displacement of iodide could *not* be invoked to account for the intermediate and products obtained.

Regarding the modest rate accelerations of ca. 45 for **2** and ca. 6–9 for **4** and **5**, it should be recalled that in an analogous carbocyclic system,[19] *cis*-and *trans*-4-hydroxycyclohexyl chloride react at the same rate in aqueous base, although 7-oxobicyclo-[2.2.1] cycloheptane is the major product only from the trans isomer. In this 6-membered ring, the transannular 4-hydroxy group participates after the rate-determining step. Formation of the bridged alkoxysulfonium intermediate was proposed to account for the acceleration of 150 in the solvolysis rates of the *trans*- vs. the *cis-p*-toluenesulfonates of 4-hydroxythiacyclohexane 1-oxide.[20] Considering that an axial OTs group undergoes solvolysis four times faster than an equatorial OTs group, the additional rate enhancement is ca. 40 due to the formation of the bridged intermediate formed by sulfoxide participation. In general only a moderate anchimeric assistance would be expected in path A (Scheme I).

Evidence for intramolecular catalysis in thioether oxidation has now been presented when SR, NR$_2$, OH, and CO$_2$H[21] are neighboring groups. Quantitative determinations of the influence of other neighboring groups on oxidation at divalent sulfur atoms are in progress.

Conclusion

The kinetics of the hydroxythiacycloalkane compounds **2**, **4**, and **5** suggest that oxidation occurs via two pathways. Both paths involve sulfurane formation and rate-determining hydroxyl participation followed by rapid decomposition of the bridged intermediate. Under ideal circumstances the bridged alkoxysulfonium salt can be precipitated from solution. This work confirms the hydroxyl group participation which was postulated to explain the lowering of the oxidation potential of **2** by 0.6 V relative to simple thioethers.[22] The stereochemistry of the products are also consistent with the formation of *trans*-4-hydroxythiacyclohexane 1-oxide from the reaction of **4** with *tert*-butyl hypochlorite in the nonpolar solvent CH$_2$Cl$_2$.[8]

Acknowledgment. We wish to thank the National Science Foundation and the National Institutes of Health for grants to W.K.M. and the Committee on Research for a grant to J.T.D. We also thank Keith A. Williams for help in synthesis, Dr. Gerry Matson and David L. deLeeuw for the ^{13}C NMR spectra, and Charles P. Nash for helpful suggestions.

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Intramolecular General-Base Catalysis of Schiff-Base Hydrolysis by Tertiary Amino Groups

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Abstract: Hydrolysis of a series of Schiff bases (**1**) derived from benzophenone and various amines has been studied kinetically in aqueous solution. A linear correlation of the log of the rate constants for the water reaction with the Schiff base pK_a (slope −0.70) shows large positive deviations for Schiff bases derived from (2-aminoethyl)diethylamine (**1e**), *N*-(2-aminoethyl)morpholine (**1f**), *N*-(2-aminoethyl)piperazine (**1h**), and 2-(aminomethyl)pyridine (**1i**) but small deviations for Schiff bases from *N*-(3-aminopropyl)morpholine (**1g**) and 2-(2-aminoethyl)pyridine (**1j**). The deviations found are attributed to intramolecular general-base catalysis of the water reaction by the internal tertiary amino groups. Magnitudes of the rate enhancement are correlated well with pK_{a1} of the internal catalyst (β = 0.49). Effective concentrations of the internal bases are estimated to range from 340 (**1e**) to 40 M (**1i**).

The importance of Schiff bases as intermediates in many of the enzymatic transformations of both carbonyl compounds and amines[1] has generated a great deal of interest in the mechanism of formation and hydrolysis of these compounds. General features of the mechanism of Schiff-base hydrolysis are now well understood.[2] Although intramolecular catalysis has been extensively studied on a variety of reactions as a relevant model for the catalytic action of various enzymes,[3] examples of intramolecular catalysis in the Schiff base hydrolysis are limited. Intramolecular general-base catalysis by an ionized *o*-hydroxy group was once suggested for the hydrolysis of Schiff bases derived from salicylaldehyde[4] and 3-hydroxypyridine-4-carboxaldehyde[5] but subsequently demonstrated to be improbable.[6] Pollack et al.[7,8] have recently presented evidence that the hydrolysis of Schiff bases derived from cyclohexene-1-carboxaldehyde is catalyzed by an internal carboxylate ion.

Since we have found indications that some internal amino groups catalyze the Schiff-base hydrolysis during our investigations of the amine catalysis of isomerization of a β,γ-unsaturated ketone,[9] systematic studies of catalysis by internal amino groups have been conducted for the hydrolysis of Schiff bases (**1a–j**) derived from benzophenone. Tertiary amino groups attached at the β-position from the imino nitrogen atom showed marked intramolecular general-base catalysis of water attack on the protonated Schiff bases **1**H$^+$, and the results of our studies are described herein.

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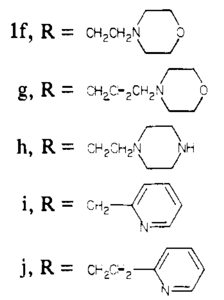
$(C_6H_5)_2C{=}N{-}R$

