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Mechanistic Assessment of S_NAr Displacement of Halides from 1-Halo-2,4-dinitrobenzenes by Selected Primary and Secondary Amines: Brønsted and Mayr Analyses

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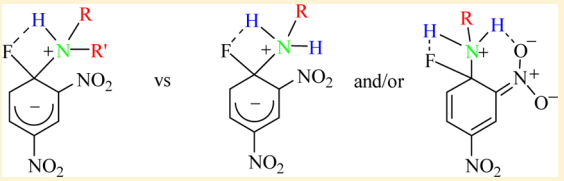
Supporting Information

ABSTRACT: Pseudo-first-order rate constants (k_{obsd}) have been measured spectrophotometrically for nucleophilic substitution reactions of 1-X-2,4-dinitrobenzenes (**1a–d**, X = F, Cl, Br, I) with various primary and secondary amines in MeCN and H_2O at 25.0 ± 0.1 °C. The plots of k_{obsd} vs [amine] curve upward for reactions of **1a** (X = F) with secondary amines in MeCN. In contrast, the corresponding plots for the other reactions of **1b–d** with primary and secondary amines in MeCN and H_2O are linear. The Brønsted-type plots for reactions of **1a–d** with a series of secondary amines are linear with β_{nuc} = 1.00 for the reaction of **1a** and 0.52 ± 0.01 for those of **1b–d**. Factors governing reaction mechanisms (e.g., solvent, halogen atoms, H-bonding interactions, amine types) have been discussed. Kinetic data were also analyzed in terms of the Mayr nucleophilicity parameter for the amines with each aromatic substrate. Provisional Mayr electrophilicity parameter (E) values for 1-X-2,4-dinitrobenzenes have been determined: E = −14.1 for X = F, E = −17.6 for X = Cl and Br, and E = −18.3 for X = I. These values are consistent with the range and order of E values for heteroaromatic superelectrophiles and normal 6-π aromatic electrophiles.



INTRODUCTION

Nucleophilic displacement of halides from aromatic[1−4] and heteroaromatic[5,6] substrates, typically activated by one or more powerful electron-withdrawing groups (e.g., NO_2, SO_2CF_3,[7,8] $F_3CSO{=}NSO_2CF_3$,[8] etc.), generally proceeds according to the S_NAr mechanism.[7−11] There has been considerable interest in investigations of nucleophilic reactions of the highly reactive 10π neutral electrophiles, such as 4,6-dinitrobenzofuroxan[12,13] and structural analogues,[14−16] many of which have been definitively classified as superelectrophiles[15] on the Mayr electrophilicity, E, scale.[17] On the other hand, there has been an equivalent surge of interest in nucleophilic aromatic displacement reactions with more standard nitroaromatic electrophiles but under more exotic conditions of medium[18]—such as the use of room temperature ionic liquids for the reaction medium[19]—or of stabilizing complexants such as cavitands.[20] Improved methods of stereoselective reaction,[21] of incorporation of these nucleophilic aromatic substitution steps in cascade or tandem sequences,[22] and in the preparation of electrophilic derivatives of water-soluble polymers[23,24] have been realized using S_NAr displacements.

The generally accepted pathways of S_NAr reaction between amines and 1-X-2,4-dinitrobenzenes are summarized in Scheme 1. In the first step (k_1), nucleophilic attack at C-1 that bears the leaving halide, X, results in formation of the zwitterionic σ-bonded (Meisenheimer) complex, MC-1-Z. While reaction at unsubstituted sites (C-3, C-5) may occur in principle, and regioselectivity in MC formation is of interest with more highly activated (i.e., electron-deficient) aromatics,[25] MC-3,5 (not shown) have not been observed in our previous study in acetonitrile[26] nor in similar investigations of amine reactions with related substrates.[23,27]

Deprotonation of the zwitterionic adduct MC-1-Z leads to the neutral Meisenheimer complex MC-1 and, then, to the product dinitroaniline, DNA, in a k_3 step involving expulsion of the leaving group, X^-, a halide in the present study. If the k_3 step is rate limiting then catalysis by excess amine may be observed. In principle, the inverse process involves loss of the leaving group from MC-1-Z to give the conjugate acid of the final product, $DNAH^+$, which rapidly equilibrates to favor the final DNA in the basic reaction medium. Alternatively, proton transfer may occur in MC-1-Z from the aminium cationic moiety to the halide leaving group in a concerted fashion, collapsing the two steps of proton transfer and loss of the (now partly protonated) leaving group into a single step. For simplicity, Scheme 1 does not show this possibility; it can be imagined as following a diagonal line from MC-1-Z to DNA, a single step.[11]

The similarity in the nucleophilic addition step in S_NAr displacement and the addition to carbonyl, C=O, step in ester decomposition, for example, is apparent. In both cases, addition

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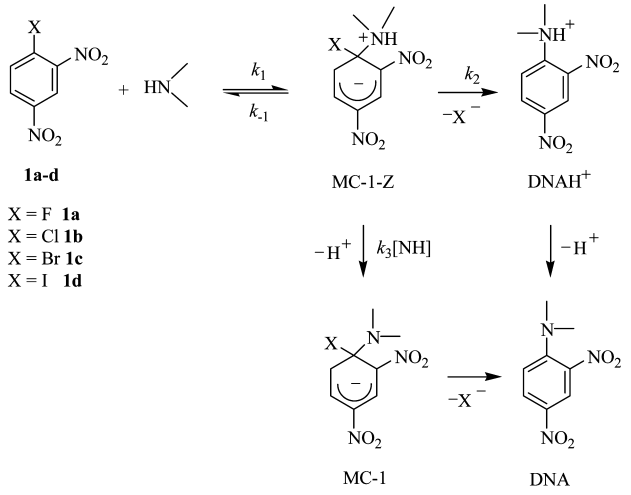
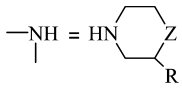
Scheme 1





