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- (40) E. M. Arnett, R. P. Quirk, and J. W. Larsen, *J. Amer. Chem. Soc.*, **92**, 3977 (1970).
- (41) The pK values of -8.1 and -6.7 for p -nitrobenzaldehyde and unsubstituted benzaldehyde, respectively, reported by Arnett, Quirk, and Larsen⁴⁰ were determined from enthalpies of protonation in fluorosulfonic acid. These values are comparable with the values of -9.2 and -7.5 obtained by correction of the H_0 values at half-protonation determined by Yates and Stewart⁴² to the scale of Jorgenson and Hartter,⁴³ and the pK of -6.7 for benzaldehyde is in good agreement with that of -6.75 reported by Greig and Johnson.⁴⁴ Slopes of 0.8 and 1.0 were found by the latter workers for plots of $\log [>C=O] / [>C=OH^+]$ against H_0 for p -methoxybenzaldehyde and unsubstituted benzaldehyde, respectively. The above evidence is inconsistent with the report of Zalewski and Dunn⁴⁵ that the protonation of benzaldehyde follows H_A with a pK of -4.87 .
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- (43) M. J. Jorgenson and D. R. Hartter, *J. Amer. Chem. Soc.*, **85**, 878 (1963).
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- (47) $pK(H_0)$ values of -9.2 , -7.7 , and -5.7 , obtained by correction of the H_0 values at half-protonation obtained by Yates and Stewart,⁴² to the scale of Jorgenson and Hartter,⁴³ were used for p -nitro-, p -chloro-, and p -methoxybenzaldehyde, respectively. These values should be self-consistent, although each appears to be about 1 pK unit too low based on more recent values.^{40,44} Correction of these values to the H_A scale⁴⁶ gives $pK(H_A)$ values of -5.6 , -4.8 , and -3.7 for p -nitro-, p -chloro-, and p -methoxybenzaldehyde, respectively; an extrapolation of the H_A scale of approximately 1 pK unit was required to estimate $pK(H_A)$ for p -nitrobenzaldehyde.
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- (50) The rate constant for breakdown of the solvation complex between ammonia and water is $6 \times 10^{11} \text{ sec}^{-1}$ (E. Grunwald and E. K. Ralph, *Accounts Chem. Res.*, **4**, 107 (1971)); the use of $k_1 = 10^{10} \text{ M}^{-1} \text{ sec}^{-1}$ and $k_r = 5 \times 10^{11} \text{ sec}^{-1}$ corresponds to an equilibrium constant of 0.02 M^{-1} for encounter complex formation (*cf.* ref 3b, footnote 31).
- (51) If the dehydration step is entirely rate limiting at high buffer concentrations, the reaction involves a simple change in rate-determining step, from carbinolamine formation to dehydration, with increasing buffer concentration, and, by analogy with other systems,^{3b,9} the slope of k_{cor} against the concentration of the catalytic species is k_{cat} . For the limiting case of the mechanism at low pH, assuming that $K_{\text{ad}}k_5a_{\text{H}^+}$ is large and $k_2 \ll k_1 + k_2$, a more complex expression for k_{cor} is obtained because of the additivity of the k_1 and sequential pathways of eq 2a, and for this limiting case the slope of k_{cor} against catalyst concentration is $k_{\text{cat}}\{(k_1a_{\text{H}^+} + k_2)/k_2\}^2$. The error introduced by assuming that the slope is equal to k_{cat} would be 6% of k_{cat} at pH 2.5, if the processes represented by $(k_1a_{\text{H}^+} + k_2)$ were entirely rate limiting at high buffer concentration but is actually smaller because of the contribution of the dehydration step at this pH. The error at higher pH values will be even smaller. Since this error is small compared with other experimental uncertainties, the slopes of k_{cor} against the concentration of acid catalyst were taken as equal to k_{cat} in all the buffer catalysis experiments.
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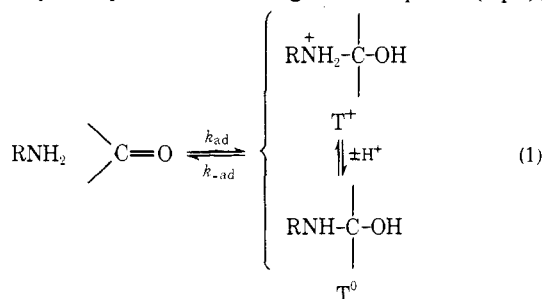
Mechanism of Carbinolamine Formation^{1a}

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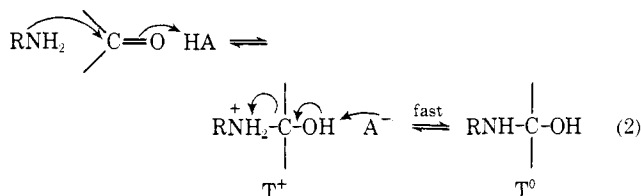
Abstract: A general mechanism is described for carbinolamine formation that is consistent with kinetic and structure-reactivity data reported in this paper and elsewhere for the reaction of amines with substituted benzaldehydes. According to this mechanism, the addition reaction that is observed at pH values below neutrality proceeds by two separate and concurrent pathways. These are (I) general acid catalysis of amine attack on the carbonyl group in a more-or-less "concerted" manner and (II) a stepwise process involving the uncatalyzed formation of a zwitterionic intermediate, T^\pm , that is subsequently trapped by a kinetically significant proton transfer process involving acids or water. For weakly basic amines and/or aldehydes for which the value of K_{ad} , the equilibrium constant for neutral carbinolamine formation, is small, the predominant pathway of hydronium ion catalyzed carbinolamine formation is the "concerted" pathway, I. This pathway is characterized by rate constants that are relatively insensitive to polar substituents on the aldehyde and the amine. For more strongly basic amines or amines and aldehydes with larger values of K_{ad} , the intermediate T^\pm for the stepwise pathway, II, is stabilized, and this pathway is favored relative to the "concerted" process. Contributions of the stepwise pathway to the observed rate of carbinolamine formation are experimentally shown by (a) breaks in pH-rate profiles indicative of changes in rate-determining step that cannot be accounted for by the transition from carbinolamine formation to dehydration and (b) strong sensitivity of the observed rate constants to polar substituents on the amine and the aldehyde under conditions where the stepwise proton transfer processes involving acids or water are kinetically significant. The pH-independent reaction that is ordinarily observed with weakly basic amines at moderately acidic pH values corresponds to a rate determining water-mediated "proton switch" that converts T^\pm to T^0 . With hydrazine derivatives possessing an acidic hydrogen in the 2 position, unusually fast rates are observed for the pH-independent process and are attributed to a facile intramolecular proton donation from N-2 of the substituted hydrazine moiety to the alcoholate oxygen atom.

We wish to describe a general mechanism for the formation of tetrahedral addition compounds (carbinolamines) from carbonyl compounds and nitrogen nucleophiles (eq 1),

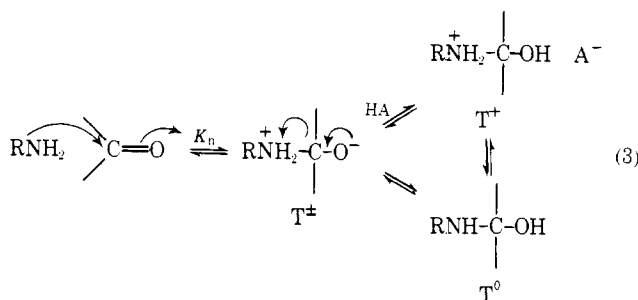


a process that constitutes the first step in the formation of imines, hydrazones, and related compounds² and is analogous to the formation of tetrahedral intermediates in the aminolysis of acyl compounds.³ At pH values below 13-14, the stable ionization state of the carbinolamine is either T^0 or T^+ , depending on the pH and the pK_a of the parent amine. Hence, carbinolamine formation at neutral or acidic pH values requires both the formation of a carbon-nitrogen bond and the addition of a proton to the oxygen atom, which undergoes a change in pK_a from approximately -5 to -8 in the aldehyde or ketone to $8-9$ in T^+ , or $13-14$ in T^0 . The observed acid catalysis of carbinolamine formation is a consequence of this requirement for protonation of the oxygen atom of the product.

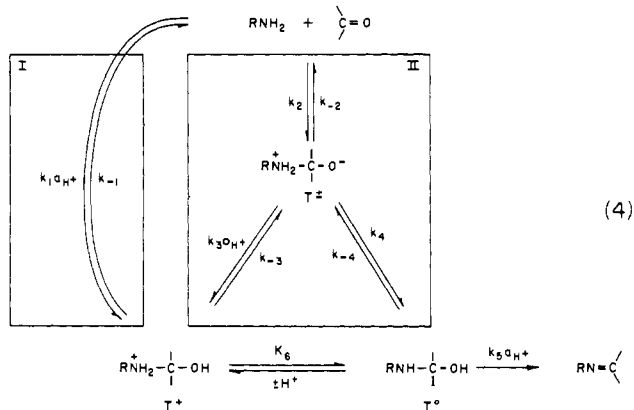
Two mechanisms that are consistent with the observed general acid catalysis of carbinolamine formation are (I) a process in which carbon–nitrogen bond formation and protonation of the oxygen atom are in some sense “concerted” (eq 2) and (II) a stepwise mechanism involving formation



of an unstable zwitterionic form (T^\pm) of the carbinolamine, which reverts rapidly to starting material unless it is trapped either by proton transfer from a molecule of acid or by an intramolecular “proton switch” that converts T^\pm directly to T^0 (eq 3).



In the preceding paper,⁴ we described evidence that both of the above pathways occur concurrently in the addition of methoxyamine to substituted benzaldehydes (eq 4). In the



present publication, we demonstrate the generality of this mechanism for other nitrogen nucleophiles by showing that three predictions based on the complete mechanism of eq 4 are confirmed by experiment. These predictions are based on the fact that the importance of pathway II relative to I for acid-catalyzed carbinolamine formation from a given set of reactants is determined by the stability of T^\pm relative to the transition state for the “concerted” mechanism of pathway I. The stability of T^\pm is increased, to an extent that is quantitatively predictable, by increasing the pK_a of the parent amine or the equilibrium constant, K_{ad} , for its addition to the aldehyde to give T^0 . Both of the above equilibrium constants are experimentally accessible. The following specific predictions have been tested. (1) Very weakly basic amines or carbonyl compounds for which K_{ad} is small should react primarily by pathway I and exhibit pH-rate profiles with a single break, corresponding to the transition from rate-limiting carbinolamine formation to dehydration.

