A Kinetic Study on Nucleophilic Displacement Reactions of Phenyl Y-Substituted-Phenyl Carbonates with Alkali Metal Ethoxides: Metal Ion Effect and Reaction Mechanism[#]

Ik-Hwan Um,*1 Ji-Yoon Seo,1 Ji-Sun Kang,1 and Jun-Sung An2

¹Department of Chemistry and Nano Science, Ewha Womans University, Seoul 120-750, Korea

²Hansung Science High School, Seoul 120-080, Korea

Received April 4, 2012; E-mail: ihum@ewha.ac.kr

Pseudo-first-order rate constants (k_{obsd}) have been measured for reactions of phenyl Y-substituted-phenyl carbonates with alkali metal ethoxides (EtOM, M = Li, Na, and K). The plot of k_{obsd} vs. [EtOM] curves upward for the reaction of diphenyl carbonate with EtOM but is linear for that with EtOK in the presence of 18-crown-6-ether (18C6), indicating that the reaction is catalyzed by M⁺ ions and the catalytic effect disappears in the presence of 18C6. The k_{obsd} values for the reactions with EtOK have been dissected into k_{EtO^-} and k_{EtOK} , i.e., the second-order rate constants for the reactions with dissociated EtO⁻ and ion-paired EtOK, respectively. The Hammett plots correlated with σ^- and σ° constants exhibit highly scattered points, while the Yukawa–Tsuno plots result in an excellent linear correlation with $\rho = 2.11$ and r = 0.21for k_{EtO^-} , and $\rho = 1.62$ and r = 0.26 for k_{EtOK} , implying that the reaction proceeds through a concerted mechanism. The catalytic effect (i.e., the k_{EtOK}/k_{EtO^-} ratio) is independent of the electronic nature of the substituent Y. Thus, it has been concluded that K⁺ ion catalyzes the reaction by increasing the electrophilicity of the reaction center.

Metal ions have often been reported to catalyze nucleophilic displacement reactions of esters as a Lewis acid catalyst.¹⁻¹⁰ Since the Lewis acidity increases with increasing the charge density of metal ions, most studies have focused on reactions involved multivalent metal ions (e.g., La³⁺, Eu³⁺, Co³⁺, Zn²⁺, Cu²⁺, Mn²⁺, etc.).¹⁻⁴ The effect of alkali metal ions on nucleophilic displacement reactions has been much less investigated, although alkali metal ions are ubiquitous and are known to play important roles in biological processes (e.g., the Na⁺/K⁺ pump to maintain high K⁺ and low Na⁺ concentration in mammalian cells).^{5–10} The first study on alkali metal ions has been performed by Buncel et al. for the nucleophilic displacement reaction of 4-nitrophenyl diphenylphosphinate (1a) (Chart 1) with alkali metal ethoxides (EtOM, where M = Li, Na, and K) in anhydrous ethanol.^{5a} They found that alkali metal ions catalyze the reaction of 1a and the catalytic effect increases as the charge density of M⁺ ions increases, i.e., $K^+ < Na^+ < Li^{+.5a}$

In contrast, we have recently reported that Li^+ ion inhibits the corresponding reaction of 4-nitrophenyl diphenylphosphinothioate (**1b**) while K⁺ and Na⁺ behave as a catalyst.⁸ A similar result has been reported for the reactions of various organophosphorus insecticides, e.g., paraoxon (**2a**), parathion (2b), methylparaoxon (3a), and methylparathion (3b).⁹ M⁺ ions catalyze the reactions of 2a and 3a in the order K⁺ < Na⁺ < Li⁺ while the reactions of 2b and 3b are catalyzed by K⁺ and Na⁺ but are inhibited by Li⁺, indicating that the effect of M⁺ ions (catalysis or inhibition) is dependent on the nature of the electrophilic centers.⁹

The effect of alkali metal ions has also been investigated in nucleophilic displacement reactions of carboxylic esters such as 4-nitrophenyl picolinate (4) and 2-pyridyl benzoate (5) with EtOM.^{10a,10b} Alkali metal ions have been reported to catalyze the reactions of 4 and 5, and the catalytic effects are in the order Na⁺ > K⁺ > Li⁺ for the reaction of 4^{10a} and Na⁺ > Li⁺ > K⁺ for that of 5.^{10b} An increase in the electrophilicity of the reaction site through a five-membered cyclic complex 4M⁺ or a six-membered cyclic complex 5M⁺ has been suggested to be responsible for the catalytic effect shown by M⁺ ions (Chart 2).^{10a,10b}

