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Metal Ion-Catalyzed Reduction of Substituted Nitrosobenzenes by 1-Benzyl-3,5-bis(1-pyrrolidinylcarbonyl)-1,4-dihydropyridine in Acetonitrile

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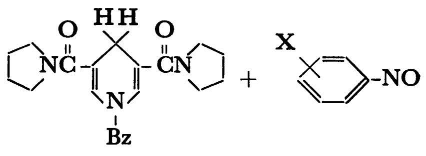
Metal ion catalyzed reduction of substituted nitrosobenzenes by 1-benzyl-3,5-bis(1-pyrrolidinylcarbonyl)-1,4-dihydropyridine (BPDH) in acetonitrile has been studied for seven bivalent metal ions. The reduction of *N*-methylacridinium salt (MA) has also been examined. In the former cases, it was found that the metal ions catalyze the reduction by forming a 1:1 complex with BPDH according to a Michaelis–Menten type saturation kinetics which allowed to derive the association constants, K_M, for the complexation and the second-order rate constants, k_2, for the reduction. A linear relationship was found between $\log k_2$ and the ionization potentials of metal ions with a positive slope. A linear Hammett relationship was also observed between $\log k_2$ and the Hammett σ constants with a positive ρ value for three metal ions. These results suggest that a bivalent metal ion is sandwiched between the BPDH and the substrate and acts as a Lewis acid to stabilize the incipient *N*-oxide anion of the substrate which is formed by hydride transfer in the transition state. In the cases of MA, all metal ions inhibited the reduction. Repulsion between the positive charges of the metal ion-BPDH complex and the substrate salt appears to be prevailing.

The role of zinc ion at the active site of alcohol dehydrogenase has attracted much attention in recent years.[1] Recent crystallographic and the related studies[2–5] have disclosed the following features for the structure of reactive ternary complex at the active site of the enzyme: (a) A zinc ion sits at the bottom of a hydrophobic pocket, (b) the oxygen atom of substrate is directly coordinated to the zinc ion, and (c) there is no direct contact between the zinc ion and the coenzyme. These features strongly suggest that the zinc ion performs as an electrophile to polarize the carbonyl group or to ionize the hydroxyl group of substrate.

In the model studies, it has also been observed that a bivalent metal ion such as Mg^{2+} or Zn^{2+} ion accelerates the rate of reduction of some carbonyl substrates,[6–22] and it has been considered that a metal ion may also polarize the substrate carbonyl group as a Lewis acid as in enzymic systems.[6–8,12,15] However, the role of a bivalent metal ion in model systems so far studied seems to be somewhat different from the one suggested for the above enzymic systems on the following grounds.[13–22] Namely, it has been demonstrated that a bivalent metal ion such as Mg^{2+} or Zn^{2+} ion forms a complex with the 1,4-dihydronicotinamide moiety of the reductants.[14–22] It has also been indicated that Mg^{2+} ion does not show any measurable complexation with such a substrate as ethyl benzoylformate, in spite of the rate acceleration.[16]

We have also been interested in the activation of model systems of NADH coenzyme by acids and metal ions. In our previous paper, we reported the carboxylic acid-catalyzed reduction of substituted nitrosobenzenes by BPDH in acetonitrile.[23,24] We proposed a mechanism that a carboxylic acid acts as a general acid by protonating the oxygen atom of nitroso group of the substrate in the transition state. The acid-catalyzed rate was faster for a substrate having a more electron-donating substituent. As a natural extension, we have now studied the metal ion-catalyzed reduction of substituted nitrosobenzenes (NB) by BPDH in acetonitrile (Eq. 1). We will describe in this paper that bivalent metal ion catalysis is much more efficient than carboxylic acid one and the rate is faster for a substrate having a more electron-withdrawing substituent, in contrast to the case of the above acid-catalysis.



BPDH

$$\xrightarrow[\text{CH}_3\text{CN, 25 °C}]{M^{2+}} \text{Products} \qquad (1)$$

Results

Products, Kinetic Analysis, and Metal Ion Catalysis. The reduction was carried out in anhydrous acetonitrile under nitrogen atmosphere. The substrate nitrosobenzenes were confirmed to be reduced to hydroxylamines quantitatively by HPLC analysis as described before.[23,24] The rates of reduction were followed spectrophotometrically by observing the decrease of absorbance at 355 nm due to the disappearence of BPDH. The rate of reduction was slow in the absence of metal ion. In the presence of a metal ion, the pseudo-first-order rate constant, k_{obsd} increased with increasing concentration of the metal ion according to a manner to obey a Michaelis–Menten type saturation kinetics, as shown in Fig. 1. Here the metal ions were used as the perchlorates with water of crystallization. The results suggest the complexation of the metal ion with either BPDH or a nitrosobenzene, or both before the rate-limiting step. As for the substrate, it was observed that the rates (k_{obsd}) were first-order with respect to the concentration of the nitrosobenzene, as shown in Fig. 2. Therefore, the complexation between the substrate nitrosobenzene and the metal ion prior to the reduction seems to be unimportant.

