Alkaline Hydrolysis of 4-Nitrophenyl X-Substituted-Benzoates Revisited: New Insights from Yukawa–Tsuno Equation

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Although numerous experimental and computational studies on hydrolysis of esters have been carried out, the reaction mechanism is not clearly understood.¹⁻¹² We have previously reported that alkaline hydrolysis of Y-substituted-phenyl benzenesulfonates $(1, Y = 2,4-(NO_2)_2, 3,4-$ (NO₂)₂, 4-Cl-2-NO₂, 4-NO₂, 4-CHO, 4-COMe, 3-COMe, 4-Cl) proceeds through a concerted mechanism based on a linear Brønsted-type plot with $\beta_{lg} = -0.55$ and an excellent linear Yukawa–Tsuno plot with $\rho_{\rm Y} = 1.83$ and $r = 0.52.^5$ In contrast, Babtie et al. have reported that alkaline hydrolysis of 1 (Y = 3-F-4-NO₂, 4-NO₂, 4-CN, 3-NO₂, 3-CN, 4-Cl, H, and 3,4-Me₂) proceeds through a concerted mechanism when the leaving group is weakly basic (e.g., $pK_a <$ 8.5) but proceeds through a stepwise mechanism for the reaction of substrates possessing a more basic leaving group on the basis of a curved Brønsted-type plot.⁶ Their quantum mechanics/molecular mechanics (QM/MM) calculations have also supported presence of a pentavalent intermediate.⁶ However, Duarte et al. have recently shown that correlation of the kinetic data reported by Babtie et al. with σ_{Y} constants results in a good linear Hammett plot.⁷ Moreover, the curved Brønsted-type plot reported by Babtie et al. becomes linear (with moderately scattered points) when three more experimental data are added (i.e., the kinetic data for the reactions of pyridine-3-yl benzenesulfonate, and its N-oxide and N-methylpyridinium derivatives). Besides, no evidence for a thermodynamically stable intermediate has been found from computational studies using HF/6-31++G* level of theory.⁷ Thus, Duarte *et al.* have concluded that the reaction proceeds through a concerted mechanism without changing the reaction mechanism.⁷



We have reported that alkaline hydrolysis of Y-substituted-phenyl phenyl carbonates (2) proceeds through a forced concerted mechanism on the basis of a linear Yukawa–Tsuno plot with $\rho_{\rm Y} = 1.21$ and $r = 0.33.^{8}$ However, the corresponding reaction of *O*-Y-substitutedphenyl *O*-phenyl thionocarbonates (**3**, a C=S analogue of **2**) has been suggested to proceed through a stepwise mechanism, in which expulsion of the leaving group occurs after the rate-determining step (RDS), on the basis of the kinetic result that σ_Y^0 constants exhibit a much better Hammett correlation than σ_Y^- constants.⁹ This demonstrates that the nature of the electrophilic center (*i.e.*, C=O vs. C=S) governs the reaction mechanism.

The nature of acyl group has also been reported to be an important factor that determines the reaction mechanism.^{10,11} Alkaline hydrolysis of Y-substituted-phenyl benzoates (4) has been reported to proceed through a stepwise mechanism, in which expulsion of the leaving group occurs after the RDS, on the basis of the kinetic result that σ_Y^{o} constants exhibits a much better Hammett correlation than σ_Y^{-} constants.¹⁰ In contrast, the reaction of Y-substituted-phenyl picolinates (5) has been suggested to proceed through a forced concerted mechanism on the basis of an excellent linear Yukawa–Tsuno plot with $\rho_Y = 0.82$ and r = 0.72,¹¹ indicating that modification of the acyl group from benzoyl in 4 to picolinyl in 5 (or phenoxycarbonyl in 2) causes a change in the reaction mechanism.

$$Ph-\overset{O}{\leftarrow} -O \xrightarrow{} V \xrightarrow{} V \xrightarrow{} O \xrightarrow{$$

Some years ago, we reported that alkaline hydrolysis of 4-nitrophenyl X-substituted benzoates (**6a–k**, Scheme 1) proceeds through a stepwise mechanism with a change in the RDS on the basis of a curved Hammett plot (*i.e.*, concave downward curvature).¹² However, if the reaction proceeds through a stepwise mechanism, expulsion of the leaving group should occur after the RDS regardless of the electronic nature of the substituent X. This is because OH⁻ ion is significantly more basic and a much poorer nucleofuge than 4-nitrophenoxide ion. Apparently, our previous report based on the nonlinear Hammett plot for the reaction of **6a–k** was incorrect.



