

Effect of Amine Nature on Reaction Rate and Mechanism in Nucleophilic Substitution Reactions of 2,4-Dinitrophenyl X-Substituted Benzenesulfonates with Alicyclic Secondary Amines

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Second-order rate constants have been measured for reactions of 2,4-dinitrophenyl X-substituted benzenesulfonates with a series of alicyclic secondary amines. The reaction proceeds through S–O and C–O bond fission pathways competitively. The S–O bond fission occurs more dominantly as the amine basicity increases and the substituent X in the sulfonyl moiety becomes more strongly electron withdrawing, indicating that the regioselectivity is governed by the amine basicity as well as the electronic nature of the substituent X. The S–O bond fission proceeds through an addition intermediate with a change in the rate-determining step at $pK_a^\circ = 9.1$. The secondary amines are more reactive than primary amines of similar basicity for the S–O bond fission. The k_1 value has been determined to be larger for reactions with secondary amines than with primary amines of similar basicity, which fully accounts for their higher reactivity. The second-order rate constants for the S–O bond fission result in linear Yukawa–Tsuno plots while those for the C–O bond fission exhibit poor correlation with the electronic nature of the substituent X. The distance effect and the nature of reaction mechanism have been suggested to be responsible for the poor correlation for the C–O bond fission pathway.

Introduction

Nucleophilic substitution reactions of carbonyl, phosphoryl, and sulfonyl derivatives have received considerable attention due to their importance in biological processes and synthetic applications.^{1–11} The mechanism

for the reaction of carbonyl esters with amines has generally been understood to proceed through a tetra-

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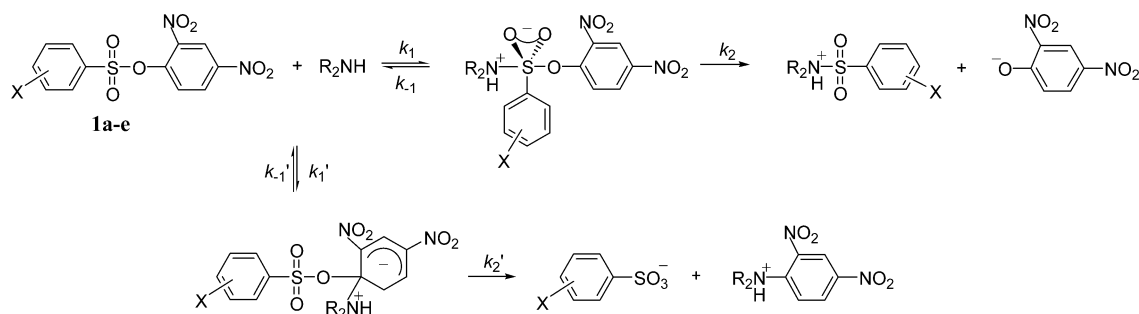
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SCHEME 1



X = 4-NO₂ (**1a**), 4-Cl (**1b**), H (**1c**), 4-Me (**1d**), 4-MeO (**1e**)

hedral addition intermediate (T[±]) in which the rate-determining step (RDS) depends on the basicity of the leaving group and nucleophiles.¹⁻⁴ It has been suggested that the RDS changes from expulsion of the leaving group from T[±] to its formation as the amine becomes more basic than the leaving group by 4–5 pK_a units.¹⁻⁴ However, the mechanism of the corresponding reactions of phosphorus and sulfur centered esters has not completely been understood.⁵⁻¹¹ Some studies have suggested that nucleophilic substitution reactions of phosphonyl and sulfonyl esters proceed through a concerted mechanism^{5,6} while other studies have argued against a concerted mechanism.⁷⁻¹¹

We have recently reported that the reaction of 2,4-dinitrophenyl X-substituted benzenesulfonates (**1a–e**) with a series of primary amines proceeds through S–O and C–O bond fission pathways competitively.¹¹ The S–O bond fission has been found to proceed through an addition intermediate with a change in the RDS from breakdown of the intermediate to its formation as the amine becomes ca. 5 pK_a units more basic than the leaving 2,4-dinitrophenoxide anion, while the C–O bond fission occurs through a Meisenheimer complex.¹¹

We have now extended our study to reactions of **1a–e** with a series of alicyclic secondary amines to investigate the effect of amine nature on the reaction rate and mechanism by comparing the data obtained in this study with those for the corresponding reactions with primary amines. The apparent second-order rate constants and the microscopic rate constants associated with the reactions of **1a–e** have been determined. In this paper, we report factors influencing the reaction mechanism and regioselectivity as well as the origin of the higher reactivity shown by alicyclic secondary amines compared with isobasic primary amines.

