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Analysis of Linear Free-Energy Relationships Combined with Activation Parameters Assigns a Concerted Mechanism to Alkaline Hydrolysis of X-Substituted Phenyl Diphenylphosphinates

Ik-Hwan Um,* Jeong-Yoon Han, and So-Jeong Hwang[a]

Abstract: A kinetic study is reported for alkaline hydrolysis of X-substituted phenyl diphenylphosphinates (**1a–i**). The Brønsted-type plot for the reactions of **1a–i** is linear over 4.5 pK_a units with $\beta_{lg} = -0.49$, a typical β_{lg} value for reactions which proceed through a concerted mechanism. The Hammett plots correlated with σ^o and σ^- constants are linear but exhibit many scattered points, while the corresponding Yukawa–Tsuno plot results in excellent linear correlation with $\rho = 1.42$ and $r = 0.35$. The r value of 0.35 implies that leaving-group departure is partially advanced at the rate-determining step (RDS). A stepwise mechanism, in which departure of the leaving group from an addition intermediate occurs in the RDS, is excluded since the incoming HO^- ion is much more basic and a poorer nucleofuge than the leaving aryloxide. A dissociative ($D_N + A_N$) mechanism is also ruled out on the basis of the small β_{lg} value. As the substituent X in the leaving group changes from H to 4-NO_2 and 3,4-$(NO_2)_2$, $\Delta H^{\neq}$ decreases from 11.3 kcal mol^{-1} to 9.7 and 8.7 kcal mol^{-1}, respectively, while $\Delta S^{\neq}$ varies from -22.6 cal mol^{-1} K^{-1} to -21.4 and -20.2 cal mol^{-1} K^{-1}, respectively. Analysis of LFERs combined with the activation parameters assigns a concerted mechanism to the current alkaline hydrolysis of **1a–i**.

Keywords: activation parameters · alkaline hydrolysis · reaction mechanism

Introduction

Certain organophosphorus compounds (e.g., soman, sarin, paraoxon, parathion, etc.) are known to possess mammalian toxicity as well as insecticidal properties, and to act as acetylcholinesterase inhibitors.[1–4] Thus, deactivation of these toxic compounds under mild conditions has become an important task in environmental chemistry. Numerous studies have been performed to enhance the rate of decomposition of toxic organophosphorus compounds.[5–12] The use of α-nucleophiles such as HOO^-, *o*-iodosylbenzoate and various oximate anions have been reported to be highly effective to destroy such toxic materials under mild conditions.[5–9] Besides, various metal ions have shown significant catalytic effects as Lewis acid catalysts in reactions of various organophosphorus compounds.[10–12]

However, mechanistic (experimental and theoretical) studies have been performed much less intensively. Accordingly, the mechanisms have not been completely understood but remain controversial (i.e., concerted vs stepwise mechanism).[13–20] Williams et al., performed nucleophilic substitution reactions of 4-nitrophenyl diphenylphosphinate with a series of aryloxides whose pK_a values increase the basicity of the leaving 4-nitrophenoxide.[13] The reactions have been concluded to proceed through a concerted mechanism since the Brønsted-type plot was found to be linear.[13] Similarly, Hengge et al. have found that alkaline hydrolysis of aryl dimethylphosphinothioates exhibits much better Hammett correlation with σ^- ($R^2 = 0.991$) than with σ^o ($R^2 = 0.933$) or σ constants ($R^2 = 0.926$).[14a] Besides, reactions of 4-nitrophenyl dimethylphosphinothioate with aryloxides also resulted in a linear Brønsted-type plot over 4.6 pK_a units with $\beta_{nuc} = 0.47$.[14a] Thus, the reactions have been concluded to proceed through a concerted mechanism with a transition-state (TS) structure similar to TS_1.[14a] This conclusion has been further supported by studies of the primary ^{18}O and secondary ^{15}N kinetic isotope effects.[14a]

On the contrary, Haake et al. have concluded that alkaline hydrolysis of X-substituted phenyl diphenylphosphinates (X = 4-MeCO, 4-Br, 4-Cl, H, 3-Me, and 4-Me) pro-

