

## Kinetic Study on S<sub>N</sub>Ar Reaction of 1-Y-Substituted-phenoxy-2,4-dinitrobenzenes with Hydroxide Ion: Effect of Substituent Y on Reactivity and Reaction Mechanism

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A kinetic study is reported for the S<sub>N</sub>Ar reaction of 1-Y-substituted-phenoxy-2,4-dinitrobenzenes (**1a-1h**) with OH<sup>-</sup> in 80 mol % H<sub>2</sub>O/20 mol % DMSO at 25.0 ± 0.1 °C. The second-order rate constant (*k*<sub>OH<sup>-</sup></sub>) 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<sub>g</sub> = -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<sub>g</sub> = -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<sub>Y</sub><sup>o</sup> constants results in a much better correlation than that correlated with σ<sub>Y</sub><sup>-</sup> 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<sub>N</sub>Ar reaction of **1a-1h** with OH<sup>-</sup> 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<sub>N</sub>Ar reaction, 1-Phenoxy-2,4-dinitrobenzene, Brønsted-type plot, Hammett plot, Reaction mechanism

### Introduction

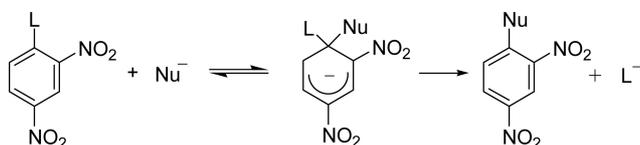
Aromatic nucleophilic substitution (S<sub>N</sub>Ar) reactions of activated aromatic or heteroaromatic compounds and their reaction mechanisms have intensively been investigated due to their importance in organic transformation.<sup>1-4</sup> To give but a few examples, S<sub>N</sub>Ar reactions have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

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

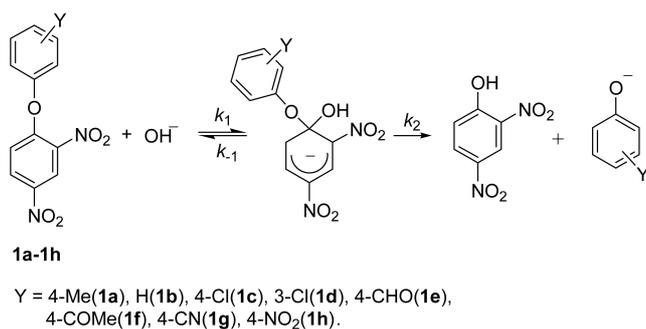
deficient aromatic or heteroaromatic compounds.<sup>13,14</sup> In contrast, some computational studies have suggested that Meisenheimer complexes may be formed as a transition state (TS) but not as an intermediate in a majority of reactions.<sup>15</sup>

S<sub>N</sub>Ar reactions have a similarity to nucleophilic substitution reactions of carboxylic esters. The apparent similarity is the nucleophilic addition step in S<sub>N</sub>Ar reaction and the addition step to carbonyl group in ester. In both cases addition to the sp<sup>2</sup> carbon leads to rehybridization to sp<sup>3</sup> to produce a tetrahedral intermediate. Elimination of the leaving group in subsequent step(s) restores the sp<sup>2</sup> carbon. A fundamental difference is that addition to a typical electron-deficient aromatic substrate in an S<sub>N</sub>Ar 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<sub>N</sub>Ar 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<sup>±</sup> and its deprotonated form T<sup>-</sup> when L = F but without the deprotonation process to form T<sup>-</sup> from T<sup>±</sup> when L = Cl, Br and I).<sup>16</sup> In our previous study on the S<sub>N</sub>Ar reactions, we applied Brønsted analysis to deduce the reaction mechanism.<sup>16</sup> Although this tool has been used extensively for nucleophilic substitution reactions of esters



Scheme 1



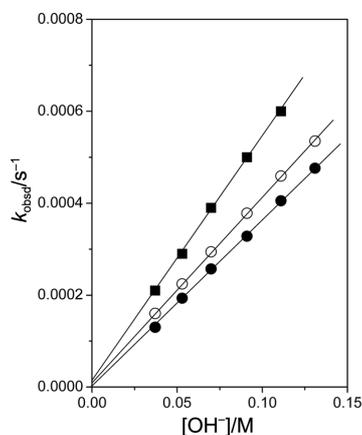
Scheme 2

with various nucleophiles,<sup>17-20</sup> its application to S<sub>N</sub>Ar reactions has been more modest.<sup>16</sup>

