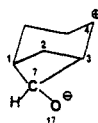


Table V. Calculated *ab Initio* Electronic Charges for CONII Axial and Equatorial 3-Cyclohexene-1-carboxaldehydes 2 and 3

atom	atom	electronic charges	
		equatorial	axial
3	C (sp <sup>2</sup> )	6.20771	6.19140
4	C (sp <sup>2</sup> )	6.20296	6.20051
7	C (sp <sup>2</sup> )	5.60850	5.60905
17	O	8.51863	8.51290

ment with MM2. Moreover, if there were a substantial overlap between the aldehyde and double bond moieties, contributing to a reduction in energy, we would expect to find this reflected in the gross orbital charges for the charge on the pertinent atoms. Specifically, resonance as shown should lead to a decrease in the electronic charge on atom 4, and an increase on atom 17 (oxygen) in the axial conformation. As indicated in Table V, the charges are essentially the same for the axial and equatorial isomers. Carbon 4 does lose a small amount of charge, but so does oxygen.



## Conclusion

MMP2 force field calculations have been carried out on several carbonyl-substituted 3-cyclohexene compounds in order to determine the quantitative results for the proposed supra annular effect. When nonbonded overlap between the alkene and axial carbonyl carbons was included in the SCF routine of the MMP2 energy minimization process, we obtained a small energy reduction of 1-2 cal/mol. When this overlap was included for the corresponding equatorial isomer, there was no energy change. Clearly, this small energy stabilization is too small to force the aldehyde substituent to adopt an axial conformation and influence the equilibrium position. GAUSSIAN 80 calculations confirm our MMP2 results. Moreover, our studies indicate that there is a preference for the aldehyde group to be equatorial, not axial. One might try to explain the reduction of reactivity for the alkene and carbonyl functionalities in various ways. However, we conclude that any explanation which requires a supra annular resonance effect to yield a ground state conformational change cannot be correct.

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**Registry No.** 2, 100-50-5; 5, 36635-34-4; 7, 36635-33-3; 9, 873-30-3; 11, 766-48-3.

## Nucleophilic Catalysis of Hydrolysis of a Schiff Base by Amines. Intramolecular Catalysis of Transimination

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Certain groups of amines were found to catalyze hydrolysis of *N*-(*o*-methoxybenzylidene)-2-methoxyethylamine through transimination. The rate-determining transimination was followed by rapid hydrolysis of an intermediate Schiff base. Rate constants for the transimination with simple, but less basic, amines change sigmoidally with pH and are buffer-dependent in accord with a mechanism involving a trapping of the incipient tetrahedral intermediate T<sub>1</sub><sup>+</sup> by a proton transfer to acids or bases. Morpholine behaved similarly. In the reaction with bifunctional amines carrying an internal amino group, rates are independent of both pH and buffer concentrations. Initial nucleophilic attack of these amines is rate determining in the whole pH range examined because of the rapid trapping of T<sub>1</sub><sup>+</sup> by an intramolecular proton transfer.

Schiff bases are important intermediates involved in many enzymic transformations.<sup>1</sup> Mechanisms of formation and hydrolysis of these compounds have been investigated in great detail and are now understood very well.<sup>2</sup> Transimination (interconversion among Schiff bases) is also a key step of biological reactions involving, e.g., pyridoxal 5'-phosphate dependent enzymes.<sup>3</sup> However, because of the close similarities of the absorption spectra of the reactants and products of this reaction, investigations using model systems pertinent to the enzyme seem to be limited.<sup>3,4</sup> Nucleophilic catalysis of Schiff base formation of anilines<sup>5</sup> and secondary amines<sup>6</sup> is known as

a typical example of such catalysis and involves transimination as a rapid process.<sup>7</sup>

The hydrolysis must also be facilitated by certain amines as a microscopic reverse of the formation but no examples of the catalysis have so far been reported. Such catalysis is effective only when the transimination is rapid and the intermediate Schiff base is more readily hydrolyzed than the starting substrate. Since the hydrolysis of Schiff base was found to be catalyzed by an internal general base<sup>8-10</sup> and the transimination may also be facilitated by the internal base, amines carrying an appropriate base group can

