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Coenzyme Models 27.

Reduction of Carbonyl and Related Compounds by an Acid-Stable NADH Analogue plus Brønsted Acid

by

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Reduction of C=C, C=O, and C=N double bonds by an acid-stable NADH analogue, 3-aminocarbonyl-N-benzyl-1, 4-dihydroquinoline (BzlQH) was reported. BzlQH reduced β-nitrostyrene in 28% yield and pyridine-2-aldehyde and the Schiff base in relatively high yields (58-85%) in the presence of Brønsted acids. In all the cases, the yield is superior to that by N-benzyl-1, 4-dihydronicotinamide under the comparable reaction conditions. The results indicate that the reduction reaction by BzlQH is largely improved by added Brønsted acids. The role of added acids was discussed in relation to the efficiency of enzymatic catalysis.

It has been found that some NADH-dependent dehydrogenases employ metal ion (Zn^{2+}) or Brønsted acid (imidazolium ion) to achieve the activation of bound carbonyl substrates. [1-3] The concept in the enzymatic catalysis suggests that nonezymatic dihydronicotinamide reduction would be also facilitated by Lewis acid or Brønsted acid. Recent studies on NADH model reduction have established that metal ion solubilized in aprotic solvents (*e. g.*, acetonitrile) acts as an efficient catalyst, although the catalytic activity disappears in protic media. [4-6] On the other hand, almost nothing is known with certainty as to the catalytic behavior of Brønsted acid, except for a few studies on acid catalysis in organic solvents. [7-9] The difficulty largely stems from the susceptibility of dihydronicotinamide (NADH analogue) to Brønsted acid; that is, dihydronicotinamides rapidly decompose in acidic media and the rate for relatively slow reduction reactions cannot be estimated accurately. Thus, the catalytic efficiency of Brønsted acid has been left as an open question.

On an attempt to utilize Brønsted acid as catalyst in protic media, we synthesized an acid-stable NADH analogue, 3-aminocarbonyl-N-benzyl-1, 4-dihydroquinoline (BzlQH). [10, 11] Since the acid-sensitive 5, 6-double bond in the 1, 4-dihydro nicotinamide structure is protected by the aromatic ring (as 4a, 8a-double bond of the quinoline structure), this material is quite stable even in an acidic aqueous solution (pH 1-4). [12] With the novel NADH analogue, we performed the reduction of C=C, C=O, and C=N double bonds and found that the reduction reactions are facilitated to a great extent by added Brønsted acids. The efficiency was compared with that of a conventional NADH analogue, N-benzyl-1, 4-dihydronicotinamide (BzlNH).

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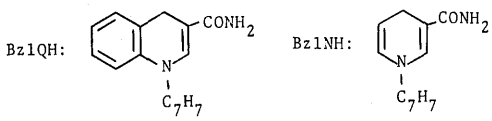


Experimental

Materials. The preparation of 3-aminocarbonyl-N-benzyl-1, 4-dihydroquinoline (BzlQH) was described previously. [11]

N-(2-Picolylidene) benzylamine was prepared from pyridine-g-aldehyde and benzylamine according to the method of Matsuo[12] and used without further characterization for the sake of synthetic simplicity.

N-Benzyl-2-picolylamine was prepared by the reduction of N-(2-picolylidene) benzylamine. Pyridine-2-aldehyde (2.36 g, 22 mmoles) and benzylamine (2.36 g, 22 mmoles) were dissolved in 20 ml of absolute ethanol and refluxed for 1 h. Ethanol was evaporated *in vacuo,* the residue being taken with 15 ml of absolute ethanol.

The solution was cooled below 0°C, and $NaBH_4$ (0.85 g, 23 mmoles) in 13 ml of absolute ethanol was added dropwise. The reaction was continued for 6.5 h at 45°C. Solvent was evaporated to dryness, and the oily residue was extracted with ether and water, the ether layer being dried over sodium sulfate. The ether layer was concentrated to dryness, taken in absolute ethanol, and dry hydrogen chloride gas was introduced. On cooling, colorless crystals were precipitated: yield 70%, mp 205-209°C. NMR ($CDCl_3$) : Ph-CH_2, 4.32ppm, 2H; Py-CH_2, 4.52 ppm, 2H; benzene ring, 7.4-7.8 ppm, 5H; pyridine ring, 7.9-8.8 ppm, 4H. Found: C, 57.03; H, 5.94; N, 10.09%. Calcd for $C_{13}H_{14}N_2 \cdot 2HCl$: 57.58; H, 5.95; N, 10.33%.

