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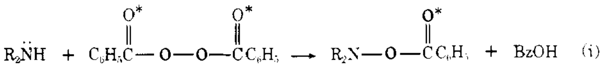

$$R_2\ddot{N}H + C_6H_5\overset{\overset{O^*}{\|}}{C}—O—O—\overset{\overset{O^*}{\|}}{C}C_6H_5 \longrightarrow R_2N—O—\overset{\overset{O^*}{\|}}{C}C_6H_5 + BzOH \quad \text{(i)}$$

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The Effect of Solvent on Intramolecular General Base Catalysis in the Hydrolysis of α,β-Unsaturated Schiff Bases

Ralph M. Pollack,* Robert H. Kayser, and James R. Damewood, Jr.

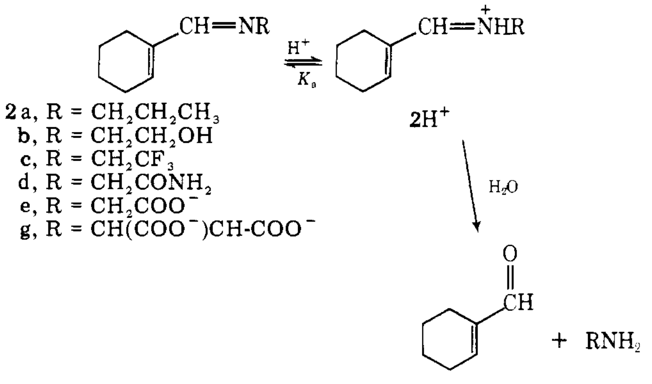
Contribution from the Laboratory for Chemical Dynamics, Department of Chemistry, University of Maryland Baltimore County, Baltimore, Maryland 21228.

Received April 14, 1977

Abstract: The hydrolytic reactions of a series of Schiff bases (**2a–g**) derived from cyclohexene-1-carboxaldehyde were examined in 50% (v/v) aqueous dioxane. The rate constants for water attack on the protonated Schiff bases ($k_1^{H_2O}$) showed relatively small rate enhancements (3- to 12-fold) over the corresponding rate constants in water, while accelerations in the rate constants for the acetate-catalyzed attack of water were somewhat larger (17- to 50-fold). A linear correlation of log $k_1^{H_2O}$ with Schiff base pK_a in 50% dioxane (slope = −0.95 ± 0.08) revealed that the rates of water attack for Schiff bases derived from glycine (**2e**) and aspartic acid (**2g**) were $>10^3$-fold larger than predicted, owing to intramolecular general base catalysis by internal carboxylate groups. Analogous to results obtained in purely aqueous solution, carbinolamine breakdown occurs through both zwitterionic and protonated carbinolamine intermediates in aqueous dioxane. The effect of decreased solvent polarity on the various rate constants reflecting rate-limiting carbinolamine breakdown was investigated and it was found that the breakdown of the protonated carbinolamine is also enhanced by the internal base in **2e**.

Introduction

Previous work has suggested that the hydrolytic reactions of Schiff bases are accelerated in aqueous dioxane solvents relative to water, despite the fact that the concentration of water is decreased.[1] In addition to modest increases in the uncatalyzed attack of water, the general base catalyzed process shows large rate enhancements in dioxane-water mixtures. In a preceding paper[2] we investigated the hydrolysis of a series of α,β-unsaturated Schiff bases (**2**) in water with a variety of imino substituents. The efficient intramolecular general base catalysis observed for **2e** and **2g** in water prompted us to examine the possible enhancement of such catalysis in less polar solvents, analogous to the acceleration observed for the intermolecular process.



2a, R = $CH_2CH_2CH_3$
b, R = CH_2CH_2OH
c, R = CH_2CF_3
d, R = CH_2CONH_2
e, R = CH_2COO^-
g, R = $CH(COO^-)CH\text{-}COO^-$

1

Results

The hydrolysis of the α,β-unsaturated Schiff bases **2a–g** was studied in 50% aqueous dioxane at 25.0 °C (μ = 0.5 with KCl). The reaction was followed spectrophotometrically at 260 (low

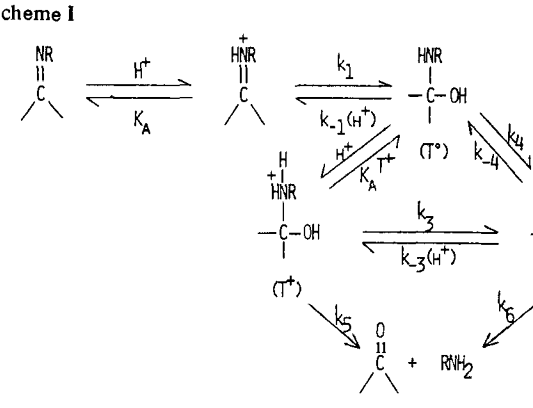
Table I. Kinetic Parameters for Rate-Determining Nucleophilic Attack for the Hydrolysis of **2** in 50% (v/v) Aqueous Dioxane[a]

