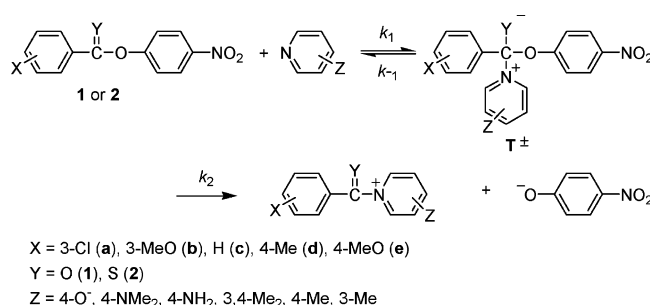# Modification of Both the Electrophilic Center and Substituents on the Nonleaving Group in Pyridinolysis of *O*-4-Nitrophenyl Benzoate and Thionobenzoates

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X = 3-Cl (**a**), 3-MeO (**b**), H (**c**), 4-Me (**d**), 4-MeO (**e**)
Y = O (**1**), S (**2**)
Z = 4-O⁻, 4-NMe₂, 4-NH₂, 3,4-Me₂, 4-Me, 3-Me

A kinetic study is reported for reactions of 4-nitrophenyl benzoate (**1c**) and *O*-4-nitrophenyl X-substituted thionobenzoates (**2a−e**) with a series of pyridines in 80 mol % H₂O/20 mol % dimethyl sulfoxide (DMSO) at 25.0 ± 0.1 °C. *O*-4-Nitrophenyl thionobenzoate (**2c**) is more reactive than its oxygen analogue **1c** toward all the pyridines studied. The Brønsted-type plot is linear with $\beta_{nuc} = 1.06$ for reactions of **1c** but curved for the corresponding reactions of **2c** with β_{nuc} decreasing from 1.38 to 0.38 as the pyridine basicity increases, indicating that the reaction mechanism is also influenced on changing the electrophilic center from C=O to C=S. The curvature center of the curved Brønsted-type plots (defined as pK_a^o) occurs at $pK_a = 9.3$ regardless of the electronic nature of the substituent X in the nonleaving group. The Hammett plot for reactions of **2a−e** with 4-aminopyridine is nonlinear, i.e., the substrates having an electron-donating substituent exhibit negative deviations from the Hammett plot. However, the Yukawa−Tsuno plot for the same reactions exhibits good linear correlation, indicating that the negative deviations shown by these substrates arise from stabilization of the ground state through resonance interaction between the electron-donating substituent X and the C=S bond.

Introduction

Acyl group transfer reactions have been the subject of extensive experimental and theoretical studies due to their importance in biological processes as well as utility in synthetic applications.[1−9] Reactions of carboxylic esters with amines have generally been understood to proceed through a zwitterionic tetrahedral intermediate (T± as shown in Scheme 1); curved Brønsted-type plots have often been observed for reactions of esters that contain a good leaving group, and this behavior has

SCHEME 1
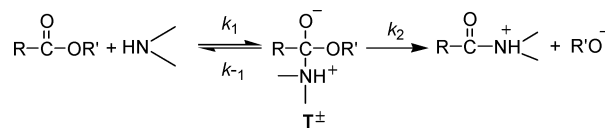
been taken to be diagnostic of a change in the rate-determining step (RDS).[1−5] Recent computational studies also favor a

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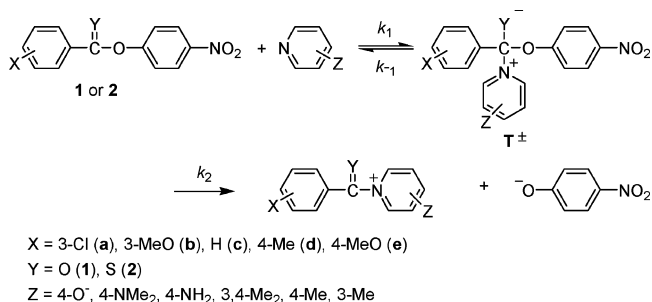
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stepwise mechanism over a concerted pathway, although some studies failed to identify the transition state and $T^{\pm}$ for aminolysis of various carboxylic esters.[6–9]

