

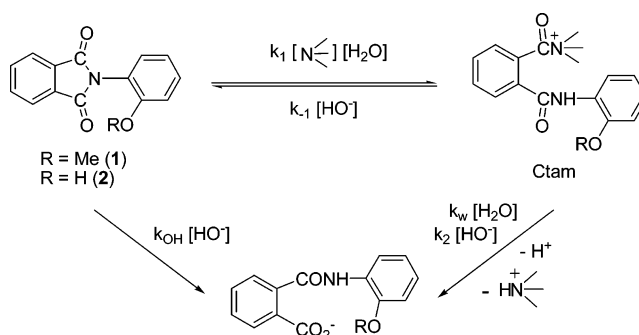
Kinetic Evidence for the Formation of Monocationic *N,N'*-Disubstituted Phthalamide in Tertiary Amine-Catalyzed Hydrolysis of *N*-Substituted Phthalimides

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

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A kinetic study on the aqueous cleavage of *N*-(2-methoxyphenyl)phthalimide (**1**) and *N*-(2-hydroxyphenyl)phthalimide (**2**), under the buffers of *N*-methylmorpholine, reveals the equilibrium presence of monocationic amide (Ctam) formed due to nucleophilic reactions of *N*-methylmorpholine with **1** and **2**. Pseudo-first-order rate constants for the reactions of water and HO^- with Ctam (formed through nucleophilic reaction of *N*-methylmorpholine with **1**) are $4.60 \times 10^{-5} \text{ s}^{-1}$ and $47.9 \text{ M}^{-1} \text{ s}^{-1}$, respectively. But the cleavage of Ctam, formed through nucleophilic reaction of *N*-methylmorpholine with **2**, involves intramolecular general base ($2'\text{-O}^-$ group of Ctam)-assisted water attack at carbonyl carbon of cationic amide group of Ctam in or before the rate-determining step.

Introduction

Mechanistic diagnosis of various types of catalytic processes has been the subject of tremendous interest during the last few decades, and many facets of these catalytic processes have been understood to a reasonable degree of confidence.¹ The surge of interest in this rather highly complex field of research is simply due to the realization that all or most of these catalytic processes are involved in most of the biocatalytic processes such as enzyme-catalyzed reactions. Despite the accumulation of large amount of information on these catalytic processes, we are still unable to answer some very simple questions such as why

certain reactions involve general acid and general base catalysis while other reactions of the same class do not involve such catalysis.²

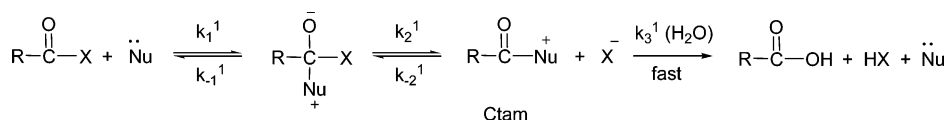
A nucleophile, devoid of hydrogen attached covalently with nucleophilic site such as tertiary amines, can catalyze the hydrolysis of esters and amides (RCOX , $\text{X} = \text{OR}_1$ and NH_2) through either intermolecular nucleophilic catalytic mechanism (Scheme 1) or intermolecular general base catalytic mechanism (Scheme 2).

In Scheme 1, depending upon the physicochemical characteristics of X and Nu , either the k_1 —or k_2 —step is the rate-determining step provided Ctam is highly reactive compared to RCOX toward H_2O . The derived rate laws shown in Scheme 1 (rate = $k_{\text{Nu}}[\text{RCOX}][\text{Nu}]$) and Scheme 2 (rate = $k_{\text{gb}}[\text{RCOX}][\text{Nu}]$ with $k_{\text{gb}} = k_{\text{gb}}' [\text{H}_2\text{O}]$ where $[\text{H}_2\text{O}] \gg [\text{RCOX}]$) are

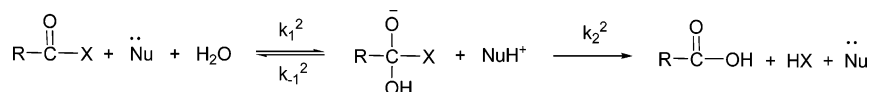
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SCHEME 1



SCHEME 2



kinetically indistinguishable, and consequently, these two alternative catalytic mechanisms cannot be easily and unambiguously differentiated from each other. However, solvent deuterium kinetic isotope effects and some other plausible chemical reasons have been used to differentiate between Schemes 1 and 2 under the typical reaction conditions.^{1g,3}

The direct and perhaps the most convincing evidence for the occurrence of reaction mechanism in Scheme 1 is to characterize experimentally the presence of Ctam during the progress of the reaction. There appears to be no such report(s) (to the best of our literature search) where an intermediate like Ctam could be characterized experimentally except when Nu is an imidazole.⁴ The stability of Ctam is significantly increased when Nu = imidazole because of the resonance dispersal of positive charge between two nitrogens (one tertiary and the other secondary) of imidazole. The present report provides, perhaps for the first time, the direct kinetic evidence for the presence of an intermediate or complex on the reaction path in the hydrolysis of *N*-(2-methoxyphenyl)phthalimide (**1**) and *N*-(2-hydroxyphenyl)phthalimide (**2**) in the presence of *N*-methylmorpholine buffers. The observed results and their probable explanations are described in this manuscript.

Results and Discussion

Effects of Total Concentration of *N*-Methylmorpholine Buffer, [Am]_T, on *k*_{obs} for the Aqueous Cleavage of **1 at 35 °C.** The aqueous cleavage of **1** was kinetically studied by carrying out kinetic runs within [Am]_T (where [Am]_T = [Am] + [AmH⁺] with Am and AmH⁺ representing unprotonated and protonated *N*-methylmorpholine, respectively) range ≥ 0.005–0.80 M at a constant pH and ionic strength (1.0 M by NaCl). Pseudo-first-order rate constants (*k*_{obs}), calculated from eq 5 (in the Experimental Section), are shown graphically in Figure 1. Such observations were obtained at different pH ranging from 7.16 ± 0.01 to 7.82 ± 0.02 as shown by Figure 1. The values of *k*_{obs}, at a constant pH, were found to fit to eq 1

$$k_{\text{obs}} = \frac{k_0 + k_{\text{b}}^{\text{app}}K[\text{Am}]_{\text{T}}}{1 + K[\text{Am}]_{\text{T}}} \quad (1)$$

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where *k*₀ = *k*_{obs} at [Am]_T = 0, *k*_b^{app} represents apparent buffer-catalyzed pseudo-first-order rate constant for the cleavage of **1** and *K* is an empirical constant (most likely an equilibrium constant for reactive complex formation between buffer and **1**). The nonlinear least-squares technique was used to calculate *k*₀, *k*_b^{app}, and *K* from eq 1, and these results are summarized in Table 1. An apparent satisfactory fit of observed data to eq 1 is evident from the standard deviations associated with the calculated kinetic parameters (*k*₀, *k*_b^{app}, and *K*) and from the plots of Figure 1 where solid lines are drawn through the calculated data points using eq 1 and the parameters listed in Table 1.