Schiff base	pK_a[b]	$10^2k_1^{H_2O}$, s^{-1}	$10^{-4}k_1^{OH^-}$, $M^{-1}\,s^{-1}$[c]	$k_1^{AcO^-}$, $M^{-1}\,s^{-1}$
2a	6.98 ± 0.02	0.054 ± 0.003	0.996 ± 0.040	0.037 ± 0.002
2b	6.70 ± 0.02	0.182 ± 0.005	4.78 ± 0.09	0.090 ± 0.004
2c	2.76 ± 0.03	670 ± 50	356 ± 53	~110
2d	4.97 ± 0.02	13.7 ± 0.5	21.9 ± 0.4	2.5 ± 0.2
2e	7.31 ± 0.02	45.0 ± 3.0	1.59 ± 0.27	
2g	7.54 ± 0.02	34.1 ± 1.5	0.676 ± 0.015	

[a] At 25 °C and ionic strength 0.50 (KCl); all errors are standard deviations. [b] Determined spectrophotometrically using the corrected pH (see Experimental Section). ($K_a = [\mathbf{2}][H^+]/[\mathbf{2}H^+]$). [c] Calculated using a value of 2.7×10^{-15} M^{-2} for the stoichiometric ionization constant for water in 50% (v/v) aqueous dioxane (see Experimental Section).

pH) or 230-235 nm (high pH), and gave excellent first-order kinetics in all cases. The kinetics of the hydrolysis of **2a-g** in 50% dioxane are quite similar to what was previously[2] observed in purely aqueous solution and the results may be interpreted in terms of the same mechanism (Scheme I). This mechanism is analogous to the scheme proposed by Sayer and Jencks[3,4] in their analysis of Schiff base formation.

Scheme I



The observed rate constants, extrapolated to zero buffer concentration (k^0_{obsd}), are plotted vs. pH in Figure 1. Values of pH (= −log [H+]) were determined by subtracting 0.18 from the pH meter reading, as described in the Experimental Section. The dependence of the rate on pH suggests that at moderate to high pH (>5 to 7, depending on the Schiff base), nucleophilic attack on the protonated Schiff base ($\mathbf{2}H^+$) is rate determining and the observed rate constants in this region are described by

$$k_{obsd} = (k_1^{H_2O} + k_1^{OH^-}[OH^-] + k_1^{cat}[B])\left(\frac{[H^+]}{[H^+] + K_a}\right) \tag{1}$$

In this equation, $k_1^{H_2O}$ and $k_1^{OH^-}$ are assigned to the rate constants for water and hydroxide in attack on $\mathbf{2}H^+$, while k_1^{cat} is the rate constant for general-base-catalyzed attack of water, and K_a is the dissociation constant of $\mathbf{2}H^+$ under the experimental.conditions. The kinetic parameters of eq 1 for **2a-g** are summarized in Table I. The rate constants for water attack ($k_1^{H_2O}$) and the catalytic constants ($k_1^{AcO^-}$) are independent of the pH meter correction necessitated in aqueous dioxane. In contrast, the absolute values of pK_a are directly dependent on the pH correction, and values of $k_1^{OH^-}$ depend on the autoprotolysis constants of water in the mixed solvent in addition to the correction needed for hydrogen ion concentration. However, the *relative* values of $k_1^{OH^-}$ and pK_a are not affected by the magnitude of these corrections in dioxane-water.

The breaks in the pH-rate profiles that occur below pH 5-7 (Figure 1) reflect the expected[5] change in rate-determining step from formation to breakdown of a carbinolamine intermediate (T°) according to Scheme II. The data below pH 5-7 were analyzed in the manner previously[2] described for the same reaction in aqueous solution. The rate constants were extrapolated to zero buffer concentration to give values of the rate constant in the absence of buffer (k^0_{obsd}). These rate constants were then expressed in terms of the steady state equation

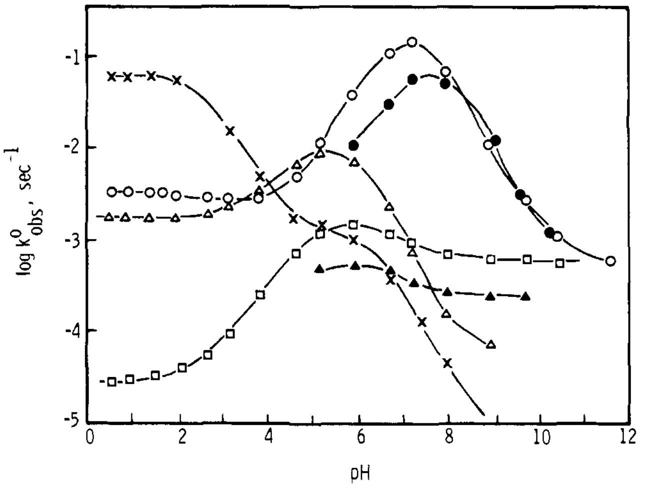


Figure 1. The pH-rate profiles for the hydrolysis of **2a** (▲), **2b**, (□), **2c** (x), **2d** (△), **2e** (○), and **2g** (●), corrected for buffer catalysis in 50% (v/v) aqueous dioxane at 25 °C (μ = 0.5). The theoretical curves were calculated using eq 1-3 from the constants in Tables I and II. The curves for **2e** and **2g** are theoretical only above pH 3 and 8, respectively.

