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Dual Substituent Effects on Pyridinolysis of Bis(aryl) Chlorothiophosphates in Acetonitrile

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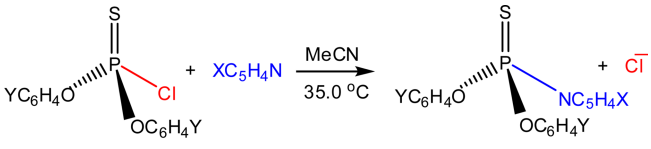
The nucleophilic substitution reactions of bis(Y-aryl) chlorothiophosphates (**1**) with X-pyridines are investigated kinetically in acetonitrile at 35.0 °C. The free energy relationships with both X and Y are biphasic concave upwards with a break point at X = 3-Ph and Y = H, respectively. The sign of cross-interaction constants (CICs; ρ_{XY}) is positive with all X and Y. Proposed mechanism is a stepwise process with a rate-limiting leaving group departure from the intermediate with all X and Y. The kinetic results of **1** are compared with those of Y-aryl phenyl chlorothiophosphates (**2**). In the case of Y = electron-withdrawing groups, the cross-interaction between Y and Y, due to additional substituent Y, is significant enough to change the sign of ρ_{XY} from negative with **2** to positive with **1**, indicative of the change of mechanism from a rate-limiting bond formation to bond breaking.

Key Words : Dual substituent effects, Cross-interaction constant, Pyridinolysis, Bis(Y-aryl) chlorothiophosphates, Thiophosphoryl transfer reaction

Introduction

The kinetic studies on the reactions of Y-aryl phenyl chlorothiophosphates [**2**; $(YC_6H_4O)(C_6H_5O)P(=S)Cl$] with X-pyridines in acetonitrile (MeCN) were reported earlier by this lab.[1] Herein, (i) the free energy relationships with X were biphasic concave upwards while those with Y were biphasic concave downwards; (ii) proposed mechanism was a stepwise process with a rate-limiting step change from bond breaking with the weaker electrophiles to bond formation with the stronger eletrophiles based on the sign of cross-interaction constants (CICs; ρ_{XY});[2] and (iii) nonlinear free energy correlations of biphasic concave upward plots with X were rationalized by a change in the attacking direction of the nucleophile from a backside with the weakly basic pyridines to a frontside attack with the strongly basic pyridines. In the present work, the nucleophilic substitution reactions of bis(Y-aryl) chlorothiophosphates [**1**; $(YC_6H_4O)_2P(=S)Cl$] with substituted pyridines are investigated kinetically in MeCN at 35.0 ± 0.1 °C (Scheme 1). The purpose of this work is to study the dual substituent effects on the reactivity and mechanism by adding the very same substituent Y in the other phenyl ring based on the selectivity parameters and CICs. 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**.



X = 4-MeO, 4-Me, H, 3-Ph, 3-Ac, 4-Ac; Y = 4-MeO, 4-Me, H, 3-MeO, 4-Cl

Scheme 1. Pyridinolysis of **1** [bis(Y-aryl) chlorothiophosphates] in MeCN at 35.0 °C.

Results and Discussion

Tables 1-3 list the second-order rate constants (k_2/M^{-1} s^{-1}), Hammett (ρ_X) and Brönsted (β_X) coefficients with X, and Hammett coefficients (ρ_Y) with Y, respectively. The ρ_Y values are calculated from the plots of log k_2 against σ_Y although all the studied substrates contain two Y-substituted phenyl rings with same substituent Y. Figures 1 and 2 show the Hammett and Brönsted plots with X, respectively, and Figure 3 shows the Hammett plots with Y. The substituent effects on the reaction rates with X and Y are compatible with a typical nucleophilic substitution reaction. The stronger nucleophile leads to the faster rate and a more electron-withdrawing substituent Y in the substrate leads to the faster rate. However, all the free energy relationships with X and Y are biphasic concave upwards with a break point at X = 3-Ph and Y = H, respectively. In the case of **2**, the free energy relationships with X are the same as in **1**, but those with Y are biphasic concave downwards with a break point at Y = H.[1]