R = H, Z = CH_2 (N = 17.35)
R = Me, Z = CH_2 (N = not known)
R = H, Z = NH (N = not known)
R = H, Z = NCH_2CH_2OH (N = not known)
R = H, Z = O (N = 15.65)

RR'NH
R = R' = Et (N = 15.10)
R = $PhCH_2$, R' = Me (N = not known)
R = R' = CH_2=$CHCH_2$ (N = not known)
R = R' = CH_2CH_2OH (N = not known)

RNH_2
R = *n*-Bu (N = 15.27)
R = *n*-Pr (N = 15.11)
R = $PhCH_2$ (N = 14.29)

to the sp^2 carbon leads to rehybridization to sp^3 to produce a tetrahedral intermediate. Elimination of the leaving group in subsequent step(s) restores the sp^2 center. 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 intermediate; aromaticity is regained upon expulsion of the leaving group. In our previous paper concerning S_NAr displacement we applied Brønsted analysis to assess the rate-determining mechanistic step.[26] Although this tool has been used extensively for nucleophilic reaction at C=O,[28−31] its application to S_NAr reactions has been more modest.[32]

The current work extends our study from aminolysis with secondary amines and 1-fluoro-2,4-dinitrobenzene (DNFB) in acetonitrile to aminolysis using various primary and secondary amines with the full series of 1-X-2,4-dinitrobenzenes, where X = F, Cl, Br, and I. The kinetic results will be dissected into the appropriate microscopic constants, and these rate constants will be considered using Brønsted analysis and also for selected amines used in this study by application of the Mayr nucleophilicity parameter, N.[17] The Mayr analysis confirms our assessment of the rate-determining steps involved with each substrate and permits us to define the electrophilicity parameter, E, for the 1-X-2,4-dinitrobenzene series. The utility of the Mayr E and N equation for prediction of reaction rate constants may be further expanded through the approximate E values determined in the current work.

RESULTS AND DISCUSSION

Reactions of 1-X-2,4-dinitrobenzenes **1a−d** with amines were monitored spectrophotometrically, and rate constants were measured under pseudo-first-order conditions with the concentration of amines maintained in greater than 20-fold excess relative to substrate concentration. All reactions obeyed first-order kinetics. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation $\ln (A_\infty - A_t) = -k_{obsd}t + C$. On the basis of duplicate runs, the uncertainty in the rate constants is estimated to be less than ±3%. The k_{obsd} values together with detailed reaction conditions are summarized in Tables S1−S46 in the Supporting Information.

As shown in Figure 1, the plot of k_{obsd} vs [amine] for the reaction of **1a** with diethylamine in MeCN curves upward as a function of increasing amine concentration but is linear for the corresponding reaction carried out in H_2O (inset, Figure 1). A similar upward curvature has been obtained for the reactions of **1a** with the other secondary amines employed in this study in MeCN, e.g., Figure 2A for the reaction with diallylamine (and Figures S1A and S2A for the reactions with *N*-methylbenzylamine and diethanolamine, respectively, in the Supporting Information). Since the upward curvature shown in Figure 1 is typical of reactions reported previously to proceed through a rate-limiting proton transfer (RLPT) mechanism, one can suggest that the reaction of **1a** with the secondary amines examined in MeCN proceeds via two intermediates (i.e., a zwitterionic adduct MC-1-Z and its deprotonated form MC-1) as shown in Scheme 1.

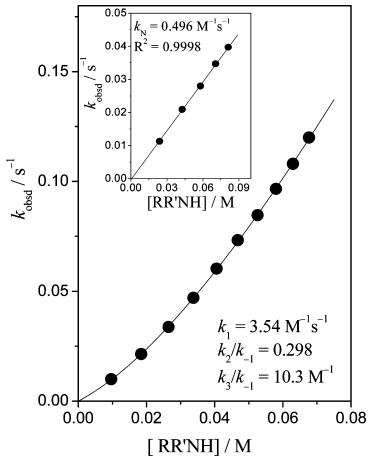


Figure 1. Plots of k_{obsd} vs [RR′NH] for the reaction of **1a** with diethylamine in MeCN and in H_2O (inset) at 25.0 ± 0.1 °C. The solid line for the reaction in MeCN was calculated by eq 1.

In contrast, the plots for the corresponding reactions of **1a** with primary amines and those for the reactions of the other 1-X-2,4-dinitrobenzenes (X = Cl, Br, I, i.e., **1b−d**) with secondary and/or primary amines in MeCN are linear and pass through the origin. *Moreover*, the reactions of **1a−d** in H_2O show linear plots (e.g., the inset of Figure 1 for the reaction of **1a** with diethylamine), indicating that the rate-limiting deprotonation process by a second amine molecule (i.e., the k_3 step in Scheme 1) is absent for these reactions.

