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A Kinetic Study on Aminolysis of 2-Pyridyl X-Substituted Benzoates: Effect of Changing Leaving Group from 4-Nitrophenolate to 2-Pyridinolate on Reactivity and Mechanism

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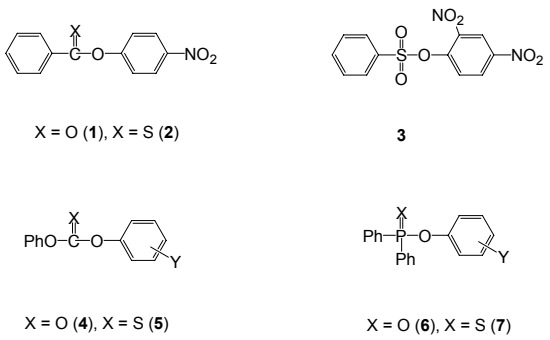
Second-order rate constants (k_N) have been measured spectrophotometrically for nucleophilic substitution reactions of 2-pyridyl X-substituted benzoates **8a-e** with a series of alicyclic secondary amines in H_2O at 25.0 ± 0.1 °C. The k_N values for the reactions of **8a-e** are slightly smaller than the corresponding reactions of 4-nitrophenyl X-substituted benzoates **1a-e** (e.g., $k_N^{1a-e}/k_N^{8a-e} = 1.1 \sim 3.1$), although 2-pyridinolate in **8a-e** is *ca*. 4.5 pK_a units more basic than 4-nitrophenolate in **1a-e**. The Brønsted-type plot for the aminolysis of **8c** (X = H) is linear with $\beta_{nuc} = 0.77$ and $R^2 = 0.991$ (Figure 1), which is typical for reactions reported previously to proceed through a stepwise mechanism with breakdown of a zwitterionic tetrahedral intermediate $T^{\pm}$ being the rate-determining step (RDS), e.g., aminolysis of 4-nitrophenyl benzoate **1c**. The Hammett plot for the reactions of **8a-e** with piperidine consists of two intersecting straight lines (Figure 2), i.e., $\rho = 1.71$ for substrates possessing an electron-donating group (EDG) while $\rho = 0.86$ for those bearing an electron-withdrawing group (EWG). Traditionally, such a nonlinear Hammett plot has been interpreted as a change in RDS upon changing substituent X in the benzoyl moiety. However, it has been proposed that the nonlinear Hammett is not due to a change in RDS since the corresponding Yukawa-Tsuno plot exhibits excellent linear correlation with $\rho = 0.85$ and $r = 0.62$ ($R^2 = 0.995$, Figure 3). Stabilization of substrates **8a-e** in the ground state has been concluded to be responsible for the nonlinear Hammett plot.

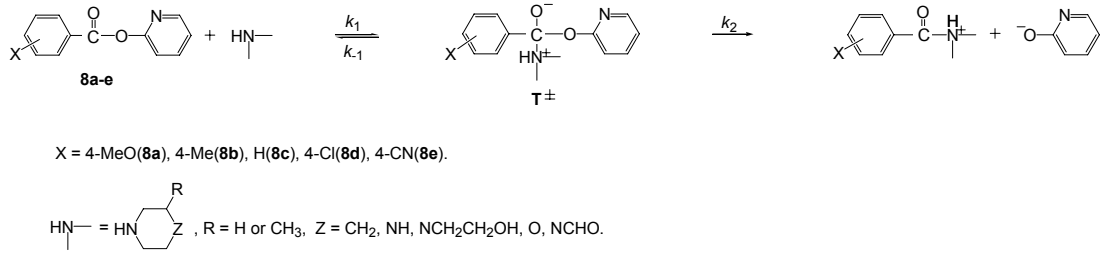
Key Words: Aminolysis, 2-Pyridyl benzoate, Rate-determining step, Brønsted-type plot, Yukawa-Tsuno plot

Introduction

Aminolysis of esters has intensively been investigated due to the importance in biological processes as well as synthetic interest.[1-10] Reactions of esters with amines have generally been reported to proceed through a concerted or a stepwise pathway depending on reaction conditions, e.g., nature of electrophilic centers (C=O, C=S, SO_2, P=O, P=S), type of amines (primary, secondary and tertiary amines), and basicity of incoming amines and leaving groups.[1-10] It is now firmly understood that aminolysis of substrates **1**, **3** and **4** proceeds through a stepwise mechanism with a zwitterionic tetrahedral intermediate $T^{\pm}$ in which the rate-determining step (RDS) is dependent on the basicity of incoming amines and leaving groups.[1-10] The reactions of thiono esters **2** and **5** with secondary amines have been reported to proceed through two intermediates, $T^{\pm}$ and its deprotonated form T^-,[6,9] while the corresponding reactions with primary amines proceed only through $T^{\pm}$.[6]



