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Choice of Solvent (MeCN vs H_2O) Decides Rate-Limiting Step in S_NAr Aminolysis of 1-Fluoro-2,4-dinitrobenzene with Secondary Amines: Importance of Brønsted-Type Analysis in Acetonitrile

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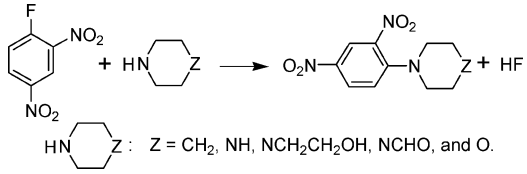

A kinetic study is reported for nucleophilic substitution reactions of 2,4-dinitro-1-fluorobenzene (DNFB) with a series of secondary amines in MeCN and H_2O at 25.0 °C. The reaction in MeCN results in an upward curvature in the plot of k_{obsd} vs [amine], indicating that the reaction proceeds through a rate-limiting proton transfer (RLPT) mechanism. On the contrary, the corresponding plot for the reaction in H_2O is linear, implying that general base catalysis is absent. The ratios of the microscopic rate constants for the reactions in MeCN are consistent with the proposed mechanism, e.g., the facts that $k_2/k_{-1} < 1$ and $k_3/k_2 > 10^2$ suggest that formation of a Meisenheimer complex occurs before the rate-limiting step and the deprotonation by a second amine molecule becomes dominant when [amine] > 0.01 M, respectively. The Brønsted-type plots for k_1k_2/k_{-1} and k_1k_3/k_{-1} are linear with β_{nuc} values of 0.82 and 0.84, respectively, which supports the proposed mechanism. The Brønsted-type plot for the reactions in H_2O is also linear with $\beta_{nuc} = 0.52$ which has been interpreted to indicate that the reaction proceeds through rate-limiting formation of a Meisenheimer complex. DNFB is more reactive toward secondary amines in MeCN than in H_2O. The enhanced basicity of amines as well as the increased stability of the intermediate whose charges are delocalized through resonance are responsible for the enhanced reactivity in the aprotic solvent.

Introduction

Nucleophilic aromatic displacement involving electron-deficient substrates, via the S_NAr mechanism,[1−4] comprises a major class of organic transformation. To give but a few examples, this substitution has been found useful in synthesis,[5,6] (including improved methods of stereoselective reaction),[7] in derivatization to extend analytical detection limits, in preparation of electrophilic derivatives of water-soluble polymers,[8,9] and in some possible environmental remediation protocols.[10−12] Fun-

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damental studies of nucleophilic aromatic substitution, therefore, continue to attract attention.[13−17]

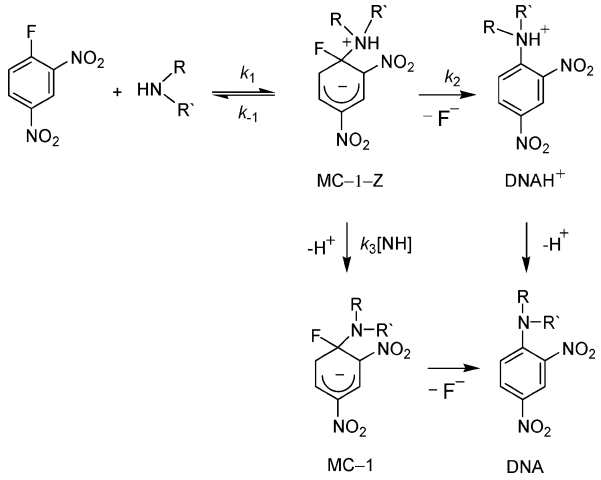
In general, the S_NAr mechanism involves a first step in which attack of a nucleophile on an electron-deficient aromatic or heteroaromatic either gives an anionic σ-bonded adduct, commonly termed a Meisenheimer complex (MC), or proceeds through a transition-state modeled on the MC. If the position of nucleophilic attack is suitably 1-X substituted (i.e., to give MC-1), expulsion of the leaving group in a second step gives the displacement product. On the other hand, although attack at an unsubstituted position, to give MC-3 or -5, usually is unproductive, reaction at such a position with an appropriate nucleophile that itself bears a leaving group and can undergo β-elimination with the ring proton provides entry into the vicarious nucleophilic substitution (VNS)[18,19] reaction. The factors that stabilize MC and correspondingly influence regioselectivity in S_NAr/VNS displacement form, therefore, one consideration in examining these reaction systems.[8,9,20−23]

Reaction of neutral nucleophiles, such as amines, with electron-deficient aromatics is at once both more complex and also more mechanistically interesting, particularly when medium effects are included in the study. These two themes constitute the focus of the current paper where 2,4-dinitro-1-fluorobenzene, Sanger's reagent, that has proven so useful in labeling protein residues,[24] is a typical electron-deficient substrate and a series of structurally related secondary amines comprise the set of nucleophiles as shown below.

