# On the Mechanism, Substituent Effects, and Intramolecular Catalysis in Schiff Base Hydrolysis

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The effects of *para* substituents on the pH-independent rates of hydrolysis of benzylideneanilines in alkaline aqueous buffers have been determined in an effort to remove complications found in earlier work from the acid-catalyzed hydrolysis and to shed light on the nature of the rate-determining step for the uncatalyzed reaction. Substituents in both rings have a relatively small effect, with hydrolysis facilitated by electron donation. Linear plots of log $k_{OBS}$ against $\sigma_p$ constants are obtained. The small negative $\rho$ values are inconsistent with rate-determining addition of water to the unprotonated Schiff base but are consistent with rate-determining attack of hydroxide ion on the protonated Schiff base. Ionized *o*-hydroxyl groups in the benzylidene ring have a strong and specific accelerating effect on the hydrolysis rate which is interpreted in terms of an intramolecular general base catalysis. Similar solvent deuterium isotope effects for the catalyzed and uncatalyzed reactions are consistent with a mechanism involving intramolecular acid catalysis of $OH^-$ attack.

Existing data on the effects of substituents on the hydrolysis rates of *p*- and *p'*-substituted N-benzylideneanilines[1] are sufficient to show that complex relationships may exist.[3,4] Willi and Robertson found that the hydrolysis rates followed a simple law over a limited

$$k_{OBS} = k_{H^+}[H^+] + k_{HA}[HA] \quad (1)$$

range of acidity and buffer concentrations in slightly acid solutions and determined the effects of substituents on $k_{H^+}$ and $k_{HA}$.[4] Bloch-Chaude reported the effects of substituents on $k_{OBS}$ measured at constant pH near neutrality, with no attempt to separate $k_{OBS}$ into components. In both of these studies, substituents that differ greatly in their electron-donating or -withdrawing capacities had a surprisingly small effect on the rate constants considered. The rate changes showed very poor correlation with the $\sigma$ values of the substituents; in general, any substituent appeared to decrease the rate of hydrolysis, relative to that for the unsubstituted parent compound.

More recent studies of the kinetics of hydrolysis of N-benzylideneaniline and its derivatives[5-7] and the *p*-substituted N-benzylidene-1,1-dimethylethylamines[8] have shown that the rate law for hydrolysis is considerably more complex than that given by eq. 1. The most general expression contains terms in $[H^+]$ and $[H^+]^2$ and composite constants involving a number of simple rate constants as well as the acid dissociation constant of the Schiff base conjugate acid. A change in the rate-determining step from addition of water to the protonated imine in weakly acidic solution to cleavage of the intermediate carbinolamine at higher acidities is manifested by a break in the pH–log $k_{OBS}$ profile for the acid-catalyzed hydrolysis.[5-7] This break occurs at different points on the profile, depending on the structures of the substrates. Willi pointed out that the observed rate constant for hydrolysis at neutral or slightly acid pH would be a composite term, where opposing substituent effects on the individual constants making up the composite term could give the observed effects of substituents on $k_{OBS}$.

Consideration of the general rate law suggested that if the rates of hydrolysis of a series of substituted N-benzylideneanilines were measured in the pH region where all the terms in $[H^+]$ and $[H^+]^2$ become negligible, a simple relationship between $k_{OBS}$ and some appropriate substituent constant might be found. We have measured substituent effects on $k_{OBS}$ for the pH-independent hydrolysis of substrates having substituents in the aniline ring because it seemed that, for this series, individual rate constants comprising a composite constant would all be correlated by a single substituent constant rather than by several substituent constants, as has been found with substituents in the aldehyde.[9,10] This latter effect alone is sufficient to give nonlinear free energy correlations. In addition, fairly extensive work has been done on the effect of substituents in aromatic aldehydes for a number of carbonyl condensations involving nitrogen nucleophiles[11] so that these structure–reactivity relationships are fairly well explained. Beside the possibility of simplifying the interpretation of results by working in the pH-independent region, we also hoped to explain the origin of some interesting *ortho* effects of ionizable hydroxyl groups.

Two kinetically indistinguishable mechanisms are possible for the first step of the hydrolysis in the pH-independent region. Either attack of water on the free imine or attack of hydroxide on the protonated imine will be consistent with the kinetics. Application of the steady-state approximation to the reactions in eq. 2 and 3 gives

$$RN{=}CHAr + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} RNHCHOHAr \quad (2)$$

$$R\overset{+}{N}H{=}CHAr + OH^- \underset{k'_{-1}}{\overset{k'_1}{\rightleftharpoons}} RNHCHOHAr \quad (2')$$

$$RNHCHOHAr \xrightarrow{k_2} RNH_2 + ArCHO \quad (3)$$

$$k_{OBS} = \frac{k_1k_2}{k_{-1} + k_2} \quad (4)$$

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(1) We retain the convention used in an earlier paper in this series,[2] where *p*-substituents refer to the benzylidene ring and *p'*- to the aniline ring.

(2) R. L. Reeves and W. F. Smith, Jr., *J. Am. Chem. Soc.*, **85**, 724 (1963).

(3) O. Bloch-Chaude, *Compt. rend.*, **239**, 804 (1954).

(4) A. V. Willi and R. E. Robertson, *Can. J. Chem.*, **31**, 361 (1953).

(5) A. V. Willi, *Helv. Chim. Acta*, **39**, 1193 (1956).

(6) R. L. Reeves, *J. Am. Chem. Soc.*, **84**, 3332 (1962).

