

REDUCTION OF NAD(P)^+ -MODEL COMPOUND BY AMINES

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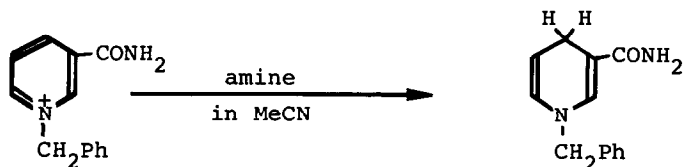
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In numerous enzyme-catalyzed reactions that depend on NAD(P)^+ and NAD(P)H , the oxidations and reductions of nitrogen-containing compounds, such as amino acids and tetrahydrofolic acids, are of biological importance.¹ Among many biomimetic reactions,² the reduction of iminium salts with 1,4-dihydro-3,5-diethoxycarbonyl-2,6-lutidine was claimed to be a model for enzymatic reductions of imines.³ In contrast, the reverse reaction, the reduction of NAD(P)^+ -model with amines, was attempted unsuccessfully.⁴ The author wishes to report that 1-benzyl-3-carbamoylpyridinium salt, a model of NAD(P)^+ , is indeed reduced by amines. The reaction may be useful to simulate enzymatic reduction of NAD(P)^+ .

The addition of 10 ml of diethylamine to 3.0 g of 1-benzyl-3-carbamoylpyridinium perchlorate in 60 ml of dry acetonitrile flushed with argon gas at room temperature in a dark produced immediately a lemon-yellow solution. After 40 hr, from the clear reddish solution the solvent and excess amine were removed under a reduced pressure to leave viscous residue, from which 20 mg of a 20:1 mixture of 1-benzyl-3-carbamoyl-1,4-dihydropyridine and its 1,6-isomer were extracted with ether. The structure of the products were confirmed by their nmr spectra.⁵

To understand the details of the reaction, the time dependence of the yields of the dihydropyridines from the reaction with $\text{N,N}'$ -diethylethylenedi-



amine were followed quantitatively with high pressure liquid chromatography (HPLC) technique. The result is illustrated in Fig.1. It is interesting to note that the yield of the 1,4-dihydropyridine derivative is as high as 18 % when the reaction is carried out in acetonitrile, whereas the yield is only 5 % when the solvent is replaced by water. The rate of the formation of the dihydro compounds depended on the concentration of the amine.

Furthermore, it was recognized that the present reduction of the NAD(P)^+ -model to the corresponding 1,4-dihydropyridine proceeds with quite high regioselectivity, which is comparable to the reduction in enzymatic systems. Although the final reaction mixture contained the 1,4- and 1,6-dihydro isomers in the equilibrium composition (91/9)⁶, this is due to the isomerization of initially formed 1,4-dihydro compound to its 1,6-isomer, which is catalyzed by

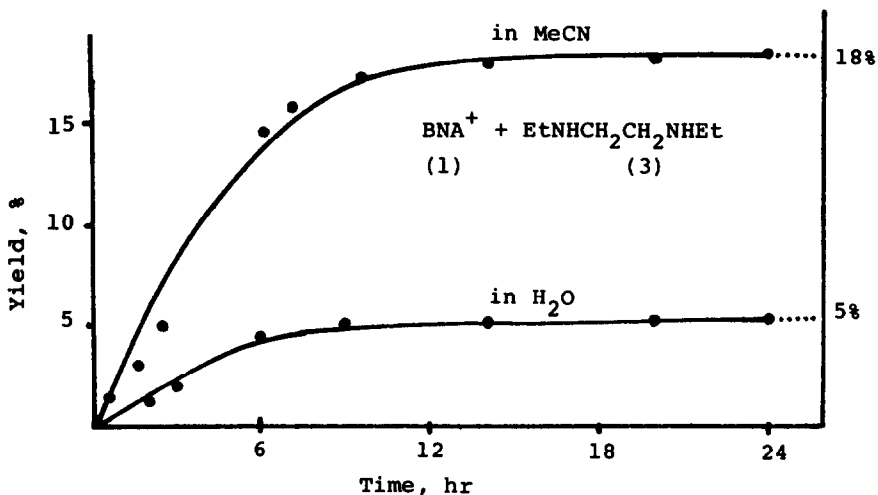


Fig. 1. Time-dependence of the yield of 1-benzyl-3-carbamoyl-1,4-dihydropyridine in the reaction of N,N' -diethylethylenediamine (1.0 mmol) with the corresponding pyridinium perchlorate or chloride (0.3 mmol) at room temperature under an atmosphere of argon in a dark.

the oxidized form of the model compound. The ratio, $>97/3$, at the initial stage is larger than it.

