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Reduction by a Model of NAD(P)H

XXIII. Kinetics for the Reduction of 2-Acylpyridines

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Kinetics for the reduction of 2-acetylpyridine and 2-benzoylpyridine with 1-benzyl-1,4-dihydronicotinamide in acetonitrile has been studied. Isotope effects of the reduction reveal that the transfer of hydrogen nucleus is involved in the rate-determining step. The effect of zinc ion on the reaction rate has been studied quantitatively and the *true* reacting species have been elucidated.

INTRODUCTION

It has been reported that the reduction of some substrates [e.g., methyl benzoylformate (*1*) and α,α,α-trifluoroacetophenone (*2*)] with an NAD(P)H-model compound is accelerated by bivalent metal ions such as zinc and magnesium ions, whereas that of others [e.g., thiopivalophenone (*3*) and hexachloroacetone (*4*)] is retarded. On the other hand, the reduction of 2-benzoylpyridine (BP) is affected by the metal ion in such a way that the rate increases, comes to a maximum, then decreases as the concentration of metal ion increases (*5*). Similar behavior is also observed for 2-acetylpyridine (AP).

There are two contradictory explanations for the existence of a maximum point in the rate-metal ion concentration profile: one proposes that the metal ion activates the substrate but deactivates the model compound by forming complexes with these compounds (*5*, *6*). The other predicts activation and deactivation of the coenzyme model and substrate, respectively (*3*, *7*).

The present paper reports the kinetics for the zinc ion-catalyzed reduction of AP and BP with 1-benzyl-1,4-dihydronicotinamide (BNAH) and discusses the implication of the results for the mechanism of the reaction, especially with respect to the role of the metal ion.

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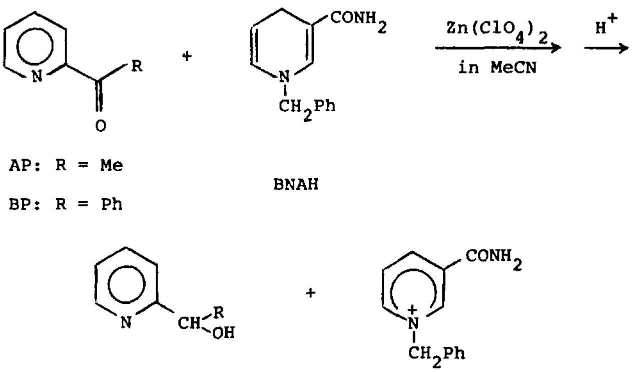

RESULTS AND DISCUSSION

Pseudo-first-order kinetics was followed spectrophotometrically by observing the decrease in the intensity of absorption from BNAH at about 360 nm. Each run gave a good first-order relationship (correlation coefficient; $r > 0.999$) for more than three half-lives. For AP, pseudo-first-order kinetics was also followed with vapor-phase chromatography by observing the decrease in the amount of AP. Although each run gave satisfactory first-order relationship (correlation coefficient; $r > 0.99$), the reproducibility from this method was not as good as that from the spectroscopy. The results are listed in Tables 1–3. The autodecomposition of BNAH is catalyzed by zinc ions. A double-reciprocal plot of k^{M}_{dec}, the observed rate constant for the autodecomposition of BNAH at an appropriate concentration of zinc ion, against $[Zn^{2+}]$, the concentration of zinc ion, gave a straight line (Fig. 1). The values for K and k_{dec}, defined by Eq. [1], were calculated to be 500 M^{-1} and 6.94×10^{-5} sec^{-1}, respectively, from the slope and intercept of the line according to Eq. [2].

$$\mathrm{BNAH} + \mathrm{Zn}^{2+} \overset{K}{\rightleftharpoons} \mathrm{BNAH} \cdot \mathrm{Zn}^{2+} \xrightarrow{k_{dec}} \qquad [1]$$

$$\frac{1}{k^{M}_{dec}} = \frac{1}{k_{dec}K[\mathrm{Zn}^{2+}]} + \frac{1}{k_{dec}}. \qquad [2]$$

It is known that at least six molecules of BNAH can coordinate onto zinc ion (*5*). However, for obtaining a rate expression, we took only two equilibria (Eqs. [3] and [4]) into account, which will be proved later to be necessary and practically sufficient.[3]

$$\mathrm{B} + \mathrm{M} \overset{K_{B1}}{\rightleftharpoons} \mathrm{B} \cdot \mathrm{M} \qquad [3]$$

$$\mathrm{B} + \mathrm{B} \cdot \mathrm{M} \overset{K_{B2}}{\rightleftharpoons} \mathrm{B}_2 \cdot \mathrm{M}. \qquad [4]$$

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[3] This treatment does not deny the existence of aggregates of higher-order.

