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PAPER

Hydrolysis of 1-(X-substituted-benzoyl)-4-aminopyridinium ions: effect of substituent X on reactivity and reaction mechanism†‡

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A kinetic study is reported for hydrolysis of 1-(X-substituted-benzoyl)-4-aminopyridinium ions **2a–i**, which were generated *in situ* from the nucleophilic substitution reaction of 2,4-dinitrophenyl X-substituted-benzoates **1a–i** with 4-aminopyridine in 80 mol% H_2O/20 mol% DMSO at 25.0 ± 0.1 °C. The plots of pseudo-first-order rate constants k_{obsd} *vs.* pyridine concentration are linear with a large positive intercept, indicating that the hydrolysis of **2a–i** proceeds through pyridine-catalyzed and uncatalyzed pathways with the rate constant k_{cat} and k_o, respectively. The Hammett plots for k_{cat} and k_o consist of two intersecting straight lines, which might be taken as evidence for a change in the rate-determining step (RDS). However, it has been proposed that the nonlinear Hammett plots are not due to a change in the RDS but are caused by stabilization of **2a–i** in the ground state through a resonance interaction between the π-electron-donor substituent X and the carbonyl functionality. This is because the corresponding Yukawa-Tsuno plots exhibit excellent linear correlations with $\rho_X = 1.45$ and $r = 0.76$ for k_{cat} while $\rho_X = 1.39$ and $r = 0.72$ for k_o. A possibility that the hydrolysis of **2a–i** proceeds through a concerted mechanism has been ruled out on the basis of the large ρ_X values. Thus, the reaction has been concluded to proceed through a stepwise mechanism in which the leaving group departs after the RDS since OH^- is more basic and a poorer nucleofuge than 4-aminopyridine.

Introduction

The Yukawa-Tsuno eqn (1) was originally derived to account for the resonance effect in decomposition of ω-diazoacetophenones in acetic acid.[1] The *r* value in eqn (1) represents the resonance demand of the reaction center or the extent of resonance contribution, while the term $(\sigma_X^+ - \sigma_X^\circ)$ is the resonance substituent constant that measures the capacity for π-delocalization of the π-electron donor substituent.[1] Eqn (1) becomes the Hammett equation when $r = 0$, but becomes the Brown-Okamoto equation when $r = 1$. It has widely been accepted that eqn (1) is a powerful tool for investigation of resonance effects in solvolyses of benzylic and related systems, in which a partial positive charge is developing in the transition state (TS).[1–3]

$$\log (k_X/k_H) = \rho_X[\sigma_X^\circ + r(\sigma_X^+ - \sigma_X^\circ)] \quad (1)$$

We have shown that eqn (1) is highly effective in clarifying ambiguities in reaction mechanisms for nucleophilic substitution reactions of various types of esters.[4–7] It is well known that reactions of esters with amines proceed through a concerted mechanism or through a stepwise pathway depending on reaction conditions (*e.g.*, the nature of the electrophilic center and reaction medium).[4–11] Aminolysis of X-substituted phenyl diphenylphosphinates has been reported to proceed through a concerted mechanism since the kinetic data result in an excellent linear Yukawa-Tsuno plot with $\rho_X = 1.91$ and $r = 0.30$.[7a] A similar conclusion has been drawn for the corresponding reactions of X-substituted phenyl diphenylphosphinothioates.[7d] In contrast, aminolysis of carboxylic esters possessing a good leaving group (*e.g.*, 2,4-dinitrophenoxide) has been reported to proceed through a stepwise mechanism on the basis of a curved Brønsted-type plot.[4,8–11] The rate-determining step (RDS) has been suggested to be dependent on the basicity of the incoming amine and the leaving group, *i.e.*, the RDS changes from the breakdown of a zwitterionic tetrahedral intermediate $T^\pm$ to its formation as the incoming amine becomes more basic than the leaving group by 4 to 5 pK_a units or the leaving group becomes less basic than the amine.[4,8–11]

Pyridinolysis of esters has also intensively been investigated and the reaction mechanisms are fairly well understood.[4a,12–15] It has been reported that reactions of pyridines with acid derivatives including esters produce acylpyridinium ions, which hydrolyze in H_2O.[4a,12–15] Although scattered information on hydrolysis of acylpyridinium ions is available, the reaction mechanism is not yet clearly understood.[12,13,14a] Castro *et al.* have recently investigated pyridine-catalyzed hydrolysis of

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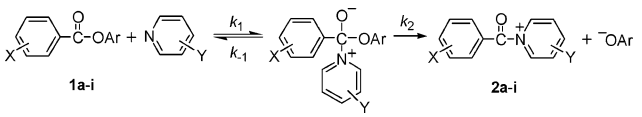
† This paper is dedicated with respect and affection to the late Professor Yuho Tsuno a true gentleman and an inspiring mentor.

