JOC The Journal of Organic Chemistry

Article

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Kinetic Study on S_NAr Reaction of 1-(Y-Substituted-phenoxy)-2,4-dinitrobenzenes with Cyclic Secondary Amines in Acetonitrile: Evidence for Cyclic Transition-State Structure

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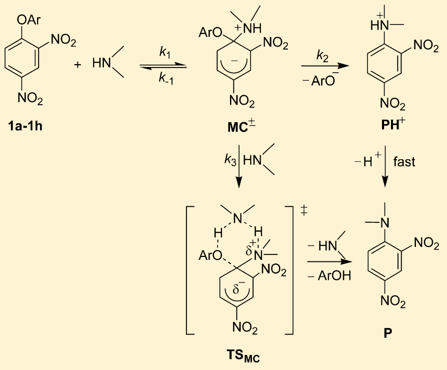
Supporting Information

ABSTRACT: A kinetic study is reported for S_NAr reactions of 1-(Y-substituted-phenoxy)-2,4-dinitrobenzenes (**1a**−**1h**) with amines in MeCN. The plots of pseudo-first-order rate constant versus amine concentration curve upward, indicating that the reactions are catalyzed by a second amine molecule. The Brønsted-type plots for the reaction of 1-(4-nitrophenyl)-2,4-dinitrobenzene (**1a**) with secondary amines are linear with β_{nuc} = 1.10 and 0.85 for the uncatalyzed and catalyzed reactions, respectively, while the Yukawa−Tsuno plots for the reactions of **1a**−**1h** with piperidine result in excellent linear correlations with ρ_Y = 1.85 and r = 0.27 for the uncatalyzed reaction and ρ_Y = 0.73 and r = 0.23 for the catalyzed reaction. The catalytic effect decreases with increasing amine basicity or electron-withdrawing ability of the substituent Y in the leaving group. Activation parameters calculated from the rate constants measured at five different temperatures for the catalyzed reaction of **1a** with piperidine are $\Delta H^‡$ = 0.38 kcal/mol and $\Delta S^‡$ = −55.4 cal/(mol K). The catalyzed reaction from a Meisenheimer complex ($MC^{\pm}$) is proposed to proceed through a concerted mechanism with a cyclic transition-state rather than via a stepwise pathway with an anionic intermediate, MC^-. Deuterium kinetic isotope effects provide further insight into the nature of the concerted transition state.



INTRODUCTION

Reactions of nucleophiles, charged or neutral, with sufficiently electron deficient aromatic substrates (activated by one or more powerful electron withdrawing groups, NO_2, SO_2CF_3,[1,2] $F_3CSO{=}NSO_2CF_3$,[2] etc.) that incorporate a leaving group, often proceed via the S_NAr mechanism[3,4] of nucleophilic aromatic displacement. In this mechanism, essentially, attack of the nucleophile at the position bearing the leaving group results in formation of a σ-bonded adduct, usually termed a Meisenheimer complex (MC),[5] in an addition step. Expulsion, often rapid, of the leaving group from the MC gives the product in the subsequent elimination step. This mechanism advanced by Bunnett and Zahler[3,4] is, therefore, of the addition−elimination kind.[6] We, among others, have noted the similarity of the S_NAr addition to sp^2-hybridized aromatic carbon to the addition of nucleophiles to the carbonyl (and related) sp^2-hybridized carbon centers in esters and derivatives and have exploited it, through Brønsted analysis, to assess the nature of the rate-determining step in the reaction of secondary amines with 2,4-dinitrofluorobenzene in acetonitrile (MeCN).[7]

Interest in the mechanism of nucleophilic aromatic displacement has been aroused in two different ways. First, impetus to explore further the reactions of electron-deficient aromatics has come from the finding that highly reactive 10π neutral heteroaromatic electrophiles (superelectrophiles) such as 4,6-dinitrobenzofuroxan (DNBF) and structural analogues[8,9] including even more electrophilic substrates,[10] according to the Mayr scale of electrophilicity,[11] undergo not only aromatic displacement reactions[8−10,12] but also Diels−Alder cycloadditions.[13,14] Not only has the synthetic versatility of these electron-poor heteroaromatics been highlighted,[15] but the demarcation boundary[16] between normal electrophiles such as 1-chloro-2,4,6-trinitrobenzene and superelectrophiles like DNBF has been defined by the Mayr scale. For superelectrophiles, interest has been stimulated in their dual reactivity as substrates for S_NAr displacements and as dienes/dienophiles in pericyclic reactions.[17,18]

Interest in normal electrophiles in nucleophilic aromatic displacement[19,20] arises partly from studies involving exotic solvent media,[21] including room temperature ionic liquids[22] and aqueous surfactant systems, notably with surfactants that include nucleophilic counterions in the surfactant headgroups.[23]

