JOC The Journal of Organic Chemistry

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Comparison of Aminolysis of 2-Pyridyl and 4-Pyridyl X-Substituted Benzoates in Acetonitrile: Evidence for a Concerted Mechanism Involving a Cyclic Transition State

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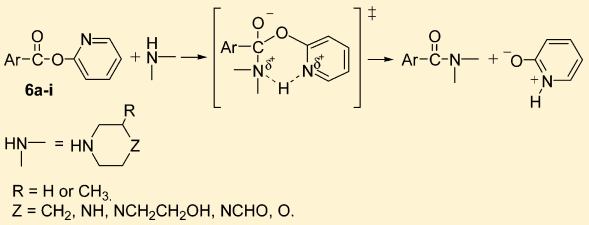
Supporting Information

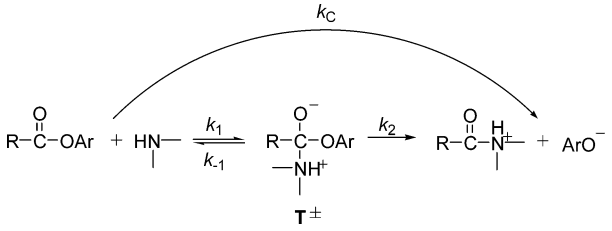
ABSTRACT: A kinetic study on reactions of 2-pyridyl X-substituted benzoates (**6a−i**) with a series of cyclic secondary amines in MeCN is reported. The Hammett plot for the reaction of **6a−i** with piperidine consists of two intersecting straight lines while the Yukawa−Tsuno plot exhibits an excellent linear correlation with ρ_X = 1.28 and r = 0.63, indicating that the nonlinear Hammett plot is not caused by a change in the rate-determining step but rather by resonance stabilization of substrates possessing an electron-donating group (EDG) in the benzoyl moiety. The Brønsted-type plots are linear with β_{nuc} = 0.59 ± 0.02, which is typical of reactions reported to proceed through a concerted mechanism. A cyclic transition state (TS), which forces the reaction to proceed through a concerted mechanism, is proposed. The deuterium kinetic isotope effect of 1.3 ± 0.1 is consistent with the proposed mechanism. Analysis of activation parameters reveals that $\Delta H^{‡}$ increases linearly as the substituent X changes from an electron-withdrawing group (EWG) to an EDG, while $T\Delta S^{‡}$ remains nearly constant with a large negative value. The constant $T\Delta S^{‡}$ value further supports the proposal that the reaction proceeds through a concerted mechanism with a cyclic TS.



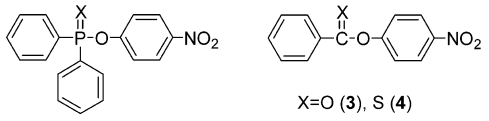
INTRODUCTION

Aminolysis of esters is an important class of reactions not only in synthetic applications but also in biological processes (e.g., peptide biosynthesis and enzyme actions).[1] Nucleophilic substitution reactions of esters with amines have been reported to proceed either through a concerted mechanism or via a stepwise pathway with a zwitterionic tetrahedral intermediate ($T^{±}$) as shown in Scheme 1, depending on reaction conditions (e.g., the nature of the electrophilic center, reaction medium, etc.).[2−7]

Scheme 1



Aminolysis of 4-nitrophenyl diphenylphosphinates (**1**) and diphenylphosphinothioates (**2**) was reported to proceed through a concerted mechanism on the basis of a linear Brønsted-type plot with β_{lg} = 0.5 ± 0.1.[6] In contrast, aminolysis of 4-nitrophenyl benzoate (**3**) was suggested to proceed through a stepwise mechanism with $T^{±}$ on the basis of a linear Brønsted-type plot with β_{nuc} = 0.81,[7a] while the corresponding reaction of *O*-4-nirophenyl thionobenzoate (**4**) was concluded to proceed through a stepwise mechanism with two intermediates (i.e., $T^{±}$ and its deprotonated form $T^{−}$) since the plots of k_{obsd} vs [amine] curved upward.[7b,c] Thus, the nature of the electrophilic center (e.g., P═O, P═S, C═O, and C═S) has been proposed an important factor to govern the reaction mechanism.[6,7]



