $CuH_{-2}A$ (λ_{max} = 525 nm, ϵ = 110, I = 0.1 M KNO_3) in the binding ability with Cu(II) ion. The results of the present solution equilibrium study well explain the predominant binding of exchangeable Cu(II) with albumin in living systems [3, 4].

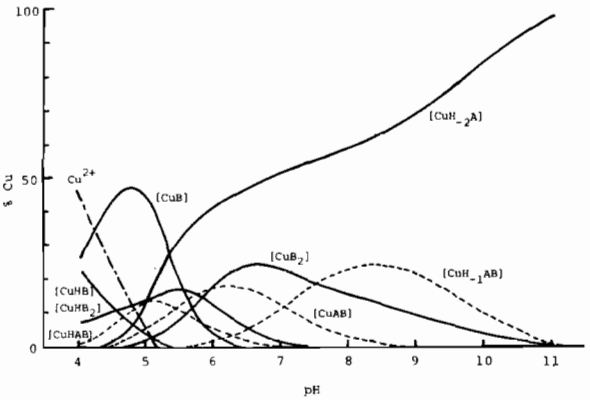

Fig. 1. pH-Profile of the computed composition of a solution of GlyGlyHis (2×10^{-3} M), His (2×10^{-3} M) and Cu^{2+} (2.016×10^{-3} M), as percentage of the total copper present.

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