‡ Electronic supplementary information (ESI) available: Kinetic conditions and results for hydrolysis of **2a–i** with 4-aminopyridine (Tables S1–S9), plots of k_{obsd} *vs.* 4-aminopyridine concentration (Figs. S1–S8), and ^1H NMR spectra for 2,4-dinitrophenyl X-substituted benzoates **1a–i** (Figs. S9–S17). See DOI: 10.1039/c1ob06137b

1-(aryloxythiocarbonyl)pyridinium ions, generated *in situ* from the reactions of phenyl and 4-nitrophenyl chlorothioformates with five differfernt Y-substituted pyridines (Y = 3,4-Me_2, 4-Me, H, 3-COMe, and 4-CN) in H_2O.[14a] They have shown that the rate constant for pyridine-catalyzed hydrolysis of the pyridinium ions increases only slightly as pyridine basicity increases, *e.g.*, the slope of the Brønsted-type plots is *ca.* 0.2. The small Brønsted coefficient has been attributed to the fact that as pK_a increases the effect of a better pyridine catalyst is compensated by a worse leaving pyridine from the corresponding acylpyridinium ions.[14a]

We have recently reported that pyridinolysis of 2,4-dinitrophenyl X-substituted benzoates **1a–i** proceeds through a stepwise mechanism, in which the RDS is dependent on the basicity of the incoming pyridine (Scheme 1).[4a] However, it has been shown that the electronic nature of the substituent X in the benzoyl moiety does not affect the RDS, since the Yukawa-Tsuno plots exhibit excellent linear correlations with $\rho_X = 0.92 \sim 1.31$ and $r = 0.79 \sim 0.92$.[4a]



Scheme 1 Pyridinolysis of 2,4-dinitrophenyl X-substituted benzoates **1a–i**.

We have now carried out hydrolysis of 1-(X-substituted-benzoyl)-4-aminopyridinium ions **2a–i**, generated *in situ* from the reactions of **1a–i** with 4-aminopyridine. The reactions of **2a–i** were carried out in a self-buffered solution (*i.e.*, 4-aminopyridine/4-aminopyridinium-ion = 1.0/1.0) to investigate the effect of the substituent X on the reaction mechanism. The hydrolysis of **2e** was also performed in 5-different buffered solutions (*i.e.*, 4-aminopyridine/4-aminopyridinium-ion = 3.0/1.0, 2.0/1.0, 1.0/1.0, 1.0/1.9, and 1.0/2.9) to characterize the reacting species. Analysis of our kinetic data using the Yukawa-Tsuno equation has led us to conclude that the hydrolysis of **2a–i** proceeds through a stepwise mechanism with the first step being the RDS for both pyridine-catalyzed and uncatalyzed reactions (Scheme 2).

Results and discussion

All reactions in this study obeyed pseudo-first-order kinetics in the presence of a large excess of 4-aminopyridine compared with the substrate. 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.* pyridine concentration were linear with a large positive intercept (Fig. 1 and Figs. S1–S8 in the ESI), indicating that the contribution of H_2O and/or OH^- ion from hydrolysis of 4-aminopyridine to k_{obsd} is significant. Thus, one can derive a rate equation as eqn (2), in which k_{cat} and k_o represent the second-order rate constant for the pyridine-catalyzed reactions and the first-order rate constant for the uncatalyzed reactions (*i.e.*, the reactions with H_2O and/or OH^-), respectively. Thus, the k_{cat} and k_o values were determined from the slope and intercept of the linear plots of k_{obsd} *vs.* pyridine concentration, respectively. The uncertainty in these values is estimated to be less than 3% from replicate runs. The k_{cat} and k_o values calculated are summarized in Table 1.

