JOC Article

Efficient Rate Enhancement Due to Intramolecular General Base (IGB) Assistance in the Hydrolysis of *N*-(*o*-Hydroxyphenyl)phthalimide

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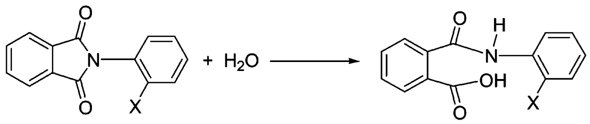

X = OH (**1**)
X = OMe (**2**)

X = OH (**3**)
X = OMe (**4**)

IGB - assisted rate enhancement due to *o* - O$^-$ in **1** is > 8 x 10^4 - fold

The rates of the hydrolyses of *N*-(*o*-hydroxyphenyl)phthalimide (**1**) and *N*-(*o*-methoxyphenyl)phthalimide (**2**), studied at different pH, show that the hydrolysis of **1** involves intramolecular general base (IGB) assistance where the *o*-O$^-$ group of ionized **1** acts as IGB and H_2O as the reactant. The rate enhancement due to the IGB-assisted reaction of H_2O with ionized **1** is $>8 \times 10^4$-fold. Pseudo-first-order rate constant for the reaction of water with **2** is $\sim 2 \times 10^3$-fold smaller than the first-order rate constant (0.10 s^{-1}) for pH-independent hydrolysis of **1** within the pH range of 9.60−10.10. Second-order rate constants (k_{OH}) for hydroxide ion-assisted hydrolysis of ionized **1** and **2** are 3.0 and 29.1 M^{-1} s^{-1}, respectively. The solvent deuterium kinetic isotope effect (dKIE) on the rate of alkaline hydrolysis of **1** and **2** reveals that the respective values of k_{OH}/k_{OD} are 0.84 and 0.78, where k_{OD} represents the second-order rate constant for DO$^-$-assisted cleavage of these imides (**1** and **2**). The value of $k_w^{H_2O}/k_d^{D_2O}$ is 2.04, with $k_w^{H_2O}$ and $k_d^{D_2O}$ representing pseudo-first-order rate constants for the reactions of ionized **1** with H_2O and D_2O, respectively.

Introduction

Intramolecular or induced intramolecular general acid (IGA)-, general base (IGB)-, and coupled IGA−IGB-assisted rate enhancements have been the subject of active study since the awareness of the fact that such rate enhancements are the essential part of the mechanism of action of many enzymes. The efficiency of intramolecular reactions is generally measured by the effective molarity (EM), which is the ratio of the unimolecular rate constant (k_1) for the intramolecular reaction to that (k_2) of the analogous (i.e., reference) bimolecular reaction.[1] Intramolecular general acid−base-assisted rate enhancement is intrinsically inefficient: EMs ranging from 1 to 10 M only.[1] Pascal has argued the low effective molarity of IGA−IGB assistance in terms of induced intramolecularity in the reference reaction.[2] Kirby and co-workers[3−7] have studied many IGA-assisted reactions where EM values for more efficient IGA-assisted reactions range from 10^3 to 10^5 M. The value of EM for IGB-assisted hydrolysis of phenyl salicylate, where the *o*-O$^-$ group acts as IGB, is $\sim 10^6$ EM.[8] We have been studying the mechanistic aspects of GA−GB catalysis in addition−elimination reactions where the leaving groups do not have free rotation around the bond being cleaved in the rate-determining step.[9] In the continuation of such study, we have investigated

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[1] Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.

[2] Pascal, R. *J. Phys. Org. Chem.* **2002**, *15*, 566.

[3] Brown, C. J.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1081.

[4] Barber, S. E.; Dean, K. E. S.; Kirby, A. J. *Can. J. Chem.* **1999**, *77*, 792.

[5] Brown, C. J.; Kirby, A. J. *J. Chem. Soc., Chem. Commun.* **1996**, 2355.

[6] Kirby, A. J.; Parkinson, A. *J. Chem. Soc., Chem. Commun.* **1994**, 707.

[7] Abell, K. W. Y.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1171.

[8] Khan, M. N. *J. Phys. Org. Chem.* **1999**, *12*, 1.

[9] (a) Khan, M. N.; Ohayagha, J. E. *J. Phys. Org. Chem.* **1991**, *4*, 547. (b) Khan, M. N. *Int. J. Chem. Kinet.* **2002**, *34*, 95.

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TABLE 1. Values of k_0 and k_b, Calculated from Equation 1, for the Cleavage of 1 Under Buffer of DABCO at pH ≥9.56[a]

pH	$10^3\ k_0$/s^{-1}	$10^3\ k_b{}^b$/M^{-1} s^{-1}
9.56 ± 0.01[c]	92.8 ± 1.4[c]	11.7 ± 2.7[c]
9.78 ± 0.01	95.5 ± 2.7	22.3 ± 5.5
9.90 ± 0.01	90.2 ± 1.3	43.7 ± 2.7
10.11 ± 0.01	95.5 ± 1.6	44.0 ± 3.1

[a] $[\mathbf{1}]_0 = 3 \times 10^{-4}$ M, 35 °C, $\lambda = 300$ nm, the aqueous reaction mixture for each kinetic run contained 1% v/v CH_3CN. [b] The values of k_b at pH <9.56 are statistically not different from zero, and total buffer concentration range is 0.10−0.80 M. [c] Error limits are standard deviations.

the kinetics of aqueous cleavage of *N*-(*o*-hydroxyphenyl)phthalimide where the expected IGA (*o*-OH) or IGB (*o*-O$^-$) rate-enhancing group is attached to the leaving group. The results and probable explanations are described in this paper.

Results

Hydrolysis of *N*-(*o*-Hydroxyphenyl)phthalimide (1) at 35 °C. A series of kinetic runs was carried out in buffer solutions of sodium acetate (pH 3.97−5.12), NaH_2PO_4 (pH 6.08−7.43), tris(hydroxymethylaminomethane) (TRIS) (pH 7.73−8.26), and 1,4-diazabicyclo[2.2.2]octane (DABCO) (pH 8.43−10.11). Pseudo-first-order rate constants (k_{obs}) were found to be independent of total buffer concentration ($[Buf]_T$) at a constant pH for acetate buffer ($[Buf]_T$ range 0.20−0.80 M), phosphate buffer ($[Buf]_T$ range 0.10−0.50 M), TRIS buffer ($[Buf]_T$ range 0.20−0.80 M), and DABCO buffer at pH ≤ 9.38 ($[Buf]_T$ range 0.10−0.80 M). A mild buffer catalysis is observed in the presence of DABCO buffers of pH ≥ 9.56. The values of k_{obs}, under such conditions, fit to eq 1

$$k_{obs} = k_0 + k_b[Buf]_T \qquad (1)$$

where $[Buf]_T$ represents the total buffer concentration of DABCO. The least-squares calculated values of buffer-independent first-order rate constants, k_0, and buffer-dependent second-order rate constants, k_b, at pH ≥ 9.56 are summarized in Table 1. Perhaps it is noteworthy that the maximum contribution of $k_b[Buf]_T$ in eq 1, obtained at the maximum value of $[Buf]_T$ = 0.8 M, is ≤28% (Table 1), and consequently, the calculated values of k_b in Table 1 may not be considered as very reliable.

Although the values of k_b are not reliable for the reason mentioned earlier in the text, the value of the second-order rate constant ($k_b{}^{SH}$) for the reaction of SH with free DABCO amine base of nearly zero is plausible for the reason that a significant value of $k_b{}^{SH}$ should have caused perhaps higher values of k_b at pH ≤9.38 because the decrease in pH increases the value of $[SH]/[S^-]$ and $pK_a{}^{SH} = 8.42$ and $pK_a{}^{Am} = 8.95$ (Am = DABCO),[10a] but under such conditions, the values of k_b are almost zero. These results show the absence of phosphate, TRIS, and DABCO (at pH ≤9.38) buffer catalysis in the aqueous cleavage of **1**. We tried to fit the values of k_{obs}, obtained at different pH ranging from 3.97 to 10.11, as shown in Figure 1, to the following empirical equation (eq 2)

$$k_{obs} = \frac{\alpha + \beta[H^+]}{[H^+] + \Phi} \qquad (2)$$

where α, β, and Φ are empirical constants and $[H^+] = 10^{-pH}/\gamma$ with activity coefficient $\gamma = 0.7$ at 1.0 M ionic strength.[11] The nonlinear least-squares calculated values of α, β, and Φ are $(4.84 \pm 0.30) \times 10^{-10}$ M s^{-1}, $(-4.9 \pm 10) \times 10^{-4}$ s^{-1}, and $(4.86 \pm 0.35) \times 10^{-9}$ M, respectively. The negative value of β with standard deviation of more than 200% merely indicates that the contribution of $\beta[H^+]$ compared to α is insignificant under the pH range of the study. Thus, the values of α and Φ were also calculated from eq 2 with β = 0, and these respective values are $(4.78 \pm 0.26) \times 10^{-10}$ M s^{-1} and $(4.79 \pm 0.31) \times 10^{-9}$ M. The fitting of observed data to eq 2 is evident from Figure 1, where a solid line is drawn through the calculated data points, and also from the values of k_{calcd} listed in Table A of Supporting Information.

