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A Mechanistic Study on Nucleophilic Substitution Reactions of Aryl Substituted Benzenesulfonates with Anionic Nucleophiles

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Second-order rate constants have been measured spectrophotometrically for the nucleophilic substitution reactions of aryl substituted benzenesulfonates (1, X-$C_6H_4SO_2$-OC_6H_4-Y) with aryloxides (Z-$C_6H_4O^-$) and ethoxide (EtO^-) in absolute ethanol at 25℃. The nucleophilicity of aryloxides increases with increasing electron donating ability of the substituent (Z) on aryloxides, and results in a good Hammett correlation with σ^- constant. The reactivity of 1 toward aryloxides and ethoxide shows also significant dependence on the electronic nature of the substituent X and Y. Large positive ρ_{acyl} values have been obtained for the reaction of **1** with phenoxide and ethoxide, indicating that the leaving group departure is little advanced at the transition-state of the rate-determining step. This has been further supported from the fact that σ^- constant gives extremely poor Hammett correlation, while σ^0 does reasonably good correlation for the reaction of **1** with ethoxide. Thus, the present sulfonyl-transfer reaction is proposed to proceed *via* a rate-determining attack of nucleophile to the sulfur atom of **1** followed by a fast leaving group departure.

Introduction

Since acyl-transfer reactions are known to be significantly important in chemistry and biochemistry, numerous studies have been performed in order to investigate the reaction mechanism.[1-3] However, detailed reaction mechanisms have not been fully understood.[4,5] Two distinct reaction pathways have been suggested, *i.e.* one-step concerted and step-wise addition-elimination pathways.[4-7] One-step mechanism has been known to proceed *via* a single transition-state in which bond formation by nucleophile occurs concertedly with leaving group departure.[4,5] On the hand, step-wise mechanism has been suggested to proceed *via* formation of an addition intermediate.[6,7]

The argument concerning reaction mechanisms is considered mainly on the basis of linear free energy relationships (LFER),[8] and the discrepancy seems to originate from lack of systematic studies. Therefore, we have performed a systematic study on LFER in order to investigate reaction mechanism. The reaction system chosen are the following nucleophilic substitution reactions of aryl substituted benzenesulfonates in absolute ethanol at 25.0℃. Unlike carboxylate esters, sulfonate esters have not been studied intensively. Furthermore, the systematic variation of substituents on the sulfonyl moiety, entering and leaving phenoxides in the present system would be considered to give us important informations concerning the reaction mechanism.

Experimental

Materials. The aryl substituted benzenesulfonates in the present study were easily prepared by a modification of the

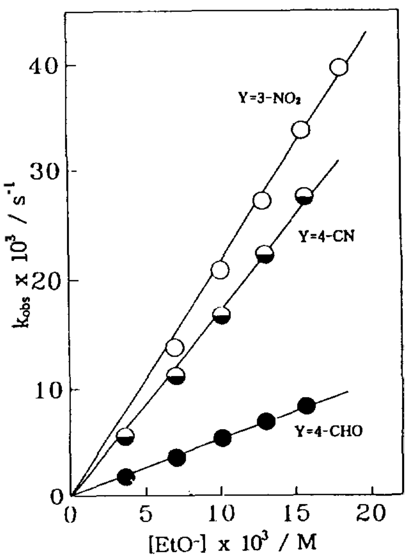
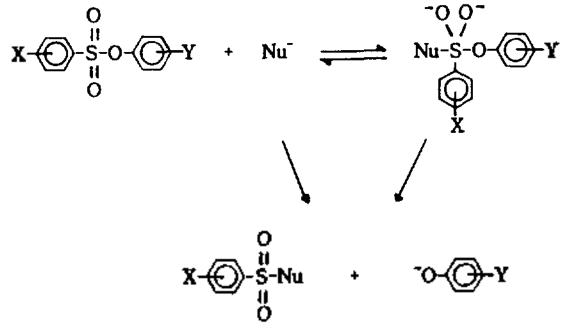


Figure 1. Plots of observed rate constant (k_{obs}) versus concentration of EtO^- for the reactions of substituted phenyl 4-nitrobenzenesulfonates ($4\text{-}NO_2\text{-}C_6H_4SO_2\text{-}OC_6H_4\text{-}Y$) with ethoxide in EtOH at 25.0℃.



