

Kinetic Study on S_NAr Reaction of 1-Y-Substituted-phenoxy-2,4-dinitrobenzenes with Hydroxide Ion: Effect of Substituent Y on Reactivity and Reaction Mechanism

Tae-Ah Kang,[†] Hyo-Jin Cho,[‡] and Ik-Hwan Um^{*}

Department of Chemistry and Nano Science and [†]Department of Life Science, Ewha Womans University, Seoul 120-750, Korea. *E-mail: ihum@ewha.ac.kr

[‡]Department of Chemistry, Duksung Women's University, Seoul 132-714, Korea
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A kinetic study is reported for the S_NAr reaction of 1-Y-substituted-phenoxy-2,4-dinitrobenzenes (**1a-1h**) with OH⁻ in 80 mol % H₂O/20 mol % DMSO at 25.0 ± 0.1 °C. The second-order rate constant (*k*_{OH⁻}) increases as the substituent Y in the leaving group changes from an electron-donating group (EDG) to an electron-withdrawing group (EWG). The Brønsted-type plot for the reactions of **1a-1h** is linear with β_g = -0.16, indicating that the reactivity of substrates **1a-1h** is little affected by the leaving-group basicity. A linear Brønsted-type plot with β_g = -0.3 ± 0.1 is typical for reactions reported previously to proceed through a stepwise mechanism in which formation of a Meisenheimer complex is the rate-determining step (RDS). The Hammett plot correlated with σ_Y^o constants results in a much better correlation than that correlated with σ_Y⁻ constants, implying that no negative charge is developing on the O atom of the leaving group (or expulsion of the leaving group is not advanced at all in the TS). This excludes a possibility that the S_NAr reaction of **1a-1h** with OH⁻ proceeds through a concerted mechanism or *via* a stepwise pathway with expulsion of the leaving group being the RDS. Thus, the current reactions have been concluded to proceed through a stepwise mechanism in which expulsion of the leaving group occurs rapidly after the RDS.

Key Words : S_NAr reaction, 1-Phenoxy-2,4-dinitrobenzene, Brønsted-type plot, Hammett plot, Reaction mechanism

Introduction

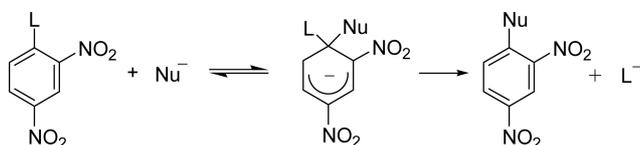
Aromatic nucleophilic substitution (S_NAr) reactions of activated aromatic or heteroaromatic compounds and their reaction mechanisms have intensively been investigated due to their importance in organic transformation.¹⁻⁴ To give but a few examples, S_NAr reactions have been found to be useful in synthesis including improved methods of stereoselective reactions,⁵⁻⁷ in derivatization to external analytical detection limits,⁸ in preparation of electrophilic derivatives of water-soluble polymers,⁹ and in some environmental remediation protocols.¹⁰⁻¹²

It is now firmly understood that S_NAr reactions follow a two-step reaction mechanism as depicted in Scheme 1 with 1-L-2,4-dinitrobenzene and an anionic nucleophile Nu⁻ (*i.e.*, formation of a negatively charged σ-complex, commonly called as a Meisenheimer complex, and followed by elimination of the leaving group, L⁻). Experimental studies including Mass spectrometry experiments have shown that stable Meisenheimer complexes may be formed for S_NAr reactions between strong nucleophiles and highly electron-

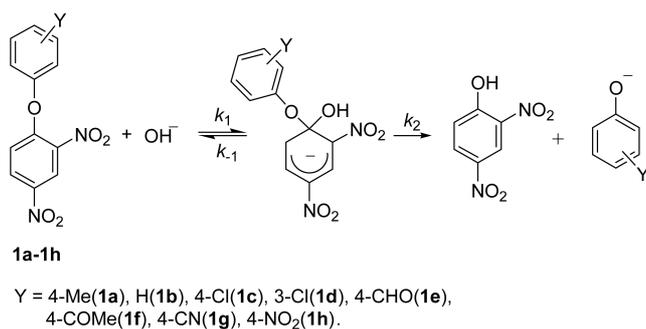
deficient aromatic or heteroaromatic compounds.^{13,14} In contrast, some computational studies have suggested that Meisenheimer complexes may be formed as a transition state (TS) but not as an intermediate in a majority of reactions.¹⁵

