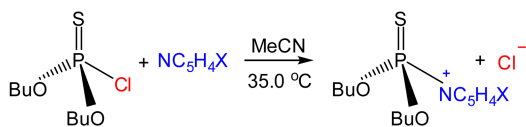


Pyridinolysis of Dibutyl Chlorothiophosphate in Acetonitrile[†]

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Received January 2, 2012, Accepted January 31, 2012**Key Words :** Thiophosphoryl transfer reaction, Pyridinolysis, Dibutyl chlorothiophosphate, Biphasic concave upward free energy relationship

In previous work, the kinetic studies of the pyridinolyses of chlorothiophosphates (dimethyl [**1**: (MeO)₂P(=S)Cl],¹ diethyl [**2**: (EtO)₂P(=S)Cl],¹ dipropyl [**3**: (PrO)₂P(=S)Cl],² Y-aryl ethyl [**5**: (EtO)(YC₆H₄O)P(=S)Cl],³ and Y-aryl phenyl [**6**: (PhO)(YC₆H₄O)P(=S)Cl]⁴ chlorothiophosphates) have been carried out by this lab. Herein, the nucleophilic substitution reactions of dibutyl chlorothiophosphate (**4**) with X-pyridines are investigated kinetically in acetonitrile (MeCN) at 35.0 ± 0.1 °C (Scheme 1). The aim of this work is to gain further systematic information into the reactivity and mechanism depending on the variation of the two ligands, R₁O and R₂O, where R₁ and R₂ are alkyl and/or phenyl (aryl). The numbering of the substrates of **1-6** follows the sequence of the size of the two ligands, R₁O and R₂O.



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

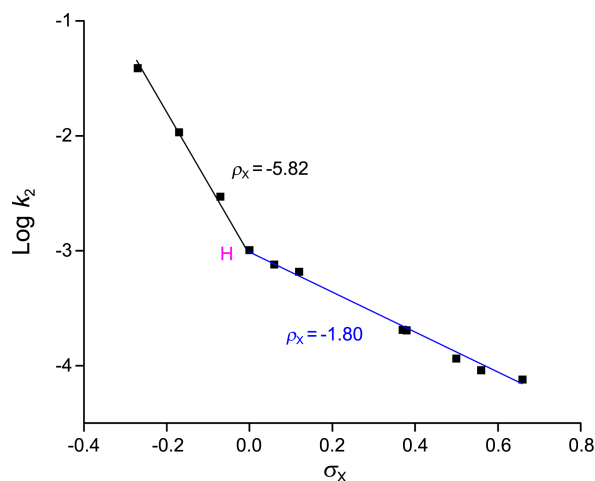
Scheme 1. The reactions of dibutyl chlorothiophosphate (**4**) with X-pyridines in MeCN at 35.0 °C.

Results and Discussion

The reactions were carried out under pseudo-first-order conditions with a large excess of pyridine. The observed pseudo-first-order rate constants (k_{obsd}) for all reactions obeyed Eq. (1) with negligible k_0 (0) in MeCN. The second-order rate constants were determined with at least five pyridine concentrations. The linear plots of Eq. (1) suggest a lack of any base-catalysis or side reaction, and the overall reaction is described by Scheme 1.

$$k_{\text{obsd}} = k_0 + k_2 [\text{XC}_5\text{H}_4\text{N}] \quad (1)$$

The second-order rate constants [k_2 (M⁻¹ s⁻¹)] are summarized in Table 1. The Brønsted β_X value was calculated by correlating $\log k_2(\text{MeCN})$ with $\text{p}K_{\text{a}}(\text{H}_2\text{O})$.⁵ This procedure of using $\text{p}K_{\text{a}}(\text{H}_2\text{O})$ instead of $\text{p}K_{\text{a}}(\text{MeCN})$ values of X-pyridines has been shown to be justified theoretically and experimentally since there is a practically constant difference between the two sets of $\text{p}K_{\text{a}}$'s in H₂O and in MeCN for various X-pyridines so that the slopes in the two solvents differ insignificantly.⁶ 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. However, both the Hammett ($\log k_2$ vs σ_X ; Fig. 1) and Brønsted [$\log k_2$ vs $\text{p}K_{\text{a}}(\text{X})$; Fig. 2] plots are biphasic concave upwards with a break point at X = H. The magnitudes of ρ_X ($= -5.82 \pm 0.03$; $r = 0.999$) and β_X

