Chem. Pharm. Bull.
31(9)3129—3138(1983)

A Kinetic Study of Hydrolysis of β-Arylaminoacrolein Derivatives

Machiko Ono, Shigenori Ohtsuka, and Shinzo Tamura*

School of Pharmaceutical Science, Toho University,
2-2-1, Miyama, Funabashi 274, Japan

(Received February 8, 1983)

The reversible acid-catalyzed hydrolysis of β-arylaminoacrolein (I) has been studied kinetically. The kinetic runs were carried out in 1% aqueous ethanol in the presence of hydrochloric acid or acetic acid as well as in acetate buffer solutions at 25 °C.

The Hammett plot for the equilibrium constant K was linear. The value of $\log K$ was expressed by the equation $\log K = 1.38\sigma - 5.55$. The loss of arylamine from the carbinolamine intermediate was rate-determining under strongly acidic conditions, while the rate of attack of water at the β-position of I was comparable to that of loss of arylamine from the intermediate under weakly acidic conditions.

The reaction suffered general acid catalysis. The solvent-catalyzed term and catalytic constants for hydronium ion and for acetic acid were evaluated for both steps. General acid catalysis of acetic acid was of minor importance for the attack of water on I. The Hammett plot for the rate of reaction of water and conjugate acid of I was linear. The value of $\log k_1^H K_{BH^+}$ was expressed by the equation $\log k_1^H K_{BH^+} = 0.468\sigma - 1.08$.

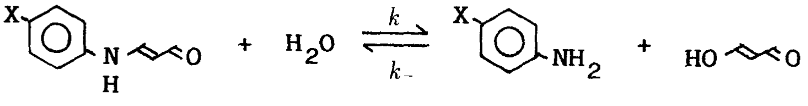
The reaction mechanism is discussed.

Keywords——kinetic study; acid-catalyzed hydrolysis; catalytic constant; Hammett plot; β-arylaminoacrolein

In a previous paper[1] we reported a kinetic study of acid-catalyzed hydrolysis of β-arylaminoacrolein derivatives (I) in 1% aqueous dioxane (Chart 1). The reaction was reversible, and the kinetic experiments were carried out in both acetate buffer and dilute hydrochloric acid solutions. The reaction had been proved to suffer general acid catalysis, and the apparent equilibrium constant K' was affected by the acidity of the solution because of the dissociation of malonaldehyde and of arylamine formed. The true equilibrium constant K is represented by Eq. (1),

$$K = \frac{[\mathrm{H}^+]K_{\mathrm{AH}^+}}{([\mathrm{H}^+] + K_{\mathrm{AH}^+})([\mathrm{H}^+] + K_{\mathrm{M}})} K' \tag{1}$$

where K_M and K_{AH^+} are the dissociation constants of malonaldehyde and the conjugate acid of arylamine, respectively, and the value of K for β-(*p*-toluidino)acrolein (Ib) had been evaluated to be 2.49×10^{-6} M in 1% aqueous dioxane, ionic strength 0.8, at 25 °C.

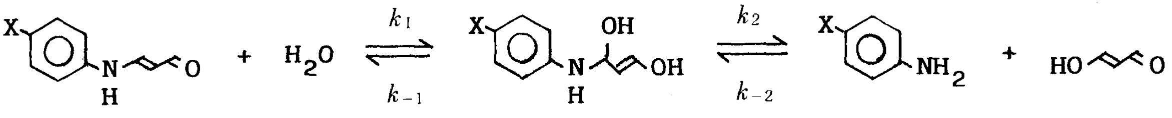


Ia: X=CH_3O Ib: X=CH_3 Ic: X=H Id: X=Cl Ie: X=NO_2

Chart 1

The dissociation constant K_{BH^+} of the conjugate acid of I had been estimated from the rate constants of hydrolysis in dilute hydrochloric acid solution, and the values obtained were as follows: β-(*p*-anisidino)acrolein (Ia), 5.50×10^{-2} M; β-(*p*-toluidino)acrolein (Ib), 8.37×10^{-2} M; β-anilinoacrolein (Ic), 1.41×10^{-1} M; β-(*p*-chloroanilino)acrolein (Id), 2.20×10^{-1} M.

From a study on the exchange of isotopic carbonyl oxygen with the medium, Bender[2)] proposed that the hydrolysis of the ester proceeds through a tetrahedral intermediate. His proposal has been supported by many investigators working on the kinetics of carbonyl addition reactions. The present hydrolysis reaction proceeds through a tetrahedral carbinolamine intermediate (II) (Chart 2).



II

Chart 2

In this paper we wish to report the estimation of k_1 and k_1k_2/k_{-1} values of the reaction in 1% aqueous ethanol solution under various conditions and to present the catalytic constants for hydronium ion and for acetic acid in both steps.

Experimental

The ultraviolet absorption (UV) spectra were measured on a Hitachi spectrophotometer, model 139, and the pH values of acetate buffer, and aqueous AcOH solutions were measured with a Toa Dempa glass electrode pH meter, model HA-5A. The ionic strength of the reaction solution was maintained at 0.4 by the addition of NaCl. All the kinetic runs were carried out at 25 °C.

Materials——The compounds Ia, Ib, Ic, and Id were prepared according to the previous papers.[3,4)] β-(p-Nitroanilino)acrolein (Ie)[5)] was prepared according to the cited reference.

