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Electronic Nature of Substituent X Governs Reaction Mechanism in Aminolysis of 4-Pyridyl X-Substituted-Benzoates in Acetonitrile

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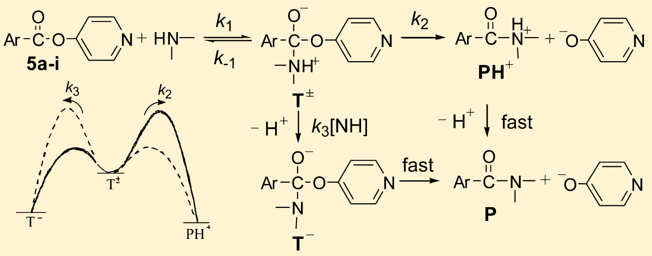
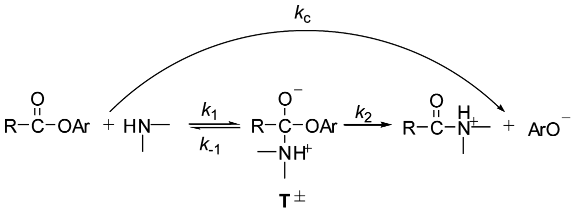
ABSTRACT: A kinetic study is reported for aminolysis of 4-pyridyl X-substituted-benzoates **5a–i**. Plots of pseudo-first-order rate constants (k_{obsd}) vs [amine] curve upward for the reactions of substrates possessing a strong electron-withdrawing group in the benzoyl moiety (**5a–d**) but are linear for the reactions of those bearing an electron-donating group (**5e–i**), indicating that the electronic nature of substituent X governs the reaction mechanism. The k_1k_2/k_{-1} and k_1k_3/k_{-1} values were calculated from the intercept and slope of the linear plots of k_{obsd}/[amine] vs [amine], respectively. The Hammett plot for k_1k_2/k_{-1} consists of two intersecting straight lines, while the Yukawa–Tsuno plot exhibits an excellent linear correlation with $\rho_X = 0.41$ and $r = 1.58$, implying that the nonlinear Hammett plot is not due to a change in rate-determining step but is caused by stabilization of substrates possessing an electron-donating group through resonance interactions. The small ρ_X suggests that the k_2/k_{-1} ratio is little influenced by the nature of substituent X. The Brønsted-type plots for aminolysis of 4-pyridyl 3,5-dinitrobenzoate 5a are linear with $\beta_{nuc} = 0.98$ and 0.79 for k_1k_2/k_{-1} and k_1k_3/k_{-1}, respectively. The effect of amine basicity on the microscopic rate constants is also discussed.



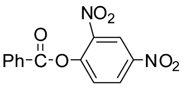
■ INTRODUCTION

Nucleophilic displacement reactions of esters with amines have intensively been investigated because of their importance in biological processes (e.g., enzyme action and peptide biosynthesis) as well as their synthetic applications.[1−11] As shown in Scheme 1, aminolyses of carboxylic esters have been reported to proceed through a stepwise mechanism with a zwitterionic tetrahedral intermediate T± or through a concerted pathway depending on the reaction conditions (e.g., the nature of the reaction medium and the electrophilic center).[1−11]

Scheme 1



Aminolysis of 2,4-dinitrophenyl benzoate **1** in H_2O has been reported to proceed through a stepwise mechanism with a change in the rate-determining step (RDS) on the basis of a curved Brønsted-type plot.[9a] In contrast, the corresponding reaction in MeCN has been suggested to proceed through a concerted mechanism on the basis of a linear Brønsted-type plot with $\beta_{nuc} = 0.40$,[9b] indicating that the nature of solvents governs the reaction mechanism. On the other hand, we have previously shown that aminolysis of *O*-Y-substituted-phenyl thionobenzoates **2** proceeds through a stepwise mechanism with two intermediates (i.e., T± and its deprotonated form T⁻),[10] while the corresponding reactions of Y-substituted-phenyl diphenylphosphinates **3** and diphenylphosphinothioates **4** proceed through a concerted mechanism,[11] implying that the nature of the electrophilic centers (e.g., C=O, C=S, P=O, and P=S) is also an important determinant of the reaction mechanism.



