Amidines. III.   A Kinetic Study of Acid Hydrolysis of Unsymmetrical N^1,N^2-Disubstituted Amidines

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Acid hydrolysis of unsymmetrical N^1,N^2-disubstituted acetamidine and formamidine was examined kinetically in aqueous dioxane solution. The reaction afforded the more basic amine and the N-acyl derivative of the less basic amine. Increasing the dioxane content in the solvent increased the reaction rate. The reaction can be rationalized in terms of specific acid-general base catalysis.

   Keywords   kinetic study; acid hydrolysis; unsymmetrical N^1,N^2-disubstituted acetamidine; unsymmetrical N^1,N^2-disubstituted formamidine; leaving tendency; reaction mechanism

DeWolfe[1] studied the acid hydrolysis of symmetrical diarylamidines kinetically, and showed that the reaction can be rationalized in terms of general base-catalyzed hydrolysis of the amidinium ions. Electron-withdrawing substituents on the aryl group increase the rate of the reaction. However, we are not aware of any systematic studies on the hydrolysis of unsymmetrical amidines.

In this work we studied the acid hydrolysis of unsymmetrical N^1,N^2-disubstituted amidines kinetically. The acid hydrolysis of unsymmetrical amidine proceeded with the fission of the bond between the central carbon and the more basic nitrogen atom to give the more basic amine and the N-acyl derivative of the less basic amine.

Experimental

N^1-Aryl-N^2-(p-nitrophenyl)acetamidine (**1**), N^1-aryl-N^2-(2,4-dinitrophenyl)acetamidine (**2**), N^1-methyl-N^2-(p-nitrophenyl)acetamidine (**3**), N^1-methyl-N^2-(2,4-dinitrophenyl)acetamidine (**4**), N^1-(p-methylbenzyl)-N^2-(p-nitrophenyl)formamidine (**5**) and N^1-aryl-N^2-(p-nitrophenyl)-formamidine (**6**) were prepared according to the preceding paper.[2] The ultraviolet (UV) spectra were measured on a Hitachi spectrophotometer, model 139.

Preparation of the Reaction Solution   A dioxane solution (1 ml) of the substrate (2 to 8×10^{-3} M) was added to 20% aqueous dioxane containing the acid catalyst in a 100 ml volumetric flask which had been prewarmed to the desired temperature, and the mixture was diluted to the mark with the same 20% aqueous dioxane solution.

Hydrolysis of 1 in the Presence of HCl   The kinetic runs were carried out in the presence of 0.1 M HCl at 40 °C. The proportions of **1**, N-acetyl-p-nitroaniline, N-acetylarylamine (XC_6H_4NHAc, Chart 1) and p-nitroaniline were calculated from the absorbances of the reaction solution at the following wavelengths: 245, 280, 320, 375 nm (**1a**); 240, 280, 320, 375 nm (**1b,c**); 250, 280, 320, 375 nm (**1d**); 245, 280, 320, 385 nm (**1e**); 245, 280, 320, 375 nm (**1f**). Absorption by arylamine could be neglected at the wavelengths used for calculation of proportions of starting material and products except for the case of **1g**. In the hydrolysis of **1g**, absorption by p-aminobenzonitrile can not be neglected. The proportion of p-nitroaniline was evaluated by measuring the absorbances at 390, 400 and 410 nm of the reaction solution, and the proportions of **1g**, N-acetyl-p-nitroaniline, N-acetyl-p-cyanoaniline and p-aminobenzonitrile were calculated from the absorbances at 240, 265, 270, 290, 300 and 320 nm after subtraction of the absorbances owing to p-nitroaniline by the least-squares method.

Measurement of K_{BH^+} of 2 and 5   The UV spectra of **2c** in 20% aqueous dioxane solution under various conditions are shown in Fig. 2. The value of K_{BH^+} of **2c** was calculated in the usual manner using λ_{max}'s of the free base (under neutral conditions) and of the conjugate acid (in the presence of 0.1 M HCl). The K_{BH^+} values (M, standard deviations are shown in parentheses) obtained were as follows: **2a**, 4.68 $(0.108) \times 10^{-4}$; **2b**, 6.06 $(0.257) \times 10^{-4}$; **2c**, 1.02 $(0.051) \times 10^{-3}$; **2d**, 2.64 $(0.109) \times 10^{-3}$.

The UV spectra of **5** in 20% aqueous dioxane solution under various conditions are shown in Fig. 7. The value of K_{BH^+} of **5** was calculated in the same manner using λ_{max}'s of the free base (in the presence of $NaHCO_3$) and of the conjugate acid (in the presence of 0.01 M HCl). The K_{BH^+} (M, standard deviation is shown in parenthesis) obtained was 4.78 $(0.148) \times 10^{-7}$.

Hydrolysis of 2 in the Presence of HCl   The kinetic runs were carried out in the presence of 6×10^{-4} to 0.1 M HCl at 25 °C. The ionic strength was maintained at 0.1 by the addition of NaCl. The proportions of **2** and N-acetyl-2,4-dinitroaniline were calculated from the absorbancies of the reaction solution at 235, 240, 260, 262, 290, 300, 335, and 350 nm (**2a**) or at 235, 240, 253, 260, 290, 300, 335, and 350 nm (**2b**—**d**) by the least-squares method.

