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Metal Ion Catalysis and Inhibition in Nucleophilic Substitution Reactions of 4-Nitrophenyl Nicotinate and Isonicotinate with Alkali Metal Ethoxides in Anhydrous Ethanol

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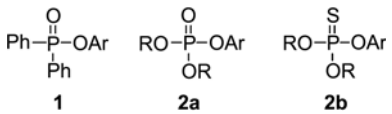
A kinetic study is reported on nucleophilic substitution reactions of 4-nitrophenyl nicotinate **5** and isonicotinate **6** with alkali metal ethoxide EtOM (M = K, Na, and Li) in anhydrous ethanol at 25.0 ± 0.1 °C. Plots of pseudo-first-order rate constant k_{obsd} *vs.* EtOM concentration exhibit upward curvature for the reactions of **5** and **6** with EtOK and EtONa but are almost linear for those with EtOLi. Dissection of k_{obsd} into k_{EtO^-} and k_{EtOM} (i.e., the second-order rate constant for the reaction with dissociated EtO^- and ion-paired EtOM, respectively) has shown that $k_{EtOK} \geq k_{EtONa} > k_{EtO^-}$ but $k_{EtOLi} < k_{EtO^-}$. It has been concluded that K^+ and Na^+ ions catalyze the reactions by increasing the electrophilicity of the carbonyl carbon atom through formation of a 4-membered cyclic transition state TS_3 or TS_4. However, M^+ ion catalysis has been found to be much less significant for the reactions of **5** and **6** than for the corresponding reactions of 4-nitrophenyl picolinate **4**, which was reported to proceed through a 5-membered cyclic transition state TS_2. Although **5** and **6** are significantly more reactive than 4-nitrophenyl benzoate **3**, the reactions of **5** and **6** result in smaller k_{EtOK}/k_{EtO^-} ratios than those of **3**. The electron-withdrawing ability of the nitrogen atom in the acyl moiety of **5** and **6** has been suggested to be responsible for the increase in reactivity and the decrease in the k_{EtOK}/k_{EtO^-} ratio.

Key Words : Alkali metal ions, Metal ion catalysis, Inhibition, Ion pair, Cyclic transition state

Introduction

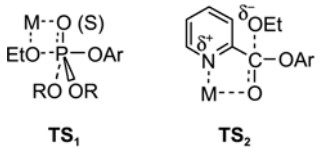
Effects of metal ions on chemical reactions have intensively been studied due to their importance in biological processes as well as synthetic applications.[1-12] It is well known that metal ions behave as Lewis acid catalysts in numerous nucleophilic substitution reactions.[1-12] Alkali metal ions are ubiquitous in nature and are known to play important roles in biological processes (e.g., a Na^+ pump which functions to keep high K^+ and low Na^+ concentrations in mammalian cells).[1] Besides, alkali metal ions have been reported to catalyze nucleophilic substitution reactions of various esters (e.g., P=O, P=S, SO_2 and C=O centered esters).[6-12]

A systematic study on alkali metal ion effects has been initiated by Buncel *et al.* for nucleophilic substitution reactions of 4-nitrophenyl diphenylphosphinate **1** with alkali metal ethoxide EtOM (M = K, Na, and Li) in anhydrous ethanol.[6] Their systematic study has shown that ion-paired EtOM species are more reactive than dissociated EtO^- and the reactivity of EtOM decreases as the size of M^+ ion increases (i.e., EtOLi > EtONa > EtOK).[6] A contrasting result has been reported for corresponding reactions of 4-nitrophenyl benzenesulfonate, i.e., dissociated EtO^- is more reactive than ion-paired EtOLi but less reactive than EtOK and EtONa.[7] Thus, the effect of M^+ ion has been concluded to be dependent on the electrophilic center (e.g., P=O *vs.* SO_2).[7,8]



