BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 43 505—509 (1970)

Asymmetric Reactions. IV. An Attempted Asymmetric Reduction by a Solution of $[Co(CN)_5]^{3-}$ and Optically Active α-Amino Acid, and Its Reactive Species[1]

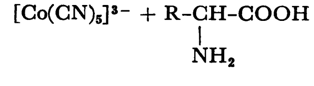
Yoshiaki OHGO, Seiji TAKEUCHI and Juji YOSHIMURA

Laboratory of Chemistry for Natural Products, Faculty of Science, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo

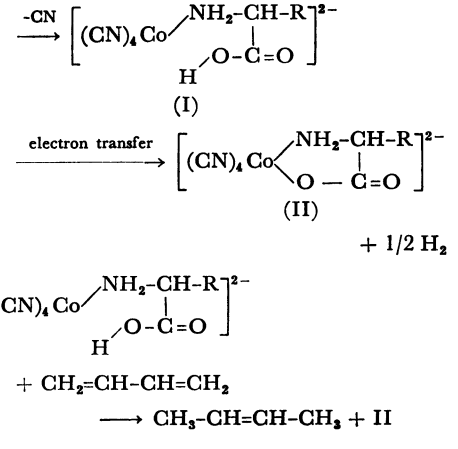
(Received August 1, 1969)

Reduction of various olefines by a solution of pentacyanocobaltate and glycine or optically active α-amino acid was studied. There is no essential difference between the reactivity of $[Co(CN)_5H]^{3-}$ to olefines and that of the solution of pentacyanocobaltate and α-amino acid. Atropic acid was reduced with the solution containing optically active α-amino acid (L-isoleucine) to give slightly optically active hydratropic acid. It was found that the main reactive species in the solution of $[Co(CN)_5]^{3-}$ and α-amino acid was $[Co(CN)_5H]^{3-}$ (this might be the reason for the asymmetric reduction not taking place effectively), and the reversible change between $[Co(CN)_5]^{3-}$ and $[Co(CN)_5H]^{3-}$ was observed depending on the pH of the solution.

It has been reported by Kwiatek *et al.* that many olefines are hydrogenated catalytically by $[Co(CN)_5]^{3-}$,[2] and recently by Suzuki and Kwan that an aqueous equimolar solution of $[Co(CN)_5]^{3-}$ and α-amino acids or other acids reduces dienes to monoenes by the following mechanism.[3]



$$[Co(CN)_5]^{3-} + \underset{NH_2}{R\text{-}CH}\text{-}COOH$$



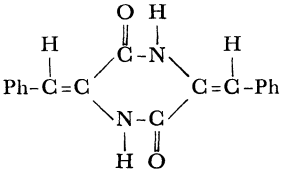
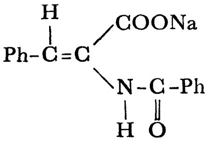
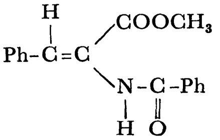
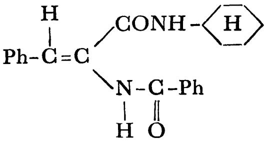
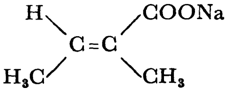
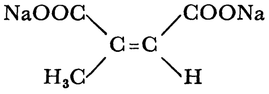
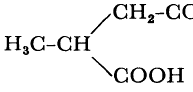
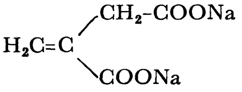
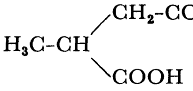
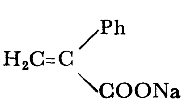
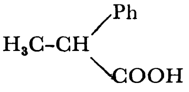
---

[1] Asymmetric Reaction. III. This Bulletin, **42**, 2957 (1969).

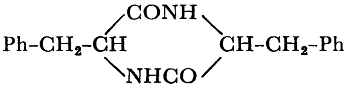
[2] J. Kwiatek, I. L. Mador and J. K. Seyler, *J. Amer. Chem. Soc.*, **84**, 304 (1962).

