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On the Mechanism of Schiff Base Formation and Hydrolysis[1]

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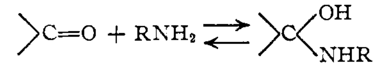
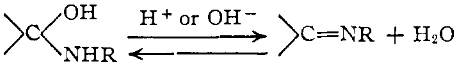
The following lines of evidence suggest that N-*p*-chlorobenzylideneaniline formation, like that of oximes and semicarbazones, undergoes a transition in rate-determining step from rate-determining dehydration of the carbinolamine addition product at neutral *p*H to rate-determining amine attack under acidic conditions: (1) A *p*H–rate maximum, which is not due to general acid catalysis, occurs near *p*H 4. (2) The hydrolysis of N-*p*-chlorobenzylideneaniline shows a break in the *p*H–rate profile consistent with a transition in rate-determining step. (3) The influence of structure on reactivity in Schiff base formation is different on the two sides of the *p*H–rate maximum. (4) Schiff base formation is more susceptible to general acid catalysis on the acid than on the alkaline side of the *p*H–rate maximum. The rate of hydrolysis of N-*p*-chlorobenzylideneaniline is markedly decreased in strong acid; the logarithm of the rate follows H_0 with a slope of 1.24 in the range 7 to 11 *M* sulfuric acid. The rate of hydrolysis in strong acid is decreased approximately twofold in deuterium oxide solution. These results suggest the involvement of several water molecules, functioning as both nucleophilic and proton transfer reagents, in the transition state. The pK_a' of N-*p*-chlorobenzylideneanilinium cation has been estimated to be 2.8.

Introduction

Evidence suggesting the involvement of azomethine intermediates in several enzymatic reactions[2-4] has focused attention on the mechanism of Schiff base formation and hydrolysis in aqueous solution. Previous studies of the hydrolysis of Schiff bases in water–alcohol mixtures have established the susceptibility of these reactions to specific and general acid catalysis.[5-7] However, the nature of the rate-determining step (eq. 1 and 2) remains unsettled. Evidence obtained by Willi suggests that in the hydrolysis reaction the addition of water to form the carbinolamine intermediate



$$\rangle C{=}O + RNH_2 \rightleftarrows \rangle C\langle^{OH}_{NHR} \qquad (1)$$



$$\rangle C\langle^{OH}_{NHR} \overset{H^+ \text{ or } OH^-}{\rightleftarrows} \rangle C{=}NR + H_2O \qquad (2)$$

(the reverse of eq. 2) is rate determining at neutral *p*H,[6] while, on the other hand, Kastening, *et al.*,[5] have concluded from polarographic measurements that the decomposition of the carbinolamine (the reverse of eq. 1) is rate-determining under these conditions. Studies on the related reactions, oxime and semicarbazone formation have demonstrated a transition from rate-determining dehydration (water addition in the reverse reaction, eq. 2) at neutral *p*H to rate-determining amine attack (carbinolamine decomposition in the reverse reaction, eq. 1) under acidic conditions.[8,9] The studies reported below were carried out in an attempt to determine whether Schiff base formation behaves in a manner similar to oxime and semicarbazone formation.

The formation of Schiff bases in aqueous solution has not been the subject of kinetic investigation, since the low equilibrium constants for these reactions make such a study difficult.[10,11] Results presented in the preceding communication[12] demonstrate that Schiff base formation is the rate-determining step in aniline-catalyzed semicarbazone formation in aqueous solution. Thus, semicarbazide acts as a trap for Schiff base and carries the reaction to completion. This system, used as a tool for the study of Schiff base formation, permits the direct kinetic study of this reaction in aqueous solution.

Experimental

Kinetic measurements were carried out at 25° as previously described.[8,9,12] The rate of Schiff base formation, measured as the rate of semicarbazone formation, was obtained by subtracting the rate of a control reaction which did not contain aniline from that of the complete reaction mixture. Where necessary, the rate constants for the aniline-catalyzed reactions were corrected to 100% reaction of the Schiff base with semicarbazide by dividing by α, which was determined in separate experiments as previously described.[12] This correction was usually small, involving a change of less than 25% in the rate constants.

Materials.—All reagents were purified and solutions prepared as previously described.[12] Deuterium oxide, 99.8%, was obtained from the Atomic Energy Commission through the courtesy of the Department of Chemistry, Harvard University. 8.24 *M* D_2SO_4 was prepared by distilling SO_3 from 30% fuming sulfuric acid into D_2O cooled in an isopropyl alcohol–Dry Ice-bath. D_2SO_4 prepared in this manner was neutralized with Na_2CO_3 in deuterium oxide and an infrared spectrum revealed that this solution contained no detectable quantity of H_2O.