Preparation of the Hydrolysis Reaction Solution——One ml of ethanol solution (2×10^{-3} M) of I was added to aqueous acetate buffer, AcOH or HCl solution in a 100 ml volumetric flask, and the sample was diluted to the mark with the same aqueous solution.

Treatment of the Kinetic Data——The rate equation of the reaction is represented by Eq. (2),

$$kt=\frac{y_e}{2-y_e}\ln\frac{y_e+y(1-y_e)}{y_e-y} \qquad (2)$$

where $(1-y)$ and $(1-y_e)$ are the proportions of I at time t and at equilibrium, respectively. The concentration of I was evaluated by measurement of the UV absorbance of the reaction solution at the maximum absorption wavelength (Ia, 329 nm; Ib, 325 nm; Ic, 323 nm; Id, 326 nm; Ie, 372 nm). The evaluation of y_e might be somewhat difficult because of the partial degradation of malonaldehyde formed during prolonged reaction.

The rate constant k was calculated from Eq. (2) using y_e measured at 24 h after the initiation of the reaction, and the values of y_e and k were corrected by use of the non-linear least-squares method. The method was carried out on the assumption that the approximate equation (3) is valid,

$$\Delta y_e\frac{\delta y}{\delta y_e}+\Delta k\frac{\delta y}{\delta k}=y-y_e \qquad (3)$$

where y_c is a calculated value from Eq. (4) using initial approximate values of y_e and k; $y_e+\Delta y_e$ and $k+\Delta k$ are the corrected values of proportion of the product at equilibrium and of the rate constant, respectively.

$$y=\frac{y_e\left\{\exp\left(\frac{2-y_e}{y_e}kt\right)-1\right\}}{1-y_e+\exp\left(\frac{2-y_e}{y_e}kt\right)} \qquad (4)$$

$$\frac{\delta y}{\delta y_e}=\frac{\exp\left(\frac{4-2y_e}{y_e}kt\right)-2kt\left(\frac{2-y_e}{y_e}\right)\exp\left(\frac{2-y_e}{y_e}kt\right)-1}{\left\{1-y_e+\exp\left(\frac{2-y_e}{y_e}kt\right)\right\}^2} \qquad (5)$$

$$\frac{\delta y}{\delta k}=\frac{t(2-y_e)^2\exp\left(\dfrac{2-y_e}{y_e}kt\right)}{\left\{1-y_e+\exp\left(\dfrac{2-y_e}{y_e}kt\right)\right\}^2} \tag{6}$$

Results

The rate constants are shown in Table I. The rate of hydrolysis of Ie was too slow to permit measurement of the rate constants in acetate buffer solution. The equilibrium constants K were calculated from Eq. (1) using apparent equilibrium constants K' obtained from the runs in acetate buffer solution for Ia—d (Table II). A Hammett plot for K gave a linear relation (Fig. 1); the log K values are represented by the equation $\log K = 1.38\sigma - 5.55$. Resonance stabilization of β-arylaminoacrolein is encouraged by the electron-donating effect of substituents on the aryl group owing to the relaxation of partial positive charge on the nitrogen atom (Chart 3).

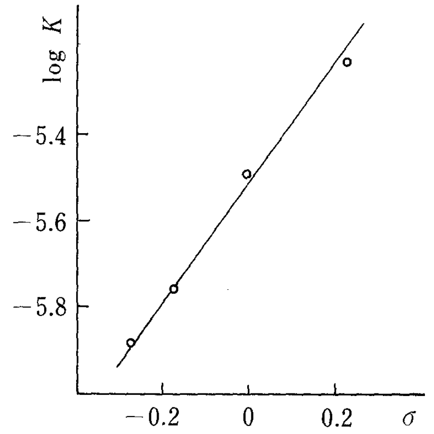


Fig. 1. Hammett Plot for K

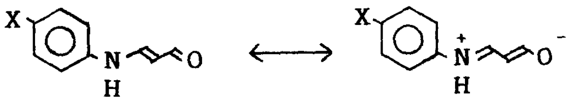


Chart 3

The reaction proceeds through two steps: the first step is acid-catalyzed addition of water to form the carbinolamine intermediate (II), and the second step is the loss of arylamine from II (Chart 2). From a kinetic study of hydrolysis of *N*-benzylidene-1,1-dimethylethylamine, Cordes and Jencks[8] concluded that the rate-determining step of the reaction is the loss of amine from the carbinolamine intermediate under strongly acidic conditions, while the attack of water on the protonated imine is rate-determining under weakly acidic conditions. Moreover, they pointed out that imine formation undergoes a transition in rate-determining step from rate-determining dehydration of the carbinolamine intermediate at neutral pH to rate-determining amine attack under acidic conditions in the reaction of benzaldehyde and aniline.[9]

The hydrolysis reaction of I suffers general acid catalysis.[1] The rate constant k is represented by Eq. (7).[10]

$$k = k^0 + k^{\mathrm{H}}[\mathrm{H}^+] + k^{\mathrm{AcOH}}[\mathrm{AcOH}] \tag{7}$$

A plot of the rate constant of the reaction in hydrochloric acid solution against the concentration of the acid gave a linear relation (Fig. 2). The value of k^0 and k^{H} were evaluated by the least-squares method. The calculated value of $k - k^0 - k^{\mathrm{H}}[\mathrm{H}^+]$ for the runs in aqueous acetic acid solution was proportional to the concentration of acetic acid (Fig. 3). This result suggests that the rate-determining step is common to both reactions, and the rate-determining step is probably the loss of arylamine from intermediate II on the basis of the consideration by