Hydrolysis of 2 in the Presence of AcOH   The kinetic runs were carried out in the presence of 0.04 to 0.50 M AcOH at 25 °C. The proportions of **2a**—**c** and N-acetyl-2,4-dinitroaniline were calculated from the absorbancies of the reaction solution at 235, 240, 255, 260, 290, 300, 335 and 350 nm by the least-squares method. The proportions of **2d** and N-acetyl-2,4-dinitroaniline were calculated from absorbancies at 260 and 290 nm.

Hydrolysis of 6a—c and 5 in the Presence of HCl   The kinetic runs were carried out in the presence of 5×10^{-4}, 7×10^{-4} and 9×10^{-4} M HCl at 25 °C. Ionic strength was maintained at 0.1 by the addition of NaCl. The absorbancies of the reaction solution were measured after the addition of $NaHCO_3$ to make 0.01 M $NaHCO_3$ solution: 2 ml of 20% dioxane solution of $NaHCO_3$ (0.0520, 0.0528 and 0.0536 M) in a 10 ml volumetric flask was diluted to the mark with the reaction solution. The proportions of the substrates and N-formyl-p-nitroaniline were calculated from the absorbancies of the solution at 315, 320, 360 and 365 nm (for **6a**—**c**) and at 310, 315, 360 and 365 nm (for **5**) by the least-squares method.

Hydrolysis of 5 in Acetate Buffer Solution   The kinetic runs were carried out in the presence of equimolar amounts of AcOH and AcONa (0.01, 0.02, 0.03, 0.04 and 0.05 M) at 25 °C. The ionic strength was maintained at 0.1 by the addition of NaCl. The absorbancies of the reaction solution were measured after the successive addition of NaOH and $NaHCO_3$: 1 ml of 20% dioxane solution of NaOH (0.10, 0.20, 0.30, 0.40 and 0.50 M) in a 10 ml volumetric flask was diluted to the mark with the reaction solution, and 1 ml of 20% dioxane solution containing 0.50 M $NaHCO_3$ in a 10 ml volumetric flask was diluted to the mark with the above solution. The proportions of **5** and N-formyl-p-nitroaniline were calculated from the absorbancies of the solution at 310, 315, 360 and 365 nm by the least-squares method.

Results

There are two possible pathways of hydrolysis of unsymmetrical amidines. One of them gives the more basic amine and the acyl derivative of the less basic amine (pathway A) and the other gives the less basic amine and the acyl derivative of the more basic amine (pathway B) (Chart 1).

N^1-(p-Chlorophenyl)-N^2-(p-nitrophenyl)acetamidine (**1d**) was hydrolyzed by warming a 75% aqueous dioxane solution of **1d** containing 0.25 M hydrochloric acid at 40 °C for 55 h. The signals of both N-acetyl-p-nitroaniline and N-acetyl-p-chloroaniline were detected in the ^{1}H nuclear magnetic resonance (^{1}H-NMR) spectrum of the crude product, showing that the hydrolysis proceeded through A and B in parallel. The ratio of pathways A and B could not be determined by the analysis of the crude product by ^{1}H-NMR because an appreciable part of N-acetyl-p-nitroaniline would be further hydrolyzed to give p-nitroaniline
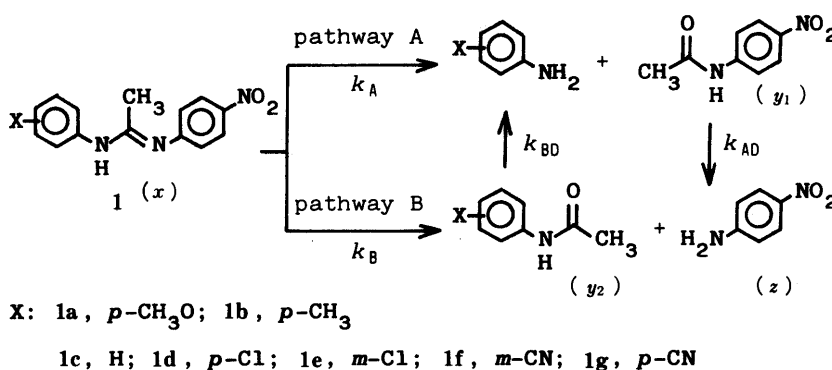
X: 1a, p-CH$_3$O; 1b, p-CH$_3$

1c, H; 1d, p-Cl; 1e, m-Cl; 1f, m-CN; 1g, p-CN

Chart 1

and acetic acid under the conditions used.

The UV spectra of 1d, N-acetyl-p-nitroaniline and N-acetyl-p-chloroaniline in 20% aqueous dioxane solution containing 0.1 M hydrochloric acid are shown in Fig. 1.

The kinetic runs of hydrolysis of 1a—g were carried out in 20% aqueous dioxane containing 0.1 M hydrochloric acid at 40 °C unless otherwise noted. The reaction was followed by measurement of UV spectra of the reaction solution. The proportion of each component was calculated from the absorbance at λ_{max} of each component. In the case of 1a—c, the proportion of N-acetylarylamine (y_2) was proved to be negligible in each measurement. The rate constant of pathway A, k_A, was calculated by using the equation, $k_A t = \ln(1/x)$, where x is the proportion of 1, and the results are shown in Table I.