The rapid hydrolysis of protonated N-*p*-chlorobenzylideneaniline makes the direct determination of the absorption spectrum of the protonated Schiff base impossible by ordinary techniques. This spectrum was estimated as follows: 0.06 ml. of 2×10^{-3} *M* N-*p*-chlorobenzylideneaniline was added to 3.0 ml. of methanol containing 1.15 *M* hydrogen chloride and the absorption spectrum was immediately recorded on a Cary recording spectrophotometer, model 14. Under these conditions, methanol adds to the protonated Schiff base fairly slowly (half-time for the addition is approximately 4 minutes). Extrapolation of the absorption at the maximum (337 mμ) to zero time gave a molar extinction coefficient at this wave length of 2.35×10^4. The shape of the absorption spectrum of protonated

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[2] E. E. Snell and W. T. Jenkins, *J. Cell. Comp. Physiol.*, **54**, Suppl. 1, 161 (1959).

[3] D. E. Metzler, M. Ikawa and E. E. Snell, *J. Am. Chem. Soc.*, **76**, 648 (1954).

[4] G. A. Hamilton and F. H. Westheimer, *ibid.*, **81**, 6332 (1959).

[5] B. Kastening, L. Holleck and G. A. Melkonian, *Z. Elektrochem.*, **60**, 130 (1956).

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[8] W. P. Jencks, *J. Am. Chem. Soc.*, **81**, 475 (1959).

[9] B. M. Anderson and W. P. Jencks, *ibid.*, **82**, 1773 (1960).

[10] P. Zuman, *Coll. Czech. Chem. Comm.*, **15**, 839 (1951).

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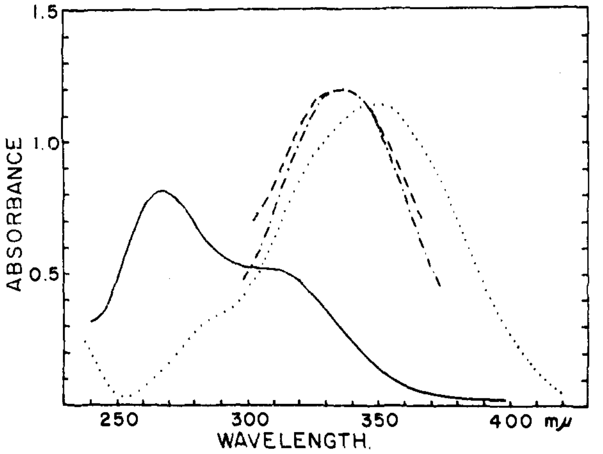

Fig. 1.—Ultraviolet spectra of 5.0 × 10^{-5} *M* N-*p*-chlorobenzylideneaniline and its conjugate acid: ———, in 0.1 *M* tris-(hydroxymethyl)-aminomethane buffer, *p*H 9.5; ......, in concentrated sulfuric acid; — · — · —, in methanolic HCl (1.15 *M*); – – – –, in 1 *M* aqueous HCl.

N-*p*-chlorobenzylideneaniline in water was obtained from an equilibrium mixture containing initially 1 × 10^{-3} *M* *p*-chlorobenzaldehyde and 0.3 *M* aniline hydrochloride in 1 *M* hydrochloric acid. Absorption due to the free aldehyde and anilinium ion was determined independently and subtracted. The molar extinction coefficient at the absorption maximum in water (335 mμ) was assumed to be the same as in methanol. The spectra of this Schiff base in water, methanolic HCl, dilute aqueous HCl and concentrated sulfuric acid are shown in Fig. 1.

The addition of methanol to protonated N-*p*-chlorobenzylideneaniline was studied as follows: 0.06 ml. of 2 × 10^{-3} *M* N-*p*-chlorobenzylideneaniline was added to methanol containing 1.15 *M* HCl, and a series of absorption spectra was taken at increasing time intervals. The absorption at 337 mμ, due to the protonated Schiff base, decreased with time and was zero after 45 minutes. At this time no appreciable absorption at 260 mμ was seen, indicating that no appreciable amount of *p*-chlorobenzaldehyde was formed. Addition of a small amount of water caused the immediate appearance of an absorption band with a maximum near 260 mμ. The product of this reaction was identified as *p*-chlorobenzaldehyde as follows: 420 mg. of N-*p*-chlorobenzylideneaniline was added to 10 ml. of methanol containing 0.75 *M* HCl and allowed to remain at room temperature for 45 minutes. Dilution with water gave a precipitate of 202 mg. of *p*-chlorobenzaldehyde (m.p. 46–48°) which was converted to the semicarbazone (m.p. 232–233°). It was not determined whether the product of the addition of methanol to the Schiff base is the acetal or the aminoacetal.