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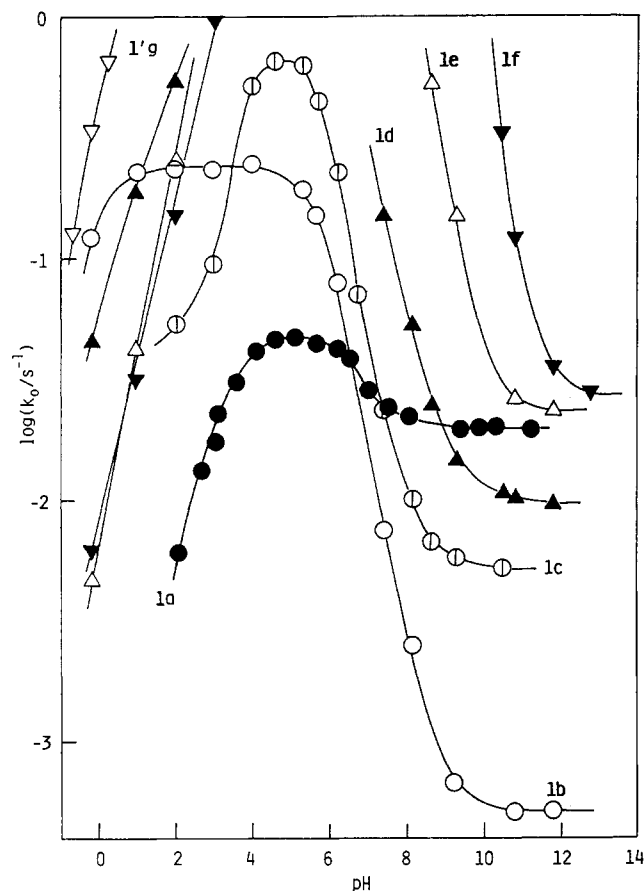
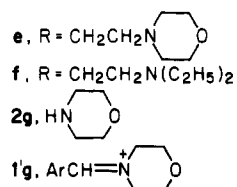
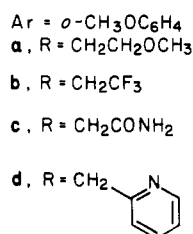
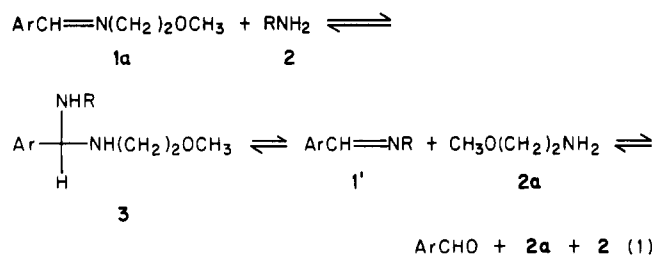


Figure 1. pH-Rate profiles for the hydrolysis of Schiff bases 1a (●), 1b (○), 1c (◇), 1d (▲), 1e (△), 1f (▼), and 1'g (▽).

be effective catalysts of the hydrolysis. This is now found to be the case, and the results are presented herein. Some simple primary and secondary amines were found to be also effective catalysts.

## Results

**Hydrolysis.** Hydrolysis of *N*-(*o*-methoxybenzylidene)-2-methoxyethylamine (1a) has been examined kinetically in the absence and presence of various amines 2 involving simple and bifunctional ones (eq 1). All



the reactions were carried out at 30 °C in aqueous solution at a constant ionic strength of 0.10 M maintained with KCl and were followed by a change in UV absorption. The spectrum of 1a has absorption maxima at 277 and 349 nm below pH 6.5 or at 250 and 306 nm above pH 7. When a

Table I. Catalytic Constants for the Hydrolysis of 1a<sup>a</sup>

base	pK <sub>BH</sub> <sup>+</sup> <sup>b</sup>	k <sub>B</sub> , M <sup>-1</sup> s <sup>-1</sup>
H <sub>2</sub> O	-1.7	8.8 × 10 <sup>-4</sup> <sup>c</sup>
ClCH <sub>2</sub> CO <sub>2</sub> <sup>-</sup>	2.80	8.4 × 10 <sup>-2</sup>
HCO <sub>2</sub> <sup>-</sup>	3.62	0.29
CH <sub>3</sub> CO <sub>2</sub> <sup>-</sup>	4.60	0.34
MES <sup>d</sup>	6.17	0.22
MM <sup>e</sup>	7.50	1.5
Me <sub>2</sub> N(CH <sub>2</sub> ) <sub>2</sub> OH	9.39	15

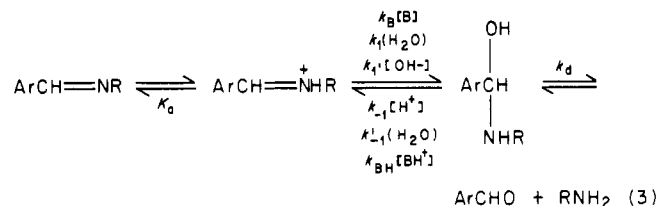
<sup>a</sup> Measured at 30 °C and ionic strength of 0.10 M. <sup>b</sup> pH of the 1:1 buffer solution. <sup>c</sup> k<sub>1</sub>/55 M. <sup>d</sup> 2-(*N*-Morpholino)ethanesulfonate. <sup>e</sup> *N*-Methylmorpholine.

small amount of 1a was added into an aqueous buffer solution, the absorption of *o*-methoxybenzaldehyde (4) (λ<sub>max</sub> 255 and 322 nm) developed at the expense of that of 1a. Isosbestic points were found at 234, 260, 298, and 329 nm in acid (pH < 6.5) and at 315 nm in alkaline solutions (pH > 7). UV spectral data are summarized in Table S1 (supplementary material).

The hydrolysis rates of 1a were first measured in usual buffer solutions of carboxylates and tertiary amines as well as HCl solutions in the pH range 2–11. Time-dependent absorbance changes observed at 280 (pH < 7) or 335 nm (pH > 7) obeyed pseudo-first-order kinetics over 4 half-lives. Buffer effects were observed below pH 10 (eq 2). Observed rate constants k<sub>obsd</sub> are summarized in Table S2 (supplementary material).

$$k_{\text{obsd}} = k_0 + k_B[\text{B}]_t \quad (2)$$

Logarithms of k<sub>0</sub> are plotted against pH in Figure 1. The pH-rate profile is typical of Schiff base hydrolysis and can be accommodated by a generally accepted mechanism given by eq 3.<sup>2</sup> The rate-determining step changes with



