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Kinetic Study on Aminolysis of 4-Chloro-2-Nitrophenyl X-Substituted-Benzoates in Acetonitrile and in 80 mol % H_2O/20 mol % DMSO: Effect of Medium on Reactivity and Reaction Mechanism

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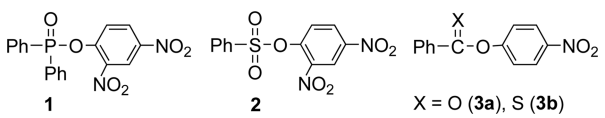
A kinetic study on aminolysis of 4-chloro-2-nitrophenyl X-substituted-benzoates (**6a-i**) in MeCN is reported. The Hammett plot for the reactions of **6a-i** with piperidine consists of two intersecting straight lines, while the Yukawa-Tsuno plot exhibits an excellent linear correlation with $\rho_X = 1.03$ and $r = 0.78$. The nonlinear Hammett plot is not due to a change in rate-determining step (RDS) but is caused by the resonance stabilization of substrates possessing an electron-donating group in the benzoyl moiety. The Brønsted-type plot for the reactions of 4-chloro-2-nitrophenyl benzoate (**6e**) with a series of cyclic secondary amines is linear with $\beta_{nuc} = 0.69$, an upper limit for reactions reported to proceed through a concerted mechanism. The aminolysis of **6e** in aqueous medium has previously been reported to proceed through a stepwise mechanism with a change in RDS on the basis of a curved Brønsted-type plot. It has been concluded that instability of the zwitterionic tetrahedral intermediate ($T^{\pm}$) in MeCN forces the reaction to proceed through a concerted mechanism. This is further supported by the kinetic result that the amines used in this study are less reactive in MeCN than in H_2O, although they are more basic in MeCN over 7 pK_a units.

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

Introduction

Nucleophilic displacement reactions of esters have extensively been investigated due to their importance in biological processes as well as in synthetic applications.[1] Experimental studies based on linear free energy relationships (LFERs) have shown that aminolysis of esters proceeds through a concerted mechanism or *via* a stepwise pathway depending on reaction conditions (*e.g.*, the nature of the electrophilic center, reaction medium, structure of esters, *etc.*).[2-8]

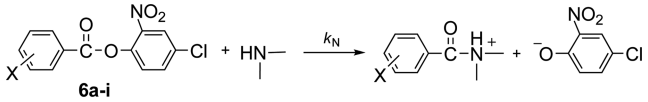
Aminolysis of 2,4-dinitrophenyl diphenylphosphinate (**1**) has been reported to proceed through a concerted mechanism on the basis of a linear Brønsted-type plot with $\beta_{nuc} = 0.38$,[2] while the corresponding reactions of 2,4-dinitrophenyl benzenesulfonate (**2**) have been concluded to proceed *via* a stepwise mechanism with a change in RDS on the basis of a curved Brønsted-type plot with $\beta_2 = 0.86$ and $\beta_1 = 0.38$.[3] Besides, aminolysis of 4-nitrophenyl benzoate (**3a**) has been suggested to proceed through a stepwise mechanism with a zwitterionic tetrahedral intermediate ($T^{\pm}$),[4] while the corresponding reaction of *O*-4-nitrophenyl thionobenzoate (**3b**) has been shown to proceed through a stepwise pathway with two intermediates ($T^{\pm}$ and its deprotonated form T^{-}).[5] These results demonstrate that the nature of the electrophilic centers (*e.g*, P=O, SO_2, C=O and C=S) governs the reaction mechanism.



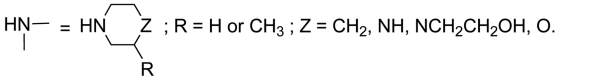
1 **2**

The nature of solvents has also been suggested to be an important factor which affects the reaction mechanism.[6] The reactions of 2,4-dinitrophenyl benzoate with a series of cyclic secondary amines in H_2O containing 20 mol % DMSO have been reported to proceed through a stepwise mechanism with a change in RDS on the basis of a curved Brønsted-type plot.[6a] In contrast, the corresponding reactions carried out in MeCN have been concluded to proceed through a concerted mechanism on the basis of a linear Brønsted-type plot with $\beta_{nuc} = 0.40$.[6b] One might expect that a zwitterionic $T^{\pm}$ can be stabilized in H_2O through H-bonding interactions. In contrast, the ionic species cannot be stabilized in MeCN due to the electronic repulsion between the negative C-O^{-} moiety of $T^{\pm}$ and the negative dipole end of MeCN. Thus, the difference in the stability of $T^{\pm}$ in the two solvents has been proposed to be responsible for the contrasting reaction mechanisms.[6b]

