

Kinetics and Mechanism of the Pyridinolysis of Aryl Ethyl Chlorothiophosphates in Acetonitrile

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The nucleophilic substitution reactions of Y-aryl ethyl chlorothiophosphates with X-pyridines are studied kinetically in acetonitrile at 55.0 °C. The Hammett and Brønsted plots for substituent X variations in the nucleophiles exhibit biphasic concave upwards with a break point at X = 3-Me. The substituents of X = 4-CN and 4-Ac show great positive deviations from both the Hammett and Brønsted plots. The Hammett plots for substituent Y variations in the substrates exhibit biphasic concave upwards with a minimum point at Y = H. The obtained values of the cross-interaction constants (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. A stepwise mechanism with a rate-limiting leaving group departure from the intermediate is proposed where the distance between X and Y does not vary from the intermediate to the second transition state. A frontside attack is proposed with the strongly basic pyridines based on the considerably great magnitudes of ρ_X and β_X values and a backside attack is proposed with the weakly basic pyridines based on the relatively small magnitudes of ρ_X and β_X . The positive deviations of the two strong π -acceptor *para*-substituents, X = 4-Ac and 4-CN, from both the Hammett and Brønsted plots are rationalized by the great extents of bond formation and breaking.

Key Words : Biphasic free energy correlation, Phosphoryl transfer reaction, Pyridinolysis, Aryl ethyl chlorothiophosphates

Introduction

This lab reported various types of phosphoryl and thio-phosphoryl transfer reactions: pyridinolysis,¹ anilinolysis,² benzylaminolysis,³ and theoretical studies.⁴ The substituent effects on the pyridinolysis mechanism are more significant compare to those on the anilinolysis mechanism. Herein, the kinetic studies on the reactions of Y-aryl ethyl chlorothiophosphates (**8**) with X-pyridines in acetonitrile (MeCN) at 55.0 ± 0.1 °C (Scheme 1) have been carried out to gain further information into the thiophosphoryl transfer reactions and substituent effects of the nucleophiles and substrates on the reaction mechanism, as well as to compare with the relevant pyridinolyses of R₁R₂P(=S)Cl-type substrates in MeCN as follows: Y-*O*-aryl methyl phosphonochloridothioates [**1**: Me(YC₆H₄O)P(=S)Cl];^{1k} Y-*O*-aryl phenyl phosphonochloridothioates [**2**: Ph(YC₆H₄O)P(=S)Cl];^{1f} diphenyl thiophosphinic chloride [**3**: Ph₂P(=S)Cl];^{1d} dimethyl chlorothiophosphate [**4**: (MeO)₂P(=S)Cl];^{1g} diethyl chlorothiophosphate [**5**: (EtO)₂P(=S)Cl];^{1g} dimethyl thio-

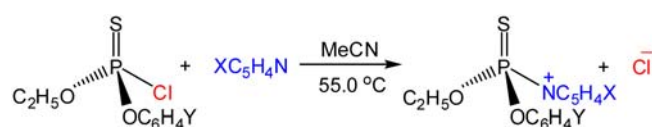
phosphinic chloride [**6**: Me₂P(=S)Cl];^{1h} Y-aryl phenyl chlorothiophosphates [**7**: (PhO)(YC₆H₄O)P(=S)Cl].^{1j} The number of substrates follows the order of the pyridinolysis rate.

Results and Discussion

The pseudo-first-order rate constants observed (k_{obsd}) for all reactions obey eq. (1) with negligible k_0 (≈ 0) in MeCN. The second-order rate constants were determined with at least five pyridine concentrations [XC₅H₄N]. No third-order or higher-order terms were detected, and no complications were found in the determination of k_{obsd} or in the linear plot of eq. (1). This suggests that there are no base-catalysis or noticeable side reactions, and the overall reaction follows the path given 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, together with selectivity parameters, ρ_X , β_X , ρ_Y , and ρ_{XY} . The β_X values were determined using $\text{p}K_a$ values in water; the slopes from the plots of $\log k_2(\text{MeCN})$ against $\text{p}K_a(\text{H}_2\text{O})$. Justification of this procedure has been experimentally and theoretically provided.⁷ The Hammett (Fig. 1; $\log k_2$ vs σ_X) and Brønsted [Fig. 2; $\log k_2$ vs $\text{p}K_a(\text{X})$] plots for substituent X variations in the nucleophiles exhibit biphasic concave upwards with a break point at X = 3-Me. The substituents of X = 4-CN and 4-Ac show great positive deviations from the Hammett and Brønsted plots. The



