CHEMISTRY LETTERS, pp. 297-300, 1977. Published by the Chemical Society of Japan

THE IMPORTANCE OF GENERAL ACID CATALYSIS IN THE DIHYDRONICOTINAMIDE REDUCTION OF CARBONYL SUBSTRATES

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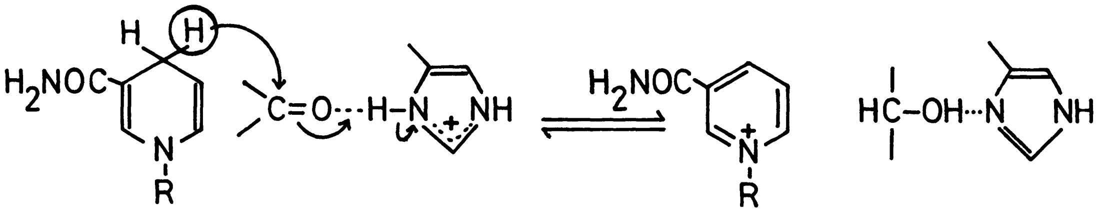
The reduction of hexachloroacetone by 1-benzyl-1,4-dihydronicotinamide in absolute ethanol and acetonitrile is general acid catalyzed. This mechanism is important in connection with the function of some NADH dependent enzymes in which the reaction can be aided by a general acid catalysis.

It has been reported that the ortho-hydroxy group plays a crucial role in the dihydronicotinamide reduction of the $>$C=O, $>$C=S, and $>$C=N double bonds attached to the aromatic ring.[1-4] We also found that the formyl group of 4(5)-(o-formylphenyl)imidazole hydrochloride readily undergoes reduction by 1-benzyl-1,4-dihydronicotinamide(BzlNH).[5] Furthermore, Wallenfels et al.[6] demonstrated that the addition of acetic acid appreciably improves the yield of dihydronicotinamide reduction of electron-deficient $>$C=C$<$ double bonds in ethanol. These results implicate that the dihydronicotinamide reduction of the carbonyl group and its analogs may be facilitated by general acid catalysis. In fact, recent X-ray crystallographic studies of NADH dependent enzymes suggest that the protonated imidazole of the histidine residue acts as a general acid during the reduction process.[7,8]



(1)

In this study, we investigated the influence of the added acid on the reaction of BzlNH and hexachloroacetone(HCAc),[9] and found that the reaction is general acid catalyzed(at least partially). The employed acids are acetic acid and the hydrochloride of tertiary amines, 2,6-lutidine, and imidazole. The hydrochloride of primary and secondary amines was not used, in order to avoid the possible formation of the Schiff base with HCAc.

BzlNH reacts with HCAc in absolute ethanol at room temperature under nitrogen stream to give 1-benzylnicotinamide chloride(1-benzyl-3-carbamoylpyridinium chloride) and hexachloroisopropanol.[12]

The kinetic study was carried out at 30°C under the pseudo-first-order condition($[\mathrm{HCAc}] \gg [\mathrm{BzlNH}] \simeq 10^{-4}$ M), and the progress of the reaction was followed spectrophotometrically at 354 nm (λ_{max} of BzlNH). In the first place, the reaction was confirmed to be first-order in BzlNH and HCAc([HCAc] = 0.01-0.1 M), and the second-order rate constant(k_2) was estimated to be 0.0525 $M^{-1}s^{-1}$ in absolute ethanol and 0.337 $M^{-1}s^{-1}$ in acetonitrile. Although the disappearance of BzlNH was markedly accelerated by addition of acids, uv spectra showed also an absorption increase at around 290 nm. This indicates the occurrence of the acid-catalyzed decomposition of BzlNH to 1,4,5,6-tetrahydronicotinamide.[13)] Thus, the observed rate of disappearance of BzlNH in the presence of acids is described by Eq. 2,

$$v_{obsd} = -\frac{d[\mathrm{BzlNH}]}{dt} = v_{red} + k_d[\mathrm{BzlNH}][\mathrm{Acid}] \qquad (2)$$

where k_d is the second-order rate constant for the acid catalyzed decomposition of BzlNH[14)] and v_{red} the overall reduction rate by BzlNH. The k_d term was separately estimated in the absence of HCAc, and v_{red} was obtained by subtracting this value from v_{obsd}. The increases in the reduction rate obtained by the addition of acid(1 M in absolute ethanol) are, for example, 5 times for 2,6-lutidine·HCl and 2 times for triethylamine·HCl.