Results

In Fig. 2, the pseudo-first-order rate constants for the formation of N-*p*-chlorobenzylideneaniline at 25° are plotted against *p*H. All points on the *p*H–rate profile have been extrapolated to zero buffer concentration. A rate maximum occurs near *p*H 4. On the alkaline side of the *p*H–rate maximum, the rate of Schiff base formation increases with increasing acidity, suggesting a predominantly acid-catalyzed reaction in this *p*H region. On the acid side of the *p*H–rate maximum, the rate decreases less rapidly than the concentration of free aniline and becomes independent of *p*H below *p*H 1, indicating the existence of a specific acid-catalyzed reaction as well as an uncatalyzed reaction of free aniline (eq. 3)

$$\begin{aligned}\text{rate} &= k_1[\mathrm{RNH_2}][\mathrm{R'CHO}] + k_2[\mathrm{RNH_2}][\mathrm{R'CHO}][\mathrm{H^+}]\\ &= k_1[\mathrm{RNH_2}][\mathrm{R'CHO}] + k_2'[\mathrm{RNH_3^+}][\mathrm{RCHO}] \qquad (3)\end{aligned}$$

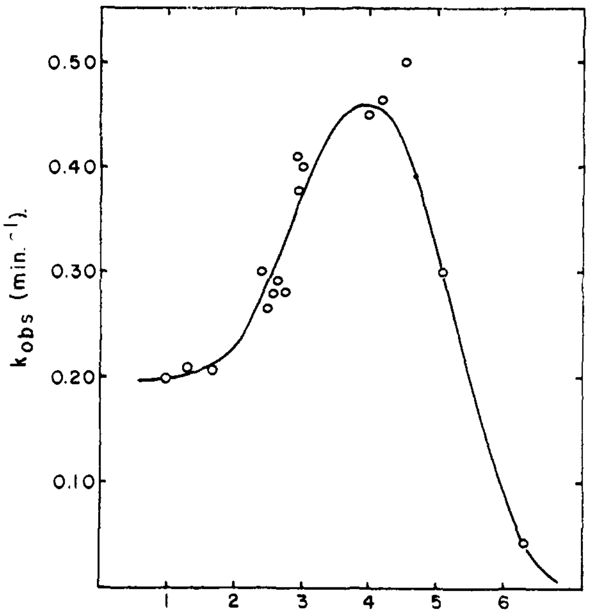

Fig. 2.—The rate of formation of N-*p*-chlorobenzylideneaniline as a function of *p*H at 25°: *p*-chlorobenzaldehyde 3.3 × 10^{-5} *M*, total aniline 0.004 *M*, total semicarbazide 0.0025 *M*, ionic strength 0.50. The buffers used are listed in Table I. All rates are extrapolated to zero buffer concentration.

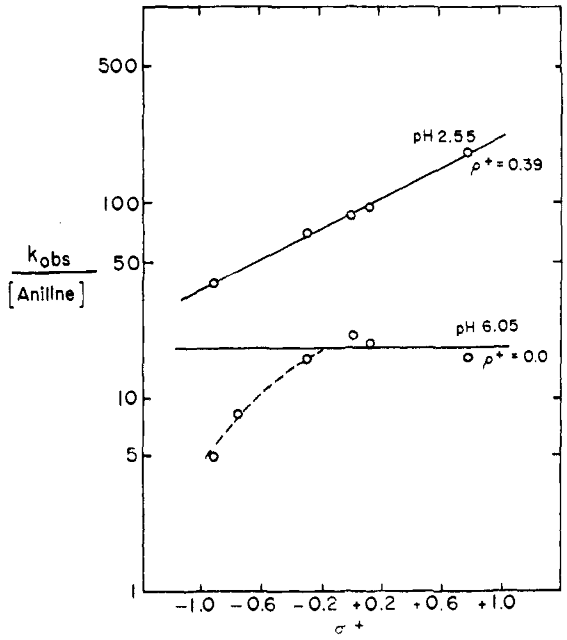

Fig. 3.—Logarithm of the second-order rate constants for the condensation of aniline with *p*-substituted benzaldehydes at 25° plotted against σ^+; *p*H 2.55, 0.04 *M* chloroacetate buffer; *p*H 6.10, 0.10 *M* phosphate buffer; ionic strength 0.50.

