A Kinetic Study on Ethylaminolysis of Phenyl Y-Substituted-Phenyl Carbonates: 
Effect of Leaving-Group Substituents on Reactivity and Reaction Mechanism

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Received March 11, 2013, Accepted March 21, 2013

A kinetic study on nucleophilic substitution reactions of phenyl Y-substituted-phenyl carbonates (5a-5j) with ethylamine in 80 mol % H2O/20 mol % DMSO at 25.0 ± 0.1 °C is reported. The plots of kobsd vs. [amine] are linear for the reactions of substrates possessing a strong electron-withdrawing group (EWG) but curve upward for those of substrates bearing a weak EWG, indicating that the electronic nature of the substituent Y in the leaving group governs the reaction mechanism. The reactions have been concluded to proceed through a stepwise mechanism with one or two intermediates (a zwitterionic tetrahedral intermediate T† and its deprotonated form T0) depending on the nature of the substituent Y. Analysis of Brønsted-type plots and dissection of kobsd into microscopic rate constants have revealed that the reactions of substrates possessing a strong EWG (e.g., 5a-5f) proceed through T† with its formation being the rate-determining step, while those of substrates bearing a weak EWG (e.g., 5g-5j) proceed through T0 and T†.

Key Words : Aminolysis, Leaving group, Brønsted-type plot, General-base catalysis, Intermediate

Introduction

Aminolyses of esters have intensively been investigated due to their importance in biological processes as well as in synthetic applications.1-11 Nucleophilic substitution reactions of esters with amines have been reported to proceed either through a concerted mechanism or through a stepwise pathway with one or two intermediates (e.g., a zwitterionic tetrahedral intermediate T† and its deprotonated form T0) depending on reaction conditions (e.g., the nature of electrophilic centers, the substituents in the leaving and nonleaving groups, solvents, etc.).1-11

Reactions of 4-nitrophenyl benzoate (1) with a series of cyclic secondary amines in 80 mol % H2O/20 mol % DMSO have been reported to proceed through a stepwise mechanism with breakdown of T† being the rate-determining step (RDS).6 However, the corresponding reactions of O-4-nitrophenyl thionobenzoate (2) have been shown to proceed through a stepwise pathway with two intermediates (e.g., T0 and T†),1a,7b while the reactions of 2 with a series of primary amines proceed through T0 only.7c On the other hand, aminolysis of 4-nitrophenyl diphenylphosphinate (3) has been reported to proceed through a concerted mechanism.8 Clearly, these results indicate that the reaction mechanism is strongly dependent on the nature of the electrophilic centers (e.g., C=O, C=S or P=O) and amines (e.g., primary or secondary amines).

The effects of medium and substituents on reaction mech-

anisms have also been studied. We have reported that aminolysis of 2,4-dinitrophenyl benzoate proceeds through a stepwise mechanism with a change in RDS in 80 mol % H2O/20 mol % DMSO (i.e., from breakdown of T† to its formation as the incoming amine becomes more basic than the leaving 2,4-dinitrophenoxide by 4 to 5 pK± units) but proceeds through a concerted pathway in MeCN.9 Interestingly, the reactions of 4-pyridyl X-substituted benzoates (4) with cyclic secondary amines in MeCN have recently been reported to proceed with T† as an intermediate when the substituent X is a weak EWG (e.g., 3,5-dinitro, 4-nitro, 4-cyano, etc.).10 This implies that the nature of leaving group and the electronic nature of substituent in the nonleaving group also affect the reaction mechanism.

Aminolysis of 4-nitrophenyl phenyl carbonate (5) in 80 mol % H2O/20 mol % DMSO has been reported to proceed through a stepwise mechanism with a change in the RDS.11 We have now extended our study to the reactions of phenyl Y substitted-phenyl carbonates (5a-5j) with ethylamine in

Scheme 1

Y = 3,4-(NO2)2 (5a), 4-NO2 (5b), 4-CHO (5c), 4-CN (5d), 4-COCH3 (5e), 4-CODEt (5f), 3-Cl (5g), 3-COCH3 (5h), 4-Cl (5i), H (5j).