A few kinetic runs for alkaline hydrolysis of **1** were also carried out within [NaOH] range of 0.0020−0.0500 M, and the values of k_{obs}, obtained under these conditions, fit to eq 3 with least-squares calculated values of $k_w{}^0$ and k_{OH} as $(96.8 \pm 3.0) \times 10^{-3}$ s^{-1} and 3.0 ± 0.1 M^{-1} s^{-1}, respectively.

$$k_{obs} = k_w{}^0 + k_{OH}[HO^-] \qquad (3)$$

The satisfactory fit of observed data to eq 3 is evident from the plot of Figure 1, where a solid line with definite positive intercept is drawn through the calculated data points. The value of $k_w{}^0$ (96.8×10^{-3} s^{-1}) is similar to α/Φ (0.10 s^{-1}) calculated from eq 2.

A few kinetic runs for the reaction of **1** were also carried out within [HCl] range of 5.0×10^{-3} to 1.0 M. The values of k_{obs}, within [HCl] range of 0.08−1.0 M, fit to eq 3 with replacement of k_{OH} and $[HO^-]$ with k_H and [HCl], respectively. The linear least-squares calculated values of $k_w{}^0$ and H^+-catalyzed second-order rate constant, k_H, are $(1.25 \pm 0.07) \times 10^{-6}$ s^{-1} and $(4.20 \pm 0.11) \times 10^{-6}$ M^{-1} s^{-1}, respectively. The linear dependence of k_{obs} versus [HCl] may be attributed from hydronium ion-catalyzed and uncatalyzed hydrolytic paths in the hydrolysis of **1** under such conditions.

Solvent Deuterium Kinetic Isotope Effect (dKIE) on the Rate of Alkaline Hydrolysis of 1 and 2. The reaction rates for the cleavage of **1** were studied at 35 °C and within [NaOD] range of 1.0×10^{-3} to 5.0×10^{-2} M in the solvents with D_2O and acetonitrile contents of 99 and 1% v/v, respectively. The observed pseudo-first-order rate constants, $k_{obs}{}^D$, as shown in Table B of Supporting Information, fit to eq 3 with replacement of k_{obs}, $k_w{}^0$, k_{OH}, and $[HO^-]$ with $k_{obs}{}^D$, $k_d{}^D$, k_{OD}, and $[DO^-]$, respectively. The linear least-squares calculated values of $k_d{}^D$ and k_{OD} are $(47.4 \pm 0.6) \times 10^{-3}$ s^{-1} and 3.58 ± 0.02 M^{-1} s^{-1}, respectively. The respective values of $k_w{}^0$ and k_{OH}, obtained under similar experimental conditions with solvents containing 99% v/v H_2O and 1% v/v acetonitrile, are $(96.8 \pm 3.0) \times 10^{-3}$ s^{-1} and 3.0 ± 0.1 M^{-1} s^{-1}. Similar D_2O solvent isotope effect on the rate of alkaline hydrolysis of **2** was also studied at 35 °C and within [NaOD] range of 3.0×10^{-3} to 5.0×10^{-3} M in the solvents with D_2O and acetonitrile contents of 98 and 2% v/v, respectively. The $k_{obs}{}^D$ values (Table C of Supporting Information) were used to calculate $k_d{}^D$ and k_{OD} from eq 3 with replacement of k_{obs}, $k_w{}^0$, k_{OH}, and $[HO^-]$ with $k_{obs}{}^D$, $k_d{}^D$, k_{OD}, and $[DO^-]$, respectively, and the respective calculated values of $k_d{}^D$ and k_{OD} are $(-12 \pm 10) \times 10^{-3}$ s^{-1} and 40.0 ± 2.7 M^{-1} s^{-1}. The negative value with standard deviation of almost 100% reveals the insignificant contribution of $k_d{}^D$ compared with k_{OD}

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[10] (a) Khan, M. N. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1129. (b) Khan, M. N. Micellar Catalysis. In *Surfactant Science Series*; CRC Press, Taylor & Francis Group, LLC: Boca Raton, FL, 2006; Vol. 133, pp 378−391. (c) Khan, M. N. *J. Chem. Soc., Perkin Trans. 2* **1990**, 435.

[11] Hine, J.; Via, F. A.; Jensen, J. H. *J. Org. Chem.* **1971**, *36*, 2926.

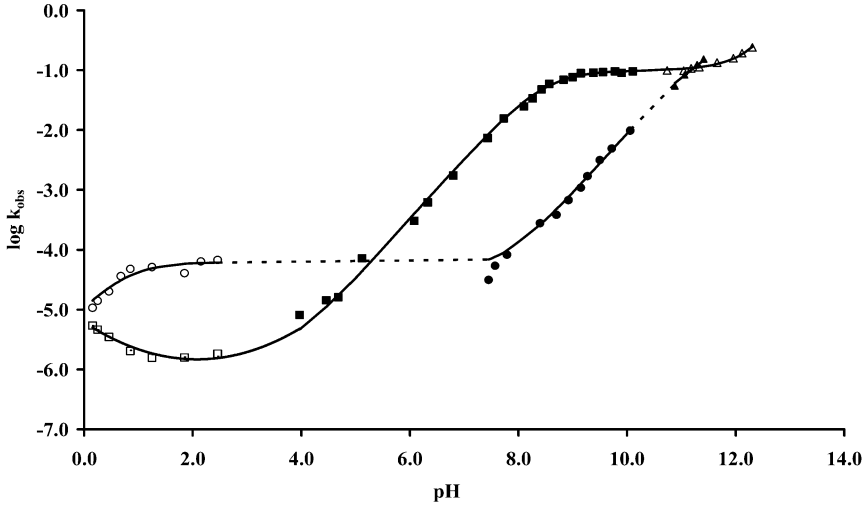

FIGURE 1. Plots showing the dependence of log k_{obs} on pH for hydrolysis of **1** (with $k_{obs} = k_0$ when $k_b \neq 0$ in eq 1 at different pH) and **2**, where pH ranges 0.16−2.46 (□) maintained by HCl, 3.97−10.11 (■) maintained by buffers, and 10.74−12.31 (△) maintained by NaOH for **1** and pH ranges 0.16−2.46 (○) maintained by HCl, 7.45−10.06 (●) maintained by buffers, and 10.88−11.41 (▲) maintained by NaOH for **2**. The solid lines are drawn through the calculated data points using eq 2 for (■), eq 3 for (□), (△), (●), and (▲), and eq 5 for (○) as described in the text. The broken line is not drawn through the calculated data points but rather drawn arbitrarily.

[NaOD] in eq 3, and hence, a relatively more reliable value of k_{OD} (37.5 ± 0.7 M^{-1} s^{-1}) was obtained from eq 3 with $k_d^D = 0$. The value of k_{OH}, obtained under similar experimental conditions with solvent containing 98% v/v H_2O and 2% v/v acetonitrile, is 29.2 ± 1.9 M^{-1} s^{-1}.

The values of k_{OH}/k_{OD} for alkaline hydrolysis of **1** ($k_{OH}/k_{OD} = 0.84$) and **2** ($k_{OH}/k_{OD} = 0.78$) are consistent with the wide held perception that DO^- (in D_2O) reacts faster than HO^- (in H_2O) with esters and amides. These values of k_{OH}/k_{OD} are in agreement with the reported values of k_{OH}/k_{OD} for alkaline hydrolysis of formamide ($k_{OH}/k_{OD} = 0.77$),[12] *endo*-5-[4′(5′)-imidazolyl]bicyclo[2.2.1]-hept-*endo*-2-yl *trans*-cinnamate (B_1, $k_{OH}/k_{OD} = 1.0$),[13] *endo*-[4′(5′)-imidazolyl]bicyclo[2.2.2]-*endo*-2-yl *trans*-cinnamate (B_2, $k_{OH}/k_{OD} = 0.95$),[13] and other simple amides and esters ($k_{OH}/k_{OD} = 0.71-0.77$).[12] The values of k_{OH}/k_{OD} for the reactions of HO^-/DO^- with ionized phenyl salicylate and methyl salicylate are 0.98 and 1.04, respectively.[14] Thus, it seems that the values of k_{OH}/k_{OD} are independent of the nature (whether nucleophilic attack or expulsion of leaving group) of the rate-determining steps involved in these addition−elimination reactions.