It was confirmed spectrophotometrically that the complexation occurs between Zn^{2+} ion and BPDH. As shown in Fig. 3a, the absorption maximum of BPDH at 355 nm in the absence of metal ion shifts to a shorter wavelength of 320 nm in the presence of Zn^{2+} ion. The plots of absorbance change as a function of the Zn^{2+} ion concentration gave a saturation curve of Fig. 3b which indicates a complexation and fits nicely with the curve for Zn^{2+} ion in Fig. 1. Thus, it is likely that the rate acceleration by Zn^{2+} ion is due to the

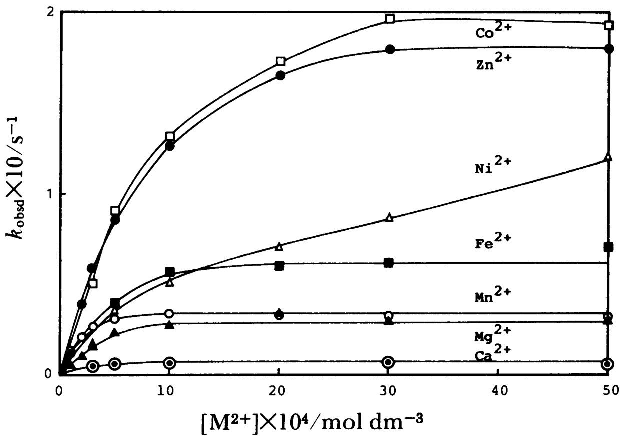


Fig. 1. Pseudo-first-order rate constants for the reduction of nitrosobenzene plotted as a function of the concentration of bivalent metal ions: In acetonitrile at 25 °C; ◎: Ca^{2+}, ▲: Mg^{2+}, ○: Mn^{2+}, ■: Fe^{2+}, △: Ni^{2+}, ●: Zn^{2+}, □: Co_q^{+}. [BPDH]=1X10^{-4} mol dm^{-3}, [C_6H_5NO]=1X10^{-3} mol dm^{-3}.

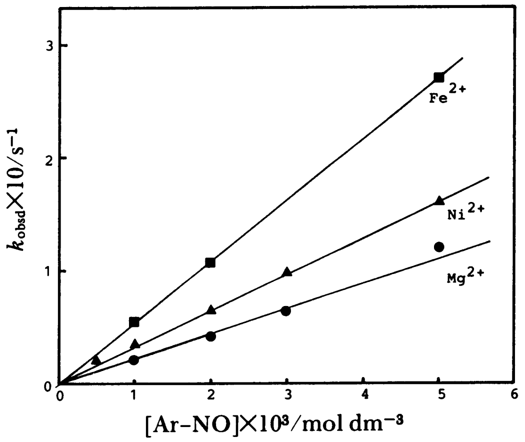


Fig. 2. Plots of pseudo-first-order rate constants as a function of substrate concentration: In acetonitrile, 25 °C; ■: Fe^{2+}, ▲: Ni^{2+}, ●: Mg^{2+}.

