Kinetic Studies on the Reactions of NADH Analogs:
Effects of 3-Substituents of 1-benzyl-1,4-Dihydropyridines

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NADH analogs, 1-benzyl-3-substituted (X)-1,4-dihydropyridines 1-4 (1: X = $CONH_2$; 2: X = $CSNH_2$; 3: X = $COOCH_3$; 4: X = $COCH_3$) were synthesized. The second order rate constants for hydration reaction and oxidation reactions by Cu^{2+}, $Fe(CN)_6^{3-}$ or methylacridinium iodide (MAI) of the compounds were determined. For all reactions investigated, the rate constants increased with decreasing electronegative character of the 3-substituents of 1,4-dihydropyridines: the decreasing order of the reaction rates was 2>1>3>4. However, the sensitivity of the reaction rates on the 3-substituents differed among the reactions. This was explained in view of mechanisms of the reactions.

Introduction

The fact that NADH is a coenzyme for many dehydrogenases has stimulated considerable efforts in synthesizing NADH model compounds and exploring the reactions involving the compounds. In particular, numerous works on reduction of various substrates by NADH model compounds have been reported with the view of illucidating the reaction mechanism, and mimicking the efficent and stereospecific reaction of NADH in biological systems.[1-3] NADH model compounds are known to undergo acid-catalyzed hydration reaction[4-6] in addition to the oxidation reactions. Thus, for efficient utilization of NADH model compounds in organic reduction reactions in water-containing media, compounds having less reactivity toward hydration reaction while having greater reducing ability are desired. Most of the work on NADH model compounds have been carried out with 1-substituted dihydronicotinamides, 3-carbamoyl-1,4-dihydropyridines.

Recently, it was reported that alcohol dehydrogenase-catalyzed oxidation of alcohols to aldehydes by oxidized form of NADH, NAD^{+}, proceeds more smoothly if the nicotinamide moiety in NAD^{+} is replaced by thionicotinamide or 3-acetylpyridine.[7] However, little work has been reported on the correlation between the nature of 3-substituents and the reactivity of 1,4-dihydropyridines. This paper describes the effects of 3-substituent on hydration and oxidation reactions of NADH analogs, 1-benzyl-3-substituted-1,4-dihydropyridines 1-4. Cupric ion, ferricyanide ion and N-methylacridinium iodide (MAI) were chosen as oxidants.

1 - 4

1: X = $CONH_2$
2: X = $CSNH_2$
3: X = $COOCH_3$
4: X = $COCH_3$
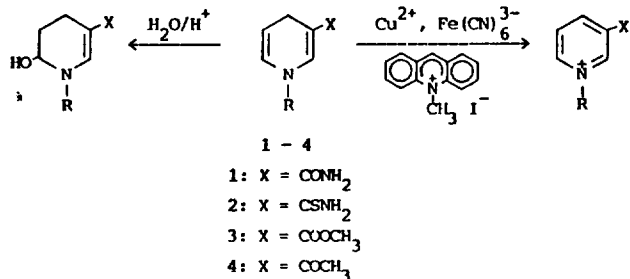
Experimental

Materials. 1-Benzyl-3-carbamoyl-1,4-dihydropyridi-

ne[8] 1 and MAI[9] were prepared according to the literature procedures. The other NADH analogs 2-4 were synthesized by modification of procedures described in the literature.[4] Preparation and characteristics of the compounds are following.

1-Benzyl-3-Thiocarbamoyl-1,4-Dihydropyridine (2). A solution of thionicotinamide (Aldrich, 3.5 g, 25 mmol) and benzyl chloride (5.0 ml, 43 mmol) in anhydrous ethanol (30 ml) was heated at reflux for 9 hrs. After cooling, precipitate was filtered and washed with CH_2Cl_2 to yield 4.2 g (63%, mp 210-212 °C) of 1-benzyl-3-thiocarbamoylpyridinium chloride: ^{1}H NMR (D_2O) δ6.0 (s, 2H), 7.58 (s, 5H), 8.15-8.5 (m, 1H), 9.1-9.3 (m, 2H) and 9.5 (broad s, 1H).

