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Schiff Bases. Kinetics of Hydrolysis of *p*-Trimethylammoniumbenzylidene-*p*′-hydroxyaniline Chloride in Aqueous Solution from *p*H 1 to 11.5

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The kinetics of the acid-catalyzed hydrolysis of a water-soluble Schiff base have been measured in aqueous solution (*p*H 1–11.5) using flow methods for the rapid rates. No measurable accumulation of an intermediate was detected. The rate of hydrolysis is strictly first-order with respect to [H$^+$] between *p*H 4 and 7 in buffers where [HA] is held constant and becomes independent of [H$^+$] at acidities greater than *p*H 2. The acid dissociation constant of the Schiff base conjugate acid was measured spectrophotometrically on flowing solutions. A mechanism for the acid hydrolysis involving only the conversion of substrate to its conjugate acid is shown to be inadequate for describing the data. General acid catalysis by acid phosphate salts is observed. A mechanism by which an intermediate, present in a low steady-state concentration, forms and breaks down by uncatalyzed and acid-catalyzed paths is in agreement with the data.

Introduction

Previous kinetic studies of the hydrolysis of benzylideneaniline in aqueous methanol[1,2] have led to somewhat different results and conclusions regarding a mechanism. In these studies the rate was found to be independent of [H$^+$] from *p*H 10 to 12 and dependent on [H$^+$] in the *p*H region 5 to 10. The rate was too rapid to follow by conventional methods at acidities greater than *p*H 5. By following the simultaneous decrease in benzylideneaniline concentration and increase in benzaldehyde concentration by a polarographic method in 30% methanol, Kastening, Holleck and Melkonian obtained evidence for the rapid accumulation of an intermediate. They proposed a mechanism in which the generally accepted[3] amino-alcohol intermediate is formed in a mobile equilibrium between benzylideneaniline and water. This intermediate then cleaves in a slow step to products (k_{I} and $k_{-\text{I}} >> k_{\text{II}}$, eq. 1). They found that the rate varies linearly with [H$^+$] over a narrow range between

$$\text{ArCH}{=}\text{NAr}' + \text{H}_2\text{O} \underset{k_{-\text{I}}}{\overset{k_{\text{I}}}{\rightleftharpoons}} \text{ArCHOHNHAr}' \underset{k_{-\text{II}}}{\overset{k_{\text{II}}}{\rightleftharpoons}} \text{ArCHO} + \text{H}_2\text{NAr}' \quad (1)$$

*p*H 6 and 7. Willi[1b] found that, in unbuffered 50% aqueous methanol solutions, the expression

$$k_{\text{obs}} = (k_2[\text{H}^+]^2 + k_1[\text{H}^+] + k_0)/(K + [\text{H}^+]) \quad (2)$$

described the rate data obtained in the *pc*H ($-\log C_{\text{H}+}$) regions 5.1–6.6 and 9.4–10.4. He proposed a mechanism in which $k_{\text{I}} << k_{\text{II}}$ and the intermediate amino alcohol forms and decomposes in uncatalyzed and acid-catalyzed steps. The discrepancy between the absence of measurable concentrations of intermediate in 50% methanol[1b] and the accumulation of intermediate amounting to 13% of the initial Schiff-base concentration in 30% methanol[2] was attributed to the difference in solvent.[1b] However, the accumulation of such a high concentration of intermediate by a slow hydration, as proposed by Willi,[1b] should lead to an induction period for formation of products. This was not observed.[2]

The apparent need for more data on this reaction has led us to investigate the hydrolysis of a solubilized Schiff base in aqueous solution at acidities up to 0.05 *N* HCl. The acid dissociation constant of the Schiff-base conjugate acid has been measured using flow methods, and the change in rate of hydrolysis at *p*H's near the pK_a determined. Studies in very dilute aqueous solutions seemed desirable because of the greater validity of *p*H measurements and their interpretation[4] in this medium. The model substrate, *p*-trimethylammonium-benzylidene-*p*′-hydroxyaniline chloride (I), was selected because it is soluble in aqueous solution at all *p*H's, because the concentration of one of the products, *p*-aminophenol (II), can readily be determined, and because I is sufficiently stable in basic solution so that stock solutions can be kept for short times without too much decomposition.

Experimental

Materials. *p*-Trimethylammoniumbenzylidene-*p*′-hydroxyaniline Chloride.—*p* - Dimethylaminobenzaldehyde (120 g.) and methyl iodide (500 g.) were refluxed 24 hr., the excess methyl iodide was evaporated, the residual salt dissolved in boiling water and the aqueous solution concentrated to 100 ml. A column of 400 ml. of Amberlite IRA-400 ion-exchange resin was treated with 300 ml. of concentrated hydrochloric acid and washed with water until a negative halide test was obtained. The solution of quaternary iodide was passed through this column and the column washed until a negative halide test was obtained. The combined eluates were taken to dryness. Ten grams of the residue and 5.5 g. of *p*-aminophenol were refluxed 3 hr. in 200 ml. of acetic acid under a nitrogen atmosphere. The Schiff base chloride precipitated on cooling and was recrystallized from acetic acid and finally from absolute ethanol.

Anal. Calcd. for $\text{C}_{16}\text{H}_{19}\text{N}_2\text{OCl}$: C, 66.1; H, 6.6; N, 9.6; Cl, 12.2. Found: C, 66.1; H, 6.8; N, 10.0; Cl, 12.5.