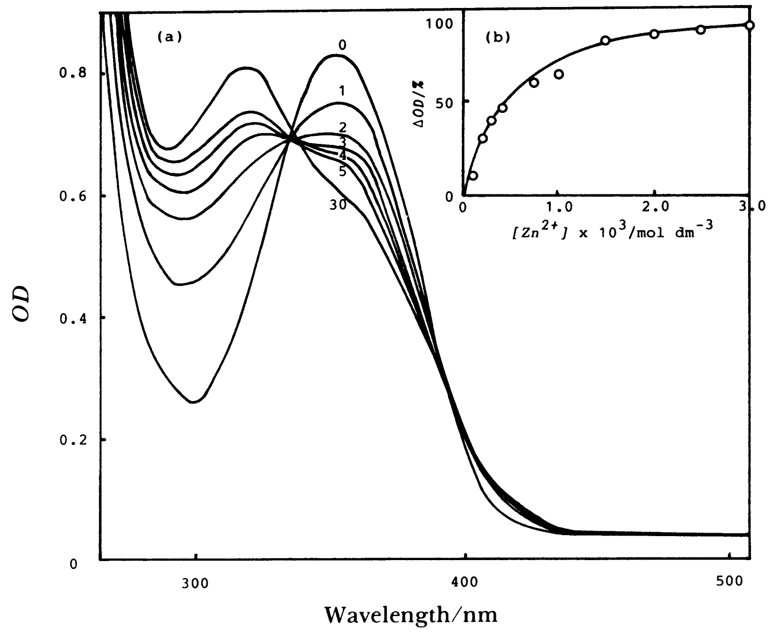


Fig. 3. Spectral changes of BPDH induced by added zinc ion: In acetonitrile, 25 °C; [BPDH]=1X10^{-4} mol dm^{-3}; (a) observed UV spectra. The numbers indicate the concentration of zinc ion [(Zn^{2+}]X10^4). The shift was saturated above 3X10^{-3} mol dm^{-3}; (b) saturation curve of absorbance change, %.

complexation of BPDH with the Zn^{2+} ion. A similar correlation between the rate acceleration and the spectral change was also confirmed for the other metal ions. Furthermore, the rate of reduction was observed to be inhibited in the presence of water and this rate inhibition was perfectly parallel to the loss of complexation as shown in Fig. 4.

The saturation curves in Fig. 1 can be described by assuming a reaction scheme shown in Scheme 1 in which BPDH (DH) and a metal ion (M^{2+}) form a 1 : 1 complex ($DH\cdot M^{2+}$) with an association constant, K_M, and the complex reacts with the substrate (ArNO) with a second-order rate constants, k_2, to give the products, D^+ and $ArNHO^-$. Uncatalyzed rate (k_2') must also be taken into account, although its contribution to the total rate was negligible. The scheme leads to a rate equation shown by Eq. 1, and under the conditions of $[M]_T \gg [DH\cdot M]$, Eqs. 2 and 3 can be derived by an approximation, where $[DH]_T$ and $[M]_T$ are the total concentration BPDH and metal ion, respectively, and $[ArNO]_0$ is the initial concentration of substrate which is used in a large excess and taken to be constant under a pseudo-first-order conditions. Experimentally, the k_2 and K_M values were obtained as usual from the reciprocal plots of Eq. 4. The results are shown in Table 1.

$$\begin{aligned}\text{Rate} &= k_{obsd}[DH]_T \\ &= k_2'[ArNO]_0[DH]_T + k_2[ArNO]_0[DH\cdot M^{2+}] \qquad (1)\end{aligned}$$

$$[DH\cdot M^{2+}] = \frac{K_M[M]_T[DH]_T}{1+K_M[M]_T} \quad ; \ [M]_T \gg [DH\cdot M^{2+}] \qquad (2)$$

$$k_{obsd} = k_0 + \frac{k_2K_M[ArNO]_0[M]_T}{1+K_M[M]_T} \ ; \quad k_0 = k_2'[ArNO]_0 \qquad (3)$$

$$\frac{1}{(k_{obsd}-k_0)} = \frac{1}{k_2[ArNO]_0} + \frac{1}{k_2K_M[ArNO]_0}\cdot\frac{1}{[M]_T} \qquad (4)$$

$$DH + M^{2+} \overset{K_M}{\rightleftharpoons} DH\cdot M^{2+} \xrightarrow{k_2[ArNO]_0} D^+ + Ar\text{-}NHO^- + M^{2+}$$

$$DH + ArNO \xrightarrow{k_2'} D^+ + ArNHO^-$$

Scheme 1.

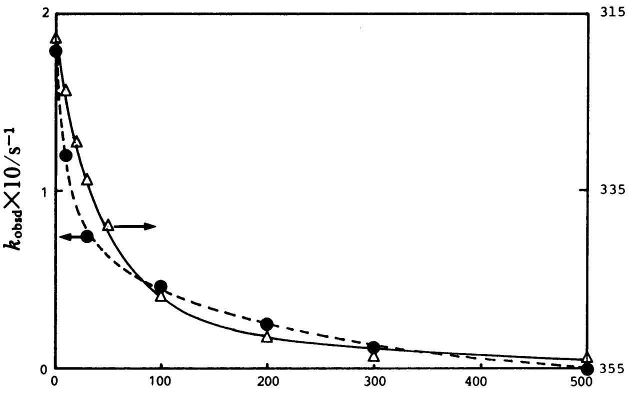


Fig. 4. Effect of H_2O on the shift of absorption maximum of BPDH (Δ) from 355 nm and the reduction rate constants of nitrosobenzene (●) in the presence of zinc ion: In acetonitrile, 25 °C; [BPDH]=1× 10^{-4} mol dm^{-3}, [C_6H_5NO]=1×10^{-3} mol dm^{-3}, [Zn^{2+}]= 3×10^{-3} mol dm^{-3}.

