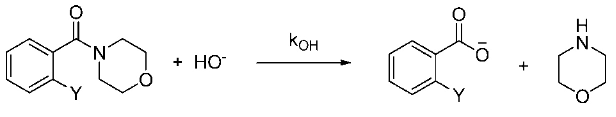
Kinetics and Mechanism of Large Rate Enhancement in the Alkaline Hydrolysis of *N′*-Morpholino-*N*-(2′-methoxyphenyl)phthalamide

Yoke-Leng Sim, Azhar Ariffin, and M. Niyaz Khan*

Department of Chemistry, Faculty of Science, University of Malaya, 50603 Kuala Lumpur, Malaysia

niyaz@um.edu.my

Received December 18, 2007



1, Y = 2-MeOC$_6$H$_4$NHOC, k_{OH} = 5.89 x 10^{-2} M^{-1} s^{-1} at 35°C
2, Y = H, k_{OH} = 6.38 x 10^{-5} M^{-1} s^{-1} at 35°C

The apparent second-order rate constant (k_{OH}) for hydroxide-ion-catalyzed conversion of **1** to *N*-(2′-methoxyphenyl)phthalamate (**4**) is ~10^3-fold larger than k_{OH} for alkaline hydrolysis of *N*-morpholinobenzamide (**2**). These results are explained in terms of the reaction scheme $\mathbf{1}\xrightarrow{k_{1obs}}\mathbf{3}\xrightarrow{k_{2obs}}\mathbf{4}$ where **3** represents *N*-(2′-methoxyphenyl)phthalimide and the values of k_{2obs}/k_{1obs} vary from 6.0 × 10^2 to 17 × 10^2 within [NaOH] range of 5.0 × 10^{-3} to 2.0 M. Pseudo-first-order rate constants (k_{obs}) for alkaline hydrolysis of **1** decrease from 21.7 × 10^{-3} to 15.6 × 10^{-3} s^{-1} with an increase in ionic strength (by NaCl) from 0.5 to 2.5 M at 0.5 M NaOH and 35 °C. The values of k_{obs}, obtained for alkaline hydrolysis of **2** within [NaOH] range 1.0 × 10^{-2} to 2.0 M at 35 °C, follow the relationship $k_{obs} = k_{OH}[\mathrm{HO}^-] + k_{OH}'[\mathrm{HO}^-]^2$ with least-squares calculated values of k_{OH} and k_{OH}' as (6.38 ± 0.15) × 10^{-5} and (4.59 ± 0.09) × 10^{-5} M^{-2} s^{-1}, respectively. A few kinetic runs for aqueous cleavage of **1**, *N′*-morpholino-*N*-(2′-methoxyphenyl)-5-nitrophthalamide (**5**) and *N′*-morpholino-*N*-(2′-methoxyphenyl)-4-nitrophthalamide (**6**) at 35 °C and 0.05 M NaOH as well as 0.05 M NaOD reveal the solvent deuterium kinetic isotope effect ($= k_{obs}^{\mathrm{H_2O}}/k_{obs}^{\mathrm{D_2O}}$) as 1.6 for **1**, 1.9 for **5**, and 1.8 for **6**. Product characterization study on the cleavage of **5**, **6**, and *N*-(2′-methoxyphenyl)-4-nitrophthalimide (**7**) at 0.5 M NaOD in D$_2$O solvent shows the imide-intermediate mechanism as the exclusive mechanism.

Introduction

The study of the mechanistic aspects of the aqueous cleavage of an amide bond under a variety of reaction conditions could be considered of significant importance because the hydrolytic degradation of protein involves apparently the hydrolysis of an essentially *N*-alkylamide bond.[1] The respective values of second-order rate constants for hydroxide ion (k_{OH}) and hydronium ion catalyzed (k_H) hydrolysis of an *N*-alkylamide bond are in the order of 10^{-6} and 10^{-7} M^{-1} s^{-1} at 35 °C.[2,3] There seems to be only one report[4] that describes a careful determination of the pseudo first-order rate constant (k_w) for the uncatalyzed reaction of water with formamide and the value of k_w is 8.4 × 10^{-8} s^{-1} at 80 °C. The intrinsic reactivity toward oxygen nucleophiles of formamide is found to be larger by more than 10^4-fold compared to that of benzamide, *N*-alkyl-substituted benzamides,[2–4] and benzanilide.[5] Thus, the values of k_w for benzamide, benzanilide, and proteins should be significantly smaller than 10^{-9} s^{-1} at 35 °C (i.e., half-life of >22 years).

The apparent specific base catalysis (i.e., k_{OH} value) is increased by ~10^6-fold in the alkaline hydrolysis of phthalamide (k_{OH} = 4.9 M^{-1} s^{-1})[6] and *N*,*N′*-dimethylphthalamide (k_{OH} = 7.6 M^{-1} s^{-1})[6] compared to that of benzamide and *N*-methylbenzamide due to occurrence of different catalytic reaction mechanisms in the alkaline hydrolysis of phthalamide and benzamide. Since the appearance of the classical paper of Shafer

---

(1) Fersht, A. R. *Enzyme Structure and Mechanism*; W. H. Freeman: San Francisco, 1977.

(2) Bunton, C. A.; Noyak, B.; O'Connor, C. J. *J. Org. Chem.* **1968**, *33*, 572.

(3) Bunton, C. A.; Farbers, S. J.; Milbank, A. J. G.; O'Connor, C. J.; Turkey, T. A. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1869.

(4) Hine, J.; King, R. S.-M.; Midden, R.; Sinha, A. *J. Org. Chem.* **1981**, *46*, 3186.

(5) Broxton, T. J.; Duddy, N. W. *Aust. J. Chem.* **1979**, *32*, 1717.

10.1021/jo702695k CCC: $40.75

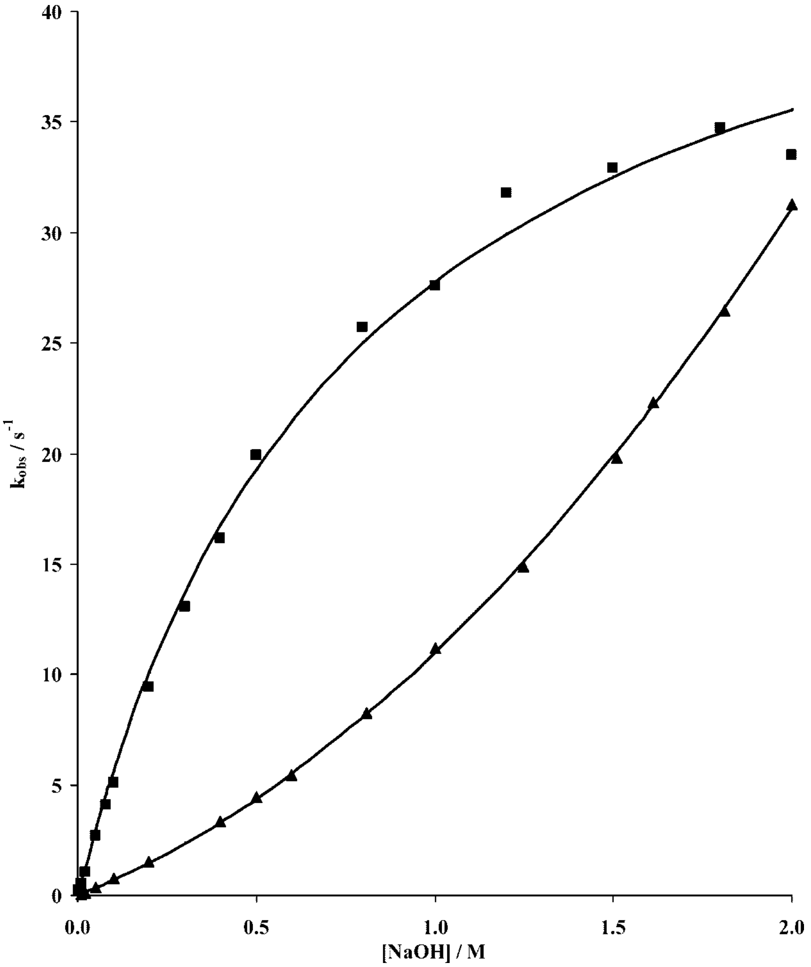


FIGURE 1. Plots showing the dependence of pseudo-first-order rate constants, k_{obs}, versus [NaOH] for alkaline hydrolysis of **1** (■, with 10^3 k_{obs} and 5.0×10^{-4} M **1**) and **2** (▲, with 10^5 k_{obs} and 6.0×10^{-4} M **2**) at 35 °C. The solid lines are drawn through the least-squares calculated data points using eq 1 (for ■) and eq 2 (for ▲), respectively.

