http://dx.doi.org/10.5012/bkcs.2013.34.11.3372

Kinetics and Mechanism of Pyridinolyses of Ethyl Methyl and Ethyl Propyl Chlorothiophosphates in Acetonitrile

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Received August 8, 2013, Accepted August 28, 2013

The kinetic studies on the reactions of ethyl methyl (**2**) and ethyl propyl (**4**) chlorothiophosphates with X-pyridines have been carried out in acetonitrile at 35.0 °C. The free energy correlations with X show biphasic concave upwards with a break point at X = H (**2**) and 3-Ph (**4**), respectively. A stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate is proposed based on the magnitudes of selectivity parameters for both substrates. The considerably large values of β_X = 1.50(**2**) and 1.44(**4**) with strongly basic pyridines and relatively small values of β_X = 0.43(**2**) and 0.36(**4**) with weakly basic pyridines are interpreted as a change of the attacking direction of the X-pyridines from a frontside to a backside attack toward the chloride leaving group.

Key Words : Thiophosphoryl transfer reaction, Pyridinolysis, Ethyl methyl and ethyl propyl chlorothiophosphates, Biphasic concave upward free energy relationship, Stepwise mechanism

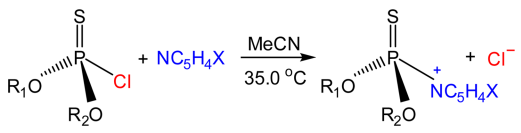
Introduction

To extend the kinetic studies on the pyridinolyses of the chlorothiophosphates [$(R_1O)(R_2O)P(=S)Cl$-type],[1] the nucleophilic substitution reactions of ethyl methyl (**2**) and ethyl propyl (**4**) chlorothiophosphates with X-pyridines are kinetically investigated in acetonitrile (MeCN) at 35.0 ± 0.1 °C (Scheme 1). The kinetic results of the present work are compared with those of dimethyl (**1**: $R_1 = R_2 = Me$),[1a] diethyl (**3**: $R_1 = R_2 = Et$),[1a] dipropyl (**5**: $R_1 = R_2 = Pr$),[1d] dibutyl (**6**: $R_1 = R_2 = Bu$),[1e] diisopropyl (**7**: $R_1 = R_2 = i$-Pr),[1f] Y-aryl ethyl (**8**: $R_1 = Et$, $R_2 = YC_6H_4$)[1c] and Y-aryl phenyl (**9**: $R_1 = Ph$, $R_2 = YC_6H_4$)[1b] chlorothiophosphates. The purpose of this work is to gain further information on the reactivity, steric effects and mechanism depending upon the variation of the two ligands (R_1O and R_2O) for the thiophosphoryl transfer reactions. **1-9** are numbered according to the sequence of the summation of the Taft steric constants of R_1 and R_2.[2]

Results and Discussion

Table 1 summarizes the second-order rate constants [$k_2(M^{-1}\ s^{-1})$] and selectivity parameters, ρ_X and β_X. The substituent effects of the nucleophiles upon the pyridinolysis rates correlate with those for a typical nucleophilic substitution reaction where the stronger nucleophile leads to a faster rate with a positive charge development at the nucleophilic N atom in the transition state (TS). However, both the Hammett (log k_2 *vs* σ_X; Figs. S1 and S2 in supporting information) and Brönsted [log k_2 *vs* pK_a(X); Figs. 1 and 2] plots are biphasic concave upwards with a break point at X = H (**2**) and 3-Ph (**4**), respectively. The rate of **2** is slightly faster than that of **4**. The magnitudes of ρ_X [= –7.27(**2**), –6.96(**4**)] and β_X [= 1.50(**2**), 1.44(**4**)] with strongly basic pyridines are 3-4 times larger than those [ρ_X = –2.54(**2**), –2.16(**4**); β_X = 0.43(**2**), 0.36(**4**)] with weakly basic pyridines.