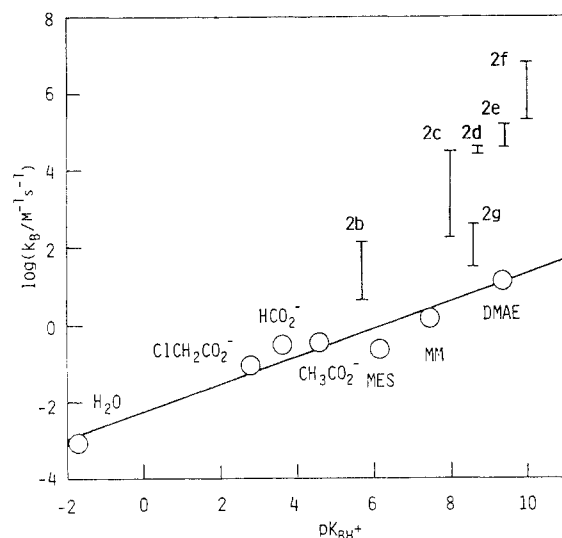
pH from formation (pH > 5) to decay (pH < 5) of an α-amino alcohol intermediate. The observed rate constants k<sub>obsd</sub> are described by eq 4. The solid curve in Figure 1

$$k_{\text{obsd}} = \left( \frac{k_1 + k_1'[\text{OH}^-] + k_B[\text{B}][\text{H}^+]}{K_a + [\text{H}^+]} \right) \left( \frac{k_d k_{-1}}{k_d/k_{-1} + [\text{H}^+]} \right) \quad (4)$$

is drawn with parameters: k<sub>1</sub> = 4.85 × 10<sup>-2</sup> s<sup>-1</sup>, k<sub>1</sub>' = 2.28 × 10<sup>5</sup> M<sup>-1</sup> s<sup>-1</sup>, K<sub>a</sub> = 1.69 × 10<sup>-7</sup> M (pK<sub>a</sub> = 6.77), and k<sub>d</sub>/k<sub>-1</sub> = 8.0 × 10<sup>-4</sup> M.

Schiff bases 1b–1f, which are possible intermediates of the amine-catalyzed hydrolysis of 1a, behave similarly in aqueous solution as examined by the UV method (UV spectral data are given in Table S1). Hydrolysis rates of these Schiff bases were measured in the same way as those of 1a, and are shown in Figure 1 (data given in Table S3). Reactions of 1d, 1e, and 1f in the intermediate pH region were too rapid to follow. The spectrum of the iminium ion 1'g is similar to that of 1 observed in acid solutions. It was hydrolyzed very rapidly and the reaction could be followed only in highly acidic solutions (Figure 1 and Table S3).

The catalytic constants k<sub>B</sub> for the hydrolysis of 1a are summarized in Table I, and plotted against pK<sub>BH</sub><sup>+</sup> of the conjugate acid of the catalytic base in Figure 2, which shows that the Brønsted β value is about 0.35. This value



**Figure 2.** Brønsted plot for general base catalysis of the hydrolysis of **1a**.

is comparable to those previously obtained. The  $\beta$  values reported were 0.36–0.45 for Schiff bases derived from cyclohexene-1-carbaldehyde<sup>8</sup> and 3-methyl-2-cyclohexenone,<sup>11</sup> and 0.27 for benzhydrylidenedimethylammonium ion.<sup>12</sup>

**Effects of Amines.** A very small amount of a primary or secondary amine (**2b–2g**) greatly accelerates the hydrolysis of **1a**. For example, bifunctional amines, **2e** and **2f**, showed more than twofold acceleration around pH 8 at a concentration as low as  $10^{-4}$  M. Spectral features of the reaction, however, seemed to be the same as those found in the absence of the amine although the initial part could not be followed precisely because of the rapidity of the reaction. An induction period or initial drop of the absorbance was hardly observed and pseudo-first-order kinetics were excellently obeyed with a few exceptions of runs at high concentration of the amine. That is, at low amine concentrations any sign of accumulation of intermediates was not found and the reaction proceeds catalytically. Effects of added **2a** were also examined at pH 6.1 and 7.5 (Table S2). Rate constants  $k_{\text{obsd}}$  were not changed by **2a** of  $\leq 0.01$  M within experimental uncertainties ( $\pm 1\%$ ) either in the absence or presence of catalytic amines ( $[2b]_t = 2 \times 10^{-3}$  M and  $[2e]_t = 10^{-4}$  M were used).

The first-order rate constants  $k_{\text{obsd}}$  usually increased linearly with amine concentration  $[2]_t$  (eq 5). In some runs

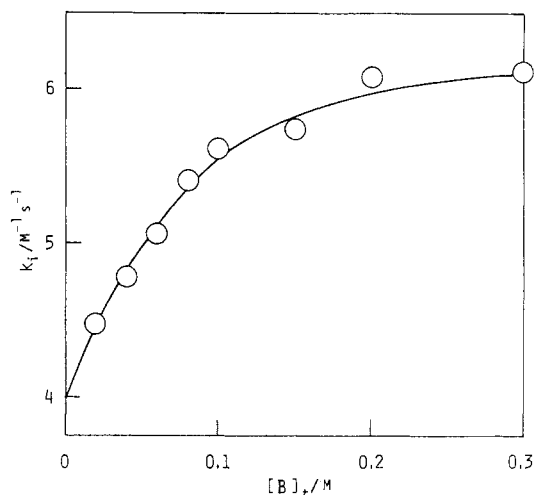
$$k_{\text{obsd}} = k_h + k_i[2]_t \quad (5)$$

at pH, where the intermediate Schiff base **1'** is hydrolyzed slowly,  $k_{\text{obsd}}$  leveled off at high  $[2]_t$ , but the second-order rate constants  $k_i$  were determined where the linearity held. That is, the rate increase induced by the amine ( $k_i[2]_t$ ) was limited to be smaller than  $1/10$  of the rate constant ( $k_h'$ ) for the hydrolysis of **1'**.

