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MECHANISM OF THE REDUCTION OF THIOBENZOPHENONE BY N-BENZYL-1,4-DIHYDRONICOTINAMIDE. A MODEL REACTION FOR BIOLOGICAL NAD(P)H-REDUCTION

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A charge-transfer intermediate has been detected, by ESR spectroscopy, for the reaction of thiobenzophenone with N-benzyl-1,4-dihydronicotinamide, a model of biological redox processes.

N-Benzyl-1,4-dihydronicotinamide (I) and related compounds have been recognized as models of NADH and NADPH, important coenzymes for biological redox processes. The mechanism of enzymatic and model reactions with N-substituted 1,4-dihydronicotinamides is believed to involve "direct hydride-transfer", although none of evidence so far obtained can discard initial formation of charge-transfer complex.[1-3)]

Very recently, Steffens and Chipman demonstrated, based on kinetic deuterium isotope effects, that the "hydride-transfer" is a two-step process and proposed that the intermediate may be a charge-transfer complex.[4)] We also would like to report our results concerning to the property of the intermediate and to the mechanism of a model reaction with I and thiobenzophenone (II). It is known that the reaction affords benzhydryl mercaptan quantitatively.[1)]

When a 1.25 : 1 mixture of I and II in 2-methyltetrahydrofuran (MTHF) was subjected to ESR spectroscopy at 77°K, signals shown by solid lines in Figure 1 were recorded. An intense signal centered at 3130 gauss has the g-value of 2.005 with line-width of 14.0 gauss and is identical to that of thiobenzophenone anion radical produced from potassium or sodium ketyl of II in MTHF at 77°K.[5)] When the mixture was warmed to room temperature (~300°K), a new signal with line-width of 17.6 gauss appeared at $g = 2.025$, as the intensity of the signal