The proportion of each component, x, y_1 (N-acetyl-p-nitroaniline), y_2 and z (p-nitroaniline) for 1d—g is represented by Eq. 1—4, respectively.

$$x = \exp[-(k_A + k_B)t] \tag{1}$$

$$y_1 = \frac{k_A}{k_A + k_B - k_{AD}} \{\exp(-k_{AD}t) - \exp[-(k_A + k_B)t]\} \tag{2}$$

$$y_2 = \frac{k_B}{k_A + k_B - k_{BD}} \{\exp(-k_{BD}t) - \exp[-(k_A + k_B)t]\} \tag{3}$$

$$z = \frac{k_B - k_{AD}}{k_A + k_B - k_{AD}} \{1 - \exp[-(k_A + k_B)t]\}$$

$$+ \frac{k_A}{k_A + k_B - k_{AD}} [1 - \exp(-k_{AD}t)] \tag{4}$$

where k_B is the rate constant of pathway B, and k_{AD} and k_{BD} are the rate constants of hydrolysis of N-acetyl-p-nitroaniline and N-acetylarylamine under the same conditions, respectively. The values of k_{AD} and k_{BD} were evaluated in separate experiments. The value of $(k_A + k_B)$ was evaluated by using Eq. 1, and Eq. 4 was transformed into Eq. 5.

$$\frac{1 - \exp(-k_{AD}t)}{k_A + k_B - k_{AD}} k_A + \frac{1 - \exp[-(k_A + k_B)t]}{k_A + k_B - k_{AD}} k_B$$

$$= z + \frac{1 - \exp[-(k_A + k_B)t]}{k_A + k_B - k_{AD}} k_{AD} \tag{5}$$

Approximate values for k_A and k_B were calculated from Eq. 5 by the least-squares method, and were corrected by means of the non-linear least-squares method. The method was
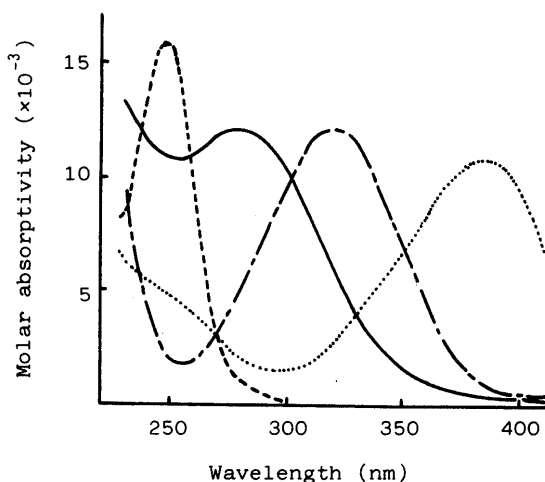

Fig. 1. UV Spectra of 1d, N-Acetyl-p-nitroaniline, N-acetyl-p-Chloroaniline and p-Nitroaniline in 20% Aqueous Dioxane in the Presence of 0.1 M HCl at 40 °C

——, 1d; ———, N-acetyl-p-nitroaniline; ------, N-acetyl-p-chloroaniline; ······, p-nitroaniline.

carried out on the assumption that the approximate Eq. 6—9 are valid,

$$x - x^c = \frac{\delta x}{\delta k_A} \Delta k_A + \frac{\delta x}{\delta k_B} \Delta k_B \tag{6}$$

$$y_1 - y_1^c = \frac{\delta y_1}{\delta k_A} \Delta k_A + \frac{\delta y_1}{\delta k_B} \Delta k_B \tag{7}$$

$$y_2 - y_2^c = \frac{\delta y_2}{\delta k_A} \Delta k_A + \frac{\delta y_2}{\delta k_B} \Delta k_B \tag{8}$$

$$z - z^c = \frac{\delta z}{\delta k_A} \Delta k_A + \frac{\delta z}{\delta k_B} \Delta k_B \tag{9}$$

where x^c, y_1^c, y_2^c and z^c are calculated values from Eq. 1, 2, 3 and 4, respectively, and $k_A + \Delta k_A$, $k_B + \Delta k_B$ are the corrected values for k_A and k_B, respectively. The results are shown in Table I.

