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Aminolysis of Y-Substituted Phenyl X-Substituted Benzoates with Piperidine: Effect of Nonleaving Group Substituent

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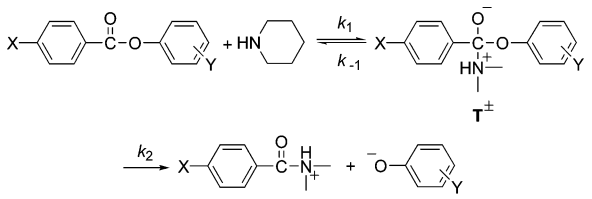

X = NO_2(**1**), Cl(**2**), H(**3**), Me(**4**), MeO(**5**)

Y = 3-COMe(**a**), 3-Cl(**b**), 4-COMe(**c**), 4-CHO(**d**), 4-NO_2(**e**), 3,4-$(NO_2)_2$(**f**)

The title reaction has been suggested to proceed through a zwitterionic tetrahedral intermediate with a change in the rate determining step on the basis of the curved Brønsted-type plots obtained. The curvature center of the curved Brønsted-type plots is at pK_a = 6.4 regardless of the electronic nature of the substituent X in the benzoyl moiety.

Aminolyses of esters have been suggested to proceed concertedly or through a stepwise mechanism with a zwitterionic tetrahedral intermediate $T^{\pm}$,[1−10] depending on the reaction conditions (e.g., solvents,[1−3] the nature of amines,[1,4,5] and the structure of substrates[1,6−10]). Aminolysis of esters with a good leaving group has often resulted in a curved Brønsted-type plot (i.e., the slope (β_{nuc}) decreases from ca. 0.8 to ca. 0.3 as the amine becomes more basic than the leaving group by 4−5 pK_a units).[1−10] Such a curved Brønsted-type plot has been interpreted as evidence of a stepwise mechanism with a change in the rate determining step (RDS).[1−10] The RDS has been suggested to change at the curvature center of the curved Brønsted-type plot, defined as pK_a°.[1−10]

The pK_a° value increases as the substituent in the nonleaving group becomes a stronger electron withdrawing group (EWG) for quinuclidinolysis of diaryl carbonates in water as reported by Gresser and Jencks.[8] This has been explained through the argument that the departure of the amine from $T^{\pm}$ is favored, over that of the leaving group, as the electron withdrawing ability of the substituent in the nonleaving group increases.[8] Castro et al. have found a similar result for pyridinolysis of 2,4-dinitrophenyl X-substituted benzoates (i.e., pK_a° = 9.5 when X = H but pK_a° > 9.5 when X = Cl, CN, or NO_2)[9] and *S*-2,4-dinitrophenyl X-substituted thiobenzoates (i.e., pK_a° increases from 8.5 to 8.9 and 9.9 as X changes from 4-Me to H and 4-NO_2, respectively) in aqueous ethanol.[10]

In contrast, we have shown that the pK_a° value is not influenced by the electronic nature of the substituent in the nonleaving group for reactions of 2,4-dinitrophenyl X-substituted benzoates and benzenesulfonates with alicyclic secondary amines in H_2O containing 20 mol % dimethyl sulfoxide (DMSO).[5,7] It has been found that the Hammett plots for these reactions are curved downwardly as the substituent in the nonleaving group changes from electron donating groups (EDG) to EWG.[5,7] Such a curved Hammett plot has traditionally been interpreted as a change in the RDS.[11] However, we have shown that stabilization of the ground state through resonance interaction between the π-electron donor substituent and the carbonyl or sulfonyl functionality is responsible for the nonlinear Hammett plots since the Yukawa−Tsuno plots for the same reactions are linear.[5,7]

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TABLE 1. Summary of Apparent Second-Order Rate Constants (k_N, M^{-1} s^{-1}) for the Reactions of Y-Substituted Phenyl X-Substituted Benzoates with Piperidine in H_2O Containing 20 mol % DMSO at 25.0 ± 0.1 °C

	pK_a	k_N (M^{-1} s^{-1})				
Y	(Y-PhOH)	X = NO_2 (**1**)	Cl (**2**)	H (**3**)	Me (**4**)	MeO (**5**)
a, 3-COMe	9.19	0.0208		0.00650		0.00226
b, 3-Cl	9.02	0.0519	0.0203	0.0159	0.0105	0.00619
c, 4-COMe	8.05	0.673		0.236		0.0982
d, 4-CHO	7.66	2.61		0.852		0.328
e, 4-NO_2	7.14	21.0[a]	8.14[a]	5.94[a]	3.68[a]	1.95[a]
f, 3,4-$(NO_2)_2$	5.42	1140	251	191	75.8	32.3

[a] Data from ref 7b.

