http://dx.doi.org/10.5012/bkcs.2014.35.6.1789

Kinetic Study on Nucleophilic Substitution Reaction of 5-Nitro-8-quinolyl Benzoate, Picolinate, Nicotinate and Isonicotinate with Alkali Metal Ethoxide: Effect of Nonleaving Group on Reactivity and Transition State Structure

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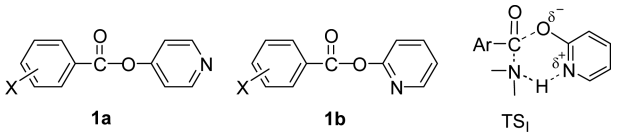
Received February 18, 2014, Accepted February 27, 2014

Pseudo-first-order rate constants (k_{obsd}) have been measured spectrophotometrically for the reactions of 5-nitro-8-quinolyl nicotinate (**4**) and 5-nitro-8-quinolyl isonicotinate (**5**) with alkali metal ethoxides (EtOM; M = K, Na and Li) in anhydrous ethanol at 25.0 ± 0.1 °C. The plots of k_{obsd} *vs*. [EtOM] curve slightly upward for the reactions with EtOK and EtONa but are linear for the reactions with EtOLi and for those with EtOK in the presence of 18-crown-6-ether. Dissection of k_{obsd} into k_{EtO^-} and k_{EtOM} (*i.e*., the second-order rate constants for the reactions with the dissociated EtO^- and ion-paired EtOM, respectively) has revealed that the reactivity increases in the order $EtO^- \approx$ EtOLi < EtOK < EtONa for the reactions of **4** and EtOLi < EtO^- < EtOK < EtONa for the reactions of **5**. Comparison of the kinetic results for the reactions of **4** and **5** with those reported previously for the corresponding reactions of 5-nitro-8-quinolyl benzoate (**2**) and picolinate (**3**) has revealed that the esters possessing a pyridine ring (*i.e*., **3**-**5**) are significantly more reactive than the benzoate ester **2** due to the presence of the electronegative N atom (*e.g*., **2** << **3** < **4** < **5**). It has been concluded that M^+ ion catalyzes the reactions of **3**-**5** by increasing the electrophilicity of the reaction center through a five-membered cyclic transition state (TS) for the reaction of **3** and *via* a four-membered cyclic TS for the reactions of **4** and **5**.

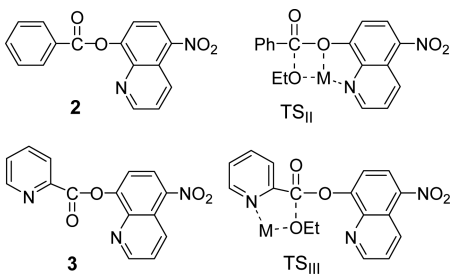
Key Words : Metal ion catalysis, Reaction mechanism, Transition state, Electrophilicity, Nucleofugality

Introduction

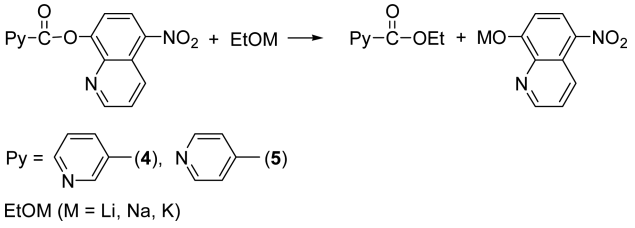
Acyl-group transfer reaction is a fundamental reaction in biological processes as well as in organic syntheses. Numerous studies have been carried out to investigate the reaction mechanism.[1-5] Reactions of carboxylic esters with amines have been reported to proceed through a concerted mechanism or via a stepwise pathway with one or two intermediates depending on the reaction conditions (*e.g*., the structure of substrates and the nature of reaction medium).[1-5] We have reported that the reactions of 4-pyridyl X-substituted-benzoate (**1a**) with a series of cyclic secondary amines in MeCN proceed through a stepwise mechanism with two intermediates (*e.g*., a zwitterionic tetrahedral intermediate $T^{\pm}$ and its deprotonated form T^-) when the substituent X is a strong electron-withdrawing group (EWG) such as 4-NO_2 or 4-CN.[5b] In contrast, the corresponding reactions of 2-pyridyl X-substituted-benzoates (**1b**, an isomer of **1a**) have been reported to proceed through a concerted mechanism with a transition-state (TS) structure similar to TS_I regardless of the electronic nature of the substituent X.[5a] Thus, it has been concluded that the intramolecular H-bonding interaction as illustrated in TS_I forces the reaction to proceed through a concerted mechanism by increasing the nucleofugality of the leaving group.[5a]