Buffers.—Eastman Practical Grade 2,6-lutidine (70%) was fractionated in the presence of aluminum chloride and the fraction boiling at 142.5° (760 mm.) was retained. Eastman Grade 2,4,6-trimethylpyridine and Eastman Spectro Grade pyridine were used without further purification. Weighed quantities of the amines were treated with known volumes of standard hydrochloric acid solution to give, after dilution, the desired *p*H and a constant concentration of conjugate acid = 0.05 *M*. Eastman Grade chloroacetic acid and trichloroacetic acid were used without further purification. Weighed samples of the acids were treated with known volumes of standard sodium hydroxide solution to give the desired *p*H and a concentration of unneutralized acid = 0.036 *M*. The ionic strength was held constant at 0.10 *M*. The acetate buffers were diluted by half in the flow machine. Phosphate buffers were prepared by mixing predetermined volumes of stock solutions of the three phosphate salts and

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[1] (a) A. V. Willi and R. E. Robertson, *Can. J. Chem.*, **31**, 361 (1953); (b) A. V. Willi, *Helv. Chim. Acta*, **39**, 1193 (1956).

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

[3] Reference 2, footnote 13.

[4] R. G. Bates, "Electrometric *p*H Determinations, Theory and Practice," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 88.

diluting them to an ionic strength of 0.05 *M*. In those runs in which the concentrations of phosphate salts were varied, a buffer of the desired *p*H and ionic strength was diluted progressively and the ionic strength readjusted by addition of potassium chloride.

Acidity Scale.—*p*H measurements were made with a Beckman general-purpose glass electrode (*vs.* S.C.E.) and a Beckman *p*H meter, Model G. The standard reference buffers were the National Bureau of Standards borax (*p*H 9.18, 25°) and phthalate (*p*H 4.01, 25°) buffers. At the ionic strengths used in this study, the *p*H of test solutions measured with these electrodes is a measure of $-\log m_{H^+}f_{H^+}$ between *p*H 3 and 11 within the precision of the *p*H measurement.[5] At *p*H <3, the liquid-junction potential error becomes more important but probably does not exceed ±0.03 *p*H unit.[6] At $\mu = 0.05$ *M*, the magnitude of the estimate of $-\log f_{H^+}$ is essentially independent of the convention used to estimate it and was taken to be 0.08.[7]

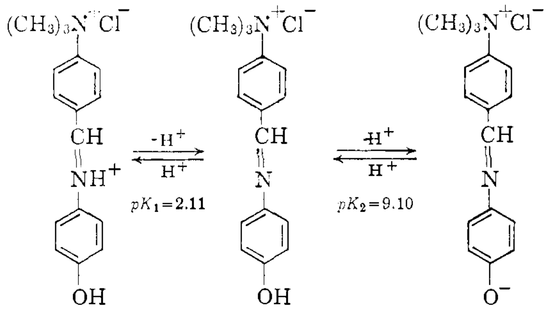
Kinetic Measurements.—*p*-Aminophenol (II) was determined polarographically in *p*H 7.36 phosphate buffer at the dropping mercury electrode. The mercury half-cell was joined to a calomel cell by an agar bridge containing saturated potassium nitrate that had been diluted by half. A potential of +0.150 v., measured against a calomel electrode, was applied across the cell. The current, measured as the potential drop across a 2500-ohm resistor, was fed into a high-impedance amplifier and thence to a Moseley Autograph XY Recorder. A complete polarogram indicated the optimum applied voltage. Calibration with deaerated solutions of analytically pure *p*-aminophenol hydrochloride gave a linear current–concentration response over the concentration range $0 - 1 \times 10^{-4}$ *M*. Neither the Schiff base nor the aldehyde gave an anodic wave. For the rate run, the applied potential was held constant and a continuous plot of current *vs.* time made. The time base for the recorder was controlled by a helipot run by a constant-speed motor.

The Schiff base was determined spectrophotometrically. The three species Ia, Ib and Ic have absorption maxima at 367, 335 and 380 mμ, respectively. The hydrolysis products have negligible absorptivities in this wave length region. Absorptivities of Ia, Ib and Ic were obtained by linear extrapolation to zero time of log absorbance *vs.* time plots. The slow runs were made by periodic absorbance measurements on solutions kept in tightly stoppered, full quartz cells. For the runs with half-times from 0.25 to 5 min., 0.50 ml. of a stock solution of I in very dilute sodium hydroxide (*p*H ≃ 9) was injected from a calibrated Cornwall hypodermic syringe into 4.00 ml. of buffer contained in a 1-cm. quartz cell. The absorbance change was plotted continuously on a Cary recording spectrophotometer, Model 14, having a thermostated cell compartment. The time lapse between mixing and the beginning of the record was 4–5 sec. (stopwatch). The very fast runs were followed using either a stopped-flow or a steady-state flow method. The flow apparatus was similar to one described previously,[8] but was modified by incorporation of a motor-driven ultraviolet spectrophotometer and ultraviolet optics.[9]

Acid Dissociation Constants.—Both pK_1 and pK_2 were determined from the change in the absorption curves with *p*H. Stock solutions of I in very dilute sodium hydroxide solution (*p*H ≃ 9) were mixed with the appropriate buffers and the absorption curves obtained. The time lapse between the preparation of the stock solution and running the absorption curve was noted and correction made for the small amount of hydrolysis occurring at the *p*H of the stock solution. To obtain pK_1, equal volumes of the stock solution and the acid buffer were mixed in the flow machine and the absorption curve of the flowing solution in the steady state was recorded on an XY recorder. Absorbance calibrations were made with standard potassium nitrate solutions or with potassium dichromate in 0.1 *N* hydrochloric acid. The shortest obtainable distance between the mixing chamber and the absorption cell of the flow machine corresponds to a reaction time of 12.2 msec. at the flow rate used. During this interval significant hydrolysis occurs at acidities greater than *p*H 4. The reaction times at each *p*H were therefore varied by insertion of spacers between the mixing chamber and the absorption cell and absorption curves were obtained under the corresponding steady-state conditions. The curves were then extrapolated to zero reaction time from plots of log absorbance *vs.* time, after each curve had been corrected for the decrease in absorbance from hydrolysis of the stock solution.

