Kinetics and Mechanism of Hydrolysis of N-(2′-Hydroxyphenyl)phthalamic Acid (1) and N-(2′-Methoxyphenyl)phthalamic Acid (2) in a Highly Alkaline Medium

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ABSTRACT: A kinetic study on hydrolysis of N-(2′-hydroxyphenyl)phthalamic acid (**1**), N-(2′-methoxyphenyl)phthalamic acid (**2**), and N-(2′-methoxyphenyl)benzamide (**3**) under a highly alkaline medium gives second-order rate constants, k_{OH}, for the reactions of HO^- with **1, 2,** and **3** as $(4.73 \pm 0.36) \times 10^{-8}$ at 35°C, $(2.42 \pm 0.28) \times 10^{-6}$ and $(5.94 \pm 0.23) \times 10^{-5}$ M^{-1} s^{-1} at 65°C, respectively. Similar values of k_{OH} for **3**, N-methylbenzanilide, N-methylbenzamide, and N,N-dimethylbenzamide despite the difference between pK_a values of aniline and ammonia of ∼10 pK units are qualitatively explained. © 2008 Wiley Periodicals, Inc. Int J Chem Kinet 41: 1–11, 2009

INTRODUCTION

Kinetics and mechanism of uncatalyzed and catalyzed aqueous cleavage of amide bond may be considered of importance partly because aqueous degradation of a protein involves the aqueous cleavage of peptide bond, which is essentially a secondary amide bond. Unfortunately, the rate of uncatalyzed hydrolysis of an amide under physiological conditions is extremely slow (half-life period, $t_{1/2}$, >220 years) [1], and kinetic study on slow reactions ($t_{1/2}$ greater than a few days) is not an attractive field of kinetic measurements because of the various unavoidable practical problems. The $t_{1/2}$ value for neutral hydrolysis of amide bond of >220 years is based upon the estimated value of the pseudo-first-order rate constant ($k_0 = 8.9 \times 10^{-11}$ s^{-1} at 35°C) for neutral hydrolysis of formamide ($k_0 = 8.0 \times 10^{-8}$ s^{-1} at 80°C [1]). The reported value of k_0 for neutral hydrolysis of a peptide bond (i.e., a secondary amide

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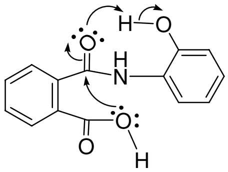
bond) at room temperature is 3×10^{-9} s^{-1} [2]. But a theoretical study [3] on the mechanism of formamide hydrolysis in water reveals two reaction steps, where the first step, the carbonyl group of the formamide molecule being hydrated to form a diol intermediate, is the rate-determining step followed by the final product formation in the fast second step. The predicted pseudo-first-order rate constant for the rate-limiting step (the first step) of the hydrolysis reaction at 25°C (3.9×10^{-10} s^{-1}) is claimed in excellent agreement with the experimental data (1.1×10^{-10} s^{-1}). Another and more recent theoretical study [4] on the mechanism of neutral hydrolysis of formamide predicts an observable activation free energy barrier of 48.7 kcal mol^{-1} and as a consequence of such a high free energy barrier, the authors raise important questions about the reliability of the experimental activation free energy of 31.0 kcal mol^{-1} and suggest that the neutral hydrolysis of formamide does not take place at all.

Kinetic studies on extremely slow reactions are generally carried out at a high temperature, as well as high [HO^-] or [H^+], and these experimentally determined rate constants are used to estimate rate constants at 37°C by using the Eyring or Arrhenius equation coupled with reaction mechanisms for HO^-- and H^+-assisted hydrolysis [1,5]. Recently, aqueous cleavage of **1** and **2** has been studied under mild acidic medium at 35°C, where an efficient intramolecular carboxyl group assisted rate enhancement is observed [6]. But a plausible intramolecular general acid assistance due to the 2′-OH group in **1** involving the transition state TS_1 could not be detected [6].



TS_1

The present study was initiated with an aim to discover the effect of [HO^-] on the rate of hydrolysis of **1** and **2** at 35°C and at an elevated temperature. To find out the approximate effect of 2-CO_2^- on k_{OH} value for **2**, the value of k_{OH} for **3** was also determined. These results as well as probable explanations are described in this paper.

EXPERIMENTAL

Materials

N-(2′-Hydroxyphenyl)phthalamic acid (**1**) and *N*-(2′-methoxyphenyl)phthalamic acid (**2**) were synthesized as described elsewhere [6]. *N*-(2′-Methoxyphenyl) benzamide (**3**) was synthesized using a literature procedure involving the reaction of benzoyl chloride with 2-methoxyaniline, and the observed spectroscopic data are in complete agreement with the corresponding reported data [7]. All other common chemicals used were commercial products of the highest available purity. Standard solutions of **1** (0.03 M) and **3** (0.005 M) were prepared in acetonitrile, whereas the standard solution of **2** (0.01 M) was prepared in 1,4-dioxan.

Kinetic Measurements

The rate of alkaline hydrolysis of **1** was studied spectrophotometrically by monitoring the disappearance of **1** at 280 nm and 35°C in aqueous solvent containing 1% v/v CH_3CN. The details of the kinetic procedure are described elsewhere [8]. The observed absorbance (A_{obs}) at different reaction times (t) was found to fit to Eq. (1)

$$A_{obs} = \delta_{app}[R_0]\exp(-k_{obs}t) + A_{\infty} \tag{1}$$

where [R_0] is the initial concentration of **1**, δ_{app} is an apparent molar extinction coefficient of the reaction mixture, $A_{\infty} = A_{obs}$ at $t = \infty$ and k_{obs} represents the pseudo-first-order rate constant for hydrolytic cleavage of **1**. The values of unknown parameters, k_{obs}, δ_{app}, and A_{∞}, were calculated from Eq. (1) using a nonlinear least-squares technique. The observed data fit to Eq. (1) is satisfactory as evident from the standard deviations associated with the calculated parameters as shown in Table I, and from the plot of A_{obs} versus t for a typical kinetic run as shown in Fig. 1, where a solid line is drawn through the calculated data points using Eq. (1) and parameters listed in Table I.

The rates of alkaline hydrolysis of **2, 3**, and 2-hydroxyaniline (**4**) were also studied by using the procedure of kinetic measurements as described above. The plot of A_{obs} versus t for a typical kinetic run for hydrolysis of **2** is also shown in Fig. 1.

