

The Effect of Alkali Metal Ions on Reactions of 8-(5-Nitroquinolyl) 3-Furoate with Alkali Metal Ethoxides in Anhydrous Ethanol

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Pseudo-first-order rate constants have been measured spectrophotometrically for the reactions of 8-(5-nitroquinolyl) 3-furoate with alkali metal ethoxides in anhydrous ethanol. The plot of k_{obs} vs the concentration of alkali metal ethoxides is linear for the reactions performed in the presence of a complexing agent, 18-crown-6 ether, but exhibits upward curvatures for the corresponding reactions performed in the absence of the complexing agent, indicating that the alkali metal ions in this study behave as catalysts. Second-order rate constants were determined for the reactions with dissociated free ethoxide (k_{EtO^-}) and with ion paired alkali metal ethoxides ($k_{\text{EtO}^- \text{M}^+}$) from ion pairing treatments. The magnitude of catalytic effect ($k_{\text{EtO}^- \text{M}^+}/k_{\text{EtO}^-}$) was found to be 1.7, 3.4 and 2.5 for the reaction of 8-(5-nitroquinolyl) 3-furoate, while 1.4, 3.6 and 4.2 for that of 4-nitrophenyl 2-furoate, 1.8, 3.7 and 2.4 for that of 8-(5-nitroquinolyl) benzoate, and 2.0, 9.8 and 9.3 for that of 8-(5-nitroquinolyl) 2-furoate with $\text{EtO}^- \text{Li}^+$, $\text{EtO}^- \text{Na}^+$ and $\text{EtO}^- \text{K}^+$, respectively. A 5-membered chelation at the leaving group is suggested to be responsible for the catalytic effect shown by alkali metal ions.

Keywords : Acyl-transfer reaction. Alkali metal ion catalysis. Ion pair, Kinetics.

Introduction

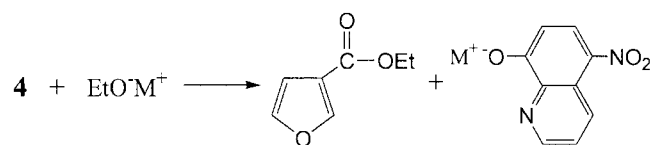
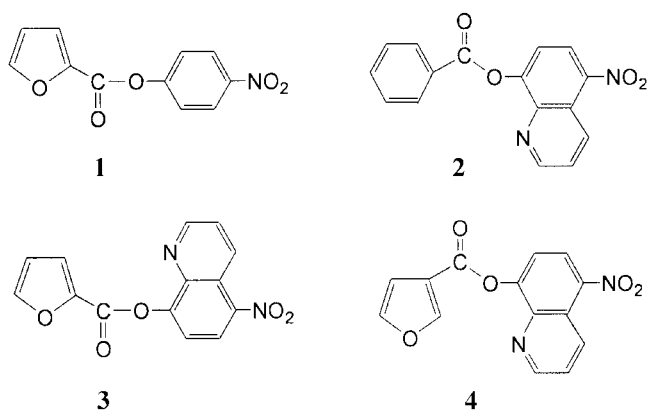
Due to importance in biological processes, acyl-group transfer reactions have been intensively investigated and their reaction mechanisms have been fairly well understood.¹⁻³ In acyl-group transfer reactions, alkali metal ions have been reported to act as a Lewis acid catalyst.⁴⁻⁸ Buncel *et al.* performed the reaction of 4-nitrophenyl diphenylphosphinate with alkali metal ethoxides ($\text{EtO}^- \text{M}^+$) in anhydrous ethanol and found that the reaction is significantly catalyzed by the alkali metal ions in the order $\text{Li}^+ > \text{Na}^+ > \text{K}^+$.^{6b} The reaction of 4-nitrophenyl benzenesulfonate with $\text{EtO}^- \text{M}^+$ in anhydrous EtOH was also found to be catalyzed by alkali metal ions, however, the catalytic effect was reported to decrease as the size of alkali metal ion decreases (*e.g.*, $\text{K}^+ > \text{Na}^+ > \text{Li}^+$).^{6c} Interestingly, we found that alkali metal ions behave as an inhibitor for the reaction of 4-

nitrophenyl diphenylphosphinate with alkali metal aryl-oxides ($\text{ArO}^- \text{M}^+$) in anhydrous EtOH.^{7a} These results clearly suggest that the effect of alkali metal ions is dependent on the electrophilic center of the substrate ($\text{P}=\text{O}$ and SO_2) as well as on the type of the nucleophiles (EtO^- and ArO^-).