Similarly, it has been expected that M^+ ions would catalyze the reaction of 4-nitrophenyl 2-hydroxybenzoate (6) with EtOM through a six-membered cyclic complex $6M^+$. Unexpectedly, we have found that M^+ ions strongly inhibit the reaction through formation of $6M^{+.10c}$ We have shown that the reaction of 6 with EtOM proceeds rapidly through an α -



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Y = H (a), 4-Cl (b), 3-Cl (c), 4-CHO (d), 4-CO₂Et (e), 4-COMe (f), 4-CN (g), 4-NO₂ (h). M = Li, Na, K, K/18C6.

Scheme 1.

oxoketene intermediate in the presence of complexing agents for M^+ ions (e.g., 18-crown-6-ether for K^+ ion and 15-crown-5-ether for Na⁺ ion), but in the absence of such complexing agents, the reaction is extremely slow.^{10c} Thus, we have concluded that M^+ ions prevent the α -oxoketene process by forming **6** M^+ , which would be highly stable.^{10c}

We have now extended our study to the reaction of phenyl Y-substituted-phenyl carbonates 7a-7h with EtOM in anhydrous ethanol to get further information on M⁺ ion effects and reaction mechanisms (Scheme 1). We wish to report that alkali metal ions catalyze the reaction by increasing the electrophilicity of the reaction center, and the reaction proceeds through a concerted mechanism, in which expulsion of the leaving group in the transition state is advanced only a little. We have also demonstrated convincingly that the Yukawa–Tsuno equation is highly effective in deduction of the reaction mechanism.

Results and Discussion

The reaction was followed spectrophotometrically by monitoring the appearance of the leaving Y-substituted phenoxide anion under pseudo-first-order conditions with large excess EtOM. All reactions in the current study obeyed pseudo-firstorder kinetics. Pseudo-first-order rate constant (k_{obsd}) was calculated from the slope of the linear plot 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 kinetic results for the reactions of diphenyl carbonate (**7a**) with EtOM are shown in Figure 1 and are summarized in Table 1. The k_{obsd} values and detailed kinetic conditions for the reactions of phenyl Y-substituted-phenyl carbonates **7b**–**7h** with EtOK are summarized in Tables S1–S7 and are illustrated graphically in Figures S1–S7 in the Supporting Information.

Effect of Alkali Metal Ions on Reactivity. As shown in Figure 1, the reactivity of EtOM is highly dependent on the nature of the M⁺ ions, i.e., it decreases in the order EtOK > EtONa > EtOLi > EtOK/18C6. Besides, the plots of k_{obsd} vs. [EtOM] for reactions of **7a** with EtOM curve upward while the plot for the reaction with EtOK in the presence of 18-crown-6-ether (18C6), a complexing agent for K⁺ ion, is linear with decreased k_{obsd} values. Such curved plots are typical for



Figure 1. Plots of k_{obsd} vs. [EtOM] for the reactions of diphenyl carbonate (7a) with EtOLi (■), EtONa (○), and EtOK (●) and with EtOK in the presence of 18C6 (□) in anhydrous EtOH at 25.0 ± 0.1 °C. [18C6]/[EtOK] = 2.0.

Table 1.	Summary	of K	Linetic	Data	for	the	Reaction	ons	of
Diphen	yl Carbona	ate (7	a) with	t EtO	M in	Anł	nydrous	EtC	ΟH
at 25.0	$\pm 0.1 ^{\circ}\text{C}$								

EtOM	$k_{\rm EtO^-}/{ m M^{-1}s^{-1}}$	$k_{\rm EtOM}/{\rm M}^{-1}{\rm s}^{-1}$	$k_{\rm EtOM}/k_{\rm EtO^-}$
EtOLi	1.00	1.36	1.36
EtONa	1.01	2.08	2.06
EtOK	0.955	4.41	4.62
EtOK/18C6	1.02		

reactions in which alkali-metal ions were reported to behave as a Lewis acid catalyst. Thus, one can suggest that M^+ ions catalyze the reaction of **7a** in the order $K^+ > Na^+ > Li^+$ and the catalytic effect shown by K^+ ion disappears in the presence of the complexing agent.