Scheme II

$$\mathbf{2} \underset{K_a}{\overset{H^+}{\rightleftharpoons}} \mathbf{2}H^+ \underset{k_{-1}[H^+]}{\overset{k_1}{\rightleftharpoons}} T° \xrightarrow{k_2°} \mathbf{1} + RNH_2$$

$$k^0_{obsd} = \frac{K_1 k_2^0 k_1^0}{k_1^0[H^+] + K_1 k_2^0}\left(\frac{[H^+]}{[H^+] + K_a}\right) \tag{2}$$

where $k_1^0 = k_1^{H_2O} + k_1^{OH^-}[OH^-]$, and the equilibrium constant for carbinolamine formation from $\mathbf{2}H^+$ (i.e., $[T°][H^+]/[\mathbf{2}H^+]$) is given as $K_1 = k_1/k_{-1}$.

Substituting values of k_1^0 measured at higher pH (where carbinolamine formation is rate determining) into eq 2 allowed $K_1k_2^0$ to be calculated in the low to moderate pH range. Plots of $K_1k_2^0$ vs. hydrogen ion concentration are nonlinear for **2b** and **2d**, consistent with the mechanism of Scheme I. The variation of $K_1k_2^0$ with hydrogen ion concentration was then analyzed[2] using eq 3, which can be derived from the detailed mechanism for carbinolamine breakdown in Scheme I.

$$K_1k_2^0 = K_1\left[\frac{k_5[H^+]}{K_a^{T^+}} + \frac{k_6K_4(k_3[H^+]/K_a^{T^+} + k_4)}{k_6K_4 + (k_3[H^+]/K_a^{T^+} + k_4)}\right] \tag{3}$$

The kinetic parameters of eq 3 for **2b** and **2d** are summarized in Table II, and Figure 2 illustrates the fit of the experimental values of $K_1k_2^0$ to this equation for the hydrolysis of **2b** in the pH range 2.1-4.6. The curves in Figure 1 are the pH-rate profiles calculated from the parameters in Tables I and II using eq 1-3 and illustrate the excellent agreement with the experimental data over the entire pH range examined.

In contrast to the results with **2b** and **2d**, the values of $K_1k_2^0$ for **2c** were found to vary linearly with hydrogen ion concentration within experimental error. This result is not unexpected in view of the linearity of the same plot in water.[2] Furthermore, the results of Sayer[4] show that for Schiff bases derived from sufficiently weakly basic amines, the stability of T± is de-

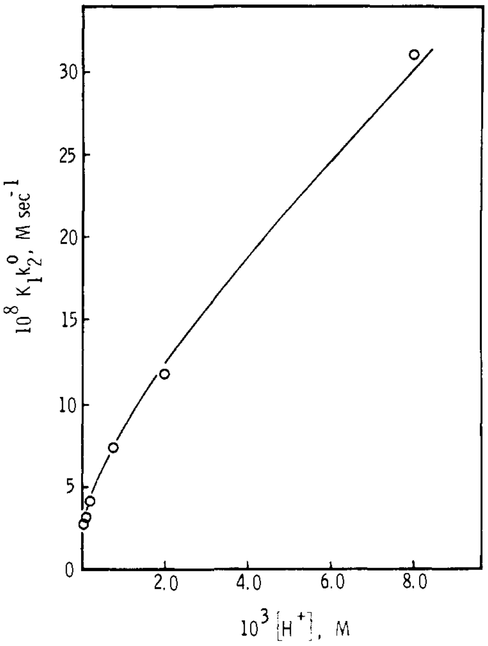


Figure 2. The dependence of $K_1k_2^0$, the rate constant reflecting rate-determining carbinolamine breakdown corrected for buffer catalysis, on hydrogen ion concentration for **2b** in the pH range 2.1-4.6. The theoretical curve was calculated using eq 3 and the parameters for **2b** in Table III.

creased to the point where the only significant routes for carbinolamine breakdown are through T$^+$ (k_5) at low pH, and through solvent-mediated isomerization of T° to T$^\pm$ (k_4) at moderate pH. Equation 3 then reduces to eq 4, allowing a determination of $K_1k_5/K_a^{T^+}$ and K_1k_4.