Recently, we performed nucleophilic substitution reactions of 4-nitrophenyl 2-furoate (**1**),^{7b} 8-(5-nitroquinolyl) benzoate (**2**)^{7c} and 8-(5-nitroquinolyl) 2-furoate (**3**)^{7d} with $\text{EtO}^- \text{M}^+$ in anhydrous EtOH, and found that alkali metal ions play as a catalyst in these acyl-group transfer reactions. We expanded our study to the reaction of 8-(5-nitroquinolyl) 3-furoate (**4**) with $\text{EtO}^- \text{M}^+$ in anhydrous EtOH in order to get more information on the role of alkali metal ions on acyl-group transfer reactions (Scheme 1).

Experimental Section

Materials. 8-(5-nitroquinolyl) 3-furoate (**4**) was prepared easily from the reaction of 3-furoyl chloride with 5-nitro-8-quinolinol in anhydrous ether in the presence of trimethyl amine. The purity of **4** was checked by means of mp and its spectral characteristics such as IR and ¹H NMR spectra. Anhydrous ethanol was prepared by the method described in literature.^{7c} The stock solutions of alkali metal ethoxides were prepared by dissolving the corresponding alkali metal



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

Scheme 1

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in anhydrous ethanol under nitrogen atmosphere. The concentration of alkali metal ethoxides was titrated against potassium hydrogen phthalate.

Kinetics. The kinetic studies were performed spectrophotometrically using a Shinco S-1130 model UV-vis spectrophotometer equipped with a Leslab RTE-110 model constant temperature circulating bath to keep the reaction mixture at 25.0 ± 0.1 °C. The reactions were followed by monitoring the appearance of the leaving group at 410 nm.

Results

Kinetic studies were performed under pseudo-first-order conditions (e.g., $[4] \ll [EtO^-M^+]$), and all the reactions were obeyed pseudo-first-order kinetics over 90% of total reactions. Pseudo-first-order rate constants (k_{obs}) were determined from the well known equation, $\ln(A_\infty - A_t) = -k_{obs}t + c$. In Table 1 are summarized k_{obs} values together with the experimental conditions for the reaction of **4** with EtO^-M^+ in anhydrous EtOH. The uncertainty in any particular measur-

Table 1. Experimental conditions and pseudo-first-order rate constants for the reaction **4** with EtO^-M^+ in anhydrous ethanol at 25.0 ± 0.1 °C

M^-	$[EtO^-M^+]/10^{-3}$ M	$k_{obs}/10^{-2}$ s $^{-1}$
Li $^-$	0.888-8.28	1.57-18.1
Na $^+$	0.790-7.64	1.33-21.5
K $^+$	1.20-6.35	2.23-15.0
K $^-$ + 18C6	1.20-5.80	1.88-7.35

[18C6]/[EtO $^-$ K $^-$]=5

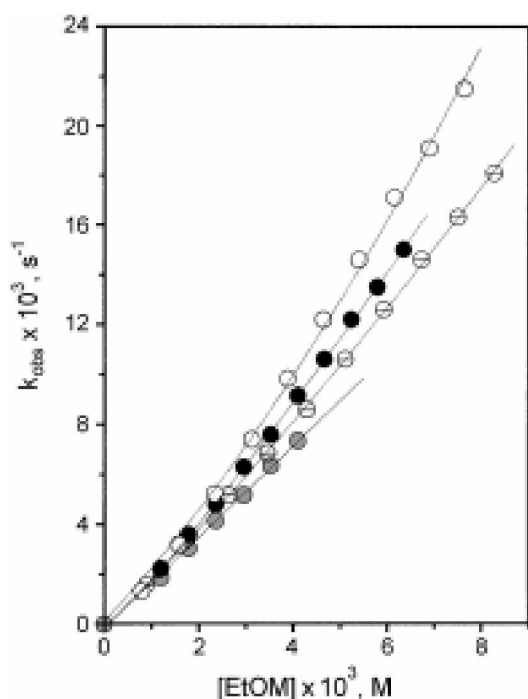


Figure 1. Kinetic data for the reactions **4** with EtO^-Li^+ (○), EtO^-Na^+ (□), EtO^-K^+ (●) and EtO^-K^+ +18C6 (●) in anhydrous ethanol at 25.0 ± 0.1 °C.

ed rate constant is estimated to be less than $\pm 3\%$ based on the results from replicate runs. The kinetic results are illustrated in Figure 1. In Figure 2 is demonstrated the effect of added complexing agent, 18-crown-6 ether (18C6), on k_{obs} for the reaction of **4** with EtO^-K^+ and EtO^-Na^+ in EtOH. The results of ion pairing treatments of kinetic data are summarized in Table 2 and demonstrated in Figure 3.

