

Kinetics and Mechanism of the Anilinolysis of Bis(aryl) Chlorophosphates in Acetonitrile

Hasi Rani Barai and Hai Whang Lee*

Department of Chemistry, Inha University, Incheon 402-751, Korea. *E-mail: hwlee@inha.ac.kr
Received April 19, 2011, Accepted April 22, 2011

The nucleophilic substitution reactions of bis(Y-aryl) chlorophosphates (**1**) with substituted anilines and deuterated anilines are investigated kinetically in acetonitrile at 35.0 °C. The kinetic results of **1** are compared with those of Y-aryl phenyl chlorophosphates (**2**). The substrate **1** has one more identical substituent Y compared to substrate **2**. The cross-interaction between Y and Y, due to additional substituent Y, is significant enough to result in the change of the sign of cross-interaction constant (CIC) from negative $\rho_{XY} = -1.31$ (**2**) to positive $\rho_{XY} = +1.91$ (**1**), indicating the change of reaction mechanism from a concerted S_N2 (**2**) to a stepwise mechanism with a rate-limiting leaving group departure from the intermediate (**1**). The deuterium kinetic isotope effects (DKIEs) involving deuterated anilines ($XC_6H_4ND_2$) show secondary inverse, $k_H/k_D = 0.61$ - 0.87 . The DKIEs invariably increase as substituent X changes from electron-donating to electron-withdrawing, while invariably decrease as substituent Y changes from electron-donating to electron-withdrawing. A stepwise mechanism with a rate-limiting bond breaking involving a predominant backside attack is proposed on the basis of positive sign of ρ_{XY} and secondary inverse DKIEs.

Key Words : Phosphoryl transfer reaction, Anilinolysis, Bis(aryl) chlorophosphates, Deuterium kinetic isotope effects, Cross-interaction constant

Introduction

The first work of this lab on the phosphoryl transfer reaction was the kinetic study on the anilinolysis of Y-aryl phenyl chlorophosphates [**2**; $(YC_6H_4O)(PhO)P(=O)Cl$] in acetonitrile.^{1a} A concerted mechanism with a late, product-like transition state (TS) was proposed on the basis of a large negative cross-interaction constant (CIC; $\rho_{XY} = -1.31$) and relatively large secondary inverse deuterium kinetic isotope effects (DKIEs) with deuterated anilines ($XC_6H_4ND_2$) ($k_H/k_D = 0.61$ - 0.87). Continuing the studies on phosphoryl transfer reactions (anilinolysis,¹ pyridinolysis,² benzylaminolysis,³ and theoretical study⁴), the nucleophilic substitution reactions of bis(Y-aryl) chlorophosphates [**1**; $(YC_6H_4O)_2P(=O)Cl$] with substituted anilines and deuterated anilines are investigated kinetically in MeCN at 35.0 ± 0.1 °C (Scheme 1). The aim of this work is to study the dual substituent effects on the reaction rate and mechanism where the substrate has the very same substituent Y in each phenyl ring, and to gain further information into the phosphoryl transfer reactions, as well as to compare the reactivity, mechanism and DKIEs of the anilinolyses of chlorophosphate substrates, $(RO)_1$ - $(RO)_2P(=O)Cl$ -type: Y-aryl phenyl (**2**),^{1a} Y-aryl ethyl [**3**;

$(YC_6H_4O)(EtO)P(=O)Cl$],^{1f} diethyl [**4**; $(EtO)_2P(=O)Cl$],^{1g} and dimethyl [**5**; $(MeO)_2P(=O)Cl$]^{1g} chlorophosphates. Herein, the difference between **1** and **2** is nothing but one substituent Y in the other phenyl ring, i.e., substrate **1** has one more same substituent Y compared to substrate **2**. The numbering of the substrates (**1-5**) follows the sequence of the size of the two ligands, $(RO)_1$ and $(RO)_2$.

Results and Discussion

The observed pseudo-first-order rate constants (k_{obsd}) were found to follow eq. (1) for all of the reactions under pseudo-first-order conditions with a large excess of aniline nucleophile. The k_0 values were negligible ($k_0 = 0$) in acetonitrile. The second-order rate constants (k_2) were determined for at least five concentrations of anilines. The linear plots of eq. (1) suggest that there is no base-catalysis or noticeable side reactions and that the overall reaction is described by Scheme 1.

$$k_{obsd} = k_0 + k_2 [XC_6H_4NH_2] \quad (1)$$

The second-order rate constants (k_2) are summarized in Table 1, together with the selectivity parameters, ρ_X , β_X , ρ_Y , and ρ_{XY} .⁷ The pK_a values of the anilines in water are used to obtain the Brønsted β_X values in MeCN, and this procedure are justified experimentally and theoretically.⁸ The ρ_Y values are calculated from the plots of $\log k_2$ against σ_Y although all of the studied substrates contain the two Y-substituted phenyl rings with same substituent Y. Figures 1, 2, and 3 show the Hammett ($\log k_2$ vs σ_X), Brønsted [$\log k_2$ vs $pK_a(X)$], and Hammett ($\log k_2$ vs σ_Y) plots, respectively.

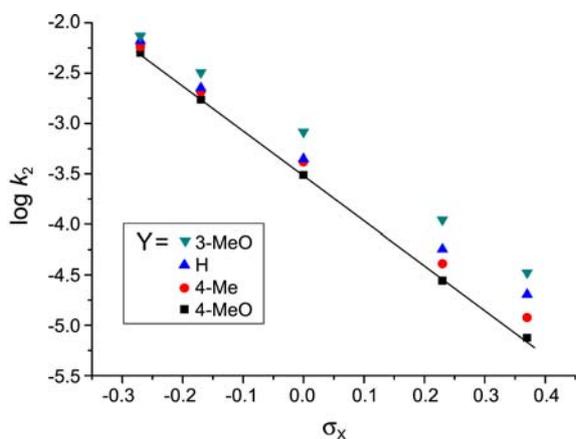
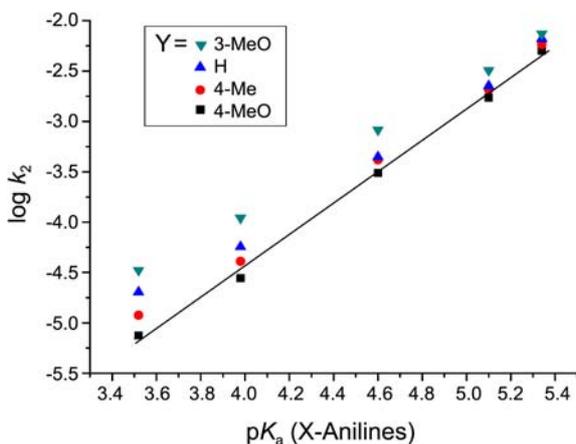


Scheme 1. The studied reaction system.