Table 1 Summary of kinetic data for the hydrolysis of 1-(X-substituted benzoyl)-4-aminopyridinium ions (**2a–i**) in 80 mol% H_2O/20 mol% DMSO at 25.0 ± 0.1 °C

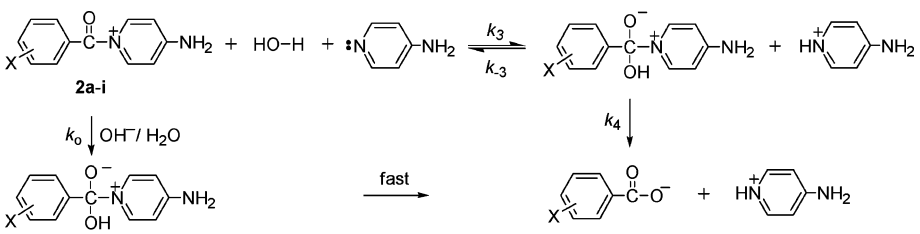
	X	$10^2\ k_{cat}/M^{-1}s^{-1}$	$10^3\ k_o/s^{-1}$
2a	4-NMe_2	0.518	0.204
2b	4-MeO	11.6	4.08
2c	4-Me	27.3	8.84
2d	3-Me	46.1	13.4
2e	H	60.1	18.0
2f	4-Cl	107	37.8
2g	3-Cl	226	64.0
2h	4-CN	760	135
2i	4-Cl-3-NO_2	965	310

$$k_{obsd} = k_{cat}[\text{4-aminopyridine}] + k_o \quad (2)$$

Effect of substituent X on reactivity and mechanism

As shown in Table 1, k_{cat} increases as the substituent X on the benzoyl moiety of **2a–i** changes from an electron-donating group (EDG) to an electron-withdrawing group (EWG), *e.g.*, it increases from 5.18×10^{-3} $M^{-1}s^{-1}$ to 6.01×10^{-1} and 9.65 $M^{-1}s^{-1}$ as X changes from 4-NMe_2 to H and 4-Cl-3-NO_2, in turn. A similar result is shown for k_o, although the magnitude of k_o is smaller than that of k_{cat}.

The effect of the substituent X on the reactivity of **2a–i** is illustrated in Fig. 2. One can see that each Hammett plot consists of two intersecting straight lines (*i.e.*, ρ_X = 2.38 ~ 2.53 for substrates possessing EDGs while ρ_X = 1.30 ~ 1.39 for those bearing EWGs). Traditionally, nonlinear Hammett plots have been taken as evidence for a change in the reaction mechanism or RDS depending on the shape of curvature.[16] Upward curvature often found for nucleophilic substitution reactions of benzylic systems has been interpreted as a change in mechanism, *i.e.*, from S_N1 for substrates possessing an EDG to S_N2 for those bearing an EWG.[16] In contrast, downward curvature has been attributed to a change



X = 4-NMe_2 (**a**), 4-MeO (**b**), 4-Me (**c**), 3-Me (**d**), H (**e**), 4-Cl (**f**), 3-Cl (**g**), 4-CN(**h**), 4-Cl-3-NO_2 (**i**).

Scheme 2 Hydrolysis of 1-(X-substituted benzoyl)-4-aminopyridinium ions **2a–i**.

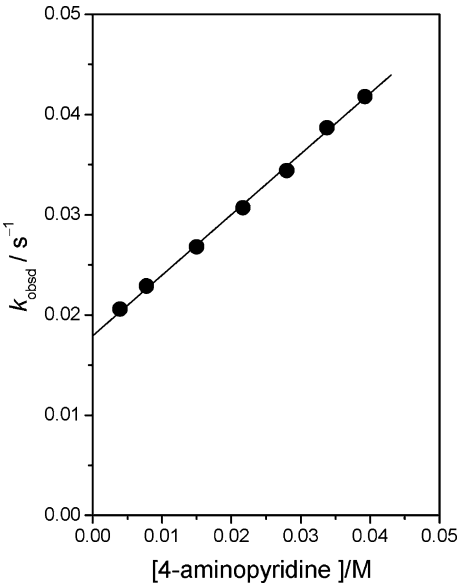


Fig. 1 Plot of k_{obsd} *vs.* 4-aminopyridine concentration for the hydrolysis of 1-benzoyl-4-aminopyridinium ion **2e** in 80 mol% H_2O/20 mol% DMSO at 25.0 ± 0.1 °C.