Accordingly, the second-order rate constants (k_1) for these reactions have been determined from the slopes of the linear plots of k_{obsd} vs [amine], and summarized in Table 1 together with the k_1 values for the reactions of **1a** with cyclic and acyclic

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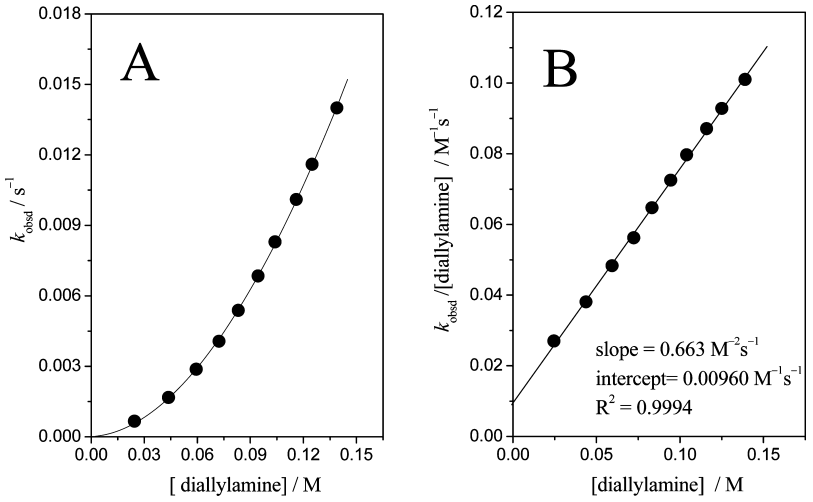

Figure 2. Plots of k_{obsd} vs [diallylamine] (A) and k_{obsd}/[diallylamine] vs [diallylamine] (B) for the reaction of **1a** with diallylamine in MeCN at 25.0 ± 0.1 °C.

Table 1. Summary of Second-Order Rate Constants (k_1/M^{-1}s^{-1}) for Reactions of 1-Halo-2,4-dinitrobenzenes 1a–d with Amines in MeCN and H_2O (in Parentheses) at 25.0 ± 0.1 °C[a]

				k_1/M^{-1}s^{-1}			
	amine	pK_a	N[b]	**1a**	**1b**	**1c**	**1d**
1	piperidine	18.8	17.35	380[c] (8.20)	0.558 (0.0432)	0.583 (0.0472)	0.167 (0.0179)
2	piperazine	18.5		394[c]	0.607	0.692	0.181
3	1-(2-hydroxyethyl) piperazine	17.6		41.9[c]	0.101	0.105	0.0317
4	1-formylpiperazine	17.0		11.1[c]	0.0653	0.0779	0.0210
5	morpholine	16.6	15.65	17.8[c]	0.0412	0.0418	0.0122
6	diethylamine	18.75	15.10	3.54 (0.496)	4.17×10^{-3} (3.36×10^{-4})	5.58×10^{-3} (4.59×10^{-4})	1.57×10^{-3} (1.30×10^{-4})
7	diallylamine			0.897			
8	*N*-methylbenzylamine			18.2			
9	diethanolamine			10.2			
10	*n*-butylamine	18.26	15.27	8.61 (0.432)	1.48×10^{-2} (9.27×10^{-4})	1.42×10^{-2} (1.09×10^{-3})	5.53×10^{-3} (4.50×10^{-4})
11	*n*-propylamine	18.22	15.11	8.05	9.46×10^{-3}	1.06×10^{-2}	2.47×10^{-3}
12	benzylamine	16.70	14.29	1.83	1.67×10^{-3}	2.01×10^{-3}	6.60×10^{-4}

[a] pK_a data in MeCN were taken from refs 31b and 33a–e. [b] *N* values were taken from ref 17. [c] k_1 values were taken from ref 26.

secondary amines (i.e., amines 1–9 in Table 1) in MeCN for comparison purposes. The k_1 values for the reactions of **1a** with the acyclic secondary amines have been determined as follows.

Dissection of k_{obsd} into Microscopic Rate Constants k_1, k_2/k_{-1}, and k_3/k_{-1} Ratios for 1a. On the basis of the kinetic results and the mechanism proposed in Scheme 1, the pseudo-first-order rate constant (k_{obsd}) can be expressed as eq 1 for the reactions of **1a** with the secondary amines in MeCN, where [RR′NH] represents the concentration of amines. Equation 1 may be simplified to eq 2 under the assumption, $k_{-1} \gg k_2 + k_3$[RR′NH]. Accordingly, the relationship of k_{obsd}/[RR′NH] vs [RR′NH] would be expected to be linear if the reactions proceed as indicated by Scheme 1. In fact, as shown in Figure 2B, the plot of k_{obsd}/[RR′NH] vs [RR′NH] is linear up to ca. 0.13 M for the reaction with diallylamine. Similar results have been obtained for the reactions of **1a** with the other secondary amines (Figures S1B and S2B, Supporting Information, for the reactions with *N*-methylbenzylamine and diethanolamine, respectively).

$$k_{obsd} = (k_1k_2[RR'NH] + k_1k_3[RR'NH]^2) / (k_{-1} + k_2 + k_3[RR'NH]) \quad (1)$$