Results

Acid Dissociation Constants.—The acid-base equilibria involving I and the corresponding pK_a's are



Ia Ib Ic

The constants are equilibrium concentration quotients and refer to dilute aqueous solutions of ionic strength 0.05 *M* at 25°. They were determined from the change in the strong, symmetrical, long-wave length absorption band with *p*H. Protonation of Ib causes a bathochromic shift of 32 mμ, similar to the shift in the same band observed on protonating azobenzene.[10] Dissociation to the phenolate Ic gives a larger bathochromic shift of 45 mμ. The values of the pK_a's were obtained from plots of $\log (A_A - A_{AB})/(A_{AB} - A_B)$ *vs.* $-\log [H^+]$, where A_A, A_B, and A_{AB} are the absorptivities at a given wave length of the acid form, basic form and mixtures of the two. The plot for pK_1 is shown in Fig. 1. The solid line in the figure is the regression line. The standard error of the regression at the value of $-\log [H^+]$ corresponding to pK_1 is 0.0146. The 95% confidence interval (7 degrees of freedom) is $\pm 0.0146 \times 2.36 = \pm 0.027$ for the error in the direction of the dependent variable. It is estimated that a systematic error, ±0.03 log unit, might exist in the $-\log [H^+]$ values.[6] By vectorial addition, a total error of ±0.04 log unit is estimated for pK_1 with 95% confidence.

Stoichiometry.—Simultaneous determination of [I] and [II] in a run at *p*H 7.36 gave the results shown in Fig. 2. The sum of the concentrations of substrate and product are constant throughout the run and equal to the initial [I]. Therefore, under the conditions of this experiment, there is no measurable accumulation of an intermediate.

Kinetics.—The disappearance of I was strictly first-order throughout any run. In the acid region, the final absorbance was zero. In neutral and basic solutions, a residual absorbance usually remained at the conclusion of a run. *p*-Aminophenol is readily oxidized in basic solutions by traces of air to give colored products. No attempt was

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(5) Reference 4, p. 60.

(6) R. G. Bates, G. D. Pinching and E. R. Smith, *J. Research Natl. Bur. Standards*, **45**, 418 (1950).

(7) I. Feldman, *Anal. Chem.*, **28**, 1859 (1959).

(8) (a) W. R. Ruby, *Rev. Sci. Instruments*, **26**, 460 (1955); (b) L. K. J. Tong and M. Carolyn Glesmann, *J. Am. Chem. Soc.*, **79**, 583 (1957).

(9) L. K. J. Tong and W. R. Ruby, unpublished work.

(10) H. H. Jaffé, Si-Jung Yeh and R. W. Gardner, *J. Mol. Spectros.*, **2**, 120 (1958).

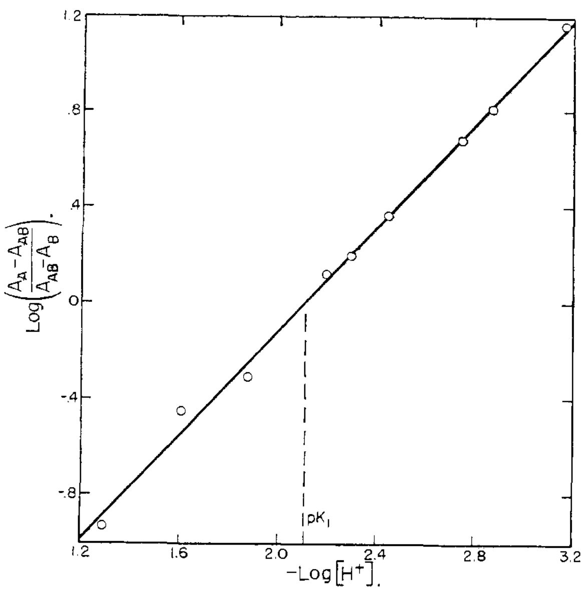

Fig. 1.—Spectrophotometric determination of the acid dissociation constant of *I*a at 25°, $\mu = 0.05$ *M*.

