

Alkali Metal Ion Catalysis in Nucleophilic Substitution Reactions of 5-Nitro-8-quinolyl Benzoate with Alkali Metal Ethoxides in Anhydrous Ethanol: Unusually High Na⁺ Ion Selectivity

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Received October 5, 2007

Pseudo-first-order rate constants (k_{obsd}) have been measured spectrophotometrically for nucleophilic substitution reactions of 5-nitro-8-quinolyl benzoate (**5**) with alkali metal ethoxides, EtO⁻M⁺ (M⁺ = Li⁺, Na⁺ and K⁺) in anhydrous ethanol (EtOH) at 25.0 ± 0.1 °C. The plots of k_{obsd} vs. [EtO⁻M⁺] exhibit upward curvatures, while the corresponding plots for the reactions of **5** with EtO⁻Na⁺ and EtO⁻K⁺ in the presence of complexing agents, 15-crown-5-ether and 18-crown-6-ether are linear with rate retardation. The reactions of **5** with EtO⁻Na⁺ and EtO⁻Li⁺ result in significant rate enhancements on additions of Na⁺ClO₄⁻, indicating that the M⁺ ions behave as a catalyst. The dissociated EtO⁻ and ion-paired EtO⁻M⁺ have been proposed to react with **5**. The second-order rate constants for the reactions with EtO⁻ (k_{EtO^-}) and EtO⁻M⁺ ($k_{\text{EtO}^- \text{M}^+}$) have been calculated from ion-pairing treatments. The k_{EtO^-} and $k_{\text{EtO}^- \text{M}^+}$ values decrease in the order $k_{\text{EtO}^- \text{Na}^+} > k_{\text{EtO}^- \text{K}^+} > k_{\text{EtO}^- \text{Li}^+} > k_{\text{EtO}^-}$, indicating that ion-paired EtO⁻M⁺ species are more reactive than the dissociated EtO⁻ ion, and Na⁺ ion exhibits the largest catalytic effect. The M⁺ ions in this study form stronger complex with the transition state than with the ground state. Coordination of the M⁺ ions with the O and N atoms in the leaving group of **5** has been suggested to be responsible for the catalytic effect shown by the alkali metal ions in this study.

Key Words : Catalysis, Alkali metal ion, Ion-pair, Electrophilicity, Nucleofugality

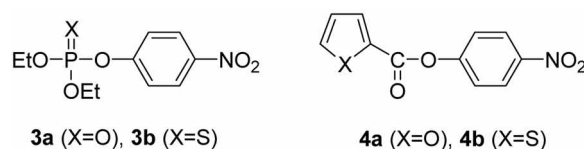
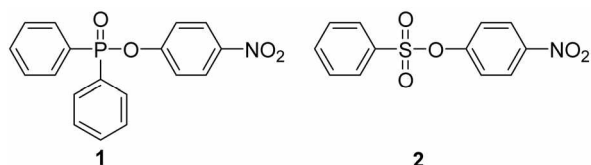
Introduction

Acyl-group transfer reactions have intensively been investigated due to the importance in biological processes.^{1,2} Metal ions such as Mg²⁺, Ca²⁺, Ni²⁺, Cu²⁺, Zn²⁺, Co²⁺, etc. have been reported to catalyze acyl-transfer reactions of various types in aqueous solution as Lewis acids,^{5,7} while La³⁺ ion has shown remarkable catalytic effects for alkaline metanalysis of phosphate di- and triesters.⁸

However, effects of alkali metal ions on acyl-group transfer reactions have much less been investigated although alkali metal ions are ubiquitous in biological systems. Buncel *et al.* have reported that alkali metal ions play an important role in the reactions of 4-nitrophenyl diphenylphosphinate (**1**) and benzenesulfonate (**2**) with alkali metal ethoxides (EtO⁻M⁺, M⁺ = Li⁺, Na⁺ and K⁺).^{9,10} In the reactions of **1**, alkali metal ions behave as a catalyst, and the catalytic effect decreases as the size of the metal ions increases (*i.e.*, Li⁺ > Na⁺ > K⁺).⁹ On the contrary, in the

reactions of **2**, the catalytic effect has been found to decrease as the size of the metal ions decreases.¹⁰