S_NAr reactions have a similarity to nucleophilic substitution reactions of carboxylic esters. The apparent similarity is the nucleophilic addition step in S_NAr reaction and the addition step to carbonyl group in ester. In both cases addition to the sp² carbon leads to rehybridization to sp³ to produce a tetrahedral intermediate. Elimination of the leaving group in subsequent step(s) restores the sp² carbon. A fundamental difference is that addition to a typical electron-deficient aromatic substrate in an S_NAr reaction entails loss of aromaticity in the formation of the Meisenheimer complex. Accordingly, expulsion of the leaving group occurs rapidly after the RDS to regain the lost aromaticity in most cases.

We have carried out S_NAr reactions of 1-L-2,4-dinitrobenzenes with a series of cyclic secondary amines in MeCN and found that the reaction proceeds with one or two intermediates depending on the nature of L (*i.e.*, a zwitterionic tetrahedral intermediate T[±] and its deprotonated form T⁻ when L = F but without the deprotonation process to form T⁻ from T[±] when L = Cl, Br and I).¹⁶ In our previous study on the S_NAr reactions, we applied Brønsted analysis to deduce the reaction mechanism.¹⁶ Although this tool has been used extensively for nucleophilic substitution reactions of esters



Scheme 1



Scheme 2

with various nucleophiles,¹⁷⁻²⁰ its application to S_NAr reactions has been more modest.¹⁶

Our study has now been extended to the S_NAr reactions of 1-(Y-substituted-phenoxy)-2,4-dinitrobenzenes with OH⁻ ion in 80 mol % H₂O/20 mol % DMSO (Scheme 2). Eight different substituents have been introduced to investigate the reaction mechanism, *e.g.*, from an electron-donating substituent (*e.g.*, 4-Me) to strong electron-withdrawing groups (*e.g.*, 4-CN and 4-NO₂). We wish to report that analysis of Brønsted-type plot and Hammett correlations with σ^- and σ^+ constants is highly effective in deduction of the reaction mechanism including the nature of the RDS.

Results and Discussion

The kinetic study was carried out under pseudo-first-order conditions in which the NaOH concentration was kept in excess of the substrate concentration. All of the reactions in this study obeyed pseudo-first-order kinetics with quantitative liberation of 2,4-dinitrophenoxide ion. Pseudo-first-order rate constants (k_{obsd}) were calculated from the slope of the plots of $\ln(A_\infty - A_t)$ vs. t , which were linear over 90% of the total reaction. The uncertainty in the k_{obsd} values is estimated to be less than $\pm 3\%$ from replicate runs. The plots of k_{obsd} vs. $[\text{OH}^-]$ were linear and passed through the origin (*e.g.*, Figure 1 for the reactions **1a-1c**). The second-order

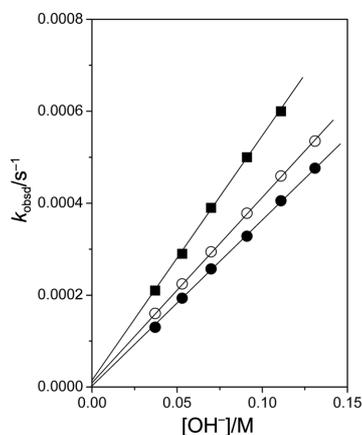


Figure 1. Plots of k_{obsd} vs. $[\text{NaOH}]$ for the S_NAr reactions of 1-Y-substituted-phenoxy-2,4-dinitrobenzoates **1a** (●), **1b** (○) and **1c** (■) with OH⁻ in 80 mol % H₂O/20 mol % DMSO at 25.0 \pm 0.1 °C.

rate constants (k_{OH^-}) were calculated from the slope of the linear plots and are summarized in Table 1 together with the ranges of the OH⁻ concentrations and k_{obsd} values.

