Imine-Forming Elimination Reactions. I. General Base and Acid Catalysis and Influence of the Nitrogen Substituent on Rates and Equilibria for Carbinolamine Dehydration[1]

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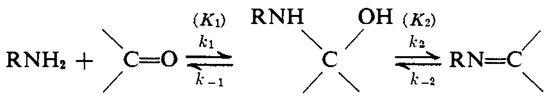
Abstract: The base-catalyzed dehydration of carbinolamines derived from substituted hydrazines and *p*-chlorobenzaldehyde is strongly accelerated by electron-withdrawing substituents on the hydrazine moiety; the value of β_N for the hydroxide ion catalyzed reaction is approximately -0.97. Electron withdrawal at nitrogen decreases the equilibrium constants for conversion of the carbinolamines to the hydrazones: $\beta_N = {\sim}0.4$. The Brønsted β value for general base catalysis of the reaction is approximately 0.7, and there is no evidence for a change in this value for the reactions of hydrazines varying in pK_a' from -7.2 to 3.44. The suggested mechanism for base-catalyzed dehydration involves true general base catalysis with a large degree of negative charge development on nitrogen and little double bond formation in the transition state. Brønsted α values for general acid catalysis of the dehydration step in substituted hydrazone formation from *p*-chlorobenzaldehyde are: hydrazine, 0.62; phenylhydrazine-*p*-sulfonic acid, 0.67; semicarbazide, 0.72; and acethydrazide, 0.72. Both general acid and general base catalysis of this reaction are believed to involve proton transfers which are in some sense concerted with changes in bonds involving carbon; these mechanisms avoid the formation of extremely unstable nitrogen anion and *O*-protonated carbinolamine intermediates. The more basic hydrazines also exhibit a pH- and buffer-independent pathway for the dehydration step, which is formulated as the uncatalyzed expulsion of hydroxide ion from the neutral carbinolamine. Both the hydronium ion catalyzed and the spontaneous reaction are accelerated by electron-donating substituents on the hydrazine; as predicted by the Hammond postulate, the acid-catalyzed reaction is less sensitive to the pK_a' of the hydrazine ($\beta_N = {\sim}0.4$) than the uncatalyzed reaction ($\beta_N = {\sim}0.8$).

The condensation of amines with carbonyl compounds to yield imines proceeds by a stepwise mechanism (eq 1) involving formation of a tetrahedral addition intermediate followed by its dehydration to yield the observed product. A change in rate-determining step for such reactions is normally observed in the weakly acidic pH range, with rate-determining dehydration of the carbinolamine (k_2) at pH values near and above neutrality.[2] This dehydration is formally analogous to the elimination of HX from a carbon system leading to an olefinic double bond. For the reactions catalyzed by bases (*e.g.*, thiosemicarbazone,[3] semicarbazone,[4] and oxime[4,5] formation), transition states related to either the E2 or the E1cb mechanisms of olefin-forming elimination reactions are possible; these correspond, respectively, to concerted general base catalysis and specific base catalysis (with or without general acid catalysis of leaving group departure) of the imine-forming elimination reactions. Differences between the transition states for olefin-forming and imine-forming eliminations might be expected to arise from the lower activation energy for proton transfer from the electronegative nitrogen atom as compared to carbon,[6] and from the availability of a nonbonded electron pair[7] on nitrogen in the carbinolamines. Studies of structure–reactivity correlations in carbon–carbon elimination reactions[8] have provided a fairly detailed understanding of the transition state charge distributions for many such reactions, and it has been our intention, in this and other studies now in progress, to apply a similar approach to simple imine-forming elimination reactions. The present paper reports the effects of varying substituents on nitrogen on the rates of uncatalyzed and acid and base catalyzed hydrazone formation from carbinolamines derived from *p*-chlorobenzaldehyde and a series of substituted hydrazines.



$$\mathrm{RNH_2} + \;{>}\mathrm{C{=}O} \underset{k_{-1}}{\overset{(K_1)\;k_1}{\rightleftharpoons}} \overset{\mathrm{RNH}\quad\mathrm{OH}}{{>}\mathrm{C}{<}} \underset{k_{-2}}{\overset{k_2\;(K_2)}{\rightleftharpoons}} \mathrm{RN{=}C}{<} \qquad (1)$$

Experimental Section

Materials. Reagent grade inorganic salts were used without further purification. Organic reagents were recrystallized, distilled, or sublimed before use. Glass-distilled water was used in all experiments. Solutions of *p*-chlorobenzaldehyde were prepared as previously described.[3] Solutions of semicarbazide were prepared by neutralizing the hydrochloride with a stoichiometric quantity of potassium hydroxide immediately before use. Phenylhydrazine-*p*-sulfonic acid was dissolved by addition of a stoichiometric quantity of potassium hydroxide to the insoluble acid form in the presence of 2.4×10^{-4} *M* Na_2EDTA. This could be conveniently accomplished while stirring, and following the pH of the solution on a pH meter.

N-Aminopyridinium chloride was prepared by a modification of the procedure of Gösl and Meuwsen[9] from 0.5 mol of pyridine and 0.25 mol of hydroxylamine-*O*-sulfonic acid which had been neutralized with 50 ml of 5.0 *N* potassium hydroxide. The chloride salt of the product was prepared by acidification with concentrated

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Table I. Experimental Conditions[a] for Determination of Rate Constants for Substituted Hydrazone Formation from *p*-Chlorobenzaldehyde

Compd	Type expt	λ, nm	Amine concn, *M*	Aldehyde concn, *M*	Product[b] λ_{max}, nm
N-Aminopyridinium chloride	First order	310	0.01	2×10^{-4}	293
$C_5H_5^+NNH_2Cl^-$		320	0.05, 0.20	5×10^{-5}	
p-Toluenesulfonylhydrazide	Initial rate	310, 315	0.005	1.5×10^{-4}[c]	277[d]
$CH_3C_6H_4SO_2NHNH_2$				7.5×10^{-4}	308[e]
	First order	300, 315	0.005	2×10^{-5}	
Acethydrazide	Initial rate	305	0.10	7.5×10^{-4}	285
$H_3CCONHNH_2$	First order	285	0.10–0.20	2×10^{-5}	
Semicarbazide	Initial rate	305	0.10	7.5×10^{-4}	284
$H_2NCONHNH_2$	First order	285	0.10	2×10^{-5}	
Ethyl carbazate	Initial rate	302	0.10	7.5×10^{-4}	
$C_2H_5OCONHNH_2$	First order	292	0.10	2×10^{-5}	280
Phenylhydrazine-*p*-sulfonic acid, $HOSO_2C_6H_4NHNH_2$	Initial rate	345	0.01	8×10^{-4}	347
Hydrazine	First order	290	0.01	6×10^{-5}	
NH_2NH_2	First order	300	0.05	$8.0\text{–}9.0 \times 10^{-5}$	272

[a] Kinetic experiments at 25° and ionic strength 1.0 (potassium chloride). [b] Extinction coefficients of the products at λ_{max} are $2.1 \pm 0.4 \times 10^4$ for all compounds. [c] Path length 5 cm. [d] At pH 4.6. [e] At pH 10.1.

hydrochloric acid of an aqueous methanolic solution of the carbonate. The product was isolated after evaporation of the filtrate, repeated evaporations from ethanol, and crystallization from absolute ethanol in a Dry Ice-2-propanol bath. It was recrystallized from ethanol-ether to give a melting point of 158-161° (lit.[10] mp 160°).

pK_a' Determinations. The pK_a' values of the nucleophiles (with the exception of *p*-toluenesulfonylhydrazide and *N*-aminopyridinium chloride) were determined by potentiometric titration at 25° and ionic strength 1.0 maintained with potassium chloride. Because of the insolubility of *p*-toluenesulfonylhydrazide and its low pK_a' this method was not practicable, and this ionization constant was determined kinetically from the pH dependence of the rate of the reaction of 5.0×10^{-3} *M* (total) *p*-toluenesulfonylhydrazide with *p*-chlorobenzaldehyde between pH 0.11 and 2.02. Under these conditions the addition of the nucleophile to the carbonyl group is rate determining. Correction was made for the pH-independent addition reaction, $k_0 = 0.63\ M^{-1}\ \text{sec}^{-1}$, as determined in 0.002 *M* formate buffers, pH 2.98-4.09. (At this buffer concentration the correction for catalysis by formic acid is approximately 1.2% or less of the total rate for the addition step. Correction of k_0 for the contribution of the hydronium ion catalyzed dehydration to the overall rate was also made as previously described;[3] such a correction amounted to approximately 15% of the overall rate at the highest pH used.) The pK_a' of *p*-toluenesulfonylhydrazide was determined from a plot of $(k_{obsd} - k_0)$ against $(k_{obsd} - k_0)/a_{H^+}$. The slope of such a plot is $-K_a'$ and the ordinate intercept is $(K_a'k_{H_3O^+} - k_0)$.

The pK_a of *N*-aminopyridinium chloride was determined spectrophotometrically in concentrated sulfuric acid solutions (70-85%). A plot of log $[(A_{B^+} - A_{obsd})/(A_{obsd} - A_{BH^{2+}})]$ at 230 nm against $-H_0$[11] is linear, with a slope of 0.95. A plot against $-H_+$[12] has a slope of approximately 4. The value of A_{B^+} was obtained in 50% sulfuric acid, and the value of $A_{BH^{2+}}$ in concentrated sulfuric acid. The value of $(A_{B^+} - A_{BH^{2+}})$ obtained from the ordinate intercept of a plot of $(A_{obsd} - A_{BH^{2+}})$ against $(A_{obsd} - A_{BH^{2+}})$ antilog $(-H_0)$ agreed with that measured directly, and the same ionization constant was obtained from the reciprocal of the slope of the above plot and the abscissa intercept of the plot of log $[(A_{B^+} - A_{obsd})/(A_{obsd} - A_{BH^{2+}})]$ against $-H_0$. Reversibility of the spectral change of *N*-aminopyridinium chloride in strong acid was demonstrated by dilution of a concentrated sulfuric acid solution of the compound with water to give a spectrum identical with that of the unprotonated base.