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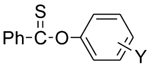

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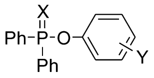

X=O (**3**), S (**4**)

The curved Brønsted-type plot often observed for aminolysis of esters possessing a weakly basic leaving group (e.g., 2,4-dinitrophenoxide) has been taken as evidence for a change in RDS,[6−9] i.e., a change in RDS occurs at $pK_a°$, defined as the pK_a at the center of the Brønsted curvature.[6,7] RDS is now firmly understood to be dependent on the basicity of the incoming amine and the leaving group; i.e., RDS changes from the breakdown of T± to its formation as the incoming amine becomes more basic than the leaving group by 4−5 pK_a units.[6−9] However, the effect of nonleaving-group substituents on $pK_a°$ is controversial. Gresser and Jencks have reported that

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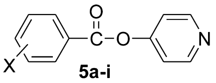
the pK_a^o for the reactions of X-substituted-phenyl 2,4-dinitrophenyl carbonates with quinuclidine increases as the substituent X changes from an electron-donating group (EDG) to an electron-withdrawing group (EWG).[6] Similar results have been reported by Castro et al. for pyridinolysis of 2,4-dinitrophenyl X-substituted-benzoates[7a−c] and aminolysis of S-2,4-dinitrophenyl X-substituted-thiobenzoates,[7d−g] and by Lee et al. for pyridinolysis of aryl dithiobenzoates[8a−d] and theoretical calculations on phenolysis of aryl acetates.[8e] Thus, it has been concluded that an EWG in the nonleaving group increases pK_a^o by decreasing the k_2/k_{-1} ratio since this EWG would decrease the rate of leaving-group departure from $T^{\pm}$ (i.e., a decrease in k_2).[6−8]

In contrast, we have previously proposed that expulsion of the nucleofuges from $T^{\pm}$ (i.e., the k_2 and k_{-1} processes) is retarded by an EWG but accelerated by an EDG.[12,13] This is because the nucleofuges depart from $T^{\pm}$ with the bonding electrons. Accordingly, the k_2/k_{-1} ratio has been suggested to be independent of the electronic nature of the nonleaving-group substituents. In fact, we have previously shown that the k_2/k_{-1} ratio is little influenced by the electronic nature of the substituent X for aminolyses of aryl X-substituted-benzoates[12a] and 2,4-dinitrophenyl X-substituted-benzenesulfonates.[12b]

We have now extended our study to the reaction of 4-pyridyl X-substituted-benzoates **5a−i** with a series of alicyclic secondary amines in MeCN to further elucidate the reaction mechanism including the microscopic rate constants associated with the reaction. We wish to report that (1) the electronic nature of the substituent X in the benzoyl moiety governs the reaction mechanism but does not affect the k_2/k_{-1} ratio, (2) the basicity of amines influences k_2 through an inductive effect, and (3) deductions of the reaction mechanism based solely on a linear or nonlinear Hammett plot can be misleading.


5a-i

X = 3,5-$(NO_2)_2$ (**a**), 4-NO_2 (**b**), 3-NO_2 (**c**), 4-CN (**d**), 4-Cl (**e**), H (**f**), 4-Me (**g**), 4-MeO (**h**), 4-Me_2N (**i**).

■ RESULTS AND DISCUSSION

The kinetic study was performed spectrophotometrically by monitoring the appearance of the leaving 4-pyridyloxide under pseudo-first-order conditions (e.g., the concentration of amines was kept in excess over that of substrates **5a−i**). All reactions obeyed first-order kinetics, and the pseudo-first-order rate constants (k_{obsd}) were calculated from the following equation: $\ln (A_\infty - A_t) = -k_{obsd}t + C$. From replicate runs, the uncertainty in the rate constants is estimated to be less than ±3%. The plot of k_{obsd} vs [amine] curves upward for the reaction of 4-pyridyl 3,5-dinitrobenzoate **5a** with piperidine as shown in Figure 1A. Similarly curved plots are shown in Figures S1A−S3A (Supporting Information (SI)) for the reactions of substrates possessing a strong EWG (e.g., **5b−d**) with piperidine and in Figures S4A−S7A (SI) for those of **5a** with the other amines used in this study. In contrast, the plots for the reactions of substrates possessing a weak EWG or an EDG (e.g., **5e−i**) with piperidine were linear and passed through the origin (Figures S8−S12 (SI)). Detailed kinetic conditions and data are summarized in Tables S1−S13 (SI).

