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The Effect of Alkali Metal Ions on Nucleophilic Substitution Reactions of Alkali Metal Ethoxides with S-p-nitrophenyl 2-thiofuroate and 2-Thiophenethiocarboxylate in Absolute Ethanol

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Received April 7, 1997

Rate constants have been measured spectrophotometrically for the reactions of alkali metal ethoxides (EtOM) with *S*-p-nitrophenyl 2-thiofuroate (**1b**) and 2-thiophenethiocarboxylate (**2b**) in absolute ethanol at 25.0±0.1 °C. **1b** is observed to be more reactive than **2b** toward all the EtOM studied. The reactivity of EtOM is in the order EtOK>EtONa>EtO^->EtOLi for both substrates, indicating that K^+ and Na^+ behave as a catalyst while Li^+ acts as an inhibitor in the present system. Equilibrium association constants of alkali metal ions with the transition state (K_a^{TS}) have been calculated from the known equilibrium association constants of alkali metal ion with ethoxide ion (K_a) and the rate constants for the reactions of EtOM with **1b** and **2b**. The catalytic effect (K_a^{TS}/K_a) is larger for the reaction of **1b** than **2b**, and decreases with decreasing the size of the alkali metal ions. Formation of 5-membered chelation at the transition state appears to be responsible for the catalytic effect.

Introduction

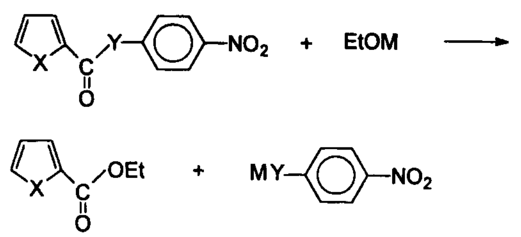
The catalytic effect of metal ions on reactions of various types of esters with bases has been intensively studied.[1-3] However, most studies have been limited to divalent metal ions such as Mg^{2+}, Zn^{2+}, Cu^{2+}... etc.[4,5] Since Lewis acidity of monovalent alkali metal ions is much weaker than that of divalent cations, the effect of alkali metal ions on acyl-transfer reactions has not attracted much attention. Only recently Buncel,[6,7] Suh,[8] Modro[9] and our group[10] have initiated to investigate the effect of alkali metal ions on acyl-transfer reactions.

Buncel *et al.* found significant catalytic effect of alkali metal ions on the reaction of p-nitrophenyl diphenylphosphinate (PNPDPP) with alkali metal ethoxides (EtOM) in absolute ethanol, and the catalytic effect increases with increasing charge density of alkali metal ions, *e.g.* $K^+<Na^+<Li^+$.[6] On the contrary, the catalytic effect was observed to be in the order $K^+>Na^+>Li^+$ for the corresponding reaction of p-nitrophenyl benzenesulfonate.[7] However, alkali metal ions were found to exhibit inhibitory effect for the reaction of PNPDPP with alkali metal aryloxides (ArOM) in absolute ethanol,[10a] but little effect for the reaction of p-nitrophenyl benzoate (PNPB) with EtOM in absolute ethanol.[10b] These results suggest that the effect of M^+ ions (as catalyst or inhibitor) is dependent on substrates (phosphorus, sulfur and carbon centered esters) as well as on nucleophiles (EtO^- and ArO^-).

Recently, we found alkali metal ions show significant effect for the reaction of p-nitrophenyl 2-furoate (**1a**) and 2-thiophenecarboxylate (**2a**) with EtOM in absolute ethanol.[10c,d] Now we have extended our study to the reaction of alkali metal ethoxides (EtOM) with *S*-p-nitrophenyl 2-thiofuroate (**1b**) and 2-thiophenethiocarboxylate (**2b**) in order to investigate the effect of the replaced O atom by S atom in the ring of the acid moiety (**1**→**2**) as well as in the ether-like C-O-C bond (**a**→**b**).