It is perhaps noteworthy that although the values of absolute residual errors (ARE = |*k*_{obsi} − *k*_{calcdi}| with *k*_{obsi} and *k*_{calcdi} representing respective observed and least-squares calculated values of rate constants at *i*th value of [Am]_T at a constant fraction of free base) are ≤ 6 %, the calculated values of *k*₀, *k*_b^{app}, and *K* at pH 7.16 and 7.27 are associated with considerably high standard deviations (Table 1). Furthermore, the negative value of *k*₀ at pH 7.27 is physically/chemically meaningless.

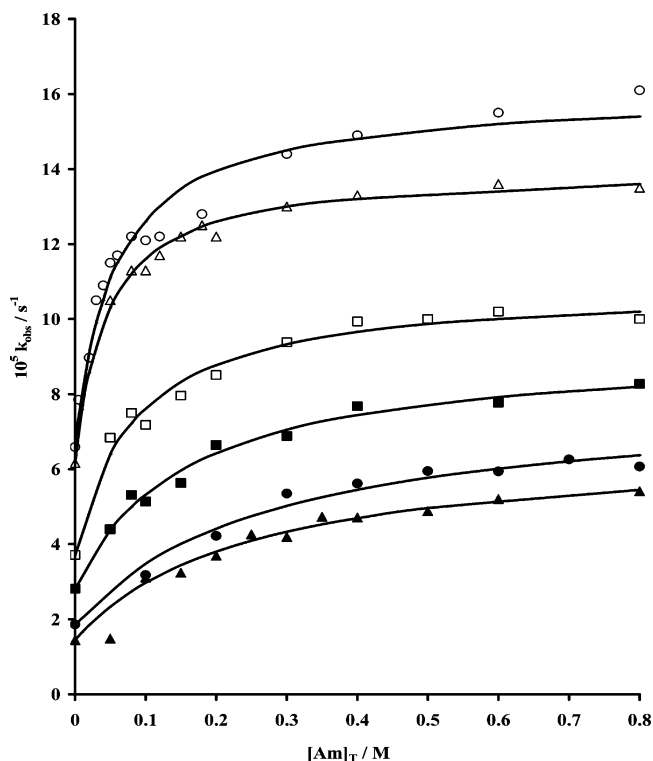


FIGURE 1. Effect of total *N*-methylmorpholine buffer concentrations, [Am]_T, on pseudo-first-order rate constants *k*_{obs} for the aqueous cleavage of **1** at pH 7.16 (▲), 7.27 (●), 7.45 (■), 7.57 (□), 7.79 (Δ), and 7.82 (○). The solid lines are drawn through the calculated data points using eq 1 and the parameters listed in Table 1.

TABLE 1. Values of Kinetic Parameters, k_0 , k_b^{app} , and K Calculated from eq 1 for the Aqueous Cleavage of **1** and **2** in the Presence of *N*-Methylmorpholine Buffers ^a

imide	pH	$10^5 k_0$ (s ⁻¹)	$10^5 k_b^{\text{app}}$ (s ⁻¹)	Y ^b	K (M ⁻¹)	[Am] _T range ^c (M)
1	7.16 ± 0.01 ^d	1.53 ± 0.63 ^d (1.44) ^e	6.72 ± 0.53 ^d (6.66 ± 0.27) ^f	1.7	3.89 ± 1.80 ^d (4.13 ± 0.53) ^f	0.10–0.80
	7.27 ± 0.01	−1.19 ± 2.57 (1.86)	7.13 ± 0.36 (7.92 ± 0.52)	1.9	10.8 ± 6.7 (3.64 ± 0.84)	0.10–0.80
	7.45 ± 0.01	3.13 ± 0.64 (2.81)	9.45 ± 0.56 (9.26 ± 0.31)	1.9	5.31 ± 2.20 (6.36 ± 0.86)	0.05–0.80
	7.57 ± 0.01	5.39 ± 0.75 (3.71)	11.5 ± 0.6 (10.9 ± 0.3)	1.5	5.54 ± 2.68 (11.8 ± 1.7)	0.05–0.80
	7.79 ± 0.01	8.27 ± 0.82 (6.16)	14.2 ± 0.2 (14.0 ± 0.1)	1.3	11.8 ± 3.9 (22.2 ± 1.9)	0.05–0.80
	7.82 ± 0.02	7.74 ± 0.51 (6.59)	16.4 ± 0.5 (16.0 ± 0.4)	2.1	11.7 ± 2.8 (18.2 ± 2.5)	0.005–0.80
		(1300) ^g	(2450 ± 30)	-	(930 ± 224)	0.002–0.15
2	8.11 ± 0.03	(3000)	(5080 ± 60)	-	(597 ± 136)	0.003–0.10

^a [1] = 2.0 × 10⁻⁴ M, λ = 290 nm, [2] = 3.0 × 10⁻⁴ M, λ = 300 nm, ionic strength 1.0 M (maintained by NaCl), T = 35 °C, aqueous reaction mixture for each kinetic run contained 2% v/v CH₃CN. ^b Y = k_{obs} (at [Am]_T^{max})/ k_{obs} (at [Am]_T^{min}) with [Am]_T^{max} and [Am]_T^{min} representing respective maximum and minimum values of [Am]_T attained in the study. ^c Total amine buffer concentration range. ^d Error limits are standard deviations. ^e Parenthesized values are buffer independent rate constants (k_0) calculated from the relationship: $k_0 = k_{\text{OH}} [\text{HO}^-]$ where $k_{\text{OH}} = 29.1 \text{ M}^{-1} \text{ s}^{-1}$, $[\text{OH}^-] = \alpha_{\text{OH}}/\gamma$ and $\gamma = 0.7$. ^f Values in parentheses are calculated from eq 1 using known k_0 values. ^g Values in parentheses are the buffer independent rate constants (k_0) calculated from the relationship $k_0 = \theta/(\alpha_{\text{H}} + \Phi)$ with $\theta = 3.34 \times 10^{-10} \text{ M s}^{-1}$ and $\Phi = 3.36 \times 10^{-9} \text{ M}$.