The curvature center of curved Brønsted plots indicates a change in RDS, and this center was defined as pK_a^o.[10–12] Gresser and Jencks reported that the pK_a^o increases as the substituent in the nonleaving group changes from an electron-donating group (EDG) to an electron-withdrawing group (EWG) for reactions of diaryl carbonates with a series of quinuclidines.[10] This has been rationalized on the basis that departure of the amine from $T^{\pm}$ (i.e., k_{-1} step; Scheme 1) is favored, over that of the leaving group (i.e., k_2 step; Scheme 1), as the substituent in the nonleaving group becomes a stronger EWG.[10] Castro et al. found a comparable result in pyridinolysis of 2,4-dinitrophenyl X-substituted benzoates; hence, $pK_a^o = 9.5$ when X = H but $pK_a^o > 9.5$ when X = 4-Cl, 4-CN, or 4-NO$_2$[11] and similarly for S-2,4-dinitrophenyl X-substituted thiobenzoates in aqueous ethanol, where pK_a^o increases from 8.5 to 8.9 and 9.9 as X is changed from 4-CH$_3$ to H and 4-NO$_2$, in turn.[12] Thus, it has been concluded that changing the substituent in the nonleaving group from an EDG to an EWG results in an increase in pK_a^o by decreasing the k_2/k_{-1} ratio.[10–12]

However, we have shown that the pK_a^o value is independent of the electronic nature of the substituent X in the nonleaving group for aminolysis of 2,4-dinitrophenyl X-substituted benzoates and benzenesulfonates.[13,14] A similar result has recently been found for reactions of Y-substituted phenyl X-substituted benzoates with piperidine.[15] Further, we have shown that the

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SCHEME 2

X = 3-Cl (**a**), 3-MeO (**b**), H (**c**), 4-Me (**d**), 4-MeO (**e**)
Y = O (**1**), S (**2**)
Z = 4-O$^-$, 4-NMe$_2$, 4-NH$_2$, 3,4-Me$_2$, 4-Me, 3-Me

pK_a^o and the k_2/k_{-1} ratio both remain nearly constant even as the substituent X in the benzoyl moiety is progressively modified from an EWG to an EDG.[13–15] The explanation is as follows. The electronic nature of the substituent X in the nonleaving group would be anticipated to influence both the k_2 and k_{-1} values, i.e., an EWG in the nonleaving group would retard the departure of the leaving group (decrease k_2) as well as the amine (also decrease k_{-1}) from $T^{\pm}$, while an EDG in the nonleaving group would accelerate both k_2 and k_{-1} processes since the nucleofuge departs with the bonding electron pair from $T^{\pm}$. Accordingly, one can predict that the k_2/k_{-1} ratio should be independent of the substituent X in the nonleaving group. This argument is consistent with our finding that pK_a^o and the k_2/k_{-1} ratio remain nearly constant on changing the electronic nature of the substituent X for the reactions mentioned above.

To obtain further information about the pK_a^o, we extended our study to reactions of 4-nitrophenyl benzoate (**1c**) and O-4-nitrophenyl X-substituted thionobenzoates (**2a–e**) using a series of pyridines whose pK_a values range from 5.09 to 11.30 (Scheme 2). Replacement of O by a polarizable S atom in the carbonyl bond of **1c** should provide insights into both the reactivity and the comparative reaction mechanism. We probed the effect of modification of the electrophilic center (C=O to C=S) on reactivity, reaction mechanism, and, notably, pK_a^o and report the kinetic results herein. In addition to our Brønsted analysis we analyzed the substituent effects according to the dual-parameter Yukawa–Tsuno equation. This combined approach has previously proven effective in elucidating mechanistic ambiguities in acyl group transfer reactions.

Results and Discussion

Reactions of O-4-nitrophenyl X-substituted thionobenzoates with pyridines proceeded with quantitative liberation of 4-nitrophenoxide (and/or its conjugate acid). The reactions were followed by monitoring the appearance of 4-nitrophenoxide at 410 nm. Kinetic study was performed under pseudo-first-order conditions; the pyridine concentration was always in excess over that of substrate. All reactions obeyed first-order kinetics over 90% of the total reaction. Pseudo-first-order rate constants (k_{obsd}) were determined from the equation $\ln(A_\infty - A_t) = -k_{obsd}t + C$. The plots of k_{obsd} vs the pyridine concentration showed excellent linearity (see Supporting Information for detailed kinetic data). The plots had only small intercept values, indicating that the contribution of H$_2$O or OH$^-$ ion from the hydrolysis of pyridines

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TABLE 1. Summary of Second-Order Rate Constants for Reactions of 4-Nitrophenyl Benzoate, 1c (X = H), and *O*-4-Nitrophenyl X-Substituted Thionobenzoates, 2a (X = 3-Cl), 2c (X = H), and 2e (X = 4-MeO), with Pyridines in 20 mol % DMSO at 25.0 ± 0.1 °C

			$k_N/M^{-1}s^{-1}$			
	Z-pyridine	pK_a	1c	2a	2c	2e
1	Z = 4-O⁻	11.30	32.7	942	296.0	70.4
2	Z = 4-NMe₂	9.12	0.347	67.1	19.2	3.61
3	Z = 4-NH₂	8.93	0.193	26.3	9.23	1.68
4	Z = 3,4-Me₂	5.78	8.36×10^{-5}	1.91×10^{-3}	7.45×10^{-4}	1.82×10^{-4}
5	Z = 4-Me	5.53	4.19×10^{-5}	9.03×10^{-4}	3.50×10^{-4}	5.58×10^{-5}
6	Z = 3-Me	5.09	8.98×10^{-6}	1.66×10^{-4}	7.66×10^{-5}	1.50×10^{-5}