The effect of structure on the rate of Schiff base formation from aniline and several *p*-substituted benzaldehydes was studied at *p*H 2.55 and *p*H 6.10 (Fig. 3). At *p*H 2.55, on the acid side of the *p*H–rate maximum, a plot of the logarithm of

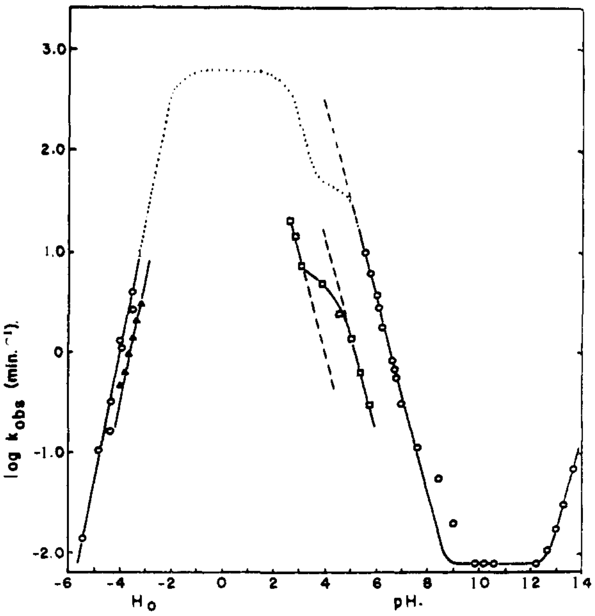

Fig. 4.—The hydrolysis of N-*p*-chlorobenzylideneaniline as a function of *p*H at 25°: O, in H_2O; phosphate (0.05 *M*, *p*H 5.6–7.6), tris-(hydroxymethyl)-aminomethane (0.05 *M*, *p*H 8.4), carbonate (0.05 *M*, *p*H 9.9–10.6), reactions in strongly acidic solution carried out in sulfuric acid; △, in D_2SO_4–D_2O; □, in 80% ethanol, in dilute HCl or formate buffer (*p*H 3.9–5.8), rates extrapolated to zero buffer concentration. N-*p*-Chlorobenzylideneaniline 3.3 – 7 × 10^{-5} *M*; ionic strength 0.50 except in 80% ethanol (0.05) and concentrated sulfuric acid. Reactions followed at 320 or 340 mμ.

the second-order rate constants against σ^+-substituent constants[13] gives a straight line with a ρ^+-value of 0.39. On the alkaline side of the *p*H-rate maximum, on the other hand, the second-order rate constants are independent of the substituent except for the *p*-OH and *p*-OCH_3 substituents, which show decreased rates relative to the unsubstituted compound.

The rate of N-*p*-chlorobenzylideneaniline formation increases with increasing buffer strength at constant *p*H. This catalysis is of the general acid, rather than the general base, type since acetic acid and propionic acid are effective catalysts at *p*H 2.5, more than two *p*H units below the pK_a of these acids. The catalytic constants for six aliphatic carboxylic acids, measured below *p*H 4, are given in Table I. Representative data, illustrating the method of calculating the catalytic constants, are given in Table II for cyanoacetic acid catalysis. As is seen from Table II, several corrections must be made to obtain the catalytic constants, which may, therefore, be in error by as much as ±30%. The logarithms of catalytic constants for carboxylic acids and for the solvated proton (1.7 × 10^6 M^{-2} min.$^{-1}$) fall near a Brönsted line of slope 0.25 when plotted against the appropriate pK_a values. The catalytic constant for acetic acid obtained at *p*H 5.10 is approximately tenfold lower than at *p*H 2.50 (Table I).

TABLE I

CATALYTIC CONSTANTS FOR GENERAL ACID CATALYSIS OF N-*p*-CHLOROBENZYLIDENEANILINE FORMATION AT 25°[a]

Acid	pK_a	Concn. range, *M*	*p*H	k_{cat}, M^{-2} min.$^{-1}$
Cyanoacetic	2.45	0.015–0.078	2.66	7.4 × 10^4
Bromoacetic	2.86	.02 – .10	2.68	7.7 × 10^4
Chloroacetic	2.90	.017– .086	3.01	5.6 × 10^4
Formic	3.75	.035– .17	2.98	3.1 × 10^4
Acetic	4.76	.05 – .30	2.50[b]	2.3 × 10^4
	4.76	.013– .10	5.10	2.5 × 10^3
Propionic	4.87	.05 – .30	2.41	2.9 × 10^4

[a] Ionic strength maintained at 0.50 by the addition of KCl. [b] In the presence of 0.02 *M* bromoacetate buffer.