1a, $R = CH_2CH_2CH_3$
b, $R = CH_2CH_2OH$
c, $R = CH_2CH_2CN$
d, $R = CH_2CN$
e, $R = CH_2CH_2N(C_2H_5)_2$



Experimental Section

Materials. The Schiff bases of benzophenone (**1a,b,e–j**) were prepared by refluxing a mixture of benzophenone, amine (1.5 equiv), and a catalytic amount of iodine in toluene for 2 days.[10] After removal of solvent, liquid products were vacuum distilled or chromatographed (alumina column) and solid ones were recrystallized. The cyano-substituted Schiff bases (**1c,d**) were prepared from benzophenone imine[11] by transimination.[12] Analyses of the Schiff bases for CHN were satisfactory except for **1i**. **1a**: bp 145–147 °C (3 mm); UV (H_2O) λ_{max} 242 nm (ϵ 1.19×10^4), (1 M HCl) λ_{max} 276 nm (ϵ 1.88×10^4). **1b**: mp 71–72 °C (hexane) (lit.[10] 73–73.5 °C); UV (H_2O) λ_{max} 244.5 nm (ϵ 1.34×10^4), (1 M HCl) λ_{max} 276 nm (ϵ 1.91×10^4). **1c**: mp 86.5–87.5 °C (hexane) (lit.[12] 85–87 °C); UV (H_2O) λ_{max} 245 nm (ϵ 1.26×10^4), (1 M HCl) λ_{max} 280 nm (ϵ 1.85×10^4). **1d**: mp 78.2–78.6 °C (hexane) (lit.[12] 79–81 °C); UV (H_2O) λ_{max} 245 nm (ϵ 1.25×10^4), (1 M HCl) λ_{max} ~280 nm. **1e**: bp 135–138 °C (1.5 mm); UV (H_2O) λ_{max} 247 nm (ϵ 1.36×10^4), (1 M HCl) λ_{max} ~280 nm. **1f** was purified by column chromatography (alumina, benzene): UV (H_2O) λ_{max} 247 nm (ϵ 1.22×10^4), (1 M HCl) λ_{max} 279 nm (ϵ 1.74×10^4). **1h**: mp 76–78 °C (ligroin); UV (H_2O) λ_{max} 245 nm (ϵ 1.23×10^4), (1 M HCl) λ_{max} 280 nm. Purifications of **1i** were unsuccessful either by distillation or by chromatography. Impure products (yellow liquid) were therefore used for kinetic studies. The UV spectral and kinetic behaviors were in accord with those expected for the structure. Impurities do not seem to affect the kinetics of Schiff-base hydrolysis at pH <7. **1j**: mp 65–66 °C (ligroin); UV (H_2O) λ_{max} 246 nm (ϵ 1.32×10^4), (1 M HCl) λ_{max} 280 nm (ϵ 1.8×10^4).

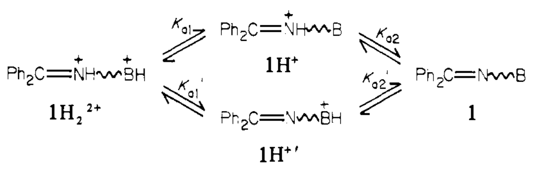
Reagent-grade inorganic chemicals and salts were used without further purification. Organic compounds used for buffer preparations were recrystallized or distilled before use. Acetonitrile was distilled from phosphorus pentoxide. Glass-distilled water was used throughout.

Kinetic Measurements. Reactions of the Schiff bases **1** were carried out at 30.0 ± 0.2 °C in aqueous solution containing 1 vol % acetonitrile and at a constant ionic strength of 0.5 maintained by adding KCl. Buffers used were HCl, chloroacetate, formate, acetate, phosphate, imidazole, *N*-methylmorpholine, triethanolamine, borate, carbonate, and NaOH, concentrations generally varying from 0.02 to 0.1 M except for HCl and NaOH solutions. Stock solutions of **1** in acetonitrile were prepared by weighing, concentrations being typically 5×10^{-3} M. The values of the pH of the buffer and reaction solutions were measured on a Hitachi-Horiba CTE F-5 pH meter.

Three milliliters of the buffer solution was equilibrated thermally at 30 °C in a Teflon-stoppered quartz cuvette inserted in a water-jacketed cell holder. Into the buffer solution was injected 30 μL of a stock solution of **1** through a microsyringe. After the solution was thoroughly mixed, the reaction was monitored by following the absorbance change at 280 nm (disappearance of iminium ions at pH < pK_a) or at 257 nm (formation of benzophenone at pH > pK_a) on a Shimadzu UV 200 spectrophotmeter. Excellent pseudo-first-order kinetics were observed for all the runs.

Determination of Dissociation Constants. Values of pK_a for the protonated Schiff bases were determined spectrophotometrically under the same conditions as the kinetic measurements. Into the buffer solution (3.0 mL) equilibrated at 30 °C in a cuvette was introduced quickly 30 μL of a stock solution of **1** in CH_3CN from a microsyringe. Initial absorbance readings at 280 nm were obtained by extrapolation to the time of mixing. The readings were reproducible within to ±5%, unless the halftime of the hydrolysis was shorter than 30 s and were obtained as averages of at least three measurements. The fraction of the iminium ion was calculated from the initial absorbance and plotted against pH.

Scheme I



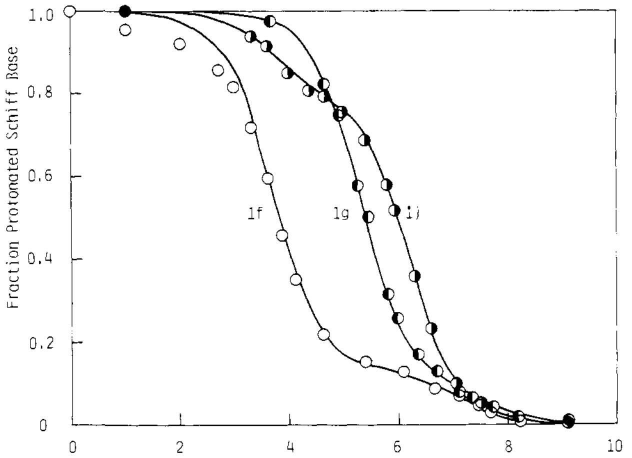


Figure 1. Spectrophotometric titration curves for **1f** (○), **1g** (◐), and **1j** (◑).

Sigmoidal curves thus obtained gave pK_a values as will be described in the Results.

Results

Spectrophotometric Determination of the pK_a Values. The absorption at 280 nm is mainly due to the protonated Schiff bases $1H^+$, the extinction coefficient ϵ_{280} being about 1.8×10^4 as compared with ϵ_{280} of the neutral species **1** of about 2×10^3. For simple Schiff bases, **1a–c**, plots of the fractions of protonated Schiff bases calculated from the absorbance readings against pH give sigmoidal curves (not shown), from which pK_a values are obtained as listed in Table I. Titration of **1d** was impossible because of the extreme lability at low pH.