Experimental

Materials. *S*-p-nitrophenyl 2-thiofuroate (**1b**, mp 134-135 °C) and 2-thiophenethiocarboxylate (**2b**, mp 147-150 °C) were easily prepared from the reactions of p-nitrothiophenol with 2-furoyl chloride and 2-thiophenecarboxyl chloride, respectively, in the presence of triethylamine in methylene chloride.[10c,d] Their purity was checked by means of melting points and spectral data such as IR and ^1H NMR characteristics. Absolute ethanol was prepared by the method des-



X = O, Y = O ; p-nitrophenyl 2-furoate (1a)
X = O, Y = S ; S-p-nitrophenyl 2-thiofuroate (1b)
X = S, Y = O ; p-nitrophenyl 2-thiophenecarboxylate (2a)
X = S, Y = S ; S-p-nitrophenyl 2-thiophenethiocarboxylate (2b)

Scheme 1.

cribed in the literature under a nitrogen atmosphere.[11] Solutions of alkali metal ethoxides were made by dissolving the corresponding alkali metal in absolute ethanol under a nitrogen atmosphere. The concentrations of alkali metal ethoxides were titrated against potassium hydrogen phthalate. All the solutions were made just before use under a nitrogen atmosphere.

Kinetics. The kinetic study was performed spectrophotometrically using a Hitachi U-2000 model UV-VIS spectrophotometer equipped with a Neslab RTE-110 model constant temperature circulating bath to keep the reaction temperature at 25.0±0.1 °C. The reaction rate was measured by monitoring the appearance of p-nitrothiophenoxide ion at 410 nm. All the reactions were carried out under pseudo-first-order conditions in which the base concentration is much excess over the substrate concentration. Hamilton gas tight syringes were used to transfer reactant solution. Other details of kinetic study are similar to the one described previously.[10]

Table 1. Kinetic Data for the Ractions of **1a** and **1b** with Alkali Metal Ethoxides (EtOM) in the Absence and Presence of Excess 18-crown-6 (18C6) in EtOH at 25.0±0.1 °C[a]

EtOM	$[\mathrm{EtOM}]\times 10^3$ M	$k_{obs}\times 10^2$ s^{-1} **1a**	$k_{obs}\times 10^2$ s^{-1} **1b**
EtOLi	1.56	4.18	2.82
	2.32	6.34	4.28
	3.07	8.59	5.69
	3.81	10.8	7.10
	4.54	13.1	8.39
	5.25	15.2	9.60
EtONa	1.64	5.11	3.55
	2.43	8.11	5.49
	3.22	11.9	7.45
	3.99	15.0	9.52
	4.76	18.6	11.7
EtOK	1.45	4.84	3.40
	2.16	7.84	5.45
	2.85	11.2	7.50
	3.54	14.6	9.65
	4.21	18.6	12.0
EtOK+18C6	0.777	1.98	1.55
[18C6]/[EtOK]	1.50	3.96	3.04
=4.0	2.17	5.90	4.45
	2.79	7.62	5.70
	3.37	9.07	6.90

[a] The data for the reactions of **1a** are obtained from ref. 10c.

Results

All the reactions were obeyed pseudo-first-order kinetics over 90% of the total reaction. Pseudo-first-order rate constants (k_{obs}) were obtained from the well known equation, $\ln(A_\infty - A_t) = -k_{obs}\cdot t + c$. The estimate error in any particular measured rate constant is less than 3%. In Tables 1 and 2 are summarized pseudo-first-order rate constants for the reaction of EtOM with **1b** and **2b**, respectively, together with the corresponding data for **1a** and **2a** for a comparison purpose. The observed rate constants are demonstrated graphically in Figures 1 and 2. The results of ion pairing treatment of kinetic data are summarized in Table 3 and shown in Figures 3 and 4. In Table 4 are listed equilibrium constants of alkali metal ions with ethoxide and transition state.

