Significant Substituent Effects on Pyridinolysis of Aryl Ethyl Chlorophosphates in Acetonitrile

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The substituent effects on the pyridinolysis (XC_5H_4N) of Y-aryl ethyl chlorophosphates are investigated in acetonitrile at 35.0 °C. The two strong π-acceptor substituents, X = 4-Ac and 4-CN in the X-pyridines, exhibit large positive deviations from the Hammett plots but little positive deviations from the Brönsted plots. The substituent Y effects on the rates are really significant and the Hammett plots for substituent Y variations in the substrates invariably change from biphasic concave downwards *via* isokinetic at X = H to biphasic concave upwards with a break point at Y = 3-Me as the pyridine becomes less basic. These are interpreted to indicate a mechanistic change at the break point from a stepwise mechanism with a rate-limiting bond formation (ρ_{XY} = –6.26) for Y = (4-MeO, 4-Me, 3-Me) to with a rate-limiting leaving group expulsion from the intermediate (ρ_{XY} = +5.47) for Y = (4-Me, H, 3-MeO). The exceptionally large magnitudes of ρ_{XY} values imply frontside nucleophilic attack transition state.

Key Words : Substituent effects, Cross-interaction constant, Phosphoryl transfer reaction, Pyridinolysis, Aryl ethyl chlorophosphates

Introduction

The cross-interaction constants (CICs) are one of the strong tools to clarify the reaction mechanism by means of the substituent effects on the rates.[1] The CIC, ρ_{ij}, is defined as Eqs. (1) and (2) where i and j represent the substituent X in the nucleophiles and/or Y in the substrates and/or Z in the leaving groups, respectively. A Taylor series expansion of log k_{ij} around $\sigma_i = \sigma_j = 0$ (i = j = H) leads to Eq. (1). Pure second- (*e.g.*, $\rho_{XX}\sigma_X{}^2$ or $\rho_{YY}\sigma_Y{}^2$ or $\rho_{ZZ}\sigma_Z{}^2$), third- (*e.g.*, $\rho_{XXY}\sigma_X{}^2\sigma_Y$ or $\rho_{XYY}\sigma_X\sigma_Y{}^2$, *etc*) and higher-derivative terms are not considered because they are normally too small to be taken into account. The magnitude of ρ_{ij} is inversely proportional to the distance between i and j through the reaction center.[1]

$$\log (k_{ij}/k_{HH}) = \rho_i{}^H\sigma_i + \rho_j{}^H\sigma_j + \rho_{ij}\sigma_i\sigma_j \qquad (1)$$

$$\rho_{ij} = \partial^2\log (k_{ij}/k_{HH})/\partial\sigma_i\partial\sigma_j = \partial\rho_i/\partial\sigma_j = \partial\rho_j/\partial\sigma_i \qquad (2)$$

Eq. (1) can be written in a different form of Eq. (3):

$$\log (k_{ij}/k_{HH}) = \rho_i{}^H\sigma_i + (\rho_j{}^H + \rho_{ij}\sigma_i)\sigma_j \qquad (3)$$

When the second term of the right-side of Eq. (3) is equal to zero, $\rho_j{}^H + \rho_{ij}\sigma_i = 0$ with $\sigma_i = \sigma_{i,iso} = -\rho_j{}^H/\rho_{ij}$, and these relations are substituted into Eq. (3), the result is the below Eq. (4).

$$\log (k_{ij,iso}/k_{HH}) = \rho_i{}^H\sigma_{i,iso} + 0 = -\rho_i{}^H\rho_j{}^H/\rho_{ij} = \text{constant} \qquad (4)$$

Then the value of k_{ij} becomes constant, *i.e.*, $k_{ij,iso}$ where the subscript 'iso' indicates isokinetic, for all j because the values of $\rho_i{}^H$, $\rho_j{}^H$ and ρ_{ij} are constant.[2] When the interaction between the substituent i and j is so strong that the magnitude of the ρ_{ij} value is great, the signs of the selectivity

