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Leaving-Group Substituent Controls Reactivity and Reaction Mechanism in Aminolysis of Phenyl Y-Substituted-Phenyl Carbonates

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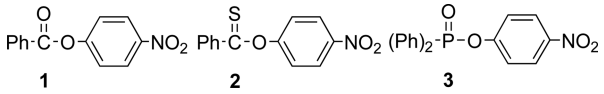
A kinetic study is reported for the nucleophilic substitution reactions of phenyl Y-substituted-phenyl carbonates (**5a-5k**) with piperidine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The plots of k_{obsd} *vs*. [piperidine] for the reactions of substrates possessing a strong electron-withdrawing group (EWG) in the leaving group (*i.e*., **5a-5i**) are linear and pass through the origin. In contrast, the plots for the reactions of substrates bearing a weak EWG or no substituent (*i.e*., **5j** or **5k**) curve upward, indicating that the electronic nature of the substituent Y in the leaving group governs the reaction mechanism. Thus, it has been suggested that the reactions of **5a-5i** proceed through a stepwise mechanism with a zwitterionic tetrahedral intermediate (*i.e*., $T^{\pm}$) while those of **5j** and **5k** proceed through a stepwise mechanism with two intermediates (*i.e*., $T^{\pm}$ and its deprotonated form T^{-}). The slope of the Brønsted-type plot for the second-order rate constants (*i.e*., k_N or Kk_2) changes from –0.41 to –1.89 as the leaving-group basicity increases, indicating that a change in the rate-determining step (RDS) occurs. The reactions of **5a-5k** with piperidine result in larger k_1 values than the corresponding reactions with ethylamine.

Key Words : Aminolysis, General-base catalysis, Brønsted-type plot, Nucleofugality, Transition state

Introduction

Aminolyses of esters have been reported to proceed through a concerted mechanism or *via* a stepwise pathway with a zwitterionic tetrahedral intermediate ($T^{\pm}$) or with two intermediates (*e.g*., $T^{\pm}$ and its deprotonated form T^{-}).[1-8] Linear free energy relationships (LFERs) such as Brønsted-type plots, Hammett plots correlated with σ^{o} and σ^{-} constants and Yukawa-Tsuno plots have been reported to be the most popular tools to investigate reaction mechanisms.[1-8] Linear Brønsted-type plots with β_{nuc} = 0.5 ± 0.1 obtained from aminolyses of esters have been taken as evidence for a concerted mechanism.[1-8] In contrast, curved Brønsted-type plots with changing the β_{nuc} value from 0.9 ± 0.2 to 0.3 ± 0.1 have often been interpreted as a change in the rate-determining step (RDS) of a stepwise mechanism, *i.e*., from breakdown of $T^{\pm}$ to its formation as the incoming amine becomes more basic than the leaving group by 4-5 pK_a units.[1-8] Hammett and Yukawa-Tsuno plots have also been employed to investigate the reaction mechanism, *e.g*., a linear Hammett plot correlated with σ^{o} constants implies that the leaving-group departure occurs after the RDS, while a linear Hammett plot correlated with σ^{-} constants or a linear Yukawa-Tsuno plot indicates that departure of the leaving group occurs in the RDS.[5-8]

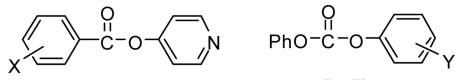
Many factors have been suggested to control the reaction mechanisms (*e.g*., the nature of electrophilic center such as C=O, C=S or P=O, and the electronic nature of the substituent in the leaving- or nonleaving group, *etc*.).[5-8] The reactions of 4-nitrophenyl benzoate (**1**) with a series of cyclic secondary amines have been reported to proceed through a stepwise mechanism in which breakdown of $T^{\pm}$ occurs in the RDS on the basis of a linear Brønsted-type plot with β_{nuc} = 0.81,[5f] while the corresponding reactions of *O*-4-nitrophenyl thionobenzoate (**2**) have been concluded to proceed through a stepwise mechanism with two intermediates (*i.e*., $T^{\pm}$ and T^{-}) since the plots of k_{obsd} *vs*. [amine] curved upward.[6] In contrast, the reactions of 4-nitrophenyl diphenylphosphinate (**3**) with primary and secondary amines have been reported to proceed through a concerted mechanism on the basis of a linear Brønsted-type plot with β_{nuc} = 0.38-0.53.[7] Thus, the nature of the electrophilic center (C=O, C=S or P=O) has been suggested to control the reaction mechanism.[5-8]