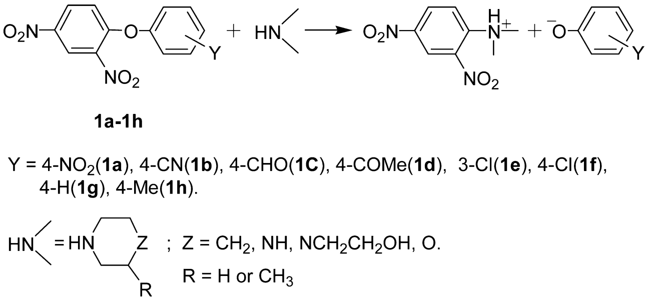
With amines, S_NAr pathways (Scheme 2) generally involve nucleophilic attack at C-1, which bears the leaving group, ArO^- 1-(Y-substituted phenoxide) in the present study, in a first step (k_1) that generates a zwitterionic Meisenheimer complex, $MC^{\pm}$.

Received: May 27, 2014
Published: July 8, 2014

Reaction at unsubstituted sites (C-3,5) may occur in principle,[24] but the corresponding Meisenheimer complexes have not been detected in the current nor previous studies of the reaction of amines with 1-X-2,4-dinitrobenzenes in acetonitrile.[7,25−27] The zwitterionic complex, MC$^{\pm}$, may be deprotonated to give MC^{-} in a second step (k_3[NH]) that is catalyzed by the amine (NH, here), after which the aryloxide is rapidly expelled to give the product P. Alternatively, the aryloxide may be ejected from MC$^{\pm}$ in a noncatalytic step to give the protonated form of the product, PH^{+}, (k_2 step) that yields the same *N*,*N*-dialkyl-2,4-dinitroaniline upon deprotonation.

In the present study, the kinetics of the reaction of a series of 1-(Y-substituted phenoxy)-2,4-dinitrobenzenes (**1a**−**1h**) with a set of secondary amines (shown in Scheme 1) have been followed in acetonitrile solvent. The results were analyzed using Brønsted-type plots, made possible by the publication of the relevant pK_a values for the conjugate acids of the amines in MeCN.[28] We have previously found such an approach useful in determining the nature of the rate-determining step in reaction of amines with 1-halo-2,4-dinitrobenzenes.[7,25] Although Brønsted analysis has been widely used for nucleophilic reactions at C=O and related electrophilic centers,[29,30] it has been applied to a more limited extent to S$_N$Ar displacements.[19,31] The presence of substituents in the 1-aryloxy moiety of the substrates also permits consideration of the reaction through the use of Hammett- and Yukawa−Tsuno-type correlations.

Scheme 1



What emerges from these assessment tools, as well as activation parameters for the catalytic path, is support for formation of a cyclic transition state (TS) involving both MC$^{\pm}$ and another molecule of the amine (k_3[NH], Scheme 3). Within this TS, both deprotonation of MC$^{\pm}$ and protonation of the aryloxide leaving group occur. A similar pathway in S$_N$Ar displacements, where proton transfer from the aminium moiety in MC$^{\pm}$ to the leaving group occurs, has been previously advanced by Rees and Capon.[6c] In water or mixed aqueous media Bernasconi[6a,b] has shown that a base-catalyzed rate limiting proton transfer from an initially formed zwitterionic intermediate (MC$^{\pm}$) to give the deprotonated intermediate (MC^{-}, Scheme 2) is rate determining, which rapidly collapses to product or where intramolecular proton transfer from nitrogen of MC$^{\pm}$ to the oxygen of aryloxyl leaving group effectively avoids free ions in solution.[4b] This could apply to the uncatalyzed pathway described below.

■ RESULTS AND DISCUSSION

The kinetic study was performed under pseudo-first-order conditions wherein the amine concentration was kept in at least 20-fold excess over the substrate concentration. All the reactions in this study obeyed first-order kinetics; the pseudo-first-order rate constants (k_{obsd}) were calculated from the equation $\ln(A_\infty - A_t) = -k_{obsd}t + C$. As shown in Figure 1A, the plot of k_{obsd} versus amine concentration curves upward for the reaction of 1-(4-nitrophenoxy)-2,4-dinitrobenzene (**1a**) with piperidine. Similarly curved plots are demonstrated for the reactions of **1a** with all the other amines used in this study and for those of the **1b**−**1h** series with piperidine in Figures S1A−S11A in the Supporting Information section. Such curved plots have often been reported for reactions in which a second amine molecule behaves as a general base catalyst.[7,25,27] Thus, one might suggest that the S$_N$Ar reactions of **1a**−**1h** proceed through a stepwise mechanism with two intermediates (i.e., MC$^{\pm}$ and MC^{-}) as shown in Scheme 2, that is, a catalytic route to form MC^{-} from MC$^{\pm}$ and thence to product, P, and a noncatalytic route to yield the product PH^{+} that equilibrates to give P.