Table 2 summarizes the second-order rate constants (k_2) with unsubstituted pyridine at 35.0 °C, natural bond order



R_1 = Me, R_2 = Et (**2**); R_1 = Et, R_2 = Pr (**4**)
X = 4-MeO, 4-Me, 3-Me, H, 3-Ph, 3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN

Scheme 1. Pyridinolyses of ethyl methyl (**2**) and ethyl propyl (**4**) chlorothiophosphates in MeCN at 35.0 °C.

Table 1. Second-Order Rate Constants ($k_2 \times 10^4/M^{-1}\ s^{-1}$) and Selectivity Parameters (ρ_X and β_X) of the Reactions of Ethyl Methyl (**2**) and Ethyl Propyl (**4**) Chlorothiophosphates with X-Pyridines in MeCN at 35.0 °C

X	$k_2 \times 10^4/M^{-1}\ s^{-1}$ (**2**)	$k_2 \times 10^4/M^{-1}\ s^{-1}$ (**4**)
4-MeO	600 ± 2	459 ± 1
4-Me	113 ± 1	111 ± 1
3-Me	23.6 ± 0.1	22.7 ± 0.1
H	6.20 ± 0.01	6.09 ± 0.01
3-Ph	4.02 ± 0.01	2.48 ± 0.02
3-Cl	0.656 ± 0.002	0.612 ± 0.001
3-Ac	0.649 ± 0.003	0.580 ± 0.001
4-Ac	0.304 ± 0.001	0.296 ± 0.003
3-CN	0.228 ± 0.002	0.218 ± 0.001
4-CN	0.128 ± 0.001	0.127 ± 0.001
$-\rho_X$	7.27 ± 0.04[a,c]/2.54 ± 0.02[b,d]	6.96 ± 0.05[g,i]/2.16 ± 0.03[h,j]
β_X	1.50 ± 0.07[a,e]/0.43 ± 0.13[b,f]	1.44 ± 0.05[g,k]/0.36 ± 0.14[h,l]

[a]X = (4-MeO, 4-Me, 3-Me, H). [b]X = (H, 3-Ph, 3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN). [c]r = 0.999. [d]r = 0.999. [e]r = 0.998. [f]r = 0.982. [g]X = (4-MeO, 4-Me, 3-Me, H, 3-Ph). [h]X = (3-Ph, 3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN). [i]r = 0.999. [j]r = 0.998. [k]r = 0.999. [l]r = 0.963.

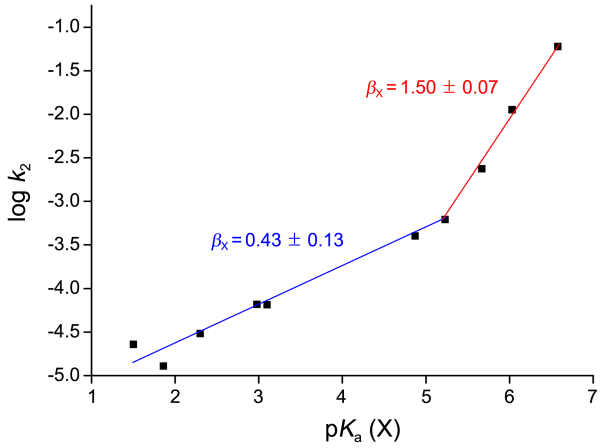


Figure 1. Brönsted plot of the reactions of ethyl methyl chlorothiophosphate (**2**) with X-pyridines in MeCN at 35.0 ºC.

(NBO) charges at the reaction center P atom in the substrate in the gas phase [B3LYP/6-311 + G(d,p) level of theory], summations of the Taft steric constants [$\Sigma E_S = E_S(R_1) + E_S(R_2)$] of the two ligands,[2] Brönsted coefficients (β_X) and cross-interaction constants (CICs; ρ_{XY})[3] for the pyridinolyses of nine chlorothiophosphates (**1-9**) in MeCN. The dependence of the two ligands on the rate is relatively weak, *e.g.*, k_2(1.54 × 10^{-3} with **1**; fastest)/k_2(0.137 × 10^{-3} with **8**; slowest) ≈ 11, whereas the rate is strongly dependent upon the substituent X in the pyridines, *e.g.*, k_2(600 × 10^{-3} with X = 4-MeO)/k_2(0.128 × 10^{-3} with X = 4-CN) ≈ 4,700 for **2** as seen in Table 1.

