

## Regioselectivity and the Nature of the Reaction Mechanism in Nucleophilic Substitution Reactions of 2,4-Dinitrophenyl X-Substituted Benzenesulfonates with Primary Amines

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Second-order rate constants have been measured for the reaction of 2,4-dinitrophenyl X-substituted benzenesulfonates with a series of primary amines. The nucleophilic substitution reaction proceeds through competitive S–O and C–O bond fission pathways. The S–O bond fission occurs dominantly for reactions with highly basic amines or with substrates having a strong electron-withdrawing group in the sulfonyl moiety. On the other hand, the C–O bond fission occurs considerably for the reactions with low basic amines or with substrates having a strong electron-donating group in the sulfonyl moiety, emphasizing that the regioselectivity is governed by both the amine basicity and the electronic effect of the sulfonyl substituent X. The apparent second-order rate constants for the S–O bond fission have resulted in a nonlinear Brønsted-type plot for the reaction of 2,4-dinitrophenyl benzenesulfonate with 10 different primary amines, suggesting that a change in the rate-determining step occurs upon changing the amine basicity. The microscopic rate constants ( $k_1$  and  $k_2/k_{-1}$  ratio) associated with the S–O bond fission pathway support the proposed mechanism. The second-order rate constants for the S–O bond fission result in good linear Yukawa–Tsuno plots for the aminolyses of 2,4-dinitrophenyl X-substituted benzenesulfonates. However, the second-order rate constants for the C–O bond fission show no correlation with the electronic nature of the sulfonyl substituent X, indicating that the C–O bond fission proceeds through an  $S_NAr$  mechanism in which the leaving group departure occurs rapidly after the rate-determining step.

### Introduction

The mechanism of nucleophilic substitution reactions of carbonyl, phosphoryl, and sulfonyl compounds has been the subject of many recent investigations due to the interest in biological processes as well as synthetic applications.<sup>1–7</sup> Aminolyses of carboxylic esters have generally been suggested to proceed through an addition intermediate in which the rate-determining step (RDS) is dependent on the basicity of the attacking amine and

the leaving group; i.e., a change in the RDS occurs from breakdown of an addition intermediate to its formation as the attacking amine becomes more basic than the leaving group by 4–5  $pK_a$  units.<sup>1a,2,3,5</sup> Therefore, the electronic nature of the substituent in the attacking amine as well as in the leaving group has been understood to influence the reaction mechanism significantly. However, we have recently shown that the electronic effect of the substituent in the benzoyl moiety (the nonleaving group) does not significantly affect the reaction mechanism for aminolyses of 4-nitrophenyl and 2,4-dinitrophenyl X-substituted benzoates.<sup>5b,c</sup> A similar result has been found for the corresponding reactions with anionic nucleophiles such as  $OH^-$ ,  $CN^-$ , and  $N_3^-$ .<sup>5a</sup>

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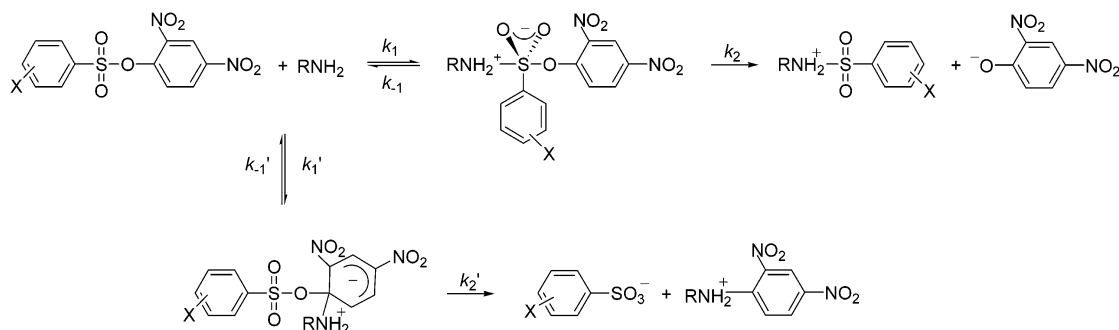
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## SCHEME 1



