

Kinetic Study on Nucleophilic Substitution Reactions of 4-Nitrophenyl X-Substituted-Benzoates with Potassium Ethoxide: Reaction Mechanism and Role of K⁺ Ion

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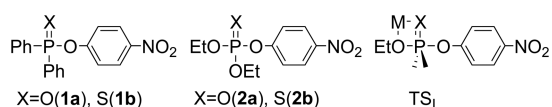
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A kinetic study on nucleophilic substitution reactions of 4-nitrophenyl X-substituted-benzoates (**7a-i**) with EtOK in anhydrous ethanol at 25.0 ± 0.1 °C is reported. The plots of pseudo-first-order rate constants (k_{obsd}) vs. [EtOK] curve upward. Dissection of k_{obsd} into the second-order rate constants for the reactions with the dissociated EtO⁻ and ion-paired EtOK (*i.e.*, k_{EtO^-} and k_{EtOK} , respectively) has revealed that the ion-paired EtOK is more reactive than the dissociated EtO⁻. Hammett plots for the reactions of **7a-i** with the dissociated EtO⁻ and ion-paired EtOK exhibit excellent linear correlations with $\rho_X = 3.00$ and 2.47, respectively. The reactions have been suggested to proceed through a stepwise mechanism in which departure of the leaving-group occurs after the RDS. The correlation of the $k_{\text{EtOK}}/k_{\text{EtO}^-}$ ratio with the σ_X constants exhibits excellent linearity with a slope of -0.53. It is concluded that the ion-paired EtOK catalyzes the reaction by increasing the electrophilicity of the reaction center rather than by enhancing the nucleofugality of the leaving group.

Key Words : Metal-ion catalysis, Electrophilicity, Nucleofugality, Stepwise mechanism, Hammett plot

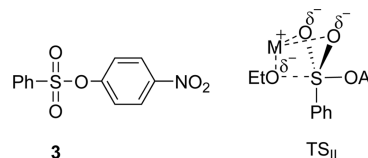
Introduction

Metal ions including alkali-metal ions have often been reported to behave as a Lewis acid catalyst or as an inhibitor in various acyl-group transfer reactions.¹⁻¹⁰ Buncl and his coworkers have reported that alkali-metal ions catalyze the phosphinyl-transfer reaction of 4-nitrophenyl diphenylphosphinate (**1a**) with alkali-metal ethoxide (EtOM; M = Li, Na, K).⁸ They have found that the catalytic effect increases as the size of M⁺ ions decreases, *e.g.*, K⁺ < Na⁺ < Li⁺, but it disappears in the presence of complexing agents such as crown ethers or cryptands.⁸ In contrast, we have shown that Li⁺ ion inhibits the corresponding reaction of 4-nitrophenyl diphenylphosphinothioate (**1b**), while K⁺ and 18-crown-ether (18C6) complex K⁺ ions catalyze the reaction.⁹ Similarly contrasting results have been reported for the reactions of 4-nitrophenyl diethyl phosphate (**2a**, paraoxon) and phosphorothioate (**2b**, parathion) with EtOM.¹⁰ Thus, a cyclic transition state (*i.e.*, TS_I) has been suggested to catalyze the reaction by increasing the electrophilicity of the reaction center on the basis of the contrasting M⁺ ion effects found for the reactions of the P=O and P=S centered electrophiles.⁸⁻¹⁰

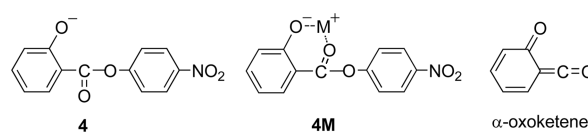


Effects of alkali-metal ions on sulfonyl-transfer reactions of 4-nitrophenyl benzenesulfonate (**3**) with EtOM have also been investigated.^{11,12} Buncl *et al.* have reported that M⁺ ions catalyze the reaction and the catalytic effect increases as the size of M⁺ ions increases, *i.e.*, Li⁺ < Na⁺ < K⁺.¹¹ The reaction has been suggested to proceed through a stepwise

mechanism in which formation of an intermediate being the rate-determining step (RDS) on the basis of the kinetic result that the Yukawa-Tsuno plots for the reactions of Y-substituted-phenyl benzenesulfonates (**3** and its derivatives) exhibit an excellent linear correlation with $\rho_Y = 2.5 \pm 0.1$ and $r = 0.27 \pm 0.02$.¹² An enhanced electrophilicity through TS_{II} has been suggested to be responsible for the M⁺ ion catalysis.¹²

