A Second Change in Rate-Determining Step and a Nonlinear Brønsted Relationship for General Base Catalysis of 2-Methylthiosemicarbazone Formation[1]

Sir:

We wish to report that the condensation of 2-methylthiosemicarbazide with *p*-chlorobenzaldehyde undergoes a second change in rate-determining step from carbinolamine dehydration to amine addition in alkaline solutions and that the Brønsted plot for general base catalysis of the addition step is nonlinear, suggesting that a transport step involving the catalyst is kinetically significant for this simple carbonyl addition reaction.

The pH–rate profile for 2-methylthiosemicarbazone formation in the absence of buffers (Figure 1, solid

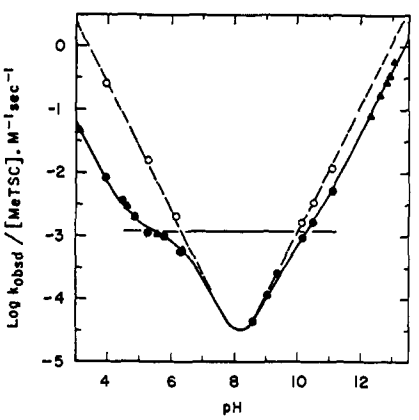
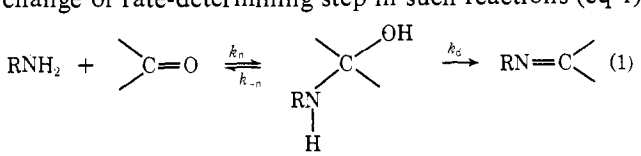


Figure 1. Dependence on pH of the second-order rate constants for *p*-chlorobenzaldehyde 2-methylthiosemicarbazone formation in water at 25° and ionic strength 1.0 (KCl): solid circles, rates extrapolated to zero buffer concentration; open circles, rates (for the dehydration step) extrapolated to infinite buffer concentration; solid triangles, rates determined in the absence of buffer. The lines are theoretical for: $k_n\,(M^{-1}\ sec^{-1}) = 63a_{H^-} + 1.2 \times 10^{-3} + 7.75a_{OH^-}$; $k_d\,(sec^{-1}) = 1.1 \times 10^4 a_{H^+} + 46a_{OH^-}$; $K_{ov}\,(M^{-1}) = 0.23$.

symbols) shows two breaks, at approximately pH 6 and 10, indicating changes in rate-determining step. A change of rate-determining step in such reactions (eq 1)



is generally observed in acidic solutions with increasing pH as the dehydration step becomes slow relative to the pH-independent addition step (horizontal line, Figure 1),[2] and a second change in rate-determining step should occur at high pH values, as base-catalyzed dehydration becomes fast, unless there is a rapid base-catalyzed addition step.[3] In this reaction the small, but unequivocal, break at high pH means that a base-catalyzed addition step has become partially rate determining. This change in rate-determining step is also manifested at both low[4] and high pH values by a non-

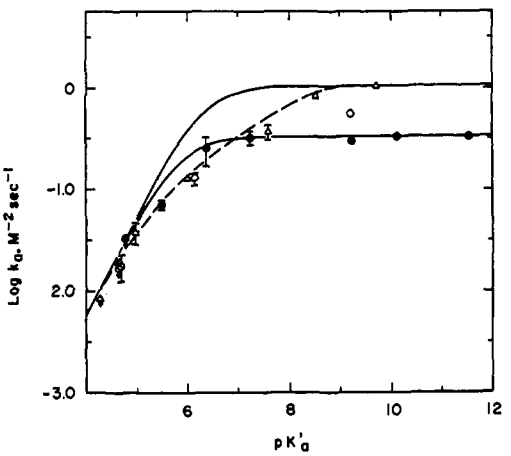
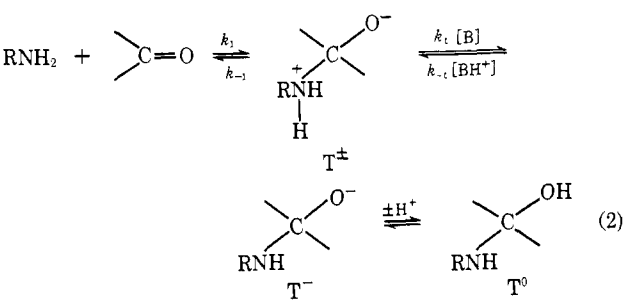


