$[\theta]_{340}$ 0, $[\theta]_{287}$ −1100, $[\theta]_{240}$ 0. O.R.D. in methanol (c 0.948, 410–280 mμ; c 0.0474, 280 −240 mμ): $[\phi]_{311}$ −7950°, $[\phi]_{305}$ −8030°, $[\phi]_{260}$ +7500°. Ultraviolet spectrum in methanol: λ_{275}^{max} ϵ 97.

6β-Nitrotestosterone acetate (XVI)[26] (Fig. 16): C.D. in methanol (c 0.775, 400–330 mμ; c 0.086, 330–275 mμ; c 0.0215, 275–260 mμ; c 0.01075, 260–240 mμ): $[\theta]_{400}$ 0, $[\theta]_{375}$ +240, $[\theta]_{357}$ 0, $[\theta]_{281}$ −16200, $[\theta]_{260}$ 0, $[\theta]_{240}$ +15100. O.R.D. in methanol (c 0.235, 400–290 mμ; c 0.0147, 290–230 mμ): $[\phi]_{302}$ −6560°. Ultraviolet spectrum in methanol: λ_{232}^{max} log ϵ 4.02.

6β-Nitro-3α,5α-cycloandrostan-17-one (XVII)[29] (Fig. 17): C.D. in methanol (c 0.708, 350–240 mμ): $[\theta]_{350}$ 0, $[\theta]_{326}$ +540, $[\theta]_{321}$ 0, $[\theta]_{305}$ +3120, $[\theta]_{288}$ 0, $[\theta]_{273}$ −2160, $[\theta]_{245}$ 0, $[\theta]_{240}$ +780. O.R.D. in methanol (c 0.0804, 350–235 mμ): $[\phi]_{316}$ +1900°, $[\phi]_{287}$ −3240°, $[\phi]_{247}$ +1080°. Ultraviolet spectrum in methanol: λ_{286}^{max} log ϵ 2.11.

6-Nitro-Δ^5-androstene-3β,17β-diol (XVIII)[26] (Fig. 18): C.D. in methanol (c 0.860, 420–365 mμ; c 0.172, 365–300 mμ; c 0.0344, 300–240 mμ): $[\theta]_{410}$ 0, $[\theta]_{395}$ +170, $[\theta]_{375}$ 0, $[\theta]_{317}$ −2170, $[\theta]_{290}$ 0, $[\theta]_{265}$ +6640. O.R.D. in methanol (c 0.068 420–320 mμ; c 0.0136, 320–310 mμ): $[\phi]_{355}$ −2950°, $[\phi]_{315}$ 0. Ultraviolet spectrum in methanol: $\lambda_{370-330}^{shoulder}$ log ϵ 2.00–2.51, λ_{258}^{max} log ϵ 3.54.

6-Nitro-Δ^5-pregnen-3β-ol-20-one acetate (XIX)[26] (Fig. 19): C.D. in methanol (c 0.3626, 400–310 mμ; c 0.0725, 310–260 mμ; c 0.03625, 260–240 mμ): $[\theta]_{395}$ 0, $[\theta]_{328}$ −3180, $[\theta]_{313}$ 0, $[\theta]_{282}$ +1180, $[\theta]_{243}$ 0. O.R.D. in methanol (c 0.0710, 410–340 mμ; c 0.0180, 340–290 mμ; c 0.0090, 290–270 mμ; c 0.00225, 270–230 mμ): $[\phi]_{364}$ −27400°, $[\phi]_{304}$ +20300°, $[\phi]_{230}$ −23600°. Ultraviolet spectrum in methanol: $\lambda_{350-320}^{shoulder}$ log ϵ 2.41–2.53, λ_{258}^{max} log ϵ 3.28.

The Mechanism of Hydrolysis of Schiff Bases Derived from Aliphatic Amines[1]
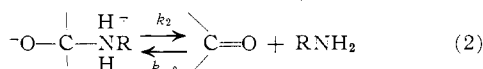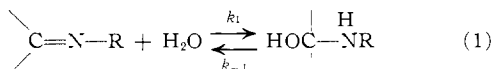
BY E. H. CORDES AND W. P. JENCKS

The rates of hydrolysis of a series of *p*- and *m*-substituted benzylidene-1,1-dimethylethylamines have been investigated in the pH range 0–14 at 25°. The rates of hydrolysis of these Schiff bases are independent of pH above pH 9 and increase slightly with electron-donating power of the polar substituent. These results suggest that, under these conditions, the attack of hydroxide ion on the protonated Schiff base is the rate-determining step. Under more acidic conditions, in which an appreciable fraction of the Schiff base exists as the conjugate acid, the hydrolysis rates increase with decreasing pH for Schiff bases possessing an electron-withdrawing substituent and decrease with decreasing pH for Schiff bases possessing an electron-donating substituent. The changes in rate with pH are correlated with the conversion of the Schiff bases to their conjugate acids, indicating that the predominant reaction under these conditions is the attack of water on the protonated Schiff base. Below pH 4, the hydrolysis rates for all of the Schiff bases decrease and eventually become linear in respect to hydroxide ion concentration. This behavior is interpreted as a transition in rate-determining step from attack of water under neutral and basic conditions to decomposition of the tetrahedral addition intermediate under acidic conditions.