**Figure 1.** The Hammett plot ($\log k_2$ vs σ_X) of the reactions of dibutyl chlorothiophosphate (**4**) with X-pyridines in MeCN at 35.0 °C.**Table 1.** Second-Order Rate Constants ($k_2 \times 10^4/\text{M}^{-1} \text{s}^{-1}$) of the Reactions of Dibutyl Chlorothiophosphate (**4**) with $\text{XC}_5\text{H}_4\text{N}$ in MeCN at 35.0 °C

X	4-MeO	4-Me	3-Me	H	3-Ph	3-MeO	3-Cl	3-Ac	4-Ac	3-CN	4-CN
$k_2 \times 10^4$	388 ± 1	107 ± 1	29.5 ± 0.1	10.1 ± 0.1	7.55 ± 0.01	6.55 ± 0.01	2.04 ± 0.01	2.02 ± 0.01	1.15 ± 0.01	0.908 ± 0.002	0.754 ± 0.001

[†]This paper is to commemorate Professor Kook Joe Shin's honourable retirement.

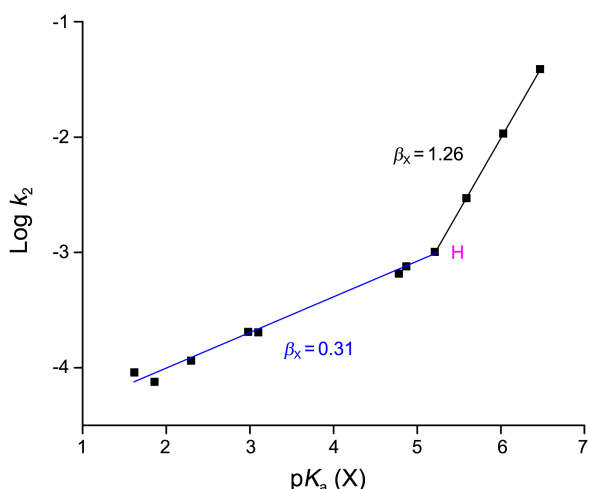


Figure 2. The Brønsted plot [$\log k_2$ vs $pK_a(X)$] of the reactions of dibutyl chlorothiophosphate (**4**) with X-pyridines in MeCN at 35.0 °C.

(= 1.26 ± 0.01 ; $r = 0.999$) values with the strongly basic pyridines ($X = 4\text{-MeO}$, 4-Me , 3-Me , H) are much greater than those [$\rho_X = -1.80 \pm 0.04$ ($r = 0.997$) and $\beta_X = 0.31 \pm 0.05$ ($r = 0.995$)] with the weakly basic pyridines ($X = \text{H}$, 3-Ph , 3-MeO , 3-Cl , 3-Ac , 4-Ac , 3-CN , 4-CN).

The second-order rate constants (k_2) with unsubstituted pyridine ($\text{C}_5\text{H}_5\text{N}$) at 35.0 °C, natural bond order (NBO) charges at the reaction center P atom in the substrate in the gas phase [B3LYP/6-311+G(d,p) level of theory],⁷ summations of the Taft's steric constants [$\Sigma E_S = E_S(\text{R}_1) + E_S(\text{R}_2)$] of the two ligands,⁸ Brønsted coefficients (β_X), cross-interaction constants (CICs; ρ_{XY}),⁹ and variation trends of the free energy relationships with X for the pyridinolyses of six (R_1O)(R_2O)P(=S)Cl-type chlorothiophosphates in MeCN are summarized in Table 2.

There is no linear correlation between the pyridinolysis rates and positive charges at the reaction center P atom in the substrate. It means that the positive charge of the reaction center P atom (i.e., electrophilicity) does not play any role to determine the pyridinolysis rates of chlorothiophosphates. The sequence of the pyridinolysis rates of **1-6** is roughly inversely proportional to the size of the two ligands (R_1O

