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Acid-Catalyzed Reduction of Ketones by an NADH Model Compound and the Relation with Acid-Catalyzed Photoinduced Electron-Transfer Reactions

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Various ketones are readily reduced by an acid-stable NADH model compound, 10-methylacridan ($AcrH_2$), in the presence of perchloric acid in acetonitrile. Rates of the acid-catalyzed reduction of ketones by unprotonated $AcrH_2$ are well correlated with rates of the acid-catalyzed photoinduced electron-transfer reactions from the excited state of $[Ru(bpy)_3]^{2+}$ to the ketones.

There has been long-standing controversy whether hydride transfer reactions from reduced nicotinamide adenine dinucleotide (NADH) and NADH model compounds to substrates occur in a one-step[1,2] or consist of overall transfer of two electrons and a proton in a e^--H^+-e^- sequence, where electron transfer is an activation process without dissociation of free radical intermediates.[3] Such mechanistic discussion has so far been limited to non-catalytic or metal ion-catalyzed reductions of substrates by NADH model compounds, in which only relatively strong oxidants can be reduced by NADH model compounds.[1-3] Since acid catalysis is known to play an essential role in the enzyme-catalyzed reduction of substrates by NADH,[4] it seems of importance to study the mechanism of acid-catalyzed reduction of substrates which would otherwise be difficult to be reduced by NADH model compounds.[5,6] We wish to report herein that various ketones can be readily reduced by an acid-stable NADH model compound, 10-methylacridan ($AcrH_2$),[6,7] providing evidence for the importance of the acid-catalyzed electron-transfer process in the acid-catalyzed hydride transfer reactions of an NADH model compound.

An NADH model compound ($AcrH_2$) shows no reactivity towards acetophenone in MeCN at 331 K. In the presence of $HClO_4$, however, acetophenone and its derivatives are readily reduced by $AcrH_2$ in deaerated MeCN to yield 10-methylacridinium ion ($AcrH^+$) and the corresponding alcohols, Eq. 1.[8] When $AcrH_2$ was replaced by

$$AcrH_2 + PhCOCH_3 + H^+ \xrightarrow{k_{obsd}} AcrH^+ + PhCH(OH)CH_3 \tag{1}$$

the 9,9'-dideuterated analogue ($AcrD_2$), the deuterium was introduced quantitatively to each alcohol, e.g., $PhCD(OH)CH_3$.[8] In the case of photoreduction of benzophenone by $AcrH_2$, the hydrogen of 10-methyl position of $AcrH_2$ has been reported to be transferred to the ketone.[9] In the present case, however, no deuterium has been incorpolated into the alcohol, when $AcrH_2$ is replaced by 10-methyl-d_3-acridan

Table 1. Observed second-order rate constants (k_{obsd}) and the primary kinetic isotope effects (k_H/k_D) for acid-catalyzed reduction of ketones by $AcrH_2$, $AcrH_2$-CD_3, and $AcrD_2$ in the presence of $HClO_4$ (2.0 mol dm^{-3}) in MeCN at 331 K and rate constants (k_{et}) of acid-catalyzed photoinduced electron-transfer reactions from $[Ru(bpy)_3]^{2+*}$ to ketones in the presence of $HClO_4$ (2.0 mol dm^{-3}) in MeCN at 298 K

No.	Substrate	k_{obsd} / $dm^3\ mol^{-1}\ s^{-1}$	k_H/k_D [a]	k_H/k_D [b]	k_{et} / $dm^3\ mol^{-1}\ s^{-1}$
1	$C_{10}H_7COCH_3$	5.2×10^{-4}		4.7	6.3×10^{8}
2	p-$MeC_6H_4COCH_3$	3.7×10^{-4}	1.0	3.4	3.8×10^{8}
3	$PhCOCH_3$	2.0×10^{-4}	1.0	4.1	1.9×10^{8}
4	$PhCOC_2H_5$	1.9×10^{-4}	1.0	4.5	1.3×10^{8}
5	$PhCOC_3H_7$	1.9×10^{-4}	1.0	4.2	1.2×10^{8}
6	p-$ClC_6H_4COCH_3$	1.7×10^{-4}			1.4×10^{8}
7	p-$CNC_6H_4COCH_3$	1.1×10^{-4}			1.0×10^{8}

a) Determined from the ratio of $AcrH_2$ to $AcrH_2$-CD_3. b) Determined from the ratio of $AcrH_2$ to $AcrD_2$.

