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# 3-AMINOCARBONYL-N-BENZYL-1,4-DIHYDROQUINOLINE: A NOVEL NADH MODEL COMPOUND WHICH RESISTS THE ACID CATALYZED DECOMPOSITION

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The title NADH model compound resists acids unlike the conventional NADH model compounds. Thus, added acids accelerate the reduction of a carbonyl substrate selectively in the general-acid catalyzed manner.

Recent X-ray crystallographic studies of NADH dependent enzymes suggest that the protonated imidazole of the histidine residue of D-glyceraldehyde-3-phosphate dehydrogenase acts as a general-acid during the reduction process.[1,2] Van Eikeren and Greier[3] and Shinkai and Kunitake[4] have found that the NADH model reduction of carbonyl substrates is also general-acid catalyzed. Therefore, the general-acid catalyzed reduction by NADH models could be an expeditious method for the reduction of carbonyls.

Here, a dilemma in the model system should be noted. The reduction reaction is always accompanied by the acid catalyzed decomposition of NADH models,[5,6] and the slope of Brönsted plot for the latter reaction is much greater than that for the former.[4] This implies that the decomposition rate is accelerated more efficiently than the reduction rate by added strong acids. Taking N-benzyl-1,4-dihydronicotinamide(BzlNH) reduction of hexachloroacetone(HCAc) in acetonitrile,[4] for instance, the observed rate of disappearance of BzlNH in the presence of acids($v_{obsd}$) is described by Eq. 1, and $k_{ga}$(rate constant for the general-acid catalyzed reduction) and $k_d$(rate constant for the acid catalyzed decomposition) by Eqs. 2 and 3, respectively,

$$v_{obsd}=(k_2 + k_{ga}[Acid])[BzlNH][HCAc] + k_d[BzlNH][Acid] \quad (1)$$

$$\log k_{ga}=A\cdot pK_a + B \quad (2)$$

$$\log k_d=a\cdot pK_a + b \quad (3)$$

where $k_2$ is the second-order rate constant for the reduction in the absence of acids and $K_a$ the acid dissociation constant of the added acids in an aqueous solution. The reaction parameters are summarized in Table 1. Assuming all the reactant concentrations to be one M, the ratio of reduction rate vs. decomposition rate($R_r/R_d$) is expressed by Eq. 4.

$$R_r/R_d=(k_2 + k_{ga})/k_d=(k_2 + 10^{A\cdot pK_a+B})/10^{a\cdot pK_a+b} \quad (4)$$

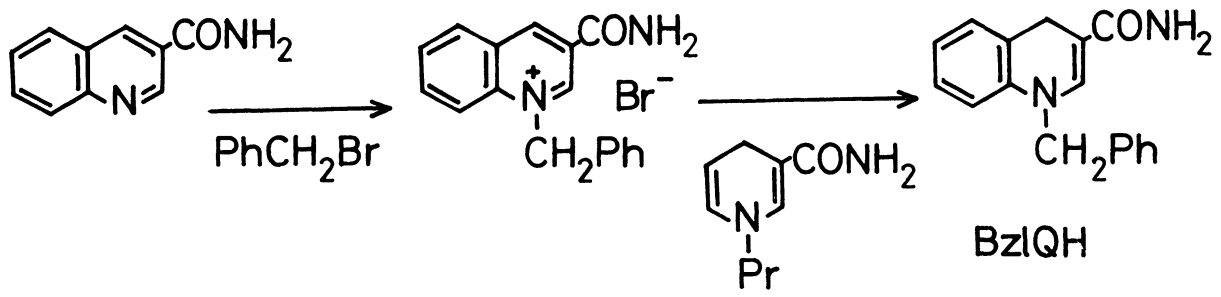
Table 1. Reaction parameters for BzlNH and BzlQH[a)]

| NADH Model | $k_2$ ($M^{-1}s^{-1}$) | A | B | a | b |
|---|---|---|---|---|---|
| BzlNH | 0.337 | -0.18 | 1.83 | -0.95 | 5.54 |
| BzlQH | 0.0090 | -0.23 | 1.03 | -0.24 | -2.99 |

a) 30°C in acetonitrile.

The logarithm of $R_r/R_d$ is plotted against $pK_a$ of the added acid(Fig. 1). The curve for BzlNH reveals that the mode of the general-acid catalyzed reaction is significantly associated with $pK_a$ of the added acid: for example, $R_r/R_d=1.24 \times 10^4$ at $pK_a=10$, while $R_r/R_d=1.96 \times 10^{-4}$ at $pK_a=0$. The $10^8$ difference in the ratio is truly remarkable. The result clearly substantiates that the addition of strong acids does not improve the yield of reduced alcohols.

