Kinetic Study on Alkaline Hydrolysis of *Y*-substituted Phenyl Picolinates: Effects of Modification of Nonleaving Group from Benzoyl to Picolinyl on Reactivity and Reaction Mechanism

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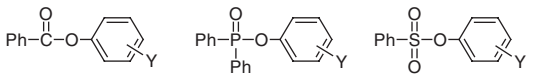
Second-order rate constants (k_{OH^-}) for alkaline hydrolysis of *Y*-substituted phenyl picolinates (**6a–6i**) have been measured spectrophotometrically. A linear Brønsted-type plot is obtained with $\beta_{lg} = -0.34$, which is typical for reactions reported previously to proceed through a stepwise mechanism with formation of an addition intermediate being the rate-determining step (RDS). However, σ_Y^o constants result in a much poorer Hammett correlation than σ_Y^- constants. Furthermore, the Yukawa-Tsuno plot exhibits an excellent linear correlation with $\rho_Y = 0.82$ and $r = 0.72$, indicating that a negative charge develops partially on the O atom of the leaving group in the RDS. Thus, the reactions have been concluded to proceed through a forced concerted mechanism with a highly unstable intermediate **7**. Comparison of the current kinetic data with those reported previously for the corresponding reactions of *Y*-substituted phenyl benzoates has revealed that modification of the nonleaving group from benzoyl to picolinyl causes not only an increase in reactivity but also a change in the reaction mechanism (*i.e.*, from a stepwise mechanism to a forced concerted pathway).

Keywords: Alkaline hydrolysis, Aryl picolinate, Electronic repulsion, Intermediate, Forced concerted mechanism

Introduction

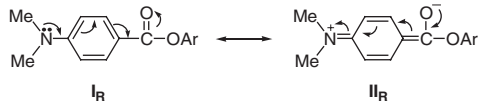
Nucleophilic substitution reactions of esters have intensively been carried out to investigate reaction mechanisms.[1–14] Reactions of esters with amines have been reported to proceed through a concerted mechanism or via a stepwise pathway depending on reaction conditions (*e.g.*, structure of esters, basicity of nucleophiles, nature of reaction medium, etc.).[1–8] A curved Brønsted-type plot often observed for aminolysis of esters possessing a weakly basic leaving group (*e.g.*, 2,4-dinitrophenoxide) has been interpreted as a change in the rate-determining step (RDS) of a stepwise reaction, while a linear Brønsted-type plot with $\beta_{nuc} = 0.4–0.5$ has been taken as evidence for a concerted mechanism.[1–8]

Reactions of esters with anionic nucleophiles have also been reported to proceed either through a concerted mechanism or via a stepwise pathway.[9–14] We have proposed that reactions of *Y*-substituted phenyl benzoates (**1**) with OH^- and CN^- proceed through a stepwise mechanism in which expulsion of the leaving group occurs after the RDS on the basis of the kinetic result that σ_Y^o constants result in a much better Hammett correlation than σ_Y^- constants.[9a] In contrast, reactions of *Y*-substituted phenyl diphenylphosphinates (**2**) and *Y*-substituted phenyl benzenesulfonates (**3**) with $C_2H_5O^-$ have been concluded to proceed through a concerted mechanism on the basis of the fact that the Yukawa-Tsuno plot exhibits an excellent linear correlation with $\rho_Y = 1.90$ and $r = 0.33$ for the reactions of **2**[10a] and with $\rho_Y = 2.61$ and $r = 0.29$ for the reactions of **3**.[10]



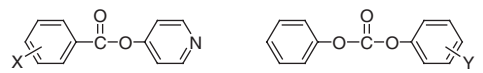
1 **2** **3**

Although it is now firmly understood that RDS for a stepwise mechanism is dependent on basicity of the leaving group and incoming nucleophile, effects of nonleaving-group substituents on the reaction mechanism including the RDS are controversial.[15–19] Gresser and Jencks have reported that the RDS for quinuclidinolysis of diaryl carbonates is governed by the electronic nature of the nonleaving-group substituents.[15] A similar conclusion has been drawn by Castro *et al*. for pyridinolysis of 2,4-dinitrophenyl *X*-substituted benzoates and aminolysis of *S*-2,4-dinitrophenyl *X*-substituted thiobenzoates,[16] and by Oh *et al*. for pyridinolysis of aryl dithiobenzoates.[17] On the contrary, we have reported that the RDS is independent of the electronic nature of the nonleaving-group substituent X for reactions of 2,4-dinitrophenyl *X*-substituted benzoates and related esters with various nucleophiles (*e.g.*, amines, hydroxide, and ethoxide ions).[10,18] We have proposed that the nonlinear Hammett plots obtained from reactions of 2,4-dinitrophenyl *X*-substituted benzoates with nucleophiles such as amines, OH^-, and $C_2H_5O^-$ ions are not due to a change in the RDS but are caused by stabilization of substrates possessing an electron-donating substituent *X* in the nonleaving group through resonance interactions as modeled by resonance structures I_R and II_R.[5–10,18]



