

## A Kinetic Study on Ethylaminolysis of Phenyl Y-Substituted-Phenyl Carbonates: Effect of Leaving-Group Substituents on Reactivity and Reaction Mechanism

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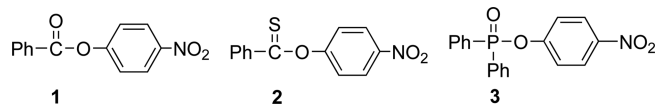
A kinetic study on nucleophilic substitution reactions of phenyl Y-substituted-phenyl carbonates (**5a-5j**) with ethylamine in 80 mol % H<sub>2</sub>O/20 mol % DMSO at 25.0 ± 0.1 °C is reported. The plots of  $k_{\text{obsd}}$  vs. [amine] are linear for the reactions of substrates possessing a strong electron-withdrawing group (EWG) but curve upward for those of substrates bearing a weak EWG, indicating that the electronic nature of the substituent Y in the leaving group governs the reaction mechanism. The reactions have been concluded to proceed through a stepwise mechanism with one or two intermediates (a zwitterionic tetrahedral intermediate T<sup>±</sup> and its deprotonated form T<sup>-</sup>) depending on the nature of the substituent Y. Analysis of Brønsted-type plots and dissection of  $k_{\text{obsd}}$  into microscopic rate constants have revealed that the reactions of substrates possessing a strong EWG (e.g., **5a-5f**) proceed through T<sup>±</sup> with its formation being the rate-determining step, while those of substrates bearing a weak EWG (e.g., **5g-5j**) proceed through T<sup>±</sup> and T<sup>-</sup>.

**Key Words** : Aminolysis, Leaving group, Brønsted-type plot, General-base catalysis, Intermediate

### Introduction

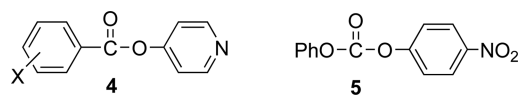
Aminolyses of esters have intensively been investigated due to their importance in biological processes as well as in synthetic applications.<sup>1-11</sup> Nucleophilic substitution reactions of esters with amines have been reported to proceed either through a concerted mechanism or through a stepwise pathway with one or two intermediates (e.g., a zwitterionic tetrahedral intermediate T<sup>±</sup> and its deprotonated form T<sup>-</sup>) depending on reaction conditions (e.g., the nature of electrophilic centers, the substituents in the leaving and nonleaving groups, solvents, etc.).<sup>1-11</sup>

Reactions of 4-nitrophenyl benzoate (**1**) with a series of cyclic secondary amines in 80 mol % H<sub>2</sub>O/20 mol % DMSO have been reported to proceed through a stepwise mechanism with breakdown of T<sup>±</sup> being the rate-determining step (RDS).<sup>6</sup> However, the corresponding reactions of *O*-4-nitrophenyl thionobenzoate (**2**) have been shown to proceed through a stepwise pathway with two intermediates (e.g., T<sup>±</sup> and T<sup>-</sup>),<sup>7a,7b</sup> while the reactions of **2** with a series of primary amines proceed through T<sup>±</sup> only.<sup>7c</sup> On the other hand, aminolysis of 4-nitrophenyl diphenylphosphinate (**3**) has been reported to proceed through a concerted mechanism.<sup>8</sup> Clearly, these results indicate that the reaction mechanism is strongly dependent on the nature of the electrophilic centers (e.g., C=O, C=S or P=O) and amines (e.g., primary or secondary amines).

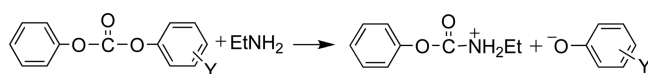


The effects of medium and substituents on reaction mech-

anisms have also been studied. We have reported that aminolysis of 2,4-dinitrophenyl benzoate proceeds through a stepwise mechanism with a change in RDS in 80 mol % H<sub>2</sub>O/20 mol % DMSO (i.e., from breakdown of T<sup>±</sup> to its formation as the incoming amine becomes more basic than the leaving 2,4-dinitrophenoxide by 4 to 5 pK<sub>a</sub> units) but proceeds through a concerted pathway in MeCN.<sup>9</sup> Interestingly, the reactions of 4-pyridyl X-substituted benzoates (**4**) with cyclic secondary amines in MeCN have recently been reported to proceed with T<sup>±</sup> as an intermediate when the substituent X is a weak EWG or an electron donating group (EDG) but with two intermediates (i.e., T<sup>±</sup> and T<sup>-</sup>) when X is a strong EWG (e.g., 3,5-dinitro, 4-nitro, 4-cyano, etc.).<sup>10</sup> This implies that the nature of leaving group and the electronic nature of substituent in the nonleaving group also affect the reaction mechanism.



