BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 43 192—195 (1970)

Cyanoethylation of Copper, Nickel, and Palladium Glycinates[*1]

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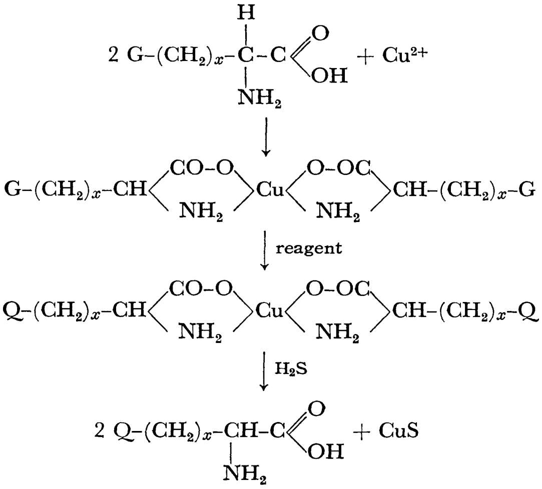
(Received June 20, 1969)

The present authors attempted the cyanoethylation of the methylene group in glycine by means of the reaction between acrylonitrile and copper, nickel, and palladium glycinates. The cyanoethylation of *N*-salicylideneglycinato-aquo copper (II) was also carried out. Four kinds of cyanoethylated complexes were obtained by changing the reaction conditions in the case of copper glycinate. In general, acrylonitrile reacted only with the hydrogen atoms of the amino group. In the case of *N*-salicylidene-glycinato-aquo copper (II), which has no hydrogen atom on the nitrogen atom, however, two methylene hydrogens were cyanoethylated with acrylonitrile.

Masking by coordination has been found to be useful in many of the synthetic reactions of α-amino acid molecules.[1] The general procedure involves coordination with a copper(II) ion to tie up the carboxyl and the α-amino group, leaving the other functional groups free to react with a reagent.



In 1956, Akabori and his co-workers synthesized threonine from copper(II) glycinate and acetaldehyde.[2] In doing so they utilized ligand polarization in addition to masking by coordination. The methylene group in copper glycinate may be more active than in free glycine, and the amino group in the copper chelates may be protected from side reactions by the coordination effect.

Recently Harada and Oh-hashi[3] have synthesized various β-hydroxy-α-amino acids using *N*-salicylideneglycinato-aquo copper(II), while Nakahara *et al.*[4] has prepared several amino acids by the reaction of this complex with various halides. In 1950, Mckinney *et al.*[5] reported the treatment of an aqueous solution of alkali metal salts of glycine with acrylonitrile. This reaction, however, have only a mono-*N*-cyanoethyl compound. In view of the masking effect and ligand polarization mentioned above, the present authors attempted the cyanoethylation of the methylene group in glycine by reactions between acrylonitrile and copper, nickel, and palladium glycinates. For the same reason, the cyanoethylation of *N*-salicylidene-glycinato-aquo copper(II) was carried out.

Experimental

The Cyanoethylation of Copper(II) Glycinate. Copper(II) glycinate was prepared according to the method described by Akabori *et al.*[2] 0.02M of copper glycinate was dissolved in 200 m*l* of aqueous pyridine composed of 150 m*l* of water and 50 m*l* of pyridine. Into this solution, acrylonitrile was stirred drop by drop. After refluxing the mixture, the dark-blue solution was evaporated to precipitate a blue complex, which was then recrystallized from water. Four kinds of cyanoethylated complexes were obtained by changing the reaction conditions, as Tables 1 and 2 show.

Regeneration of the Ligand. The cyanoethylated complex was dissolved in hot water and neutralized with hydrochloric acid. Hydrogen sulfide gas was bubbled through the solution until the blue color had disappeared, and then the precipitated cupric sulfide

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[*1] Presented at the 18th Meeting on Coordination Chemistry of Japan, Kyoto, September, 1968.

[1] M. M. Jones "Ligand Reactivity and Catalysis," Academic Press, New York and London (1968).

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

[3] K. Harada and J. Oh-hashi, *J. Org. Chem.*, **32**, 1103 (1967).

[4] A. Nakahara, S. Nishikawa and J. Mitani, This Bulletin, **40**, 2212 (1967).

[5] L. L. Mckinney, E. H. Uhing, E. A. Setzkorn and J. C. Cowan, *J. Amer. Chem. Soc.*, **72**, 2599 (1950).