$$K_1k_2^0 = K_1\left[\frac{k_5[\mathrm{H}^+]}{K_a^{T^+}} + k_4\right] \tag{4}$$

The rate constants for **2e** could not be analyzed below pH 3 owing to protonation of the internal carboxylate group. From pH 3.4 to 7, however, a plot of $K_1k_2^0$ vs. [H$^+$] for **2e** showed no significant deviation from linearity. The linearity of this plot requires that eq 3 reduce to a simple two-parameter equation. A variety of limiting cases may be envisioned[4] which would account for this linearity, depending on the magnitudes of the ratios k_5/k_3 and k_6/k_{-4}. However, the slope will correspond to $K_1k_5/K_a^{T^+}$ in all cases, except the case when $k_6K_4 \gg (k_4 + k_3[\mathrm{H}^+]/K_a^{T^+})$. If this inequality holds, eq 3 will reduce to

$$K_1k_2^0 = K_1\left[\frac{(k_5 + k_3)[\mathrm{H}^+]}{K_a^{T^+}} + k_4\right] \tag{5}$$

However, the condition $k_6K_4 \gg (k_4 + k_3[\mathrm{H}^+]/K_a^{T^+})$ appears unreasonable for the following reason.[6] A limit for k_6/k_{-4} (i.e., k_6K_4/k_4) may be obtained from the observed variation of this ratio for **2b** and **2d** in 50% dioxane (Table II) and in water.[2] The values for k_6/k_{-4} decrease with increasing Schiff base pK_a in both solvent systems, indicating that this ratio for **2e** would be somewhat less than it is for **2b**, i.e., close to unity in 50% dioxane in the absence of any enhancement in k_6 or k_{-4} due to the internal base. Because there is no reasonable mechanism which would allow breakdown of T$^\pm$ to be subject to internal general base catalysis, no acceleration in k_6 due to the carboxylate group in **2e** is expected. Therefore, whether or not k_{-4} is enhanced by the carboxylate group of **2e**, k_6 should not be significantly larger than k_{-4} and we may assign the slope of the plot of $K_1k_2^0$ vs. [H$^+$] to $K_1k_5/K_a^{T^+}$ with some confidence.

Table II. Kinetic Parameters for Scheme I for Rate-Determining Breakdown of Carbinolamine in 50% (v/v) Aqueous Dioxane[a]

	Schiff base			
	2b	**2c**	**2d**	**2e**
$10^8K_1k_4$, M s^{-1}	4.2	210	21	
$10^7K_1K_4k_6$, M s^{-1}	0.86		12	≥0.52
$10^3K_1k_3/K_a^{T^+}$, s^{-1}	0.18 (1.8)		1.5 (2.7)	
$10^3K_1k_5/K_a^{T^+}$, s^{-1}	0.028 (4.1)	65 (3.8)	1.75 (2.7)	2.8

[a] Determined at 25 °C and ionic strength 0.5 (KCl). Numbers in parentheses correspond to the ratio of the rate constant in aqueous dioxane to the same constant in water.[2]

Table III. Comparison of the Rate Constants for the Hydrolysis of **2** in 50% (v/v) Aqueous Dioxane with Rate Constants Measured in Water[a]

Schiff base	$k_1^{\mathrm{H_2O}}(\mathrm{D})/k_1^{\mathrm{H_2O}}(\mathrm{W})$	$k_1^{\mathrm{AcO^-}}(\mathrm{D})/k_1^{\mathrm{AcO^-}}(\mathrm{W})$	pK_a(D) − pK_a(W)
2a	4.95	41.7	−1.36
2b	2.90	16.5	−0.79
2c	9.30	55	−1.60
2d	3.32	20.5	−0.84
2e	12.2		−0.26
2g	10.7		−0.10

[a] (D) denotes constants measured in 50% aqueous dioxane (Table I), (W) indicates constants determined in water (see Table I in ref 2).

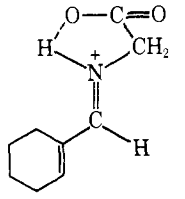
The intercept of the plot of $K_1k_2^0$ vs. [H$^+$] ($5.2 \pm 0.4 \times 10^{-8}$ M s^{-1}) for **2e** cannot be definitively assigned because of the possibility of internal catalysis enhancing K_1k_4. A similar type of intramolecular proton transfer has been postulated[4] to explain the enhanced rate of conversion of T$^\pm$ to T° in the formation of hydrazines from *p*-chlorobenzaldehyde. If K_1k_4 is increased such that $k_4 \gg k_6K_4$, then the intercept would correspond to $K_1K_4k_6$, while if no acceleration in K_1k_4 occurs, such that $k_4 \approx K_4k_6$, then the intercept would be the quantity $K_1K_4k_6k_4/(K_4k_6 + k_4)$. Consequently, all that can be said is that the intercept represents a lower limit for $K_1K_4k_6$.

Discussion

Solvent Effect on Schiff Base pK_a's. The effect of changing the solvent from water to 50% dioxane on the pK_a's of the iminium ions depends strongly on the nature of the R group on the nitrogen (Table III). For nonpolar R groups (**2a** and **2c**), the protonated Schiff bases are stronger acids relative to protonated solvent in dioxane-water than in pure water by about 30-fold, whereas those compounds with carboxylate ions (**2e**H$^+$ and **2g**H$^+$) show only a slightly greater tendency to dissociate in dioxane-water solutions than they do in water at the same concentration of acid. Compounds **2b** and **2d**, with hydroxyl and amide groups, respectively, behave in between the other two types, showing pK_a decreases of ca. 0.8 log units in 50% dioxane-water.