[3] T. Suzuki and T. Kwan, *Nippon Kagaku Zasshi*, **88**, 395 (1967); *ibid.*, **88**, 400 (1967).

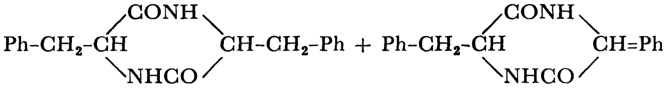
Table 1. Hydrogenation of monoenes

Substrate	Solvent	Complex	Product and yield
	Pyridine and water	$[Co(CN)_5H]^{3-}$ (a)	(c)
		Co-Gly (b)	(d)
	Water	$[Co(CN)_5H]^{3-}$ Co-Gly	(e)
	Pyridine and water	$[Co(CN)_5H]^{3-}$ Co-Gly	(e)
	Ethanol and water	$[Co(CN)_5H]^{3-}$ Co-Gly	(e)
	Water	$[Co(CN)_5H]^{3-}$ Co-Gly	(e)
	Water	Co-Gly	 15%
 (f)	Water	Co-Gly	 70%
 (f)	Water	Co-Gly	 Quantitatively
		Co-L-Isol (b)	(g)

(a) Reaction time of catalytic hydrogenation by $[Co(CN)_5]^{3-}$ was 4 to 5 days at room temperature.
(b) Co-Gly or Co-L-Isol represents the solution of $[Co(CN)_5]^{3-}$ and glycine or L-isoleucine. Reaction time was 1 day at room temperature.
(c) Both double bonds were reduced quantitatively.



(d) Mixture of fully and partially hydrogenated products was obtained.



(e) The starting material was recorded quantitatively.
(f) These material were known to be reduced by $[Co(CN)_5H]^{3-}$.[2]
(g) Raw product had $[\alpha]_D$ +0.2° but distillate had slightly negative rotation which was converted to acylthiourea derivative ($[\alpha]_{436}$ −0.2°).

They suggested that dienes are reduced to monoenes *via* coordination to the cobalt (Co^{II}) of the intermediate complex (I).

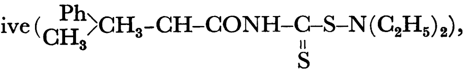
If monoenes which form asymmetric carbon after reduction can be reduced with the solution of $[Co(CN)_5]^{3-}$ and optically active α-amino acid by the similar mechanism, the coordination of monoenes to the intermediate complex (I) will be affected stereospecifically by the optically active α-amino acid, and an asymmetric reduction will take place.

This paper gives a comparison of the reactivity of a solution of $[Co(CN)_5]^{3-}$ and α-amino acid with that of $[Co(CN)_5H]^{3-}$ to monoenes, and a discussion on whether asymmetric reduction takes place.

Results and Discussion

The results of hydrogenation with a solution of $[Co(CN)_5]^{3-}$ and glycine are summarized in Table 1 in comparison with that of $[Co(CN)_5H]^{3-}$.

As shown in Table 1, the reactivities of $[Co(CN)_5H]^{3-}$ and Co-Gly are similar to each other, and atropic acid is reduced to hydratropic acid quantitatively.

Experiments were carried out to see whether an asymmetric reduction would occur, using atropic acid as substrate and L-isoleucine as an optically active α-amino acid (in an aqueous solution of $[Co(CN)_5{}^{3-}]$). Atropic acid was reduced by this solution quantitatively to give crude hydratropic acid having slightly positive rotation ($[\alpha]_D + 0.2°$), but the optical acivity of hydratropic acid purified by distillation changed to a very small negative value. The acylthiourea derivative of the hydratropic acid was synthesized and the ORD spectrum4) was measured in order to identify the substance having slightly negative rotation with hydratropic acid. However, because of the very low optical activity ($[\alpha]_{436} - 0.2°$) of the purified acylthiourea derivative ( $\left(\begin{smallmatrix}Ph\\CH_3\end{smallmatrix}\!\!>\!CH_3\text{-}CH\text{-}CONH\text{-}\underset{\underset{S}{\|}}{C}\text{-}S\text{-}N(C_2H_5)_2\right)$, identification of the optically active material by ORD spectrum failed. Nevertheless, we could not consider it due to contaminant, because the sample was extremely pure. If this optical activity is that of acylthiourea derivative of hydratropic acid, the optical yield is 0.1% (acylthiourea derivative of optically pure hydratropic acid has $[\alpha]_{436} - 200°$).

