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MECHANISM OF ACID-CATALYSED REDUCTION OF AROMATIC ALDEHYDES AND *p*-BENZOQUINONE DERIVATIVES BY AN NADH MODEL COMPOUND

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Abstract - A series of aromatic aldehydes have successfully been reduced by *N*-methylacridan (AcH_2) in the presence of perchloric acid ($HClO_4$) in a mixture of acetonitrile and acetic acid (MeCN/MeCOOH, 4:1 v/v) at 323 K. The effects of $HClO_4$ as well as $Mg(ClO_4)_2$ on hydride-transfer reactions from AcH_2 to a series of *p*-benzoquinone derivatives (Q) in MeCN have also been examined. Perchloric acid shows both accelerating and retarding effects on the hydride-transfer reactions depending on the *p*-benzoquinone derivative. It is shown that AcH_2 forms a 1 : 1 complex with $HClO_4$ and the protonated species AcH_3^+ is inactive for the reduction of *p*-benzoquinone derivatives. Thus, for *p*-benzoquinone derivatives being weak oxidants such as *p*-benzoquinone which have the redox potentials $E^0(Q/Q^{\bar{\cdot}}) < 0$, $HClO_4$ shows an overall accelerating effect on the reduction which proceeds through the acid-catalysed reaction of free AcH_2 with Q, while for those being the stronger oxidants such as 2,3-dichloro-5,6-dicyano-*p*-benzoquinone which have $E^0(Q/Q^{\bar{\cdot}}) > 0$, $HClO_4$ shows an overall retarding effect on the reduction where $HClO_4$ has hardly catalysed the reaction of free AcH_2 with Q. A proposed reaction mechanism involving electron transfer from AcH_2 to Q followed by proton transfer from AcH_2^+ to $Q^{\bar{\cdot}}$ in the rate-determining step of the hydride-transfer reactions provides a quantitative evaluation of the single and unified correlation of the logarithm of the rate constant for the hydride-transfer reactions from free AcH_2 to Q with the redox potential of Q in the absence and presence of $Mg(ClO_4)_2$ or $HClO_4$. The electronic substituent effects on the rate of acid-catalysed reduction of aromatic aldehydes by AcH_2 are shown to be very small, as being compatible with those observed for liver alcohol dehydrogenase (LADH)-catalysed reduction of the corresponding aldehydes by NADH. Moreover, the absolute value of the rate constant for the hydride-transfer step from free AcH_2 to the protonated benzaldehyde in our model system is also shown to be compatible with that in the LADH-enzyme system.

Liver alcohol dehydrogenase (LADH) catalyses the reduction of carbonyl compounds to the corresponding alcohols by NADH [equation (1)], where acid

$$\mathrm{NADH} + {>}{=}\mathrm{O} + \mathrm{H^+} \xrightarrow[\mathrm{LADH}]{} \mathrm{NAD^+} + {\vdash}\!\!\!{-}\mathrm{OH} \qquad (1)$$

catalysis is known to play an important role as indicated by small substituent effects on the enzyme-catalysed reduction of substituted benzaldehydes by NADH because of the polarization of the carbonyl function by zinc ion on the enzyme surface acting as a strong Lewis acid.[1-3] In order to understand the mechanism of the LADH-catalysed reactions of NADH with substrates, the mechanisms of non-enzymatic hydride-transfer reactions from NADH or its model compounds to substrates have been extensively studied.[4] However, there is still controversy concerning whether hydride transfer occurs in one-step[5-13] or consists of overall transfer of two electrons and a proton in a e^--H^+-e^- sequence through an intermediate charge-transfer (CT) complex.[14-19]

We have recently reported definitive proofs of the existence of an intermediate CT complex formed between an NADH model compound, 1-benzyl-1,4-dihydronicotinamide (BNAH), and *p*-benzoquinone derivatives Q by the isolation of the CT complexes as well as the detection of the transient CT spectra during the hydride-transfer reactions from BNAH to Q.[20] In these reactions, the mechanistic distinction between a one-step or multistep besides the formation of an intermediate CT complex has been shown to depend on the lifetime of the radical ion pair $[BNAH^{+\bullet}\ Q^{-\bullet}]$ formed by the first electron transfer from BNAH to Q in the CT complex [BNAH Q].[20] We have also shown that the effects of Mg^{2+} ion on the hydride-transfer reactions from BNAH to a series of *p*-benzoquinone derivatives in MeCN can be evaluated quantitatively by the change of the redox potentials of BNAH and Q in the presence of Mg^{2+} ion.[21] However, NADH (or its model compounds) alone, or in the presence of Mg^{2+} or Zn^{2+} ion, can reduce only activated carbonyl compounds that are much stronger oxidants than benzaldehyde, a typical substrate for the LADH-catalysed reaction of NADH.[4,11] As such, the accelerating effect of Mg^{2+} or Zn^{2+} ion is too small to compare not only the absolute values of the rate constants but also the relative reactivities of substrates in nonenzymatic reactions of NADH or its model compounds with those in the LADH-catalysed reactions of NADH. Thus, in order to understand the huge reactivities in the LADH-enzyme system, it seems to be of significant interest to study the acid-catalysed reactions of NADH model compounds with nonactivated carbonyl compounds such as benzaldehyde, comparing the reactivities with those in the LADH-catalysed reactions. Such studies on the acid-catalysed reduction of non-activated carbonyl compounds by NADH model compounds have so far been limited to only a few cases,[22] and thus, no comparison of the reactivities of substrates in a model system with those in the LADH-enzyme system has been performed since most NADH model compounds are known to decompose in the presence of acids.[23]

In this study, we report successful reduction of a series of aromatic aldehydes by a simple acid-stable NADH model compound, *N*-methylacridan (AcH_2), in the presence of perchloric acid ($HClO_4$) in a mixture of acetonitrile and acetic acid (MeCN/MeCOOH, 4:1 v/v), which enables us to compare the reactivities of the model system with those in the LADH-enzyme system for the first time. The effects of $HClO_4$ or $Mg(ClO_4)_2$ on the hydride transfer reactions from AcH_2 to a series of *p*-benzoquinone derivatives in MeCN are also examined and the reaction mechanism will be discussed based on the correlations between the observed rate constants and the redox potentials of Q in the absence and presence of $HClO_4$ or $Mg(ClO_4)_2$ in MeCN.

Results and Discussion

Reduction of Benzaldehyde and *p*-Benzoquinone Derivatives by AcH_2.

