Kinetic Study on Aminolysis of 4-Chloro-2-Nitrophenyl X-Substituted- benzoates in Acetonitrile and in 80 mol % H2O/20 mol % DMSO: Effect of Medium on Reactivity and Reaction Mechanism

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A kinetic study on aminolysis of 4-chloro-2-nitrophenyl X-substituted-benzoates (6a-i) in MeCN is reported. The Hammett plot for the reactions of 6a-i with piperidine consists of two intersecting straight lines, while the Yukawa-Tsuno plot exhibits an excellent linear correlation with \( \rho \chi = 1.03 \) and \( r = 0.78 \). The nonlinear Hammett plot is not due to a change in rate-determining step (RDS) but is caused by the resonance stabilization of substrates possessing an electron-donating group in the benzoyl moiety. The Bronsted-type plot for the reactions of 4-chloro-2-nitrophenyl benzoate (6e) with a series of cyclic secondary amines is linear with \( \beta_{\text{max}} = 0.69 \), an upper limit for reactions reported to proceed through a concerted mechanism. The aminolysis of 6e in aqueous medium has previously been reported to proceed through a stepwise mechanism with a change in RDS on the basis of a curved Bronsted-type plot. It has been concluded that instability of the zwitterionic tetrahedral intermediate (T\(^\ast\)) in MeCN forces the reaction to proceed through a concerted mechanism. This is further supported by the kinetic result that the amines used in this study are less reactive in MeCN than in H\(_2\)O, although they are more basic in MeCN over 7 pK\(_a\) units.

**Key Words**: Aminolysis, Concerted mechanism, Hammett plot, Yukawa-Tsuno plot, Bronsted-type plot

**Introduction**

Nucleophilic displacement reactions of esters have extensively been investigated due to their importance in biological processes as well as in synthetic applications. Experimental studies based on linear free energy relationships (LFERs) have shown that aminolysis of esters proceeds through a concerted mechanism or via a stepwise pathway depending on reaction conditions (e.g., the nature of the electrophilic center, reaction medium, structure of esters, etc.).

Aminolysis of 2,4-dinitrophenyl diphenylphosphinate (1) has been reported to proceed through a concerted mechanism on the basis of a linear Bronsted-type plot with \( \beta_{\text{max}} = 0.38 \), while the corresponding reactions of 2,4-dinitrophenyl benzenesulfonate (2) have been concluded to proceed via a stepwise mechanism with a change in RDS on the basis of a curved Bronsted-type plot with \( \beta_2 = 0.86 \) and \( \beta_1 = 0.38 \). Besides, aminolysis of 4-nitrophenyl benzoate (3a) has been suggested to proceed through a stepwise mechanism with a zwitterionic tetrahedral intermediate (T\(^\ast\)), while the corresponding reaction of O-4-nitrophenyl thionobenzoate (3b) has been shown to proceed through a stepwise pathway with two intermediates (T\(^\ast\) and its deprotonated form T\(^-\)). These results demonstrate that the nature of the electrophilic centers (e.g., P=O, SO\(_2\), C=O and C=S) governs the reaction mechanism.

The nature of solvents has also been suggested to be an important factor which affects the reaction mechanism. The reactions of 2,4-dinitrophenyl benzoate with a series of cyclic secondary amines in H\(_2\)O containing 20 mol % DMSO have been reported to proceed through a stepwise mechanism with a change in RDS on the basis of a curved Bronsted-type plot. In contrast, the corresponding reactions carried out in MeCN have been concluded to proceed through a concerted mechanism on the basis of a linear Bronsted-type plot with \( \beta_{\text{max}} = 0.40 \). One might expect that a zwitterionic T\(^\ast\) can be stabilized in H\(_2\)O through H-bonding interactions. In contrast, the ionic species cannot be stabilized in MeCN due to the electronic repulsion between the negative C-O\(^-\) moiety of T\(^\ast\) and the negative dipole end of MeCN. Thus, the difference in the stability of T\(^\ast\) in the two solvents has been proposed to be responsible for the contrasting reaction mechanisms.