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[a] Prof. Dr. I.-H. Um, J.-Y. Han, S.-J. Hwang
Division of Nano Sciences and Department of Chemistry
Ewha Womans University, Seoul 120-750 (Korea)
Fax: (+82) 2-3277-2844
E-mail: ihum@ewha.ac.kr

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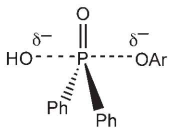
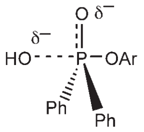
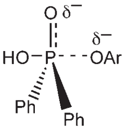


TS_1



TS_2

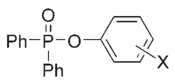


TS_3

ceeds through a stepwise mechanism on the basis of the fact that σ^{o} constants exhibit a better Hammett correlation than σ^{-} constants.[16] Similar results have been reported for alkaline hydrolysis of *O*-X-substituted phenyl dimethylphosphinothioates (X = 4-NO_2, 4-Br, H, and 4-Me),[17] imidazole catalyzed hydrolysis of X-substituted phenyl diphenylphosphinates (X = 4-NO_2, 3-NO_2, 4-MeCO, 4-Cl, and H)[18] and alkaline ethanolysis of X-substituted phenyl dimethylphosphinates (X = 4-NO_2, 3-NO_2, 4-MeCO, 4-Cl, H, and 4-Me).[10a] Thus, these reactions have been concluded to proceed through a stepwise mechanism with a TS structure similar to TS_2.[10a,16–18]

We have recently shown that σ^{o} constants result in a better Hammett correlation than with σ^{-} constants for alkaline ethanolysis of aryl diphenylphosphinates,[19] and aminolyses of aryl diphenylphosphinates[20a] and their thio analogues, *O*-aryl diphenylphosphinothioates.[20b] Traditionally, this result has been taken as evidence for a stepwise mechanism with a TS structure similar to TS_2.[10a,16–18] However, we have concluded that the reaction proceeds through a concerted mechanism, since the Yukawa–Tsuno plots for the same reactions exhibit significantly better correlation than the Hammett plots correlated with σ^{o} constants alone.[19,20]

We have extended our study to alkaline hydrolysis of X-substituted phenyl diphenylphosphinates (**1a**–**i**) at various temperatures. The kinetic data have been analyzed using various LFERs together with activation parameters (e.g., $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$). Analysis of LFER's combined with the activation parameters permits unambiguous assignment of the mechanism of the phosphinyl-transfer reaction. Besides, we have shown that deduction of reaction mechanism based just on the result from Hammett correlations with σ^{o} or σ^{-} constants alone can be misleading.



X = 3,4-$(NO_2)_2$ (**1a**), 4-NO_2 (**1b**), 4-CHO (**1c**), 4-CN (**1d**),
4-COMe (**1e**), 3-Cl (**1f**), 3-COMe (**1g**), 4-Cl (**1h**), H (**1i**).

Results and Discussion

All reactions in this study obeyed pseudo-first-order kinetics with quantitative liberation of X-substituted phenoxide. Pseudo-first-order rate constants (k_{obsd}) were determined from the equation $\ln(A_{\infty}-A_t) = -k_{obsd}t + C$. The plots of k_{obsd} versus $[HO^-]$ were linear passing through the origin, which indicates that the contribution of H_2O to k_{obsd} is negligible. Thus, the rate law is given by Equation (1).

$$\text{rate} = k_{obsd}[\text{Sub}], \text{ where } k_{obsd} = k_{HO^-}[HO^-] \qquad (1)$$

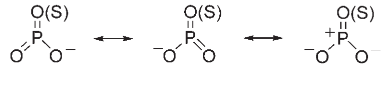
The second-order rate constants (k_{HO^-}) were determined from the slopes of the linear plots of k_{obsd} versus $[HO^-]$ and summarized in Tables 1 and 2. The uncertainty in k_{HO^-} is estimated to be less than 3 % from replicate runs. The activation parameters ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) were calculated from the Eyring equation.[21] Kinetic conditions and results are detailed in the Supporting Information.

Table 1. Summary of second-order rate constants (k_{HO^-}) for alkaline hydrolysis of X-substituted phenyl diphenylphosphinates (**1a**–**i**) in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C.