An acid-stable NADH model compound AcH_2 reacts readily with benzaldehyde in the presence of $HClO_4$ (5.0×10^{-2} mol dm^{-3}) in a mixture of acetonitrile and acetic acid (CD_3CN/MeCOOH, 4:1 v/v) under degassed conditions at 323 K to form *N*-methylacridinium ion (AcH^+) and benzyl alcohol; the latter further reacts with acetic acid in the presence of $HClO_4$ to yield benzylacetate as shown in Figure 1 (Scheme 1). In fact, it was confirmed that benzyl alcohol is readily converted

$$\begin{tikzcd} AcH_2 + PhCHO + H^+ \arrow[r] & AcH^+ + PhCH_2OH \arrow[d, "MeCOOH/HClO_4"] \\ & PhCH_2OCOMe \end{tikzcd}$$

Scheme 1.

to benzyl acetate in the presence of $HClO_4$ (5.0×10^{-2} mol dm^{-3}) in CD_3CN/MeCOOH (4:1 v/v) (Scheme 1). The products were identified by electronic and ^1H nmr spectra as well as GC (see Experimental). The acid-catalysed reduction of benzaldehyde by AcH_2 occurred also by using a mixture of CD_3CN and CF_3COOH as a solvent, when $PhCH_2OH$ was converted to $PhCH_2OCOCF_3$.[24] No reduction of benzaldehyde has been observed in the absence of $HClO_4$.

Colter et al.[25] has reported that AcH_2 can reduce *p*-benzoquinone derivatives Q with electron-withdrawing substituents such as 2,3-dicyano-*p*-benzoquinone and *p*-chloranil in the absence of protons in MeCN by the hydride-transfer reactions from AcH_2 to Q [equation (2)]. The

$$AcH_2 + Q \longrightarrow AcH^+ + QH^- \qquad (2)$$

hydroquinone anion QH^- is known to be converted immediately to $Q^{\cdot-}$ and QH_2 in MeCN [equation (3)].[20,25] For *p*-benzoquinone derivatives which are weaker oxidants

$$2QH^- + Q \longrightarrow 2Q^{\cdot-} + QH_2 \qquad (3)$$

than chloro-*p*-benzoquinone (*p*-benzoquinone, methyl-, 2,6-dimethyl-, trimethyl-, and tetramethyl-*p*-benzoquinone), the hydride-transfer reaction [equation (2)] has not been observed probably because of the occurrence of the back hydride transfer from QH^- to AcH^+. In the presence of $Mg(ClO_4)_2$ or $HClO_4$, however, the hydride-transfer reactions [equation (2)] occurred for all the *p*-benzoquinone derivatives described above.

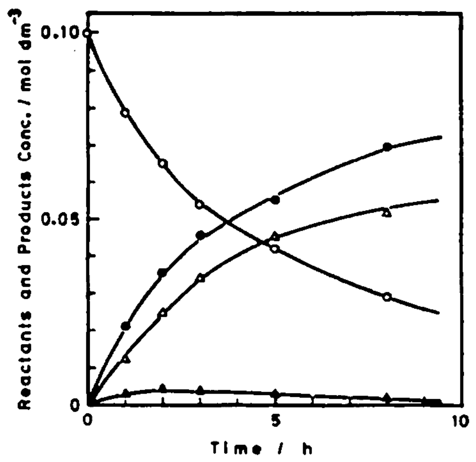

Figure 1. Acid-catalysed reduction of benzaldehyde (0.10 mol dm^{-3}) by AcH_2 (0.10 mol dm^{-3}) in the presence of $HClO_4$ (0.20 mol dm^{-3}) in CD_3CN/MeCOOH (4:1 v/v) at 323 K; AcH_2 (○), AcH^+ (●), $PhCH_2OCOMe$ (△), $PhCH_2OH$ (▲).

Kinetics.

The kinetics of the reduction of benzaldehyde and *p*-benzoquinone derivatives were studied by observing the increase in absorbance due to AcH^+ in the visible region ($\lambda_{max.}$ 358 nm, ε 2.00×10^4 dm^3 mol^{-1} cm^{-1}). The reactions were carried out under pseudo-first-order conditions with at least 10-fold excess of a substrate, where plots of $\ln[(A_\infty - A_t)/(A_\infty - A_0)]$ *vs.* time (A_0, A_t, and A_∞ are the absorbances at time 0, t, and at the completion of the reaction, respectively) were linear over more than several half-lives. By varying the concentration of the excess substrate, the pseudo-first-order rate constants were found to be proportional to the substrate concentrations. Thus, the rate of the formation of AcH^+ in the presence of an excess substrate S is given by equation (4). The

$$\frac{d[AcH^+]}{dt} = k_{obs.}([AcH^+]_\infty - [AcH^+])[S] \qquad (4)$$

second-order rate constants $k_{obs.}$ for the reduction of *p*-benzoquinone derivatives by AcH_2 [equation (2)] are listed in Table 1, together with the redox potentials $E^0(Q/Q^{\cdot-})$.[20]

When $HClO_4$ is added to the AcH_2-*p*-benzoquinone derivative system, the $k_{obs.}$ value increases or decreases depending on the *p*-benzoquinone derivative as shown in Figure 2, where the $k_{obs.}$ value in the case of a weak oxidant such as *p*-benzo-

Table 1. Rate constants $k_{obs.}$ ($dm^3\ mol^{-1}\ s^{-1}$) for the reduction of *p*-benzoquinone derivatives Q by AcH_2 in the absence and presence of $HClO_4$ or $Mg(ClO_4)_2$ at 298 K and the redox potentials of Q $E^0(Q/Q^{\overline{\cdot}})$ (*vs.* s.c.e.) in MeCN

		$E^0(Q/Q^{\overline{\cdot}})$[a]	$k_{obs.}$[b] in the presence of $HClO_4$ (mol dm^{-3})		$k_{obs.}$[b] in the presence of $Mg(ClO_4)_2$
Entry	*p*-Benzoquinone derivative	V	0	1.0×10^{-2}	0.10
1	2,3-Dichloro-5,6-dicyano-*p*-benzoquinone	0.51	1.5×10^6	2.3×10^5	1.4×10^6
2	2,3-Dicyano-*p*-benzoquinone	0.28	1.1×10^4	7.3×10^3	1.9×10^4
3	*p*-Chloranil	0.01	1.2×10	6.3	1.7×10
4	*p*-Bromanil	0	9.0	8.0	1.5×10
5	2,6-Dichloro-*p*-benzoquinone	-0.18	1.5×10^{-1}	2.7×10	8.1×10^{-1}
6	Chloro-*p*-benzoquinone	-0.34	7.8×10^{-3}	2.3×10	1.2×10^{-1}
7	*p*-Benzoquinone	-0.50		9.9×10	1.6×10^{-2}
8	Methyl-*p*-benzoquinone	-0.58		7.3×10	4.4×10^{-3}
9	2,6-Dimethyl-*p*-benzoquinone	-0.67		6.1	9.8×10^{-4}
10	Trimethyl-*p*-benzoquinone	-0.75		1.7	2.6×10^{-4}
11	Tetramethyl-*p*-benzoquinone	-0.84		6.7×10^{-2}	