(7) E. H. Cordes and W. P. Jencks, *ibid.*, **84**, 832 (1962).

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

(9) W. P. Jencks in "Progress in Physical Organic Chemistry," S. G. Cohen, A. Streitwieser, Jr., and R. W. Taft, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, pp. 110–117.

(10) T. I. Crowell, C. E. Bell, and D. H. O'Brien, *J. Am. Chem. Soc.*, **86**, 4973 (1964).

(11) See ref. 9, pp. 110–122.

or

$$k_{OBS} = \frac{k_1}{(k_{-1}/k_2) + 1} \qquad (4a)$$

Similar treatment of eq. 2′ and 3 gives

$$k_{OBS} = \frac{k'_1 k_2}{K_{SH^+}(k'_{-1} + k_2)} \qquad (5)$$

where $K_{SH^+} = [RN{=}CHAr][H^+]/[R\overset{+}{N}H{=}CHAr]$.

The use of free energy correlations of rates for a series of systematically varied structures as a criterion of mechanism will rest on the following premises. (1) If $k_{OBS}$ is not a composite but can be identified with a single mechanistic rate constant, a linear correlation will be obtained. (2) If $k_{OBS}$ is a composite involving only products of mechanistic rate constants and/or equilibrium constants, a linear correlation can result, where $\rho_{k_{OBS}} = \Sigma\rho_i$, if the same $\sigma$ constants are appropriate for each $k_i$. (3) If $k_{OBS}$ is a composite from which each constant cannot be individually factored, a complex correlation can result. Equation 4 can be considered in the light of these premises. If $k_2 \gg k_{-1}$, $k_{OBS} = k_1$, and the rate-determining step is attack of water on the Schiff base, the intermediate passes rapidly to products. In this case, $k_{OBS}$ can be identified with specific rate constant for a single step, and a linear relationship between log $k_{OBS}$ and an appropriate $\sigma$ value would be expected. The Hammett plot should have a positive $\rho$ value. If $k_{-1} \gg k_2$, $k_{OBS} = k_1k_2/k_{-1}$, the product of an equilibrium constant and a specific rate constant. The rate-determining step is the cleavage of the intermediate to products. Substituents would undoubtedly have a different effect on $k_1/k_{-1}$ than on $k_2$; a plot of $k_{OBS}$ *vs.* $\sigma$ would be the resultant. It should be linear with a slope that would depend on the signs and magnitudes of the $\rho$ values for the equilibrium and for the rate. If there are opposing substituent effects on $k_1/k_{-1}$ and on $k_2$ for a series of Schiff bases, the over-all effect on $k_{OBS}$ could be small, but the effect should be linear and continuous. A third case is where $k_{-1} \simeq k_2$. If $(k_{-1} \simeq k_2) > k_1$, attack by water is rate determining and $k_{OBS}$ is a composite that is not completely factorable (eq. 4). The ratio $k_{-1}/k_2$ is not a constant, but can vary among compounds in a series, so that more complex substituent effects might be observed. The case where $(k_{-1} \simeq k_2) < k_1$ is not consistent with the observation that the carbinolamine does not accumulate. Similar considerations will apply to eq. 5 where the limiting cases are given by $k_{OBS} = k'_1/K_{SH^+}$ and by $k_{OBS} = k'_1k_2/K_{SH^+}k'_{-1}$, respectively.

## Results

The rates of hydrolysis of the water-soluble benzylideneanilines **1–8**, **15**, and **16** were measured spectrophotometrically in aqueous buffers in the pH range 7–12 to determine the pH-independent region for each compound. The observed first-order rate constants for the "water" reactions are summarized in Table I. For those Schiff bases containing ionizable hydroxyl groups, independent spectrophotometric determination of the p$K_a$'s established the pH region in which the hydroxyl group was completely ionized. The p$K_a$ values for the corresponding anilium cations are much smaller than those for the phenolic OH's.[2] The p$K_a$'s of the OH groups are given in Table II and are indicated as dashed vertical lines in the partial pH–log $k_{OBS}$ profiles in Figure 2. The profiles for the *p*′-OH- and *p*-OH-substituted compounds (**2** and **6**) show that the pH region in which acid catalysis is important comes too close to the p$K_a$ for the OH groups to permit a direct measurement of the pH-independent rate for the un-ionized species. A value of about $1 \times 10^{-4}$ sec.$^{-1}$ can be estimated for un-ionized **2** by subtracting the acid-catalyzed component from $k_{OBS}$ at a pH equal to p$K_a$ = −2, using the previously published data.[6] The data for the *p*′-unsubstituted (**5**) and the *p*′-chloro (**15**) derivatives show that at pH 11.1 and 10.6, respectively, the base-catalyzed hydrolysis[12] is beginning to become important. This suggests that electron withdrawal shifts the log $k_{OBS}$–pH profiles laterally along the pH scale toward lower pH values.