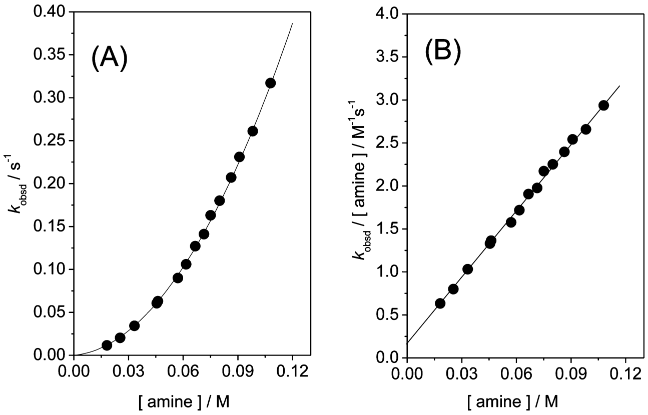


Figure 1. Plots of k_{obsd} vs [amine] (A) and k_{obsd}/[amine] vs [amine] (B) for the reaction of 4-pyridyl 3,5-dinitrobenzoate **5a** with piperidine in MeCN at 25.0 ± 0.1 °C.

Effect of Substituent X on Reaction Mechanism. As shown in Figure 1A, the plot of k_{obsd} vs [amine] for the reaction of **5a** with piperidine curves upward. Similarly curved plots are shown in Figures S1A−S3A (SI) for the reactions of **5b−d** with piperidine. Such a curved plot is typical for reactions in which a second amine molecule behaves as a general base catalyst.[5a,10] Thus, one might suggest that the reactions of **5a−d** proceed through a stepwise mechanism with two intermediates, $T^{\pm}$ and its deprotonated form T^-, as shown in Scheme 2. In contrast, the reactions of substrates possessing a weak EWG or an EDG in the benzoyl moiety (e.g., **5e−i**) resulted in linear plots of k_{obsd} vs [amine] (Figures S8−S12 (SI)), indicating that the deprotonation process from $T^{\pm}$ to yield T^- is absent. This demonstrates convincingly that the electronic nature of substituent X in the nonleaving group governs the reaction mechanism.

One can express k_{obsd} for the reactions of **5a−d** as eq 1 on the basis of the kinetic results and the mechanism proposed in Scheme 2. Eq 1 can be simplified as eq 2 under the assumption $k_{-1} \gg k_2 + k_3[\text{amine}]$. Accordingly, the plot of k_{obsd}/[amine] vs [amine] is expected to be linear if the above assumption is valid.

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

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

In fact, as shown in Figure 1B, the plot of k_{obsd}/[amine] vs. [amine] is linear for the reaction of **5a**. The corresponding plots for the reactions of **5b−d** are also linear as shown in Figures S1B−S3B (SI), thereby validating the assumption $k_{-1} \gg k_2 + k_3[\text{amine}]$. Accordingly, k_1k_2/k_{-1} and k_1k_3/k_{-1} values for the reactions of **5a−d** were calculated from the intercept and the slope of the linear plots of k_{obsd}/[amine] vs [amine], respectively, and are summarized in Table 1. Since the deprotonation process from $T^{\pm}$ to yield T^- (i.e., the k_3 process) is absent for the reactions of **5e−i**, the second-order rate constants k_1k_2/k_{-1} for the reactions of **5e−i** were calculated from the slope of the linear plots of k_{obsd} vs [amine]. As shown in Table 1, k_1k_2/k_{-1} decreases as the substituent X changes from a strong EWG to a strong EDG; e.g., it decreases from 1.54×10^{-1} M^{-1} s^{-1} to 3.51×10^{-2} and 3.23×10^{-3} M^{-1} s^{-1} as the substituent X changes from 3,5-$(NO_2)_2$ to H and 4-Me_2N, in turn. A similar result is shown for k_1k_3/k_{-1}, although the

Scheme 2

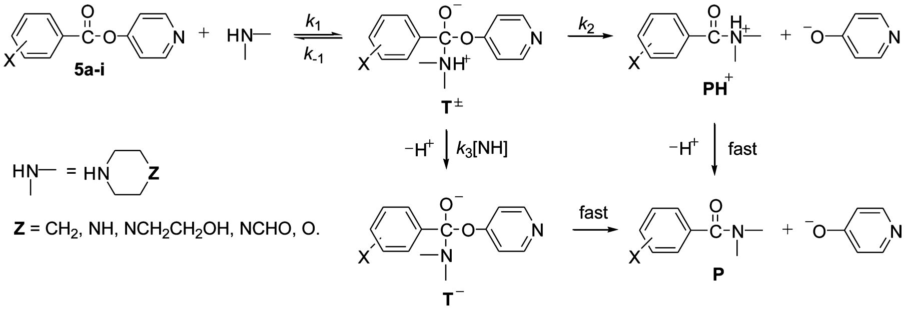


Table 1. Summary of the Second- (k_1k_2/k_{-1}) and the Third- (k_1k_3/k_{-1}) Order Rate Constants for the Reactions of 4-Pyridyl X-Substituted-Benzoates 5a−i with Piperidine in MeCN at 25.0 ± 0.1 °C