[a] Taken from ref. 20. [b] The experimental errors are within ±5 %.

quinone increases to reach a plateau value $k_{max.}$ with increasing $HClO_4$ concentration, while the $k_{obs.}$ value in the case of stronger oxidants such as 2,3-dichloro-5,6-dicyano-*p*-benzoquinone decreases. Such a saturation behavior of $k_{obs.}$ as a function of $[HClO_4]$ in the case of *p*-benzoquinone (Q) may be explained by assuming the following reactions, where AcH_2 forms a complex with H^+ [equation (5)] and

$$AcH_2 + H^+ \overset{K}{\rightleftharpoons} AcH_3^+ \qquad (5)$$

AcH_3^+ is inactive for the reduction of Q which proceeds through the acid-catalysed reaction of free AcH_2 with Q [equation (6)]. Accrding to equations (5) and (6), $k_{obs.}$ is expressed as a function of $[HClO_4]$ by equation (7), which agrees with the observed

$$AcH_2 + Q + H^+ \xrightarrow{k[H^+]} AcH^+ + QH_2 \qquad (6)$$

$$k_{obs.} = \frac{k[HClO_4]}{1 + K[HClO_4]} \qquad (7)$$

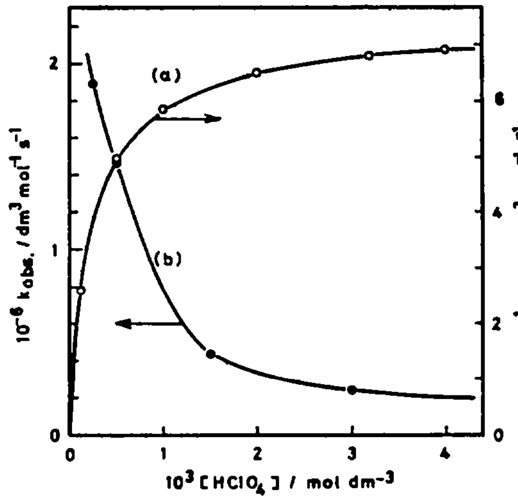

Figure 2. Plots of $k_{obs.}$ *vs.* the $HClO_4$ concentration for the reduction of (a) *p*-benzoquinone and (b) 2,3-dichloro-5,6-dicyano-*p*-benzoquinone by AcH_2 in the presence of various concentrations of $HClO_4$ at 298 K.

dependence of $k_{obs.}$ on $[HClO_4]$ (Figure 2a). On the other hand, in the case of 2,3-dichloro-5,6-dicyano-p-benzoquinone (Q'), the presence of $HClO_4$ may cause no accelerating effect on the reaction of free AcH_2 with Q' which is known to have no interaction with $HClO_4$ under the conditions in Figure 2b [equation (8)].[26]

$$AcH_2 + Q' + H^+ \xrightarrow{k'} AcH^+ + Q'H_2 \qquad (8)$$

Thus, in this case, $k_{obs.}$ decreases with increasing $[HClO_4]$ because of the formation of inactive AcH_3^+ [equation (5)] as expressed by equation (9), agreeing with

$$k_{obs.} = \frac{k'}{1 + K[HClO_4]} \qquad (9)$$

the result in Figure 2b.

The complex formation between AcH_2 and H^+ [equation (5)] is confirmed by the downfield shifts of the proton resonances of ^1H nmr spectra of AcH_2 in the presence of various concentrations of $HClO_4$ in CD_3CN as shown in Figure 3, where the chemical shifts referenced to free AcH_2 $\delta - \delta_f$ are increased with increasing $[HClO_4]/[AcH_2]$ value up to a plateau value corresponding to the completion of the complex formation. The stoichiometry of the complex formation is shown to be 1 : 1 as indicated by the abscissa of the intercept of the initial linear branch of the curve with the extrapolated plateau line (Figure 3). The proton may interact with the N atom of AcH_2 since only the ^{13}C resonance of the methyl carbon which is bonded to N atom of AcH_2 was shifted significantly from 33.8 ppm in the absence of $HClO_4$ to 51.5 ppm in the presence of $HClO_4$ (0.3 mol dm^{-3}) in CD_3CN. The formation constant K [equation (5)] was determined by the change in absorbance due to AcH_2 ($\lambda_{max.}$ 285 nm, ε 1.46 x 10^4 dm^3 mol^{-1} cm^{-1}) in the presence of various concentrations of $HClO_4$ $(A_0 - A)/(A_0 - A_\infty)$ which is expressed as a function of $[HClO_4]$ by equation (10),

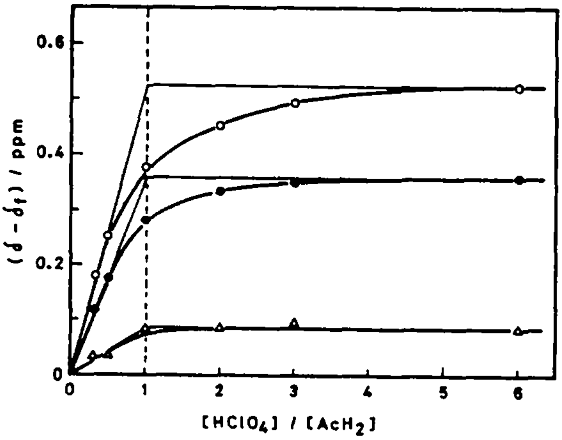

Figure 3. Plots of the chemical shifts of AcH_2 proton resonances in the presence of various concentrations of $HClO_4$ referenced to those in the absence of $HClO_4$ $(\delta - \delta_f)$ as a function of the ratio of the initial concentration of $HClO_4$ to that of AcH_2 (5.0 x 10^{-2} mol dm^{-3}) in CD_3CN.

$$\frac{A_0 - A}{A_0 - A_\infty} = \frac{K[HClO_4]}{1 + K[HClO_4]} \qquad (10)$$

where A_0, A, and A_∞ are the absorbances at 285 nm in the absence and presence of a certain concentration of $HClO_4$, and the presence of a large excess $HClO_4$ such that all AcH_2 molecules form the 1 : 1 complex with H^+, respectively. The K value was determined as 1.1 x 10^4

Table 2. Formation constants K of AcH_3^+ in the presence of different concentrations of H_2O in MeCN at 298 K

H_2O mol dm^{-3}	K dm^3 mol^{-1}
<1.0 x 10^{-2}	1.1 x 10^4
2.8 x 10^{-2}	1.1 x 10^3
1.0 x 10^{-1}	2.4 x 10^2

dm^3 mol^{-1} from the slope of the plot of $(A_0 - A_\infty)/(A_0 - A)$ *vs.* $[HClO_4]^{-1}$ and it decreases by the addition of H_2O as shown in Table 2.