Introduction

The formation and hydrolysis of a number of Schiff bases, oximes. semicarbazones, and related compounds has been shown to proceed through eq. 1 and 2. with step 1 rate-determining at neutral and alkaline pH

$$\underset{/}{\overset{\backslash}{C}}{=}N{-}R + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftarrows} } HO\overset{H}{\underset{}{C}}{-}NR \qquad (1)$$

$$^-O{-}\overset{H^-}{\underset{H}{C}}{-}NR \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} \underset{/}{\overset{\backslash}{C}}{=}O + RNH_2 \qquad (2)$$

values and step 2 rate-determining at acidic pH values.[2-8] Although the formation and hydrolysis of benzylidineanilines has been studied in some detail, much less information is available regarding the reactions of Schiff bases formed from more basic amines. Morton and Pitt have shown that the rate of retinylidenemethylamine hydrolysis is much slower in acid than in neutral solution[9] and this behavior has been interpreted in terms of a change in rate-determining step from 1 to 2 at low pH values.[5] The condensation of ammonia and primary amines with aromatic aldehydes in methanol proceeds at a rate proportional to the concentrations of the un-ionized reactants and is subject to general acid catalysis by acetic acid.[10-12] The experiments reported here were carried out to ob-

tain further information on the mechanism and catalysis of the hydrolysis of Schiff bases formed from strongly basic amines. Such Schiff bases are of biological importance in a large number of enzymic reactions involving pyridoxal phosphate,[13,14] enzymic aldolization,[15-17] and decarboxylation[18,19] reactions and, probably, in the visual pigment. rhodopsin.[20-21] The experiments were carried out with Schiff bases formed from substituted benzaldehydes and *t*-butylamine in order to avoid the possibility of

$$\underset{/}{\overset{\backslash}{C}}{=}NCH \rightleftarrows HCN{=}\overset{\backslash}{\underset{/}{C}}$$
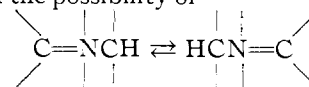
tautomerization; subsequent studies with the corresponding ethylamine Schiff bases showed that this precaution was probably unnecessary. because the hydrolysis of these compounds proceeds in a manner similar to that of the *t*-butylamine compounds, without detectable tautomerization.

Experimental

Kinetic measurements were carried out spectrophotometrically with a Zeiss PMQ II spectrophotometer equipped with a cell holder maintained at 25° as previously described.[2-3] In all

(1) Supported by grants from the National Science Foundation (GB-431 and G-14723) and the National Cancer Institute of the National Institutes of Health (CA-03975).

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kinetic runs, ionic strength was maintained at 0.50 by the addition of KCl. All kinetic runs were carried out in water containing approximately 3% ethanol. Measurements of pH were made with a glass electrode and a Radiometer PHM 4b pH meter.

Infrared spectra were recorded on a Perkin–Elmer infrared spectrophotometer, model 21.

Materials.—p-Nitro- and p-methoxybenzylidenethylamines were prepared according to published procedures[22,23]; p- and m-substituted benzylidene-1,1-dimethylethylamines were prepared by suspending the appropriate benzaldehyde in an aqueous solution containing excess t-butylamine. This suspension was stirred at room temperature for 45 min., during which the Schiff base separated. The solid Schiff bases were collected by filtration and recrystallized from ethanol. In the case of the liquid Schiff bases the aqueous layer was saturated with KOH, the layers were separated with a separatory funnel, and the Schiff base was purified by vacuum distillation.[24] Yields greater than 75% were obtained in all cases. Elemental analyses, boiling and melting points, and position of the imine stretching frequencies in chloroform for the substituted benzylidene-1,1-dimethylethylamines are: H: C 82.05 (81.92), H 9.30 (9.33), N 8.91 (8.70), 63–64° (1.0 mm.), 6.09 μ; p-NO$_2$: C 63.95 (64.04), H 6.92 (6.85), N 13.64 (13.58), 72–75°, 6.08 μ; p-Cl: C 67.22 (67.50), H 7.37 (7.22), N 7.00 (7.16), Cl 18.12 (18.09), 89–90° (1.0 mm.), 6.08 μ; p-CH$_3$: C 81.99 (82.21), H 9.81 (9.80), N 7.81 (7.99), 83–84° (1.4 mm.); 6.09 μ; p-OCH$_3$: C 75.26 (75.34), H 8.92 (8.98), N 7.32 (7.18), 110–113° (2.1 mm.), 6.09 μ; m-Br: C, 53.92 (55.00), H 5.79 (5.89), N 5.81 (5.83), Br 34.40 (33.28), 90–94° (1.6 mm.), 6.09 μ. The elemental analysis for m-bromobenzylidene-1,1-dimethylethylamine indicates that the compound is not completely pure. It is felt that the data for this Schiff base are not greatly in error as a result of this contamination, but they are presented with this qualification. Reagent grade inorganic salts were used without further purification. Other reagents were recrystallized or redistilled before use. Solutions of Schiff bases were prepared in ethanol just prior to use. Distilled water was used throughout.

Analysis of Products.—At the conclusion of kinetic runs with several benzylidene-1,1-dimethylethylamines carried out at different pH values over the entire pH region investigated, ultraviolet spectra were recorded on a Cary model 14 recording spectrophotometer. In all cases, the spectra obtained were identical with those of authentic samples of the parent benzaldehydes. t-Butylamine was identified as the other product of the hydrolysis reaction as follows: 1.2 × 10^{-3} mole of benzylidene-1,1-dimethylethylamine was dissolved in water containing an equivalent amount of hydrochloric acid. The reaction was permitted to go to completion (20 hr.) at room temperature and the products were titrated with a standard sodium hydroxide solution on a Radiometer PHM 4b pH meter equipped with external electrodes. Greater than a 90% yield of a compound having a pK_a of 10.46 was obtained. A sample of t-butylamine hydrochloride titrated in a similar fashion yielded a pK_a of 10.63. The slightly low pK_a value obtained with the reaction mixture may be the result of the formation of small amounts of the Schiff base as the amine is converted to the free base form.
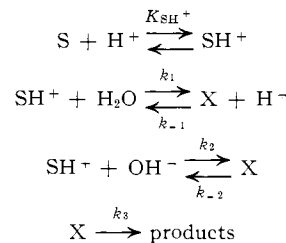
At the conclusion of each kinetic run involving the benzylideneethylamines, an ultraviolet spectrum of the reaction mixture was recorded as indicated above. In all cases, the spectra obtained indicated that the reaction had yielded at least 90% of the appropriate benzaldehyde.

