

## Reactions of Metal Chelates. III. The Reactions of Bis(salicylaldehydato)copper(II) with Amides and Esters of Glycine and Glycylglycine

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The reactions of bis(salicylaldehydato)copper(II) in acidic, neutral and basic media with glycineamide, glycinester, glycylglycinamide and glycylglycinester have been systematically investigated. The reaction products have, in all cases, been isolated as crystals and characterized. As a result of this investigation, six new copper(II) chelates of Schiff bases derived from salicylaldehyde and glycine- or glycylglycine-amide have been obtained. The interrelation between those chelates has also been disclosed.

In a previous paper<sup>1)</sup> it was reported that bis(salicylaldehydato)copper(II), I, reacts readily with glycine or glycylglycine to form salicylidene-glycinato- or -glycylglycinato-chelate, respectively, II, III.

We have further reported that the reaction at pH 4.5 between the same chelate, I, and tri-<sup>2)</sup> or tetra-glycine<sup>3)</sup> results in the hydrolytic cleavage of a peptide linkage, producing salicylidene-glycylglycinatocuprate(II), III, and free glycine or glycylglycine, respectively. From biochemical interest, the investigation has been extended to reactions of the same chelate, I, with some derivatives of amino acids and peptides.

This paper describes the reactions of bis(salicylaldehydato)copper(II), I, in acidic, neutral and basic media with glycineamide, glycinester, glycylglycinamide and glycylglycinester. The preparation and properties of six new copper(II) chelates, which have been obtained as a result of this investigation, are also described.

**The Reaction of Bis(salicylaldehydato)copper(II), I, with Glycinamide.** The reaction between complex, I, and glycineamide varies widely with the hydrogen ion concentration in solutions. Although the reactions proceed rapidly at room temperature both in acidic and basic solutions to form the one-to-one type copper(II)-Schiff base complexes, the resulting chelate from acidic solution is green, while that from basic solution red-purple, indicating that they have different structure from each other. The structure of the green complex is easily concluded to be IV in Fig. 1 in the light

of properties of acidamide found in the case of pyridine-2-carboxamide complexes,<sup>4-6)</sup> and results of elemental analysis and electrophoretic investigation of the complex. As is clear from the structural formula, IV, the carboxamide group of the glycineamide moiety in the green complex is linked to copper(II) through the oxygen atom, and the ligand at the fourth coordination position around copper(II) is water molecule; hence the complex is a univalent cation, being isolated as chloride, bromide, perchlorate, sulfate, etc. On the other hand, the structure of the red-purple complex isolated from a basic solution is somewhat difficult to determine, since the complex shows a considerably subnormal magnetic moment (1.15 B. M. for copper atom). As has been established by Kishita *et al.*,<sup>7)</sup> the subnormal magnetic moment of this kind can be elucidated in terms of binuclear structure, V, in which an interaction is expected between copper(II) atoms.

Although there is another possible binuclear structure as represented by V', in which the bridging atoms are phenolic oxygen atoms, this structure is supposed to be less plausible from a stereochemical point of view. In other words, the steric hindrance between the benzene ring of salicylaldehyde moiety and the carboxamide nitrogen might eliminate the possibility of the structure V'. The binuclear complex, V, can be dissolved in an alkaline solution, but the structure of the complex

4) K. Yamasaki and M. Sekizaki, *This Bulletin*, **38**, 2206 (1965).

5) A. Masuko, T. Nomura and Y. Saito, *ibid.*, **40**, 511 (1967).

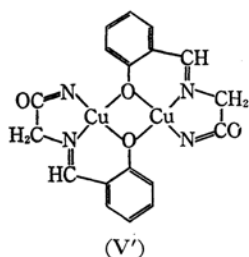
6) Y. Nawata, H. Iwasaki and Y. Saito, *ibid.*, **40**, 515 (1967).

7) For example, M. Kishita, Y. Muto and M. Kubo, *Australian J. Chem.*, **10**, 386 (1957).

1) A. Nakahara, *This Bulletin*, **32**, 1195 (1959).