TABLE I

RATE CONSTANTS FOR THE HYDROLYSIS OF *p*′- AND *p*-SUBSTITUTED N-BENZYLIDENEANILINES AT 25° AND IONIC STRENGTH 0.05 *M*

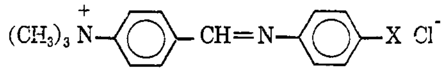
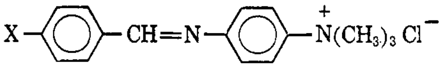
| Structure | X | pH | $10^5k_{OBS}$, sec.$^{-1}$ |
|---|---|---|---|
| A.  | | | |
| 1 | N(CH$_3$)$_2$ | 9.50 | 10.65 |
| | | 10.50 | 10.45 |
| 2a | O$^-$ | 10.72 | 19.5 |
| | | 10.83 | 20.8 |
| | | 11.44 | 18.1 |
| 3 | OCH$_3$ | 10.21 | 5.64 |
| | | 10.70 | 6.35 |
| | | 11.06 | 6.00 |
| 4 | CH$_3$ | 10.13 | 7.13 |
| | | 10.63 | 7.50 |
| | | 11.13 | 7.13 |
| 5 | H | 10.15 | 5.75 |
| | | 10.67 | 5.45 |
| | | 11.10 | 7.43 |
| 15 | Cl | 9.51 | 3.29 |
| | | 10.11 | 3.29 |
| | | 10.61 | 4.35 |
| | | 11.11 | 8.94 |
| B.  | | | |
| 16 | N(CH$_3$)$_2$ | 8.91 | 25.9 |
| | | 10.13 | 25.7 |
| | | 11.10 | 26.6 |
| 6 | O$^-$ | 9.26 | 29.7 |
| | | 10.36 | 29.8 |
| | | 10.62 | 28.8 |
| 7 | OCH$_3$ | 11.22 | 10.2 |
| 8 | H | 9.58 | 5.95 |
| | | 10.77 | 6.37 |

TABLE II

ACID DISSOCIATION CONSTANTS OF THE PHENOLIC GROUPS OF BENZYLIDENEANILINES AT 25° AND IONIC STRENGTH 0.05 *M*

| Structure | p$K_a$ |
|---|---|
| 2 | 9.10 |
| 6 | 8.19 |
| 9 | 9.49 |
| 12 | 8.89 |
| 13 | 11 |

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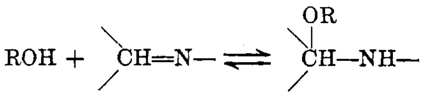
[12] B. Kastening, L. Holleck, and G. A. Melkonian, *Z. Elektrochem.*, **60**, 130 (1956).

Attempts to prepare the $p'$-nitro derivative as a pure product failed. Refluxing equimolar amounts of the aldehyde and $p$-nitroaniline in glacial acetic acid for 3 days gave a slow color change from yellow to red. Cooling gave a mixture of red needles and a light yellow, benzene-insoluble material that was assumed to be unreacted aldehyde. Mechanical separation of the red product and solution in hot acetic acid gave, on cooling, another mixture of the red needles and light-colored material. The infrared spectrum of the latter product showed the aldehyde carbonyl bond at 5.8 $\mu$. The spectrum of the red needles showed the C=N bond at 6.1 $\mu$. This suggests that an equilibrium mixture of Schiff base and reactants is formed in acetic acid and that the separated Schiff base reverts to the same equilibrium mixture when redissolved in this solvent. The red product gave a strong absorption band at 465 m$\mu$ in "dried" acetone that rapidly disappeared over a period of 10 min. Absorption at this wave length is characteristic of the protonated Schiff base. The red product dissolved readily in methanol to give a deep yellow solution that faded completely within a minute. Injection of a small volume of an acetone solution into aqueous pH 9.5 buffer gave immediate loss of the long wave length band. A shoulder was present at 320 m$\mu$, that did not change over a 16-hr. period. These results indicate that if we are dealing with the Schiff base, it is more unstable by several orders of magnitude than all the others we have studied. We hesitate to draw any mechanistic conclusions from these observations until a pure product is prepared and characterized.[13]

All the hydrolyses proceeded by first-order kinetics through 80–90% of the reaction. The $p'$-chloro derivative showed somewhat anomalous behavior when a 0.01 *M* solution in methanol or ethanol was diluted to $10^{-4}$ *M* with aqueous buffer. The Schiff base absorption band at 320 m$\mu$ first increased, reached a maximum, and then decreased at a rate equal to the hydrolysis rate. No change in the shape of the absorption curve could be seen. This behavior occurred regardless of whether one started with the solid Schiff base or whether the aldehyde and $p$-chloroaniline were allowed to equilibrate in the alcohol. The rate of the initial rise was considerably more rapid than the subsequent hydrolysis. The initial reaction was not observed when the solid Schiff base was dissolved directly into the aqueous solution. These observations suggest that alcohol can add reversibly to N-benzylideneanilines possessing sufficiently strong electron-withdrawing substituents and may explain some of the behavior of the $p'$-nitro derivative. The initial increase in Schiff base concentration must be from a reversible reaction of the Schiff base itself and not from a reversible reaction of the aldehyde, such as acetal hydrolysis. The equilibrium concentration of Schiff base is immeasurably small at the reactant concentrations used here so that a reaction between aldehyde and aniline that leads to an observable increase in Schiff base concentration is impossible. The data suggest that in anhydrous alcohol some of the carbinolamine ether may form. The



$$\mathrm{ROH} + \;\rangle\mathrm{CH{=}N{-}} \rightleftharpoons \;\rangle\overset{\mathrm{OR}}{\mathrm{C}}\mathrm{H{-}NH{-}}$$

rate of the initial decay of the imine–alcohol adduct increased with pH in the pH range 9.5–11, showing that the reaction is base catalyzed.

