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A Kinetic Study of the Reaction of 1-Propyl-1,4-dihydronicotinamide with Hexacyanoferrate(III)

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The reaction of 1-propyl-1,4-dihydronicotinamide with hexacyanoferrate(III) in 20% aqueous methanol follows a second-order rate law with first order with respect to each reactant concentration. Kinetic parameters are $\Delta H^{\neq}$: $(8.8\pm0.4)\times10^3$ J mol^{-1} and $\Delta S^{\neq}$: -1.8×10^2 J mol^{-1} K^{-1}, the observed kinetic isotope effect, k_H/k_D, being 1.51. The mechanism of the reaction is discussed.

The reaction of unsaturated organic compounds by *N*-substituted dihydronicotinamide has been extensively investigated as a model of reduction by coenzymes NADH and NADPH.[1] The formation of an intermediate complex(es) during the course of the reaction has been reported for various systems.[2] The facility of electron-transfer mechanism for such a net hydride-transfer reaction in biological systems was suggested.[3]

However, the mechanism of this apparent hydride-transfer reaction has not yet been clarified: an initial electron-transfer followed by a hydrogen (as a hydrogen atom, or a proton and an electron) on one hand and a hydride-transfer on the other.[1a] Argument was given as to the single- or multi-step character of the reduction.[4]

In the present paper, we would like to report the details of a kinetic study of the electron-transfer reaction of 1-propyl-1,4-dihydronicotinamide (PNAH) with hexacyanoferrate(III),[5] showing the mechanism of a simplified reduction by PNAH together with some parameters of the reaction.

Experimental

Materials. PNAH-4,4-d_2 was prepared by the repeated reduction of 1-propyl-3-carbamoylpyridinium salt with alkaline dithionite in D_2O and re-oxidation of the resulting dihydronicotinamide with ethyl benzoylformate three times. The deuterium content was estimated by the integral ratios of NMR signals (deuterium purity; 94±5%). Solvents for spectroscopic measurement were Dotait spectro-grade reagents and used after distillation under nitrogen. Inorganic reagents (analytically pure reagents, Nakarai Chem. Co.) were used.

Kinetic Measurement. The solution for kinetic measurement was prepared by injecting 10 μl of a 1.00×10^{-2} M-methanol solution of PNAH into a 4.0 ml portion of 20% aqueous methanol containing 2.00—8.00×10^{-4} M of $K_3Fe(CN)_6$ and 0.75—1.00×10^{-2} M of K_2CO_3 in a serum-capped optical cuvett under nitrogen. Solutions of Li_2CO_3 and KCN, or solid $K_4Fe(CN)_6$ were added when necessary. Reaction rates were measured by the spectroscopic method monitoring the absorbance change at 356 nm on a thermostatted Union Giken SM 401 spectrophotometer. The concentration of potassium ion was adjusted by using potassium chloride.

Results

Stoichiometry. The stoichiometry of the reaction was determined by titration of a 4.0 ml portion of the solution of $K_3Fe(CN)_6$ (2.00×10^{-3} M) and K_2CO_3 (1.00×10^{-2} M) with 1.25×10^{-4} M equivalents of PNAH in 20% aqueous methanol (Fig. 1). Two moles of hexacyanoferrate(III) were consumed by 1 mol of PNAH giving rise to the product solution, the spectrum of which was identical with that of the authentic sample of 1-propyl-3-carbamoylpyridinium salt (PNA^+) and hexacyanoferrate(II).

