Kinetic Study on Nucleophilic Substitution Reactions of 4-Nitrophenyl X-Substituted-2-Methylbenzoates with Cyclic Secondary Amines in Acetonitrile: Reaction Mechanism and Failure of Reactivity-Selectivity Principle

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A kinetic study is reported on nucleophilic substitution reactions of 4-nitrophenyl X-substituted-2-methyl-benzoates (**5a-e**) with a series of cyclic secondary amines in MeCN at 25.0 ± 0.1 °C. The Hammett plots for the aminolysis of **5a-e** are nonlinear, *e.g.*, substrates possessing an electron-donating group (EDG) in the benzoyl moiety deviate negatively from the linear line composed of substrates bearing no EDG. In contrast, the Yukawa-Tsuno plots for the same reactions exhibit excellent linear correlations with $\rho_X = 0.30$-0.59 and $r = 0.90$-1.15, indicating that the nonlinear Hammett plots are caused by stabilization of the substrates possessing an EDG through resonance interactions but are not due to a change in the rate-determining step (RDS). The Brønsted-type plots are linear with $\beta_{nuc} = 0.66$-0.82. Thus, the aminolysis of **5a-e** has been suggested to proceed through a stepwise mechanism in which departure of the leaving group occurs at the RDS. The ρ_X and β_{nuc} values for the aminolysis of **5a-e** increase as the reactivity of the substrates and amines increases, indicating that the reactivity-selectivity principle is not applicable to the current reactions.

Key Words : Aminolysis, Reaction mechanism, Hammett plot, Yukawa-Tsuno plot, Brønsted-type plot

Introduction

Nucleophilic substitution reactions of esters with amines are an important class of reactions in biological processes as well as synthetic applications.[1] Thus, numerous studies have been carried out to investigate the reaction mechanism. Aminolysis of esters has been reported to proceed through a stepwise mechanism with one or two intermediates (*e.g.*, a zwitterionic tetrahedral intermediate $T^{\pm}$ and its deprotonated form T^{-}), or *via* a concerted pathway depending on the reaction conditions (*e.g.*, the nature of electrophilic center, reaction medium, electronic nature of the substituent in the nonleaving group, basicity of the leaving group, *etc.*).[2-12]

Reactions of 4-nitrophenyl benzoate (**1a**) with a series of cyclic secondary amines have been suggested to proceed through a stepwise mechanism on the basis of a linear Brønsted-type plot with $\beta_{nuc} = 0.81$,[7] while the corresponding reactions of *O*-4-nitrophenyl thionobenzoate (**1b**) have been reported to proceed through two intermediates (*i.e.*, $T^{\pm}$ and T^{-}) since the plots of k_{obsd} *vs.* [amine] exhibit upward curvature.[8] In contrast, aminolyses of 4-nitrophenyl diphenylphosphinate (**2a**)[9] and diphenylphosphinothioate (**2b**)[10] have been proposed to proceed through a concerted mechanism on the basis of a linear Brønsted-type plot with $\beta_{nuc} = 0.38$-0.53. This demonstrates convincingly that the nature of the electrophilic center (*e.g.*, C=O, C=S, P=O, P=S) is an important factor which governs the reaction mechanism.
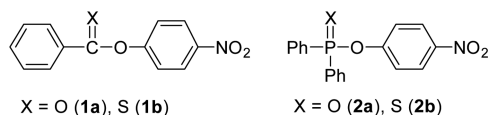
The nature of reaction medium has also been reported to influence the reaction mechanism.[11a] We have reported that the Brønsted-type plot for the reactions of 2,4-dinitrophenyl benzoate, a derivative of **1a**, with a series of cyclic secondary amines curves downward (*i.e.*, β_{nuc} decreases from 0.74 to 0.34 as the amine basicity increases) in 80 mol % H_2O/20 mol % DMSO[11a] but is linear with $\beta_{nuc} = 0.40$ in MeCN.[11b] Thus, the reactions have been suggested to proceed through a stepwise mechanism with a change in the RDS in the aqueous medium but *via* a concerted pathway in the aprotic solvent.[11]

The electronic nature of the substituent X in the nonleaving group has been reported to control the reaction mechanism in aminolysis of 4-pyridyl X-substituted-benzoates (**3**) in MeCN.[12] We have shown that the plots of k_{obsd} *vs.* [amine] curve upward for the reactions of substrates possessing a strong electron-withdrawing group (EWG) in the benzoyl moiety of **3** but are linear for the reactions of those bearing a weak EWG or an EDG.[12] Thus, the reactions have been concluded to proceed through a stepwise mechanism with two intermediates (*i.e.*, $T^{\pm}$ and T^{-}) when the substrate possesses a strong EWG in the benzoyl moiety.[12] However, the deprotonation process from $T^{\pm}$ to yield T^{-} is absent when the substrate bears a weakly EWG or an electron-donating group (EDG).[12]