and Morawetz,[6] the reaction mechanisms of intramolecular carboxamido group assisted alkaline hydrolysis of another amide group and related reactions have been extensively studied.[7] Although many facets of these reactions are well understood, no attempt seems to have been made to understand the effects of steric crowding of the intramolecular nucleophilic site on the intramolecular rate assistance in these reactions. The values of k_{OH} for the cleavage of amide and ester bonds of 2-$H_2NCOC_6H_4CO_2Me$, 2-$H_2NCH_2C_6H_4CO_2Me$, 2-$H_2NCH_2C_6H_4CONH_2$, and 2-$HOCH_2C_6H_4CONH_2$ are 3.1×10^3 (25.9 °C),[6] 7×10^3 (30 °C),[8] 0.16 (30 °C),[9] and 0.15 M^{-1} s^{-1} (30 °C),[10] respectively. These results show that the values of k_{OH} are weakly and highly dependent on pK_a values of the conjugate acids of intramolecular nucleophile and leaving groups, respectively. The present study was initiated (i) to find out whether the alkaline aqueous cleavage of amide bond of **1** involves the intramolecular carboxamido group assistance and (ii) to discover the effect of molecular crowding at the nucleophilic site on the rate of intramolecular carboxamide-assisted cleavage of amide bond. The results and their probable mechanistic explanations are described.

Results and Discussion

Effects of [NaOH] on Pseudo-First-Order Rate Constants (k_{obs}) for the Amide Bond Cleavage of 1. A series of kinetic runs was carried out for the alkaline aqueous cleavage of **1** within [NaOH] range 5.0×10^{-3} to 2.0 M at 35 °C where the ionic strength was kept constant at 1.0 and 2.0 M (by NaCl) for kinetic runs within [NaOH] range 5.0×10^{-3} to 1.0 M and 1.2−2.0 M, respectively. The observed data (k_{obs} versus [NaOH]) are shown graphically by Figure 1. The values of k_{obs} were found to fit reasonably well to the following empirical equation:

$$k_{obs} = \frac{\alpha[HO^-]}{1 + \beta[HO^-]} \tag{1}$$

where α and β represent empirical constants. Nonlinear least-squares calculated values of α and β are $(6.32 \pm 0.30) \times 10^{-2}$ M^{-1} s^{-1} and 1.28 ± 0.10 M^{-1}, respectively. Although the change in ionic strength from 1.0 to 2.0 M seems to have kinetically insignificant effect on k_{obs}, the values of k_{obs} obtained at 1.0 M ionic strength only were also treated with eq 1. The

---

(6) Shafer, J. A.; Morawetz, H. *J. Org. Chem.* **1963**, *28*, 1899.

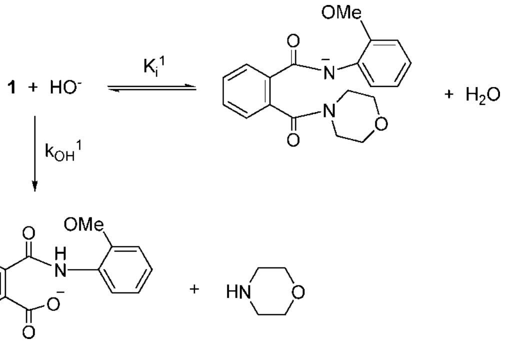
(7) (a) Chiong, N. G.; Lewis, S. D.; Shafer, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 418. (b) Belke, C. J.; Su, S. C. K.; Shafer, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 4552. (c) Fife, T. H.; Duddy, N. W. *J. Am. Chem. Soc.* **1983**, *105*, 74. (d) Fife, T. H.; Chauffe, L. *J. Org. Chem.* **2000**, *65*, 3579. (e) Fife, T. H.; Singh, R.; Bembi, R. *J. Org. Chem.* **2002**, *67*, 3179.

(8) Fife, T. H.; DeMark, B. R. *J. Am. Chem. Soc.* **1976**, *98*, 6978.

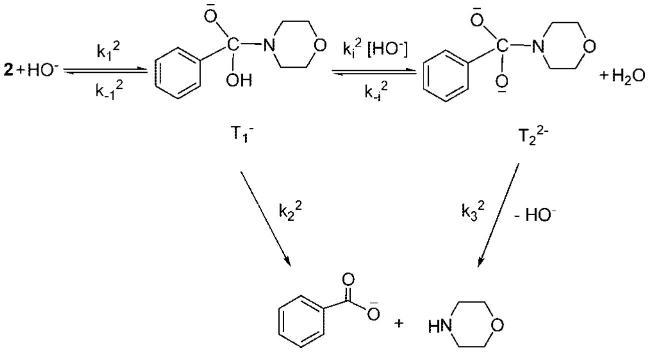
(9) Fife, T. H.; DeMark, B. R. *J. Am. Chem. Soc.* **1977**, *99*, 3075.

(10) Okuyama, T.; Schmir, G. L. *J. Am. Chem. Soc.* **1972**, *94*, 8805.

SCHEME 1



SCHEME 2

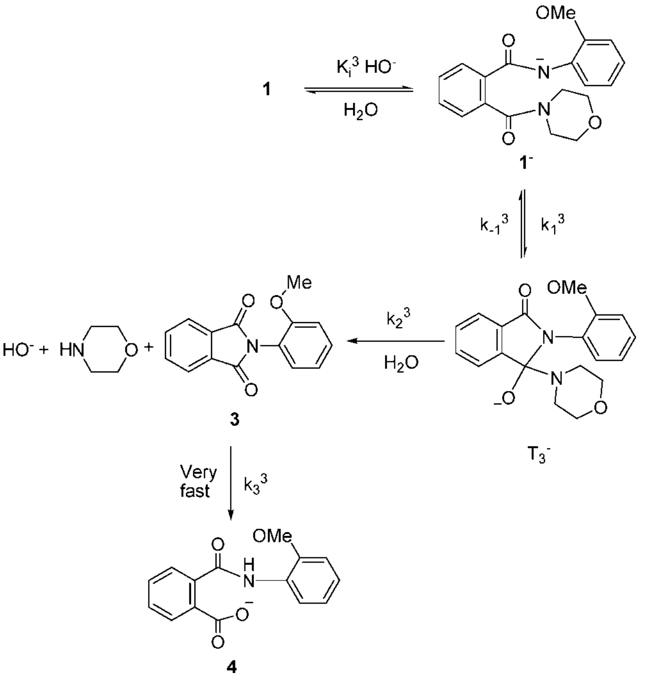


nonlinear least-squares calculated values of α and β are (5.89 ± 0.18) × 10^{-2} M^{-1} s^{-1} and 1.10 ± 0.08 M^{-1}, respectively. These results show that the values of α and β decreased by 7% and 14%, respectively, with the change in ionic strength from 2.0 to 1.0 M.

To discover the effects of ionic strength, μ, a few kinetic runs were carried out at 0.5 M NaOH, 35 °C and within [NaCl] range 0.0–2.0 M. The values of k_{obs} revealed an almost linear decrease with an intercept and slope of (23.5 ± 0.2) × 10^{-3} s^{-1} and −(3.12 ± 0.13) × 10^{-3} M^{-1} s^{-1}, respectively. These results show that the increase in μ from 1.0 to 2.0 M decreased k_{obs} by ~16%.

