Chem. Pharm. Bull. 37(11) 2902—2908 (1989) Vol. 37, No. 11

A Kinetic Study of Alkaline Hydrolysis of β-Arylaminoacrolein

Machiko ONO,[a] Reiko TODORIKI,[a] Akihisa MITAKE,[a] Miho YUKAWA,[b] Yoshinobu GOTO,[b] and Shinzo TAMURA*,[a]

School of Pharmaceutical Sciences, Toho University,[a] 2–2–1 Miyama, Funabashi 274, Japan and Faculty of Pharmaceutical Sciences, Fukuoka University,[b] Nanakuma, Jonan-ku, Fukuoka 814–01, Japan. *Received January 25, 1989*

Alkaline hydrolysis of β-arylaminoacrolein (1), a vinylog of amides, was studied kinetically. The kinetics involved terms both first and second order in hydroxide ion. The first step of the reaction (rate constant k_1) is an attack of hydroxide ion on the β-position of 1, and the tetrahedral intermediate formed was partitioned in two ways: one without the aid of hydroxide ion ($k_2(k_1/k_{-1})$), and the other with the aid of hydroxide ion ($k_3(k_1/k_{-1})$). The rate constants, k_1, $k_2(k_1/k_{-1})$ and $k_3(k_1/k_{-1})$ were obtained for 12 substrates, and the activation parameters, $\Delta H^{\neq}$ and $\Delta S^{\neq}$, of each step were evaluated for 5 substrates. The k_2/k_{-1} values decreased with increasing electron-withdrawing effect of aryl substituents. The differences of ΔH_f between the intermediates and the starting materials were evaluated by molecular orbital (MO) calculations. The results showed that k_2 decreases with increasing electron-withdrawing effect of the substituents. The second step of the second-order reaction, $k_2(k_1/k_{-1})$, is partitioning of anionic intermediates catalyzed by water as a general acid. While the second step of the third-order reaction, $k_3(k_1/k_{-1})$, for "typical" substrates is departure of the arylamino group from the anionic intermediates catalyzed by both hydroxide ion and water, that for β-(p-nitrophenylamino)acrolein (1j) is direct expulsion of p-nitroanilide ion from the dinegatively charged intermediate.

Keywords alkaline hydrolysis; kinetic study; β-arylaminoacrolein; MO calculation; activation parameter; reaction mechanism; isotope effect

While the alkaline hydrolysis of esters obeys first order kinetics in hydroxide ion except for a very few cases, *e.g.*, the hydrolysis of cobalt(II), pentaammine (trifluoroacetato),[1)] that of amides follows a kinetics higher than first order due to the poorer leaving ability of the amino group.[2-4)]

In this paper we will report a kinetic study of the alkaline hydrolysis of β-arylaminoacrolein (1), a vinylog of amides, which can be hydrolyzed at measurable rates at 25 °C in 1% aqueous EtOH solution in the presence of NaOH (Chart 1).

Precise values of the rate constants, k_1, k_2 (k_1/k_{-1}) and k_3 (k_1/k_{-1}) could be obtained, and the results together with MO calculations on the energy difference between the tetrahedral intermediates (2) and the starting materials are consistent with the reaction mechanism proposed by DeWolfe and Newcomb[4)] for the alkaline hydrolysis of *N*-acylaniline.

While the rate constants of the first step of the present reaction, k_1, shown a linear logarithmic relation with Hammett's substituent constants, σ, with a ρ value of 0.81 ± 0.074 for **1a**—**j**, the rate constants of the second step of the second-order reaction, $k_2(k_1/k_{-1})$, show almost no variation with changing substituents for the same substrates. Consequently, k_2/k_{-1} decreases with increasing electron-withdrawing effect of the substituents on the aryl group.

The differences of ΔH_f between the tetrahedral intermediates and the starting materials were evaluated by semiempirical molecular orbital calculation (MNDO method) for **1a**, **1b**, **1d**, **1f** and **1h**. The results show that the greater is the electron-withdrawing effect of the substituents, the lower is the energy level of the intermediates, putting the energy levels of the reactants at the same level. As a result, k_2 should decrease with increasing electron-withdrawing effect of the substituents on the aryl group.

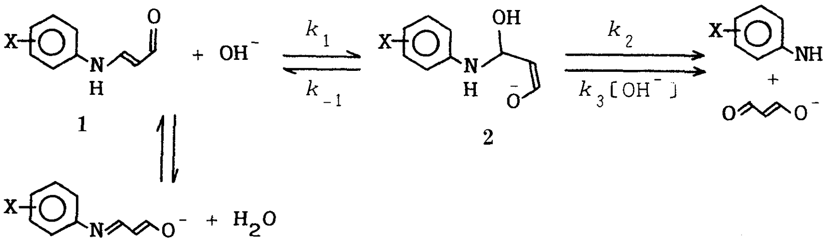
Experimental

Absorption spectra were measured on a Hitachi spectrophotometer, model 139, and proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on JNM-PMX 60 and JNM-GX 400 NMR spectrometers with Me_4Si as an internal standard.

The ionic strength of the reaction solution was maintained at 1.0 by the addition of NaCl. The kinetic runs were carried out at 25 °C unless otherwise noted.

Materials Compounds **1a**, **1b**, **1c**, **1d**, **1f** and **1g** were prepared according to the previous papers[5,6)] and compounds **1e**[7)] and **1j**[8)] were prepared according to the cited references.

β-(p-Cyanophenylamino)acrolein (1h) p-Aminobenzonitrile (2.36 g, 20 mmol) was dissolved in 30 ml of hot AcOH, and 5 ml of H_2O was added to the solution. Freshly distilled β-ethoxyacrolein[6)] (2.20 g, 22 mmol) was



X: **1a**, p-CH_3O; **1b**, p-CH_3; **1c**, m-CH_3; **1d**, H;
1e, m-CH_3O; **1f**, p-Cl; **1g**, m-Cl; **1h**, p-CN;
1i, m-NO_2; **1j**, p-NO_2; **1k**, o-CH_2OH; **1l**, o-C_2H_5

Chart 1

added to the solution, and the mixture was allowed to stand overnight at room temperature. The deposited crude **1h** was collected and recrystallized from EtOH to give 2.83 g (82%) of pure **1h**. mp 194 °C (dec.). *Anal.* Calcd for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.69; H, 4.68; N, 16.27. MS *m/z*: 172 (M^+, 100%), 143 (44), 118 (43). ^{1}H-NMR (60 MHz, CD_3SOCD_3): 5.56 (1H, dd, *J*=9, 13 Hz, H-α), 7.27 (2H, d, *J*=8 Hz, H-2,6), 7.70 (2H, d, *J*=8 Hz, H-3,5), 8.09 (1H, t, *J*=13 Hz, H-β), 9.26 (1H, d, *J*=9 Hz, CHO), 10.28 (1H, d, *J*=13 Hz, NH).