TABLE II

CATALYSIS OF N-*p*-CHLOROBENZYLIDENEANILINE FORMATION BY CYANOACETIC ACID[c]

Aniline,[a] *M* × 10^5	Cyanoacetic acid,[b] *M*	k_1, min.$^{-1}$	Δk_1, min.$^{-1}$	k_2, M^{-1} min.$^{-1}$ × 10^{-3}	α	k_2/α, M^{-1} min.$^{-1}$ × 10^{-3}
0.00	0.0152	0.149				
7.45	.0152	.513	0.364	4.9	0.74	6.65
0.00	.0304	.198				
7.45	.0304	.660	.462	6.2	.74	8.40
0.00	.0451	.246				
7.65	.0451	.770	.524	6.85	.74	9.25
0.00	.0775	.347				
7.30	.0775	.955	.608	8.35	.74	11.30

[a] As the free base. [b] As the undissociated acid. [c] Carried out at *p*H 2.66 in the presence of 0.005 *M* semicarbazide at 25°.

The hydrolysis of N-*p*-chlorobenzylideneaniline was studied in the *p*H range 5.10 to 14. The *p*H–rate profile (Fig. 4) shows base-catalyzed, acid-catalyzed and uncatalyzed (or solvent-catalyzed) reactions and is similar to the *p*H-rate profile obtained by Kastening, *et al.*[5] Willi had observed a break in the *p*H-rate profile in the acid-catalyzed region in the hydrolysis of N-benzylideneaniline in 50% methanol.[6] In water, this break occurs at a *p*H at which the rate of hydrolysis is too fast to measure. Such a break is observed, however, in the hydrolysis of N-*p*-chlorobenzylideneaniline in 80% ethanol (Fig. 4). Rates measured in 80% ethanol have been extrapolated to zero buffer concentration and *p*H values in 80% ethanol were determined with a glass electrode and the Radiometer PHM-4b *p*H meter, standardized with 0.01 *M* HCl in 80% ethanol.[14] In strong acid, the rate of hydrolysis of this Schiff base again becomes slow enough to measure. In the range 7 to 11 *M* sulfuric acid, the logarithm of the rate of hydrolysis follows H_0[15] with a slope of 1.24. In deuteriosulfuric acid, the rate is decreased by about twofold compared to the rate in sulfuric acid (Fig. 4). In the range *p*H 5 to 7 *M* sulfuric acid, the rate of hydrolysis of N-*p*-chlorobenzylideneaniline is too fast to measure. The rate of hydrolysis in this region has been calculated as follows: The *p*H-independent first-order rate constant for the formation of Schiff base is 0.19 min.$^{-1}$ in the presence of 0.004 *M* anilinium ion (Fig. 2), giving a value of k_1 (eq. 4) of 47.5 M^{-1} min.$^{-1}$. The equi-

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(13) H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958).

(14) V. Gold, "*p*H Measurements," John Wiley and Son, Inc., New York, N. Y., 1956.

(15) M. A. Paul and F. A. Long, *Chem. Revs.*, **57**, 1 (1957).

$$\rangle C{=}O + RNH_3^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{Schiff base}{\cdot}H^+ \; K_1 \qquad (4)$$

librium constant for this reaction, K_1, is 0.080 M^{-1} (see below), and k_{-1} is, therefore, 595 min.$^{-1}$ (dotted line in Fig. 4). The shape of the curve on the alkaline side of the rate maximum is determined by the pK_a of the protonated Schiff base. In order to maintain the continuity of the over-all pH–rate profile, a break in the curve similar to that observed in 80% ethanol must occur, although the exact position of the break is not determined by the available data.