Table I. Experimental Conditions for Reaction of Nitrogen Nucleophiles with Substituted Benzaldehydes at 25°

Benzaldehyde	Nucleophile	λ , nm	Aldehyde concn, M
<i>p</i> -Cl	Chloromethanesulfonylhydrazide ^a (CMSH)	290	5×10^{-5}
	2-Methylsemicarbazide ^a (MeSC)	285	2×10^{-5}
	Acetylhydrazide ^a (AHZ)	285	2×10^{-5}
	Semicarbazide ^a (SC)	285	2×10^{-5}
	Phenylhydrazine- <i>p</i> -sulfonate ^a (PHS)	345	2×10^{-5}
	Hydroxylamine ^b (HA)	296	3×10^{-4c} 1.5×10^{-4d} $2.5\text{--}5.0 \times 10^{-5e}$
<i>p</i> -NO ₂	2-Methyl-3-thiosemicarbazide ^a (MeTSC)	340	1×10^{-5}
	Semicarbazide ^a	320	4×10^{-5}
<i>p</i> -OCH ₃	2-Methyl-3-thiosemicarbazide ^a	320	2×10^{-5}
	Semicarbazide ^a	287 ^f	4×10^{-5f}
		335 ^g	$0.6\text{--}1.9 \times 10^{-5g}$

^a Ionic strength 1.0 (KCl) except in concentrated HCl solutions.

^b Ionic strength 0.5 (KCl) except in concentrated HCl solutions.

^c In 0.25–1.5 *M* HCl solutions. ^d In 2.0–3.0 *M* HCl solutions.

^e In 3.0–5.7 *M* HCl solutions. ^f In 0.01–1.0 *M* HCl solutions.

^g In 3.0–5.0 *M* HCl solutions.

Increasing the basicity of the amine or the value of K_{ad} should increase the relative contribution of pathway II, which involves a second change in rate-determining step and gives rise to a pH-rate profile with two negative breaks in the pH range below neutrality. (2) The observed rate constants for the hydronium ion catalyzed reaction of very weakly basic amines should be insensitive to polar substituents on the aldehyde, whereas the rate constants ($K_{ad}k_3$) for more strongly basic amines, under conditions where the proton transfer process is rate determining, are strongly sensitive to aldehyde substituents. (3) The correlation between $\log k_H$ for hydronium ion catalyzed carbinolamine formation and the quantity ($0.8 pK_a' + \log K_{ad}$) for the amine should be nonlinear, with a transition from a slope less than 1.0 to a slope of 1.0 with increasing values of pK_a' and K_{ad} resulting from a change in mechanism from pathway I to pathway II as the stability of T^\pm is increased.

Experimental Section

Materials. 2-Methylsemicarbazide was prepared by a modification of the method of Taylor and Hartke,⁵ in which the order of addition of potassium cyanate (0.25 mol) and methylhydrazine (0.27 mol) was reversed. The crude product obtained after evaporation of the aqueous reaction mixture was recrystallized once from ethanol and one or two times from chloroform, mp 113–116° (lit. 117°). Chloromethanesulfonylhydrazide was prepared according to the method of Senning.⁶ In our experience, appreciable amounts of product could be recovered both from the ether-soluble portion and from the precipitate that remained after completion of the reaction. The product isolated from both fractions was washed with a small quantity of cold water and recrystallized from ethanol, mp 78–80° (lit. 76.5–78°). Other organic reagents were commercially available products and were recrystallized, or sublimed. Inorganic chemicals and formic and acetic acids used in buffers were reagent grade and were used without further purification. Glass-distilled water was used in all experiments.

Kinetics. Reactions in water at 25° and ionic strength 1.0 (except in strongly acidic solutions) were followed spectrophotometrically, under pseudo-first-order conditions, using procedures that have been described previously.^{4,7,8} Table I summarizes the wavelengths and aldehyde concentrations used for the kinetic experiments.

Where necessary, observed rate constants were corrected⁸ for the contribution of the dehydration step to the overall rate, using published values^{7,9} for the rate constants, $K_{ad}k_5$, under conditions where hydronium ion catalyzed dehydration is rate limiting. For

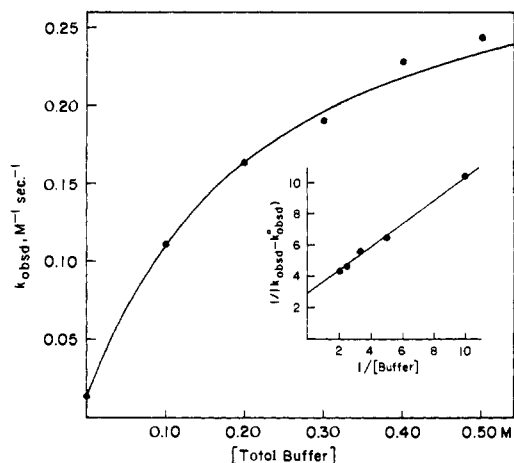


Figure 1. Experimental determination of the limiting rate constant, $K_{ad}k_{5aH^+}$, for dehydration of the carbinolamine derived from *p*-chlorobenzaldehyde and 2-methylsemicarbazide in the presence of acetic acid-potassium acetate buffer, pH 4.99, ionic strength 1.0. The line is a theoretical curve based on a limiting rate constant of $0.34 M^{-1} sec^{-1}$ determined from the ordinate intercept of the double reciprocal plot (inset) and an apparent catalytic constant of $1.5 M^{-2} sec^{-1}$ for total buffer at this pH.

the reaction of 2-methylsemicarbazide and *p*-chlorobenzaldehyde, a value of $3.3 \times 10^4 M^{-1} sec^{-1}$ for this rate constant was obtained from the limiting rate at high concentrations of acetate buffer, which was determined from the ordinate intercept of a double reciprocal plot¹⁰ of observed rate constants against buffer concentration at pH 4.99 (Figure 1). For the reaction of *p*-nitrobenzaldehyde and semicarbazide, $K_{ad}k_5$ was determined at pH 5.70 and 6.19 in 0.01 *M* phosphate buffer in the presence of 0.001–0.004 *M* semicarbazide. The correction for equilibrium formation of the carbinolamine adduct, by use of the equilibrium constant, K_{ad} , for carbinolamine formation of $40.1 M^{-1}$ determined in 25% ethanol¹¹ was 16% of the overall rate. Hence a 20% error¹² in K_{ad} would correspond to an error of <4% in the corrected value of $K_{ad}k_5$.

Corrections for general acid catalysis by buffers and the conjugate acids of the amine nucleophiles were made by extrapolation to zero of plots of k_{obsd} , the second-order rate constant in terms of amine free base, against buffer or amine concentration, or in some cases by subtraction of the rate constant due to such catalysis calculated from values of k_{cat} and catalyst concentration. The values of k_{cat} for reactions of *p*-chlorobenzaldehyde that were used for these corrections were 5.2 and $230 M^{-2} sec^{-1}$ for catalysis of the addition of 2-methylsemicarbazide and acetylhydrazide, respectively, by the conjugate acids of the nucleophiles, and $750 M^{-2} sec^{-1}$ for catalysis of the addition of phenylhydrazine-*p*-sulfonate by formic acid. In cases where the dehydration step made a significant contribution to the overall rate, corrections for general acid catalysis were made using k_{ad} , the second-order rate constants for the addition step (since only this step is subject to buffer catalysis under the present experimental conditions); k_{obsd}^0 , the second-order rate constant at zero buffer concentration, was then calculated from k_{ad} as previously described.³

The reactions of semicarbazide with *p*-methoxybenzaldehyde in the H_0 region and phenylhydrazine-*p*-sulfonate with *p*-chlorobenzaldehyde at pH ≤ 1.0 did not proceed to completion with the concentrations of nucleophile that were used. Under these conditions, k_f' , the second-order rate constant (in terms of total amine) for the forward reaction, was obtained from the slope of a plot of k_{ψ} , the observed pseudo-first-order rate constant, against total amine concentration, and k_{obsd} , the second-order rate constant in terms of amine free base, was calculated from the relationship $k_{obsd} = k_f'/\alpha$, where α is the fraction of the nucleophile in the free base form. Three concentrations of amine between 0.01 and 0.03 *M* and between 0.20 and 0.60 *M* were used for reactions of phenylhydrazine-*p*-sulfonate with *p*-chlorobenzaldehyde and semicarbazide with *p*-methoxybenzaldehyde, respectively. No evidence for significant reversibility of the reaction of semicarbazide with *p*-nitrobenzaldehyde, at H_0 values > -1.75 and 0.1–0.3 *M* total amine,

was obtained, and at $H_0 = -1.75$ the correction for reversal of this reaction was $\leq 6\%$ of the pseudo-first-order rate constant in the presence of 0.3 *M* amine.

Correction for the reversibility of oxime formation from *p*-chlorobenzaldehyde at high acidity was made by subtracting the observed rate constant for oxime hydrolysis from the pseudo-first-order rate constant for oxime formation (eq 5). The validity of this

$$k_f'[\text{N}]_{\text{total}} = k_{\psi} - k_r \quad (5)$$

correction was confirmed at several values of H_0 by the agreement, within 5–17% of the values of k_f' calculated in this way at two different hydroxylamine concentrations, and by the agreement within $\sim 6\%$ of values of k_f' in 0.5 and 1.0 *M* HCl determined from eq 5 with values calculated from the observed rate constants and published equilibrium constants⁹ for oxime formation and protonation. These corrections for the reverse reaction did not exceed 20% of the observed rate constants at the highest hydroxylamine concentration used.

The oxime was prepared from *p*-chlorobenzaldehyde (5 mmol) and hydroxylamine hydrochloride (5 mmol) in ethanol-water containing 1:1 potassium acetate-acetic acid buffer (10 mmol) (after recrystallization from ethanol, mp 105–110° (lit.¹³ 106–108°)), or by the reaction of 1 *M* aldehyde and hydroxylamine hydrochloride in ethanol-water or acetonitrile-water containing 2 *M* HCl. Observed rate constants¹⁴ for hydrolysis of the oxime prepared by these three methods agreed within $\pm 5\%$.