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

3   **4**
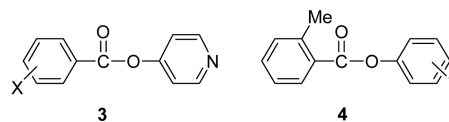
In our recent report, nucleophilic substitution reactions of
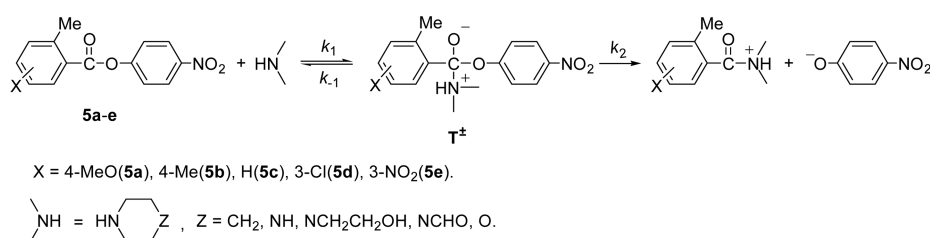
Scheme 1

Y-substituted-phenyl 2-methylbenzoates (**4**) with piperidine in MeCN proceed through a stepwise mechanism with a change in the RDS on the basis of the kinetic result that the Brønsted-type plot exhibits downward curvature (*e.g.*, β_{lg} decreases from –1.05 to –0.41 as the leaving-group basicity decreases).[13] Our study has now been extended to the reactions of 4-nitrophenyl X-substituted-2-methylbenzoates (**5a-e**) with a series of cyclic secondary amines in MeCN (Scheme 1) to investigate the effect of substituent X in the nonleaving group on the reaction mechanism.

Results and Discussion

The kinetic study was performed under pseudo-first-order conditions in which the amine concentration was kept at least 20 times in excess of the substrate concentration. The reactions obeyed first-order kinetics in all cases and the pseudo-first-order rate constants (k_{obsd}) were calculated from the equation, $\ln (A_{\infty} - A_{\text{t}}) = -k_{\text{obsd}}t + C$. The plots of k_{obsd} *vs.* amine concentrations are linear and pass through the origin, indicating that general-base catalysis by a second amine molecule is absent. Accordingly, the second-order rate constants (k_{N}) were calculated from the slope of the linear plots. The k_{N} values calculated in this way are summarized in Table 1. The uncertainty in the k_{N} values is estimated to be less than ± 3% based on the replicate runs.

Effect of Substituent X on Reactivity and Reaction Mechanism. As shown in Table 1, the k_{N} values increase as the substituent X in the benzoyl moiety changes from an EDG to an EWG, *e.g.*, the k_{N} value for the reactions with piperidine increases from 2.88×10^{-2} M^{-1}s^{-1} to 7.79×10^{-2} and 2.07×10^{-1} M^{-1}s^{-1} as the substituent X changes from 4-MeO to H and 3-NO$_2$, in turn. Similar results are demonstrated for the corresponding reactions with the other amines. However, the dependence of the k_{N} value on the electronic

nature of the substituent X is not significant for the reactions with weakly basic amine, *e.g.*, the k_{N} for the reaction with morpholine increases from 1.02×10^{-3} M^{-1}s^{-1} to 2.08×10^{-3} and 3.06×10^{-3} M^{-1}s^{-1}, in turn.

The effect of the substituent X on the k_{N} value is illustrated in Figure 1. The Hammett plots are not linear for the reactions of **5a-e** with all the amines studied. It is seen that substrates possessing an EDG in the benzoyl moiety (*i.e.*, **5a** and **5b**) deviate negatively from the linear line composed of the substrates bearing no EDG. It is also noted that such deviation is more significant for the substrate possessing a stronger EDG (*i.e.*, **5a**) than that bearing a weaker EDG (*i.e.*, **5b**).
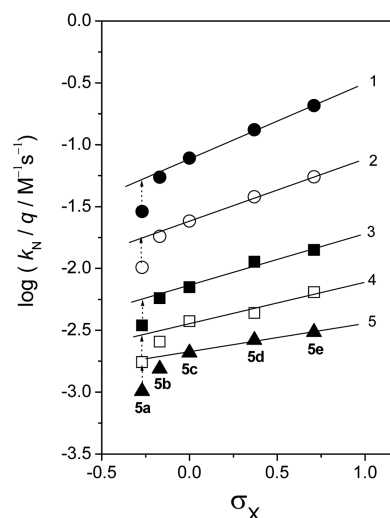
Nonlinear Hammett plots have been interpreted as a

Figure 1. Hammett plots for the reactions of 4-nitrophenyl X-substituted-2-methylbenzoates (**5a-e**) with cyclic secondary amines in MeCN at 25.0 ± 0.1. The identity of points is given in Table 1.