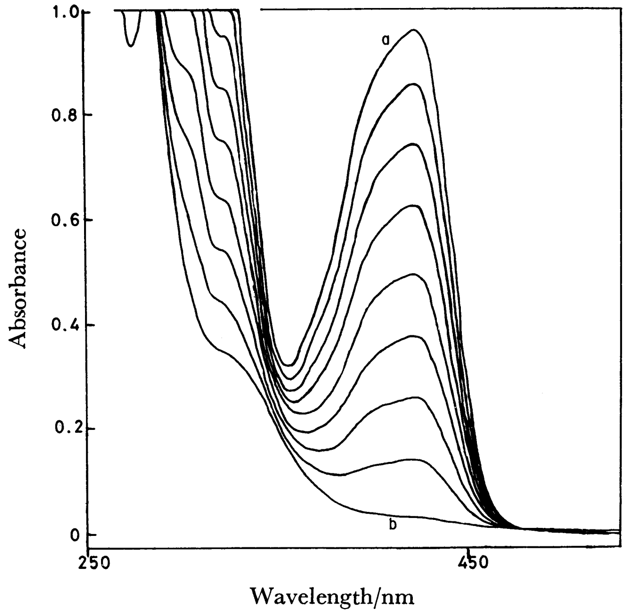

Fig. 1. Spectra of titration.
$[Fe(CN)_6{}^{3-}]$, 2.00×10^{-3} M; [PNAH], 1.25×10^{-4} M equivalent each at 298 K in 20% aqueous methanol. a, Initial spectrum; b, end spectrum.

$$PNAH + 2Fe(CN)_6{}^{3-} \longrightarrow PNA^+ + 2Fe(CN)_6{}^{4-} + H^+ \qquad (1)$$

Kinetic Study. A good pseudo-first-order kinetics (correlation coefficient: $\gamma > 0.999$) was observed throughout the experiments for over 90% of the reaction with an excess of hexacyanoferrate(III). However, the reproducibility of the rates of different batches was not very good, suggesting the presence of some impurity which affects the reaction rate. The results are given in Table 1. The apparent rate constants thus obtained are linearly correlated with the concentration of hexacyanoferrate(III) by a straight line that passes through the origin ($\gamma=0.9994$) indicating the second-order rate law with the rate constant (k) of $(6.68\pm0.08)\times10$ M^{-1} s^{-1} ($[K^+]$ of 1.80×10^{-2} M, $[CO_3{}^{2-}]$ of 0.750×10^{-2} M, and pH of 10.92). The change of basicity of the solution, and the addition of hexa-

TABLE 1. RATE CONSTANTS OF THE REACTION OF PNAH WITH $K_3Fe(CN)_6$[a)]

$[Fe(CN)_6^{3-}]$ / 10^{-3} M	[PNAH] / 10^{-5} M	$[K^+]$ / 10^{-2} M	$[CO_3^{2-}]$ / 10^{-2} M	k_{obsd} / $10^{-2}\ s^{-1}$	k / $10\ M^{-1}\ s^{-1}$	Remarks
0.500	2.50	0.650	0.250	1.50	3.01	
0.500	2.50	0.650	0.250	1.02	2.03	PNAH-d_2
0.800	2.50	1.80	0.750	5.24	6.55	
0.700	2.50	1.80	0.750	4.70	6.71	
0.600	2.50	1.80	0.750	4.04	6.73	
0.500	2.50	1.80	0.750	3.26	6.52	
0.400	2.50	1.80	0.750	2.66	6.65	
0.300	2.50	1.80	0.750	2.01	6.70	
0.200	2.50	1.80	0.750	1.32	6.60	
0.500	2.50	1.80	0.750	2.86	5.72	[KCN], 1.50×10^{-3} M
2.00	5.00	2.60	1.00	3.71	1.85	
2.00	5.00	2.60	1.00	3.65	1.82	$[PNA^+Br^-]$, 4.60×10^{-3} M
0.500	2.50	2.15	1.00	3.25	6.51	298 K
0.500	2.50	2.15	1.00	3.47	6.93	303 K
0.500	2.50	2.15	1.00	3.72	7.43	308 K
0.500	2.50	2.15	1.00	4.07	8.15	313 K
0.500	2.50	2.15	1.00	4.32	8.65	318 K

a) Reaction rate was measured at 298 K under nitrogen in 20% aqueous methanol unless otherwise stated.