β-(*m*-Nitrophenylamino)acrolein (1i) *m*-Nitroaniline (2.76 g, 20 mmol) was treated as described above and the resulting crude **1i** was recrystallized from acetone to give 3.15 g (82%) of pure **1i**. mp 190 °C (dec.). *Anal.* Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.09; H, 4.19; N, 14.44. MS *m/z*: 192 (M^+, 100%), 145 (66), 117 (80). ^{1}H-NMR (60 MHz, CD_3SOCD_3): 5.55 (1H, dd, *J*=9, 13 Hz, H-α), 7.50—8.00 (4H, m, Ar), 8.17 (1H, t, *J*=13 Hz, H-β), 9.33 (1H, d, *J*=9 Hz, CHO), 10.33 (1H, d, *J*=13 Hz, NH).

β-(*o*-Hydroxymethylphenylamino)acrolein (1k) *o*-Aminobenzyl alcohol (1.22 g, 10 mmol) was dissolved in 5 ml of MeOH, and a trace of $NaHCO_3$ and a solution of freshly distilled β-ethoxyacrolein[6)] (1.00 g, 10 mmol) in 10 ml of MeOH were added to the solution. The mixture was refluxed for 6 h on a water bath and filtered. The filtrate was concentrated under reduced pressure, and the residue was treated with 5 ml of a mixture of ether and MeOH (4 : 1). The precipitate was filtered off, and 5 ml of ether was added to the filtrate. The precipitate (0.86 g) was recrystallized from benzene to give 0.53 g (30%) of pure **1k**. mp 99 °C. *Anal.* Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.63; H, 6.33; N, 7.90. MS *m/z*: 177 (M^+, 49%), 130 (100). ^{1}H-NMR showed that **1k** consisted of *s-trans* and *s-cis* forms (1 : 1.6) in $CDCl_3$ solution. ^{1}H-NMR (400 MHz): 2.79 (t, *J*=4 Hz, *s-cis* OH), 3.09 (t, *J*=4 Hz, *s-trans* OH), 4.78 (d, *J*=4 Hz, *s-trans* CH_2), 4.79 (d, *J*=4 Hz, *s-cis* CH_2), 5.36 (dd, *J*=2, 7 Hz, *s-cis* H-α), 5.72 (dd, *J*=8, 13 Hz, *s-trans* H-α), 7.04—7.36 (m, Ar), 7.35 (ddd, *J*=3, 7, 13 Hz, *s-cis* H-β), 7.59 (t, *J*=13 Hz, *s-trans* H-β), 8.67 (d, *J*=13 Hz, *s-trans* NH), 9.28 (d, *J*=8 Hz, *s-trans* CHO), 9.30 (dd, *J*=2, 3 Hz, *s-cis* CHO), 12.08 (d, *J*=13 Hz, *s-cis* NH).

β-(*o*-Ethylphenylamino)acrolein (1l) *o*-Ethylaniline (1.21 g, 10 mmol) was treated as above, and the resulting crude oil (1.94 g) was subjected to column chromatography (Al_2O_3) successively with benzene (300 ml) and MeOH (100 ml). The MeOH layer was concentrated under reduced pressure, and the residue was subjected to preparative thin layer chromatography (PTLC) (silica gel) with a mixture of benzene and AcOEt (5 : 1) to give crude **1l** (0.76 g). Recrystallization from petroleum benzin gave 0.51 g (29%) of pure **1l**. mp 67.5 °C. *Anal.* Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.22; H, 7.52; N, 8.15. MS *m/z*: 175 (M^+, 100%), 132 (97). ^{1}H-NMR showed that **1l** consisted of *s-trans* and *s-cis* forms (1 : 2) in $CDCl_3$ solution. ^{1}H-NMR (400 MHz): 1.28 (t, *J*=7 Hz, *s-trans* CH_3), 1.31 (t, *J*=7 Hz, *s-cis* CH_3), 2.64 (q, *J*=7 Hz, *s-trans* CH_2), 2.74 (q, *J*=7 Hz, *s-cis* CH_2), 5.35 (dd, *J*=2, 7.5 Hz, *s-cis* H-α), 5.67 (dd, *J*=8, 13 Hz, *s-trans* H-α), 6.89 (d, *J*=13 Hz, *s-trans* NH), 7.05—7.27 (m, Ar), 7.39 (ddd, *J*=3, 7.5, 12.5 Hz, *s-cis* H-β), 7.55 (t, *J*=13 Hz, *s-trans* H-β), 9.32 (d, *J*=8 Hz, *s-trans* CHO), 9.33 (dd, *J*=2, 3 Hz, *s-cis* CHO), 11.97 (d, *J*=12.5 Hz, *s-cis* NH).

Kinetic Runs An EtOH solution (1 ml, 2×10^{-3} M) of **1** was added to aqueous NaOH solution (0.02—0.50 M) in a 100 ml volumetric flask, and the sample was diluted to the mark with the same aqueous solution.

The rates of hydrolysis were measured spectrophotometrically at λ_{max} of each substrate. For all substrates but **1j**, absorption by arylamine and malonaldehyde was negligible at λ_{max} of **1** (Fig. 1). The apparent pseudo first-order rate constant, k_{obs}, was obtained by plotting ln A_0/A *vs.* time, where *A* is the absorbance of the reaction solution and A_0 is that immediately after dissolution. The absorption spectra of **1j** and *p*-nitroaniline are shown in Fig. 2, and k_{obs} of the hydrolysis of **1j** was obtained by plotting ln $(\varepsilon_0-\varepsilon')/(\varepsilon-\varepsilon')$ *vs.* time where ε_0 is the molar absorptivity of **1j** at λ_{max}, ε' is that of *p*-nitroaniline at the same wavelength, and ε is the ratio of absorbance of the reaction solution at the same wavelength *versus* the initial concentration of **1j**. The absorbances of the reaction solutions of **1b** at 220—400 nm and of **1j** at 220—450 nm were in good agreement with the values calculated from the concentrations of **1**, arylamine and malonaldehyde using the molar absorptivity of each compound at given wavelengths.

