Kinetic Study on Aminolysis of 4-Pyridyl Benzoate and *O*-4-Pyridyl Thionobenzoate in Acetonitrile: Factors Influencing Reactivity and Reaction Mechanism

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A kinetic study on nucleophilic substitution reactions of 4-pyridyl benzoate (**2a**) and *O*-4-pyridyl thionobenzoate (**2b**) with a series of cyclic secondary amines in acetonitrile at 25.0°C is reported. Plots of pseudo-first-order rate constant (k_{obsd}) vs. [amine] are linear and pass through the origin for the reactions of **2a** but curve upward for those of **2b**. The upward curvature observed for the reactions of **2b** is typical for reactions that proceed through a stepwise mechanism with a zwitterionic intermediate $T^{\pm}$, which decomposes to the products via uncatalyzed and catalyzed routes competitively. The reaction of **2a** has been suggested to proceed through a stepwise mechanism with $T^{\pm}$, in which expulsion of the leaving group occurs in the rate-determining step on the basis of a linear Brønsted-type plot with $\beta_{nuc} = 0.77$. The catalyzed reaction of **2b** from $T^{\pm}$ has been proposed to proceed through a concerted mechanism with a six-membered cyclic transition state rather than via a stepwise pathway with an anionic intermediate T^{-}. Factors influencing reactivity and reaction mechanism are discussed in detail.

Keywords: Aminolysis, *O*-4-Pyridyl thionobenzoate, Catalyzed reaction, Brønsted plot, Concerted mechanism

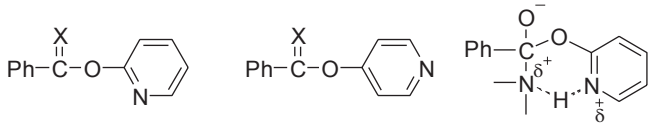
Introduction

Nucleophilic displacement reaction of esters with amines is recognized as one of the most important reactions in organic and bioorganic chemistry.[1] Numerous studies have been performed to investigate the reaction mechanism using various linear free energy relationships (*e.g.*, Brønsted-type, Hammett, Yukawa-Tsuno equations, etc.).[2–8] Reactions of carboxylic esters with amines have been reported to proceed either 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 reaction conditions such as nature of the reaction medium (*e.g.*, protic or aprotic solvents), type of the electrophilic center (*e.g.*, C=O, C=S, P=O, SO_2, etc.), basicity of the incoming amine and leaving group, etc.[2–8]

Reactions of 2,4-dinitrophenyl benzoate with a series of cyclic secondary amines in MeCN have been reported to proceed through a concerted mechanism on the basis of a linear Brønsted-type plot with $\beta_{nuc} = 0.40$.[5a] In contrast, the corresponding reactions carried out in aqueous medium have been suggested to proceed through a stepwise mechanism with a change in the rate-determining step (RDS) on the basis of a biphasic Brønsted-type plot,[5b] indicating that nature of the reaction medium governs the reaction mechanism. On the other hand, aminolysis of 2,4-dinitrophenyl diphenylphosphinate (a P=O electrophile) has been reported to proceed through a concerted mechanism on the basis of a linear Brønsted-type plot with $\beta_{nuc} = 0.5 \pm 0.1$,[6] while the corresponding reaction of 2,4-dinitrophenyl benzenesulfonate (an SO_2 electrophile) has been proposed to proceed through a stepwise mechanism, in which the RDS changes from breakdown of the addition intermediate to its formation as the incoming amine becomes more basic than the nucleofuge by 4 to 5 pK_a units.[7]

We have recently reported that reactions of 2-pyridyl benzoate (**1a**) with a series of cyclic secondary amines in MeCN proceed through a forced concerted mechanism on the basis of a linear Brønsted-type plot with $\beta_{nuc} = 0.61$.[8a] The reaction was originally expected to proceed through a stepwise mechanism with a six-membered cyclic intermediate (*i.e.*, TS_I), which could be stabilized through the H-bonding interaction. Nevertheless, we have proposed that the H-bonding interaction forces the reaction to proceed through a concerted mechanism.[8a] In contrast, the corresponding reaction of *O*-2-pyridyl thionobenzoate (**1b**, a thiono analog of **1a**) has been reported to proceed through a stepwise mechanism with $T^{\pm}$, which decomposes to the

products through catalyzed and uncatalyzed routes, on the basis of upward curvature observed in the plots of k_{obsd} vs. [amine].[8c]