TABLE 2. Summary of Microscopic Rate Constants for Reactions of *O*-4-Nitrophenyl X-Substituted Thionobenzoates, 2a (X = 3-Cl), 2c (X = H), and 2e (X = 4-MeO), with Pyridines in 20 mol % DMSO at 25.0 ± 0.1 °C

		k_2/k_{-1}			$k_1/M^{-1} s^{-1}$		
	Z-pyridine	2a	2c	2e	2a	2c	2e
1	Z = 4-O⁻	110	100	115	951	299	71
2	Z = 4-NMe₂	0.655	0.661	0.653	170	48.3	9.14
3	Z = 4-NH₂	0.419	0.427	0.416	89.0	30.9	5.72
4	Z = 3,4-Me₂	2.57×10^{-4}	3.02×10^{-4}	2.37×10^{-4}	7.44	2.47	0.769
5	Z = 4-Me	1.43×10^{-4}	1.70×10^{-4}	1.31×10^{-4}	6.33	2.06	0.426
6	Z = 3-Me	5.08×10^{-5}	6.17×10^{-5}	4.61×10^{-5}	3.27	1.24	0.325

TABLE 3. Summary of Second-Order Rate Constants (k_N) for Reactions of *O*-4-Nitrophenyl X-Substituted Thionobenzoates (2a−e) with 4-Aminopyridine in 20 mol % DMSO at 25.0 ± 0.1 °C

entry	X	$k_N/M^{-1} s^{-1}$
2a	3-Cl	26.3
2b	3-MeO	11.5
2c	H	9.23
2d	4-Me	4.07
2e	4-MeO	1.68

to k_{obsd} is negligible. The second-order rate constants (k_N) were determined from the slope of these linear plots. Generally five different pyridine concentrations were used to determine k_N values. It is estimated from replicate runs that the uncertainty in the rate constants is less than 3%. Kinetic data are summarized in Tables 1−3.

One of the initial products (i.e., 1-thionobenzoylpyridinium ion or its oxygen analogue) was not isolated but hydrolyzed to yield thiobenzoate (or benzoate for reactions of 1c). Similar pyridinium intermediates have been reported in pyridinolyses of 2,4-dinitrophenyl methyl thionocarbonate, methyl chloroformate, and acetic anhydride.[16,17] Since the pyridinium intermediate in the current reactions does not absorb at 410 nm, where the reactions were monitored, the k_N values obtained are the rate constants for formation of the intermediate and 4-nitrophenoxide ion.

Effect of Replacing C=O by C=S on Reactivity and Mechanism. Table 1 shows that *O*-4-nitrophenyl thionobenzoate (2c) is more reactive than its oxygen analogue 1c. One might expect that replacement of the O atom in the C=O bond of 1c by a polarizable S atom would enhance the electrophilicity of the reactive center by increasing polarizability. This argument is supported by ¹³C NMR spectra as well as the difference in the bond energy between C=O and C=S bonds. Hence, the

chemical shift for the carbon atom of the C=O and C=S bonds in compounds 1c and 2c has been reported to be 163.8 and 209.8 ppm, respectively.[18] Such a large downfield shift suggests that the carbon atom of the C=S bond bears greater positive charge than that of the C=O bond. Besides, it is well known that the overlap between 2p and 3p orbitals that make up the π-bond component of the C=S bond is weaker than that between 2p orbitals in a C=O bond.[19] Thus, the fact that 2c is more reactive than 1c is consistent with the argument that the former would be more electrophilic than the latter.

However, 2c has been reported to be less reactive than 1c toward strongly basic OH⁻ and EtO⁻ ions.[18,20] Similarly, Castro et al. reported that 4-nitrophenyl chlorothionoformate and bis-(4-nitrophenyl) thionocarbonate are less reactive than their oxygen analogues toward aryloxides and alicyclic secondary amines, respectively,[21] indicating that the reactivity of thiono compounds is, at least partly, dependent on the nature of nucleophiles. The contrasting reactivity order is consistent with a hard and soft acids and bases (HSAB) analysis[22] since the softer thiocarbonyl group (relative to carbonyl) would exhibit lower reactivity toward hard bases such as OH⁻, EtO⁻, ArO⁻, and alicyclic secondary amines. On the contrary, pyridines have been suggested to be relatively soft nucleophiles compared to isobasic alicyclic secondary amines.[16a] Thus, the current result that 2c is more reactive than 1c toward pyridines is also in accordance with the HSAB principle.