According to DeWolfe's results,[1] acid hydrolysis of diarylamidine would be subjected to specific acid-general base catalysis. The reaction is initiated by the attack of water on the conjugate acid of amidine, followed by general base-catalyzed departure of the amino group from the protonated tetrahedral intermediate (IHa or IHb, Chart 2). The rate constant, k_A, increased with increasing electron-withdrawing effect of the substituents on the N^1-aryl group, and electron-withdrawing substituents on the N^1-aryl
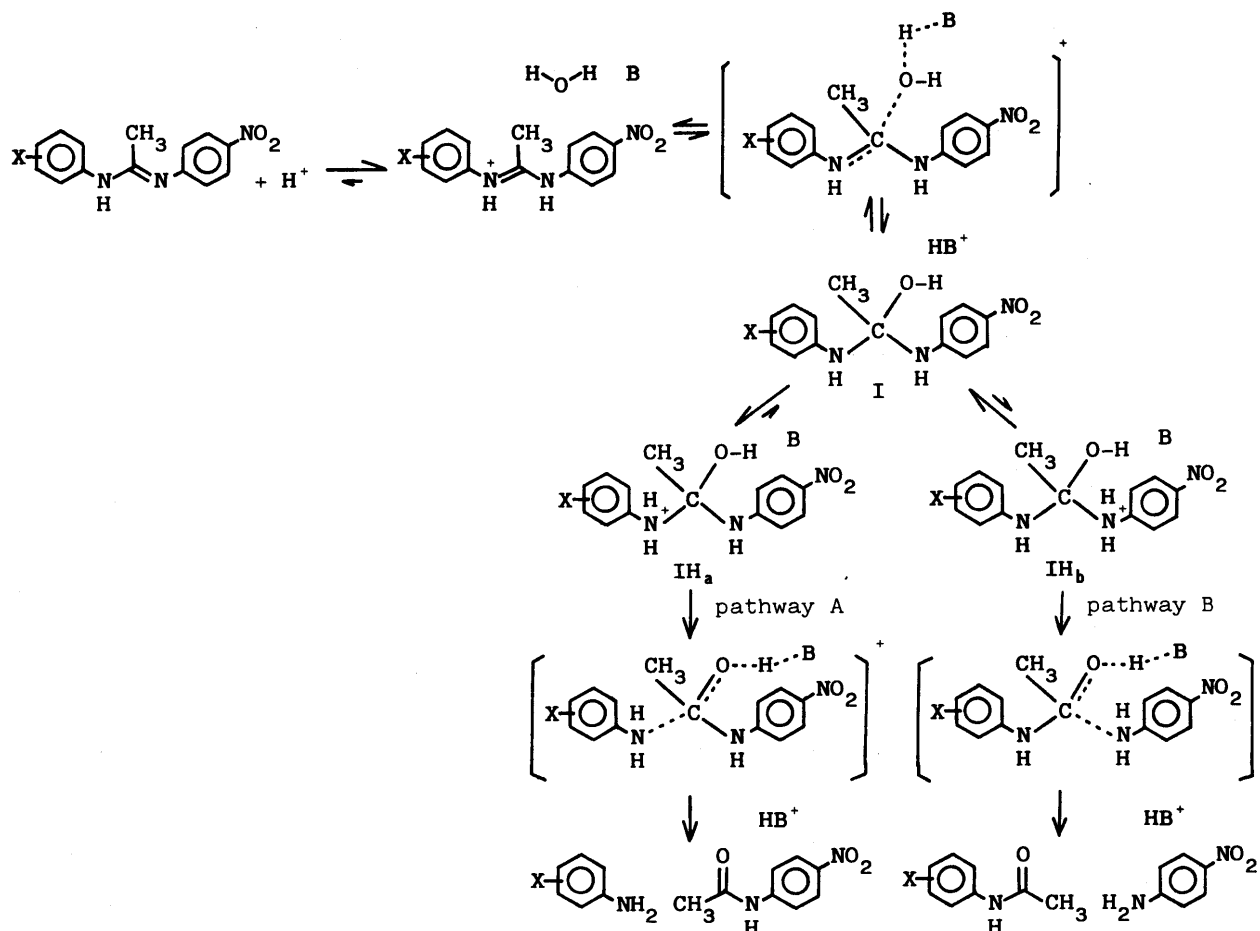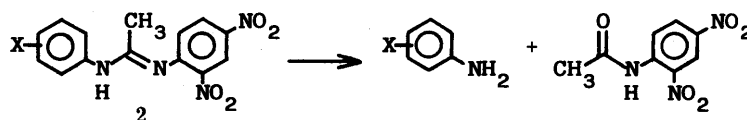
Chart 2

X: 2a, p-CH$_3$O; 2b, p-CH$_3$; 2c, H; 2d, p-Cl

Chart 3

group cause a decrease of k_A/k_B. In the tetrahedral intermediate (I), an increase in amine basicity is expected to cause a large increase in the amount of amine protonation and a moderate decrease in the leaving ability of the protonated amine. Protonation of intermediate (I) is expected to take place mostly at the more basic nitrogen, resulting in formation of IHa. The rate of the second step is a function of the extent of protonation and the leaving ability of the protonated amino moiety. Although the leaving ability of the protonated amino moiety in IHb is greater than that in IHa, the reaction proceeds mostly through IHa because the large extent of protonation at the more basic nitrogen can overcome differences in the leaving ability of the protonated amino moieties. A pathway including the protonated intermediate IHa (pathway A) would be expected to predominate over the other pathway including IHb (pathway B, Chart 2). Robinson and Jencks[3] pointed out that the hydrolysis of $N^{5,10}$-methenyltetrahydrofolic acid takes place with the expulsion of the more basic nitrogen to give N^{10}-formyltetrahydrofolic acid.

Hand and Jencks[4] reported that the reaction of ethyl N-methylbenzimidate and ammonia gave N-methylbenzamidine at pH 9.8 while it gave unsubstituted benzamidine at pH 7.9. They pointed out that the attack of ammonia is rate-limiting and the tetrahedral intermediate formed rapidly loses ethanol to give the monosubstituted amidine at pH 9.8 while departure of ethanol from the intermediate is rate-limiting at pH 7.9. Bender and Thomas[5] found that electron-releasing aryl substituents facilitate product formation from the tetrahedral intermediate over the reverse reaction in the alkaline hydrolysis of N-acetylarylamine. They pointed out that the protonation of the aryl-amino nitrogen of the tetrahedral intermediate enhances the leaving ability of the arylamino group. In alkaline hydrolysis of β-arylaminoacrolein, the ratio of rate of product formation to that of the reverse process from the tetrahedral intermediate increased with increasing electron-releasing effect of aryl substituents.[6]