In the investigations with a variety of amines, it was found that aliphatic amines such as NH_3 , $i\text{-Pr}_2\text{NH}$, Et_3N , $\text{NH}_2\text{CH}_2\text{CH}_2\text{OH}$, $\text{NH}(\text{CH}_2\text{CH}_2\text{OH})_2$, and $\text{N}(\text{CH}_2\text{CH}_2\text{OH})_3$ gave the 1,4-dihydro compound in 7-15% yield, which is comparable to that with diethylamine. Amines containing aromatic groups, such as dibenzylamine, benzhydrylamine, and 1-aminofluorene, were less effective than aliphatic amines. $\text{N,N}'$ -Dicyanomethylamine gave neither colored solution with the NAD(P)^{\pm} model nor any dihydro compound. The basicity or ionization potential of an amine seems to play an important role for the reduction.

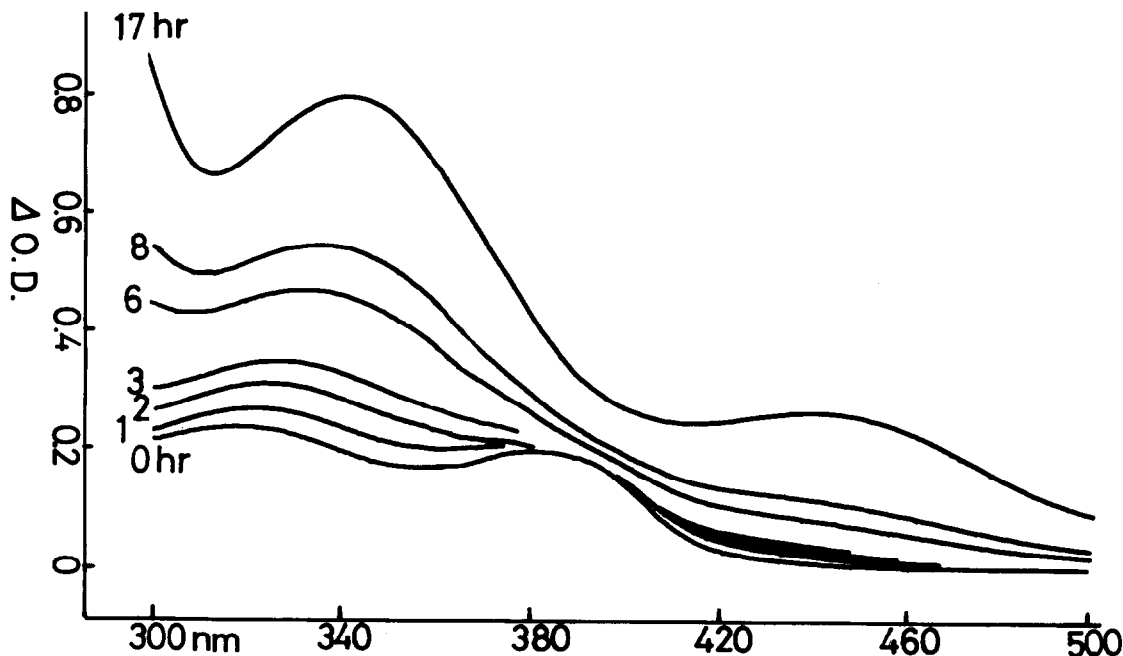


Fig. 2. Time-dependent differential absorption spectra for the reaction of 1-benzyl-3-carbamoylpyridinium perchlorate (4.9×10^{-3} M) and $\text{N,N}'$ -diethylethylenediamine (5.4×10^{-3} M) in acetonitrile.

Reactions of the model compound with amines are very complex. Fig. 2 shows the differential absorption spectra of the reaction mixture at appropriate time intervals. The spectrum after 17 hr has two absorption maxima at 350 and 450 nm: the former can be assigned to that from the 1,4- and 1,6-dihydropyridines by comparing the spectra of the authentic samples. The origin of the latter is

not assigned yet. Detailed analyses of products with HPLC confirmed the formations of products that have respective absorption maxima at 350, 359, 369, and 379 nm in addition to the previously described products.

From the spectrum shown in Fig. 2, it is recognizable that there appear two transient absorptions at 385 and 320 nm immediately after the mixing of two components. Though there is no evidence for the absorption at 385 nm, the maximum at 320 nm may be assigned to that for a charge transfer complex. The differential absorption maximum at the same wave length was also observed when triethylamine was used as an amine.

It is well known that amines are generally good electron donors, which is supported by the formation of charge-transfer complexes with electron deficient compounds, and by the susceptibility to oxidations with a variety of oxidizing agents. On the other hand, pyridinium compounds are good electron acceptors: 1-substituted-3-carbamoylpyridinium cations form charge transfer complexes with many electron donors as reviewed by Slifkin.⁷ The intermediary of a charge transfer complex in the reaction of NAD(P)^+ -model compound with an amine was also proposed by Kano and Matsuo.⁴

References and Notes

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