and 178. *Anal.* Calcd for $C_{21}H_{18}$: C, 93.29; H, 6.71. Found: C, 93.16; H, 6.84.

Irradiation of 30 mg of **4** and 50 mg of **5** for 10 hr under the same conditions resulted in the recovery of unreacted starting materials in quantitative amounts.

Hydrogenation of the Valence Tautomer 12. A solution of 25 mg (0.09 mmol) of **12** in 30 ml of ethanol was hydrogenated over 15 mg of 10% palladium on charcoal at atmospheric pressure until 1 equiv (3 ml) of hydrogen was consumed. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. Recrystallization from ethanol gave 20 mg (80%) of the dihydro derivative **13** as colorless prisms: mp 126–128°; ir (KBr) 2920, 1470, 1460, 750, and 740 cm^{-1}; nmr ($CDCl_3$) δ 1.65 (m, 6 H), 2.05 (m, 4 H), 4.01 (d, 1 H, J = 3.0 Hz), 4.07 (d, 1 H, J = 2.0 Hz), and 7.10 (m, 8 H). *Anal.* Calcd for $C_{21}H_{20}$: C, 92.60; H, 7.40. Found: C, 92.45; H, 7.54.

Photolysis of Adducts 4, 5, and 10 through a Quartz Filter. **4**, **5**, and **10** (30 mg) were dissolved with 50 ml of benzene, respectively. Each solution was irradiated for 3.5 hr at room temperature with a 100-W high-pressure mercury lamp fitted with a quartz filter under nitrogen. The solvent was removed under reduced pressure and the residue was analyzed by tlc and glpc. The results are given in Table II.

Quantum Yield Determination. A solution of 1.54 mg (0.0087 mmol) of **1** and 92 mg (1.0 mmol) of **2** in 100 ml of ethanol was prepared. The solution in a quartz tube (3.5 ml) was degassed with nitrogen and irradiated at 3650 Å using a filter. Light output was monitored by potassium ferrioxalate actinometry according to the method of Hatchard and Parker.[27] The consumption of **1** was monitored by uv spectroscopy using 0–0 band of absorption (λ_{max} 374 nm). Several measurements were taken at different conversions (<10% conversion) and the average value was used. The result was shown in Table IV.

Fluorescence Quenching. Fluorescence intensities were measured with an Hitachi MPF-2A fluorescence photometer, using an excitation wavelength of 374 nm. Samples (3 ml) containing 2.21×10^{-6} M of anthracene (**1**) and varing concentrations of cycloheptatriene (**2**) in ethanol were placed in a quartz cell. The intensities were measured three times for each cell and an average value for each sample was used. The results are shown in Figure 2.

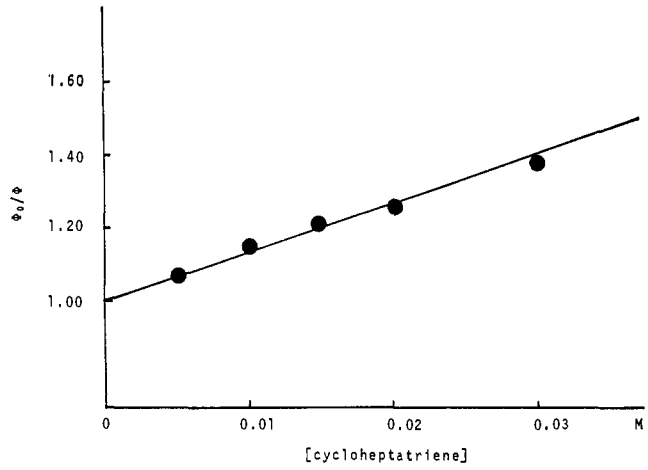

Figure 2. Stern-Volmer plot of fluorescence quenching of anthracene (**1**) by cycloheptatriene (**2**) in ethanol; slope = 13.5 M^{-1}.

Acknowledgment. The authors wish to thank Professor T. Goto of the Faculty of Agriculture, Nagoya University, for measurement of fluorescence spectroscopy and Dr. T. Takagi of the Faculty of Engineering, Nagoya University, for many helpful discussions and determination of quantum yield.

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Mechanism and Catalysis of 2-Methyl-3-thiosemicarbazone Formation. A Second Change in Rate-Determining Step and Evidence for a Stepwise Mechanism for Proton Transfer in a Simple Carbonyl Addition Reaction[1]

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Abstract: 2-Methyl-3-thiosemicarbazone formation from *p*-chlorobenzaldehyde undergoes a change in rate-determining step at high pH, similar to that at low pH, from rate-determining dehydration of the carbinolamine intermediate to partially rate-determining attack of the nucleophile on the carbonyl group. The attack step is subject to general base catalysis. Brønsted plots for tertiary amines and oxygen anions exhibit breaks for bases of pK_a less than 6. This curvature is consistent with that expected for a simple rate-determining proton transfer reaction between the dipolar addition intermediate $T^{\pm}$ and the catalyzing base. However, the break occurs at a higher pK_a than expected from the estimated pK_a value for $T^{\pm}$ of 3.1. Better agreement is found for a preassociation mechanism with rapid, stepwise proton transfer within an encounter complex after the formation of $T^{\pm}$. According to this mechanism, N–C bond formation within an encounter complex that contains the base catalyst is rate determining with strong bases and there is a change to rate-determining proton transfer with weaker bases. The magnitude of the observed catalytic constants is consistent with that expected for such a mechanism, but is significantly smaller than expected for a concerted mechanism. General acid catalysis of 2-methyl-3-thiosemicarbazide addition to *p*-chlorobenzaldehyde by carboxylic and cacodylic acids closely resembles that observed for the addition of other weakly basic amines (α = 0.2). It is suggested that general acid, unlike general base, catalysis involves some stabilization of the transition state for carbon-nitrogen bond formation by the catalyst.

A growing body of evidence concerning general acid–base catalysis of complex reactions involving proton transfers to or from electronegative atoms suggests that in some cases these proton transfers proceed by discrete steps, rather than by a process that is

(1) Supported by grants from the National Science Foundation (GB 4648) and the National Institute of Child Health and Human Development of the National Institutes of Health (HD 01247).

concerted with other atomic motions along the reaction coordinate.[2-9] Experimental support for the participation of kinetically significant stepwise proton transfer processes in complex acid and base catalyzed reactions includes changes in rate-determining step which cannot be accounted for by bond forming and breaking processes involving carbon,[2,3,4a] breaks in Brønsted plots or a Brønsted slope of 1.0 for general acid or base catalysis,[2,4-6] other sharp breaks in structure–reactivity correlations,[7] solvent isotope effects,[8] and dependence of the reaction rate on the viscosity of the medium.[9]

The addition of nitrogen nucleophiles to the carbonyl group has been extensively studied,[10] and the general nature of the rate-determining processes involving the carbon, oxygen, and nitrogen atoms is well defined. These reactions ordinarily proceed by a stepwise mechanism (eq 1–1c) with carbinolamine

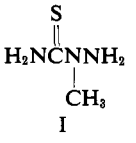
$$RNH_2 + >C{=}O \underset{k_{-n}}{\overset{k_n}{\rightleftharpoons}} RN(H)-C(OH)< \xrightarrow{k_d} RN{=}C< \quad (1)$$

$$k_n = k_n^0 + k_n^H[H^+] + k_n^{OH}[OH^-] + \Sigma k_n^{cat}[cat] \quad (1a)$$

$$k_{-n} = k_{-n}^0 + k_{-n}^H[H^+] + k_{-n}^{OH}[OH^-] + \Sigma k_{-n}^{cat}[cat] \quad (1b)$$

$$k_d = k_d^H[H^+] + k_d^{OH}[OH^-] + \Sigma k_d^{cat}[cat] \quad (1c)$$

formation (k_n) rate determining at acidic pH and dehydration (k_d) rate determining at neutral and alkaline pH values. With weakly basic nucleophiles, each step is subject to both acid and base catalysis. The change in rate-determining step at low pH, manifested by a break in the pH–rate profile, is a consequence of the fact that the uncatalyzed attack of the nucleophile (k_n^0) becomes slower than the acid catalyzed dehydration step ($k_d^H[H^+]k_n/k_{-n}$) as the pH is decreased. A second change in rate-determining step and a second, symmetrical break in the pH–rate profile should occur at high pH as the uncatalyzed attack step becomes slower than the base catalyzed dehydration step ($k_d^{OH}[OH^-]k_n/k_{-n}$), unless there is also a rapid base-catalyzed pathway for the attack step. We report here the observation of such a change, from rate-determining dehydration to addition, for the formation of the imine from 2-methyl-3-thiosemicarbazide (I)



I

and *p*-chlorobenzaldehyde at high pH. This has made possible a detailed study of the mechanism of the base catalyzed addition step. The nonlinear Brønsted plot for general base catalysis of this step suggests that it proceeds through a stepwise mechanism of proton transfer and carbon–nitrogen bond formation. These results have been reported in a preliminary communication.[11]

Experimental Section

Materials. 2-Methyl-3-thiosemicarbazide was prepared from methylhydrazine hydrochloride and potassium thiocyanate and recrystallized twice by the method of Jensen, *et al.*[12] Contamination by the weakly acidic 1-methyl isomer was removed by brief treatment with 1 *M* potassium hydroxide at room temperature followed by thorough washing with cold water and recrystallization, if necessary.

Dichloromethylphosphonyl dichloride was prepared following the method of Kinnear and Perren,[13] except that the initially formed aluminum complex was hydrolyzed by the addition of ice (14 mol) to the reaction mixture after dilution with methylene chloride and cooling in a Dry Ice–ethanol bath. The distilled dichloride, bp 67–69° (1.6 mm), was hydrolyzed in water,[14] and the acid, isolated after prolonged vacuum drying of the hydrolysate over potassium hydroxide, was purified as the monopotassium salt by neutralization of an aqueous solution of the acid to approximately pH 3 and crystallization of the salt from water–ethanol. The product, mp 245–248° dec, had an equivalent weight of 206 (theoretical, 203) determined by titration with potassium hydroxide.

Ethylphosphonic acid was prepared by hydrolysis[15] of the diethyl ester (Pfaltz and Bauer) by refluxing in 8 *M* hydrochloric acid for 15 hr. After solvent removal, the acid was subjected to prolonged drying *in vacuo* over sodium hydroxide to remove hydrochloric acid. The monopotassium salt was formed by neutralization of a concentrated aqueous solution of the crude acid (mp 52–60°) to pH 5 with potassium hydroxide, evaporation to dryness, and recrystallization of the product from methanol–ethanol, or by neutralization of a methanolic solution of the acid with methanolic potassium hydroxide and crystallization from methanol–isopropyl alcohol. Titration of material prepared by the first method indicated that it contained about 4 mol % of free acid. This was converted to the monopotassium salt by addition of the calculated amount of methanolic potassium hydroxide to a methanol solution of the salt and crystallization by the addition of ethanol. Titration of the purified product gave an equivalent weight of 150 (theoretical, 148).

Trichloromethylphosphonic acid (Pfaltz and Bauer) was converted to the dipotassium salt by neutralization to pH 7.8 and recrystallization from ethanol–water. Titration with 1 equiv of potassium hydroxide gave a molecular weight of 315 (theoretical for the dihydrate, 312).