Z = CH_2, NH, NCH_2CH_2OH, NCHO, and O.

Here, the putative first-step in the S_NAr process (Scheme 1) leads to formation of a zwitterionic MC-1-Z from which two competitive processes for decomposition have been postulated: expulsion of the fluoride ion leaving group (k_2, where k_1 may become rate-limiting) followed by rapid proton loss from the protonated product dinitroaniline, $DNAH^+$, to give the new

SCHEME 1



substituted aniline, DNA, or alternatively, base-catalyzed deprotonation of MC-1-Z (the k_3 step in Scheme 1) to yield a new amino-Meisenheimer complex, MC-1, that loses fluoride ion to give the same new aniline product. (An alternative pathway (not shown in Scheme 1) involves proton transfer from nitrogen to fluorine in MC-1-Z, with the possible intermediacy of solvent to relay the proton, leading to expulsion of HF and direct formation of DNA in a single step. (Bernasconi, C. F. *MTP Int. Rev. Sci. Org. Chem. Ser. 1*, **1973**, *3*, 33−63). The amine concentration-dependent behavior (at higher amine concentrations) found in the current study suggests that although this process may compete with the k_2 path shown in Scheme 1, it cannot compete with the k_3 path under these conditions. The discussion of the mechanism and, notably, of the importance of solvent choice in determining the rate-determining step is otherwise unchanged and this alternative will not be discussed further. We thank a referee for calling our attention to this alternative.)

Although in theory a reaction may also occur at the unsubstituted C-3 and C-5 positions,[20] attack at these sites with the secondary amines involved in the current study would not lead to a stable final product, and any Meisenheimer complexes that would arise from such attack would simply constitute a reservoir of DNFB and the relevant secondary amine. In water or in an aprotic polar solvent such as dimethyl sulfoxide (DMSO) or acetonitrile (MeCN), Scheme 1 is sufficient representation of the pathways leading to S_NAr displacement, but the situation is more complex in aprotic nonpolar solvents such as benzene, ethyl acetate, or tetrahydrofuran[25] where deprotonation of a zwitterionic Meisenheimer complex like MC-1-Z may involve an amine dimer competing with free amine[26] or two molecules of free amine acting in concert.[27] Mixed ethyl acetate-chloroform media have been used to probe mechanistic changeover in 2,6-dinitro-1-fluorobenzene/secondary amine systems.[28]

The importance of solvent choice in determining the nature of the mechanism of aminolysis with electron-deficient sub-

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strates such as DNFB cannot be overemphasized.[29−31] Moreover, for synthetic utility a solvent should not only promote reactivity but be readily removed (recycled); in this case, MeCN is to be preferred over DMSO. Further, a recent calculational study confirmed that the intermediate MC-1 (DNFB + N_3^-) to have enhanced stability in aprotic solvents (MeCN, DMSO) relative to protic ones (H_2O, EtOH).[32]

There is a similarity between stepwise nucleophilic attack at C═O of esters and S_NAr displacement in that both involve: (1) initial addition with rehybridization of the C-center from sp^2 to sp^3 to give a tetrahedral intermediate and (2) elimination of a leaving group in a second-step to regenerate the sp^2 center. In both general addition−elimination systems, either the first or second step may be rate-limiting. However, in S_NAr displacement, the process involves loss of aromaticity in step 1 and rearomatization in step 2; the importance of electron withdrawing substituents that effectively delocalize negative charge in the MC has been highlighted.[1−4]

Brønsted analysis has previously been found to be a useful tool to determine mechanism in C═O and related ester systems,[33−36] though less commonly used for S_NAr.[17b,37,38] We extend our study now to S_NAr aminolysis with DNFB in MeCN, a synthetically useful solvent. This study is possible now because pK_a values of the secondary amines used in this study in MeCN have only recently become available.[39]

The results will be discussed in terms of comparison of Brønsted-type slope parameters (β_{nuc}) for the reactions in acetonitrile and water. The utility of the Brønsted analysis in assigning the mechanism and particularly the rate-limiting step will be discussed.

Results and Discussion

The kinetic study was performed under pseudo-first-order conditions with the concentration of amines in excess over the substrate concentration. All of the reactions obeyed first-order kinetics over 90% of the total reaction. No spectroscopic evidence was found for formation of nonproductive MC-3 or MC-5 adducts. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation $\ln(A_\infty - A_t) = -k_{obsd}t + C$. It is estimated from replicate runs that the uncertainty in the rate constants is less than ± 3 %. The k_{obsd} values with the reaction conditions are summarized in Tables S1−S12 in the Supporting Information.