Table I. Experimental (k) and Calculated (k_c) Rate Constants (s^{-1}) of Hydrolysis of β-Arylaminoacrolein in 1% Aqueous Ethanol, Ionic Strength 0.4, at 25 °C

$10^5[H^+]$	[AcOH]	Ia		Ib		Ic		Id		Ie
		10^5k	10^5k_c	10^5k	10^5k_c	10^5k	10^5k_c	10^5k	10^5k_c	10^5k
2.94	0.12	2.63	2.58	2.41	2.32	1.98	1.97	1.61	1.50	
2.94	0.18	2.97	3.01	2.75	2.75	2.51	2.40	1.96	1.87	
2.94	0.24	3.40	3.34	3.07	3.09	2.73	2.76	2.25	2.21	
2.94	0.30	3.61	3.62	3.22	3.37	2.97	3.10	2.48	2.53	
2.94	0.36	3.70	3.87	3.45	3.62	3.08	3.41	2.57	2.85	
5.88	0.12	3.44	3.47	2.92	2.91	2.42	2.46	1.94	2.05	
5.88	0.18	4.16	4.19	3.56	3.54	3.14	3.04	2.44	2.51	
5.88	0.24	4.74	4.73	4.12	4.04	3.74	3.52	3.05	2.92	
5.88	0.30	5.36	5.19	4.58	4.45	4.01	3.93	3.44	3.29	
5.88	0.36	5.62	5.58	4.81	4.80	4.41	4.31	3.61	3.64	
8.83	0.12	4.01	4.04	3.23	3.31	2.76	2.81	2.35	2.45	
8.83	0.18	5.03	5.01	4.14	4.12	3.39	3.52	3.10	3.03	
8.83	0.24	5.85	5.76	4.78	4.76	4.15	4.11	3.54	3.51	
8.83	0.30	6.39	6.38	5.32	5.30	4.72	4.61	3.94	3.94	
8.83	0.36	6.78	6.91	5.76	5.75	4.97	5.06	4.36	4.33	
98	0.04	3.73	3.70	3.11	3.06	2.84	2.82	2.99	2.95	
121	0.06	4.96	4.83	3.96	4.01	3.76	3.72	3.99	3.95	
138	0.08	5.94	5.89	5.01	4.89	4.58	4.54	4.89	4.85	
155	0.10	6.91	6.95	5.68	5.77	5.36	5.36	5.71	5.75	
170	0.12	7.90	7.98	6.60	6.63	6.08	6.16	6.56	6.61	2.25
209	0.18									2.75
240	0.24									3.23
268	0.30									3.60
294	0.36									3.94
200		3.03	3.12	2.64	2.72	2.71	2.76	3.01	3.00	
300		4.23	4.27	3.85	3.78	3.96	3.94	4.34	4.38	
400		5.49	5.41	4.85	4.83	5.13	5.12	5.69	5.76	
500		6.45	6.56	5.85	5.89	6.28	6.30	7.15	7.14	5.25
600		7.78	7.70	6.95	6.94	7.49	7.48	8.56	8.52	6.18
700										7.34
800										8.55

Table II. Equilibrium Constants K of Acid-Catalyzed Hydrolysis of β-Arylaminoacrolein in 1% Aqueous Ethanol Ionic Strength 0.4, at 25 °C[a]

Ia	Ib	Ic	Id
1.31×10^{-6}	1.76×10^{-6}	3.28×10^{-6}	6.06×10^{-6}

[a] To calculate K from Eq. (1), the following K_M[6] and K_{AH^+}[7] values were used: $K_M = 2.00 \times 10^{-5}$; K_{AH^+}: p-anisidine, 4.57×10^{-6}; p-toluidine, 8.32×10^{-6}; aniline, 2.51×10^{-5}; p-chloroaniline, 1.10×10^{-4}.

Cordes and Jencks.[8,9] The values of k^0, k^H, and k^{AcOH} were evaluated from the rate constants of the reaction in hydrochloric acid and acetic acid solutions by the least-squares method with the three variables, and are shown in parentheses in Table III as k^0_{II}, k^H_{II}, and k^{AcOH}_{II}. A plot of the rate constant of the reaction in acetate buffer at constant pH against the concentration of acetic acid, however, did not give a linear relation (Fig. 5). Probably the rate of the first step is comparable to that of the second step in this case.