Discussion

Effect of Alkali Metal Ions on Reaction Rates. As shown in Figure 1, the plot of k_{obs} vs $[EtO^-M^+]$ is linear for the reaction of **4** with EtO^-K^+ in the presence of 18C6. However, the corresponding plot for the reaction with EtO^-M^+ in the absence of 18C6 exhibits upward curvature as the concentration of EtO^-M^+ increases. The degree of upward curvature increases in the order $EtO^-Li^+ < EtO^-K^+ < EtO^-Na^+$. Therefore, it is proposed that the reaction of **4** with EtO^-M^+ is catalyzed by alkali metal ions in the order $Li^+ < K^+ < Na^+$. Similar nonlinear plots have been reported

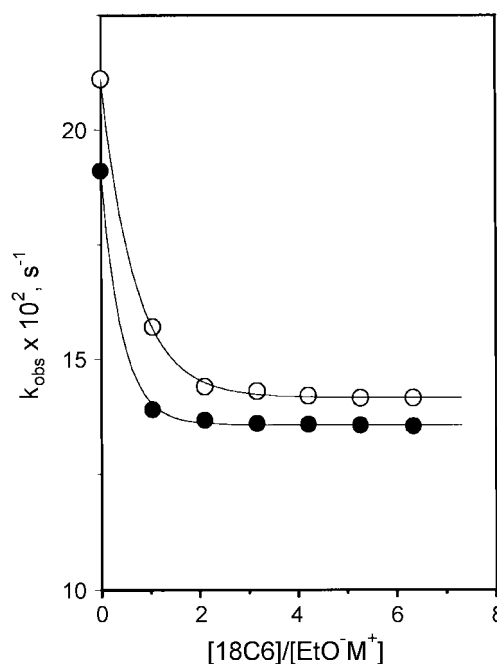


Figure 2. Effect of added 18C6 on the reaction of **4** with EtO^-Na^+ (○) and EtO^-K^+ (●) in anhydrous EtOH at 25.0 ± 0.1 °C. ($[EtO^-Na^+] = 7.64 \times 10^{-3}$ M; $[EtO^-K^+] = 7.59 \times 10^{-3}$ M)

Table 2. Second-order rate constants ($M^{-1}s^{-1}$) for various ethoxide species from ion pair treatment of kinetic data for the reaction of EtO^-M^+ with **1**, **2**, **3** and **4** in anhydrous ethanol at 25.0 ± 0.1 °C

	k_{EtO^-}	$k_{EtO^-Li^+}$	$k_{EtO^-Na^+}$	$k_{EtO^-K^+}$
1 ^a	24.5 ± 0.2	35.4 ± 0.2	84.3 ± 5.6	105 ± 3.0
2 ^b	1.66 ± 0.1	2.91 ± 0.1	6.06 ± 0.2	3.96 ± 0.1
3 ^c	4.81 ± 0.2	9.81 ± 0.7	47.0 ± 0.5	44.8 ± 0.7
4	1.62 ± 0.1	2.74 ± 0.2	5.49 ± 0.2	4.00 ± 0.1