($AcrH_2$-CD_3), Table 1.[8] Thus, the hydrogen of the 9-methylene position rather than the 10-methyl position is transferred to the carbonyl oxygen.

Rates of the acid-catalyzed reduction of various ketones by $AcrH_2$ were followed by the formation of $AcrH^+$, which obeyed the second-order kinetics showing the first-order dependence on the concentration of each reactant. The observed second-order rate constants (k_{obsd}) of the acid-catalyzed reduction of ketones by $AcrH_2$ in the presence of $HClO_4$ (70%, 2.0 mol dm^{-3}) at 331 K are listed in Table 1. The k_{obsd} value remained rather constant with the change in the $HClO_4$ concentration from 0.2 to 2.0 mol dm^{-3}. Since $AcrH_2$ is known to be protonated in the presence of $HClO_4$ in MeCN and the protonated species ($AcrH_3^+$) is inactive as a reductant,[6] the acid catalysis for the reduction of ketones by unprotonated $AcrH_2$ may be canceled out by the protonation of $AcrH_2$. When $AcrH_2$ is replaced by $AcrH_2$-CD_3, no kinetic isotope effects has been observed (Table 1). When $AcrH_2$ is replaced by $AcrD_2$, however, the primary kinetic isotope effect (k_H/k_D = 3.4-4.7) is observed (Table 1). Thus, a transfer of hydrogen from the 9-methylene position rather than 10-methyl position of $AcrH_2$ should be involved in the rate-determining step.

The luminescence of $[Ru(bpy)_3]^{2+*}$ (λ_{max} 608 nm) is known to be quenched by electron transfer from $[Ru(bpy)_3]^{2+*}$ to ketones in the presence of $HClO_4$ in MeCN (Eq. 2),[10] although no quenching has been observed in the absence of $HClO_4$.

$$[\mathrm{Ru(bpy)_3}]^{2+*} + \rangle\mathrm{C{=}O} + \mathrm{H^+} \xrightarrow{k_{et}} [\mathrm{Ru(bpy)_3}]^{3+} + -\dot{\mathrm{C}}\mathrm{OH} \tag{2}$$

The k_{et} value increased linearly with an increase in the $HClO_4$ concentration, and the k_{et} values of various ketones in the presence of $HClO_4$ (2.0 mol dm^{-3}) at 298 K are also listed in Table 1. The acceleration of the electron-transfer rate by the presence of $HClO_4$ is caused by the protonation of the radical anions of ketones, since the one-electron reduction potentials of ketones are known to be shifted to the positive direction significantly by the protonation of the radical anions.[10] The electron transfer to the protonated ketones is unlikely to occur since little protonation of ketones (<< 1%) has been observed in the presence of $HClO_4$ in MeCN and thus the rate constant of electron transfer from $[Ru(bpy)_3]^{2+*}$ to the protonated ketones, if any, would exceed the diffusion limit.

Addition of H_2O to the $[Ru(bpy)_3]^{2+*}$-ketone system resulted in the significant decrease in the k_{et} values, since the acid strength of $HClO_4$ in MeCN decreases with an increase in the H_2O concentration. The effect of H_2O was also examined on the reduction of acetophenone by $AcrH_2$ in the presence of $HClO_4$ in MeCN. By taking account for the protonation equilibrium of $AcrH_2$, the k_{obsd} values of the reduction of acetophenone by unprotonated $AcrH_2$[11] in the presence of $HClO_4$ in MeCN containing various concentrations of H_2O are compared with the k_{et} values of the acid-catalyzed photoinduced electron-transfer reaction from $[Ru(bpy)_3]^{2+*}$ to acetophenone in the presence of the same concentrations of $HClO_4$ and H_2O in MeCN as shown in Fig. 1, where the k_{obsd} values of various ketones are also compared with the corresponding k_{et} values in Table 1. As demonstrated in Fig. 1, there is an excellent correlation between the k_{obsd} and k_{et} values with the slope of unity. Such a straightforward correlation of reactivities of ketones between the acid-catalyzed reduction by $AcrH_2$ and the photoinduced electron-transfer reactions of $[Ru(bpy)_3]^{2+*}$ indicates clearly that the activation barrier of the acid-catalyzed two-electron reduction of ketones is related well to the barrier of the corresponding one-electron reduction.