Effects of [NaOH] on k_{obs} for Alkaline Hydrolysis of *N*-Morpholinobenzamide (2). On the basis of product characterization and the fact that the observed data (A_{obs} versus time, *t*) of alkaline hydrolysis of **1** followed a strictly simple first-order rate law, one might argue in the favor of the occurrence of a reaction mechanism as shown in Scheme 1. However, the calculated value of k_{OH} (≡ α = 5.89 × 10^{-2} M^{-1} s^{-1} at 35 °C) for **1** is significantly larger than k_{OH} for alkaline hydrolysis of *N*-methylbenzanilide[5] (k_{OH} = 1.10 × 10^{-4} M^{-1} s^{-1} at 65.5 °C) and the values of k_{OH} for benzamide, *N*-methylbenzamide, and *N*,*N*-dimethylbenzamide at 100.4 °C are 15.7 × 10^{-4}, 7.20 × 10^{-4}, and 15.2 × 10^{-4} M^{-1} s^{-1}, respectively.[2] The values of k_{OH} for hydrolysis of $C_6H_5CO_2Me$,[12] 2-$MeO_2CC_6H_4CO_2Me$,[11] 2-$Me_2NCONHC_6H_4CO_2Me$,[12] 2-$MeOC_6H_4CO_2Me$,[13] $C_6H_5CONH_2$,[2,14] and 2-$MeOC_6H_4CONH_2$[14] are 0.125 (30 °C),[12] 0.130 (25 °C)[11], 0.263 (30 °C),[12] 0.062 (35 °C),[13] 1.58 × 10^{-3} (100.4 °C),[2] ~1.10 × 10^{-3} (100 °C),[14] and 1.10 × 10^{-3} M^{-1} s^{-1} (100 °C),[14] respectively. In view of these results, the >10^3-fold larger value of k_{OH} for **1** compared with that for *N*-methylbenzanilide rules out the occurrence of reaction mechanism shown in Scheme 1 because the pK_a of morpholine may not be expected to be significantly lower than that of *N*-methylaniline.

SCHEME 3



Furthermore, these reported values of k_{OH} for the cleavage of amide and ester bonds predict that the value of k_{OH} for the alkaline hydrolysis of **2** should be comparable with k_{OH} for **1** if hydrolysis of both **1** and **2** involves a reaction mechanism similar to that in Scheme 1 with $K_i^1 = 0$ for **2**. To test this prediction practically, a few kinetic runs were carried out for alkaline hydrolysis of **2** within [NaOH] range 1.0 × 10^{-2} to 2.0 M at 35 °C, 2.0 M ionic strength (by NaCl), and 6.0 × 10^{-4} M **2**. The observed pseudo-first-order rate constants (k_{obs}) are shown graphically in Figure 1. These values of k_{obs} were fitted to eq 2:

$$k_{obs} = k_w + k_{OH}[HO^-] + k_{OH}'[HO^-]^2 \qquad (2)$$

where k_w, k_{OH}, and k_{OH}' represent uncatalyzed first-order, hydroxide ion catalyzed second-order, and third-order rate constants, respectively. The least-squares calculated respective values of k_w, k_{OH}, and k_{OH}' are (5.15 ± 7.48) × 10^{-7} s^{-1}, (6.27 ± 0.22) × 10^{-5} M^{-1} s^{-1}, and (4.64 ± 0.11) × 10^{-5} M^{-2} s^{-1}. The value of k_w with a standard deviation of more than 100% is considered to be unreliable. The respective contributions of the k_w term and the $k_{OH}'[HO^-]^2$ term are ≤14% at ≥0.05 M NaOH and ≤3% at ≤0.05 M NaOH. Thus, a relatively more reliable value of k_w may be expected to result if the data treatment with eq 2 involves k_{obs} values at ≤0.05 M NaOH. The least-squares fit of k_{obs} values (at ≤0.05 M NaOH) to eq 2 with $k_{OH}' = 0$ gave k_w and k_{OH} as (−3.2 ± 0.6) × 10^{-7} s^{-1} and (7.93 ± 0.18) × 10^{-5} M^{-1} s^{-1}, respectively. The negative value of k_w shows that the k_w value is not different from zero under the experimental condition of the study.

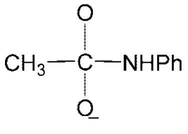
The k_{obs} values were also treated with eq 2 where k_w was set to zero, and the least-squares calculated values of k_{OH} and k_{OH}' turned out to be (6.38 ± 0.15) × 10^{-5} M^{-1} s^{-1} and (4.59 ± 0.09) × 10^{-5} M^{-2} s^{-1}, respectively. These calculated values of k_{OH} and k_{OH}' are changed by only ≤1.8% compared to those obtained from eq 2 with k_w = 5.15 × 10^{-7} s^{-1}. The extent of

---

(11) Khan, M. N. *Indian J. Chem.* **1986**, *25A*, 831.
(12) Hegarty, A. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1970**, *92*, 6575.
(13) Khan, M. N.; Olagbemiro, T. O. *J. Org. Chem.* **1982**, *47*, 3695.
(14) Bruice, T. C.; Tanner, D. W. *J. Org. Chem.* **1965**, *30*, 1668.

reliability of the observed data fit to eq 2 is evident from the standard deviations (2%) associated with the calculated values of k_{OH} and k_{OH}' and from the plot of Figure 1 where a solid line is drawn through the least-squares calculated data points. The value of k_{OH} (6.38×10^{-5} M^{-1} s^{-1}) for **2** is only ~1.7-fold smaller than k_{OH} value (11.0×10^{-5} M^{-1} s^{-1} at 65.5 °C) for *N*-methylbenzanilide.[5] However, the value of k_{OH} for **2** is ~10^3-fold smaller than k_{OH} ($\equiv \alpha = 5.89 \times 10^{-2}$ M^{-1} s^{-1} at 35 °C) for **1**. Thus, it is almost certain that different reaction mechanisms are involved in the alkaline hydrolysis of **1** and **2**.

Mechanistic Discussion of Alkaline Hydrolysis of 2. The kinetic term similar to $k_{OH}'[HO^-]^2$ of eq 2 was the basis for Biechler and Taft to propose for the first time in 1957 the presence of a highly reactive oxy dianionic tetrahedral intermediate, *T*, on the reaction path in the hydrolysis of acetanilide under highly alkaline medium.[15] The kinetic equation similar to eq 2 with $k_w = 0$ has been used in the kinetic studies on alkaline hydrolysis of β-sulfam[16a] and several amides and imides.[16] In view of these studies, a plausible reaction mechanism for hydrolysis of **2**, under highly alkaline medium, may be shown in Scheme 2 where the k_2^2-step and the k_3^2-step are presumably rate-determining. The observed rate law: rate = $k_{obs}[\mathbf{2}]_T$ and Scheme 2 can lead to eq 3:



$$\mathrm{CH_3{-}\overset{O^-}{\underset{O^-}{C}}{-}NHPh}$$

T

$$k_{obs} = k_2^2 K_1^2[HO^-] + k_3^2 K_i^2 K_1^2 [HO^-]^2 \qquad (3)$$

where $K_1^2 = k_1^2/k_{-1}^2$ and $K_i^2 = k_i^2/k_{-i}^2$. Equation 3 is similar to eq 2 with $k_w = 0$, $k_{OH} = k_2^2K_1^2$, and $k_{OH}' = k_3^2K_i^2K_1^2$. The assumption that the k_2^2-step and the k_3^2-step are rate-determining would be correct only if $k_{-1}^2 > k_2^2$, $k_{-1}^2 > k_i^2[HO^-]$, and $k_{-i}^2 > k_3^2$. The pK_a of T_1^- may be estimated as 14.8 (see Appendix in the Supporting Information, SI) and hence the k_i^2-step and the k_{-i}^2-step involve proton transfer in the thermodynamically favorable and unfavorable direction, respectively. Under such situation, the values of k_i^2 and k_{-i}^2 should be ~10^{10} and ~10^9 M^{-1} s^{-1}, respectively.[17] Since k_{-1}^2 must be larger than k_i^2 $[HO^-]$ and k_2^2 because the k_1^2-step cannot be rate-determining and the maximum value of k_i^2 $[HO^-] = 2 \times 10^{10}$ s^{-1} (maximum $[HO^-]$ = 2.0 M), therefore k_{-1}^2 should be larger than 2×10^{10} s^{-1}. The presence of equilibrium between T_1^- and T_2^{2-} (Scheme 2) requires that k_i^2 $[HO^-] > k_2^2$. Thus, the expected inequality of $k_{-1}^2 > k_i^2$ $[HO^-] > k_2^2$ shows that the k_2^2-step is rate-determining.