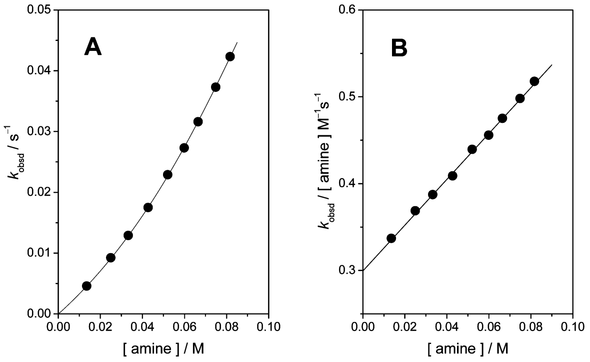
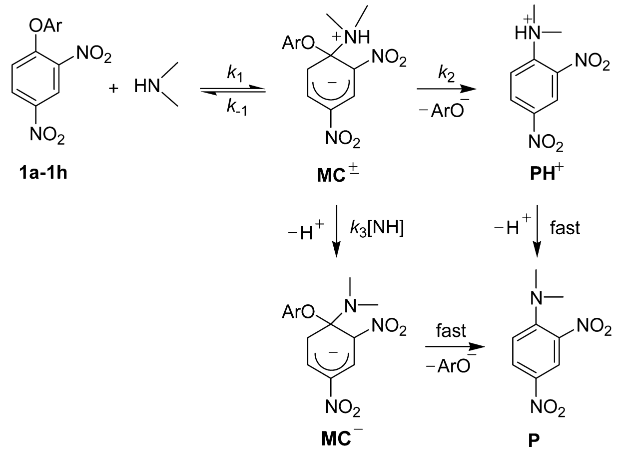


Figure 1. Plots of k_{obsd} vs [amine] (A) and k_{obsd}/[amine] vs [amine] (B) for the reaction of 1-(4-nitrophenoxy)-2,4-dinitrobenzene (**1a**) with piperidine in MeCN at 25.0 ± 0.1 °C.

Scheme 2



In low polarity aprotic solvents such as benzene or cyclohexane, 2,4-dinitroanisole reacts with cyclohexylamine to give an upward curved plot similar to Figure 1A; however, the plot comparable to Figure 1B is linear at higher temperatures but shows downward curvature at lower temperatures. These results have been attributed by Nudelman and Palleros[6d] and Hirst[6e] to amine dimers in solution that lead to cyclic transition states including the amine and MC$^{\pm}$ that collapse either to products, P, or to MC$^{\pm}$. One can derive eq 1 on the basis of the kinetic results and the reaction mechanism suggested in Scheme 2. Equation 1 transforms into eq 2 under the assumption that $k_{-1} \gg k_2 + k_3[\text{amine}]$. Thus, the plot of $k_{\text{obsd}}/[\text{amine}]$ versus [amine] is expected to be linear if the assumption is valid.

$$k_{\text{obsd}} = \frac{(k_1k_2[\text{amine}] + k_1k_3[\text{amine}]^2)}{(k_{-1} + k_2 + k_3[\text{amine}])} \qquad (1)$$

$$k_{\text{obsd}}/[\text{amine}] = Kk_2 + Kk_3[\text{amine}], \quad \text{where} \quad K = k_1/k_{-1} \qquad (2)$$

In fact, as shown in Figure 1B, the plot of $k_{\text{obsd}}/[\text{amine}]$ versus [amine] is linear with a large positive intercept for the reaction of **1a** with piperidine. The corresponding plots for the reactions of **1a** with all the other amines studied and for those of **1b**−**1h** with piperidine are also linear as shown in Figures S1B−S11B (Supporting Information). This indicates that the assumption $k_{-1} \gg k_2 + k_3[\text{amine}]$ is valid under the reaction conditions in all cases. Thus, the rate constants for the noncatalytic and catalytic reactions (i.e., Kk_2 and Kk_3, respectively) have been calculated from the intercept and slope of the linear plots, in turn. The Kk_2 and Kk_3 values calculated in this way are summarized in Table 1 for the reactions of **1a** with a series of cyclic secondary amines and in Table 2 for those of **1a**−**1h** with piperidine.

Table 1. Summary of Kinetic Data for the Reactions of 1-(4-Nitrophenoxy)-2,4-dinitrobenzene (1a) with a Series of Cyclic Secondary Amines in MeCN at 25.0 ± 0.1 °C[a]

	amines	pK_a	Kk_2 (M^{-1} s^{-1})	Kk_3 (M^{-2} s^{-1})	k_3/k_2 (M^{-1})
1	piperidine	18.8	0.300	2.64	8.80
2	3-methylpiperidine	18.6	0.221	2.25	10.2
3	piperazine	18.5	0.136	3.22	23.7
4	1-(2-hydroxyethyl) piperazine	17.6	0.0125	0.175	14.0
5	morpholine	16.6	0.00132	0.0448	33.9

[a] The pK_a values in MeCN were taken from refs 25 and 28.