In addition, it has been known that there are equilibria between the substrate and zinc ion (Eqs. [5] and [6]) (*8*).

$$\mathrm{S} + \mathrm{M} \overset{K_{S1}}{\rightleftharpoons} \mathrm{S} \cdot \mathrm{M} \qquad [5]$$

$$\mathrm{S} + \mathrm{S} \cdot \mathrm{M} \overset{K_{S2}}{\rightleftharpoons} \mathrm{S}_2 \cdot \mathrm{M}. \qquad [6]$$

TABLE 1

REDUCTION OF 2-ACETYLPYRIDINE IN ACETONITRILE AT 50°C, FOLLOWED BY SPECTROSCOPY

10^2[AP] (*M*)	10^2[Zn^{2+}] (*M*)	10^4[BNAH] (*M*)	10^4 *k* (sec^{-1})
0.00	0.499	0.959	0.500[a]
0.00	0.707	0.989	0.533[a]
0.00	1.01	1.05	0.590[a]
0.00	1.50	0.959	0.618[a]
0.262	1.03	1.00	0.819
0.492	1.50	1.05	1.11
0.492	1.50	1.09	1.18
0.499	1.01	0.989	1.27
0.502	0.495	1.11	1.95
0.502	2.00	0.989	0.824
0.649	1.03	0.989	1.44
0.656	1.03	1.00	1.64
0.748	0.613	0.989	2.17
0.748	1.50	0.989	1.34
0.748	2.02	0.989	1.01
0.749	0.501	0.989	2.48
0.749	1.00	0.989	1.61
0.968	1.47	0.989	1.86
0.992	0.601	1.02	3.24
0.992	2.02	0.989	1.34
1.00	0.100	1.05	1.28
1.00	0.300	1.02	2.91
1.00	0.409	1.08	3.45
1.00	0.801	1.02	2.54
1.02	0.204	1.05	2.08
1.02	1.50	0.959	1.67
1.02	1.64	1.05	2.31
1.03	1.23	1.08	1.89
1.04	0.500	1.05	3.43
1.56	1.49	0.995	2.77
1.93	0.495	1.11	3.31
1.98	2.02	0.711	2.64
1.98	2.02	0.989	2.68
2.30	1.47	0.958	4.78
2.77	0.495	1.11	3.06
3.03	2.02	0.989	4.62
3.26	1.49	0.989	5.26

[a] Rate constants for metal ion-catalyzed decomposition of BNAH.

TABLE 2

REDUCTION OF 2-ACETYLPYRIDINE IN ACETONITRILE AT 50°C, FOLLOWED BY VAPOR-PHASE CHROMATOGRAPHY[a]

$10^2[Zn^{2+}]$ (*M*)	10^4 *k* (sec^{-1})
0.1	0.2–0.5
0.7	2.5–3.1
1.0	2.4–2.8
1.4	2.2–3.0
1.7	0.6–1.6

[a] [BNAH] = 2.0×10^{-2} *M*, [AP] = 1.0×10^{-3} *M*.

In Eqs. [3]–[6], B, S, and M denote BNAH, AP or BP, and zinc ion [in the form of either $Zn(ClO_4)_2$, $ZnClO_4^+$, Zn^{2+}, or two or three of these[4]), respectively (*1, 8*).

The stoichiometric concentrations of reagents (subscripted by T) can be expressed by Eqs. [7]–[9].

$$\begin{aligned}[B]_T &= [B] + [BM] + 2[B_2M] \\ &= [B] + K_{B1}[B][M] + 2K_{B1}K_{B2}[B]^2[M] \qquad [7]\end{aligned}$$

$$\begin{aligned}[S]_T &= [S] + [SM] + 2[S_2M] \\ &= [S] + K_{S1}[S][M] + 2K_{S1}K_{S2}[S]^2[M] \qquad [8]\end{aligned}$$

$$\begin{aligned}[M]_T &= [M] + [BM] + [SM] + [B_2M] + [S_2M] \\ &= [M] + K_{B1}[B][M] + K_{S1}[S][M] + K_{B1}K_{B2}[B]^2[M] \\ &\quad + K_{S1}K_{S2}[S]^2[M]. \qquad [9]\end{aligned}$$

Under the condition of $[B]_T \ll [S]_T$ (condition listed in Tables 1 and 3) we may be able to neglect the contribution of B_2M, and then the concentrations of free (uncomplexed) BNAH and the substrate are given by Eqs. [10] and [11].