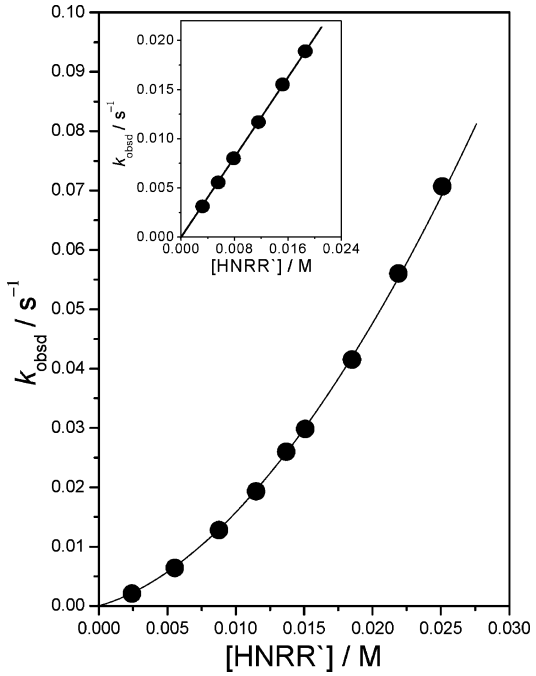

FIGURE 1. Plots of k_{obsd} vs [HNRR′] for the reactions of DNFB with morpholine in MeCN and in H_2O (inset) at 25.0 ± 0.1 °C. The solid line for the reaction in MeCN was calculated by eq 1.

The plot of k_{obsd} vs [HNRR′] for the reaction of DNFB with morpholine in MeCN curves upward as a function of increasing amine concentration (Figure 1). A similar result has been obtained for reactions with all the other amines studied in MeCN (Figures S1−S4 in the Supporting Information). Such upward curvature is typical for reactions that proceed through a rate-limiting proton transfer (RLPT) mechanism.[15] Accordingly, one can suggest that the reactions in MeCN proceed through two central intermediates (a zwitterionic adduct MC-1-Z and its deprotonated form MC-1) as shown in Scheme 1. In contrast, the plots for the corresponding reactions in H_2O are linear passing through the origin in all cases (e.g., the inset of Figure 1 for the reaction with morpholine). The linear plot implies that the rate-limiting deprotonation process by a second amine molecule (i.e., the k_3 step in Scheme 1) is absent for the reactions in H_2O.

Determination of Microscopic Rate Constants. On the basis of the kinetic result and the mechanism proposed in Scheme 1, one can express the pseudo-first-order rate constant (k_{obsd}) for the reactions in MeCN as eq 1, in which [HNRR′] represents the concentration of amine. Equation 1 can be simplified as eq 2 under the assumption, $k_{-1} \gg k_2 + k_3$[HNRR′]. Thus, one can expect that the plot of k_{obsd}/[HNRR′] vs [HNRR′] is linear if the reaction proceeds as in Scheme 1.

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

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

In fact, as shown in Figure 2, the plot of k_{obsd}/[HNRR′] vs [HNRR′] is linear for the reaction with morpholine up to ca. 0.025 M. The plot for the reaction with 1-formylpiperazine (see Figure S5 in the Supporting Information) is also linear up to ca. 0.01 M, indicating that the above assumption is valid for the reactions with these weakly basic amines in the low concentration region. However, as shown in the inset of Figure 2, the plot for the reaction with piperidine exhibits a downward curvature as the amine concentration increases beyond 0.01 M.

A similar downward curvature is obtained for the reaction with piperazine (see Figure S6 in the Supporting Information), indicating that the above assumption is invalid for the reactions with the strongly basic amines when the concentration of these amines increases highly. This argument is in accord with the idea that k_{-1} decreases with increasing amine basicity, and the term k_3[HNRR′] becomes larger with increasing the concentration of amines. When the concentration of amines is high enough, then $k_2 \ll k_3$[HNRR′] and eq 1 can be reduced to eq 3. As shown in Figure 3, the plot of [HNRR′]/k_{obsd} vs 1/[HNRR′] for the reaction with piperidine is linear in the region where the amine concentration exceeds ca. 0.01 M but exhibits a downward curvature as amine concentration decreases. A similar result is obtained for the other amines studied, indicating that the assumption $k_2 \ll k_3$[HNRR′] is valid only when [HNRR′] > 0.01 M.