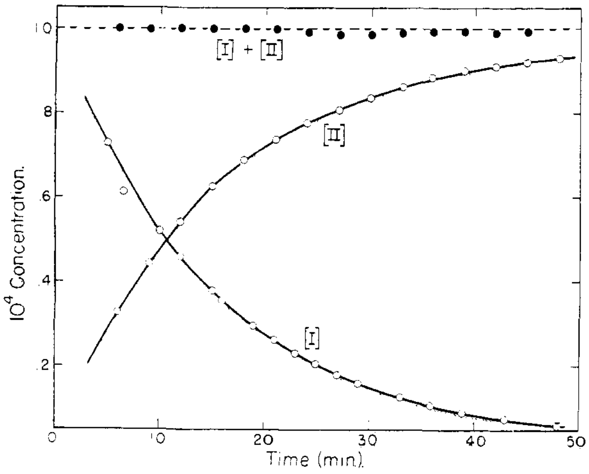

Fig. 2.—Rates of change of the concentrations of Schiff base (I) and of *p*-aminophenol (II) at *p*H 7.36; initial concentration = 1.00×10^{-4} *M*.

made, therefore, to measure the final absorbance. Instead, rate constants were computed by the Guggenheim method[11] in this *p*H region. Some runs were carried out with a varied excess of *p*-trimethylammonium-benzaldehyde chloride (III) so that the observed first-order rate constant for the disappearance of I (k') is

$$k' = k_f + k_r[\text{III}] \qquad (3)$$

where k_f and k_r are rate constants for the forward and reverse reactions, respectively. Plots of k' *vs.* [III] were linear and gave values of k_f that agreed with the values obtained at the same *p*H in the absence of added aldehyde. The rate data are given in Table I and the effect of acidity on the observed k_f is shown in Fig. 3.

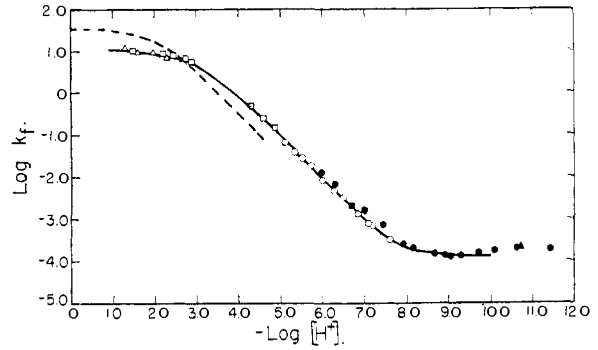

Fig. 3.—Effect of acidity on the rate of hydrolysis of I at 25° and ionic strength 0.05 *M*. Buffers: Δ, dil. HCl; □, chloroacetate, trichloroacetate or acetate; ○, pyridine bases; ●, phosphate; ▲, dimethylpiperidine; ■, phosphate, extrapolated to zero phosphate concentration ($\mu = 0.10$ *M*); ----, $-\log [SH^+]/([S] + [SH^+])$ *vs.* $-\log [H^+]$.

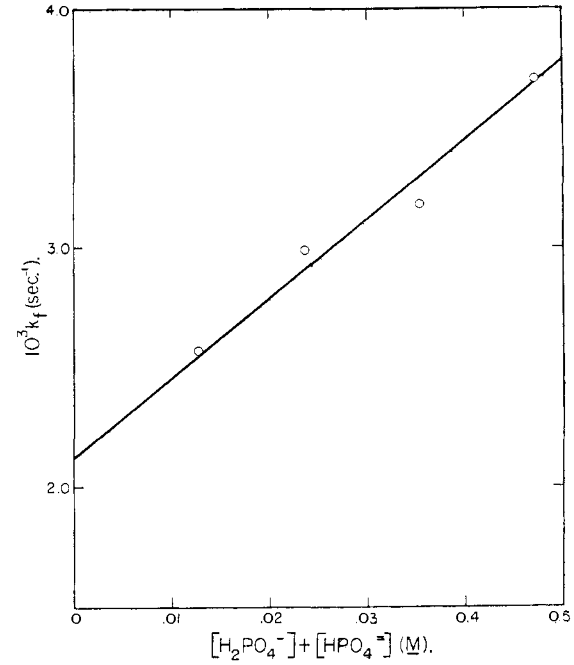

Fig. 4.—Effect of phosphate buffer concentration on the rate of hydrolysis of I at 25°, $\mu = 0.10$ *M*.

In the *p*H region 5.5–7.5, both phosphate buffers and buffers prepared from pyridine bases (pyridine 2,6-lutidine and 2,4,6-trimethylpyridine) were used. With the organic bases, the concentrations of acid species (BH^+) could be held constant, whereas with the phosphate buffers they could not. In this *p*H range, the rates were faster for a given *p*H in the phosphate buffers than in the pyridine buffers. Increasing the phosphate concentration at constant *p*H and ionic strength gave a linear increase in the rate of hydrolysis, demonstrating general acid catalysis by the species, $H_2PO_4^-$ and/or $HPO_4^=$ (Fig. 4). The value of the rate constant obtained by extrapolation to zero phosphate concentration agrees with the value obtained in the 2,6-lutidine buffers at the same *p*H. This result indicates that the general acids, BH^+, have no catalytic effect. At high *p*H, the rates are the same in phosphate and dimethylpiperidine buffers.