There is no linear correlation between the rates and NBO charges at the reaction center P atom in the substrates. These suggest that that the inductive effects of the two ligands are not a major factor determining the pyridinolysis rates of the chlorothiophosphates.[4] The Taft eq., 'log $k_2 = \delta\Sigma E_S + C$', is introduced to understand the steric effect of the two ligands on the rate. Herein, '$\Sigma E_S = E_S(R_1) + E_S(R_2)$' is employed instead of '$\Sigma E_S = E_S(R_1O) + E_S(R_2O)$' because the data of $E_S(R_iO)$ is not available [E_S(R) = 0(Me); –0.07(Et); –0.36(Pr); –0.39(Bu); –0.47(*i*-Pr); –2.48(Ph)].[2] Figure 3 shows the Taft plot of log k_2 with unsubstituted pyridine (C_5H_5N) against the summation of the Taft steric constants of the two ligands for the pyridinolyses of nine chlorothiophosphates (**1-9**) in MeCN at 35.0 ºC. The plot gives the sensitivity coefficient of δ = 0.14 ± 0.06 (r = 0.668; poor linearity) with nine substrates of **1-9**. This indicates that the steric effects of the two ligands

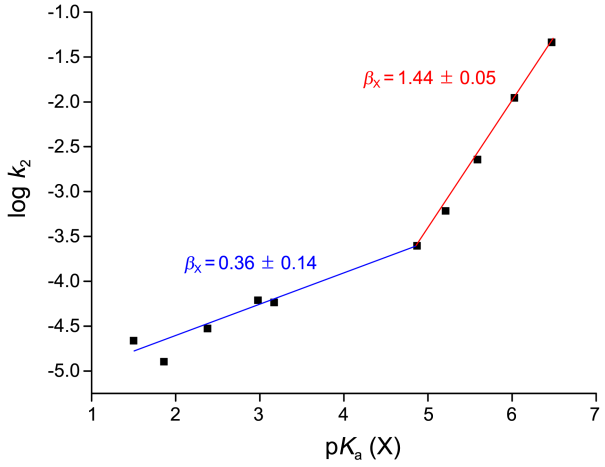


Figure 2. Brönsted plot of the reactions of ethyl propyl chlorothiophosphate (**4**) with X-pyridines in MeCN at 35.0 ºC.

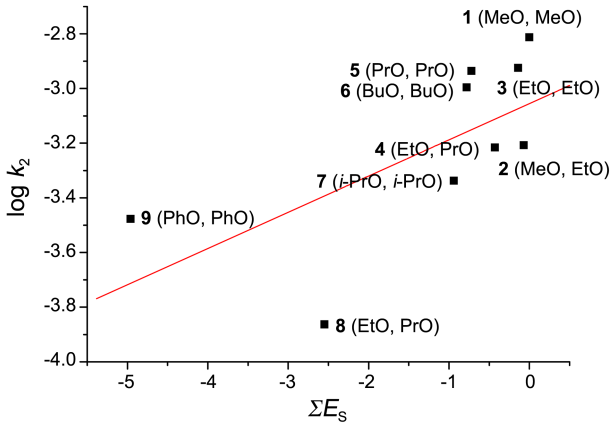


Figure 3. Taft plot of log k_2 *vs* ΣE_S for the reactions of **1-9** with C_5H_5N in MeCN at 35.0 ºC. The number of the substrate and two ligands are displayed next to the corresponding point.