Product Characterization

The products in the respective alkaline hydrolysis of **2** and **3** were confirmed by comparing the values of molar extinction coefficients, δ, obtained from A_{∞} values (calculated from Eq. (1)) with the corresponding δ values of authentic samples of phthalic acid or benzoic acid and 2-methoxyaniline obtained under conditions of kinetic runs. These observations showed that the products were 100% phthalic acid and 2-methoxyaniline for **2** and benzoic acid and 2-methoxyaniline for **3**.

Table I Kinetic Parameters, k_{obs}, δ_{app}, and A_∞, Calculated from Eq. (1) for Alkaline Hydrolysis of **1**[a]

[NaOH] (M)	$10^2 A_\infty^{est\,b}$	$10^8\ k_{obs}$ (s^{-1})	$10^{-1}\ \delta_{app}$ (M^{-1} cm^{-1})	$10^2 A_\infty$	$10^{-6} t_{fin}^c$ (s)	A_{obs}^d	$10^8 k_{calcd}^e$ (s^{-1})
1.2	8.6	4.74 ± 0.15^f	591 ± 7^f	8.8 ± 2.0^f	9.25	1.280	4.40
	8.6^g	4.74 ± 0.15	591 ± 7	8.7 ± 2.0			
	21.3	5.21 ± 0.17	549 ± 7	21.5 ± 1.9			4.77
	21.3^g	5.19 ± 0.16	549 ± 7	21.4 ± 1.9			
1.5	8.6	5.95 ± 0.10	597 ± 4	8.5 ± 1.2	9.25	1.105	5.70
	21.3	6.22 ± 0.12	555 ± 4	21.2 ± 1.2			6.19
1.8	8.6	6.27 ± 0.10	590 ± 4	8.7 ± 1.1	9.25	1.095	7.01
	21.3	6.89 ± 0.10	548 ± 4	21.4 ± 1.0			7.61
2.0	8.6	7.76 ± 0.15	605 ± 6	8.4 ± 1.5	9.25	0.960	7.88
	21.3	8.55 ± 0.20	564 ± 6	21.0 ± 1.7			8.56

[a] $[\mathbf{1}_0] = 3.0 \times 10^{-4}$ M, $\lambda = 320$ nm, ionic strength 2.0 M (by NaCl), $T = 35$°C, aqueous reaction mixture for each kinetic run contained 1% v/v CH_3CN.

[b] Unless otherwise noted, $t = 3.0 \times 10^8$ s for A_∞^{est} values.

[c] Time for the final observed absorbance (A_{obs}).

[d] Observed absorbance at t_{fin}.

[e] Calculated from Eq. (4) with $k_0 = 0$ and k_{OH} values shown in Table V.

[f] Error limits are standard deviations.

[g] $t = 1.5 \times 10^8$ s for A_∞^{est} values.

RESULTS

Alkaline Hydrolysis of N-(2′-Hydroxyphenyl)phthalamic Acid (1)

Because of the extremely slow rate of reaction of **1** with HO^- at 35°C, only a few kinetic runs were carried out within the [NaOH] range 1.2–2.0 M for the reaction period of 2570 h, which is equivalent to only 0.6 and 1.0 half-lives at 1.2 and 2.0 M NaOH, respectively. The nature of Eq. (1) is such that the use of the nonlinear least-squares technique cannot yield reliable values of kinetic parameters (k_{obs}, δ_{app}, and A_∞) if the

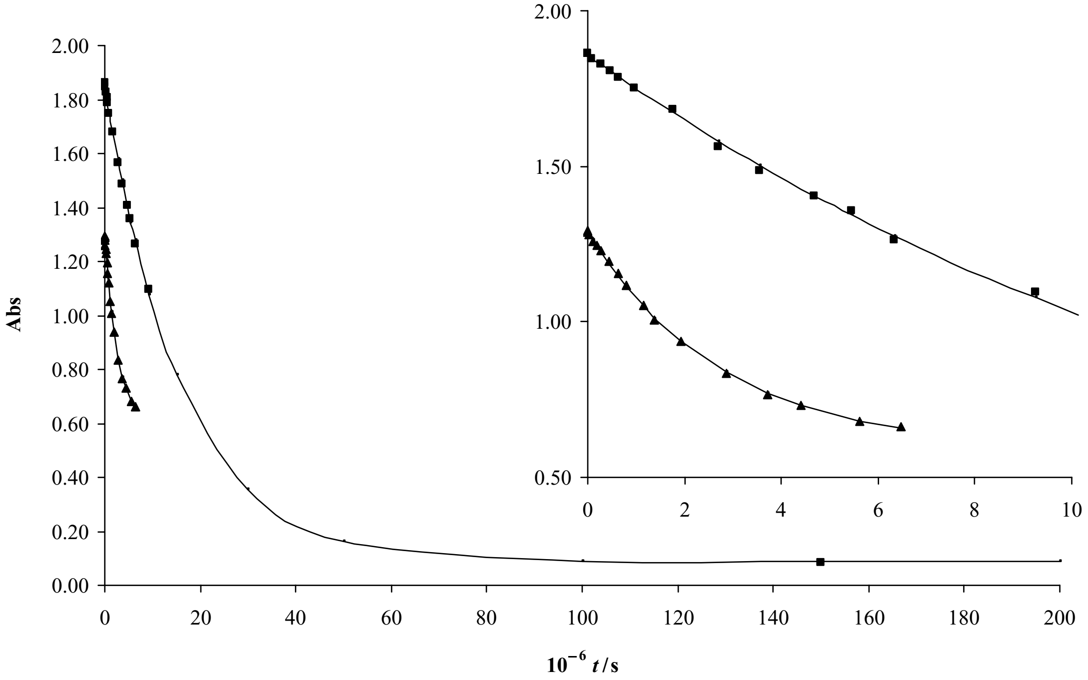


Figure 1 The plots showing the absorbance (Abs) versus time (t) for alkaline hydrolysis of **1** and **2** at [NaOH] = 1.80 M, where $[\mathbf{1}_0] = 3.0 \times 10^{-4}$ M (■), $[\mathbf{2}_0] = 2.0 \times 10^{-4}$ M (▲) and 35°C. The solid lines are drawn through the calculated data points using Eq. (1) as described in the text. Inset shows the observed and calculated data points until $t = 1.0 \times 10^7$ s.