Aminolysis of 4-nitrophenyl phenyl carbonate (**5**) in 80 mol % H<sub>2</sub>O/20 mol % DMSO has been reported to proceed through a stepwise mechanism with a change in the RDS.<sup>11</sup> We have now extended our study to the reactions of phenyl Y-substituted-phenyl carbonates (**5a-5j**) with ethylamine in



**Scheme 1**

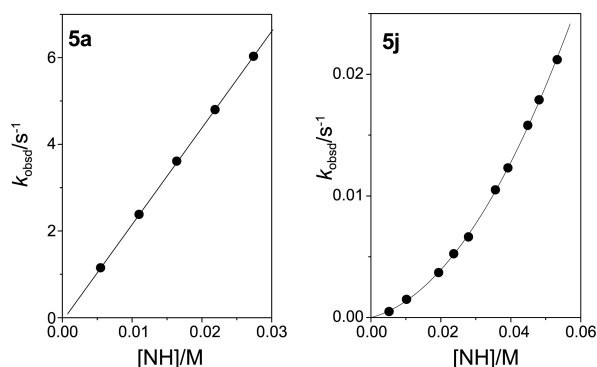
80 mol % H<sub>2</sub>O/20 mol % DMSO to investigate the effect of leaving-group substituent Y on the reactivity and reaction mechanism (Scheme 1).

## Results and Discussion

The reactions were followed spectrophotometrically by monitoring the appearance of Y-substituted-phenoxide under pseudo-first-order conditions (*e.g.*, the concentration of ethylamine was kept in excess over that of substrates). All reactions obeyed first-order kinetics and the pseudo-first-order rate constants ( $k_{\text{obsd}}$ ) were calculated from the equation,  $\ln(A_{\infty} - A_t) = -k_{\text{obsd}}t + C$ . The uncertainty in the  $k_{\text{obsd}}$  values was estimated to be less than  $\pm 3\%$  from replicate runs. The plots of  $k_{\text{obsd}}$  vs. [amine] are illustrated in Figure 1 for the ethylaminolysis of 3,4-dinitrophenyl phenyl carbonate (**5a**) and diphenyl carbonate (**5j**) to show the effect of the substituent Y on the reaction mechanism.

**Effect of Leaving-Group Substituent on Reaction Mechanism.** As shown in Figure 1, the plot of  $k_{\text{obsd}}$  vs. [amine] for the reaction of 3,4-dinitrophenyl phenyl carbonate (**5a**) is linear and passes through the origin. A similar result has been obtained for the reactions of substrates possessing a strong EWG in the leaving group (*e.g.*, **5b-5f**). This indicates that a general base catalysis by a second ethylamine molecule is absent and the contribution of H<sub>2</sub>O and/or OH<sup>-</sup> ion from hydrolysis of ethylamine to  $k_{\text{obsd}}$  is negligible for the reactions of **5a-5f**. In contrast, the plot for the reaction of diphenyl carbonate (**5j**) curves upward. Similarly curved plots have been observed for the reactions of substrates bearing a weak EWG (*e.g.*, **5g-5i**). Such a curved plot is typical of reactions reported previously to proceed through general base catalysis by a second amine molecule.<sup>1,7,10</sup> Thus, one can propose that ethylamine behaves as a general base catalyst as well as a nucleophile for the reactions of substrates bearing a weak EWG (*e.g.*, **5g-5j**).