Mechanistic Discussion of Alkaline Hydrolysis of 1. Phthalamide, *N*,*N*′-di-, and trisubstituted phthalamides are known to undergo efficient hydroxide ion catalyzed intramolecular cyclization to form respective phthalimide and N-substituted phthalimides in aqueous solution.[18] The nearly 10^3-fold larger rate of alkaline hydrolysis of **1** compared with that of **2** may be explained in terms of a plausible reaction mechanism as shown in Scheme 3. Perhaps it is noteworthy that the rate law: rate = $k_{OH}[\mathbf{1}][H_2O]$ (the corresponding reaction mechanism is shown in Scheme 3) is kinetically indistinguishable from the rate law: rate = $k_{OH}'[\mathbf{1}][HO^-]$ (the corresponding reaction mechanism is not shown). However, on the basis of arguments described elsewhere,[19] the preferred reaction mechanism of the present reacting system is shown in Scheme 3, where the k_2^3-step is considered rate-determining.

The value of the second-order rate constant (k_{OH}) for hydroxide ion catalyzed hydrolysis of **3** is 29.1 M^{-1} s^{-1} [20] under the present reaction conditions. Thus, the values of k_3^3 vary from 14.6×10^{-2} to 58.2 s^{-1} within [NaOH] range 5.0×10^{-3} to 2.0 M of the study. Thus, the values of k_3^3/k_{obs} vary from 6.0×10^2 to 17×10^2, and consequently **3** cannot be detected directly by any conventional method under the present reaction conditions. A skeptic might argue that nondetectability of **3** does not essentially prove or disprove the validity of the reaction mechanism of Scheme 3. Although it seems difficult to offer a satisfactory and convincing explanation to this skepticism, it is difficult also to ignore or reject the possibility of the formation of **3** on the reaction path for two reasons: (i) We could not find any other plausible reaction mechanism that could explain the formation of **4** with a rate larger than the rate of alkaline hydrolysis of **2** by a factor of ~10^3-fold. (ii) Several reports on closely related reactions revealed spectrophotometric evidence for the formation of phthalimide and its N-substituted derivatives.[18,19]

The observed rate law, rate = k_{obs} $[\mathbf{1}]_T$, and Scheme 3 can lead to eq 4:

$$k_{obs} = \frac{k_2^3 K_1^3 K'^3_i[HO^-]}{1 + K'^3_i[HO^-]} \qquad (4)$$

where $K'^3_i = K_i^3/[H_2O] = K_a^{\mathbf{1}}/K_w$ with $K_a^{\mathbf{1}} = [\mathbf{1}^-][H^+]/[\mathbf{1}]$, and $K_1^3 = k_1^3/k_{-1}^3$. Comparison of eq 4 with eq 1 gives $\alpha = k_2^3K_1^3K'^3_i$ and $\beta = K'^3_i = K_a^{\mathbf{1}}/K_w$. The significantly larger pK_a of the conjugate acid of the leaving group in the k_2^3-step compared with that in the k_{-1}^3-step and the release of the five-membered ring strain in the k_{-1}^3-step cause $k_{-1}^3 \gg k_2^3$ and this inequality validates the assumption that the k_2^3-step is rate-determining. The calculated value of β ($= K_a^{\mathbf{1}}/K_w = 1.10$ M^{-1}) gives p$K_a^{\mathbf{1}} = 13.6$ with p$K_w = 13.62$.[21] The value of p$K_a^{\mathbf{1}}$ may be compared with the reported pK_a of benzamide of 14−15[22] and σ_I for H and C_6H_5 as 0.0 and 0.12,[23] respectively. The pK_a of benzamide is also expected to be reduced by the replacement of *o*-H by *o*-$CON(CH_2CH_2)_2$.

The experimentally determined second-order rate constants, k_{OH}, ($\equiv \alpha = k_2^3K_1^3K'^3_i$) for hydroxide ion catalyzed cyclization reactions of methyl *o*-carbamoylbenzoate, methyl *o*-aminomethylbenzoate, phthalamide, *N*,*N*′-dimethylphthalamide, and *o*-aminomethylbenzamide are 3.1×10^3 (25.9 °C),[6] 7×10^3 (30 °C),[8] 4.9 (25.9 °C),[6] 7.6 (25.9 °C),[6] and 0.16 M^{-1} s^{-1} (30 °C),[9] respectively. It appears from these results that the pK_a of the neutral nucleophile has essentially no effect on the k_{OH} value, whereas the pK_a of the conjugate acid of the leaving group has

---

(15) Biechler, S. S.; Taft, R. W., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 4927.

(16) (a) Baxter, N. J.; Rigoreau, L. J. M.; Laws, A. P.; Page, M. I. *J. Am. Chem. Soc.* **2000**, *122*, 3375. (b) Khan, M. N. Micellar Catalysis. In *Surfactant Science Series*; CRC Press, Taylor & Francis Group, LLC: Boca Raton, FL, 2006; *Vol. 133*,Chapters 2 and 7 and references therein.

(17) Fife, T. H.; Bambery, R. J.; DeMark, B. R. *J. Am. Chem. Soc.* **1978**, *100*, 5500. and references therein.

(18) (a) Khan, M. N. *J. Chem. Soc., Perkin Trans. 2* **1990**, 435. (b) Khan, M. N. *Indian J. Chem.* **1991**, *30A*, 777. (c) Khan, M. N. *Indian J. Chem.* **1994**, *33B*, 646.

(19) Khan, M. N. *J. Chem. Soc., Perkin Trans. 2* **1988**, 213.

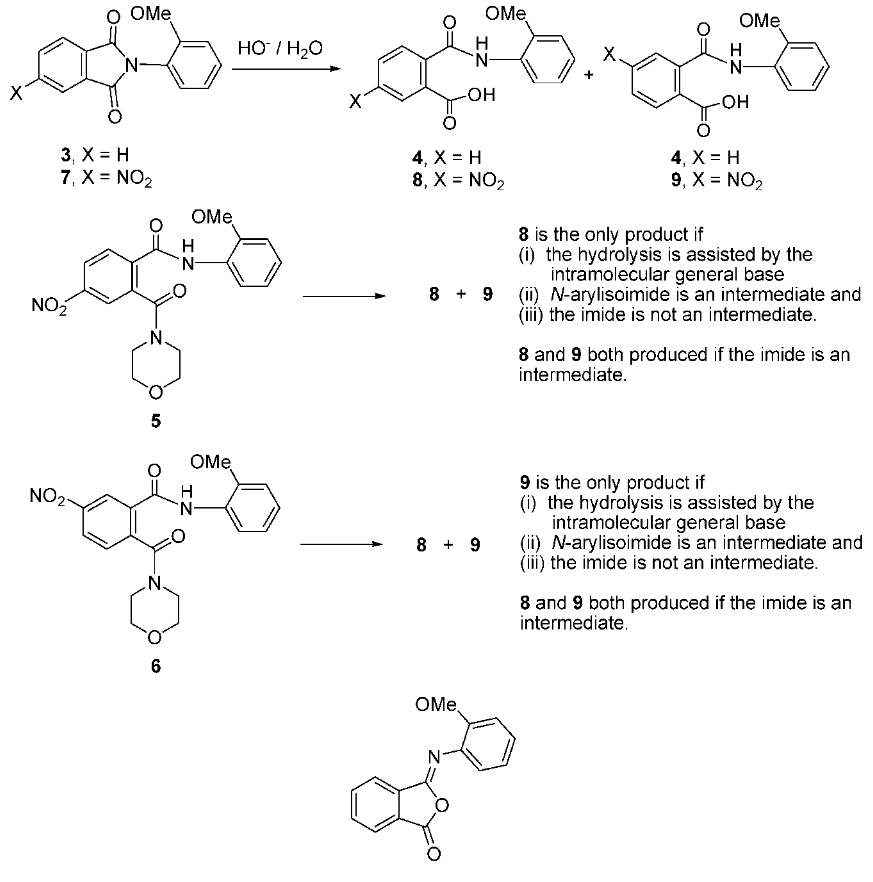
(20) Sim, Y.-L.; Ariffin, A.; Khan, M. N. *J. Org. Chem.* **2007**, *72*, 2392.

