Kinetic Study on Aminolysis of Aryl X-Substituted-Cinnamates in Acetonitrile: Differential Medium Effect Determines Reactivity and Reaction Mechanism[1]

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[1]This article is dedicated to Prof. Emeritus Erwin Buncel, Queen's University, our teacher and mentor in the exploration of physical organic chemistry.

Abstract

A kinetic study on nucleophilic substitution reactions of 2,4-dinitrophenyl X-substituted-cinnamates (**1a-1f**) and Y-substituted-phenyl cinnamates (**2a-2g**) with a series of alicyclic secondary amines in MeCN at 25.0 ± 0.1 °C is reported. The Brønsted-type plots for the reactions of **1a-1f** are linear with β_{nuc} = 0.47 ~ 0.50, indicating that the bond formation between the amine nucleophile and the electrophilic center is advanced slightly in the transition state (TS). The Brønsted-type plot for the reactions of **2a-2g** with piperidine is also linear with β_{lg} = –0.66, a typical β_{lg} value for reactions reported previously to proceed through a concerted mechanism. Furthermore, the Hammett plot correlated with σ^- constants results in much better linearity than that correlated with σ^o constants, implying that expulsion of the leaving-group is advanced in the rate-determining step (RDS). Thus, the reactions are concluded to proceed through a concerted mechanism. The Hammett plots for the reactions of **1a-f** consist of two intersecting straight lines, while the corresponding Yukawa-Tsuno plots exhibit excellent linear correlations with ρ_X = 0.62 ~ 0.71 and r = 0.65 ~ 0.68. Apparently, the nonlinear Hammett plots are not due to a change in the reaction mechanism (or the RDS) but are caused by stabilization of the substrate possessing an electron-donating group (EDG) in the cinnamoyl moiety through resonance interactions between the EDG and the C=O bond of the substrate. Medium effects on reactivity and reaction mechanism are also discussed.

Keywords: Aminolysis, Brønsted-type plot, Yukawa-Tsuno plot, Concerted mechanism, Differential medium effect

Introduction

Aminolysis of esters has been reported to proceed either through a concerted mechanism or via a stepwise pathway with one or two intermediates (i.e., a zwitterionic tetrahedral intermediate $T^{\pm}$ and its deprotonated form T^{-}) as shown in Scheme 1.[1-10] Factors suggested to affect the reaction mechanism include: nature of the electrophilic center (P=O, P=S, C=O and C=S), basicity of the leaving group and the incoming amine, electronic nature of the substituent in the nonleaving group, type of reaction medium (protic vs. aprotic solvents), etc.[1-10]

We have reported that aminolyses of 2,4-dinitrophenyl diphenylphosphinate (a P=O centered electrophile) and *O*-2,4-dinitrophenyl diphenylphosphinothioate (a P=S centered electrophile) proceed through a concerted mechanism on the basis of a linear Brønsted-type plot with $\beta_{nuc} = 0.5 \pm 0.1$.[5] In contrast, aminolyses of 2,4-dinitrophenyl benzoate and 2,4-dinitrophenyl phenyl carbonate (C=O centered electrophiles) have been suggested to proceed via a stepwise mechanism with a change in the rate-determining step (RDS) as the incoming amine becomes more basic than the leaving group by 4 ~ 5 pK_a units,[6,7] while the corresponding reactions of *O*-2,4-dinitrophenyl thionobenzoate and *O*-2,4-dinitrophenyl phenyl thionocarbonate (C=S centered electrophiles) proceed through a stepwise mechanism, in which breakdown of $T^{\pm}$ to the products occurs via catalytic and uncatalytic routes competitively.[7,8]

The nature of the reaction medium (e.g., protic or aprotic solvent) has also been reported to govern the reaction mechanism. We have found that aminolyses of aryl benzoates and aryl phenyl carbonates proceed through a stepwise mechanism both in H_2O and in MeCN.[6,7] However, the reactions in the

aqueous medium proceed through the uncatalytic route only, while those in MeCN proceed via the catalytic and uncatalytic routes competitively.[6,7] Importantly, the catalytic path involves a 6-membered cyclic transition state (TS) in which a proton is efficiently transferred from amine to the leaving group.[6,7] A key question arises: Is this catalytic path general for similar aminolyses of esters in MeCN?