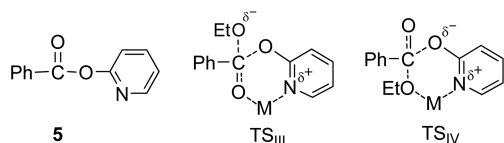


One might expect that M⁺ ions catalyze the reaction of 4-nitrophenyl salicylate (**4**) with EtOM through the cyclic complex **4M**, which could increase the electrophilicity of the reaction center. However, we have reported that M⁺ ions strongly inhibit the reaction.¹³ More interestingly, the reaction rate has been found to decrease as the concentration of EtOM increases.¹³ Thus, the cyclic complex **4M** has been suggested to inhibit the reaction of **4** by retarding the subsequent E1cb reaction which yields an α -oxoketene.¹³

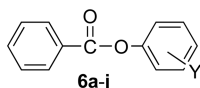


The reaction of 2-pyridyl benzoate (**5**) with EtOM has been performed to obtain further information on M⁺ ion effects.¹⁴ We have proposed that M⁺ ions catalyze the reaction by increasing either the electrophilicity of the reaction center or nucleofugality of the leaving group through a

stable cyclic transition state (e.g., TS_{III} or TS_{IV}).¹⁴



We have recently reported that benzoyl-transfer reaction of Y-substituted-phenyl benzoates (**6a-j**) with EtOK proceeds through a stepwise mechanism, in which departure of the leaving group occurs after the RDS, on the basis of the kinetic result that σ^o constants result in a much better linear correlation than σ^- constants.¹⁵ K^+ ion has been suggested to catalyze the reaction by increasing the electrophilicity of the reaction center rather than by enhancing the nucleofugality of the leaving group, on the basis of the kinetic results that (1) the reaction proceeds through a stepwise mechanism with formation of an intermediate being the RDS and (2) the catalytic effect is independent of the electronic nature of the substituent Y in the leaving group.¹⁵



Y = 4-Me (**6a**), 3-Me (**6b**), H (**6c**), 4-Cl (**6d**), 3-COMe (**6e**), 3-Cl (**6f**), 4-COOEt (**6g**), 4-COMe (**6h**), 4-CN (**6i**), 4-NO₂ (**6j**)

Our study has been extended to the reactions of 4-nitrophenyl X-substituted-benzoates (**7a-i**) with EtOK in anhydrous ethanol to obtain further information on the reaction mechanism and the role of K^+ ion (Scheme 1). We have also investigated the effects of the substituent X on the role of K^+ ion as well as the reaction mechanism.

Results

The kinetic study was performed spectrophotometrically under pseudo-first-order conditions in which the concentration of EtOK was in large excess over that of **7a-i**. The reaction obeyed pseudo-first-order kinetics and proceeded with quantitative liberation of 4-nitrophenoxide ion. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation, $\ln(A_\infty - A_t) = -k_{\text{obsd}}t + C$. It is estimated from replicate runs that the uncertainty in the k_{obsd} values is less than $\pm 3\%$. The second-order rate constants for the reactions of **7a-i** with the dissociated EtO^- and ion-paired EtOK (i.e., k_{EtO^-} and k_{EtOK} , respectively) were calculated from the ion-pairing treatment of the kinetic data and are summarized in Table 1 together with the $k_{\text{EtOK}}/k_{\text{EtO}^-}$ ratios.