Spectrophotometric titration curves for the Schiff bases carrying an additional basic center are not always simple. Acid dissociations of diprotonated Schiff bases take place as shown in Scheme I. Since the extinction coefficients of the two protonated species $1H_2^{2+}$ and $1H^+$ (iminium ions) at 280 nm can be taken to be identical and those of **1** and $1H^{+\prime}$ to be equally small, the fraction of protonated Schiff base x is easily obtained from the observed initial absorbance. The titration curve of a biphasic sigmoid can then be obtained by plotting x against pH as described by eq 1.

$$x = ([1H_2^{2+}] + [1H^+])/[1]_{total} = \frac{[H^+]^2 + K_{a1}[H^+]}{[H^+]^2 + K_{A1}[H^+] + K_{A1}K_{A2}} \qquad (1)$$

Apparent pK_a's, pK_{A1} and pK_{A2}, are correlated with microscopic dissociation constants by eq 2–4.[13,14] The curve has an intermediate plateau region of $x = K_{a1}/K_{A1}$.

$$K_{A1} = K_{a1} + K_{a1}' \qquad (2)$$

$$1/K_{A2} = 1/K_{a2} + 1/K_{a2}' \qquad (3)$$

$$K_{A1}K_{A2} = K_{a1}K_{a2} = K_{a1}'K_{a2}' \qquad (4)$$

However, the curve for **1e** was a simple sigmoid of pK_a = 3.80, which corresponds to pK_{a1}', because K_{a1} is negligibly small as

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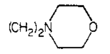
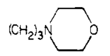
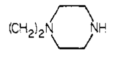
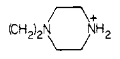
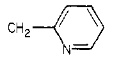
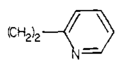
Table I. Dissociation Constants and Rate Constants for Nucleophilic Attack in the Hydrolysis of 1a–d

Schiff base	R	pK_a[a] (RNH_3^+)	pK_a	10^3k_1, s^{-1}	10^4k_{OH}, s^{-1}	$10^{-3}k_1'$, $M^{-1}\ s^{-1}$	10^2k_{phos}, $M^{-1}\ s^{-1}$
1a	$(CH_2)_2CH_3$	10.53	6.98	0.35	1.0	0.71	0.18
1b	$(CH_2)_2OH$	9.50	6.24	2.0	1.0	3.9	1.3
1c	$(CH_2)_2CN$	7.7	4.58	30	0.05	9.8	30
1d	CH_2CN	5.3	(2.6)[b]	650			

[a] Taken from ref 18. [b] Obtained kinetically.

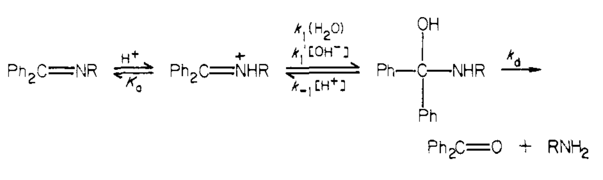
Table II. Dissociation Constants and Rate Constants for Nucleophilic Attack in the Hydrolysis of 1e–j

Schiff base	R	pK_a[a,b] (RNH_3^+)	pK_{A_1}[c]	pK_{A_2}[c]	pK_{a_1}[b]	pK_{a_2}[b]	pK_{a_1}'[b]	pK_{a_2}'[b]	10^2k_1, s^{-1}	10^3k_i, s^{-1}	10^4k_{OH}, s^{-1}	$10^2\bar{k}_2$, s^{-1}	$\bar{k}_1'$, $M^{-1}\ s^{-1}$	$10^{-3}k_2'$, $M^{-1}\ s^{-1}$
1e	$(CH_2)_2NEt_2$	10.02 7.07	3.80 (4.0)	(9.8)	[7.1]	[6.6]	3.9	9.8	4.2	1.5	0.44	238	1.28×10^7	0.75
1f		9.45 4.84	3.7	7.1	4.6	6.2	3.76	7.04	7.6	55	0.35	43.7	7.47×10^8	1.50
1g		[10.1]	5.3	7.7	6.3	6.7	5.35	7.65	0.53	0.80	0.51	0.090	2.72×10^5	0.69
1h		9.63 8.51		(9.2)[d]	[5.5]	[6.3]	[3.5]	[8.3]		1.4	0.37	125[e]	2×10^9 [e]	1.26
1hH+		[9.0]	(2.1)[f]	5.8 (5.9)	2.1	5.8	[3.2]	[4.7]	7.9[f]	54	14	5.4	3×10^{10} [e]	160[e]
1i		8.12[g] 2.58	(2.2)[f]	5.5	2.3	5.4	[2.8]	[4.9]	40[f]	55		6.9	2.4×10^{10}	
1j		8.75[g] 3.46	3.7	6.2 (6.3)	3.8	6.1	4.4	5.5	2.4	2.5	0.30	0.31	3.4×10^7	1.62

[a] Taken from ref 18. [b] Values in brackets are estimated, see text. [c] Values in parentheses were obtained kinetically. [d] The value is due to the terminal secondary nitrogen. [e] For calculations see text. [f] Relatively unreliable. [g] Values for dimethylamino derivatives ($R\overset{+}{N}HMe_2$).

compared with K_{a1}'. The spectrophotometrically measured process becomes simply $1H_2^{2+} \rightleftharpoons 1H^{+\prime} + H^+$ because of a negligible contribution from $1H^+$. The curves for **1h**,i are also essentially simple sigmoids of pK_a = 5.8 and 5.5, respectively, both of which are largely due to pK_{a2}. (The readings at lower pH are less reliable.) The spectrophotometrically significant process in these cases is $1H^+ \rightleftharpoons 1 + H^+$, owing to negligible contribution of $1H^{+\prime}$. The titration curves for **1f,g,j** are biphasic as shown in Figure 1 and nicely fit eq 1 with parameters given in Table II. In these cases all the individual pK_a values can be determined.