Thus, the values of k_0 , k_b^{app} , and K at pH 7.16 and 7.27 are not very reliable. It is evident from these data that a satisfactory fit of the observed data to a multiparameters kinetic equation does not depend only upon considerably low values of ARE but also on the calculated values of various kinetic parameters. In the case of an empirical multiparameter kinetic equation, it is generally difficult to test the reliability of the values of various empirical constants/parameters because the physicochemical nature of these empirical constants is generally unknown. It is therefore advisable to use a kinetic equation with the least possible number of kinetic parameters. The validity of the values of the least-squares calculated kinetic parameters decreases with the increase in the number of such parameters of the kinetic equation. It is quite possible that a large positive error in one of the parameters is counterbalanced/compensated by almost equally large negative error in the other parameters leaving no net effect on the low ARE values.

In the present reaction system, the relatively more reliable values of k_0 at different pH were obtained from the relationship $k_0 = k_{\text{OH}}[\text{HO}^-]$ where k_{OH} represents second-order rate constant for the reaction of HO⁻ with **1** and $[\text{HO}^-] = 10^{\text{pH}-\text{p}K_{\text{w}}/\gamma}$ with $\text{p}K_{\text{w}} = 13.62^5$ (where K_{w} is the ionic product of water) and activity coefficient $\gamma = 0.76$ at 1.0 M ionic strength. The value of $k_{\text{OH}} = 29.1 \text{ M}^{-1} \text{ s}^{-1}$ was obtained by carrying out kinetic runs on alkaline hydrolysis of **1** at 1.0 M ionic strength, 35 °C, and varying concentration of NaOH as well as different pH of buffers where buffer catalysis was insignificant compared to $k_{\text{OH}}[\text{HO}^-]$.⁷ These calculated values of k_0 were used to calculate k_b^{app} and K from eq 1 using a nonlinear least-squares method for two unknown parameters. Such calculated values of k_b^{app} and K at different pH are also summarized in Table 1. The quality of the fit of observed data (k_{obs} versus [Am]_T) to eq 1 is evident from the plots of Figure 1 where solid lines are drawn through the least-squares calculated data points and from the standard deviations associated with the calculated parameters, k_b^{app} and K , as shown in Table 1. It is evident from Table 1 that a moderate change (15–30%) in k_0 values leaves k_b^{app}

almost unchanged and changes K values significantly (56–112%) at higher pH. Thus, under such conditions, K values are less reliable.

An analytical look at eq 1 reveals that (i) if $k_b^{\text{app}}/k_0 \gg 1$ then the increase in [Am]_T should cause nonlinear increase in k_{obs} , (ii) if $k_b^{\text{app}}/k_0 = 1$, then k_{obs} should be independent of [Am]_T, and (iii) if $k_b^{\text{app}}/k_0 \ll 1$ then the increase in [Am]_T should result in a nonlinear decrease in k_{obs} . The values of k_b^{app}/k_0 decrease from 4.6 to 2.4 with increase in pH from 7.16 to 7.82 for *N*-methylmorpholine buffer (Table 1). It is evident from the plots of Figure 1 that the observed data at pH 7.79 for *N*-methylmorpholine buffer can fit equally well (in terms of low ARE values) to both eqs 1 and 2, and consequently, the calculated parameters k_b^{app} , K , and α , β may not be considered as reliable under such conditions. In eq 2, α and β represent empirical constants. It seems that the nature of eq 1 is such that the use of either a nonlinear least-squares method or a linear least-squares method to a linearized form of eq 1 cannot yield reliable values of both k_b^{app} and K if $k_b^{\text{app}}/k_0 < 3$ and $Y < 1.5$ where $Y = k_{\text{obs}}$ (at [Am]_T^{max})/ k_{obs} (at [Am]_T^{min}) with [Am]_T^{max} and [Am]_T^{min} representing respective maximum and minimum values of [Am]_T attained in the study.

$$k_{\text{obs}} = \alpha + \beta[\text{Am}]_{\text{T}} \quad (2)$$

Effects of Total Buffer Concentration, [Am]_T, of *N*-Methylmorpholine on k_{obs} for the Aqueous Cleavage of **2 at 35 °C.** A few kinetic runs were carried out for the aqueous cleavage of **2** within the [Am]_T range 0.2–0.8 M at a constant pH 7.03 ± 0.01 and 1.0 M ionic strength. The values of k_{obs} versus [Am]_T are shown graphically in Figure 2. Similar observations were obtained at different pH, 7.23 ± 0.03, 7.57 ± 0.02, 7.66 ± 0.01, 7.88 ± 0.01, and 8.12 ± 0.01 as shown graphically in Figure 2. There is a regular yet small decrease (~5, 17, 27, 35, 24, and 30% at respective pH 7.03, 7.23, 7.57, 7.66, 7.88, and 8.11) in k_{obs} with the increase in [Am]_T from 0.02 to 0.8 M (Figure 2). The increase in [Me₄NCl] from 0.01 to 1.0 M decreased k_{obs} for hydrolysis of **1** or **2** at 1.0 × 10⁻³ M NaOH by ~20%. Similarly, the increase in [NaBr] from 0.0 to 1.0 and 1.5 M decreased k_{obs} for hydrolysis of **2** at 1.0 × 10⁻³ M NaOH by ~20 and 30%, respectively. The equilibrium