**TABLE 1. Summary of Second-order Rate Constants ( $k_N^{\text{tot}}$  and  $k_N^{\text{S-O}}$ ) for the Reaction of 2,4-Dinitrophenyl Benzenesulfonate with Primary Amines in Water Containing 20 mol % DMSO at  $25.0 \pm 0.1$  °C**

no.	RNH <sub>2</sub>	pK <sub>a</sub> <sup>a</sup>	10 <sup>3</sup> [RNH <sub>2</sub> ] <sup>b</sup> / M	10 <sup>3</sup> k <sub>N</sub> <sup>tot</sup> / M <sup>-1</sup> s <sup>-1</sup>	10 <sup>3</sup> k <sub>N</sub> <sup>S-O</sup> / M <sup>-1</sup> s <sup>-1</sup>
1	ethylamine	10.67	29.1–56.2	1290 ± 20	1290
2	propylamine	10.89	33.3–57.0	1050 ± 20	1050
3	ethylenediamine	10.32	46.8–81.0	832 ± 7	832
4	glycine	10.06	39.3–66.8	555 ± 4	555
5	ethanolamine	9.67	78.6–146	312 ± 6	312
6	benzylamine	9.46	46.8–81.0	260 ± 2	257
7	glycylglycine	8.31	119–198	45.0 ± 0.3	43.7
8	glycine ethyl ester	7.68	82.2–206	21.5 ± 0.5	19.1
9	1,2-diaminopropane–H <sup>+</sup>	7.13	79.8–200	14.3 ± 0.19	12.7
10	trifluoroethylamine	5.70	123–206	0.593 ± 0.023	0.468

<sup>a</sup> pK<sub>a</sub> values were measured in H<sub>2</sub>O containing 20 mol % DMSO as in the kinetic study (see the text). <sup>b</sup> The concentration of free base.

We have now extended our study to reactions of 2,4-dinitrophenyl X-substituted benzenesulfonates with a series of primary amines. Nucleophilic substitution reactions of sulfonate esters have previously been reported to proceed through competitive S–O and C–O bond fission pathways.<sup>8,9</sup> The regioselectivity has been reported to be influenced greatly by the solvent, the polarizability of the nucleophiles, and steric effects.<sup>8,9</sup> However, the effect of the substituent in the sulfonyl moiety on both the regioselectivity and reaction mechanism has not systematically been investigated. In this paper we report the detailed reaction mechanism for both the S–O and C–O bond fission pathways together with the effect of the sulfonyl substituent on the regioselectivity (see Scheme 1).

## Results

The reactions of 2,4-dinitrophenyl X-substituted benzenesulfonates with primary amines proceed through both the S–O and C–O bond fission pathways as shown in Scheme 1. The S–O bond fission that leads to formation of 2,4-dinitrophenoxide ion and benzenesulfonamides was found to occur dominantly for the reactions with highly basic amines or for those with a strong electron-withdrawing group (EWG) in the sulfonyl moiety of the substrates. On the other hand, the C–O bond fission that yields substituted anilines and benzenesulfonates was found to occur considerably for the reactions with low basic amines or with a strong electron-donating group (EDG) in the sulfonyl moiety of the substrates.

All the reactions studied in this work obeyed pseudo-first-order kinetics under excess amine. Pseudo-first-order rate constants ( $k_{\text{obsd}}$ ) 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 concentrations of nucleophile were used to obtain second-order rate constants from the slope of the linear plot of  $k_{\text{obsd}}$  vs the concentration of the amine nucleophile. The second-order rate constant obtained in this way corresponds to the overall rate constant ( $k_N^{\text{tot}}$ ). The plots of  $k_{\text{obsd}}$  vs amine concentration are linear and pass through the origin, indicating that there is no general-base catalysis by a second amine molecule, and the contribution by H<sub>2</sub>O or HO<sup>-</sup> ion from the solvolysis to  $k_{\text{obsd}}$  is negligible. Therefore, the second-order rate constant for the S–O bond fission process ( $k_N^{\text{S-O}}$ ) and the one for the C–O bond fission ( $k_N^{\text{C-O}}$ ) were calculated from the following relationships:

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

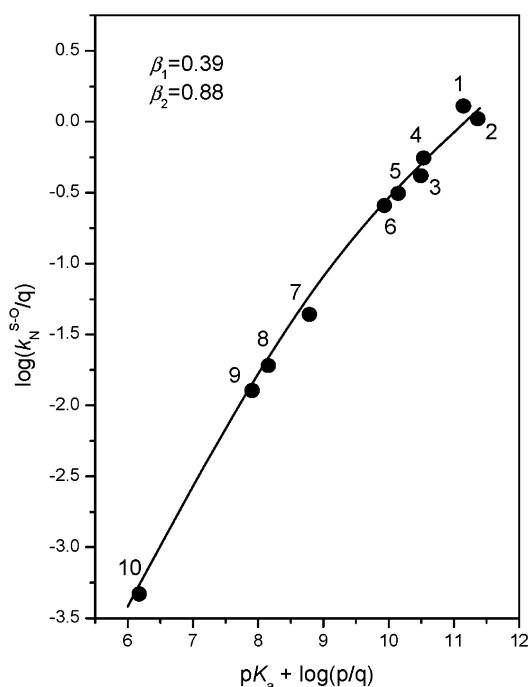
$$k_N^{\text{C-O}} = k_N^{\text{tot}} - k_N^{\text{S-O}} \quad (2)$$

## Discussion

**Effect of Amine Basicity on the Rates and Mechanism for the S–O Bond Fission.** As shown in Table 1, the second-order rate constant for the S–O bond fission pathway ( $k_N^{\text{S-O}}$ ) increases with increasing amine basicity for the reaction of 2,4-dinitrophenyl benzenesulfonate with 10 different amines whose basicity spans a range of ca. 5 pK<sub>a</sub> units. The effect of amine basicity on reactivity is graphically demonstrated in Figure 1 for the S–O bond fission process. One can see a nonlinear Brønsted-type plot which is statistically corrected by

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**FIGURE 1.** Brønsted-type plot for S–O bond fission for the reaction of 2,4-dinitrophenyl benzenesulfonate with primary amines in water containing 20 mol % DMSO at  $25.0 \pm 0.1$  °C. The numbers refer to the amines in Table 1. The solid line was calculated by eq 3.

using  $p$  and  $q$ , i.e.,  $p = 3$  (except  $p = 6$  for 1,2-diaminopropane–H<sup>+</sup>) and  $q = 1$  (except  $q = 2$  for ethylenediamine).<sup>10</sup> Nonlinear Brønsted-type plots have often been observed for aminolyses of esters with a good leaving group (e.g., 2,4-dinitrophenyl acetate and benzoate); i.e., the magnitude of the  $\beta_{\text{nuc}}$  values decreases from  $0.8 \pm 0.3$  to  $0.3 \pm 0.2$  as the attacking amine becomes more basic than the leaving group by 4–5  $pK_a$  units.<sup>1a,2,3,5,7</sup> Such a curved Brønsted-type plot has been interpreted as a change in the RDS upon changing the amine basicity. The nonlinear Brønsted-type plot in Figure 1 has been analyzed using eq 3,<sup>2,7a</sup>

$$\log(k_N^{S-O}/k_N^\circ) = \beta_2(pK_a - pK_a^\circ) - \log[(1 + \alpha)/2] \quad (3)$$

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

where  $\beta_1$  and  $\beta_2$  represent the slope of the Brønsted-type plot in Figure 1 for the reaction with strongly and weakly basic RNH<sub>2</sub>, respectively. The parameters  $k_N^\circ$  and  $pK_a^\circ$  refer to a hypothetical amine, for which  $k_{-1} = k_2$  in Scheme 1. The parameters determined are as follows:  $\log k_N^\circ = 1.16$ ,  $pK_a^\circ = 8.89$ ,  $\beta_1 = 0.39$ , and  $\beta_2 = 0.88$ . Therefore, one can suggest that the RDS for the reaction of 2,4-dinitrophenyl benzenesulfonate with RNH<sub>2</sub> changes from the  $k_2$  to the  $k_1$  step as the amine basicity increases on the basis of the magnitude of the  $\beta_1$  and  $\beta_2$  values.