For the simple amines (**2b**, **2c**, and **2g**), the rate constants  $k_i$  are dependent on the concentration  $[B]_t$  of a second buffer used to maintain pH constant. This buffer dependence was usually linear as expressed by eq 6, but

$$k_i = k_a' + k_{ab}'[B]_t \quad (6)$$

at pH 8 with **2g** it leveled off with increasing concentration



**Figure 3.** Curved buffer dependence of the rate of the morpholine-catalyzed reaction of **1a** in *N*-methylmorpholine buffer solutions at pH 8.0.

of the buffer (Figure 3). In the case of bifunctional primary amines (**2d**, **2e**, and **2f**) carrying an internal tertiary amino group, however, the third-order term was very small (**2d**) or not observed within experimental errors, and  $k_{ab}'$  was taken to be zero. Rate constants  $k_a'$  and  $k_{ab}'$  were obtained by the least-squares treatments of data according to eq 5 and/or 6, and are summarized in Table II ( $k_{\text{obsd}}$  in Table S2). Standard deviations given are, however, only nominal to indicate the linearity because of limited number of the data.

## Discussion

**Amine Catalysis.** The amine-catalyzed hydrolysis of **1a** must take place through transimination (eq 1). Figure 1 shows that the intermediate Schiff bases **1'** are hydrolyzed more readily than **1a** in the pH range concerned. The less basic Schiff bases derived from 2,2,2-trifluoroethylamine (**2b**) and glycine (**2c**) are more reactive than **1a** at low pH where the reaction of the protonated Schiff base with water prevails,<sup>2</sup> but above pH 6.5 the hydrolysis becomes slow as the concentration of the reactive protonated species ( $1'H^+$ ) decreases. The cationic Schiff base **1'g**, which is derived from a secondary amine **2g** and cannot release a proton, is very reactive as compared with the initial Schiff base **1a** which is deprotonated at higher pH. Schiff bases with internal basic substituents are hydrolyzed very rapidly owing to the intramolecular catalysis<sup>8–10</sup> and are much more reactive than **1a** in almost the whole pH range. The amine **2a** did not show any catalysis of the hydrolysis.

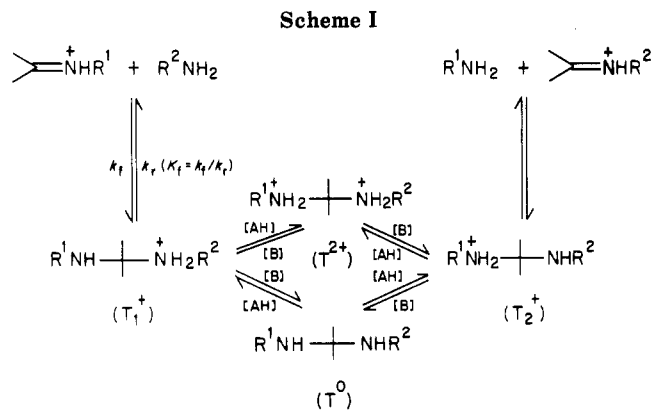
The reactions involved are simplified and schematically described by eq 7. In the pH range examined and the



limited concentration of the amine  $[2]_t$  used, the rate for the hydrolysis of **1'** is greater than that of **1a** ( $k_h' > k_h$ ) and the rate increase induced by the amine was limited to be smaller than  $1/10$  of the hydrolysis rate of **1'** ( $k_i[2]_t < k_h'/10$ ). Since  $[2a]_t$  is usually much lower than  $[2]_t$  and the rate constants for the forward and reverse transiminations may be on the same order of magnitude ( $k_1 \approx k_1'$ ),  $k_i'[2a]_t$  is much less than  $k_h'$ . This was confirmed by the observation that added **2a** does not affect the acceleration induced by the typical catalytic amines, **2b** and **2e**.

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If  $k_h' < k_i'[2a]_t$  and the transimination step were a rapid equilibrium, then added **2a** should have reduced  $k_{\text{obsd}}$  through the reduction in equilibrium concentration of the intermediate **1'**. The transimination step ( $k_i$ ) is rate determining for catalysis of the hydrolysis by the amine.

