Aminolyses of 2,4-Dinitrophenyl 2-Furoate and Benzoate:
Effect of Nonleaving Group on Reactivity and Mechanism

Ik-Hwan Um,* Sun-Mee Chun, and Kalsoom Akhtar
Division of Nano Sciences and Department of Chemistry, Ewha Womans University, Seoul 120-750, Korea
*E-mail: ihum@ewha.ac.kr
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Second-order rate constants \(k_N\) have been determined spectrophotometrically for reactions of 2,4-dinitrophenyl 2-furoate \((2)\) with a series of alicyclic secondary amines in 80 mol % H\(_2\)O/20 mol % dimethyl sulfoxide (DMSO) at 25.0 °C. The furoate 2 is more reactive than 2,4-dinitrophenyl benzoate \((1)\) toward all the amines studied. The higher acidity of 2-furoic acid \((pK_a = 3.16)\) compared with benzoic acid \((pK_a = 4.20)\) has been suggested to be responsible for the reactivity order, at least in part. The Brønsted-type plots for the reactions of 1 and 2 are curved downwardly, indicating that the aminolyses of both 1 and 2 proceed through a zwitterionic tetrahedral intermediate \((T^\pm)\) with a change in the rate-determining step on changing the amine basicity. Dissection of the \(k_N\) values into their microscopic rate constants has revealed that the \(pK_{ao}\) and \(k_2/k_{-1}\) ratios for the reactions of 1 and 2 are identical, indicating that the nature of the nonleaving group \((i.e.,\ benzoyl\ and\ 2-furoyl)\) does not affect the reaction mechanism. The \(k_1\) values have been found to be larger for the reactions of 2 than for those of 1, which is fully responsible for the fact that the former is more reactive than the latter.

Key Words: Aminolysis, Nonleaving group, Yukawa-Tsuno plot, Rate-determining step, Reaction mechanism

Introduction

Aminolysis of esters with a good leaving group has often resulted in a curved Brønsted-type plot, \(i.e.,\) a large slope \((\beta_2 = 0.8 \pm 0.2)\) for reactions with weakly basic amines but a small one \((\beta_1 = 0.3 \pm 0.1)\) for reactions with strongly basic amines.\(^1\)\(^{-11}\) Accordingly, aminolyses of esters have generally been understood to proceed through a zwitterionic tetrahedral intermediate \((T^\pm)\) with a change in the rate-determining step \((RDS)\).\(^1\)\(^{-11}\)

It has been reported that the RDS changes at \(pK_{ao}\) \((i.e.,\) the curvature center of the curved Brønsted-type plot) from breakdown of \(T^\pm\) to its formation as the attacking amine becomes more basic than the leaving group by 4 to 5 \(pK_a\) units.\(^5\)\(^{-11}\) Gresser and Jencks have found that the \(pK_{ao}\) value increases as the substituent in the nonleaving group becomes a stronger electron withdrawing group \((EWG)\) for quinuclidinolysis of diaryl carbonates in water.\(^6\) This result has been explained through the argument that an EWG in the nonleaving group would increase \(k_2\) and \(k_{-1}\), while an EDG would decrease \(k_2\) and \(k_{-1}\), since both the leaving group and amine depart from \(T^\pm\) with the bonding electrons. Thus, it has been concluded that the \(k_2/k_{-1}\) ratio is independent of the electronic nature of the substituent X in the nonleaving group.

We have extended our kinetic study to reactions of 2,4-dinitrophenyl 2-furoate \((2)\) with a series of alicyclic secondary amines as shown in Scheme 1. The kinetic data in the current study have been compared with those for the corresponding reactions of 2,4-dinitrophenyl benzoate \((1)\) to

In contrast, we have recently shown that the \(pK_{ao}\) value and the \(k_2/k_{-1}\) ratio are not influenced by the electronic nature of the substituent X in the nonleaving group for aminolyses of 2,4-dinitrophenyl X-substituted benzoates and benzenesulfonates.\(^9\)\(^{-11}\) We have argued that an electron donating group \((EDG)\) in the nonleaving group would increase \(k_2\) and \(k_{-1}\), while an EWG would decrease \(k_2\) and \(k_{-1}\), since both the leaving group and amine depart from \(T^\pm\) with the bonding electrons. Thus, it has been concluded that the \(k_2/k_{-1}\) ratio is independent of the electronic nature of the substituent X in the nonleaving group.

