K⁺ Ion Catalysis in Nucleophilic Displacement Reaction of Y-Substituted-Phenyl Picolinates with Potassium Ethoxide: Effect of Substituent Y on Reactivity and Transition State Structure

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Pseudo-first-order rate constants ($k_{\text{obsd}}$) have been measured spectrophotometrically for the nucleophilic substitution reaction of Y-substituted-phenyl picolinates (7a-f) with potassium ethoxide (EtOK) in anhydrous ethanol at 25.0 ± 0.1 °C. The plot of $k_{\text{obsd}}$ vs. [EtOK] curves upward while the plot of $k_{\text{obsd}}/[\text{EtO}^-]_\text{eq}$ vs. $[\text{EtO}^-]_\text{eq}$ is linear with a positive intercept in all cases. Dissection of $k_{\text{obsd}}$ into $k_{\text{intra}}$ and $k_{\text{cat}}$ (i.e., the second-order rate constants for the reactions with the dissociated EtO⁻ ion and ion-paired EtOK, respectively) has revealed that the ion-paired EtOK is more reactive than the dissociated EtO⁻. The σ⁺ constants result in a much better Hammett correlation than σ⁻ constants, indicating that the reaction proceeds through a stepwise mechanism in which the leaving group departs after the rate-determining step (RDS). K⁺ ion catalyzes the reaction by increasing the electrophilicity of the reaction center through formation of a cyclic transition state (TS). The catalytic effect decreases as the substituent Y becomes a stronger electron-withdrawing group (EWG). Development of a positive charge on the N atom of the picolinyl moiety through resonance interactions is responsible for the decreasing K⁺ ion catalysis.

Key Words: Aryl picolinates, Metal-ion catalysis, Hammett plot, Electrophilicity, Nucleofugality

Introduction

Nucleophilic substitution reactions of esters with amines have been intensively been investigated due to their importance in biological processes as well as in synthetic applications. The reactions have been reported to proceed through a concerted mechanism or via a stepwise pathway, in which the rate-determining step (RDS) is dependent on the basicity of the incoming amine and the leaving group. In general, the RDS changes from breakdown of a tetrahedral intermediate (T') to its formation as the amine becomes more basic than the leaving group by 4 to 5 pKₐ units. Reactions of esters with anionic nucleophiles have also been carried out intensively to investigate the reaction mechanism. Interestingly, alkali metal ions have been reported to behave as a Lewis acid catalyst or as an inhibitor in nucleophilic substitution reactions of esters with alkali-metal ethoxides (EtOM; M = K, Na, Li) depending on the nature of the electrophilic center (e.g., P=O, P=S, SO₂, C=O). Buncel et al. have reported that the reaction of 4-nitrophenyl diphenylphosphinate (1) with EtOM is catalyzed by M⁺ ions and the catalytic effect increases as the size of M⁺ ions decreases (e.g., K⁺ > Na⁺ > Li⁺). In contrast, we have shown that the corresponding reaction of 4-nitrophenyl diphenylphosphonothioate (2) is inhibited by Li⁺ ion but is catalyzed by K⁺ ion and the K⁺ ion complexed by 18-crown-6-ether (18C6), indicating that the role of M⁺ ions is dependent on the electronic nature of the reaction centers (e.g., P=O vs. P=S). Alkali metal ions have also been reported to catalyze the reactions of 4-nitrophenyl benzoate (3) and 5-nitro-8-quinolyl benzoate (4) with EtOM (M = K, Na, Li) in anhydrous ethanol. The catalytic effect decreases in the order K⁺ > Na⁺ > Li⁺ for the reaction of 3 but in the order Na⁺ > K⁺ > Li⁺ for the reaction of 4. Thus, M⁺ ions have been reported to catalyze the reactions of 3 and 4 by increasing either the electrophilicity of the reaction center through formation of cyclic transition state (TS) or the nucleofugality of the leaving group via TSII on the basis of the contrasting M⁺ ion effects.