Table 1. Summary of Second-Order Rate Constants for the Reactions of 4-Nitrophenyl X-Substituted-2-Methylbenzoates (**5a-e**) with Cyclic Secondary Amines in MeCN at 25.0 ± 0.1 ℃

	amines	$pK_a{}^a$	$10^2 k_{\text{N}}$/M^{-1}s^{-1}				
			5a	**5b**	**5c**	**5d**	**5e**
1	piperidine	18.8	2.88	5.47	7.79	13.2	20.7
2	piperazine	18.5	2.04	3.63	4.83	7.60	11.0
3	1-(2-hydroxyethyl)piperazine	17.6	0.346	0.576	0.705	1.13	1.41
4	1-formylpiperazine	17.0	0.175	0.256	0.375	0.436	0.643
5	morpholine	16.6	0.102	0.154	0.208	0.263	0.306

*^{a}The pK_a data for the conjugate acids of amines in MeCN were taken from ref. 14. X = 4-MeO (**5a**), 4-Me (**5b**), H (**5c**), 3-Cl (**5d**), 3-NO$_2$ (**5e**).*

change in the reaction mechanism or RDS depending on the type of curvature.[15] Concave upward curvature has often been reported for nucleophilic substitution reactions of benzylic systems which proceed through an S_N1 mechanism for substrates possessing an EDG (*i.e.*, a negative ρ_X) but *via* an S_N2 mechanism for substrates bearing an EWG (*i.e.*, a positive ρ_X).[15] In contrast, convex downward curvature has been interpreted as a change in the RDS on changing the substituents from EDGs to EWGs.[15] Thus, one might suggest that the nonlinear Hammett plots obtained from the reactions of **5a-e** indicate a change in the RDS of a stepwise mechanism, *i.e.*, from formation of $T^\pm$ (*i.e.*, the k_1 step) to its breakdown (*i.e.*, the k_2 step) as the substituent X changes from EDGs to EWGs. This idea appears to be reasonable since an EDG in the benzoyl moiety of the substrate would retard the rate of nucleophilic attack (*i.e.*, a decrease in k_1) but accelerate departure of the leaving 4-nitrophenoxide (*i.e.*, an increase in k_2) while an EWG would increase k_1 but decrease k_2.

However, we propose that the nonlinear Hammett plots are not due to a change in the RDS. Because the RDS is not governed by the magnitude of k_1 and k_2 values but should be determined by the k_2/k_{-1} ratio (*e.g.*, RDS = the k_1 step when $k_2/k_{-1} > 1$ while RDS = the k_2 step when $k_2/k_{-1} < 1$). We propose that the nonlinear Hammett plots shown in Figure 1 are caused by stabilization of substrates possessing an EDG (*e.g.* **5a** and **5b**) through resonance interactions between the electron-donating substituent X and the C=O bond as illustrated by the resonance structures I ↔ II. This is because such resonance interactions could stabilize the GS of the substrate and cause a decrease in the reactivity (*i.e.*, negative deviation from the Hammett plots).
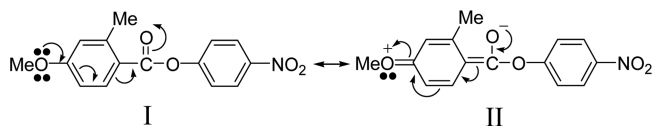
To examine the validity of the above argument, the Yukawa-Tsuno Eq. (1) has been employed. Eq. (1) was originally derived to account for the kinetic results obtained from solvolysis of benzylic systems in which a positive charge develops partially at the reaction center.[16] The r value in eq. (1) represents the resonance demand of the reaction center or the extent of resonance contribution, while the term $(\sigma_X^+ - \sigma_X^o)$ is the resonance substituent constant that measures the capacity for π-delocalization of the π-electron donor substituent.[16,17]