Figure 2. Plot showing the effect of added 18C6 on k_{obsd} for the reaction of diphenyl carbonate (7a) with EtOK in anhydrous EtOH at 25.0 ± 0.1 °C. [EtOK] = 19.4 mM.





To examine the validity of the above argument, the reaction of **7a** with EtOK has been performed at a fixed EtOK concentration with varying the concentration of 18C6, i.e., [EtOK] = 19.4 mM and the [18C6]/[EtOK] = 0, 0.4, 0.7, 1.0, 1.4, 2.1, 2.8, and 3.6. As shown in Figure 2, the k_{obsd} value decreases rapidly upon addition of the complexing agent up to [18C6]/[EtOK] = 1.0 and then remains constant thereafter. This supports clearly the preceding argument that K⁺ ion catalyzes the reaction of **7a** and the catalytic effect disappears completely when [18C6]/[EtOK] \geq 1.0.

Dissection of k_{obsd} into k_{EtO^-} and k_{EtOM} . To quantify the catalytic effect exerted by M⁺ ions, k_{obsd} has been dissected into k_{EtO^-} and k_{EtOM} , i.e., the second-order rate constant for the reaction with the dissociated EtO⁻ and ion-paired EtOM, respectively. EtOM was reported to exist as a dimer or other aggregates in a high concentration region (e.g., [EtOM] > 0.1 M).¹¹ However, EtOM was suggested to exist as dissociated and ion-paired species in concentration below 0.1 M.¹¹ Since the current reactions are carried out in a low-concentration region (e.g., [EtOM] < 0.1 M), EtOM would exist as the dissociated EtO⁻ and ion-paired EtOM. Accordingly, one can suggest that both the dissociated EtO⁻ and the ion-paired EtOM react with the substrate with a rate constant k_{EtO^-} and k_{EtOM} , respectively, as shown in Scheme 2.



Figure 3. Plots illustrating dissection of k_{obsd} into k_{EtO^-} and k_{EtOM} for the reactions of diphenyl carbonate (**7a**) with EtOLi (**1**), EtONa (**C**), and EtOK (**•**) in anhydrous EtOH at 25.0 \pm 0.1 °C.

One can derive a rate equation as eq 1 on the basis of the reactions proposed in Scheme 2. Under a pseudo-firstorder kinetic condition, k_{obsd} can be expressed as eq 2. Since the dissociation constant $K_d = [EtO^-]_{eq}[M^+]_{eq}/[EtOM]_{eq}$, and $[EtO^-]_{eq} = [M^+]_{eq}$ at equilibrium, eq 2 becomes eq 3. The concentrations of $[EtO^-]_{eq}$ and $[EtOM]_{eq}$ can be calculated from the K_d value reported previously (i.e., $K_d = 4.72 \times 10^{-3}$, 9.80×10^{-3} , and 1.11×10^{-2} M for EtOLi, EtONa, and EtOK, in turn)¹² and the initial concentration of EtOM (i.e., [EtOM]) using eqs 4 and 5.

$Rate = k_{EtO^{-}}[EtO^{-}]_{eq}[7] + k_{EtOM}[EtOM]_{eq}[7]$	(1)

 $k_{\rm obsd} = k_{\rm EtO^{-}} [{\rm EtO^{-}}]_{\rm eq} + k_{\rm EtOM} [{\rm EtOM}]_{\rm eq}$ (2)

 $k_{\text{obsd}} / [\text{EtO}^-]_{\text{eq}} = k_{\text{EtO}^-} + k_{\text{EtOM}} [\text{EtO}^-]_{\text{eq}} / K_{\text{d}}$ (3)

$$[EtOM] = [EtO-]eq + [EtOM]eq$$
(4)

$$[\text{EtO}^{-}]_{\text{eq}} = [-K_{\text{d}} + (K_{\text{d}}^{2} + 4K_{\text{d}}[\text{EtOM}])^{1/2}]/2$$
(5)