entry	X	k_1k_2/k_{-1} (M^{-1} s^{-1})	k_1k_3/k_{-1} (M^{-2} s^{-1})
5a	3,5-$(NO_2)_2$	0.154	25.9
5b	4-NO_2	0.0642	1.10
5c	3-NO_2	0.0740	0.699
5d	4-CN	0.0562	0.499
5e	4-Cl	0.0436	
5f	H	0.0351	
5g	4-Me	0.0232	
5h	4-MeO	0.0149	
5i	4-Me_2N	0.00323	

third-order rate constants are much larger than the second-order rate constants.

To account for our finding that the electronic nature of the substituent X governs the reaction mechanism, a qualitative energy profile for the processes that yield T^- and PH^+ from $T^\pm$ is demonstrated in Figure 2. The reaction would proceed through the deprotonation process (i.e., the k_3 process) when the energy barrier to form T^- from $T^\pm$ is lower than that to form PH^+ (i.e., the solid line) but through the k_2 process when the energy barrier to form PH^+ from $T^\pm$ is lower than that to form T^- (i.e., the dotted line).

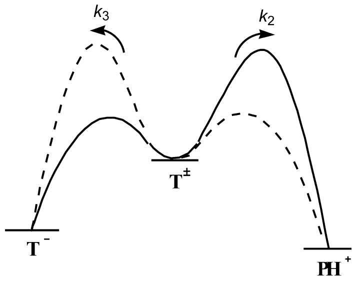


Figure 2. A qualitative energy profile for the processes that yield T^- and PH^+ from $T^\pm$.

The energy barrier for the k_2 and k_3 processes in the current system would be affected by the electronic nature of the substituent X in the benzoyl moiety. An EWG would be expected to lower the energy barrier to form T^- from $T^\pm$ by increasing the acidity of the aminium moiety but to raise the energy barrier to form PH^+ by decreasing the electron density of the reaction center. On the contrary, an EDG would raise the energy barrier to form T^- from $T^\pm$ but would lower the energy barrier to form PH^+ from $T^\pm$. Accordingly, one might expect that the reactions of substrates possessing an EWG proceed through the k_3 process, while the reactions of those bearing an EDG proceed through the k_2 process. This idea is consistent with the fact that the reactions of **5a−d** proceed through the deprotonation process from $T^\pm$ to yield T^-, while those of **5e−i** proceed without the deprotonation process.

Change in RDS vs Ground-State Stabilization. The effect of the substituent X on the second-order rate constant (i.e., k_1k_2/k_{-1}) is illustrated in Figure 3. The Hammett plot for the reactions of **5a−i** with piperidine consists of two intersecting straight lines; i.e., the ρ_X changes from 0.44 to 1.26 as the substituent X changes from EWGs to EDGs. Such a nonlinear Hammett plot has traditionally been interpreted as a change in RDS upon changing substituents.[1c,14] In fact, Jencks et al. have attributed the curved Hammett plot found in the reactions of X-substituted benzaldehydes with semicarbazide in a weakly acidic medium (pH = 3.9) to a change in RDS.[1c] Thus, one might suggest that the nonlinear Hammett plot shown in Figure 2 is due to a change in RDS. This appears to be reasonable since an EWG in the benzoyl moiety would accelerate the rate of nucleophilic attack (i.e., an increase in k_1) but retard the expulsion of the leaving group from $T^\pm$ (i.e., a decrease in k_2). On the contrary, an EDG would decrease k_1 but increase k_2. Accordingly, one might suggest that the RDS changes from the k_2 step to the k_1 process as the substituent X changes from EWGs to EDGs.

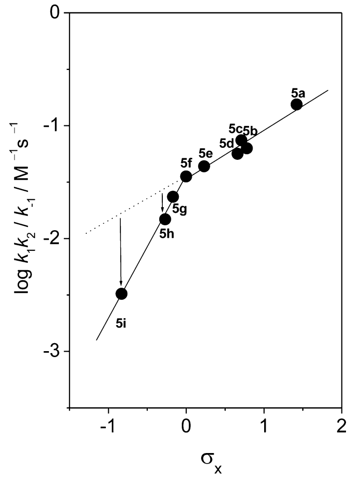
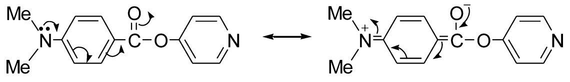


Figure 3. Hammett correlation of k_1k_2/k_{-1} for the reactions of 4-pyridyl X-substituted-benzoates **5a−i** with piperidine in MeCN at 25.0 ± 0.1 °C. The identity of the points is given in Table 1.

