Kinetics and Mechanism of Azidolysis of Y-Substituted Phenyl Benzoates

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Second-order rate constants (k0) have been measured spectrophotometrically for reactions of Y-substituted phenyl benzoates (1a-h) with azide ion (N3-) in 80 mol % H2O/20 mol % DMSO at 25.0 ± 0.1°C. The Brønsted-type plot for the azidolysis exhibits a downward curvature, i.e., the slope (k0) changes from -0.97 to -20 as the basicity of the leaving group decreases. The pKz (defined as the pKa at the center of the Brønsted curvature) is 4.8, which is practically identical to the pKa of the conjugate acid of N3- ion (4.73). Hammel plots correlated with σ and σ constants exhibit highly scattered points for the azidolysis. On the contrary, the corresponding Yuka-Tsuno plot results in an excellent linear correlation with ρ = 2.45 and r = 0.40, indicating that the leaving group departs in the rate-determining step. The curved Brønsted-type plot has been interpreted as a change in the rate-determining step in a stepwise mechanism. The microscopic rate constants (k1 and k2/k1 ratio) have been calculated for the azidolysis and found to be consistent with the proposed mechanism.

Key Words: Acyl-transfer reaction, Azidolysis. Brønsted-type plot, Hammel plot, Yuka-Tsuno plot

Introduction

Nucleophilic substitution reactions of carbonyl, sulfonyl, and phosphonyl derivatives have been intensively investigated due to the importance in biological processes as well as in synthetic applications. Reactions of carboxylic esters with neutral nucleophiles (e.g., amines and pyridines) are now firmly understood to proceed through a zwitterionic tetrahedral intermediate T with a change in the rate-determining step (RDS) on the basis of curved Brønsted-type plots found for reactions of esters with a good leaving group. The RDS has generally been suggested to change from breakdown of T to its formation as the attacking amine becomes more basic than the leaving group by 4 to 5 pKa units.

However, reactions with anionic nucleophiles (e.g., OH- and aryloxides) have not been clearly understood. In a series of important studies, Williams and coworkers have concluded that reactions of 4-nitrophenyl acetate with substituted phenoxides proceed through a concerted mechanism. The evidence consisted mainly of the absence of a break or curvature in the Brønsted-type plot when the pKa of the aryloxides corresponded to that of the leaving 4-nitrophenoxide. The concerted mechanism has further been supported through structure-reactivity correlations reported by Jencks, Rossi, and Castro, as well as the study of kinetic isotope effect by Hengge and Marcus analysis by Guthrie.

On the contrary, Buncel et al. have concluded that acyl-transfer to aryloxides occurs through a stepwise mechanism with formation of an adduct intermediate being the RDS on the basis of Hammel plots exhibiting rather poor correlation with σ constants but better correlation with σ constants. A similar result has been reported for reactions of aryldiphosphinoranes with OH- and for those of aryldimethylphosphinates with ethoxide ion. Furthermore, we have presented the first spectroscopic evidence, along with kinetic evidence, for an addition intermediate in the reaction of a cyclic sulfinate ester with sodium ethoxide in anhydrous ethanol.

We have recently performed nucleophilic substitution reactions of ary benzoxoates and thiobenzoates with OH- and CN- ions and reported that the reactions proceed through a stepwise mechanism. We have extended our study to reactions of Y-substituted phenyl benzoates (1a-h) with N3- ion to get further information on the reaction mechanism involving anionic nucleophiles.

Results and Discussion

Reactions of 1a-h with N3- ion proceeded with quantitative liberation of Y-substituted phenoxide ion and/or its conjugate acid. The kinetic study was performed under pseudo-first-order conditions, e.g., the N3- ion concentration in excess over the substrate concentration. All the reactions obeyed first-order kinetics. Pseudo-first-order rate constants (kobs) were calculated from the equation ln(Ao - At) = -kobs t + C. The plots of kobs vs. N3- ion concentration are linear. Thus, the apparent second-order rate constants (k2) were determined from the slope of the linear plots of kobs vs. [N3-], and summarized in Table 1.

Brønsted-type Correlation. Table 1 shows that the apparent second-order rate constant (k2) is significantly dependent on the leaving group basicity, e.g., the k2 value decreases from 0.224 M-1s-1 to 2.34 × 102 and 6.42 × 103 M-1s-1 as the pKa of the conjugate acid of the leaving aryloxide increases from 4.11 to 7.14 and 8.98, respectively.