Hydrolysis of N^1-aryl-N^2-(2,4-dinitrophenyl)acetamidine (2), which carries more electron-withdrawing sub-
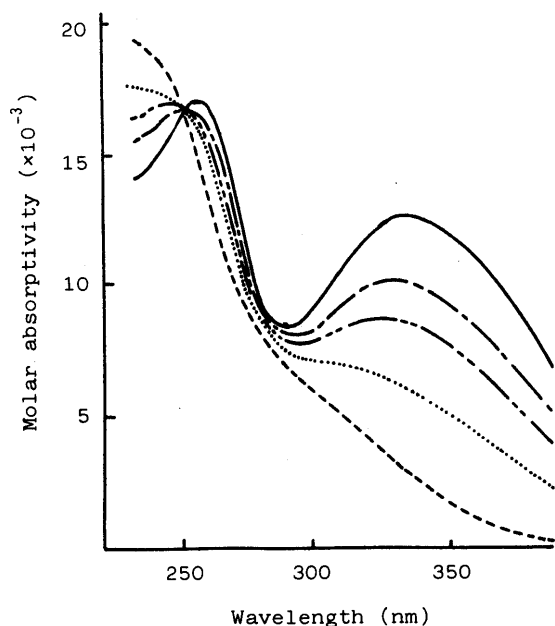
Fig. 2. UV Spectra of **2c** in 20% Aqueous Dioxane at 25 °C (———); in the Presence of 4×10^{-4} M HCl (————); in the Presence of 8×10^{-4} M HCl (——); in the Presence of 2×10^{-3} M HCl ($\cdots\cdots$); in the Presence of 1×10^{-1} M HCl (-----)
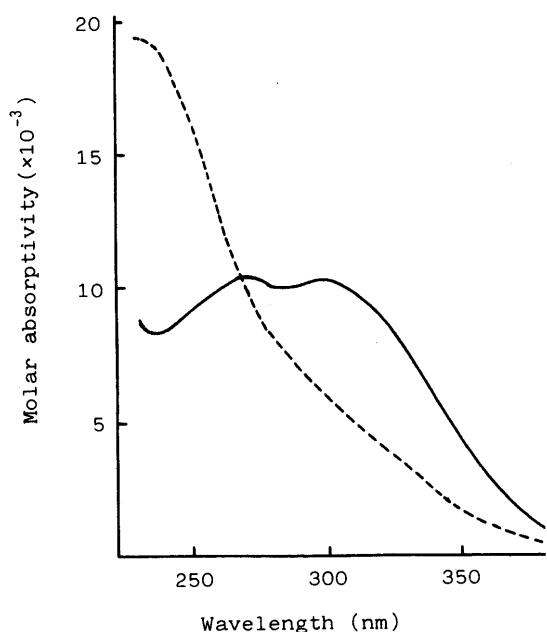

Fig. 3. UV Spectra of **2c** and N-Acetyl-2,4-dinitroaniline in 20% Aqueous Dioxane in the Presence of 0.1 M HCl at 25 °C

-----, **2c**; ———, N-acetyl-2,4-dinitroaniline.

stituents on the N^2-aryl group than **1**, proceeded with measurable rates in 20% aqueous dioxane solution containing various concentrations of hydrochloric acid at 25 °C (Chart 3). The UV spectra of N^1-phenyl-N^2-(2,4-dinitrophenyl)acetamidine (**2c**) in 20% aqueous dioxane solution containing various concentrations of hydrochloric acid at 25 °C are shown in Fig. 2. The reaction was followed by measuring the UV spectra of the reaction solution. Proportions of **2** and N-acetyl-2,4-dinitroaniline were calculated from the absorbance at λ_{max} of each component (Fig. 3). In each measurement, the absorbance of the reaction
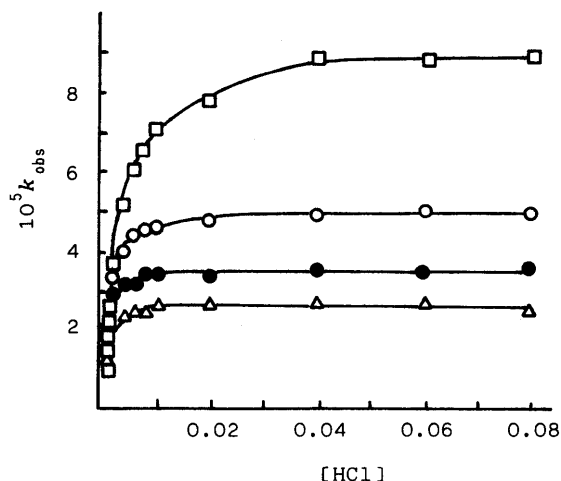

Fig. 4. Plots of Apparent Rate Constant, k_{obs}, of Hydrolysis of **2** in 20% Aqueous Dioxane versus [HCl] at 25 °C

Ionic strength 0.1. △, **2a**; ●, **2b**; ○, **2c**; □, **2d**.