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

In contrast, the plot of k_{obsd}/[RR′NH] vs [RR′NH] for the reaction with diethylamine is linear only up to ca. 0.04 M (Figure S3A in the Supporting Information) but curves downward as the concentration of amine increases further, indicating that the above assumption is invalid for the reaction with diethylamine in the high concentration region. However, this is not surprising since the term k_3[RR′NH] increases with increasing amine concentration. Understandably, then, when the amine concentration is high enough, in fact: $k_2 \ll k_3$[RR′NH]. Then, eq 1 simplifies to eq 3. As shown (Figure S3B in the Supporting Information), the plot of [RR′NH]/k_{obsd} vs 1/[RR′NH] is linear in the region where the amine concentration exceeds 0.04 M but exhibits downward curvature as the amine concentration decreases. Considering the plot in terms of two distinct regions permits extraction of $1/k_1$ and $1/Kk_3$ values from the intercept and slope of the linear part of the curvilinear plots, respectively. More reliable values of k_1 and then k_2/k_{-1}, k_3/k_{-1} ratios have been determined through nonlinear least-squares fitting of eq 1 to the experimental data using the $1/k_1$ and $1/Kk_3$ values obtained above as input values

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Table 2. Summary of Microscopic Rate Constants for the Reactions of 1-Fluoro-2,4-dinitrobenzene 1a with Secondary Amines in MeCN at 25.0 ± 0.1 °C[a]

	amine	k_1 (M^{-1} s^{-1})	k_2/k_{-1}	Kk_2 (M^{-1} s^{-1})	k_3/k_{-1} (M^{-1})	Kk_3 (M^{-2} s^{-1})
1	piperidine	380	0.293	111	50.3	19000
2	piperazine	394	0.137	54.0	42.5	16700
3	1-(2-hydroxyethyl) piperazine	41.9	0.182	7.63	32.0	1340
4	1-formylpiperazine	11.1	0.180	2.00	32.3	359
5	morpholine	17.8	0.0400	0.712	5.74	102
6	diethylamine	3.54	0.298	1.05	10.3	36.5
7	diallylamine	0.897	0.00530	0.00475	0.877	0.787
8	*N*-methylbenzylamine	18.2	0.0639	1.16	4.36	79.4
9	diethanolamine	10.2	0.0110	0.112	0.148	1.51

[a]The data for the reactions with amines 1−5 were taken from ref 26. The k_1, k_2/k_{-1}, and k_3/k_{-1} ratios for the reactions with amines 6−9 were determined from nonlinear least-squares fitting of eq 1.

for the reactions with all the secondary amines studied. The microscopic rate constants determined in this way are summarized in Table 2.

$$[RR'NH]/k_{obsd} = 1/k_1 + 1/Kk_3[RR'NH] \quad (3)$$

As shown in Table 2, $k_2/k_{-1} \ll 1$ for the reactions of **1a** with amines 7−9, indicating that the assumption $k_{-1} \gg k_2 + k_3[RR'NH]$ is valid. This accounts for the linear plots of $k_{obsd}/[RR'NH]$ vs $[RR'NH]$ (Figure 2B and Figures S1B, S2B in the Supporting Information). In contrast, $k_2/k_{-1} = 0.298$ for the reaction with diethylamine, implying that the assumption $k_{-1} \gg k_2 + k_3[RR'NH]$ is invalid in the high amine concentration region. This explains why the plot of $k_{obsd}/[RR'NH]$ vs $[RR'NH]$ (Figure S3A in the Supporting Information) curves downward when the concentration of diethylamine exceeds 0.04M.

Reactions of 1a with Secondary Amines in MeCN. As discussed above on the basis of the upward curvature in the plot of k_{obsd} vs [amine] (e.g., Figure 1), reaction of **1a** with the secondary amines (cyclic or acyclic) studied in MeCN plausibly proceeds through two intermediates (i.e., a zwitterionic adduct MC-1-Z and its deprotonated form MC-1). In contrast, such a deprotonation process is absent for the reactions of the other 1-X-2,4-dinitrobenzenes (i.e., X = Cl, Br, I, **1b−d**) with the same secondary amines in MeCN, indicating that the nucleofugal (i.e., atom) effect on the reaction mechanism is significant.

To account for our finding that the nature of the nucleofuge governs the presence/absence of the deprotonation process, a qualitative energy profile is illustrated in Figure 3 for the processes from MC-1-Z to $DNAH^+$ and MC-1 (cf., Scheme 1).

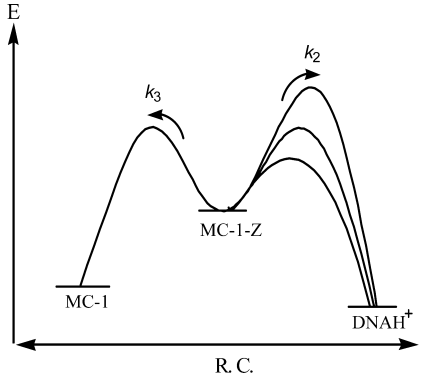

Figure 3. Qualitative comparative energy profile for the process from MC-1-Z to $DNAH^+$ and MC-1.

The energy barrier for the k_2 process (i.e., departure of the leaving group from MC-1-Z to give $DNAH^+$) is expected to be strongly dependent on the nucleofugality of the leaving X^- ion. In contrast, the energy barrier for the k_3 process (i.e., to form MC-1 from MC-1-Z) should be little influenced by the nature of X. Besides, the energy barrier for the k_3 process would be independent of amine basicity, since a more basic amine would deprotonate more rapidly the aminium moiety of MC-1-Z but, conversely, the aminium ion would tend to hold the proton more strongly as the amine becomes more basic. Thus, the reaction mechanism (i.e., presence or absence of the k_3 process) would be mainly governed by the nucleofugality of the leaving X^- ion.