Entry	X	pK_a (X-PhOH)	k_{HO^-}/M^{-1} s^{-1}
1a	3,4-$(NO_2)_2$	5.42	200
1b	4-NO_2	7.14	21.3
1c	4-CHO	7.66	9.11
1d	4-CN	7.95	13.3
1e	4-COMe	8.05	6.57
1f	3-Cl	9.02	3.81
1g	3-COMe	9.19	3.38
1h	4-Cl	9.38	2.44
1i	H	9.95	0.690

Effect of leaving-group basicity on reactivity: As shown in Table 1, the second-order rate constant decreases as the leaving group becomes more basic, that is, it decreases from 200 $M^{-1}s^{-1}$ to 6.57 and 0.690 $M^{-1}s^{-1}$ as the pK_a of the conjugate acid of the leaving aryloxide increases from 5.42 to 8.05 and 9.95, respectively. The effect of the leaving-group basicity on reactivity is illustrated in Figure 1. The Brønsted-type plot is linear over 4.5 pK_a units with $\beta_{lg} = -0.49 \pm 0.04$.

The β_{lg} value determined in the current reactions is substantially smaller than that reported for hydrolyses of aryl phosphate dianions ($\beta_{lg} = -1.2$)[22a] and their thio analogues, *O*-aryl phosphorothioate dianions ($\beta_{lg} = -1.1$).[22b] Such large β_{lg} values for the latter reactions indicate that the dissociation of the P–OAr bond is significantly advanced in the TS. Furthermore, the resulting metaphosphate intermediate can be stabilized through resonance interactions as shown below. Thus, the reactions have been concluded to proceed through a dissociative ($D_N + A_N$) mechanism.[22]



However, one can exclude a ($D_N + A_N$) mechanism in the current hydrolysis of **1a**–**i** since a metaphosphate intermediate is not possible and the β_{lg} of −0.49 is too small for an ($D_N + A_N$) mechanism. In addition, it has been argued that metaphosphate is not an intermediate for reactions of aryl phosphates in aqueous medium.[23]

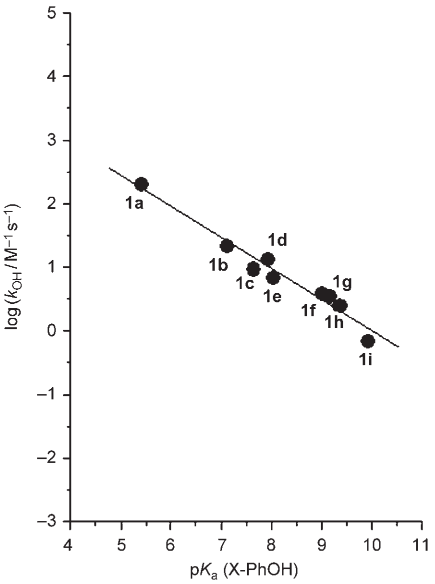


Figure 1. Brønsted-type plot for alkaline hydrolysis of X-substituted phenyl diphenylphosphinates (**1a**–**i**) in 80 mol% H_2O/20 mol% DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1; $\beta_{lg} = -0.49 \pm 0.04$, $R^2 = 0.980$.

The β_{lg} value obtained from the current reactions can be compared with that reported for reactions which have been suggested to proceed through a concerted mechanism, for example, $\beta_{lg} = -0.54 \pm 0.04$ for alkaline ethanolysis of aryl diphenylphosphinates,[19] $\beta_{lg} = -0.47$ for alkaline hydrolysis of aryl dimethylphosphinates,[24] $\beta_{lg} = -0.51$ for reactions of aryl diethyl phosphates with PhO^- in water,[25] $\beta_{lg} = -0.54$ and -0.52 for reactions of *O*-aryl dimethylphosphinothioates with HO^- and PhO^-, respectively,[14a] and $\beta_{lg} = -0.39 \pm 0.04$ for reactions of *O*-aryl dimethyl phosphorothioates with PhO^- in water.[26] Since $\beta_{lg} = -0.5 \pm 0.1$ appears to be typical for reactions which proceed through a concerted mechanism, one can suggest that the current hydrolysis of **1a**–**i** proceeds through a concerted mechanism.

