Kinetic and Mechanistic Studies on Quinuclidinolysis of Y-substituted-Phenyl Picolinates: Effect of Amine Nature on Reactivity and Transition-State Structure

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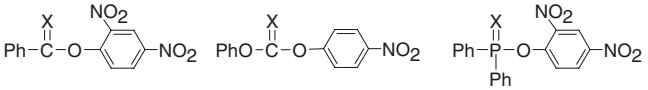
Second-order rate constants (k_N) have been measured spectrophotometrically for reactions of Y-substituted-phenyl picolinates (**7a–7i**) with a series of quinuclidines in 80 mol% H_2O/20 mol% DMSO at 25.0 ± 0.1 °C. The Brønsted-type plot for the reactions of **7a–7i** with quinuclidine is linear with $\beta_{lg} = -0.80$. The Yukawa-Tsuno plot exhibits an excellent linear correlation with $\rho_Y = 2.37$ and $r = 0.52$, indicating that a negative charge develops partially on the O atom of the leaving group in the rate-determining transition state (TS). The Brønsted-type plot for the reactions of 2-chloro-4-nitrophenyl picolinate (**7a**) with a series of quinuclidines is also linear with $\beta_{nuc} = 0.83$. Thus, it was concluded that the reactions proceed through a stepwise mechanism, in which expulsion of the leaving group occurs in the rate-determining step. Comparison of the current kinetic data with those reported previously for the corresponding reactions with piperidine revealed that quinuclidine is *ca.* 10^2-fold less reactive than piperidine. This is in contrast to the reports that quinuclidines are more reactive than isobasic secondary amines toward diaryl carbonates and related esters. Effects of amine nature on reactivity and TS structures are discussed.

Keywords: Y-substituted-phenyl picolinates, Quinuclidinolysis, Brønsted-type plot, Yukawa-Tsuno plot, Rate-determining step

Introduction

Aminolyses of esters have been intensively investigated due to their importance in biological processes (*e.g.*, enzyme actions and peptide biosynthesis) as well as in synthetic applications.[1–10] Nucleophilic substitution reactions of esters with amines have been reported to proceed through a concerted mechanism or via a stepwise pathway with one or two intermediates (*e.g.*, a zwitterionic tetrahedral intermediate $T^{\pm}$ and its deprotonated form T^{-}) depending on the reaction conditions (*e.g.*, nature of the reaction medium and electrophilic center).[2-10]

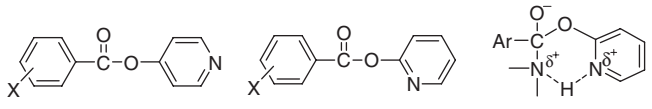
Reactions of 2,4-dinitrophenyl benzoate (**1a**) with a series of cyclic secondary amines in 80 mol% H_2O/20 mol% DMSO have been suggested to proceed through a stepwise mechanism with a change in the rate-determining step (RDS) on the basis of a curved Brønsted-type plot.[6a] However, the corresponding reactions carried out in an aprotic solvent MeCN have been concluded to proceed via a concerted mechanism on the basis of a linear Brønsted-type plot with $\beta_{nuc} = 0.40$,[6b] indicating that the reaction mechanism is dependent on the nature of the reaction medium. In contrast, reactions of *O*-2,4-dinitrophenyl thionobenzoate (**1b**, a thio analog of **1a**) with cyclic secondary amines have been reported to proceed through a stepwise mechanism with two intermediates (*i.e.*, $T^{\pm}$ and T^{-}) in H_2O as well as in MeCN on the basis of an upward curvature found in the plots of k_{obsd} vs. [amine].[7] A similar result has been reported for the reactions of **2a** and **2b**, *e.g.*, aminolysis of phenyl 4-nitrophenyl carbonate (**2a**) proceeds through a stepwise mechanism with a change in the RDS while the corresponding reaction of *O*-phenyl *O*-4-nitrophenyl thionocarbonate (**2b**, a thio analog of **2a**) proceeds via a stepwise mechanism with two intermediates (*i.e.*, $T^{\pm}$ and T^{-}).[8] However, reactions of 2,4-dinitrophenyl diphenylphosphinate (**3a**) and diphenylphosphinothioate (**3b**, a thio analog of **3a**) with primary and cyclic secondary amines have been reported to proceed through a concerted mechanism on the basis of linear Brønsted-type plots with $\beta_{nuc} = 0.4 \pm 0.1$.[9]