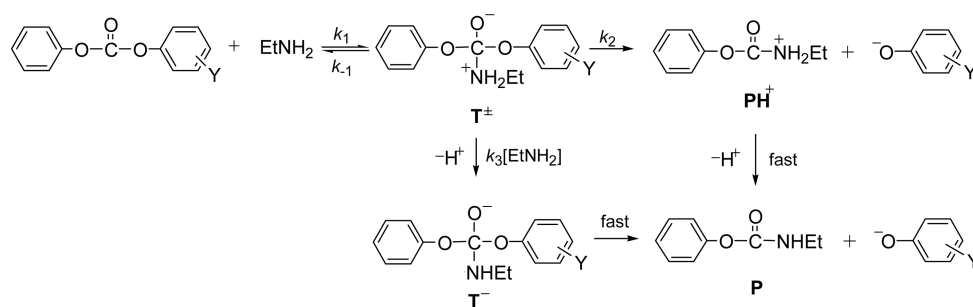
The contrasting plots shown in Figure 1 for the reactions of **5a** and **5j** demonstrate convincingly that the electronic nature of the leaving-group substituent Y governs the reaction mechanism (*e.g.*, absence or presence of general base catalysis). Thus, one can suggest that the reactions of **5a-5j** with ethylamine proceed through a stepwise mechanism with one or two intermediates (*i.e.*, T<sup>±</sup> and/or its deprotonated form T<sup>-</sup>) as shown in Scheme 2 depending on the electronic nature of the substituent Y.



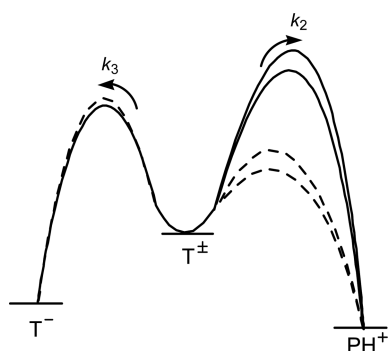
**Figure 1.** Plots of  $k_{\text{obsd}}$  vs. [amine] for ethylaminolysis of 3,4-dinitrophenyl phenyl carbonate (**5a**) and diphenyl carbonate (**5j**) in 20 mol % DMSO/80 mol % H<sub>2</sub>O at  $25.0 \pm 0.1$  °C.

To account for the contrasting reaction mechanisms, a qualitative energy diagram for the processes that yield T<sup>-</sup> and PH<sup>+</sup> from T<sup>±</sup> is illustrated in Figure 2. It is evident that the energy barrier to form PH<sup>+</sup> from T<sup>±</sup> (*i.e.*, the  $k_2$  route in Scheme 2) is dependent on the nucleofugality of the leaving group while that to form T<sup>-</sup> (*i.e.*, the  $k_3$  route in Scheme 2) is governed by the acidity of the NH<sup>+</sup> moiety of T<sup>±</sup>. One might expect that the nucleofugality of the leaving aryloxy in substrates **5a-5j** would decrease as the substituent Y becomes a weaker EWG or *vice versa*. Accordingly, the energy barrier for the  $k_2$  route would increase significantly as the substituent Y changes from 3,4-(NO<sub>2</sub>)<sub>2</sub> to a weaker EWG such as 3-Cl, 3-COMe, 4-Cl or H. In contrast, the energy barrier for the  $k_3$  route would be little influenced by the electronic nature of the substituent Y. This is because the substituent Y is too far away to affect the acidity of the NH<sup>+</sup> moiety of T<sup>±</sup> through an inductive effect. Besides, the aminium moiety of T<sup>±</sup> is unchanged (*i.e.*, ethylamine). Thus, the energy barrier for the  $k_3$  route would remain nearly constant while that for the  $k_2$  process would increase or decrease depending on the electronic nature of the substituent Y (Figure 2).

It is apparent that the reaction would proceed through the  $k_2$  route when the energy barrier to form PH<sup>+</sup> from T<sup>±</sup> is lower than that to form T<sup>-</sup> (*i.e.*, the dashed lines) but through the deprotonation process (*i.e.*, the  $k_3$  route) when the energy barrier to form T<sup>-</sup> from T<sup>±</sup> is lower than that to form PH<sup>+</sup> (*i.e.*, the solid lines). This idea is consistent with the fact that the reactions of substrates possessing a strong EWG (*e.g.*, **5a-5f**) proceed through the  $k_2$  route while those of substrates



**Scheme 2**

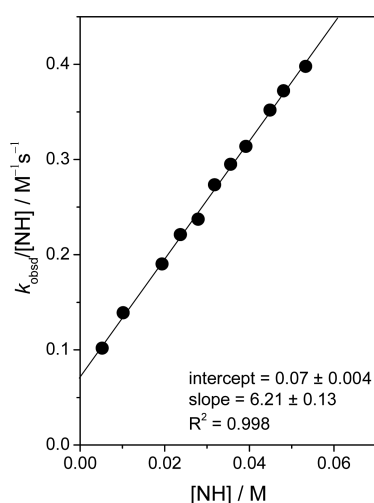


**Figure 2.** A qualitative energy profile for the processes that yield  $T^-$  and  $PH^+$  from  $T^\ddagger$ .

bearing a weak EWG (e.g., **5g-5j**) proceed through the  $k_3$  route.