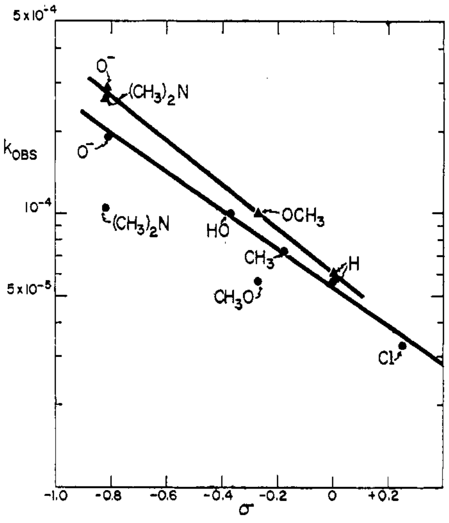


Figure 1.—Plots of log $k_{\mathrm{OBS}}$ for the uncatalyzed hydrolysis of Schiff bases against $\sigma_p$ constants: ●, $p'$-substituents, $\rho = -0.71$; ▲, $p$-substituents, $\rho = -0.81$.

Figure 1 shows plots of log $k_{\mathrm{OBS}}$ for the hydrolysis of the $p'$- and for the $p$-substituted substrates as a function of the Hammett $\sigma_p$ constants. The values of the $\sigma_p$ constants are all based on the acid dissociation constants of substituted benzoic acids at 25°, extrapolated to infinite dilution, following the recommendation of McDaniel and Brown.[15] The $\sigma_p$ constant for $O^-$ is that calculated by Hine for the same equilibrium.[16] In general, excellent correlation is obtained, considering the small over-all variation in rate in traversing the series. The $p'$-dimethylamino (**1**) and $p'$-methoxy (**3**) derivatives show deviations from the correlation line that are considerably in excess of experimental error (see Table I for the precision in measuring rate constants). The cause for the deviation of **1** can be rationalized (see Discussion); no assignable cause for the deviation of **3** could be found. The $\rho$ values for hydrolysis of the $p'$- and $p$-substituted substrates are $-0.71$ and $-0.81$, respectively.

During this study of substituent effects on the "water" reaction, we have found a marked acceleration of the hydrolysis rate that is associated with ionization of a salicylidene OH. The log $k_{\mathrm{OBS}}$–pH profiles are shown in Figure 2 for a number of benzylideneanilines with ionizable OH groups in the *ortho* and *para* position of both rings. Ionization of the $p$-OH's in either ring increases the rate slightly and is of the magnitude of the other small effects of *para* electron-donating substituents. Ionization of the $o$-OH in the aniline ring of **9** causes a small decrease in rate. The change in rate follows approximately the ratio $[\mathrm{RO}^-]/([\mathrm{RO}^-] + [\mathrm{ROH}])$, as determined by the p$K_a$ for that group. The

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[13] A kinetic study of the hydrolysis of $p$-unsubstituted N-benzylidene-$p'$-substituted anilines in alkaline buffers parallels the results which we have obtained, but with no unusual reactivity associated with the $p'$-nitro derivative.[14] We are indebted to Dr. Cordes for making these data available to us prior to publication.

[14] E. H. Cordes, unpublished results.

[15] D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).

[16] J. Hine, *J. Am. Chem. Soc.*, **82**, 4877 (1960).

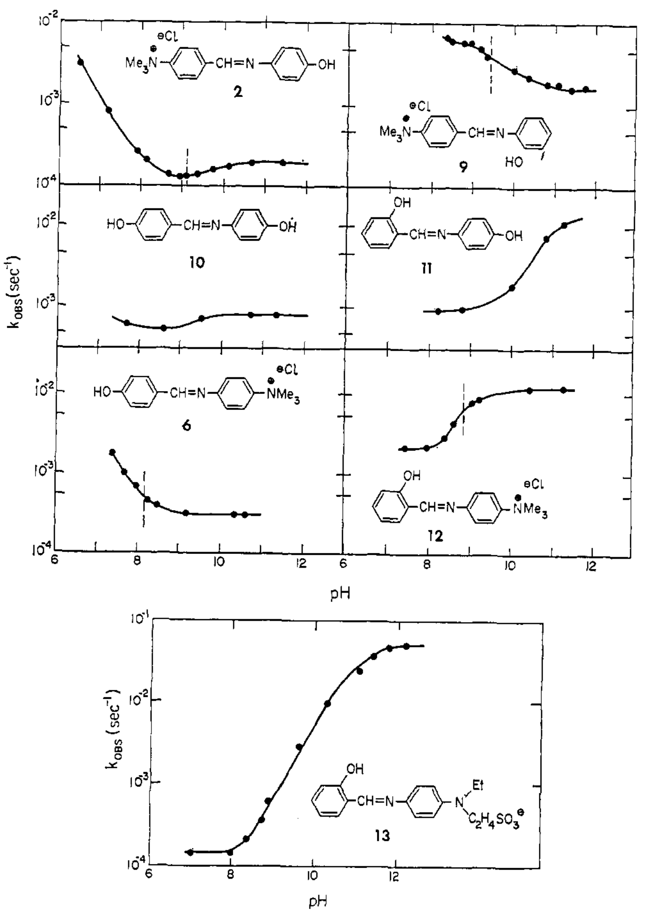

Figure 2.—Plots of log $k_{OBS}$ for hydrolysis of Schiff bases against pH at 25° and $\mu$ = 0.05 *M*. Vertical dashed lines are pH values equal to the p*K*'s for ionization of the phenolic OH's.

