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ACID CATALYZED REDUCTION OF NITROSOBENZENE BY 3,5-DIPYRROLIDINOCARBAMOYL-N-BENZYL-1,4-DIHYDROPYRIDINE AS A NADH ANALOG

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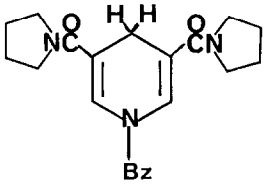
Acid catalyzed reduction of substituted nitrosobenzenes to the hydroxylamines by 3,5-dipyrrolidinocarbamoyl-N-benzyl-1,4-dihydropyridine has been studied in anhydrous acetonitrile.

Acid catalysis in the reactions of coenzyme NAD(P)H and its analogs is an interesting subject as the model catalysis of certain dehydrogenase enzymes[1,2] as well as for the synthetic application of NADH analogs.[3] A problem for studying such acid catalysis is instability of conventional NADH analogs toward acids. In order to overcome this problem, Shinkai et al designed 3-carbamoyl-N-benzyl-1,4-dihydroquinoline (2) as an acid stable NADH analog.[4] In this communication, we wish to report that 3,5-dipyrrolidinocarbamoyl-N-benzyl-1,4-dihydropyridine (1) is much more active than 2 and more acid stable than a conventional NADH analog, N-benzyl-1,4-dihydronicotinamide (3), in the acid catalyzed reduction of substituted nitrosobenzenes (4). Reduction of nitrosobenzene by NAD(P)H is of interest in connection to the carcinogenesis in biological systems. Among several model studies in the literature,[5-8] the work of Becker and



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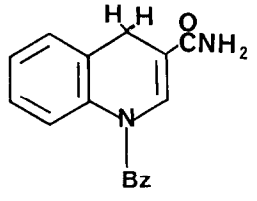

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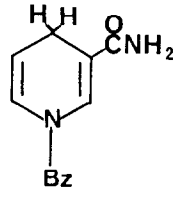

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Sternson is the most relevant to the present study. They observed a quantitative reduction of nitrosobenzene to phenylhydroxylamine in the non-enzymatic reduction by NAD(P)H in aqueous buffer solutions(pH 5.7-7.4), but they did not observe any buffer catalysis.[8)]

The present reaction was carried out in anhydrous acetonitrile under nitrogen atmosphere.[9)] The acid used was dichloroacetic acid.[10)] The time-dependent composition of the reaction mixture could be successfully analyzed by HPLC.[11)] The results are shown in Eq. 1 and Fig. 1: nitrosobenzene (4) was quantitatively reduced to the hydroxylamine (5) when reacted with two molar excess of 1 in the presence of dichloroacetic acid, accompanied with the formation of a small amount of azoxybenzene (6). One may also notice in Fig. 1 that the disappearance of 1 and 4 and the appearance of 5 occurred almost in the same rate and much faster than the formation of 6. Furthermore, the curve for 1 indicates that after completion of reduction the remaining excess 1 was stable without undergoing further acid promoted decomposition.

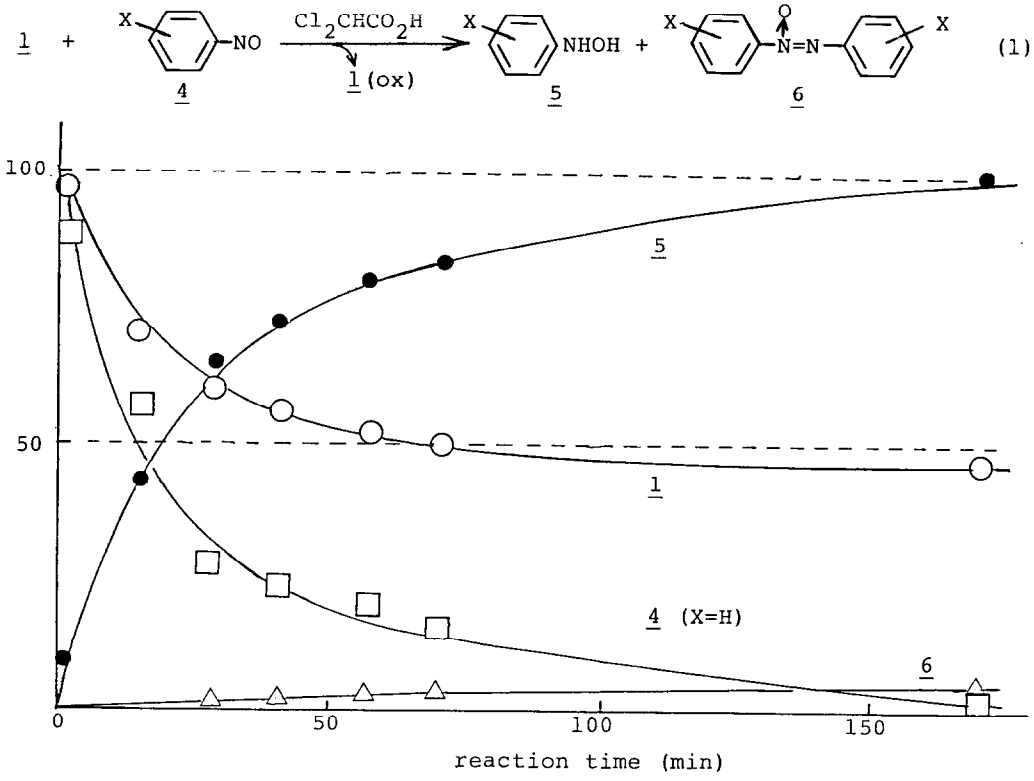

Figure 1. Time dependent % reaction or yield: [1]=1x10^{-3}M, [4]=0.5x10^{-3}M, [Cl_2CHCO_2H]=10x10^{-3}M in acetonitrile, 25°C.