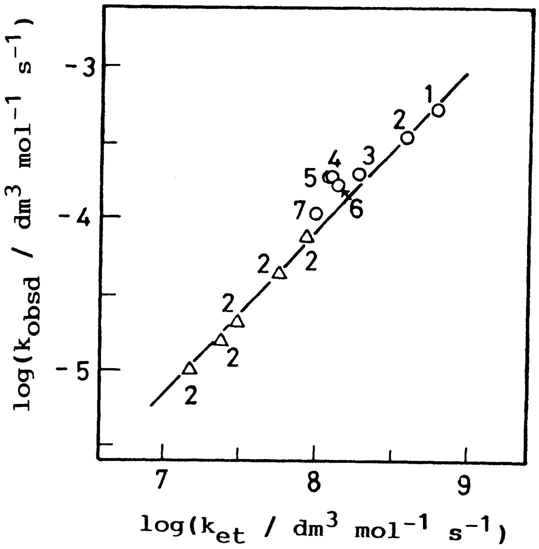
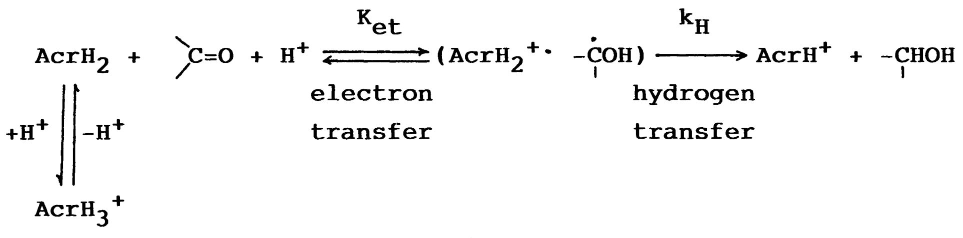


Fig. 1. Comparison of the rate constants k_{obsd} of acid-catalyzed reduction of ketones by unprotonated $AcrH_2$ in the absence (○) and the presence of added water (△) in MeCN containing 2.0 mol dm^{-3} $HClO_4$ at 331 K with the corresponding rate constants k_{et} of photoinduced electron transfer from $[Ru(bpy)_3]^{2+*}$ to the ketones at 298 K. The numbers refer to the ketones in Table 1.

Based on the above results, the reaction mechanism of the acid-catalyzed reduction of ketones by $AcrH_2$ may be given as Scheme 1, where acid-catalyzed



Scheme 1.

electron transfer from $AcrH_2$ to ketones occurs to give a radical pair ($AcrH_2^{+\bullet}$ $-\underset{|}{\dot{C}}OH$) which disappears by hydrogen transfer from $AcrH_2^{+\bullet}$ to the alcohol radical to yield $AcrH^+$ and the corresponding alcohol. Since the acid-catalyzed electron transfer is still highly endothermic based on the one-electron oxidation potential of $AcrH_2$ (0.80 V vs. SCE)[3] and the one-electron reduction potentials of ketones in the presence of $HClO_4$ ($\cong$ -1 V vs. SCE),[10] the reaction would never occur without a follow-up exothermic reaction, i.e., hydrogen transfer from $AcrH_2^{+\bullet}$ to the alcohol radical, following the endothermic acid-catalyzed electron-transfer equilibrium (K_{et}). In such a case, both the electron transfer and hydrogen transfer processes may constitute the activation barrier of the over-all reaction. This may be the reason why the k_{obsd} values are well related to the corresponding k_{et} values (Fig. 1) and why the kinetic isotope effect in Table 1, ascribed to those of hydrogen transfer from $AcrH_2^{+\bullet}$ to the alcohol radical, is observed. Although it may be very difficult, unless impossible, to detect the radical pair in Scheme 1, an alternative reaction pathway, i.e., direct transfer of an hydride ion from $AcrH_2$ to the protonated ketone may be unlikely to occur, since no protonation of ketones used in this study has been observed and no protonated ketone is involved in the acid-catalyzed electron-transfer reactions as described above.

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