X = 4-MeO, 4-Me, 3-Me, H, 3-Ph, 3-Cl, 4-Ac, 3-CN, 4-CN
Y = 4-MeO, 4-Me, 3-Me, H, 3-MeO
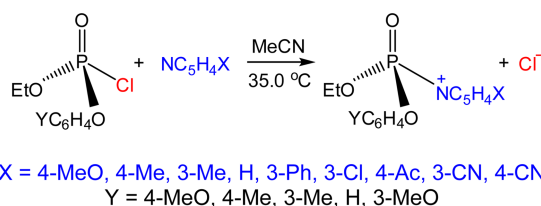
Scheme 1. Pyridinolysis of Y-aryl ethyl chlorophosphates (**1**) in MeCN at 35.0 °C.

parameters (ρ_X, ρ_Y, or ρ_Z) are sometimes changing consistently from positive ($\rho_j > 0$) *via* null ($\rho_j = 0$; isokinetic) to negative ($\rho_j < 0$) as the substituent i becomes more electron-withdrawing (or -donating) group.[3] The reactions of some substrates with X-anilines gave isokinetic phenomena, $\rho_j = 0$ at $\sigma_{i,iso}$, as follows: (i) 1-Y-aryl ethyl chloride with ρ_{XY} = –2.05, giving $\rho_X = 0$ at $\sigma_{Y,iso} = -0.23$;[4] (ii) Y-benzhydryl chlorides with ρ_{XY} = –1.46, giving $\rho_X = 0$ at $\sigma_{Y,iso} = 0.22$;[5] (iii) Y-benzoyl bromides with ρ_{XY} = –0.62, giving $\rho_Y = 0$ at $\sigma_{X,iso} = 0.94$;[6] (iv) cumyl Z-arenesulfonates with ρ_{XZ} = –0.75, giving $\rho_Z = 0$ at $\sigma_{X,iso} = 0.83$.[7]

In the present work, the nucleophilic substitution reactions of Y-aryl ethyl chlorophosphates (**1**) with X-pyridines are studied kinetically in acetonitrile (MeCN) at 35.0 ± 0.1 °C (Scheme 1). The aim of this work is to gain further information on the substituent effects of the nucleophiles and substrates on the reaction mechanism mainly based on the CICs, free energy relationships and strong π-acceptor *para*-substituents in the pyridines.

Results and Discussion

Tables 1-3 list the second-order rate constants ($k_2/M^{-1}\ s^{-1}$),

Table 1. Second-Order Rate Constants ($k_2 \times 10^3$/M^{-1} s^{-1}) of the Reactions of **1** with XC_5H_4N in MeCN at 35.0 ºC

X^a \ Y^b	4-MeO	4-Me	3-Me	H	3-MeO
4-MeO	526 ± 3	844 ± 5	1200 ± 20	789 ± 5	540 ± 5
4-Me	169 ± 2	246 ± 3	266 ± 3	205 ± 4	158 ± 3
3-Me	66.4 ± 0.2	97.5 ± 0.5	123 ± 2	116 ± 3	92.6 ± 0.4
H	35.0 ± 0.3	35.3 ± 0.2	35.6 ± 0.4	35.4 ± 0.2	35.1 ± 0.2
3-Ph	14.6 ± 0.2	12.8 ± 0.3	9.26 ± 0.03	10.2 ± 0.3	14.6 ± 0.3
3-Cl	0.184 ± 0.003	0.121 ± 0.002	0.0983 ± 0.0003	0.116 ± 0.004	0.174 ± 0.004
4-Ac	3.47 ± 0.01	2.44 ± 0.02	1.48 ± 0.04	2.11 ± 0.03	2.86 ± 0.05
3-CN	0.0201 ± 0.0003	0.00851 ± 0.00006	0.00347 ± 0.00005	0.00723 ± 0.00006	0.0140 ± 0.0006
4-CN	0.0868 ± 0.0004	0.0531 ± 0.0005	0.0268 ± 0.0004	0.0303 ± 0.0004	0.0542 ± 0.0007

^{a}The sequence of the X-pyridines in the first column is followed the order of the corresponding σ_X value, neither second-order rate constant nor pK_a value. The order of the pK_a values of the X-pyridines is as follows: X = 4-MeO > 4-Me > 3-Me > H > 3-Ph > 3-Cl > 4-Ac > 4-CN > 3-CN. ^{b}The sequence of the Y-substrates in the first row is followed the order of the corresponding σ_Y value.