We have extended our study to the reactions of Y-substituted phenyl X-substituted benzoates with piperidine to obtain more conclusive information about the p$K_a°$ and reaction mechanism. Various substituents X and Y have been employed both in the nonleaving and in the leaving group, respectively. In the previous studies,[2−10] the leaving group was fixed with a weakly basic aryloxide or thioaryloxide (e.g., 2,4-dinitrophenoxide or 2,4-dinitrothiophenoxide), while the basicity of the attacking amine and the substituent in the nonleaving group were changed. In the current study, the nucleophile is fixed with piperidine, a strongly basic alicyclic secondary amine, while the substituents both in the leaving and in the nonleaving groups are changed.

All reactions in this study obeyed pseudo-first-order kinetics over 90% of the total reaction. Pseudo-first-order rate constants (k_{obsd}) have been determined from the equation $\ln(A\infty - A_t) = -k_{obsd}t + C$. All the plots of k_{obsd} versus the piperidine concentration were linear passing through the origin, indicating that general base catalysis by a second amine molecule is absent and that the contribution of H_2O and/or OH^- from hydrolysis to the k_{obsd} is negligible. Thus, the rate law is given by eq 1, in which [S] and [NH] represent the concentration of the substrate and piperidine, respectively. The apparent second-order rate constants (k_N) have been determined from the slopes of the linear plots of k_{obsd} versus the piperidine concentration and summarized in Table 1. The uncertainty in the k_N values is estimated to be less than 3% from replicate runs. The detailed reaction conditions and kinetic results are shown in the Supporting Information.

$$\text{rate} = k_{obsd}[S], \text{ where } k_{obsd} = k_N[NH] \quad (1)$$

Effect of Leaving Group Substituent on Reactivity and Mechanism. As shown in Table 1, the k_N for the reactions with piperidine increases as the substituent X or Y becomes a stronger EWG. The effect of the substituent Y in the leaving group on reactivity is illustrated in Figure 1. The Brønsted-type plots for the reactions of **1a**−**f**, **3a**−**f**, and **5a**−**f** with piperidine are curved downwardly as the basicity of the leaving group decreases. Such a nonlinear Brønsted-type plot is typical for the aminolysis of esters, which proceeds through a zwitterionic tetrahedral intermediate ($T^{\pm}$) with a change in the RDS (Scheme 1) (i.e., from breakdown of $T^{\pm}$ to its formation as the basicity of the leaving group decreases).

The nonlinear Brønsted-type plots shown in Figure 1 have been analyzed using a semiempirical equation (eq 2) on the basis of the proposed mechanism.[7a,8,10,12] In eq 2, β_{lg1} and β_{lg2} represent the slope of the Brønsted-type plots for the weakly basic and strongly basic leaving groups, respectively, while $k_N°$ refers to the k_N value at p$K_a°$.