Applying the steady-state conditions to the addition intermediate for the S–O bond fission process, eqs 4 and 5 can be derived, where [S] and [RNH<sub>2</sub>] represent the

**TABLE 2.** Summary of Microscopic Rate Constants Associated with the Reaction of 2,4-Dinitrophenyl Benzenesulfonate with Primary Amines for the S–O Bond Fission Process in Water Containing 20 mol % DMSO at  $25.0 \pm 0.1$  °C

no.	RNH <sub>2</sub>	$pK_a$	$k_2/k_{-1}$	$10^2 k_1/M^{-1} s^{-1}$
1	ethylamine	10.67	12.8	139
2	propylamine	10.89	16.4	111
3	ethylenediamine	10.32	6.12	48.4
4	glycine	10.06	6.41	64.2
5	ethanolamine	9.67	4.13	38.8
6	benzylamine	9.46	3.26	33.6
7	glycylglycine	8.31	0.890	9.28
8	glycine ethyl ester	7.68	0.437	6.28
9	1,2-diaminopropane–H <sup>+</sup>	7.13	0.330	5.12
10	trifluoroethylamine	5.70	0.0469	1.05

concentration of the substrate and the amine studied, respectively.

rate for S–O bond fission =

$$k_1 k_2 [S][\text{RNH}_2]/(k_{-1} + k_2) \quad (4)$$

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

To obtain more information about the RDS, the  $k_2/k_{-1}$  ratio associated with the aminolyses of 2,4-dinitrophenyl benzenesulfonate has been determined using the method reported previously (see also eqs S1–S6 in the Supporting Information).<sup>2,5</sup> Table 2 shows that the  $k_2/k_{-1}$  ratio decreases as the amine basicity decreases. The plot of  $\log(k_2/k_{-1})$  versus amine basicity results in excellent linearity with a  $-\beta_{-1}$  value of 0.49 (see Figure S1 in the Supporting Information). The magnitude of the  $\beta_{-1}$  value represents the sensitivity parameter for the  $k_{-1}$  step, since the  $k_2$  value has been suggested to be independent of amine basicity.<sup>11,12</sup> It is also noted that the  $k_2/k_{-1}$  ratio is smaller than unity for the weakly basic amines ( $pK_a < 8.89$ ) but larger than unity for the strongly basic amines ( $pK_a > 8.89$ ). Therefore, the  $k_2/k_{-1}$  ratio obtained in the present study clearly supports the preceding proposal that the RDS changes from the  $k_2$  to the  $k_1$  step as the amine basicity exceeds  $pK_a = 8.89$ .

To calculate  $k_1$  values, eq 5 should be rearranged as eq 6. Since  $k_N^{S-O}$  and  $k_2/k_{-1}$  values are available in the present system,  $k_1$  values can be calculated from eq 6.

$$k_1 = k_N^{S-O} (k_{-1}/k_2 + 1) \quad (6)$$

The  $k_1$  values determined in this way are summarized in Table 2. One can see that the  $k_1$  value increases with increasing amine basicity. A good linear Brønsted-type plot has been obtained with a  $\beta_1$  value 0.41 (see Figure S2 in the Supporting Information). The  $\beta_1$  value is slightly smaller than the  $-\beta_{-1}$  value (=0.49) in the present system, indicating that the amine basicity is less sensitive to the  $k_1$  step than to the  $k_{-1}$  step.

**Effect of the Sulfonyl Substituent on the Rates and Mechanism for the S–O Bond Fission.** As shown

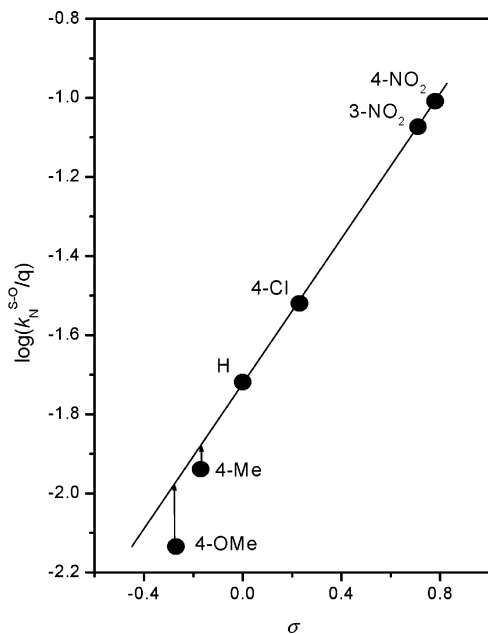
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**TABLE 3. Summary of Second-order Rate Constants ( $k_N^{S-O}$ ) for the Reaction of 2,4-Dinitrophenyl X-Substituted Benzenesulfonates with Benzylamine, Glycine Ethyl Ester, and Trifluoroethylamine in Water Containing 20 mol % DMSO at  $25.0 \pm 0.1$  °C**