The k_2 and K_M values as the Functions of Ionization Potentials of Metal Ions. In Table 1 are shown the ionization potentials (I_P) of metal ions[25] in addition to the above k_2 and K_M values. It can be seen that there is a good linear relationship between I_P and $\log k_2$ values, as shown in Fig. 5. It indicates that a metal ion having a higher I_P is more active. In Fig. 6 is also shown a correlation between I_P and $\log K_M$ values. Although the correlation is not so good as in the case

Table 1. Second-Order Rate Constants and Association Constants for the Metal Ion-Catalyzed Reduction of Nitrosobenzene by BPDH in Acetonitrile (25 °C)[a)]

M^{2+}	$\frac{I_P}{eV}$	$\frac{k_2}{s^{-1}\,mol^{-1}\,dm^3}$	$\frac{K_M}{mol^{-1}\,dm^3}$
Ni^{2+}	18.17	261	245
Zn^{2+}	17.96	180	1865
Co^{2+}	17.06	195	1060
Fe^{2+}	16.18	70.9	2523
Mn^{2+}	15.64	32.2	6932
Mg^{2+}	15.04	30.8	2899
Ca^{2+}	11.87	7.2	10430

a) [BPDH] = 1 × 10^{-4} mol dm^{-3}, [C_6H_5NO] = 1 × 10^{-3} mol dm^{-3}.

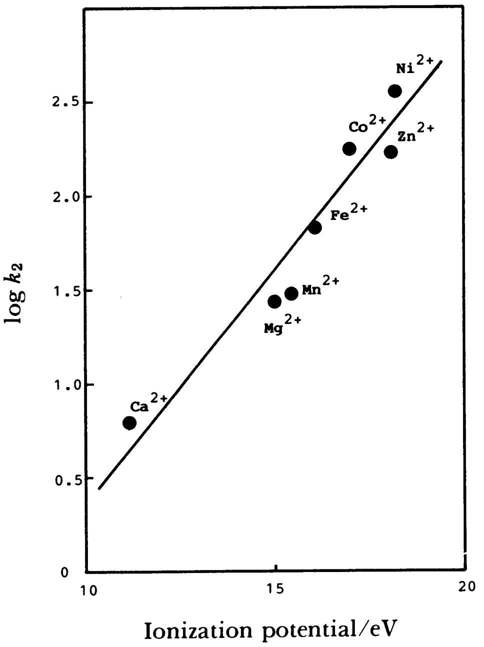


Fig. 5. Correlation between I_P and $\log k_2$.

of Fig. 5, there is a clear tendency that a metal ion having a lower I_P forms a stronger complex with the dihydropyridine (BPDH). The Table 1 also indicates that, at a high metal ion concentration, i.e., $K_M[M]_T \gg 1$, the observed reactivity (k_{obsd}) is governed by k_2 value (see Eq. 3) which is in the order of $Ni^{2+} > Co^{2+} > Zn^{2+} > Fe^{2+} > Mn^{2+} > Mg^{2+} > Ca^{2+}$, but at a low metal ion concentration, i.e., $K_M[M]_T \ll 1$, the reactivity is governed by k_2K_M which is in the order of $Zn^{2+} > Mn^{2+} > Co^{2+} > Fe^{2+} > Mg^{2+} > Ca^{2+} > Ni^{2+}$. It may be interesting that biologically important Zn^{2+} ion is the most active at a low metal ion concentration.

The Effects of Substrate-Substituents on the Rates. Figure 1 indicates that the rates of reaction (k_{obsd}) become saturated with the use of 3×10^{-3} M† of metal ion in the presence of 1×10^{-4} M of BPDH and 1×10^{-3} M of NB (X=H) for all the metal ions except for Ni^{2+} ion. For the other substituted NB's (X=p-CH_3 to m-CF_3), the rate saturation was also observed at the metal ion concentration of 3×10^{-3} M except for Ni^{2+} ion. Therefore, these saturated rates can be used as the substitutes of k_2 values (see Eq. 3) to examine the Hammett relationships. The results are shown in Table 2 and Fig. 7. A good linear relationship can be seen for each of the five metal ions. The ρ values

Table 2. Saturation Rate Constants for the Reduction of Nitrosobenzenes by BPDH in the Presence of Metal Ions in Acetonitrile (25 °C)[a)]

	k_2[b)] / s^{-1} mol^{-1} dm^3				
	Co^{2+}	Zn^{2+}	$Ni^{2+,c)}$	Mn^{2+}	Mg^{2+}
p-Me	154	133	59.4	23.4	22.1
m-Me	182	154	74.7	28.0	26.3
H	202	174	87.2	32.3	30.7
p-Cl	307	275	136	62.2	63.1
m-Cl	397	358	183	92.0	96.6
m-CF_3	437	382	—	102	101

a) [BPDH] = 1×10^{-4} mol dm^{-3}, [ArNO] = 1×10^{-3} mol dm^{-3}, [metal ion] = 1×10^{-3} mol dm^{-3}. b) $k_2 = k_{obsd}$/[ArNO]. c) These values are not the saturated rate constants.