(21) Ritchie, C. D.; Wright, D. J.; Huang, D.-S.; Kamego, A. A. *J. Am. Chem. Soc.* **1975**, *97*, 1163.

(22) Barlin, G. B.; Perrin, D. D. *Quart. Rev. Chem. Soc.* **1966**, *20*, 75.

(23) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

SCHEME 4



a significant effect on k_{OH} values. These results are consistent with the reaction mechanism shown in Scheme 3. The value of k_{OH} (= 5.89×10^{-2} M^{-1} s^{-1}) for **1** at 35 °C is nearly 40- and 20-fold smaller than k_{OH} for phthalamide (at 25.9 °C)[6] and *N*-piperidinylphthalamide (at 35 °C),[24] respectively. These results may be explained in terms of larger steric crowding at the intramolecular nucleophilic site of **1** than that of phthalamide and *N*-piperidinylphthalamide.

Alkaline Aqueous Cleavage of Amide Bond of 5 and 6 at 35 °C. Evidence other than kinetics for intermediacy of imide (**3**), based upon a synthetic approach, may be described as follows. The idea behind these synthetic experiments is that the symmetrical imide, such as **3**, contains two identical electrophilic carbonyl groups and as a consequence the nucleophilic attack by HO^-/H_2O can occur equally well at these two identical electrophilic centers, producing equimolar hydrolysis products that are the same (**4**). With the addition of the nitro group at the 4-position in the imide (**7**), the hydrolysis products **8** and **9** are distinguishable (Scheme 4). If the imide-intermediate mechanism is the exclusive mechanism, then the same ratio of **8** and **9** would be formed for each isomer (**5** and **6**) as shown in Scheme 4. If instead (i) amide anions were involved in an intramolecular general base-assisted hydrolysis or (ii) mechanism involving intermediacy of *N*-arylisophthalimide (**10**) (these alternative mechanisms are not entirely and unambiguously excluded by kinetic data), then only one product would be observed from each isomer (**5** and **6**), i.e. only **8** from **5** and only **9** from **6** (Scheme 4).

The rate of alkaline aqueous cleavage of **5** was studied at 0.05 M NaOH and 0.05 M NaOD in the respective H_2O and D_2O solvents containing 3% v/v CH_3CN and 1.5×10^{-4} M **5** at 1.0 M ionic strength (by NaCl). These kinetic runs yielded the values of pseudo-first-order rate constants, $k_{obs}^{H_2O}$ and $k_{obs}^{D_2O}$ as $(1.47 \pm 0.04) \times 10^{-3}$ s^{-1} and $(8.36 \pm 0.34) \times 10^{-4}$ s^{-1}, respectively. Similar kinetic runs, under almost identical conditions, were carried out with **6** and gave $10^3k_{obs}^{H_2O} = 2.10 \pm 0.04$ s^{-1} and $10^3k_{obs}^{D_2O} = 1.11 \pm 0.02$ s^{-1}. In order to compare the solvent deuterium kinetic isotope effects (dKIE) for the cleavage of **5** and **6** with that of **1**, two kinetic runs for the aqueous cleavage of **1** were carried out at 35 °C, 0.05 M NaOH and 0.05 M NaOD in the respective H_2O and D_2O solvents containing 2% v/v CH_3CN and 5.0×10^{-4} M **1** at 1.0 M ionic strength (by NaCl). These kinetic runs gave $k_{obs}^{H_2O}$ and $k_{obs}^{D_2O}$ as $(2.83 \pm 0.03) \times 10^{-3}$ s^{-1} and $(1.72 \pm 0.02) \times 10^{-3}$ s^{-1}, respectively. The value of dKIE $= k_{obs}^{H_2O}/k_{obs}^{D_2O} = 1.6$, which may be compared with dKIE for **5** and **6**. The value of $k_{obs}^{H_2O}/k_{obs}^{D_2O}$ (1.8) for **5** is similar to that for **6** (1.9). These values of dKIE may be compared with dKIE of 1.2 reported for hydroxide ion catalyzed cyclization of methyl 2-aminomethylbenzoate.[8] These results support for the occurrence of similar mechanism in the aqueous cleavage of **5** and **6** and rule out the mechanism involving intermediacy of **10**. In view of eq 1 and Scheme 3, $k_{obs} = k_2^3K_1^3K_i'^3$ because, at 0.05 M NaOH, $1 + K_i'^3[HO^-] \approx 1$ and hence $k_{obs}^{H_2O}/k_{obs}^{D_2O} = \{(k_2^3K_1^3K_a^{\mathbf{1}})^{H_2O}K_w^{D_2O}\}/\{(k_2^3K_1^3K_a^{\mathbf{1}})^{D_2O}K_w^{H_2O}\}$ where $K_i'^3 = K_a^{\mathbf{1}}/K_w$ and $K_w^{H_2O} = a_Ha_{OH}$. Using the values of $K_w^{H_2O}/K_w^{D_2O} = 6.5$,[25] $K_a^{\mathbf{1}\ H_2O}/K_a^{\mathbf{1}\ D_2O} = 4.2$,[26] and $k_{obs}^{H_2O}/k_{obs}^{D_2O} = 1.6$, one

---

(24) Khan, M. N. *Colloids Surfactants A* **2001**, *181*, 99.

(25) Bender, M. L.; Kezdy, F. J.; Zerner, B. *J. Am. Chem. Soc.* **1963**, *85*, 3017.

