Catalytic Hydration of Pyridinecarbonitriles in the Presence of $[Cu(en)_2]Cl_2 \cdot 2H_2O$ and $CuCl_2 \cdot 2H_2O$

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(Received December 25, 1973)

Spectrophotometric studies on the catalytic hydration of 2-pyridinecarbonitrile derivatives in the presence of $[Cu(en)_2]Cl_2 \cdot 2H_2O$ and $CuCl_2 \cdot 2H_2O$ under nearly neutral conditions revealed that the products are their amides. In some cases, the yields were calculated from the weight of amides obtained. The hydration of the nitrile group was influenced by electronic and steric effects. Selective hydration of the nitrile group in α-position was observed in the case of dinitrile. The selectivity was applied to hydrolysis of nitriles to carboxylic acids.

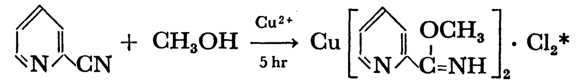
It has been reported[1)] that 2-pyridinecarbonitrile is easily hydrated to 2-pyridinecarboxamide in the presence of various complexes of Cu(II), Ni(II), and Co(II) in neutral solution at 60 °C. The nitrile group in α-position is presumed to interact with metal ions coordinated to the ring nitrogen and the activated nitrile group undergoes hydration to afford the free amide through ligand exchange. In order to elucidate the phenomenon, we studied the hydration of some 2-pyridinecarbonitrile derivatives (Table 1) in the presence of $[Cu(en)_2]Cl_2 \cdot 2H_2O$ and $CuCl_2 \cdot 2H_2O$. The results are given in this paper together with a discussion from theoretical and synthetic viewpoints.

Aqueous solutions of the nitriles containing the catalysts were kept at 60 °C (or 80 °C) for 5 hr in a sealed glass tube. The reactions were followed spectrophotometrically[1)] and the yields of the reaction products were calculated.

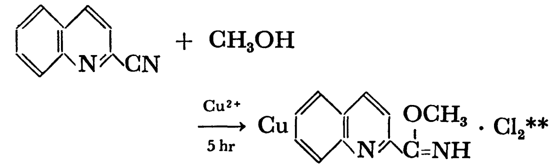
Results and Discussion

The reaction conditions and main results are summarized in Tables 2 and 3. The UV analytical method could not be applied to compound III. No reaction occurred in IV and V at 60 °C even with a large amount of catalyst and an elongated reaction time of 20 hr. They were thus treated at 80 °C and the yields were calculated from the weight of free amides obtained (Table 3). I was a little more reactive than II as observed in the reactions with a large amount of the catalyst(Table 2). It was assumed that the higher basicity of I than II due to the methyl group made the pyridine ring easy to undergo coordination. On the other hand, II was more reactive than III presumably by electronic effect of the cyano group in 4-position(Table 3). The low reactivity of IV and V was attributed to steric hindrance in the coordination to the catalysts. In their Cu(II) ion catalyzed reactions, the amide complexes were not obtained, presumably for the same reason. In order to examine the reactivity of V, it was refluxed 5 hr with both catalysts and about 10% of the amide was obtained. We tried the addition of methanol to II and V in the presence of Cu(II) ion under reflux as follows:

(II)

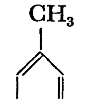
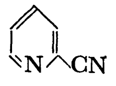
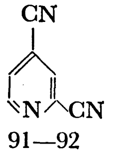
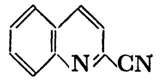
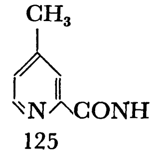
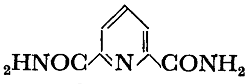
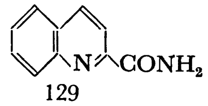


(V)



The reaction product from V was *O*-methyl-2-quinolinecarboximidate copper(II) chloride instead of bis-coordinated ligand complex. This also suggests a

TABLE 1. 2-PYRIDINECARBONITRILE DERIVATIVES AND THEIR HYDRATION PRODUCTS (AMIDES)

	I	II	III	IV	V
Samples mp °C	 88—89	 28—29	 91—92	 126—127	 93—94
Amides mp °C	 125	 105	 255 (dec)	 300 (dec)	 129

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* This complex was also prepared from bis(2-pyridinecarbonitrile)copper(II) chloride in methanol on addition of triethylamine: S. Suzuki, M. Nakahara, and K. Watanabe, This Bulletin, **47**, 645 (1974).