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

Therefore, $1/k_1$ and $1/Kk_3$ values have been extracted from the intercept and slope of the linear part of the curved plots, respectively. More reliable values of k_1, k_2/k_{-1}, and k_3/k_{-1} have been determined through the nonlinear least-squares fitting of eq 1 to the experimental data by using the $1/k_1$ and $1/Kk_3$ values obtained above as input values. The values of k_1, k_2/k_{-1}, and k_3/k_{-1} determined in this way are summarized in Table 1. The k_3/k_2 ratios which were calculated from the $k_3/k-1$ and $k_2/k-1$ ratios are also included in Table 1.

As shown in Table 1, the k_1 value for the reaction with piperidine is in good agreement with k_N value (e.g., 290−320 $M^{-1}s^{-1}$) reported previously for the same reaction performed at 30 °C in MeCN.[40] Nudelman et al. found the k_N value to be insensitive to the piperidine concentration. This is because the concentration of piperidine employed in these studies ranged up to 0.0025 M for the reaction at 30 °C or 0.005 M at 15 °C.[40] In such low concentration regimes, the contribution of the k_3-[HNRR′]^2 term to k_{obsd} should be negligible (see eq 1). In fact, as shown in Figure S1, the plot of k_{obsd} vs amine concentrations for the reaction of DNFB with piperidine appears to be linear up to ca. 0.008 M of piperidine but exhibits an upward curvature as the concentration of piperidine increases further.

It is apparent from Table 1 that $k_2/k_{-1} < 1$ but $k_3/k_2 > 10^2$ for reactions with all the amines studied in MeCN. The fact that $k_2/k_{-1} < 1$ indicates that formation of a Meisenheimer complex occurs before the rate-limiting step. Besides, $k_3/k_2 > 10^2$ implies that the k_3 process becomes dominant when the amine concentration is high enough (e.g., [HNRR′] > 0.01 M). Thus, the microscopic rate constants determined above can account for the nonlinear plots shown in Figures 2 and 3 (and also Figures S5−S6 in the Supporting Information).

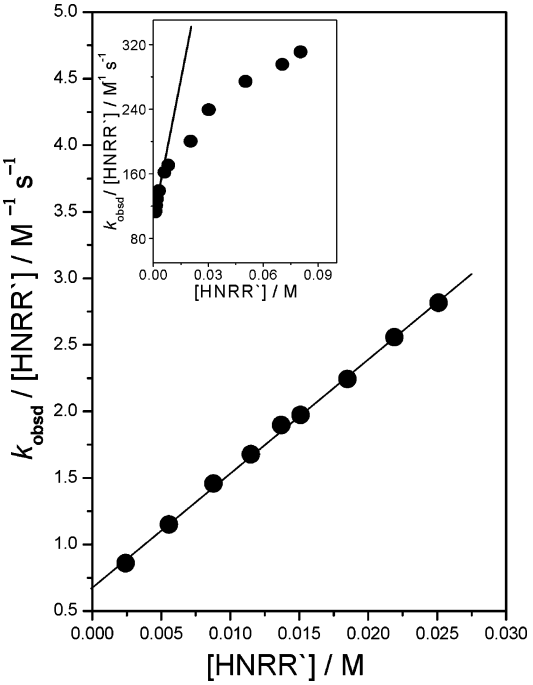

FIGURE 2. Plots of k_{obsd}/[HNRR′] vs [HNRR′] for the reactions of DNFB with morpholine and piperidine (Inset) in MeCN at 25.0 ± 0.1 °C.

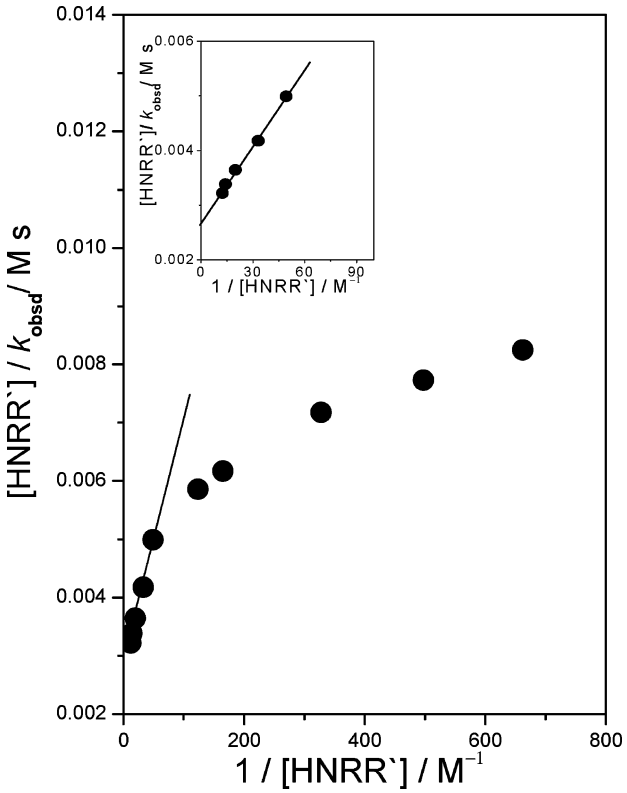

FIGURE 3. Plot of [HNRR′′]/k_{obsd} vs 1/[HNRR′] for the reactions of DNFB with piperidine in MeCN at 25.0 ± 0.1 °C. Insert highlights the linear region of the plot.