Anal. Calcd for $K_2CCl_3O_3P \cdot 2H_2O$: C, 3.85; H, 1.28; Cl, 34.90. Found: C, 4.02; H, 1.09; Cl, 35.1.

Potassium β-glycerophosphate and potassium methylarsonate were prepared from the corresponding barium salts, which were precipitated from water–ethanol after treatment of solutions of the sodium salts with barium chloride. Barium β-glycerophosphate was dissolved in water containing a small amount of hydrochloric acid and barium sulfate was precipitated by the addition of a stoichiometric amount of potassium sulfate (calculated from the dry weight of the barium salt). After filtration and evaporation of the solution, potassium β-glycerophosphate was obtained as a powder containing a mixture of the mono- and dipotassium salts and approximately 5% (weight) of a neutral impurity which corresponded to the amount of potassium chloride expected to have arisen from the hydrochloric acid added to barium β-glycerophosphate. Barium methylarsonate was treated with a stoichiometric quantity of sulfuric acid, calculated from titration of the barium salt with hydrochloric acid. After filtration the solution was neutralized to approximately pH 11 with potassium hydroxide. The final

(2) R. E. Barnett and W. P. Jencks, *J. Amer. Chem. Soc.*, **91**, 2358 (1969).
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(11) J. M. Sayer and W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 3262 (1972).
(12) K. A. Jensen, U. Anthoni, B. Kägi, C. Larsen, and C. Th. Pedersen, *Acta Chem. Scand.*, **22**, 1 (1968).
(13) A. M. Kinnear and E. A. Perren, *J. Chem. Soc.*, 3437 (1952).
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concentration of dipotassium methylarsonate in the solution was determined by potentiometric titration with hydrochloric acid.

Other organic compounds were commercial products, and were purified by distillation, sublimation, or crystallization. Inorganic salts were reagent grade and were used without further purification. Glass-distilled water was used in all experiments. Concentrated ethanolic solutions of *p*-chlorobenzaldehyde were prepared and diluted with water on the day of use. Final reaction mixtures at pH >7 contained approximately 10^{-4} *M* EDTA.

pK_a' Determinations. The pK_a' of 2-methyl-3-thiosemicarbazide, at 25° and ionic strength 1.0 (KCl), was found to be 1.20 by spectrophotometric titration at 250 and 230 nm of approximately 5×10^{-5} *M* methylthiosemicarbazide. The absorbance of the neutral amine, A_{RNH_2}, was measured in 0.1 *M* phosphate buffer, pH 6.48, and the absorbance change for complete protonation was obtained from the ordinate intercepts of plots of $(A_{obsd} - A_{RNH_2})$ against $(A_{obsd} - A_{RNH_2})/a_{H^+}$ (at 250 nm) or $(A_{RNH_2} - A_{obsd})$ against $(A_{RNH_2} - A_{obsd})/a_{H^+}$ (at 230 nm). The pK_a' values of most base catalysts used were determined by potentiometric titration at 25° of 0.05 *M* solutions, adjusted to give ionic strength 1.0 (KCl) at the midpoint of the titration. The pK_a' of nicotinic acid was determined spectrophotometrically from the absorbance at 260 nm of a 1.5×10^{-4} *M* solution in a series of buffers of pH 3.11–7.12.

Kinetics. Rates of the reaction of 2-methyl-3-thiosemicarbazide with *p*-chlorobenzaldehyde at 25° and ionic strength 1.0 were followed spectrophotometrically at 313 (or 315) nm, using a Zeiss PMQII spectrophotometer equipped with a Beckman recorder, or a Gilford Model 2000 recording spectrophotometer. Pseudo-first-order rate constants were determined for reactions having half-times $\leq$15 min using $1\text{–}2 \times 10^{-5}$ *M p*-chlorobenzaldehyde and 0.01 or 0.02 *M* 2-methyl-3-thiosemicarbazide. The reaction proceeds to completion, as indicated by the observation of the same absorbance change and second-order rate constant for the reaction of 1.3×10^{-5} *M p*-chlorobenzaldehyde with 0.01 and 0.02 *M* methylthiosemicarbazide, pH 12.9; the product has an ultraviolet spectrum that closely resembles that of the neutral unsubstituted thiosemicarbazone. Between pH 3.5 and 11.5, where the reaction is slow, initial rates of reaction were determined using 0.01–0.05 *M* nucleophile and approximately 7.5×10^{-4} *M* aldehyde. The absorbance of the product at time infinity was obtained by allowing the reaction of a sample of the aldehyde solution with 0.03 *M* 2-methyl-3-thiosemicarbazide to proceed to completion in the presence of 0.1 *M* potassium hydroxide. After neutralization, an aliquot of this reaction mixture was added to a solution having the same composition as the reaction mixture used for each kinetic determination. Small corrections were made for the absorbance of a blank solution of methylthiosemicarbazide incubated with potassium hydroxide for the same length of time as the reaction mixture containing *p*-chlorobenzaldehyde.

The addition reaction catalyzed by bases of pK_a' less than 10 was normally followed at pH 10.9–11.2, maintained with potassium hydroxide. In most experiments the pH was measured at the beginning and the end of each kinetic run, and runs which exhibited a change in pH of >0.04 unit were discarded. Corrections for the effect on the baseline rate of small differences in pH among kinetic runs at varying catalyst concentrations were made by one of three methods: (a) graphically, from interpolation of semilogarithmic plots of k_{obsd} against pH at different catalyst concentrations; (b) from the formula $k_{std} = k_{obsd} + \Delta k_0$, where Δk_0 is the difference between the baseline rates at the observed pH value and some standard pH, calculated from the steady-state rate law of eq 2,

$$k_0\ (M^{-1}\ \text{sec}^{-1}) = \frac{(k_n^{OH}[OH^-] + k_n^0)(K_{ad}k_d^{OH}[OH^-])}{k_n^{OH}[OH^-] + k_n^0 + K_{ad}k_d^{OH}[OH^-]} \quad (2)$$

in which k_n^{OH} and k_n^0 are the rate constants for the hydroxide ion catalyzed and uncatalyzed addition step and $K_{ad}k_d^{OH}$ is the apparent rate constant for hydroxide ion catalyzed dehydration; (c) by correction of k_{obsd} at each pH for the contribution of the dehydration rate, $K_{ad}k_d^{OH}[OH^-]$, at that pH, to give a value of the rate constant for the addition step at the observed pH, which was then corrected to a standard pH value by the formula $k_{std}^{addn} = k_{obsd}^{addn} + k_n^{OH}([OH^-]_{std} - [OH^-]_{obsd})$. Provided pH variations were small, the choice of method used for making pH corrections did not significantly affect the derived rate constants.

Since both the addition and the dehydration step are kinetically significant below pH 6.5 and above pH 9.5, rate constants for the addition step at varying catalyst concentrations were calculated from eq 3. At a given pH, k_∞, the limiting rate constant at infinite

$$k_{addn} = \frac{k_{obsd}}{1 - k_{obsd}/k_\infty} \quad (3)$$

catalyst concentration, is equal to $K_{ad}k_d^{OH}[OH^-]$, since the dehydration step is not significantly catalyzed by general bases under the experimental conditions used. Alternatively, the catalytic constants were determined from plots of $1/(k_{obsd} - k_0)$ against 1/[B], or $1/(k_\infty - k_{obsd})$ against [B], where [B] is the concentration of general base catalyst and k_0 is the observed rate constant in the absence of added catalyst. Using both types of plots, and a method of successive approximations for k_0 and k_∞ if necessary, the best values of k_0 and k_∞ were calculated for a given buffer catalysis experiment. For both types of plots the ordinate intercept is $1/(k_\infty - k_0)$; the slope of $1/(k_{obsd} - k_0)$ against 1/[B] is $(1/k^{cat})\{k_\infty/(k_\infty - k_0)\}^2$, and the slope of $1/(k_\infty - k_{obsd})$ against [B] is k^{cat}/k_∞^2. Analogous procedures were used to analyze the kinetic data on the acid limb of the pH–rate profile.

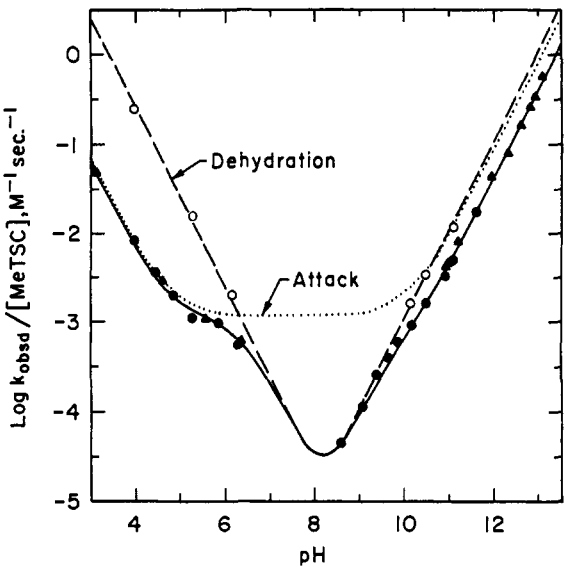


Figure 1. Dependence on pH of the second-order rate constants for the formation of *p*-chlorobenzaldehyde 2-methyl-3-thiosemicarbazone in water at 25° and ionic strength 1.0 (KCl): (●) rate constants extrapolated to zero buffer concentration; (▲) rate constants determined in the absence of buffer; (○) rate constants (for the dehydration step) extrapolated to infinite buffer concentration. The dotted line shows the rate constant k_n for the attack step and the dashed line shows the rate constant $K_{ad}k_d$ for the dehydration step. The lines are theoretical for the rate and equilibrium constants of Table I.

Equilibrium Constant for Carbinolamine Formation. The equilibrium constant, K_{ad}, for carbinolamine formation from 2-methyl-3-thiosemicarbazide and pyridine-4-carboxaldehyde (PA) was determined spectrophotometrically[16] from the initial decrease in absorbance at 290 nm, extrapolated to zero time, upon addition of approximately 0.01 *M* pyridine-4-carboxaldehyde to 0.02–0.10 *M* 2-methyl-3-thiosemicarbazide solutions in 0.4 *M* imidazole buffer, pH 7.65. A path length of 0.05 cm was used. The absorbance change resulting from complete conversion of pyridine-4-carboxaldehyde to its additon compound was equal to 99% of the total aldehyde absorbance at 290 nm, as estimated from the absorbance at 290 nm of the bisulfite addition compound. The equilibrium constant for addition of 2-methyl-3-thiosemicarbazide to *p*-chlorobenzaldehyde was calculated from the observed constant for pyridine-4-carboxaldehyde and the relationship[16] $K_{obsd}^{PA} = 35K^{PCBA}$.

Results

The dependence on pH of the observed rate constants for 2-methyl-3-thiosemicarbazone formation at zero buffer concentration is shown by the solid sym-

(16) E. G. Sander and W. P. Jencks, *ibid.*, 90, 6154 (1968).