Results

The reaction of **1a–e** with secondary amines proceeded competitively through the S–O and C–O bond fission pathways as shown in Scheme 1. The S–O bond fission that yields benzenesulfonamides and 2,4-dinitrophenoxide occurred exclusively for the reactions with strongly basic secondary amines such as piperidine and 3-methylpiperidine. On the other hand, the C–O bond fission that

leads to formation of substituted benzenesulfonates and anilines increased as the amine basicity decreased or the substituent X changed from a strong electron-withdrawing group (EWG) to a strong electron-donating group (EDG).

All the reactions in the present study obeyed pseudo-first-order kinetics in the presence of excess amine. Pseudo-first-order rate constants (k_{obsd}) were calculated 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. The plots of k_{obsd} vs amine concentration were linear passing through the origin, indicating that general base catalysis by the second amine molecule is absent and the contribution of OH[−] and/or H₂O to the k_{obsd} value is negligible. Five different amine concentrations were generally used to determine the second-order rate constants from the linear plot. The second-order rate constant determined in this way corresponds to the overall rate constant ($k_{\text{N}}^{\text{tot}}$).¹¹ Thus, the second-order rate constant for the S–O bond fission ($k_{\text{N}}^{\text{S-O}}$) and the C–O bond fission ($k_{\text{N}}^{\text{C-O}}$) processes were calculated from the following relationships:

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

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

Discussion

Effect of Amine Nature on Reaction Mechanism

for S–O Bond Fission. As shown in Table 1, the second-order rate constants ($k_{\text{N}}^{\text{tot}}$ and $k_{\text{N}}^{\text{S-O}}$) for the reaction of 2,4-dinitrophenyl benzenesulfonate (**1c**) with secondary amines decreases as the amine basicity decreases. The effect of amine basicity on rates for the S–O bond fission process is illustrated in Figure 1. The Brønsted-type plot exhibits a downward curvature, i.e., the β_{nuc} value decreases from 0.86 to 0.38 as the amine basicity increases. A similar biphasic Brønsted-type plot has been demonstrated in Figure 1 for the corresponding reactions with primary amines.

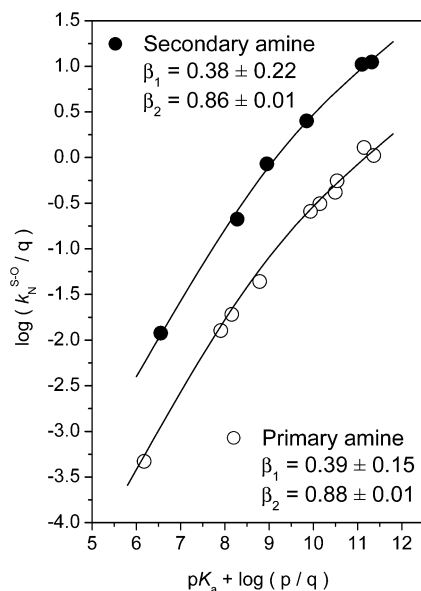
A change in the RDS has been suggested to be responsible for such a biphasic Brønsted-type plot, i.e., $k_{-1}/k_2 > 1$ for reactions with weakly basic amines, $k_{-1}/k_2 = 1$ at pK_a^o, the center of curvature on the Brønsted-type plot and $k_{-1}/k_2 < 1$ for reactions with strongly basic amines.¹⁻⁴ Thus, the nonlinear Brønsted-type plot in Figure 1 for the reaction of **1c** with secondary

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TABLE 1. Summary of Apparent Second-Order Rate Constants (k_N^{tot} , $k_N^{\text{S-O}}$, and $k_N^{\text{C-O}}$) for Reactions of 2,4-Dinitrophenyl Benzenesulfonate (1c**) with Alicyclic Secondary Amines in 80 mol % H₂O/20 mol % DMSO at 25.0 ± 0.1 °C**

| amine | pK _a ^a | 10 ⁴ k _N ^{tot} /M ⁻¹ s ⁻¹ | 10 ⁴ k _N ^{S-O} /M ⁻¹ s ⁻¹ | 10 ³ k _N ^{C-O} /M ⁻¹ s ⁻¹ | % ^b |
|--------------------|------------------------------|--|--|--|----------------|
| piperidine | 11.02 | 111 ± 3 | 111 ± 3 | | 100 |
| 3-methylpiperidine | 10.80 | 105 ± 1 | 105 ± 1 | | 100 |
| piperazine | 9.85 | 52.0 ± 0.3 | 50.4 | 160 | 97 |
| morpholine | 8.65 | 9.80 ± 0.08 | 8.53 | 127 | 87 |
| 1-formylpiperazine | 7.98 | 2.60 ± 0.03 | 2.11 | 49.0 | 81 |
| piperazinium ion | 5.95 | 0.181 ± 0.003 | 0.119 | 6.20 | 66 |

^a pK_a values in 80 mol % H₂O/20 mol % DMSO were taken from ref 4f. ^b Percent S–O bond fission.

