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Complexation of NADH Analogs with Divalent Metal Ions: Dependence on the 3-Substituent of 1-Benzyl-1,4-dihydropyridines

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In light of the critical role of divalent metal ions in the chemistry of coenzyme NADH analogs, complexation of 1-benzyl-3-substituted(X)-1,4-dihydropyridines (**1**, X=$CONH_2$; **2**, X=$CSNH_2$; **3**, X=$COOCH_3$; **4**, X=$COCH_3$) with divalent metal ions (Mg^{2+}, Zn^{2+}, and Co^{2+}) in dry acetonitrile was studied spectroscopically and kinetically. Presence of the metal ions causes red-shift of absorption band of NADH analogs and the rate retardation for the reaction between NADH analogs and *N*-methylacridinium ion. Analysis of the spectroscopic and kinetic data indicates that the NADH analogs form 1 : 1 complexes with the metal ions. The decreasing order of the magnitude of the association constants, **K**, is **1** ≅ **2** ≫ **4** ≫ **3** for a given metal ion, and $Mg^{2+} \gg Zn^{2+} > Co^{2+}$ for a given NADH analog. The results strongly suggest that the primary binding site for the metal ions is the carbonyl oxygen (or thiocarbonyl sulfur) of the 3-substituent and that the amide nitrogen atom of the 3-substituent of **1** and **2** also ligates the metal ions, forming a bidentate structure and providing extra stability to the complexes of **1** and **2**. Inhibition of reaction between NADH analogs and *N*-methylacridinium ion by the metal ions is attributed to inaccessibility of *N*-methylacridinium ion to the NADH analogs complexed with metal ions due to electrostatic repulsion.

INTRODUCTION

The effects of divalent metal ions on the reduction of various substrates by NADH analogs have attracted much attention in light of the role of metal ions in alcohol dehydrogenase enzymes requiring NADH as a cofactor (*1*). Divalent metal ions affect kinetics and, sometimes, even the stereochemistry of the reduction of organic substrates by NADH model compounds (*1–11*). The catalytic effect of metal ions on the reduction of trifluoroacetophenone by 1-benzyl-1,4-dihydronicotinamide (BNAH) in aqueous SDS micellar media has also been reported (*2*).

Several investigators have studied complex formation of divalent metal ions such as Mg^{2+} and Zn^{2+} with 1,4-dihydronicotinamide derivatives (*3–8*). It has been suggested that a ternary complex involving a NADH model compound, a substrate, and a metal ion is responsible for the rate and stereochemical effects of metal ions (*1, 4, 9–11*). However, the results of systematic quantitative studies on the complex formation have scarcely been reported.

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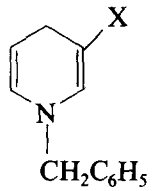
This paper describes the spectroscopic determination of the association constants (*K*) of divalent metal ions with 1,4-dihydropyridines (**1**–**4**) bearing various 3-substituents.



1, $X = CONH_2$ **2**, $X = CSNH_2$
3, $X = COOCH_3$ **4**, $X = COCH_3$

It was hoped that dependence of the complexation properties of the NADH analogs on the 3-substituents might provide valuable information on the nature of the complex. The effect of the metal ions on the rate of reduction of *N*-methylacridinium iodide (MAI) by the NADH analogs has also been studied. This allows the kinetic determination of the association constants. The coordinating abilities among divalent metal ions (Mg^{2+}, Zn^{2+}, and Co^{2+}) to the NADH analogs are compared.

EXPERIMENTAL

Materials. The NADH analogs **1**–**4** were prepared by reacting appropriate pyridine derivatives (Aldrich) with benzyl chloride, followed by reduction with sodium dithionite (*12*). MAI was obtained from reaction of acridine (Aldrich) with methyl iodide (*12*). Vacuum-dried $Mg(ClO_4)_2$, $ZnCl_2$, and $CoCl_2$ were used as metal ion sources. Anhydrous CN_3CN, which was dried over CaH_2 and distilled prior to use, was employed as solvent for all solutions.

Spectroscopic studies. The final concentration of NADH analog was 1.0×10^{-4} M and the metal ion concentration was varied appropriately. All spectroscopic measurements were carried out at 30°C with a Unicam SP 1800 or Contron Uvicon 860 uv–vis spectrophotometer equipped with a thermostatted cell holder. Difference spectra for complexation of NADH analogs with Mg^{2+} and Zn^{2+} were recorded by taking spectra of NADH analogs–metal ion mixtures against solutions of NADH analogs as the metal ions do not have appreciable absorption above 290 nm. For Co^{2+} complexes, the difference spectra were obtained by recording spectra of mixtures against unmixed components using divided cells.