X	$10^3 k_N^{S-O} / M^{-1} s^{-1}$		
	benzylamine	glycine ethyl ester	trifluoroethylamine
4-NO <sub>2</sub>	1830 ± 10	98 ± 2	1.86 ± 0.04
3-NO <sub>2</sub>	1570 ± 5	84.5 ± 0.7	1.57 ± 0.04
4-Cl	401 ± 4	30.2 ± 0.4	0.558 ± 0.006
H	257 ± 2	19.1 ± 0.5	0.468 ± 0.023
4-CH <sub>3</sub>	138 ± 3	11.5 ± 0.2	0.300 ± 0.006
4-OCH <sub>3</sub>	83.9 ± 1.4	7.33 ± 0.03	0.189 ± 0.008



**FIGURE 2.** Hammett plot for S–O bond fission for the reaction of 2,4-dinitrophenyl X-substituted benzenesulfonates with glycine ethyl ester in H<sub>2</sub>O containing 20 mol % DMSO at  $25.0 \pm 0.1$  °C.

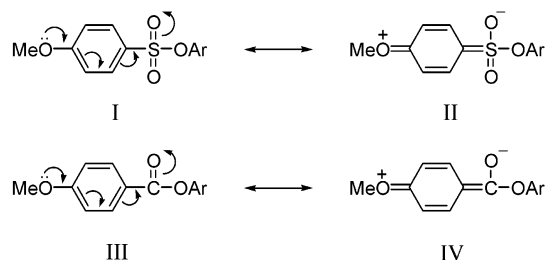
in Table 3, the  $k_N^{S-O}$  value for the reaction of 2,4-dinitrophenyl X-substituted benzenesulfonates increases with increasing electron-withdrawing ability of the sulfonyl substituent X for a given amine. The effect of the sulfonyl substituent X on the  $k_N^{S-O}$  value has been graphically illustrated in Figure 2. One can notice that the point for the substrate, which is substituted with 4-MeO or 4-Me in the sulfonyl moiety, deviates negatively from linearity for the reaction with glycine ethyl ester. A similar result has also been obtained for the corresponding reactions with benzylamine and trifluoroethylamine (see Figures S3 and S4 in the Supporting Information). Although the degree of deviation is not significant, one might attribute such a deviation to a change in the RDS or reaction mechanism upon changing the sulfonyl substituent X. In fact, Jencks, Lee, and Castro et al. concluded that a change in the RDS occurs upon changing the substituent X in the nonleaving group.<sup>13–15</sup> Furthermore, Vizgert reported that the hydrolysis of 2,4-dini-

trophenyl X-substituted benzenesulfonates proceeds by mixed S<sub>N</sub>1 and S<sub>N</sub>2 mechanisms when the sulfonyl moiety is substituted with strong EDGs such as 2,4,6-trimethyl.<sup>16</sup> Since 4-MeO is also a strong EDG, one might expect an S<sub>N</sub>1 mechanism to occur in the present aminolysis.

However, an S<sub>N</sub>1 mechanism can be clearly ruled out in the present system on the basis of the experimental result that the  $k_{obsd}$  value increases linearly with increasing concentration of the attacking amine as mentioned in the Results. Besides, if the reaction of the substrate with the 4-MeO or 4-Me group in the sulfonyl moiety proceeded through an S<sub>N</sub>1 mechanism, the points for these substrates should have deviated positively from the Hammett plot. In fact, an upward curvature in the Hammett plots has often been reported for nucleophilic substitution reactions of the benzylic system or those of various carboxylic esters (e.g., substituted phenyl esters of 4-nitrophenylacetic acid) in which a change in reaction mechanism occurs from S<sub>N</sub>1 to S<sub>N</sub>2 for the former case and from a bimolecular reaction (either one step or a stepwise addition–elimination mechanism) to an E1cB mechanism for the latter case.<sup>17</sup> Therefore, the negative deviation shown by the two substrates would not be due to a change in the reaction mechanism.