It is now firmly understood that the basicity of the leaving group and incoming amine determines the RDS for reactions which proceed through a stepwise mechanism, i.e., a change in the RDS for a stepwise reaction occurs from breakdown of $T^{\pm}$ to its formation as the incoming amine becomes more basic than the leaving group (or the leaving group becomes less basic than the amine nucleophile) by 4 – 5 pK_a units.[2-7] However, the effect of any nonleaving-group substituent on the RDS is not so clearly understood. Gresser and Jencks have concluded that the RDS for the reactions of diaryl carbonates with quinuclidines is dependent on the electronic nature of the substituent in the nonleaving group of the substrate.[2c] A similar conclusion has been drawn by Castro et al. for pyridinolysis of 2,4-dinitrophenyl X-substituted-benzoates and *S*-2,4-dinitrophenyl X-substituted-thiobenzoates.[9] On the contrary, we have shown that the electronic nature of the substituent X in the nonleaving group does not affect the RDS for aminolysis of various esters, e.g., 2,4-dinitrophenyl X-substituted-benzoates,[5a] *O*-4-nitrophenyl X-substituted-thionobenzoates,[8] and 2,4-dinitrophenyl X-substituted-benzenesulfonates.[10]

We have now carried out a systematic study on nucleophilic substitution reactions of 2,4-dinitrophenyl X-substituted-cinnamates (**1a-1f**) and Y-substituted-phenyl cinnamates (**2a-2g**) with a series of alicyclic secondary amines in MeCN (Scheme 2). We have introduced not only a series of structurally similar amines, whose pK_a values are known in MeCN, but also various substituents X and Y in the cinnamoyl moiety and the leaving aryloxide, respectively, to investigate the reaction mechanism thoroughly. Medium effects on the reactivity and reaction mechanism have also been discussed by comparing the current kinetic data with those reported previously for the corresponding reactions performed in H_2O.[11] The current study probes the generality of the stepwise mechanism in

MeCN where catalysis via the 6-membered cyclic TS dominates.

Experimental

Materials. Compounds **1a-1f** and **2a-2g** were readily prepared from the reaction of X-substituted-cinnamoyl chloride with the relevant Y-substituted-phenol under presence of triethylamine in anhydrous ether as reported previously.[11,12] Their purity was checked by means of melting point and ^{1}H NMR spectrum. MeCN was dried and purified by distillation over phosphorus pentoxide under nitrogen. Amines and other chemicals were of the highest quality commercially available and used as purchased.

Kinetics. The kinetic study was performed using a UV-vis spectrophotometer for slow reactions ($t_{1/2} \geq$ 10 s) or a stopped-flow spectrophotometer for fast reactions ($t_{1/2}$ < 10 s) equipped with a constant temperature circulating bath to maintain the reaction temperature at 25.0 ± 0.1°C. All reactions were carried out under pseudo-first-order conditions in which the amine concentration was a minimum of 20 times greater than the substrate concentration. Solutions were transferred using gas-tight syringes under nitrogen. The reactions were followed by monitoring the leaving aryloxide (or its conjugate acid) at a fixed wavelength corresponding to the maximum absorption of Y-$C_6H_4O^-$ (λ_{max}). Other details in experimental methods were similar to the ones described previously.[5,6]

Product Analysis. Y-Substituted-phenoxide (Y-$C_6H_4O^-$ and/or its conjugate acid Y-C_6H_4OH) was liberated quantitatively and identified as one of the reaction products by comparison of the UV-vis spectra after completion of the reactions with those of the authentic samples under the same kinetic conditions.

Results

All reactions in this study obeyed first-order kinetics. Pseudo-first-order rate constants (k_{obsd}) were determined from the equation $\ln (A_\infty - A_t) = -k_{obsd}t + C$ via plots of $\ln (A_\infty - A_t)$ versus time t. 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 in this study. Thus, the second-order rate constants (k_N) were calculated from the slope of linear plots of k_{obsd} vs. amine concentration. It is estimated from at least three replicate runs that the uncertainty in rate constants is less than ± 3 %. The k_N values determined in this way are listed in Tables 1 – 3.

Discussion

Effect of Amine Basicity on Reactivity and Mechanism. As shown in Table 1, the second-order rate constant for the reactions of 2,4-dinitrophenyl X-substituted-cinnamates (X = 4-NO_2, H and 4-MeO) decreases as the amine basicity decreases except for the reaction with piperazine which possesses two basic sites (e.g., k_N for the reaction of **1a** decreases from 929 to 217 and 77.9 $M^{-1}s^{-1}$ as the pK_a for the conjugate acid of the amine decreases from 18.8 to 17.6 and 16.6, in turn). A similar result is shown for the corresponding reactions of **1c** and **1e**, although the reactivity of these substrates decreases as the substituent X in the cinnamoyl moiety changes from a strong electron-withdrawing group (EWG) to an electron-donating group (EDG).

The effect of amine basicity on reactivity is illustrated in Figure 1. The Brønsted-type plots exhibit excellent linear correlations ($R^2 > 0.99$) with $\beta_{nuc} = 0.47 \sim 0.50$ when k_N and pK_a values are statistically corrected using p and q (i.e., $p = 2$ and $q = 1$ except $q = 2$ for the reaction with piperazine).[14] Such small β_{nuc} values found in this study imply that bond formation between the amine nucleophile and the electrophilic center is advanced only a little in the TS. Two possibilities arise for the current reactions, i.e., either the reactions proceed through a concerted mechanism with a TS structure similar to TS_1 or via a stepwise pathway with TS_2 (Chart 1), where expulsion of the leaving group is not advanced.

