Stereoselective Reaction of Formaldehyde with *N*-Salicylideneglycyl-L-valinatocopper(II)

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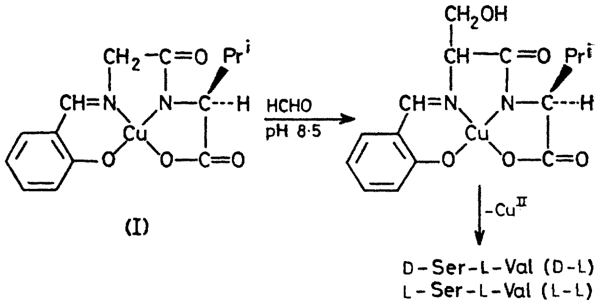
Summary The glycine residue in *N*-salicylideneglycyl-L-valinatocopper(II) reacts with formaldehyde in aqueous solution at pH 8·5 and the resulting complex gives seryl-L-valine containing optically active serine.

The chemical reactivity of glycine (Gly) co-ordinated to Cu^{II} with various aldehydes in alkaline aqueous solutions has been studied by many workers.[1] These reactions give rise to β-hydroxy-α-amino-acids. Similar reactions of glycylglycine[2] and glycylglycylglycine[3] in the presence of Cu^{II} with aldehydes also yield oligopeptides containing *N*-terminal β-hydroxy-amino-acids.

We report here on the sterically controlled reaction of the Gly residue in *N*-salicylideneglycyl-L-valinatocopper(II) (I) with formaldehyde. The new *N*-terminal serine residue in the product, seryl-L-valine (Ser-L-Val), might be expected to be optically active as a result of asymmetric induction owing to the vicinal effect of the isopropyl group of the L-valine residue in (I).



Scheme

A mixture of (I)† ($5{\cdot}2 \times 10^{-5}$ M) and sodium hydrogen carbonate (1×10^{-3} M) was dissolved in water (30 ml) and the precipitated barium hydrogen carbonate was removed by filtration. To this filtrate (pH 8·5) was added aqueous formaldehyde (6×10^{-3} M) and the mixture was heated at 45 and at 80 °C. After completion of the reaction, the resulting complex was decomposed by H$_2$S gas at pH 2 and then the acidic solution was treated with a Dowex-50 cation exchange resin. The reaction products, two diastereoisomers of Ser-L-Val, and unchanged Gly-L-Val were analysed by an amino acid analyser.

The results obtained are shown in the Table. The yields of Ser–L–Val increase with reaction time at 45 °C; however, the optical purities of the D-Ser residue decreased from 11 to 5%. In the reactions at 80 °C, the yields of the

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† Ba$_{0{\cdot}5}$[Cu(Sal=Gly–L-Val)]·3·5 H$_2$O: the violet crystals were prepared from bis-salicylaldehydecopper(II) and Gly–L-Val; C$_{14}$H$_{22}$-Ba$_{0{\cdot}5}$CuN$_2$O$_{7{\cdot}5}$: satisfactory analytical data were obtained.

TABLE. Results of the reaction of (I) with formaldehyde[a]

Temp./°C	Time/h	Ser–L-Val/%		Optical purity of Ser[b]/%	HMSV[c]/%	Recovery of Gly–L-Val/%
		D–L	L–L			
45	12	8·9	7·2	11	—	70·8
	25	17·7	14·4	10	—	26·4
	50	28·8	25·3	6·5	2	18·5
	75	29·3	26·3	5·4	2	10·3
	100	35·6	32·2	5·0	4	8·1
80	1	15·5	13·2	8·0	—	72·0
	2	24·6	22·7	4·0	0·7	51·8
	4	32·7	32·1	0·9	2	23·5
	6	39·1	39·2	0·1	4	13·7
	12	32·0	38·4	9·1	10	1·8
	25	16·0	22·4	16·7	20	trace
	50[d]	1·9	2·9	21	25	trace

[a] Analysis: Yanagimoto amino acid analyser LC-5S, column: 0·8 × 50 cm, resin: cation exchange resin SCX 1001, elution buffer: pH 4·25 citrate buffer. [b] Optical purity = |(D–L − L–L)/(D–L + L–L)| × 100%. [c] α-Hydroxymethylseryl-L-valine. [d] No racemization of the L-Val residue.

products increase up to 78·3% after 6 h and then decrease gradually. The ratio of the two diastereoisomers of Ser–L–Val depends on the reaction time. Excess of D-Ser–L-Val present in the initial stages of the reaction is changed into an excess of L-Ser–L-Val after at least 6 h. The epimerization of the Ser residue from the D- to L-isomer at 80 °C could be explained by a first-order asymmetric transformation. If this is the case, the reaction of (I) with formaldehyde would be kinetically as well as thermodynamically controlled.

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