It is well known that metal ions play an important role in acyl-group transfer reactions. Metal ions have often been reported to catalyze the reactions by increasing either the electrophilicity of the reaction center or the nucleofugality of the leaving group.[6-12] For example, M^+ ion catalyzes the reactions of 5-nitro-8-quinolyl benzoate (**2**) with alkali-metal ethoxides (EtOM; M = K, Na and Li) by increasing the nucleofugality of the leaving group through TS_{II}, which is similar to the TS structure reported for the aminolysis of **1b** (*i.e*., TS_I).[12e] In contrast, we have reported that M^+ ions catalyze the reactions of 5-nitro-8-quinolyl picolinate (**3**) with EtOM (M = K, Na, Li) by increasing the electrophilicity of the reaction center through TS_{III}.[12a]



Our study has now been extended to the reactions of 5-nitro-8-quinolyl nicotinate (**4**) and isonicotinate (**5**) with EtOM in anhydrous ethanol (Scheme 1). The kinetic results obtained in this study have been compared with those



Scheme 1

reported previously for the corresponding reactions of 5-nitro-8-quinolyl benzoate (**2**)[12e] and picolinate (**3**)[12a] to investigate the effect of changing the nonleaving group (*i.e.*, from the benzoyl group in **2** to the picolinyl, nicotinyl and isonicotinyl groups in **3**, **4** and **5**, in turn) on the reactivity and TS structures.

Results and Discussion

All the reactions in this study proceeded with quantitative liberation of 5-nitro-8-quinolinolate ion as determined spectrophotometrically. First-order kinetics were observed under the reaction conditions with EtOM concentration in large excess. Pseudo-first-order rate constants (k_{obsd}) were obtained from the slope of the plots of ln ($A_\infty - A_t$) *vs*. *t*, which were linear over 90% reaction (*e.g.*, $R^2 > 0.9995$). It is estimated from replicate runs that the uncertainty in the k_{obsd} values is less than ± 3%. Tables 1 and 2 present the k_{obsd} data as function of [EtOM] for the reactions of 5-nitro-8-quinolyl nicotinate (**4**) and 5-nitro-8-quinolyl isonicotinate (**5**), respectively.

Effect of M^+ Ion on Reactivity. As shown in Figure 1(a), the plots of k_{obsd} *vs*. [EtOM] for the reactions of **4** with EtOK and EtONa exhibit slightly upward curvature, while those for the reactions with EtOLi and with EtOK in the presence of 18-crown-6-ether (18C6) are linear with nearly the same slope. Similarly curved plots are illustrated in the inset of Figure 1(a) for the corresponding reactions of 5-nitro-8-quinolyl benzoate (**2**). In contrast, Figure 1(b) shows that the plots for the reactions of **3** curve strongly upward. Such upward curvature in the plots of k_{obsd} *vs*. [EtOM] is typical for reactions of esters in which M^+ ion behaves as a Lewis

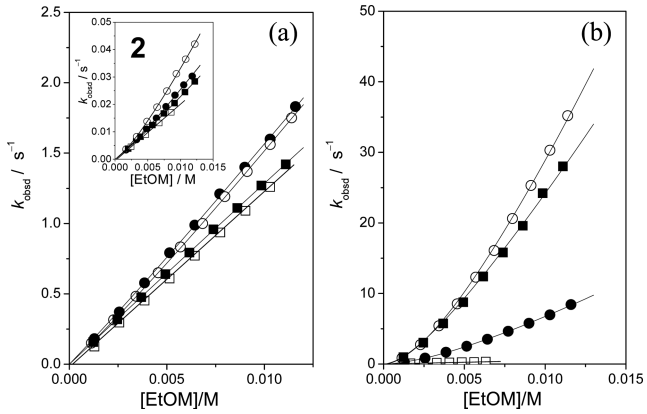


Figure 1. Plots of k_{obsd} *vs*. [EtOM] for the reactions of 5-nitro-8-quinolyl nicotinate **4** (**a**), benzoate **2** (inset) and picolinate **3** (**b**) with EtOK (●), EtONa (○), EtOLi (■) and EtOK with 18C6 (□) in anhydrous EtOH at 25.0 ± 0.1 °C. [18C6]/[EtOK] = 4.0. Data for the reactions of **2** and **3** were taken from refs. 12e and 12a, respectively.