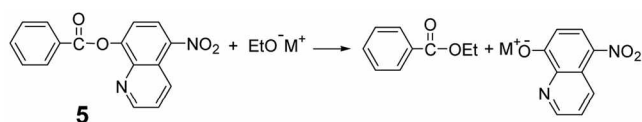
We have recently shown that alkali metal ions behave as a catalyst in the reactions of 4-nitrophenyl diethyl phosphate (**3a**) with EtO⁻M⁺, but as an inhibitor for the corresponding reactions of 4-nitrophenyl diethyl phosphinothioate (**3b**).¹¹ Both the catalytic and inhibitory effects have been found to decrease as the size of the metal ions increases (*i.e.*, Li⁺ > Na⁺ > K⁺).¹¹ These results clearly suggest that the effect of alkali metal ions is strongly dependent on the nature of the electrophilic center of the substrates (*e.g.*, P=O vs. SO₂ or P=O vs. P=S). The contrasting effects shown by these alkali metal ions have been explained by Eisenman's theory of ion exchange selectivity patterns being determined by competition between electrostatic factors and solvational energies or by the hard and soft acids and bases theory.⁹⁻¹¹



The effect of alkali metal ions on reactions of carboxylic esters has also been investigated.¹² It has been reported that the effect of M⁺ ions (M⁺ = Li⁺, Na⁺ and K⁺) is negligible for the reactions of 4-nitrophenyl benzoate with EtO⁻M⁺ in anhydrous ethanol (EtOH).^{12a} However, we have shown that M⁺ ions exhibit catalytic effect in the reactions of 4-nitrophenyl 2-furoate (**4a**) and 4-nitrophenyl 2-thiophenecarbox-

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$M^+ = Li^+, Na^+ \text{ and } K^+$

Scheme 1

ylate (**4b**) with EtO^-M^+ in the order $K^+ > Na^+ > Li^+$.^{12bc}

We have extended our study to reactions of 5-nitro-8-quinolyl benzoate (**5**) with EtO^-M^+ ($M^+ = Li^+, Na^+$ and K^+) in anhydrous EtOH to get more information on the effect of M^+ ions on reactions of carboxylic esters (Scheme 1). We wish to report our finding that the M^+ ions behave as a catalyst in the reactions of **5** with EtO^-M^+ , and the catalytic effect decreases in the order $Na^+ > K^+ > Li^+$, an unusually high Na^+ ion selectivity.

Results and Discussion

The kinetic study was performed spectrophotometrically under pseudo-first-order conditions with a large excess of EtO^-M^+ . All the reactions in current study obeyed pseudo-first-order kinetics. Pseudo-first-order rate constants (k_{obsd}) were obtained from the plots of $\ln(A_\infty - A_t)$ vs. t . It is estimated from replicate runs that the uncertainty in the k_{obsd} values is less than $\pm 3\%$. The k_{obsd} values for the reactions of **5** with EtO^-M^+ are summarized in Table 1 and illustrated in Figure 1. The second-order rate constants (k_{EtO^-} and $k_{EtO^-M^+}$) were determined from the ion-pairing treatment of the kinetic data and summarized in Table 2.

Effect of Alkali Metal Ions on Reactivity. As shown in Figure 1, the reactions of **5** with EtO^-M^+ result in upward curvatures in the plots of k_{obsd} vs. $[EtO^-M^+]$. The upward curvature is most remarkable for the reaction with EtO^-Na^+ . The corresponding plot for the reactions of **5** with EtO^-Na^+ in the presence of 15-crown-5-ether (15C5), a complexing agent for Na^+ ion, is linear with a significant decrease in reactivity. A similar result is shown for the reactions of **5** with EtO^-K^+ in the presence of 18-crown-6-ether (18C6), a complexing agent for K^+ ion. Thus, one can suggest that alkali metal ions catalyze the current reactions and the catalytic effect decreases in the order $EtO^-Na^+ > EtO^-K^+ > EtO^-Li^+$ on the basis of the degree of the upward curvatures