Table 2. Summary of the Second-Order Rate Constants ($k_2 \times 10^3$/M^{-1} s^{-1}), NBO Charges at the Reaction Center P Atom, Summations of the Taft Steric Constants (ΣE_S), Brönsted Coefficients (β_X) and CICs (ρ_{XY}) for the Pyridinolyses of **1-9** in MeCN

Substrate	$k_2 \times 10^3$[a]	Charge at P	$-\Sigma E_S$[c]	β_X	ρ_{XY}
1: $(MeO)_2P(=S)Cl$	1.54	1.687	0	1.09/0.20[d]	–
2: (MeO)(EtO)P(=S)Cl	0.620	1.693	0.07	1.50/0.43[d]	–
3: $(EtO)_2P(=S)Cl$	1.19	1.701	0.14	1.02/0.29[d]	–
4: (EtO)(PrO)P(=S)Cl	0.609	1.700	0.43	1.44/0.36[d]	–
5: $(PrO)_2P(=S)Cl$	1.16	1.723	0.72	1.08/0.31[d]	–
6: $(BuO)_2P(=S)Cl$	1.01	1.703	0.78	1.26/0.31[d]	–
7: $(i\text{-PrO})_2P(=S)Cl$	0.460	1.723	0.94	0.99/0.15[d]	–
8: (EtO)(YC_6H_4O)P(=S)Cl	0.137[b]	1.687[b]	2.55[b]	2.31–2.33/0.45–0.47[d]	0/0/0/0[e]
9: (PhO)(YC_6H_4O)P(=S)Cl	0.333[b]	1.661[b]	4.96[b]	1.36–1.50/0.23–0.48[d]	2.42/5.14/–1.02/–0.04[e]

[a]Value with C_5H_5N at 35.0 ºC. [b]Value with Y = H. [c]$\Sigma E_S = E_S(R_1) + E_S(R_2)$. [d]Strongly/weakly basic pyridines. [e]*a*-block(strong nucleophiles and weak electrophiles)/*b*-block(weak nucleophiles and weak electrophiles)/*c*-block(strong nucleophiles and strong electrophiles)/*d*-block(weak nucleophiles and strong electrophiles).

are not major factor but minor one determining the pyridinolysis rates of the chlorothiophosphates.

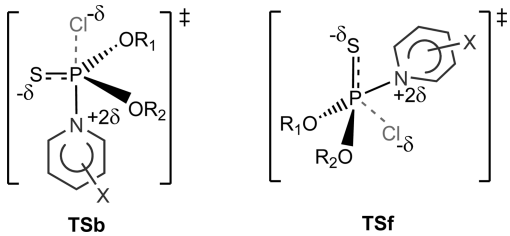
In contrast to the pyridinolyses of the chlorothiophosphates, the anilinolysis rates of the chlorothiophosphates[5] and aminolysis (anilinolysis[5b,c,6] and pyridinolysis)[1a,7] rates of the chlorophosphates exhibit consistent dependence upon the steric effects of the two ligands, but divided into two groups; *a* group containing two alkoxy ligands and *b* group containing phenoxy ligand(s). This suggests that the steric effects of the two ligands on the rate in the *a* group are essentially 'different' from those in the *b* group, and that the steric effects of the two ligands play an important role in determining the anilinolysis rates of the P=S systems and aminolysis (anilinolysis and pyridinolysis) rates of the P=O systems.

The free energy relationships with X of **1**-**9** are all biphasic concave upwards. The β_X values of **1**, **3** and **5**-**7** are similar: β_X = 1.0-1.3 with strongly basic pyridines and β_X = 0.2-0.3 with weakly basic pyridines, strongly suggesting the same pyridinolysis mechanisms.[1a,d-f] A concerted mechanism was proposed for the pyridinolyses of **1**, **3** and **5**-**7**.[1a,d-f] The β_X (= 2.31-2.33) values of **8** with strongly basic pyridines are the greatest among all the pyridinolyses of the P=O and P=S systems involving chloride leaving group, studied in this lab.[1e] The β_X (= 1.4-1.5) values of **9** with strongly basic pyridines are relatively large.[1b] The β_X values of **8** and **9** with weakly basic pyridines are somewhat greater than those of **1**, **3** and **5**-**7**. In the present work of **2** and **4**, the β_X values of 1.50(**2**) and 1.44(**4**) with strongly basic pyridines and 0.43(**2**) and 0.36(**4**) with weakly basic pyridines are close to those of **9**.