These results are similar to those previously observed with simple amines. As solvent polarity is decreased, the thermodynamic pK_a's of protonated amines generally decrease.[7,8] Marshall and Grunwald[9] found that the pK_a's of several protonated arylamines as well as ammonium ion and trimethylammonium ion are all 0.4-0.9 pK units lower in 45% dioxane-water solution than in water. In contrast, the thermodynamic pK_a of the ammonium group of glycine is reported[10a] to *increase* from a value of 9.6 in water to 10.2 in 45% dioxane. In addition the pK_a increase of the glycine carboxyl group in

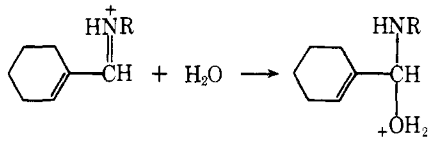
45% dioxane (from 2.35 in water to 3.1 in 45% dioxane)[10a] is significantly less than the corresponding pK_a increase for acetic acid (1.6 pK_a units).[10b] This suggests that electrostatic interactions in the glycine zwitterion become more important in dioxane–water mixtures and apparently stabilize both the ammonium and carboxylate ions. Similar intramolecular interactions in the zwitterions of **2e** and **2g** may account for the relatively small pK_a decreases observed in 50% dioxane. Hydrogen bonded structures such as **3** probably are more important in the stabilization of **2e** and **2g** in dioxane–water than in strictly aqueous solution.[11]



3

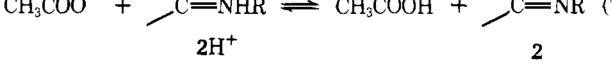
Further support for the importance of intramolecular interactions in aqueous dioxane is provided by the smaller decreases observed in the measured pK_a's of **2b** and **2d** compared to **2a** and **2c** (Table III). Both **2b** and **2d** should also be capable of stabilizing the positive change on the iminium ion in 50% dioxane by intramolecular hydrogen bonding via the alcohol and amide functional groups whereas such stabilization is not available for either **2a** or **2c**. The smaller effect of these two groups on the pK_a's of **2b** and **2d** relative to the effect of the carboxylate ions in **2e** and **2g** is expected due to their relative hydrogen bonding capabilities.

Rate-Determining Nucleophilic Attack. The rate constants for nucleophilic attack on $2H^+$ in 50% aqueous dioxane are compared to the kinetic parameters obtained for the corresponding hydrolysis in water in Table III. For Schiff bases **2a–d** the rate of water attack ($k_1^{H_2O}$) is greater by a factor of three- to ninefold in the mixed solvent, similar to the rate increase in 50% dioxane for the hydrolysis of 2,2,2-trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylamine (sixfold), and an analogous explanation appears reasonable.[1b] Formation of the transition state during the attack of water on $2H^+$ involves the transfer of a positive charge from a nitrogen to an oxygen (eq 6). Since the equilibrium constant for transfer of a proton from a protonated Schiff base to solvent increases as the percent dioxane increases, it might be expected that the rate of attack of water on $2H^+$ would also increase in dioxane-rich media. We have shown[1b] that changes in the Schiff base pK_a can adequately account for the rate constant variation in aqueous dioxane solutions for the hydrolysis of 2,2,2-trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylamine.



(6)

The rate constant for the general-base-catalyzed hydrolysis of **2a–d** shows a larger solvent effect than $k_1^{H_2O}$ (Table III). The catalytic constants for acetate in aqueous dioxane are 17- to 55-fold greater than the corresponding rate constants in water.[13] The greater enhancement of k_1^{cat} relative to $k_1^{H_2O}$ may be due to the destabilizing effect of the mixed solvent on the two ionic reactants involved in the acetate-catalyzed hydrolysis. An estimate of the *maximum* rate acceleration to be expected from this effect may be obtained by considering the solvent effect on a simple charge neutralization process (eq 7).



$$\mathrm{CH_3COO^-} + \underset{2H^+}{\mathrm{>C{=}\overset{+}{N}HR}} \rightleftharpoons \mathrm{CH_3COOH} + \underset{\mathbf{2}}{\mathrm{>C{=}NR}} \quad (7)$$