Since $k_{obs.}/k_{max.}$ which is derived from equation (7) should have the same dependence on $[HClO_4]$ as $(A_0 - A)/(A_0 - A_\infty)$ in equation (10), the validity of equation (7) is tested by comparing between $k_{obs.}/k_{max.}$ and $(A_0 - A)/(A_0 - A_\infty)$ as a function of $[HClO_4]$ in the presence of different concentrations of H_2O as shown in Figure 4, which confirms that both of them have the same dependence on $[HClO_4]$.

The $k_{obs.}$ values for the reduction of a series of *p*-benzoquinone derivatives by AcH_2 in the presence of 1.0×10^{-2} mol dm^{-3} $HClO_4$ in MeCN at 298 K are listed in Table 1. The effects of $Mg(ClO_4)_2$ on the reduction of Q by AcH_2 were also investigated and the $k_{obs.}$ values in the presence of 0.10 mol dm^{-3} Mg^{2+} ion in MeCN at 298 K are tabulated together in Table 1.

The addition of acetic acid enhances significantly the rate of the reduction of *p*-benzoquinone by AcH_2 in the presence of 1.0×10^{-2} mol dm^{-3} $HClO_4$ in MeCN as shown in Figure 5a, where the $k_{obs.}$ value increases with increasing volume % of MeCOOH in a mixture of MeCN and MeCOOH. Thus, by using a mixture of MeCN and MeCOOH as a solvent, it is possible to reduce benzladehyde by AcH_2 with appreciable rates in the presence of $HClO_4$ (5.0×10^{-2} mol dm^{-3}) (Figure 5b). The dependence of $k_{obs.}$ on $[HClO_4]$ for the acid-catalysed reduction of benzaldehyde by AcH_2 in MeCN/MeCOOH (4:1 v/v) at 323 K also obeyed equation (7) as shown in Figure 6, from which the K value is determined as 2.0×10^2 dm^3 mol^{-1}. The $k_{obs.}$ values for the reduction of a series of aromatic aldehydes by AcH_2 in the presence of 5.0×10^{-2} mol dm^{-3} $HClO_4$ in MeCN/MeCOOH (4:1 v/v) at 323 K are listed in Table 3.

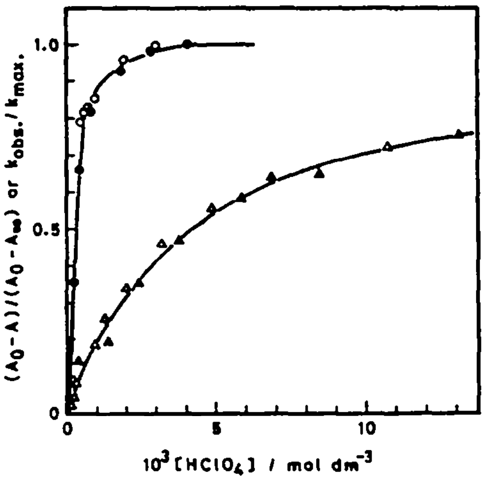

Figure 4. Plots of $(A_0 - A)/(A_0 - A_\infty)$ for AcH_2 and $k_{obs.}/k_{max.}$ for the reduction of *p*-benzoquinone by AcH_2 in the presence of $HClO_4$ in MeCN containing H_2O *vs.* the $HClO_4$ concentration; $(A_0 - A)/(A_0 - A_\infty)$ (○) and $k_{obs.}/k_{max.}$ (●) at $[H_2O] < 1.0 \times 10^{-2}$ mol dm^{-3}, $(A_0 - A)/(A_0 - A_\infty)$ (△) and $k_{obs.}/k_{max.}$ (▲) at $[H_2O] = 0.10$ mol dm^{-3}.

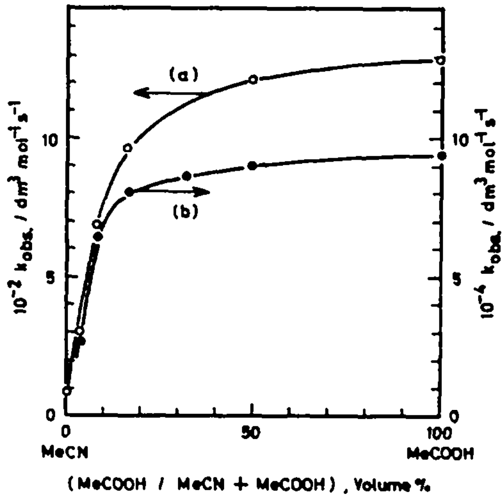

Figure 5. Plots of $k_{obs.}$ for the reduction of (a) *p*-benzoquinone and (b) benzaldehyde by AcH_2 in the presence of 1.0×10^{-2} and 5.0×10^{-2} mol dm^{-3} $HClO_4$ in MeCN/MeCOOH at 298 and 323 K, respectively, as a function of the volume % of MeCOOH.

Mechanism of Hydride-transfer Reaction from AcH_2 to Q.

In Figure 7, the logarithms of rate constants $k_{obs.}$ in Table 1 are plotted against the redox potentials of Q $E^0(Q/Q^{-\bullet})$ in MeCN. The log $k_{obs.}$ value in the absence of $HClO_4$ or $Mg(ClO_4)_2$ shows an approximately linear correlation with the $E^0(Q/Q^{-\bullet})$ value, while the log $k_{obs.}$ values in the presence of $HClO_4$ (1.0×10^{-2} mol dm^{-3}) are either larger or somewhat smaller than those in its absence for *p*-benzoquinone derivatives having lower redox potentials $E^0(Q/Q^{-\bullet}) < 0$ and higher redox potentials $E^0(Q/Q^{-\bullet}) > 0$, respectively (Figure 7). Thus, $HClO_4$ shows both accelerating and retarding effects depending on the electron-acceptor ability of *p*-benzoquinone derivative. On the other hand, $Mg(ClO_4)_2$ shows only an accelerating effect for *p*-benzoquinone derivatives having lower redox potentials $E^0(Q/Q^{-\bullet}) < 0$ (Figure 7). In the following discussion, we show how such complex effects of $HClO_4$ and $Mg(ClO_4)_2$ on the reduction of Q by AcH_2 can be evaluated quantitatively based on the reaction mechanism.

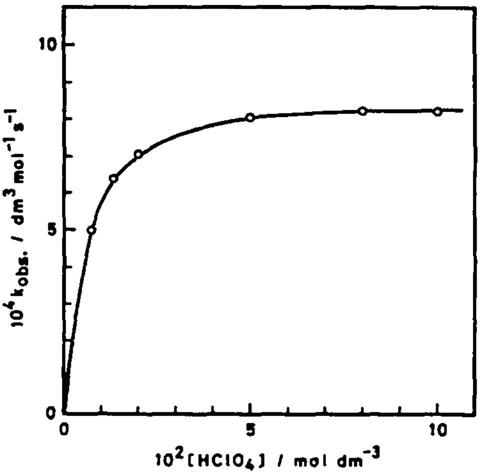

Figure 6. Plot of $k_{obs.}$ *vs.* the $HClO_4$ concentration for the reduction of benzaldehyde by AcH_2 in the presence of $HClO_4$ (5.0×10^{-2} mol dm^{-3}) in MeCN/MeCOOH (4:1 v/v) at 323 K.