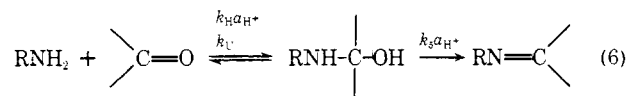
The complex pH-rate profiles for the reactions of phenylhydrazine-*p*-sulfonate with *p*-chlorobenzaldehyde and semicarbazide with *p*-nitrobenzaldehyde, which involve five regions corresponding to five kinetically significant processes, were analyzed as described for the reaction of methoxyamine with *p*-chloro- and *p*-nitrobenzaldehydes in the preceding publication.⁴

Equilibrium Constants. The equilibrium constant, K_{ad} , for carbinolamine formation from *p*-chlorobenzaldehyde and 2-methylsemicarbazide was determined spectrophotometrically⁷ at 260 nm in 0.04 *M* potassium phosphate-biphosphate buffer, pH 7.4, using six concentrations of 2-methylsemicarbazide between 0.1 and 1.0 *M*. An aldehyde concentration of approximately $4 \times 10^4 M$ was used, with an optical path length of 0.2 cm. The instability of chloromethanesulfonylhydrazide at pH values near neutrality precluded measurement of K_{ad} for this nucleophile and *p*-chlorobenzaldehyde.

The $pK_{a'}$ of 2-methylsemicarbazide was measured by potentiometric titration of a 0.1 *M* solution of the compound with 2.0 *N* HCl at 25° and ionic strength 1.0 ± 0.08 (KCl). Appropriate corrections were made for the titration of a blank solution of 1.0 *M* KCl. The $pK_{a'}$ of chloromethanesulfonylhydrazide was determined as previously described for *p*-toluenesulfonylhydrazide,⁷ from the nonlinear dependence on $\text{antilog}(-\text{pH})$ of the apparent rate constant for the reaction of this compound (0.01 *M*) with *p*-chlorobenzaldehyde between pH 0.06 and 1.1.

Results

The observed pH-rate profiles (Figure 2) for hydrazone formation from *p*-chlorobenzaldehyde and the present series of substituted hydrazines (with the exception of phenylhydrazine-*p*-sulfonate; see below) are consistent with a simple two-step mechanism for carbonyl additions of this type.^{2,12} At low pH there is a region of slope -1.0 corresponding to hydronium ion catalysis of the formation of the tetrahedral adduct (k_H , eq 6) and at intermediate pH, a re-



gion of slope that approaches zero, corresponding to uncatalyzed formation of the adduct (k_U). A change in rate-determining step that gives a negative break in the pH-rate profile occurs for these reactions at pH 4–6, and at higher pH the dehydration of the tetrahedral intermediate is rate determining.

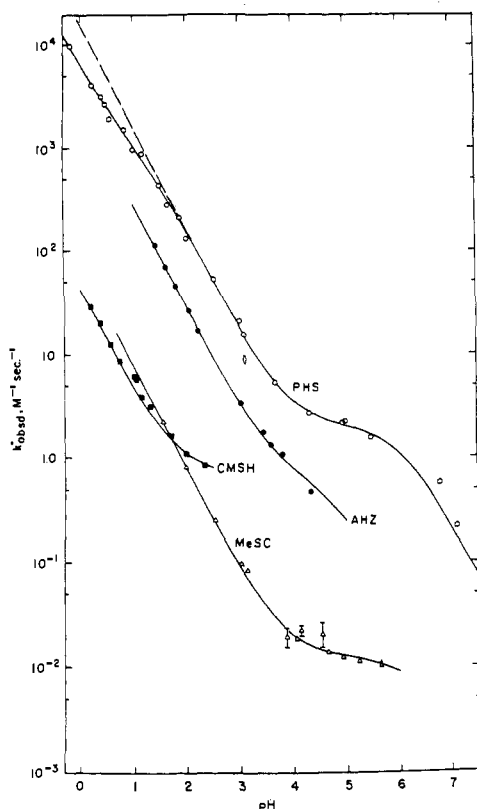


Figure 2. Dependence on pH of the second-order rate constants in the forward direction, corrected for catalysis by buffers and the conjugate acids of the nucleophiles, for the reactions of substituted hydrazines (as the free bases) with *p*-chlorobenzaldehyde at 25° and ionic strength 1.0. The solid lines are theoretical curves based on the rate constants of Table II for carbinolamine formation and published values (ref 7) of $K_{ad}k_5$ for dehydration of the carbinolamines derived from phenylhydrazine-*p*-sulfonate and acethydrazide. The broken line for phenylhydrazine-*p*-sulfonate indicates the rate constants that would be observed at low pH in the absence of a second break in the pH-rate profile for this reaction.

Because k_U for hydroxylamine is large (10^4 – 10^6 times faster than the pH-independent rate constants observed at intermediate pH values for the hydrazine nucleophiles), hydronium ion catalysis of the reaction of this compound is not measurable at pH values greater than zero. Such catalysis is apparent, however, in the H_0 acidity range, as shown

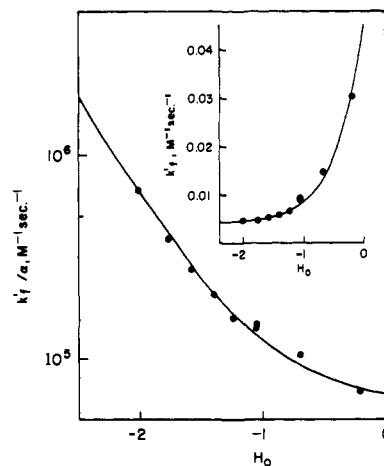


Figure 3. Dependence on H_0 of the second-order rate constants in the forward direction for the addition of hydroxylamine free base (concentration based on $pK_a' = 6.15$; see text) to *p*-chlorobenzaldehyde in hydrochloric acid solutions at 25°. The inset shows the forward rate constants for the reaction in terms of total hydroxylamine as a function of H_0 . The lines are theoretical curves based on the value of k_H from Table II and $k_U = 6.4 \times 10^4 M^{-1} \text{sec}^{-1}$, determined in the present work at hydrochloric acid concentrations $\geq 1.0 M$.

by a slope for the pH-rate profile (in terms of hydroxylamine free base) that approaches -1.0 at large negative values of H_0 (Figure 3). This is equivalent to the finding of an apparent rate constant for the reaction in terms of total hydroxylamine that is independent of acidity in strongly acidic solution (inset, Figure 3). The concentrations of free base used in the calculation of the second-order rate constants, k_{obsd}^0 , in Figures 2 and 3 were determined from the measured pK_a' values of the nucleophiles at ionic strength 1.0 (0.5 for hydroxylamine⁹) and the observed pH (at concentrations of hydrochloric acid $< 1.0 M$) or H_0 (at concentrations of hydrochloric acid $\geq 1.0 M$).^{15,16} Rate constants, k_U and k_H , for pH-independent and hydronium ion catalyzed carbinolamine formation are given in Table II. The value of $k_H = 5.8 \times 10^3 M^{-2} \text{sec}^{-1}$ for the addition of hydroxylamine to *p*-chlorobenzaldehyde found in this work is consistent with the value of $3.3 \times 10^3 M^{-2} \text{sec}^{-1}$ found by Martin¹⁸ for the reaction of this nucleophile with acetone, and the observation that the rate constant for the hydronium ion catalyzed reaction of *p*-chlorobenzaldehyde with methoxyamine under strongly acidic conditions is approximately twice as fast as that for acetone.¹⁷

Table II. Kinetic Constants for Carbinolamine Formation from Nitrogen Nucleophiles and *p*-Chlorobenzaldehyde^a

Nucleophile		pK_a'	K_{ad}, M^{-1}	$k_U, M^{-1} \text{sec}^{-1}$	$k_H, M^{-2} \text{sec}^{-1}$
Chloromethanesulfonylhydrazide (CMSH)	$\text{ClCH}_2\text{SO}_2\text{NHNH}_2$	0.55	<i>c</i>	0.65	43
2-Methyl-3-thiosemicarbazide ^d (MeTSC)	$\text{H}_2\text{NC}(\text{S})\text{N}(\text{CH}_3)\text{NH}_2$	1.20	0.23	1.2×10^{-3}	63
<i>p</i> -Toluenesulfonylhydrazide (THZ)	$\text{H}_3\text{CC}_6\text{H}_4\text{SO}_2\text{NHNH}_2$	1.09 ^e	1.7 ^e	0.63 ^e	132
Thiosemicarbazide ^f (TSC)	$\text{H}_2\text{NC}(\text{S})\text{NHNH}_2$	1.88	1.7	0.10	156
2-Methylsemicarbazide (MeSC)	$\text{H}_2\text{NC}(\text{O})\text{N}(\text{CH}_3)\text{NH}_2$	2.54	0.9	1.2×10^{-2}	77
Acethydrazide (AHZ)	$\text{H}_3\text{CC}(\text{O})\text{NHNH}_2$	3.44 ^e	0.7 ^e	0.65	3000
Semicarbazide (SC)	$\text{H}_2\text{NC}(\text{O})\text{NHNH}_2$	3.86 ^e	3.1 ^h	0.48 ⁱ	1600 ⁱ
Phenylhydrazine- <i>p</i> -sulfonate (PHS)	$-\text{O}_3\text{SC}_6\text{H}_4\text{NHNH}_2$	4.90 ^e	1.8 ^e	2.0 ^j	1.0×10^{4k}
Methoxyamine ^p (MA)	CH_3ONH_2	4.73	13.4	25 ^j	4.0×10^{4k}
Hydroxylamine (HA)	HONH_2	6.15 ^a	23.5 ^a	1150 ^l	2070 ^{m,o}
				3.85×10^{4a}	5800 ⁿ

^a At 25°, ionic strength 1.0 *M* unless otherwise noted. ^b In terms of antilog ($-\text{pH}$) except where otherwise noted. Published values (concentration basis) were multiplied by a correction factor of 1.1. ^c Not measured experimentally because of the instability of the nucleophile; estimated value 0.5–3.0 M^{-1} based on observed values of K_{ad} for the other substituted hydrazines. ^d Reference 10. ^e Reference 7. ^f Reference 8. ^g W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **90**, 2622 (1968). ^h E. G. Sander and W. P. Jencks, *ibid.*, **90**, 6154 (1968). ⁱ These values are similar to published values for k_U and k_H at ionic strength 0.5 of 0.43 $M^{-1} \text{sec}^{-1}$ and 1500 $M^{-2} \text{sec}^{-1}$, respectively (ref 12). ^j For the stepwise proton transfer process, $K_n k_4$ (see text). ^k For the stepwise proton transfer process, $K_n k_5$ (see text). ^l For uncatalyzed attack, k_2 . ^m Approximate value (see text). ⁿ In terms of h_0 . ^o For the process defined by k_1 (see text). ^p Reference 4. ^q At ionic strength 0.5; ref 9.