TABLE 3

REDUCTION OF 2-BENZOYLPYRIDINE IN ACETONITRILE AT 50°C, FOLLOWED BY SPECTROSCOPY

10^2[BP] (*M*)	$10^2[Zn^{2+}]$ (*M*)	10^4[BNAH] (*M*)	10^4 *k* (sec^{-1})
0.314	0.306	1.01	14.3
2.58	0.864	1.00	8.82
2.58	1.30	1.00	10.1
2.58	1.47	1.00	10.0
2.58	1.79	1.00	11.4
2.58	2.18	1.00	11.7
2.58	2.36	1.00	11.9
2.58	2.41	1.00	11.3
2.58	4.16	1.00	10.1
2.58	5.95	1.00	8.32

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[4] We cannot specify the reacting species.

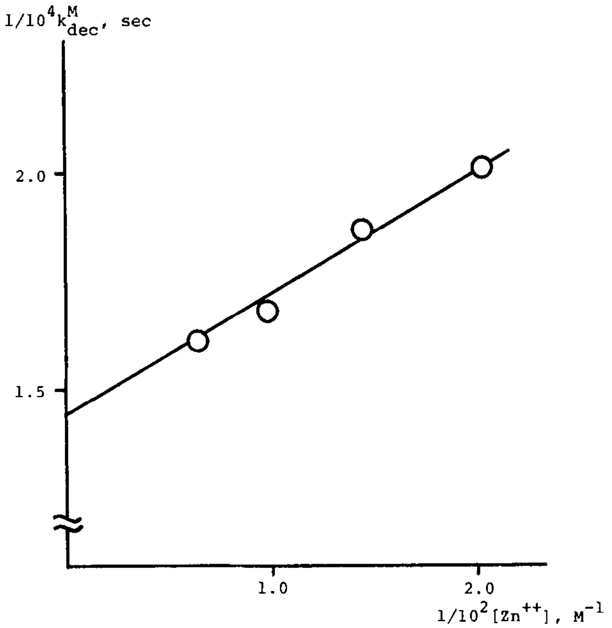

FIG. 1. Dependence of the rate constant for autodecomposition of BNAH on the concentration of zinc perchlorate in acetonitrile at 50°C; [BNAH] = 1.0×10^{-4} *M*.

$$[B] = [B]_T/(1 + K_{B1}[M]) \qquad [10]$$

$$[S] = \frac{-(1 + K_{S1}[M]) + \{(1 + K_{S1}[M])^2 + 8K_{S1}K_{S2}[S]_T[M]\}^{1/2}}{4K_{S1}K_{S2}[M]}. \qquad [11]$$

The concentration of free (uncomplexed) metal ion at defined $[B]_T$, $[S]_T$, and $[M]_T$ is given by an equation derived by substituting Eq. [9] with a pair of Eqs. [10] and [11], with which we can also calculate the concentrations of free BNAH and the substrate.

Assuming the following reactions (Eqs. [12]–[15])

$$\left.\begin{array}{r} BM + S \xrightarrow{k_{11}} \\ B_2M + S \xrightarrow{k_{12}} \\ SM + B \xrightarrow{k_{21}} \\ S_2M + B \xrightarrow{k_{22}} \end{array}\right\} \text{products} \qquad \begin{array}{r} [12] \\ [13] \\ [14] \\ [15] \end{array}$$

we obtain a rate expression shown by Eq. [16] for the experimental conditions of $[B]_T \ll [S]_T$.

$$\text{rate} = (k_{11}K_{B1} + k_{21}K_{S1} + k_{22}K_{S1}K_{S2}[S])[B][S][M]. \qquad [16]$$

On the other hand, the experimentally obtained reaction rate is given by Eq. [17].