Determination of pK_a values.—In the pH region 5–9, the ultraviolet absorption maxima of the benzylidene-1,1-dimethylethylamines undergo a pronounced shift to longer wave lengths, as the Schiff bases are converted to their conjugate acids. The pK_a values for the conjugate acids of the Schiff bases were determined spectrophotometrically by recording changes in optical density at an appropriate wave length as a function of time at a series of pH values over the range of dissociation. The optical density readings were extrapolated to zero time and plotted against pH. The pK_a values were obtained from the inflection point of the plot of optical density against pH.

In all cases, except for the p-chloro derivative, the changes in the spectra of the Schiff bases with pH were accompanied by changes in the rate of hydrolysis (Fig. 1). pK_a values for the protonated Schiff bases were also estimated, where possible, from the mid-point in the break in the pH–rate profile. The pK_a values obtained from the spectral and kinetic data agreed to within 0.2 pH unit in all cases.

In the case of p-nitrobenzylidene-1,1-dimethylethylamine, the rates of hydrolysis in the region of appreciable Schiff base protonation were too fast to permit accurate extrapolations of optical density readings to zero time. Therefore, an accurate spectral titration curve for the protonation of this substrate could

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not be obtained. Furthermore, the estimation of the pK_a for this protonated Schiff base from the break in the pH–rate profile is rendered uncertain since it is not clear from the pH-rate profile that the leveling off in the hydrolysis rate is caused by complete conversion of the Schiff base to the conjugate acid (Fig. 1). Therefore, the pK_a for the conjugate acid of this substrate was obtained independently from an analysis of the steady-state rate equation for this reaction. Assuming steady-state conditions in respect to the carbinolamine intermediate (X), and that only the neutral (or dipolar) form of the carbinolamine intermediate decomposes to products, this reaction may be formulated as

$$S + H^+ \underset{}{\overset{K_{SH}^+}{\rightleftharpoons}} SH^+$$

$$SH^+ + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} X + H^-$$

$$SH^+ + OH^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} X$$

$$X \overset{k_3}{\longrightarrow} products$$

The rate expression for this reaction is

$$k_{obs} = \frac{k_1 k_3 (H^+) + 10^{-14} k_2 k_3}{[(H^+) + K_{SH}][k_{-1}(H^-) + k_{-2} + k_3]} \quad (3)$$

In the pH region of interest, the contribution to the observed rate from the attack of hydroxide ion on the protonated Schiff base is negligible and 3 reduces to

$$k_{obs} = \frac{k_1 k_3 (H^-)}{[(H^+) + K_{SH}][k_3 + k_{-1}(H^-)]} \quad (4)$$

From the observed first-order rate constant at pH 7 (corrected for the contribution of the pH-independent reaction), where $K_{SH} >> (H^+)$ and $k_2 >> k_{-1}(H^+)$, eq. 4 gives

$$k_1 = 4.2 \times 10^6 K_{SH} \quad (5)$$

From the observed first-order rate constant at pH 1, where $(H^+) >> K_{SH}$ and $k_{-1}(H^+) >> k_2$, eq. 4 gives

$$k_1 k_3 / k_{-1} = 0.10 \quad (6)$$

Putting eq. 5 and 6 into eq. 4 yields

$$k_{obs} = \frac{4.2 \times 10^6 K_{SH} (H^+)}{[(H^+) + K_{SH}][1 + 4.2 \times 10^7 K_{SH} (H^-)]} \quad (7)$$

K_{SH} was then evaluated from the measured k_{obs} values at several values of (H$^+$). A value of 4.0 × 10^{-6} M^{-1} was obtained, from which a pK_a for the conjugate acid of p-nitrobenzylidene-1,1-dimethylethylamine of 5.40 was calculated. This is in good agreement with a value of 5.35 obtained from the mid-point of the break in the pH–rate profile for this Schiff base.

Under alkaline conditions, pH > 8, $10^{-14}k_2k_3 >> k_1k_3(H^-)$, $K_{SH} >> (H^+)$, and $k_{-2} + k_3 >> k_{-1}(H^+)$. Using the observed first-order rate constant at alkaline pH, eq. 3 yields

$$1.9 \times 10^8 = k_2 k_3 / (k_{-2} + k_3) = k_2 \quad (8)$$

Putting eq. 5, 6, and 8 in eq. 3, and realizing that $k_{-2}/k_3 << 1$, yields

$$k_{obs} = \frac{16.8(H^-) + 1.9 \times 10^{-6}}{[(H^+) + 4.0 \times 10^{-6}][1.68 \times 10^2(H^+) + 1]} \quad (9)$$

The pH–rate profile for the hydrolysis of p-nitrobenzylidene-1,1-dimethylethylamine in Fig. 1 is a theoretical curve calculated from eq. 9.