To a solution of 1-benzyl-3-thiocarbamoylpyridinium chloride (1.5 g, 5.7 mmol) in water (30 ml) at 0-4 °C, an aqueous solution of Na_2CO_3 (2.7 g in 15 ml H_2O) was added. Maintaining the temperature at 0-4 °C, dithionite ($Na_2S_2O_4$, 3.5 g) was added and the reaction mixture was stirred for 30 min. The precipitate was filtered and recrystallized from ethanol-water to get 1.0 g (75%, mp 103-107 °C) of 2: ^{1}H NMR($CDCl_3$) δ3.1-3.3(m, 2H), 4.27 (s, 2H), 4.55-4.9 (m, 1H), 5.6-6.0 (m, 3H), 7.18 (s, 1H) and 7.3 (s, 5H).

1-Benzyl-3-Carbomethoxy-1,4-Dihydropyridine (3). A solution of methyl nicotinate (Aldrich, 1.8 g, 13 mmol) and benzyl chloride (2.5 ml, 21 mmol) in anhydrous ethanol (20 ml) was heated at reflux for 4 hrs. After removal of solvent and excess benzyl chloride by rotary evaporator and then Kugelrohr apparatus at reduced pressure, white solid was obtained. Washing the solid with ether produced 1.8 g (53%, mp 142-146 °C) of 1-benzyl-3-carbomethoxypyridinium chloride: ^{1}H NMR (D_2O) δ 4.18 (s, 3H), 6.1 (s, 2H), 7.62 (s, 5H), 8.3-8.58 (m, 1H), 9.2-9.5 (m, 2H) and 9.7 (broad s, 1H).

The dithionite reduction of the salt was carried out as described for the preparation of 2. The crude product was filtered from the reaction mixture, washed with water and recrystallized from ethanol-water to yield 3 (mp 48-50 °C): ^{1}H NMR ($CDCl_3$) δ3.1-3.2 (m, 2H), 3.7 (s, 3H), 4.3 (s, 2H), 4.8-4.9 (m, 1H), 5.6-5.85 (m, 1H), 7.15 (s, 1H) and 7.35 (s, 5H).

1-Benzyl-3-Acetyl-1,4-Dihydropyridine (4). A solution of 3-acetylpyridine (Aldrich, 2 ml, 18 mmol) and benzyl chloride (3.1 ml, 27 mmol) in anhydrous ethanol (20 ml) was refluxed for 5 hrs. The reaction mixture was concentrated to. *ca.* half of the original volume, followed by addition

of ethyl acetate to cause precipitation. The precipitate was filtered and recrystallized from ethanol–ethyl acetate to afford 1-benzyl-3-acetylpyridinium chloride (3.2 g, 80%, mp 184–185 °C): ^{1}H NMR (D_2O) δ2.9 (s, 3H), 6.1 (s, 2H), 7.6 (s, 5H), 8.35–8.55 (m, 1H), 9.1–9.4 (m, 2H) and 9.6 (s, 1H).

To a solution of 1-benzyl-3-acetylpyridinium chloride (1g, 4 mmol) in water (30 m*l*) at 40 °C, an aqueous solution of Na_2CO_3 (1.8 g) and $Na_2S_2O_4$ (4.2 g) in water (10 m*l*) was added dropwise. The reaction mixture was stirred for 30 mins at 40 °C to yield orange precipitate. The precipitate was filtered and recrystallized from ethanol–water to produce 4 (0.53 g, 62%, mp 64–68.5 °C): ^{1}H NMR $(CDCl_3)$ δ2.15 (s, 3H), 3.1–3.2 (m, 2H), 4.4 (s, 2H), 4.8–5.1 (m, 1H), 5.7–5.9 (m, 1H), 7.1 (s, 1H) and 7.4 (s, 5H).

Kinetics. The reactions were followed by decrease in the absorbance of **1–4** at absorption maxima (354–376 nm) of the respective compounds for hydration reaction, and oxidation reactions by Cu^{2+} and $Fe(CN)_6^{3-}$. For oxidation reaction by MAI, decrease of the characteristic absorption of MAI at 415 nm was followed. A Unicam SP 1800 UV–VIS spectrophotometer equipped with a thermostatted cell holder was used. The reaction temperature was 5.0 °C for oxidation by MAI, and 30.0 °C for other reactions. The compounds **1–4** were dissolved in anhydrous ethanol or acetonitrile. The reactions were initiated by adding the substrate solutions to HCl, $CuCl_2$, $Fe(CN)_6^{3-}$ solutions in water or MAI solution in acetonitrile. Except the reaction with MAI, in which anhydrous CH_3CN was used as a solvent, the final solvent composition was 5% ethanol–95% water at ionic strength 0.1 M adjusted with KCl. The initial concentration of **1–4** was 1.0×10^{-4} M.