**Calculations of Rate Constants  $k_N$ ,  $Kk_2$  and  $Kk_3$ .** On the basis of the proposed reactions in Scheme 2,  $k_{\text{obsd}}$  can be expressed as Eqs. (1) and (2) for the reactions of **5a-5f** and for those of **5g-5j**, respectively. Thus, the  $k_N$  values for the reactions of **5a-5f** have been calculated from the slope of the linear plots of  $k_{\text{obsd}}$  vs. [amine]. Since  $k_N = k_1k_2/(k_{-1} + k_2)$ ,  $k_N = k_1k_2/k_{-1}$  (i.e.,  $Kk_2$ ) when  $k_{-1} \gg k_2$  while  $k_N = k_1$  when  $k_{-1} \ll k_2$ . On the other hand, Eq. (2) can be simplified as Eq. (3) under the assumption,  $k_{-1} \gg k_2 + k_3[\text{amine}]$ . Thus, one might expect that the plots of  $k_{\text{obsd}}/[\text{amine}]$  vs. [amine] are linear. In fact, as shown in Figure 3, the plot for the reaction of **5j** with ethylamine exhibits an excellent linear correlation, indicating that the above assumption is valid for the reaction condition. Similarly linear plots have been obtained for the reactions of **5g-5i**. Accordingly, the second-order rate constant  $k_1k_2/k_{-1}$  (i.e.,  $Kk_2$ ) and the third-order rate constant  $k_1k_3/k_{-1}$  (i.e.,  $Kk_3$ ) have been calculated from the intercept and the slope of the linear plots, respectively. The rate constants  $k_N$ ,  $Kk_2$  and  $Kk_3$  calculated in this way are summarized in Table 1.

$$k_{\text{obsd}} = k_N[\text{amine}], \text{ where } k_N = k_1k_2/(k_{-1} + k_2) \quad (1)$$



**Figure 3.** Plot of  $k_{\text{obsd}}/[\text{amine}]$  vs. [amine] for the reaction of diphenyl carbonate (**5j**) with ethylamine in 20 mol % DMSO/80 mol %  $H_2O$  at  $25.0 \pm 0.1$  °C.

**Table 1.** Summary of Kinetic Data for the Reactions of Phenyl Y-Substituted-Phenyl Carbonates (**5a-5j**) with Ethylamine in 20 mol % DMSO/80 mol %  $H_2O$  at  $25.0 \pm 0.1$  °C

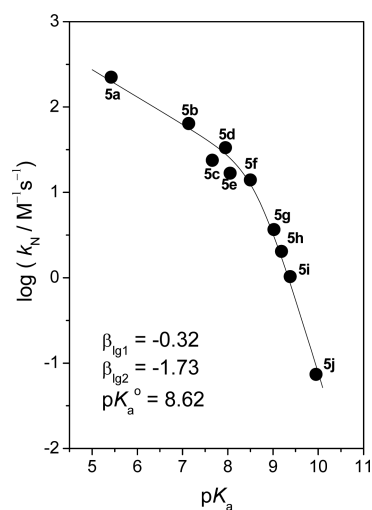
	Y	$pK_a$	$k_N(\text{or } k_1)/M^{-1}s^{-1}$	$Kk_2/M^{-1}s^{-1}$	$Kk_3/M^{-1}s^{-1}$
<b>5a</b>	3,4-(NO <sub>2</sub> ) <sub>2</sub>	5.42	223	-	-
<b>5b</b>	4-NO <sub>2</sub>	7.14	63.9	-	-
<b>5c</b>	4-CHO	7.66	23.8	-	-
<b>5d</b>	4-CN	7.95	33.3	-	-
<b>5e</b>	4-COMe	8.05	16.7	-	-
<b>5f</b>	4-COOEt	8.50	14.0	-	-
<b>5g</b>	3-Cl	9.02	7.57	3.66	15.0
<b>5h</b>	3-COMe	9.19	4.91	2.02	14.5
<b>5i</b>	4-Cl	9.38	5.24	0.970	13.6
<b>5j</b>	H	9.95	5.20	0.070	6.21

$$k_{\text{obsd}} = (k_1k_2[\text{amine}] + k_1k_3[\text{amine}]^2)/(k_{-1} + k_2 + k_3[\text{amine}]) \quad (2)$$