Table 3. Rate constants $k_{obs.}$ for the acid-catalysed reduction of aromatic aldehydes by AcH_2 in the presence of $HClO_4$ (5.0×10^{-2} mol dm^{-3}) in MeCN/MeCOOH (4:1 v/v) and k_h for the LADH-catalysed reduction by NADH

Aromatic aldehyde	$10^3 k_{obs.}$ dm^3 mol^{-1} s^{-1}	$10^{-2} k_h$[a] s^{-1}
p-Nirobenzaldehyde	1.8	
p-Chlorobenzaldehyde	1.0	4.1
Benzaldehyde	0.80	3.4
p-Methylbenzaldehyde	1.1	
p-Methoxybenzaldehyde	2.1	2.5
β-Naphthaldehyde	1.9	4.2

[a] Taken from ref. 1.

First, the correlation between log $k_{obs.}$ and $E^0(Q/Q^{-\bullet})$ in the absence of $HClO_4$ or $Mg(ClO_4)_2$ in Figure 7 is discussed by applying the reaction mechanism for the hydride-transfer reactions from an NADH model compound BNAH to Q reported previously[20,21] to the present system [equation (11)]. According to equation (11),

$$AcH_2 + Q \underset{}{\overset{K_{et}}{\rightleftharpoons}} [AcH_2^{+\bullet}\ Q^{-\bullet}] \xrightarrow{k_H} [AcH\bullet\ QH\bullet] \xrightarrow{fast} AcH^+ + QH^- \tag{11}$$

the observed rate constant $k_{obs.}$ for the overall hydride-transfer reaction from AcH_2 to Q is given by equation (12),

$$k_{obs.} = k_H K_{et} \tag{12}$$

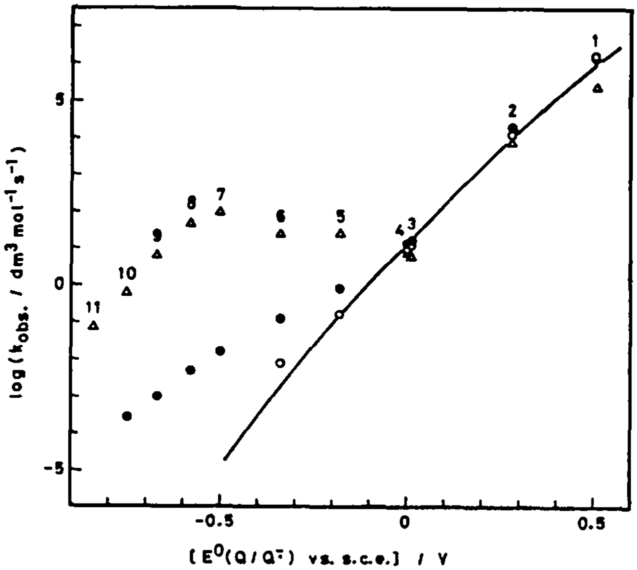

Figure 7. Plots of log $k_{obs.}$ for the hydride-transfer reactions from AcH_2 to *p*-benzoquinone derivatives Q in the absence (○) and the presence of 0.10 mol dm^{-3} $Mg(ClO_4)_2$ (●), and in the presence of 1.0 x 10^{-2} mol dm^{-3} $HClO_4$ (△) at 298 K *vs.* the redox potential of Q $E^0(Q/Q^{\cdot-})$ in MeCN. The solid line is drawn by the simulation in the absence of $Mg(ClO_4)_2$ or $HClO_4$ based on the reaction mechanism [equation (11)], see text. The numbers refer to *p*-benzoquinone derivatives in Table 1.

where K_{et} corresponds to the formation constant of the radical ion pair $[AcH_2^{\cdot+}\ Q^{\cdot-}]$, and k_H is the rate constant of the proton transfer from $AcH_2^{\cdot+}$ to $Q^{\cdot-}$ in the radical ion pair. The rate constant for the electron transfer from AcH• to QH• following the proton transfer is not included in $k_{obs.}$ since the electron transfer, being highly exothermic [the oxidation potential of AcH• (-0.43 V *vs.* s.c.e.)[27] is much more negative than the reduction potential of QH•[28]], may be very rapid.

The log K_{et} value is related to the Gibbs energy change of the electron transfer ($AcH_2 + Q \rightarrow AcH_2^{\cdot+} + Q^{\cdot-}$) ΔG^0_{et} by equation (13),[20,21]

$$\log K_{et} = - \Delta G^0_{et}/2.3RT + C_1 \qquad (13)$$

where C_1 corresponds to the work term required to bring the products $AcH_2^{\cdot+}$ and $Q^{\cdot-}$ to their mean separation in the activated complex, which has been determined as 5.3.[20,21,29] The ΔG^0_{et} value is obtained from the redox potentials of AcH_2 (0.80 V *vs.* s.c.e.)[27] and Q (the values are listed in Table 1) by equation (14). By

$$\Delta G^0_{et}/F = E^0(AcH_2^{\cdot+}/AcH_2) - E^0(Q/Q^{\cdot-}) \qquad (14)$$

combining equations (13) and (14), log K_{et} is given as a linear function of $E^0(Q/Q^{\cdot-})$ with a slope of F/2.3RT corresponding to 16.9 at 298 K [equation (15)].

$$\log K_{et} = FE^0(Q/Q^{\cdot-})/(2.3RT) - 8.2 \qquad (15)$$

On the other hand, the activation Gibbs energy of the proton transfer from $AcH_2^{\cdot+}$ to $Q^{\cdot-}$ ($\Delta G^{\ddagger}_H$) can be expressed as a function of the Gibbs energy change of the proton transfer ΔG_H by using the Marcus formalism [equations (16)-(18)],[20,21,30]

$$\Delta G_H^{\ddagger} = \Delta G_{H0}^{\ddagger}[1 + (\Delta G_H/4\Delta G_{H0}^{\ddagger})]^2 \quad \text{when } -4\Delta G_{H0}^{\ddagger} < \Delta G_H < 4\Delta G_{H0}^{\ddagger} \tag{16}$$

$$\Delta G_H^{\ddagger} \cong 0 \quad \text{when } \Delta G_H < -4\Delta G_{H0}^{\ddagger} \tag{17}$$

$$\Delta G_H^{\ddagger} \cong \Delta G_H \quad \text{when } \Delta G_H > 4\Delta G_{H0}^{\ddagger} \tag{18}$$

where $\Delta G_{H0}^{\ddagger}$ is the intrinsic barrier for the proton transfer which corresponds to the activation Gibbs energy when $\Delta G_H = 0$. The Gibbs energy change of the proton transfer ΔG_H is known to be related to that of the electron transfer ΔG_{et}^0 by equation (19),[20,21]

$$\Delta G_H = -0.58\ \Delta G_{et}^0 + C_2 \tag{19}$$

where the constant C_2 has been determined as 57 kJ mol^{-1}.[21] Thus, the proton-transfer rate constant k_H [= $(\kappa T/h)\exp(-\Delta G_H^{\ddagger}/RT)$] can be evaluated as a function of ΔG_{et}^0 by using equations (16)-(19) provided that the $\Delta G_{H0}^{\ddagger}$ value is given.