However, aminolysis of **6** and **7** has not been clearly understood.[8,11] Cook *et al*. have concluded that aminolysis of **6** and **7** proceeds through a stepwise mechanism in which breakdown of a pentacoordinate intermediate is the RDS on the basis of leaving-group effects, solvent effects, and activation parameters.[11a] In contrast, we have proposed that nucleophilic substi-



Scheme 1

tution reactions of **6** and **7** with amines[8] and anionic nucleophiles (e.g., hydroxide and ethoxide ions)[12] proceed through a concerted mechanism on the basis of linear free energy relationships together with activation parameters.

We have now performed nucleophilic substitution reactions of 2-pyridyl X-substituted benzoates **8a-e** with a series of alicyclic secondary amines (Scheme 1). The kinetic data have been compared with those reported previously for the corresponding reactions of 4-nitrophenyl X-substituted benzoates **1a-e** to investigate the effect of changing the leaving group from 4-nitrophenolate to 2-pyridinolate on reaction mechanism as well as reactivity.[5d]

Esters possessing a 2-pyridyl moiety were previously reported as an excellent acylating agent in reactions with Grignard reagents as well as in reactions with cupric bromide or lithium dialkylcuprate.[13,14] Besides, we have recently shown that alkali metal ions (e.g., Li^+, Na^+, K^+) catalyze reactions of **8a-e** with alkali metal ethoxides in anhydrous ethanol by forming a 6-membered cyclic complex.[15] Although scattered information on reactions of **8a-e** is available, their mechanisms have not been systematically investigated.[13-15] We wish to report that reactions of **8a-e** with a series of alicyclic secondary amines proceed through a stepwise mechanism, in which departure of leaving group from $T^{\pm}$ occurs in rate-determining step (RDS).

Results and Discussion

The kinetic study was performed under pseudo-first-order conditions in which the amine concentration was kept in excess over the substrate concentration. The reactions obeyed first-order kinetics and pseudo-first-order rate constants (k_{obsd}) were calculated from the equation, $\ln (A_\infty - A_t) = -k_{obsd}t + C$. Plots of k_{obsd} *vs*. [amine] were linear and passed through the origin, indicating that general base catalysis by a second amine molecule is absent. The second-order rate constants (k_N) were calculated from the slope of the linear plots. Based on replicate runs, it is estimated that the uncertainty in the k_N values is less than ± 3%. The k_N values determined in this way are summarized in Table 1 for the reactions of **8c** with 6 different amines and in Table 2 for the reactions of **8a-e** with piperidine.

Effect of changing leaving group from 4-nitrophenolate to 2-pyridinolate on reactivity and mechanism. As shown in Table 1, the reactivity of amines in the reactions with **8c** decreases as their basicity decreases, e.g., k_N decreases from 3.68 $M^{-1}s^{-1}$ to 0.279 and 0.00906 $M^{-1}s^{-1}$ as the pK_a of amines decreases from 11.22 to 9.82 and 7.98, respectively. A similar result is shown for the corresponding reactions of 4-nitrophenyl benzoate **1c**. Interestingly, the k_N value for the reaction of **8c** is slightly smaller than that for the reactions of **1c**, although the former possesses *ca*. 4.5 pK_a units more basic leaving group than the latter (i.e., the pK_a values are 11.62 and 7.14 for 2-pyridinol and 4-nitrophenol, respectively).[16] This is quite an unexpected result since the reactivity of aryl benzoates toward amine nucleophiles has been reported to be strongly dependent on the basicity of the leaving aryloxides.[5b]

To investigate reaction mechanism, Brønsted-type plots have been constructed in Figure 1 for the aminolyses of **8c** and **1c**. The Brønsted-type plot for the aminolysis of **8c** exhibits excellent linear correlation with $\beta_{nuc} = 0.77 \pm 0.05$, which is almost identical to that for the corresponding reactions of **1c** shown in the inset of Figure 1 (e.g., a linear plot with $\beta_{nuc} = 0.81$). Thus, one can suggest that the aminolyses of **1c** and **8c** proceed through the same mechanism.