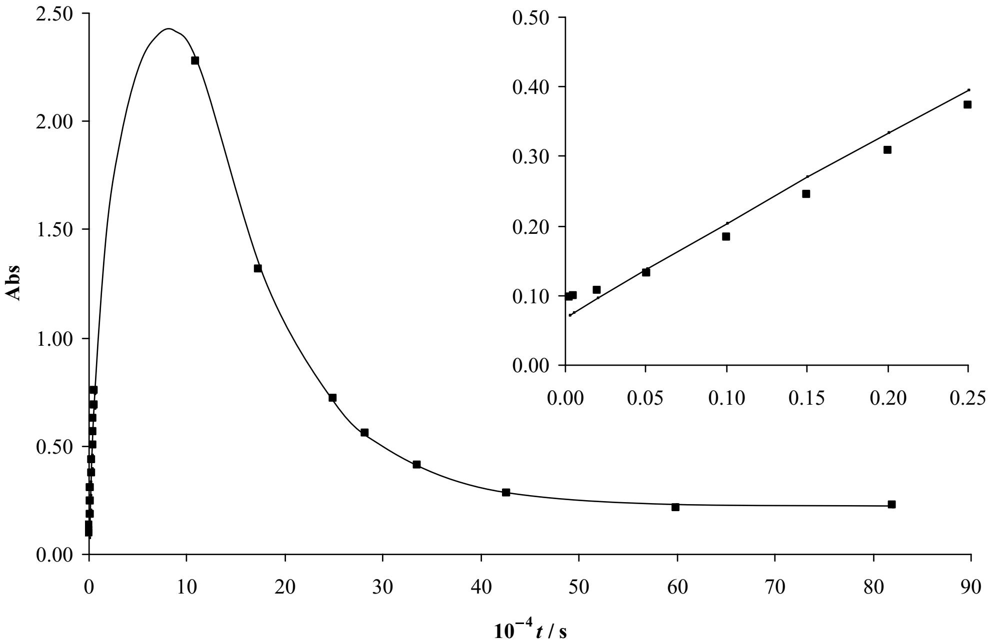


Figure 2 The plot showing the dependence of absorbance (Abs) versus time (t) for alkaline degradation of 2-hydroxyaniline (**4**) in the presence of phthalic acid, where [$\mathbf{4}_0$] = [Phthalic acid] = 3.0×10^{-4} M, [NaOH] = 1.51 M, and 35°C. The solid lines are drawn through the calculated data points using Eqs. (2) and (1) for initial and final phase of degradation as described in the text.

kinetic run was monitored for the reaction period of ≤ 1 half-life [9]. Thus, to get the reliable values of kinetic parameters, the value of A_{obs} at $t > 10$ half-lives should be known [9]. The expected hydrolysis products of **1** are 2-hydroxyaniline and phthalic acid. The authentic samples of 2-hydroxyaniline and phthalic acid were used to obtain δ for these compounds under the reaction conditions of the kinetic runs which in turn gave $A_{\infty}^{\text{est}} = 0.085$ (where $A_{\infty}^{\text{est}} = A_{\text{obs}}$ at $t \geq 10$ half-lives). The use of $A_{\text{obs}} = 0.085$ at $t \geq 10$ half-lives resulted in the values of k_{obs}, δ_{app}, and A_{∞} as shown in Table I. It is also evident from Table I that the change in t (for A_{∞}^{est} values) from 3.0×10^{8} s (i.e., ~22 half-lives) to 1.5×10^{8} s (i.e., ~11 half-lives) for the reaction at 1.2 M NaOH did not essentially change the values of k_{obs}, δ_{app}, and A_{∞}.

In the process of determining δ values of the mixture of authentic 2-hydroxyaniline and phthalic acid at 320 nm in an alkaline medium, it was noticed that the absorbance of the aqueous alkaline mixture changed with time, indicating the instability of the authentic sample mixture under the alkaline pH. To explore some details of this observation, such as possible pseudo-first-order rate constant(s) for the alkaline degradation of 2-hydroxyaniline in the presence and absence of phthalic acid, a few kinetic runs were carried out at 35°C and varying concentrations of NaOH. The values of A_{obs} versus reaction time (t) for a typical kinetic run, monitored at 320 nm, are shown graphically in Fig. 2. The plot of Fig. 2 reveals the presence of a maximum which, in turn, implies the formation of, at least, one moderately reactive intermediate in the alkaline degradation of 2-hydroxyaniline. It is well known that 2- and 4-hydroxyanilines undergo a rather complex oxidative degradation process under an alkaline medium [10]. The attempt was therefore made to determine only the values of rate constants for the alkaline degradation processes of 2-hydroxyaniline under the strictly reaction conditions of the kinetics of alkaline hydrolysis of **1** so that one could find the answer to the question: Why did the observed data (A_{obs} versus t) for alkaline hydrolysis of **1** obey strictly the first-order kinetics despite the fact that the degradation of 2-hydroxyaniline (an expected immediate stable hydrolysis product of **1**) followed complex two irreversible consecutive reaction paths?

Aqueous Alkaline Degradation of 2-Hydroxyaniline

A few kinetic runs were carried out for the aqueous degradation of 2-hydroxyaniline (in the absence and presence of 3.0×10^{-4} M phthalic acid) within the [NaOH] range 1.2–2.0 M at 35°C and 2.0 M ionic strength. The plot of A_{obs} versus t revealed, at least, one maximum (Fig. 2). However, the rate of initial phase