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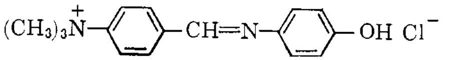
[11] E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

TABLE I

THE EFFECT OF ACIDITY ON THE RATE OF HYDROLYSIS OF



at 25° and Ionic Strength 0.05 *M*

Buffer	[HA], *M*	[H⁺], *m*	*k*, sec.⁻¹	$10^{-3}\,k/[\mathrm{H^+}]$
Hydrochloric acid		0.051	11.7	
Hydrochloric acid		.045	11.4	
Trichloroacetate	0.018	.041	9.60	
Hydrochloric acid		.025	9.52	
Hydrochloric acid		.013	8.90	
Hydrochloric acid		.005	6.96	
Chloroacetate	0.018	6.3×10^{-3}	8.63	
Chloroacetate	.018	3.6×10^{-3}	7.80	
Chloroacetate	.018	1.8×10^{-3}	6.68	
Chloroacetate	.018	1.3×10^{-3}	5.46	
Acetate	.029	4.78×10^{-5}	0.478	10.0
Acetate	.029	2.57×10^{-5}	.247	9.61
Acetate	.029	1.32×10^{-5}	.146	11.0
Pyridine	.050	7.58×10^{-6}	6.52×10^{-2}	8.62
Pyridine	.050	4.47×10^{-6}	3.87×10^{-2}	8.66
Pyridine	.050	2.82×10^{-6}	2.72×10^{-2}	9.64
Phosphate		2.69×10^{-6}	2.92×10^{-2}	10.86
Phosphate		2.51×10^{-6}	$2.55 \times 10^{-2\,a}$	10.16
Pyridine	.050	1.82×10^{-6}	1.86×10^{-2}	10.27
Phosphate		1.02×10^{-6}	$1.26 \times 10^{-2\,a}$	12.35
Lutidine	.050	9.55×10^{-7}	8.51×10^{-3}	8.92
Lutidine	.050	5.13×10^{-7}	4.68×10^{-3}	9.13
Phosphate		5.13×10^{-7}	$6.78 \times 10^{-3\,a}$	13.22
Phosphate		4.37×10^{-7}	6.70×10^{-3}	15.32
Lutidine	.050	3.23×10^{-7}	3.18×10^{-3}	9.84
Phosphate		2.14×10^{-7}	$2.1 \times 10^{-3\,b}$	9.8
Lutidine	.050	2.00×10^{-7}	1.85×10^{-3}	9.25
Lutidine	.050	1.42×10^{-7}	1.35×10^{-3}	9.50
Phosphate		1.02×10^{-7}	1.62×10^{-3}	15.87
Collidine	.050	7.95×10^{-8}	7.75×10^{-4}	9.74
Lutidine	.050	6.46×10^{-8}	6.83×10^{-4}	10.60
Phosphate		3.63×10^{-8}	7.05×10^{-4}	
Collidine	.050	2.46×10^{-8}	3.02×10^{-4}	
Phosphate		1.15×10^{-8}	2.56×10^{-4}	
Phosphate		6.92×10^{-9}	1.97×10^{-4}	
Phosphate		2.04×10^{-9}	1.45×10^{-4}	
Phosphate		1.18×10^{-9}	1.31×10^{-4}	
Phosphate		8.51×10^{-10}	1.38×10^{-4}	
Phosphate		4.78×10^{-10}	1.44×10^{-4}	
Phosphate		1.82×10^{-10}	1.50×10^{-4}	
Phosphate		7.95×10^{-11}	1.67×10^{-4}	
Phosphate		2.29×10^{-11}	1.95×10^{-4}	
Dimethylpiperidine	.050	1.78×10^{-11}	2.08×10^{-4}	
Phosphate		4.37×10^{-12}	1.81×10^{-4}	

[a] Runs carried out in excess aldehyde. [b] Extrapolated to zero phosphate concentration.

The rate constant for the uncatalyzed reaction (pH 9) is given by $k = 4.9 \times 10^6 \exp(-14400/RT)$.

Discussion

The fact that the acid-catalyzed rate increases linearly with [H⁺] at pH's greater than pK_1 and becomes independent of [H⁺] at pH's less than pK_1 suggests that the acid catalysis involves only the conversion of the Schiff base to its conjugate acid in a rapid pre-equilibrium, followed by slow attack by water.[12] This postulate has a reasonable theoretical basis, since the anil carbon assumes considerable carbonium-ion character in the conjugate acid ($-\mathrm{CH}{=}\overset{+}{\mathrm{N}}\mathrm{H}- \leftrightarrow -\overset{+}{\mathrm{C}}\mathrm{H}-\mathrm{NH}-$) and thus is rendered more susceptible to nucleophilic attack by solvent. Quantitatively, however, the hydrolysis rate does not exactly follow the conversion of substrate to its conjugate acid. Since pK_1 is known, the fraction of the total substrate present as the conjugate acid at a given pH is known, and is shown as the dashed line in Fig. 3. The positioning of this curve on the vertical axis is somewhat arbitrary but the placement in the horizontal direction is fixed by experiment (pK_1). The pK would have to be changed by 0.8 unit to obtain a fit, while the estimated error in the measurement of pK_1 is ±0.04 unit. Thus, although it appears that much of the acid catalysis is related to the conversion of Ib to Ia, additional effects of the acid must be considered. The mechanism proposed by Willi[1b] offers a possible explanation of these additional effects. We introduce the following notation

$$\mathrm{S} = \mathrm{ArCH{=}NAr'} \qquad [\mathrm{S}]_t = [\mathrm{S}] + [\mathrm{SH^+}]$$
$$\mathrm{SH^+} = \mathrm{ArCH{=}NH^+Ar'}$$

$$\mathrm{SHOH} = \mathrm{ArCHOHNHAr'} \qquad [\mathrm{SHOH}]_t =$$
$$\mathrm{SH_2OH^+} = \mathrm{ArCHOHNH_2{}^+Ar'} \qquad [\mathrm{SHOH}] + [\mathrm{SH_2OH^+}]$$

$$\mathrm{S} + \mathrm{H^+} \overset{K_1'}{\rightleftharpoons} \mathrm{SH^+}\ (\text{fast})\ K_1' = 1/K_{\mathrm{SH^+}} = 1/K_1 \quad (4)$$