TABLE I. Rate Constants of Hydrolysis of **1** in the Presence of 0.1 M HCl at 40 °C[a]

	Solvent	$10^6 k_A$ (s^{-1})	$10^6 k_B$ (s^{-1})	k_A/k_B
1a	20% dioxane	1.85 (0.029)		
1b	20% dioxane	3.34 (0.055)		
1c	20% dioxane	5.65 (0.045)		
1d	20% dioxane	12.3 (0.64)	1.41 (0.379)	8.7
1e	20% dioxane	18.5 (0.48)	1.76 (0.297)	10.5
1f	20% dioxane	36.9 (1.36)	5.02 (0.841)	7.4
1g	20% dioxane	98.2 (2.90)	42.3 (2.13)	2.3
1d	40% dioxane	27.4 (0.95)	2.48 (0.519)	11.0
1d	60% dioxane	48.9 (1.28)	5.23 (0.756)	9.3
1d	40% EtOH	17.1 (0.81)	1.98 (0.444)	8.6

a) Standard deviations are shown in parentheses.

solution at every 5 nm in the range of 230 to 400 nm was in good agreement with the values calculated from the concentrations of **2** and N-acetyl-2,4-dinitroaniline using the extinction coefficient of each component at the given wavelength. The results showed that the reaction proceeded one-sidedly to expel the more basic arylamine. The rate constants of hydrolysis of **2a**—**d** at various concentrations of hydrochloric acid are shown in Fig. 4. Plots of k_{obs} versus hydrochloric acid concentration showed a gradually decreasing slope, and reached plateau values at above 0.04 M hydrochloric acid showing that the substrates were almost entirely converted to their reactive conjugate acids. Chandler et al.[7] pointed out that the rate of acid hydrolysis of 1-[N-(tert-butyl)formimidoyl]imidazole became pH-independent at near pH 4. The rate constants of the reaction of the conjugate acid of **2** and water, k^H, are represented by the equation, $k^H = k_{obs}([H^+] + K_{BH^+})/[H^+]$, and are shown in Table II. The k^H's in 20% aqueous dioxane solution are related to Hammett's substituent constant, σ, by the equation: $\log k^H = 1.00\sigma - 4.30$ ($r = 0.9981$).

The rate constants of hydrolysis of **2a**—**d** in 20% aqueous dioxane solution in the presence of various concentrations of acetic acid are shown in Fig. 5. Assuming that the reaction can be rationalized in terms of general base-catalyzed hydrolysis of the amidinium ion, the rate con-

stants can be represented by Eq. 10.

$$k_{obs} = \frac{\sqrt{K_a}\sqrt{[AcOH]}}{K_{BH^+} + \sqrt{K_a}\sqrt{[AcOH]}}(k^H + k^{AcO^-}[AcO^-]) \qquad (10)$$

where K_a is the dissociation constant of acetic acid in 20% aqueous dioxane, and was calculated from the UV spectra of 20% aqueous dioxane solution of 2 containing acetic acid using known values of K_{BH^+} of 2 to be 4.77×10^{-6} M at 25 °C. DeWolfe and Roberts[8] reported the dissociation constant of acetic acid in 21.4% aqueous dioxane solution to be 4.41×10^{-6} M at 35 °C. The concentration of acetate ion in 20% aqueous dioxane solution containing 0.5 M acetic acid was calculated to be 1.54×10^{-3} M. The acetate ion-catalyzed term may be insignificant owing to the low
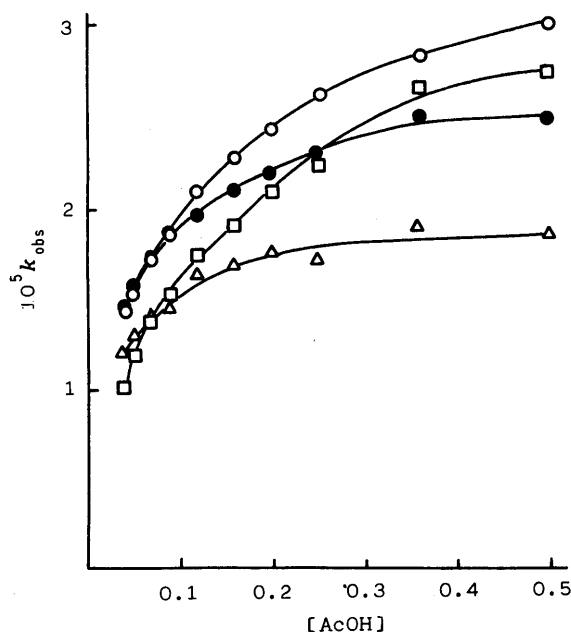
concentration of acetate ion. Neglecting the term $k^{AcO^-}[AcO^-]$, Eq. 10 is transformed into

$$\frac{1}{k_{obs}} = \frac{K_{BH^+}}{k^H\sqrt{K_a}}\frac{1}{\sqrt{[AcOH]}} + \frac{1}{k^H} \qquad (11)$$

