

Dual Substituent Effects on Anilinolysis of Bis(aryl) Chlorothiophosphates

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The reactions of bis(Y-aryl) chlorothiophosphates (**1**) with substituted anilines and deuterated anilines are investigated kinetically in acetonitrile at 55.0 °C. The Hammett plots for substituent Y variations in the substrates show biphasic concave upwards with a break point at Y = H. The cross-interaction constants (ρ_{XY}) are positive for both electron-donating and electron-withdrawing Y substituents. The kinetic results of **1** are compared with those of Y-aryl phenyl chlorothiophosphates (**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 ρ_{XY} from negative with **2** to positive with **1**. The effect of the cross-interaction between Y and Y on the rate changes from negative role with electron-donating Y substituents to positive role with electron-withdrawing Y substituents, resulting in biphasic concave upward free energy correlation with Y. A stepwise mechanism with a rate-limiting leaving group departure from the intermediate involving a predominant frontside attack hydrogen bonded, four-center-type transition state is proposed based on the positive sign of ρ_{XY} and primary normal deuterium kinetic isotope effects.

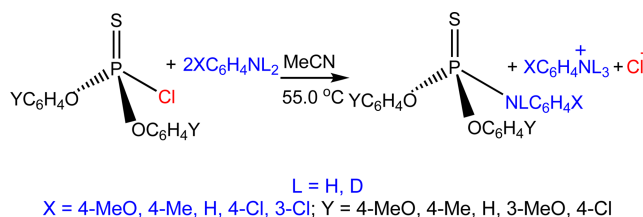
Key Words : Dual substituent effect, Anilinolysis, Bis(aryl) chlorothiophosphate, Deuterium kinetic isotope effect, Cross-interaction constant

Introduction

A concerted mechanism involving a frontside nucleophilic attack was proposed for the anilinolysis of Y-aryl phenyl chlorothiophosphates [**2**; (YC₆H₄O)(PhO)P(=S)Cl] in acetonitrile (MeCN)¹ based on the negative cross-interaction constant (CIC; $\rho_{XY} = -0.22$)² and primary normal deuterium kinetic isotope effects (DKIEs; $k_H/k_D = 1.11$ -1.33). The kinetic studies on the reactions of bis(Y-aryl) chlorothiophosphates [**1**; (YC₆H₄O)₂P(=S)Cl] with substituted anilines and deuterated anilines are investigated kinetically in MeCN at 55.0 ± 0.1 °C (Scheme 1). The aim of this work is to study the dual substituent effects on the reaction mechanism where the substrate has the same substituent Y in each phenyl ring.

Results and Discussion

Table 1 lists the second-order rate constants of k_H and k_D



Scheme 1. Reactions of bis(Y-aryl) chlorothiophosphates (**1**) with XC₆H₄NH₂(D₂) in MeCN.

with XC₆H₄NH₂ and XC₆H₄ND₂, respectively. The substituent effects on the 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 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 in the transition state (TS). However, the

Table 1. Second-Order Rate Constants ($k_{H(D)} \times 10^5/M^{-1}s^{-1}$) of the Reactions of Bis(Y-aryl) Chlorothiophosphates (**1**) with XC₆H₄NH₂(D₂) in MeCN at 55.0 °C

X \ Y		4-MeO	4-Me	H	3-MeO	4-Cl
4-MeO	k_H	84.9 ± 0.1	108 ± 1	126 ± 1	156 ± 1	444 ± 1
	k_D	70.5 ± 0.1	87.8 ± 0.1	99.1 ± 0.1	121 ± 1	340 ± 2
4-Me	k_H	22.7 ± 0.4	24.2 ± 0.3	25.6 ± 0.2	46.5 ± 0.1	134 ± 1
	k_D	19.3 ± 0.1	20.1 ± 0.1	20.6 ± 0.1	37.0 ± 0.1	104 ± 1
H	k_H	6.30 ± 0.02	7.28 ± 0.01	10.1 ± 0.1	15.1 ± 0.1	40.7 ± 0.4
	k_D	5.55 ± 0.01	6.24 ± 0.01	8.41 ± 0.01	12.4 ± 0.1	32.1 ± 0.1
4-Cl	k_H	0.783 ± 0.002	0.924 ± 0.001	0.951 ± 0.003	1.78 ± 0.02	5.26 ± 0.01
	k_D	0.725 ± 0.001	0.842 ± 0.001	0.854 ± 0.001	1.54 ± 0.01	4.25 ± 0.01
3-Cl	k_H	0.214 ± 0.001	0.265 ± 0.001	0.343 ± 0.001	0.536 ± 0.002	1.71 ± 0.01
	k_D	0.204 ± 0.001	0.248 ± 0.002	0.314 ± 0.001	0.466 ± 0.002	1.43 ± 0.01