Linear Brønsted-type plots with $\beta_{nuc} = 0.5 \pm 0.1$ have often been reported for reactions that proceed through a concerted mechanism, e.g., aminolyses of 2,4-dinitrophenyl diphenylphosphinate, *O*-2,4-dinitrophenyl diphenylphosphinothioate[5] and *S*-2,4-dinitrophenyl thiobenzoate.[9a] Therefore, literature

comparison suggests that the current reactions proceed also through a concerted mechanism.

However, one cannot exclude the possibility that the current reactions proceed through a stepwise mechanism with TS_2, because the β_{nuc} value found in this study is larger only slightly than an upper limit of β_{nuc} for reactions proceeding through a stepwise mechanism with formation of $T^{\pm}$ being the RDS (e.g., $\beta_{nuc} = 0.36 \pm 0.18$ for aminolysis of aryl benzoates).[6a] Thus, the linear Brønsted-type plots shown in Figure 1 alone are insufficient to conclude whether the reactions proceed through a concerted mechanism with a TS structure similar to TS_1 or via a stepwise pathway involving TS_2. The key is that for the TS_2 path *expulsion of the leaving group cannot be advanced*.

Effect of Leaving-Group Basicity on Reactivity and Mechanism. To examine whether expulsion of the leaving group is advanced in the RDS or not, reactions of Y-substituted-phenyl cinnamates (**2a-2g**) with piperidine have been carried out. As shown in Table 2, the second-order rate constant, k_N, decreases as the basicity of the leaving aryloxide increases, e.g., k_N decreases from 90.3 to 3.93×10^{-2} and 1.11×10^{-3} $M^{-1}s^{-1}$ as the pK_a of the conjugate acid of the leaving group increases from18.7 to 23.1 and 25.3, in turn (Table 2).

The effect of leaving-group basicity on the reactivity of **2a-2g** is shown graphically in Figure 2. The Brønsted-type plot exhibits an excellent linear correlation with $\beta_{lg} = -0.66$. Such a good linear plot ($R^2 = 0.996$) implies that the reactions proceed without changing the reaction mechanism (or the RDS), even though the basicity of the leaving group varies ca. 7 pK_a units.

A curved Brønsted-type plot has often been reported for aminolysis of esters, which proceeds through a stepwise mechanism with a change in the RDS, e.g., β_{lg} changes from $-(1.5 \pm 0.3)$ to $-(0.3 \pm 0.1)$ as the RDS changes from breakdown of $T^{\pm}$ to its formation.[2-6] Clearly, the β_{lg} value found in this study (i.e., $\beta_{lg} = -0.66$) is too large for reactions proceeding through a stepwise mechanism with formation of $T^{\pm}$ being the RDS. Furthermore, a β_{lg} value of $-(0.6 \pm 0.1)$ is typical for reactions reported previously to proceed through a concerted mechanism, e.g., aminolysis of aryl diphenylphosphinates and *O*-aryl

diphenylphosphinothioates.[5] Thus, one can also conclude that the current reactions proceed through a concerted mechanism with a TS structure similar to TS_1 but not via a stepwise pathway with TS_2.

To obtain more confirmative information on the TS structure, Hammett plots have been constructed using σ^- and σ^o constants. It is noted that the major difference between TS_1 and TS_2 is the position of the partial negative charge. In TS_1, a partial negative charge develops on the O atom of the leaving aryloxide, which can be delocalized on the substituent Y in the leaving group through resonance interaction. In contrast, in TS_2, a negative charge develops partially on the O atom of the carbonyl group but not on the leaving group, as a result of the fact that leaving-group expulsion is not advanced in TS_2.

Accordingly, if expulsion of the leaving group occurs in the RDS (i.e., TS_1), use of σ^- constants should result in a better Hammett correlation than using σ^o constants. On the contrary, if expulsion of the leaving group is not advanced in the RDS (i.e., TS_2), σ^o constants should exhibit a better correlation with log k_N than σ^- constants. In fact, Figures 3A and B show that the Hammett plot correlated with σ^- constants results in a much better correlation (A, $\rho_Y = 2.89$ and $R^2 = 0.990$) than that obtained with σ^o constants (B, $\rho_Y = 3.67$ and $R^2 = 0.916$). This indicates clearly that expulsion of the leaving group occurs in the TS and that the reactions proceed through a concerted mechanism with TS_1.

Effect of Nonleaving-Group Substituent X on Reactivity and Reaction Mechanism. Our study has further extended to the reactions of 2,4-dinitrophenyl X-substituted-cinnamates (**1a-1f**) with piperidine, piperazine and morpholine nucleophiles to investigate effects of the electronic nature of substituent X on reactivity and reaction mechanism. As shown in Table 3, the reactivity of **1a-1f** decreases as the substituent X in the cinnamoyl moiety changes from a strong EWG to a strong EDG, e.g., the k_N value for the reactions with piperidine decreases from 929 to 249 and 78.0 $M^{-1}s^{-1}$ as X changes from 4-NO_2 to H and 4-OH, respectively. Similar results are shown for the reactions with piperazine and morpholine, although the less basic piperazine exhibits larger k_N values than the more basic piperidine. However, this is not unusual given that piperazine possesses two nucleophilic sites.