However, we propose that the nonlinear Hammett plot is not due to a change in RDS, because the RDS should be determined by the k_2/k_{-1} ratio but not by the magnitude of k_1 and k_2 (i.e., RDS = the k_1 process when $k_2/k_{-1} > 1$, but RDS = the k_2 process when $k_2/k_{-1} < 1$). Furthermore, k_1 and k_2 cannot be compared directly since the former is a second-order rate constant while the latter is a first-order rate constant.

A careful examination of the nonlinear Hammett plot in Figure 3 reveals that the substrates possessing an EDG in the benzoyl moiety (e.g., **5g−i**) deviate negatively from the linear line composed of substrates possessing an EWG (e.g., **5a−f**). Furthermore, the negative deviation is more significant for the substrate possessing a stronger EDG. The substrates possessing an EDG (e.g., **5g−i**) would be stabilized through resonance interactions between the substituent X and the carbonyl functionality as illustrated in the resonance structures I and II. Such resonance interactions would be more significant for the substrate possessing a stronger EDG. Thus, one can suggest that the stabilization of substrates **5g−i** through resonance interactions is responsible for the negative deviation.



I **II**

To examine the above idea, the Yukawa−Tsuno equation (eq 3) has been employed. The *r* value in eq 3 represents the resonance demand of the reaction center or the extent of resonance contribution between the reaction site and the substituent X, while the term $(\sigma_X{}^+ - \sigma_X{}^o)$ is the resonance substituent constant that measures the capacity for π-delocalization of the π-electron donor substituent.[15−17] Eq 3 was originally derived to account for kinetic results obtained from solvolyses of benzylic systems in which a partial positive charge is developing in the transition state.[15] However, we have previously shown that eq 3 is highly effective in clarifying ambiguities in reaction mechanisms for aminolyses of various esters[10−12] and Michael-type additions of amines to activated acetylenes.[18]

$$\log k_X/k_H = \rho_X[\sigma_X{}^o + r(\sigma_X{}^+ - \sigma_X{}^o)] \qquad (3)$$

As shown in Figure 4, the Yukawa−Tsuno plot for the reactions of **5a−i** with piperidine exhibits an excellent linear correlation with $\rho_X = 0.41$ and $r = 1.58$. Such a linear Yukawa−Tsuno plot with a large *r* value confirms that the nonlinear Hammett plot shown in Figure 3 is clearly not due to a change in RDS but rather to the stabilization of the substrates possessing an EDG through resonance interactions as modeled by the resonance structures I and II.

Effect of Substituent X on k_2/k_{-1} and k_3/k_{-1} Ratios. The effect of the substituent X on k_1k_3/k_{-1} for the reactions of **5a−d** is illustrated in Figure 5. The Hammett plot exhibits an excellent correlation with $\rho_X = 2.22$, which is much larger than the ρ_X value of 0.41 found from the Yukawa−Tsuno correlation of k_1k_2/k_{-1} (Figure 4). This is consistent with the reports that ρ_X for k_1k_2/k_{-1} is smaller than that for k_1k_3/k_{-1}. Menger et al. reported that reactions of 4-chlorophenyl X-substituted-benzoates (X = 4-NO_2, 4-Cl, H, 4-Me) with pyrrolidine in MeCN proceed through the deprotonation process from $T^{\pm}$ and that the ρ_X value is much smaller for k_1k_2/k_{-1} than for k_1k_3/k_{-1}, i.e., $\rho_X = 1.01$ and 2.06 for k_1k_2/k_{-1} and k_1k_3/k_{-1}, respectively.[5a] Similarly, Kirsh et al. reported that $\rho_X = 1.08$ and 1.88 for k_1k_2/k_{-1} and k_1k_3/k_{-1}, respectively, for the reactions of 4-chlorophenyl X-substituted-benzoates with NH_3 in H_2O.[5b]

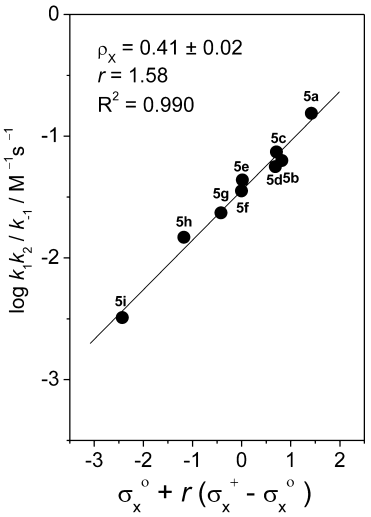


Figure 4. Yukawa−Tsuno correlation of k_1k_2/k_{-1} for the reactions of 4-pyridyl X-substituted-benzoates **5a−i** with piperidine in MeCN at 25.0 ± 0.1 °C. The identity of the points is given in Table 1.