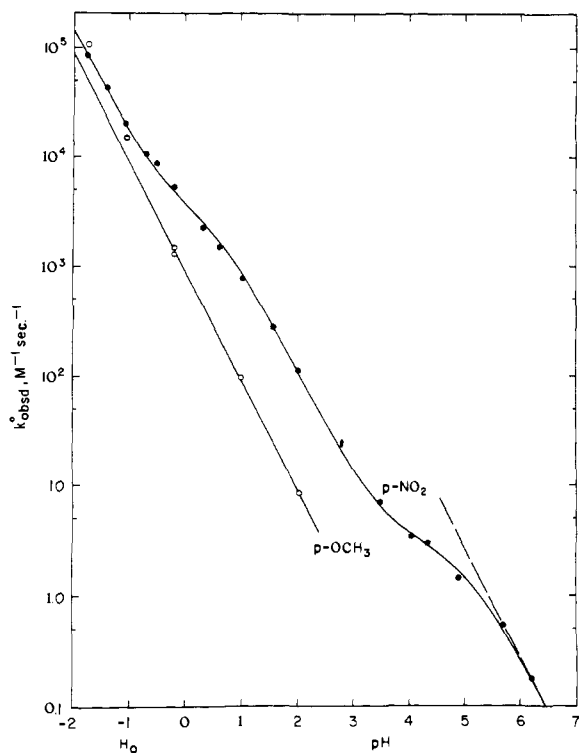


Figure 4. Dependence on pH of the second-order rate constants in the forward direction, corrected for catalysis by semicarbazide cation, for the reaction of semicarbazide free base with *p*-nitro- (●) and *p*-methoxybenzaldehyde (○) at 25°. The solid line for *p*-nitrobenzaldehyde is a theoretical curve based on eq 7 and 7a and the rate constants of Table III. The broken line for this compound indicates the rate constants for the hydronium ion catalyzed dehydration step.

In addition to a break at pH ~6 corresponding to a transition from rate-determining formation to dehydration² of the tetrahedral adduct, the pH-rate profile for the reaction of phenylhydrazine-*p*-sulfonate with *p*-chlorobenzaldehyde (Figure 2) shows a second small break at pH ~1.5 and observed rate constants at low pH that are approximately twofold smaller than predicted (broken line) from the pH-rate profile above pH 2.0. This break cannot be a result of protonation of the sulfonate group of this compound with a pK_a of ~1.5 since the pK_a values of *p*-toluenesulfonic acid and 2,5-dimethylbenzenesulfonic acid in water are -1.06 and -0.4, respectively,¹⁹ and the positively charged hydrazinium substituent would be expected to make the pK_a of phenylhydrazine-*p*-sulfonic acid even lower.²⁰

A second break in the pH-rate profile is also observed for the reaction of semicarbazide with *p*-nitrobenzaldehyde (Figure 4). Analogous breaks observed at high acidity in the pH-rate profiles for carbinolamine formation from substituted benzaldehydes and methoxyamine⁴ have been shown not to be artifacts arising from the use of the H_0 acidity function with methoxyamine since the negative breaks become apparent at pH values near 1.0, well above the transition from the H_0 to the pH scale. Moreover, no break is observed in the low pH or H_0 range for the analogous reaction of methoxyamine with acetone.¹⁷ A similar conclusion was drawn for semicarbazide from the absence of a negative break at low pH in the pH-rate profile for the addition of semicarbazide to *p*-methoxybenzaldehyde (Figure 4, open circles). The positive deviations of the points observed at the highest acidities for this aldehyde are presumably caused by a salt effect on the rate constant that is inadequately taken into account by the use of H_0 . A similar salt effect may well exist also for the reaction of *p*-nitrobenzal-

Table III. Kinetic Constants for Semicarbazone Formation from *p*-Nitrobenzaldehyde at 25°^a

$k_1,^b M^{-2} \text{sec}^{-1}$	1500
$k_2, M^{-1} \text{sec}^{-1}$	3000
$K_n k_3, M^{-2} \text{sec}^{-1}$	1.0×10^4
$K_n K_4, M^{-1} \text{sec}^{-1}$	3.2
$K_{ad} k_5,^c M^{-2} \text{sec}^{-1}$	2.72×10^5

^a Ionic strength 1.0 (KCl), except at HCl concentrations $\geq 1.0 M$. Rate constants are defined for the processes of eq 4. ^b Based on H_0 . ^c Based on antilog (-pH).

Table IV. Second-Order Rate Constants for Hydronium Ion Catalyzed Carbinolamine Formation from 2-Methyl-3-thiosemicarbazide and Substituted Benzaldehydes^a

Substituent	$k_H, M^{-2} \text{sec}^{-1}$
<i>p</i> -OCH ₃	66
<i>p</i> -Cl ^b	63
<i>p</i> -NO ₂	126

^a At 25°, ionic strength 1.0 (KCl). Rate constants are based on antilog (-pH). ^b Reference 10. The reported rate constant (based on hydronium ion concentration) was corrected by a factor of 1.1.

dehyde, but is masked by the break in the pH-rate profile for this compound in the acidic region. The possible existence of positive deviations due to a salt effect at low H_0 values, while affecting the quantitative accuracy of the rate constant, cannot be the cause of the observed fact that the rate constants for *p*-nitrobenzaldehyde at high acidity are approximately fivefold lower than predicted from the pH-rate profile for this compound at pH 1.5-3.

The second break in the pH-rate profiles for the reactions of phenylhydrazine-*p*-sulfonate with *p*-chlorobenzaldehyde and of semicarbazide with *p*-nitrobenzaldehyde is analogous to that described in the preceding paper⁴ for the reactions of methoxyamine with substituted benzaldehydes. The five regions that are observed in these pH-rate profiles correspond to major contributions from the observed rate constants, k_1 , k_2 , $K_n k_3$, $K_n k_4$, and $K_{ad} k_5$, in order of increasing pH. Individual rate constants (Tables II and III) corresponding to these processes were calculated as previously described, and the theoretical pH-rate profiles for these reactions are based on these rate constants. Because of the small difference between the observed rate constants, k_1 and $K_n k_3$, for the two hydronium ion catalyzed pathways, the rate constant, k_2 , for the uncatalyzed attack of phenylhydrazine-*p*-sulfonate on *p*-chlorobenzaldehyde could not be determined accurately; its value is estimated to be $1000 \pm 300 M^{-1} \text{sec}^{-1}$.

Rate constants for the reactions of 2-methyl-3-thiosemicarbazide with *p*-nitro- and *p*-methoxybenzaldehyde were determined at five concentrations of hydronium ion between 0.005 and 0.025 *M*. Under these conditions, the second-order rate constant for the reaction, in terms of amine free base, is linearly dependent on hydronium ion concentration, and the uncatalyzed reaction of the nucleophile is insignificant. No catalysis by the conjugate acid of the nucleophile was observed at pH 1.63, as shown by the agreement of the second-order rate constants determined at 0.01 and 0.02 *M* total 2-methyl-3-thiosemicarbazide. Rate constants, k_H , for the hydronium ion catalyzed reaction of this nucleophile with three substituted benzaldehydes are given in Table IV.

Discussion

We propose the following general mechanism, which is consistent with experimental data reported here and elsewhere, for carbinolamine formation in aqueous solution under acidic and neutral conditions. Carbinolamine forma-

tion proceeds by two concurrent pathways: one pathway involves a proton transfer from an acid catalyst to the carbonyl oxygen atom in a manner that is more-or-less "concerted" with the formation of the carbon-nitrogen bond and involves no kinetically significant intermediate, whereas the other pathway involves the formation of an intermediate, the unstable zwitterionic form of the carbinolamine, which breaks down rapidly to reactants unless it is trapped by a proton transfer process that is kinetically significant at weakly acidic pH values. For amines of moderate basicity and equilibrium affinity for the carbonyl group, the zwitterionic intermediate is relatively stable, and the stepwise pathway is favored at weakly acidic pH. Carbinolamine formation from these amines undergoes a change in rate-determining step with decreasing pH, as the hydronium ion catalyzed proton transfer to the zwitterionic intermediate becomes fast relative to the uncatalyzed attack and departure of the amine, resulting in a break in the pH-rate profile at pH 0-2, and at still lower pH the reaction undergoes a change in mechanism from the stepwise to the "concerted" pathway catalyzed by the hydronium ion. With very weakly basic amines and/or those whose equilibrium constants for addition to the carbonyl group are small, the zwitterionic intermediate is less stable, and the "concerted" pathway, which avoids the formation of this intermediate, is the only kinetically significant pathway for hydronium ion catalysis of the addition reactions of these amines. The pH-independent reaction that is kinetically significant at pH 4-5 for carbonyl additions of both weakly and moderately basic amines ordinarily corresponds to a rate-determining solvent-mediated "proton switch" between the nitrogen and oxygen atoms of the zwitterionic intermediate.

The effect of the relative magnitudes of the "concerted" (I) and stepwise (II) pathways on the shape of the observed pH-rate profiles for carbonyl addition reactions is shown in Figure 5. A pH-rate profile of type A is observed if the stepwise pathway (II) for hydronium ion catalysis is unfavorable relative to the "concerted" process (I). In this case, the latter pathway is the only significant route for hydronium ion catalysis of the addition step. The pH-independent reaction occurs by a different, stepwise mechanism involving rate-determining solvent-mediated isomerization of T^\pm to T^0 . Only one change in rate-determining step for imine formation is observed as a function of pH, corresponding to the transition from formation to dehydration of the carbinolamine intermediate.

A pH-rate profile of type B, with two negative breaks and five regions corresponding to five kinetically significant rate constants, is observed when hydronium ion catalysis *via* the stepwise mechanism (II) is significant relative to the concerted pathway (I). Since for the stepwise pathway (II) there are three sequential kinetically significant steps, the pH-rate profile for a reaction in which this pathway is significant should contain two negative breaks, corresponding to (1) the transition at low pH from uncatalyzed attack (k_2) to hydronium ion catalyzed proton transfer ($K_n k_3$) as acid-catalyzed proton transfer to T^\pm becomes slow relative to the reversion of T^\pm to reactants, and (2) the transition² at higher pH from rate-limiting solvent catalyzed proton transfer ($K_n k_4$) to hydronium ion catalyzed dehydration ($K_{ad} k_5$). The "concerted" pathway (I) for hydronium ion catalysis, with a rate constant k_1 , becomes the predominant mechanism only at very low pH values where the uncatalyzed attack of the amine is rate determining for the stepwise pathway.