One might expect that the plot of $k_{obsd}/[EtO^-]_{eq}$ vs. $[EtO^-]_{eq}$ is linear with a positive intercept, if the reaction proceeds as proposed in Scheme 2. In fact, Figure 3 shows that the plots for the reaction of **7a** with EtOM are linear with a positive intercept, indicating that the above equations derived from the reactions proposed in Scheme 2 are correct. Thus, one can calculate the k_{EtO^-} and k_{EtOM}/K_d values from the intercept and the slope of the linear plots, respectively. The k_{EtOM} value can be calculated from the k_{EtOM}/K_d ratios determined above and the K_d value reported previously. The calculated k_{EtO^-} and k_{EtOM}/K_d ratios are summarized in Table 1.

As shown in Table 1, the k_{EtO^-} value calculated from the intercept of the linear plots of $k_{\text{obsd}}/[\text{EtO}^-]_{\text{eq}}$ vs. $[\text{EtO}^-]_{\text{eq}}$ is practically identical to the k_{EtO^-} value of 1.02 M⁻¹ s⁻¹, which is calculated from the slope of the linear plot of k_{obsd} vs. [EtOK]





Table 2. Summary of Kinetic Data for the Reactions of Phenyl Y-Substituted-Phenyl Carbonates **7a–7h** with EtOK in Anhydrous EtOH at 25.0 ± 0.1 °C

Compound	Y	$k_{ m EtO^-} / { m M}^{-1} { m s}^{-1}$	$k_{\rm EtOK}$ $/{ m M}^{-1}{ m s}^{-1}$	$k_{ m EtOK} / k_{ m EtO^-}$
7a	Н	0.955	4.41	4.62
7b	4-Cl	5.11	15.2	2.97
7c	3-Cl	8.21	22.8	2.78
7d	4-CHO	22.0	51.6	2.35
7e	4-CO ₂ Et	11.4	37.9	3.32
7f	4-COMe	13.4	48.0	3.58
7g	4-CN	52.7	87.6	1.66
7h	4-NO ₂	82.5	151	1.83

in the presence of 18C6. In contrast, k_{EtOM} increases from $1.36 \,\text{M}^{-1} \,\text{s}^{-1}$ to 2.08 and 4.41 $\text{M}^{-1} \,\text{s}^{-1}$ as M^+ changes from Li⁺ to Na⁺ and K⁺ ions, in turn. Thus, one can suggest that the ion-paired EtOM is more reactive than the dissociated EtO⁻, and the metal ion effect (i.e., the $k_{\text{EtOM}}/k_{\text{EtO}}$ ratio) increases as the size of M⁺ ions increases, i.e., Li⁺ < Na⁺ < K⁺.

One might suggest that M^+ ions catalyze the reaction of **7a** by increasing the electrophilicity of the reaction center through formation of a four-membered cyclic transition state as modeled by TS_1 or by enhancing the nucleofugality of the leaving aryloxide via TS_2 (Chart 3). It is apparent that the enhanced nucleofugality through TS_2 is effective only when expulsion of the leaving-group occurs in the rate-determining step (RDS), but would be ineffective for reactions in which the leaving-group departs after RDS. Thus, we have performed reactions of phenyl Y-substituted-phenyl carbonates **7b**–**7h** with EtOK in anhydrous ethanol to investigate the reaction mechanism. The kinetic results will be discussed in the following section.

Reaction Mechanism. As shown in Figures S1–S7 in the Supporting Information, the plots of k_{obsd} vs. [EtOK] for the reactions of **7b–7h** with EtOK curve upward, while those of $k_{obsd}/[EtO^-]_{eq}$ vs. $[EtO^-]_{eq}$ are linear with a positive intercept in all cases. Thus, the k_{EtO^-} and k_{EtOK}/K_d values were determined from the intercept and slope of the linear plots, respectively, while the k_{EtOK} values were calculated from the k_{EtOK}/K_d values determined above and the K_d value reported previously for EtOK. The k_{EtO^-} and k_{EtOK} values calculated in this way are summarized in Table 2.

