Metal Ion Catalysis in Nucleophilic Displacement Reactions of 2-Pyridyl X-Substituted Benzoates with Potassium Ethoxide in Anhydrous Ethanol

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A kinetic study on nucleophilic displacement reactions of 2-pyridyl X-substituted benzoates **1a-e** with potassium ethoxide (EtOK) in anhydrous ethanol is reported. Plots of pseudo-first-order rate constants (k_{obsd}) *vs.* [EtOK]$_o$ exhibit upward curvature. The k_{obsd} value at a fixed [EtOK]$_o$ decreases steeply upon addition of 18-crown-6-ether (18C6) to the reaction mixture up to [18C6]/[EtOK]$_o$ = 1 and then remains nearly constant thereafter. In contrast, k_{obsd} increases sharply upon addition of LiSCN or KSCN. Dissection of k_{obsd} into k_{EtO^-} and k_{EtOM} has revealed that ion-paired EtOK is more reactive than dissociated EtO$^-$, indicating that K$^+$ ion acts as a Lewis acid catalyst. Hammett plots for the reactions of **1a-e** with dissociated EtO$^-$ and ion-paired EtOK result in excellent linear correlation with ρ values of 3.01 and 2.67, respectively. The k_{EtOK}/k_{EtO^-} ratio increases as the substituent X in the benzoyl moiety becomes a stronger electron-donating group. K$^+$ ion has been concluded to catalyze the current reaction by stabilizing the transition state through formation of a 6-membered cyclic complex.

Key Words: 2-Pyridyl benzoate, Metal ion catalysis, Ion-pair, Transition state, Hammett plot
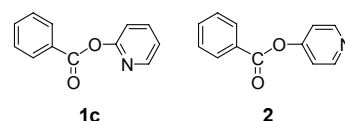
Introduction

Metal ion effects on acyl-group transfer reactions have intensively been investigated due to their importance in biological processes as well as in organic syntheses.[1-10] Multivalent metal ions (e.g., Mg^{2+}, Mn^{2+}, Cu^{2+}, Zn^{2+}, La^{3+}, Eu^{3+}, Co^{3+}) have been reported to be a strong Lewis acid catalyst in acyl-group transfer reactions.[1-4] However, the effect of alkali metal ions has been found to be strongly dependent on the nature of electrophilic centers.[5-10] Buncel *et al.* have initiated the first systematic study to investigate the role of alkali metal ions and found that M$^+$ ions catalyze nucleophilic substitution reactions of 4-nitrophenyl diphenylphosphinate and related esters with alkali metal ethoxides (EtOM, M = Li$^+$, Na$^+$, K$^+$) in anhydrous ethanol.[5] The catalytic effect has been found to increase as the size of M$^+$ ion decreases (i.e., Li$^+$ > Na$^+$ > K$^+$).[5] A contrasting catalytic effect has been reported for reactions of 4-nitrophenyl benzenesulfonate with EtOM in anhydrous ethanol, i.e., the catalytic effect increases with increasing the size of M$^+$ ions (i.e., Li$^+$ < Na$^+$ < K$^+$), indicating that the nature of the electrophilic center influences the role of M$^+$ ions.[7] We have also shown that the nature of electrophilic centers (i.e., P=O *vs.* P=S) governs the role of M$^+$ ions in alkaline ethanolysis of insecticides 4-nitrophenyl diethyl phosphinate (paraoxon) and phosphinothioate (parathion), i.e., M$^+$ ions strongly catalyze the reaction of paraoxon (i.e., P=O) in the order Li$^+$ > Na$^+$ > K$^+$ while Li$^+$ inhibits the corresponding reaction of parathion (i.e., P=S).[8]

