

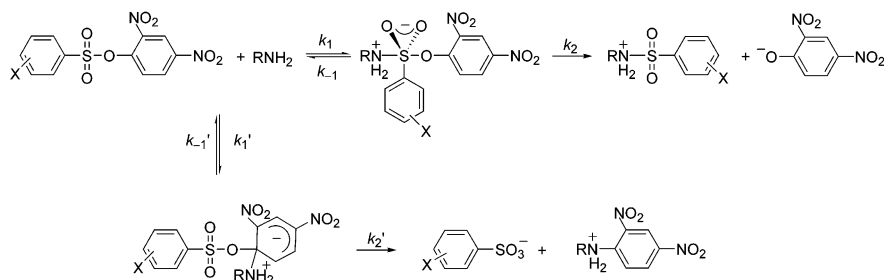
Effect of Substituent on Regioselectivity and Reaction Mechanism in Aminolysis of 2,4-Dinitrophenyl X-Substituted Benzenesulfonates

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We report on a kinetic study for the nucleophilic substitution reactions of 2,4-dinitrophenyl X-substituted benzenesulfonates (X = 4-MeO, **1a**, and X = 4-NO₂, **1c**) with a series of primary amines in 80 mol % H₂O/20 mol % DMSO at 25.0 °C. The reactions proceed through S–O and C–O bond fission pathways competitively. The fraction of the S–O bond fission increases as the attaching amine becomes more basic and the substituent X changes from 4-MeO to 4-NO₂, indicating that the regioselectivity is governed by the electronic nature of the substituent X as well as the basicity of amines. The S–O bond fission has been suggested to proceed through an addition intermediate with a change in the rate-determining step (RDS) at pK_a^o = 8.9 ± 0.1. The electronic nature of the substituent X influences k_N^{S–O} and k₁ values, but not the k₂/k₋₁ ratios and the pK_a^o value significantly. Stabilization of the ground state (GS) through resonance interaction between the electron-donating substituent and the electrophilic center has been suggested to be responsible for the decreased reactivity of **1a** compared to **1c**. The second-order rate constants for the C–O bond fission exhibit no correlation with the electronic nature of the substituent X. The distance effect and the nature of the reaction mechanism have been suggested to be responsible for the absence of the correlation.

Introduction

Nucleophilic substitution reactions of carbon-, phosphorus-, and sulfur-centered esters have been the subject of extensive experimental^{1–12} and theoretical studies.^{13–16} Aminolysis of esters has been suggested to proceed either in a stepwise manner with one or two intermediates or concertedly without an intermediate.^{1–16} Although some computational results failed to identify the transition

state (TS) and the zwitterionic intermediate for aminolysis of various carboxylic esters, recent computational studies favor a stepwise mechanism over a concerted pathway.^{14–16} Curved Brønsted-type plots, which have often been obtained for aminolysis of carboxylic esters with a good leaving group, also support a stepwise mechanism.^{1–4} Thus, it is now firmly established that reactions of esters with amines proceed in a stepwise manner with a change in the RDS at pK_a^o, which has been defined as the pK_a value at the center of the curvature of a curved Brønsted-type plot.^{1–4,7–12}

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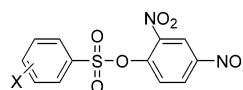
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Jencks et al. have found that the pK_a° value increases as the nonleaving phenoxy moiety becomes less basic (more electron-withdrawing) in the reactions of X-substituted phenyl 3,4-dinitrophenyl carbonates with quinuclidines.¹⁷ A similar result has been reported by Castro et al. for the pyridinolysis of 2,4-dinitrophenyl X-substituted benzoates (X = H, 4-Cl, and 4-NO₂): $pK_a^\circ = 9.5$ when X = H, but $pK_a^\circ > 9.5$ when X = 4-Cl and 4-NO₂.¹⁸ More recently, the pK_a° value for the aminolysis of S-4-nitrophenyl X-substituted thiobenzoates has been shown to increase from 10.0 to 10.4 and >11 as the substituent in the nonleaving group X changes from H to 4-Cl and

4-NO₂, respectively, in the reaction with alicyclic secondary amines,^{19a} and $pK_a^\circ = 9.7$ when X = H but $pK_a^\circ > 9.7$ when X = 4-Cl and 4-NO₂ in the reaction with pyridines.^{19b}