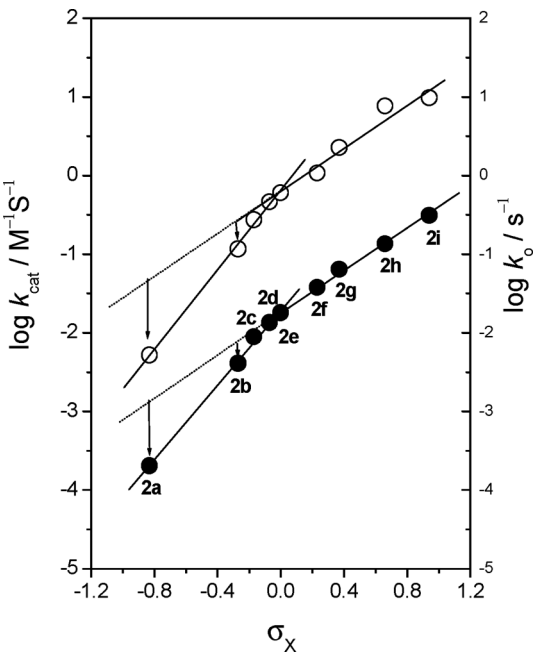


Fig. 2 Hammett plots for the hydrolysis of **2a–i** in 80 mol% H_2O/20 mol% DMSO at 25.0 ± 0.1 °C: (○ for k_{cat} and ● for k_o). The identity of the points is given in Table 1.

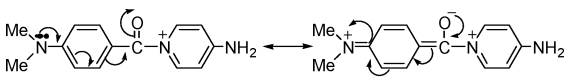
in RDS upon changing the substituent from EDGs to EWGs.[16] In fact, the downward Hammett plot found for reactions of a series of X-substituted benzaldehydes with semicarbarzide in a weakly acidic medium (*e.g.*, pH = 3.9) has been concluded to be a change in RDS.[16b]

Accordingly, one might suggest that the nonlinear Hammett plots in Fig. 2 are due to a change in RDS, *i.e.*, from the formation of an intermediate to its breakdown to yield the reaction products as the substituent X in the benzoyl moiety of **2a–i** changes from EDGs to EWGs. This idea appears to be reasonable for the pyridine-catalyzed process, since one might expect that an EDG in the benzoyl moiety would retard nucleophilic attack (*i.e.*, a decrease in k_3 in Scheme 2) but would accelerate departure of the leaving group (*i.e.*, an increase in k_4 in Scheme 2). In contrast, an EWG would increase k_3 but decrease k_4. Thus, the nonlinear Hammett plot might be interpreted as a change in RDS upon changing the substituent X in the benzoyl moiety of **2a–i** from EDGs to EWGs.

Origin of the nonlinear Hammett plot

However, we propose that the nonlinear Hammett plots shown in Fig. 2 are not due to a change in the RDS on the basis of the following reasons: (1) The RDS should be determined by the k_4/k_{-3} ratio (*i.e.*, RDS = the k_3 step when $k_4/k_{-3} > 1$ or RDS = the k_4 step when $k_4/k_{-3} < 1$) but not by the magnitude of k_3 and k_4. Furthermore, k_3 and k_4 values cannot be compared directly since the former is a second-order rate constant while the latter is a first-order rate constant. (2) Both k_4 and k_{-3} processes would be accelerated by an EDG in the benzoyl moiety but would be retarded by an EWG, since the nuclefuges depart with the bonding electrons. Thus, the k_4/k_{-3} ratio would be independent of the electronic nature of the substituent X in the benzoyl moiety.

The origin of the nonlinear Hammett plots that we propose is stabilization of pyridinium ions **2a–i** in the ground state (GS) through resonance interactions as modeled by resonance structures I and II. Such resonance interactions would stabilize their GS and cause a decrease in their reactivity, as suggested previously for solvolysis of methyl chloroformate.[17] This idea is consistent with the fact that the pyridinium ions possessing an EDG in the benzoyl moiety deviate negatively from the linear Hammett plot composed of those bearing EWGs (*i.e.*, **2e–i**). Furthermore, such negative deviation is more significant for the pyridinium ion bearing a stronger EDG.



