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Effect of *o*-Methyl Group on Rate, Mechanism, and Resonance Contribution: Aminolysis of Y-Substituted Phenyl X-Substituted 2-Methylbenzoates

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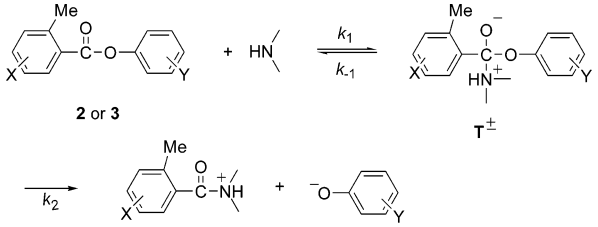

2 ; Y = 4-NO_2 , X = 4-MeO(**2a**), 4-Me(**2b**), H(**2c**), 3-Cl(**2d**), 3-NO_2(**2e**)

3 ; X = H , Y = 3-COMe(**3a**), 4-COMe(**3b**), 4-CHO(**3c**), 4-NO_2(**3d**), 3,4-$(NO_2)_2$(**3e**)

Second-order rate constants have been determined spectrophotometrically for the reactions of 4-nitrophenyl X-substituted 2-methylbenzoates (**2a**−**e**) and Y-substituted phenyl 2-methylbenzoates (**3a**−**e**) with alicyclic secondary amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The *o*-methyl group in the benzoyl moiety of **2a**−**e** retards the reaction rate but does not influence the reaction mechanism. The Hammett plots for the reactions of **2a**−**e** are nonlinear, while the corresponding Yukawa−Tsuno plots are linear with large *r* values (1.06−1.70). The linear Yukawa−Tsuno plots suggest that stabilization of the ground-state through resonance interaction between the electron donating substituent X and the carbonyl group is responsible for the nonlinear Hammett plots, while the large *r* values imply that the ground-state resonance interaction is significant. The reactions of **2a**−**e** resulted in smaller ρ_X values but larger *r* values than the corresponding reactions of 4-nitrophenyl X-substituted benzoates (**1a**−**e**). The small ρ_X value for the reactions of **2a**−**e** (e.g., $\rho_X = 0.22$) is suggested to be responsible for the large *r* value (e.g., $r = 1.70$). The reactions of **3a**−**e** with piperidine are proposed to proceed in a stepwise manner with a change in the rate-determining step on the basis of the curved Brønsted-type plot obtained. Microscopic rate constants associated with the reactions of **3a**−**e** are also consistent with the proposed mechanism.

Introduction

Aminolyses of esters have been suggested to proceed either concertedly or in a stepwise manner with a zwitterionic tetrahedral intermediate $T^{\pm}$, depending on the reaction conditions.[1−13] Factors influencing the reaction mechanism have intensively been investigated, e.g., solvents,[2,3] the nature of the amines,[4−6] and the structure of the substrates.[5−13] Particularly, the effect of substrate

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(1) (a) Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511−527. (b) Page, M. I.; Williams, A. *Organic and Bio-organic Mechanisms*; Longman: Harlow, U.K., 1997; Chapter 7. (c) Castro, E. A. *Chem. Rev.* **1999**, *99*, 3505−3524.
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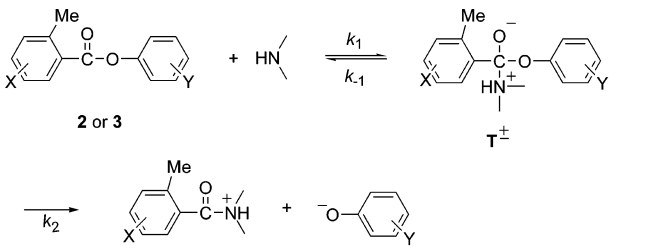
SCHEME 1



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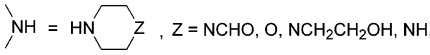
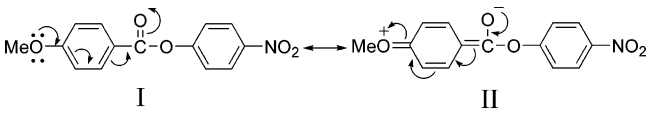


structures on the reactivity and reaction mechanism has intrigued chemists for a long time.[5−13]

Jencks et al. have concluded that the nonleaving phenoxy moiety influences the reaction mechanism for the reactions of X-substituted phenyl 3,4-dinitrophenyl carbonates with quinuclidines.[7] A similar conclusion has been drawn by Castro et al. for aminolyses of 2,4-dinitrophenyl X-substituted benzoates[8] and *S*-4-nitrophenyl X-substituted thiobenzoates.[9] They have suggested that an electron-withdrawing substituent in the nonleaving group retards the rate of the leaving group departure from $T^{\pm}$ (the k_2 in Scheme 1) but accelerates the expulsion of the amine from $T^{\pm}$ (the k_{-1} in Scheme 1).[7−9] Thus, it has been concluded that the substituent in the nonleaving group of the carbonates and benzoates affects the reaction mechanism.[7−9]

