

The Catalytic Effect of Alkali Metal Ions on Reactions of 8-(5-Nitroquinolyl) 2-Furoate with Alkali Metal Ethoxides in Anhydrous Ethanol

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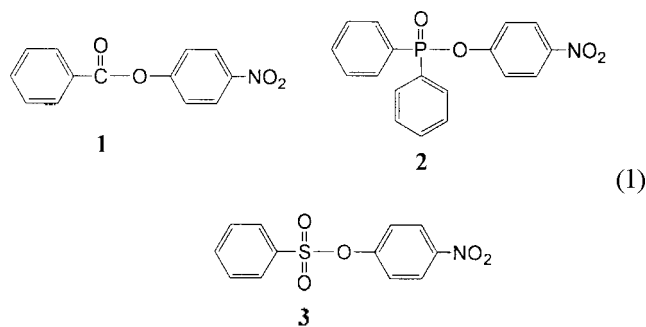
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Pseudo-first-order rate constants have been measured spectrophotometrically for the title reactions. The plot of k_{obs} vs the concentration of alkali metal ethoxides is linear for the reactions performed in the presence of complexing agent, 18-crown-6 ether, but curved upwardly for the corresponding reactions performed in the absence of the complexing agent, indicating that the alkali metal ions studied in this study behave as a catalyst. The catalytic effect was found to increase in the order $\text{Li}^+ \ll \text{K}^- \leq \text{Na}^+$. 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 2.3, 9.5 and 8.7 for the reaction of 8-(5-nitroquinolyl) 2-furoate, while 1.4, 3.6 and 4.2 for that of 4-nitrophenyl 2-furoate, indicating that the catalytic effect is larger in the reaction of the former substrate than in that of the latter one. The larger catalytic effect was attributed to two possible complexing sites with alkali metal ions in the former substrate.

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

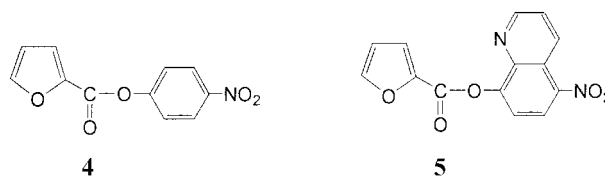
Introduction

Acyl-group transfer reactions have been intensively investigated due to importance in biological processes.¹⁻³ In acyl-group transfer reactions, metal ions have been reported to act as a Lewis acid catalyst.⁴⁻⁸ However, the studies of metal ions have been mostly directed to divalent metal ions such as Ni^{2+} , Zn^{2+} , Cu^{2+} , etc.^{4,5} The effect of alkali metal ions on acyl-group transfer reaction has been much less investigated.⁶⁻⁸



Buncel *et al.* performed the reaction of 4-nitrophenyl benzoate (**1**) with alkali metal ethoxides ($\text{EtO}^- \text{M}^+$) in anhydrous ethanol and found that the effect of alkali metal ions (Li^- , Na^- and K^-) on the acyl-group transfer reaction is insignificant.^{6a} However, the reaction of 4-nitrophenyl diphenylphosphinate (**2**) with $\text{EtO}^- \text{M}^+$ in anhydrous EtOH was found to be significantly catalyzed by the alkali metal ions in the order $\text{Li}^+ > \text{Na}^+ > \text{K}^-$.^{6b} On the contrary, the catalytic effect was found to decrease as the size of alkali metal ion decreases (*e.g.*, $\text{K}^+ > \text{Na}^+ > \text{Li}^+$) for the corre-

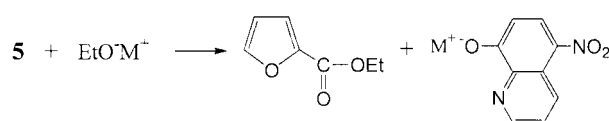
sponding reaction of 4-nitrophenyl benzenesulfonate (**3**) with $\text{EtO}^- \text{M}^+$ in anhydrous EtOH.^{6c} Interestingly, we found that alkali metal ions behave as an inhibitor for the reaction of **2** with alkali metal aryloxides ($\text{ArO}^- \text{M}^+$) in anhydrous EtOH.^{7a} These results clearly suggest that the effect of alkali metal ions is dependent on the electrophilic center of the substrate ($\text{C}=\text{O}$, $\text{P}=\text{O}$ 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 (**4**) with $\text{EtO}^- \text{M}^+$ in anhydrous EtOH, and found alkali metal ions play as a catalyst in the acyl-group transfer reaction.^{7b} We expanded our study to the reaction of 8-(5-nitroquinolyl) 2-furoate (**5**) with $\text{EtO}^- \text{M}^+$ in anhydrous EtOH in order to get further information on the role of alkali metal ions on acyl-group transfer reactions (Scheme 1).