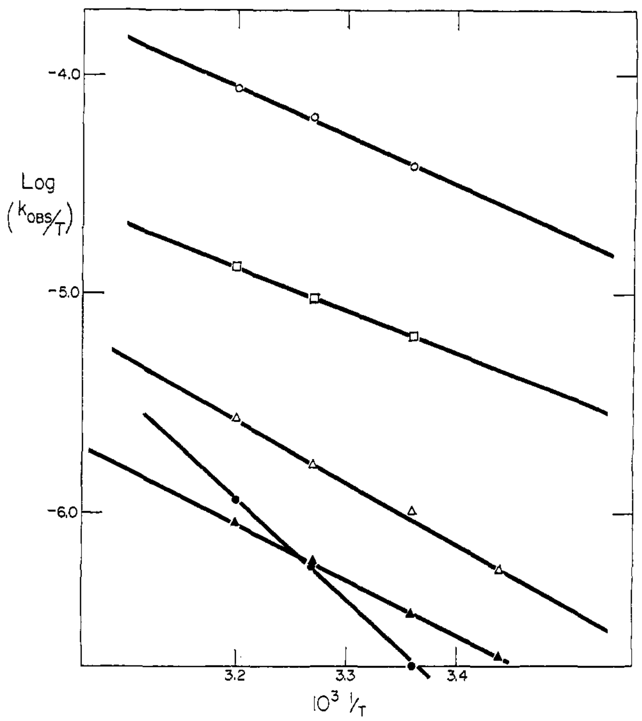

Figure 3.—The effect of temperature on the hydrolysis rates of some substituted N-benzylideneanilines: ○, *o*-O⁻; □, *o*-OH; △, *p*-O⁻; ▲, *p*-OCH$_3$; ●, H.

most marked rate changes are found when the *o*-OH of the benzylidene ring is ionized. In the case of **12**, the rate of the ionized form is about five times that of the un-ionized species, and the rate change exactly parallels the ratio [RO$^-$]/([RO$^-$] + [ROH]) over the pH range 8.5–11. With **11**, the separate p$K_a$'s for the *o*- and *p*-OH's could not be determined from changes in the absorption spectrum, but the rate data suggest a p$K_a$ for the *o*-OH of about 11. The most pronounced acceleration of rate was found upon ionization of **13**, where the ionized species hydrolyzes 360 times faster than the un-ionized form. The small difference between the absorption curves of the two species of **13** and the high rates of hydrolysis at pH's near the p$K_a$ precluded accurate measurement of the p*K* value. The absorption maximum, extrapolated to zero reaction time, showed the greatest change at about pH 11, indicating that the p$K_a$ has this approximate value. The pH–log $k_{OBS}$ plot also indicates a p$K_a$ of approximately 11.

Solvent deuterium isotope effects on the hydrolysis rates of **6** and **12** were determined at pH 11 where the *p*- and *o*-OH's are completely ionized. Although the magnitude of such an effect is hardly predictable from first principles, it was hoped that a difference in the effect on hydrolysis rates of **6** and **12** might qualitatively suggest a difference in the involvement of water in the two cases and help explain the nature of the acceleration by an ionized salicylidene OH. No significant difference was found, however. The value of $k^H/k^D$ for dissociated *p*-OH (**6**) was 1.6; the ratio for dissociated *o*-OH (**12**) was 1.5.

The methyl ether of **13** (**14**) was prepared and the uncatalyzed hydrolysis rate compared with those of un-ionized and ionized **13**. The ratio $k_{o\text{-OMe}}/k_{o\text{-OH}}$ is 6.7, and $k_{o\text{-O}^-}/k_{o\text{-OMe}}$ is 51.2. Despite the usual difficulty in interpreting *ortho*-substituent effects, the effect of ionized salicylidene OH appears to be unique and to involve more than a simple electronic effect.

The temperature coefficients of the hydrolysis rates of **6a** (ionized *p*-OH), **7** (*p*-OMe), **12** (*o*-OH), **12a** (*o*-O$^-$), and **8** (unsubstituted) were measured to see whether the enhanced rates of ionized N-salicylideneanilines reflect markedly different activation parameters. The temperature coefficient for the un-ionized *p*-OH was not measured for the reason cited above. For these reactions, where $k_{OBS}$ is likely to be a composite constant, apparent Arrhenius activation parameters derived from the temperature coefficients must only be treated as empirical constants. Attempts to derive entropies and enthalpies of activation from them are meaningless unless it can be shown that $k_{OBS}$ is identical with a specific rate constant for a single reaction or the entropy and enthalpy change for the appropriate equilibria and/or rates are separately determined. The apparent Arrhenius parameters are given in Table III. Figure 3 shows a plot of log ($k_{OBS}/T$) *vs.* $1/T$, following the method of Petersen for testing the existence of isokinetic temperatures.[17] The plots show the absence of an isokinetic temperature, using this criterion. In view of this, the compensation of the apparent exponential and pre-exponential Arrhenius parameters for the hydrolysis rates is probably illusory. What appears to be compensation is probably a result of the fact that the two terms are not independently determined but are both derived from the same set of data.[17]

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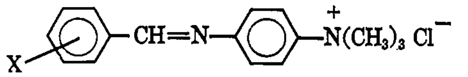
[17] R. C. Petersen, *J. Org. Chem.*, **29**, 3133 (1964).