Kinetics. Rates of reactions at 25° and ionic strength 1.0 (maintained with potassium chloride) were followed spectrophotometrically using a Zeiss PMQII spectrophotometer or a Gilford Model 2000 recording spectrophotometer. Spectral data for the products and the wavelengths and conditions used in the kinetic experiments are summarized in Table I. Where practicable, conditions were chosen such that pseudo-first-order kinetics were followed. Where instability of the nucleophile or product or the excessive time required for completion of the reaction rendered this method undesirable, initial rates (0.5-5% of total reaction) were followed. The technique employed in these experiments and the method of determining end points were similar to those used previously.[3] The following conditions were used for formation of the products to determine absorbance at time infinity: 6×10^{-3} *M* semicarbazide hydrochloride, acethydrazide, or ethyl carbazate plus 1.3×10^{-2} *M* hydrochloric acid; 2.7×10^{-3} *M* *p*-toluenesulfonylhydrazide plus 1.1×10^{-2} *M* hydrochloric acid and approximately 7% ethanol to prevent precipitation of the product; 2.7×10^{-3} *M* phenylhydrazine-*p*-sulfonic acid (potassium salt) plus 0.01 *M* potassium acetate buffer, 50% free base, and 6.7×10^{-4} *M* Na_2EDTA. At pH values below 7 the absorbance of the *p*-toluenesulfonylhydrazone of *p*-chlorobenzaldehyde at 310 nm is much lower than at higher pH, presumably as a result of protonation of the anion, and the product was insufficiently soluble to give good absorbance values at $l = 1$ cm; hence at low pH 5-cm path length cuvettes were used for the determination of product absorbance (3×10^{-5} *M*) and for the initial rate determination at an aldehyde concentration of 1.5×10^{-4} *M*.

Some difficulty was experienced as a result of decomposition of phenylhydrazine-*p*-sulfonic acid to yield optically absorbing products at the higher pH values. As this decomposition was reproducible at a given pH, a correction was made for it where necessary by subtracting the linear absorbance change observed upon addition of a solution of phenylhydrazine-*p*-sulfonic acid in the absence of aldehyde to a solution identical in composition with that used for each kinetic experiment. These corrections did not exceed 8% of the total absorbance change observed in the presence of aldehyde.

Rate constants, K_1k_2, for *p*-toluenesulfonylhydrazone formation at high pH were corrected for ionization of *p*-toluenesulfonylhydrazide to the anion (p$K_a' = 11.02$, determined by potentiometric titration of 0.02 *M* *p*-toluenesulfonylhydrazide with 1.0 *N* potassium hydroxide at 25°, ionic strength 1.0). No correction for the ionization of acethydrazide was required up to pH 12.50, as indicated by linear plots of k_{obsd} against hydroxide ion concentration. This suggests that the pK_a' for anion formation from acethydrazide under our conditions must be significantly higher than the value of 12.6 from potentiometric titration in water reported by Kaae and Senning[13] and may be closer to the value of 13.04 reported by Titov and coworkers.[14]

Rate constants for carbinolamine dehydration were calculated from the observed rate constants and the equilibrium constants for carbinolamine formation according to the equation $k_{2app} = k_{obsd}/K_1[N]$ at nucleophile concentrations much less than K_1 or the equa-

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tion $k_{2_{app}} = k_{obsd}(1 + K_1[N])/K_1[N]$ at higher nucleophile concentrations. The slopes of plots of the apparent rate constant against total buffer concentration were generally determined at two or more buffer compositions, and rate constants for general acid and general base catalysis were obtained from intercepts at 0.0 and 1.0 of plots of these observed slopes against the mole fraction of buffer in the acidic or basic form.

Rate constants, k_f, for the forward reaction of *N*-aminopyridinium chloride with *p*-chlorobenzaldehyde were determined from the observed pseudo-first-order rate constants, k_{obsd}, for approach to equilibrium of this reaction using the equation $k_f = k_{obsd}/([N] + 1/K_{12})$, where K_{12} is the overall equilibrium constant for imine formation.

Equilibrium constants for the formation of carbinolamines from *p*-chlorobenzaldehyde with acethydrazide and ethyl carbazate were determined spectrophotometrically in phosphate buffer, pH 7.5, from the initial rapid drop in absorbance at 270 (ethyl carbazate) or 260 nm (acethydrazide) upon addition of a solution of *p*-chlorobenzaldehyde of known absorbance to a solution containing a given concentration of amine. Concentrations of nucleophile from 0.1 to 0.5 *M* and a path length of 0.2 cm were used. Because of the high ultraviolet absorbance and side reactions of potassium phenylhydrazine-*p*-sulfonate and the low solubility of *p*-toluenesulfonylhydrazide, concentrations of these compounds sufficient to convert a significant fraction of *p*-chlorobenzaldehyde to the tetrahedral adducts could not be used. The considerably higher affinity of nucleophiles for pyridine-4-carboxaldehyde (PA) made it possible to determine equilibrium constants for addition to this compound at lower nucleophile concentrations. Estimates of the equilibrium constants for addition of the same nucleophiles to *p*-chlorobenzaldehyde were obtained from the relationship $K_{obsd}^{PA} = 35K^{PCBA}$.[15] The equilibrium constant for addition of *p*-toluenesulfonylhydrazide to pyridine-4-carboxaldehyde was determined by the absorbance decrease at 290 nm, extrapolated to zero time, of approximately 7×10^{-4} *M* pyridine-4-carboxaldehyde in solutions containing 0.002–0.010 *M* *p*-toluenesulfonylhydrazide. The pH was maintained at 7.4–7.5 with 0.02 *M* imidazole buffer, 35% hydrochloride. The extrapolation of absorbance *vs.* time was not linear for the first 20–30 sec of reaction, possibly as a result of the time required to establish a new equilibrium between the hydrated and unhydrated forms of the aldehyde in the presence of the nitrogen nucleophile. Values of the absorbance of hydrated plus unhydrated aldehyde at zero time were obtained by extrapolation from the linear portions of the plots (30–250 sec after mixing).

Since potassium phenylhydrazine-*p*-sulfonate absorbs strongly at wavelengths suitable for measuring the absorbance of pyridine-4-carboxaldehyde, a kinetic method was used to determine the equilibrium constant for its addition to this aldehyde. The pseudo-first-order rate constants for *p*-sulfophenylhydrazone formation from pyridine-4-carboxaldehyde in 0.1 *M* imidazole buffer, at pH 7.13 and ionic strength 1.0, were measured as a function of nucleophile concentration between 0.0025 and 0.06 *M* by following the appearance of product at 360 nm. The equilibrium constant for carbinolamine formation was obtained from the negative abscissa intercept of a linear plot of $1/k_{obsd}$ against $1/[N]$.

The equilibrium constant for carbinolamine formation from formaldehyde and *N*-aminopyridinium chloride was determined according to the procedure of Abrams[16] by measuring the absorbance change at 232 nm upon reaction of formaldehyde (0.01–1.00 *M*) with 10^{-4} *M* *N*-aminopyridinium chloride in 0.05 *M* phosphate buffer, pH 6.94. A stable final absorbance value corresponding to amine plus adduct at each formaldehyde concentration was obtained after 10 to 30 min. The concentration of the stock formaldehyde solution was determined by titration (to an end point of pH 9.6) of the base liberated by the reaction of approximately 10 mmol of formaldehyde with 50 ml of 1.0 *M* sodium sulfite. The γ value for *N*-aminopyridinium chloride and the equilibrium constant for addition to *p*-chlorobenzaldehyde were estimated from the observed equilibrium constant for addition of this nucleophile to formaldehyde and the structure–reactivity correlations of Sander and Jencks.[15]

Overall equilibrium constants, K_{12}, for imine formation from *p*-chlorobenzaldehyde were determined by measuring the increase in absorbance of a solution of 5×10^{-5} *M* aldehyde as a function of nucleophile concentration at four or more different nucleophile concentrations. Measurements were made after allowing the reaction mixtures (in a total volume of 50 ml) to equilibrate under argon at 25° for several hours. The fraction of aldehyde converted to product was determined from the relationship $f = (A - A_0)/(P - A_0)$, where A is the observed absorbance at a given amine concentration, A_0 is the absorbance of aldehyde, and P is the absorbance of a solution in which sufficient amine free base is present to drive the reaction to completion. The amine concentration was corrected for formation of product where necessary; this correction never exceeded 8% of the total amine concentration. At the pH of 1.02 employed for semicarbazide and acethydrazide, each amine exists primarily as its conjugate acid, so that K_{12}, the equilibrium constant for addition of the free base, is given by

$$(a_{H^+}/K_a')[f/(1 - f)[N]]$$

or by $1/K_a$ times the negative abscissa intercept of a plot of $1/(A - A_0)$ against $a_{H^+}/[N]$. K_{12} for *p*-toluenesulfonylhydrazone formation at pH 0.27 or 0.07 was calculated from the relationship $K_{12} = f/(1 - f)[N]\alpha$ where α is the fraction of the nucleophile present as the free base, or from plots of $1/(A - A_0)$ against $1/\alpha[N]$. The overall equilibrium constant for imine formation from *N*-aminopyridinium chloride and *p*-chlorobenzaldehyde was determined from the absorbance change at 330 nm produced by the reaction of 0.02–0.10 *M* *N*-aminopyridinium chloride with 4×10^{-4} *M* *p*-chlorobenzaldehyde in 0.10 *M* triethylenediamine buffer, pH 9.19. The equilibrium constant was evaluated from the negative abscissa intercept of a plot of $1/\Delta A$ against $1/[N]$ and from the negative reciprocal of the slope of a plot of ΔA against $\Delta A/[N]$.