The equilibrium constant, K_1, defined as

$$K_1 = \frac{(\text{Schiff base}{\cdot}H^+)}{(\text{aldehyde})(\text{aniline}{\cdot}H^+)}$$

for the addition of aniline to p-chlorobenzaldehyde under acidic conditions was measured at several wave lengths by the method of Bloch-Chaudé.[11] The conditions were chosen so that absorption due to the protonated Schiff base was much more important than that due to the unprotonated species. The extinction coefficients for the protonated Schiff base were taken from the data in Fig. 1. The results are given in Table III. The value of 0.080 M^{-1} for K_1, together with the dissociation constant for anilinium ion, K_2, and the equilibrium constant for the formation of the unprotonated Schiff base, K_3, allows the calculation of the dissociation constant for the protonated Schiff base, K_4, since

TABLE III

EQUILIBRIUM CONSTANT FOR FORMATION OF N-p-CHLOROBENZYLIDENEANILINIUM CATION IN ACIDIC SOLUTION AT 25°[a]

Wave length, mμ	pH	K_1, M^{-1}
340	2.05	0.087
340	2.20	.087
340	2.40	.087
340	2.55	.087
340	2.90	.087
360	2.05	.081
360	2.20	.087
360	2.40	.079
360	2.55	.076
360	2.90	.087
380	2.02	.070
380	2.35	.072
380	2.70	.076
380	3.05	.066
380	3.50	.092
	Average	0.080

[a] 2.0×10^{-3} M p-chlorobenzaldehyde, 0.05 M aniline hydrochloride, 0.10 M bromoacetate buffer, ionic strength 0.50.

$$K_4 = K_2K_3/K_1$$

Since[12] $K_3 = 4.55\ M^{-1}$, K_4 is $1.57 \times 10^{-3}\ M^{-1}$ and the pK_a' of N-p-chlorobenzylideneanilinium cation is 2.80.

The pK_a' of N-p-chlorobenzylideneaniline cation may be determined independently from the change in the shape of the Schiff base absorption curve with pH by the following graphical method: The ratio of absorbance due to total Schiff base at 310 mμ to the absorbance at 340 mμ (due mainly to the protonated Schiff base) was plotted against pH over the range pH 2.05 to 4.30. From the absorption ratios at pH values at which the Schiff base is completely protonated and completely unprotonated and the data in Fig. 1, a pK_a' for the Schiff base cation of 2.75 was calculated.

Discussion

Three lines of evidence indicate that Schiff base formation undergoes a transition in rate-determining step from rate-determining dehydration of the carbinolamine addition product at neutral pH to rate-determining amine attack under acidic conditions. First, semicarbazone and oxime formation, reactions related to Schiff base formation, exhibit a pH-rate maximum similar to that in the formation of N-p-chlorobenzylideneaniline (Fig. 2). The former reactions proceed by the two-step reaction mechanism shown in eq. 1 and 2. Near neutral pH, the acid-catalyzed dehydration of the carbinolamine addition product is rate determining. Such a rate-determining dehydration may account for a leveling off, but not a decrease in the rate with decreasing pH.[8] At low pH values the rate of dehydration becomes very fast and, at the same time, the rate of amine attack is retarded because of conversion of the amine to its conjugate acid. Consequently, a change in rate-determining step occurs and the attack of the amine (eq. 3) becomes rate determining, accounting for the observed decrease in the rate on the acid side of the pH–rate maximum. The opposing effects of general acid catalysis and protonation of the attacking amine[16] cannot account for the pH–rate maximum in Schiff base formation since the rate constants (Fig. 2) have been corrected for the effects of general acid catalysis, which are small under the experimental conditions employed. In the reverse reaction, Schiff base hydrolysis, a change in rate-determining step requires a break in the acid-catalyzed region of the pH–rate profile. Such a break has been observed by Willi in the hydrolysis of N-benzylideneaniline in 50% methanol.[6] Willi's interpretation of this break, although stated in somewhat different terms, is equivalent to postulating a change in rate-determining step. In the hydrolysis of N-p-chlorobenzylideneaniline in water, this break is not seen in the region in which the rate is slow enough to measure. In 80% ethanol, however, this break occurs (Fig. 4) and is evidence for a change in rate-determining step. The pH profile for hydrolysis in water (dotted line), calculated from the rate and equilibrium constants for Schiff base formation and the pK_a' of the protonated Schiff base, exhibits a break similar to that found in 80% ethanol.

Second, a comparison of the effects of structure on reactivity on the two sides of the pH–rate maximum provides further evidence for a change in rate-determining step in Schiff base formation (Fig. 3). At pH 2.55, in the region of rate-determining amine attack, the second-order rate constants for the addition of aniline to substituted

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(16) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 333.