acid catalyst.[11,12] In fact, we have reported that the reactions of **3** with EtOM are strongly catalyzed by the M^+ ions.[12a] Thus, one can suggest that K^+ and Na^+ ions catalyze the reactions of **4**, although the catalytic effect would not be large for the reactions, since the upward curvature is insignificant.

We have previously reported that the reactions of **3** with EtOM are strongly catalyzed by M^+ ions through a TS structure similar to TS_{III}, which increases the electrophilicity of the reaction center.[12a] However, such a cyclic TS is structurally impossible for the reactions of **2** and **4**. This accounts for the kinetic results that the catalytic effect is significant for the reactions of **3** but is insignificant for those of **2** and **4**. To support this idea, reactions of 5-nitro-8-quinolyl isonicotinate (**5**) with EtOM have been carried out. Since the reactions of **5** cannot proceed through TS_{III} either, one might expect that the kinetic result for the reactions of **5** would be similar to that for the reactions of **2** and **4** but would be significantly different from that reported for the reactions of **3**.

As shown in Figure 2, the plot of k_{obsd} *vs*. [EtOM] curves slightly upward for the reactions with EtOK and EtONa but

Table 1. Summary of Kinetic Data for the Reactions of 5-Nitro-8-quinolyl Nicotinate (**4**) 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	0.181	1.14	0.150	1.23	0.157
2.57	0.371	2.28	0.315	2.46	0.318
3.86	0.578	3.42	0.483	3.69	0.476
5.14	0.792	4.56	0.650	4.93	0.640
6.43	0.988	5.70	0.833	6.16	0.793
7.71	1.21	6.84	1.00	7.39	0.958
9.00	1.40	7.98	1.19	8.62	1.11
10.3	1.60	9.12	1.37	9.85	1.27
11.6	1.83	10.3	1.56	11.1	1.42
–	–	11.4	1.75	–	–

Table 2. Summary of Kinetic Data for the Reactions of 5-Nitro-8-quinolyl Isonicotinate (**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	0.95	1.40	1.06	1.23	0.882
2.57	1.95	2.80	2.19	2.46	1.72
3.86	3.03	4.20	3.32	3.69	2.58
6.43	5.11	5.60	4.58	4.93	3.42
7.71	6.16	7.00	5.87	6.16	4.17
9.00	7.28	8.40	7.18	7.39	4.98
10.3	8.50	9.80	8.48	8.62	5.76
–	–	11.2	9.72	9.85	6.54
–	–	12.6	11.2	11.1	7.26

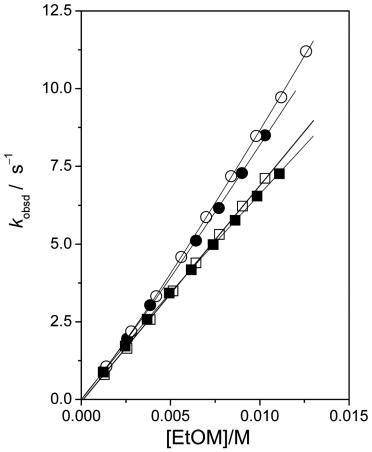
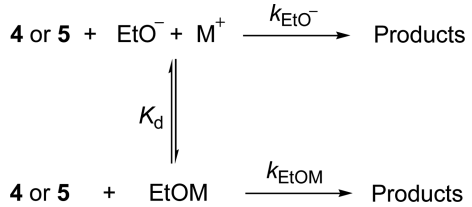


Figure 2. Plots of k_{obsd} *vs*. [EtOM] for the reactions of 5-nitro-8-quinolyl isonicotinate (**5**) with EtOK (●), EtONa (○), EtOLi (■) and EtOK with 18C6 (□) in anhydrous EtOH at 25.0 ± 0.1 °C. [18C6]/[EtOK] = 4.0.