Discussion

The Effect of Alkali Metal Ions on Reaction Rate. It can be seen from Figure 1 that the reactivity of alkali metal ethoxides (EtOM) is dependent on the kind of alkali metal ions, *i.e.* EtOK and EtONa show upward curvatures

Table 2. Kinetic Data for the Reactions of **2a** and **2b** with Alkali Metal Ethoxides (EtOM) in the Absence and Presence of Excess 18-crown-6 (18C6) in EtOH at 25.0±0.1 °C[a]

EtOM	$[\mathrm{EtOM}]\times 10^3$ M	$k_{obs}\times 10^2$ s^{-1} **2a**	$k_{obs}\times 10^2$ s^{-1} **2b**
EtOLi	1.32		1.61
	2.62		3.15
	3.81		4.71
	5.12		6.03
	7.51		8.99
	3.81-16.5	2.98-13.6	
EtONa	1.11		1.46
	2.20		3.03
	3.81		5.39
	4.85		7.01
	6.40		9.70
	2.04-14.3	1.52-14.2	
EtOK	1.79		2.68
	2.95		4.49
	4.10		6.53
	5.23		8.61
	6.35		10.8
	3.54-11.3	3.00-10.8	
EtOK+18C6	1.20		1.48
[18C6]/[EtOK]	2.37		3.13
=4.0	3.53		4.69
	4.67		6.33
	6.81		9.10
	3.54-15.3	2.86-12.9	

[a] The data for the reactions of **2a** are obtained from ref. 10d.

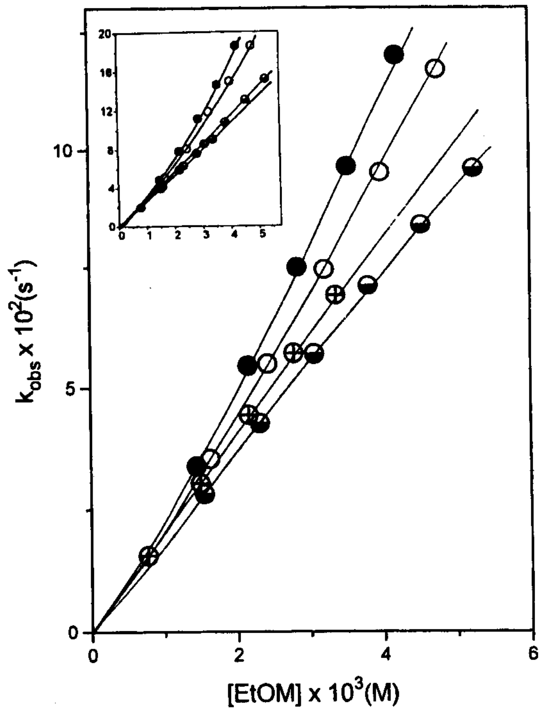


Figure 1. Kinetic data for the reactions of **1b** with EtOK (●), EtONa (○), EtOK-18C6 (⊕) and EtOLi (◒) in absolute ethanol at 25.0±0.1 °C. The inlet of the figure represents the kinetic results for the corresponding reaction of **1a**.

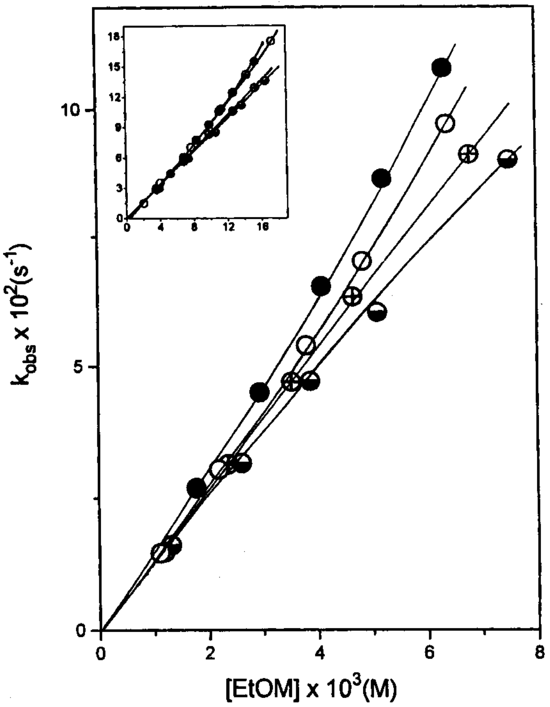


Figure 2. Kinetic data for the reactions of **2b** with EtOK (●), EtONa (○), EtOK-18C6 (⊕) and EtOLi (◒) in absolute ethanol at 25.0±0.1 °C. The inlet of the figure represents the kinetic results for the corresponding reaction of **2a**.