An electron-withdrawing group (EWG) in the nonleaving group has been suggested to favor amine expulsion (k_{-1}) from the zwitterionic intermediate relative to the leaving group departure (k_2).^{17–19} Accordingly, Jencks and Castro et al. have proposed that the k_2/k_{-1} ratio decreases on changing the substituent in the nonleaving group from an EDG to an EWG, and the decrease in the k_2/k_{-1} ratio is responsible for the increase in the pK_a° value.^{17–19} However, we have shown that the k_2/k_{-1} ratio and pK_a° value are not influenced significantly by changing the substituent in the nonleaving group from a strong electron-donating group (EDG) to a strong EWG in the reactions of 2,4-dinitrophenyl X-substituted benzoates with a series of primary and alicyclic secondary amines.^{4a,20}



1a, X = 4-MeO; **1b**, X = H; **1c**, X = 4-NO₂

We have recently performed a kinetic study for the reactions of 2,4-dinitrophenyl benzenesulfonate (**1b**) with a series of primary and secondary amines, and found that the nature of amines (e.g., primary vs secondary amines) does not influence the pK_a° value and k_2/k_{-1} ratio significantly.^{11a,b} To obtain more information about the reaction mechanism, we have extended our kinetic study to the reactions of 2,4-dinitrophenyl X-substituted benzenesulfonates (X = 4-MeO, **1a**, and X = 4-NO₂, **1c**) with 10 different primary amines in 80 mol % H₂O/20 mol % DMSO. We report the electronic effect of the substituent X on regioselectivity, rate, and mechanism, including the k_2/k_{-1} ratio and pK_a° value by comparing the kinetic data for the reactions of **1a** and **1c** in this study with those reported previously for the corresponding reaction of **1b**.

Results and Discussion

The reactions of **1a** and **1c** with primary amines proceed through S–O and C–O bond fission pathways competitively as shown in Scheme 1. The fractions of the S–O bond fission are summarized in Table 1. The S–O bond fission that leads to formation of 2,4-dinitrophenoxide ion and substituted benzenesulfonamides was found to occur exclusively in the reactions of **1b** and **1c** with strongly basic amines. On the other hand, the C–O bond fission that yields substituted anilines and benzenesulfonates was found to occur considerably in the reactions of **1a** with weakly basic amines, indicating that the regioselectivity is governed by the basicity of amines as well as the electronic nature of the substituent X in the sulfonyl moiety.

All the reactions studied in this work obeyed pseudo-first-order kinetics under excess amine over 90% of the

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SCHEME 1

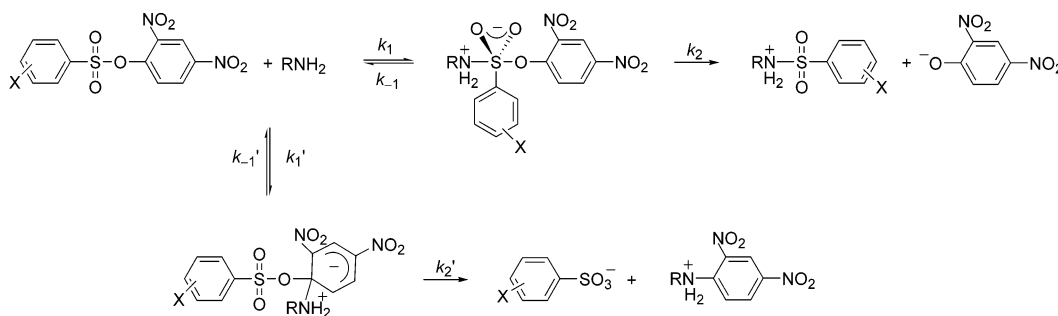


TABLE 1. Summary of Second-Order Rate Constants for the S–O Bond Fission in the Reaction of 1a–c with Primary Amines in 80 Mol % H₂O/20 Mol % DMSO at 25.0 ± 0.1 °C^a

no.	amine	pK _a ^b	10 ³ × k _N ^{S-O} (M ⁻¹ s ⁻¹)		
			1a	1b ^c	1c
1.	ethylamine	10.67	312 (0.94)	1290 (1.00)	10500 (1.00)
2.	propylamine	10.89	297 (0.96)	1050 (1.00)	8610 (1.00)
3.	ethylenediamine	10.32	241 (0.93)	832 (1.00)	5960 (1.00)
4.	glycine	10.06	158 (0.93)	555 (1.00)	3830 (1.00)
5.	ethanolamine	9.67	90.5 (0.91)	312 (1.00)	1860 (1.00)
6.	benzylamine	9.46	83.9 (0.86)	257 (0.99)	1830 (1.00)
7.	glycylglycine	8.51	16.2 (0.84)	43.7 (0.97)	255 (1.00)
8.	glycine ethyl ester	7.68	7.33 (0.76)	19.1 (0.89)	100 (0.99)
9.	1,2-diaminopropane-H ⁺	7.13	5.27 (0.76)	12.7 (0.89)	79.0 (0.97)
10.	trifluoroethylamine	5.70	0.189 (0.67)	0.468 (0.79)	1.86 (0.92)