is linear for that with EtOK in the presence of 18C6. In contrast, the plot for the reaction with EtOLi curves downward with slightly decreased k_{obsd} values. Similar results (*i.e*., downward curvature) have been reported for reactions with EtOLi in which Li^+ ion behaves as an inhibitor (*e.g*., reactions of parathion and 4-nitrophenyl diphenylphosphinothioate with EtOLi in anhydrous ethanol).[12f] Thus, one can suggest that the reaction of **5** is catalyzed by K^+ and Na^+ ions but is inhibited by Li^+ ion, although the catalytic and inhibitory effects are not significant. This is similar to the result for the reactions of **4** but is in contrast to that for the reactions of **3** (*i.e*., strong M^+ ion catalysis).

Dissection of k_{obsd} into k_{EtO^-} and k_{EtOM}. To quantify the catalytic or inhibitory effects exerted by the M^+ ions, the k_{obsd} values have been dissected into k_{EtO^-} and k_{EtOM} (*i.e*., the second-order rate constants for the reactions with the dissociated EtO^- ion and ion-paired EtOM, respectively). Pechanec *et al*. reported that EtOM exists as dimers or other aggregates in a high concentration region (*e.g*., [EtOM] > 0.1 M).[13] In the concentration of EtOM below 0.1 M as in this study, EtOM would exist mainly as the dissociated and ion-paired species. Accordingly, both dissociated EtO^- and ion-paired EtOM would react with substrates **4** and **5** as shown in Scheme 2.

One can derive Eq. (1) on the basis of the kinetic results and the reactions proposed in Scheme 2. Under pseudo-first-order kinetic conditions (*e.g*., [EtOM] >> [**4** or **5**]), k_{obsd} can



Scheme 2. Reactions of **4** or **5** with the dissociated EtO^- and ion-paired EtOM.

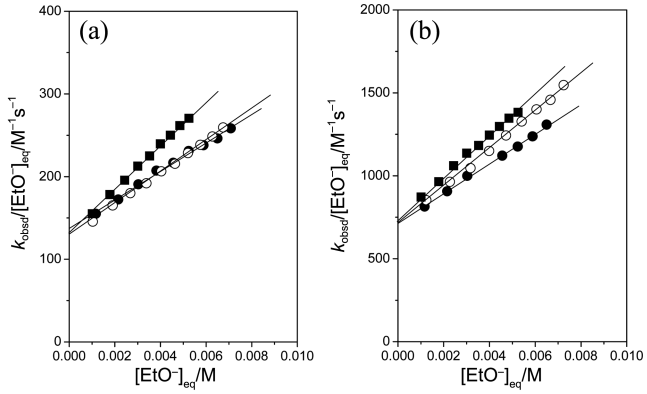


Figure 3. Plots of $k_{obsd}/[EtO^-]_{eq}$ *vs.* $[EtO^-]_{eq}$ for reactions of 5-nitro-8-quinolyl nicotinate **4** (a) and isonicotinate **5** (b) with EtOK (●), EtONa (○), and EtOLi (■) in anhydrous EtOH at 25.0 ± 0.1 °C.

be converted to Eq. (2). Since the dissociation constant $K_d = [EtO^-]_{eq}[M^+]_{eq}/[EtOM]_{eq}$, and $[EtO^-]_{eq} = [M^+]_{eq}$ at equilibrium, Eq. (2) can be expressed as Eq. (3). The $[EtO^-]_{eq}$ and $[EtOK]_{eq}$ values can be calculated from the reported K_d value for EtOM (*i.e*., $K_d = 11.1 \times 10^{-3}$, 9.80×10^{-3} and 4.72×10^{-3} M for EtOK, EtONa and EtOLi, in turn)[14] and the initial concentration of EtOM using Eqs. (4) and (5).

$$\text{Rate} = k_{EtO^-}[EtO^-]_{eq}[\mathbf{4} \text{ or } \mathbf{5}] + k_{EtOM}[EtOM]_{eq}[\mathbf{4} \text{ or } \mathbf{5}] \quad (1)$$

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

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

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

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

One might expect that the plot of $k_{obsd}/[EtO^-]_{eq}$ *vs*. $[EtO^-]_{eq}$ would be linear if the reaction proceeds as proposed in Scheme 2. In fact, the plots shown in Figure 3 exhibit excellent linear correlations, indicating that the derived equations based on the reactions proposed in Scheme 2 are correct.