The effect of substituent X on reactivity is illustrated in Figure 4. It is noted that each Hammett plot consists of two intersecting straight lines, i.e., the ρ_X value for the reactions with piperidine increases from 0.75 to 1.38 as the substituent X changes from EWGs to EDGs. Comparable results are shown for the corresponding reactions with piperazine and morpholine. Since nonlinear or biphasic Hammett plots have often been taken as evidence for a change in RDS,[17] one might suggest that the current aminolysis proceeds also through a stepwise mechanism with a change in RDS, e.g., from rate-determining formation of $T^{\pm}$ to its breakdown as the substituent X changes from EDGs to EWGs.

The above argument appears to be reasonable since the rate of nucleophilic attack (the k_1 process in Scheme 1) would be accelerated by an EWG in the cinnamoyl moiety but retarded by an EDG. Thus, a large ρ_X value would be expected when formation of $T^{\pm}$ is the RDS. In contrast, an EWG in the cinnamoyl moiety would inhibit expulsion of the leaving group from $T^{\pm}$ (the k_2 process in Scheme 1), because the leaving aryloxide departs from $T^{\pm}$ with its bonding electron pair. Therefore, it is plausible to expect a small ρ_X value when breakdown of $T^{\pm}$ to the products is the RDS due to the opposite substituent effects. In fact, Jencks found that the ρ_X value for reactions of X-substituted benzaldehydes with semicarbazide in weakly acidic medium (e.g., pH = 3.9) decreases from 0.91 to nearly zero as the substituent X changes from EDGs to EWGs, and attributed the nonlinear Hammett plot to a change in the RDS.[17a]

However, we propose that the nonlinear Hammett plots shown in Figure 4 are not due to a change in the RDS. In fact, the current kinetic results discussed above support the idea that the reactions proceed through a concerted mechanism. We, thus, propose that the nonlinear Hammett plots are due to stabilization of the substrate in the ground state (GS) through resonance interactions as illustrated by resonance structures I and II (Chart 2). This idea is consistent with the fact that the substrates possessing an EDG in the cinnamoyl moiety exhibit negative deviation from the linear line composed of substrates **1a-c** and such deviation is more significant for the substrate bearing a stronger EDG (e.g., **1f**).

To verify the above argument, Yukawa-Tsuno plots have been constructed in Figure 5. It is noted that the *r* value in the Yukawa-Tsuno equation (1) represents the resonance demand of the reaction center or the extent of the resonance contribution, while the term ($\sigma^+ - \sigma^o$) stands for the resonance substituent constant that measures the capacity for π-delocalization of a given π-electron donor substituent.[18,19]

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

As shown in Figure 5, the Yukawa-Tsuno plots exhibit excellent linear correlations ($R^2 > 0.995$) with $\rho_X = 0.62 \sim 0.71$ and $r = 0.66 \pm 0.02$. Such linear Yukawa-Tsuno plots indicate that the nonlinear Hammett plots in Figure 4 are clearly not due to a change in the RDS. Thus, one can conclude that the electronic nature of the substitutent X in the cinnamoyl moiety does not influence the reaction mechanism including the RDS, although it affects the reactivity of the substrates. Furthermore, the current study has clearly shown that deduction of reaction mechanism based solely on a linear or nonlinear Hammett plot may be misleading.

Differential Medium Effects on Zwitterionic Intermediate $T^{\pm}$ vs. Concerted Transition State TS_1. As discussed above, aminolysis of **1a-1f** and **2a-2g** in MeCN proceeds through a concerted mechanism with a TS structure similar to TS_1. This is the same mechanism reported previously for the corresponding reaction carried out in H_2O,[11] indicating that *the nature of the reaction medium (e.g., protic vs. aprotic) does not affect the reaction mechanism for the aminolysis of* **1a-1f** *and* **2a-2g**. However, Tables 1 ~ 3 show that the amines used in this study are more reactive in MeCN than in H_2O. This is an unexpected result based on the Hughes-Ingold rule.[20] According to the rule, rates of nucleophilic substitution reactions between neutral reactants are expected, and have been found, to decrease upon changing the reaction medium from a protic solvent to an aprotic one.[21,22] In fact, our previous studies on aminolyses of various esters (e.g., phenyl Y-substituted-phenyl carbonates,[7] *O*-4-nitrophenyl X-substituted-thionobenzoates[8b] and 4-pyridyl X-substituted-benzoates[23]), which proceed through a stepwise mechanism with $T^{\pm}$ as an intermediate, have shown that the amines become less

reactive up to 400 times upon changing the medium from H_2O to MeCN.