Scheme 1
80 mol % H₂O/20 mol % DMSO to investigate the effect of leaving-group substituent Y on the reactivity and reaction mechanism (Scheme 1).

Results and Discussion

The reactions were followed spectrophotometrically by monitoring the appearance of Y-substituted-phenoxide under pseudo-first-order conditions (e.g., the concentration of ethylamine was kept in excess over that of substrates). All reactions obeyed first-order kinetics and the pseudo-first-order rate constants (k_{obsd}) were calculated from the equation,

\[ \ln \left( A_e - A_t \right) = -k_{obsd}t + C \]

The uncertainty in the k_{obsd} values was estimated to be less than ± 3% from replicate runs. The plots of k_{obsd} vs. [amine] are illustrated in Figure 1 for the ethylaminolysis of 3,4-dinitrophenyl phenyl carbonate (5a) and diphenyl carbonate (5j) to show the effect of the substituent Y on the reaction mechanism.

Effect of Leaving-Group Substituent on Reaction Mechanism. As shown in Figure 1, the plot of k_{obsd} vs. [amine] for the reaction of 3,4-dinitrophenyl phenyl carbonate (5a) is linear and passes through the origin. A similar result has been obtained for the reactions of substrates possessing a strong EWG in the leaving group (e.g., 5b-5f). This indicates that a general base catalysis by a second ethylamine molecule is absent and the contribution of H₂O and/or OH⁻ ion from hydrolysis of ethylamine to k_{obsd} is negligible for the reactions of 5a-5f. In contrast, the plot for the reaction of diphenyl carbonate (5j) curves upward. Similarly curved plots have been observed for the reactions of substrates bearing a weak EWG (e.g., 5g-5i). Such a curved plot is typical of reactions reported previously to proceed through general base catalysis by a second amine molecule.¹,²,¹⁰ Thus, one can propose that ethylamine behaves as a general base catalyst as well as a nucleophile for the reactions of substrates bearing a weak EWG (e.g., 5g-5j).

The contrasting plots shown in Figure 1 for the reactions of 5a and 5j demonstrate convincingly that the electronic nature of the leaving-group-substituent Y governs the reaction mechanism (e.g., absence or presence of general base catalysis). Thus, one can suggest that the reactions of 5a-5j with ethylamine proceed through a stepwise mechanism with one or two intermediates (i.e., T⁺ and/or its deprotonated form T⁻) as shown in Scheme 2 depending on the electronic nature of the substituent Y.

![Scheme 2](image)

**Figure 1.** Plots of k_{obsd} vs. [amine] for ethylaminolysis of 3,4-dinitrophenyl phenyl carbonate (5a) and diphenyl carbonate (5j) in 20 mol % DMSO/80 mol % H₂O at 25.0 ± 0.1 °C.

To account for the contrasting reaction mechanisms, a qualitative energy diagram for the processes that yield T⁻ and PH⁻ from T⁺ is illustrated in Figure 2. It is evident that the energy barrier to form PH⁻ from T⁺ (i.e., the k₂ route in Scheme 2) is dependent on the nucleofugality of the leaving group while that to form T⁻ (i.e., the k₁ route in Scheme 2) is governed by the acidity of the NH⁻ moiety of T⁺. One might expect that the nucleofugality of the leaving aryloxide in substrates 5a-5j would decrease as the substituent Y becomes a weaker EWG or vice versa. Accordingly, the energy barrier for the k₂ route would increase significantly as the substituent Y changes from 3,4-(NO₂)₂ to a weaker EWG such as 3-Cl, 3-COMe, 4-Cl or H. In contrast, the energy barrier for the k₁ route would be little influenced by the electronic nature of the substituent Y. This is because the substituent Y is too far away to affect the acidity of the NH⁻ moiety of T⁺ through an inductive effect. Besides, the aminium moiety of T⁻ is unchanged (i.e., ethylamine). Thus, the energy barrier for the k₁ route would remain nearly constant while that for the k₂ process would increase or decrease depending on the electronic nature of the substituent Y (Figure 2).