Taken altogether, the observed rate constants $k_{obs.}$ for the hydride-transfer reactions from AcH_2 to Q have been calculated from equations (12) and (14)-(19) as a function of $E^0(Q/Q^{\bar{\cdot}})$ by using the value of $\Delta G_{H0}^{\ddagger} = 12.6$ kJ mol^{-1} which is a typical value as the intrinsic barrier of proton-transfer reactions found in the literature.[31] The results are shown as the solid line in Figure 7, where the calculated line agrees well with the experimental plot in the absence of $HClO_4$ or $Mg(ClO_4)_2$ in MeCN, supporting strongly the reaction mechanism [equation (11)]. The same correlation between log $k_{obs.}$ and $E^0(Q/Q^{\bar{\cdot}})$ has been applied to the hydride transfer reactions from BNAH to Q,[20] when the difference in the redox potentials between AcH_2 (0.80 V) and BNAH (0.57 V)[27] is taken account. Thus, the difference in the reactivity between AcH_2 and BNAH can be ascribed to the difference in their redox potentials in the correaltion of log $k_{obs.}$ with $\Delta G_{et}^0/F$.[32]

The effect of Mg^{2+} ion on the reduction of Q by AcH_2 (Figure 7) as well can be evaluated based on the reaction mechanism [equation (11)] as follows. In the presence of Mg^{2+} ion (0.10 mol dm^{-3}), the redox potentials of *p*-benzoquinone derivatives having $E^0(Q/Q^{\bar{\cdot}}) < 0$ in the absence of Mg^{2+} ion are known to be shifted to the positive direction due to the complex formation between Q and Mg^{2+} ion [equation (20)],[21] while those of *p*-benzoquinone derivatives having $E^0(Q/Q^{\bar{\cdot}}) > 0$

$$Q + Mg^{2+} \rightleftharpoons [Q\ Mg^{2+}] \tag{20}$$

are unaffected by the presence of Mg^{2+} ion,[21] agreeing with the results shown by the closed circles in Figure 7, where the acceleration effect of Mg^{2+} ion is observed only for the reduction of Q in the former case [i.e., $E^0(Q/Q^{\bar{\cdot}}) < 0$]. In fact, the plot of log $k_{obs.}$ in the presence of Mg^{2+} ion (0.10 mol dm^{-3}) *vs.* the redox potential of Q in the presence of the same concentration of Mg^{2+} ion $E(Q/Q^{\bar{\cdot}}\ Mg^{2+})$[21] (closed circles in Figure 8) shows a reasonable agreement with that in the absence of Mg^{2+} ion (open circles in Figure 7 which are also shown in Figure 8). Thus, the effect of Mg^{2+} ion on the reduction of Q by AcH_2 has been evaluated quatitatively by the change of the redox potentials of Q in the presence of Mg^{2+} ion due to the complex formation with Mg^{2+} ion [equation (20)], which causes the change of the formation constant of the radical ion pair $[AcH_2^{+\cdot}\ Q^{\bar{\cdot}}\ Mg^{2+}]$ as a function of ΔG_{et}^0 [equations (13)-(15)] as well as the rate constant of the subsequent proton transfer which is also the function of ΔG_{et}^0 [equations (16)-(19)], since the redox potential of AcH_2 which has no carbonyl group to interact with Mg^{2+} ion is unaffected by the presence of Mg^{2+} ion.[27]

The effect of $HClO_4$ on the reduction of Q by AcH_2 is more complicated than that of $Mg(ClO_4)_2$ since AcH_2 forms an inactive complex with H^+ [equation (5)]. In order to discriminate the contribution due to the complex formation, the rate constants $k^*_{obs.}$ for the reactions of free AcH_2 with Q in the presence of $HClO_4$ (1.0×10^{-2} mol dm^{-3}) in MeCN have been determined by multiplying $k_{obs.}$ by $1 + K[HClO_4]$ from equations (7) and (9), where the K value is taken as 1.1×10^3 dm^3 mol^{-1} which is the value in the presence of 2.8×10^{-2} mol dm^{-3} H_2O (Table 2), since an MeCN solution containing 1.0×10^{-2} mol dm^{-3} $HClO_4$ is prepared by adding an aqueous solution of 60% $HClO_4$ to MeCN which contains 2.8×10^{-2} mol dm^{-3}.

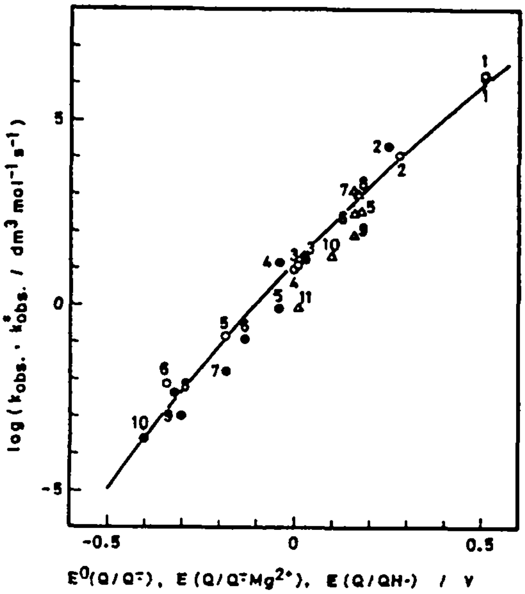

Figure 8. Plots of log $k_{obs.}$ and log $k^*_{obs.}$ for the hydride-transfer reactions from AcH_2 to p-benzoquinone derivatives Q in the absence (○) and the presence of 0.10 mol dm^{-3} $Mg(ClO_4)_2$ (●), and in the presence of 1.0 x 10^{-2} mol dm^{-3} $HClO_4$ (△) at 298 K *vs.* the redox potential of Q $E^0(Q/Q^{\overline{\cdot}})$, $E(Q/Q^{\overline{\cdot}}\ Mg^{2+})$ and $E(Q/QH\cdot)$ in the absence and the presence of 0.10 mol dm^{-3} $Mg(ClO_4)_2$, and in the presence of 1.0×10^{-2} mol dm^{-3} $HClO_4$, respectively, in MeCN. The $k^*_{obs.}$ values which correspond to the rate constants for the reactions of free AcH_2 with Q in the presence of $HClO_4$ have been evaluated by multiplying $k_{obs.}$ by $1 + K[HClO_4]$, see text. The solid line shows the simulation curve which is the same as that in Figure 7.