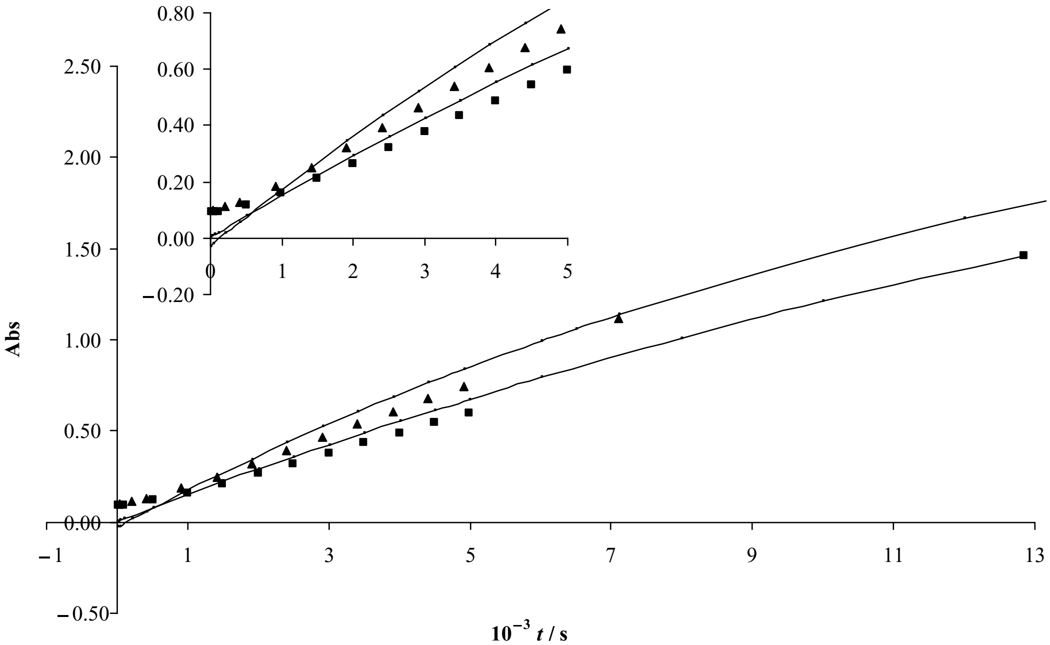


Figure 3 The plots showing the absorbance (Abs) versus time (t) for alkaline degradation of 2-hydroxyaniline (**4**) at different [NaOH] in the absence of phthalic acid, where $[\mathbf{4}_0] = 3.0 \times 10^{-4}$ M, 35°C and [NaOH] = 1.0 M (■) and 2.0 M (▲) respectively. The solid lines are drawn through the calculated data points using Eq. (1) as described in the text. Inset shows the observed and calculated data points until $t = 5.0 \times 10^3$ s.

of degradation appeared to be much faster than that of the final phase of the degradation and consequently the observed data (A_{obs} versus t) for the initial and final phases of degradation were treated with Eqs. (2) and (1), respectively.

$$A_{\mathrm{obs}} = \delta_{\mathrm{app}}[\mathrm{R}_0][1 - \exp(-k_{\mathrm{obs}}t)] + A_0 \qquad (2)$$

Although the nonlinear least-squares fit of the observed data to Eq. (2) seems satisfactory in terms of standard deviations associated with the calculated parameters (k_{obs}, δ_{app}, and A_0), a critical look at the plots of Figs. 2 and 3 shows small yet a regular deviations of observed data points from the least-squares calculated solid lines. Similar distinct deviations for the initial phase of the reaction were observed for all kinetic runs within the [NaOH] range 1.0–2.0 M. Thus, it seems that the initial phase of the reaction does not represent a strictly one-step reaction. The observed data for the final phase of degradation showed a perfect fit to Eq. (1) (Fig. 2 and Table II), and these data reveal nearly 6-fold larger rate constant for the initial phase than that for the final phase degradation of 2-hydroxyaniline in the absence and presence of 3.0×10^{-4} M phthalic acid.

The aim of the kinetic study for the degradation of 2-hydroxyaniline in the absence and presence of phthalic acid is to discover the possible effect(s) of the product formation on the pseudo-first-order kinetics of alkaline hydrolysis of **1**. Thus, although the complexity of the kinetics of the alkaline degradation of 2-hydroxyaniline in the absence and presence of phthalic acid is not fully resolved, it is almost certain that the rate constant for the slowest step of the alkaline degradation of 2-hydroxyaniline is more than 100-fold larger than that for alkaline hydrolysis of **1** (Table I), and consequently the instability of the product (2-hydroxyaniline) is not expected to cause deviation of the observed data from the first-order kinetic plot for the alkaline hydrolysis of **1**. However, a relatively more reliable observed data treatment to Eq. (1) requires the use of the value of $A_{\infty}^{\mathrm{est}}$ as 0.213 (absorbance due to final alkaline degradation product(s) of 2-hydroxyaniline in the presence of 3.0×10^{-4} M phthalic acid; Table II) rather than 0.086 (absorbance due to 3.0×10^{-4} M 2-hydroxyaniline and 3.0×10^{-4} M phthalic acid). The observed data for alkaline hydrolysis of **1** were also treated with Eq. (1) using A_{obs} ($A_{\infty}^{\mathrm{est}}$) = 0.213 at $t = 3.0 \times 10^8$ s, and the calculated values of k_{obs}, δ_{app}, and A_{∞} are summarized in Table I.

Effects of [NaOH] on the Rate of Alkaline Hydrolysis of N-(2′-Methoxyphenyl)phthalamic Acid (2)

To find the relative effects of 2-OH and 2-OMe on the rates of hydrolysis of **1** and **2** under highly alkaline

Table II Kinetic Parameters, k_{obs}, δ_{app}, and A_0, Calculated from Eq. (2) for Initial Phase and Eq. (1) for Final Phase of Alkaline Degradation of 2-Hydroxyaniline[a]