X = 4-CH₃O, 4-CH₃, H, 4-Cl, 3-NO₂, 4-NO₂

Y = 3-CHO, 4-COCH₃, 4-CHO, 4-CN, 3-NO₂, 4-NO₂

Nu⁻ = EtO⁻

(Z = 4-CH₃O, 4-CH₃, H, 3-CHO, 3-Cl, 4-COCH₃, 4-CN, 4-CHO)

method in the literature[9] using substituted benzenesulfonyl chlorides and the corresponding phenol. Their purity was checked by means of their melting point and spectral data such as IR and ¹H-NMR characteristics. The benzenesulfonyl chlorides, phenols and other chemicals were of the highest quality available (Aldrich) and were generally recrystalized before use. Absolute ethanol was prepared by the method described in the literature[9] under a nitrogen atmosphere.

Kinetics. The kinetic studies were performed with a Hitachi U-2000 Model UV-Vis spectrophotometer equipped with a Neslab RTE-110 Model constant temperature circulating bath to keep the temperature in the UV cell at 25.0± 0.1 ℃. The reactions were followed by monitoring the appearance of the leaving phenoxides at a fixed wavelength corresponding the maximum absorption (λ_{max}) of $Y\text{-}C_6H_4O^-$. All the reactions were carried out under pseudo-first-order conditions in which the concentration of nucleophile was generally 20 times, but at least 10 times greater than the substrate concentration. The stock solutions of the nucleophilic phenoxides were made of with potassium ethoxide solution and 2 equivalent corresponding phenol to suppress formation of ethoxide ion by solvolysis as described previously[10] and stored under a nitrogen atmosphere. The concentration of potassium ethoxide solution was titrated against potassium hydrogen phthalate. Typically, reaction was initiated by adding 5 μl of 0.02 M solution of the substrate in CH_3CN by syringe to a 10 mm UV cell containing 2.50 ml of absolute ethanol and the nucleophile solution. All the transfer of reactant solutions were carried out by means of Hamilton gas-tight syringes.

Table 1. Summary of Second Order Rate Constants (k_2, $M^{-1}s^{-1}$) for the Reaction of 2,4-Dinitrophenyl Benzenesulfonate with Aryloxides ($Z\text{-}C_6H_4O^-$) in EtOH at 25.0℃[a]

	Z	σ	σ⁻	k_2, $M^{-1}s^{-1}$
1	4-CH₃O	−0.27		2.85
2	4-CH₃	−0.17		1.53
3	H	0.00		0.874
4	3-CHO	0.35		0.343
5	3-Cl	0.37		0.307
6	4-COCH₃	0.50	0.87	0.0391
7	4-CN	0.66	1.00	0.0337
8	4-CHO	0.42	1.13	0.0180

[a] The substituent constant values (σ, σ⁻) were taken from reference 18.

Results

All the reactions studied here obeyed pseudo-first-order kinetics up to over 90% of the total reaction. Pseudo-first-order rate constants (k_{obs}) were obtained from the Guggenheim equation, $\ln(A_\infty - A_t) = -k_{obs}t + C$. Correlation coefficients of the linear regressions were usually higher than 0.9995. Generally, five different concentrations of nucleophile solution were used to get second-order rate constants (k_2) from the slope of the plot of k_{obs} *vs* concentration of nucleophile. In Figure 1 are demonstrated typical plots of k_{obs} *vs* concentration of nucleophile solution. Standard deviations of the slopes were less than 3%. Second-order rate constants obtained in this way are summarized in Tables 1-3 together with various σ constants of the corresponding substituent. The kinetic data are shown graphically in Figures 2-5.

Discussion

The effect of substituents on the entering group. Second-order rate constants have been summarized in Table 1 and demonstrated graphically in Figure 2 for the reaction of 2,4-dinitrophenyl benzenesulfonate with substituted phenoxides. As shown in the table, the nucleophilic reactivity of the phenoxides increases with increasing electron donating ability of the substituents. On the other hand, phenoxides containing electron withdrawing substituents exhibit decreased reactivities. The decrease in nucleophilicity appears to be more significant for the phenoxide containing CN,

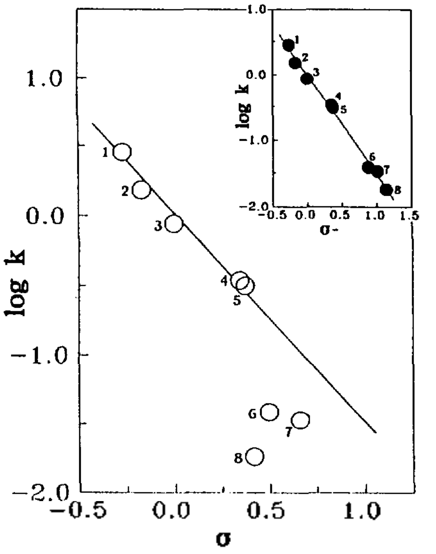


Figure 2. Hammett plots for the reaction of 2,4-dinitrophenyl benzenesulfonate ($C_6H_5SO_2$-OC_6H_3-2,4-NO_2) with aryloxides (Z-$C_6H_4O^-$) in EtOH at 25.0℃. The numbers refer to the aryloxide in Table 1.