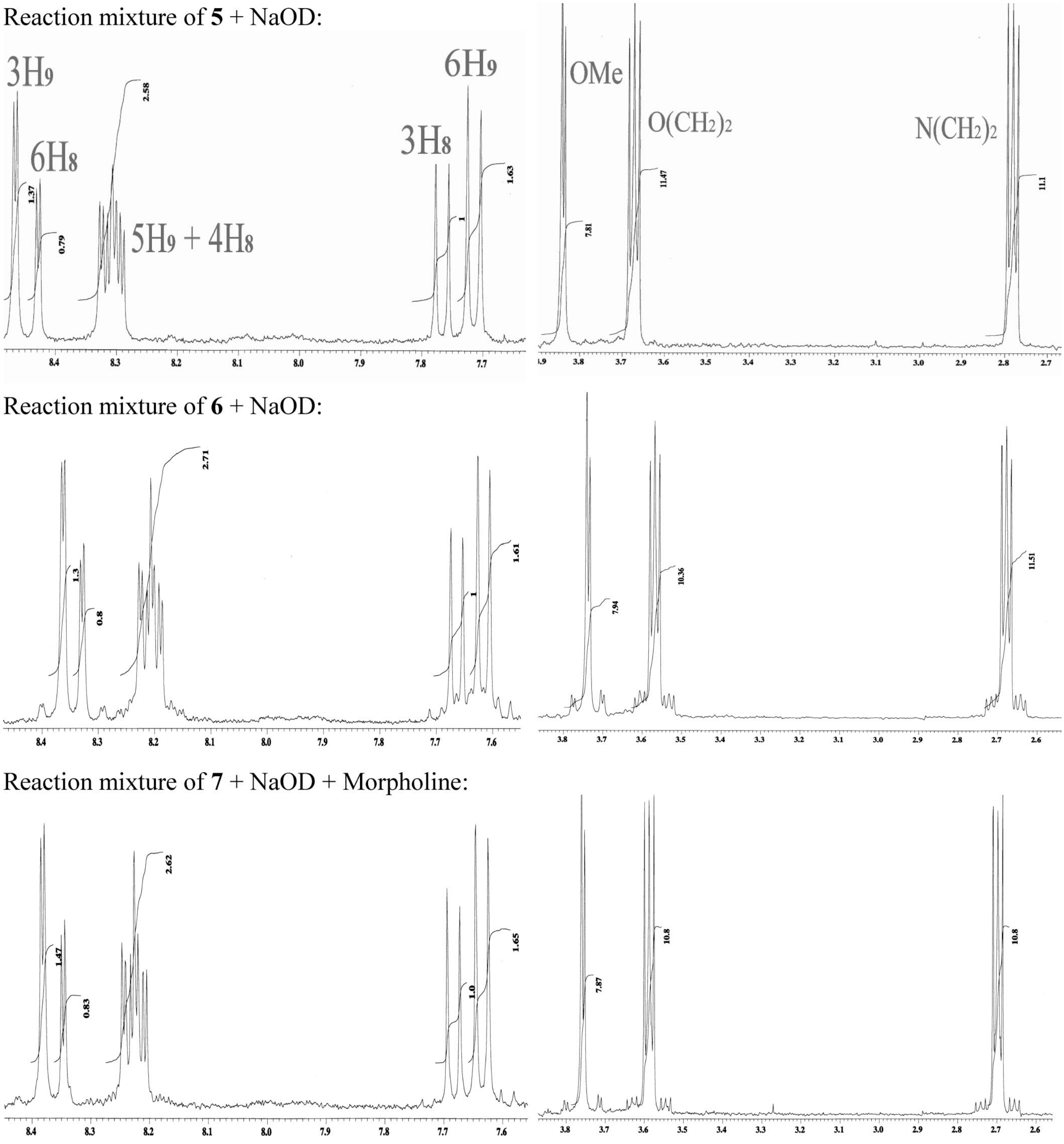


FIGURE 2. ^{1}H NMR peaks for 3-H (d), 6-H (d), and OMe (two overlapping singlet, s) of **8** and **9** and two sets of methylene protons (t) of morpholine, O(CH$_2$)$_2$ and N(CH$_2$)$_2$, for hydrolysis products of **5**, **6**, and **7** (where equimolar morpholine was externally added to the hydrolysis products of **7**). The symbol xH$_y$ represents the H attached to the x-C of compound y.

gets $(k_2{}^3K_1{}^3)^{\mathrm{H_2O}}/(k_2{}^3K_1{}^3)^{\mathrm{D_2O}} = 2.5$. The dKIE of magnitude of 2.5 is consistent with the proposal of $k_2{}^3$ as the rate-determining step in Scheme 3.

The nearly 40% larger value of k_{obs} for **6** ($10^3\ k_{\mathrm{obs}} = 2.10$ s^{-1}) compared with that for **5** ($10^3\ k_{\mathrm{obs}} = 1.47$ s^{-1}) is plausible in view of the fact that the powerful electron-withdrawing resonance effect of the NO$_2$ group activates the electrophilic center more strongly in **6** than in **5** (where the NO$_2$ group is at the *m*-position with respect to the electrophilic center). However, different resonance effects of the NO$_2$ group on nucleophilic centers in **5** and **6** are not expected to have any significant effects on k_{obs} values because the reported results on closely related reactions show that k_{obs} values are almost independent and highly dependent on the respective pK_a of conjugate acids of nucleophiles and leaving groups.[6,8]

To characterize the alkaline aqueous degradation products of **5**, **6**, and **7** by the use of ^{1}H NMR spectrometric technique,

---

(26) Capon, B.; Ghosh, B. C. J. *Chem. Soc. B* **1966**, 472.

TABLE 1. Characteristic Peaks with Integration (In) of Different Chemical Shifts (δ_H) for 8, 9, and Morpholine Obtained from Alkaline Aqueous Cleavage of 5, 6, and 7

	8				**9**				**8 + 9**		morpholine											
substrate	δ_{3H} ppm	In^{3H}	δ_{6H} ppm	In^{6H}	δ_{3H} ppm	In^{3H}	δ_{6H} ppm	In^{6H}	δ_{OMe} ppm	In^{OMe}	$\delta_{O(CH_2)_2}$ ppm	In^{OCH}	$\delta_{N(CH_2)_2}$ ppm	In^{NCH}	R_1[a]	R_2[b]	R_3[c]	R_4[d]	R_5[e]	R_6[f]	R_7[g]	R_8[h]
5	7.77	1.00	8.43	0.79	8.47	1.37	7.72	1.63	3.84	7.81	3.67	11.47	2.78	11.10	1.73	1.63	0.91	0.94	0.92	0.75	0.95	0.78
6	7.66	1.00	8.33	0.80	8.36	1.30	7.62	1.61	3.74	7.94	3.57	10.36	2.68	11.51	1.63	1.61	1.02	0.92	1.01	0.81	0.91	0.73
7[i]	7.68	1.00	8.35	0.83	8.38	1.47	7.63	1.65	3.76	7.87	3.59	10.80	2.70	10.80	1.77	1.65	0.97	0.97	0.98	0.85	0.98	0.85

[a] $R_1 = (In^3H)^{\mathbf{9}}/(In^6H)^{\mathbf{8}}$. [b] $R_2 = (In^6H)^{\mathbf{9}}/(In^3H)^{\mathbf{8}}$. [c] $R_3 = [4(In^{OMe})^{\mathbf{8+9}}]/[3(In^{OCH})]$. [d] $R_4 = [4(In^{OMe})^{\mathbf{8+9}}]/[3(In^{NCH})]$. [e] $R_5 = 4Y_1/(In^{OCH})$. [f] $R_6 = 4Y_2/(In^{OCH})$. [g] $R_7 = 4Y_1/(In^{NCH})$. [h] $R_8 = 4Y_2/(In^{NCH})$; $Y_1 = (In^3H)^{\mathbf{8}} + (In^6H)^{\mathbf{9}}$ and $Y_2 = (In^6H)^{\mathbf{8}} + (In^3H)^{\mathbf{9}}$. [i] Equimolar morpholine was externally added to the product mixture.

these reactions were carried out in D_2O under reaction conditions similar to those for the kinetic runs (mentioned earlier) except that the initial concentrations of **5**, **6**, and **7** were kept at 1.39×10^{-2} M and the hydroxide ion concentration at 0.50 M. The reactions were allowed to progress for >10 half-lives. Then the ^1H NMR spectra of the reaction products mixtures were obtained. In order to compare the spectrum of the aqueous alkaline hydrolysis products of **7** with the corresponding spectra of alkaline aqueous degradation products of **5** and **6**, a specific amount of morpholine was added to the hydrolysis product mixture of **7**, which could produce the concentration of morpholine into the product mixture equivalent to the initial concentration of **7**. The ^1H NMR spectra of the reaction products of **5** and **6** are identical to that of **7** containing an externally added molar amount of morpholine identical to the initial molar amount of **7** (Figures I−III in Supporting Information). A specific segment of these spectra containing peaks of only 3-H and 6-H of **8** and **9** and two sets of methylene protons of morpholine (hydrolysis products of **8** and **9** as well as equimolar externally added to the hydrolysis product of **7**) is shown in Figure 2. The chemical shifts (δ_H) and the integration (In) values of these peaks are summarized in Table 1. The molar ratio of the products, [**9**]/[**8**], formed from alkaline aqueous cleavage of **5**, **6**, and **7** should be equal to $R_1 = (In^3H)^{\mathbf{9}}/(In^6H)^{\mathbf{8}}$ or $R_2 = (In^6H)^{\mathbf{9}}/(In^3H)^{\mathbf{8}}$. Similarly, molar ratio of the products, ([**8**] + [**9**])/[morpholine], formed from alkaline aqueous cleavage of **5** and **6** should be equal to $R_3 = [4(In^{OMe})^{\mathbf{8+9}}]/[3(In^{OCH})^{Mor}]$, $R_4 = [4(In^{OMe})^{\mathbf{8+9}}]/[3(In^{NCH})^{Mor}]$, $R_5 = 4Y_1/(In^{OCH})^{Mor}$, $R_6 = 4Y_2/(In^{OCH})^{Mor}$, $R_7 = 4Y_1/(In^{NCH})^{Mor}$ or $R_8 = 4Y_2/(In^{NCH})^{Mor}$, where Mor = morpholine, OCH = $O(CH_2)_2$, NCH = $N(CH_2)_2$, $Y_1 = (In^3H)^{\mathbf{8}} + (In^6H)^{\mathbf{9}}$ and $Y_2 = (In^6H)^{\mathbf{8}} + (In^3H)^{\mathbf{9}}$. The calculated values of R_1, R_2, R_3, R_4, R_5, R_6, R_7, and R_8 are summarized in Table 1 which reveals that within the limits of experimental errors: (i) the values of molar ratio of products **8** and **9** remained the same, whether **5**, **6**, or **7** was the reactant, and (ii) the values of the molar ratio of ([**8**] + [**9**])/[morpholine] remained almost 1 (Table 1). These observations support the imide-intermediate mechanism (Scheme 3) as the exclusive mechanism for the alkaline aqueous cleavage of **1**.