The effect of M$^+$ ions on alkaline ethanolysis of aryl benzoates has been reported to be insignificant.[5a] However, M$^+$ ions have been reported to catalyze reactions of carboxylic esters which can form a 5- or 6-membered cyclic complex with M$^+$ ions in the transition state (e.g., I or II).[9] In the preceding paper, M$^+$ ions have shown large catalytic effect in alkaline ethanolysis of
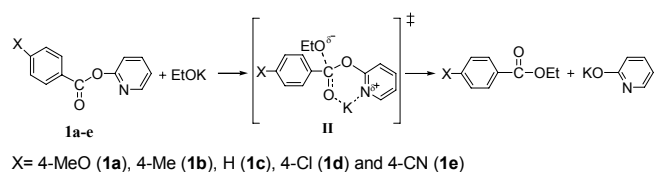
2-pyridyl benzoate **1c**.[11] Esters possessing a 2-pyridyl moiety were previously reported as an excellent acylating agent in reactions with Grignard reagents as well as in reactions with cupric bromide or lithium dialkylcuprate.[12,13] The reaction has been suggested to proceed through a 6-membered cyclic complex (e.g., III), in which Mg^{2+} ion acts as a strong Lewis acid catalyst.[12,13]
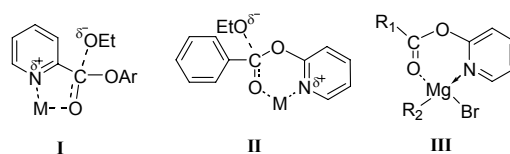
We proposed in the preceding paper that alkaline ethanolysis of **1c** proceeds through II, which was proven by performing the corresponding reaction of 4-pyridyl benzoate **2**.[11] As predicted, the large catalytic effect observed in the reaction of **1c** disappeared for the reaction of **2**, in which 6-membered cyclic transition state II is not possible.[11] Thus, the M$^+$ ion catalysis found in the reaction of **1c** has been attributed to stabilization of the transition state through II.[11]

We have extended our study to reactions of 2-pyridyl X-substituted benzoates **1a-b** and **1d-e** with EtOK in anhydrous ethanol (Scheme 1) to investigate the effect of substituent X in the benzoyl moiety. We have introduced two electron-withdrawing groups (i.e., X = 4-Cl and 4-CN) and two electron-donating ones

3544 *Bull. Korean Chem. Soc.* **2010**, Vol. 31, No. 12

Jae-In Lee et al.

Scheme 1

X= 4-MeO (**1a**), 4-Me (**1b**), H (**1c**), 4-Cl (**1d**) and 4-CN (**1e**)

(i.e., X = 4-Me and 4-MeO) on the benzoyl moiety of **1c**, which would affect charge polarization of the C=O bond in **1a-e**.

Results and Discussion

The reactions were performed under pseudo-first-order conditions with a large excess of EtOK, and monitored spectrophotometrically by following the appearance of the leaving 2-pyridyloxide at 298 nm. All reactions in the current study obeyed pseudo-first-order kinetics. Pseudo-first-order rate constants (k_{obsd}) were calculated from the slope of the linear plots of $\ln (A_\infty - A_t)$ *vs. t*. The correlation coefficients of the linear plots are higher than 0.9995. From replicate runs, the uncertainty in the k_{obsd} values is estimated to be less than $\pm 3\%$. The k_{obsd} values and detailed kinetic conditions for the reactions of 2-pyridyl 4-X-substituted benzoates **1a** (X = MeO), **1b** (X = Me), **1d** (X = Cl), and **1e** (X = CN) with EtOK are summarized in Tables S1 - S4 in the Supporting Information. The plots of k_{obsd} *vs.* [EtOK]$_o$ for the reaction of **1d** and **1e** with EtOK are illustrated in Figures S1 and S2, while the plots of $k_{obsd}/[EtO^-]_{eq}$ *vs.* $[EtO^-]_{eq}$ for the reactions of **1a**, **1b**, **1d**, and **1e** with EtOK are demonstrated in Figures S3 - S6, in turn in the Supporting Information.

Effect of alkali metal ions on reactivity. As shown in Figures 1A and 1B, the plots of k_{obsd} *vs.* [EtOK]$_o$ for reactions of **1a** and **1b** with EtOK exhibit upward curvature as the concentration of EtOK increases. Similar nonlinear plots are obtained for the corresponding reactions of **1d** and **1e** (see Figures S1 and S2 in the Supporting Information), although these substrates are significantly more reactive than **1a** and **1b**. Such upward curvature is typical for catalytic reactions, e.g., general base catalysis in ester aminolysis[14,15] and alkali metal ion catalysis in alkaline ethanolysis of various esters.[5-9,11] Thus, one can suggest that reactions of **1a**, **1b**, **1d**, and **1e** with EtOK are also catalyzed by K^+ ion.