CHO, or $COCH_3$ at the 4-position. This is clearly demonstrated in Figure 2, *i.e.* the logarithmic second-order rate constants for these phenoxides exhibit significantly negative deviations from the Hammett linear line.

The negative charge on the oxygen atom of a phenoxide anion can be delocalized to the substituent by direct resonance when CN, CHO or $COCH_3$ is substituted at the 4-position. However, the charge delocalization is not possible for the phenoxide containing Cl or CHO at the 3-position and for the ones containing electron donating substituents. The charge delocalization in this manner would cause an extra stabilization and result in further decrease in the nucleophilicity of the phenoxides.

Therefore, the negative deviations shown by 4-CN-$C_6H_4O^-$, 4-CHO-$C_6H_4O^-$ and 4-$COCH_3$-$C_6H_4O^-$ are not considered due to any mechanistic difference for these phenoxides from the other ones. Instead, resonance stability would be responsible for the negative deviations. This argument can be supported from the inset of Figure 2. As shown in the figure, the logarithmic second-order rate constants give a good Hammett correlation with σ^- constants which represent resonance effect together with inductive effect for the substituent.[11]

Although validity of the traditional interpretation of Hammett ρ value has been questioned for decades,[12,13] it conveys most important information regarding the transition state structure.[8,14] The magnitude of ρ value has been most widely used as a relative measure of electron transmission or a degree of bond formation at the transition state (TS) of the rate-determining step (RDS).[10,15] The ρ_{nuc} value obtained in the present reaction system is −1.53. This large ρ_{nuc} value implies that the degree of electron transmission and bond formation at the TS is significantly advanced. Therefore, it is considered that the attack of the phenoxides to the sulfur atom of the sulfonate ester is deeply involved in the RDS.

Table 2. Summary of Second-Order Rate Constants (k_2, $M^{-1}s^{-1}$) for the Reaction of 2,4-Dinitrophenyl Substituted Benzenesulfonates (X-$C_6H_4SO_2$-OC_6H_3-2,4-NO_2) with Phenoxide ($C_6H_5O^-$) in EtOH at 25.0℃[a]

	X	σ	k_2, $M^{-1}s^{-1}$
1	4-CH_3O	−0.27	0.253
2	4-CH_3	−0.17	0.443
3	H	0.00	0.874
4	4-Cl	0.23	2.30
5	3-NO_2	0.71	64.5
6	4-NO_2	0.78	113

[a] The substituent constant values (σ) were taken from reference 18.

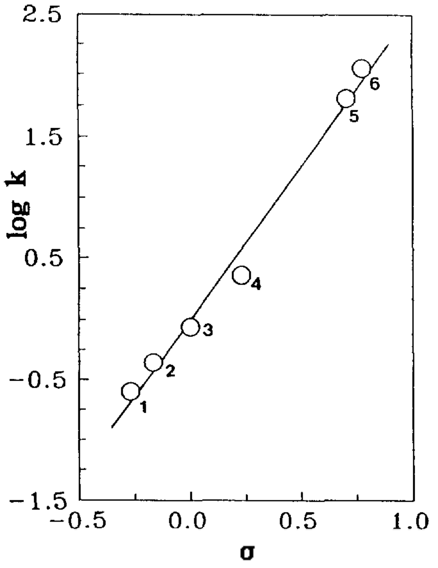


Figure 3. Hammett plot for the reaction of 2,4-dinitrophenyl substituted benzenesulfonates (X-$C_6H_4SO_2$-OC_6H_3-2,4-NO_2) with phenoxide in EtOH at 25.0℃. The numbers refer to the substrate in Table 2.

The effect of substituent on the acyl group. Second-order rate constants have been summarized in Table 2 for the reactions of 2,4-dinitrophenyl substituted benzenesulfonates with phenoxide. It is demonstrated that the reactivity of the sulfonate esters increases with increasing electron withdrawing ability of the substituent on the acyl moiety,[16] indicating that the TS of the reaction is stabilized by the presence of electron withdrawing substituents. For a quantitative analysis of the substituent effect on rate, a Hammett plot has been constructed in Figure 3. An excellent linearity has been obtained from the correlation of logarithmic second-order rate constant with σ constant. The ρ_{acyl} value obtained is +2.52, indicating that the reactivity of the sulfonate esters is significantly influenced by the electronic nature of the substituents.

