

Kinetic Study on Nucleophilic Displacement Reactions of Y-Substituted-Phenyl 2-Methylbenzoates with Cyclic Secondary Amines in Acetonitrile: Effects of Modification of 2-MeO in Benzoyl Moiety by 2-Me on Reactivity and Reaction Mechanism

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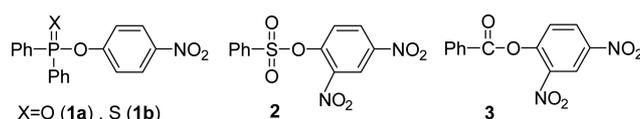
The second-order rate constants (k_N) have been measured spectrophotometrically for nucleophilic substitution reactions of Y-substituted-phenyl 2-methylbenzoates (**6a-e**) with a series of cyclic secondary amines in MeCN at 25.0 ± 0.1 °C. Comparison of the k_N values for the reactions of 4-nitrophenyl 2-methylbenzoate (**6d**) with those reported previously for the corresponding reactions of 4-nitrophenyl 2-methoxybenzoate (**5**) reveals that **6d** is significantly less reactive than **5**, indicating that modification of 2-MeO in the benzoyl moiety of **5** by 2-Me (*i.e.*, **5** \rightarrow **6d**) causes a significant decrease in reactivity. This supports our previous report that aminolysis of **5** proceeds through a six-membered cyclic intermediate, which is highly stabilized through intramolecular H-bonding interactions. The Brønsted-type plot for the reactions of **6d** with a series of cyclic secondary amines is linear with $\beta_{\text{nuc}} = 0.71$, which appears to be a lower limit of β_{nuc} for a stepwise mechanism with breakdown of an intermediate (T^\ddagger) being rate-determining step (RDS). The Brønsted-type plot for the reactions of **6a-e** with piperidine is curved, *i.e.*, the slope of Brønsted-type plot (β_{lg}) decreases from -1.05 to -0.41 as the leaving-group basicity decreases. The nonlinear Brønsted-type plot has been taken as evidence for a stepwise mechanism with a change in RDS (*e.g.*, from the k_2 step to the k_1 process as the leaving-group basicity decreases). Dissection of k_N into the microscopic rate constants associated with the reactions of **6a-e** with piperidine (*e.g.*, k_1 and k_2/k_{-1} ratio) also supports the proposed mechanism.

Key Words : Aminolysis, Brønsted-type plot, Stepwise mechanism, Rate-determining step, Medium effect

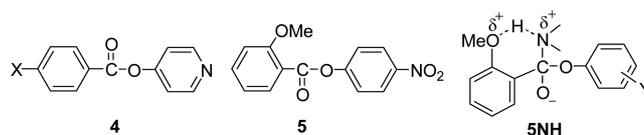
Introduction

Aminolysis of esters has been reported to proceed through a concerted mechanism or *via* a stepwise pathway with a zwitterionic tetrahedral intermediate (T^\ddagger) depending on reaction conditions (*e.g.*, the nature of electrophilic center, reaction medium, basicity of leaving group, *etc.*).¹⁻¹⁰ Reactions of 2,4-dinitrophenyl diphenylphosphinate (**1a**) with primary and secondary amines have been concluded to proceed through a concerted mechanism on the basis of linear Brønsted-type plots with $\beta_{\text{nuc}} = 0.38$ and 0.53 for the reactions with primary and secondary amines, respectively.^{6a,c} A similar conclusion has been drawn for the corresponding reactions of 2,4-dinitrophenyl diphenylphosphinothioate (**1b**).^{6b} The concerted mechanism has been further supported by an excellent linear Yukawa-Tsuno plot with $\rho_Y = 2.24$ and $r = 0.22$ for the reactions of Y-substituted-phenyl diphenylphosphinates (including **1a**) with ethylamine.^{6a} On the contrary, aminolysis of 2,4-dinitrophenyl benzenesulfonate (**2**) has been suggested to proceed through a stepwise mechanism with a change in rate-determining step (RDS) based on a curved Brønsted-type plot, *i.e.*, the slope of the plot (β_{nuc}) decreases from 0.88 to 0.41 as the basicity of the incoming amine increases.⁷ Thus, the nature of the electrophilic center (P=O, P=S and SO₂) has been suggested to

