Aminolyses of 2,4-Dinitrophenyl and 3,4-Dinitrophenyl 2-Furoates:
Effect of ortho-Substituent on Reactivity and Mechanism

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Second-order rate constants (kN) have been measured spectrophotometrically for reactions of 3,4-dinitrophenyl 2-furoate (2) with a series of secondary alicyclic amines in 80 mol % H2O/20 mol % dimethyl sulfoxide (DMSO) at 25.0 °C. The Brønsted-type plot exhibits a downward curvature for the aminolysis of 2, which is similar to that reported for the corresponding reactions of 2,4-dinitrophenyl 2-furoate (1). Substrate 2 is less reactive than 1 toward all the amines studied but the reactivity difference becomes smaller as the amine basicity increases. Dissection of the second-order rate constants into the microscopic rate constants has revealed that the reaction of 2 results in a smaller $k_2/k_1$ ratio but slightly larger $k_1$ value than that of 1. Steric hindrance has been suggested to be responsible for the smaller $k_1$ value found for the reactions of 1, since the ortho-substituent of 1 would inhibit the attack of amines (i.e., the $k_1$ process).

Key Words: Aminolysis, Brønsted-type plot, Steric hindrance, Reaction mechanism, ortho-Effect

Introduction

Aminolyses of esters have been intensively investigated including computational studies due to their importance in biological processes as well as in synthetic applications.1-9 The reactions have generally been understood to proceed through a zwitterionic tetrahedral intermediate (T±). The rate-determining step (RDS) has been suggested to be dependent on the basicity of the attacking amine and the leaving group, i.e., it changes from breakdown of T± to its formation as the attacking amine becomes more basic than the leaving group by 4 to 5 pKₐ units.1-5

Esters with 2,4-dinitrophenoxide as a leaving group (e.g., 1) have often exhibited a lower reactivity than those with 3,4-dinitrophenoxide (e.g., 2),10,11 although 2,4-dinitrophenoxide is expected to be more nucleofugic than 3,4-dinitrophenoxide on the basis of the fact that the former is less basic than the latter. Since the substituent at the ortho-position would cause steric hindrance, Jencks et al. have suggested that steric effect is responsible for the decreased reactivity shown by esters with a substituent at the ortho-position of the leaving group.11 However, the steric effect has never been investigated in a microscopic rate constant level.

We have recently performed a kinetic study on aminolysis of 2,4-dinitrophenyl 2-furoate (1) and concluded that the reaction proceeds through a zwitterionic tetrahedral intermediate (T±) with a change in the RDS on changing the basicity of amines.12 The kinetic study has now been extended to reactions of 3,4-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 reported for the corresponding reactions of 1 to investigate the effect of changing the leaving group from 2,4-dinitrophenoxide to 3,4-dinitrophenoxide on reactivity and reaction mechanism (i.e., an ortho-substituent effect) in a microscopic rate constant level.

Results and Discussion

Reactions of 2 with all the amines studied proceeded with quantitative liberation of 3,4-dinitrophenoxide ion. The reactions were followed by monitoring the appearance of the leaving group at 410 nm. Kinetic study was performed under pseudo-first-order conditions, i.e., the concentration of amines was at least 20 times in excess over that of the substrate 2. All reactions obeyed first-order kinetics. Pseudo-first-order rate constants (kobsd) were determined from the equation, ln(A∞ − At) = −kobsd + C. The plots of kobsd 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 given as eq. (1). The second-order rate constants (\( k_N \)) were determined from the slope of the linear plots of \( k_{\text{obsd}} \) vs. the amine concentration. Generally five different amine concentrations were used to determine \( k_N \) values. It is estimated from replicate runs that the uncertainty in the rate constants is less than 3%. The \( k_N \) values determined in this way are summarized in Table 1 together with those reported for the corresponding reactions of 1 for comparison purpose.

\[
\text{rate} = k_{\text{obsd}}[2], \text{where} \ k_{\text{obsd}} = k_N[\text{amine}] \quad (1)
\]

**Effect of ortho-Substituent on Reactivity and Mechanism.** As shown in Table 1, the second-order rate constant for the reaction of 2 decreases as the basicity of amines decreases, \( i.e., k_N \) decreases from 396 M\(^{-1}\)s\(^{-1}\) to 30.2 and 0.383 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.

The effect of amine basicity on reactivity is illustrated in Figure 1. The Brønsted-type plot exhibits a downward curvature for the reactions of 1 and 2, when \( k_N \) and \( pK_a \) are statistically corrected using \( p \) and \( q \) (\( i.e., p = 2 \) except \( p = 4 \) for piperazinium ion and \( q = 1 \) except \( q = 2 \) for piperazine).\(^{13}\) It is also noted that the slope of the Brønsted-type plots is a little larger for the reactions of 2 than for those of 1.

Figure 1 shows that 2 is less reactive than 1 toward all the amines studied. However, interestingly, the reactivity difference between 1 and 2 becomes smaller as the amine basicity increases. Moreover, 2 would be expected to be more reactive than 1 when the amine basicity increases further (\( i.e., pK_a > 11.5 \)).