$$\text{rate} = k_{obs}[B]_T \qquad \text{for } [B]_T \ll [S]_T. \qquad [17]$$

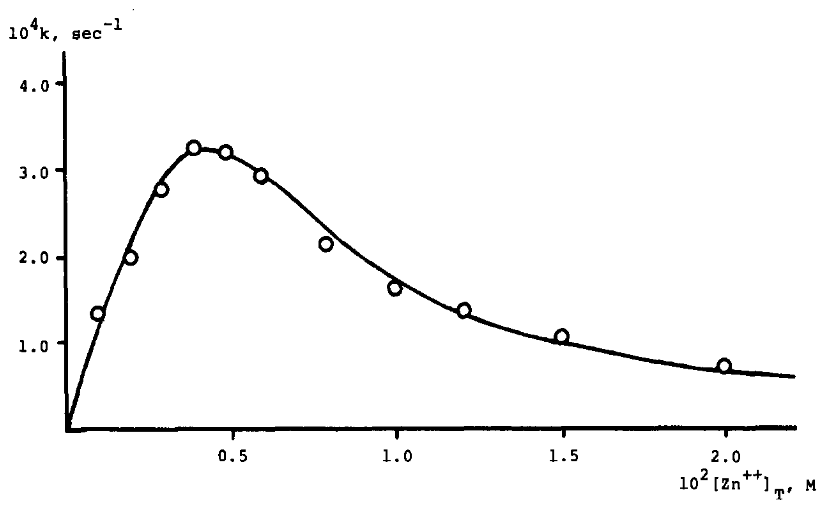

FIG. 2. Dependence of the rate constant for the reduction of 2-acetylpyridine on the concentration of zinc perchlorate under the condition of [BNAH] $\ll$ [AP] (data from Table 1). Circles and the line represent experimental (in acetonitrile at 50°C) and calculated rate constants, respectively. k denotes either k_{obs} or the computed rate constant.

Finally, we obtain Eq. [18] from Eqs. [16] and [17]

$$k_{obs}[B]_T = (k_{11}K_{B1} + k_{21}K_{S1} + k_{22}K_{S1}K_{S2}[S])[B][S][M] \quad \text{for } [B]_T \ll [S]_T. \quad [18]$$

Similarly, under the condition of $[B]_T \gg [S]_T$ (conditions listed in Table 2), we obtain the final relationship as shown in Eq. [19] after neglecting the $[S_2M]$ term.

$$k'_{obs}[S]_T = (k_{11}K_{B1} + k_{21}K_{S1} + k_{12}K_{B1}K_{B2}[B])[B][S][M] \quad \text{for } [B]_T \gg [S]_T. \quad [19]$$

Equation [18] or [19] predicts that a straight line must be obtained when $k_{obs}[B]_T/[B][S][M]$ or $k'_{obs}[S]_T/[B][S][M]$ is plotted against [S] or [B], respectively.

Reduction of AP

With initial stoichiometric concentrations of each reagent employed for experiments, we computed, with Eqs. [18] and [19], a set of appropriate values of equilibrium constants to simulate the k_{obs} (or k'_{obs}) to $[M]_T$ relationship. The equilibrium constants were changed from 100 to 5000 M^{-1} independently with an interval of 50 M^{-1}, and it was found that a set of

$$K_{B1} = 500\ M^{-1}$$
$$K_{B2} = 1100\ M^{-1}$$
$$K_{S1} = 500\ M^{-1}$$
$$K_{S2} = 600\ M^{-1}$$

gave the best fit. The value of K_{B1} is in an excellent agreement with that of K previously obtained from the kinetics. The results are shown in Figs. 2 and 3.

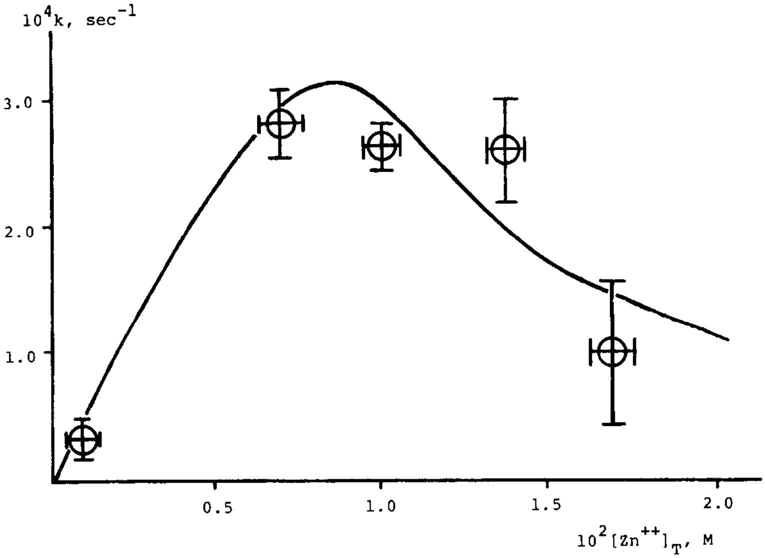

FIG. 3. Dependence of the rate constant for the reduction of 2-acetylpyridine on the concentration of zinc perchlorate under the condition of [BNAH] ≫ [AP] (data from Table 2). Circles and the line represent experimental (in acetonitrile at 50°C) and calculated rate constants, respectively. k denotes either k_{obs} or the computed rate constant.