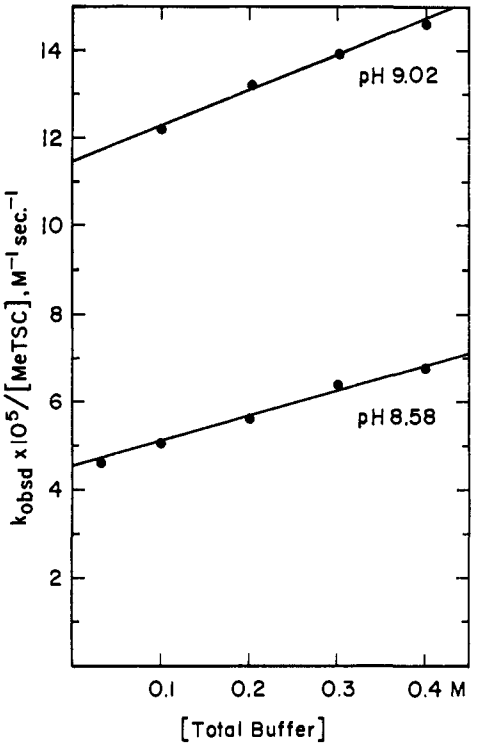


Figure 2. Catalysis of the dehydration step in 2-methyl-3-thiosemicarbazone formation from *p*-chlorobenzaldehyde at 25°, ionic strength 1.0, by triethylenediamine buffer, 40% (upper line) and 20% (lower line) free base. An average value of 2.4×10^{-4} M^{-2} sec^{-1} was calculated for $K_{ad}k_d^{cat}$ for general base catalysis of the dehydration step from the slopes of the two lines.

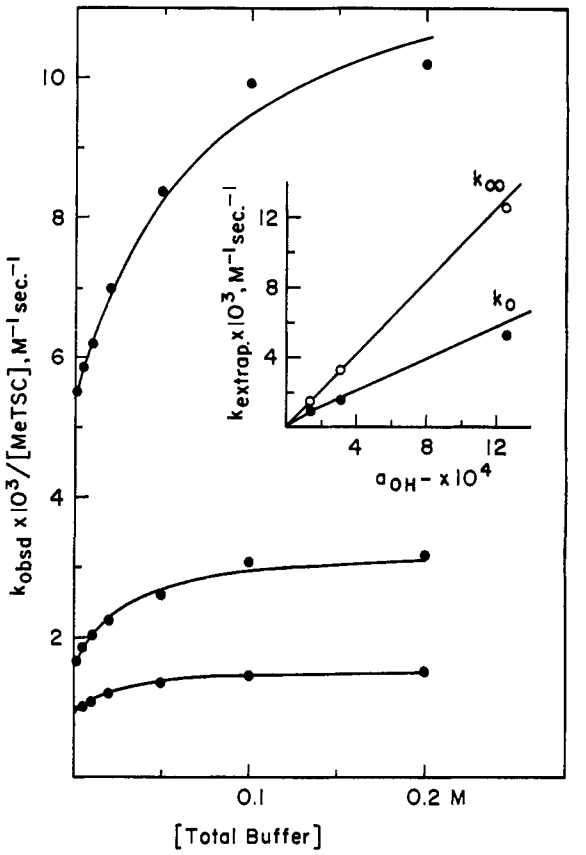


Figure 3. Effect of increasing concentration of 3-quinuclidinol buffers on the rate constants for 2-methyl-3-thiosemicarbazone formation in the pH region where a change in rate-determining step occurs. Lower line, 50% free base, pH 10.15; middle line, 70% free base, pH 10.50; upper line, 90% free base, pH 11.10. The solid lines are theoretical curves based on values of k_0 and k_∞ extrapolated from the data of each experiment as described in the Experimental Section, with $k_n^{cat} = 0.33$ M^{-2} sec^{-1} for quinuclidinol free base. The inset shows the dependence of the extrapolated values for the buffer-independent rate constants, k_0 and k_∞, on a_{OH^-}. The lines in the inset are based on the rate constants of Table I.

bols in Figure 1. The break in the pH–rate curve near pH 6 is attributed to the transition from rate-determining addition (k_n, eq 1) at low pH to rate-determining dehydration (k_d) at higher pH that is characteristic of carbonyl addition reactions of this type.[10,17,18] A small but definite second break in the linear relationship at high pH corresponds to a decrease of approximately 2.5-fold in the observed rate constant for the hydroxide ion catalyzed reaction at pH >11 relative to the value at pH 8.5–9.5. Such a break in the pH–rate relationship is predicted for the mechanism of eq 1 when $k_{-n}^{OH} \leq k_d^{OH}$, and the steady-state rate law at high pH values (where the acid-catalyzed reaction is insignificant) is given by eq 2.

The behavior of the reaction in the presence of buffer catalysts in different regions of the pH–rate curve provides confirmatory evidence for the change in rate-determining step at high pH. At pH 8.58 and 9.02 (Figure 2) the reaction is weakly catalyzed by triethylenediamine buffers and the rate increases linearly with increasing buffer concentration up to 0.4 *M*. Similar buffer catalysis is observed for the dehydration step in the formation of thiosemicarbazones[18] and other weakly basic hydrazone derivatives.[19] At higher pH, marked catalysis by very low concentrations of buffers is observed (Figure 3) and the dependence of the rate on catalyst concentration is nonlinear, even at buffer concentrations less than 0.05 *M*. Such behavior indicates a change in rate-determining step at these pH values, from a buffer-catalyzed to an uncatalyzed (or weakly catalyzed) process as the catalyst concentration is increased, and is analogous to the observed curvature in plots of rate against buffer concentration for general acid catalysis of semicarbazone[17] and thiosemicarbazone[18] formation. Under conditions in which buffer catalysis of the dehydration step is insignificant (at high pH and buffer concentrations less than 0.2 *M*) the steady-state rate law for the reaction, including terms for buffer catalysis, is given by eq 4. The rate constant, k_0, at zero buffer concentration is given by eq 2, and the limiting rate constant at high buffer concentrtions, k_∞, is $K_{ad}k_d^{OH}[OH^-]$. Rearrangement of eq 4 and linear extrapolation to zero and infinite buffer concentrations by the methods described in the Experimental Section yield values for k_0 and k_∞ which are plotted in the inset of Figure 3 and as the solid and open symbols, respectively, in Figure 1. The dashed line in Figure 1 represents the rate of the dehydration step, $K_{ad}k_d$. The limiting

$$k_{obsd}\ (M^{-1}\,sec^{-1}) = \frac{(k_n^0 + k_n^{OH}[OH^-] + k_n^{cat}[buffer])K_{ad}k_d^{OH}[OH^-]}{k_n^0 + k_n^{OH}[OH^-] + k_n^{cat}[buffer] + K_{ad}k_d^{OH}[OH^-]} \quad (4)$$

(17) E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, 84, 4319 (1962).
(18) J. M. Sayer and W. P. Jencks, *ibid.*, 91, 6353 (1969).
(19) J. M. Sayer, M. Peskin, and W. P. Jencks, *ibid.*, 95, 4277 (1973).

values of the rate constants at high buffer concentration are consistent with the observed rate constant for hydroxide ion catalyzed dehydration (extrapolated to zero buffer concentration) at pH 8.5–9.5. Nonlinear plots of rate constant against buffer concentration are also observed in the acid-catalyzed region below pH 6.5, and extrapolation of these curves to infinite buffer concentration gives the rate constant for hydronium ion catalysis of the dehydration step. Buffer-independent rate constants for the addition and dehydration steps of 2-methyl-3-thiosemicarbazone formation are summarized in Table I.

Table I. Buffer-Independent Kinetic Constants for 2-Methyl-3-thiosemicarbazone and Thiosemicarbazone Formation from *p*-Chlorobenzaldehyde at 25°, Ionic Strength 1.0[a]

	2-Methyl-3-thiosemicarbazide	Thiosemicarbazide[b]
pK_a'	1.20	1.88
k_n^0, M^{-1} sec^{-1}	1.2×10^{-3}	0.1
k_n^H, M^{-2} sec^{-1}	57[c]	140
k_n^{OH}, M^{-2} sec^{-1}	5.2[d]	≥ 80
k_{-n}^{OH}, M^{-1} sec^{-1}	23	≥ 47
k_d^H, M^{-1} sec^{-1}	1.0×10^{4}[c]	8.8×10^{3}
k_d^{OH}, M^{-1} sec^{-1}	31[d]	42
$K_{ad} = k_n/k_{-n}$, M^{-1}	0.23[e]	1.7

[a] Constants are defined for the processes shown in eq 1. The rate constants are based on hydroxide and hydronium ion concentrations. [b] Reference 18. [c] Calculated from the observed pH and the empirical relationship antilog $(-pH) = 0.9c_{H^+}$. [d] Calculated from the observed pH and the relationship antilog (pH − 14) $= 0.67c_{OH^-}$: J. F. Kirsch and W. P. Jencks, *J. Amer. Chem. Soc.*, **86**, 833 (1964). [e] Calculated from an observed equilibrium constant of 8.1 M^{-1} for addition to pyridine-4-carboxaldehyde and the relationship $K^{PCBA} = K_{obsd}^{PA}/35$ (ref 16).

General Base Catalyzed Addition. The catalytic constants for general base catalysis were determined as described in the Experimental Section. Quantitative interpretation of the nonlinear plots for buffer catalysis requires an accurate value of k_∞, the limiting rate constant at high buffer concentration. This rate constant may be obtained either from double reciprocal plots or from the rate constant $K_{ad}k_d^{OH}$, as described above. Values of k_∞ calculated by the latter method were corrected for small specific salt and medium effects of the added bases on the dehydration reaction measured at pH 8.8–8.9 (Table II). Most oxygen dianions cause approximately the same acceleration of $K_{ad}k_d^{OH}$ at a given concentration and with these bases potassium sulfate was used to maintain a constant dianion concentration and, hence, a known and essentially constant value of k_∞ in a given experiment. Cacodylate also increases $K_{ad}k_d^{OH}$, while acetate, propionate, and tertiary amines inhibit this step. As no suitable model compound was available for these bases, corrections for the medium effect at each base concentration were applied to the calculated value of $K_{ad}k_d^{OH}$ (in 1 M potassium chloride) before using this limiting rate constant to calculate the rate constants for the addition step. No corrections were applied for the strongly basic amines triethylenediamine, 3-quinuclidinol, or quinuclidine; the good agreement of the extrapolated k_∞ values for 3-quinuclidinol (Figure 3 and open symbols of Figure 1) with the $K_{ad}k_d^{OH}$ values that were observed at lower pH values suggests that moderate concentrations of this amine cause no significant change in $K_{ad}k_d^{OH}$.

Table II. Salt and Medium Effects of Bases on the Rate of the Hydroxide Ion Catalyzed Dehydration Step in 2-Methyl-3-thiosemicarbazone Formation[a]

Compd	Concn, M	% baseline rate
Sulfate[b,c]	0.10	105
	0.20	115
	0.30	124
Trichloromethylphosphonate[b,d]	0.30	112
Dichloromethylphosphonate[b,d]	0.20	111
Ethylphosphonate[b,d]	0.10	107
β-Glycerophosphate[b,d]	0.19	123
Acetate[b,d]	0.50	92
	0.95	86
Propionate[b,c]	0.25	96
	0.50	88
	0.75	85
	1.00	75
Cacodylate[b,d]	0.20	114
Pyridine[d]	0.20	84
4-Methylpyridine[c]	0.10	82
	0.20	68
	0.30	53
Nicotinate[b,d]	0.20	73
Imidazole[d]	0.20	90
N-Methylimidazole[d]	0.20	84
N-Methylmorpholine[d]	0.18[e]	93

[a] At 25°, ionic strength 1.0. [b] Potassium salt. [c] In 0.05 M ethylenediamine buffer, 30% free base, pH 8.8. [d] In 0.02 M hexafluoroisopropyl alcohol buffer, 30% free base, pH 8.8–8.9 [e] Free base concentration.