TABLE III

APPARENT ARRHENIUS ACTIVATION PARAMETERS FOR THE UNCATALYZED RATES OF HYDROLYSIS OF



| X | Log $A'$ (25°) | $-E_a'$, kcal./mole |
|---|---|---|
| H | 8.2 | 16.8 |
| $p$-O$^-$ | 6.2 | 13.9 |
| $p$-OCH$_3$ | 5.4 | 12.8 |
| $o$-O$^-$ | 7.5 | 11.6 |
| $o$-OH | 4.4 | 9.8 |

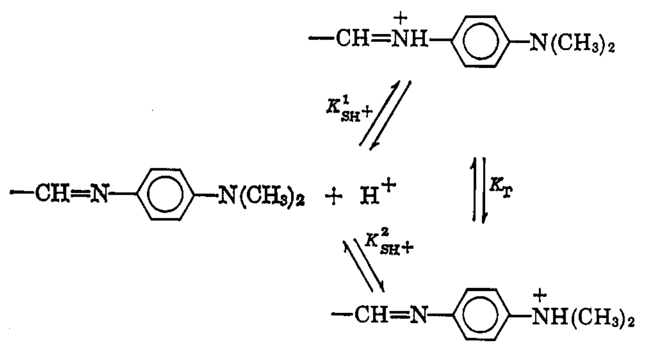
## Discussion

The small negative value of $\rho$ for the hydrolysis rates of the two series of substrates seems inconsistent with a mechanism where $k_{OBS} = k_1$, *i.e.*, where addition of water to the imine free base is slow and cleavage to products is fast. In those cases where detailed studies have been made, nucleophilic additions to $p$-substituted benzaldehydes give correlations with positive $\rho$ or $\rho^+$ values. It would also be expected that electron-withdrawing $p'$-substituents in benzylideneanilines would increase the carbonium ion character of the imine carbon in the initial state and delocalize the developing negative charge from the nucleophile in the transition state, giving rise to a positive $\rho$ value.

The alternative and kinetically indistinguishable mechanism, where addition of OH$^-$ to $>CH=\overset{+}{N}H-$ is slow and cleavage of the carbinolamine is rapid, is consistent with the results. In this case, $k_{OBS} = k_1/K_{SH^+}$ and the observed $\rho$ value is the sum of the $\rho$ values for the specific rate constant for addition ($k'_1$) and for the basicity constant, $1/K_{SH^+}$. The correlation of $1/K_{SH^+}$ for the $p'$-derivations **2**, **3**, and **4** has a $\rho$ value of $-1.5$.[2] Since $\rho$ for $k'_1$ is expected to be positive, the over-all $\rho$ value must be less negative than $-1.5$, or positive, for this mechanism to be admissible. The observed $\rho$ of $-0.71$ is in accord with these considerations. If this mechanism is correct, a $\rho$ value of $+0.8$ for $k'_1$ is calculated from the difference in the $\rho$ values for $k_{OBS}$ and for $1/K_{SH^+}$.

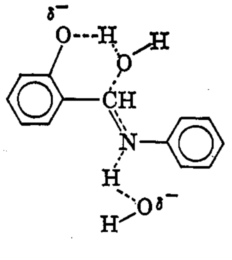
A mechanism involving rate-determining attack of water on the unprotonated imine, where the partitioning coefficient $k_{-1}/k_2$ has values in the range 99–0.01, might be consistent with the results if the $\rho$ value for $k_{-1}/k_2$ is more positive than the $\rho$ value for $k_1$ (eq. 4a). In this case, however, the right-hand side of eq. 4a is not a linear function, so that uniform changes in $k_1$ and in $k_{-1}/k_2$ do not produce uniform changes in $k_{OBS}$. A continuous, but nonlinear, Hammett plot should result. We believe that our measurements are sufficiently precise and cover a wide enough range of structures to permit rejection of this possibility.

Failure of the hydrolysis rate of the $p'$-dimethylamino derivative to correlate with the rates of the other substrates can be rationalized by a mechanism involving attack of OH$^-$ on $>CH=\overset{+}{N}H-$. It has been shown that monoprotonation of this compound gives the dimethylammonium ion almost exclusively.[2] The concentration of the anilium ion is too low to permit an estimate of the tautomeric equilibrium constant, $k_T$, for the two conjugate acids, so that the acid dissociation constant for the anilium ion, $K^1_{SH^+}$, the only one of mechanistic significance, is unknown



In view of the existence of these more complex equilibria, which are unique for this substituent, it seems reasonable that the change in structure might not produce the same change in $K^1_{SH^+}$ that changing other substituents produces. The failure of $k_{OBS}$ for this substituent to correlate with the others could reflect the failure of $K^1_{SH^+}$ to correlate with the other $K_{SH^+}$ values.

The accelerating effect of the salicylidene OH group must be due to more than a strong mesomeric effect, since this effect should also operate from the *para* position. A beneficial field effect seems unlikely since it is not operative from the aniline ring, although the $o$-OH groups are about equidistant from the $>C=N-$ bond in both cases. Intramolecular nucleophilic attack on the imine carbon with expulsion of the aniline moiety seems unreasonable since it would require formation of a four-membered ring fused to a benzene ring. We believe that a mechanism involving intramolecular, general base catalysis by the salicylidene OH group provides the most satisfying interpretation of the results. Two reaction schemes which are quite different mechanistically but give rise to identical kinetics are possible. In the first, the ionized OH acts as a base, removing a proton from water as it adds to the unprotonated Schiff base. By this mechanism, the spatial specificity is attributed to the ability to form the six-membered transition state, with the negative charge delocalized over the substituent, the C=N bond, and probably, two water molecules. The rate increases as the concentration of the ionized species increases and becomes independent of pH when ionization is complete. The alternative scheme involves general acid catalysis of OH$^-$ attack by the un-ionized salicylidene OH. The rate increases in proportion to the OH$^-$ concentration in the pH region where the concentra-