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

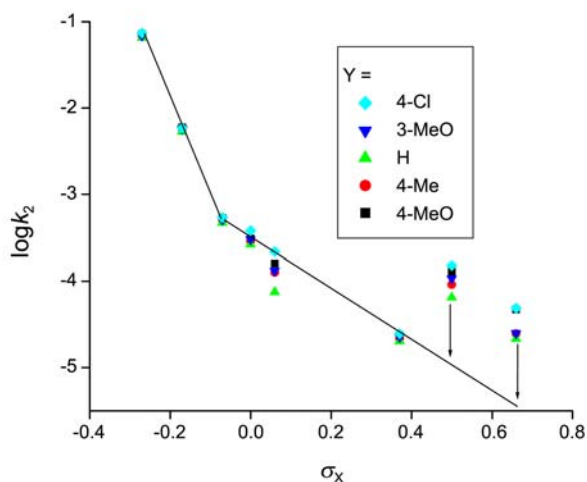
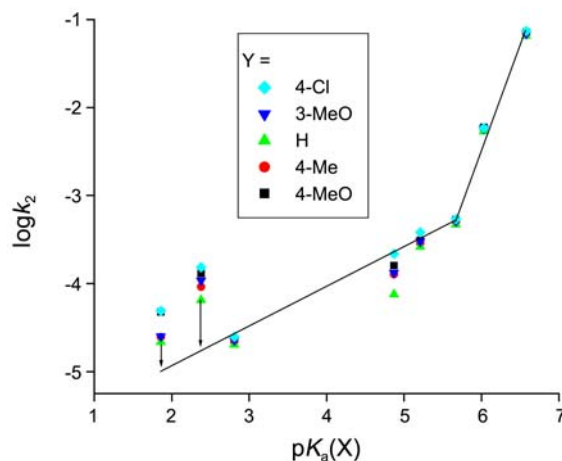
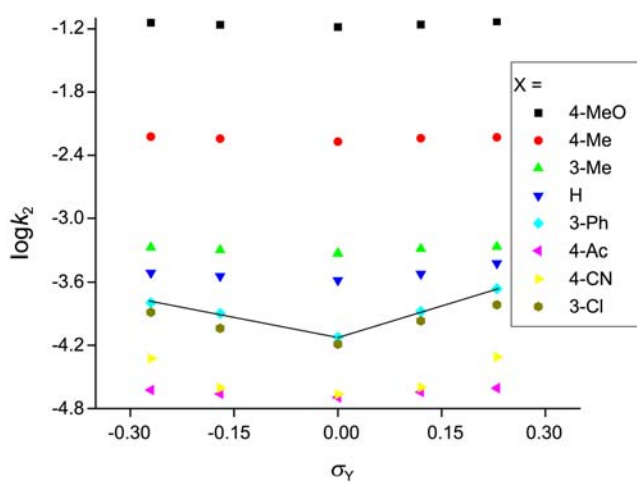
Scheme 1. The studied reaction system.

Table 1. Second-Order Rate Constants ($k_2 \times 10^3/\text{M}^{-1} \text{s}^{-1}$) and Selectivity Parameters^a of the Reactions of Y-Aryl Ethyl Chlorothiophosphates (**8**) with X-Pyridines in MeCN at 55.0 °C

X \ Y	4-MeO	4-Me	H	3-MeO	4-Cl	ρ_Y^h	ρ_Y^j
4-MeO	71.8	69.0	65.4	69.2	74.1	-0.15 ± 0.01	0.24 ± 0.01
4-Me	5.97	5.69	5.34	5.77	5.87	-0.18 ± 0.01	0.18 ± 0.01
3-Me	0.530	0.501	0.469	0.514	0.538	-0.19 ± 0.01	0.26 ± 0.01
H	0.309	0.287	0.263	0.301	0.381	-0.26 ± 0.01	0.70 ± 0.02
3-Ph	0.160	0.127	0.0752	0.133	0.218	-1.23 ± 0.02	2.01 ± 0.01
3-Cl	0.0238	0.0218	0.0202	0.0227	0.0247	-0.26 ± 0.01	0.38 ± 0.01
4-CN	0.0474	0.0248	0.0216	0.0252	0.0489	-1.07 ± 0.13	1.53 ± 0.10
4-Ac	0.130	0.0916	0.0649	0.108	0.153	-1.09 ± 0.03	1.62 ± 0.02
$-\rho_X^{b,c}$	10.7 ± 0.01	10.7 ± 0.01	10.7 ± 0.01	10.7 ± 0.01	10.7 ± 0.03		
$\beta_X^{b,d}$	2.31 ± 0.17	2.32 ± 0.17	2.33 ± 0.17	2.31 ± 0.17	2.32 ± 0.16	$\rho_{XY}^j = 0/0/0/0$	
$-\rho_X^{e,f}$	3.01 ± 0.07	3.02 ± 0.11	2.97 ± 0.23	3.02 ± 0.11	3.09 ± 0.04		
$\beta_X^{e,g}$	0.46 ± 0.08	0.46 ± 0.13	0.45 ± 0.24	0.46 ± 0.12	0.47 ± 0.04		