It is apparent that the reaction would proceed through the k₂ route when the energy barrier to form PH⁻ from T⁺ is lower than that to form T⁻ (i.e., the dashed lines) but through the deprotonation process (i.e., the k₁ route) when the energy barrier to form T⁻ from T⁺ is lower than that to form PH⁻ (i.e., the solid lines). This idea is consistent with the fact that the reactions of substrates possessing a strong EWG (e.g., 5a-5f) proceed through the k₂ route while those of substrates
bearing a weak EWG (e.g., 5g-5j) proceed through the $k_3$ route.

Calculations of Rate Constants $k_N$, $K_{k_2}$ and $K_{k_3}$. On the basis of the proposed reactions in Scheme 2, $k_{\text{obsd}}$ can be expressed as Eqs. (1) and (2) for the reactions of 5a-5f and for those of 5g-5j, respectively. Thus, the $k_N$ values for the reactions of 5a-5f have been calculated from the slope of the linear plots of $k_{\text{obsd}}$ vs. [amine]. $k_{\text{N}} = k_i k_2 / (k_1 + k_2)$ when $k_1 >> k_2$ while $k_{\text{N}} = k_i$ when $k_1 << k_2$. On the other hand, Eq. (2) can be simplified as Eq. (3) under the assumption, $k_1 >> k_2 + k_i$ [amine]. Thus, one might expect that the plots of $k_{\text{obsd}}$ [amine] vs. [amine] are linear. In fact, as shown in Figure 3, the plot for the reaction of 5j with ethylamine exhibits an excellent linear correlation, indicating that the above assumption is valid for the reaction condition. Similarly linear plots have been obtained for the reactions of 5g-5i. Accordingly, the second-order rate constant $k_i k_2 / k_1$ (i.e., $K_{k_2}$) and the third-order rate constant $k_i k_3 / k_1$ (i.e., $K_{k_3}$) have been calculated from the intercept and the slope of the linear plots, respectively. The rate constants $k_N$, $K_{k_2}$ and $K_{k_3}$ calculated in this way are summarized in Table 1.

\[
\begin{align*}
    k_{\text{obsd}} &= k_N \text{[amine]} & \text{(1)} \\
    k_{\text{obsd}} &= (k_i k_2 \text{[amine]} + k_i k_3 \text{[amine]}^2) / (k_1 + k_2 + k_i \text{[amine]}) & \text{(2)} \\
    k_{\text{obsd}} \text{[amine]} &= K_{k_2} + K_{k_3} \text{[amine]} & \text{(3)}
\end{align*}
\]

Analysis of Brønsted-type Plot. As shown in Table 1, the rate constants decrease as the leaving-group basicity increases. The effect of leaving-group basicity on the second-order rate constants $k_N$ for the reactions of 5a-5f and on $K_{k_2}$ for those of 5g-5j is illustrated in Figure 4. The Brønsted-type plot is nonlinear, e.g., the $\beta_{k_2}$ value changes from −0.32 for the reactions of 5a-5f to −1.73 for those of 5g-5j. Such a nonlinear Brønsted-type plot has often been reported for reactions which proceed through a stepwise mechanism with a change in the RDS. Thus, one can suggest that the nonlinear Brønsted-type plot is due to a change in the RDS, i.e., from formation of $T^+$ to its formation as the incoming amine becomes more basic than the leaving 4-nitrophenoxide ion by ca. 2.3 pK$\alpha$ units.