It is perhaps noteworthy that the effects of the nitro group on the rate of alkaline aqueous cleavage of **5** and **6**, where the nitro group is at the respective *m*- and *p*-position with respect to the electrophilic reaction site may be expressed by the value of $(k_{obs})^{\mathbf{6}}/(k_{obs})^{\mathbf{5}} = 1.43$ (where $(k_{obs})^{\mathbf{6}} = 2.10 \times 10^{-3}$ s^{-1} and $(k_{obs})^{\mathbf{5}} = 1.47 \times 10^{-3}$ s^{-1} at 0.05 M NaOH). The nearly identical value of [**9**]/[**8**] (1.67), whether **5**, **6**, or **7** was the reactant, revealed the expected significantly larger effect of NO_2 from the *p*-position than from *m*-position to the electrophilic reaction site (i.e., CO group) in the alkaline hydrolysis of **7**.

Experimental Section

Materials. *N*-Morpholinobenzamide (**2**) was synthesized using a literature procedure involving the reaction of benzoyl chloride with morpholine, and the observed spectroscopic data are in complete agreement with the corresponding reported data.[27] All common chemicals used were commercial products of highest available purity. Standard solutions of **1** (2.5×10^{-2} M) and **2** (3.0×10^{-2} M) were prepared in acetonitrile. COSY, HMQC, HMBC, and NOESY experiments were used to confirm the NMR peak assignments in compounds **5** and **6**.

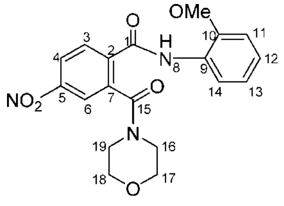
Synthesis of *N*′-Morpholino-*N*-(2′-methoxyphenyl)phthalamide (1). Morpholine (1.00 mL, 11.5 mmol) in THF (3.0 mL) was added slowly to *N*-(2′-methoxyphenyl)phthalimide (**2**) (3.35 g, 13.2 mmol) in THF (3.0 mL). The resulting solution was refluxed for ~17 h. The solvent was removed under reduced pressure to give a brown gel (3.57 g, 91%). Purification was carried out with column chromatography using hexane/ethyl acetate (EtOAc) as eluent starting from 1:0 to 0:1 of hexane/EtOAc. After removal of the solvent, the resulting brownish gel was recrystallized from EtOAc to give white crystals of **1** (2.03 g, 57%), mp 128−130 °C. δ_H (400 MHz, $CDCl_3$, TMS): 3.27 (broad, 2H), 3.64 (broad, 6H), 3.89 (s, 3H), 6.91 (d $J = 9.3$, 1H), 6.98−7.02 (m, 1H), 7.07−7.11 (m, 1H), 7.35 (d $J = 8.8$, 1H), 7.49−7.57 (m, 2H), 7.78 (d $J = 7.6$, 1H), 8.44 (d $J = 7.8$, 1H), 8.58 (s, 1H). δ_C (100 MHz, $CDCl_3$): 42.3, 47.7, 55.8, 66.49, 66.53, 110.2, 120.1, 121.1, 124.3, 126.8, 127.6, 128.1, 129.4, 131.2, 134.3, 135.4, 148.4, 165.3, 169.7. ν_{max} (Nujol/cm^{-1}): 3452, 3426 ($\nu_{NRR'}$), 1656, 1633 ($\nu_{C=O}$) cm^{-1}. UV (CH_3CN): λ_{max}= 282 nm, $\delta = 6560$ M^{-1} cm^{-1}; $R_f = 0.13$ (EtOAc/hexane = 1:1). ^1H, ^{13}C, and COSY NMR spectra of **1** are in Supporting Information.

Synthesis of *N*′-Morpholino-*N*-(2′-methoxyphenyl)-5-nitrophthalamide (5) and *N*′-morpholino-*N*-(2′-methoxyphenyl)-4-nitrophthalamide (6). Morpholine (0.16 g, 1.84 mmol) was added with thorough mixing to *N*-(2′-methoxyphenyl)-4-nitrophthalimide (**7**) (0.52 g, 1.76 mmol) in THF (10.0 mL). The resulting reaction mixture was refluxed overnight (~17 h), and the completion of reaction was monitored by TLC. Two distinct spots on TLC indicated the formation of two isomeric products. Separation and purification of these two isomeric products (as fractions I and II) was carried out with column chromatography using mixed EtOAc/chloroform 1:2 as eluent. However, the two fractions of isomers (I and II) still contained minor amounts of **7**. With the addition of a minimum amount of chloroform, a solid compound formed in fraction I and a crystalline compound formed in fraction II. The solid and crystalline compounds were washed quickly with diethyl ether and acetone, filtered, and dried under high vacuum to produce nice yellow products of both isomers: isomer A (solid compound) 59.3 mg and isomer B (crystalline compound) 101 mg. The structural identification by NMR spectroscopy using HMQC, HMBC, and NOESY experiments revealed isomer A as **5** and isomer B as **6**. Considerable low yield of isomeric products **5** and

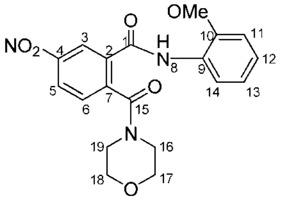
---

(27) Lysen, M.; Kelleher, S.; Begtrup, M.; Kristensen, J. L. *J. Org. Chem.* **2005**, *70*, 5342.