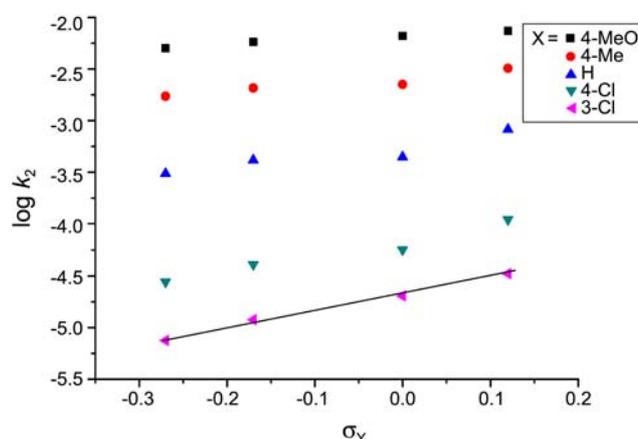
Table 1. The second-order rate constants ($k_2 \times 10^4/\text{M}^{-1}\text{s}^{-1}$) and selectivity parameters^a (ρ_X , β_X , ρ_Y , and ρ_{XY}) of the reactions of **1** [bis(Y-aryl) chlorophosphates] with $\text{XC}_6\text{H}_4\text{NH}_2$ in MeCN at 35.0 °C

X \ Y	4-MeO	4-Me	H	3-MeO	ρ_Y^d
4-MeO	50.2 ± 0.7	57.7 ± 0.4	65.9 ± 0.2	73.8 ± 1.4	0.41 ± 0.01
4-Me	17.2 ± 0.1	20.7 ± 0.3	22.4 ± 0.6	32.0 ± 0.1	0.62 ± 0.04
H	3.07 ± 0.01	4.15 ± 0.02	4.43 ± 0.02	8.24 ± 0.12	0.96 ± 0.08
4-Cl	0.277 ± 0.002	0.409 ± 0.002	0.568 ± 0.007	1.10 ± 0.03	1.43 ± 0.06
3-Cl	0.0751 ± 0.0001	0.119 ± 0.004	0.202 ± 0.001	0.334 ± 0.003	1.61 ± 0.02
$-\rho_X^b$	4.43 ± 0.02	4.21 ± 0.03	3.93 ± 0.06	3.67 ± 0.02	$\rho_{XY} =$
β_X^c	1.56 ± 0.07	1.48 ± 0.07	1.38 ± 0.10	1.29 ± 0.04	1.91 ± 0.05 ^e

^aThe σ values were taken from ref 5. The $\text{p}K_a$ values of X-anilines in water were taken from ref 6. ^bCorrelation coefficient, $r \geq 0.999$. ^c $r \geq 0.997$. ^d $r \geq 0.924$. ^e $r = 0.998$.

**Figure 1.** The Hammett plots ($\log k_2$ vs σ_X) of the reactions of **1** [bis(Y-aryl) chlorophosphates] with $\text{XC}_6\text{H}_4\text{NH}_2$ in MeCN at 35.0 °C.**Figure 2.** The Brønsted plots [$\log k_2$ vs $\text{p}K_a(\text{X})$] of the reactions of **1** [bis(Y-aryl) chlorophosphates] with $\text{XC}_6\text{H}_4\text{NH}_2$ in MeCN at 35.0 °C.

The substituent effects on the reaction rates are compatible with a typical nucleophilic substitution reaction. The stronger nucleophile leads to the faster rate with positive charge development at the nucleophilic nitrogen atom ($\rho_X < 0$ and $\beta_X > 0$) and a more electron-withdrawing substituent Y in the substrate leads to the faster rate with negative charge development at the reaction center phosphorus atom ($\rho_Y > 0$) in the TS. The magnitudes of ρ_X and β_X values are relatively

**Figure 3.** The Hammett plots ($\log k_2$ vs σ_Y) of the reactions of **1** [bis(Y-aryl) chlorophosphates] with $\text{XC}_6\text{H}_4\text{NH}_2$ in MeCN at 35.0 °C.

large and comparable with those of **2**. The magnitudes of ρ_Y values are approximately two times greater than those of **2**. However, the variation tendencies of ρ_X and ρ_Y values for substituents Y and X variations, respectively, are opposite to those of **2**.

When both the nucleophile and substrate have only one substituent X and Y, respectively, a Taylor series expansion of $\log k_{XY}$ around $\sigma_X = \sigma_Y = 0$ leads to eq. (2a).⁹ Herein, pure second- (e.g., $\rho_{XX}\sigma_X^2$ or $\rho_{YY}\sigma_Y^2$), third- (e.g., $\rho_{XXY}\sigma_X^2\sigma_Y$ or $\rho_{XYX}\sigma_X\sigma_Y^2$), and higher-derivative terms (e.g., $\rho_{XXXY}\sigma_X^3\sigma_Y$ or $\rho_{XXYY}\sigma_X^2\sigma_Y^2$, etc) are neglected since they are normally too small to be taken into account. The sign of the CIC (ρ_{XY}) is negative in a normal $\text{S}_{\text{N}}2$ reaction (or in a stepwise reaction with a rate-limiting bond formation), and positive in a stepwise reaction with a rate-limiting leaving group expulsion from the intermediate.⁷ The magnitude of the CIC is inversely proportional to the distance between X and Y through the reaction center; the tighter the TS, the greater the magnitude of the CIC.⁷

$$\log(k_{XY}/k_{\text{HH}}) = \rho_X\sigma_X + \rho_Y\sigma_Y + \rho_{XY}\sigma_X\sigma_Y \quad (2a)$$

$$\rho_{XY} = \partial^2 \log(k_{XY}/k_{\text{HH}}) / \partial \sigma_X \partial \sigma_Y = \partial \rho_X / \partial \sigma_Y = \partial \rho_Y / \partial \sigma_X \quad (2b)$$