The rates of reduction were measured spectrophotometrically by observing the decrease of absorbance of either dihydropyridine (1, 2 or 3) or nitrosobenzene[12] and they were found to be first order with respect to each concentration of nitrosobenzene and dihydropyridine (Eq. 2). The observed second-order rate constants (k_{obs}) were found to be further composed of uncatalyzed (k_{un}) and acid catalyzed ($k_H[AH]$) terms as shown in Eq. 3 and Fig. 2.

$$\text{Rate} = k_{obs}[\text{nitrosobenzene}][\text{dihydropyridine}] \quad (2)$$

$$k_{obs} = k_{un} + k_H[AH] \quad (3)$$

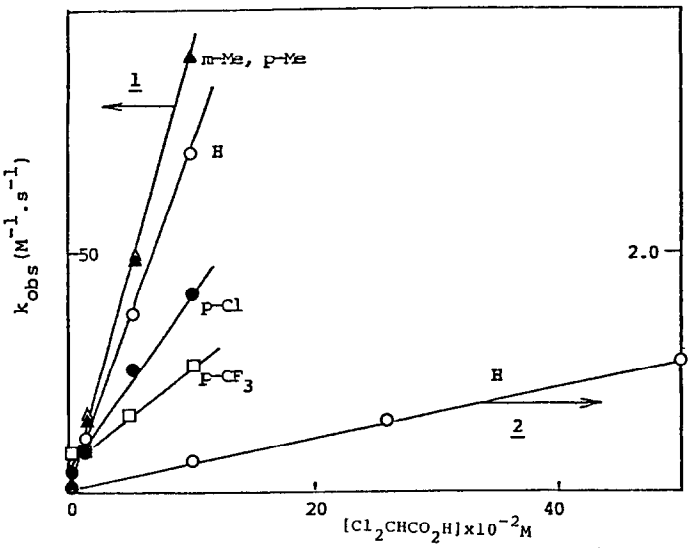

Figure 2. Catalysis of dichloroacetic acid: [1]=[2]=1x10^{-4}M, [4]=2x10^{-3}M, 25°C.

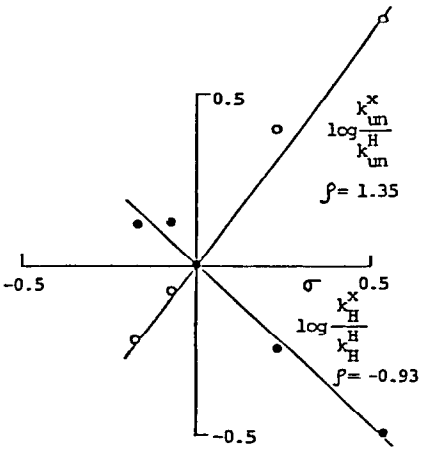

Figure 3. Hammett plots of k_{un}, k_H rate constants in Fig. 2.

An interesting feature in Fig. 2 is the reactivities of dihydropyridines. Clearly, 1 is much more reactive than 2 in both uncatalyzed and acid catalyzed rates, i.e. $k_{un}(1)/k_{un}(2) = 15$ and $k_H(1)/k_H(2) = 332$, respectively, for unsubstituted substrate (4, X=H). In the case of conventional NADH model, 3, dichloroacetic acid rather inhibited the reduction.[13] Another more important feature in Fig. 2 is the opposing substituent effects on the k_{un} and k_H values. As shown in Fig. 3, the Hammett plots of k_{un} and k_H values gave a positive ρ for k_{un}, while a negative ρ for k_H values, indicating electron-withdrawing substituents to enhance the uncatalyzed rates, while electron-donating substituents to enhance the acid catalyzed rates. The latter negative ρ value may suggest the importance of preequilibrium formation of protonated nitrosobenzene as the hydride acceptor, although other general-acid catalyzed one-step hydride trans-

fer from dihydropyridine to unprotonated nitrosobenzene may also be conceivable.[14]

Whatever mechanisms follow, the above results have demonstrated the utility of 1 as a novel NADH analog in studying acid catalysis. It should also be mentioned that in the previous studies on the acid catalysis of NADH model hexachloroacetone and trifluoroacetophenone were the only two substrates.[4,15-17]

References and Notes

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9) 1 was prepared as usual by reacting acid chloride of pyridine-3,5-dicarboxylic acid with pyrrolidine followed by N-benzylation and reduction with dithionite: mp 46°, λ_{max}= 355 nm (ε=6000 $M^{-1}cm^{-1}$). ^1H NMR and elemental analysis accorded with the structure.
10) Other haloacetic acids were also effective, depending upon their acidities.
11) HPLC analysis was performed by using JASCO(UNIDEC-100-II, UNIFLOW-211) and Shimadzu(C-R1B) instruments: column, JASCO Finepak SIL C_{18}; solvent, CH_3CN: H_2O=2:1; retention times(min), 5(2.3) benzaldehyde(inner standard)(2.9) 4 (3.4) 6(6.6) 1(8.3).
12) The absorption at 370 and 307 nm were used for the monitor of 1 and 4, respectively.
13) Preliminary results suggest that the protonation of carbamoyl group leads to the deactivation of the dihydropyridine ring. The ease of protonation as judged from the red shift of absorption maxima near 350-360 nm was in the order of 3> 2> 1.
14) Here, hydride means "hydride equivalent" without making distinction between one-step H^- transfer and multistep e^-, H^+, e^- transfer which are the subject of recent controversy (see example, Powell and T.C. Bruice, J. Am. Chem. Soc., 105, 7139(1983)).
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