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Catalytic Function of Metal Salts on the Reduction of Pyridine-2-carbaldehyde by 1-Benzyl-1,4-dihydronicotinamide

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Synopsis. A catalytic function of metal salts on the reduction of pyridine-2-carbaldehyde by 1-benzyl-1,4-dihydronicotinamide was discussed kinetically. The reduction rate was affected not only by the nature of metal cation but by that of counter anion.

Because of a biochemical significance the reactions of 1,4-dihydronicotinamide derivatives, as a model for the reduced nicotinamide-adenine dinucleotide, have been studied by many workers.[1] Although it was known that zinc ion was essential for the activity of alcohol dehydrogenase,[2] only few investigations were reported about the catalytic function of metal ions for the reactions to which 1,4-dihydronicotinamide derivatives participated. Sigman *et al.*[3] reported that zinc ion efficiently catalyzed the reduction of 1,10-phenanthroline-2-carbaldehyde to 1,10-phenanthrolin-2-ylmethanol by 1-propyl-1,4-dihydronicotinamide. Shinkai *et al.*[4] presented that pyridoxal derivatives were reduced by 1,4-dihydropyridine derivatives and that the reductions were facilitated by metal ions. In the present study the reduction of pyridinecarbaldehyde (2-, 3-, 4-) by 1-benzyl-1,4-dihydronicotinamide(NBNH)[5] was attempted and the catalytic function of some metal salts (metal cations and their counter anions) was discussed.

Results and Discussion

Pyridine-2-carbaldehyde(2-PCHO) was found to be reduced to 2-(hydroxylmethyl)pyridine by NBNH in the presence of $Zn(OAc)_2$. The reaction rate was evaluated kinetically. 3-PCHO was not reduced and 4-PCHO was reduced with difficulty, the pseudo first-order rate constant(k) of which was twenty eight times smaller than that of 2-PCHO. This implies that a direct activation of carbonyl group by Zn^{2+} which was fixed in the neighborhood of the carbonyl group by coordination with the nitrogen atom of pyridine ring is an important factor for the reduction of PCHO, though the reaction mechanism is not obvious. Suggestive evidences for the direct activation were obtained from the UV and NMR spectra of methanolic solution of PCHO–$Zn(OAc)_2$ mixture. The UV spectrum of the mixture for 2-PCHO showed a new absorption peak at 390 nm, while that of 3- and 4-PCHO did not show any appreciable change. The difference in $\Delta\tau$ for the ring protons among the three isomers did not give any useful information but the magnitude of the diminution of aldehyde proton peak was in the order, 2-PCHO> 4-PCHO>3-PCHO≃0.

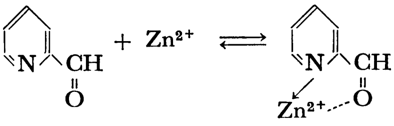

Table 1. Pseudo first-order rate constants catalyzed by bivalent metal cations

	Zn^{2+}	Pb^{2+}	Cb^{2+}	Cu^{2+}
Metal[a] $\times 10^3$ M	6.95	7.18	7.04	0.70
2-PCHO $\times 10^2$ M	3.48	3.43	3.43	3.52
k[b] $\times 10^5$ s^{-1}	7.31	2.23	2.06	10.10

a) Counter anion is OAc^-. b) At 29 °C in methanol, [NBNH] $= 7.0 \times 10^{-5}$ M.

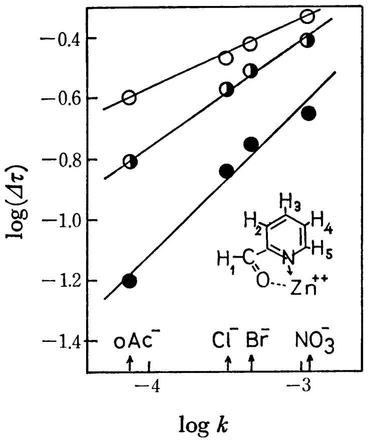

Fig. 1. Relation between log k and log ($\Delta\tau$) at 29 °C in methanol.
In pseudo first-order rate constants measurement, $[Zn^{2+}] = 7.45 \times 10^{-3}$ M, $[2\text{-PCHO}] = 3.50 \times 10^{-2}$ M, $[NBNH] = 7.01 \times 10^{-5}$ M.
In NMR spectra measurement, $[Zn^{2+}] = 0.25$ M, $[2\text{-PCHO}] = 0.50$ M, $\Delta\tau = \tau$ (none)—τ (added Zn^{2+} salts)
—●—: H_2, —○—: H_3, —◑—: H_4