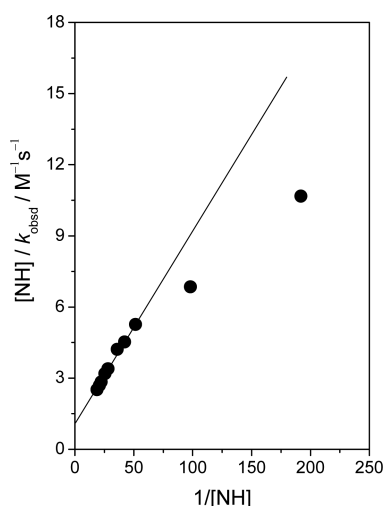
$$k_{\text{obsd}}/[\text{amine}] = Kk_2 + Kk_3[\text{amine}], \text{ where } K = k_1/k_{-1} \quad (3)$$

**Analysis of Brønsted-type Plot.** As shown in Table 1, the rate constants decrease as the leaving-group basicity increases. The effect of leaving-group basicity on the second-order rate constants  $k_N$  for the reactions of **5a-5f** and on  $Kk_2$  for those of **5g-5j** is illustrated in Figure 4. The Brønsted-type plot is nonlinear, e.g., the  $\beta_{\text{lg}}$  value changes from  $-0.32$  for the reactions of **5a-5f** to  $-1.73$  for those of **5g-5j**. Such a nonlinear Brønsted-type plot has often been reported for reactions which proceed through a stepwise mechanism with a change in the RDS.<sup>1</sup> Thus, one can suggest that the nonlinear Brønsted-type plot is due to a change in the RDS, i.e., from formation of  $T^\ddagger$  for the reactions of **5a-5f** to its breakdown to the reaction products for the reactions of **5g-5j**.

It has been reported that the RDS for the reactions of 4-nitrophenyl phenyl carbonate (**5b**) with a series of primary amines including ethylamine changes from breakdown of  $T^\ddagger$  to its formation as the incoming amine becomes more basic than the leaving 4-nitrophenoxide ion by ca. 2.3  $pK_a$  units.<sup>11a</sup>



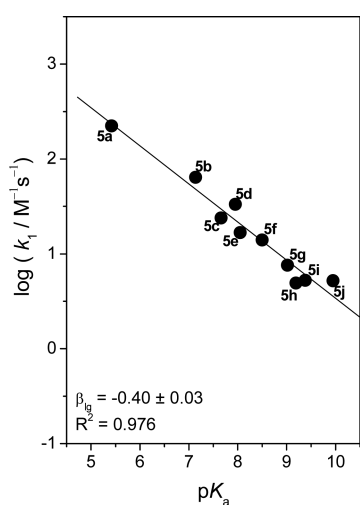
**Figure 4.** Plot of  $\log(k_N \text{ (or } Kk_2))$  vs.  $pK_a$  of the conjugate acids of Y-substituted phenoxides for the reactions of **5a-5j** in 20 mol % DMSO/80 mol %  $H_2O$  at  $25.0 \pm 0.1$  °C.



**Figure 5.** Plot of  $[\text{amine}]/k_{\text{obsd}}$  vs.  $1/[\text{amine}]$  for the reaction of diphenyl carbonate (**5j**) with ethylamine in 20 mol % DMSO/80 mol %  $\text{H}_2\text{O}$  at  $25.0 \pm 0.1$  °C.

The  $\text{p}K_{\text{a}}$  of the conjugate acid of ethylamine is 10.67. Thus, one might expect that the RDS for the current reactions changes at  $\text{p}K_{\text{a}}$  near 8.4. In fact, the break in the Brønsted-type plot in Figure 4 occurs at  $\text{p}K_{\text{a}}$  8.62, indicating that the nonlinear Brønsted-type plot is indeed due to a change in the RDS and that  $k_{\text{N}} = k_1$  for the reactions of **5a-5f**.