It is clear that medium effects on the stability of $T^{\pm}$ and TS_1 would be different. The negative charge on the O atom of $T^{\pm}$ could be stabilized through strong H-bonding interactions in H_2O but would be highly destabilized in MeCN due to the electronic repulsion between the negatively charged O atom of $T^{\pm}$ and the negative dipole end of MeCN.[21,22] This idea is consistent with the report that amines become less reactive in MeCN for the reactions proceeding through $T^{\pm}$,[7,8b,23] although the amines are 6 ~ 8 pK_a units more basic in this aprotic solvent.[13] In contrast, one might expect that the difference in stability of TS_1 in the two solvents is not significant. In this regard, in TS_1 charge is delocalized and, therefore, TS_1 would be neither strongly stabilized through H-bonding interactions in H_2O nor highly destabilized by electronic repulsion in MeCN. This accounts for the kinetic results that the amines are more reactive in MeCN, where amines are more basic by 6 ~ 8 pK_a units, than in water even though the reactions proceed through the same mechanism (i.e., a concerted mechanism) in both solvents.

We have recently shown that aminolyses of various esters (e.g., 4-nitrophenyl 3,5-dinitrobenzoate, 4-pyridyl X-substituted-benzoates, phenyl Y-substituted-phenyl carbonates, etc.) in MeCN proceed through a stepwise mechanism with $T^{\pm}$, which decomposes to reaction products through catalytic and uncatalytic routes competitively.[7,8b,23] The catalytic route proceeds through a 6-membered cyclic TS (e.g., TS_3 in Chart 3) to gain stability via intramolecular H-bonding interactions. Note that the second amine molecule in TS_3 relays a proton from the aminium moiety of $T^{\pm}$ to the leaving aryloxide. It is apparent that such proton transfer could also increase nucleofugality of the anionic leaving-group in the aprotic solvent (MeCN). On the contrary, protonation of the leaving group by a second amine molecule is not necessary for the reactions carried out in the aqueous medium, because the anionic nucleofuge (e.g., ArO^-) could be stabilized through H-bonding with H_2O. This idea is consistent with the report that decomposition of $T^{\pm}$ to products occurs through catalytic and uncatalytic routes competitively in MeCN but the catalytic route is often absent in H_2O.[7,8b,23] Thus, we propose that differential medium effects on

$T^{\pm}$ and TS_1 are responsible for the contrasting reactivity and reaction mechanism observed for the reactions in MeCN and in H_2O.

Conclusion

We have concluded that the current reactions of **1a-1f** and **2a-2g** proceed through a concerted mechanism with a TS structure similar to TS_1 and that nature of the reaction medium (e.g., protic versus aprotic) and substituents X and Y affects reaction rates but does not influence the reaction mechanism on the basis of the following kinetic results:

(1) The Brønsted-type plots for the reactions of 2,4-dinitrophenyl X-substituted-cinnamates (**1a-1f**) are linear with $\beta_{nuc} = 0.47 \sim 0.50$, indicating that bond formation between the nucleophilic amine and the electrophilic center is advanced only a little in the TS.

(2) The Brønsted-type plot for the reactions of Y-substituted-phenyl cinnamates (**2a-2g**) with piperidine is linear with $\beta_{lg} = -0.66$, a typical β_{lg} value for reactions proceeding through a concerted mechanism.[5-9]

(3) The use of σ^- constants result in a better Hammett correlation than σ^o constants for the reactions of **2a-2g** with piperidine, indicating that expulsion of the leaving group is advanced in the RDS.

(4) The Hammett plots for the reactions of **1a-f** with piperidine, piperazine and morpholine are nonlinear while the corresponding Yukawa-Tsuno plots exhibit excellent linear correlations with significant *r*, resonance interaction values. This indicates that the nonlinear Hammett plots are not due to a change in RDS in a stepwise mechanism but are caused by stabilization of the substrates possessing an EDG in the cinnamoyl moiety through resonance interactions.

(5) The amines used in this study are more reactive in MeCN than in H_2O, implying that destabilization of TS_1 in the aprotic solvent is not significant and that the enhanced amine basicity is responsible for their increased reactivity in the aprotic solvent. In other words, this result highlights a

differential solvent effect in these systems.

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Caption

Scheme 1. Reaction pathways for aminolysis of esters.

Scheme 2. Aminolysis of Y-substituted-phenyl X-substituted-cinnamates (**1a-1f** and **2a-2g**).

Chart 1. Two possible transition state structures.

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Chart 3. 6-Membered cyclic TS proposed previously for aminolysis of aryl benzoates in MeCN.

Figure 1. Brønsted-type plots for aminolysis of 2,4-dinitrophenyl X-substituted-cinnamates in MeCN at 25.0 ± 0.1 °C. X = 4-NO_2 (**1a**, ▲); X = H (**1c**, ○); X = 4-MeO (**1e**, ●). The identity of points is given in Table 1.