X = O(**1a**), S(**1b**). X = O(**2a**), S(**2b**). X = O(**3a**), S(**3b**).

We have reported that intramolecular H-bonding interaction is also an important factor that controls the reaction mechanism. Reactions of 4-pyridyl X-substituted-benzoates (**4**) with cyclic secondary amines in MeCN have been suggested to proceed through a stepwise mechanism with one or two intermediates depending on the electronic nature of the substituent X in the benzoyl moiety (*e.g.*, with $T^{\pm}$ and T^{-} when the substituent X is a strong electron-withdrawing group such as 4-NO_2 or 4-CN, but with $T^{\pm}$ only when X is a weak electron-withdrawing group or an electron-donating group).[10a] In contrast, the corresponding reactions of 2-pyridyl X-substituted-

benzoates (**5**) have been proposed to proceed through a forced concerted mechanism with an unstable cyclic intermediate as modeled by **6**.[10b] It is noted that the H-bonding interaction shown in **6** could decrease the basicity of the leaving group dramatically by changing the nucleofuge from a strongly basic 2-pyridyloxide (pK_a of its conjugate acid is 11.62 in H_2O) to a weakly basic 2-pyridinium oxide (pK_a of its conjugate acid is 0.75 in H_2O) or its tautomer 2-pyridone. Thus, we have proposed that the intramolecular H-bonding interactions in **6** shorten its lifetime and force the reaction to proceed through a concerted mechanism by decreasing the basicity of the leaving group over 10 pK_a units.[10b]

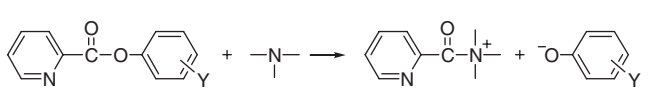


4 **5** **6**

We have now extended our study to reactions of Y-substituted-phenyl picolinates (**7a–7i**) with a series of quinuclidines in 80 mol% H_2O/20 mol% DMSO to obtain further information on the reaction mechanism (Scheme 1). The kinetic data obtained from the current study have been compared with those reported previously for the corresponding reactions with a series of cyclic secondary amines[10c] to investigate the effects of amine nature (*e.g.*, secondary amines vs. tertiary amines) on reactivity and transition-state (TS) structures.

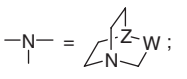
Results and Discussion

The kinetic study was carried out under pseudo-first-order conditions in which the concentration of quinuclidine was kept in excess of the substrate concentration. All the reactions in this study obeyed pseudo-first-order kinetics and proceeded with quantitative liberation of Y-substituted-phenoxide ion (and/or its conjugate acid). Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation, $\ln(A_\infty - A_t) = -k_{obsd}t + C$. The plots of $\ln(A - A_t)$ *vs.* t were linear over 90% of the total reaction. The uncertainty in the k_{obsd} values is estimated to be less than ± 3% from replicate runs. The plots of k_{obsd} vs. [quinuclidine] were linear. Thus, the second-order rate constants (k_N) were calculated from the slope of the linear plots. The k_N values calculated in this way are summarized in Tables 1 and 2 for the reactions of Y-substituted-phenyl picolinates (**7a–7i**) with quinuclidine and for those of 2-chloro-4-nitrophenyl picolinate (**7a**) with a series of quinuclidine derivatives, respectively.