Kinetic studies. The reaction was initiated by adding 0.50 ml of MAI solution in CH_3CN via a syringe to 3.0 ml of NADH analog solution containing desired amount of a metal ion in a cuvette. Both solutions were preequilibriated at 30°C. The final concentration of both NADH analog and MAI was 5.0×10^{-5} M. The reaction was followed by a decrease in the absorbance of MAI at 415 nm and the rate constants were determined by second-order kinetics (see Results section). The final concentration of a metal ion in a reaction mixture was 0 or $\geq 2.5 \times 10^{-4}$ M.

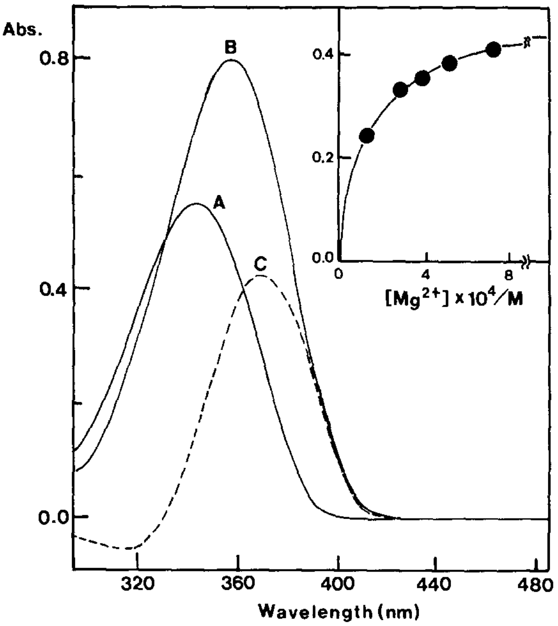


FIG. 1. Absorption spectra of **1** (1.0×10^{-4} M) in the absence (A) and in the presence (B) of 0.1 M $Mg(ClO_4)_2$ in acetonitrile at 30°C. Spectrum C is the difference spectrum (B − A) of the metal ion complexation. Inset is the plot of absorbance values at a wavelength of absorption maximum of the difference spectra as a function of Mg^{2+} concentration.

RESULTS

Spectroscopic determination of association constants of NADH analogs with metal ions. NADH analogs have a broad absorption band with a maximum around 350 nm. Addition of divalent metal ion to an acetonitrile solution of NADH analog causes spectral red-shift of the absorption band and an increase in the maximum absorption. An exception to this was the case of **3** with Zn^{2+} or Co^{2+}, from which we could not observe significant spectral change even when the concentration of the metal ions was as high as 0.1 M. In Fig. 1, we presented a typical effect of metal ion on absorption spectrum of the NADH analog. The spectroscopic data for NADH analogs **1–4** in the absence and presence of a large excess of the metal ions are summarized in Table 1.

The spectral changes of NADH analogs upon addition of metal ions reflect association of the metal ions with NADH analogs. The association constants (K) can be calculated from the spectroscopic titration results. For this, we determined absorbance of difference spectra for association of NADH analogs with metal ions as a function of metal ion concentration (for example, see inset of Fig. 1). When a metal ion (M^{2+}) forms a 1 : 1 complex with NADH analog (XNAH) (Eq. [1]), the fraction (α) of XNAH complexed with the metal ion is related to absorbance in the difference spectrum (ΔA) by Eq. [2] (*3*),

TABLE 1

Absorption Maxima for NADH Analogs in the Presence and Absence of Metal Ions in Acetonitrile at 30°C[a]

NADH analog	X	λ/nm[b] Without M^{2+}	With Mg^{2+}	With Zn^{2+}	With Co^{2+}
1	$CONH_2$	343	356(367)	362(373)	367(378)
2	$CSNH_2$	343	356(367)	362(373)	367(378)
3	$COOCH_3$	347	357(380)	347[c]	347[c]
4	$COCH_3$	358	379(394)	380(396)	371(401)

[a] $[\text{NADH analog}]_0 = 1.0 \times 10^{-4}$ M; $[M^{2+}]_0 = 0.1$ M.

[b] Numbers in parentheses are the wavelengths of maximum absorption in difference spectra.