[NaOH] Reaction									
	Initial Phase				Final Phase				
[NaOH] (M)	$10^6\ k_{\text{obs}}$ (s^{-1})	$10^{-2}\ \delta_{\text{app}}$ ($M^{-1}\ cm^{-1}$)	$10^2\ A_0$	$10^{-4}\ t^b_{\text{fin}}$ (s)	$10^6\ k_{\text{obs}}$ (s^{-1})	$10^{-2}\ \delta_{\text{app}}$ ($M^{-1}\ cm^{-1}$)	$10^2\ A_\infty$	$10^{-4}\ t^c_{\text{ini}}$ (s)	$10^{-4}\ t^b_{\text{fin}}$ (s)
1.0	45.5 ± 3.5^d	110 ± 3^d	0.39 ± 3.07^d	8.06					
	$(42.8 \pm 2.3)^e$	$(113 \pm 2)^e$	$(3.9 \pm 2.4)^e$	$(8.00)^e$	$(7.72 \pm 0.04^d)^e$	$(197 \pm 1^d)^e$	$(23.6 \pm 0.2^d)^e$	(12.0)	$(120)^d$
1.2	52.7 ± 4.2	107 ± 3	-1.0 ± 3.6	8.06					
	(42.2 ± 2.3)	(122 ± 3)	(4.7 ± 2.0)	(4.91)	(8.76 ± 0.05)	(210 ± 1)	(22.7 ± 0.3)	(12.0)	(120)
1.5	64.9 ± 6.3	101 ± 3	-1.1 ± 4.6	8.06					
	(51.7 ± 3.9)	(118 ± 4)	(2.0 ± 3.3)	(4.90)	(9.95 ± 0.11)	(218 ± 3)	(18.4 ± 0.4)	(12.0)	(120)
	(63.7 ± 1.7)	(73.9 ± 0.7)	(6.8 ± 0.9)	(10.9)	(10.4 ± 0.3)	(221 ± 12)	(21.3 ± 0.9)	(17.2)	(82.0)
1.8	64.7 ± 7.2	104 ± 4	-2.9 ± 5.5	7.46					
	(48.6 ± 4.0)	(123 ± 4)	(4.6 ± 2.8)	(4.10)	(10.8 ± 0.1)	(220 ± 2)	(16.2 ± 0.2)	(11.2)	(119)
2.0	70.0 ± 8.5	99.3 ± 4.3	-2.8 ± 6.0	7.47					
	(57.9 ± 4.1)	(115 ± 3)	(3.6 ± 2.8)	(4.10)	(11.4 ± 0.1)	(221 ± 3)	(16.0 ± 0.3)	(11.2)	(119)

[a] [2–Hydroxyaniline$_0$] = 3.0×10^{-4} M, $\lambda = 320$ nm, ionic strength 2.0 M (by NaCl), $T = 35°$C, aqueous reaction mixture for each kinetic run contained 1% v/v CH_3CN.

[b] Time for the final observed absorbance of the data treatment.

[c] Time for the first absorbance of the data treatment.

[d] Error limits are standard deviations.

[e] Reaction mixture contained 3.0×10^{-4} M phthalic acid.

medium, a few kinetic runs were carried out for the hydrolysis of **2** under the experimental conditions almost similar to that for **1** and also at 65°C. The values of k_{obs}, δ_{app}, and A_∞, calculated from Eq. (1) within the [NaOH] range 1.0–2.0 M, are summarized in Table III. The kinetic runs were carried out until 2.5–3.6 half-lives of the reactions at 35°C, and the final products, 2-methoxyaniline and phthalic acid, were found to be stable under such conditions.

Effects of [NaOH] on the Rate of Alkaline Hydrolysis of N-(2′-Methoxyphenyl)benzamide (3)

The rate of alkaline hydrolysis of **3** was studied within the [NaOH] range 0.5–2.0 M at 35 and 65°C. The observed data (A_{obs} versus t) showed a reasonably good fit to Eq. (1), and the least-squares calculated values of k_{obs}, δ_{app}, and A_∞ are shown in Table IV. An attempt to obtain k_{obs} at [NaOH] < 0.5 M was unsuccessful because the reaction rates became too slow to monitor conveniently.

DISCUSSION

The rates of alkaline hydrolysis of **1** and **3** were studied in an aqueous solvent containing 1% v/v CH_3CN, and it is known* that CH_3CN molecules hydrolyze to produce acetic acid and ammonia as final hydrolysis products. The rate of alkaline hydrolysis of CH_3CN is shown to follow a consecutive reaction scheme as shown by Eq. (3) [11], where the k_1 and k_2 steps involve HO^- as a catalyst and a reactant (nucleophile), respectively.

$$CH_3CN + H_2O \xrightarrow{k_1[HO^-]} CH_3CONH_2 \xrightarrow{k_2[HO^-]} CH_3CO_2^- + NH_3 \qquad (3)$$

This implies that the k_1 step does not consume HO^-, whereas the k_2 step consumes HO^-. The values of k_2/k_1 = 19 [11] and $k_2 = 3.8 \times 10^{-5}\ M^{-1}\ s^{-1}$ (25°C), $8.6 \times 10^{-5}\ M^{-1}\ s^{-1}$ (35°C), $3.1 \times 10^{-4}\ M^{-1}\ s^{-1}$ (50°C) [12], and $3.7 \times 10^{-5}\ M^{-1}\ s^{-1}$ (25°C) [11]. In view of these reported data, the value of k_1 is 95-fold and 0.8-fold larger than the second-order rate constant (k_{OH}) for hydroxide ion-catalyzed hydrolysis of **1** and **3**, respectively, provided k_2/k_1 remained unchanged with the increase of the temperature from 25 to 35°C. Thus, the hydrolysis products of 1% v/v CH_3CN are expected to consume ~0.19 M NaOH and as a consequence this [HO^-] (=0.19 M) correction was considered in the observed data analysis for alkaline hydrolysis of **1** and **3**.

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*We thank one of the reviewers for informing us about this.

Table III Kinetic Parameters, k_{obs}, δ_{app}, and A_∞, Calculated from Eq. (1) for Alkaline Hydrolysis of **2**[a]

[NaOH] (M)	Temperature (°C)	$10^8 k_{obs}$ (s^{-1})	$10^{-1}\ \delta_{app}$ ($M^{-1}\ cm^{-1}$)	$10^2 A_\infty$	$10^{-5} t^{b}_{fin}$ (s)	$10^2 A^{c}_{obs}$	$10^8 k^{d}_{calcd}$ (s^{-1})	$10^8 k^{e}_{calcd}$ (s^{-1})
1.0	35	27.0 ± 0.6[f]	290 ± 3[f]	72.5 ± 0.7[f]	64.9	82.6	26.2	22.0
1.2		29.7 ± 0.8	303 ± 4	68.7 ± 0.8	64.9	77.6	28.5	26.4
1.5		27.9 ± 1.6	339 ± 10	56.6 ± 2.0	65.6	69.0	31.9	33.0
1.8		36.8 ± 0.7	348 ± 3	59.4 ± 0.6	64.9	66.2	35.4	39.6
2.0		38.3 ± 1.2	361 ± 5	55.4 ± 1.0	64.9	61.3	37.7	44.0
0.5	65[g]	93.7 ± 3.5	269 ± 4	65.0 ± 0.7	4.83	98.8	95.7	121
1.0		246 ± 12	268 ± 6	65.0 ± 1.2	4.83	81.4	238	242
1.2		294 ± 22	268 ± 9	65.4 ± 1.8	4.82	79.5	295	290
1.5		378 ± 12	262 ± 4	65.3 ± 0.7	4.80	74.5	381	362
1.8		453 ± 18	264 ± 5	66.3 ± 0.9	4.79	73.5	466	435
2.0		535 ± 18	265 ± 4	65.5 ± 0.7	4.78	69.6	523	483

[a] $[\mathbf{2}_0] = 2.0 \times 10^{-4}$ M, $\lambda = 280$ nm, ionic strength 2.0 M (by NaCl), aqueous reaction mixture for each kinetic run contained 2% v/v 1,4-dioxan.