$$\mathrm{S} + \mathrm{H_2O} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathrm{SHOH}\ (\text{slow}) \quad (5)$$

$$\mathrm{SH^+} + \mathrm{H_2O} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \mathrm{SHOH} + \mathrm{H^+}\ (\text{slow}) \quad (6)$$

$$\mathrm{SHOH} + \mathrm{H^+} \overset{K_4}{\rightleftharpoons} \mathrm{SH_2OH^+}\ (\text{fast})\ K_4 = 1/K_{\mathrm{SH_2OH^+}} \quad (7)$$

$$\mathrm{SHOH} \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} \mathrm{B} + \mathrm{C}\ (\text{slow}) \quad (8)$$

$$\mathrm{SH_2OH^+} \underset{k_{-6}}{\overset{k_6}{\rightleftharpoons}} \mathrm{B} + \mathrm{C} + \mathrm{H^+}\ (\text{slow}) \quad (9)$$

where B and C are the products. The following assumptions are made: (1) $[\mathrm{SHOH}]_t$ makes no contribution to the total absorbance at the analytical wave length so that the disappearance of $[\mathrm{S}]_t$ is the only quantity measured experimentally. (2) The steady-state approximation can be applied to $[\mathrm{SHOH}]_t$. Since it has been shown that there is no accumulation of intermediates, both assumptions seem justified. Therefore

$$-\mathrm{d}[\mathrm{S}]_t/\mathrm{d}t = k_5[\mathrm{SHOH}] + k_6[\mathrm{SH_2OH^+}] = k_5[\mathrm{SHOH}] + k_6K_4[\mathrm{SHOH}][\mathrm{H^+}] \quad (10)$$

From the steady-state approximation

$$\mathrm{d}[\mathrm{SHOH}]/\mathrm{d}t = 0$$

so that

$$[\mathrm{SHOH}] = \frac{k_2[\mathrm{S}] + k_3[\mathrm{SH^+}] + [\mathrm{B}][\mathrm{C}](k_{-5} + k_{-6}[\mathrm{H^+}])}{k_{-2} + k_5 + (k_{-3} + k_6K_4)[\mathrm{H^+}]} \quad (11)$$

Since the product $k_r[\mathrm{B}][\mathrm{C}]$ makes no contribution to the observed rates in the absence of added B or C, terms in [B] [C] may be neglected in equating k_f to a derived expression. It follows that

$$\text{forward rate} = \frac{k_2k_5[\mathrm{S}] + k_3k_5[\mathrm{SH^+}] + k_2k_6K_4[\mathrm{S}][\mathrm{H^+}] + k_3k_6K_4[\mathrm{SH^+}][\mathrm{H^+}]}{k_{-2} + k_5 + (k_{-3} + k_6K_4)[\mathrm{H^+}]} = k_f([\mathrm{S}] + [\mathrm{SH^+}]) \quad (12)$$

so that

$$k_f = \frac{[\mathrm{H^+}]}{[\mathrm{H^+}] + K_{\mathrm{SH^+}}} \left(\frac{k_2k_5K_{\mathrm{SH^+}}/[\mathrm{H^+}] + k_3k_5 + k_2k_6K_4K_{\mathrm{SH^+}} + k_3k_6K_4[\mathrm{H^+}]}{k_{-2} + k_5 + (k_{-3} + k_6K_4)[\mathrm{H^+}]}\right) \quad (13)$$

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[12] R. P. Bell, "Acid-Base Catalysis," Oxford University Press, New York, N. Y., 1941, p. 126.

or

$$k_f = (A + B[\mathrm{H}^+] + C[\mathrm{H}^+]^2)/(D + E[\mathrm{H}^+] + F[\mathrm{H}^+]^2) \quad (14)$$

At acidities where previous rate measurements have been made,[1,2] $K_{\mathrm{SH}^+} >> [\mathrm{H}^+]$ and eq. 13 reduces to

$$k_f = \frac{k_2k_5 + (k_3k_5 + k_2k_6K_4)[\mathrm{H}^+] + k_3k_6K_4/K_{\mathrm{SH}^+}[\mathrm{H}^+]^2}{k_{-2} + k_5 + (k_{-3} + k_6K_4)[\mathrm{H}^+]} \quad (15)$$

which has the same form as the rate law of Willi[1b] (eq. 2).

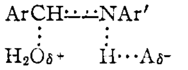
It is obviously not possible to evaluate any of the individual rate constants or even to assign absolute values to the parameters in eq. 14. However, some values can be assigned to ratios of the parameters. At high acidity, only the terms in $[\mathrm{H}^+]^2$ are important so that $k_f = C/F \simeq 11$, and the observed rate is independent of $[\mathrm{H}^+]$. In basic solution, the terms involving $[\mathrm{H}^+]$ are negligible and $k_f = A/D = 1.3 \times 10^{-4}$ and the rate is again independent of $[\mathrm{H}^+]$. At intermediate acidities, where the rate varies linearly with $[\mathrm{H}^+]$, the important terms are either $B[\mathrm{H}^+]/D$ or $C[\mathrm{H}^+]^2/E[\mathrm{H}^+]$ and the ratio B/D or C/E has the value 9.5×10^3. Thus three degrees of freedom remain for selecting values for the six parameters of eq. 14. For illustration, one set of parameters that was chosen to test the fit of (14) to the data is given by

$$k_f = \frac{1.30 \times 10^{-5} + 0.95 \times 10^3\,[\mathrm{H}^+] + 1.10 \times 10^6\,[\mathrm{H}^+]^2}{1.00 \times 10^{-1} + 3.60 \times 10^2\,[\mathrm{H}^+] + 1.00 \times 10^5\,[\mathrm{H}^+]^2} \quad (16)$$