However, we have shown that the k_2/k_{-1} ratio is independent of the electronic nature of the substituent X for the reactions of 4-nitrophenyl X-substituted benzoates (**1a**−**e**) with a series of alicyclic secondary amines.[10] A similar result has been shown for the aminolyses of 2,4-dinitrophenyl X-substituted benzoates[5] and benzenesulfonates[6] and the alkaline hydrolyses of 2,4-dinitrophenyl X-substituted benzoates[11a] and their thiono analogues.[11b] In all cases, the Hammett plots have been found to be curved downwardly (i.e., electron-donating substituents exhibit negative deviations from the Hammett plots, and the degree of deviations is more significant for a stronger electron-donating substituent). Traditionally, such a curved Hammett plot has been interpreted as a change in the rate-determining step.[13,14] However, we have suggested that the stabilization of the ground-state as illustrated by resonance structures **I** ↔ **II** is responsible for the nonlinear Hammett plots, since



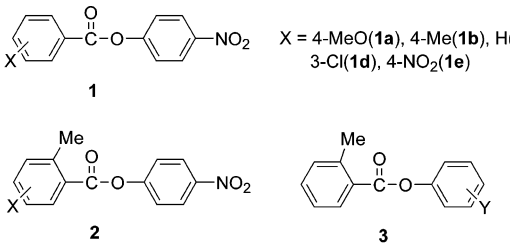
the corresponding Yukawa−Tsuno plots are all linear with large *r* values.[5,6,10,11]

The *r* value in the Yukawa−Tsuno equation (eq 1)

$$\log (k^{X}/k^{H}) = \rho_{X}[\sigma^{o} + r(\sigma^{+} - \sigma^{o})] \qquad (1)$$

represents the resonance demand of the reaction center or the extent of resonance contribution.[15−17] The largest *r* value reported for benzylic systems is 1.53 for solvolysis of 1-aryl-2,2,2-trifluoroethyl tosylates, in which the resonance demand is remarkably high due to the strong electron-withdrawing ability of the α-CF_3 group.[15−17] On the other hand, the *r* value has been suggested to decrease significantly as the planarity of the aryl moiety and the reaction center is hindered by twisting the aryl moiety.[15,18]

Thus, we have extended our study to the reactions of 4-nitrophenyl X-substitued 2-methylbenzoates (**2a**−**e**)



and Y-substituted phenyl 2-methylbenzoates (**3a**−**e**) with a series of alicyclic secondary amines, as shown in

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TABLE 1. Apparent Second-Order Rate Constants (k_N, M^{-1} s^{-1}) for the Reactions of 4-Nitrophenyl X-Substituted Benzoates (1b, 1c, and 2c) with Alicyclic Secondary Amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C[a]

		$10^2k_N/M^{-1}$ s^{-1}		
amines[a]	pK_a[b]	**1c** (X = H)	**1b** (X = 4-Me)	**2c** (X = 2-Me)
1, 1-formylpiperazine	7.98	1.00 ± 0.04	0.707 ± 0.001	0.217 ± 0.001
2, morpholine	8.65	8.76 ± 0.07	6.59 ± 0.01	1.22 ± 0.01
3, 1-(2-hydroxyethyl)piperazine	9.38	19.5 ± 0.3	14.7 ± 0.3	2.63 ± 0.01
4, piperazine	9.85	85.1 ± 0.2	62.9 ± 0.1	10.9 ± 0.04
5, piperidine	11.02	594 ± 2	368 ± 1	50.4 ± 0.3

[a] The numbers 1−5 refer to the labels in Figure 1. [b] The pK_a data in 20 mol % DMSO and the rate constant data for the reactions of **1b** and **1c** were taken from ref 10.

Scheme 1. One might expect that the *o*-methyl group would influence the reactivity of **2a**−**e** and **3a**−**e**. More importantly, the C═O bond would experience steric hindrance exerted by the *o*-methyl group in the benzoyl moiety of **2a**−**e** and **3a**−**e**. The steric hindrance would disturb the planarity of the benzoyl moiety. If the C═O bond and the phenyl ring in the benzoyl moiety of **2a**−**e** are not on the same plane, the resonance contribution of the π-electron donor substituent should decrease significantly. Thus, one might expect that the *r* value, representing the resonance contribution, should be smaller for the reactions of **2a**−**e** than for the corresponding reactions of **1a**−**e**. We report the effect of the *o*-methyl group in the benzoyl moiety of **2a**−**e** and **3a**−**e** on reaction rates, mechanism, and *r* values together with factors influencing the magnitude of the Brønsted β value.

Results and Discussion

All the reactions in this study obeyed pseudo-first-order kinetics in the presence of a large excess of amine. Pseudo-first-order rate constants (k_{obsd}) were determined from the equation $\ln(A_\infty - A_t) = -k_{obsd}t + C$. The correlation coefficient for the linear regressions was always higher than 0.9995. All the plots of k_{obsd} vs amine concentration were linear, passing through the origin, indicating that general base catalysis by a second amine molecule is absent and the contribution of H_2O and/or OH^- from hydrolysis to the k_{obsd} is negligible. Second-order rate constants (k_N) were determined from the slope of the linear plots of k_{obsd} vs amine concentration and are summarized in Tables 1−3. 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.

