Spin Trapping Experiments on NADH Analogues and the Role of Radicals in Carbonyl Reductions†

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Summary ^{1}H N.m.r. and gas chromatographic analysis of the reactants and products show that the reaction of *N*-benzyl-1,4-dihydronicotinamide (NBDN), an analogue of NADH, with pyridine-2-carbaldehyde does not pass through a radical intermediate during either a thermal or a photolytic reaction; photolysis led to the removal of NBDN but *not* to the production of the reduced substrate and radicals detected with e.s.r. spectroscopy were shown to be artifacts.

DURING reductions of thiobenzophenone,[1] α-diketones,[2] and *gem*-bromonitro-compounds[3] by the analogue of NADH, *N*-benzyl-1,4-dihydronicotinamide (NBDN) (I, $R^3 = PhCH_2$), radicals have been detected. Evidence from deuterium isotope effects on the rates and product yields, isotope effects on the reduction of the zinc complex of 1,10-phenanthroline-2-carbaldehyde and trifluoroacetone,[4] and flow spectrophotometry data from the reduction of the *N*-methylacridinium ion[5] show that at least one intermediate lies between the reactants and final products.

The NADH-enzyme reaction is generally accepted to proceed through a formal hydride transfer. However, both charge-transfer complexes[5] and free-radical intermediates[1] have been proposed for the NBDN model reaction. It thus seems worthwhile to investigate the model reaction further. We show that a free-radical intermediate for the NBDN model reaction with the pyridine-2-carbaldehyde substrate is highly unlikely.

The free-radical path was suggested since visible light irradiation accelerates the disappearance of NBDN, and free radicals were detected by e.s.r. spectroscopy. To examine the effect of light, the kinetics of the reaction were studied, the loss of NBDN being followed by means of the change in absorbance at 340nm in acetonitrile. An accelerated drop in absorbance occurs in the presence and absence of zinc ions when the substrate and NBDN solution is irradiated. However, 100 MHz ^{1}H n.m.r. spectroscopy shows that the illumination alone caused no change in the quantity of substrate (II), nor was any alcohol formed. The same result was found by using gas chromatography (2 m × 2 mm Porasil Q column at 230 °C; H_2, N_2, and air, all at 2 kg cm^{-2}). In addition, the n.m.r. spectrum of NBDN changed very slightly; the interpretation of this slight change is unclear.

In calculating the rates from the kinetic results we allowed for the photochemical loss of NBDN. In contrast with previous findings on other systems,[6] the photochemical reaction rates and products remained the same as the thermally activated reaction conducted in the dark. The above evidence argues strongly that the photochemical reaction and thermal reaction of NBDN are in fact competitive for NBDN.

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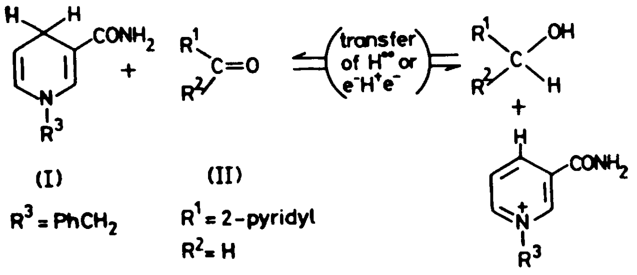
† No reprints available.



Scheme

A further test for radicals used the spin trapping[7] agent 2-methyl-2-nitrosopropane. At ambient temperature in the presence of zinc, the reaction shown in the Scheme proceeds to completion in *ca.* 1 h.[8] In the presence of spin trap, no radical signal was detected at any time during this reaction when carried out in the dark. In the presence of light (60 W incandescent lamp), an e.s.r. 1:1:1 triplet signal, $\bar{g}$ 2·005, $\bar{A}_N$ 16·0 G, peak-to-peak width 1·0 G, was seen. An identical signal under the same conditions is obtained with pyridine-2-methanol, pyridine, 2,6-lutidine, triethylamine, triphenylphosphine, and NADH. From this we conclude that even though radicals are detected under these conditions they do not lie on the reaction pathway leading to a reduction of the substrate. A common product found on irradiation of systems including this spin trap is the di-t-butyl nitroxide radical.[7] However the signals we observed were different from those of the authentic di-t-butyl nitroxide radical ($\bar{g}$ 2·005, $\bar{A}_N$ 15·6 G, peak-to-peak width 3·0 G).

We have also observed that when Et_3N is present the α-diketone benzil gives an e.s.r. singlet signal in the absence of the spin trap on illumination only. The presence of the dihydronicotinamide molecule is therefore not necessary for the observation of a radical in this system.

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