As shown in Table 1, the k_N value for reactions of 2c with pyridines decreases as the basicity of pyridines decreases, i.e., it decreases from 296 to 9.23 and 7.66×10^{-5} M⁻¹ s⁻¹ as the pK_a of the conjugate acid of pyridines decreases from 11.30 to 8.93 and 5.09. A similar result has been shown for the

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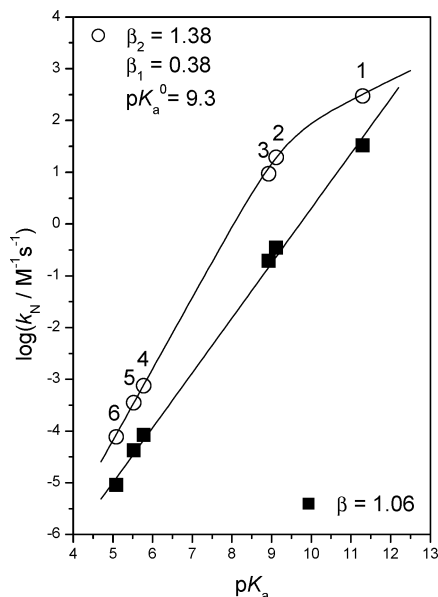(22) Pearson, R. G. *J. Chem. Educ.* **1968**, *45*, 581−587.

FIGURE 1. Brønsted plots for reactions of *O*-4-nitrophenyl thionobenzoate (**2c**, ○) and 4-nitrophenyl benzoate (**1c**, ■) with pyridines in 20 mol % DMSO at 25.0 ± 0.1 °C. The assignment of numbers is given in Table 1.

FIGURE 2. Brønsted plots for reactions of *O*-4-nitrophenyl X-substituted thionobenzoates, **2a** (■), **2c** (○), and **2e**(●), with pyridines in 20 mol % DMSO at 25.0 ± 0.1 °C. The assignment of numbers is given in Table 1.

corresponding reactions of **1c**. The effect of pyridine basicity on reactivity has been illustrated in Figure 1. The Brønsted plot for reactions of **2c** is curved. Such a nonlinear Brønsted plot is typical for reactions which proceed through a stepwise mechanism with a change in the RDS.[1−5] Thus, one can suggest that the pyridinolysis of **2c** proceeds through a zwitterionic tetrahedral intermediate (T$^\pm$) in which the RDS is dependent on the basicity of pyridines as shown in Scheme 2. On the other hand, the Brønsted plot for the corresponding reactions of **1c** is linear with a β_{nuc} value of 1.06. Such a linear Brønsted plot with a large β_{nuc} value indicates that the pyridinolysis of **1c** proceeds through an addition intermediate (T$^\pm$) with its breakdown being the RDS.

The RDS for aminolyses of carboxylic esters has been reported to change from breakdown of T$^\pm$ (the k_2 step) to its formation (the k_1 step) as the amine nucleophile becomes more basic than the leaving group by 4−5 pK_a units.[1−5] Given that the pK_a of 4-nitrophenol in 20 mol % DMSO has been reported to be ca. 7.8,[23] the p$K_a{}^{\circ}$ for the pyridinolysis of **1c** would be expected to occur at a pK_a value between 11.8 and 12.8. Lack of such a strongly basic pyridine precludes observation of a curved Brønsted-type plot for reactions of **1c** with pyridines. On the other hand, the p$K_a{}^{\circ}$ found here in the pyridinolysis of **2c** is 9.3 (Figure 1), only 1.5 pK_a units more basic than the leaving 4-nitrophenoxide ion. Clearly, the generalization that an amine nucleophile be 4−5 pK_a units more basic than the leaving group to effect a change in RDS must be revised for aminolysis of thionobenzoate esters.

Effect of Substituent X on p$K_a{}^{\circ}$. To investigate the effect of the substituent X in the thionobenzoyl moiety on p$K_a{}^{\circ}$, Brønsted-type plots have been constructed for reactions of **2a** (X = 3-Cl), **2c** (X = H), and **2e** (X = 4-MeO) with pyridines. Figure 2 shows that all the Brønsted plots are curved with a similar shape. The curved Brønsted plots have been analyzed
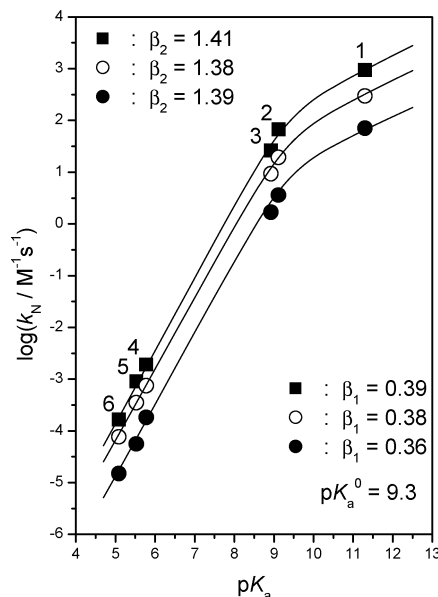
using a semiempirical equation (eq 1)[10,24] on the basis of the proposed mechanism shown in Scheme 2. The parameters β_1 and β_2 represent the slope of the curved Brønsted plots in Figure 2 for reactions with strongly basic and weakly basic pyridines, respectively. Here k_N refers to the k_N value at pK_a where k_2/k_{-1} = 1.