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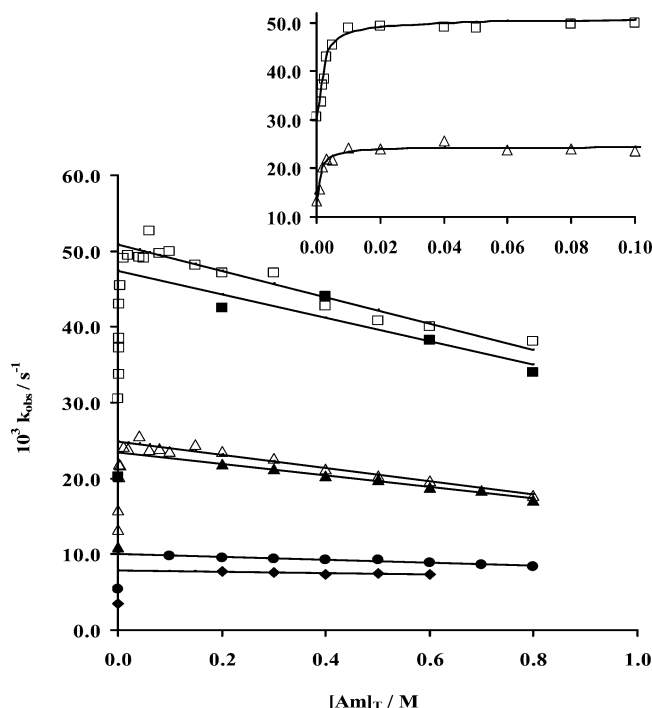


FIGURE 2. Plots showing the dependence of pseudo-first-order rate constants k_{obs} on total *N*-methylmorpholine buffer concentrations, $[\text{Am}]_{\text{T}}$, for the aqueous cleavage of **2** at pH 7.03 (◆), 7.23 (●), 7.57 (▲), 7.65 (△), 7.88 (■), and 8.11 (□), respectively. The solid lines are drawn through the calculated data points using eq 2 and the parameters listed in Table 2 as well as eq 1 and the parameters listed in Table 1 for the plots (pH 7.65 △ and pH 8.11 □) shown as inset.

nucleophilic substitution cationic–anionic product (**14**[−], Scheme 5) formed in the reaction of *N*-methylmorpholine with anionic **2** contains an additional positive charge compared to anionic **2**. The rate of hydrolysis of **14**[−] may be more sensitive to the specific salt effect compared to that of anionic **2**. Although we could not find any report on the effects of salt(s) on the rate of hydrolysis of closely related cationic amide(s), the mild decrease (5–35%) in k_{obs} with an increase in $[\text{Am}]_{\text{T}}$ (Figure 2) may be ascribed to a *N*-methylmorpholinium chloride salt effect. Pseudo-first-order rate constants for hydrolysis of acetylimidazole at 0.1 M HCl and 25 °C decreased by ~67% with the increase in $[\text{NaCl}]$ from 0.0 to 3.0 M.^{4a}

Following the suggestion of one of the reviewers, a few more kinetic runs were carried out at two higher pH values (pH 7.65 ± 0.02 and 8.11 ± 0.03) where the values of $[\text{Am}]_{\text{T}}$ were attained as low as 0.001 and 0.0015 M. The values of k_{obs} as shown in Figure 2 reveal the presence of maxima in the plots of k_{obs} versus $[\text{Am}]_{\text{T}}$. Although the decrease in pH (ΔpH) during a kinetic run was significant at $[\text{Am}]_{\text{T}} \leq 0.005$ M (e.g., $\Delta\text{pH} = 0.10, 0.21, 0.30$, and 0.49 at $[\text{Am}]_{\text{T}} = 0.005, 0.003, 0.002$ and 0.0015 M, respectively, at pH 8.11 as well as $\Delta\text{pH} = 0.10, 0.18, 0.25$, and 0.54 at respective $[\text{Am}]_{\text{T}} = 0.005, 0.003, 0.002$, and 0.001 M at pH 7.65), the observed data (A_{obs} versus t) for all these kinetic runs fit perfectly to eq 6 for the reaction periods of >10 half-lives. The values of k_{obs} , within $[\text{Am}]_{\text{T}}$ range 0.003–0.10 M at pH 8.11 and 0.002–0.15 M at pH 7.65, were found to fit to eq 1 with $k_{\text{b}}^{\text{app}}$ and K as unknown parameters, and the least-squares calculated values of $k_{\text{b}}^{\text{app}}$ and K are summarized in Table 1. These calculated values of $k_{\text{b}}^{\text{app}}$ and K predict the decrease in k_{obs} compared to the corresponding calculated rate constants (k_{calcd}) by ~15, 10, and 9% at respective $[\text{Am}]_{\text{T}} =$

0.0015, 0.0020, and 0.0025 M at pH 8.11 as well as ~15% at $[\text{Am}]_{\text{T}} = 0.001$ M and pH 7.65.

Although weak effects of $[\text{Am}]_{\text{T}}$ on k_{obs} do not appear to be irregular, one might consider k_{obs} values to be independent of $[\text{Am}]_{\text{T}}$ at a constant pH. But this is not correct for the reason that average values of k_{obs} ($= k_{\text{av}}$) as shown in Table 2 are nearly 2-fold larger than the corresponding values of k_0 calculated from the relationship $k_0 = \theta/(a_{\text{H}} + \Phi)$ with $\theta = 3.34 \times 10^{-10}$ M s^{−1} and $\Phi = 3.36 \times 10^{-9}$ M.⁷ Thus, it is apparent that the observed data at pH 7.03, 7.23, 7.57, and 7.88 (Figure 2) should obey eq 1.

An attempt to fit the observed data at pH 7.03, 7.23, 7.57, and 7.88 to eq 1 was unsuccessful. However, these observed data were used to calculate α and β from eq 2 where, at least, the values of α may be considered as very close to $k_{\text{b}}^{\text{app}}$ values because the average values of k_{obs} ($= k_{\text{av}}$) at different pH, obtained within $[\text{Am}]_{\text{T}}$ range at a constant pH attained in the study, are not significantly different from the corresponding values of α (Table 2). Furthermore, the values of α at pH 7.66 and 8.12 (Table 2) are similar to $k_{\text{b}}^{\text{app}}$ values at the corresponding pH (Table 1). The least-squares calculated values of α and β at different pH are summarized in Table 2.

Discussion

The second-order rate constant (k_{OH}) for hydroxide ion catalyzed cleavage of the amide bond in phthalimide ($k_{\text{OH}} = 4.9 \text{ M}^{-1} \text{ s}^{-1}$)⁸ is ~10⁷-fold larger than that in benzamide ($k_{\text{OH}} = 6 \times 10^{-7} \text{ M}^{-1} \text{ s}^{-1}$).⁹ More than a million-fold rate enhancement in the alkaline hydrolysis of phthalimide is attributed to intramolecular carboxamide group assistance in the mild alkaline medium. The kinetics of the rate of aqueous cleavage of phthalimide under the buffers of primary¹⁰ and secondary amines¹¹ have been found to be complicated due to fast equilibrium formation of *N*-substituted phthalimide followed by a slow rate of hydrolysis of phthalimide as shown in Scheme 3.