The Hammett plots of **8** for the substituent Y variations in the substrates are biphasic concave upwards with a break (minimum) point at Y=H while those of **9** are concave downwards with a break point at Y=H. Thus, the four values of CICs, ρ_{XY}, were obtained for both **8** and **9**. In the case of **8**, the CICs (ρ_{XY}) are all null in spite of the biphasic free energy correlations for both substituent X and Y variations, because the ρ_X values with both strongly and weakly basic pyridines are almost constant. This reaction is the only one, having all ρ_{XY} = 0 with four blocks until now: *a*-block (strong nucleophiles and weak electrophiles), *b*-block (weak nucleophiles and weak electrophiles), *c*-block (strong nucleophiles and strong electrophiles) and *d*-block (weak nucleophiles and strong electrophiles). Herein, the null of ρ_{XY} value implies that the distance between X and Y does not vary from the intermediate to the second TS, in which the reaction proceeds through a stepwise mechanism with a rate-limiting leaving group departure from the intermediate.[8] In the case of **9**, a stepwise process was proposed involving a rate-limiting step change from bond breaking with *a*- and *b*-blocks based on the large positive ρ_{XY} value to bond formation with *c*- and *d*-blocks based on the negative ρ_{XY} value.[9]

The biphasic concave upward free energy relationships with X were interpreted as a change of the nucleophilic attacking direction from a frontside attack TSf with strongly basic pyridines based on the large magnitudes of β_X values to a backside attack involving in-line-type TSb with weakly basic pyridines based on the relatively small magnitudes of β_X values. It is worthy of note that a frontside attack TSf yields greater magnitudes of ρ_X and β_X values compared to a backside attack.[10]

In the present work of **2** and **4**, the β_X values [1.50(**2**) and 1.44(**4**) with strongly basic pyridines and 0.43(**2**) and 0.36(**4**) with weakly basic pyridines] are quite similar to those of **9** with Y = electron-donating (*a*, *b*-blocks),[1b] in which the proposed mechanism is a stepwise process with a rate-limiting leaving group expulsion from the intermediate. Thus, the authors accordingly propose the pyridinolysis mechanism of **2** as a stepwise process with a rate-limiting leaving group departure from the intermediate, and a change of the nucleophilic attacking direction from a frontside attack TSf with strongly basic pyridines based on the large β_X value to a backside attack involving in-line-type TSb



TSb **TSf**

Scheme 2. Backside attack TSb and frontside attack TSf.

Table 3. Proposed Mechanism and Attacking Direction for the Pyridinolyses of **1**-**9** in MeCN

Substrate	Proposed mechanism	Attacking direction
1: $(MeO)_2P(=S)Cl$	concerted	front/backside[a]
2: (MeO)(EtO)P(=S)Cl	stepwise with bond breaking	front/backside[a]
3: $(EtO)_2P(=S)Cl$	concerted	front/backside[a]
4: (EtO)(PrO)P(=S)Cl	stepwise with bond breaking	front/backside[a]
5: $(PrO)_2P(=S)Cl$	concerted	front/backside[a]
6: $(BuO)_2P(=S)Cl$	concerted	front/backside[a]
7: $(i\text{-}PrO)_2P(=S)Cl$	concerted	front/backside[a]
8: $(EtO)(YC_6H_4O)P(=S)Cl$	all blocks; stepwise with bond breaking	front/backside[a]
9: $(PhO)(YC_6H_4O)P(=S)Cl$	*a*,*b*-blocks; stepwise with bond breaking *c*,*d*-blocks; stepwise with bond formation	front/backside[a]

[a]Strongly/weakly basic pyridines.