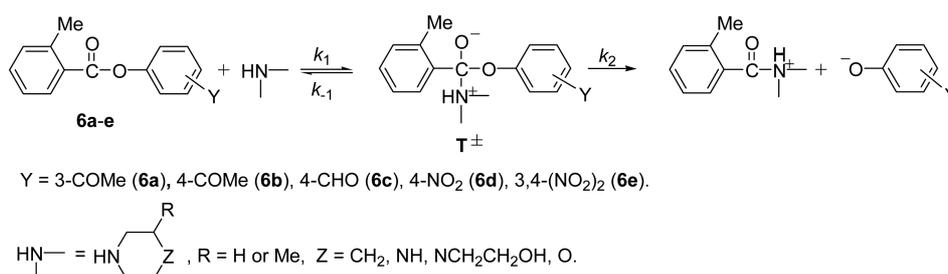
affect the reaction mechanism.^{6,7}



The nature of the reaction medium has been suggested to be also an important factor to determine the reaction mechanism. We have reported that the Brønsted-type plot for the reactions of 2,4-dinitrophenyl benzoate (**3**) with a series of secondary amines is curved in H₂O (*i.e.*, β_{nuc} decreases from 0.74 to 0.34 as the basicity of the incoming amine increases)^{8a} but is linear with $\beta_{\text{nuc}} = 0.40$ in MeCN.^{8b} Thus, the reactions have been proposed to proceed through a stepwise mechanism with a change in RDS in the aqueous medium^{8a} but *via* a concerted pathway in the aprotic solvent.^{8b}



However, we have recently reported that aminolysis of esters possessing a highly basic leaving group (*e.g.*, 4-pyridyl benzoate, **4**) or bearing 2-methoxy group in the nonleaving benzoyl moiety (*e.g.*, 4-nitrophenyl 2-methoxybenzoate, **5**)



Scheme 1

proceeds through a stepwise mechanism even in MeCN.^{9,10} A decreased nucleofugality of the highly basic 4-pyridyloxide in **4** and the stability gained from the H-bonding interactions in the cyclic intermediate (*i.e.*, **5NH**) have been suggested to lead the reactions to proceed through a stepwise mechanism.^{9,10}

Our study has now been extended to reactions of Y-substituted-phenyl 2-methylbenzoates (**6a-e**) with a series of cyclic secondary amines in MeCN to get further information on the reaction mechanism (Scheme 1). The kinetic results in this study have been compared with those reported previously for the corresponding reactions of **5**¹⁰ to investigate the effect of changing the 2-MeO in the benzoyl moiety of **5** by 2-Me on reactivity and reaction mechanism.

Results and Discussion

All the reactions in this study were carried out under pseudo-first-order conditions in which the amine concentration was kept in excess of the substrate concentration, and obeyed first-order kinetics. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation, $\ln(A_\infty - A_t) = -k_{\text{obsd}}t + C$. The plots of k_{obsd} vs. [amine] were linear and passed through the origin, indicating that general-base catalysis by a second amine molecule is absent. The second-order rate constants (k_N) were calculated from the slope of the linear plots of k_{obsd} vs. [amine]. It is estimated that the uncertainty in the k_N value is less than $\pm 3\%$ based on the replicate runs. The k_N values are summarized in Table 1 for the reactions of 4-nitrophenyl 2-methylbenzoate (**6d**) with a series of cyclic secondary amines and in Table 2 for those of Y-substituted-phenyl 2-methylbenzoates (**6a-e**) with piperidine.

Effect of Amine Basicity on Reactivity and Reaction Mechanism. Table 1 shows that the k_N value for the reaction of **6d** decreases as the amine basicity decreases, *e.g.*, it decreases from $77.9 \times 10^{-3} \text{ M}^{-1}\text{s}^{-1}$ to 7.05×10^{-3} and $2.08 \times 10^{-3} \text{ M}^{-1}\text{s}^{-1}$ as the $\text{p}K_a$ of the conjugate acid of the incoming amine decreases from 18.8 to 17.6 and 16.6, in turn. The k_N values for the corresponding reactions of **5** exhibit a similar trend. However, Table 1 shows that the k_N values are significantly larger for the reactions of **5** than for those of **6d**, indicating that replacing 2-MeO in the benzoyl moiety of **5** by 2-Me causes a significant decrease in reactivity. One can suggest that the large difference in the reactivities of **5** and **6d** is not due to the difference in the inductive or steric