In view of Scheme 3, a plausible reaction mechanism for the cleavage of **1** in the presence of buffers of tertiary amines ($\text{R}_1\text{R}_2\text{R}_3\text{N}$) may be shown in Scheme 4.

The observed rate law ($\text{rate} = k_{\text{obs}}[\text{1}]_{\text{T}}$ where $[\text{1}]_{\text{T}} = [\text{1}] + [\text{11}]$) and Scheme 4 can lead to eq 3

$$k_{\text{obs}} = \frac{k_{\text{OH}}^4[\text{HO}^-] + (k_{\text{w}}^4[\text{H}_2\text{O}] + k_2^4[\text{HO}^-])K'[\text{Am}]_{\text{T}}}{1 + K'[\text{Am}]_{\text{T}}} \quad (3)$$

where $K' = f_{\text{b}}K^4[\text{H}_2\text{O}]/[\text{HO}^-]$, $f_{\text{b}} = K_{\text{a}}^{\text{Am}}/(a_{\text{H}} + K_{\text{a}}^{\text{Am}})$, $K_{\text{a}}^{\text{Am}} = [\text{Am}]a_{\text{H}}/[\text{AmH}^+]$, $K^4 = [\text{11}][\text{HO}^-]/[\text{1}][\text{H}_2\text{O}][\text{Am}] = k_1^4/k_{-1}^4$, and $\text{Am} = \text{R}_1\text{R}_2\text{R}_3\text{N}$. Equation 3 is similar to eq 1 with $k_0 = k_{\text{OH}}^4[\text{HO}^-]$, $k_{\text{b}}^{\text{app}} = k_{\text{w}}^4[\text{H}_2\text{O}] + k_2^4[\text{HO}^-]$, and $K = K'$. The relationships $k_{\text{b}}^{\text{app}} = k_{\text{w}}^4[\text{H}_2\text{O}] + k_2^4[\text{HO}^-]$ and $K = f_{\text{b}}K^4[\text{H}_2\text{O}]/[\text{HO}^-]$ predict that the plots of $k_{\text{b}}^{\text{app}}$ versus $[\text{HO}^-]$ and $K[\text{HO}^-]$ versus f_{b} should be linear. Such plots as shown in Figures 3 and 4 appear to be linear but with significant deviations of observed data points from linearity at higher values of f_{b} in Figure 4. As discussed earlier in the text, the values of K at higher values of f_{b} are not reliable, and consequently, the large

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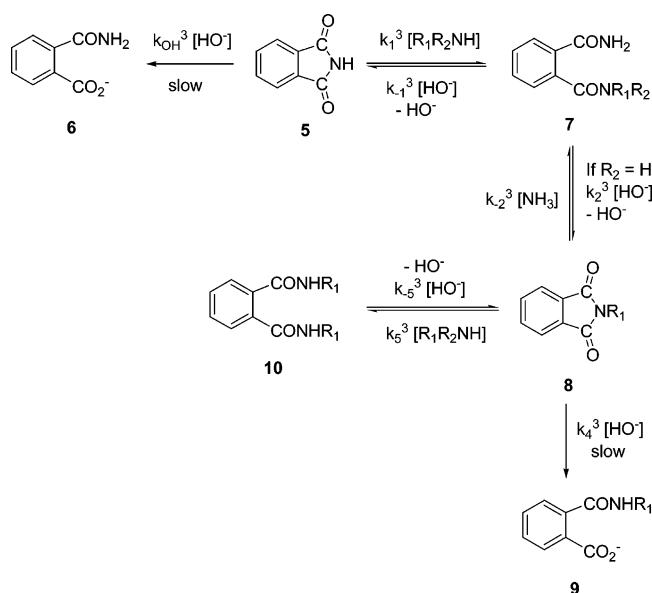
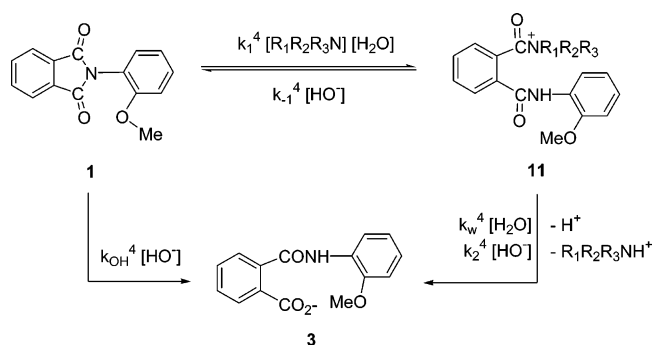
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TABLE 2. Values of α and β , Calculated from eq 2 for the Aqueous Cleavage of **2** in the Presence of *N*-Methylmorpholine Buffers ^a

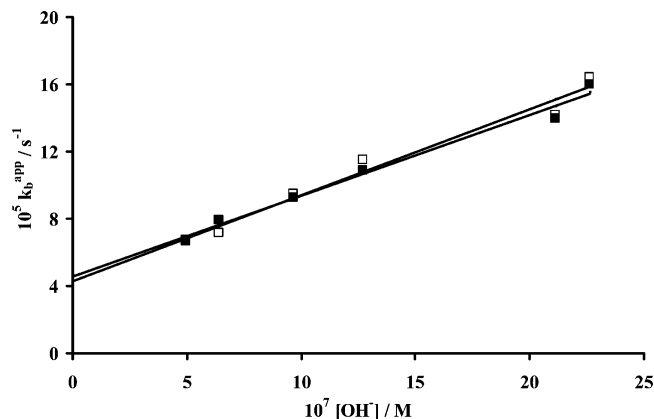
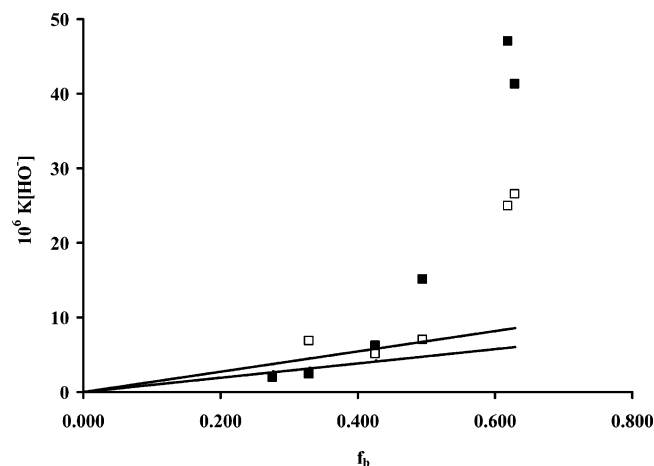
pH	$10^3\alpha$ (s ⁻¹)	$10^3\beta$ (M ⁻¹ s ⁻¹)	10^3k_{av} ^b (s ⁻¹)	10^3k_0 ^c (s ⁻¹)	R^d	[Am] _T range ^e (M)
7.03 ± 0.01 ^f	7.85 ± 0.13 ^f	- 0.88 ± 0.31 ^f	7.50 ± 0.16 ^f	3.45	1.0	0.20–0.60
7.23 ± 0.03	9.99 ± 0.09	- 1.89 ± 0.18	9.14 ± 0.48	5.37	1.1	0.10–0.80
7.57 ± 0.02	23.4 ± 0.2	- 7.58 ± 0.35	19.6 ± 1.6	11.0	1.2	0.20–0.80
7.66 ± 0.01	24.9 ± 0.3	- 8.80 ± 0.70	22.5 ± 2.3	13.2	1.1	0.02–0.80
7.88 ± 0.01	47.4 ± 3.0	- 15.5 ± 5.5	39.7 ± 4.5	20.2	1.2	0.20–0.80
8.12 ± 0.01	50.9 ± 0.5	- 17.4 ± 1.5	46.5 ± 4.5	30.5	1.1	0.02–0.80