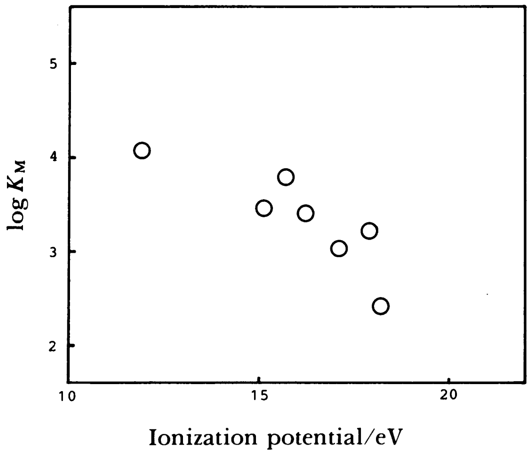


Fig. 6 Correlation between I_P and log K_M.

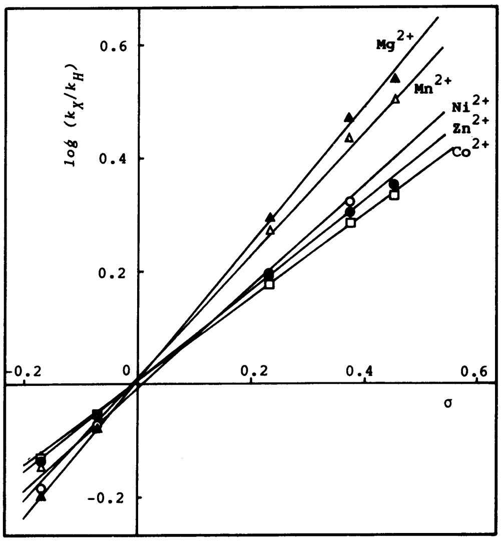


Fig. 7. Hammett substituent effect on the rates of metal ion-catalyzed reduction of nitrosobenzenes by BPDH: In acetonitrile, 25 °C; [BPDH]=1×10^{-4} mol dm^{-3}, [ArNO]=1×10^{-3} mol dm^{-3}, [metal ion]=3×10^{-3} mol dm^{-3}.

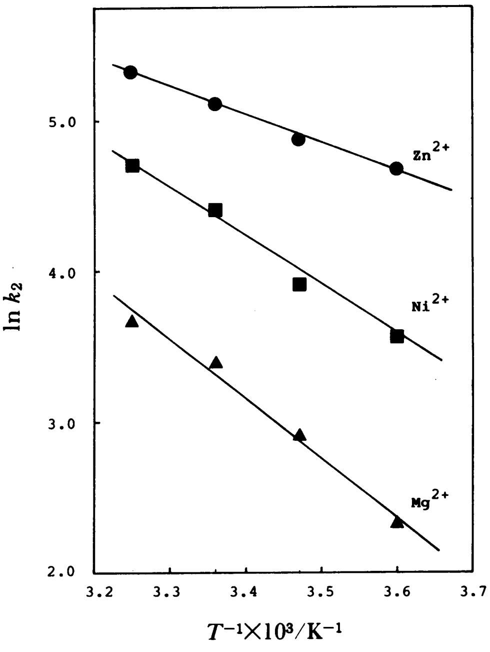


Fig. 8. Arrhenius plots for the metal ion-catalyzed reduction of nitrosobenzene by BPDH: In acetonitrile, 25 °C; [BPDH]=1×10^{-4} mol dm^{-3}, [C_6H_5NO]=1×10^{-3} mol dm^{-3}, [metal ion]=3×10^{-3} mol dm^{-3}.

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† 1 M=1 mol dm^{-3}.