The effect of leaving group basicity on reactivity is illustrated in Figure 1. Esters with 2,4-dinitrophenoxide as a
Table 1: Summary of Apparent Second-order and Microscopic Rate Constants for Reactions of Y-Substituted Phenyl Benzoxates (1a-h) with N3 in 20 mol % DMSO/80 mol % H2O at 25.0 ± 0.1 °C

<table>
<thead>
<tr>
<th>Y</th>
<th>$k_2$ (Y-PhOH)</th>
<th>$10^2 k_3/M^2s^{-1}$</th>
<th>$10^2 k_3/M^2s^{-1}$</th>
<th>$10^2 k_3/k_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a, 2,4-(NO2)2</td>
<td>4.11</td>
<td>224 ± 3</td>
<td>383</td>
<td>340</td>
</tr>
<tr>
<td>1b, 3,4-(NO2)2</td>
<td>5.42</td>
<td>124 ± 11</td>
<td>496</td>
<td>33.3</td>
</tr>
<tr>
<td>1c, 4-NO2</td>
<td>7.14</td>
<td>2.34 ± 0.09</td>
<td>151</td>
<td>1.58</td>
</tr>
<tr>
<td>1d, 4-CHO</td>
<td>7.66</td>
<td>0.479 ± 0.049</td>
<td>76.8</td>
<td>0.628</td>
</tr>
<tr>
<td>1e, 4-CN</td>
<td>7.95</td>
<td>0.993 ± 0.062</td>
<td>266</td>
<td>0.375</td>
</tr>
<tr>
<td>1f, 4-COCH3</td>
<td>8.05</td>
<td>0.232 ± 0.040</td>
<td>74.0</td>
<td>0.314</td>
</tr>
<tr>
<td>1g, 4-COOEt</td>
<td>8.50</td>
<td>0.151 ± 0.006</td>
<td>107</td>
<td>0.142</td>
</tr>
<tr>
<td>1h, 3-CHO</td>
<td>8.98</td>
<td>0.064 ± 0.012</td>
<td>106</td>
<td>0.0605</td>
</tr>
</tbody>
</table>

Figure 1: Bronsted-type plots for azidolysis of Y-substituted phenyl benzoxates (●, 1a-h) and cinnamates (□) at 25.0 ± 0.1 °C. The identity of the points is given in Table 1. The data for the azidolysis of aryl cinnamates were taken from ref. 20.

leaving group (e.g., 1a) have often exhibited a negative deviation from Bronsted-type plot. Jencks et al. have attributed such negative deviation to steric hindrance caused by the presence of a NO2 group at the 2-position of the leaving arylxide. The effect of steric hindrance has been suggested to be 0.12 log units. Thus, the point for the reaction of 1a in Figure 1 has been corrected by 0.12 log units.

As shown in Figure 1, the Bronsted-type plot for the azidolysis of 1a-h exhibits a downward curvature. The current Bronsted-type plot can be compared with the one reported for azidolysis of Y-substituted phenyl cinnamates (Y = 3,4-(NO2)2, 4-NO2, 3-NO2, and 4-Cl). Suh et al. have reported a linear Bronsted-type plot with $\beta_2 = -0.95$ for the reactions of aryl cinnamates with $N_3$ and concluded that the reactions proceed through a stepwise mechanism with the second step being the RDS on the basis of the magnitude of the $\beta_2$ value. The Bronsted-type plot shown in Figure 1 is almost identical to the one reported by Suh et al. when the point for the reaction of 1a is excluded (see the open circles in Figure 1). Thus, one can suggest that the current azidolysis proceeds through a stepwise mechanism as shown in Scheme 1, and a change in the RDS is responsible for the curved Bronsted-type plot.

Hammett Correlations. To examine the above argument, Hammett plots have been constructed using the kinetic data in Table 1. Hammett correlations with $\sigma'$ and $\sigma$ constants have often been found to be useful to determine reaction mechanisms, especially to get information on the RDS. For example, one might expect a better Hammett correlation with $\sigma'$ than $\sigma$ constants if the departure of the leaving group occurs in the RDS, or $\sigma'$ constants would result in a better linear correlation than $\sigma$ constants if the leaving group departs after the RDS.

As shown in Figures 2A and 2B. $\sigma'$ constants result in only slightly better correlation than $\sigma$ constants (i.e., $R^2 = 0.979$ for $\sigma'$ and $R^2 = 0.971$ for $\sigma$ constants). Besides, both Hammett plots exhibit highly scattered points. Thus, one cannot obtain any conclusive information on the reaction mechanism from these Hammett plots.