Kinetics. The observed rate constants extrapolated to zero buffer concentration k_0 are plotted against pH in Figures 2 and 3. Complex pH–rate profiles observed are due to the ionization of an additional internal base group. For those Schiff bases without internal base groups (**1a–d**), the kinetic curves are analyzed according to the generally accepted mechanism given by eq 5.[2] At higher pH, nucleophilic attack of H_2O and OH^- on



$$\mathrm{Ph_2C{=}NR} \underset{K_a}{\overset{H^+}{\rightleftharpoons}} \mathrm{Ph_2C{=}\overset{+}{N}HR} \underset{k_{-1}[H^+]}{\overset{k_1(H_2O),\ k_1'[OH^-]}{\rightleftharpoons}} \mathrm{Ph{-}\underset{Ph}{\overset{OH}{C}}{-}NHR} \xrightarrow{k_d} \mathrm{Ph_2C{=}O} + \mathrm{RNH_2} \qquad (5)$$

the protonated Schiff base to form a carbinolamine intermediate is rate determining and the observed rate constants in this region are described by eq 6, where k_B is the rate constant for general-base-catalyzed attack of H_2O and other parameters are given in eq 5. The pH–rate profiles are sigmoidal curves with asymptotes k_1 and k_{OH} ($=k_1'K_w/K_a$) at lower and higher pH limits, respectively. Solid curves of Figures 2 and 3 are drawn with parameters given in Table I.

$$k_{\mathrm{obsd}} = (k_1 + k_1'[\mathrm{OH^-}] + k_B[\mathrm{B}])\frac{[\mathrm{H^+}]}{[\mathrm{H^+}] + K_a} \qquad (6)$$

In the lower pH region where acid inhibition is observed, the breakdown of the carbinolamine intermediate becomes a rate-determining step. The buffer-independent rate constants are expressed by eq 7.

$$k_0 = \frac{K_1k_d}{[\mathrm{H^+}] + K_1k_d/k_1}\,\frac{[\mathrm{H^+}]}{[\mathrm{H^+}] + K_a} \qquad (7)$$

Scheme II

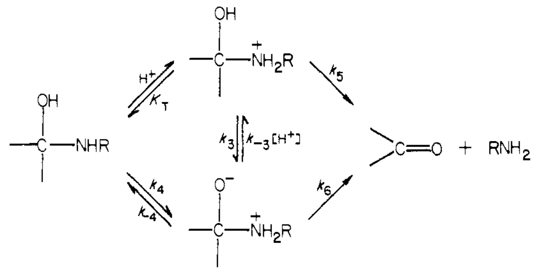


Table III. Rate Constants for Carbinolamine Breakdown in the Hydrolysis of 1

Schiff base	$10^6K_1k_4$, $M^{-1}\ s^{-1}$	$10^3K_1K_4k_6$, $M^{-1}\ s^{-1}$	$10^3K_1k_3/K_T$, s^{-1}
1b	1.0	0.3	1.1
1c	0.88	10	5.3
1e		6.5	
1f		12	
1g	25	1	2.0
1hH+		40	
1i		60	
1j	60	3	3.5

Additional breaks of the curves in this region are found at pH values near 3 and 1 for both **1b** and **1c**. This must be ascribed to the fact that the breakdown of the carbinolamine involves further changes in the rate-determining step. Such a mechanism was presented by Pollack et al.[7] as shown in Scheme II, and the rate constant for the breakdown k_d is described by eq 8. The

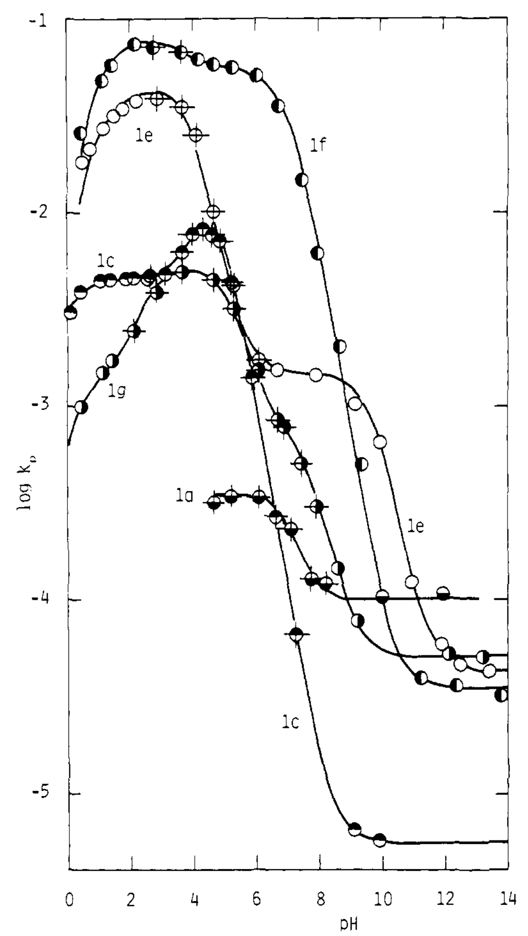
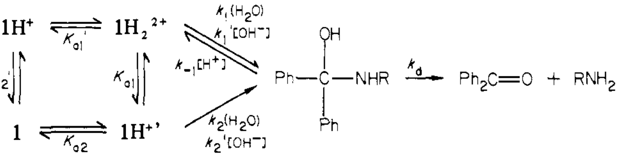


Figure 2. pH-rate profiles for the hydrolysis of **1a** (◒), **1c** (◓), **1e** (○), **1f** (◐), and **1g** (◑). Crossed points were obtained by the extrapolation from buffer-dependent rate constants.