^aThe σ values were taken from ref. 5. The pK_a values were taken from ref. 6. ^bX = (4-MeO, 4-Me, 3-Me). ^cCorrelation coefficients, r , are better than 0.999. ^d $r \geq 0.994$. ^eX = (3-Me, H, 3-Ph, 3-Cl). ^f $r \geq 0.950$. ^g $r \geq 0.944$. ^hY = (H, 3-MeO, 4-Cl). ⁱY = (4-MeO, 4-Me, H). $r \geq 0.874$. ^jY = H, 3-MeO, 4-Cl. $r \geq 0.932$. ^kAll of four blocks.

magnitudes of the ρ_X and β_X values with the strongly basic pyridines (X = 4-MeO, 4-Me, 3-Me) are considerably greater than those with the weakly basic pyridines (X = 3-Me, H, 3-Ph, 3-Cl). Moreover, the ρ_X and β_X values are almost constant regardless of substituent Y: $\rho_X = 10.7 \pm 0.00$ and $\beta_X = 2.32 \pm 0.01$ with the strongly basic pyridines, and $\rho_X = 3.02 \pm 0.07$ and $\beta_X = 0.46 \pm 0.01$ with the weakly basic pyridines. These results indicate greater degree of bond formation (or greater positive charge development on the nucleophilic N atom) with the strongly basic pyridines than with the weakly basic pyridines. The substituent X effects in the nucleophiles on the rates are in line with those for a typical nucleophilic substitution reaction with positive charge development at the nucleophilic N atom ($\rho_X < 0$ and $\beta_X > 0$) in the transition state (TS). The Hammett plots (Fig. 3; $\log k_2$ vs σ_Y) for substituent Y variations in the substrates exhibit biphasic concave upwards with a minimum point at Y = H, resulting in unusual *negative* ρ_Y values for electron-donating substituents (Y = 4-MeO, 4-Me, H) and positive ρ_Y

**Figure 1.** The Hammett plots ($\log k_2$ vs σ_X) of the reactions of Y-aryl ethyl chlorothiophosphates (**8**) with X-pyridines in MeCN at 55.0 °C.**Figure 2.** The Brønsted plots [$\log k_2$ vs $pK_a(X)$] of the reactions of Y-aryl ethyl chlorothiophosphates (**8**) with X-pyridines in MeCN at 55.0 °C.**Figure 3.** The Hammett plots ($\log k_2$ vs σ_Y) of the reactions of Y-aryl ethyl chlorothiophosphates (**8**) with X-pyridines in MeCN at 55.0 °C.

values for electron-withdrawing substituents ($Y = \text{H}, 3\text{-MeO}, 4\text{-Cl}$). The negative ρ_Y values imply that the charge at the reaction center P atom in the TS becomes more positive than in the ground state.

The cross-interaction constants (CICs; ρ_{XY}), eqs. (2), are one of the strong tools to substantiate the reaction mechanism.⁸ Herein, X and Y represent the substituents in the nucleophile and substrates, respectively. The sign and magnitude of the CICs have made it possible to correctly interpret the reaction mechanism and degree of tightness of the TS, respectively. In general, the ρ_{XY} has a negative value in a stepwise mechanism with a rate-limiting bond formation and a concerted $\text{S}_{\text{N}}2$. In contrast, it has a positive value for a stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate. The magnitude of ρ_{XY} is inversely proportional to the distance between X and Y through the reaction center.⁸

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

$$\rho_{XY} = \partial \rho_X / \partial \sigma_Y = \partial \rho_Y / \partial \sigma_X \quad (2b)$$

In general, the four values of ρ_{XY} can be obtained by dividing into four blocks since both the Hammett plots for substituent X and Y variations are biphasic with break points. However, the ρ_X values with both the strongly and weakly basic pyridines are almost constant, and as a result, all of the ρ_{XY} values for four blocks become null, i.e., $\rho_{XY} = \partial \rho_X / \partial \sigma_Y = 0$. This phenomenon can be occurred when: (i) X and Y are apart too far to interact, resulting in the absence of the cross-interaction between X and Y; (ii) the distance between X and Y does not vary, resulting in the invariable of the cross-interaction between X and Y. For the first time, the null of ρ_{XY} value is observed with the whole spectrum of X and Y regardless of the nature, electron-donating or electron-withdrawing.

