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Acid-Catalyzed Electron-Transfer Processes in Hydride-Tansfer Reactions from 10-Methylacridan to p-Benzoquinone Derivatives

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The pH dependences of the second-order rate constants and the primary kinetic isotope effects for hydride-transfer reactions from an acid-stable NADH model compound, 10-methylacridan ($AcrH_2$), to a series of p-benzoquinone derivatives (Q) in H_2O-EtOH (5:1 v/v) have revealed that the hydride transfer proceeds via acid-catalyzed electron-transfer from $AcrH_2$ to Q.

When one-electron oxidants are used as electron acceptors for the two-electron oxidation of reduced nicotinamide adenine dinucleotide (NADH) and NADH model compounds, it has been well established that the two-electron oxidation proceeds by an electron-proton-electron sequence.1) When two-electron oxidants are used as hydride acceptors, however, it has been very difficult to distinguish between an inner-sphere electron-transfer process resulting in the subsequent proton-electron (or hydrogen) transfer in the cage and a one-step hydride-transfer process, since there are no detectable intermediates in both cases.2-4) In such a case, the distinction can be made only by examining the correlations between the rate constants and the free energy change of each process (electron transfer vs. hydride transfer). In this context, we have recenly reported that the rate constants of hydride-transfer reactions of various NADH model compounds including different types to a series of p-benzoquinopne derivatives are correlated with the free energy changes of electron transfer better than those of hydride transfer.5) However, such mechanistic distinction has so far been limited to non-catalytic or metal ion-catalyzed reductions of substrates by NADH model compounds.2-5) Since acid catalysis is known to play an essential role in the enzyme-catalyzed reduction of substrates by NADH,6) it is required to study the mechanism of acid-catalyzed reduction of substrates by NADH model compounds.

We wish to report herein that acid-catalyzed reduction of a series of p-benzoquinone derivatives (Q) by an acid-stable NADH model compound proceeds via acid-catalyzed electron transfer process. 10-Methylacridan ($AcrH_2$) is used as an acid-stable NADH model compound,7) since NADH and ordinary NADH model compounds are known to be subjected to the acid-catalyzed hydration.8)

One-electron reduction potentials (E_{red}) of quinones (Q) are known to be shifted to the positive direction by the protonation of $Q^{-\bullet}$ as given by Eq. 1,

$$E_{red} = E^0_{red} + (2.3RT/F)(pK_1 - pH) \qquad (1)$$

where $pH < pK_1$, E^0_{red} is the one-electron reduction potential of Q in the absence of an acid, and K_1 is the acid dissociation constant of the corresponding semiquione derivatives ($QH^\bullet$).[9-11] Under the conditions that $pH > pK_1$, the E_{red} value is independent of pH (equal to E^0_{red}). In accordance with such pH dependence of E_{red} (Eq. 1), the rate of electron transfer from cis-dialkylcobalt(III) complexes to Q has been shown to depend on pH; the rate is independent of pH in the region $pH > pK_1$, but increases in the region $pH < pK_1$.[11] On the other hand, the two-electron reduction potentials of Q are also known to be shifted to the positive direction by the protonation of QH^- and Q^{2-} (pK_2 and pK_3, respectively) under the conditions that $pH < pK_2 < pK_3$.[9,10] Thus, if a one-step hydride transfer occurs, the rate would increase in the region $pH < pK_3$. Since the values of pK_1, pK_2, and pK_3 have well been established and they are different from each other,[9-11] examination of the pH dependence of the rate of hydride transfer from an NADH model compound to Q will provide an unequivocal basis to determine whether the activation barrier is determined by the one-electron or two-electron process.