benzaldehydes follow σ^+ with a slope of 0.39. At this *p*H the small ρ^+-value may reflect an incomplete cancellation of the opposing effects of polar substituents on protonation of the substrate and attack of the amine. The correlation of the rates with σ^+, rather than σ, is not surprising since the carbonyl carbon atom will possess some carbonium ion character in the acid-catalyzed reaction. The base strengths of *p*-substituted benzylideneanilines, as measured by their complexing ability with *p*-nitrophenol in carbon tetrachloride solution[17] and the protonation of aromatic aldehydes,[18] both follow σ^+. At *p*H 6.1, in the region of rate-determining dehydration, on the other hand, the second-order rate constants for all substituents except *p*-OH and *p*-OCH_3 are the same. This behavior is analogous to that observed in semicarbazone formation[9] and can be accounted for in terms of the opposing effects of polar substituents on the equilibrium constant for carbinolamine formation and on the rate of acid-catalyzed dehydration of the carbinolamine.[18a] The non-linear Hammett plot reported here and those reported for similar reactions, including the condensation of *n*-butylamine with substituted piperonals,[19] the hydrolysis of N-benzylideneanilines,[7] substituted benzophenone oxime formation[20] and substituted benzaldehyde semicarbazone formation in 75% ethanol,[21] can be accounted for in two ways. First, as in the present case, the decreased rate constants for the *p*-OH and *p*-OCH_3 substituents may be attributed to the unequal relative importance of electron donation by resonance in the addition and dehydration steps of the reaction. Electron donation by resonance, particularly from the *p*-position, is more important in the stabilization of the benzaldehyde than in promoting the dehydration of the carbinolamine intermediate,[22] thus accounting for the decreased over-all rates with substituents which donate electrons strongly by resonance. Second, a non-linear Hammett plot may result from a change in rate-limiting step with changing substituent at a constant *p*H as, for example, in the case of semicarbazone formation from substituted benzaldehydes at *p*H 3.75.[9] Regardless of the explanation for the particular behavior found at either of the *p*H values, the important point is that the behavior is different, supporting the thesis that different rate-determining steps are being studied at the two *p*H values.

Third, the differing susceptibility of N-*p*-chlorobenzylideneaniline formation to general acid catalysis on the two sides of the *p*H–rate maximum is evidence for a change in rate-determining step. Although both steps are subject to general acid catalysis, the catalytic constant for acetic acid is approximately tenfold greater at *p*H 2.50 than at *p*H 5.10 (Table I). General acid catalysis of Schiff base formation in methanol has been previously reported by Santerre, *et al.*,[19] and Willi and Robertson[7] have reported general acid catalysis of Schiff base hydrolysis. In these studies it is not clear which step of the reaction is being catalyzed.

In moderately concentrated solutions of sulfuric acid, the rate of hydrolysis of N-*p*-chlorobenzylideneaniline is slow enough to measure and decreases rapidly with increasing acid concentration (Fig. 4). In the region 7 to 11 *M* sulfuric acid, the logarithm of the observed rate constant for hydrolysis of this Schiff base is linearly related to H_0 (slope 1.24), $H_0 + \log C_{H^+}$ (slope 1.34), and $\log a_{H_2O}$[23,24] (slope 3.12). A number of acid-catalyzed reactions, including the hydrolysis of amides,[25–29] the hydrolysis of the heterocyclic amide N-acetylimidazole,[30,31] and the hydrolysis of the Schiff base 4-(2,3-dimethylanilino)-pent-3-en-2-one,[32] exhibit decreased rates in moderately concentrated acid solutions in which the substrates are completely protonated, and show similar behavior with respect to these parameters. Such behavior appears to be characteristic of reactions involving several molecules of water in the transition state, functioning as both nucleophilic and proton transfer reagents. The following lines of evidence suggest that water functions as a proton transfer agent, as well as a nucleophilic reagent, in the hydrolysis of N-*p*-chlorobenzylideneaniline: (1) General acid catalysis of this reaction demonstrates that proton transfer between substrate and catalyst is involved in the transition state and suggests that the specific acid-catalyzed reaction is, in fact, general acid catalysis by the hydrated proton or its kinetic equivalent. (2) The twofold decrease in rate in D_2SO_4 compared to that in H_2SO_4 strongly suggests proton transfer in the rate-determining step. (3) The value of the slope of the logarithm of the rate plotted against H_0 is close to that for the rate retardation of proton transfer in aqueous solution,[33] and for the rate decrease in the diazotization of aniline in concentrated acid solution,[34] in which proton transfer

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[18a] NOTE ADDED IN PROOF: E. F. Pratt and M. J. Kamlet, *J. Org. Chem.*, **26**, 4029 (1961), have shown that the acid-catalyzed reactions of benzaldehydes with aniline in benzene solution exhibit a ρ value of 1.54 for benzaldehyde substituents. The authors suggest that this ρ value is accounted for by a greater effect of substituents on the nucleophilic reaction than on pre-equilibrium protonation; it might also be accounted for by a greater effect on pre-equilibrium addition compound formation than on dehydration. In either case it is evident that the situation in benzene is quite different from that in aqueous solution.

