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Synthetic Studies of Amino Acids by the Use of the Copper(II) Complex. IV.[1d] A Facile Procedure for Isolating Amino Acids from Their Copper(II) Complexes by Means of Amberlite IR-120B

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It has been shown in a series of investigation[1] that the base-catalyzed condensation reaction of *N*-pyruvylideneglycinatoaquocopper(II) with a variety of aldehydes is useful for the preparation of β-hydroxy amino acids and 2-amino-2-deoxyaldonic acids. The isolation of the resultant amino acids from the corresponding copper(II) complexes has been performed by the treatment of their aqueous solutions with hydrogen sulfide gas or sodium sulfide, followed by the filtration of the precipitated cupric sulfide, adsorption on a column of Amberlite IR-120B(H form), and elution with a dilute aqueous ammoniacal solution. However, treatment with sodium sulfide makes the resultant solution strongly alkaline, and an alkaline condition is unsuitable for such amino acids as 2-amino-2-deoxyaldonic acids susceptible to isomerization. Moreover, hydrogen sulfide gas is, if anything, unsuitable for the isolating procedure in view of its toxicity. In these connections, an investigation was undertaken in order to establish a more favorable procedure for the isolation of amino acids by the use of some reagents;[2] the application of Amberlite IR-120B(H form) was proved to afford amino acids in high yields quite simply.

A solution of *N*-pyruvylideneglycinatoaquocopper(II)[1c] (10 mmol) in distilled water (100 ml) was treated on a column (3×9 cm) of the resin, washed with distilled water, and then eluted with a dilute

Table 1. An examination on the washing procedure with distilled water prior to the elution with aqueous ammoniacal solution[a]

Run	The volume of water for washing, l	Yield of isolated glycine	
		g	%
1	5	0.732	97.6
2	3	0.727	96.9
3	1	0.702	93.6

a) All the examinations were carried out by the use of 10 mmol of *N*-pyruvylideneglycinatoaquocopper(II) dissolved in distilled water (100 ml). In each case, the elution was carried out with 2000 ml of 0.5 M aqueous ammoniacal solution.

Table 2. An examination on the eluting procedure with 0.5 M aqueous ammoniacal solution after the washing with distilled water[a]

Fractions[b]	Yield of isolated glycine	
	g	%
1	0.722	96.3
2	0.005	0.7
3	0.003	0.3
4	0.002	0.3

a) All the examinations were carried out by the use of 10 mmol of *N*-pyruvylideneglycinatoaquocopper(II) dissolved in distilled water (100 ml). Prior to the elution, the column was washed with distilled water (5000 ml). b) The eluate was divided into the fractions of 500 ml, and the fractions were numbered in turn in the order of eluting-out.

Table 3. Isolation of amino acids from the corresponding copper(II) complexes by the use of Amberlite IR-120 B[a]

Copper(II) complexes	Mol. weight	Yield of isolated glycine or alanine	
		g	%
N-Pyruvylidene-glycinatoaquocopper(II)[b]	260	0.732	97.6
Bisglycinatocopper(II)[c]	230	1.485	99.0
N-Salicylidene-glycinatoaquocopper(II)[d]	278	0.564	75.2
N-Pyruvylidene-glycinatopyridinecopper(II)[e]	339	0.705	94.0
Bisalaninatocopper(II)	258	1.768	98.6

a) All the isolations were carried out by the use of 10 mmol of the corresponding copper(II) complexes and the column (3×9 cm) of the resin(H form). b) On removing the copper(II) ion by treating with hydrogen sulfide gas prior to the treatment on the column, glycine was obtained in 82.1% yield. c) Glycine was obtained in 97.5% yield by decomposing the complex with concentrated aqueous ammoniacal solution prior to the treatment on the column. d) The yield is considered to be arisen from the low solubility of the complex. e) On treating the complex as described in b), glycine was obtained in 82.0% yield.

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[1] a) T. Ichikawa, S. Maeda, Y. Araki, and Y. Ishido, *J. Amer. Chem. Soc.*, **92**, 5514 (1970); b) T. Ichikawa, T. Okamoto, S. Maeda, S. Ohdan, Y. Araki, and Y. Ishido, *Tetrahedron Lett.*, **1971**, 79; c) T. Ichikawa, S. Maeda, T. Okamoto, Y. Araki, and Y. Ishido, This Bulletin, **44**, 2779 (1971); d) S. Ohdan, T. Okamoto, S. Maeda, T. Ichikawa, Y. Araki, and Y. Ishido, *ibid.*, **46**, 981 (1973).

[2] a) The copper(II) complex was not decomposed by a concentrated aqueous ammoniacal solution, although it has been well known that bisglycinatocopper(II) can be decomposed by the solution; b) The separation of the excess amines from glycine could not be achieved distinctly by the same ion-exchange resin-column technique, although the complex was decomposed by the use of 1.5—2.0 equivalents of ethylenediamine, diethylenetriamine, and triethylenetetramine respectively; c) Amberlite IR–120B (H form) was used since *N*-salicylideneglycinatoaquocopper(II) has been shown to be decomposed by 6 M aqueous hydrochloric acid [K. Harada and J. Oh-hashi, *J. Org. Chem.*, **32**, 1103 (1967)].