Table 2. Hammett ($\rho_{X(H \text{ and } D)}$) and Brønsted ($\beta_{X(H \text{ and } D)}$) Coefficients with X for the Reactions of Bis(Y-aryl) Chlorothiophosphates (**1**) with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$ in MeCN at 55.0 °C^a

Y	4-MeO	4-Me	H	3-MeO	4-Cl
$-\rho_{X(H)}$	3.94 ± 0.07	3.92 ± 0.11	3.88 ± 0.14	3.77 ± 0.07	3.70 ± 0.06
$-\rho_{X(D)}$	3.85 ± 0.07	3.82 ± 0.10	3.78 ± 0.14	3.69 ± 0.07	3.64 ± 0.07
$\beta_{X(H)}$	1.39 ± 0.10	1.38 ± 0.11	1.36 ± 0.15	1.33 ± 0.10	1.30 ± 0.10
$\beta_{X(D)}$	1.36 ± 0.09	1.33 ± 0.12	1.33 ± 0.17	1.30 ± 0.10	1.28 ± 0.10

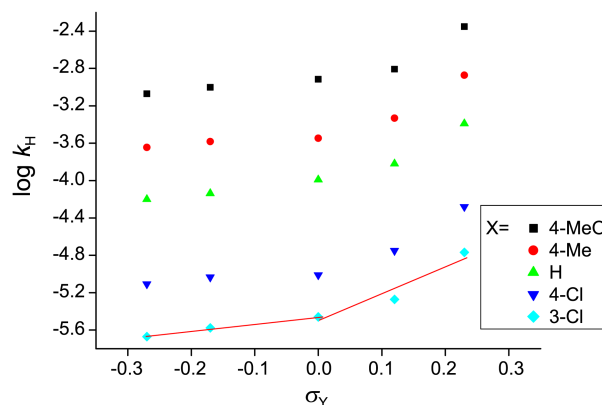
^aCorrelation coefficients (r) of ρ_X and β_X values are better than 0.997

Hammett ($\log k_H$ vs σ_Y) plots for substituent Y variations in the substrates show biphasic concave upwards with a break point at Y = H (Fig. 1). The rate with aniline is always faster than its corresponding deuterated aniline, resulting in primary normal DKIEs ($k_H/k_D > 1$). The Hammett ($\rho_{X(H \text{ and } D)}$) and Brønsted ($\beta_{X(H \text{ and } D)}$) coefficients for substituent X variations in the nucleophiles are summarized in Table 2, and the Hammett coefficients ($\rho_{Y(H \text{ and } D)}$) with Y are summarized in Table 3. The $\rho_{Y(H \text{ and } D)}$ values are calculated from the plots of $\log k_{(H \text{ and } D)}$ against σ_Y although all the studied substrates contain the two Y-substituted phenyl rings. The Hammett ($\log k_H$ vs σ_X), Hammett ($\log k_D$ vs σ_X), Brønsted [$\log k_H$ vs $\text{p}K_a(\text{X})$] and Brønsted [$\log k_D$ vs $\text{p}K_a(\text{X})$] plots with X, and Hammett ($\log k_D$ vs σ_Y) plots with Y are shown in Figures S1-S5, respectively (supporting information). The magnitudes of ρ_X , ρ_Y and β_X with anilines are larger than those with deuterated anilines. The magnitudes of $\rho_{X(H)}$ ($= -3.70$ to -3.94) and $\beta_{X(H)}$ ($= 1.30$ - 1.39) values of **1** are comparable with those of **2** ($\rho_{X(H)} = -3.81$ to -4.01 and $\beta_{X(H)} = 1.34$ - 1.41). The magnitudes of $\rho_{Y(H \text{ and } D)}$ values with electron-withdrawing Y ($= \text{H}$, 3-MeO, 4-Cl) are much greater than those with electron-donating Y ($= 4\text{-MeO}$, 4-Me, H). From now on, for convenience, electron-donating Y ($= 4\text{-MeO}$, 4-Me, H) and electron-withdrawing Y ($= \text{H}$, 3-MeO, 4-Cl) substituents are described as *e-d* and *e-w* block, respectively.