We have extended our kinetic study to reactions of 2,4-dinitrophenyl 2-furoate \((2)\) with a series of alicyclic secondary amines as shown in Scheme 1. The kinetic data in the current study have been compared with those for the corresponding reactions of 2,4-dinitrophenyl benzoate \((1)\) to

\[
\begin{align*}
\text{NO}_2 &\quad \text{C} &\quad \text{O} &\quad \text{NO}_2 + \text{HN} &\quad k_1 &\quad k_{-1} &\quad \text{HN} &\quad \text{C} &\quad \text{O} &\quad \text{NO}_2 \\
1 &\quad \text{or} &\quad 2
\end{align*}
\]

\[
\begin{align*}
&\quad \text{HN} \quad \text{Z} &\quad R = \text{H} \quad \text{or} \quad \text{CH}_3, \quad \text{Z} = \text{CH}_2, \quad \text{NH}, \quad \text{O}, \quad \text{NCHO}, \quad \text{NH}_2^+ \\
&\quad \text{R} \\
\end{align*}
\]

Scheme 1
investigate the effect of changing the nonleaving group from benzoyl to 2-furoyl on reactivity and reaction mechanism, particularly on $pK_a$ and $k_2/k_1$ ratio.

**Results and Discussion**

Reactions of 2 with all the amines studied proceeded with quantitative liberation of 2,4-dinitrophenoxide ion. The reactions were followed by monitoring the appearance of 2,4-dinitrophenoxide ion at 400 nm. Kinetic study was performed under pseudo-first-order conditions; the amine concentration was always in excess over that of the substrate 2. All reactions obeyed first-order kinetics over 90% of the total reaction. Pseudo-first-order rate constants $(k_{\text{obsd}})$ were determined from the equation, $\ln(A_0 - A_t) = -k_{\text{obsd}} t + C$. The plots of $k_{\text{obsd}}$ vs. the amine concentration were linear passing through the origin, indicating that general base catalysis by a second amine molecule is absent and the contribution of OH$^-$ ion from the hydrolysis of amines to $k_{\text{obsd}}$ is negligible. Thus, the rate equation can be expressed as eq (1). The second-order rate constants $(k_2)$ were determined from the slope of these linear plots. Generally five different amine concentrations were used to determine $k_2$ values. It is estimated from replicate runs that the uncertainty in the rate constants is less than 3%. The $k_2$ values determined in this way are summarized in Table 1.

$$\text{rate} = k_2[2][\text{amine}] \quad (1)$$

**Effect of Nonleaving Group on Reactivity.** As shown in Table 1, the $k_2$ value for the reaction of 2 decreases as the basicity of amines decreases, i.e., it decreases from 427 M$^{-1}$s$^{-1}$ to 43.5 and 1.47 M$^{-1}$s$^{-1}$ as the $pK_a$ of amines decreases from 11.02 to 8.65 and 5.95, respectively. A similar result is shown for the corresponding reactions of 1. However, the furoate 2 is more reactive than the benzate 1 for all the amines studied.

We have recently shown that the effect of substituent in the nonleaving group on reactivity is significant for nucleophilic substitution reactions of aryl X-substituted benzoates and benzensulfonates with primary and secondary amines, as well as with anionic nucleophiles such as OH$^-$, CN$^-$, and $N_3^-$. In all cases, the reactivity of these esters increased as the substituent X in the benzoyl or the sulfonyl moiety becomes a stronger EWG.$^{9-12}$ We have found that the Yukawa-Tsuno plots for these reactions are linear with $r$ values ranging from 0.4 to 1.6.$^{9-12}$ Since the $r$ value in the Yukawa-Tsuno plot represents a relative extent of resonance contribution between the electron donating substituent (e.g., 4-MeO) and the reaction center (e.g., the carbonyl or sulfonyl group), the ground state has been suggested to be stabilized through resonance as illustrated by resonance structures I $\leftrightarrow$ II.

![Chemical structure](Image)

The effect of delocalizability of ring electrons to the carbonyl group (i.e., resonance structures III $\leftrightarrow$ IV, where R = benzoyl, 2-furoyl, and 2-thiophenecarboxyl) has also been studied theoretically.$^{15}$ Lee et al. have reported that the delocalizability of ring electrons decreases in the order 2-furoyl > 2-thiophenecarboxyl > benzoyl on the basis of the ab initio calculations at the MP2/6-31G*/MP2/6-31G* level.$^{15}$ Furthermore, the natural bond orbital (NBO) positive charge on the carbonyl carbon has been computed to be in the reverse order, i.e., 2-furoyl (0.328) < 2-thiophenecarboxyl (0.351) < benzoyl (0.376),$^{15}$ indicating that the benzoate I is more electrophilic than the furoate 2. Accordingly, one might expect that 1 is more reactive than 2. However, Table 1 shows that 2 is more reactive than 1 toward all the amines studied. Thus, one can suggest that the delocalizability of ring electron (or the NBO positive charge) cannot determine the reactivity of 1 and 2 toward the amines in the current study.