1 **2a** **2b**

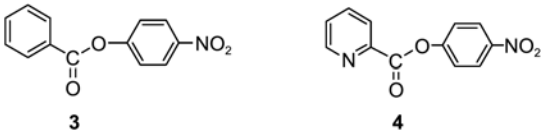
We have performed alkaline ethanolysis of 4-nitrophenyl diethyl phosphate **2a** and phosphinothioate **2b** to investigate the effect of modification of the electrophilic center from P=O to P=S.[9] It has been found that M^+ ions catalyze the reaction of **2a** in the order $Li^+ > Na^+ > K^+$, but inhibit the reaction of **2b**.[9] The inhibitory effect for the reactions of **2b** has been shown to increase as the size of M^+ ions decreases, i.e., $K^+ < Na^+ < Li^+$, indicating that M^+ ion effect is also dependent on the nature of the electrophilic center (P=O *vs.* P=S).[9] Thus, the reactions of **2a** and **2b** with EtOM have been proposed to proceed through a 4-membered cyclic transition state as modeled by TS_1 on the basis of the contrasting M^+ ion effects.[9]



TS_1 **TS_2**

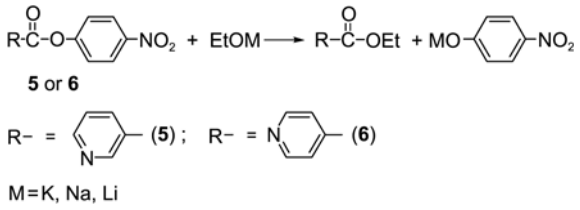
The role of M^+ ions in alkaline ethanolysis of carboxylic esters has also been investigated. M^+ ions have been reported to behave as Lewis acid catalysts, although catalytic effects are strongly dependent on the structure of carboxylic esters.[10-12] We have reported that reactions of 4-nitrophenyl benzoate **3** are catalyzed by M^+ ions in the order $K^+ > Na^+ > Li^+$, although the catalytic effect is not significant.[10a] In contrast, the effect of M^+ ions on the reactions of 4-nitrophenyl picolinate **4** has been shown to be much larger with a high Na^+ ion selectivity, i.e., the catalytic effect is in the order $Na^+ > K^+ > Li^+$.[10b] Accordingly, enhanced electrophilicity through formation of a 5-membered cyclic transition

state as modeled by TS_2, which is not possible for the reactions of **3**, has been proposed to be responsible for the large M^+ ion catalysis.[10b]



3 **4**

We have extended our study to reactions of 4-nitrophenyl nicotinate **5** and isonicotinate **6** with EtOM (Scheme 1) to examine our previous proposal that TS_2, which is not possible for the reactions of **5** and **6**, is responsible for the large M^+ ion effect with a high Na^+ ion selectivity.[10b] Our kinetic results have also been compared with those reported previously for the corresponding reactions of **3** to investigate the effect of replacing a CH group in the benzoyl moiety of **3** by an N atom (i.e., **3** → **5** and **3** → **6**) on reactivity.



Scheme 1

Results

The kinetic study was performed spectrophotometrically under pseudo-first-order conditions with a large excess of EtOM. All reactions in the current study obeyed pseudo-first-order kinetics. Pseudo-first-order rate constants (k_{obsd}) were obtained from the slope of linear 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 ± 3%. The concentration of EtOM and k_{obsd} values for the reactions of **5** and **6** with EtOM are summarized in Tables 1 and 2, respectively. The second-order rate constants (k_{EtO^-} and k_{EtOM}) for the reactions of **5** and **6** were determined from the ion-pairing treatment of the kinetic data and summarized in Table 3.

Table 1. Summary of kinetic data for reactions of 4-nitrophenyl nicotinate **5** with EtOM in anhydrous EtOH at 25.0 ± 0.1 °C

[EtOK]/mM	k_{obsd}/s^{-1}	[EtONa]/mM	k_{obsd}/s^{-1}	[EtOLi]/mM	k_{obsd}/s^{-1}
1.29	0.976	1.14	0.861	1.23	0.91
2.57	2.01	2.28	1.8	2.46	1.82
3.86	3.11	3.42	2.74	3.69	2.73
5.14	4.17	4.56	3.69	4.93	3.57
6.43	5.33	5.7	4.64	6.16	4.43
7.71	6.34	6.84	5.63	7.39	5.31
9	7.55	7.98	6.64	8.62	6.13
10.3	8.73	9.12	7.58	9.85	6.98
11.6	9.87	10.3	8.52	11.1	7.89
-	-	11.4	9.73	-	-