Useful information can be obtained from the magnitude of β_{nuc} value and the shape of Brønsted-type plots.[1-10] A linear Brønsted-type plot with a β_{nuc} value of 0.5 ± 0.1 is typical for reactions reported previously to proceed through a concerted mechanism.[1-10] In contrast, a curved Brønsted-type plot (e.g., $\beta_{nuc} = 0.8 \pm 0.1$ for reactions with weakly basic amines while $\beta_{nuc} = 0.3 \pm 0.1$ for those with strongly basic amines) has been taken as evidence for a stepwise mechanism with a change in RDS, i.e., from breakdown of $T^{\pm}$ to its formation as the amine basicity increases.[1-10] Thus, one can suggest that the current aminolysis of **8c** proceeds through a stepwise mechanism in which breakdown of $T^{\pm}$ to reaction products is the RDS on the basis of the linear Brønsted-type plot with $\beta_{nuc} = 0.77$. This is consistent with the report that the aminolysis of **1c** proceeds through a stepwise mechanism with breakdown of $T^{\pm}$ to the reac-

Table 1. Summary of second-order rate constants (k_N) for nucleophilic substitution reactions of 4-nitrophenyl benzoate **1c** and 2-pyridyl benzoate **8c** with alicyclic secondary amines in H_2O at 25.0 ± 0.1 °C[a]

entry	Amines	$10^2 k_N/M^{-1}s^{-1}$	
		1c	**8c**
1	piperidine	594	368
2	3-methylpiperidine	-	280
3	piperazine	85.2	27.9
4	1-(2-hydroxyethyl)piperazine	19.5	8.51
5	morpholine	8.76	3.42
6	N-formylpiperazine	1.00	0.906

[a]The kinetic data for the reactions of **1c** were taken from ref. 5d.

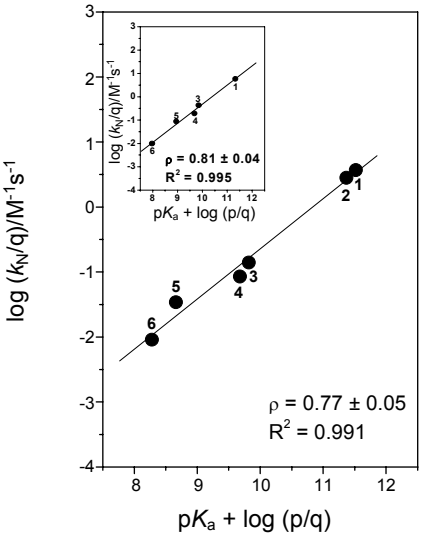


Figure 1. Brønsted-type plots for nucleophilic substitution reactions of 2-pyridyl benzoate **8c** and 4-nitrophenyl benzoate **1c** (inset) with alicyclic secondary amines in H_2O at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

Table 2. Summary of second-order rate constants for nucleophilic substitution reactions of 4-nitrophenyl X-substituted benzoates **1a-e** and 2-pyridyl X-substituted benzoates **8a-e** with piperidine in H_2O at 25.0 ± 0.1 °C[a]

entry	X	$k_N/M^{-1}s^{-1}$	
		1	**8**
a	MeO	1.95	1.26
b	Me	3.68	1.97
c	H	5.94	3.68
d	Cl	8.14	4.15
e	CN	18.7	12.8

[a]The kinetic data for the reactions of **1c** were taken from ref. 5d.

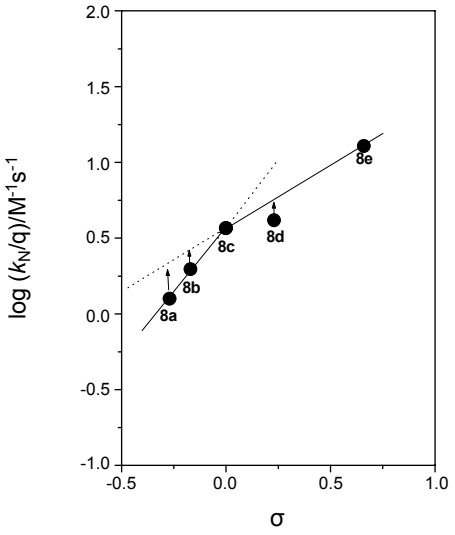


Figure 2. Hammett plot for nucleophilic substitution reactions of 2-pyridyl X-substituted benzoates **8a-e** with piperidine in H_2O at 25.0 ± 0.1 °C. The identity of points is given in Table 2.

tion products being the RDS,[5d] indicating that modification of the leaving group from 4-nitrophenolate to 2-pyridinolate does not influence the reaction mechanism.

