Aminolysis of 2,4-Dinitrophenyl and 3,4-Dinitrophenyl Benzoates: Effect of ortho-Nitro Group on Reactivity and Mechanism

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Second-order rate constants ($k_O$) have been measured spectrophotometrically for reactions of 3,4-dinitrophenyl benzoates (5b) with a series of alicyclic secondary amines in 80 mol % H$_2$O/20 mol % DMSO at 25.0 ± 0.1 °C. The kinetic data have been compared with the data reported previously for the corresponding reactions of 2,4-dinitrophenyl benzoates (5a) to investigate the effect of changing the nucleofuge from 2,4-dinitrophenoxide to 3,4-dinitrophenoxide on reactivity and mechanism. The kinetic results show that aminolyses of 5a and 5b proceed through the same mechanism, i.e., a zwitterionic tetrahedral intermediate (T$^*$) with a change in the rate-determining step (RDS). Substrate 5a is more reactive than 5b when breakdown of T$^*$ is the RDS but less reactive when formation of T$^*$ is the RDS. Dissection of $k_O$ values into the microscopic rate constants ($e.g., k_1$ and $k_2/k_1$ ratio) has revealed that 5a results in larger $k_2/k_1$ ratios but smaller $k_1$ values than 5b for all the amines studied. Since 2,4-dinitrophenoxide is less basic and a better nucleofuge than 3,4-dinitrophenoxide, the larger $k_2/k_1$ ratios determined for the reactions of 5a than for those of 5b are as expected. The steric hindrance exerted by the ortho-nitro group on 5a contributes to the smaller $k_1$ values found for the reactions of 5a than for those of 5b.

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

Introduction

Aminolysis of esters has generally been understood to proceed through a stepwise mechanism with a zwitterionic tetrahedral intermediate, T$^*$. Curved Brønsted-type plots have often been reported for reactions of esters which possess a good leaving group (e.g., from a large $\beta_{nu}$ to a small one as the attacking amine becomes more basic than the leaving group by 4 to 5 pK$\alpha$ units). Such a curved Brønsted-type plot has often been suggested as evidence for a change in rate-determining step (RDS) of a stepwise mechanism.

Brønsted and Hammett equations have most commonly been employed to investigate reaction mechanism and/or to correlate reactivity with basicity or substituent constants. It is well known that nucleophilicity increases with increasing the basicity of nucleophiles while nucleofugality decreases with increasing the basicity of nucleofuges. However, Gresser and Jencks found that 2,4-dinitrophenyl phenyl carbonate is less reactive than 3,4-dinitrophenyl phenyl carbonate toward quinuclidines, although 2,4-dinitrophenoxide is less basic than 3,4-dinitrophenoxide by ca. 1.3 pK$\alpha$ units. Gresser and Jencks concluded that steric hindrance is responsible for the decreased reactivity of 2,4-dinitrophenyl phenyl carbonate compared to 3,4-dinitrophenyl phenyl carbonate, since the nitro group at the ortho-position may cause steric hindrance.

A similar result has been reported for aminolysis of 2,4-dinitrophenyl and 3,4-dinitrophenyl 2-furoates (1a and 1b) and 2-thiophenecarboxylates (2a and 2b). We found that 1a is only slightly more reactive than 1b toward piperidine, while 2a is even less reactive than 2b. Dissection of the macroscopic second-order rate constant ($k_O$) into the microscopic rate constants (e.g., $k_1$ and $k_2/k_1$) has shown that 1a and 2a exhibit smaller $k_1$ values but larger $k_2/k_1$ ratios than 1b and 2b, respectively. Our studies on the aminolyses of 1a, b and 2a, b have shown that steric hindrance contributes to the smaller $k_1$ values for the reactions of the substrates with an ortho-nitro group (e.g., 1a and 2a).

However, we have found that the steric hindrance reported for the reactions of the carbonyl esters (1a and 2a) is absent for aminolyses of phosphorus centered esters, since 2,4-
The plots of were determined from the equation, \( \ln( ) \) of a curved Brønsted-type plot. were used to determine the amine concentration. Five different amine concentrations including phenyl diphenylphosphinates and diphenylphosphinothioates have been found to be linear for aminolyses of Y-substituted dinitrophenyl benzoate (5a) with secondary alicyclic secondary amines in 20 mol % DMSO at 25.0 ± 0.1°C.