Table 2. Summary of kinetic data for reactions of 4-nitrophenyl isonicotinate **6** with EtOM in anhydrous EtOH at 25.0 ± 0.1 °C

[EtOK]/mM	k_{obsd}/s^{-1}	[EtONa]/mM	k_{obsd}/s^{-1}	[EtOLi]/mM	k_{obsd}/s^{-1}
1.29	5.81	1.14	4.96	1.23	5.25
2.57	12.2	2.28	10.1	2.46	10.4
3.86	18.5	3.42	15.6	3.69	15.5
5.14	25.0	4.56	20.8	4.93	20.1
6.43	31.0	5.70	25.7	6.16	25.3
7.71	37.5	6.84	31.1	7.39	30.1
9.00	43.4	7.98	37.0	8.62	34.7
10.3	50.2	9.12	42.2	9.85	39.4
11.6	57.2	10.3	47.3	11.1	44.1
-	-	11.4	52.7	-	-

Discussion

As shown in Figure 1, the plot of k_{obsd} *vs*. [EtOM] exhibits slightly upward curvature for the reactions of **5** with EtOK and EtONa, while the one for the corresponding reaction with EtOLi appears to be almost linear. Besides, the reactivity of EtOM is dependent on the size of M^+ ions, e.g., the k_{obsd} value at a given concentration of EtOM decreases in the order EtOK ≥ EtONa > EtOLi. In contrast, as shown in the inset of Figure 1, the plot for the reactions of **4** exhibits upward curvature regardless of the size of M^+ ions with a reactivity order EtONa > EtOK > EtOLi.

The upward curvature for the reactions of **5** with EtOK and EtONa is typical for alkaline ethanolysis of various esters in which M^+ ions have been reported to behave as a catalyst.[6-12] In fact, M^+ ions have been concluded to catalyze the reactions of **4** by increasing the electrophilicity of the reaction center through formation of a 5-membered cyclic

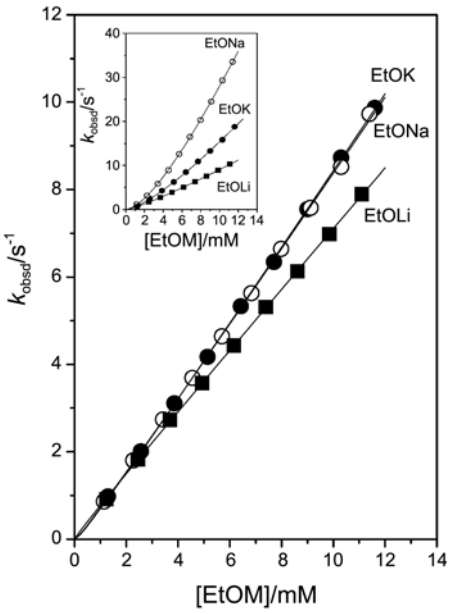


Figure 1. Plots of k_{obsd} *vs*. [EtOM] for reactions of 4-nitrophenyl nicotinate **5** and picolinate **4** (inset) with EtOK (●), EtONa (○), and EtOLi (■) in anhydrous EtOH at 25.0 ± 0.1 °C. Data for the reactions of **4** were taken from ref. 10b.

transition state (i.e., TS_2).[10b] However, the upward curvature observed for the reactions of **5** is much less significant than that for the corresponding reactions of **4**, indicating that M^+ ion effect is not so significant for the reactions **5**. This is consistent with the fact that the reactions of **5** cannot proceed through a 5-membered cyclic transition state similar to TS_2.

To support the above idea, we have performed the reactions of **6** with EtOM, in which formation of TS_2 is not possible either. The kinetic results are demonstrated graphically in Figure 2. It is noted that the reactivity of EtOM toward **6** decreases in the order EtOK > EtONa > EtOLi, which is similar to the reactivity order found for the corresponding reactions of **5** (Figure 1). However, the plot of k_{obsd} *vs*. [EtOM] appears to be linear for the reactions with EtOK and EtONa while the one for the corresponding reaction with EtOLi exhibits slightly downward curvature. Such downward curvature is also contrasting to the upward curvature found for the reactions of **4** regardless of the size of M^+ ions as shown in the inset of Figure 1.

