The Formation of Peptide Bonds at the Coordination Sites around Copper(II)

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In a previous paper[1] we reported the metal ion promoted hydrolysis of some oligopeptides. The structure of the intermediate complexes postulated then has recently led us to undertake the formation reaction of peptide bonds, without being confined to the cleavage reaction of them. This was because of the successful experiments of Buckingham[2] and Collman[3]; they reported that treatment of β_2-[Co(trien)Cl(glyOEt)]$(ClO_4)_2$ with glycine ethyl ester in nonaqueous solution results in the rapid condensation of two glycinester residues and the formation of the β_2-[Co(trien)glyglyOEt] ion.

Now we have also succeeded in finding out another type of formation reaction of peptide bonds by using copper(II) complex of the Schiff base derived from salicylaldehyde and glycinamide. The outline of the reactions can be represented by the schemes (1) and (2):

$$\text{Cu(Salal=Glyam)}^{*1} + \text{GlyOEt} \xrightarrow[\text{5 min, in DMFA}]{\text{KOH, 25°C}} \text{Cu(Salal=Glyglyam}^{*1}\text{)}, \qquad (1)$$

$$\text{Cu(Salal=Glyam)} + \alpha\text{-AlaOEt} \xrightarrow[\text{5 min, in DMFA}]{\text{KOH, 25°C}} \text{Cu(Salal=}\alpha\text{-Alaglyam)}. \qquad (2)$$

The isolation of resulting chelates shown in the schemes (1) and (2) has been carried out by using a Sephadex column and the techniques of vacuum condensation. The confirmation of peptide bond formation has been attained on the basis of three experimental results. Firstly, the infrared spectrum of the resulting chelate in the scheme (1) has shown good agreement with that of the standard samples, whose structure was already established as the copper(II) chelate of the Schiff base derived from salicylaldehyde and glycylglycinamide.[4] Secondly, the results of amino acid analyses*2 of the reaction products have clearly shown the presence of glycylglycine or its amide in the solution for the scheme (1), and α-alanylglycine or its amide in the solution for the scheme (2), respectively. Thirdly, the one- and two-dimensional paperchromatographic tests have unambiguously shown that the reaction product for the schemes (1) or (2) is not the complex with glycylglycine or α-alanylglycine but that with glycylglycinamide or α-alanylglycinamide, respectively.

Comparison between the reactions of Buckingham or Collman and of the present authors is of interest. In the reaction of Buckingham or Collman, the condensation reaction occurs between the terminal carbethoxy group of the glycinester in coordination and the amino group of free glycinester. On the other hand, in the present authors' reaction, condensation occurs between the imino-nitrogen of the glycinamide moiety in coordination and the carbethoxy group of free glycinester. Accordingly, the reaction of glycine residue in coordination with free α-alanine is expected to give glycyl-α-alanine in the Buckingham-Collman reaction, and reversely α-alanylglycine in the present authors' reaction, as has already been described. The present reaction can be interpreted to proceed as depicted in Fig. 1, though it still awaits further pursuit.

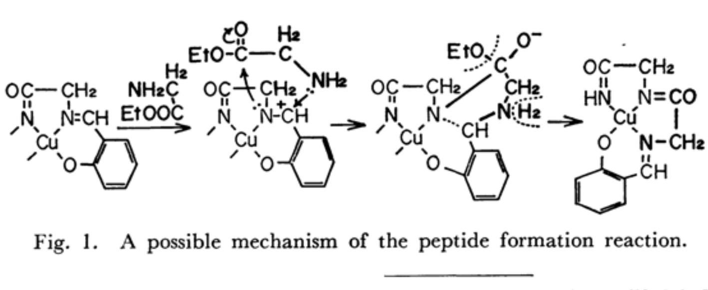

Fig. 1. A possible mechanism of the peptide formation reaction.

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[1] A. Nakahara, K. Hamada, Y. Nakao and T. Higashiyama, *Coordin. Chem. Rev.*, **3**, 207 (1968).

[2] D. A. Buckingham, L. G. Marzilli and A. M. Sargeson, *J. Am. Chem. Soc.*, **89**, 2772 (1967).

[3] J. P. Collman and E. Kimura, *ibid.*, **89**, 6096 (1967).

[4] K. Hamada, H. Ueda, Y. Nakao and A. Nakahara, This Bulletin, in press.

*1 The notation "Salal=Glyam" or "Salal=Glyglyam" denotes the Schiff base derived from salicylaldehyde and glycinamide or glycylglycinamide, respectively.

*2 The sample solutions for the paperchromatography and amino acid analysis were free from copper(II) by treating with hydrogen sulfide.