Table 1. The cyanoethylation of copper(II) glycinate

Code	Reaction conditions: Temp. (°C)	Reaction conditions: Time (hr)	Reaction conditions: Mole ratio (glycinate/AN)	Appearance of compound	Yield (%)	Infrared absorption max. of ν C≡N(cm^{-1})
1	80	4	1/2	Blue-violet needles	50	2250
2	110	4	1/2	Dark blue needles	50	(disappeared)
3	80	4	1/20	Blue plates	60	2245 and 2265
4	80 110	4 4	1/20	Light blue needles	40	2250

was filtered. The solution was neutralized with aqueous sodium carbonate and evaporated to dryness. The white residue obtained was recrystallized from water.

The Cyanoethylation of Palladium Glycinate. Palladium glycinate was prepared according to the method described by Pinkard *et al.*6)

0.02M of palladium glycinate was dissolved in 80 m*l* of aqueous pyridine composed of 40 m*l* of pyridine and 40 m*l* of water. To this solution, 0.08M acrylonitrile was added, drop by drop. Then the temperature was gradually raised and the reaction was continued for 4—5 hr at the boiling point. After an insoluble matter had been filtered out, the solution was evaporated to obtain a brownish porous material (yield 40%). The product was recrystallized from water.

The infrared spectrum of this complex is shown in Fig. 1, where it is compared with palladium(II) *N*-cyanoethylglycinate. The infrared spectrum of palladium(II) *N*-cyanoethylglycinate shows one NH stretching band at 3230 cm^{-1}, while this complex has no absorption band in this region.

The results of the elementary analysis of the complex (tetracyanoethylglycinate) were as follows:

Found: C, 39.75; H, 4.47; N, 17.66%. Calcd for $C_{16}H_{20}N_6O_4Pd \cdot H_2O$: C, 39.75; H, 4.55; N, 17.36%.

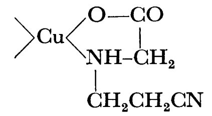
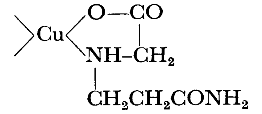
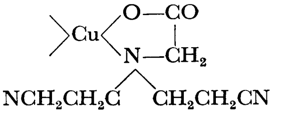
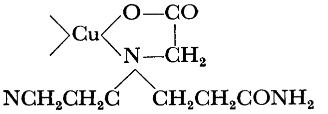
The NMR spectra of this complex were compared with *N*-cyanoethylglycine (CH_2 at $\tau=7.70$ in DMSO-d_6) and palladium(II) *N*-cyanoethylglycinate (CH_2 at $\tau=6.67$ in DMSO-d_6). The signal centered at $\tau=6.40$ in DMSO-d_6 was considered to be due to the methylene group of the glycine part.

The Cyanoethylation of Nickel Glycinate. Nickel glycinate was prepared according to the method described by Sen *et al.*7)

The cyanoethylation was carried out under the same conditions as was the cyanoethylation of palladium glycinate. As this complex could not be recrystallized, it was repeatedly reprecipitated from an ethanol-water system to produce a light blue powder in an 80% yield. The infrared spectrum agreed with that of the authentic nickel *N*-cyanoethylglycinate prepared from cyanoethylglycine and basic nickel carbonate.

The Cyanoethylation of *N*-Salicylideneglycinatoaquo Copper(II): [SAGCu(II)H_2O]. SAGCu(II)H_2O was prepared by the method of Nakahara.8) 0.02M of SAGCu(II)H_2O was dissolved in 50 m*l* of hot pyridine. Into this solution, 0.04M of acrylonitrile was stirred, drop by drop. The temperature was gradually raised to the boiling point of the solvent, after which the reaction was continued for 3—4 hr. After the reaction had been completed, the solution was evaporated to precipitate a dark green complex; this complex was then recrystallized from water to obtain deep green needles in a yield of 35%. The cyanoethylated complex of the *N*-salicylideneglycinato copper(II) coordinated with pyridine was dark brown, while the hydrate was dark green. Slow recrystallization from water yielded deep green needles forming a hexa-hydrate complex. This hexa-hydrated complex lost water to the monohydrated complex when dried under reduced pressure

Table 2. The elementary analyses of copper(II) cyanoethyl glycinates

Code	Proposed structures	Elementary analyses
1		Calcd for $C_{10}H_{14}N_4O_4Cu.H_2O$: C, 35.77; H, 4.80; N, 16.69; Cu, 18.92%. Found: C, 35.93; H, 4.83; N, 16.98; Cu, 19.13%.
2		Calcd for $C_5H_{10}N_2O_3$:* C, 41.10; H, 6.85; N, 19.18%. Found: C, 40.99; H, 6.97; N, 19.65%.
3		Calcd for $C_{16}H_{20}N_6O_4Cu.H_2O$: C, 43.49; H, 4.98; N, 19.02; Cu, 14.38%. Found: C, 43.24; H, 5.08; N, 18.87; Cu, 14.50%.
4		Calcd for $C_{16}H_{24}N_6O_6Cu.H_2O$: C, 42.09; H, 5.44; N, 17.59; Cu, 13.30%. Found: C, 41.89; H, 5.46; N, 17.40; Cu, 13.20%.