1 **2** **3**

We have recently reported that the reactions of 4-pyridyl X-substituted benzoates (**4**) with a series of cyclic secondary amines in MeCN proceed through a stepwise mechanism with one or two intermediates depending on the electronic nature of the substituent X in the benzoyl moiety, *e.g*., the reactions of substrates possessing a weak electron-withdrawing group (EWG) or an electron-donating group (EDG) proceed through a stepwise mechanism with one intermediate $T^{\pm}$, while those of substrates bearing a strong EWG proceed through a stepwise pathway with two intermediates $T^{\pm}$ and T^{-}.[5a] This demonstrates that the electronic nature of the substituents in the nonleaving group is an important factor which controls the reaction mechanism.[5a] The effect of leaving group substituents on the reaction mechanism has also been reported to be significant for ethylaminolysis of

phenyl Y-substituted-phenyl carbonates (**5a-5k**), *e.g.*, the reactions of substrates possessing a strong EWG in the leaving group proceed through a stepwise mechanism with one intermediate $T^{\pm}$, while those of substrates bearing a weak EWG proceed with two intermediates $T^{\pm}$ and T^{-}.[9]



4 **5a-5k**

The nature of amines (*e.g.*, primary *vs.* secondary) has also been reported to affect the reaction mechanism as well as the reactivity. As mentioned above, the reactions of **2** with secondary amines have been reported to proceed through a stepwise mechanism with two intermediates $T^{\pm}$ and T^{-}. In contrast, the reactions of **2** with a series of primary amines have been reported to proceed without the deprotonation process from $T^{\pm}$ to yield T^{-}, indicating that the nature of amines controls the reaction mechanism.[6b] Besides, secondary amines have often been reported to be more reactive than isobasic primary amines.[5e,8b,9,10-14] Thus, we have extended our study to the reactions of **5a-5k** with piperidine to obtain further information on the reaction mechanism. We have also compared the kinetic data obtained in this study with those reported previously for the corresponding reactions with ethylamine to investigate the effect of amine nature on reactivity and reaction mechanism.

Results and Discussion

All of the reactions in this study obeyed pseudo-first-order kinetics in the presence of large excess of piperidine. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation $\ln (A_\infty - A_t) = -k_{obsd}t + C$. The uncertainty in the k_{obsd} values is estimated to be less than 3% from replicate runs. The correlation coefficient for the linear regressions was always higher than 0.9995. The plots of k_{obsd} *vs.* [amine] for the reaction of substrates possessing a strong EWG in the leaving group (*i.e.*, **5a-5i**) are linear and pass through the origin, *e.g.*, Figure 1 (**5a**). In contrast, the plots of k_{obsd} *vs.* [amine] for the reactions of substrates bearing a weak EWG or no substituent (*i.e.*, **5j** or **5k**) curve upward, *e.g.*, Figure 1 (**5k**).

Effect of Leaving-Group Substituent Y on Reaction Mechanism. The fact that the plots of k_{obsd} *vs.* [amine] for the reactions of substrates possessing a strong EWG are linear and pass through the origin indicates that general-base catalysis by piperidine is absent and the contribution of H_2O and/or OH^- from hydrolysis of piperidine to k_{obsd} is negligible. In contrast, the upward curvature shown in Figure 1 (**5k**) implies that piperidine behaves as a general-base catalyst as well as a nucleophile for the reactions of substrates bearing a weak or no substituent (*i.e.*, **5j** or **5k**). Such contrasting plots demonstrate convincingly that the electronic nature of the substituent Y in the leaving group governs the reaction mechanism. Thus, one can suggest that the reactions of **5a-5k** with piperidine proceed through a stepwise mechanism with one or two intermediates depending on the electronic nature of the substituent Y (Scheme 1).

