Acid Catalysed Reduction of Aromatic Aldehydes by an NADH Model Compound

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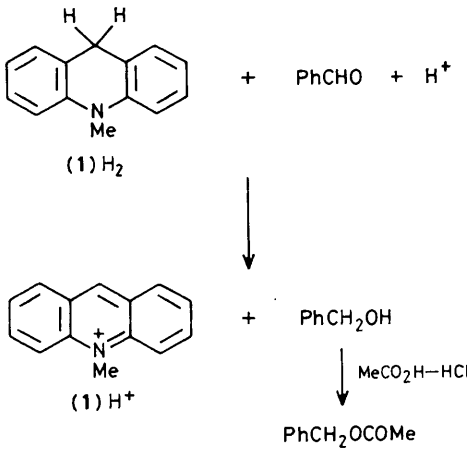
The electronic substituent effects on the rates of acid catalysed reduction of aromatic aldehydes by an acid-stable NADH model compound (*N*-methylacridan) are shown to be very small, compatible with those observed for liver alcohol dehydrogenase catalysed reduction of aromatic aldehydes by NADH.

The electronic substituent effects on the rates of liver alcohol dehydrogenase (LADH) catalysed reduction of substituted benzaldehydes by NADH are known to be very small,[1,2] implying the importance of the electrophilic catalysis in the transfer of hydride to the positively charged carbonyl carbon of the enzyme-bound zinc complex.[3] However, no appropriate model system has hitherto been reported to study the kinetics of the acid catalysed reduction of aromatic aldehydes under mild conditions, since most NADH model compounds are known to decompose in the presence of acids, and an NADH model compound alone or in the presence of Zn^{2+} or Mg^{2+} ions can reduce only activated carbonyl compounds



which are much stronger oxidants than benzaldehyde.[4,5] Although a few acid-stable NADH model compounds have recently been used for the sluggish reduction of benzaldehyde under severe conditions,[6] such systems are unsuitable for kinetic study.

In this communication, we report the successful reduction of a series of aromatic aldehydes by a simple acid-stable NADH model compound, *N*-methylacridan (**1**)H_2, in the presence of perchloric acid ($HClO_4$) in a mixture of acetonitrile and acetic acid ($MeCN$–$MeCO_2H$, 4 : 1 v/v), which enables us to compare the electronic substituent effects in a model system with those in the LADH catalysed reduction for the first time.

The acid-stable NADH model compound (**1**)H_2 reacts readily with benzaldehyde in the presence of $HClO_4$ in $MeCN$–$MeCO_2H$ (4 : 1 v/v) under deaerated conditions at 323 K to afford *N*-methylacridinium ions, (**1**)H^+, and benzyl acetate ($PhCH_2OCOMe$); the latter is formed by the reaction of benzyl alcohol with acetic acid in the presence of $HClO_4$ [equation (1)].[7] The products were identified from both the electronic and ^1H n.m.r. spectra. No reduction of benzaldehyde by (**1**)H_2 has been observed in the absence of $HClO_4$ or $MeCO_2H$.

$$(\mathbf{1})H_2 + H^+ \overset{K}{\rightleftharpoons} (\mathbf{1})H_3^+ \quad (2)$$

$$(\mathbf{1})H_2 + PhCHO + H^+ \xrightarrow{k[H^+]} (\mathbf{1})H^+ + PhCH_2OH \quad (3)$$

$$k_{obs.} = k[HClO_4]/(1 + K[HC\ O_4]) \quad (4)$$

The kinetics of the acid catalysed reduction of a series of *p*-substituted benzaldehydes and β-naphthaldehyde were studied by observing the increase in absorbance due to (**1**)H^+ ($\lambda_{max.}$ 358 nm, ε 2.00×10^4 $dm^3\ mol^{-1}\ cm^{-1}$) at 323 K. All samples were degassed and sealed in a high vacuum prior to the reaction. For each aromatic aldehyde, the rate law was found to be first-order with respect to (**1**)H_2 as well as aromatic aldehyde. The second-order rate constant $k_{obs.}$ increases on increasing the $HClO_4$ concentration in $MeCN$–$MeCO_2H$ (4 : 1 v/v) and reaches a constant value $k_{max.}$ when $[HClO_4] \geqslant 5.0 \times 10^{-2}$ mol dm^{-3} as shown in Figure 1(a). Such saturation behaviour of $k_{obs.}$ as a function of $[HClO_4]$ may be explained by assuming the reactions shown in equations (2) and (3) where (**1**)H_2 forms a complex with H^+ [equation (2)] and only free (**1**)H_2 is active for the acid catalysed reduction of benzaldehyde [equation (3)]. According to equations (2) and (3), $k_{obs.}$ is expressed as a function of $[HClO_4]$ by equation (4), which agrees with the observed

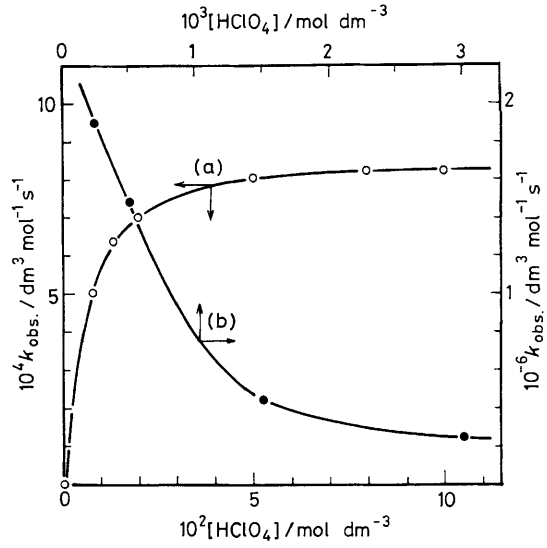


Figure 1. Dependence of the rate constants $k_{obs.}$ on the $HClO_4$ concentration for (a) the acid catalysed reduction of PhCHO (0.10—1.0 mol dm^{-3}) by (**1**)H_2 (1.0×10^{-3}—1.0×10^{-2} mol dm^{-3}) in $MeCN$–$MeCO_2H$ (4 : 1 v/v) at 323 K and (b) the reduction of ddbq (1.5×10^{-4} mol dm^{-3}) by (**1**)H_2 (1.5×10^{-5} mol dm^{-3}) in MeCN at 298 K.