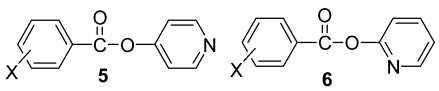
Linear free energy relationships such as Brønsted-type and Hammett equations are the most common and popular tools for deducing reaction mechanisms. A curved Brønsted-type plot, which is often observed for the aminolysis of esters possessing a weakly basic leaving group (e.g., 2,4-dinitrophenoxide), has been taken as evidence for a change in the rate-determining step (RDS) of a stepwise mechanism.[2] It is now firmly understood that RDS changes at pK_a^{o}, defined as the pK_a at the center of the Brønsted curvature, from breakdown of $T^{±}$ to its formation as the incoming amine becomes more basic than the leaving group (or the leaving group becomes less basic than the leaving group) by 4−5 pK_a units.[2] However, the effect

Received: November 28, 2013
Published: January 7, 2014

   dx.doi.org/10.1021/jo402629e | J. Org. Chem. 2014, 79, 1206−1212

of nonleaving-group substituents on the pK_a° is controversial. Gresser and Jencks found that the pK_a° for the quinuclidinolysis of 2,4-dinitrophenyl X-substituted phenyl carbonates increases as the substituent X becomes a stronger electron-withdrawing group (EWG).[8] Similar results were reported by Castro et al. for the pyridinolysis of 2,4-dinitrophenyl X-substituted benzoates and the aminolysis of *S*-2,4-dinitrophenyl X-substituted thiobenzoates[9] and by Oh et al. for the pyridinolysis of aryl dithiobenzoates.[10] Thus, it has been concluded that an EWG in the nonleaving group of esters increases pK_a° by decreasing the k_2/k_{-1} ratio.[8−10] In contrast, we have suggested that the k_2/k_{-1} ratio is not governed by the electronic nature of the nonleaving-group substituents, since an EWG in the nonleaving group would retard both the k_2 and k_{-1} processes while an electron-donating group (EDG) would accelerate them.[11] This is because the nucleofuges (e.g., amine and aryloxide) depart from $T^\pm$ with the bonding electrons. In fact, we have previously shown that the k_2/k_{-1} ratio is little influenced by the electronic nature of the substituent X for the aminolysis of 2,4-dinitrophenyl X-substituted benzoates and X-substituted benzenesulfonates.[11]

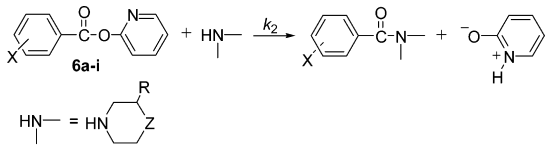
In contrast, we have recently reported that the electronic nature of the substituent X governs the reaction mechanism but not the RDS for the aminolysis of 4-pyridyl X-substituted benzoates (**5a−i**) in MeCN; i.e., the plot of k_{obsd} vs [amine] curves upward when the substituent X is a strong EWG but is linear when the substituent X is a weak EWG or an EDG.[12] Thus, it has been concluded that the reaction of substrates possessing a strong EWG in the benzoyl moiety proceeds through a stepwise mechanism with two intermediates ($T^\pm$ and 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.[12]



X = 3,5-$(NO_2)_2$ (**a**), 4-NO_2 (**b**), 3-NO_2 (**c**), 4-CN (**d**), 4-Cl (**e**), H (**f**), 4-Me (**g**), 4-MeO (**h**), 4-Me_2N (**i**).

Our study has now been extended to the reactions of 2-pyridyl X-substituted benzoates (**6a−i**) with a series of cyclic secondary amines in MeCN to obtain further information on the reaction mechanism (Scheme 2). We wish to report that

Scheme 2



R = H or CH_3.
Z = CH_2, NH, NCH_2CH_2OH, NCHO, O.

the electronic nature of the substituent X in the nonleaving group does not affect the reaction mechanism including the k_2/k_{-1} ratio, which is contrary to the result reported recently for the corresponding reactions of **5a−i**. However, modification of the leaving group from 4-pyridyloxide (**5a−i**) to 2-pyridyloxide (**6a−i**) changes the reaction mechanism from a stepwise mechanism to a concerted pathway.