We performed a kinetic study on aminolysis of 2,4-dinitrophenyl benzoate (5a) and concluded that the reaction proceeds through a change in the RDS on the basis of a curved Brønsted-type plot. The kinetic study has now been extended to reactions of 3,4-dinitrophenyl benzoate (5b) with a series of alicyclic secondary amines (Scheme 1). The kinetic data in the current study have been compared with those reported previously for the corresponding reactions of 3,4-di nitrophenyl benzoate (5a, b) with secondary alicyclic amines in 80 mol % H2O/20 mol % DMSO [7].

\[
Y = 2,4-(NO_2)_2 \text{ (5a) : } Y = 3,4-(NO_2)_2 \text{ (5b)}
\]

Scheme 1

Results and Discussion

The reactions of 5b with all the amines studied in this work obeyed first-order kinetics and proceeded with quantitative liberation of 3,4-dinitrophenoxide ion under pseudo-first-order conditions. Pseudo-first-order rate constants (kobs) were determined from the equation, \( \ln(A - A_t) = -k_{obs}t + C \). The plots of kobs 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 H2O and/or OH− ion from the hydrolysis of amines to kobs is negligible. Accordingly, the rate equation can be given as eq (1). The second-order rate constants (kN) were determined from the slope of the linear plots of kobs vs. the amine concentration. Five different amine concentrations were used to determine kN values. It is estimated from replicate runs that the uncertainty in the rate constants is less than 3%. The kN values determined in this way are summarized in Table 1.

\[
\text{rate} = k_{obs}[5b], \text{ where } k_{obs} = k_{N}[\text{amine}] \quad (1)
\]

Effect of ortho-Nitro Group on Reactivity and Mechanism. Table 1 shows that the second-order rate constant (kN) for the reaction of 5b decreases with decreasing the basicity of amines, i.e., kN decreases from 191 M⁻¹s⁻¹ to 10.0 and 0.0867 M⁻¹s⁻¹ as the pKa of amines decreases from 11.02 to 8.65 and 5.95, respectively. A similar result is presented for the corresponding reactions of 5a. It is noted that 5b is less reactive than 5a when the attacking amines are weakly basic (i.e., pKa ≤ 9.85) but becomes more reactive as the amine basicity increases further (i.e., pKa ≥ 10.80).

In Figure 1 is demonstrated the effect of amine basicity on reactivity as well as the effect of changing the nucleofuge from 2,4-dinitrophenoxide to 3,4-dinitrophenoxide. The Brønsted-type plot for the reactions of 5b is curved downwardly, when kobs and pKa are statistically corrected using p and q (i.e., p = 2 except p = 4 for pipercazine ion and q = 1 except q = 2 for pipercazine). Similar result is shown for the corresponding reactions of 5a. However, the slopes of the Brønsted-type plots are slightly different, i.e., the slope decreases from 0.83 to 0.34 and from 0.74 to 0.34 as the

![Figure 1. Brønsted-type plots for the reactions of 5a (○) and 5b (●) with secondary alicyclic amines in 80 mol % H2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.](image)

Table 1. Summary of Second-order Rate Constants (kN, M⁻¹s⁻¹) for Reactions of 2,4-Dinitrophenyl Benzote (5a) and 3,4-Dinitrophenyl Benzote (5b) with Secondary Alicyclic Amines in 20 mol % DMSO at 25.0 ± 0.1°C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amines</th>
<th>pKa</th>
<th>kN / M⁻¹s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>piperidine</td>
<td>11.02</td>
<td>174</td>
</tr>
<tr>
<td>2</td>
<td>3-methylpiperidine</td>
<td>10.80</td>
<td>167</td>
</tr>
<tr>
<td>3</td>
<td>pipercaine</td>
<td>9.85</td>
<td>82.1</td>
</tr>
<tr>
<td>4</td>
<td>morpholine</td>
<td>8.65</td>
<td>19.6</td>
</tr>
<tr>
<td>5</td>
<td>1-formylpipercaine</td>
<td>7.98</td>
<td>5.43</td>
</tr>
<tr>
<td>6</td>
<td>pipercazinium ion</td>
<td>5.95</td>
<td>0.467</td>
</tr>
</tbody>
</table>

*pKa values and the data for reaction of 5a were taken from ref. 7.
amine basicity increases for the reactions of 5b and 5a, respectively. It is also noted that 5a is more reactive than 5b when the attacking amine is weakly basic but becomes slightly less reactive when the amine is strongly basic (e.g., pKₐ ≥ 10.80).