Product Analyses. The product of the reaction of *p*-chlorobenzaldehyde with semicarbazide in 1 *M* potassium hydroxide has been shown by Anderson and Jencks[4] to be identical with the semicarbazone prepared under acidic conditions. *p*-Chlorobenzaldehyde toluenesulfonylhydrazone was prepared by the addition of 5 mmol of aldehyde in 10 ml of absolute ethanol to 40 ml of a solution of 5 mmol of toluenesulfonylhydrazide and 5.5 mmol of potassium hydroxide in 40 ml of 25% ethanol at 25° under argon. After 1 hr the solution was neutralized to pH 4.5 by addition of 5.5 mmol of hydrochloric acid, and the precipitated product was collected and crystallized from ethanol–water. The yield after two recrystallizations was 1.1 g (71%), mp 148–151° dec. The spectrum of this product in 0.1 *M* imidazole buffer (70% base), pH 7.6–7.7, ionic strength 1.0, was identical with that of the product formed in 0.01 *M* hydrochloric acid from *p*-toluenesulfonylhydrazide and *p*-chlorobenzaldehyde.

Anal.[17] Calcd for $C_{14}H_{13}ClN_2O_2S$: C, 54.45; H, 4.24; N, 9.07. Found: C, 54.34; H, 4.27; N, 9.09.

The identity of the product formed from *p*-chlorobenzaldehyde and *p*-toluenesulfonylhydrazide near neutral pH was checked by measurement of the initial rates of the reaction in 0.10 *M* imidazole buffer, pH 7.77, at four different wavelengths between 305 (the absorption maximum of the toluenesulfonylhydrazone at this pH) and 335 nm. Ratios of the initial rates (absorbance change/min) at 320 and 335 nm to the initial rate at 305 nm were 0.78 and 0.38, respectively, as compared with $A_{320}/A_{305} = 0.85$ and $A_{335}/A_{305} = 0.43$ determined from the spectrum in imidazole buffer of the product isolated from the reaction in strongly basic solution. Agreement within ±12% was obtained among the pseudo-first-order rate constants calculated from initial rate measurements at each of the above wavelengths, using as A_{final} the absorbance of product formed from the stock aldehyde solution and toluenesulfonylhydrazide in strong acid.

The acethydrazone and ethylcarbazone of *p*-chlorobenzaldehyde were prepared in 0.02 *M* potassium hydroxide, ionic strength 1.0, from 4×10^{-5} *M* aldehyde and 0.1 *M* nitrogen base. The spectra of the mixtures, read against blanks containing 0.1 *M* acethydrazide or ethyl carbazate, after acidification to a pH of ~7 to neutralize the product anions, were identical with the spectra of the acethydrazide and ethylcarbazate adducts of *p*-chlorobenzaldehyde prepared in formate buffers, pH 3.41 and 3.89, respectively, and resembled the spectrum of *p*-chlorobenzaldehyde semicarbazone. The spectrum of the hydrazone prepared under the conditions of the kinetic experiments in 0.02 *M* potassium hydroxide, pH 12.2, ionic strength 1, from 4×10^{-5} *M* aldehyde in the presence of 0.05 *M* hydrazine, was identical with the spectrum of the product formed from *p*-chlorobenzaldehyde and hydrazine at pH 6.8, so that no change in the products of these reactions upon changing from acidic or neutral to strongly basic conditions is indicated.

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Table II. Rate and Equilibrium Constants for the Formation of Substituted *p*-Chlorobenzaldehyde Hydrazones, RR′NN=CHC$_6$H$_4$Cl

RR′NNH$_2$	pK_a′	K_1, M^{-1}	K_2	K_{12}, M^{-1}	$k_2^{H^+}$,[a] M^{-1} sec^{-1}	$k_2^{OH^-}$,[b] M^{-1} sec^{-1}	k_2^0, sec^{-1}
N-Aminopyridinium chloride	−7.2	~0.01[c]		29		7.0×10^5	
p-Toluenesulfonylhydrazide (THZ)	1.09	1.7[d]	1.4×10^4	2.4×10^4	3.3×10^4	1.1×10^3	$\leq 8 \times 10^{-4}$
2-Methyl-3-thiosemicarbazide[e] (MeTSC)	1.20	0.23[d]			9.8×10^3	31	
Thiosemicarbazide[f] (TSC)	1.88	1.7			8.8×10^3	42	$\leq 2 \times 10^{-5}$
Acethydrazide (AHZ)	3.44	0.7	7.9×10^4	5.5×10^4	5.0×10^4	14	$\leq 3.3 \times 10^{-5}$
Ethyl carbazate (ECZ)	3.64	1.0				3.2	
Semicarbazide (SCZ)	3.86[g]	3.1[h]	1.6×10^5	5.1×10^6	5.2×10^4	0.32	1.5×10^{-5}
Phenylhydrazine-*p*-sulfonic acid (PHS)	4.90	1.8[d]			1.2×10^6	0.15	1.3×10^{-3}
Hydrazine	8.26	14[h]			1.8×10^6		1.7×10^{-2}

[a] Calculated from the observed pH and the empirical relationship antilog (−pH) = $0.9C_{H^+}$. [b] Based on hydroxide ion concentration, or the observed pH and the empirical relationship antilog (pH−14) = $0.67C_{OH^-}$: J. F. Kirsch and W. P. Jencks, *J. Amer. Chem. Soc.*, **86**, 833 (1964). [c] Based on an observed equilibrium constant of 16 for addition to hydrated plus unhydrated formaldehyde and the structure-reactivity relationships of ref 15. [d] Based on observed equilibrium constants for addition to pyridine-4-carboxaldehyde and the relationship $K_{obsd}^{PA} = 35K^{PCBA}$ (ref 15). [e] J. M. Sayer and W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 3262 (1972). [f] Reference 3. [g] W. P. Jencks and M. Gilchrist. *J. Amer. Chem. Soc.*, **90**, 2622 (1968). [h] Reference 15.

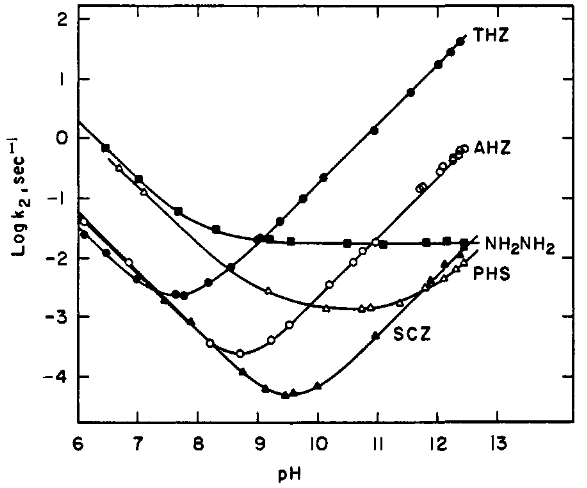


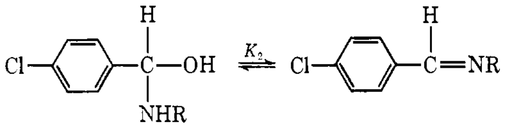
Figure 1. Dependence on pH of the logarithms of the rate constants, k_2, for dehydration of the carbinolamine adducts formed from *p*-chlorobenzaldehyde and hydrazine derivatives at 25°, ionic strength 1.0 (KCl). Rate constants were determined in dilute solutions of potassium hydroxide (pH >11.5) or were extrapolated to zero buffer concentration. The lines represent the theoretical curves for the kinetic constants of Table II. Abbreviations are listed in Table II.

The progress of the reaction of potassium phenylhydrazine-*p*-sulfonate (5 mmol) with *p*-chlorobenzaldehyde (5 mmol) in 10 ml of 40% ethanol containing 0.10 *M* potassium hydroxide was followed by removal of 0.2-ml samples, whose spectra were recorded after dilution to 2.0×10^{-4} *M* with water. The reaction followed satisfactory second-order kinetics as indicated by a linear plot of $1/(A_\infty - A_t)$ against time and the peak at 347 nm corresponded well in position and magnitude with the peak observed from the reaction of 0.02 *M* phenylhydrazine-*p*-sulfonic acid and *p*-chlorobenzaldehyde at pH 4.90 and ionic strength 1.0.

The product of the reaction of 1 *M* *N*-aminopyridinium chloride and 1 *M* *p*-chlorobenzaldehyde was formed in approximately 90% ethanol containing 0.05 *M* 3-quinuclidinol buffer, 50% base. The spectrum of a diluted sample of this product in 0.05 *M* phosphate buffer, pH 7.1, had the characteristic peak at 293 nm observed for a sample of the imine isolated from the reaction of equimolar proportions of the aldehyde and hydrazinium salt in 90% ethanol containing approximately 1 *M* hydrochloric acid. Hydrolysis of the product of the base-catalyzed reaction upon dilution to 7×10^{-4} *M* with 0.05 *M* triethylenediamine buffer, pH 9.0, gave products whose spectral characteristics agreed with those of an equimolar mixture of *p*-chlorobenzaldehyde and *N*-aminopyridinium chloride.