RESULTS AND DISCUSSION

The kinetic study was carried out spectrophotometrically by monitoring the appearance of the leaving 2-pyridyloxide under pseudo-first-order conditions (e.g., the concentration of amines was kept in large excess of that of substrates **6a−i**). All of 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 uncertainty in the rate constants was estimated to be less than ±3% from replicate runs. The plots of k_{obsd} vs [amine] were linear and passed through the origin in all cases, indicating that general base catalysis by a second amine molecule is absent. Thus, the second-order rate constants (k_N) were calculated from the slope of the linear plots of k_{obsd} vs [amine]. The k_N values calculated in this way are summarized in Tables 1−4.

Table 1. Summary of Second-Order Rate Constants for Nucleophilic Substitution Reactions of 2-Pyridyl X-Substituted Benzoates (6a−i) with Piperidine in MeCN at 25.0 ± 0.1 °C

entry	X	$k_N/M^{-1}s^{-1}$
6a	3,5-$(NO_2)_2$	4.48 ± 0.03
6b	4-NO_2	0.556 ± 0.006
6c	3-NO_2	0.545 ± 0.006
6d	4-CN	0.409 ± 0.007
6e	4-Cl	0.118 ± 0.001
6f	H	0.0558 ± 0.0009
6g	4-Me	0.0313 ± 0.0005
6h	4-MeO	0.0161 ± 0.0003
6i	4-Me_2N	0.00144 ± 0.00004

Effect of Substituent X on Reactivity. The k_N values for the reactions of **6a−i** with piperidine is summarized in Table 1. The k_N value is strongly dependent on the electronic nature of the substituent X; e.g., it decreases from 4.48 M^{-1} s^{-1} to 5.58 × 10^{-2} M^{-1} s^{-1} and then to 1.44 × 10^{-3} M^{-1} s^{-1} as the substituent X changes from 3,5-$(NO_2)_2$ to H and then to 4-Me_2N.

The effect of the substituent X on the reactivity of **6a−i** is illustrated in Figure 1. The Hammett plot consists of two intersecting straight lines, i.e., the ρ_X changes from 1.33 to 1.94

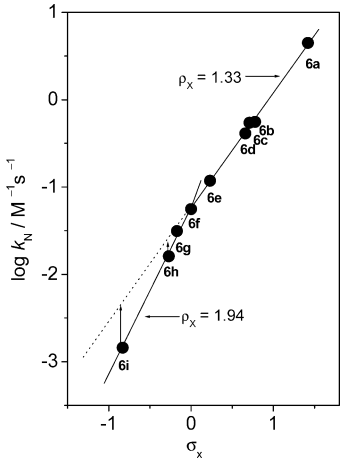


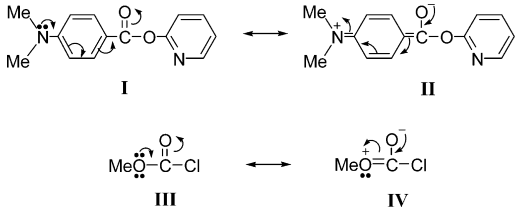
Figure 1. Hammett plot for the reactions of 2-pyridyl X-substituted benzoates (**6a−i**) with piperidine in MeCN at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

dx.doi.org/10.1021/jo402629e | *J. Org. Chem.* 2014, 79, 1206−1212

as the substituent X changes from EWGs to EDGs. Traditionally, such a nonlinear Hammett plot has been interpreted as a change in the RDS of a stepwise reaction.[1,13] In fact, Jencks has previously concluded that the reactions of X-substituted benzaldehydes with semicarbazide in a weakly acidic medium (pH = 3.9) proceed through a stepwise mechanism with a change in RDS on the basis of a nonlinear Hammett plot, i.e., from a large positive ρ_X to a small one as the substituent X changes from EDGs to EWGs.[1c] Thus, one might suggest that the reactions of **6a**–**i** with piperidine proceed through a stepwise mechanism with a change in RDS on the basis of the nonlinear Hammett plot shown in Figure 1, i.e., from formation of $T^{\pm}$ (the k_1 step) to its breakdown (the k_2 step) as the substituent X changes from EDGs to EWGs. This idea appears to be reasonable because an EWG in the benzoyl moiety would accelerate the nucleophilic attack (i.e., an increase in k_1) but retard departure of the negatively charged leaving group (i.e., a decrease in k_2), while an EDG would decrease the k_1 step but increase the k_2 process.