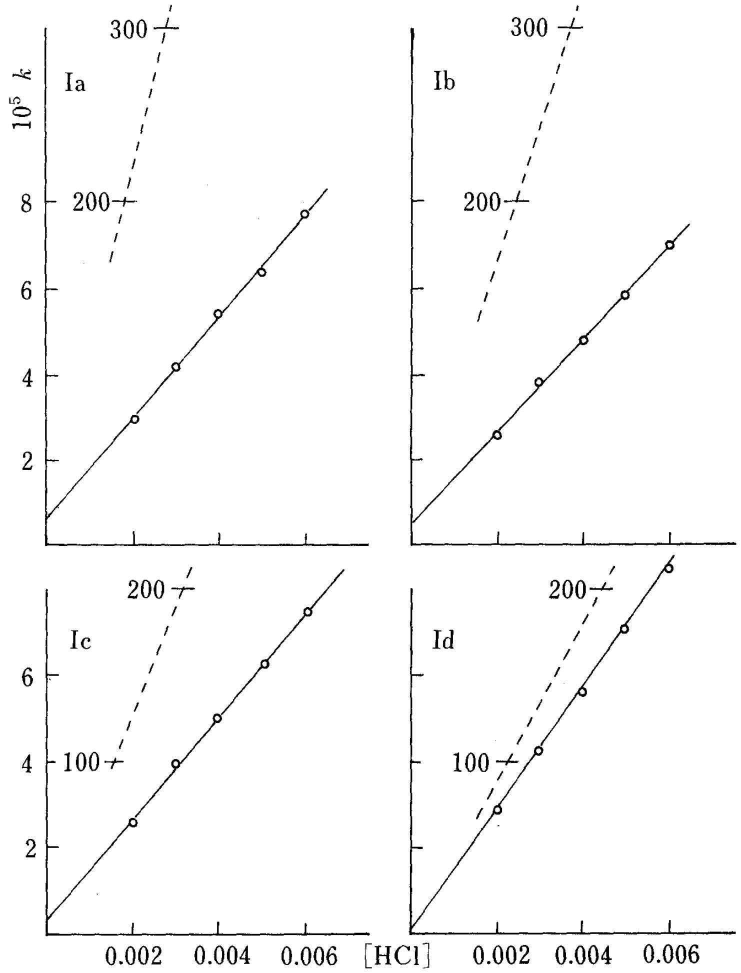


Fig. 2. Experimental and Calculated Rate Constants of Hydrolysis of I in 1% Aqueous EtOH in the Presence of HCl

——, k_c; ------, k_{I}.
The plot of k_{II} is not shown because it is almost identical to that of k_c.

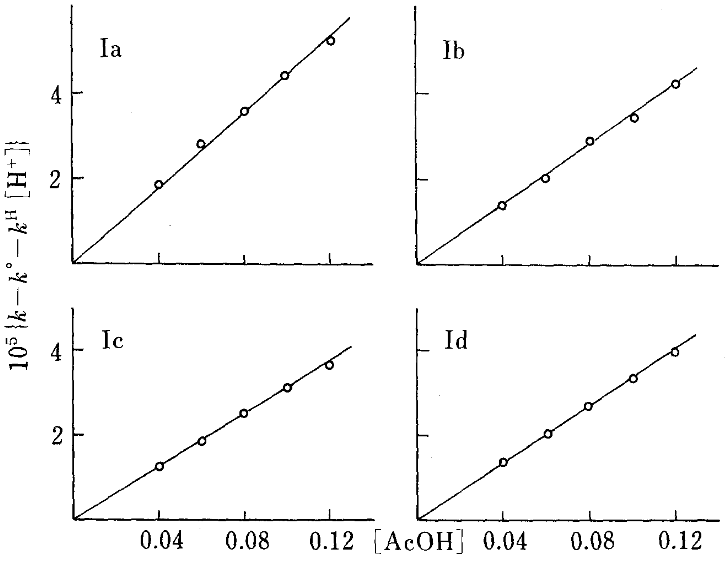


Fig. 3. Plot of Acetic Acid-Catalyzed Term against the Concentration of AcOH for the Runs Carried Out in 1% Aqueous EtOH in the Presence of AcOH

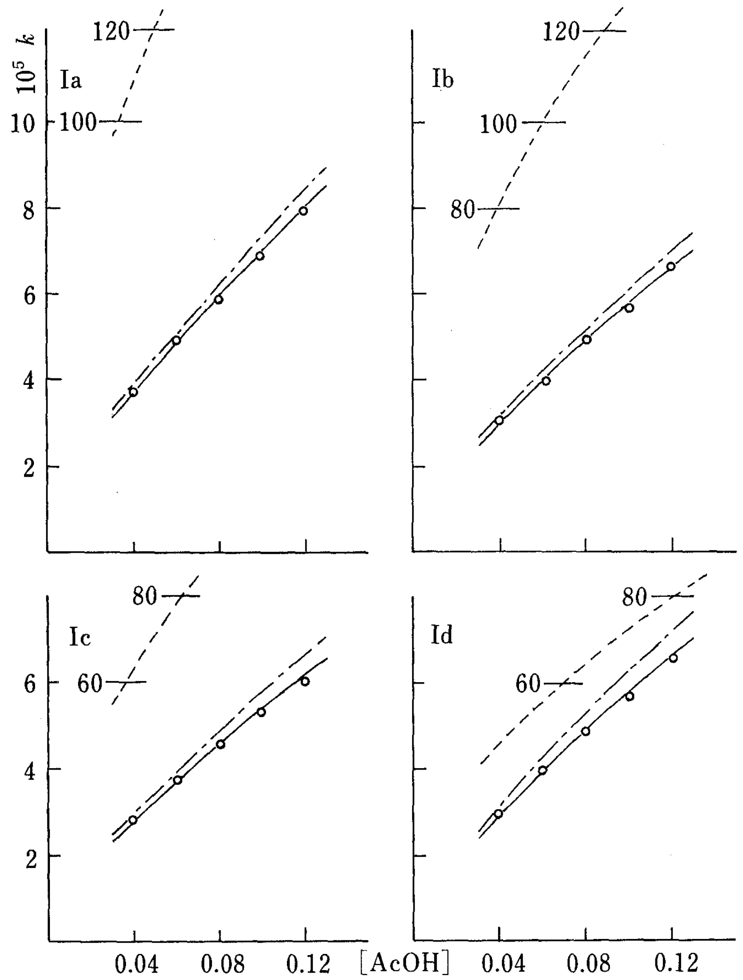


Fig. 4. Experimental and Calculated Rate Constants of Hydrolysis of I in 1% Aqueous EtOH in the Presence of AcOH

——, k_c; ------, k_I; – – – –, k_{II}.