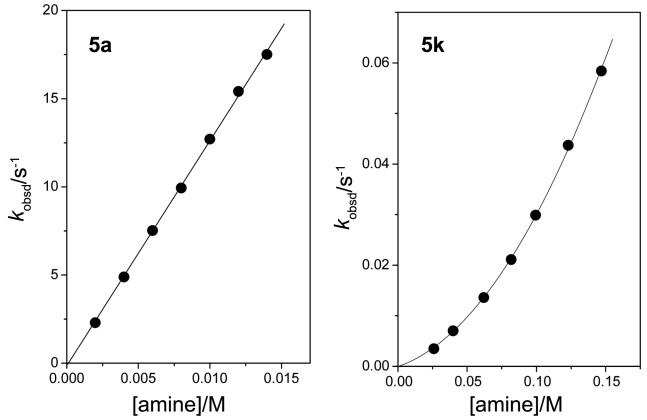
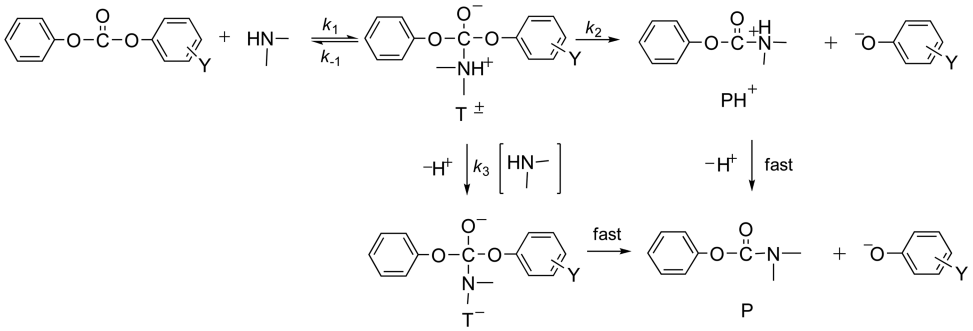


Figure 1. Plots of k_{obsd} *vs.* [amine] for the reaction of 3,4-dinitrophenyl phenyl carbonate (**5a**) and diphenyl carbonate (**5k**) with piperidine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C.

To account for the above idea that the electronic nature of the substituent Y in the leaving group governs the reaction mechanism, a qualitative energy diagram is illustrated in Figure 2 for the processes from $T^{\pm}$ to form PH^+ (*i.e.*, the k_2 process) and T^- (*i.e.*, the k_3 process). It is apparent that the energy barriers to yield PH^+ and T^- from $T^{\pm}$ would be dependent on the nucleofugality of the leaving group and the acidity of the aminium moiety of $T^{\pm}$, respectively. One might expect that the nucleofugality is strongly affected by the electronic nature of the substituent Y, *i.e.*, the energy barrier for the k_2 route would decrease significantly as the substituent Y becomes a stronger EWG or *vice versa*. On the contrary, the energy barrier for the k_3 route would be little



Scheme 1

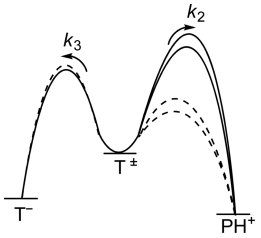


Figure 2. A qualitative energy profile for the processes that yield T^- and PH^+ from $T^{\pm}$.

influenced by the electronic nature of the substituent Y due to the long distance between the substituent Y and the aminium moiety of $T^{\pm}$.

It is evident that the reaction would proceed through the k_2 route when the energy barrier to form PH^+ from $T^{\pm}$ is lower than that to form T^- (*i.e.*, the dashed lines in Figure 2) but through the k_3 route when the energy barrier to form T^- from $T^{\pm}$ is lower than that to form PH^+ (*i.e.*, the solid lines in Figure 2). This idea is consistent with the experimental results that the reactions of substrates possessing a strong EWG (*i.e.*, **5a-5i**) proceed through the k_2 route because a strong EWG in the leaving group decreases the energy barrier for the k_2 route, while those of substrates bearing a weak or no substituent (*i.e.*, **5j** or **5k**) proceed *via* the k_3 route because the energy barrier for the k_2 route increases as the substituent Y becomes a weaker EWG.

Calculations of Rate Constants k_N, Kk_2 and Kk_3. On the basis of the reactions illustrated in Scheme 1, k_{obsd} can be expressed as Eq. (1) for the reactions of **5a-5i**, in which piperidine acts only as a nucleophile. Thus, the second-order rate constants (k_N) have been calculated from the slope of the linear plots of k_{obsd} *vs*. [amine], and are summarized in Table 1. In contrast, Eq. (2) represents the k_{obsd} for the reactions of **5j** and **5k**, in which piperidine behaves as a general-base catalyst as well as a nucleophile. Eq. (2) becomes Eq. (3) under the assumption that $k_{-1} >> k_2 + k_3$[amine]. Thus, one might expect a linear plot of k_{obsd}/[amine] *vs*. [amine] if the assumption is valid.