A plot of log \( k_N \) for the reactions of 1 vs. log \( k_N \) for the corresponding reactions of 2 has been constructed to investigate the effect of the ortho-NO\(_2\) on reaction mechanism. As shown in Figure 2, an excellent linear correlation is obtained (\( e.g., R^2 = 0.9991 \)) with a slope of 1.21. Such a good linear plot suggests that the reactions of 1 and 2 proceed through the same mechanism. The slope of 1.21 is consistent with the fact that 2 is more sensitive than 1 toward the amine basicity (see Figure 1). Accordingly, one can suggest that shifting the NO\(_2\) group from the ortho-position to the meta-position can influence the reactivity but not the reaction mechanism.

The reactions of 1 with the current secondary alicyclic amines have been suggested to proceed through T\(^+\) with a change in the RDS at \( pK_a = 9.1 \), which is ca. 5 \( pK_a \) units more basic than the leaving 2,4-dinitrophenoxide (\( i.e., pK_a \) of 2,4-dinitrophenol = 4.11). Thus, one can suggest that the current reactions of 2 proceed also through T\(^+\) with a change in the RDS as shown in Scheme 1 on the basis of the curved Brønsted-type plot in Figure 1 and the linear plot in Figure 2.

**Table 1. Summary of Second-order Rate Constants (\( k_N, \text{M}^{-1}\text{s}^{-1} \)) for Reactions of 3,4-Dinitrophenyl 2-Furoates (2) and 2,4-Dinitrophenyl 2-Furoates (1) with a Series of Secondary Alicyclic Amines in 20 mol % DMSO at 25.0 ± 0.1 °C**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amines</th>
<th>( pK_a )</th>
<th>( k_N / \text{M}^{-1}\text{s}^{-1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>piperidine</td>
<td>11.02</td>
<td>396</td>
</tr>
<tr>
<td>2.</td>
<td>3-methylpiperidine</td>
<td>10.80</td>
<td>329</td>
</tr>
<tr>
<td>3.</td>
<td>piperazine</td>
<td>9.85</td>
<td>175</td>
</tr>
<tr>
<td>4.</td>
<td>morpholine</td>
<td>8.65</td>
<td>30.2</td>
</tr>
<tr>
<td>5.</td>
<td>1-formylpiperazine</td>
<td>7.98</td>
<td>5.75</td>
</tr>
<tr>
<td>6.</td>
<td>piperazinium ion</td>
<td>5.95</td>
<td>0.383</td>
</tr>
</tbody>
</table>

\(^{13}\) The data for the reactions of 1 were taken from ref. 12.
Evaluation of Microscopic Rate Constants. The non-linear Brønsted-type plot shown in Figure 1 for the aminolysis of 2 has been analyzed using a semiempirical equation (eq. 2)\textsuperscript{11,14} on the basis of the proposed mechanism. The parameters $\beta_1$ and $\beta_2$ represent the slope of the curved Brønsted plot in Figure 1 for the reactions with strongly basic and weakly basic amines, respectively. Here $k_N$ is the $k_N$ value at pK\text{a}$^+$ (i.e., the pK\text{a} at the center of Brønsted curvature where $k_2/k_1 = 1$).

\[
\log \left( \frac{k_N}{k_N^o} \right) = \beta_2(pK_a - pK_a^o) - \log \left( 1 + \alpha \right)/2
\]

where $\log \alpha = (\beta_2 - \beta_1)(pK_a - pK_a^o)$

(2)

The parameters determined from the fitting of eq. (2) to the experimental points are $\beta_1 = 0.33$, $\beta_2 = 0.76$, and pK\text{a}$^o = 10.4$ for the reactions of 2. The $\beta_1$ value for the reactions of 1 is the same as that reported for the reactions of 1, while $\beta_2$ is slightly larger for the reactions of 2 ($\beta_2 = 0.76$) than for those of 1 ($\beta_2 = 0.73$). The $pK_a^o$ value for the reactions of 1 is 10.4, which is ca. 5 pK\text{a} units larger than the pK\text{a} of 3,4-dinitrophenol (i.e., 5.42). Thus, the $pK_a^o$ value of 10.4 for the reactions of 2 is consistent with the report that a change in the RDS occurs as the attacking amine becomes more basic than the leaving aryloxide by 4 to 5 pK\text{a} units.