The value of $k_w^{H_2O}/k_d^{D_2O}$ ($=k_w^0/k_d^D$) = 2.04 for **1** may be compared with the reported values for hydrolysis of phenyl salicylate ($k_w^{H_2O}/k_d^{D_2O} = 1.6$,[15] 1.7[16]), *p*-nitrophenyl 5-nitrosalicylate ($k_w^{H_2O}/k_d^{D_2O} = 1.7$[17]), catechol monobenzoate ($k_w^{H_2O}/k_d^{D_2O} = 1.8$[16]), and B_1 and B_2 ($k_w^{H_2O}/k_d^{D_2O} = 3.0$[13]), where the occurrence of intramolecular general base (IGB) assistance has been strongly supported by some indirect chemical evidence.

Since the *o*-OH group is only five atoms away from the electrophilic carbonyl carbon, it is quite plausible to think that pH-independent cleavage of **1** might involve an intramolecular nucleophilic addition−elimination process, as shown in Scheme 1. Such a reaction mechanism predicts $k_w^{H_2O}/k_d^{D_2O} \approx 1.0$, and thus, the observed value of $k_w^{H_2O}/k_d^{D_2O} = 2.04$ rules out the possibility of the occurrence of the reaction mechanism shown in Scheme 1. However, a skeptic might argue that $k_w^{H_2O}/k_d^{D_2O}$ of >1 may be expected if the product in the k_2^1 step is **5** formed through transition state TS_1. If this view is plausible, then it is difficult to explain the observed unity or slightly inverse solvent deuterium kinetic isotope effect (dKIE) obtained for alkaline hydrolysis of esters and amides, including formamide,[12,13] where it is almost certain that expulsion of the leaving group is the rate-determining step (similar to the k_2^1 step) in an addition−elimination mechanism for hydrolysis of amides and nonactivated esters, while nucleophilic attack is the rate-determining step for hydrolysis of activated esters. Although solvent dKIE does not seem to favor the reaction mechanism shown by Scheme 1, there is always a significant amount of uncertainty in the mechanistic conclusion drawn from solvent dKIE. However, other indirect evidence for the absence of formation of $\mathbf{5}^-$ through reaction steps shown in Scheme 1 may be described below.

A brief and plausible reaction scheme for the aqueous cleavage of S^- by both hydrolysis (k_w step) and O-cyclization (k_f step) may be shown in Scheme 2 where k_f^2, k_b^2, k_w^2, and k_{OH}^2 represent pseudo-first-order rate constants.

The detailed mechanism for the reaction $S^- \rightleftharpoons \mathbf{5} \rightarrow \mathbf{3}^-$ is shown in Scheme 1, and thus comparing Scheme 2 and Scheme 1, $k_f^2 = k_1^1k_2^1/k_{-1}^1$ and $k_b^2 = (k_{-2}^1K_a[HO^-])/K_w$ provided $a_H \gg K_a$ where $K_a = [\mathbf{5}^-]a_H/[\mathbf{5}]$ and $K_w = a_Ha_{OH}$. If $k_b^2 = k_b'[HO^-]$, then $k_b' = k_{-2}^1K_a/K_w$. The reported values of k_b' for some related reactions are shown in Table 2.

The reported data listed in Table 2 demonstrate that the k_b' values are highly sensitive and almost insensitive to the pK_a of conjugate acid of the leaving group anion (pK_a^{Le}) and nucleophilic anion (pK_a^{Nu}), respectively. In all these reactions, the expulsion of the leaving group does not accompany with any

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[12] Slebocka-Tilk, H.; Neverov, A. N.; Brown, R. S. *J. Am. Chem. Soc.* **2003**, *125*, 1851 and references cited therein.

[13] Komiyama, M.; Roesel, T. R.; Bender, M. L. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 23.

[14] Khan, M. N. *J. Chem. Soc., Perkin Trans. 2* **1990**, 675.

[15] Khan, M. N. *J. Chem. Soc., Perkin Trans. 2* **1989**, 199.

[16] Capon, B.; Ghosh, B. C. *J. Chem. Soc. B* **1966**, 472.

[17] Bender, M. L.; Kezdy, F. J.; Zerner, B. *J. Am. Chem. Soc.* **1963**, *85*, 3017.

[18] Shafer, J. A.; Morawetz, H. *J. Org. Chem.* **1963**, *28*, 1899.

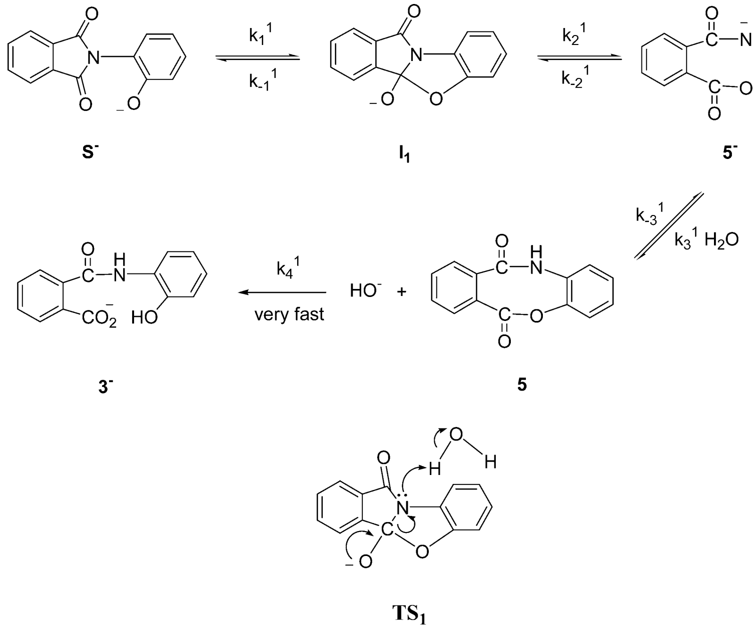
[19] Fife, T. H.; DeMark, B. R. *J. Am. Chem. Soc.* **1976**, *98*, 6978.

[20] Fife, T. H.; Benjamin, B. M. *J. Am. Chem. Soc.* **1973**, *95*, 2059.

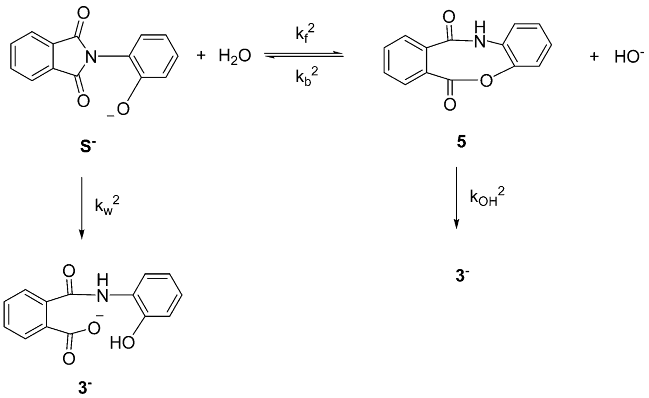
[21] Khan, M. N. *J. Chem. Soc., Perkin Trans. 2* **1988**, 213.

[22] Khan, M. N.; Ismail, E. *J. Phys. Org. Chem.* **2004**, *17*, 376.

SCHEME 1



SCHEME 2



release of ring strain for the reason that the leaving groups in these cyclization reactions have free rotation about the bond being cleaved during the rate-determining step. In view of the reported values of k_b' and pK_a^{Le} in Table 2, it may be reasonable to assume the value k_b' of 10^5-10^6 M^{-1} s^{-1} for conversion of **5** to S^-.

If one assumes arbitrarily an equal contribution of the k_w^2 step and k_f^2 step in Scheme 2, then the value of k_f^2 is 0.05 s^{-1} because $k_{obs} = k_w^2 + k_f^2 = 0.1$ s^{-1} at pH 9.60. The expected value of $k_b' = 10^5-10^6$ M^{-1} s^{-1} gives $k_b^2 = 9-90$ s^{-1} at pH 9.60. Thus, $[\mathbf{5}]/[S^-] = k_f^2/k_b^2 \approx 5.6 \times 10^{-3}$ to 5.6×10^{-4} and consequently $[\mathbf{5}]/([\mathbf{5}] + [S^-]) \approx 5.6 \times 10^{-3}$ to 5.6×10^{-4} at pH 9.60. This shows the equilibrium presence of **5** and S^- as 0.56−0.06% and 99.4−99.9%, respectively. Such a low presence of **5** (<0.6%) is hard to detect by any spectral method. Furthermore, the half-life period for irreversible disappearance of S^- in the k_w^2 step (Scheme 2) is only ∼14 s if $k_w^2 = 0.05$ s^{-1}.