The amine-dependent rate constants  $k_a'$  (Table II) seem to show bell-shaped change with pH but the deviations are large from the bell composed of Schiff-base  $\text{p}K_a$  and amine  $\text{p}K_a$ . That is, the second-order rate constants  $k_a$  corrected for the fractions of the reactive species of transimination, protonated substrate **1aH<sup>+</sup>** and free amine base **2**, according to eq 8 are dependent on pH as summarized in

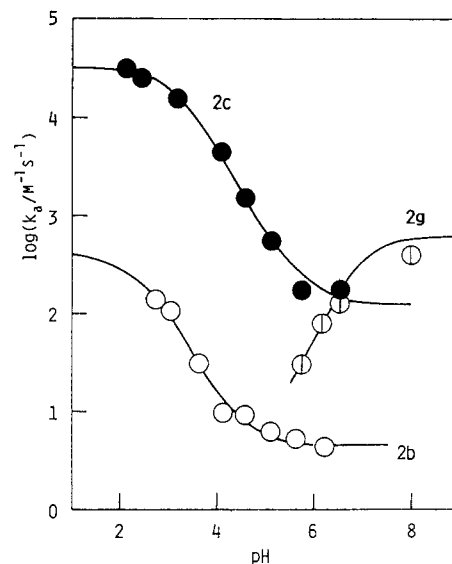
$$k_a = k_a' \left( \frac{K_a + [\text{H}^+]}{[\text{H}^+]} \right) \left( \frac{K_A + [\text{H}^+]}{K_A} \right) \quad (8)$$

$$k_a = k_a' \left( \frac{K_a + [\text{H}^+]}{[\text{H}^+]} \right) \left( \frac{K_A + [\text{H}^+] + [\text{H}^+]^2/K_{A1}}{K_A} \right) \quad (9)$$

Table II. Here, diprotonation of **2d** and **2e** does not influence the fraction of the free base in the pH range concerned, but that of **2f** occurs at moderately high pH ( $\text{p}K_{A1} = 7.07$ ).<sup>13</sup> To calculate  $k_a$  for the latter, diprotonation was considered (eq 9). The  $k_a$  values are  $10$ – $10^5$  times greater than those expected for simple general base catalysis according to the Brønsted relation (Figure 2), indicating that the amine catalysis observed is not due to the simple base catalysis. The amine **2a** did not show any appreciable effect on the rate at low concentrations. The buffer-dependent rate constants  $k_{ab}'$  are also corrected for the reactive species in the same way to give  $k_{ab}$  as listed in Table II.

**Transimination.** The amine-dependent rate constants  $k_a$  and  $k_{ab}$  refer to the transimination step. The observed pH dependence of  $k_a$  for the simple amines implies a change in rate-determining step occurring during the transimination. Transimination takes place through a stepwise mechanism involving the general acid-base catalyzed trapping of the incipient tetrahedral intermediate  $T_1^+$  by proton transfer according to Scheme I.<sup>3,14,15</sup> It was found that a proton transfer step that is immediately adjacent to the attack or expulsion of the less basic amine molecule is in general rate determining.<sup>14</sup> This is applicable also to the present reactions.

In the reactions involving a simple amine **2c**, the rate constants  $k_a$  for the buffer-independent reaction between the protonated Schiff base **1aH<sup>+</sup>** and free amine base **2c**



**Figure 4.** pH- $\log k_a$  profiles for the reactions catalyzed by **2b** (O), **2c** (●), and **2g** (○). The curves are drawn with kinetic parameters given in text.

changes sigmoidally with pH as shown in Figure 4. When pH is lowered, the pH-independent water reaction is taken over around pH 5–6 by the hydronium ion catalyzed reaction which levels off around pH 2–3 to result in another pH-independent limiting rate constant. This pH-rate profile is similar to that found for the reaction of *N*-(*p*-methoxybenzylidene)pyrrolidinium ion with hydroxylamine.<sup>14</sup> In the rate-determining step, the incipient tetrahedral intermediate  $T_1^+$  is trapped by water ( $k_{\text{H}_2\text{O}}$ ) at higher pH and by  $\text{H}_3\text{O}^+$  in the intermediate pH region at a diffusion-controlled rate ( $k_{\text{H}^+}$ ) to give a dicationic intermediate  $T_2^+$ . At still lower pH, when  $k_{\text{H}^+}[\text{H}^+]$  exceeds the rate constant ( $k_r$ ) for the reversion to the starting substrate, the rate-determining step changes to the formation of  $T_1^+$  ( $k_f$ ). Thus  $k_a$  is described by eq 10, where

$$k_a = \frac{K_f k_{\text{H}_2\text{O}} + K_f k_{\text{H}^+} [\text{H}^+]}{1 + (k_{\text{H}^+}/k_r) [\text{H}^+]} \quad (10)$$

$K_f (=k_f/k_r)$  is the equilibrium constant for the formation of  $T_1^+$ . The solid line for **2c** in Figure 4 is drawn with parameters:  $K_f k_{\text{H}^+} = 5.6 \times 10^7 \text{ M}^{-2} \text{ s}^{-1}$ ,  $K_f k_{\text{H}_2\text{O}} = 1.3 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ ,  $k_{\text{H}^+}/k_r = 1.8 \times 10^3 \text{ M}^{-1}$  ( $k_f = 3.1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ ).

The rate constants  $k_a$  for the reaction of **2b** changes similarly with pH, and we may assume the same mechanism for the transimination with **2b** as that with **2c**. The sigmoid curve for **2b** in Figure 4 is reasonably reproduced by assuming the limiting rate constant at low pH to be  $k_f = 4.0 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ , leading to values:  $K_f k_{\text{H}^+} = 1.2 \times 10^5 \text{ M}^{-2} \text{ s}^{-1}$ ,  $K_f k_{\text{H}_2\text{O}} = 4.6 \text{ M}^{-1} \text{ s}^{-1}$ ,  $k_{\text{H}^+}/k_r = 3.0 \times 10^2 \text{ M}^{-1}$ . If we assume the rate constant for the diffusion-controlled proton transfer to be  $k_{\text{H}^+} = 2 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ ,<sup>16</sup> the equilibrium constants  $K_f$  are  $6 \times 10^{-6}$  and  $2.8 \times 10^{-3} \text{ M}^{-1}$  for **2b** and **2c**, respectively. In accord with a mechanism involving rate-determining proton transfer, buffer effects were observed for the catalysis by the simple amines. Both general acid and base catalyses seem to be operative ( $k_{ab}$  in Table II) but detailed analysis was not possible.