Theoretical studies based on rapid advances in computational methods have also reported that the reaction medium is a crucial factor which affects the reaction mechanism.[9-11] The existence of $T^{\pm}$ in the gas phase or in aprotic solvents has often been questioned, *e.g.*, Ilieva *et al*. have failed to identify $T^{\pm}$ for the reaction of methyl formate with ammonia,[9] while Sung *et al*. have reported that at least five explicit water molecules are required to stabilize $T^{\pm}$ in the reaction of phenyl acetate with ammonia.[11] However, we have recently

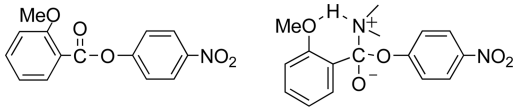


X = 3,5-NO_2 (**6a**), 4-NO_2 (**6b**), 4-CN (**6c**), 3-Cl (**6d**), H (**6e**), 3-CH_3 (**6f**), 4-CH_3 (**6g**), 4-OCH_3 (**6h**), 4-$N(CH_3)_2$ (**6i**).



Scheme 1

reported that aminolysis of 4-nitrophenyl 2-methoxybenzoate (**4**) proceeds through a stepwise mechanism with $T^{\pm}$ even in MeCN.[12a] It has been proposed that the zwitterionic $T^{\pm}$ gains stability through the H-bonding interactions as modeled by **5** even in the aprotic solvent.[12a]



Our study has now been extended to the reactions of 4-chloro-2-nitrophenyl X-substituted-benzoates (**6a-i**) with a series of cyclic secondary amines in MeCN to obtain further information on the reaction mechanism. The kinetic results have been compared with those reported recently for the corresponding reactions carried out in H_2O containing 20 mol % DMSO[13] to investigate the effect of medium on reactivity and 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. All the reactions in this study obeyed first-order kinetics and the pseudo-first-order rate constants (k_{obsd}) were calculated from the equation, $\ln (A_\infty - A_t) = -k_{obsd}t + C$. The plots of k_{obsd} *vs.* [amine] 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 uncertainty in the k_N values is estimated to be less than ± 3% based on the replicate runs. The k_N values calculated in this way are summarized in Table 1 for the reactions of **6a-i** with piperidine and in Table 2 for the reactions of 4-chloro-2-nitrophenyl benzoate (**6e**) with a series of cyclic secondary amines together with the k_N values reported previously for the corresponding reactions carried out in 80 mol % H_2O/20 mol % DMSO[13] for comparison.

Effect of Substituent X on Reactivity and Reaction Mechanism. The k_N values for the reactions of 4-chloro-2-nitrophenyl X-substituted-benzoates (**6a-i**) with piperidne have been measured in MeCN to investigate the effect of the substituent X on the reactivity and reaction mechanism. As shown in Table 1, k_N decreases as the substituent X changes from a strong electron-withdrawing group (EWG) to a strong electron-donating group (EDG), *e.g.*, it decreases from 108 $M^{-1}s^{-1}$ to 3.52 and 0.131 $M^{-1}s^{-1}$ as the substituent X changes from 3,5-$(NO_2)_2$ to H and 4-$N(CH_3)_2$, in turn.

Table 1. Summary of Second-Order Rate Constants (k_N) for the Reactions of 4-Chloro-2-Nitrophenyl X-Substituted-Benzoates (**6a-i**) with Piperidine in MeCN at 25.0 ± 0.1 °C

	X	$k_N/M^{-1}s^{-1}$
6a	3,5-$(NO_2)_2$	108
6b	4-NO_2	24.8
6c	4-CN	19.3
6d	3-Cl	12.0
6e	H	3.52
6f	3-CH_3	2.97
6g	4-CH_3	2.03
6h	4-OCH_3	0.878
6i	4-$N(CH_3)_2$	0.131