Effect of Amine Basicity on Reactivity and Reaction Mechanism. As shown in Table 1, the rate constant for the noncatalytic reactions decreases as the amine basicity decreases, e.g., Kk_2 decreases from 0.300 to 0.00132 M^{-1} s^{-1}, a greater than 200-fold decrease in this kinetic term, as the pK_a value of the conjugate acid of the entering amine decreases from 18.8 to 16.6, respectively. The rate constant for the catalytic reactions also decreases with decreasing the amine basicity, although Kk_3 is generally larger than Kk_2 for a given amine. It is also notable that the catalytic effect exerted by a second amine molecule (i.e., the k_3/k_2 ratio) decreases with increasing amine basicity.

The effect of amine basicity on the rate constants Kk_2 and Kk_3 are illustrated in Figure 2. The Brønsted-type plots exhibit excellent linear correlations with $\beta_{\text{nuc}} = 1.10$ for the uncatalyzed route and $\beta_{\text{nuc}} = 0.85$ for the catalyzed process, when the rate constants and pK_a values are statistically corrected using p and q (i.e., $p = 2$ while $q = 1$ except $q = 2$ for piperazine).[32] It is notable that the β_{nuc} value for the catalyzed reaction is clearly smaller than that for the uncatalyzed reaction.

Gresser and Jencks have concluded that amine basicity does not affect k_2 for the reactions of aryl 2,4-dinitrophenyl carbonates with quinuclidine, since there is little or no electron donation from the aminium moiety of T$^{\pm}$ to expel the leaving group.[33] A similar conclusion has been reported by Castro et al. for aminolyses of ethyl phenyl thionocarbonate,[34a] methyl 4-nitrophenyl thionocarbonate,[34b] 4-methylphenyl 4-nitrophenyl thionocarbonate,[34c] and 3-methoxyphenyl 4-nitrophenyl thionocarbonate.[34d] In these examples, the nucleophilic amine attacks a C═O or C═S moiety. However, we,[7,25] among others, have previously drawn the connection between stepwise reaction of amines at the sp^2-hybrized carbon of carbonyls and at the sp^2-hybrized carbon of an electron deficient aromatic ring, as in the current study.

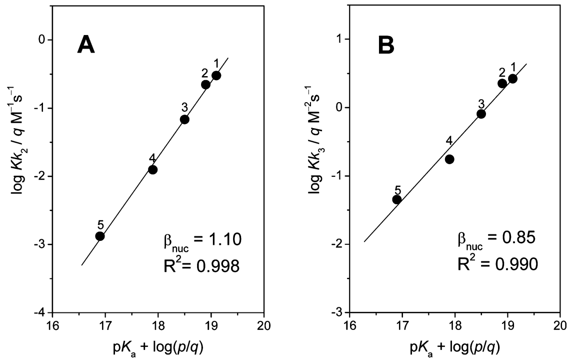


Figure 2. Brønsted-type plots of Kk_2 (A) and Kk_3 (B) for the reactions of 1-(4-nitrophenoxy)-2,4-dinitrobenzene (**1a**) with a series of cyclic secondary amines in MeCN at 25.0 ± 0.1 °C. The assignment of numbers is given in Table 1.

On the other hand, it is reasonable to expect that the k_3 value in Scheme 2 would not be affected by amine basicity either. Because a more basic amine would tend to deprotonate the aminium moiety of MC$^{\pm}$ more rapidly, while the aminium moiety would equally tend to hold the proton more strongly as the amine becomes more basic. Accordingly, one might expect that both k_2 and k_3 would be independent of amine basicity, if the current reaction proceeds as shown in Scheme 2. However, Figure 2 shows that, in fact, the Brønsted-type plot using Kk_2 results in a larger β_{nuc} value than that involving Kk_3, a clear indication that k_2 is more sensitive to amine basicity than k_3. This is contrary to expectations if the reactions proceed as proposed in Scheme 2. Thus, one might suggest that the current catalyzed reaction may not proceed as shown in Scheme 2.

Effect of Leaving-Group Basicity on Reactivity and Reaction Mechanism. To obtain further information on the reaction mechanism, reactions of 1-(Y-substituted-phenoxy)-2,4-dinitrobenzenes (**1a**−**1h**) with piperidine were performed. The rate constants for the uncatalyzed and catalyzed reactions are summarized in Table 2. As shown in Table 2, the Kk_2 value decreases as the substituent Y in the leaving group changes from a strong electron-withdrawing group (EWG) to an electron-donating group (EDG); for example, it decreases from 0.300 to 0.0191 and 0.00257 M^{-1} s^{-1} as the substituent Y changes from 4-NO_2 to 3-Cl and to 4-Me, in turn. The Kk_3 value also decreases from 2.64 to 1.18 and 0.499 $M^{-2}s^{-1}$ as the substituent Y changes from 4-NO_2 to 3-Cl and to 4-Me, in turn. However, it is notable that the catalytic effect exerted by a second amine molecule (i.e., the k_3/k_2 ratio) decreases as the substituent Y becomes a stronger EWG.

