

Nucleophilic Substitution Reactions of *O*-Methyl *N,N*-Diisopropylamino Phosphonochloridothioate with Anilines and Pyridines

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The kinetic studies on the reactions of *O*-methyl *N,N*-diisopropylamino phosphonochloridothioate with *X*-anilines and *X*-pyridines have been carried out in acetonitrile. The free energy relationship with *X* in the anilines exhibits biphasic concave upwards with a break region between *X* = (H and 4-F), giving unusual negative β_X and positive ρ_X values with weakly basic anilines. The unusual phenomenon is rationalized by isokinetic relationship. A stepwise mechanism with a rate-limiting leaving group departure from the intermediate is proposed based on the selectivity parameter and variation trend of the deuterium kinetic isotope effects with *X*. The free energy relationship with *X* in the pyridines exhibits biphasic concave upwards with a break point at *X* = 3-MeO. A concerted mechanism is proposed based on relatively small β_X value, and frontside and backside nucleophilic attack are proposed with strongly and weakly basic pyridines, respectively.

Key Words : Thiophosphoryl transfer reaction, Anilinolysis, Pyridinolysis, *O*-Methyl *N,N*-diisopropylamino phosphonochloridothioate, Biphasic concave upward free energy relationship

Introduction

To extend the kinetic studies on the aminolyses, anilinolysis and pyridinolysis, of the phosphonochloridothioates, the nucleophilic substitution reactions of *O*-methyl diisopropylamino phosphonochloridothioate (**7**) with substituted anilines (and deuterated anilines) and pyridines are kinetically investigated in acetonitrile (MeCN) at 65.0 ± 0.1 and 45.0 ± 0.1 °C, respectively (Schemes 1 and 2). The kinetic results of the present work are compared with those of the anilinolyses¹ and pyridinolyses² of *Y-O*-aryl methyl [1; Me(YC₆H₄O)P(=S)Cl],^{1b,2b} *O*-methyl phenyl [2; Ph(MeO)P(=S)Cl],^{1c,2d} *O*-ethyl phenyl [3; Ph(EtO)P(=S)Cl],^{1d,2d} *O*-propyl phenyl [4; Ph(PrO)P(=S)Cl],^{1e,2e} *O*-*i*-propyl phenyl [5; Ph(*i*-PrO)P(=S)Cl],^{1e,2e} *Y-O*-aryl phenyl [6; Ph(YC₆H₄O)P(=S)Cl]^{1c,2a} and *Y-S*-aryl phenyl [8; Ph(YC₆H₄S)P(=S)Cl]^{1a,2c} phosphonochloridothioates. The aim of this

work is to obtain further information on the reactivities, selectivity parameters, substituent effects, free energy correlations, deuterium kinetic isotope effects (DKIEs) and mechanisms of the thiophosphoryl transfer reactions.

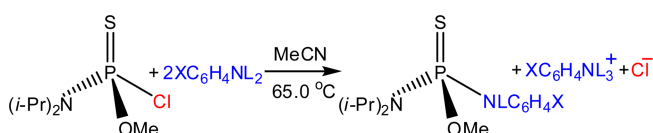
Results and Discussion

Anilinolysis. Table 1 lists the second-order rate constants (k_H and k_D) in MeCN at 65.0 °C, together with the selectivity parameters (ρ_X and β_X) and DKIEs (k_H/k_D). The Brønsted β_X (Figure 1) and Hammett ρ_X (Figure S1) plots show biphasic concave upward free energy relationships with a break region between *X* = (H and 4-F). The rate is compatible with

Table 1. Second-Order Rate Constants ($k_{H(D)} \times 10^4/M^{-1} s^{-1}$), Selectivity Parameters ($\rho_{X(H \text{ and } D)}$ and $\beta_{X(H \text{ and } D)}$) and DKIEs (k_H/k_D) of the Reactions of **7** with XC₆H₄NH₂(D₂) in MeCN at 65.0 °C

X	$k_H \times 10^4$	$k_D \times 10^4$	k_H/k_D
4-MeO	59.3 ± 0.3	48.1 ± 0.1	1.23 ± 0.01 ^k
4-Me	20.4 ± 0.3	18.9 ± 0.1	1.08 ± 0.02
3-Me	8.31 ± 0.01	8.40 ± 0.01	0.989 ± 0.002
H	4.35 ± 0.01	4.54 ± 0.01	0.958 ± 0.003
4-F	2.40 ± 0.01	2.64 ± 0.01	0.909 ± 0.005
3-MeO	4.04 ± 0.03	4.59 ± 0.01	0.880 ± 0.007
4-Cl	11.4 ± 0.1	13.2 ± 0.1	0.864 ± 0.010
3-Cl	40.9 ± 0.1	47.5 ± 0.1	0.861 ± 0.003
$\rho_{X(H)}/\rho_{X(D)}$	-4.18 ± 0.02 ^{a,b/}	-3.77 ± 0.02 ^{a,g/}	
	3.99 ± 0.01 ^{c,d}	4.06 ± 0.01 ^{c,h}	
$\beta_{X(H)}/\beta_{X(D)}$	1.43 ± 0.09 ^{a,e/}	1.29 ± 0.08 ^{a,i/}	
	-1.27 ± 0.08 ^{c,f}	-1.30 ± 0.08 ^{c,j}	

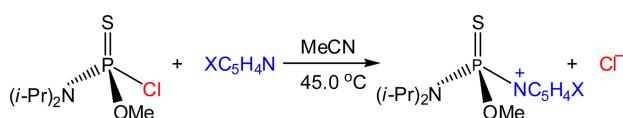
^aX = EDSS. ^bCorrelation coefficient, $r = 0.999$. ^cX = EWSs. ^d $r = 0.999$. ^e $r = 0.990$. ^f $r = 0.993$. ^g $r = 0.999$. ^h $r = 0.999$. ⁱ $r = 0.990$. ^j $r = 0.993$. ^kStandard error $\{= 1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D)^2]^{1/2}\}$.