^aData from reference.^{7b}Data from reference.^{7c}Data from reference.^{7d}

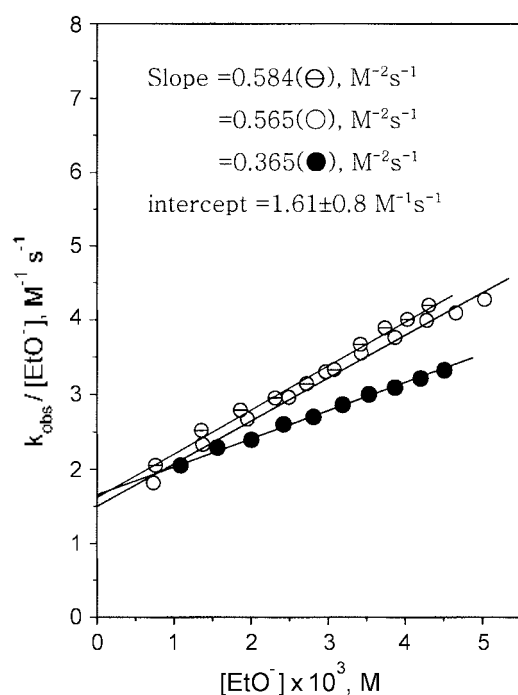


Figure 3. Plots illustrating dissection of observed rates into rate constants due to dissociated and ion paired ethoxide for the reactions of **4** with EtO^-Li^+ (Θ), EtO^-Na^+ (\circ) and EtO^-K^+ (\bullet) in anhydrous EtOH at 25.0 ± 0.1 °C.

for the reactions of EtO^-M^+ with substrates **1**, **2** and **3**.^{7b-d} However, the degree of upward curvature has been reported to increase in the order $\text{EtO}^-\text{Li}^+ < \text{EtO}^-\text{Na}^+ < \text{EtO}^-\text{K}^+$ for the reaction of **1**.^{7b} and $\text{EtO}^-\text{Li}^+ < \text{EtO}^-\text{K}^+ < \text{EtO}^-\text{Na}^+$ for the reactions of **2**^{7c} and **3**.^{7d} indicating that the order of catalytic effect is dependent on substrates.

In Figure 2 is demonstrated the effect of added 18C6 on the magnitude of k_{obs} value for the reaction of **4** with EtO^-Na^+ and EtO^-K^+ in anhydrous EtOH. The k_{obs} value for the reaction of **4** with EtO^-K^+ decreases sharply on addition of the complexing agent 18C6, and the k_{obs} value remains almost constant when the ratio of $[\text{18C6}]/[\text{EtO}^-\text{K}^+]$ exceeds about 1. However, the k_{obs} value for the corresponding reaction with EtO^-Na^+ decreases steadily until the ratio of $[\text{18C6}]/[\text{EtO}^-\text{Na}^+]$ becomes about 2-3. It has been well known that 18C6 is an effective complexing agent for K^+ ion but less effective in complexing Na^+ ion, since the size of Na^+ ion is much smaller than the cavity size of 18C6.⁹ This argument is consistent with the result shown in Figure 2. The sharp decrease in k_{obs} value for the reaction of **4** with EtO^-K^+ on addition of 18C6 suggests that complexation of K^+ ion by 18C6 would be completed when the ratio of $[\text{18C6}]/$

$[\text{EtO}^-\text{K}^+]$ becomes near 1, while the steady decrease in k_{obs} value on addition of 18C6 for the reaction with EtO^-Na^+ indicates that higher concentration of 18C6 is required to complex Na^+ ion completely in the reaction of **4** with EtO^-Na^+ .

Dissection of Nucleophilicity of Free and Ion Paired Ethoxides. Based on decreasing k_{obs} values on addition of 18C6 shown in Figure 2, one can suggest that the present reaction would proceed with dissociated free EtO^- and with ion paired EtO^-M^+ competitively as shown in Scheme 2, in which K_a represents the association constant of alkali metal ethoxide, eq. (1), while k_{EtO^-} and $k_{\text{EtO}^-\text{M}^+}$ are the second-order rate constant for the reaction of **4** with free EtO^- and with ion paired EtO^-M^+ , respectively.

$$K_a = [\text{EtO}^-\text{M}^+]/[\text{EtO}^-][\text{M}^+] = [\text{EtO}^-\text{M}^+]/[\text{EtO}^-]^2 \quad (1)$$

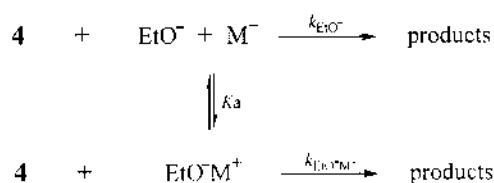
$$\text{Rate} = k_{\text{EtO}^-} [\text{EtO}^-] [\text{4}] + k_{\text{EtO}^-\text{M}^+} [\text{EtO}^-\text{M}^+] [\text{4}] \quad (2)$$

$$k_{\text{obs}} = k_{\text{EtO}^-} [\text{EtO}^-] + k_{\text{EtO}^-\text{M}^+} [\text{EtO}^-\text{M}^+] \quad \text{or} \\ k_{\text{obs}}/[\text{EtO}^-] = k_{\text{EtO}^-} + K_a k_{\text{EtO}^-\text{M}^+} [\text{EtO}^-] \quad (3)$$