In the hydration reaction, desired H^+ concentration $(1 \times 10^{-3}$–1×10^{-4} M) was obtained by addition of HCl. The reaction media for Cu^{2+} oxidation contained HCl in range of 5×10^{-5}–1×10^{-3} M to prevent precipitation of Cu^{2+} as $Cu(OH)_2$. For the ferricyanide ion oxidation, the solution was made basic by the addition of K_2CO_3 to retard the hydration reaction of the substrates. Final concentration of both K_2CO_3 and $K_3Fe(CN)_6$ was 1.0×10^{-3} M. In the reaction with MAI, the final concentration of MAI was 5.0×10^{-5} M and the concentration of **1–4** was either highly excess $(3.0 \times 10^{-4}$ M) or the same $(5.0 \times 10^{-5}$ M) as that of MAI.

For hydration reaction, cupric ion and ferricyanide ion oxidation reactions, the kinetic data were analyzed by pseudo first order kinetics. The rate constants of the reaction with MAI were determined by either pseudo first order kinetics (when [substrate] ≫ [MAI]) or second order kinetics (when [substrate] = [MAI]).

Results

Hydration. The hydration reaction of 1-benzyl-1,4-dihydronicotinamide was studied by several investigators,[4–6] and it was found that the reaction was first order with respect to both the substrate and H^+. Figure 1 shows the pseudo first order kinetic plots (eq 1) for the disappearance of **1–4** in acidic media.

$$\ln A_t - \ln A_o = k_{\psi} t \tag{1}$$

A_t and A_o are absorbances of the reacting solutions at t and $t = 0$, respectively, taken at λ_{max} of the substrates: 354 for **1**,
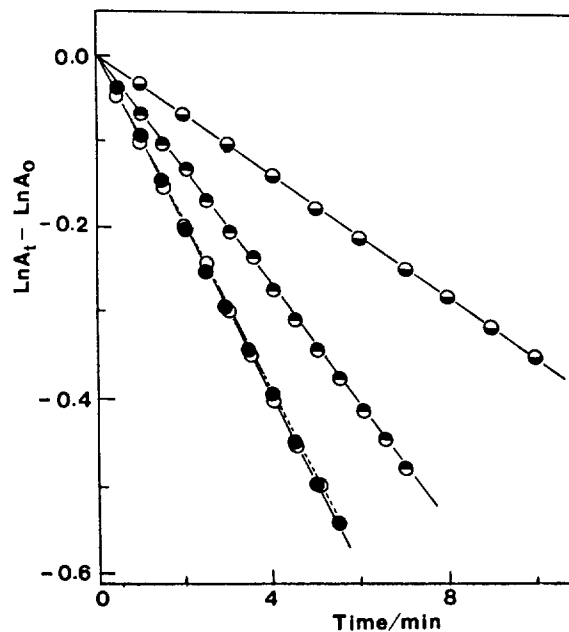

Figure 1. Pseudo first order kinetic plots for disappearance of 3-substituted (X)-1-benzyl-1,4-dihydropyridines according to eq. 1: (○), for **1** (X = $CONH_2$); (●), for **2** (X = $CSNH_2$); (◐), for **3** (X = $COOCH_3$); (◑), for **4** (X = $COCH_3$). Concentrations of HCl are 0.1 mM for **1** and **2**, 0.2 mM for **3**, and 1.0 mM for **4**.