The above idea that K^+ ion acts as a catalyst was examined by performing reactions of **1b** with EtOK in the presence of 18-crown-6 (18C6), a complexing agent for K^+ ion, at a given [EtOK]$_o$ with varying [18C6]/[EtOK]$_o$ ratios. The kinetic result is illustrated in Figure 2, in which the k_{obsd} value at a fixed [EtOK]$_o$ decreases steeply upon addition of 18C6 up to [18C6]/[EtOK]$_o$ = 1 and then remains nearly constant thereafter. This supports the preceding argument that K^+ ion catalyzes the current reaction in the absence of 18C6. Besides, the fact that k_{obsd} remains nearly constant when [18C6]/[EtOK]$_o \geq 1$ implies that 18C6 complexes K^+ ion completely when [18C6]/[EtOK]$_o$ = 1. This is consistent with the report that 18C6 is a highly effective complexing agent for K^+ ion.[16]

To give further evidence that alkali metal ions behave as a catalyst, the reaction of **1b** with EtOK was performed in the pre-
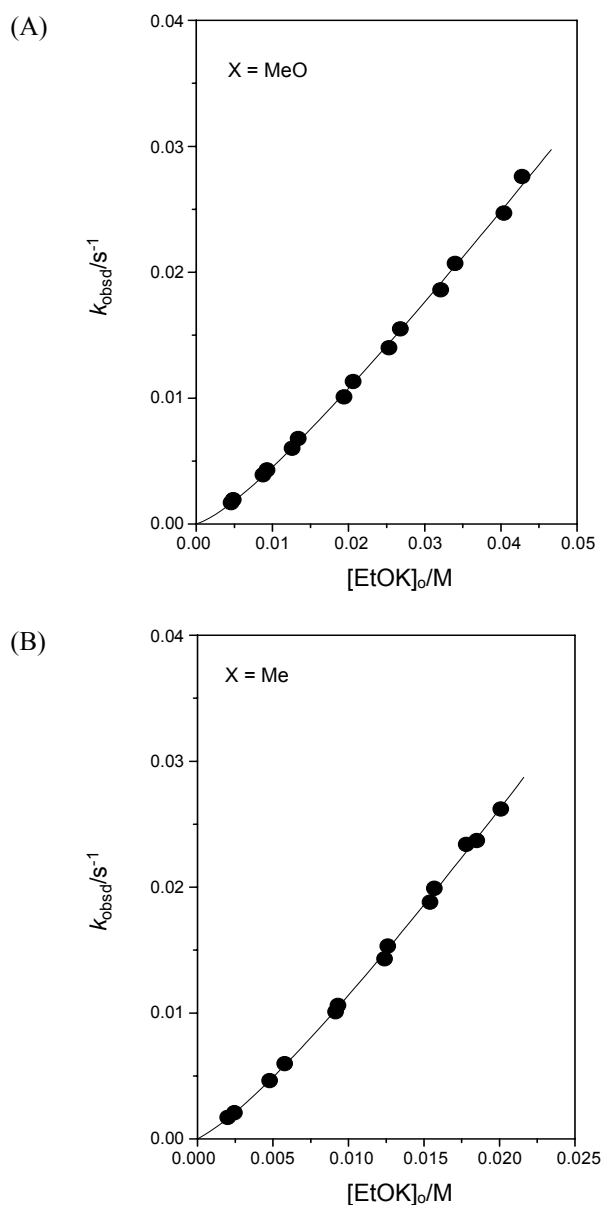

Figure 1. Plots of k_{obsd} *vs.* [EtOK]$_o$ for reactions of 2-pyridyl 4-methoxylbenzoate **1a** (A) and 4-methylbenzoate **1b** (B) with EtOK in anhydrous EtOH at 25.0 ± 0.1 °C. The curved lines were drawn from eq (2).

sence of LiSCN at a given [EtOK]$_o$ with varying [LiSCN]/[EtOK]$_o$ ratios. As shown in Figure 3, the k_{obsd} value at a fixed [EtOK]$_o$ increases rapidly upon addition of LiSCN up to ca. [LiSCN]/[EtOK]$_o$ = 4 and then the increase in k_{obsd} becomes insignificant upon further addition of LiSCN. In our preliminary experiment, **1b** was found to be stable in LiSCN solution. This indicates that SCN^- ion is not nucleophilic. Thus, the increase in k_{obsd} upon addition of LiSCN is not due to SCN^- ion but due to Li^+ ion. A similar result has been obtained when KSCN was added to the reaction mixture, although the effect of the added KSCN on k_{obsd} is less significant than that of LiSCN. This argument is consistent with our preceding paper that Li^+ ion is a stronger catalyst than K^+ ion in alkaline ethanolysis of **1c**.[11]