$$\log k^X/k^H = \rho_X[\sigma_X^o + r(\sigma_X^+ - \sigma_X^o)] \qquad (1)$$

As shown in Figure 2, Yukawa-Tsuno plots for the reactions of **5a-e** exhibit excellent linear correlations with the ρ_X = 0.31-0.60 and r = 0.90-1.15. The linear Yukawa-Tsuno plots clearly indicate that the reactions proceed without changing the RDS (or reaction mechanism) on changing the substituent X in the benzoyl moiety. Furthermore, the large r values suggest that the resonance contribution is significant
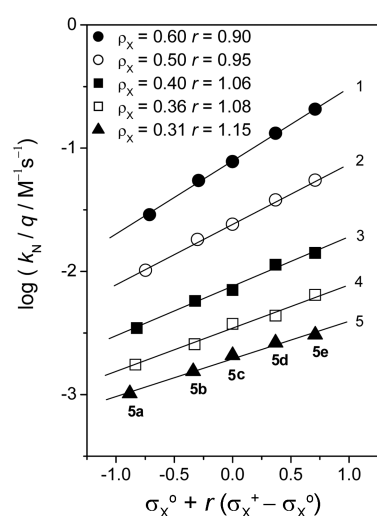

Figure 2. Yukawa-Tsuno plots for the reactions of 4-nitrophenyl X-substituted-2-methylbenzoates (**5a-e**) with cyclic secondary amines in MeCN at 25.0 ± 0.1. The identity of points is given in Table 1.

in the current reactions. Thus, one can conclude that the nonlinear Hammett plots shown in Figure 1 are caused by stabilization of substrates possessing an EDG through resonance interactions.

Effect of Amine Basicity on Reactivity and Reaction Mechanism. As shown in Table 1, the k_N values for the reactions of **5a-e** decrease as the amine basicity decreases, *e.g.*, the k_N value for the reactions of **5a** decreases from 2.88 × 10^{-2} M^{-1}s^{-1} to 3.46 × 10^{-3} and 1.02 × 10^{-3} M^{-1}s^{-1} as the pK_a of the conjugate acid of the amine decreases from 18.8 to 17.6 and 16.6, in turn. Similar results are shown for the reactions of **5b-e** although the k_N value for a given substrate increases less significantly as the substituent X changes from an EWG to a stronger EDG as mentioned in the preceding
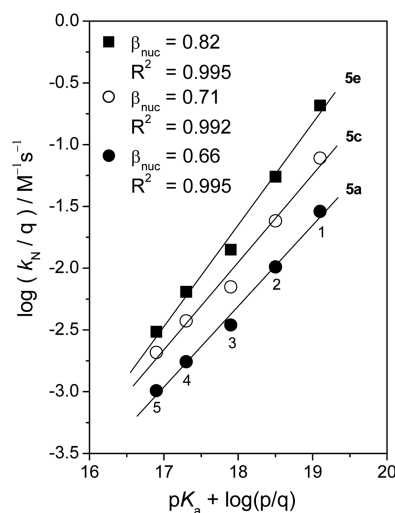

Figure 3. Brønsted-type plots for reactions of 4-nitrophenyl X-substituted-2-methylbenzoates (**5a**, **5c** and **5e**) with a series of cyclic secondary amines in MeCN at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

section.

The effect of amine basicity on reactivity is illustrated in Figure 3. The statistically corrected Brønsted-type plots using *p* and *q* (*e.g.*, *p* = 2 and *q* = 1 except *q* = 2 for piperazine)[18] are linear with a β_{nuc} value of 0.66, 0.71 and 0.82 for the reactions of **5a**, **5c** and **5e**, in turn. Similarly linear plots are obtained for the reactions of **5b** and **5d** with a β_{nuc} value of 0.71 and 0.78, respectively (Figures not shown). It is noted that the β_{nuc} value becomes smaller for the reactions of substrates possessing a stronger EDG in the benzoyl moiety (or the reactivity of the substrate decreases).

The β_{nuc} value of 0.71-0.82 obtained for the reactions of **5b-e** is typical of reactions reported previously to proceed through a stepwise mechanism in which departure of the leaving group occurs in the RDS.[2,7-12] In contrast, the β_{nuc} value of 0.66 obtained for the reactions of **5a** appears to be slightly smaller than the lower limit for reactions reported to proceed through a stepwise mechanism.[2,7-12] Nevertheless, we propose that the reactions of **5a** proceed also through a stepwise mechanism in which departure of the leaving group (*i.e.*, 4-nitrophenoxide) occurs at the RDS. Because, as discussed in the preceding section, the electronic nature of the substituent X in the benzoyl moiety of **5a-e** does not affect the reaction mechanism including the RDS. Thus, one can suggest that the magnitude of β_{nuc} value cannot be an absolute measure to deducing the reaction mechanism.