**FIGURE 1.** Brønsted-type plots for the reactions of 2,4-dinitrophenyl benzenesulfonate (**1c**) with primary and alicyclic secondary amines for the S–O bond fission process in 80 mol % H₂O/20 mol % DMSO at 25.0 ± 0.1 °C. The solid lines were calculated by eq 3. Data for the reactions with primary amines were taken from ref 11.

amines has been analyzed using eq 3²

$$\log(k_N^{\text{S-O}}/k_N^{\circ}) = \beta_2(\text{p}K_a - \text{p}K_a^{\circ}) - \log[(1 + \alpha)/2]$$

where

$$\log \alpha = (\beta_2 - \beta_1)(\text{p}K_a - \text{p}K_a^{\circ}) \quad (3)$$

The parameters β_1 and β_2 represent the slope of the Brønsted-type plot for the reaction with strongly and weakly basic secondary amines, respectively, while k_N° refers to the $k_N^{\text{S-O}}$ value at $\text{p}K_a^{\circ}$. The β_1 , β_2 , and $\text{p}K_a^{\circ}$ values for the reactions of **1c** with secondary amines have been determined to be 0.86, 0.38, and 9.1, respectively. Therefore, one can suggest that the reaction of **1c** with secondary amines proceeds through an addition intermediate in which the RDS changes at $\text{p}K_a$ ca. 9.1 from breakdown of the intermediate to its formation as the amine basicity increases. The $\text{p}K_a^{\circ}$ value for the reaction of **1c** with primary amines has been reported to be 8.9,¹¹ which is almost the same as that for the reaction of **1c** with secondary amines within an experimental error range, indicating that the nature of amine (e.g., primary vs secondary amines) does not affect $\text{p}K_a^{\circ}$ significantly.

Effect of Amine Nature on Reaction Rate for the S–O Bond Fission. As shown in Figure 1, secondary amines are more reactive than isobasic primary amines. The reactivity of amines has often been reported to increase as the amine nature changes from primary to secondary and tertiary amines successively.^{2a,b,12–14} Since solvation energy has been reported to decrease in the order $\text{RNH}_3^+ > \text{R}_2\text{NH}_2^+ > \text{R}_3\text{NH}^+$, solvent effect has generally been suggested to be responsible for the increasing reactivity order.^{2a,b,12–14} However, no systematic analysis has yet been performed in terms of microscopic rate constants. Therefore, we have evaluated the microscopic rate constants associated with the reaction of **1c** with secondary amines to investigate the origin of their enhanced reactivity compared with isobasic primary amines for the first time.

rate for S–O bond fission =

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

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

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 [R₂NH] represent the concentration of the substrate and the amine studied, respectively. As shown in eq 5, a larger $k_N^{\text{S-O}}$ value can be obtained by increasing k_1 or by decreasing k_{-1} . However, k_2 cannot affect the $k_N^{\text{S-O}}$ value since it has been reported to be independent of the nature and basicity of amines.^{15–17} Thus, the microscopic rate constants (e.g., k_1 and k_{-1}/k_2) associated with the present reactions are necessary to investigate the origin of the larger $k_N^{\text{S-O}}$ value shown by the secondary amines compared with isobasic primary amines as well as the reaction mechanism.

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TABLE 2. Summary of Microscopic Rate Constants Associated with Reactions of 2,4-Dinitrophenyl Benzenesulfonate (1c**) with Alicyclic Secondary Amines for the S–O Bond Fission Process in 80 mol % H₂O/20 mol % DMSO at 25.0 ± 0.1 °C^a**

| amine | pK _a | k ₋₁ /k ₂ | k ₁ /M ⁻¹ s ⁻¹ |
|--------------------|-----------------|---------------------------------|---|
| piperidine | 11.02 | 0.0885 | 12.1 |
| 3-methylpiperidine | 10.80 | 0.113 | 11.7 |
| piperazine | 9.85 | 0.448 | 7.30 |
| morpholine | 8.65 | 1.21 | 1.89 |
| 1-formylpiperazine | 7.98 | 2.56 | 0.743 |
| piperazinium ion | 5.95 | 16.9 | 0.213 |

^a pK_a values in 80 mol % H₂O/20 mol % DMSO were taken from ref 4f.