The fact that the reactivities of $[Co(CN)_5H]^{3-}$ and Co-Gly are similar to each other and the optical yield is very small lets us deduce that the intermediate complex such as I to which α-amino acid coordinates directly may not play an essential role in this hydrogenation reaction. On the other hand, it is known that dienes are reduced to monoenes by a solution of $[Co(CN)_5]^{3-}$ and organic or inorganic acids3) instead of α-amino acids, and the formation of $[Co(CN)_5H]^{3-}$ by aging of an aqueous solution of $[Co(CN)_5]^{3-}$ is promoted by cesium chloride and other salts.5) Thus, it was deduced that α-amino acid might promote the aging reaction as cesium chloride. As metal hydride signal of $[Co(CN)_5H]^{3-}$ was known to be observed at high magnetic field of the nuclear magnetic resonance spectrum,6) the NMR spectrum of Co-Gly was measured. The results are shown in Table 2 and Fig. 1.

Fig. 1. NMR spectrum.

Metal hydride signal was observed at high magnetic field and the chemical shift of the hydride formed in Co-Gly was almost the same as that of $[Co(CN)_5H]^{3-}$, and the amount of the hydride did not depend on the amount of α-amino acid (glycine). Thus, this hydride is considered to be $[Co(CN)_5H]^{3-}$ and the main reactive species in the hydrogenation with the aqueous solution of $[Co(CN)_5]^{3-}$ and glycine, *i.e.* α-amino acid. It was also found that the pH of the solution was an important factor in the formation of $[Co(CN)_5H]^{3-}$ from the following experiment. The color of the solution of $[Co(CN)_5]^{3-}$ changes from green to yellow and *vice versa* depnending on the pH:7)

$$\underset{\text{green}}{[Co(CN)_5]^{3-}} \underset{\text{pH increase on addition of NaOH}}{\overset{\text{pH decrease on addition of glycine}}{\rightleftarrows}} \text{yellow}$$

The spectrophotometric change of an aqueous solution of $[Co(CN)_5]^{3-}$ and glycine is shown in Fig. 2. Absorption of $[Co(CN)_5]^{3-}$ at 970 mμ8) decreased gradually on standing for 16 hr at room temperature, and increased on addition of an

---

4) C. Djerassi, K. Undheim and Anne-Marie Weidler, *Acta Chem. Scand.*, **16**, 1147 (1962).

5) N. K. King and M. E. Winfield, *J. Amer. Chem. Soc.*, **80**, 2060 (1958).

6) W. P. Griffith and G. Wilkinson, *J. Chem. Soc.*, **1959**, 2757.

7) The pH of a solution of $Co(CN)_5{}^{-3}$ prepared by dissolving $CoCl_2 \cdot 6H_2O$ (3.18 g) and KCN (4.5 g) in H_2O (26 m*l*) was about 13. On addition of molar equivalent glycine the pH decreased to 9.5.

8) N. K. King and M. E. Winfield, *J. Amer. Chem. Soc.*, **83**, 3366 (1961).