The expected value of k_b' $(=k_b^2/[HO^-])$ is in the range of 10^5-10^6 M^{-1} s^{-1}, which is nearly 1.5×10^5 to 1.5×10^6-fold larger than k_{OH} for alkaline hydrolysis of phenyl benzoate ($k_{OH} = 0.68$ M^{-1} s^{-1}). The values of k_{OH} for alkaline hydrolysis of *N*-methylphthalimide[23] and methyl benzoate[24] are 27 and 1.25×10^{-1} M^{-1} s^{-1}, respectively. The values of pK_a of conjugate acids of the leaving groups, amide anion, and methoxide ion in these respective reactions are 14−15[25] and ∼15,[26] and therefore, the ratio 27/0.125 = 216 reflects the rate enhancement due to release of the five-membered ring strain in the alkaline hydrolysis of *N*-methylphthalimide. The release of the eight-membered ring strain in the conversion of **5** to $\mathbf{3}^-$ may increase the k_{OH} value but certainly <200-fold because the eight-membered ring is probably less strained than a five-membered ring. The value of pK_a of $\mathbf{3}^-$ is 9.7, which is not significantly different from pK_a of phenol ($pK_a = 9.9$). Even if the increase in k_{OH}^2 due to release of the eight-membered ring strain is 200-fold, the value of the pseudo-first-order rate constant (k^2) for the concurrent conversion of S^- to $\mathbf{3}^-$ through the k_{OH}^2 step is $\sim 7 \times 10^{-5}$ to 7×10^{-6} s^{-1} ($k^2 = k_{OH}^2{}_{,eff}\, k_f^2[HO^-]/k_b'[HO^-]$, where $k_{OH}^2{}_{,eff} = 200 \times k_{OH}$), which is $\sim 1.4 \times 10^{-3}$ to 1.4×10^{-4}-fold smaller than k_w^2 (0.05 s^{-1}).

Furthermore, in a recently published report[27] on the intramolecular carboxylic group-assisted cleavage of **3** at 0.05 M HCl, the reactant **3** was generated in situ from alkaline hydrolysis of S^-, and the rate of reaction was initiated by adding 0.20 mL of 1.25 M HCl to the alkaline reaction mixture (4.80 mL) at ∼100 half-lifes of the reaction, which gave **3** in aqueous acidic solution containing 0.049 M HCl. One kinetic run was also carried out at 0.05 M HCl using synthesized **3** as the reactant. In both reactions (one with synthetic **3** and the other with **3** obtained in situ from alkaline hydrolysis of S^-), the final products were 100% phthalic acid and *o*-hydroxyaniline. Since product **5** cannot hydrolyze to a significant extent within ∼900 s (equivalent to ∼100 half-lifes for hydrolysis of **1** under a pH range of 9.60−10.11) at pH 9.60, a significant parallel formation of **5** could have caused less than 100% formation of phthalic acid and *o*-hydroxyaniline in the acidic aqueous cleavage of **3**, where

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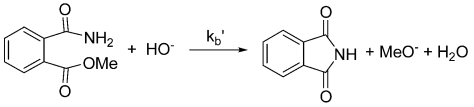
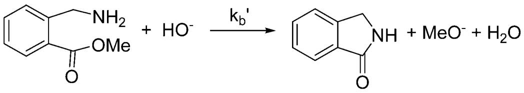
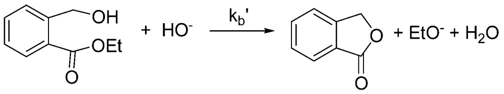
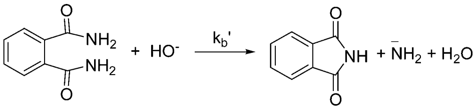
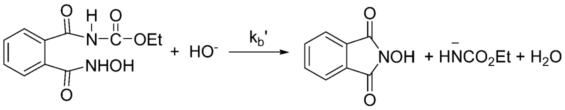
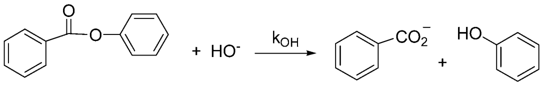
(23) Ariffin, A.; Khan, M. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1037.
(24) Hegarty, A. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1970**, *92*, 6575.
(25) Barlin, G. B.; Perrin, D. D. *Quart. Rev. Chem. Soc.* **1966**, *20*, 75.
(26) Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451.
(27) Sim, Y.-L.; Azhar A.; Khan, M. N. *Int. J. Chem. Kinet.* **2006**, *38*, 746.

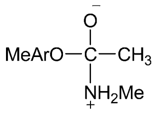
TABLE 2. Values of k_b' for Cyclization Reactions Related to One in the k_b^2 Step of Scheme 2

reaction	k_b' / M^{-1} s^{-1} at 35 °C	pK_a^{Le}	pK_a^{Nu}	ref.
	6.0 x 10^3	15	14 – 15	18
	9.9 x 10^3	15	27 – 34	19
	1.4 x 10^4	15	15	20
	11.5	35	14 – 15	18
	5.5 x 10^4	15	<< 14	21
$\mathbf{5} + HO^- \xrightarrow{k_b'} S^- + H_2O$		8.5	13.7	present work
	0.68	9.9	15.6	22

3 was generated in situ from alkaline hydrolysis of S^- because the rate of H^+-assisted hydrolysis is expected to be much slower than HO^--assisted hydrolysis of **5**. So it is certain beyond any reasonable doubt that the immediate detectable hydrolysis product of S^- is **3**.

A perfect simple first-order rate law has been found for the rate of reaction monitored both by disappearance of reactant (S^-) at 300 nm and appearance of product **3** at 320 nm as a function of reaction time for the reaction period of ~7.5 half-lifes for each kinetic run. The value of k_{obs} for the kinetic run carried out at 300 nm was similar to k_{obs} for the same kinetic run carried out at 320 nm. The immediate products for these kinetic runs were also the same in view of similar UV spectra of authentic **3** and reaction mixtures obtained under similar experimental conditions at 60−120 s (~10−20 half-lifes). These observations support the conclusion that the immediate hydrolysis product of S^- is **3**. In a closely related study on the aqueous cleavage of *N*-(2-aminophenyl)phthalimide at pH range of 0−6, Perry[28] could not detect N-cyclization product similar to O-cyclization product **5** of S^-.

One of the reviewers suggested that I_1 might be equal or even more stable than S^- at basic pH, which is apparently incomprehensible in view of the kinetic analysis described earlier in the text. However, if the assumption that I_1 might be equal or even more stable than S^-, then the value of equilibrium constant K_1^1 ($=k_1^1/k_{-1}^1$ in Scheme 1) must be ≥ 1 at basic pH. The experimentally determined value of k_{obs} within pH range of 9.60−10.11 is 0.10 s^{-1}, and under such reaction conditions, $k_{obs} = k_2^1K_1^1$ which gives $k_2^1 \leq 0.10$ s^{-1}. The value of k_2^1 of ≤ 0.10 s^{-1} is $>10^{10}$-fold smaller than rate constant ($=3 \times 10^9$ s^{-1}) for the expulsion of methylamine from T,[29] which is difficult to explain in terms of structural features of I_1 and T (pK_a of $MeNH_3^+$ is 10.85 and pK_a of amide group of **5** is ≤14 at 30 °C and under similar conditions). Furthermore, the ^1H NMR spectrum of **1** in 100% v/v D_2O solvent containing 3.2×10^{-2} M **1** and 8.7×10^{-2} M NaOD obtained quickly turned out to be similar to the ^1H NMR spectrum of authentic **3** obtained under similar conditions. This shows nearly 100% conversion of **1** to **3** within the time period of obtaining the ^1H NMR spectrum. This is plausible for the fact that 10 half-lifes (equivalent to ~99.9% completion of the reaction) for hydrolysis of **1**, under the conditions of obtaining the ^1H NMR spectrum, is equivalent to only ~70 s. Thus, these observations do not show the presence of a ^1H NMR detectable amount of I_1 during the course of the reaction.



T

Hydrolysis of *N*-(*o*-Methoxyphenyl)phthalimide (2) at 35 °C. The rate of hydrolysis of **2** was studied at different [NaOH] ranging from 2.0×10^{-3} to 5.0×10^{-3} M, and observed pseudo-first-order rate constants (k_{obs}) were fit to eq 3, which resulted in k_w^0 and k_{OH} of $(-1.4 \pm 0.6) \times 10^{-2}$ s^{-1} and 33.8 ± 1.6 M^{-1} s^{-1}, respectively. The calculated negative value of k_w^0 is meaningless, and therefore, k_{OH} was also calculated from eq 3 with $k_w^0 = 0$, and such a calculated value of k_{OH} is 29.2 ± 1.9 M^{-1} s^{-1}. In an attempt to get a reliable value of k_w^0, the rate of hydrolysis of **2** was also carried out at different pH ranging from 7.45 to 10.06 maintained by *N*-methyl morpholine and DABCO buffers. The values of k_{obs} at different total amine buffer concentrations, $[Buf]_T$ ($[Buf]_T$ range is 0.2−0.8 M for both *N*-methyl morpholine and DABCO buffers) fit to an empirical equation (eq 4)

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(28) Perry, C. J. *J. Chem. Soc., Perkin Trans. 2* **1997**, 977.