[c] No appreciable change in absorption spectrum is found upon the addition of the metal ions.

$$\text{XNAH} + M^{2+} \rightleftharpoons \text{XNAH-}M^{2+} \qquad K = \frac{[\text{XNAH-}M^{2+}]}{[\text{XNAH}][M^{2+}]}, \tag{1}$$

$$\alpha = \frac{[\text{XNAH-}M^{2+}]}{([\text{XNAH-}M^{2+}] + [\text{XNAH}])} = \frac{\Delta A}{\Delta A_\infty}, \tag{2}$$

where ΔA_∞ is the maximum absorbance in difference spectra at a measuring wavelength when all XNAH molecules form the complex; K denotes the association constant.

Usually two methods are used to evaluate K. One is the use of Eq. [3],

$$(\alpha^{-1} - 1)^{-1} = K([M^{2+}]_0 - \alpha[\text{XNAH}]_0), \tag{3}$$

which is obtained by combining Eqs. [1] and [2]. This equation requires prior determination of ΔA_∞, but can be applied to any set of experimental data obtained over a wide range of total concentration of M^{2+}, $[M^{2+}]_0$, at a given initial concentration of XNAH, $[\text{XNAH}]_0$ (*3*). The other method is the use of the Benesi–Hildebrand equation (Eq. [4]) which holds at $[\text{XNAH}]_0 \ll [M^{2+}]_0$ but does not require a ΔA_∞ value for determination of K (*13*).

$$\frac{\Delta A}{[M^{2+}]_0} = K\,\Delta A_\infty - K\,\Delta A. \tag{4}$$

The plots of ΔA for association of **1** and **2** with Mg^{2+} or Zn^{2+} as a function of the concentration of the metal ions gave saturation curves as depicted in Fig. 1. For these systems, the absorbance values at a large excess of the metal ions were taken as ΔA_∞ and the plots of $(\alpha^{-1} - 1)^{-1}$ against $([M^{2+}]_0 - \alpha[\text{XNAH}]_0)$ (Eq. [3]) are shown in Fig. 2. Good linearity of the plots indicates the formation of 1 : 1 complexes. The association constants K are obtained from the slopes of the plots and listed in Table 2.

For association of **3** and **4** with all the metal ions, and **1** and **2** with Co^{2+}, ΔA increased gradually with the concentration of the metal ions without showing

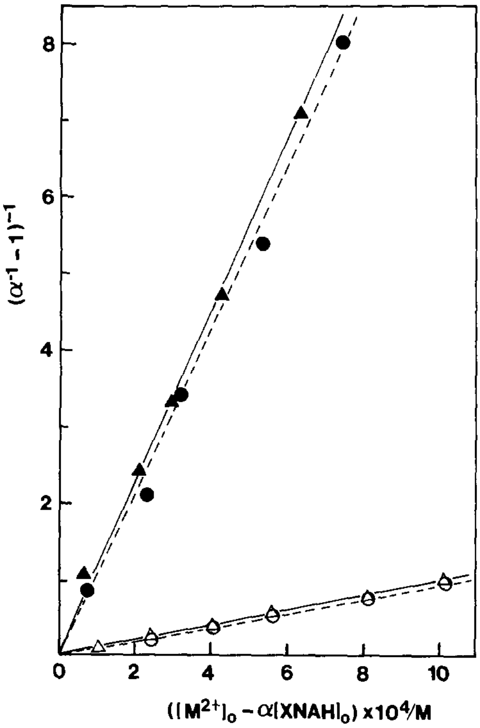


FIG. 2. Plots of spectroscopic titration data of **1** and **2** with Mg^{2+} or Zn^{2+} according to Eq. [3]: (▲) **1** with Mg^{2+}, (△) **1** with Zn^{2+}, (●) **2** with Mg^{2+}, (○) **2** with Zn^{2+}.

TABLE 2

Association Constants K of NADH Analogs with Metal Ions and Second-Order Rate Constants k_2^0 for the Reaction between NADH Analogs and MAI in Acetonitrile at 30°C[a]

NADH analog	X	$K(\mathrm{M}^{-1})$[b] Mg^{2+}	Zn^{2+}	Co^{2+}	$k_2^0/(\mathrm{M}^{-1}\ \mathrm{s}^{-1})$
1	$CONH_2$	11,200 (11,000)[c]	970 (1000)[c]	450	82
2	$CSNH_2$	10,600 (11,000)[c]	920 (1000)[c]	370	85
3	$COOCH_3$	12	—[d]	—[d]	34
4	$COCH_3$	430	23	17	22

[a] k_2^0 is taken in the absence of divalent metal ions.

[b] Determined by spectroscopic methods.

[c] Obtained from kinetic results.

[d] No evidence of appreciable association is observed.