Hydrolysis of 1b in EtOD–D_2O solution H–D exchange proceeded gradually at the α-position of **1b** in alkaline EtOD–D_2O solution. To avoid this complexity, the substrate was deuterated before use: a solution of **1b** in MeOD containing some MeONa was warmed at 55 °C for 30 min, and saturated with CO_2. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give *N*,α-dideuterio-β-(*p*-methylphenylamino)acrolein. The completion of deuteration was ascertained by measurement of the ^{1}H-NMR ($CDCl_3$). The kinetic runs were carried out in the same manner as described in the preceding section.

Measurement of K_a The absorption spectrum of **1b** in 1% aqueous EtOH solution showed a very small bathochromic shift and a hypsochromic change in the presence of NaOH (Fig. 3), while the spectrum of **1j** showed a larger bathochromic shift in the presence of NaOH (Fig. 4). The spectrum of **1h** showed a closely similar pattern to that of **1j**. The dissociation constants of **1**, K_a, were measured in two ways (methods 1 and 2).

Method 1: The molar absorptivity of **1** was measured in 1% aqueous EtOH solution at an appropriate wavelength in the presence of 0.01—0.50 M NaOH, and K_a and the molar absorptivity of the conjugate base of **1**, ε_{B^-}, were calculated by the least-squares method from the equation, $(\varepsilon_{BH}-\varepsilon)[H^+]=K_a\varepsilon-K_a\varepsilon_{B^-}$, where ε_{BH} is the molar absorptivity of **1** in 1% aqueous EtOH solution.

Method 2: The ε_{B^-} values of **1j** were calculated by method 1 at λ_{max}'s of **1j** and of the conjugate base, and K_a was calculated in the usual manner using the absorbance of the solution in the presence of 0.01—0.04 M NaOH at the given two wavelengths. The K_a values of **1j** and of **1h** thus obtained were in good agreement with those evaluated by method 1.

The results were as follows (standard deviations are given in paren-

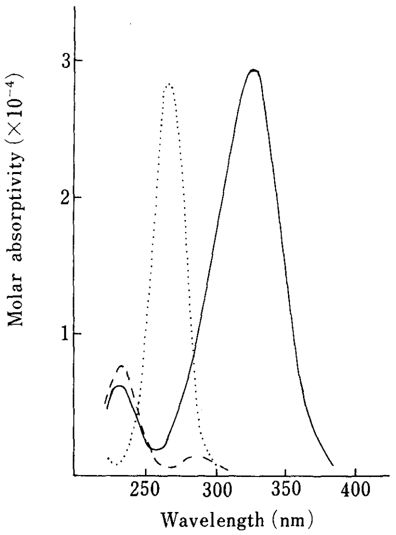


Fig. 1. Absorption Spectra of **1b**, *p*-Toluidine and Malonaldehyde in 1% Aqueous EtOH in the Presence of 0.10 M NaOH

——, **1b**; ----, *p*-toluidine; · · · ·, malonaldehyde.

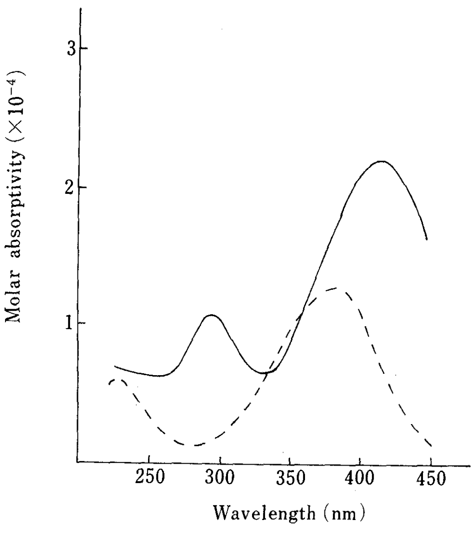


Fig. 2. Absorption Spectra of **1j** and *p*-Nitroaniline in 1% Aqueous EtOH in the Presence of 0.10 M NaOH

——, **1j**; ----, *p*-nitroaniline.

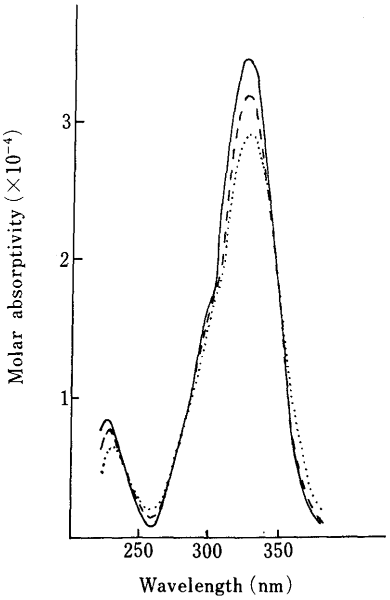


Fig. 3. Absorption Spectra of **1b** in 1% Aqueous EtOH (——), in the Presence of 0.02 M NaOH (----), and in the Presence of 0.10 M NaOH (····)

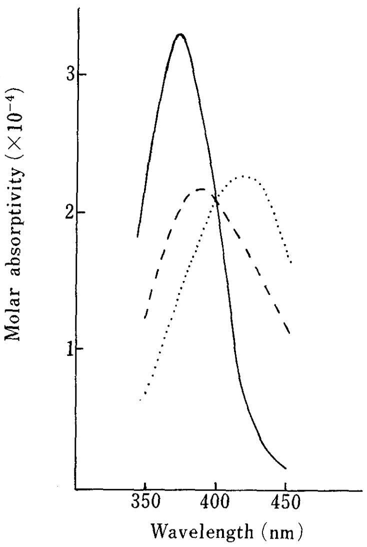


Fig. 4. Absorption Spectra of **1j** in 1% Aqueous EtOH (——), in the Presence of 0.02 M NaOH (----), and in the Presence of 0.30 M NaOH (····)

theses): $10^{14}K_a$ (M): **1a**, 7.20 (1.061); **1b**, 6.47 (0.627); **1c**, 9.21 (0.893); **1d**, 10.4 (0.38); **1e**, 14.8 (0.51); **1f**, 22.9 (2.10); **1g**, 33.0 (1.56); **1h**, 53.4 (1.65); **1i**, 80.1 (2.59); **1j**, 83.9 (6.74); **1k**, 12.0 (2.80) and **1l**, 7.90 (1.074). The K_a values of **1a**—**k** were well correlated to the σ substituent constants by the relation, $\log K_a = 1.11(0.051)\sigma - 12.94(0.022)$. The K_a values of **1a**, **1b**, **1d**, **1f** and **1j** were also measured at 21, 29, 33 and 41 °C by the same methods, and the values obtained were consistent with those measured at 25 °C within the experimental error.