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

Our study has now been extended to aminolysis of 4-pyridyl benzoate (**2a**) and *O*-4-pyridyl thionobenzoate (**2b**) in MeCN to investigate effect of changing the electrophilic center from C=O to C=S on reactivity and reaction mechanism. The kinetic data obtained in this study have been compared with those reported for the corresponding reactions of **1a** and **1b**[8c] to explore effects of modification of the leaving group from 2-pyridyloxide to 4-pyridyloxide on reactivity and reaction mechanism.

Results and Discussion

The kinetic study was carried out spectrophotometrically under pseudo-first-order conditions, *e.g.*, [amine] >> [substrate]. Pseudo-first-order rate constants (k_{obsd}) were calculated from the slope of linear plots of ln ($A_\infty - A_t$) vs. *t*. The plots of k_{obsd} vs. [amine] were linear and passed through the origin for the reactions of **2a** (Figure not shown). Thus, the second-order rate constants (k_N) were calculated from the slope of the linear plots and are summarized in Table 1 together with those reported previously for the corresponding reactions of **1a** for comparison. In contrast, the plot of k_{obsd} vs. [amine] curves upward for the reaction of **2b** with piperidine (Figure 1(a)). Similarly curved plots were observed for the reactions of **2b** with all the other amines used in this study.

Reactions of 1a and 2a (C═O Electrophiles). Table 1 shows that the k_N value for the reaction of **2a** decreases as the amine basicity decreases, *e.g.*, it decreases from 0.0351 to 0.000701 M^{-1} s^{-1} as the pK_a of the conjugate acid of the incoming amine decreases from 18.8 to 16.6, respectively.

Table 1. Summary of kinetic data for reactions of 2-pyridyl benzoate (**1a**) and 4-pyridyl benzoate (**2a**) with cyclic secondary amines in MeCN at 25.0 ± 0.1°C[a]

	Amines	pK_a	$k_N/M^{-1}s^{-1}$	
			1a	**2a**
1	Piperidine	18.8	0.0558	0.0351
2	3-Methylpiperidine	18.6	0.0438	—
3	Piperazine	18.5	0.0433	0.0208
4	1-(2-Hydroxyethyl)-piperazine	17.6	0.00859	0.00326
5	Morpholine	16.6	0.00266	0.000701

[a] The data for the reactions of **1a** were taken from Ref. 8c.

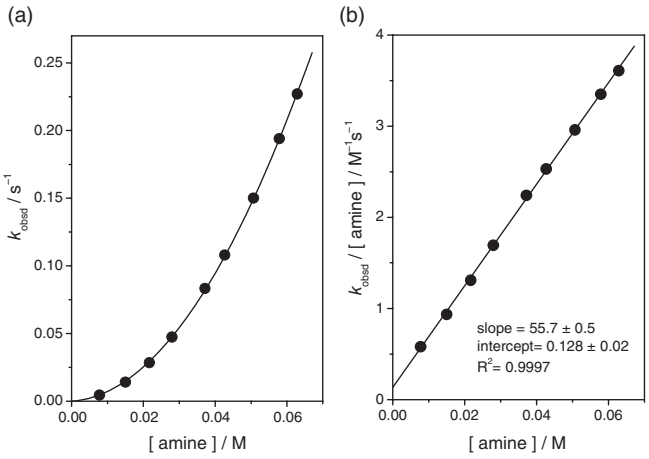


Figure 1. Plot of k_{obsd} vs. [amine] (a) and k_{obsd}/[amine] vs. [amine] (b) for the reaction of *O*-4-pyridyl thionobenzoate (**2b**) with piperidine in MeCN at 25.0 ± 0.1°C.