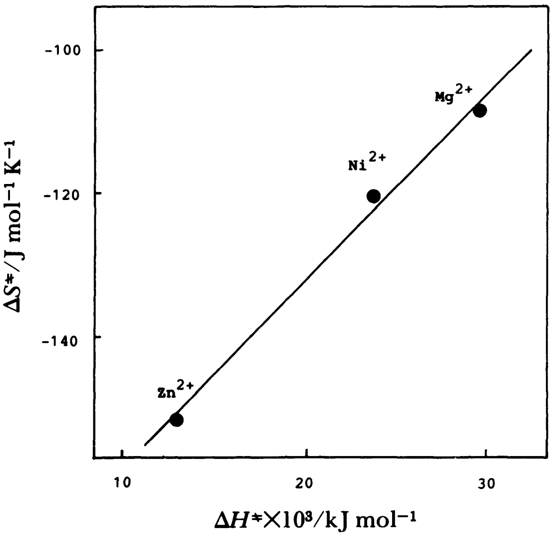

Fig. 9. Isokinetic relationship between $\Delta H^{\neq}$ and $\Delta S^{\neq}$ for three metal ions.

Table 3. Temperature Effect on the Second-Order Rate Constants for the Reduction of Nitrosobenzene by BPDH in the Presence of Metal Ions in Acetonitrile[a)]

	$\frac{k_2}{\text{s}^{-1}\text{ mol}^{-1}\text{ dm}^3}$		
T	Zn^{2+}	Ni^{2+}	Mg^{2+}
5 °C	108	36.5	10.1
15 °C	131	51.1	18.5
25 °C	171	83.4	30.0
35 °C	206	109	39.7
$\frac{\Delta H^{\neq}}{\text{kJ mol}^{-1}}$	13.0	23.9	30.0
$\frac{\Delta S^{\neq}}{\text{J K}^{-1}\text{ mol}^{-1}}$	152	121	109
$\frac{T\Delta S^{\neq}}{\text{kJ mol}^{-1}}$	45.2	36.0	32.4

a) [BPDH] = 1×10^{-4} mol dm^{-3}, [C_6H_5NO] = 1×10^{-3} mol dm^{-3}, [metal ion] = 3×10^{-3} mol dm^{-3}.

obtained from the slopes of the straight lines are 0.76, 0.81, 0.89, 1.12, and 1.23 for Co^{2+}, Zn^{2+}, Ni^{2+}, Mn^{2+}, and Mg^{2+} ion, respectively. The ρ value for Ni^{2+} ion may be somewhat larger than that expected for the saturated rates. At any rate, these ρ values are all positive, indicating that the rate-determining k_2 step is assisted by an electron-withdrawing substituent on the substrate NB. It is also noticed that the ρ value is smaller for a more active metal ion.

Temperature Effects. The temperature effects on the above saturation rates were examined for three metal ions as shown in Table 3 and in Figs. 8 and 9. It may be seen that the weight of $\Delta H^{\neq}$ term to the total rate is relatively small as compared to the $\Delta S^{\neq}$ term, especially in the case of Zn^{2+} ion. A linear isokinetic relationship in Fig. 9 may indicate the mechanism of catalysis to be the same for these three metal ions.

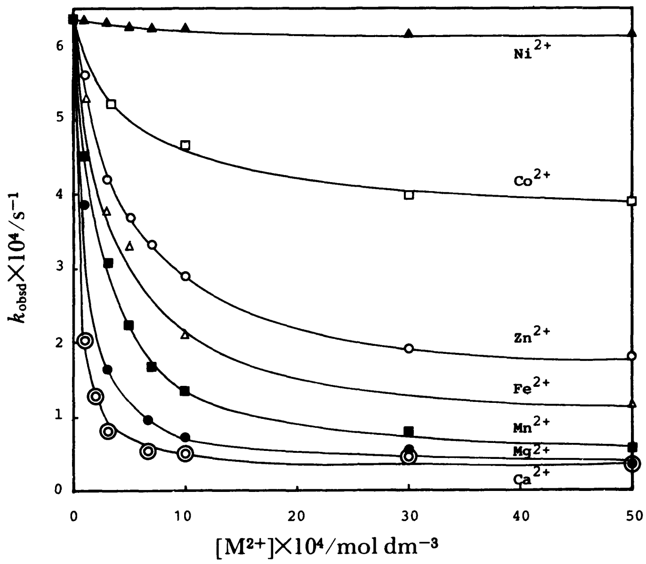

Fig. 10. Pseudo-first-order rate constants for the reduction of *N*-methylacridinium salt plotted as the function of the concentration of various metal ions: in acetonitrile, 25 °C; [BPDH]=1×10^{-4} mol dm^{-3}, [MA]=1×10^{-4} mol dm^{-3}.