[b] Reaction time for final observed data point.

[c] Value of A_{obs} at $t = t_{fin}$.

[d] Calculated from Eq. (4) with k_0 and k_{OH} values shown in Table V.

[e] Calculated from Eq. (4) with $k_0 = 0$ and k_{OH} value summarized in Table V.

[f] Error limits are standard deviations.

[g] Data treatment for all kinetic runs was carried out by including a data point at $t \geq 10$ half-lives with $A_{obs} = A^{est}_\infty$ (0.650).

Pseudo-first-order rate constants (k_{obs}) for alkaline hydrolysis of **1** showed an apparent good fit to Eq. (4)

$$k_{obs} = k_0 + k_{OH}[HO^-] \qquad (4)$$

where k_0 and k_{OH} represent the pseudo-first-order rate constant for the reaction of **1** with H_2O and the second-order rate constant for the reaction of **1** with HO^-, respectively. The least-squares calculated values of k_0

Table IV Kinetic Parameters, k_{obs}, δ_{app} and A_∞, Calculated from Eq. (1) for Alkaline Hydrolysis of **3**[a]

[NaOH] (M)	Temperature (°C)	$10^7 k_{obs}$ (s^{-1})	$10^{-1}\ \delta_{app}$ ($M^{-1}\ cm^{-1}$)	$10^2 A_\infty$	$10^{-4} t^{b}_{fin}/(s)$	$10^2 A^{c}_{obs}$	$10^7 k^{d}_{calcd}$ (s^{-1})
0.5	35	19.2 ± 1.0[e]	531 ± 10[e]	14.7 ± 0.5[e]	19.2	33.1	20.9
1.0		50.0 ± 3.4	584 ± 20	11.5 ± 0.9	19.1	20.8	49.3
1.2		63.1 ± 2.2	590 ± 10	12.0 ± 0.5	18.6	20.1	60.7
1.5		79.7 ± 5.2	612 ± 18	11.9 ± 0.9	18.6	16.5	77.7
1.8		89.6 ± 6.1	626 ± 18	11.5 ± 0.9	18.6	15.4	94.8
2.0		108 ± 5	613 ± 11	12.2 ± 0.6	18.6	14.9	106
0.5	65	200 ± 8	487 ± 8	14.7 ± 0.4	12.9	16.3	177
		202 ± 13	501 ± 11	15.3 ± 0.6	12.8	17.1	188
1.0		456 ± 7	566 ± 3	11.7 ± 0.1	12.8	11.8	476
		491 ± 37	530 ± 17	15.7 ± 0.7	12.6	16.0	500
1.2		571 ± 12	559 ± 5	12.1 ± 0.2	10.8	12.3	595
		626 ± 25	567 ± 10	14.0 ± 0.4	12.7	13.7	625
1.5		795 ± 21	565 ± 6	12.5 ± 0.3	7.51	12.8	774
		759 ± 24	526 ± 8	16.5 ± 0.3	12.6	16.5	812
1.8		928 ± 23	584 ± 6	12.1 ± 0.3	3.91	12.8	954
		1070 ± 64	558 ± 14	16.4 ± 0.6	7.00	16.5	999
2.0		1100 ± 40	584 ± 7	12.7 ± 0.4	3.89	13.1	1070
		1100 ± 50	552 ± 10	15.7 ± 0.4	7.00	16.2	1120

[a] $[\mathbf{3}_0] = 5.0 \times 10^{-5}$ M, $\lambda = 260$ nm, ionic strength 2.0 M (by NaCl), aqueous reaction mixture for each kinetic run contained 1% v/v CH_3CN.

[b] Reaction time for final observed data point.

[c] Value of A_{obs} at $t = t_{fin}$.

[d] Calculated from Eq. (4) with k_0 and k_{OH} as shown in Table V.

[e] Error limits are standard deviations.

Table V Values of k_0 and k_{OH} Calculated from Eq. (3)

Amides	Temperature (°C)	$10^8 k_0$ (s^{-1})	$10^8 k_{\mathrm{OH}}$ ($\mathrm{M}^{-1}\ \mathrm{s}^{-1}$)
1	35	$1.2 \pm 1.1^{a,b}$	$3.86 \pm 0.76^{a,b}$
	35	0	4.73 ± 0.36
	35	1.3 ± 1.1^{c}	3.40 ± 0.72^{c}
	35	0	4.35 ± 0.35
2	35	14.8 ± 4.9	11.4 ± 3.2
	35	0	22.0 ± 3.7
	65	-47 ± 11	285 ± 8
	65	0	242 ± 28
3	35	33 ± 33	568 ± 27
	35	0	604 ± 25
	65	$(-81 \pm 292) \times 10^2$	$(59.7 \pm 2.3) \times 10^2$
	65	0	$(59.4 \pm 2.3) \times 10^2$
	65	$(-0.5 \pm 4.7) \times 10^2$	$(62.4 \pm 3.8) \times 10^2$
	65	0	$(62.2 \pm 3.2) \times 10^2$

[a] The values of k_0 and k_{OH} were calculated from k_{obs} values obtained with $A_\infty^{\mathrm{est}} = 0.213$ (Table I).

[b] Error limits are standard deviations.