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TABLE 1. Summary of Microscopic Rate Constants for the Reactions of DNFB with Alicyclic Secondary Amines in MeCN at 25.0 ± 0.1 °C[a]

	amine	pK_a	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}	k_3/k_2/ M^{-1}
1.	piperidine	18.8	380 ± 3	0.293	111	50.3	19000	172
2.	piperazine	18.2	394 ± 3	0.137	54.0	42.5	16700	310
3.	1-(2-hydroxyethyl) piperazine	17.6	41.9 ± 1.5	0.182	7.63	32.0	1340	176
4.	1-formylpiperazine	17.0	11.1 ± 0.5	0.180	2.00	32.3	359	179
5.	morpholine	16.0	17.8 ± 0.7	0.0400	0.712	5.74	102	144

[a] The pK_a data in MeCN were taken from ref 39.

By analogy to C=O ester aminolysis that can give a zwitterionic tetrahedral intermediate analogus to MC-1-Z, one might expect that k_2 is independent of the amine basicity since there is little or no electron donation from the cationic amine moiety of MC-1-Z to exert the push to expel the leaving group.[41,42] However, k_3 would be little influenced by amine basicity. This is because a more basic amine tends to deprotonate MC-1-Z more rapidly, but it becomes a weaker acid in the zwitterionic intermediate and would hold the proton more strongly.[43] As a result of this compensatory effect, the k_3/k_2 ratio is expected to be insensitive to amine basicity. In fact, as shown in Table 1, the k_3/k_2 ratio remains nearly constant except for the reaction with piperazine, which exhibits a larger k_3/k_2 ratio than others. The larger k_3/k_2 ratio obtained for the reaction with piperazine can be ascribed to the fact that piperazine has two basic sites to deprotonate. This argument can be further supported from the linear plot of log k_3/k_2 vs pK_a with a slope close to zero when k_3 and pK_a values were statistically corrected using p (numbers of protons which can be deprotonated from the conjugate acid of the amine) and q (numbers of nucleophilic sites of the amine), i.e., $p = 2$ (except $p = 4$ for piperazinium ion) and $q = 1$ (except $q = 2$ for piperazine)[44] (Figure S7 in Supporting Information).

Brønsted-Type Treatment (MeCN). As shown in Figure 4, Brønsted-type plots for Kk_2 and Kk_3 values exhibit good linear correlations when Kk_2, Kk_3, and pK_a are statistically corrected by using p and q. It is noted that the slope for Kk_2 is practically identical to that for Kk_3 (i.e., $\beta_{Kk2} = 0.82$ and $\beta_{Kk3} = 0.84$), which is consistent with the preceding argument that k_2 and k_3 are insensitive to the basicity of amines. The magnitude of these β_{Kk2} and β_{Kk3} values will receive our scrutiny subsequently.

Medium Effect on Reaction Mechanism: Comparison of Brønsted-Type Treatment (H_2O vs MeCN). It is apparent from the inset of Figure 1 that the effect of medium is significant, since the plot of k_{obsd} vs [HNRR′] for the reaction performed in H_2O is linear passing through the origin. The linear plot of k_{obsd} vs amine concentration clearly indicates that the deprotonation process found for the reactions in MeCN is absent for the reactions in H_2O (i.e., the k_3 step in Scheme 1).

The fact that the plot of k_{obsd} vs amine concentration passes through the origin for the reaction in H_2O suggests that the contribution of hydroxide and/or water to the k_{obsd} value is negligible. Thus, the pseudo-first-order rate constant (k_{obsd}) can be expressed as eq 4. The apparent second-order rate constants (k_N) for the reactions of DNFB in H_2O have been determined from the slope of the linear plots of k_{obsd} vs amine concentration and summarized in Table 2.