 $\begin{array}{l} \mathsf{X} = 3,5\text{-}(\mathsf{NO}_2)_2 \ (\textbf{6a}), \ 4\text{-}\mathsf{CI}\text{-}3\text{-}\mathsf{NO}_2 \ (\textbf{6b}), \ 4\text{-}\mathsf{NO}_2 \ (\textbf{6c}), \ 4\text{-}\mathsf{CN} \ (\textbf{6d}), \ 3\text{-}\mathsf{CI} \ (\textbf{6e}), \\ 4\text{-}\mathsf{CI} \ (\textbf{6f}), \ \mathsf{H} \ (\textbf{6g}), \ 3\text{-}\mathsf{CH}_3 \ (\textbf{6h}), \ 4\text{-}\mathsf{CH}_3 \ (\textbf{6i}), \ 4\text{-}\mathsf{OCH}_3 \ (\textbf{6j}), \ 4\text{-}\mathsf{N(CH}_3)_2 \ (\textbf{6k}) \end{array} \right.$

Scheme 1. Alkaline hydrolysis of 4-nitrophenyl X-substituted benzoates (6a–k).

Thus, we have revisited alkaline hydrolysis of 4nitrophenyl X-substituted benzoates (6a-k) to investigate the cause of the nonlinear Hammett plot as well as the reaction mechanism. We wish to report that the nonlinear Hammett plot reported previously for the reactions of 6a-k is not due to a change in the RDS but is caused by resonance stabilization of the substrates possessing an electrondonating group (EDG) on the fourth position of the benzoyl moiety. The current study has also highlighted that one has to be extremely careful in interpretation of a nonlinear Hammett plot.

The second-order rate constants (k_{OH} -) for the reactions of **6a-k** are summarized in Table 1 together with those reported previously. As shown in Table 1, the k_{OH} - values measured in this study are practically the same as those reported previously within an experimental error range. The effect of the substituent X on reactivity is illustrated in Figure 1. The Hammett plot consists of two intersecting straight lines, *i.e.*, the ρ_X value decreases as the substituent X changes from EDGs to electron-withdrawing groups (EWGs). Such nonlinear Hammett plot has traditionally been interpreted as a change in the RDS.¹³ In fact, we have previously reported that the reaction of **6a-k** proceeds through a stepwise mechanism with a change in the RDS.¹²

Table 1. Summary of second-order rate constants for alkaline hydrolysis of 4-nitrophenyl X-substituted-benzoates (**6a–k**) in 80 mol % H₂O/20 mol % DMSO at 25.0 \pm 0.1°C.

	Х	$k_{\rm OH} - /{\rm M}^{-1}{\rm s}^{-1}$
6a	3,5-(NO ₂) ₂	4960 ± 140 (5010)
6b	4-Cl-3-NO ₂	706 ± 18 (715)
6c	4-NO ₂	507 ± 15 (531)
6d	4-CN	329 ± 13 (354)
6e	3-Cl	$74.5 \pm 1.8 \ (73.8)$
6f	4-Cl	$40.5 \pm 1.1 \ (39.6)$
6g	Н	$13.4 \pm 0.4 \ (13.4)$
6h	3-CH ₃	(8.90)
6i	4-CH ₃	$5.96 \pm 0.20~(5.65)$
6j	4-OCH ₃	$2.91 \pm 0.08 \; (2.64)$
6k	4-N(CH ₃) ₂	0.156 ± 0.005 (—)

The data in the parenthesis are taken from Ref. 12.



Figure 1. Hammett plots for alkaline hydrolysis of 4-nitrophenyl X-substituted-benzoates (6a-k) in 80 mol % H₂O/20 mol % DMSO at $25.0 \pm 0.1^{\circ}$ C.

However, as mentioned above, if the reaction proceeds through a stepwise mechanism, expulsion of the leaving group should occur after the RDS regardless of the electronic nature of the substituent X in the nonleaving group. Thus, one might attribute the nonlinear Hammett plot to a change in the reaction mechanism, *e.g.*, from a stepwise mechanism, in which expulsion of the leaving group occurs after the RDS, to a concerted mechanism as the substituent X changes from EWGs to EDGs. This idea can be supported by the report that modification of the acyl group from benzoyl in **4** to picolinyl in **5** (or phenoxycarbonyl in **2**) causes a change in the reaction mechanism from a stepwise mechanism to a forced concerted pathway.^{8–11}

However, we propose that the nonlinear Hammett plot shown in Figure 1 is not due to a change in the reaction mechanism based on the following reasons. Substrates possessing an EDG at the 4-position of the benzoyl moiety (*e. g.*, **6k**) could be stabilized through resonance interactions as illustrated by the resonance structures I_R and II_R . It is apparent that such resonance interaction could cause a decrease in reactivity by stabilizing the ground state (GS) of the substrate. In fact, a careful examination of the nonlinear Hammett plot in Figure 1 reveals that substrates bearing an EDG deviate negatively from the linear line composed with substrates holding an EWG (*i.e.*, **6a–f**). Furthermore, such negative deviation is more significant for the substrate possessing a stronger EDG (*e.g.*, **6k**). Thus, we propose that the nonlinear Hammett plot is caused by resonance stabilization of the GS of the substrates possessing an EDG in the benzoyl moiety.