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

\[
k_N = k_1(k_2/k_1 + k_2)
\]

(3)

The $k_2/k_1$ 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, $\beta_1$ and $\beta_2$ can be expressed as eqs. (6) and (7), respectively.

\[
k_N = k_1k_2/k_1 + k_2
\]

(4)

\[
k_N = k_1, \text{ when } k_2 \ll k_1
\]

(5)

\[
\beta_1 = d(log k_1)/d(pK_a)
\]

(6)

\[
\beta_2 = d(log k_2/k_1)/d(pK_a)
\]

(7)

\[
k_2 = k_1\beta_2/\beta_1 = k_2\beta_1/\beta_2 = k_1(k_2/k_1) + 1
\]

(10)

The data for the reactions of 1 were taken from ref. 12.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>pK\text{a}</th>
<th>$k_j/k_i$</th>
<th>$k_j$/M\text{–1}s\text{–1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>piperidine</td>
<td>11.02</td>
<td>2.44</td>
<td>558 (482)</td>
</tr>
<tr>
<td>2.</td>
<td>3-methylpiperidine</td>
<td>10.80</td>
<td>2.00</td>
<td>493 (466)</td>
</tr>
<tr>
<td>3.</td>
<td>piperazine</td>
<td>9.85</td>
<td>0.580 (2.00)</td>
<td>477 (336)</td>
</tr>
<tr>
<td>4.</td>
<td>morpholine</td>
<td>8.65</td>
<td>0.238 (0.872)</td>
<td>157 (93.4)</td>
</tr>
<tr>
<td>5.</td>
<td>1-formylpiperazine</td>
<td>7.98</td>
<td>0.123 (0.470)</td>
<td>52.7 (38.5)</td>
</tr>
<tr>
<td>6.</td>
<td>pipеразинион</td>
<td>5.95</td>
<td>0.022 (0.096)</td>
<td>17.7 (16.8)</td>
</tr>
</tbody>
</table>

Figure 3. Plots of log $k_2/k_1$ versus pK\text{a} for the reactions of 1 (○) and 2 (●) with a series of secondary alicyclic amines in 80 mol % H\text{2}O/20 mol % DMSO at 25.0 ± 0.1°C.

Table 2. Summary of Microscopic Rate Constants $k_j/k_i$, Ratios and $k_j$ values for the Reactions of 2 (and 1, in parentheses) with a Series of Secondary Alicyclic Amines in 80 mol % H\text{2}O/20 mol % DMSO at 25.0 ± 0.1°C

Effect of ortho-Substituent on Microscopic Rate Constants. It has been suggested that $k_2$ is independent of the basicity of amines, since the N atom of the aminium moiety of $T^+$ cannot exert a push to expel the leaving aryloxide from $T^+$ due to the lack of an electron pair on its nitrogen atom.\textsuperscript{11,15} However, the $k_1$ value would decrease as the amine basicity increases. Accordingly, one might expect that the $k_2/k_1$ ratio would increase as the amine basicity increases. In fact, Table 2 shows that the $k_2/k_1$ ratio increases as the amine basicity increases for the aminolyses of 1 and 2.

The effect of amine basicity on the $k_2/k_1$ ratio is illustrated in Figure 3. The plots of log $k_2/k_1$ vs. pK\text{a} are linear for the reactions of 1 and 2, although the slope of the linear plots is slightly larger for the reactions of 2 (i.e., $\beta_1 = 0.43$) than for those of 1 (i.e., $\beta_1 = 0.40$). The larger $\beta_1$ value obtained for the reactions of less reactive 2 appears to be consistent with the so-called reactivity-selectivity principle (RSP).\textsuperscript{16}

One might expect that the reactions of 2 would result in a smaller $k_2$ value than those of 1, since 3,4-dinitrophenoxide is more basic and a poorer leaving group than 2,4-dinitrophenoxide. However, the $k_1$ value would not be influenced by the basicity of the leaving group. Thus, one might expect...
that the \( k_2/k_1 \) ratio is smaller for the reactions of 2 than for those of 1. In fact, Figure 3 shows that the \( k_2/k_1 \) ratio is smaller for the reactions of 2 than for those of 1 for a given amine.

As shown in Figure 4, \( k_1 \) increases linearly with increasing amine basicity for the reactions of 1 and 2. However, the \( k_1 \) value is slightly larger for the reactions of 2 than for those of 1, although 2 has a more basic leaving group than 1 (see Table 2). Since the ortho-NO₂ in substrate 1 would cause steric hindrance in the \( k_1 \) process, one can suggest that steric effect is responsible for the fact that the reaction of 1 results in a smaller \( k_1 \) value than that of 2 for a given amine.

Conclusions

The current study has allowed us to conclude the following: (1) Aminolyses of 1 and 2 proceed through \( T^* \) with a change in the RDS. (2) Substrate 2 is less reactive than substrate 1 toward all the secondary amines studied. However, the difference in reactivity becomes smaller as the amine basicity increases. (3) Dissection of \( k_2 \) into the microscopic rate constants has revealed that aminolysis of 2 results in smaller \( k_2/k_1 \) ratio but larger \( k_1 \) value than that of 1. (4) Steric hindrance has been suggested to be responsible for the smaller \( k_1 \) value obtained from the reactions of 1.

Experimental Section

Materials. Substrate 2 was readily prepared from the reaction of 3,4-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. 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 H₂O, 20 mol % DMSO/80 mol % H₂O was used as the reaction medium. Doubly glass distilled water was further boiled and cooled under nitrogen just before use.

Products Analysis. 3,4-Dinitrophenoxide ion at 410 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.

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References