The rate constant k is represented by Eq. (8) on a steady-state assumption (Chart 2),

$$k=\frac{k_1k_2}{k_{-1}+k_2} \tag{8}$$

Substituting $k_1k_2/k_{-1}=k_{II}$ in Eq. (8), we obtain

$$k=\frac{k_1k_{II}}{k_1+k_{II}} \tag{9}$$

and

$$k_1=\frac{kk_{II}}{k_{II}-k} \tag{10}$$

The reaction suffers general acid catalysis, and rate constants k_1 and k_{-1} are represented by Eqs. (11) and (12), respectively,

$$k_1=k_1^0+k_1^{H}[H^+]+k_1^{AcOH}[AcOH] \tag{11}$$

$$k_{-1}=k_{-1}^0+k_{-1}^{H}[H^+]+k_{-1}^{AcOH}[AcOH] \tag{12}$$

Assuming that k_1^0 is a solvent-catalyzed term, catalytic constants can be expressed by the

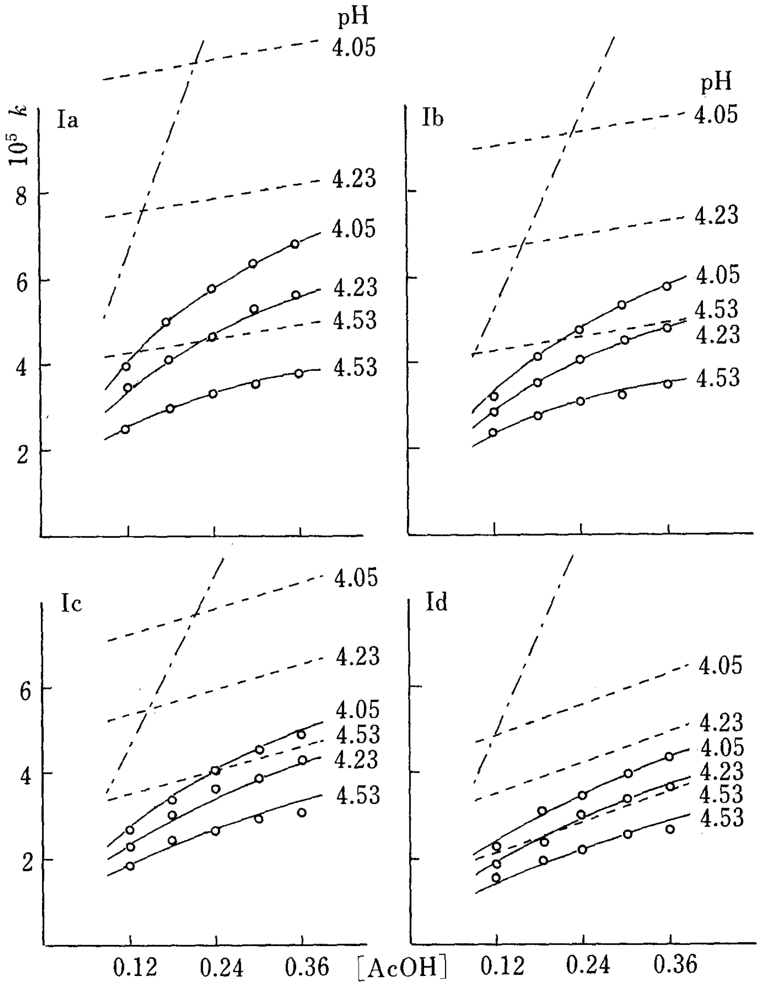


Fig. 5. Experimental and Calculated Rate Constants of Hydrolysis of I in 1% Aqueous EtOH in the Presence of AcOH and AcONa

——, k_c; ------, k_I; – – – – –, k_{II} at pH 4.23.
Plots of k_{II} at pH 4.05 and 4.53 are not shown because they are almost identical to that of k_{II} at pH 4.23.

Brønsted catalysis law as follows: $k^0_1 = 55.5G(K_{H_2O})^\alpha$, $k^H_1 = G(K_{H_3O^+})^\alpha$, and $k^{AcOH}_1 = G(K_{AcOH})^\alpha$, where K_{H_2O}, $K_{H_3O^+}$, and K_{AcOH} are the dissociation constants of water, hydronium ion and acetic acid, respectively. Because the reverse reaction must proceed through the same transition state, catalytic constants of the reverse reaction can be written as follows: $k^0_{-1} = 55.5G_-(K_{H_2O})^\alpha$, $k^H_{-1} = G_-(K_{H_3O^+})^\alpha$, and $k^{AcOH}_{-1} = G_-(K_{AcOH})^\alpha$. Then,