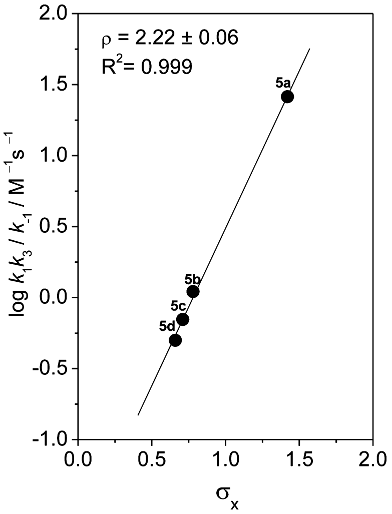


Figure 5. Hammett correlation of k_1k_3/k_{-1} for reactions of 4-pyridyl X-substituted-benzoates **5a−d** with piperidine in MeCN at 25.0 ± 0.1 °C. The identity of the points is given in Table 1.

The effect of the substituent X in the nonleaving group on the k_2/k_{-1} ratio is controversial. The k_2/k_{-1} ratio has been reported to decrease as the substituent X changes from an EDG to an EWG for the reactions of 2,4-dinitrophenyl X-substituted-phenyl carbonates with quinuclidine,[6] for reactions of 2,4-dinitrophenyl X-substituted-benzoates with pyridines,[7a−c] and for reactions of *S*-2,4-dinitrophenyl X-substituted-thiobenzoates with amines.[7d−g] However, we have shown that the k_2/k_{-1} ratio is independent of the electronic nature of the substituent X for aminolyses of aryl X-substituted-benzoates[12a] and 2,4-dinitrophenyl X-substituted-benzenesulfonates.[12b]

It is apparent that the microscopic rate constants k_1, k_{-1}, k_2, and k_3 associated with the current reactions would be influenced by the electronic nature of the substituent X in the benzoyl moiety. As the substituent X changes from an EDG to an EWG, the electrophilicity of the reaction center (i.e., the carbonyl carbon) and the acidity of the aminium moiety of $T^{\pm}$ would increase. Thus, one might expect that k_1 and k_3 increase as the electron-withdrawing ability of the substituent X increases, whereas k_{-1} and k_2 would decrease with increasing the electron-withdrawing ability of the substituent X, since the nucleofuges (i.e., piperidine and 4-pyridyloxide) depart from T$^{\pm}$ with the bonding electrons. Accordingly, the k_2/k_{-1} ratio would be independent of the electronic nature of the substituent X, while the k_3/k_{-1} ratio would increase steeply as the substituent X changes from an EDG to an EWG. This idea is consistent with the result that ρ_X is only 0.41 for k_1k_2/k_{-1} but 2.22 for k_1k_3/k_{-1}.

Effect of Amine Basicity on k_2. To investigate the effect of the amine basicity on the reaction mechanism, reactions of 4-pyridyl 3,5-dinitrobenzoate **5a** with a series of alicyclic secondary amines were performed. As shown in Figures S4A–S7A (SI), the plots of k_{obsd} vs [amine] curve upward for the reactions of **5a** with all the amines studied, indicating that the reaction proceeds through the deprotonation process from T$^{\pm}$ to yield T^{-}. On the other hand, the plots of k_{obsd}/[amine] vs [amine] shown in Figures S4B–S7B (SI) are linear with a positive intercept, implying that $k_{-1} \gg k_2 + k_3$. Thus, the k_1k_2/k_{-1} and k_1k_3/k_{-1}values were calculated from the intercept and slope of the linear plots of k_{obsd}/[amine] vs [amine] and are summarized in Table 2.