^a [2₀] = 3.0 × 10⁻⁴ M, λ = 300 nm, ionic strength 1.0 M, T = 35 °C, aqueous reaction mixture for each kinetic run contained 1% v/v CH₃CN. ^b Average values of k_{obs} obtained within [Am]_T range attained in the study. ^c The values of k_0 were calculated from the relationship: $k_0 = \theta/(a_H + \Phi)$ with $\theta = 3.34 \times 10^{-10}$ M s⁻¹ and $\Phi = 3.36 \times 10^{-9}$ M. ^d $R = \alpha/k_{av}$. ^e Total buffer concentration range. ^f Error limits are standard deviations.

SCHEME 3**SCHEME 4**

deviations of data points from linearity of the plot of $K[HO^-]$ versus f_b at higher values of f_b are understandable. The least-squares calculated respective values of $k_w^4 [H_2O]$ and k_2^4 are $(4.60 \pm 0.45) \times 10^{-5} \text{ s}^{-1}$ and $47.9 \pm 3.1 \text{ M}^{-1} \text{ s}^{-1}$ with k_0 as the known parameter and $(4.27 \pm 0.59) \times 10^{-5} \text{ s}^{-1}$ and $51.3 \pm 4.0 \text{ M}^{-1} \text{ s}^{-1}$ with k_0 as the unknown parameter. The least-squares calculated value of $K^4[H_2O]$, from the equation $K[HO^-] = K^4[H_2O]f_b$, is $(13.6 \pm 5.8) \times 10^{-6}$ with k_0 as the known parameter and $(14.8 \pm 10.9) \times 10^{-6}$ with k_0 as the unknown parameter.

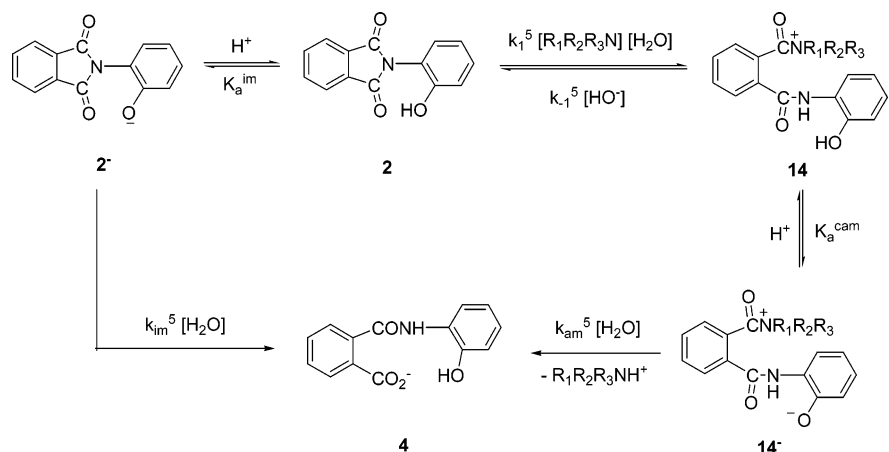
The respective values of $k_w^4[H_2O]$ ($= 4.60 \times 10^{-5} \text{ s}^{-1}$) and k_2^4 ($= 47.9 \text{ M}^{-1} \text{ s}^{-1}$) for *N*-methylmorpholinolysis of **1** are ~70-fold and ~2-fold larger than the corresponding rate constants k_w ($= 6.74 \times 10^{-7} \text{ s}^{-1}$)¹² and k_{OH}^4 ($= 29.1 \text{ M}^{-1} \text{ s}^{-1}$) for

**FIGURE 3.** Plot showing the dependence of k_b^{app} on $[HO^-]$ for *N*-methylmorpholine buffer-catalyzed hydrolysis of **1** where the solid lines are drawn through the calculated data points using relationship: $k_b^{app} = k_w^4 [H_2O] + k_2^4 [HO^-]$ for k_b^{app} derived from eq 1 with k_0 as known parameter (■) and k_0 as unknown parameter (□).**FIGURE 4.** Plot of $K[HO^-]$ versus fractions of free base, f_b , for the aqueous cleavage of **1** under *N*-methylmorpholine buffer where the values of K were calculated from eq 1 considering k_0 as unknown parameter (□) and known parameter (■).

hydrolysis of **1**.⁷ Similarly, the values of $k_w^4[H_2O]$ is (2.7×10^3) -fold smaller than k_w ($= 12.2 \times 10^{-2} \text{ s}^{-1}$) for the reaction of water with acetylimidazolium ion.^{4a} But the value of k_2^4 ($= 47.9 \text{ M}^{-1} \text{ s}^{-1}$) is only 20-fold smaller than k_{OH} ($\{= 970 \text{ M}^{-1} \text{ s}^{-1} = 2.7 \times 10^{-4}/(10^{(7-13.62)}/\gamma)\}$ with $\gamma = 0.86$ at 0.2 M ionic strength} for the reaction of HO^- with acetylimidazolium ion.^{4a} The addition–elimination reaction mechanism for the reactions of water with **1**, **11**, and acetylimidazolium ion involves expulsion of leaving group as the rate-determining step. But nucleophilic attack by hydroxide ion becomes the rate-determining

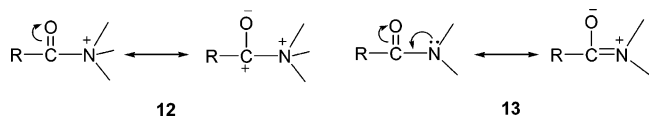
(12) Cheong, M.-Y.; Ariffin, A.; Khan, M. N. Unpublished observations.