The effect of $HClO_4$ on the redox potential of Q may be evaluated from the effect of $HClO_4$ on the electron-transfer reactions from *cis*-diethylcobalt(III) complex, *cis*-$[Et_2Co(bpy)_2]^+$ (bpy = 2,2'-bipyridine), to Q in MeCN [equation (21)],[26] as follows. The

$$cis\text{-}[Et_2Co(bpy)_2]^+ + Q \xrightarrow{k_{obs.}} cis\text{-}[Et_2Co(bpy)_2]^{2+} + Q^{\overline{\cdot}} \qquad (21)$$

logarithm of the observed second-order rate constant in the absence of $HClO_4$ in MeCN at 298 K is expressed as a linear function of $E^0(Q/Q^{\overline{\cdot}})$ [equation (22)].[33] In the presence of $HClO_4$,

$$\log k_{obs.} = 15.3E^0(Q/Q^{\overline{\cdot}}) - 2.5 \qquad (22)$$

the $k_{obs.}$ value increased linearly with increasing $HClO_4$ concentration in the case of p-benzoquinone derivatives having $E^0(Q/Q^{\overline{\cdot}}) < 0$ in the absence of $HClO_4$ in MeCN, while the $k_{obs.}$ value in the case of a strong oxidant such as 2,3-dichloro-5,6-dicyano-p-benzoquinone has not been affected by the presence of $HClO_4$.[26] Thus, the redox potentials of Q in the presence of $HClO_4$ (1.0×10^{-2} mol dm^{-3}) in MeCN $E(Q/QH\cdot)$ may be evaluated from equation (22) by comparing the $k_{obs.}$ values for the electron-transfer reactions from *cis*-$[Et_2Co(bpy)_2]^+$ to Q in the presence of $HClO_4$ (1.0×10^{-2} mol dm^{-3})[34] with those in its absence. The evaluated values of $E(Q/QH\cdot)$ are shifted to the positive direction in the presence of $HClO_4$ due to the partial protonation of Q [equation (23)]. Similarly, the redox potential of AcH_2 may also be shifted to

$$Q + H^+ \rightleftharpoons QH^+ \qquad (23)$$

the positive direction in the presence of $HClO_4$ due to the complex formation with

$HClO_4$ [equation (5)], and thereby, AcH_3^+ is much less reactive than AcH_2 towards the reduction of Q.

Then, the logarithms of the rate constants for the reactions of free AcH_2 with Q in the presence of 1.0 x 10^{-2} mol dm^{-3} $HClO_4$ in MeCN at 298 K (log $k^*_{obs.}$) are plotted against the E(Q/QH•) values as shown by the open triangles in Figure 8, where the plot of log $k^*_{obs.}$ *vs.* E(Q/QH•) agrees well with those of log $k_{obs.}$ *vs.* E($Q/Q^{\bar{\cdot}}$ Mg^{2+}) in the presence of 0.10 mol dm^{-3} Mg^{2+} ion (closed circles) and log $k_{obs.}$ *vs.* E^0($Q/Q^{\bar{\cdot}}$) in its absence (open circles). Thus, the retarding and accelerating effects of $HClO_4$ depending on *p*-benzoquinone derivatives (Figure 7) are well explained by the combination of the contributions from the formation of an inactive complex AcH_3^+ and the acid-catalysed reactions of free AcH_2 with Q, where the magnitudes of the catalytic effect depending on Q have been evaluated quantitatively by the change of the redox potential of Q in the presence of $HClO_4$. The single and unified correlation of log $k^*_{obs.}$ with E(Q/QH•) as well as log $k_{obs.}$ with E^0($Q/Q^{\bar{\cdot}}$) and E($Q/Q^{\bar{\cdot}}$ Mg^{2+}) (Figure 8) supports uniformly the reaction mechanism [equation (11)].

Comparison between the Acid-catalysed Reduction of Aromatic Aldehydes by AcH_2 and the LADH-catalysed Reduction by NADH.

A very small electronic substituent effect on the observed rate constant $k_{obs.}$ for the reduction of a series of aromatic aldehydes by AcH_2 (e.g., the ratio for *p*-nitrobenzaldehyde and *p*-methoxybenzaldehyde is 0.9) is compatible with that on the rate constant k_h for the hydride-transfer step in the LADH-catalysed reduction of the corresponding aldehydes which were determined by using a transient kinetics under a single turnover condition[1] as shown in Table 3. Such a small electronic substituent effect is observed also on the $k_{obs.}$ values for the acid-catalysed reduction of *p*-benzoquinone derivatives in Table 1 (e.g., the ratio for *p*-chloranil and 2,6-dimethyl-*p*-benzoquinone is 1.0), and may be ascribed to the much lowered sensitivity of the redox potential of Q in the presence of $HClO_4$ E(Q/QH•) to the electron-withdrawing or -donating substituents as shown by the open triangles in Figure 8. The E(Q/QH•) value consists of E^0($Q/Q^{\bar{\cdot}}$) in the absence of $HClO_4$ and the positive shift due to the partial protonation of Q by $HClO_4$ [equation (23)], when the reduced species $Q^{\bar{\cdot}}$ is protonated to yield QH•,[35] and therefore the electronic substituent effect on the former E^0($Q/Q^{\bar{\cdot}}$) may be cancelled out largely by the opposite effect on the latter (e.g., the electron-withdrawing substituent causes the positive shift of E^0($Q/Q^{\bar{\cdot}}$), while at the same time decreases the magnitude of the positive shift due to the protonation because of the weaker interaction of Q with H^+). Thus, similar insensitive substituent effects between the model system and the LADH-enzyme system (Table 3) suggest that the acceptor ability of aromatic aldehydes (irrespective of an electron or a hydride) may remain constant, because of such a cancellation effect of the substituent on the intrinsic acceptor ability of aromatic aldehydes in the absence of a catalyst and on the magnitude of the enhancement of the acceptor ability due to either protonation in the model system or coordination of zinc ion to the aldehyde on the enzyme surface acting as a strong Lewis acid.