356 for **2**, 355 for **3**, and 376 nm for **4**. Good linearity in the plots indicates that the hydration reaction of NADH analogs studied here also follows pseudo first order kinetics. In agreement with a previous study on 1-substituted-1,4-dihydronicotinamides,[6] the k_{ψ} values were propertional to $[H^+]$ (data not shown). The second order rate constants, k_H, for hydration, were obtained from the slopes of k_{ψ} vs $[H^+]$ plots. The results were collected in Table 1. Table 1 shows great sensitivity of the hydration reaction rate on the nature of 3-substituents. The decreasing order of the rate constant for hydration reaction of 1,4-dihydropyridines was **2** (X = $CSNH_2$)>**1** (X = $CONH_2$)>**3** (X = $COOCH_3$)>**4** (X = $COCH_3$). This order is the same as the increasing order of the electron-withdrawing character of the substituent at 3-position of 1,4-dihydropyridine. This is in a line with reactivity-electron-donating ability relationship observed with various 1-substituents of 1,4-dihydronicotinamide,[6] and agrees with the conclusion that protonation of NADH analogs is the rate-determining step of hydration reaction.[5]

Cupric Ion Oxidation. In our previous study,[10] we have shown that cupric ion oxidation of 1-substituted-1,4-dihydronicotinamides in aqueous solution follows first order kinetics with respect to both the substrate and Cu^{2+} in the presence of dioxygen and the oxidation reaction occurred in concurrence with the acid-catalyzed hydration reaction of the substrate. Thus the pseudo first order rate constant, k_{ψ}, for disappearance of NADH analogs in the presence of both H^+ and Cu^{2+} is expressed as eq. 2.

$$k_{\psi} = k_H [H^+] + k_{cu} [Cu^{2+}] \tag{2}$$

where k_{Cu} is the second order rate constant for oxidation by Cu^{2+}. The k_{ψ} values at various concentrations of Cu^{2+} were determined at a given concentration of H^+. The results were
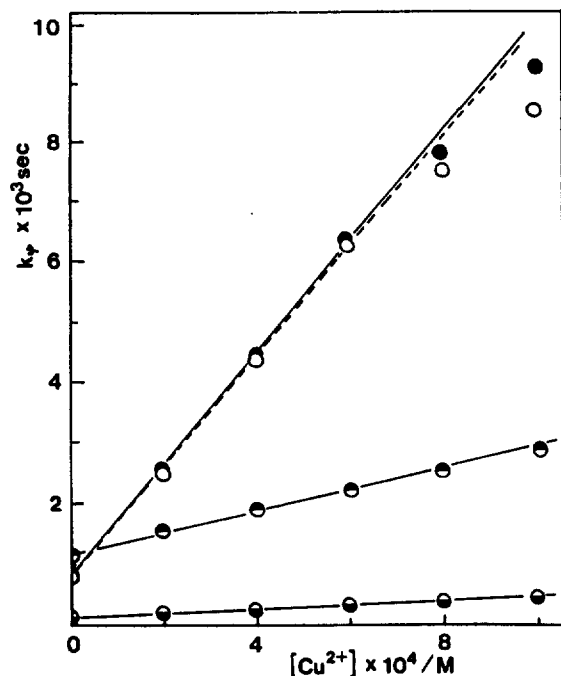
Figure 2. Variation of the pseudo first order rate constant k_ψ for disappearance of NADH analogs with concentration of Cu^{2+}. Concentrations of HCl were 0.050 mM for 1 (O) and 2 (●), and 0.20 mM for 3 (⊖) and 4 (⊖).

Table 1. Second Order Rate Constants of Hydration (k_H), Cupric Ion Oxidation (k_{Cu}), Ferricyanide Ion Oxidation ($k_{Fe(CN)_6}$) and Methylacridinium Ion Oxidation (k_{MAI}) of 1-Benzyl-3-Substituted (X)-1,4-Dihydropyridines.[a,b]

Compounds	X	k_H	k_{Cu}	$k_{Fe(CN)_6}$	k_{MAI}
1	$CONH_2$	16	8.8	48	32
2	$CSNH_2$	17	8.9	58	34
3	$COOCH_3$	5.7	1.8	18	14
4	$COCH_3$	0.59	0.37	1.8	8.0

[a] In $M^{-1}sec^{-1}$ units. [b] k_{MAI}'s were measured at 5.0 °C in anhydrous acetonitrile and others were determined at 30.0 °C in 5% C_2H_5OH–95% H_2O.