Results

In Fig. 1, the logarithms of the first-order rate constants for the hydrolysis of a series of substituted benzylidene-1,1-dimethylamines are plotted as a function of pH over the pH range 0–14. The rate constants in Fig. 1 have not, with a few exceptions, been corrected for buffer catalysis. Separate studies of acetate catalysis of the hydrolysis of benzylidene-1,1-dimethylethylamine indicated that the maximum error introduced into the rate constants by neglecting buffer catalysis under the conditions of these experiments (0.02 M buffer) is about 5% (see Fig. 5). Furthermore, the pH-independent reactions which occur above pH 9 are not subject to detectable buffer catalysis (see below). The experimentally determined dissociation constants for the protonated Schiff bases (see Experimental section) and several individual rate constants contained in or derived from the data in Fig. 1 are collected in Table I. These are discussed in a subsequent section.
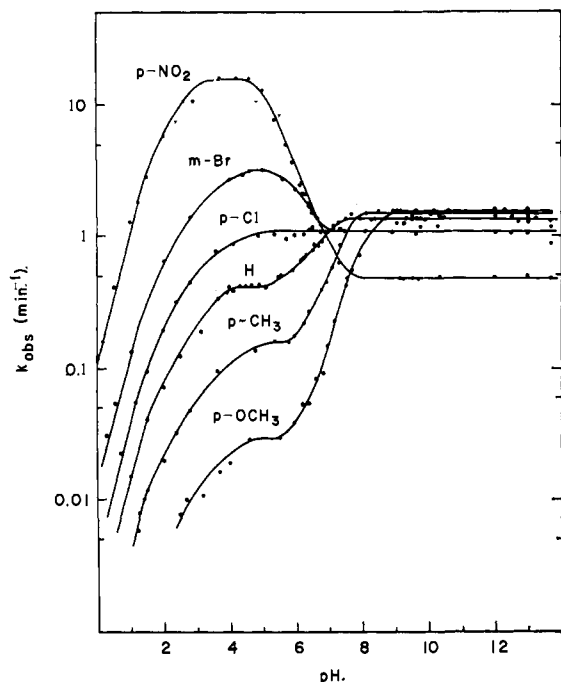
Fig. 1.—Logarithm of the first-order rate constants for the hydrolysis of substituted benzylidene-1,1-dimethylethylamines as a function of pH at 25°; 0.02 M chloroacetate, acetate, phosphate, borate, and carbonate buffers employed in the appropriate pH ranges. Ionic strength maintained at 0.50 by the addition of KCl.

In order to ensure that the pH–rate behavior observed for the hydrolysis of benzylidene-1,1-dimethylethylamines is not a consequence, in part, of steric effects due to the bulky t-butyl group, the rates of hydrolysis of p-methoxy- and p-nitrobenzylidene-ethylamines were studied as a function of pH. The logarithms of the observed first-order rate constants for the hydrolysis of these substrates are plotted against pH in Fig. 2. The pH–rate behavior of the benzylideneethylamines is qualitatively similar to that of the
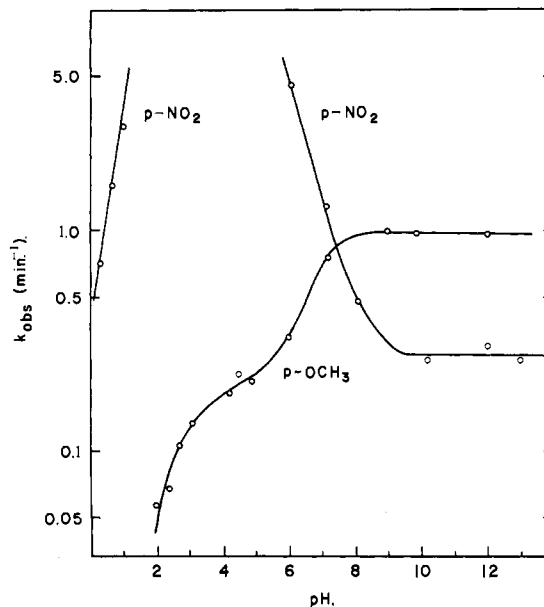
TABLE I
RATE CONSTANTS FOR THE HYDROLYSIS OF SUBSTITUTED BENZYLI-
DENE-1,1-DIMETHYLETHYLAMINES AND DISSOCIATION CONSTANTS
FOR THE PROTONATED SCHIFF BASES AT 25° AND IONIC STRENGTH
0.5

Substituent	K_{SBH^+},[a] M	k_1,[b] min.$^{-1}$	k_{calcd},[c] M^{-1} min.$^{-1}$	k_{H_2O},[d] min.$^{-1}$	pH 1, k_{obsd}, min.$^{-1}$
p-Nitro-	3.98×10^{-6}	0.48	1.91×10^8	16	11
m-Bromo-	7.95×10^{-7}			3.1	0.12
p-Chloro-	3.16×10^{-7}	1.09	3.45×10^7	1.1	.038
Unsubstituted	1.99×10^{-7}	1.34	3.00×10^7	0.41	.014
p-Methyl-	3.98×10^{-8}	1.50	5.98×10^6	.16	.004
p-Methoxy-	1.98×10^{-8}	1.54	3.05×10^6	.029	

[a] Dissociation constants for the protonated benzylidene-1,1-dimethylethylamines. [b] Observed first-order rate constant for the pH-independent reaction above pH 9. [c] Calculated second-order rate constant for attack of hydroxide ion on the protonated Schiff bases. [d] Observed rate constants for the attack of water on the protonated Schiff bases, estimated from the rates of hydrolysis in the pH region 4–5.

corresponding benzylidene-1,1-dimethylethylamines. The rates of the pH-independent reactions differ by less than twofold, while the rates at more acid pH values are somewhat faster than those of the corresponding benzylidene-1,1-dimethylethylamines. Thus, substitution of a t-butyl for an ethyl group does not have a large steric effect on the reaction rate. The hydrolysis of N-benzalaminooctanes in dioxane–water–acetic acid decreases by less than tenfold as the position of the nitrogen atom is varied from the 1- to the 2- to the