![Figure 2. A qualitative energy profile for the processes that yield $T^+$ and $PH^+$ from $T^-$](image)

![Figure 3. Plot of $k_{\text{obsd}}$ [amine] vs. [amine] for the reaction of diphenyl carbonate (5j) with ethylamine in 20 mol % DMSO/80 mol % H$_2$O at 25.0 ± 0.1 °C.](image)

![Figure 4. Plot of log $k_i$ (or $K_{k_2}$) vs. pK$\alpha$ of the conjugate acids of Y-substituted phenoxides for the reactions of 5a-5j in 20 mol % DMSO/80 mol % H$_2$O at 25.0 ± 0.1 °C.](image)

Table 1. Summary of Kinetic Data for the Reactions of Phenyl Y-Substituted-Phenyl Carbonates (5a-5j) with Ethylamine in 20 mol % DMSO/80 mol % H$_2$O at 25.0 ± 0.1 °C

<table>
<thead>
<tr>
<th>Y</th>
<th>$pK_{a}$</th>
<th>$k_3$(or $k_1$) M$^{-1}$ s$^{-1}$</th>
<th>$K_{k_2}$ M$^{-1}$ s$^{-1}$</th>
<th>$K_{k_3}$ M$^{-1}$ s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>3.4</td>
<td>5.42</td>
<td>223</td>
<td>-</td>
</tr>
<tr>
<td>5b</td>
<td>4-NO$_2$</td>
<td>7.14</td>
<td>63.9</td>
<td>-</td>
</tr>
<tr>
<td>5c</td>
<td>4-CHO</td>
<td>7.66</td>
<td>23.8</td>
<td>-</td>
</tr>
<tr>
<td>5d</td>
<td>4-CN</td>
<td>7.95</td>
<td>33.3</td>
<td>-</td>
</tr>
<tr>
<td>5e</td>
<td>4-COMe</td>
<td>8.05</td>
<td>16.7</td>
<td>-</td>
</tr>
<tr>
<td>5f</td>
<td>4-COOEt</td>
<td>8.50</td>
<td>14.0</td>
<td>-</td>
</tr>
<tr>
<td>5g</td>
<td>3-Cl</td>
<td>9.02</td>
<td>7.57</td>
<td>3.66</td>
</tr>
<tr>
<td>5h</td>
<td>3-COMe</td>
<td>9.19</td>
<td>4.91</td>
<td>2.02</td>
</tr>
<tr>
<td>5i</td>
<td>4-Cl</td>
<td>9.38</td>
<td>5.24</td>
<td>0.970</td>
</tr>
<tr>
<td>5j</td>
<td>H</td>
<td>9.95</td>
<td>5.20</td>
<td>0.070</td>
</tr>
</tbody>
</table>

\[
k_{\text{obsd}} = (k_i k_2 \text{[amine]} + k_i k_3 \text{[amine]}^2) / (k_1 + k_2 + k_i \text{[amine]}) & \text{(2)}
\]
\[
k_{\text{obsd}} \text{[amine]} = K_{k_2} + K_{k_3} \text{[amine]} & \text{, where } K = k_i / k_1 & \text{(3)}
\]
The pK_α of the conjugate acid of ethylamine is 10.67. Thus, one might expect that the RDS for the current reactions changes at pK_α near 8.4. In fact, the break in the Bronsted-type plot in Figure 4 occurs at pK_α 8.62, indicating that the nonlinear Bronsted-type plot is indeed due to a change in the RDS and that k_ν = k_1 for the reactions of 5a-5f.