Results

Equilibria for Carbinolamine Formation and Dehydration. Table II lists the equilibrium constants for carbinolamine formation from *p*-chlorobenzaldehyde and substituted hydrazines. Values of K_{12}, the overall equilibrium constant for substituted hydrazone formation from *p*-toluenesulfonylhydrazide, acethydrazide, and semicarbazide, and K_2, the equilibrium constant for the partial reaction of eq 2, derived from the relationship $K_2 = K_{12}/K_1$, are also shown.



$$\text{Cl}\text{-C}_6\text{H}_4\text{-}\underset{\text{NHR}}{\overset{\text{H}}{\text{C}}}\text{-OH} \overset{K_2}{\rightleftharpoons} \text{Cl-C}_6\text{H}_4\text{-}\overset{\text{H}}{\text{C}}\text{=NR} \quad (2)$$

Kinetics. Figure 1 shows the dependence on pH of the first-order rate constants, extrapolated to zero buffer concentration, for dehydration of the carbinolamines formed from *p*-chlorobenzaldehyde and *p*-toluenesulfonylhydrazide, acethydrazide, semicarbazide, phenylhydrazine-*p*-sulfonic acid, and hydrazine at 25° and ionic strength 1.0. In the pH range above 6.0, where carbinolamine dehydration is rate determining, the reaction is subject to both hydronium and hydroxide ion catalysis and in several cases also exhibits a spontaneous reaction, k_2^0. Acid catalysis and the spontaneous reaction become more important relative to base catalysis as the basicity of the hydrazine increases, so that base catalysis becomes progressively more difficult to detect with strongly basic amines. This trend is already apparent with phenylhydrazine-*p*-sulfonic acid (pK_a′ = 4.9) and in the case of hydrazine (pK_a′ = 8.3) no hydroxide ion catalysis is detectable at pH values below 13.

The reaction of *p*-toluenesulfonylhydrazide exhibits an approximately 50% increase in observed rate constant over that calculated from the hydronium and hydroxide ion catalyzed rates at the minimum in the pH-rate profile. However, small discrepancies between the spectral characteristics of the product of this reaction and authentic *p*-toluenesulfonylhydrazone (see Experimental Section) suggest that part of the observed rate constant in this pH region may not be due to *p*-

toluenesulfonylhydrazone formation. A small (10–20%) rate enhancement also occurs at the minimum of the pH–rate curve for acethydrazide, and the upper limit (Table II) for the spontaneous reaction of this compound was calculated on the basis of this observation.

The dehydration of the carbinolamine intermediates is subject to general acid and general base catalysis by buffers ($k_2^{GA} + k_2^{GB}$, Table III). General acid catalysis becomes relatively more important as the pK_a' of the substituted hydrazine increases, and this is the only type of buffer catalysis observable for hydrazines of basicity equal to or greater than that of semicarbazide. An upper limit for k_2^{GB} for general base catalyzed semicarbazone formation by quinuclidine was calculated from the observed rate for the general acid catalyzed reaction at pH 9.5 (99% conjugate acid), and the assumption that a 20% rate increase due to combined general acid and general base catalysis at pH 10.97 (80% acid) would have been detectable. A similar limit for k_2^{GB} for quinuclidinol was calculated from the observed catalysis (primarily general acid) at pH 10.80 and 10.00 and the assumption that the slope at each pH value was accurate to ±10%.

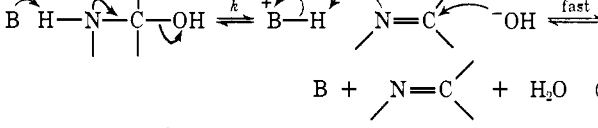
Discussion

Equilibria for Carbinolamine Formation and Dehydration. Equilibrium constants for carbinolamine formation from this series of substituted hydrazines and *p*-chlorobenzaldehyde (Table II) are comparable in magnitude and show no correlation with the pK_a' values of the hydrazines over a range of pK_a' from 1.1 to 4.9. The higher value of K_1 for hydrazine (pK_a' = 8.3) is partly the result of a statistical factor of 2 and probably also reflects the smaller steric requirements of the unsubstituted hydrazine group. The approximately 100-fold lower value of K_1 (*ca.* 0.01) for *N*-aminopyridinium chloride as compared with the other substituted hydrazines suggests that the affinity of this compound for the carbonyl group may resemble that of anilines, whose equilibrium constants for addition to formaldehyde[16] are 2–3 orders of magnitude lower than the analogous equilibrium constant for semicarbazide and formaldehyde.[15] The observed lack of sensitivity of K_1 to the pK_a' of substituted hydrazines is in agreement with the low sensitivity to substituents found for the equilibrium constants for addition of anilines[16] and secondary aliphatic amines[18] to formaldehyde.

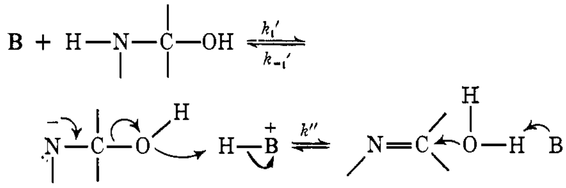
Values of K_2 for dehydration of the carbinolamines to the hydrazones, unlike those of K_1, are influenced by polar substituents on nitrogen and show a tendency to increase with increasing pK_a' of the hydrazines. A β_N value of approximately 0.4 may be estimated from K_2 for three compounds, *p*-toluenesulfonylhydrazide, acethydrazide, and semicarbazide. This effect is in accord with the increase in electronegativity expected for a change from sp^3 to sp^2 hybridization[19] and consequent greater electron demand at nitrogen in the imine, as well as the electron-withdrawing effect of the aromatic ring.

Hine and coworkers[20] have observed that K_{12} for imine formation from isobutyraldehyde and primary aliphatic amines is also increased by electron-donating substituents on the amine; however, in this system, unlike hydrazone formation from aromatic aldehydes, the substituent effect is almost entirely on K_1. The cause of the difference between the two systems is not clear.

General Base Catalysis. The results of this work confirm the importance of a general base catalyzed pathway for carbinolamine dehydration in imine formation from weakly basic amines. Two kinetically indistinguishable mechanisms for this reaction, as previously discussed for thiosemicarbazone formation,[3] are a "concerted"[21] reaction involving true general base catalysis occurring more or less simultaneously with expulsion of hydroxide ion (eq 3) and a preequilibrium proton abstraction from nitrogen followed by general acid catalysis of the departure of hydroxide ion (eq 4).



(3)



(4)

The extreme instability of the hypothetical amine anion intermediate of mechanism 4 is indicated by the following calculation.[3] The pK for N-protonation of the carbinolamine derived from acethydrazide is estimated to be approximately 1.2 from the pK_a' of 3.44 for acethydrazide and structure–reactivity correlations for amine ionization.[22] If the pK of ammonium ion is 9 and pK^0 for anion formation from ammonia is 35,[26] the relationship p$K'_{NH_4^+}$ − pK'_{CA^+} = X(p$K^0_{NH_3}$ − pK^0_{CA}) may be used to calculate pK^0_{CA}, for dissociation of the carbinolamine to the nitrogen anion. The relative sensitivity to substituent effects, X, of the dissociation of the neutral amine to an anion as compared to that of the protonated amine is expected to be between 0.86[27] and 1.3.[28,29] This gives a pK^0 value of 27 ± 2 for

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(21) (a) W. P. Jencks, *Chem. Rev.*, **72**, 705 (1972). (b) The term "concerted" refers here to a mechanism in which C–N bond cleavage is accompanied by a significant amount of proton transfer, so that the transition state occurs in the central region of the three-dimensional energy contour diagrams for these reactions; it does not attempt to distinguish between mechanisms in which the proton is at a potential energy maximum or is stabilized by hydrogen bonding in a potential well in the transition state.

(22) ρ^* for the dissociation of substituted ammonium ions was taken as −3.4, from a modification (J. Fox and W. P. Jencks, unpublished) of the relationship described by Hall;[23] a σ^* value of 0.765 was used for the hydroxybenzyl group.[24] The effect of the *p*-chloro substituent was estimated using ρ = −1.06 for the pK_a values of benzylamines.[25] The solvation effect upon conversion of a primary to a secondary amine with an equal value of $\Sigma\sigma^*$ was assumed to cause a decrease in pK_a of 1.10 units.[23]

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(27) H. Walba and R. Ruiz-Velasco, Jr., *J. Org. Chem.*, **34**, 3315 (1969).

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(29) R. Stewart and D. Dolman, *ibid.*, **45**, 925 (1967).