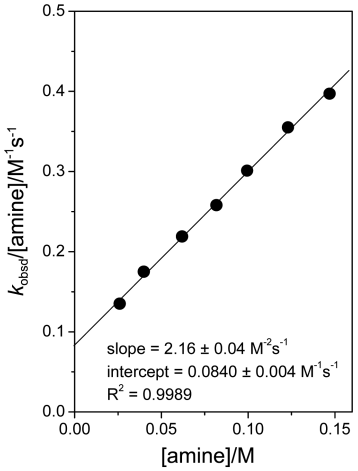


Figure 3. Plot of k_{obsd}/[amine] *vs*. [amine] for the reaction of diphenyl carbonate (**5k**) with piperidine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C.

Table 1. Summary of Kinetic Data for the Reactions of Phenyl Y-Substituted-Phenyl Carbonates (**5a-5k**) with Piperidine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C[a]

	Y	pK_a	k_N/M^{-1}s^{-1}	Kk_2/M^{-1}s^{-1}	Kk_3/M^{-2}s^{-1}
5a	3,4-$(NO_2)_2$	5.42	1280	-	-
5b	4-NO_2	7.14	292	-	-
5c	4-CHO	7.66	92.5	-	-
5d	4-CN	7.95	110	-	-
5e	3-NO_2	8.35	54.1	-	-
5f	4-CO_2Et	8.50	24.9	-	-
5g	3-CHO	8.98	3.87	-	-
5h	3-Cl	9.02	3.95	-	-
5i	3-COMe	9.19	2.09	-	-
5j	4-Cl	9.38	-	0.765	8.82
5k	H	9.95	-	0.0840	2.16

[a]pK_a values were taken from: Jencks, W. P.; Regenstein, J. In *Handbook of Biochemistry*, 2nd ed.; Sober, H. A., Ed.; Chemical Rubber Publishing Co.: Cleveland, OH, 1970; p J-195.

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

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

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

In fact, as shown in Figure 3, the plot of k_{obsd}/[amine] *vs*. [amine] is linear with a large intercept for the reaction of **5k**. A similar result has been observed for the reaction of **5j**, indicating that the assumption that $k_{-1} >> k_2 + k_3$[amine] is valid under the reaction conditions. Thus, the second- and third-order rate constants (*i.e.*, Kk_2 and Kk_3, respectively) have been calculated from the intercept and slope of the linear plot, respectively, and are summarized in Table 1.

Dissection of k_N and Kk_2 into k_1 and k_2/k_{-1}. As shown in Table 1, the rate constants decrease as the leaving-group basicity increases, *e.g.*, k_2 decreases from 1280 M^{-1}s^{-1} to 54.1 and 2.09 M^{-1}s^{-1} as the pK_a of the conjugate acid of the leaving group increases from 5.42 to 8.35 and 9.19, in turn. The effect of leaving-group basicity on the rate constants is illustrated in Figure 4. The Brønsted-type plot for the second-order rate constants k_N or Kk_2 obtained from the reactions of **5a-5k** with piperidine curves downward, indicating that a change in the RDS occurs upon changing the leaving-group basicity. Thus, the nonlinear Brønsted-type plot has been analyzed using a semiempirical equation, Eq. (4),[15] in which β_{lg1} and β_{lg2} represent the slope of the Brønsted-type plot shown in Figure 4 for the weakly basic and strongly basic leaving groups, respectively, while k_N^o refers to the k_N value at pK_a^o (defined as the pK_a at the center of the Brønsted curvature, where $k_2 = k_{-1}$). The β_{lg1}, β_{lg2}, and pK_a^o values determined are –0.41, –1.89, and 8.34, respectively.

$$\log (k_N/k_N^o) = \beta_{lg1}(pK_a - pK_a^o) - \log [(1 + \alpha)/2]$$

$$\text{where } \log \alpha = (\beta_{lg1} - \beta_{lg2})(pK_a - pK_a^o) \quad (4)$$