TABLE 2. Summary of Apparent Second-Order Rate Constants (k_N) for the Reactions of DNFB with Alicyclic Secondary Amines in H_2O at 25.0 ± 0.1 °C

	amine	pK_a	k_N / M^{-1}s^{-1}
1.	piperidine	11.22	9.37
2.	piperazine	9.82	5.48
3.	1-(2-hydroxyethyl) piperazine	9.38	1.43
4.	morpholine	8.36	1.07
5.	1-formylpiperazine	7.98	0.444
6.	piperazinium ion	5.68	0.0163

$$k_{obsd} = k_N[\text{HNRR}'], \text{ where } k_N = k_1k_2/(k_{-1} + k_2) \quad (4)$$

As shown in the Table 2, the k_N value for the aqueous reactions decreases as the basicity of the amines decreases. The effect of amine basicity on reactivity is illustrated in Figure 5. The statistically corrected Brønsted-type plot using p and q is linear, indicating that the reaction proceeds without changing the rate-limiting step or mechanism on changing the amine basicity over a range of 5.5 pK_a units. Crampton et al. have recently reiterated that formation of a Meisenheimer complex is the rate-limiting step for S_NAr reactions in which general base catalysis is absent.[1,16a] Since the plots of k_{obsd} vs [HNRR′] for the current reactions in H_2O are linear, general base catalysis by a second amine molecule is definitely absent. Thus, one can propose the reactions of DNFB in H_2O proceed through rate-limiting formation of MC-1-Z (Scheme 1).

The above argument is consistent with the magnitude of β_{nuc} values. The β_{nuc} value determined for the reactions in H_2O is 0.52 (Figure 5), which is comparable to those reported for reactions of 2,4-dinitrohalobenzenes with primary amines in H_2O (i.e., β_{nuc} varies from 0.42 to 0.45 and 0.52 as the halogen atom changes from F to I and Cl, in turn).[37,38] However, the β_{nuc} value obtained for the reaction of DNFB in H_2O is much smaller than that found for the corresponding reactions in MeCN, i.e., $\beta_{Kk3} = 0.84$ or $\beta_{Kk2} = 0.82$ (Figure 4).

The large β_{Kk3} or β_{Kk2} values found for the reactions in MeCN are in accord with the RLPT mechanism, in which bond formation between the amine nucleophile and the electrophilic site of DNFB is fully advanced in the rate-limiting transition state. On the contrary, the smaller β_{nuc} value shown in Figure 5 can account for the proposal that the reactions of DNFB with the amines in H_2O proceed through rate-limiting formation of MC-1-Z, in which bond formation is not much advanced.

Halogen Atom Effect. The reaction of DNFB with piperidine in MeCN was suggested to proceed through a rate-limiting formation of a Meisenheimer complex on the basis of the kinetic result that DNFB is much more reactive than 2,4-dinitrochlorobenzene (DNCB) in the aprotic solvent.[40] Nudelman et al. have found that DNFB is 375 times more reactive than DNCB toward piperidine in MeCN. It is well-known that fluoride ion

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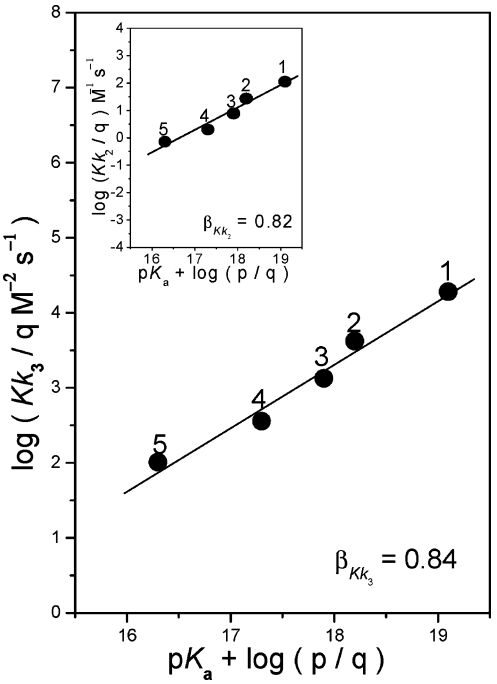

FIGURE 4. Brønsted-type plots for the reactions of DNFB with alicyclic secondary amines in MeCN at 25.0 ± 0.1 °C. The assignment of numbers is as given in Table 1.

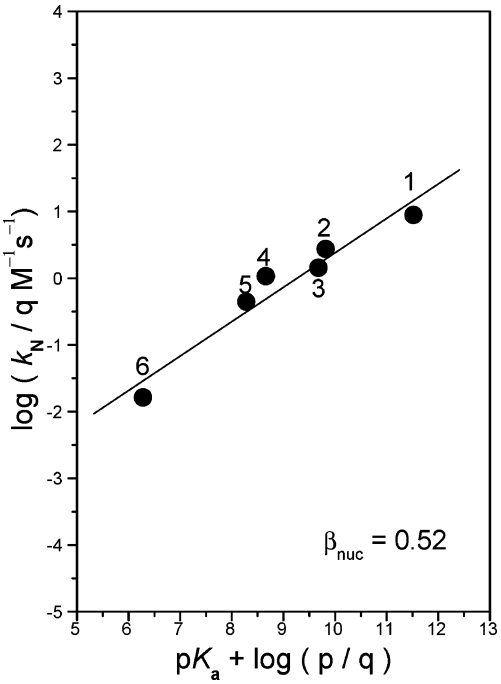

FIGURE 5. Brønsted-type plot for the reactions of DNFB with alicyclic secondary amines in H_2O at 25.0 ± 0.1 °C. The assignment of numbers is given in Table 2.