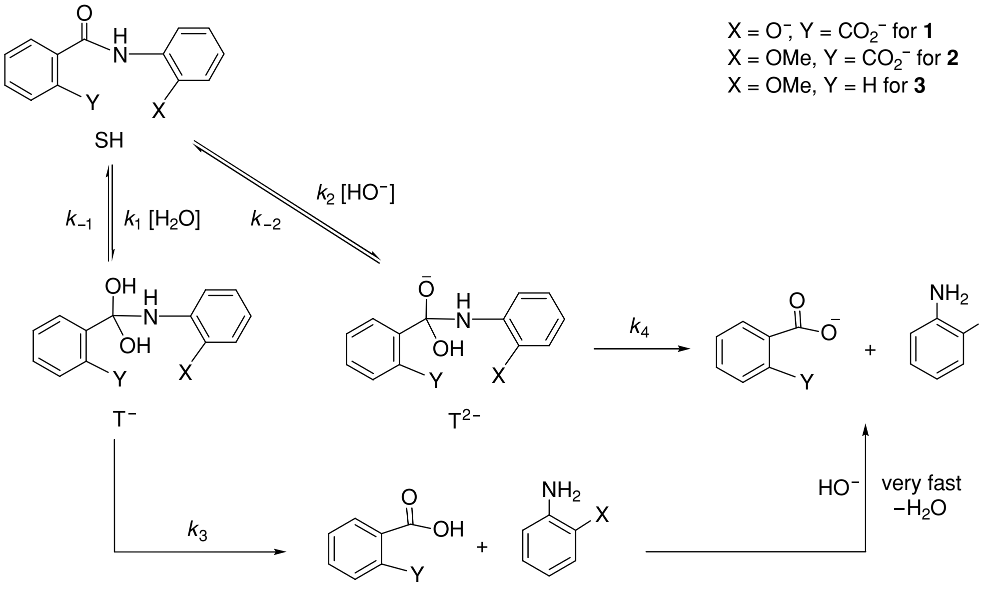
[c] The values of k_0 and k_{OH} were calculated from k_{obs} values obtained with $A_\infty^{\mathrm{est}} = 0.086$ (Table I).

and k_{OH} are summarized in Table V. The values of k_0 with standard deviations of more than 100% are considered to be highly unreliable. The maximum contribution of k_0 compared to k_{OH} [HO$^-$] is <15% within the experimental conditions of the study, and therefore k_0 may be neglected compared to k_{OH} [HO$^-$]. The values of k_{OH} were also calculated from Eq. (4) with $k_0 = 0$, and these calculated values, as shown in Table V, increased by <12% compared to the corresponding values obtained with $k_0 \neq 0$. The extent of reliability of the observed data fit to Eq. (4) is evident from k_{calcd} values summarized in Table I.

The respective values of p$K_{\mathrm{a}1}$ and p$K_{\mathrm{a}2}$ of **1** are 3.34 and 9.52 at 35°C [13]. The value of p$K_{\mathrm{a}3}$, which corresponds to the ionization of amide group of **1**, should be >15 because the pK_{a} of benzamide is 14–15 [14]. Thus, a plausible mechanism for hydrolysis of **1** under the present experimental conditions may be expressed by Scheme 1, where pK_{a} of conjugate acid of the leaving group is larger in the k_3 and k_4 steps than that in the k_{-1} and k_{-2} steps, respectively. These conclusions reveal that $k_{-1} \gg k_3$ and $k_{-2} \gg k_4$ and consequently k_3 and k_4 steps are the rate–determining steps. The observed rate law, rate $= k_{\mathrm{obs}}$ $[\mathbf{1}]_{\mathrm{T}}$, and Scheme 1 can lead to Eq. (5), which is similar to Eq. (4) with $k_0 = k_3 K_1$ [H$_2$O] and $k_{\mathrm{OH}} = k_4 K_2$. In Eq. (5), $K_1 = k_1/k_{-1}$, and $K_2 = k_2/k_{-2}$.

$$k_{\mathrm{obs}} = k_3 K_1 [\mathrm{H_2O}] + k_4 K_2 [\mathrm{HO}^-] \qquad (5)$$

The values of k_{obs}, obtained within the [NaOH] range 1.0–2.0 M at 35 and 65°C, for hydrolytic cleavage of **2** show apparently satisfactory fit to Eq. (4) in terms of absolute residual errors (ARE $= (k_{\mathrm{obsi}} - k_{\mathrm{calcdi}})/k_{\mathrm{obsi}}$, where k_{obsi} and k_{calcdi} represent respective experimentally determined and the least-squares calculated rate constant at the ith value of [NaOH]; Table III). Although the minimum contribution of k_0 compared with k_{OH}[HO$^-$] is ~40% at 35°C, the calculated value of k_0 ($14.8 \times 10^{-8}\ \mathrm{s}^{-1}$) is unexpectedly large for the following reasons: The reported respective values of k_0, k_{OH}, and the hydronium ion-catalyzed second-order rate constant (k_{H}) for hydrolysis of formamide are $8.4 \times 10^{-8}\ \mathrm{s}^{-1}$, 0.211 and $1.78 \times 10^{-2}\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$ at 80°C, respectively [1], and the values of k_{OH} for hydrolysis of benzamide, N-methylbenzamide, and N,N-dimethylbenzamide are 14.2×10^{-4}, 6.40×10^{-4}, and $10.3 \times 10^{-4}\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$, respectively, at 100.4°C [15]. Similarly, the values of k_{H} for hydrolysis of respective benzamide, N-methylbenzamide, and N,N-dimethylbenzamide are 39×10^{-5}, 6.4×10^{-5}, and $10 \times 10^{-5}\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$ at 100.4°C [16]. These reported results demonstrate that the intrinsic reactivity toward hydrolysis is significantly larger for formamide than that for benzamide and N-substituted benzamide, and consequently the value of k_0 for benzamide and **2** should be significantly smaller than that for formamide ($k_0 = 8.4 \times 10^{-8}\ \mathrm{s}^{-1}$ at 80°C). Thus, the apparent satisfactory observed data fit to Eq. (4) in terms of ARE at 35°C is considered to be unreliable because the calculated value of k_0 is unexpectedly large. Similarly, the least-squares calculated negative value of k_0 ($-4.7 \times 10^{-7}\ \mathrm{s}^{-1}$) at 65°C is meaningless and consequently k_0 may be considered as negligible compared with k_{OH}[HO$^-$] in Eq. (4). Thus, a reliable value of k_{OH} was obtained from Eq. (4) with $k_0 = 0$, and such



Scheme 1

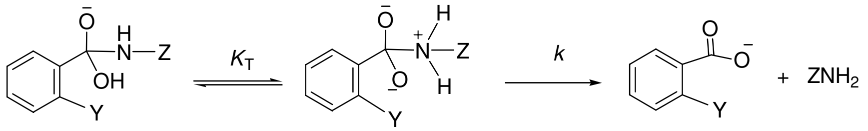
a calculated value of k_{OH} is shown in Table V. Therefore, the observed data were treated with Eq. (4) and the least-squares calculated values of k_{OH} with $k_0 = 0$ are summarized in Table V. The plausible reaction mechanism for hydrolysis of **2** is shown in Scheme 1, where k_3 and k_4 steps are rate determining.

