Reaction of *N*-Propyl-1,4-dihydronicotinamide with Ferricyanide Ion

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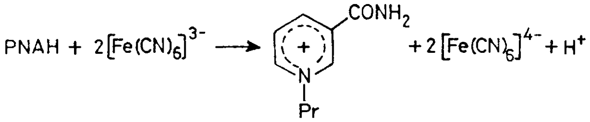
Summary The reaction of *N*-propyl-1,4-dihydronicotinamide (PNAH) with ferricyanide ion follows a second-order rate law with rate = $k[\mathrm{Fe(CN)_6}^{3-}]$ [PNAH], $\Delta H^{\ddagger}$ 2 kcal mol^{-1}, $\Delta S^{\ddagger}$ −43 cal mol^{-1} K^{-1} and an observed kinetic deuterium isotope effect, k_H/k_D, of 1·68.

N-Alkylnicotinamide and its reduced form are well accepted as model compounds for the nicotinamide nucleotides and several workers have investigated their chemical behaviour.[1–3] It is not certain whether the reduction of carbonyl compounds with dihydronicotinamide involves hydride transfer or an electron transfer followed by hydrogen (H or $H^+ + e$) transfer, although the possibility of the latter has been referred to frequently. We report that the reduction of ferricyanide ion by *N*-propyl-1,4-dihydronicotinamide (PNAH) proceeds through a rate-determining electron transfer and that this may be extended to reduction of other substrates.

The kinetic measurements were performed spectrophotometrically in 20% aqueous methanol under nitrogen, monitoring the absorbance change at 356 nm. Initial concentrations were: 2×10^{-4}—8×10^{-4} M $\mathrm{Fe(CN)_6}^{3-}$, $2{\cdot}5 \times 10^{-5}$ M PNAH, and 1×10^{-2} M $\mathrm{CO_3}^{2-}$. Since the rate was dependent on the concentration of potassium ions, it was kept constant at $2{\cdot}15 \times 10^{-2}$ M by using KCl solution. The reaction was not affected by the change in ionic strength. The results of these kinetic measurements are in accordance with the simple second order rate law, rate = $k[\mathrm{Fe(CN)_{63}}^{-}]$ [PNAH], and kinetic parameters obtained between 20 and 45 °C are $\Delta H^{\ddagger}$ = 2 kcal mol^{-1} and $\Delta S^{\ddagger}$ = − 43 cal mol^{-1} K^{-1}. Spectrophotometric titration showed that 2 mol of the ferricyanide ion reacted with 1 mol of PNAH. The corresponding pyridinium salt was obtained quantitatively in a preparative-scale experiment. The stoicheiometry of the reaction is shown in equation (1).



(1)

It is known that the ferricyanide ion is inert towards ligand substitution by associative pathway, and substitution *via* dissociative pathway can be ruled out since in the present reaction the rate is independent of the addition of the cyanide ion. Also, the enthalpy of activation is too small to be attributed to a bond cleavage. Therefore it appears that the reaction proceeds *via* a rate-determining electron-transfer mechanism.

The kinetic isotope effect, k_H/k_D, measured at 25 °C using *N*-propyl-4,4-dideuterio-1,4-dihydronicotinamide ([$^2H_2$]PNAH, 88% purity) was found to be 1·68 after correction for isotopic purity. The observed value for the isotope effect is large enough to predict the weakening of the C(4)–H σ-bond at the transition state and could be interpreted as follows. Transfer of an electron from PNAH to the ferricyanide ion makes the 1,4-dihydropyridine ring more positive in the transition state than in the ground state, and the electron-donating hyperconjugative participation of the C(4)–H σ-bond to the π-system in 1,4-dihydropyridine ring becomes significant in the electron-deficient transition state, which weakens the C(4)–H σ-bond. Thus, formally, an electron flows from the C(4)–H σ-bond to the ferricyanide ion through π-bonds in PNAH and it is a proton (or a hydrogen atom), not a hydride ion, which is released from PNAH during its oxidation. It has been shown that the C(4)–H σ-bond contribution to the excited state of 1,4-dihydronicotinamide is important.[4]

It is noteworthy that the value for the isotope effect in the reduction of the ferricyanide ion is almost the same as that reported for the reduction of 1,10-phenanthroline-2-carbaldehyde with PNAH–[$^2H_2$]PNAH in the presence of zinc ions ($k_H/k_D = 1{\cdot}72$).[2,5] The present result supports unequivocally the idea that the proposed intermediate in the reduction of 1,10-phenanthroline-2-carbaldehyde is a charge-transfer complex. Depending on the ability of a substrate to accept an electron, the process of transfer of a proton from PNAH to the substrate becomes more or less involved in the transition state. For example, a large kinetic isotope effect ($k_H/k_D = 3{\cdot}96$) together with parameters of activation ($\Delta^{\ddagger} = 5$ kcal mol^{-1}, $\Delta S^{\ddagger} = -46$ cal mol^{-1} K^{-1}) for the reduction of hexachloroacetone[3] may be interpreted in terms of substrate-assisted elimination of a proton from the 1,4-dihydropyridine ring. A large discrepancy in kinetic and product isotope effects[2,5] also indicates that electron transfer is followed by proton transfer.

The present result, therefore, suggests that the kinetic isotope effect of *ca.* 1·7 is the smallest limiting value for the reduction of an organic molecule with an NAD(P)H-model compound.

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