It is known that a change in RDS occurs at the center of the Brønsted curvature, defined as pKₐ°. The pKₐ° for ester aminolysis has generally been reported to be 4 to 5 pKₐ units higher than the pKₐ of the conjugate acid of leaving group. It is also noted that the Brønsted curvature, defined as pKₐ°, has been constructed. As shown in Figure 2, an excellent linear plot suggests that the reactions of 5b were determined to be 9.1, which is ca. 5 pKₐ units higher than the pKₐ of 2,4-dinitrophenol (i.e., pKₐ = 4.11), the conjugate acid of the leaving group. Thus, the curved Brønsted-type plot for the reactions of 5a has been constructed. As shown in Figure 2, an excellent linear plot was interpreted as a change in the RDS on the basis of the curved Brønsted-type plot. The center of the Brønsted curvature was determined to be 9.1, which is ca. 5 pKₐ° units higher than the pKₐ° of 2,4-dinitrophenol (i.e., pKₐ° = 4.11), the conjugate acid of leaving group. Thus, the curved Brønsted-type plot for the reactions of 5a has been constructed. As shown in Figure 2, an excellent linear plot was interpreted as a change in the RDS on the basis of the curved Brønsted-type plot.

To test whether the aminolyses of 5a and 5b proceed through the same mechanism or not, a plot of log kₙ for the reactions of 5a vs. log kₙ for the corresponding reactions of 5b has been constructed. As shown in Figure 2, an excellent linear correlation is obtained (i.e., R² = 0.9992) with a slope of 1.29. Such a good linear plot suggests that the reactions of 5a and 5b proceed through the same mechanism. The fact that the slope is larger than unity implies that 5b is more sensitive than 5a toward amine basicity. Accordingly, one can conclude that modification of the nucleofuge from 2,4-dinitrophenoxide to 3,4-dinitrophenoxide influences the reactivity but not the reaction mechanism.

**Dissection of Macroscopic Rate Constants into Microscopic Rate Constants.** On the basis of the mechanism proposed above, the curved Brønsted-type plot for the aminolysis of 5b has been analyzed using a semiempirical equation (eq. 2). The parameters β₁ and β₂ represent the slope of the curved Brønsted plot for the reactions with strongly basic and weakly basic amines, respectively. Here kN° refers to the kN value at pKₐ°. The parameters determined from the fitting of eq. (2) to the experimental points are β₁ = 0.34, β₂ = 0.83, and pKₐ° = 10.4 for the reactions of 5b.

\[
\log (kN/kN°) = \beta_2(pK_a - pK_a°) - \log [(1 + \alpha)/2] 
\]

where \( \log \alpha = (\beta_2 - \beta_1)(pK_a - pK_a°) \) (eq. 2)

The kN values for the reactions of 5b have been dissected into their microscopic rate constants through eqs. (3)-(10) as shown below. The macroscopic 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.

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

(3)

The k½/k₁ ratios associated with the aminolysis of 5b have been determined using eqs. (4)-(9). Eq. (3) can be simplified to eq. (4) or (5). Then, β₁ and β₂ can be expressed as eqs. (6) and (7), respectively.

\[
k_N = k_2/k_{-1}, \text{ when } k_2 << k_{-1} \quad (4) \\
k_N = k_1, \text{ when } k_2 >> k_{-1} \quad (5) \\
b_1 = d(log k_1)/d(pK_a) \quad (6) \\
b_2 = d(log k_2/k_{-1})/d(pK_a) = b_1 + d(log k_{2/k_{-1}})/d(pK_a) \quad (7) 
\]