Rate constants k^{GB} for general base catalysis of the addition step are summarized in Table III. No catalysis by the acidic form of the buffer was observed for 3-quinuclidinol or quinuclidine, which were examined at several buffer ratios. Weaker bases were examined under conditions in which at least 98% of the catalyst was present as the free base and it was estimated, from the known catalytic constant for acetic acid, that catalysis by the acidic form of these buffers made no significant contribution to the observed rate constants.

General Acid Catalyzed Addition. Buffer catalysis of 2-methyl-3-thiosemicarbazone formation is also observed at low pH. Rate constants for general acid catalysis of the addition step (Table IV) were obtained after correction of the observed rate constants for the contribution of the buffer-independent dehydration step, $K_{ad}k_d^H[H^+]$. For cacodylic and maleic acids, corrections were made for catalysis by the conjugate bases at low pH; such corrections were insignificant for the other catalysts.

Discussion

The well-known change in the rate-determining step of semicarbazone formation and related reactions in the low pH region takes place because the rate of the pH-independent attack of the amine nucleophile can no longer keep up with the rate of acid-catalyzed dehydration of the carbinolamine addition compound as the pH decreases.[10] The rate constant for the attack step, shown by the dotted line in Figure 1 for the reaction of 2-methylthiosemicarbazide with *p*-chlorobenzaldehyde, is essentially independent of pH between pH 5 and 9. At high pH values a base-catalyzed dehydration mechanism becomes significant for the reac-

Table III. General Base Catalysis of 2-Methyl-3-thiosemicarbazide Attack on *p*-Chlorobenzaldehyde at 25°, Ionic Strength 1.0

Catalyst	pK_a'[a]	No. of runs	Concn range (free base), *M*	pH	k^{GB},[b] M^{-2} $sec^{-1} \times 10^2$
Trichloromethylphosphonate (1)	4.28	6	0.05-0.30	10.88	≤ 0.85
Acetate (2)	4.65[c]	8	0.20-1.0	11.25	1.7 ± 0.9
Propionate (3)	4.70	7	0.10-0.60	11.26	
		4	0.10-0.70	11.10	1.8 ± 0.5
Nicotinate (4)	4.78	9	0.02-0.20	11.20	≤ 3.3
Dichloromethylphosphonate (5)	4.97	10	0.05-0.30	10.90	
		9	0.05-0.30	10.80	3.8 ± 0.9
Pyridine (6)	5.51[d]	11	0.01-0.18[e]	11.20	7.0 ± 0.7
β-Glycerophosphate (7)	6.00	4	0.02-0.20	10.90	12.5 ± 1
Cacodylate (8)	6.15	6	0.02-0.10	11.10	13 ± 2
4-Methylpyridine (9)	6.33[d]	9	0.01-0.14[e]	11.18	25 ± 8
N-Methylimidazole (10)	7.20[f]	7	0.005-0.10	11.17	29 ± 3
Imidazole (11)	7.24[c]	10	0.01-0.20	10.88	35 ± 5
Ethylphosphonate (12)	7.60	11	0.005-0.20	10.90	36.5 ± 6.5
N-Methylmorpholine (13)	7.83[g]	6	0.005-0.20	11.26	4.3 ± 0.5
Methylarsonate (14)	8.53	12	0.005-0.10	10.92	83 ± 9
Borate (15)	8.9[c]	6	0.005-0.20	10.97	16 ± 1
Triethylenediamine (16)	9.22[c]	6	0.005-0.20	11.25	30 ± 3
Hexafluoroisopropyl oxide (17)	9.22[c]	5	0.01-0.05	10.97	
		9	0.005-0.20	10.90	55 ± 5
Carbonate (18)	9.7	5	0.01-0.20	12.00	108 ± 8
3-Quinuclidinol (19)	10.13[c]	6	5×10^{-4}-1×10^{-1}	10.15	
		8	7×10^{-4}-1.4×10^{-1}	10.50	
		7	9×10^{-4}-1.8×10^{-1}	11.10	33 ± 3
Quinuclidine (20)	11.55[g]	10	0.008-0.04	10.96	
		5	0.005-0.10	11.58	33 ± 3
Hydroxide ion	15.7				520

[a] Determined by titration at 25°, ionic strength 1.0 (KCl) unless otherwise noted. [b] Limits estimated by inspection of plots of k_{addn} against buffer concentration. [c] Reference 18. [d] A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, **92**, 5432 (1970). [e] Corrected for self-association of the substituted pyridines.[d] [f] In 1.0 *M* tetramethylammonium chloride: D. G. Oakenfull and W. P. Jencks, *J. Amer. Chem. Soc.*, **93**, 178 (1971). [g] Reference 5.

Table IV. General Acid Catalysis of 2-Methyl-3-thiosemicarbazide Attack on *p*-Chlorobenzaldehyde at 25°, Ionic Strength 1.0 (KCl)

Catalyst	pK_a'	No. of runs	Concn range (free acid), *M*	pH	Fraction as acid	k^{GA}, M^{-2} sec^{-1}
H_3O^+	−1.7					57
Glycine	2.48[a]	7	0.0025-0.10	2.94	0.25	6.0
Acetic acid	4.65[a]	7	0.001-0.040	5.22	0.20	
		6	0.008-0.160	3.97	0.80	2.2
Maleate monoanion	5.6[b]	4	0.002-0.008	6.29	0.20	
		7	0.004-0.016	5.81	0.40	0.25
Cacodylic acid	6.15	13	0.0045-0.090	5.18	0.90	1.0[c]

[a] Reference 18. [b] D. R. Robinson and W. P. Jencks, *J. Amer. Chem. Soc.*, **89**, 7088 (1967). [c] Corrected for catalysis by the conjugate base determined at high pH (Table III).

tions of weakly basic amines,[18-20] and a second change in rate-determining step should occur when the rate of the pH-independent addition step can no longer keep up with the rate of this base-catalyzed dehydration. Such a change in rate-determining step has not been observed previously, because the addition step is also subject to base catalysis and the rate of base-catalyzed addition is sufficiently fast that it never becomes rate determining.

In the case of the 2-methylthiosemicarbazide reaction the base-catalyzed addition is relatively slow and a (partial) change in rate-determining step occurs at approximately pH 10 because the base-catalyzed addition step (dotted line, Figure 1) is not fast relative to the dehydration step (dashed line). The break in the logarithmic plot of Figure 1 at high pH values is less striking than that at low pH, but corresponds to a 2.5-fold decrease in observed rate constants and is well beyond experimental error. More dramatic evidence for the change in rate-determining step is found in the nonlinear plots for general base catalysis at high pH values (Figure 3). The curvature in these plots is a consequence of the change from partially rate-determining addition, which is highly susceptible to catalysis, to rate-determining dehydration, for which general base catalysis is much less important. The solid lines in Figure 1 and the inset of Figure 3 were calculated from the rate constants for the individual steps, shown by the dotted and dashed lines in Figure 1, and show good agreement with experiment.

The change in rate-determining step at high pH is observed for the reaction of 2-methylthiosemicarbazide and not for that of thiosemicarbazide because the rate constants $k_n^{OH} = 5.2\ M^{-2}\ sec^{-1}$ and $k_{-n}^{OH} = 23\ M^{-1}\ sec^{-1}$ for the attack and elimination of the methyl compound are smaller than the corresponding rate constants of $\geq 80\ M^{-2}\ sec^{-1}$ and $\geq 47\ M^{-1}\ sec^{-1}$ for the unsubstituted compound, although the rate constants for the base-catalyzed dehydration step are almost the same for the two compounds (Table I). The mechanism for this base-catalyzed addition-elimination reaction that will be presented below involves the development of a positive charge on the entering or leaving nitrogen atom in the transition state. The low pK_a' of 1.20 for the dissociation of the conjugate acid of 2-methylthiosemicarbazide, compared with 1.88 for the

(20) B. M. Anderson and W. P. Jencks *J. Amer. Chem. Soc.*, **82**, 1773 (1960); A. Williams and M. L. Bender, *ibid.*, **88**, 2508 (1966); M. Masui and H. Ohmori, *J. Chem. Soc. B*, 762 (1967); E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, **84**, 832 (1962); J. Archila, H. Bull, C. Lagenaur, and E. H. Cordes, *J. Org. Chem.*, **36**, 1345 (1971).

unsubstituted compound (Table I), is evidence that positive charge development is relatively unfavorable on the 1-nitrogen atom of the methyl compound, presumably because of a solvation effect of the methyl group.[21] This is consistent with the observed change in rate-determining step.

The other rate constants (Table I) for the individual steps in uncatalyzed and hydronium and hydroxide ion catalyzed 2-methyl-3-thiosemicarbazone formation are similar in magnitude to those previously determined for the formation of the unsubstituted thiosemicarbzone.[18] The approximately tenfold lower value of K_{ad}, the equilibrium constant for carbinolamine formation, for the methyl-substituted compound is probably a result of steric hindrance in the methyl-substituted carbinolamine. Further evidence for steric hindrance in this compound is provided by the observation that the rate constant for dehydration of the methyl-substituted carbinolamine catalyzed by triethylenediamine is 1×10^{-3} M^{-1} sec^{-1}, or about eight times less than the corresponding rate constant for the unsubstituted thiosemicarbazide derivative, whereas the rate constants for catalysis by the less bulky hydroxide ion are approximately equal for the two compounds.