(29) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6970.

$$k_{obs} = \frac{k_0 + k_b^{app}K[\mathrm{Buf}]_T}{1 + K[\mathrm{Buf}]_T} \qquad (4)$$

where k_b^{app} represents the apparent buffer-catalyzed pseudo-first-order rate constant for the cleavage of **2** and K is an empirical constant (most likely an equilibrium constant for reactive complex formation between **2** and buffer). The nonlinear least-squares calculated values of k_0, k_b^{app}, and K at a typical pH 8.94 ± 0.03 in DABCO buffer are $(1.10 \pm 0.09) \times 10^{-3}$ s^{-1}, $(4.01 \pm 0.26) \times 10^{-3}$ s^{-1}, and 2.40 ± 0.59 M^{-1}, respectively. The values of k_0 fit to eq 3 where $k_{obs} = k_0$, $[\mathrm{HO}^-] = 10^{\mathrm{pH}-\mathrm{p}K_w}/\gamma$ with pK_w = 13.62[30] and activity coefficient, $\gamma = 0.70$.[11] The least-squares calculated values of k_w^0 and k_{OH} are $(5.3 \pm 7.0) \times 10^{-5}$ s^{-1} and 25.3 ± 0.5 M^{-1} s^{-1}, respectively. The calculated value of k_w^0 with standard deviation of more than 100% merely indicates that the contribution of k_w^0 is insignificant compared with $k_{OH}[\mathrm{HO}^-]$ in eq 3. Thus, the k_{OH} ($=29.1 \pm 6.7$ M^{-1} s^{-1}) was also calculated from eq 3 with $k_w^0 = 0$. The satisfactory fit of k_0 to eq 3 is evident from the plot of log k_{obs} versus pH (with $k_{obs} = k_0$) shown in Figure 1, where a solid line is drawn through the calculated data points, and also from k_{calcd} values summarized in Table D of Supporting Information.

The rate of aqueous cleavage of **2** has also been studied within [HCl] range of 0.005−1.0 M. Although some light precipitates visible to the naked eye appear in the reaction mixtures after ~0.5 and 4 h at 0.02 and 0.5 M HCl, respectively, the reaction mixtures remained transparent, and the observed data apparently fit to eq 9 for the reaction period of ≥10 half-lifes for all kinetic runs. The values of k_{obs} followed the following empirical equation (eq 5)

$$k_{obs} = \frac{k_w^0}{1 + K[\mathrm{HCl}]} \qquad (5)$$

where k_w^0 ($=k_{obs}$ at [HCl] = 0) and K are empirical constants. The nonlinear least-squares calculated values of k_w^0 and K are $(6.20 \pm 0.49) \times 10^{-5}$ s^{-1} and 3.35 ± 0.96 M^{-1}, respectively.

Discussion

A brief reaction scheme for buffer-independent cleavage of **1** at pH ≥4 is shown in Scheme 3.

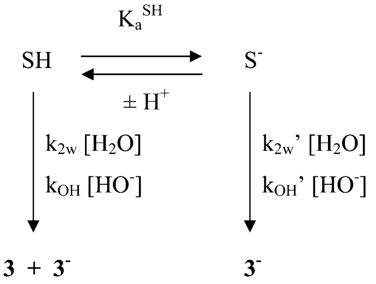
The mechanisms for the k_{2w} step and k_{2w}' step are similar to the one shown in Scheme 7 with replacement of X with OH and O$^-$, respectively. Similarly, the mechanisms for the k_{OH} step and k_{OH}' step are similar to the one shown in Scheme 7 with respective replacement of X with *o*-OH and *o*-O$^-$. Scheme 3 can lead to the rate law for the aqueous cleavage of **1** at pH ≥4 as expressed by eq 6

$$\text{rate} = k_{2w}[\mathrm{H_2O}][\mathrm{SH}] + k_{2w}'[\mathrm{H_2O}][\mathrm{S^-}] + k_{OH}[\mathrm{HO^-}][\mathrm{SH}] + k_{OH}'[\mathrm{HO^-}][\mathrm{S^-}] \qquad (6)$$

where SH and S$^-$ represent nonionized and ionized form of **1**, respectively. The observed rate law (rate = $k_{obs}[\mathbf{1}]_T$, where $[\mathbf{1}]_T = [\mathrm{SH}] + [\mathrm{S^-}]$) and eq 6 can lead to eq 7

$$k_{obs} = \frac{k_w[\mathrm{H^+}] + k_w'K_a^{SH}}{[\mathrm{H^+}] + K_a^{SH}} + \frac{(k_{OH}[\mathrm{H^+}] + k_{OH}'K_a^{SH})[\mathrm{HO^-}]}{[\mathrm{H^+}] + K_a^{SH}} \qquad (7)$$

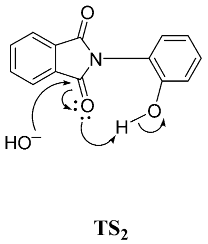
SCHEME 3



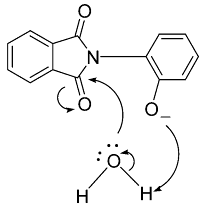
where $k_w = k_{2w}[\mathrm{H_2O}]$, $k_w' = k_{2w}'[\mathrm{H_2O}]$, and $K_a^{SH} = [\mathrm{S^-}][\mathrm{H^+}]/[\mathrm{SH}]$. Comparison of eqs 2 and 3 with eq 7 gives $\beta = k_w$, $\alpha = k_w'K_a^{SH} + k_{OH}K_w'$ with $K_w' = [\mathrm{H^+}][\mathrm{HO^-}]$ and $\Phi = K_a^{SH}$. The value of K_a^{SH} $\{= \Phi = (4.79 \pm 0.31) \times 10^{-9}$ M$\}$ is comparable to K_a^{SH} ($=5.33 \times 10^{-9}$ M) at 35 °C determined independently by UV spectrophotometric technique. At significantly high pH where $[\mathrm{H^+}] \ll K_a^{SH}$, and $k_w[\mathrm{H^+}] \ll k_w' K_a^{SH}$, eq 7 reduced to eq 8 which is similar to eq 3 with $k_w^0 = k_w' + k_{OH} K_w'/K_a^{SH}$ and $k_{OH} = k_{OH}'$.

$$k_{obs} = k_w' + k_{OH}K_w'/K_a^{SH} + k_{OH}'[\mathrm{HO^-}] \qquad (8)$$

The kinetic terms $k_{2w}'[\mathrm{H_2O}][\mathrm{S^-}]$ and $k_{OH}[\mathrm{HO^-}][\mathrm{SH}]$ in eq 6 are kinetically indistinguishable. However, if these kinetic steps do not involve an efficient intramolecular assistance/catalysis, then $k_{2w}'[\mathrm{H_2O}][\mathrm{S^-}]$ may be neglected compared to $k_{OH}[\mathrm{HO^-}][\mathrm{SH}]$ for the fact that, although $[\mathrm{H_2O}] >> [\mathrm{HO^-}]$ under the experimental conditions imposed, HO$^-$ is a much stronger nucleophile than H$_2$O (pK_a of H$_2$O is 15.74, while pK_a of H$_3$O$^+$ is −1.74). Thus, under this conditions, $\alpha = k_{OH}K_w'$, and hence $k_{OH} = \alpha/K_w' = 1.0 \times 10^4$ M^{-1} s^{-1} with $10^{14} K_w' = 4.9$ M^2.[30] The value of $k_{OH} = 1.0 \times 10^4$ M^{-1} s^{-1} is ~330-fold larger than k_{OH} ($=30$ M^{-1} s^{-1}) for **2**, which cannot be explained in terms of simple resonance and polar effects of *o*-OH and *o*-OMe substituents because $\sigma^*_{OH} = \sigma^*_{OMe} = 1.81$[31] and $\sigma_{p-OH} = -0.37$[32] as well as $\sigma_{p-OMe} = -0.27$.[33] Nearly 330-fold larger value of k_{OH} for **1** than that for **2** demonstrates the occurrence of intramolecular general acid (IGA)-assisted reaction of HO$^-$ with nonionized **1** (=SH) involving transition state TS$_2$. However, under such circumstances, the occurrence of kinetically indistinguishable intramolecular general base (IGB)-assisted reaction of H$_2$O with ionized **1** (=S$^-$) involving transition state TS$_3$ cannot be ruled out based upon simply much lower nucleophilicity of H$_2$O compared to that of HO$^-$.



