

## Biomimetic Zinc Catalysis: an Unusually Rapid and Specific Carbonyl Reduction Using a Co-enzyme Model of NADH

By ROGER A. HOOD and REG. H. PRINCE

(University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW)

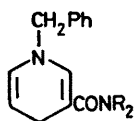
**Summary** An unusually fast, specific, zinc-catalysed reduction of pyridine-2-carbaldehyde by an alcohol dehydrogenase co-enzyme model *N'**N'*-diethyl-*N*-benzyl-1,4-dihydronicotinamide is described.

THE NADH co-enzyme model, *N*-benzyl-1,4-dihydronicotinamide (Ia), has been used previously<sup>1-4</sup> to reduce various pyridinecarbaldehyde substrates in the presence of a zinc compound as a catalyst. We now describe some unusual features in the zinc-catalysed reduction of the same substrates in acetonitrile by the substituted model *N'**N'*-diethyl-*N*-benzyl-1,4-dihydronicotinamide (Ib). Attention is drawn to the unusually high speed of the reaction, the kinetic differences between (Ia) and (Ib), and the unusually high specificity of (Ib) towards one of the isomeric forms of the substrate. Of the three pyridinecarbaldehyde substrates only pyridine-2-carbaldehyde (II) was reduced. The rate of reduction of (II) with (Ib) was *ca.* 200 times greater than that with (Ia) under the same conditions and the stopped-flow method was required to study the kinetics of the reaction.<sup>5</sup>

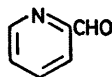
Like other dihydropyridines (Ib) has a characteristic u.v. absorbance near 340 nm which is lost upon oxidation and may be used for following reaction rates. Anhydrous zinc bromide was used to catalyse the reduction of (II) by (Ib); in the absence of a zinc compound the reaction is extremely slow.

There is a kinetic difference between the zinc bromide catalysis of reductions by (Ia) and (Ib); in the zinc bromide concentration range studied, 0–30 mM, the reduction is half order in ZnBr<sub>2</sub> for (Ia)<sup>1</sup> whereas it is of first order for (Ib). The reaction of (II) with (Ib) was carried out under pseudo first-order conditions with various excess of concentrations of (II) and the reaction was found to be first-order with respect to (Ib) and first-order with respect to (II) with a rate constant of  $7.2 \pm 0.2 \times 10^2 \text{ l mol}^{-1} \text{ s}^{-1}$  for 30 mM ZnBr<sub>2</sub>. Evidence for a radical mechanism was sought as previously described<sup>6</sup> using the spin trapping technique and, as with (Ia), no participating radicals were observed.

No reaction occurred with the 3- and 4-substituted aldehydes, even after 3 h, as shown by the unchanging n.m.r. spectra of the mixtures. Reduction of these substrates is presumably prevented because in a reactive ternary complex<sup>1,2,4b</sup> [(Ib)-Zn<sup>II</sup>-aldehyde] the distance between the transferring hydrogen and the carbonyl oxygen of the aldehyde when the zinc species bonds *via* the substrate nitrogen atom<sup>7</sup> and the nicotinamide oxygen atom<sup>2</sup> is too large for transfer to occur within the complex. Models show that with (II) the transferring hydrogen in a complex having the ligands bound in this way is ideally placed for reduction to occur.



(I)  
a; R = H  
b; R = Et



(II)

The very fast rate of reduction of (II) by (Ib) compared with (Ia) may be due to a faster rate of hydrogen transfer from the donor or a higher concentration of the reactive ternary complex,<sup>2</sup> or both. This question is difficult to answer owing to the difficulty of determining the concentration of the ternary complex. However, an analysis<sup>7,8</sup> of the proton shifts of (Ia) and (Ib) with increasing metal halide concentration in terms of the equilibrium constants  $K_1$  and  $K_2$  for the binding of one and two molecules of (Ia) and (Ib),

respectively, to zinc show that for (Ia),  $K_1 = ca. 1$  and  $K_2 = ca. 1.7$  whereas for (Ib)  $K_1 = ca. 0.07$  and  $K_2 = ca. 0.7$ . Therefore, if the ternary complex (Ia,b)-M-(II) behaves similarly to (Ia,b)<sub>2</sub>-M then considerably less ternary complex is formed with (Ib) and a greater rate of hydrogen transfer must be invoked to account for the difference in reactivity between (Ia) and (Ib).

(Received, 16th November 1978; Com. 1230.)

<sup>1</sup> M. Hughes and R. H. Prince, *Chem. and Ind.*, 1975, 648; *Bio-org. Chem.*, 1977, 6, 137.

<sup>2</sup> M. Hughes and R. H. Prince, *J. Inorg. Nuclear Chem., Bioinorg. Section*, 1978, 703, 713, 719.

<sup>3</sup> R. A. Gase, G. Boxhoorn, and U. K. Pandit, *Tetrahedron Letters*, 1976, 2889; M. Shirai, T. Chisina, and M. Tanaka, *Bull. Chem. Soc. Japan*, 1975, 48, 1079.

<sup>4</sup> (a) W. Tagaki, H. Sakai, Y. Yano, K. Ozeki, and Y. Shimizu, *Tetrahedron Letters*, 1976, 2541; (b) K. Watanabe, R. Kawaguchi, and H. Kato, *Chem. Letters*, 1978, 255.

<sup>5</sup> R. A. Hood, Ph.D. Thesis, Cambridge University, 1978.

<sup>6</sup> R. A. Hood, R. H. Prince, and K. A. Rubinson, *J.C.S. Chem. Comm.*, 1978, 300.

<sup>7</sup> P. Wyeth, Ph.D. Thesis, University of Cambridge, 1977.

<sup>8</sup> J. Reuben, *Progr. N.M.R. Spectroscopy*, 1974, 9, 1.