Effect of substituent X on RDS. It is well known that RDS of aminolysis of carboxylic esters is dependent on the basicity of the incoming amine and the leaving group, i.e., RDS changes from breakdown of $T^{\pm}$ to its formation as the incoming amine becomes more basic than the leaving group (or the leaving group becomes less basic than the amine) by 4 to 5 pK_a units.[1-10] However, the effect of nonleaving-group substituents on RDS is not clearly understood.[5-7,17-20] It has been suggested that an electron-withdrawing group (EWG) in the nonleaving group decreases the rate of leaving-group departure (the k_2 process) but increases expulsion of the amine from $T^{\pm}$ (the k_{-1} process) in nucleophilic substitution reactions of diaryl carbonates with quinuclidines.[17] Thus, it has been concluded that an EWG decreases the k_2/k_{-1} ratio.[17] A similar conclusion has been drawn in aminolyses of aryl 4-nitrophenyl carbonates and related compounds,[18,19] and in pyridinolyses of aryl dithionactates and furan-2-carbodithioates.[20] In contrast, we have shown that the k_2/k_{-1} ratio is not influenced by the electronic nature of nonleaving-group substituents in aminolyses of various types of esters.[5-7]

To investigate the effect of substituent X in the benzoyl moiety on RDS, k_N values have been measured for reactions of 2-pyridyl X-substituted benzoates **8a-e** with piperidine, and summarized in Table 2 together with the k_N values for the corresponding reactions of 4-nitrophenyl X-substituted benzoates **1a-e** for comparison. As shown in Table 2, the k_N value for the reactions of **8a-e** increases as the substituent X changes from an electron-donation group (EDG) to an EWG, e.g., from 1.26 $M^{-1}s^{-1}$ to 3.68 and 12.8 $M^{-1}s^{-1}$ as X changes from 4-MeO to H and 4-CN, respectively. A similar reactivity trend is shown for the corresponding reactions of **1a-e**. It is also noted that the reactivity of **8a-e** is similar to that of **1a-e** toward piperidine.

To investigate the effect of substituent X on mechanism, a Hammett plot is constructed in Figure 2 for the reactions of 2-pyridyl X-substituted benzoates **8a-e** with piperidine. The Hammett plot consists of two intersecting straight lines, i.e., $\rho = 1.71$ for substrates possessing an EDG while $\rho = 0.86$ for those bearing an EWG.. Such a biphasic Hammett plot has traditionally been interpreted as a change in RDS.[1-10] In fact, Jencks has concluded that a change in RDS is responsible for the nonlinear Hammett plot found for reactions of X-substituted benzaldehydes with semicarbazide in a weakly acidic medium (pH = 3.9), i.e., from a large ρ to a small one as the substituent X changes from EDGs to EWGs.[21]

Thus, one might suggest that the nonlinear Hammett plot shown in Figure 2 is due to a change in RDS upon changing the substituent X, i.e., from formation of $T^{\pm}$ to its breakdown as substituent X changes from EDGs to EWGs. This idea appears to be reasonable on the basis of the fact that the ρ value decreases as the substituent X changes from EDGs to EWGs. One might expect a large ρ value when formation of $T^{\pm}$ (the k_1 process) is the RDS, since k_1 would be decreased by an EDG but increased by an EWG. In contrast, a small ρ value is expected when breakdown of $T^{\pm}$ (the k_2 process) is the RDS due to the opposite substituent effect (i.e., an EDG would decrease k_1 but increase k_2 while an EWG would increase k_1 but decrease k_2). However, we propose that the nonlinear Hammett plot shown in Figure 2 is not due to a change in RDS. This is because RDS is not determined by the magnitude of k_2 and k_1 values but governed by the k_2/k_{-1} ratio (e.g., the k_1 process = RDS when $k_2/k_{-1} > 1$ while the k_2 process = RDS when $k_2/k_{-1} < 1$).