L = H or D

X = 4-MeO, 4-Me, 3-Me, H, 4-F, 3-MeO, 4-Cl, 3-Cl

Scheme 1. Anilinolysis of *O*-methyl *N,N*-diisopropylamino phosphonochloridothioate (**7**) in MeCN at 65.0 °C.



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

Scheme 2. Pyridinolysis of **7** in MeCN at 45.0 °C.

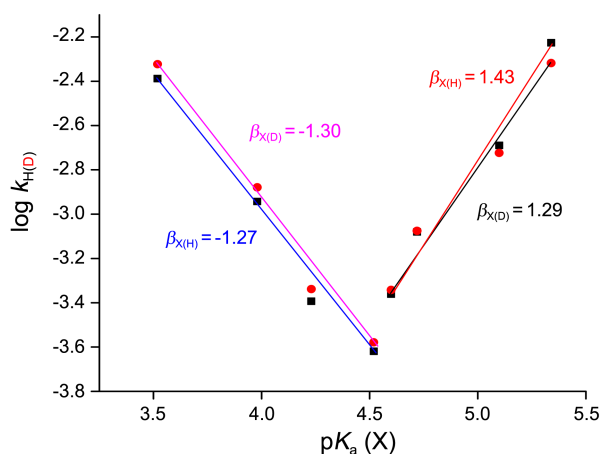


Figure 1. Brønsted plots of the reactions of **7** with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$ in MeCN at 65.0 °C.

a typical nucleophilic substitution reaction with partial positive charge development at the nucleophilic N atom in the transition state (TS) for $\text{X} = (4\text{-MeO}, 4\text{-Me}, 3\text{-Me}, \text{H})$ [electron-donating substituents (EDSs)]. On the other hand, the rate is not consistent with a typical nucleophilic substitution reaction for $\text{X} = (4\text{-F}, 3\text{-MeO}, 4\text{-Cl}, 3\text{-Cl})$ [electron-withdrawing substituents (EWSs)], giving unusual negative β_{X} (and positive ρ_{X}) values. The magnitudes of the $k_{\text{H}}/k_{\text{D}}$ values invariably decrease from the primary normal DKIEs ($k_{\text{H}}/k_{\text{D}} = 1.23\text{--}1.08 > 1$) with $\text{X} = (4\text{-MeO}, 4\text{-Me})$ to the secondary inverse DKIEs ($k_{\text{H}}/k_{\text{D}} = 0.99\text{--}0.86 < 1$) with $\text{X} = (3\text{-Me}, \text{H}, 4\text{-F}, 3\text{-MeO}, 4\text{-Cl}, 3\text{-Cl})$ as the aniline becomes less basic.

Table 2 summarizes the second-order rate constants (k_{H}) with unsubstituted aniline ($\text{C}_6\text{H}_5\text{NH}_2$) at 55.0 °C, natural bond order (NBO) charges at the reaction center P atom in the gas phase [B3LYP/6-311+G(d,p) level of theory],³ summations of the Taft steric constants of Ph and R_i [$\Sigma E_{\text{S}} = E_{\text{S}}(\text{Ph}) + E_{\text{S}}(\text{R}_i)$; $E_{\text{S}}(\text{R}_i) = 0.00(\text{Me}); -0.07(\text{Et}); -0.36(\text{Pr}); -0.47(i\text{-Pr}); -2.48(\text{Ph})$],⁴ Brønsted coefficients ($\beta_{\text{X}(\text{H})}$), cross-interaction constants (CICs, ρ_{XY}),⁵ DKIEs ($k_{\text{H}}/k_{\text{D}}$) and variation trends of the $k_{\text{H}}/k_{\text{D}}$ values with X of the reactions of **1–8** with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$ in MeCN. The variation trends of $k_{\text{H}}/k_{\text{D}}$ values with X are represented with arrow. The vertical

arrows (\uparrow or \downarrow) indicate the direction of the consistent increase of $k_{\text{H}}/k_{\text{D}}$ value with X. For example, the symbol of \uparrow indicates that $k_{\text{H}}/k_{\text{D}}$ value increases as the aniline becomes more basic. The symbol of $\uparrow\downarrow$ indicates that $k_{\text{H}}/k_{\text{D}}$ value increases or decreases with X depending on Y.⁶

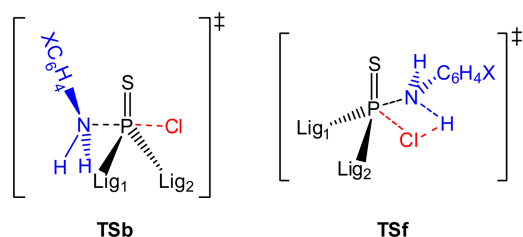
There is no linear correlation between the anilinolysis rates of **1–8** and positive NBO charges at the reaction center P atom, implying that the inductive effects of the two ligands do not play any role to decide the reactivity of anilinolyses of phosphonochloridothioates. The anilinolysis rates of six substrates (**1–6**) are inversely proportional (roughly) to the size of the two ligands, suggesting that the steric effects of the two ligands are the major factor to determine the anilinolysis rates.⁷ Taking into account considerably slower rate of **7** (with two ligands of *i*-Pr₂N and MeO) compared to that of **2** (with two ligands of Ph and MeO), *i.e.*, $k_{\text{H}}(\mathbf{3})/k_{\text{H}}(\mathbf{2}) = 23.3$, the steric hindrance of *i*-Pr₂N group seems to be much greater than that of phenyl group in the TS.