Table 2. Summary of the Second- (k_1k_2/k_{-1}) and Third- (k_1k_3/k_{-1}) Order Rate Constants for the Reactions of 4-Pyridyl 3,5-Dinitrobenzoate 5a with Amines in MeCN at 25.0 ± 0.1 °C[a]

entry	amines	pK_a	k_1k_2/k_{-1} (M^{-1} s^{-1})	k_1k_3/k_{-1} (M^{-2} s^{-1})
1	piperidine	18.8	0.154	25.8
2	piperazine	18.5	0.0943	33.5
3	1-(2-hydroxyethyl) piperazine	17.6	0.0132	3.65
4	1-formylpiperazine	17.0	0.00280	0.801
5	morpholine	16.6	0.00112	0.502

[a] The pK_a data in MeCN were taken from ref 19.

As shown in Table 2, k_1k_2/k_{-1} decreases as the basicity of the incoming amine decreases; e.g., it decreases from 0.154 M^{-1} s^{-1} to 0.0132 and 0.00112 M^{-1} s^{-1} as the pK_a of the conjugate acids of amines decreases from 18.8 to 17.6 and 16.6, in turn. A similar result is shown for k_1k_3/k_{-1}, although k_1k_3/k_{-1} is much larger than k_1k_2/k_{-1} for a given amine. The effects of amine basicity on the k_1k_2/k_{-1} and k_1k_3/k_{-1} values are illustrated in Figure 6A and B, respectively. The Brønsted-type plots exhibit excellent linear correlations with $\beta_{nuc} = 0.98$ for k_1k_2/k_{-1} and $\beta_{nuc} = 0.79$ for k_1k_3/k_{-1}, when the rate constants and pK_a values are corrected statistically by p and q (i.e., $p = 2$ while $q = 1$ except $q = 2$ for piperazine).[20] It is noted that k_1k_2/k_{-1} is more sensitive to the amine basicity than k_1k_3/k_{-1}. This is opposite to the preceding result that k_1k_2/k_{-1} is significantly less sensitive to the electronic nature of the substituent X in the benzoyl moiety than k_1k_3/k_{-1}.

It is well-known that k_3 is independent of the amine basicity. It is apparent that a more basic amine would deprotonate more rapidly from the aminium moiety of T$^{\pm}$, while the aminium ion would tend to hold the proton more strongly as the amine becomes more basic. In contrast, the effect of amine basicity on k_2 is not clearly understood. It has been reported that k_2 is independent of the amine basicity. Gresser and Jencks have concluded that amine basicity does not affect k_2 in aminolysis of diaryl carbonates, since there is little or no electron donation from the aminium moiety of T$^{\pm}$ to push out the nucleofuge.[6] A similar conclusion has been drawn by Castro et al. for aminolyses of ethyl phenyl thionocarbonate,[21a] methyl 4-nitrophenyl thionocarbonate,[21b] 4-methylphenyl 4-nitrophenyl thionocarbonate,[21c] and 3-methoxyphenyl 4-nitrophenyl thionocarbonate.[21d] However, we propose that the basicity of amines affects k_2 through an inductive effect, although the "push" by the aminium moiety of T$^{\pm}$ is absent. It is evident that the basicity of the amines used in this study is determined by the "Z" moiety in the cyclic amines (e.g., the pK_a of the conjugate acids of amines decreases from 18.8 to 17.6 and 16.6 as the Z moiety changes from CH_2 to NCH_2CH_2OH and O, in turn). Furthermore, the electronic nature of the Z moiety in the aminium moiety of T$^{\pm}$ would affect the electron density of the reaction site (i.e., the central carbon atom) through an inductive effect, although the effect would not be significant because of the long distance between the Z moiety and the reaction site (Figure 7). Accordingly, k_2 would decrease as the Z moiety changes from CH_2 to an electronegative oxygen atom (or as the amine changes from a strongly basic piperidine to a weakly basic morpholine). This idea is supported by the fact that k_1k_2/k_{-1} is more sensitive than k_1k_3/k_{-1} to the amine basicity (Figure 6A,B).

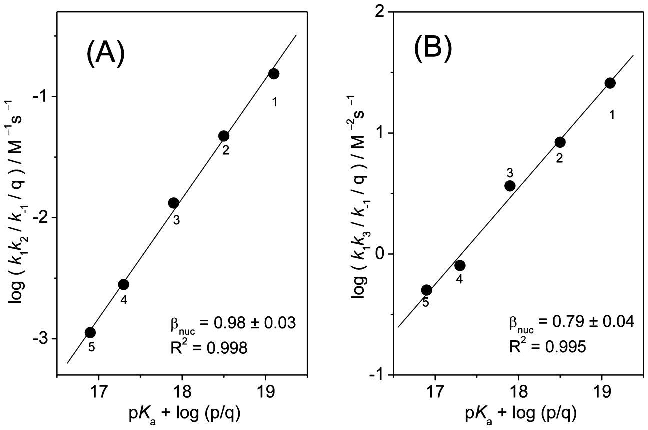


Figure 6. Brønsted-type plots of k_1k_2/k_{-1} (A) and k_1k_3/k_{-1} (B) for reactions of 4-pyridyl 3,5-dinitrobenzoates **5a** with a series of alicyclic secondary amines in MeCN at 25.0 ± 0.1 °C. The identity of the points is given in Table 2.