General Base Catalyzed Addition. The Brønsted plot for general base catalysis of the attack step in 2-methyl-3-thiosemicarbazone formation by bases of widely varying pK_a and structure is shown in Figure 4. Although different classes of catalysts follow different Brønsted relationships,[22] particularly in the high pK_a range, the Brønsted correlation is nonlinear for any given class of base. For cyclic, unhindered tertiary amines, the Brønsted plot undergoes a transition from a slope ≥ 0.5 for weakly basic amines to a slope ≤ 0.05 for strongly basic amines (filled circles). A similar transition from slope ≥ 0.6 to slope ≤ 0.2 is observed for oxygen dianions (open triangles). Borate and *N*-methylmorpholine show negative deviations from the Brønsted lines for the other oxygen and nitrogen bases. The break in the Brønsted plot becomes apparent with bases of p$K_a \leq 6$. The break is sharper than would ordinarily be expected from the variation in the structure of a single transition state over this small range of substituent variation in the catalyst[24,25] and provides

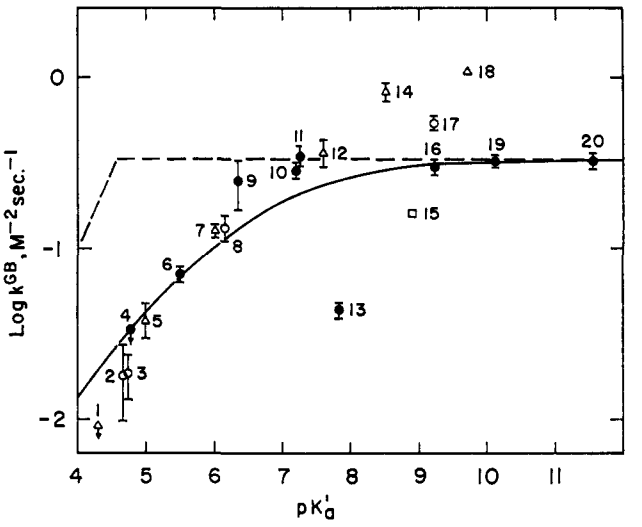


Figure 4. Brønsted plot for general base catalysis of the additon of 2-methyl-3-thiosemicarbazide to *p*-chlorobenzaldehyde at 25° and ionic strength 1.0. Numbering of the catalysts is given in Table III. The solid line is a theoretical curve for the preassociation mechanism of eq 8 with pK_{a4} = 3.3 and the individual rate and equilibrium constants given in the text. The broken line shows the limiting slopes of 1.0 and 0 obtained from the fit of the data to the Brønsted curve for a simple diffusion-controlled proton transfer (eq 6).

evidence for a change in the transition state with changing basicity of the catalyst, *i.e.*, a change in rate-determining step (this change in rate-determining step of the general base catalyzed *addition* reaction should not be confused with the change in rate-determining step of the overall reaction from addition to dehydration with increasing catalyst concentration).

The change in rate-determining step means that the addition reaction must involve at least two kinetically significant steps and since there is only a single step involving the formation or breaking of bonds to the central carbon atom in the addition reaction, some process involving the base that catalyzes proton transfer must become kinetically significant. The simplest explanation of this type of behavior is that the rate-determining step of the catalyzed reaction is a simple proton transfer step that is diffusion controlled in the direction that is thermodynamically strongly favorable (mechanism I, eq 5).[2,4,5,25,26] According to this mech-

$$RNH_2 + \underset{\diagdown}{\overset{\diagup}{C{=}O}} \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} \underset{T^{\pm}}{\overset{+}{R}NH_2{-}\overset{|}{\underset{|}{C}}{-}O^-} \underset{k_{-B}}{\overset{k_B[B]}{\rightleftharpoons}} RNH{-}\overset{|}{\underset{|}{C}}{-}O^- + BH^+ \xrightarrow{\text{fast}} RNH{-}\overset{|}{\underset{|}{C}}{-}OH \quad (5)$$

T^- $\qquad$ T^0

anism, the unstable intermediate $T^{\pm}$ that is formed initially by the attack of amine on the carbonyl group reverts rapidly to starting materials (k_{-a}) unless it is trapped by an encounter with a base that removes a proton from the attacking nitrogen atom so that amine

(21) F. E. Condon, *J. Amer. Chem. Soc.*, **87**, 4491 (1965).

(22) The application of statistical corrections[23] to the pK_a values and the catalytic constants of Table III and Figure 4 does not significantly affect the shape of the Brønsted plots. The validity of using such corrections for the rates of fast proton transfer reactions or processes occurring within an encounter complex depends on the detailed mechanism of such processes. If the lifetime of the initial encounter complex in a "diffusion controlled" proton transfer reaction is long enough to permit rotation of the catalyst before it dissociates, then the formation of every encounter complex (regardless of orientation) should lead to reaction and the use of statistical corrections is not valid for strong bases. If, on the other hand, dissociation of the complex is faster than rotation of the molecules within it the chances of forming a properly oriented, "productive" complex will be greater for a base with more than one proton binding site, and statistical corrections should be applied. The foregoing argument is based on the assumption that the orientation of the members of the initial encounter complex is random; a different uncertainty is introduced if orientation of the catalyst for proton transfer occurs simultaneously with the diffusion process.

(23) R. P. Bell and P. G. Evans, *Proc. Roy. Soc., Ser. A*, **291**, 297 (1966).

(24) (a) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, pp 155–182; (b) A. O. Cohen and R. A. Marcus, *J. Phys. Chem.*, **72**, 4249 (1968); (c) M. L. Ahrens, M. Eigen, W. Kruse, and G. Maass, *Ber. Bunsenges. Phys. Chem.*, **74**, 380 (1970); (d) M. M. Kreevoy and D. E. Konasewich, *Advan. Chem. Phys.*, **21**, 243 (1971); (e) A. Streitwieser, Jr., W. B. Hollyhead, A. H. Pudjaatmaka, P. H. Owens, T. L. Kruger, P. A. Rubenstein, R. A. MacQuarrie, M. L. Brokaw, W. K. C. Chu, and H. M. Niemeyer, *J. Amer. Chem. Soc.*, **93**, 5008 (1971); (f) A. Streitwieser, Jr., W. B. Hollyhead, G. Sonnichsen, A. H. Pudjaatmaka, C. J. Chang, and T. L. Kruger, *ibid.*, **93**, 5096 (1971), and references therein.

(25) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964).

(26) W. P. Jencks, *Chem. Rev.*, **72**, 705 (1972).

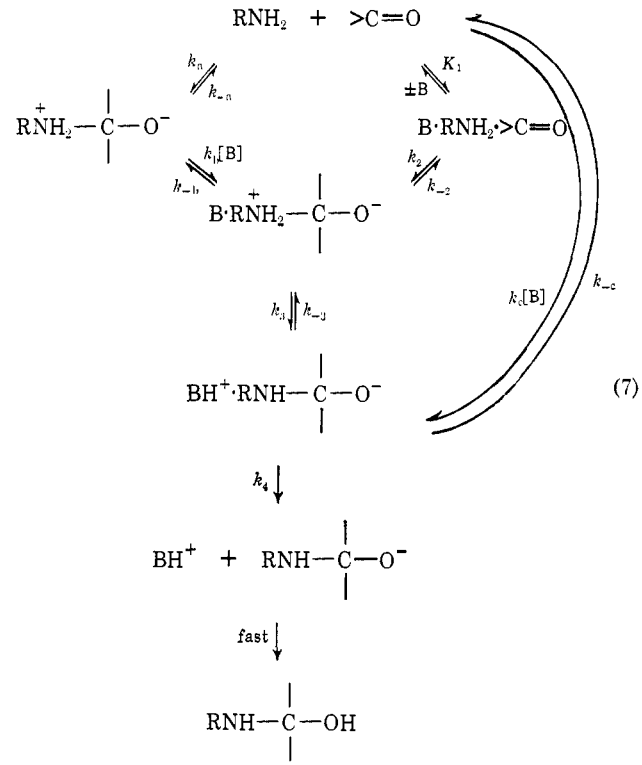
expulsion is prevented. The rate of this proton transfer step will be diffusion controlled and therefore independent of catalyst basicity for strong bases and will follow a Brønsted slope of 1.0 for weak bases; for bases of intermediate strength the plot will be curved and the point of intersection of the lines of slope $\beta = 0$ and $\beta = 1.0$ will be close to the pK_a of the intermediate $T^{\pm}$.[25] The observed nonlinear Brønsted plot (Figure 4) is consistent with that expected for this mechanism. Since the oxygen anion is much more basic than the nitrogen atom in T^-, this intermediate will undergo protonation on oxygen at least as fast as on nitrogen, so that formation of the uncharged addition compound T^0 from T^- will be fast and k_B will be largely or entirely rate determining.

The position of the break in Figure 4, however, is at a higher pK_a than expected from the estimated pK_a value of $T^{\pm}$. The pK_a of $T^{\pm}$ is estimated to be approximately 3.1, 1.9 units above the pK_a of the parent amine (see Appendix). The position of the limiting line of slope $\beta = 1.0$ and, hence, the position of the break that corresponds to the pK_a of $T^{\pm}$ cannot be determined directly from inspection of Figure 4, but this pK_a can be estimated by fitting the data to a line with the curvature that has been observed by Eigen and coworkers for simple proton transfer reactions.[25] The observed rate constants for simple proton transfer reactions in the region near $\Delta pK = 0$ are considerably smaller than expected for a simple diffusion-controlled mechanism, presumably because some aspect of the proton transfer process itself, k_3 in the expanded mechanism of eq 6, is

$$B + T^{\pm} \underset{k_{-b}}{\overset{k_b}{\rightleftharpoons}} [B \cdot T^{\pm} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} BH^+ \cdot T^-] \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} BH^+ + T^- \quad (6)$$

kinetically significant. The observed Brønsted curves for these reactions may be fit by assuming that near the region of $\Delta pK = 0$, $\log k_3 = 10 + 0.5\Delta pK$ and that the rate constants for the separation of reactants and products, k_{-b} and k_4, are 10^{11} sec^{-1}.[27] The Brønsted plot for the general base catalyzed addition reaction may be fit by a curve of identical shape. In the group of catalysts examined, the change in rate-determining step is from diffusion-controlled encounter for basic catalysts ($\beta = 0$) to a predominantly rate-determining k_3 step for the less basic catalysts. The dashed lines show the limiting slopes of 0 and 1.0 for this curve; the limiting slope of 1.0 is approached but not reached. According to the mechanism of eq 6, the limiting lines should intersect at $\Delta pK = 0$. This intersection gives a pK_a value for $T^{\pm}$ of no less than 4.5. This pK_a is appreciably larger than the estimated value of 3.1 and would require that the pK_a of the conjugate acid of 2-methylthiosemicarbazide be increased by at least 3.3 pK units in the intermediate $T^{\pm}$. Although these estimates are certainly not precise, they suggest that alternative mechanisms to account for the nonlinear Brønsted plot deserve consideration.

The break in the Brønsted plot will occur at a pK_a greater than the pK_a of $T^{\pm}$ if, as in mechanism I, the separation of T^- and BH^+ is rate determining for weak bases, and some process with an absolute rate that is faster than the *absolute rate* of the encounter of free $T^{\pm}$ with the base catalyst is rate determining for strong bases. This is possible only if free $T^{\pm}$ is not an intermediate in the reaction. Two such alternative mechanisms that can lead to a break in the Brønsted plot at a point above the pK_a' of $T^{\pm}$ are shown in eq 7 and are



(7)

illustrated schematically in Figures 5 and 6. Mechanism II involves a preassociation of the catalyzing base, amine, and aldehyde in an encounter complex (K_1) followed by the formation of $T^{\pm}$ within the encounter complex (k_2), proton transfer (k_3), and a dissociation or rotation (k_4) before product formation. For weak bases the rate-determining step is k_4, the same as for the simple proton transfer mechanism of eq 6, so that the Brønsted line for weak bases will be the same as that for mechanism I (Figure 5). However, if the preassociation[30] (or "spectator"[8]) mechanism II represents the lowest energy path, the rate in the region in which the k_2 step is rate determining will be higher than that of mechanism I so that the break in the Brønsted plot will occur at a higher pK_a value (Figure 5). Mechanism II will be the lowest energy path if the rate constant for expulsion of the protonated amine from $T^{\pm}$, k_{-2}, is faster than the rate constant, k_{-b}, for the dissociation of base from the encounter complex (the dashed and solid lines in Figure 6). The steady-state rate law for mechanism II is given by eq 8.

$$k^{GB} = K_1k_2k_3k_4/(k_{-2}k_{-3} + k_{-2}k_4 + k_3k_4) \quad (8)$$

(27) When the reactants or products are oppositely charged ions, k_b/k_{-b} or k_4/k_{-4}, respectively, will be changed because of an electrostatic effect and the position of $\Delta pK = 0$ will be changed by a corresponding amount.[26] We assume here that the error introduced by neglecting the electrostatic effect of the oxygen anion, which is two atoms removed from the site of proton transfer, is small compared to other uncertainties. It is of interest that a plot of log k against ΔpK for the reaction of acetate ion with a series of carboxylic acids gives a slope close to 0.5 over a range of 5 pK units[28] and the rate of proton transfer between the two oxygen atoms of carboxylic acids, which may involve proton transfer to an intermediate solvent molecule in the rate-determining step, shows the same sensitivity to substituents in the acid.[29]

(28) M.-L. Ahrens and G. Maass, *Angew. Chem., Int. Ed. Engl.*, 7, 818 (1968).