The $k_{obs.}$ value in Table 3 approximately corresponds to k/K [see equation (7)], where k is the third-order rate constant for the acid-catalysed reduction of aromatic aldehydes by AcH_2 and K is the formation constant of AcH_3^+ [equation (5)] (K = 2.0 x 10^2 dm^3 mol^{-1} in MeCN/MeCOOH at 323 K as described above), while k_h in the LADH-enzyme system is the first-order rate constant for the hydride-transfer step in the enzyme-bound ternary complex. Thus, in order to compare the absolute value of the reactivity in our model system with that in the LADH-enzyme system, it is necessary to evaluate the rate constant k_h for the hydride-transfer step from free AcH_2 to the protonated benzaldehyde in the encounter complex [equation (24)]. The concentration of the protonated benzaldehyde $PhCHOH^+$ may be

$$AcH_2 + PhCHOH^+ \underset{}{\overset{K_{diff}}{\rightleftharpoons}} [AcH_2\ PhCHOH^+] \xrightarrow{k_h} AcH^+ + PhCH_2OH \quad (24)$$

evaluated from the H_0 acidity function and the pK_{BH^+} value of PhCHO (pK_{BH^+} = -7.1)[36] by using equation (25).[37] The H_0 value of a mixture of MeCN and MeCOOH

$$\log([PhCHOH^+]/[PhCHO]) = pK_{BH^+} - H_0 \quad (25)$$

(4:1 v/v) containing 5.0×10^{-2} mol dm^{-3} $HClO_4$ was determined as -2.7 by indicator methods[37] (see Experimental). Then, the first-order rate constant k_h for the hydride-transfer step from free AcH_2 to $PhCHOH^+$ in the encounter complex [equation (24)] has been determined as 6.9×10^2 s^{-1} by multiplying the k_{obs} value (8.0×10^{-4} dm^3 mol^{-1} s^{-1}) by $1 + K[HClO_4]$ (= 11), $10^{(pK_{BH^+} - H_0)}$ (= $10^{4.4}$), and K_{diff}^{-1} (= 3.1)[38]. The k_h value is the same order of magnitude as that in the LADH-enzyme system ($k_h = 3.4 \times 10^2$ s^{-1}), although the $k_{obs.}$ value is apparently much smaller than the k_h value because of the formation of an inactive complex AcH_3^+ and the small concentration of the reactive species $PhCHOH^+$. Thus, the present study has demonstrated for the first time that the huge reactivity of the LADH-enzyme system which has often created some mysterious image of the enzyme is compatible with that in a simple nonenzymatic system where the enormous enhancement of the reactivity is caused by the protonation of a substrate.

Experimental

Materials.—*N*-methylacridan was prepared according to the literature.[10] *N*-methylacridinium perchlorate was prepared by the addition of magnesium perchlorate to *N*-methylacridinium iodide in H_2O. Most *p*-benzoquinone derivatives (2,3-dichloro-5,6-dicyano-*p*-benzoquinone, *p*-chloranil, *p*-bromanil, 2,6-dichloro-*p*-benzoquinone, *p*-benzoquinone, methyl-, 2,6-dimethyl-,and tetramethyl-*p*-benzoquinone), aromatic aldehydes (*p*-nitrobenzaldehyde, *p*-chlorobenzaldehyde, benzaldehyde, *p*-methylbenzaldehyde, *p*-methoxybenzaldehyde and β-naphthaldehyde) and the corresponding alcohols were obtained commercially and purified by the standard methods.[39] Chloro-*p*-benzoquinone, 2,3-dicyano-*p*-benzoquinone and trimethyl-*p*-benzoquinone were prepared from the corresponding hydroquinones according to the literature.[40] Anhydrous magnesium perchlorate and perchloric acid (60%) were obtained from Nakarai Chemicals and Wako Pure Chemicals, respectively. Acetonitrile which was also obtained commercially was purified and dried with calcium hydride by the standard procedure,[39] and stored under nitrogen atomosphere.

Acid-catalysed Reduction of Aromatic Aldehydes by AcH_2.—Typically, a mixture of CD_3CN and MeCOOH (4:1 v/v, 0.50 cm^3) containing benzaldehyde (0.10 mol dm^{-3}) and $HClO_4$ (0.20 mol dm^{-3}) was introduced into a Schlenk tube which was connected to an nmr tube. The Schlenk tube was equipped also with a side arm where 9.8 mg (0.05 mmol) AcH_2 was placed. After the solution in the nmr tube was thoroughly degassed in vacuum by the successive freez-pump-thaw cycles, the solution was mixed with AcH_2 in the side arm, and the nmr tube containing the reactant solution was sealed in vacuum. Such a rigorous deaeration was required in order to avoid the acid-catalysed oxidation of AcH_2 by oxygen. Then, the nmr tube was immersed in a water bath which was thermostated at 323 K. The progress of the reaction was monitored by measuring the nmr spectra periodically. After the completion of the reaction, the products were identified also by a GC analysis using a gascropack 54 column.

Spectral Measurements.—^1H and ^{13}C nmr spectra of AcH_2 in the presence of various concentrations of $HClO_4$ in CD_3CN were recorded on JEOL JNM-PS-100 and JNM-FX60S spectrometer, respectively. The electronic absorption spectra of AcH_2 in the presence of various concentrations of $HClO_4$ in MeCN were measured using a Union SM-401 spectrophotometer with a quartz cell (1 cm i.d.) placed in a compartment which was thermostated at 298 K. The H_0 value of a mixture of MeCN and MeCOOH (4:1 v/v) containing 5.0×10^{-2} mol dm^{-3} $HClO_4$ was determined as -2.7 by using *o*-nitroaniline ($pK_{BH^+} = -0.29$)[37] and *o*-nitro-*p*-chloroaniline ($pK_{BH^+} = -1.03$)[37] as indicators.

Kinetic Measurements.—Kinetic measurements were performed using a Union RA-103 stopped flow spectrophotometer and a Union SM-401 spectrophotometer for the reduction of *p*-benzoquinone derivatives by AcH$_2$ under deaerated conditions with half-lives < 10 s and >> 10 s, respectively. Reaction rates were followed by the increase in absorbance due to AcH$^+$ in the visible region (λ_{max} 358 nm, ε 2.00 x 10^4 dm^3 mol^{-1} cm^{-1}) under pseudo-first-order conditions using more than 10-fold excess of substrates in the presence of Mg(ClO$_4$)$_2$ or HClO$_4$, and in its absence at 298 K. Pseudo-first-order rate constants were determined by least-squares curve fitting using a Union System 77 microcomputer. In the case of the reaction of AcH$_2$ with chloro-*p*-benzoquinone in the absence of Mg(ClO$_4$)$_2$ or HClO$_4$ in MeCN at 298 K, more than 500-fold excess of the quinone was used in order to avoid the contribution of the back reaction. Rates of the acid-catalysed reduction of aromatic aldehydes by AcH$_2$ in MeCN/MeCOOH in the presence of HClO$_4$ at 323 K were followed under degassed conditions by sealing a pyrex tube which was connected to a square cuvette (1 mm i.d.) in vacuum.

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