Hammett versus Yukawa–Tsuno plots: One might expect that σ^- constants would result in a better Hammett correlation than σ^o constants if breakdown of the P–OAr bond occurs in the RDS either in a concerted mechanism with a TS structure similar to TS_1 or in a stepwise mechanism with TS_3. On the contrary, σ^o constants would exhibit a better Hammett correlation than σ^- constants if the bond rupture occurs after the RDS with a TS structure similar to TS_2. In fact, Haake et al. have concluded that alkaline hydrolysis of X-substituted phenyl diphenylphosphinates (X = 4-MeCO, 4-Br, 4-Cl, H, 3-Me, and 4-Me) proceeds through a stepwise mechanism with a TS structure similar to TS_2 on the basis of the fact that σ^o constants exhibit a better Hammett correlation than σ^- constants.[16] A similar conclusion has been drawn for hydrolysis of *O*-X-substituted phenyl dimethylphosphinothioates (X = 4-NO_2, 4-Br, H, and 4-Me),[17] imidazole catalyzed hydrolysis of X-substituted phenyl diphenylphosphinates (X = 4-NO_2, 3-NO_2, 4-MeCO, 4-Cl, and H)[18] and alkaline ethanolysis of X-substituted phenyl dimethylphosphinates (X = 4-NO_2, 3-NO_2, 4-MeCO, 4-Cl, H, and 4-Me).[10a]

To determine the mechanism for the reactions of **1a**–**i**, Hammett plots have been constructed using σ^o and σ^- constants in Figure 2A and B, respectively. A careful examination of Figure 2A and B reveals that σ^o constants exhibit only a slightly better correlation than σ^- constants (i.e., $R^2 = 0.982$ for σ^o and $R^2 = 0.974$ for σ^- constants). Thus, one cannot obtain any conclusive information on the reaction mechanism by the traditional method using σ^o or σ^- constants.

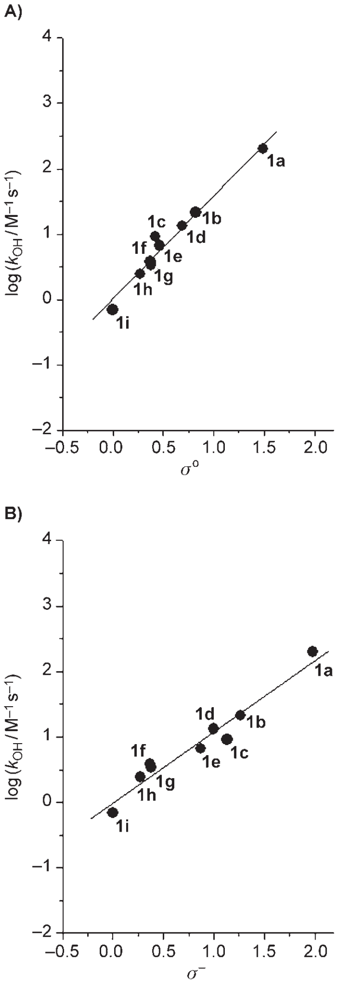


Figure 2. Hammett correlations with A) σ^o ($\rho = 1.60$; $R^2 = 0.982$) and B) σ^- ($\rho = 1.09$; $R^2 = 0.974$) constants for alkaline hydrolysis of X-substituted phenyl diphenylphosphinates (**1a**–**i**) in 80 mol% H_2O/20 mol% DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

We have recently reported that the Yukawa–Tsuno equation [Eq. (2)] is highly effective to elucidate ambiguities in reaction mechanisms of phosphinyl transfer and related reactions.[19,20,27] Thus, a Yukawa–Tsuno plot has been constructed for the current hydrolysis of **1a**–**i**. As shown in

Figure 3, the Yukawa–Tsuno plot exhibits an excellent correlation (i.e., $R^2=0.996$) with $\rho=1.42$ and $r=0.35$. Since the r value determined in the current reactions is neither 0 nor 1, the Yukawa–Tsuno plot results in much better linear correlation than the Hammett plot using σ^o or σ^- constants alone.