Dissection of k_{obsd} into k_{EtOK} and k_{EtO^-}. EtOM (M = Li, Na, K) has been reported to exist as dimers or other aggregates in a high
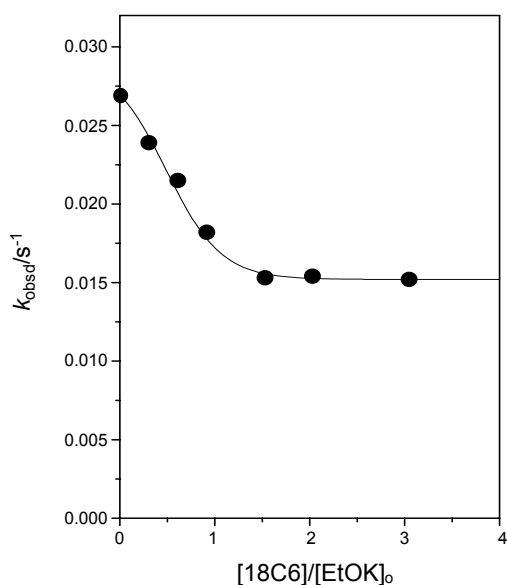
Figure 2. Plot showing effect of added 18C6 on k_{obsd} for the reaction of 2-pyridyl 4-methylbenzoate **1b** with EtOK in anhydrous EtOH at $25.0 \pm 0.1\ ^{\circ}$C. [EtOK]$_o$ = 20.5 mM.
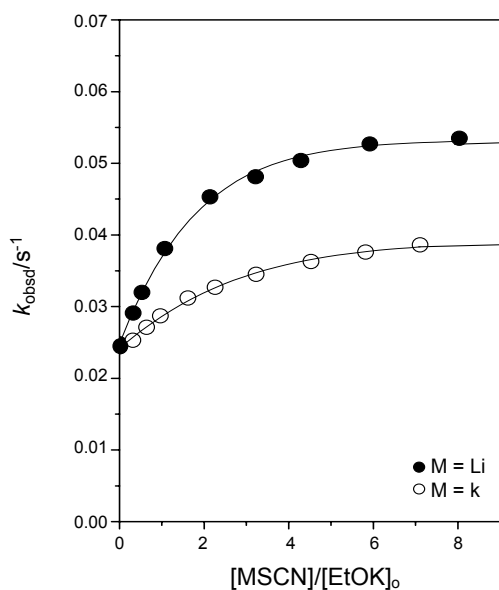

Figure 3. Plots showing the effect of added LiSCN(●) and KSCN(○) on k_{obsd} for the reaction of 2-pyridyl 4-methylbenzoate **1b** with EtOK in anhydrous EtOH at $25.0 \pm 0.1\ ^{\circ}$C. [EtOK]$_o$ = 19.4 mM.

concentration region (e.g., [EtOM]$_o$ > 0.1 M) but as dissociated EtO$^-$ and ion-paired EtOM when [EtOM]$_o$ < 0.1 M.[17] Thus, one might expect that substrates **1a**, **1b**, **1d**, and **1e** would react with both dissociated EtO$^-$ and ion-paired EtOK as shown in Scheme 2.

On the basis of the mechanism proposed in Scheme 2, a rate equation can be derived as eq (1), in which k_{EtO^-} and k_{EtOM} represent the second-order rate constant for the reaction with dissociated EtO$^-$ and ion-paired EtOK, respectively. Under a pseudo-first-order kinetic condition, k_{obsd} can be expressed as
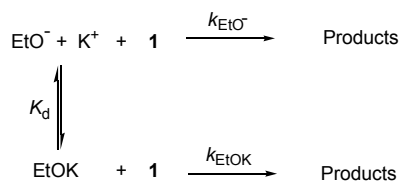
Scheme 2

eq (2), which becomes eq (3) since the dissociation constant K_d = [EtO$^-$]$_{eq}$[K$^+$]$_{eq}$/[EtOK]$_{eq}$, and [EtO$^-$]$_{eq}$= [K$^+$]$_{eq}$ at the equilibrium. Besides, the concentrations of [EtO$^-$]$_{eq}$ and [EtOK]$_{eq}$ can be calculated from the reported K_d value and the initial concentration [EtOK]$_o$.