![Chemical structure](Image)

2-Furoic acid ($pK_a = 3.16$) is 1.04 $pK_a$ units more acidic than benzoic acid ($pK_a = 4.20$).$^{16}$ Thus, one might suggest that the high acidity of 2-furoic acid is responsible, at least in part, for the fact that 2 is more reactive than 1. This argument is consistent with our recent reports that an acid strengthening substituent X in the benzoyl or benzensulfonfyl moiety increases the reactivity of aryl X-substituted benzoates or benzensulfonates toward various nucleophiles.$^{9-12}$

**Effect of Nonleaving Group on Reaction Mechanism.** In Figure 1 is demonstrated the effect of amine basicity on reactivity. The Bronsted-type plots exhibit downward curvature for reactions of 1 and 2. Such a nonlinear Bronsted-type plot has often been found for aminolysis of esters with a good leaving group and suggested as evidence of a stepwise mechanism with a change in the RDS. In fact, we have

![Chemical structure](Image)

**Table 1. Summary of Second-order Rate Constants ($k_2$, M$^{-1}$s$^{-1}$) for the Reactions of 2,4-Dinitrophenyl Benzoate (1) and 2-Furoate (2) with Alicyclic Secondary Amines in 80 mol % H$_2$O/20 mol % DMSO at 25.0 ± 0.1 °C**

<table>
<thead>
<tr>
<th>No.</th>
<th>Amines</th>
<th>$pK_a$</th>
<th>$k_2$/M$^{-1}$s$^{-1}$</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>piperidine</td>
<td>11.02</td>
<td>174$^a$</td>
<td>427</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3-methyl piperidine</td>
<td>10.80</td>
<td>167$^a$</td>
<td>402</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>piperazine</td>
<td>9.85</td>
<td>82.1$^a$</td>
<td>224</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>morpholine</td>
<td>8.65</td>
<td>19.6$^a$</td>
<td>43.5</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1-formyl piperazine</td>
<td>7.98</td>
<td>5.43$^a$</td>
<td>12.3</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>piperazinium ion</td>
<td>5.95</td>
<td>0.467$^a$</td>
<td>1.47</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Data taken from ref. 9b.
recently reported that the reactions of 1 with all the amines employed in this study proceed through T± with a change in the RDS from the breakdown of T± to its formation as the amine becomes more basic than the leaving 2,4-dinitrophenoxide ion by ca. 5 pK±a units. Thus, one can suggest that the aminolysis of 2 proceeds also through T± on the basis of the nonlinear Brønsted-type plot as shown in Figure 1. This argument can be supported from the linear correlation between the logarithmic second-order rate constants for the reactions of 1 and 2. As shown in Figure 2, the log kN for the reactions of 2 exhibits a good linear correlation with that for the corresponding reactions of 1 with a slope close to unity.

The nonlinear Brønsted-type plot shown in Figure 1 for the aminolysis of 2 has been analyzed using a semiempirical equation (eq 2)6,17 on the basis of the proposed mechanism shown in Scheme 1. The parameters βi and β± represent the slope of the curved Brønsted plots in Figure 1 for the reactions with strongly basic and weakly basic amines, respectively. Here kN° refers to the kN value at pK±a where k/k± = 1. The parameters determined from the fitting of eq (2) to the experimental points are βi = 0.33, β± = 0.73, and pK±a = 9.1. Although the βi and β± values are slightly smaller for the reactions of 2 than for those of 1 (i.e., βi = 0.34 and β± = 0.74), the pK±a value is the same, i.e., pK±a = 9.1 for both reactions of 1 and 2. This result is consistent with our previous conclusion that the nature of the nonleaving group does not influence the pK±a value.5,9-11

\[
\log (k_N/k_N°) = \beta (p_{K±a} - p_{K±a°}) - \log (1 + \alpha)/2
\]

where \(\log \alpha = (\beta_i - \beta_j)(p_{K±a} - p_{K±a°})\) (2)

The kN values for the reactions of 2 have been dissected into their microscopic rate constants to obtain further information about the reaction mechanism. The apparent second-order rate constant kN can be expressed as eq (3) by applying the steady-state conditions to the intermediate on the basis of the proposed mechanism.

\[
k_N = k_i k_2 / (k_{-1} + k_2)
\]

(3)

The k2/k_{-1} ratios associated with the aminolysis of 2 have been determined using eqs (4)-(9). Eq (3) can be simplified to eq (4) or (5). Then, βi and β± can be expressed as eqs (6) and (7), respectively.

\[
k_N = k_i k_2 / k_{-1}, \text{ when } k_2 \ll k_{-1}
\]

(4)

\[
k_N = k_i, \text{ when } k_2 \gg k_{-1}
\]

(5)

\[
\beta_i = d(\log k_i) / d(p_{K±a})
\]

(6)

\[
\beta± = d(\log k_2 / k_{-1}) / d(p_{K±a})
\]