I_R II_R

In contrast, we have recently reported that the reaction mechanism for aminolysis of 4-pyridyl *X*-substituted benzoates (**4**) in MeCN is governed by the electronic nature of the substituent *X*, *i.e.*, the plot of k_{obsd} vs. [amine] curves upward when the substituent *X* is a strong electron-withdrawing group (EWG) but is linear when the substituent *X* is a weak EWG or an electron-donating group (EDG).[19a] Thus, we have concluded that the reaction of substrates possessing a strong EWG in the benzoyl moiety proceeds through a stepwise mechanism with two intermediates (*i.e.*, a zwitterionic tetrahedral intermediate $T^{\pm}$ and its deprotonated form T^{-}) but the deprotonation process to yield T^{-} from $T^{\pm}$ is absent for the reaction of substrates bearing a weak EWG or an EDG in the benzoyl moiety.[19a]



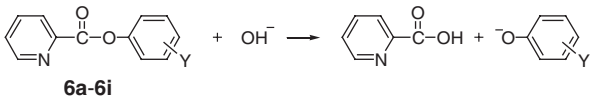
4 **5**

Modification of the nonleaving group from benzoyl to phenoxycarbonyl has also been reported to cause a change in reaction mechanism. As mentioned earlier, alkaline hydrolysis of *Y*-substituted phenyl benzoates (**1a–1i**) has been proposed to proceed through a stepwise mechanism in which expulsion of the leaving group occurs after the RDS.[9a] In contrast, the corresponding reaction of *Y*-substituted phenyl phenyl carbonates (**5**) has been concluded to proceed through a forced concerted mechanism.[20]

We have now extended this study to alkaline hydrolysis of *Y*-substituted phenyl picolinates (**6a–6i**) to obtain further information on the reaction mechanism (Scheme 1). Comparison of the kinetic results obtained in this study with those reported previously for the corresponding reaction of *Y*-substituted phenyl benzoates (**1a–1i**) has revealed that modification of the nonleaving group from benzoyl to picolinyl causes not only an increase in reactivity but also a change in the reaction mechanism (*i.e.*, from a stepwise mechanism to a forced concerted pathway).

Results and Discussion

The kinetic study was carried out under pseudo-first-order conditions in which the NaOH concentration was kept at least 20 times in excess of the substrate concentration. All the reactions in this study obeyed first-order kinetics and the pseudo-first-order rate constants (k_{obsd}) were calculated from the equation, $\ln(A_\infty - A_t) = -k_{obsd}t + C$. The plots of k_{obsd} vs. OH^- concentrations were linear and passed through the origin, indicating that contribution of H_2O to k_{obsd} is negligible. Accordingly, the second-order rate constants (k_{OH^-}) were calculated from the slope of the linear plots. The k_{OH^-} values calculated in this way are summarized in Table 1 together with those reported previously for the corresponding reactions of *Y*-substituted phenyl benzoates (**1a–1i**) for comparison. The uncertainty in the k_{OH^-} values is estimated to be less than ±3% based on the replicate runs.



6a-6i

Y = 4-NO_2(**6a**),4-CHO(**6b**),4-CN(**6c**),4-COMe(**6d**), 4-CO_2Et(**6e**),3-Cl(**6f**),4-Cl(**6g**),H(**6h**),4-Me(**6i**).

Scheme 1. Alkaline Hydrolysis of **6a-6i**.

Reaction Mechanism. As shown in Table 1, the k_{OH^-} value for the reactions of *Y*-substituted phenyl picolinates (**6a–6i**) decreases as the leaving group basicity increases, *e.g.*, it decreases from 91.3 to 31.6 and 7.53 $M^{-1}s^{-1}$ as the pK_a of the conjugate acid of the leaving group increases from 7.14 to 8.50 and 10.19, in turn. A similar result is demonstrated for the corresponding reactions of *Y*-substituted phenyl benzoates (**1a–1i**), although the benzoate esters are less reactive than the corresponding picolinate esters. This demonstrates that modification of the nonleaving group from benzoyl to picolinyl causes an increase in reactivity. The effect of nonleaving group on reactivity will be discussed subsequently.