presented in Figure 2. Good linearity between k_ψ and $[Cu^{2+}]$ is evident from this figure. The slight deviation from linearity at high concentration of Cu^{2+} for 1 and 2 was attributed to formation of complexes between Cu^{2+} and the substrates.[10] The k_{Cu} values were determined from slopes of Figure 2 (for 1 and 2, we took data obtained at low $[Cu^{2+}]$). The values were tabulated in Table 1. It is clear that the second order rate constant k_{Cu} for the oxidation of NADH analogs by Cu^{2+} varies sensitively with 3-substituents. Again, k_{Cu} decreases as the 3-substituent of 1,4-dihydropyridine is more electronegative as in hydration reaction. The parallelism between k_{Cu} and k_H accords with the observation made in 1-substituted-1,4-dihydronicotinamides.[10]

Ferricyanide Ion Oxidation. Disappearance of 1–4 in the presence of 1.0×10^{-3} M $K_3Fe(CN)_6$ in 1.0×10^{-3}M aqueous K_2CO_3 solution was followed. In this case, the absorbance at the measuring wavelengths did not become zero after completion of the reaction due to absorption by Fe
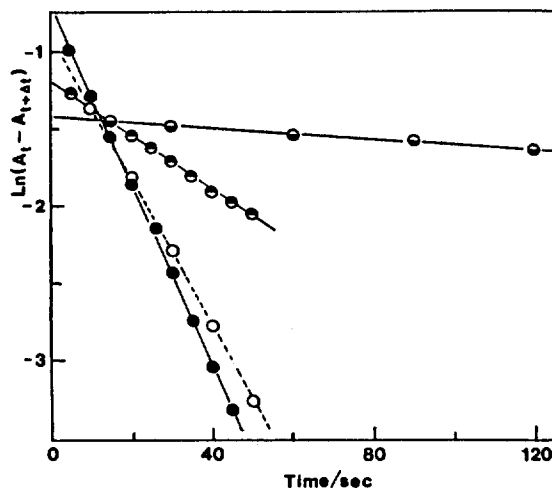

Figure 3. Pseudo first order kinetic plots for disappearance of NADH analogs according to eq. 3 in the presence of 1.0 mM $K_3Fe(CN)_6$ and 1.0 mM K_2CO_3. Legends are same as in Figure 1.
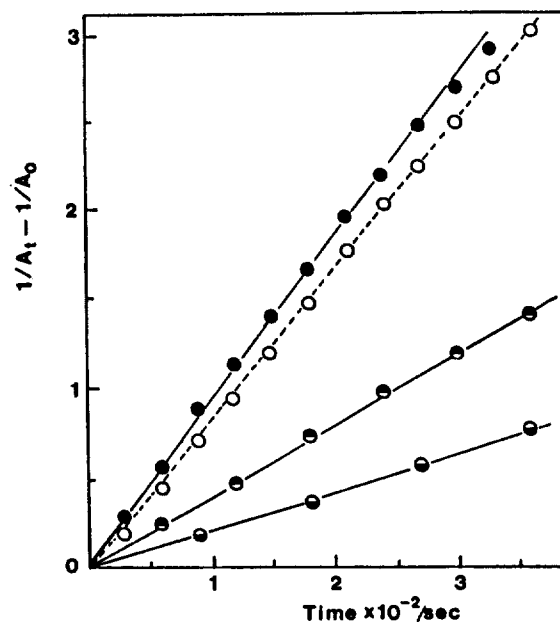

Figure 4. Second order kinetic plots for disappearance of MAI according to eq. 4 in the presence of equimolar concentration (0.05 mM) of NADH analogs in acetonitrile. Legends are same as in Figure 1.