Figure 2. Brønsted-type plot for the reactions of Y-substituted-phenyl cinnamates (**2a-2g**) with piperidine in MeCN at 25.0 ± 0.1 °C. The identity of points is given in Table 2.

Figure 3. Hammett plots correlated with σ^- (A) and σ^o constants (B) for the reactions of Y-substituted-phenyl cinnamates (**2a-2g**) with piperidine in MeCN at 25.0 ± 0.1 °C. The identity of points is given in Table 2.

Figure 4. Hammett plots for reactions of 2,4-dinitrophenyl X-substituted-cinnamates **(1a-1f)** with piperidine (●), piperazine (□) and morpholine (○) in MeCN at 25.0 ± 0.1 °C. The identity of points is given in Table 3.

Figure 5. Yukawa-Tsuno plots for reactions of 2,4-dinitrophenyl X-substituted-cinnamates **(1a-1f)** with piperidine (●), piperazine (□), and morpholine (○) in MeCN at 25.0 ± 0.1 °C. The identity of points is given in Table 3.

Tables 1 ~ 3 for cjc-2018-0310

Table 1. Summary of Second-Order Rate Constants (k_N) for Aminolysis of 2,4-Dinitrophenyl X-Substituted-cinnamates (**1a**, **1c** and **1e**) in MeCN at 25.0 ± 0.1 °C.

			k_N / $M^{-1}s^{-1}$		
	amine	pK_a[a]	**1a** (X = 4-NO_2)	**1c** (X = H)	**1e** (X = 4-MeO)
1	piperidine	18.8	929 ± 19 (640)[b]	249 ± 5 (193)[b]	109 ± 3 (92.5)[b]
2	3-methylpiperidine	18.6	758 ± 17 (621)[b]	218 ± 5 (186)[b]	102 ± 3 (83.8)[b]
3	piperazine	18.5	1020 ± 30 (264)[b]	258 ± 7 (115)[b]	114 ± 4 (50.7)[b]
4	1-(2-hydroxyethyl) piperazine	17.6	217 ± 6	63.0 ± 1.3	27.3 ± 0.8
5	morpholine	16.6	77.9 ± 2.1 (65.0)[b]	24.4 ± 0.5 (22.7)[b]	11.0 ± 0.2 (10.6)[b]

[a]The pK_a data in MeCN were taken from ref. 13. [b]The k_N values in the parenthesis were taken from ref. 11 for the corresponding reaction in H_2O.

Table 2. Summary of the Second-Order Rate Constants (k_N) for Reactions of Y-Substituted-phenyl Cinnamates (**2a-2g**) with Piperidine in MeCN at 25.0 ± 0.1 °C.

entry	Y	pK_a (Y-C_6H_4OH)	10^2 k_N / $M^{-1}s^{-1}$
2a	3,4-$(NO_2)_2$	18.7[a]	9030 ± 185 (156)[c]
2b	4-NO_2	20.9[a]	166 ± 4 (12.3)[c]
2c	4-CHO	22.4[b]	19.2 ± 0.6 (4.03)[c]
2d	4-COMe	23.1[b]	3.93 ± 0.11 (1.71)[c]
2e	4-CO_2Et	23.8[b]	2.62 ± 0.05 (1.24)[c]
2f	3-$COCH_3$	25.0[b]	0.124 ± 0.003 (0.160)[c]
2g	4-Cl	25.3[b]	0.111 ± 0.003

[a]The pK_a values of Y-substituted phenols in MeCN were taken from ref. 15. [b]The pK_a values

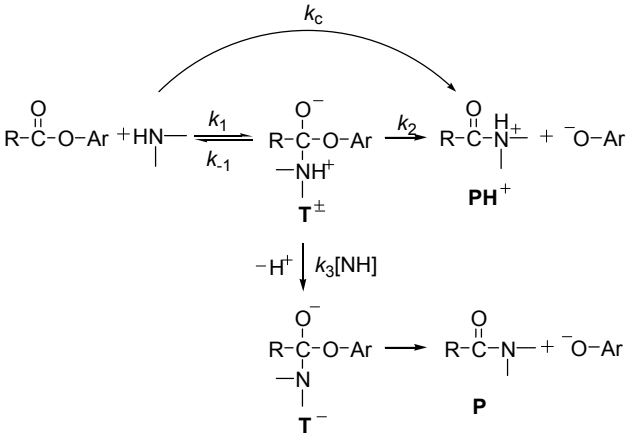
were calculated from the equation, pK_a (in MeCN) = 1.65 pK_a (in H_2O) + 9.8, which was derived from the pK_a data in refs. 15 and 16. [c]The k_N values in the parenthesis were taken from ref. 11 for the corresponding reaction in H_2O.

Table 3. Summary of Second-Order Rate Constants for Aminolysis of 2,4-Dinitrophenyl X-Substituted-Cinnamates (**1a-1f**) in MeCN at 25.0 ± 0.1 °C.