Effect of *o*-Methyl Group on Rate and Mechanism. As shown in Table 1, **1b** is only slightly less reactive than **1c**, while **2c** is up to ca. 12 times less reactive than **1c** (e.g., the second-order rate constant ratio k_N^{1c}/k_N^{1b} = 1.4−1.6 while k_N^{1c}/k_N^{2c} = 4.6−12). One can suggest that the electron-donating ability of the methyl group in the benzoyl moiety of **1b** and **2c** is responsible for their low reactivity. However, if the electronic effect were the only factor to determine the reactivity, **1b** and **2c** should have exhibited a similar reactivity, since the electronic effect of the methyl group in **1b** and **2c** was suggested to be similar.[19] Thus, the fact that **2c** is much less reactive than **1b** indicates that the electronic effect is not solely responsible for the low reactivity of **2c**. One can attribute the lower reactivity of **2c** compared with **1b** to the steric hindrance exerted by the *o*-methyl group in **2c**.

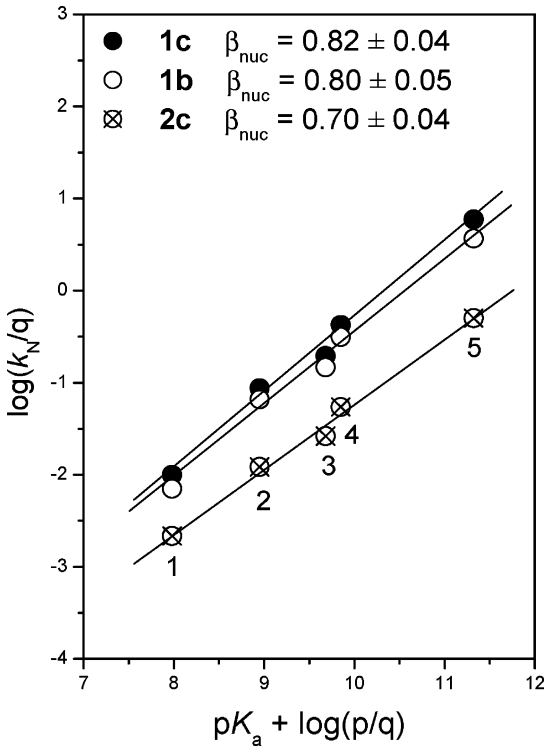

FIGURE 1. Brønsted-type plots for the reactions of 4-nitrophenyl X-substituted benzoates (**1b**, **1c**, and **2c**) with alicyclic secondary amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of the points is given in Table 1.

Table 1 shows that the second-order rate constant k_N for the aminolysis of **1b**, **1c**, and **2c** increases as the basicity of amines increases. The effect of amine basicity on the reactivity is illustrated in Figure 1. The Brønsted-type plots are all linear with a similar β_{nuc} value.

The magnitude of β_{nuc} values has been used as a measure of reaction mechanism.[1] The β_{nuc} value has generally been reported to be 0.5 ± 0.1 for reactions that proceed through a concerted mechanism.[1,20,21] On the other hand, for reactions proceeding in a stepwise manner, the β_{nuc} value has often been shown to decrease from

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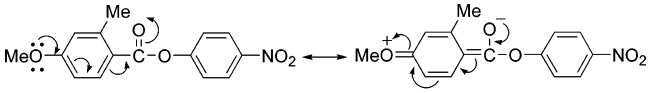
TABLE 2. Summary of Apparent Second-Order Rate Constants (k_N, M^{-1} s^{-1}) for the Reactions of 4-Nitrophenyl X-Substituted 2-Methylbenzoates (2a−e) with Alicyclic Secondary Amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C

	$10^2 k_N/M^{-1}$ s^{-1}		
no., X	1-formyl-piperazine	1-(2-hydroxyethyl)-piperazine	piperidine
2a, 4-MeO	0.105 ± 0.001	1.12 ± 0.01	19.8 ± 0.1
2b, 4-Me	0.168 ± 0.001	1.96 ± 0.04	37.2 ± 0.1
2c, H	0.217 ± 0.001	2.63 ± 0.01	50.4 ± 0.3
2d, 3-Cl	0.245 ± 0.002	3.20 ± 0.02	75.0 ± 0.4
2e, 3-NO_2	0.292 ± 0.001	4.25 ± 0.02	120 ± 0.3

0.9 ± 0.2 to 0.3 ± 0.1 as the nucleophile becomes more basic than the leaving group.[1−10] A change in the rate-determining step has been suggested to be responsible for the decrease in the β_{nuc} value.[1−10] The β_{nuc} values determined in this study for the reactions of **1b**, **1c**, and **2c** are 0.80, 0.82, and 0.70, respectively. These β_{nuc} values are typical for aminolysis reactions that proceed through $T^{\pm}$, with its breakdown to the products being the rate-determining step. Thus, one can suggest that the aminolysis of **2c** also proceeds through a stepwise mechanism, as suggested previously for the reactions of **1b** and **1c**,[10] indicating that the *o*-methyl group in **2c** does not influence the reaction mechanism.

Effect of *o*-Methyl Group on *r* and ρ_X Values. As shown in Table 2, the reactivity of **2a**−**e** increases as the substituent X changes from an electron-donating group to an electron-withdrawing group. The effect of substituent X on the reactivity is illustrated in Figure 2.