Table 3. Second-order Rate Constants for Various Ethoxide Species from Ion Pairing Treatment of Kinetic Data for the Reactions of EtOM with (**1b**) and (**2b**) in EtOH at 25.0±0.1 °C

EtOM	(1b)		(2b)	
	k_{EtO^-}, $M^{-1}s^{-1}$	k_{EtOM}, $M^{-1}s^{-1}$	k_{EtO^-}, $M^{-1}s^{-1}$	k_{EtOM}, $M^{-1}s^{-1}$
EtOLi	18.6±0.30	18.3±0.60	12.1±0.20	11.9±0.34
	(24.2±0.1)[a]	(36.2±0.2)	(7.34±0.2)	(8.83±0.2)
EtONa	19.7±0.20	37.3±0.8	12.3±0.17	20.9±0.51
	(23.7±1.5)	(83.1±5.7)	(6.76±0.3)	(13.8±0.6)
EtOK	19.7±0.60	56.0±2	11.8±0.30	30.3±3
	(24.9±0.4)	(106±2)	(6.75±0.2)	(14.2±0.4)
EtOK	21.3±0.30		13.8±0.10	
+18C6	(27.0±0.2)		(8.51±0.1)	

[a] The data in parentheses are obtained from ref. 10c, d for the corresponding reactions of **1a** and **2a**.

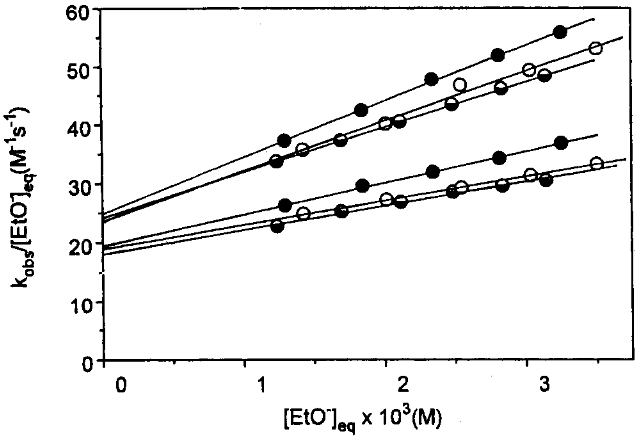


Figure 3. Plots illustrating dissection of observed rates into rate constants due to dissociated and ion paired ethoxide for the reactions of **1a** and **1b** with EtOK (●), EtONa (⊕), and EtOLi (◒) in absolute ethanol at 25.0±0.1 °C.

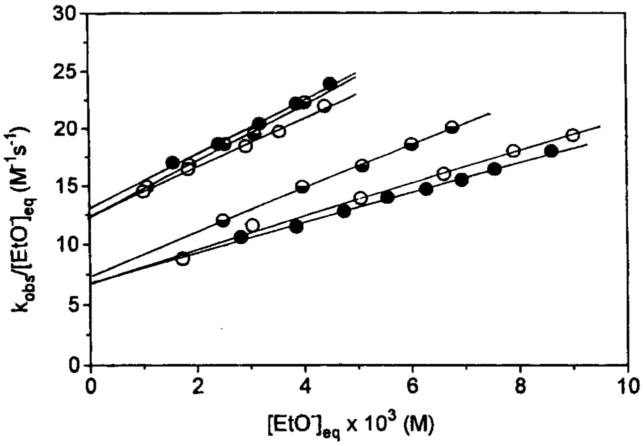


Figure 4. Plots illustrating dissection of observed rates into rate constants due to dissociated and ion paired ethoxide for the reactions of **2a** and **2b** with EtOK (●), EtONa (○), and EtOLi (◒) in absolute ethanol at 25.0±0.1 °C.