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 ºC

Y	4-MeO	4-Me	3-Me	H	3-MeO
$-\rho_X{}^a$	5.45 ± 0.12	6.15 ± 0.17	6.70 ± 0.15	6.19 ± 0.16	5.64 ± 0.17
$\beta_X{}^b$	0.87 ± 0.09	0.98 ± 0.08	1.07 ± 0.10	0.99 ± 0.10	0.91 ± 0.06

^{a}Two strong π-acceptor, X = (4-Ac, 4-CN), are excluded. ^{b}All X.

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

Y \ X	4-MeO	4-Me	3-Me	H	3-Ph	3-Cl	4-Ac	3-CN	4-CN
l-block^a	1.79 ± 0.02	0.99 ± 0.05	1.34 ± 0.03	0.04 ± 0.01	−0.99 ± 0.03	−1.36 ± 0.04	−1.85 ± 0.03	−3.82 ± 0.01	−2.55 ± 0.03
r-block^b	−1.78 ± 0.04	−1.16 ± 0.02	−0.67 ± 0.02	−0.03 ± 0.01	1.07 ± 0.03	1.32 ± 0.02	1.46 ± 0.04	3.10 ± 0.08	1.66 ± 0.05

^{a}Y = (4-MeO, 4-Me, 3-Me). ^{b}Y = (3-Me, H, 3-MeO).

Hammett (ρ_X) and Brönsted (β_X) coefficients with X, and Hammett coefficients (ρ_Y) with Y in MeCN at 35.0 ºC. For convenience, henceforth, the substituent X in the nucleophiles and Y in the substrates are divided into two blocks, respectively, as follows: (i) s-block with X = (4-MeO, 4-Me, 3-Me); (ii) w-block with X = (3-Ph, 3-Cl, 4-Ac, 3-CN, 4-CN); (iii) l-block with Y = (4-MeO, 4-Me, 3-Me); and (iv) r-block with Y = (3-Me, H, 3-MeO).[8] The rate is faster with a stronger nucleophile which is compatible with a typical

nucleophilic substitution reaction with partial positive charge development at the nucleophile N atom in the transition state (TS). The two strong π-acceptor substituents (X = 4-Ac, 4-CN), however, exhibit great positive deviations from the Hammett plots (Fig. 1) while little positive deviation from the Brönsted plots (Fig. 2). The rate with Y is not consistent with a typical nucleophilic substitution reaction. The Hammett plots (Fig. 3) for substituent Y variations show a break point at Y = 3-Me, and gradually change from biphasic concave
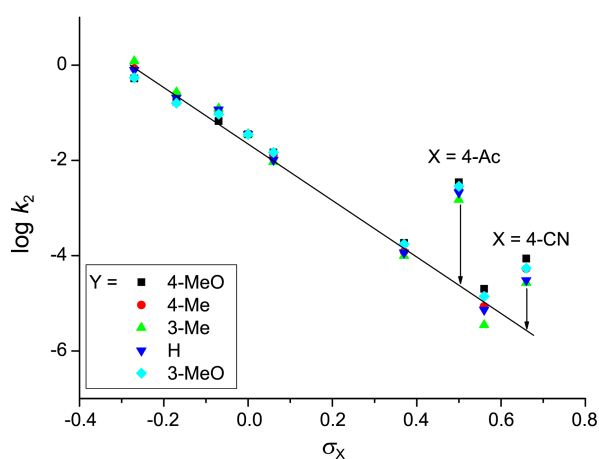
Figure 1. Hammett plots with X of the reactions of **1** with XC_5H_4N in MeCN at 35.0 ºC.
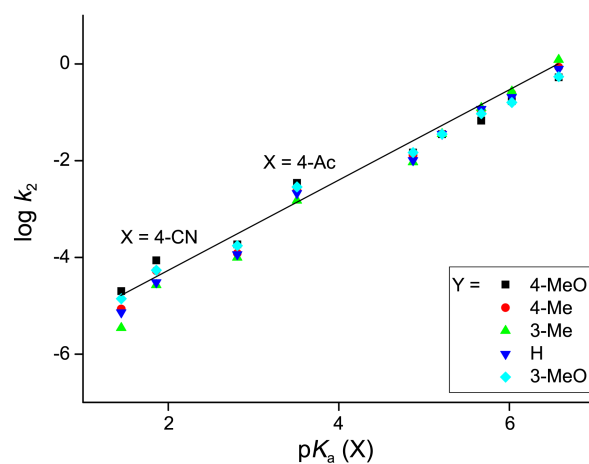
Figure 2. Brönsted plots with X of the reactions of **1** with XC_5H_4N in MeCN at 35.0 ºC.
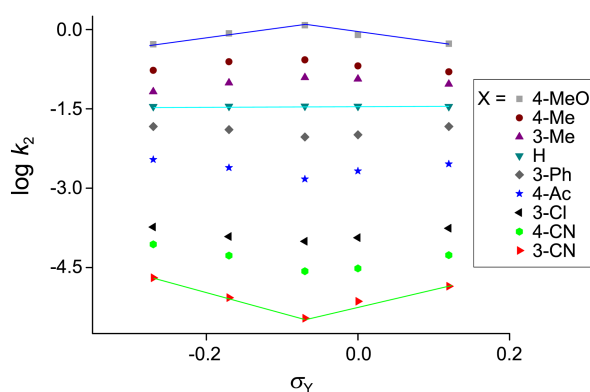
Figure 3. Hammett plots with Y of the reactions of **1** with XC$_5$H$_4$N in MeCN at 35.0 °C.