Table III. General Base and Acid Catalysis of Imine Formation from Substituted Hydrazines and *p*-Chlorobenzaldehyde at 25°[a]

Catalyst	pK_a'[b]	Concn range (total), *M*	Fraction as base	pH	Nucleophile concn (free base), *M*	$k_{\text{obsd}}\left(\frac{1+K_1[\text{N}]}{K_1[\text{N}]}\right)$, M^{-1} sec^{-1}	k_2^{GB}, M^{-1} sec^{-1}	k_2^{GA}, M^{-1} sec^{-1}
N-Aminopyridinium Chloride								
Imidazole (**3**)	7.24	0.08–0.40	0.30	6.80	0.20	0.097 ± 0.003	0.32 ± 0.03	
		0.08–0.40	0.50	7.19	0.20	0.15 ± 0.02[c]		
Triethylenediamine (**4**)	9.22	0.08–0.40	0.30	8.77	0.05	6.2 ± 1.1	23 ± 2	
		0.08–0.40	0.50	9.17	0.01	12		
		0.08–0.40	0.70	9.55	0.01	17 ± 2		
3-Quinuclidinol (**6**)	10.13	0.08–0.40	0.20	9.55	0.01	25	120	
		0.08–0.40	0.50	10.10	0.01	58		
p-Toluenesulfonylhydrazide								
Phosphate (**2**)	6.46	0.025–0.10	0.30	6.10	0.005	7.75×10^{-2}	$\leq 1.6 \times 10^{-2}$	0.11
		0.025–0.10	0.50	6.48	0.005	5.5×10^{-2}		
Imidazole (**3**)	7.24	0.05–0.30	0.35	7.00	0.005	3.2×10^{-3}	$6 \pm 1 \times 10^{-3}$	$\leq 0.4 \times 10^{-3}$
		0.08–0.40	0.70	7.62	0.005	4.8×10^{-3}		
		0.05–0.40	0.75	7.77	0.005	5.0×10^{-3}		
		0.08–0.40	0.90	8.18	0.005	4.3×10^{-3}		
3-Chloroquinuclidine (**5**)	9.09	0.02–0.12	0.25	8.55	0.005	4.0×10^{-2}	0.15	
		0.02–0.10	0.50	9.06	0.005	7.3×10^{-2}		
Triethylenediamine (**4**)	9.22	0.08–0.40	0.40	9.00	0.005	9.8×10^{-2}	0.23	
		0.08–0.40	0.60	9.37	0.005	0.14		
3-Quinuclidinol (**6**)	10.13	0.08–0.40	0.30	9.74	0.0046	0.18	0.53	
		0.08–0.40	0.50	10.11	0.0045	0.26 ± 0.01		
Quinuclidine (**7**)	11.55	0.04–0.20	0.10	10.57	0.0037	0.5 ± 0.2	6 ± 3	
		0.04–0.20	0.20	10.95	0.0027	1.2 ± 0.5		
Acethydrazide								
Phosphate (**2**)	6.46	0.02–0.10	0.30	6.11	0.10	0.19		0.23 ± 0.02
		0.02–0.10	0.40	6.30	0.10	0.11		
		0.02–0.10	0.50	6.49	0.10	0.09		
Imidazole (**3**)	7.24	0.02–0.40	0.30	6.85	0.10	3×10^{-3}	$\leq 5 \times 10^{-4}$	$(4.0 \pm 0.5) \times 10^{-3}$
		0.08–0.40	0.70	7.58	0.10	1.2×10^{-3}		
Triethylenediamine (**4**)	9.22	0.08–0.40	0.10	8.21	0.10	1.0×10^{-3}	2.3×10^{-3}	8.7×10^{-4}
		0.08–0.40	0.50	9.22	0.10	1.6×10^{-3}		
		0.08–0.40	0.70	9.56	0.10	1.9×10^{-3}		
3-Quinuclidinol (**6**)	10.13	0.10–0.40	0.54	10.20	0.20	4.1×10^{-3}	8.8×10^{-3}	
		0.10–0.40	0.80	10.76	0.18	7.5×10^{-3}		
Quinuclidine (**7**)	11.55	0.05–0.20	0.10	10.61	0.20	≤ 0.01	0.10	
		0.05–0.20	0.20	10.97	0.20	0.019		
Semicarbazide								
Imidazole (**3**)	7.24	0.10–0.40	0.60	7.46	0.10	1×10^{-3}		2.8×10^{-3}
		0.10–0.40	0.80	7.87	0.10	6.8×10^{-4}		
Triethylenediamine (**4**)	9.22	0.10–0.40	0.27	8.75	0.10	5.0×10^{-4}		6.8×10^{-4}
		0.10–0.40	0.48	9.14	0.10	3.5×10^{-4}		
		0.10–0.40	0.70	9.59	0.10	1.8×10^{-4}		
3-Quinuclidinol (**6**)	10.13	0.10–0.38	0.17	9.46	0.10	1.3×10^{-4}	$\leq 7 \times 10^{-5}$	1.6×10^{-4}
		0.10–0.40	0.43	10.00	0.10	9.5×10^{-5}		
Quinuclidine (**7**)	11.55	0.20–0.80	0.01	9.4–9.5	0.10	$(1.7 \pm 0.4) \times 10^{-5}$	$\leq 1.6 \times 10^{-3}$	$(1.7 \pm 0.4) \times 10^{-5}$
		0.05–0.20	0.20	10.97	0.10	≤ 0.025		
Phenylhydrazine-*p*-sulfonic Acid								
Triethylenediamine (**4**)	9.22	0.08–0.40	0.50	9.17	0.01	2.3×10^{-2}		4.7×10^{-2}
		0.10–0.40	0.90	10.14	0.01	4.5×10^{-3}		
3-Quinuclidinol (**6**)	10.13	0.08–0.40	0.50	10.14	0.01	5.7×10^{-3}		1.15×10^{-2}
		0.10–0.40	0.80	10.72	0.01	2.0×10^{-3}		
Quinuclidine (**7**)	11.55	0.08–0.40	0.04	10.12	0.01	2.2×10^{-3}		2.3×10^{-3}
		0.05–0.20	0.20	10.89	0.01	$(2.2 \pm 0.3) \times 10^{-3}$		
		0.05–0.20	0.40	11.38	0.01	$(1.7 \times 0.7) \times 10^{-3}$		
Hydrazine								
Acetate (**1**)	4.65	0.05–0.40	0.10	5.63	1.2×10^{-4}	8.5 ± 0.3		85 ± 3
Phosphate (**2**)	6.46	0.02–0.10	0.50	6.44	7.5×10^{-4}	3.6		7.0
		0.02–0.10	0.75	7.00	2.6×10^{-3}	1.6		
Hydrazine (**8**)	8.26	0.02–0.10	0.20	7.67	0.004–0.02	≤ 0.14		≤ 0.17
		0.02–0.10	0.50	8.29	0.01–0.05	≤ 0.48		
Triethylenediamine (**4**)	9.22	0.08–0.40	0.50	9.16	0.043	0.11		0.23
		0.08–0.40	0.70	9.56	0.047	0.074		
3-Quinuclidinol (**6**)	10.13	0.08–0.40	0.10	9.22	0.044	5.5×10^{-2}		5.8×10^{-2}
		0.10–0.40	0.70	10.52	0.05	1.3×10^{-2}		
		0.10–0.40	0.90	11.1	0.05	6.7×10^{-3}		

[a] Ionic strength 1.0 (KCl). [b] Based on observed pH of buffer solutions under the experimental conditions; *cf.* ref 3. [c] Corrected for inhibition of the hydroxide ion catalyzed reaction by imidazole free base; this inhibition was about 5% of the baseline rate at the highest imidazole concentration.

the carbinolamine.[30] Values of k'' for dehydration of the anion of this carbinolamine catalyzed by the conjugate acids of quinuclidinol and triethylenediamine, calculated assuming $pK_{CA}^0 = 27 \pm 2$, are in the range 10^{13}–10^{17} M^{-1} sec^{-1}. Such a calculation suggests that the intermediate is too unstable for its breakdown at a rate equal to or less than the diffusion controlled limit[6] to account for the observed rate of the reaction, and represents a less ambiguous situation than that previously described for thiosemicarbazide,[3] in which a k'' of 10^{10}–10^{12} M^{-1} sec^{-1} was required by the mechanism of eq 4 and a clear choice between mechanisms was not possible.

The extremely short lifetime of the hypothetical carbinolamine anion is a consequence not only of its thermodynamic instability relative to its conjugate acid, but of the extremely high reactivity of the carbon–oxygen bond in this anion. Extrapolation of a structure–reactivity correlation (see below) relating the rate of uncatalyzed carbinolamine dehydration to the pK_a' of the parent hydrazine gives a rate constant of 10^{11}–10^{14} sec^{-1} for a compound of $pK_a = 27 \pm 2$. The analogous semicarbazide and phenylhydrazinesulfonic acid derivatives would be even less stable. Hence, the anions derived from moderately basic carbinolamines may not exist long enough in solution to justify their consideration as true reaction intermediates in any case, and the role of catalysis in systems of this type may be to avoid the necessity of forming such highly unstable intermediates. A preassociation[33] or "spectator"[34] mechanism, in which breakdown of the anion is faster than diffusion away of BH^+ from the ion pair $[R^-NC(R')HOH \cdot BH^+]$ but the catalyst does not directly participate in the transition state for this breakdown, is on the limit of possibility[35] but should give a β value of 1.0 for general base catalysis rather than the observed value of 0.70. Similarly, the short lifetime of the intermediate would not provide sufficient time for a molecule of catalyst to carry a proton from nitrogen to oxygen in a "one-encounter" mechanism[36] analogous to that of eq 4. Furthermore, the failure of the toluenesulfonylhydrazide reaction to exhibit any unusual catalysis by phosphate dianion, which may be able to react as a bifunctional acid–base catalyst[37] without the need for intra-complex rotation, suggests that such a very rapid one-encounter mechanism is unlikely.