Our study has now been extended to the S<sub>N</sub>Ar reactions of 1-(Y-substituted-phenoxy)-2,4-dinitrobenzenes with OH<sup>-</sup> ion in 80 mol % H<sub>2</sub>O/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-NO<sub>2</sub>). We wish to report that analysis of Brønsted-type plot and Hammett correlations with σ<sup>-</sup> and σ<sup>o</sup> 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*<sub>obsd</sub>) were calculated from the slope of the plots of ln(*A*<sub>∞</sub> - *A*<sub>*t*</sub>) vs. *t*, which were linear over 90% of the total reaction. The uncertainty in the *k*<sub>obsd</sub> values is estimated to be less than ± 3% from replicate runs. The plots of *k*<sub>obsd</sub> vs. [OH<sup>-</sup>] were linear and passed through the origin (*e.g.*, Figure 1 for the reactions **1a-1c**). The second-order



**Figure 1.** Plots of *k*<sub>obsd</sub> vs. [NaOH] for the S<sub>N</sub>Ar reactions of 1-Y-substituted-phenoxy-2,4-dinitrobenzoates **1a** (●), **1b** (○) and **1c** (■) with OH<sup>-</sup> in 80 mol % H<sub>2</sub>O/20 mol % DMSO at 25.0 ± 0.1 °C.

rate constants (*k*<sub>OH<sup>-</sup></sub>) were calculated from the slope of the linear plots and are summarized in Table 1 together with the ranges of the OH<sup>-</sup> concentrations and *k*<sub>obsd</sub> 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*<sub>OH<sup>-</sup></sub> increases from 3.62 × 10<sup>-3</sup> M<sup>-1</sup>s<sup>-1</sup> to 12.1 × 10<sup>-3</sup> M<sup>-1</sup>s<sup>-1</sup> as the substituent Y changes from 4-Me to Y = 4-NO<sub>2</sub>, respectively. The change in substituent Y from 4-Me to 4-NO<sub>2</sub> increases the leaving-group basicity over 3 p*K*<sub>a</sub> units. Interestingly, the *k*<sub>OH<sup>-</sup></sub> value increases only *ca.* 3 times upon increasing leaving-group basicity over 3 p*K*<sub>a</sub> units, indicating that the effect of leaving-group basicity on the reactivity is insignificant.

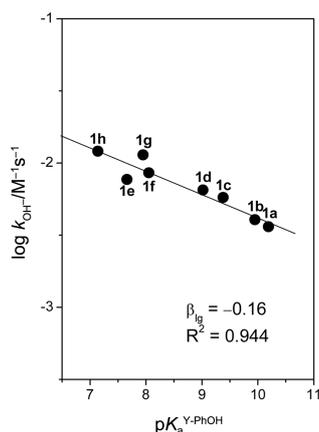
One might suggest that the effect of leaving-group basicity on reactivity is dependent on the nature of reaction mechanism. The reactivity would be strongly influenced by the leaving-group basicity for reactions in which expulsion of the leaving group occurs in the RDS either in a concerted mechanism 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<sub>N</sub>Ar reaction of 1-X-2,4-dinitrobenzene (X = F, Cl, Br, I) with amines (*i.e.*, F<sup>-</sup> ≫ Cl<sup>-</sup> ≈ Br<sup>-</sup> > I<sup>-</sup>).<sup>16</sup> This is a reversed reactivity order reported for S<sub>N</sub>2 reactions of alkyl halides R-X (*i.e.*, F<sup>-</sup> ≪ Cl<sup>-</sup> ≈ Br<sup>-</sup> < I<sup>-</sup>). However, the reactivity order found in the current study has often been found for S<sub>N</sub>Ar reactions in which formation of a Meisenheimer complex is the RDS.<sup>2-4</sup> 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<sub>lg</sub> value of -0.16, although the correlation coefficient is not excellent (*i.e.*, R<sup>2</sup> = 0.944). Such a small β<sub>lg</sub>

**Table 1.** Summary of Second-Order Rate Constants (*k*<sub>OH<sup>-</sup></sub>) for the S<sub>N</sub>Ar Reactions of 1-Y-Substituted-Phenoxy-2,4-dinitrobenzenes (**1a-1h**) with OH<sup>-</sup> in 80 mol % H<sub>2</sub>O/20 mol % DMSO at 25.0 ± 0.1 °C<sup>a</sup>

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

<sup>a</sup>The p*K*<sub>a</sub> data were taken from ref.21.