In the present work, the modified eq. (3) is introduced in which the cross-interaction between Y (in one phenyl ring) and Y (in the other phenyl ring) is included, since all of the

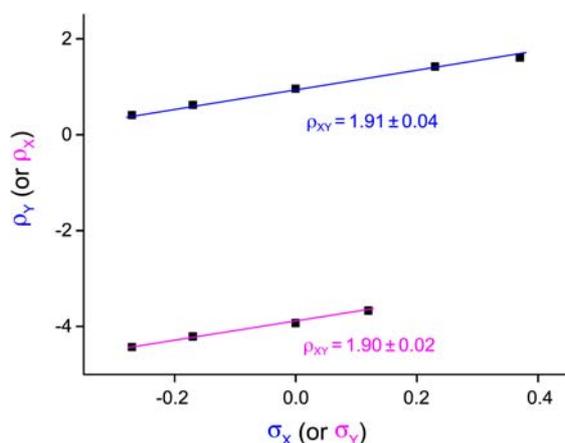


Figure 4. Determination of ρ_{XY} according to eq. (2b) and (3a), $\rho_{XY} = \partial\rho_X/\partial\sigma_Y = \partial\rho_Y/\partial\sigma_X$. The plots of ρ_X vs σ_Y and ρ_Y vs σ_X of the reactions of **1** [bis(Y-aryl) chlorophosphates] with $\text{XC}_6\text{H}_4\text{NH}_2$ in MeCN at 35.0 °C. The value of $\rho_{XY} = 1.91 \pm 0.05$ ($r = 0.998$) is obtained by multiple regression.

studied substrates have identical substituent Y in each phenyl ring. The third and fourth term on the right-side of eq. (3a) indicate the cross-interaction between X and two Y, and Y (in one phenyl ring) and Y (in the other phenyl ring), respectively. The value of ρ_{YY} reflects the cross-interaction between the two substituents, Y and Y, in the TS. Herein, Y and Y denote the substituent in each phenyl ring in the same substrate. In eq. (3a), pure second-, third-, and higher-derivative terms are not considered as in eq. (2). The values of ρ_X , ρ_Y , ρ_{XY} , and ρ_{YY} obtained by multiple regression are described in eq. (3b). The values of $\rho_X = -3.93$ when Y = H ($\sigma_Y = 0$) and $\rho_Y = 0.96$ when X = H ($\sigma_X = 0$) in Table 1 are not far from those of eq. (3b), $\rho_X = -3.91$ and $\rho_Y = 1.08$. As a matter of course, the value of $\rho_{XY} = 1.91$ (Fig. 4) has the same value both in eq. (2) and eq. (3b) since ρ_{XY} is defined as $\partial\rho_X/\partial\sigma_Y = \partial\rho_Y/\partial\sigma_X$. Note that the ρ_{YY} value is as large as 0.90, i.e., nearly half of the value of ρ_{XY} . To understand the contribution of pure second-derivative term ($\rho_{YY}\sigma_Y^2$) on the reaction rate, eq. (3a) is applied to the anilinolysis of **2** in which the substrate has only one substituent Y, and eq. (3c) is obtained. Herein, the $\rho_{YY}\sigma_Y^2$ is pure second-derivative term and reflects Y-Y self-interaction. The values of $\rho_X = -3.74$ when Y = H ($\sigma_Y = 0$)^{1a} and $\rho_Y = 0.54$ when X = H ($\sigma_X = 0$)^{1a} are close to those of eq. (3c), $\rho_X = -3.76$ and $\rho_Y = 0.52$. In eq. (3c), the $\rho_{YY} = 0.02$ implies that there is little Y-Y self-interaction in the TS, i.e., too small to be taken into account as expected.¹⁰ These results support that the value of $\rho_{YY} = 0.90$ in eq. (3b) is absolutely attributed to the cross-interaction between Y and Y in each phenyl ring.

$$\log(k_{XY}/k_{HH}) = \rho_X\sigma_X + \rho_Y\sigma_Y + \rho_{XY}\sigma_X\sigma_Y + \rho_{YY}\sigma_Y^2 \quad (3a)$$

$$\log(k_{XY}/k_{HH}) = -3.91\sigma_X + 1.08\sigma_Y + 1.91\sigma_X\sigma_Y + 0.90\sigma_Y^2 \quad (3b)$$

$$\log(k_{XY}/k_{HH}) = -3.76\sigma_X + 0.52\sigma_Y - 1.31\sigma_X\sigma_Y + 0.02\sigma_Y^2 \quad (3c)$$

The difference between **1** and **2** is one substituent Y in the other phenyl ring, i.e., substrate **1** has one more same substituent Y in the other phenyl ring compared to sub-