SCHEME 5



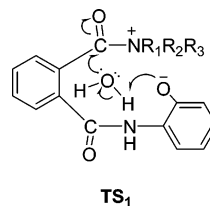
ing step in the reactions of HO^- with **1**, **11**, and acetylhydrazide. Thus, the values of k_2^4 and k_w^4 should be expected to be weakly and highly sensitive to the pK_a of the leaving groups, respectively.

The values of hydroxide ion catalyzed second-order rate constants ($k_{\text{OH}} = k_2^4$) are $\sim 10^7$ – 10^8 -fold larger than the values of k_{OH} for alkaline hydrolysis of *N*-methylbenzanilide,¹³ benzamide,⁹ *N*-methylbenzamide,⁹ *N,N*-dimethylbenzamide,⁹ and *N*-benzylphthalamic acid.¹³ More than 10^7 -fold larger reactivity of cationic amides than that of neutral amides toward HO^- cannot be attributed to only pK_a values of leaving groups in these reactions but also to electrostatic effects as well as to the loss of the electron-donation resonance effect of an amino group in the cationic amide compared to that in neutral amide as shown in **12** and **13**.



The values of k_{obs} for hydrolysis of **2** at a constant pH 7.57 $\pm$ 0.02 and different $[\text{Am}]_{\text{T}}$ with Am representing *N*-methylmorpholine are 170- to 270-fold larger than k_{obs} for hydrolysis of **1** under similar experimental conditions (Figures 1 and 2). Such an apparent significantly larger rate of hydrolysis of **2** than that of **1** in the presence of *N*-methylmorpholine buffers of constant pH is due to the respective presence and absence of intramolecular general base (IGB) assistance in the hydrolysis of **2** and **1**. Mechanistic details of IGB-assisted hydrolysis of **2**, where $o\text{-O}^-$ group acts as IGB, have been described elsewhere.⁷ Although the values of $k_{\text{b}}^{\text{app}}$ and K could not be calculated from eq 1 using the observed data on the aqueous cleavage of **2** in the presence of *N*-methylmorpholine buffers, the values of α (Table 2) may represent the approximate values of $k_{\text{b}}^{\text{app}}$ as mentioned earlier in the text. Nearly 2-fold larger values of α compared to those of k_0 (Table 2) reveal that the cationic amide (**14**) formed from nucleophilic reaction of *N*-methylmorpholine and **2** converts to hydrolysis product (**4**) involving IGB assistance as shown in TS_1 . In view of these conclusions, a brief reaction mechanism for the aqueous

cleavage of **2** in the presence of *N*-methylmorpholine buffers may be shown in Scheme 5.



The observed rate law (rate = $k_{\text{obs}}[\text{2}]_{\text{T}}$ where $[\text{2}]_{\text{T}} = [\text{2}] + [\text{2}^-] + [\text{14}] + [\text{14}^-]$) and Scheme 5 can lead to eq 4 (a brief derivation of eq 4 is mentioned in the Supporting Information)

$$k_{\text{obs}} = \frac{k_{\text{im}}^5 f_{\text{b}}^{\text{im}} [\text{H}_2\text{O}] + k_{\text{am}}^5 f_{\text{b}}^{\text{cam}} [\text{H}_2\text{O}] K' [\text{Am}]_{\text{T}}}{1 + K' [\text{Am}]_{\text{T}}} \quad (4)$$

where $f_{\text{b}}^{\text{im}} = K_{\text{a}}^{\text{im}}/(a_{\text{H}} + K_{\text{a}}^{\text{im}})$, $f_{\text{b}}^{\text{cam}} = K_{\text{a}}^{\text{cam}}/(a_{\text{H}} + K_{\text{a}}^{\text{cam}})$ and $K' = f_{\text{b}}^{\text{im}} K^5 [\text{H}_2\text{O}]/(f_{\text{a}}^{\text{cam}} [\text{HO}^-])$ with $K^5 = k_1^5/k_{-1}^5$, $f_{\text{a}}^{\text{im}} = 1 - f_{\text{b}}^{\text{im}}$, $f_{\text{a}}^{\text{cam}} = 1 - f_{\text{b}}^{\text{cam}}$, $f_{\text{b}} = K_{\text{a}}^{\text{Am}}/(a_{\text{H}} + K_{\text{a}}^{\text{Am}})$, $K_{\text{a}}^{\text{Am}} = [\text{Am}]/a_{\text{H}}/[\text{AmH}^+]$ and Am = unprotonated *N*-methylmorpholine. Equation 4 is similar to eq 1 with $k_0 = k_{\text{im}}^5 f_{\text{b}}^{\text{im}} [\text{H}_2\text{O}]$, $k_{\text{b}}^{\text{app}} = k_{\text{am}}^5 f_{\text{b}}^{\text{cam}} [\text{H}_2\text{O}]$, and $K = K'$.

The distinct difference between the shape of the plots of Figures 1 and 2 is basically due to the mechanistic difference in the aqueous cleavages of **1** and **2** in the presence of *N*-methylmorpholine buffers as depicted in Schemes 4 and 5. The value of rate constant for the reaction of water with **1** is negligible compared to that of HO^- with **1** at pH $\geq$ 7.0. But the value of $k_w^4 [\text{H}_2\text{O}]$ is not negligible compared to $k_{\text{OH}}^4 [\text{HO}^-]$ even at pH 7.8. Thus, the values of $k_{\text{b}}^{\text{app}}/k_0$ increase with the decrease in pH for the aqueous cleavage of **1** in *N*-methylmorpholine buffers. However, the values of $k_{\text{im}}^5 [\text{H}_2\text{O}]$ and $k_{\text{am}}^5 [\text{H}_2\text{O}]$ remained essentially unchanged with the change in pH for the cleavage of **2** in *N*-methylmorpholine buffers. This chemical characteristic predicts that the values of $k_{\text{b}}^{\text{app}}/k_0$ should remain almost unchanged with change in pH provided $K_{\text{a}}^{\text{im}} \approx K_{\text{a}}^{\text{cam}}$. The observed values of $\alpha/k_0 \approx 2$ at different pH (Table 2) is the reflection of this prediction.