Yukawa-Tsuno Correlation. We have recently shown that the dual-parameter Yukawa-Tsuno equation (eq. 1) is highly effective to elucidate ambiguities in the reaction mechanism of benzoyl-, sulfonyl-, and phosphinyl-transfer reactions. Thus, a Yukawa-Tsuno plot has been constructed for the reactions of 1b-h with $N_3$. As shown in Figure 3, the Yukawa-Tsuno plot exhibits an excellent linear correlation ($i.e., R^2 = 0.999$) with $\rho = 2.45$ and $r = 0.40$.

\[
\log k/k_0 = \rho (\sigma' + r(\sigma - \sigma'))
\]

(1)

The $r$ value in the Yukawa-Tsuno equation represents the resonance demand of the reaction center or the extent of

![Scheme 1](image)

![Figure 2](image)
resonance contribution. The fact that $r = 0.40$ in the current azidolysis indicates that a partial negative charge develops on the O atom of the leaving aryloxide in the rate-determining transition state, which can be delocalized on the substituent Y through resonance interaction. Thus, the linear Yukawa-Tsuno plot with $r = 0.40$ indicates clearly that departure of the leaving group occurs in the RDS for the azidolysis of 1b-h.

One can suggest two transition-state (TS) structures, TS$_1$ and TS$_2$. TS$_1$ represents the TS for a concerted mechanism, in which the N-C bond formation and C-OAr bond rupture occur at the same time. TS$_2$ corresponds to the TS for a stepwise mechanism, where the N-C bond formation is complete and the leaving group departs partially in the TS of the RDS. Departure of the leaving group is advanced partially for both TS$_1$ and TS$_2$. However, the $p$ value of 2.45 in Figure 3 is typical for reactions which proceed through rate-determining breakdown of an intermediate. Thus, one can suggest that the azidolysis of 1b-h proceeds through TS$_2$.

**Dissection of $k_5$ into $k_1$ and $k_2/k_4$ Ratio.** The nonlinear Bronsted-type plot shown in Figure 1 can be analyzed using a semiempirical equation (eq. 2), in which $\beta_{g1}$ and $\beta_{g2}$ represent the slope of the Bronsted-type plot at the low and the high $pK_a$ region, respectively. The curvature center of the curved Bronsted-type plot has been defined as $pK_a^b$ (i.e., the $pK_a$ where the RDS changes). The $k_5^o$ refers the $k_5$ value at $pK_a^o$. The parameters determined from the fitting of eq. 2 to the experimental points are $\beta_{g1} = -0.20$, $\beta_{g2} = -0.97$, and $pK_a^o = 4.8$ for the reactions of 1a-h with N$_2$.

$$\log (k_5/k_4)^o = \beta_{g1}(pK_a - pK_a^o) + \log [(1 + \alpha/2)]$$

where $\log \alpha = (\beta_{g2} - \beta_{g1})(pK_a - pK_a^o)$

(2)

The $pK_a^o$ of 4.8 is practically identical to the $pK_a$ of the conjugate acid of N$_2$ (4.73). This indicates that the nucleofugality of azide is similar to that of the isobasic aryloxide. This is contrasting to the report by Suh et al. They performed azidolysis of aryloxinamid and concluded that azide is a better nucleofug than the aryloxides employed in their study. Such conclusion was possible since N$_2$ is a 0.7 $pK_a$ units less basic than the least basic leaving aryloxide (i.e., 3,4-dinitrophenoxide).

The microscopic rate constants (i.e., $k_1$ and $k_2/k_4$ ratios) associated with the reactions of 1a-h with N$_2$ have been calculated using the method reported by Castro et al. on the assumption that the reactions proceed through a stepwise mechanism as shown in Scheme 1. The rate equation and the apparent second-order rate constant ($k_i$) for the current reactions can be expressed as eqs. (5) and (6). Eq. (4) can be simplified to eq. (5) or (6). Then, $\beta_{g1}$ and $\beta_{g2}$ can be expressed as eqs. (7) and (8), respectively.

$$\text{Rate} = k_0 [\text{substrate}][\text{N}_2]$$

(3)

$$k_5 = k_1(k_2 + k_4)$$

(4)

$$k_5 = k_2/k_4$$ when $k_2 < k_4$ (5)

$$k_5 = k_1$$ when $k_2 > k_4$ (6)

$$\beta_{g1} = d \log k_1/d(pK_a)$$

(7)

$$\beta_{g2} = d \log (k_2/k_4)/d(pK_a)$$

(8)