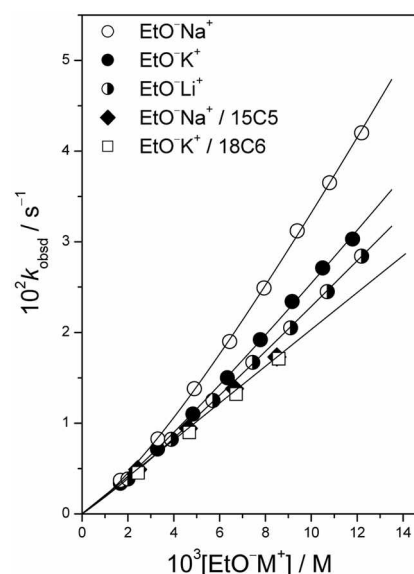


Figure 1. Plots of k_{obsd} vs. $[EtO^-M^+]$ for reactions of 5-nitro-8-quinolyl benzoate (**5**) with EtO^-Na^+ (\circ), EtO^-K^+ (\bullet), EtO^-Li^+ (\ominus), $EtO^-Na^+/15C5$ (\blacklozenge ; $[15C5]/[EtO^-Na^+] = 5.0$), and $EtO^-K^+/18C6$ (\square ; $[18C6]/[EtO^-K^+] = 5.0$) in anhydrous EtOH at 25.0 ± 0.1 °C.

in Figure 1.

To investigate the relative catalytic effect of Na^+ and Li^+ , the reactions of **5** with EtO^-Na^+ and EtO^-Li^+ have been performed under various concentrations of $Na^+ClO_4^-$ or $Li^+ClO_4^-$. The kinetic results are illustrated in Figure 2. As shown in the Figure for reactions with EtO^-Na^+ and EtO^-Li^+ , addition of $Na^+ClO_4^-$ results in significant rate enhancement. Besides, such rate enhancement appears to be more significant for the reaction with EtO^-Li^+ than for that with EtO^-Na^+ . On the contrary, the rate constant for the reaction of **5** with EtO^-Na^+ decreases upon initial addition of $Li^+ClO_4^-$ and then increases but only slightly upon further addition of the lithium salt, indicating that the catalytic effect by Li^+ ion is negligible.

Dissection of k_{obsd} into k_{EtO^-} and $k_{EtO^-M^+}$. It has been reported that EtO^-M^+ may exist as dimers or other aggregates in the high concentration (> 0.1 M).¹² However, in concentration below 0.1 M as in the current study, EtO^-M^+ has been suggested to exist mainly as dissociated and ion-paired species. Since both dissociated EtO^- and ion-paired

Table 1. Kinetic Data for Reactions of 5-Nitro-8-quinolyl Benzoate (**5**) with EtO^-M^+ in Anhydrous EtOH at 25.0 ± 0.1 °C

$10^3[EtO^-K^+]/M$	$10^3k_{obsd}/s^{-1}$	$10^3[EtO^-Na^+]/M$	$10^3k_{obsd}/s^{-1}$	$10^3[EtO^-Li^+]/M$	$10^3k_{obsd}/s^{-1}$
1.68	3.36	1.68	3.69	—	—
3.29	7.14	3.31	8.25	2.01	3.84
4.84	11.0	4.90	13.8	3.90	8.21
6.34	15.0	6.44	19.0	5.71	12.5
7.78	19.2	7.94	24.9	7.45	16.7
9.17	23.4	9.39	31.2	9.10	20.5
10.5	27.1	10.8	36.5	10.7	24.5
11.8	30.3	12.2	42.0	12.2	28.4

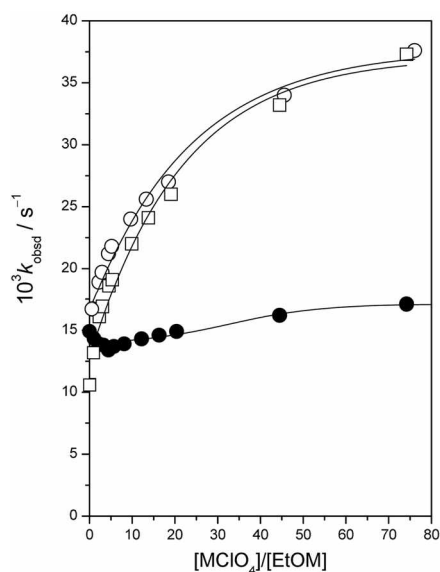


Figure 2. Plots showing effect of added salts ($MClO_4^-$) on the reactivity for reactions of 5-nitro-8-quinoyl benzoate (**5**) with EtO^-M^+ in anhydrous EtOH at 25.0 ± 0.1 °C. $EtO^-Na^+ + Na^+ClO_4^-$ (\circ), $EtO^-Li^+ + Na^+ClO_4^-$ (\square), $EtO^-Na^+ + Li^+ClO_4^-$ (\bullet). $[EtO^-Na^+] = 5.08 \times 10^{-3}$ M, $[EtO^-Li^+] = 4.93 \times 10^{-3}$ M.