All the Hammett plots are nonlinear, while the Yukawa−Tsuno plots shown in the inset of Figure 2 are all linear with large *r* values, indicating that the nonlinear Hammett plots are definitely not due to a change in the rate-determining step. One can attribute the negative deviation shown by **2a** from the Hammett correlation to the ground-state stabilization through a resonance interaction between the *p*-methoxy and the carbonyl group, as illustrated by resonance structures **III** ↔ **IV**. Thus,



III IV

the present result confirms our previous proposal that determination of the reaction mechanism based just on a linear or nonlinear Hammett plot can be misleading.[5,6,10,11]

Although the *r* and ρ_X values might include some extent of uncertainty due to the limited number of substituents, the *r* value determined in this study increases from 1.06 to 1.45 and 1.70 as the ρ_X value decreases from 0.49 to 0.31 and 0.22 for the reactions of **2a**−**e** with piperidine, 1-(2-hydroxyethyl)piperazine, and 1-formylpiperazine, respectively. A similar inverse relationship between the *r* and ρ_X values has been reported

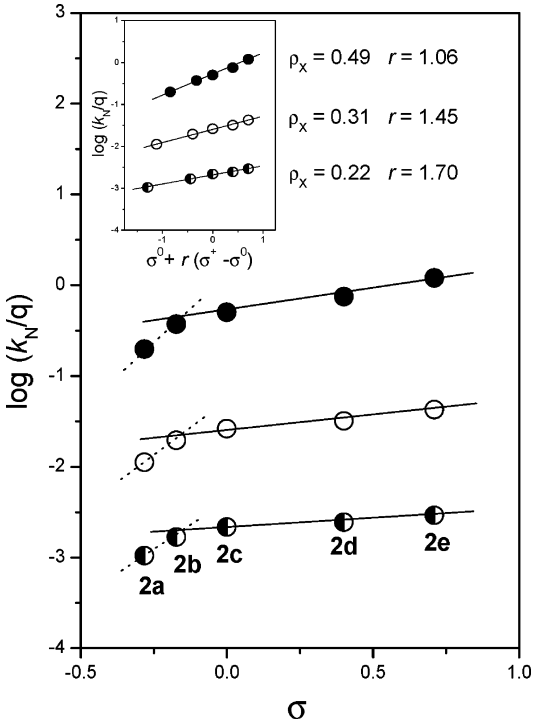


FIGURE 2. Hammett and Yukawa−Tsuno plots (the inset) for the reactions of 4-nitrophenyl X-substituted 2-methylbenzoates (**2a**-**e**) with piperidine (●), 1-(2-hydroxyethyl)piperazine (○), and 1-formylpiperazine (◐) in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C.

for aminolyses of **1a**−**e**,[10] 2,4-dinitrophenyl X-substituted benzoates.[5a] For example, the *r* values reported are 0.75, 1.05, 1.20, 1.29, and 1.38 while the ρ_X values are 0.75, 0.54, 0.51, 0.44, and 0.42 for the reactions of **1a**−**e** with piperidine, piperazine, 1-(2-hydroxyethyl)piperazine, morpholine, and 1-formylpiperazine, respectively.[10] The relationship between the *r* and ρ_X values is illustrated in Figure 3. As shown, the *r* value increases linearly as the ρ_X value decreases.

One might expect that the *o*-methyl group in the benzoyl moiety of **2a**−**e** would twist the phenyl ring and the C═O bond by exerting steric hindrance. If the benzoyl moiety is not planar, the resonance interaction between the electron-donating substituent X and the carbonyl group should decrease. Then, the *r* value, representing the resonance contribution, should be smaller for the reactions of **2a**−**e** than for the corresponding reactions of **1a**−**e**. However, unexpectedly, the *r* values have been determined to be larger for the former reactions than for the latter reactions (see also Figure 3). Furthermore, the *r* value of 1.70 for the reactions of **2a**−**e** with 1-formylpiperazine is even larger than the largest *r* value ever reported for the solvolysis of 1-aryl-2,2,2-trifluoroethyl tosylates.[17] Thus, one can suggest that the *o*-methyl group does not inhibit the ground-state resonance interaction (e.g., **III** ↔ **IV**).

We have calculated the ground-state structure of **2c** by a density functional theory (DFT) method (at the B3LYP/6-31+G* level). The result of the molecular orbital calculations has revealed that the phenyl ring and the carbonyl group of **2a**−**e** are not on the same plane as expected (see the calculated structures of **1c** and **2c** shown in the Supporting Information). The dihedral

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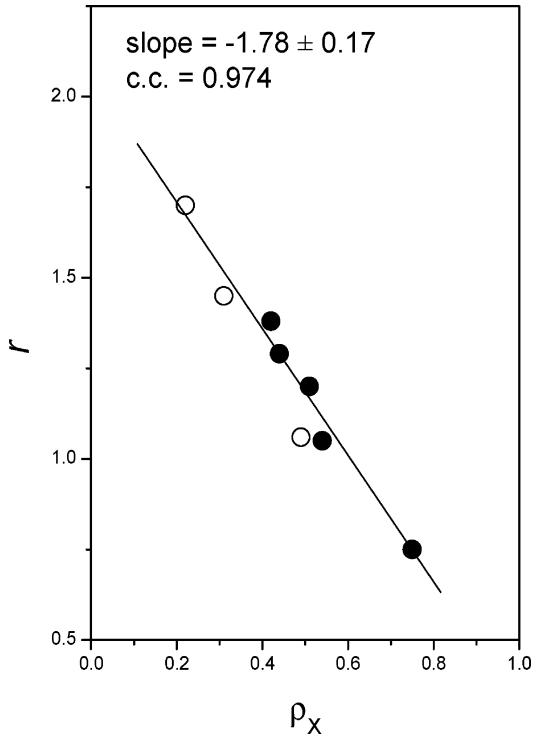