Effect of K^+ Ion on Reactivity. As shown in Figure 1, the plot of k_{obsd} vs. [EtOK] curves upward for the reaction of 4-

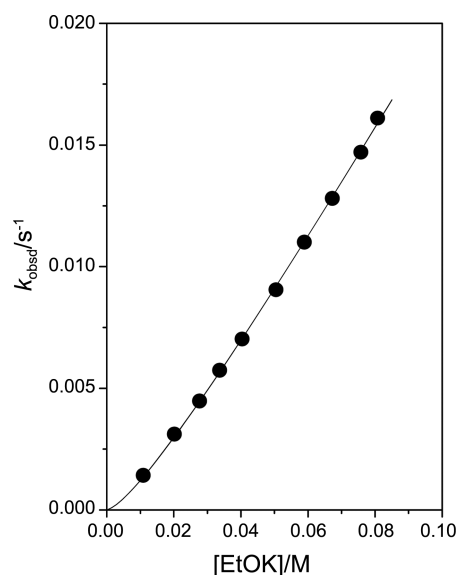


Figure 1. Plot of k_{obsd} vs. [EtOK] for the reactions of 4-nitrophenyl 4-dimethylaminobenzoate (**7a**) with EtOK in anhydrous EtOH at 25.0 ± 0.1 °C. [**7a**] = 2×10^{-5} M.

nitrophenyl 4-dimethylaminobenzoate (**7a**) with EtOK. Similarly curved plots were obtained for the reactions of substrates possessing an electron-donating or a weak electron-withdrawing substituent X in the benzoyl moiety (e.g., **7b-g**). In contrast, the plots of k_{obsd} vs. [EtOK] for the reactions of substrates bearing a strong electron-withdrawing

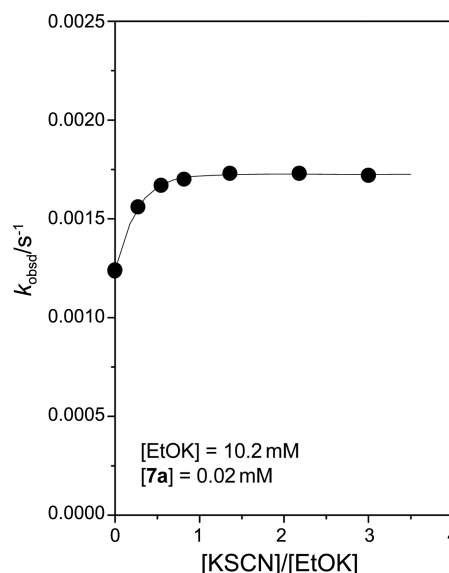
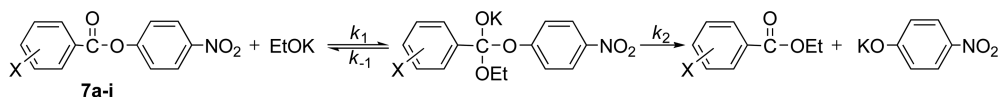
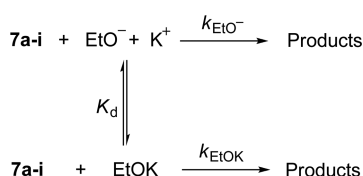


Figure 2. Effect of added KSCN on reactivity for the reaction of 4-nitrophenyl 4-dimethylaminobenzoate (**7a**) with EtOK in EtOH at 25.0 ± 0.1 °C.



X = 4-NMe₂ (**7a**), 4-OMe (**7b**), 4-^tBu (**7c**), 4-Me (**7d**), 3-Me (**7e**), H (**7f**), 4-Cl (**7g**), 4-CN (**7h**), 4-NO₂ (**7i**).

Scheme 1



Scheme 2. Reactions of **7a-i** with the dissociated EtO^- and ion-paired EtOK.

substituent X (e.g., **7h** and **7i**) were almost linear (Figures not shown). The curved plot shown in Figure 1 is typical for alkaline ethanolysis of esters in which alkali-metal ions behave as a Lewis acid catalyst.⁸⁻¹² Thus, one can suggest that K^+ ion catalyzes the reactions of **7a-i** with EtOK, although the catalytic effect becomes insignificant for the reactions of substrates possessing a strong electron-withdrawing substituent in the benzoyl moiety (e.g., **7h** and **7i**).