Figure 3 illustrates a qualitative comparative energy profile where reaction would proceed through MC-1-Z to MC-1 if the energy barrier for the k_2 process is higher than that for the k_3 path. Note that a concerted path where HX is lost in a single step is not portrayed in Figure 3, for simple clarity. On the contrary, the reactions would proceed through MC-1-Z to $DNAH^+$ if the energy barrier to form $DNAH^+$ from MC-1-Z is lower than that to form MC-1. Since F^- ion is known to be an extremely poor nucleofuge in dipolar aprotic solvents such as MeCN or DMSO, where this hard anionic leaving group would be expected to be highly destabilized in the aprotic solvent, the energy barrier for the k_2 process is reasonably higher for the reaction of **1a** compared to that for the reactions of **1b−d**. This idea accounts for the current results, namely, that the reaction of **1a** with secondary amines in MeCN proceeds through the RLPT mechanism while the k_3 process is absent for the corresponding reactions of **1b−d**. On the other hand, the energy barrier for the k_2 process is expected to be lowered for reaction of **1a** in H_2O, since the nucleofugality of F^- ion in water, where H-bonding provides stabilization, is not as poor as that in the aprotic solvent. This idea is consistent with the fact that the k_3 process is absent for reaction of **1a** with secondary amines in H_2O.

Effect of Amine Nature on Reaction Mechanism. Our previous study has shown that the reaction of **1a** with the cyclic secondary amines (i.e., amines 1−5 in Table 1) in MeCN proceeds via the k_3 path regardless of amine basicity.[26] The reaction of **1a** with acyclic secondary amines (amines 6−9) employed in this study in MeCN also exhibit upward curvature in the plots of k_{obsd} vs [amine]. Thus, one can suggest that the reaction of **1a** with secondary amines (either cyclic or acyclic) in MeCN proceeds through the k_3 path. In contrast, the linear plots of k_{obsd} vs [amine] for the reactions of **1a** with primary amines in MeCN indicate that the reactions proceed without

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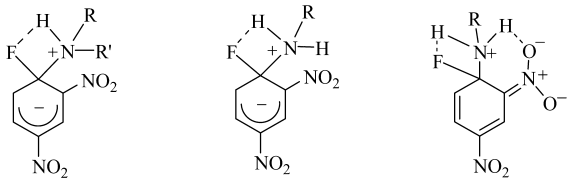
intervention of the k_3 process. Clearly, the current study highlights the importance of the nature of amines (i.e., primary and secondary amines) that governs the presence or absence of the k_3 process for the reactions of **1a** in MeCN.

Since the F atom can form H-bonds, one can propose that intramolecular H-bonding structures as modeled by I, II, and III are possible for the reactions of **1a**. It is apparent that such H-bonding interactions would be expected to be more significant for reactions in MeCN than in H_2O. The 4-membered H-bonded structures can stabilize the transition state (or intermediate) and would assist the nucleofugality of F^- ion. Accordingly, the energy barrier for the k_2 process shown in Figure 3 would decrease through the H-bonding interaction.



I II III

Understandably, intramolecular H-bonding would be more facile for the reaction with primary amines (e.g., II) than for that with secondary amines (e.g., I) on a simple statistical basis, since the former has two hydrogens to engage in H-bonding. Furthermore, the reactions with primary amines can also involve H-bonding between the H atom of the aminium ion moiety and the negatively charged O atom of the nitro group at 2-position (e.g., III), which would cause further stabilization of the transition state (or intermediate). This idea can explain why the k_3 process is absent for the reactions with the primary amines.

Analysis of Brønsted-Type Plots. As shown in Figure 4, the Brønsted-type plots are all linear for the reactions of **1a–d** with structurally similar amines 1–5, when the k_1 and pK_a values are corrected statistically using p and q (i.e., $p = 2$ and $q = 1$ except $q = 2$ for piperazine).[34] Interestingly, the β_{nuc} value for the reactions of **1a** is significantly different from that for the corresponding reactions of **1b–d**, i.e., $\beta_{nuc} = 1.00$ for **1a** and 0.53 or 0.52 for **1b–d**. The β_{nuc} value of 1.00 is consistent with the proposed mechanism for the reactions of **1a** in MeCN, in which bond formation at the rate-determining step (RDS) is fully advanced. In contrast, the β_{nuc} value of 0.53 or 0.52 for reaction of **1b–d** indicates that bond formation in the transition state of the RDS is not much advanced. The small β_{nuc} value is consistent with the preceding argument that the reactions of **1b–d** proceed through a rate-determining formation of MC-1-Z (k_1, Scheme 1), in which bond formation at the RDS is partially advanced, on the basis of the fact that the k_3 process in Scheme 1 is absent. Thus, the difference in the β_{nuc} value for the reaction of **1a–d** also supports the proposed mechanisms.