3-Aminocarbonyl-N-benzyl-1, 2, 3, 4-tetrahydroquinoline was prepared by catalytic hydrogenation of 3-aminocarbonyl-N-benzyl-quinolinium bromide ($BzlQ^+$) . Platinum catalyst on wet carbon (0.012 g) was placed in a four-necked flask, and the flask was degassed. $BzlQ^+$ (0.40 g, 1.17 mmoles) in 25 ml of freshly-distilled methanol was added dropwise from a neck, and hydrogen gas was introduced into the flask from another neck. The reaction mixture was stirred efficiently, and the reaction was continued for 10 h at room temperature. After filtration of catalyst, solvent was evaporated *in vacuo.* The thin-layer chromatographic analysis (silica-gel and chloroform) indicated that the residue is a mixture of $BzlQ^+$ (R_f=0-0.2) and unknown product (R_f= 0.6-0.8). The unknown product (mp 148-150°C) was separated by thin-layer chromatography and subjected to NMR measurement. NMR (Me_2SO-d_6) : 3-CH and 4-CH_2, 2.8-2.9 ppm, 3H; 2-CH_2, 3.52 ppm, 2H; Ph-CH_2, 4.60 ppm, 2H; quinoline ring (5, 6, 7, 8), 5.9-7.1 ppm, 4H; benzene ring, 7.40 ppm, 5H. The spectrum is in good correspondence to that of 3-aminocarbonyl-N-(p-fluorobenzyl)-1, 2, 3, 4-tetrahydroquinoline.[13] Thus, the material was identified to be 3-aminocarbonyl-N-benzyl-1, 2, 3, 4-tetrahydroquinoline.

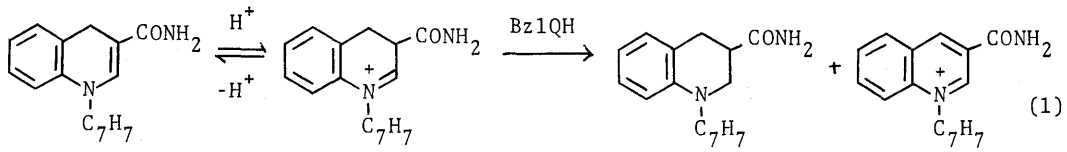
Product Analyses. Acid-catalyzed decomposition of BzlQH was conducted as follows. BzlQH (0.10 g, 0.38 mmoles) was dissolved in 60 ml of an aqueous ethanol solution (ethanol: water=40: 20 in volume), and 1 ml of conc. HCl was added. The solution was left at room temperature for 1.5 months. Solvent was evaporated *in vacuo,* the residual solid being extracted with chloroform and water. The chloroform layer separated was dried over sodium sulfate. The concentrated solutions were subjected to the analysis by high-pressure liquid chromatography (Shimadzu LC-2F).

Reaction of BzlQH (0.26 g, 1 mmole) and β-nitrostyrene (0.15 g, 1 mmole) was performed in two different reaction media: (i) in a mixed solvent of ethanol (20 ml) and conc. HCl (1 ml) and in a mixed solvent of acetic acid (5 ml), water (5 ml), and ethanol (1 ml). The reactions were continued for 6 h at 78-82°C in the dark. The method of the product analysis has been described in a previous paper.[9]

Reaction conditions for BzlQH reduction of pyridine-2-aldehyde and N- (2-picolylidene) - benzylamine are recorded under the corresponding Tables.