In contrast, we have reported that the rate of reactions of 4-nitrophenyl salicylate (5) with EtOM decreases steeply as...
the concentration of EtOM increases. More interestingly, addition of inert salts such as LiSCN and KSCN to the reaction mixture causes a significant decrease in reactivity. Thus, M⁺ ions have been suggested to act as a strong inhibitor by forming a cyclic complex 5M, which inhibits the subsequent reaction to produce α-oxoketene 6.

M⁺ ions have been reported to catalyze the reaction of 4-nitrophenyl picolinate (7a) with EtOM and the catalytic effect increases in the order Li⁺ > K⁺ > Na⁺. M⁺ ions would catalyze the reaction by increasing either the electrophilicity of the reaction center or the nucleofugality of the leaving group. However, the enhanced nucleofugality would be effective only for reactions in which leaving-group departure occurs in the RDS but would be ineffective for reactions in which departure of the leaving group occurs after the RDS. Thus, detailed information on the reaction mechanism is necessary to investigate the role of M⁺ ions. Our study has now been extended to the reaction of Y-substituted-phenyl picolinates (7b-f) with EtOK in anhydrous ethanol to investigate the reaction mechanism including the nature of RDS. We wish to report that the reaction proceed through a stepwise mechanism in which expulsion of the leaving group occurs after the RDS and that K⁺ ion catalyzes the reaction by increasing the electrophilicity of the reaction center as shown in Scheme 1.

**Results and Discussion**

The kinetic study was performed spectrophotometrically under pseudo-first-order conditions in which the concentration of EtOK was in large excess over that of substrates 7b-f. All the reactions in this study obeyed pseudo-first-order kinetics and proceeded with quantitative liberation of Y-substituted-phenoxide ion. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation, ln \((A_\infty - A_t)\) = −kt + C. The correlation coefficient for the linear plots of ln \((A_\infty - A_t)\) vs. t was better than 0.9995 in all cases. It is estimated from replicate runs that the uncertainty in the k_{obsd} values is less than ± 3%. The kinetic conditions and results are summarized in Table 1.

As shown in Figure 1, the plots of k_{obsd} vs. [EtOK] curve upward for the reactions of 4-cyanophenyl picolinate (7b) and 4-acetylphenyl picolinate (7c) with EtOK. Similarly curbed plots were obtained for the reactions of the other aryl picolinates 7d-f (Figures not shown). Such upward curvature is typical for nucleophilic substitution reactions of esters with alkali-metal ethoxide (EtOM), in which alkali-metal ion behaves as a Lewis acid catalyst and the ion-paired EtOM is more reactive than the dissociated EtO⁻. In fact, we have previously reported that M⁺ ions catalyze the reaction of 4-nitrophenyl picolinate (7a) with EtOM (M = K, Na, and Li). To examine the above idea that K⁺ ion catalyzes the reaction, the k_{obsd} values have been dissected into k_{EtO⁻} and k_{EtOK} (i.e., the second-order rate constants for the reactions with the dissociated EtO⁻ ion and ion-paired EtOK, respectively). It was reported that EtOK exists as dimers or other aggregates in a high

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**Table 1.** Kinetic Data for the Reactions of Y-Substituted-Phenyl Picolinates (7b-f) with EtOK in Anhydrous Ethanol at 25.0 ± 0.1 °C

<table>
<thead>
<tr>
<th>[EtOK]/mM</th>
<th>k_{obsd}/s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>7b</td>
<td>7c</td>
</tr>
<tr>
<td>1.15</td>
<td>0.44</td>
</tr>
<tr>
<td>2.25</td>
<td>1.14</td>
</tr>
<tr>
<td>3.98</td>
<td>2.48</td>
</tr>
<tr>
<td>5.44</td>
<td>3.86</td>
</tr>
<tr>
<td>6.64</td>
<td>5.11</td>
</tr>
<tr>
<td>7.85</td>
<td>6.52</td>
</tr>
<tr>
<td>8.97</td>
<td>7.85</td>
</tr>
<tr>
<td>9.96</td>
<td>9.10</td>
</tr>
</tbody>
</table>