6 may be attributed to (i) both isomers **5** and **6** appeared to be unstable in the contact with silica gel, and (ii) low solubility of the crude products in EtOAc which could have caused precipitation in the column during eluting process. Analytical and NMR spectral data for **5**: $C_{19}H_{19}N_3O_6$. δ_H (400 MHz, $CDCl_3$, TMS): 3.27 (t J = 5.04, 2H, (Morp)CH_2), 3.64 (m, 6H, (Morp)CH_2), 3.89 (s, 3H, Ar-OCH_3), 6.90−6.92 (dd J = 8.24 and 1.40, 1H, ArH^{11}), 7.01 (t J = 7.80, 1H, ArH^{13}), 7.10−7.15 (td J = 7.80 and 1.36, 1H, ArH^{12}), 7.94 (d J = 8.68, 1H, ArH^3), 8.20 (d J = 2.28, 1H, ArH^6), 8.34 (dd J = 8.68 and 2.28, 1H, ArH^4), 8.40 (dd J = 7.80 and 1.36, 1H, ArH^{14}), 8.59 (s, 1H, NH^8). δ_C (100 MHz, $CDCl_3$): 42.5, 47.8 (2CH$_2$(Morp)), 55.9 (Ar−OCH$_3$), 66.4, 66.5 (2CH$_2$(Morp)), 110.4 (ArC^{11}), 120.3 (ArC^{14}), 121.2 (ArC^{13}), 122.2 (ArC^6), 124.4 (ArC^4), 125.2 (ArC^{12}), 127.0 (ArC^9), 129.8 (ArC^3), 136.9 (ArC^2), 139.9 (ArC^7), 148.5 (ArC^5), 149.0 (ArC^{10}), 163.5 (C^1), 167.2 (C^{15}). R_f = 0.46 (EtOAc/hexane = 1:1). ^1H, ^{13}C, COSY, and HMQC NMR spectra of **5** are in Supporting Information. Analytical and NMR spectral data for **6**: $C_{19}H_{19}N_3O_6$. δ_H (400 MHz, $CDCl_3$, TMS): 3.24 (t J = 5.04, 2H, (Morp)CH_2), 3.71 (m, 6H, (Morp)CH_2), 3.89 (s, 3H, Ar-OCH_3), 6.91 (d J = 8.24, 1H, ArH^{11}), 7.00 (t J = 7.80, 1H, ArH^{13}), 7.12 (m, 1H, ArH^{12}), 7.53 (d J = 8.24, 1H, ArH^6), 8.37 (dd J = 8.24 and 1.84, 1H, ArH^5), 8.38 (d J = 8.68, 1H, ArH^{14}), 8.60 (d J = 1.84, 1H, ArH^3), 8.61 (s, 1H, NH^8). δ_C (100 MHz, $CDCl_3$): 42.4, 47.7 (2CH$_2$(Morp)), 55.9 (Ar−OCH$_3$), 66.4, 66.5 (2CH$_2$(Morp)), 110.3 (ArC^{11}), 120.3 (ArC^{14}), 121.2 (ArC^{13}), 123.5 (ArC^3), 125.1 (ArC^{12}), 125.9 (ArC^5), 127.0 (ArC^9), 128.3 (ArC^6), 136.1 (ArC^2), 141.3 (ArC^7), 148.0 (ArC^4), 148.6 (ArC^{10}), 163.0 (C^1), 167.7 (C^{15}). R_f = 0.23 (EtOAc/hexane = 1:1). ^1H, ^{13}C, COSY, HMQC, HMBC, and NOESY NMR spectra of **6** are in Supporting Information.



5



6

It is perhaps worth mentioning that the attempt to separate the isomeric product mixture obtained from the reaction of synthesized *N*-(2′-methoxyphenyl)-4-methylphthalimide with morpholine was unsuccessful.

Synthesis of *N*-(2′-Methoxyphenyl)-4-nitrophthalimide (7). 4-Nitrophthalic anhydride (1.08 g, 5.58 mmol) and 0.692 mL of *o*-methoxyaniline (0.76 g, 6.14 mmol) were added into a 25.0 mL round-bottom flask containing 10.0 mL of glacial acetic acid. A precipitate formed immediately after addition of amine at room condition. The reaction mixture was then refluxed for 2 h after which TLC indicated the completion of the reaction. The reaction mixture was allowed to cool to room temperature and then poured into distilled water. The resulting yellow precipitates were filtered and dried to give 1.58 g (95.0%) of crude product. Further purification carried out by recrystallization with ethanol (95%) afforded fine pale yellow needles of **7** (1.42 g, 85.5%). δ_H (400 MHz, $CDCl_3$, TMS): 3.80 (s, 3H), 7.06−7.09 (m, 2H), 7.27 (dd J = 7.56 and 1.6, 1H) 7.47 (dt J = 8.24 and 1.8, 1H), 8.13 (d J = 8.24, 1H), 8.65 (dd J = 8.24 and 2.28, 1H), 8.75 (d J = 1.84, 1H). δ_C (100 MHz, $CDCl_3$): 55.9, 112.3, 119.2, 119.6, 121.1, 125.0, 129.4, 129.8, 131.3, 133.7, 136.7, 151.9, 155.2, 165.0, 165.3.

Kinetic Measurements. The rates of alkaline hydrolysis of **1** and **2** were studied spectrophotometrically by monitoring the disappearance of **1** at 310 nm and **2** at 250 nm. The temperature was kept constant at 35 °C and aqueous reaction mixture for each kinetic run contained 2% v/v CH_3CN for **1** and **2**. The details of the kinetic procedure were the same as described elsewhere.[18a] The observed absorbance (A_{obs}) at different reaction times (t) were found to fit to eq 5:

$$A_{obs} = \delta_{app}[R_0]\exp(-k_{obs}t) + A_\infty \qquad (5)$$

where $[R_0]$ is the initial concentration of **1** or **2**, δ_{app} is the apparent molar extinction coefficient of the reaction mixture, $A_\infty = A_{obs}$ at $t = \infty$, and k_{obs} represents pseudo-first-order rate constant for alkaline hydrolysis of **1** or **2**. The rates of reactions were generally carried out for the reaction period of ≥8 half-lives. Only for the reactions at 0.01 and 0.02 M NaOH for hydrolysis of **2**, the respective observed maximum values of t correspond to 1.4 and 3.3 half-lives. However, the more reliable values of k_{obs} for these kinetic runs were obtained from eq 5 by data analysis, which included a data point at $t \geq 7$ half-lives with $A_{obs} = A_\infty^{est}$ where A_∞^{est} values were obtained from the sum of absorbance of expected hydrolytic products benzoate ion and morpholine at this particular wavelength. The satisfactory observed data fit to eq 5 is evident from the standard deviations of <8% for calculated kinetic parameters, k_{obs}, δ_{app}, and A_∞. However, the standard deviations associated with these calculated kinetic parameters were <2% for **1** and **2** within [NaOH] range 5.0×10^{-3} to 2.0 M and 5.0×10^{-2} to 2.0 M, respectively. The rates of alkaline aqueous cleavage of **5** and **6** were studied spectrophotometrically by monitoring the appearance of product for **5** at 290 nm and disappearance of **6** at 265 nm. The observed data (A_{obs} versus t) for **6** and **5** fit satisfactorily to eqs 5 and

$$A_{obs} = \delta_{app}[R_0][1 - \exp(-k_{obs}t)] + A_0 \qquad (6)$$

where $A_0 = A_{obs}$ at $t = 0$. Details of the data analysis have been described elsewhere.[16b]

Product Characterization. Alkaline hydrolytic products for **1** were ascertained spectrophotometrically to be **4** and morpholine. The calculated values of A_∞ (from eq 5) at 310 nm and under different reaction conditions gave the value of $\delta = (1473 \pm 29)$ M^{-1} cm^{-1} for product, which is similar to the observed value of δ = 1480 M^{-1} cm^{-1} obtained using authentic **4**. The value of δ for authentic 2-methoxyaniline at 310 nm is 80 M^{-1} cm^{-1}. These observations show nearly 100% conversion of **1** to **4** under the present experimental conditions. The products in the alkaline hydrolysis of **2** were confirmed by comparing the values of molar extinction coefficients, δ, obtained from A_∞ values (calculated from eq 5) with the corresponding δ values of authentic samples of benzoic acid and morpholine obtained under conditions of kinetic runs. These observations showed that the 100% products were benzoic acid and morpholine for **2**.

Acknowledgment. The authors thank the Ministry of Science, Technology and Innovation for ScienceFund (Project No. 14-02-03-4014) and the University of Malaya for financial support. The authors also thank to Ms. Norzalida Zakaria for her help in carrying out the NMR (HMQC, HMBC, and NOESY) experiments. The authors express their deep gratitude and thanks to Professor Daniel A. Singleton of Texas A&M University for suggesting experiments as an additional possible test for an imide-intermediate mechanism.

Supporting Information Available: Appendix; ^1H NMR spectra for alkaline aqueous cleavage of **5**, **6**, and **7** (Figures I−III); ^1H, ^{13}C, and COSY NMR spectra of **1**; ^1H, ^{13}C, COSY, and HMQC NMR spectra of **5**; and ^1H, ^{13}C, COSY, HMQC, HMBC, and NOESY NMR spectra of **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702695K