To support the above idea that K^+ ion behaves as a catalyst, reactions of 4-nitrophenyl 4-dimethylaminobenzoate (**7a**) with a given concentration of EtOK have been performed under various concentrations of KSCN as a K^+ ion source. As shown in Figure 2, k_{obsd} increases as the concentration of KSCN in the reaction medium increases up to $[\text{KSCN}]/[\text{EtOK}] \approx 1$ and remains nearly constant thereafter. This supports the preceding idea that K^+ ion catalyzes the reactions of **7a-i**.

Dissection of k_{obsd} into k_{EtO^-} and k_{EtOK} . To quantify the catalytic effect exerted by K^+ ion, the k_{obsd} values have been dissected into the second-order rate constants for the reactions of **7a-i** with the dissociated EtO^- and ion-paired EtOK (i.e., k_{EtO^-} and k_{EtOK} , respectively). It has previously been reported that EtOK exists as dissociated EtO^- and ion-paired EtOK when $[\text{EtOK}] < 0.1 \text{ M}$.¹⁶ Since the concentration of EtOK used in this study was lower than 0.1 M, substrates **7a-i** would react with the dissociated EtO^- and ion-paired EtOK as shown in Scheme 2.

One can derive Eq. (1) on the basis of the reactions proposed in Scheme 2. Under pseudo-first-order kinetic conditions (e.g., $[\text{EtOK}] \gg [\text{7a-i}]$), k_{obsd} can be expressed as Eq. (2). It is noted that the dissociation constant $K_d = [\text{EtO}^-]_{\text{eq}}[\text{K}^+]_{\text{eq}}/[\text{EtOK}]_{\text{eq}}$, and $[\text{EtO}^-]_{\text{eq}} = [\text{K}^+]_{\text{eq}}$ at equilibrium. Thus, Eq. (2) can be converted to Eq. (3). The concentrations of $[\text{EtO}^-]_{\text{eq}}$ and $[\text{EtOK}]_{\text{eq}}$ can be calculated from the reported K_d value for EtOK (i.e., $K_d = 1.11 \times 10^{-2} \text{ M}$)¹⁷ and the initial concentration $[\text{EtOK}]$ using Eqs. (4) and (5).

$$\text{Rate} = k_{\text{EtO}^-}[\text{EtO}^-]_{\text{eq}}[\text{7a-i}] + k_{\text{EtOK}}[\text{EtOK}]_{\text{eq}}[\text{7a-i}] \quad (1)$$

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

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

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

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

Thus, one might expect that the plot of $k_{\text{obsd}}/[\text{EtO}^-]_{\text{eq}}$ vs. $[\text{EtO}^-]_{\text{eq}}$ would be linear with a positive intercept if the reaction proceeds as proposed in Scheme 2. In fact, the plot shown in Figure 3 is linear with a positive intercept, indicat-

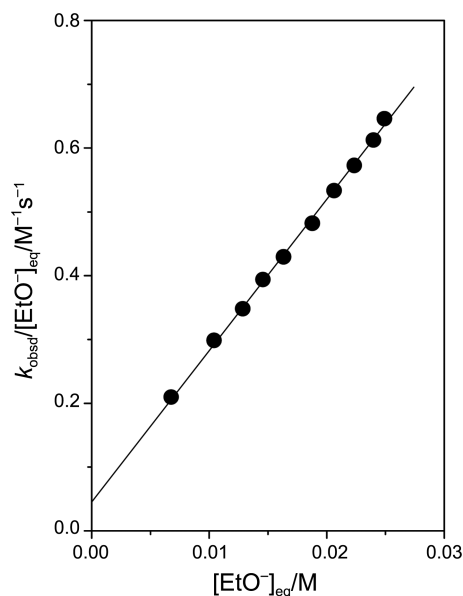


Figure 3. Plot illustrating dissection of k_{obsd} into the second-order rate constants k_{EtO^-} and k_{EtOK} for the reaction of 4-nitrophenyl 4-dimethylaminobenzoate (**7a**) with EtOK in anhydrous EtOH at $25.0 \pm 0.1 \text{ }^\circ\text{C}$.

ing that the derived equations based on Scheme 2 are correct. Accordingly, one can calculate the k_{EtO^-} and k_{EtOK}/K_d values from the intercept and the slope of the linear plot, respectively. The k_{EtOK} value can be calculated from the above k_{EtOK}/K_d values and the reported K_d value for EtOK. In Table 1 are summarized the calculated k_{EtO^-} and k_{EtOK} values for the reactions of **7a-i**.