The primary acid catalyzed decomposition proceeds via protonation at 5-carbon of 1,4-dihydronicotinamide.[5,6)] It occurred to us that 1,4-dihydronicotinamide, the 5,6-double bond of which is protected from electrophilic attack, may be stable in acidic media and may serve as a useful reducing agent in general-acid catalyzed reduction of carbonyls. We thus prepared 3-aminocarbonyl-N-benzyl-1,4-dihydroquinoline(BzlQH)[7)] in which the 5,6-double bond is involved in the aromatic ring and examined the effectiveness in the general-acid catalyzed reduction reactions.[8)]




The $k_2$ value for BzlQH reduction of HCAc in acetonitrile was $9.0 \times 10^{-3}$ $M^{-1}$ $s^{-1}$(Table 1), so that BzlQH is 37 times less reactive than BzlNH.[4)] It was found that BzlQH is surprisingly stable in acidic media compared with BzlNH: for example, BzlQH is $3.0 \times 10^3$ times more stable in acetic acid($k_d=8.01 \times 10^{-7}$ $M^{-1}s^{-1}$ for BzlQH and $2.40 \times 10^{-3}$ $M^{-1}s^{-1}$ for BzlNH) and $4.4 \times 10^4$ times more stable in aqueous ethanol($[H_2O]=0.21$ M) containing hydrochloric acid($k_d=2.00 \times 10^{-5}$ $M^{-1}s^{-1}$ for BzlQH and 0.872 $M^{-1}s^{-1}$ for BzlNH).[9)] The Brönsted parameters for the BzlQH reduction of HCAc in acetonitrile were evaluated by plotting log $k_{ga}$ and log $k_d$

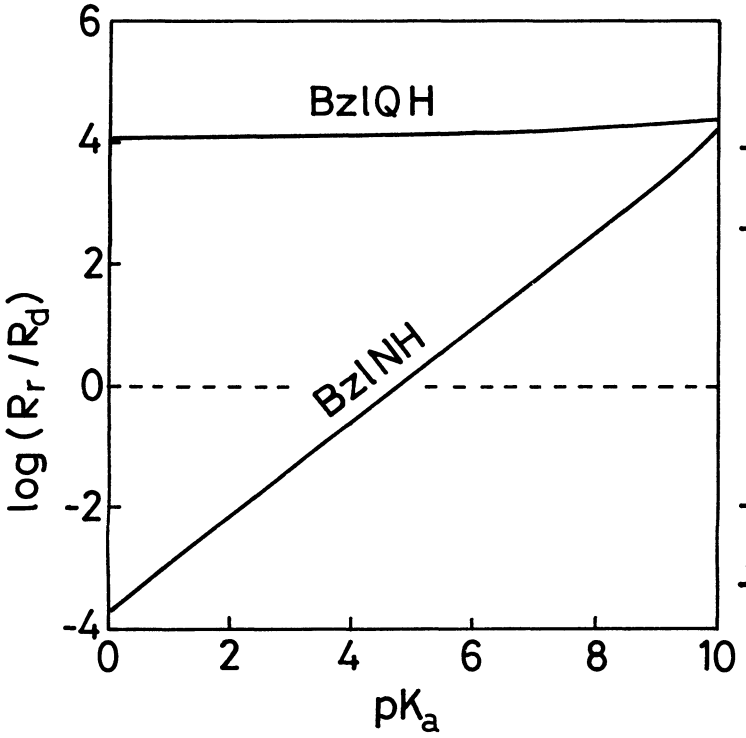



Fig. 1. The curves of $\log(R_r/R_d)$ vs. $pK_a$ in water which were depicted according to Eq. 4 and reaction parameters in Table 1.