2) A. Nakahara, K. Hamada, I. Miyachi and K. Sakurai, *This Bulletin*, **40**, 2826 (1967).

3) A. Nakahara, K. Hamada, Y. Nakao and T. Higashiyama, *Coord. Chem. Rev.*, **3**, 207 (1968).



in the solution has not been determined; hence the structure of the complex in the solution is still uncertain whether the binuclear structure is maintained or not.

In neutral solutions the chelate I reacts less rapidly than in acidic or basic solutions with glycylglycine. The resulting compound is not the one-to-one but one-to-two type copper(II)-Schiff base complex, in which the carboxamide groups are free from coordination as illustrated in VI. As is understood from its structural formula, this complex is an uncharged neutral complex.

The interrelation between those chelates, IV, V and VI, has also been clarified to some extent. First, chelate IV changes to V by adjusting the pH of the solution to about 12; this isomerization is almost reversible, and accordingly, chelate IV is reproduced from V by readjusting the pH of the solution to about 4.0. However, the procedure is always accompanied by the precipitation of blue-purple crystalline powder at pH-values near 7.5. Though this precipitate is expected to have an interesting structure, the details on this particular compound is not clarified yet. Secondly, the chelate VI also changes readily to IV or V according to the pH-value of the solution, but these rearrangements are, of course, not reversible.

As has been reported previously,<sup>3)</sup> glycylglycine-Schiff base coordinated around copper(II) in the same fashion as that depicted in the structural formula, IV, is easily hydrolyzed into the free glycine and glycine-Schiff base complex in aqueous media at low pH and especially at high temperature. However, in the present case, the hydrolysis of the carboxamide group has not been observed at least under the same condition. Though this finding seems to be inconsistent with the results of Meriwether and Westheimer,<sup>8)</sup> who reported the metal ion-promoted-hydrolysis of glycylglycine and of phenylalanyl-glycylglycine, their experiments were made in a slightly alkaline solution, while the present datum has been obtained from an investigation on a slightly acidic solution.

Thus it can be said that carboxamide  $-\text{CO}-\text{NH}_2$  linkage is definitely more stable at low pH against the hydrolytic cleavage reaction than peptide linkage.

#### The Reaction of Bis(salicylaldehyde)copper(II), I, with Glycylglycine.

This reaction is very monotonous, and always results in the formation of the one-to-two type copper(II)-Schiff base complex, (VII),<sup>1,9)</sup> regardless of the hydrogen ion concentration in solutions. The hydrolysis of the ester groups of complex, VII, in aqueous media has not been observed under mild conditions, perhaps because of its poor solubility. At any rate, since the ester groups of glycylglycine moieties in chelate VII are located away from the central metal ion, the electron-withdrawing effect of metal ion would not reach the ester group to catalyze the hydrolytic reaction.

#### The Reaction of Bis(salicylaldehyde)copper(II), I, with Glycylglycinamide.

This reaction varies also delicately with the hydrogen ion concentration in solutions. In acidic solutions, the reaction product is an olive-green Schiff base complex, in which the glycylglycinamide moiety is linked to copper(II) only through the nitrogen of the terminal amino group and the oxygen of the peptide linkage as indicated in (VIII). The structure is supported not only by the results of elemental analysis but also by the paper chromatographic identification of the glycylglycinamide after decomposing the chelate with hydrogen sulfide. Chelate VIII is easily hydrolyzed into the free glycylglycinamide and the *N*-salicylidene-glycinato-aquo-copper(II), II, by heating at 70°C and at pH-value near 2.8.<sup>3)</sup>

On the other hand, the resulting compounds from the reactions in neutral or basic solutions are copper(II) tetradentate chelates of Schiff base derived from salicylaldehyde and glycylglycinamide. However, the chelate from neutral solution is navy-blue, while that from basic solution is red-brown. The difference is apparently due to a linkage isomerism; the carboxamide group in the navy-blue chelate is considered to be linked to copper(II) through oxygen atom, and the same group in the red-brown chelate through nitrogen atom as illustrated in IX and X, respectively. This consideration is strongly supported by the fact that chelate IX is an uncharged neutral complex, whereas chelate X a univalent anion. Hydrolysis of the terminal carboxamide group has not been observed in either complexes under conditions that would be observed in case of peptide linkage. The results of experiments of paper-electrophoresis clearly indicate that the olive-green complex is a cation, the navy-blue complex an uncharged molecule, and the red-brown complex an anion. The mutual transformation between the three chelates, VIII, IX and X, is readily attained only by changing the pH of solutions.