$$\log(k_N/k_N{}^{\circ}) = \beta_2(\mathrm{p}K_a - \mathrm{p}K_a{}^{\circ}) - \log(1 + \alpha)/2$$

where

$$\log \alpha = (\beta_2 - \beta_1)(\mathrm{p}K_a - \mathrm{p}K_a{}^{\circ}) \qquad (1)$$

The β_1 and β_2 values determined for reactions of **2a**, **2c**, and **2e** are shown in Figure 2. Note that the p$K_a{}^{\circ}$ determined is 9.3 *regardless of the nature of the substituent X in the thionobenzoyl moiety*, indicating that the electronic character of the substituent X in the nonleaving group does not influence the p$K_a{}^{\circ}$ value. This contrasts with the finding of Jencks and Castro that an EWG in the nonleaving group increases the p$K_a{}^{\circ}$ value for aminolyses of various esters.[10−12] However, the current result is consistent with our previous report that the p$K_a{}^{\circ}$ and k_2/k_{-1} ratio are independent of the nature of the substituent X in the nonleaving group for aminolysis of aryl X-substituted benzoates and benzenesulfonates.[13,14]

The k_N values for reactions of **2a**, **2c**, and **2e** have been dissected into their microscopic rate constants to further support the argument that the k_2/k_{-1} ratio is independent of the nature of the substituent X. The apparent second-order rate constant k_N can be expressed as eq 2 by applying the steady-state conditions to the intermediate on the basis of the proposed mechanism shown in Scheme 2.

$$k_N = k_1 k_2/(k_{-1} + k_2) \qquad (2)$$

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The k_2/k_{-1} ratios associated with the pyridinolysis of **2a**, **2c**, and **2e** have been determined using eqs 3–8. Equation 2 can be simplified to eq 3 or 4. Then, β_1 and β_2 can be expressed as eqs 5 and 6, respectively.

$$k_N = k_1 k_2/k_{-1}, \text{ when } k_2 \ll k_{-1} \tag{3}$$

$$k_N = k_1, \text{ when } k_2 \gg k_{-1} \tag{4}$$

$$\beta_1 = d(\log k_1)/d(pK_a) \tag{5}$$

$$\beta_2 = d(\log k_1 k_2/k_{-1})/d(pK_a) = \beta_1 + d(\log k_2/k_{-1})/d(pK_a) \tag{6}$$

Equation 6 can be rearranged as eq 7. Integration of eq 7 from pK_a° results in eq 8. Since $k_2 = k_{-1}$ at pK_a°, the term $(\log k_2/k_{-1})_{pK_a^\circ}$ is zero. Therefore, one can calculate the k_2/k_{-1} ratios for the pyridinolysis of **2a**, **2c**, and **2e** from eq 8 using $pK_a^\circ = 9.3$, $\beta_1 = 0.39$, 0.38, and 0.36, and $\beta_2 = 1.41$, 1.38, and 1.39, respectively.

$$\beta_2 - \beta_1 = d(\log k_2/k_{-1})/d(pK_a) \tag{7}$$

$$(\log k_2/k_{-1})_{pK_a} = (\beta_2 - \beta_1)(pK_a - pK_a^\circ) \tag{8}$$

The k_1 values have been determined from eq 9 using the k_N values in Table 1 and the k_2/k_{-1} ratios determined above. The k_2/k_{-1} ratios and k_1 values derived are summarized in Table 2.

$$k_N = k_1 k_2/(k_{-1} + k_2) = k_1 /(k_{-1}/k_2 + 1) \tag{9}$$

As shown in Table 2, the k_2/k_{-1} ratio for reactions of **2a**, **2c**, and **2e** is highly sensitive to the basicity of pyridines, i.e., it decreases significantly as the basicity of pyridines decreases. However, the k_2/k_{-1} ratio is independent of the electronic nature of the substituent X in the nonleaving group, i.e., it remains nearly constant on changing the substituent X from 3-Cl (**2a**) to H (**2c**) or 4-MeO (**2e**) for reaction with a given pyridine. The effect of the substituent X and pyridine basicity on the k_2/k_{-1} ratio is illustrated in Figure 3. The plots of log k_2/k_{-1} vs the pK_a of the conjugate acid of pyridines are linear with a β_{-1} value of ca. 1.0, indicating that the k_2/k_{-1} ratio is highly sensitive to the pyridine basicity. Furthermore, the plots are nearly identical and the pK_a where $k_2/k_{-1} = 1$ (pK_a°) is 9.3 regardless of the nature of the substituent X. Thus, this result clearly supports our preceding proposal that the pK_a° and the k_2/k_{-1} ratio are independent of the electronic nature of the substituent X in the nonleaving group.