The carbinolamine derived from *p*-chlorobenzaldehyde and 2-methyl-3-thiosemicarbazide[38] undergoes hydroxide ion catalyzed dehydration at a rate approximately equal to that of the unmethylated thiosemicarbazide derivative (Table II). This suggests that no significant role is played by intramolecular proton transfer involving initial ionization of the moderately acidic proton in the 2 position of the substituted hydrazine (eq 5). Analogous 1,2-proton shifts in carbon

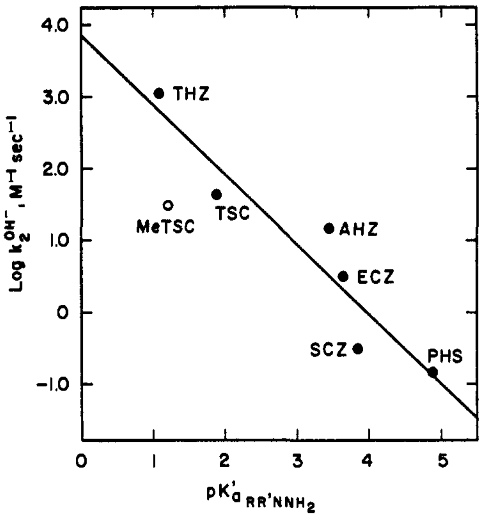
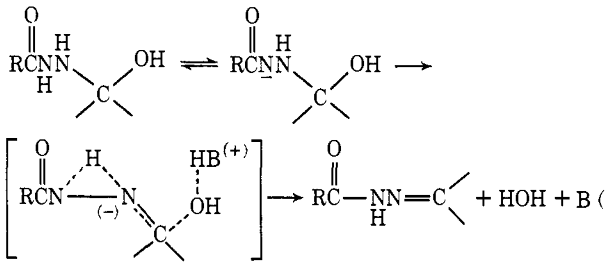


Figure 2. Relationship between the rate constant for hydroxide ion catalyzed carbinolamine dehydration at 25°, ionic strength 1.0, and the pK_a' of the parent amine for a series of substituted hydrazines. Abbreviations are given in Table II. A line of slope −0.97 (least squares; 2-methyl-3-thiosemicarbazide omitted) has been drawn through the points.


(5)

systems are symmetry forbidden and the absence of such a shift has been demonstrated in a carbanion reaction.[39] A similar intramolecular reaction involving ionization at the 4 position of semicarbazide derivatives is also not reasonable since it does not account for the rapid rates of hydroxide ion catalyzed dehydration of the acethydrazide and toluenesulfonylhydrazide derivatives.

The high sensitivity of base-catalyzed dehydration to electron-withdrawing substituents in the hydrazine moiety is reflected in the slope of close to −1.0 for the plot of log $k_2^{OH^-}$ against the pK_a' of the hydrazine derivative (Figure 2). Although the measured pK_a' values of the hydrazines refer to dissociation of the cations, the equilibrium constants, K^0, for ionization of neutral amines to the anions show a similar sensitivity to substituent effects, with $\Delta pK^0 = 1.3\Delta pK_a$ (for anilines, with pK^0 values determined in tetramethylammonium hydroxide–DMSO–water)[28,29] and $\Delta pK^0 = 0.86\Delta pK_a$ (for substituted benzimidazoles in water).[27] We conclude that the β value of −0.97 for base catalyzed carbinolamine dehydration suggests that close to a full

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[30] This estimate of pK^0 represents a lower limit, as it is based on a pK_a value for the cationic carbinolamine[22] which includes the ΔpK introduced by differences in solvation[31,32] between primary and secondary amines; the estimated pK_a of 1.2 for the carbinolamine is 1.1 units lower than would be expected for purely inductive effects, and the derived pK^0 for its anionic dissociation may be erroneously low since solvation effects on the two ionizations are probably not parallel.

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(34) L. D. Kershner and R. L. Schowen, *ibid.*, **93**, 2014 (1971).

(35) From the observed rate constants for general base catalysis, a range of 10^{14}–10^{18} sec^{-1} is calculated for the rate constant for hydroxide ion expulsion from the complex of acethydrazide–carbinolamine anion and protonated triethylenediamine or quinuclidinol using the pK_a values in the text, and an estimated equilibrium constant of 0.1 M^{-1} for encounter complex formation.

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(38) J. M. Sayer and W. P. Jencks, *ibid.*, **94**, 3262 (1972).

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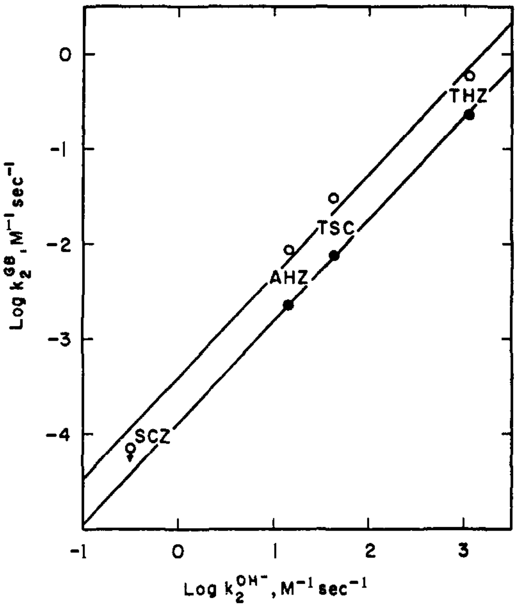

Figure 3. Comparison of the relative rates for hydroxide ion and amine catalyzed carbinolamine dehydration. Upper line, catalysis by 3-quinuclidinol; lower line, triethylenediamine. The slopes of the lines are 1.1 for both amines.

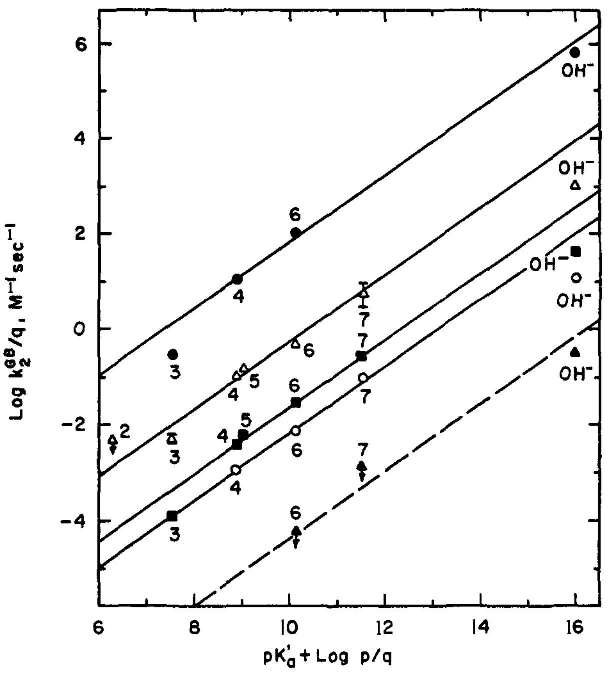

Figure 4. Brønsted plots for general base catalysis of carbinolamine dehydration in the reactions of *p*-chlorobenzaldehyde with *N*-aminopyridinium chloride (●), *p*-toluenesulfonylhydrazide (△), thiosemicarbazide (■) (ref 3), acethydrazide (○), and semicarbazide (▲). The points for semicarbazide represent upper limits for the catalytic constants of tertiary amine bases (see text). Numbering of catalysts is given in Table III. Statistical corrections were applied according to R. P. Bell and P. G. Evans [*Proc. Roy. Soc., Ser. A*, **291**, 297 (1966)]. The lines are drawn with slopes of 0.70.

negative charge is developed on nitrogen in the transition state. The observed scatter in the Brønsted plot may result either from deviations from a linear correlation between pK^0 for anion formation and pK_a' values of the cations or from factors influencing the activation energy for the hydroxide ion catalyzed elimination other than the ease with which the nitrogen supports a partial negative charge in the transition state.

The observation (Figure 3) that plots of log k_2^{GB} for quinuclidinol and triethylenediamine against $k_2^{OH^-}$ for the compounds exhibiting catalysis by tertiary amines are linear, with slopes equal to or slightly greater than 1.0, suggests that there is no major difference between the transition states for the hydroxide ion and the buffer-catalyzed reactions. The Brønsted β value of 0.7 (Figure 4) observed for general base catalysis of the reaction is also consistent with a transition state in which the transferred proton is more closely associated with the catalyst molecule than with the reactant. The large sensitivity to substituents on the nitrogen atom cannot be explained by a substituent effect on the developing double bond. Electron-donating substituents stabilize this double bond in the product, as indicated by a positive β_N value of approximately 0.4 for the dependence of log K_2 on pK_a' of the hydrazine (Table II); *i.e.*, the effect of substituents on the equilibrium is opposite to the effect on the *rate* of dehydration. In the attack of hydroxide ion on neutral Schiff bases derived from benzaldehyde and anilines,[40] which corresponds to the reverse of hydroxide ion catalyzed dehydration of the carbinolamines, the large positive ρ values observed for substituted anilines also suggest a large development of negative charge on the nitrogen atom. Such a transition state resembles in some respects the transition states for E2 elimination reactions of "poor" leaving groups[8a] from carbon–carbon systems, which appear to possess considerable carbanion character. In an extreme example, a ρ value of 4.4 is observed for base catalyzed olefin formation from substituted phenethyl sulfoxides.[41]

Two lines of reasoning suggest that the present reactions, unlike some base-catalyzed eliminations from carbon–carbon systems,[42] do not proceed by a simple, rate-determining proton transfer to the catalyst. (1) The rate constant for proton abstraction by 3-quinuclidinol from the carbinolamine derived from acethydrazide is 10^{-5}–10^{-9} M^{-1} sec^{-1}, based on a pK of 27 ± 2 for carbinolamine ionization (see above) and the assumption that the reverse reaction, protonation of the nitrogen anion by the conjugate acid of 3-quinuclidinol, has a diffusion-controlled rate constant of 10^{10} M^{-1} sec^{-1}. The fact that the observed catalytic constant for 3-quinuclidinol, 9 × 10^{-3} M^{-1} sec^{-1}, is at least three orders of magnitude faster than the calculated rate constant for proton transfer to form the nitrogen anion, suggests that this anion cannot be an intermediate. (2) For a highly unfavorable simple proton transfer between electronegative atoms, the Brønsted β value should be unity.[6] The large unfavorable ΔpK_a between the base catalyst and the carbinolamine anions requires a Brønsted β of 1.0 for general base catalysis of the dehydration if proton transfer from the carbinolamine to the catalyst is rate determining, and the observed β value of 0.7 is not in accord with such a mechanism.