For convenience, henceforth, the substituents X in the nucleophiles and Y in the substrates are divided into two blocks, respectively, as follows: (i) *u*-block with X = (4-MeO, 4-Me, H, 3-Ph); (ii) *d*-block with X = (3-Ph, 3-Ac, 4-Ac); (iii) *l*-block with Y = (4-MeO, 4-Me, H); and (iv) *r*-block with Y = (H, 3-MeO, 4-Cl).[3] Thus, there are four blocks with X and Y: *u,l*-, *d,l*-, *u,r*- and *d,r*-block. The magnitudes of the ρ_X and β_X values with *u*-block are 4-6 times larger than those with *d*-block. The magnitudes of the ρ_X values with **1** are somewhat smaller than those with **2**: ρ_X = –6.86 to –6.39 (*u*-block) and –1.54 to –1.22 (*d*-block) with **1** while ρ_X = –7.31 to –6.62 (*u*-block) and –2.72 to –1.24 (*d*-

Table 1. Second-Order Rate Constants ($k_2 \times 10^4/M^{-1}\,s^{-1}$) of the Reactions of **1** with XC_5H_4N in MeCN at 35.0 °C

X \ Y	4-MeO	4-Me	H	3-MeO	4-Cl
4-MeO	194 ± 1	224 ± 1	267 ± 1	295 ± 1	585 ± 1
4-Me	30.9 ± 0. 1	34.5 ± 0.1	37.0 ± 0.2	57.1 ± 0.1	127 ± 2
H	2.38 ± 0.01	2.91 ± 0.01	3.33 0.01	4.70 ± 0.02	9.86 ± 0.01
3-Ph	1.01 ± 0.01	1.31 ± 0.01	1.66 ± 0.01	2.19 ± 0.01	4.74 ± 0.01
3-Ac	0.380 ± 0.001	0.475 ± 0.001	0.822 ± 0.001	0.976 ± 0.001	1.86 ± 0.01
4-Ac	0.201 ± 0.001	0.267 ± 0.001	0.440 ± 0.001	0.608 ± 0.001	1.40 ± 0.01

Table 2. Hammett (ρ_X) and Brönsted (β_X) Coefficients with X of the Reactions of **1** with XC_5H_4N in MeCN at 35.0 °C

X \ Y		4-MeO	4-Me	H	3-MeO	4-Cl
u-block	$-\rho_X$[a]	6.86 ± 0.06	6.70 ± 0.08	6.62 ± 0.11	6.45 ± 0.04	6.39 ± 0.03
	β_X[b]	1.34 ± 0.05	1.31 ± 0.07	1.30 ± 0.10	1.26 ± 0.05	1.25 ± 0.06
d-block	$-\rho_X$[c]	1.54 ± 0.07	1.53 ± 0.05	1.24 ± 0.09	1.23 ± 0.04	1.22 ± 0.02
	β_X[d]	0.28 ± 0.02	0.28 ± 0.01	0.23 ± 0.05	0.22 ± 0.01	0.22 ± 0.05

[a]Correlation coefficients (r) are better than 0.996. [b]r ≥ 0.999. [c]r ≥ 0.975. [d]r ≥ 0.991.

Table 3. Hammett Coefficients (ρ_Y) with Y of the Reactions of **1** with XC_5H_4N in MeCN at 35.0 °C

Y \ X	4-MeO	4-Me	H	3-Ph	3-Ac	4-Ac
l-block[a]	0.51 ± 0.01	0.28 ± 0.01	0.52 ± 0.03	0.78 ± 0.03	1.26 ± 0.02	1.26 ± 0.03
r-block[b]	1.46 ± 0.11	2.31 ± 0.07	2.04 ± 0.08	1.97 ± 0.10	1.53 ± 0.09	2.17 ± 0.09

[a]r ≥ 0.963. [b]r ≥ 0.940.