Experimental Section

Materials. 8-(5-nitroquinolyl) 2-furoate (**5**) was synthe-



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

Scheme 1

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sized from the reaction of 2-furoyl chloride with 5-nitro-8-quinolinol in anhydrous ether in the presence of trimethyl amine. The purity of **5** 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.^{7b} The stock solutions of alkali metal ethoxides were prepared by dissolving the corresponding alkali metal 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. All the reactions were performed under pseudo-first-order reaction conditions in which alkali metal ethoxides were over 20 times more concentrated than the substrate **5**.

Results

All the reactions were performed under pseudo-first-order conditions (*e.g.*, $[\mathbf{5}] \ll [\text{EtO}^-\text{M}^+]$), and obeyed pseudo-first-order kinetics over 90% of the total reactions. Pseudo-first-order rate constants (k_{obs}) were obtained from the well known equation, $\ln(A_\infty - A_t) = -k_{\text{obs}}t + c$. In Table 1 are summarized k_{obs} values obtained in this way together with the experimental conditions for the reaction of **5** with EtO^-M^+ in anhydrous EtOH. It is estimated from replicate runs that the uncertainty in any particular measured rate constant is less than $\pm 3\%$. The kinetic results are illustrated in Figure 1 together with the ones for the corresponding reactions of **4** with EtO^-M^+ for a comparison purpose. In Figure 2, the effect of added complexing agent, 18-crown-6 ether (18C6), on k_{obs} is demonstrated for the reaction of **5** with EtO^-K^+ in EtOH. The results of ion pairing treatments of kinetic data are summarized in Table 2 and demonstrated in Figure 3.

Discussion

As shown in Figure 1, the plot of k_{obs} vs $[\text{EtO}^-\text{K}^+]$ is linear for the reaction of **5** with EtO^-K^+ in the presence of 18C6, while the one for the corresponding reaction in the absence of 18C6 is nonlinear. A careful examination of Figure 1

Table 1. Experimental conditions and k_{obs} values for the reaction of 8-(5-nitroquinolyl) 2-furoate (**5**) with EtO^-M^+ in anhydrous EtOH at 25.0 ± 0.1 °C

M^+	$[\text{EtO}^-\text{M}^+] \times 10^3, \text{M}$	$k_{\text{obs}} \times 10^2, \text{s}^{-1}$
Li^+	0.888-12.0 (1.56-5.25) ^a	0.437-7.88 (4.18-15.2)
Na^+	1.11-6.40 (1.64-4.76)	0.986-11.5 (5.11-18.6)
K^+	1.20-6.91 (1.56-7.34)	1.01-12.0 (4.18-21.6)
$\text{K}^+ + 18\text{C6}$	1.20-8.00 (0.55-4.11)	0.55-4.11 (1.98-9.07)

[18/6]/[EtO⁻K⁺]=5(4)

^aThe data in parentheses are taken from ref. 12 for the corresponding reaction of 4-nitrophenyl 2-furoate (**4**).

reveals that the plot for the reaction with EtO^-Li^+ is slightly upward but the ones for the reactions with EtO^-K^+ and EtO^-Na^+ are significantly curved. Such upward curvatures indicate that these alkali metal ions behave as a catalyst in the present reaction.