(7)

\[
\beta_i = \beta_i + d(\log k_2 / k_{-1}) / d(p_{K±a})
\]

(8)

\[
\beta± - \beta_i = d(\log k_2 / k_{-1}) / d(p_{K±a})
\]

(9)

Eq (7) can be rearranged as eq (8). Integral of eq (8) from pK±a results in eq (9). Since k2 = k_{-1} at pK±a °, the term (log k2 / k_{-1})pK±a ° is zero. Therefore, one can calculate the k2/k_{-1} ratios for the aminolysis of 2 from eq (9) using pK±a ° = 9.1, βi = 0.33, and β± = 0.73.

\[
\beta± - \beta_i = (\beta± - \beta_i)(p_{K±a} - p_{K±a°})
\]

(10)

The kN values have been determined from eq (10) using the kN values in Table 1 and the k2/k_{-1} ratios calculated above. The k2/k_{-1} ratios and kN values are summarized in Table 2.

\[
k_N = k_i k_2 / (k_{-1} + k_2)
\]

(11)

\[
k_N = k_i / (k_{-1} + k_2 + 1)
\]

(12)
basicity of amines, while \( k_{-1} \) would decrease as the amine basicity increases.\(^{6-11}\) Accordingly, one might expect that the \( k_2/k_{-1} \) ratio would increase as the amine basicity increases. Table 2 shows that the \( k_2/k_{-1} \) ratio increases as the amine basicity increases, which is consistent with the expectation. Table 2 also shows that the \( k_2/k_{-1} \) ratios for the reactions of 2 are the same as those for the reactions of 1. This result supports our previous conclusion that the electronic nature of substituent X in the benzoyl or benzenesulfonyl moiety does not affect the \( k_2/k_{-1} \) ratio.\(^{3-11}\)

As shown in Table 2, \( k_1 \) increases with increasing amine basicity for both reactions of 1 and 2. The effect of amine basicity on \( k_1 \) is illustrated in Figure 3. Both Brønsted-type plots are linear with almost the same slope. It is noted that the \( k_1 \) value is larger for the reactions of 2 than for those of 1 for a given amine, which is fully responsible for the fact that the former exhibits higher reactivity than the latter.

### Conclusions

The current study has allowed us the following conclusions: (i) The furoate 2 is more reactive than the benzoate 1. The higher acidity of 2-furoic acid compared with benzoic acid is responsible, at least in part, for the higher reactivity of 2. (ii) The aminolysis of 2 has been suggested to proceed through \( T^+ \) with a change in the RDS on the basis of the nonlinear Brønsted-type plot. (iii) The \( pK_a \) and \( k_2/k_{-1} \) ratios for the reactions of 1 and 2 are identical, indicating that the nature of the nonleaving group (i.e., benzoyl and 2-furoyl) does not affect the reaction mechanism. (iv) The \( k_1 \) value is larger for the reactions of 2 than for those of 1, which is fully responsible for the fact that the former is more reactive than the latter.

### Experimental Section

#### Materials

Substrate 2 was readily prepared from the reaction of 2,4-dinitrophenol and 2-furoyl chloride in the presence of triethylamine in anhydrous ether. The purity was confirmed by its melting point and \( ^1 \)H NMR spectrum. Amines and other chemicals were of the highest quality available and were generally recrystallized or distilled before use. Due to the low solubility of 2 in pure \( \text{H}_2\text{O} \), aqueous DMSO was used as the reaction medium (i.e., 20 mol % DMSO/80 mol % \( \text{H}_2\text{O} \)). Doubly glass distilled water was further boiled and cooled under nitrogen just before use.

#### Kinetics

The kinetic studies were performed at 25.0 ± 0.1°C with a UV-Vis spectrophotometer equipped with a constant temperature circulating bath for slow reactions (e.g., \( t_{1/2} \geq 10 \) s) or with a stopped-flow spectrophotometer for fast reactions (e.g., \( t_{1/2} < 10 \) s). The reactions were followed by monitoring the appearance of 2,4-dinitrophenoxide ion at 400 nm. All the reactions were carried out under pseudo-first-order conditions in which the amine concentration was at least 20 times greater than that of the substrate.

Typically, reaction was initiated by adding 5 \( \mu \text{L} \) of 0.02 M of a substrate solution in MeCN by a 10 \( \mu \text{L} \) syringe into a 10 mm UV cell containing 2.50 mL of the reaction medium and the amine. The amine stock solution of \( ca. 0.2 \) M was prepared in a 25.0 mL volumetric flask under nitrogen by adding 2 equiv of amine to 1 equiv of standardized \( \text{HCl} \) gas-tight syringes.

#### Products Analysis

The amount of 2,4-dinitrophenoxide ion was determined quantitatively by comparison of the UV-Vis spectra after the completion of the reactions with those of the authentic samples under the same reaction conditions.

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### References