To examine the above argument, the  $k_1$  values for the reactions of **5g-5j** have been calculated using the following method. Eq. (2) can be converted to Eq. (4) under the assumption,  $k_2 \ll k_3[\text{amine}]$ . Thus, the plot of  $[\text{amine}]/k_{\text{obsd}}$  vs.  $1/[\text{amine}]$  would be expected to be linear if the assumption is valid. However, as shown in Figure 5, the plot is linear only when the amine concentration is high (e.g.,  $> 0.02$  M), indicating that the assumption that  $k_2 \ll k_3[\text{amine}]$  is valid only when the amine concentration is high enough. Accordingly, the  $1/k_1$  values for the reactions of **5g-5j** have been estimated from the intercept of the plots of  $[\text{amine}]/k_{\text{obsd}}$  vs.



**Figure 6.** Plot of  $\log k_1$  vs.  $\text{p}K_{\text{a}}$  for the reactions of phenyl Y-substituted-phenyl carbonates (**5a-5j**) with ethylamine in 20 mol % DMSO/80 mol %  $\text{H}_2\text{O}$  at  $25.0 \pm 0.1$  °C.

$1/[\text{amine}]$ . More reliable  $k_1$  values have been determined from the nonlinear least-squares fitting of Eq. (2) to the experimental data by using the  $1/k_1$  values obtained above as input values. The  $k_1$  values determined are summarized in Table 1.

$$[\text{amine}]/k_{\text{obsd}} = 1/k_1 + k_{-1}/k_1 k_3 [\text{amine}] \quad (4)$$

The effect of leaving-group basicity on the  $k_{\text{N}}$  values for the reactions of **5a-f** and on the  $k_1$  values for those of **5g-j** is illustrated in Figure 6. The Brønsted-type plot is linear with  $\beta_{\text{ig}} = -0.40$ . This supports clearly that  $k_{\text{N}} = k_1$  for the reactions of **5a-f** and that the nonlinear Brønsted-type plot shown in Figure 4 is indeed due to a change in the RDS, i.e., from formation of  $\text{T}^{\ddagger}$  (the  $k_1$  step) to its breakdown to the products (the  $k_2$  step) as the substituent Y changes from a strong EWG (e.g., **5a-5f**) to a weak EWG (e.g., **5g-5j**).

## Conclusions

The kinetic study on ethylaminolysis of phenyl Y-substituted-phenyl carbonates (**5a-5j**) has allowed us to conclude the following: (1) The electronic nature of the substituent Y governs the reaction mechanisms as well as the reactivity of the substrates. (2) The reactions of substrates possessing a strong EWG (e.g., **5a-5f**) proceed through a stepwise mechanism, in which formation of  $\text{T}^{\ddagger}$  is the RDS. (3) The reactions of substrates bearing a weak EWG (e.g., **5g-5j**) proceed also through a stepwise mechanism but with two intermediates (e.g.,  $\text{T}^{\ddagger}$  and  $\text{T}^{\ddagger}$ ). (4) The electronic nature of the substituent Y affects the energy barrier for the  $k_2$  route. In contrast, the energy barrier for the  $k_3$  route is little influenced by the substituent Y.

## Experimental Section

**Materials.** Substrates **5a-5j** were readily prepared from the reactions of phenyl chloroformate with Y-substituted phenol in the presence of triethylamine in anhydrous ether as reported previously.<sup>12</sup> The crude products were purified by column chromatography and the purity was checked by their melting points and  $^1\text{H}$  NMR spectra. Ethylamine hydrochloride and other chemicals were of the highest quality available. Doubly glass distilled water was further boiled and cooled under nitrogen just before use.

**Kinetics.** Kinetic study was performed using a UV-Vis spectrophotometer for slow reactions (e.g.,  $t_{1/2}$  10 s) and a stopped-flow spectrophotometer for fast reactions (e.g.,  $t_{1/2} < 10$  s) equipped with a constant-temperature circulating bath. All the reactions were carried out under pseudo-first-order conditions in which the amine concentration was kept at least 20 times greater than the substrate concentration. Typically, the reaction was initiated by adding 5  $\mu\text{L}$  of a 0.02 M of substrate stock solution in MeCN by a 10  $\mu\text{L}$  syringe to a 10 mm UV cell containing 2.50 mL of the reaction medium and ethylamine. The ethylamine stock solution of ca. 0.2 M was prepared in a 25.0 mL volumetric flask by adding 2 equiv. of ethylamine hydrochloride and 1 equiv. of

NaOH solution to make a self-buffered solution. The reactions were followed by monitoring the appearance of Y-substituted phenoxide. Reactions were followed generally for 9-10 half-lives and  $k_{\text{obsd}}$  were calculated using the equation,  $\ln(A - A_i)$  vs.  $t$ .

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