* Organic ligand only.

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6) F. W. Pinkard, E. Sharratt, W. Wardlaw and E. G. Cox, *J. Chem. Soc.*, **1934**, 1012.

7) D. N. Sen, S. Mizushima, C. Curran and J. V. Quagliano, *J. Amer. Chem. Soc.*, **77**, 211 (1955).

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

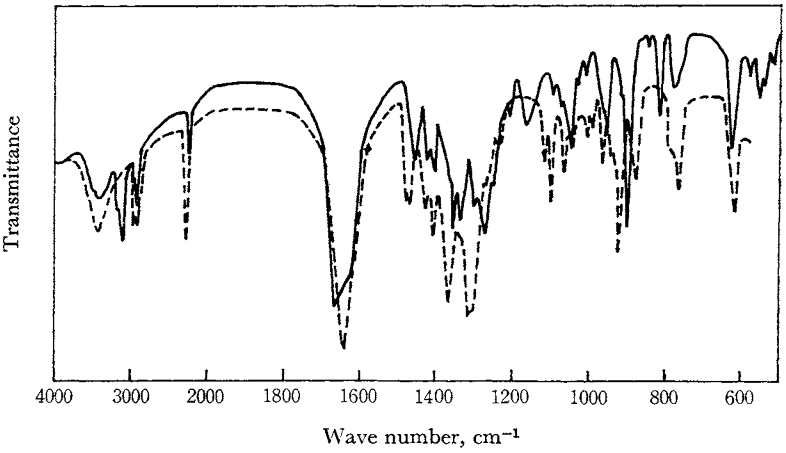

Fig. 1. The IR spectra of palladium(II) cyanoethylglycinates.
—— Paladium(II) *N*-cyanoethylglycinate
------ Palladium(II) tetracyanoethylglycinate

at 80—90°C for 5 hr.

The elementary analysis of the mono-hydrate form gave the following results:

Found: C, 49.38; H, 4.20; N, 11.44; Cu, 17.32%. Calcd for $C_{15}H_{15}N_3O_4Cu$: C, 49.38; H, 4.14; N, 11.52; Cu, 17.42%.

The Synthesis of *N*-Cyanoethylglycine. *N*-Cyanoethylglycine was prepared according to the method of Mckinney *et al.*[5]

Copper *N*-Cyanoethylglycinate. *N*-Cyanoethylglycine was dissolved in hot water, and then basic copper carbonate was added to precipitate *N*-cyanoethylglycine copper. The product was recrystallized from water to produce blue violet needles.

Palladium *N*-Cyanoethylglycinate. *N*-Cyanoethylglycine was dissolved in water, and then $K_2(PdCl_4)$ was added. After standing for 24 hr, the solution was neutralized with aqueous sodium hydroxide. The separated yellow solid was recrystallized from water to produce yellow needles.

Nickel *N*-Cyanoethylglycinate. The basic nickel carbonate was added in small portions to a hot aqueous solution of *N*-cyanoethylglycine to produce nickel *N*-cyanoethylglycinate. As the complex could not be recrystallized, purification was carried out by repeated reprecipitation from an ethanol-water system until a light blue, deliquescent powder was obtained.

Results and Discussion

The infrared spectrum (Fig. 2) of the (code 1) complex is in good agreement with the spectrum of the copper *N*-cyanoethylglycinate.