Results

Acid-Catalyzed Decomposition of BzlQH. Although BzlQH is fairly stable against acids,[10] an absorption band at around 350 nm slowly disappeared in acidic media without giving rise to a new absorption band at 290 nm which is attributed to 1, 4, 5, 6-tetrahydronicotinamide.[14] It is presumed, therefore, that the decomposition mechanism of BzlQH is somewhat different from that of 1, 4-dihydronicotinamde. The decomposition products (see Extperimental) were analyzed by using high-pressure liquid chromatography. The concentrated solution of the chloroform layer gave two peaks: they were identified to be BzlQH and 3-aminocarbonyl-N-benzyl-1, 2, 3, 4-terahydroquinoline by comparing with the authentic samples. On the other hand, the aqueous layer contained only $BzlQ^+$. The relative molar ratio of BzlQH: 3-aminocarbonyl-N-benzyl-1, 2, 3, 4-tetrahydroquinoline: $BzlQ^+$ calculated from the integral intensity of each peak was 1:11:230. The result suggests that the decomposition of BzlQH proceeds (at least partially) according to the disproportionation mechanism as Eq. 1.



(1)

A similar disproportionation has been reported for the decomposition of Hantzsch ester in concentrated mineral acid.[15]

The disproportionation mechanism of Eq. 1 requires that $BzlQ^+$ and tetrahydroquinoline are yielded in an equimolar ratio. It is not clear at present why the yield of $BzlQ^+$ greatly exceeds that of tetrahydroquinoline. The discrepancy may be rationalized in terms of pyrolysis and air oxidation of BzlQH.[16]

Reduction of β-Nitrostyrene. BzlQH reduction of β-nitrostyrene to β-nitroethylbenzene was performed in an ethanol-HCl solution and in an aqueous acetate buffer solution (see Experimental) . The former solvent did not give the reduced product as much as detectable by the NMR method.[9] On the other hand, β-nitroethylbenzene was recovered in 28% yield from the aqueous acetic acid solvent. It was confirmed that β-nitrostyrene is not reduced in the absence of acetic acid. The yield is superior to that in BzlNH reduction (16% in methanol-acetic acid and 22% in acetonitrile $Mg(ClO_4)_2$).[9]

Reduction of Pyridine-2-aldehyde (2-PyCHO). 2-Acylpyridine which is frequently emplyed as substrate for metal-assisted BzlNH reduction[4,5] can be reduced by BzlQH and Brønsted acid. Table 2 shows the reduction of 2-PyCHO in an aqueous ethanol solution buffered with acetic acid. It is seen from Table 1 that (i) 2-PyCHO is readily reduced by BzlQH in acetate buffer, whereas BzlNH is less effective reducing reagent under these acidic reaction conditions and (ii) metal ion (Zn^{2+}) does not or hardly catalyze the reduction reaction in this buffer solution. It is worth while mentioning that the yield (58%) is remarkably enhanced.

Table 1. Reduction of pyridine-2-aldehyde in the presence of acetic acid and/or $ZnCl_2$[a)]

NADH analogue	$[ZnCl_2]$ M	Yield of 2-(hydroxymethyl) pyridine (%)	Recovered pyridine-2-aldehyde (%)
BzlQH	0	58	14
BzlQH	1.0	65	17
BzlNH	0	12	80
BzlNH	1.0	0	90

a) 50°C for 48 h in the dark in 33 vol% aqueous ethanol buffered with acetic acid (2 M) and potassium acetate (2 M). [BzlQH]= [BzlNH] =0.033M, [2-PyCHO]=0.033 M

Table 2. Reduction of N-(2-picolylidene) benzylamine in the presence of acetic acid and $ZnCl_2$[a)]

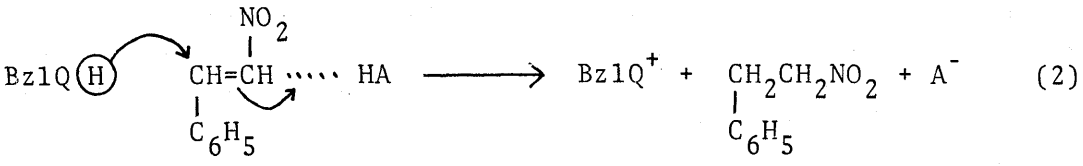
NADH analogue	$[ZnCl_2]$ M	Yield of N-benzyl-2-picolylamine (%)
BzlQH	0	58
BzlQH	0.50	85
BzlNH	0	38
BzlNH	0.50	45

a) 48 h in refluxing ethanol. [BzlQH]= [BzlNH]=0.050 M, [AcOH]=1.5 M.