To examine the validity of the above proposal, Yukawa– Tsuno plot has been constructed using the kinetic data in Table 1. Although the Yukawa–Tsuno equation (Eq. (1)) was derived to account for the experimental results for solvolysis of benzylic system,^{14,15} we have shown that Eq. (1) is highly effective in deduction of the reaction mechanism for various nucleophilic substitution reactions of various esters.¹⁶

$$\log k_{\rm X}/k_{\rm H} = \rho_{\rm X} [\sigma_{\rm X}^{\rm o} + r(\sigma_{\rm X}^{\rm +} - \sigma_{\rm X}^{\rm o})]$$
(1)

As shown in Figure 2, the Yukawa–Tsuno plot exhibits an excellent linear correlation ($R^2 = 0.998$) with $\rho_X = 1.83$ and r = 0.50. This indicates that the nonlinear Hammett plot for the reaction of **6a–k** is clearly not due to a change in the RDS (or reaction mechanism). It is noted that the *r*value in Eq. (1) represents extent of the resonance contribution.^{14,15} Thus, an *r*-value of 0.50 found in this study is consistent with our proposal that resonance stabilization of the substrate possessing an EDG in the benzoyl moiety is responsible for the negative deviation from the linear Hammett plot composed with the substrates possessing an EWG in the benzoyl moiety (*e.g.*, **6a–f**).

Many factors have been reported to influence the magnitude of the ρ_X value (e.g., the charge type and basicity of nucleophiles, the distance from the reaction center to the substituent, the nature of the reaction mechanism, etc.).^{16,17} One might expect a large ρ_X value for reactions which proceed through a stepwise pathway with expulsion of the leaving group occurring after the RDS. Because electrophilicity of the reaction center would be increased by an EWG in the benzoyl moiety but decreased by an EDG. In contrast, a small ρ_X value would be expected for reactions that proceed through a concerted mechanism or via a stepwise pathway with expulsion of the leaving group occurring in the RDS. Because an EWG in the benzoyl moiety would accelerate rate of the nucleophilic attack but would retard rate of the leaving-group expulsion. In fact, a small ρ_X value (e.g., $\rho_{\rm X}$ < 1) has often been reported for reactions that proceed through a concerted mechanism.¹⁷ Thus, a ρ_X value of 1.83 found in this study is quite large and is consistent with our previous report that alkaline hydrolysis of Y-substitutedphenyl benzoates proceed through a stepwise mechanism with formation of an addition intermediate being the RDS.



Figure 2. Yukawa–Tsuno plot for alkaline hydrolysis of 4nitrophenyl X-substituted-benzoates (**6a–k**) in 80 mol % H₂O/ 20 mol % DMSO at $25.0 \pm 0.1^{\circ}$ C.

In summary, although the Hammett plot for the alkaline hydrolysis of **6a–k** consists of two intersecting straight lines, the Yukawa–Tsuno plot exhibits an excellent linear correlation with $\rho_X = 1.83$ and r = 0.50. Thus, the nonlinear Hammett plot is clearly not due to a change in the RDS (or the reaction mechanism) but is caused by resonance stabilization of the substrates bearing an EDG in the benzoyl moiety. The large ρ_X value found for the current reaction is consistent with the previous report that alkaline hydrolysis of Y-substituted-phenyl benzoates (**4**) proceeds through a stepwise mechanism with formation of an addition intermediate being the RDS. The current study has also demonstrated that deduction of the reaction mechanism based just on a linear or nonlinear Hammett plot could lead a wrong conclusion.

Experimental

Materials. Compounds **6a–k** were readily prepared from the reaction of X-substituted-benzoyl chloride and 4nitrophenol in anhydrous ether in the presence of triethylamine as reported previously.¹⁰ Their purity was confirmed from melting points and ¹H NMR characteristics. Doubly glass distilled H_2O was further boiled and cooled under nitrogen atmosphere just before use. NaOH stock solution was titrated using potassium hydrogen phthalate. Dimethyl sulfoxide (DMSO) and other chemicals used were of the highest quality available.

Kinetics. The kinetic study was performed using a UV– Vis spectrophotometer for slow reactions $(t_{1/2} > 10 \text{ s})$ or a stopped-flow spectrophotometer for fast reactions $(t_{1/2} \le 10 \text{ s})$ equipped with a constant temperature circulating bath to keep the reaction temperature at $25.0 \pm 0.1^{\circ}$ C. All reactions in this study were carried out under pseudo-firstorder conditions in which NaOH concentration was at least 20 times greater than the substrate concentration. The reactions were followed by monitoring the appearance of 4nitrophenoxide ion up to nine half-lives. The plots of the pseudo-first-order rate constants (k_{obsd}) vs. [OH⁻] were linear and passed through the origin, indicating that contribution of H₂O to k_{obsd} is negligible. Thus, second-order rate constants (k_{OH}) were calculated from the slope of linear plots and summarized in Table 1.

Product Analysis. 4-Nitrophenoxide ion was liberated quantitatively and identified as one of the reaction products by comparison of the UV–Vis spectra obtained after completion of the reactions with those of authentic samples under the same kinetic conditions.

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