The microscopic rate constants associated with the reac-

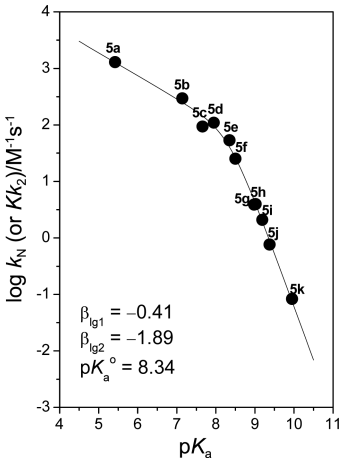


Figure 4. Brønsted-type plot for the reactions of phenyl Y-substituted-phenyl carbonates (**5a-5k**) with piperidine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of the points is given in Table 1.

tions of **5a-5k** with piperidine (*e.g.*, k_2/k_{-1} ratios and k_1 values) have been calculated as follows. Eq. (5) can be simplified to Eqs. (6) and (7). Then, β_{lg1} and β_{lg2} can be expressed as Eqs. (8) and (9), respectively.

$$k_N = k_1k_2/(k_{-1} + k_2) = k_1/(k_{-1}/k_2 + 1) \quad (5)$$

$$k_N = k_1k_2/k_{-1}, \text{ when } k_2 << k_{-1} \quad (6)$$

$$k_N = k_1, \text{ when } k_2 >> k_{-1} \quad (7)$$

$$\beta_{lg1} = d(\log k_1)/d(pK_a) \quad (8)$$

$$\beta_{lg2} = d(\log k_1k_2/k_{-1})/d(pK_a) = \beta_{lg1} + d(\log k_2/k_{-1})/d(pK_a) \quad (9)$$

Eq. (9) can be rearranged as Eq. (10). Integral of Eq. (10) from pK_a^o results in Eq. (11). Since $k_2 = k_{-1}$ at pK_a^o, the term $(\log k_2/k_{-1})_{pKa}^o$ is zero. Therefore, one can calculate the k_2/k_{-1} ratio for the reactions of **5a-5k** with piperidine from Eq. (11) using $\beta_{lg1} = -0.41$, $\beta_{lg2} = -1.89$ and pK_a^o = 8.34. The k_1 values have been determined from Eq. (5) using the k_N values in Table 1 and the k_2/k_{-1} ratios calculated above. The results are summarized in Table 2.

$$\beta_{lg2} - \beta_{lg1} = d(\log k_2/k_{-1}) / d(pK_a) \quad (10)$$

$$(\log k_2/k_{-1})_{pKa} = (\beta_{lg2} - \beta_{lg1})(pK_a - pK_a^o) \quad (11)$$

Table 2. Summary of Kinetic Data for the Reactions of Phenyl Y-Substituted-Phenyl Carbonates (**5a-5k**) with Piperidine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C[a]

	Y	pK_a	k_1/M^{-1}s^{-1}	k_2/k_{-1}
5a	3,4-$(NO_2)_2$	5.42	1280 (223)[b]	21000
5b	4-NO_2	7.14	297 (63.9)[b]	59.7
5c	4-CHO	7.66	102 (23.8)[b]	10.1
5d	4-CN	7.95	139 (33.3)[b]	3.78
5e	3-NO_2	8.35	110 (16.7)[b]	0.966
5f	4-CO_2Et	8.50	67.9 (14.0)[b]	0.580
5g	3-CHO	8.98	38.1 (–)[b]	0.113
5h	3-Cl	9.02	44.0 (7.57)[b]	0.0985
5i	3-COMe	9.19	39.9 (4.91)[b]	0.0552
5j	4-Cl	9.38	27.2 (5.24)[b]	0.0289
5k	H	9.95	20.4 (5.20)[b]	0.00414

[a]pK_a values were taken from: Jencks, W. P.; Regenstein, J. In *Handbook of Biochemistry*, 2nd ed.; Sober, H. A., Ed.; Chemical Rubber Publishing Co.: Cleveland, OH, 1970; p J-195. [b]The data in the parenthesis are the k_1 values for the reactions with ethylamine taken from ref 9.