EtO^-M^+ can react with the substrate **5** as shown in Scheme 2. one can derive a rate equation as eq. (1), in which k_{EtO^-} and $k_{EtO^-M^+}$ represent the second-order rate constants for the reaction with the dissociated EtO^- and ion-paired EtO^-M^+ , respectively. The pseudo-first-order rate constant (k_{obsd}) can be expressed as eq. (2).

Since the association constant, $K_{ass} = [EtO^-M^+]/[M^+][EtO^-]$ and $[EtO^-] = [M^+]$ at the equilibrium, eq. (2) becomes eq. (3). The concentration of EtO^- and EtO^-M^+ at the equilibrium can be calculated from the reported K_{ass} and the initial EtO^-M^+ concentration.

$$\text{Rate} = k_{EtO^-}[EtO^-][\mathbf{5}] + k_{EtO^-M^+}[EtO^-M^+][\mathbf{5}] \quad (1)$$

$$k_{obsd} = k_{EtO^-}[EtO^-] + k_{EtO^-M^+}[EtO^-M^+] \quad (2)$$

$$k_{obsd}/[EtO^-] = k_{EtO^-} + K_{ass} k_{EtO^-M^+} [EtO^-] \quad (3)$$

If the current reactions proceed as shown in Scheme 2, the plots of $k_{obsd}/[EtO^-]$ vs. $[EtO^-]$ should be linear and pass through a common intercept. In fact, as shown in Figure 3, all the plots are linear and pass through a common intercept regardless of the nature of M^- ions, indicating that both dissociated EtO^- and ion-paired EtO^-M^+ react with substrate **5**. Thus, one can determine the k_{EtO^-} and $K_{ass} k_{EtO^-M^+}$ values

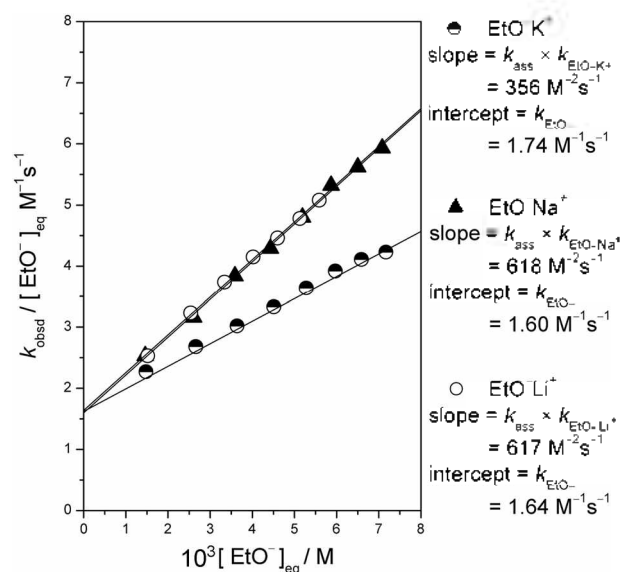
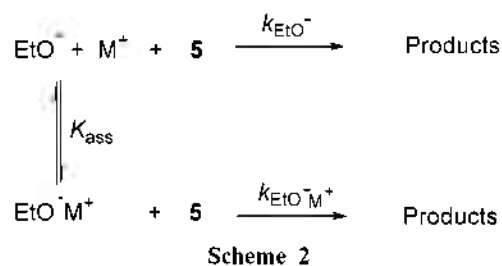


Figure 3. Plots illustrating dissection of k_{obsd} into rate constants due to dissociated and ion-paired ethoxides for reactions of 5-nitro-8-quinoyl benzoate (**5**) with EtO^-M^+ in anhydrous EtOH at 25.0 ± 0.1 °C.