FIGURE 3. Plot showing dependence of the r value on the ρ_X value for the aminolysis of **2a**−**e** (○) and **1a**−**e** (●) in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C.

angle between the phenyl ring and the C═O bond in the benzoyl moiety of **2c** is ca. 6°.

It has been suggested that the efficiency of resonance interaction is proportional to $\cos^2\theta$, where θ is the dihedral angle between the two overlapping p-orbitals.[15,18] The θ determined in this study is ca. 6°. Since $\cos^2 6° \approx 1$, the o-methyl group would not reduce the efficiency of the resonance interaction between the electron-donating substituent X and the carbonyl bond in the benzoyl moiety of **2a**−**e**. This accounts for the result that the r values are not smaller for the reactions of **2a**−**e** than for the corresponding reactions of **1a**−**e**. Since the ρ_X values and the observed r values exhibit an inverse relationship in this and other aminolysis reactions, as mentioned above, one can attribute the large r value found for the reactions of **2a**−**e** to the decreased ρ_X values by the o-methyl group in the benzoyl moiety of **2a**−**e**.

Effect of Leaving Group Substituent on Rate and Mechanism. To obtain more information about the reaction mechanism, the reactions of **3a**−**e** with piperidine have been performed. As shown in Table 3, the reactivity of **3a**−**e** increases as the leaving group becomes less basic, i.e., the second-order rate constant k_N increases from 5.00×10^{-5} M^{-1} s^{-1} to 8.05×10^{-2} and 13.5 M^{-1} s^{-1} as the substituent Y in the leaving group changes from 3-COMe to 4-CHO and 3,4-$(NO_2)_2$, respectively.

The effect of leaving group basicity on reactivity is illustrated in Figure 4. The Brønsted-type plot for the reactions of **3a**−**e** with piperidine is curved downwardly as the basicity of the leaving aryloxide decreases. Such a curved Brønsted-type plot is typical for reactions that proceed through $T^{\pm}$ with a change in the rate-determining step. Thus, on the basis of the proposed mechanism

TABLE 3. Summary of Apparent Second-Order Rate Constants (k_N, M^{-1} s^{-1}) for the Reactions of Y-Substituted Phenyl 2-Methylbenzoates (3a−e) with Piperidine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C

no., Y	pK_a (Y-C_6H_4OH)[a]	$10^2 k_N$/M^{-1} s^{-1}
3a, 3-COMe	9.19	$(5.00 \pm 0.01) \times 10^{-3}$
3b, 4-COMe	8.05	1.03 ± 0.01
3c, 4-CHO	7.66	8.05 ± 0.08
3d, 4-NO_2	7.14	50.4 ± 0.3
3e, 3,4-$(NO_2)_2$	5.42	1350 ± 2

[a] pK_a values were taken from Jencks, W. P.; Regenstein, J. In *Handbook of Biochemistry*, 2nd ed.; Sober, H. A., Ed.; Chemical Rubber Publishing Co.: Cleveland, OH, 1970; p J-195.

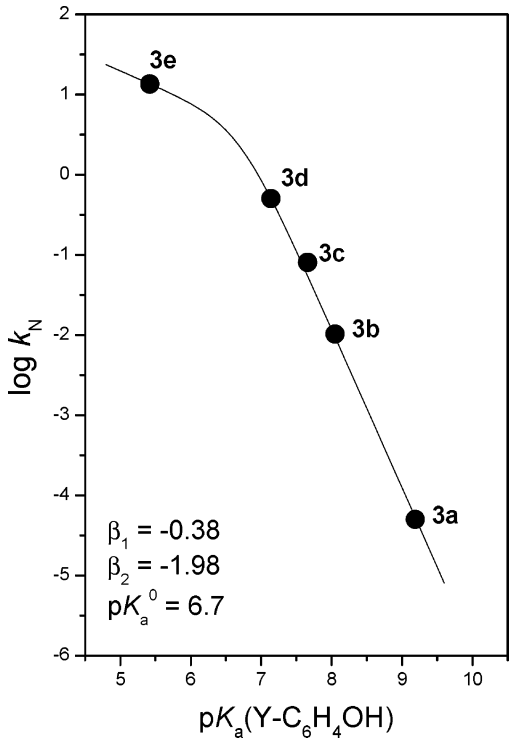

FIGURE 4. Brønsted-type plot for the reactions of Y-substituted phenyl 2-methylbenzoates (**3a**−**e**) with piperidine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C.

in Scheme 1, the nonlinear Brønsted-type plot shown in Figure 4 has been analyzed using a semiempirical equation (eq 2).