in the plot of k_{obs} *vs* the concentration of EtOM, while the plots of EtOLi and EtOK with excess 18-crown-6 ether (18C6) are essentially linear. A careful examination of Fig-

Table 4. Summary of Equilibrium Constants for the Association of Alkali Metal Ion with Ethoxide (K_a) and Transition State (K_a^{TS})

M^+	K_a, M^{-1}	K_a^{TS}, M^{-1}			
		1a	1b	2a	2b
K^+	90[a]	350	237	150	198
Na^+	102[a]	318	179	165	154
Li^+	212[a]	278	182	220	183

[a] The K_a values are taken from ref. 13.

ure 1 reveals that the reactivity of **1b** decreases in the order EtOK>EtONa>EtOK with excess 18C6>EtOLi, but that of **1a** is in the order EtOK>EtONa>EtOLi≃EtOK with excess 18C6. Similar results are obtained for the reaction of EtOM with **2a** and **2b** in absolute EtOH, as shown in Figure 2, *i.e.* EtOK is much more reactive than EtONa and EtOLi toward **2a** and **2b**. The dependance of reactivity of EtO^- on alkali metal ions clearly suggests that alkali metal ions are involved in the present acyl-transfer reaction. Particularly, the upward curvatures shown by EtOK and EtONa imply that the present reaction is catalyzed by these alkali metal ions.

Recently, Buncel[7] and Um[10b] demonstrated similar reactivity orders for the reaction of aryl sulfonates with EtOM in absolute EtOH, *i.e.* the reactivity of EtOM decreases in the order EtOK>EtONa>EtO^->EtOLi. However, the reactivity order in the present system is opposite from the one for the reaction of aryl phosphinates with EtOM in absolute EtOH, in which the reactivity of EtOM is in the order EtOLi>EtONa>EtOK>EtO^-.[6] Therefore, the present results suggest that the effect of alkali metal ions is significantly dependent on the structure of substrates.

Dissection of Nucleophilicity of Free and Ion Paired Ethoxides. The polarity of EtOH is much smaller than that of H_2O. Therefore, EtOH can not solvate ionic species as effectively as water. However, it has been suggested that alkali metal ions can be stabilized in EtOH through interactions with counter anions, *e.g.* by forming ion pair, dimer and other aggregates in high concentration.[12] Pechanec *et al.* reported that alkali metal ethoxides form dimers and other aggregates in high concentration but exist as dissociated free ethoxide (EtO^-) and ion paired alkali metal ethoxides (EtOM) in absolute EtOH, when the concentration is relatively low (<0.1 M).[12] Since the concentration of EtOM used in the present study is much lower than 0.1 M, the major species in the reaction mixture would be considered to be free ethoxide (EtO^-) and ion paired one (EtOM). Therefore, the present reaction would occur competitively with EtO^- and EtOM as shown in Scheme 2, in which K_a refers to the association constant of alkali metal ethoxide, eqn. (1), and k_{EtO^-} and k_{EtOM} represent second-order rate constant for the reaction of **1** (or **2**) with free ethoxide (EtO^-) and ion paired alkali metal ethoxide (EtOM), respectively.

$$\begin{array}{ccc} \mathbf{1}\text{ (or }\mathbf{2}\text{)} + EtO^- + M^+ & \xrightarrow{k_{EtO^-}} & \text{products} \\ \Big\updownarrow K_a & & \\ \mathbf{1}\text{ (or }\mathbf{2}\text{)} + EtOM & \xrightarrow{k_{EtOM}} & \text{products} \end{array}$$

Scheme 2.