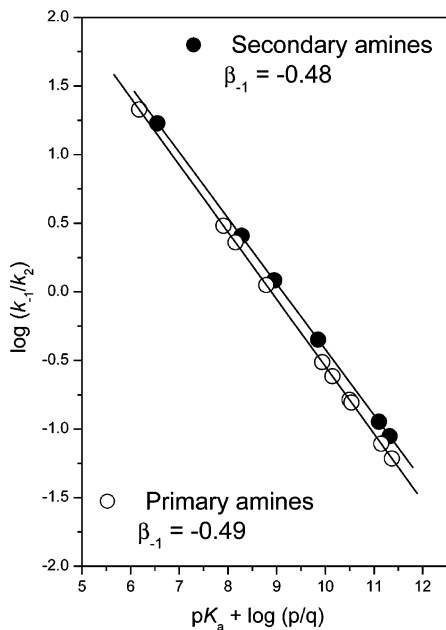


FIGURE 2. Brønsted-type plots of $\log k_{-1}/k_2$ vs pK_a for reactions of 2,4-dinitrophenyl benzenesulfonate (**1c**) with primary and alicyclic secondary amines for the S–O bond fission in 80 mol % H₂O/20 mol % DMSO at 25.0 ± 0.1 °C. Data for the reactions with primary amines were taken from ref 11.

The k_{-1}/k_2 ratios associated with the reactions of **1c** with secondary amines have been determined using the method reported by Castro et al.² (see also eqs S1–S6 in the Supporting Information). Equation 5 can be rearranged to eq 6, which has allowed us to calculate the k_1 value from k_{-1}/k_2 and k_N^{S-O} . In Table 2 are summarized the microscopic rate constants (k_{-1}/k_2 and k_1) determined in this way.

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

Table 2 shows that the k_{-1}/k_2 ratio increases as the amine basicity decreases, i.e., $k_{-1}/k_2 < 1$ for $pK_a \geq 9.85$ while $k_{-1}/k_2 > 1$ for $pK_a \leq 8.65$, supporting the preceding proposal that the RDS of the present reaction changes at pK_a ca. 9.1. The effect of amine basicity on the k_{-1}/k_2 ratio is illustrated in Figure 2. The Brønsted-type plots are linear for both reactions with primary and secondary amines. Interestingly, the k_{-1}/k_2 ratio for the secondary amines is slightly larger than that for the isobasic

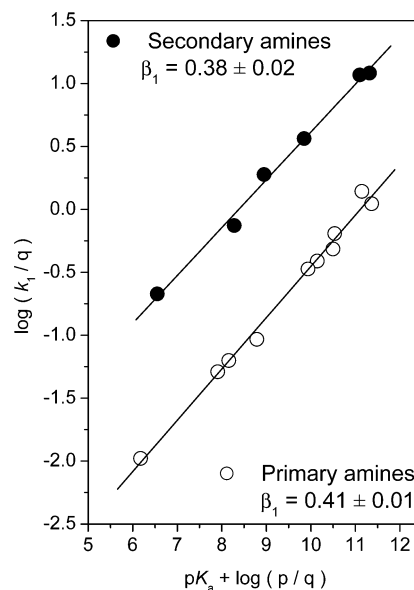


FIGURE 3. Brønsted-type plots for the reactions of 2,4-dinitrophenyl benzenesulfonate (**1c**) with primary and alicyclic secondary amines for the S–O bond fission process in 80 mol % H₂O/20 mol % DMSO at 25.0 ± 0.1 °C. Data for the reactions with primary amines were taken from ref 11.

primary amines, indicating that the k_{-1}/k_2 ratio cannot be responsible for the higher reactivity of secondary amines.

As shown in Figure 3, the k_1 value increases linearly as the amine basicity increases for both reactions with primary and secondary amines. If steric effect plays an important role, the k_1 value is expected to be larger for the reactions with primary amines compared with those with secondary amines of similar basicity. However, unexpectedly, secondary amines exhibit much larger k_1 values than primary amines of similar basicity, indicating that steric effect is insignificant in the present system.

