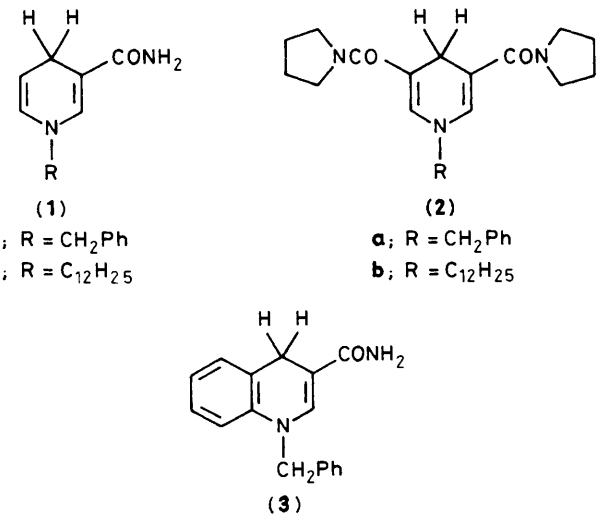
Zinc Ion and Micelle Catalysed Reduction of Pyridine-2-carbaldehyde by 1-Dodecyl-3,5-bis(pyrrolidin-1-ylcarbonyl)-1,4-dihydropyridine as a NADH Analogue in Aqueous Media

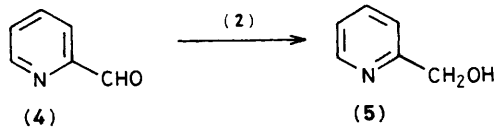
Hiroshi Awano and Waichiro Tagaki*

Department of Applied Chemistry, Faculty of Engineering, Osaka City University, Sugimoto 3, Sumiyoshi-ku, Osaka, Japan

1-Dodecyl-3,5-bis(pyrrolidin-1-ylcarbonyl)-1,4-dihydropyridine was found to be active in the reduction of pyridine-2-carbaldehyde in aqueous media when catalysed by zinc ion and anionic SDS ($C_{12}H_{25}OSO_3Na$) micelle.

Metal ion catalysed reduction of carbonyl compounds by 1,4-dihydropyridine has attracted much attention[1] in connection with the role of zinc ion at the active site of alcohol dehydrogenase.[2] However, it is generally difficult in aqueous media to reduce a carbonyl substrate by a conventional analogue of NADH coenzyme like (**1**), since it undergoes readily acid catalysed hydration[3] or adduct formation with carbonyl substrates.[4] Both hydration and adduct formation occur on the enamine 5,6-double bond of the dihydropyridine ring. The other enamine 2,3-double bond is inert because of its conjugation with the carbamoyl group. Therefore it would be expected that such reactions on the 5,6-double bond would also be inhibited by attaching another carbamoyl group at the 5-position. In fact, we found recently that 1-benzyl-3,5-bis(pyrrolidin-1-ylcarbonyl)-1,4-dihydropyridine (**2a**) was resistant to acid decomposition and was quite reactive in the acid catalysed reduction of nitrosobenzene in dry acetonitrile.[5] We now report that in neutral aqueous media (**2**) is able to reduce pyridine-2-carbaldehyde (**4**) to 2-pyridylmethanol (**5**) when catalysed by zinc ion and anionic SDS ($C_{12}H_{25}$-





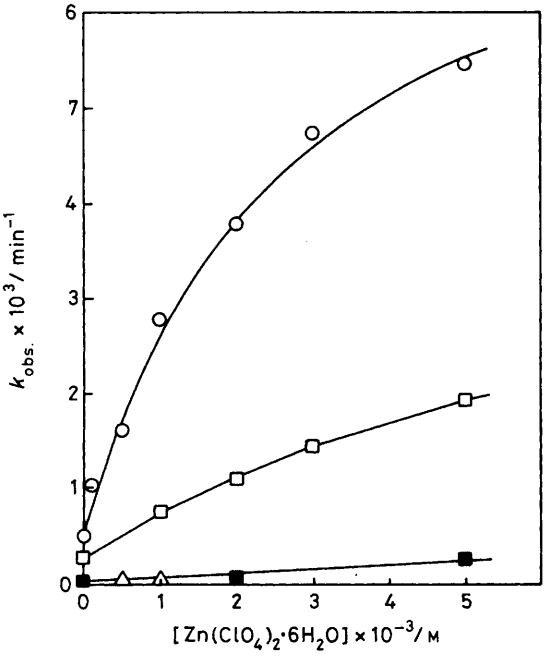


Figure 1. Plots of the pseudo-first-order rate constants *vs.* zinc ion concentration, 50 °C, pH 7.30 (0.05 M *N*-ethylmorpholine–*N*-ethylmorpholine–HCl buffer, μ = 0.05 M (NaCl), [(**2**)] 1 × 10^{-4} M, [(**4**)] = 1 × 10^{-2} M, [SDS] = [CTAB] = 1 × 10^{-2} M, ○; (**2b**) (SDS), □; (**2a**) (SDS), ■; (**2a**) (no SDS), △; (**2b**) (CTAB). Solid lines for ○ and □ are calculated ones (see text).