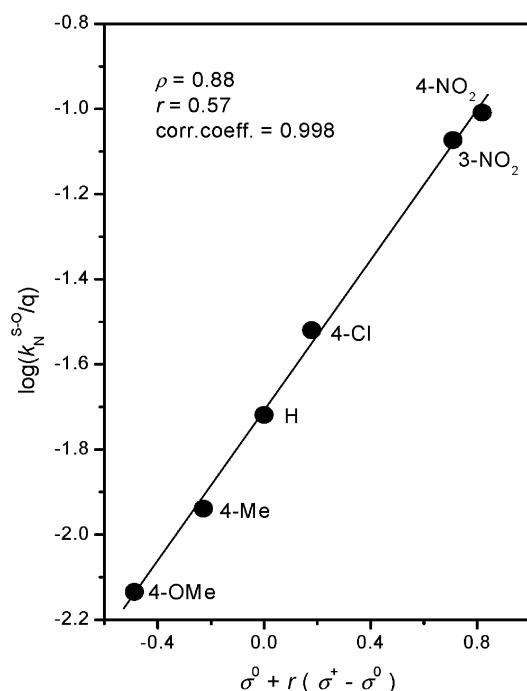
The RDS of a stepwise reaction as in the present system is determined by the magnitude of the  $k_2/k_{-1}$  ratio; i.e., the RDS is the  $k_1$  step when  $k_2/k_{-1} > 1$ , but the  $k_2$  step when  $k_2/k_{-1} < 1$ . The electronic nature of the sulfonyl substituent X would influence the magnitude of the  $k_2$  and  $k_{-1}$  values; i.e., an EWG in the sulfonyl moiety would decrease the  $k_2$  and  $k_{-1}$  values, while an EDG would increase the  $k_2$  and  $k_{-1}$  values. However, the magnitude of the  $k_2/k_{-1}$  ratios would be independent of the electronic nature of the sulfonyl substituent, since the electronic effect of the sulfonyl substituent X on the  $k_2$  and  $k_{-1}$  values would be in the same direction. In fact, we have recently shown that the substituent X on the benzoyl moiety does not significantly affect the  $k_2/k_{-1}$  ratio for reactions of 2,4-dinitrophenyl X-substituted benzoates with amines<sup>5c</sup> and with various anionic nucleophiles.<sup>5a</sup>

On the basis of above, we propose that the origin of the negative deviations shown by the substrates with an electron-donating substituent in the sulfonyl moiety (shown in Figures 2, S3, and S4) is due to stabilization of the ground state (GS) through resonance interaction between the electron-donating substituent in the sulfonyl moiety and the S=O bond as illustrated by resonance structures I and II. In this situation, the Yukawa–Tsuno



equation (eq 7)<sup>18</sup> is more appropriate than the Hammett equation. The term  $\sigma^+ - \sigma^0$  is the resonance substituent constant measuring the capability for  $\pi$ -delocalization of

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**FIGURE 3.** Yukawa–Tsuno plot for S–O bond fission for the reaction of 2,4-dinitrophenyl X-substituted benzenesulfonates with glycine ethyl ester in H<sub>2</sub>O containing 20 mol % DMSO at 25.0 ± 0.1 °C.

the  $\pi$ -electron donor substituent, while the  $r$  value is a parameter characteristic of the given reaction, representing the extent of resonance contribution.<sup>18</sup> The Yukawa–

$$\log(k^X/k^H) = \rho[\sigma^o + r(\sigma^+ - \sigma^o)] \quad (7)$$

Tsuno equation becomes the Hammett equation when  $r = 0$ , or the Brown–Okamoto equation when  $r = 1$ . As shown in Figure 3, the Yukawa–Tsuno plot exhibits good linearity for the reactions with glycine ethyl ester ( $r = 0.57$ ). A similar result has been obtained for the corresponding reactions with benzylamine and trifluoroethylamine with  $r$  values of 0.49 and 0.55, respectively (see Figures S5 and S6 in the Supporting Information). Therefore, one can attribute the negative deviations (shown in Figures 2, S3, and S4) to the GS stabilization by resonance but not to a change in the RDS. Since the  $r$  value is neither 0 nor 1, the Yukawa–Tsuno plot results in much better correlation than the Hammett or Brown–Okamoto plot, in which  $\sigma$  or  $\sigma^+$  constants are used alone.