downwards with *s*-block, *via* linear (almost isokinetic) with X = H, to biphasic concave upwards with *w*-block. These phenomena with both biphasic concave downward and upward free energy correlations depending on the substituents are unprecedented one, showing the surprising substituent effects on the kinetics and mechanism. Note that (i) isokinetic phenomena are observed with both *l*- and *r*-block, $\rho_Y \approx 0$, $\rho_Y = 0.04$ of *l*-block and $\rho_Y = -0.03$ of *r*-block, at $\sigma_{X,iso} \approx 0$ or X = H; and (ii) thus, unusual negative values of ρ_Y (< 0) are obtained with both *w,l*- and *s,r*-block as seen in Figure 3. The negative value of ρ_Y indicates partial positive charge development at the oxygen atom of the phenoxy ligand in the TS, contrary to a typical nucleophilic substitution reaction.

The two strong π-acceptor *para*-substituents, X = (4-Ac, 4-CN), exhibit great positive deviations from the Hammett plots for substituent X variations regardless of the nature of Y as seen in Figure 1. This behavior indicates that the two π-acceptor substituents yield exalted reactivity. The exalted basicity (or enhanced nucleophilicity) of the strong π-acceptor groups would be owing to the weak π-donor effects.[9] The Hammett σ_p values of the π-acceptor substituents represent the inductive and π-electron-withdrawing effects. However, the experimental pK_a value only represents the inductive effect of X, because protonation/deprotonation takes place at the σ lone pair on N which is orthogonal to the ring π-system.[9a] As a result, the protonation/deprotonation does not disturb the ring π-system, but the positive charge center in the conjugate acid, naturally, attracts π-electrons inductively without through-conjugation between the σ-lone pair and the π-acceptor *para*-substituent. Thus, the pK_a values of π-acceptor substituents correctly reflect the substituent effects when the N atom of pyridine becomes positively charged in the TS because the determination of pK_a involves a positive charge on N atom (azonium type).

$$\overset{+}{-N=}$$

As observed in the present work, the two π-acceptor substituents exhibited positive deviations from the Hammett plots, while little deviations from the Brönsted plots, for the

pyridinolyses of (i) methyl chloroformate in MeCN[9a] and water;[10] (ii) Y-benzenesulfonyl chlorides in MeOH;[11] (iii) Y-benzyl bromides in DMSO;[12] and (iv) Y-phenacyl bromides in MeCN.[13] These indicate that the N atom of pyridine becomes positively charged in the TS, and that the degree of the bond formation is considerably extensive. On the contrary, the two π-acceptor substituents did not exhibit deviations from either the Hammett or Brönsted plots for the pyridinolysis of Y-aryl phenyl chlorophosphates.[14] No positive deviations for the π-acceptor in both plots were rationalized by the early TS with little positive charge development on the N atom of pyridine. The early TS, in which the extent of both the bond formation and leaving group departure is small, was supported by the small magnitudes of Brönsted coefficients and CIC: $\beta_X = 0.16\text{-}0.18$ and $\rho_{XY} = -0.15$.[14]