7a-7i

Y = 2-Cl-4-NO_2(**7a**), 4-NO_2(**7b**), 4-CHO(**7c**), 4-CN(**7d**), 4-COMe(**7e**), 4-COOEt(**7f**), 3-Cl(**7g**), 4-Cl(**7h**), H(**7i**).



Z = CH and W = CH_2 (quinuclidine)
Z = CH and W = CHOH (3-hydroxyquinuclidine)
Z = CH and W = CHCl (3-chloroquinuclidine)
Z = N and W = CH_2 (1,4-diazabicyclo[2.2.2]octane)
Z = CH and W = CO (3-quinuclidinone).

Scheme 1. Quinuclidinolysis of **7a-7i**.

Effects of Leaving Group Basicity on Reactivity. As shown in Table 1, the k_N value for the reactions of **7a–7i** with quinuclidine decreases as the basicity of the leaving group increases, *e.g.*, it decreases from 8.70 M^{-1} s^{-1} to 0.217 and 0.00280 M^{-1} s^{-1} as the pK_a of the conjugate acid of the leaving aryloxide increases from 5.45 to 7.95 and 9.95, respectively. A similar result is demonstrated for the reactions with piperidine, although the cyclic secondary amine is *ca.* 10^2-fold more reactive than the similarly basic tertiary amine. The effect of amine nature on reactivity will be discussed subsequently.

The effect of amine basicity on reactivity is illustrated in Figure 1. The Brønsted-type plot for the reactions of **7a–7i** with quinuclidine is linear with $\beta_{lg} = -0.80$. A similarly linear plot is demonstrated for the corresponding reactions with piperidine, although the slope for the piperidinolysis is larger ($\beta_{lg} = -1.04$) than that for the quinuclidinolysis. The linear Brønsted-type plots in Figure 1 are in contrast to the curved Brønsted-type plot reported by Gresser and Jencks for the reactions of phenyl Y-substituted-phenyl carbonates with quinuclidine (*i.e.*, β_{lg} changes from −1.3 to −0.2 as the leaving group becomes less basic than quinuclidine by 3–5 pK_a units).[13]

Table 1. Summary of kinetic data for the reactions of Y-substituted-phenyl picolinates (**7a–7i**) with quinuclidine and piperidine in 80 mol% H_2O/20 mol % DMSO at 25.0 ± 0.1 °C.

			k_N (M^{-1} s^{-1})	
Entry	Y	pK_a[a]	Quinuclidine	Piperidine[b]
7a	2-Cl-4-NO_2	5.45	8.70	—
7b	4-NO_2	7.14	0.829	211
7c	4-CHO	7.66	0.161	49.5
7d	4-CN	7.95	0.217	—
7e	4-COMe	8.05	0.0610	18.0
7f	4-COOEt	8.50	0.0601	12.7
7g	3-Cl	9.02	0.0125	2.34
7h	4-Cl	9.38	0.00811	0.783
7i	H	9.95	0.00280	0.230

[a] The pK_a data of Y-substituted-phenols were taken from Ref 11. [b] The kinetic data for the reactions with piperidine were taken from Ref 10c.

Table 2. Summary of kinetic data for the reactions of 2-chloro-4-nitrophenyl picolinate (**7a**) with quinuclidines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C.

	Entry	pK_a[a]	k_N (M^{-1} s^{-1})
1.	Quinuclidine	11.4	8.70
2.	3-Hydroxyquinuclidine	9.8	0.888
3.	3-Chloroquinuclidine	9.0	0.0732
4.	1,4-Diazabicyclo[2.2.2]octane	8.9	0.176
5.	3-Quinuclidinone	7.5	0.00593

[a] pK_a data were taken from Ref 12.