The  $r$  value obtained in the present system is ca. 0.53 ± 0.04. This value is much smaller than the one obtained in aminolyses of 4-dinitrophenyl X-substituted benzoates

**TABLE 4.** Summary of Second-order Rate Constants ( $k_N^{C-O}$ ) for the Reaction of 2,4-Dinitrophenyl X-Substituted Benzenesulfonates with Ethylamine, Benzylamine, Glycine Ethyl Ester, and Trifluoroethylamine in Water Containing 20 mol % DMSO at 25.0 ± 0.1 °C

X	$10^3 k_N^{C-O} / M^{-1} s^{-1}$			
	ethylamine	benzylamine	glycine ethyl ester	trifluoroethylamine
4-NO <sub>2</sub>	a	a	3.03	0.162
3-NO <sub>2</sub>	a	a	5.39	0.235
4-Cl	a	4.05	3.36	0.122
H	a	2.60	2.37	0.125
4-CH <sub>3</sub>	19.8	12.0	2.19	0.100
4-OCH <sub>3</sub>	19.9	13.7	2.32	0.093

<sup>a</sup> The rate constant could not be determined due to the fact that no detectable C–O bond fission products were found.

( $r = 0.7–1.4$ ),<sup>5b</sup> indicating that the resonance contribution is less significant for the sulfonate system than for the benzoate system. Since the overlap of 2p and 3p orbitals to form a C=S bond is not efficient,<sup>19</sup> the contribution of the resonance structure for the sulfonate system (I ↔ II) would not be as significant as that for the benzoate system (III ↔ IV). This argument explains the large difference in the  $r$  value between the sulfonate and the benzoate systems.

**Effect of Amine Basicity and Sulfonyl Substituent on the Regioselectivity for the C–O Bond Fission.** In Table 4 are summarized the second-order rate constants for the C–O bond fission process ( $k_N^{C-O}$ ) for reactions of 2,4-dinitrophenyl X-substituted benzenesulfonates with four different amines. The  $k_N^{C-O}$  value for the weakly basic amines such as trifluoroethylamine ( $pK_a = 5.70$ ) and glycine ethyl ester ( $pK_a = 7.68$ ) could be determined for all the substrates regardless of the electronic nature of the substituent X on the sulfonyl moiety. However, the  $k_N^{C-O}$  value for the reactions with strongly basic benzylamine ( $pK_a = 9.46$ ) and ethylamine ( $pK_a = 10.67$ ) could not be measured for the reaction of the substrates in which a strong EWG such as 4-NO<sub>2</sub> or 3-NO<sub>2</sub> is substituted in the sulfonyl moiety, since the reactions of these substrates produce no detectable C–O bond fission products. Therefore, one can suggest that the regioselectivity is governed by both the basicity of the amines and the electronic nature of the sulfonyl substituent X.

Table 4 shows that the  $k_N^{C-O}$  value increases as the amine basicity increases when the sulfonyl substituent X is an EDG such as 4-Me or 4-MeO. However, the correlation of  $k_N^{C-O}$  with amine basicity is not good (figure not shown). Furthermore, one can notice that there is no correlation between the  $k_N^{C-O}$  value and the electronic nature of the sulfonyl substituent X for a given amine. This quite contrasts the result obtained for the S–O bond fission process, e.g., a good linear Yukawa–Tsuno plot with a large  $\rho$  value as shown in Figure 3. One might suggest two plausible reasons for the contrasting results: (1) the proximity effect and (2) the nature of the reaction mechanism. The reaction site of the C–O bond fission is farther from the substituent X