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**Figure 1.** Plots of k_{obsd} vs. [EtOK] for the reaction of 4-cyanophenyl picolinate 7b (●) and 4-acetylphenyl picolinate 7c (○) with EtOK in anhydrous EtOH at 25.0 ± 0.1 °C.
concentration (e.g., [EtOK] > 0.1 M). However, EtOK was suggested to exist mainly as the dissociated and ion-paired species in a low concentration (e.g., [EtOK] < 0.1 M). Since [EtOK] << 0.1 M in this study, one might expect that both the dissociated EtO^- and ion-paired EtOK would react with substrates 7a-f as shown in Scheme 2.

Thus, Eq. (1) can be derived on the basis of the kinetic results and the reactions proposed in Scheme 2. Under pseudo-first-order kinetic conditions (e.g., [EtOK] >> [7]), k_diss can be expressed as Eq. (2). It is noted that the dissociation constant \( k_d = [\text{EtOK}]_{\text{eq}}/\text{EtO}^- \) and \( [\text{EtOK}]_{\text{eq}} = [\text{EtO}^-] \) at equilibrium. Accordingly, Eq. (2) can be converted to Eq. (3). The \([\text{EtO}^-]_{\text{eq}}\) and \([\text{EtOK}]_{\text{eq}}\) values can be calculated from the reported \( k_d \) value of 11.1 × 10^{-3} M for EtOK and the initial concentration of EtOK using Eqs. (4) and (5).

\[
\text{Rate} = k_{\text{EOS}}[\text{EtO}^-]_{\text{eq}}[7] + k_{\text{EOK}}[\text{EtOK}]_{\text{eq}}[7] \\
k_{\text{diss}} = k_{\text{EOS}}[\text{EtO}^-]_{\text{eq}} + k_{\text{EOK}}[\text{EtOK}]_{\text{eq}} \\
k_{\text{diss}}/[\text{EtO}^-]_{\text{eq}} = k_{\text{EOS}} + k_{\text{EOK}}/[\text{EtOK}]_{\text{eq}} \\
[\text{EtOK}]_{\text{eq}} = [\text{EtO}^-]_{\text{eq}}/[K_d] \\
[\text{EtO}^-]_{\text{eq}} = [-K_d + (K_d^2 + 4K_d)^{1/2}]/2
\]

One might expect that the plot of \( k_{\text{diss}}/[\text{EtO}^-]_{\text{eq}} \) vs. \([\text{EtO}^-]_{\text{eq}}\) would be linear if the reaction proceeds as proposed in Scheme 2. In fact, the plots shown in Figure 2 exhibit excellent linear correlations with positive intercepts, indicating that the derived equations based on the reactions proposed in Scheme 2 are correct. Accordingly, one can calculate the \( k_{\text{EOS}} \) and \( k_{\text{EOK}}/K_d \) values from the intercept and the slope of the linear plot, respectively. The \( k_{\text{EOS}} \) value can be calculated from the above \( k_{\text{EOS}}/K_d \) values and the reported \( K_d \) value for EtOK. In Table 2 are summarized the calculated \( k_{\text{EOS}} \) and \( k_{\text{EOK}}/K_d \) values for the reactions of 7a-f.

As shown in Table 2, the \( k_{\text{EOS}} \) value is much larger than the \( k_{\text{EOK}}/K_d \) value in all cases. This supports the preceding idea that the ion-paired EtOK is more reactive than the dissociated EtO^-.

Deduction of Reaction Mechanism. K^+ ion would catalyze the reaction of 7a-f by increasing the nucleofugality of the leaving Y-substituted-phenoxide or by increasing the electrophilicity of the reaction center. However, enhanced nucleofugality of the leaving group cannot be a cause of the K^+ ion catalysis for reactions in which departure of the leaving group occurs after the rate-determining step (RDS).