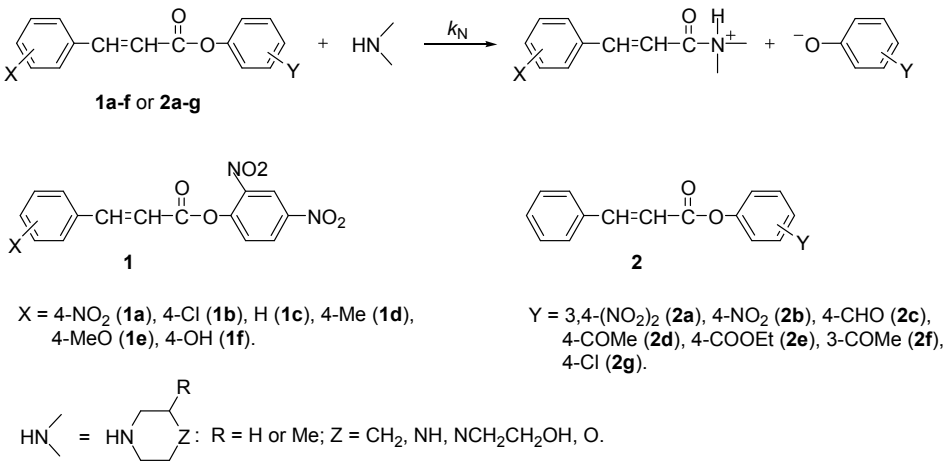
		k_N / $M^{-1}s^{-1}$		
entry	X	piperidine	piperazine	morpholine
1a	4-NO_2	929 ± 26 (640)[a]	1020 ± 30	77.9 ± 2.3 (65.0)[a]
1b	4-Cl	337 ± 8 (253)[a]	360 ± 10	30.9 ± 0.6 (27.0)[a]
1c	H	249 ± 5 (193)[a]	258 ± 7	24.4 ± 0.7 (22.7)[a]
1d	4-Me	165 ± 5 (140)[a]	193 ± 6	16.8 ± 0.3 (15.8)[a]
1e	4-MeO	109 ± 3 (92.5)[a]	114 ± 4	11.0 ± 0.2 (10.6)[a]
1f	4-OH	78.0 ± 2.3	90.2 ± 2.1	9.34 ± 0.19

[a]The k_N values in the parenthesis were taken from ref. 11 for the corresponding reaction in H_2O.

Schemes 1 and 2 for cjc-2018-0310



Scheme 1. Reaction pathways for aminolysis of esters



Scheme 2. Aminolysis of Y-substituted-phenyl X-substituted-cinnamates (**1a-1f** and **2a-2g**).

Charts 1 ~ 3 for cjc-2081-0310

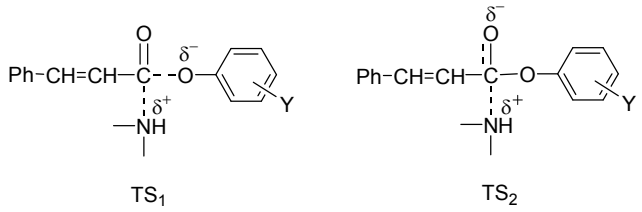


Chart 1. Two possible transition state structures.

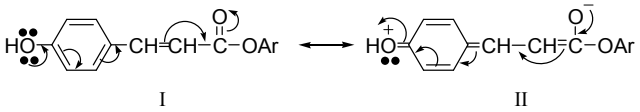


Chart 2. Resonance structures that stabilize the GS of the substrate.

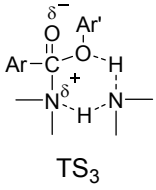


Chart 3. 6-Membered cyclic TS proposed previously for aminolysis of aryl benzoates in MeCN.

Figures 1 ~ 5 for cjc-2018-0310

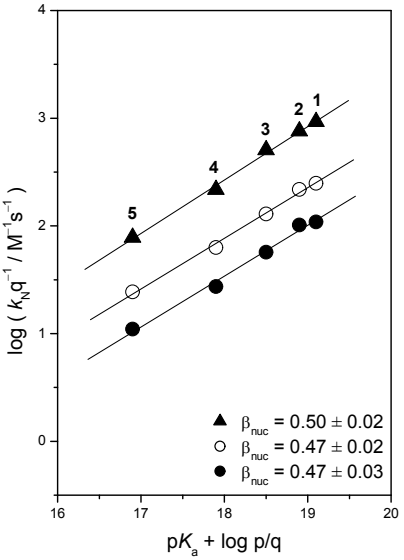


Figure 1. Brønsted-type plots for aminolysis of 2,4-dinitrophenyl X-substituted-cinnamates in MeCN at 25.0 ± 0.1 °C. X = 4-NO_2 (**1a**, ▲); X = H (**1c**, ○); X = 4-MeO (**1e**, ●). The identity of points is given in Table 1.