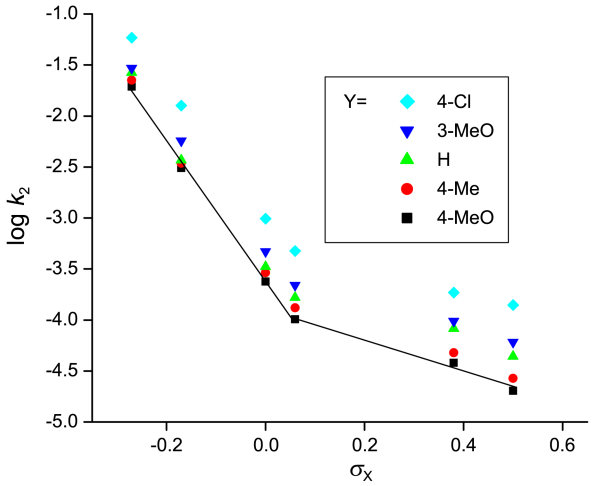


Figure 1. Hammett plots with X of the reactions of **1** with XC_5H_4N in MeCN at 35.0 °C.

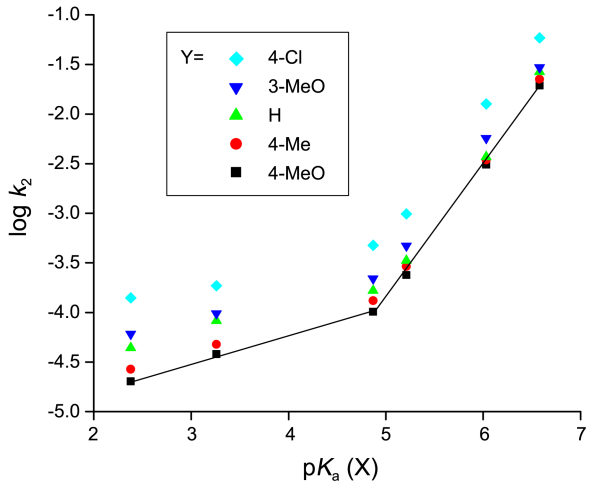


Figure 2. Brönsted plots with X of the reactions of **1** with XC_5H_4N in MeCN at 35.0 °C.

block) with **2**. This indicates that the substituent effects of X on the rates with **1** are smaller than those with **2**. At a glance, one might estimate that the ρ_Y values with **1** would be two times larger than those with **2** because the substrate **1** has one more substituent Y in the other phenyl ring compared to the substrate **2**. But actually, the magnitudes of the ρ_Y values with **1** are more or less complicated depending on the kind of block when comparing those with **2**: (i) ρ_Y = 0.28-0.78 with **1** while 0.46-1.20 with **2** for *u,l*-block; (ii) 1.46-2.21 with **1** while 1.18-3.45 with **2** for *d,l*-block; (iii) 0.78-1.26 with **1** while 0.21-0.69 with **2** for *u,r*-block; and (iv) 1.53-2.17 with **1** while 0.23-0.28 with **2** for *d,r*-block. The substituent effects of Y on the rates with **1** are different from those with **2**: (i) the ρ_Y values with **1** are almost smaller than those with **2** for *u,l*- and *d,l*-block; (ii) while those with **1** are much larger than those with **2** for *u,r*- and *d,r*-block; and (iii) even more, those with **1** are 7-8 times larger than those with **2** for *d,r*-block. These indicate that the substituent effects of Y on the rates sometimes play positive and/or negative role in the rate depending upon the nature of X and/or Y.

Figure 4 shows four ρ_{XY} values with four blocks, according to the definition of CIC, Eqs. (1) and (2),[2] because both the Hammett plots for substituent X and Y variations are biphasic with a break point, and multiple regressions result

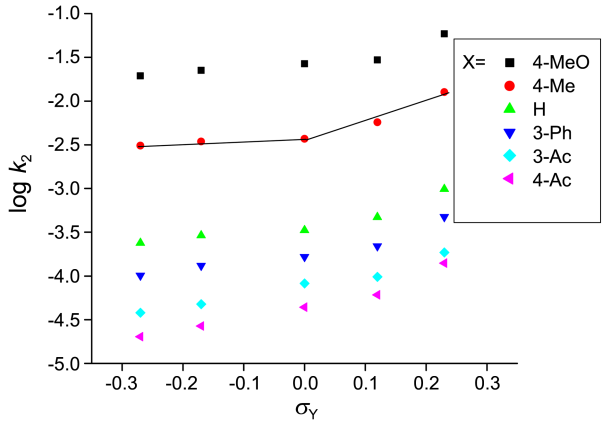


Figure 3. Hammett plots with Y of the reactions of **1** with XC_5H_4N in MeCN at 35.0 °C.

