

A Polarimetric Study of the Reaction of Bis(L-serinato)copper(II) with Formaldehyde

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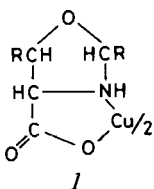
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Polarimetric data have shown that the base-catalyzed reaction of bis(L-serinato)copper(II) with excess formaldehyde proceeds via the initial dissociation of the proton on the nitrogen atom of the amino acid chelate. A bis(oxazolidine)copper(II) complex appears as an intermediate but this species is not detected polarimetrically at 50 °C and above.

Introduction

Before 1971, the base-catalyzed reaction of α -aminoacidato metal(II) complexes with aldehydes had been assumed to proceed *via* the loss of a proton on the α -carbon atom of the amino acid chelate as the first step of the reaction [1-9]. Subsequent attack of the resultant carbanion by the aldehyde supposedly occurred giving rise to an α -hydroxymethyl derivative.

An important discovery was made when Aune *et al.* [8] found that the condensation of glycine with acetaldehyde in the presence of basic copper carbonate yields the bis(oxazolidine)copper(II) complex, 1, (R = CH₃).

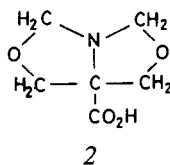


A reaction mechanism which took into account the dissociation of the nitrogen proton was proposed but the first step in the reaction was still considered to be the formation of the α -carbanion.

In 1971, Ichikawa *et al.* [9] postulated a new mechanism for this type of reaction based on the initial dissociation of the proton of the nitrogen atom of the amino acid chelate. However, until recently, there was little evidence for the reaction mechanism.

A preliminary investigation [10] has shown that in the reaction of the optically active bis(L-serinato)-

copper(II) with formaldehyde in alkaline medium to give the optically inactive copper(II) complex of 2, the formation of a mono-N-hydroxymethyl species appears as the first step in the reaction rather than the removal of the hydrogen atom on the α -carbon atom. The present paper gives details of a polarimetric study of the reaction.



Experimental

Reagents

Bis(L-serinato)copper(II) (Cu(L-ser)₂) was prepared according to the method of Van Der Helm [11].

Sodium bicarbonate (Analytical Reagent Grade) and formaldehyde (supplied as a 40% W/V solution) were obtained from May and Baker Pty. Ltd., Australia.

Measurement of Optical Rotation

All optical rotations were measured on a Perkin Elmer Model 141M Spectrophotometer. Measured angles were reproducible to $\pm 0.002^\circ$.

A solution consisting of Cu(L-ser)₂ (0.055 g, 2.0×10^{-4} mol), formaldehyde (3.0×10^{-2} mol) and sodium bicarbonate (0.066 g, 8.0×10^{-4} mol) was made up to 50 cm³ with distilled water (formaldehyde to Cu(L-ser)₂ mole ratio = 150:1) and stored in a flask which was thermostatted at the desired temperature in a water bath. The optical rotations were measured at regular intervals in a 1-dm 6-cm³ quartz cell which had two nipples which provided connections through which water from the external thermostat circulated. The cell was constantly checked for air bubbles or solids which could cause erroneous readings.

The reaction was studied at 40, 50, 60 and 70 °C using in each case the same formaldehyde to Cu(L-ser)₂ mole ratio.

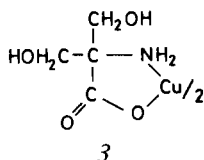
As preliminary investigations have shown that the reaction obeys first order kinetics, the rate constant, k_{obs} , of a reaction was determined by the equation:

$$-\log\left(\frac{|\alpha_t|}{|\alpha_0|}\right) = \frac{k_{\text{obs}} \times t}{2.303} + c$$

where $|\alpha_t|$ is the magnitude of the optical rotation α_t° at time t , $|\alpha_0|$ is the magnitude of the optical rotation α_0° at zero time and c is a constant.

Results and Discussion

If the reaction of Cu(L-ser)₂ with excess formaldehyde in an alkaline medium is contradictorily assumed to proceed *via* the initial formation of a carbanion, the formation of bis(α -hydroxymethyl-(serinato)copper(II)), **3**, will be expected (this will involve an electrophilic attack by formaldehyde on the carbanion).



Since the optical activity of Cu(L-ser)₂ (Molecular rotation $[M]_{366}^{40^\circ} = -66.0$) is attributed to the presence of the asymmetric α -carbon atom, substitution of the methylene proton by a hydroxymethyl group to form **3** will result in the loss of asymmetry of the α -carbon atom with a consequent loss of optical activity. Therefore, it is expected that the initial reaction will result in a less negative rotation for the reaction mixture.

However, polarimetric data for the reaction carried out at 40 °C (Table I) show that the optical rotation becomes more negative during the initial stages of the reaction and this is followed by a slow loss of optical activity. These observations are indicative of the formation of an optically active intermediate species (which exhibits negative optical rotation) which subsequently undergoes racemization. Since a very highly negative reading is never obtained, it seems logical to suggest that during the early stages of the reaction both processes (*i.e.* formation of the intermediate species and racemization) take place simultaneously.

A $\log |\alpha_t|$ versus time plot of the above polarimetric data (Fig. 1) essentially reveals two straight lines, indicating two competing reactions [12]. Initially the process of intermediate formation predominates but after about 7 min, racemization assumes the dominant role.

TABLE I. Optical Rotation of Reaction Mixture at 40 °C.