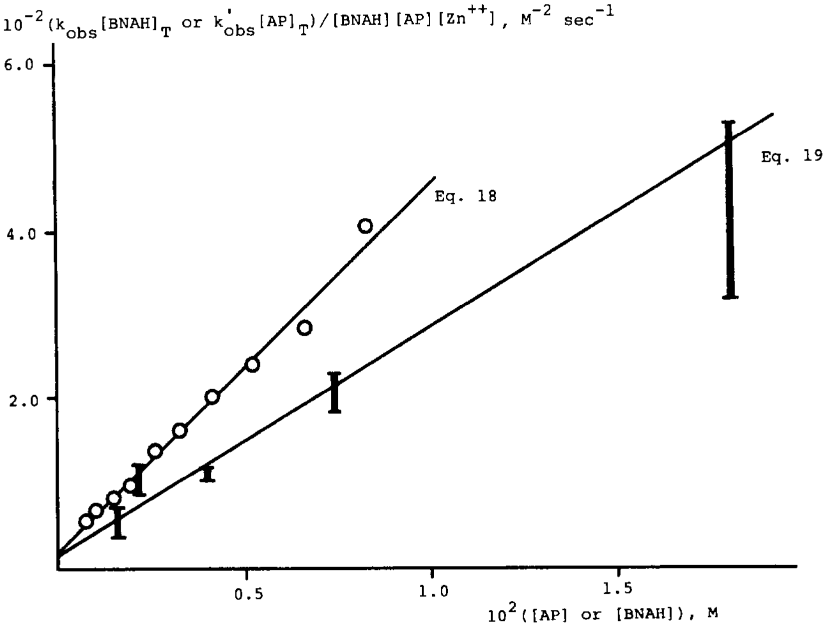

FIG. 4. Dependence of the observed rate on the concentration of 2-acetylpyridine or of BNAH in acetonitrile at 50°C. The straight lines represent computed values.

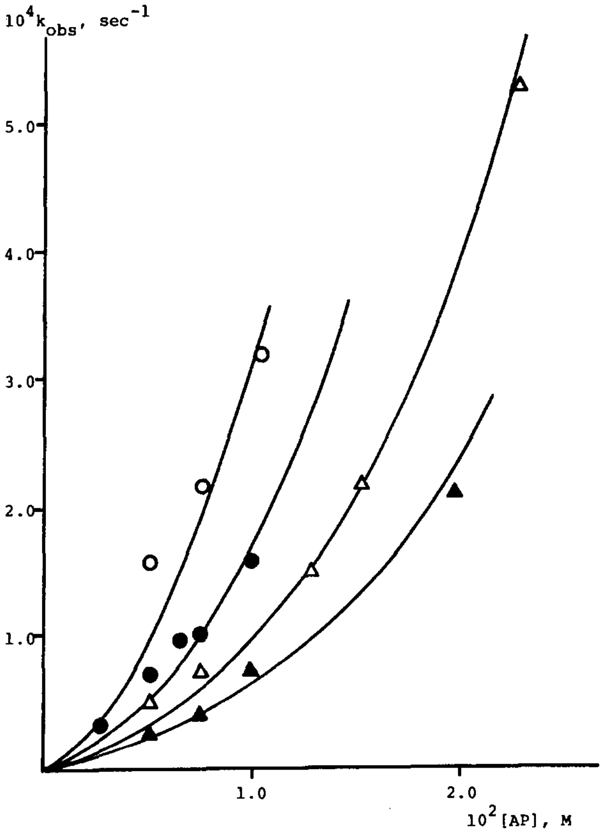

FIG. 5. Dependence of the rate constant for the reduction of 2-acetylpyridine on the concentration of 2-acetylpyridine at various concentrations of zinc perchlorate in acetonitrile at 50°C. The lines represent calculated rate constants. ○; $[Zn^{2+}] = 0.5 \times 10^{-2}$ *M*: ●; $[Zn^{2+}] = 1.0 \times 10^{-2}$ *M*: △; $[Zn^{2+}] = 1.5 \times 10^{-2}$ *M*: ▲; $[Zn^{2+}] = 2.0 \times 10^{-2}$ *M*.