However, we do not attribute the nonlinear Hammett plot to a change in RDS, since RDS should be determined by the k_2/k_{-1} ratio but not by the magnitude of k_1 and k_2 (i.e., RDS = the k_1 step when $k_2/k_{-1} > 1$ but RDS = the k_2 step when $k_2/k_{-1} < 1$). Furthermore, k_1 and k_2 cannot be compared directly since the former is a second-order rate constant with a unit of $M^{-1}\ s^{-1}$, while the latter is a first-order rate constant whose unit is s^{-1}.

Scrutiny of the nonlinear Hammett plot in Figure 1 reveals that the substrates possessing an EDG in the benzoyl moiety (e.g., **6g**–**i**) deviate negatively from the linear line composed of the substrates bearing an EWG (e.g., **6a**–**f**). Furthermore, the negative deviation is more significant for the substrate possessing a stronger EDG. It is apparent that an EDG in the benzoyl moiety could stabilize the GS of the substrate through resonance interactions between the EDG in the benzoyl moiety and the C═O bond as modeled by the resonance structures I and II. Since such resonance stabilization could cause a decrease in reactivity, we propose that stabilization of the substrate possessing an EDG is responsible for the nonlinear Hammett plot. This idea is consistent with the conclusion drawn for the solvolysis of methyl chloroformate and acetyl chloride in aqueous acetone.[14a] The former has been reported to be 9×10^3 times less reactive than the latter.[14a] Kevill has concluded that the GS stabilization through resonance interactions (e.g., III ↔ IV), analogous to that suggested in the current systems, is responsible for the decreased reactivity of methyl chloroformate since such resonance interaction is not possible for acetyl chloride.[14b]



To examine the validity of the above argument, the Yukawa–Tsuno equation (eq 1) has been used. Equation 1 was originally derived to rationalize the kinetic data obtained from solvolysis of benzylic systems in which a partial positive charge develops in the transition state (TS).[15,16] The r value in eq 1 represents the resonance demand of the reaction center or the extent of resonance contribution between the reaction site and the substituent X, while the term $(\sigma_X^+ - \sigma_X^\circ)$ is the resonance substituent constant that measures the capacity for π-delocalization of the π-electron donor substituent.[15,16]

$$\log k_N^X/k_N^H = \rho_X[\sigma_X^\circ + r(\sigma_X^+ - \sigma_X^\circ)] \quad (1)$$

As shown in Figure 2, the Yukawa–Tsuno plot for the reactions of **6a**–**i** with piperidine exhibits an excellent linear

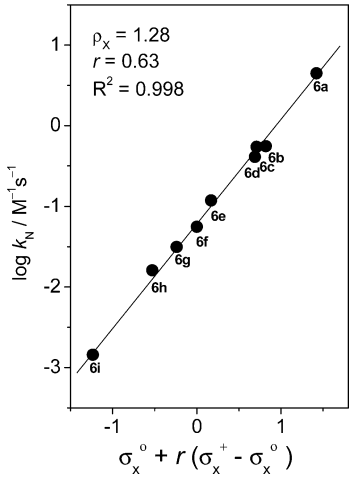


Figure 2. Yukawa–Tsuno plot for the reactions of 2-pyridyl X-substituted benzoates (**6a**–**i**) with piperidine in MeCN at 25.0 ± 0.1 °C. The points are identified in Table 1.

correlation with $\rho_X = 1.28$ and $r = 0.63$. Such a linear Yukawa–Tsuno plot clearly indicates that the nonlinear Hammett plot is not caused by a change in RDS but rather by the resonance stabilization of substrates possessing an EDG in the benzoyl moiety and, further, that the electronic nature of the substituent X in the nonleaving group does not cause a change in the RDS of the current reaction.

Deduction of Reaction Mechanism. The linear Yukawa–Tsuno plot with $\rho_X = 1.28$ and $r = 0.63$ alone does not give any conclusive information on the reaction mechanism, e.g., a concerted or stepwise mechanism. To further elucidate the reaction mechanism, the k_N values for the reactions of 2-pyridyl 3,5-dinitrobenzoate (**6a**), 2-pyridyl 4-nitrobenzoate (**6b**), and 2-pyridyl benzoate (**6f**) with a series of cyclic secondary amines in MeCN were measured. As shown in Table 2, the k_N for the

Table 2. Summary of Second-Order Rate Constants (k_N) for the Reactions of 2-Pyridyl 3,5-Dinitrobenzoate (6a), 2-Pyridyl 4-Nitrobenzoate (6b) and 2-Pyridyl Benzoate (6f) with Amines in MeCN at 25.0 ± 0.1 °C[a]