We suggest that the catalyzed reaction proceeds through a more or less concerted[21] transition state

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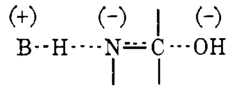
(40) J. Archila, H. Bull, C. Lagenaur, and E. H. Cordes, *J. Amer. Chem. Soc.*, 36, 1345 (1971).

(41) R. Baker and M. J. Spillett, *J. Chem. Soc. B*, 481 (1969).

(42) For an example, see F. G. Bordwell, M. M. Vestling, and K. C. Yee, *J. Amer. Chem. Soc.*, **92**, 5950 (1970).



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similar to 1 in which there are significant changes in the orders of bonds to both the proton and to carbon. Although we do not wish to comment on the detailed mechanism of coupling of the various atomic motions, the β value of 0.7 suggests that proton transfer is far advanced, but not complete, and the high sensitivity to substituents at nitrogen suggests that there has been relatively little delocalization of charge into the developing double bond in the transition state.

The negative deviation of 2-methyl-3-thiosemicarbazide from the Brønsted plot of Figure 2 may be attributed to an "abnormal" pK_a' value for this compound, presumably the result of a solvation effect,[32] and to steric constraints imposed on the transition state by the methyl group. A significant steric effect of the 2-methyl group is suggested by the observation that the equilibrium constant for addition to the carbonyl group (K_1) is approximately five- to tenfold smaller for 2-methyl-3-thiosemicarbazide than for the other substituted hydrazines. *N*-Aminopyridinium chloride (not shown), which is a different type of compound from the acyl- and sulfonylhydrazines, exhibits a large negative deviation from the Brønsted plot. Its very low pK_a is due at least in part to resonance involving the aromatic ring, which is possible in this aniline-like compound but not in the other substituted hydrazines.

Brønsted plots shown in Figure 4 give no indication of any change in the large sensitivity of the catalytic constants to the basicity of the catalyst for a series of hydrazines whose pK_a' values vary from -7.2 to 3.9. The lines have been drawn with a slope of 0.70, based upon catalysis of the reactions of *p*-toluenesulfonylhydrazide, thiosemicarbazide,[3] and acethydrazide by bicyclic tertiary amines. A common slope fits, within experimental error, the points corresponding to these catalysts for the three reactions investigated in detail. Imidazole and hydroxide ion show negative deviations from the Brønsted plots. No general base catalysis was detected for the reaction of semicarbazide. The broken line of Figure 4 has been drawn through the limiting rate constants for tertiary amines, estimated as described in the Results section and with the assumption that the point for hydroxide ion lies one-half to one logarithmic unit below the Brønsted line, as is observed in the reactions of acethydrazide and thiosemicarbazide. The lower limit for β estimated in this way is 0.70. The limited data for *N*-aminopyridinium chloride (pK_a = -7.2) are also consistent with a slope of 0.7, with a negative deviation for imidazole. Since the pK_a' for anion formation from *N*-aminopyridinium chloride, measured by spectrophotometric titration in potassium hydroxide solutions,[43] is close to 14, the point for hydroxide ion catalysis of the reaction involving this compound probably represents specific base catalysis; its agreement with the Brønsted slope determined by the tertiary amines is presumably fortuitous.

Considerations of the effect of structure on reactivity[44,45] predict that a change in electron-donating ability of the hydrazine moiety should influence the susceptibility, β, of the dehydration reaction to general base catalysis, according to eq 6, in which pK_a^N is used

$$(\mathrm{p}K_{a_1}^{N} - \mathrm{p}K_{a_2}^{N}) = c_5(\beta_2 - \beta_1) \tag{6}$$

as a measure of the electron-donating ability of the amine. In the mechanism of eq 3, electron-withdrawing amine substituents are expected to cause a shift toward a more product-like transition state and a larger β value for general base catalysis, in accordance with the Hammond[46] postulate. Electron-withdrawing substituents on the amine should also cause an increase in the Brønsted β value by increasing the anionic character of the transition state.[21a] The data obtained for hydrazone formation within the present range of hydrazine pK_a' and reactivity indicate that the β values are constant within the limits of experimental uncertainty for amines of pK_a' = -7.2 to 3.9. The value of $1/c_5$ (eq 6) provides a measure of the sensitivity of β to changes in reactivity of the amine; for carbinolamine dehydration, $1/c_5$, based on the β values for *N*-aminopyridinium chloride, toluenesulfonylhydrazide, thiosemicarbazide,[3] acethydrazide, and semicarbazide, is 0 ± 0.01. This may be compared with $1/c_2 = 0.05$ for general acid catalyzed addition of nucleophiles to aldehydes[47] and $1/c_2 = 0.03$ for general acid catalyzed addition of substituted anilines to formaldehyde[16] (from eq 7).

$$(\mathrm{p}K_{a_1}^{N} - \mathrm{p}K_{a_2}^{N}) = c_2(\alpha_2 - \alpha_1) \tag{7}$$

General Acid Catalysis. Carbinolamine dehydration in this series of compounds is also subject to general acid catalysis. An unambiguous assignment of the site of catalysis in reactions of this type is possible from the observed general acid catalysis of nitrone formation, which establishes the mechanism as true general acid catalysis, with proton donation to the departing hydroxyl group.[48] Brønsted plots for general acid catalyzed dehydration of four of the compounds (Figure 5) exhibit a degree of scatter similar to that observed previously for the reaction with hydroxylamine,[48] but if a comparison is made based on the rate constants for hydronium ion and the bicyclic tertiary amines there is a small but definite increase in α with decreasing basicity of the hydrazine (Table IV). Such an increase is

Table IV. Brønsted α Values for General Acid Catalysis of the Dehydration of Carbinolamines Formed from *p*-Chlorobenzaldehyde and Hydrazines in Water[a]

Amine	pK_a'	α
Thiosemicarbazide[b]	1.88	~0.73
Acethydrazide	3.44	0.72
Semicarbazide	3.86	0.72
Phenylhydrazine-*p*-sulfonic acid	4.90	0.67
Hydrazine	8.26	0.62

[a] Ionic strength 1.0. [b] Reference 3.

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(43) J. Sayer and W. P. Jencks, unpublished data.

(44) E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, **84**, 4319 (1962).

(45) G. E. Lienhard and W. P. Jencks, *ibid.*, 88, 3982 (1966). The coefficient c_5 is placed on the wrong side of eq 19 in this paper.

(46) G. S. Hammond, *ibid.*, 77, 334 (1955).

(47) L. do Amaral, W. A. Sandstrom, and E. H. Cordes, *ibid.*, **88**, 2225 (1966).

(48) J. E. Reimann and W. P. Jencks, *ibid.*, **88**, 3973 (1966).

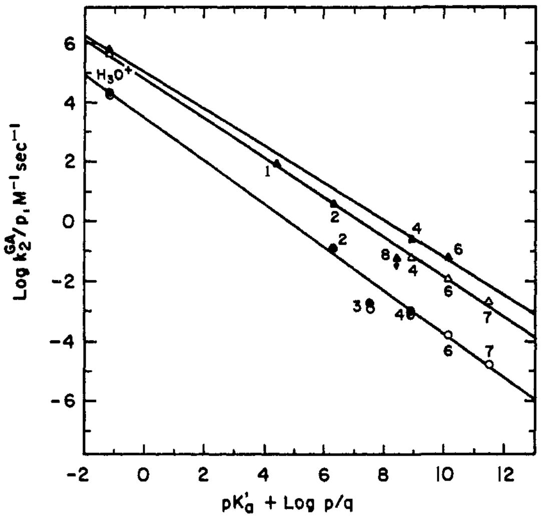


Figure 5. Brønsted plots for general acid catalysis of carbinolamine dehydration in the reactions of *p*-chlorobenzaldehyde with hydrazine (▲), phenylhydrazine-*p*-sulfonic acid (△), semicarbazide (○), and acethydrazide (●). Statistical corrections applied according to R. P. Bell and P. G. Evans [*Proc. Roy. Soc., Ser. A*, **291**, 297 (1966)]. Numbering of catalysts is given in Table III. Slopes of the lines are: hydrazine, 0.62; phenylhydrazine-*p*-sulfonic acid, 0.67; semicarbazide and acethydrazide, 0.72.

predicted by the Cordes eq 7 for a reaction subject to true general acid catalysis; the value of $1/c_2$ is approximately 0.02 for this series.[49]

Dihydrogen phosphate monoanion does not deviate significantly from the Brønsted plots for acid catalyzed carbinolamine dehydration. Hence, concerted bifunctional acid–base catalysis[37] by this compound does not appear to play an important role in the mechanism of carbinolamine dehydration. Water exhibits a positive deviation from the Brønsted plots of about an order of magnitude when these plots are drawn through the point for hydronium ion.

A stepwise mechanism of catalysis involving a thermodynamically unfavorable proton transfer from catalysts with pK_a' values well above the pK_a' for O-protonation of the carbinolamine would be expected to give a Brønsted α value of 1.0, as described earlier for the general base catalyzed reaction. The observed Brønsted slopes are significantly less than 1.0, based on the points for catalysis by the conjugate acids of bicyclic tertiary amines and consistent with the point for hydronium ion. Electron-withdrawing substituents on nitrogen decrease the rate (β_N = ~0.4 for the hydronium-ion catalyzed reaction, Figure 6), suggesting that there is significant electron donation from the nitrogen atom in the transition state. This suggests that the general acid catalyzed dehydration is in some sense concerted,[21] with a transition state **2** involving partial proton transfer as well as carbon–oxygen bond cleavage.