Figure 4 represents straight lines predicted by Eqs. [18] and [19]. From the slopes and intercepts of two straight lines

$$k_{12} = 4.93 \times 10^{-2}\ M^{-1}\ \text{sec}^{-1},$$

$$k_{22} = 1.47 \times 10^{-1}\ M^{-1}\ \text{sec}^{-1},$$

and

$$k_{11} + k_{21} = 3.86 \times 10^{-2}\ M^{-1}\ \text{sec}^{-1}$$

were obtained. Figure 5 witnesses that the computed set of values of equilibrium and rate constants also reproduces k_{obs}'s obtained under different initial concentrations of each reagent. Small deviations of theoretically predicted rate constants from the experimental ones at low concentrations of zinc ion observed in Fig. 5 may be due to the neglection of $[B_2M]$ term on the derivation of Eq. [10].

The value of K_{B1} measured with spectrophotometric method (*9*) was 450 M^{-1}, which is again in good agreement with the computed and kinetically elucidated values.[5] Unfortunately, however, we could not observe the value of K_{S1} or K_{S2}, because, at the region of very high concentrations of zinc ion, no isosbestic point was identified. At the region of low concentrations of zinc ion, the equilibrium constant ($K_{app} = K_{S1}K_{S2}$) is too large to be observed in reasonable accuracy.

The fact that plots made in Fig. 4 give straight lines as theoretically predicted by Eqs. [18] and [19] reveals that neither equilibria in higher order (e.g., $B_2M + B \rightleftharpoons B_3M$) nor reactions between complexes (e.g., $BM + SM \rightarrow$ products) are necessary to be taken into account. Moreover, the computation with the inclusion of the reaction between BM and SM in the reaction scheme did not simulate the experimentally obtained results with any set of equilibrium and rate constants.

Although we cannot estimate the values for k_{11} and k_{21} independently, it is interesting to note that the termolecular complexes (S_2M and B_2M) are more reactive than the bimolecular ones (SM and BM). The present results, which suggest that the more strongly complexed species are less reactive, are in line with the general concept that catalytic effects are most pronounced when the catalyst favorably affects the transition state (*10*).[6] It follows as a corollary that stable complexes in the ground state will adversely influence the reaction. Comparison of rate data (k_{22} with k_{12}) indicates that while both species S_2M and B_2M contribute effectively to the reaction, the metal-complexed ketone (S_2M) is three times more reactive than the complexed BNAH species (B_2M). It should, however, be

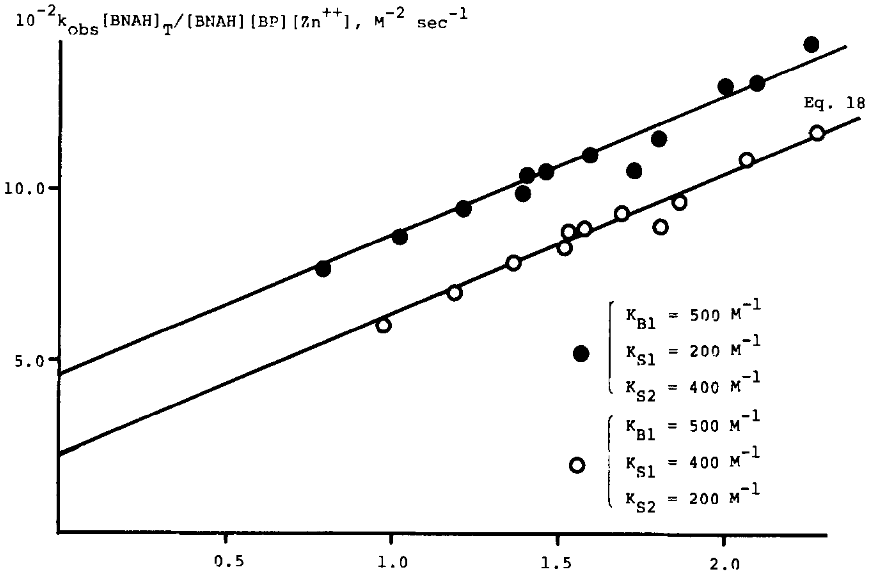

FIG. 6. Dependence of the observed rate on the concentration of 2-benzoylpyridine in acetonitrile at 50°C. The straight lines represent computed values.

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[5] The value of 650 ± 100 M^{-1} has been reported: M. Hughes, Ph.D. Thesis, Univ. of Cambridge, 1975.

[6] The metal ion-induced perturbation of a ligand in B_2M or S_2M might be smaller than that in BM or SM.

pointed out that the differences in the reactivities of the metal ion-complexed species are, in addition to the stability of the complexes, also determined by the nature (energetics) of the transition states (e.g., $S_2M \cdots B$ and $B_2M \cdots S$). It has been shown recently that the catalytic activity of the zinc ion in the reduction of 2-pyridinecarbaldehyde (*11*) is affected by the nature of the counterion. The latter will influence both the electronic nature and the precise structure of the complexed species, and thereby the free energy of the transition state of the reaction.