$$\log (k_N/k_N^\circ) = \beta_1(pK_a - pK_a^\circ) - \log [(1 + \alpha)/2]$$

where

$$\log \alpha = (\beta_1 - \beta_2)(pK_a - pK_a^\circ) \qquad (2)$$

In eq 2, β_1 and β_2 represent the slope of the Brønsted-type plot shown in Figure 4 for the weakly basic and strongly basic leaving groups, respectively, while k_N° refers to the k_N value at pK_a° (defined as the center of the curvature of the curved Brønsted-type plot, where $k_2 = k_{-1}$). The β_1, β_2, and pK_a° values determined are −0.38, −1.98, and 6.7, respectively. The β_1 value might involve some extent of uncertainty due to limited points. Interestingly, the β_2 value is much larger than unity. The origin of the large β_2 value will be discussed later.

The pK_a° determined in this study is 6.7, which is ca. 4.3 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 reports that the rate-determining step changes 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] Thus, one can suggest that the reactions of **3a**−**e** proceed through $T^{\pm}$ with a change in the rate-determining step at pK_a ca. 6.7, i.e., the reactions of **3a**−**d** with piperidine proceed through the rate-determining breakdown of $T^{\pm}$ to the products while the reaction of **3e** with piperidine proceeds through the rate-determining formation of $T^{\pm}$.

Origin of Large Brønsted β Values. We have determined the microscopic rate constants associated with the reactions of **3a**−**e** with piperidine to investigate further information about the reaction mechanism and the origin of the large Brønsted β value determined in this study. On the basis of the proposed mechanism in Scheme 1, the apparent second-order rate constant k_N can be expressed as eqs 3 and 4 by applying the steady-state conditions to the intermediate.

$$\text{rate} = k_1k_2\,[\text{substrate}][\text{piperidine}]/(k_{-1} + k_2) \quad (3)$$

$$k_N = k_1k_2/(k_{-1} + k_2) = k_1/(k_{-1}/k_2 + 1) \quad (4)$$

The k_2/k_{-1} ratios for the reactions of **3a**−**e** with piperidine have been calculated as follows. Equation 4 can be simplified to eqs 5 and 6. Then, β_1 and β_2 can be expressed as eqs 7 and 8, respectively.

$$k_N = k_1k_2/k_{-1} \quad \text{when } k_2 \ll k_{-1} \quad (5)$$

$$k_N = k_1 \quad \text{when } k_2 >> k_{-1} \quad (6)$$

$$\beta_1 = \mathrm{d}(\log k_1)/\mathrm{d}(\mathrm{p}K_a) \quad (7)$$

$$\beta_2 = \mathrm{d}(\log k_1k_2/k_{-1})/\mathrm{d}(\mathrm{p}K_a) = \beta_1 + \mathrm{d}(\log k_2/k_{-1})/\mathrm{d}(\mathrm{p}K_a) \quad (8)$$

Equation 8 can be rearranged as eq 9. Integration of eq 9 from pK_a° results in eq 10. Since $k_2 = k_{-1}$ at pK_a°, the term $(\log k_2/k_{-1})_{pK_a}$ is zero. Therefore, one can calculate the k_2/k_{-1} ratio for the reactions of Y-substituted phenyl 2-methylbenzoates with piperidine from eq 10 using $\beta_1 = -0.38$, $\beta_2 = -1.98$, pK_a° = 6.7.

$$\beta_2 - \beta_1 = \mathrm{d}(\log k_2/k_{-1})/\mathrm{d}(\mathrm{p}K_a) \quad (9)$$

$$(\log k_2/k_{-1})_{pK_a} = (\beta_2 - \beta_1)(\mathrm{p}K_a - \mathrm{p}K_a°) \quad (10)$$

The k_1 values have been determined from eq 4 using the k_N values in Table 3 and the k_2/k_{-1} ratios calculated above. The results are summarized in Table 4.

Table 4 exhibits that the k_1 value increases as the leaving group basicity decreases, i.e., k_1 increases from 0.482 to 2.85 and 13.6 $M^{-1}\,s^{-1}$ as the pK_a of the conjugate acid of the leaving aryloxide decreases from 9.19 to 7.66 and 5.42, respectively. The effect of the leaving group basicity on the k_1 value is illustrated in Figure 5. The Brønsted-type plot is linear with a β value of −0.38,

TABLE 4. Summary of the Microscopic Rate Constants Associated with the Reactions of Y-Substituted Phenyl 2-Methylbenzoates (3a−e) with Piperidine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C

no., Y	pK_a	$k_1/M^{-1}\,s^{-1}$	k_2/k_{-1}
3a, 3-COMe	9.19	0.482	1.04×10^{-4}
3b, 4-COMe	8.05	1.50	0.00692
3c, 4-CHO	7.66	2.85	0.0291
3d, 4-NO_2	7.14	3.05	0.198
3e, 3,4-$(NO_2)_2$	5.42	13.6	112