$(CN)_6^{3-}$. Thus, we adopted eq. 3 for the plots of the kinetic data assuming first order reaction.[11,12]

$$\ln [A_t - A_{t+\Delta t}] = -k_\psi t + \text{constant} \qquad (3)$$

Figure 3 shows plots of the experimental data according to eq. 3. Pseudo first order kinetics were well obeyed in all cases. This agrees well with the reports of first order kinetics for $Fe(CN)_6^{3-}$ oxidation of 1-substituted-1,4-dihydronicotinamides.[12,13] Control experiments in the absence of $Fe(CN)_6^{3-}$, but in the presence of 1.0×10^{-3} M K_2CO_3, demonstrated that the substrates did not undergo hydration. The second order rate constants, $k_{Fe(CN)_6}$, for ferricyanide oxidation of NADH analogs were obtained by dividing the slopes of the plots by $[Fe(CN)_6^{3-}]$. The results were listed in Table 1. The

value 48 $M^{-1}sec^{-1}$ of $k_{Fe(CN)_6}$ for **1** determined in this study is quite different from the reported value of 0.89 $M^{-1}sec^{-1}$ obtained from 80% H_2O-20% CH_3CN medium.[12] This might be primarily due to the difference in solvent systems used.[14] As in the hydration and Cu^{2+} oxidation reactions, ferricyanide ion oxidation reaction was also retarded with more electron-withdrawing 3-substituents in 1,4-dihydropyridines.

Acridinium Ion Oxidation. The reduction of N-methylacridinium ion (MAI) with 1,4-dihydronicotinamide has been studied by several groups.[15-17] It has been found that the reaction is first order with respect to MAI as well as to the substrate. NADH analogs **1-4** were reacted with equimolar concentration $(5.0 \times 10^{-5}$ M) of MAI in dry acetonitrile. Figure 4 shows plot of absorbance of MAI at 415 nm according to second order kinetics, eq. 4.

$$1/A_t - 1/A_o = k_{MAI}/\varepsilon b \times t \qquad (4)$$

where ε is the molar absorptivity of MAI in acetonitrile at 5 °C, 3680 $cm^{-1}M^{-1}$, and b is the light-pathlength, 1 cm. The second order rate constants k_{MAI} for the oxidation reactions of **1-4** by MAI were obtained by multiplying the slopes of the plots by $\varepsilon b = 3680$ M^{-1} and summarized in Table 1. We also studied the reaction by pseudo first order kinetics in condition of [substrate] $\gg$ [MAI]. The second order rate constant k_{MAI} determined from the pseudo first order kinetics agreed well with those from Figure 4. As in other reactions of NADH analogs **1-4** studied here, the rate constants of acridinium ion oxidation reactions of **1-4** were smaller for 1,4-dihydropyridines having 3-substituent with greater electron-withdrawing character.

Discussion

Table 1 shows that the hydration reaction and the oxidation reactions (by Cu^{2+}, $Fe(CN)_6^{3-}$ and acridinium ions) of NADH analog **1—4** are retarded with more electronegative 3-substituent in 1,4-dihydropyridine moiety. Though there is good parallelism between the rate constants of the reactions of NADH analogs and electronic characters of 3-substituent, regardless of reaction types, the sensitivity of the rate constants on the 3-substituent differs significantly among the reactions. In hydration and ferricyanide ion oxidation reaction, the sensitivity was virtually same. However, the reaction rate of acridinium ion oxidation was much less sensitive on the 3-substituent than the other reactions.

The difference in sensitivities of the reactivity of NADH analogs on the nature of 3-substituent among the reactions can be interpreted in connection with the reaction mechanisms. The oxidation of NADH analogs by MAI, which is a net hydride ion acceptor, can proceed by one-step hydride transfer mechanism.[17] On the other hand, the oxidation by inorganic electron acceptors such as Cu^{2+} and $Fe(CN)_6^{3-}$ involves rate determining one-electron transfer process.[10,12] The weakest dependence of acridinium ion oxidation on the 3-substituent of 1,4-dihydropyridine indicates that development of a positive charge in the dihydropyridine ring at the transition state of the rate-determining step for the reaction between MAI and NADH analogs in acetonitrile is less than that in the other reactions. This supports a suggestion by Bunting *et al.*[17] that the lowest energy pathway for the reaction of 1,4-dihydronicotinamide with MAI in ace-

tonitrile medium is the one-step hydride transfer involving only fractional positive charge development on the nicotinamide moiety in the transition state. The reaction mechanism of the oxidation reactions of NADH analogs can be altered by solvent system.[17] In this aspect, there is good possibility that the difference in the reaction mechanisms for oxidation reactions by MAI and by the inorganic oxidants arises from the effects of solvent on the reaction mechanism. (Works on the effects of solvents and other factors on the reactions of NADH analogs **1-4** are in progress.)