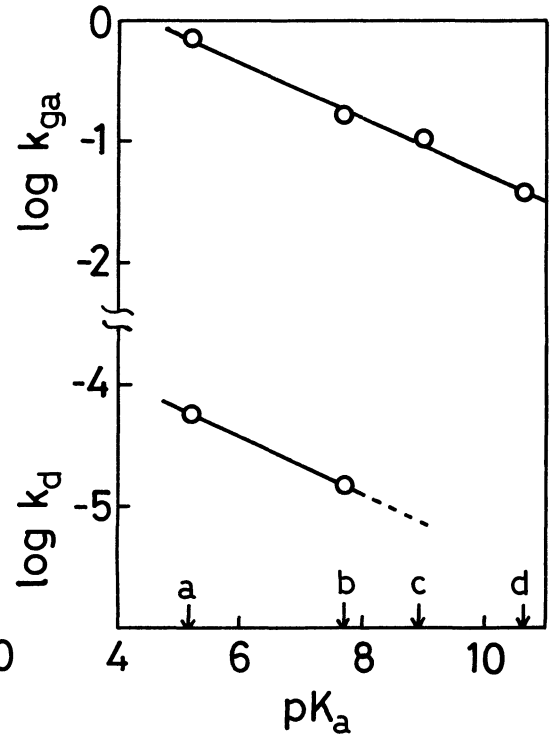



Fig. 2. Log $k_{ga}$ ($M^{-2}s^{-1}$) and log $k_d$ ($M^{-1}s^{-1}$) vs. $pK_a$ in water. (a) Pyridine·HCl, (b) N-ethylmorpholine·HCl, (c) N,N-dimethylbenzylamine·HCl, and (d) triethylamine·HCl. The $k_d$ value for the latter two hydrochlorides could not be determined accurately due to the slow rates.

against $pK_a$ for four hydrochlorides(Fig. 2: for the detail of the method see Ref. 4). The least-squares computation of the experimental data provided the reaction parameters listed in Table 1. It is noteworthy that the a-value(slope of Brönsted plot) for BzlQH is much smaller than that for BzlNH.

The curve of $\log(R_r/R_d)$ against $pK_a$ was depicted according to Eq. 4 and the reaction parameters in Table 1(Fig. 1). Figure 1 shows that, in marked contrast to the behavior of BzlNH, BzlQH is totally used for the reduction reaction and the fraction wasted for the decomposition is less than 0.01%. Also significant is that $R_r/R_d$ is almost independent of $pK_a$(i.e., $R_r/R_d = 1.51 \times 10^4$ at pH=10 and $1.05 \times 10^4$ at $pK_a$=0).

The foregoing results suggest that BzlQH reduction of carbonyls can be performed in very strong acid solutions. Preliminary experiments in this laboratory indicate that in the presence of hydrochloric acid BzlQH reduces p-nitrobenzaldehyde to p-nitrobenzyl alcohol in 10% yield,[10] whereas BzlNH does not

give the reduced products under the comparable conditions(both in the presence and the absence of hydrochloric acid). It is thus anticipated that the NADH model reduction with BzlQH plus strong acid would be applicable more generally to the reduction of carbonyls and related compounds.

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7) 3-Aminocarbonylquinoline, mp 194-195°C(lit. 198-199°C: F. C. Uhle and W. A. Jacobs, J. Org. Chem., 10, 76(1945)). 3-Aminocarbonyl-N-benzylquinolinium bromide, mp(dec) 223-225°C, yield 45%. BzlQH, mp(dec) 155°C, yield 71-84%, NMR($Me_2SO$-$d_6$): $NH_2$, 3.42 ppm, 2H; 4-$CH_2$, 3.82 ppm, 2H; N-$CH_2$, 5.00 ppm, 2H; $C_6H_5$, 7.52 ppm, 5H; $C_6H_4$ and 2-CH, 6.9-7.9 ppm, 5H.

8) 30 ± 0.1°C in acetonitrile. The progress of the reaction was followed spectrophotometrically at 350 nm for BzlNH and at 340 nm for BzlQH. In all the cases, excess HCAc(0.5 M) was employed.

9) BzlQH(0.118 g: $4.48 \times 10^{-4}$ mole) was dissolved in a mixed solvent of ethanol (40 ml) and conc. HCl(20 ml), and stirred for four days at room temperature in the dark. About 40% of BzlQH was recovered by TLC method from the reaction mixture. In the residual product mixture, 3-aminocarbonyl-N-benzylquinolinium chloride was identified by NMR and TLC. The NMR spectrum($Me_2SO$-$d_6$) also showed strong peaks at 1.0-1.5 ppm, which may be ascribed to 3-aminocarbonyl-N-benzyl-1,2,3,4-tetrahydroquinoline.[6] For the identification, the authentic sample is now being prepared from 3-aminocarbonyl-N-benzylquinolinium chloride and sodium dithionite.

10) The reaction mixture([BzlQH]=[p-nitrobenzaldehyde]=[HCl]=$3.4 \times 10^{-4}$ M in ethanol) was refluxed for 6 h in the dark.

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