Acid-catalysed Multi-electron Reduction of Nitrobenzene Derivatives by a Dihydronicotinamide Adenine Dinucleotide (NADH) Model Compound, 9,10-Dihydro-10-methylacridine

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Acid-catalysed multi-electron reduction of nitrobenzene derivatives by a dihydronicotinamide adenine dinucleotide (NADH) model compound proceeds efficiently under mild conditions in the presence of perchloric acid in acetonitrile.

The redox reactions of 1,4-dihydropyridine derivatives have attracted considerable interest in terms of the vital role of dihydronicotinamide adenine dinucleotide (NADH) as electron sources in enzymatic redox reactions which include both two- and multi-electron reductions of substrates by NADH.[1,2] An earlier report of a multi-electron reduction involves a typical NADH model compound, 1-benzyl-1,4-dihydronicotinamide, which reduces nitrobenzene to aniline, phenylhydroxylamine, and hydrazobenzene.[3] However, severe reaction conditions (heating at 412 K in neat nitrobenzene) were required to bring about this reduction.[3] As such, no efficient catalytic systems involving multi-electron reduction of organic substrates by NADH model compounds have so far been reported, although we have recently reported a catalytic system for the four-electron reduction of dioxygen by an NADH model compound.[4]

We report herein what we believe to be the first example of efficient multi-electron reduction of nitrobenzene derivatives by an NADH model compound in the presence of $HClO_4$ in acetonitrile. An acid-stable NADH model compound, 9,10-dihydro-10-methylacridine ($AcrH_2$),[5] is used as a reductant for the acid-catalysed reactions, since NADH and ordinary NADH model compounds are known to decompose in the presence of acid.[6]

The $AcrH_2$ shows no reactivity towards nitrobenzene or nitrosobenzene in MeCN at 313 K. When $HClO_4$ was added to the $AcrH_2$–nitrobenzene system, however, nitrobenzene was readily reduced by $AcrH_2$ to yield the four-electron reduction product, phenylhydroxylamine, as shown in Table 1 (Scheme 1). Nitrosobenzene is known to be a much better oxidant than nitrobenzene,[7] and thus, phenylhydroxylamine has been reported to be formed readily by the two-electron reduction of nitrosobenzene by NADH model compounds.[8] In our system, the two-electron reduction of nitrosobenzene in the presence of $HClO_4$ in MeCN is completed upon mixing the reactants (Table 1). The second-order rate constant at 298 K was determined as 2.3×10^3 dm^3 mol^{-1} s^{-1} from the increase in the absorbance due to $AcrH^+$ ($\lambda_{max.}$ 358 nm) using a

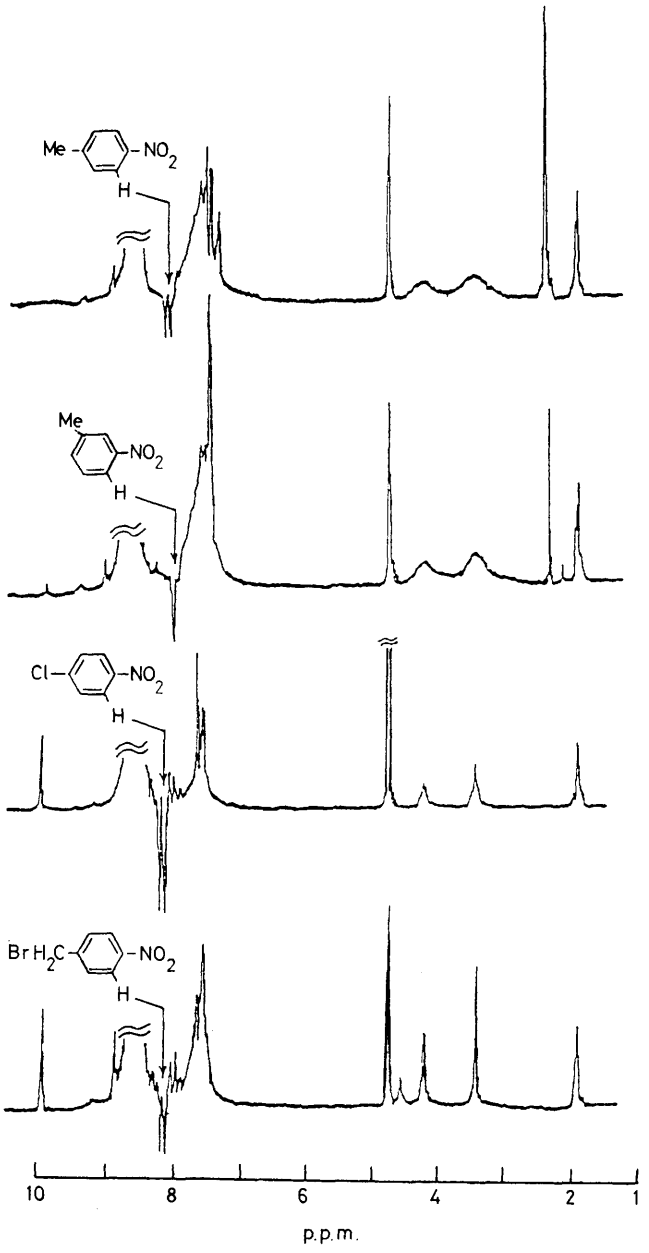


Figure 1. CIDNP spectra observed in the acid-catalysed reduction of nitrobenzene derivatives (4.0×10^{-2} mol dm^{-3}) by $AcrH_2$ (0.15 mol dm^{-3}) in the presence of 2.0 mol dm^{-3} $HClO_4$ (70%) in CD_3CN at 338 K.

stopped-flow technique. Thus, the rate-determining step of the four-electron reduction of nitrobenzene may be the two-electron reduction of nitrobenzene to nitrosobenzene.