Computational Procedure MO calculations were carried out at the restricted Hartree-Fock level by using the MNDOM program with parameters described by Dewar and co-workers.⁹⁾ All equilibrium geometries were determined by minimizing the total energy with respect to all geometrical variables using the standard DFP (Davidon-Fletcher-Powell) algorithm,¹⁰⁾ in the MNDO method, without any assumptions. The optimized geometries of **1d** and its tetrahedral intermediate are shown in Figs. 5 and 6, respectively. The bond lengths and angles are also indicated in the figures.

The difference in ΔH_f between the reactants (β-arylaminoacrolein and OH^-) and the tetrahedral intermediate **2**, $\Delta\Delta H_f$, was given by the following equation,

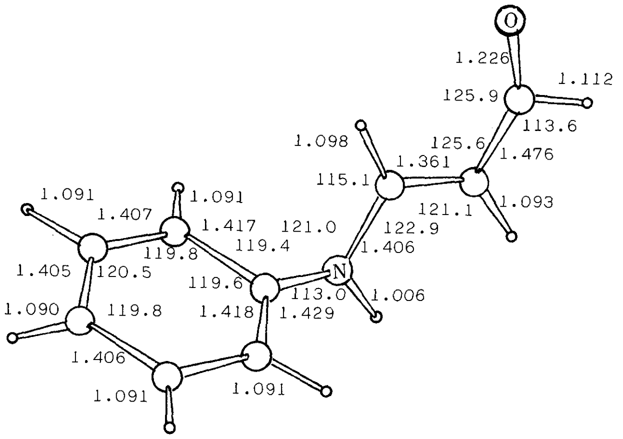
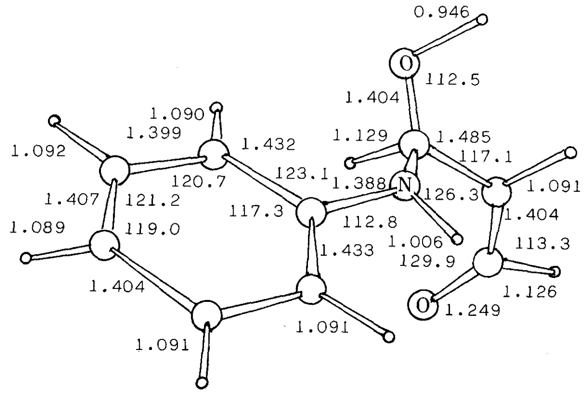


Fig. 5. The Optimized Geometry of **1d** with the Bond Lengths (r/Å) and Bond Angles (ϕ/°)



$r(\mathrm{N{-}C}^\beta) = 1.514$

$\angle \mathrm{C}^\beta\mathrm{NC} = 128.1$ $\angle \mathrm{HC}^\beta\mathrm{N} = 108.1$ $\angle \mathrm{OC}^\beta\mathrm{N} = 105.7$

Fig. 6. The Optimized Geometry of the Tetrahedral Intermediate **2** Formed in the Reaction of **1d** and OH^- with Bond Lengths (r/Å) and Bond Angles (ϕ/°).

$$\Delta\Delta H_f = \Delta H_f(\mathbf{2}) - [\Delta H_f(\beta\text{-arylaminoacrolein}) + \Delta H_f(\mathrm{OH}^-)]$$

where a value of $-5.8\,\mathrm{kcal\,mol^{-1}}$ was used for the heat of formation (ΔH_f) of OH^- ¹¹⁾

Results and Discussion

Mathematical Treatment of Experimental Data Plots of k_{obs} *vs.* $[\mathrm{OH}^-]$ showed a gradually decreasing slope (Fig. 7) due to the partial conversion of the substrates to their unreactive conjugate bases. True rate constants k are expressed by the equation, $k = k_{\mathrm{obs}}(K_a + [\mathrm{H}^+])/[\mathrm{H}^+]$. Plots of k *vs.* $[\mathrm{OH}^-]$ showed an increasing slope (Fig. 8), suggesting that the reaction contains a component which follows second-order kinetics in hydroxide ion.

The reaction pathway is shown in Chart 1 and the rate constant k is expressed by Eq. 1.

$$k = \frac{k_1(k_2/k_3)[\mathrm{OH}^-] + k_1[\mathrm{OH}^-]^2}{k_{-1}/k_3 + k_2/k_3 + [\mathrm{OH}^-]} \tag{1}$$

Eriksson³⁾ showed that alkaline hydrolysis of trifluoroacetanilide obeys the same equation, and estimated the values of k_1, k_{-1}/k_3 and k_2/k_3 from the approximate equation: k_{obs} of the reaction reached a plateau value at large $[\mathrm{OH}^-]$, and k_1 could be calculated from the approximate equation, $k_{\mathrm{obs}} = k_1K_W/(K_a + [\mathrm{H}^+])$. The values of

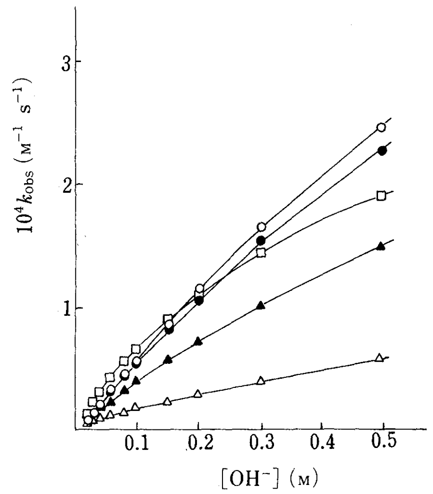


Fig. 7. Plots of Apparent Rate Constants, k_{obs}, of Alkaline Hydrolysis of **1** in 1% Aqueous EtOH *versus* [OH⁻] at 25 °C

Ionic strength 1.0. ○, **1b**; ●, **1d**; △, **1f**; ▲, **1h**; □, **1j**.