(29) E. Grunwald and S. Meiboom, *J. Amer. Chem. Soc.*, **85**, 2047 (1963); E. Grunwald, *Progr. Phys. Org. Chem.*, **3**, 339 (1965).

(30) W. P. Jencks and K. Salvesen, *J. Amer. Chem. Soc.*, **93**, 1419 (1971).

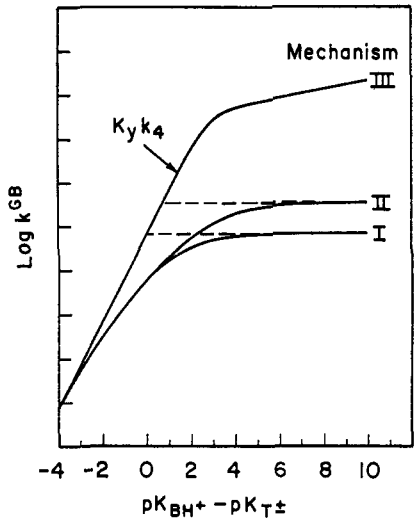


Figure 5. Diagram showing how the break in a nonlinear Brønsted plot changes for a simple rate-determining proton transfer (mechanism I), a preassociation mechanism (mechanism II), and a concerted mechanism (mechanism III).

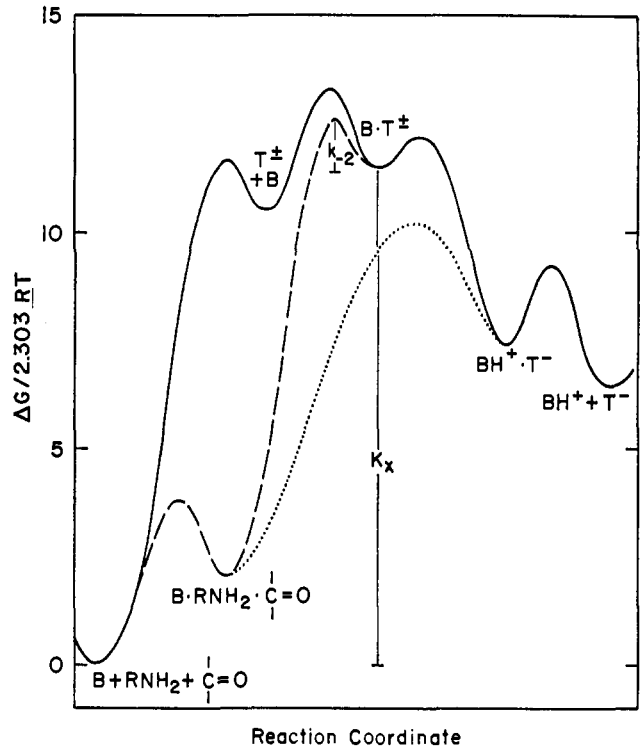


Figure 6. Reaction coordinate diagrams for a simple rate-determining proton transfer (mechanism I, —), a preassociation mechanism (mechanism II, - - - - -), and a concerted mechanism (mechanism III, ...). The curves are calculated for a base of pK_a = 7.1 and a pK_a of $T^\pm$ of 3.1. The magnitudes of K_x and k_{-2}, used to calculate k^{GB}, are indicated.

If the lifetime of $T^\pm$ is so short that it does not exist as a discrete intermediate, mechanisms I and II are impossible and the reaction must proceed through mechanism III in which proton transfer and carbon–nitrogen bond formation to give T^- occur in a more-or-less concerted manner with the rate constant k_c. The steady-state rate law for this mechanism is given by eq 9. For strongly basic catalysts the catalyzed attack

$$k^{GB} = k_c k_4/(k_{-c} + k_4) \qquad (9)$$

step, k_c, is rate determining. For weakly basic catalysts the relatively strong acid BH^+ will catalyze a rapid breakdown of T^-, so that the rate of the back reaction, k_{-c}, will exceed k_4 and k_4 will become rate determining, as in the case of mechanisms I and II, but the rate constants for strong bases will be higher, as shown by the upper line in Figure 5 and the dotted line in Figure 6. These mechanisms and the changes in the position of the break in the Brønsted plot are essentially the converse of those proposed previously for the base-catalyzed hydrazinolysis of acetylimidazole.[5]

The solid line in Figure 4 has been calculated for mechanism II using the steady-state eq 8 with K_1k_2 = 0.33 M^{-2} sec^{-1} (from k^{GB} for strongly basic amines), and assuming that k_{-2}, for the breakdown of $T^\pm$, is 5×10^{11} sec^{-1}, log $k_3 = 10 + 0.5\Delta pK$, $k_4 = 10^{11}$ sec^{-1}, and the pK_a of $T^\pm$ = 3.3. The calculated line shows satisfactory agreement with the observed rate constants and, in particular, shows a break at approximately the expected pK value. The observed break in the Brønsted curve of Figure 4 is a consequence of a change in rate-determining step from N–C bond formation within the encounter complex (k_2) with strong bases to predominantly rate-determining proton transfer (k_3) for the weaker bases examined; the dissociation step k_4, with a β value of 1.0, becomes rate determining only with bases that are so weak that they would not give detectable catalysis under the conditions of our experiments.

We prefer mechanism II to mechanism III for the following reasons, although the uncertainty in the data and calculations are such that mechanism III cannot be definitely excluded. First, the Brønsted slope β for strongly basic tertiary amines is not significantly different from zero ($\beta \leq 0.05$, Figure 4), whereas a slope of greater than zero is expected for a concerted reaction mechanism. Second, the absolute magnitude of rate constants k^{GB} for catalysis by strong bases may be calculated for the two mechanisms from known or estimated equilibrium and rate constants for the formation of $T^\pm$ and T^-. These calculations provide direct evidence that the rate constants required for mechanism II are reasonable and give better agreement with the observed rate constants for mechanism II than for mechanism III.

If the assumption is made that $k_{-2} = 5 \times 10^{11}$ sec^{-1}, the absolute magnitude of the observed rate constant, k^{GB}, for strong bases may be calculated for mechanism II. For strong bases, $k^{GB} = K_1k_2$, and it may be shown algebraically or from the reaction coordinate diagram of Figure 6 that $k^{GB} = k_{-2}K_x$, where $K_x = K_{ad}K_zK_{assoc}$; *i.e.*, K_x is the equilibrium constant for the formation of $B \cdot T^\pm$ from starting materials (eq 10). Based on values of $k_{-2} = 5 \times 10^{11}$ sec^{-1}, K_{ad} =

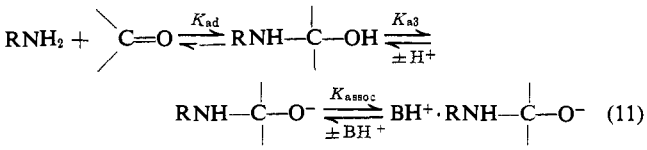
$$RNH_2 + \underset{|}{C}=O \overset{K_{ad}}{\rightleftharpoons} RNH-\underset{|}{C}-OH \overset{K_z}{\rightleftharpoons}$$

$$\overset{+}{R}NH_2-\underset{|}{C}-O^- \overset{K_{assoc}}{\underset{\pm B}{\rightleftharpoons}} B \cdot \overset{+}{R}NH_2-\underset{|}{C}-O^- \qquad (10)$$

0.23 M^{-1} (see Experimental Section), $K_z = 10^{-9.9}$ (see Appendix), and K_{assoc} = 0.1 M^{-1} for the formation of

an encounter complex,[31] the calculated value of k^{GB} is 1.5 M^{-2} sec^{-1} for basic amines, which may be compared with the experimental value of 0.33 M^{-2} sec^{-1}. If the other constants are held fixed, exact agreement with $k^{GB} = 0.33\ M^{-2}$ sec^{-1} is obtained with a value of $K_{assoc} = 0.022\ M^{-1}$, which is within the range of proposed values for encounter complex formation[31] and is not unreasonable if K_{assoc} includes the requirement that the reactants in the encounter complex be oriented in such a manner that proton transfer may take place.

An analogous calculation for mechanism III may be made as follows. The observed rate constant for the reaction catalyzed by weak bases is given by $k^{GB} = k_4K_y$, in which $K_y = K_{ad}K_{a3}K_{assoc}/K_{BH^+}$ is the equilibrium constant for the formation of $BH^+ \cdot T^-$ (eq 11) and



$$RNH_2 + \underset{}{\overset{}{>}}C{=}O \overset{K_{ad}}{\rightleftharpoons} RNH{-}\underset{}{\overset{}{C}}{-}OH \overset{K_{a3}}{\underset{\pm H^+}{\rightleftharpoons}} RNH{-}\underset{}{\overset{}{C}}{-}O^- \overset{K_{assoc}}{\underset{\pm BH^+}{\rightleftharpoons}} BH^+ \cdot RNH{-}\underset{}{\overset{}{C}}{-}O^- \quad (11)$$

K_{BH^+} is the dissociation constant of BH^+. Taking values of $k_4 = 10^{11}$ sec^{-1}, $K_{a3} = 10^{-13}$ M (see Appendix), $K_{ad} = 0.23\ M^{-1}$, and $K_{assoc} = 0.1\ M^{-1}$, then $k_4K_y = 2.3 \times 10^{-4}/K_{BH^+}\ M^{-2}$ sec^{-1}. For mechanism III the change in rate-determining step that occurs at the break in the Brønsted plot requires that at the break point $k_4K_y = k_c$, and the experimental observation that this break occurs at $pK_a \sim 6$ gives $k_c = k_4K_y = 2.3 \times 10^{-4}/10^{-6}$, or 230 M^{-2} sec^{-1}. This value of k_c is *ca.* 10^3 larger than the observed catalytic constant for strong bases, so that this calculation does not support a concerted mechanism of catalysis. It should be noted that the break in the Brønsted plot that is expected for mechanism III is sharper than for mechanisms I or II because only two steps are involved; in mechanisms I and II the kinetically significant proton transfer step in the region near $\Delta pK = 0$ leads to a gradual change from slope 0 to 1.0.