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. (1).³ 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., $\rho_{XXX}\sigma_X^3$ or $\rho_{YYY}\sigma_Y^3$, etc) are neglected because they are normally too small to be taken into account. Figure 2 shows the positive values of $\rho_{XY(H)} = 0.22$ and 0.81 with *e-d* and *e-w* block, respectively. Figure S6 also shows the positive

Table 3. Hammett Coefficients ($\rho_{Y(H \text{ and } D)}$) with Y for the Reactions of Bis(Y-aryl) Chlorothiophosphates (**1**) with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$ in MeCN at 55.0 °C

X	$\rho_{Y(H)}^a$	$\rho_{Y(D)}^b$	$\rho_{Y(D)}^a$	$\rho_{Y(D)}^b$
4-MeO	0.61 ± 0.03	2.35 ± 0.16	0.52 ± 0.03	2.30 ± 0.16
4-Me	0.19 ± 0.01	3.11 ± 0.09	0.10 ± 0.01	3.04 ± 0.09
H	0.78 ± 0.01	2.61 ± 0.12	0.68 ± 0.01	2.51 ± 0.11
4-Cl	0.29 ± 0.03	3.21 ± 0.09	0.24 ± 0.03	3.02 ± 0.09
3-Cl	0.75 ± 0.01	3.01 ± 0.14	0.69 ± 0.01	2.84 ± 0.14

^aY = (4-MeO, 4-Me, H; *e-d* block). ^bY = (H, 3-MeO, 4-Cl; *e-w* block).^{a,b}Correlation coefficients (r) of ρ_Y values are better than 0.982.**Figure 1.** Hammett plots with Y of the reactions of bis(Y-aryl) chlorothiophosphates (**1**) with $\text{XC}_6\text{H}_4\text{NH}_2$ in MeCN at 55.0 °C.

values of $\rho_{XY(D)} = 0.28$ and 0.59 with *e-d* and *e-w* block, respectively (supporting information). Both anilines and deuterated anilines, the magnitude of ρ_{XY} value with *e-w* block is larger than that with *e-d* block.⁴ This suggests that the distance between X and Y with *e-w* block is closer than that with *e-d* block in the TS (*vide infra*).⁵

$$\log(k_{XY}/k_{HH}) = \rho_X\sigma_X + \rho_Y\sigma_Y + \rho_{XY}\sigma_X\sigma_Y \quad (1)$$

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

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 because all the studied substrates have identical substituent Y in each phenyl ring. The third and fourth terms on the right-side of Eq. (3) 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 $\rho_{YY(H)}$ reflects the cross-interaction between the two substituents, Y and Y, in the TS. In Eq. (3), pure second-, third-, and higher-derivative terms are not considered as in Eq. (1). The values of $\rho_{X(H)}$, $\rho_{Y(H)}$, $\rho_{XY(H)}$ and $\rho_{YY(H)}$ obtained by multiple regression are described in Eqs. (4) and (5) with *e-d* and *e-w* block, respectively. As a matter of course, the values of $\rho_{XY(H)} = 0.22$ [Eq. (4)] and 0.81 [Eq. (5)] with *e-d* and *e-w* block, respectively, have the same values calculated from Eq. (2) because ρ_{XY} is defined as $\partial \rho_X / \partial \sigma_Y = \partial \rho_Y / \partial \sigma_X$.

$$\log(k_{XY(H)}/k_{HH(H)}) = \rho_{X(H)}\sigma_X + \rho_{Y(H)}\sigma_Y + \rho_{XY(H)}\sigma_X\sigma_Y + \rho_{YY(H)}\sigma_Y\sigma_Y \quad (3)$$

$$\log(k_{XY(H)}/k_{HH(H)}) = -3.88\sigma_X + 0.23\sigma_Y + 0.22\sigma_X\sigma_Y - 1.11\sigma_Y\sigma_Y \text{ (e-d block)} \quad (4)$$