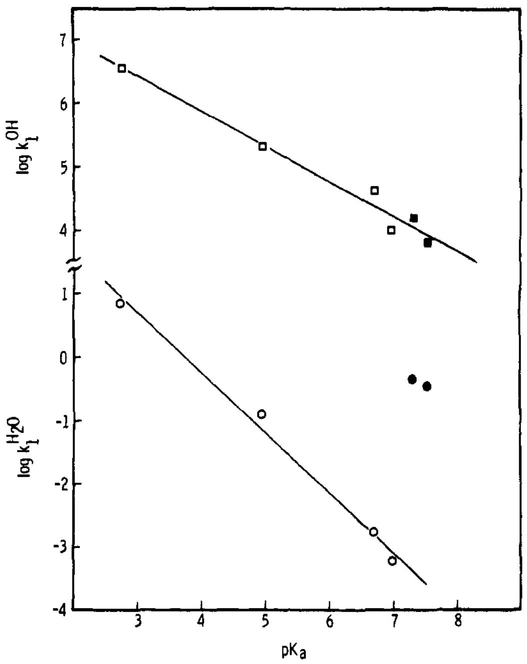


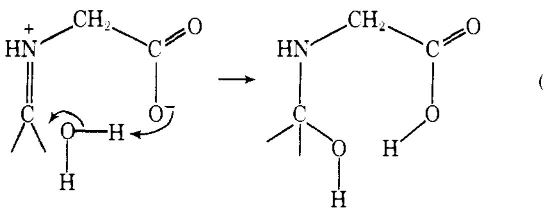
Figure 3. Correlations of the rate constants for water attack, $k_1^{H_2O}$ (○, slope = −0.96) and hydroxide ion attack, $k_1^{OH^-}$ (□, slope = −0.55) with Schiff base pK_a. Solid points (● and ■) are for Schiff bases with internal carboxylate groups (**2e** and **2g**).

The decrease in the Schiff base pK_a's in 50% dioxane, coupled with an increase in the pK_a of acetic acid ($\Delta pK_a = pK(D) - pK(W) = 1.46$),[14] increases the ratio $[CH_3COOH][\mathbf{2}]/[CH_3COO^-][2H^+]$ by 180- to 10^3-fold in the mixed solvent compared to water. The corresponding rate increase in k_1^{cat} (17- to 55-fold) is significantly less than the increase in the ratio $[CH_3COOH][\mathbf{2}]/[CH_3COO^-][2H^+]$ indicating that charge destruction in the transition state for the acetate-catalyzed hydrolysis of $2H^+$ is not complete. This conclusion is consistent with structure-reactivity correlations for k_1^{cat} in water (e.g., $\beta \simeq 0.4$)[2].

In order to evaluate the possibility of intramolecular catalysis of water attack by the carboxylate ions of **2e** and **2g** the rate constants for water and hydroxide ion attack on $2H^+$ in aqueous dioxane were plotted vs. the Schiff base pK_a in the mixed solvent (Figure 3). The correlation for $k_1^{H_2O}$ has a larger slope (-0.96 ± 0.08) than the one for $k_1^{OH^-}$ (-0.55 ± 0.05) similar to the slopes of analogous plots for $k_1^{H_2O}$ and $k_1^{OH^-}$ in water[2] and consistent with the concept that the transition state for water attack is reached later than that for attack by hydroxide ion.[15] While $k_1^{OH^-}$ for **2e** and **2g** lie close to the line described by the other Schiff bases, the values of $k_1^{H_2O}$ for **2e** and **2g** both show large positive deviations ($>10^3$-fold) from the correlation for $k_1^{H_2O}$ in Figure 3. Because the internal carboxylate groups of **2e** and **2g** appear to enhance $k_1^{H_2O}$, but not $k_1^{OH^-}$, the positive deviations of $k_1^{H_2O}$ in Figure 3 may be ascribed to intramolecular general base catalysis by the internal bases.[16]

Although the hydrolysis of **2e** and **2g** in water also involves intramolecular catalysis,[2] the enhancement of $k_1^{H_2O}$ for **2e** and **2g** in water is only about 60-fold, much less than the acceleration of 10^3-fold seen in aqueous dioxane. Intramolecular catalysis by the anionic carboxylate group results in charge destruction in the transition state (eq 8), and lowering the solvent polarity should cause a significant rate increase in this process, analogous to the effect in the intermolecular process.

The presence of the second carboxylate group in **2g** does not appear to cause any additional increase in the rate of water attack on the iminium ion in aqueous dioxane. The positive deviation for **2g** from the correlation for $k_1^{H_2O}$ (Figure 3) is



(8)

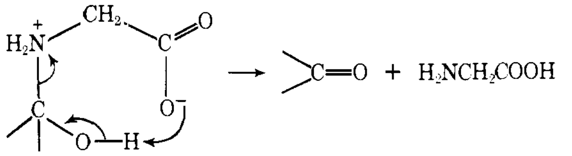
about the same as for **2e**. The relatively inefficient catalysis by a carboxylate group separated from the imino linkage by two carbon atoms was also observed for the hydrolysis of Schiff bases in water.[2] This result is analogous to a similar effect reported by Hine et al.[17] for internal catalysis by protonated amine groups in Schiff base formation.

Carbinolamine Breakdown. The breakdown of carbinolamine intermediates to the corresponding amine and carbonyl compound is a complex process. Several different pathways are available for this reaction (Scheme I).[3,4] The neutral carbinolamine (T°) may decompose to products through either a positively charged intermediate (T^+) or a dipolar ion ($T^\pm$). Depending on the reaction conditions, either formation or breakdown of these intermediates may be rate determining.