OSO_3Na) micelle. Under the same conditions, (**1**) led only to adduct formation.[4a]† Similar zinc ion catalysed reduction of (**4**) to (**5**) in aqueous media has already been reported to occur by using 1-benzyl-3-carbamoyl-1,4-dihydroquinoline (**3**) as the reductant.[6] However, the reaction system was not a micellar one and other features such as the zinc ion dependency or photosensitivity of rates seem to be quite different from those reported here.

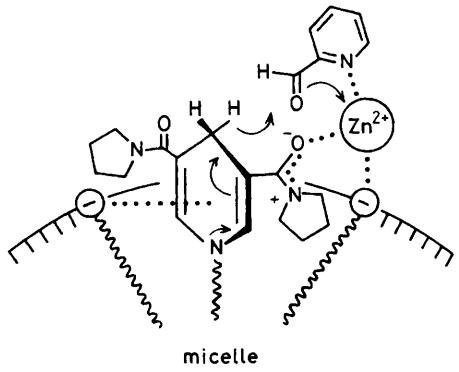


Figure 2. Schematic illustration of complexation at the transition state of hydride transfer.

The reduction was carried out at 50 °C in aqueous *N*-ethylmorpholine buffer (pH 7.30) under nitrogen. Product analysis was performed for freeze-dried reaction mixtures [(**2**) = (**4**) = Zn^{II} = SDS = 1 × 10^{-2} M] by extraction with acetone and by chromatographic analyses of the acetone extract. T.l.c., h.p.l.c., and spectroscopic (i.r. and n.m.r.) analyses indicated that (**4**) was quantitatively reduced to (**5**). The rates of reduction were measured spectrophotometrically by observing the decrease of the dihydropyridine absorption of (**2**) at 370 nm. The rates were sensitive to air oxidation, but not photosensitive unlike the case of (**3**).[6] The rates increased with increasing zinc ion concentration to give saturation curves as shown in Figure 1. With a constant zinc ion concentration, the rates were first-order with respect to the concentration of (**2**) and of (**4**) separately. Figure 1 shows that the rates for (**2a**) in the presence of SDS (1 × 10^{-2} M)‡ are much larger than in its absence. This rate enhancing micellar effect[7] becomes much larger for the more lipophilic (**2b**), although the non-micellar rates for (**2b**) could not be measured owing to low solubility of (**2b**) in the buffer without SDS. In sharp contrast, the reaction of (**2b**) was almost completely inhibited in the cationic CTAB ($C_{16}H_{33}NMe_3^+Br^-$) micelle. It is interesting that both (**2b**) and (**2a**) in the SDS micelle show some activity even in the absence of zinc ion. These activities were not merely due to the spontaneous decomposition of (**2**), but also due to the reduction, because the rates were much slower in the absence of (**4**), and (**5**) could be detected in the products. The saturation curves in Figure 1 can be analysed by assuming the reaction scheme in equation (1) involving pre-equilibrium formation of the ternary complex of (**2**)·(**4**)·Zn^{2+}.§ Equation (1) leads to equation (2) which allows Lineweaver–Burk plots

$$(2) + (4) + Zn^{2+} \overset{K}{\rightleftharpoons} \text{complex} \xrightarrow{k_c} \text{products} \quad (1)$$

$$k_{obs.} = k_0 + \frac{k_c[(4)][Zn^{2+}]}{K + [(4)][Zn^{2+}]} \quad (2)$$

† (**1**) can also reduce (**4**) to (**5**) in dry acetonitrile, see refs. 1b and 4a.

‡ The critical micelle concentration values of the SDS micelle were little affected by varing zinc ion concentration in this buffer system at 50 °C; 1.26 × 10^{-3} M ([Zn^{2+}] = 0), and 1.51 × 10^{-3} M ([Zn^{2+}] = 5 × 10^{-3} M), measured by the surface tension method using a Shimazu ST-1 apparatus.

§ Kinetically similar results can be obtained by assuming a binary complex of (**2**)·Zn^{2+} or (**4**)·Zn^{2+} ion. It is not feasible at present to determine which is more important among these binary and ternary complexes.

of $1/(k_{obs.}-k_0)$ *vs.* $1/[Zn^{2+}]$ to be constructed giving K and k_c values for (**2a**) of 8.4×10^{-5} M^2 and 4.55×10^{-3} min^{-1}, respectively, and for (**2b**) of 2.58×10^{-5} M^2 and 7.69×10^{-3} min^{-1}. Although not shown in equation (1), it is conceivable that the catalytic activity of the anionic micelle is due to the binding of zinc ion to the micellar phase as well as to the stabilization of the pyridinium cation developed at the transition state of hydride transfer through the electrostatic field effect as represented schematically in Figure 2.

Although primitive, the above system appears to be the first example of an artificial alcohol dehydrogenase having all the components of catalysis, *i.e.* zinc ion, coenzyme, and apoenzyme (SDS micelle).

Received, 25th March 1985; Com. 400

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