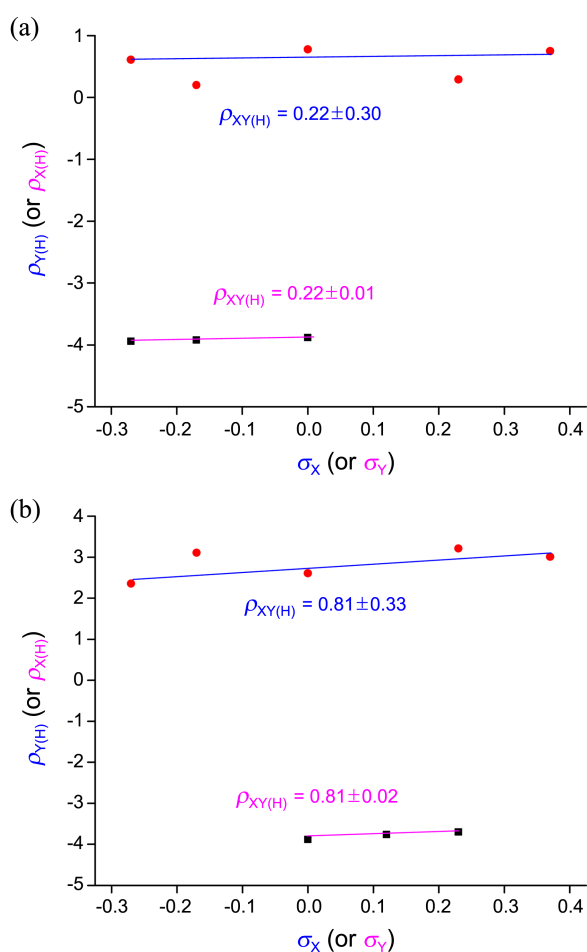


Figure 2. Plots of $\rho_{Y(H)}$ vs σ_X and $\rho_{X(H)}$ vs σ_Y of the reactions of bis(Y-aryl) chlorothiophosphates with $\text{XC}_6\text{H}_4\text{NH}_2$ in MeCN at 55.0 °C to determine $\rho_{XY(H)}$ according to Eq. (2). The values of $\rho_{XY(H)} = 0.22 \pm 0.10$ ($r = 0.992$) and 0.81 ± 0.12 ($r = 0.988$) with (a) *e-d* and (b) *e-w* block, respectively, are obtained by multiple regression.

$$\log(k_{XY(H)}/k_{HH(H)}) = -3.88\sigma_X + 0.29\sigma_Y + 0.81\sigma_X\sigma_Y + 11.1\sigma_Y\sigma_Y \text{ (e-w block)} \quad (5)$$

Note the sign and magnitudes of $\rho_{YY(H)}$ values of -1.11 (negative and five times greater than $\rho_{XY(H)}$) and $+11.1$ (positive and fourteen times greater than $\rho_{XY(H)}$) with *e-d* and *e-w* block, respectively. The $\rho_{YY(D)}$ values with deuterated anilines, -1.01 with *e-d* and 10.9 with *e-w* block, are quite similar to those with anilines.⁶ These results suggest that: (i) the values of $\rho_{YY(H)} = -1.11$ and 11.1 with *e-d* and *e-w* block, respectively, are attributed to the cross-interaction between Y and Y in each phenyl ring in the TS; (ii) the cross-interaction between the two substituents, Y and Y, is significant in the TS; (iii) the cross interaction between Y and Y with *e-w* block is much greater than that with *e-d* block in the TS; (iv) the negative sign of $\rho_{YY(H)}$ with *e-d* block indicates that the cross-interaction between Y and Y reduces the rate, *i.e.*, negative role in the rate, whereas the positive sign of $\rho_{YY(H)}$ with *e-w* block implies that the cross-interaction between Y and Y induces remarkable enhancement of the rate *i.e.*, positive role in the rate; and finally (v) the opposite effect of

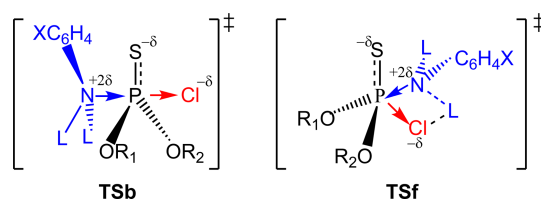
the cross-interaction between Y and Y on the rate with *e-d* and *e-w* block leads to biphasic concave upward free energy relationship for substituent Y variations with a break point at $Y = \text{H}$.