The mechanism of catalysis that is favored for reactions of this type depends on the relative amounts of stabilization of the transition states by the base catalyst and the lifetime of the intermediate $T^{\pm}$, which will vary with the basicity of the attacking amine. If the preassociation mechanism II is correct for the reaction of 2-methylthiosemicarbazide with *p*-chlorobenzaldehyde, nucleophilic attack by less basic amines would give an "intermediate" with little, if any, significant lifetime and a larger free energy advantage would be gained from partial proton transfer from $T^{\pm}$ to a base, so that a transition to the concerted mechanism would be expected. The β value for general base catalysis of the addition of thiourea to formaldehyde by bases with a pK_a far above that of $T^{\pm}$ is 0.61, consistent with such a transition to a concerted mechanism.[26,38] With a more basic amine the lifetime of the intermediate $T^{\pm}$ is expected to be longer so that a stable product may be formed by a simple proton transfer reaction after the diffusion-controlled encounter of $T^{\pm}$ with a base (mechanism I). The reaction of piperazine with pyridine-4-carboxaldehyde appears to proceed by this mechanism.[39]

How can the attack of 2-methylthiosemicarbazide on the carbonyl group occur through a preassociation mechanism, with little or no proton transfer to the catalyzing base in the transition state for N–C bond formation, if the catalyst is located in an encounter complex so that proton transfer occurs immediately upon the formation of $T^{\pm}$? The addition reaction involves a change in the acidity of the N–H of 2-methylthiosemicarbazide from a pK_a of approximately 26 in the amine[18] to approximately 3 in $T^{\pm}$, *i.e.*, a decrease of some 23 pK units. If 0.8 of this change in acidity has occurred in the transition state for C–N bond formation, the pK_a of the transition state will be about 8. With a base of $pK = 10$ there will be little or no advantage to be gained from partial proton transfer in the transition state, so that it does not appear unreasonable that proton transfer should occur after N–C bond formation in a stepwise reaction mechanism. The rate constant for catalysis by hydroxide ion ($pK = 15.7$) is 16 times larger than those for basic amines and five times larger than for carbonate ion. It is possible that this enhanced rate reflects a significant degree of stabilization of the transition state for C–N bond formation by this much stronger base.

The two- to threefold larger catalytic constants for other basic oxygen anions compared with amines may be attributed to an electrostatic effect. For mechanism II this reflects electrostatic stabilization of the transition state for carbon–nitrogen bond formation, k_2. Borate and *N*-methylmorpholine show negative deviations from the Brønsted plot. Deviations of the magnitude observed could occur if the rate constant for the proton transfer process within the complex is about 5×10^{11} sec^{-1} (for borate) or 10^{11} sec^{-1} (for *N*-methylmorpholine). Borate transfers a proton by a mechanism which must also involve the cleavage of a B–O bond[40] and proton transfers involving *N*-alkylmorpholines are abnormally slow, probably because of a steric or conformational effect;[41] hence it is not surprising that proton transfers involving these two bases are somewhat slower than expected for thermodynamically favorable "ultra-fast" proton transfers[42] involving normal acids and bases.

(31) Estimates of K_{assoc} for noninteracting molecules range from 0.017 M^{-1}, estimated by Hine for an "intimate encounter complex" with significant steric requirements,[32] to 0.2 M^{-1} for a nearest neighbor pair[33] and 0.5 M^{-1} for association of (dissimilar) substituted phenols in methanol.[34] The "translational contribution to $\Delta G^{\pm}$" of 2.4 kcal/mol for a bimolecular reaction,[24d,35] calculated from $-kT \ln (hZ/kT)$ with $Z = 10^{11}$ l. mol^{-1} sec^{-1}, corresponds to the formation of a encounter complex with $K_{assoc} = 0.018\ M^{-1}$, and the same value for K_{assoc} is obtained from the unitary entropy of 7.98 eu for a solute in aqueous solution.[36] Estimation of K_{assoc} from experimental data is possible, given $\log k_f \simeq 9.3$ for diffusion-controlled proton transfer to amines in water in the thermodynamically favorable direction[25] and an estimate of k_r from the rate constants determined by Grunwald and coworkers for diffusional separation of amines and solvating water.[37] For reactants without unusual hydrophobic interactions typical values of K_{assoc} from the ratio of the forward and reverse rate constants are 0.01 M^{-1} for ammonia and 0.2 M^{-1} for trimethylamine.

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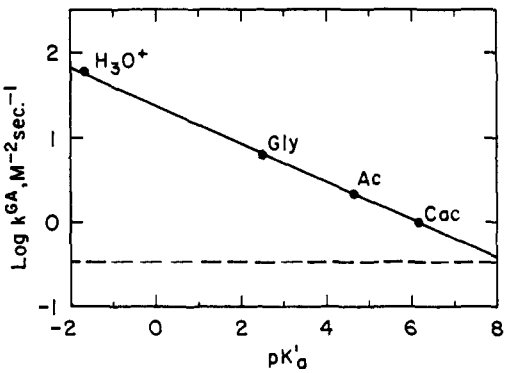
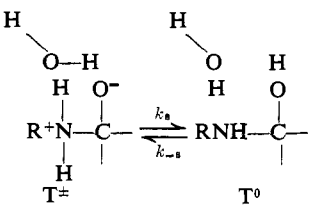


Figure 7. Brønsted plot for general acid catalysis of the addition of 2-methyl-3-thiosemicarbazide to *p*-chlorobenzaldehyde at 25°, ionic strength 1.0. The solid line has a slope of 0.22. The broken line indicates the maximum rate constant expected for a mechanism involving stepwise proton transfer, based on the limiting value of the catalytic constants observed for general base catalysis by tertiary amines.

The uncatalyzed addition of 2-methyl-3-thiosemicarbazide to *p*-chlorobenzaldehyde may be attributed to a rate-determining "proton switch" between the nitrogen and oxygen atoms of T± (eq 12). From the



(12)

observed rate constant for this reaction and an equilibrium constant of 3×10^{-11} M^{-1} for the formation of T± from starting materials, a value of 4×10^{7} sec^{-1} is calculated for the rate constant for this process. Rate constants on the order of 10^{6}–10^{8} sec^{-1} have been observed or estimated for similar proton transfers in the thermodynamically favorable direction between oxygen atoms in carboxylic acids,[43] nitrogen atoms in hexaamminoplatinum(IV) chloride,[44] nitrogen and sulfur in cysteine derivatives,[45] and oxygen and nitrogen in a zwitterionic tetrahedral intermediate derived from 2-methyl-Δ^2-thiazoline.[2]

General Acid Catalysis. The attack of 2-methylthiosemicarbazide on *p*-chlorobenzaldehyde is subject to general acid as well as general base catalysis. Two experimental observations suggest that this catalysis, in contrast to catalysis by bases, involves stabilization of the transition state for carbon–nitrogen bond formation by a significant amount of proton transfer from the catalyst. (1) The Brønsted plot for the acid-catalyzed reaction has a slope of $\alpha = 0.2$ (Figure 7). The attack of thiosemicarbazide exhibits a very similar Brønsted plot, in which the solvated proton and a series of carboxylic acids of $pK_a' = 1.1$–4.7 show a good fit to a line of slope $\alpha = 0.15$.[18] We conclude that the value of α is certainly larger than zero. This suggests that there is a small, but significant, amount of proton transfer from the catalyst in the transition state of the catalyzed reaction. (2) The observed rate constants for catalysis by glycine and acetic acid are approximately

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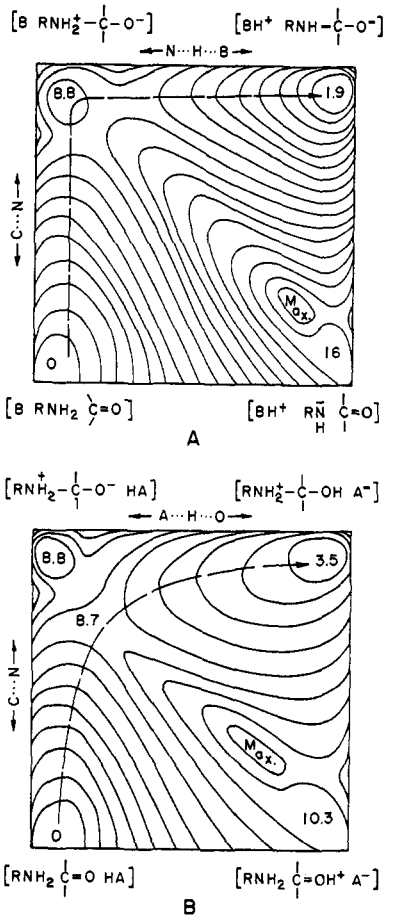


Figure 8. Representation of energy surfaces for catalysis by a general base of $pK_a = 10$ (A) and by a general acid of $pK_a = 3$ (B) of the addition of 2-methyl-3-thiosemicarbazide to *p*-chlorobenzaldehyde. Energy differences are calculated based on a mole fraction standard state and each contour line represents 1 logarithmic unit.

an order of magnitude larger than those for general base catalysis by basic amines, which is shown by the dashed line in Figure 7. If the rate-determining step of the base-catalyzed reaction is either the unassisted formation of T± in a preassociation mechanism or the diffusion-controlled encounter of T± with a molecule of catalyst, the same step cannot be rate determining, and free T± cannot be an intermediate, in the faster general acid catalyzed reaction. The observed faster rate constants for catalysis by relatively strong acids are, therefore, attributed to stabilization of the transition state by some degree of proton transfer from the catalyst, either by hydrogen bonding[46] or by an actual coupling of proton transfer with carbon–nitrogen bond formation. Since the pK_a of the oxygen atom that is protonated by the acid is approximately 8.3, the free energy advantage from such catalysis will decrease and then disappear with weaker acids. This corresponds to a change to a preassociation mechanism and a break in the Brønsted plot analogous to that for the base-catalyzed mechanism.

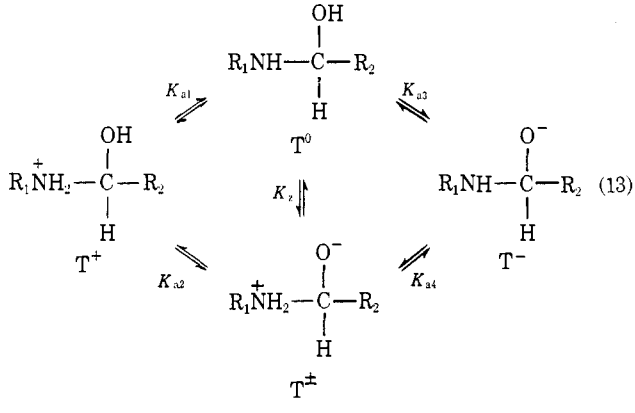
A possible explanation for the difference in mechanism of the base and acid catalyzed reactions is apparent upon inspection of the reaction coordinate energy contour diagrams[26] for the two reactions shown in Figures 8A and 8B, respectively. The encounter

(46) J. Hine, *J. Amer. Chem. Soc.*, 94, 5766 (1972).

complexes containing T± and a molecule of acid or base catalyst, shown in the upper left corner of the diagrams, have the same energy relative to the reactants, in the lower left corner. However, the intermediate nitrogen anion that would be formed if proton transfer to a base of $pK = 10$ preceded amine attack, in the lower right corner of Figure 8A, is considerably higher in energy than the protonated carbonyl group that would be formed from an acid of $pK_a = 3$ in the analogous case, in the lower right corner of Figure 8B. The pK_a of 2-methylthiosemicarbazide is presumably close to the value of 26 estimated for thiosemicarbazide[18] and the pK_a of the conjugate acid of *p*-chlorobenzaldehyde is -7.3.[47] The instability of the nitrogen anion intermediate will raise the energy of the lower right corner of the diagram and tend to force the lowest energy path for the base-catalyzed reaction toward the stepwise mechanism passing through the B·T± intermediate in the upper left corner of the diagram. In the acid-catalyzed reaction, the relative stability of the protonated carbonyl group intermediate will result in a lower energy for the intermediate in the lower right corner and, other things being equal, will favor the concerted reaction path through the central region of the diagram. Since the intermediate T± is already of borderline stability, with a lifetime estimated to be on the order of 10^{-12} sec, it is not unreasonable that even a relatively small change in the energy surface would be sufficient to shift the reaction path from this extremely unstable intermediate to a "concerted" mechanism.