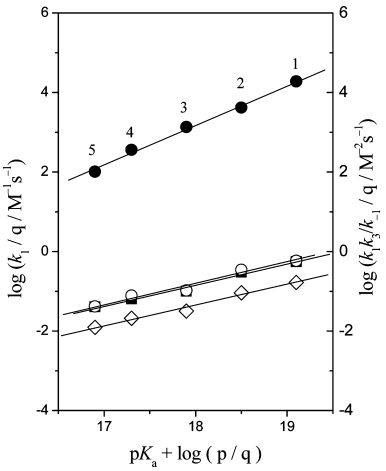


Figure 4. Brønsted-type plots for reactions of **1a–d** with cyclic secondary amines 1–5 in MeCN at 25.0 ± 0.1 °C: **1a** (●, $\beta_{nuc} = 1.00$), **1b** (■, $\beta_{nuc} = 0.53$), **1c** (○, $\beta_{nuc} = 0.53$), **1d** (◇, $\beta_{nuc} = 0.52$). Note that the k_1k_3/k_{-1} values (taken from Table 2) for the reaction of **1a** are used in the Brønsted-type correlation with $q = 4$ for piperazine. The assignment of numbers is given in Tables 1 and 2.

Note that the Brønsted-type plot that was previously reported for aminolysis of **1a** with amines 1–5 (Table 1) *in* H_2O also had a slope, β_{nuc}, of 0.52,[26] which was taken as evidence for rate-limiting formation of MC-1-Z. The similarity of β_{nuc} for aminolysis of **1a** in H_2O and β_{nuc} for **1b–d** in MeCN suggests that all of these systems involve rate-determining amine attack on the various substrates, where the rate-determining step is dependent on the solvent.

Effect of Electronegativity of Halogens on Reactivity. As shown in Table 1, regardless of the nature of amine and medium, the reactivity of 1-X-2,4-dinitrobenzenes **1a–d** increases as X becomes more electronegative (i.e., F > Cl ≈ Br > I), which is opposite to the reactivity order expected from the nucleofugality of the leaving X^- ions. The effect of electronegativity of X on reactivity is illustrated in Figure 5 for the reactions of **1a–d** with piperidine. One can see linear correlations between the reactivity and electronegativity of X (except X = Cl, which exhibits a negative deviation from linearity) for both reactions in MeCN and H_2O, although **1a–d** are more reactive in the aprotic solvent than in water. Similar results are obtained for the reactions with diethylamine and *n*-butylamine.

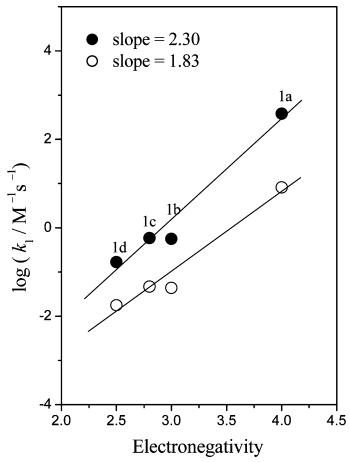


Figure 5. Plots of log k_1 vs electronegativity of X for reactions of **1a–d** with piperidine in MeCN (●) and H_2O (○) at 25.0 ± 0.1 °C. Note that the k_1 values for the reaction of **1a** in MeCN are used in the correlation.

One would expect the opposite result for reactions in which departure of the leaving group occurs in the RDS, since the leaving-group ability increases in the order $F^- < Cl^- < Br^- < I^-$. Accordingly, the fact that the reactivity increases with decreasing nucleofugality of X^- ions indicates that expulsion

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of the leaving group occurs after the RDS. This is consistent with the preceding argument that the reactions of **1b−d** proceed through a rate-determining formation of MC-1-Z on the basis of the β_{nuc} value of 0.53 or 0.52 and absence of the k_3 process.

Figure 5 shows that the reactions in MeCN result in a larger slope in the plot of log k_1 vs electronegativity than those in H_2O, indicating that the effect of electronegativity of X on reactivity is more sensitive for the reactions in the aprotic solvent than for those in water. This is consistent with the report that electronic effects become more significant as the medium polarity decreases, e.g., the ρ value for dissociation of benzoic acids in H_2O is 1.00 but was reported to be 1.96 and 2.4 in ethanol and MeCN, respectively.[35]

Mayr Analysis. Assignment of the Electrophilicity, *E*, for the 1-X-2,4-Dinitrobenzenes. The Mayr group has defined an equation whereby absolute nucleophilicities and electrophilicities, assigned the symbols *N* and *E*, respectively, may be defined from rate constant data:

$$\log k = s(E + N) \quad (4)$$

The defining eq 4 uses rate constant data measured at 20 °C and is only valid for second-order rate constants with values $\leq 10^8$ M^{-1} s^{-1} (i.e., below the region of encounter-control).[17,36] The slope parameter, *s*, and the *N* value characterize nucleophilicity. Normally, only the *E* value is required to describe electrophilicity in a reaction. For S_N2 displacements a further term, *s*, specific to the electrophile (as is *E*) has been shown to be required.[37a] (Recently, the Mayr group has also defined a nucleofugality parameter for fluoride ion in protic solvents or mixed solvents with a protic component.)[37b]

Normally, the *N* parameter is defined via eq 4 as the *x* intercept when log *k* has the value 0 (i.e., $N = -E$ at this point).[36b] The essential form of this linear free energy relationship (LFER) is made more obvious after expanding the equation:

$$\log k = sN + sE \quad (5)$$

If kinetic data for a single electrophile (invariant *E* value) are plotted against *N* for a series of nucleophiles, namely the primary and secondary amines of the present work where the *N* values are known, then the slope of the line (if linearity is good) provides the sensitivity of the reaction to nucleophilicity, *s*, as the slope. The *N* values for the amines *used* were available from the extensive tabulated data at the Web site maintained by the Mayr group.[17c] Since *E* is a constant and the slope, *s*, is constant for a good linear plot, the *sE* term is a constant, the *y* intercept of the plot. From this intercept the electrophilicity, *E*, for the single electrophile may be extracted. Note that in the present work the rate constants were determined at 25 °C, and the *E* values defined here should be taken as provisional values, as a result. Nonetheless, the trends found here in the *E* values provide important insights into the nucleophilic aromatic displacements (vide infra).

