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REACTION OF N-BENZYL-1,4-DIHYDRONICOTINAMIDE WITH PYRIDINE-2-CARBOXALDEHYDE. FORMATION OF A NEW ADDUCT

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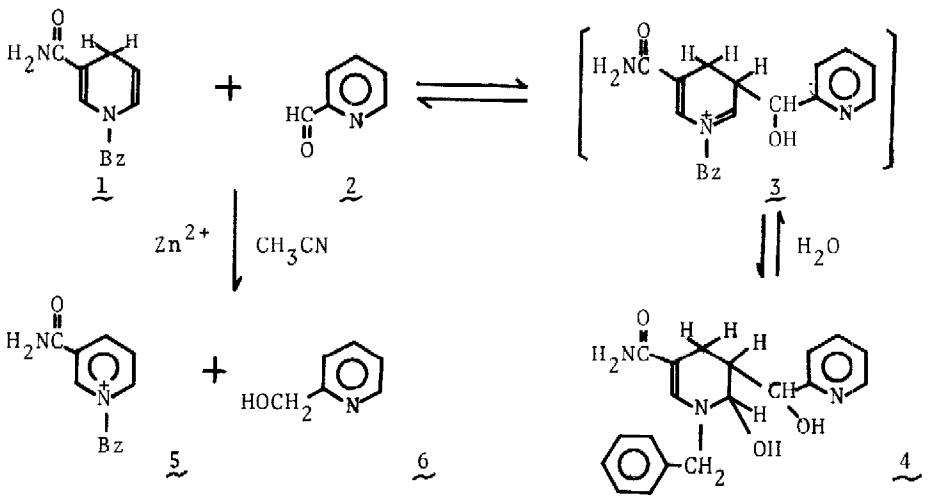
Many model oxidation-reduction reactions of nicotinamide coenzymes and the related enzymic processes are usually considered to involve direct hydrogen transfer between the coenzyme and substrate (e.g. hydride transfer mechanism).[1] However, there has been raised a question whether the hydride transfer occurs by intermolecular concerted or two-step process of initial electron transfer followed by proton transfer. The latter two-step process was suggested by Steffens and Chipman to occur through a non-covalent charge-transfer complex formed in the reaction of 1-substituted 1,4-dihydronicotinamide with trifluoroacetophenone.[2] Electron-transfer was also detected by Ohno and Kito in a reaction of thiobenzophenone.[3] Meanwhile, Dunn proposed an intramolecular hydride transfer to occur through the formation of a covalent complex between aldehyde and dihydronicotinamide.[4] However, this proposal was later ruled out by Pandit and co-workers based on the evidences obtained in the reduction of unsaturated acid chloride with 4,4-dideuterio Hantzsch ester.[5]

We wish to report herein the isolation of a new adduct (4) in the reaction of 1-benzyl-1,4-dihydronicotinamide (1) with pyridine-2-carboxaldehyde (2) in aqueous solution (scheme 1). Whereas, the reduction product of 2-hydroxymethyl pyridine (6) was isolated when the reaction was carried out in anhydrous acetonitrile containing Zn^{2+} ion. These findings seem to shed further lights on the above hydride transfer mechanism.

The compound 1 is fairly stable in an aqueous solution of N-ethylmorpholine buffer (pH 7-8, under N_2) with a characteristic absorption at 350 nm. The addition of 2 initiates the decrease of 350 nm absorption with the concomitant increase of 290 nm absorption to give an isosbestic point at 315 nm. The rates of these spectral changes are first order with respect to each concentration of 1 and 2. The rate is faster at a lower pH and also in the presence of Zn^{2+} ion. These observations suggest an addition reaction of 1 and 2, although the spectral change is very similar to that observed in an acid-catalyzed addition of water to 1.[6] For product analysis, 1 (0.214g, 1 mmole) and 2 (0.107g, 1 mmole) in 10 ml of aqueous buffer solution (N-ethylmorpholine, pH 7) was reacted for 25 hr (under N_2, room temp), and the mixture was extracted with chloroform to give 4: Colorless needles (from CH_2Cl_2), 0.22g (65% yield), mp.158-159°c; λmax, 290 nm



Scheme 1

(ε=20,200, in H_2O), 285 nm (ε=14,300, in CH_3CN): C, H, N% found (66.95, 6.11, 12.23), calcd. for $C_{19}H_{21}N_3O_3$ (67.25, 6.19, 12.38). The figure shows the nmr spectrum of the product which is consistent with the structure of 4: δ ppm, $2H^4$ (1.5-1.9, m), H^5 (1.93, d), NCH_2 (4.40, q), aldehyde CH (4.56, q) and OH (5.23, d), H^6 (4.90, d) and ring OH (5.90, d), amide-NH_2 (6.22, s), H^2 (7.14, s), and phenyl and pyridyl aromatic protons (7.3-8.5, m). In a D_2O solution, signals for the two OH and amide-NH_2 protons disappear with the corresponding change of multiplicity of H^6 and aldehyde-CH protons. Decoupling by irradiating two OH and aldehyde CH protons also support the above signal assignments.