Effect of Substituent Y on Reactivity. As shown in Table 1, the reactivity of **1a-1h** increases as the substituent Y in the leaving group changes from an electron-donating group (EDG) to a strong electron-withdrawing group (EWG), *e.g.*, k_{OH^-} increases from $3.62 \times 10^{-3} \text{ M}^{-1}\text{s}^{-1}$ to $12.1 \times 10^{-3} \text{ M}^{-1}\text{s}^{-1}$ as the substituent Y changes from 4-Me to Y = 4-NO₂, respectively. The change in substituent Y from 4-Me to 4-NO₂ increases the leaving-group basicity over 3 pK_a units. Interestingly, the k_{OH^-} value increases only *ca.* 3 times upon increasing leaving-group basicity over 3 pK_a units, indicating that the effect of leaving-group basicity on the reactivity is insignificant.

One might suggest that the effect of leaving-group basicity on reactivity is dependent on the nature of reaction mechanism. The reactivity would be strongly influenced by the leaving-group basicity for reactions in which expulsion of the leaving group occurs in the RDS either in a concerted mechanism or in a stepwise pathway. In contrast, the reactivity of substrates would be little affected by leaving-group basicity for reactions in which expulsion of the leaving group occurs after the rate-determining step (RDS). We have recently shown that the second-order rate constant decreases with decreasing leaving-group basicity for the S_NAr reaction of 1-X-2,4-dinitrobenzene (X = F, Cl, Br, I) with amines (*i.e.*, F⁻ \gg Cl⁻ \approx Br⁻ $>$ I⁻).¹⁶ This is a reversed reactivity order reported for S_N2 reactions of alkyl halides R-X (*i.e.*, F⁻ \ll Cl⁻ \approx Br⁻ $<$ I⁻). However, the reactivity order found in the current study has often been found for S_NAr reactions in which formation of a Meisenheimer complex is the RDS.²⁻⁴ Thus, the kinetic result that the reactivity of **1a-1h** is little affected by the leaving-group basicity suggests that the current reactions proceed through a stepwise mechanism, in which formation of a Meisenheimer complex is the RDS.

Deduction of Reaction Mechanism. To examine the above idea, Brønsted-type plot for the reactions of **1a-1h** has been constructed in Figure 2. The Brønsted-type plot is linear with a β_{lg} value of -0.16 , although the correlation coefficient is not excellent (*i.e.*, $R^2 = 0.944$). Such a small β_{lg}

Table 1. Summary of Second-Order Rate Constants (k_{OH^-}) for the S_NAr Reactions of 1-Y-Substituted-Phenoxy-2,4-dinitrobenzenes (**1a-1h**) with OH⁻ in 80 mol % H₂O/20 mol % DMSO at 25.0 \pm 0.1 °C^a

Y	pK _a ^{Y-PhOH}	10 ² [OH ⁻]/M	10 ⁴ k_{obsd} /s ⁻¹	10 ³ k_{OH^-} /M ⁻¹ s ⁻¹
1a 4-Me	10.19	3.71-13.1	1.93-4.76	3.62
1b H	9.95	3.71-13.1	1.60-4.59	4.05
1c 4-Cl	9.38	3.71-11.1	2.53-6.79	5.77
1d 3-Cl	9.02	3.71-11.1	2.42-7.27	6.50
1e 4-CHO	7.66	3.71-11.1	3.64-9.25	7.70
1f 4-COMe	8.05	3.71-11.1	3.58-9.95	8.56
1g 4-CN	7.95	2.42-9.10	3.17-10.8	11.4
1h 4-NO ₂	7.14	2.42-9.10	3.04-11.2	12.1

^aThe pK_a data were taken from ref.21.