Interestingly, the cupric ion oxidation reaction rate was slightly less sensitive on the 3-substituent than the hydration reaction. This is quite contrast to the results of our previous study,[10] which showed the greater dependence of the cupric ion oxidation rate on the electron-withdrawing character of 1-substituent of dihydronicotinamide than the hydration reaction rate. This might come from the fact that 3-substituent plays an additional role in the cupric ion oxidation reaction, in addition to the simple electronic effect. The proposed formation of complex between Cu^{2+} and NADH analog as an intermediate step for the oxidation reaction[10] might be responsible for this. In this case, the 3-substituent might be directly involved in the complexation.

In conclusion, the hydration and oxidation reaction rates of NADH analogs are slower as the 3-substituent in 1,4-dihydropyridine moiety is more electron-withdrawing. The sensitivity of reaction rates on the 3-substituent was smallest for the acridinium ion oxidation in dry acetonitrile, and was largest for hydration and ferricyanide ion oxidation reactions. The difference in the sensitivity of the reaction rates on the 3-substituent among reaction types can be attributed to the differences in the reaction mechanisms.

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The Critical Phenomena of a Model for the Metabolic Control System with Positive Feedback

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The static and dynamic phenomena of a model for the metabolic control system with positive feedback are discussed with the static and dynamic renormalization group theory. Then, the explicit results for the static and dynamic exponents are obtained up to the second order of ε-expansion, ε being $4-d$, where d is the space dimensionality of the system.

Introduction

One of the most interesting phenomena in a metabolic system is the control mechanism, which regulates the flux of material through the various metabolic pathways. There are two kinds of the metabolic control mechanisms, which are accomplished by negative or positive feedback.[1-4] The most important physical phenomenon by the negative feedback is the biochemical oscillation.[1,3-4] That oscillation can be a sustained oscillation or a limit cycle. The essence in the metabolic control system with positive feedback is the biochemical hysteresis.[1-3] In a real system the mechanism is so complicated that it is necessary to extract the essential physical phenomena of the real system. In fact, there exist simple kinetic models consisted of many dimensional ordinary differential equations for the concentrations of the reactants in the metabolite.[1-4] Even though they are simplified or oversimplified, they are at least compatible with the experimental results qualitatively. Many authors have studied the dynamics of the metabolic control models. However, there are still a lot of works to be investigated. One of them is the critical behavior of the model with positive feedback.

The purpose of the present paper is to investigate the behavior of a model for the metabolic control system with positive feedback near the critical point by using the well-known renormalization group(RG) method.[5-8] As usual, we shall separate the critical behavior into the static and the dynamic behaviors. In both cases the results will be obtained up to the second order of ε in the ε-expansion, ε being $4-d$, where d is the space dimensionality of the system.

In section II we discuss general properties of the model given in references 1-3. The deviation of the concentrations of the reactants from the values at the steady state is assum-

ed to be due to the Langevin random forces, which satisfy the Gaussian condition.[9] We obtain a nonlinear equation for the fluctuating concentrations near the critical point, which is very similar to the time-dependent Landau-Ginzburg equation for the classical Ising spin system.[7-8] In the next section the Gaussian approximation is applied to discuss the static critical behavior of the model and then the RG method is used to the nonlinear effect on the critical exponents.[5-7] In section IV the dynamic RG method, which is just the extension of the static RG method, is used to obtain the dynamic exponents. In this case we simplify the dynamic process by assuming that there are very rapid and sufficient energy exchanges between the system and the surroundings. Finally, we discuss the present results and compare these with the numerical values of the exponents from other systems.[10-15]

Theory

Let us consider a kinetic equation for a model of metabolic control system with positive feedback given as[1-3]

$$\dot{X}_1 = f(X_n) - k_1 X_1$$
$$\dot{X}_i = X_{i-1} - k_i X_i, \quad (2 \le i \le n) \tag{2.1}$$

where X_i and k_i are the dimensionless concentration of the i-th component and corresponding rate constant, respectively, and

$$f(X_n) = \frac{u + X_n^p}{1 + X_n^p} \tag{2.2}$$

In Eq. (2.2) p is the cooperativity of the system and u is the controllable parameter depending on temperature. Let us define a function, g as