Fig. 2.—Logarithm of the first-order rate constants for the hydrolysis of p-nitro- and p-methoxybenzylideneethylamines as a function of pH at 25°; 0.02 M chloroacetate, acetate, phosphate, borate, and carbonate buffers employed in the appropriate pH ranges. Ionic strength maintained at 0.50 by the addition of KCl.
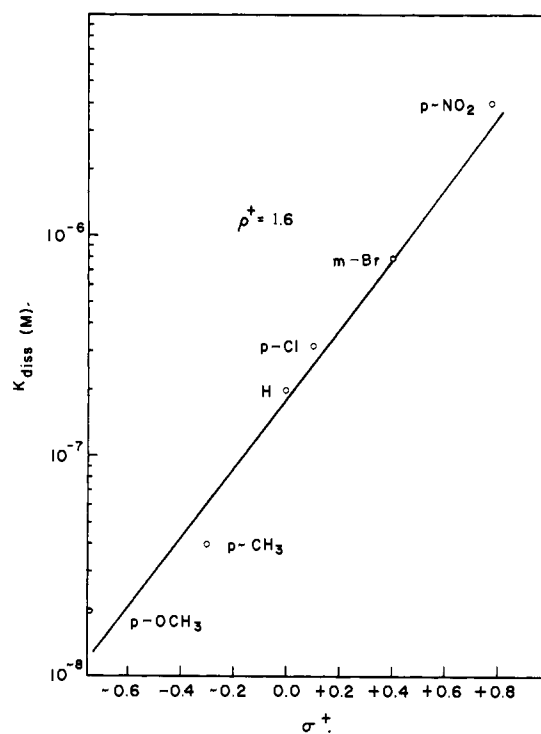

Fig. 3.—Logarithm of the dissociation constants of the conjugate acids of substituted benzylidene-1,1-dimethylethylamines plotted against the σ^+-substituent constants.

3-position of the octane chain.[25] Both the rate and equilibrium constants for the formation of Schiff bases from piperonal at 25° are approximately 30-fold larger for the reaction with n-butylamine than for that with t-butylamine[16]; this suggests that the rates of hydrolysis of the two Schiff bases should be similar.

In Fig. 3, the logarithms of the dissociation constants (Table I) of the conjugate acids of the benzylidene-1,1-dimethylethylamines are plotted against the σ^+-sub-

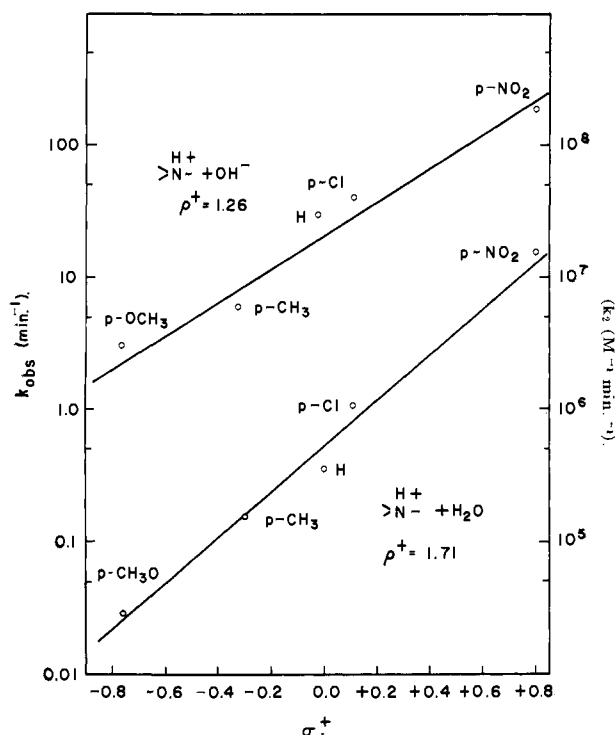(25) G. Geiseler, F. Asinger, and G. Hennig, Chem. Ber., 94, 1008 (1961).

Fig. 4.—Logarithms of the calculated second-order rate constants for the attack of hydroxide ion (upper line) and observed first-order rate constants for the attack of water (lower line) on the conjugate acids of substituted benzylidene-1,1-dimethylethylamines at 25° plotted against the σ^+-substituent constants.

stituent constants.[26] In this case, as well as in others discussed below, the data were correlated somewhat better by the σ^+-, rather than σ-substituent constants. The ρ^+-value for the dissociation constants is 1.6.

In the pH region 9–14, all of the substituted benzylidene-1,1-dimethylethylamines examined exhibit only a pH-independent reaction (Fig. 1). The observed first-order rate constants for this reaction are quite insensitive to the nature of the polar substituent, since the rate varies by only threefold in going from the p-nitro- to the p-methoxy Schiff base. These rate constants are correlated moderately well by the σ^+-substituent constants with a ρ^+-value of -0.21 (plot not shown).

At pH values more acidic than pH 9, the rates of Schiff base hydrolysis become pH-dependent, except for the p-chloro compounds, and are correlated with the conversion of the substrates to their conjugate acids (see Experimental). Schiff bases possessing an electron-withdrawing substituent exhibit an increased rate of hydrolysis upon protonation while Schiff bases possessing an electron-donating substituent exhibit rate decreases upon protonation.

In the pH region near pH 4 to 5, in which all of the Schiff bases exist predominantly as the conjugate acids, the hydrolysis rates again become pH-independent (Fig. 1). The logarithms of the first-order rate constants for the hydrolysis of the benzylidene-1,1-dimethylethylamines under these conditions are plotted against the σ^+-substituent constants in Fig. 4 (lower line) and follow a ρ^+-value of 1.71.