A pH-rate profile of type C should be observed if the rate for the stepwise pathway of hydronium ion catalyzed carbinolamine formation is increased still further so that

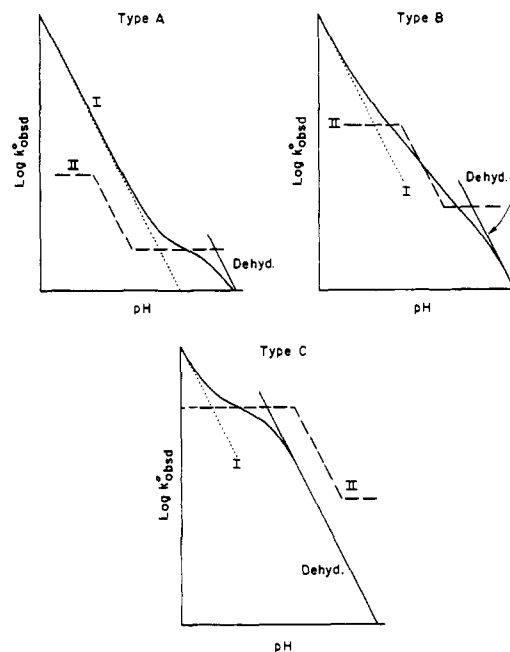


Figure 5. Diagram illustrating the way in which varying the relative importance of the "concerted" (I, dotted lines) and stepwise (II, dashed lines) pathways for carbinolamine formation affects the shape of the observed pH-rate profiles (solid curves) for substituted hydrazone and oxime formation.

the rate constant ($K_n k_3$) that would be observed if the proton transfer process were rate limiting is greater than the rate constant ($K_{ad} k_5$) that is observed when the hydronium ion catalyzed dehydration step is rate limiting. In this case the proton transfers that interconvert T^\pm and T^0 are faster than the hydronium ion catalyzed dehydration of T^0 , and the proton transfer process never becomes kinetically significant. The only change in rate-determining step that is observed is the transition from uncatalyzed attack (k_2) to hydronium ion catalyzed dehydration ($K_{ad} k_5$) with increasing pH.

Based on the foregoing considerations, the following predictions were made. (1) Amines of moderate basicity and K_{ad} value should exhibit pH-rate profiles of type B, with two negative breaks and five regions, analogous to methoxyamine.⁴ Decreasing the basicity of the amine should decrease the stability of T^\pm and shift the pH-rate profile to type A. For reactions of a given amine, variations in polar substituents on the aldehyde that decrease K_{ad} will also shift the pH-rate profile from type B to type A. (2) The hydronium ion catalyzed addition of very weakly basic amines to all substituted benzaldehydes should occur almost entirely *via* the "concerted" pathway (with pH-rate profiles of type A) and should exhibit rate constants that are essentially independent of substituents on the aldehyde, analogous to the "concerted" reaction of methoxyamine.⁴ (3) The correlation of $\log k_H$ for hydronium ion catalysis of carbinolamine formation at weakly acidic pH (the middle region of the pH-rate profiles, Figure 5) with $\log K_n$ for equilibrium formation of the zwitterionic intermediate T^\pm should be nonlinear, with a change in slope from <1.0 to 1.0 , as a result of a change in the predominant reaction pathway in this pH region from stepwise to "concerted" as the stability of T^\pm is decreased.

The Shape of pH-Rate Profiles. The complete steady-state rate law⁴ for the mechanism of eq 4 is given by eq 7 and 7a, where k_{obsd}^0 is the observed second-order rate constant (in terms of amine free base) for imine formation at zero buffer concentration, k_{ad}^0 is the corresponding second-

$$k_{\text{obsd}}^0 = k_{\text{ad}}^0 K_{\text{ad}} k_5 a_{\text{H}^+} / (k_{\text{ad}}^0 + K_{\text{ad}} k_5 a_{\text{H}^+}) \quad (7)$$

$$k_{\text{ad}}^0 = k_1 a_{\text{H}^+} + K_n k_2 (k_4 + k_3 a_{\text{H}^+}) / (k_2 + K_n k_4 + K_n k_3 a_{\text{H}^+}) \quad (7a)$$

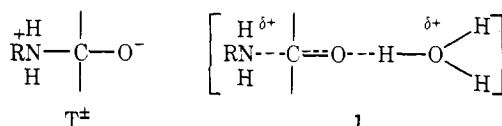
order rate constant for the *addition step*, and $K_n = k_2/k_{-2}$ is the equilibrium constant for formation of T^\pm from reactants. For a reaction in which all the terms are of comparable magnitude, a pH-rate profile of type B is observed, with two negative breaks and five regions, corresponding (in order of increasing pH) to significant contributions of the processes with observed rate constants k_1 , k_2 , $K_n k_3$, $K_n k_4$, and $K_{\text{ad}} k_5$. If, as is ordinarily found for the uncatalyzed reactions (see below), k_2 is greater than $K_n k_4$, and in addition, $K_n k_3$ is small relative to k_1 , eq 7a reduces to eq 8 when $k_2 > K_n k_3 a_{\text{H}^+}$, and to eq 9 at low pH where $k_2 < K_n k_3 a_{\text{H}^+}$. Hence, no change in rate-determining step oc-

$$k_{\text{ad}}^0 = k_1 a_{\text{H}^+} + K_n k_4 \quad (8)$$

$$k_{\text{ad}}^0 = k_1 a_{\text{H}^+} \quad (9)$$

cur for the *addition* process, and the single change in rate-determining step that is observed corresponds to the normal² transition from rate limiting addition to dehydration, giving a simple pH-rate profile of type A.

The magnitude of $K_n k_3$ for the stepwise pathway of hydronium ion catalysis, relative to k_1 for the "concerted" pathway, should be increased (giving rise to pH-rate profiles of types B or C) by increasing the basicity of the parent amine or by increasing the equilibrium constant, K_{ad} , for its addition to the carbonyl group. These two factors should stabilize the zwitterionic intermediate, T^\pm , for the stepwise pathway to a greater extent than they stabilize the transition state **1** for the "concerted" process, in which the carbon-nitrogen bond is presumably not fully formed, and



only a partial positive charge resides on nitrogen. Quantitatively, the effect of pK_a' for the parent amine and K_{ad} on the rate of the stepwise process may be estimated as follows. Since k_3 , the rate constant for the thermodynamically favorable proton transfer from the hydronium ion to T^\pm , is diffusion controlled²¹ and hence independent of the structure of the amine and the aldehyde, the observed rate constant, $K_n k_3$, when the hydronium ion catalyzed proton transfer process is rate determining, should have exactly the same dependence on amine and aldehyde structure as the equilibrium constant K_n for formation of T^\pm from starting materials. This equilibrium constant is equal to the product of the experimentally determined equilibrium constant, K_{ad} , for formation of the neutral carbinolamine, T^0 , and K_z

$$K_n = K_{\text{ad}} K_z \quad (10)$$

for isomerization of T^0 to T^\pm (eq 10). Increasing the pK_a of the amine should increase K_z with a slope, β_{nuc} , of a plot of $\log K_z$ against pK_a of approximately 0.8 since the stabilizing effect of base strengthening substituents on the positive charge at nitrogen ($\beta = 1.0$) will be slightly offset by a destabilizing effect on the negative charge at oxygen ($\beta = -0.2$).¹⁰ K_z is expected to be insensitive to changes in substituents on the benzaldehyde ring.^{4,22,23}

Based on the foregoing considerations, we predicted that the reaction of phenylhydrazine-*p*-sulfonate ($pK_a' = 4.90$;

$K_{\text{ad}} = 1.8 M^{-1}$) with *p*-chlorobenzaldehyde should exhibit a pH-rate profile of type B analogous to that observed for methoxyamine, an amine of similar basicity. The experimentally observed rate constant, $K_n k_3$, under conditions where the proton transfer process is rate determining in the reaction of phenylhydrazine-*p*-sulfonate was predicted to be approximately fivefold smaller than the corresponding rate constant of $4.0 \times 10^4 M^{-2} \text{sec}^{-1}$ for methoxyamine⁴ ($pK_a' = 4.73$; $K_{\text{ad}} = 13.4 M^{-1}$), giving a predicted absolute value of $\sim 8000 M^{-2} \text{sec}^{-1}$. If k_1 ($2070 M^{-2} \text{sec}^{-1}$ for methoxyamine) is relatively insensitive to a small change in the pK_a' of the nucleophile, a fivefold decrease in the rate of the parallel process, $K_n k_3$, is not large enough to change the shape of the pH-rate profile, and a pH-rate profile of type B with two breaks, similar to that observed with methoxyamine, was expected. The observed pH-rate profile (Figure 1) and the absolute value of $1.0 \times 10^4 M^{-2} \text{sec}^{-1}$ for $K_n k_3$ are in good agreement with these predictions.

As the basicity of the amine is decreased, $K_n k_3$ should eventually become smaller than k_1 , if β_{nuc} for k_1 is less than the value of 0.8 expected for $K_n k_3$, and the pH-rate profile should shift to type A. The absence of any negative break in the pH-rate profile for the addition of thiosemicarbazide ($pK_a' = 1.88$; $K_{\text{ad}} = 1.7 M^{-1}$) to *p*-chlorobenzaldehyde⁸ between pH 0 and 4.0 is in agreement with this interpretation.

The effect of variation of the carbonyl compound with a single amine is exemplified by the pH-rate profiles of type B and A observed for the reaction of semicarbazide with *p*-nitro- and *p*-methoxybenzaldehyde, respectively (Figure 4). For the reaction of semicarbazide ($pK_a' = 3.86$) with *p*-nitrobenzaldehyde, the rate constant, $K_n k_3$, for the stepwise pathway of hydronium ion catalysis was predicted to be $1.3 \times 10^4 M^{-2} \text{sec}^{-1}$, as follows. The corresponding rate constant for methoxyamine⁴ is $2.6 \times 10^5 M^{-2} \text{sec}^{-1}$. From the values of 3.1 and $13.4 M^{-1}$ for the equilibrium constants, $K_{\text{ad}}^{p\text{-Cl}}$, for addition of semicarbazide and methoxyamine, respectively, to *p*-chlorobenzaldehyde, and the assumption that *relative* values of K_{ad} are independent of the aldehyde,²⁴ $K_{\text{ad}}^{p\text{-NO}_2}$ for semicarbazide and *p*-nitrobenzaldehyde is expected to be approximately four times smaller than $K_{\text{ad}}^{p\text{-NO}_2}$ for methoxyamine. This will decrease $K_n k_3$ for semicarbazide relative to methoxyamine by a factor of 4, and the lower basicity of semicarbazide ($\Delta pK = 0.87$; $\beta_{\text{nuc}} = 0.8$) will decrease $K_n k_3$ by an additional factor of 5, to give a predicted value of $K_n k_3$ for semicarbazide and *p*-nitrobenzaldehyde of $1.3 \times 10^4 M^{-2} \text{sec}^{-1}$. If k_1 for the "concerted" process ($1930 M^{-2} \text{sec}^{-1}$ for methoxyamine) is approximately the same for semicarbazide, the estimated value of $K_n k_3$ should be significantly larger than k_1 but smaller than $K_{\text{ad}} k_5$ ($2.72 \times 10^5 M^{-2} \text{sec}^{-1}$; Table III), and a pH-rate profile of type B is expected for semicarbazide and *p*-nitrobenzaldehyde. This prediction is borne out by experiment (Figure 4). The experimental value of $K_n k_3$ is $1.0 \times 10^4 M^{-2} \text{sec}^{-1}$, compared with the predicted value of $1.3 \times 10^4 M^{-2} \text{sec}^{-1}$.