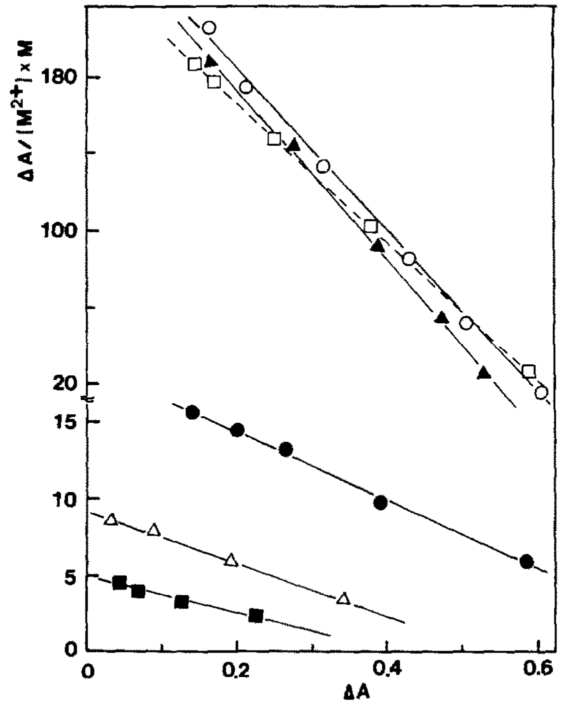


FIG. 3. Benesi–Hildebrand plots (Eq. [4]) of absorbance titration data of NADH analogs with metal ions: (▲) **1** with Co^{2+}, (□) **2** with Co^{2+}, (■) **3** with Mg^{2+}, (○) **4** with Mg^{2+}, (●) **4** with Zn^{2+}, (△) **4** with Co^{2+}.

saturation even when we raised $[M^{2+}]$ to 0.1 M. Therefore, we used Eq. [4] to determine K values of these systems (Fig. 3). Again, good linearity of the plots implies formation of 1 : 1 complexes. K values were calculated from the slopes of the plots and included in Table 2.

Metal ion effect on the reduction of N-methylacridinium iodide by NADH analogs. The reduction reaction of MAI with NADH analogs is first-order with respect to both MAI and NADH analogs (*12*). The absorbance at 415 nm, where MAI shows maximum absorption and NADH analogs do not absorb appreciably, from a solution of an equimolar mixture of MAI and the NADH analog follows Eq. [5],

$$1/A_t - 1/A_0 = k_2/\varepsilon b \times t, \qquad [5]$$

where ε is the molar absorptivity of MAI in the reaction medium, 3680 cm^{-1} M^{-1} at 30°C, and b is the light path length, 1 cm; A_t and A_0 are the absorbance values at times t and $t = 0$, respectively. Figure 4 shows plots of kinetic data for the reactions of **1** with MAI in the presence of various concentrations of Mg^{2+}. It is evident from the figure that the reaction also follows the second-order kinetics in the presence of a large excess of Mg^{2+}: when $[Mg^{2+}]_0 < 2 \times 10^{-4}$ M, i.e., $[Mg^{2+}]_0/[\mathbf{1}]_0 < 4$, the plot of $1/A_t$ vs t deviates significantly from linearity as the fraction of **1** complexed with Mg^{2+} varies significantly during the reaction. The second-order

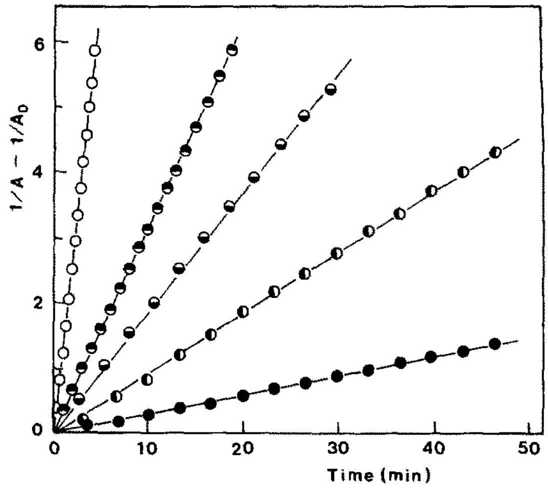


FIG. 4. The second-order kinetic plots (Eq. [5]) for the reaction between **1** and MAI in the presence of various concentration of Mg^{2+} in acetonitrile at 30°C. [Mg^{2+}]: 0.0 (○), 0.28 (◓), 0.58 (◒), 0.96 (◐), and 4.82 mM (●). [**1**] = [MAI] = 5.0×10^{-5} M.

rate constants, k_2's, are calculated from the slopes of the plots and aforementioned ε value. As can be noted from Fig. 4, the presence of Mg^{2+} remarkably retards the reaction between **1** and MAI. The inhibitory effect of metal ions on the reactions between NADH analogs and MAI was also observed for other systems, except for the case of **3** with Zn^{2+} or Co^{2+}. The dependence of k_2 values on the concentration of metal ions is shown in Fig. 5.