At pH values below pH 4, the hydrolysis rates for all of the Schiff bases decrease with increasing acidity and eventually become first-order in respect to hydroxide ion concentration. At pH 1.0, the rates of hydrolysis of all of the Schiff bases except the p-methoxy com-

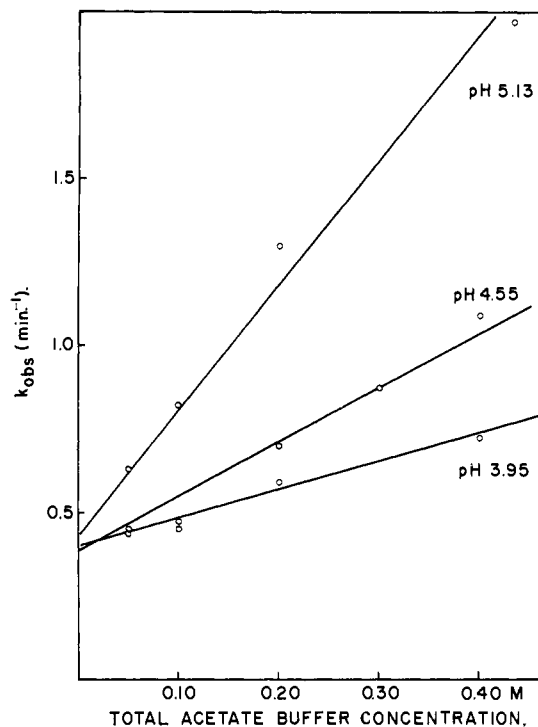(26) H. C. Brown and Y. Okamoto, J. Am. Chem. Soc., 80, 4979 (1958).

Fig. 5.—First-order rate constants for the hydrolysis of benzylidene-1,1 dimethylethylamine plotted against the total concentration of acetate buffer at several pH values at 25°.

pound are linear in respect to hydroxide ion concentration and the first-order rate constants are well correlated by the σ^+-substituent constants with a ρ^+-value of 2.17 (plot not shown).

In Fig. 5, the first-order rate constants for the hydrolysis of benzylidene-1,1-dimethylethylamine are shown as a function of the concentration of acetate buffer at pH 3.95, 4.55, and 5.13. The effectiveness of acetate buffers as catalysts for this reaction increases with increasing pH, indicating that the rate of the catalyzed reaction depends on the concentration of acetate ion rather than acetic acid.

The observed rates of benzylidene-1,1-dimethylethylamine hydrolysis are independent of the concentration of carbonate buffer at pH 9.25 (0.05–0.20 M) and at pH 10.40 (0.05–0.50 M) and of the concentration of imidazole at pH 10.02 (0.05–0.50 M).

The first-order rate constant for the hydrolysis of p-methylbenzylideneaniline in the pH range 10–12 was measured in 0.02 M carbonate buffer and a value of 0.031 min.$^{-1}$ was obtained.

Discussion

Any proposed mechanism for the hydrolysis of substituted benzylidene-1,1-dimethylethylamines must account for the complex variation of the rate with pH shown in Fig. 1. Although the explanation for this behavior would probably not have been immediately obvious in the absence of other information, analogy with the known mechanism of several related reactions provides a satisfactory explanation for the data. A number of other mechanisms which we have considered fail to account for the observed variation of the rates with pH.

The proposed explanation rests on the following principles, which have been established for related reactions[2–6,8]:
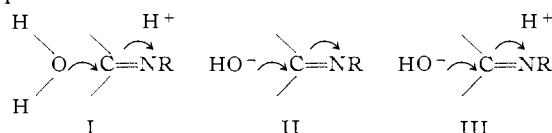
(1) At alkaline pH the rate-determining step of the over-all process of nitrogen derivative formation is the uncatalyzed, base-catalyzed, or acid-catalyzed dehydration of the carbinolamine addition intermediate
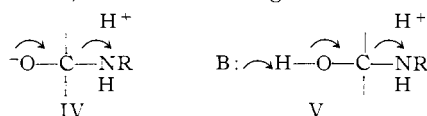
(eq. 1, k_{-1}). In the reverse, hydrolytic reaction, this corresponds to rate-determining attack of water or hydroxide ion in this pH region (eq. 1, k_1).

(2) At acidic pH the rate-determining step of nitrogen derivative formation is the acid-catalyzed or uncatalyzed attack of free nitrogen base on the carbonyl group (eq. 2, k_{-2}). In the reverse reaction, this corresponds to rate-determining loss of amine from the carbinolamine addition intermediate (eq. 2, k_2).

(3) The dehydration of carbinolamine addition intermediates formed from weakly basic amines is aided by acid and base catalysis, while the dehydration of the intermediates formed from more strongly basic amines may also occur by the expulsion of hydroxide ion, without catalysis. In the reverse reactions, which must proceed through identical transition states, these processes correspond to the addition of water to the protonated imine I, the addition of hydroxide ion to the free imine II, and the addition of hydroxide ion to the protonated imine III.

$$
\begin{array}{ccc}
\underset{\text{I}}{\overset{\text{H}}{\underset{\text{H}}{\text{O}}}}\text{—C}\overset{\text{H}^+}{=}\text{NR} & \underset{\text{II}}{\text{HO}^-\text{—C}=\text{NR}} & \underset{\text{III}}{\text{HO}^-\text{—C}\overset{\text{H}^+}{=}\text{NR}}
\end{array}
$$

(4) Strongly basic amines attack the carbonyl group readily, without acid catalysis, while the attack of weakly basic amines is aided by general acid catalysis. In the reverse, hydrolytic reactions, strongly basic amines are expelled from the dipolar intermediate IV, while weakly basic amines are expelled from a cationic intermediate V, with the aid of general base catalysis.

$$
\begin{array}{cc}
\underset{\text{IV}}{\overset{\text{H}^+}{^-\text{O}}\text{—C—NR}} & \underset{\text{V}}{\text{B:}\text{H—O—C}\overset{\text{H}^+}{\text{—NR}}}
\end{array}
$$