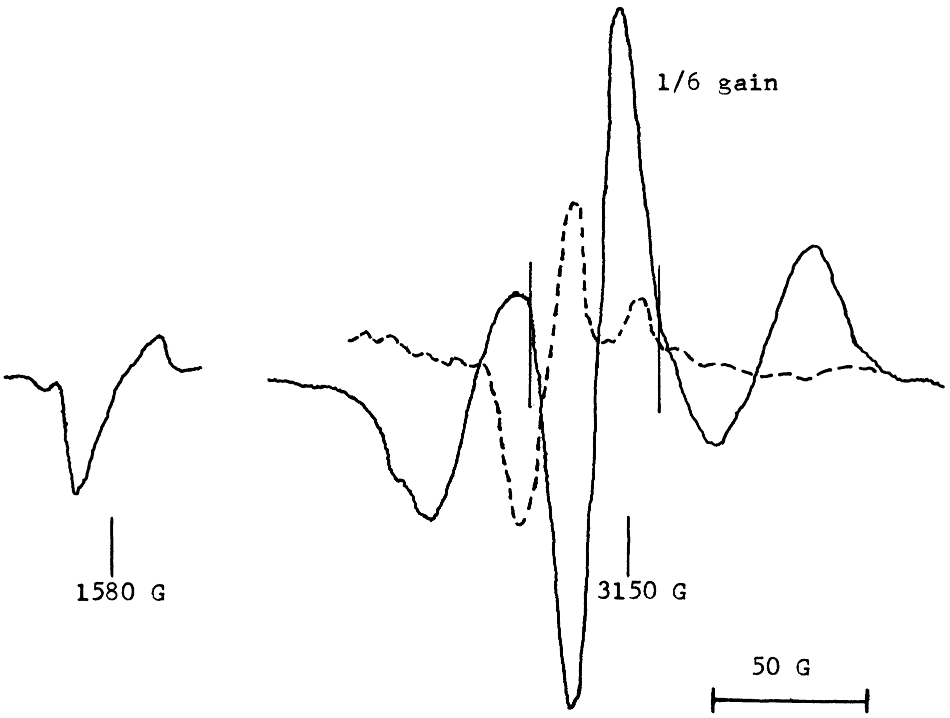


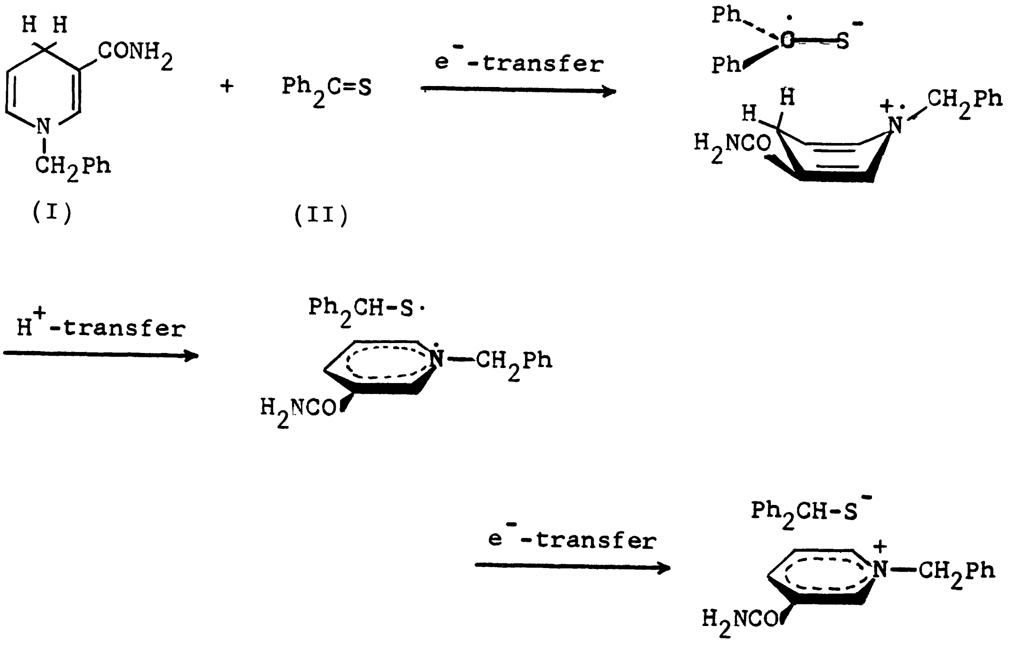
Figure 1. ESR spectra of a mixture of N-benzyl-1,4-dihydronicotinamide and thiobenzophenone in 2-methyltetrahydrofuran at 77°K (———) and room temperature (-----).

at g = 2.005 decreased remarkably (dashed line in Figure 1). The origin of the new singal is not yet confirmed. However, its g-value is large enough to suggest the formation of a thiyl radical.

In the spectrum at 77°K, there exist a pair of weak signals that appear symmetrically with respect to the magnetic field strength of 3150 gauss with separation of about 128 gauss. These signals are ascribable to the $\Delta m = \pm 1$ transition of a triplet radical pair. The corresponding half-field signal due to $\Delta m = \pm 2$ transition is also observable at 1580 gauss. Thus, the spectrum can be interpreted on the basis of a randomly oriented set of triplets, in which a part of the anion radical of II is paired with the counter cation radical. The average distance between interacting ion radicals are calculated to be about

6Å according to a point-spin-density approximation.6,7)

The above results indicate that the reaction proceeds through a charge-transfer intermediate. The next and rate-determining step may be the "proton-transfer" as following, although the transfer of hydrogen atom cannot be discarded at present.



Effects of solvents, isotopes, substituents, and radical scavengers so far reported1-4) are consistent with the above mechanism. Although whether or not the enzymatic reaction actually follows the above pathway is open to question, we believe that the "electron-transfer" mechanism is energetically more plausible than the "direct hydride-transfer" process8) and a function of enzymes is, as previouly postulated, to polarize the substrate to form a charge-transfer complex with NAD(P)H.9,10)

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6. Although another couple of signals corresponding to 2D separation was too weak to be detected, it is safe to estimate $E \approx 0$ for randomly oriented radical pairs.

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