Table 4. Activation Parameters for the Reactions of **1-9** with C_5H_5N in MeCN

Substrate	$\Delta H^{\ddagger}$/kcal mol^{-1}	$-\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}	Ref.
1: $(MeO)_2P(=S)Cl$	7.1	48	1a
2: (MeO)(EtO)P(=S)Cl	7.8[a]	48[a]	this work
3: $(EtO)_2P(=S)Cl$	6.0	53	1a
4: (EtO)(PrO)P(=S)Cl	5.9[a]	54[a]	this work
5: $(PrO)_2P(=S)Cl$	4.7	57	1d
6: $(BuO)_2P(=S)Cl$	9.3	42	1e
7: $(i\text{-PrO})_2P(=S)Cl$	15.2	25	1f
8: $(EtO)(YC_6H_4O)P(=S)Cl$	5.9[b]	57[b]	1c
9: $(PhO)(YC_6H_4O)P(=S)Cl$	6.4[b]	53[b]	1b

[a]See Tables S1 and S2 in supporting information. [b]Value with Y=H.

(Scheme 2) with weakly basic pyridines based on the relatively small β_X value. Table 3 summarizes the proposed mechanism and the attacking direction of the pyridine toward the chloride leaving group.

Activation parameters, enthalpies and entropies of activation, for the pyridinolyses (with C_5H_5N) of **1-9** are summarized in Table 4. The enthalpies of activation are relatively small (5-9 kcal mol^{-1}) and entropies of activation are relatively large negative values (–42 to –57 cal mol^{-1} K^{-1}), except **4** where the enthalpy of activation is relatively large ($\Delta H^{\ddagger}$ = 15.2 kcal mol^{-1}) and entropy of activation is relatively small negative value ($\Delta S^{\ddagger}$ = –25 cal mol^{-1} K^{-1}).[11] The small value of activation enthalpy and large negative value of activation entropy are typical for the aminolyses (pyridinolyses or anilinolyses) of P=S (and P=O) systems regardless of the mechanism, concerted, stepwise with a rate-limiting bond making or stepwise with a rate-limiting bond breaking. In other words, it is sometimes dangerous to clarify the mechanism by means of the activation parameters.

Experimental Section

Materials. HPLC grade MeCN (water content 0.005%) and GR grade X-pyridines were used without further purification. Ethyl methyl (**2**) and ethyl propyl (**4**) chlorothiophosphates were prepared *via* one step synthetic route. Ethyl dichlorothiophosphate was reacted with methanol and propanol for **2** and **4**, respectively, at –10.0 °C with constant stirring. The product mixture was dried under reduced pressure and isolated by column chromatography [ethyl acetate (10% and 1% for **2** and **4**, respectively) + *n*-hexane].[12] The analytical and spectroscopic data of the substrates gave the following results (see supporting information):

(MeO)(EtO)P(=S)Cl: Colorless liquid; ^{1}H-NMR (400 MHz, $CDCl_3$ & TMS) δ 1.39-1.43 (aliphatic, 3H, t), 3.85-3.93 (aliphatic, 3H, br), 4.27-4.32 (aliphatic, 2H, q); ^{13}C-NMR (100 MHz, $CDCl_3$ & TMS) δ 15.61, 55.39, 66.34; ^{31}P-NMR (162 MHz, $CDCl_3$ & TMS) δ 81.72 (1P, s, P=S); GC-MS (EI, *m/z*) 174 (M^+).

(EtO)(PrO)P(=S)Cl: Colorless liquid; ^{1}H-NMR (400 MHz, $CDCl_3$ & TMS) δ 0.98-1.02 (aliphatic, 3H, t), 1.40-1.44 (aliphatic, 3H, t), 1.75-1.81 (aliphatic, 2H, m), 4.16-4.27 (aliphatic, 2H, q), 4.29-4.32 (aliphatic, 2H, t); ^{13}C-NMR (100 MHz, $CDCl_3$ & TMS) δ 9.97, 15.62, 23.16, 66.09, 71.47; ^{31}P-NMR (162 MHz, $CDCl_3$ & TMS) δ 74.42 (1P, s, P=S); GC-MS (EI, *m/z*) 202 (M^+).

Kinetic Procedure. Rates were measured conductometrically at 35.0 °C as reported earlier.[1] Initial concentrations of substrates and nucleophiles were as follows; [substrate] = 5 × 10^{-3} M and [XC_5H_4N] = (0.10-0.30) M.