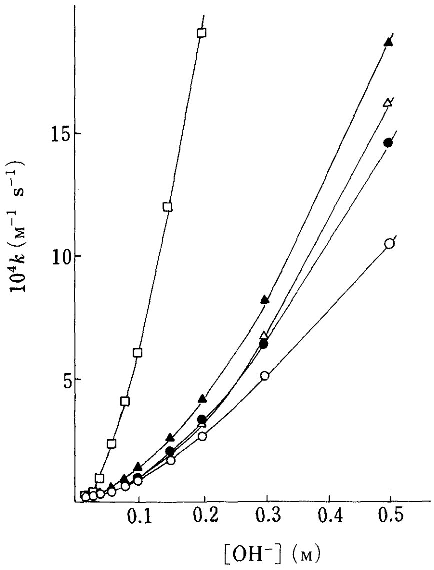


Fig. 8. Plots of Rate Constants, k, of Alkaline Hydrolysis of **1** in 1% Aqueous EtOH *versus* [OH⁻] at 25

Ionic strength 1.0, ○, **1b**; ●, **1d**; △, **1f**; ▲, **1h**; □, **1j**.

k_{-1}/k_3 and k_2/k_3 could be calculated from Eq. 1 using k_1 so obtained.

The [OH⁻]-rate profile for the present reaction (Fig. 7) did not show a plateau even at large [OH⁻], and the values of k_1 could not be obtained in the same way as in the hydrolysis of trifluoroacetanilide.

We established a more general method to obtain rate constants of alkaline hydrolysis of amides and related substrates. Both sides of Eq. 1 are divided by [OH⁻] to give Eq. 2.

$$\frac{k}{[\mathrm{OH}^-]}=\frac{k_1(k_2/k_3)+k_1[\mathrm{OH}^-]}{k_{-1}/k_3+k_2/k_3+[\mathrm{OH}^-]} \qquad (2)$$

Neglecting the third and later terms of Maclaurin's series of the right-hand side of Eq. 2, we obtain

$$\frac{k}{[\mathrm{OH}^-]}=\frac{k_1(k_2/k_3)}{k_{-1}/k_3+k_2/k_3}+\frac{k_1(k_{-1}/k_3)}{(k_{-1}/k_3+k_2/k_3)^2}[\mathrm{OH}^-] \qquad (3)$$

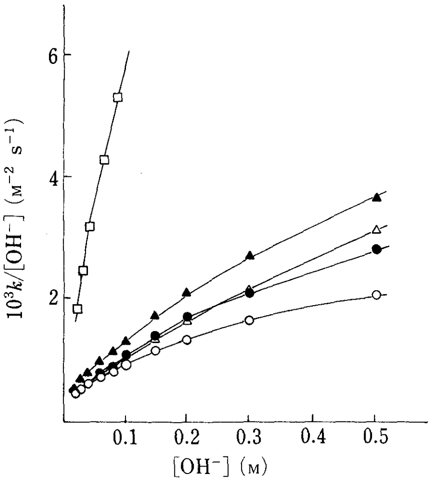


Fig. 9. Plots of $k/[\mathrm{OH}^-]$ *versus* [OH⁻]

○, **1b**; ●, **1d**; △, **1f**; ▲, **1h**; □, **1j**.

Plots of $k/[\mathrm{OH}^-]$ *vs.* [OH⁻] were linear at below 0.06 M [OH⁻] (Fig. 9). Slopes and intercepts of the right-hand side of Eq. 3 were calculated by the least-squares method. The latter was divided by the former to give $(k_2/k_3)(k_{-1}/k_3+k_2/k_3)/(k_{-1}/k_3)$, which can be approximated as k_2/k_3 because k_{-1}/k_3 is seven or more times larger than k_2/k_3.[12] Using the approximate values of k_2/k_3, the values of k_1 and k_{-1}/k_3 were calculated from Eq. 4 by the least-squares method.

$$(k_2/k_3)[\mathrm{OH}^-]+[\mathrm{OH}^-]^2k_1-k(k_{-1}/k_3)=k(k_2/k_3+[\mathrm{OH}^-]) \qquad (4)$$

To obtain better approximate values of k_2/k_3, the initial approximate values of k_2/k_3 obtained above were multiplied by $(k_{-1}/k_3)/(k_{-1}/k_3+k_2/k_3)$. Then, the least-squares calculation was repeated once more using the improved values of k_2/k_3.

Finally, k_1 and k_1/k_3 obtained from Eq. 4 were corrected by means of the non-linear least-squares method. The method was carried out on the assumption that the approximate Eq. 5 is valid,

$$\frac{\delta k}{\delta k_1}\Delta k_1+\frac{\delta k}{\delta(k_{-1}/k_3)}\Delta(k_{-1}/k_3)=k-k_c \qquad (5)$$

where k_c is the calculated rate constant from Eq. 1, and $k_1+\Delta k_1$ and $(k_{-1}/k_3)+\Delta(k_{-1}/k_3)$ are corrected values for k_1 and k_{-1}/k_3, respectively. Then, k_2/k_3 was corrected by averaging the values of k_2/k_3 calculated from Eq. 6 using the corrected values of k_1 and k_{-1}/k_3.

$$k_2/k_3=\frac{k(k_{-1}/k_3)+k[\mathrm{OH}^-]-k[\mathrm{OH}^-]^2}{k_1[\mathrm{OH}^-]-k} \qquad (6)$$

This procedure was repeated twenty to thirty times. The results are shown in Table I.

As can be seen from Table I, the rates of the first step are of similar magnitude to those of the second step for all substrates, so the reaction has no definite rate-limiting step.

The alkaline hydrolysis of **1a**, **1b**, **1d**, **1f** and **1j** was also studied kinetically at 21, 29, 33 and 41 °C, and the rate constants obtained and the activation parameters, $\Delta S^{\neq}$ and $\Delta H^{\neq}$, of each step are shown in Table II.