			$k_N/M^{-1}\ s^{-1}$		
	amines	pK_a	6a	6b	6f
1	piperidine	18.8	4.48	0.556	0.0558
2	3-methylpiperidine	18.6	4.00	0.500	0.0438
3	piperazine	18.5	4.14	0.486	0.0433
4	1-(2-hydroxyethyl) piperazine	17.6	1.03	0.110	0.00859
5	morpholine	16.6	0.251	0.0265	0.00266
			β_{nuc} = 0.58	β_{nuc} = 0.61	β_{nuc} = 0.61

[a]The pK_a data in MeCN were taken from refs 17 and 18.

dx.doi.org/10.1021/jo402629e | J. Org. Chem. 2014, 79, 1206–1212

reaction of **6a** decreases with decreasing amine basicity; e.g., it decreases from 4.48 M^{-1} s^{-1} to 0.251 M^{-1} s^{-1} as the pK_a of the conjugate acid of amines decreases from 18.8 to 16.6, respectively. A similar result is shown for the reactions of **6b** and **6f**, although they are less reactive than **6a**.

The effect of amine basicity on reactivity is graphically illustrated in Figure 3 for the reactions of **6a**. The Brønsted-

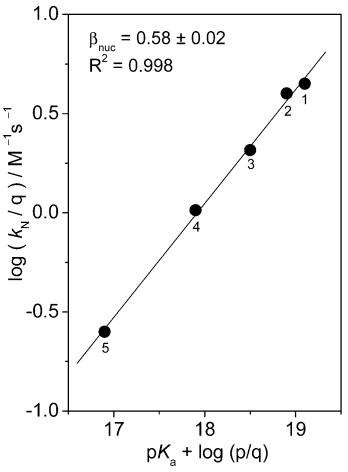
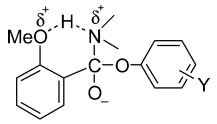


Figure 3. Brønsted-type plot for the reactions of 2-pyridyl 3,5-dinitrobenzoate (**6a**) with a series of cyclic secondary amines in MeCN at 25.0 ± 0.1 °C. The points are identified in Table 2.

type plot exhibits an excellent linear correlation with β_{nuc} = 0.58 when the k_N and pK_a values are corrected statistically using p and q (*i.e.*, p = 2 while q = 1 except q = 2 for piperazine).[19] A similar result is shown for the corresponding reactions of **6b** and **6f** with β_{nuc} = 0.61 in the Supporting Information (Figures S1 and S2). The β_{nuc} value of 0.58 (or 0.61) is much smaller than that reported for reactions which proceed through a stepwise mechanism, e.g., β_{nuc} = 0.98 for the corresponding reactions of 4-pyriyl 3,5-dinitrobenzoate (**5a**).[12] Since a linear Brønsted-type plot with β_{nuc} = 0.5 ± 0.1 is typical of reactions reported previously to proceed through a concerted mechanism,[2] we suggest that the current reactions also proceed through a concerted mechanism regardless of the electronic nature of the substituent X. This is in contrast to the report that the corresponding reactions of **5a**−**i** (the isomers of **6a**−**i**) proceed through a stepwise mechanism with one or two intermediates depending on the electronic nature of the substituent X, e.g., through $T^{\pm}$ and T^{-} for the reaction of substrates possessing a strong EWG (**5a**−**d**) but via $T^{\pm}$ only for the reaction of those bearing a weak EWG or an EDG (**5e**−**i**).[12] *Clearly, the modification of the leaving group from 4-pyridyloxide to 2-pyridyloxide affects the* reaction *mechanism.*

It has been reported that the aminolysis of 4-nitrophenyl 2-methoxybenzoate in MeCN proceeds through a stepwise mechanism with an intermediate as modeled by V, which is stabilized through the intramolecular H-bonding interaction between the 2-MeO group and the aminium moiety of $T^{\pm}$.[18] This idea has been further supported by the experimental result that the substrate possessing a 2-MeO group at the 2-position of the benzoyl moiety is much more reactive than those bearing a 2-MeO group at the 3- or 4-position; e.g., 4-nitrophenyl 2-methoxybenzoate is 20 and 74 times more reactive than its isomers 4-nitrophenyl 3-methoxybenzoate and 4-nitrophenyl 4-methoxybenzoate, respectively.[18]