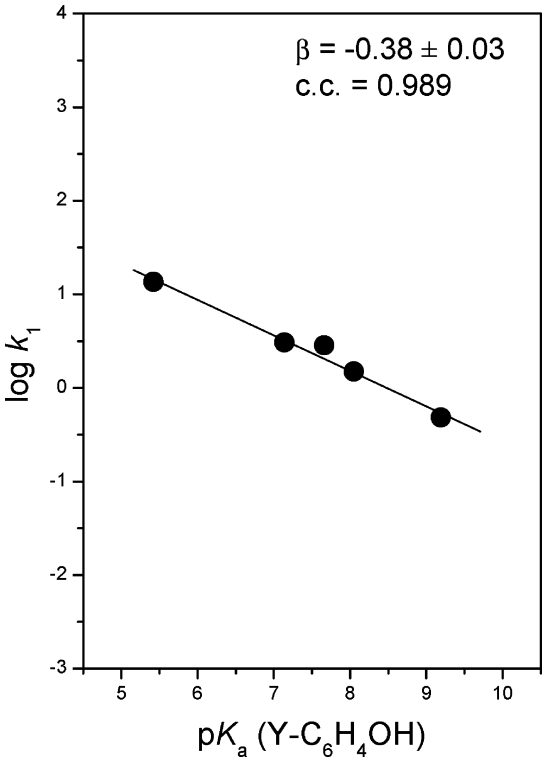

FIGURE 5. Brønsted-type plot for k_1 for the reactions of Y-substituted phenyl 2-methylbenzoates (**3a**−**e**) with piperidine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C.

indicating that the electrophilicity of the carbonyl carbon of **3a**−**e** increases as the substituent Y in the leaving group becomes a stronger electron-withdrawing group. However, one can suggest that the electronic nature of substituent Y does not significantly influence the rate of nucleophilic attack on the basis of the small β value.

We have recently reported that the β values are −0.49 and −0.34 for the alkaline hydrolysis of Y-substituted phenyl benzoates[11a] and their thiono analogues,[11b] respectively. These reactions have been suggested to proceed through an addition intermediate with its formation being the rate-determining step.[11] Besides, a β value of ca. 0.3 ± 0.1 has often been reported for aminolyses of various esters in which the formation of $T^{\pm}$ is the rate-determining step.[1] Thus, a β value of ca. 0.3 ± 0.1 appears to be typical for the nucleophilic attack process or for reactions which proceed through a rate-determining formation of $T^{\pm}$, regardless of the type of nucleophiles (neutral amines or anions) and the electrophilic centers (carbonyl or thionocarbonyl).

Table 4 shows that the k_2/k_{-1}ratio increases as the leaving group becomes less basic, i.e., $k_2/k_{-1} < 1$ for p$K_a \geq 7.14$, while $k_2/k_{-1} > 1$ for p$K_a \leq 5.42$. This result

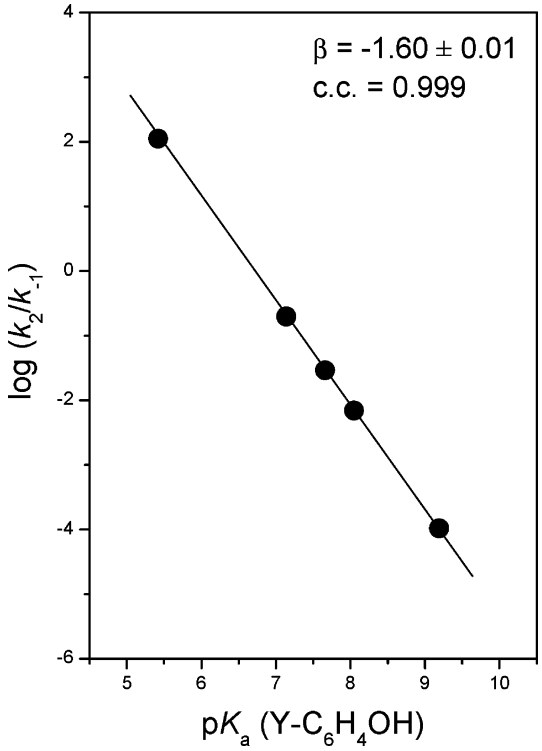

FIGURE 6. Plot of log k_2/k_{-1} vs pK_a for the reactions of Y-substituted phenyl 2-methylbenzoates (**3a**−**e**) with piperidine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C.

is consistent with the preceding proposal, on the basis of the curved Brønsted-type plot shown in Figure 4, that the reactions of **3a**−**e** with piperidine proceed through a stepwise mechanism with a change in the rate-determining step.

The effect of leaving group basicity on the k_2/k_{-1} ratio is demonstrated in Figure 6. The plot is linear with a β value of −1.60. Since the nucleofugality of the leaving group from $T^{\pm}$ would be influenced significantly by the electronic nature of the substituent Y in the leaving group, the k_2 value would increase strongly as the substituent Y becomes a stronger electron-withdrawing group or as the leaving group becomes less basic. On the contrary, the expulsion of the amine from $T^{\pm}$ would be more difficult as the electron-withdrawing ability of the substituent Y increases. Accordingly, the k_2/k_{-1} ratio should exhibit great dependence on the electronic nature of the substituent Y, which is responsible for the large β value (−1.60) shown in Figure 6.