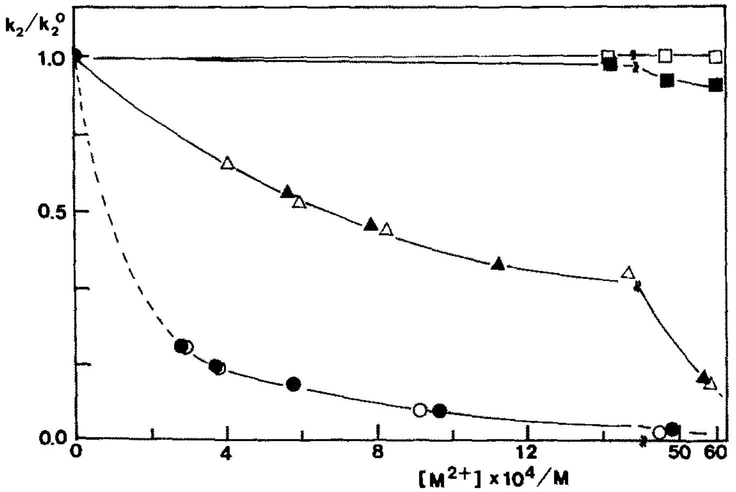
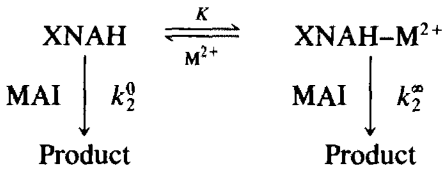


FIG. 5. Metal ion inhibition for the reactions of NADH analogs with MAI: (●) **1** by Mg^{2+}, (△) **1** by Zn^{2+}, (○) **2** by Mg^{2+}, (▲) **2** by Zn^{2+}, (■) **3** by Mg^{2+}, (□) **3** by Zn^{2+}. k_2^0 is the second-order rate constant for the reaction in metal ion-free solution (see Table 2).

There is a good correlation between the magnitude of the association constant of a NADH analog with a metal ion and the effectiveness of the metal ion for the inhibition of the reaction of the NADH analog with MAI. Thus, the effect of metal ions (M^{2+}) on the reactions between NADH analogs (XNAH) and MAI may be ascribed to the complexation between the NADH analogs and the metal ions. The reaction in the presence of the metal ion is written as Scheme 1.



SCHEME 1

Assuming rapid equilibrium between the free XNAH and XNAH–M^{2+}, the rate constants are related to K and $[M^{2+}]$ by Eqs. [6] and [7],

$$k_2 = k_2^0 + \frac{K[M^{2+}](k_2^0 - k_2^\infty)}{1 + K[M^{2+}]}, \qquad [6]$$

$$(1 - k_2/k_2^0)^{-1} = (1 - k_2^\infty/k_2^0)^{-1} + \{(1 - k_2^\infty/k_2^0)K\}^{-1}[M^{2+}]^{-1}, \qquad [7]$$

where k_2^∞ is the second-order rate constant of MAI with the metal ion complex, XNAH–M^{2+}. Under the condition of $[M^{2+}]_0 \gg [XNAH]_0$, $[M^{2+}]$ in Eqs. [6] and [7] can be replaced by $[M^{2+}]_0$. The plots of $(1 - k_2/k_2^0)^{-1}$ vs $[M^{2+}]_0^{-1}$ (Eq. [7]) are shown in Fig. 6 for the reduction reaction of MAI by **1** or **2** in the presence of Mg^{2+} or Zn^{2+}. Good linearity of the plots indicates the validity of Scheme 1. By dividing the intercept by the slope, the complex formation constants K are obtained and included in Table 2. The K values calculated from the kinetic data show an excellent agreement with those from spectroscopic measurements described in the previous section.

The intercepts of the plots in Fig. 6 are found to be virtually 1 for all cases studied here. This indicates that XNAH molecules complexed with the metal ions are well protected against the reaction by MAI.