Hammett plots have been constructed using σ_Y^- and σ_Y° constants to examine the reaction mechanism proposed in

Table 2. Summary of Kinetic Data for the Reactions of 1-(Y-Substituted-phenoxy)-2,4-dinitrobenzenes (1a−1h) with Piperidine in MeCN at 25.0 ± 0.1 °C

	Y	$Kk_2/M^{-1}\ s^{-1}$	$Kk_3/M^{-2}s^{-1}$	$k_3/k_2/M^{-1}$
1a	4-NO_2	0.300 (0.321)[a]	2.64 (2.03)[a]	8.80 (6.32)[a]
1b	4-CN	0.105	2.47	23.5
1c	4-CHO	0.0627	1.76	28.1
1d	4-COMe	0.0356	1.50	42.1
1e	3-Cl	0.0191	1.18	61.8
1f	4-Cl	0.0143	1.05	73.4
1g	H	0.00459	0.577	126
1h	4-Me	0.00257	0.499	194

[a] The rate constants for the reactions with deuterated piperidine.

Scheme 2. One might expect that the Hammett plot of Kk_2 with σ_Y^- constants would result in a better linear correlation than that built with σ_Y° constants, because expulsion of the charged aryloxide leaving group occurs in the rate-determining step (RDS) for the uncatalyzed reaction. In contrast, σ_Y° constants would exhibit a better Hammett correlation than σ_Y^- constants for the catalyzed process, if the reaction proceeds as shown in Scheme 2. This is because the reaction mechanism proposed in Scheme 2 describes expulsion of the leaving group from MC^- as occurring in a rapid separate step after the RDS.

As shown in Figure 3, σ_Y° constants result in a marginally better Hammett correlation ($R^2 = 0.98$) than σ_Y^- constants for the uncatalyzed reactions ($R^2 = 0.97$). A similar result has been demonstrated in Figure S12 in the Supporting Information section for the catalyzed reactions (i.e., the Hammett plot constructed with σ_Y° constants results in a slightly better correlation than that using σ_Y^- constants). However, both Hammett plots exhibit many scattered points. Thus, one cannot obtain any conclusive information on the TS structure from these poorly correlated Hammett plots.

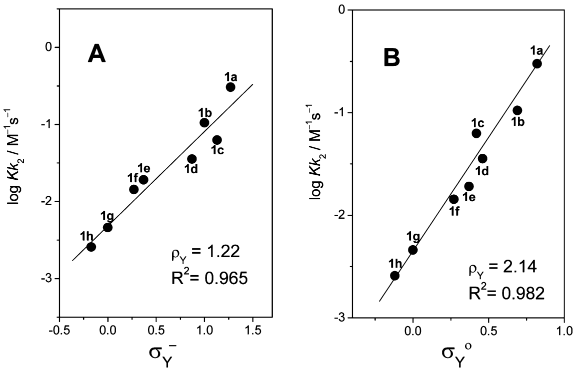


Figure 3. Hammett correlations of log Kk_2 with σ_Y^- (A) and σ_Y° (B) constants for the reactions of 1-(Y-substituted-phenoxy)-2,4-dinitrobenzenes (**1a**−**1h**) with piperidine in MeCN at 25.0 ± 0.1 °C. The assignment of numbers is given in Table 2.

We have previously found that the Yukawa−Tsuno equation, eq 3, is highly effective to clarify ambiguities in the reaction mechanism for nucleophilic substitution reactions of various types of esters with neutral amines,[30,35] as well as with anionic nucleophiles (e.g., N_3^-, CN^-, OH^-, and $CH_3CH_2O^-$).[36] Thus, Yukawa−Tsuno plots have been constructed to probe the nature of the reaction mechanism. As shown in Figure 4, the Yukawa−Tsuno plots exhibit excellent linear correlations ($R^2 > 0.99$ for both) with $\rho_Y = 1.85$ and $r = 0.27$ for the uncatalyzed reaction and $\rho_Y = 0.73$ and $r = 0.23$ for the catalyzed reaction.

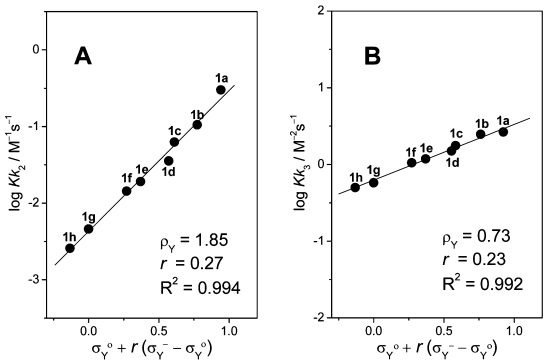


Figure 4. Yukawa−Tsuno plots for the reactions of 1-(Y-substituted-phenoxy)-2,4-dinitrobenzenes (**1a**−**1h**) with piperidine in MeCN at 25.0 ± 0.1 °C (A) for Kk_2 and (B) for Kk_3. The assignment of numbers is given in Table 2.