Effect of Amine Nature on Reactivity. As shown in Table 2, the k_1 value for the reaction with piperidine is larger than that for the corresponding reaction with ethylamine. This is consistent with the reports that primary amines are less reactive than isobasic secondary or tertiary amines, *e.g.*, in the comprehensive investigation by Heo and Bunting for reactions of 72 primary and secondary amines with 1-methyl-4-vinylpyridinium ion,[10] in the recent systematic study by Mayr *et al.* for reactions of benzhydrylium ions,[11] in deprotonation of carbon acids such as nitroethane,[12a] 4-nitrophenyl and 2,4-dinitrophenylacetonitriles,[12b-d] in combination reactions of tris(*p*-anisyl)methyl cation,[13] in nucleophilic displacement reactions of chloramines[14a] and *N*-(4,6-diphenoxy-1,3,5-triazine-2-yl) pyridinium ion.[14b] We have also shown that primary amines are less reactive in aminolysis of 2,4-dinitrophenyl benzoate[5e] and benzenesulfonate.[8b] Solvent effect has been suggested to be responsible for the low reactivity shown by primary amines, since solvation energy increases in the order $R_3NH^+ < R_2NH_2^+ < RNH_3^+$.[16,17] However, we have shown that secondary amines exhibit larger k_1 values than isobasic primary amines from dissection of the apparent second-order rate constants (*i.e.*, k_N) for the reactions of 4-nitrophenyl phenyl carbonate with a series of primary and secondary amines into the microscopic rate constants (*i.e.*, k_1 and k_2/k_{-1}).[18]

The effect of leaving-group basicity on the k_1 values for the reactions with piperidine is illustrated in Figure 5. The Brønsted-type plot for the corresponding reactions with ethylamine is also demonstrated for comparison. Figure 5 shows that the Brønsted-type plots are linear with $\beta_{lg} = -0.41$ and –0.40 for the reactions with piperidine and ethylamine,

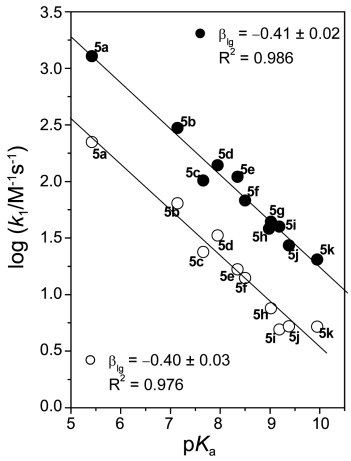


Figure 5. Brønsted-type plot for the reactions of phenyl Y-substituted-phenyl carbonates (**5a-5k**) with piperidine (●) and ethylamine (○) in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of the points is given in Table 2.

respectively. This indicates that the reactions with piperidine and ethylamine proceed through similar TS structures, although piperidine exhibits much larger k_1 values than ethylamine. Thus, one can suggest that the higher reactivity shown by piperidine (a secondary amine) compared with ethylamine (a primary amine) is not due to any difference in the reaction mechanism (or TS structures) but is due to the fact that the secondary amine results in larger k_1 values than the primary amine. This is consistent with our previous report that secondary amines exhibit larger k_1 values than isobasic primary amines.[18] Thus, one can suggest that secondary amines are more nucleophilic than isobasic primary amines.

Conclusions

The kinetic study on the reactions of **5a-5k** with piperidine has allowed us to conclude the following: (1) The reactions proceed through a stepwise mechanism with one or two intermediates depending on the electronic nature of the substituent Y in the leaving group, *i.e*., the reactions of substrates possessing a strong EWG in the leaving group (*i.e*., **5a-5i**) proceed through the k_2 route with $T^{\pm}$, while those of substrates bearing a weak EWG or no substituent (*i.e*., **5j** or **5k**) proceed through the k_3 route with $T^{\pm}$ and T^{-}. (2) The electronic nature of the substituent Y in the leaving group governs the reaction mechanism by increasing or decreasing the energy barrier for the k_2 route. (3) The Brønsted-type plot for the second-order rate constants k_N or Kk_2 curves downward with $\beta_{lg1} = -0.41$, $\beta_{lg2} = -1.89$ and $pK_a^o = 8.34$, indicating that a change in the RDS occurs at $pK_a = 8.34$. (4) The Brønsted-type plots for the k_1 values obtained from the reactions with piperidine and ethylamine are linear with $\beta_{lg} = -0.41$ and -0.40, respectively, indicating that both reactions proceed through similar TS structures. (5) Piperidine results in larger k_1 values than ethylamine, which is responsible for the fact that the secondary amine is more reactive than the primary amine toward **5a-5k**.

Experimental Section

Materials. Substrates **5a-5k** were readily prepared from the reactions of phenyl chloroformate with Y-substituted phenol in the presence of triethylamine in anhydrous ether as reported previously.[19] The crude products were purified by column chromatography and the purity was checked by their melting points and ^{1}H NMR spectra. Piperidine and other chemicals were of the highest quality available. Doubly glass distilled water was further boiled and cooled under nitrogen just before use.