Downward curvature in the plot of k_{obsd} *vs*. [EtOM] has often been reported for nucleophilic substitution reactions of esters with EtOLi, in which Li^+ ion behaves as an inhibitor, e.g., reactions of 4-nitrophenyl dimethyl phosphinothioate (**2b**) and 4-nitrophenyl benzenesulfonate as well as reactions of 4-nitrophenyl diphenylphosphinate with alkali metal phenoxides (PhOM).[8] Thus, one can suggest that Li^+ ion inhibits the current reactions of **6** on the basis of the downward curvature shown in Figure 2.

Dissection of k_{obsd} into k_{EtO^-} and k_{EtOM}. To examine the above argument, k_{obsd} values have been dissected into k_{EtO^-} and k_{EtOM}, i.e., the second-order rate constant for the reaction with dissociated EtO^- and ion-paired EtOM, respectively. EtOM has been reported to exist as dimers or other aggregates in a high concentration region (e.g., [EtOM] > 0.1 M)

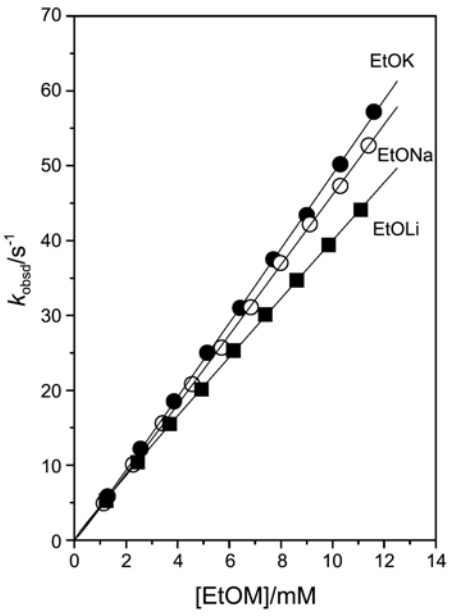
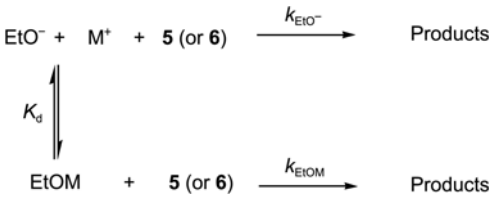


Figure 2. Plots of k_{obsd} *vs*. [EtOM] for reactions of 4-nitrophenyl isonicotinate **6** with EtOK (●), EtONa (○), and EtOLi (■) in anhydrous EtOH at 25.0 ± 0.1 °C.



Scheme 2

but as dissociated EtO^- and ion-paired EtOM when [EtOM] < 0.1 M.[13] Thus, one might expect that substrates **5** and **6** would react with dissociated EtO^- and ion-paired EtOM as shown in Scheme 2 since the concentration of EtOM in the current reactions is much lower than 0.1 M.

One can derive eq. (1) on the basis of the mechanism proposed in Scheme 2. Under pseudo-first-order kinetic conditions, k_{obsd} can be expressed as eq. (2), which becomes eq. (3) since the dissociation constant $K_d = [EtO^-]_{eq}[M^+]_{eq}/[EtOM]_{eq}$, and $[EtO^-]_{eq} = [M^+]_{eq}$ at equilibrium.

$$\text{Rate} = k_{EtO^-}[EtO^-]_{eq}[\mathbf{5} \text{ or } \mathbf{6}] + k_{EtOM}[EtOM]_{eq}[\mathbf{5} \text{ or } \mathbf{6}] \quad (1)$$

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

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

The concentrations of $[EtO^-]_{eq}$ and $[EtOM]_{eq}$ can be calculated from the reported K_d values and the initial concentration [EtOM] using eqs. (4) and (5). Thus, one might expect that the plot of $k_{obsd}/[EtO^-]_{eq}$ *vs*. $[EtO^-]_{eq}$ is linear with a positive intercept. In fact, the plots shown in Figures 3(a) and 3(b) for the reactions of **5** and **6** with EtOM are linear with a positive intercept, indicating that the proposed mechanism and equations are reliable.