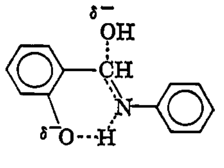
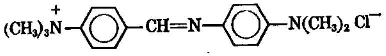
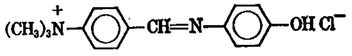
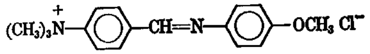
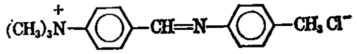
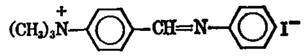
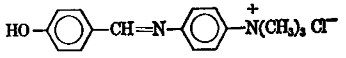
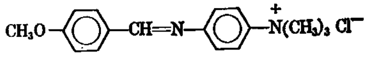
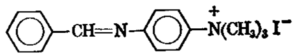
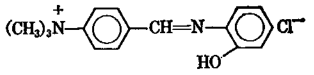
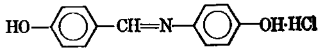
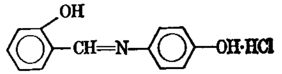
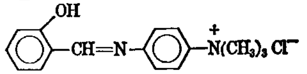
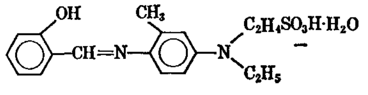
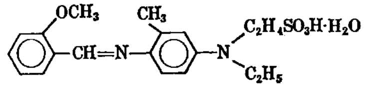
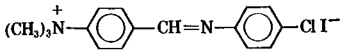


TABLE IV

PREPARATION AND PROPERTIES OF SCHIFF BASES

| No. | Structure | M.p., °C. | Reaction solvent | Reaction time, hr. | Calcd., % C | Calcd., % H | Calcd., % N | Calcd., % Cl (I) | Found, % C | Found, % H | Found, % N | Found, % Cl (I) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 |  | 236–238 | $H_2O$ | 0.5 | 68.0 | 7.6 | 13.2 |  | 67.6 | 7.5 | 13.1 |  |
| 2 |  | 216 dec. | HOAC | 3 | 66.1 | 6.6 | 9.6 | 12.2 | 66.1 | 6.8 | 10.0 | 12.5 |
| 3 |  | 187.5–188.5 | EtOH | 0.25 | 67.0 | 6.9 | 9.1 | 11.6 | 66.5 | 6.6 | 9.4 | 11.9 |
| 4 |  | 175–176 | EtOH | 0.25 | 70.7 | 7.3 | 9.7 | 12.3 | 70.5 | 7.2 | 10.1 | 12.7 |
| 5 |  | 180 dec. | HOAC | 1 | 52.5 | 5.2 | 7.7 | 34.7 | 52.2 | 5.4 | 7.3 | 34.3 |
| 6 |  | 220–225 dec. | $H_2O$–HCl | 0.25 | 66.1 | 6.6 | 9.6 | 12.2 | 65.4 | 6.4 | 9.4 | 12.6 |
| 7 |  | 195–198 | EtOH | 2 | 67.0 | 6.9 | 9.2 | 11.6 | 65.2[a] | 6.7 | 9.7 | 12.6 |
| 8 |  | 190–200 dec. | EtOH | 2 | 52.5 | 5.2 | 7.7 | 34.7 | 52.1 | 5.2 | 7.7 | 34.8 |
| 9 |  | 189–190 | EtOH | 0.25 | 66.1 | 6.6 | 9.6 | 12.2 | 65.8 | 6.3 | 9.4 | 12.2 |
| 10 |  | 250–255 dec. | EtOH | 2 | 62.5 | 4.8 | 5.6 | 14.2 | 61.8 | 4.8 | 5.6 | 14.6 |
| 11 |  | 196–208 | EtOH | 2 | 62.5 | 4.8 | 5.6 | 14.2 | 61.7 | 4.7 | 5.6 | 14.3 |
| 12 |  | 201–202 | EtOH | 1.5 | 66.1 | 6.6 | 9.6 | 12.2 | 64.8 | 6.4 | 9.8 | 12.3 |
| 13 |  | 177–179 dec. | MeOH–$H_2O$ |  | 56.8 | 6.3 | 7.4 |  | 56.8 | 6.2 | 7.4 |  |
| 14 |  | 185–205 | EtOH–$H_2O$ |  | 58.0 | 6.6 | 7.1 |  | 58.2 | 6.6 | 7.0 |  |
| 15 |  | 233–236 dec. | HOAC | 12 | 48.0 | 4.5 |  |  | 48.1 | 4.7 |  |  |

[a] Recrystallized twice after analysis before use.

tion of un-ionized catalyst is essentially constant, and becomes pH independent after ionization because the linear increase in $OH^-$ concentration is balanced by a linear decrease in catalyst concentration. Thus, the rate reaches a plateau because of catalyst saturation by the first mechanism and because of catalyst exhaustion by the second. The log $k_{OBS}$–pH profiles are identical for both mechanisms.

The second mechanism is preferred because it is analogous to the most acceptable mechanism for the uncatalyzed hydrolysis. In addition, since the same nucleophile is involved in the catalyzed and uncatalyzed reaction, no difference in solvent deuterium isotope is expected for the two reaction paths.