When partial deprotonation of the aniline occurs in a rate-limiting step by hydrogen bonding (*e.g.*, TSf in Scheme 3), the $k_{\text{H}}/k_{\text{D}}$ values are greater than unity, primary normal ($k_{\text{H}}/k_{\text{D}} > 1.0$).⁸ In contrast, the DKIEs can only be secondary inverse ($k_{\text{H}}/k_{\text{D}} < 1.0$) when an increase in the steric congestion occurs in the bond-making process because the N–H(D) vibrational frequencies invariably increase upon going to the TS (*e.g.*, TSb in Scheme 3).⁹ The real primary normal DKIE due to the hydrogen bond between the hydrogen of the N–H(D) moiety and Cl leaving group should be greater than the observed value because the observed DKIEs would be the sum of: (i) the primary normal DKIE, $k_{\text{H}}/k_{\text{D}} > 1$, because of the partial deprotonation of one of the two N–H(D) bonds in the TSf for a frontside attack; (ii) the secondary inverse DKIE, $k_{\text{H}}/k_{\text{D}} < 1$, because of the steric hindrance that increases the out-of-plane bending vibrational frequencies of the other N–H(D) bond in TSf for a frontside attack; (iii) lowering the $k_{\text{H}}/k_{\text{D}}$ value because of the nonlinear and unsymmetrical structure of $\text{N}\cdots\text{H}(\text{D})\cdots\text{Cl}$ in TSf; and finally (iv) lowering the $k_{\text{H}}/k_{\text{D}}$ value because of heavy atom (N in the nucleophile and Cl in the leaving group) contribution to the reaction-coordinate motion. When the reaction proceeds simultaneously through both pathways, backside (TSb) and

Table 2. Summary of the Second-Order Rate Constants ($k_{\text{H}} \times 10^3/\text{M}^{-1} \text{s}^{-1}$) with $\text{C}_6\text{H}_5\text{NH}_2$, NBO Charges at the Reaction Center P Atom, ΣE_{S} , $\beta_{\text{X}(\text{H})}$, ρ_{XY} , $k_{\text{H}}/k_{\text{D}}$ and Variation Trends of $k_{\text{H}}/k_{\text{D}}$ Values with X for the Reactions of **1–8** with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$ in MeCN

Substrate	$10^3 k_{\text{H}}^a$	Charge at P	$-\Sigma E_{\text{S}}^d$	$\beta_{\text{X}(\text{H})}$	ρ_{XY}	$k_{\text{H}}/k_{\text{D}}$	Trend
1: Me(YC ₆ H ₄ O)P(=S)Cl	7.25 ^b	1.432 ^b	< 2.48 ^b	0.14–0.46/1.31–1.54 ^e	–0.95/0.77 ^e	1.03–1.30/0.37–0.57 ^e	$\uparrow/\uparrow\downarrow^e$
2: Ph(MeO)P(=S)Cl	7.53	1.472	2.48	1.26	–	1.08–1.17	\downarrow
3: Ph(EtO)P(=S)Cl	6.93	1.478	2.55	1.23	–	0.93–1.28	\downarrow
4: Ph(PrO)P(=S)Cl	5.02	1.479	2.84	1.04	–	1.02–1.48	\downarrow
5: Ph(<i>i</i> -PrO)P(=S)Cl	4.00	1.488	2.95	1.10	–	0.63–0.99	\uparrow
6: Ph(YC ₆ H ₄ O)P(=S)Cl	1.50 ^b	1.462 ^b	4.96	1.22–1.33	–0.38	0.44–1.34	\downarrow
7: (<i>i</i> -Pr ₂ N)(MeO)P(=S)Cl	0.323 ^c	1.673	–	1.43/–1.27 ^f	–	0.96–1.23/0.86–0.91 ^f	\uparrow
8: Ph(YC ₆ H ₄ S)P(=S)Cl	0.175 ^b	0.999 ^b	> 4.96 ^b	1.21–1.25	–0.31	0.65–0.98	\uparrow

^aValue at 55.0 °C. ^bValue with Y = H. ^cEmpirical value. ^dNote that the value of ΣE_{S} is not ' $E_{\text{S}}(\text{Ph}) + E_{\text{S}}(\text{R}_i\text{O})$ ' but ' $E_{\text{S}}(\text{Ph}) + E_{\text{S}}(\text{R}_i)$ ' for **2–6** because the data of Taft steric constants of R_iO are not available. The ΣE_{S} values of **1** and **8** are estimated. ^eX = (4-MeO, 4-Me, H)/X = (4-Cl, 3-Cl, 3-NO₂). ^fX = EDSs/EWSs.



Scheme 3. Backside attack in-line-type TSb and frontside attack involving hydrogen-bonded, four-center-type TSf (Lig₁ and Lig₂ represent the two ligands).

frontside (TSf) attack, the observed DKIEs are the sum of both effects, secondary inverse and primary normal, and the obtained value of $k_{\text{H}}/k_{\text{D}}$ can be greater or lesser than unity depending on the fraction of the two pathways.