It is demonstrated that $k_{\rm EtO^-}$ increases as the substituent Y becomes a stronger electron-withdrawing group (EWG), e.g., it increases from 0.955 M⁻¹ s⁻¹ to 11.4 and 82.5 M⁻¹ s⁻¹ as the substituent Y changes from H to 4-CO₂Et and 4-NO₂, respectively. A similar result is shown for $k_{\rm EtOK}$, although the ion-paired EtOK is more reactive than the dissociated EtO⁻.



Figure 4. Hammett plots of $k_{\rm EtO^-}$ correlated with σ^- and σ° (inset) for the reactions of phenyl Y-substituted-phenyl carbonates **7a–7h** with EtOK in anhydrous EtOH at 25.0 ± 0.1 °C.

The reactions of 7a-7h with EtOK would proceed through a concerted mechanism or through a stepwise pathway with a tetrahedral intermediate. If the current reaction proceeds through a concerted mechanism, a partial negative charge would develop on the oxygen atom of the leaving group. Such a negative charge can be delocalized to the substituent Y through resonance interactions. Thus, one might expect that σ^- constants should give a better Hammett correlation than σ° constants, if the reaction proceeds through a concerted mechanism. On the contrary, if the reaction proceeds through a stepwise mechanism, formation of an intermediate should be RDS. This is because EtO⁻ is much more basic and a poorer nucleofuge than Y-substituted phenoxide anion (i.e., $k_{-1} \ll k_2$). Thus, if the reaction proceeds through a stepwise mechanism, no negative charge would develop on the oxygen atom of the leaving group. In this case, σ° constants should result in a better Hammett correlation than σ^- constants.

To investigate whether the reaction proceeds through a concerted mechanism or through a stepwise pathway with formation of an intermediate being the RDS, Hammett plots for k_{EtO^-} have been constructed in Figure 4 using σ^- and σ° constants. One can see that the Hammett plot correlated with σ^- constants results in a poor correlation with highly scattered points ($R^2 = 0.933$). The corresponding plot correlated with σ° constants results in a slightly better correlation but exhibits still many scattered points ($R^2 = 0.978$).

A similar result is demonstrated in Figure 5 for k_{EtOK} , i.e., the Hammett plot correlated with σ^- constants results in a poor correlation ($R^2 = 0.949$), while σ° constants shows a slightly better correlation ($R^2 = 0.976$). However, both Hammett plots

exhibit many scattered points. Thus, one cannot get conclusive information on reaction mechanism from these Hammett plots.

It is well known that the Yukawa–Tsuno eq 6 is a powerful tool for investigation of resonance effects in solvolyses of



Figure 5. Hammett plots of k_{EtOK} correlated with σ^- and σ° (inset) for the reactions of phenyl Y-substituted-phenyl carbonates **7a–7h** with EtOK in anhydrous EtOH at 25.0 ± 0.1 °C.

benzylic systems, in which a partial positive charge develops in the transition state.^{13–15} We have also shown that eq 6 is highly effective in clarifying ambiguities in reaction mechanisms for nucleophilic displacement reactions of various esters^{16–19} as well as Michael-type addition of amines to activated acetylenes.²⁰ Thus, Yukawa–Tsuno plots have been constructed to get more conclusive information on the reaction mechanism.

$$\log(k_{\rm Y}/k_{\rm H}) = \rho[\sigma^\circ + r(\sigma^- - \sigma^\circ)] \tag{6}$$

As shown in Figure 6, the Yukawa-Tsuno plots exhibit excellent linear correlations with $\rho = 2.11$ and r = 0.21 for k_{EtO^-} , and $\rho = 1.62$ and r = 0.26 for k_{EtOK} . Since the r value represents the extent of resonance contribution, one might suggest that a small negative charge develops, which can be delocalized on the substituent Y in the leaving group. Besides, the ρ values of 2.11 and 1.62 for the reactions with the dissociated EtO⁻ and ion-paired EtOK, respectively are larger than those reported for alkaline hydrolysis of Y-substituted phenyl benzoates ($\rho = 1.32$)^{16f} and thionobenzoates $(\rho = 1.11)$,^{17c} which were suggested to proceed through a stepwise mechanism with formation of an intermediate being the RDS on the basis of the fact that σ° constants result in much better correlation than σ^- constants. Thus, one can conclude that the reactions of 7a-7h with the dissociated EtO⁻ and ion-paired EtOK proceed through a concerted mechanism in which expulsion of the leaving group in the transition state is advanced only a little on the basis of the small r values.