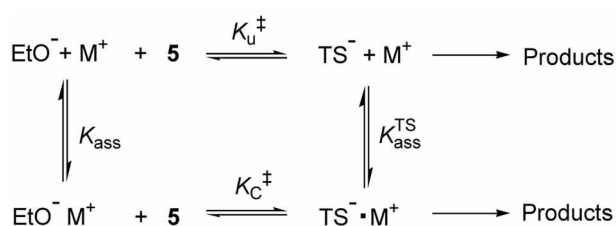
Table 2. Summary of Second-Order Rate Constants from Ion-Pairing Treatment of Kinetic Data for Reactions of 5-Nitro-8-quinoyl Benzoate (**5**) with Alkali Metal Ethoxides in Anhydrous EtOH at 25.0 ± 0.1 °C

EtO^-M^+	$k_{EtO^-}/M^{-1}s^{-1}$	$k_{EtO^-M^+}/M^{-1}s^{-1}$	$k_{EtO^-M^+}/k_{EtO^-}$
EtO^-K^+	1.74	3.96	2.37
EtO^-Na^+	1.60	6.06	3.63
EtO^-Li^+	1.64	2.91	1.74

from the intercept and the slope of the linear plots, respectively. Since the K_{ass} values of EtO^-Li^+ , EtO^-Na^+ and EtO^-K^+ have been reported to be 212, 102, and 90 M^{-1} for this series,¹⁴ the corresponding $k_{EtO^-M^+}$ value can be calculated from the slope of the linear plots in Figure 3. The k_{EtO^-} and $k_{EtO^-M^+}$ values determined in this way are summarized in Table 2.

Table 2 shows that the ion-paired species EtO^-M^+ is ca. 2 to 4 fold more reactive than the dissociated EtO^- , i.e., the k_{EtO^-} value is ca. $1.66 M^{-1}s^{-1}$ while the $k_{EtO^-M^+}$ values for EtO^-K^+ , EtO^-Na^+ and EtO^-Li^+ are 3.96, 6.06 and 2.91 $M^{-1}s^{-1}$, respectively. This is consistent with the preceding argument that the alkali metal ions catalyze the current reactions of **5**, and the catalytic effect decreases in the order $Na^+ > K^+ > Li^+$.

The order of catalytic effects found in this study is quite unusual since it has generally been reported to decrease with increasing (or decreasing) the size of alkali metal ions depending on the nature of the electrophilic center, i.e., $EtO^-Li^+ > EtO^-Na^+ > EtO^-K^+$ for alkaline ethanolysis of 4-nitrophenyl diphenylphosphinate (**1**)^{9a,b} and 4-nitrophenyl diethyl phosphate (**3a**)¹¹ while $EtO^-K^+ > EtO^-Na^+ > EtO^-Li^+$ for reactions of 4-nitrophenyl diethyl phosphinothioate (**3b**)¹¹ and 4-nitrophenyl benzenesulfonate (**2**).¹⁰



Scheme 3

Table 3. Association Constants for Various Alkali Metal Ions with the Ground State (K_{ass}) and Transition State ($K_{\text{ass}}^{\text{TS}}$) for Reactions of 5-Nitro-8-quinolyl Benzoate (**5**) in Anhydrous EtOH at 25.0 ± 0.1 °C^a

Metal Ion	$K_{\text{ass}}/\text{M}^{-1}$	$K_{\text{ass}}^{\text{TS}}/\text{M}^{-1}$
K ⁺	90	213
Na ⁺	102	370
Li ⁺	212	369

^a K_{ass} values were taken from ref. 14.

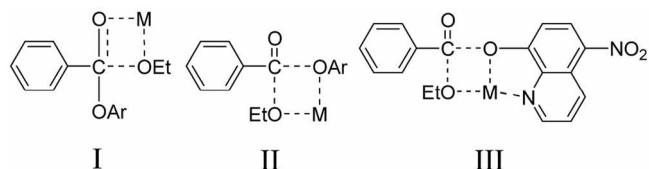
Interaction of M⁺ Ions with Ground State and Transition State. Alkali metal ions cannot be solvated in anhydrous EtOH as strongly as in H₂O. Accordingly, alkali metal ions in the ground state (GS) can be stabilized mainly through ion-pairing of M⁺ ions with EtO⁻ in EtOH. On the other hand, M⁺ ions can be stabilized through complexation with negatively charged transition state (TS). Then, the degree of stabilization of the GS and TS can be evaluated using a method developed by Kurz¹⁵ and in different forms by Mandolini¹⁶ and Tee.¹⁷

