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THE ROLE OF METAL IONS IN NADH MODEL REACTIONS

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Pyridine-2-carbaldehyde and formylferrocene were reduced with 1-benzyl-1,4-dihydronicotinamide and zinc acetate in isopropyl alcohol at 50°C. The reactions were promoted when the quantity of Zn^{2+} added was increased. No reduction was observed with Pt(II) or Ni(II). Ternary complex as an intermediate was implied.

It was known that zinc ion was essential for the activity of alcohol dehydrogenase. Some investigations on the function of metal ions in the reaction of NADH model compounds were reported$^{1)}$. In the present study reactions of NADH model compounds with metal ions were attempted in order to examine the catalytic behavior of ions from stereochemical view point.

1-Benzyl-1,4-dihydronicotinamide(NBNH) as model compound, and pyridine-2-carbaldehyde and formylferrocene as substrate were employed for the reactions. An isopropyl alcohol solution of NBNH, pyridine-2-carbaldehyde, and zinc acetate (10^{-3} M each) was kept at 50°C, then, reduction of the aldehyde proceeded gradually. The reaction was followed by the decrease of UV spectra at 353 nm of NBNH. No side reactions were observed under this reaction conditions. When Zn^{2+} ion was not added to the reaction mixture, almost no reduction occurred. The reactions were promoted evidently when the quantity of Zn^{2+} ion added was increased as shown in Fig. 1. The reduction of formylferrocene was proceeded smoothly under the same reaction conditions as mentioned above$^{2)}$. In this case, no reaction occurred also without Zn^{2+} ion catalyst. Alcohols as the reaction products were determined by column chromatography, gas chromatography or UV spectrum.

Concerning the catalytic behavior of Zn^{2+} ion, it has been found that addition reaction of methanol to NBNH took place(5,6-position of the pyridine ring) in the presence of Zn^{2+} ion catalyst. For instance, when the reduction of pyridine-2-carbaldehyde with NBNH and Zn^{2+} ion was carried out in methanol, the addition of methanol occurred along with the reduction of the aldehyde and an absorption at 288 nm was observed[3]. It was already known that this addition proceeded with acid catalyst[4]. In the case of formylferrocene, however, only the reduction took place and no addition of methanol was observed. This fact suggested a steric hindrance of the bulky ferrocene rings on the NBNH. Then to examine the steric effect, ferrocene was added to a methanol solution of NBNH and Zn^{2+} and no addition was observed as was expected[5]. It is assumed that this steric hindrance of ferrocene rings for the methanol addition to NBNH is probably due to an interaction of NBNH-Zn^{2+}-ferrocene.

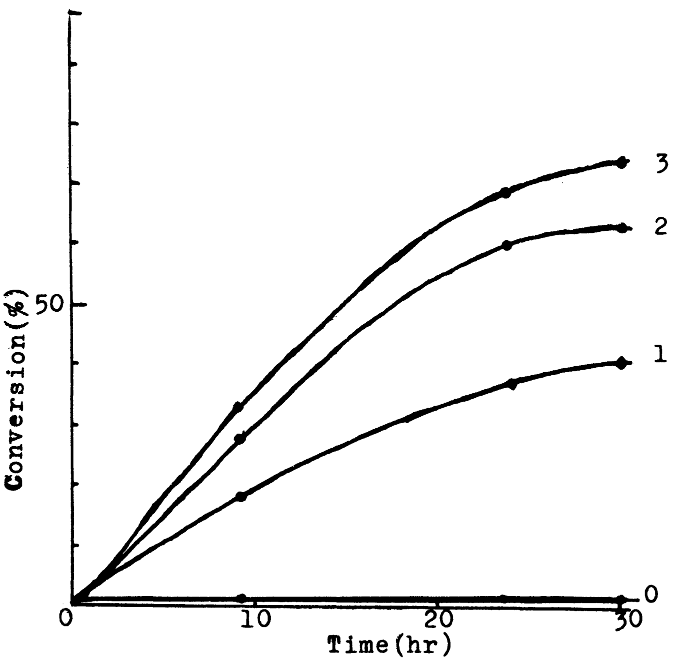
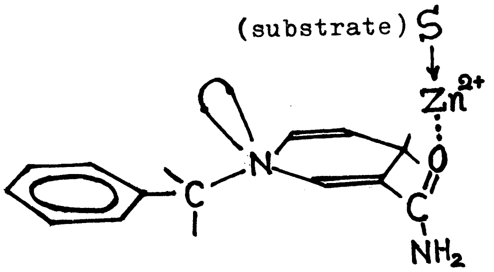


Fig.1 Reduction of pyridine-2-carbaldehyde NBNH: 10^{-3}M, Py-2-CHO: 10^{-3}M, in i-PrOH 50°C, 0: no Zn^{2+}, 1: Zn^{2+} 10^{-3}M, 2: Zn^{2+} 2×10^{-3}M, 3: Zn^{2+} 3×10^{-3}M. Conversion was calculated by the decrease of NBNH(353 nm).