TABLE 2. NMR SPECTRA OF HYDRIDES

Reaction system	Time (min)	Spacing between chemical shift of hydride and sodium acetate	Co-H/Co
$[Co(CN)_5]^{3-} + H_2O$	20	14.1 ppm	0.18
$[Co(CN)_5]^{3-}$ + 1/2 glycine	24	14.2 ppm	0.50
$[Co(CN)_5]^{3-}$ + glycine	20	14.4 ppm	0.45

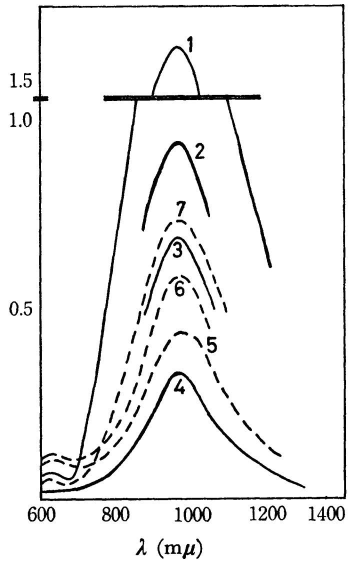
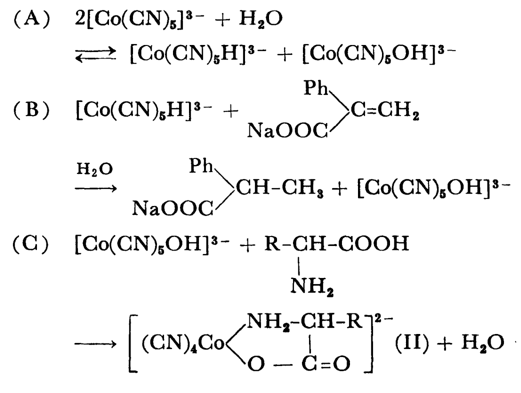


Fig. 2. Spectrophotometric change of a solution $[Co(CN)_5]^{3-}$ and glycine.

—— 1 10 min after preparation of the solution (0.038 M; 0.38 g of $CoCl_2 \cdot 6H_2O$ in 35 ml of water)
—— 2 50 min
—— 3 90 min
—— 4 16 hr aqueous NaOH solution was added

- - - 5 10 min after the addition of NaOH solution
- - - 6 3 hr
- - - 7 19 hr

aqueous sodium hydroxide. From this it is apparent that there is an equillibrium $[Co(CN)_5]^{3-} \rightleftarrows [Co(CN)_5H]^{3-}$ in the solution of $[Co(CN)_5]^{3-}$ and glycine, and the equillibrium shifts to the right with decrease of pH and to the left by the addition of alkali.[9] Consequently, the following reactions are considered to occur mainly in the hydrogenation with the solution of $[Co(CN)_5]^{3-}$ and α-amino acid.



$$\text{(A)}\quad 2[Co(CN)_5]^{3-} + H_2O \rightleftarrows [Co(CN)_5H]^{3-} + [Co(CN)_5OH]^{3-}$$

$$\text{(B)}\quad [Co(CN)_5H]^{3-} + (Ph)(NaOOC)C{=}CH_2 \xrightarrow{H_2O} (Ph)(NaOOC)CH{-}CH_3 + [Co(CN)_5OH]^{3-}$$

$$\text{(C)}\quad [Co(CN)_5OH]^{3-} + R{-}CH(NH_2){-}COOH \longrightarrow \left[(CN)_4Co\langle{}^{NH_2-CH-R}_{O-C=O}\right]^{2-}\ \text{(II)} + H_2O$$

The reactive species $[Co(CN)_5H]^{3-}$ formed in the reaction (A) which is promoted by α-amino acid reduces olefine to saturated compound in the reaction (B). $[Co(CN)_5OH]^{3-}$ formed incidentally with $[Co(CN)_5H]^{3-}$ reacts with α-amino acid to give the complex(II) isolated by Suzuki and Kwan.[3)]

Thus, the asymmetric grouping of the optically active amino acid can not effectively control the coordination of olefines to the metal of the reactive species.