Eq. (7) can be rearranged as eq. (8). Integral of eq. (8) from pKₐ° results in eq. (9). Since \( k_2 = k_1 \) at pKₐ°, the term \( \log k_{2/k_{-1}} \) is zero. Therefore, one can calculate the k₂/k₁ ratios for the aminolysis of 5b from eq. (9) using pKₐ° = 10.4, β₁ = 0.34, and β₂ = 0.83. The k₁ values have been determined from eq. (10) using the kN values in Table 1 and the k₂/k₁ ratios calculated above. The k₂/k₁ ratios and k₁ values are summarized in Table 2 together with the data for the corresponding reactions of 5a.

\[
b_2 - b_1 = d(log k_2/k_{-1})/d(pK_a) \\
(log k_{2/k_{-1}})_{pK_a} = (b_2 - b_1)(pK_a - pK_a°) \quad (9) 
\]

**Table 2. Summary of Microscopic Rate Constants k₂/k₁ Ratios and k₁ Values for the Reactions of 5b and 5a (in parentheses) with Secondary Aliphatic Amines in 80 mol % H₂O/20 mol % DMSO at 25.0 ± 0.1 °C**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>pKₐ</th>
<th>k₂/k₁</th>
<th>k₁ (M⁻¹s⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>piperidine</td>
<td>11.02</td>
<td>2.82(7.73)</td>
<td>258(197)</td>
</tr>
<tr>
<td>2</td>
<td>3-methylpiperidine</td>
<td>10.80</td>
<td>2.20(6.31)</td>
<td>265(193)</td>
</tr>
<tr>
<td>3</td>
<td>piperazine</td>
<td>9.85</td>
<td>0.538(2.00)</td>
<td>176(123)</td>
</tr>
<tr>
<td>4</td>
<td>morpholine</td>
<td>8.65</td>
<td>0.195(0.871)</td>
<td>61.3(42.1)</td>
</tr>
<tr>
<td>5</td>
<td>1-formylpiperazine</td>
<td>7.98</td>
<td>0.091(0.470)</td>
<td>31.7(17.0)</td>
</tr>
<tr>
<td>6</td>
<td>piperazinium ion</td>
<td>5.95</td>
<td>0.0130(0.096)</td>
<td>6.7(5.26)</td>
</tr>
</tbody>
</table>

*The data in the parentheses for the reactions of 5a were taken from ref. 7b.*
Effect of ortho-Nitro Group on Microscopic Rate Constants. As shown in Table 2, the $k_2/k_1$ ratio decreases as the amine basicity decreases. It is noted that $k_2/k_1 > 1$ when $pK_a$ is 10.80 but $k_2/k_1 < 1$ when $pK_a$ is 9.85 for the reactions of 5b. On the other hand, $k_2/k_1 > 1$ when $pK_a$ is 9.85 but $k_2/k_1 < 1$ when $pK_a$ is 8.65 for the reactions of 5a. This is in accord with the proposal that the RDS for the aminolysis of 5a and 5b changes at $pK_a$ of 9.1 and 10.4, respectively.

The effect of amine basicity on the $k_2/k_1$ ratio is illustrated in Figure 3. The plots are linear with slopes of 0.40 and 0.49 for the reactions of 5a and 5b, respectively. The $k_2$ value has been suggested to be independent of amine basicity, since the push by the N atom of the aminium moiety of $T^-$ to expel the leaving group is absent. On the other hand, $k_1$ would decrease with increasing amine basicity. This idea is consistent with the positive slope shown in Figure 3.

It is noted that 5a exhibits a larger $k_2/k_1$ ratio than 5b for a given amine. Since 2,4-dinitrophenoxide is less basic and a better nucleofuge than 3,4-dinitrophenoxide, one can expect 5a would exhibit a larger $k_2$ value than 5b. In contrast, the leaving group basicity would not influence the $k_1$ value significantly. Therefore, the fact that 5a results in a larger $k_2/k_1$ ratio than 5b is consistent with the expectation on the basis of the basicity of the leaving groups.