A linear relation was obtained by plotting the left-hand side of Eq. 11 versus the reciprocal of the square root of acetic acid concentration, showing that the above postulate is valid (Fig. 6). The values of k^H were calculated by using the equation, $k^H = k_{obs}(K_{BH^+} + \sqrt{K_a}\sqrt{[AcOH]})/\sqrt{K_a}\sqrt{[AcOH]}$, to be as follows ($s^{-1}$, standard deviations are shown in parentheses): 2a, 2.52 (0.076) × 10^{-5}; 2b, 3.52 (0.051) × 10^{-5}; 2c, 4.89 (0.167) × 10^{-5}; 2d, 7.70 (0.221) × 10^{-5}. The results are in good agreement with the values obtained by hydrolysis of 2a—d in the presence of hydrochloric acid (Table II). The results showed that the reaction is not subject to general acid catalysis.
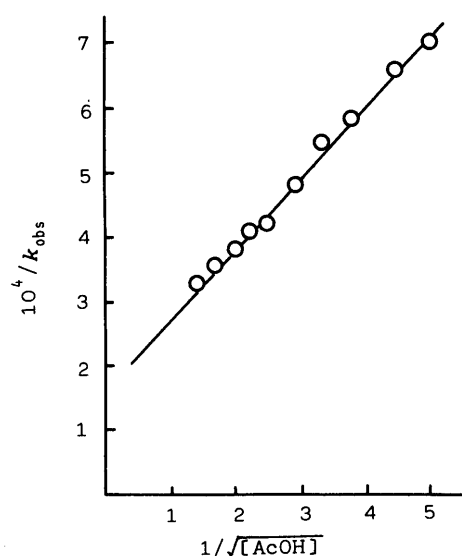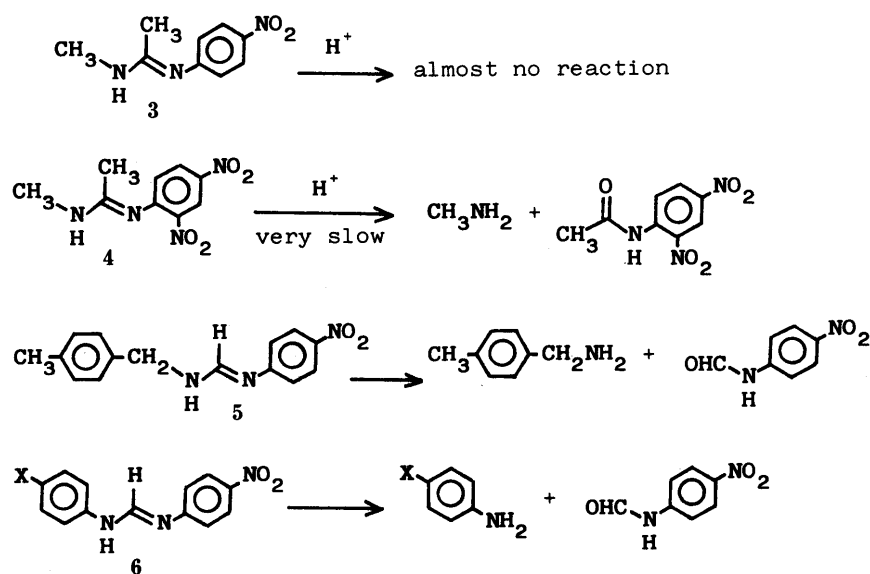

Fig. 5. Plots of Apparent Rate Constant, k_{obs}, of Hydrolysis of 2 in 20% Aqueous Dioxane versus [AcOH] at 25 °C

△, 2a; ●, 2b; ○, 2c; □, 2d.

Fig. 6. Plots of Reciprocal of Apparent Rate Constant of Hydrolysis of 2c versus Reciprocal of the Square Root of [AcOH] in 20% Aqueous Dioxane at 25 °C

X: 6a, CH₃O; 6b, CH₃; 6c, H; 6d, Cl

Chart 4

Table II. Rate Constants (k^H) of the Reaction of the Conjugate Acid of 2 and H_2O at 25°C[a]

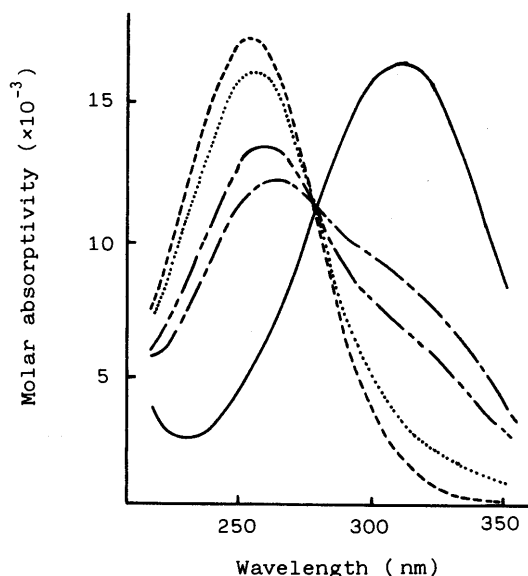|	Solvent	$10^5 k^H$ (s^{-1})
2a	20% dioxane	2.59 (0.059)
2b	20% dioxane	3.55 (0.072)
2c	20% dioxane	4.94 (0.246)
2d	20% dioxane	8.45 (0.676)
2c	10% dioxane	3.12 (0.078)
2c	30% dioxane	7.54 (0.207)
2c	40% dioxane	10.4 (0.061)

a) Standard deviations are shown in parentheses.

Fig. 7. UV Spectra of 5 in 20% Aqueous Dioxane at 25°C in the Presence of 0.01 M $NaHCO_3$ (——); in the Presence of AcOH and AcONa (1:8) (— — —); in the Presence of AcOH and AcONa (1:5) (-- -- --); in the Presence of AcOH and AcONa (1:1) (·····) and in the Presence of 0.01 M HCl (------)

Ionic strength 0.1.

The UV spectrum of a 20% aqueous dioxane solution of N^1-methyl-N^2-(p-nitrophenyl)acetamidine (3) showed almost no change after heating for 10 h in the presence of 0.1 M hydrochloric acid at 60°C. The change of the UV spectrum of a 20% aqueous dioxane solution of N^1-methyl-N^2-(2,4-dinitrophenyl)acetamidine (4) showed about 50% progress of hydrolysis of the substrate after 3 d in the presence of 0.1 M hydrochloric acid at 25°C. Even in the presence of a strongly electron-withdrawing group on the aryl moiety, acid hydrolysis of N^1-alkyl-N^2-aryl-acetamidine proceeds much more slowly than that of N^1,N^2-diarylacetamidine (Chart 4).