If the current reaction proceeds through a concerted mechanism, a partial negative charge would develop at the O atom of the leaving group. Since such negative charge could be delocalized to the substituent Y through resonance interactions, Hammett correlation with \( \sigma^- \) constants should result in a better correlation than \( \sigma^+ \) constants. In contrast, if the current reaction proceeds through a stepwise mechanism, departure of the leaving group would not be advanced in the transition state (TS). Because EtO^- is much more basic and a poorer nucleofuge than Y-substituted-phenoxide. Accordingly, no negative charge would develop on the O atom of the leaving group if the reaction proceeds through a stepwise mechanism. In this case, \( \sigma^- \) constants should give a better Hammett correlation than \( \sigma^- \) constants.

To deduce the reaction mechanism, Hammett plots have been constructed using \( \sigma^- \) and \( \sigma^+ \) constants. As shown in Figure 3(a), \( \sigma^- \) constants result in a much better linear correlation than \( \sigma^- \) constants (the inset) for the reaction with the dissociated EtO^-.

Table 2. Summary of Second-Order Rate Constants (\( k_{\text{EOS}} \) and \( k_{\text{EOK}}/K_d \)) Calculated from Ion-pairing Treatment of the Kinetic Data for the Reactions of Y-Substituted-Phenyl Picolinites (7a-f) with EtOK in Anhydrous EtOH at 25.0 ± 0.1°C

<table>
<thead>
<tr>
<th>Y</th>
<th>( k_{\text{EOS}}/M^{-1}s^{-1} )</th>
<th>( k_{\text{EOK}}/M^{-1}s^{-1} )</th>
<th>( k_{\text{EOS}}/K_d )</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>4-NO_2</td>
<td>486</td>
<td>3370</td>
</tr>
<tr>
<td>7b</td>
<td>4-CN</td>
<td>215</td>
<td>2110</td>
</tr>
<tr>
<td>7c</td>
<td>4-COMe</td>
<td>61.5</td>
<td>673</td>
</tr>
<tr>
<td>7d</td>
<td>4-COOEt</td>
<td>49.7</td>
<td>678</td>
</tr>
<tr>
<td>7e</td>
<td>4-CI</td>
<td>11.1</td>
<td>377</td>
</tr>
<tr>
<td>7f</td>
<td>H</td>
<td>1.43</td>
<td>114</td>
</tr>
</tbody>
</table>

*The kinetic data for the reaction of 7a were taken from ref. 12.*

Figure 2. Plots of \( k_{\text{diss}}/[\text{EtO}^-]_{\text{eq}} \) vs. \([\text{EtO}^-]_{\text{eq}}\) for the reactions of 4-cyanophenyl picolinate (7b, ○) and 4-acetylphenyl picolinate (7c, O) with EtOK in anhydrous EtOH at 25.0 ± 0.1°C.
departure of the leaving group is involved in the RDS either for a concerted mechanism or for a stepwise pathway. Thus, one can conclude that the current reaction proceeds through a stepwise mechanism in which expulsion of the leaving group occurs after the RDS.

**TS Structures and Role of K⁺ Ion.** Three different TS structures are plausible to explain the catalytic effect exerted by K⁺ ion. TS_{III} could increase the nucleofugality of the leaving group, while TS_{IV} and TS_{V} could enhance the electrophilicity of the reaction center. Since expulsion of the leaving group occurs after the RDS in this study, the reaction cannot be catalyzed by increasing the nucleofugality of the leaving group through TS_{III}. One can also exclude a possibility that K⁺ ion catalyzes the reaction through TS_{IV}, in which the K⁺ and EtO⁻ ions in TS_{IV} are not ion-paired species. This is because the current reaction is catalyzed by the ion-paired EtOK but not by the dissociated K⁺. Thus, one can conclude that K⁺ ion catalyzes the reaction of 7a-f by increasing the electrophilicity of the reaction center through a TS structure similar to TS_{V}.