strate **2**. It is evident that the cross-interaction, $\rho_{YY}\sigma_Y\sigma_Y = 0.90\sigma_Y\sigma_Y$, between the two substituents, Y and Y, in **1** is really significant. An additional substituent Y to the other phenyl ring actually affects the values of ρ_X and ρ_Y . Although the overall magnitudes of ρ_X and ρ_Y values of **1** are comparable to those of **2** [$\rho_X = -1.29$ to -1.56 (**1**) and -1.24 to -1.68 (**2**); $\rho_Y = (0.41-1.61)/2 = 0.21-0.81$ (**1**) and $0.22-0.87$ (**2**)], the variation tendencies of the ρ_X and ρ_Y values of **1** are completely opposite to those of **2**. In **2**, the values of ρ_X and ρ_Y invariably decrease ($\partial\rho_X < 0$ and $\partial\rho_Y < 0$) as the substituent Y and X change from electron-donating to electron-withdrawing ($\partial\sigma_Y > 0$ and $\partial\sigma_X > 0$): $\rho_X = -3.42$ (Y = 4-MeO) > -3.55 (4-Me) > -3.74 (H) > -4.09 (4-Cl) > -4.63 (4-CN) and $\rho_Y = 0.87$ (X = 4-MeO) > 0.77 (4-Me) > 0.54 (H) > 0.22 (4-Cl).^{1a} As a result, the negative sign with relatively large magnitude of $\rho_{XY} (= -1.31 \pm 0.20$ with $r = 0.998$) was obtained according to eq. (2b); $\rho_{XY} = \partial\rho_X/\partial\sigma_Y = \partial\rho_Y/\partial\sigma_X = (-)/(+) < 0$.^{1a} On the contrary, in **1**, the values of ρ_X and ρ_Y invariably increase ($\partial\rho_X > 0$ and $\partial\rho_Y > 0$) as Y and X change from electron-donating to electron-withdrawing ($\partial\sigma_Y > 0$ and $\partial\sigma_X > 0$): $\rho_X = -4.43$ (Y = 4-MeO) < -4.21 (4-Me) < -3.93 (H) < -3.67 (3-MeO) and $\rho_Y = 0.41$ (X = 4-MeO) < 0.62 (4-Me) < 0.96 (H) < 1.43 (4-Cl) < 1.61 (3-Cl). Thus, the positive sign with great magnitude of $\rho_{XY} = +1.91 \pm 0.05$ ($r = 0.998$) is obtained according to eqs. (2) and (3a); $\rho_{XY} = \partial\rho_X/\partial\sigma_Y = \partial\rho_Y/\partial\sigma_X = (+)/(+) > 0$. Thus, the authors suggest that an additional substituent Y to the other phenyl ring changes the reaction mechanism from a concerted $\text{S}_{\text{N}}2$ in **2** to a stepwise with a rate-limiting leaving group departure from the intermediate in **1** on the basis of the change of sign of ρ_{XY} from negative ($\rho_{XY} = -1.31$ in **2**) to positive ($\rho_{XY} = +1.91$ in **1**).

In addition to the CICs, the DKIEs ($k_{\text{H}}/k_{\text{D}}$) are also one of the strong tools to clarify the reaction mechanism. When partial deprotonation of the aniline occurs in a rate-limiting step by hydrogen bonding, the $k_{\text{H}}/k_{\text{D}}$ values are greater than unity, primary normal ($k_{\text{H}}/k_{\text{D}} > 1.0$).¹¹ In contrast, the DKIEs can only be secondary inverse ($k_{\text{H}}/k_{\text{D}} < 1.0$) in a normal $\text{S}_{\text{N}}2$ reaction, since the N-H(D) vibrational frequencies invariably

Table 2. The DKIEs ($k_{\text{H}}/k_{\text{D}}$) for the reactions of **1** [bis(Y-aryl) chlorophosphates] with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$ in MeCN at 35.0 °C

X	Y	$k_{\text{H}} \times 10^4/\text{M}^{-1} \text{s}^{-1}$	$k_{\text{D}} \times 10^4/\text{M}^{-1} \text{s}^{-1}$	$k_{\text{H}}/k_{\text{D}}$
4-MeO	4-MeO	50.2 ± 0.7	68.3 ± 0.3	0.74 ± 0.01^a
	4-Me	57.7 ± 0.4	88.7 ± 0.4	0.65 ± 0.01
	H	65.9 ± 0.2	115 ± 1	0.58 ± 0.01
	3-MeO	73.8 ± 1.4	134 ± 1	0.55 ± 0.01
H	4-MeO	3.07 ± 0.01	3.56 ± 0.01	0.86 ± 0.01
	4-Me	4.45 ± 0.02	5.02 ± 0.02	0.83 ± 0.01
	H	4.43 ± 0.02	5.74 ± 0.01	0.77 ± 0.01
	3-MeO	8.24 ± 0.12	11.3 ± 0.01	0.73 ± 0.01
4-Cl	4-MeO	0.277 ± 0.002	0.283 ± 0.002	0.98 ± 0.01
	4-Me	0.409 ± 0.002	0.428 ± 0.001	0.96 ± 0.01
	H	0.568 ± 0.007	0.596 ± 0.001	0.95 ± 0.01
	3-MeO	1.10 ± 0.03	1.17 ± 0.01	0.94 ± 0.03

^aStandard error $\{= 1/k_{\text{D}}[(\Delta k_{\text{H}})^2 + (k_{\text{H}}/k_{\text{D}})^2 \times (\Delta k_{\text{D}})^2]^{1/2}\}$ from ref 12.

increase upon going to the TS because of an increase in steric congestion in the bond-making process.¹¹ In the present work, the DKIEs are all secondary inverse, $k_{\text{H}}/k_{\text{D}} < 1.0$, (Table 2), indicating that partial deprotonation of the aniline does not occur in a rate-limiting step by hydrogen bonding. The DKIEs invariably increase as substituent X changes from electron-donating to electron-withdrawing, $k_{\text{H}}/k_{\text{D}}(\text{X} = 4\text{-MeO}) < k_{\text{H}}/k_{\text{D}}(\text{H}) < k_{\text{H}}/k_{\text{D}}(4\text{-Cl})$ (contrary to **2**), while invariably decrease as substituent Y changes from electron-donating to electron-withdrawing, $k_{\text{H}}/k_{\text{D}}(\text{Y} = 4\text{-MeO}) > k_{\text{H}}/k_{\text{D}}(4\text{-Me}) > k_{\text{H}}/k_{\text{D}}(\text{H}) > k_{\text{H}}/k_{\text{D}}(3\text{-MeO})$.