Substitution of *p*-methoxy- for *p*-nitrobenzaldehyde changes the pH-rate profile from type B to type A. This substituent change should decrease K_{ad} by a factor^{4,11} of *ca.* 120. Since k_1 is insensitive to the nature of the aldehyde,⁴ rate constants, k_1 (pathway I) of $1500 M^{-2} \text{sec}^{-1}$ and $K_n k_3$ (pathway II) of *ca.* $1.0 \times 10^4 / 120 = 80 M^{-2} \text{sec}^{-1}$, are predicted for hydronium ion catalysis of the reaction of *p*-methoxybenzaldehyde and semicarbazide, from the corresponding experimental rate constants (Table III) for *p*-nitrobenzaldehyde. If $K_n k_3 \ll k_1$, k_1 represents the only kinetically significant pathway for hydronium ion catalysis of the addition step, and a pH-rate profile of type A

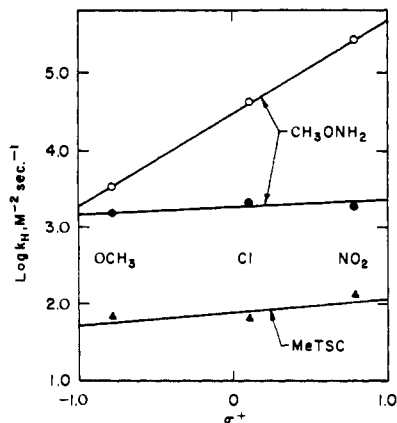


Figure 6. Comparison of the observed ρ^+ value for hydronium ion catalyzed carbinolamine formation from 2-methyl-3-thiosemicarbazide (\blacktriangle) with the ρ^+ values for the “concerted” (\bullet) and stepwise (\circ) pathways for hydronium ion catalyzed carbinolamine formation from methoxyamine. The slopes of the lines are: 2-methyl-3-thiosemicarbazide, 0.17; methoxyamine (“concerted”), 0.10; methoxyamine (stepwise), 1.2.

should be observed. The absence of any negative inflection in the pH-rate profile between $H_0 -1.7$ and pH 2.0 (Figure 4) is consistent with this expectation.

Structure-Reactivity Correlations. The Aldehyde. The second mechanistic prediction that was made involves the effect of amine structure on the sensitivity of hydronium ion catalyzed carbinolamine formation to substituents on the aldehyde. According to our hypothesis, for an amine of sufficiently low pK_a' and K_{ad} , the “concerted” pathway with transition state **1** should always be more favorable than the stepwise pathway involving the intermediate T^\ddagger with a complete carbon-nitrogen bond and a full positive charge on nitrogen. Since the rate constant, k_1 , for the “concerted” process is almost completely insensitive to substituents on the aldehyde,⁴ whereas $K_n k_3$ for the stepwise process is strongly dependent on the nature of the aldehyde, the observed rate constants, k_H , for hydronium ion catalysis of carbinolamine formation from such a weakly basic amine should be insensitive to polar substituents on the aldehyde, and k_H values for more strongly basic amines should exhibit an increased dependence on aldehyde substituents as the stepwise pathway becomes more important. For an amine of intermediate basicity, a change in the predominant mechanism, from “concerted” to stepwise, as K_{ad} is increased, resulting in a nonlinear dependence of $\log k_H$ on $\log K_{ad}$, is expected.

It was expected that the very weak base, 2-methyl-3-thiosemicarbazide ($pK_a' = 1.20$), might provide an example of an amine for which the “concerted” pathway of hydronium ion catalysis is predominant for benzaldehydes with widely varying values of K_{ad} . Acid-catalyzed formation of the carbinolamine from this amine and *p*-chlorobenzaldehyde has previously been assigned to the “concerted” pathway since the observed rate constants are too large to be accounted for by a mechanism involving T^\ddagger as an intermediate.¹⁰ If the “concerted” pathway of hydronium ion catalysis is always the predominant one, the rate constants, k_H , for this amine should be insensitive to substituents on the benzaldehyde. A comparison of the plot of $\log k_H$ against σ^+ for 2-methyl-3-thiosemicarbazide with similar plots of $\log k_1$ (lower line) and $\log K_n k_3$ (upper line) for methoxyamine is shown in Figure 6. In accordance with our hypothesis, ρ^+ for 2-methyl-3-thiosemicarbazide is much smaller than expected for a stepwise process ($K_n k_3$) and is similar to that observed for the “concerted” reaction of methoxyamine.

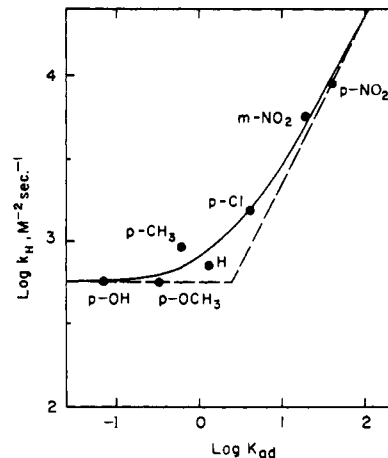


Figure 7. Dependence of the observed rate constants at pH > 2.0 for hydronium ion catalyzed carbinolamine formation from semicarbazide and substituted benzaldehydes in water at ionic strength 0.5 (ref 12) on $\log K_{ad}$ for equilibrium formation of the carbinolamines in 25% ethanol at ionic strength 0.32 [ref 11: R. Wolfenden and W. P. Jencks, *J. Amer. Chem. Soc.*, **83**, 2763 (1961)]. The solid line is the theoretical curve for a change in mechanism with increasing values of K_{ad} from a limiting slope of 0 to 1.0.

For an amine of intermediate basicity such as semicarbazide ($pK_a' = 3.86$), the stepwise and “concerted” pathways are relatively close in energy, and a change in the favored pathway at intermediate pH values from “concerted” to stepwise occurs as the tendency of the aldehyde to add a molecule of amine, and hence the stability of the intermediate T^\ddagger relative to starting materials, is increased. This is shown by the change in the shape of the pH-rate profile from type A (Figure 5) for *p*-methoxybenzaldehyde to type B for *p*-nitrobenzaldehyde (Figure 4). As a consequence of this change in mechanism, a plot of $\log k_H$ against $\log K_{ad}$ for the hydronium ion catalyzed reaction of semicarbazide with substituted benzaldehydes at pH 2–3 should undergo a change in slope, from ~ 0 to ~ 1.0 , as K_{ad} for the aldehyde is increased. A plot against $\log K_{ad}$ of the values of $\log k_H$ for a series of substituted benzaldehydes determined at pH values > 2 by Cordes and Jencks¹² is given in Figure 7. The relatively poor Hammett correlation of these data with a single straight line of slope $\rho^+ = 0.71$ found by these workers is easily explained if the reaction undergoes a change in mechanism and a corresponding change in Hammett slope with increasing electrophilicity of the aldehyde. The data of Figure 7 agree well with two lines of slope 0 and 1.0 for the “concerted” and stepwise pathways, respectively, and a transition point (where both mechanisms make an equal contribution to the observed rate) in the region approximately corresponding to unsubstituted benzaldehyde. This corresponds to a nonlinear Hammett correlation with limiting slopes, ρ^+ , of approximately 0 and 1.5 for electron-donating and electron-withdrawing aldehydes, respectively; the ρ^+ value for K_{ad} , determined from the data of Anderson and Jencks¹¹ for this equilibrium in 25% ethanol, is 1.5.

Evidence consistent with some contribution of a stepwise mechanism of *general* acid catalysis of carbinolamine formation from semicarbazide and *p*-chlorobenzaldehyde, which lies just above the transition point from the “concerted” to the stepwise mechanism (Figure 7), is provided by the apparent curvature in the Brønsted plot for general acid catalysis of this reaction that has been pointed out by Barnett.²⁵ This curvature, analogous to that observed for catalysis of the reaction of methoxyamine and *p*-methoxybenzaldehyde,⁴ suggests that general acid catalysis of the addition of semicarbazide to *p*-chlorobenzaldehyde may pro-

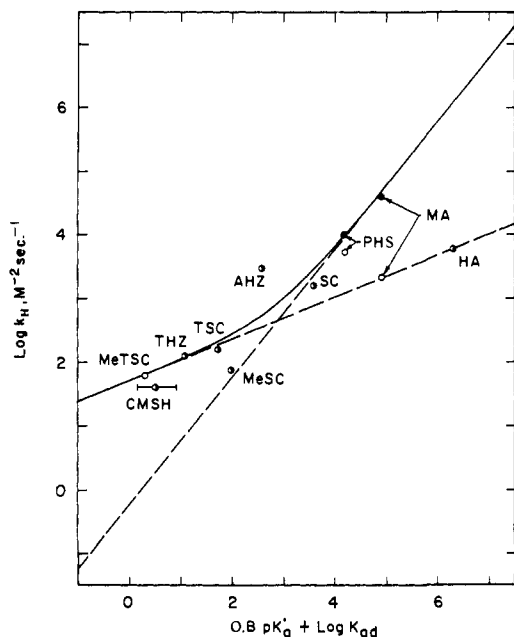


Figure 8. Dependence of the logarithms of the rate constants for hydronium ion catalyzed carbinolamine formation from *p*-chlorobenzaldehyde and substituted hydrazines and hydroxylamines on pK_a' and $\log K_{ad}$ for the nucleophiles. Abbreviations are given in Table II. The solid symbols (\bullet) have been assigned unequivocally to the stepwise ($K_n k_3$) and the open symbols (\circ) to the "concerted" (k_1) pathway. The slopes of the lines corresponding to k_1 and $K_n k_3$ are 0.33 and 1.0, respectively. The solid line represents the sum of the two pathways.

ceed at least in part *via* a stepwise pathway with a rate-determining proton transfer step.