An analysis of the reactions via the species SM and BM is of interest. The transition state for the process will involve the termolecular system made up of S, M, and B, which will be formed by perturbation of SM by addition of B or perturbation of BM upon addition of S. While it is not possible to evaluate k_{11} and k_{21}, in view of the above mentioned mechanistic picture and the fact that the complexation constants for both species are very similar, the contribution of species BM and SM may be expected to be comparable (*10*).

Reduction of BP

The analysis of experimental data for BP with Eq. [18] (Figs. 6 and 7) resulted in

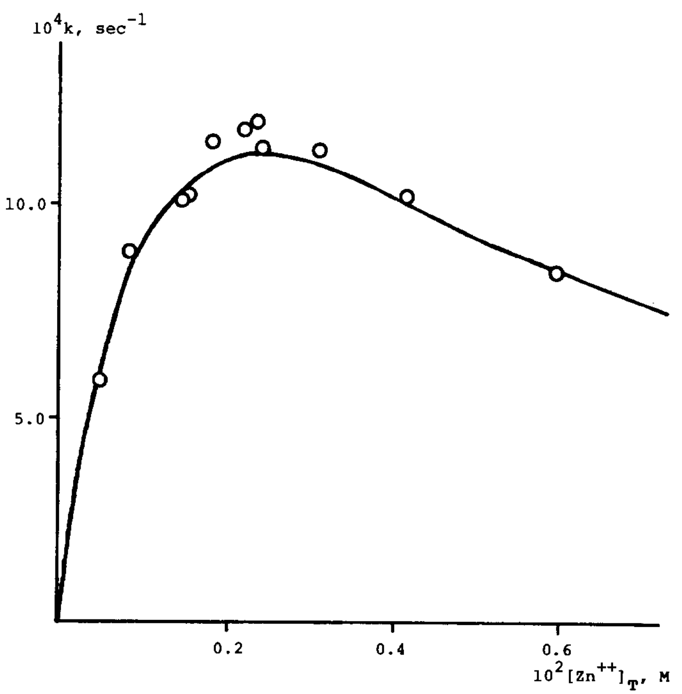

FIG. 7. Dependence of the rate constant for the reduction of 2-benzoylpyridine on the concentration of zinc perchlorate under the condition of [BNAH] $\ll$ [BP] (data from Table 3). Circles and the line represent experimental (in acetonitrile at 50°C) and calculated rate constants, respectively. k denotes either k_{obs} or the computed rate constant.

two sets of equilibrium constants:

$$\begin{array}{lcl} K_{B1} = 500\ M^{-1} & & K_{B1} = 500\ M^{-1} \\ K_{S1} = 200\ M^{-1} & \text{or} & K_{S1} = 400\ M^{-1} \\ K_{S1} = 400\ M^{-1} & & K_{S2} = 200\ M^{-1} \end{array}$$

from which we calculated rate constants to be

$$k_{22} = 4.88\ M^{-1}\ \text{sec}^{-1}$$

$$k_{11}K_{B1} + k_{21}K_{S1} = 2.37 \times 10^2\ M^{-2}\ \text{sec}^{-1}$$

or

$$k_{22} = 4.80\ M^{-1}\ \text{sec}^{-1}$$

$$k_{11}K_{B1} + k_{21}K_{S1} = 4.68 \times 10^2\ M^{-2}\ \text{sec}^{-1}.$$

Since we have no data on k'_{obs} to $[M]_T$ relationship, we cannot identify the value of K_{B2} and also cannot define the proper set of K_{S1} and K_{S2}. However, the excellent agreement of K_{B1} value with those mentioned above as well as the order of magnitude of K_{S1} and K_{S2} again proves the validity of analysis. It is noteworthy that the reduction of BP is much faster than that of AP.

Isotope Effects

Kinetic deuterium isotope effects observed by using BNAH-4,4-d_2 were 3.21 ± 0.01 and 3.28 ± 0.05 for AP and BP, respectively. These values are identical to the product isotope effect (isotopic distribution in the product) of 3.2 ± 0.1 observed for AP. The results of the isotope effects indicate that the hydrogen "nucleus" is transferred from the reductant to the substrate in the rate-determining step of the reaction. Other steps, such as electron movements, prior to or following the nucleus-transfer, while not excluded, would constitute relatively fast processes, which would lead to intermediates that are not identifiable in the energy-reaction coordinate profile (*7b*).