The variation of k_f with $[\mathrm{H}^+]$ calculated from eq. 16 is shown as the solid line in Fig. 3. In the derivation and in the fit, the slight increase in the uncatalyzed rate of Ib due to ionization to Ic is neglected as this is incidental to the mechanism. Other values of the parameters could have been selected for an equally satisfactory fit, as long as the restrictions just given are fulfilled. Several other empirical equations were found to fit the data, but these either failed to fit when the added restriction of the measured K_{SH^+} was inserted or were not derivable in equivalent form from reasonable mechanisms.

The data establish that the acid catalysis is more complex than just the simple pre-equilibrium model involving substrate and its conjugate acid. If the only effect of acid were to convert S to SH^+, the rate should vary as $[\mathrm{SH}^+]/([\mathrm{S}] + [\mathrm{SH}^+])$, given by the dashed line in Fig. 3. The observation of first-order dependence of the rate of hydrolysis of I on $[\mathrm{H}^+]$ over such a wide range of $[\mathrm{H}^+]$ appears to be fortuitous for the model compound studied here because of the relative magnitudes of the parameters of eq. 14. The hydrolysis of other Schiff bases would require different relative values of the parameters such that, taken in combination, an apparent linear dependence of k_f on $[\mathrm{H}^+]$ might be observed over a much narrower range of $[\mathrm{H}^+]$. It is possible to obtain an inflection in the log k_f − log $[\mathrm{H}^+]$ profile if appropriate values of the parameters are chosen, and this appears to be the case for the hydrolysis of benzylidene aniline in 50% aqueous methanol.[1b,13]

The mechanism suggested involves pre-equilibria between substrate and its conjugate acid and between intermediate and its conjugate acid. No provision is made for the accommodation of general acids in the activated complex. The substrate is probably made more susceptible to solvent attack both by conversion to conjugate acid and by hydrogen-bonding of an acid, HA, to the anil nitrogen. In the latter case, the transition state becomes



$$\mathrm{ArCH}\overset{\cdot\cdot}{-}\overset{\cdot\cdot}{-}\mathrm{NAr'} \;\; (\mathrm{H_2O}_{\delta+} \cdots \mathrm{C};\; \mathrm{N} \cdots \mathrm{H}\cdots\mathrm{A}_{\delta-})$$

In the uncatalyzed "water" reaction, solvent may play the dual role of acid and nucleophile. The nature of the acid catalysis becomes a matter of timing in the proton-transfer step. If proton transfer is completed before nucleophilic attack, the rate depends only on $[\mathrm{H}^+]$ and the source of the proton is unimportant. On the other hand, if proton transfer assists or completes solvent attack so the two processes proceed in a concerted manner, general acid catalysis will be observed, as for example by acid phosphate or acetic acid.[1a]

In acid solution, acid-catalyzed decomposition of the intermediate must become partially rate-determining in order for the corresponding terms to appear in the rate law. We conclude that the formation of the amino alcohol and its decomposition both contribute as rate-determining steps. If, at low *p*H, the rate depends in part on the equilibrium concentration of amino alcohol, the question arises as to whether the intermediate could be present at detectable levels at these acidities. From the data it can be stated that if intermediate is formed in a pre-equilibrium to give a significant concentration, the equilibrium is completely established within 12 msec., since good first-order kinetics for disappearance of I were observed in these solutions for times greater than 12 msec. It is assumed that the intermediate has no absorbance at the analytical wave length. Furthermore, if a significant concentration of intermediate is present at low *p*H, the equilibrium concentration must be the same within the limits of experimental

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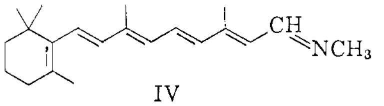
(13) After preparation of this manuscript, a kinetic study of the hydrolysis of *p*-chlorobenzylideneaniline appeared.[14] A similar linear dependency of k_f on $[\mathrm{H}^+]$ was observed for this Schiff base over the *p*H range 8–5. On the assumption that the (unmeasured) shape of the *p*H–rate profile is determined by pK_{SH^+} at acidities near pK_{SH^+}, and from the fact that an inflection in the profile occurs in 80% ethanol at *p*H ≅ 4, it was reasoned that an inflection in the profile in aqueous solution must occur at a *p*H between the pK_{SH^+} and the *p*H at which the last measurements were made. While the present results show that an inflection in the rate profile is not necessary and that the change in the rate with acidity is not determined by K_{SH^+} at *p*H's near pK_{SH^+}, the present study and that of Cordes and Jencks lead to the same conclusion regarding the mechanism, *i.e.*, in moderately acid solution (*p*H 1–4), the cleavage of the amino-alcohol intermediate becomes partially or wholly rate determining. We do not believe the kinetics alone justify the conclusion that at acidities near neutrality the only rate-determining step is nucleophilic attack of water on the Schiff base conjugate acid and that at acidities near the pK_{SH^+} the rate-determining step changes to one involving *only* cleavage of the intermediate. Analogies with other mechanisms of formation and cleavage of C=N bonds,[15] where the change in rate-determining step is more demonstrable, lend more credence to similar assumptions for Schiff base hydrolysis.