Steric effect would be significant for reactions in which the extent of bond formation between the electrophilic center and nucleophile is greatly advanced. The extent of bond formation in the present system is considered to be insignificant on the basis of the small β_1 value (e.g., 0.38 and 0.41 for the reactions of **1c** with secondary and primary amines, respectively), which accounts for the absence of the steric effect in the present system. Therefore, one can suggest that the larger k_1 value for the reaction with secondary amines is fully responsible for the higher reactivity shown by secondary amines compared with the primary amines of similar basicity.

Effect of Nonleaving Group Substituents on Rates and Mechanism for the S–O Bond Fission. The effect of nonleaving group substituents on reaction mechanism is controversial.^{5f,11,17–20} Castro et al. have suggested that the electronic nature of the substituent in the nonleaving group affects the pK_a° value for aminolyses of 2,4-dinitrophenyl and *S*-4-nitrophenyl X-substituted benzoates in aqueous ethanol.¹⁸ A similar conclusion has

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TABLE 3. Summary of Second-Order Rate Constants (k_N^{S-O}) for the Reactions of 2,4-Dinitrophenyl X-Substituted Benzenesulfonates (1a–e) with Piperidine and Piperazinium Ion for the S–O Bond Fission in 80 mol % H₂O/20 mol % DMSO at 25.0 ± 0.1 °C

| X | $k_N^{S-O}/M^{-1} s^{-1}$ | |
|-------------------|---------------------------|---------------------------------|
| | piperidine | piperazinium ion |
| 4-NO ₂ | 49.9 ± 0.5 | (35.5 ± 0.2) × 10 ⁻³ |
| 4-Cl | 15.1 ± 0.3 | (16.5 ± 0.6) × 10 ⁻³ |
| H | 11.1 ± 0.3 | (11.9 ± 0.3) × 10 ⁻³ |
| 4-Me | 8.20 ± 0.05 | (8.84 ± 0.3) × 10 ⁻³ |
| 4-MeO | 5.30 ± 0.07 | (6.70 ± 0.2) × 10 ⁻³ |

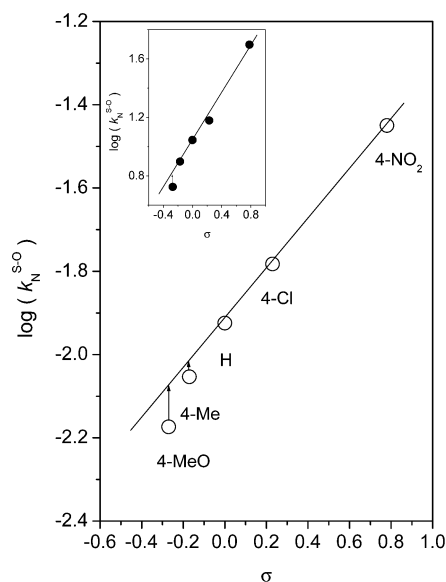


FIGURE 4. Hammett plots for the reactions of 2,4-dinitrophenyl X-substituted benzenesulfonates with piperidine (●, the inset) and piperazinium ion (○) for the S–O bond fission process in 80 mol % H₂O/20 mol % DMSO at 25.0 ± 0.1 °C.

been drawn for aminolyses of carbonate, thio, and dithio esters by Jencks¹⁹ and Lee et al.²⁰ However, we have recently reported that the effect of substituent in the nonleaving group on reaction mechanism is insignificant for various reactions of aryl benzoates and sulfonates with amines as well as anionic nucleophiles (e.g., OH⁻, CN⁻, and N₃⁻) in 80 mol % H₂O/20 mol % DMSO.^{5t,11,17}

To investigate the effect of nonleaving group substituent on the reaction mechanism, we have performed reactions of 2,4-dinitrophenyl X-substituted benzenesulfonates (1a–e) with piperidine and piperazinium ion. One might expect a significant difference in the substituent effect between the two reaction series since their RDS is considered to be not the same as discussed in the preceding section (e.g., the k_1 step for strongly basic piperidine and the k_2 step for weakly basic piperazinium ion).

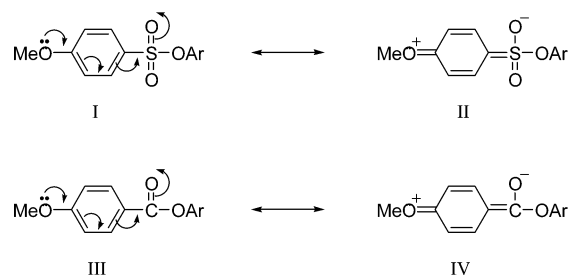
In Table 3 are summarized the second-order rate constants for the reactions of 1a–e with piperidine and piperazinium ion determined for the S–O bond fission.