The rate constants  $k_a$  for the reaction of morpholine **2g** show hydroxide catalysis in contrast to those for **2b** and **2c**. Between pH 6 and 7,  $T_1^+$  may be trapped by  $\text{OH}^-$  (at a diffusion-controlled rate) to give a neutral intermediate  $T^0$  ( $K_f k_{\text{OH}^-} K_w = 6 \times 10^{-5} \text{ s}^{-1}$ ). Although we could not get

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Table II. Rate Constants for the Transimination of 1a with Various Amines 2

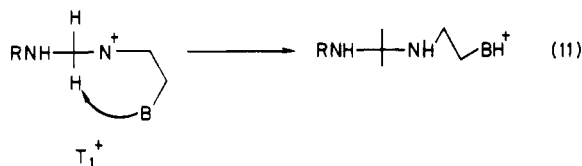
pH	buffer <sup>a</sup>	$10^2[2]_{\max}^b$ M	$k_a',^c$ $M^{-1} s^{-1}$	$k_{ab}',^c$ $M^{-2} s^{-1}$	$k_a$ $M^{-1} s^{-1}$	$k_{ab}$ $M^{-2} s^{-1}$
<b>2b</b> ( $pK_A = 5.70$ )						
2.75 <sup>d</sup>	HCl	1.5	0.16 (0.02) <sup>e</sup>		140	
3.05 <sup>d</sup>	HCl	1.0	0.24 (0.02) <sup>e</sup>		105	
3.62 <sup>f</sup>	formate	1.0	0.26 (0.05) <sup>e</sup>		31	
4.15	acetate	0.6	0.28 (0.04)	8.1 (0.6)	9.9	290
4.60	acetate	0.3	0.697 (0.017)	35.6 (0.3)	9.50	488
5.12	acetate	0.3	1.31 (0.11)	53.2 (2.0)	6.47	260
5.67	MES	0.3	2.36 (0.13)	13.2 (2.4)	5.28	30.0
6.22	MES	0.3	2.58 (0.01)	35.2 (0.2)	4.30	58.8
<b>2c</b> ( $pK_A = 8.00$ )						
2.11	HCl	1.0	0.041 (0.003) <sup>e</sup>		$3.2 \times 10^4$	
2.44 <sup>f</sup>	CA	0.75	0.069 (0.002) <sup>e</sup>		$2.5 \times 10^4$	
3.18	CA	0.75	0.245 (0.007)	0.32 (0.13)	$1.62 \times 10^4$	$2.20 \times 10^4$
4.08	acetate	0.3	0.537 (0.055)	4.60 (1.01)	$4.47 \times 10^3$	$3.84 \times 10^4$
4.60	acetate	0.3	0.624 (0.021)	9.81 (0.19)	$1.57 \times 10^3$	$2.49 \times 10^4$
5.12	acetate	0.3	0.723 (0.017)	16.8 (0.3)	$5.57 \times 10^2$	$1.31 \times 10^4$
5.77	MES	0.3	0.870 (0.416)	35.4 (7.7)	$1.64 \times 10^2$	$0.66 \times 10^4$
6.57	MES	0.2	3.08	210	$1.8 \times 10^2$	$0.98 \times 10^4$
<b>2g</b> ( $pK_A = 8.62$ )						
5.77	MES	0.3	0.039 (0.002)	1.46 (0.03)	30.4	$1.15 \times 10^3$
6.17 <sup>g</sup>	MES	0.3	0.228 (0.013)	5.08 (0.14)	80.6	$1.80 \times 10^3$
6.57	MES	0.3	0.687 (0.004)	14.3 (0.1)	127	$2.63 \times 10^3$
8.00 <sup>h</sup>	MM	0.3	4.15 (0.02)	15.6 (0.4)	386	$1.45 \times 10^3$
pH	buffer ( $10^2[B]_t/M$ )	$10^4[2]_{\max}$ M	$k_a',^e$ $M^{-1} s^{-1}$	$10^{-4}k_a$ $M^{-1} s^{-1}$		
<b>2d</b> ( $pK_A = 8.70$ )						
5.61	MES (9.0)	4	31.0 (1.2)	4.08		
6.22	MES (2.5)	2	71.6 (1.2)			
	MES (5.0)	4	74.0 (0.4)	2.91		
	MES (9.0)	4	78.7 (2.3)			
6.55	MES (9.0)	4	129 (2)	2.94		
7.00	MM (9.0)	4	213 (1)	2.93		
7.61 <sup>d</sup>	MM (2.5)	1	236 (4)	2.55		
	MM (5.0)	1	248 (3)			
<b>2e</b> ( $pK_A = 9.40$ )						
6.18	MES (5.0)	3	74.5 (0.3)	15.5		
6.22	MES (9.0)	3	66.8 (1.2)	13.0		
6.87	MM (9.0)	3	180 (3)	13.8		
7.50	MM (9.0)	3	267 (3)	13.7		
8.12	MM (9.0)	3	277 (3)	13.0		
8.49	borate (9.0)	3	242 (1)	11.8		
8.82	borate (9.0)	3	191 (2)	10.4		
9.19	borate (5.0)	3	120 (1)	8.33		
9.24	borate (9.0)	3	111 (2)	8.04		
9.58	borate (9.0)	3	59.8 (2.8)	6.42		
9.88	borate (9.0)	3	23.4 (0.6)	4.02		
<b>2f</b> ( $pK_A = 10.02$ ) <sup>i</sup>						
6.22	MES (9.0)	10	90.7 (2.6)	593 (18.2)		
6.78	MES (9.0)	10	134 (1)	139 (14.3)		
7.18	MM (9.0)	10	170 (3)	74.7 (16.7)		
7.81	MM (9.0)	10	156 (1)	36.0 (21.2)		
7.84	MM (5.0)	6	152 (4)	35.1 (19.5)		
8.95	DMAE (9.0)	10	109 (2)	21.5 (20.2)		
9.89	DMAE (9.0)	10	64.8 (1.2)	20.2 (20.1)		