** New compound: Found: C, 41.33; H, 3.15; N, 8.70; Cl, 22.37% Calcd: C, 40.88; H, 3.12; N, 8.73; Cl, 22.15%.

TABLE 2. CATALYTIC HYDRATION OF NITRILES. I
Reactivities of nitriles (%): spectrophotometry, sample: 5×10^{-3} mol/l, reaction temp.: 60 °C, reaction time: 5 hr

Catalyst	mol/sample	pH	I	II	IV	V
$[Cu(en)_2]\cdot Cl_2\cdot 2H_2O$	1/8	7.6	20	20	0	0
$[Cu(en)_2]\cdot Cl_2\cdot 2H_2O$	2	7.6	97	51	0	0
$CuCl_2\cdot 2H_2O$	3	4—5	100	95	0	0

Calculated from the remaining starting materials, separated by means of ion exchange resin and analyzed by UV method.

TABLE 3. CATALYTIC HYDRATION OF NITRILES. II
(yields of free amides %)
sample: 1.6×10^{-3} mol/l, reaction temp.: 80 °C, reaction time: 5 hr

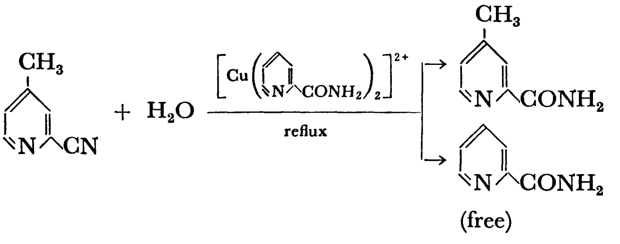
Catalyst	mol/sample	pH	II	III[a)]	IV[b)]	V
$[Cu(en)_2]Cl_2\cdot 2H_2O$	1/8	8	54	46	24	+
$CuCl_2\cdot 2H_2O$	1/8	4—5	49	32	2	+

a) Product: 4-cyano-2-pyridinecarboxamide. b) Product: 2,6-pyridinedicarboxamide.

steric hindrance in the coordination of the bulky ligand.

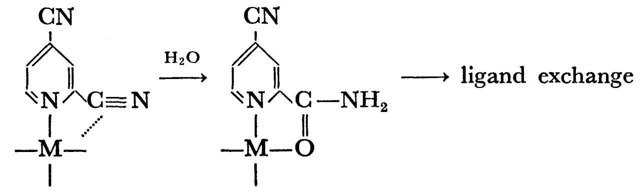
Thus, the electronic and steric effects of substituents were observed apparently in these catalytic hydration. The reactivity of compounds I–V was in the order: I>II>III>IV>V. This is attributed to their coordination ability caused by an electronic or steric factor which would also influence the mode of the reaction of IV.

In the reaction with $[Cu(en)_2]Cl_2\cdot 2H_2O$, all the reaction products, amides, were obtained in free form (Table 3). On the other hand, in the reaction with Cu(II) ion, I and II afforded stable copper(II) complexes of their amides. Thus, the net yield of amide from II should be estimated to be greater than 49% (free amide). However, III afforded scarcely any copper(II) complex of the amide, although free amide was obtained to some extent. The amide complexes obtained from I and II were found to have excellent catalytic ability. We examined the ligand exchange of the complex catalysts and found the formation of mixed amides in free form as follows:



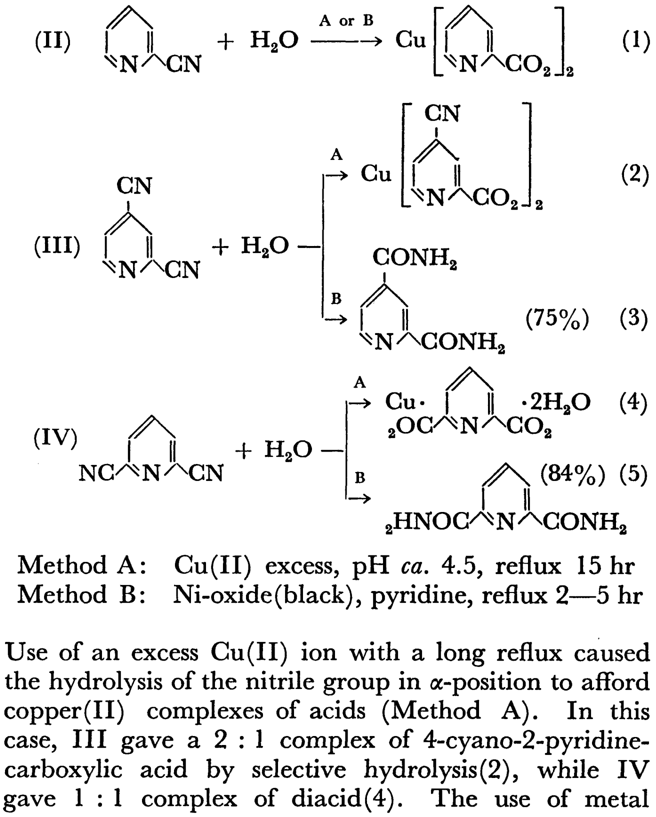
This suggested a catalytic function of labile metal complexes through ligand exchange.1)

Remarkable selective hydration of the nitrile group in α-position was observed in dinitrile III to give 4-cyano-2-pyridinecarboxamide (Tables 1 and 3). In contrast, no selectivity was observed in the reaction with dinitrile IV. This indicates a particular interaction of metal ion with nitrile group in α-position.



Such selectivity was not observed in the reaction in the presence of catalysts such as mineral acids, alkali, metals, or metal oxides.

For the synthetic application of this catalytic hydration, we tried selective hydrolysis of III with Cu(II) ion and nickel oxide catalysts under neutral conditions. For the sake of comparison, reactions of II and IV were also examined. It was found that selective hydrolysis of dinitrile III occurrs with Cu(II) ion, and simultaneous hydration occurrs in the presence of Ni- (or Cu) oxide catalyst. The results are summarized as follows:



Method A: Cu(II) excess, pH *ca.* 4.5, reflux 15 hr
Method B: Ni-oxide(black), pyridine, reflux 2—5 hr

Use of an excess Cu(II) ion with a long reflux caused the hydrolysis of the nitrile group in α-position to afford copper(II) complexes of acids (Method A). In this case, III gave a 2 : 1 complex of 4-cyano-2-pyridinecarboxylic acid by selective hydrolysis(2), while IV gave 1 : 1 complex of diacid(4). The use of metal oxides2) or metal3) catalysts is excellent for the purpose of synthesizing amides from nitriles under neutral conditions, but the method lacks selectivity. Thus, III and IV gave free diamides in good yields(3 and 5, respectively) in contrast to the metal ion catalyzed reactions. II undergoes hydrolysis with metal oxide to afford copper(II) complex of 2-pyridinecarboxylic acid as in the case of Cu(II) ion catalyzed reactions(1). Although 4-carbamoyl-2-pyridinecarboxylic acid complex was expected, no selective hydrolysis of α-nitrile group in III was observed.

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Materials. 4-Methyl-2-pyridinecarbonitrile was prepared4) from 4-methylpyridine, recrystallized from ethanol mp 88—89 °C. Commercial 2-pyridinecarbonitrile was recrystallized from ether, mp 28—29 °C. 2,4-Pyridinedicarbonitrile: 4-pyridinecarbonitrile-*N*-oxide was prepared[5] from 4-pyridinecarbonitrile and hydrogen peroxide solution, mp 206—215 °C. This was heated with dimethylsufonic acid and potassium cyanide to give 2,4-pyridinedicarbonitrile.[6] The crude dinitrile was purified by means of column chromatography(alumina) with benzene, mp 91—92 °C. 2,6-Pyridinedicarbonitrile was prepared[5,6] from 2-pyridinecarbonitrile by a similar method, mp 126—127 °C. 2-Quinolinecarbonitrile was prepared[7] from quinoline and recrystallized from methanol, mp 93—94 °C. $[Cu(en)_2]Cl_2 \cdot 2H_2O$ was prepared and recrystallized several times. Commercial extra-pure $CuCl_2 \cdot 2H_2O$ was used. Nickel oxide (black) was prepared by the decomposition of nickel carbonate at 250—300 °C.