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

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

Accordingly, k_{EtO^-} and k_{EtOM}/K_d values have been calculated from the intercept and the slope of the linear plots, respectively. The k_{EtOM} values can be calculated from the k_{EtOM}/K_d values calculated above and the reported K_d value for EtOM (i.e., $K_d = 4.72 \times 10^{-3}$, 9.80×10^{-3}, and 11.1×10^{-3} M, in turn).[14] The k_{EtO^-} and k_{EtOM} values calculated in this way are summarized in Table 3 together with those reported previously for the corresponding reactions of **3** and **4** for comparison. It is seen from Table 3 that the rate constant decreases in the order $k_{EtOK} > k_{EtONa} > k_{EtO^-} > k_{EtOLi}$ for the reactions of **5** and **6**, which is contrasting to that reported previously for the reactions of **3** (i.e., $k_{EtOK} > k_{EtONa} > k_{EtOLi} > k_{EtO^-}$) and for those of **4** (i.e., $k_{EtONa} > k_{EtOK} > k_{EtOLi} > k_{EtO^-}$). Thus, one can suggest that M^+ ion effect is also dependent on the nature of the acyl moiety.

To give more credence to the k_{EtO^-} values shown in Table 3, reactions of **5** and **6** with EtOK have been performed in the excess presence of 18-crown-6-ether (18C6). It is well known that 18C6 is highly effective in complexing K^+ ion.[15] Accordingly, in the presence of the complexing agent, EtOK would be present as dissociated EtO^- and 18C6-complexed

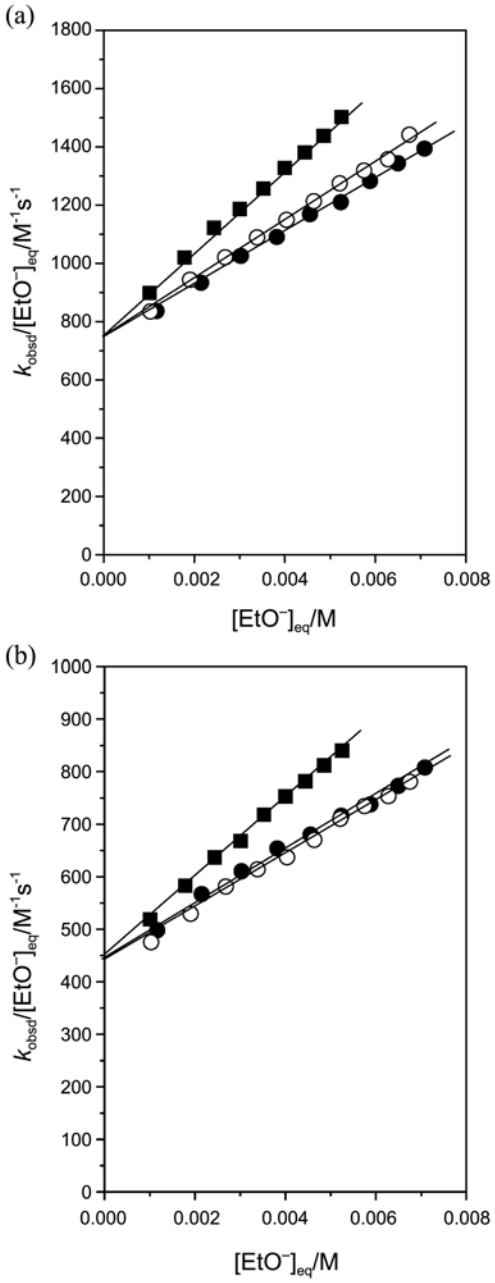


Figure 3. Plots of $k_{obsd}/[EtO^-]_{eq}$ *vs.* $[EtO^-]_{eq}$ for reactions of 4-nitrophenyl nicotinate **5** (a) and isonicotinate **6** (b) with EtOK (●), EtONa (○), and EtOLi (■) in anhydrous EtOH at 25.0 ± 0.1 °C.