In Figure 4 are demonstrated Bronsted-type plots for $k_1$ for the reactions of 5a and 5b. The plots are linear with similar slopes, $i.e.$, $\beta_1 = 0.33$ and 0.34 for the reactions of 5a and 5b, respectively. Interestingly, 5b exhibits slightly larger $k_1$ values than 5a for all the amines studied. This is an unexpected result, since the C=O bond of 5b would be less electrophilic than that of 5a on the basis of the fact that 3,4-dinitrophenoxide is more basic than 2,4-dinitrophenoxide. Accordingly, the basicity difference between the two leaving groups cannot account for the difference in $k_1$ values determined for the aminolyses of 5a and 5b.

The ortho-NO$_2$ in the nucleofuge of 5a would exert steric hindrance when the amine approaches to the electrophilic center to form an intermediate, $T^-$ ($i.e.$, the $k_1$ step). This, one can suggest that steric hindrance exerted by ortho-NO$_2$ is responsible for the fact that 5a results in smaller $k_1$ values than 5b.

However, the steric hindrance exerted by ortho-NO$_2$ is insignificant when the $k_2$ step is RDS. This is because 5a results in larger $k_2$ values than 5b when the $k_2$ step is the RDS ($i.e.$, $pK_a < 10.4$) but smaller $k_N$ values when the $k_1$ step is the RDS ($i.e.$, $pK_a > 10.4$). This argument can be further supported by the fact that $k_N = k_1 k_2/k_1$ when the $k_2$ step is the RDS and the $k_2/k_1$ ratios have been shown to be larger for the reactions of 5a than those of 5b (see Table 2 and Figure 3).

Conclusions

The current study has allowed us to conclude the following: (1) Modification of nucleofuge from 2,4-dinitrophenoxide to 3,4-dinitrophenoxide influences reactivity but does not affect mechanism for the aminolyses of 5a and 5b. (2) Substrate 5a is more reactive than 5b when the $k_1$ step is the RDS but less reactive when the $k_1$ step is the RDS. (3) Steric hindrance exerted by the ortho-nitro group is responsible for the fact that $k_1$ is smaller for the reactions of 5a than those of 5b. (4) Substrate 5a exhibits larger $k_2/k_1$ ratios than those of 5b as expected from the fact that 2,4-dinitrophenoxide is less basic and a better nucleofuge than 3,4-dinitrophenoxide.
Aminolysis of 2,4-Dinitrophenyl and 3,4-Dinitrophenyl Benzoates

Experimental Section

Materials. Substrate 5b was readily prepared from the reaction of 3,4-dinitrophenol and benzoyl chloride in the presence of triethylamine in anhydrous ether and purified by column chromatography: mp = 110-111 °C; 1H NMR (250 MHz, CDCl3) δ 7.54-7.60 (t, J = 7.5 Hz, 2H), 7.65-7.69 (dd, J1 = 10.0 Hz, J2 = 2.5 Hz, 1H), 7.76-7.70 (t, J = 7.5 Hz, 1H), 7.85-7.86 (d, J = 2.5 Hz, 1H), 8.06-8.10 (d, J = 10.0 Hz, 1H), 8.18-8.21 (d, J = 7.5 Hz, 2H). Anal. Calcd for C13H12NO5: C, 54.17; H, 2.80. Found: C, 54.08; H, 2.82. Other chemicals including amines were of the highest quality available. Doubly glass distilled water was further boiled and cooled under nitrogen just before use.

Kinetics. Due to the low solubility of 5b in pure H2O, 20 mol % DMSO/80 mol % H2O was used as the reaction medium for the kinetic study. The kinetic studies were performed with a Scinco S-3100 UV-Vis spectrophotometer equipped with a constant temperature circulating bath at 25.0 ± 0.1 °C for slow reactions (e.g., i1/2 > 10 s) or with an Applied Photophysics Stopped-flow spectrophotometer for fast reactions (e.g., i1/2 < 10 s). The reactions were performed under pseudo-first-order conditions, i.e., the amine concentration was at least 20 times greater than that of the substrate 5b and followed by monitoring the appearance of the leaving 3,4-dinitrophenoxide ion at 410 nm.

Products Analysis. 3,4-Dinitrophenoxide ion was liberated quantitatively and identified as one of the reaction products 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