Effect of leaving-group basicity on reactivity is illustrated in Figure 1. The Brønsted-type plot is linear with $\beta_{lg} = -0.34$, indicating that the reactions of **6a–6i** proceed without changing the reaction mechanism including the RDS. A β_{lg} value of −0.34 is typical for reactions reported previously to proceed through a stepwise mechanism in which expulsion of the leaving group occurs after the RDS.[2–8] Thus, one might suggest that the current reactions proceed also through a stepwise mechanism with formation of an addition intermediate being the RDS.

To examine the validity of the above idea, Hammett plots have been constructed using σ_Y^o and σ_Y^- constants. If the reactions of **6a–6i** 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 *Y*-substituted phenoxide. In this case, σ_Y^o constants should

Table 1. Summary of kinetic data for the reactions of *Y*-substituted phenyl picolinates (**6a–6i**) and *Y*-substituted phenyl benzoates (**1a–1i**) with NaOH in H_2O at 25.0 ± 0.1 °C.

Entry	*Y*	p$K_a^{Y\text{-PhOH}}$	$k_{OH^-}/M^{-1}s^{-1}$	
			6	**1**[a]
a	4-NO_2	7.14	91.3	13.4
b	4-CHO	7.66	64.3	4.72
c	4-CN	7.95	51.8	7.95
d	4-COMe	8.05	35.3	3.27
e	4-CO_2Et	8.50	31.6	3.11
f	3-Cl	9.02	20.5	—
g	4-Cl	9.38	19.2	1.35
h	H	9.95	9.15	0.449
i	4-Me	10.19	7.53	0.316

[a] The data for the reaction of *Y*-substituted phenyl benzoates (**1a–1i**) were taken from Ref. 9a.

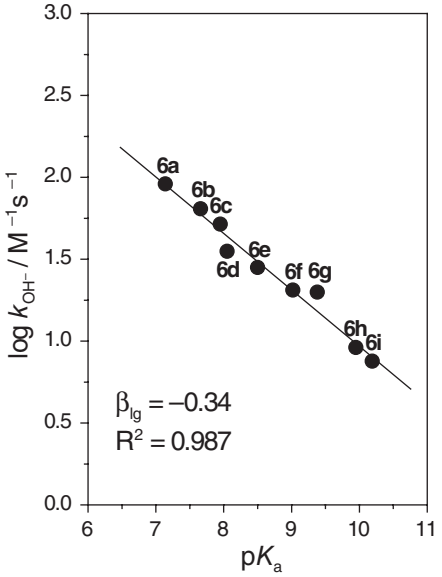


Figure 1. Brønsted-type plot for the reactions of *Y*-substituted phenyl picolinates (**6a–6i**) with OH^- in H_2O at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

result in a better Hammett correlation than σ_Y^- constants. On the contrary, if expulsion of the leaving group is involved in the RDS, whether the reactions proceed through a concerted mechanism or via a stepwise pathway, a negative charge would develop partially on the O atom of the leaving group. As 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.

As shown in Figure 2(a), the Hammett plot correlated with σ_Y^o constants is linear but exhibits highly scattered points ($R^2 = 0.935$). This is contrary to expectations if the current reactions proceed through a stepwise mechanism with formation of an addition intermediate being the RDS. Figure 2(b) shows that σ_Y^- constants result in a slightly better Hammett correlation ($R^2 = 0.989$) than σ_Y^o constants but the Hammett plot also exhibits many scattered points. Accordingly, one cannot get any conclusive information on the reaction mechanism from these Hammett plots.