Table 1. Summary of Second-Order Rate Constants for the Reactions of 4-Nitrophenyl 2-Methoxybenzoate (**5**) and 4-Nitrophenyl 2-Methylbenzoates (**6d**) with Cyclic Secondary Amines in MeCN at 25.0 ± 0.1 °C

	amines	$\text{p}K_a^a$	$10^3 k_N / \text{M}^{-1}\text{s}^{-1}$	
			6d	5 ^b
1	piperidine	18.8	77.9	12200
2	3-methylpiperidine	18.6	—	10800
3	piperazine	18.5	48.3	11500
4	1-(2-hydroxyethyl)piperazine	17.6	7.05	2190
5	1-formylpiperazine	17.0	3.75	—
6	morpholine	16.6	2.08	370

^aThe $\text{p}K_a$ data for the conjugate acids of amines in MeCN were taken from refs. 10 and 12. ^bThe kinetic data for the reactions of **5** were taken from ref. 10.

effects exerted by the MeO and Me groups in the *o*-position of the benzoyl moiety. This is because their inductive and steric effects would not be so different.¹¹ The significantly higher reactivity shown by **5** appears to be consistent with our previous proposal that the reactions of **5** proceed through the cyclic intermediate **5NH**, which gains a high stability through the intramolecular H-bonding interaction.¹⁰

In Figure 1(a) is demonstrated the effect of amine basicity on reactivity of **6d** toward the cyclic secondary amines. The Brønsted-type plot exhibits an excellent linear correlation with $\beta_{\text{nuc}} = 0.71$ when the k_N and $\text{p}K_a$ values are corrected statistically using p and q (*i.e.*, $p = 2$ and $q = 1$ except $q = 2$

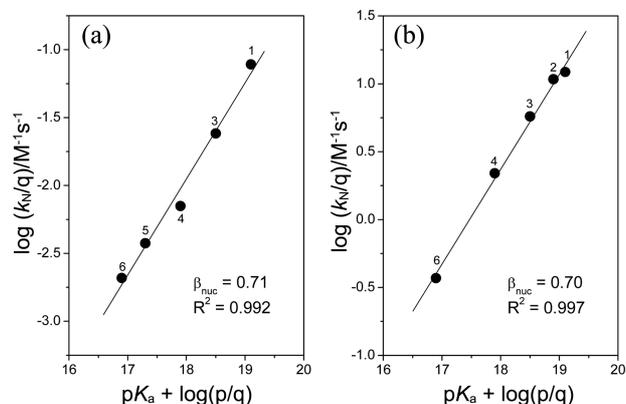


Figure 1. Brønsted-type plots for the reactions of 4-nitrophenyl 2-methylbenzoate (**a**) and 2-methoxybenzoate (**b**) with cyclic secondary amines in MeCN at 25.0 ± 0.1 °C. The identity of the points is given in Table 1.

for piperazine).¹³ This is almost identical to the Brønsted-type plot for the aminolysis of **5** as shown in Figure 1(b), which has been reported to proceed through a stepwise mechanism with the leaving-group departure being the RDS on the basis of a linear Brønsted-type plot with $\beta_{\text{nuc}} = 0.70$.¹⁰ Thus, it is proposed that the aminolysis of **6d** proceeds also through a stepwise mechanism with breakdown of the intermediate being RDS. One can also suggest that the modification of 2-MeO by 2-Me does not influence the reaction mechanism and that a β_{nuc} value of 0.70 or 0.71 is a lower limit of β_{nuc} for reactions proceeding through a stepwise mechanism in which departure of the leaving-group occurs in the RDS.