The β_{lg} value obtained in this study is a little smaller than that reported previously for reactions that proceed through a stepwise mechanism with breakdown of an addition intermediate being the RDS (*e.g.*, $\beta_{lg} = -1.1 \pm 0.2$) but is much larger than that for reactions in which expulsion of the leaving group occurs after the RDS (*e.g.*, $\beta_{lg} = -0.3 \pm 0.1$).[2,12,13] Besides, the current β_{lg} value of –0.80 is also larger than that reported for a concerted mechanism (*e.g.*, $\beta_{lg} = -0.5 \pm 0.1$ for aminolysis of Y-substituted-phenyl diphenylphosphinates and diphenylphosphinothioates).[2,9] Accordingly, the linear Brønsted-type plot with $\beta_{lg} = -0.80$ alone does not lead to a conclusion whether the current reactions proceed through a stepwise mechanism or via a concerted pathway.

It is well known that Hammett plots correlated with σ^- and σ^o constants give useful information on the reaction mechanism including the RDS. If the reactions of **7a–7i** with quinuclidine proceed through a concerted mechanism or via a stepwise pathway with expulsion of the leaving group being the RDS, a negative charge would develop partially on the O atom of the leaving Y-substituted-phenoxide. Since such a negative charge can be delocalized to the substituent Y through resonance interactions, one might expect that σ_Y^- constants should result in a better Hammett correlation than σ_Y^o constants. In contrast, if the reactions proceed through a stepwise mechanism, in which expulsion of the leaving group occurs after the RDS, no negative charge would develop on the O atom of the leaving group in the rate-determining TS. In this case, σ_Y^o constants should result in a better Hammett correlation than σ_Y^- constants. Thus, Hammett plots have been constructed using σ_Y^o and σ_Y^- constants. As shown in Figure 2, the Hammett plot correlated with σ_Y^o constants exhibits highly scattered points ($R^2 = 0.936$). The plot correlated with σ_Y^- constants results in a slightly better correlation ($R^2 = 0.978$), but it still exhibits many scattered points. Accordingly, one cannot obtain useful information on the RDS from these Hammett plots.

To obtain more conclusive information on the RDS of the current reactions, the Yukawa-Tsuno equation has been employed. Eq. (1) was originally derived to account for the kinetic results obtained from solvolysis of benzylic systems in which a positive charge develops partially at the reaction center.[14] We have shown that Eq. (1) is also highly effective to elucidate uncertainties in reaction mechanisms for nucleophilic substitution reactions of esters with various nucleophiles (*e.g.*, neutral amines as well as anionic nucleophiles such as OH^-, N_3^-, and CN^-).[5,9,10,15]

$$\log k^Y/k^H = \rho_Y[\sigma_Y^o + r(\sigma_Y^- - \sigma_Y^o)] \quad (1)$$

In fact, the Yukawa-Tsuno plot shown in Figure 3 for the quinuclidinolysis of **7b–7i** exhibits excellent linearity ($R^2 = 0.991$) with $\rho_Y = 2.37$ and $r = 0.52$. This is comparable with the linear Yukawa-Tsuno plot for the corresponding reactions

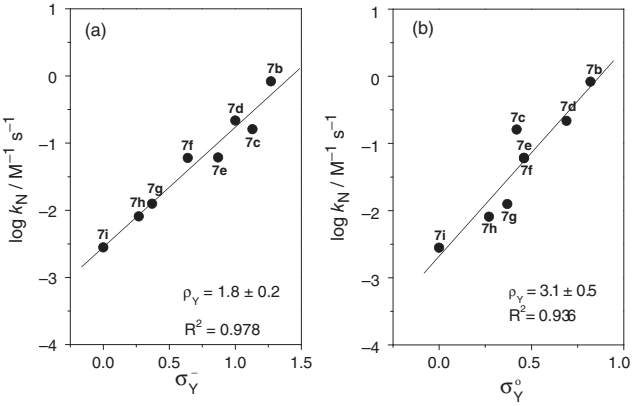


Figure 2. Hammett plots correlated with σ_Y^- (**a**) and σ_Y^o (**b**) for the reactions of Y-substituted-phenyl picolinates (**7b–7i**) with quinuclidine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