## Experimental

**Materials.**—The preparation of the quaternary aldehyde salt was described previously.[6] *p*-Trimethylammoniumaniline chloride was prepared by refluxing *p*-dimethylaminoacetanilide with methpl iodide, hydrolyzing and exchanging the iodide ion of the quaternary salt for chloride on Amberlite IRA-400 ion-exchange resin. Chloride salts of the Schiff bases were generally more soluble than the iodides. The Schiff bases were prepared by warming together the aldehyde and amine in an appropriate solvent. The reaction solvents and times, melting points, and elemental analyses are given in Table IV.

**Kinetics.**—For most of the runs, a weighed sample of Schiff base, sufficient to give a $1 \times 10^{-4}$ *M* solution after dilution, was dissolved in 1 ml. of ethanol in a volumetric flask and thermostated at 25.0°. This sample was diluted to 100 ml. with aqueous phosphate or carbonate buffer having an ionic strength of 0.05. The disappearance of Schiff base was followed on a Beckman DU spectrophotometer at a wave length that gave the greatest difference in absorbance between the Schiff base and aldehyde. The first-order rate constants were calculated by the Guggenheim method. For those runs that were too rapid to be followed conveniently by this method, 40 µl. of the ethanolic solution of Schiff base was injected into 4 ml. of buffer in a quartz cuvette, and the absorbance change monitored continuously at the appropriate wave length with a Cary Model 14 recording spectrophotometer.

The pH values were measured at the temperature of the kinetic runs with a glass electrode that had been standardized with 0.01 *M* sodium tetraborate reference buffer at the same temperature. The runs in deuterium oxide were buffered with 1% sodium carbonate. The carbonate was dried several hours at 130°. Identical runs were made in water. The pH of the solutions was 11.2, so that the hydroxyl groups of **6** and **12** were completely ionized. Under these conditions, the differences between p$K_a$ ($H_2O$) and p$K_a$ ($D_2O$) and between pH and pD were not important.

**Acid Dissociation Constants.**—The p$K_a$'s for the ionizable hydroxyl groups were obtained from the absorption curves determined in buffers of different pH. In those cases where the hydrolysis was rapid enough to give trouble, the absorbance at the analytical wave length was measured as a function of time at each pH and was then extrapolated at zero time. All measurements were made at 25° and an ionic strength of 0.05.

**Acknowledgment.**—The help of Dr. Wendell F. Smith, Jr., in preparing many of the compounds, and of Mr. Richard W. Andrus, for technical assistance, is gratefully acknowledged. We are indebted to Dr. E. H. Cordes for helpful discussion of this work.

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# Rearrangement of Some Piperidine N-Oxides to Hexahydro-1,2-oxazepines[1]

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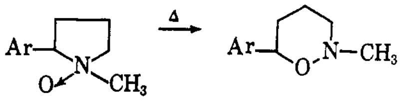
*Received April 26, 1965*

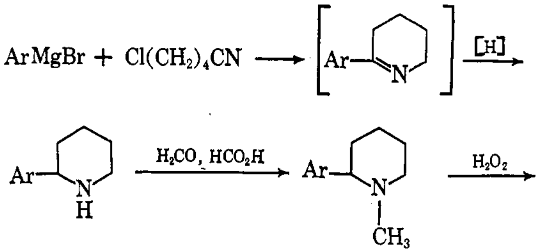
Pyrrolidine N-oxides bearing a 2-aryl substituent are known to rearrange with ring expansion to form tetrahydro-2H-1,2-oxazines. Similar piperidine N-oxides have now been found to follow the same course, and for the first time compounds with the hexahydro-1,2-oxazepine ring system have been made available. The reactions were performed at 170° in dimethylacetamide and were accompanied by some loss of oxygen from the N-oxides. The infrared, n.m.r., and mass spectra of the products support the assigned ring structure.

It is known that pyrrolidine N-oxides, if substituted in the α-position by 3-pyridyl[2] or aryl[3a] groups, can be rearranged thermally to tetrahydro-2H-1,2-oxazines. The reaction is a special case of the Meisenheimer N to O rearrangement of allyl- or benzylamine oxides. Ap-

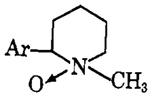


plication of this reaction to similarly substituted piperidine N-oxides could lead to hexahydro-1,2-oxazepines, an apparently unknown class of compounds.[3b] We describe conditions for the performance of this synthesis in this paper.

Three 1-methyl-2-arylpiperidine N-oxides (II) were prepared for this study by the following reactions.



Ia, Ar = $C_6H_5$
b, Ar = *p*-$CH_3C_6H_4$
c, Ar = *p*-$ClC_6H_4$



IIa-c

The oxides, characterized as the picrates, were used without purification in subsequent reactions. Immedi-

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[1] Presented at the Southeastern Regional Meeting of the American Chemical Society, Charleston, W. Va., Oct. 1964.

[2] C. H. Rayburn, W. R. Harlan, and H. R. Hanmer, *J. Am. Chem. Soc.*, **72**, 1721 (1950); T. Kisaki, M. Ihida, and E. Tamaki, *Bull. Agr. Chem. Soc. Japan*, **24**, 719 (1960).

[3] (a) L. D. Quin and G. L. Roof, *J. Org. Chem.*, **27**, 4451 (1962). (b) Hexahydro-2-methyl-7-(3-pyridyl)-1,2-oxazepine has now been reported; it was prepared similarly by thermal rearrangement of N-methylanabasine N-oxide: W. Carruthers and R. A. W. Johnstone, *J. Chem. Soc.*, 1653 (1965).