Table 2 and Figure 4 show that k_1 increases in tandem with increases in pyridine basicity. The β_1 value is ca. 0.38, which is much smaller than the β_{-1} value of ca. 1.0, indicating that k_1 is much less sensitive than the k_2/k_{-1} ratio to the pyridine basicity. Also, the k_1 value increases as the substituent X changes from an EDG to an EWG. This contrasts with the fact that the k_2/k_{-1} ratio remains nearly constant on changing the substituent X for the reactions with a given pyridine. Thus, one can conclude that the k_1 value determines the reactivity of **2a–e** toward pyridines.

Effect of Nonleaving Group Substituent on Mechanism. To investigate the effect of the substituent X in the thionobenzoyl moiety on the reaction mechanism, reactions of **2a–e** with 4-aminopyridine have been performed. The k_N values determined are summarized in Table 3.

It can be seen in Table 3 that the k_N value increases as the substituent X in the thionobenzoyl group changes from an EDG
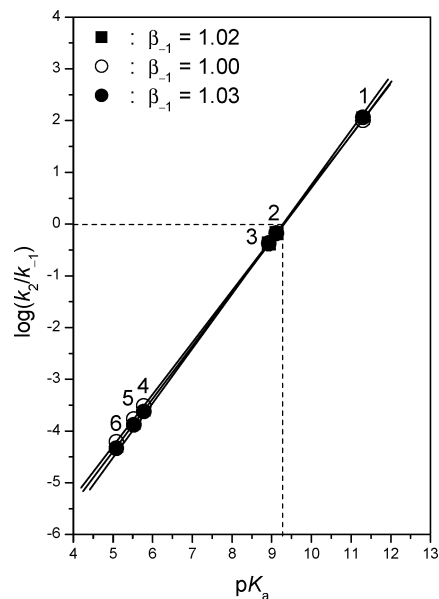

FIGURE 3. Plots of log k_2/k_{-1} vs pK_a for reactions of *O*-4-nitrophenyl X-substituted thionobenzoates, **2a** (■), **2c** (○), and **2e**(●), with pyridines in 20 mol % DMSO at 25.0 ± 0.1 °C. The assignment of numbers is given Table 2.
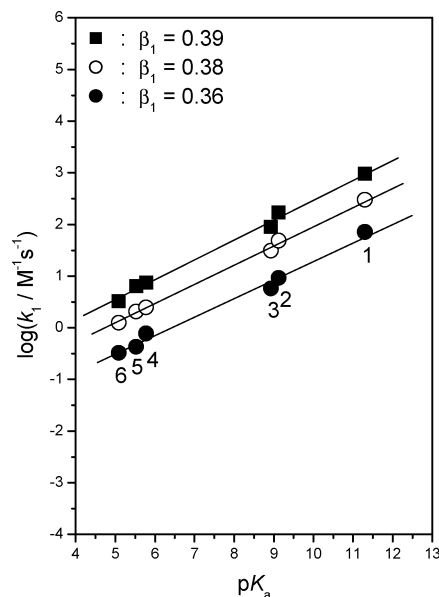

FIGURE 4. Brønsted plots for k_1 for reactions of *O*-4-nitrophenyl X-substituted thionobenzoates, **2a** (■), **2c** (○), and **2e**(●), with pyridines in 20 mol % DMSO at 25.0 ± 0.1 °C. The assignment of numbers is given Table 2.