One can derive a rate equation as shown in eq. (2). Since the reactions were performed under pseudo-first-order conditions (e.g., $[\text{4}] \ll [\text{EtO}^-\text{M}^+]$), eq. (2) can be simplified to eq. (3). If the reaction proceeds as shown in Scheme 2, the plot of $k_{\text{obs}}/[\text{EtO}^-]$ vs $[\text{EtO}^-]$ should be linear. In fact, as shown in Figure 3, the plot of $k_{\text{obs}}/[\text{EtO}^-]$ vs $[\text{EtO}^-]$ is linear for all the alkali metal ethoxides studied, indicating that the present reaction proceeds *via* metal ion catalyzed and uncatalyzed processes competitively. Therefore, one can calculate k_{EtO^-} and $K_a k_{\text{EtO}^-\text{M}^+}$ values from the intercepts and slopes of the linear plots, respectively. The K_a values of EtO^-M^+ in anhydrous EtOH have been reported to be 212, 102 and 90 M^{-1} for EtO^-Li^+ , EtO^-Na^+ and EtO^-K^+ , respectively.¹⁰ Accordingly, the second-order rate constant ($k_{\text{EtO}^-\text{M}^+}$) for the reaction with ion paired EtO^-M^+ can be calculated using the reported K_a values. The k_{EtO^-} and $k_{\text{EtO}^-\text{M}^+}$ values determined in the present reactions are summarized in Table 2 together with the corresponding k_{EtO^-} and $k_{\text{EtO}^-\text{M}^+}$ values for the reactions of **1**, **2** and **3** for a comparison purpose.

It has been generally known that the leaving group ability increases as the basicity of the leaving group decreases.¹¹ Since the $\text{p}K_a$ values of 4-nitrophenol and 5-nitro-8-quinolinol are reported to be 7.1 and 6.0, respectively,^{7c} one might expect **3** is more reactive than **1**. However, the results shown in Table 2 are contrary to the expectation. Recently we attributed this unexpected result to the nature of the rate-determining step (RDS) for the reaction of EtO^-M^+ with **1** and with **3**.^{7d} If the leaving group departure occurs after the RDS, the basicity of the leaving group would not influence the leaving group ability significantly. This argument is consistent with our previous proposal in the reaction of EtO^-Na^+ with a series of substituted phenyl benzoates in EtOH, in which the nucleofugality of aryloxides was demonstrated to be poorly correlated with the basicity of aryloxides.¹²

We recently demonstrated the reactivity of aryl substituted benzoates is governed significantly by the nature of the



Scheme 2

substituent on the benzoyl moiety, *i.e.*, an acid strengthening substituent in the benzoyl moiety increases reactivity while an acid weakening substituent decreases the reactivity toward anionic and neutral nucleophiles.^{12,13} A similar result has been reported for hydrolysis of aryl substituted benzoates.¹⁴ Substrates **2**, **3** and **4** have a common leaving group. Accordingly, the effect of leaving group on reactivity of these substrates would be absent. However, the acyl moiety of these substrates are different, *e.g.*, benzoyl, 2-furoyl and 3-furoyl for **2**, **3** and **4**, respectively. The pK_a of benzoic, 2-furoic and 3-furoic acid has been reported to be 4.20,^{15a} 3.16^{15b} and 3.95,^{15b} respectively. Therefore, one might expect that the reactivity is in the order $3 > 4 > 2$. In fact, As shown in Table 2, k_{EtO^-} for the reaction of **3** is about three times larger than those for the reactions of **2** and **4**. But **4** is slightly less reactive than **2**, indicating that the reactivity of these substrates is not solely governed by the acidity of the acyl moiety.