The biphasic concave downward free-energy correlations with a break region between X = H and 4-Cl were observed for the anilinolyse of **1**:^{1b} herein, (i) the $k_{\text{H}}/k_{\text{D}}$ values explicitly show a break region between X = H and 4-Cl; (ii) as a results, the DKIEs are distinctly divided into two parts, primary normal ($k_{\text{H}}/k_{\text{D}} = 1.03\text{--}1.30$) with strongly basic anilines (X = 4-MeO, 4-Me, H) while extraordinary secondary inverse ($k_{\text{H}}/k_{\text{D}} = 0.37\text{--}0.57 \ll 1$) with weakly basic anilines (X = 4-Cl, 3-Cl, 3-NO₂), rationalized by predominant frontside attack TSf with strongly basic anilines while predominant backside attack TSb with weakly basic anilines; and (iii) the proposed mechanism is a stepwise process with a rate-limiting bond formation for strongly basic anilines, while with a rate-limiting bond breaking for weakly basic anilines, based on the negative and positive ρ_{XY} values, respectively.¹⁰

In the present work, however, the magnitudes of the $k_{\text{H}}/k_{\text{D}}$ values consistently decrease as the aniline becomes less basic, from $k_{\text{H}}/k_{\text{D}} = 1.23$ (primary normal) with X = 4-MeO to 0.86 (secondary inverse) with X = 3-Cl. The $k_{\text{H}}/k_{\text{D}}$ values with X do not show any break region (or point) in spite of unusual negative β_{X} (and positive ρ_{X}) values with X = EWSs. This may indicate that: (i) the TS structure is gradually changed from dominant frontside attack involving hydrogen-bonded, four-center-type TSf to dominant backside attack in-line-type TSb as the aniline becomes less basic; and (ii) the anilinolysis mechanism with X = EDSs is the same as that with X = EDSs, although the attacking direction of the nucleophile is gradually changed with X.

Focus will now shift to the discrete biphasic free energy correlation with X and unusual negative β_{X} value with X = EWSs, and discuss the following three plausible cases: (i) The discrete free energy relationships are reported because of a desolvation step prior to the rate-limiting nucleophilic attack with a smaller value of β_{X} when the nucleophile is anion and the solvent is polar protic, *e.g.*, water.¹¹ However, in the present work, the negative β_{X} value with X = EWSs is not ascribed to a desolvation step because the aniline nucleophile is neutral and the MeCN solvent is dipolar aprotic; (ii) The negative β_{X} value can be observed because of TS imbalance phenomenon.¹² The authors reported that the sign of β_{X} changes from negative with relatively strong electron-

donating Y substituents to positive with more electron-withdrawing Y for the reactions of 1-(Y-phenyl)ethyl chlorides with X-anilines in methanol.^{13,14} The anilinolyse of Y-benzhydryl chlorides in MeOH-MeCN also exhibited the change of the sign of β_{X} depending on Y substituents.^{14,15} The negative β_{X} values were interpreted in terms of a TS structure in which nearly complete bond formation between the nucleophile and cation formed in an ion-pair pre-equilibrium is coupled with a TS imbalance phenomenon, advocated by Jencks and Bernasconi.¹² However, the negative β_{X} value of the present work is inadequate to a TS imbalance phenomenon because the existence of cation formed in an ion-pair pre-equilibrium of **7** can be hardly expected with X = EWSs. Moreover, when partial cleavage of the N-H(D) bond occurs with a TS imbalance phenomenon, the DKIEs should be primary normal,¹⁶ opposite to the results of the secondary inverse DKIFs with X = EWSs in the present work; and (iii) The unusual negative β_{X} (and positive ρ_{X}) value with X = EWSs generally implies that the nucleophilic N atom becomes more negative in the TS compared to in the ground state (GS). The authors reported the anilinolysis of Y-aryl phenyl isothiocyanophosphates in MeCN, and the free energy relationships with X exhibit biphasic concave upwards with a break region between X = H and 4-Cl, giving unusual negative β_{X} value with weakly basic anilines (X = 4-Cl and 3-Cl).¹⁷ The negative β_{X} values with weakly basic anilines were substantiated by very tight TS, in which the extent of the bond formation is great and the degree of the bond breaking is considerably small. In other words, the TS structure is similar to that as if the isothiocyanate is the nucleophile and aniline is the leaving group. The proposed very tight TS is possible because the isothiocyanate is a poor leaving group. In the present, however, ‘very tight TS’ model is inadequate because the chloride is better leaving group compared to the aniline.