to an EWG. Recently, Neuvonen et al. reported a similar result, i.e., an EWG in the leaving or nonleaving group of aryl acetates or alkyl benzoates increases the reactivity of the esters along with upfield ^{13}C NMR chemical shifts of the carbonyl carbon and higher frequencies of the C=O stretching vibration. The increased reactivity of esters with a strong EWG, therefore, has been attributed to destabilization of the ground state due to decreased resonance stabilization of the esters as illustrated by resonance structures I ↔ II ↔ III on the basis of the upfield ^{13}C NMR chemical shifts and higher frequencies of the C=O stretching vibration.[25] Thus, one might attribute the higher
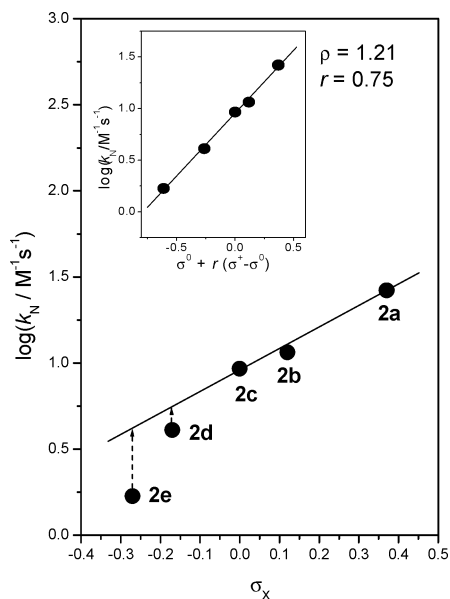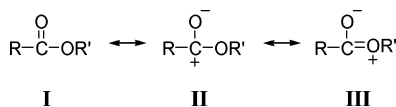
FIGURE 5. Hammett and Yukawa−Tsuno (inset) plots for reactions of *O*-4-nitrophenyl X-substituted thionobenzoates (**2a**−**e**) with 4-aminopyridine in 20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 3.

reactivity of **2a** compared to **2e** to destabilization of the ground state of **2a** as a result of decreased resonance stabilization.

To examine this interpretation, a Hammett plot was constructed for reactions of **2a**−**e** with 4-aminopyridine. If destabilization of the ground state through decreased resonance interaction were responsible for the high reactivity shown by substrates having an EWG in the thionobenzoyl moiety (e.g., **2a** and **2b**), these substrates should give rise to positive deviations from the Hammett plot. As shown in Figure 5, the Hammett plot is nonlinear. Notably, substrates **2a** and **2b** do not exhibit positive deviations, but rather **2a**, **2b**, and **2c** define the Hammett correlation and **2d** and **2e** exhibit negative deviations from this Hammett line. Moreover, the degree of the negative deviation is more significant for the substrate having a stronger EDG (i.e., **2e**). This finding alone suggests that the negative deviation shown by **2d** and **2e** arises from stabilization of the ground state through resonance interaction between the EDG and the thiocarbonyl group as illustrated in the resonance structures IV ↔ V.
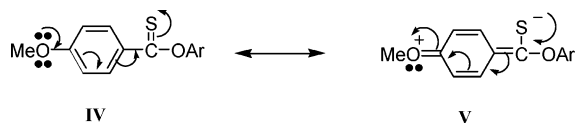

Furthermore, the above argument can be clearly supported from the linear Yukawa−Tsuno plot shown in the inset of Figure 5 for the same reactions. The *r* value in the Yukawa−Tsuno

(25) (a) Neuvonen, H.; Neuvonen, K.; Pasanen, P. *J. Org. Chem.* **2004**, *69*, 3794−3800. (b) Neuvonen, H.; Neuvonen, K.; Koch, A.; Kleinpeter, E.; Pasanen, P. *J. Org. Chem.* **2002**, *67*, 6995−7003. (c) Neuvonen, H.; Neuvonen, K. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1497−1502.

equation (eq 10) represents the resonance demand of the reaction center or the extent of the resonance contribution, while the term $(\sigma^+ - \sigma^\circ)$ is the resonance substituent constant that measures the capacity for π-delocalization of a given π-electron donor substituent.[26,27]

$$\log(k^X/k^H) = \rho \, [\sigma^\circ + r \, (\sigma^+ - \sigma^\circ)] \qquad (10)$$

The Yukawa−Tsuno equation transforms into the Hammett equation when $r = 0$ or into the Brown−Okamoto equation when $r = 1$. Since the *r* value determined (i.e., 0.75) is neither 0 nor 1, the Yukawa−Tsuno plot exhibits much better linear correlation than the Hammett or the Brown−Okamoto plot in which σ or σ^+ constants alone are used. The linear Yukawa−Tsuno plot shown in the inset of Figure 5 yields a relatively large *r* value of 0.75 which indicates that stabilization of the ground state through the resonance interactions (IV ↔ V) is responsible for the negative deviation shown by substrates **2d** and **2e** from the Hammett plot. Therefore, one can conclude that stabilization of the ground state by an EDG through resonance interaction is more important than destabilization of the ground state through decreased resonance interaction by an EWG in governing reactivity of esters. A similar conclusion has been drawn for solvolysis of methyl chloroformate and acetyl chloride in aqueous acetone. The former has been reported to be 9×10^3 times less reactive than the latter.[28] Kevill recently concluded that ground-state stabilization through resonance interaction (e.g., VI ↔ V), analogous to that suggested in the current systems, is responsible for the decreased reactivity of methyl chloroformate since such resonance interaction is not possible for acetyl chloride.[29]
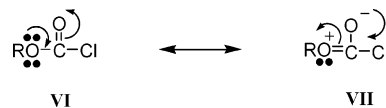
Conclusions