$$\log k_N^Y/k_N^H = \rho_Y[\sigma_Y^\circ + r(\sigma_Y^- - \sigma_Y^\circ)] \qquad (3)$$

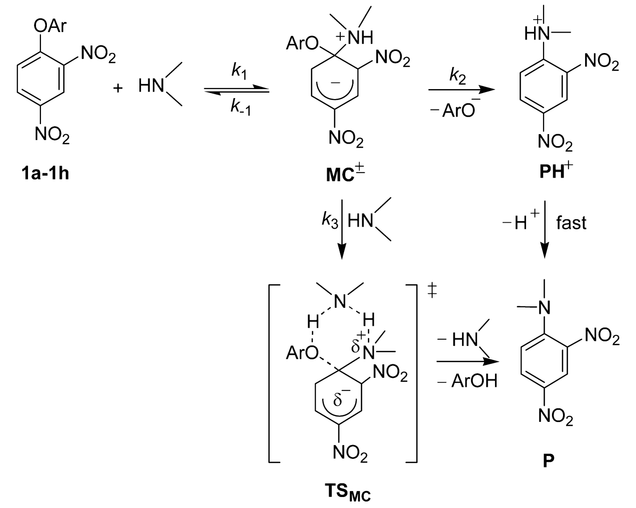
The r value in eq 3 represents the resonance demand of the reaction center or the extent of resonance contribution between the reaction site and the substituent Y, while the term ($\sigma_Y^- - \sigma_Y^\circ$) is the resonance substituent constant that measures the capacity for π-delocalization of the π-electron acceptor substituent.[37,38] The r value of 0.23 or 0.27 obtained for the catalyzed or uncatalyzed reactions indicates that a partial negative charge develops on the O atom of the leaving group, which can be delocalized to the substituent Y through resonance interactions. Thus, one can suggest that expulsion of the leaving group occurs in the RDS although the degree of the C−OAr bond rupture is advanced only a little in the TS on the basis of the small r values.

The r value of 0.27 for the uncatalyzed reactions is consistent with the reaction mechanism proposed in Scheme 2, in which expulsion of the leaving group occurs in the RDS. However, the r value of 0.23 for the catalyzed reactions is clearly inconsistent with the reaction mechanism proposed in Scheme 2 where the RDS envisaged for the catalyzed reaction is the deprotonation process to form MC^- from $MC^\pm$ and where expulsion of the leaving group from MC^- occurs after this RDS. This constitutes the second piece of evidence that the catalyzed reactions do not proceed as shown in Scheme 2. Rather, this is consistent with the Brønsted analysis of the sensitivity of k_2 compared with k_3 to amine basicity in the preceding section where it was shown that the catalyzed reactions result in a smaller β_{nuc} value than the uncatalyzed reactions.

Deduction of Reaction Mechanism. To account for the kinetic results that expulsion of the leaving group occurs in the RDS for the catalyzed reactions, we propose that the current S_NAr reaction proceeds as shown in Scheme 3. The new mechanism proposed in Scheme 3 is that the catalytic process from $MC^\pm$ proceeds through a concerted mechanism with a cyclic TS as modeled by TS_{MC} rather than through a stepwise pathway with an anionic intermediate MC^-, that is, the second amine molecule deprotonates from the aminium moiety of $MC^\pm$ as a general base catalyst and simultaneously donates its proton to the O atom of the leaving group as a general acid catalyst.

While a similar mechanism involving a TS akin to TS_{MC} (Scheme 3) has been advanced in *nonpolar aprotic* solvents,

Scheme 3



rate-limiting proton transfer has been most commonly found in aqueous or aquatic cosolvent media,[6] and the specific base−general acid route most commonly found in *polar aprotic* solvents,[3a,4] to the best of our knowledge this is the first suggestion of such a cyclic six-member transition state in the catalyzed conversion of MC$^{\pm}$ direct to products in acetonitrile, a polar aprotic solvent.

The concerted mechanism proposed in Scheme 3 for the catalyzed process can be further supported by the experimental results that the β_{nuc} value is smaller for the catalyzed reaction than for the uncatalyzed reaction and that the k_3/k_2 ratio decreases as the amine basicity increases. As mentioned in the preceding section, the k_2 and k_3 values would be independent of amine basicity if the reactions proceed with MC$^{\pm}$ and MC^{-} as shown in Scheme 2. However, if the catalyzed reactions proceed via a TS modeled by TS$_{\text{MC}}$ (rather than with a discrete anionic intermediate MC^{-}) as shown in Scheme 3, amine basicity should affect k_3, because the proton transfer from the second amine molecule to the O atom of the leaving group would be retarded as a function of increasing amine basicity. Accordingly, *the catalytic effect would decrease as the amine basicity increases*. This argument accounts for the kinetic result that the k_3/k_2 ratio decreases as the amine basicity increases (Table 1) and that the catalyzed reactions result in a smaller β_{nuc} value than the uncatalyzed reactions (Figure 2).