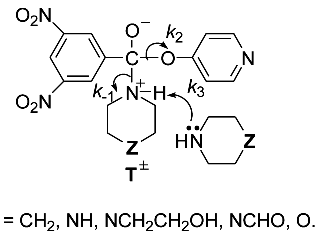


Figure 7. T$^{\pm}$ structure for the reaction of **5a** with alicyclic secondary amines.

■ CONCLUSIONS

The current study has allowed us to conclude the following: (1) The electronic nature of the substituent X in the benzoyl moiety governs the reaction mechanism; i.e., the reactions of substrates possessing a strong EWG proceed through the deprotonation process to form T^{-} from T$^{\pm}$, while the reactions of those bearing a weak EWG or an EDG proceed without the deprotonation process. (2) An EWG increases k_1 and k_3 by increasing the electrophilicity of the reaction center and the acidity of the aminium moiety of $T^{\pm}$, respectively, but decreases k_{-1} and k_2 by decreasing the electron density of the reaction site. (3) The nonlinear Hammett plot for k_1k_2/k_{-1} is not caused by a change in RDS but rather by the stabilization of substrates **5g−i** through resonance interactions in the ground state. (4) The small ρ_X value of 0.41 for k_1k_2/k_{-1}indicates that the k_2/k_{-1} ratio is little influenced by the electronic nature of the substituent X. (5) The electronic nature of the Z moiety in the aminium moiety of $T^{\pm}$ affects k_2 through an inductive effect, although the effect is not significant.

Overall, our study has demonstrated a pitfall in the traditional interpretation of nonlinear Hammett plots and clarified the controversy regarding the effect of the nonleaving-group substituent X on the k_2/k_{-1} ratio as well as the effect of the amine basicity on k_2 values.

■ EXPERIMENTAL SECTION

Materials. Compounds **5a−i** were readily prepared from the reactions of X-substituted-benzoyl chloride with 4-hydroxypyridine in methylene chloride as reported previously.[22] The crude products were purified by column chromatography, and their purity was checked by their melting points and ^{1}H NMR spectra for the known compounds. The identity of the unknown compound (i.e., 4-pyridyl 4-cyanobenzoate **5d**) was checked by elementary analysis and ^{1}H NMR spectrum (Supporting Information). Other chemicals, including the amines, were of the highest quality available.

4-Pyridyl 4-Cyanobenzoate (5d). Data: mp 160−162 °C; ^{1}H NMR characteristics (500 MHz, $CDCl_3$) δ 8.729−8.718 (d, J = 5.5 Hz, 2H), 8.314−8.298 (d, J = 8.0 Hz, 2H), 7.859−7.843 (d, J = 8.0 Hz, 2H), 7.301−7.289 (d, J = 6.0 Hz, 2H); and elemental analysis (Calcd for $C_{13}H_8N_2O_2$: C, 69.64; H, 3.60. Found: C, 69.70; H, 3.58).

Kinetics. Kinetic study was performed using a UV−vis spectrophotometer equipped with a constant-temperature circulating bath. The reactions were followed by monitoring the appearance of 4-pyridyloxide at 292 nm. All the reactions were carried out under pseudo-first-order conditions in which the amine concentration was at least 20 times greater than the substrate concentration. Typically, the reaction was initiated by adding 5 μL of a 0.02 M of substrate stock solution in MeCN by a 10 μL syringe to a 10 mm UV cell containing 2.50−3.00 mL of MeCN and the amine nucleophile. Generally, reactions were followed for 9−10 half-lives, and k_{obsd} values were calculated using the equation, ln $(A_\infty - A_t)$ vs t. The conditions and the k_{obsd} values are summarized in Tables S1−S13 (SI).

Product Analysis. 4-Pyridyloxide and/or its conjugate acid was liberated quantitatively and identified as one of the products by comparison of the UV−vis spectra under the same kinetic conditions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures S1−S12 for plots of k_{obsd} vs [amine] and Tables S1−S13 for the kinetic conditions and data for the reactions of **5b−d** with piperidine and for those of **5a** with the secondary amines. ^{1}H NMR spectra for compound **5d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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