Accordingly, one can suggest that K^+ ion catalyzes the reaction by increasing the electrophilicity of the reaction center through TS_1 or by enhancing the nucleofugality of the leaving aryloxide via TS_2 as mentioned in the preceding section. One might expect that the catalytic effect shown by K^+ ion is dependent on the electronic nature of the substituent Y, if the increased nucleofugality via TS_2 is responsible for the K^+ ion



Figure 6. Yukawa–Tsuno plots of k_{EtO^-} (a) and k_{EtOK} (b) for the reactions of phenyl Y-substituted-phenyl carbonates 7a–7h with EtOK in anhydrous EtOH at 25.0 ± 0.1 °C.

catalysis (proximal). In contrast, if K^+ ion catalysis is due to the enhanced electrophilicity through TS_1 , the catalytic effect would be little influenced by the electronic nature of the substituent Y (distal). Table 2 shows that the catalytic effect (i.e., the k_{EtOK}/k_{EtO^-} ratio) is independent of Y. Thus, one can conclude that M^+ ions catalyze the reactions of **7a**–**7h** with EtOK by increasing the electrophilicity of the reaction center through **TS**₁.

Conclusion

The current study has allowed us to conclude the following: (1) The plot of k_{obsd} vs. [EtOM] curves upward for the reaction of **7a** with EtOM but is linear for that with EtOK in the presence of 18C6, indicating that the reaction is catalyzed by M⁺ ions but the catalytic effect disappears in the presence of the complexing agent. (2) The σ^- and σ° constants result in poor Hammett correlations with many scattered points, while the Yukawa– Tsuno plots exhibit excellent linear correlations with $\rho = 2.11$ and r = 0.21 for k_{EtO^-} , and $\rho = 1.62$ and r = 0.26 for k_{EtOK} . Thus, the reaction proceeds through a concerted mechanism, in which departure of the leaving group in the transition state is advanced only a little. (3) The $k_{\text{EtOK}}/k_{\text{EtO}^-}$ ratio is independent of the electronic nature of the substituent Y, indicating that K⁺ ion catalyzes the reaction by increasing the electrophilicity of the reaction center through **TS**₁.

Overall, our study has revealed the role of M^+ ions and the reaction mechanism through the Yukawa–Tsuno equation.

Experimental

Materials. Compounds **7a–7h** were prepared readily as reported previously²¹ from the reaction of phenyl chloroformate and the respective Y-substituted phenol in the presence of triethylamine in anhydrous ether. The crude products were purified by column chromatography and their purity was checked by their melting points and ¹H NMR spectra. The EtOM stock solutions were prepared by dissolving the respective alkali metal in anhydrous ethanol under N₂ and stored in a refrigerator. The concentration of EtOM was measured by titration with monopotassium phthalate. 18-Crown-6ether (18C6) was recrystallized from acetonitrile and dried under vacuum. The anhydrous ethanol was further dried over magnesium and distilled under N₂ just before use.

Kinetics. Kinetic study was performed using a UV–vis spectrophotometer equipped with a constant-temperature circulating bath. The reactions were followed by monitoring the appearance of Y-substituted phenoxide ion. Reactions were followed generally for 9–10 half-lives and k_{obsd} were calculated using the equation, $\ln(A_{\infty} - A_t)$ vs. *t*. The plots of $\ln(A_{\infty} - A_t)$ vs. time were linear over 90% of the total reaction.

Products Analysis. Y-Substituted phenoxide was liberated quantitatively and identified as one of the products in the reactions of **7a–7h** by comparison of the UV–vis spectrum after completion of the reaction with that of authentic sample under the same reaction conditions.

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Supporting Information

The k_{obsd} values and detailed kinetic conditions for the reactions of **7b**–**7h** with EtOK are summarized in Tables S1–S7. The plots of k_{obsd} vs. [EtOK] and $k_{obsd}/[EtO^-]_{eq}$ vs. [EtO⁻]_{eq} are illustrated in Figures S1–S7. This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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