It is also notable that the k_3/k_2 ratio decreases as the substituent Y in the leaving group becomes a stronger EWG (Table 2) and that the ρ_Y value is much smaller for the catalyzed reactions than for the uncatalyzed reactions (Figure 4). One might expect a large ρ_Y value for the uncatalyzed reactions, since the k_2 value would increase as the substituent Y becomes a stronger EWG. In contrast, the k_3 value in Scheme 3 would decrease as the substituent Y becomes a stronger EWG. Because a stronger EWG in the leaving group would retard the proton transfer from the second amine molecule to the O atom of the leaving group by decreasing the electron density of the O atom. Accordingly, the catalytic effect exerted by the second amine molecule would decrease on changing the substituent Y in the leaving group from 4-Me to 4-NO$_2$. This idea is consistent with the kinetic result that the ρ_Y value is much smaller for the catalyzed reactions than for the uncatalyzed reactions (Figure 4) and that the k_3/k_2 ratio decreases as the substituent Y in the leaving group becomes a stronger EWG (Table 2).

Deduction of TS Structure from Activation Parameters. To obtain further information on the TS structure, activation parameters ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) for the reaction of **1a** with piperidine have been calculated from the rate constants measured at five different temperatures. As shown in Figure S13 in the Supporting Information, the plots of k_{obsd} versus [amine] curve upward (A), while those of k_{obsd}/[amine] versus [amine] are linear with positive intercept (B) in all temperatures studied. Thus, the Kk_2 and Kk_3 values for the reaction of **1a** with piperidine calculated from the intercept and slope of the linear plots are summarized in Table 3. As shown in Table 3, the rate constants increase with increasing reaction temperature. However, the effect of reaction temperature on the rate constants is almost negligible for the catalyzed reaction; for example, Kk_3 increases from 2.44 to 2.64 and 2.73 M^{-2} s^{-1} as the reaction temperature increases from 15.0 to 25.0 and 35.0 °C, in turn.

Table 3. Summary of Kinetic Data for the Reactions of 1-(4-Nitrophenoxy)-2,4-dinitrobenzene (1a) with Piperidine at Five Different Temperatures

	Kk_2, M^{-1} s^{-1}	Kk_3, M^{-2}s^{-1}
15.0 °C	0.217	2.44
20.0 °C	0.258	2.54
25.0 °C	0.300	2.64
30.0 °C	0.349	2.67
35.0 °C	0.409	2.73
$\Delta H^{\ddagger}$, kcal mol^{-1}	4.95	0.38
$\Delta S^{\ddagger}$, cal mol^{-1} K^{-1}	−44.3	−55.4

The Arrhenius plots illustrated in Figure S14 (Supporting Information) exhibit excellent linear correlations. Thus, the activation parameters ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) calculated from the Arrhenius plots are considered reliable. The $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values shown in Table 3 for the uncatalyzed reaction are 4.95 kcal mol^{-1} and −44.3 cal mol^{-1} K^{-1}, respectively. Interestingly, the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values for the catalyzed reaction are 0.38 kcal mol^{-1} and −55.4 cal mol^{-1}K^{-1}, respectively. This indicates that the catalyzed reaction is governed almost entirely by the $T\Delta S^{\ddagger}$ term rather than by the $\Delta H^{\ddagger}$ term. More importantly, the large negative $\Delta S^{\ddagger}$ value indicates that the TS for the catalyzed reaction is highly ordered even in MeCN, which is known to be a poor solvent for ionic species.[39] This is consistent with the preceding proposal that the catalyzed reaction proceeds through a cyclic TS structure as modeled by TS$_{\text{MC}}$, in which the rotational and vibrational degrees of freedom are restricted to a certain degree. The large negative $\Delta S^{\ddagger}$ value found for the catalyzed reaction also supports the preceding argument that expulsion of the leaving group is advanced only a little in the TS on the basis of the small *r* value found in Figure 4.