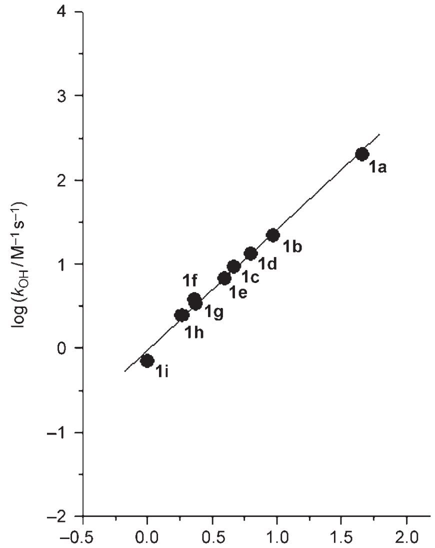


Figure 3. Yukawa–Tsuno plot for alkaline hydrolysis of X-substituted phenyl diphenylphosphinates (**1a–i**) in 80 mol% H_2O/20 mol% DMSO at 25.0±0.1 °C; $\rho = 1.42$, $r = 0.35$, $R^2 = 0.996$.

$$\log k^X/k^H = \rho[\sigma^o + r(\sigma^- - \sigma^o)] \qquad (2)$$

The r value in the Yukawa–Tsuno equation represents the resonance demand of the reaction center or the extent of resonance contribution.[28] The fact that $r=0.35$ in the current reactions indicates that a partial negative charge develops (in the RDS) on the O atom of the leaving aryloxide, which can be delocalized on the substituent X through resonance interactions. Thus, the current result indicates that breakdown of the P−OAr bond occurs in the RDS whether the reactions proceed through TS_1 or TS_3. However, one can exclude TS_3 clearly in the current reactions on the basis of the fact that the incoming hydroxide is much more basic and a poorer nucleofuge than the leaving aryloxide. Thus, one can suggest that the present reactions of **1a–i** proceed through a concerted mechanism with TS_1.

Table 2. Summary of kinetic results for alkaline hydrolysis of **1a**, **1b**, and **1i** in 80 mol% H_2O/20 mol% DMSO at five different temperatures.

	k_{HO^-}/M^{-1}s^{-1}						
	15.0 °C	20.0 °C	25.0 °C	35.0 °C	45.0 °C	$\Delta H^{\neq}$/kcal mol^{-1}	$\Delta S^{\neq}$/cal mol^{-1} K^{-1}
1a	116	153	200	341	543	8.7±0.2	−20.2±0.6
1b	11.9	16.2	21.3	38.5	65.5	9.7±0.1	−21.4±0.4
1i	0.344	0.475	0.690	1.28	2.52	11.3±0.2	−22.6±0.8

The above argument is inconsistent with the conclusion drawn by Haake,[16] by Istomin,[17] and by Williams et al.[18] for alkaline hydrolysis of aryl diphenylphosphinates. They concluded that the reactions proceed through a TS structure similar to TS_2, since σ^o (or σ) constants exhibited better Hammett correlations than σ^- constants.[16–18] We suggest that the discrepancy in the mechanism may be due to limited numbers of substituents employed to construct a Hammett plot with σ^- constants (e.g., only 4-NO_2 or 4-MeCO has a σ^- constant among four or six different substituents employed by Istomin or by Haake et al., respectively), or in the other case, to a failure of choosing a proper LFER such as the Yukawa–Tsuno equation. In fact, we have found that the kinetic data reported by Williams et al.[18] result in much better correlation in the Yukawa–Tsuno plot ($R^2=0.995$) than in the Hammett plot using σ constants ($R^2=0.977$).

The ρ value of 1.42 shown in Figure 3 is comparable to that reported for reactions which have been suggested to proceed through TS_1, for example, $\rho=1.17$ for alkaline hydrolysis of *O*-aryl dimethylphosphinothioates,[14a] $\rho=1.98$ for alkaline ethanolysis of aryl diphenylphosphinates,[19] and $\rho=1.91$ for aminolysis of aryl diphenylphosphinates and their thio analogs, *O*-aryl diphenylphosphinothioates.[20] However, substantially larger ρ values have been reported for reactions which proceed through a stepwise mechanism with breakdown of intermediate being the RDS, for example, $\rho=3.01$ for aminolysis of X-substituted phenyl benzoates.[27a] Thus, the fact that $\rho=1.42$ in the current reactions also supports a concerted mechanism.