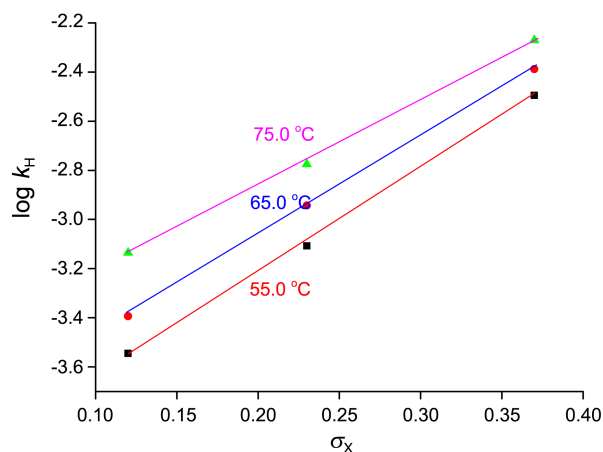
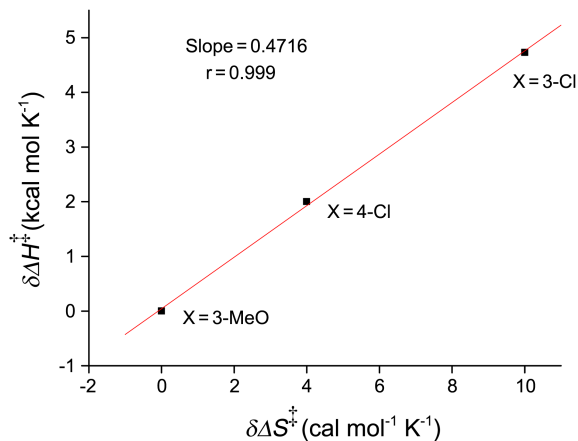
In the present work, it is the suggestion of the authors that unusual negative β_{X} (and positive ρ_{X}) value with X = EWSs is attributed to isokinetic relationship. For a large number of reaction series, it is found that $\delta\Delta H^{\ddagger}$ and $\delta\Delta S^{\ddagger}$ are proportional, resulting in isokinetic relationship.¹⁸ The second-order rate constants at 55.0, 65.0 and 75.0 °C, and enthalpies and entropies of activation with 3-methoxy-, 4-chloro- and 3-chloro-anilines are summarized in Table 3. The enthalpy and entropy of activation remarkably decrease as the aniline becomes less basic, and the ρ_{X} value decreases as the reaction temperature becomes higher as seen in Figure 2. As a result, the calculated isokinetic temperature is $T_{\text{ISOKINETIC}} = 471.6 \text{ K} = 198 \text{ }^{\circ}\text{C}$, according to Eq. (3) and Figure 3, where the ρ_{X} value is null.

$$\delta\Delta G^{\ddagger} = \delta\Delta H^{\ddagger} - T\delta\Delta S^{\ddagger} = 0; \text{ when } \delta\Delta H^{\ddagger} = T_{\text{ISOKINETIC}} \delta\Delta S^{\ddagger} \quad (3)$$

A concerted mechanism was proposed for the anilinolyse of **2-5** based on the magnitudes of the Brønsted coefficient: $\beta_{\text{X(H)}} = 1.26(\mathbf{2})$, $1.23(\mathbf{3})$, $1.04(\mathbf{4})$ and $1.10(\mathbf{5})$ comparable with $\beta_{\text{X(H)}}(\mathbf{6}) = 1.22\text{--}1.33$ and $\beta_{\text{X(H)}}(\mathbf{8}) = 1.21\text{--}1.25$, because a concerted mechanism was proposed based on the negative ρ_{XY} values for the anilinolyse of both **6** and **8**. In the present

Table 3. Second-Order Rate Constants ($k_H \times 10^4/M^{-1} s^{-1}$) at 55.0, 65.0 and 75.0 °C, and Activation Parameters for the Reactions of **7** with 4-MeO, 4-Cl and 3-Cl Anilines in MeCN

X \ t (°C)	55.0	65.0	75.0	$\Delta H^\ddagger/kcal mol^{-1}$	$-\Delta S^\ddagger/cal mol^{-1} K^{-1}$
3-MeO	2.85 ± 0.01	4.04 ± 0.03	7.33 ± 0.01	9.8	45
4-Cl	7.81 ± 0.01	11.4 ± 0.1	16.8 ± 0.1	7.8	49
3-Cl	32.0 ± 0.1	40.9 ± 0.1	53.6 ± 0.1	5.0	55

**Figure 2.** Hammett plots of $\log k_H$ vs σ_X for the reactions of **7** with 3-MeO, 4-Cl and 3-Cl anilines in MeCN. The ρ_X values are 4.21 ± 0.02 ($r = 0.999$), 4.02 ± 0.01 ($r = 0.999$) and 3.46 ± 0.02 ($r = 0.999$) at 55.0, 65.0 and 75.0 °C, respectively.**Figure 3.** Isokinetic relationship for the reactions of **7** with 3-MeO, 4-Cl and 3-Cl anilines in MeCN, giving the slope of isokinetic temperature, slope = $T_{ISOKINETIC} = 471.6 K = 198 \text{ }^\circ C$ ($r = 0.999$).

work, the authors propose a stepwise mechanism with a rate-limiting leaving group departure from the intermediate for both X = EDSs and EWSs based on: (i) the Brønsted coefficient of $\beta_{X(H)} = 1.43(7)$ with X = EDSs is comparable with $\beta_{X(H)}(1) = 1.31-1.54$ with weakly basic anilines where a

Table 4. Summary of the Free Energy Correlations with X and Anilinolysis Mechanisms for the Reactions of **1-8** with $XC_6H_4NH_2(D_2)$ in MeCN

Substrate	Free energy correlation with X	Mechanism
1: Me(YC ₆ H ₄ O)P(=S)Cl	biphasic concave downward	bond formation/breaking ^a
2: Ph(MeO)P(=S)Cl	linear	concerted
3: Ph(EtO)P(=S)Cl	linear	concerted
4: Ph(PrO)P(=S)Cl	linear	concerted
5: Ph(<i>i</i> -PrO)P(=S)Cl	linear	concerted
6: Ph(YC ₆ H ₄ O)P(=S)Cl	linear	concerted
7: (<i>i</i> -Pr ₂ N)(MeO)P(=S)Cl	biphasic concave upward	bond breaking ^a
8: Ph(YC ₆ H ₄ S)P(=S)Cl	linear	concerted

^aStrongly/weakly basic anilines. ‘Bond formation/breaking’ indicates a stepwise mechanism with a rate-limiting bond formation and with a rate-limiting leaving group expulsion from the intermediate, respectively.