One would attribute the large ρ_{acyl} value to a proximity effect, since the reaction center is closely connected to the aromatic ring in the present reaction system. However, the nature of the reaction mechanism would be considered to be more responsible for the large ρ_{acyl} value. Since an electron withdrawing substituent on the acyl moiety can decrease the electron density of the reaction center, the electrophili-

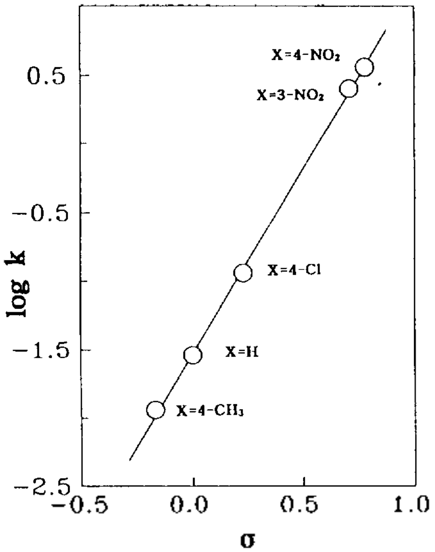


Figure 4. Hammett plot for the reaction of 4-nitrophenyl substituted benzenesulfonates (X-$C_6H_4SO_2$-OC_6H_4-4-NO_2) with ethoxide in EtOH at 25.0℃. The kinetic data were taken from reference 17.

city of the substrates would be enhanced when it is substituted on the acyl moiety. Accordingly, the attack of nucleophilic phenoxide would be aided by the presence of electron withdrawing substituents on the acyl moiety and cause a large positive ρ_{acyl} value. On the other hand, leaving group departure would be inhibited significantly by the presence of electron withdrawing substituents on the acyl moiety. Therfore, a negative ρ_{acyl} value would be obtained for the leaving group departing process. Such an opposing substituent effects would effectively cancel each other and the rate would be little influenced upon changing substituents (*e.g.* a small ρ_{acyl} value), if the leaving group departure is involved in the RDS whether the reaction proceeds *via* one-step or step-wise mechanism. However, if the leaving group departure is not involved in the RDS, the opposing substituent effects would be absent, and would result in a large positive ρ_{acyl} value. Therefore, the ρ_{acyl} value of +2.52 obtained in the present system indicates clearly that the leaving group departure is not the slow step. Consequently, one-step concerted mechanism is excluded for the present reaction system.

Determination of reaction mechanism based on the magnitude of ρ values in this way has successfully been applied to the reaction of substituted benzaldehydes with semicarbazide.[17] Jencks *et al.* observed significantly large positive ρ value for the reactions run in an acidic medium,[17] in which the RDS has been known to be the addition of semicarbazide to the carbonyl carbon of benzaldehydes to form a carbinolamine. On the other hand, the reactivity of benzaldehydes was reported to be little sensitive to the electronic nature of the substituents in neutral pH,[17] in which the dehydration of the carbinolamine has been known to be the RDS.

A further evidence supporting the proposed reaction mechanism has been obtained in the reaction of 4-nitrophenyl substituted benzenesulfonates with ethoxide. As shown in Figure 4, the reactivity of the substrate increases with increasing electron withdrawing ability of the substituent. As a result, a good Hammett correlation is obtained with a large positive ρ_{acyl} value (+2.68). This value is comparable with the one obtained from the reaction of 2,4-dinitrophenyl substituted benzenesulfonates with phenoxide (ρ_{acyl}= +2.52),[18] and supports the argument that the leaving group departure is not involved in the RDS. Therefore, the slow step of the present sulfonyl-transfer reaction would be considered to be the attack of nucleophile to the sulfur atom of the sulfonyl group.

Table 3. Summary of Second-Order Rate Constants (k_2, $M^{-1}s^{-1}$) for the Reaction of Substituted Phenyl 4-Nitrobenzenesulfonates (4-NO_2-$C_6H_4SO_2$-OC_6H_4-Y) with Ethoxide (EtO^-) in EtOH at 25.0 ℃[a]

	Y	σ^-	σ^0	k_2, $M^{-1}s^{-1}$
1	3-CHO	0.36	0.36	0.110
2	4-$COCH_3$	0.87	0.46	0.344
3	4-CHO	1.13	0.49	0.544
4	4-CN	1.00	0.69	1.81
5	3-NO_2	0.71	0.70	2.30
6	4-NO_2	1.27	0.82	3.61

[a] The substituent constant values (σ^-, σ^0) were taken from reference 18.