TS$_2$



TS$_3$

It is almost impossible to ascertain with absolute certainty whether transition state TS$_2$ or TS$_3$ is involved in the pH-

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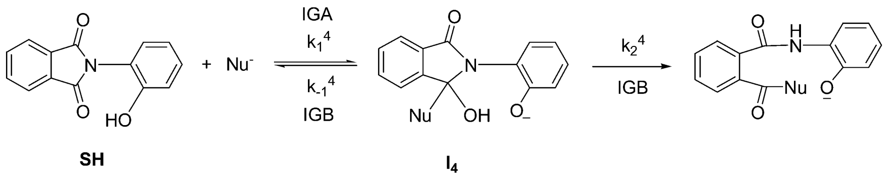
[30] Ritchie, C. D.; Wright, D. J.; Huang, D.-S.; Kamego, A. A. *J. Am. Chem. Soc.* **1975**, *97*, 1163.

[31] Fastrez, J. *J. Am. Chem. Soc.* **1977**, *99*, 7004.

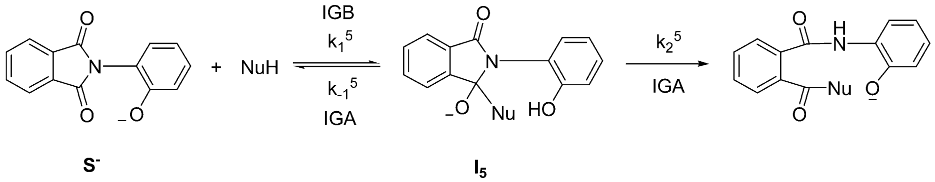
[32] Hine, J. *Structural Effects on Equilibria in Organic Chemistry*; Wiley: New York, 1975; pp 98−99.

[33] Khan, M. N. *J. Mol. Catal.* **1987**, *40*, 195.

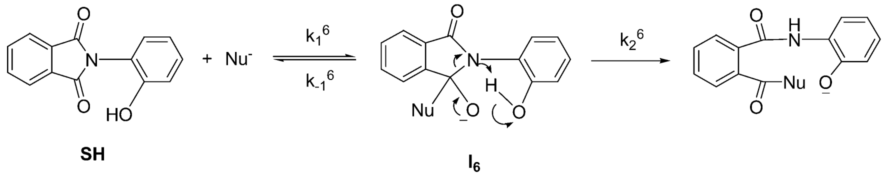
SCHEME 4



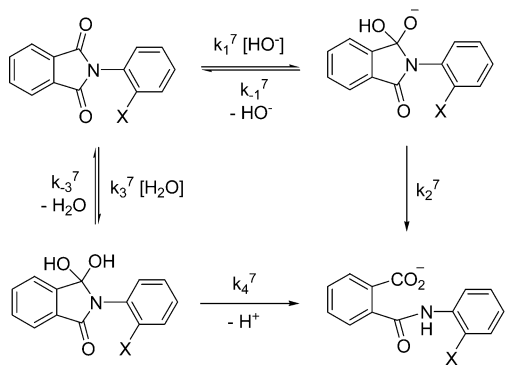
SCHEME 5



SCHEME 6



SCHEME 7



independent hydrolysis of **1** because both transition states constitute kinetically indistinguishable kinetic terms in the rate law. The notion of absolute certainty in almost any scientific domain, including the reaction mechanism, is difficult to show with a high degree of confidence. Indirect evidence (both experimental and theoretical) could be provided to give preference to one among alternative transition states or reaction mechanisms. Such an attempt is described below:

(a) An apparent look at TS_2 and TS_3 reveals that solvent dKIE might be used to differentiate between the occurrence of TS_2 and TS_3. The observed value of $k_w^{H_2O}/k_d^{D_2O} = 2.04$ is consistent with the reaction mechanism involving transition state TS_3. However, if the reaction mechanism involving TS_2 in the critical rate-determining step is assumed to be operative, then k_{OH}/k_{OD} ($=k_w^H K_a^H K_w^D/k_d^D K_a^D K_w^H$, where K_a^H and K_a^D represent ionization constant of SH in H_2O and D_2O, respectively, $K_w^H = a_H a_{OH}$ and $K_w^D = a_D a_{OD}$) will give the measure of the solvent dKIE. Using the values of $K_w^H/K_w^D = 6.5$,[17] $K_a^H/K_a^D = 4.2$,[16] and $k_w^H/k_d^D = 2.04$, one gets $k_{OH}/k_{OD} = 1.32$. The values of k_{OH}/k_{OD} for alkaline hydrolysis of esters and amides vary from 0.7 to 1.0.[12,13] The calculated value of k_{OH}/k_{OD} (=1.32) for pH-independent hydrolysis of **1** is slightly higher than the upper range of k_{OH}/k_{OD} (=1.0), and consequently, it seems that solvent dKIE is not in the favor of TS_2. Perhaps it is noteworthy that such solvent dKIE could not differentiate between intramolecular general acid (IGA)-assisted nucleophilic reaction of HO⁻ with nonionized salicylate esters and IGB-assisted nucleophilic reaction of H_2O with ionized salicylate esters.[17,33] However, other indirect evidence reveals the occurrence of IGB-assisted hydrolysis of ionized salicylate esters.[17,33]

(b) The classical way of differentiating between TS_2 and TS_3 is to use nucleophiles devoid of hydrogen at the nucleophilic atom (such as $R_1R_2R_3N$).[17,33] Thus, to find out whether TS_2 or TS_3 is involved in the hydrolysis of **1**, the rates of cleavages of **1** and **2** have been studied in the presence of buffers of DABCO (pH range 8.43 ± 0.03 to 10.11 ± 0.01 for **1** and 8.84 ± 0.01 to 10.11 ± 0.01 for **2**). The values of k_{obs} for the cleavage of **1** remain almost independent of total DABCO buffer concentration within its range of 0.1−0.8 M at a constant pH ≤9.38. The attempt to fit k_{obs} to eq 1 resulted in k_b values that were slightly negative under such conditions. These results show that DABCO is nonreactive toward the cleavage of **1**. However, the values of k_{obs} for the cleavage of **2** at different total DABCO buffer concentration ranging from 0.2 to 0.8 M at a constant pH fit to eq 4. The value of k_b^{app} at constant pH 8.94 ± 0.03 is (4.01 ± 0.26) × 10^{-3} s^{-1}. The absence and presence of DABCO buffer catalysis in the aqueous cleavage of **1** and **2**, respectively, support the occurrence of IGB assistance (i.e., TS_3) in the reaction of H_2O with **1** under alkaline pH.

However, a skeptic might argue that the reactions of nonionized **1** (i.e., SH) with HO⁻ and DABCO involve, most likely, nucleophilic attack (i.e., the k_1^4 step) and expulsion of the leaving group (i.e., the k_2^4 step) as the rate-determining step in an addition−elimination mechanism, as shown in Scheme 4. Intramolecular general acid (IGA)-assisted rate enhancement is expected only when the k_1^4 step is the rate-determining step, while such rate enhancement disappears when the k_2^4 step becomes the rate-determining step. So the absence of IGA assistance in the reaction of DABCO with SH does not necessarily negate the presence of TS_2. However, this speculative perception is not entirely correct in view of the following consideration. It has been convincingly shown that the rate of expulsion of a leaving group from an intermediate like I_4 depends upon the pK_a of the conjugate acid of the leaving group and the electronic push provided by the other atoms attached to the carbon to which the leaving group is also attached.[29] It is apparent from the structural feature of I_4 that, although the magnitudes of k_{-1}^4 and k_2^4 should be significantly larger in the presence than in the absence of IGB assistance, the magnitudes of the ratio k_2^4/k_{-1}^4 should be same in the presence and absence of such IGB assistance because the electronic push provided by OH group in the cleavage of C−Nu and C−N bonds in I_4 is the same. Thus, the IGA assistance is reflected by the value of k_1^4 and not by the value of k_2^4/k_{-1}^4. Since experimentally determined rate constant $k_b = k_1^4$ if the k_1^4 step is the rate-determining step and $k_b = k_1^4k_2^4/k_{-1}^4$ if the k_2^4 step is the rate-determining step, the presence of IGA assistance should increase the k_b value compared to the absence of such assistance regardless of whether the k_1^4 or k_2^4 step is the rate-determining step. Almost zero value of k_b^{SH} (where k_b^{SH} represents the second-order rate constant for the reaction of DABCO with SH) and significant value of k_b^{app} (eq 4) for DABCO-catalyzed cleavage of respective SH and **2** rules out the possibility of occurrence of TS_2 (i.e., Scheme 4 with $Nu^- = HO^-$).