Values of combinations of several of these parameters could be obtained for **2b–e** and these are given in Table II, along with the ratios of the rate constants in aqueous dioxane to the same constants in water. The trends observed for these constants are similar to the ones in water; all pathways show a rate increase as the acidity of the protonated Schiff base is increased.

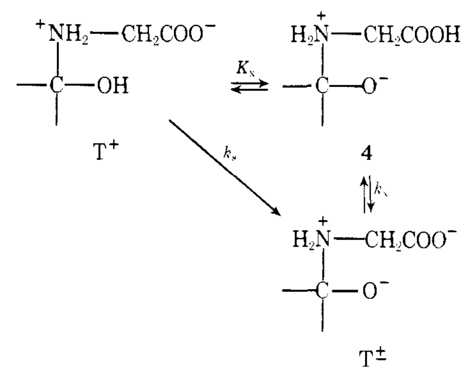
The effect of solvent variation can be determined for the quantities $k_1k_3/K_a{}^{T^+}$ and $K_1k_5/K_a{}^{T^+}$ since these constants are independent of the absolute value of pH. Small increases (two- to fourfold) are observed in $K_1k_3/K_a{}^{T^+}$ and $K_1k_5/K_a{}^{T^+}$ for **2b–d** in 50% dioxane. It is not possible to make a meaningful comparison of the rate ratios which reflect rate-determining formation and breakdown of $T^\pm$ (K_1k_4 and $K_1K_4k_6$) in the two solvent systems since they are pH dependent and the pH scales in water and 50% dioxane are not directly comparable.[7]

The effect of the carboxylate group of **2e** on the rate of carbinolamine breakdown can be determined for the pathway through T^+. A comparison of the values of $K_1k_5/K_a{}^{T^+}$ for **2b** ($pK_a = 6.70$) and for **2e** ($pK_a = 7.31$) should give a minimum estimate of the catalytic effect of this group since the trend in $K_1k_5/K_a{}^{T^+}$ is toward lower values as the Schiff base pK_a increases for compounds *without* internal carboxyl groups (Table II). The observed increase of 100-fold for **2e** compared to **2b** suggests that breakdown of the protonated carbinolamine (T^+) to products *is* subject to internal catalysis. Since the ratio $K_1/K_a{}^{T^+}$ is almost certainly similar for **2e** and **2b**, this rate increase is probably due to an effect of the carboxylate group on the magnitude of k_5. Breakdown of T^+ to products involves rate-determining proton transfer and is catalyzed by external bases. Therefore, intramolecular general base catalysis may be envisioned to proceed through the process of eq 9.



(9)

It is not possible to determine definitively if the k_3 process is subject to internal catalysis by the carboxylate group of **2e**. However, although conversion of T^+ to $T^\pm$ is catalyzed by external bases, internal catalysis of this step for **2e** is not expected to be any more efficient than the solvent-catalyzed reaction. Unlike an external catalyst, the internal carboxyl group is not free to diffuse away to form $T^\pm$. Instead, the internal base must first remove the proton from T^+ and then transfer this proton to the solvent[18] (eq 10).



(10)

Although the carboxyl group of **2e** could act as a catalyst to produce **4**, which could then deprotonate to give $T^\pm$, it can be readily calculated that the overall rate of this process is identical with the rate of solvent-mediated conversion of T^+ to $T^\pm$. Direct conversion of T^+ to $T^\pm$ would occur at a rate controlled by the difference in the pK_a's of the hydroxyl group of T^+ (pK_{OH}) and protonated solvent (pK_{SH^+}) according to[19]

$$\log k_s \approx 10 - (pK_{OH} - pK_{SH^+}) \qquad (11)$$

The rate constant for conversion of T^+ to $T^\pm$ through **4** (k_c) is given by

$$\log k_c = \log k_x + \log K_x \qquad (12)$$

Substituting values of $\log k_x$ ($\approx 10 - pK_{COOH} + pK_{SH^+}$) and $\log K_x$ ($= pK_{COOH} - pK_{OH}$) into eq 12 gives the equivalent of eq 11 again, showing that this process should not increase the overall rate for conversion of T^+ to $T^\pm$.

Summary

Intramolecular general base catalysis of Schiff base hydrolysis by carboxylate ions in relatively nonpolar solvents (e.g., 50% dioxane) is very efficient. Both formation of the carbinolamine intermediate and its breakdown through T^+ are accelerated. An estimate of the magnitude of the combined effects of intramolecular catalysis and solvent variation may be obtained by comparing the rates of reaction for **2e** in 50% dioxane and **2b** in water. These compounds have similar basicity in water ($pK_a{}^{2e} = 7.57$, $pK_a{}^{2b} = 7.49$),[2] but only **2e** has an internal carboxylate ion. The rate constant for water attack on **2e**H^+ in 50% dioxane ($0.45\ s^{-1}$) is ca. 700-fold greater than it is for **2b**H^+ in water ($6.3 \times 10^{-4}\ s^{-1}$). A similar comparison of the rates of carbinolamine breakdown through the protonated intermediate (T^+) shows a rate enhancement of ca. 400-fold for **2e** in aqueous dioxane relative to **2b** in water.