The effect of the substituent X on the reactivity of **6a-i** is demonstrated in Figure 1. The Hammett plot consists of two intersecting straight lines, *e.g.*, the slope is 1.01 for the reactions of substrates possessing an EWG and is 1.76 for those of substrates bearing an EDG. It is apparent that an EWG in the benzoyl moiety of **6a-i** would decrease the electron density of the carbonyl carbon. Consequently, an EWG in the benzoyl moiety of **6a-i** would accelerate the rate of nucleophilic attack to form $T^{\pm}$ (*i.e.*, an increase in k_1) but would retard the rate of leaving-group departure from $T^{\pm}$ (*i.e.*, a decrease in k_2). On the contrary, an EDG in the benzoyl moiety of **6a-i** would decrease k_1 but would increase k_2 by increasing the electron density of the reaction center. Thus, one might suggest that the piperidinolysis of **6a-i** proceeds through a stepwise mechanism with a change in RDS on changing the electronic nature of the substituent X on the basis of the nonlinear Hammett plot.

However, we propose that the nonlinear Hammett plot is not caused by a change in RDS. Because RDS is not determined by the magnitude of k_1 and k_2. Furthermore, k_1 and k_2 cannot be compared directly since the former is a second-

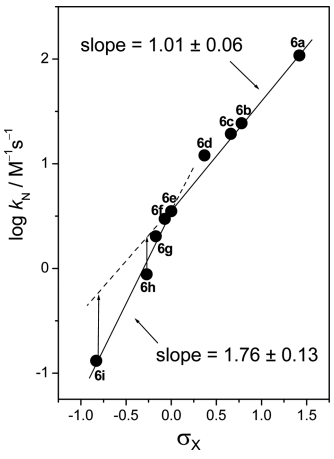
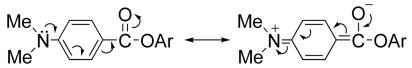


Figure 1. Hammett plot for the reactions of 4-chloro-2-nitrophenyl X-substituted-benzoates (**6a-i**) with piperidine in MeCN at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

order rate constant while the latter is a first-order rate constant. The RDS should be determined by the k_2/k_{-1} ratio (*i.e.*, RDS = the k_1 step when $k_2/k_{-1} > 1$ but RDS = the k_2 step when $k_2/k_{-1} < 1$).

A careful examination of the nonlinear Hammett plot shown in Figure 1 reveals that the substrates possessing an EDG (*e.g.*, **6g**, **6h** and **6i**) deviate negatively from the linear line composed of the substrates bearing an EWG. Besides, the deviation is more significant as the substituent X becomes a stronger EDG. An EDG in the benzoyl moiety could stabilize the ground state (GS) of the substrate through resonance interactions as illustrated by resonance structures I and II. Since such resonance interactions could decrease their reactivity, we propose that the nonlinear Hammett plot is caused by the resonance stabilization of the substrates possessing an EDG in the benzoyl moiety.



I II

To examine the above argument, the Yukawa-Tsuno equation (1) has been employed. 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.[14,15] Eq. (1) was originally derived to rationalize the kinetic results obtained from solvolysis of benzylic systems in which a positive charge develops partially in the transition state (TS).[14] However, we have recently shown that Eq. (1) is also highly effective in elucidation of ambiguities in the reaction mechanism, *e.g.*, for aminolysis of esters[12,13] as well as for nucleophilic substitution reactions of various esters with anionic nucleophiles (*e.g.*, OH^-, CN^-, N_3^- and $CH_3CH_2O^-$).[16]

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

Thus, a Yukawa-Tsuno plot has been constructed. As shown in Figure 2, the Yukawa-Tsuno plot results in an excellent linear correlation with $\rho_X = 1.03$ and $r = 0.78$. The *r* value of 0.78 indicates that the resonance contribution is significant. Thus, one can conclude that the nonlinear Hammett plot for the reactions of **6a-i** is not caused by a change in RDS but is due to stabilization of the substrate possessing an EDG through resonance interactions. Furthermore, the current study demonstrates that deduction of the reaction mechanism based just on a linear or nonlinear Hammett plot can be misleading.