Although the value of only one out of eight computed equilibrium and rate constants has been confirmed experimentally, the fact that four experimental plots (Figs. 2, 3, 5, and 7) can be simulated independently by the computed set of constants may intensify the validities of the computed constants and the proposed reaction scheme. The present investigation allows the following conclusions with respect to the mechanism of the zinc ion-catalyzed reduction of substrates by NAD(P)H-models. The metal ion influences the reaction by lowering the free energy of activation of the overall process (*12*). Since kinetic isotope effects in the reductions of AP and BP are identical to the isotope distribution in the products, it is not possible to recognize the contribution of the metal ion-activation to the electron transfer step. In this connection, however, it is pertinent to compare the reduction of AP with that of BP. The faster reduction of the latter ketone can be accounted for in terms of the more favorable influence of the metal cation upon the radical anion formed by electron transfer to BP. Analysis of the kinetic data has revealed that metal ion complexes of both the substrate (S) and the reductant

(B) constitute species which react with the second organic reactant (B or S, respectively) to form the products. In view of this, the inhibitory action of the metal ion, at higher concentrations, may be attributed to the destructive effect of the additional metal ion upon the various reactive intermediates involving BNAH, substrate, and the metal ion (viz. $B_2M \cdots S$, $S_2M \cdots B$, and $S \cdots M \cdots B$) (*9*).

EXPERIMENTAL

Materials. 1-Benzyl-1,4-dihydronicotinamide (BNAH) and BNAH-4-*d* were prepared according to a literature procedure (*13*). Preparation of BNAH-4,4-d_2 was described previously (*3, 14*). 2-Acetylpyridine, 2-benzoylpyridine, and zinc perchlorate were commercially available (Nakarai Chem. Co.). These materials were purified by recrystallization prior to use (*7a*). Zinc perchlorate was dried at 120°C *in vacuo* for 5 hr and used immediately. Acetonitrile was distilled once on phosphorus pentoxide and kept over Molecular Sieves 4A.

Procedure. Kinetic procedures were described previously (*3, 7a*). The rate constant, k_{obs}, was calculated by subtracting the rate constant for the autodecomposition of BNAH at an appropriate concentration of zinc ion, $k^{\mathrm{M}}_{\mathrm{dec}}$, from that experimentally observed and listed in Table 1, k (Eq. [20]).

$$k_{\mathrm{obs}} = k - k^{\mathrm{M}}_{\mathrm{dec}}. \qquad [20]$$

It was confirmed that the values of pseudo-first-order rate constants observed were constant regardless of the presence (3.0×10^{-2} *M*) or absence of lithium perchlorate for the kinetic runs with appropriate concentrations of zinc perchlorate. The kinetic deuterium isotope effects were measured under the conditions of $[\mathrm{BNAH}]_T = [\mathrm{Zn}^{2+}]_T = 1.0 \times 10^{-4}\ M$ with $[\mathrm{AP}]_T = 0.5 \times 10^{-2}\ M$ and $[\mathrm{AP}]_T = 1.0 \times 10^{-2}\ M$ for AP, and $[\mathrm{BNAH}]_T = 1.0 \times 10^{-4}\ M$ with $[\mathrm{BP}]_T = [\mathrm{Zn}^{2+}]_T = 2.6 \times 10^{-3}\ M$ and $[\mathrm{BP}]_T = [\mathrm{Zn}^{2+}]_T = 3.1 \times 10^{-3}\ M$ for BP, respectively. The reproducibility from the kinetics of BP run under the condition of $[\mathrm{BP}] \ll [\mathrm{BNAH}]$ was worse than that shown in Fig. 3 for AP. Therefore, we could not obtain reliable data to discuss on this subject.

Deuterium contents were analyzed on a Varian T-60 nmr spectrometer and on a Shimadzu LKB-9000S GC-MS spectrometer equipped by a PACK 300DG-b Computing System (*7c*). Experimental equilibrium and rate constants, K_{B1}, $k^{\mathrm{M}}_{\mathrm{dec}}$, and k were observed on a Union Giken SM-401 spectrophotometer. Equilibrium and rate constants were computed by a FACOM 230 OS2/VS with a FORTRAN IV program. The computed equilibrium constants have uncertainties of ±100 M^{-1}. Within this range the correlation coefficients for the linearities of lines shown in Figs. 4 and 6 are larger than 0.99.

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[7] This reference erroneously mentions that the complex is made of four molecules of BNAH.