Figure 2. Brønsted plot for general base catalysis by oxygen monoanions (○), dianions (△), and cyclic tertiary amines (●) of 2-methylthiosemicarbazide addition to *p*-chlorobenzaldehyde at 25° and ionic strength 1.0. The arrows indicate upper limits of k_a for bases which gave no observable catalysis.

linear increase in rate with increasing buffer concentrations. The rate levels off at high buffer concentrations, at which the dehydration step (which is relatively insensitive to buffer catalysis) becomes entirely rate determining; the rate constants for this step are shown as the open circles in Figure 1.

The Brønsted plot for general base catalysis of the addition step by oxygen mono- and dianions and by cyclic, unhindered tertiary amines is shown in Figure 2. Catalytic constants were obtained from experiments in the pH range 10–12; the observed rate constants were corrected for the contribution of the dehydration step at each buffer concentration.[3] The points for basic oxyanions and amines fall on different lines, but both Brønsted lines are curved. Catalysis by amines displays little or no sensitivity to amine basicity with basic amines ($\beta < 0.2$) but drops sharply for weakly basic amines ($\beta \geqslant 0.5$); a similar transition is observed for oxygen dianions with limiting values of $\beta \geqslant 0.6$ and $\beta \leqslant 0.2$ for weakly and strongly basic oxyanions, respectively. The solid lines in Figure 2 show the limiting transition from a slope of $\beta = 0$ to $\beta = 1.0$ for a diffusion-controlled proton transfer reaction and the dashed line shows the degree of curvature actually observed for simple proton transfer from ammonium ion to oxyanions;[5] the experimental points are consistent with such a nonlinear relationship.

The nonlinear Brønsted plot establishes that there is a change in the nature of the rate-determining step for catalysis of the addition reaction by weak and strong bases. The simplest interpretation is that simple diffusion-controlled proton transfer is rate determining in one or the other direction (eq 2). According to this



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interpretation, base catalysis permits the formation of product by removing a proton from the unstable dipolar intermediate $T^{\pm}$, which would otherwise break down rapidly to starting materials.[6] Other, more complex, interpretations are possible, but the data suggest (a) that the addition reaction involves at least two steps and an intermediate and (b) at least one of these steps involves transport of the catalyst for proton transfer.

The equilibrium constant K_1 for the formation of $T^{\pm}$ from amine and aldehyde may be estimated from the overall equilibrium constant for the addition step, K_{ov}, and the equilibrium constant $K^{\pm}$ for the formation of $T^{\pm}$ from T^0. The extreme instability of $T^{\pm}$ is apparent in the value $\log K_1 = -11.3 \pm 1.0$, obtained from estimates[7] of $\log K_{ov} = -0.64$ and $\log K^{\pm} = -10.7 \pm 1.0$. The observed rate constant of the 3-quinuclidinol-catalyzed reaction then corresponds to a value of $\log k_t = 10.8 \pm 1.0$ (M^{-1} sec^{-1}) for this strong base catalyst. Thus, if $T^{\pm}$ is formed as an intermediate, it must react with the catalyst with a rate constant in the range expected for a diffusion-controlled reaction.[5] The expulsion of methylthiosemicarbazide ($pK_a' = 1.2$) from $T^{\pm}$ (k_{-1}) must be extremely fast; the corresponding adducts formed from still weaker nucleophiles will have too short a lifetime to exist as intermediates, so that the addition of such nucleophiles must occur through a more or less concerted mechanism of catalysis.

(6) J. E. Reimann and W. P. Jencks, *J. Amer. Chem. Soc.*, **88**, 3973 (1966).