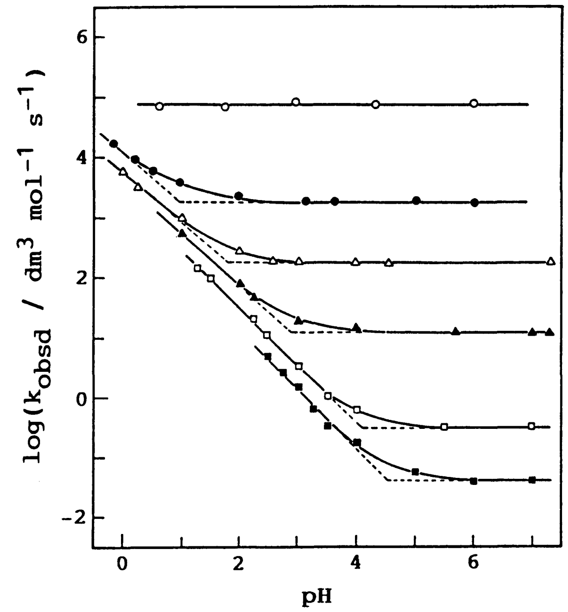

Fig. 1. Plots of log k_{obsd} vs. pH for reduction of TCNQ (○) and p-benzoquinone derivatives; p-chloranil (●), 2,6-dichlloro-p-benzoquinone (△), chloro-p-benzoquinone (▲), p-benzoquinone (□), and methyl-p-benzoquinone (■), in H_2O-EtOH (5:1 v/v) at 298 K. In the pH region where $QH^\bullet$ is protonated,[11] the kinetics was complicated by the comproportionation reaction between Q and QH_2, and thus the rate constants in such a region are not included here.

The pH dependences of the observed second-order rate constants (k_{obsd}) of hydride transfer reactions from $AcrH_2$ to various p-benzoquinone derivatives (Q) in aqueous solution (H_2O-EtOH; 5:1 v/v) at 298 K were determined by monitoring the formation of $AcrH^+$ (λ_{max} 358 nm).[12] The results are shown in Fig. 1. In the case of 7,7,8,8-tetracyano-p-quinodimethan (TCNQ), the log k_{obsd} value is independent of pH, since no protonation of $TCNQ^{-\bullet}$ has occurred in the pH region examined in Fig. 1. The log k_{obsd} value of each Q is independent of pH in the region $pH > pK_{obsd}$, but increases with decreasing pH in the region $pH < pK_{obsd}$. The pK_{obsd} values, thus determined for five different p-benzoquinone derivatives, agree well with the corresponding pK_1 values of $QH^\bullet$, which are clearly different from the pK_2 or pK_3 values (Table 1). Moreover, the primary kinetic isotope effects (k_H/k_D), determined from the ratio of the rate constants of $AcrH_2$ to the 9,9'-dideuterated analog ($AcrD_2$), exhibit the pH dependence in accordance with the pH dependence of E_{red} (Eq. 1), as shown in Fig. 2. In the case of TCNQ, the k_H/k_D value is close to

Table 1. Acid Dissociation Constants of Reduced p-Benzoquinone Derivatives (pK_{obsd}), Determined from the pH Dependence of Rate Constants k_{obsd} for Hydride-Transfer Reactions from $AcrH_2$ to p-Benzoquinone Derivatives (Q) in H_2O-EtOH (5:1 v/v) at 298 K, and the Comparison with those of $QH^{\bullet}$ (pK_1), QH_2 (pK_2), and QH^- (pK_3)

p-Benzoquinone derivative	pK_{obsd} a)	pK_1 b)	pK_2 b)	pK_3 b)
p-Chloranil	0.9	0.9 c)	5.6	8.2
2,6-Dichloro-p-benzoquinone	1.8	2.1	7.9	10.0
Chloro-p-benzoquinone	2.9	3.1 c)	8.9 d)	10.7 d)
p-Benzoquinone	4.1	4.1	9.9	11.4
Methyl-p-benzoquione	4.5	4.45	10.1	11.5

a) Determined from the results in Fig. 1. b) Taken from Ref. 9 unless otherwise noted. c) Taken from Ref. 5. d) Assumed to be the average of 2,6-dichloro-p-benzoquinone and p-benzoquinone.

unity, independent of pH. The k_H/k_D value of each p-benzoquinone derivative is constant in the region pH > pK_1 where the k_{obsd} is independent of pH, but decreases to a much smaller value in the region pH = pK_1 where the k_{obsd} value increases with decreasing pH. Such a change in the k_H/k_D value indicates the change of species which accepts hydrogen between the region pH = pK_1.