As shown in Table 1, the second-order rate constant for the reactions of **7a-i** with the ion-paired EtOK (i.e., k_{EtOK}) increases as the substituent X in the benzoyl moiety changes from a strong electron-donating group (EDG) to a strong electron-withdrawing group (EWG), e.g., k_{EtOK} increases from $0.269 \text{ M}^{-1}\text{s}^{-1}$ to 19.8 and $2090 \text{ M}^{-1}\text{s}^{-1}$ as the substituent X changes from 4-NMe₂ to H and 4-NO₂, in turn. A similar result is demonstrated for the corresponding reactions with the dissociated EtO^- . However, k_{EtOK} is larger than k_{EtO^-} , indicating that the ion-paired EtOK is more reactive than the

Table 1. Summary of Second-Order Rate Constants from Ion-Pairing Treatment of the Kinetic Data for Reactions of 4-Nitrophenyl X-Substituted-Benzoates (**7a-i**) with EtOK in Anhydrous EtOH at $25.0 \pm 0.1 \text{ }^\circ\text{C}$

	X	$k_{\text{EtOK}}/\text{M}^{-1}\text{s}^{-1}$	$k_{\text{EtO}^-}/\text{M}^{-1}\text{s}^{-1}$	$k_{\text{EtOK}}/k_{\text{EtO}^-}$
7a	4-NMe ₂	0.269	0.0362	7.43
7b	4-OMe	3.51	1.04	3.38
7c	4-tBu	10.4	3.67	2.83
7d	4-Me	8.25	3.61	2.29
7e	3-Me	14.6	5.70	2.56
7f	H	19.8	8.86	2.23
7g	4-Cl	91.0	54.9	1.66
7h	4-CN	1200	1110	1.08
7i	4-NO ₂	2090	2060	1.01

dissociated EtO^- . It is also noted that the catalytic effect exerted by K^+ ion decreases as the substituent X changes from a strong EDG to a strong EWG, e.g., the $k_{\text{EtOK}}/k_{\text{EtO}^-}$ ratio decreases from 7.43 to 2.23 and 1.01 as the substituent changes from 4-Me₂N to H and 4-NO₂, in turn. This indicates that the catalytic effect of K^+ ion is negligible for the reactions of substrates possessing a strong EWG (e.g., **7h** and **7i**), and is consistent with the result that the plots of k_{obsd} vs. $[\text{EtOK}]$ for the reactions of **7h** and **7i** are almost linear, as mentioned in the preceding section.

Deduction of Reaction Mechanism. Detailed information on the reaction mechanism is necessary to understand the role of K^+ ion in current study. Nucleophilic substitution reactions of esters have been reported to proceed either through a concerted mechanism or via a stepwise pathway depending on the nature of the electrophilic center, e.g., a concerted mechanism for reactions of Y-substituted-phenyl diphenylphosphinates and diphenylphosphinothioates with EtO^- (i.e., P=O and P=S centered electrophiles)^{9,18} while a stepwise mechanism for the corresponding reactions of Y-substituted-phenyl benzoates¹⁵ and benzenesulfonates¹² (i.e., C=O and SO₂ centered electrophiles).

To investigate the reaction mechanism, Hammett plots for the reactions of **7a-i** with the dissociated EtO^- and ion-paired EtOK have been constructed. As shown in Figure 4, the Hammett plots exhibit an excellent linear correlation with $\rho_X = 3.00$ and 2.47 for the reactions with the dissociated EtO^- and ion-paired EtOK , respectively.