is a poorer nucleofuge than chloride ion in an aprotic solvent such as MeCN.[40] Thus, the fact that DNFB is much more reactive than DNCB in the aprotic solvent led them to conclude that the leaving group (F^- or Cl^-) departs after the rate-limiting step.[40] However, the current results (i.e., the upward curvature in the plots of k_{obsd} vs [HNRR′] and the microscopic rate constants shown in Table 1) clearly indicate that formation of a Meisenheimer complex occurs before the rate-limiting step. Thus, the fact that DNFB is more reactive than DNCB in MeCN cannot be an unambiguous measure of which step is rate-limiting.

To investigate the origin of the high reactivity of DNFB compared with DNCB, the reaction of the latter compound with piperidine in MeCN has been performed in this study. As shown in Figure 6, the plot of k_{obsd} vs [HNRR′] is linear passing through the origin with a slope (k_N) of 0.558 M^{-1} s^{-1}. Such a linear plot is consistent with the report that the reaction of DNCB with piperidine in MeCN proceeds through formation of an intermediate in the rate-limiting step.[45] Accordingly, the k_N for the reaction of DNCB with piperidine in MeCN represents the rate constant for the amine-attack process (i.e., the k_1 in Scheme 1).

Since $k_N = k_1$ for the reaction of DNCB in MeCN, one can compare the k_N for the reaction of DNCB (0.558 $M^{-1}s^{-1}$) with the k_1 for that of DNFB (i.e., 380 $M^{-1}s^{-1}$ in Table 1). The ratio of these rate constants, k_1(DNFB)/k_N(DNCB) is 681. However, this result does not indicate that DNFB is always 681 times more reactive than DNCB. This argument is evident from Figure 6, i.e., the plot of k_{obsd} vs [HNRR′] is curved upward for the reaction of DNFB but linear for the corresponding reaction of DNCB. It is noteworthy that the ratio of the observed-rate constants, k_{obsd}(DNFB)/k_{obsd}(DNCB) is highly dependent on the amine concentration, which is not possible if the reactions of DNFB and DNCB proceed via the same mechanism. Thus, one can attribute the enhanced reactivity of DNFB compared with DNCB in MeCN to the enhanced electrophilicity of the C-1 site of the former; it is expected to have a more electrophilic site than the latter on the basis of the electronegativity of F vs Cl.

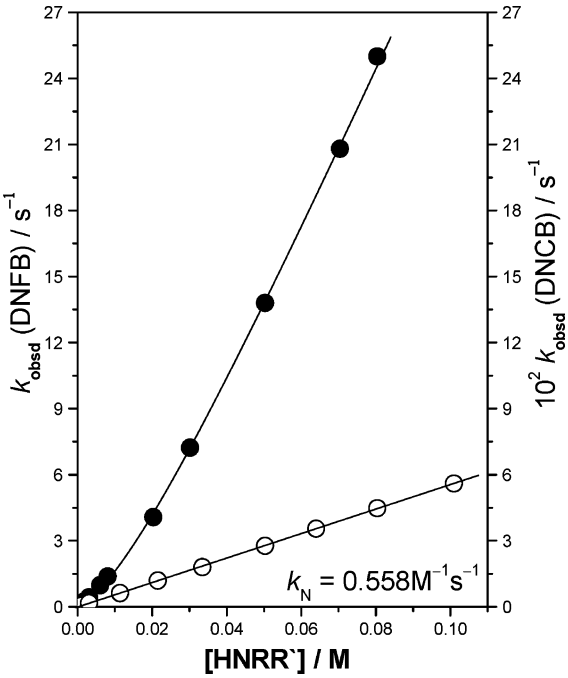

FIGURE 6. Plots of k_{obsd} vs [HNRR′] for the reactions of piperidine with DNFB (●) and with DNCB (○) in MeCN at 25.0 °C.