K^+ ion but not as ion-paired EtOK. Then, one might expect that substrates **5** and **6** would react mainly with dissociated EtO^- in the presence of 18C6. In fact, as shown in Figure 4, the plots of k_{obsd} *vs*. [EtOK] exhibit excellent linear correlation and pass through the origin for both reactions of **5** and **6**. Thus, one might suggest that the slope of these linear plots represents the second-order rate constant for the reaction with dissociated EtO^- (i.e., k_{EtO^-}). The k_{EtO^-} values calculated in this way are 724 ± 35 and 4350 ± 300 $M^{-1}s^{-1}$ for the reaction of **5** and **6**, respectively. As expected, these values are identical to the k_{EtO^-} values calculated from ion-pairing treatment (Table 3) within an experimental error range.

Table 3. Summary of second-order rate constants (k_{EtO^-} and k_{EtOM}) calculated from ion-pairing treatment of kinetic data for the reactions of 4-nitrophenyl benzoate **3**, picolinate **4**, nicotinate **5**, and isonicotinate **6** with EtOM in anhydrous ethanol at 25.0 ± 0.1 °C

	$k_{EtO^-}/M^{-1}s^{-1}$	$k_{EtOK}/M^{-1}s^{-1}$	$k_{EtONa}/M^{-1}s^{-1}$	$k_{EtOLi}/M^{-1}s^{-1}$
3[a]	10.5	17.5	16.6	13.1
4[b]	436	3370	6640	1350
5	748	1040	992	656
6	4510	5530	5140	3560

[a]Data for the reactions of **3** were taken from ref. 10a. [b]Data for the reactions of **4** were taken from ref. 10b.

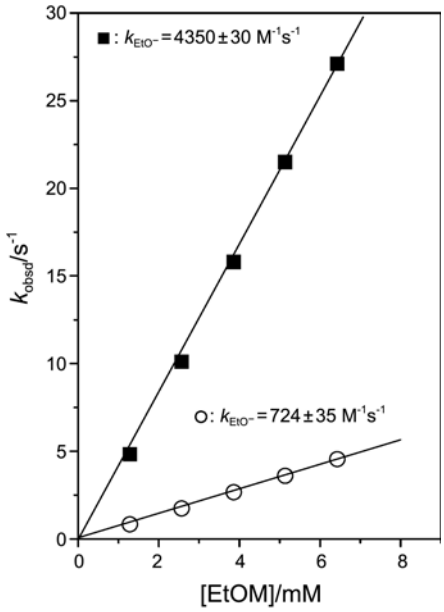
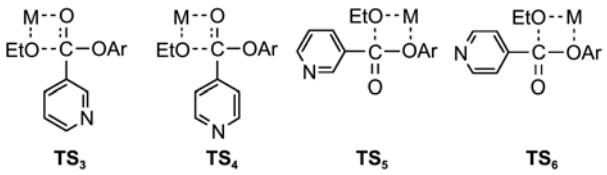


Figure 4. Plots of k_{obsd} *vs*. [EtOK] for reactions of 4-nitrophenyl nicotinate **5** (○) and isonicotinate **6** (■) with EtOK in the presence of 18C6 in anhydrous EtOH at 25.0 ± 0.1 °C. [18C6]/[EtOK] = 2.0.

Role of M^+ ion. The fact that k_{EtOK} $k_{EtONa} > k_{EtO^-}$ indicates that K^+ and Na^+ ions catalyze the reaction. On the contrary, Li^+ ion inhibits the reaction since $k_{EtOLi} < k_{EtO^-}$. One can propose that K^+ and Na^+ ions catalyze the reactions of **5** and **6** by increasing the electrophilicity of the carbonyl carbon through formation of a 4-membered cyclic transition state (i.e., TS_3 or TS_4) or by increasing the nucleofugality of the leaving 4-nitrophenoxide through formation of TS_5 or TS_6. However, one might suggest that the size of Li^+ ion is not proper to form 4-membered cyclic transition states (e.g., TS_3 ~ TS_6).



Enhanced nucleofugality through TS_5 or TS_6 would be effective only when expulsion of the leaving group is involv-

ed in rate-determining step (RDS) but ineffective when leaving-group departure occurs after RDS. Alkaline hydrolysis and ethanolysis of carboxylic esters have been reported to proceed through a stepwise mechanism.[16,17] If the current reactions proceed also through a stepwise mechanism, leaving-group departure should occur after RDS since EtO^- is much more basic and a poorer leaving group than 4-nitrophenoxide. Thus, one might suggest that M^+ ion catalysis found in the reactions of **5** and **6** is due to enhanced electophilicity through TS_3 or TS_4, but not due to increased nucleofugality through TS_5 or TS_6.