The reduction of 2-PCHO was catalyzed by other bivalent metal salts than $Zn(OAc)_2$, such as $Pb(OAc)_2$, $Cd(OAc)_2$, and $Cu(OAc)_2$, each of which was unreactive to NBNH. As shown in Table 1, the k values for these salts as catalyst decreased in the order, $Cu^{2+} > Zn^{2+} > Pb^{2+} > Cd^{2+}$, agreeing with the order of the stability constants of the complexes between pyridine-2-carboxylic acid and the corresponding metal ions.[6] Interestingly the k values were altered by change of the counter ions of Zn^{2+}, decreasing in the order, $NO_3^- > Br^- > Cl^- > OAc^-$. The $\Delta\tau$ in the NMR spectra of the 2-PCHO–zinc salts mixture was varied by change of the counter anion. A good linear relationship, as shown in Fig. 1, was observed between log($\Delta\tau$) and log *k*. This shows that the catalytic function of metal salts for the reduction of 2-PCHO by NBNH results from their strong coordination to the substrate and that the coordination strength depends not only on the nature of metal cation but on that of counter anion. Salicylaldehyde, thiophene-2-carbaldehyde and furfural were not reduced by NBNH in the presence of Zn$(OAc)_2$. This suggests the coordination of Zn^{2+} to oxygen atom or sulfur atom is too weak to fix the Zn^{2+} in the proximity of the carbonyl group.

Experimental

Kinetic Procedures. Reaction was started by mixing methanol solutions of 2-PCHO, metal salt and NBNH in a quartz cell which was placed in a water jacket maintained at a working temperature. The rate was determined spectrophotometrically by following the decrease in the absorbance at 355 nm due to NBNH. To eliminate an increment of the absorbance due to 2-PCHO–metal ion complexes which showed a weak absorbance at 355 nm, differential spectra were taken by employing a solution of 2-PCHO–metal ion mixture as a reference. An obvious isosbestic point was observed at 310 nm. Under the condition where aldehyde and metal ion were present in great excess with respect to NBNH, the rate of disappearance of NBNH depended on first order of its concentration. The pseudo first-order rate constant (*k*) was obtained from the slope of the plot of log [(NBNH)] against time. Metal salts were used as hydrate except $ZnCl_2$ and $ZnBr_2$; $Zn(OAc)_2 \cdot 2H_2O$, $Pb(OAc)_2 \cdot 3H_2O$, $Cd(OAc)_2 \cdot 2H_2O$, $Cu(OAc)_2 \cdot H_2O$, and $Zn(NO_3)_2 \cdot 6H_2O$.

Products Analysis. 2-PCHO (5.0 g; 0.047 mol), NBNH (1.5 g; 0.070 mol) and $Zn(OAc)_2$ (6.6 g; 0.023 mol) were dissolved into methanol (100 ml) and the solution was allowed to stand for two days at 40 °C. The methanol was removed by vaccum distillation from the reaction mixture. After dissolving the residue in water, enough amount of EDTA tetra sodium salt was added to chelate the all zinc ion and filtered. The filtrate was extracted with ether. The ether solution was dried over sodium sulfate and then the ether was evaporated. The gas chromatographic analysis (Apiezone grease L-30, 150 °C: retension time 2.45 min) and the picrate (mp 158 °C, lit.[7] 159 °C) confirmed the formation of 2-(hydroxymethyl)pyridine. A part of the aqueous filtrate was passed through an anionic resin (Amberlite IRA-400). The eluted solution showed the same UV spectrum as that of an authentic 1-benzyl-3-carbamoylpyridinium chloride (λ_{max} 265 nm in H_2O).

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