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

One can derive a rate equation and observed pseudo-first-order rate constants (k_{obs}) as Eqn's (2) and (3), in which [**1** (or **2**)], [EtO^-] and [EtOM] represent the concentration of the substrate **1** (or **2**), free ethoxide and ion paired alkali metal ethoxide, respectively. Eqn. (3) can be rewritten as Eqn. (4) using Eqn's. (1) and (3).

$$\text{Rate} = k_{EtO^-}[EtO^-]\,[\mathbf{1}\text{ (or }\mathbf{2}\text{)}] + k_{EtOM}[EtOM]\,[\mathbf{1}\text{ (or }\mathbf{2}\text{)}] \quad (2)$$

$$k_{obs} = k_{EtO^-}[EtO^-] + k_{EtOM}[EtOM] \quad (3)$$

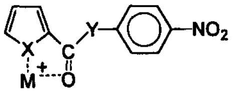
$$\frac{k_{obs}}{[EtO^-]} = k_{EtO^-} + K_a \cdot k_{EtOM}[EtO^-] \quad (4)$$

One would expect linearity in the plots of $k_{obs}/[EtO^-]$ *vs* [EtO^-]. In fact, the plots of $k_{obs}/[EtO^-]$ *vs* [EtO^-] show good linearity for all the alkali metal ethoxides as shown in Figures (3) and (4). The slope and intercept of these plots represent $K_a \cdot k_{EtOM}$ and k_{EtO^-}, respectively. One can notice that the intercepts in Figures 3 and 4 are almost same for a given substrate, as expected.

Since K_a values for EtOM in absolute EtOH are available in literature,[14] second-order rate constants for free ethoxide (k_{EtO^-}) and ion paired alkali metal ethoxides (k_{EtOM}) can be calculated. The values of k_{EtO^-} and k_{EtOM} determined in this way are summarized in Table 3 for the reaction of EtOM with **1** and **2** in the present system. As shown in Table 3, the k_{EtO^-} values obtained in this way are practically same as the ones obtained from the slope of the plots of kobs vs [EtOK-18C6].

As expected from Figures 1 and 2, the second-order rate constant (k_{EtOM}) for the reactions of **1a** and **2a** decreases in the order EtOK>EtONa>EtOLi>EtO^-, while the one for **1b** and **2b** is in the order EtOK>EtONa>EtO^->EtOLi. In all cases, k_{EtOM} appears to be larger than k_{EtO^-} except k_{EtOLi} for the reaction with **1b** and **2b**, indicating that ion paired EtOM is more reactive than free ethoxide except EtOLi for the reaction with **1b** and **2b**.

Transition State *vs* Ground State Stabilization. Alkali metal ions can stabilize the ground state (GS) of the nucleophile by forming ion paired species or the GS of the substrate by forming a 5-membered chelation as shown below (I). Such a chelation would cause significant charge polarization of the C=O bond, and would change the ^{13}C chemical shift of carbon atom in the C=O bond significantly to down field. However, our preliminary ^{13}C NMR study has revealed that the ^{13}C NMR spectrum of **1a** in the presence of K^+ ion is exactly same as the one in the absence of K^+ ion in DMSO. This NMR study clearly rules out the possibility of chelation like I at the GS.



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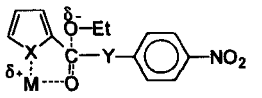

II

The fact that K^+ and Na^+ ions catalyze the present reaction suggests that the interaction of these cations with the anionic TS is more significant than with the GS. Kurz *et al.* have suggested Scheme 3 to calculate association constant for the catalytic interaction of alkali metal ions with the TS.[13] In this scheme, S represents the substrate, $K_u^{\neq}$ and $K_c^{\neq}$ are the equilibrium constants for the formation of the uncatalyzed and catalyzed TS ($TS^{\neq}$ and $TS^{\neq}M$), while K_a and K_a^{TS} are the equilibrium association constants of alkali metal ions (M^+) with EtO^- and with the TS, respectively.

$$\begin{tikzcd}
S + EtO^- + M^+ \arrow[r, shift left, "K_u^{\neq}"] \arrow[d, shift left, "K_a"] & TS^{\neq} + M^+ \arrow[l, shift left] \arrow[r] \arrow[d, shift left, "K_a^{TS}"] & \text{Products} \\
S + EtOM \arrow[u, shift left] \arrow[r, shift left, "K_c^{\neq}"] & TS^{\neq}M \arrow[l, shift left] \arrow[u, shift left] \arrow[r] & \text{Products}
\end{tikzcd}$$

Scheme 3.