I II

To examine the validity of the above argument, Yukawa–Tsuno plots have been constructed. As shown in Fig. 3, the Yukawa–Tsuno plots exhibits excellent linear correlation with $\rho_X = 1.45$ and $r = 0.76$ for the catalyzed reaction while $\rho_X = 1.39$ and $r = 0.72$ for the uncatalyzed process. The linear Yukawa–Tsuno plots clearly indicate that the nonlinear Hammett plots are not due to a change in RDS but are caused by the stabilization of **2a–i** in the GS through resonance interactions as mentioned above. This idea is consistent with our previous proposal that deduction of reaction mechanisms based solely on a linear or nonlinear Hammett plot can be misleading.[4–6]

Deduction of reaction mechanism

To investigate the reacting species, hydrolysis of **2e** has been performed in five different pyridine/pyridinium-ion buffer solutions (*i.e.*, pyridine/pyridinium-ion = 3.0/1.0, 2.0/1.0, 1.0/1.0, 1.0/1.9, and 1.0/2.9). The kinetic results are summarized in Table 2 and illustrated in Fig. 4A and 4B.

As shown in Fig. 4A, the plots of k_{obsd} *vs.* $[pyridine]_{tot}$, the total concentration of pyridine and pyridinium ion, are linear with

Table 2 Summary of the kinetic results for hydrolysis of 1-benzoyl-4-aminopyridinium ion **2e** in 5 different pyridine/pyridinium-ion buffer solutions at 25.0 ± 0.1 °C

Pyridine/pyridinium-ion	pH	$10^3\ k_{cat}/M^{-1}s^{-1}$	$10^3\ k_o/s^{-1}$
3.0/1.0	9.41	616	33.4
2.0/1.0	9.23	611	26.8
1.0/1.0	8.93	601	18.0
1.0/1.9	8.66	617	13.9
1.0/2.9	8.47	619	12.6

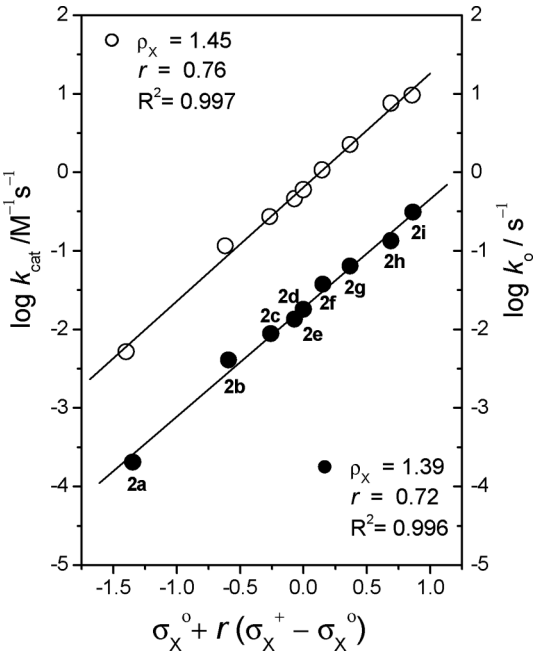


Fig. 3 Yukawa-Tsuno plots for the hydrolysis of **2a–i** in 80 mol% H_2O/20 mol% DMSO at 25.0 ± 0.1 °C: (○ for k_{cat} and ● for k_o). The identity of the points is given in Table 1.

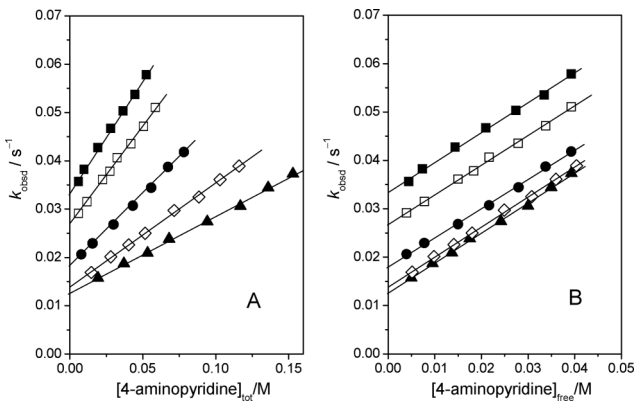


Fig. 4 Plots of k_{obsd} *vs.* $[4\text{-aminopyridine}]_{tot}$ (A) and k_{obsd} *vs.* $[4\text{-aminopyridine}]_{free}$ (B) for hydrolysis of 1-benzoyl-4-aminopyridinium ion **2e** in 5 different pyridine/pyridinium-ion buffer solutions at 25.0 ± 0.1 °C. pyridine/pyridinium-ion = 3.0/1.0 (■), 2.0/1.0 (□), 1.0/1.0 (●), 1.0/1.9 (◇), 1.0/2.9 (▲).