To obtain more definitive information on the reaction mechanism, Yukawa-Tsuno equation has been employed that 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.[21] However, we have shown that Eq. (1) is highly effective to elucidate uncertainties in reaction mechanisms for nucleophilic substitution reactions of esters with various nucleophiles (*e.g.*, amines, OH^-, and CN^-).[5–8,19]

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

As shown in Figure 3, the Yukawa-Tsuno plot exhibits an excellent linear correlation ($R^2 = 0.993$) with $\rho_Y = 0.82$ and

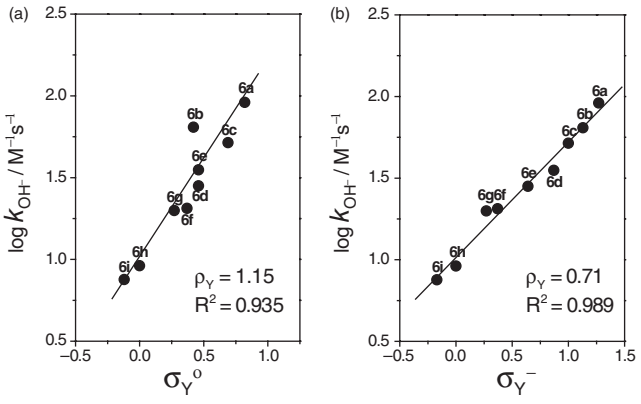


Figure 2. Hammett plots correlated with (a) σ_Y^o and (b) σ_Y^- for the reactions of *Y*-substituted phenyl picolinates (**6a–6i**) with NaOH in H_2O at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

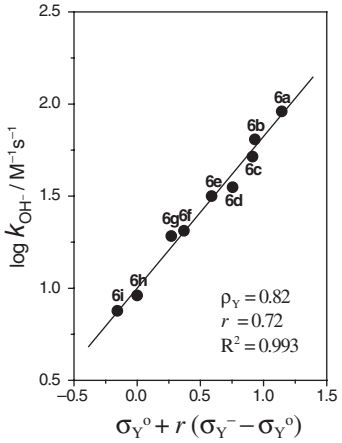


Figure 3. Yukawa-Tsuno plot for the reactions of *Y*-substituted phenyl picolinates (**6a–6i**) with NaOH in H_2O at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

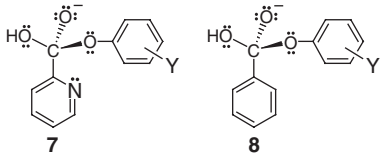
$r = 0.72$. The r value in Eq. (1) represents the resonance demand of the reaction center or the extent of resonance contribution, while the term $(\sigma_Y^- - \sigma_Y^o)$ is the resonance substituent constant that measures the capacity for π-delocalization of the π-electron acceptor substituent.[21,22] The r value of 0.72 found for the reactions of **6a–6i** clearly indicates that a negative charge develops partially on the O atom of the leaving group that can be delocalized to the substituent *Y* through resonance interactions. Thus, one can suggest that expulsion of the leaving group is involved in the RDS either in a concerted mechanism or in a stepwise pathway with expulsion of the leaving group being the RDS. However, one can exclude a possibility that the reactions of **6a–6i** with OH^- proceed through a stepwise mechanism in which expulsion of the leaving group occurs in the RDS. This is because OH^- is much more basic and a poorer nucleofuge than all the *Y*-substituted phenoxides used in this study. Thus, we propose that the current reactions proceed through a concerted mechanism.

Effects of Changing Nonleaving Group from Benzoyl to Picolinyl on Reactivity and Reaction Mechanism. As

mentioned in the preceding section, the picolinate esters (**6a–6i**) are more reactive than the corresponding benzoate esters. One might attribute the enhanced reactivity of the picolinate esters to the increased electrophilicity of the reaction center through an inductive effect exerted by the electronegative N atom in the picolinyl moiety. However, we propose that other than an inductive effect (*e.g.*, differences in the reaction mechanism) is also responsible for their enhanced reactivity.

As mentioned earlier, alkaline hydrolysis of *Y*-substituted phenyl benzoates (**1a–1i**) was reported to proceed through a stepwise mechanism in which expulsion of the leaving group occurs after the RDS on the basis of the fact that σ_Y^o constants result in a much better Hammett correlation than σ_Y^- constants (Figure 4).[9a] As modification of the nonleaving group from benzoyl to picolinyl has caused a change in the reaction mechanism from a stepwise mechanism to a concerted pathway, direct comparison of rate constants for the reactions of **6a–6i** with those for the corresponding reactions of the benzoate esters (**1a–1i**) has no significant meaning.