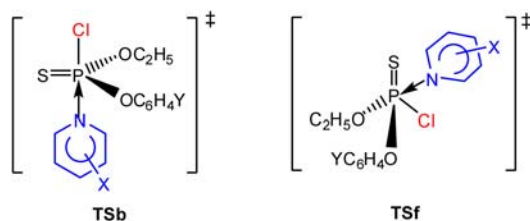
Thus, the authors conclude that the null of ρ_{XY} value in the present work indicates a *special* stepwise mechanism with a rate-limiting leaving group departure from the intermediate where the distance between X and Y does not vary from the intermediate to the second TS. It is worthy of note that the magnitudes of ρ_X and β_X values involving a frontside attack TSf are greater than those involving a backside attack TSb (Scheme 2).^{1c} The authors propose the attacking direction of the nucleophile for the studied reaction system, divided into four blocks, as follows: (block *a*) a frontside attack TSf with the stronger nucleophiles and weaker electrophiles based on the considerably great magnitudes of ρ_X and β_X values; (block *b*) a backside attack TSb with the weaker nucleo-

philes and electrophiles based on the relatively small magnitudes of ρ_X and β_X ; (block *c*) a frontside attack TSf with the stronger nucleophiles and electrophiles on the basis of the considerably great magnitude of ρ_X and β_X values; (block *d*) a backside attack TSb with the weaker nucleophiles and stronger electrophiles on the basis of relatively small magnitudes of ρ_X and β_X values.

The two strong π -acceptor *para*-substituents, X = 4-Ac and 4-CN in X-pyridines, exhibit positive deviations from both the Hammett (Fig. 1) and Brønsted plots (Fig. 2) for substituent X variations in the nucleophiles. 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.^{6c,9} The Hammett σ_p values of the π -acceptor substituents represent the inductive and π -electron-withdrawing effects. However, the experimental $\text{p}K_{\text{a}}$ value only represents the inductive effect of X, since protonation/deprotonation takes place at the σ lone pair on N which is orthogonal to the ring π -system.^{6c} 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 $\text{p}K_{\text{a}}$ values of π -acceptor substituents correctly reflect the substituent effects when the N atom of pyridine becomes positively charged in the TS, since the determination of $\text{p}K_{\text{a}}$ involves a positive charge on N (azonium type).



The two π -acceptor substituents exhibited positive deviations from the Hammett plots, while no deviations from the Brønsted plots, for the pyridinolyses of methyl chloroformate in MeCN^{6c} and water,¹⁰ benzenesulfonyl chlorides in MeOH,¹¹ benzyl bromides in DMSO¹² and phenacyl bromides in MeCN.¹³ This indicated that the N atom of pyridine becomes positively charged in the TS. In the pyridinolysis of Y-aryl phenyl chlorophosphates [(PhO)(YC₆H₄O)P(=O)Cl], the two π -acceptor substituents did not exhibit deviations from either the Hammett or Brønsted plots.^{1a} 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 CIC, $\rho_{XY} = -0.15$. In the present work, the two strong π -acceptor substituents, X = 4-Ac and 4-CN, exhibit positive deviations from both the Hammett and Brønsted plots for substituent X variations in the nucleophiles as observed of the pyridinolysis of *Z-N*-aryl-*P,P*-diphenyl phosphinic amides [Ph₂P(=O)NHC₆H₄Z] in DMSO.¹¹ This indicates that the degree of positive charge development on the N atom of pyridine is substantial in the TS. As mentioned earlier, the extent of bond formation in the intermediate is the same as in the TS since the ρ_{XY} value is



Scheme 2. Backside attack TSb and frontside attack TSf.

Table 2. Summary of the Second-Order Rate Constants ($k_2 \times 10^3/\text{M}^{-1} \text{s}^{-1}$) at 35.0 °C, NBO Charges at the Reaction Center P Atom, and Selectivity Parameters (β_X and ρ_{XY}) for the Reactions of **1-8** with X-Pyridines in MeCN