V **VI**

A similar cyclic intermediate would be possible for the reactions of **6a**−**i** as modeled by VI, which might gain high stability through the intramolecular H-bonding interaction. However, a careful examination of VI reveals that the H-bonding interaction would cause a significant decrease in the leaving-group basicity by changing the highly basic 2-pyridyloxide (e.g., the pK_a = 11.62 in H_2O) to the weakly basic 2-pyridiniumoxide (e.g., the pK_a = 0.75 in H_2O) or to its tautomer 2-pyridone. It is apparent that the decreased basicity of the leaving group would cause a remarkable increase in its nucleofugality. Thus, we suggest that the intramolecular H-bonding interaction in the intermediate VI shortens its lifetime and forces the aminolysis of **6a**−**i** to proceed through a concerted mechanism with a TS structure similar to VI. It is noted that the intramolecular H-bonding interaction shown in VI is structurally not possible for the reactions of **5a**−**i**. This accounts for the contrasting reaction mechanisms, i.e., a stepwise mechanism for the reactions of **5a**−**i** and a concerted pathway for those of **6a**−**i**.

Deuterium Kinetic Isotope Effect (DKIE). To examine the validity of the above argument that the intramolecular H-bonding interaction governs the reaction mechanism, second-order rate constants for the reactions of **6a**, **6b**, and **6f** with deuterated piperidine (i.e., k_N^D) were measured. The rate constants for the uncatalyzed and catalyzed reactions of 4-pyridyl 3,5-dinitrobenzoate (**5a**) with deuterated piperidine (i.e., Kk_2^D and Kk_3^D, respectively) were also measured for comparison. The plot of k_{obsd} vs [amine] curves upward for the reaction of **5a** with deuterated piperidine, while the plot of k_{obsd}/[amine] vs [amine] is linear (Figure S3 A and B in the SI). Thus, the rate constants Kk_2^D and Kk_3^D for the uncatalyzed and catalyzed reactions were calculated from the intercept and slope of the linear plot of k_{obsd}/[amine] vs [amine], respectively. The kinetic results are summarized in Table 3.

Table 3. Summary of Second-Order Rate Constants for the Reactions of 2-Pyridyl 3,5-Dinitrobenzoate (6a), 2-Pyridyl 4-Nitrobenzoate (6b), 2-Pyridyl Benzoate (6f), and 4-Pyridyl 3,5-Dinitrobenzoate (5a) with Piperidine (k_N^H) and Deuterated Piperidine (k_N^D) in MeCN at 25.0 ± 0.1 °C[a]

	k_N^H/M^{-1} s^{-1}	k_N^D/M^{-1} s^{-1}	k_N^H/k_N^D
6a	4.48	3.02	1.48
6b	0.556	0.442	1.26
6f	0.0558	0.0442	1.26

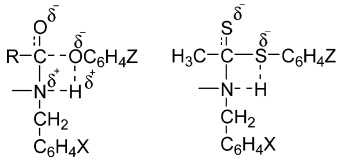
[a]DKIE for the reaction of **5a**: Kk_2^H/Kk_2^D = 0.154/0.182 = 0.85 and Kk_3^H/Kk_3^D = 25.8/11.6 = 2.22.

As shown in Table 3, the DKIE (i.e., the k_N^H/k_N^D ratio) is 1.48 for the reaction of **6a** and 1.26 for those of **6b** and **6f**. In contrast, the DKIE for the reaction of **5a** is 0.85 and 2.22 for the uncatalyzed route and the catalyzed route, respectively. The DKIE of 0.85 is mainly a reflection of the reduced steric hindrance, since the amplitude of the stretching vibration of a N−D bond is smaller than that of a N−H bond. Thus, the inversed DKIE is as expected for the uncatalyzed reaction, in which the deprotonation process to yield T^{-} from $T^{\pm}$ is absent.

dx.doi.org/10.1021/jo402629e | J. Org. Chem. 2014, 79, 1206−1212

The primary normal DKIE of 2.22 for the catalyzed route is also consistent with the proposed mechanism, in which the deprotonation process by a second piperidine molecule occurs in the RDS.