Appendix

The pK of T± (pK_{a4}, eq 13) and other equilibrium



(13)

constants for protonic equilibria involving the tetrahedral intermediate may be estimated from structure–reactivity correlations.[5] Following the considerations of Fox and Jencks,[48] a value of $\rho_I = 8.4$ for the dissociation constants of substituted ammonium ions and alcohols is used.

(i) The value of pK_{a1} is estimated to be -1.6 ± 0.3. (a) The pK_a' of 1,2-dimethyl-3-thiosemicarbazide at ionic strength 1.0 is 1.31.[49] Using σ_I values[50] of 0.10 and 0.25 for phenyl and hydroxyl groups, respectively, correction for these substituents gives $pK_{a1} = -1.7$ for R_2 = phenyl. Correction for the *p*-chloro substituent ($\rho = 1.06$ for the dissociation of benzylammonium ions)[51] gives a further decrease in pK_{a1} of -0.24 for the *p*-chloro compound, so that pK_{a1} for T^+ is -1.9. (b) An alternative method for calculating pK_{a1} employs the correlation of Hall[52] with $\rho^* = -3.23$ for secondary amines. Starting with 1,2-dimethyl-3-thiosemicarbazide ($pK_a' = 1.31$),[49] substitution of a hydroxybenzyl group ($\sigma^* = 0.765$)[53] for the methyl group gives $pK_{a1} = -1.2$ for the phenyl, and $pK_{a1} = -1.4$ for the *p*-chlorophenyl compound, T^+. (c) Substitution of a hydroxyl group for the hydrogen in the 1-methyl group of 1,2-dimethyl-3-thiosemicarbazide should decrease the pK by 1.88 units,[54] giving $pK_a = -0.57$ for the hydroxymethylamine. Correction for phenyl substitution ($\Delta pK = -8.4 \times 0.1$) and for the *p*-chloro group ($\Delta pK = -0.24$) gives $pK_{a1} = -1.65$ for T±.

(ii) A value of $pK_{a2} = 8.3$ may be obtained from the estimated pK_a of 9.98 for $CH_3N^+H_2CH_2OH$.[54] The value of σ_I for the substituent $H_2NC(S)N(CH_3)$ may be estimated as approximately 0.30 (midway between the σ_I values of 0.28 and 0.32 for $CH_3C(O)NH$[50] and $PhSO_2NH$,[55] respectively). Substitution of this substituent for methyl in $CH_3N^+H_2CH_2OH$ will lower the pK $(-8.4)(0.30)/2$ or 1.25 units if the fall-off factor for transmission of substituent effects through nitrogen[56] is taken as 2.0. α-Phenyl substitution for hydrogen lowers the pK_a of an aldehyde hydrate 0.2 unit,[59] and the effect of the *p*-chloro group ($\Delta pK = -0.25$, from $\rho = 1.11$ for the ionization of trifluoroacetophenone hydrates[60]) should further decrease pK_{a2} to 8.3.

(iii) The value of pK_{a3} is estimated to be 13.0 ± 0.4. (a) The pK_a for the dissociation of the hydroxyl group of $H_2NNHCHPhOH$ is estimated to be 14.4 from the relationship derived by Takahashi, *et al.*, for alcohol ionization,[61] using $\sigma^* = 0.6$ for the phenyl,[50] and $\sigma^* = 0.93$ for the hydrazine[50] substituent. The effect of substituting the group $H_2NC(S)N(CH_3)$ for NH_2 is to lower the pK of hydrazine 7 units, and transmission through one carbon[62] and one nitrogen[56] atom will reduce this acid-strengthening effect by a factor of about 1/(2.5)(2.0), so that ΔpK for the alcohol is -1.4. Correction for the *p*-chloro substituent ($\Delta pK = -0.25$) gives a pK_{a3} for T^0 of 12.8. (b) Substitution of the methylthioureido group ($\sigma_I \simeq 0.30$; see above) for the NH_2 group ($\sigma_I = 0.10$)[50] in the hydrazine compound ($pK = 14.4$) gives $\Delta pK = -8.4(0.30 - 0.10)/2.0$ or

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(56) The fall-off factor for transmission of substituent effects through a nitrogen atom in substituted hydrazines is similar to that for carbon in the phenylhydrazine series[57] and appears to be considerably smaller (1.37) in the alkylhydrazine series;[58] since the source of this discrepancy is unclear, we have used the average value of 2.0 in these calculations.
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(62) P. R. Wells, "Linear Free Energy Relationships," Academic Press, New York, N. Y., 1968, p 39.

-0.84; this correction plus that for *p*-chloro substitution gives $pK_{a3} = 13.3$. At ionic strength 1.0 the value of pK_{a3} may be decreased by 0.1–0.2 unit; these estimates are based on reference pK_a values at low or zero ionic strength. The estimates of pK_{a1} and pK_{a2} are based on measured pK_a values of reference compounds at ionic strength 1.0.

(iv) From the relationship among the equilibria of eq 3, pK_{a4} for the dissociation of $T^{\pm}$ is equal to $pK_{a1} + pK_{a3} - pK_{a2} = (-1.6 + 13.0 - 8.3) = 3.1$.

The value of log K_z for the interconversion of T^0 and $T^{\pm}$ calculated from these ionization constants is -9.9 ± 1.0. A value of log $K_z = -9.4$, consistent with this estimate, is obtained by the following extrapolation from the value of log $K_z = -1.9$ at 35° estimated from the data of Hine and coworkers[54] for the analogous equilibrium between the zwitterionic and neutral forms of the carbinolamine derived from isobutyraldehyde and methylamine. The assumption is made that substituent effects at the central carbon atom are equal for the ionization of the oxygen- and nitrogen-bound protons and hence do not affect K_z. The use of $pK_a = 10.62$ for methylammonium ion at 25°[63] gives log $K_z = -1.8$ for the methylamine adduct of isobutyraldehyde at 25°. Changing the amine from methylamine to methylthiosemicarbazide will decrease pK_{a4} with a β value of 1.0, assuming that substituent effects are additive; the effect of nitrogen substituents on K_{a3} will be attenuated by transmission through a nitrogen and a carbon atom, giving a β value for this equilibrium of approximately 1/(2.5)(2.0) or 0.2. Hence, the β value for K_z is approximately 0.8, and log K_z for the methylthiosemicarbazide adduct is $-1.9 - (0.8)(10.6 - 1.2)$ or -9.4.

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Base Hydrolysis of Coordinated Acetonitrile

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Contribution from the Research School of Chemistry, Australian National University, Canberra, 2600, Australia. *Received April 13, 1973*

Abstract: The base hydrolysis of acetonitrile to acetamide is catalyzed by a factor of 2×10^6 on coordination to $Co(NH_3)_5^{3+}$. Hydroxide appears to attack the carbon atom of the nitrile group, while in a separate and concurrent process the methyl protons exchange. On addition of acid to the acetamido complex produced, protonation occurs on the carbonyl oxygen ($pK_a = 3.02$; $\mu = 1.0$ *M*, $NaClO_4$; $T = 25°$) rather than on the amide nitrogen atom.

The metal ion promoted hydrolysis of nitriles has been studied for several nitriles.[1-3] In cases where valid comparisons can be made, the corresponding N-bonded carboxamide product is formed at a rate 10^6–10^7 faster than for the base hydrolysis of the noncoordinated nitrile.[1,3]

However, in the system $[Co(en)_2X(NCCH_2NH_2)]^{2+}$ (X = Cl, Br) a different reaction occurs under basic conditions, and a tridentate amidine complex is formed by attack of a coordinated amide ion (formed by deprotonation of an amine proton of en) at the nitrile C atom.[4] Consequently, it was of interest to determine whether $[Co(NH_3)_5(N{\equiv}CCH_3)]^{3+}$ would react by direct hydroxide ion attack at the nitrile group to give the N-bonded acetamido complex, or by attack of a deprotonated ammine on the nitrile group to produce coordinated acetamidine. The present paper reports the investigation of the base hydrolysis of $[Co(NH_3)_5(N{\equiv}CCH_3)]^{3+}$, and of the properties of the hydrolysis product.

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Experimental Section

Analytical reagents were used without further purification. $[Co(NH_3)_5(N{\equiv}CC_6H_5)](ClO_4)_3$ and $[Co(NH_3)_5(NHCOC_6H_5)]I_2$ (and the protonated species as the chloride salt) were obtained as described previously.[3] Electronic spectra were measured on a Cary 14 spectrophotometer, and pmr spectra on either a Varian HA-100 or a JEOL MH-100 spectrometer using TMS as external reference or *tert*-butyl alcohol as internal reference.

Preparation of $[Co(NH_3)_5(N{\equiv}CCH_3)](ClO_4)_3$ was effected as previously reported in the literature,[5] or on a larger scale by the following method. $[Co(NH_3)_5I](ClO_4)_2$[6] (9.42 g, 0.02 mol) and $AgClO_4$ (4.2 g, 0.02 mol) were stirred for 5 min in dried acetone (15 ml). Acetonitrile (50 ml) was added and the mixture stirred overnight at room temperature. Ether (50 ml) was added, and the yellow product and precipitated silver iodide were filtered off. The complex was extracted with warm water (40 ml), acidified with a few drops of acetic acid, and precipitated by the addition of $NaClO_4$ and cooling. $[Co(NH_3)_5(N{\equiv}CCH_3)](ClO_4)_3$ (8.2 g, 85%) was filtered off, washed with ethanol and ether, and air dried. The complex was recrystallized from warm acidified water. The visible spectrum of the complex in 10^{-3} *M* $HClO_4$ gave ϵ_{467}^{max} 63 and ϵ_{333}^{max} 56. *Anal.* Calcd for $CoN_6C_2H_{18}Cl_3O_{12}$: Co, 12.19; C, 4.97; H, 3.75; N, 17.38. Found: Co, 12.21; C, 5.21; H, 4.07; N, 17.06.

Isolation of Base Hydrolysis Product. $[Co(NH_3)_5(N{\equiv}CCH_3)](ClO_4)_3$ (1.21 g, 0.0025 mol) was dissolved in water (25 ml) and NaOH solution added (2.5 ml of 1.2 *M*, 0.0030 mol). After 10 sec excess $NaClO_4$ was added to precipitate the red hydrolysis product,

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