$$\text{Rate} = k_{EtO^-}[\text{EtO}^-]_{eq}[\mathbf{1}] + k_{EtOK}[\text{EtOK}]_{eq}[\mathbf{1}] \qquad (1)$$

$$k_{obsd} = k_{EtO^-}[\text{EtO}^-]_{eq} + k_{EtOK}[\text{EtOK}]_{eq} \qquad (2)$$

$$k_{obsd}/[\text{EtO}^-]_{eq} = k_{EtO^-} + k_{EtOK}[\text{EtO}^-]_{eq}/K_d \qquad (3)$$

$$[\text{EtOK}]_o = [\text{EtO}^-]_{eq} + [\text{EtOK}]_{eq} \qquad (4)$$

$$[\text{EtO}^-]_{eq} = [-K_d + (K_d^2 + 4K_d[\text{EtOK}]_o)^{1/2}]/2 \qquad (5)$$

Thus, one might expect that the plot of k_{obsd}/[EtO$^-$]$_{eq}$ *vs.* [EtO$^-$]$_{eq}$ is linear with a positive intercept. In fact, the plots shown in Figures S3 - S6 (in the Supporting Information) for the reactions of **1a**, **1b**, **1d**, and **1e** with EtOK are linear with positive intercepts, indicating that the proposed mechanism as well as the derived equations are correct. Thus, one can calculate the k_{EtO^-} and k_{EtOK}/K_d values from the intercept and the slope of the linear plots, respectively. The k_{EtOK} value can be calculated from the above k_{EtOK}/K_d values and the reported K_d value of 11.1×10^{-3} M for EtOK.[18] The calculated k_{EtO^-} and k_{EtOM} values in this way are summarized in Table 1.

It is seen from Table 1 that k_{EtOM} is larger than k_{EtO^-} regardless of the electronic nature of the substituent X in the benzoyl moiety, indicating that the ion-paired EtOK is more reactive than the dissociated EtO$^-$. This accounts for the upward curvature shown in Figures 1A and 1B (and Figures S1 and S2 in the Supporting Information).

As expected, the k_{EtO^-} and k_{EtOM} values increase as the substituent X in the benzoyl moiety changes from an electron-donating group (EDG) to an electron-withdrawing group (EWG), e.g., as the substituent X changes from 4-MeO to H and 4-CN, k_{EtO^-} increases from 0.209 M^{-1}s^{-1} to 1.45 and 157 M^{-1}s^{-1} while k_{EtOM} increases from 0.898 M^{-1}s^{-1} to 4.90 and 293 M^{-1}s^{-1}, in turn. However, the k_{EtOK}/k_{EtO^-} ratio decreases as the substituent X changes from an EDG to an EWG.

The effect of the electronic nature of substituent X on k_{EtO^-} and k_{EtOM} values is illustrated in Figures 4A and 4B. The Hammett plots exhibit excellent linear correlation with large ρ values, i.e., ρ = 3.01 for the reaction with dissociated EtO$^-$ while ρ = 2.67 for those with ion-paired EtOK, indicating that the electronic nature of substituent X influences the reactivity greatly but does not alter the reaction mechanism. Besides, the difference

Table 1. Summary of second-order rate constants from ion-pairing treatment of kinetic data for reactions of 2-pyridyl X-substituted benzoates **1a-e** with EtOK in anhydrous EtOH at 25.0 ± 0.1 °C[a]

X	$k_{\text{EtO}^-}/\text{M}^{-1}\text{s}^{-1}$	$k_{\text{EtOK}}/\text{M}^{-1}\text{s}^{-1}$	$k_{\text{EtO}^-}/k_{\text{EtO}^-}$
4-MeO (**1a**)	0.209	0.898	4.30
4-Me (**1b**)	0.638	2.03	3.18
4-H (**1c**)	1.45	4.90	3.38
4-Cl (**1d**)	7.62	21.4	2.81
4-CN (**1e**)	157	293	1.87