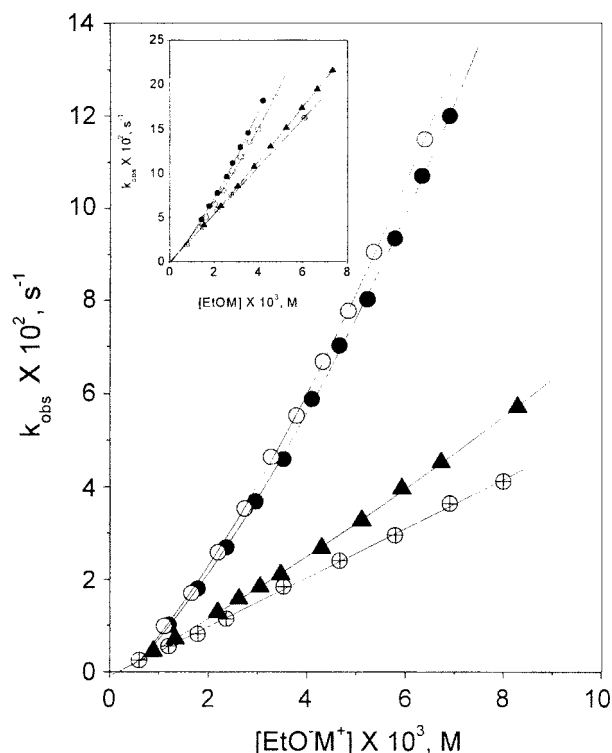


Figure 1. Kinetic data for the reactions of 8-(5-nitroquinolyl) 2-furoate (**5**) with EtOLi (\blacktriangle), EtONa (\circ), EtOK (\bullet), EtOK-18C6 (\oplus) and in anhydrous ethanol at 25.0 ± 0.1 °C. The inset of the figure represents the kinetic results for the corresponding reaction of 4-nitrophenyl 2-furoate (**4**).

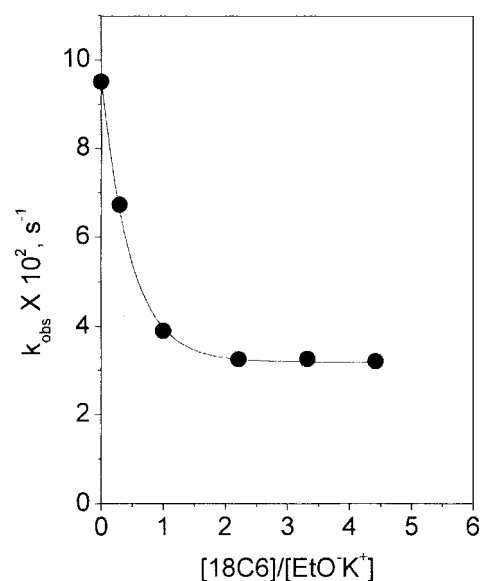


Figure 2. Effect of added 18C6 on the reaction of 8-(5-nitroquinolyl) 2-furoate (**5**) with EtO^-K^+ in anhydrous EtOH at 25.0 ± 0.1 °C. ($[\text{EtO}^-\text{K}^+] = 3.91 \times 10^{-3} \text{M}$).

Table 2. Second-order rate constants for various ethoxide species from ion pair treatment of kinetic data for the reaction of 8-(5-nitroquinolyl) 2-furoate (**5**) with EtO^-M^+ in anhydrous EtOH at 25.0 ± 0.1 °C

EtO^-M^+	$k_{\text{EtO}^-}, \text{M}^{-1}\text{s}^{-1}$	$k_{\text{EtO}^-\text{M}^+}, \text{M}^{-1}\text{s}^{-1}$
EtO^-Li^+	$4.29 \pm 0.1 (24.2 \pm 0.1)^a$	$9.81 \pm 0.7 (36.2 \pm 0.2)$
EtO^-Na^+	$4.97 \pm 0.2 (23.7 \pm 1.5)$	$47.0 \pm 0.5 (83.1 \pm 5.7)$
EtO^-K^+	$5.16 \pm 0.4 (24.9 \pm 0.4)$	$44.8 \pm 0.7 (106 \pm 2.0)$

^aThe data in parentheses are taken from ref. 12 for the corresponding reaction of 4-nitrophenyl 2-furoate (**4**).

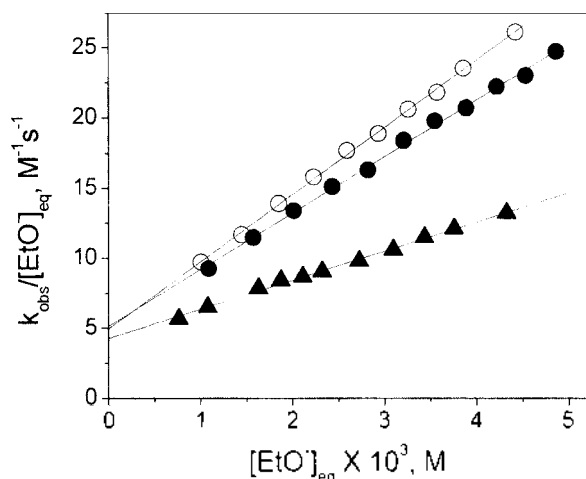
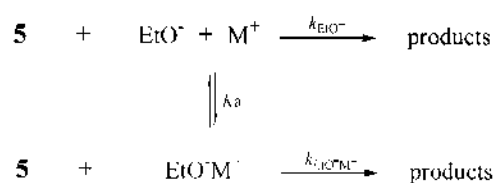


Figure 3. Plots illustrating dissection of observed rates into rate constants due to dissociated and ion paired ethoxide for the reactions of 8-(5-nitroquinolyl) 2-furoate (**5**) with EtOLi (▲), EtONa (○) and EtOK (●) in anhydrous EtOH at 25.0 ± 0.1 °C.