These considerations apply to the hydrolysis of t-butylamine and ethylamine Schiff bases as follows:

Above pH 9, the rates of hydrolysis of substituted benzylidene-1,1-dimethylethylamines are independent of pH (Fig. 1). This pH-independent reaction may be accounted for in terms of either rate-determining attack of a water molecule on the free Schiff base or, since under these conditions only a small fraction of the Schiff base exists as the conjugate acid, rate-determining attack of a hydroxide ion on the protonated Schiff base. If the attack of water were rate-determining, it would be expected that the hydrolysis rates would be accelerated by electron-withdrawing polar substituents. On the other hand, in the case of the attack of hydroxide ion on the protonated Schiff base, the effects of polar substituents on the pre-equilibrium protonation reaction will oppose those for the attack of hydroxide ion and, consequently, the observed hydrolysis rates should show a smaller dependence or no dependence on the nature of the polar substituents. The observation that the hydrolysis rates are only slightly dependent on the nature of the polar substituent and that electron-withdrawing substituents actually retard the hydrolysis rates slightly ($\rho^+ = -0.21$) is inconsistent with the first possibility and strongly suggests that this reaction involves attack of hydroxide ion on the protonated Schiff base. Second-order rate constants for the attack of hydroxide ion on the protonated Schiff bases were calculated from the observed rates of hydrolysis in the pH-independent region and the dissociation constants for the protonated Schiff bases (Table I). Logarithms of the calculated second-order rate constants are plotted against the σ^+-substituent constants in Fig. 4 and a ρ^+-value of 1.26 is obtained.

A similar pH-independent reaction has been observed for the hydrolysis of the related Schiff bases, benzylideneanilines, by several investigators.[5,7,8,27] Willi has suggested that this reaction may also involve rate-determining attack of hydroxide ion on the protonated substrate.[7] This suggestion is supported by the observation that the first-order rate constant for the pH-independent hydrolysis of p-methylbenzylideneaniline, 0.031 min.$^{-1}$, is greater than that for the p-chloro compound, 0.0079 min.$^{-1}$.[5] From the known pK_a value for the conjugate acid of p-chlorobenzylideneaniline, 2.80,[5] the second-order rate constant for the attack of hydroxide ion on the protonated Schiff base is calculated to be 1.25×10^9 M^{-1} min.$^{-1}$, about 30-fold greater than the corresponding rate constant for the t-butylamine Schiff base (Table I). This increase in reactivity reflects the greater electron-withdrawing power of the phenyl, relative to the t-butyl, group and, possibly, stabilization of the transition state in the case of the aniline Schiff base by resonance delocalization of the incipient lone electron pair on nitrogen.

Under more acidic conditions, in which the benzylidene-1,1-dimethylethylamines are partly converted to their conjugate acids, the hydrolysis rates become pH-dependent. Schiff bases possessing an electron-withdrawing substituent exhibit either no change or an increase in hydrolysis rate with increasing acidity. On the other hand, Schiff bases possessing an electron-donating substituent exhibit decreased rates of hydrolysis with increasing acidity. Since the variations in the rates of hydrolysis parallel the conversion of the Schiff bases to their conjugate acids, as indicated by changes in the ultraviolet spectra of the substrates, the reaction of water with the protonated Schiff bases must become the predominant reaction path as the pH is lowered. Under conditions in which the Schiff bases are completely converted to their conjugate acids, the hydrolysis rates again become pH-independent and reflect the rate of attack of water on the fully protonated Schiff bases (Fig. 1). The observed rate constants for the attack of water on the protonated Schiff bases show a strong dependence on the nature of the polar substituent, $\rho^+ = 1.71$ (Fig. 4). This value is comparable to the ρ-value of 2.0 found by Culbertson for the hydrolysis of fully protonated diphenylketimines.[28]

The observed rates of hydrolysis at alkaline pH are independent of pH because the concentrations of hydroxide ion and of the protonated Schiff base vary in an equal and opposite manner as the pH is changed. With decreasing pH the substrate becomes fully protonated so that this compensation no longer occurs and the decrease in the concentration of hydroxide ion results in a decrease in that part of the observed rate which is due to this reaction. Thus, a decrease in rate is observed for those compounds for which the attack of water on the protonated Schiff base is slow, and an increase in rate is observed for those compounds for which the corresponding reaction is fast.

The ρ^+-value for the attack of hydroxide ion on the protonated Schiff bases, 1.26, is appreciably lower than that for the attack of water on these substrates, 1.71. This finding suggests, in accordance with the considerations of Hammond[29] and Leffler,[30] that the transition state for the reaction involving hydroxide ion as the nucleophilic reagent is reached earlier than

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

(28) J. B. Culbertson, J. Am. Chem. Soc., **73**, 4818 (1951).

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

(30) J. E. Leffler, Science, **117**, 340 (1953).

that for the reaction involving the weaker nucleophilic reagent, water. This conclusion may be formalized quantitatively by the equation

$$\frac{pK_{A1} - pK_{A2}}{\rho_1 - \rho_2} = C = \frac{\sigma_i}{\beta_1 - \beta_0}$$

This relationship is analogous to several derived earlier and may be obtained in the same fashion.[6] The pK_a values of the conjugate acids of the nucleophilic reagents are employed here as measures of nucleophilic reactivity and β is the usual Brönsted parameter[31] indicating the sensitivity of the reaction rate to changes in the nucleophilicity of the attacking reagent. From the observed ρ^+-values, C is calculated to be approximately -39. This large C-value reflects the rather modest change in the observed ρ^+-values with a change of 17 orders of magnitude in the basicity of the nucleophilic reagent. Values of β calculated from the data for water and hydroxide ion do not show an appreciable variation with substrate reactivity as the substituent is varied from p-methoxy to p-nitro, in accord with the large absolute value of C.