^a Data in parentheses are the fractions of S–O bond fission. ^b pK_a data in 80 mol % H₂O/20 mol % DMSO were taken from ref 11a. ^c Rate constant data for the reaction of 1b were taken from ref 11a.

total reaction. Pseudo-first-order rate constants (k_{obsd}) were obtained from the equation, $\ln(A_{\infty} - A_t) = -k_{\text{obsd}}t + c$. Correlation coefficients of the linear regressions were usually higher than 0.9995. Generally, five different amine concentrations were used to obtain second-order rate constants from the slope of the linear plot of k_{obsd} vs amine concentration. The plots of k_{obsd} vs amine concentration are linear passing through the origin, indicating that the contribution by H₂O and/or HO⁻ ion from the solvolysis to k_{obsd} is negligible. The second-order rate constant obtained in this way corresponds to the overall second-order rate constant ($k_{\text{N}}^{\text{tot}}$).¹¹ The $k_{\text{N}}^{\text{tot}}$ values obtained in this way are summarized in Table S1 in Supporting Information. The second-order rate constant for the S–O bond fission ($k_{\text{N}}^{\text{S-O}}$) and the one for the C–O bond fission ($k_{\text{N}}^{\text{C-O}}$) were calculated from the following relationships:

$$k_{\text{N}}^{\text{S-O}} = k_{\text{N}}^{\text{tot}} \times \text{the fraction of S-O bond fission} \quad (1)$$

$$k_{\text{N}}^{\text{C-O}} = k_{\text{N}}^{\text{tot}} - k_{\text{N}}^{\text{S-O}} \quad (2)$$

Reaction Mechanism for S–O Bond Fission. As shown in Table 1, the reactivity of amines toward substrate 1a increases with increasing amine basicity for the S–O bond fission process. A similar result has been obtained for the corresponding reactions with 1b and 1c. The effect of amine basicity on rates is illustrated in Figure 1. The statistically corrected Brønsted-type plots

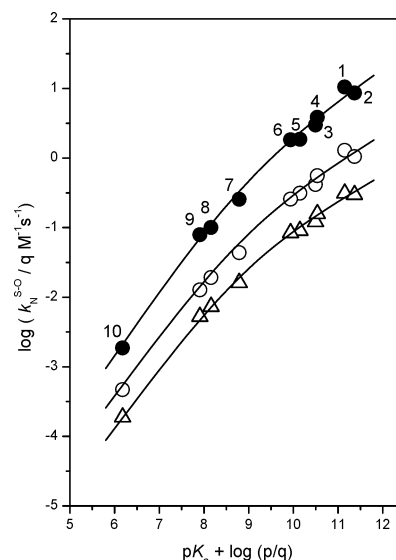


FIGURE 1. Brønsted-type plots for the S–O bond fission in the reactions of 1a (Δ), 1b (○), and 1c (●) with primary amines in 80 mol % H₂O/20 mol % DMSO at 25.0 ± 0.1 °C. The numbers refer to the amines in Table 1. The solid lines were calculated by eq 3.

using p and q ²¹ for the reactions of 1a–c exhibit a downward curvature, e.g., from a large slope ($\beta_2 = 0.86$ – 0.94) to a small one ($\beta_1 = 0.35$ – 0.46) upon increasing the amine basicity. Such a biphasic Brønsted-type plot suggests that the reactions of 1a–c with these amines

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proceed through an addition intermediate with a change in the RDS.

The nonlinear Brønsted-type plots shown in Figure 1 have been analyzed using a semiempirical equation (eq 3)²² on the basis of the proposed mechanism shown in Scheme 1. β_1 and β_2 represent the slope of the Brønsted-type plots in Figure 1 for the reactions with strongly basic and weakly basic amines, respectively. The k_N° refers to the k_N^{S-O} value at pK_a° where $k_2/k_{-1} = 1$.

$$\log(k_N^{S-O}/k_N^\circ) = \beta_2(pK_a - pK_a^\circ) - \log(1 + \alpha)/2$$

where $\log \alpha = (\beta_2 - \beta_1)(pK_a - pK_a^\circ)$ (3)

The β_1 values determined are 0.35, 0.41, and 0.46, while the β_2 values are 0.86, 0.88, and 0.94 for the reactions of **1a**, **1b**, and **1c**, respectively. The magnitude of β_1 and β_2 values for the present study increases as the substituent X in the nonleaving group changes from an EDG to an EWG. However, the β_1 and β_2 values obtained in the present reactions are in agreement with those reported in stepwise aminolyses of various types of carbonyl and sulfonyl esters (e.g., $\beta_1 = 0.3 \pm 0.2$ and $\beta_2 = 0.9 \pm 0.2$).^{1-4,11} Thus, one can suggest that the S–O bond fission in the aminolysis of **1a–c** proceeds through a stepwise mechanism with a change in the RDS.