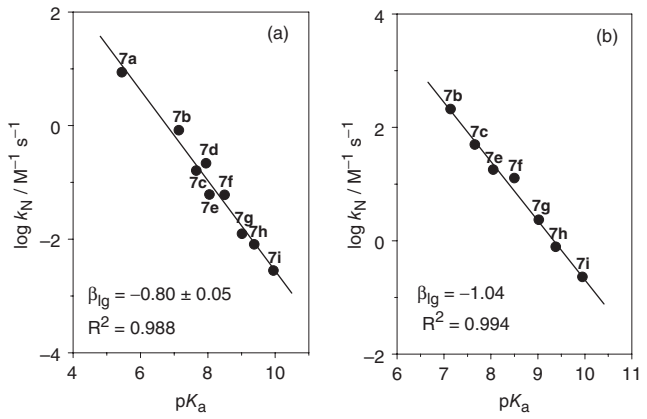


Figure 1. Brønsted-type plots for the reactions of Y-substituted-phenyl picolinates (**7a–7i**) with quinuclidine (**a**) and piperidine (**b**) in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

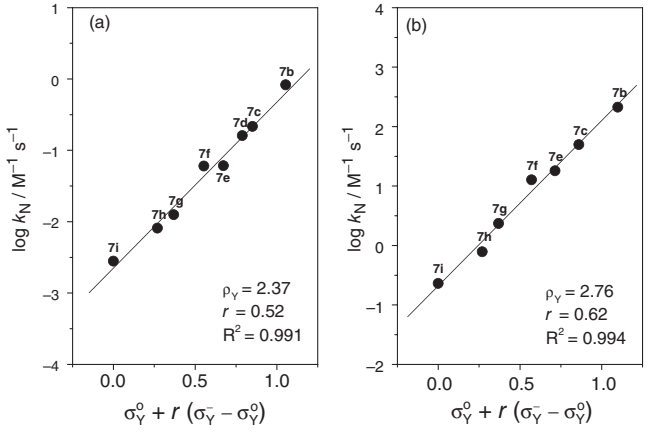


Figure 3. Yukawa-Tsuno plots for the reactions of Y-substituted-phenyl picolinates (**7b–7i**) with quinuclidine (a) and piperidine (b) in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

with piperidine (*e.g.*, $\rho_Y = 2.76$, $r = 0.62$, and $R^2 = 0.994$). The r value in Eq. (1) represents the resonance demand of the reaction center or the extent of resonance contribution, while the term $(\sigma_Y^- - \sigma_Y^o)$ is the resonance substituent constant that measures the capacity for π-delocalization of the π-electron acceptor substituent.[14,16] The r value of 0.52 found for the reactions with quinuclidine clearly indicates that a negative charge develops partially on the O atom of the leaving group, which can be delocalized to the substituent Y through resonance interactions.

Effect of Amine Basicity on Reactivity. To obtain further information on the reaction mechanism, second-order rate constants for reactions of 2-chloro-4-nitrophenyl picolinate (**7a**) with a series of quinuclidines have been measured. As shown in Table 2, the k_N value for the reaction of **7a** decreases with decreasing basicity of quinuclidines, *e.g.*, it decreases from 8.70 $M^{-1}s^{-1}$to 0.888 and 0.00593 $M^{-1}s^{-1}$ as the pK_a of the conjugate acid of quinuclidine decreases from 11.4 to 9.8 and 7.5, respectively.

The effect of nucleophile basicity on reactivity is illustrated in Figure 4. The statistically corrected Brønsted-type plot for the reactions of **7a** with quinuclidines results in an excellent linear correlation with $\beta_{nuc} = 0.83$, which is comparable with that reported previously for reactions proceeding through a stepwise mechanism with expulsion of the leaving group being the RDS (*e.g.*, $\beta_{nuc} = 0.86$ for the reactions of methyl 4-nitrophenyl carbonate with quinuclidines[12b] and $\beta_{nuc} = 0.78$ for the reactions of 4-nitrophenyl picolinate (**7b**) with a series of cyclic secondary amines[10c]). However, a β_{nuc} value of 0.83 observed in this study is much larger than a β_{nuc} value 0.5 ± 0.1 reported previously for reactions that proceed through a concerted mechanism (*e.g.*, aminolysis of **3a** and **3b** and quinuclidinolysis of methyl 2,4-dinitrophenyl carbonate).[9,12b] Thus, one can conclude that the current reactions proceed through a stepwise mechanism in which expulsion of the leaving group occurs in the RDS.