(14) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 832 (1962).

(15) (a) W. P. Jencks, *ibid.*, **81**, 475 (1959); (b) B. M. Anderson and W. P. Jencks, *ibid.*, **82**, 1773 (1960).

error at every pH between 1 and 3 since, in the measurement of pK_1, if some species other than Ia and Ib were present in varying concentration, the straight-line plot of unit slope in Fig. 1 would not have been obtained.



IV

Semi-quantitative hydrolysis and spectral data for solutions of retinylidenemethylamine (IV) in the pH region 1.0–8.6 indicate that the hydrolysis of this Schiff base has a maximum rate at around pH 5.7.[16] The stability of IV in acid solution is considerably greater than that of any diaryl Schiff base reported. At pH 2.0, it appears to be more stable than I by at least five orders of magnitude. Our rate law and the suggested mechanism do not accommodate a maximum in the log k_r–pH profile. The interpretation of the data on the stability of IV is complicated by the fact that the solutions contained a dispersing agent, Tween 80, which could have stabilized the Schiff base by mixed micelle formation. It has been shown here that some surfactants can stabilize ionic Schiff bases markedly in mildly acid solution at concentrations greater than the critical micelle concentration. It has also been demonstrated that surfactants decrease the rates of hydrolysis of certain indoaniline dyes by several orders of magnitude,[17] presumably by incorporation into micelles. It may be that the uncharged IV and charged conjugate acid have different distribution coefficients between micelle and bulk solvent or different stabilities in their respective micelles. Nevertheless, the observations suggest that an investigation of a solubilized dialkyl anil, having a larger pK than the diaryl Schiff bases, might yield additional information regarding the mechanism of the acid-catalyzed hydrolysis of the —C=N— bond.

Acknowledgment.—We wish to acknowledge aid from W. R. Ruby in the polarographic work and helpful discussions of the kinetics with L. K. J. Tong.

(16) R. A. Morton and G. A. J. Pitt, *Biochem. J.*, **59**, 128 (1955).

(17) R. L. Reeves and L. K. J. Tong, *J. Am. Chem. Soc.*, **84**, 2050 (1962).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA, LOS ANGELES 7, CALIF.]

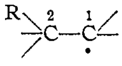
Reactions of the 2-Bornyl Radical. II. A Free Radical Wagner–Meerwein Rearrangement[1]

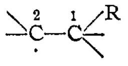
BY JEROME A. BERSON, CARL J. OLSEN[2] AND JASJIT SINGH WALIA

RECEIVED MARCH 2, 1962

The thermal decomposition of 2-azobornane in the solvents diphenyl ether and n-hexadecane at temperatures above 250° gives a mixture of hydrocarbons, among which is 2,3,3-trimethylnorbornane (isocamphane), resulting from formal Wagner–Meerwein rearrangement. The latter hydrocarbon arises by a cleavage–recyclization mechanism, an interpretation supported by the formation of isocamphane as well as bornane, 1-p-menthene, tricyclene and bornene in the decomposition of either 2-azocamphane or 1-azo-bis-2-(2,2,3-trimethyl-3-cyclopentenyl)-ethane. Further support for classical rather than mesomeric product-forming intermediates is provided from the normal rates of decomposition of the azo compounds, from the dependence of the product distribution on the source of radicals, and from the stereochemistry of the hydrogen-abstraction by the 2,3,3-trimethyl-2-norbornyl radical, which gives both isomers of isocamphane.

The system I, embodying the formal prerequisites for a vicinal (*i.e.*, 1,2) intramolecular free radical





I R = alkyl II

alkyl group rearrangement to II, has been generated in many reactions,[3] but the rearrangement has consistently failed to occur. Until such a migration has been observed, however, it is impossible to know the rigor of the interdiction against it. A major difficulty in previous studies has been that the methods by which system I has been generated unavoidably have permitted the radical to suffer some fate other than rearrangement: Diversion to a stable product by hydrogen abstraction, dimerization, and disproportionation are usually fast processes, and the alkyl radical rearrangement has not been able to compete with them under the conditions examined. In many cases, aryl groups have been attached to C.2, and these have migrated in preference to the alkyl group. Further, most of the reactions have been carried out at relatively low temperatures, so that processes of high activation energy could not have occurred. In these respects, the alkyl group rearrangement may be said not to have received a fair chance. In the present paper,[1c] we report the first clearly intramolecular example of a free radical alkyl group rearrangement of the type I → II.

Results

The 2-bornyl radical affords a suitable system for study because rearrangements of the related cation are well known and provide a sinigficant comparison

(1) Taken from portions of the dissertations presented by (a) Carl John Olsen and (b) Jasjit Singh Walia in partial fulfillment of the requirements for the degree of Doctor of Philosophy. (c) For a preliminary report, see J. A. Berson, C. J. Olsen and J. S. Walia, *J. Am. Chem. Soc.*, **82**, 5000 (1960). (d) This research was supported in part by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command under Contract No. AF18(600)-1544. Reproduction in whole or in part is permitted for any purpose of the United States Government. Also supported in part by the Office of Ordnance Research under Contract No. DA-04-495-ORD-532. We are indebted to these agencies, to the Alfred P. Sloan Foundation, and to the Richfield Oil Corporation for support.

(2) Richfield Oil Fellow, 1956–1957.

(3) For a summary of references, see ref. 1c.