The variation tendencies of the ρ_X and ρ_Y values with Y and X, respectively, of **1** are opposite to those of **2**. As a result, the sign of $\rho_{XY(H)}$ with **1** is opposite to that of $\rho_{XY(H)}$ with **2**. This implies that an additional substituent Y to the other phenyl ring in the substrate changes the reaction mechanism from a concerted $\text{S}_{\text{N}}2$ in **2** (based on $\rho_{XY(H)} = -1.31$) to a stepwise process with a rate-limiting leaving group departure from the intermediate in **1** (based on $\rho_{XY(H)} = +0.22$ and $+0.81$ with *e-d* and *e-w* block, respectively).⁵

The nonlinear free energy correlation of a concave upward plot is generally diagnostic of a change in the reaction mechanism, while nonlinear free energy correlation of the concave downward plot is generally interpreted as a rate-limiting step change from bond breaking with less basic nucleophiles to bond formation with more basic nucleophiles.⁷ In the present work, however, the concave upward free energy correlation with Y is interpreted as a change in the effect of the cross-interaction between Y and Y on the rate from negative with *e-d* block to positive role with *e-w* block.

The DKIEs can only be secondary inverse ($k_{\text{H}}/k_{\text{D}} < 1.0$) when an increase in the steric congestion occurs in the bond-making process (*e.g.* TSb in Scheme 2) because the N–H(D) vibrational frequencies invariably increase upon going to the TS.⁸ In contrast, when partial deprotonation of the aniline occurs in a rate-limiting step by hydrogen bonding (*e.g.* TSf in Scheme 2), the $k_{\text{H}}/k_{\text{D}}$ values are greater than unity, primary normal ($k_{\text{H}}/k_{\text{D}} > 1.0$).⁹ In the present work, the DKIEs are all primary normal ($k_{\text{H}}/k_{\text{D}} > 1.0$; Table 4), indicating that partial deprotonation of the aniline occurs in a rate-limiting step by hydrogen bonding. The DKIEs invariably decrease as substituent X changes from electron-donating to electron-withdrawing, and invariably increase as substituent Y changes from electron-donating to electron-withdrawing. Accordingly, the max value of DKIE ($k_{\text{H}}/k_{\text{D}} = 1.31$) is observed with $X = 4\text{-MeO}$ and $Y = 4\text{-Cl}$, indicating that the extent of the hydrogen bonding is the largest in the TS. The larger values of primary normal DKIEs with *e-w* block than those with *e-d* block indicate that the extent of hydrogen bond with *e-w* block is greater than that with *e-d* block in the TS. This is consistent with larger magnitude of the ρ_{XY} value with *e-w* block than that with *e-d* block (*vide supra*).

In summary, the authors propose a stepwise mechanism with a rate-limiting leaving group expulsion from the inter-



Scheme 2. Backside attack in-line-type TSb and frontside attack hydrogen bonded, four-center-type TSf (L = H or D).

Table 4. The DKIEs (k_H/k_D) for the Reactions of Bis(Y-aryl) Chlorothiophosphates (**1**) with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$ in MeCN at 55.0 °C

X \ Y	4-MeO	4-Me	H	3-MeO	4-Cl
4-MeO	1.20 ± 0.01	1.23 ± 0.01	1.27 ± 0.01	1.29 ± 0.01	1.31 ± 0.01
4-Me	1.18 ± 0.02	1.20 ± 0.01	1.24 ± 0.01	1.26 ± 0.01	1.29 ± 0.01
H	1.14 ± 0.01	1.17 ± 0.01	1.20 ± 0.01	1.22 ± 0.01	1.27 ± 0.01
4-Cl	1.08 ± 0.01	1.10 ± 0.01	1.11 ± 0.01	1.16 ± 0.01	1.24 ± 0.01
3-Cl	1.05 ± 0.01	1.07 ± 0.01	1.09 ± 0.01	1.15 ± 0.01	1.20 ± 0.01

^aStandard error $\{= 1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D)^2]^{1/2}\}$ from ref 10.