DISCUSSION

The strong absorption band of NADH analogs (1,4-dihydropyridines) near 350 nm could be ascribed to the n–π^* transition of dihydropyridine moiety (*5*). There are two conceivable modes of complexation between a NADH analog and a metal ion: one is the complexation of the metal ion on the carbonyl oxygen (or thiocarbonyl sulfur for **2**) atom of the 3-substituent of the dihydropyridine ring; the other is on the ring nitrogen. From spectroscopic studies of 3-(*N,N*-disubstituted carbamoyl)-1,4-dihydropyridines and MO considerations, Tagaki and co-workers have proposed that the former type of complexation causes a red-shift of the

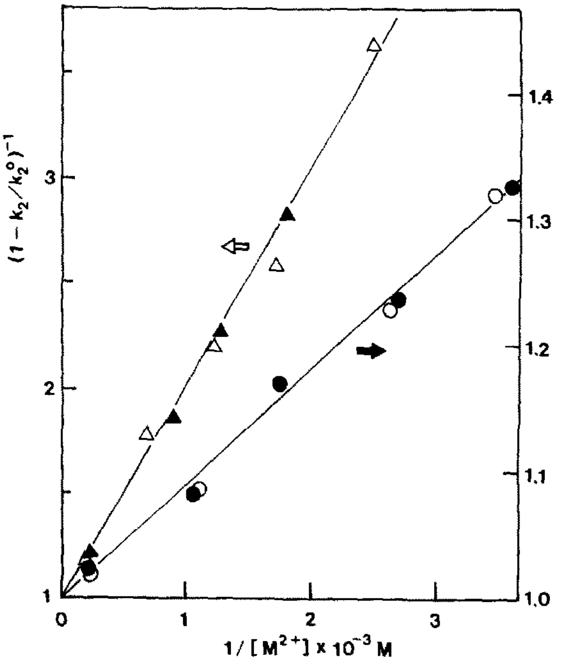
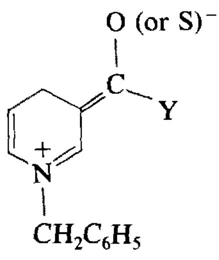


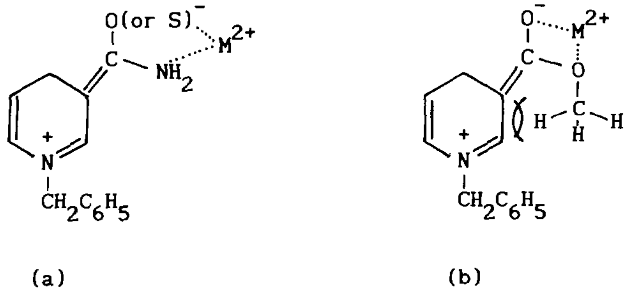
FIG. 6. Kinetic data for the reaction between MAI and NADH analogs in the presence of metal ions plotted according to Eq. [7]: (●) **1** with Mg^{2+}, (△) **1** with Zn^{2+}, (○) **2** with Mg^{2+}, (▲) **2** with Zn^{2+}.

absorption band, while the latter results in a blue-shift (*4*, *5*). The results of ^1H and ^{13}C NMR studies (*6*) as well as uv–vis spectroscopic studies (*5*) indicate that Zn^{2+} ions bind to the carboxamide oxygen of 1-benzyl-1,4-dihydronicotinamide, **1**.

For NADH analogs studied here, the absorption maximum shifts toward longer wavelength upon complexation with the metal ions. This is strongly suggestive that the primary binding site of the metal ions in the NADH analogs **1–4** is the carbonyl oxygen (for **1**, **3**, and **4**) or the thiocarbonyl sulfur (for **2**) of the 3-substituent of the dihydropyridine ring. The absorption at a longer wavelength from NADH analog–metal ion complexes is ascribed to the contribution of the resonance form **A**, in which the lone pair of electrons of the ring nitrogen conjugate further with the π-system of the carbonyl group, to the electronic transition (*5*, *11*). Obviously, the resonance form **A** is stabilized upon binding of the metal ions to the carbonyl oxygen or the thiocarbonyl sulfur atom.



A



(a) (b)

FIG. 7. Possible modes of complexation between NADH analogs and the metal ions: (a) **1** and **2**; (b) **3**. See text for explanation.

It was reported that the association constants of 1-benzyl-1,4-dihydronicotinamide (BNAH), **1**, in dry acetonitrile are 11,000–12,000 M^{-1} for Mg^{2+} at 25°C (*3*) and 500 M^{-1} for Zn^{2+} at 50°C (*8*). Considering the effect of temperature on the association constant, our results (Table 1) agree well with these values. Also, the 1 : 1 stoichiometry of the complexes is consistent with the conclusions of the reports (*3, 8*): a 2 : 1 stoichiometry was proposed for Mg^{2+} complexes of some chiral NADH model compounds (*7*).