Thus, the pH dependences of both the rate constants and the primary kientic isotope effects strongly indicate that the activation barriers of the apparent hydride transfer reactions are correlated with the free energy changes of the acid-catalyzed electron transfer but not with those of the hydride transfer. Since no protonation of Q has occurred in the pH region examined in this study, the acid-catalyzed electron transfer from $AcrH_2$ to Q may occur in the region pH < pK_1 as shown in Scheme 1. With decreasing pH,

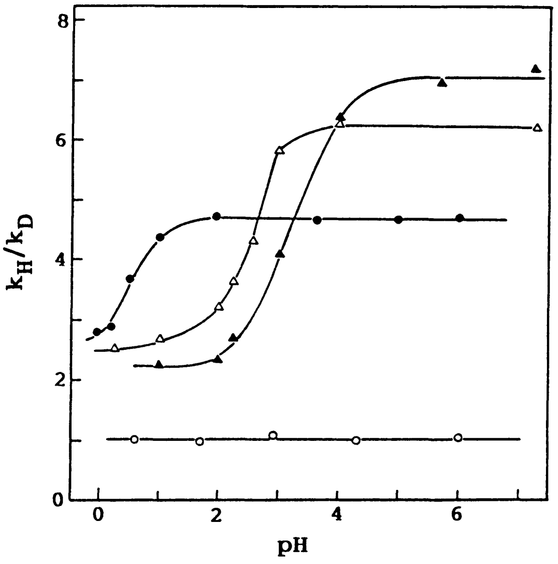

Fig. 2. Plots of the priamry kientic isotope effects (k_H/k_D) vs. pH for reduction of TCNQ (○), p-chloranil (●), 2,6-dichloro-p-benzoquinone (△), and chloro-p-benzoquinone (▲) by $AcrH_2$ and $AcrD_2$ in H_2O-EtOH (5:1 v/v) at 298 K.

$$\mathrm{pH} < \mathrm{p}K_1:\ \mathrm{AcrH_2 + Q + H^+} \underset{k_b}{\overset{k_{et}}{\rightleftharpoons}} (\mathrm{AcrH_2}^{+\bullet}\ \mathrm{QH}^{\bullet}) \xrightarrow{k_H} \mathrm{AcrH^+ + QH_2}$$

Scheme 1.

the acid-catalyzed electron transfer becomes energetically more favorable according to Eq. 1. Then, the acid-catalyzed electron transfer results in the formation of a radical pair ($AcrH_2^{+\bullet}$ $QH^{\bullet}$) which may disappear by the hydrogen transfer from

$AcrH_2^{+\cdot}$ to $QH^\cdot$ (Scheme 1). The proton transfer from $AcrH_2^{+\cdot}$ to $QH^\cdot$ may be unlikely to occur, since the pK_1 value of $QH_2^{+\cdot}$ is much larger than that of $QH^\cdot$,11) and thereby the proton transfer is energetically unfavorable. Under the conditions that $k_H >> k_b$ in Scheme 1, the forward electron transfer k_{et} becomes the rate-dtermining step. This may be the reason why the observed k_H/k_D value decreases significantly in the region pH = pK_1. On the other hand, in the region pH > pK_1, the hydride transfer from $AcrH_2$ to Q proceeds via an inner-sphere electron transfer from $AcrH_2$ to Q to give a radical ion pair ($AcrH_2^{+\cdot}$ $Q^{-\cdot}$) which disappears by proton transfer from $AcrH_2^{+\cdot}$ to $Q^{-\cdot}$, followed by the subsequent facile electron transfer from $AcrH^\cdot$ to $QH^\cdot$ to yield $AcrH^+$ and QH_2 (or QH^-).5) In this case, the observed kinetic isotope effect has been ascribed to those of the proton transfer process.

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12) No hydration of p-benzoquinone derivatrives may occur in the pH region examined, since no change of the electronic spectra has been observed.

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