Activation parameters and reaction mechanism: To further probe the above argument, activation parameters ($\Delta H^{\neq}$ and $\Delta S^{\neq}$) have been determined from the rate constants measured at five different temperatures for reactions of 3,4-dinitrophenyl, 4-nitrophenyl, and phenyl diphenylphosphinates (**1a**, **1b**, and **1i**, respectively) with HO^- ion. The kinetic results are summarized in Table 2 and illustrated graphically in Figure 4. As shown in Figure 4, the Eyring plots exhibit excellent linear correlations, indicating that the $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values determined in this study are accurate and reliable.

The electronic nature of the substituent X in the leaving aryloxide would influence the bond dissociation energy of the P−OAr bond. Furthermore, the energy required to break the P−OAr bond is reflected in $\Delta H^{\neq}$. Thus, if the reaction proceeds through a concerted mechanism as discussed above, $\Delta H^{\neq}$ should be strongly dependent on the electronic nature of the substituent X. In fact, Table 2 shows that $\Delta H^{\neq}$ increases from 8.7 kcal mol^{-1} to 9.7 and 11.3 kcal

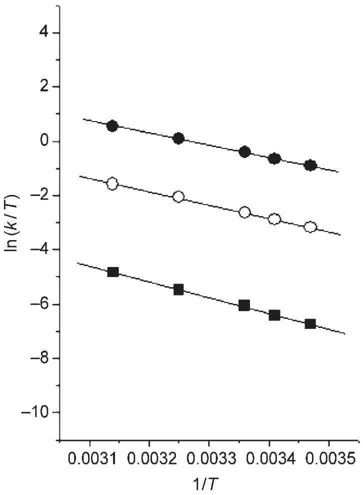


Figure 4. Eyring plots for alkaline hydrolysis of **1a** (●, slope: −4400, intercept: 14.4), **1b** (○, slope: −4900, intercept: 13.8), and **1i** (■, slope: −5700, intercept: 13.2.4) in 80 mol% H_2O/20 mol% DMSO at five different temperatures.

mol^{-1} as the substituent X changes from 3,4-$(NO_2)_2$ to 4-NO_2 and H. The effect of the substituent X on $\Delta H^{\neq}$ is illustrated in Figure 5, which exhibits an excellent linear correlation with a large slope. Such a strong dependence of $\Delta H^{\neq}$ on the substituent X in the leaving group cannot be expected for reactions in which the departure of the leaving group occurs after the RDS (e.g., TS_2).

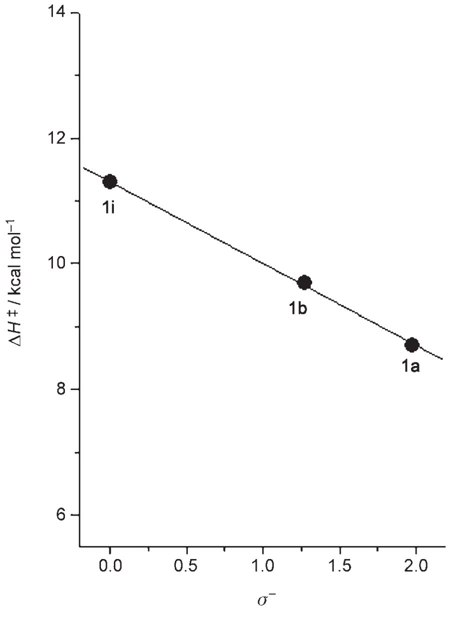


Figure 5. Plot of $\Delta H^{\neq}$ versus σ^- constants for alkaline hydrolysis of phenyl diphenylphosphinate (**1i**), 4-nitrophenyl diphenylphosphinate (**1b**) and 3,4-dinitrophenyl diphenylphosphinate (**1a**) in 80 mol% H_2O/20 mol% DMSO at 25.0±0.1 °C; slope: −1.31, $R^2 = 0.995$.

A similar result has been reported for the reactions of morpholine with 2,4-dinitrophenyl, 4-nitrophenyl, and phenyl acetates.[29] Jencks et al. have shown that the reactions proceed through an addition intermediate with its breakdown being the RDS (i.e., TS_3), and the $\Delta H^{\neq}$ value increases from 9.1 kcal mol^{-1} to 10.7 and 14.3 kcal mol^{-1} as the substituent changes from 2,4-$(NO_2)_2$ to 4-NO_2 and H, respectively.[29] Thus, one might suggest that $\Delta H^{\neq}$ is even more strongly dependent on the electronic nature of the substituent in the leaving group for reactions which proceed through a stepwise mechanism with leaving-group departure being the RDS.