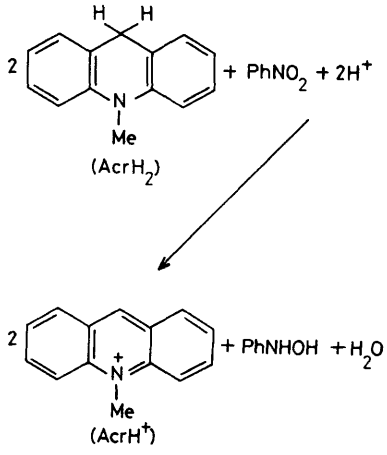
When *p*-nitrotoluene is used as a substrate, the acid-catalysed reduction by $AcrH_2$ yields the six-electron reduction product, *i.e.*, *p*-methylaniline (Table 1). The reduction of *p*-ethylnitrobenzene and *p*-nitrobenzyl bromide also gives the corresponding six-electron reduction products, *p*-ethylaniline and *p*-aminobenzyl bromide, respectively (Table 1).

When ^{1}H n.m.r. spectra were measured at 338 K upon mixing a CD_3CN solution of $AcrH_2$ containing 2.0 mol dm^{-3} $HClO_4$ with various nitrobenzene derivatives, the emission signals due to the *ortho* protons of nitrobenzene derivatives are observed in the first scan (250 s) as shown in Figure 1. The reaction rates at 338 K were fast and each reaction was

Table 1. Acid-catalysed reductions of nitrosobenzene and nitrobenzene derivatives by $AcrH_2$ in the presence of $HClO_4$ in acetonitrile.

Substrate /mol dm^{-3}	$AcrH_2$ /mol dm^{-3}	Temp. /K	Time /min	Product yield/%[a]
$PhNO_2$[b] (0.05)	0.10	313	36	PhNHOH (90)[c]
PhNO[d] (0.10)	0.15	298	—[e]	PhNHOH (100)
p-$MeC_6H_4NO_2$[b] (0.04)	0.20	338	15	*p*-$MeC_6H_4NH_2$ (82)
p-$EtC_6H_4NO_2$[b] (0.04)	0.10	333	50	*p*-$EtC_6H_4NH_2$ (60)[f]
p-$NO_2C_6H_4CH_2Br$[b] (0.04)	0.20	338	7	*p*-$NH_2C_6H_4CH_2Br$(50)

[a] The products were analysed by ^{1}H n.m.r. spectroscopy in CD_3CN. [b] In the presence of 2.0 mol dm^{-3} $HClO_4$. [c] The PhNHOH decomposed slowly in a prolonged reaction time, but no azoxybenzene or hydrazobenzene was formed under the present experimental conditions. [d] In the presence of 0.30 mol dm^{-3} $HClO_4$. [e] The reaction was completed upon mixing the reactants. [f] Another product was *p*-$NH_2C_6H_4CH(OH)Me$ (40%) which corresponds to a rearranged product of *p*-EtC_6H_4NHOH.



Scheme 1

completed in several scans. As the temperature was lowered, the rates were slowed down, and the emission intensities decreased. On the other hand, the absorption signals due to $AcrH_2$ [δ 3.44 (s, 3H), 4.20 (s, 2H), 7.5 (m, 8H)] show significant broadening when the emission signals of nitrobenzene derivatives are observed (Figure 1). In addition, the reaction was strongly inhibited by the presence of oxygen. Such strong oxygen inhibition is recognized as the most unique characteristic of nitroreductase.[9] The inhibition effect of oxygen, the observation of CIDNP spectra and the signal broadening in Figure 1 strongly suggest that the acid-catalysed reduction of nitrobenzene derivatives by $AcrH_2$ proceeds by free radical chain reactions.

$$AcrH_2 + X\text{-}C_6H_4NO_2H^{\bullet} \rightarrow AcrH^{\bullet} + X\text{-}C_6H_4NO + H_2O \quad (1)$$

$$AcrH^{\bullet} + X\text{-}C_6H_4NO_2 + H^+ \rightarrow AcrH^+ + X\text{-}C_6H_4NO_2H^{\bullet} \quad (2)$$

The chain propagation step may include the hydrogen abstraction from $AcrH_2$ [equation (1)], since large primary kinetic isotope effects were observed (k_H/k_D 6.0 and 6.8 for *p*-$MeC_6H_4NO_2$ and $PhNO_2$, respectively) when $AcrH_2$ was replaced by the 9,9′-dideuteriated analogue ($AcrD_2$). The $AcrH^{\bullet}$ radical, which is known as a strong reductant,[10,11] may be readily oxidized by X-$C_6H_4NO_2$ in the presence of $HClO_4$

to yield $AcrH^+$, accompanied by regeneration of $X\text{-}C_6H_4NO_2H^\bullet$ [equation (2)]. A chain carrier radical $AcrH^\bullet$ is known to be readily trapped by oxygen to yield $AcrH^+$ in the presence of $HClO_4$ in MeCN.[10] This may be the reason why oxygen can inhibit the reaction strongly. The exchange reaction between $AcrH^\bullet$ and $AcrH_2$ may cause the signal broadening of the ^1H n.m.r. spectra as observed in Figure 1. The two-electron reduction product, $X\text{-}C_6H_4NO$, may be reduced readily to $X\text{-}C_6H_4NHOH$ by $AcrH_2$, as examined independently in the case of PhNO (Table 1). Whether $X\text{-}C_6H_4NHOH$ can be reduced further by $AcrH_2$ or not depends on the substituent X (Table 1).

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