in: (i) ρ_{XY} = 0.88 with *u,l*-block; (ii) 1.18 with *d,l*-block; (iii) 0.99 with *u,r*-block; and (iv) 0.09 with *d,r*-block.[4] The signs of ρ_{XY} of **1** are all positive with four blocks. In contrast to **1**, the signs of ρ_{XY} of **2** are: (i) positive with *u,l*- and *d,l*-block; and (ii) negative with *u,r*- and *d,r*-block.[1]

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

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

Regarding the sign of ρ_{XY}, both **1** and **2** show positive with *u,l*- and *d,l*-block, however, **1** shows positive and **2** shows negative with *u,r*- and *d,r*-block. This suggests that the pyridinolysis mechanism is the same for both **1** and **2** with *u,l*- and *d,l*-block, but the mechanism is different between **1** and **2** with *u,r*- and *d,r*-block. It is the suggestion of the authors that the proposed mechanism of the pyridinolysis of **1** is a stepwise process with a rate-limiting leaving group departure from the intermediate with all four blocks, because the sign of ρ_{XY} is positive in a stepwise reaction with a rate-limiting bond breaking while negative in a stepwise reaction with a rate-limiting bond formation (or in a normal S_N2 reaction).[2] This implies that the additional Y in the other phenyl ring results in the change of mechanism from a rate-limiting bond formation with **2** to a rate-limiting leaving group expulsion from the intermediate with **1** for *u,r*- and *d,r*-block. The magnitudes of the ρ_{XY} values with **1** are smaller (*u,l*- and *d,l*-block) or nearly the same (*u,r*- and *d,r*-block) compared to those with **2**: ρ_{XY} = 0.88(**1**) < 2.42(**2**), 1.18(**1**) < 5.14(**2**), 0.99(**1**) ≈ |–1.02|(**2**) and 0.09(**1**) ≈ |–0.04|(**2**) with *u,l*-, *d,l*-, *u,r*- and *d,r*-block, respectively. The distances between X and Y with **1** would be longer than that with **2** for