The DKIE value of 1.48 or 1.26 observed for the reactions of **6a**, **6b**, and **6f** is similar to those reported for reactions proceeding through a concerted mechanism with a TS structure similar to VII or VIII; e.g., DKIE = 1.21−1.48 for reactions of aryl cyclopropanecarboxylates with deuterated benzylamines in MeCN,[20] and DKIE = 1.05−1.36 for reactions of aryl dithioacetates with deuterated benzylamines in MeCN.[21] Thus, the DKIE value of 1.48 or 1.26 observed for the current reactions of **6a**, **6b**, and **6f** supports the preceding argument that the reactions proceed through a forced concerted mechanism with a TS structure similar to VI, in which the H-transfer from the aminium moiety to the N atom of the leaving group occurs in the RDS.



VII VIII

Analysis of Activation Parameters. To obtain further information on the TS structure, activation parameters (i.e., $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) were calculated using the kinetic data obtained for the reactions of **6a**, **6b**, **6f**, and **6h** with piperidine at five different temperatures (i.e., 15.0, 20.0, 25.0, 30.0, and 35.0 °C). The Arrhenius equation, $k = Ae^{-E_a/RT}$, was used to calculate enthalpies of activation. Equation 2 is derived from the Arrhenius equation. The slope of the linear plot of ln k_N vs $1/T$ is equal to $-E_a/R$ (Figure S4 in the Supporting Information). The enthalpy of activation ($\Delta H^{\ddagger}$) was then calculated using eq 3. The entropies of activation ($\Delta S^{\ddagger}$) were calculated from eq 4. The $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values calculated in this way are summarized in Table 4.

$$\ln k_N = -E_a/RT + \ln A \quad (2)$$

$$\Delta H^{\ddagger} = E_a - RT \quad (3)$$

$$\Delta S^{\ddagger} = R(\ln A - \ln T - \ln K_B/h - 1) \quad (4)$$

Table 4 shows that $\Delta H^{\ddagger}$ is strongly dependent on the electronic nature of the substituent X; e.g., it increases from 3.85/kcal mol^{-1} to 4.80 and then to 7.04/kcal mol^{-1} as the substituent X changes from 3,5-$(NO_2)_2$ in **6a** to 4-NO_2 in **6b** and then to 4-MeO in **6h** (see also a linear plot of $\Delta H^{\ddagger}$ vs σ_X shown in Figure S5 in the Supporting Information). In contrast, $\Delta S^{\ddagger}$ remains nearly constant at ca. 43 cal mol^{-1} K^{-1} regardless of the electronic nature of the substituent X, indicating that the substituent dependence of the reactivity of **6a**−**i** is governed almost entirely by the $\Delta H^{\ddagger}$ term rather than by the $T\Delta S^{\ddagger}$ term. More importantly, the large negative $\Delta S^{\ddagger}$ indicates that the TS is highly ordered. This is consistent with the proposal that the reactions of **6a**−**i** with amines proceed through a TS structure similar to VI, in which the rotational and vibrational degrees of freedom are restricted to a certain degree. Furthermore, the fact that $\Delta S^{\ddagger}$ remains nearly constant indicates that the intramolecular H-bonding interaction shown in VI is not influenced by the electronic nature of the substituent X. This is also consistent with the kinetic result that the electronic nature of the substituent X does not affect the reaction mechanism in this study.

CONCLUSIONS

Based on the experimental results, we present the following conclusions. (1) The nonlinear Hammett plot is not caused by a change in RDS but rather by stabilization of the substrate possessing an EDG through resonance interactions. (2) The linear Brønsted-type plot with β_{nuc} = 0.60 ± 0.01 obtained in this study supports the proposal that the aminolysis of **6a**−**i** proceeds through a forced concerted mechanism with a TS structure similar to VI. (3) The DKIE value of 1.48 (or 1.26) is consistent with the cyclic TS structure, in which the proton transfer from the aminium moiety of VI to the N atom of the leaving group occurs in RDS. (4) The large negative $\Delta S^{\ddagger}$ value further supports the proposal that the reactions of **6a**−**i** proceed through a cyclic TS structure. (5) Modification of the leaving group from 4-pyridyloxide to 2-pyridyloxide affects the reaction mechanism by changing it from a stepwise mechanism to a concerted pathway.

EXPERIMENTAL SECTION

Materials. Compounds **6a**−**i** were readily prepared from the reaction of the respective X-substituted benzoyl chloride with 2-hydroxypyridine in methylene chloride as reported previously.[22] The crude products were purified by column chromatography, and their purity was confirmed from mps and ^{1}H NMR characteristics for the known compounds. The final yields of products are 35−43%. The identity of the unknown compounds (i.e., **6a**, **6b**, and **6i**) was confirmed by elementary analysis, mps, and ^{1}H NMR spectra (Supporting Information). MeCN was distilled over P_2O_5 and stored under nitrogen. The amines and other chemicals used were of the highest quality available.