Scheme III



parameters to reproduce the pH-rate curves for **1b,c**[15] were calculated in the same way as in the literature[7] and are given in Table III.

$$k_d = \frac{k_5[H^+]}{K_T} + \frac{k_6K_4(k_3[H^+]/K_T + k_4)}{k_6K_4 + k_3[H^+]/K_T + k_4} \tag{8}$$

For the Schiff bases carrying an internal base group, biphasic sigmoidal curves are observed in the higher pH region where nucleophilic attack is rate determining,[16] accompanied by an acid inhibition in the lowest pH region. Biphasic curves of the higher pH region are represented by eq 9 according to Scheme III. The

$$k_0 = \frac{k_1[H^+]^2 + k_iK_{A1}[H^+] + k_{OH}K_{A1}K_{A2}}{[H^+]^2 + K_{A1}[H^+] + K_{A1}K_{A2}} \tag{9}$$

$$k_i = (k_2K_{a1} + k_1'K_w)/K_{A1} \tag{10}$$

$$k_{OH} = k_2'K_w/K_{a2} \tag{11}$$

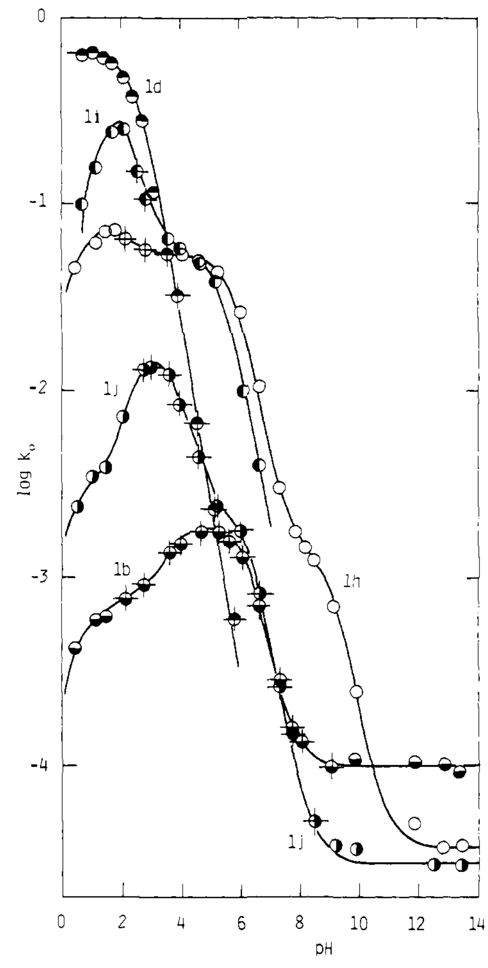


Figure 3. pH-rate profiles for the hydrolysis of **1b** (◒), **1d** (◓), **1h** (○), **1i** (◐), and **1j** (◑). Crossed points were obtained by the extrapolation from buffer-dependent rate constants.

term k_i, the k_0 value for an intermediate plateau region, in principle involves two reactions, H_2O attack on $1H^+$[17] and OH^- attack on $1H_2^{2+}$. The acid inhibition observed in the lowest pH region is ascribed to the rate-determining breakdown of the carbinolamine derived from the diprotonated species $1H_2^{2+}$ and analyzed by eq 7 and 8. The kinetic parameters are summarized in Tables II and III, and solid curves of Figures 2 and 3 are drawn with these parameters.

Although buffer catalysis was not extensively examined, a significant buffer effect was not always observed at total buffer concentrations less than 0.1 M, which was the maximum concentration generally employed. Crossed points in Figures 2 and 3 indicate that buffer catalysis was definitely recognized. Some Schiff bases, which contain an internal general-base group, undergo buffer catalysis only in a very limited range of pH (**1f,h,i**). Rate constants for phosphate-catalyzed water attack on simple Schiff bases are given in Table I.

Discussion

Dissociation Constants. In order to make quantitative analyses of the rate constants obtained, it is necessary to know the microscopic dissociation constants K_{a1}, K_{a2}, K_{a1}', and K_{a2}'. Some of them could be determined from the biphasic titration curves of Figure 1. Others may be estimated by an appropriate linear free energy relationship.

The dissociation constants of the iminium ion $1H^+$ and the corresponding ammonium ion show an excellent correlation as seen in Figure 4: $pK_{a2} = (0.85 \pm 0.02)pK_a - (1.93 \pm 0.17)$. From this correlation, pK_{a2} values for **1e** (and then pK_{a1} according to

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[15] The hydrolysis rate of **1c** has recently been found to be constant (3.0×10^{-3} s^{-1}) over pH 0.5–3.5 at 25 °C ($\mu = 1.0$), which has been attributed to the rate-determining decay of the protonated carbinolamine (k_5).[12] However, this plateau was ascribed to the k_3 term according to the analysis of Pollack,[7] since we have found another break at a still lower pH of about 0.5.

[16] The curve for **1h** is a triphasic sigmoid owing to the additional two basic centers.

[17] The fraction of the reactive monoprotonated substrate is given by $[1H^+]/([1H^+] + [1H^{+\prime}]) = K_{a1}/K_{A1}$.

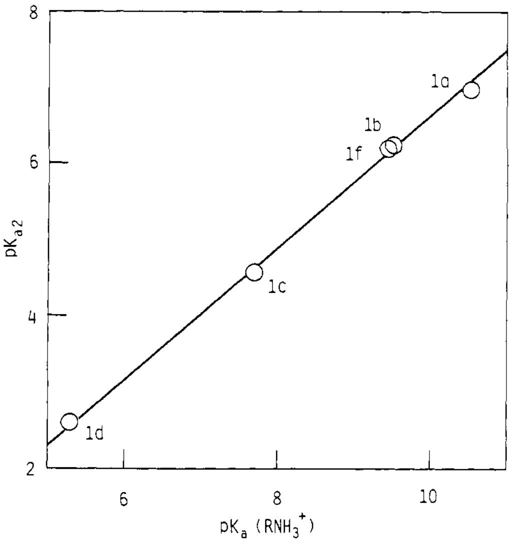

Figure 4. Correlation of Schiff base pK_{a2} with pK_a of the corresponding primary amines.

eq 4) and for **1h** have been estimated. The value of pK_{a1} is greater than pK_{a2} for **1e**; a triethylamine carrying an iminium ion group at the β-position is more basic than an imine carrying a diethylamino group at the β-position. The value of pK_a for morpholinopropylamine (RNH_2 for **1g**) is deduced to be 10.1 from the same correlation. This value, 0.6 p*K* unit greater than that for morpholinoethylamine ($pK_a = 9.45$),[18] is reasonable as compared with a similar pK_a difference between ethylenediamine ($pK_a = 9.98$)[18] and trimethylenediamine ($pK_a = 10.62$).[18] In the same way, $pK_a(RNH_3^+)$ for **1i,j** are evaluated to be 8.6 and 9.3, respectively. They are both 0.5 p*K* unit greater than those of the corresponding dimethylamino derivatives given in Table I. N-Methylation of amines usually lowers the pK_a value by a few tenths of a p*K* unit. A hypothetical value of $pK_a(RNH_3^+)$ for **1hH**$^+$ is also estimated to be 9.0. A remote positive charge in the piperazine ring may lower the pK_a by 0.6 p*K* unit.