Theoretical studies based on rapid advances in computational methods have also reported that the reaction medium is a crucial factor which affects the reaction mechanism. The existence of T\(^\ast\) in the gas phase or in aprotic solvents has often been questioned, e.g., Ilieva et al. have failed to identify T\(^\ast\) for the reaction of methyl formate with ammonia, while Sung et al. have reported that at least five explicit water molecules are required to stabilize T\(^\ast\) in the reaction of phenyl acetate with ammonia. However, we have recently
Aminolysis of 4-Chloro-2-Nitrophenyl Benzoate in MeCN

Scheme 1

Our study has now been extended to the reactions of 4-chloro-2-nitrophenyl X-substituted-benzoates (6a-i) with a series of cyclic secondary amines in MeCN to obtain further information on the reaction mechanism. The kinetic results have been compared with those reported recently for the corresponding reactions carried out in H₂O containing 20 mol % DMSO¹⁵ to investigate the effect of medium on reactivity and reaction mechanism.

Results and Discussion

The kinetic study was performed under pseudo-first-order conditions in which the amine concentration was kept at least 20 times in excess of the substrate concentration. All the reactions in this study obeyed first-order kinetics and the pseudo-first-order rate constants (kobsd) were calculated from the equation, ln ([A]₀ - [A]) = -kobsd t + C. The plots of kobsd vs. [amine] are linear and pass through the origin, indicating that general-base catalysis by a second amine molecule is absent. Accordingly, the second-order rate constants (kₙ) were calculated from the slope of the linear plots. The uncertainty in the kₙ values is estimated to be less than ±3% based on the replicate runs. The kₙ values calculated in this way are summarized in Table 1 for the reactions of 6a-i with piperidine and in Table 2 for the reactions of 4-chloro-2-nitrophenyl benzoate (6e) with a series of cyclic secondary amines together with the kₙ values reported previously for the corresponding reactions carried out in 80 mol % H₂O/20 mol % DMSO¹³ for comparison.

Effect of Substituent X on Reactivity and Reaction Mechanism. The kₙ values for the reactions of 4-chloro-2-nitrophenyl X-substituted-benzoates (6a-i) with piperidine have been measured in MeCN to investigate the effect of the substituent X on the reactivity and reaction mechanism. As shown in Table 1, kₙ decreases as the substituent X changes from a strong electron-withdrawing group (EWG) to a strong electron-donating group (EDG), e.g., it decreases from 108 M⁻¹s⁻¹ to 3.52 and 0.131 M⁻¹s⁻¹ as the substituent X changes from 3,5-(NO₂)₂ to H and 4-N(CH₃)₂, in turn.

The effect of the substituent X on the reactivity of 6a-i is demonstrated in Figure 1. The Hammett plot consists of two intersecting straight lines, e.g., the slope is 1.01 for the reactions of substrates possessing an EWG and is 1.76 for those of substrates bearing an EDG. It is apparent that an EWG in the benzoyl moiety of 6a-i would decrease the electron density of the carbonyl carbon. Consequently, an EWG in the benzoyl moiety of 6a-i would accelerate the rate of nucleophilic attack to form T⁺ (i.e., an increase in k₁) but would retard the rate of leaving-group departure from T⁺ (i.e., a decrease in k₂). On the contrary, an EDG in the benzoyl moiety of 6a-i would decrease k₁ but would increase k₂ by increasing the electron density of the reaction center. Thus, one might suggest that the piperidinolysis of 6a-i proceeds through a stepwise mechanism with a change in RDS on changing the electronic nature of the substituent X on the basis of the nonlinear Hammett plot.

However, we propose that the nonlinear Hammett plot is not caused by a change in RDS. Because RDS is not determined by the magnitude of k₁ and k₂, Furthermore, k₁ and k₂ cannot be compared directly since the former is a second-
order rate constant while the latter is a first-order rate constant. The RDS should be determined by the $k_2/k_1$ ratio (i.e., RDS = the $k_1$ step when $k_2/k_1 > 1$ but RDS = the $k_2$ step when $k_2/k_1 < 1$).

A careful examination of the nonlinear Hammett plot shown in Figure 1 reveals that the substrates possessing an EDG (e.g., 6g, 6h and 6i) deviate negatively from the linear line composed of the substrates bearing an EWG. Besides, the deviation is more significant as the substituent X becomes a stronger EDG. An EDG in the benzoyl moiety could stabilize the ground state (GS) of the substrate through resonance interactions as illustrated by resonance structures I and II. Since such resonance interactions could decrease their reactivity, we propose that the nonlinear Hammett plot is caused by the resonance stabilization of the substrates possessing an EDG in the benzoyl moiety.

$$\text{Me}_2\text{C}^+\text{C}^\equiv\text{N}^+\text{Ar} \quad \text{Me}_2\text{C}^+\text{C}^\equiv\text{N}^+\text{Ar}$$