Thus, when X = 4-MeO and Y = 3-MeO, the min value of DKIE ($k_{\text{H}}/k_{\text{D}} = 0.55$) is observed (Table 3), indicating that the degree of bond formation is largest and the steric congestion is greatest in the TS. The smallest magnitudes of $\rho_{\text{X}} = -3.67$ (Y = 3-MeO) and $\rho_{\text{Y}} = 0.41$ (X = 4-MeO) suggest that the positive and negative charge developments at the nitrogen and phosphorus atom, respectively, are smallest in the TS. This implies that the TS is very tight in which the degree of bond formation is largest while the degree of bond breaking is smallest. When X = 4-Cl and Y = 4-MeO, on the contrary, the max value of DKIE ($k_{\text{H}}/k_{\text{D}} = 0.98$) is observed (Table 3), indicating that the degree of bond formation is the smallest and the steric congestion is the smallest in the TS. The largest magnitudes of $\rho_{\text{X}} = -4.43$ (Y = 4-MeO) and $\rho_{\text{Y}} = 1.61$ (X = 4-Cl) suggest that the positive and negative charge developments at the nitrogen and phosphorus atom, respectively, are greatest in the TS. This implies that the TS is somewhat looser compared to that when X = 4-MeO and Y = 3-MeO in which the degree of bond formation is smallest while the degree of bond breaking is largest. This suggestion is completely contrary to normal expectation: (i) the greater degree of bond formation leads to a greater magnitude of ρ_{X} value and greater positive charge development at the nucleophilic reaction center; (ii) the greater degree of bond breaking leads to a greater magnitude of ρ_{Y} value and

Table 3. The DKIEs ($k_{\text{H}}/k_{\text{D}}$), ρ_{X} , and ρ_{Y} for the reactions of **1** [bis(Y-aryl) chlorophosphates] with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$ in MeCN at 35.0 °C

X \ Y	4-MeO	4-Me	H	3-MeO	ρ_{Y}
4-MeO	0.74 ± 0.01	0.65 ± 0.01	0.58 ± 0.01	0.55 ± 0.01	0.41 ± 0.01
H	0.86 ± 0.01	0.83 ± 0.01	0.77 ± 0.01	0.73 ± 0.01	0.96 ± 0.08
4-Cl	0.98 ± 0.01	0.96 ± 0.01	0.95 ± 0.01	0.94 ± 0.03	1.61 ± 0.02
$-\rho_{\text{X}}$	4.43 ± 0.02	4.21 ± 0.03	3.93 ± 0.06	3.67 ± 0.02	

Table 4. The DKIEs ($k_{\text{H}}/k_{\text{D}}$), ρ_{X} , and ρ_{Y} for the reactions of **2** [Y-aryl phenyl chlorophosphates] with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$ in MeCN at 55.0 °C^a

X \ Y	4-Me	H	4-Cl	ρ_{Y}
4-MeO	0.87 ± 0.03	0.77 ± 0.05	0.65 ± 0.02	0.87 ± 0.01
H	0.85 ± 0.01	0.75 ± 0.06	0.64 ± 0.05	0.54 ± 0.01
4-Cl	0.81 ± 0.01	0.71 ± 0.02	0.61 ± 0.02	0.22 ± 0.01
$-\rho_{\text{X}}$	3.55 ± 0.20	3.74 ± 0.21	4.09 ± 0.19	

^aAll of the values are taken from ref 1a.

greater negative charge development at the substrate reaction center.

On the contrary, in **2**, the results of DKIEs are consistent with normal expectation for the magnitudes of ρ_{X} and ρ_{Y} values. When X = 4-MeO and Y = 4-Cl, the min value of DKIE ($k_{\text{H}}/k_{\text{D}} = 0.65$) is observed (Table 4), indicating that the degree of bond formation is largest and the steric congestion is greatest in the TS. The largest magnitudes of $\rho_{\text{X}} = -4.09$ (Y = 4-Cl) and $\rho_{\text{Y}} = 0.87$ (X = 4-MeO) suggest that the positive and negative charge developments at the nitrogen and phosphorus atom, respectively, are largest in the TS. This implies that the TS is very late in which both the degrees of bond formation and breaking are largest. When X = 4-Cl and Y = 4-Me, the max value of DKIE ($k_{\text{H}}/k_{\text{D}} = 0.81$) is observed (Table 4), indicating that the degree of bond formation is the smallest and the steric congestion is the smallest in the TS. The smallest magnitudes of $\rho_{\text{X}} = -3.55$ (Y = 4-Me) and $\rho_{\text{Y}} = 0.22$ (X = 4-Cl) suggest that the positive and negative charge developments at the nitrogen and phosphorus atom, respectively, are smallest in the TS. This implies that both the degrees of bond formation and breaking are smallest.

In this respect, DKIEs have provided a useful means to determine the TS structures in nucleophilic substitution reactions, and how the reactants, especially through changes in substituents, alter the TS structures. Incorporation of deuterium in the nucleophile has an advantage in that the α -DKIEs reflect *only* the degree of bond formation, especially for the secondary inverse DKIEs. Thus, the greater the extent of bond formation, the greater the steric congestion, and the smaller the $k_{\text{H}}/k_{\text{D}}$ value becomes. These results indicate that the DKIEs are one of the strong tools to substantiate the TS structure, and that the determination of TS structure with ρ_{X} and ρ_{Y} values is not sometimes adequate.

The second-order rate constants (k_{H}) of the reactions of five chlorophosphates (when Y = H) with unsubstituted aniline ($\text{C}_6\text{H}_5\text{NH}_2$) at 55.0 °C, natural bond order (NBO) charges at the P reaction center in the gas phase [B3LYP/6-311+G(d,p) level of theory],¹³ Brønsted and Hammett coefficients (β_{X} and ρ_{Y}), CICs (ρ_{XY}), and DKIEs ($k_{\text{H}}/k_{\text{D}}$) of the reactions of five chlorophosphates with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$ in MeCN are summarized in Table 5. Solely considering the magnitudes of the positive charges at the reaction center P atom, the sequence of the anilinolysis rate should be **4** > **3** > **2** > **5** (note **1** = **2** when Y = H). However, the observed sequence of the rate, **5** > **4** > **3** > **2**, is not consistent with expectations for the electronic influence of the two ligands. It is evident that the magnitude of the positive charge at the reaction center P atom does not play any role to determine the anilinolysis rate of the chlorophosphate systems. The second-order rate constants for the reactions of four chlorophosphates (**2**, **3**, **4**, and **5**) with $\text{C}_6\text{H}_5\text{NH}_2$ in MeCN at 55.0 °C give the relative rate ratio of 4.8(**5**)⁴¹ : 3.2(**4**)⁴¹ : 2.2(**3**)^{4d} : 1(**2**).¹⁵ The sequence of the anilinolysis rates of the chlorophosphates, **5** > **4** > **3** > **2**, is inversely proportional to the size of the two ligands; PhO,PhO (**2**) > PhO,EtO (**3**) >