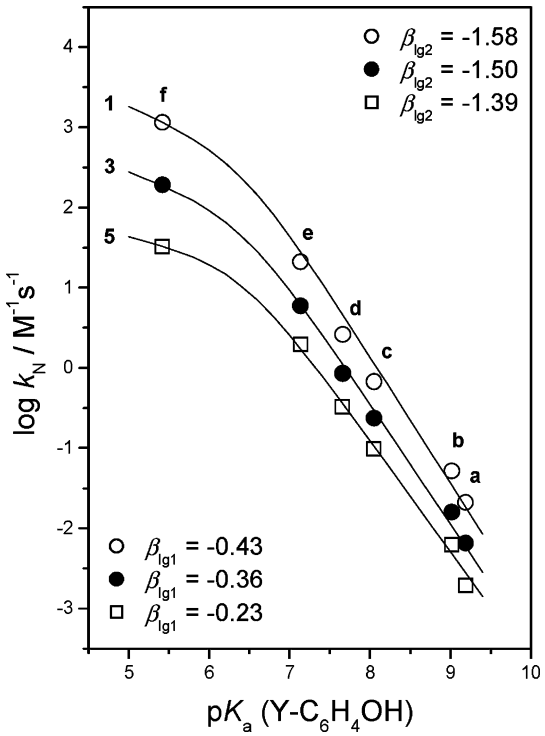
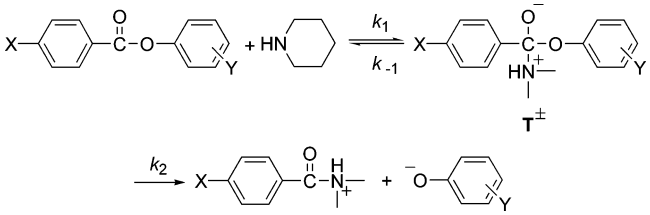


FIGURE 1. Brønsted-type plots for the reactions of **1a**−**f**(○), **3a**−**f**(●), and **5a**−**f**(□) with piperidine in H_2O containing 20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

SCHEME 1



X = NO_2(**1**), Cl(**2**), H(**3**), Me(**4**), MeO(**5**)

Y = 3-COMe(**a**), 3-Cl(**b**), 4-COMe(**c**), 4-CHO(**d**), 4-NO_2(**e**), 3,4-$(NO_2)_2$(**f**)

$$\log(k_N/k_N°) = \beta_{lg1}(pK_a - pK_a°) - \log[(1+\alpha)/2], \quad \text{where } \log\alpha = (\beta_{lg1} - \beta_{lg2})(pK_a - pK_a°) \quad (2)$$

The p$K_a°$ determined for the reactions of **1a**−**f**, **3a**−**f**, and **5a**−**f** with piperidine is 6.4, which is ca. 4.6 pK_a units smaller than the pK_a of the conjugate acid of the attacking piperidine (pK_a = 11.02). This is consistent with the report that a change in the RDS occurs when the attacking amine becomes more basic than the leaving group by 4−5 pK_a units or the leaving group becomes less basic than the amine nucleophile by 4−5 pK_a units.[1,3,5,8−10] It is noted that the p$K_a°$ determined in this study remains constant regardless of the electronic nature of the substituent in the nonleaving group. This result supports our previous conclusion that the p$K_a°$ is not influenced by the electronic nature of the substituent in the nonleaving group for aminolyses of 2,4-dinitrophenyl X-substituted benzoates and benzenesulfonates.[5,7]

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However, Castro et al. have recently argued against our conclusion.[10a,b] They have suggested that the aminolysis of 2,4-dinitrophenyl X-substituted benzoates performed by us proceeds very likely through a concerted mechanism, although the kinetic study resulted in curved Brønsted-type plots.[10a,b] It is because the slopes of the curved Brønsted-type plots are not in accordance with those obtained for reactions that have been suggested to proceed through a stepwise mechanism (i.e., $\beta_2 =$ 0.74 at the low pK_a region is not large enough, e.g., $\beta_2 = 0.8-1.0$), while $\beta_1 = 0.34$ at the high pK_a region is not small enough for a stepwise mechanism (e.g., $\beta_1 = 0.1-0.3$).[10a,b]

To examine the previous argument, the microscopic rate constants (i.e., the k_2/k_{-1} ratio and k_1) associated with the reactions of **1a**−**f**, **3a**−**f**, and **5a**−**f** with piperidine have been calculated as shown in the Supporting Information using the eqs S1−S8. The k_2/k_{-1} ratio has been calculated to be strongly dependent on the basicity of the leaving group (i.e., the k_2/k_{-1} for the reactions of **1a**−**f** increases from 6.19×10^{-4} to 0.0356 and 13.4 as the substituent Y in the leaving group changes from 3-COMe to 4-CHO and 3,4-$(NO_2)_2$, respectively (Table S20 in the Supporting Information)). A similar result has been obtained for the reactions of **3a**−**f** and **5a**−**f**. On the contrary, the k_2/k_{-1} ratio is not dependent on the substituent X in the nonleaving group. As shown in Table S20, the k_2/k_{-1} ratio remains nearly constant on changing the substituent X in the benzoyl moiety (e.g., $(6.20 \pm 0.4) \times 10^{-4}$ for the least reactive **1a**, **3a**, and **5a** or 13.4 ± 0.3 for the most reactive **1f**, **3f**, and **5f**). Thus, the current result is consistent with our preceding argument that the k_2/k_{-1} ratio is independent of the electronic nature of the substituent in the nonleaving group for the aminolysis of 2,4-dinitrophenyl benzoates and benzenesulfonates.[5,7]