To examine the above argument, the Yukawa-Tsuno equation (1) has been employed. The $r$ value in Eq. (1) represents the resonance demand of the reaction center or the extent of resonance contribution, while the term $(\sigma_X^* - \sigma_X^0)$ is the resonance substituent constant that measures the capacity for $\pi$-delocalization of the $\pi$-electron donor substituent.\textsuperscript{14,15} Eq. (1) was originally derived to rationalize the kinetic results obtained from solvolysis of benzyllic systems in which a positive charge develops partially in the transition state (TS).\textsuperscript{14} However, we have recently shown that Eq. (1) is also highly effective in elucidation of ambiguities in the reaction mechanism, e.g., for aminolysis of esters\textsuperscript{12,13} as well as for nucleophile substitution reactions of various esters with anionic nucleophiles (e.g., $\text{OH}^-$, $\text{CN}^-$, $\text{N}_3^-$ and $\text{CH}_3\text{CH}_2\text{O}^-$).\textsuperscript{16}

$$\log k^\circ/k^{1} = \rho_X[\sigma_X^0 + r(\sigma_X^* - \sigma_X^0)] \quad (1)$$

Thus, a Yukawa-Tsuno plot has been constructed. As shown in Figure 2, the Yukawa-Tsuno plot results in an excellent linear correlation with the $r$ value in Eq. (1) represents the resonance demand of the reaction center or the extent of resonance contribution. Thus, one can conclude that the nonlinear Hammett plot for the reactions of 6a-i is not caused by a change in RDS but is due to stabilization of the substrate possessing an EDG through resonance interactions. Furthermore, the current study demonstrates that deduction of the reaction mechanism based just on a linear or nonlinear Hammett plot can be misleading.

The $\rho_X$ value of 1.03 for the reactions of 6a-i is much larger than that reported for reactions proceeding through a stepwise mechanism in which departure of the leaving-group occurs in RDS, e.g., $\rho_X = 0.5 \pm 0.1$ for the reactions of 4-nitrophenyl X-substituted-2-methylenzoates\textsuperscript{17} and $\rho_X = 0.41$ for those of 4-pyridyl X-substituted-benzoates in MeCN.\textsuperscript{12b} In contrast, the $\rho_X$ value of 1.03 in this study is similar to those of 1.30 and 0.98 reported for the reactions of 2,4-dinitrophenyl X-substituted-benzoates with piperidine and morpholine in MeCN, respectively, which have previously been proposed to proceed through a concerted mechanism.\textsuperscript{6b} Thus, one might suggest that the current reactions of 6a-i with piperidine proceed through a concerted mechanism on the basis of the $\rho_X$ value. However, the $\rho_X$ value alone is not sufficient to deduce the reaction mechanism.

**Effect of Medium on Reactivity and Reaction Mechanism.** The $k_0$ values for the reactions of 4-chloro-2-nitrophenyl benzoate (6e) with a series of cyclic secondary amines in MeCN have been measured to obtain further information on the reaction mechanism by comparing them with those reported previously for the corresponding reactions carried out in H$_2$O containing 20 mol % DMSO.\textsuperscript{13} As shown in Table 2, the $k_0$ value for the reactions performed in MeCN decreases as the amine basicity decreases, e.g., it decreases from 3.52 M$^{-1}$s$^{-1}$ to 0.400 and 0.111 M$^{-1}$s$^{-1}$ as the $k_0$ of the conjugate acid of amines decreases from 18.8 to 17.6 and 16.6, in turn. A similar result is shown for the reactions carried out in H$_2$O containing 20 mol % DMSO. It is noted that the amines are less reactive in MeCN than in the aqueous medium, although the amines used in this study

**Table 2. Summary of Second-Order Rate Constants ($k_0$) for the Reactions of 4-Chloro-2-Nitrophenyl Benzoate (6e) with Cyclic Secondary Amines in MeCN and in 80 mol % H$_2$O/20 mol % DMSO at 25.0 ± 0.1 °C**

<table>
<thead>
<tr>
<th>amines</th>
<th>MeCN</th>
<th>80 mol % H$_2$O</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$pK_a$</td>
<td>$k_0$/M$^{-1}$s$^{-1}$</td>
</tr>
<tr>
<td>1 piperidine</td>
<td>18.8</td>
<td>3.52</td>
</tr>
<tr>
<td>2 3-methylpiperidine</td>
<td>18.6</td>
<td>2.50</td>
</tr>
<tr>
<td>3 piperazine</td>
<td>18.5</td>
<td>2.35</td>
</tr>
<tr>
<td>4 1-(2-hydroxyethyl)piperazine</td>
<td>17.6</td>
<td>0.400</td>
</tr>
<tr>
<td>5 morpholine</td>
<td>16.6</td>
<td>0.111</td>
</tr>
<tr>
<td>6 piperazinium ion</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

aThe $k_0$ and kinetic data for the reactions in 80 mol % H$_2$O/20 mol % DMSO were taken from ref. 13. bThe $pK_a$ value in MeCN were taken from ref. 12.
are more basic in MeCN over 7 pKₐ units. This demonstrates convincingly that the reactivity of amines is not governed solely by the amine basicity.