Table 5. Activation Parameters for the Reactions of Bis(Y-aryl) Chlorothiophosphates (**1**) with $\text{C}_6\text{H}_5\text{NH}_2$ in MeCN

Y	$t/^\circ\text{C}$	$k_H \times 10^5 / \text{M}^{-1} \text{s}^{-1}$	$\Delta H^\ddagger / \text{kcal mol}^{-1}$	$-\Delta S^\ddagger / \text{cal mol}^{-1} \text{K}^{-1}$
4-MeO	55.0	6.30 ± 0.02	6.9 ± 0.1	57 ± 1
	65.0	8.96 ± 0.02		
	75.0	12.3 ± 0.1		
4-Me	55.0	7.28 ± 0.01	7.5 ± 0.1	55 ± 1
	65.0	10.6 ± 0.1		
	75.0	15.0 ± 0.1		
H	55.0	10.1 ± 0.1	7.7 ± 0.2	54 ± 1
	65.0	14.6 ± 0.1		
	75.0	21.3 ± 0.1		
3-MeO	55.0	15.1 ± 0.1	7.2 ± 0.1	52 ± 1
	65.0	22.5 ± 0.1		
	75.0	32.4 ± 0.2		
4-Cl	55.0	40.7 ± 0.4	8.5 ± 0.2	49 ± 1
	65.0	62.7 ± 0.1		
	75.0	91.1 ± 0.1		

mediate based on the positive ρ_{XY} values for both *e-d* and *e-w* blocks despite the biphasic concave upward free energy relationship, and dominant frontside nucleophilic attack involving a hydrogen bonded, four-center-type TSf based on the primary normal DKIEs. Concave upward free energy correlation with Y is ascribed to the opposite effect of the cross-interaction between Y and Y in the same substrate with *e-d* and *e-w* block.

Activation parameters, enthalpies and entropies of activation, are determined as shown in Table 5. The enthalpies of activation are relatively low and entropies of activation are relatively large negative value. The relatively low values of activation enthalpies (7-9 kcal mol⁻¹) and relatively large negative values of activation entropies (-49 to -57 cal mol⁻¹ K⁻¹) are typical for the aminolyses of P=S(O) systems.

Experimental Section

Materials. Bis(Y-aryl) chlorothiophosphates were prepared by reacting thiophosphoryl chloride with substituted phenol for 3 h in the presence of triethylamine in methylene chloride on cooling bath at -10.0 °C with constant stirring. Triethylamine hydrochloride was separated by filtration. The filtrate was treated with water-NaHCO₃ and ether for work up after removal of solvent under reduced pressure. Ether

extracted organic part was dried over anhydrous MgSO₄ for 6-8 h. The product mixture was isolated by filtration and finally separated through column chromatography (silica gel, ethyl acetate/*n*-hexane) and dried under reduced pressure using oil diffusion pump and were identified by TLC, ¹H-NMR, ¹³C-NMR, ³¹P-NMR and GC-MS. The physical constants after column chromatography (silicagel/ethylacetate + *n*-hexane) were as follows¹¹ (supporting information);

Bis(4-methoxyphenyl) Chlorothiophosphate: White solid crystal; mp 64.0-65.0 °C; ¹H-NMR (400 MHz, CDCl₃ and TMS) δ 3.81 (s, 6H), 6.89-6.91 (d, 4H), 7.21-7.26 (d, 4H); ¹³C-NMR (100 MHz, CDCl₃ and TMS) δ 55.6, 114.7, 122.2, 129.4, 140.1, 154.4; ³¹P-NMR (162 MHz, CDCl₃ and TMS) δ 66.6 (1P, P=S); GC-MS (EI, *m/z*) 344 (M⁺).

Bis(4-methylphenyl) Chlorothiophosphate: White solid crystal; mp 54.0-55.0 °C; ¹H-NMR (400 MHz, CDCl₃ and TMS) δ 2.36 (s, 6H), 7.19-7.21 (s, 8H); ¹³C-NMR (100 MHz, CDCl₃ and TMS) δ 20.8, 121.0, 130.3, 136.1, 148.1; ³¹P-NMR (162 MHz, CDCl₃ and TMS) δ 65.2 (1P, P=S); GC-MS (EI, *m/z*) 312 (M⁺).

Bis(3-methoxyphenyl) Chlorothiophosphate: Liquid; ¹H-NMR (400 MHz, CDCl₃ and TMS) δ 3.82 (s, 6H), 6.85-6.87 (t, 4H), 6.91-6.93 (d, 2H), 7.26-7.31 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃ and TMS) δ 55.53, 107.4, 112.2, 113.3, 130.1, 151.0, 160.7; ³¹P-NMR (162 MHz, CDCl₃ and TMS) δ 63.6 (1P, P=S); GC-MS (EI, *m/z*) 344 (M⁺).