<sup>a</sup> MES, 2-(*N*-morpholino)ethanesulfonate; CA, chloroacetate; MM, *N*-methylmorpholine; DMAE, 2-(dimethylamino)ethanol. <sup>b</sup> Maximum amine concentrations used for the rate determinations. <sup>c</sup> Calculated by the least-squares method (eq 6) usually from three  $k_i$  values, which were obtained as slopes of  $k_{\text{obs}}[2]_t$  plots (eq 5) at  $[B]_t = 0.025, 0.050,$  and  $0.075$  M, and standard deviations are given in parentheses as nominal values to indicate the linearity. <sup>d</sup> The rate leveled off at higher amine concentrations. <sup>e</sup> Standard deviations from the linear dependency on the amine concentrations. <sup>f</sup> Buffer effects were not observed. <sup>g</sup> The rate constants were calculated from  $k_i$  obtained at seven different buffer concentrations ( $[B]_t = 0.02\text{--}0.14$  M). <sup>h</sup> The rate constants were calculated from four  $k_i$  values obtained at  $[B]_t = 0.02\text{--}0.08$  M. At higher  $[B]_t$ ,  $k_i$  leveled off. <sup>i</sup> Corrections for the diprotonation ( $pK_{A1} = 7.07$ ) were also considered to calculate  $k_a$  (see text).

enough data at higher pH,  $k_a$  seems to level off to reflect the rate-determining formation of  $T_1^+$ . The limiting rate constant ( $k_f = 5 \times 10^2 M^{-1} s^{-1}$ ), which is compatible to the limiting rate of the curved buffer dependence observed at pH 8 (Figure 3, the limiting rate constant  $k_i$  ( $6.1 M^{-1} s^{-1}$ ) is corrected to be  $5.7 \times 10^2 M^{-1} s^{-1}$  according to an equation similar to eq 8), gives a partial sigmoid curve in Figure 4. The equilibrium constant is estimated to be  $K_f = 0.2 M^{-1}$  by using  $K_w = 1.47 \times 10^{-14} M^2$  and  $k_{OH} = 2 \times 10^{10} M^{-1} s^{-1}$ .<sup>16</sup>

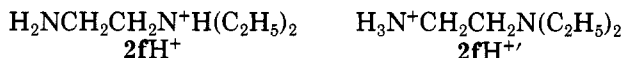
On the whole, the reaction mechanism involving rate-determining proton transfer observed before for transimination with hydroxylamine<sup>14,15</sup> is shown to be applicable also to the reactions with simple amines.

The catalysis of hydrolysis by bifunctional amines was found to be almost independent of buffer concentration. This strongly suggests that trapping of the incipient intermediate  $T_1^+$  takes place by an intramolecular proton transfer according to eq 11. The rate constants  $k_a$  for 2d



and **2e** are roughly constant in the pH range examined. The buffer- and pH-independent rate constants for these amines must reflect the formation of  $T_1^+$  ( $k_f$ ) because the ensuing proton transfers involving the internal base are rapid. That is, the nucleophilic reaction of the amine **2** is rate determining ( $k_a = k_f$ ).

In the case of **2f**,  $k_a$  calculated by eq 9 seems to change greatly with pH. This might come from the reaction of the monoprotonated species  $2fH^+$ . This and other mon-



oprotonated species  $2fH^{+'}$  may have similar  $pK_a$ <sup>17</sup> and exist in a similar concentration in solution. The nucleophilic reactivity of  $2fH^+$  ( $pK_{A1} = 7.07$ ) may be about  $1/100$  of that of **2f** ( $pK_A = 10.02$ ) as estimated from the Bronsted-type correlation of  $\beta_{\text{Nuc}} \approx 0.7$  mentioned below (Figure 5). Thus,  $k_a'$  is described by eq 12. Values of  $k_a$  calculated

$$k_a' = \left( \frac{K_A K_{A1} k_a + K_{A1} k_a [\text{H}^+] / 200}{K_A K_{A1} + K_{A1} [\text{H}^+] + [\text{H}^+]^2} \right) \left( \frac{[\text{H}^+]}{K_a + [\text{H}^+]} \right) \quad (12)$$

from this equation are given in parentheses in Table II, and are essentially independent of pH. This must correspond to  $k_f$  as is the case for **2d** and **2e**.