Discussion of the Mechanism Bender and Ginger[13] showed that k_2/k_{-1} of the alkaline hydrolysis of benzamide in aqueous dioxane solution increases with increasing water content in the solvent. On the basis of microscopic reversibility of the reaction steps, this fact implies that the first step of the reaction forming the tetrahedral intermediate is not an attack of a water molecule aided by hydroxide ion as a general base catalyst, but a nucleophilic attack of hydroxide ion on the carbonyl carbon atom.

The ratio k_H/k_D was found to be 0.84 for k_1 of alkaline hydrolysis of **1b** indicating that the reaction is initiated by a nucleophilic attack of hydroxide ion at the β-position of **1** and the participation of water as a general acid catalyst is not significant. This result is not unexpected because it is well-known that the deuterioxide ion in deuterium oxide is a better nucleophile than hydroxide ion in protium oxide. Bunton *et al.*[14] reported that the ratios k_H/k_D are 0.85—1.0 for the first step of alkaline hydrolysis of benzamides.

The activation entropy $\Delta S^{\neq}$ of k_1 of the present reaction lies in the range of -15 to -20 cal K^{-1} mol^{-1} (Table II) suggesting that the reaction is bimolecular,[15] and giving further support to the above conclusion.

The tetrahedral intermediate is assumed to exist largely in a conjugate base in the aqueous alkaline solution as judged by the pK_a values of the related species, hemiorthoesters (p$K_a \approx 11$ to 12).[16] The second step of the second order reaction is the departure of the arylamino group catalyzed by water as a general acid catalyst (Chart 2).

The kinetic results (Table I) show that k_1 is affected by the electronic effect of the aryl substituents whereas $k_2(k_1/k_{-1})$ is not, suggesting the following two reaction profiles (a) and (b).

Table I. Rate Constants of Alkaline Hydrolysis of **1** in 1% Aqueous EtOH at 25 °C. Ionic Strength 1.0[a]

	10^3k_1 ($\text{M}^{-1}\,\text{s}^{-1}$)	$10^4k_2(k_1/k_{-1})$ ($\text{M}^{-1}\,\text{s}^{-1}$)	$10^3k_3(k_1/k_{-1})$ ($\text{M}^{-2}\,\text{s}^{-1}$)
1a	2.73 (0.051)	4.05 (1.525)	15.3 (0.98)
1b	3.68 (0.027)	4.06 (0.171)	8.33 (0.139)
1b[b]	4.37 (0.036)	3.54 (0.129)	7.36 (0.125)
1c	6.08 (0.112)	3.23 (0.221)	7.43 (0.258)
1d	6.88 (0.037)	3.99 (0.095)	8.71 (0.088)
1e	8.66 (0.170)	3.48 (0.175)	6.82 (0.231)
1f	9.14 (0.065)	4.63 (0.168)	11.0 (0.15)
1g	9.41 (0.163)	4.16 (0.364)	9.71 (0.303)
1h	16.5 (0.58)	4.01 (0.271)	6.77 (0.373)
1i	18.8 (0.18)	5.49 (0.167)	11.0 (0.17)
1j	29.1 (0.11)	5.66 (0.709)	71.5 (0.61)
1k	3.43 (0.027)	11.6 (0.18)	24.2 (0.77)
1l	1.88 (0.009)	2.35 (0.049)	3.24 (0.033)

a) Standard deviations are shown in parentheses. *b*) In EtOD–D_2O solution.

(a) k_1 increases with increasing electron-withdrawing effect of the substituents on the aryl group (*i.e.*, the energy level of TS1 becomes lower), and k_{-1} increases as well (*i.e.*, the energy level of **2** remains unchanged), whereas k_2/k_{-1} decreases, and consequently k_2 remains unchanged.

(b) While k_1 increases in a similar manner to that in (a), k_{-1} remains almost unchanged (*i.e.*, the energy level of **2** becomes relatively lower). As k_2/k_{-1} decreases, k_2 decreases as well.

The MNDO calculations are suggestive of the reaction

Table II. Rate Constants and Activation Parameters of Alkaline Hydrolysis of **1** in 1% Aqueous EtOH at 21, 29, 33 and 41 °C. Ionic Strength 1.0[a]

	°C	10^3k_1 ($\text{M}^{-1}\,\text{s}^{-1}$)	$10^4k_2(k_1/k_{-1})$ ($\text{M}^{-1}\,\text{s}^{-1}$)	$10^3k_3(k_1/k_{-1})$ ($\text{M}^{-2}\,\text{s}^{-1}$)
1a	21	1.92 (0.018)	3.08 (0.653)	11.9 (0.40)
	29	4.04 (0.012)	7.32 (0.229)	15.4 (0.13)
	33	6.42 (0.037)	10.3 (0.46)	17.1 (0.25)
	41	11.9 (0.23)	18.8 (0.94)	25.9 (0.97)
$\Delta H^{\neq}$ (kcal mol^{-1})		16.4 (0.60)	16.5 (1.20)	5.9 (1.00)
$\Delta S^{\neq}$ (cal K^{-1} mol^{-1})		−15.0 (1.98)	−18.3 (3.95)	−47.0 (3.30)
1b	21	2.40 (0.020)	2.76 (0.180)	6.96 (0.143)
	29	5.23 (0.037)	5.52 (0.214)	10.3 (0.16)
	33	7.43 (0.042)	7.84 (0.185)	13.1 (0.16)
	41	14.0 (0.69)	15.2 (1.47)	19.0 (1.65)
$\Delta H^{\neq}$ (kcal mol^{-1})		15.5 (0.36)	14.9 (0.20)	8.8 (0.25)
$\Delta S^{\neq}$ (cal K^{-1} mol^{-1})		−17.8 (1.19)	−24.1 (0.67)	−38.5 (0.82)
1d	21	4.23 (0.087)	2.56 (0.319)	7.64 (0.327)
	29	9.16 (0.074)	5.65 (0.174)	11.4 (0.17)
	33	14.0 (0.30)	8.25 (0.336)	13.5 (0.48)
	41	21.7 (0.40)	15.4 (0.56)	22.5 (0.70)
$\Delta H^{\neq}$ (kcal mol^{-1})		14.3 (1.17)	15.7 (0.47)	9.4 (0.67)
$\Delta S^{\neq}$ (cal K^{-1} mol^{-1})		−20.5 (3.86)	−21.3 (1.55)	−36.2 (2.21)
1f	21	5.49 (0.106)	3.05 (0.343)	9.14 (0.358)
	29	12.9 (0.12)	6.85 (0.231)	13.6 (0.23)
	33	16.8 (0.25)	8.81 (0.433)	18.5 (0.50)
	41	32.3 (0.26)	17.8 (0.52)	28.3 (0.39)
$\Delta H^{\neq}$ (kcal mol^{-1})		15.1 (0.85)	15.3 (0.53)	10.0 (0.50)
$\Delta S^{\neq}$ (cal K^{-1} mol^{-1})		−17.1 (2.82)	−22.4 (1.75)	−33.7 (1.65)
1j	21	19.2 (0.09)	4.28 (0.752)	51.2 (0.56)
	29	42.8 (0.94)	7.86 (2.173)	110 (4.7)
	33	51.3 (1.10)	8.43 (1.960)	176 (7.1)
	41	93.0 (1.20)	16.9 (2.58)	365 (8.6)
$\Delta H^{\neq}$ (kcal mol^{-1})		13.5 (0.86)	11.5 (1.07)	17.8 (0.57)
$\Delta S^{\neq}$ (cal K^{-1} mol^{-1})		−20.3 (2.85)	−34.7 (3.54)	−4.0 (1.87)