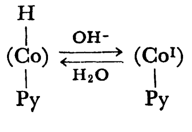
Experimental

Reduction of Monoenes by a Solution of $[Co(CN)_5]^{3-}$ and Glycine, or $[Co(CN)_5H]^{3-}$. The solution of $[Co(CN)_5]^{3-}$ and glycine was prepared by Kwan's method.[3)] In the case of $[Co(CN)_5H]^{3-}$, 1/2 mole of the substrate was used to 1 mole of cobalt chloride, and 1/3 mole in the case of the solution of $[Co(CN)_5]^{3-}$ and glycine. Water-insoluble substrates were reacted in the mixture of water and organic solvents (see Table 1), and recovered by the addition of a large amount of water. Carboxylic acids were used as sodium salts, and the products were extracted with ether after acidification with hydrochloric acid.

Reduction of Atropic Acid by a Solution of $[Co(CN)_5]^{3-}$ and L-Isoleucine. To a solution of 9.4 g of cobalt chloride (0.04 mol) in 100 ml water, 13.0 g of potassium cyanide (0.20 mol) in 40 ml of water was added. When the solution became homogeneous and dark green, 5.2 g of L-isoleucine (0.04 mol) dissolved in 200 ml of water was added. The color of the solution turned to yellow within 10 min and 2.0 g of sodium atropate (0.013 mol) in 40 ml of water was then added. All the procedure was carried out under nitrogen atmosphere. After 1 day the solution was acidified with

---

[9] An analogous phenomenon was observed in formation of alkylcobaloximes. Near neutral medium only α-substitutedcobaloximes was formed and alkaline solution addition in the β-position took place. In order to explain the differences Schranzer and Windgassen postulated an pH-dependent equilibrium. G. N. Schrauzer and R. J. Windgassen, *J. Amer. Chem. Soc.*, **89**, 1999 (1967).



$$\overset{H}{\underset{Py}{(Co)}} \underset{H_2O}{\overset{OH^-}{\rightleftarrows}} \underset{Py}{(Co^I)}$$

hydrochloric acid and extracted with ether and dried with calcium chloride. The ether solution was evaporated and 1.7 g of residual oil was obtained. This was found to be identical with the authentic hydratropic acid in IR spectrum. The optical activity of the product was slightly positive ($[\alpha]_D$ +0.2°, *c* 10, ethanol), and no contamination of L-isoleucine in the product was detected by paper chromatography, using *n*-butanol saturated with water as a developing solvent and ninhydrin or BTB as coloring reagents (R_f: L-isoleucine 0.31, hydratropic acid 0.89, product 0.88). However, the optical activity of the material which was obtained by distillation of the product showed a slightly negative rotation. The main fraction was distilled at 82—83°C/0.05 mmHg and 1.45 g of purified material was obtained. The acylthiourea derivative of the purified hydratropic acid was synthesized[4] and the crude crystals obtained was recrystallized twice from *n*-hexane and about 0.5 g of crystals was obtained, mp 106—7°C. The silica-gel TLC showed one spot (developing solvent; ethyl acetate: pyridine= 1 : 1). Elemental analysis was as follows, Found: C, 63.94; H, 7.54; N, 10.25; S, 12.28%. Calcd for $C_{14}H_{20}N_2OS$: C, 63.61; H, 7.63; N, 10.60; S, 12.13%. The specific rotation was $[\alpha]_{436}$ −0.2° (*c* 12, benzene) and the optical yield was only 0.1%.

Measurement of NMR Spectra. The NMR spectrum was measured with a JNM-4H-100 Spectrometer (Japan Electron Optics Laboratory Co., Ltd.) at 100 Mc/sec. The concentration of the solution of $[Co(CN)_5]^{3-}$ and glycine was 0.5 M (0.18 g) of $CoCl_2 \cdot 6H_2O$ in 25 m*l* of water). As internal standard sodium acetate was used and the quantity of the hydride formed in the solution was estimated from the ratio of the integration of the hydride signal to that of sodium acetate. The average value taken from integration repeated a few times was used.

The authors are grateful to Ajinomoto Co., Inc., for the gift of amino acids, to Dr. Khoko Tanabe for the measurement of ORD spectra and to Mr. Kiyoshi Fukukawa for the measurement of NMR spectra.