Effect of Leaving-Group Basicity on Reactivity and Reaction Mechanism. One might argue that a linear Brønsted-type plot with $\beta_{\text{nuc}} = 0.71$ is not sufficient to deduce the reaction mechanism. To get more conclusive information on the reaction mechanism, reactions of Y-substituted-phenyl 2-methylbenzoates (**6a-e**) with piperidine have been carried out. Piperidine was chosen as a nucleophile since it is the most basic secondary amines available. Thus, one might expect a curved Brønsted-type plot if the reactions of **6a-e** with piperidine proceed through a stepwise mechanism with a change in RDS.

As shown in Table 2, the k_{N} value for the reactions of **6a-e** with piperidine increases as the leaving-group basicity decreases, *e.g.*, it increases from $3.21 \times 10^{-6} \text{ M}^{-1}\text{s}^{-1}$ to 3.74×10^{-3} and $8.86 \text{ M}^{-1}\text{s}^{-1}$ as the $\text{p}K_{\text{a}}$ of the conjugate acid of the leaving group decreases from 25.0 to 22.1 and 17.9, in turn.

The effect of leaving-group basicity on reactivity is illustrated in Figure 2. The Brønsted-type plot for the reactions of **6a-e** with piperidine is curved. Such a curved Brønsted-type plot is typical of reactions reported previously to proceed through a stepwise mechanism with a change in the RDS, *e.g.*, quinuclidinolysis of diaryl carbonates,¹⁵ piperidinolysis of aryl benzoates¹⁶ and aryl 2-methoxybenzoates.¹⁰ Thus, the nonlinear Brønsted-type plot observed for the current reactions can be taken as evidence for a change in RDS of a stepwise reaction, *e.g.*, the RDS changes from the breakdown of T^{\ddagger} to its formation as the leaving-group basicity decreases. This is consistent with the preceding proposal that the reaction of **6d** with the cyclic secondary amines proceeds through a stepwise mechanism on the basis of the linear Brønsted-type plot with $\beta_{\text{nuc}} = 0.71$.

Thus, the nonlinear Brønsted-type plot has been analyzed

Table 2. Summary of Second-Order Rate Constants for the Reactions of Y-Substituted-Phenyl 2-Methylbenzoates (**6a-e**) with Piperidine in MeCN at $25.0 \pm 0.1 \text{ }^{\circ}\text{C}$ ^a

	Y	$\text{p}K_{\text{a}}^{\text{Y-PhOH}}$	$k_{\text{N}}/\text{M}^{-1}\text{s}^{-1}$
6a	3-COMe	25.0	3.21×10^{-6}
6b	4-COMe	22.9	8.26×10^{-4}
6c	4-CHO	22.1	3.74×10^{-3}
6d	4-NO ₂	20.7	7.79×10^{-2}
6e	3,4-(NO ₂) ₂	17.9	8.86

^aThe $\text{p}K_{\text{a}}$ data for Y-substituted-phenol in MeCN were taken from ref 14.

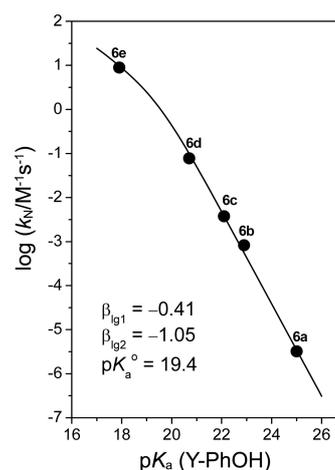


Figure 2. Brønsted-type plot for the reactions of Y-substituted-phenyl 2-methylbenzoates (**6a-e**) with piperidine in MeCN at $25.0 \pm 0.1 \text{ }^{\circ}\text{C}$. The identity of the points is given in Table 2.

using a semiempirical equation, Eq. (1), in which β_{lg1} and β_{lg2} represent the slope of the Brønsted-type plot shown in Figure 2 for the reactions substrates possessing a weakly basic leaving group and a strongly basic leaving group, respectively, while k_{N}° refers to the k_{N} value at $\text{p}K_{\text{a}}^{\circ}$ (defined as the $\text{p}K_{\text{a}}$ at the center of the Brønsted curvature, where $k_2 = k_{-1}$).¹⁵ The β_{lg1} , β_{lg2} , and $\text{p}K_{\text{a}}^{\circ}$ values determined are -0.41 , -1.05 , and 19.4 , in turn.