The effect of the leaving group basicity on the k_2/k_{-1} ratio is illustrated in Figure S1 in the Supporting Information. It is shown that $k_2 = k_{-1}$ at p$K_a = 6.4$, regardless of the substituent in the nonleaving group. Besides, the k_2/k_{-1} ratio exhibits a strong dependence on the basicity of the leaving group (i.e., the slope of the linear plots is ca. 1.15 ± 0.01). Such a large slope can be explained as follows. The nucleofugality of the leaving group from $T^{\pm}$ (k_2) would be influenced by the electronic nature of the substituent Y in the leaving group (i.e., k_2 would increase as the substituent Y becomes a stronger EWG (or as the leaving group becomes less basic)). On the contrary, expulsion of the amine from $T^{\pm}$ (k_{-1}) would be more difficult as the substituent Y becomes a stronger EWG since the amine departs from $T^{\pm}$ with the bonding electron pair. Accordingly, the k_2/k_{-1} ratio is strongly dependent on the electronic nature of the leaving group substituent.

Using the k_N values in Table 1 and the k_2/k_{-1} ratios in Table S20 in the Supporting Information, the k_1 values have been calculated and summarized in Table S21 in the Supporting Information. One can see that k_1 increases as the leaving group basicity decreases. The effect of the leaving group basicity on k_1 is illustrated in Figure S2 in the Supporting Information. The slope of the linear Brønsted-type plots ($-\beta_{lg1}$) increases as the reactivity increases (i.e., $-\beta_{lg1}$ increases from 0.23 to 0.33 and 0.39 as the substituent X changes from 4-MeO to H and 4-NO_2, respectively), indicating that the reactivity−selectivity principle (RSP) is not applicable to the current reaction system. Similar results have been reported for the aminolyses of 4-nitrophenyl X-substituted benzoates, 2,4-dinitrophenyl X-substituted benzenesulfonates, and other related esters.[5,13] In all cases, β_{nuc} has been reported to increase as the substituent X in the nonleaving group changes from an EDG to an EWG.[5,13]

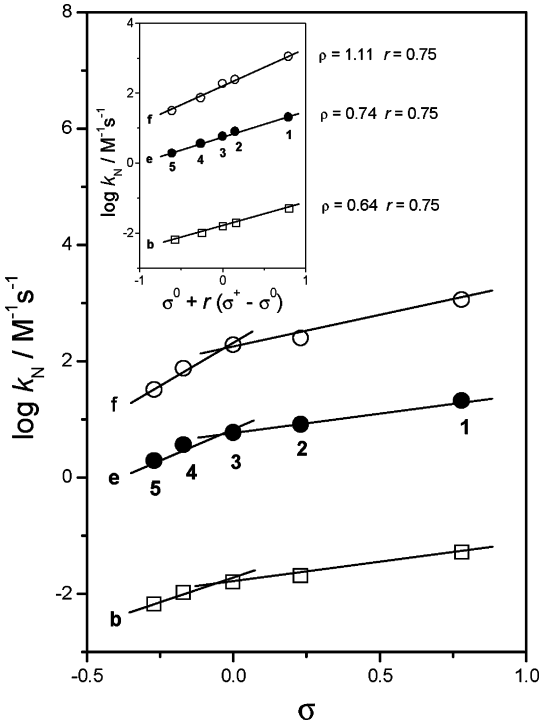

FIGURE 2. Hammett plots and Yukawa−Tsuno plots (inset) for the reactions of **1b**−**5b**(□), **1e**−**5e**(●), and **1f**−**5f**(○) with piperidine in H_2O containing 20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