One can see that the degree of upward curvature is more significant for the reaction of **5** than **4**. It is also demonstrated that the curvature is strongly dependent on the nature of the alkali metal: the degree of upward curvature increases in the order $\text{EtO}^-\text{Li}^+ \ll \text{EtO}^-\text{K}^+ \leq \text{EtO}^-\text{Na}^+$ for the reaction of **5**, and $\text{EtO}^-\text{Li}^+ < \text{EtO}^-\text{Na}^+ < \text{EtO}^-\text{K}^+$ for the reaction of **4**. The catalytic effect of alkali metal ions has been generally reported to be in the order $\text{Li}^- > \text{Na}^+ > \text{K}^+$ or the reverse, depending on substrates.^{6,7} Therefore, the order of catalytic effect in the present system is unusual.

Since EtOH is less polar than H_2O , ionic species would be less solvated in EtOH than in H_2O . However, ionic species can be stabilized by forming ion pair, dimer and other aggregates in high concentration. Pechanec *et al.* reported that alkali metal ethoxides form dimers and other aggregates in high concentration but exist as dissociated free EtO^- in low concentration (< 0.1 M) in anhydrous EtOH.⁹ Since the concentration of EtO^-M^+ is much lower than 0.1 M in the present study, EtO^-M^+ would exist both dissociated and ion paired species. 18C6 has been known to be highly effective to complex K^+ ion.¹⁰ Therefore, EtO^-K^+ would exist as dissociated EtO^- in the presence of 18C6. In Figure 2 is demonstrated the effect of added 18C6 to the reaction mixture on k_{obs} for the reaction of **5** with EtO^-K^+ in EtOH. One can see that the k_{obs} value decreases sharply on the initial addition of 18C6. However, the k_{obs} value remains nearly constant when



Scheme 2

the $[\text{18C6}]/[\text{EtO}^-\text{K}^+]$ value reaches about 1. Such a rate retardation upon addition of the complexing agent supports the preceding argument that the present acyl-group transfer reaction is catalyzed by alkali metal ions.

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 refers to the association constant of alkali metal ethoxide, eq. (1), and k_{EtO^-} and $k_{\text{EtO}^-\text{M}^+}$ represent the second-order rate constant for the reaction of **5** with free EtO^- and with ion paired EtO^-M^+ , respectively.

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

$$\text{Rate} = k_{\text{EtO}^-}[\text{EtO}^-][\mathbf{5}] + k_{\text{EtO}^-\text{M}^+}[\text{EtO}^-\text{M}^+][\mathbf{5}] \quad (2)$$

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

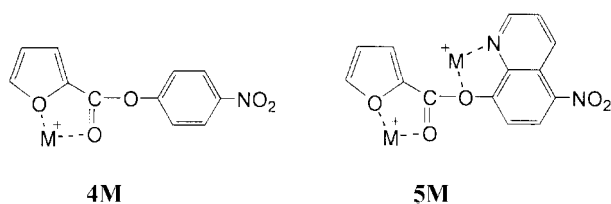
One can derive a rate equation as eq. (2). Under pseudo-first-order reaction conditions ($[\mathbf{5}] \ll [\text{EtO}^-\text{M}^+]$), eq. (2) can be simplified to eq. (3). If the present reaction proceeds as shown in Scheme 2, one would expect linear correlations between $k_{\text{obs}}/[\text{EtO}^-]$ and $[\text{EtO}^-]$. 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. Therefore, k_{EtO^-} and $K_a k_{\text{EtO}^-\text{M}^+}$ values were determined from the intercepts and slopes of the plots, respectively. Since the K_a value of EtO^-M^+ in anhydrous EtOH is available in literature,⁹ the second-order rate constant for the reaction with ion paired EtO^-M^+ can be calculated. The k_{EtO^-} and $k_{\text{EtO}^-\text{M}^+}$ values determined in this way are summarized in Table 2.