[a]The data for the reaction of **1c** were taken from the preceding paper.[11]

(A)

(B)
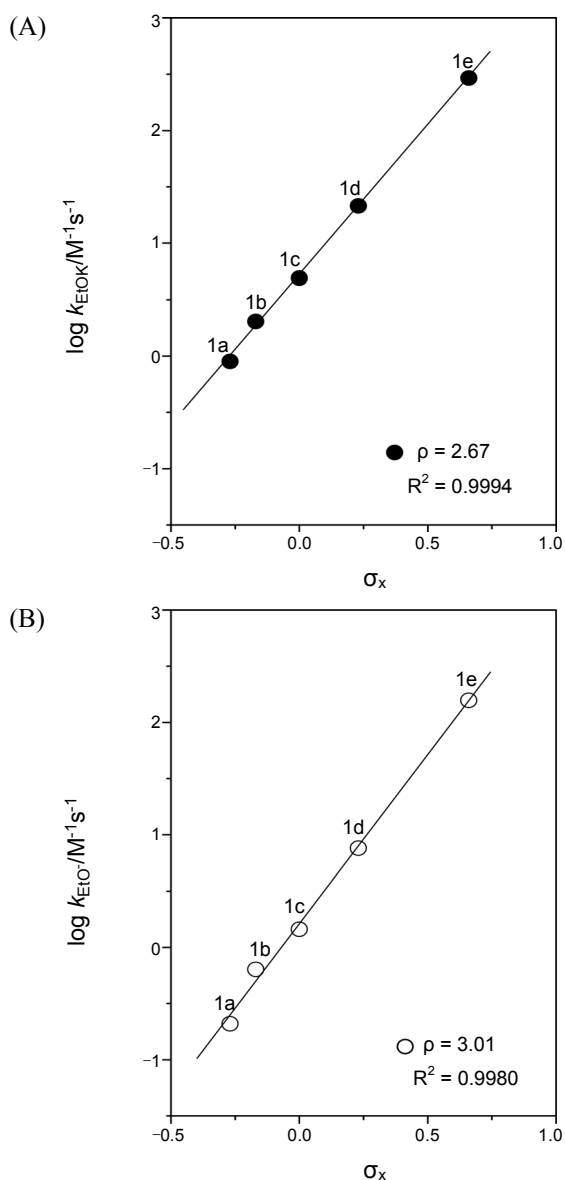
Figure 4. Hammett plots for reactions of 2-pyridyl X-substituted benzoates **1a-e** with EtOK in anhydrous EtOH at 25.0 ± 0.1 °C. log k_{EtOK} *vs.* σ_X (A) while log k_{EtO^-} *vs.* σ_X (B). The identity of points is given in Table 1.

in the ρ values appears to be in accord with the reactivity-selectivity principle,[19] since the less reactive EtO$^-$ exhibits higher sensitivity toward the nature of the substituent X than the more
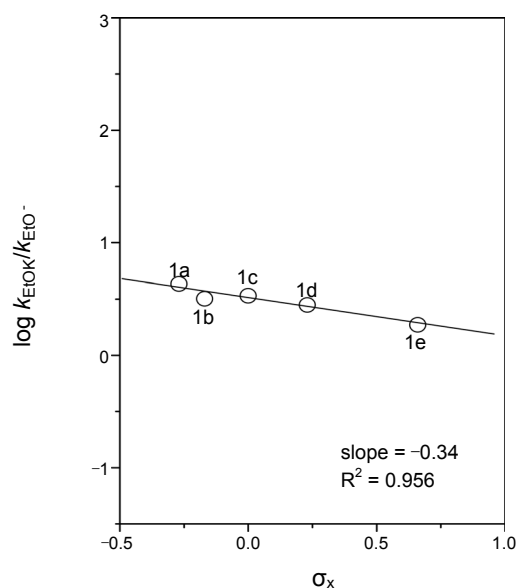
Figure 5. Plot of log $k_{\text{EtOK}}/k_{\text{EtO}^-}$ *vs.* σ_X for reactions of 2-pyridyl X-substituted benzoates **1a-e** with EtOK in anhydrous EtOH at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

reactive EtOK.