Reduction of Schiff Base of 2-PyCHO. The reduction of N-(2-picolylidene) benzylamine (PyCH=NBzl) is summarized in Table 2. As reported earlier,[17] protonated Schiff bases can be reduced by BzlNH in relatively low yield (*e. g.*, 19% for N-(p-nitro-benzylidene) benzylamine hydrochloride). It is argued that the Schiff base is activated as electrophile through protonation, but it causes inevitably the acid-catalyzed decomposition of BzlNH.[17] Table 2 proves that PyCH=NBzl is reduced by BzlQH, an acid-stable NADH analogue, more efficiently than acid-sensitive BzlHN in a mixed solvent of ethanol-acetic acid. The reduced product was not given in the absence of acetic acid. Contrary to the reduction of 2-PyCHO, the reduction of the Schiff base was facilitated by added metal ion (Zn^{2+}). In particular, BzlQH reduction in the presence of both acetic acid and Zn^{2+} ion resulted in high yield (85%).

Discussion

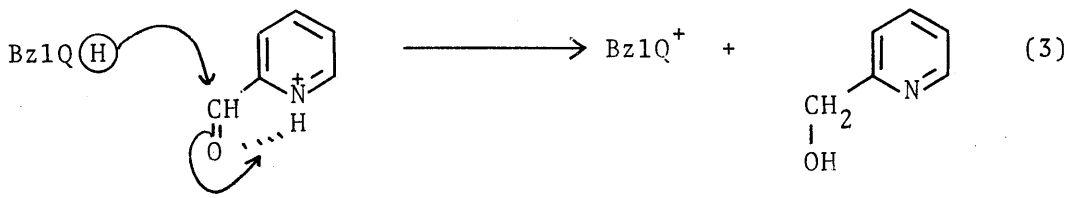
The BzlQH reduction of the C=C, C=O, and C=N double bonds was achieved in the presence of Brønsted acids. It should be noted, however, that the detailed mechanism is quite different. Since the protonation of the C=C double bond by added Brønsted acids in a preequilibrium step is hardly conceivable, the reduction of β-nitrostyrene proceeds with the aid of general-acid catalysis (Eq. 2).[7, 10, 11]



(2)

On the other hand, 2-PyCHO was efficiently reduced by BzlQH in the acetate buffer solution. Presuming from the pK_a value of 2-PyCHO (3.8),[18] about 10% of 2-PyCHO must exist as N-protonated species in this buffer solution. It is readily supposed, therefore, that the reduction

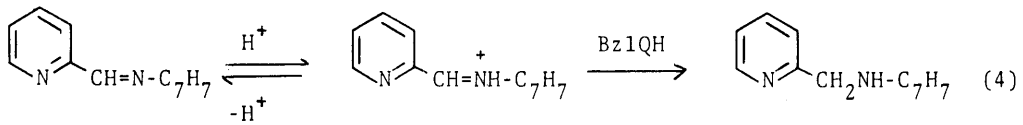
proceeds with participation of the neighboring NH^+ group (Eq. 3).



(3)

The mechanism is quite similar to the reduction of aromatic aldehydes facilitated by the ortho-hydroxyl group.[19, 20] The carbonyl group is also activated by the polarization caused by the election-withdrawing nature of the pyridinium group. This problem is discussed by Creighton *et al.* [21] in detail.

The pK_a value of the Schiff base is much higher than that of Brønsted acids used, [18] so that the reduction would proceed mainly via pre-equilibrium protonation of the Schiff base (*i. e.*, specific acid catalysis) as Eq. 4.



(4)

In all the cases, BzlQH reduction provided higher yields than BzlNH reduction under the comparable reaction conditions. It is undoubted that the efficiency of BzlQH stems from the stability of BzlQH against acids. The results indicate that BzlQH serves as an excellent reducing agent when combined with Brønsted acids.

References and Notes

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