Effect of Nonleaving Group Substituent on Reactivity and Mechanism. As shown in Table 1, k_N increases as the substituent X in the nonleaving group changes from an EDG to an EWG. The effect of substituent X on the rate is illustrated in Figure 2. All the Hammett plots consist of two intersecting straight lines. A curvature in Hammett plots has generally been interpreted as a change in the RDS or the reaction mechanism depending on the shape of the curvature: convex and concave (i.e., downward and upward curvature, respectively).[11,14−16] The downward curvature in the Hammett plots observed in this study might be interpreted as a change in the RDS (i.e., from the breakdown of $T^{\pm}$ to its formation as the substituent X changes from EWG to EDG). This argument appears to be reasonable, at first sight, since an EWG in the benzoyl moiety would accelerate the attack of the nucleophile (k_1) but retard the departure of the negatively charged leaving group from $T^{\pm}$ (k_2), while an EDG would decrease k_1 but increase k_2.

However, we propose that the curved Hammett plots shown in Figure 2 are not due to a change in the RDS, on the basis of the following argument. The RDS is not determined by the magnitude of k_1 and k_2. This is because k_1 and k_2 cannot be

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compared directly due to the difference in their units (e.g., M^{-1} s^{-1} vs s^{-1}). Accordingly, the RDS should be determined by the k_2/k_{-1} ratio. It is obvious that k_2 and k_{-1} are strongly dependent on the basicity of the leaving group and the nucleophile, respectively. The nucleophile used in this study is piperidine, and the leaving group is also fixed for a given Hammett plot in Figure 2. Accordingly, the k_2/k_{-1} ratio should be constant for each Hammett plot since the k_2/k_{-1} ratio has been shown to remain nearly constant on changing the electronic nature of the substituent in the benzoyl moiety (Table S20 in the Supporting Information). Thus, one cannot attribute the nonlinear Hammett plots in Figure 2 to a change in the RDS.

A careful examination of Figure 2 reveals that the substrate with a π-electron donating substituent in the benzoyl moiety deviates negatively from the Hammett plots. Besides, the deviation is more significant for the substrate with a stronger EDG. Accordingly, one can ascribe the nonlinear Hammett plots to stabilization of the ground state through the resonance interaction between the π-electron donor substituent and the carbonyl functionality. This argument can be further supported by employing the Yukawa−Tsuno equation (eq 3).[17,18] As shown in the inset of Figure 2, the Yukawa−Tsuno plots exhibit excellent linearity with an r value of 0.75 in all cases.

$$\log k_X/k_H = \rho[\sigma^\circ + r(\sigma^+ - \sigma^\circ)] \qquad (3)$$

In summary, (1) the reactions of Y-substituted phenyl X-substituted benzoates with piperidine proceed through $T^{\pm}$ with a change in the RDS. (2) A change in the RDS occurs at $pK_a = 6.4$, which is independent of the substituent X in the nonleaving group.

Experimental Section

Y-substitued phenyl X-substituted benzoates were readily prepared and purified as reported.[3c,19,20] A kinetic study was performed with a UV−vis spectrophotometer for slow reactions ($t_{1/2} > 10$ s) or a stopped-flow spectrophotometer for fast reactions ($t_{1/2} \leq 10$ s). Detailed kinetic methods and a product analysis are described in the Supporting Information.

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Supporting Information Available: Tables S1−S19 for the kinetic conditions and results for the reactions of Y-substituted phenyl X-substituted benzoates with piperidine. Eqs S1−S8 to determine the microscopic rate constants k_1 and the k_2/k_{-1} ratios. Table S20 for the summary of the k_2/k_{-1} ratios in the reactions of **1a**−**f**, **3a**−**f**, and **5a**−**f** with piperidine. Figure S1 for the plots of log k_2/k_{-1} versus pK_a for the reactions of **1a**−**f**(**?**), **3a**−**f**(**?**), and **5a**−**f**(**?**) with piperidine. Table S21 for the summary of k_1 in the reactions of **1a**−**f**, **3a**−**f**, and **5a**−**f** with piperidine. Figure S2 for the plots of log k_1 versus pK_a for the reactions of **1a**−**f**(**?**), **3a**−**f**(**?**), and **5a**−**f**(**?**) with piperidine. This material is available free of charge via the Internet at http://pubs.acs.org.

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