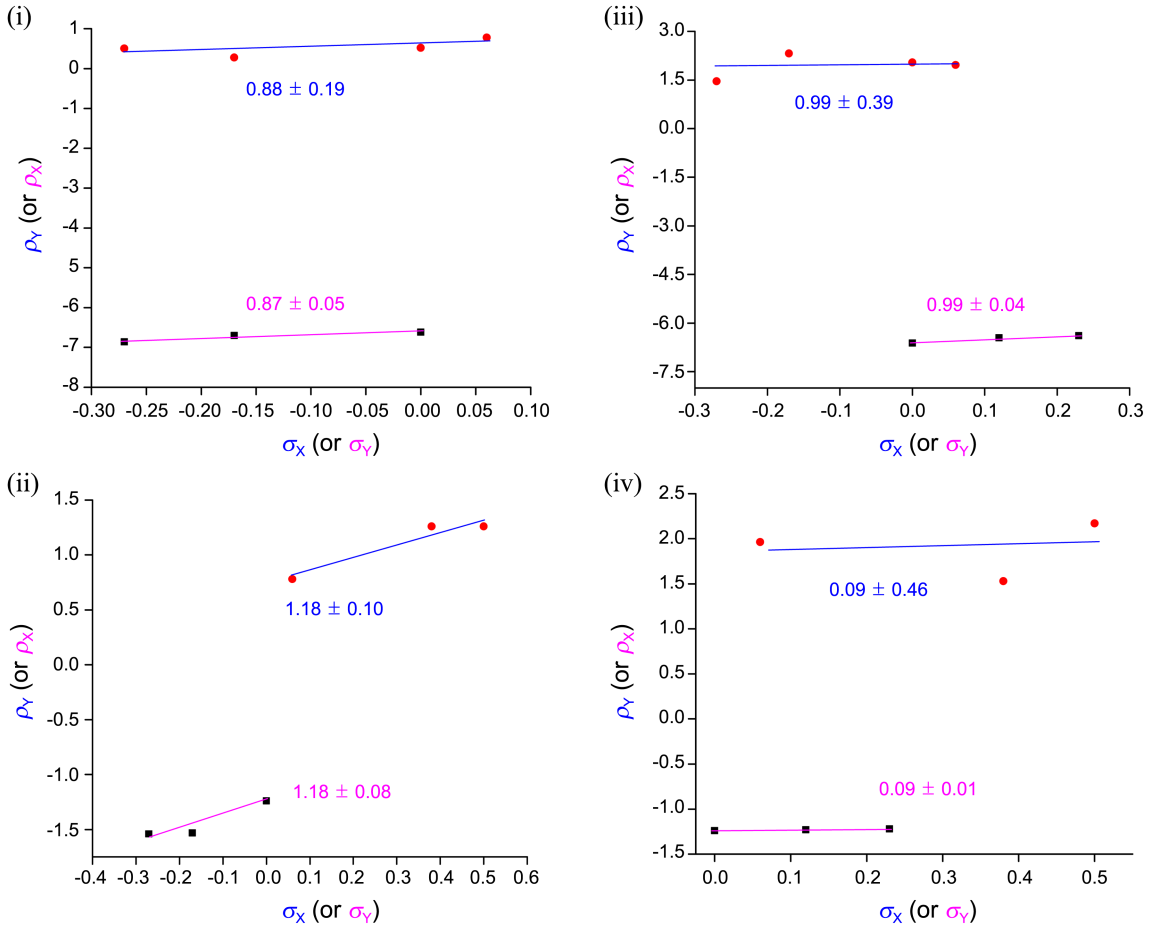


Figure 4. Determination of CICs of the reactions of **1** with XC_5H_4N in MeCN at 35.0 °C. The ρ_{XY} values obtained by multiple regressions are: (i) ρ_{XY} = 0.88 ± 0.08 (r = 0.995) with *u,l*-block; (ii) 1.18 ± 0.05 (r = 0.980) with *d,l*-block; (iii) 0.99 ± 0.09 (r = 0.993) with *u,r*-block; and (iv) 0.09 ± 0.09 (r = 0.953) with *d,r*-block.

u,l- and *d,l*-block, and those with **1** and **2** would be similar for *u,r*- and *d,r*-block, because the magnitude of the CIC is inversely proportional to the distance between X and Y through the reaction center in the TS (*vide infra*).[2]

In the case of the anilinolysis, substrate **2** exhibited linear free energy correlations with both X and Y,[5] while substrate **1** exhibited linear with X and biphasic concave upward free energy relationships with Y.[6] The sign of ρ_{XY} was negative with **2**, while the sign of ρ_{XY} was positive for both electron-donating and -withdrawing Y substituents despite biphasic concave upward free energy relationships. This indicated that the reaction mechanism was changed from a concerted (or a stepwise with a rate-limiting bond formation) with **2** to a stepwise with a rate-limiting bond cleavage with **1** due to additional substituent Y. The cross-interaction between Y and Y was so significant that the change of the sign of ρ_{XY} from negative with **2** to positive with **1** occured.[6]

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).[2] 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 $\rho_{XYY}\sigma_X\sigma_Y^2$), 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 because they are normally too small to be taken into account. In the present work, the modified Eq. (3) is employed 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 term 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, in the transition state (TS). The values of ρ_X, ρ_Y, ρ_{XY} and ρ_{YY} with four blocks obtained by multiple regressions are described in Eqs. (4)-(7), respectively.