We have proposed that M^+ ions catalyze reactions of **3** with EtOM by increasing electrophilicity through formation of a 4-membered cyclic transition state similar to TS_3 or TS_4.[10a] Table 3 shows that M^+ ion catalysis is much less significant for the reactions of **3**, **5** and **6** than for that of **4** (e.g., k_{EtOK}/k_{EtO^-} = 1.2 ~ 1.7 for the reactions of **3**, **5** and **6** while k_{EtOK}/k_{EtO^-} = 7.7 and k_{EtONa}/k_{EtO^-} = 15.2 for the reaction of **4**). This is consistent with the expectation that such 4-membered cyclic transition states (e.g., TS_3 or TS_4) would be less stable than a 5-membered cyclic transition state (e.g., TS_2).

We have recently reported that the electronic nature of acyl-group substituent influences the reactivity and k_{EtOK}/k_{EtO^-} ratio, e.g., introduction of an electron-withdrawing group on the benzoyl moiety increases k_{EtOK} and k_{EtO} values but decreases the k_{EtOK}/k_{EtO^-} ratio in the reactions of 4-pyridyl X-substituted benzoates with EtOK.[10d] Table 3 shows that modification of the acyl group from benzoyl to nicotinoyl and isonicotinoyl (**3** → **5** and **3** → **6**) results in a significant increase in reactivity (e.g., k_{EtO^-} = 10.5, 748 and 4510 $M^{-1}s^{-1}$ for the reactions of **3**, **5** and **6**, in turn) but decreases the k_{EtOK}/k_{EtO^-} ratio from 1.7 to 1.4 and 1.2 as the substrate changes from **3** to **5** and **6**, respectively. Thus, one might suggest that presence of the electronegative nitrogen atom in the acyl moieties of **5** and **6** is responsible for a significant increase in k_{EtO^-} value with a smaller k_{EtOK}/k_{EtO^-} ratio.

Conclusions

The current study has allowed us to conclude the following: (1) K^+ and Na^+ ions catalyze the reactions of **5** and **6** while Li^+ ion behaves as an inhibitor since $k_{EtOK} \geq k_{EtONa} > k_{EtO^-} > k_{EtOLi}$. (2) The reactions of **5** and **6** proceed through a 4-membered cyclic transition state (i.e., TS_3 or TS_4), which would be less stable than the 5-membered cyclic transition state TS_2 suggested previously for the reactions of **4**. (3) Modification of acyl group from benzoyl (**3**) to nicotinoyl (**5**) and isonicotinoyl (**6**) results in an increase in k_{EtO^-} but a decrease in the k_{EtOK}/k_{EtO^-} ratio.

Experimental Section

Materials. Compounds **5** and **6** were readily prepared from the reactions of 4-nitrophenol with nicotinoyl and isonicotinoyl chlorides, respectively in the presence of triethylamine in anhydrous ether. The crude compounds **5** and **6** were purified by column chromatography. The stock solutions of EtOM were prepared by dissolving the respective alkali metal in anhydrous ethanol under N_2 and stored in the refrigerator. The concentrations of EtOM were determined by titration with mono potassium phthalate. 18-Crown-6-ether was recrystallized from acetonitrile and dried under vacuum. The anhydrous ethanol used was further dried over magnesium and distilled under N_2 just before using.

Kinetics. Kinetic study was performed using a stopped-flow spectrophotometer equipped with a constant-temperature circulating bath. The reactions were followed by monitoring the appearance of the leaving 4-nitrophenoxide at 400 nm. Generally, reactions were followed for 9-10 half-lives and k_{obsd} values were calculated using the equation, ln $(A_\infty - A_t)$ *vs*. *t*.

Product Analysis. 4-Nitrophenoxide was liberated quantitatively and identified as one of the reaction products by comparison of the Uv-vis spectra after completion of the reactions with those of the authentic samples under the reaction conditions.

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