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NAD(P)$^+$-NAD(P)H MODEL. REDUCTION OF PYRIDINIUM SALTS TO 1,4-DIHYDROPYRIDINES USING GLYCERALDEHYDE

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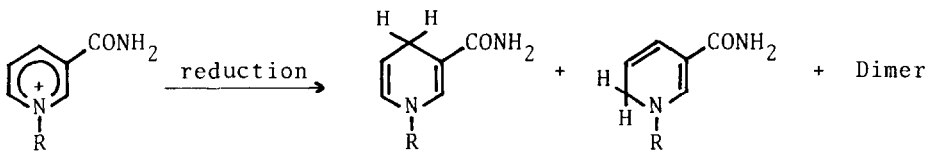
Summary: N-Substituted 3-carbamoylpyridinium salts were reduced by glyceraldehyde to give 1,4-dihydronicotinamide derivatives, which may be regarded as a model for oxidation by glyceraldehyde-3-phosphate dehydrogenase.

As model reactions for alcohol dehydrogenases, many reports have been published in last two decades on the reduction of carbonyl compounds using 1,4-dihydropyridine derivatives(*1*). However, the reverse model reaction, that is, the reduction of pyridinium salts have not been reported so much(*2*). Sodium dithionite is only an effective reductant for the production of 1,4-dihydropyridines up to the present. By the use of other reductants such as sodium borohydride as well as electrochemical reduction produce not only 1,4-dihydro-isomer but also 1,6-dihydro-isomer and dimers of dihydropyridines(*3*). Though

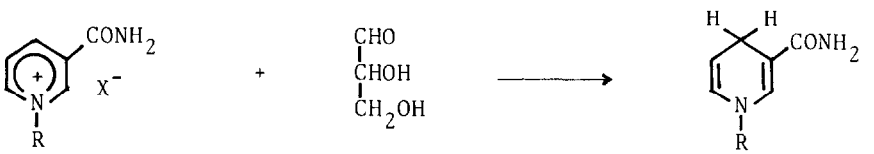


several attempts have been made on the reduction of pyridinium salts by alkoxides or alcohols, the reaction affords a variety of unidentified products and the desired compound has never been isolated(*4*).

Another important enzyme concerning the reduction of NAD$^+$ is glyceraldehyde-3-phosphate dehydrogenase, which catalyzes the reduction of NAD$^+$ to NADH coupled

with conjugate oxidation of glyceraldehyde-3-phosphate to 1,3-diphosphoglycerate(5). We report here a similar type of reaction observed in a model system.

A typical reaction was as follows: 0.05*M* sodium tetraborate solution of glyceraldehyde (1) and N-benzyl-3-carbamoylpyridinium chloride (BNA^+Cl^-) was stirred in the presence of chloroform. The amount of N-benzyl-1,4-dihydronicotinamide (BNAH) extracted in chloroform, which had UV-absorption maximum at around 355 nm, was monitored until the intensity came to an asymptote. The reaction took for about a day at reflux temperature of chloroform or several days at room temperature. The chloroform solution was dried over anhydrous sodium sulfate and evaporated. The NMR spectrum of the product was identical with that of BNAH. Oxidized product from the substrate, *e. g.*, glyceric acid, however, has not been identified yet despite of our efforts.



PNA^+Br^-:R = Pr, X = Br
BNA^+Cl^-:R = CH_2Ph, X = Cl

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PNAH:R = Pr
BNAH:R = CH_2Ph

The results are shown in the Table. The reaction must be carried out in a buffered alkaline solution because BNAH is decomposed owing to the hydration at lower pH region(6). However, under a relatively strong alkaline condition (Entry 5) the yield of BNAH is reduced because of facile decomposition of BNA^+Cl^-. The ratio of the amount of 1 to BNA^+Cl^- did not affect the yield of BNAH. In addition to 1, glycolaldehyde (2) can be employed as a reductant.