Medium Effect on Reactivity. It is well-known that the rate of reactions between neutral molecules decreases on changing

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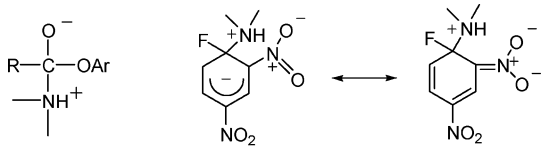
the medium from H_2O to a dipolar aprotic solvent such as MeCN. In fact, we have recently shown that the amines used in this study exhibit a similar or even decreased reactivity in aminolysis of carboxylic esters on changing the medium from H_2O to MeCN,[43,46] although these amines become more basic in the aprotic solvent by 7−9 pK_a units.[39] Unlike aminolysis of carboxylic esters, the current S_NAr reactions exhibit higher reactivity in the aprotic solvent than in H_2O. Here the k_1 value in Table 1 for the reaction in MeCN is 17 (morpholine) to 72 (piperazine) times larger than the k_N value for the corresponding reaction in H_2O (Table 2).

One can account for the contrasting medium effects found for the current reactions and aminolysis of esters in terms of the structures of their intermediates. It has generally been understood that aminolysis of carboxylic esters proceeds through a zwitterionic intermediate as illustrated in Structure I, in which the negative and positive charges are mainly localized on the O or the N atom. Water molecules can stabilize such charge localized species through H-bonding interaction. However, H-bonding interaction is absent in MeCN. Furthermore, there would be large electronic repulsion between the negative charge of the intermediate I and the negative dipole end of MeCN. This argument accounts for the fact that the reactivity of amines toward esters decreases on changing the medium from H_2O to MeCN, although amines become 7 and 9 pK_a units more basic in the aprotic solvent.[43]



I **II$_a$** **II$_b$**

On the other hand, the negative charge on the intermediate of the current S_NAr reaction is highly delocalized through the resonance interaction as illustrated in the resonance structures II_a and II_b.[47] Such charge delocalized species are not solvated strongly in H_2O and would not experience significant desolvation on changing the medium from H_2O to MeCN. This argument together with the enhanced basicity of amines, explains the enhanced aminolytic reactivity in MeCN as compared to H_2O in the present S_NAr reaction systems.

Conclusions

The current study has allowed us to conclude the following: (1) The effect of medium on reactivity and reaction mechanism is significant for the current S_NAr reactions; the reaction of DNFB in MeCN proceeds through an RLPT mechanism, while the one in H_2O proceeds through a Meisenheimer complex (MC-1-Z) with its formation being the rate-limiting step. (2) The microscopic rate constants determined for the reactions in MeCN (e.g., $k_2/k^{-1} < 1$ and $k_3/k_2 > 10^2$) account for the curvature found in the plots of k_{obsd} vs [HNRR′] and support the proposed mechanism. (3) The Brønsted coefficients obtained in this study ($\beta_{Kk2} = 0.82$ and $\beta_{Kk3} = 0.84$ in MeCN and $\beta_{nuc} = 0.52$ in H_2O) are also consistent with the proposed mechanisms. (4) DNFB is significantly more reactive than DNCB in MeCN, indicating that the fluorine atom in DNFB is more effective than the chlorine atom in DNCB in enhancing the electophilicity of the C-1 reaction site.

Experimental Section

Materials. 2,4-Dinitrofluorobenzene and alicyclic secondary amines 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 the maximum absorption (λ_{max}, e.g., 379 nm for *N*-2,4-dinitrophenylpiperidine).

Typically, the reaction was initiated by adding 3 μL of a 0.02 M DNFB stock solution in MeCN by a 10 μL syringe to a 10 mm UV cell containing 2.50 mL of the reaction medium and amine. The amine sock solution of ca. 0.2 M for the reactions in H_2O was prepared in 25.0 mL volumetric flask under nitrogen by adding 2 equiv of amine to 1 equiv of standardized HCl solution to obtain a self-buffered solution. Transfers of solutions were carried out by means of gastight syringes. All reactions were carried out under pseudo-first-order conditions in which amine concentrations were at least 50 times greater than the substrate concentration. The kinetic conditions and pseudo-first-order rate constants are summarized in Tables S1−S12 in the Supporting Information.

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. For example, $\epsilon = 15800\ M^{-1}cm^{-1}$ at 379 nm for *N*-2,4-dinitrophenylpiperidine in MeCN.

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Supporting Information Available: Plots of k_{obsd} vs [HNRR′] for the reactions of DNFB with piperidine, piperazine, 1-(2-hydroxyethyl)piperazine, and 1-formylpiperazine (Figures S1−S4). Plots of k_{obsd}/[HNRR′] vs [HNRR′] for the reaction of DNFB with 1-formylpiperazine and piperazine (Figures S5 and S6). Plot of log k_3/k_2 vs pK_a for the reactions of DNFB with amines in MeCN (Figure S7). The kinetic conditions and results for the reactions of DNFB with amines in MeCN and in H_2O (Tables S1−S11). The kinetic conditions and results for the reactions of DNCB with piperidine in MeCN (Table S12). This material is available free of charge via the Internet at http://pubs.acs.org.

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