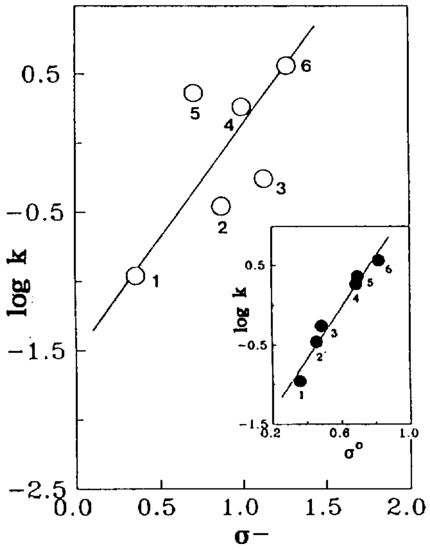


Figure 5. Hammett plots for the reaction of substituted phenyl 4-nitrobenzenesulfonates (4-NO_2-$C_6H_4SO_2$-OC_6H_4-Y) with ethoxide in EtOH at 25.0℃. The numbers refer to substrate in Table 3.

The effect of substituent on the leaving group. In order to examine the degree of leaving group departure at the TS of the RDS, the reactions of substituted phenyl 4-nitrobenzenesulfonates with ethoxide were investigated. In Table 3 are summarized the kinetic results, in which the reactivity of the substrates seems to increase with increasing electron withdrawing ability of the substituent on the leaving group. However, a careful examination of the data reveals interesting phenomena. NO_2 group in the 3-position of the aromatic ring is a weaker electron withdrawing substituent than $COCH_3$ group in the 4-position based on σ^- constant.

However, the rate enhancing effect of the former substituent is more significant than that of the latter. A similar result can be seen for CN and CHO in the 4-position, *i.e.* σ^- values for 4-CN and 4-CHO are 1.00 and 1.13, and k_2 values are 1.81 and 0.544 $M^{-1}s^{-1}$, respectively. Such unusual substituent effects on rate have been demonstrated in Figure 5, in which σ^- constants exhibit an extremely poor correlation with logarithmic second-order rate constants.

If the leaving group departure is advanced at the TS of the RDS, the developing negative charge on the oxygen atom of the leaving phenoxides would be delocalized on the substituents at 4-position by direct resonance as discussed in the preceding section. Therefore, one would expect that σ^- constant gives a good Hammett correlation in this case. However, the correlation of σ^- constant with log k_2 has been demonstrated to be extremely poor (Figure 5), indicating that the negative charge on the oxygen atom of the leaving phenoxides is insignificantly developed at the TS of the RDS. This is quite consistent with the preceding argument, based on the magnitude of the ρ_{acyl} values, *i.e.* the leaving group departure is not involved in the RDS.

Since σ^0 scale was devised mainly from the ionization of substituted phenylacetic acids ($X\text{-}C_6H_4CH_2CO_2H$), this scale fits best for insulated reaction systems in which through-conjugation is entirely excluded by the presence of CH_2 group.[19] Therefore, σ^0 scale has been used as a measure of inductive effect without any resonance contribution. As shown in the inset of Figure 5, σ^0 constant gives better Hammett correlation than σ^-. This result indicates that the electron withdrawing substituents accelerate the reaction rate simply by enhancing electrophilicity of the substrates by inductive effects of the substituents. Therefore, the finding of a better Hammett correlation with σ^0 than σ^- constant in the present system provides a conclusion that the degree of leaving group departure at the TS of the RDS is negligible in the present sulfonyl transfer reaction system.

Conclusions

The present studies of substituent effect on rate have allowed us the following conclusions. (1) Substituent constants should be carefully chosen in order to elucidate the TS structure of the RDS properly. (2) The present sulfonyl-transfer reaction proceeds *via* a rate-determining attack of nucleophiles to the sulfur atom of the substrates followed by a fast leaving group departure, and one-step reaction mechanism is excluded.

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16. The term "acyl group" has been defined to mean to electrophilic component (A) of any acid (A-OH) such as carbonyl (RCO), phosphoryl (O_3P^{2-}), sulfuryl (O_3S^-), sulfonyl (RSO_2), sulfenyl (RS), or phosphinyl (R_2PO) by Williams; Williams, A. *Acc. Chem. Res.* **1989**, *22*, 387.
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