$$\log(k_{\text{N}}/k_{\text{N}}^{\circ}) = \beta_{\text{lg1}}(\text{p}K_{\text{a}} - \text{p}K_{\text{a}}^{\circ}) - \log[(1 + \alpha)/2]$$

$$\text{where } \log \alpha = (\beta_{\text{lg1}} - \beta_{\text{lg2}})(\text{p}K_{\text{a}} - \text{p}K_{\text{a}}^{\circ}) \quad (1)$$

Dissection of k_{N} into k_1 and k_2/k_{-1} . The microscopic rate constants associated with the reactions of **6a-e** with piperidine (*e.g.*, the k_1 and k_2/k_{-1} ratios) have been calculated as follows. Eq. (2) can be simplified to Eqs. (3) and (4). Then, β_{lg1} and β_{lg2} can be expressed as Eqs. (5) and (6), respectively.

$$k_{\text{N}} = k_1 k_2 / (k_{-1} + k_2) = k_1 / (k_{-1}/k_2 + 1) \quad (2)$$

$$k_{\text{N}} = k_1 k_2 / k_{-1}, \text{ when } k_2 \ll k_{-1} \quad (3)$$

$$k_{\text{N}} = k_1, \text{ when } k_2 \gg k_{-1} \quad (4)$$

$$\beta_{\text{lg1}} = d(\log k_1) / d(\text{p}K_{\text{a}}) \quad (5)$$

$$\begin{aligned} \beta_{\text{lg2}} &= d(\log k_1 k_2 / k_{-1}) / d(\text{p}K_{\text{a}}) \\ &= \beta_{\text{lg1}} + d(\log k_2 / k_{-1}) / d(\text{p}K_{\text{a}}) \end{aligned} \quad (6)$$

Eq. (6) can be rearranged as Eq. (7). Integral of Eq. (7) from $\text{p}K_{\text{a}}^{\circ}$ results in Eq. (8). Since $k_2 = k_{-1}$ at $\text{p}K_{\text{a}}^{\circ}$, the term $(\log k_2 / k_{-1})_{\text{p}K_{\text{a}}^{\circ}}$ is zero. Therefore, one can calculate the k_2/k_{-1} ratio for the reactions of **6a-e** with piperidine from Eq. (8) using $\beta_{\text{lg1}} = -0.41$, $\beta_{\text{lg2}} = -1.05$ and $\text{p}K_{\text{a}}^{\circ} = 19.4$. The k_1 values have been determined from eq (2) using the k_{N} values in Table 2 and the k_2/k_{-1} ratios calculated above. The results are summarized in Table 3.

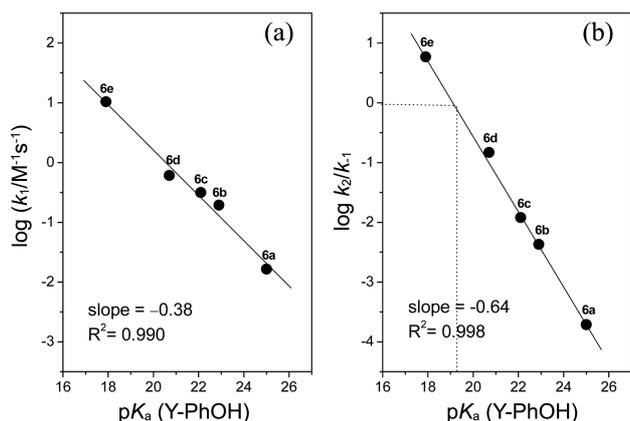
$$\beta_{\text{lg2}} - \beta_{\text{lg1}} = d(\log k_2 / k_{-1}) / d(\text{p}K_{\text{a}}) \quad (7)$$

$$(\log k_2 / k_{-1})_{\text{p}K_{\text{a}}} = (\beta_{\text{lg2}} - \beta_{\text{lg1}})(\text{p}K_{\text{a}} - \text{p}K_{\text{a}}^{\circ}) \quad (8)$$

The effects of leaving-group basicity on k_1 and the k_2/k_{-1}

Table 3. Summary of the Microscopic Rate Constants Associated with the Reactions of Y-Substituted-Phenyl 2-Methylbenzoates (**6a-e**) with Piperidine in MeCN at 25.0 ± 0.1 °C