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It is shown that the second-order rate constant for the reactions with piperidine decreases as the substituent in the nonleaving sulfonyl moiety changes from an EWG to an EDG, i.e., from 49.9 to 11.1 and 5.30 M⁻¹ s⁻¹ as the substituent X changes from 4-NO₂ to H and 4-MeO, respectively. A similar result can be seen for the corresponding reactions with piperazinium ion, although it is ca. 10³ times less reactive than piperidine.

The effect of sulfonyl substituent X on rates has been demonstrated in Figure 4. The point for X = 4-MeO exhibits a negative deviation from the linear Hammett plots for both reactions with piperazinium ion and piperidine. One might consider that a change in the RDS or mechanism is responsible for the negative deviation from the linear Hammett plot. However, we have recently shown that such a negative deviation is not due to a change in RDS or reaction mechanism but due to stabilization of the ground-state through resonance between the electron donating substituent and the sulfonyl or carbonyl group as shown in resonance structures I ↔ II and III ↔ IV.^{4c,11,17a}



If the ground-state resonance stabilization is responsible for the negative deviation shown in Figure 4, one can expect that the Yukawa–Tsuno equation (eq 7)²¹ would give much better correlation than the Hammett equation.

$$\log(k^X/k^H) = \rho[\sigma^+ + r(\sigma^- - \sigma^0)] \quad (7)$$

In fact, the Yukawa–Tsuno plots in Figure 5 exhibit much better correlation than the Hammett plots in Figure 4, indicating that the resonance structure II is responsible for the negative deviation shown by 4-MeO from the linear Hammett plots. Thus, the present study further confirms our previous proposal that the electronic nature of the substituent in the nonleaving group does not affect the reaction mechanism and the negative deviation on the Hammett plots is due to ground-state stabilization through resonance.

The Yukawa–Tsuno equation has been applied to numerous reaction systems in which a partial positive charge develops in the transition state of the RDS.^{21–24}

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(23) (a) Nakashima, T.; Fujiyama, R.; Kim, H. J.; Fujio, M.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 429–438. (b) Nakashima, T.; Fujiyama, R.; Fujio, M.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1043–1047. (c) Nakashima, T.; Fujiyama, R.; Fujio, M.; Tsuno, Y. *Tetrahedron Lett.* **1999**, *40*, 539–542.

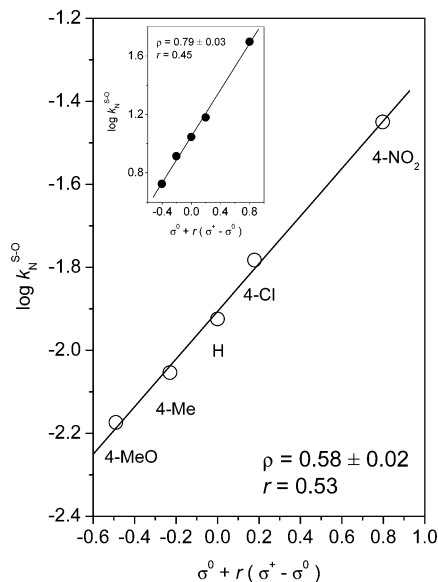


FIGURE 5. Yukawa–Tsuno plots for the reactions of 2,4-dinitrophenyl X-substituted benzenesulfonates with piperidine (●) and piperazinium ion (○) for the S–O bond fission process in 80 mol % H₂O/20 mol % DMSO at 25.0 ± 0.1 °C.

Since an EDG can stabilize a positively charged transition state, the point for an EDG in the nonleaving group has often exhibited a positive deviation from the Hammett plot with a negative ρ value.^{21–24} Interestingly, the present reaction system results in an opposite result, e.g., a negative deviation with a positive ρ value. However, the present result is not so surprising but consistent with our proposal that an EDG in the nonleaving group stabilizes the ground-state of the substrate as shown in the resonance structures I ↔ II.