In the (code 2) complex the cyano group is hydrolyzed to the acid amide form (NH stretching at 3400 cm⁻¹, NH_2 deformation at 1620 cm⁻¹). The

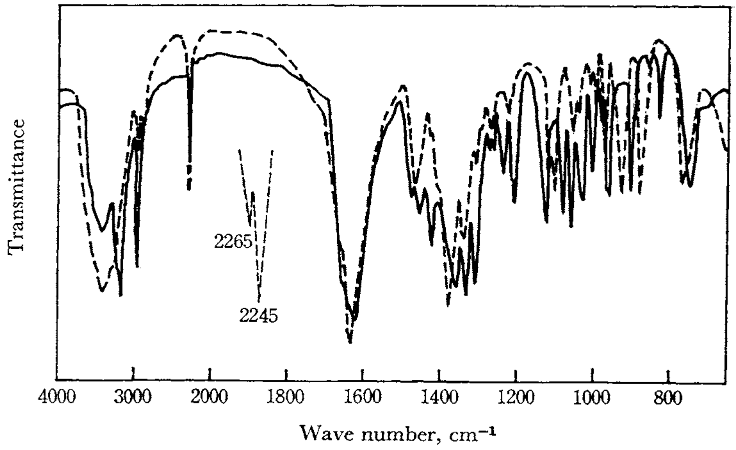

Fig. 2. The IR spectra of copper(II) cyanoethylglycinates.
—— Copper(II) *N*-cyanoethylglycinate (code 1)
------ Copper(II) tetracyanoethylglycinate (code 3)

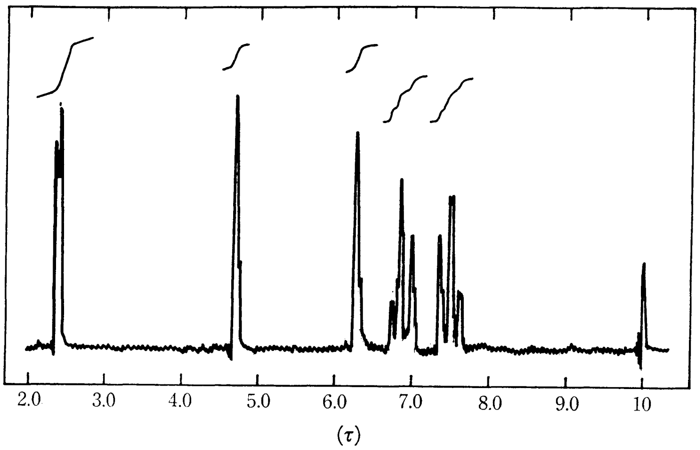

Fig. 3. The NMR spectrum of *N*,*N*-bis(cyanoethyl)glycine *p*-bromophenacyl ester (60 Mc, in $CDCl_3$)

appearance of two absorption bands due to CN stretching vibrations near 2250 cm^{-1} and the disappearance of the NH stretching vibration at 3200 cm^{-1} of the complex (code 3) suggest that two cyanoethyl groups were introduced to the amino nitrogen atom. From the results of the elementary analysis, the complex may be considered to be hydrate. As it was difficult to purify the complex, the copper was precipitated as copper sulfide and the organic ligand was isolated as the *p*-bromophenacyl derivative (light yellow needles, mp 63°C). The NMR spectrum of the *p*-bromophenacyl ester (see Fig. 3), obtained using chloroform-d as the solvent, that the acid part of the ester is *N*,*N*-bis(cyanoethyl)-glycine (CN stretching at 2250 cm^{-1}, CO stretching at 1733 and 1697 cm^{-1}).

The (code 4) complex was obtained by raising the reaction temperature to 110°C. On the basis of a comparison of the infrared spectra, it may be supposed that one of the cyanoethyl groups introduced at first was hydrolyzed to the amide group (one CN streching band and a new NH stretching band appeared).

As the SAGCu(II)·H_2O had no active hydrogen atom on the nitrogen atom, the two active hydrogen atoms of the glycine methylene group were cyanoethylated with acrylonitrile.

In the case of copper, palladium, and nickel glycinate, the amino group was supposed to be protected by coordination and cyanoethylation should have occurred at the methylene group of the glycine part. However, acrylonitrile reacted with the hydrogen atoms of the amino group. From the copper glycinate, a tetracyanoethyl complex was obtained by the additonal cyanoethylation of the dicyanoethylated compound, but no higher cyanoethylation occurred. The results for the nickel glycinate were the same as for the cyanoethylation of glycine itself, metal complexing had no effect.

In comparison to nickel glycinate, the palladium glycinate was easily cyanoethylated to the tetracyanoethyl compound. In this case, the cyanoethyl group was stable and was not hydrolyzed by alkali. As we would expect two cyanoethyl groups to be replaced on the free glycine, the reaction was repeatedly attempted by changing the amount of alkali and acrylonitrile. However, only the mono-*N*-cyanoethyl compound was obtained.

It is of interest that though only one of the amino hydrogens in free glycine was cyanoethylated in alkali, the two hydrogen atoms were replaced when coordinating with a transition metal ion (Cu^{2+}, Pd^{2+}, but not Ni^{2+}).