Acid hydrolysis of N^1-(p-methylbenzyl)-N^2-(p-nitropheny)formamidine (5) proceeded much more quickly than that of 3. ^{1}H-NMR analysis of the crude product which was obtained by standing of an aqueous dioxane solution of 5 for 16 h in the presence of acetic acid at room temperature showed that the reaction proceeds one-sidedly to give N-formyl-p-nitroaniline and p-methylbenzylamine (Chart 4).

The UV spectra of a 20% aqueous dioxane solution of 5 under various conditions are shown in Fig. 7. Acid hydrolysis of 5 was followed spectrophotometrically at 25°C.

Proportions of 5 and N-formyl-p-nitroaniline were calculated from the absorbancies of the neutralized reaction solution. Hydrolysis of 5 proceeded with a rate constant of $1.90 \pm 0.133 \times 10^{-5}$ or $1.98 \pm 0.167 \times 10^{-5}$ s^{-1}, in the presence of 7×10^{-4} or 9×10^{-4} M hydrochloric acid, respectively. Rate constants of hydrolysis of 5, k_{obs}, in 20% aqueous dioxane solution containing acetic acid and sodium acetate (1:1) are represented by Eq. 12 on the assumption that the reaction can be rationalized in terms of general base-catalyzed hydrolysis of the conjugate acid of 5,

$$\frac{[H^+] + K_{BH^+}}{[H^+]} k_{obs} = k^H + k^{AcO^-}[AcO^-] \tag{12}$$

A linear relation was obtained by plotting the left-hand side of Eq. 12 versus concentration of acetate ion. The values of k^H and k^{AcO^-} were calculated to be $2.13 \pm 0.022 \times .10^{-5}$ s^{-1} and $4.26 \pm 0.068 \times 10^{-4}$ s^{-1} M^{-1}, respectively. These results support the validity of the above assumption (Chart 2).

Hydrolysis of N^1-aryl-N^2-(p-nitrophenyl)formamidine (6a—c) proceeded much faster than that of 5 in the presence of 9×10^{-4} M hydrochloric acid.[9] The rate constants obtained were as follows (s^{-1}, standard deviations are shown in parentheses): 6a, 1.07 (0.034) × 10^{-3}; 6b, 2.02 (0.140) × 10^{-3}; 6c, 3.92 (0.176) × 10^{-3} (Chart 4). The precise value for the rate constant of hydrolysis of 6d could not be obtained because the reaction proceeded too rapidly to allow the proportion of each component in the reaction solution to be determined.

Discussion on the Reaction Mechanism

DeWolfe[1] found that the rates of acid hydrolysis of symmetrical diarylamidines decreased rapidly with increasing acidity of the reaction media. He concluded that the transition state for hydrolysis must include two molecules of water, and proposed a reaction mechanism in which partition of the protonated tetrahedral intermediate with the aid of two molecules of water is rate-limiting. He claimed that this mechanism would account for the large negative value (−20 eu) of activation entropy of the reaction. The value is, however, a usual one for a bimolecular process. For example, activation entropies for the first step of alkaline hydrolysis of β-arylaminoacrolein lie in the range of −15 to −20 eu.[6]

Our experimental results on the acid hydrolysis of unsymmetrical amidines can be understood as follows. First, electron-withdrawing N^1-substituents increase the reaction rate. Second, the tetrahedral intermediates (I, Chart 2) have a tendency to expel the more basic amine under acidic conditions (pathway A).

Blackburn and Jencks[10] found that the hydrolysis of N-(methoxymethylene)morpholinium methosulfate gave N-formylmorpholine under alkaline conditions, but gave methyl formate and morpholine under acidic conditions. They concluded that the protonated morpholino group would possess better leaving ability than the methoxyl group. Their conclusion accounts well for the well-known fact that hydrolysis of imidates affords an amide and an alcohol under alkaline conditions but an amine and an ester under acidic conditions.

Bender and Ginger[11] proved the first step to be rate-limiting in acid hydrolysis of benzamide on the basis of a study on the exchange of isotopic carbonyl oxygen with the

medium. This can be rationalized in terms of a similar pattern of partition of the tetrahedral intermediate to the breakdown of the intermediate of acid hydrolysis of N-(methoxymethylene)morpholinium methosulfate. In the hydrolysis of amidine, most of the tetrahedral intermediate (I, Chart 2) would be protonated under acidic conditions. Because the protonated amino group has a greater tendency to leave than the hydroxyl group, probably attack of water on the amidinium ion is the rate-limiting step in the acid hydrolysis of amidine. The rates of hydrolysis of 1d and 2c increased with increasing dioxane content in the solvent (Tables I and II). This can be rationalized by a mechanism according to which charge is dispersed on going from the reactants to the transition state, and is in accord with the reaction mechanism in which the reaction of amidinium ion and water is rate-limiting (Chart 2).

References and Notes

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9) Hydrolysis of 6a was proved to proceed one-sidedly to give N-formyl-p-nitroaniline and p-anisidine on the basis of ^{1}H-NMR analysis of the crude products. In the hydrolysis of 6b—d, the existence of a minor pathway leading to N-formylarylamine and p-nitroaniline was observed. The ratio of N-formylarylamine to N-formyl-p-nitroaniline formed was proved to be one-twentieth or less.

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