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BIOMIMETIC REDUCTION OF INACTIVATED CARBONYL COMPOUNDS BY AN ACID-STABLE NADH ANALOGUE PLUS BRÖNSTED ACID

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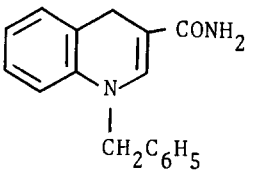
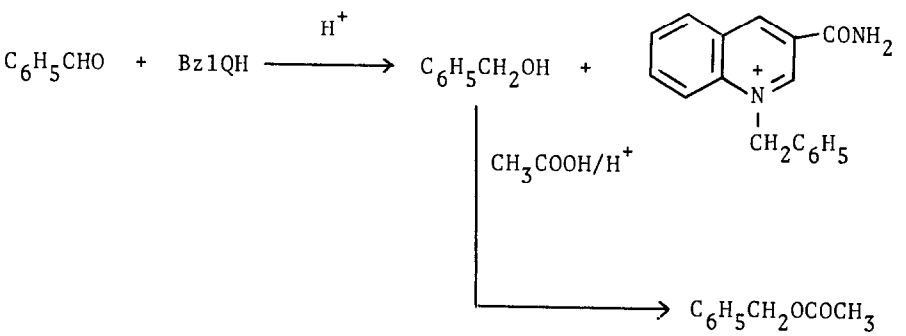
The NADH model reduction of inactivated carbonyl compounds was achieved by the combination of an acid-stable NADH analogue and strong proton sources(HCl or benzenesulfonic acid).

In contrast to the inability of 1,4-dihydronicotinamides(NADH analogues) to reduce all but the most activated carbonyl compounds, NADH-dependent enzymes exhibit a noteworthy reactivity toward inactivated carbonyl substrates.[1] The versatility of the enzymes is due mainly to the activation of bound substrates by acidic species(Zn^{2+} or protonated imidazole).[2,3] It thus seems interesting to adopt the enzymatic, bifunctional concept to achieve the biomimetic reduction of inactivated carbonyl compounds.

Very recently, Ohnishi and Kitami[4] reported that, with the aid of Mg^{2+} ion, benzaldehyde is reduced by 1,4-dihydronicotinamides(10 times excess) in 2-9% yield. This may be a suitable model system for alcohol dehydrogenase which requires Zn^{2+} ion in the active site. On the other hand, there is no proper precedent for glyceraldehyde-3-phosphate dehydrogenase which adopts protonated imidazole as acid source, except a recent contribution by Yoneda and Sakuma[5] in which 5-deaza-1,5-dihydroisoalloxazine was employed as a NADH analogue. We recently found that 3-aminocarbonyl-N-benzyl-1,4-dihydroquinoline(BzlQH), in which an acid-sensitive 5,6-double bond of the 1,4-dihydronicotinamide structure is protected as a 4a,8a-double bond of the quinoline structure, is quite stable against proton acids and thus becomes a useful model compound to assess the NADH-dependent reaction which occurs with the aid of Brönsted acids.[6] In this communication, we wish to address the application of the enzymatic, bifunctional concept to the reduction of inactivated carbonyl compounds by the use of BzlQH plus Brönsted acids.

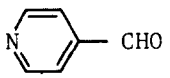
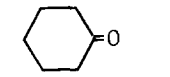
BzlQH: 

A typical experimental run is as follows: a mixture of BzlQH(1.2 mmol) and carbonyl substrate(1.2 mmol) was dissolved in 3 ml of acetic acid and was refluxed in the dark for 4 hr in the presence or absence of strong acid (conc. HCl or benzenesulfonic acid: 2 times excess). The reaction mixture was analyzed by gas chromatography or high-speed liquid chromatography. The reduced products identified were corresponding alcohol and acetyl ester, affording the following reaction scheme.



The results of the product analysis are summarized in Table 1. In the absence of strong proton sources, benzaldehyde was converted to benzyl acetate only in 1% yield. Since benzaldehyde is scarcely reducible by BzlQH in the absence of acid species,[7] the poor conversion would be attributable to the action of acetic acid as general-acid.[6] On the other hand, addition of strong acids such as conc. HCl or benzenesulfonic acid remarkably enhanced the yield of benzyl alcohol and benzyl acetate, the highest yield being observed for the reduction by BzlQH + benzenesulfonic acid(total yield, 30%). The result indicates that the presence of strong acid sources

Table 1. Reduction of Inactivated Carbonyl Compounds by BzlQH plus Bronsted Acids

Carbonyl	Acid	Yiled(%) of R_1R_2CHOH	Yiled(%) of $R_1R_2CHOCOCH_3$	Total Yield (%)
C_6H_5CHO	None	0	1	1
	HCl	10	11	21
	HCl[a]	9	12	21
	HCl[b]	8	10	18
	$C_6H_5SO_3H$	1	29	30
	HCl	10	1	11
	$C_6H_5SO_3H$	4	5	9
	HCl	0	3	3
	$C_6H_5SO_3H$	0	5	5

[a] BzlQH:benzaldehyde:HCl=2:1:2(mole ratio). [b] 3-Carboxy-N-benzyl-1,4-dihydroquinoline was used instead of BzlQH.

is indispensable to the reaction. Probably, the reaction proceeds via protonation of benzaldehyde in a pre-equilibrium step(at least partially), since the acidity of HCl and benzenesulfonic acid is comparable with that of conjugate acid of benzaldehyde(i.e., $C_6H_5CHOH^+$).[8]

Table 1 also shows that the reduction by BzlQH + conc. HCl gives both benzyl alcohol and benzyl acetate, while the reduction in the presence of benzenesulfonic acid results predominantly in benzyl acetate. The difference is explicable by such that the conversion of alcohol to the corresponding ester occurs preferably in the anhydrous reaction medium.

Pyridine-4-aldehyde and cyclohexanone were also reduced by BzlQH plus strong proton sources, but the yields were relatively low(Table 1).

It has been established that the ortho-hydroxyl group assists greatly the NADH model reduction of carbonyl groups attached to the aromatic ring. Thus, nonenzymatic reduction of salicylaldehyde and 3-hydroxypyridine-4-aldehyde has been reported, but benzaldehyde and pyridine-4-aldehyde have not been subjected to the nonenzymatic dihydronicotinamide reduction under the comparable reaction condition.[9] Probably, intermolecular proton source causes the decomposition of 1,4-dihydronicotinamide more rapidly than the

acid-catalyzed reduction of carbonyl groups. The present study demonstrates, however, that the nonenzymatic dihydronicotinamide reduction can be aided by intermolecular proton sources, the mechanistic role of which is attributed probably to specific acid catalysis. The system is of great significance because of the analogy with the reduction process of glyceraldehyde-3-phosphate dehydrogenase which may be expressed by NADH---$\rangle$C=O---imidazoleH$^+$ $\rightleftharpoons$ NADH---$\rangle$C=OH$^+$---imidazole $\longrightarrow$ NAD$^+$---$\rangle$CHOH---imidazole.[3] It would require little comment that the novel reduction process reported here becomes observable due to the stability of BzlQH against acid species.[6]

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