The magnitude of the r value in a Yukawa–Tsuno plot represents a relative extent of resonance contribution. The r value has been reported to be as large as 1.53 for solvolysis of 1-aryl-2,2,2-trifluoroethyl tosylates, in which the resonance demand is significantly high due to the α -CF₃ group.²⁴ The r value for the reactions of **1a–e** with secondary amines has been determined to be in a range 0.45–0.53. A similar r value (0.49–0.57) has recently been reported for the corresponding reactions with primary amines,¹¹ indicating that the nature of amine (primary vs secondary amines) does not affect the r value greatly. However, the r value for the sulfonyl system appears to be significantly smaller than that for the carbonyl system; i.e., the r value has been reported to be in a range 0.7–1.3 for the reaction of 4-nitrophenyl X-substituted benzoates with secondary amines in the same medium as in the present system.^{4c} Thus, one can suggest that the resonance contribution is much less significant for I ↔ II than for III ↔ IV. This argument is consistent with the report that a C=S bond is weaker than a C=C bond due to inefficient overlap of 2p and 3p orbitals.²⁵

The rate of nucleophilic attack (k_1) would be accelerated by an EWG in the nonleaving sulfonyl moiety but

TABLE 4. Summary of Second-Order Rate Constants (k_N^{C-O}) for the Reaction of 2,4-dinitrophenyl X-Substituted Benzenesulfonates (**1a–e**) with Piperidine and Piperazinium Ion in 80 mol % H₂O/20 mol % DMSO at 25.0 ± 0.1 °C

| X | $10^3 k_N^{C-O}/M^{-1} s^{-1}$ | |
|-------------------|--------------------------------|------------------|
| | piperidine | piperazinium ion |
| 4-NO ₂ | <i>a</i> | 10.0 |
| 4-Cl | <i>a</i> | 5.20 |
| H | <i>a</i> | 6.20 |
| 4-Me | <i>a</i> | 4.16 |
| 4-MeO | <i>a</i> | 3.60 |

^a The k_N^{C-O} value for reactions with piperidine could not be determined due to the fact that no detectable C–O bond fission products were found.

retarded by an EDG. Thus, one might expect a large ρ value for a reaction in which nucleophilic attack is the RDS. However, the rate of leaving group departure (k_2) would be decreased by an EWG in the nonleaving group but increased by an EDG. Accordingly, one can expect that the magnitude of the ρ value would be small for a reaction in which leaving group departure is involved in the RDS due to the opposing substituent effect. The ρ values in Figure 5 have been determined to be 0.79 and 0.58 for the reactions with piperidine and piperazinium ion, respectively. As discussed in the preceding section, the RDS of the present reaction has been suggested to change from the k_2 to the k_1 step as the nucleophile varies from weakly basic piperazinium ion to strongly basic piperidine. The result exhibiting a larger ρ for the reactions with piperidine (0.79) than with piperazinium ion (0.58), although the difference is not significant, is consistent with the argument that the nature of the RDS affects the magnitude of the ρ value.

Effect of Amine Basicity and Sulfonyl Substituent X on Rate for C–O Bond Fission. As shown in Table 1, the k_N^{C-O} value for the reaction of **1c** with secondary amines increases as the amine basicity increases up to $pK_a = 9.85$. However, no k_N^{C-O} value could be determined for the more basic amines such as piperidine and 3-methylpiperidine since no detectable C–O bond fission products were found. Consequently, the plot of $\log k_N^{C-O}$ vs amine basicity exhibited a poor correlation (figure not shown). A similar result is shown in Table 4 (e.g., no k_N^{C-O} values for the reactions of **1a–e** with strongly basic piperidine), indicating that the regioselectivity is significantly influenced by the amine basicity. One can also suggest that the regioselectivity is determined by the electronic nature of the substituent X from the result in Table S2 in the Supporting Information which shows that the percent of the C–O bond fission increases as the substituent X changes from an EWD to an EDG.

The magnitude of the k_N^{C-O} value, shown in Table 4, for the reaction with piperazinium ion exhibits poor correlation with the electronic nature of the substituent X. This is a contrasting result to that obtained for the S–O bond fission process (e.g., good linear Yukawa–Tsuno plots as shown in Figure 5). However, a similar result has recently been reported for the corresponding reaction with primary amines,¹¹ indicating that the poor correlation of the k_N^{C-O} value with the electronic nature of the substituent X is common for reactions of **1a–e** with

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secondary amines as well as primary amines for the C–O bond fission.

One can suggest two plausible explanations for the poor correlation of the $k_{\text{N}^{\text{C}-\text{O}}}$ value with the nature of substituent X: (1) the distance effect and (2) the nature of the reaction mechanism. The inductive effect exerted by the substituent X would diminish with increasing the distance between the substituent and the reaction site. As shown in Scheme 1, the substituent X is one atom farther from the reaction site of the C–O bond fission than that of the S–O bond fission. Accordingly, one might expect that the effect of sulfonyl substituent X on rate is less significant for the C–O bond fission process than for the S–O bond fission.