$$\frac{k_1}{k_{-1}} = \frac{k^o_1}{k^o_{-1}} = \frac{k^H_1}{k^H_{-1}} = \frac{k^{AcOH}_1}{k^{AcOH}_{-1}} = \frac{G}{G_-} \qquad (13)$$

and

$$k_{II} = \frac{G}{G_-}(k^o_2 + k^H_2[H^+] + k^{AcOH}_2[AcOH]) \qquad (14)$$

substituting $Gk^0_2/G_- = k^0_{II}$, $Gk^H_2/G_- = k^H_{II}$, and $Gk^{AcOH}_2/G_- = k^{AcOH}_{II}$ in Eq. (14), we obtain

$$k_{II} = k^0_{II} + k^H_{II}[H^+] + k^{AcOH}_{II}[AcOH] \qquad (15)$$

The value of k_{II} of the reaction in acetate buffer was calculated from equation 15 using the values of k^0, k^H, and k^{AcOH} which were obtained from the runs in hydrochloric and acetic

Table III. Catalytic Constants of Acid-Catalyzed Hydrolysis of β-Arylaminoacrolein[a)]

	Ia	Ib	Ic	Id
k_{I}^{0}	7.78×10^{-6}	1.48×10^{-5}	1.04×10^{-5}	1.40×10^{-6}
(s^{-1})	(8.72×10^{-6})	(1.67×10^{-5})	(1.17×10^{-5})	(1.68×10^{-6})
$k_{\mathrm{I}}^{\mathrm{H}}$	1.09	8.13×10^{-1}	6.36×10^{-1}	4.57×10^{-1}
$(\mathrm{s}^{-1}\,\mathrm{M}^{-1})$	(1.19)	(9.04×10^{-1})	(7.20×10^{-1})	(5.16×10^{-1})
$k_{\mathrm{I}}^{\mathrm{AcOH}}$	2.70×10^{-5}	2.75×10^{-5}	4.89×10^{-5}	5.83×10^{-5}
$(\mathrm{s}^{-1}\,\mathrm{M}^{-1})$	(1.52×10^{-5})	(1.47×10^{-5})	(4.02×10^{-5})	(5.46×10^{-5})
k_{II}°	8.58×10^{-6}	6.29×10^{-6}	4.18×10^{-6}	2.50×10^{-6}
(s^{-1})	(8.72×10^{-6})	(6.37×10^{-6})	(4.50×10^{-6})	(2.76×10^{-6})
$k_{\mathrm{II}}^{\mathrm{H}}$	1.16×10^{-2}	1.07×10^{-2}	1.20×10^{-2}	1.42×10^{-2}
$(\mathrm{s}^{-1}\,\mathrm{M}^{-1})$	(1.14×10^{-2})	(1.05×10^{-2})	(1.17×10^{-2})	(1.37×10^{-2})
$k_{\mathrm{II}}^{\mathrm{AcOH}}$	4.60×10^{-4}	3.76×10^{-4}	3.39×10^{-4}	3.79×10^{-4}
$(\mathrm{s}^{-1}\,\mathrm{M}^{-1})$	(4.31×10^{-4})	(3.49×10^{-4})	(3.09×10^{-4})	(3.34×10^{-4})
$k_{\mathrm{II}}^{\mathrm{H}}/k_{\mathrm{II}}^{\mathrm{AcOH}}$	25.2	28.5	35.4	37.5
$k_{\mathrm{I}}^{\mathrm{H}}K_{\mathrm{BH^+}}$	6.00×10^{-2}	6.80×10^{-2}	8.97×10^{-2}	1.01×10^{-1}

a) The initial approximate value of each catalytic constant used for the non-linear least-squares method is shown in parentheses.

acid solutions as k_{II}^{0}, $k_{\mathrm{II}}^{\mathrm{H}}$, and $k_{\mathrm{II}}^{\mathrm{AcOH}}$. Using k_{II} thus calculated, the catalytic constants of the first step (k_{I}^{0}, $k_{\mathrm{I}}^{\mathrm{H}}$, and $k_{\mathrm{I}}^{\mathrm{AcOH}}$) were evaluated from Eqs. (10) and (11) by the least-squares method, and are shown in parentheses in Table III.

The values of k_{II}^{0}, $k_{\mathrm{II}}^{\mathrm{H}}$, and $k_{\mathrm{II}}^{\mathrm{AcOH}}$ were corrected by means of the non-linear least-squares method using the experimental rate constants obtained from the runs carried out in hydrochloric acid, acetic acid and acetate buffer solutions. The method was carried out on the assumption that the approximate equation (16) is valid,

$$\Delta k_{\mathrm{II}}^{\circ}\frac{\delta k}{\delta k_{\mathrm{II}}^{\circ}}+\Delta k_{\mathrm{II}}^{\mathrm{H}}\frac{\delta k}{\delta k_{\mathrm{II}}^{\mathrm{H}}}+\Delta k_{\mathrm{II}}^{\mathrm{AcOH}}\frac{\delta k}{\delta k_{\mathrm{II}}^{\mathrm{AcOH}}}=k-k_{\mathrm{c}} \tag{16}$$