A reaction mechanism involving stepwise proton transfer may well be impossible because of the extreme instability of the O-protonated carbinolamine intermediate required by such a mechanism. Preliminary data[43] indicate that the rate constants for base-catalyzed elimination of alkoxide ions from carbinolamine ethers are very sensitive to the pK_a of the departing alcohol. Assuming a similar β value (for the leaving group) of 0.8–1.0 for the uncatalyzed elimination reaction, it is possible to calculate a rate constant for the elimination of water (pK_a = −1.7) from the protonated carbinolamine if the rate constant for hydroxide ion expulsion from the neutral carbinolamine (*i.e.*, the uncatalyzed reaction) is known. Such a calculation gives rate constants for water elimination from the O-protonated carbinolamines derived from semicarbazide and hydrazine of 10^9–10^{12} and 10^{12}–10^{15} sec^{-1}, respectively. This suggests that these intermediates must be extremely unstable and possibly have no finite lifetime at all. General acid catalysis in this system provides a reaction pathway which avoids the formation of these high-energy intermediates, just as general base catalysis avoids the formation of unstable carbinolamine N-anions as discussed in the preceding section.

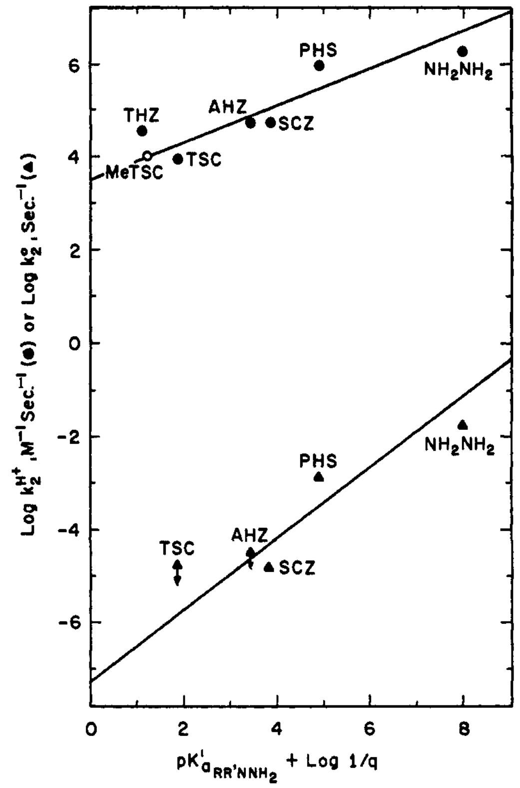
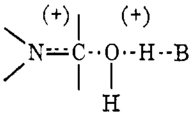


Figure 6. Relationships between the rate constants for hydronium ion and uncatalyzed carbinolamine dehydration and the basicity of the parent hydrazines. The pK_a' of hydrazine is statistically corrected by a factor of 2. Upper line, hydronium ion catalysis (slope 0.40); lower line, uncatalyzed reaction (slope 0.77).



$$\begin{array}{c} \overset{(+)}{>N{=\!=}C}\cdots\overset{(+)}{O}\cdots H\cdots B \\ \quad\quad | \quad\; | \\ \quad\quad\quad\;\; H \end{array}$$

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The Spontaneous Reaction. The "water" reaction is best formulated as an uncatalyzed expulsion of hydroxide ion from the neutral carbinolamine, rather than as general acid or base catalysis by water; this corresponds to the reverse of the mechanism for pH-

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[49] Although the previously reported α value of 0.77 for the corresponding reaction with hydroxylamine[48] (pK_a' = 6.1) is larger than those for hydrazines, the hydroxylamine value is based on a different series of catalysts and a comparison of the rate constants for the hydronium and imidazolium ions, which are common to both series, gives rate ratios $k_2^{H^+}/k_2^{ImH^+}$ of 5.3×10^6 and 1.3×10^7 for hydroxylamine and acethydrazide, respectively, confirming the trend in the hydrazine series.

independent imine hydrolysis.[50] There is no driving force for concerted proton transfer from water to the incipient hydroxide ion (to produce a new water molecule and a new hydroxide ion), and such a proton transfer would impose additional entropic requirements on the transition state.[21a,51] The alternative "concerted" mechanism for the water reaction in which water acts as a general base to remove a proton from nitrogen may be excluded on similar grounds, at least for the more basic amines. The pK_a' values for the protonated imines which are the immediate products of the elimination reaction should be about four to seven units below those of the parent amines,[50a,52,53] *i.e.*, between 0 and -3 for semicarbazide, and between 1 and 4 for hydrazine. Since the pK_a of the hydronium ion is -1.7, there is little or no thermodynamic advantage derived from proton transfer to water in the transition state and "concerted" catalysis by water is unlikely. The points for the water reactions fall far above the Brønsted lines for general base catalysis and roughly an order of magnitude above the Brønsted lines for general acid catalysis.

The slope, β_N, of approximately 0.8 for the dependence of the rate of the uncatalyzed reaction on the pK_a' of the parent hydrazine (Figure 6) suggests a transition state midway between starting material and product for this reaction, since β_N for the complete transformation of carbinolamine to protonated hydrazone should be 1.4 if β_N for the equilibrium formation of neutral products is 0.4 and β_N for imine protonation is 1.0. Cordes and coworkers[40] have suggested on the basis of secondary isotope effects that the transition state for hydroxide ion attack on protonated imines derived from an aliphatic amine closely resembles the tetrahedral carbinolamine. Thus the transition state for the reverse reaction, uncatalyzed formation of Schiff bases from strongly basic carbinolamines, appears to be less far advanced toward product than the analogous hydrazone-forming elimination.

The uncatalyzed reaction is more sensitive to the nature of the amine ($\beta_N = \sim 0.8$) than the hydronium-ion catalyzed reaction ($\beta_N = \sim 0.4$, Figure 6). This is in accord with the previously described structure–reactivity considerations,[44] and is a result of the fact that the transition state for the uncatalyzed reaction is reached later than that for the hydronium ion catalyzed reaction, and hence is more sensitive to stabilization of the incipient double bond by electron donation from the amine.

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(50) (a) K. Koehler, W. Sandstrom, and E. H. Cordes, *J. Amer. Chem. Soc.*, **86**, 2413 (1964); (b) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, p 491.

(51) W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 4731 (1972).

(52) E. H. Cordes and W. P. Jencks, *ibid.*, **85**, 2843 (1963).

(53) R. Wolfenden and W. P. Jencks, *ibid.*, **83**, 2763 (1961).

Nucleophilic Alkylidene Transfer Reagents. Anions of *N*-(*p*-Tolylsulfonyl)sulfoximines[1a]

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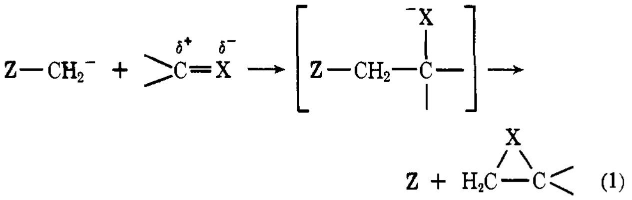
Abstract: A number of symmetrical *S*,*S*-dialkyl- and *S*-alkyl-*S*-aryl-*N*-(*p*-tolylsulfonyl)sulfoximines have been prepared (Table I); the general method used was the copper-catalyzed reaction of *p*-toluenesulfonyl azide with sulfoxides. *S*,*S*-Dimethyl-*N*-(*p*-tolylsulfonyl)sulfoximine was prepared in 90% yield by the cupric ion-catalyzed reaction of Chloramine-T with DMSO. Reaction of these sulfoximines with sodium hydride or *n*-butyllithium afforded sulfonimidoyl-stabilized carbanions which act as nucleophilic alkylidene transfer reagents upon reaction with substrates containing electrophilic double bonds; ketones reacted to yield oxiranes, imines gave aziridines, and α,β-unsaturated ketones afforded cyclopropanes (Table II). Cycloalkylidene group transfer yielded spiro compounds. Examples are given showing the addition of these stabilized anions to an oxirane, a carbodiimide, and a nitrile. Reaction of the sodium or lithium salt of (−)-(*R*)-*S*-methyl-*S*-phenyl-*N*-(*p*-tolylsulfonyl)sulfoximine with benzalacetophenone gave (1*R*,2*R*)-*trans*-1-benzoyl-2-phenylcyclopropane 49% optically pure; reaction with acetophenone gave (−)-2-methyl-2-phenyloxirane ([α]D −6.9°); reaction with benzalaniline afforded (−)-1,2-diphenylaziridine ([α]D −12.9°).

The addition of an alkylidene group across an electrophilic double bond to form a three-membered ring is usually achieved by employing diazoalkanes or sulfonium ylides. Such reactions can be illustrated in the most general terms by eq 1. The driving forces for these nucleophilic alkylidene transfer reactions are (1) the formation of a relatively stable intermediate adduct and (2) the expulsion of a good leaving group by the intermediate. In the typical cases noted above, both the reagent (diazo compounds



$$Z{-}CH_2^- + \;>\overset{\delta^+}{C}{=}\overset{\delta^-}{X} \longrightarrow \left[Z{-}CH_2{-}\overset{{}^-X}{\underset{|}{\overset{|}{C}}}{-}\right] \longrightarrow Z + H_2C\overset{X}{\frown}C< \qquad (1)$$

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(1) (a) Part XLII in the series "Chemistry of Sulfoxides and Related Compounds." We gratefully acknowledge support by the National Science Foundation (GP 19623). (b) Research Scientist on leave from CSIRO, Canberra, Australia.

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