Structure-Reactivity Correlations. The Nucleophile. The third prediction based on the mechanistic scheme of eq 4 is that a plot of $\log k_H$ for hydronium ion catalyzed carbinolamine formation against $\log K_n$, the equilibrium constant for formation of T^\pm from starting materials, should be nonlinear, reflecting a change in mechanism from stepwise to "concerted" as the stability of T^\pm is decreased. A measure of the relative values of K_n for the intermediates formed from different amines with a single aldehyde is given by eq 11, which was derived from eq 10 and the relationship $\Delta \log$

$$\Delta \log K_n = \Delta \log K_{ad} + 0.8 \Delta pK_{nuc} \quad (11)$$

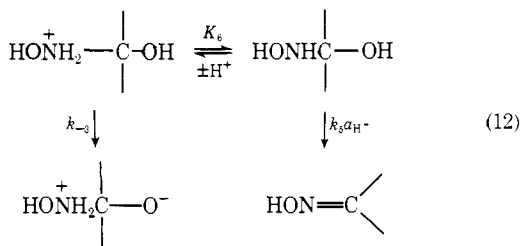
$K_2 = 0.8 \Delta pK_{nuc}$, corresponding to $\beta_{nuc} = 0.8$ for K_2 . The slope of a plot of $\log k_H$ against the quantity ($\log K_{ad} + 0.8 pK_{nuc}$) should measure the degree of resemblance of the transition state to T^\pm ; for a diffusion-controlled protonation of T^\pm this slope should be 1.0. Such a plot of the observed values of $\log k_H$ for the reactions of a series of substituted hydrazines and hydroxylamines with *p*-chlorobenzaldehyde is given in Figure 8. A line of slope 1.0 has been drawn through the two solid points for methoxyamine and phenylhydrazine-*p*-sulfonate, which have been assigned to the stepwise process, $K_n k_3$, from analysis of pH-rate profiles. The observed rate constants for the weakly basic amines chloromethanesulfonylhydrazide, 2-methyl-3-thiosemicarbazide, *p*-toluenesulfonylhydrazide, and thiosemicarbazide fall above this line of slope 1.0 for the stepwise pathway. This is consistent with a different mechanism for the hydronium ion catalyzed reactions of these compounds. The observed rate constant, k_H , for 2-methyl-3-thiosemicarbazide is also assigned to the process, k_1 , by an independent criterion, the similarity of the ρ^+ values for this reaction and for k_1 for methoxyamine. The observations that the addition of 2-methyl-3-thiosemicarbazide is subject to general acid ca-

talysis by buffers, and that the hydronium ion lies on the Brønsted plot for this buffer catalysis,¹⁰ provide evidence that hydronium ion catalysis *via* pathway I for this compound involves true, "concerted" general acid catalysis, rather than specific acid catalysis.⁴

A line of slope 0.33 through the points corresponding to k_1 for 2-methyl-3-thiosemicarbazide and methoxyamine (open symbols, Figure 8) is in good agreement with the observed values of k_H for other weakly basic amines that are too fast to be accounted for by the stepwise process, $K_n k_3$. The solid line represents the values of k_H that should be observed for the overall reaction if a change in mechanism from the "concerted" to the stepwise pathway occurs with increasing values of pK_a' and K_{ad} . The observed value of k_H for acetylhydrazide shows a positive deviation, and that for 2-methylsemicarbazide shows a negative deviation from this line, and k_1 for phenylhydrazine-*p*-sulfonate also shows a positive deviation from the line of slope 0.33 correlating the values of k_1 . The existence of these deviations is probably a result of a relatively poor correlation of k_1 with K_n and is not surprising in view of the fact that the stability of transition state 1 for the "concerted" process probably does not exhibit the same relative sensitivity to $\log K_{ad}$ and pK_a' as does that of T^\pm .

The existence of a change in *mechanism* (and not merely in the finer details of transition state structure) for the acid-catalyzed addition step in the formation of hydrazones and related compounds as a function of the basicity of the amine means that interpretations of mechanism based on the Hammond postulate (e.g. the correlation of Brønsted α values for general acid catalysis with pK_{nuc}),¹² which require the existence of a continuous variation in transition state structure with varying basicity of the nucleophile, are not valid for this system. The theory of the "Hammond postulate" correlations of this kind is not in question here, and a meaningful correlation of α with amine basicity might be found if a sufficiently large range of very weakly basic amines, which should react by the single more-or-less "concerted" process of pathway I, could be investigated. Experimental results presently available, however, do not include such a series.

The large (~ 200 -fold) negative deviation of hydroxylamine (Figure 8) from the line of slope 1.0 for $K_n k_3$ and the observation that this point falls on the line corresponding to k_1 indicate that the only observable mechanism of hydronium ion catalysis for this compound is *via* the "concerted" pathway I. Why is a stepwise mechanism for hydronium ion catalysis of the addition of this relatively strongly basic and nucleophilic amine not observed, when the rate constant, $K_n k_3$, for this mechanism (estimated by extrapolation from the line of slope 1.0 for methoxyamine and phenylhydrazine-*p*-sulfonate) is approximately $10^6 M^{-2} \text{sec}^{-1}$, 200 times larger than the observed rate constant? Either or both of the following considerations may account for this observation. (1) The reaction of hydroxylamine ($pK_a' = 6.15$), the most basic amine in this series, may have a pH-rate profile corresponding to type C (Figure 5). The observed rate constant, $K_{ad} k_5$, under conditions where the hydronium ion catalyzed dehydration step is rate determining, is $1.3 \times 10^6 M^{-2} \text{sec}^{-1}$ at ionic strength 0.5. Hence the estimated value of $10^6 M^{-2} \text{sec}^{-1}$ for $K_n k_3$, the rate constant that would be observed if proton transfer were rate determining, suggests that the rate of this process must be close to, and could be larger than, the rate of the dehydration step.²⁶ This corresponds to a situation (eq 12) in which k_5 for conversion of T^0 to the oxime is slower than k_{-3}/K_6 for the proton transfer step in the reverse direction, and proton transfer never becomes rate determining. (2) If the un-



catalyzed intramolecular proton transfer process (k_4 , eq 4) that converts T^\pm to T^0 is *faster* than the uncatalyzed expulsion (k_{-2}) of hydroxylamine from T^\pm , the steady-state rate law for the addition step (eq 7a) reduces to eq 13, and the

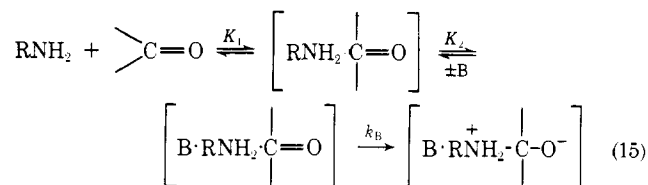
$$k_{\text{ad}}^0 = k_1 a_{\text{H}^+} + k_2 \quad (13)$$

rate law for the overall reaction is given by eq 14, corre-

$$k_{\text{obsd}}^0 = \frac{K_{\text{ad}} k_5 a_{\text{H}^+} (k_1 a_{\text{H}^+} + k_2)}{K_{\text{ad}} k_5 a_{\text{H}^+} + k_1 a_{\text{H}^+} + k_2} \quad (14)$$

sponding to a reaction with only two kinetically significant steps, carbinolamine formation and dehydration, in which simple proton transfer never becomes rate determining. An unusually high value for the rate constant for intramolecular proton transfer is expected for hydroxylamine (see below) because of the possibility of intramolecular proton donation from the hydroxylamine oxygen to the alcoholate anion of T^\pm .

pH-Independent Reactions. Figure 9 shows the dependence on amine basicity of the observed rate constants, k_{U} , for uncatalyzed (or solvent-catalyzed) carbinolamine formation from *p*-chlorobenzaldehyde, with rate-determining steps corresponding to k_2 (upper line) and $K_{\text{n}}k_4$ (lower line). These two steps have been conclusively identified for the reactions of methoxyamine and phenylhydrazine-*p*-sulfonate, for which the uncatalyzed attack of the nucleophile (k_2) and the solvent mediated isomerization of T^\pm ($K_{\text{n}}k_4$) occur in separate, kinetically distinguishable steps that are rate determining in different regions of the pH-rate profile. The values of k_2 for these two amines were determined experimentally from the pH-rate profiles. For 2-methyl-3-thiosemicarbazide, the "concerted" pathway for hydronium ion catalysis is faster than the stepwise pathway (see above); hence the pH-rate profile is presumably of type A (Figure 5), and the process corresponding to k_2 cannot be observed directly. A range for k_2 for this amine was estimated from the rate constant, k^{GB} , for attack of the nucleophile within a termolecular encounter complex of the nucleophile, the aldehyde, and a general base catalyst¹⁰ (eq 15). For catalysis of this reaction by strong bases, k_{B} is rate



determining, and the observed third-order rate constant, k^{GB} , is given by eq 16. In the preassociation mechanism

$$k^{\text{GB}} = K_1 K_2 k_{\text{B}} \quad (16)$$

proposed for the base-catalyzed reaction,¹⁰ the base plays no chemical role in the process represented by k^{GB} and the observed second-order rate constant, k_2 , for the attack step in the absence of the base should differ from k^{GB} only by

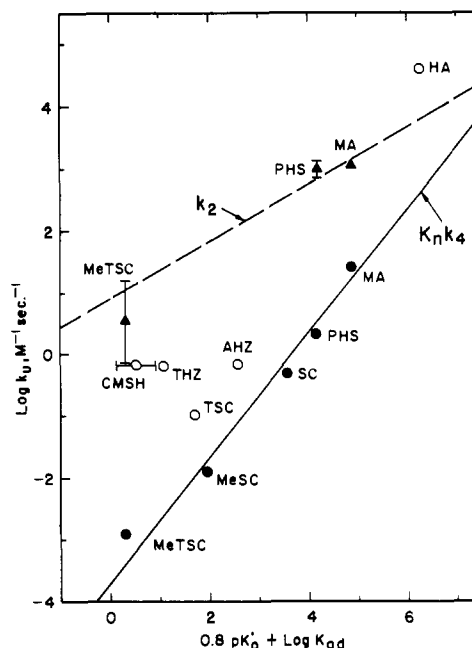
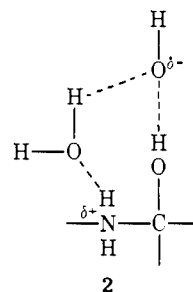


Figure 9. Dependence of the logarithms of the rate constants, k_2 (\blacktriangle) and $K_{\text{n}}k_4$ (\bullet) for uncatalyzed formation of carbinolamines from *p*-chlorobenzaldehyde and substituted hydrazines and hydroxylamines on $\text{p}K_{\text{a}}'$ and $\log K_{\text{ad}}$ for the nucleophiles. Abbreviations are given in Table II. The limits shown for k_2 for 2-methyl-3-thiosemicarbazide were estimated from the data of ref 10 (see text). The slopes of the lines corresponding to k_2 and $K_{\text{n}}k_4$ are 0.45 and 1.0, respectively. The open symbols (O) represent compounds possessing an acidic hydrogen α to the nucleophilic nitrogen.

the association constant for encounter complex formation and should be equal to $K_1 k_{\text{B}}$. If $\log K_1$ is taken as $^{10} -1.0 \pm 0.7$ and the observed value of k^{GB} for strong bases is $0.33 \text{ M}^{-2} \text{ sec}^{-1}$, k_2 for 2-methyl-3-thiosemicarbazide is equal to k^{GB}/K_1 , between 0.7 and $16 \text{ M}^{-1} \text{ sec}^{-1}$. This estimate and the experimental values of k_2 for methoxyamine and phenylhydrazine-*p*-sulfonate were used to determine the upper line of Figure 9.