Table 5. Summary of the second-order rate constants ($k_{\text{H}} \times 10^3/\text{M}^{-1} \text{s}^{-1}$) with $\text{C}_6\text{H}_5\text{NH}_2$ at 55.0 °C, NBO charges at the P reaction center, Brønsted and Hammett coefficients (β_{X} and ρ_{Y}), CICs (ρ_{XY}), and DKIEs ($k_{\text{H}}/k_{\text{D}}$) of the reactions of **1**, **2**, **3**, **4**, and **5** with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$ in MeCN

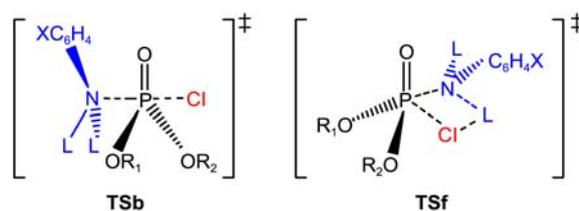
Substrate	$k_{\text{H}} \times 10^3$	charge at P	β_{X}	ρ_{Y}	ρ_{XY}	$k_{\text{H}}/k_{\text{D}}$	ref
1 ; $(\text{YC}_6\text{H}_4\text{O})_2\text{P}(=\text{O})\text{Cl}$	0.891 ^a	2.230 ^a	1.29-1.56 ^b	0.41-1.61 ^b	+1.91 ^b	0.55-0.98 ^b	this work
2 ; $(\text{YC}_6\text{H}_4\text{O})(\text{PhO})\text{P}(=\text{O})\text{Cl}$	0.891 ^a	2.230 ^a	1.24-1.68 ^c	0.22-0.87 ^c	-1.31 ^c	0.61-0.87 ^c	1a
3 ; $(\text{YC}_6\text{H}_4\text{O})(\text{EtO})\text{P}(=\text{O})\text{Cl}$	2.00 ^a	2.233 ^a	1.09-1.20 ^c	0.41-0.90 ^c	-0.60 ^c	1.07-1.28 ^c	1f
4 ; $(\text{EtO})_2\text{P}(=\text{O})\text{Cl}$	2.82	2.236	1.06 ^c	–	–	0.71-0.92 ^c	1g
5 ; $(\text{MeO})_2\text{P}(=\text{O})\text{Cl}$	4.28	2.226	0.962 ^c	–	–	0.80-0.98 ^c	1g

^aThe values of Y = H at 55.0 °C. ^bThe values at 35.0 °C. ^cThe values at 55.0 °C.

EtO, EtO (**4**) > MeO, MeO (**5**). The greater the size of the two ligands, the anilinolysis rate becomes slower. This means that the steric effects of the two ligands are the predominant factor to determine the reactivity of the anilinolysis of chlorophosphates.

The values of ρ_{Y} of **1** are almost two times greater than those of **2** since the values of ρ_{Y} of **1** are calculated not with $2 \times \sigma_{\text{Y}}$ but with $1 \times \sigma_{\text{Y}}$, i.e., the contribution of one Y to ρ_{Y} is the same as in **2**. It is worthy of note that the magnitudes of the selectivity parameters (β_{X} and ρ_{Y}) of **1** and **2** are similar [$\beta_{\text{X}} = 1.29-1.56$ (**1**) and $1.24-1.68$ (**2**); $\rho_{\text{Y}} = (0.41-1.61)/2 = 0.21-0.81$ (**1**) and $0.22-0.87$ (**2**) as mentioned already] despite the different reaction mechanism of a concerted (**2**) and stepwise with a rate-limiting bond breaking step (**1**). This implies that the clarification of the reaction mechanism with the values of ρ_{X} , β_{X} , and/or ρ_{Y} is sometimes dangerous, and the CICs are one of strong tools to substantiate the mechanism. The anilinolyses of the chloro(or thiochloro)-phosphate derivatives normally proceed through a normal $\text{S}_{\text{N}}2$ concerted mechanism because of a good leaving group mobility of Cl. Until now, only the reactions of *O*-aryl methyl phosphonochloridothioate [$\text{Me}(\text{YC}_6\text{H}_4\text{O})\text{P}(=\text{S})\text{Cl}$] with the weakly basic anilines in MeCN at 55.0 °C yielded a positive value of $\rho_{\text{XY}} = +0.77$,^{1k} and now the present work yields a positive value of $\rho_{\text{XY}} = +1.91$. Considering the two Ys in the two phenyl rings, the magnitude of ρ_{XY} per one Y would be $1.91/2 = +0.96$.

The DKIEs of four chlorophosphates [**1** ($k_{\text{H}}/k_{\text{D}} = 0.55-0.98$), **2** ($k_{\text{H}}/k_{\text{D}} = 0.61-0.87$), **4** ($k_{\text{H}}/k_{\text{D}} = 0.71-0.92$), and **5** ($k_{\text{H}}/k_{\text{D}} = 0.80-0.98$)] are secondary inverse. However, in **3**, the subtle combination of small ethoxy and large phenoxy ligand gave primary normal DKIEs ($k_{\text{H}}/k_{\text{D}} = 1.07-1.28$). The authors proposed that the anilinolyses of **2**, **4**, and **5** proceed through a concerted mechanism involving a predominant backside attack TSb on the basis of the negative sign of ρ_{XY} and the secondary inverse DKIEs, whereas the anilinolysis of **3** proceeds through a concerted mechanism involving a predominant frontside attack with a hydrogen-bonded, four-center-type TSf on the basis of the negative sign of ρ_{XY} and the considerably large primary normal DKIEs. In the present work, the authors propose a stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate involving a predominant backside attack TSb on the basis of the positive sign of $\rho_{\text{XY}} (= +1.91)$ and the secondary inverse DKIEs ($k_{\text{H}}/k_{\text{D}} = 0.55-0.98$).



Experimental Section

Materials. Bis(phenyl) chlorophosphate (GR grade) and MeCN (HPLC-grade; water content is less than 0.005%) were used for kinetic studies without further purification. Anilines were redistilled or recrystallized before use. Deuterated anilines were prepared by heating anilines, deuterium oxide (99.9 atom % D), and one drop of HCl catalyst at 90 °C for 72 hours, and after numerous attempts, anilines were deuterated more than 98%, as confirmed by ¹H NMR.