Figure 4 shows the determination of ρ_{XY} according to Eq. (2), $\rho_{XY} = \partial\rho_Y/\partial\sigma_X = \partial\rho_X/\partial\sigma_Y$, giving the great magnitudes of CICs: $\rho_{XY} = -6.26$ with *l*-block and $\rho_{XY} = +5.47$ with *r*-block.[15] It is the suggestion of the authors that the reaction proceeds through a stepwise process with a rate-limiting bond formation with *l*-block while through a stepwise process with a rate-limiting leaving group departure from the
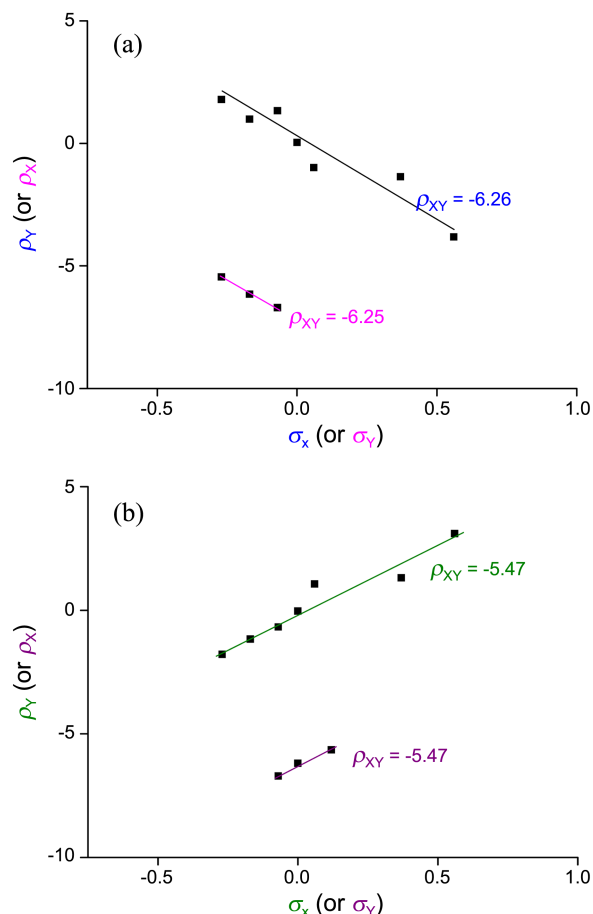
Figure 4. Plots of ρ_Y (or ρ_X) *vs* σ_X (or σ_Y) to calculate the ρ_{XY} values of the reactions of **1** with X-pyridines in MeCN at 35.0 °C. The obtained ρ_{XY} values by multiple regressions are: (a) $\rho_{XY} = -6.26 \pm 0.13$ (r = 0.995) with *l*-block; (b) $\rho_{XY} = +5.47 \pm 0.15$ (r = 0.994) with *r*-block. Note that the two strong π-acceptor X = (4-Ac, 4-CN) are not considered to calculate the ρ_{XY} values.

intermediate with *r*-block, based on the sign of ρ_{XY}, negative with *l*-block while positive with *r*-block.[16] Isokinetic phenomena are observed, $\rho_Y \approx 0$ at X = H for both *l*-and *r*-block, due to the great magnitudes of CICs. The values of $\sigma_{X,iso}$ and $k_{XY,iso}$ can be calculated from Eq. (4);[17] these values for *l*-block are as follows;

$$\sigma_{X,iso} = -\rho_X^H \rho_Y^H / \rho_{XY} = -(0.04)/(-6.26) = 0.0064$$
$$(\approx 0; X = H); k_{XY,iso} = 32.3 \times 10^{-3}/M^{-1} s^{-1}$$

and these values for *r*-block are as follows;

$$\sigma_{X,iso} = -\rho_X^H \rho_Y^H / \rho_{XY} = -(-0.03)/(5.47) = 0.0055$$
$$(\approx 0; X = H); k_{XY,iso} = 32.7 \times 10^{-3}/M^{-1} s^{-1}$$