and R_2O); the greater the size of the two ligands, the rate becomes slower. These results indicate that the steric effects of the two ligands play an important role to determine the reactivity of the chlorothiophosphates. The Taft's Eq. (2) can be used to rationalize the steric effect on the reaction rate where k_2 is the second-order rate constant with unsubstituted pyridine in MeCN at 35.0 °C, E_S is the Taft's steric constant [$E_S(\text{R}) = 0(\text{Me})$; $-0.07(\text{Et})$; $-0.36(\text{Pr})$; $-0.39(\text{Bu})$; $-2.48(\text{Ph})$], ΣE_S is the summation of the steric constants of the two ligands, and δ is the sensitivity coefficient.⁸ Herein, ' $\Sigma E_S = E_S(\text{R}_1) + E_S(\text{R}_2)$ ' is introduced instead of ' $\Sigma E_S = E_S(\text{R}_1\text{O}) + E_S(\text{R}_2\text{O})$ ' since the data of $E_S(\text{R}_i\text{O})$ is not available. Figure 3 shows the plot of $\log k_2$ with unsubstituted pyridine ($\text{C}_5\text{H}_5\text{N}$) against the summation of the Taft's steric constants of the two ligands of the reactions of six chlorothiophosphates (**1-6**) in MeCN at 35.0 °C, giving the sensitivity coefficients of $\delta 0.16$ ($r = 0.754$) with six substrates of **1-6**, $\delta 0.41$ ($r = 0.973$) with five substrates of **1-5**, and $\delta 0.12$ ($r = 0.989$) with five substrates of **1, 2, 3, 4, and 6**.

$$\log k_2 = \delta \Sigma E_S + C \quad (2)$$

The anilinolysis rates (with $\text{C}_6\text{H}_5\text{NH}_2$) of the chlorothiophosphates of **1-6** in MeCN at 55.0 °C are also predominantly

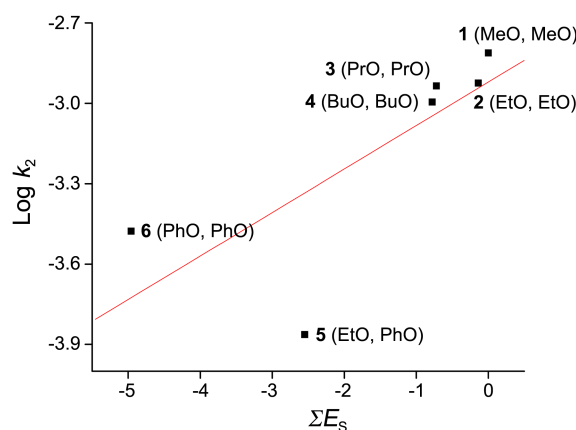


Figure 3. The plot of $\log k_2$ vs ΣE_S , according to the Taft Eq. (2), for the reactions of **1-6** with $\text{C}_5\text{H}_5\text{N}$ in MeCN at 35.0 °C. The number of the substrate and two ligands are displayed next to the corresponding point.

Table 2. Summary of the Second-Order Rate Constants (k_2 with $\text{C}_5\text{H}_5\text{N}$ at 35.0 °C), NBO Charges at the Reaction Center P Atom, Summations of the Taft's Steric Constants (ΣE_S) of the Two Ligands, Brønsted Coefficients (β_X), CICs (ρ_{XY}), and Variation Trends of Free Energy Relationships with X for the Pyridinolyses of **1-6** in MeCN

Substrate	$k_2 \times 10^{3a}$	Charge at P	$-\Sigma E_S^d$	β_X	ρ_{XY}	Trend
1: (MeO) ₂ P(=S)Cl	1.54 ^b	1.687	0	1.09/0.20 ^e	–	V ^g
2: (EtO) ₂ P(=S)Cl	1.19 ^b	1.701	0.14	1.02/0.29 ^e	–	V
3: (PrO) ₂ P(=S)Cl	1.16	1.723	0.72	1.08/0.31 ^e	–	V
4: (BuO) ₂ P(=S)Cl	1.01	1.703	0.78	1.26/0.31 ^e	–	V
5: (EtO)(YC ₆ H ₄ O)P(=S)Cl	0.137 ^c	1.687 ^c	2.55 ^c	2.31-2.33/0.45-0.47 ^e	0/0/0/0 ^f	V
6: (PhO)(YC ₆ H ₄ O)P(=S)Cl	0.333 ^c	1.661 ^c	4.96 ^c	1.36-1.50/0.23-0.48 ^e	2.42/5.14/–1.02/–0.04 ^f	V

^aSecond-order rate constant with unsubstituted pyridine ($X = \text{H}$) at 35.0 °C. ^bExtrapolated value in the Arrhenius plot. ^cThe value with $Y = \text{H}$. ^dNote that the value of ΣE_S is not ' $E_S(\text{R}_1\text{O}) + E_S(\text{R}_2\text{O})$ ' but ' $E_S(\text{R}_1) + E_S(\text{R}_2)$ ' because of a lack of data of $E_S(\text{R}_i\text{O})$. ^eStrongly basic/weakly basic pyridines. ^fStronger nucleophiles and weaker electrophiles/weaker nucleophiles and weaker electrophiles/stronger nucleophiles and stronger electrophiles/weaker nucleophiles and stronger electrophiles. ^gThe symbol of V indicates biphasic concave upward free energy correlation with a break point for the substituent X variations in the nucleophiles.