Plots of v_{red} vs. [Acid](0.01-1.0 M) gave good linear relations($r > 0.998$), and k_{ga}(rate constant for general acid catalysis; Eq. 3) for five acids was determined from the slope by the least-squares method.

$$v_{red} = k_2[\mathrm{BzlNH}][\mathrm{HCAc}] + k_{ga}[\mathrm{BzlNH}][\mathrm{HCAc}][\mathrm{Acid}] \qquad (3)$$

The logarithm of k_{ga} was plotted against pK_a(in water) of the added acid(Fig. 1). If the plot for acetic acid is excluded, plots of log k_{ga} vs. pK_a(in water) give good straight lines with the slope of -0.20(in absolute ethanol) and -0.18 (in acetonitrile). Similarly, plots of log k_d vs. pK_a(in water) for four hydrochloride salts give straight lines(plots not shown) with the slope of -0.92(in absolute ethanol) and -0.95(in acetonitrile). The downward deviation of the plots for acetic acid(both k_{ga} and k_d) is attributed to the fact that pK_a in water is employed. Although 4-picoline shows similar pK_a values in water(6.02) and in methanol(6.09), the pK_a of acetic acid(4.76 in water) is estimated to be 9.7 in methanol.[15)]

The amine hydrochlorides can act as general acids or specific acids. Assuming the specific catalysis, the hypothetical second-order rate constant for the reduction of protonated HCAc is estimated to be 10^{15}-10^{17} $M^{-1}s^{-1}$(see Ref. 16), which is more than several orders of magnitude greater than that of the diffusion-controlled reaction($\approx 10^{11}$ $M^{-1}s^{-1}$). This difference cannot be explained even by the possible pK_a shifts for protonated HCAc in organic media. Therefore, the specific acid catalysis may be dismissed, and amine hydrochlorides would act as general acid during the course of the BzlNH reduction. van Eikeren and Grier[18)] mention that the reduction of trifluoroacetophenone in acetonitrile displays general acid catalysis.

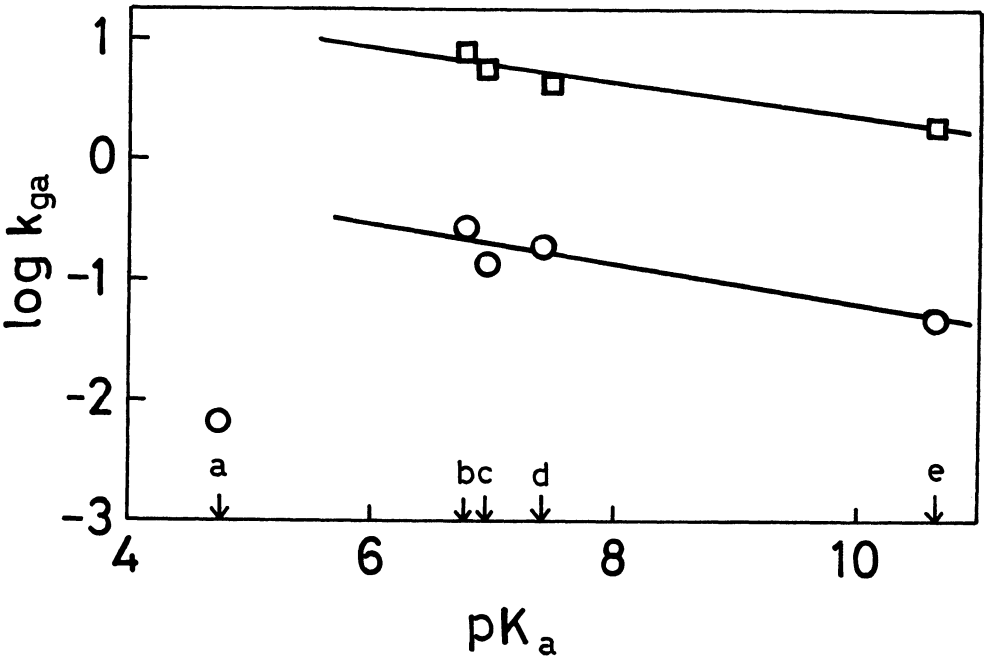


Fig. 1. Logarithm of k_{ga} ($M^{-2}s^{-1}$) vs. pK_a in water.
(○) absolute ethanol, (□) acetonitrile. (a) acetic acid, (b) 2,6-lutidine•HCl, (c) imidazole•HCl, (d) N-methylmorpholine•HCl, (e) triethylamine•HCl.

The fact that BzlNH reduction can be general acid catalyzed provides the following important implications. (1) In NADH dependent reactions, negative charge is developed on the oxygen in the transition state. Since negative charge is destabilized by hydrophobic environments as well as by aprotic solvents,[18] the enzymatic reduction in relatively hydrophobic environments of apoenzymes would become energetically unfavorable, unless hydrogen transfer is aided by general acid catalysis. (2) The higher is the pK_a of product alcohols, the more becomes necessary the aid of general acid catalysis(Jencks' libido rule[19]). Therefore, general acid catalysis would become more important in the reduction of inactivated carbonyl substrates. (3) Based on the principle of the microscopic reversibility, the reduction of nicotinamides by alcohols, the model studies of which have few precedents, would become possible by the aid of general base catalysis.

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16) pK$_a$(in water) for the conjugate acid of HCAc would be about -9(or below).17) Since the the rate constant for the reduction in ethanol is larger than 0.1 M^{-1} s^{-1} for a amine hydrochloride with pK$_a$ = 7(Fig. 1), the hypothetical second-order rate constant for the reduction of protonated HCAc would have to be 10^{15}-10^{17} $M^{-1}s^{-1}$(for the detail of calculation, see E. H. Cordes and W. P. Jencks, J. Am. Chem. Soc., 84, 4319(1962)).

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(Received January 22, 1977)