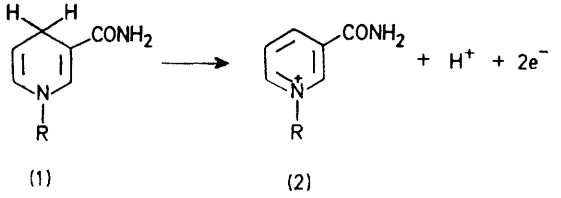
Reaction of *N*-Benzyl-1,4-dihydronicotinamide with Geminal Bromo-nitro Compounds

By RONALD J. KILL and DAVID A. WIDDOWSON*
(*Chemistry Department, Imperial College, London* SW7 2AY)

Summary Geminal bromo-nitro compounds are reduced by *N*-benzyl-1,4-dihydronicotinamide (**1**; R = $PhCH_2$) to the corresponding nitroalkanes by an initial electron transfer process.

REDUCTIONS *in vivo* which involve NAD(P)H as co-factor and *in vitro* with 1,4-dihydronicotinamide models can be formally expressed as in Scheme 1. The *in vivo* evidence and most of the model systems have been interpreted in

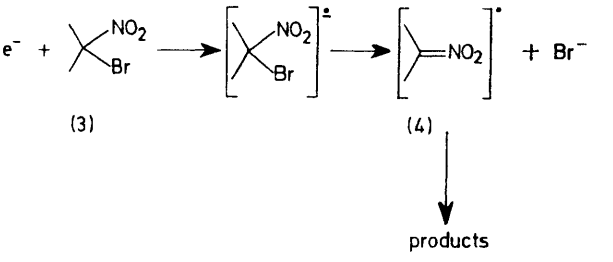


(1) (2)

SCHEME 1

terms of hydride ion transfer from the dihydronicotinamide (**1**) to the substrates.[1] Much of the evidence however, does not rule out an initial electron transfer.[2] This is a process which has received little attention in model systems and yet the ready occurrence of such a process could have profound implications on the interpretation of NADH dependent reactions. This would particularly apply to the interaction with biological substrates with known one-electron redox properties such as the flavins.[3] Initially, however, it is necessary to establish that the oxidation of dihydronicotinamides (and the reverse reduction) can occur by this means. Whilst one-electron redox reactions have been suggested for dihydronicotinamides[4] definitive evidence is lacking. We now present data which demonstrate the existence of such reactivity.

As substrates, geminal bromo-nitro alkanes were chosen because of their proven ability as electron acceptors,[5] and because, in a formal sense the electron is ejected in a bromide ion and is thus separated from the subsequent fate of the hydrogen atom (Scheme 2). In addition, these quaternary compounds are not subject to attack by weak nucleophiles and direct hydride attack at carbon is prohibited.



(3) (4)

SCHEME 2

The dihydronicotinamide (**1**; R = $PhCH_2$) reacted with 2-bromo-2-nitropropane (**3**) in acetonitrile or chloroform solution at room temperature, under a nitrogen atmosphere, to give *N*-benzylnicotinamidium bromide and 2-nitropropane as the sole isolable products, apart from traces of acetone. In the presence of oxygen, acetone was the major product from the C-3 unit.

In order to facilitate handling, and to examine the stereochemical consequence of this reaction, 2-*exo*-bromo-2-*endo*-nitrobornane (**5**)[6] was treated with (**1**; R = $PhCH_2$) in acetonitrile under the above conditions. After 24 h the yield of 2-nitrobornane was 97% (by g.l.c.) and the isolated yield of *N*-benzylnicotinamidium bromide (**2**, Br^-) was 95%. A trace of camphor was also produced. In the presence of oxygen the yield of camphor increased to 80%. When the reaction mixture was irradiated with light from a 500 W tungsten lamp, the reaction was complete in 3 h. In total

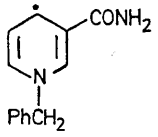
darkness the reaction proceeds slowly. The dihydronicotinamide (**1**; R = $PhCH_2$) alone is subject to photochemical decomposition,[7] and to photochemical redox reactions.[8] The electron transfer to and the breakdown of the bromonitro-compounds is also subject to photochemical acceleration.[9] In the present case, a distinction between the possible photochemical involvements awaits further experiment, but both redox processes are considered to involve a single electron transfer.

Kinetic experiments, carried out in purified, degassed acetonitrile solution at 25 °C showed the reaction to follow bimolecular kinetics (second order rate constant $3{\cdot}172 \times 10^{-3}$ l mol^{-1} s^{-1}), and to be first order in each reactant. The addition of *p*-dinitrobenzene, a known electron transfer inhibitor,[10] suppressed the reduction of the bromonitroalkane. The addition of benzoyl peroxide as a radical initiator caused a slight increase in the rate of disappearance of (**1**; R = $PhCH_2$). In the absence of initiator, no induction period was evident. The [4,4-$^2H_2$]-dihydronicotinamide (**1**, R = $PhCH_2$) under strictly aprotic conditions afforded [2-^{2}H]-2-nitrobornane.