dependent upon the steric effects over the inductive effects of the two ligands, giving the sensitivity coefficients of: δ 0.16 ($r = 0.878$) with six substrates of **1-6**; δ 0.17 ($r = 0.915$) with five substrates of **1**, **2**, **4**, **5**, and **6**; δ 0.18 ($r = 0.959$) with four substrates of **1**, **2**, **5**, and **6**; δ 0.13 ($r = 0.967$) with four substrates of **2**, **4**, **5**, and **6**; and δ 0.21 ($r = 0.998$) with three substrates of **1**, **5**, and **6**.¹⁰

As seen in Table 2, the β_X values of **1-4** are similar: $\beta_X = 1.0$ - 1.3 with the strongly basic pyridines and $\beta_X = 0.2$ - 0.3 with the weakly basic pyridines, strongly suggesting the same reaction mechanisms of the pyridinolyses of **1-4**. The β_X (≈ 2.3) value of **5** with the strongly basic pyridines is the greatest one among all over the pyridinolyses of the P=O and P=S systems studied by this lab. The β_X ($= 1.4$ - 1.5) values of **6** with the strongly basic pyridines are relatively great. The β_X values of **5** and **6** with the weakly basic pyridines are somewhat greater than those of **1-4**. The Hammett plots of **5** for the variation of substituent Y in the substrate are biphasic concave upwards with a break (minimum) point at Y = H while those of **6** are concave downwards with a break point at Y = H. Thus, the four values of CICs, ρ_{XY} , were obtained for both **5** and **6**. In **5**, the CICs, ρ_{XY} are all null in spite of the biphasic free energy correlations for both substituent X and Y variations, since the ρ_X values with both the strongly and weakly basic pyridines are almost constant. This reaction is the only one, having all $\rho_{XY} = 0$ with four blocks until now: stronger nucleophiles and weaker electrophiles, weaker nucleophiles and weaker electrophiles, stronger nucleophiles and stronger electrophiles, and weaker nucleophiles and stronger 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 transition state (TS), in which the reaction proceeds through a stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate.¹¹ A frontside attack TSf (Scheme 2) was proposed with the strongly basic pyridines based on the considerably great magnitudes of β_X value and a backside attack involving in-line-type TSb (Scheme 2) was proposed with the weakly basic pyridines based on the relatively small magnitudes of β_X . In **6**, a stepwise process was proposed involving a rate-limiting step change from bond breaking with the weaker electrophiles based on the large positive ρ_{XY} value to bond formation with the stronger electrophiles based on the negative ρ_{XY} value.¹² The nonlinear free energy correlations of biphasic concave upward plots with X in the nucleophiles were rationalized by a change in the attacking

direction of the nucleophile from a backside with less basic pyridines to a frontside attack with more basic pyridines.

In the present work, the free energy correlations for substituent X variations in the pyridines are biphasic concave upwards. The biphasic concave upward free energy relationships are interpreted as a change of the nucleophilic attacking direction from a frontside attack TSf with the strongly basic pyridines based on the considerably great magnitudes of β_X value to a backside attack involving in-line-type TSb with the weakly basic pyridines based on the relatively small magnitudes of β_X in a concerted process, the same mechanism as in **1-3**.

In general, the nonlinear free energy correlation of a concave upward plot is diagnostic of a change in the reaction mechanism, such as parallel reactions where the reaction path is changed depending on the substituents, while nonlinear free energy correlation of the biphasic concave downward plot is diagnostic of a rate-limiting step change from bond breaking with less basic nucleophiles to bond formation with more basic nucleophiles.¹³ It is the suggestion of the authors that the concave upward Hammett and Brønsted plots can also be diagnostic of a change in the attacking direction of the nucleophile depending on the substituents from backside to frontside. 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.¹⁴

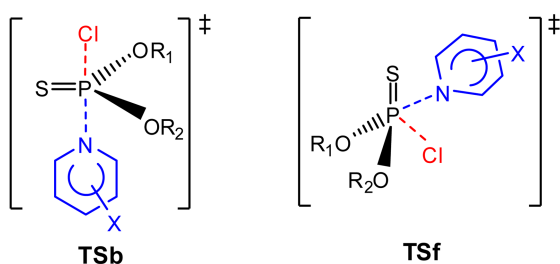
The free energy relationships with X for the pyridinolyses of **1-6** are all biphasic concave upwards while those for the anilinolyses of **1-6** are all linear.¹⁰ The free energy correlations with Y (substituent in the substrate) for the pyridinolyses of **5** and **6** are concave upwards and downwards, respectively, while those for the anilinolysis of **5** and **6** are linear.^{10a,b} This means that the substituent effects of X and Y on the pyridinolyses are surprising compared to the anilinolyses.