Further evidence for the cyclic TS has been obtained from studies of the deuterium kinetic isotope effect (DKIE) for the reaction of **1a** with piperidine and deuterated piperidine. Table 2 shows that Kk_2 = 0.321 and Kk_3 = 2.03 for the reactions of **1a** with deuterated piperidine (i.e., DKIE < 1 for the uncatalyzed reaction, while DKIE > 1 for the catalyzed process). The inverse DKIE for the uncatalyzed reaction is mainly a reflection of the reduced steric hindrance, since the amplitude of the stretching vibration of a N−D bond is smaller than that of a N−H bond. An inverse DKIE is expected for the uncatalyzed reaction, since the deprotonation process occurs after the RDS. The normal DKIE for the catalyzed reaction is consistent with the proposed mechanism, in which the deprotonation and the donation of a proton by a second amine molecule occur in the RDS. However, the DKIE for the catalyzed reaction is 1.30, which appears to be quite small for a primary DKIE. One might suggest that the small DKIE for the catalyzed reaction is in accord with the preceding proposal that the degree of proton transfer (or C−OAr bond rupture) is advanced only a little in the TS of RDS on the basis of the small *r* values found for the reactions of **1a**−**1h**. Another possible reason that might account for the small primary DKIE can be found from the model transition state, TS_{MC}, which is shown in Scheme 3 as being not only cyclic but symmetrical. In fact, the DKIE results for the catalyzed pathway suggest that proton transfer either from the aminium site or to the aryloxyl oxygen site occurs neither in a linear fashion (which should yield close to a maximum primary DKIE, that is, ca. 7) nor in the symmetrical structure shown.[40] Proton transfer from the ammonium moiety to the amine or from the amine to the aryloxyl oxygen occurs in a nonsynchronous manner. This factor also accounts for the relatively low DKIE for a rate-limiting process involving proton transfer.

Taken in total, the kinetic results analyzed by the Brønsted treatment, the substituent effect analysis via the Yukawa−Tsuno correlations, the activation parameters with their large negative entropy of activation (cf. also Figure S15 in Supporting Information), and, finally, the DKIE data strongly support a concerted pathway for breakdown of the $MC^{\pm}$ to products. This pathway involves a cyclic transition state in which proton transfer from the aminium moiety to the aryloxyl oxygen of the leaving group that is expelled simultaneously occurs through a relay involving another molecule of the secondary amine. This deprotonation/protonation while concerted is not synchronous.

■ CONCLUSIONS

The current study has allowed us to conclude the following: (1) The curved plots of k_{obsd} versus [amine] indicate that the current S_NAr reactions are catalyzed by a second amine molecule. (2) The Brønsted-type plots for the reactions of **1a** with a series of cyclic secondary amines are linear with β_{nuc} = 1.10 and 0.85 for the uncatalyzed and catalyzed reactions, respectively. (3) The Yukawa−Tsuno plots for the reactions of **1a**−**1h** with piperidine result in excellent linear correlations with $\rho_Y = 1.85$ and $r = 0.27$ for the uncatalyzed reaction and $\rho_Y = 0.73$ and $r = 0.23$ for the catalyzed reaction, indicating that expulsion of the leaving group occurs in the RDS although the C−OAr bond rupture is advanced only a little. (4) The catalytic effect decreases as the amine becomes more basic or the substituent Y becomes a stronger EWG. (5) The catalyzed reaction from $MC^{\pm}$ proceeds through a concerted mechanism with a cyclic TS as modeled by TS_{MC} rather than via a stepwise pathway with the anionic MC^{-}. The cyclic transition state is unlikely to be symmetrical, however, and DKIE data suggest that the proton transfers are not synchronous in TS_{MC}. (6) The large negative $\Delta S^{\ddagger}$ value with a small $\Delta H^{\ddagger}$ value is consistent with the cyclic TS structure, in which expulsion of the leaving group is advanced only a little.

■ EXPERIMENTAL SECTION

Materials. Substrates **1a**−**1h** were readily prepared from the reaction of 1-fluoro-2,4-dinitrobenzene with the respective Y-substituted-phenol under the presence of triethylamine in anhydrous diethyl ether as reported previously.[27] The crude products were purified by short pathway silica gel column chromatography. Their purity was checked by their melting point, ^1H and ^{13}C NMR spectra; these were in good agreement with literature. Amines and other chemicals were of the highest quality available and used without further purification.

Kinetics. Kinetic study was carried out by using a UV−vis spectrophotometer equipped with a constant-temperature circulating bath to maintain the reaction temperature at 25.0 ± 0.1 °C. The reactions were followed by monitoring the appearance of *N*-(2,4-dinitrophenyl)amines at a fixed wavelength corresponding to their maximum absorption (λ_{max}, e.g., 379 nm for *N*-2,4-dinitrophenylpiperidine). All reactions were carried out under pseudo-first-order conditions in which the concentration of amines was kept at least 20 times greater than that of the substrate. Typically, the reaction was initiated by adding 5 μL of a 0.01 M of substrate stock solution in MeCN by a 10 μL syringe to a 10 mm UV cell containing 2.50 mL of solvent and the amine nucleophile. Reactions were followed generally up to 9−10 half-lives, and k_{obsd} were calculated using the equation $\ln(A_\infty - A_t) = -k_{obsd}t + C$. Based on the replicate runs, it is estimated that the uncertainty in the k_{obsd} values is less than ±3%.

Products Analysis. *N*-(2,4-Dinitrophenyl)piperidine was identified as one of the products by comparison of the UV−vis spectra at the end of the reactions with the authentic sample.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed kinetic conditions and results. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (Grant 2012-R1A1B-3001637). J.M.D. thanks Grenfell Campus-Memorial University (Vice-President's Research Fund) for support and Dr. D-R. Parkinson for valuable discussions.

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