To examine the above argument, the k_1 values for the reactions of 5g-5j have been calculated using the following method. Eq. (2) can be converted to Eq. (4) under the assumption, k_2 << k_1[amine]. Thus, the plot of [amine]_kobsd vs. 1/[amine] would be expected to be linear if the assumption is valid. However, as shown in Figure 5, the plot is linear only when the amine concentration is high (e.g., > 0.02 M), indicating that the assumption that k_2 << k_1[amine] is valid only when the amine concentration is high enough. Accordingly, the 1/k_1 values for the reactions of 5g-5j have been estimated from the intercept of the plots of [amine]_kobsd vs. 1/[amine]. More reliable k_1 values have been determined from the nonlinear least-squares fitting of Eq. (2) to the experimental data by using the 1/k_1 values obtained above as input values. The k_1 values determined are summarized in Table 1.

\[
\frac{[\text{amine}]}{k_{\text{obsd}}} = \frac{1}{k_1 + k_2 / k_3 \cdot [\text{amine}]} \quad (4)
\]

The effect of leaving-group basicity on the k_ν values for the reactions of 5a-f and on the k_1 values for those of 5g-j is illustrated in Figure 6. The Bronsted-type plot is linear with \[\beta_\nu = -0.40\]. This supports clearly that k_ν = k_1 for the reactions of 5a-f and that the nonlinear Bronsted-type plot shown in Figure 4 is indeed due to a change in the RDS, i.e., from formation of T^+ (the k_1 step) to its breakdown to the products (the k_2 step) as the substituent Y changes from a strong EWG (e.g., 5a-5f) to a weak EWG (e.g., 5g-5j).

**Conclusions**

The kinetic study on ethylaminolysis of phenyl Y-substituted-phenyl carbonates (5a-5j) has allowed us to conclude the following: (1) The electronic nature of the substituent Y governs the reaction mechanisms as well as the reactivity of the substrates. (2) The reactions of substrates possessing a strong EWG (e.g., 5a-5f) proceed through a stepwise mechanism, in which formation of T^+ is the RDS. (3) The reactions of substrates bearing a weak EWG (e.g., 5g-5j) proceed also through a stepwise mechanism but with two intermediates (e.g., T^+ and T). (4) The electronic nature of the substituent Y affects the energy barrier for the k_1 route. In contrast, the energy barrier for the k_1 route is little influenced by the substituent Y.

**Experimental Section**

**Materials.** Substrates 5a-5j were readily prepared from the reactions of phenyl chloroformate with Y-substituted phenol in the presence of triethylamine in anhydrous ether as reported previously.12 The crude products were purified by column chromatography and the purity was checked by their melting points and 1H NMR spectra. Ethylamine hydrochloride and other chemicals were of the highest quality available. Doubly glass distilled water was further boiled and cooled under nitrogen just before use.

**Kinetics.** Kinetic study was performed using a UV-Vis spectrophotometer for slow reactions (e.g., \(t_{1/2} > 10\) s) and a stopped-flow spectrophotometer for fast reactions (e.g., \(t_{1/2} < 10\) s) equipped with a constant-temperature circulating bath. All the reactions were carried out under pseudo-first-order conditions in which the amine concentration was kept at least 20 times greater than the substrate concentration. Typically, the reaction was initiated by adding 5 μL of a 0.02 M 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 ethylamine. The ethylamine stock solution of ca. 0.2 M was prepared in a 25.0 mL volumetric flask by adding 2 equiv. of ethylamine hydrochloride and 1 equiv. of...

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**Figure 5.** Plot of [amine]_kobsd vs. 1/[amine] for the reaction of diphenyl carbonate (5j) with ethylamine in 20 mol % DMSO/80 mol % H_2O at 25.0 ± 0.1 °C.

**Figure 6.** Plot of log k_1 vs. pK_α for the reactions of phenyl Y-substituted-phenyl carbonates (5a-5j) with ethylamine in 20 mol % DMSO/80 mol % H_2O at 25.0 ± 0.1 °C.
NaOH solution to make a self-buffered solution. The reactions were followed by monitoring the appearance of Y-substituted phenoxide. Reactions were followed generally for 9-10 half-lives and $k_{\text{obsd}}$ were calculated using the equation, $ln (A - A_0) vs t$.

**Acknowledgments.** This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2012-R1A1B3001637).

**References**