Accordingly, the k_{EtO^-} and k_{EtOM}/K_d values were calculated from the intercept and the slope of the linear plot, respectively. The k_{EtOM} values were calculated from the above k_{EtOM}/K_d values and the reported K_d value for EtOM. In Table 3 are summarized the calculated k_{EtO^-} and k_{EtOM} values for the reactions of **4** and **5**. The k_{EtO^-} and k_{EtOM} values reported previously for the corresponding reactions of **2** and **3** are also summarized in Table 3 for comparison.

Table 3. Summary of k_{EtO^-} and k_{EtOM} for the Reactions of 5-Nitro-8-quinolyl Benzoate (**2**), Picolinate (**3**), Nicotinate (**4**), and Isonicotinate (**5**) in Anhydrous Ethanol at 25.0 ± 0.1 °C

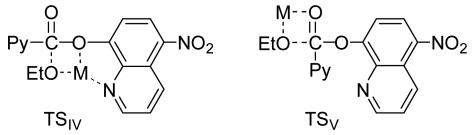
ester	$k_{EtO^-}/M^{-1}s^{-1}$	$k_{EtOLi}/M^{-1}s^{-1}$	$k_{EtONa}/M^{-1}s^{-1}$	$k_{EtOK}/M^{-1}s^{-1}$
2	1.64	2.91	6.06	3.96
3	52.7	4700	7410	1760
4	126	128	191	193
5	704	571	1130	1000

Factors Governing Reactivity of 2-5 toward EtO^-. It is well known that the reactivity of esters is strongly affected by the electronic nature of the substituent in the leaving and nonleaving groups. An acid strengthening substituent or an electron-withdrawing group (EWG) increases the reactivity of esters by increasing either the nucleofugality of the leaving group or the electrophilicity of the reaction center.[2-5] Since esters **2-5** possess the same leaving group (*i.e.*, 5-nitro-8-quinolinolate ion), their reactivity would be determined mainly by the electrophilicity of the reaction center (*i.e.*, benzoyl, picolinyl, nicotinyl and isonicotinyl). The pK_a values of benzoic, picolinic, nicotinic and isonicotinic acids are 4.19, 5.40, 4.86 and 4.96, in turn.[15] Since benzoic acid is the strongest acid among them, one might expect that benzoate ester **2** would be the most reactive substrate. However, Table 3 shows that the rate constant for the reactions with EtO^- (*i.e.*, k_{EtO^-}) increases in the order **2** << **3** < **4** < **5**. This indicates that the reactivity of these esters toward the dissociated EtO^- is not governed solely by acidity of the acid moiety of **2-5**.

One might expect that the presence of an electronegative N atom in the pyridine ring of **3-5** increases the electrophilicity of the reaction center through polar effects (inductive and field effects). In fact, pyridine is considered as a π-deficient heterocycle and an analogue of benzene ring that carries an EWG. This idea can account for the kinetic result that the esters possessing a pyridine ring (*i.e.*, **3-5**) are significantly more reactive than the benzoate ester **2**. It is apparent that the inductive effect exerted by the electronegative N atom becomes weaker with increasing the distance between the N atom and reaction center. Thus, one might expect that the reactivity decreases in the order **3** > **4** > **5**, if the inductive effect is an important factor that controls the reactivity of **3-5**. However, Table 3 shows that the reactivity order is opposite to the expectation (*i.e.*, **3** < **4** < **5**), indicating that the reactivity of **3-5** toward EtO^- is not controlled by the inductive effect exerted by the N atom.

The dipole moment of pyridine is 2.37 debyes.[16] Since the negative dipole end is on the N atom, attack of the anionic nucleophile (*i.e.*, the dissociated EtO^- ion) on the reaction center of **3-5** would be more difficult as the N atom is closer to the reaction center (*e.g.*, the field effect). This idea is consistent with the order of reactivity of **3-5** toward the dissociated EtO^- ion (*i.e.*, **3** < **4** < **5**). Thus, one can suggest that the reactivity of **3-5** toward EtO^- is mainly governed by the field effect rather than by the inductive effect.