The formation of 4 seems to be explained only by assuming the hydration of intermediate adduct 3 which is essentially the same intermediate as proposed by Dunn[4] for aldehyde reduction. Although this Dunn's proposal was ruled out by Pandit and co-workers[5], it should be pointed out that the latter workers used unsaturated acid chlorides as the substrates for the reduction, instead of aldehyde. Thus it is still of interest to know whether 3 undergoes an intramolecular oxidation-reduction to give 5 and 6. We have examined the question by the following approaches. When 4 (10^{-4} M) and ZnX_2 (10^{-3} M) were mixed in anhydrous CH_3CN (25°c), the absorption of 4 at 285 nm decreased with the apparent rate constants of kobs=1.12 x $10^{-1}min^{-1}$(X=Cl) and 2.5 x $10^{-1}min^{-1}$($X=ClO_4$). Concomitantly, the absorption of 1 at 350 nm appeared and increased up to a maximum which corresponds to ~55% dissociation of 4 to 1 and 2, and then this 350 nm absorption decreased slowly to give a final spectra of 1:1 mixture of 5 and 6 (near 260 nm). In consistent with these spectral changes, 2 was detected by glc

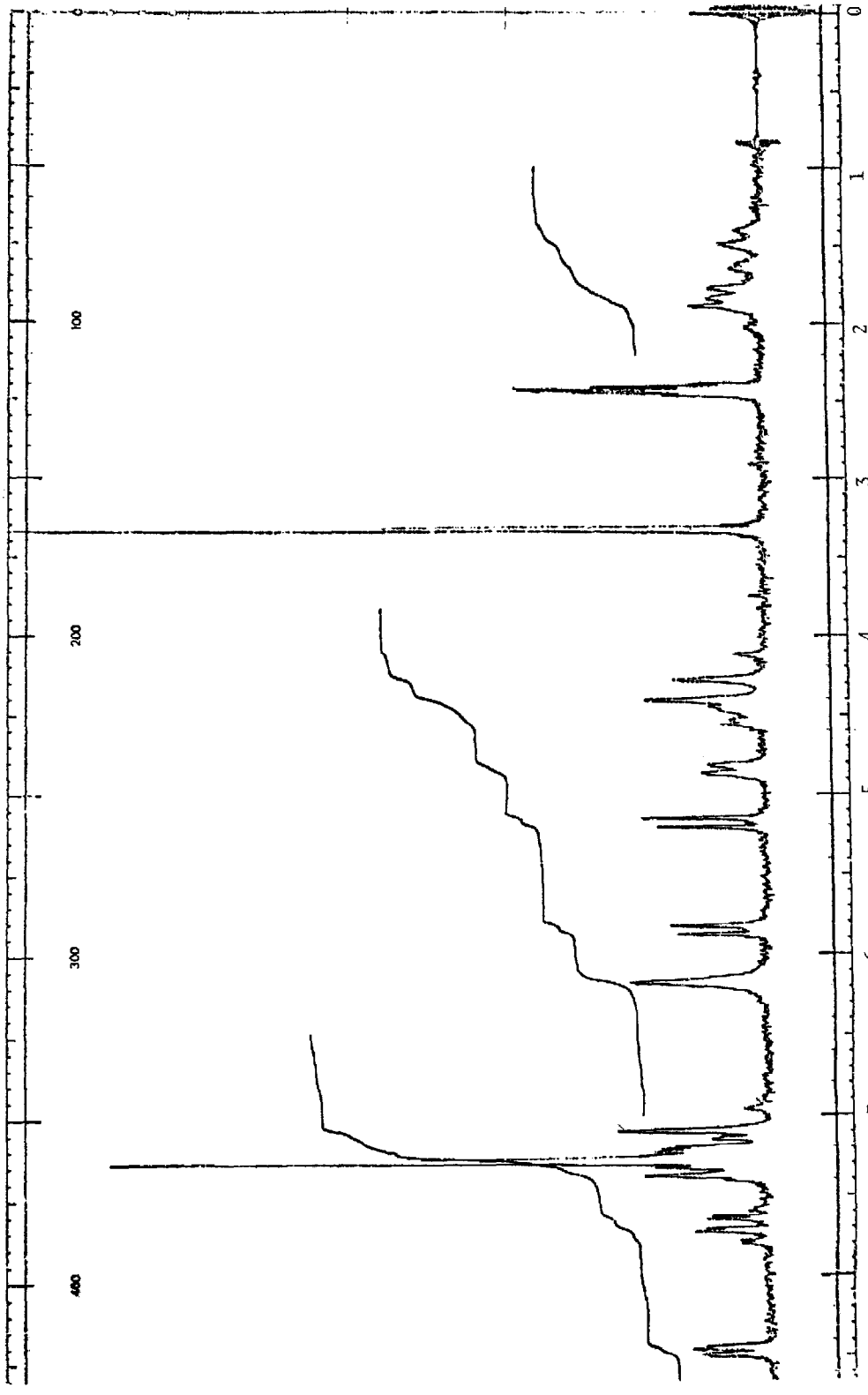


Figure. NMR spectrum of the adduct 4. Varian Model HA-100Mc. In DMSO-d_6 at 30°c (internal TMS).

after quenching the reaction mixture with an EDTA solution (at a maximum of 350 nm absorption), and also 6 was detected by tlc, glc and as the picrate from the final reaction mixture[7] in which 2 was no more found. Furthermore, the dissociation of 4 was found to be very sensitive to a trace of water in the solvent. Thus, (a) the appearence of 350 nm absorption was no more observed in a CH_3CN solution containing 0.1% of water. Instead, (b) a time dependent shift of 285 nm absorption of 4 toward 260 nm was recorded with an isosbestic point at 275 nm. Finally, (c) such a spectral shift was completely reversed toward 4 when the solution of (b) was diluted 2-fold with water.

The above observations strongly suggest that an intramolecular hydride transfer mechanism via a covalent complex like 3 is very unlikely in support of the view of Pandit and co-workers. The present results may also suggest an importance of water or microenvironmental solvent effects at the active site of alcohol dehydrogenase.[8]

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