The present study leads to the following conclusions. (1) Modification of the electrophilic center from C=O to C=S (**1c** → **2c**) results in an increase in the reactivity toward pyridines but a significant decrease in the pK_a° value. (2) The k_2/k_{-1} ratio is highly sensitive to the basicity of pyridines but independent of the electronic nature of the substituent X in the nonleaving group, i.e., the k_2/k_{-1} ratio remains nearly constant on changing the substituent X for reactions with a given pyridine. Accordingly, the pK_a° value is not influenced by the electronic nature of the substituent X in the thionobenzoyl moiety. (3) The Hammett plot for reactions of **2a**−**e** with 4-aminopyridine is not linear, i.e., substrates bearing an EDG (e.g., **2d** and **2e**) exhibit negative deviations from the Hammett plot. On the other hand, the Yukawa−Tsuno plot for the same reaction exhibits

(26) (a) Tsuno, Y.; Fujio, M. *Adv. Phys. Org. Chem.* **1999**, *32*, 267−385. (b) Tsuno, Y.; Fujio, M. *Chem. Soc. Rev.* **1996**, *25*, 129−139. (c) Yukawa, Y.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 965−970.
(27) (a) Fujio, M.; Rappoport, Z.; Uddin, M. K.; Kim, H. J.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 163−169. (b) Nakata, K.; Fujio, M.; Nishimoto, K.; Tsuno, Y. *J. Phys. Org. Chem.* **2003**, *16*, 323−335. (c) Uddin, M. K.; Fujio, M.; Kim, H. J.; Rappoport, Z.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1371−1379.
(28) Ugi, I.; Beck, F. *Chem. Ber.* **1961**, *94*, 1839.
(29) (a) Kevill, D. N.; D'Souza, M. J. *J. Org. Chem.* **2004**, *69*, 7044−7050. (b) Kevill, D. N. In *The Chemistry of the Functional Groups. The Chemistry of Acyl Halides*; Patai, S., Ed.; Wiley: New York, 1972; Chapter 12.

excellent linear correlation with an *r* value of 0.75. Thus, stabilization of the ground state through resonance interaction is responsible for the negative deviation shown by **2d** and **2e**.

Experimental Section

Materials. Substrates **2a**−**e** were readily prepared from the reaction of 4-nitrophenol and X-substituted thionobenzoyl chloride in the presence of triethylamine in anhydrous ether as reported previously.[5d−f,30] Their purity was confirmed by their melting points and ^{1}H NMR spectra. Pyridines and other chemicals were of the highest quality available and generally recrystallized or distilled before use. Due to the low solubility of **2a**−**e** in pure H_2O, aqueous DMSO was used as the reaction medium (i.e., 20 mol % DMSO/ 80 mol % H_2O). Doubly glass distilled water was further boiled and cooled under nitrogen just before use.

Kinetics. The kinetic studies were performed at 25.0 ± 0.1 °C with a UV−vis spectrophotometer equipped with a constant temperature circulating bath for slow reactions (e.g., $t_{1/2} \geq 10$ s) or with a stopped-flow spectrophotometer for fast reactions (e.g., $t_{1/2} < 10$ s). The reactions were followed by monitoring the appearance of 4-nitrophenoxide ion at 410 nm (or 4-nitrophenol at 340 nm for reactions with weakly basic pyridines). All reactions were carried out under pseudo-first-order conditions in which the pyridine concentration was at least 20 times greater than that of substrate.

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(30) Campbell, P.; Lapinskas, B. A. *J. Am. Chem. Soc.* **1977**, *99*, 5378− 5382.

Typically, the reaction was initiated by adding 5 μL of a 0.02 M substrate solution in MeCN by a 10 μL syringe into a 10 mm UV cell containing 2.50 mL of the reaction medium and pyridine. The pyridine stock solution of ca. 0.2 M was prepared in a 25.0 mL volumetric flask under nitrogen by adding 2 equiv of pyridine to 1 equiv of standardized HCl solution in order to obtain a self-buffered solution. All transfers of reaction solutions were carried out by means of gastight syringes. The kinetic conditions and results are shown in the Supporting Information.

Products Analysis. The amount of 4-nitrophenoxide (and/or 4-nitrophenol) was determined quantitatively by comparison of the UV−vis spectra after completion of the reactions with those of the authentic samples under the same reaction conditions. Other products, such as 1-thionobenzoylpyridinium ion, were not isolated, but its hydrolyzed product, thiobenzoate, was identified by HPLC.

Supporting Information Available: Tables S1−S18 for the kinetic conditions and data for reactions of **2a**, **2c**, and **2e** with six different pyridines, Tables S19 and S20 for the kinetic data for reactions of **2b** and **2d** with 4-aminopyridine, and Table S21 for the kinetic result for the reaction of **1c** with 4-oxidopyridine. This material is available free of charge via the Internet at http://pubs.acs.org.

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