The effect of the leaving-group substituent Y on the catalytic effect exerted by K⁺ ion (i.e., the \( k_{\text{EtOK}}/k_{\text{EtO}} \) ratio) is illustrated in Figure 4. One can see that the \( k_{\text{EtOK}}/k_{\text{EtO}} \) ratio decreases linearly as the substituent Y in the leaving group becomes a stronger EWG, although the correlation coefficient of the linear plot is not very good (\( R^2 = 0.958 \)). The \( k_{\text{EtOK}}/k_{\text{EtO}} \) ratio should have resulted in a good correlation with the electronic nature of the substituent Y if the reaction is catalyzed by increasing the nucleofugality of the leaving group through TS_{III}. In contrast, if the reaction is catalyzed by increasing the electrophilicity through TS_{V}, the correlation of \( k_{\text{EtOK}}/k_{\text{EtO}} \) ratio with the electronic nature of the substituent Y would not be excellent because of the long distance between the substituent Y and the N atom of the picolinyl moiety of TS_{V}. Thus, the poor correlation shown in Figure 4 clearly supports the proposed TS structure (i.e., TS_{V}) and reaction mechanism.

**Conclusions**

The kinetic study on the reaction of 7a-f with EtOK has allowed us to conclude the following: (1) Dissection of \( k_{\text{obsd}} \) into \( k_{\text{EtO}} \) and \( k_{\text{EtOK}} \) has revealed that the ion-paired EtOK is more reactive than the dissociated EtO⁻. (2) The Hammett plots correlated with \( \sigma^+ \) constants result in much better linearity than those correlated with \( \sigma^- \) constants, indicating that the reaction proceeds through a stepwise mechanism in which expulsion of the leaving group occurs after the RDS.
K+ ion catalyzes the reaction by increasing the electrophilicity of the reaction center through TS, (4) The catalytic effect decreases as the substituent Y becomes a stronger EWG. (5) Development of a positive charge on the N atom through resonance interactions is responsible for the decreasing K+ ion catalysis.

Experimental Section

Materials. Y-Substituted-phenyl picolinates (7a-f) were readily prepared by adding Y-substituted-phenol to the solution of picolinyl chloride in the presence of triethylamine in anhydrous diethyl ether as reported previously. The crude products were purified by column chromatography (silica gel, methylene chloride/n-hexane 50/50). Their purity was checked by their melting points and 1H NMR spectra.

Kinetics. The kinetic study was carried out with a UV-vis spectrophotometer for slow reactions (e.g., t1/2 > 10 s) or a stopped-flow spectrophotometer for fast reactions (e.g., t1/2 ≤ 10 s) equipped with a constant temperature circulating bath to maintain the temperature in the reaction cell at 25.0 ± 0.1 °C. The reaction was followed by monitoring the appearance of Y-substituted-phenoxide ion. All reactions were carried out under pseudo-first-order conditions in which EtOK concentration was at least 20 times greater than the substrate concentration. The stock solution of EtOK was prepared by dissolving freshly cleaned potassium metal in anhydrous ethanol under nitrogen and stored in the refrigerator. The concentration of EtOK was determined by titration with potassium hydrogen phthalate. The anhydrous ethanol was further dried over magnesium and was distilled under N2 just before use. All solutions were prepared freshly just before use under nitrogen and transferred by gas-tight syringes. Typically, the reaction was initiated by adding 5 µL of a 0.01 M solution of the substrate in CH3CN by a 10 µL syringe to a 10 mm quartz UV cell containing 2.50 mL of the thermostatted reaction mixture made up of anhydrous ethanol and aliquot of the EtOK solution.

Product Analysis. Y-Substituted-phenoxide ion was readily prepared by adding Y-substituted-phenol to the solution of picolinyl chloride in the presence of triethylamine in anhydrous diethyl ether as reported previously. The anhydrous ethanol was further dried over magnesium and was distilled under N2 just before use. All solutions were prepared freshly just before use under nitrogen and transferred by gas-tight syringes. Typically, the reaction was initiated by adding 5 µL of a 0.01 M solution of the substrate in CH3CN by a 10 µL syringe to a 10 mm quartz UV cell containing 2.50 mL of the thermostatted reaction mixture made up of anhydrous ethanol and aliquot of the EtOK solution.

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References

1. (a) Page, M. I.; Williams, A. Organic and Bio-organic Mechanisms;