Table 2 shows that the association constants of NADH analogs with metal ions vary quite sensitively depending on the nature of both the 3-substituent of the dihydropyridine ring and the metal ion: the decreasing order of the association constants is $\mathbf{1} \cong \mathbf{2} \gg \mathbf{4} \gg \mathbf{3}$ for a given metal ion and $Mg^{2+} \gg Zn^{2+} > Co^{2+}$ for a given NADH analog. It is difficult to correlate directly the magnitude of the association constants with the electronic properties of the 3-substituents. We have shown that the reactivity of NADH analogs **1–4** for various types of reactions is in the order $\mathbf{2} \geq \mathbf{1} > \mathbf{3} > \mathbf{4}$, which is the decreasing order of the electron-donating character of the 3-substituent (*12*). (For the rate constants of the reactions of XNAH with MAI in the absence of metal ion, see Table 2.) The similarity between **1** and **2** in the magnitude of the association constant with the metal ion, in the spectral change associated with the complexation, and in the kinetic behavior in the reaction with MAI indicates that the carboxamide and thiocarboxamide groups of the 3-position of 1,4-dihydropyridine exhibit very similar affinity to metal ions and electronic effect.

The effect of 3-substituents on the association constants of the NADH analogs with metal ions is much greater than that on the reactivity of the NADH analogs. One possible explanation for this is involvement of the amide nitrogen in the complexation of **1** and **2**, which would result in the complexes of bidentate structure as shown in Fig. 7a. It is natural to conclude that the additional coordination enhances the stability of the complexes. The suggested coordination of metal ions to the two atoms of the 3-substituent would be far less feasible for **3** than for **1** and **2**, because the oxygen atom has less electron-donating ability than the nitrogen atom. Moreover, such binding, if any, would result in nonbonding interaction between the methyl group and the dihydropyridine ring (see Fig. 7b). Thus, the binding of a metal ion to **3** seems to be monodentate as the binding to **4** which does not have possible additional binding site in the 3-subtituent ($X = COCH_3$). It is expected that the binding to **4** would be stronger than that to **3** since formation of the further conjugated resonance structure **A** would be easier in **4** than **3** due to more electron-withdrawing character of the acetyl group than the ester group. These structural and electronic considerations seem to successfully account for the order of complex formation constants among NADH analogs investigated in this study.

The order of the association constants among metal ions ($Mg^{2+} \gg Zn^{2+} > Co^{2+}$) is the same as that reported for complexation of the metal ions by 1-benzyl-3,5-bis(1-pyrrolidinylcarbonyl)-1,4-dihydropyridine (BPDH) (*4*). However, the order is the reverse of that reported for complexation of the metal ions with pyridine and salicylaldehyde (*14*). Many workers have presented the order of catalytic efficiency of divalent metal ions in metal ion-catalyzed reductions by NADH models (*1b*). Studies on the reduction of pyridoxal phosphate and its analogs by 2,6-dimethyl-3,5-dicarboalkoxy-1,4-dihydropyridine in the presence of a metal ion showed the order of effectiveness of metal ion catalysis to be $Ni^{2+} > Co^{2+} > Zn^{2+} > Mn^{2+} > Mg^{2+}$ (*15*), which correlates nicely with the order of stability of metal ion complexes of the aforementioned pyridine and salicylaldehyde (*14*). A similar study for the reaction of metal-1,10-phenanthroline-linked dihydronicotinamide with 2-pyridinecarboxaldehyde showed that the efficiency of metal ion activation is of the order of $Zn^{2+} \gg Mg^{2+}$, $Ni^{2+} > Co^{2+} > Cd^{2+}$ (*11*). However, explanations for the variation among metal ions are scarce: Ohno *et al.* (*16*) claimed that the catalytic efficiency of a metal ion depends largely on the charge density, while Awano *et al.* (*4*) concluded that an ion from the metal atom having a lower second ionization potential (Ip) forms a stronger complex with BPDH. Neither of these interpretations can explain the complex of Zn^{2+} being stronger than that of Co^{2+}: both Ip and ionic radius of Co^{2+} are smaller than the corresponding values of Zn^{2+}. It seems that more detailed studies on the complexes, both theoretical and structural, are required to interpret the variation of binding affinity of metal ions for NADH analogs.