Effect of Nonleaving Group Substituent on pK_a° and k_2/k_{-1} Ratio for S–O Bond Fission. The pK_a° value has been determined to be 8.9 ± 0.1 for the reactions of **1a–c** regardless of the substituent X, indicating that the electronic nature of the substituent in the nonleaving group does not affect the pK_a° value significantly in the present reactions. This contrasts with the Jencks and Castro's finding that an EWG in the nonleaving group increases the pK_a° value for aminolyses of various esters.¹⁷⁻¹⁹ However, the present result is consistent with our previous report that the pK_a° value for aminolysis of 2,4-dinitrophenyl X-substituted benzoates is independent of the electronic nature of the substituent X in the nonleaving group.²⁰

$$k_N^{S-O} = k_1 k_2 / (k_{-1} + k_2)$$

$$= k_1 / (k_{-1}/k_2 + 1) \quad (4)$$

Dissection of the k_N^{S-O} value into its microscopic rate constants is necessary to investigate the electronic effect of the substituent X on the k_2/k_{-1} ratio as well as pK_a° value for the present aminolysis of **1a–c**. Since the apparent second-order rate constant k_N^{S-O} can be expressed as eq 4 on the basis of the proposed mechanism in Scheme 1, the k_2/k_{-1} ratios associated with the aminolysis of **1a–c** have been determined by the method described in Supporting Information (eqs S1–S6). The k_1 values have been determined from eq 4 using the k_N^{S-O} values in Table 1 and the k_2/k_{-1} ratios determined above. The k_2/k_{-1} ratios and k_1 values determined are summarized in Tables 2 and 3, respectively.

As shown in Table 2, the k_2/k_{-1} ratio increases as the basicity of amines increases, i.e., $k_2/k_{-1} < 1$ for $pK_a \leq 8.51$ and $k_2/k_{-1} > 1$ for $pK_a \geq 9.46$ for the reactions of **1a**.

TABLE 2. Summary of k_2/k_{-1} Ratios for the S–O Bond Fission in the Reaction of **1a–c** with Primary Amines in 80 Mol % H₂O/20 Mol % DMSO at 25.0 ± 0.1 °C

no.	amine	pK_a	k_2/k_{-1}		
			1a	1b^a	1c
1.	ethylamine	10.67	14.0	12.6	12.6
2.	propylamine	10.89	18.1	16.2	16.2
3.	ethylenediamine	10.32	6.52	6.05	6.05
4.	glycine	10.06	6.84	6.34	6.34
5.	ethanolamine	9.67	4.33	4.08	4.08
6.	benzylamine	9.46	3.38	3.22	3.22
7.	glycylglycine	8.51	0.876	0.880	0.880
8.	glycine ethyl ester	7.68	0.418	0.433	0.433
9.	1,2-diaminopropane-H ⁺	7.13	0.312	0.327	0.327
10.	trifluoroethylamine	5.70	0.0409	0.0463	0.0463

^a Data for the reaction of **1b** were taken from ref 11a.

TABLE 3. Summary of k_1 Values for the S–O Bond Fission in the Reaction of **1a–c** with Primary Amines in 80 Mol % H₂O/20 Mol % DMSO at 25.0 ± 0.1 °C

no.	amine	pK_a	$10^3 \times k_1$ (M ⁻¹ s ⁻¹)		
			1a	1b^a	1c
1.	ethylamine	10.67	334	1390	11300
2.	propylamine	10.89	313	1110	9140
3.	ethylenediamine	10.32	278	969	6940
4.	glycine	10.06	181	643	4430
5.	ethanolamine	9.67	111	388	2320
6.	benzylamine	9.46	109	337	2400
7.	glycylglycine	8.51	34.7	93.3	545
8.	glycine ethyl ester	7.68	24.9	63.3	331
9.	1,2-diaminopropane-H ⁺	7.13	22.2	51.6	321
10.	trifluoroethylamine	5.70	4.81	10.6	42.0

^a Data for the reaction of **1b** were taken from ref 11a.