From transition state theory, one can derive Eqn. (5).

$$K_a^{TS} = \frac{k_{EtOM} \cdot K_a}{k_{EtO^-}} \tag{5}$$

Therefore, K_a^{TS} values can be calculated using the known association constant (K_a)[14] of the metal-ethoxide ion pairs and the second-order rate constants of free ethoxide (k_{EtO^-}) and ion paired EtOM (k_{EtOM}). The K_a^{TS} values determined in this way are summarized in Table 4. One can notice that the magnitude of K_a^{TS} is much larger than that of K_a, except Li^+ for the reactions of **1b** and **2b**. Alkali metal ions would behave as a catalyst when the K_a^{TS} value is larger than K_a value ($K_a^{TS}/K_a>1$), and as an inhibitor when K_a^{TS} is smaller than K_a ($K_a^{TS}/K_a<1$). Accordingly, the catalytic effect would increase with increasing the K_a^{TS}/K_a value. This is consistent with the fact that K^+ ion shows the largest K_a^{TS}/K_a value and exhibits the largest catalytic effect, while Li^+ ion demonstrates the smallest K_a^{TS}/K_a value and exerts the smallest catalytic effect (or even inhibition effect for the reaction of **1b** and **2b**).

A careful examination of Table 4 reveals that K_a^{TS}/K_a values are larger for the oxygen esters (**1a, 2a**) than the corresponding thiol esters (**2a, 2b**) except the reaction of **2a** and **2b** with EtOK. Furthermore, K_a^{TS}/K_a values are larger for the furoate system (**1a, 1b**) than its sulfur analogue, thiophenecarboxylate system (**2a, 2b**). Since alkali metal ions and sulfur atom are considered to be hard acids and a soft base, respectively, the small K_a^{TS}/K_a values for the sulfur containing esters appear to be consistent with the hard soft acids and bases (HSAB) principle.[15]

Role of Alkali Metal ions. Interaction of alkali metal ions with the oxygen (or sulfur) atom of the leaving phenoxide (or thiophenoxide) would enhance the nucleofugality of the leaving group. This effect would be significant when the leaving group departure is involved in the rate determining step (RDS), but would be insignificant if the leaving group departure occurs rapidly after the RDS. Since the present type acyl-transfer reaction has been suggested to proceed *via* a rate determining formation of tetrahedral intermediate followed by fast leaving group departure,[16] the interaction of alkali metal ions with the oxygen atom in the leaving aryloxide would influence little effect on the reaction rate. This argument can be further supported by comparing the reactivity of the oxygen esters (**1a** and **2a**) with that of the corresponding thiol esters (**1b** and **2b**). Since the pK_a of thiophenols has been suggested to be about 4 pK_a units lower than that of the corresponding phenol,[17] a thiophenoxide is considered to be much better nucleofuge than the corresponding phenoxide. Therefore, one might expect **1b** and **2b** are significantly more reactive than **1a** and **2a**, respectively. However, the thiol ester **2b** is slightly more reactive than the oxygen ester **2a** (Table 2). Moreover, **1b** is even less reactive than **1a** (Table 1) toward free ethoxide as well as ion paired alkali metal ethoxides. The present results clearly suggest that enhancement of nucleofugality would influence little effect on reaction rates, and therefore, the interaction of alkali metal ions with the oxygen atom in the leaving group is not considered to be significant in the present system.