We have recently shown that Yukawa-Tsuno equation, eq (1) is highly effective to elucidate ambiguities in reaction mechanisms of various nucleophilic substitution reactions.[5-8,12] Thus, a Yukawa-Tsuno plot has been constructed for the reactions of **8a-e** with piperidine. As shown in Figure 3, the Yukawa-Tsuno plot exhibits excellent linear correlation with $\rho = 0.85$ and $r = 0.62$. A similar result is shown in the inset of Figure 3 for the corresponding reactions of **1a-e** (e.g., $\rho = 0.75$ and $r = 0.75$). Such an excellent linear plot indicates clearly that RDS is not changed upon changing the substituent X.

$$\log (k_N^X/k_N^H) = \rho[\sigma^o + r(\sigma^+ - \sigma^o)] \quad (1)$$

The r value in the Yukawa-Tsuno equation represents resonance demand of the reaction center or the extent of resonance contribution, where as the term ($\sigma^+ - \sigma^\circ$) represents the reso-

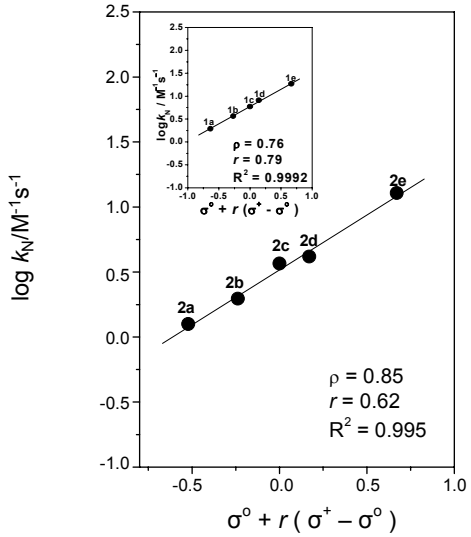
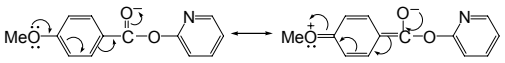


Figure 3. Yukawa-Tsuno plot for nucleophilic substitution reactions 4-nitrophenyl X-substituted benzoates **1a-e** (inset) and 2-pyridyl X-substituted benzoates **8a-e** with piperidine in H_2O at 25.0 ± 0.1 °C. The identity of points is given in Table 2.

nance substituent constant that measures the capacity for π-delocalization of a given π-electron donor substituent.[22,23] The *r* value for the reactions of **8a-e** with piperidine is 0.62, indicating that the resonance contribution is significant. Thus, one can suggest that resonance stabilization as illustrated in resonance structures I and II is responsible for the nonlinear Hammett plot shown in Figure 2, since such resonance interaction would cause a decrease in reactivity by stabilizing the ground state of substrates **8a-e**. This argument can be further supported from the fact that substrates possessing a π-electron donating substituent (e.g., 4-Cl, 4-Me and 4-MeO) exhibit negative deviation from the Hammett plot and the negative deviation is more significant for the substrate possessing a stronger EDG (e.g., X = 4-MeO).



I II

Conclusions

The current study has allowed us to conclude the following: (1) The k_N values of **8a-e** are similar to those of **1a-e** although 2-pyridinolate in **8a-e** is *ca*. 4.5 pK_a units more basic than 4-nitrophenolate in **1a-e**. (2) Aminolyses of **8a-e** and **1a-e** proceed through a stepwise mechanism in which breakdown of $T^{\pm}$ to the products is RDS regardless of the nature of the leaving group (i.e., 4-nitrophenolate or 2-pyridinolate). (3) Hammett plot for the reactions of **8a-e** consists of two intersecting straight lines. However, the nonlinear Hammett plot is not due to a change in RDS. (4) Yukawa-Tsuno plot for the reactions of **8a-e** exhibits excellent linear correlation with $r = 0.62$, indicating that stabilization of **8a-e** through resonance interactions in the ground state is responsible for the nonlinear Hammett plot. (5) Deduction of reaction mechanism based just on linear or nonlinear Hammett plots can be misleading.

Experimental Section

Materials. Substrates **8a-e** were readily prepared from the reaction of X-substituted benzoyl chloride with 2-hydroxypyridine in the presence of triethylamine in anhydrous ether. Their purity was confirmed from melting point and spectral data such as ^{1}H NMR. Secondary amines and other chemicals were of the highest quality available. Doubly glass distilled water was further boiled and cooled under nitrogen just before use.

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 the reactions were carried out under pseudo-first-order conditions in which the amine concentration was at least 20 times greater than the substrate concentration. Typically, the reaction was initiated by adding 5 μL of a 0.01 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 amine nucleophile. The reactions were followed by monitoring the leaving 2-pyridinolate at 298 nm.

Product analysis. 2-Pyridinolate was liberated and identified as one of the reaction products by comparison of the UV-vis spectra after completing the reactions with those of authentic samples under the same kinetic conditions.

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