Metal Ion Inhibition in the Reduction of *N*-Methylacridinium Cation (MA). As shown in Fig. 10, the reduction of MA ion by BPDH was found to be inhibited by all metal ions. The order of inhibition is $Ni^{2+}<Co^{2+}<Zn^{2+}<Fe^{2+}<Mn^{2+}<Mg^{2+}<Ca^{2+}$ and almost the same as in the order of the association constants between BPDH and metal ions shown in Table 1. It may be suggested that the inhibition is due to a charge repulsion between the positive charge of substrate salt and metal ion–BPDH complex.

Discussion

It has been established in the model studies of NADH coenzyme that the metal ions such as Zn^{2+} and Mg^{2+} enhance the rates of reduction of some carbonyl substrates.[6–22)] However, much remain to be clarified for the mechanism of metal ion catalysis. As mentioned in the introductory part, it has been proposed that a metal ion may polarize the substrate carbonyl group as a Lewis acid to facilitate the reduction.[6–8,12,15)] However, confusing facts for this idea are the spectral evidence for the complexation between a metal ion and the dihydropyridine moiety, but not between a metal ion and the substrate carbonyl group. Namely, the electronic absorption at around 350 nm due to the π-π^* transition of the dihydropyridine moiety undergoes a red shift on complexation with a metal ion.[9,14–16,18,19)] Two explanations were proposed for the modes of complexation. Ohno et al.

proposed a sandwich type complexation for the transition state of reduction in which Mg^{2+} ion is located between the dihydropyridine and the substrate based on the electronic and infrared spectra.[13,16,17] Gase et al., however, explained differently based on the ^{13}C NMR spectra that Mg^{2+} ion coordinates to the amide oxygen of 1-benzyl-1,4-dihydronicotinamide.[20] Hughes et al. also considered the complexation on the amide moiety based on the electronic[9] and ^{1}H and ^{13}C NMR[14] spectra.

The present BPDH was also found to show a strong complexation with a bivalent metal ion in dry acetonitrile as manifested from the changes of absorption spectra at around 355 nm (Fig. 3) and from the saturation kinetics (Fig. 1). Here it should be noticed that the spectral change was a blue shift of 355 nm absorption, in contrast to a red shift mentioned above. There may be two conceivable types of complexation which result in different spectral changes as illustrated in Fig. 11. One is the complexation on the amide–oxygen (a) which would result in a red shift because of the metal ion stabilization of an excited state. The other is the complexation on the dihydropyridine ring involving an enamine π-system (b) which would result in a blue shift because of the metal ion destabilization of an excited state.[21,22] The observed blue shift seems to conform to the latter possibility.

As shown in Table 1 and Fig. 6, there is a tendency that a metal ion having a lower I_P forms a stronger complex with BPDH. As for the transition metal ions, it can also be shown that the magnitude of $\log K_M$ increases linearly with increasing ionic radius of metal ion in the order of $Ni^{2+}<Co^{2+}<Zn^{2+}<Fe^{2+}<Mn^{2+}$. This order is contrary to that of commonly observed Irving–Williams series.[26] This order is also difficult to correlate with the softness parameters σ_P of Pearson and Mawby[27] and σ_A of Ahrland[28] proposed for these metal ions. On the other hand, the rates of exchange of hydrated water molecule of aqua complexes of metal ions are known to be in the order of $Ni^{2+}<Co^{2+}<Fe^{2+}<Mn^{2+}$,[29] similarly as in the above order. For further discussions, however, it is necessary to know the ligand-exchange equilibrium between the hydrated water and BPDH since in this study the hydrated metal ions were used.

It is well-known that the pK_a's of aqua complexes of metal ions are linearly correlated with the ionization potentials (I_P) of metal ions.[30] Namely, the acidity of hydrated water becomes stronger on a metal ion of higher I_P. Thus, a linear correlation between the k_2 and the I_P values in Fig. 5 strongly suggests that the k_2 step is facilitated by the stabilization of the incipient *N*-oxide anion formed as the proceeding of hydride transfer in the transition state. The postulated mechanism is illustrated in Fig. 12. The figure also indicates a concerted process in which the exchange of ligand on the metal ion occurs from the dihydropyridine to the anion of product hydroxylamine. In this mechanism, it is important to know whether a metal ion does polarize the substrate N=O double bond before the hydride transfer or not, which might be answerd by looking at the Hammett substituent effect. In Fig. 7, the Hammett ρ values were observed to be in a range 0.76—1.23 which indicates the k_2 step to be facilitated by an electron-withdrawing substituent of the substrate. On the other hand, we reported previously that the ρ values for uncatalyzed and the carboxylic acid-catalyzed rates are 1.35 and −0.93, respectively.[24] The present ρ values are thus very close to that of uncatalyzed rates, suggesting that, in the present metal ion-catalyzed reduction, the substrate NO bond is not perturbed much by metal ion before the hydride transfer. It should be noticed that a negative ρ value (−0.93) for the carboxylic acid-catalysis indicates the importance of protonation of NO group in the transition state. Thus, the metal ion catalysis is found to be quite different from the carboxylic acid catalysis in anhydrous acetonitrile.