One can also account for the large β_2 value (−1.98) shown in Figure 4 using the microscopic rate constants determined above. Equation 4 becomes eq 5 when the breakdown of $T^{\pm}$ to the products is the rate-determining step. In this case, the k_N value is determined by both k_1 and k_2/k_{-1} ratio. Thus, the β value for k_N should be the sum of the β values for k_1 and k_2/k_{-1} ratio. The slopes of the Brønsted-type plots shown in Figures 5 and 6 are −0.38 and −1.60, respectively. The sum of these values is −1.98, which is the same as the β_2 value shown in Figure 4. Thus, the present study shows that the Brønsted β value can be much larger than unity, depending on the nature of the reaction mechanism and the rate-determining step, e.g., a stepwise mechanism with the second step being the rate-determining step as in the present study.

Conclusions

The present study has allowed us to conclude the following: (1) The *o*-methyl group of **2c** retards the reactivity by exerting steric hindrance but does not influence the reaction mechanism. (2) The Yukawa−Tsuno plots are linear with large r values for the reactions of **2a**−**e**. The r value increases as the ρ_X value decreases, and the reactions of **2a**−**e** exhibit larger r values than the corresponding reactions of **1a**−**e**. (3) The density functional theory (DFT) calculations have revealed that the phenyl ring and the carbonyl group of **2c** are twisted with a dihedral angle θ of ca. 6°. The small θ does not reduce the ground-state resonance interaction; instead, it increases the r value by decreasing the ρ_X value. (4) The reactions of **3a**−**e** proceed through a stepwise mechanism with a change in the rate-determining step (pK_a° = 6.7). (5) The Brønsted β value can be much larger than unity for reactions that proceed through $T^{\pm}$ with its breakdown being the rate-determining step.

Experimental Section

Materials. Compounds **2a**−**e** and **3a**−**e** were readily prepared from the reactions of Y-substituted phenol and X-substituted 2-methylbenzoic acid under the presence of dicyclohexyldiimide (DCC) in methylene chloride and purified by column chromatography. Their purity was checked by their melting points, ^{1}H NMR spectra, and elemental analysis data (see Supporting Information). Amines and other chemicals used are of the highest quality available and were generally recrystallized or distilled before use. Due to the low solubility of these compounds in pure water, aqueous DMSO (20 mol % DMSO/80 mol % H_2O) was used as the reaction medium. Doubly glass-distilled water was further boiled and cooled under nitrogen just before use.

Kinetics. The kinetic study was performed with a UV−vis spectrophotometer equipped with a constant temperature circulating bath at 25.0 ± 0.1 °C. The reactions were followed by monitoring the appearance of Y-substituted phenoxide at a fixed wavelength corresponding to the λ_{max}. All the reactions were carried out under pseudo-first-order conditions in the presence of excess amine. Typically, the reaction was initiated by adding 5 μL of a 0.02 M of substrate solution in MeCN by a 10 μL gastight syringe to a 10 mm quartz UV cell containing 2.50 mL of the thermostated reaction mixture made up of solvent and an aliquot of the amine stock solution. The amine stock solution of ca. 0.2 M was prepared by dissolving 2 equiv of free amine and 1 equiv of standardized HCl solution to make a self-buffered solution. All the solutions were transferred by gastight syringes under nitrogen. Generally, the amine concentration was varied over the range (1−100) × 10^{-3} M, while the substrate concentration was 4 × 10^{-5} M. The plots of $\ln(A_\infty - A_t)$ vs time were linear over ca. 90% of the total reaction. Usually five different amine concentrations were used to determine the k_N value from the slope of the linear plot of k_{obsd} vs amine concentration.

Calculations. Density functional theory (DFT) calculations were performed with the Gaussian 98 system of programs.[22a] The DFT method is particularly useful for calculations involving a large number of nonhydrogen atoms at the correlated level. The B3LYP hybride exchange-correlation functionals are known to give good equilibrium geometries and vibrational frequencies and accurate molecular atomization energies.[22b] Geometries were optimized and confirmed by calculating the harmonic frequencies at the B3LYP/6-31+G* level.

Products Analysis. 4-Nitrophenoxide (or Y-substituted phenoxide) was liberated quantitatively and identified as one of the reaction products in the reactions of **2a**−**e** (or **3a**−**e**) by comparison of the UV−vis spectra after the completion of the reactions with those of the authentic samples under the same reaction conditions.

(22) (a) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98, Revision A.6.* Gaussian, Inc., Pittsburgh, PA, 1998. (b) Levine, I. N. *Quantum Chemistry*, 5th ed.; Prentice Hall: Upper Saddle River, NJ, 2000; p 573.

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Supporting Information Available: General synthetic procedures for the preparation of compounds **2a**−**e** and **3a**−**e** and their analytical data, such as their ^{1}H NMR spectra, elemental analysis data, and lists of their melting points; the kinetic conditions and results for the reactions of **2c** with a series of alicyclic secondary amines (Tables S1−S5), for the reactions of **2a**−**e** with 1-formylpiperazine, 1-(2-hydroxyethyl)-piperazine, and piperidine (Tables S6 −S17), and for the reactions of **3a**−**e** with piperidine (Tables S18−S22); the structures of **1c** and **2c** calculated by a DFT method (at the B3LYP/6-31+G* level) and their calculated electronic energies and **Z**-matrixes. This material is available free of charge via the Internet at http://pubs.acs.org.

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