Evidence for Failure of Reactivity-Selectivity Principle. It is well known that the magnitude of ρ_X and β_{nuc} values represents a sensitivity (or selectivity) parameter for a series of reactions. The ρ_X and β_{nuc} values have generally been reported to be larger for the less reactive reactions than for the more reactive ones, which is in accord with the reactivity-selectivity principle (RSP).[19,20] However, the ρ_X value shown in Figure 4 (**a**) increases linearly with increasing the basicity (or reactivity) of the incoming amine. Similarly, the β_{nuc} value illustrated in Figure 4 (**b**) also increases linearly with increasing the σ_X constant of the substituent X (or with increasing reactivity of the substrate). This is quiet an unexpected result from the RSP.
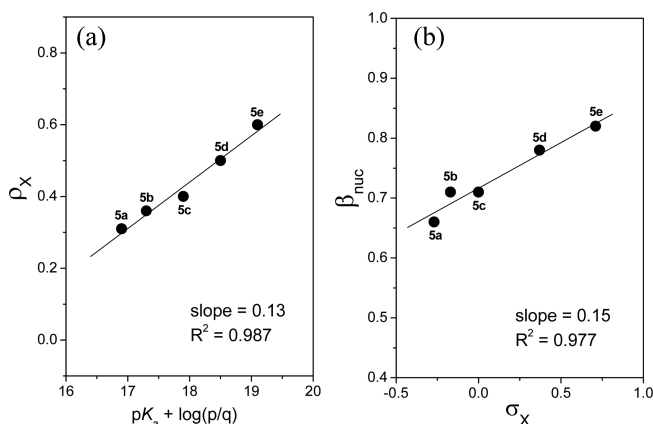

Figure 4. Correlations of ρ_X with pK_a of the conjugate acid of amines (**a**) and β_{nuc} with σ_X of the substituent X (**b**) for the aminolysis of 4-nitrophenyl X-substituted-2-methylbenzoates (**5a-e**) in MeCN at 25.0 ± 0.1 ℃.

The magnitude of ρ_X values represents a relative degree of the rehybridization of the C=O bond at the TS (or the charge transfer from the N atom of the attacking amine to the carbonyl carbon of substrates **5a-e**). It is apparent that the charge transfer from the amine to the substrates would increase with increasing the amine basicity. Thus, one might expect that the ρ_X value increases as the basicity of the attacking amine increases. In fact, Figure 4(a) shows a good linear correlation between the ρ_X value and the pK_a of the conjugate acid of the amine with a slope of 0.13. This is clearly against the RSP.

It is also known that the magnitude of the β_{nuc} value represents a relative degree of bond formation between the incoming amine and the substrate (or a formal charge of the N atom of the attacking amine at the TS). Accordingly, one might expect that the degree of bond formation would increase with increasing the electrophilicity of the C=O bond of the substrates **5a-e**. It is clear that the electrophilicity of the reaction center would increase on changing the substituent X from an EDG to an EWG. Thus, one might expect that the β_{nuc} value, representing a degree of bond formation or a formal charge, is dependent on the electronic nature of the substituent X. In fact, Figure 4(a) shows a good linear correlation between the β_{nuc} value and the σ_X constant of the substituent X. This is also against the RSP.

Conclusions

The current study has allowed us to conclude the following: (1) The Hammett plots for the aminolysis of **5a-e** are nonlinear, while the Yukawa-Tsuno plots exhibit excellent linear correlations with ρ_X = 0.30-0.59 and *r* = 0.90-1.15, indicating that the nonlinear Hammett plots are caused by stabilization of the substrates possessing an EDG and that the electronic nature of the substiuent X does not affect the RDS. (2) The Brønsted-type plots for the reactions of **5a-e** are linear with β_{nuc} = 0.66-0.82. The reactions are suggested to proceed through a stepwise mechanism in which departure of the leaving group occurs at the RDS. (3) The ρ_X and β_{nuc} values for the aminolysis of **5a-e** increase as the reactivity of the reactants (*i.e.*, the substrates and amines) increases, indicating that the RSP is not applicable to the current reactions.

Experimental Section

Materials. Compounds **5a-e** were readily prepared from the reaction of the respective X-substituted-2-metylbenzoyl chloride with 4-nitrophenol in anhydrous ether in the presence of triethylamine as reported previously.[21] Their purity was confirmed from melting points and ^{1}H NMR characteristics. MeCN was distilled over P_2O_5 and stored under nitrogen. The amines and other chemicals used 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 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 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 4-nitrophenoxide up to 9 halflives.

Product Analysis. 4-Nitrophenoxide (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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