a) Standard deviations are shown in parentheses.

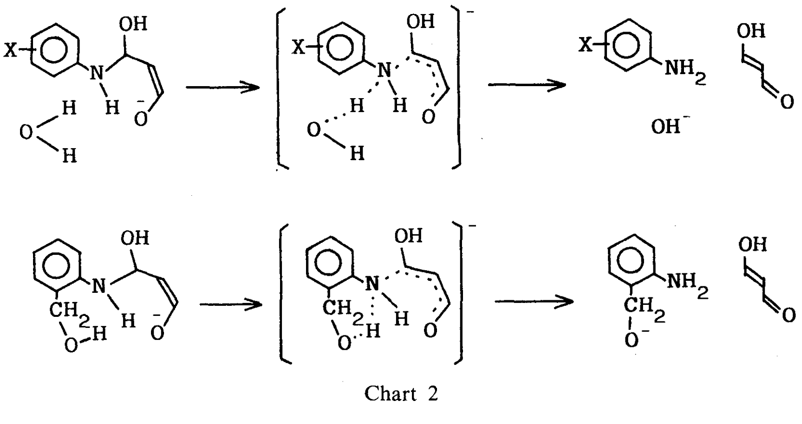


Chart 2

profile (b) as described below. As shown in Table III, it is evident that as the electron-withdrawing effect increases, the difference $\Delta\Delta H_f$ between ΔH_f of **2** and that of the reactants becomes larger, *i.e.*, the energy level of the **2** becomes lower. The energy level of TS1 becomes lower owing to the electron-withdrawing group as described above, *i.e.*, k_{-1} remains almost unchanged and hence k_2 decreases. Figure 10 shows the enthalpy profiles and related enthalpies for the alkaline hydrolysis of β-arylaminoacrolein. In order to see easily the relative differences between energy levels, the energy levels of the reactants are put at the same level.

The rate constant k_2 decreases with increasing electron-withdrawing effect of the aryl substituents presumably by diminishing the basicity of the arylamino nitrogen and so reducing the effectiveness of water as a general acid catalyst. DeWolfe and Newcomb[4] pointed out the same phenomenon in the alkaline hydrolysis of acetanilides.

Table III. ΔH_f (kcal mol^{-1}) of Reactants, Tetrahedral Intermediates (**2**) and Products, Differences of ΔH_f ($\Delta\Delta H_f$, kcal mol^{-1}) between Reactants and **2**, and Energies (eV) of Lowest Unoccupied Molecular Orbital (LUMO) of β-Arylaminoacroleins

	1a	**1b**	**1d**	**1f**	**1h**
Reactants	−34.5	−3.4	4.4	−2.9	35.3
ΔH_f **2**	−115.0	−82.7	−74.0	−86.3	−51.3
Products	−116.2	−84.6	−76.7	−84.8	−46.7
$\Delta\Delta H_f$	−80.5	−79.3	−78.4	−83.4	−86.6
LUMO energies	−0.190	−0.277	−0.199	−0.597	−0.900

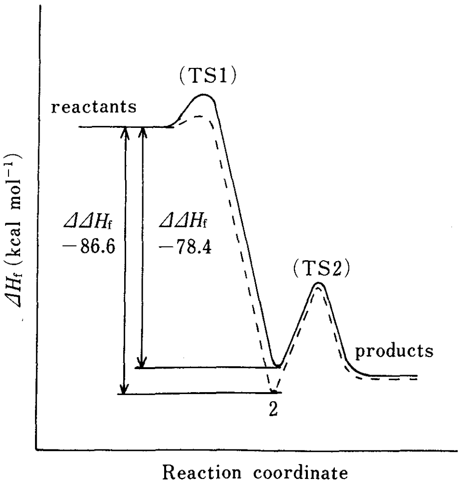


Fig. 10. Enthalpy Profile for the Alkaline Hydrolysis of β-Arylaminoacrolein

——, β-phenylaminoacrolein (**1d**); – – – –, β-(p-cyanophenylamino)acrolein (**1h**).

The existence of catalysis by water is verified by the especially large $k_2(k_1/k_{-1})$ for **1k** (Table I), indicating that the o-CH$_2$OH group catalyzes the reaction intramolecularly (Chart 2). Moreover, $k_2(k_1/k_{-1})$ of **1l**, which has a bulky group at the o-position, was smaller than those of other substrates examined, providing further evidence to support the mechanism shown in Chart 2. The transformation of the intermediate into the products is aided by water as a general acid catalyst, whereas the reverse reaction to the starting materials proceeds without catalysis by water.

In a kinetic study of acid-catalyzed hydrolysis of **1**,[17] we evaluated the catalytic constants of all the steps. The results show that the general acid-catalyzed transformation of the intermediate to the products is more favourable relative to the reverse reaction in the presence of electron-donating substituents on the aryl group: $k_2^{\mathrm{AcOH}}/k_{-1}^{\mathrm{AcOH}}$, **1a**, 17.0; **1b**, 13.7; **1d**, 6.9; **1f**, 6.5.