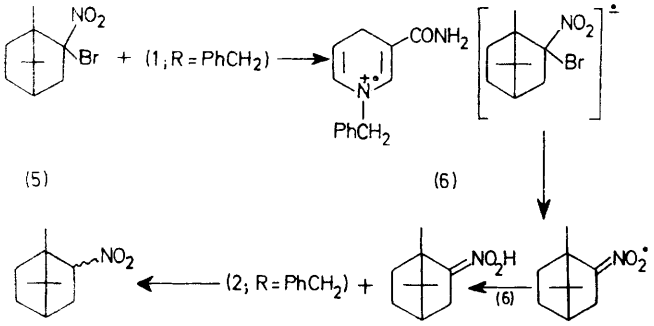
In the presence of deuterium oxide, the 4-protiodihydronicotinamide again gave [2-^{2}H]-2-nitrobornane. Under the reaction conditions 2-nitrobornane did not undergo hydrogen exchange with deuterium oxide. The hydrogen at C-4 of (**1**; R = $PhCH_2$) must, therefore, be abstracted by oxygen of the nitronate radical. Isomerisation of the *aci*-nitro product to the nitroalkane leads to the incorporation of hydrogen from protic solvent when present. The reduction of (+)-2-*exo*-bromo-2-*endo*-nitrobornane gave a product, $[\alpha]_D$ + 4·0°, identical in all respects with the base-equilibrated mixture (95% *endo*, 5% *exo*) of 2-nitrobornane isomers.[11]

An e.s.r. study of the reaction run in degassed acetonitrile at 0·5 M concentration showed the presence of a radical at *ca.* 10^{-7} M concentration. The signal was a 1:1:1 triplet, a_N 15 G, which intensified on irradiation of the solution with visible light. This is consistent with the nitronate radical (**4**),[12] and with the above observations of the effect of light on the overall reaction.

These results can be accommodated by a mechanistic pathway which requires the rate determining transfer of an electron from (**1**; R = $PhCH_2$) to the acceptor molecule. The subsequent fate of the ion radical pair (**6**) produced would then be a simple collapse to products (Scheme 3). An electron transfer chain process[5] is ruled out by the results of the kinetics experiments. The interception of a nitroalkane radical by oxygen is known to lead to ketonic products.[13] The lack of an induction period, and of products arising from oxygen interception of the 4-pyridyl radical (**7**) also suggest that a simple radical chain process



(7)



SCHEME 3

involving hydrogen abstraction from (**1**, R = $PhCH_2$) is not involved. This is confirmed by the ineffectiveness of radical initiation and the observation that oxygen does not quench the reaction.

It is evident from the foregoing that 1,4-dihydronicotinamide (**1**; R = $PhCH_2$) is capable of acting as an electron donor under mild conditions.

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[1] F. H. Westheimer, *Adv. Enzymol.*, 1962, **24**, 472; H. Sund in 'Biological Oxidations,' ed T. P. Singer, Interscience, New York, 1968, p. 603; J. W. Jacob, J. T. McFarland, I. Wainer, D. Jeanmaier, C. Ham, K. Ham, H. Wnuk, and M. Lam, *Biochemistry*, 1974, **13**, 60; R. H. Abeles, R. F. Hutton, and F. H. Westheimer, *J. Amer. Chem. Soc.*, 1957, **79**, 712; H. Sund, H. Diekmann, and K. Wallenfels, *Adv. Enzymol.*, 1964, **26**, 144; J. P. Klinman, *J. Biol. Chem.*, 1972, **247**, 7977.

[2] Y. Ohnishi, T. Numakunai, and A. Ohno, *Tetrahedron Letters*, 1975, 3813; J. L. Kurz, R. Hutton, and F. H. Westheimer, *J. Amer. Chem. Soc.*, 1961, **83**, 584.

[3] For a general account see 'The Enzymes,' ed. P. D. Boyer, Vol. XII, 3rd edn., 1975, Academic Press, New York.

[4] K. Wallenfels, W. Ertel, A. Hockendorf, J. Reiser, and K. H. Uberschor, *Naturwiss.*, 1975, **62**, 459.

[5] G. A. Russell and W. Danen, *J. Amer. Chem. Soc.*, 1966, **88**, 5663.

[6] M. O. Forster, *J. Chem. Soc.*, 1899, 1141; *ibid.*, 1900, 251; D. Brueckner, R. A. Hamon, J. M. Robertson, and G. A. Sim, *ibid.*, 1962, 799; *Proc. Chem. Soc.*, 1961, 306; Y. Brunel, H. Lemaire and A. Rassat, *Bull. Soc. chim. France*, 1964, 1895.

[7] U. Eisner, J. R. Williams, B. W. Matthews, and H. Ziffer, *Tetrahedron*, 1970, **26**, 899 and references cited therein.

[8] J. D. Sammes and D. A. Widdowson, *J.C.S. Chem. Comm.*, 1972, 1023.

[9] G. A. Russell and W. C. Danen, *J. Amer. Chem. Soc.*, 1968, **90**, 347.

[10] R. C. Kerber, G. W. Urry, and N. Kornblum, *J. Amer. Chem. Soc.*, 1964, **86**, 3904; 1965, **87**, 4520; N. Kornblum, R. E. Michel, and R. C. Kerber, *ibid.*, 1966, **88**, 5560, 5562.

[11] H. Toivonen, *Suomen Kem.*, 1971, **44**, 54.

[12] *Cf.* L. H. Piette, P. Ludwig, and R. N. Adams, *J. Amer. Chem. Soc.*, 1962, **84**, 4212.

[13] G. A. Russell, *J. Amer. Chem. Soc.*, 1954, **76**, 1595.