A brief reaction mechanism for IGB-assisted nucleophilic cleavage of S^- is shown in Scheme 5. It is evident from Scheme 5 that IGB-assisted rate enhancements are expected when either the k_1^5 step or k_2^5 step is the rate-determining step, and expected IGA-assisted rate enhancements in the k_{-1}^5 step and k_2^5 step do not change the value of k_2^5/k_{-1}^5 compared to k_2^5/k_{-1}^5 value in the absence of IGA assistance. However, if the expected IGA-assisted rate enhancements in the k_{-1}^5 step and k_2^5 step are such that the value of k_2^5/k_{-1}^5 becomes larger than the k_2^5/k_{-1}^5 value in the absence of IGA assistance, then the value of k_b ($=k_1^5k_2^5/k_{-1}^5$) would be larger than k_b^0 (where $k_b^0 = k_1^5k_2^5/k_{-1}^5$ when the value of k_2^5/k_{-1}^5 remains unchanged compared to the k_2^5/k_{-1}^5 value in the absence of IGA assistance). On the other hand, if the IGA assistance decreases the value of k_2^5/k_{-1}^5 compared to k_2^5/k_{-1}^5 in the absence of IGA assistance, then k_b would be smaller than k_b^0. Thus, the value of IGB-assisted rate enhancement depends not only on the IGB assistance in the k_1^5 step but also on expected IGA assistance in the k_{-1}^5 step and k_2^5 step under the conditions when the k_2^5 step is the rate-determining step.

An alternative reaction mechanism for IGA-assisted nucleophilic cleavage of SH is shown in Scheme 6, which predicts the absence of IGA-assisted rate enhancement if the k_1^6 step is the rate-determining step. However, under the reaction conditions where the k_2^6 step is the rate-determining step, IGA-assisted rate enhancement is expected to occur. The rate-determining steps in the reactions of SH with HO^- and DABCO are the k_1^6 step and k_2^6 step, respectively, and consequently, IGA-assisted rate enhancement should be absent and present in the reactions of SH with HO^- and DABCO, respectively. However, experimentally observed large rate enhancement in the pH-independent rate of hydrolysis of **1** and absence of DABCO buffer catalysis in the hydrolysis of **1** rule out the possibility of occurrence of reaction mechanism shown in Scheme 6.

(c) Pseudo-first-order rate constant (k_w^0) for pH-independent (at pH >1 and <2.5, where concentration of ionized **1** is almost zero) hydrolysis of **1** ($10^6\ k_w^0 = 1.25\ s^{-1}$) is ∼40−50-fold smaller than the corresponding rate constant for **2** ($10^6\ k_w^0 = 62.0\ s^{-1}$) (Figure 1). Under such condition, the occurrence of IGB-assisted reaction of H_2O with S^- involving TS_3 is impossible because $[S^-] \approx 0$. Nearly 40−50-fold larger value of k_w^0 for **2** than that for **1** rules out the presence of IGA assistance involving a transition state similar to TS_2 with replacement of nucleophile from HO^- to H_2O. As explained earlier, IGA assistance should be detectable under the condition where either nucleophilic attack or expulsion of the leaving group is the rate-determining step. Thus, these observations support the absence of IGA assistance under both acidic and alkaline pH.

The occurrence of IGB assistance makes the kinetic term $k_{OH}[HO^-][SH]$ insignificant compared to the kinetically indistinguishable kinetic term $k_{2w}'[H_2O][S^-]$ in eq 6 and consequently $\alpha = k_w'K_a^{SH} = k_w'\ \Phi$. The calculated values of α ($=4.78 \times 10^{-10}$ M s^{-1}) and Φ ($=4.79 \times 10^{-9}$ M) from eq 2 give $k_w' = 0.10\ s^{-1}$. The value of $k_w' = 0.10\ s^{-1}$ is 8×10^4-fold larger than k_w^0 ($=1.25 \times 10^{-6}\ s^{-1}$), where k_w^0 represents the pseudo-first-order rate constant for pH-independent hydrolysis of nonionized **1** (SH). Perhaps the more accurate rate enhancement due to IGB-assisted hydrolysis of ionized **1** (S^-) should be equal to k_w'(for **1**)/k_w'(for **6**), where **6** represents ionized *N*-(*p*-hydroxyphenyl)phthalimide. The values of σ_{p-OH}, σ_{p-O^-}, and $\sigma^+_{p-O^-}$ are −0.37, −0.81 (not very reliable),[34] and −2.6,[35] respectively. The value of pK_a of the 2-hydroxyanilinium ion is larger than the pK_a of the anilinium ion by only 0.03 pK units,[36] which shows that $\sigma_{o-OH} \approx 0$. These Hammett substituent constant values predict that k_w'(for **6**) < k_w^0(for SH) provided $\rho > 0$, and consequently, the rate enhancement due to IGB-assisted hydrolysis of S^- should be larger by $>8 \times 10^4$-fold. The value of the Taft reaction constant for alkaline hydrolysis of N-substituted phthalimides is 1.0.[37]

A brief and plausible mechanism for alkaline hydrolysis of **2** is shown in Scheme 7 with X = OMe, where the k_1^7 step and k_3^7 step are presumably rate-determining steps. Hydroxide ion-assisted hydrolysis of S^- is also expected to involve reaction steps shown by the k_1^7 and k_2^7 steps in Scheme 7 with $X = O^-$. First- and second-order rate constants, k_w and k_{OH}, calculated from eq 3, may be expressed as $k_{OH} = k_1^7$ and $k_w^0 = k_3^7[H_2O]$.

The value of k_{OH} for **2** is nearly 2-fold smaller than k_{OH} for the cleavage of *N*-(*p*-methoxyphenyl)phthalimide (*p*-PT).[38] If polar (σ_I) and resonance (σ_R) components of σ_{o-OMe} and σ_{p-OMe} are the only factors responsible for the k_{OH} values, then the k_{OH} value for *p*-PT should have been lower than that for **2** because substituent OMe acts as an electron donor by resonance interaction, and this electron donor ability of OMe from the *para* position is stronger than from the *ortho* position. The change in coplanarity between the *o*-OMe substituent and the benzene ring due to significant steric hindrance of *o*-OMe with imide functionality reduces the electron-donating ability by resonance of *o*-OMe compared to *p*-OMe. However, the values of k_{OH} seem to be almost insensitive to polar and resonance effects of substituents attached to the leaving aryl group for the reason that k_{OH} values are almost the same for hydrolysis of *p*-PT and *N*-(phenyl)phthalimides.[39] This is plausible in view

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[34] Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

[35] Um, I.-K.; Lee, J.-Y.; Fujio, M.; Tsuno, Y. *Org. Biomol. Chem.* **2006**, *4*, 2979. We thank one of the reviewers for providing $\sigma^+_{p-O^-}$ value and reference.

[36] Sim, Y.-L.; Ahmad, W. H. W.; Ariffin, A.; Khan, M. N. Submitted for publication.

[37] Khan, M. N. *Int. J. Chem. Kinet.* **1987**, *19*, 143.

[38] Sim, Y.-L.; Ariffin, A.; Khan, M. N. *Int. J. Chem. Kinet.* **2004**, *36*, 316.

[39] Ariffin, A.; Leng, S. Y.; Lan, L. C.; Khan, M. N. *Int. J. Chem. Kinet.* **2005**, *37*, 147.

of the reaction mechanism shown in Scheme 7, which predicts a significant sensitivity of k_{OH} values to substituents of leaving aryl groups only when the k_2^7 step is the rate-determining step. However, the rate-determining step is the k_1^7 step. However, nearly 2-fold smaller value of k_{OH} for **2** than for *p*-PT does reveal a significant amount of steric hindrance affecting the nucleophilic attack by nucleophile at the carbonyl carbon in the k_1^7 step (Scheme 7). Nearly 9-fold smaller value of k_{OH} for S^- than k_{OH} for **2** may be attributed to electrostatic repulsive interaction between the anionic nucleophile (HO^-) and the *o*-O^- group of S^- in the k_1^7 step.

Conclusions

Pseudo-first-order rate constants for hydrolysis of **1** and **2** under varying pH reveal the occurrence of IGB assistance in the hydrolytic cleavage of **1** where the *o*-O^- group of ionized **1** (S^-) acts as IGB. The occurrence of kinetically indistinguishable IGA assistance due to the *o*-OH group of nonionized **1** (SH) in the reaction of HO^- with SH has been ruled out based upon indirect experimental evidence. The estimated rate acceleration due to the IGB-assisted reaction of H_2O with S^- is $> 8 \times 10^4$-fold.

Experimental Section

Stock solutions of *N*-(*o*-hydroxyphenyl)phthalimide (**1**) (0.03 M) and *N*-(*o*-methoxyphenyl)phthalimide (**2**) (0.01 M) were prepared in acetonitrile. The buffer solutions of desired pH were freshly prepared just before the start of the kinetic runs. The values of pH for all kinetic runs at pH >3 were measured at the end of the kinetic runs using a digital pH meter at 35 °C. The pH meter was calibrated just before the pH measurements with standard pH buffers of pH 4.02 and 6.98 for pH <7.00 and of pH 6.98 and 9.16 for pH >7.00. The pH meter was not used to determine the pH of the reaction mixtures at [HCl] ranging from 5.0×10^{-3} to 1.0 M. The pH values of these reaction mixtures were calculated from the relationship $\mathrm{pH} = -\log(\gamma[\mathrm{H}^+])$, where activity coefficient $\gamma = 0.70$ at 1.0 M ionic strength.