Spectrophotometry (Table 2). In a sealed glass tube was placed 10 ml of a solution containing nitrile (5×10^{-3} mol/l) and catalyst, and the reaction mixture was kept at 60 °C for 5 hr. After the reaction, an aliquot quantity of the reaction mixture was poured into a column packed with ion exchange resin (Dowex 50, 2 × H-type) and developed with water (resin in column: diameter 1 cm, length 3 cm). The elute was a solution of unreacted pure nitrile which was separated completely from the reaction mixture. The decrease in the amount of starting material was followed spectrophotometrically (I: 274 nm, II: 265 nm, IV: 225 nm, V: 303 nm), and the yield of the reaction products, amides, was calculated. Yield(%) = 100 − unreacted nitrile. The separation was examined by the blank test. In the case of V, a water–ethanol mixture(2 : 1) was used for development.

Synthetic Method (Table 3). In a sealed flask was placed 50 ml of a solution containing nitrile (7.8×10^{-3} mol) and catalyst(9.7×10^{-4} mol) and the reaction mixture was kept at 80 °C for 5 hr. In the cases of III, IV, and V, deposition of white crystals was observed during the course of the reaction. After the reaction, the mixture was cooled and the precipitate was filtered off, dried and washed with benzene. The amide crystals thus obtained were recrystallized from acetic acid.

4-Cyano-2-pyridinecarboxamide. Mp 255—256 °C(dec), lit,[5] 256—258 °C. IR: νN–H 3410, νC≡N 2245, νC=O 1700 cm^{-1}, (KBr). Found: C, 56.87; H, 3.37; N, 28.38%. Calcd for $C_7H_5N_3O$: C, 57.14; H, 3.43; N, 28.56 %.

2,6-Pyridindiecarboxamide. Mp 298—302 °C(dec), lit,[6] 295—297 °C. IR: νN–H 3410, νC=O 1680 cm^{-1} (KBr). Found: C, 50.97; H, 4.32; N, 25.28%. Calcd for $C_7H_7N_3O_2$: C, 50.90; H, 4.28; N, 25.45%.

2-Quinolinecarboxamide(trace). Mp 129—131 °C, lit,[7] 132—133 °C. Determined by mixed melting point method and IR: νN–H 3440, νC=O 1680 cm^{-1}(KBr).

Hydration with Nickel Oxide Catalyst(black). Fifty ml of an aqueous solution containing nitrile(1g), II, III, or IV, and nickel oxide(0.1 g) was refluxed for 2—5 hr. In the reaction with IV, pyridine was added in order to dissolve the nitrile completely. After the reaction, the catalyst was filtered while hot and the filtrate was cooled. Amide crystals were precipitated, and were then filtered and recrystallized from water.

2,4-Dipyridinecarboxamide. Mp 256 °C, lit,[8] 258 °C. IR: νN–H 3450, 3310, νC=O 1715, 1695 cm^{-1} (KBr). Found: C, 50.97; H, 4.25; N, 25.33%. Calcd for $C_7H_7N_3O_2$: C, 50.90; H, 4.28; N, 25.45%.

Hydrolysis with Copper(II) Ion. A solution(100 ml) containing nitrile(1g), II, III, or IV, and $CuCl_2 \cdot 2H_2O$ (1.32 g) was refluxed for 15 hr(homogeneous, pH *ca.* 4.5). After the reaction, the reaction mixture was concentrated to a small quantity under reduced pressure, and then cooled. Crystals deposited were filtered, washed with ethanol, and recrystallized from water, dried *in vacuo*.

Copper (II) complex of 4-cyano-2-pyridinecarboxylic acid. IR: νC≡N 2240, νC=O 1650 cm^{-1}. Found: C, 46.76; H, 1.79; N, 16.17; Cl, 0%. Calcd for $C_{17}H_6O_4N_4Cu$: C, 46.99; H, 1.68; N, 15.67; Cl, 0%.

Copper(II) complex of 2,6-pyridinedicarboxylic acid. IR: νO–H 3440, νC=O 1160 cm^{-1}. Found: C, 31.80; H, 2.57; N, 5.38; Cl, 0%. Calcd for $C_7H_7NO_6Cu$: C, 31.76; H, 2.65; N, 5.29; Cl, 0%. When 2,6-pyridinedicarboxamide was treated similarly, the same complex was obtained.

The authors wish to express their hearty thanks to Dr. Shinnichiro Suzuki, Osaka University, for his valuable advice.

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