rate-limiting bond breaking is proposed; and (ii) as mentioned earlier, the gradual DKIEs variation with X indicates that the mechanism is not changed with both X = EDSs and EWSs. Table 4 lists the free energy relationships for substituent X variations in the anilines and proposed mechanisms for the anilinolyses of **1-8**. The variation trends of the k_H/k_D values with X are not correlated with the anilinolysis mechanism as seen in Tables 2 and 4.¹⁹

Pyridinolysis. Table 5 lists the second-order rate constants (k_{pyr}) of the pyridinolysis in MeCN at 45.0 °C. The substituent effects of the nucleophiles upon the pyridinolysis rates correlate with those for a typical nucleophilic substitution reaction. Both the Brønsted (Figure 4) and Hammett (Figure S2) plots, however, are biphasic concave upwards with a break point at X = 3-MeO. The magnitudes of the ρ_X ($= -3.76 \pm 0.03$; $r = 0.999$) and β_X ($= 0.83 \pm 0.02$; $r = 0.999$) values with strongly basic pyridines (X = 4-MeO, 4-Me, 3-Me, H, 3-Ph, 3-MeO) are much greater than those [$\rho_X = -0.89 \pm 0.01$ ($r = 0.998$) and $\beta_X = 0.14 \pm 0.05$ ($r = 0.960$)] with weakly basic pyridines (X = 3-MeO, 3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN).

Table 6 lists the second-order rate constants ($k_2 \times 10^3/M^{-1} s^{-1}$) with unsubstituted pyridine at 35.0 °C, Brønsted coeffi-

Table 5. Second-Order Rate Constants ($k_{pyr} \times 10^4/M^{-1} s^{-1}$) of the Reactions of **7** with XC_5H_4N in MeCN at 45.0 °C

X	4-MeO	4-Me	3-Me	H	3-Ph	3-MeO	3-Cl	3-Ac	4-Ac	3-CN	4-CN
$k_{pyr} \times 10^4$	12.9	5.24	2.28	1.18	0.656	0.475	0.300	0.291	0.228	0.193	0.159
	± 0.1	± 0.1	± 0.01	± 0.01	± 0.002	± 0.001	± 0.001	± 0.002	± 0.003	± 0.001	± 0.001

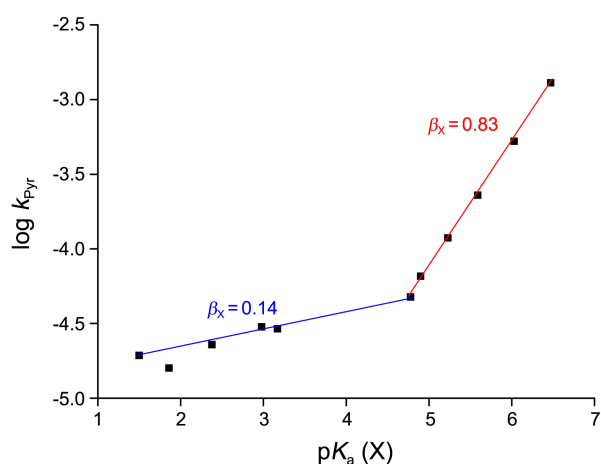
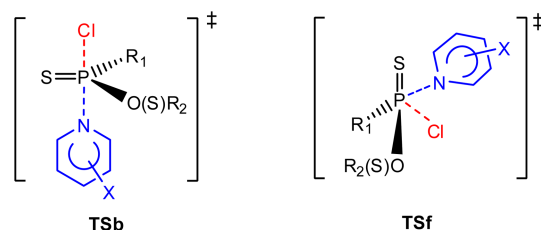


Figure 4. Brønsted plot of the reactions of **7** with $\text{XC}_5\text{H}_4\text{N}$ in MeCN at 45.0 °C.

coefficients (β_X), cross-interaction constants (CICs; ρ_{XY})⁵ and free energy correlations for the substituent X and Y variations in the nucleophiles and substrates, respectively, of the pyridinolyses of **1-8** in MeCN. The substituent effects of X and Y on the pyridinolysis rates are more significant compared to those on the anilinolysis rates, so that the free energy correlations of the pyridinolyses are more complex compared to those of the anilinolyses. The two substrates of **1** and **7** exhibit biphasic free energy correlations, not with Y

but with X, in the anilinolyses. On the contrary, only one substrate of **6** exhibits linear free energy correlation with X and Y, and furthermore, the two substrates of **1** and **8** exhibit biphasic free energy correlations with both X and Y in the pyridinolyses. The pyridinolysis rates do not show linear correlation with the positive NBO charge at the reaction center P atom, as observed in the anilinolysis rates. The pyridinolysis rates of **2-5** show linear correlation with the size of the two ligands.²⁰

In view of biphasic concave upward free energy correlations for substituent X variations of **2-5**, **7** and **8**, the greater β_X values with strongly basic pyridines compared to those with weakly basic pyridines indicate a frontside attack TSf with strongly basic pyridines and a backside attack TSb with weakly basic pyridines (Scheme 4). It is well known that a weakly basic group has a greater apicophilicity so that



Scheme 4. Backside attack TSb and frontside attack TSf for the reactions of phosphonochloridothioates with X-pyridines.