Table 1. Rate constants $k_{max.}$ for the acid catalysed reduction of aromatic aldehydes by *N*-methylacridan in the presence of $HClO_4$ (5.0×10^{-2} mol dm^{-3}) in $MeCN$–$MeCO_2H$ (4 : 1 v/v) and k_h for the LADH catalysed reduction by NADH.

Aromatic aldehyde	$10^3 k_{max.}$ / $dm^3\ mol^{-1}\ s^{-1}$	$10^{-2} k_h$ / s^{-1} [a]
p-Nitrobenzaldehyde	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.

dependence of $k_{obs.}$ on $[HClO_4]$, Figure 1(a). In fact, the complex formation between (**1**)H_2 and $HClO_4$ with a 1 : 1 stoicheiometry was confirmed by the changes in the ^1H and ^{13}C n.m.r. spectra as well as the electronic spectra of (**1**)H_2 in the presence of various concentrations of $HClO_4$. The formation constant *K* was determined as 1.1×10^4 $dm^3\ mol^{-1}$ in MeCN and it decreased on the addition of H_2O or $MeCO_2H$. Inactivity of the complex (**1**)H_3^+ for the reduction of a substrate is well demonstrated for the reduction of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (ddbq) which is reported to have little interaction with $HClO_4$,[8] as shown in Figure 1(b), where the rate constant $k_{obs.}$ decreases as the free (**1**)H_2 concentration decreases on increasing the $HClO_4$ concentration in MeCN [equation (2)]. Thus, the rates of the acid catalysed reduction of benzaldehyde are limited by the formation of an inactive protonated complex (**1**)H_3^+ and then, the saturated rate constant $k_{max.}$ corresponds to k/K from equation (4).

The $k_{max.}$ values for a series of aromatic aldehydes are listed in Table 1, which shows a very small electronic substituent effect; for example, the $k_{max.}$ value for *p*-nitrobenzaldehyde is similar to that for *p*-methoxybenzaldehyde. Although the absolute $k_{max.}$ values cannot be compared directly with the k_h

values for the hydride-transfer step from NADH to the carbonyl of enzyme-bound complex[1] without the knowledge of the concentration of the protonated carbonyl compound in the acid catalysed reduction [equation (3)], the very small electronic substituent effect in our model system is shown to be compatible with that observed in the LADH catalysed reduction of the corresponding aldehydes, which is also shown in Table 1 for comparison. The effect of substituents is presumably minimal because although protonation of the carbonyl oxygen is favoured by electron-donating substituents these substituents retard subsequent hydride transfer from (**1**)H_2 to the protonated carbonyl compounds.

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References

1 J. W. Jacobs, J. T. McFarland, I. Wainer, D. Jeanmaier, C. Ham, K. Hamm, M. Wnuk, and M. Lam, *Biochemistry*, 1974, **13**, 60.
2 D. K. Srivastava and S. A. Bernhard, *Biochemistry*, 1984, **23**, 4538; R. T. Dworschack and B. V. Plapp, *ibid.*, 1977, **16**, 2716.
3 N. N. Becker and J. D. Roberts, *Biochemistry*, 1984, **23**, 3336; E. Cedergren-Zeppezauer, J.-P. Samama, and H. Eklund, *ibid.*, 1982, **21**, 4895; C. T. Angelis, M. F. Dunn, D. C. Muchmore, and R. M. Wing, *ibid.*, 1977, **16**, 2922; J. T. McFarland and Y.-H. Chu, *ibid.*, 1975, **14**, 1140; K. M. Welsh, D. J. Creighton, and J. P. Klinman, *ibid.*, 1980, **19**, 2005; H. Eklund, B. V. Plapp, J.-P. Samama, and C.-I. Brändén, *J. Biol. Chem.*, 1982, **257**, 14349.
4 U. Eisner and J. Kuthan, *Chem. Rev.*, 1972, **72**, 1; D. M. Stout and A. I. Meyer, *ibid.*, 1982, **82**, 223.
5 S. Fukuzumi, N. Nishizawa, and T. Tanaka, *J. Org. Chem.*, 1984, **49**, 3571; *J. Chem. Soc., Perkin Trans. 2*, 1985, 371.
6 S. Shinkai, H. Hamada, and O. Manabe, *Tetrahedron Lett.*, 1979, 1397; A. Ohno, Y. Ishikawa, S. Ushida, and S. Oka, *ibid.*, 1982, **23**, 3185; F. Yoneda, Y. Sakuma, and Y. Nitta, *Chem. Lett.*, 1978, 1177.
7 A. P. Hagen, T. S. Miller, R. L. Bynum, and V. P. Kapila, *J. Org. Chem.*, 1982, **47**, 1345.
8 S. Fukuzumi, K. Ishikawa, and T. Tanaka, *Nippon Kagaku Kaishi*, 1985, 62.