The rate constants  $k_f$  must depend on the nucleophilicity or the basicity of the amines **2**. Logarithms of  $k_f$  are correlated linearly with  $pK_A$  of the conjugate acids of **2** with a slope  $\beta_{\text{Nuc}} \approx 0.7$  in Figure 5, involving a large downward deviation of the point for morpholine **2g**. This correlation includes both simple and bifunctional amines and is consistent with the above conclusion that  $k_f$  refers to the rate-determining attack of the amine **2** to form  $T_1^+$  rather than the expulsion of **2a** from  $T_2^+$ . Intramolecular catalysis does not seem to be effective in this step although it does operate effectively in the ensuing proton transfer step. Deviation of a point for the secondary amine **2g** is natural, since its nucleophilicity should be smaller owing to adverse steric effects.

### Conclusion

Bifunctional primary amines carrying an internal (tertiary) amino group are effective catalysts of Schiff base hydrolysis. The initial nucleophilic attack on the iminium ion by the amine is rate determining for the overall reaction. Ensuing steps, proton-transfer step(s) of the transimination and the hydrolysis of the intermediate Schiff base, are facilitated by the intramolecular general base (acid) catalysis.

### Experimental Section

**Materials.** Schiff bases **1a**, **1d**, **1e**, and **1f** were prepared simply by mixing equivalent amounts of *o*-methoxybenzaldehyde (**4**) and appropriate amines.<sup>18</sup> The products were taken up in ether after

(17) Values of  $pK_a$  for the conjugate acids of ethylamine and triethylamine are 10.63 and 10.65, respectively.<sup>13</sup>

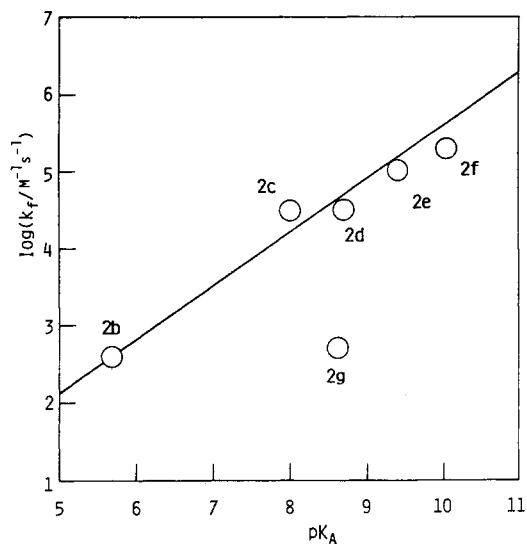


Figure 5. Correlation of  $\log k_f$  with  $pK_A$  for various amines.

a 1-h reaction, dried over  $\text{MgSO}_4$ , and distilled. Some reaction mixtures were directly subjected to vacuum distillation. Boiling points were **1a**, 131 °C (4 mmHg); **1d**, 148 °C (2 mmHg); **1e**, 150 °C (oven temperature for the Kugelrohr distillation at 2 mmHg); **1f**, 142 °C (2 mmHg). For the preparations of **1b** and **1c**, 4 and HCl salts of the amines were mixed in benzene solution with a small excess of triethylamine. Resulting salts were removed by washing with aqueous sodium bicarbonate. The residues were dried over  $\text{MgSO}_4$ . The product **1b** was distilled [bp 98 °C (5 mmHg)] and **1c** was recrystallized from benzene-acetonitrile (mp 138–140 °C). The iminium salt **1'g** was prepared from **4** and morpholinium perchlorate by the method of Leonard and Paukstelis.<sup>19</sup> The products were recrystallized from benzene-acetonitrile; mp 164–166 °C. All the substrates gave satisfactory CNH analyses. UV spectral data are summarized in Table S2. All the other chemicals were obtained as before.<sup>10,20</sup> Glass-distilled water was used throughout.

**Kinetic Measurements.** All the aqueous solutions containing appropriate amounts of buffer and amine were prepared at room temperature and adjusted to an ionic strength of 0.10 M with KCl. Reactions were started by adding 30  $\mu\text{L}$  of the substrate acetonitrile solution ( $1\text{--}4 \times 10^{-3}$  M) from a microsyringe into a 3-mL buffer solution equilibrated at 30 ( $\pm 0.1$ ) °C in a stoppered quartz cuvette inserted in a water-jacketed cell holder. The reaction was followed by the increase at 335 nm or the decrease at 280 nm on a Shimadzu UV-200 or UV-140 spectrophotometer. Pseudo-first-order rate constants were calculated by a modified Guggenheim method.<sup>21</sup> Infinite absorbances calculated were checked occasionally and found to agree with those observed. The rate constants derived from the linear correlations (eq 2, 5, and 6) were obtained by the least-squares method. Values of pH of buffer and reaction solutions were measured on a Hitachi-Horiba F7 pH meter.

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**Registry No.** **1a**, 93549-60-1; **2b**, 753-90-2; **2c**, 598-41-4; **2d**, 3731-51-9; **2e**, 2038-03-1; **2f**, 100-36-7; **2g**, 110-91-8.

**Supplementary Material Available:** Tables of rate constants for the reactions of **1a** and the hydrolysis of other Schiff bases, and UV spectral data of the substrates (6 pages). Ordering information is given on any current masthead page.

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