In summary, the kinetic studies on the pyridinolysis of dibutyl chlorothiophosphate have been carried out in MeCN at 35.0 °C. The free energy correlations are biphasic concave upwards with a break point at X = H. A concerted S_N2 mechanism is proposed with a change of the attacking direction of the X-pyridine from a frontside attack with the strongly basic pyridines to a backside attack with the weakly basic pyridines.

Experimental Section

Materials. Dibutyl chlorothiophosphate (commercially available), GR grade pyridines and HPLC grade acetonitrile (water content is less than 0.005%) were used for kinetic studies without further purification.

Kinetic Procedure. Rates were measured conductometrically at 35.0 °C. The conductivity bridge used in this work was a self-made computer automated A/D converter conductivity bridge. The pseudo-first-order rate constants, k_{obsd} were measured by curve fitting analysis in origin program with a large excess of pyridines, [substrate] = 1×10^{-3} M and [XC₅H₄N] = (0.02-0.10) M. Second-order rate constants, k_2 ,



Scheme 2. Backside attack TSb and frontside attack TSf.

were obtained from the slope of a plot of k_{obsd} vs $[X\text{-pyridine}]$ with at least five concentrations of pyridine. The pseudo-first-order rate constant values (k_{obsd}) were the average of at least three runs that were reproducible within $\pm 3\%$.

Product Analysis. Dibutyl chlorothiophosphate was reacted with excess 4-methylpyridine, for more than 15 half-lives at 35.0 °C in MeCN. Acetonitrile 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. Analytical and spectroscopic data of the product gave the following results (see supplementary materials with activation parameters).

[(BuO)₂P(=S)NC₅H₄-4-CH₃]⁺Cl⁻. Brown liquid; ¹H NMR (400 MHz, CDCl₃) δ 0.88-0.92 (6H, t, $J = 7.2$ Hz, 2CH₃), 1.14-1.21 (2H, m, CH₂), 1.21-1.41 (4H, m, 2CH₂), 1.61-1.67 (2H, m, CH₂), 2.32 (3H, s, CH₃), 4.10-4.16 (4H, m, 2OCH₂), 7.08-7.10 (2H, d, $J = 5.2$ Hz, pyridinium), 8.42-8.44 (2H, d, $J = 6.0$ Hz, pyridinium); ¹³C NMR (100 MHz, CDCl₃) δ 13.46, 15.24 (CH₃), 18.27, 18.57, 18.90 (CH₂), 20.95 (CH₃), 31.81 (CH₂), 63.60, 69.00 (OCH₂), 103.84, 124.68, 147.60, 148.90 (C=C, pyridinium); ³¹P NMR (162 MHz, CDCl₃) δ 58.41 (s, 1P, P=S); MS (EI) m/z 337 (M⁺).

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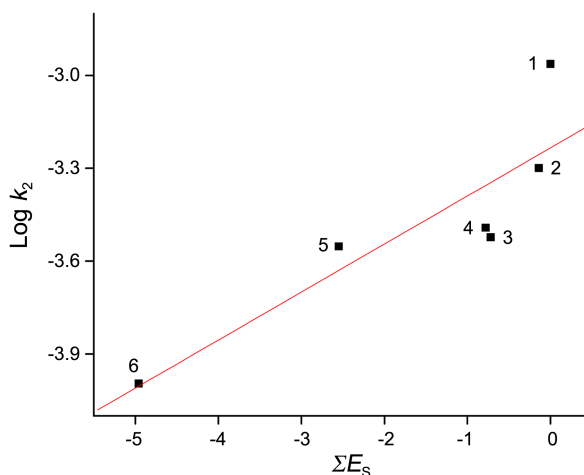


Figure R1. The plot of $\log k_2$ vs ΣE_s for the reactions of **1-6** with $C_6H_5NH_2$ in MeCN at 55.0 °C.

- 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.
- In general, the negative sign of ρ_{XY} implies that the reaction proceeds through a concerted mechanism, while a stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate with the positive sign of ρ_{XY} , and the magnitude of ρ_{XY} value is inversely proportional to the distance between X and Y through the reaction center.
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