One can also suggest that the nature of the reaction mechanism is responsible for the poor Hammett correlation for the C–O bond fission process. $\text{S}_{\text{N}}\text{Ar}$ reactions have generally been suggested to proceed through a Meisenheimer complex, in which the formation of the complex is the RDS in most cases.^{26,27} When the RDS is the expulsion of the leaving group from the Meisenheimer complex, the $k_{\text{N}^{\text{C}-\text{O}}}$ value should increase with increasing the electron-withdrawing ability of the substituent in the leaving sulfonyl moiety. However, if the leaving group departure occurs after the RDS, the nature of the substituent in the leaving group would not affect the $k_{\text{N}^{\text{C}-\text{O}}}$ value significantly. Thus, the result that the $k_{\text{N}^{\text{C}-\text{O}}}$ value exhibits poor correlation with the nature of substituent X is consistent with the generally suggested mechanism that the expulsion of the leaving group (e.g., the X-substituted benzenesulfonate in the present system) from the Meisenheimer complex occurs rapidly after the RDS.

Conclusions

The present study has allowed us to conclude the following: (1) The reaction of **1a–e** with alicyclic secondary amines proceeds through the S–O and C–O bond fission pathways competitively. The regioselectivity is governed by the amine basicity and the electronic nature of the sulfonyl substituent X. (2) The S–O bond fission proceeds through an addition intermediate with a change in the RDS at $\text{p}K_{\text{a}}^{\circ} = 9.1$. The nature of amine (e.g., primary vs secondary amines) does not affect the $\text{p}K_{\text{a}}^{\circ}$ value significantly. (3) Secondary amines are more reactive than isobasic primary amines for the S–O bond fission. The larger k_1 value for the reaction with second-

ary amines is fully responsible for their higher reactivity. (4) The ground-state stabilization by resonance structures $\text{I} \leftrightarrow \text{II}$ is responsible for the negative deviation on the Hammett plots for reactions of **1a–e**. However, the resonance contribution to the ground-state stabilization is less significant for the sulfonyl system than for the corresponding carbonyl system. (5) The magnitude of the $k_{\text{N}^{\text{C}-\text{O}}}$ values exhibits poor correlation with the electronic nature of the sulfonyl substituent X. The distance effect and the nature of the reaction mechanism have been suggested to be responsible for the poor correlation.

Experimental Section

Materials. 2,4-Dinitrophenyl X-substituted benzenesulfonates (**1a–e**) were prepared as reported previously.¹¹ Amines and other chemicals were of the highest quality available and were recrystallized or distilled before use whenever necessary. The reaction medium was H_2O containing 20 mol % DMSO to eliminate solubility problems. DMSO was distilled over calcium hydride at a reduced pressure and stored under nitrogen. Doubly glass distilled water was further boiled and cooled under nitrogen just before use.

Kinetics. The kinetic studies were performed using a UV–vis spectrophotometer equipped with a constant-temperature circulating bath for slow reactions ($t_{1/2} > 10$ s) or a stopped-flow spectrophotometer for fast reactions ($t_{1/2} \leq 10$ s). The reactions were followed by monitoring the appearance of 2,4-dinitrophenoxide ion, as an S–O bond fission product. Typically, the reaction was initiated by adding 5 μL of a 0.02 M substrate stock solution in CH_3CN by a 10 μL syringe to a 10 mm UV cell containing 2.50 mL of the reaction medium and the amine: $[\text{substrate}] = \text{ca. } 4 \times 10^{-5} \text{ M}$, $[\text{amine}] = \text{ca. } (1.5\text{--}95) \times 10^{-3} \text{ M}$. 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 to 1 equiv of standardized HCl solution to obtain a self-buffered solution. All the transfers of solutions were carried out by means of gastight syringes. Concentrations and pseudo-first-order rate constants (k_{obsd}) for the individual kinetic experiment are given in the Supporting Information.

Product Analysis. The amount of 2,4-dinitrophenoxide ion formed during the S–O bond fission process was determined quantitatively by measuring the optical density with the same UV–vis spectrophotometer used for the kinetic study. Other products (e.g., benzenesulfonate, 1-(phenylsulfonyl)piperidine, and 1-piperidino-2,4-dinitrobenzene) were analyzed by HPLC. The eluent was 50/50 MeCN/MeOH (v/v) with with 1 mL/min flow rate.

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Supporting Information Available: Equations to determine the k_{-1}/k_2 ratio (eqs S1–S6) and Tables S1–S16 for the results of the kinetic studies for reactions of **1a–e** with alicyclic secondary amines in 80 mol % H_2O /20 mol % DMSO at 25.0 ± 0.1 °C. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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