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

$$\log (k_{XY}/k_{HH}) = -6.60\sigma_X + 0.24\sigma_Y + 0.88\sigma_X\sigma_Y - 1.42\sigma_Y^2 \quad (r = 0.993;\ u,l\text{-block}) \quad (4)$$

$$\log (k_{XY}/k_{HH}) = -1.26\sigma_X + 0.71\sigma_Y + 1.18\sigma_X\sigma_Y - 0.06\sigma_Y^2 \quad (r = 0.980;\ d,l\text{-block}) \quad (5)$$

$$\log (k_{XY}/k_{HH}) = -6.60\sigma_X + 0.14\sigma_Y + 0.99\sigma_X\sigma_Y + 8.32\sigma_Y^2 \quad (r = 0.997;\ u,r\text{-block}) \quad (6)$$

$$\log (k_{XY}/k_{HH}) = -1.24\sigma_X + 0.16\sigma_Y + 0.09\sigma_X\sigma_Y + 8.83\sigma_Y^2 \quad (r = 0.987;\ d,r\text{-block}) \quad (7)$$

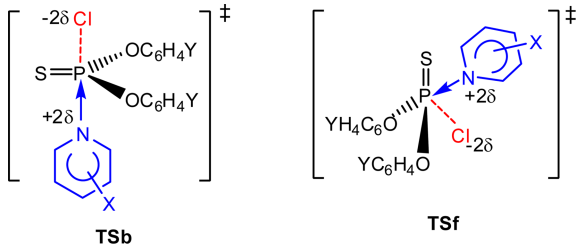
As a matter of course, the ρ_{XY} values calculated from Eq. (3) are the same as those from Eq. (2) because ρ_{XY} is defined as $\partial\rho_X/\partial\sigma_Y = \partial\rho_Y/\partial\sigma_X$. The signs and magnitudes of the ρ_{YY} values are as follows: (i) ρ_{YY} = –1.42 (negative) and 1.6 times greater than ρ_{XY} with *u,l*-block; (ii) –0.06 (negative) and 20 times smaller (nearly zero)[7] than ρ_{XY} with *d,l*-block; (iii) +8.32 (positive) and 8.4 times greater than ρ_{XY} with *u,r*-block; and (iv) +8.83 (positive) and 98 times greater than ρ_{XY} with *d,r*-block. Negative ρ_{YY} values with *u,l*- and *d,l*-block (Y = electron-donating groups) imply the negative role on the rate. The rate becomes slower due to the cross-interaction between Y and Y in the TS, however, the degree of rate retardation is not extensive. On the other hand, positive ρ_{YY} values with *u,r*- and *d,r*-block (Y = electron-withdrawing groups) imply positive role on the rate. The rate becomes faster due to the cross-interaction between Y and Y in the TS, and the degree of rate enhancement is really great. In other words, negative role on the rate is not significant and positive role on the rate is important. As a result, the effect of the cross-interaction between Y and Y with *u,r*- and *d,r*-block is significant enough to change the mechanism from a rate-limiting bond formation with **2** to a rate-limiting bond cleavage with **1**, while the mechanism with *u,l*- and *d,l*-block is the same, a rate-limiting leaving group departure from the intermediate, with both **1** and **2**.

The nucleophilic attacking direction towards the leaving group chloride is dependent upon the nature of X. As mentioned earlier, the magnitudes of the ρ_X and β_X values with *u*-block are 4-6 times greater than those with *d*-block, indicative of larger degree of bond formation with *u*-block than with *d*-block in the TS. It is well known that a weakly basic group has a greater apicophilicity so that apical approach is favored for such nucleophiles, and the apical bonds are longer than the equatorial bonds.[8] Thus, proposed TS structures are backside apical attack TSb with *d,l*- and *d,r*-block while frontside equatorial attack TSf with *u,l*-block and *u,r*-block (Scheme 2). As a result, the degree of bond formation with *u,l*-block and *u,r*-block is somewhat larger than that with *d,l*- and *d,r*-block. In general, the nonlinear free energy correlation of a concave upward plot is diagnostic of a change in the reaction mechanism where the reaction path is changed depending on the substituents.[9] The biphasic concave upward free energy correlation is also diagnostic of a change in the nucleophilic attacking direction towards the leaving group from frontside with the strongly basic nucleophiles to backside with the weakly basic nucleophiles. Taking into account the ρ_{XY} value in each block, it may be possible to estimate the relative degree of bond breaking in the TS (*vide supra*): (i) *u,l*-block, the degree of bond breaking is extensive based on ρ_{XY} = 0.88; (ii) *d,l*-block, the degree of bond breaking is extensive based on ρ_{XY} = 1.18; (iii) *u,r*-block, the degree of bond breaking is not extensive based on ρ_{XY} = 0.99; and (iv) *d,r*-block, the degree of bond breaking is considerably extensive based on ρ_{XY} = 0.09.[10] Table 4 summarizes the nucleophilic attacking direction and degree of bond formation and breaking in each block in the TS.