The Role of Alkali Metal Ions. Table 2 shows that k_{EtO-M^+} values are much larger than k_{EtO^-} for a given substrate, indicating that alkali metal ions catalyze the reaction and the ion paired EtO^-M^+ is more reactive than the dissociated free EtO^- toward **1**, **2**, **3** and **4** in anhydrous EtOH. For example, in the reaction of **4**, the k_{EtO^-} value is $1.62 M^{-1}s^{-1}$ while the k_{EtO-M^+} value changes from $2.74 M^{-1}s^{-1}$ to 5.49 and $4.00 M^{-1}s^{-1}$ as the metal ion changes from Li^+ to Na^+ and K^+ , indicating that the catalytic effect increases in the order $Li^+ < K^+ < Na^+$. This is consistent with the preceding proposal based on the degree of upward curvature in the plots of k_{obs} vs $[EtO^-M^+]$ shown in Figure 1. Similar results are shown in Table 2, *i.e.*, Na^+ ion exhibits the largest catalytic effect in the reactions of **2** and **3** with EtO^-M^+ . However, the k_{EtO-M^+} value for the reaction of **1** increases in the order $Li^+ < Na^+ < K^+$. Interestingly, Na^+ ion shows the largest catalytic effect for the reaction of **2**, **3** and **4** in which the leaving group is 5-nitro-8-quinolinolate anion.

A 5-membered chelation is possible at the acyl moiety of substrate **1** as shown in **1M** with alkali metal ions. Such a complexation would increase the electrophilicity of the carbonyl carbon of **1**. In fact, as shown in Table 2, the reaction of **1** with EtO^-M^+ is catalyzed by alkali metal ions, *i.e.*, k_{EtO-M^+}/k_{EtO^-} is 1.4, 3.4 and 4.2 for the reaction of **1** with

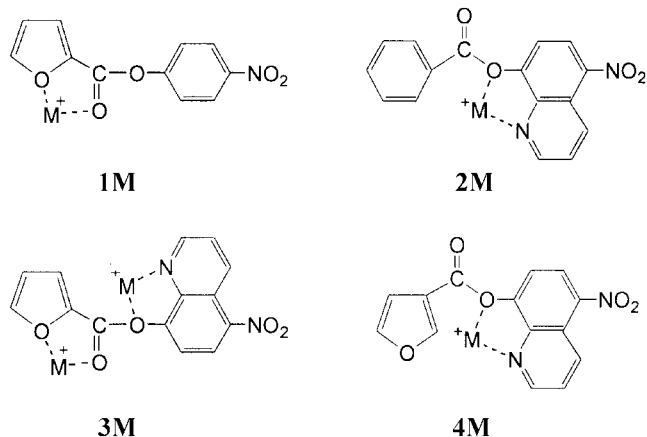
EtO^-Li^+ , EtO^-Na^+ and EtO^-K^+ , respectively. Therefore, one can suggest that the 5-membered chelation at the acyl moiety is responsible for the catalytic effect shown by alkali metal ions in the reaction of **1**.

The leaving group in substrates **2**, **3** and **4** can make complexes with alkali metal ions as shown in **2M**, **3M** and **4M**. The complexes shown in **2M**, **3M** and **4M** can increase the electrophilicity of the carbonyl carbon of these substrates, and would be responsible for the catalytic effect shown by M^+ ions. As shown in **3M**, substrate **3** can form two 5-membered chelations both at the acyl moiety and at the leaving group, while the other substrates can make only one chelation either at the acyl moiety (**1M**) or at the leaving group (**2M** and **4M**). Since both chelations at the acyl moiety and at the leaving group would increase the electrophilicity of the carbonyl carbon, one might expect the catalytic effect is most significant for the reaction of **3** with EtO^-M^+ . In fact, the catalytic effect is observed to be largest for the reaction of **3**, *i.e.*, k_{EtO-M^+}/k_{EtO^-} is 2.0, 9.8 and 9.3 for the reaction with EtO^-Li^+ , EtO^-Na^+ and EtO^-K^+ , respectively. The catalytic effect resulted from the chelation at the acyl moiety (**1M**) is nearly the same as the one resulted from the chelation at the leaving group (**2M** and **4M**) for the reactions with EtO^-Li^+ and with EtO^-Na^+ . However, the k_{EtO-K^+}/k_{EtO^-} value for the reaction of **1** is much larger than the ones for the reactions of **2** and **4**, indicating that the catalytic effect of K^+ ion is more significant in the acyl moiety than in the leaving group.

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