The β_{lg} value of –0.34 shown in Figure 1 for the reactions of **6a–6i** is too small for a concerted mechanism but is typical for reactions reported previously to proceed through a stepwise mechanism in which expulsion of the leaving group occurs after the RDS.[2–8] However, the current reactions of **6a–6i** have been proposed to proceed through a concerted mechanism on the basis of the linear Yukawa-Tsuno plot with $\rho_Y = 0.82$ and $r = 0.72$ (Figure 3). Thus, one might suggest that the reactions of **6a–6i** proceed through a forced concerted mechanism with a plausible intermediate as modeled by **7**, which is similar to the intermediate **8** suggested previously for the corresponding reactions of *Y*-substituted phenyl benzoates (**1a–1i**).[9a] One might expect that **7** is highly unstable due to the electronic repulsions between the nonbonding electrons on the N atom in the picolinyl moiety and those on the three O atoms bonded to the reaction center. It is apparent that expulsion of the leaving group from **7** to yield reaction products diminishes the electronic repulsions by increasing the dihedral angle from *ca.* 109° (an sp^3 hybridization in **7**) to 120° (an sp^2 hybridization in the product). Thus, one can propose that instability of **7** through the electronic repulsions forces the reactions of **6a–6i** to proceed through a concerted mechanism.



Conclusions

The kinetic study on the alkaline hydrolysis of **6a–6i** has allowed us to conclude the following: (1) The Brønsted-type plot is linear with $\beta_{lg} = -0.34$, which is typical for reactions reported previously to proceed through a stepwise mechanism with formation of an addition intermediate being the RDS. (2) However, σ_Y^o constants result in a much poorer Hammett correlation than σ_Y^- constants. Furthermore, the Yukawa-Tsuno plot exhibits an excellent linear correlation with $\rho_Y = 0.82$ and $r = 0.72$, indicating clearly that expulsion of the leaving group is involved in the RDS. (3) Thus, the reactions of **6a–6i** are proposed to proceed through a forced concerted mechanism with a highly unstable intermediate **7**. (4) Instability of **7** originates from electronic repulsions between the nonbonding electrons on the N atom in the picolinyl moiety and those on the three O atoms bonded to the reaction center. (5) Modification of the nonleaving group from benzoyl to picolinyl causes not only an increase in reactivity but also a change in the reaction mechanism (*i.e.*, from a stepwise mechanism to a forced concerted pathway).

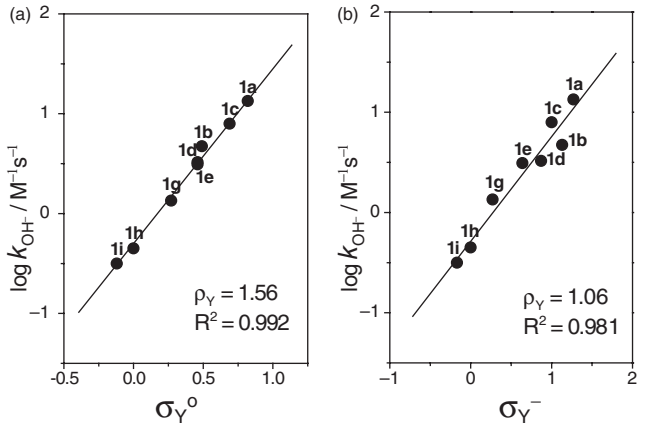


Figure 4. Hammett plots correlated with (a) σ_Y^o and (b) σ_Y^- for the reactions of *Y*-substituted phenyl benzoates (**1a–1i**) with OH^- in 80 mol% H_2O/20 mol% DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

Experimental

Materials. Compounds **6a–6i** were readily prepared from the reaction of picolinic acid with the respective *Y*-substituted phenol in methylene chloride in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) as reported previously.[23] Their purity was confirmed from melting points and ^1H NMR characteristics. Doubly glass distilled H_2O was further boiled and cooled under nitrogen atmosphere just before use. NaOH stock solution was titrated using potassium hydrogen phthalate. DMSO and other chemicals used were of the highest quality available.

Kinetics. The kinetic study was performed using a UV–Vis spectrophotometer equipped with a constant temperature circulating bath to keep the reaction temperature at 25.0 ± 0.1 °C. All of the reactions in this study were carried out under pseudo-first-order conditions in which NaOH concentration was at least 20 times greater than the substrate concentration. Typically, the reaction was initiated by adding 5 μL of a 0.02 M of substrate stock solution in MeCN by a 10 μL syringe to a 10-mm UV cell containing 2.50 mL of the reaction medium

and NaOH solution. The reactions were followed by monitoring the appearance of *Y*-substituted phenoxide ion up to nine half-lives.

Product Analysis. *Y*-substituted phenoxide ion was liberated quantitatively and identified as one of the reaction products by comparison of the UV–Vis spectra obtained after completion of the reactions with those of authentic samples under the same kinetic conditions.

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