#### The Reaction of Bis(salicylaldehyde)copper(II), I, with Glycylglycinester.

8) L. Meriwether and F. H. Westheimer, *J. Am. Chem. Soc.*, **78**, 5119 (1956).

9) P. Pfeiffer, W. Offermann and H. Werner, *J. prakt. Chem.*, **159**, 313 (1942).

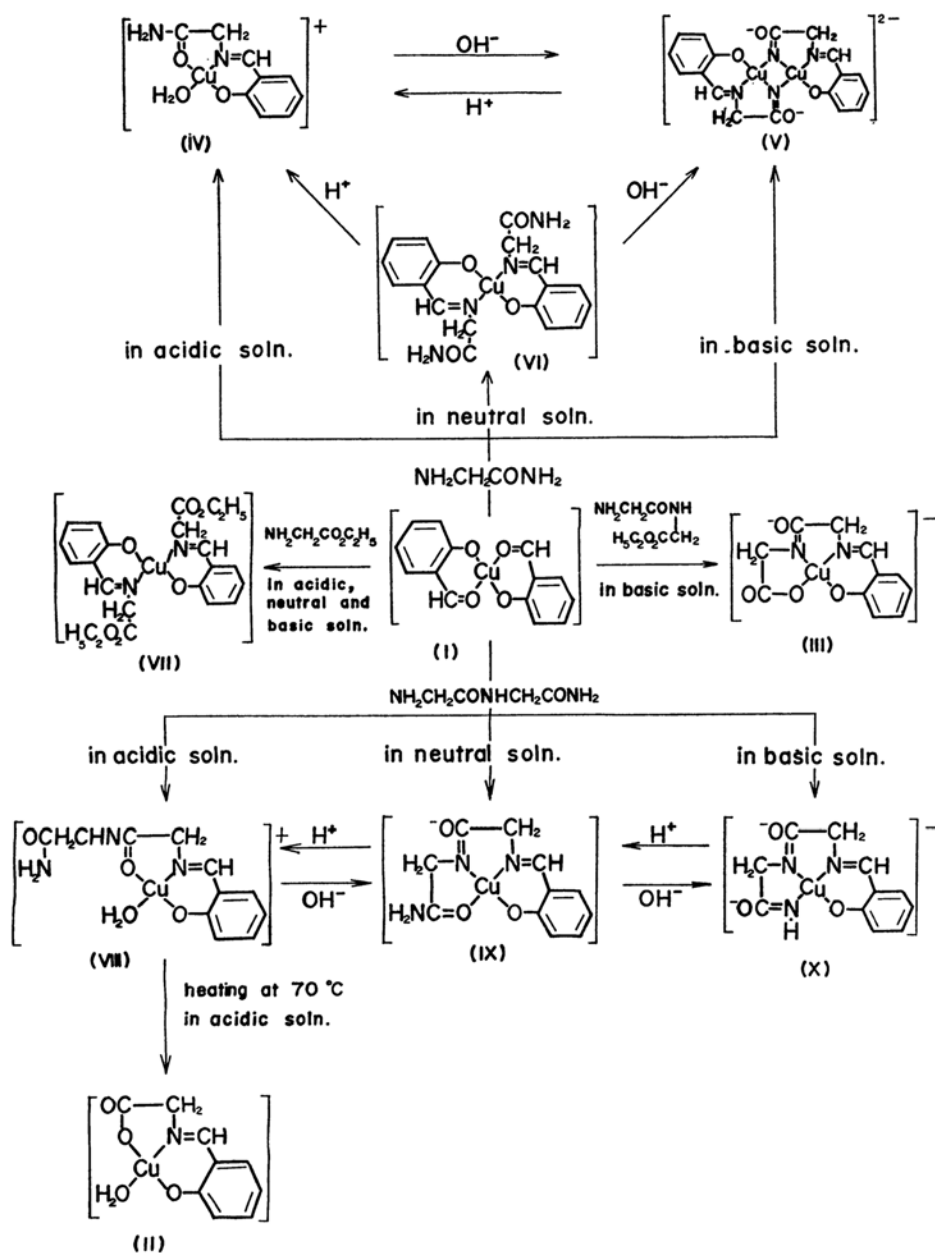


Fig. 1. The reactions of bis(salicylaldehyde)copper (II) with amides and esters of glycine and glycylglycine. The complexes, IV, V, VI, VIII, IX, and X, are new compounds.

product in basic solutions from the system containing chelate I and glycylglycinester is the *N*-salicylidene-glycylglycinatocuprate(II), III,<sup>11</sup> indicating that hydrolysis of ester group proceeds quite readily and rapidly.

The phenomenon is understood in terms of a catalytic effect of metal ion as has very often been observed in researches on metal chelates of esters.<sup>10</sup>

10) For example, R. J. Angelici and D. Hopgood, *J. Am. Chem. Soc.*, **90**, 2514 (1968).

## Experimental

**Preparations of Amides and Esters of Glycine and Diglycine.** Glycinamide was prepared according to directions of Bergell and Wulffing<sup>11</sup>

Glycylglycinamide was Prepared as acetate according to the method of Fruton and Bergmann.<sup>12</sup> Glycine-

11) P. Bergell and H. V. Wulffing, *Z. Physiol. Chem.*, **64**, 348 (1910).

12) J. S. Fruton and M. Bergmann, *J. Biol. Chem.*, **145**, 253 (1942).

and glycylglycine were obtained from glycine and glycylglycine, respectively, by treating with absolute ethanol saturated with dried hydrogen chloride. All these amides and esters were identified through the elemental analyses. The preparation and purification of bis(salicylaldehydato)copper(II), I, was performed in the same way as that described in the first paper of this series.<sup>2)</sup>