(7) K_{ov} was calculated from an observed equilibrium constant of 8.1 M^{-1} for the addition of 2-methylthiosemicarbazide to pyridine-4-aldehyde (25°, ionic strength 1.0) and the relationship $K_{ov}^{pyr\text{-}4\text{-}ald}/K_{ov}^{PCBA} = 35$ (E. G. Sander and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 6154 (1968)). The value of $K^{\pm}$ was estimated from the value $\log K^{\pm} = -1.3 \pm 0.6$ for carbinolamines formed from primary aliphatic amines[8] and the assumption that substituent effects on the ionization of substituted ammonium ions are additive. The same value was obtained from estimates of the individual ionization constants for the interconversion of $T^{\pm}$ and T^0 (ref 8; H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **79**, 5441 (1957); S. Takahashi, L. A. Cohen, H. K. Miller, and E. G. Peake, *J. Org. Chem.*, **36**, 1205 (1971)).

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The Uncatalyzed Aminolysis of Acetylimidazole. A Limiting Product-Like Transition State for Acyl Transfer[1]

Sir:

We wish to report an unusually large sensitivity to the basicity of the attacking amine in the uncatalyzed aminolysis of acetylimidazole. The value of β_{nuc} of approximately 1.6 indicates that little or no proton removal has occurred from the attacking amine in the product-like transition state of this reaction.

Acyl compounds with good leaving groups (phenyl acetates,[2] acetylimidazolium ion[3]) readily undergo aminolysis without proton removal from the attacking amine, as shown by the similar reactivities of primary, secondary, and tertiary amines. These reactions generally show a large sensitivity to the basicity of the attacking amine with values of β_{nuc} (the slope of plots of $\log k$ against the pK_a of the conjugate acid of the amine) in the range 0.8–1.0. With poor leaving groups (*e.g.*, methyl formate[4]) this uncatalyzed reaction path is unfavorable and leaving group expulsion is made possible by proton transfer. Free acetylimidazole, with a leaving group of $pK_a = 14.2$,[5] appears to be in an intermediate position. Although the predominant aminolysis reaction occurs with general base catalysis and weakly basic amines simply act as general base catalysts of hydrolysis,[3] strongly basic amines react with acetylimidazole in an uncatalyzed, second-order aminolysis reaction which is faster than general base catalyzed hydrolysis and exhibits a value of β_{nuc} of approximately 1.6 (Figure 1). The rate constants (Table I) were obtained from the intercepts of plots of observed second-order rate constants against amine concentration, corrected for any reaction of amine with acetylimidazolium ion (based on rate constants obtained at lower pH values).[3]

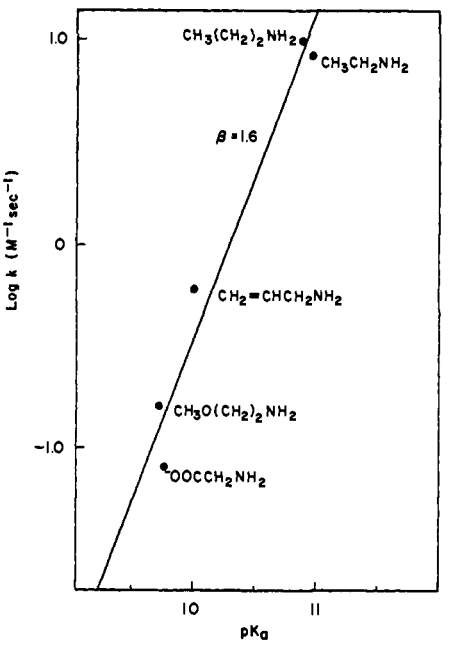

Figure 1. Dependence of the second-order rate constants for the uncatalyzed aminolysis of free acetylimidazole on the basicity of the amine at 25°, ionic strength 1.0.

Table I. Rate Constants for the Uncatalyzed Reactions of Primary Amines with Free Acetylimidazole[a]

Amine	pK_a	k, M^{-1} sec^{-1}
n-Propylamine	10.89	10
Ethylamine	10.97	8.2
Allylamine	10.02	0.6
Glycine	9.76	0.08
Methoxyethylamine	9.72	0.16

[a] 25°, ionic strength 1.0 (KCl).

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