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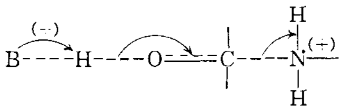
is thought to be rate determining. (4) The rate follows the activity of water to about the third power, implying that several (but not necessarily three[30]) molecules of water are involved in the transition state. Only one water molecule can be accounted for on the basis of water acting as a nucleophilic reagent alone. Thus, a reasonable transition state for Schiff base hydrolysis in acidic solution is that shown below, and the rate decrease in acidic solution is a consequence of the retardation of proton removal from the hydroxyl group of the carbinolamine, as well as a lower equilibrium concentration of carbinolamine because of the decreased availability of water in moderately concentrated acid solutions. This explanation requires that the reverse reaction, specific acid-catalyzed attack of aniline on the aldehyde be, in fact, general acid catalysis of aniline addition by the hydrated proton. The hypothesis[32] that the rate retardation observed for the hydrolysis of 4-(2,3-dimethylanilino)-pent-3-en-2-one in concentrated sulfuric acid is a consequence of the slower rate of addition of water to the protonated than to the free Schiff base seems unlikely on chemical grounds, particularly in view of the acid catalysis of the present reaction in dilute acid.



The hydrolysis of more basic Schiff bases, including retinylidenemethylamine[35] and 2-methyl-Δ^2-thiazoline,[36] is also retarded in acidic solution. However, the cause of the rate retardation in these cases is quite different from that with the less basic compounds. The hydrolysis of retinylidenemethylamine, for instance, is very slow even at pH 1,[35] where the rate of proton transfer is unaffected by variations in the acidity. In this case, the attack of the more basic amine is probably not subject to acid catalysis, and the pH–rate maximum may be explained by a change in rate-determining step somewhat similar to that described above for Schiff base formation; *i.e.*, the rate maximum in these reactions corresponds to the break near pH 4 in benzylideneaniline hydrolysis.

The pK_a' of N-p-chlorobenzylideneaniline is approximately 1.8 pH units lower than that of aniline. This decreased basicity may be ascribed to two competing factors: the rehybridization of the orbital containing the unshared electron pair on the nitrogen atom and the loss of conjugation of the unshared electron pair with the aromatic ring. Formation of semicarbazones of aromatic aldehydes, in which only the first factor is present, yields products having pK_a values about five pH units lower than semicarbazide itself.[22] Therefore, the loss of conjugation with the ring of the unshared electron pair on nitrogen must raise the pK_a of the Schiff base about three units relative to aniline, a value which seems reasonable since it has been estimated that the decreased basicity of aniline relative to ammonia (about 5 pH units) is due about equally to the electron-withdrawing power of the aromatic ring and to conjugation of the unshared electron pair with the ring.[37] Ricketts and Cho have observed that protonated water-stable Schiff bases formed from p-aminoazobenzene have pK_a values which are about 0.5 pH unit below the pK_a of the parent amine,[38] in general agreement with the result found in the present case.

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC., SUMMIT, N. J.]

The Arylation of Enamines[1a]

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Very reactive aryl halides attacked enamines by C-arylation to give α-aryl ketones on hydrolysis. With less reactive aryl halides, N-arylation and cleavage to N-arylated secondary amines was found. Aryliodonium salts and enamines produced α-aryl ketones in low yield after hydrolysis. Phenyldiazonium fluoroborate reacted primarily to form an α-phenylhydrazone imonium salt. The condensation of cyclohexanone enamines with quinone dibenzenesulfonimide led directly to an N,N'-dibenzenesulfonylaminotetrahydrocarbazole. Benzyne reacted with 1-pyrrolidinocyclohexene to produce, on hydrolysis, 2-phenylcyclohexanone and/or a benzocyclobutene derivative, depending on reaction conditions and the method of benzyne generation.

The Stork enamine reaction[2] is a convenient route for the alkylation and acylation of ketones. Conversion of a ketone to an enamine intermediate results not only in activation of an α-carbon to electrophilic attack but also provides selectivity with unequally substituted α- and α'-positions and usually allows termination of the reaction at the monoaddition stage.[3,4] A continued interest in

[1] (a) This paper was presented at the Enamine Symposium of the 140th National Meeting of the A.C.S., Chicago, Ill., September 6, 1961. (b) Present address: Chemistry Department, University of Vermont, Burlington, Vt.

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