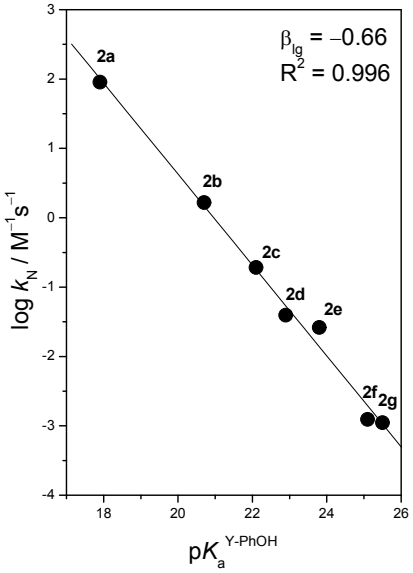


Figure 2. Brønsted-type plot for the reactions of Y-substituted-phenyl cinnamates (**2a-2g**) with piperidine in MeCN at 25.0 ± 0.1 °C. The identity of points is given in Table 2.

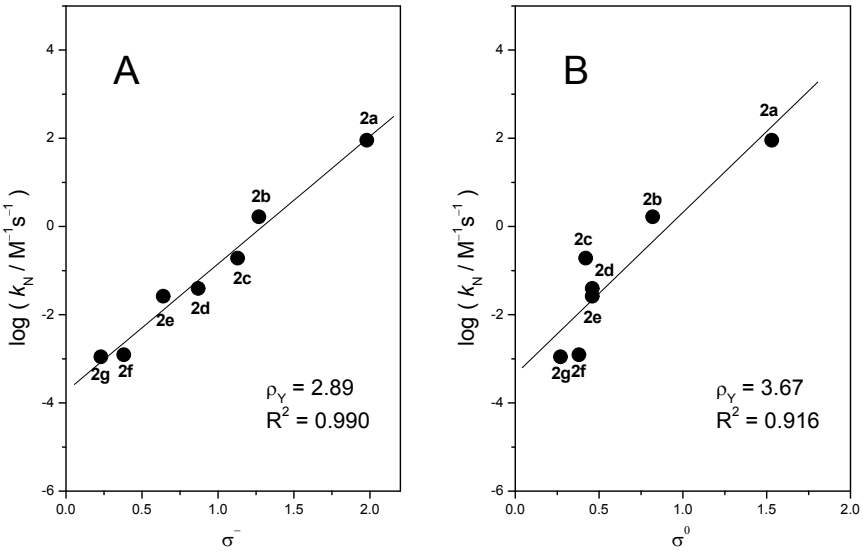
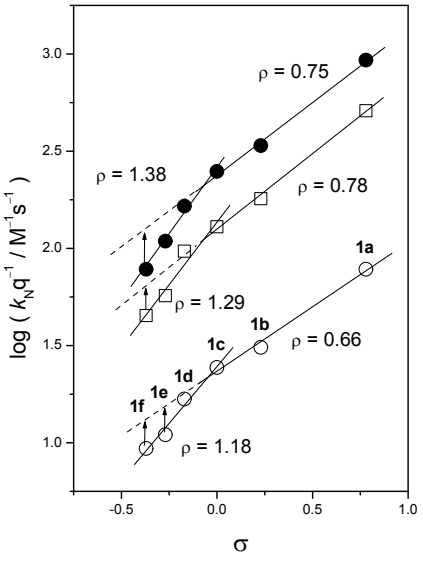


Figure 3. Hammett plots correlated with σ^- (A) and σ^o constants (B) for the reactions of Y-substituted-phenyl cinnamates (**2a-2g**) with piperidine in MeCN at 25.0 ± 0.1 °C. The identity of points is given in Table 2.



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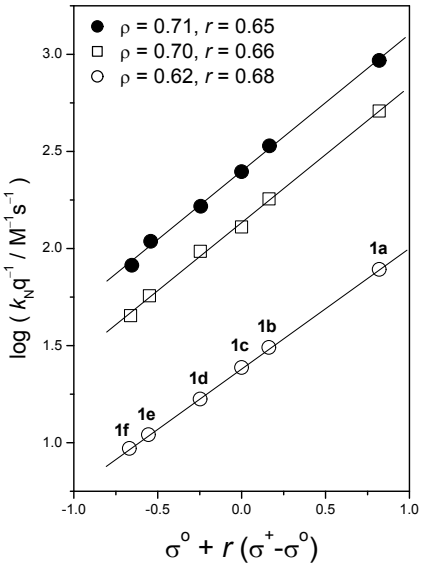

Figure 5. Yukawa-Tsuno plots for reactions of 2,4-dinitrophenyl X-substituted-cinnamates **(1a-1f)** with piperidine (●), piperazine (□), and morpholine (○) in MeCN at 25.0 ± 0.1 °C. The identity of points is given in Table 3.