A sandwich structure in Fig. 12 proposed for the ternary complex in the transition state appears to be similar to that proposed by Ohno et al. for the

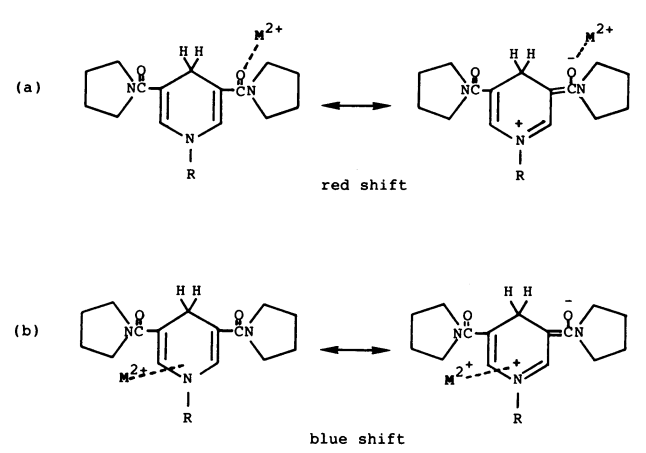

Fig. 11. Schematic illustration to explain a red shift (a) and blue shift (b) of electronic absorption at around 355 nm of BPDH on complexation with a metal ion.

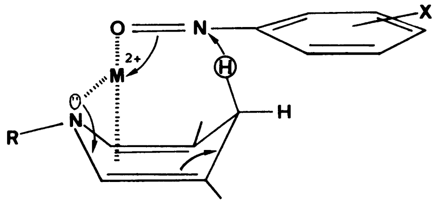

Fig. 12. Schematic illustration of the transition state for an M^{2+} ion-catalyzed reduction of substituted nitrosobenzene.

reduction of carbonyl substrate.[13,16,17] Important difference is that in the latter model electron movement occurs from the dihydropyridine to the substrate through the metal ion, in a reversed way as considered in the former case.

In Fig. 12, it is assumed that the hydrogen to be transferred is the pseudo axial one in the 4-position in the boat conformation of 1,4-dihydropyridine moiety. This assumption is based on a recent proposal that the axial hydrogen is more reactive than the equatorial one.[31] Finally, it must be mentioned that a metal coordination on the amide group may also explain most of the present results except the blue shift of electronic absorption on complexation.

In conclusion, the function of a metal ion seems to be dual in the present system: (a) to form a ternary complex, and (b) to facilitate the hydride transfer by stabilizing the incipient product anion. The two functions seem to be compensating to each other so that a metal ion such as Zn^{2+} ion having a proper balance in the two functions becomes the most active under certain conditions.

Experimental

Materials. Anhydrous acetonitrile was prepared by distilling over phosphorus pentoxide. Substituted nitrosobenzenes were prepared by the reduction of the corresponding commercially available nitrobenzenes with zinc powder as reported previously.[24] Metal ions were used as the perchlorates which were commercially available as special grade reagents.

1-Benzyl-3,5-bis(1-pyrrolidinylcarbonyl)-1,4-dihydropyridine (BPDH) was prepared according to a previous method, mp. 46 °C.[24]

Product analysis was performed for unsubstituted nitrosobenzene (X=H) by HPLC method as described before.[24]

Kinetics. The procedures were essentially the same as those reported previously.[24] In a 1 cm quartz UV cell stoppered with a rubber septum cover was placed a 3 mL acetonitrile solution of BPDH and the solution was well bubbled with acetonitrile saturated pure nitrogen gas through inserted needles. Stock solutions of nitrosobenzene and metal ion in acetonitrile were treated similarly. Then the quartz cell was mounted on a water-jacketed UV cell holder and nitrosobenzene and a metal ion stock solutions in water bath were kept at 25 °C for 15 min. The reaction was started by adding 10 μL each of the solution of nitrosobenzene and the metal ion in this order to the quartz cell by a Hamilton microsyringe. The rates of reduction were followed by monitoring the decrease of absorbance of BPDH at 355 nm. In most cases the reaction was carried out under pseudo-first-order conditions by using 10 molar excess of nitrosobenzene over BPDH.

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