Product Analysis. Ethyl methyl (**2**) and ethyl propyl (**4**) chlorothiophosphates were reacted with excess pyridine, for more than 15 half-lives at 35.0 °C in MeCN, respectively. 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 (see supporting information):

[(MeO)(EtO)P(=S)NC$_5$H$_5$]$^+$Cl$^-$: Light brown gummy solid; ^{1}H-NMR (400 MHz, MeCN-d_3) δ 1.10-1.13 (aliphatic, 3H, t), 3.39-3.44 (aliphatic, 2H, q), 4.38 (aliphatic, 3H, s), 7.80-7.84 (aromatic, 2H, t), 8.31 (aromatic, 1H, t), 8.72-8.74 (aromatic, 2H, d); ^{13}C-NMR (100 MHz, MeCN-d_3) δ 17.0, 64.1, 66.9, 128.1, 129.6, 130.9, 144.8, 145.4, 146.9; ^{31}P-NMR (162 MHz, MeCN-d_3) δ 43.9 (1P, s, P=S); LC-MS for $C_8H_{13}ClNO_2PS$ (EI, *m/z*), 254 (M^+).

[(EtO)(PrO)P(=S)NC$_5$H$_5$]$^+$Cl$^-$: Colorless liquid; ^{1}H-NMR (400 MHz, $CDCl_3$ & TMS) δ 0.99-1.04 (aliphatic, 3H, t), 1.74-1.77 (aliphatic, 3H, t), 2.10-2.14 (aliphatic, 2H, m), 4.99-5.01 (aliphatic, 2H, t), 5.10-5.12 (aliphatic, 2H, q), 8.08-8.11 (aromatic, 2H, t), 8.21 (aromatic, 1H, br), 8.53-8.59 (aromatic, 2H, t); ^{13}C-NMR (100 MHz, $CDCl_3$ & TMS) δ 10.4, 17.2, 25.1, 57.4, 63.2, 127.3, 128.4, 141.0, 145.0, 145.8; ^{31}P-NMR (162 MHz, $CDCl_3$ & TMS) δ 54.0 (1P, s, P=O); LC-MS for $C_{10}H_{17}ClNO_2PS$ (EI, *m/z*), 281(M^+).

Acknowledgments. This work was supported by Inha University Research Grant.

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4. In general, the aminolysis rates of phosphoryl and thiophosphoryl transfer reactions involving tetracoordinate phosphorus atom with the leaving group of chloride are not dependent upon the inductive effects of the two ligands. However, the rate of P=O system is

sometimes much faster than that of its P=S counterpart because of the so-called "thio effect".

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8. The value of ρ_{XY} could be null when the X and Y are too far apart to interact each other. The observed $\rho_{XY} = 0$ with four blocks is the very special.
9. In general, the negative sign of ρ_{XY} implies that the reaction proceeds through a stepwise mechanism with a rate-limiting bond formation (or a concerted mechanism), while the positive sign of ρ_{XY} implies a stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate.
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11. The activation parameters for the aminolyses, pyridinolyses with C_5H_5N and anilinolyses with C_5H_5N, of **7** and its P=O counterpart **7'** in MeCN are summarized in Table R1. The relatively large value of activation enthalpy and small negative value of activation entropy for the pyridinolysis of **7** are unusual. The anilinolysis of **7** and aminolyses (pyridinolysis and anilinolysis) of **7'** gave relatively small value of activation enthalpies and relatively large negative value of activation entropies.

Table R1. Activation Parameters for the Aminolyses of **7'** and its P=O Counterpart **7** in MeCN

Substrate	Aminolysis	$\Delta H^{\ddagger}$/kcal mol^{-1}	$-\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}	Ref.
7: (*i*-PrO)$_2$P(=S)Cl	pyridinolysis	15.2	25	1d
7': (*i*-PrO)$_2$P(=O)Cl	pyridinolysis	5.5	50	7b
7: (*i*-PrO)$_2$P(=S)Cl	anilinolysis	9.4	47	5d
7': (*i*-PrO)$_2$P(=O)Cl	anilinolysis	7.2	51	6b

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