The rate constants k_{obs}, obtained for hydrolysis of **3** within the [NaOH] range 0.5–2.0 M, showed a good fit to Eq. (4). However, the least-square calculated values of k_0 and k_{OH} revealed a negative values of k_0 (Table V) at both 35 and 65°C, which are meaningless. Hence, the values of k_{OH} were also calculated from Eq. (4) with $k_0 = 0$ and such values are also shown in Table V. The negative values of k_0 show that the contribution of k_0 is nearly insignificant compared to $k_{\mathrm{OH}}[\mathrm{HO}^-]$ in Eq. (4) within the [NaOH] range 0.5–2.0 M.

The reaction mechanism for alkaline hydrolysis of **3** may be considered similar to the one shown in Scheme 1 with the replacement of 2′-$\mathrm{CO_2^-}$ by 2-H in SH. The leaving groups (HO^-) in k_{-1} and k_{-2} steps are much better than the leaving groups in k_3 and k_4 steps in terms of $\mathrm{p}K_\mathrm{a}$ of the conjugate acids of leaving groups. Consequently, $k_{-1} \gg k_3$ and $k_{-2} \gg k_4$ and these inequalities lead to the k_3 and k_4 steps as the rate determining.

Perhaps it is interesting to note that almost all theoretical studies on the mechanism of aqueous alkaline hydrolysis of formamide [17–21], *N*-methylacetamide, *N*,*N*-dimethylformamide (DMF), and *N*,*N*-dimethylacetamide (DMA) [21] revealed that hydroxide ion nucleophilic attack at the carbonyl carbon in the formation of reactive tetrahedral intermediate is the rate-determining step, whereas the breakdown of this reactive tetrahedral intermediate to form the hydrolysis products is a fast step. This finding is apparently contrary to what one believes in terms of relative leaving abilities of the leaving groups in the partitioning of the reactive tetrahedral intermediate. In view of these theoretical studies, the rate law for alkaline hydrolysis of amides or, at least, formamide, *N*-methylacetamide, DMF and DMA should be as rate $= k_{\mathrm{OH}}[\mathrm{HO}^-]$[amide]. But the alkaline hydrolysis of several tertiary amides [22–26] and closely related compound [27] revealed the rate law as rate $= (k_{\mathrm{OH}}[\mathrm{HO}^-] + k'_{\mathrm{OH}}[\mathrm{HO}^-]^2)$[amide], which cannot be explained convincingly in terms of these theoretical studies [17–21]. Even the practical application of the concept of dianionic tetrahedral intermediate, derived from the kinetic term $k'_{\mathrm{OH}}[\mathrm{HO}^-]^2$ in the rate law, has been used in the synthesis of amines [28].

The value of k_{OH} for **1** is nearly 5-fold smaller than that for **2**, which may be attributed to unfavorable electrostatic effect of ionized phenolic group of **1**. Nearly 9-fold smaller value of k_{OH} for the reaction of HO^- with anionic *N*-(2′-hydroxyphenyl)phthalimide than that with *N*-(2′-methoxyphenyl)phthalimide was attributed to similar electrostatic effect [29]. The value of k_{OH} (6.1×10^{-5} $\mathrm{M^{-1}\ s^{-1}}$) for **3** may be compared with k_{OH} value (11×10^{-5} $\mathrm{M^{-1}\ s^{-1}}$) [5] for the reaction of HO^- with *N*-methylbenzanilide obtained at 65°C. The values of k_{OH} for **2** and **3** reveal nearly 20-fold decrease in $\mathrm{k_{OH}}$ caused by the presence of a 2-$\mathrm{CO_2^-}$ group of **2**. The replacement of 2-H by 2-$\mathrm{CO_2^-}$ decreased the value of k_{OH} by nearly 18-fold for the alkaline hydrolysis of methyl benzoate [30].



$Z = 2\text{–}O^{-}C_6H_4$, $Y = CO_2^-$ for **1**
$= 2\text{–}OMeC_6H_4$, $Y = CO_2^-$ for **2**
$= 2\text{–}OMeC_6H_4$, $Y = H$ for **3**

Scheme 2

It is perhaps noteworthy that the values of k_{OH} for **3** and N-methylbenzanilide are similar to k_{OH} for N-methylbenzamide and N,N-dimethylbenzamide at 100.4°C [16], despite the fact that pK_a of ammonia is larger than pK_a of aniline by 10 pK units [31]. A qualitative explanation of these results may be described as follows: To avoid the formation of highly unstable anion, $2\text{-}XC_6H_5NH^-$, in the k_4 step (Scheme 1) under aqueous medium, the k_4 step is proposed to involve additional steps as shown in Scheme 2, where the k step is the rate determining and pK_a of the ZNH_2^+ group is significantly larger for Z = R than that for Ar [32].

It is evident from Schemes 1 and 2 that $k_4 = kK_T$. It can be easily realized from Schemes 1 and 2 that (a) k_2 (for Z = Ar, aryl group) > k_2 (for Z = R, alkyl group), (b) k_{-2} (for Z = Ar) $\le$ k_{-2} (for Z = R), (c) k (for Z = Ar) > k (for Z = R), and (d) K_T (for Z = Ar) < K_T (for Z = R). The inequalities (a)–(d) show that K_2K_Tk (for Z = Ar) may not be expected to be significantly different from K_2K_Tk (for Z = R). The values of k_{OH} for **2** and **3** are ~10- to 11-fold larger at 65°C than those at 35°C (Table V). This shows that the rate is increased by ~2.2-fold for each increase of 10 K. Application of this empirical rule gives ~20-fold rate change with the change in temperature from 65 to 101°C. However, electrophilic sites of **3** and N-methylbenzanilide are sterically more hindered compared to that of N,N-dimethylbenzamide and this could reduce k_{OH} values for amides with relatively more sterically hindered electrophilic sites.

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