### The Reaction of bis(salicylaldehydato)copper (II),

**I. The Reaction of Complex I with Glycinamide.** A one-to-one molar mixture of complex I and glycinamide hydrochloride in aqueous ethanol was divided into three parts. The pH-values of each solution were adjusted to 3.0, 7.0 and 12.0, respectively, by using dilute solutions of sodium hydroxide and hydrochloric acid. Each reaction mixture was then stirred at room temperature for about half an hour.

From the acidic solution, a green crystalline powder was deposited, which was filtered and recrystallized from an aqueous ethanol solution to give a green prism.

The structure of this complex was easily concluded to be IV from coincidence of its decomposing temperature and infrared spectrum with those of complex IV, which can more conveniently be obtained, for the purpose of preparation, from a reaction at pH 3.0 of a system containing 1 : 1 : 1 copper(II) : salicylaldehyde : glycinamide. Mp 178—186°C (decomp.). Found: C, 37.19; H, 3.35; N, 9.44%. Calcd for  $\text{CuC}_6\text{H}_{11}\text{O}_3\text{N}_3\text{Cl}$ : C, 36.74; H, 3.77; N, 9.52%. The elemental analysis of sulfate of the same complex was also performed. Found: C, 33.24; H, 3.81; N, 8.43; Cu, 19.87%. Calcd for  $\text{CuC}_6\text{H}_{11}\text{O}_3\text{N}_3 \cdot \frac{1}{2}\text{SO}_4 \cdot \text{H}_2\text{O}$ : C, 33.30; H, 4.00; N, 8.63; Cu, 19.54%. Mp 180—200°C (decomp.). Magnetic moment,  $\mu_{\text{eff}} = 1.84$  B. M. (15°C).