It is possible that enzymes which function through Schiff base intermediates may utilize the combination of an apolar active site and a carboxylate ion acting as a general base to facilitate the formation and hydrolysis of these compounds. Although formation and hydrolysis of Schiff bases are usually rapid, model systems often cannot interconvert Schiff bases and carbonyl compounds rapidly enough to account for enzymatic rates.[20] This problem is particularly acute when Schiff bases of α,β-unsaturated ketones are involved owing to their relatively slow rates of hydrolysis.[21] In this regard, it appears that this type of catalysis could be further enhanced by decreasing the solvent polarity even more. Even though the initial reactants are ionic (protonated Schiff base and internal carboxylate ion), a lowered solvent polarity does not appreciably alter the ΔpK_a between these groups in **2e**. Consequently it would be expected that these groups would still exist in the ionic forms, even in solvents of very low ionizing power.

Experimental Section

Materials. The Schiff bases of 1-cyclohexene-1-carboxaldehyde (**2a–g**) were available from previous work.[2] Chloroacetic acid and potassium acetate were reagent grade and used without purification. Triethanolamine and trimethylamine were purified by recrystallization of their hydrochloride salts from ethanol-water and chloroform, respectively. Dioxane was purified by refluxing over sodium and distilling, followed by fractional distillation. Tests for peroxides (2% KI) using freshly distilled dioxane were negative, but after storage for a number of weeks, further tests did indicate the presence of some peroxides. However, rates of hydrolysis were found to be the same in buffered solutions prepared from either freshly distilled or aged dioxane.[22]

Kinetic Methods. All kinetic measurements were carried out as previously described[2] at 25.0 ± 0.2 °C and at ionic strength 0.50 maintained with potassium chloride. All solutions were 50% aqueous dioxane by volume (mole fraction of dioxane = 0.174) obtained by mixing equal volumes of water and dioxane. In order to keep the pH constant, buffered solutions were prepared using HCl, chloroacetate, acetate, triethanolamine, trimethylamine, and KOH. The total buffer concentrations did not exceed 0.10 M, except for solutions of 0.25 M HCl.

Linear buffer plots were extrapolated to zero buffer concentration by a weighted least-squares analysis. Curved buffer plots were extrapolated to zero buffer concentration using observed rate constants obtained at low buffer concentrations (≤ 0.03 M). The errors introduced by this empirical extrapolation were only significant in the pH region where the hydrolysis undergoes a change in rate-determining step from breakdown to formation of the carbinolamine intermediate. However, the rate constants (k_1^0 and $K_1k_2^0$, see eq 2) were calculated without using the data in this pH range and were found to be consistent with extrapolated rates in the pH region in question. Rate constants for water ($k_1^{H_2O}$) and hydroxide ion attack ($k_1^{OH^-}$) and catalytic constants (k_1^{cat}) were obtained using eq 1 as previously described.[2] Values of $K_1k_2^0$ were obtained from eq 2 using observed rates extrapolated to zero buffer concentration and known values of k_1^0 as previously outlined.[2]

Dissociation constants for the protonated Schiff bases (K_a) were determined in 50% aqueous dioxane by the procedure already described[2] using values of hydrogen ion concentration calculated as shown below.

pH Measurements. Hydrogen ion concentration in aqueous dioxane was measured with a Corning 112 pH meter equipped with a combination glass electrode calibrated at pH 7 and either pH 4 or 10 with aqueous standards. pH meter readings (B) in aqueous dioxane were converted to $-\log [H^+]$ using the equation[24a] $-\log [H^+] = B + \log U_H$. The correction term $\log U_H$ was calculated[24b] from measured values of B for 0.25 to 0.002 M HCl in dioxane-water (ionic strength maintained at 0.5 with KCl). Log U_H was essentially constant over this acid concentration range ($\log U_H = -0.18 \pm 0.02$). Therefore at 25 °C, $-\log [H^+] = B - 0.18$ for 50% (v/v) dioxane-water at ionic strength 0.5. Results presented are expressed in terms of pH determined in this manner with the realization that $-\log [H^+]$ is actually pC_H in accordance with IUPAC recommendations.[25] Hydroxide ion concentration was calculated from the pH (as defined above) using the stoichiometric ionization constant for water ($K_w = 2.7 \times 10^{-15}$) in the mixed solvent. This value of K_w was calculated from pH meter readings (B) of 0.005–0.05 N KOH (ionic strength maintained at 0.5 with KCl), using the equation $pK_w = B + \log U_H - \log [OH^-]$ and the known stoichiometric concentrations of KOH.

Acknowledgment. This work was supported by Grant GM20188 from the National Institutes of Health. We wish to thank Professors W. P. Jencks and E. Grunwald for helpful comments.

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