Time/min	α_t°
1	-0.240
2	-0.248
3	-0.270
4	-0.280
5.5	-0.289
6.5	-0.295
8	-0.292
9.5	-0.293
11	-0.293
13.5	-0.292
15	-0.292
17	-0.291
20	-0.290
23	-0.289
25	-0.288
29.5	-0.287
32	-0.286
37.5	-0.284
44	-0.282
50	-0.280
57	-0.277
66	-0.275
74	-0.272
84	-0.269
92	-0.266
100	-0.264
110	-0.260
120	-0.258
130	-0.255
140 ^a	-0.254

^aOptical reading was not continued after this point as solid formation could be detected.

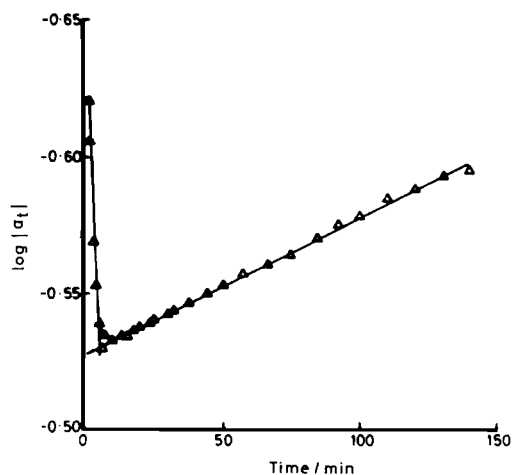
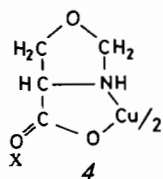


Fig. 1. Plot of $\log |\alpha_t|$ vs. time for base-catalyzed reaction of Cu(L-ser)₂ with excess formaldehyde at 40 °C.

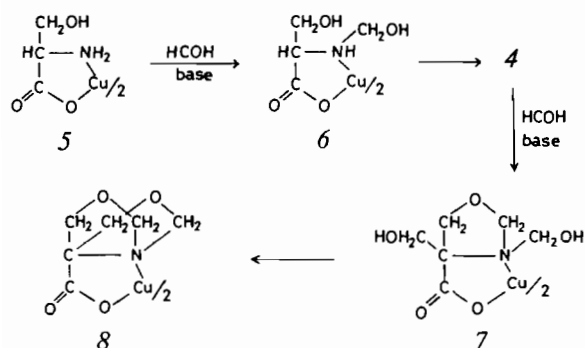
The base-catalyzed reaction of Cu(L-ser)₂ with formaldehyde to form the copper(II) complex of **2** has been shown to give rise to the optically active

intermediate, **4** [10, 13, 14], the formation of which must necessitate the loss of a proton from the amino nitrogen of Cu(L-ser)_2 in preference to that on the α -carbon atom. This initial step is followed by the



electrophilic attack of formaldehyde on the nitrogen to form a mono-N-hydroxymethyl derivative. (Formaldehyde is a strong hydroxymethylating agent and has been used widely as such [15]). Cyclization of the hydroxymethyl groups then occurs by an Aldol condensation reaction to give the intermediate **4**.

The lability of the hydrogen atoms on the amino nitrogen has been demonstrated by the isolation of the complexes $\text{K}[\text{Ni}(\text{NHCH}_2\text{CO}_2)(\text{NH}_2\text{CH}_2\text{CO}_2)]$ and $\text{K}[\text{Ni}(\text{NHCH}_2\text{CO}_2)_2]$ [16] and by an NMR study of similar complexes of cobalt under alkaline conditions [17]. Rate exchange studies of several coordinated amino acids have shown that, in the presence of base, the protons on the α -carbon atom are also labile [17, 18]. Hence, in the present reaction, the formation of **4** is followed by further addition of hydroxymethyl groups on the secondary nitrogen atom and the α -carbon atom (this step leads to loss of optical activity) and subsequent cyclization to give the copper(II) complex of **2**. The mechanism of the overall reaction is depicted schematically as follows:



When the reaction was studied polarimetrically at 50 °C, the rate of formation of the intermediate was increased so much that it was not detected at all. However the rate of loss of optical activity was observed to be significantly enhanced. Further increase in temperature leads to greater increase in the rate of loss of optical activity (Table II).

At a lower formaldehyde to Cu(L-ser)_2 mole ratio (12:1), two competing reactions are again observed [12, 19]. Once again, the process of intermediate formation predominates during the initial stages of the reaction. However, racemization assumes the dominant role more slowly, *i.e.* only after 18 min.

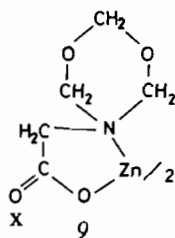
TABLE II. Rate Constants for Base-Catalyzed Reaction of Cu(L-ser)_2 with Excess Formaldehyde.

Temperature/°C	k_1^a/min^{-1}	k_2^b/min^{-1}
40	0.57	1.18×10^{-3}
50	c	2.27×10^{-3}
60	c	6.55×10^{-3}
70	c	21.56×10^{-3}

^a k_1 is the rate constant for the formation of the intermediate species. Calculated as in Ref. 12. ^b k_2 is the rate constant of the racemization reaction. ^cIntermediate formation could not be detected.

The rate constants for the processes of intermediate formation and racemization are 0.41 and $1.04 \times 10^{-3} \text{ min}^{-1}$ respectively (*cf.* Table II), indicating that intermediate formation takes place about 400 times more quickly than racemization.

In the absence of base, the reaction of formaldehyde with bis(glycinato)zinc(II) has been shown to give the zinc(II) complex, **9**, in which the α -carbon atom of the amino acid chelate is unaffected by formaldehyde attack [20]. However, when Cu(L-ser)_2 was reacted with formaldehyde in the absence of base a mixture of blue, green and white solids was obtained and pure products of the reaction have hitherto not been isolated.



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