In the current study, the reaction mechanism can be expressed as in Scheme 3, which describes a set of equilibria among the reactants and TS's for catalyzed and uncatalyzed pathways. In this scheme, K_u^\ddagger and K_c^\ddagger represent the equilibrium constants for formation of the uncatalyzed and catalyzed TS's, while K_{ass} and $K_{\text{ass}}^{\text{TS}}$ are the association constants for ion-pairing of M⁺ with EtO⁻ and the TS, respectively. The $K_{\text{ass}}^{\text{TS}}$ values for the various M⁺ ions can be calculated from the relationship, $K_{\text{ass}}^{\text{TS}} = K_{\text{ass}} k_{\text{EtO}^- \cdot \text{M}^+} / k_{\text{EtO}^-}$ together with the reported K_{ass} values and the respective rate constants.¹⁵

The $K_{\text{ass}}^{\text{TS}}$ values determined in this study are summarized in Table 3. The $K_{\text{ass}}^{\text{TS}}$ value is larger than the corresponding K_{ass} value regardless of the nature of the alkali metal ions, indicating that M⁺ ions associate more strongly with TS than GS. Interestingly, Na⁺ ion exhibits the largest $K_{\text{ass}}^{\text{TS}}$ value, while K_{ass} value increases as the size of M⁺ ion decreases. This result clearly accounts for the unusually high Na⁺ ion selectivity found in this study.

Transition-state Structure. Alkali metal ions would catalyze the current reaction by increasing the electrophilicity or the nucleofugality through complexed structures I, II and III in the TS, *i.e.*, structure I would increase the electrophilicity of the carbonyl carbon of **5**, while structures II and III would enhance the nucleofugality of the leaving group. However, the possibility of catalysis through structures I and II would not be high. This is because the catalysis

by alkali metal ions has been reported to be negligible for reactions of 4-nitrophenyl benzoate with EtO⁻M⁺ (M⁺ = K⁺, Na⁺ and Li⁺) in anhydrous ethanol.^{12a} Furthermore, complexation of M⁺ ion as in structures I and II would not be as strong as in structure III. Thus, structure III is considered to be mainly responsible for the catalytic effect shown by the alkali metal ions in the current reactions.



Since the M⁺ ion in structure III would increase the nucleofugality of the leaving group, the catalysis by alkali metal ions is only possible when the leaving group departure is involved in the rate-determining step (RDS) either in a concerted or stepwise mechanism. On the other hand, when the leaving group departure occurs after the RDS structure III would not exert catalytic effects. Accordingly, the catalysis shown by alkali metal ions in this study would imply that the leaving group departure is involved in the RDS for the current reactions. However, the current result alone cannot distinguish whether the reaction proceeds through a concerted or stepwise mechanism. More systematic studies are required to determine the reaction mechanism.

Conclusions

The present study has allowed us to conclude the following: (1) Ion-paired EtO⁻M⁺ species are more reactive than the dissociated EtO⁻ ion toward substrate **5**. (2) Na⁺ ion exhibits the largest catalytic effect among the alkali metal ions studied, *i.e.*, the reactivity decreases in the order EtO⁻Na⁺ > EtO⁻K⁺ > EtO⁻Li⁺ > EtO⁻. (3) The alkali metal ions in this study form stronger complex with the transition state than with the ground state regardless of the nature of the metal ions. (4) Coordination of M⁺ ion with the O and N atoms in the quinolyl moiety of **5** (*i.e.*, TS structure III) is mainly responsible for the catalysis shown by the M⁺ ions.

Experimental Section

Materials. Compound **5** was prepared from the reaction of benzoyl chloride with 5-nitro-8-quinolinol in the presence of triethylamine in anhydrous ether. The solutions of EtO⁻M⁺ were prepared by dissolving the respective alkali metal in anhydrous ethanol under N₂ and stored in the refrigerator. The concentrations of EtO⁻M⁺ were determined by titration with standard HCl solution. 18-Crown-6-ether was recrystallized from Acetonitrile and dried under vacuum. The anhydrous ethanol used was further dried over magnesium and distilled under N₂.

Kinetics. Kinetic study was performed using a Scinco S-3100 UV-vis spectrophotometer equipped with a constant-temperature circulating bath. The reactions were followed

by monitoring the appearance of the leaving group at 455 nm. Pseudo-first-order conditions with EtO^-M^+ at least 20 times greater than substrate concentration were used. Generally, reactions were followed for 9-10 half-lives and k_{obsd} were calculated using the equation, $\ln(A_{\infty} - A_t)$ vs. t .

Acknowledgment. This work was supported by a grant from KOSEF of Korea (R01-2004-000-10279-0).

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