The ρ_X value of 1.03 for the reactions of **6a-i** is much larger than that reported for reactions proceeding through a stepwise mechanism in which departure of the leaving-group occurs in RDS, *e.g.*, $\rho_X = 0.5 \pm 0.1$ for the reactions of 4-nitrophenyl X-substituted-2-methylbenzoates[17] and $\rho_X = 0.41$ for those of 4-pyridyl X-substituted-benzoates in MeCN.[12b] In contrast, the ρ_X value of 1.03 in this study is similar to those of 1.30 and 0.98 reported for the reactions of 2,4-dinitrohenyl X-substituted-benzoates with piperidine

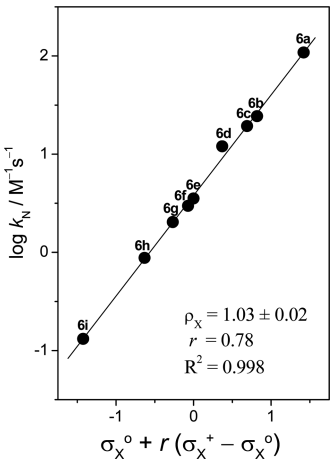


Figure 2. Yukawa-Tsuno plot for the reactions of 4-chloro-2-nitrophenyl X-substituted-benzoates (**6a-i**) with piperidine in MeCN at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

and morpholine in MeCN, respectively, which have previously been proposed to proceed through a concerted mechanism.[6b] Thus, one might suggest that the current reactions of **6a-i** with piperidine proceed through a concerted mechanism on the basis of the ρ_X value. However, the ρ_X value alone is not sufficient to deduce the reaction mechanism.

Effect of Medium on Reactivity and Reaction Mechanism. The k_N values for the reactions of 4-chloro-2-nitrophenyl benzoate (**6e**) with a series of cyclic secondary amines in MeCN have been measured to obtain further information on the reaction mechanism by comparing them with those reported previously for the corresponding reactions carried out in H_2O containing 20 mol % DMSO.[13] As shown in Table 2, the k_N value for the reactions performed in MeCN decreases as the amine basicity decreases, *e.g.*, it decreases from 3.52 $M^{-1}s^{-1}$ to 0.400 and 0.111 $M^{-1}s^{-1}$ as the pK_a of the conjugate acid of amines decreases from 18.8 to 17.6 and 16.6, in turn. A similar result is shown for the reactions carried out in H_2O containing 20 mol % DMSO. It is noted that the amines are less reactive in MeCN than in the aqueous medium, although the amines used in this study

Table 2. Summary of Second-Order Rate Constants (k_N) for the Reactions of 4-Chloro-2-Nitrophenyl Benzoate (**6e**) with Cyclic Secondary Amines in MeCN and in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C[a]

amines	MeCN		80 mol % H_2O	
	pK_a[b]	$k_N/M^{-1}s^{-1}$	pK_a	$k_N/M^{-1}s^{-1}$
1 piperidine	18.8	3.52	11.02	5.91
2 3-methylpiperidine	18.6	2.50	10.80	5.17
3 piperazine	18.5	2.35	9.85	2.16
4 1-(2-hydroxyethyl)piperazine	17.6	0.400	9.38	0.579
5 morpholine	16.6	0.111	8.65	0.305
6 piperazinium ion	–	–	5.95	0.00215

[a]The pK_a and kinetic data for the reactions in 80 mol % H_2O/20 mol % DMSO were taken from ref. 13. [b]The pK_a value in MeCN were taken from ref. 12.

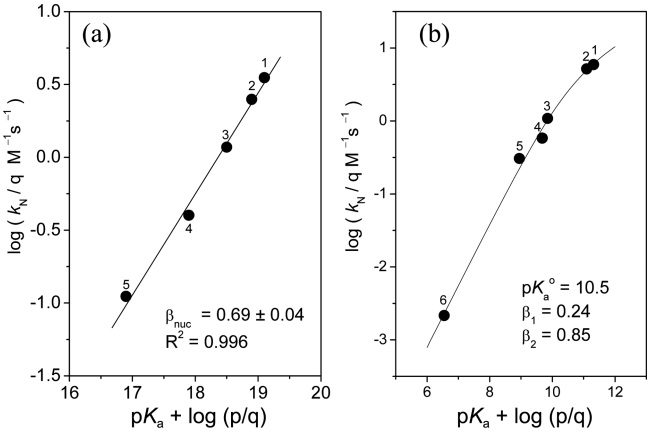


Figure 3. Brønsted-type plots for the reactions of 4-chloro-2-nitrophenyl benzoate (**6e**) with cyclic secondary amines in MeCN (a) and in 80 mol % H_2O/20 mol % DMSO (b) at 25.0 ± 0.1 °C. The identity of points is given in Table 2.

are more basic in MeCN over 7 pK_a units. This demonstrates convincingly that the reactivity of amines is not governed solely by the amine basicity.