Interaction of alkali metal ions with the oxygen atom in the C=O bond of the present esters would accelerate the reaction rate by stabilizing the anionic TS. Since the ionic interaction would become stronger with increasing the charge density of alkali metal ions, the catalytic effect is expected to increase in the order $K^+<Na^+<Li^+$. This is contrary to the expectation, *i.e.* the catalytic effect decreases in the order $K^+>Na^+>Li^+$. Therefore, such ionic interaction is not considered to be significant in the present system. This argument is consistent with the result of our recent study for the reaction of p-nitrophenyl benzoate (PNPB) with EtOM in absolute EtOH, in which alkali metal ions exhibit little effect on reaction rates.[10b] For the PNPB system, alkali metal cations can exert ionic interaction with the negative end of the carbonyl oxygen at the TS, but chelation II is not possible due to absence of a hetero atom in the aromatic ring of the acyl moiety. Therefore, 5-membered chelation II at the TS is considered to be responsible for the catalytic effect observed in the present furoyl and thiophenecarboxyl system. Based on the fact that the catalytic effect increases with increasing the radius of the cation (*e.g.* $K^+>Na^+>Li^+$), the size of alkali metal ions appears to play an important role on the formation of the 5-membered chelate II at the TS of the present system.

Conclusions

The present study has allowed us to conclude the following. (1) Alkali metal ions exhibit catalytic effect for the reaction EtOM with **1a**, **1b**, **2a**, and **2b** in absolute ethanol and the catalytic effect increases with increasing the radius of alkali metal ions (*e.g.* $K^+>Na^+>Li^+$) except the reaction of EtOLi with **1b** and **2b**. (2) The catalytic effect is larger for the oxygen esters (**1a, 2a**) than the corresponding thiol esters (**1b, 2b**) in general. (3) Formation of 5-membered chelation II at the TS is responsible for the catalytic effect. (4) The size is more important than the charge density of alkali metal ions for the formation of chelate II.

Acknowledgment. This research was supported by grants from the Basic Science Research Institute Program of Ministry of Education of Korea (BSRI-96-3422) and from Ewha Womans University.

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A Synthetic Approach to 11-Oxabicyclo[6.2.1]undecyl Bicyclics

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Received April 7, 1997

Through a sequence of reactions including Diels-Alder cycloaddition of a furan diene as the key step, 11-oxatricyclo$[6.2.1.0^{1,6}]$undecyl rings were synthesized from 5-methylfurfural with the goal of developing a synthetic protocol to 11-oxabicyclo[6.2.1]undecyl system. The strategy to incorporate an oxygen atom at C6 carbon of tricyclic **11** or **16** by Baeyer-Villiger oxidation was unsuccessful, implicating that there is too much steric congestion around the carbonyl ketone. As an alternative approach, bicyclic **23** and **24** were prepared from 2-methylfuran *via* known tricyclic **20**. Cyclization of bicyclic **23** and **24** under several reaction conditions also failed to produce hydroxylated product **25** and **26**.

Introduction

11-oxabicyclo[6.2.1]undecene skeleton constitutes a key structural feature in various natural products which are members of the furan-type germacranolide[1] or the eunicellanolide.[2] This bicyclic system contains a unique and interesting framework in which 5- and 9-membered rings were combined with an oxygen bridge. Recently, Boeckman and coworkers first synthesized (+)-eremantholide A by a strategy that forms this framework through cyclization of 9-membered ring at the final stage of their synthesis.[3] As a part of our study on the synthesis of zexbrevin[1a] and related compounds, we started an investigation to devise a general and efficient synthetic route to this type of bicyclics. Here we wish to report our results in the construction of the 11-oxabicyclo[6.2.1]undecene skeleton.

As depicted in retrosynthetic Scheme 1, we planned to build the bicyclic skeleton **1** from tricyclic 11-oxatricyclo$[6.2.1.0^{1,6}]$undecane ring system **2** by a ring expansion through a carbon-carbon bond cleavage.[4] The properly functionalized **2** might be formed from tricyclic **3** by concomitant epoxidation and Baeyer-Villiger oxidation. The tricyclic precursor **3** could be derived from the intramolecular Diels-Alder reaction of a furan diene such as **4**, which has numerous precedents.[5] Our synthetic approach, therefore, started with 5-methylfurfural as a starting material.

Synthesis of tricyclic ketone 11. Iodide **5**, which is a proper five-carbon side chain for the synthesis of enone **4**, was prepared from γ-hydroxymethyl-γ-butyrolactone[6] by successive reactions of LAH reduction, acetonide protection and iodide substitution as shown in Scheme 2. Even though Grignard formation from iodide **5** was not realized, lithi-