As shown in Figs. 4 and 5, the presence of the divalent metal ions inhibits the reduction of MAI by the NADH analogs. Dependence of the rate constant of the reaction upon [M^{2+}] fits nicely with Scheme 1, showing that the reaction between the XNAH–M^{2+} complex and MAI is extremely unfavorable. It may be suggested that the inhibition of the reaction by M^{2+} is due to electrostatic repulsion between the *N*-methylacridinium ion and the complex cation. Shinkai *et al.* suggested that an added Mg^{2+} ion changes the path of the reaction between **1** and MAI to a simple one-step type reaction from a two-step reaction (*17*). However, no evidence of such change in reaction mechanism is found from this study.

In conclusion, the present study demonstrates that the primary binding site of NADH analogs for divalent metal ions is carbonyl oxygen or thiocarbonyl sulfur, and amide nitrogen atom also ligates the metal ion, forming a bidentate structure and providing extra stability to the complexes of **1** and **2** compared to **3** and **4**. The order of stability of the metal ion complexes is $Mg^{2+} \gg Zn^{2+} > Co^{2+}$. Formation of the complex protects NADH analog molecules against the reaction by MAI due to charge repulsion.

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REFERENCES

1. (a) Inouye, Y., Oda, J., and Bada, N. (1983) *in* Asymmetric Synthesis (Morrison, J. D., Ed.), Vol. 2, pp. 91–124, Academic Press, New York; (b) Yasui, S., and Ohno, A. (1986) *Bioorg. Chem.* **14,** 70, and references therein.
2. Park, K. K., Suh, J. H., and Park, J. W. (1988) *Bull. Korean Chem. Soc.* **9,** 329.
3. Fukuzumi, S., Kondo, Y., and Tanaka, T. (1983) *Chem. Lett.* 485.
4. Awano, H., Takemoto, K., Ohya, H., Tomio, M., Tamagaki, S., and Tagaki, W. (1987) *Bull. Chem. Soc. Jpn.* **60,** 1887.
5. Tamagaki, S., Simojo, Y., Mimura, T., and Tagaki, W. (1989) *Bull. Chem. Soc. Jpn.* **62,** 1593, and references therein.
6. Hughes, M., Prince, R. H., and Wyeth, P. (1978) *J. Inorg. Nucl. Chem.,* 713.
7. (a) Amano, M., Baba, N., Oda, J., and Inouye, Y. (1984) *Bioorg. Chem.* **12,** 299; (b) Baba, N., Amono, M., Oda, J., and Inouye, Y., (1984) *J. Am. Chem. Soc.* **106,** 1481.
8. Ohno, A., Yasui, S., Gase, R. A., Oka, S., and Pandit, U. K. (1980) *Bioorg. Chem.,* **9,** 199.
9. Talma, A. G., Jouin, P., De Vries, J. G., Troostwijk, C. B., Buning, G. H. W., Waninge, J. K., Visscher, J., and Kellogg, R. M. (1985) *J. Am. Chem. Soc.* **107,** 3981.
10. Fukuzumi, S., Nishizawa, N., and Tanaka, T. (1983) *Chem. Lett.* 1755.
11. Engbersen, J. F. J., Koudijs, A., and van der Plas, H. C. (1990) *J. Org. Chem.* **55,** 3647.
12. Park, K. K., Kim, H.-G., and Park, J. W., (1989) *Bull. Korean Chem. Soc.* **10,** 448.
13. Benesi, H. A., and Hildebrand, H. (1949) *J. Am. Chem. Soc.* **71,** 2703.
14. (a) Brewer, D. G., and Wong, P. T. T., (1966) *Can. J. Chem.* **44,** 1407; (b) Mellor, D. P., and Maley, L. (1947) *Nature (London)* **159,** 370; (c) Martell, A. E., and Calvin, M. (1952) *in* Chemistry of the Metal Chelate Compounds, p. 546, Prentice-Hall, New York.
15. (a) Shinkai, S., and Bruice, T. C. (1972) *J. Am. Chem. Soc.* **94,** 8258; (b) Shinkai, S., and Bruice, T. C. (1973) *Biochemistry* **12,** 1750.
16. Ohno, A., Kimura, T., Yamamoto, H., Kim, S. G., Oka, S. and Ohnishi, Y. (1977) *Bull. Chem. Soc. Jpn.* **50,** 1535.
17. Shinkai, S., Ide, T., Hamada, H., Manabe, O., and Kunitake, T., (1977) *J. Chem. Soc. Chem. Commun.* 848.