different slopes and intercepts (*i.e.*, the slope and intercept decrease as the fraction of pyridine in the buffer solutions decreases). In contrast, the plots of k_{obsd} *vs.* $[\text{pyridine}]_{free}$, the concentration of the free pyridine, in Fig. 4B exhibit almost the same slope (*i.e.*, k_{cat} = 0.61 ± 0.01 $M^{-1}s^{-1}$), although the intercept of the plots (*i.e.*, k_o) is dependent on the buffer ratios. It is noted that the intercepts in Fig. 4A are identical to those in Fig. 4B. Besides, one can get a rate constant of 0.61 ± 0.01 $M^{-1}s^{-1}$ by dividing the slopes in Fig. 4A by the fraction of pyridine in the buffer solutions. These results indicate clearly that pyridine (but not pyridinium ion) catalyzes the reaction as a general-base catalyst and OH^- ion is also a nucleophilic species in this study.

To prove the above argument that OH^- ion is also a nucleophilic species in this study, the k_o values in Table 2 have been dissected into the rate constants for OH^- and H_2O reactions. The rate constant measured for the hydrolysis of **2e** in the absence of the pyridine/pyridinium-ion buffer is 0.0095 s^{-1} (*i.e.*, the contribution of H_2O reaction to k_o).[18] Since k_o represents the total rate constants for the reactions with OH^- and H_2O, one can calculate the rate constant for the OH^- reaction by subtracting 0.0095 s^{-1} from the k_o value determined from the intercept of the linear plots in Fig. 4. The pHs of the buffer solutions can be calculated from the Henderson–Hasselbalch equation using the pK_a value of 8.93 reported previously for 4-aminopyridinium ion in 80 mol% H_2O/20 mol% DMSO[4e] and the buffer ratios employed in this study (Table 2). As shown in Fig. 5, the plot of log (k_o – 0.0095) *vs.* the pH of the reaction medium exhibits an excellent linear correlation with a slope of 0.97 ± 0.03. This supports clearly the preceding argument that OH^- ion is a nucleophilic species in this study.

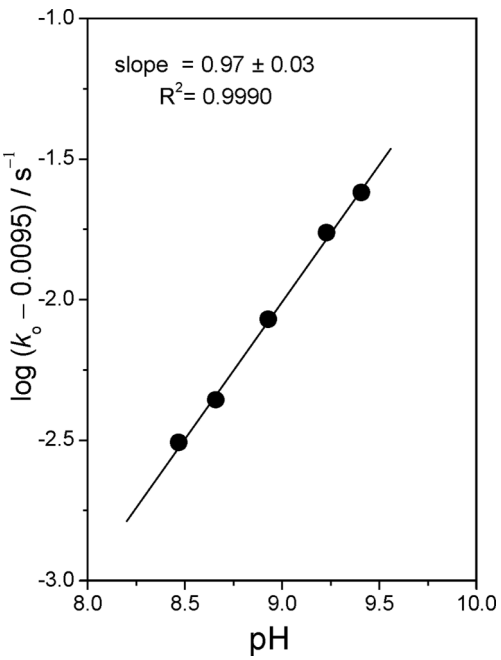
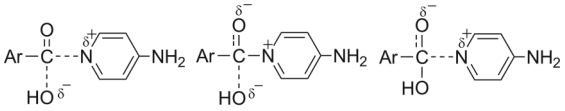


Fig. 5 Plot of log (k_o – 0.0095) *vs.* pH of the reaction medium for the hydrolysis of 1-benzoyl-4-aminopyridinium ion **2e** in 80 mol% H_2O/20 mol% DMSO at 25.0 ± 0.1 °C.

The reaction of **2a–i** with OH^- ion would proceed through an S_N2-like concerted mechanism with a TS structure similar to TS_1 or through a stepwise pathway with an intermediate. The latter mechanism can have one of the two TS structures (*i.e.*, TS_2 and TS_3) depending on the RDS, *i.e.*, TS_2 represents the TS structure in the rate-determining formation of the intermediate

while TS_3 applies to that in the rate-determining breakdown of the intermediate.