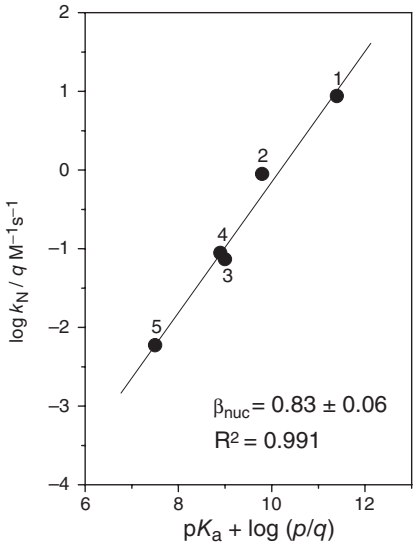
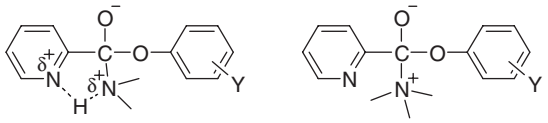


Figure 4. Brønsted-type plot for the reactions of 2-chloro-4-nitrophenyl picolinate (**7a**) with quinuclidines in 80 mol % H_2O/ 20 mol % DMSO at 25.0 ± 0.1 °C. The plot was statistically corrected using p and q (*i.e.*, $p = 1$ and $q = 1$ except $q = 2$ for 1,4-diazabicyclo [2.2.2]octane).[17] The identity of points is given in Table 2.

Effect of Amine Nature on Reactivity and TS Structure. As shown in Table 1, quinuclidine is *ca.* 10^2-fold less reactive than the similarly basic piperidine. One might suggest that steric hindrance exerted by quinuclidines is responsible for the decreased reactivity, since tertiary amines are bulkier than cyclic secondary amines. However, we propose that amine nature is also responsible for the kinetic result that quinuclidines are much less reactive than isobasic secondary amines on the basis of the following reason. We have previously proposed that reactions of **7a–7i** with cyclic secondary amines proceed through a cyclic intermediate as modeled by **8**, which could gain great stability through intermolecular H-bonding interactions.[10c] However, such cyclic intermediate is structurally not possible for the reactions with quinuclidines (*e.g.*, intermediate **9**). Stabilization of the intermediate through such H-bonding interactions would lead to stabilization of the TS on the basis of Hammond postulate.[18] Thus, one might suggest that the enhanced stability of intermediate **8** through the H-bonding interactions is primarily responsible for the kinetic result that piperidine is much more reactive toward **7a–7i** than the similarly basic quinuclidine.



8 **9**

It has generally been understood that β_{nuc} represents a relative degree of bond formation between the nucleophile and the electrophilic center, while β_{lg} stands for a relative degree of leaving group expulsion. The β_{nuc} value of 0.83 ± 0.06 shown in Figure 4 for the reactions of **7a** with quinuclidines is almost the same as that reported previously for the reactions of **7a** with cyclic secondary amines ($\beta_{nuc} = 0.78 \pm 0.04$),[10c] indicating that the degree of bond formation between the nucleophile and electrophilic center is practically the same for both series of the reactions. In contrast, β_{lg} for the reactions of **7a–7i** with quinuclidine is -0.80 ± 0.05, which is smaller than the β_{lg} value of -1.04 ± 0.05 for the reactions with piperidine (Figure 1). This indicates that expulsion of the leaving group in the rate-determining TS is clearly less advanced for the reactions with quinuclidines than that for the reactions with piperidine.