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in the sulfonyl moiety than that of the S–O bond fission. Since the inductive effect of the substituent diminishes with the distance between the substituent and the reaction site, one can expect that the effect of the sulfonyl substituent would be less significant for the C–O bond fission than for the S–O bond fission process. The nature of the reaction mechanism would also be responsible for the absence of the substituent effect on the  $k_{\text{N}}^{\text{C-O}}$  value. It has well been known that  $\text{S}_{\text{N}}\text{Ar}$  reactions proceed through a Meisenheimer complex, in which the RDS can be either formation or breakdown of the complex.<sup>20</sup> If the leaving group departure from the Meisenheimer complex occurs in the RDS, the magnitude of the  $k_{\text{N}}^{\text{C-O}}$  value should increase linearly with increasing electron-withdrawing ability of the substituent X in the leaving sulfonyl moiety. However, as shown in Table 4, the  $k_{\text{N}}^{\text{C-O}}$  value remains nearly constant upon changing the substituent X from a strong EDG (e.g., 4-MeO) to a strong EWG (e.g., 4-NO<sub>2</sub>) for a given amine. Therefore, the present result clearly suggests that the C–O bond fission proceeds through an  $\text{S}_{\text{N}}\text{Ar}$  mechanism in which the leaving group departure from the Meisenheimer complex occurs rapidly after the RDS.

## Conclusions

The present study has allowed us to conclude the following: (1) The nucleophilic substitution reaction proceeds through the S–O and C–O bond fission pathways. The S–O bond fission occurs dominantly when the amine is strongly basic or the substituent in the sulfonyl moiety of the substrate is an EWG. However, the C–O bond fission process occurs considerably when the amine is weakly basic or the sulfonyl substituent X is a strong EDG, indicating that the regioselectivity is governed by both the amine basicity and the electronic nature of the substituent X in the sulfonyl moiety of the substrate. (2) The S–O bond fission proceeds through an addition intermediate, in which the RDS for this process is dependent on the basicity of the amine nucleophile, but independent of the electronic nature of the substituent in the sulfonyl moiety of the substrate. (3) The  $k_{\text{N}}^{\text{S-O}}$  values for the reactions of 2,4-dinitrophenyl X-substituted benzenesulfonates result in a linear Yukawa–Tsuno plot with a large  $\rho$  value. However, the  $k_{\text{N}}^{\text{C-O}}$  values for the corresponding reactions show no correlation with the electronic nature of the sulfonyl substituent X, suggesting that the C–O bond fission proceeds through an  $\text{S}_{\text{N}}\text{Ar}$  mechanism in which the leaving group departure from the Meisenheimer complex occurs rapidly after the RDS.

## Experimental Section

**Materials.** 2,4-Dinitrophenyl X-substituted benzenesulfonates were prepared from the reaction of 2,4-dinitrophenol and X-substituted benzenesulfonyl chlorides in the presence

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of triethylamine in anhydrous ether. Their purity was checked by means of their melting point and spectral data such as IR and <sup>1</sup>H NMR characteristics. Amines and other chemicals were of the highest quality available and were generally recrystallized or distilled before use. The reaction medium was H<sub>2</sub>O containing 20 mol % DMSO to eliminate solubility problems. 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 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 concentration of the nucleophile was at least 20 times greater than the substrate concentration. Typically, the reaction was initiated by adding 5  $\mu\text{L}$  of a 0.02 M substrate solution in MeCN by a 10  $\mu\text{L}$  syringe into a 10 mm UV cell containing 2.50 mL of the reaction medium and the amine nucleophile. The amine stock solution of ca. 0.2 M 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 to obtain a self-buffered solution. All the transfers of reaction solutions were carried out by means of gastight syringes.

**Product 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  $\pm$  0.1 °C. Other products such as 2,4-dinitro-*N*-ethylaniline 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 UV–vis and HPLC were found to be consistent with each other within an experimental error range (<3%) in all cases.

**Determination of p*K*<sub>a</sub>.** p*K*<sub>a</sub> values of the conjugate acids of the amines were determined by measuring the pH of solutions containing equal amounts of the amine and the corresponding amine hydrochloride with a glass electrode in H<sub>2</sub>O containing 20 mol % DMSO.<sup>7a</sup> The pH values of the solutions were practically independent of the amine concentration in the range of (20–200)  $\times$  10<sup>–3</sup> M, which is the concentration range used for the kinetic experiment.

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**Supporting Information Available:** Equations to determine the  $k_2/k_{-1}$  ratio (eqs S1–S6), Brønsted-type plots for  $k_2/k_{-1}$  and  $k_1$  for the S–O bond fission process (Figures S1 and S2), and Hammett and Yukawa–Tsuno plots for reactions of 2,4-dinitrophenyl X-substituted benzenesulfonates with benzylamine and trifluoroethylamine (Figures S3–S6). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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