Effect of substituent X on stability of transition-state. The current reaction would proceed either through a concerted mechanism or through a stepwise pathway. If the reaction proceeds through a stepwise mechanism, the rate-determining step (RDS) should be formation of an addition intermediate since the incoming EtO$^-$ is significantly more basic than the leaving 2-pyridyloxide. Thus, one might suggest that K$^+$ ion catalyzes the current reaction by stabilizing the transition state through formation of a 6-membered cyclic complex II for a concerted mechanism or by stabilizing an intermediate for a stepwise pathway, in which the intermediate would be similar to II.

It is apparent that an EDG in the benzoyl moiety of the substrate could increase the stability of II by increasing the charge density on the O atom of the C=O bond. In contrast, the stability of II would be decreased by an EWG in the benzoyl moiety since it would inhibit development of a negative charge on the O atom of the C=O bond in the transition state. This idea is consistent with the result shown in Table 1 that K$^+$ ion catalysis decreases as substituent X changes from an EDG to an EWG.

To provide further evidence for the argument that the catalytic effect is governed by the electronic nature of the substituent X in the benzoyl moiety, a plot of $k_{\text{EtOK}}/k_{\text{EtO}^-}$ *vs.* σ_X has been constructed. As shown in Figure 5, catalysis by K$^+$ ion, represented by the $k_{\text{EtOK}}/k_{\text{EtO}^-}$ ratio, is dependent linearly on the nature of the substituent X with a slope of -0.34. Such linear correlation with a negative slope supports the idea that the transition state II is more stabilized as the substituent X becomes a stronger EDG.

Conclusions

(1) It has been concluded that K$^+$ ion catalyzes the current reaction on the basis of the kinetic results: (i) upward curvature

observed in the plots of k_{obsd} *vs.* [EtOK]$_o$. (ii) decreases in k_{obsd} upon addition of a complexing agent 18C6 and increases in k_{obsd} upon addition of LiSCN or KSCN. (iii) ion-paired EtOK is more reactive than dissociated EtO$^-$, i.e., $k_{EtOK} > k_{EtO^-}$. (2) K$^+$ ion catalyzes the current reaction by stabilizing the transition state through formation of a 6-membered cyclic complex (e.g., II). (3) The electronic nature of substituent X influences the reactivity greatly but does not alter the reaction mechanism. (4) The catalytic effect shown by K$^+$ ion increases as substituent X in the benzoyl moiety of **1a-e** becomes a stronger EDG.

Experimental Section

Materials. Compounds **1a**, **1b**, **1d**, and **1e** were prepared readily from the reaction of X-substituted benzoyl chloride and 2-hydroxypyridine in anhydrous ether. The crude products were purified by recrystallization and their purity was checked by their melting points and ^{1}H and ^{13}C NMR spectra (see the Supporting Information). The solution of EtOK was prepared by dissolving potassium metal in anhydrous ethanol under N$_2$ and stored in the refrigerator. The concentration of EtOK was measured by titration with mono potassium phthalate. Crown ether (18C6) was recrystallized from acetonitrile and dried under vacuum. The anhydrous ethanol was further dried over magnesium and distilled under N$_2$ just before use.

Kinetics. Kinetic study was performed using a UV-vis spectrophotometer for slow reactions ($t_{1/2} \geq 10$ s) and a stopped-flow spectrophotometer for fast reactions ($t_{1/2} < 10$ s) equipped with a constant-temperature circulating bath. The reactions were followed by monitoring the appearance of the leaving 2-pyridyloxide at 298 nm. Reactions were followed generally for 9 - 10 half-lives and k_{obsd} were calculated using the equation, ln (A_∞ - A_t) *vs. t*.

Product analysis. 2-Pyridyloxide was liberated quantitatively and identified as one of the reaction products by comparison of the Uv-vis spectra after completion of the reactions with those of the authentic samples under the reaction conditions.

Supporting Information. Kinetic conditions and results for the reactions of **1a**, **1b**, **1d** and **1e** with EtOK. Plots of k_{obsd} *vs.* [EtOK]$_o$ for the reaction of **1d** and **1e** with EtOK. Plots of k_{obsd}/[EtO$^-$]$_{eq}$ *vs.* [EtO$^-$]$_{eq}$ for the reactions of **1a**, **1b**, **1d**, and **1e** with EtOK. ^{1}H and ^{13}C NMR spectra of **1a**, **1b**, **1d** and **1e**.

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