A similar result is obtained for reactions of **1b** and **1c**. This is consistent with the preceding proposal that a change in the RDS occurs at pK_a ca. 8.9 for the reactions of **1a–c**.

The effect of amine basicity on the k_2/k_{-1} ratio has been illustrated in Figure 2. The statistically corrected Brønsted-type plots for the reactions of **1a–c** are linear with a similar slope (e.g., $-\beta_1 = 0.50 \pm 0.01$). The k_2 value has been suggested to be independent of the amine basicity.^{1a,23-25} On the other hand, the k_{-1} value would decrease as the amine basicity increases since an amine becomes a poorer nucleofuge with increasing its basicity. Thus, one can suggest that the decreasing k_{-1} value is mainly responsible for the increasing k_2/k_{-1} ratio as the basicity of amines increases.

Figure 2 demonstrates that the k_2/k_{-1} ratio is almost identical for the reactions of **1a–c**. This result clearly reconfirms our previous proposal that the electronic nature of the substituent X in the nonleaving group does not affect the k_2/k_{-1} ratio significantly for aminolysis of aryl X-substituted benzoates^{4a,20} and for alkaline hydrolysis of aryl X-substituted benzoates and thionobenzoates.^{12a,b}

We have suggested that an EWG in the nonleaving group would decrease both k_2 and k_{-1} values since the nucleofuge departs with the electron pair originally bonded to the remainder of the intermediate.^{4a,12,20} On the contrary, an EDG would increase both k_2 and k_{-1} values.^{4a,12,20} Since the substituent effect on k_2 and k_{-1} values would be in a parallel direction, one can suggest

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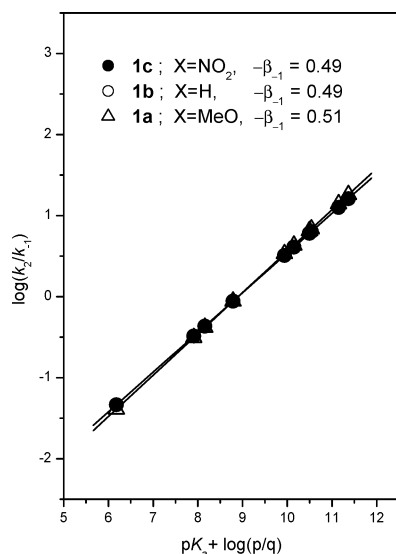


FIGURE 2. Effect of amine basicity on the k_2/k_{-1} ratio for the S–O bond fission in the reactions of **1a** (Δ), **1b** (\circ), and **1c** (\bullet) with primary amines in 80 mol % $\text{H}_2\text{O}/20$ mol % DMSO at 25.0 ± 0.1 °C.

that the k_2/k_{-1} ratio is little influenced by the electronic nature of the substituent in the nonleaving group. This argument can be further supported by the present result exhibiting that the k_2/k_{-1} ratio for the reactions of **1a–c** is almost identical regardless of the electronic nature of the substituent X.

Effect of Nonleaving Group Substituent on Reactivity for S–O Bond Fission. As shown in Table 1, the reactivity of substrates **1a–c** increases as the nonleaving group substituent X changes from an EDG to an EWG (e.g., **1a** < **1b** < **1c**) for the S–O bond fission. A larger $k_N^{\text{S-O}}$ value can be obtained by increasing k_1 and/or the k_2/k_{-1} ratio. As mentioned in the preceding section, the k_2/k_{-1} ratio for the reactions of **1a–c** with a given amine is almost identical regardless of the nature of substituent X. On the other hand, Table 3 demonstrates that the magnitude of the k_1 value increases in the order **1a** < **1b** < **1c** for a given amine. Thus, one can suggest that the larger k_1 value for the reaction of **1c** is fully responsible for the higher reactivity of **1c** compared with **1a** and **1b**.

The effect of amine basicity on the k_1 value is illustrated in Figure 3. The statistically corrected Brønsted-type plots are linear with β_1 values of 0.35, 0.41, and 0.46 for the reactions of **1a**, **1b**, and **1c**, respectively. Since the magnitude of the β_{nuc} value represents the relative degree of bond formation between the nucleophile and the electrophilic center at the TS, one can suggest that the TS of the k_1 step becomes tighter as the substrate becomes more electrophilic on changing the substituent X in the nonleaving group from an EDG to an EWG.