It has been presumed that the reaction of NADH and aldehyde with Zn^{2+} ion proceed through the formation of ternary complex intermediate, NADH-Zn^{2+} - aldehyde. In the model reactions, however, no reduction took place with ordinary aldehyde such as acetaldehyde etc.. Accordingly, nitrogen atom in pyridine ring of pyridine-2-carbaldehyde may assist the coordination of -CHO group to Zn^{2+} ion through the interaction of Zn^{2+} and the **N** atom. **And,** formylferrocene may has a certain coordination ability to Zn^{2+} ion to some extent. Actually, a zinc complex of ferrocene methanol was obtained from a methanol solution[6].

Pandit reported that Mg^{2+} ion has an interaction with amide oxgen in an NADH model compound by NMR studies[1d]. From a view point of a stable conformation of NBNH in the ground state, it may be reasonable that the ternary complex has an interaction of $CONH_2$(NBNH)-Zn^{2+}-aldehyde. In this case, hydrogen atom at 4-position of the pyridine ring in NBNH can be located nearest to -CHO group of the substrate without any steric hindrance. It is also satisfactory conformation for the alcohol coordinated to Zn^{2+} ion to attack on 5,6-position of the pyridine ring in NBNH.

In order to examine effect of other metal ions, the reaction with Pt(II) or Ni(II) ion catalyst instead of Zn(II) was carried out. As the result, no reduction of pyridine-2-carbaldehyde took place but a complex of Pt or Ni was obtained. It has been assumed that the Pt-complex is a π-complex of NBNH formulated as NBNH·$PtCl_2$ although the exact structure is unkown[7]. As for the behavior of Ni(II), there are some complicated problems still to be examined by further studies.



References and Notes

1) a) Y. Ohnishi, M. Kagami, and A. Ohno, J. Am. Chem. Soc., 97, 4776 (1975).
   b) D. J. Creighton, J. Hajdu, and D. S. Sigman, ibid., 98, 4619 (1976).
   c) W. Tagaki, H. Sakai, Y. Yano, K. Ozeki, and Y. Shimizu, Tetrahedron Lett., 2541 (1976).
   d) R. A. Gase, G. Boxhoon, and U. K. Pandit, ibid., 2889 (1976).
   e) A. Ohno, T. Kimura, H. Yamamoto, S. G. Kim, S. Oka, and Y. Ohnishi, Bull. Chem. Soc. Japan, 50, 1535 (1977).

2) For instance, the reduction proceeded about 30% for 9 hrs (NBNH:Formylferrocene:Zn^{2+} = 1:1:1).

3) Methanol adduct: Yellowish white crystal, mp 122°C. Elemental analysis,

Found: C, 67.95%; H, 7.26%; N, 11.21%. Calcd for $C_{14}H_{18}N_2O$: C, 68.26%; H, 7.38%; N, 11.37%.
According to Tagaki's method[1c)], the reaction mixture was extracted with $CHCl_3$ but no addition product of NBNH and pyridine-2-carbaldehyde(mp 158°C, λ_{max} 290 nm) was obtained.

4) C. S. Y. Kim and S. Chaykin, Biochem., 7, 2339 (1968).

5) It seemed that the addition of alcohol to NBNH was largely affected by steric hindrance. Isopropyl alcohol did not undergo addition to NBNH owing to the steric hindrance under this reaction condition, so i-PrOH could be used for the reaction solvent.

6) Zn^{2+} complex of ferrocene methanol: It was assumed that two molecules of ferrocene methanol coordinated to Zn^{2+} ion. Brownish yellow crystal, mp 114-117°C, IR: almost the same with that of ferrocene methanol, UV: no absorption(in methanol). Elemental analysis, Found: C, 53.61%; H, 4.84%. Calcd for $C_{22}H_{24}O_2Fe_2Zn$: C, 53.30%; H, 4.85%. It is under further examination.

7) Pt(II) complex of NBNH ($NBNH\cdot PtCl_2$): Light brownish crystal, mp about 200°C, IR: $\nu_{C=C}$ 1450 cm^{-1}(shift), UV: no absorption(in methanol). Elemental analysis, Found: C,32.44%; H, 3.01%; N, 5.65%. Calcd for $C_{13}H_{14}N_2OCl_2Pt$: C, 32.50%; H, 2.91%; N, 5.83%.
cf. Cyclooctadiene-Pt(II) complex: J. N. P. Chatt, L. M. Vallarino, and L. M. Venaizi, J. Chem. Soc., 1957, 2496.

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