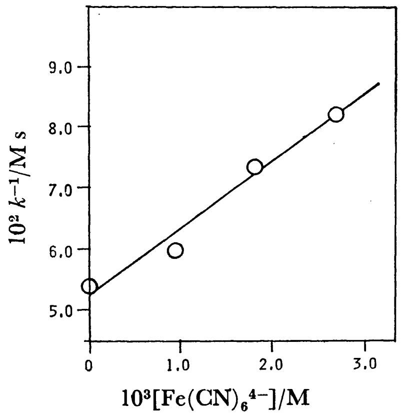

Fig. 2. Dependence of the rate on $Fe(CN)_6^{4-}$ concentrations.
[PNAH], 5.00×10^{-5} M; $[K_2CO_3]$, 1.00×10^{-2} M (pH =10.97), $[Fe(CN)_6^{3-}]$, 2.00×10^{-3} M at 298 K in 20% aqueous methanol under nitrogen.

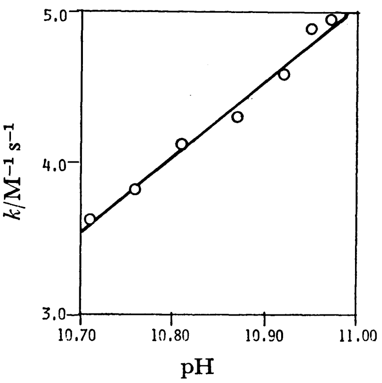

Fig. 3. Effect of the basicity.
$[K_3Fe(CN)_6]$, 5.00×10^{-4} M; [PNAH], 2.50×10^{-5} M; $[K_2CO_3]$, 2.50×10^{-3} M; $[Li_2CO_3]$, 0.00—0.75×10^{-2} M at 298 K in 20% aqueous methanol under nitrogen.

$$-\frac{d[PNAH]}{dt} = k_{obsd}[PNAH] = k[Fe(CN)_6^{3-}][PNAH] \quad (2)$$

cyanoferrate(II) or some alkali-metal ions[6)] affected the reaction rate. Slight retardation took place by addition of cyanide ion, but not by that of other anions such as chloride and perchlorate. Ionic strength had almost no effect either.[6,7)] Linear relationship holds between the reciprocal of the rate constant and the concentration of hexacyanoferrate(II) (Fig. 2). The dependence of rate on basicity was measured with the use of lithium carbonate, since lithium ion does not affect the reaction rate, in contrast to other alkali-metal ions.[6)] The rate was accelerated by increasing basicity (Fig. 3).

Kinetic Parameters. Kinetic parameters measured in the temperature range 298 K—318 K were $\Delta H^{\neq}$: $(8.8\pm0.4)\times10^3$ J mol^{-1} and $\Delta S^{\neq}$: -1.8×10^2 J mol^{-1} K^{-1} ($\gamma=0.997$) at pH of 10.97 and potassium ion concentration of 2.15×10^{-2} M.

The kinetic deuterium isotope effect observed by using PNAH-4,4-d_2 at 298 K was 1.51 ± 0.03.[8)]

Discussion

Only a hydride ion, a hydrogen atom, and an electron give rise to the reducing equivalent of the reduction by PNAH. However, the mechanism is complicated. The hydride-transfer mechanism is simple; the reduction itself should be a single-step reaction no matter whether there is a step for the complex-formation preceding the reduction. A single-step transfer of hydrogen and a reducing equivalent, however, does not necessarily indicate the hydride-transfer mechanism (*vide infra*). The electron-transfer mechanism, in contrast, has many possibilities. The reducing equivalent could be transferred to a substrate at the initial step or after a certain modification of the reductant in a slow step or in an equilibrium preceding the slow step. Even when an electron is transferred at the initial slow step, the hydrogen at the C_4-position of PNAH could be transferred as a hydrogen atom or a proton in the succeeding step. These elementary steps might occur simultaneously at different reaction sites.