Kinetics. The kinetic study was performed with a UV-vis spectrophotometer for slow reactions (*e.g*., $t_{1/2} > 10$ s) or a stopped-flow spectrophotometer for fast reactions (*e.g*., $t_{1/2} \leq 10$ s) equipped with a constant temperature circulating bath at 25.0 ± 0.1 °C. The reactions were followed by monitoring the appearance of Y-substituted phenoxide at a fixed wavelength corresponding to the λ_{max}. All the reactions were carried out under pseudo-first-order conditions in the presence of excess piperidine. Typically, the reaction was initiated by adding 5 μL of a 0.02 M of substrate solution in MeCN by a 10 μL gastight syringe to a 10 mm quarts UV cell containing 2.50 mL of the thermostated reaction mixture made up of solvent and an aliquot of the amine stock solution. The piperidine stock solution of *ca.* 0.2 M was prepared by dissolving 2 equiv. of piperidine and 1 equiv. of standardized HCl solution to make a self-buffered solution. All the solutions were transferred by gastight syringes under nitrogen. Generally, the concentration of piperidine was varied over the range (1–150) × 10^{-3} M, while the substrate concentration was *ca*. 4 × 10^{-5} M. The plots of ln ($A_\infty - A_t$) *vs*. *t* were linear over *ca*. 90% of the total reaction.

References

1. (a) Page, M. I.; Williams, A. *Organic and Bio-organic Mechanisms*; Longman: Singapore, 1997; Chapter 7. (b) Castro, E. A. *Chem. Rev.* **1999**, *99*, 3505-3524. (c) Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511-527. (d) Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345-375. (e) Jencks, W. P. *Acc. Chem. Res*. **1980**, *13*, 161-169.
2. (a) Castro, E. A.; Aliaga, M.; Campodonico, P. R.; Cepeda, M.; Contreras, R.; Santos, J. G. *J. Org. Chem*. **2009**, *74*, 9173-9179. (b) Castro, E. A.; Ramos, M.; Santos, J. G. *J. Org. Chem*. **2009**, *74*, 6374-6377. (c) Castro, E. A. *Pure Appl. Chem.* **2009**, *81*, 685-696. (d) Castro, E. A.; Aliaga, M.; Santos, J. G. *J. Org. Chem.* **2005**, *70*, 2679-2685. (e) Castro, E. A.; Gazitua, M.; Santos, J. G. *J. Org. Chem.* **2005**, *70*, 8088-8092.
3. (a) Menger, F. M.; Smith, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 3824-3829. (b) Maude, A. B.; Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1997**, 179-183. (c) Maude, A. B.; Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1995**, 691-696. (d) Menger, F. M.; Brian, J.; Azov, V. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 2581-2584. (e) Perreux, L.; Loupy, A.; Delmotte, M. *Tetrahedron* **2003**, *59*, 2185-2189. (f) Fife, T. H.; Chauffe, L. *J. Org. Chem*. **2000**, *65*, 3579-3586. (g) Linas, A.; Page, M. I. *Org. Biomol. Chem.* **2004**, *2*, 651-654.
4. (a) Oh, H. K.; Ku, M. H.; Lee, H. W.; Lee, I. *J. Org. Chem*. **2002**, *67*, 8995-8998. (b) Oh, H. K.; Ku, M. H.; Lee, H. W.; Lee, I. *J. Org. Chem*. **2002**, *67*, 3874-3877. (c) Oh, H. K.; Kim, S. K.; Lee, H. W.; Lee, I. *New J. Chem*. **2001**, *25*, 313-317. (d) Oh, H. K.; Kim, S. K.; Cho, I. H.; Lee, H. W.; Lee, I. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2306-2310. (e) Lim, W. M.; Kim, W. K.; Jung, H. J.; Lee, I. *Bull. Korean Chem. Soc*. **1995**, *16*, 252-256.
5. (a) Um, I. H.; Bae, A. R. *J. Org. Chem.* **2012**, *77*, 5781-5787. (b) Um, I. H.; Bae, A. R. *J. Org. Chem.* **2011**, *76*, 7510-7515. (c) Um, I. H.; Im, L. R.; Kim, E. H.; Shin, J. H. *Org. Biomol. Chem.* **2010**, *8*, 3801-3806. (d) Um, I. H.; Lee, J. Y.; Ko, S. H.; Bae, S. K. *J. Org. Chem*. **2006**, *71*, 5800-5803. (e) Um, I. H.; Kim, K. H.; Park, H. R.; Fujio, M.; Tsuno, Y. *J. Org. Chem.* **2004**, *69*, 3937-3942. (f) Um, I. H.; Min, J. S.; Ahn, J. A.; Hahn, H. J. *J. Org. Chem.* **2000**, *65*, 5659-5663.
6. (a) Um, I. H.; Hwang, S. J.; Yoon, S. R.; Jeon, S. E.; Bae, S. K. *J. Org. Chem.* **2008**, *73*, 7671-7677. (b) Um, I. H.; Lee, S. E.; Kwon, H. J. *J. Org. Chem.* **2002**, *67*, 8999-9005. (c) Um, I. H.; Kim, E. H.; Lee, J. Y. *J. Org. Chem.* **2009**, *74*, 1212-1217.
7. (a) Um, I. H.; Han, J. Y.; Shin, Y. H. *J. Org. Chem.* **2009**, *74*, 3073-3078. (b) Um, I. H.; Akhtar, K.; Shin, Y. H.; Han, J. Y. *J. Org. Chem.* **2007**, *72*, 3823-3829. (c) Um, I. H.; Park, J. E.; Shin, Y. H. *Org. Biomol. Chem.* **2007**, *5*, 3539-3543. (d) Um, I. H.; Shin, Y. H.; Han, J. Y.; Mishima, M. *J. Org. Chem.* **2006**, *71*, 7715-7720.
8. (a) Um, I. H.; Hong, J. Y.; Seok, J. A. *J. Org. Chem.* **2005**, *70*, 1438-1444. (b) Um, I. H.; Chun, S. M.; Chae, O. M.; Fujio, M.; Tsuno, Y. *J. Org. Chem.* **2004**, *69*, 3166-3172. (c) Um, I. H.; Hong, J. Y.; Kim, J. J.; Chae, O. M.; Bae, S. K. *J. Org. Chem.* **2003**, *68*,