Eq. (8) can be rearranged as eq. (9). Integral of eq. (9) from $pK_a^o$ results in eq. (10). Since $k_2 = k_4$ at $pK_a^o$, the term $(\log k_2/k_4)_{pK_a^o}$ is zero. Therefore, one can calculate the $k_2/k_4$ ratios for the reactions of 1a-h from eq. (10) using $pK_a = 4.8$, $\beta_{g1} = -0.20$ and $\beta_{g2} = -0.97$.

$$\beta_{g2} - \beta_{g1} = \log (k_2/k_4)/d(pK_a)$$

(9)

$$\log (k_2/k_4)_{pK_a} = (\beta_{g2} - \beta_{g1})(pK_a - pK_a^o)$$

(10)

The $k_1$ values have been determined from eq. (11) using the $k_0$ values in Table 1 and the $k_2/k_4$ ratios calculated above. The $k_1$ and $k_2/k_4$ ratios obtained in this way are summarized in Table 1 and illustrated graphically in Figure 4.

$$k_5 = k_1(k_2 + k_4) = k/k_4 + 1$$

(11)

Table 1 shows that $k_5/k_4 > 1$ for the reaction of 1a but $k_5/k_4 < 1$ for the reactions of 1b-h. This result is consistent with the preceding proposal that the azidolysis of 1a-h proceeds through a stepwise mechanism with a change in the RDS, i.e., the RDS is breakdown of the addition intermediate for the azidolysis of 1b-h but its formation for the
As shown in the inset of Figure 4, the Bronsted-type plot for the k1 values results in a poor correlation with \( \beta_k = -0.15 \), indicating that the effect of leaving group basicity on k1 is insignificant for the current azidolysis. On the contrary, one might expect that the effect of leaving group basicity is significant for the \( k_2/k_{-1} \) ratio, since \( k_2 \) would be strongly dependent on the leaving group basicity while \( k_{-1} \) for \( \text{N}_3^- \) ion would remain nearly constant. In fact, as shown in Figure 4, the plot of log \( k_2/k_{-1} \) vs \( pK_a \) results in a large negative slope (-0.77). Thus, the microscopic rate constants are also consistent with the proposal that the current azidolysis proceeds through a stepwise mechanism with a change in the RDS.

Conclusions

The current study has allowed us to conclude the following: (1) The Bronsted-type plot for the azidolysis of 1a-h exhibits a downward curvature, i.e., \( \beta_p = -0.20 \) and \( \beta_p = -0.97 \). (2) The Hammett plots correlated with \( \sigma \) or \( \sigma^+ \) constants for the reactions of 1b-h do not give any conclusive information on the reaction mechanism, since both plots show highly scattered points. (3) The corresponding Yukawa-Tsuno plot results in excellent linearity with \( \rho = 2.45 \) and \( r = 0.40 \), indicating that the leaving group departure occurs in the RDS. (4) The current azidolysis proceeds through a stepwise mechanism with a change in the RDS. (5) The microscopic rate constants (\( k_1 \) and \( k_2/k_{-1} \)) calculated are consistent with the proposed mechanism.

Experimental Section

Materials. Y-Substituted phenyl benzoates (1a-h) were readily prepared as reported previously \(^{16} \) from the reactions of Y-substituted phenol with benzoyl chloride under the presence of triethylamine in anhydrous ether and purified by column chromatography. The purity was checked by their mps and spectral data such as \(^1\)H NMR and IR spectra.

Kinetics. The kinetic study was performed with a Scinco S-3100 Model UV-vis spectrophotometer equipped with a constant temperature circulating bath. The reactions were followed by monitoring the appearance of Y-substituted phenoxide. Due to the low solubility of the substrates in pure water, aqueous DMSO (80 mol %, H2O/20 mol % DMSO) was used as the reaction medium. Doubly glass distilled water was further boiled and cooled under nitrogen just before use.

All the reactions were carried out under pseudo-first-order conditions in the presence of excess azide ion. Typically, the reaction was initiated by adding 5 \( \mu \)L of a 0.01 M of substrate solution in MeCN by a 10 \( \mu \)L gastight syringe to a 10 mm quartz UV cell containing 2.50 mL of the thermostated reaction mixture made up of solvent and an aliquot of the \( \text{NaN}_3 \) stock solution. The stock solution of \( \text{NaN}_3 \) was prepared in 0.1 M triethyl amine buffer solution (pH = 10.72).

Products Analysis. Y-Substituted phenoxides (and/or the conjugate acids) were 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 sample under the same reaction conditions.

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References