As shown in Table 2 for the reaction of **5** with EtO^-M^+ , the k_{EtO^-} values for EtO^-Na^+ and EtO^-K^+ are practically the same within experimental error, while the one for EtO^-Li^+ is slightly smaller than the others. The magnitude of $k_{\text{EtO}^-\text{M}^+}$ is significantly dependent on the identity of alkali metal ions, e.g., $k_{\text{EtO}^-\text{Li}^+} \ll k_{\text{EtO}^-\text{K}^+} \leq k_{\text{EtO}^-\text{Na}^+}$. Besides, $k_{\text{EtO}^-\text{M}^+}$ values are larger than k_{EtO^-} . These results are consistent with the preceding argument that the ion paired EtO^-M^+ is more reactive than the dissociated EtO^- toward **5**, and the catalytic effect is in the order $\text{Li}^- \ll \text{K}^+ < \text{Na}^+$.

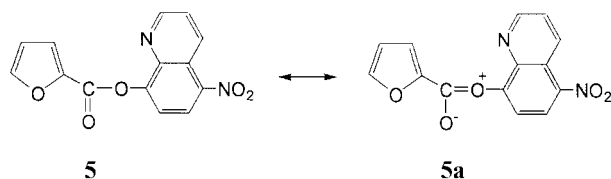
As shown in Table 2, the magnitude of k_{EtO^-} and $k_{\text{EtO}^-\text{M}^+}$ is larger for the reaction of 4-nitrophenyl 2-furoate (**4**) than for that of 8-(5-nitroquinolyl)-2-furoate (**5**), indicating that **4** is more reactive than **5** in the present reaction condition. It has been generally understood that the leaving group ability (nucleofugality) increases with decreasing the basicity of the leaving group.¹¹ The $\text{p}K_a$ values have been reported to be 7.1 and 6.0 for the conjugate acid of the leaving group of **4** and **5**, respectively.¹² Therefore, one might expect that **5** is more

reactive than **4**, but the results shown in Table 2 are contrary to the expectation. However, the present results are not unusual, since deviations in Brønsted-type plots have been often reported for reactions in which the leaving group departure occurs after the rate-determining step (RDS).¹³ Reactions of carboxylic esters with amines have been known to proceed through an addition intermediate and the RDS is dependent on the basicity of the leaving group and the nucleophilic amines.¹⁴⁻¹⁶ However, the corresponding reactions with anionic nucleophiles have not been completely understood. Some studies have suggested that nucleophilic substitution reactions of carboxylic esters with anionic nucleophiles proceed through an addition intermediate,^{17,18} while other studies support one-step concerted mechanism.^{3,19} Therefore, if the leaving group departure occurs after the RDS, the basicity of the leaving group would not exhibit a good correlation with its nucleofugality.

Table 2 demonstrates that the metal ion effect is more significant for the reactions of **5** than **4**. *e.g.*, the $k_{\text{EtO}^- \text{M}^+}/k_{\text{EtO}^-}$ values are 2.3, 9.5 and 8.7 for the reaction of **5** with $\text{EtO}^- \text{Li}^+$, $\text{EtO}^- \text{Na}^+$ and $\text{EtO}^- \text{K}^+$, respectively, while 1.4, 3.6 and 4.2 for the reaction of **4** with $\text{EtO}^- \text{Li}^+$, $\text{EtO}^- \text{Na}^+$ and $\text{EtO}^- \text{K}^+$, respectively. The catalytic effect of these alkali metal ions has been suggested to originate from an increase in the electrophilicity of the carbonyl carbon of **4** by formation of a complex as shown below (**4M**).^{7b}



However, in the substrate **5**, two complexation sites are possible. *e.g.* **5M**. The complexation at the leaving group moiety as in **5M** would increase the electrophilicity of the carbonyl carbon by decreasing the resonance contribution of **5a**. The resonance structure of **5a** would decrease the electrophilicity of the carbonyl carbon of **5**, and would result in rate retardation. A similar argument has been suggested by Neuvonen *et al.* recently in the hydrolysis of aryl acetates and methyl benzoates. Based on the catalytic effect shown by alkali metal ions in the present system, the complexation shown in **4M** and **5M** should be more significant at the transition state than at the ground state.



The present study has shown that the catalytic effect of the alkali metal ions is larger for the reaction of **5** than for that of **4**. The enhanced catalytic effect found in the reactions of **5** can be attributed to the two possible complexation sites (*e.g.* **4M** vs **5M**). However, further study is necessary to deter-

mine relative contributions of the two possible complexations.

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