From the reaction mixture of pH-value near 12, a red-purple crystal was isolated. The structure of this complex was concluded to be V, on the basis of the results of elemental analysis and the magnetic datum. Mp 218—220°C (decomp.). Found: C, 36.22; H, 3.73; N, 9.17; Cu, 21.59%. Calcd for  $\text{Na}_2\text{Cu}_2\text{C}_{18}\text{H}_{14}\text{O}_4\text{N}_4$ : C, 36.30; H, 3.70; N, 9.41; Cu, 21.34%. Magnetic moment,  $\mu_{\text{eff}} = 1.15$  B. M. (15°C).

The reaction mixture of pH-value near 7.0 gave an olive-green precipitate, which was recrystallized from aqueous ethanol to give a one-to-two copper(II)-Schiff base complex. Mp 255—265°C (decomp.). Found: C, 51.63; H, 4.97; N, 13.90%. Calcd for  $\text{CuC}_{18}\text{H}_{18}\text{O}_4\text{N}_4$ : C, 51.73; H, 4.34; N, 13.41%.

Though the two complexes, IV and V, can be prepared either through the reaction between bis(salicylaldehydato)copper(II) and glycinamide or by the direct reaction between copper (II), salicylaldehyde and glycinamide, this particular one-to-two copper(II)-Schiff base complex can be prepared only through the

reaction between bis(salicylaldehydato)copper(II) and glycinamide.

**The Reaction of the Complex I with Glycylglycinamide.** A similar procedure to that employed for the reaction of complex I with glycinamide was adopted. In order to isolate the reaction products it was necessary, in some cases, to concentrate the solution *in vacuo*. Recrystallization was performed by using aqueous ethanol and keeping the pH-value near 3.0, 7.0 and 12.0, respectively. The resulting chelate from the acidic solution is an olive-green crystalline powder, which decomposes at 195—198°C. Found: C, 36.94; H, 3.91; N, 11.57%. Calcd for  $\text{CuC}_{11}\text{H}_{12}\text{O}_3\text{N}_3\text{Cl} \cdot 1.5\text{H}_2\text{O}$ : C, 36.67; H, 4.05; N, 11.66%. The product from the neutral solution is a navy-blue crystalline powder, which decomposes at 262—263°C. Found: C, 42.47; H, 3.69; N, 13.63%. Calcd for  $\text{CuC}_{11}\text{H}_{11}\text{O}_3\text{N}_3 \cdot \text{H}_2\text{O}$ : C, 41.96; H, 4.13; N, 13.34%. The complex obtained from the basic solution is a red-brown prism, which decomposes at 282—290°C. Found: C, 35.10; H, 4.09; N, 10.82%. Calcd for  $\text{NaCuC}_{11}\text{H}_{10}\text{O}_3\text{N}_3 \cdot 3\text{H}_2\text{O}$ : C, 35.44; H, 4.33; N, 11.27%.

**The Reactions of the Complex I with Glycine- and Glycylglycine.** A one-to-one molar mixture of complex I and glycinester in aqueous ethanol (50% by volume) was stirred and heated at 60°C for half an hour.

The reaction product was soon deposited as an olive-green powder, and was recrystallized from ethanol. No difference in the reaction product was observed within wide range of pH and molar ratio of complex I to glycinester. The resulting complex was identified as the one-to-two type copper(II)-Schiff base chelate as illustrated in VII, from the coincidence in infrared spectrum of the complex with that obtained by Pfeiffer *et al.*<sup>9)</sup>

The reaction of complex I with glycylglycine was performed only at pH value near 8.5 by a similar procedure as described above. The reaction product was, after recrystallization, a red-purple needle. The structure of this compound was easily concluded as sodium *N*-salicylidene-glycylglycinatocuprate(II), III, on the basis of the coincidence of its infrared spectrum with that of the standard sample.<sup>1)</sup>

**Magnetic Measurements.** The magnetic susceptibility was determined at 15°C by using a Gouy magnetic apparatus. From susceptibilities observed, the magnetic moments were evaluated per copper atom.

**Paper-electrophoretic experiments, amino acid analyses and the measurements of infrared spectra** were made with the use of a Yanagimoto EC-10, a Yanagimoto LC-5 and a Hitachi EPI-S2, respectively.

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