A similar result is demonstrated for the reaction of **1a**. However, **1a** is more reactive than **2a** although the former possesses a more basic leaving group than the latter (*e.g.*, pK_a = 11.62 and 11.06 for 2-hydroxypyridine and 4-hydroxypyridine, respectively).[9]

The effect of amine basicity on reactivity is illustrated in Figure 2. The Brønsted-type plots for the reactions of **1a** and **2a** are linear with β_{nuc} = 0.61 and 0.77, respectively. A β_{nuc} value of 0.77 is a lower limit for reactions reported previously to proceed through a stepwise mechanism, in which expulsion of the leaving group from $T^{\pm}$ occurs in the RDS.[2–5] Thus, we propose that the aminolysis of **2a** proceeds through a stepwise mechanism with $T^{\pm}$ as an intermediate. In contrast, the aminolysis of **1a** has been reported to proceed through a forced concerted mechanism with a six-membered cyclic TS (*i.e.*, TS_I), where the intramolecular H-bonding transforms the leaving group from strongly basic 2-pyridyloxide (pK_a = 11.62 in H_2O) to weakly basic 2-pyridinium oxide (pK_a = 0.75 in H_2O) or its tautomer 2-pyridone.[9] Such cyclic TS is structurally not possible for the reaction of **2a**. Accordingly, the nucleofuge for the reaction of **2a** is highly basic 4-pyridyloxide (pK_a = 11.06 in H_2O). This idea accounts for the contrasting reaction mechanism and for the kinetic result that **1a** is more reactive than **2a**.

Reactions of 1b and 2b (C═S electrophiles). As shown in Figure 1(a), the plot of k_{obsd} vs. [amine] curves upward for the reaction of **2b** with piperidine. Such upward curvature is typical for reactions that proceed through a stepwise mechanism with $T^{\pm}$, which decomposes to the products via uncatalyzed and catalyzed routes competitively.[2–5] Thus, the second-order and third-order rate constants (Kk_2 and Kk_3, respectively) were calculated from Eq. (2), which is simplified from Eq. (1) under the assumption $k_{-1} >> k_2 + k_3$[amine]. As shown in Figure 1(b), the plot of k_{obsd}/[amine] vs. [amine] exhibits an excellent linear correlation with a positive intercept, indicating that the above

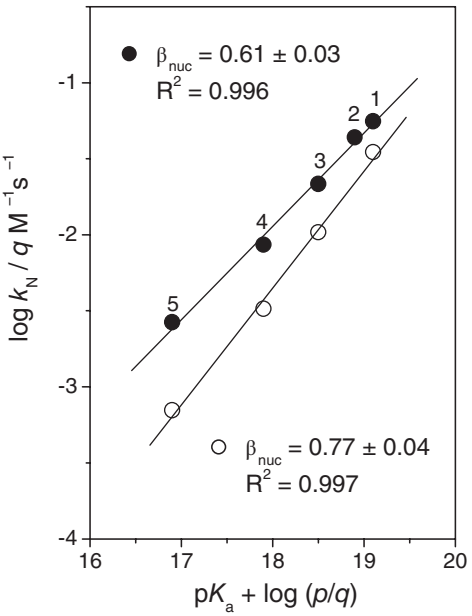


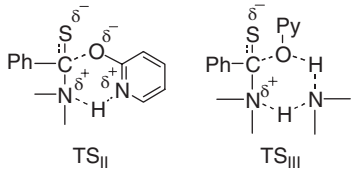
Figure 2. Brønsted-type plots for the reactions of 2-pyridyl benzoate (**1a**, ●) and 4-pyridyl benzoate (**2a**, ○) with cyclic secondary amines in MeCN at 25.0 ± 0.1°C.

assumption is valid. Similarly linear plots were observed for the reactions of **2b** with the other amines studied (Figure not shown). Thus, the Kk_2 and Kk_3 values for the reactions of **2b** were calculated from the intercept and slope of the linear plots, and are summarized in Table 2 together with those reported previously for the corresponding reactions of **1b** for comparison.

$$k_{obsd} = \left(k_1k_2[\text{amine}] + k_1k_3[\text{amine}]^2\right)/(k_{-1} + k_2 + k_3[\text{amine}]) \quad (1)$$

$$k_{obsd}/[\text{amine}] = Kk_2 + Kk_3[\text{amine}], \text{ where } K = k_1/k_{-1} \quad (2)$$