One can get useful information on the reaction mechanism from the magnitude of ρ_X values. It is expected that an EWG in the nonleaving group would increase the electrophilicity of the reaction center but decrease the nucleofugality of the leaving group, while an EDG would decrease the electrophilicity but increase the nucleofugality. Consequently, the

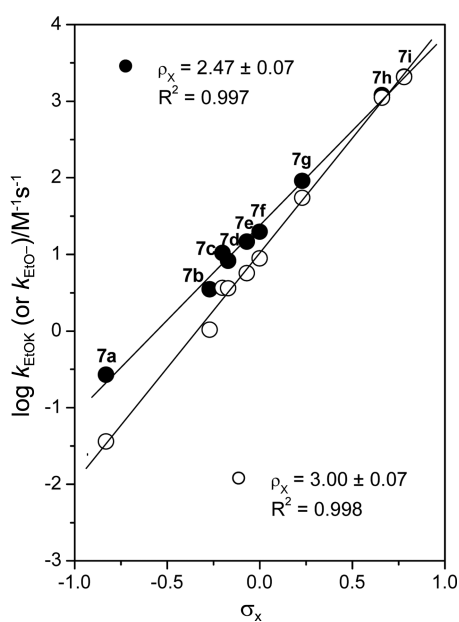
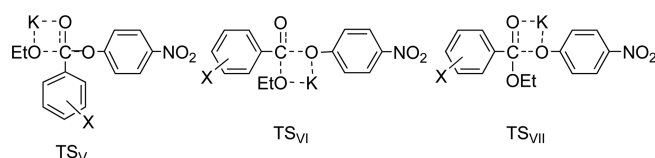


Figure 4. Hammett plots for the reactions of **7a-i** with the ion-paired EtOK (●) and dissociated EtO^- (○) in anhydrous EtOH at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

ρ_X value for a concerted reaction cannot be large due to the opposing substituent effects. In fact, a small ρ_X value has often been reported for reactions which proceed through a concerted mechanism (e.g., $\rho_X = -0.3$ for an $\text{S}_{\text{N}}2$ reaction of benzyl bromides with OH^-).¹⁹ In contrast, the ρ_X value for a stepwise reaction has been reported to be strongly dependent on the RDS, i.e., a small ρ_X value ($\rho_X = 0.6 \pm 0.1$) for reactions in which the leaving group departs in the RDS,²⁰ while a large ρ_X value ($\rho_X = 2.0 \pm 0.3$) for reactions in which the leaving group departs after the RDS.²¹

Thus, one can suggest that the reactions of **7a-i** with the dissociated EtO^- and ion-paired EtOK proceed through a stepwise mechanism in which departure of the leaving group occurs after the RDS on the basis of the large ρ_X value obtained in the current reactions. This idea is further supported by our report that the reactions of Y-substituted-phenyl benzoates (**6a-j**) with the dissociated EtO^- and ion-paired EtOK proceed through a stepwise mechanism with formation of an intermediate being the RDS.¹⁵

Role of K^+ Ion. The kinetic result that the ion-paired EtOK is more reactive than the dissociated EtO^- suggests that the ion-paired EtOK catalyzes the reactions of **7a-i** by increasing either the electrophilicity of the reaction center through TS_{V} or the nucleofugality of the leaving 4-nitrophenoxide through TS_{VI} . However, one can exclude TS_{VII} , in which K^+ ion increases both the electrophilicity of the reaction center and the nucleofugality of the leaving group. This is because EtO^- and K^+ ions in TS_{VII} are not ion-paired species.



It is apparent that catalysis through TS_{VI} is effective only for reactions in which departure of the leaving group occurs in the RDS but is ineffective for reactions in which the leaving group departs after the RDS. Since the current reactions have been discussed to proceed through a stepwise mechanism in which departure of the leaving group occurs after the RDS, one can exclude a possibility that the reactions are catalyzed by increasing the nucleofugality of the leaving group through TS_{VI} . Thus, one can conclude that the ion-paired EtOK catalyzes the reactions of **7a-i** by increasing the electrophilicity of the reaction center through TS_{V} . This is consistent with our previous report that the ion-paired EtOK catalyzes the reactions of Y-substituted-phenyl benzoates (**6a-j**) by increasing the electrophilicity of the reaction center through a TS structure similar to TS_{V} .¹⁵

The catalytic effect through TS_{V} would be more strongly dependent on the electronic nature of the substituent X in the benzoyl moiety of **7a-i** than on that of the substituent Y in the nonleaving group of **6a-j**. This is because the substituent X is one atom closer to the C=O bond than the substituent Y. Thus, one might expect that the $k_{\text{EtOK}}/k_{\text{EtO}^-}$ ratio would exhibit a better correlation with the electronic nature of the