Role of M^+ Ions: Increase in Electrophilicity or Nucleofugality. As shown in Table 3, the ion-paired EtOM is significantly more reactive than the dissociated EtO^- for the reaction of **3** regardless of the nature of M^+ ions (*e.g.*, k_{EtOM}/k_{EtO^-} = 33.4-141). In contrast, EtOK and EtONa are only slightly more reactive than EtO^- for the reactions of **2**, **4** and **5**, while EtOLi is slightly less reactive than EtO^- for the reaction of **5**. These results are consistent with the preceding argument that M^+ ions strongly catalyze the reactions of **3** through TS_{III}, which is structurally not possible for the reactions of **2**, **4** and **5**.



One might suggest that M^+ ions catalyze the reactions of **4** and **5** by increasing either the nucleofugality of the leaving group through TS_{IV} or the electrophilicity of the reaction center *via* TS_V. However, the enhanced nucleofugality through TS_{IV} would be ineffective for reactions in which expulsion of the leaving-group occurs after the rate-determining step (RDS). The reactions of **4** and **5** with EtOM would proceed either through a stepwise mechanism or *via* a concerted pathway. If the reactions proceed through a stepwise mechanism, departure of the leaving group would occur after the RDS. This is because EtO^- ion is significantly more basic and a poorer nucleofuge than 5-nitro-8-quinolinolate ion. We reported that the reactions of aryl benzoates with EtO^- and PhO^- in anhydrous EtOH proceed through a stepwise mechanism.[17] Besides, our preliminary experiment showed that the reactions of aryl picolinates with EtOM also proceed through a stepwise mechanism in which expulsion of the leaving group occurs after RDS. Thus, one can suggest that the reactions of **4** and **5** with EtOM would proceed also through a stepwise mechanism and that M^+ ions catalyze the reactions by increasing the electrophilicity of the reaction center through a TS structure similar to TS_V. It is evident that the four-membered cyclic TS structure (TS_V) is much less stable than the five-membered TS structure (TS_{III}), which was suggested as a TS structure for the reactions of **3**. This accounts for the kinetic results that the catalytic effect exerted by M^+ ions is significant for the reactions of **3** but is insignificant for those of **4** and **5**.

Conclusions

The kinetic study on the reactions of **4** and **5** with EtOM has led us to conclude the following: (1) Dissection of k_{obsd} into k_{EtO^-} and k_{EtOM} has revealed that the reactivity increases in the order $EtO^- \approx$ EtOLi < EtOK < EtONa for the reactions of **4** and EtOLi < EtO^- < EtOK < EtONa for the reactions of **5**. (2) The esters possessing a pyridine ring (*i.e.*, **3-5**) are significantly more reactive than the benzoate ester **2**. The reactivity of **3-5** toward the dissociated EtO^- ion increases in the order **3** < **4** < **5**, indicating that the field effect is more important than the inductive effect. (3) K^+ and Na^+ ions catalyze the reactions of **4** and **5** by increasing the electrophilicity through TS_V rather than by enhancing the nucleofugality through TS_{IV}.

Experimental Section

Materials. 5-Nitro-8-quinolyl nicotinate (**4**) and isonicotinate (**5**) were readily prepared by adding 5-nitro-8-quinolinol to the solution of the respective acid chloride in the presence of triethylamine in anhydrous diethyl ether as reported previously.[12e] The crude products were purified by

column chromatography (silica gel, methylene chloride/*n*-hexane 50/50). The purity was checked by their melting points and ^{1}H NMR spectra. The 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 standard HCl solution. 18-Crown-6-ether was recrystallized from acetonitrile and dried over P_2O_5 in vacuo. The anhydrous ethanol used was further dried over magnesium and distilled under N_2.

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 5-nitro-8-quinolinolate ion at 450 nm. Pseudo-first-order conditions with EtOM at least 20 times greater than substrate concentration were used. Generally, reactions were followed for 9-10 half-lives and k_{obsd} were calculated from the slope of the linear plots of ln $(A_\infty - A_t)$ *vs.* *t*.

Product Analysis. 5-Nitro-8-quinolinolate ion was liberated quantitatively and identified as one of the products by comparison of the Uv-vis spectra under the same kinetic conditions.

Acknowledgments. This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2012-R1A1B-3001637).

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