The fact that the Brønsted-type and Yukawa–Tsuno plots are linear in the current hydrolysis of **1a**–**i** indicates that the reaction proceeds through a common TS structure (i.e., the degree of leaving-group departure is constant regardless of the electronic nature of the substituent X in the leaving group). In this case, solvation of the negatively charged TS would be more important than other factors (e.g., tightness or looseness) to determine $\Delta S^{\neq}$.

The negative charge developing on the O atom of the leaving aryloxide can be delocalized on the substituent X through resonance interactions. Furthermore, as the substituent X changes from H to 3,4-$(NO_2)_2$, delocalization of such partial negative charge would be more significant, which would cause a decrease in solvation of the TS by decreasing H-bonding in the aqueous medium. Thus, one can expect that $\Delta S^{\neq}$ would become less negative for the reaction of **1a** (X = 3,4-$(NO_2)_2$) than for that of **1i** (X = H). In fact, as shown in Table 2, the $\Delta S^{\neq}$ value changes from −22.6 cal mol^{-1} K^{-1} to −21.4 and −20.2 cal mol^{-1} K^{-1} as the substituent X varies from H to 4-NO_2 and 3,4-$(NO_2)_2$, respectively. Thus, the change in $\Delta S^{\neq}$ on changing the substituent X, although it is not large, is consistent with the proposed mechanism.

Conclusion

The present study has allowed us to conclude the following:

1) The reactions of **1a**–**i** have been suggested to proceed through a concerted mechanism on the basis of the linear Brønsted-type plot with $\beta_{lg} = -0.49$.
2) The Yukawa–Tsuno plot exhibits much better correlation ($R^2 = 0.996$) with $r = 0.35$ than the Hammett plot correlated with σ^o constants ($R^2 = 0.982$), indicating that departure of the leaving group is advanced partially in the RDS. However, TS_3 has been excluded since HO^- ion is more basic and a poorer nucleofuge than the leaving phenoxide ion.
3) The $\Delta H^{\neq}$ values are strongly dependent on the electronic nature of the substituent X in the leaving group, indicating that the leaving-group departure occurs in the RDS.
4) The $\Delta S^{\neq}$ value becomes less negative as the substituent X varies from H to 4-NO_2 and 3,4-$(NO_2)_2$, which has

been attributed to a decrease in solvation of the negatively charged TS_1 on changing the substituent X.

5) Deduction of reaction mechanism based just on the result from Hammett correlations with σ^o or σ^- constants alone can be misleading.

Experimental Section

Materials: X-substituted phenyl diphenylphosphinates (**1a–i**) were synthesized by modification of literature as reported previously.[19,20] The concentration of NaOH stock solution was determined by titration with potassium hydrogen phthalate. Doubly glass distilled H_2O was further boiled and cooled under N_2 to remove CO_2 just before use. Other chemicals were the highest grade available.

Kinetics: Kinetic studies were performed with a UV/Vis spectrophotometer for slow reactions ($t_{1/2} = 10$ s) or with a stopped-flow spectrophotometer for fast reactions ($t_{1/2} < 10$ s) equipped with a constant temperature circulating bath. The reactions were followed by monitoring the appearance of the leaving aryloxide at a fixed wavelength corresponding to the maximum absorbance (λ_{max}) of $X\text{-}C_6H_4O^-$. All the reactions were carried out under pseudo-first-order conditions in the presence of excess NaOH. Typically, the reaction was initiated by adding 5 μL of a 0.02 M of substrate solution in MeCN by a 10 μL gastight syringe to a 10 mm quartz UV cell containing 2.50 mL of the thermostated reaction mixture made up of CO_2-free H_2O and an aliquot of NaOH stock solution. All the solutions were transferred by gastight syringes under nitrogen. Usually five different concentrations of NaOH solution were used to determine second-order rate constant (k_{HO^-}) from the slope of the linear plot of k_{obsd} vs NaOH concentration.

Products analysis: X-substituted phenoxide was liberated quantitatively and identified as one of the reaction products by comparison of the UV/Vis spectra after the completion of the reactions with those of the authentic samples under the same reaction conditions.

Acknowledgements

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