As shown in Table 2, the Kk_2 value for the reaction of **2b** decreases as the amine basicity decreases, *e.g.*, it decreases from 0.128 to 0.00623 $M^{-1}s^{-1}$ as the pK_a of the conjugate acid of the incoming amine decreases from 18.8 to 16.6, respectively (*i.e.*, ca. 20 times decrease in the Kk_2 value). The Kk_3 values for the reactions of **1b** and **2b** exhibit a similar trend. In contrast, the Kk_2 value for the reaction of **1b** decreases only from 10.6 to 6.12 $M^{-1}s^{-1}$ although the amine basicity decreases over 2 pK_a units.



The reaction of **1b** has previously been reported to proceed through a stepwise mechanism with $T^{\pm}$, which decomposes to the products via uncatalyzed and catalyzed routes.[8c] Both uncatalyzed and catalyzed reactions of **1b** have been suggested to proceed through a six-membered cyclic TS (*i.e.*, TS_{II} and TS_{III} for the uncatalyzed and catalyzed reaction, respectively: Note that the OPy in TS_{III} represents 2-pyridyloxide), which would gain stability to a certain degree through the intramolecular H-bonding interaction.[8c] However, such cyclic TS is structurally not possible for the uncatalyzed reaction of **2b**. This idea accounts for the kinetic result that the Kk_2 value for the reaction of **1b** is much larger than that for the corresponding reaction of **2b**.

The effect of amine basicity on the rate constants is illustrated in Figure 3 for the reactions of **1b** and **2b**. The Brønsted-type plots exhibit excellent linear correlations when the pK_a and rate constants were statistically corrected using p and q (p = 2, while q = 1 except q = 2 and 4 for the uncatalyzed and catalyzed reactions with piperazine, respectively).[10] It is noted that a β_{nuc} value of 0.12 for the uncatalyzed reaction of **1b** is unusually small. However, this also supports our previous proposal that the uncatalyzed reaction of **1b** proceeds through TS_{II}, in which a proton transfer from the aminium moiety of TS_{II} to the N atom of the leaving group occurs simultaneously with expulsion of the leaving group.[8c]

We propose that the reaction of **2b** proceeds through a stepwise mechanism with $T^{\pm}$, which decomposes to the products via uncatalyzed and catalyzed routes as shown in Scheme 1. The catalyzed reaction of **2b** from $T^{\pm}$ proceeds

Table 2. Summary of kinetic data for reactions of *O*-2-pyridyl thionobenzoate (**1b**) and *O*-4-pyridyl thionobenzoate (**2b**) with cyclic secondary amines in MeCN at 25.0 ± 0.1°C[a]

			$Kk_2/M^{-1}s^{-1}$		$Kk_3/M^{-2}s^{-1}$	
	Amines	pK_a	**1b**	**2b**	**1b**	**2b**
1	Piperidine	18.8	10.6	0.128	396	55.7
2	3-Methylpiperidine	18.6	10.9	0.104	284	42.9
3	Piperazine	18.5	21.8	0.106	796	86.1
4	1-(2-Hydroxyethyl)piperazine	17.6	8.37	0.0216	84.0	8.47
5	Morpholine	16.6	6.12	0.00623	23.5	2.64

[a] The kinetic data for the reactions of **1b** were taken from Ref. 8c.