Kinetic Measurements. The rates of hydrolysis of **1** in the presence of different [HCl], [NaOH], and buffers of different pH were studied spectrophotometrically at 1.0 M ionic strength (NaCl) and 35 °C by monitoring the disappearance of **1** at 300 nm as a function of reaction time (t). Similarly, the rates of hydrolysis of **2** were studied at 290 nm by measuring the appearance of the hydrolysis product of **2** and disappearance of **2** periodically at pH ≥ 7.16 and pH ≤ 2.46, respectively. Pseudo-first-order rate constants (k_{obs}) for hydrolysis of **1** and **2** were calculated from eqs 9 and 10 for the reaction rate monitored by measuring respective disappearance of reactant and appearance of products as a function of t.[10b]

$$A_{obs} = \delta_{app}[X]_0 \exp(-k_{obs}t) + A_\infty \tag{9}$$

$$A_{obs} = \delta_{app}[X]_0[1 - \exp(-k_{obs}t)] + A_0 \tag{10}$$

In eqs 9 and 10, A_{obs} represents absorbance of the reaction mixture at a fixed wavelength (λ); δ_{app} is an apparent molar extinction coefficient of reaction mixture at λ; $[X]_0$ is the initial concentration of reactant, **1** or **2**, $A_\infty = A_{obs}$ at $t = \infty$ and $A_0 = A_{obs}$ at $t = 0$. The observed data (A_{obs} versus t), obtained for all kinetic runs, were found to fit to eq 9 or eq 10 up to 3.5 (slowest reaction(s)) − 100 (fastest reaction(s)) half-lifes of the reactions. In the observed data treatment with eqs 9 and 10, k_{obs}, δ_{app}, and A_∞ or A_0 were considered as three unknown parameters. A UV−visible spectrophotometer equipped with thermostated multicell compartment was used throughout the studies. The initial concentrations of **1** and **2**, in each kinetic run, were kept constant at 3.0×10^{-4} and 2.0×10^{-4} M, respectively. The details of the kinetic procedure and data analysis are described elsewhere.[10]

TABLE 3. Values of Molar Extinction Coefficients of 1, 2, 3, 4, 7, 8, and 9 and Reaction Product Mixtures at $t = \infty$ for Hydrolysis of 1 and 2[a]

		$\lambda = 300$ nm					$\lambda = 290$ nm			
pH	δ^1	δ^3	δ^7	δ^8	δ_∞^{P1}	δ^2	δ^4	δ^8	δ^9	δ_∞^{P2}
<2.5	2680 [2400]	1930 [3730]	40 [30]	30 [470]		2160	4550	470	175	
>11.0	7530 [6870]	5560 [3740]	3410 [3330]	~10 [75]		3100	5530	75	2190	
0.16					70					560
0.25					90					640
0.46					150					670
7.16										5570
7.79										5580
10.25										5610
10.74					5370					
11.41										5450
11.66					5650					
12.31					5450					

[a] $[\mathbf{1}]_0 = 3 \times 10^{-4}$ M; $[\mathbf{2}]_0 = 2 \times 10^{-4}$ M; values in square brackets are at 290 nm; the unit of molar extinction coefficient is $M^{-1}\ cm^{-1}$; δ_∞^{P1} and δ_∞^{P2} are apparent molar extinction coefficients of reaction product mixtures at $t = \infty$ for hydrolysis of **1** and **2**, respectively.

Product Identification. In order to identify the products of acidic and alkaline hydrolysis of **1** and **2**, the molar extinction coefficients of expected hydrolysis products, *N*-(*o*-hydroxyphenyl)phthalamic acid (**3**), *N*-(*o*-methoxyphenyl)phthalamic acid (**4**), *o*-hydroxyaniline (**7**), phthalic acid (**8**), and *o*-methoxyaniline (**9**) have been determined under the reaction conditions of kinetic runs using authentic samples of these compounds. These results are summarized in Table 3. The values of δ_∞^P ($=A_\infty/[X]_0$) for a few typical kinetic runs are also listed in Table 3, which reveal **3** and **4** as the hydrolysis products of **1** at pH ≥ 6.1 and **2** at pH ≥ 7.2, respectively. However, at pH ≤ 2.46, the hydrolysis products are **7** + **8** for **1** and **8** + **9** for **2**. These observations are conceivable for the reason that the rate of hydrolysis of **3** is >100-fold larger than that of its formation from **1** within [HCl] range of 5.0×10^{-3} to 1.0 M.[27] Similarly, the pseudo-first-order rate constant (k_{obs}) for the hydrolytic cleavage of **4** at 35 °C, 0.05 M HCl, is $130 \times 10^{-5}\ s^{-1}$,[27] which is ~19-fold larger than k_{obs} obtained within [HCl] range of 5.0×10^{-3} to 1.0 M for the formation of **4** from **2**.

The values of δ_∞^{P2} at pH >11 and <1 for the hydrolysis of **2** reveal the absence of possible hydrolysis of the methoxy group, that is, hydrolytic conversion of **2** to **1** and **4** to **3**, at these extreme pH values. However, the possibility of hydrolysis of the methoxy group of **2** to produce **1** under very low and very high pH may be ruled out for the following reasons. (i) The values of δ_∞^{P2} are significantly different from the values of δ^1 or δ^3 at these extreme pH values (Table 3). (ii) If the rate of formation of **1** from **2** is much faster than the rate of hydrolysis of **1** under such conditions, then the log k_{obs} − pH profiles for hydrolysis of **1** and **2** should have been the same. Contrary to this, such log k_{obs} − pH profiles for **1** and **2**, as shown in Figure 1, are very different from each other. (iii) If the rate of hydrolysis of **1** is much faster than the rate of its formation from hydrolytic cleavage of the *o*-methoxy group of **2**, then the values of δ_∞^{P2} should have been similar to the sum of δ^7 and δ^8. However, such similarity does not exist at pH >11 (Table 3). Although the values of δ_∞^{P2} at pH <2.5 are not significantly different from $\delta^7 + \delta^8$, the values of k_{obs} for hydrolysis of **2** are significantly larger than those for hydrolysis of **1** under such conditions (Figure 1).

Spectrophotometric Determination of pK_a^{SH} of 1 at 30 °C. Significant initial absorbance, A^0_{obs} (i.e., observed absorbance at reaction time $t = 0$), change (~1.39 absorbance units) has been observed at 300 nm, 3.0×10^{-4} M **1** and within the pH range of

6.08−10.11 at 1.0 M ionic strength. These values of A^0_{obs} were used to calculate K_a^{SH}, δ_{SH}, and δ_{S^-} from eq 11

$$A^0_{obs} = [X]_0 \frac{\delta_{SH}[H^+] + \delta_{S^-}K_a^{SH}}{[H^+] + K_a^{SH}} \qquad (11)$$

where K_a^{SH} is the ionization constant of **1**, δ_{SH} and δ_{S^-} represent molar extinction coefficients of nonionized and ionized **1**, at 300 nm, respectively, and $[X]_0$ is the initial concentration of **1** and $[H^+] = 10^{-pH}/\gamma$ with activity coefficient $\gamma = 0.7$ at 1.0 M ionic strength.[11] The nonlinear least-squares calculated respective values of K_a^{SH}, δ_{SH}, and δ_{S^-} are $(3.91 \pm 0.29) \times 10^{-9}$ M, $(2.80 \pm 0.07) \times 10^3$ M^{-1} cm^{-1}, and $(7.53 \pm 0.07) \times 10^3$ M^{-1} cm^{-1}. A satisfactory fit of observed data to eq 11 is evident from the standard deviations associated with the calculated parameters, K_a^{SH}, δ_{SH}, and δ_{S^-} and from the percent residual errors $[=100(A^0_{obs} - A^0_{calcd})/A^0_{obs}]$ of ≤4%. The calculated values of δ_{SH} and δ_{S^-} may be compared with the corresponding values obtained experimentally at 300 nm and 0.05 M HCl ($\delta_{SH} = 2.56 \times 10^3$ M^{-1} cm^{-1}) as well as 0.005 M NaOH ($\delta_{S^-} = 7.46 \times 10^3$ M^{-1} cm^{-1}).

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Supporting Information Available: Experimental section for general procedures of synthesis of *N*-(*o*-hydroxyphenyl)phthalimide (**1**) and *N*-(*o*-methoxyphenyl)phthalimide (**2**), Figures I and II as well as Tables A, B, C, and D. This material is available free of charge via the Internet at http://pubs.acs.org.

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