The magnitudes of ρ_{XY} for both *l*- and *r*-block are exceptionally great. The obtained magnitudes of ρ_{XY} (= −6.26 and +5.47) are the unprecedented large values for the phosphoryl transfer reactions studied in this lab.[15] The unusual large magnitudes of ρ_{XY} imply that the nucleophile and substrate are in close enough proximity to interact 'very' strongly. In other words, the degree of the bond formation is really extensive in the TS for both *l*- and *r*-block. This suggestion is in agreement with the results of the behavior of the two strong π-acceptor *para*-substituents, X = 4-Ac and 4-CN in X-pyridines which is indicative of the 'very' extensive bond formation and positive charge development on N atom in the TS. The equatorial nucleophilic attack should lead to a tighter P–N bond in the trigonal bipyramidal pentacoordinate (TBP-5C) structure,[18] because the equatorial bonds are shorter than the apical bonds.[19] Hence a larger magnitude of ρ_{XY} is obtained compared to the apical nucleophilic attack. Thus the authors propose the frontside equatorial attack TS (Scheme 2) based on the large magnitudes of ρ_{XY} for both *l*- and *r*-block, and the behavior of the two strong π-acceptor *para*-substituents, X = 4-Ac and 4-CN.

As mentioned earlier: (i) the nitrogen atom of the pyridine becomes considerably positively charged in the TS based on the behavior of the two strong π-acceptor *para*-substituents; (ii) very extensive bond formation occurs in the TS based on the large magnitudes of ρ_{XY} for both *l*-and *r*-block; and (iii) partial positive charge develops on the oxygen atom of the
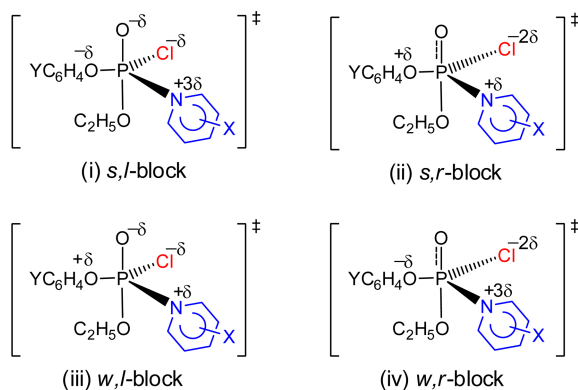
phenoxy ligand with both *w,l*- and *s,r*-block in the TS based on the negative ρ_Y value. Accordingly, the TS structures and charge distribution with four-blocks [(i) *s,l*-; (ii) *s,r*-; (iii) *w,l*-; and (iv) *w,r*-block] are described in Scheme 2. It should be noted that the description of the charge distribution in the TS is nothing but qualitative, never quantitative, to achieve the electronic balance. The negative ρ_Y values with *w,l*- and *s,r*-block are observed when one substituent (X or Y) is electron-donating and the other (X or Y) is electron-withdrawing group. On the contrary, the positive ρ_Y values with *s,l*- and *w,r*-block are observed when both substituent, X and Y, are either electron-donating or electron-withdrawing groups.

Experimental Section

Materials. Y-aryl ethyl chlorophosphates were prepared as previously described.[20] The physical constants of Y = (4-MeO, 4-Me, H, 3-MeO) were reported earlier[20] and those of ethyl 3-methylphenyl chlorophosphate were as follows (supporting information):

$(C_2H_5O)(3\text{-}CH_3\text{-}C_6H_4O)P(=O)Cl$: Colorless oily liquid. ^1H NMR (200 MHz, $CDCl_3$) δ 1.46 (t, 3H), 2.34 (s, 3H), 4.34-4.43 (m, 2H), 7.03-7.24 (m 4H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.67, 21.17, 66.58, 116.82-149.68; ν_{max} (neat), 3060-2979 (Arom. Str.), 2919-2865 (Alph. Str.), 1616, 1583, 1496, 1306 (P=O str.), 1154 (P-O-Ph Str.), 790 (P-Cl str.); EI-MS *m/z* 234 (M).

Kinetic Measurements. The second-order rate constants and selectivity parameters were obtained as reported earlier.[13,14] For the present work, the concentrations of [substrate] = 3×10^{-3} M and [X-pyridine] = (0.1-0.3) M were used.