Neuvonen et al. have recently reported that a stronger EWG in the leaving or nonleaving group of aryl acetates or alkyl benzoates increases the reactivity of the esters with upfield ^{13}C NMR chemical shifts of the carbonyl carbon and higher frequencies of the C=O stretching

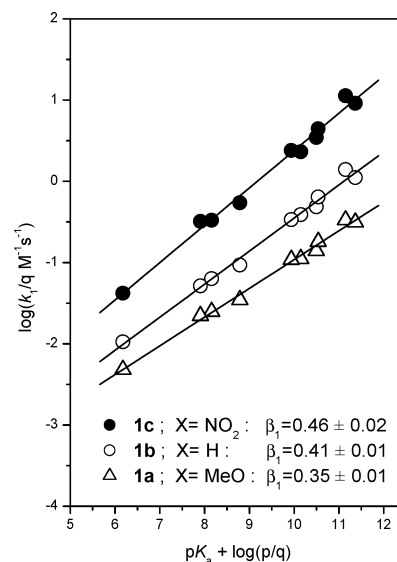
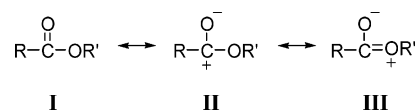


FIGURE 3. Brønsted-type plots ($\log k_1$ vs $\text{p}K_a$) for the S–O bond fission in the reactions of **1a** (Δ), **1b** (\circ), and **1c** (\bullet) with primary amines in 80 mol % $\text{H}_2\text{O}/20$ mol % DMSO at 25.0 ± 0.1 °C.

vibration.²⁶ The increased reactivity of esters with a strong EWG has been attributed to destabilization of the GS due to decreased resonance stabilization of the esters as illustrated by resonance structures I \leftrightarrow II \leftrightarrow III on the basis of the upfield ^{13}C NMR chemical shifts and higher frequencies of the C=O stretching vibration.²⁶ Thus, one might attribute the higher reactivity of **1c** compared to **1a** and **1b** to destabilization of the GS of **1c** due to decreased resonance stabilization.



We have recently shown that the Hammett plots for aminolyses of 4-nitrophenyl and 2,4-dinitrophenyl X-substituted benzoates are nonlinear, i.e., the benzoate with an EDG deviates negatively from the Hammett plots.^{4a,d} A similar result has been obtained for aminolysis of 2,4-dinitrophenyl X-substituted benzenesulfonates^{11a,b} and for alkaline hydrolysis of 2,4-dinitrophenyl X-substituted benzoates^{12a} and *O*-4-nitrophenyl X-substituted thionbenzoates.^{12b} In all cases, the esters with an EDG (e.g., 4-MeO, 4-Me, etc.) exhibit negative deviations from the Hammett plot. Since the corresponding Yukawa–Tsunoi plots are linear, stabilization of the GS as illustrated by the resonance structures IV \leftrightarrow V and VI \leftrightarrow VII has been suggested to be responsible for the

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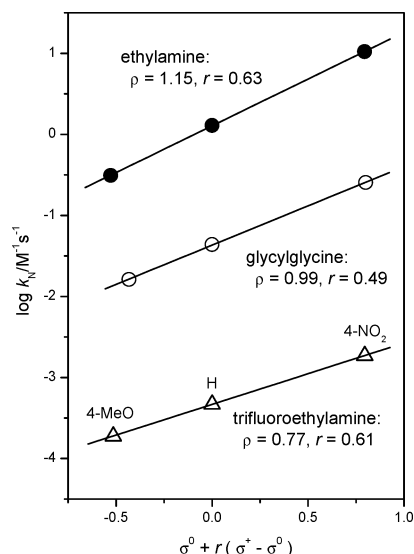
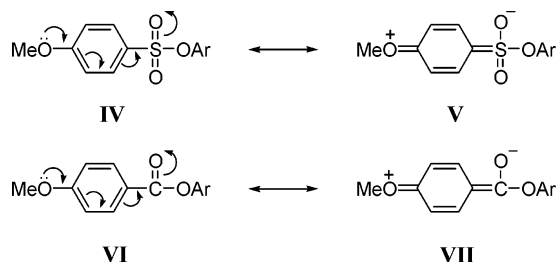


FIGURE 4. Yukawa–Tsuno plots for the S–O bond fission in the reaction of **1a–c** with ethylamine (●), glycylglycine (○), and trifluoroethylamine (△) in 80 mol % H₂O/20 mol % DMSO at 25.0 ± 0.1 °C. The ρ value might include the uncertainty inherent in a three-point analysis.

negative deviation exhibited by the esters with an electron donor substituent in the nonleaving group.^{4a,4d,11,12}