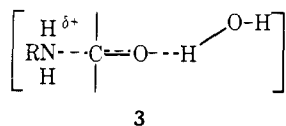
The solid circles of Figure 9 for the uncatalyzed reactions of 2-methyl-3-thiosemicarbazide, 2-methylsemicarbazide, and semicarbazide fall well below the upper line corresponding to the rate constants k_2 for methoxyamine and phenylhydrazine-*p*-sulfonate. Hence the uncatalyzed reaction that is observed at moderately acidic pH values for weakly basic hydrazine derivatives is assigned to the rate-determining solvent-catalyzed proton transfer process, $K_{\text{n}}k_4$. The slope of the line through the solid circles is 1.0, consistent with a transition state 2 for this process that



closely resembles the intermediate, T^\pm , in its sensitivity to K_{ad} and amine basicity. A transition state with significant positive charge on nitrogen has also been proposed for this process on the basis of the accelerating effect of electron-donating aldehyde substituents on k_4 for methoxyamine.⁴ The large secondary deuterium isotope effects²⁸ that are

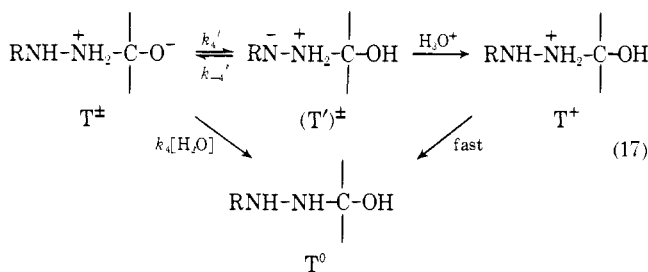
observed for pH-independent carbinolamine formation appear to be not inconsistent with transition state **2** in which the carbon-nitrogen bond is fully formed.

It should be noted that, on theoretical grounds, this pH-independent reaction cannot involve "concerted" carbon-nitrogen bond formation and general acid catalysis by water (transition state **3**) if T^\pm has a finite lifetime since proton transfer to T^\pm is thermodynamically unfavorable and hence cannot provide any stabilization²⁹ for transition state **3**. The

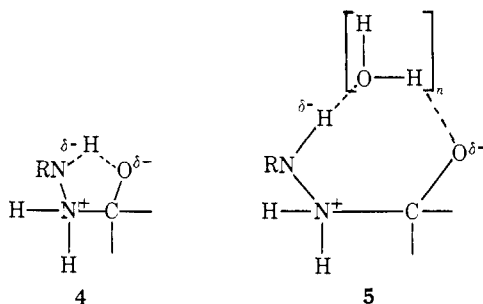


observation, in this and the preceding⁴ paper, of two distinct pH-independent processes, k_2 and $K_n k_4$, corresponding to different regions of the pH-rate profile, provides direct experimental evidence for the "nonconcertedness" of the pH-independent reaction.

The points corresponding to chloromethanesulfonylhydrazide, *p*-toluenesulfonylhydrazide, thiosemicarbazide, and acetylhydrazide (open circles, Figure 9) show positive deviations of approximately one to two orders of magnitude from the solid line corresponding to $K_n k_4$. These substituted hydrazines possess an acidic proton in the 2 position, which is well situated to participate in an intramolecular proton transfer process (k_4' , eq 17) that may occur either



directly (transition state **4**) or through one or more water molecules (transition state **5**). For these compounds, the



pK_a values^{7,8,30} for dissociation of the 2 proton of the hydrazine moiety are in the range 9.7–13. The juxtaposition of a positive charge in T^\pm should lower this pK_a by ~ 12 units;³¹ the electron-donating substituent (*p*-ClC₆H₄)(O⁻)HC will offset this effect on slightly,³² and the pK_a for conversion of T^\pm to the corresponding N-2 anion is therefore expected to be in the range of -2 to $+2$. Hence the proton transfer process, k_4' , should be strongly favorable thermodynamically and should occur faster than the water-mediated proton switch process, k_4 , which is expected to have a rate constant³³ on the order of 10^7 – 10^8 sec⁻¹. The reverse process, k_{-4}' , is thermodynamically unfavorable and should be slow relative to the protonation of $(\text{T}')^\pm$ by the hydronium ion at pH values where k_4' is kinet-

ically significant, so that some aspect of the intramolecular proton transfer process, k_4' , should be the rate-determining step for this mechanism. We conclude that for substituted hydrazines with a moderately acidic proton in the 2 position, stepwise intramolecular general acid catalysis by this acidic group provides a reasonable pathway for unusually fast "uncatalyzed" carbinolamine formation.

For the intermediate, T^\pm , derived from hydroxylamine, the pK_a of the hydroxylamine oxygen is estimated to be 3.7 from the pK_a' of 3.4 for trimethylamine *N*-oxide¹² and structure-reactivity correlations.^{10,27} Hence intramolecular proton transfer from this oxygen (k_4') may also be significant for this compound. The observed rate constant for the uncatalyzed reaction of hydroxylamine lies two orders of magnitude above the line corresponding to $K_n k_4$ and is at least as large as the predicted value of k_2 for uncatalyzed attack (Figure 9, upper line). This is consistent with the hypothesis that intramolecular proton transfer from the hydroxylamine oxygen atom, k_4' , is sufficiently fast that the uncatalyzed attack step becomes rate determining under all conditions for pH-independent carbinolamine formation from this compound.

Acknowledgment. We are most grateful to Professor William P. Jencks for valuable comments and suggestions.

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- (17) Use of H_0 values and the pK_a' of 6.15 determined at ionic strength 0.5 for hydroxylamine to calculate the free base concentration for this amine in the H_0 range gave a value of k_U for the uncatalyzed reaction of this compound of $6.4 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$, as compared with $3.9 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$ obtained from measurements in weakly acidic solution⁹ at ionic strength 0.5. This observation means that a discontinuity in the calculated value of k_U for this uncatalyzed reaction exists between the H_0 and pH regions. This discontinuity presumably results from the fact that $\gamma_{\text{NH}^+} / \gamma_{\text{NH}^+}$ for the neutral transition state for the uncatalyzed reaction. If the pK_a value of 5.97 for hydroxylamine at ionic strength zero [T. C. Bissot, R. W. Parry, and D. H. Campbell, *J. Amer. Chem. Soc.*, **79**,

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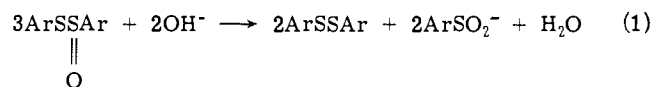
Mechanism of the Alkaline Hydrolysis of Aryl Thiolsulfonates and Thiolsulfonates¹

John L. Kice* and Thomas E. Rogers

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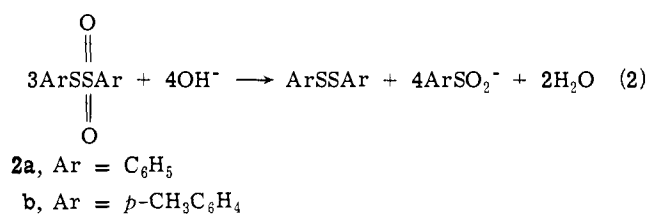
Abstract: The kinetics of the alkaline hydrolysis of phenyl benzenethiolsulfinate (**1a**) and phenyl benzenethiolsulfonate (**2a**) have been studied in 60% dioxane containing 0.005–0.05 N OH⁻ by stopped-flow spectrophotometry. The results show that **2a** hydrolyzes significantly faster than **1a** and that large amounts of **1a** are formed as an intermediate in the hydrolysis of **2a**. Initial attack of hydroxide ion on **2a** yields PhSO₂⁻ and benzenesulfenic acid. The anion of the sulfenic acid then rapidly attacks some of the remaining **2a** to yield **1a** and PhSO₂⁻. Initial attack of OH⁻ on **1a** occurs at comparable rates at both phenyl sulfur, to give PhSOH plus PhSO⁻, and sulfinyl sulfur, to give PhS⁻ plus PhSO₂H. It is important to stress that the results are *not* compatible with schemes in which attack of hydroxide on **1a** occurs exclusively at one sulfur. As long as any **2a** is present, the PhS⁻ formed by attack of hydroxide ion on the sulfinyl sulfur of **1a** reacts very rapidly with **2a** to yield phenyl disulfide and PhSO₂⁻. When **2a** is not present, the PhS⁻ reacts at a slower but still rapid rate with remaining **1a** to give the disulfide and PhSO⁻. The present results and conclusions are compared with earlier conflicting suggestions regarding the mechanism of alkaline hydrolysis of thiolsulfonates and thiolsulfonates, and it is concluded that, while they support in general the suggestions made by Savige, *et al.*, they are contrary in most important respects to the proposals advanced by Oae, *et al.*

In alkaline solution, aryl thiolsulfonates, **1**, undergo hydrolysis very readily to afford sulfinate ion and aryl disulfide as the final products (eq 1). The same stoichiometry



1a, Ar = C₆H₅
b, Ar = p -CH₃C₆H₄

also applies for the hydrolysis of the thiolsulfinate derived from cystine.² The more highly oxidized aryl thiolsulfonates, **2**, also give sulfinate ion and disulfide on alkaline hydrolysis, although in different proportion (eq 2).³ The thiolsulfonate from cystine behaves similarly.^{2b} Both reactions are intriguing from a mechanistic point of view because



there are a variety of possible reaction paths that can be suggested for each.

Savige and coworkers^{2b} reported that at pH 5–7 cystine monoxide (the thiolsulfinate) was more stable than cystine dioxide (the thiolsulfonate) and in fact was formed as a detectable intermediate during the initial stages of the hydrolysis of the dioxide. On the other hand, Oae and coworkers