2-Pyridyl 3,5-Dinitrobenzoate (6a). Data: mp 120−122 °C; ^{1}H NMR characteristics (500 MHz, $CDCl_3$) δ 9.359−9.355 (d, J = 2 Hz, 2H), δ 9.321−9.313 (t, J = 2 Hz, 1H), δ 8.512−8.504 (dd, J = 2 Hz, 1H), δ 7.953−7.918 (dt, J = 7.5 Hz, 1H), δ 7.397−7.372 (dd, J = 7.5 Hz, 1H), δ 7.280−7.263 (d, J = 8 Hz, 1H); and elemental analysis (Calcd for $C_{12}H_7N_3O_6$: C, 49.84; H, 2.44. Found: C, 49.89; H, 2.42).

Table 4. Summary of Kinetic Results for the Reactions of 2-Pyridyl X-Substituted Benzoates (6a, 6b, 6f, and 6h)[a] with Piperidine at Five Different Temperatures

	10^2 k_N/M^{-1}s^{-1}						
	15.0 °C	20.0 °C	25.0 °C	30.0 °C	35.0 °C	$\Delta H^{\ddagger}$/kcal mol^{-1}	$\Delta S^{\ddagger}$/eu
6a	358	405	448	512	598	3.85	−42.6
6b	41.3	44.9	55.6	62.9	75.0	4.80	−43.6
6f	3.46	4.32	5.58	6.39	7.85	6.58	−42.3
6h	0.946	1.25	1.61	1.88	2.27	7.04	−43.2

[a]X = 3,5-$(NO_2)_2$ (**6a**), 4-NO_2 (**6b**), H (**6f**), 4-MeO (**6h**).

dx.doi.org/10.1021/jo402629e | J. Org. Chem. 2014, 79, 1206−1212

2-Pyridyl 3-Nitrobenzoate (6b). Data: mp 88−90 °C; ^{1}H NMR characteristics (500 MHz, $CDCl_3$) δ 9.074−9.067 (t, J = 2 Hz, 1H), δ 8.564−8.524 (dd, J = 7 Hz, 1H), δ 8.522−8.506 (d, J = 8 Hz, 1H), δ 8.500−8.484 (dd, J = 8 Hz, 1H), δ 7.915−7.880 (dt, J = 8 Hz, 1H), δ 7.763−7.732 (*t*, 8 Hz, 1H), δ 7.349−7.323 (dd, J = 8 Hz, 1H), δ 7.257−7.241 (d, J = 8 Hz, 1H); and elemental analysis (Calcd for $C_{12}H_8N_2O_4$: C, 59.02; H, 3.30. Found: C, 59.07; H, 3.28).

2-Pyridyl 4-*N*,*N*-Dimethylaminobenzoate (6i). Data: mp 160−162 °C; ^{1}H NMR characteristics (500 MHz, $CDCl_3$) δ 8.446−8.433 (dd, J = 2 Hz, 1H), δ 8.089−8.072 (d, J = 8 Hz, 2H), δ 7.817−7.783 (dt, J = 8 Hz, 1H), δ 7.231−7.196 (m, 2H), δ 6.696−6.678 (d, J = 8 Hz, 2H), δ 3.072 (s, 6H); and elemental analysis (Calcd for $C_{14}H_{14}N_2O_2$: C, 69. 41; H, 5.82. Found: C, 69.37; H, 5.84).

Kinetics. The kinetic study was performed using a UV−vis spectrophotometer equipped with a constant temperature circulating bath. All of the reactions in this study 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 0.02 M 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. The reactions were followed by monitoring the appearance of the leaving group up to nine half-lives.

Product Analysis. 2-Pyridyloxide was liberated quantitatively and identified as one of the products by comparison of the UV−vis spectrum at the end of reaction with that of the authentic sample under the experimental conditions.

■ ASSOCIATED CONTENT

Supporting Information

Kinetic conditions and results including ^{1}H NMR spectra for compounds **6a**, **6b**, and **6i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ 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). T.I.U. is also grateful for the Intensive Science Program of Dongbuk High School.

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