Scrutiny of the proposed intermediates **8** and **9** reveals that the positive charge on the N atom of their aminium moiety is different, *i.e.*, a partial positive charge in **8** and a full positive one in **9**. One might expect that expulsion of the leaving group from **9**, in which the N atom bonded to the reaction center is fully charged, would be more difficult than from **8**, where the N atom is partially charged. This idea accounts for the fact that β_{lg} is smaller for the reactions proceeding through intermediate **9** than for those proceeding via **8**.

Conclusions

The current study has allowed us to conclude the following: (1) The Brønsted-type plot for the reactions of **7a–7i** with quinuclidine is linear with $\beta_{lg} = -0.80 \pm 0.05$, which is smaller than that reported for the corresponding reactions with piperidine (*i.e.*, $\beta_{lg} = -1.04 \pm 0.05$). (2) The Yukawa-Tsuno plot results in excellent linearity with $\rho_Y = 2.37$ and $r = 0.52$, indicating that a partial negative charge develops on the O atom of the leaving group in the rate-determining TS. (3) The Brønsted-type plot for the reactions of **7a** with a series of quinuclidines is linear with $\beta_{nuc} = 0.83 \pm 0.06$, which is practically the same as that reported previously for the corresponding reactions with secondary amines (*i.e.*, $\beta_{nuc} = 0.78 \pm 0.04$). (4) The reactions with quinuclidines proceed through a stepwise mechanism, in which expulsion of the leaving group occurs in the RDS. (5) Analysis of β_{nuc} and β_{lg} values suggests that expulsion of the leaving group from the intermediate in the rate-determining TS is less advanced for the reactions with quinuclidines than that for the reactions with secondary amines, while bond formation between the nucleophile and electrophilic center is practically the same for both reactions. (6) Piperidine is *ca.* 10^2-fold more reactive than quinuclidine toward **7a–7i**. This supports the proposal that the reactions of **7a–7i** with secondary amines proceed through a stabilized cyclic intermediate, which is structurally not possible for the reactions with quinuclidines.

Experimental

Materials. Y-substituted-phenyl picolinates (**7a–7i**) were readily prepared from the reaction of picolinic acid with Y-substituted-phenol in methylene chloride under the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) as reported previously.[10c] The crude product was purified by column chromatography and the purity was checked by their melting point and spectral data such as ^{1}H and ^{13}C NMR spectra. Double glass distilled H_2O was further boiled and cooled under nitrogen just before use. DMSO and other chemicals were of the highest quality available.

Kinetics. The kinetic study was carried out using a UV–vis spectrophotometer equipped with a constant temperature circulating bath to maintain the reaction mixture at 25.0 ± 0.1 °C. The reactions were followed by monitoring the appearance of Y-substituted-phenoxide ion. All the reactions in this study were performed under pseudo-first-order conditions, in which the concentration of quinuclidine was kept in excess of the substrate concentration. Owing to low solubility of **7a–7i** in pure water, aqueous DMSO (*i.e.*, 80 mol% H_2O/20 mol% DMSO) was used as the reaction medium.

Typically, the reaction was initiated by adding 5 μL of a 0.02 M solution of the substrate in acetonitrile to a 10-mm quartz UV cell containing 2.50 mL of the thermostated reaction mixture made up of solvent and aliquot of the quinuclidine stock solution. All solutions were transferred by gastight syringes. Generally, the concentration of quinuclidines in the reaction mixtures was *ca.* $(5–100) \times 10^{-3}$ M, while the concentration of the substrate was *ca.* 4×10^{-5} M. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation, $\ln(A_\infty - A_t) = -k_{obsd}t + C$. The plots of $\ln(A–A_t)$ vs. time were linear over 90% of the total reaction.

Products Analysis. Y-substituted-phenoxide ion (and/or its conjugate acid) was liberated quantitatively and identified as one of the products by comparison of the UV–vis spectrum after completion of the reaction with that of an authentic sample under the same reaction condition.

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