Product Analysis. Ethyl 4-methoxyphenyl chlorophosphate was refluxed with equimolar amount of 4-acetylpyridine for more than 15 half-lives in MeCN at 35.0 °C. Solvent was evaporated under reduced pressure. Then 5 mL 50% ethylacetate/*n*-hexane mixed solution was added to it for washing. Several attempts were taken for this purpose. Solvent was then removed under oil-diffusion pump to finalize reddish-brown oily liquid product. The physical constants of product were as follows (supporting information):

$[(C_2H_5O)(4\text{-}CH_3O\text{-}C_6H_4O)P(=O)(4\text{-}CH_3CO\text{-}C_5H_4N)]^+Cl^-$: Reddish-brown oil. ^1H NMR (400 MHz, CD_3CN) δ 1.24 (t, 3H, CH_3), 2.61 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 4.05 (m, 2H, CH_2), 6.71-7.10 (m, 4H, Arom.), 7.96 (d, 2H, Pydn. *J* = 1.6 Hz), 8.75 (d, 2H, Pydn. *J* = 1.7 Hz); ^{13}C NMR (100 MHz, CD_3CN) δ 16.64, 27.47, 56.27, 64.22, 115.47-154.44, 122.22, 126.25, 130.42, 148.19, 197.77; ^{31}P NMR (162 MHz, $CDCl_3$) *d* 4.80 (1P, s, P=O). LC-MS *m/z* 388 (M$^+$).

Scheme 2. Proposed frontside equatorial attack TS structures with: (i) *s,l*-; (ii) *s,r*-; (iii) *w,l*-; and (iv) *w,r*-block.

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2. The ρ_i^H value with j = H is constant, the ρ_j^H value with i = H is constant and the CIC (ρ_{ij}) value with the studied reaction system is constant.

3. In the case of relatively small magnitude of CIC, the inversion of sign of ρ_i do not occur because the magnitude of $\rho_{ij}\sigma_i$ is too small to overwhelm the magnitude of ρ_j^H.

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8. The *s*- and *w*-block with X indicate the *s*trongly and *w*eakly basic pyridines, respectively. The substituent of X = H is not included either in *s*- or in *w*-block. The *l*- and *r*-block with Y indicate *l*eft-side and *r*ight-side of Figure 3, respectively.

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15. The twenty one k_2 values (seven nucleophiles × three substrates) are employed to calculate the ρ_{XY} values with both *l*- and *r*-block. The ρ_{XY} value of the normal S_N2 reaction is *ca.* −0.7.[1] The second (ρ_{XY} = 5.14) and third largest CIC (ρ_{XY} = 3.16) values were obtained for the pyridinolyses of Y-aryl phenyl chlorothiophosphates (Hoque, M. E. U.; Dey, S.; Kim, C. K.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 1138) and Y-aryl phenyl isothiocyanophosphates (Adhikary, K. K.; Lee, H. W.; Lee, I. *Bull. Korean Chem. Soc.* **2003**, *24*, 1135), respectively. In the case of the anilinolysis, the largest magnitude of CIC (ρ_{XY} = 1.41) was obtained for Y-aryl phenyl isothiocyanophosphates (Barai, H. R.; Lee, H. W. *Beilstein J. Org. Chem.* **2013**, *9*, 615).

16. In general, the sign of the CIC (ρ_{XY}) is negative in a stepwise process with a rate-limiting bond formation (or in a normal S_N2 reaction) and positive in a stepwise process with a rate-limiting leaving group expulsion from the intermediate.

17. Compare the second-order rate constants between: the empirical values of [35.0(4-MeO), 35.3(4-Me) and 35.6(3-Me) × 10^{-3} with X = H] and isokinetic 32.3 × 10^{-3} from Eq. (4) for *l*-block; and the empirical values of [35.6(3-Me), 35.4(H) and 35.1(3-MeO) × 10^{-3} with X = H] and isokinetic 32.7 × 10^{-3} M^{-1} s^{-1} from Eq. (4) for *r*-block.

18. The actual TS structure would be between *cis*-basal-type and TBP-5C-type, *i.e.*, more or less distorted TBP-5C (Thatcher, G. R. J.: Kluger, R. *Adv. Phys. Org. Chem.* **1989**, *25*, 99).

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