Figure 6 (and Figures S4−S6 in the Supporting Information) depict Mayr plots as outlined above for **1a−d**, in turn. For all plots the same rate constant for formation of MC-1-Z, i.e., k_1, was employed in the log *k* term. The plots all have reasonable linearity ($R^2 \geq 0.979$). This linearity indicates a dependence of the rate constant on the nucleophilicity values of the amines. A plot with extensive scatter or a break in the line would either indicate no reliance on amine nucleophilicity or possibly a change in mechanism. Moreover, the slopes of the plots all are similar in value (ca. 0.8) as might be expected in reactions where the only change in the electrophile stems from changing F in **1a** to Cl in **1b** and so forth.

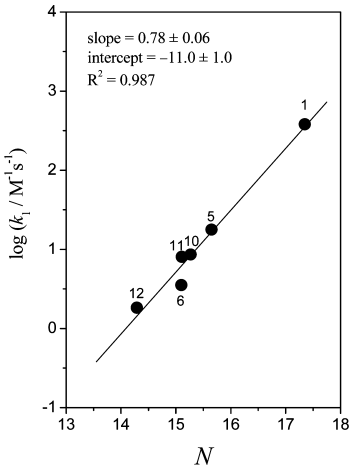

Figure 6. Plot of log k_1 vs *N* for the reactions of 1-fluoro-2,4-dinitrobenzene **1a** with amines in MeCN at 25.0 ± 0.1 °C. The assignment of numbers is given in Table 1.

The values of the electrophilicity parameters, *E*, determined as outlined above are, for each 1-X-2,4-dinitrobenzene: $E = -14.1$ for X = F, $E = -17.6$ for X = Cl and Br, and $E = -18.3$ for X = I. These values, albeit provisional ones, are nonetheless consistent with values recently assigned to other electrophiles that engage either in Meisenheimer adduct formation or in S_NAr displacement reactions. Thus, the standard benchmark normal (6π electron) aromatic electrophile in Meisenheimer complexation is 1,3,5-trinitrobenzene (TNB) with an *E* value of −13.19.[12] The most reactive of the 1-X-2,4-dinitrobenzene series is the 1-fluoro derivative with an approximate *E* value of −14.1. It is reasonable that 1-fluoro-2.4-dinitrobenzene be less electrophilic than TNB, but it is equally sound that it is the most electrophilic of the 1-X-2,4-dinitrobenzene series.

Electrophiles that engage in Meisenheimer adduct formation/S_NAr displacement may be profitably divided into superelectrophiles, such as 4,6-dinitrobenzofuroxan (DNBF),[38,39] and normal electrophiles typified by TNB, but also by the 1-X-2,4-dinitrobenzene series of this work.[3,4,14,15b] The basis of the demarcation between the two classes of electrophiles is the Mayr electrophilicity parameter, *E*.[36] Superelectrophiles have *E* values less negative that −8; DNBF has a electrophilicity of −5.06 on the Mayr scale, while the even more electrophilic 4,6-dinitrotetrazolo[1,5-*a*]pyridine has become the new standard for superelectrophiles with an *E* value of −4.67.[15b] Superelectrophiles are not only highly reactive in Meisenheimer complex formation/S_NAr displacement[40] but also show significant and versatile Diels−Alder reactivity,[12,14] displaying a range of modes of cycloaddition[41−45] with dienes. Electrophiles near $E = -8$ are termed borderline such as *N*-(2,4-dinitrophenyl)-4,6-dinitrobenoztriazole 1-oxide (DNP-DNBT),[15b] a member of a series of 4,6-dinitrobenzotriazole 1-oxides[14−16,46] substituted by nitroaryl groups attached to 2-*N* of the 5-membered ring. As mentioned, electrophiles with *E* values significant more negative than −8, such as TNB and the present 1-X-2,4-dinitrobenzene series, are normal electrophiles and do not show Diels−Alder-type reactivity.[15b]

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The distinction between the two sets of electrophiles appears to reside in the degree of aromaticity found in each set: the heteroaromatic 10π superelectrophiles also have significantly reduced aromaticity relative to the normal 6π normal electrophiles.

The current 1-X-2,4-dinitrobenzene series are normal electrophiles. The differences in E values along the series are consistent with a wide range of kinetic studies of S_NAr displacement with the series.[47,48] The E values estimated in the current study indicate that 1-fluoro-2,4-dinitrobenzene is much more electrophilic ($E = -14.1$) than the chloro or bromo derivatives whose E values are identical ($E = -17.6$), and these substrates have electrophilicities greater than that of 1-iodo-2,4-dinitrobenzene but to a smaller degree (ΔE (I − Cl/Br) = 0.7 versus ΔE (F − Cl/Br) = 3.5). The order of the electrophilicities found here is in broad agreement with the leaving group order found in a number of previous S_NAr studies (based on rate constants, k_1, for the initial addition step): F ≫ Cl ≈ Br > I.[47,48] As has previously been noted, however, this order is also modified by the nature of the nucleophile. For methoxide (in methanol) the order is: F ≫ Cl > Br > I whereas for methanethiolate the order is F ≫ Br > Cl > I.[49] Here the change in order is attributable to the significantly divergent polarizabilities of the nucleophiles.[47,49b]