Nonlinear plots of k_{obs} versus $[\text{Am}]_{\text{T}}$, similar to those in Figures 1 and 2, could not be observed in the aqueous cleavage of phthalimide, *N*-bromopropylphthalimide, and *N*-hydroxyphthalimide.

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

thalimide in the buffers of DABCO,¹⁴ phthalimide in the buffers of triethanolamine,¹⁵ *N*-ethoxycarbonylphthalimide in the buffers of DABCO,¹⁶ and maleimide¹⁷ in the buffers of DABCO, triethanolamine, trimethylamine, and triethylamine. The most obvious reason for these observations is the presence of inequality $k_{-1}^4 [\text{HO}^-] \ll (k_w^4 [\text{H}_2\text{O}] + k_2^4 [\text{HO}^-])$ when **1** is replaced by maleimide, phthalimide and *N*-alkyl substituted phthalimides. The magnitude of k_{-1}^4 may not be very sensitive to the nature of substituent attached to *N* in phthalimide moiety



where R = H, OH, CH₂CH₂CH₂Br, and CO₂C₂H₅.⁷ But the magnitudes of k_w^4 and k_2^4 may be expected to be significantly sensitive to the steric requirements of R. Thus, the presence of inequality $k_{-1}^4 [\text{HO}^-] \gg (k_w^4 [\text{H}_2\text{O}] + k_2^4 [\text{HO}^-])$ in the cleavage of **1** is presumably caused by the significant steric hindrance of R in k_w^4 —and k_2^4 —steps. The k_{-1}^4 step becomes insignificant compared to k_w^4 —and k_2^4 —steps when **1** is replaced by esters or amides where k_{-1}^4 —step involves intermolecular bimolecular process.

Conclusions

Pseudo-first-order rate constants (k_{obs}) for aqueous cleavage of **1** in the presence of *N*-methylmorpholine buffers revealed the nonlinear plots of k_{obs} versus [Am]_T (total tertiary amine buffer concentration) where the slope of a typical plot decreased with the increase in [Am]_T at a constant pH. Such nonlinear plots are attributed to the kinetically detectable equilibrium presence of cationic amide (**11**) formed due to nucleophilic substitution reaction of tertiary amine with **1**. Although the mechanistic aspects of tertiary amine-catalyzed hydrolysis of esters, imides and amides have been discussed extensively in terms of nucleophilic—and general base—catalyzed hydrolysis mechanisms, direct experimental evidence, similar to one described in this manuscript, for the presence of highly reactive cationic amide intermediates in the nucleophilic reactions of tertiary amines except imidazole⁴ with esters, imides, and amides is lacking in almost all previous reports.^{14–18}

Experimental Section

Materials. *N*-(2-Methoxyphenyl)phthalimide (**1**) and *N*-(2-hydroxyphenyl)phthalimide (**2**) were synthesized as described elsewhere.⁷ All other chemicals used were commercial products of

highest available purity. *N*-Methylmorpholine was doubly distilled before use. Standard solutions of **1** (0.01 M) and **2** (0.03 M) were prepared in acetonitrile. Stock aqueous solutions of *N*-methylmorpholine were freshly prepared. Similarly, buffer solutions of desired pH were prepared just before the start of kinetic runs.

Kinetic Measurements. The rates of hydrolysis of **1** and **2**, in the presence of a constant total buffer concentration ([Buf]_T), at constant pH and 35 °C, were studied spectrophotometrically by monitoring periodically the respective appearance of reaction product of **1** at 290 nm and disappearance of reactant (**2**) at 300 nm. Details of the kinetic procedure have been described in a previous report.¹⁴ The observed data (A_{obs} versus t , where A_{obs} represents absorbance at any reaction time t) followed eq 5 for appearance of hydrolysis product of **1** and eq 6 for disappearance of reactant **2**. In eqs 5 and 6

$$A_{\text{obs}} = \delta_{\text{app}}[\text{R}_0][1 - \exp(-k_{\text{obs}}t)] + A_0 \quad (5)$$

$$A_{\text{obs}} = \delta_{\text{app}}[\text{R}_0] \exp(-k_{\text{obs}}t) + A_{\infty} \quad (6)$$

δ_{app} is the apparent molar extinction coefficient of the reaction mixture, $[\text{R}_0]$ represents the initial concentration of reactants **1** and **2**, $A_0 = A_{\text{obs}}$ at $t = 0$, $A_{\infty} = A_{\text{obs}}$ at $t = \infty$, and k_{obs} is the pseudo-first-order rate constant for hydrolysis of **1** and **2**. The rates of reactions under variety of reaction conditions were generally monitored for the reaction period of more than 4–18 half-lives. The observed data fit to either eq 5 or eq 6 was satisfactory for all kinetic runs as evident from <1 % standard deviations associated with calculated kinetic parameters, k_{obs} , δ_{app} and A_0 or A_{∞} as well as from $\leq 1\%$ absolute residual errors, $\text{ARE} = |A_{\text{obsi}} - A_{\text{calcdi}}|$ where A_{obsi} and A_{calcdi} are observed and least-squares calculated absorbance at i th reaction time, t_i , respectively. The value of δ_{app} is related to the molar extinction coefficients of **1** (δ_1), **2** (δ_2), and product (δ_p) by the relationship $\delta_{\text{app}} = \delta_p - \delta_1$ (for eq 5) and $\delta_{\text{app}} = \delta_2 - \delta_p$ (for eq 6).

Product Characterization. UV spectra of reaction mixtures at ≥ 3 half-lives (for **1**) and ≥ 20 half-lives (for **2**) for the kinetic runs at 0.20 M [Am]_T with Am = *N*-methylmorpholine and 1.0 M ionic strength were found to be similar to the UV spectra of the corresponding authentic *N*-(2-methoxyphenyl)phthalamic acid (**3**) and *N*-(2-hydroxyphenyl)phthalamic acid (**4**) under similar experimental conditions (Figures I and II in the Supporting Information).

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Supporting Information Available: Figures 1 and 2, derivation of eq 4. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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