The value of pK_{a1} for **1h** may be evaluated from the linear correlation of pK_{a1} with pK_a[18] for the secondary amines corresponding to the base groups of **1e,f,h,hH**$^+$ (i.e., Et_2NH, $CH_2CH_2OCH_2CH_2NH$, $CH_2CH_2HNCH_2CH_2NH$, and $H_2^+NCH_2CH_2NHCH_2CH_2$); the correlation is that of a unit slope (not shown). The pK_{a2}' values for **1h,hH**$^+$ are obtained in the same way from the correlation of a unit slope between pK_{a2}' and pK_a for the secondary amines as an extrapolation of the correlation for **1e,f**. The values of pK_{a1}' are calculated according to eq 4. Finally, pK_{a1}' (and thus pK_{a2}') for **1i** is estimated from the linear correlation of a unit slope between pK_{a1}' and pK_{a2} for **1e,f,h,hH**$^+$. This correlation involving **1h,hH**$^+$ indicates the self-consistency of the estimations.

Rates of Hydrolysis. Observed rate constants have been analyzed according to the mechanism of eq 5.[2] Nucleophilic attack of H_2O and OH^- on the protonated Schiff base to form the carbinolamine intermediate is rate determining at higher pH. The rate constants for the water reaction (k_1) are logarithmically plotted against the Schiff base pK_a (pK_{a1}' for **1e–j**) in Figure 5, with open and half-filled circles, the slope being −0.70. Similar correlations for the water reaction of hydrolysis of Schiff bases derived from substituted benzaldehydes[19] and from cyclohexene-1-carboxaldehyde[7] gave a slope close to −1.0, which is consistent with a later transition state.[7,19] The absolute magnitude of the slope (0.70) found here is significantly smaller than unity, suggesting an earlier transition state than those in the previous examples with aldimines.[7,19] Steric effects of the benzhydrylidene group of **1** might be one of the possible factors responsible for the above difference. An additional positive charge of $1H_2^{2+}$ (the internal ammonium ion) does not seem to show any significant influence on the water attack (**1e–j**). The k_1 and pK_{A1} values for **1hH**$^+$ may include relatively large experimental uncertainties because of a sudden change in rate-determining step at pH <3 (see the curve in Figure 3).

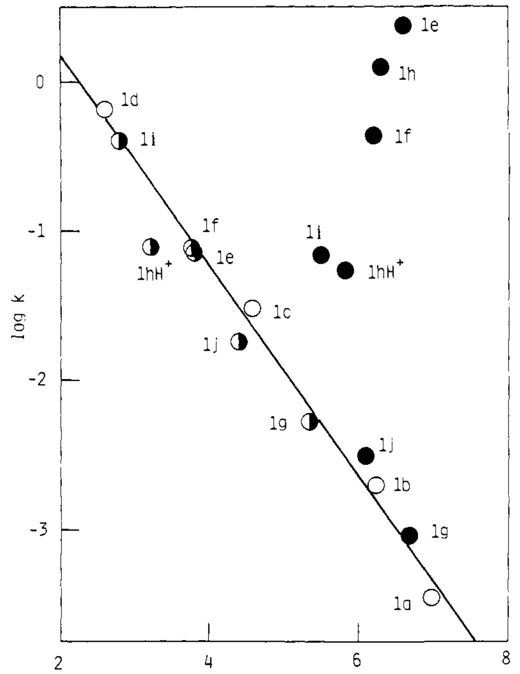

Figure 5. Correlation of the rate constants for the water reaction with Schiff base pK_a for the hydrolysis of **1**: ○, simple Schiff bases; ◑, $1H_2^{2+}$; ●, $\bar{k}_2$ for Schiff bases carrying an internal base group.

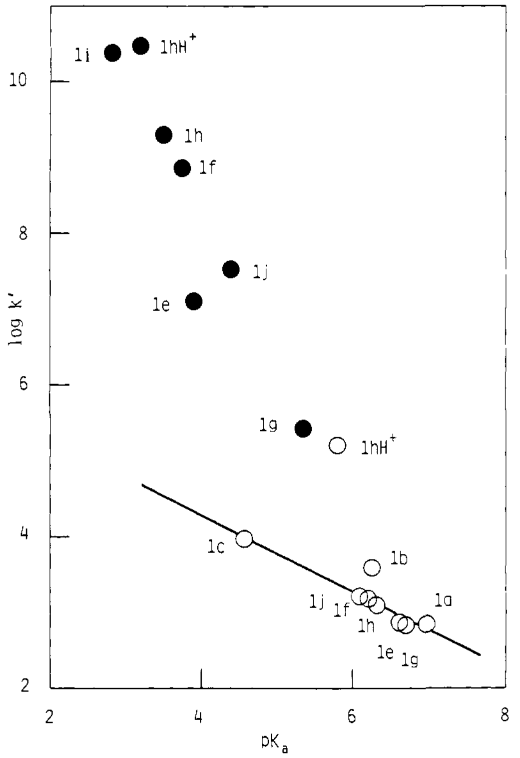

Figure 6. Correlation of the rate constants for the hydroxide reaction with Schiff base pK_a for the hydrolysis of **1**: ○, k_1' or k_2'; ●, $\bar{k}_1'$.