Since hexacyanoferrate(III) is inert for substitution reaction in the ordinary time scale,[9] the possibility of direct hydride-transfer yielding an iron hydride is eliminated. A certain retarding effect by cyanide ion is observed but it is too small for a mass law effect on a reactive intermediate existing in very low concentration. A mechanism with the initial fast equilibrium generating a hydride ion, which reduces hexacyanoferrate(III) in a slow step, is unlikely in the light of hydride chemistry. Since the rate increases with the basicity of solution, one might expect a process of deprotonation of PNAH preceding the net reduction. This mechanism is discarded by the absence of deuterium exchange between PNAH and D_2O under basic conditions and also by the small deuterium isotope effect. The difficulty of deprotonation from such an electron-rich compound would be easily expected.

The above discussion leads to the initial electron-transfer mechanism as the only reasonable possibility for the present reaction shown in the following.

$$\mathrm{PNAH} + \mathrm{Fe(CN)_6}^{3-} \xrightarrow[\text{slow}]{k} \mathrm{PNAH}^{\cdot+} + \mathrm{Fe(CN)_6}^{4-} \qquad (3)$$

$$\mathrm{PNAH}^{\cdot+} \longrightarrow \mathrm{PNA}^{\cdot} + \mathrm{H}^{+} \qquad (4)$$

$$\mathrm{PNA}^{\cdot} + \mathrm{Fe(CN)_6}^{3-} \xrightarrow[\text{fast}]{} \mathrm{PNA}^{+} + \mathrm{Fe(CN)_6}^{4-} \qquad (5)$$

The linear dependence of the reciprocal of the rate constant on the concentration of hexacyanoferrate(II) suggests that Eq. 3 is reversible at high concentrations of hexacyanoferrate(II). However, under the usual reaction conditions with no extra hexacyanoferrate(II), the ratio of the rate of the back reaction of Eq. 3 to that of Eq. 4, calculated from the slope of Fig. 2, is 2×10^{-2} even at the end of the reaction. So the net reaction under the usual reaction conditions proceeds according to the reaction sequences presented above. The good correlation coefficient for the pseudo-first order kinetics observed throughout the experiments supports the conclusion.

The values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ lie within the region of outer-sphere electron-transfer reaction,[10] which could be taken as evidence of the mechanism presented. The reaction of radical species with hexacyanoferrate(III), corresponding to Eq. 5, is fast.[11]

The acceleration of the reaction by increasing basicity suggests that the deprotonation step also participates in the rate-determining step. In this context, the work of electrochemical oxidation of dihydronicotinamide presents an important evidence.[12] The oxidation potential of dihydronicotinamide is slightly lowered in the presence of a base, indicating the assistance of a base for the initial electron-transfer step. A possible picture of the transition state of the electron-transfer reaction is shown in Fig. 4. Expectation of the base working only in the step of Eq. 4 which competes with the back reaction of Eq. 3 is not in line with our result quantitatively.

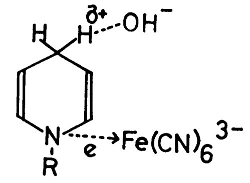

Fig. 4. A possible sketch of the transition state.

The observed value of the kinetic deuterium isotope effect is too large to be accounted for by the normal secondary isotope effect, and too small to be the rate-determining deprotonation. However, it should be noted that a similar value (1.4) of deuterium isotope effect was reported for the oxidation of tetracyanodiamineferrate(III) into diimine complex,[13] which proceeds through the rate-determining electron-transfer reaction followed by the loss of hydrogen.

The present study has revealed that the reduction by PNAH under weakly basic conditions proceeds through a mechanism with an electron-transfer followed by a proton-transfer and that the transfer of a proton participates in the initial rate-determining electron-transfer step, though slightly. The transfer of the second electron is fast.

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