5180-5185.
9. Song, Y. J.; Kim, M. Y.; Um, I. H. *Bull. Korean Chem. Soc.* **2013**, *34*, 1722-1726.
10. Heo, C. K. M.; Bunting, J. W. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2279-2290.
11. Brotzel, F.; Chu, Y. C.; Mayr, H. *J. Org. Chem.* **2007**, *72*, 3679-3688.
12. (a) Gregory, M. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1967**, *89*, 2327-2330. (b) Bernasconi, C. F.; Hibdon, S. A. *J. Am. Chem. Soc.* **1983**, *105*, 4343-4348. (c) Bernasconi, C. F.; Perea-Loenzo, M.; Brown, S. D. *J. Org. Chem.* **2007**, *72*, 4416-4423.
13. Bunton, C. A.; Huang, S. K. *J. Am. Chem. Soc.* **1974**, *96*, 515-522.
14. (a) Yagil, G.; Anbar, M. *J. Am. Chem. Soc.* **1962**, *84*, 1797-1803. (b) Cullum, N. R.; Rettura, D.; Whitmore, J. M. J.; Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1559-1564.
15. Gresser, M.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963-6970.
16. (a) Gregory, M. J.; Bruice, T. C. *J. Am. Chem. Soc*. **1967**, *89*, 2327-2330. (b) Bruice, T. C.; Donzel, A.; Huffman, R. W.; Butler, A. R. *J. Am. Chem. Soc*. **1967**, *89*, 2106-2121.
17. (a) Bernasconi, C. F.; Hibdon, S. A. *J. Am. Chem. Soc*. **1983**, *105*, 4343-4348. (b) Bernasconi, C. F.; Perez-Lorenzo, M.; Brown, S. D. *J. Org. Chem*. **2007**, *72*, 4416-4423. (c) Spencer, T. A.; Kendall, M. C. R.; Reingold, I. D. *J. Am. Chem. Soc*. **1972**, *94*, 1250-1254.
18. Um, I. H.; Yoon, S. R.; Park, H. R.; Han, H. J. *Org. Biomol. Chem*. **2008**, *6*, 1618-1624.
19. Castro, E. A.; Angel, M.; Arellano, D.; Santos, J. G. *J. Org. Chem*. **2001**, *66*, 6571-6575.