where k_{c} is calculated rate constant from Eq. (9), and $k_{\mathrm{II}}^{0}+\Delta k_{\mathrm{II}}^{0}$, $k_{\mathrm{II}}^{\mathrm{H}}+\Delta k_{\mathrm{II}}^{\mathrm{H}}$, and $k_{\mathrm{II}}^{\mathrm{AcOH}}+\Delta k_{\mathrm{II}}^{\mathrm{AcOH}}$ are corrected values for k_{II}^{0}, $k_{\mathrm{II}}^{\mathrm{H}}$, and $k_{\mathrm{II}}^{\mathrm{AcOH}}$, respectively, and

$$\frac{\delta k}{\delta k_{\mathrm{II}}^{\circ}}=\left(\frac{k_{\mathrm{I}}}{k_{\mathrm{I}}+k_{\mathrm{II}}}\right)^{2} \tag{17}$$

$$\frac{\delta k}{\delta k_{\mathrm{II}}^{\mathrm{H}}}=[\mathrm{H}^{+}]\left(\frac{k_{\mathrm{I}}}{k_{\mathrm{I}}+k_{\mathrm{II}}}\right)^{2} \tag{18}$$

and

$$\frac{\delta k}{\delta k_{\mathrm{II}}^{\mathrm{AcOH}}}=[\mathrm{AcOH}]\left(\frac{k_{\mathrm{I}}}{k_{\mathrm{I}}+k_{\mathrm{II}}}\right)^{2} \tag{19}$$

Catalytic constants of the first step (k_{I}^{0}, $k_{\mathrm{I}}^{\mathrm{H}}$, and $k_{\mathrm{I}}^{\mathrm{AcOH}}$) are recalculated from Eqs. (10) and (11) by the least-squares method using the corrected values of k_{II}^{0}, $k_{\mathrm{II}}^{\mathrm{H}}$, and $k_{\mathrm{II}}^{\mathrm{AcOH}}$, and the experimental rate constants obtained from the runs carried out in acetate buffer solution.

This procedure was repeated twenty times. The results are shown in Table III. The initial approximate value of each catalytic constant is shown in parentheses in the same table. Experimental rate constants are shown in Figs. 2, 4, and 5 together with the calculated rate constants of both steps. The solvent-catalyzed and acetic acid-catalyzed terms in the first step and the solvent-catalyzed term in the second step make only a little contribution to each rate constant. The values of k_{I}^{0}, $k_{\mathrm{I}}^{\mathrm{AcOH}}$, and k_{II}^{0} in Table III might, therefore, contain some error.

As stated in the earlier part of this report, hydrolysis of Ie could not be followed in acetate buffer solution. From the rate constants in hydrochloric acid and acetic acid solutions, the catalytic constants of the second step were estimated by the least-squares method to be as follows: k_{II}^{0}, $1.63 \times 10^{-6}\,\text{s}^{-1}$; k_{II}^{H}, $1.03 \times 10^{-2}\,\text{s}^{-1}\,\text{M}^{-1}$; $k_{\text{II}}^{\text{AcOH}}$, $2.27 \times 10^{-5}\,\text{s}^{-1}\,\text{M}^{-1}$.

Discussion

The reaction proceeds through the carbinolamine intermediate (II) (Chart 2). Both steps suffer general acid catalysis as indicated in Fig. 5. The first step is more sensitive to hydronium ion catalysis than the second step, while the latter suffers general acid catalysis to a larger extent than the former. The value of k_{I} is much greater than that of k_{II} under strongly acidic conditions. The rate of the reaction is, therefore, completely governed by the second step in hydrochloric acid solution (Eq. (9)). The plot of the rate constant against the concentration of the acid gave a linear relation (Fig. 2).

Under weakly acidic conditions, k_{I} and k_{II} take comparable values. The plot of the rate constant of the reaction in acetate buffer solution against the concentration of acetic acid at constant pH did not give a linear relation (Fig. 5). The value of k_{II} increases more rapidly than that of k_{I} with increasing concentration of acetic acid at constant pH. The rate of the reaction is governed by the first step to a larger extent with increasing concentration of acetic acid, resulting in the change in curvature of the plot.

In their report on a kinetic study of the acid-catalyzed formation of *p*-chlorobenzylideneaniline from *p*-chlorobenzaldehyde and aniline, Cordes and Jencks[9] revealed that the catalytic constant for acetic acid is approximately tenfold greater at pH 2.50 (amine attack is rate-determining) than at pH 5.10 (dehydration of the carbinolamine intermediate is rate-determining). Their observation is consistent with our results shown in Table III.

In Eq. (9), k_{I} and k_{II} are in equivalent positions. Mathematical treatment of the kinetic results by itself cannot determine which step is rate-determining under strongly acidic conditions.

However, the above-mentioned observation by Cordes and Jencks[9] together with their conclusion obtained from kinetic studies of the hydrolysis of *N*-benzylidene-1,1-dimethylethylamine[8] and the reaction of benzaldehyde and aniline[9] is consistent with our conclusion that the second step in the hydrolysis of I is rate-determining under strongly acidic conditions.