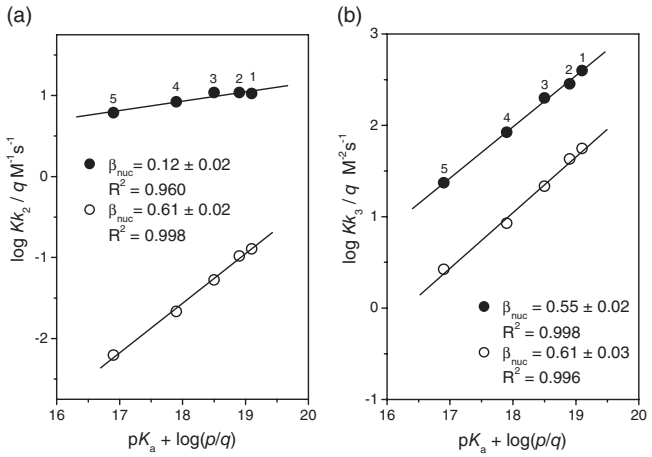
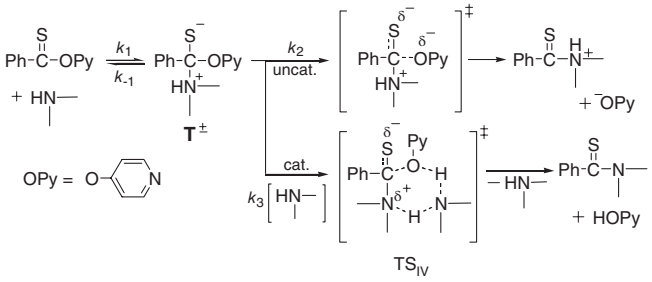


Figure 3. Brønsted-type plots for the reactions of *O*-2-pyridyl thionobenzoate (**1b**, ●) and *O*-4-pyridyl thionobenzoate (**2b**, ○) with cyclic secondary amines in MeCN at 25.0 ± 0.1°C: Kk_2 (a) and Kk_3 (b).

through a concerted mechanism with a six-membered cyclic TS as modeled by TS_{IV}. It is noted that TS_{IV} is similar to TS_{III} reported previously for the catalyzed reaction of **1b** except OPy, which represents 2-pyridyloxide in TS_{III} and 4-pyridyloxide in TS_{IV}.

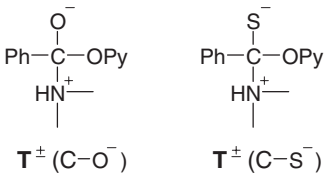
It has traditionally been understood that a second amine molecule in the catalyzed reaction deprotonates the aminium moiety of $T^{\pm}$ to form an anionic intermediate T^{-}.[2–5] Thus, one might suggest that the catalytic reaction of **2b** also proceeds with two intermediates ($T^{\pm}$ and T^{-}). However, we propose that the catalyzed reaction of **2b** from $T^{\pm}$ proceeds through a concerted mechanism with a six-membered cyclic TS as modeled by TS_{IV} (Scheme 1) rather than via a stepwise pathway with a discrete anionic intermediate T^{-}. This is because the anionic T^{-} would be highly destabilized in MeCN due to electronic repulsion between the anionic solute and the negative dipole end of the reaction medium, MeCN.[11] Furthermore, if the catalyzed reaction proceeds through a stepwise mechanism with T^{-} as an intermediate, the leaving group is highly basic 4-pyridyloxide anion, which would be strongly destabilized in MeCN. In contrast, if the catalyzed reaction proceeds through a concerted mechanism with a cyclic TS as modeled by T_{IV}, the electronic repulsion could be reduced



Scheme 1. The reaction mechanism proposed for the aminolysis of **2b** in MeCN.

significantly, since the negative charge in TS_{IV} is delocalized. Moreover, if the catalyzed reaction of **2b** proceeds through TS_{IV}, the leaving group becomes 4-hydroxypyridine, which is a much better nucleofuge than the strongly basic 4-pyridyloxide anion.

Effect of Changing Electrophilic Center from C=O to C=S on Reactivity and Reaction Mechanism. From Tables 1 and 2, one can notice that **2a** is less reactive than its thiono analog **2b**. Furthermore, the reaction of **2a** has been proposed to proceed through a stepwise mechanism with a zwitterionic intermediate as modeled by $\mathbf{T}^{\pm}$(C–O^{-}), which decomposes to the products in the RDS, on the basis of a linear Brønsted-type plot with β_{nuc} = 0.77. In contrast, the upward curvature shown in Figure 1(a) indicates that the reaction of **2b** proceeds through a stepwise mechanism with a zwitterionic intermediate as modeled by $\mathbf{T}^{\pm}$(C–S^{-}), which decomposes to the products via uncatalyzed and catalyzed routes competitively. These results demonstrate clearly that modification of the electrophilic center from C=O to C=S affects not only the reactivity but also the reaction mechanism.