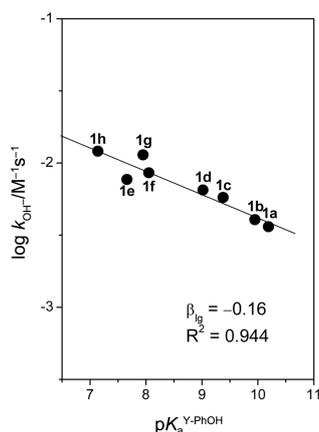


Figure 2. Brønsted-type plot for the S_NAr reactions of Y-substituted-phenoxy-2,4-dinitrobenzenes (**1a-1h**) with OH⁻ in 80 mol % H₂O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

value is consistent with the kinetic result that the k_{OH^-} value for the reactions of **1a-1h** increases only *ca.* 3 times upon decreasing leaving-group basicity over 3 pK_a units. A similar result has previously been reported for the S_NAr reaction of 1-Y-substituted-phenoxy-2,4-dinitrobenzenes (Y = H, 2-NO₂, 3-NO₂, and 4-NO₂) with OH⁻ in H₂O (*i.e.*, a linear Brønsted-type plot with $\beta_g = -0.215$).²² However, the β_g value of -0.16 is much smaller than that reported for reactions of Y-substituted-phenyl diphenylphosphinates with OH⁻ ($\beta_g = -0.49$)^{23a} and with ethoxide ion ($\beta_g = -0.54$),^{23b,c} and for those of Y-substituted-phenyl benzenesulfonates with EtO⁻ ($\beta_g = -0.64$).^{23d} It is noted that these reactions were concluded to proceed through a concerted mechanism on the basis of the linear Brønsted-type plot with $\beta_g = -0.5 \pm 0.1$.²³

The β_g value of -0.16 obtained from the current reaction is typical for reactions reported previously to proceed through a stepwise mechanism in which formation of an addition intermediate is the RDS.¹⁷⁻²⁰ In fact, we have previously reported that nucleophilic substitution reactions of Y-substituted-phenyl 2-methoxybenzoates with piperidine proceed through a stepwise mechanism with a change in the RDS on the basis of a nonlinear Brønsted-type plot (*i.e.*, from breakdown of an intermediate to its formation as the leaving-group basicity decreases).^{24a} Similar results have been reported for piperidinolysis of Y-substituted-phenyl benzoates^{24b} and 2-methylbenzoates,^{24c} which were reported to proceed through a stepwise mechanism with a change in RDS. Thus, one can suggest that the current reactions of **1a-1h** with OH⁻ proceed through a stepwise mechanism in which expulsion of the leaving group occurs rapidly after the RDS. This idea can be further supported by the fact that the aromaticity of the benzene ring can be recovered through expulsion of the leaving group from the Meisenheimer complex.

To obtain more conclusive information on the reaction mechanism, Hammett plots have been constructed using σ_Y^0 and σ_Y^- constants in Figure 3. If the current reaction proceeds through a stepwise mechanism in which expulsion of the leaving group occurs after the RDS, no negative charge

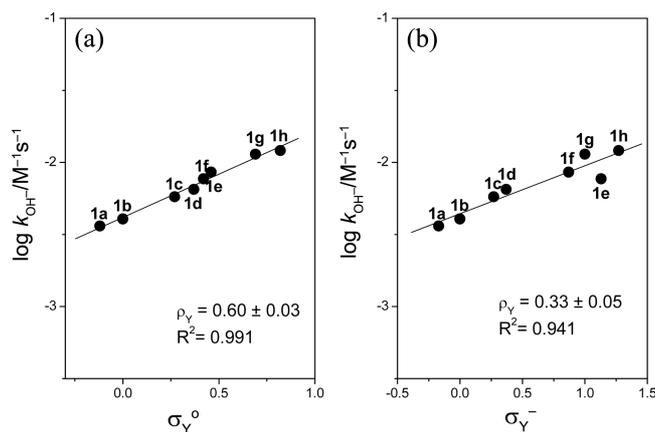


Figure 3. Hammett plots correlated with σ_Y^0 (a) and σ_Y^- (b) constants for the S_NAr reactions of Y-substituted-phenoxy-2,4-dinitrobenzenes (**1a-1h**) with OH⁻ in 80 mol % H₂O/20 mol % DMSO at 25.0 ± 0.1 °C.

would develop on the O atom of the leaving group in the TS. In this case, σ_Y^0 constants should result in a better Hammett correlation than σ_Y^- constants. In contrast, if expulsion of the leaving group occurs in the RDS either in a concerted mechanism or in a stepwise reaction, a negative charge would develop partially on the O atom of the leaving group. Since such a negative charge can be delocalized on the substituent Y through resonance interactions, σ_Y^- constants should give a better Hammett correlation than σ_Y^0 constants.