Experimental Section

Materials. The substrates were prepared as reported earlier.[6]

Kinetic Measurements. The second-order rate constants and selectivity parameters were obtained as reported earlier.[1] The initial concentrations of [substrate] = 5×10^{-3} M and [X-pyridine] = (0.1-0.3) M were used.



Scheme 2. Proposed TS structures: backside apical attack TSb with *d,l*- and *d,r*-block, and frontside equatorial attack TSf with *u,l*- and *u,r*-block.

Table 4. Nucleophilic Attacking Direction and Degree of Bond Formation and Breaking in the TS of the Reactions of **1** with XC_5H_4N in MeCN at 35.0 °C

block	direction	formation[a]	breaking[a]
u,l	frontside	large	large
d,l	backside	small	small
u,r	frontside	large	large
d,r	backside	small	very large

[a]Qualitative consideration of the relative magnitudes.

Product Analysis. Bis(4-methylphenyl)chlorothiophosphate was reacted with excess pyridine, for more than 15 half-lives at 35.0 °C in MeCN. Solvent was removed under reduced pressure. The product was isolated by adding ether and insoluble fraction was collected. The product was purified to remove excess pyridine by washing several times with ether and MeCN. Analytical and spectroscopic data of the product gave the following results (supporting information):

$[(4\text{-}CH_3C_6H_4O)_2P(=S)NC_5H_5]^+Cl^-$. Colorless liquid; ^{1}H-NMR (400 MHz, MeCN-d_3) δ 2.09 (s, 6H), 7.13 (d, 4H), 7.94 (t, 3H), 8.45 (m, 3H), 8.67 (s, 4H); ^{13}C-NMR (100 MHz, MeCN-d_3) δ 20.8, 121.9, 128.2, 130.7, 142.4, 146.7, 156.1; ^{31}P-NMR (162 MHz, MeCN-d_3) δ 52.2 (1P, s, P=S); LC-MS for $C_{19}H_{19}ClNO_2PS$ (EI, *m/z*), 392 (M^+).

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3. The *u*- and *d*-block with X represent *u*p-side and *d*own-side in Table 1, respectively. The *l*- and *r*-block with Y represent *l*eft-side and *r*ight-side in Table 1, respectively.
4. The ρ_{XY} values are calculated with twelve second-order rate constants (four nucleophiles × three substrates) for *u,l*-block and *u,r*-block while with nine second-order rate constants (three nucleophiles × three substrates) for *d,l*-block and *d,r*-block. The correlation coefficient of r = 0.953 with *d,r*-block is not tolerable, but the positive sign and very small magnitude of ρ_{XY} are acceptable.
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7. The values of σ_Y, employed in the present work, are less than unity ($\sigma_Y \leq |0.27|$). Thus, $\rho_{YY}\sigma_Y\sigma_Y = 0.06\sigma_Y^2$ is almost equal to null ($0.06\sigma_Y^2 \leq 0.004 \approx 0$) with *d,l*-block.
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10. These statements are based on the following assumptions: (i) the magnitude of the ρ_{XY} value is inversely proportional to the distance between X and Y through the reaction center P atom in the TS; (ii) The magnitudes of the ρ_{XY} values of 0.88(*u,l*-), 1.18(*d,l*-) and 0.99(*u,r*-block) are nearly the same; and (iii) ρ_{XY} value of 0.09(*d,r*-block) is considerably small.