The Yukawa–Tsuno equation (eq 5) has been applied to numerous reactions in which a partial positive charge develops in the TS of the RDS.^{27,28} The r value represents the resonance demand of the reaction center or the extent of the resonance contribution, while the term $(\sigma^+ - \sigma^o)$ is the resonance substituent constant that measures the capacity for π -delocalization of the π -electron donor substituent.

$$\log(k_X/k_H) = \rho[\sigma^o + r(\sigma^+ - \sigma^o)] \quad (5)$$

As shown in Figure 4, the Yukawa–Tsuno plots are linear. However, the corresponding Hammett plots demonstrated in Figure S1 in Supporting Information exhibit much poorer linearity for the reactions of **1a–c** with ethylamine, glycylglycine, and trifluoroethylamine. Clearly, the points for the reactions of **1a** exhibit negative deviations from the Hammett plots shown in Figure S1. Thus, one can suggest that resonance stabilization of the

TABLE 4. Summary of Second-Order Rate Constants for the C–O Bond Fission in the Reaction of **1a–c** with Primary Amines in 80 Mol % H₂O/20 Mol % DMSO at 25.0 ± 0.1 °C^a

no.	amine	pK _a	10 ³ k _N ^{C–O} (M ⁻¹ s ⁻¹)		
			1a	1b	1c
1.	ethylamine	10.67	20	b	b
2.	propylamine	10.89	12	b	b
3.	ethylenediamine	10.32	18	b	b
4.	glycine	10.06	12	b	b
5.	ethanolamine	9.67	8.9	b	b
6.	benzylamine	9.46	14	3.0 ^c	b
7.	glycylglycine	8.51	3.1	1.3 ^c	b
8.	glycine ethyl ester	7.68	2.3	2.4 ^c	1.0
9.	1,2-diaminopropane-H ⁺	7.13	1.7	1.6 ^c	2.4
10.	trifluoroethylamine	5.70	0.093	0.13 ^c	0.16

^a Since the k_N^{C-O} values were determined indirectly using eqs 1 and 2, some uncertainty might be involved in the k_N^{C-O} values.

^b Rate constant could not be determined due to the fact that no detectable C–O bond fission products were found. ^c Rate constant data for the reaction of **1b** were taken from ref 11a.

GS of **1a** as illustrated by resonance structures IV ↔ V is responsible for its decreased reactivity. This argument can be supported by the linear Yukawa–Tsuno plots obtained in the present (Figure 4) and in the other systems (e.g., aminolyses of 2,4-dinitrophenyl X-substituted benzoates^{4a,d} and alkaline hydrolyses of 2,4-dinitrophenyl X-substituted benzoates^{12a} and *O*-4-nitrophenyl X-substituted thionobenzoates^{12b}).

Reaction Mechanism for C–O Bond Fission. Table 4 demonstrates the second-order rate constants for the C–O bond fission process (k_N^{C-O}) for the reactions of **1a–c**. The k_N^{C-O} values have been determined for the reaction of **1a** with all the amines studied. However, the k_N^{C-O} values could not be determined for the reactions of **1b** and **1c** with strongly basic amines since no detectable C–O bond fission products were found for the reactions of **1b** and **1c** with strongly basic amines.

As shown in Table 4, the k_N^{C-O} value increases with increasing the basicity of amines for the reaction of **1a**. The effect of amine basicity on the k_N^{C-O} value is illustrated in Figure S2 in Supporting Information. The statistically corrected Brønsted-type plot for the reaction of **1a** exhibits a downward curvature. Such a nonlinear Brønsted-type plot might be attributed to a change in the RDS, i.e., from breakdown of the Meisenheimer complex to its formation as the amine basicity increases.

However, one can propose another explanation for the nonlinear Brønsted-type plot. As noted above, the reactions of **1a–c** proceed through the S–O and C–O bond fission pathways competitively. Table 1 demonstrates that the fraction of the C–O bond fission for the reaction of **1a** decreases with increasing the amine basicity, i.e., the percent of the C–O bond fission decreases from 33 to 14 and 4% as the amine changes from weakly basic trifluoroethylamine to more basic benzyl and propylamine, respectively. Thus, one can also attribute the nonlinear Brønsted-type plot shown in Figure S2 for the reaction of **1a** to the decrease in the fraction of the C–O bond fission with increasing the amine basicity.

Table 4 shows that the k_N^{C-O} value is independent of the electronic nature of the substituent X in the sulfonyl moiety of **1a–c**. One might suggest two plausible explanations for the absence of the correlation between the

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k_N^{C-O} value and the electronic nature of substituent X: (1) the distance effect and (2) the nature of the reaction mechanism.