The catalytic constant for hydronium ion is much greater than that for acetic acid in the first step. This means that the transition state of the first step occurs at a late stage, in which a

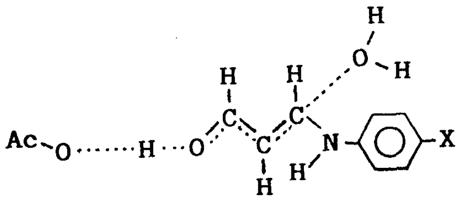


Chart 4

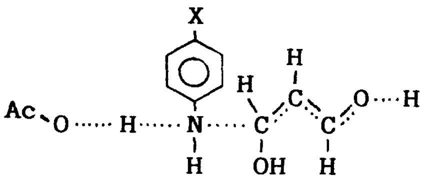


Chart 5

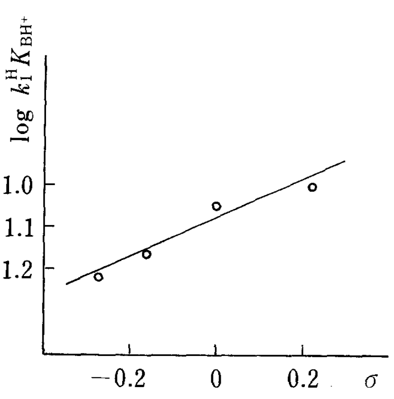


Fig. 6. Hammett Plot for $k_{\text{I}}^{\text{H}}K_{\text{BH}^+}$

considerable degree of bond formation exists between water and I (Chart 4).

The rate of the reaction of water and the conjugate acids of Ia—d is given by $k_{\text{I}}^{\text{H}}K_{\text{BH}^+}$ (Table III). A Hammett plot for $k_{\text{I}}^{\text{H}}K_{\text{BH}^+}$ gave a linear relation (Fig. 6), and $\log k_{\text{I}}^{\text{H}}K_{\text{BH}^+}$ is represented by the equation $\log k_{\text{I}}^{\text{H}}K_{\text{BH}^+} = 0.468\sigma - 1.08$. The attack of water at the β-position of the conjugate acid of I is accelerated by the electron-withdrawing effect of the substituents on the aryl group.

As regards the catalytic constant for general acids (characterized by 1 and 2) in a carbonyl addition reactions, Cordes and Jencks[11] deduced a relation between the nucleophilicity (n_{k}) of the reagent (characterized by k) and α represented by Eq. (20) on the bases of Brønsted catalysis law and the Swain–Scott equation, $\log k_{\text{j,k}} = \log k_{\text{j,0}} + s_{\text{j}}n_{\text{k}}$, where the catalyzing acid is characterized by j,

$$\frac{\text{p}K_{\text{a2}} - \text{p}K_{\text{a1}}}{s_1 - s_2} = \frac{n_{\text{k}}}{\alpha_{\text{k}} - \alpha_{\text{o}}} = C_2 \qquad (20)$$

They concluded that C_2 should be negative.[12]

The value of $k_{\text{II}}^{\text{H}}/k_{\text{II}}^{\text{AcOH}}$ increases with decreasing electron-donating effect of the substituents on the aryl group (Table III). This means that the degree of proton transfer between the carbinolamine intermediate and the catalyzing acid in the transition state increases with decreasing basicity of the leaving arylamine, in accord with the conclusion of Cordes and Jencks that C_2 should be negative (Chart 5).

A similar tendency was observed on the relation between k_{II}^{H} and $k_{\text{II}}^{\text{AcOH}}$ of Ie. However, the accuracy of the value of $k_{\text{II}}^{\text{AcOH}}$ is poor because the acetic acid-catalyzed term makes only a little contribution to the rate constant in this case. The mechanism of the hydrolysis of Ie cannot yet be discussed in detail.

Acknowledgement The authors are grateful to Professor J. F. Bunnett for his valuable advice.

References and Notes

1) S. Tamura, M. Ono, and K. Furuyama, *Chem. Pharm. Bull.*, **28**, 2356 (1980).
2) M. L. Bender, *J. Am. Chem. Soc.*, **73**, 1626 (1951).
3) S. Tamura and E. Yabe, *Chem. Pharm. Bull.*, **21**, 2105 (1973).
4) S. Tamura and E. Takeda, *Chem. Pharm. Bull.*, **27**, 403 (1979).
5) M. Ono, H. Tanaka, and S. Tamura, *Chem. Pharm. Bull.*, **30**, 1933 (1982).
6) F. Masuo and Y. Kimura, *Nippon Kagaku Zasshi*, **81**, 434 (1960).
7) A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, **1961**, 388.
8) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **85**, 2843 (1963).
9) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 832 (1962).
10) Decrease in UV absorbance of solutions of Ia—d in 1% aqueous ethanol at each maximum absorption wavelength showed that the hydrolysis reactions proceeded to the following extents (in proportions) after 23 d standing at 25°C: Ia, 0.324; Ib, 0.208; Ic, 0.183; Id, 0.202. In the presence of 0.36 M sodium acetate, the reaction proceeded to the following extents (in proportions) under the same conditions: Ia, 0.198; Ib, 0.149; Ic, 0.136; Id, 0.161. These results show that the reaction is not catalyzed by acetate ion.
11) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 4319 (1962).
12) In a subsequent paper (G. E. Lienhard and W. P. Jencks, *J. Am. Chem. Soc.*, **88**, 3982 (1966)) and book (W. P. Jencks, "Catalysis in Chemistry and Enzymology" ed. by McGraw-Hill Book Campany, 1969, p. 196), Jencks revised the relation to $\text{p}K_{\text{a2}} - \text{p}K_{\text{a1}} = C_2(s_2 - s_1)$ and $n_{\text{k}} = C_2(\alpha_0 - \alpha_{\text{k}})$. In this case, C_2 should be positive.