A similar correlation for the hydroxide reaction, plots of log k_1' vs. pK_a for **1a–c** and log k_2' vs. pK_{a2} for **1e–j**, is shown in Figure 6 with open circles (slope −0.50). The slope is close to that found

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Table IV. Deviations of k_i Terms from the Correlations between the Rate Constants and Schiff Base pK_a

Schiff base	pK_{a1}	water reaction[a]	effective concn,[b] M	hydroxide reaction[c]
1e	7.1	2700	340	6×10^2
1f	4.6	250	180	3×10^4
1g	6.3	1		6×10
1h	5.5	850	320	6×10^4
$1hH^+$[d]	2.1	16	60	5×10^5
1i	2.3	12	40	3×10^5
1j	3.8	1		3×10^3

[a] $\bar{k}_2/k_2^0$. [b] k_2^B/k_B^0. [c] $\bar{k}_1'/k_1'^0$. [d] The k_2' value is 60-fold greater than that expected for pK_{a2}.

for the hydroxide reaction of Schiff bases from cyclohexene-1-carboxaldehyde[7] and suggests an earlier transition state as compared with the water reaction. Reaction of a strong nucleophile like OH^- may only barely be subject to steric effects. The k_{OH} term (k_2') for **1hH**$^+$ corresponds to the k_i term for **1h** and requires careful considerations (vide infra).

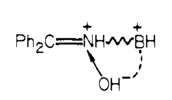
The k_i terms for **1e–j** involve contributions from two reactions, H_2O attack on $1H^+$ and OH^- attack on $1H_2^{2+}$, as described by eq 10. It is impossible to separate these contributions kinetically. Hypothetical rate constants for the water reaction ($\bar{k}_2$) and for the hydroxide reaction ($\bar{k}_1'$) are calculated respectively by assuming that the other contribution is negligible.

$$\bar{k}_2 = k_i K_{A1}/K_{a1} \quad (12)$$

$$\bar{k}_1' = k_i K_{A1}/K_w \quad (13)$$

The values of $\bar{k}_2$ and $\bar{k}_1'$ are summarized in Table II. In calculations of these values for **1h** and **1hH**$^+$, an appropriate modification was made to allow for the different species present.[20] Logarithms of $\bar{k}_2$ and $\bar{k}_1'$ are plotted against pK_{a2} and pK_{a1}' in Figures 5 and 6, respectively, with closed circles. Most of the points deviate greatly in a positive sense from the lines defined by the simple water and hydroxide reactions. Magnitudes of the deviations[21] are summarized in Table IV.

The slope of the plots of log $\bar{k}_1'$ vs. pK_{a1} (closed circles of Figure 6) is about −2, which is greatly different from that for simple Schiff bases and is apparently artificial. Moreover, the $\bar{k}_1'$ values for **1hH**$^+$ and **1i** are on the order of the diffusion limit. The k_i term cannot therefore be ascribed to the hydroxide reaction. The only possible reason for the enhanced reactivities in the hydroxide reaction would be a favorable electrostatic interaction between an additional positive charge of $1H_2^{2+}$ and the attacking hydroxide ion as shown by **2**. The effects of an internal positive charge on the nucleophilic attack of OH^- have not been well examined. Alkaline hydrolysis of acetylcholine has been estimated to be about twice as rapid as that of 2-nitroethyl acetate.[22,23] A trimethylammonium substitution at the γ-position of methyl butyrate showed a 7.5-fold acceleration in alkaline hydrolysis.[22,24] We have found that acetylthiocholine is 4.2 times as reactive as *N*-(2-acetylthioethyl)morpholine in the hydroxide ion reaction.[25] These results indicate that a positive charge separated by four bonds from the reaction center shows only a small electrostatic acceleration in the nucleophilic attack of hydroxide ion on the carbonyl group. In the present reaction, the effects of an additional positive charge of $1H_2^{2+}$ may be reduced by the positive charge at the iminium nitrogen atom, and thus the additional electrostatic effects are less than those observed in ester hydrolysis. Furthermore, electrostatic deceleration by an internal negative charge has never been detected in the hydroxide reaction of the hydrolysis of Schiff bases derived from amino acids.[7] Thus, the positive deviations found in the hydroxide reaction cannot be explained by the electrostatic effects. Any contribution from the hydroxide reaction to the k_i term must therefore be less than a few percent, even in the case of **1g** (60-fold acceleration). It is no doubt negligibly small in all the other cases.



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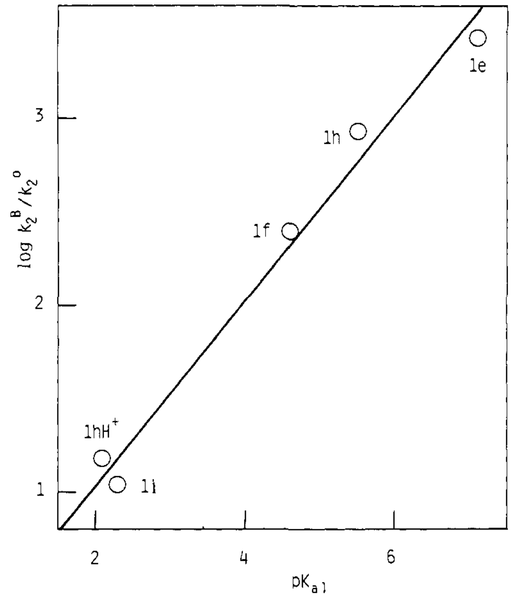
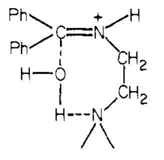


Figure 7. Correlation of the magnitudes of rate enhancement induced by internal general bases with their pK_a values.

Consequently, the k_i terms are essentially due to the water reaction of $1H^+$ carrying an internal base group. Positive deviations found in the correlation of Figure 5 are consistent with an internal general-base catalysis of nucleophilic attack by water as found previously with internal carboxylate ions.[7] Hine et al.[26–31] have found that the reverse reaction, dehydration of the carbinolamine to form an iminium ion, is effectively catalyzed by an internal general acid (a protonated tertiary amine group) in the Schiff base formation from ω-dimethylamino alkylamines.