The effect of amine basicity on reactivity is illustrated in Figure 3. The Brønsted-type plot for the reactions in MeCN is linear with βₑₑ = 0.69 when the kₛ and pKₐ values are statistically corrected by p and q (e.g., p = 2 and q = 1 except q = 2 for piperazine). In contrast, the plot for the corresponding reactions carried out in the aqueous medium curves downward with β₁ = 0.85, β₂ = 0.24 and pKₐ = 10.5. The nonlinear Brønsted-type plot for the reactions carried out in the aqueous medium has been reported as evidence for a stepwise mechanism with a change in RDS, e.g., the RDS changes from the breakdown of T⁺ to its formation as the pKₐ of the amine exceeds 10.5. The βₑₑ value of 0.69 is an upper limit for reactions reported previously to proceed through a concerted mechanism. Thus, one might suggest that the aminolysis of 4-Chloro-2-Nitrophenyl Benzoate in MeCN proceeds through a concerted mechanism on the basis of a large pKₐ change from the breakdown of T⁺ to its formation as the pKₐ of the amine exceeds 10.5. This idea is consistent with the preceding proposal that the aminolysis of 6a-i with piperidine in MeCN proceed through a concerted mechanism on the basis of a large pKₐ value. It is apparent that the nature of the reaction medium affects the reaction mechanism. One might expect that the T⁺ for the reactions performed in the aqueous medium would be stable enough for a stepwise mechanism through strong H-bonding interactions with H₂O molecules. However, such H-bonding interactions are not possible in MeCN. Besides, it is well known that MeCN is a poor solvent for ionic species. Accordingly, the T⁺ for the reactions carried out in the aprotic solvent would be highly unstable. This idea accounts for the kinetic result that amines are less reactive in MeCN than in H₂O containing 20 mol % DMSO although they are more basic in MeCN over 7 pKₐ units. Thus, one can conclude that instability of T⁺ in MeCN forces the reaction to proceed through a concerted mechanism.

Conclusions

1. The Hammett plot for the reactions of 6a-i with piperidine consists of two intersecting straight lines while the Yukawa-Tsuno plot exhibits an excellent linear correlation, indicating that the nonlinear Hammett plot is not due to a change in RDS but is caused by the resonance stabilization of substrates possessing an EDG in the benzoyl moiety. The identity of points is given in Table 2.

2. Aminolysis of 4-Chloro-2-Nitrophenyl Benzoate in MeCN proceeds through a concerted mechanism. Instability of T⁺ in MeCN forces the reaction to proceed through a concerted mechanism.

Experimental Section

Materials. Compounds 6a-i were readily prepared from the reaction of the respective X-substituted-benzoyl chloride with 4-chloro-2-nitrophenol in anhydrous ether in the presence of triethylamine as reported previously. The crude products were purified by column chromatography. The purity of substrates 6a-i was confirmed from melting points and ¹H NMR characteristics. MeCN was distilled over P₂O₅ and stored under nitrogen. The amines and other chemicals used were of the highest quality available.

Kinetics. The kinetic study was performed using a UV-vis spectrophotometer for slow reactions (e.g., t₁/₂ > 10 s) or a stopped-flow spectrophotometer for fast reactions (e.g., t₁/₂ ≤ 10 s) equipped with a constant temperature circulating bath to keep the reaction temperature at 25.0 ± 0.1 °C. All of the reactions in this study were carried out under pseudo-first-order conditions in which the amine concentration was at least 20 times greater than the substrate concentration. Typically, the reaction was initiated by adding 5 μL of a 0.02 M solution of substrate 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 reactions were followed by monitoring the appearance of 4-Chloro-2-nitrophenoxide up to 9 half-lives.

Product Analysis. 4-Chloro-2-nitrophenoxide (and/or its conjugate acid) was liberated quantitatively and identified as one of the reaction products by comparison of the UV-vis spectra obtained after completing the reactions with those of authentic samples under the same kinetic conditions.

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