Y	pK _a (Y-PhOH)	k ₁ /M ⁻¹ s ⁻¹	k ₂ /k ₋₁
6a	3-COMe	25.0	0.0165
6b	4-COMe	22.9	0.194
6c	4-CHO	22.1	0.315
6d	4-NO ₂	20.7	0.607
6e	3,4-(NO ₂) ₂	17.9	10.4

**Figure 3.** Brønsted-type plots for the reactions of Y-substituted-phenyl 2-methylbenzoates (**6a-e**) with piperidine in MeCN at 25.0 ± 0.1 °C. (a) for k_1 and (b) for k_2/k_{-1} . The identity of points is given in Table 3.

ratios for the reactions of **6a-e** with piperidine are illustrated in Figure 3. The Brønsted-type plots exhibit excellent linear correlations with a slope -0.38 for k_1 (a) and -0.64 for k_2/k_{-1} (b). A similar result has been reported for reactions which proceed through a stepwise mechanism with formation of an intermediate being the RDS (e.g., for piperidinolysis of **6a-e** in aqueous medium¹⁶ and for reactions of *O*-aryl thiono-benzoates with anionic nucleophiles such as OH⁻, CN⁻, and N₃⁻ ions).¹⁷

Figure 3(b) shows that the k_2/k_{-1} ratio increases as the leaving-group basicity decreases, i.e., $k_2/k_{-1} > 1$ when $pK_a < 19.4$, while $k_2/k_{-1} < 1$ when $pK_a > 19.4$. This is consistent with the preceding argument that the reaction of **6a-e** with piperidine proceeds through a stepwise mechanism with a change in RDS upon changing the leaving-group basicity, e.g., breakdown of T[±] is RDS when $pK_a > 19.4$ but formation of T[±] is RDS when $pK_a < 19.4$.

Conclusions

The current study has allowed us to conclude the following: (1) 4-Nitrophenyl 2-methoxybenzoate (**5**) is significantly more reactive than 4-nitrophenyl 2-methylbenzoate (**6d**), indicating that replacing the 2-MeO in the benzoyl moiety of **5** by 2-Me causes a significant decrease in reactivity. This supports our previous proposal that the aminolysis of **5** proceeds through a six-membered cyclic intermediate (i.e.,

5NH), which is highly stabilized through intramolecular H-bonding interactions. (2) The Brønsted-type plots for the reactions of **5** and **6d** are linear with $\beta_{\text{nuc}} = 0.70$ or 0.71, indicating that modification of the 2-MeO by 2-Me does not affect the reaction mechanism. A β_{nuc} value of 0.70 or 0.71 appears to be a lower limit for reactions which proceed through a stepwise mechanism with leaving-group departure being RDS. (3) The curved Brønsted-type plot observed for the reactions of **6a-e** with piperidine supports a stepwise mechanism with a change in RDS (e.g., from the k_2 step to the k_1 process as the leaving-group basicity decreases).

Experimental Section

Materials. Compounds **6a-e** were readily prepared from the reaction of 2-methylbenzoyl chloride with Y-substituted phenol in anhydrous ether in the presence of triethylamine as reported previously.¹⁶ Their purity was confirmed from melting points and ¹H NMR characteristics. MeCN was distilled over P₂O₅ and stored under nitrogen. The amines and other chemicals used in this study were of the highest quality available.

Kinetics. The kinetic study was performed using a UV-vis spectrophotometer equipped with a constant temperature circulating bath to keep the reaction temperature at 25.0 ± 0.1 °C. All the reactions were carried out under pseudo-first-order conditions in which the amine concentration was at least 20 times greater than the substrate concentration. Typically, the reaction was initiated by adding 5 μL of a 0.02 M of substrate stock solution in MeCN by a 10 μL syringe to a 10 mm UV cell containing 2.50 mL of the reaction medium and amine. The reactions were followed by monitoring the appearance of Y-substituted-phenoxide ion up to 9 to 10 half-lives.

Product Analysis. Y-Substituted-phenoxide (and/or its conjugate acid) was liberated quantitatively and identified as one of the reaction products by comparison of the UV-vis spectra obtained after completing the reactions with those of authentic samples under the same kinetic conditions.

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