We would like to emphasize that the present reaction affords BNAH in more than 97% purtity with at most 3% contamination of 1,6-dihydro-isomer. The regioselectivity of the reaction is very attractive, because other reductants except dithionite produce significant amount of the 1,6-isomer(2,3) and this isomer is ineffective to the reduction of organic substrates. When the reduction was performed in deuterium oxide (Entry 12), 2- and 6-positions of the 1,4-

TABLE. Reduction of N-Substituted-3-carbamoylpyridinium Salt

Entry	Pyridinium salt	Aldehyde	Solvent	Reaction Time	% Yield of 1,4-dihydronicotinamide[a]
1[b]	BNA^+Cl^-, 50mg (0.01*M*)	1, 36mg (0.02*M*)	0.05*M* $Na_2B_4O_7$, 20ml (pH:10.3 - 10.5)	1 d	4
2[b]	BNA^+Cl^-, 50mg (0.01*M*)	1, 36mg (0.02*M*)	0.05*M* $Na_2B_4O_7$, 20ml (pH:10.3 - 10.5)	6 d	10
3[c]	BNA^+Cl^-, 50mg (0.01*M*)	1, 18mg (0.01*M*)	0.05*M* $Na_2B_4O_7$, 20ml (pH: 9.3 - 9.5)	18 h	18 (15)
4[c]	BNA^+Cl^-, 50mg (0.01*M*)	1, 18mg (0.01*M*)	0.05*M* $Na_2B_4O_7$, 20ml (pH: 9.9 - 10.0)	18 h	15 (11)
5[c]	BNA^+Cl^-, 50mg (0.01*M*)	1, 18mg (0.01*M*)	0.30*M* Na_2HPO_4, 20ml (pH:11.4 - 11.5)	10 h	7
6[c]	BNA^+Cl^-, 50mg (0.01*M*)	1, 36mg (0.02*M*)	0.05*M* $Na_2B_4O_7$, 20ml (pH: 9.3 - 9.5)	18 h	17
7[c]	BNA^+Cl^-, 50mg (0.01*M*)	1, 90mg (0.05*M*)	0.05*M* $Na_2B_4O_7$, 20ml (pH: 9.3 - 9.5)	18 h	15
8[c]	BNA^+Cl^-, 50mg (0.05*M*)	1, 18mg (0.05*M*)	0.05*M* $Na_2B_4O_7$, 4ml (pH: 9.4 - 10.3)	18 h	23 (21)
9[c]	BNA^+Cl^-, 50mg (0.01*M*)	1, 18mg (0.01*M*)	1:1 mixture of 0.05*M* $Na_2B_4O_7$ and methanol, 20ml (pH:10.0)	18 h	20
10[c]	PNA^+Br^-,[d] 49mg (0.01*M*)	1, 18mg (0.01*M*)	0.05*M* $Na_2B_4O_7$, 20ml (pH: 9.3 - 9.5)	18 h	8 (7)
11[c]	BNA^+Cl^-, 50mg (0.01*M*)	2, 12mg (0.01*M*)	0.05*M* $Na_2B_4O_7$, 20ml (pH: 9.3 - 9.5)	18 h	18 (17)
12[c]	BNA^+Cl^-, 50mg (0.01*M*)	1, 18mg (0.01*M*)	0.05*M* $Na_2B_4O_7$, in D_2O (pD: 9.9)	18 h	17

[a] Yields, which were calculated on the basis of pyridinium salt, were measured by UV-absorbance at 355 nm (ε = 7200 for BNAH and 7000 for PNAH). Yields in parentheses were measured by NMR using *p*-nitrotoluene as an internal standard. [b] Reaction at room temperature. [c] Reaction at reflux temperature of chloroform. [d] N-Propyl-3-carbamoylpyridinium bromide.

dihydropyridine ring were deuterated in 100% and 35%, respectively, but no deuterium was found at the 4-position. Since we confirmed that BNA^+Cl^- fully incorporates deuteriums in the 2- and 6-positions when it is stirred in deuterium oxide under a same condition as descrived above, except that 1 is absent, it can be concluded that the hydrogen at the 4-position of BNAH is transferred directly from 1.

In spite of the quantitative disappearance of BNA^+Cl^-, the yield of BNAH is at most 20%, the reason of which is that BNA^+Cl^- forms an certain adduct with 1 as a side product. After the reaction the aqueous layer contains an unextracted substance with an UV-absorption maxiumum at 371 nm. On this basis, we suppose that the present reaction involves at least two reactions; one is an adduct formation and the other is the Cannizzaro-type (net) hydride transfer(7) from an aldehyde to a pyridinium salt. Previously, Hirano *et. al.* reported that reduced keratin from human hair catalized the reduction of NAD to NADH by glyceraldehyde(8). They might observe the same reaction as described in the present letter. Detailed studies on the reaction including stereochemistry is under progress.

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