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Buffer dependence data are informative. The water reaction of the hydrolysis of simple Schiff bases **1a–d** is subject to general-base catalysis. However, any significant buffer effects have not been observed in the intermediate plateau region of the pH-rate curves for **1e,f,h,i**. *Intramolecular* participation of the base group may be stronger than the *intermolecular* catalysis by the

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(20) There are three mono- and diprotonated species of **1h**. A similar modification was necessary to calculate k_2' value for **1hH**$^+$.

(21) The deviations correspond to the values $\bar{k}_2/k_2^0$ and $\bar{k}_1'/k_1'^0$, where k_2^0 and $k_1'^0$ are those expected for a simple Schiff base of the same pK_a.

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external general base. By contrast, the hydrolyses of **1g,j** were accelerated by added buffers in the plateau region where the k_i term makes a major contribution to the rate. Points for these Schiff bases fall closely on the correlation line for the water reaction in Figure 5. Schiff bases **1g,j**, whose internal base group is separated from the reaction center by the insertion of an additional methylene group, hardly undergo the intramolecular general-base-catalyzed water reaction and instead are subject to catalysis by external general bases.

The apparent rate constant $\bar{k}_2$ for the water reaction involving internal catalysis would be the sum of the rate constant appropriate for the pK_{a2} (k_2^0) for the uncatalyzed reaction and that for intramolecular general-base-catalyzed reaction (k_2^B). The deviations observed are described by eq 14. The logarithms of k_2^B/k_2^0 are

$$\bar{k}_2/\bar{k}_2^0 = 1 + k_2^B/k_2^0 \qquad (14)$$

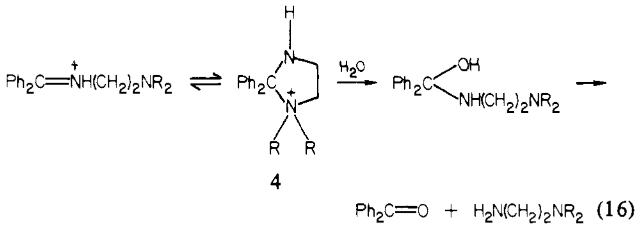
linearly correlated with pK_{a1} (basicity of the internal catalyst) in Figure 7 (slope $\beta = 0.49$). All the catalytic sites concerned are separated four bonds from the reaction center, the reaction proceeding through a transition state of a 7-membered ring such as **3**, and therefore a steric factor may not be so influential on the catalytic efficiency. The correlation of Figure 7 lends further support for the mechanism involving intramolecular general-base catalysis.

Although intermolecular general-base catalysis of the water reaction of **1** was not studied extensively, rate constants for H_2O (k_1) and phosphate (k_{phos}) given in Table I enables us to estimate the Brønsted coefficient β at about 0.3. This value is comparable to the Brønsted β of 0.27 previously observed for general-base-catalyzed attack of water on the cationic Schiff base, benzhydrylidenedimethylammonium ion.[32] The β values of 0.36–0.45 were observed with Schiff bases derived from cyclohexene-1-carboxaldehyde[7] and 3-methyl-2-cyclohexenone.[33] The estimated Brønsted β value may be used to estimate the effective concentration of the catalytic amino group resulting from the forced proximity to the reaction center. The rate enhancement due to the internal catalysis, k_2^B/k_2^0, should be compared with the *intermolecular* catalytic constant for a general base of the pK_{a1} (pK_a of the internal catalyst) relative to the rate constant for the water catalysis, k_B^0/k_2^0. The latter value was derived from eq 15, where the estimated Brønsted β value (0.3) and pK_a of

$$k_B^0/k_2^0 = 10^{0.3(pK_{a1}+1.7)}/55 \qquad (15)$$

hydronium ion (−1.7) were used. Effective concentrations, k_2^B/k_B^0, so calculated are summarized in Table IV. The effective concentrations ranging from 340 to 40 M for internal bases of pK_a = 7.1–2.1 may be comparable to the value of 30 M previously obtained for the internal carboxylate ion of $pK_a \simeq 2.35$.[7] The negligible internal catalysis found for **1g,j** would not be unexpected. The efficiency of internal catalysis is diminished by the insertion of an additional methylene group between the internal base and the reaction center, by a factor of 100–150 for ketonic derivatives,[26,29] while the factor is only 8–30 for aldehydic derivatives.[7,28,29] Less reactive ketonic compounds may be more susceptible to general catalysis.

Although intramolecular general-base catalysis of the water reaction seems to conform with all the observations, an alternate explanation for the enhanced reactivities of **1e,f,h,i** must be considered. A reaction occurring through a 1,3-imidazolidinium intermediate **4** with nucleophilic participation of the internal base group would not be improbable. The hydrolysis of some imidazolidine derivatives has recently been investigated kinetically and it was concluded that the hydrolysis proceeds through the intermediate formation of an iminium ion **5** and the hydrolytic decay of the latter is rate determining.[34,35] Intramolecular general-base catalysis was suggested to occur in this hydrolysis of the cationic Schiff base intermediate.[35] Therefore, the hydrolysis of the Schiff bases **1e–j** which are structurally similar to the intermediate iminium ion **5** cannot involve the imidazolidinium ion **4** as a mechanistically significant intermediate. The intramolecular nucleophilic acceleration by the internal amino group in the hydrolysis of **1e,f,h,i** should be ruled out. In conclusion, the intramolecular general-base catalysis by the tertiary amino group is most likely responsible for the enhanced reactivities of **1e,f,h,i** in the attack of water on the protonated Schiff bases.



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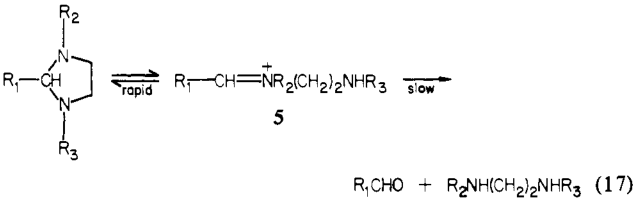

(17)

Acknowledgment. We thank H. Matsuda for experimental work with **1c** and **d**.

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