The first-order rate constant for the attack of water on protonated p-chlorobenzylidene-1,1-dimethylamine is 1.1 min.$^{-1}$ (Table I) while the corresponding value for p-chlorobenzylideneaniline has been calculated to be 1.58×10^4 min.$^{-1}$,[5] more than four orders of magnitude greater than that of the t-butylamine Schiff base. Thus the reactivity of the protonated aniline Schiff base compared to that of the protonated t-butylamine Schiff base in the reaction with water is much greater than in the case of the reaction of the same protonated substrates with hydroxide ion, in which the rate ratio is only thirty. This finding is also in accord with the concept that the transition state for the attack of water is reached later than that for the attack of hydroxide ion, since stabilization of the transition state by resonance delocalization of the incipient lone electron pair on nitrogen in the case of the aniline Schiff base will become more important as the amount of $>C{=}N$ breakage in the transition state increases.

Under still more acidic conditions, the rates of hydrolysis of all of the benzylidene-1,1-dimethylethylamines exhibit decreases and eventually become linear in respect to hydroxide ion concentration (Fig. 1). This break in the pH–rate profile is interpreted as a transition in rate-determining step from rate-determining water or hydroxide ion attack under neutral or basic conditions to rate-determining decomposition of the carbinolamine intermediate under acidic conditions (eq. 1 and 2). For strongly basic amines, the transition state for this decomposition is expected to have the dipolar structure IV. The concentration of this species, which has no net charge, will decrease with increasing acidity under conditions in which the starting Schiff base is completely protonated. When the rate of this decomposition becomes slower than the pH-independent rate of attack of water on the protonated Schiff base, a change in rate-determining step occurs and the observed rate decreases with increasing acidity. In other words, it is necessary to remove protons from the oxygen atom in order to obtain sufficient driving force to expel the free amine, and in acid solution this becomes progressively more difficult.

A steady-state equation for the hydrolysis of p-nitrobenzylidene-1,1-dimethylethylamine, based on the above several considerations regarding this reaction, has been developed (eq. 9, Experimental). The pH–rate profile for this Schiff base (Fig. 1) is a theoretical curve based on eq. 9. The agreement between the experimental points and the theoretical line is satisfac-

(31) R. P. Bell, "Acid–Base Catalysis," Oxford University Press, London, 1941.

tory throughout the entire pH range investigated. Thus, the proposed mechanism for this reaction accounts quantitatively for the complete observed pH–rate profile.

The observation that, under acidic conditions, the rates of hydrolysis of benzylidene-1,1-dimethylethylamines are inversely related to hydrogen ion concentration indicates that, in the reverse direction, the attack of t-butylamine on the aldehydes is not subject to appreciable acid catalysis. This conclusion accords with previous findings, which indicate that the susceptibility of carbonyl addition reactions to acid catalysis decreases as the reactivity of the attacking reagent is increased.[6] Thus, acid catalysis is very important for the attack of water[32-33] and semicarbazide[2-6] on the carbonyl group but is of minor importance for the attack of the stronger base, hydroxylamine.[2]

The rates of hydrolysis of benzylidene-1,1-dimethylethylamines at pH 1 are strongly influenced by the nature of the polar substituent (ρ^+ 2.17). This presumably reflects principally the expected effects of polar substituents on the pre-equilibrium addition of water (eq. 1).

In the pH range pH 4 to 5, the hydrolysis of benzylidene-1,1-dimethylamine is subject to general base catalysis by acetate ion (Fig. 5). Although a quantitative interpretation is difficult because the lower part of this pH region approaches the pH at which a change in rate-determining step occurs and the rate can only be described accurately by a steady-state treatment, the attack of water on the protonated Schiff base is rate-determining over most of this pH region and the catalysis may be ascribed with confidence to facilitation of the attack of water by acetate ion. This catalysis is kinetically equivalent to the previously observed general acid catalysis of benzylideneaniline hydrolysis under conditions in which the Schiff base is in the form of the free base[5,12,34] because

$$\text{rate} = k(\text{SB})(\text{HB}^+) = \frac{kK_{\text{SBH}^+}}{K_{\text{HB}^+}} (\text{SBH}^+)(\text{B}) =$$
$$k'(\text{SBH}^+)(\text{B}) \quad (10)$$

The observed catalysis of the hydrolysis of the conjugate acid of benzylidene-1,1-dimethylethylamine by acetate ion is of particular interest because the common kinetic ambiguity in distinguishing general acid from specific acid–general base catalysis, represented by eq. 10, is resolved in this instance. Since the substrate is already fully protonated, the role of the catalyst cannot be to donate a proton to the substrate VI, but must be to aid the removal of a proton from an attacking water molecule (VII). It is not surprising that the attack of the much more basic hydroxide ion on the protonated Schiff base proceeds without the aid of catalysts (III).

VI VII
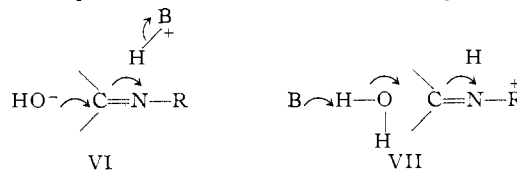
It is probable that the catalysis of Schiff base formation by acetic acid observed by Santerre, Hansrote, and Crowell[12] occurs by mechanism VII in reverse, i.e., by general acid catalysis of the dehydration of the carbinolamine addition intermediate.

(32) R. P. Bell and W. C. E. Higginson, *Proc. Roy. Soc.* (London), **A197**, 141 (1949).

(33) R. P. Bell and M. B. Jensen, *ibid.*, **A261**, 34 (1961).

(34) A. Willi and R. F. Robertson, *Can. J. Chem.*, **31**, 361 (1953).