Table 4. Isolation of glycine from *N*-pyruvylideneglycinatoaquocopper(II) in alkaline solution by the treatment with Amberlite IR-120 B[a]

Run	Solvent system	Conditions		Yield of isolated glycine	
		pH[b]	Treating time, hr	g	%
1	H_2O (100 ml)	9.5	0	0.677	90.3
2	H_2O-DMF (80+80 ml)	9.0	0	0.715	95.3
3	H_2O-DMF (80+80 ml)	9.0	2	0.511	68.1

a) All the isolations were carried out by the use of *N*-pyruvylideneglycinatoaquocopper(II) and a column (3×9 cm) of the resin(H form). The washing of the column and the elution were carried out with distilled water (5000 ml) and 0.5 M aqueous ammoniacal solution (2000 ml), respectively. b) These conditions were adjusted by the use of a pH meter and by the addition of 1 M aqueous sodium hydroxide solution.

aqueous ammoniacal solution; the eluate was then concentrated *in vacuo* to give white crystals of glycine in a 97.6% yield. Incidentally, the amounts of solvents necessary for the washing and the elution were found to be 1000 ml and 500 ml respectively by such examinations as are shown in Tables 1 and 2. By the application of best condition, the isolation of glycine and alanine were attempted with respect to bisglycinatocopper(II),[3] *N*-salicylideneglycinatoaquocopper(II),[4] *N*-pyruvylideneglycinatopyridinecopper(II),[1c] and bisalaninatocopper(II);[5] they were proved to give the corresponding amino acids in 99.0, 75.2, 94.0, and 98.6% respectively, under the conditions summarized in Table 3. Except in the case of *N*-pyruvylideneglycinatopyridinecopper(II), these results are greatly improved in comparison with those obtained by conventional procedures. On the basis of these results, the isolation of glycine with respect to *N*-pyruvylideneglycinatoaquocopper(II) treated under the conditions(pH 9.5) previously used in the base-catalyzed condensation reaction;[1] glycine was thus obtained in a 90.3% yield, as is shown in Table 4. Furthermore, the base-catalyzed condensation reaction of the complex with some aldehydes can not be carried out even in aqueous methanol because of their low solubility; it is thus necessary to examine the application of other solvents to the reaction. The isolation of glycine from the complex in aqueous *N*,*N*-dimethylformamide was attempted as is shown in the table as a model experiment postulating the case that the condensation reaction was carried out in the solvent system. The yield is also fairly good in this case (95.3%).[6] On the other hand, the treatment of the complex under the same condition for 2 hr was proved to afford glycine in a 68.1% yield, and it was concluded that the condensation reaction can be carried out in aqueous *N*,*N*-dimethylformamide since the extent of the degradation of glycine in the complex is comparable with that observed in an aqueous solution.[1c].

It can thus be concluded that the isolating procedure involving a simple treatment on a column of Amberlite IR-120B(H form) is facile and useful for the isolation of amino acids from the corresponding copper(II) complexes.

Experimental

Isolation of Glycine from the Aqueous Solution of N-*Pyruvylideneglycinatoaquocopper(II).* A solution of *N*-pyruvylideneglycinatoaquocopper(II)[1c] (2.600 g, 10 mmol) in distilled water (100 ml) was treated on a column(3×9 cm) of Amberlite IR-120B(H form). This column was then washed with distilled water(5000 ml) and eluted with a 0.5 M aqueous ammoniacal solution(2000 ml). The eluate was concentrated *in vacuo* almost to dryness and subsequently triturated with ethanol(10 ml) to give glycine(0.732 g, 97.6%); mp 232°C (decomp.). The IR spectrum of this product was identical with that of the authentic specimen.

Incidentally, the alkaline solution was prepared by the addition of a 1 M aqueous sodium hydroxide solution, and its pH was adjusted by the use of a pH meter.

Isolation of Amino Acids from Bisglycinatocopper(II),[3] N-*Salicylideneglycinatoaquocopper(II),*[4] N-*Pyruvylideneglycinatopyridinecopper(II),*[1c] *and Bisalaninatocopper(II).*[5] The isolations were accomplished under the conditions described in each table in the same way as has been described for the preceeding experiment.

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[3] M. Sato, K. Okawa, and S. Akabora, This Bulletin, **30**, 937 (1957).

[4] A. Nakahara, *ibid.*, **32**, 1195 (1959).

[5] Z. E. Gol' braikh, *Zh. Neorg. Khim.*, **1**, 1739 (1956); *Chem. Abstr.*, **51**, 2446c (1957).

[6] When the solution was treated with hydrogen sulfide gas according to the conventional procedure, the resultant fine precipitates of cupric sulfide could not be filtered off; they passed through the filter cell on filtration. The cupric sulfide remained in the isolated glycine in spite of the filtration and treatment on a column of the resin.