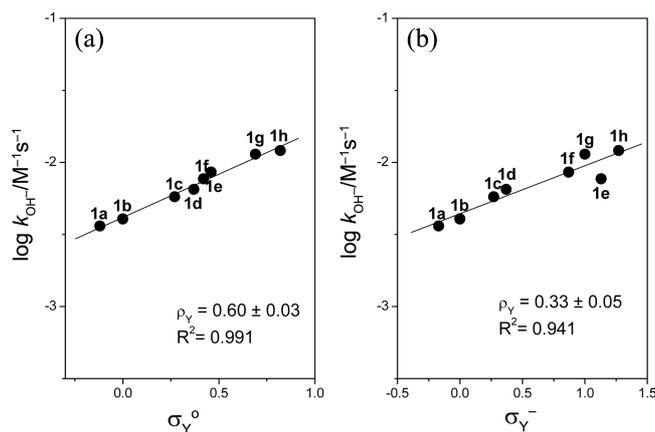


**Figure 2.** Brønsted-type plot for the S<sub>N</sub>Ar reactions of Y-substituted-phenoxy-2,4-dinitrobenzenes (**1a-1h**) with OH<sup>-</sup> in 80 mol % H<sub>2</sub>O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

value is consistent with the kinetic result that the  $k_{\text{OH}^-}$  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<sub>N</sub>Ar reaction of 1-Y-substituted-phenoxy-2,4-dinitrobenzenes (Y = H, 2-NO<sub>2</sub>, 3-NO<sub>2</sub>, and 4-NO<sub>2</sub>) with OH<sup>-</sup> in H<sub>2</sub>O (*i.e.*, a linear Brønsted-type plot with  $\beta_g = -0.215$ ).<sup>22</sup> However, the  $\beta_g$  value of -0.16 is much smaller than that reported for reactions of Y-substituted-phenyl diphenylphosphinates with OH<sup>-</sup> ( $\beta_g = -0.49$ )<sup>23a</sup> and with ethoxide ion ( $\beta_g = -0.54$ ),<sup>23b,c</sup> and for those of Y-substituted-phenyl benzenesulfonates with EtO<sup>-</sup> ( $\beta_g = -0.64$ ).<sup>23d</sup> It is noted that these reactions were concluded to proceed through a concerted mechanism on the basis of the linear Brønsted-type plot with  $\beta_g = -0.5 \pm 0.1$ .<sup>23</sup>

The  $\beta_g$  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.<sup>17-20</sup> 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).<sup>24a</sup> Similar results have been reported for piperidinolysis of Y-substituted-phenyl benzoates<sup>24b</sup> and 2-methylbenzoates,<sup>24c</sup> 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<sup>-</sup> 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  $\sigma_Y^0$  and  $\sigma_Y^-$  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  $\sigma_Y^0$  (a) and  $\sigma_Y^-$  (b) constants for the S<sub>N</sub>Ar reactions of Y-substituted-phenoxy-2,4-dinitrobenzenes (**1a-1h**) with OH<sup>-</sup> in 80 mol % H<sub>2</sub>O/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,  $\sigma_Y^0$  constants should result in a better Hammett correlation than  $\sigma_Y^-$  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,  $\sigma_Y^-$  constants should give a better Hammett correlation than  $\sigma_Y^0$  constants.

As shown in Figure 3, the Hammett plot correlated with  $\sigma_Y^0$  constants (a) exhibit a much better correlation than that correlated with  $\sigma_Y^-$  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<sup>-</sup> is significantly more basic and a poorer nucleofuge than Y-substituted-phenoxy ion. Thus, one can conclude that the current S<sub>N</sub>Ar 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<sub>N</sub>Ar reactions of **1a-1h** with OH<sup>-</sup> has led us to conclude the following: (1) The  $k_{\text{OH}^-}$  value increases as the leaving-group basicity decreases. However, the dependence of  $k_{\text{OH}^-}$  on the leaving-group basicity is not significant. (2) The Brønsted-type plot the reactions of **1a-1h** is linear with a  $\beta_g$  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  $\sigma_Y^0$  constants results in a much better correlation than that correlated with  $\sigma_Y^-$

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  $^1\text{H}$  and  $^{13}\text{C}$  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  $25.0 \pm 0.1$  °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  $\mu\text{L}$  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.*  $4 \times 10^{-5}$  M. Pseudo-first-order rate constants ( $k_{\text{obsd}}$ ) 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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