As shown in Figure 3, the Hammett plot correlated with σ_Y^0 constants (a) exhibit a much better correlation than that correlated with σ_Y^- constants (b). This indicates that no negative charge is developing on the O atom of the Y-substituted-phenoxy (*i.e.*, expulsion of the leaving group is not advanced at all in the TS). This is not possible for reactions which proceed through a concerted mechanism. Furthermore, if the current reaction proceeds through a stepwise mechanism, expulsion of the leaving group should occur rapidly after the RDS. Because OH⁻ is significantly more basic and a poorer nucleofuge than Y-substituted-phenoxy ion. Thus, one can conclude that the current S_NAr reaction proceeds through a stepwise mechanism in which expulsion of the leaving group occurs rapidly after the RDS. This idea is also consistent with the preceding proposal based on the linear Brønsted-type plot with $\beta_g = -0.16$.

Conclusions

The current study on the S_NAr reactions of **1a-1h** with OH⁻ has led us to conclude the following: (1) The k_{OH^-} value increases as the leaving-group basicity decreases. However, the dependence of k_{OH^-} on the leaving-group basicity is not significant. (2) The Brønsted-type plot the reactions of **1a-1h** is linear with a β_g value of -0.16, which is typical for reactions reported to proceed through a stepwise mechanism with formation of an addition intermediate being the RDS. (3) The Hammett plot correlated with σ_Y^0 constants results in a much better correlation than that correlated with σ_Y^-

constants, implying that no negative charge is developed on the O atom of the leaving group (or expulsion of the leaving group is not advanced) in the RDS. (4) The current reactions proceed through a stepwise mechanism in which expulsion of the leaving group occurs rapidly after the RDS.

Experimental Section

Materials. Y-Substituted-phenoxy-2,4-dinitrobenzenes (**1a-1h**) were readily prepared from the reaction of 1-fluoro-2,4-dinitrobenzene with Y-substituted-phenol in anhydrous ether under the presence of triethylamine. The crude product was purified by column chromatography and the purity was checked by the melting point and spectral data such as ^1H and ^{13}C NMR spectra. NaOH and other chemicals were of the highest quality available.

Kinetics. The kinetic study was carried out using a UV-Vis spectrophotometer equipped with a constant temperature circulating bath to maintain the reaction mixture at 25.0 ± 0.1 °C. The reactions were followed by monitoring the appearance of 2,4-dinitrophenoxide ion at 400 nm. All of the reactions in this study were performed under pseudo-first-order conditions, in which the concentration of NaOH was kept in excess of the substrate concentration.

Typically, the reaction was initiated by adding 5 μL of a 0.02 M solution of the substrate in acetonitrile to a 10-mm quartz UV cell containing 2.50 mL of the thermostated reaction mixture made up of the solvent and aliquot of the NaOH stock solution. All solutions were transferred by gas-tight syringes. Generally, the concentration of NaOH in the reaction mixtures was *ca.* $(2-13) \times 10^{-2}$ M, while the concentration of the substrate was *ca.* 4×10^{-5} M. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation, $\ln(A_{\infty} - A_t) = -k_{\text{obsd}}t + C$. The plots of $\ln(A_{\infty} - A_t)$ vs. time were linear over 90% of the total reaction.

Products Analysis. 2,4-Dinitrophenoxide ion was liberated quantitatively and identified as one of the products by comparison of the UV-Vis spectrum after completion of the reaction with that of authentic sample under the same reaction condition.

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