Table 6. Summary of the Second-Order Rate Constants ($k_{\text{Pyr}} \times 10^3/\text{M}^{-1} \text{s}^{-1}$) with $\text{C}_5\text{H}_5\text{N}$ at 35.0 °C, β_X , ρ_{XY} and Free Energy Correlations with X and Y of the Reactions of **1-8** with X-Pyridines in MeCN

Substrate	$10^3 k_{\text{Pyr}}^a$	β_X	ρ_{XY}	X variation	Y variation
1: Me($\text{YC}_6\text{H}_4\text{O}$)P(=S)Cl	14.3 ^a	0.66-1.04/2.08-2.38 ^c	-1.76/0/2.80/0 ^d	discrete ^e	Λ^g
2: Ph(MeO)P(=S)Cl	6.87	1.42/0.46 ^c	–	V ^f	–
3: Ph(EtO)P(=S)Cl	5.47	1.39/0.46 ^c	–	V ^f	–
4: Ph(PrO)P(=S)Cl	3.22	2.09/0.48 ^c	–	V ^f	–
5: Ph(<i>i</i> -PrO)P(=S)Cl	2.35	2.01/0.47 ^c	–	V ^f	–
6: Ph($\text{YC}_6\text{H}_4\text{O}$)P(=S)Cl	11.2 ^a	0.87-0.95	-0.46	linear	linear
7: (<i>i</i> -Pr ₂ N)(MeO)P(=S)Cl	0.0741 ^b	0.83/0.14 ^c	–	V ^f	–
8: Ph($\text{YC}_6\text{H}_4\text{S}$)P(=S)Cl	1.10 ^a	1.42-1.49/0.46-0.55 ^c	0/0.97/1.42/0.44 ^d	V ^f	V_{min}^h

^aValue with Y = H. ^bEmpirical value. ^cStrongly/weakly basic pyridines. ^d*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). ^eBiphasic discrete two plots, neither concave upwards nor downwards. ^fBiphasic concave upwards. ^gBiphasic concave downwards. ^hBiphasic concave upwards with a minimum point.

Table 7. Summary of the Free Energy Correlations with X and Y, and Pyridinolysis Mechanisms of the Reactions of **1-8** with X-Pyridines in MeCN^a

Substrate	X variation	Y variation	Mechanism
1: Me($\text{YC}_6\text{H}_4\text{O}$)P(=S)Cl	discrete	Λ	bond formation/breaking/breaking/breaking ^b
2: Ph(MeO)P(=S)Cl	V	–	bond breaking/breaking
3: Ph(EtO)P(=S)Cl	V	–	bond breaking/breaking
4: Ph(PrO)P(=S)Cl	V	–	bond breaking/breaking
5: Ph(<i>i</i> -PrO)P(=S)Cl	V	–	bond breaking/breaking
6: Ph($\text{YC}_6\text{H}_4\text{O}$)P(=S)Cl	linear	linear	concerted
7: (<i>i</i> -Pr ₂ N)(MeO)P(=S)Cl	V	–	concerted
8: Ph($\text{YC}_6\text{H}_4\text{S}$)P(=S)Cl	V	V_{min}	bond breaking/breaking/breaking/breaking ^b

^aDiscrete, V, Λ , V_{min} : see the footnotes in Table 6. ^b*a*-/*b*-/*c*-/*d*-block: see the footnotes in Table 6.

Table 8. Activation Parameters for the Reactions of **1-8** with Aniline and Pyridine in MeCN

Nucleophile	Substrate	$\Delta H^\ddagger/\text{kcal mol}^{-1}$	$-\Delta S^\ddagger/\text{cal mol}^{-1} \text{K}^{-1}$	Ref.
Aniline	1: Me(YC ₆ H ₄ O)P(=S)Cl	0.3-1.0	65-68	1b
	2: Ph(MeO)P(=S)Cl	4.5	55	1e
	3: Ph(EtO)P(=S)Cl	4.6	55	1d
	4: Ph(PrO)P(=S)Cl	4.7	55	1e
	5: Ph(<i>i</i> -PrO)P(=S)Cl	5.1	54	1e
	6: Ph(YC ₆ H ₄ O)P(=S)Cl	2.5-4.7	58-65	1c
	7: (<i>i</i> -Pr ₂ N)(MeO)P(=S)Cl	5.0-9.8	45-55	present work
	8: Ph(YC ₆ H ₄ S)P(=S)Cl	2.5-4.5	58-69	1a
Pyridine	1: Me(YC ₆ H ₄ O)P(=S)Cl	3.0-11.0	35-57	2b
	2: Ph(MeO)P(=S)Cl	6.5	47	2d
	3: Ph(EtO)P(=S)Cl	8.4	42	2d
	4: Ph(PrO)P(=S)Cl	11.6	32	2e
	5: Ph(<i>i</i> -PrO)P(=S)Cl	9.2	40	2e
	6: Ph(YC ₆ H ₄ O)P(=S)Cl	2.7-5.7	46-59	2a
	7: (<i>i</i> -Pr ₂ N)(MeO)P(=S)Cl	8.6	50	present work
	8: Ph(YC ₆ H ₄ S)P(=S)Cl	3.8	65	2c

apical approach is favored for such nucleophiles.²¹ The apical nucleophilic attack should lead to a looser P–N bond in the TBP-5C structure because the apical bonds are longer than the equatorial bonds, and hence a smaller magnitude of β_X is obtained.

In the present work, the authors propose a concerted mechanism based on relatively small β_X values, $\beta_X = 0.83$ and 0.14 with strongly and weakly basic pyridines, respectively, comparable with the $\beta_X (= 0.87-0.95)$ values for the pyridinolyses of **6** in which a concerted mechanism was proposed.^{2a} A frontside and backside attack is proposed with strongly and weakly basic pyridines, respectively. The reaction mechanisms of **1-6** and **8** were proposed based on the β_X and ρ_{XY} values.^{2a-e} The proposed mechanisms of the phosphonochloridothioates are listed in Table 7.