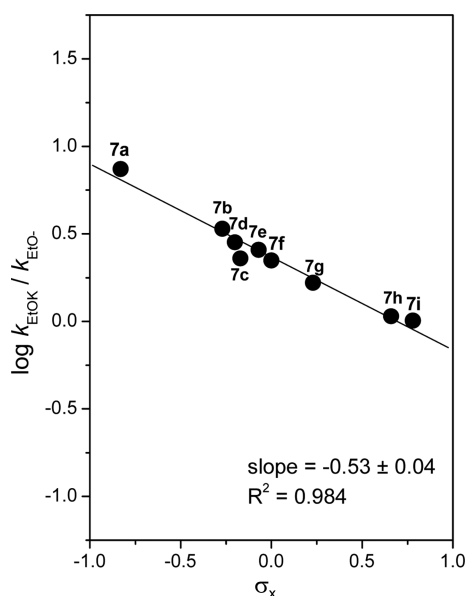


Figure 5. Plot showing the relationship between the catalytic-effect exerted by K^+ ion (i.e., $k_{\text{EtOK}}/k_{\text{EtO}^-}$) and σ_X constants for the reactions of **7a-i** with EtOK. The identity of points is given in Table 1.

substituent X than with that of the substituent Y.

To examine the above idea, the $k_{\text{EtOK}}/k_{\text{EtO}^-}$ ratio for the reactions of **7a-i** has been correlated with the σ_X constants in Figure 5. One can see an excellent linear correlation with a slope of -0.53 . This is in contrast to our previous report that the $k_{\text{EtOK}}/k_{\text{EtO}^-}$ ratio for the reactions of Y-substituted-phenyl benzoates (**6a-j**) is independent of the electronic nature of the substituent Y.¹⁵ Thus, the contrasting results further support the conclusion that the reactions of **7a-i** with EtOK are catalyzed by increasing the electrophilicity of the reaction center through TS_V .

Conclusions

The current study has allowed us to conclude the following: (1) The plots of k_{obsd} vs. $[\text{EtOK}]$ curve upward. Dissection of k_{obsd} into the second-order rate constants k_{EtOK} and k_{EtO^-} has revealed that the ion-paired EtOK is more reactive than the dissociated EtO^- . (2) Hammett plots for the reactions of **7a-i** with the dissociated EtO^- and ion-paired EtOK exhibit an excellent linear correlation with $\rho_X = 3.00$ and 2.47 , respectively. The large ρ_X value has been taken as evidence for a stepwise mechanism, in which departure of the leaving-group occurs after the RDS. (3) The ion-paired EtOK catalyzes the reactions of **7a-i** by increasing the electrophilicity of the reaction center through TS_V rather than by enhancing the nucleofugality of the leaving group through TS_{VI} .

Experimental Section

Materials. 4-Nitrophenyl X-substituted-benzoates (**7a-i**) were readily prepared by adding 4-nitrophenol to the solu-

tion of X-substituted-benzoyl chloride, *N,N'*-dicyclohexylcarbodiimide and 4-dimethylaminopyridine in methylene chloride as reported previously.¹⁵ The crude product was purified by column chromatography (silica gel, methylene chloride/*n*-hexane 50/50). The purity was checked by their melting points and ^1H NMR spectra.

Kinetics. The kinetic study was performed with a UV-vis spectrophotometer for slow reactions (e.g., $t_{1/2} > 10$ s) or with a stopped-flow spectrophotometer for fast reactions (e.g., $t_{1/2} \leq 10$ 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 4-nitrophenoxide ion at 400 nm. 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 potassium metal in anhydrous ethanol under nitrogen and stored in the refrigerator. The concentration of EtOK was determined by titration with mono potassium phthalate. The anhydrous ethanol was further dried over magnesium and was distilled under N_2 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 CH_3CN 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. 4-Nitrophenoxide ion was liberated quantitatively and identified as one of the products by comparison of the UV-vis spectrum at the end of reaction with the authentic sample under the experimental condition.

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