The Mayr E values for the 1-X-2,4-dinitrobenzene series are cross-correlated with the electronegativities of the 1-X halo groups. Thus, the rate constants correlate with these electronegativities and, similarly, the provisional E values determined in the present work also correlate with the electronegativities of the 1-halo substituents (E versus electronegativity; $E = 2.87 \times$ electronegativity −25.7, $R^2 = 0.984$; Figure S7 in the Supporting Information). This is understandable since in these reactions the only change is the minor modulation of the 1-X leaving group whose influence on attack of the amine nucleophile in the first step (rate determining for **1b**-**1d** in MeCN) rests primarily on the increase in electrophilicity that is directly linked to the electronegativity of the 1-halo group.

Although approximate, the E values determined here should allow the estimation of rate constants for other nucleophilic aromatic displacements with nucleophiles whose N values are known.[17c]

CONCLUSIONS

The current study has demonstrated that the reactions of **1a** with secondary amines in MeCN proceed through an RLPT process. However, the deprotonation process by a general base is absent for the corresponding reactions in H_2O and for the other reactions, e.g., reactions of **1b−d** with secondary amines and those of **1a−d** with primary amines in *either* MeCN *or* H_2O. Thus, we have concluded the following: (1) Poor nucleofugality of F^- ion in the aprotic solvent is responsible for preference for the k_3 pathway, since the corresponding reactions of **1b−d** proceed without this deprotonation process. (2) The deprotonation process is absent for the reactions of **1a** in H_2O, because the nucleofugality of F^- ion in water is not as poor as that in the aprotic solvent. (3) The reactions of **1a** with primary amines in MeCN proceed without the k_3 process. Facile intramolecular H-bonding is responsible for the absence of the k_3 process. (4) Analysis of the linear Brønsted-type plots also supports the proposed mechanisms, i.e., $\beta_{nuc} = 1.00$ for the reactions of **1a** with secondary amines in MeCN, which proceed through MC-1-Z to MC-1, while $\beta_{nuc} = 0.52$ or 0.53 for those of **1b−d**, in which formation of MC-1-Z is the RDS (partial bond formation in the TS). (5) The fact that the plots of log k_1 vs electronegativity result in good correlations with large positive slopes implies that expulsion of the leaving group occurs after the RDS. This conclusion is bolstered by the finding of a good correlation between the appropriate rate constants and the Mayr nucleophilicity parameters, N, for the amines. These correlations permit definition of approximate E, electrophilicity, parameters for the series of 1-X-2,4-dinitrobenzenes: $E = -14.1$ for X = F, $E = -17.6$ for X = Cl and Br, and $E = -18.3$ for X = I. The E values are cross-correlated with the electronegativity values of the 1-halo substituents in the series.

Importantly, the E parameters will allow estimation of rate constants for S_NAr displacements with other nucleophiles whose N values have been characterized.[17c] In turn, the ability to estimate these rate constants is expected to be of value in organic syntheses involving these 1-X-2,4-dinitrobenzenes (or in molecules containing the 2,4-dinitrobenzene moiety), particularly those for which competitive nucleophilic attack may arise. The approach used here to estimate Mayr electrophilicities, E, may also be applicable to other systems that we have studied and so open another pathway of analysis for a wide range of nucleophilic−electrophilic reactions.[50,51]

EXPERIMENTAL SECTION

Materials. 1-X-2,4-Dinitrobenzenes **1a−d** and all amines studied were of the highest quality available. MeCN was distilled over P_2O_5 and stored under nitrogen. Doubly glass-distilled water was further boiled and cooled under nitrogen just before use.

Kinetics. The kinetic study was performed using a UV−vis spectrophotometer for slow reactions ($t_{1/2} > 10$ s) or a stopped-flow spectrophotometer for fast reactions ($t_{1/2} \leq 10$ s) equipped with a constant temperature circulating bath. The reactions were followed by monitoring the appearance of *N*-(2,4-dinitrophenyl)amines at a fixed wavelength corresponding to the maximum absorption (λ_{max}, e.g., 379 nm for *N*-2,4-dinitrophenylpiperidine). Typically, the reaction was initiated by injection of 3 μL of a 0.02 M 1-fluoro-2,4-dinitrobenzene **1a** stock solution (MeCN) via a 10 μL syringe into a 10 mm UV cell containing 2.50 mL of the reaction medium and amine. The amine stock solution (ca. 0.2 M) for the reactions in H_2O 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 give a self-buffered solution. Transfer of solutions was carried out by means of gastight syringes. All reactions were carried out under pseudofirst-order conditions in which amine concentrations were at least 20 times greater than the substrate concentration.

Product Analysis. *N*-(2,4-Dinitrophenyl)amine 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

Plots of k_{obsd} vs [amine] (A) and k_{obsd}/[amine] vs [amine] (B) for the reactions of **1a** with *N*-methylbenzylamine and diethanolamine, respectively. Plots of k_{obsd}/[amine] vs [amine] (A) and [amine]/k_{obsd} vs 1/[amine] (B) for the reaction of **1a** with diethylamine. Mayr plots of log k_1 vs N for the reactions of **1b−d** with various amines in MeCN. Plot of the Mayr E value estimated for 1-X-2,4-dinitrobenzenes vs electronegativity of the halogen atoms. Tables containing the 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.

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