Kinetic Measurement. Conductometric rate measurements were carried out using self-made computer-interfaced automatic A/D converter conductivity bridges. The pseudo-first-order rate constants (k_{obsd}) were determined using large excess of nucleophiles where $[\text{X-anilines}] = 0.10-0.30 \text{ M}$ and $[\text{Substrate}] = 3.00 \times 10^{-3} \text{ M}$. Rates were measured as previously described.¹ The values of pseudo-first-order rate constants were average of at least three runs that were reproducible within $\pm 3\%$.

Synthesis of Substrates. The substrates, bis(Y-aryl) chlorophosphates (Y = 4-MeO, 4-Me, and 3-MeO), were synthesized by reacting phosphorus oxychloride with Y-phenol in the presence of triethylamine in methylene chloride at $-10 \text{ }^\circ\text{C}$.¹⁴ Triethylammonium chloride was separated by filtration. The remaining mixture was treated with water and diethyl ether for work up. Organic layer of diethyl ether was dried over anhydrous MgSO_4 for 6-8 hr. The product mixture was separated through column chromatography (silica gel, ethyl acetate/*n*-hexane) and dried under reduced pressure. The substrates were characterized by the spectral analysis, TLC, ¹H-NMR, ¹³C-NMR, ³¹P-NMR, GC-MS and Element Analysis (EA), as follows:

Bis(4-methoxyphenyl) Chlorophosphate [(4-CH₃O-C₆H₄O)₂P(=O)Cl]: Light brown oily liquid; ¹H-NMR (400 MHz, CDCl₃ & TMS) δ 3.80-3.81 (aliphatic, 6H, m), 6.88-6.90 (aromatic, 4H, m); 7.20-7.22 (aromatic, 4H, m); ¹³C-NMR (100 MHz, CDCl₃ & TMS) δ 55.65 (aliphatic, 2C, s),

114.89-157.68 (aromatic, 12C, m); ^{31}P -NMR (162 MHz, CDCl_3 & TMS) δ 1.66 (PO, 1P, s); GC-MS (EI, m/z) 328 (M^+).

Bis(4-methylphenyl) Chlorophosphate [(4- CH_3 - $\text{C}_6\text{H}_4\text{O}$) $_2$ - $\text{P}(=\text{O})\text{Cl}$]: Oily colorless liquid; ^1H -NMR (400 MHz, CDCl_3 & TMS) δ 2.26-2.40 (aliphatic, 6H, m), 7.01-7.23 (aromatic, 8H, m); ^{13}C -NMR (100 MHz, CDCl_3 & TMS) δ 20.75 (aliphatic, 2C, d, $J=7.0$ Hz), 119.84-148.26 (aromatic, 12C, m); ^{31}P -NMR (162 MHz, CDCl_3 & TMS) δ -3.44 (PO, 1P, s); GC-MS (EI, m/z) 296 (M^+).

Bis(3-methoxyphenyl) Chlorophosphate [(3- CH_3O - $\text{C}_6\text{H}_4\text{O}$) $_2$ - $\text{P}(=\text{O})\text{Cl}$]: Oily colorless liquid; ^1H -NMR (400 MHz, CDCl_3 & TMS) δ 3.81 (aliphatic, 6H, m), 6.81-6.92 (aromatic, 6H, m); 7.26-7.31 (aromatic, 2H, m); ^{13}C -NMR (100 MHz, CDCl_3 & TMS) δ 55.55 (aliphatic, 2C, s), 101.48-160.83 (aromatic, 12C, m); ^{31}P -NMR (162 MHz, CDCl_3 & TMS) δ -0.068 (P=O, 1P, s); GC-MS (EI, m/z) 328 (M^+) and Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{ClO}_5\text{P}$: C 51.16, H 4.29; Found: C 51.26, H 4.15.

Product Analysis. Bis(phenyl) chlorophosphate was reacted with excess amount of 4-methoxyaniline for more than 15 half-lives in MeCN at 35.0 °C. The product was isolated through column chromatography (50% ethyl acetate/*n*-hexane) after treatment with ether and dilute HCl, then dried under reduced pressure. The analytical data are summarized as follows:

($\text{C}_6\text{H}_5\text{O}$) $_2\text{P}(=\text{O})(\text{NHC}_6\text{H}_4\text{-4-OCH}_3)$: White solid crystal, mp 139.0-140.0 °C; ^1H -NMR (400 MHz, CDCl_3 & TMS) δ 3.79 (aliphatic, 3H, s), 5.73 (aliphatic, 1H, s), 6.83-6.86 (aromatic, 2H, m), 7.04-7.07 (aromatic, 2H, m), 7.13-7.20 (aromatic, 6H, m), 7.21-7.31 (aromatic, 4H, m); ^{13}C -NMR (100 MHz, CDCl_3 & TMS) δ 55.53 (aliphatic, 1C, s), 114.67-150.37 (aromatic, 18C, s); ^{31}P -NMR (162 MHz, CDCl_3 & TMS) δ -1.43 (P=O, 1P, s); GC-MS (EI, m/z) 355 (M^+) and Anal. Calcd for $\text{C}_{19}\text{H}_{18}\text{NO}_4\text{P}$: C 64.22, H 5.11, N 3.94; Found: C 64.06, H 5.29, N 3.93.

Acknowledgments. This work was supported by the Brain Korea 21 Program from National Research Foundation of Korea.