Bis(4-chlorophenyl) Chlorothiophosphate: Liquid; ¹H-NMR (400 MHz, CDCl₃ and TMS) δ 7.23 (d, 2H), 7.25 (d, 2H), 7.37 (d, 2H), 7.39 (d, 2H); ¹³C-NMR (100 MHz, CDCl₃ and TMS) δ 122.6, 130.0, 132.2, 148.5; ³¹P-NMR (162 MHz, CDCl₃ and TMS) δ 64.1 (1P, P=S); GC-MS (EI, *m/z*) 353 (M⁺).

Kinetics Measurement. The second-order rate constants and selectivity parameters were obtained as previously described.¹ Initial concentrations were as follows; [substrate] = 5 × 10⁻³ M and [nucleophile] = (0.10-0.30) M.

Product Analysis. Diphenyl chlorothiophosphate was reacted with excess aniline for more than 15 half-lives at 55.0 °C in MeCN. Solvent was evaporated under reduced pressure. The product mixture was treated with ether by a work-up process with dilute HCl and dried over anhydrous MgSO₄. Then the product was isolated through column chromatography (30% ethyl acetate/*n*-hexane) and then dried under reduced pressure. The analytical and spectroscopic data of the product gave the following results (supporting information):

[(C₆H₅O)₂P(=S)NHC₆H₅]: Brown liquid; ¹H-NMR (400

MHz, CDCl₃ and TMS) δ 3.39 (s, br., 1H), 6.68-6.70 (m, 5H), 6.74-6.78 (m, 3H), 7.13-7.22 (m, 6H), 7.27-7.38 (m, 1H); ¹³C-NMR (100 MHz, CDCl₃ and TMS) δ 118.3, 118.4, 121.3, 121.4, 122.9, 125.6, 129.6, 138.9, 150.3; ³¹P-NMR (162 MHz, CDCl₃ and TMS) δ 62.6 (1P, P=S); GC-MS (EI, m/z) 341 (M⁺).

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References and Notes

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4. Fifteen $k_{\text{H(D)}}$ values are employed to calculate the $\rho_{\text{XY(H or D)}}$ values. There is no conflict of the signs of $\rho_{\text{XY(H or D)}}$. Larger magnitude of the $\rho_{\text{XY(H or D)}}$ value with *e-w* block compared to that with *e-d* block may be acceptable over the experimental error.
5. The sign of the CIC (ρ_{XY}) is negative in a normal S_N2 mechanism (or in a stepwise process with a rate-limiting bond formation), and positive in a stepwise process with a rate-limiting leaving group expulsion from the intermediate. 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.
6. The values of $\rho_{\text{X(D)}}$, $\rho_{\text{Y(D)}}$, $\rho_{\text{XY(D)}}$ and $\rho_{\text{Y(D)}}$ obtained by multiple regression are described in Eqs. (R2) and (R3) with *e-d* and *e-w* block, respectively.

$$\log(k_{\text{XY(D)}/k_{\text{HH(D)}}}) = \rho_{\text{X(D)}}\sigma_{\text{X}} + \rho_{\text{Y(D)}}\sigma_{\text{Y}} + \rho_{\text{XY(D)}}\sigma_{\text{X}}\sigma_{\text{Y}} + \rho_{\text{Y(D)}}\sigma_{\text{Y}} \quad (\text{R1})$$

$$\log(k_{\text{XY(D)}/k_{\text{HH(D)}}}) = -3.78\sigma_{\text{X}} + 0.17\sigma_{\text{Y}} + 0.28\sigma_{\text{X}}\sigma_{\text{Y}} - 1.01\sigma_{\text{Y}}\sigma_{\text{Y}} \text{ (e-d block)} \quad (\text{R2})$$

$$\log(k_{\text{XY(D)}/k_{\text{HH(D)}}}) = -3.77\sigma_{\text{X}} + 0.24\sigma_{\text{Y}} + 0.59\sigma_{\text{X}}\sigma_{\text{Y}} + 10.9\sigma_{\text{Y}}\sigma_{\text{Y}} \text{ (e-w block)} \quad (\text{R3})$$

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