The inductive effect would decrease with increasing the distance between the substituent and the reaction center. Since the substituent X is one atom farther away from the reaction center of the C–O bond fission than that of the S–O bond fission, the reactivity for the C–O bond fission process would be less significantly influenced by the electronic nature of the substituent X.

The nature of the reaction mechanism is also considered to be responsible for such a poor correlation. S_NAr reactions have generally been suggested to proceed through a Meisenheimer complex as shown in Scheme 1.^{29,30} If the departure of the leaving group from the Meisenheimer complex were involved in the RDS, the reactivity of **1a–c** should have increased as the substituent X in the sulfonyl moiety (i.e., the leaving group for the C–O bond fission pathway) changes from 4-MeO to H and 4-NO₂. In fact, the k_N^{C-O} value exhibits no correlation with the electronic nature of the substituent X in the sulfonyl moiety, indicating that the leaving group departure is not involved in the RDS. This argument is consistent with the report that the RDS for S_NAr reactions is the formation of the Meisenheimer complex in most cases.^{29,30}

Conclusion

The present study has allowed us to conclude the following: (1) The reaction of **1a–c** with the primary amines for the S–O bond fission proceeds through an addition intermediate with a change in the RDS from breakdown of the intermediate to its formation as the amine basicity increases (e.g., $pK_a^\circ = 8.9 \pm 0.1$). (2) The electronic nature of the substituent in the nonleaving group does not influence the pK_a° value significantly. (3) The k_N^{S-O} and k_1 values increase as the substituent in the nonleaving group changes from an EDG to an EWG (i.e., **1a** < **1b** < **1c**), while the k_2/k_{-1} ratio remains nearly constant upon changing the substituent, indicating that the k_1 value governs the order of the reactivity of substrates **1a–c** in the present system. (4) Stabilization of the GS of the substrate **1a** illustrated by resonance structures IV and V is responsible for the lower reactivity of **1a** compared to **1b** and **1c**. (5) The k_N^{C-O} values exhibit no correlation with the electronic nature of the substituent X in the sulfonyl moiety. The distance effect and the nature of the reaction mechanism have been suggested to be responsible for the absence of the correlation.

Experimental Section

Materials. Substrates **1a** and **1c** were readily prepared by reaction of 2,4-dinitrophenol and X-substituted benzenesulfonyl chloride in the presence of triethylamine in anhydrous ether. Amines and other chemicals were of the highest quality available and generally recrystallized or distilled before use. Due to the low solubility of **1a** and **1c** in pure H₂O, aqueous DMSO was used as the reaction medium (i.e., 20 mol % DMSO/80 mol % H₂O). DMSO was distilled over calcium hydride at a reduced pressure (bp 64–66 °C at 6–7 mmHg) and stored under nitrogen. 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. The reactions were followed by monitoring the appearance of 2,4-dinitrophenoxide ion, an S–O bond fission product, at 405 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 μ L of a 0.02 M substrate solution in MeCN with a 10 μ L syringe into a 10 mm UV cell containing 2.50 mL of the reaction medium and the amine. The ca. 0.2 M amine stock solution was prepared in a 25.0 mL volumetric flask under nitrogen by adding 2 equiv of amine hydrochloride to 1 equiv of standardized NaOH solution in order to obtain a self-buffered solution. All the transfers of reaction solutions were carried out by means of gastight syringes. The kinetic conditions and results are shown in Tables S2–S21 in Supporting Information.

Products Analysis. The amount of 2,4-dinitrophenoxide formed during the S–O bond fission process was determined quantitatively by measuring the optical density using a UV–vis spectrophotometer at 25.0 ± 0.1 °C. Other products such as *N*-ethyl-2,4-dinitroaniline and *N*-ethylbenzenesulfonamide were analyzed by HPLC. The flow rate was 1 mL/min, and the eluent was 50/50 MeCN/MeOH (v/v). Quantitative analysis was performed by comparison of the HPLC peak area of the reaction mixture with that of the authentic sample. The results obtained from the UV–vis and HPLC were found to be consistent each other within an experimental error range (<3%) in all cases.

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Supporting Information Available: Method to determine the k_2/k_{-1} ratio (eqs S1–S6); Hammett plots for the S–O bond fission (k_N^{S-O}) in the reaction of **1a–c** (Figure S1); Brønsted-type plot for the C–O bond fission (k_N^{C-O}) in the reaction of **1a** (Figure S2); summary of total second-order rate constants for the reaction of **1a–c** (Table S1); kinetic results for the reactions of **1a** and **1c** with 10 primary amines (Tables S2–S21). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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