TS_1 TS_2 TS_3

It is well known that ρ_X for reactions which proceed through an S_N2 mechanism is small (*e.g.*, $\rho_X = -0.2 \pm 0.1$ for solvolysis of 2-phenylethyl tosylates and benzyl tosylates, and $\rho_X = 0.3 \pm 0.1$ for nucleophilic substitution reactions of diaryl chlorophosphates with anilines).[19,20] Thus, a small ρ_X value would be expected if the current reactions proceed through a concerted mechanism with a TS structure similar to TS_1. The ρ_X value of 1.45 or 1.39 for the current reactions appears to be too large for reactions which proceed through a concerted mechanism. Thus, one might suggest that the hydrolysis of **2a–i** proceeds through a stepwise mechanism with a TS structure similar to TS_2 or TS_3.

It is noted that OH^- ion is the nucleophilic species for both pyridine-catalyzed and uncatalyzed hydrolyses of **2a–i**. Furthermore, the ρ_X values for both processes are nearly the same (Fig. 3), indicating that the hydrolysis of **2a–i** proceeds through the same mechanism for both the pyridine-catalyzed and uncatalyzed processes. However, one might exclude the possibility that the reaction proceeds through TS_3, since OH^- is significantly more basic and a poorer nucleofuge than 4-aminopyridine. Accordingly, it is concluded that the hydrolysis of **2a–i** proceeds through a stepwise mechanism with a TS structure similar to TS_2.

Conclusions

The current study has allowed us to conclude the following: (1) Hydrolysis of **2a–i** proceeds through pyridine-catalyzed and uncatalyzed pathways. (2) The Hammett plots for the pyridine-catalyzed and uncatalyzed reactions of **2a–i** consist of two intersecting straight lines, while the corresponding Yukawa–Tsuno plots exhibit excellent linear correlations with $\rho_X = 1.39 \sim 1.45$ and $r = 0.72 \sim 0.76$. (3) The nonlinear Hammett plots are not due to a change in the RDS but are caused by stabilization of **2a–i** in the GS through the resonance interaction between the π-electron donor substituent and the carbonyl functionality in the GS. (4) The possibility that the reactions of **2a–i** proceed through a concerted mechanism has been ruled out on the basis of the large ρ_X values. (5) The hydrolysis of **2a–i** proceeds through a stepwise mechanism, in which the first step (*i.e.*, attack of OH^- ion to the carbonyl carbon atom of **2a–i**) is the RDS, since OH^- ion is significantly more basic and a poorer nucleofuge than 4-aminopyridine.

Experimental

Materials

2,4-Dinitrophenyl X-substituted benzoates **1a–i** were prepared readily from the reactions of 2,4-dinitrophenol and X-substituted benzoyl chlorides in anhydrous ether in the presence of triethylamine as reported previously.[8d,e] The crude products were purified through column chromatography. The purity of **1a–i** was checked by means of their melting points and ^1H NMR characteristics. Other chemicals used were of the highest quality. Doubly glass-distilled water was further boiled and cooled under nitrogen just before use.

Kinetics

The kinetic studies were performed at 25.0 ± 0.1 °C with a UV-Vis spectrophotometer equipped with a constant temperature circulating bath. The pyridine-catalyzed hydrolysis of 1-(X-substituted benzoyl)-4-aminopyridinium ions (*i.e.*, **2a–i**) was followed at 307 nm by monitoring the disappearance of the pyridinium ion obtained *in situ* from the reaction of **1a–i** with 4-aminopyridine. All the reactions were carried out under pseudo-first-order conditions in which the concentration of 4-aminopyridine was at least 20 times greater than that of the substrate. Typically, reaction was initiated by adding 5 μL of 0.02 M of substrate **1a–i** solution in MeCN by a 10 μL syringe into a 10 mm UV cell containing 2.50 mL of the reaction medium and 4-aminopyridine. The pyridine stock solution of *ca*. 0.2 M was prepared in a 25.0 mL volumetric flask under nitrogen by adding 2 equiv. of 4-aminopyridine to 1 equiv. of standardized HCl solution in order to obtain a 1 : 1 self-buffered solution. All the transfers of reaction solutions were carried out by means of gas-tight syringes.

Acknowledgements

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