References and Notes

- (a) Guha, A. K.; Lee, H. W.; Lee, I. *J. Chem. Soc., Perkin Trans. 2* **1999**, 765. (b) Lee, H. W.; Guha, A. K.; Lee, I. *Int. J. Chem. Kinet.* **2002**, *34*, 632. (c) Hoque, M. E. U.; Dey, S.; Guha, A. K.; Kim, C. K.; Lee, B. S.; Lee, H. W. *J. Org. Chem.* **2007**, *72*, 5493. (d) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2007**, *28*, 936. (e) Dey, N. K.; Han, I. S.; Lee, H. W. *Bull. Korean Chem. Soc.* **2007**, *28*, 2003. (f) Hoque, M. E. U.; Dey, N. K.; Kim, C. K.; Lee, B. S.; Lee, H. W. *Org. Biomol. Chem.* **2007**, *5*, 3944. (g) Dey, N. K.; Hoque, M. E. U.; Kim, C. K.; Lee, B. S.; Lee, H. W. *J. Phys. Org. Chem.* **2008**, *21*, 544. (h) Lumbiny, B. J.; Lee, H. W. *Bull. Korean Chem. Soc.* **2008**, *29*, 2065. (i) Dey, N. K.; Hoque, M. E. U.; Kim, C. K.; Lee, B. S.; Lee, H. W. *J. Phys. Org. Chem.* **2009**, *22*, 425. (j) Dey, N. K.; Kim, C. K.; Lee, H. W. *Bull. Korean Chem. Soc.* **2009**, *30*, 975. (k) Hoque, M. E. U.; Guha, A. K.; Kim, C. K.; Lee, B. S.; Lee, H. W. *Org. Biomol. Chem.* **2009**, *7*, 2919. (l) Dey, N. K.; Lee, H. W. *Bull. Korean Chem. Soc.* **2010**, *31*, 1403. (m) Dey, N. K.; Kim, C. K.; Lee, H. W. *Org. Biomol. Chem.* **2011**, *9*, 717.
- (a) Guha, A. K.; Lee, H. W.; Lee, I. *J. Org. Chem.* **2000**, *65*, 12. (b) Lee, H. W.; Guha, A. K.; Kim, C. K.; Lee, I. *J. Org. Chem.* **2002**, *67*, 2215. (c) Adhikary, K. K.; Lee, H. W.; Lee, I. *Bull. Korean Chem. Soc.* **2003**, *24*, 1135. (d) Hoque, M. E. U.; Dey, N. K.; Guha, A. K.; Kim, C. K.; Lee, B. S.; Lee, H. W. *Bull. Korean Chem. Soc.* **2007**, *28*, 1797. (e) Adhikary, K. K.; Lumbiny, B. J.; Kim, C. K.; Lee, H. W. *Bull. Korean Chem. Soc.* **2008**, *29*, 851. (f) Lumbiny, B. J.; Adhikary, K. K.; Lee, B. S.; Lee, H. W. *Bull. Korean Chem. Soc.* **2008**, *29*, 1769. (g) Dey, N. K.; Hoque, M. E. U.; Kim, C. K.; Lee, H. W. *J. Phys. Org. Chem.* **2010**, *23*, 1022. (h) Dey, N. K.; Adhikary, K. K.; Kim, C. K.; Lee, H. W. *Bull. Korean Chem. Soc.* **2010**, *31*, 3856. (i) Dey, N. K.; Kim, C. K.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 709. (j) Hoque, M. E. U.; Dey, S.; Kim, C. K.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 1138. (k) Guha, A. K.; Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 1375. (l) Guha, A. K.; Kim, C. K.; Lee, H. W. *J. Phys. Org. Chem.* **2011**, *24*, 474.
- Adhikary, K. K.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 1625.
- (a) Lee, I.; Kim, C. K.; Li, H. G.; Sohn, C. K.; Kim, C. K.; Lee, H. W.; Lee, B. S. *J. Am. Chem. Soc.* **2000**, *122*, 11162. (b) Han, I. S.; Kim, C. K.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 889.
- Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.
- Streitwieser, A., Jr.; Heathcock, C. H.; Kosower, E. M. *Introduction to Organic Chemistry*, 4th ed.; Macmillan: New York, 1992; p 735.
- (a) Lee, I. *Chem. Soc. Rev.* **1990**, *19*, 317. (b) Lee, I. *Adv. Phys. Org. Chem.* **1992**, *27*, 57. (c) Lee, I.; Lee, H. W. *Collect. Czech. Chem. Commun.* **1999**, *64*, 1529.
- The $\Delta pK_a = pK_a(\text{MeCN}) - pK_a(\text{H}_2\text{O})$ values for structurally similar amines are nearly constant, so determination of β_X by plotting $\log k_2(\text{MeCN})$ against $pK_a(\text{H}_2\text{O})$ is probably justified. [(a) Ritchie, C. D. *Solute-Solvent Interactions*; Coetzee, J. F., Ritchie, C. D., Ed.; Marcel Dekker: New York, 1969; Ch. 4. (b) Coetzee, J. F. *Prog. Phys. Org. Chem.* **1967**, *4*, 54. (c) Spillane, W. J.; Hogan, G.; McGrath, P.; King, J.; Brack, C. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2099. (d) Oh, H. K.; Woo, S. Y.; Shin, C. H.; Park, Y. S.; Lee, I. *J. Org. Chem.* **1997**, *62*, 5780.]
- Wold, S.; Sjöström, M. *Correlation Analysis in Chemistry*; Chapman, N. B., Shorter, J., Eds.; Plenum: New York, 1978; Chapter 4.
- The values of σ_X and σ_Y are normally less than unity, and the value of σ_X^2 or σ_Y^2 becomes much smaller than unity. Thus, $\rho_{XY}\sigma_X\sigma_Y = 0.02\sigma_Y^2$ is almost equal to null (≈ 0).
- (a) Lee, I.; Koh, H. J.; Lee, B. S.; Lee, H. W. *J. Chem. Soc., Chem. Commun.* **1990**, 335. (b) Poirier, R. A.; Youliang, W.; Westaway, K. C. *J. Am. Chem. Soc.* **1994**, *116*, 2526. (c) Lee, I. *Chem. Soc. Rev.* **1995**, *24*, 223. (d) Marlier, J. F. *Acc. Chem. Res.* **2001**, *34*, 283. (e) Westaway, K. C. *Adv. Phys. Org. Chem.* **2006**, *41*, 217. (f) Villano, S. M.; Kato, S.; Bierbaum, V. M. *J. Am. Chem. Soc.* **2006**, *128*, 736. (g) Gronert, S.; Fajin, A. E.; Wong, L. *J. Am. Chem. Soc.* **2007**, *129*, 5330.
- Crumpler, T. B.; Yoh, J. H. *Chemical Computations and Errors*; John Wiley: New York, 1940; p 178.
- Hehre, W. J.; Random, L.; Schleyer, P. V. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986; Chapter 4.
- Wadsworth, W. S., Jr.; Wilde, R. L. *J. Org. Chem.* **1976**, *41*, 2635.