The effect of amine basicity on reactivity is illustrated in Figure 3. The Brønsted-type plot for the reactions in MeCN is linear with β_{nuc} = 0.69 when the k_N and pK_a values are statistically corrected by p and q (*e.g.*, p = 2 and q = 1 except q = 2 for piperazine).[18] In contrast, the plot for the corresponding reactions carried out in the aqueous medium curves downward with β_2 = 0.85, β_1 = 0.24 and pK_a^o = 10.5. The nonlinear Brønsted-type plot for the reactions carried out in the aqueous medium has been reported as evidence for a stepwise mechanism with a change in RDS, *e.g.*, the RDS changes from the breakdown of $T^{\pm}$ to its formation as the pK_a of the amine exceeds 10.5.[13]

The β_{nuc} value of 0.69 is an upper limit for reactions reported previously to proceed through a concerted mechanism. Thus, one might suggest that the aminolysis of **6e** in MeCN proceeds through a concerted mechanism with large bond-formation between the amine nucleophile and the carbonyl carbon in the TS on the basis of the β_{nuc} value of 0.69. This idea is consistent with the preceding proposal that the reactions of **6a-i** with piperidine in MeCN proceed through a concerted mechanism on the basis of a large ρ_X value.

It is apparent that the nature of the reaction medium affects the reaction mechanism. One might expect that the $T^{\pm}$ for the reactions performed in the aqueous medium would be stable enough for a stepwise mechanism through strong H-bonding interactions with H_2O molecules. However, such H-bonding interactions are not possible in MeCN. Besides, it is well known that MeCN is a poor solvent for ionic species.[19] Accordingly, the $T^{\pm}$ for the reactions carried out in the aprotic solvent would be highly unstable. This idea accounts for the kinetic result that amines are less reactive in MeCN than in H_2O containing 20 mol % DMSO although they are more basic in MeCN over 7 pK_a units. Thus, one can conclude that instability of $T^{\pm}$ in MeCN forces the reaction to proceed through a concerted mechanism.

Conclusions

(1) The Hammett plot for the reactions of **6a-i** with piperidine consists of two intersecting straight lines while the Yukawa-Tsuno plot exhibits an excellent linear correlation, indicating that the nonlinear Hammett plot is not due to a change in RDS but is caused by the resonance stabilization of substrates possessing an EDG in the benzoyl moiety. (2) The ρ_X value for the reactions of **6a-i** is much larger than that reported for reactions proceeding through a stepwise mechanism but is similar to that reported for reactions proceeding *via* a concerted pathway. (3) The amines used in this study are less reactive in MeCN than in H_2O containing 20 mol % DMSO, although the amines are over 7 pK_a units more basic in MeCN, indicating that the reactivity of amines is not governed solely by the basicity of amines. (4) The Brønsted-type plot for the aminolysis of **6e** in MeCN is linear with β_{nuc} = 0.69, while the plot for the corresponding reactions in the aqueous medium curves downward. (5) The aminolysis of **6a-i** in MeCN proceeds through a concerted mechanism. Instability of $T^{\pm}$ in MeCN forces the reaction to proceed through a concerted mechanism.

Experimental Section

Materials. Compounds **6a-i** were readily prepared from the reaction of the respective X-substituted-benzoyl chloride with 4-chloro-2-nitrophenol in anhydrous ether in the presence of triethylamine as reported previously.[13] The crude products were purified by column chromatography. The purity of substrates **6a-i** 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 for slow reactions (*e.g.*, $t_{1/2}$ > 10 s) or a stopped-flow spectrophotometer for fast reactions (*e.g.*, $t_{1/2} \leq$ 10 s) 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-chloro-2-nitrophenoxide up to 9 half-lives.

Product Analysis. 4-Cloro-2-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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