Activation Parameters. The enthalpies and entropies of activation, for the anilinolysis and pyridinolysis of **7** are summarized in Table R1,²² and those of **1-8** are summarized in Table 8. The relatively low value of activation enthalpy and large negative value of activation entropy are typical for the aminolyses of P=S (and P=O) systems. It is worthy of note that the clarification of the reaction mechanism by means of the activation parameters is not easy for the aminolyses of P=S (and P=O) systems.

Experimental Section

Materials. *O*-Methyl *N,N*-diisopropylamino phosphonochloridothioate was prepared by one step synthetic route. *N,N*-Diisopropylamino methoxy chlorophosphine was stirred about 3.0 h with sulfur in THF at -5.0 °C. The solvent was removed under reduced pressure and a liquid product was isolated through column chromatography (10% ethyl acetate + *n*-hexane). Analytical and spectroscopic data of the product gave the following results (supporting information):

(*i*-Pr₂N)(MeO)P(=S)Cl: Liquid; ¹H NMR (400 MHz,

MeCN-*d*₃) δ 1.24-1.32 (d, 12H), 3.79 (s, 3H), 3.83-3.97 (m, 2H); ¹³C NMR (100 MHz, MeCN-*d*₃) δ 22.3, 49.7, 54.3; ³¹P NMR (162 MHz, MeCN-*d*₃) δ 83.9 (1P, P=S); GC-MS (EI, *m/z*) 229 (*M*⁺).

Kinetic Procedure. The second-order rate constants and selectivity parameters were obtained as previously described: anilinolysis¹ and pyridinolysis.² Initial concentrations for both anilinolysis and pyridinolysis were as follows; [substrate] = 5×10^{-3} M and [nucleophile] = (0.10-0.30) M.

Product Analysis. In the anilinolysis, *O*-methyl phenyl phosphonochloridothioate was reacted with excess aniline for more than 15 half-lives at 65.0 °C in MeCN. The aniline hydrochloride salt was separated by filtration. Acetonitrile was removed under reduced pressure. The product was isolated through treatment with ether and dilute HCl by a work up process and, then dried over MgSO₄. After filtration the product was isolated by evaporating the solvent under reduced pressure. In the pyridinolysis, *O*-methyl *N,N*-diisopropylamino phosphonochloridothioate was reacted with excess pyridine, for more than 15 half-lives at 45.0 °C in MeCN. Solvent was removed under reduced pressure. The product was isolated after treatment with ether and acetonitrile, and then dried under reduced pressure. The analytical and spectroscopic data of the product gave the following results (supporting information):

(*i*-Pr₂N)(MeO)P(=S)NHC₆H₅: Brown liquid; ¹H-NMR (400 MHz, MeCN-*d*₃) δ 1.02-1.34 (d, 12H), 1.36-1.47 (m, 2H), 3.45 (s, 3H), 6.64-6.70 (d, 2H), 7.08-7.21 (t, 2H) 7.32-7.41 (d, 1H), 9.19 (s, br., 1H); ¹³C-NMR (100 MHz, MeCN-*d*₃) δ 19.3, 48.2, 49.2, 115.4, 130.1, 138.8, 142.0, 149.1, 158.8; ³¹P-NMR (162 MHz, MeCN-*d*₃) δ -11.7 (1P, P=S); GC-MS (EI, *m/z*) 286 (*M*⁺).

(*i*-Pr₂N)(MeO)P(=S)NC₅H₅⁺Cl⁻: Gummy solid crystal; ¹H-NMR (400 MHz, D₂O) δ 1.21-1.34 (d, 12H), 3.52-3.55 (m, 2H), 4.43 (s, 3H), 8.07-8.09 (d, 2H), 8.56-8.62 (t, 1H), 8.81-8.82 (d, 2H); ¹³C-NMR (100 MHz, D₂O) δ 18.5, 41.3,

47.4, 127.3, 128.1, 144.4, 145.2, 153.4; ^{31}P -NMR (162 MHz, D_2O) δ -13.7 (1P, s, P=O); LC-MS for $\text{C}_{12}\text{H}_{22}\text{N}_2\text{OPSCl}$ (m/z), 308 (M^+).

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- Regarding **8**, the size of PhS is more or less larger than that of PhO and, thus, the steric effects of the two ligands of **8** with Ph and PhS are somewhat greater than those of **7** with Ph and PhO in the TS. However, the anilinolysis rate of **8** is nine times slower than that of **7** which cannot be rationalized by the steric effects of the two ligands. The considerably slower rate of **8** compared to that of **7** is attributed to the considerably smaller positive NBO charge at P atom of **8** compared to that of **7**, (NBO charge) = 1.462(**4**)-0.999(**5**) = 0.463.
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- Enthalpy and Entropy of Activation for the Reactions of **7** with Aniline and Pyridine in MeCN.

Table R1. Activation Parameters^a for the Reactions of **7** with Aniline and Pyridine in MeCN

Nucleophile	$t/^\circ\text{C}$	$k_2 \times 10^4$ / $\text{M}^{-1} \text{s}^{-1}$	$\Delta H^\ddagger/\text{kcal}$ mol^{-1}	$-\Delta S^\ddagger/\text{cal}$ $\text{mol}^{-1} \text{K}^{-1}$
$\text{C}_6\text{H}_5\text{NH}_2$	55.0	3.23 ± 0.01	6.2 ± 0.1	56 ± 1
	65.0	4.35 ± 0.01		
	75.0	5.90 ± 0.01		
$\text{C}_5\text{H}_5\text{N}$	35.0	0.741 ± 0.001	8.6 ± 0.1	50 ± 1
	45.0	1.18 ± 0.01		
	55.0	1.85 ± 0.01		

^aCalculated by Eyring equation