no	R ₁	R ₂	$k_2 \times 10^{3a}$	charge at P	β_X	ρ_{XY}	ref.
1	Me	YC ₆ H ₄ O	14.3 ^b	1.432	0.66-1.04/2.08-2.38 ^e	-1.76/0/2.80/0 ^f	1k
2	Ph	YC ₆ H ₄ O	11.2 ^b	1.462	0.87-0.95	-0.46	1f
3	Ph	Ph	1.83	1.236	1.53/0.38 ^e	-	1d
4	MeO	MeO	1.54 ^c	1.687	1.09/0.20 ^e	-	1g
5	EtO	EtO	1.19 ^c	1.701	1.02/0.29 ^e	-	1g
6	Me	Me	0.744	1.180	0.97/0.27 ^e	-	1h
7	PhO	YC ₆ H ₄ O	0.333 ^b	1.661	1.36-1.50/0.23-0.48 ^e	2.42/5.14/-1.02/-0.04 ^f	1j
8	EtO	YC ₆ H ₄ O	0.137 ^{b,d}	1.687	2.31-2.33/0.45-0.47	0/0/0/0 ^f	this work

^aFor the reactions with unsubstituted pyridine (X = H) at 35.0 °C. ^bFor the reactions of unsubstituted substrate (Y = H). ^cExtrapolated values from the Arrhenius plots. ^dEmpirical kinetic data. ^eFor more/less basic pyridines. ^fThe stronger nucleophiles and weaker electrophiles/weaker nucleophiles and electrophiles/stronger nucleophiles and electrophiles/weaker nucleophiles and stronger electrophiles.

null. Taking into account the negative ρ_Y value with electron-donating substituents Y (= 4-MeO, 4-Me, H) in Figure 3, the extents of bond formation and breaking in the TS must be great enough to give the negative ρ_Y value, and the TS should be very late, product-like.

The second-order rate constants with unsubstituted pyridine at 35.0 °C, natural bond order (NBO) charges at the reaction center P atom [B3LYP/6-311+G(d,p) level of theory],¹⁴ and selectivity parameters (β_X and ρ_{XY}) for the pyridinolyses of eight R₁R₂P(=S)Cl-type substrates (**1-8**) in MeCN are summarized in Table 2. The sequence of the substrate number follows the order of the second-order rate constant. The second-order rate constants do not correlate with the positive charge of the reaction center P or the size of the two ligands (R₁ and R₂). The pyridinolysis of **2** only exhibits linear free energy correlations for both substituent X and Y variations. The biphasic concave upward free energy correlations for substituent X variations for **3-7** were rationalized by the attacking direction change from a frontside with the strongly basic pyridines to a backside with the weakly basic pyridines. In **1**, discrete free energy correlations were found for substituent X variations while concave downward free energy correlation was found for substituent Y variations. In **7**, free energy correlations were concave upwards for substituent X variations while concave downwards for substituent Y variations. As can be seen, the substituent effects on the pyridinolyses of R₁R₂P(=S)Cl-type substrates are really dramatic.

Experimental Section

Materials. Y-Aryl ethyl chlorothiophosphates were prepared as described previously.^{2f} GR grade pyridines were used without further purification and all other materials were as reported previously.¹

Kinetic Procedure. Rates were measured conductometrically at 55.0 °C. The conductivity bridge used in this work was a self-made computer automated A/D converter conductivity bridge. Pseudo-first-order rate constants, k_{obsd} were measured by curve fitting analysis in origin program with a large excess of pyridines, [Substrates] = 5×10^{-4} M

and [X-Pyridine] = (0.05-0.13) M. Second-order rate constants, k_2 , were obtained from the slope of a plot of k_{obsd} vs. [X-Pyridine] with at least five concentrations of pyridine. The k_2 values are the averages of more than three runs.

Product Analysis. Y-aryl ethyl chlorothiophosphates was reacted with excess pyridine for more than 15 half-lives at 55.0 °C in acetonitrile. Acetonitrile was evaporated under reduced pressure and ether was added. The product was isolated as ether insoluble fraction. The product was purified to remove excess pyridine by washing several times with 30% ethylacetate and n-Hexane mixture. Analytical data of the product were as follows:

[(C₂H₅O)(4-MeO-C₆H₄)P(=S)NC₅H₅]⁺Cl⁻. Gummy and greasy material; ¹H NMR (400 MHz, CD₃CN) δ 1.20 (t, 3H, Aliphatic), δ 3.74 (m, 5H, Aliphatic), 6.82-7.15 (m, 4H, phenyl), 7.92-8.73 (m, 5H, pyridine); ¹³C NMR (100 MHz, CDCl₃) δ 15.64 (1C, CH₃), 55.59 (1C, CH₂), 66.77 (1C, OCH₃), 114.60-157.65 (11C, Aromatic); ³¹P NMR (162 MHz, CDCl₃) δ 70.36 (s, 1P, P=S); m/z 345 (M⁺).

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