In the alkaline hydrolysis of "typical" formanilides ($\Delta H^{\neq} \approx 8$ to 10 kcal mol^{-1}, $\Delta S^{\neq} \approx -45$ to -49 cal K^{-1} mol^{-1}), DeWolfe and Newcomb[4] attributed the second step of the third order reaction to the departure of the arylamino group from the intermediate aided by both hydroxide ion as a general base and water as a general acid catalyst, while the dinegatively charged intermediate derived from p-nitro-(and probably p-cyano-)formanilides ($\Delta H^{\neq} \approx$ 12 to 14 kcal mol^{-1}, $\Delta S^{\neq} \approx -31$ to -33 cal K^{-1} mol^{-1}) directly expels the arylamide ion. They evaluated $\Delta H^{\neq}$ and $\Delta S^{\neq}$, however, not from the rate constants, $k_3(k_1/k_{-1})$, but directly from k_{obs} of the reaction.

In the present study we could calculate $\Delta H^{\neq}$ and $\Delta S^{\neq}$ of each step (Table II), and the results show that the second step of the third-order reaction is the departure of the arylamino group catalyzed by both hydroxide ion and water for "typical" substrates. Thus, the values of $\Delta S^{\neq}$ of $k_3(k_1/k_{-1})$ were about 10 cal K^{-1} mol^{-1} lower than those of $k_2(k_1/k_{-1})$ for "typical" substrates, suggesting that both hydroxide ion and water participate in the second step of the third order reaction as a general base and a general acid catalyst, respectively.

The larger $\Delta H^{\neq}$ and less negative $\Delta S^{\neq}$ of $k_3(k_1/k_{-1})$ for **1j** (Table II) suggest that the dinegatively charged intermediate derived from **1j** directly expels the p-nitroanilide ion (Chart 3).

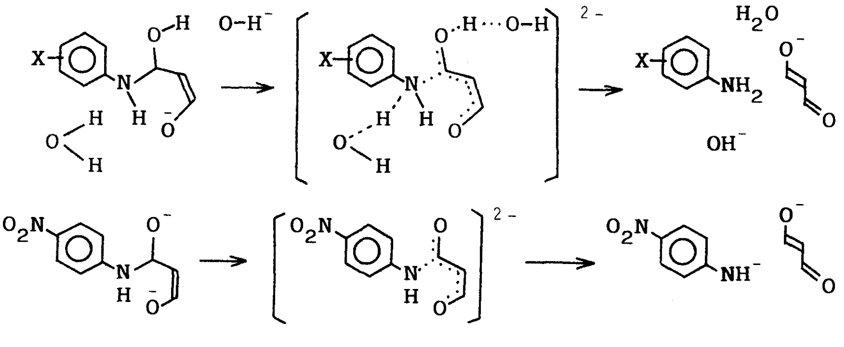


Chart 3

Acknowledgements The authors are grateful to Professor Yutaka Kawazoe for his valuable advice. Thanks are also due to the Computation Center of Fukuoka University for the use of a FACOM M-380R computer.

References and Notes

1) R. B. Jordan and H. Taube, *J. Am. Chem. Soc.*, **88**, 4406 (1966).
2) M. L. Bender and R. J. Thomas, *J. Am. Chem. Soc.*, **83**, 4183 (1961).
3) S. O. Eriksson, *Acta Pharm. Suecica*, **6**, 139 (1969).
4) R. H. DeWolfe and R. C. Newcomb, *J. Org. Chem.*, **36**, 3870 (1971).
5) S. Tamura and E. Yabe, *Chem. Pharm. Bull.*, **21**, 2105 (1973).
6) S. Tamura and E. Takeda, *Chem. Pharm. Bull.*,.**27**, 403 (1979).
7) S. Tamura, M. Ono, and K. Furuyama, *Chem. Pharm. Bull.*, **28**, 2356 (1980).
8) M. Ono, H. Tanaka, and S. Tamura, *Chem. Pharm. Bull.*, **30**, 1933 (1982).
9) M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, **99**, 4899, 4907 (1977); M. J. S. Dewar, M. L. McKee, and H. S. Rzepa, *ibid.*, **100**, 3607 (1978); M. J. S. Dewar and M. L. McKee, *ibid.*, **100**, 7499 (1978); E. Osawa, IMS Computer Center Library, Program No. 1110.
10) R. Fletcher and M. J. D. Powell, *Comput. J.*, **6**, 163 (1963); W. C. Davidon, *ibid.*, **10**, 406 (1968).
11) M. J. S. Dewar and H. S. Rzepa, *J. Am. Chem. Soc.*, **100**, 784 (1978).
12) As a preliminary treatment, the rate constants were estimated from an approximate equation. Assuming $k_3[\mathrm{OH^-}] \gg k_2$ at large $[\mathrm{OH^-}]$, Eq. 1 is transformed to $[\mathrm{OH^-}]^2 k_1 - k(k_{-1}/k_3 + k_2/k_3) = k[\mathrm{OH^-}]$. The values of k_1 and $(k_{-1}/k_3 + k_2/k_3)$ were calculated using k's at $[\mathrm{OH^-}] = 0.30$ and 0.50 M. The values of k_2/k_3 were calculated from the equation

$$k_2/k_3 = \frac{k(k_{-1}/k_3 + k_2/k_3 + [\mathrm{OH^-}]) - k_{-1}[\mathrm{OH^-}]^2}{k_1[\mathrm{OH^-}]}$$

using k at $[\mathrm{OH^-}] = 0.02$ M and the values of k_1 and $(k_{-1}/k_3 + k_2/k_3)$ described above. The approximate values of k_{-1}/k_3 thus obtained were seven or more times larger than those of k_2/k_3 for all substrates examined.
13) M. L. Bender and R. D. Ginger, *Suomen Kemistilehti*, **33B**, 25 (1960).
14) C. A. Bunton, B. Nayak, and C. O'Connor, *J. Org. Chem.*, **33**, 572 (1968).
15) J. F. Bunnett, "Investigation of Rates and Mechanisms of Reactions. Part 1," 3rd ed., John Wiley and Sons, Inc., New York, 1974, p. 422.
16) B. Capon and A. K. Ghosh, *J. Am. Chem. Soc.*, **103**, 1765 (1981); R. A. McClelland and L. J. Santry, *Acc. Chem. Res.*, **16**, 394 (1983).
17) M. Ono, S. Ohtsuka, and S. Tamura, *Chem. Pharm. Bull.*, **31**, 3129 (1983).