It is well-known that anions are highly destabilized in MeCN due to electronic repulsion between the anion and the negative dipole end of MeCN.[11] The negative charge in the C–O^{-} moiety of $\mathbf{T}^{\pm}$(C–O^{-}) would be localized on the small O atom. In contrast, the negative charge in the C–S^{-} moiety of $\mathbf{T}^{\pm}$(C–S^{-}) would be dispersed on the large and polarizable S atom. Accordingly, $\mathbf{T}^{\pm}$(C–S^{-}) would be less unstable than $\mathbf{T}^{\pm}$(C–O^{-}) in MeCN. This idea accounts for the kinetic results that Kk_2 for the uncatalyzed reaction of the thiono compound (**2b**) is larger than the second-order rate constant (k_N) for the corresponding reaction of its oxygen analog (**2a**).

Since π-bonding energy of a C=S bond is weaker than that of a C=O bond, one might expect that the tendency of the C–S^{-} moiety of $\mathbf{T}^{\pm}$(C–S^{-}) to form a C=S bond (and to expel the leaving group) is weaker than that of the C–O^{-} moiety of $\mathbf{T}^{\pm}$(C–O^{-}). In fact, Castro *et al*. have suggested that the lifetime of $\mathbf{T}^{\pm}$ is longer for reactions of substrates possessing a C=S electrophilic center than for those of substrates bearing a C=O electrophilic center.[12] Thus, one can suggest that the longer lifetime of $\mathbf{T}^{\pm}$(C–S^{-}) induces the reactions of substrates possessing a C=S electrophilic center (*e.g.*, **1b** and **2b**) to proceed through both uncatalyzed and catalyzed routes.

Conclusions

The current study has shown that reactivity and reaction mechanism are strongly influenced not only by the nature

of the electrophilic center (C=O vs. C=S) but also by the leaving group (2-pyridyloxide vs. 4-pyridyloxide): (1) Aminolysis of **2a** proceeds through a stepwise mechanism with an addition intermediate $\mathbf{T}^{\pm}$(C–O^{-}), in which expulsion of the leaving group occurs in the RDS. This is in contrast to the reaction mechanism reported previously for the corresponding reaction of **1a**. (2) The reactions of **1b** and **2b** proceed through a stepwise mechanism with an addition intermediate $\mathbf{T}^{\pm}$(C–S^{-}), which decomposes to the products via uncatalyzed and catalyzed routes competitively. (3) The catalyzed reactions of **1b** and **2b** from $\mathbf{T}^{\pm}$(C–S^{-}) proceed through a concerted mechanism with a six-membered cyclic TS (*i.e.*, TS_{III} and TS_{IV}, respectively) rather than via a stepwise pathway with an anionic intermediate T^{-}. (4) The thiono compounds **1b** and **2b** are more reactive than their oxygen analogs **1a** and **2a**, respectively, because $\mathbf{T}^{\pm}$(C–S^{-}) would be less unstable than $\mathbf{T}^{\pm}$(C–O^{-}) in MeCN. (5) The weak tendency of C–S^{-} to form a C=S bond compared to C–O^{-} induces the reactions of the thiono compounds (**1b** and **2b**) to proceed through the uncatalyzed and catalyzed routes competitively.

Experimental section

Materials. 4-Pyridyl benzoate (**2a**) and *O*-4-pyridyl thionobenzoate (**2b**) were prepared from the reaction of 4-hydroxypyridine with benzoyl chloride and thionobenzoyl chloride, respectively, as reported previously.[8] The purity was checked by the melting point and spectral data such as ^{1}H and ^{13}C NMR spectra as described previously.[8] Other chemicals, including MeCN and all the amines used, were of the highest quality available.

Kinetics. The kinetic study was carried out using a UV–Vis spectrophotometer for slow reactions (*e.g.*, $t_{1/2} \geq 10$ s) or a stopped-flow spectrophotometer for fast reactions (*e.g.*, $t_{1/2} < 10$ s) equipped with a constant temperature circulating bath to maintain the reaction temperature at 25.0 ± 0.1°C. The reactions were carried out under pseudo-first-order conditions, in which the concentration of the amine was kept in excess over that of the substrate as described previously.[8]

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